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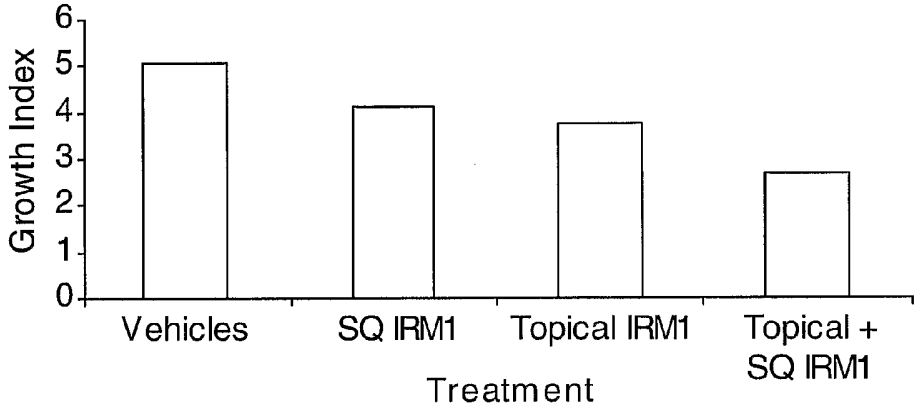
(54) **Title:** MULTI-ROUTE ADMINISTRATION OF IMMUNE RESPONSE MODIFIER COMPOUNDS



(57) **Abstract:** A method of treating disease with immune response modifier (IRM) compounds by using at least two different routes of administration, such as administering at least one IRM to a subject locally (e.g., topically) at a disease site in combination with separately administering at least one IRM to the subject systemically (e.g., orally or by injection).

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MULTI-ROUTE ADMINISTRATION OF IMMUNE RESPONSE MODIFIER COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. provisional application 60/640873, filed December 30, 2004, the entire contents of which is hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention relates to administration of immune response modifier (IRM) compounds for use in treating disease.

BACKGROUND

There has been a major effort in recent years, with substantial progress being made, to develop drugs that can beneficially modify the immune system. For examples, various imidazoquinoline amine, imidazopyridine amine, 6,7-fused cycloalkylimidazopyridine amine, 1,2-bridged imidazoquinoline amine, thiazoloquinoline amine, oxazoloquinoline amine, thiazolopyridine amine, oxazolopyridine amine, imidazonaphthyridine amine, imidazotetrahydronaphthyridine amine, and thiazolonaphthyridine amine compounds have demonstrated potent immunostimulating, antiviral and antitumor (including anticancer) activity, and have also been shown to be useful as vaccine adjuvants and treatment of TH2-mediated diseases.

The mechanism for the immunostimulatory 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' activities. One of the predominant immunostimulating responses to these compounds can be the induction of interferon (IFN)-α production, which is believed to be very important in the acute

antiviral and antitumor activities seen. Moreover, up regulation of other cytokines such as, for example, tumor necrosis factor (TNF), Interleukin-1 (IL-1), IL-6, and IL-12 also have potentially beneficial activities and are believed to contribute to the antiviral, antitumor, and other properties of these compounds.

One area of particular interest for IRMs has been treatment of skin cancers, the incidence of which has been rapidly increasing worldwide. The drug product Aldara™ (containing the IRM compound imiquimod) has recently been approved for treatment of superficial basal cell carcinoma (BCC), as well as actinic keratosis.

However, surgical removal is still by far the most common treatment for skin cancers, including melanomas, BCCs, and SCCs. This can take the form of electrodesiccation and curettage, cryosurgery, simple wide excision, micrographic surgery, or laser therapy. Other treatments, used when the cancers are detected at a later stage of development, are external radiation therapy, chemotherapy, or to a lesser extent, bio-immunotherapy or photodynamic therapy. Unfortunately, though, there has been very limited success in treating or preventing recurrence of these cancers, especially malignant melanoma, once they have reached more advanced stages. Follow-up surgery is often necessary, with the risk of further disfigurement and scarring. And once the cancer has metastasized there is a high risk of mortality.

Accordingly, there is a continuing need for new treatment methods to provide the enhanced therapeutic benefit from IRM compounds, particularly for conditions such as life-threatening cancers.

SUMMARY

It is now believed that there is a benefit to treating conditions with IRM compounds where one or more IRM compounds is administered via at least two distinct routes of delivery in combination, for example systemically (e.g., by injection) and locally (e.g., topically). It is believed that this provides a way of synergistically targeting the immune system directly to the disease while boosting the immune response throughout the body, e.g., so as to treat or prevent metastasized cancers or infections that may have spread. In a sense, local administration to a tumor or infection site directly can be used as an opportunity to sensitize the immune system to the specific disease being treated, while

the broad immune response induced by non-local application can seek out and target the disease elsewhere in the body.

While applicable for many diseases, it is believed that this new approach will provide benefits in treating malignant melanoma, which despite massive efforts has remained one of the most difficult cancers to treat. Although topical Aldara has shown some activity against melanoma skin lesions, surgery is the conventional treatment. However, it is believed that by administering IRMs locally to the melanoma lesion site on the skin (even after the main lesion has been surgically removed) in combination with systemic delivery, there is a better chance of addressing the high risk that the cancer has already metastasized at the time of initial surgery.

Thus, the present invention is directed to multi-route dosing regimes for administration of one or more IRM compounds. In one embodiment, the present invention provides a method of treating disease with an immune response modifier including administering at least one IRM to a subject topically in combination with separately administering at least one IRM to the subject systemically.

Such multi-route regimens are useful for treating a variety of diseases including cancer (e.g., melanoma and carcinomas) as well as viral, fungal, protazoal, or bacterial infections. Such multi-route regimens are particularly useful for treating melanoma, in particular, by applying at least one IRM topically (or locally via, e.g., subcutaneous, intra-dermal, or intra-tumoral injection) to a melanoma lesion and separately administering at least one IRM systemically.

Herein, topical application involves application to dermal and mucosal tissues, including vaginal, rectal, nasal, buccal, and pulmonary applications. Herein, systemic application involves oral and parenteral (including subcutaneous (subQ or SC) if the intended result is systemic distribution as opposed to local delivery into a lesion), intramuscular (IM), intraperitoneal (IP), intravenous (IV), intrathecal, intraventricular, etc.) administration.

The IRM can be selected from the group consisting of imidazoquinoline amines, tetrahydroimidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines, oxazolopyridine amines, thiazolopyridine amines,

oxazolonaphthyridine amines, thiazolonaphthyridine amines, 1*H*-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, tetrahydronaphthyridine amines, and combinations thereof.

The present invention also provides an aqueous pharmaceutical composition suitable for parental administration. The composition includes: an immune response modifier compound (IRM); a pharmaceutically acceptable acid (e.g., citric acid, hydrochloric acid, lactic acid, acetic acid, or aspartic acid); a tonicity adjuster (e.g., mannitol, glycerin, sorbitol, or dextrose); sterile water; and optionally a pH adjuster (e.g., NaOH); with the proviso that the IRM is other than 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine or 4-amino-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol.

The invention includes, but is not limited to, the following embodiments:

1. A method of treating disease with immune response modifiers (IRMs) by administering at least one IRM compound via at least two different routes of delivery.
2. The method of embodiment 1, wherein there is only one IRM compound active moiety is used.
3. The method of embodiment 2, wherein two different salt forms of the IRM compound active moiety are used.
4. The method of embodiment 1, wherein at least two different IRM compound active moieties are used.
5. The method of any preceding embodiment, wherein the routes of delivery include local delivery and systemic delivery.
6. The method in claim 5, wherein the local route of delivery is topical delivery.
7. The method of embodiment 6, wherein topical delivery is achieved using an IRM-containing gel or cream formulation.
8. The method of embodiments 5, 6 or 7, wherein systemic delivery is achieved by injection or oral delivery.
9. The method of any preceding embodiment, wherein the disease being treated is cancer.
10. The method of embodiment 9, wherein an IRM is delivered locally directly to the cancer and an IRM is delivered systemically to the entire body.

11. The method of embodiment 10, wherein the IRM delivered locally is injected directly into the cancer.

12. The method of any one of embodiments 1 through 8, wherein the disease is a viral, fungal, protazoal, or bacterial infection.

13. A method of treating melanoma with an immune response modifier (IRM), the method comprising:

applying at least one IRM topically to a melanoma lesion on a subject in combination with separately administering at least one IRM to the subject systemically.

14. The method of embodiment 13, wherein the IRM administered topically is administered to a dermal or mucosal tissue.

15. The method of embodiment 14 wherein the IRM administered topically is administered to a vaginal, rectal, nasal, buccal, or pulmonary surface.

16. The method of any preceding embodiment wherein the IRM is a compound having a 2-aminopyridine fused to a five membered nitrogen-containing heterocyclic ring.

17. The method of embodiment 16 wherein the immune response modifier 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, imidazotetrahydronaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines, oxazolopyridine amines, thiazolopyridine amines, oxazolonaphthyridine amines, thiazolonaphthyridine amines, 1*H*-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines, and combinations thereof.

18. The method of embodiment 16, wherein the immune response modifier is selected from the group consisting of imidazoquinoline amines, tetrahydroimidazoquinoline amines, imidazopyridine amines, and combinations thereof.

19. The method of embodiment 16, wherein the immune response modifier is selected from the group consisting of amide substituted imidazoquinoline amines, sulfonamide substituted imidazoquinoline amines, urea 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, 6-, 7-, 8-, or 9-aryl or heteroaryl substituted imidazoquinoline

amines, 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 tetrahydroimidazoquinoline amines, sulfonamido ether substituted tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline ethers, thioether substituted tetrahydroimidazoquinoline amines, amide substituted imidazopyridine amines, sulfonamide substituted imidazopyridine amines, urea substituted imidazopyridine amines, aryl ether substituted imidazopyridine amines, heterocyclic ether substituted imidazopyridine amines, amido ether substituted imidazopyridine amines, sulfonamido ether substituted imidazopyridine amines, urea substituted imidazopyridine ethers, thioether substituted imidazopyridine amines, and combinations thereof.

20. The method of embodiment 19, wherein the immune response modifier is selected from the group consisting of amide substituted imidazoquinoline amines, sulfonamide substituted imidazoquinoline amines, urea substituted imidazoquinoline amines, thioether substituted imidazoquinoline amines, 7-aryl substituted imidazoquinoline amines, 7-heteroaryl substituted imidazoquinoline amines, sulfonamide substituted tetrahydroimidazoquinoline amines, and combinations thereof.

21. The method of embodiment 17, wherein the immune response modifier is an imidazoquinoline amine.

22. The method of embodiment 19, wherein the immune response modifier is a sulfonamide substituted imidazoquinoline amine.

23. The method of embodiment 16, wherein the immune response modifier is selected from the group consisting of N-[4-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide, N-{2-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]-1,1-dimethyleethyl}methanesulfonamide, pharmaceutically acceptable salts thereof, and combinations thereof.

24. The method of any preceding embodiment, wherein an IRM is administered systemically in a formulation comprising:

a pharmaceutically acceptable acid;

a tonicity adjuster;

sterile water; and

optionally a pH adjuster;

with the proviso that the IRM is other than 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine or 4-amino-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol.

25. The method of embodiment 24, wherein the formulation comprises 0.4 wt-% to 0.5 wt-% citric acid, 4 wt-% to 5 wt-% mannitol, and water, wherein the formulation is adjusted to a pH of 5 with the pH adjuster.

26. An aqueous pharmaceutical composition suitable for parental administration comprising:

an immune response modifier compound (IRM);

a pharmaceutically acceptable acid;

a tonicity adjuster;

sterile water; and

optionally a pH adjuster;

with the proviso that the IRM is other than 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine or 4-amino-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol.

The terms "comprises" and variations thereof do not have a limiting meaning where these terms appear in the description and embodiments.

As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably.

Also herein, the recitations of numerical ranges by endpoints include all numbers subsumed within that range (e.g., 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.80, 4, 5, etc.).

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 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 a multi-route dosing regime for administration of one or more IRM compounds. In one embodiment, the present invention provides a

method of treating disease with an immune response modifier including administering at least one IRM to a subject locally (e.g., topically or via injection into a lesion) in combination with separately administering at least one IRM to the subject systemically. Herein, the subject is typically a mammal, and may be a human.

The IRM administered by one route (e.g., topically) may be the same or different than the IRM administered via another route (e.g., systemically). Alternatively, the IRM may be the same compound, or may be the same compound active moiety but in a different salt form thereof.

The multi-route regimens of the present invention are useful for treating a variety of diseases including cancer (e.g., melanoma and carcinomas) as well as viral, fungal, protazoal, or bacterial infections. Herein, treating includes therapeutic and/or prophylactic treating.

Such multi-route regimens are particularly useful for treating melanoma, although other types of cancers can be treated. For example, in one approach, an IRM is injected directly into a tumor for local effect and especially to target the immune system to the tumor, and an IRM is also delivered systemically to boost body-wide immune response to the tumor (especially if there is a risk it has metastasized). Non-limiting examples of other cancers for which the present invention may be useful include breast cancer, stomach cancer, colorectal cancer, prostate cancer, testicular cancer, head and neck cancer, lung cancer, etc. Any cancer where there is a localized tumor site to which an IRM can be delivered, in combination with administration via a different route of delivery (which will often be systemic delivery, but could be other routes as well).

In some embodiments, IRMs of the present invention may be administered to the subject in combination with other modes of treatment. This is particularly true for cancer therapy. Such other modes of cancer therapy include, but are not limited to, radiation treatment, brachytherapy, external beam radiation, chemotheraphy, hormone therapy, immunomodulatory therapy, therapeutic vaccine therapy, and antibody therapy. The administration of the agents of the present invention can take place before, during, or after the other therapy. Likewise, the IRMs may be delivered via different routes simultaneously or at different times.

For cancer treatment, the efficacy of treatment may be assessed by various parameters well known in the art. This includes, but is not limited to, determination of

tumor size, location and vascularization, as determined by such methods including, but not limited to, X-rays, scans, magnetic resonance imaging, computerized tomography, and/or various nuclear medicine techniques and algorithms to evaluate tumor size and burden in three dimensions. Angiography can be used to evaluate vascularization of tumors and other tissues. Other methods of determining tumor location, stage, and grade include, but are not limited to, gene arrays, immuno-histochemistry, and/or other techniques for measuring biomarkers relevant to assessing a disease.

The efficacy of the administration of an IRM effective for the treatment of cancer may be demonstrated by such means, including, but not limited to, the inhibition of tumor growth, the inhibition of tumor progression, the inhibition of tumor spread, the inhibition of tumor invasiveness, the inhibition of tumor vascularization, the inhibition of tumor angiogenesis, and/or the inhibition of tumor metastasis.

The inhibition of tumor growth is a decrease in the growth rate of a tumor. It includes, but is not limited to, at least one of a decrease in tumor weight or tumor volume, a decrease in tumor doubling time, a decrease in the growth fraction or number of tumor cells that are replicating, a decrease in the rate in which tumor cells are shed, and/or a decrease in the ratio of cell production to cell loss within a tumor. The inhibition of tumor growth can also include the inhibition of tumor growth of primary lesions and/or any metastatic lesions.

For oral cancer, the inhibition of tumor progression includes the disruption or halting of the progression of premalignant lesions, also called leukoplakia, to malignant carcinoma.

The inhibition of tumor spread is the decrease in the dissemination of a tumor to other locations. This dissemination to other locations can be the result of the seeding of a body cavity or surface with cancerous cells from a tumor and/or the transport of tumor cells through the lymphatic system and/or circulatory system. The inhibition of tumor spread can also include the inhibition of tumor spread in primary lesions and/or any metastatic lesions.

The inhibition of tumor invasiveness is the decrease in the infiltration, invasion, and/or destruction of the surrounding local tissues, including, but not limited to organs, blood vessels, lymphatics, and/or body cavities. The inhibition of tumor invasiveness can

also include the inhibition of tumor invasiveness in primary lesions and/or any metastatic lesions.

The inhibition of tumor vascularization is the decrease in the formation of blood vessels and lymphatic vessels within a tumor and to and from a tumor. The inhibition of tumor vascularization can also include the inhibition of tumor vascularization in primary lesions and/or any metastatic lesions.

The inhibition of tumor angiogenesis is a decrease in the formation of new capillaries and microvessels within a tumor. The inhibition of tumor angiogenesis can also include the inhibition of tumor angiogenesis in primary lesions and/or any metastatic lesions.

The inhibition of tumor metastasis is a decrease in the formation of tumor lesions that are discontinuous with the primary tumor. With metastasis, tumor cells break loose from the primary lesion, enter blood vessels or lymphatics and produce a secondary growth at a distant site. In some cases the distribution of the metastases may be the result of the natural pathways of the drainage of the lymphatic and/or circulatory system. In other cases, the distribution of metastases may be the result of a tropism of the tumor to a specific tissue or organ. For example, prostate tumors may preferentially metastasis to the bone. The tumor cells of a metastatic lesion may in turn metastasize to additional locations. This may be referred to as a metastatic cascade. Tumor cells may metastasize to sites including, but not limited to, liver, bone, lung, lymph node, spleen, brain or other nervous tissue, bone marrow, or an organ other than the original tissue of origin. The inhibition of tumor metastasis includes the inhibition of tumor metastasis in primary lesions and/or any metastatic lesions.

Herein, local application includes, e.g., topical application as well as injectable applications (e.g., intra-dermal, intra-tumoral, or subcutaneous) intended for local distribution only, without substantial systemic delivery. Herein, topical application involves application to dermal and mucosal tissues, including vaginal, rectal, nasal, buccal, and pulmonary applications. Herein, systemic application involves oral and parenteral (including subcutaneous (subQ or SC) if intended for systemic distribution as opposed to local administration), intramuscular (IM), intraperitoneal (IP), intravenous (IV), intrathecal, intraventricular, etc.) administration. Thus, formulations of the present invention can be administered to a subject (e.g., mammal, particularly a human) in various

ways, for example, by spraying, injection, inhalation (e.g., from a nebulizer or spray pump atomizer), gel, cream, foam, transdermal patch, suppository, etc.

Formulations of the present invention suitable for topical administration are disclosed in, e.g., U.S. Patent Publication No. US 2003/0199538 and International Publication No. WO 2003/045391. A typical formulation for topical administration includes, for example, isostearic acid (e.g., 15-35 wt-%), medium-chain triglycerides (e.g., 5-10 wt-%), propylene glycol (e.g., 5-10 wt-%), parabens (e.g., methyl, ethyl, and mixtures thereof) (e.g., 0.1-0.5 wt-%), edetate disodium (e.g., 0.01-0.1 wt-%), polymers such as CARBOMERS and POLOXAMERS (e.g., 4.0-5.0 wt-%), and water (preferably sterile water), wherein the formulation is optionally adjusted to a desired pH, preferably a pH of 5.8 (e.g., by NaOH). An IRM can be incorporated into such a formulation in a variety of concentrations.

Formulations of the present invention suitable for parenteral administration conveniently include a sterile aqueous preparation of the desired compound, or dispersions of sterile powders including the desired compound, which are preferably isotonic with the blood of the subject. Isotonic agents that can be included in the liquid preparation include sugars, buffers, and salts such as sodium chloride. Solutions of the desired compound can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions of the desired compound can be prepared in water, ethanol, a polyol (such as glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, glycerol esters, and mixtures thereof.

A typical formulation for systemic administration (e.g., IV and SC) includes, for example, citric acid or other pharmaceutically acceptable acid (e.g., hydrochloric acid, lactic acid, acetic acid, aspartic acid), mannitol or other tonicity adjuster (e.g., glycerin, sorbitol, dextrose), and water (preferably, sterile water), wherein the formulation is optionally adjusted to a desired pH, preferably a pH of 5, by a suitable pH adjuster (e.g., by NaOH). The pharmaceutically acceptable acid is preferably present in the formulation (i.e., composition) in an amount of at least 0.4 wt-%, although lower concentrations, such as 0.3%, may also be used, , and preferably no more than 0.5 wt-%, based on the total weight of the formulation. The tonicity adjuster is preferably present in the formulation in an amount of at least 4 wt-%, and preferably no more than 5 wt-%, based on the total weight of the formulation. Additional information regarding formulations for injection can

be found in co-pending application attorney docket number 61658WO003, entitled Immune Response Modifier Formulations and Methods, filed even date herewith.

The IRM can be incorporated into such a formulation in a variety of concentrations. Typical formulations include one or more IRMs in amounts of at least 0.001 wt-%, and preferably at least 0.2 wt-%, and even up to 1.5 wt-%, based on the total weight of the formulation. An IRM can be incorporated into such a formulation in a variety of concentrations.

Formulations of the present invention suitable for oral administration can include those discussed above for systemic administration, wherein the formulations are suitably diluted. For example, such formulations can be diluted with dextrose or other suitable diluents to a total volume of 10 mL.

Other oral formulations may include discrete units such as tablets, troches, capsules, lozenges, wafers, or cachets, each containing a predetermined amount of the IRM, as a powder, in granular form, incorporated within liposomes, or as a solution or suspension in an aqueous liquid or non-aqueous liquid such as a syrup, an elixir, an emulsion, or a draught.

The tablets, troches, pills, capsules, and the like may also contain one or more of the following: a binder such as gum tragacanth, acacia, corn starch, or gelatin; an excipient such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid, and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, fructose, lactose, or aspartame; and a natural or artificial flavoring agent. When the unit dosage form is a capsule, it may further contain a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac, sugar, and the like. A syrup or elixir may contain one or more of a sweetening agent, a preservative such as methyl- or propylparaben, an agent to retard crystallization of the sugar, an agent to increase the solubility of any other ingredient, such as a polyhydric alcohol, for example glycerol or sorbitol, a dye, and flavoring agent. The material used in preparing any unit dosage form is substantially nontoxic in the amounts employed. The compound may be incorporated into sustained-release preparations and devices if desired.

Formulations for rectal or vaginal administration may be presented as a suppository with a suitable carrier such as cocoa butter, or hydrogenated fats or hydrogenated fatty carboxylic acids.

Nasal spray formulations can include purified aqueous solutions of the desired compound with preservative agents and isotonic agents. Such formulations are preferably adjusted to a pH and isotonic state compatible with the nasal mucous membranes. Preferably, such formulations are in solution form at room temperature (i.e., 25°C-30°C). Also, such formulations are sufficiently low in viscosity (less than 100 centipoise (cps)) at room temperature. At such low viscosity level, the compositions are typically and preferably sprayable. In this context, "sprayable" means the formulation can be delivered using a conventional pump spray device.

The amount of an IRM compound that will be therapeutically effective in a specific situation will depend on such things as the activity of the particular compound, the dosing regimen, the application site, the particular formulation, and the condition being treated. As such, specific administration amounts described herein are only exemplary. Those skilled in the art will be able to determine appropriate therapeutically effective amounts based on the guidance provided herein, information available in the art pertaining to those compounds, and routine testing.

Typical topical formulations include one or more IRMs in amounts of at least 0.01 wt-%, and even up to 3.0 wt-%, based on the total weight of the formulation. A preferred systemic formulation includes one or more IRMs in amounts of 0.1 wt-% to 1.6 wt-%, based on the total weight of the formulation. A typical injection volume of 1.5 mL.

In some embodiments, the methods of the present invention include systemically administering sufficient formulation to provide a dose of IRM compound of, for example, from 10 ng/kg to 50 mg/kg to the subject, although in some embodiments the methods may be performed by administering IRM compound in concentrations outside this range. In some of these embodiments, the method includes systemically administering sufficient formulation to provide a dose of IRM compound of from 100 ng/kg to 5 mg/kg to the subject, for example, a dose of from 1 μg/kg to 1 mg/kg.

In some embodiments, the methods of the present invention include topically administering sufficient formulation of IRM compound, for example, from 0.0001wt-% to 10wt-% to the subject, although in some embodiments the methods may be performed by

administering IRM compound in concentrations outside this range. In some of these embodiments, the method includes topically administering sufficient formulation of IRM compound from 0.001wt-% to 5wt-% to the subject, for example, from 0.01wt-% to 3wt-%.

IRM Compounds

IRM compounds used herein are generally agonists of toll-like receptors (TLRs) 7, 8, and/or 9. Some IRM oligonucleotide sequences contain cytosine-guanine dinucleotides (CpG) and are described, for example, in U.S. Patent Nos. 6,194,388; 6,207,646; 6,239,116; 6,339,068; and 6,406,705. Some CpG-containing oligonucleotides can include synthetic immunomodulatory structural motifs such as those described, for example, in U.S. Patent Nos. 6,426,334 and 6,476,000. Other IRM nucleotide sequences lack CpG sequences and are described, for example, in International Patent Publication No. WO 00/75304. Other IRMs include biological molecules such as aminoalkyl glucosaminide phosphates (AGPs) and are described, for example, in U.S. Patent Nos. 6,113,918; 6,303,347; 6,525,028; and 6,649,172. CpGs and other biological IRMs are considered relatively large molecules and many are TLR 9 agonists.

However, TLR 7 and/or 8 agonists may be preferred, and small-molecule IRMs are generally preferred for methods involving multi-route administration including topical delivery. Examples of small organic molecule IRMs (e.g., molecular weight under about 1000 Daltons, preferably under about 500 Daltons, as opposed to large biologic protein, peptides, and the like) are disclosed in, for example, 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; 6,083,505; 6,110,929; 6,194,425; 6,245,776; 6,331,539; 6,376,669; 6,451,810; 6,525,064; 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; 6,756,382; European Patent 0 394 026; U.S. Patent Publication Nos. 2002/0016332; 2002/0055517; 2002/0110840; 2003/0133913; 2003/0199538; and 2004/0014779; and International Patent Publication No. WO 04/058759.

IRM compounds suitable for use in the invention preferably include small-molecule IRM 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 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; 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 tetrahydroimidazoquinoline amines, sulfonamido ether substituted 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 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; imidazotetrahydronaphthyridine amines; oxazoloquinoline amines; thiazoloquinoline amines; oxazolopyridine amines; thiazolopyridine amines; oxazolonaphthyridine amines; thiazolonaphthyridine amines; and 1*H*-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines. Various combinations of these IRMs can be used if desired.

In certain embodiments, the immune response modifier is selected from the group consisting of imidazoquinoline amines, tetrahydroimidazoquinoline amines, imidazopyridine amines, and combinations thereof.

In certain embodiments, the immune response modifier is selected from the group consisting of amide substituted imidazoquinoline amines, sulfonamide substituted imidazoquinoline amines, urea 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, 6-, 7-, 8-, or 9-aryl or heteroaryl substituted imidazoquinoline amines, 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 tetrahydroimidazoquinoline amines, sulfonamido ether substituted tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline ethers, thioether substituted tetrahydroimidazoquinoline amines, amide substituted imidazopyridine amines, sulfonamide substituted imidazopyridine amines, urea substituted imidazopyridine amines, aryl ether substituted imidazopyridine amines, heterocyclic ether substituted imidazopyridine amines, amido ether substituted imidazopyridine amines, sulfonamido ether substituted imidazopyridine amines, urea substituted imidazopyridine ethers, thioether substituted imidazopyridine amines, and combinations thereof.

In certain embodiments, the immune response modifier is selected from the group consisting of amide substituted imidazoquinoline amines, sulfonamide substituted imidazoquinoline amines, urea substituted imidazoquinoline amines, thioether substituted imidazoquinoline amines, 7-aryl substituted imidazoquinoline amines, 7-heteroaryl substituted imidazoquinoline amines, sulfonamide substituted tetrahydroimidazoquinoline amines, and combinations thereof.

In certain embodiments, the immune response modifier is an imidazoquinoline amine. In certain embodiments, the immune response modifier is a sulfonamide substituted imidazoquinoline amine.

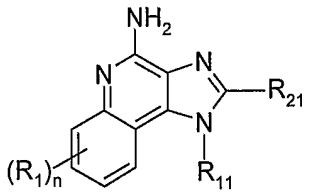
In certain embodiments, the immune response modifier is selected from the group consisting of N-[4-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide, N-{2-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]-1,1-dimethyleethyl}methanesulfonamide, 4- amino-α,α-dimethyl -2-ethoxymethyl-1H-imidazo[4,5-c]quinolin-1-ethanol, pharmaceutically acceptable salts thereof, and combinations thereof.

The IRM compounds and salts thereof described herein include any of their pharmaceutically acceptable forms, such as isomers (e.g., diastereomers and 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 combinations of the enantiomers.

The immune response modifier can, for example, be a salt of an acid selected from the group consisting of a carboxylic acid, a halo acid, sulfuric acid, phosphoric acid, dicarboxylic acid, tricarboxylic acid, and combinations thereof. In certain embodiments, the salt of the immune response modifier can be a salt of an acid selected from the group consisting of hydrobromic acid, hydrochloric acid, lactic acid, glutamic acid, gluconic acid, tartaric acid, succinic acid, and combinations thereof.

Exemplary IRM Compounds

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

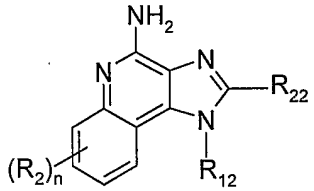
wherein

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 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 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 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

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;



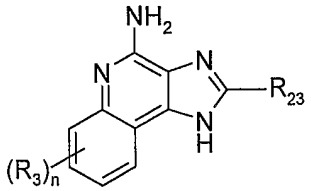
II

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;

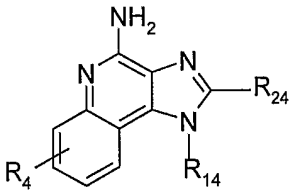


III

wherein

R_{23} 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_3 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_3 groups together contain no more than six carbon atoms;



IV

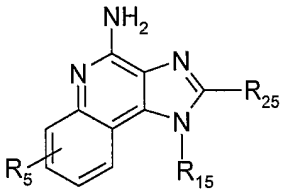
wherein

R_{14} is $-CHR_xR_y$ wherein R_y is hydrogen or a carbon-carbon bond, with the proviso that when R_y is hydrogen R_x is alkoxy of one to four carbon atoms, hydroxyalkoxy of one to four carbon atoms, 1-alkynyl of two to ten carbon atoms, tetrahydropyranyl, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, or 2-, 3-, or 4-pyridyl, and with the further

proviso that when R_y is a carbon-carbon bond R_y and R_x together form a tetrahydrofuranyl group optionally substituted with one or more substituents independently 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;



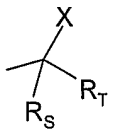
V

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 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_{25} is



wherein

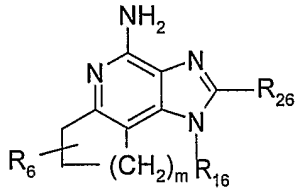
R_S and R_T are independently selected from hydrogen, alkyl of one to four carbon atoms, phenyl, and substituted phenyl wherein the substituent is selected from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen;

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 contains one to four carbon atoms, hydroxyalkyl of one to four carbon atoms, haloalkyl of one to four carbon atoms, alkylamido wherein the alkyl group contains one to four carbon atoms, amino, substituted amino wherein the substituent is alkyl or hydroxyalkyl of one to four carbon atoms, azido, chloro, hydroxy, 1-morpholino, 1-pyrrolidino, alkylthio of one to four carbon atoms; and

R_5 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;

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

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, 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 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, with the proviso that any such alkyl, substituted alkyl, alkenyl, substituted alkenyl, hydroxyalkyl, alkoxyalkyl, or acyloxyalkyl group does not have a fully carbon substituted carbon atom bonded directly to the nitrogen atom; benzyl; (phenyl)ethyl; and phenyl; said benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently 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 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 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_y is a carbon-carbon bond R_y and R_x together form a tetrahydrofuranyl group optionally substituted with one or more substituents independently selected from hydroxy and hydroxyalkyl of one to four carbon atoms;

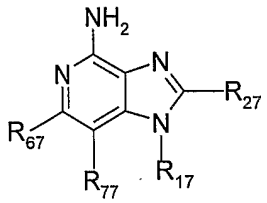
R_{26} is selected from hydrogen; straight chain or branched chain alkyl containing one to eight carbon atoms; straight chain or branched chain hydroxyalkyl containing one to six carbon atoms; morpholinoalkyl; benzyl; (phenyl)ethyl; and phenyl, the benzyl,

(phenyl)ethyl, or phenyl substituent being optionally substituted on the benzene ring by a moiety selected from methyl, methoxy, and halogen; and -C(R_S)(R_T)(X) wherein R_S and R_T 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 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

R_6 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

wherein

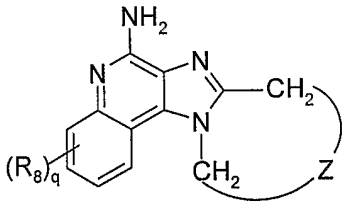
R_{17} is selected from hydrogen; -CH_2R_W wherein R_W is selected from straight chain, branched chain, or cyclic alkyl containing one to ten carbon atoms, straight chain or branched chain alkenyl containing two to ten carbon atoms, straight chain or branched chain hydroxyalkyl containing one to six carbon atoms, alkoxyalkyl wherein 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 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 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 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

wherein

Z is selected from

$-(CH_2)_p-$ wherein p is 1 to 4;

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

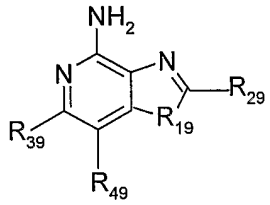
$-(CH_2)_a-(Y)-(CH_2)_b-$ wherein a and b are integers and a+b is 0 to 3, and Y is O, S, or $-NR_J-$ wherein R_J is hydrogen or alkyl of one to four carbon atoms;

q is 0 or 1; and

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:



IX

wherein:

R_{19} is selected from oxygen, sulfur and selenium;

R_{29} is selected from

-hydrogen;

-alkyl;

-alkyl-OH;

-haloalkyl;

-alkenyl;

-alkyl-X-alkyl;

-alkyl-X-alkenyl;

-alkenyl-X-alkyl;

-alkenyl-X-alkenyl;

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

-alkyl-N_3;

-alkyl-O-C(O)-$N(R_{59})_2$;

-heterocyclyl;

-alkyl-X-heterocyclyl;

-alkenyl-X-heterocyclyl;

-aryl;

-alkyl-X-aryl;

-alkenyl-X-aryl;

-heteroaryl;

-alkyl-X-heteroaryl; and

-alkenyl-X-heteroaryl;

R_{39} and R_{49} are each independently:

-hydrogen;

-X-alkyl;

-halo;

-haloalkyl;

$-N(R_{59})_2$;

or when taken together, R_{39} and R_{49} form a fused

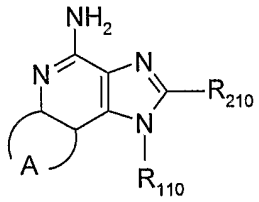
aromatic, heteroaromatic, cycloalkyl or heterocyclic ring;

X is selected from–O–, –S–, $–NR_{59}–$, –C(O)–, –C(O)O–, –OC(O)–, and a bond; and

each R_{59} is independently H or $C_{1\text{-}8}$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:



X

wherein

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

R_{110} is selected from:

- hydrogen;

$-C_{1\text{-}20}$ alkyl or $C_{2\text{-}20}$ alkenyl that is unsubstituted or substituted by one or more substituents selected from:

-aryl;
-heteroaryl;
-heterocyclyl;
-O-C_{1-20} alkyl;
-O-(C_{1-20} alkyl)$_{0-1}$-aryl;
-O-(C_{1-20} alkyl)$_{0-1}$-heteroaryl;
-O-(C_{1-20} alkyl)$_{0-1}$-heterocyclyl;
-CO-O-C_{1-20} alkyl;
-S(O)$_{0-2}$-C_{1-20} alkyl;
-S(O)$_{0-2}$–(C_{1-20} alkyl)$_{0-1}$-aryl;
-S(O)$_{0-2}$–(C_{1-20} alkyl)$_{0-1}$-heteroaryl;
-S(O)$_{0-2}$–(C_{1-20} alkyl)$_{0-1}$-heterocyclyl;
-N(R_{310})$_2$;
-N_3;
oxo;
-halogen;
-NO_2;
-OH; and
-SH; and

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

-aryl;
-heteroaryl;
-heterocyclyl;
-O-C_{1-20} alkyl;
-O-(C_{1-20} alkyl)$_{0-1}$-aryl;
-O-(C_{1-20} alkyl)$_{0-1}$-heteroaryl;
-O-(C_{1-20} alkyl)$_{0-1}$-heterocyclyl;
-CO-O-C_{1-20} alkyl;
-S(O)$_{0-2}$-C_{1-20} alkyl;

-$S(O)_{0-2}$–(C_{1-20} alkyl)$_{0-1}$-aryl;

-$S(O)_{0-2}$–(C_{1-20} alkyl)$_{0-1}$-heteroaryl;

-$S(O)_{0-2}$–(C_{1-20} alkyl)$_{0-1}$-heterocyclyl;

-$N(R_{310})_2$;

-NR_{310}-CO-O-C_{1-20} alkyl;

-N_3;

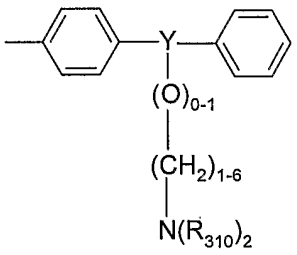
oxo;

-halogen;

-NO_2;

-OH; and

-SH; or R_{410} is



wherein Y is –N- or –CR-;

R_{210} is selected from:

-hydrogen;

-C_{1-10} alkyl;

-C_{2-10} alkenyl;

-aryl;

-C_{1-10} alkyl-O-C_{1-10} alkyl;

-C_{1-10} alkyl-O-C_{2-10} alkenyl; and

-C_{1-10} alkyl or C_{2-10} alkenyl substituted by one or more substituents selected from:

-OH;

-halogen;

-$N(R_{310})_2$;

-CO-$N(R_{310})_2$;

-CO-C_{1-10} alkyl;

-N_3;

-aryl;

-heteroaryl;

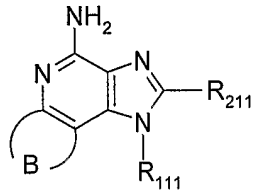
-heterocyclyl;

-CO-aryl; and

-CO-heteroaryl;

each R_{310} is independently selected from hydrogen and C_{1-10} alkyl; and

each R is independently selected from hydrogen, C_{1-10} alkyl, C_{1-10} alkoxy, halogen and trifluoromethyl;



XI

wherein

B is -NR-$C(R)_2$-$C(R)_2$-$C(R)_2$-; -$C(R)_2$-NR-$C(R)_2$-$C(R)_2$-; -$C(R)_2$-$C(R)_2$-NR-$C(R)_2$- or -$C(R)_2$-$C(R)_2$-$C(R)_2$-NR-;

R_{111} is selected from:

- hydrogen;

-C_{1-20} alkyl or C_{2-20} alkenyl that is unsubstituted or substituted by one or more substituents selected from:

-aryl;

-heteroaryl;

-heterocyclyl;

-O-C_{1-20} alkyl;

-O-(C_{1-20} alkyl)$_{0-1}$-aryl;

-O-(C_{1-20} alkyl)$_{0-1}$-heteroaryl;

-O-(C_{1-20} alkyl)$_{0-1}$-heterocyclyl;

-CO-O-C_{1-20} alkyl;

-S(O)$_{0-2}$-C_{1-20} alkyl;

-S(O)$_{0-2}$–(C_{1-20} alkyl)$_{0-1}$-aryl;

-S(O)$_{0-2}$–(C_{1-20} alkyl)$_{0-1}$-heteroaryl;

-S(O)$_{0-2}$–(C_{1-20} alkyl)$_{0-1}$-heterocyclyl;

-$N(R_{311})_2$;

-N_3;

oxo;

-halogen;

-NO_2;

-OH; and

-SH; and

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

-aryl;

-heteroaryl;

-heterocyclyl;

-O-C_{1-20} alkyl;

-O-(C_{1-20} alkyl)$_{0-1}$-aryl;

-O-(C_{1-20} alkyl)$_{0-1}$-heteroaryl;

-O-(C_{1-20} alkyl)$_{0-1}$-heterocyclyl;

-CO-O-C_{1-20} alkyl;

-S(O)$_{0-2}$ -C_{1-20} alkyl;

-S(O)$_{0-2}$ –(C_{1-20} alkyl)$_{0-1}$-aryl;

-S(O)$_{0-2}$ –(C_{1-20} alkyl)$_{0-1}$-heteroaryl;

-S(O)$_{0-2}$ –(C_{1-20} alkyl)$_{0-1}$-heterocyclyl;

-$N(R_{311})_2$;

-NR_{311}-CO-O-C_{1-20} alkyl;

-N_3;

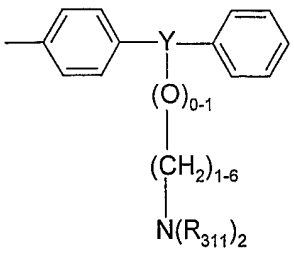
oxo;

-halogen;

-NO_2;

-OH; and

-SH; or R_{411} is



wherein Y is –N- or –CR-;

R_{211} is selected from:

-hydrogen;

-C_{1-10} alkyl;

-C_{2-10} alkenyl;

-aryl;

-C_{1-10} alkyl -O-C_{1-10}-alkyl;

-C_{1-10} alkyl-O-C_{2-10} alkenyl; and

-C_{1-10} alkyl or C_{2-10} alkenyl substituted by one or more substituents selected from:

-OH;

-halogen;

-$N(R_{311})_2$;

-CO-$N(R_{311})_2$;

-CO-C_{1-10} alkyl;

-N_3;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

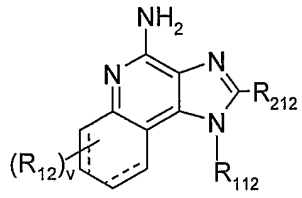
-CO-heteroaryl;

each R_{311} is independently selected from hydrogen and C_{1-10} alkyl; and

each R is independently selected from hydrogen, 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 XII, XIII and XIV below:



XII

wherein

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

-alkyl;
-alkenyl;
-alkynyl;
-$(alkyl)_{0-1}$-aryl;
-$(alkyl)_{0-1}$-(substituted aryl);
-$(alkyl)_{0-1}$-heteroaryl;
-$(alkyl)_{0-1}$-(substituted heteroaryl);
-O-alkyl;
-O-$(alkyl)_{0-1}$-aryl;
-O-$(alkyl)_{0-1}$-(substituted aryl);
-O-$(alkyl)_{0-1}$-heteroaryl;
-O-$(alkyl)_{0-1}$-(substituted heteroaryl);
-CO-aryl;
-CO-(substituted aryl);
-CO-heteroaryl;
-CO-(substituted heteroaryl);
-COOH;
-CO-O-alkyl;
-CO-alkyl;

-$S(O)_{0-2}$ -alkyl;

-$S(O)_{0-2}$ –$(alkyl)_{0-1}$-aryl;

-$S(O)_{0-2}$ –$(alkyl)_{0-1}$-(substituted aryl);

-$S(O)_{0-2}$ –$(alkyl)_{0-1}$-heteroaryl;

-$S(O)_{0-2}$ –$(alkyl)_{0-1}$-(substituted heteroaryl);

-$P(O)(OR_{312})_2$;

-NR_{312}-CO-O-alkyl;

-N_3;

-halogen;

-NO_2;

-CN;

-haloalkyl;

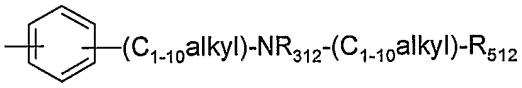
-O-haloalkyl;

-CO-haloalkyl;

-OH;

-SH; and in the case that R_{412} is alkyl, alkenyl, or heterocyclyl, oxo;

or R_{412} is



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

R_{212} is selected from:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-(substituted aryl);

-heteroaryl;

-(substituted heteroaryl);

-heterocyclyl;

-(substituted heterocyclyl);

-alkyl-O-alkyl;

-alkyl-O-alkenyl; and

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

-OH;

-halogen;

-$N(R_{312})_2$;

-$CO\text{-}N(R_{312})_2$;

-$CO\text{-}C_{1\text{-}10}$ alkyl;

-$CO\text{-}O\text{-}C_{1\text{-}10}$ alkyl;

-N_3;

-aryl;

-(substituted aryl);

-heteroaryl;

-(substituted heteroaryl);

-heterocyclyl;

-(substituted heterocyclyl);

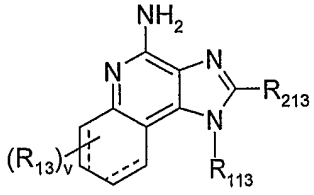
-CO-aryl; and

-CO-heteroaryl;

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

v is 0 to 4;

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



XIII

wherein

R_{113} is -alkyl-NR_{313}- SO_2 -X-R_{413} or -alkenyl-NR_{313}- SO_2 –X-R_{413} ;

X is a bond or –NR_{513}-;

R_{413} 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;

-substituted cycloalkyl;

-substituted aryl;

-substituted heteroaryl;

-substituted heterocyclyl;

-O-alkyl;

-O-$(alkyl)_{0-1}$-aryl;

-O-$(alkyl)_{0-1}$-substituted aryl;

-O-$(alkyl)_{0-1}$-heteroaryl;

-O-$(alkyl)_{0-1}$-substituted heteroaryl;

-O-$(alkyl)_{0-1}$-heterocyclyl;

-O-$(alkyl)_{0-1}$-substituted heterocyclyl;

-COOH;

-CO-O-alkyl;

-CO-alkyl;

-$S(O)_{0-2}$ -alkyl;

-$S(O)_{0-2}$ –$(alkyl)_{0-1}$-aryl;

-$S(O)_{0-2}$ –$(alkyl)_{0-1}$-substituted aryl;

-$S(O)_{0-2}$ –$(alkyl)_{0-1}$-heteroaryl;

-$S(O)_{0-2}$ –$(alkyl)_{0-1}$-substituted heteroaryl;

-$S(O)_{0-2}$ –$(alkyl)_{0-1}$-heterocyclyl;

-$S(O)_{0-2}$ –$(alkyl)_{0-1}$-substituted heterocyclyl;

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

-$(alkyl)_{0-1}$-NR_{313}-CO-O-alkyl;

-(alkyl)$_{0-1}$-NR$_{313}$-CO-alkyl;

-(alkyl)$_{0-1}$-NR$_{313}$-CO-aryl;

-(alkyl)$_{0-1}$-NR$_{313}$-CO-substituted aryl;

-(alkyl)$_{0-1}$-NR$_{313}$-CO-heteroaryl;

-(alkyl)$_{0-1}$-NR$_{313}$-CO-substituted heteroaryl;

-N_3;

-halogen;

-haloalkyl;

-haloalkoxy;

-CO-haloalkyl;

-CO-haloalkoxy;

-NO_2;

-CN;

-OH;

-SH; and in the case that R_{413} is alkyl, alkenyl, or heterocyclyl, oxo;

R_{213} is selected from:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

- alkyl-O-alkyl;

- alkyl-O- alkenyl; and

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

-OH;

-halogen;

-N(R_{313})$_2$;

-CO-N(R_{313})$_2$;

-CO-C_{1-10} alkyl;

-CO-O-C_{1-10} alkyl;

-N_3;

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

-heterocyclyl;

-substituted heterocyclyl;

-CO-aryl;

-CO-(substituted aryl);

-CO-heteroaryl; and

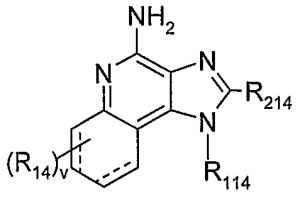
-CO-(substituted heteroaryl);

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;

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



XIV

wherein

R_{114} is -alkyl-NR_{314}-CY-NR_{514}-X-R_{414} or

-alkenyl-NR_{314}-CY- NR_{514}-X- R_{414}

wherein

Y is =O or =S;

X is a bond, -CO- or –SO_2-;

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;
-substituted aryl;
-substituted heteroaryl;
-substituted heterocyclyl;
-O-alkyl;
-O-$(alkyl)_{0-1}$-aryl;
-O-$(alkyl)_{0-1}$-substituted aryl;
-O-$(alkyl)_{0-1}$-heteroaryl;
-O-$(alkyl)_{0-1}$-substituted heteroaryl;
-O-$(alkyl)_{0-1}$-heterocyclyl;
-O-$(alkyl)_{0-1}$-substituted heterocyclyl;
-COOH;
-CO-O-alkyl;
-CO-alkyl;
-$S(O)_{0-2}$-alkyl;
-$S(O)_{0-2}$–$(alkyl)_{0-1}$-aryl;
-$S(O)_{0-2}$–$(alkyl)_{0-1}$-substituted aryl;
-$S(O)_{0-2}$–$(alkyl)_{0-1}$-heteroaryl;
-$S(O)_{0-2}$–$(alkyl)_{0-1}$-substituted heteroaryl;
-$S(O)_{0-2}$–$(alkyl)_{0-1}$-heterocyclyl;
-$S(O)_{0-2}$–$(alkyl)_{0-1}$-substituted heterocyclyl;
-$(alkyl)_{0-1}$-$NR_{314}R_{314}$;
-$(alkyl)_{0-1}$-NR_{314}-CO-O-alkyl;
-$(alkyl)_{0-1}$-NR_{314}-CO-alkyl;
-$(alkyl)_{0-1}$-NR_{314}-CO-aryl;
-$(alkyl)_{0-1}$-NR_{314}-CO-substituted aryl;

-(alkyl)$_{0-1}$-NR$_{314}$-CO-heteroaryl;

-(alkyl)$_{0-1}$-NR$_{314}$-CO-substituted heteroaryl;

-N_3;

-halogen;

-haloalkyl;

-haloalkoxy;

-CO-haloalkoxy;

-NO_2;

-CN;

-OH;

-SH; and, in the case that R_{414} is alkyl, alkenyl or heterocyclyl, oxo;

with the proviso that when X is a bond R_{414} can additionally be hydrogen;

R_{214} is selected from:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

- alkyl-O-alkyl;

-alkyl-O- alkenyl; and

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

-OH;

-halogen;

-N(R_{314})$_2$;

-CO-N(R_{314})$_2$;

-CO-C_{1-10} alkyl;

-CO-O-C_{1-10} alkyl;

-N_3;

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

-heterocyclyl;

-substituted heterocyclyl;

-CO-aryl;

-CO-(substituted aryl);

-CO-heteroaryl; and

-CO-(substituted heteroaryl);

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

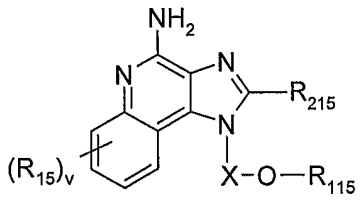
R_{514} is selected from hydrogen and C_{1-10} alkyl, or R_{414} and R_{514} can combine to form a 3 to 7 membered heterocyclic or substituted heterocyclic ring;

v is 0 to 4;

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:



XV

wherein: X is $-CHR_{515}-$, $-CHR_{515}$-alkyl-, or $-CHR_{515}$-alkenyl-;

R_{115} is selected from:

$-R_{415}-CR_{315}-Z-R_{615}$—alkyl;

-R_{415}–CR_{315}–Z–R_{615}—alkenyl;

-R_{415}–CR_{315}–Z–R_{615}—aryl;

-R_{415}–CR_{315}–Z–R_{615}—heteroaryl;

-R_{415}–CR_{315}–Z–R_{615}—heterocyclyl;

-R_{415}–CR_{315}–Z–H;

-R_{415}–NR_{715} –CR_{315}–R_{615}—alkyl;

-R_{415}–NR_{715} –CR_{315}–R_{615}—alkenyl;

-R_{415}–NR_{715}–CR_{315}–R_{615}–aryl;

-R_{415}–NR_{715}–CR_{315}–R_{615}–heteroaryl;

-R_{415}–NR_{715}–CR_{315}–R_{615}–heterocyclyl; and

-R_{415}–NR_{715} –CR_{315}–R_{815};

Z is –NR_{515}–, –O–, or –S–;

R_{215} is selected from:

-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;

-$N(R_{515})_2$;

-CO-$N(R_{515})_2$;

-CO-$C_{1\text{-}10}$ alkyl;

-CO-O-$C_{1\text{-}10}$ alkyl;

-N_3;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

-CO-heteroaryl;

R_{315} is =O or =S;

R_{415} is alkyl or alkenyl, which may be interrupted by one or more –O– groups;

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

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

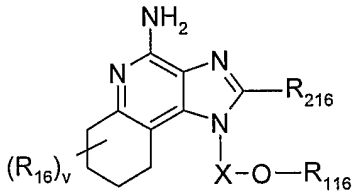
R_{715} is H, C_{1-10} alkyl, or arylalkyl; or R_{415} and R_{715} can join together to form a ring;

R_{815} is H or C_{1-10} alkyl; or R_{715} and R_{815} can join together to form a ring;

Y is –O– or $–S(O)_{0-2}$-;

v is 0 to 4; and

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



XVI

wherein: X is $–CHR_{516}$-, $-CHR_{516}$-alkyl-, or $–CHR_{516}$-alkenyl-;

R_{116} is selected from:

$-R_{416}–CR_{316}–Z–R_{616}$—alkyl;

$-R_{416}–CR_{316}–Z–R_{616}$—alkenyl;

$-R_{416}–CR_{316}–Z–R_{616}$—aryl;

$-R_{416}–CR_{316}–Z–R_{616}$—heteroaryl;

$-R_{416}–CR_{316}–Z–R_{616}$—heterocyclyl;

$-R_{416}–CR_{316}–Z–H$;

-R_{416}–NR_{716} –CR_{316}–R_{616}—alkyl;

-R_{416}–NR_{716} –CR_{316}–R_{616}—alkenyl;

-R_{416}–NR_{716}–CR_{316}–R_{616}–aryl;

-R_{416}–NR_{716}–CR_{316}–R_{616}–heteroaryl;

-R_{416}–NR_{716}–CR_{316}–R_{616}–heterocyclyl; and

-R_{416}–NR_{716} –CR_{316}–R_{816};

Z is –NR_{516}–, –O–, or –S–;

R_{216} is selected from:

-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;

-$N(R_{516})_2$;

-CO-$N(R_{516})_2$;

-CO-$C_{1\text{-}10}$ alkyl;

-CO-O-$C_{1\text{-}10}$ alkyl;

-N_3;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

-CO-heteroaryl;

R_{316} is =O or =S;

R_{416} is alkyl or alkenyl, which may be interrupted by one or more –O– groups;

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

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

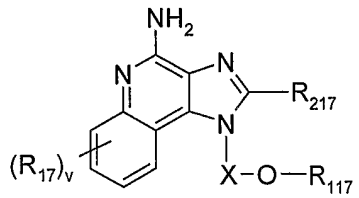
R_{716} is H, C_{1-10} alkyl, arylalkyl; or R_{416} and R_{716} can join together to form a ring;

R_{816} is H or C_{1-10} alkyl; or R_{716} and R_{816} can join together to form a ring;

Y is –O– or $–S(O)_{0-2}$-;

v is 0 to 4; and

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



XVII

wherein: X is $–CHR_{317}$-, $-CHR_{317}$-alkyl-, or $–CHR_{317}$-alkenyl-;

R_{117} is selected from:

-alkenyl;

-aryl; and

$-R_{417}$–aryl;

R_{217} is selected from:

-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;

-$N(R_{317})_2$;

-$CO\text{-}N(R_{317})_2$;

-$CO\text{-}C_{1\text{-}10}$ alkyl;

-$CO\text{-}O\text{-}C_{1\text{-}10}$ alkyl;

-N_3;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

-CO-heteroaryl;

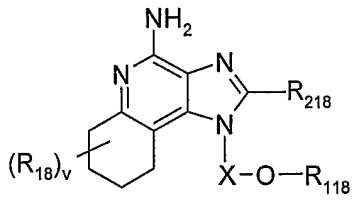
R_{417} is alkyl or alkenyl, which may be interrupted by one or more –O– groups;

each R_{317} is independently H or $C_{1\text{-}10}$ alkyl;

each Y is independently –O– or $–S(O)_{0\text{-}2}$-;

v is 0 to 4; and

each R_{17} present is independently selected from $C_{1\text{-}10}$ alkyl, $C_{1\text{-}10}$ alkoxy, hydroxy, halogen, and trifluoromethyl;



XVIII

wherein: X is $–CHR_{318}$-, $-CHR_{318}$-alkyl-, or $–CHR_{318}$-alkenyl-;

R_{118} is selected from:

-aryl;

-alkenyl; and

-R_{418}–aryl;

R_{218} 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:

-OH;

-halogen;

-$N(R_{318})_2$;

-CO-$N(R_{318})_2$;

-CO-C_{1-10} alkyl;

-CO-O-C_{1-10} alkyl;

-N_3;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

-CO-heteroaryl;

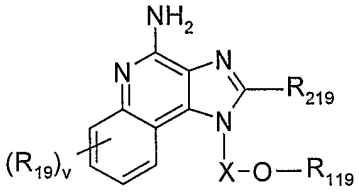
R_{418} is alkyl or alkenyl, which may be interrupted by one or more –O– groups;

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

each Y is independently –O– or –$S(O)_{0-2}$-;

v is 0 to 4; and

each R_{18} present is independently selected C_{1-10} alkyl, C_{1-10} alkoxy, hydroxy, halogen, and trifluoromethyl;



XIX

wherein: X is $-CHR_{319}$-, $-CHR_{319}$-alkyl-, or $-CHR_{319}$-alkenyl-;

R_{119} is selected from:

-heteroaryl;

-heterocyclyl;

$-R_{419}-$ heteroaryl; and

$-R_{419}-$heterocyclyl;

R_{219} is selected from:

-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;

$-N(R_{319})_2$;

$-CO-N(R_{319})_2$;

$-CO-C_{1-10}$ alkyl;

-CO-O-C_{1-10} alkyl;

$-N_3$;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

-CO-heteroaryl;

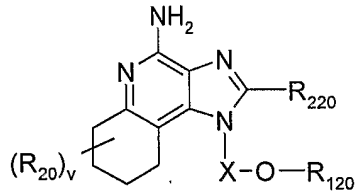
R_{419} is alkyl or alkenyl, which may be interrupted by one or more –O– groups;

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

each Y is independently –O– or $-S(O)_{0-2}-$;

v is 0 to 4; and

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



XX

wherein: X is $-CHR_{320}-$, $-CHR_{320}$-alkyl-, or $-CHR_{320}$-alkenyl-;

R_{120} is selected from:

-heteroaryl;

-heterocyclyl;

$-R_{420}-$ heteroaryl; and

$-R_{420}-$heterocyclyl;

R_{220} is selected from:

-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;

-$N(R_{320})_2$;

-$CO\text{-}N(R_{320})_2$;

-$CO\text{-}C_{1\text{-}10}$ alkyl;

-$CO\text{-}O\text{-}C_{1\text{-}10}$ alkyl;

-N_3;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

-CO-heteroaryl;

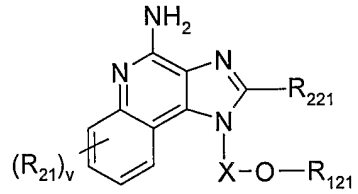
R_{420} is alkyl or alkenyl, which may be interrupted by one or more –O– groups;

each R_{320} is independently H or $C_{1\text{-}10}$ alkyl;

each Y is independently –O– or $–S(O)_{0\text{-}2}$-;

v is 0 to 4; and

each R_{20} present is independently selected from $C_{1\text{-}10}$ alkyl, $C_{1\text{-}10}$ alkoxy, hydroxy, halogen, and trifluoromethyl;



XXI

wherein: X is $-CHR_{521}$-, $-CHR_{521}$-alkyl-, or $-CHR_{521}$-alkenyl-;

R_{121} is selected from:

$-R_{421}—NR_{321}—SO_2—R_{621}$—alkyl;

$-R_{421}—NR_{321}—SO_2—R_{621}$—alkenyl;

$-R_{421}–NR_{321}–SO_2–R_{621}$–aryl;

$-R_{421}–NR_{321}–SO_2–R_{621}$–heteroaryl;

$-R_{421}–NR_{321}–SO_2–R_{621}$–heterocyclyl;

$-R_{421}—NR_{321}—SO_2—R_{721}$;

$-R_{421}$-NR_{321}-SO_2-NR_{521}-R_{621}-alkyl;

$-R_{421}$-NR_{321}-SO_2-NR_{521}-R_{621}-alkenyl;

$-R_{421}$-NR_{321}-SO_2-NR_{521}-R_{621}-aryl;

$-R_{421}$-NR_{321}-SO_2-NR_{521}-R_{621}-heteroaryl;

$-R_{421}$-NR_{321}-SO_2-NR_{521}-R_{621}-heterocyclyl; and

$-R_{421}$-NR_{321}-SO_2-NH_2;

R_{221} is selected from:

-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;

-$N(R_{521})_2$;

-$CO\text{-}N(R_{521})_2$;

-$CO\text{-}C_{1\text{-}10}$ alkyl;

-$CO\text{-}O\text{-}C_{1\text{-}10}$ alkyl;

-N_3;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

-CO-heteroaryl;

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

R_{321} is H, $C_{1\text{-}10}$ 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;

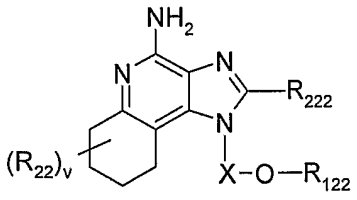
each R_{521} is independently H, $C_{1\text{-}10}$ alkyl, or $C_{2\text{-}10}$ alkenyl;

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

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

v is 0 to 4; and

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



XXII

wherein: X is –CHR_{522}-, -CHR_{522}-alkyl-, or –CHR_{522}-alkenyl-;

R_{122} is selected from:

-R_{422}—NR_{322}—SO_2—R_{622}—alkyl;

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

-R_{422}–NR_{322}–SO_2–R_{622}–aryl;

-R_{422}–NR_{322}–SO_2–R_{622}–heteroaryl;

-R_{422}–NR_{322}–SO_2–R_{622}–heterocyclyl;

-R_{422}—NR_{322}—SO_2—R_{722};

-R_{422}-NR_{322}-SO_2-NR_{522}-R_{622}-alkyl;

-R_{422}-NR_{322}-SO_2-NR_{522}-R_{622}-alkenyl;

-R_{422}-NR_{322}-SO_2-NR_{522}-R_{622}-aryl;

-R_{422}-NR_{322}-SO_2-NR_{522}-R_{622}-heteroaryl;

-R_{422}-NR_{322}-SO_2-NR_{522}-R_{622}-heterocyclyl; and

-R_{422}-NR_{322}-SO_2-NH_2;

R_{222} is selected from:

-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;

-$N(R_{522})_2$;

-CO-$N(R_{522})_2$;

-CO-$C_{1\text{-}10}$ alkyl;

-CO-O-$C_{1\text{-}10}$ alkyl;

-N_3;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

-CO-heteroaryl;

Y is -O- or -$S(O)_{0-2}$-;

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

each R_{422} is independently alkyl or alkenyl, which may be interrupted by one or more –O– groups; or R_{322} and R_{422} can join together to form a ring;

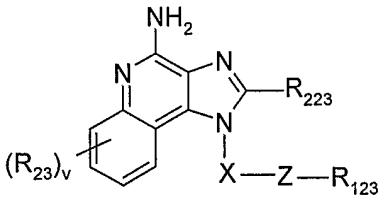
each R_{522} is independently H, C_{1-10} alkyl, or C_{2-10} alkenyl;

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;

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;



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:

-alkyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-alkenyl;

-R_{423}–aryl;

-R_{423}– heteroaryl; and

-R_{423}–heterocyclyl;

R_{223} is selected from:

-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;

-$N(R_{323})_2$;

-CO-$N(R_{323})_2$;

-CO-C_{1-10} alkyl;

-CO-O-C_{1-10} alkyl;

-N_3;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

-CO-heteroaryl;

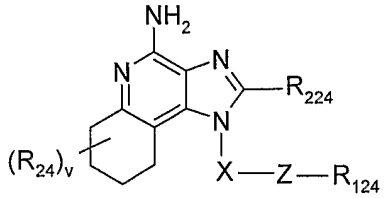
each R_{323} is independently H or C_{1-10} alkyl;

each R_{423} is independently alkyl or alkenyl;

each Y is independently –O– or –$S(O)_{0-2}$-;

v is 0 to 4; and

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



XXIV

wherein: X is $-CHR_{324}-$, $-CHR_{324}$-alkyl-, or $-CHR_{324}$-alkenyl-;

Z is –S-, -SO-, or $-SO_2-$;

R_{124} is selected from:

-alkyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-alkenyl;

$-R_{424}$–aryl;

$-R_{424}$– heteroaryl; and

$-R_{424}$–heterocyclyl;

R_{224} is selected from:

-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;

$-N(R_{324})_2$;

-CO-N(R_{324})$_2$;

-CO-C_{1-10} alkyl;

-CO-O-C_{1-10} alkyl;

-N_3;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

-CO-heteroaryl;

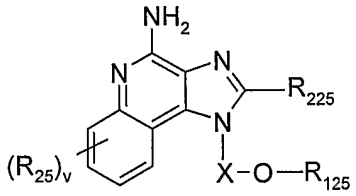
each R_{324} is independently H or C_{1-10} alkyl;

each R_{424} is independently alkyl or alkenyl;

each Y is independently –O– or –S(O)$_{0-2}$-;

v is 0 to 4; and

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



XXV

wherein: X is –CHR$_{525}$-, -CHR$_{525}$-alkyl-, or –CHR$_{525}$-alkenyl-;

R_{125} is selected from:

-R_{425}–NR_{825}–CR_{325}—NR_{525}–Z–R_{625}–alkyl;

-R_{425}–NR_{825}–CR_{325}—NR_{525}–Z–R_{625}–alkenyl;

-R_{425}–NR_{825}–CR_{325}—NR_{525}–Z–R_{625}–aryl;

-R_{425}–NR_{825}–CR_{325}—NR_{525}–Z-R_{625}–heteroaryl;

-R_{425}–NR_{825}–CR_{325}—NR_{525}–Z–R_{625}–heterocyclyl;

-R_{425}-NR_{825}—CR_{325}—$NR_{525}R_{725}$;

-R_{425}–NR_{825}–CR_{325}—NR_{925}–Z—R_{625}–alkyl;

-R_{425}–NR_{825}–CR_{325}—NR_{925}–Z—R_{625}–alkenyl;

-R_{425}–NR_{825}–CR_{325}—NR_{925}–Z—R_{625}–aryl;

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

-R_{425}–NR_{825}–CR_{325}—NR_{925}–Z—R_{625}–heterocyclyl;

R_{225} is selected from:

-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;

-$N(R_{525})_2$;

-CO-$N(R_{525})_2$;

-CO-$C_{1\text{-}10}$ alkyl;

-CO-O-$C_{1\text{-}10}$ alkyl;

-N_3;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

-CO-heteroaryl;

each R_{325} is =O or =S;

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

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

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

R_{725} is H or C_{1-10} alkyl which may be interrupted by a hetero atom, or R_{725} can join with R_{525} to form a ring;

R_{825} is H, C_{1-10} alkyl, or arylalkyl; or R_{425} and R_{825} can join together to form a ring;

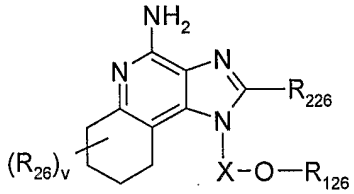
R_{925} is C_{1-10} alkyl which can join together with R_{825} to form a ring;

each Y is independently –O– or $-S(O)_{0-2}-$;

Z is a bond, –CO–, or $-SO_2-$;

v is 0 to 4; and

each R_{25} present is independently selected C_{1-10} alkyl, C_{1-10} alkoxy, hydroxy, halogen, and trifluoromethyl;



XXVI

wherein: X is $-CHR_{526}-$, $-CHR_{526}$-alkyl-, or $-CHR_{526}$-alkenyl-;

R_{126} is selected from:

$-R_{426}-NR_{826}-CR_{326}=NR_{526}-Z-R_{626}$-alkyl;

$-R_{426}-NR_{826}-CR_{326}=NR_{526}-Z-R_{626}$-alkenyl;

$-R_{426}-NR_{826}-CR_{326}=NR_{526}-Z-R_{626}$-aryl;

$-R_{426}-NR_{826}-CR_{326}=NR_{526}-Z-R_{626}$-heteroaryl;

$-R_{426}-NR_{826}-CR_{326}=NR_{526}-Z-R_{626}$-heterocyclyl;

$-R_{426}-NR_{826}-CR_{326}=NR_{526}R_{726}$;

$-R_{426}-NR_{826}-CR_{326}=NR_{926}-Z=R_{626}$-alkyl;

$-R_{426}-NR_{826}-CR_{326}=NR_{926}-Z=R_{626}$-alkenyl;

$-R_{426}-NR_{826}-CR_{326}=NR_{926}-Z=R_{626}$-aryl;

$-R_{426}-NR_{826}-CR_{326}=NR_{926}-Z=R_{626}$-heteroaryl; and

$-R_{426}-NR_{826}-CR_{326}=NR_{926}-Z=R_{626}$-heterocyclyl;

R_{226} is selected from:

-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;

$-N(R_{526})_2$;

$-CO-N(R_{526})_2$;

$-CO-C_{1-10}$ alkyl;

$-CO-O-C_{1-10}$ alkyl;

$-N_3$;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

-CO-heteroaryl;

each R_{326} is =O or =S;

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

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

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

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

R_{826} is H, C_{1-10} alkyl, or arylalkyl; or R_{426} and R_{826} can join together to form a ring;

R_{926} is C_{1-10} alkyl which can join together with R_{826} to form a ring;

each Y is independently –O– or $–S(O)_{0-2}–$;

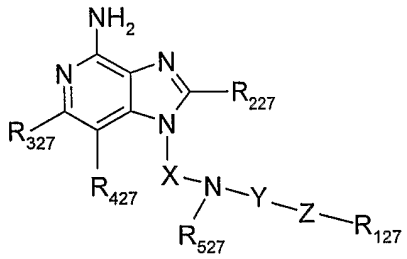
Z is a bond, –CO–, or $–SO_2–$;

v is 0 to 4; and

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

and pharmaceutically acceptable salts of any of the foregoing.

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



XXVII

wherein X is alkylene or alkenylene;

Y is –CO– or –CS;

Z is a bond, –O–, or –S–;

R_{127} is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from:

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-substituted cycloalkyl;

-substituted aryl;

-substituted heteroaryl;

-substituted heterocyclyl;

-O-alkyl;

-O-(alkyl)$_{0-1}$-aryl;

-O-(alkyl)$_{0-1}$-(substituted aryl);

-O-(alkyl)$_{0-1}$-heteroaryl;

-O-(alkyl)$_{0-1}$-(substituted heteroaryl);

-O-(alkyl)$_{0-1}$-heterocyclyl;

-O-(alkyl)$_{0-1}$-(substituted heterocyclyl);

-COOH;

-CO-O-alkyl;

-CO-alkyl;

-S(O)$_{0-2}$ -alkyl;

-S(O)$_{0-2}$ –(alkyl)$_{0-1}$-aryl;

-S(O)$_{0-2}$ –(alkyl)$_{0-1}$-(substituted aryl);

-S(O)$_{0-2}$ –(alkyl)$_{0-1}$-heteroaryl;

-S(O)$_{0-2}$ –(alkyl)$_{0-1}$-(substituted heteroaryl);

-S(O)$_{0-2}$ –(alkyl)$_{0-1}$-heterocyclyl;

-S(O)$_{0-2}$ –(alkyl)$_{0-1}$-(substituted heterocyclyl);

-(alkyl)$_{0-1}$-N(R_{627})$_2$;

-(alkyl)$_{0-1}$-NR_{627}-CO-O-alkyl;

-(alkyl)$_{0-1}$-NR_{627}-CO-alkyl;

-(alkyl)$_{0-1}$-NR_{627}-CO-aryl;

-(alkyl)$_{0-1}$-NR_{627}-CO-(substituted aryl);

-(alkyl)$_{0-1}$-NR_{627}-CO-heteroaryl;

-(alkyl)$_{0-1}$-NR_{627}-CO-(substituted heteroaryl);

-N_3;

-halogen;

-haloalkyl;

-haloalkoxy;

-CO-haloalkyl;

-CO-haloalkoxy;

-NO_2;

-CN;

-OH;

-SH; and in the case of alkyl, alkenyl, and heterocyclyl, oxo;

R_{227} is selected from:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

-alkyl-O-alkyl;

-alkyl-S-alkyl;

-alkyl-O-aryl;

-alkyl-S-aryl:

-alkyl-O- alkenyl;

-alkyl-S- alkenyl; and

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

-OH;

-halogen;

-$N(R_{627})_2$;

-$CO\text{-}N(R_{627})_2$;

-$CS\text{-}N(R_{627})_2$;

-$SO_2\text{-}N(R_{627})_2$;

-$NR_{627}\text{-}CO\text{-}C_{1\text{-}10}$ alkyl;

-$NR_{627}\text{-}CS\text{-}C_{1\text{-}10}$ alkyl;

-$NR_{627}\text{-}SO_2\text{-}C_{1\text{-}10}$ alkyl;

-$CO\text{-}C_{1\text{-}10}$ alkyl;

-$CO\text{-}O\text{-}C_{1\text{-}10}$ alkyl;

-N_3;

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

-heterocyclyl;

-substituted heterocyclyl;

-CO-aryl;

-CO-(substituted aryl);

-CO-heteroaryl; and

-CO-(substituted heteroaryl);

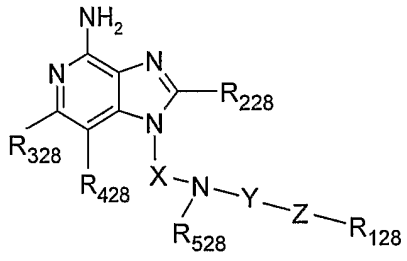
R_{327} and R_{427} are independently selected from hydrogen, alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino, and alkylthio;

R_{527} is H or C_{1-10} alkyl, or R_{527} can join with X to form a ring that contains one or two heteroatoms; or when R_{127} is alkyl, R_{527} and R_{127} can join to form a ring;

each R_{627} is independently H or C_{1-10}alkyl;

and pharmaceutically acceptable salts thereof.

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



XXVIII

wherein X is alkylene or alkenylene;

Y is $-SO_2-$;

Z is a bond or $-NR_{628}-$;

R_{128} is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from:

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-substituted cycloalkyl;

-substituted aryl;

-substituted heteroaryl;

-substituted heterocyclyl;

-O-alkyl;

-O-(alkyl)$_{0-1}$-aryl;

-O-(alkyl)$_{0-1}$-(substituted aryl);

-O-(alkyl)$_{0-1}$-heteroaryl;

-O-(alkyl)$_{0-1}$-(substituted heteroaryl);

-O-(alkyl)$_{0-1}$-heterocyclyl;

-O-(alkyl)$_{0-1}$-(substituted heterocyclyl);

-COOH;

-CO-O-alkyl;

-CO-alkyl;

-S(O)$_{0-2}$ -alkyl;

-S(O)$_{0-2}$ –(alkyl)$_{0-1}$-aryl;

-S(O)$_{0-2}$ –(alkyl)$_{0-1}$-(substituted aryl);

-S(O)$_{0-2}$ –(alkyl)$_{0-1}$-heteroaryl;

-S(O)$_{0-2}$ –(alkyl)$_{0-1}$-(substituted heteroaryl);

-S(O)$_{0-2}$ –(alkyl)$_{0-1}$-heterocyclyl;

-S(O)$_{0-2}$ –(alkyl)$_{0-1}$-(substituted heterocyclyl);

-(alkyl)$_{0-1}$-N(R_{628})$_2$;

-(alkyl)$_{0-1}$-NR_{628}-CO-O-alkyl;

-(alkyl)$_{0-1}$-NR_{628}-CO-alkyl;

-(alkyl)$_{0-1}$-NR_{628}-CO-aryl;

-(alkyl)$_{0-1}$-NR_{628}-CO-(substituted aryl);

-(alkyl)$_{0-1}$-NR_{628}-CO-heteroaryl;

-(alkyl)$_{0-1}$-NR_{628}-CO-(substituted heteroaryl);

-N_3;

-halogen;

-haloalkyl;

-haloalkoxy;

-CO-haloalkyl;

-CO-haloalkoxy;

-NO_2;

-CN;

-OH;

-SH; and in the case of alkyl, alkenyl, and heterocyclyl, oxo;

R_{228} is selected from:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

-alkyl-O-alkyl;

-alkyl-S-alkyl;

-alkyl-O-aryl;

-alkyl-S-aryl:

-alkyl-O- alkenyl;

-alkyl-S- alkenyl; and

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

-OH;

-halogen;

-$N(R_{628})_2$;

-$CO\text{-}N(R_{628})_2$;

-$CS\text{-}N(R_{628})_2$;

-$SO_2\text{-}N(R_{628})_2$;

-NR_{628}-CO-C_{1-10} alkyl;
-NR_{628}-CS-C_{1-10} alkyl;
-NR_{628}-SO_2-C_{1-10} alkyl;
-CO-C_{1-10} alkyl;
-CO-O-C_{1-10} alkyl;
-N_3;
-aryl;
-substituted aryl;
-heteroaryl;
-substituted heteroaryl;
-heterocyclyl;
-substituted heterocyclyl;
-CO-aryl;
-CO-(substituted aryl);
-CO-heteroaryl; and
-CO-(substituted heteroaryl);

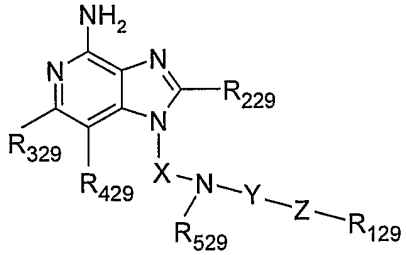
R_{328} and R_{428} are independently selected from hydrogen, alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino, and alkylthio;

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.

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



XXIX

wherein X is alkylene or alkenylene;

Y is –CO– or –CS;

Z is $–NR_{629}$-, $-NR_{629}$-CO-, $-NR_{629}$-SO_2-, or $–NR_{729}$-;

R_{129} is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from:

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-substituted cycloalkyl;

-substituted aryl;

-substituted heteroaryl;

-substituted heterocyclyl;

-O-alkyl;

-O-$(alkyl)_{0-1}$-aryl;

-O-$(alkyl)_{0-1}$-(substituted aryl);

-O-$(alkyl)_{0-1}$-heteroaryl;

-O-$(alkyl)_{0-1}$-(substituted heteroaryl);

-O-$(alkyl)_{0-1}$-heterocyclyl;

-O-$(alkyl)_{0-1}$-(substituted heterocyclyl);

-COOH;

-CO-O-alkyl;

-CO-alkyl;

-$S(O)_{0-2}$-alkyl;

-$S(O)_{0-2}$–$(alkyl)_{0-1}$-aryl;

-$S(O)_{0-2}$–$(alkyl)_{0-1}$-(substituted aryl);

-$S(O)_{0-2}$–$(alkyl)_{0-1}$-heteroaryl;

-$S(O)_{0-2}$–$(alkyl)_{0-1}$-(substituted heteroaryl);

-$S(O)_{0-2}$–$(alkyl)_{0-1}$-heterocyclyl;

-$S(O)_{0-2}$–$(alkyl)_{0-1}$-(substituted heterocyclyl);

-$(alkyl)_{0-1}$-$N(R_{629})_2$;

-(alkyl)$_{0-1}$-NR$_{629}$-CO-O-alkyl;

-(alkyl)$_{0-1}$-NR$_{629}$-CO-alkyl;

-(alkyl)$_{0-1}$-NR$_{629}$-CO-aryl;

-(alkyl)$_{0-1}$-NR$_{629}$-CO-(substituted aryl);

-(alkyl)$_{0-1}$-NR$_{629}$-CO-heteroaryl;

-(alkyl)$_{0-1}$-NR$_{629}$-CO-(substituted heteroaryl);

-P(O)(O-alkyl)$_2$;

-N_3;

-halogen;

-haloalkyl;

-haloalkoxy;

-CO-haloalkyl;

-CO-haloalkoxy;

-NO_2;

-CN;

-OH;

-SH; and in the case of alkyl, alkenyl, and heterocyclyl, oxo;

R_{229} is selected from:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

-alkyl-O-alkyl;

-alkyl-S-alkyl;

-alkyl-O-aryl;

-alkyl-S-aryl:

-alkyl-O- alkenyl;

-alkyl-S- alkenyl; and

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

-OH;

-halogen;

-$N(R_{629})_2$;

-$CO\text{-}N(R_{629})_2$;

-$CS\text{-}N(R_{629})_2$;

-$SO_2\text{-}N(R_{629})_2$;

-$NR_{629}\text{-}CO\text{-}C_{1\text{-}10}$ alkyl;

-$NR_{629}\text{-}CS\text{-}C_{1\text{-}10}$ alkyl;

-$NR_{629}\text{-}SO_2\text{-}C_{1\text{-}10}$ alkyl;

-$CO\text{-}C_{1\text{-}10}$ alkyl;

-$CO\text{-}O\text{-}C_{1\text{-}10}$ alkyl;

-N_3;

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

-heterocyclyl;

-substituted heterocyclyl;

-CO-aryl;

-CO-(substituted aryl);

-CO-heteroaryl; and

-CO-(substituted heteroaryl);

R_{329} and R_{429} are independently selected from hydrogen, alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino, and alkylthio;

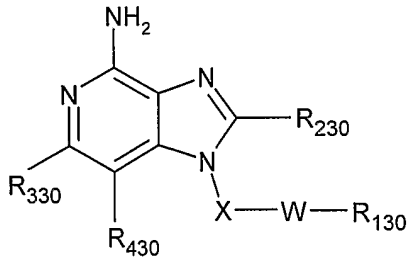
R_{529} is H or $C_{1\text{-}10}$ alkyl, or R_{529} can join with X to form a ring that contains one or two heteroatoms;

each R_{629} is independently H or $C_{1\text{-}10}$alkyl;

R_{729} is H or $C_{1\text{-}10}$ alkyl which may be interrupted by a heteroatom; or when R_{129} is alkyl, R_{729} and R_{129} 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 1H-imidazo[4,5-c]pyridin-4-amines defined by Formula XXX below:



XXX

wherein:

X is -CH(R_{530})-, -CH(R_{530})-alkylene-, -CH(R_{530})-alkenylene-, or CH(R_{530})-alkylene-Y-alkylene-;

Y is –O–, or –S(O)$_{0-2}$–;

-W-R_{130} is selected from -O-$R_{130-1-5}$ and –S(O)$_{0-2}$-R_{130-6};

$R_{130-1-5}$ is selected from

-R_{630}–C(R_{730})–Z–R_{830}—alkyl;

-R_{630}–C(R_{730})–Z–R_{830}—alkenyl;

-R_{630}–C(R_{730})–Z–R_{830}—aryl;

-R_{630}–C(R_{730})–Z–R_{830}—heteroaryl;

-R_{630}–C(R_{730})–Z–R_{830}—heterocyclyl;

-R_{630}–C(R_{730})–Z–H;

-R_{630}–N(R_{930})–C(R_{730})–R_{830}—alkyl;

-R_{630}–N(R_{930})–C(R_{730})–R_{830}—alkenyl;

-R_{630}–N(R_{930})–C(R_{730})–R_{830}–aryl;

-R_{630}–N(R_{930})–C(R_{730})–R_{830}–heteroaryl;

-R_{630}–N(R_{930})–C(R_{730})–R_{830}–heterocyclyl;

-R_{630}–N(R_{930})–C(R_{730})–R_{1030};

-R_{630}—N(R_{930})—SO_2—R_{830}—alkyl;

-R_{630}—N(R_{930})—SO_2—R_{830}—alkenyl;

-R_{630}–N(R_{930})–SO_2–R_{830}–aryl;

-R_{630}–$N(R_{930})$–SO_2–R_{830}–heteroaryl;

-R_{630}–$N(R_{930})$–SO_2–R_{830}–heterocyclyl;

-R_{630}—$N(R_{930})$—SO_2—R_{1030};

-R_{630}-$N(R_{930})$-SO_2-$N(R_{530})$-R_{830}-alkyl;

-R_{630}-$N(R_{930})$-SO_2-$N(R_{530})$-R_{830}-alkenyl;

-R_{630}-$N(R_{930})$-SO_2-$N(R_{530})$-R_{830}-aryl;

-R_{630}-$N(R_{930})$-SO_2-$N(R_{530})$-R_{830}-heteroaryl;

-R_{630}-$N(R_{930})$-SO_2-$N(R_{530})$-R_{830}-heterocyclyl;

-R_{630}-$N(R_{930})$-SO_2-NH_2;

-R_{630}–$N(R_{930})$–$C(R_{730})$—$N(R_{530})$–Q–R_{830}–alkyl;

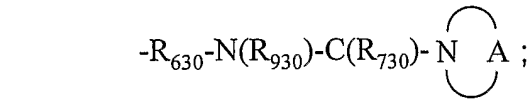
-R_{630}–$N(R_{930})$–$C(R_{730})$—$N(R_{530})$–Q–R_{830}–alkenyl;

-R_{630}–$N(R_{930})$–$C(R_{730})$—$N(R_{530})$–Q–R_{830}–aryl;

-R_{630}–$N(R_{930})$– $C(R_{730})$—$N(R_{530})$–Q-R_{830}–heteroaryl;

-R_{630}–$N(R_{930})$– $C(R_{730})$—$N(R_{530})$–Q–R_{830}–heterocyclyl;

-R_{630}-$N(R_{930})$—$C(R_{730})$—$N(R_{530})_2$;



-R_{630}–$N(R_{930})$–$C(R_{730})$—$N(R_{1130})$–Q—R_{830}–alkyl;

-R_{630}–$N(R_{930})$–$C(R_{730})$—$N(R_{1130})$–Q—R_{830}–alkenyl;

-R_{630}–$N(R_{930})$–$C(R_{730})$—$N(R_{1130})$–Q—R_{830}–aryl;

-R_{630}–$N(R_{930})$– $C(R_{730})$—$N(R_{1130})$–Q—R_{830}–heteroaryl;

-R_{630}–$N(R_{930})$– $C(R_{730})$—$N(R_{1130})$–Q—R_{830}–heterocyclyl;

-R_{630}–$N(R_{930})$– $C(R_{730})$—$N(R_{1130})$H;

-alkenyl;

-aryl;

-R_{630}–aryl;

-heteroaryl;

-heterocyclyl;

-R_{630}– heteroaryl; and

-R_{630}–heterocyclyl;

Z is–$N(R_{530})$–, –O–, or –S–;

Q is a bond, –CO–, or –SO_2–;

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

R_{130-6} is selected from:

-alkyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-alkenyl;

-R_{630}–aryl;

-R_{630}– heteroaryl; and

-R_{630}–heterocyclyl;

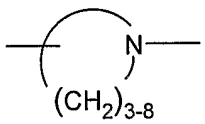
each R_{530} is independently hydrogen, C_{1-10} alkyl, or C_{2-10} alkenyl;

R_{630} is alkylene, alkenylene, or alkynylene, which may be interrupted by one or more -O- groups;

R_{730} is =O or =S;

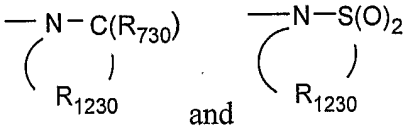
R_{830} is a bond, alkylene, alkenylene, or alkynylene, which may be interrupted by one or more -O- groups;

R_{930} is hydrogen, C_{1-10} alkyl, or arylalkyl; or R_{930} can join together with any carbon atom of R_{630} to form a ring of the formula



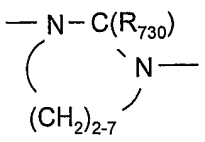
;

R_{1030} is hydrogen or C_{1-10} alkyl; or R_{930} and R_{1030} can join together to form a ring selected from



and ;

R_{1130} is C_{1-10} alkyl; or R_{930} and R_{1130} can join together to form a ring having the structure



;

R_{1230} is C_{2-7} alkylene which is straight chain or branched, wherein the branching does not prevent formation of the ring; and

R_{230}, R_{330} and R_{430} are independently selected from hydrogen and non-interfering substitutents;

and pharmaceutically acceptable salts thereof.

Illustrative non-interfering R_{230} substituents include:

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-alkylene-Y-alkyl;

-alkylene-Y- alkenyl;

-alkylene-Y-aryl; and

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

-OH;

-halogen;

$-N(R_{530})_2$;

$-C(O)-C_{1-10}$ alkyl;

$-C(O)-O-C_{1-10}$ alkyl;

$-N_3$;

-aryl;

-heteroaryl;

-heterocyclyl;

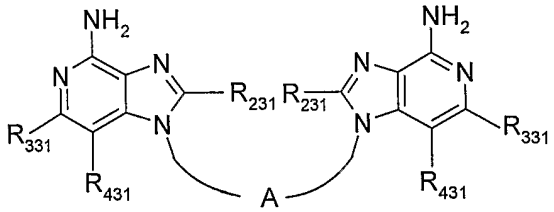
-C(O)-aryl; and

-C(O)-heteroaryl.

Illustrative non-interfering R_{330} and R_{430} substitutents 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):



XXXI

wherein:

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-;

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;

any of which may be optionally interrupted by -O-, -N(R_{531})-, or –S(O)$_2$-;

each Y is independently selected from the group consisting of:

a bond;

-N(R_{531})C(O)-;

-C(O)N(R_{531})-;

-N(R_{531})C(O)N(R_{531})-;

- N(R_{531})S(O)$_2$-;

-S(O)$_2$N(R_{531})-;

-OC(O)O-;

-OC(O)-;

-C(O)O-;

-N(R_{531})C(O)O-; and

-OC(O)N(R_{531})-;

W is selected from the group consisting of:

straight or branched chain C_{2-20} alkylene;

straight or branched chain C_{2-20} alkenylene;

straight or branched chain C_{4-20} alkynylene;

straight or branched chain perfluoro C_{2-20} alkylene;

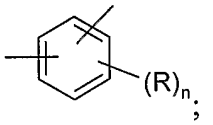
C_{1-4} alkylene-O-C_{1-4} alkylene;

-C(O)-;

$-S(O)_2-$;

-OC(O)O-;

$-N(R_{531})C(O)N(R_{531})-$;



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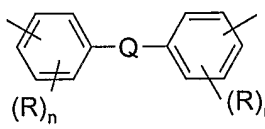

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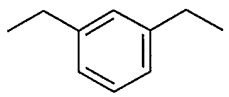

;

1,5-naphthylene;

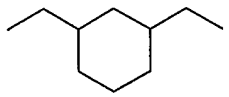
2,6-pyridinylene;

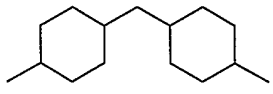
1,2-cyclohexylene;

1,3-cyclohexylene;

1,4-cyclohexylene;

trans-1,4-cyclohexylene;


;


; and

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

wherein n is 0 - 4; each R is independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, and halogen; and Q is selected from the group consisting of a bond, $-CH_2-$, and -O-;

R_{231} is selected from the group consisting of:

-hydrogen;
-alkyl;
-alkenyl;
-aryl;
-substituted aryl;
-heteroaryl;
-substituted heteroaryl;
-alkyl-X-alkyl;
-alkyl-X-aryl;
-alkyl-X- alkenyl; and
-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:
-OH;
-halogen;
-$N(R_{631})_2$;
-$C(O)$-$N(R_{631})_2$;
-$C(S)$-$N(R_{631})_2$;
-$S(O)_2$-$N(R_{631})_2$;
-$N(R_{631})$-$C(O)$-C_{1-10} alkyl;
-$N(R_{631})$-$C(S)$-C_{1-10} alkyl;
-$N(R_{631})$- $S(O)_2$-C_{1-10} alkyl;
-$C(O)$-C_{1-10} alkyl;
-$C(O)$-O-C_{1-10} alkyl;
-N_3;
-aryl;
-substituted aryl;
-heteroaryl;
-substituted heteroaryl;
-heterocyclyl;
-substituted heterocyclyl;
-C(O)-aryl;
-C(O)-(substituted aryl);

-C(O)-heteroaryl; and

-C(O)-(substituted heteroaryl);

R_{331} and R_{431} are each independently selected from the group consisting of:

-hydrogen;

-halogen;

-alkyl;

-alkenyl;

-X-alkyl; and

-$N(R_{631})_2$;

or when taken together, R_{331} and R_{431} form a fused aryl or heteroaryl ring that is unsubstituted or substituted by one or more substituents selected from the group consisting of:

-halogen;

-alkyl;

-alkenyl;

-X-alkyl; and

-$N(R_{631})_2$;

or when taken together, R_{331} and R_{431} 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:

-halogen;

-alkyl;

-alkenyl;

-X-alkyl; and

-$N(R_{631})_2$;

each R_{531} is independently selected from the group consisting of:

hydrogen;

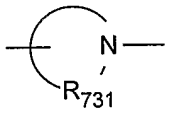
C_{1-6} alkyl;

C_{3-7} cycloalkyl; and

benzyl; or

when Y is –$N(R_{531})C(O)$-, -$C(O)N(R_{531})$-, -$N(R_{531})C(O)N(R_{531})$-,

$-N(R_{531})S(O)_2-$, $-S(O_2)N(R_{531})-$, $-N(R_{531})C(O)O-$, or $-OC(O)N(R_{531})-$ and the nitrogen of the $N(R_{531})$ group is bonded to Z, then R_{531} can join with Z to form a ring having the structure



;

each R_{631} is independently hydrogen or $C_{1\text{-}10}$ alkyl;

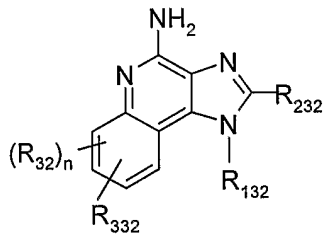
R_{731} is $C_{3\text{-}8}$ alkylene; and

X is -O- or -S-;

with the proviso that if W is $-C(O)-$, $-S(O)_2-$, $-OC(O)O-$, or $-N(R_{531})C(O)N(R_{531})-$ 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 1H-imidazo[4,5-c]quinolin-4-amines of the following Formula (XXXII):



XXXII

wherein:

R_{32} 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 substitutents;

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:

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_{832})$-,

-$C(R_{632})$-,

-$C(R_{632})$-O-,

-O-$C(R_{632})$-,

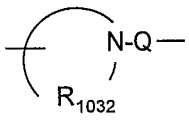
-O-C(O)-O-,

-$N(R_{832})$-Q-,

-$C(R_{632})$-$N(R_{832})$-,

-O-$C(R_{632})$-$N(R_{832})$-,

-$C(R_{632})$-$N(OR_{932})$-,



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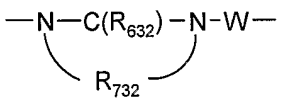
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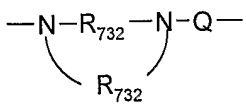
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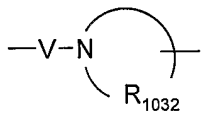
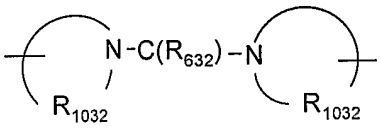
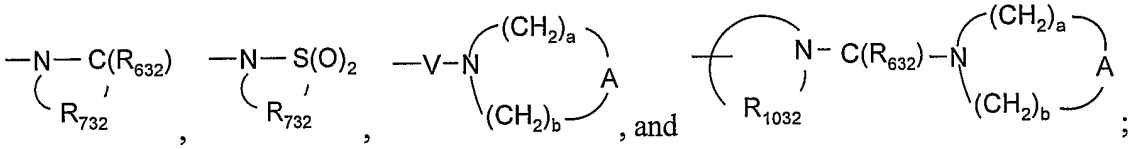

, and


;

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

R_{432} 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_{532} is selected from the group consisting of:


;

each R_{632} is independently selected from the group consisting of =O and =S;

each R_{732} is independently C_{2-7} alkylene;

each R_{832} is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_{932} 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)-, -$S(O)_{0-2}$-, -CH_2-, and -$N(R_{432})$-;

Q is selected from the group consisting of a bond, -$C(R_{632})$-, -$C(R_{632})$-$C(R_{632})$, -$S(O)_2$-, -$C(R_{632})$-$N(R_{832})$-W-, -$S(O)_2$-$N(R_{832})$-, -$C(R_{632})$-O-, and -$C(R_{632})$-$N(OR_{932})$-;

V is selected from the group consisting of -$C(R_{632})$-, -O-$C(R_{632})$-, -$N(R_{832})$-$C(R_{632})$-, 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 is ≤ 7;

and pharmaceutically acceptable salts thereof.

Illustrative non-interfering R_{132} substituents include:

-R_{432},

-X-R_{432},

-X-Y-R_{432},

-X-Y-X-Y-R_{432}, and

-X-R_{532};

wherein:

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:

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_{832})$-,

-$C(R_{632})$-,

-$C(R_{632})$-O-,

-O-$C(R_{632})$-,

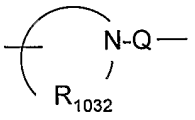
-O-C(O)-O-,

-$N(R_{832})$-Q-,

-$C(R_{632})$-$N(R_{832})$-,

-O-C(R_{632})-N(R_{832})-,

-C(R_{632})-N(OR_{932})-,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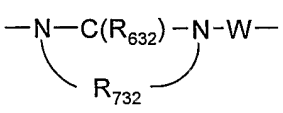
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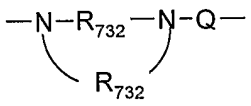
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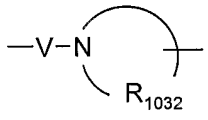
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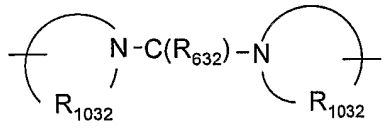
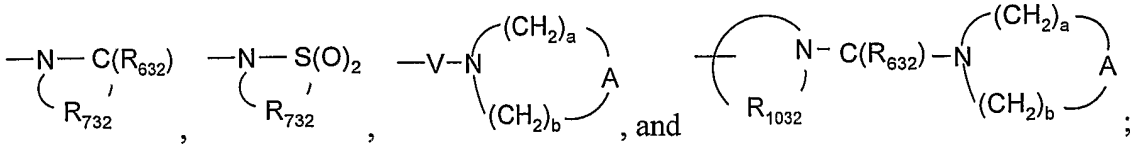

;

R_{432} 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_{532} is selected from the group consisting of:


;

each R_{632} is independently selected from the group consisting of =O and =S;

each R_{732} is independently C_{2-7} alkylene;

each R_{832} is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

each R_{932} is independently 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)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_{432})-$;

each Q is independently selected from the group consisting of a bond, $-C(R_{632})-$, $-C(R_{632})-C(R_{632})-$, $-S(O)_2-$, $-C(R_{632})-N(R_{832})-W-$, $-S(O)_2-N(R_{832})-$, $-C(R_{632})-O-$, and $-C(R_{632})-N(OR_{932})-$;

each V is independently selected from the group consisting of $-C(R_{632})-$, $-O-C(R_{632})-$, $-N(R_{832})-C(R_{632})-$, and $-S(O)_2-$;

each W is independently 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 $a + b \leq 7$;

Illustrative non-interfering R_{232} substitutents include:

$-R_{432}$,

$-X-R_{432}$,

$-X-Y-R_{432}$, and

$-X-R_{532}$;

wherein:

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:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_{832})-$,

$-C(R_{632})-$,

$-C(R_{632})-O-$,

$-O-C(R_{632})-$,

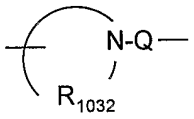
-O-C(O)-O-,

$-N(R_{832})-Q-$,

$-C(R_{632})-N(R_{832})-$,

$-O-C(R_{632})-N(R_{832})-$,

$-C(R_{632})-N(OR_{932})-$,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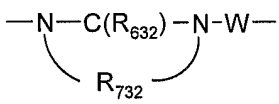
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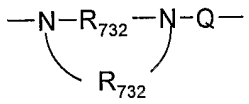
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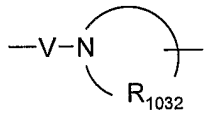
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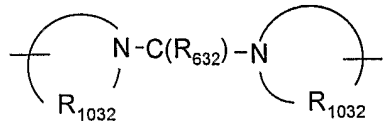
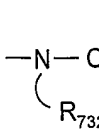

;

R_{432} 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_{532} is selected from the group consisting of: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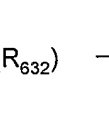
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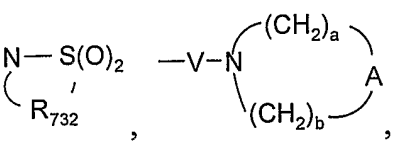
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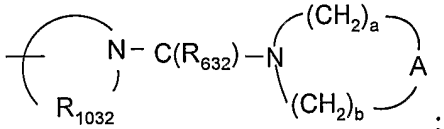
;

each R_{632} is independently selected from the group consisting of =O and =S;

each R_{732} is independently C_{2-7} alkylene;

each R_{832} is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_{932} 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)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_{432})-$;

Q is selected from the group consisting of a bond, $-C(R_{632})-$, $-C(R_{632})-C(R_{632})-$, $-S(O)_2-$, $-C(R_{632})-N(R_{832})-W-$, $-S(O)_2-N(R_{832})-$, $-C(R_{632})-O-$, and $-C(R_{632})-N(OR_{932})-$;

V is selected from the group consisting of $-C(R_{632})-$, $-O-C(R_{632})-$, $-N(R_{832})-C(R_{632})-$, 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 $a + b \leq 7$;

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 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. 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. Likewise, "alkylenyl", "alkenylenyl", and "alkynylenyl" are the divalent forms of the "alkyl",

"alkenyl", and "alkynyl" groups defined above. For example, an arylalkylenyl 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, trifluoromethyl, and the like. Similarly, the term "fluoroalkyl" is inclusive of groups that are substituted by one or more fluorine atoms, including perfluorinated groups (e.g., trifluoromethyl).

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 "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, 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 heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. Exemplary heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, 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 "heterocyclylenyl" 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-XXXI 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, aryloxycarbonyl, heteroaryloxycarbonyl, arylthiocarbonyl, heteroarylthiocarbonyl, alkanoyloxy, alkanoylthio, alkanoylamino, aroyloxy, aroylthio, aroylamino, alkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryldiazinyl, alkylsulfonylamino, arylsulfonylamino, arylalkylsulfonylamino, alkylcarbonylamino, alkenylcarbonylamino, arylcarbonylamino, arylalkylcarbonylamino, heteroarylcarbonylamino, heteroarylalkycarbonylamino, alkylsulfonylamino, alkenylsulfonylamino, arylsulfonylamino, arylalkylsulfonylamino, heteroarylsulfonylamino, heteroarylalkylsulfonylamino, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, arylalkylaminocarbonyl, alkenylaminocarbonyl, heteroarylaminocarbonyl, heteroarylalkylaminocarbonyl, alkylaminocarbonylamino, alkenylaminocarbonylamino, arylaminocarbonylamino, arylalkylaminocarbonylamino, heteroarylaminocarbonylamino, 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.

When a group (or substituent or variable) is present more that once in any Formula described herein, each group (or substituent or variable) is independently selected, whether explicitly stated or not. For example, for the formula $-N(R_{631})_2$ each R_{631} group is independently selected. In another example, when an R_{232} and an R_{332} group both contain an R_{432} group, each R_{432} group is independently selected. In a further example, when more than one Y group is present (i.e., R_{232} and R_{332} both contain a Y group) and each Y group contains one or more R_{832} groups, then each Y group is independently selected, and each R_{832} group is independently selected.

In certain embodiments, the immune response modifier 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, imidazotetrahydronaphthyridine

amines, oxazoloquinoline amines, thiazoloquinoline amines, oxazolopyridine amines, thiazolopyridine amines, oxazolonaphthyridine amines, thiazolonaphthyridine amines, 1*H*-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines, and combinations thereof.

EXAMPLES

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention. Unless otherwise provided, all percentages are given as w/w% (i.e., weight percents or wt-%).

Table 1

Compound	Chemical Name	Reference
IRM1	N-[4-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide	U.S. 6,331,539#
IRM2	N-{2-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide	U.S. 6,677,349 Example 268

This compound is not specifically exemplified but can be readily prepared using the synthetic methods disclosed in the cited reference.

Systemic Formulation

Formulations of IRM1 are prepared as described in Table 2 and Table 3 capable of being administered intra-venously or subcutaneously as follows:

Table 2

Intra-venous & Subcutaneous Formulations (%w/w)			
Ingredient	Placebo	0.2	0.4
IRM 1	0	0.2	0.4
Citric Acid	0.42	0.42	0.42
Mannitol	4.50	4.50	4.50

Sodium Hydroxide, 1N, qs to pH=5	~4.00	(3.80)	(3.80)
Sterile Water for Injection, qs	~91.38	(90.88)	(90.88)
Total	100	100	100

Table 3

Intra-venous & Subcutaneous Formulations (%w/w)		
Ingredients	0.15	0.15
IRM 1	0.15	0.15
Citric acid	0.42	-
Acetic Acid	-	0.3
Mannitol	4.5	4.0
1N NaOH	3.9	3.5
Water	qs	qs
pH	5.0	5.0

Topical Formulation

IRM compounds are prepared as a 0.01, 0.3, 1.0, or 3% cream formulation as disclosed in US Patent Publication No. US 2003/0199538 and International Patent Publication No. WO 03/045391.

Example 1

Following surgical excision of their lesions, patients with melanoma cutaneous metastasis or lentigo maligna melanoma lesions are treated at the excision site with IRM1 or IRM2 at a concentration of 0.01, 0.3, 1.0, or 3% cream formulation as disclosed in US Patent Publication No. US 2003/0199538 and International Patent Publication No. WO 03/045391. The placebo, IRM1, or IRM2 cream formulation is applied three times a week for four weeks.

Following the four weeks of topical application, patients are treated with an intra-venous (I.V.) formulation of IRM1 as described in Table 2 and Table 3. The I.V. formulation is injected three times a week for two to eight weeks with the placebo or a dosing level of 0.008, 0.016, or 0.032 mg/kg.

Example 2

Following surgical excision of their lesions, patients with melanoma cutaneous metastasis or lentigo maligna melanoma lesions are treated with the intra-venous (I.V.) formulation as described above. The I.V. formulation is injected three times a week for two weeks with the placebo or a dosing level of 0.004 to 0.108 mg/kg.

Following the two weeks of systemic administration of IRM1, patients are treated topically with IRM1 or IRM2 at a concentration of 0.01, 0.3, 1.0, or 3% cream formulation as described above. The placebo, IRM1, or IRM2 cream formulations is applied three times a week for four weeks.

Once the four weeks of topically applied IRM1 or IRM2 is completed, patients resume systemic administration of IRM1 for an additional two to 24 weeks.

Example 3

Patients with melanoma cutaneous metastasis or lentigo maligna melanoma lesions are treated at the lesion site with IRM1 or IRM2 at a concentration of 0.01, 0.3, 1.0, or 3% cream formulation as disclosed in US Patent Publication No. US 2003/0199538 and International Patent Publication No. WO 03/045391. The placebo, IRM1, or IRM2 cream formulation is applied three times a week for four weeks.

Following the four weeks of topical application, patients are treated with an intra-venous (I.V.) formulation of IRM1 as described in Table 2 or Table 3. The I.V. formulation is injected three times a week for two to eight weeks with the placebo or a dosing level of 0.004 to 0.108 mg/kg.

Example 4

Patients with melanoma cutaneous metastasis or lentigo maligna melanoma lesions are treated with an intra-venous (I.V.) formulation as described above. The I.V. formulation is injected three times a week for two weeks with the placebo or a dosing level of 0.004 to 0.108 mg/kg.

Following the two weeks of systemic administration of IRM1, patients are treated topically with IRM1 or IRM2 at a concentration of 0.01, 0.3, 1.0, or 3% cream formulation as described above. The placebo, IRM1, or IRM2 cream formulations is applied three times a week for four weeks.

Once the four weeks of topically applied IRM1 or IRM2 is completed, patients resume systemic administration of IRM1 for an additional two to 24 weeks.

Example 5

Topical formulations of IRM1 and a vehicle were formulated as shown in Table 3.

Table 3

Materials	Vehicle	5% IRM1
IRM1	-	5.00
Isostearic acid	31.00	31.00
Crodamol	5.00	5.00
Propylene glycol, USP	9.00	9.00
Methylparaben, NF	0.20	0.20
Ethylparaben, NF	0.20	0.20
Purified water, USP	48.4	44.4
Carbopol 980, NF	0.90	0.60
Poloxamer 188, NF	3.75	3.75
EDTA, USP	0.05	0.05
20% w/w NaOH solution (qs pH 5.8 +/-0.2)	1.50	0.80

Eleven-week-old female Balb/c mice (Charles River Laboratories, Wilmington, MA) were injected intra-dermally with 5×10^5 mouse colon carcinoma-26 cells (MC26) expressing luciferase (ATCC, Manassas, VA) on day 0. Mice were divided into five groups: topical vehicle, subcutaneous vehicle (SQ vehicle), IRM1 topical (topical IRM1), IRM1 subcutaneous (SQ IRM1), and IRM1 topical and subcutaneous (topical + SQ IRM1). Eighteen hours after injection of the cells, 30 microliters of vehicle or 5% IRM1 topical formulations, described in Table 3, was applied to the tumor site. Six hours later, mice were injected subcutaneously with 10 millograms per kilogram of IRM1 in a 1 milligram per milliliter IRM1, 0.03M citrate buffered saline solution or a vehicle 0.03M citrate buffered saline solution. On days 1, 5, and 6 mice were anesthetized with vaporized 3% isoflurane and in vivo photon counts of luciferin were measured using a Xenogen IVIS imaging system (Alameda, CA) following the manufacturer's protocol. The tumor growth index for each treatment group was calculated by dividing each group's day 5 or day 6 tumor photon counts by their day 1 tumor photon counts. The results indicate a surprising benefit when a combination of topical and systemic routes were used. The results for the day 6 tumor growth are found in Figure 1, in which the topical and SQ vehicles were averaged together (vehicles).

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. 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 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.

WHAT IS CLAIMED IS:

1. A method of treating disease with immune response modifiers (IRMs) by administering at least one IRM compound via at least two different routes of delivery.

2. The method of claim 1, wherein there is only one IRM compound active moiety is used.

3. The method of claim 2, wherein two different salt forms of the IRM compound active moiety are used.

4. The method of claim 1, wherein at least two different IRM compound active moieties are used.

5. The method of claim 1, wherein the routes of delivery include local delivery and systemic delivery.

6. The method in claim 5, wherein the local route of delivery is topical delivery.

7. The method of claim 6, wherein topical delivery is achieved using an IRM-containing gel or cream formulation.

8. The method of claim 5, wherein systemic delivery is achieved by injection or oral delivery.

9. The method of claim 1, wherein the disease being treated is cancer.

10. The method of claim 9, wherein an IRM is delivered locally directly to the cancer and an IRM is delivered systemically to the entire body.

11. The method of claim 10, wherein the IRM delivered locally is injected directly into the cancer.

12. The method of claim 1, wherein the disease is a viral, fungal, protazoal, or bacterial infection.

13. A method of treating melanoma with an immune response modifier (IRM), the method comprising:

applying at least one IRM topically to a melanoma lesion on a subject in combination with separately administering at least one IRM to the subject systemically.

14. The method of claim 13, wherein the IRM administered topically is administered to a dermal or mucosal tissue.

15. The method of claim 14 wherein the IRM administered topically is administered to a vaginal, rectal, nasal, buccal, or pulmonary surface.

16. The method of claim 13 wherein the IRM is a compound having a 2-aminopyridine fused to a five membered nitrogen-containing heterocyclic ring.

17. The method of claim 16 wherein the immune response modifier 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, imidazotetrahydronaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines, oxazolopyridine amines, thiazolopyridine amines, oxazolonaphthyridine amines, thiazolonaphthyridine amines, 1*H*-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines, and combinations thereof.

18. The method of claim 16, wherein the immune response modifier is selected from the group consisting of imidazoquinoline amines, tetrahydroimidazoquinoline amines, imidazopyridine amines, and combinations thereof.

19. The method of claim 16, wherein the immune response modifier is selected from the group consisting of amide substituted imidazoquinoline amines, sulfonamide substituted imidazoquinoline amines, urea 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, 6-, 7-, 8-, or 9-aryl or heteroaryl substituted imidazoquinoline amines, 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 tetrahydroimidazoquinoline amines, sulfonamido ether substituted tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline ethers, thioether substituted tetrahydroimidazoquinoline amines, amide substituted imidazopyridine amines, sulfonamide substituted imidazopyridine amines, urea substituted imidazopyridine amines, aryl ether substituted imidazopyridine amines, heterocyclic ether substituted imidazopyridine amines, amido ether substituted imidazopyridine amines, sulfonamido ether substituted imidazopyridine

amines, urea substituted imidazopyridine ethers, thioether substituted imidazopyridine amines, and combinations thereof.

20. The method of claim 19, wherein the immune response modifier is selected from the group consisting of amide substituted imidazoquinoline amines, sulfonamide substituted imidazoquinoline amines, urea substituted imidazoquinoline amines, thioether substituted imidazoquinoline amines, 7-aryl substituted imidazoquinoline amines, 7-heteroaryl substituted imidazoquinoline amines, sulfonamide substituted tetrahydroimidazoquinoline amines, and combinations thereof.

21. The method of claim 17, wherein the immune response modifier is an imidazoquinoline amine.

22. The method of claim 19, wherein the immune response modifier is a sulfonamide substituted imidazoquinoline amine.

23. The method of claim 16, wherein the immune response modifier is selected from the group consisting of N-[4-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide, N-{2-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]-1,1-dimethyleethyl}methanesulfonamide, pharmaceutically acceptable salts thereof, and combinations thereof.

24. The method of any preceding claim, wherein an IRM is administered systemically in a formulation comprising:

a pharmaceutically acceptable acid;

a tonicity adjuster;

sterile water; and

optionally a pH adjuster;

with the proviso that the IRM is other than 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine or 4-amino-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol.

25. The method of claim 24, wherein the formulation comprises 0.4 wt-% to 0.5 wt-% citric acid, 4 wt-% to 5 wt-% mannitol, and water, wherein the formulation is adjusted to a pH of 5 with the pH adjuster.

26. The method of claim 24, wherein the formulation comprises 0.2 wt-% to 0.5 wt-% acetic acid, 4 wt-% to 5 wt-% mannitol, and water, wherein the formulation is adjusted to a pH of 5 with the pH adjuster.

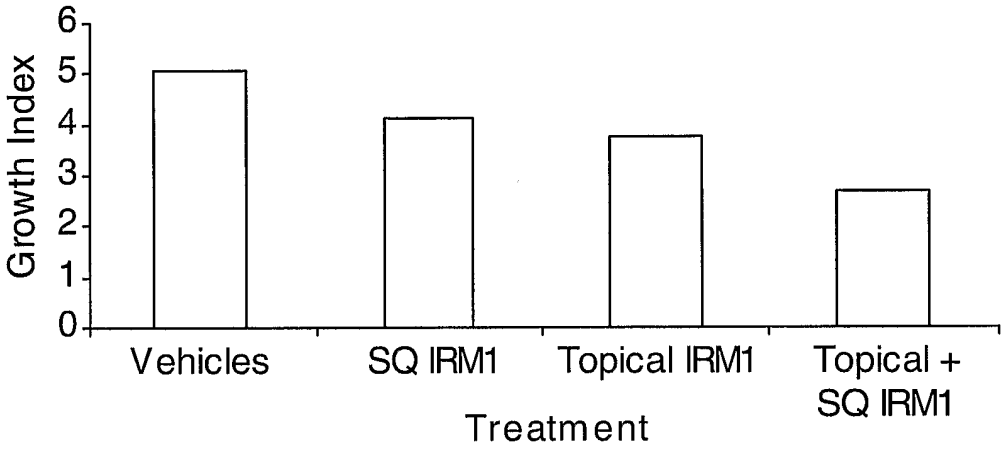
Growth Index
6
5
4
3
2
1
0
Vehicles
SQ IRM1
Topical IRM1
Topical + SQ IRM1
Treatment

Fig. 1