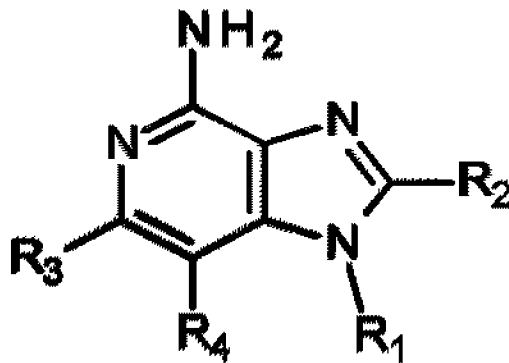




(86) Date de dépôt PCT/PCT Filing Date: 2016/08/26  
(87) Date publication PCT/PCT Publication Date: 2017/03/09  
(45) Date de délivrance/Issue Date: 2023/10/03  
(85) Entrée phase nationale/National Entry: 2018/02/20  
(86) N° demande PCT/PCT Application No.: US 2016/048830  
(87) N° publication PCT/PCT Publication No.: 2017/040233  
(30) Priorité/Priority: 2015/08/31 (US62/211,894)

(51) Cl.Int./Int.Cl. *C07D 471/04* (2006.01),  
*A61K 31/4353* (2006.01), *A61P 37/00* (2006.01)  
(72) Inventeur/Inventor:  
GRIESGRABER, GEORGE W., US  
(73) Propriétaire/Owner:  
3M INNOVATIVE PROPERTIES COMPANY, US  
(74) Agent: SMART & BIGGAR LP

(54) Titre : COMPOSES IMIDAZO[4,5-C] CYCLIQUES SUBSTITUES PAR GUANIDINE  
(54) Title: GUANIDINE SUBSTITUTED IMIDAZO[4,5-C] RING COMPOUNDS



(57) **Abrégé/Abstract:**

Imidazo[4,5-c] ring compounds, (particularly imidazo[4,5-c]quinolines, 6,7,8,9- tetrahydroimidazo[4,5-c]quinolines, imidazo[4,5-c]naphthyridines, and 6,7,8,9- tetrahydroimidazo[4,5-c]naphthyridine compounds) having a guanidine substituent at the 1-position, pharmaceutical compositions containing the compounds, and methods of making the compounds are disclosed. Methods of use of the compounds as immune response modifiers, for inducing cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases are also disclosed.

**ABSTRACT**

Imidazo[4,5-c] ring compounds, (particularly imidazo[4,5-c]quinolines, 6,7,8,9- tetrahydroimidazo[4,5-c]quinolines, imidazo[4,5-c]naphthyridines, and 6,7,8,9- tetrahydroimidazo[4,5-c]naphthyridine compounds) having a guanidine substituent at the 1- position, pharmaceutical compositions containing the compounds, and methods of making the compounds are disclosed. Methods of use of the compounds as immune response modifiers, for inducing cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases are also disclosed.

## GUANIDINE SUBSTITUTED IMIDAZO[4,5-c] RING COMPOUNDS

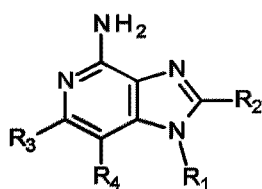
### BACKGROUND

Some drug compounds act by stimulating certain key aspects of the immune system, as well as by suppressing certain other aspects (e.g., U.S. Patent Numbers. 6,039,969 and 6,200,592). These compounds are sometimes referred to as immune response modifiers (IRMs). Some IRM compounds are useful for treating viral diseases, neoplasias, and T<sub>H</sub>2-mediated diseases; some are useful as vaccine adjuvants.

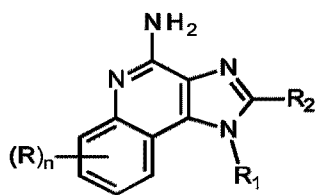
IRM compounds have been reported based on the following bicyclic and tricyclic ring systems: 1H-imidazo[4,5-c]quinolin-4-amines (e.g., U.S. Patent Number 4,689,338); 1H-imidazo[4,5-c]pyridin-4-amines (e.g., U.S. Patent Number 5,446,153); 1H-imidazo[4,5-c][1,5]naphthydin-4-amines (e.g., U.S. Patent Number 6,194,425); thiazolo[4,5-c]quinolone-4-amines and oxazolo[4,5-c]quinolone-4-amines (e.g., U.S. Patent Number 6,110,929); 6,7,8,9-1H-tetrahydro-1H-imidazo[4,5-c]quinolin-4-amines (e.g., U.S. Patent Number 5,352,784); 2H-pyrazolo[3,4-c]quinolone-4-amines (e.g., U.S. Patent Number 7,544,697); and N-1 and 2-substituted 1H-imidazo[4,5-c]quinolin-4-amines (e.g., U.S. Patent Numbers 6,331,539, 6,451,810, 6,664,264, 8,691,837, 8,088,790, 8,673,932, 8,697,873, 7,915,281).

### SUMMARY

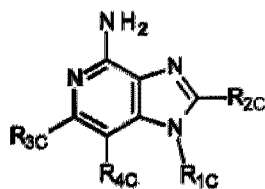
New compounds that can be useful in inducing cytokine biosynthesis in animals are disclosed. Such compounds are of the following Formulas I, II, and XIV:



Formula I



Formula II



Formula XIV

wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_1C$ ,  $R_2C$ ,  $R_3C$ ,  $R_4C$ , and  $n$  are as defined below. A common structural feature of the compounds of Formulas I, II, and XIV is the inclusion of a guanidino substituent as a component of  $R_1$  and  $R_1C$ .

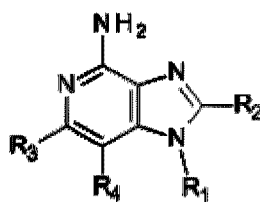
- 5 In addition, more specific examples of such compounds include the compounds of Formulas III-XIII and Formulas XV-XVIII which are defined below, as well as salts, particularly pharmaceutically acceptable salts, thereof.

- 10 The compounds and salts, such as pharmaceutically acceptable salts, of Formulas I-XVIII can be useful as immune response modifiers due to their ability to induce cytokine biosynthesis (e.g., induce the synthesis of at least one cytokine) and otherwise modulate the immune response when administered to animals. The compounds can therefore be useful in the treatment of a variety of conditions such as viral diseases and tumors that are responsive to such changes in the immune response.

- 15 Pharmaceutical compositions containing an effective amount of one or more compounds of Formulas I-XVIII and salts, particularly pharmaceutically acceptable salts, thereof and methods of inducing cytokine biosynthesis in an animal, treating a viral disease in an animal, and treating a neoplastic disease in an animal by administering to the animal one or more compounds of the Formulas I-XVIII, and/or pharmaceutically acceptable salts thereof are also disclosed.

Methods for synthesizing compounds of Formulas I-XVIII are provided.

Thus, there is provided a compound of the Formula (I):

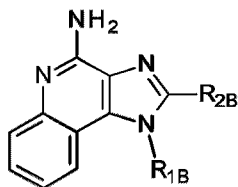


Formula I

- 20 wherein:  
 $R_3$  and  $R_4$  are taken together to form a fused benzene ring, a fused pyridine ring, a fused cyclohexene ring, or a fused tetrahydropyridine ring; wherein the fused benzene ring, fused pyridine ring, fused cyclohexene ring, or fused tetrahydropyridine ring is either unsubstituted or substituted by one or more R groups;  
 25 R is selected from the group consisting of halogen, hydroxyl, alkyl, alkoxy, haloalkyl,

- C(O)-O-alkyl, -C(O)-OCH<sub>2</sub>Ph, -C(O)-O-aryl, amino, alkylamino, dialkylamino, aryl, arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, heteroarylalkyleneoxy, and heteroaryloxy, wherein the alkyl, aryl, arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, heteroarylalkyleneoxy, and heteroaryloxy groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, haloalkyl, hydroxyl, hydroxyalkylenyl, alkoxyalkylenyl, arylalkyleneoxy, nitrile, amino, alkylamino, and dialkylamino;
- 5 **R<sub>1</sub>** is -W-X-N(H)-C(=NH)-NH<sub>2</sub>;
- W** is selected from the group consisting of a covalent bond, -O-, and -NH-;
- 10 **X** is selected from the group consisting of -CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>-, -CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-O-CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-O-CH<sub>2</sub>CH<sub>2</sub>-O-CH<sub>2</sub>CH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2-4</sub>-(OCH<sub>2</sub>CH<sub>2</sub>)<sub>1-5</sub>, and -(CH<sub>2</sub>)<sub>2-6</sub>-(OCH<sub>2</sub>CH<sub>2</sub>)<sub>1-4</sub>;
- 15 **R<sub>2</sub>** is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, -O-alkyl, hydroxyalkylenyl, alkoxyalkylenyl, alkylaminoalkylenyl, hydroxyl, -CH<sub>2</sub>-NH-O-alkyl, and -CH<sub>2</sub>NHC(O)-alkyl;
- wherein
- alkyl groups contain from 1 to 14 carbon atoms,
- 20 haloalkyl groups are alkyl groups that are substituted by one or more halogen atoms,
- aryl groups are selected from the group consisting of phenyl, naphthyl, and biphenyl,
- alkylenyl groups contain from 1 to 14 carbon atoms,
- alkylene groups contain from 1 to 14 carbon atoms,
- heteroaryl groups are a ring or ring system that contains 2 to 12 carbon atoms, 1 to 3 rings, 1 to
- 25 4 heteroatoms with O, S, and N as the heteroatoms,
- alkenyl groups contain from 2 to 14 carbon atoms,
- alkynyl groups contain from 2 to 14 carbon atoms,
- cycloalkyl groups contain from 3 to 10 ring carbon atoms, and
- unless otherwise defined, groups having the prefix "alk-" contain from 1 to 14 carbon atoms,
- 30 or a pharmaceutically acceptable salt thereof.

There is also provided a compound of the Formula XIII:



Formula XIII

wherein:

R<sub>1B</sub> is selected from the group consisting of -X<sub>B</sub>-N(H)-C(=NH)-NH<sub>2</sub>;

X<sub>B</sub> is selected from the group consisting of -CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-,  
 5 -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-,  
 -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>-, -CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>-,  
 -CH<sub>2</sub>CH<sub>2</sub>-O-CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-O-CH<sub>2</sub>CH<sub>2</sub>-O-CH<sub>2</sub>CH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2-4</sub>-(OCH<sub>2</sub>CH<sub>2</sub>)<sub>1-5</sub>,  
 and -(CH<sub>2</sub>)<sub>2-6</sub>-(OCH<sub>2</sub>CH<sub>2</sub>)<sub>1-4</sub>;

R<sub>2B</sub> is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, -O-alkyl, hydroxyalkylenyl,  
 10 alkoxyalkylenyl, alkylaminoalkylenyl, hydroxyl, -CH<sub>2</sub>-NH-O-alkyl, and  
 -CH<sub>2</sub>NHC(O)-alkyl;

wherein

alkyl groups contain from 1 to 14 carbon atoms,

alkylenyl groups contain from 1 to 14 carbon atoms,

15 alkenyl groups contain from 2 to 14 carbon atoms,

alkynyl groups contain from 2 to 14 carbon atoms, and

unless otherwise defined, groups having the prefix "alk-" contain from 1 to 14 carbon atoms,

or a pharmaceutically acceptable salt thereof.

20 There is also provided use of the compound or salt as described herein for the treatment of a viral  
 disease or a neoplastic disease in an animal.

There is also provided a pharmaceutical composition comprising the compound or salt as  
 described herein in combination with a pharmaceutically acceptable carrier.

The above summary is not intended to describe each disclosed embodiment or every  
 implementation of the present invention. The description that follows more particularly exemplifies  
 25 illustrative embodiments. In several places throughout the description, guidance is provided through lists  
 of examples, which 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 exhaustive list.

## DETAILED DESCRIPTION

As used herein, "a", "an", "the", "at least one", and "one or more" are used interchangeably and are intended to include both the singular and the plural except in cases where the singular alone is specifically called for or clearly required by the context.

As used herein, “preferred” and “preferably” refer to embodiments of the disclosure that may afford certain benefits, under certain circumstances. However, other embodiments may also be preferred, under the same or other circumstances. Furthermore, the recitation of one or more preferred embodiments does not imply that other embodiments are not useful, and is not intended to  
5 exclude other embodiments from the scope of the invention.

“Ph” is used as an abbreviation for a phenyl radical.

As used herein, “pharmaceutically acceptable carriers” include those carriers that can deliver therapeutically effective amounts of one or more of the compounds or salts of the disclosure to a subject by a chosen route of administration, are generally tolerated by the subject, and have an  
10 acceptable toxicity profile (preferably minimal to no toxicity at an administered dose). Some suitable pharmaceutically acceptable carriers are described in Remington’s Pharmaceutical Sciences, 18<sup>th</sup> Edition (1990), Mack Publishing Co. and can be readily selected by one of ordinary skill in the art.

“Therapeutically effective amount” and “effective amount” are defined as an amount of compound or salt sufficient to induce a therapeutic or prophylactic effect, such a cytokine induction,  
15 immunomodulation, antitumor activity, and/or antiviral activity.

“Independently,” when used to describe the identity of one or more variable reference elements (such as when used in the phrase “independently selected” or “independently selected from the group”), means that each occurrence of any of the variable elements may have the same or different identity, within the specified limitations, regardless of the identity of any other occurrence of the  
20 reference element(s). Thus, if there are two occurrences of reference element “A,” and reference element “A” can be independently selected from identity “B” or identity “C”, each of the two occurrences of “A” can be either “B” or “C”, in any combination (e.g., “B,B”; “B,C”; “C,B”; or “C,C”). Alternatively, if there are two different reference elements (reference element “D” and reference element “E”) that can occur together and reference element “D” and reference element “E”  
25 can each be independently selected from identity “F” or identity “G”, then each occurrence of “D” can be “F” or “G” and likewise each occurrence of “E” can be “F” or “G”, to produce any combination of “D” and “E” (e.g., “D”=“F” and “E”=“F”; “D”=“F” and “E”=“G”; “D”=“G” and “E”=“F”; or “D”=“G” and “E”=“G”).

The terms “alkyl”, “alkenyl”, “alkynyl” and the prefix “alk-” are inclusive of straight chain  
30 groups, branched chain groups, cyclic groups, and combinations thereof, e.g. cycloalkyl and cycloalkenyl. Alkyl groups are saturated aliphatic hydrocarbons. Alkenyl groups are unsaturated aliphatic hydrocarbons having one or more carbon-carbon double bonds. Alkynyl groups are unsaturated aliphatic hydrocarbons having one or more carbon-carbon triple bonds. Unless otherwise specified, these groups contain from 1 to 14 carbon atoms, with alkenyl groups containing from 2 to  
35 14 carbon atoms and alkynyl groups containing from 2-14 atoms. In some embodiments, these groups have a total of up to 14 carbon atoms, up to 12 carbon atoms, up to 10 carbon atoms, up to 8 carbon



atoms, up to 6 carbon atoms, up to 5 carbon atoms, up to 4 carbon atoms, up to 3 carbon atoms, or up to 2 carbon atoms. In some embodiments, these groups have at least 1 carbon atom, at least 2 carbon atoms, at least 3 carbon atoms, or at least 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, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexylmethyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, norbornenyl, and the like

The term "haloalkyl" is inclusive of alkyl 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, pentafluoroethyl and the like.

Unless otherwise specified, "alkylene", "alkenylene", and "alkynylene" are the diradical equivalents of the "alkyl", "alkenyl", and "alkynyl" defined above. The terms, "alkylenyl", "alkenylenyl", and "alkynylenyl" are used when "alkylene", "alkenylene", and "alkynylene" respectively, are substituted. For example, an alkoxyalkylenyl group comprises an alkylene moiety to which an alkoxy group is attached (e.g.,  $-\text{CH}_2\text{OCH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{OCH}_3$ ,  $-\text{CH}_2\text{OCH}_2\text{CH}_3$ , etc.). As a further example, a hydroxyalkylenyl group comprises an alkylene moiety to which a hydroxyl group is attached (e.g.,  $-\text{CH}_2\text{OH}$ ,  $-\text{CH}_2\text{CH}_2\text{OH}$ , etc.). As yet another example arylalkylenyl group comprises an alkylene moiety to which an aryl group is attached [e.g.,  $-\text{CH}_2\text{Ph}$ ,  $-\text{CH}_2\text{CH}_2\text{Ph}$ , etc.].

An alkylene group with carbon atoms optionally "interrupted" by one or more -O- groups refers to having carbon atoms on either side of the -O-. Examples include  $-\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_2-$ ,  $-(\text{CH}_2)_{2-4}-(\text{OCH}_2\text{CH}_2-)_{1-5}$ ,  $-(\text{CH}_2)_{2-6}-(\text{OCH}_2\text{CH}_2-)_{1-4}$ , etc.

Some examples of alkylamino groups include  $-\text{NHCH}_3$ ,  $-\text{NHCH}_2\text{CH}_3$ ,  $-\text{NHCH}(\text{CH}_3)_2$ , etc. It is understood that the two alkyl groups of a dialkylamino group can be the same or different alkyl groups. Some examples of dialkylamino groups include  $-\text{N}(\text{CH}_3)_2$ ,  $-\text{N}(\text{CH}_2\text{CH}_3)_2$ ,  $-\text{N}(\text{CH}_3)(\text{CH}_2\text{CH}_3)$ ,  $-\text{N}(\text{CH}_3)(\text{CH}_2\text{CH}_2\text{CH}_3)$ , etc.

Some examples of alkylaminoalkylenyl groups include  $-\text{CH}_2\text{NHCH}_3$ ,  $-\text{CH}_2\text{NHCH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{NHCH}_3$ , etc.

Some examples of benzyloxyalkylenyl groups include  $-\text{CH}_2\text{OCH}_2\text{Ph}$ ,  $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{Ph}$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{OCH}_2\text{Ph}$ , etc.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl (designated by the abbreviation "Ph" herein), naphthyl, and biphenyl.

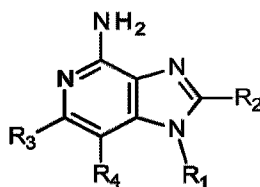
The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g. O, S, N). In some embodiments, the term "heteroaryl" includes a ring or ring system that contains 2-12 carbon atoms, 1-3 rings, 1-4 heteroatoms, with O, S, and N as the heteroatoms.

Exemplary heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, quinoxaliny, benzothiazolyl, naphthyridinyl, ixoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and the like. Preferred heteroaryl groups include, thienyl, pyridyl, quinolinyl, indolyl and imidazolyl.

The terms “arylene”, “-arylene-“, “heteroarylene”, and “-heteroarylene-“ are the diradical equivalents of the “aryl” and “heteroaryl” groups defined above. The terms “arylenyl” and “heteroarylenyl” are used when “arylene” and “heteroarylene” are substituted. For example an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached (e.g., -Ph-CH<sub>3</sub>).

The term “compound” includes not only the specific structural formula as drawn or named, but also its configurational isomers, stereoisomers, such as enantiomers, diastereomers, and meso isomers, as well as combinations of one or more of any of the foregoing, except in cases when a specific isomer, enantiomer, or the like is specifically called out. For those structures that exist as tautomers, the term “compound” is intended to include all tautomers, even when only one is drawn, unless only a single tautomer is explicitly recited. For structures that are able to form salts, “compound” also includes salts, unless a “free” or “free base” form, which refers to non-salt forms, of the compound is specifically recited. Particular salts are pharmaceutically acceptable salts, such as those described in Berge, Stephen M., “Pharmaceutical Salts”, *Journal of Pharmaceutical Sciences*, 1977, 66, pages 1-19. Salts can be prepared by reacting a free compound (that is, one not in a salt form) with an inorganic or organic acid such as, for example, hydrochloric acid, sulfuric acid, hydrobromic acid, methane sulfonic acid, ethane sulfonic acid, malic acid, maleic acid, acetic acid, trifluoroacetic acid, para-toluenesulfonic acid, salicylic acid, succinic acid, tartaric acid, citric acid, pamoic acid, xinafoic acid, oxalic acid, and the like. Typical pharmaceutically acceptable salts include hydrochloride and dihydrochloride.

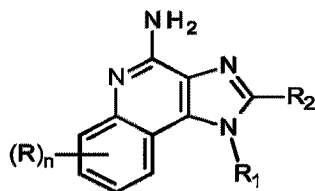
This disclosure provides compounds of the following Formula I:



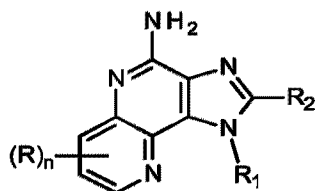
Formula I

wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> are as defined below; and pharmaceutically acceptable salts thereof.

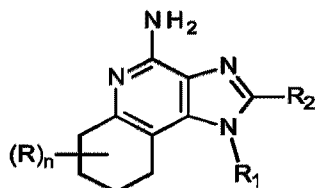
Examples of compounds of Formula I are more specifically defined by the following Formulas II-V:



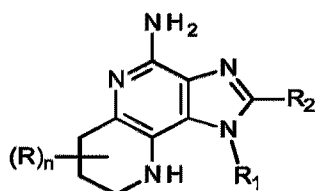
Formula II



Formula III



Formula IV



Formula V

- 5 wherein R, R<sub>1</sub>, R<sub>2</sub>, and n are as defined below, as well as salts, particularly pharmaceutically acceptable salts, thereof.

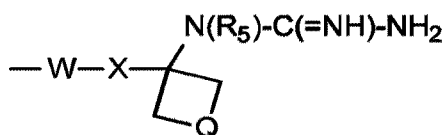
For compounds and salts, such as pharmaceutically acceptable salts, of Formula I, R<sub>3</sub> and R<sub>4</sub> are taken together to form a fused benzene ring, a fused pyridine ring, a fused cyclohexene ring, or a fused tetrahydropyridine ring; wherein the fused benzene ring, fused pyridine ring, fused cyclohexene ring, or fused tetrahydropyridine ring is either unsubstituted or substituted by one or more R groups.

For compounds and salts, such as pharmaceutically acceptable salts, of Formulas I-V: R is selected from the group consisting of halogen, hydroxyl, alkyl, alkoxy, haloalkyl, -C(O)-O-alkyl, -C(O)-OCH<sub>2</sub>Ph, -C(O)-O-aryl, amino, alkylamino, and dialkylamino, aryl, arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, heteroarylalkyleneoxy, and heteroaryloxy, wherein the alkyl, aryl, arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, heteroarylalkyleneoxy, and heteroaryloxy groups can be unsubstituted or

substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, haloalkyl, hydroxyl, hydroxyalkylenyl, alkoxyalkylenyl, arylalkyleneoxy, nitrile, amino, alkylamino, and dialkylamino;

n is an integer from 0 to 2;

- 5  $R_1$  is selected from the group consisting of  $-W-X-N(R_5)-C(=NH)-NH_2$ ,  $-W-Z-N(R_5)-C(=NH)-NH_2$ , and



;

W is selected from the group consisting of a covalent bond,  $-O-$ , and  $-NH-$ ;

- 10 X is selected from the group consisting of alkylene, alkenylene, and alkynylene, wherein any of the alkylene, alkenylene, and alkynylene groups can be optionally interrupted by one or more  $-O-$  groups;

Z is selected from the group consisting of

$-X\text{-arylene-X-}$ ,

$-X\text{-heteroarylene-X-}$ ,

$-X\text{-arylene-}$ , and

- 15  $-X\text{-heteroarylene-}$ ;

$R_2$  is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl,  $-O\text{-alkyl}$ , hydroxyalkylenyl, alkoxyalkylenyl, alkylaminoalkylenyl, hydroxyl,  $-CH_2\text{-NH-O-alkyl}$ , and  $-CH_2\text{NHC(O)-alkyl}$ ;

- 20  $R_5$  is selected from the group consisting of hydrogen, alkyl, arylalkylenyl, alkoxyalkylenyl, aryloxyalkylenyl, benzyloxyalkylenyl, aryl- $(CH_2)_{2-6}\text{-O-alkylenyl}$ , and cycloalkylalkylenyl, wherein any of the alkyl, arylalkylenyl, alkoxyalkylenyl, aryloxyalkylenyl, benzyloxyalkylenyl, aryl- $(CH_2)_{2-6}\text{-O-alkylenyl}$ , and cycloalkylalkylenyl groups can be either unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, alkoxy, alkyl, haloalkyl, and nitrile;

- 25 Q is selected from the group consisting of a bond,  $-CH_2-$ ,  $-CH_2CH_2-$ ,  $-CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2CH_2CH_2-$ ,  $-CH_2\text{-O-CH}_2-$ , and  $-OCH_2-$ .

In some embodiments of Formula I,  $R_3$  and  $R_4$  are taken together to form a fused benzene ring, a fused pyridine ring, or a fused cyclohexene ring.

- 30 In some embodiments of Formula I,  $R_3$  and  $R_4$  are taken together to form a fused benzene ring or a fused cyclohexene ring.

In some embodiments of Formula I,  $R_3$  and  $R_4$  are taken together to form a fused benzene ring or a fused pyridine ring.

In some embodiments of Formula I,  $R_3$  and  $R_4$  are taken together to form a fused benzene ring.

In some embodiments of Formula I, R<sub>3</sub> and R<sub>4</sub> are taken together to form a fused benzene ring, a fused pyridine ring, or a fused cyclohexene ring; wherein the fused benzene ring, fused pyridine ring, or fused cyclohexene ring is either unsubstituted or substituted by one and only one R group.

5 In some embodiments of Formula I, R<sub>3</sub> and R<sub>4</sub> are taken together to form a fused benzene ring or a fused pyridine ring; wherein the fused benzene ring or fused pyridine ring is either unsubstituted or substituted by one and only one R group.

In some embodiments of Formulas II-V, n is 0 or 1.

In some embodiments of Formulas II-V, n is 0.

10 In some embodiments of Formulas I-V, R is selected from the group consisting of halogen, hydroxyl, alkyl, alkoxy, haloalkyl, -C(O)-O-alkyl, -C(O)-O-CH<sub>2</sub>Ph, -C(O)-O-aryl, amino, alkylamino, and dialkylamino.

In some embodiments of Formulas I-V, R is selected from the group consisting of alkyl, aryl, arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, heteroarylalkyleneoxy, and heteroaryloxy, wherein the alkyl, aryl, arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, heteroarylalkyleneoxy, and heteroaryloxy groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, haloalkyl, hydroxy, hydroxyalkylenyl, alkoxyalkylenyl, arylalkyleneoxy, nitrile, amino, alkylamino, and dialkylamino.

In some embodiments of Formulas I-V, R is selected from the group consisting of aryl, arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, heteroarylalkyleneoxy, and heteroaryloxy.

25 In some embodiments of Formulas I-V, R is selected from the group consisting of hydroxyl, F, Cl, -CF<sub>3</sub>, -O-C<sub>1-6</sub>alkyl, and -C<sub>1-6</sub>alkyl.

In some embodiments of Formulas I-V, R is selected from the group consisting of hydroxyl, F, Cl, -CF<sub>3</sub>, -OCH<sub>3</sub>, -OCF<sub>3</sub>, -OCH<sub>2</sub>CH<sub>3</sub>, -OCH(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, and -CH(CH<sub>3</sub>)<sub>2</sub>.

In some embodiments of Formulas I-V, R is -C(O)OC<sub>1-4</sub>alkyl.

30 In some embodiments of Formulas I-V, R is selected from the group consisting of -CO<sub>2</sub>CH<sub>3</sub>, -CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CO<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, -CO<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CO<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CO<sub>2</sub>-CH<sub>2</sub>Ph, and -CO<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>.

In some embodiments of Formulas I-V, R<sub>2</sub> is selected from the group consisting hydrogen, alkyl, alkoxyalkylenyl, alkylaminoalkylenyl, and hydroxyalkylenyl.

35 In some embodiments of Formulas I-V, R<sub>2</sub> is selected from the group consisting hydrogen, alkyl, and alkoxyalkylenyl.

In some embodiments of Formulas I-V,  $R_2$  is selected from the group consisting of hydrogen,  $-CH_3$ ,  $-CH_2CH_3$ ,  $-CH_2CH_2CH_3$ ,  $-CH_2CH_2CH_2CH_3$ ,  $-CH_2OCH_3$ ,  $-CH_2OCH_2CH_3$ ,  $-CH_2CH_2OCH_3$ ,  $-CH_2NHCH_3$ ,  $-CH_2NHCH_2CH_3$ ,  $-CH_2CH_2NHCH_3$ ,  $-CH_2OH$ ,  $-CH_2CH_2OH$ , and  $-CH_2NHOCH_3$ .

5 In some embodiments of Formulas I-V,  $R_2$  is selected from the group consisting of hydrogen,  $-CH_3$ ,  $-CH_2CH_3$ ,  $-CH_2CH_2CH_3$ ,  $-CH_2CH_2CH_2CH_3$ ,  $-CH_2OCH_3$ ,  $-CH_2OCH_2CH_3$ , and  $-CH_2CH_2OCH_3$ .

In some embodiments of Formulas I-V,  $R_2$  is  $-CH_2NHC(O)CH_3$  or  $-CH_2NHC(O)cyclopropyl$ .

In some embodiments of Formulas I-V,  $R_5$  is hydrogen or alkyl.

10 In some embodiments of Formulas I-V,  $R_5$  is hydrogen,  $C_{1-8}$  alkyl, or  $-CH_2Ph$ .

In some embodiments of Formulas I-V,  $R_5$  is hydrogen or  $C_{1-4}$  alkyl.

In some embodiments of Formulas I-V,  $R_5$  is hydrogen.

In some embodiments of Formulas I-V,  $R_5$  is selected from the group consisting of hydrogen,  $-CH_3$ ,  $-CH_2CH_3$ ,  $-CH(CH_3)_2$ ,  $-CH_2CH_2CH_3$ ,  $-CH_2CH_2CH_2CH_3$ ,  $-CH_2CH(CH_3)_2$ ,  $-C(CH_3)_3$ ,  $-CH_2CH_2CH_2CH_2CH_3$ ,  $-CH_2CH_2CH(CH_3)_2$ , cyclopentyl, cyclohexyl,  $-CH_2(cyclopentyl)$ ,  $-CH_2(cyclohexyl)$ , and  $-CH_2CH_2-O-CH_3$ .

15 In some embodiments of Formulas I-V,  $R_5$  is selected from the group consisting of hydrogen, alkyl,  $-CH_2Ph$ ,  $-CH_2CH_2Ph$ ,  $-CH_2CH_2-O-Ph$ ,  $-CH_2CH_2-O-CH_2Ph$ , and  $-(CH_2)_{2-6}-O-(CH_2)_{1-6}Ph$ , wherein Ph can be either unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, alkyl, alkoxy, haloalkyl, and nitrile.

20 In some embodiments of Formulas I-V, W is a covalent bond or  $-O-$ .

In some embodiments of Figures I-V, W is a covalent bond.

In some embodiments of Formulas I-V, X is alkylene optionally interrupted by one or more  $-O-$  groups.

25 In some embodiments of Formulas I-V, X is a  $C_{2-12}$  alkylene optionally interrupted by one or more  $-O-$  groups.

In some embodiments of Formulas I-V, X is  $C_{2-8}$  alkylene.

In some embodiments of Formulas I-V, X is  $C_{2-6}$  alkylene.

30 In some embodiments of Formulas I-V, X is  $C_{2-5}$  alkylene.

In some embodiments of Formulas I-V, X is a  $C_{2-8}$  alkylene optionally interrupted by one or more  $-O-$  groups.

In some embodiments of Formulas I-V, X is selected from the group consisting of  $-CH_2CH_2-$ ,  $-CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$ ,  $-CH_2C(CH_3)_2-$ ,  $-CH_2C(CH_3)_2CH_2-$ ,  $-CH_2CH_2-O-CH_2CH_2-$ ,  $-CH_2CH_2-O-CH_2CH_2-O-CH_2CH_2-$ ,  $-(CH_2)_{2-4}-(OCH_2CH_2-)_{1-5}$ , and

$-(\text{CH}_2)_{2-6}-(\text{OCH}_2\text{CH}_2-)_{1-4}$ .

In some embodiments of Formulas I-V, Z is  $-\text{C}_{1-5}\text{alkylene-arylene-C}_{1-5}\text{alkylene-}$  or  $-\text{C}_{1-5}\text{alkylene-heteroarylene-C}_{1-5}\text{alkylene-}$ .

In some embodiments of Formulas I-V, Z is  $-\text{CH}_2\text{-phenylene-CH}_2\text{-}$ .

5 In some embodiments of Formulas I-V,  $\text{R}_1$  is  $-\text{X-N(H)-C(=NH)-NH}_2$ .

In some embodiments of Formulas I-V, X is alkylene optionally interrupted by one or more  $-\text{O-}$  groups;  $\text{R}_2$  is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl; and  $\text{R}_5$  is hydrogen.

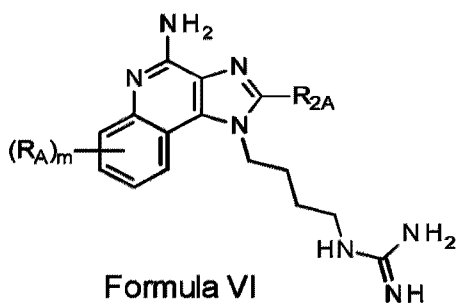
10 In some embodiments of Formulas II-V, X is alkylene optionally interrupted by one or more  $-\text{O-}$  groups;  $\text{R}_2$  is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl;  $\text{R}_5$  is hydrogen; n is 0 or 1; R is selected from the group consisting of halogen, hydroxyl, alkyl, alkoxy, and haloalkyl; and  $\text{R}_5$  is hydrogen.

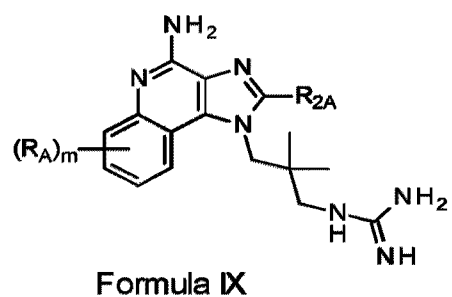
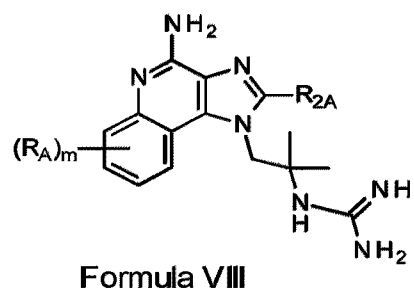
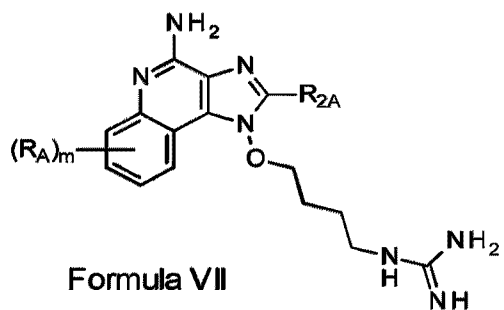
15 In some embodiments of Formulas II-V, W is a covalent bond; X is  $-\text{CH}_2\text{-}$ ; Q is selected from the group consisting of a covalent bond,  $-\text{CH}_2\text{-}$ ,  $-\text{CH}_2\text{CH}_2\text{-}$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{-}$ , and  $-\text{CH}_2\text{-O-CH}_2\text{-}$ ;  $\text{R}_2$  is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl; n is 0 or 1; R is selected from the group consisting of halogen, hydroxyl, alkyl, alkoxy, and haloalkyl.

In some embodiments of Formulas I-V, X is alkylene; and  $\text{R}_2$  is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

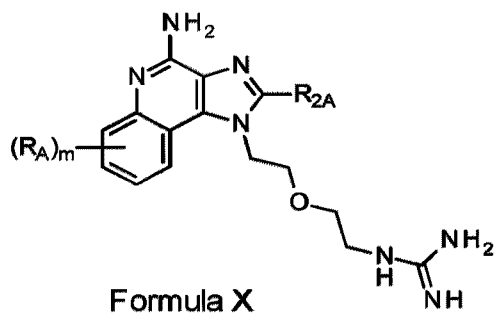
20 In some embodiments of Formulas I-V, the compound is present in the form of a salt. The salt is typically a pharmaceutically acceptable salt. Most commonly, the salt is a hydrochloride or dihydrochloride salt.

This disclosure also provides compounds of the following Formulas VI-XII:

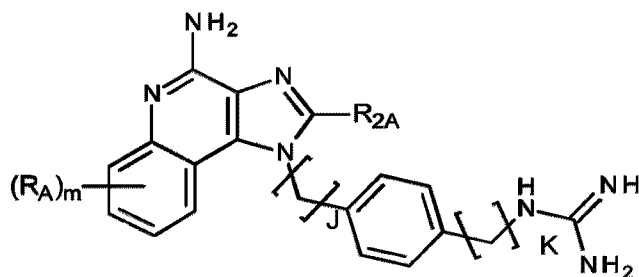




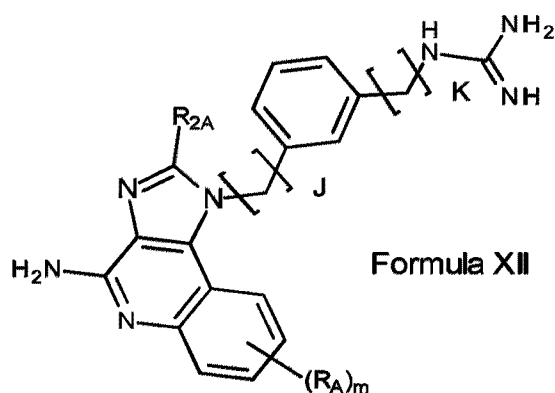
5







Formula XI



Formula XII

5

wherein  $R_A$ ,  $R_{2A}$ ,  $m$ ,  $J$ , and  $K$  are defined for Formulas VI-XII below; and pharmaceutically acceptable salts thereof.

For the compounds of Formulas VI-XII:

$m$  is an integer from 0 to 2;

10  $J$  is an integer from 1 to 5;

$K$  is an integer from 0 to 7;

$R_A$  is selected from the group consisting of halogen, hydroxyl, alkyl, alkoxy, haloalkyl, -C(O)-O-alkyl, -C(O)-O-CH<sub>2</sub>Ph, -C(O)-O-aryl, amino, alkylamino, and dialkylamino, aryl, arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, heteroarylalkyleneoxy, and heteroaryloxy, wherein the alkyl, aryl, arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, heteroarylalkyleneoxy, and heteroaryloxy groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, haloalkyl, hydroxyl, hydroxyalkylenyl, alkoxyalkylenyl, arylalkyleneoxy, nitrile, amino, alkylamino, and dialkylamino;

20

$R_{2A}$  is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, -O-alkyl, hydroxyalkylenyl, alkoxyalkylenyl, alkylaminoalkylenyl, hydroxyl, -CH<sub>2</sub>-NH-O-alkyl, and -CH<sub>2</sub>NHC(O)-alkyl.

In some embodiments of Formulas VI-XII,  $R_A$  is selected from the group consisting of halogen, hydroxy, alkyl, alkoxy, haloalkyl, -C(O)-O-alkyl, -C(O)-O-CH<sub>2</sub>Ph, -C(O)-O-aryl, amino, alkylamino, and dialkylamino.

In some embodiments of Formulas VI-XII,  $R_A$  is selected from the group consisting of alkyl, aryl, arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, heteroarylalkyleneoxy, and heteroaryloxy, wherein the alkyl, aryl, arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, heteroarylalkyleneoxy, and heteroaryloxy groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, haloalkyl, hydroxy, hydroxyalkylenyl, alkoxyalkylenyl, arylalkyleneoxy, nitrile, amino, alkylamino, and dialkylamino.

In some embodiments of Formulas VI-XII,  $R_A$  is selected from the group consisting of aryl, arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, heteroarylalkyleneoxy, and heteroaryloxy.

In some embodiments of Formulas VI-XII,  $m$  is 0 or 1.

In some embodiments of Formulas VI-XII,  $m$  is 0.

In some embodiments of Formulas XI-XII,  $J$  is 1 and  $K$  is an integer from 0 to 4.

In some embodiments of Formulas XI-XII,  $K$  is 1 and  $J$  is an integer from 1 to 4.

In some embodiments of Formulas XI-XII,  $K$  is 1 and  $J$  is 1.

In some embodiments of Formulas VI-XII,  $R_{2A}$  is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, alkylaminoalkylenyl, and hydroxyalkylenyl.

In some embodiments of Formulas VI-XII,  $R_{2A}$  is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

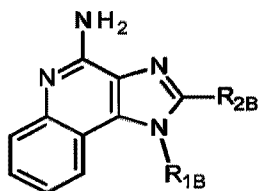
In some embodiments of Formulas VI-XII,  $R_{2A}$  is selected from the group consisting of hydrogen, -CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>OCH<sub>3</sub>, -CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, -CH<sub>2</sub>NHCH<sub>3</sub>, -CH<sub>2</sub>NHCH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>NHCH<sub>3</sub>, -CH<sub>2</sub>OH, -CH<sub>2</sub>CH<sub>2</sub>OH, and -CH<sub>2</sub>NHOCH<sub>3</sub>.

In some embodiments of Formulas VI-XII,  $R_{2A}$  is selected from the group consisting of hydrogen, -CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>OCH<sub>3</sub>, -CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, and -CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>.

In some embodiments of Formulas VI-XII,  $R_{2A}$  is -CH<sub>2</sub>NHC(O)CH<sub>3</sub> or -CH<sub>2</sub>NHC(O)cyclopropyl.

In some embodiments of Formulas VI-XII, the compound is present as a salt, typically a pharmaceutically acceptable salt. When a salt is used, it is most commonly a hydrochloride or dihydrochloride salt.

5 This disclosure also provides compounds of the following Formula XIII:



Formula XIII

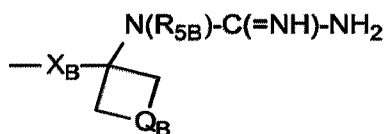
wherein R<sub>1B</sub>, and R<sub>2B</sub>, and are as defined below; as well as salts thereof, which are typically pharmaceutically acceptable salts.

10 For compounds and salts, such as pharmaceutically acceptable salts, of Formula XIII:

R<sub>1B</sub> is selected from the group consisting of

-X<sub>B</sub>-N(R<sub>5B</sub>)-C(=NH)-NH<sub>2</sub> ,

-Z<sub>B</sub>-N(R<sub>5B</sub>)-C(=NH)-NH<sub>2</sub> ; and



;

15 X<sub>B</sub> is selected from the group consisting of alkylene, alkenylene, and alkynylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted by one or more -O- groups;

Z<sub>B</sub> is selected from the group consisting of

-X<sub>B</sub>-arylene-X<sub>B</sub>-,

-X<sub>B</sub>-heteroarylene-X<sub>B</sub>-,

20 -X<sub>B</sub>-arylene-, and

-X<sub>B</sub>-heteroarylene-;

R<sub>2B</sub> is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, -O-alkyl, hydroxyalkylenyl, alkoxyalkylenyl, alkylaminoalkylenyl, hydroxyl, -CH<sub>2</sub>-NH-O-alkyl, and -CH<sub>2</sub>NHC(O)-alkyl;

25 R<sub>5B</sub> is selected from the group consisting of hydrogen, alkyl, arylalkylenyl, alkoxyalkylenyl, aryloxyalkylenyl, benzyloxyalkylenyl, aryl-(CH<sub>2</sub>)<sub>2-6</sub>-O-alkylenyl, and cycloalkylalkylenyl, wherein any of the alkyl, arylalkylenyl, alkoxyalkylenyl, aryloxyalkylenyl, benzyloxyalkylenyl, aryl-(CH<sub>2</sub>)<sub>2-6</sub>-O-alkylenyl, and cycloalkylalkylenyl groups can be either unsubstituted or substituted with one or

more substituents independently selected from the group consisting of halogen, hydroxyl, alkoxy, alkyl, haloalkyl, and nitrile;

$Q_B$  is selected from the group consisting of a bond,  $-CH_2-$ ,  $-CH_2CH_2-$ ,  $-CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2CH_2CH_2-$ ,  $-CH_2-O-CH_2-$ , and  $-OCH_2-$ .

- 5 In some embodiments of Formula XIII,  $R_{2B}$  is selected from the group consisting hydrogen, alkyl, alkoxyalkylenyl, alkylaminoalkylenyl, and hydroxyalkylenyl.

In some embodiments of Formula XIII,  $R_{2B}$  is selected from the group consisting hydrogen, alkyl, and alkoxyalkylenyl.

- 10 In some embodiments of Formula XIII,  $R_{2B}$  is selected from the group consisting of hydrogen,  $-CH_3$ ,  $-CH_2CH_3$ ,  $-CH_2CH_2CH_3$ ,  $-CH_2CH_2CH_2CH_3$ ,  $-CH_2OCH_3$ ,  $-CH_2OCH_2CH_3$ ,  $-CH_2CH_2OCH_3$ ,  $-CH_2NHCH_3$ ,  $-CH_2NHCH_2CH_3$ ,  $-CH_2CH_2NHCH_3$ ,  $-CH_2OH$ ,  $-CH_2CH_2OH$ , and  $-CH_2NHOCH_3$ .

- 15 In some embodiments of Formula XIII,  $R_{2B}$  is selected from the group consisting of hydrogen,  $-CH_3$ ,  $-CH_2CH_3$ ,  $-CH_2CH_2CH_3$ ,  $-CH_2CH_2CH_2CH_3$ ,  $-CH_2OCH_3$ ,  $-CH_2OCH_2CH_3$ , and  $-CH_2CH_2OCH_3$ .

In some embodiments of Formula XIII,  $R_{2B}$  is  $-CH_2NHC(O)CH_3$  or  $-CH_2NHC(O)cyclopropyl$ .

In some embodiments of Formula XIII,  $X_B$  is alkylene optionally interrupted by one or more -O- groups.

- 20 In some embodiments of Formula XIII,  $X_B$  is a  $C_{2-12}$ alkylene optionally interrupted by one or more -O- groups.

In some embodiments of Formula XIII,  $X_B$  is a  $C_{2-8}$ alkylene optionally interrupted by one or more -O- groups.

In some embodiments of Formula XIII,  $X_B$  is  $C_{2-8}$ alkylene.

- 25 In some embodiments of Formula XIII,  $X_B$  is  $C_{2-6}$ alkylene.

In some embodiments of Formula XIII,  $X_B$  is  $C_{2-5}$ alkylene.

In some embodiments of Formula XIII,  $X_B$  is selected from the group consisting of  $-CH_2CH_2-$ ,  $-CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$ ,  $-CH_2C(CH_3)_2-$ ,  $-CH_2C(CH_3)_2CH_2-$ ,  $-CH_2CH_2-O-CH_2CH_2-$ ,  $-CH_2CH_2-O-CH_2CH_2-O-CH_2CH_2-$ ,  $-(CH_2)_{2-4}-(OCH_2CH_2-)_{1-5}$ , and  $-(CH_2)_{2-6}-(OCH_2CH_2-)_{1-4}$ .

- 30 In some embodiments of Formula XIII,  $Z_B$  is  $-C_{1-5}$ alkylene-arylene- $C_{1-5}$ alkylene- or  $-C_{1-5}$ alkylene-heteroarylene- $C_{1-5}$ alkylene-.

- 35 In some embodiments of Formula XIII,  $Z_B$  is  $-CH_2$ -phenylene- $CH_2-$ .

In some embodiments of Formula XIII,  $R_{5B}$  is hydrogen or alkyl.

In some embodiments of Formula XIII,  $R_{5B}$  is hydrogen,  $C_{1-8}$ alkyl, or  $-CH_2Ph$ .

In some embodiments of Formula XIII,  $R_{5B}$  is hydrogen or  $C_{1-4}$ alkyl.

In some embodiments of Formula XIII,  $R_{5B}$  is hydrogen.

In some embodiments of Formula XIII,  $R_{5B}$  is selected from the group consisting of hydrogen, -CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>3</sub>, -CH(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>,  
 5 -CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, -C(CH<sub>3</sub>)<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, cyclopentyl, cyclohexyl, -CH<sub>2</sub>(cyclopentyl), -CH<sub>2</sub>(cyclohexyl), and -CH<sub>2</sub>CH<sub>2</sub>-O-CH<sub>3</sub>.

In some embodiments of Formula XIII,  $R_{5B}$  is selected from the group consisting of hydrogen, alkyl, -CH<sub>2</sub>Ph, -CH<sub>2</sub>CH<sub>2</sub>Ph, -CH<sub>2</sub>CH<sub>2</sub>-O-Ph, -CH<sub>2</sub>CH<sub>2</sub>-O-CH<sub>2</sub>Ph,  
 10 and -(CH<sub>2</sub>)<sub>2-6</sub>-O-(CH<sub>2</sub>)<sub>1-6</sub>Ph, wherein Ph can be either unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, alkyl, alkoxy, and, nitrile.

In some embodiments of Formula XIII,  $R_{1B}$  is -X<sub>B</sub>-N(H)-C(=NH)-NH<sub>2</sub>.

In some embodiments of Formula XIII, X<sub>B</sub> is alkylene optionally interrupted by one or more -O- groups;  $R_{2B}$  is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl;  $R_{5B}$  is  
 15 hydrogen.

In some embodiments of Formula XIII, X<sub>B</sub> is alkylene;  $R_{2B}$  is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

In some embodiments of Formula XIII, X<sub>B</sub> is -CH<sub>2</sub>-; Q<sub>B</sub> is selected from the group consisting of a covalent bond, -CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, and -CH<sub>2</sub>-O-CH<sub>2</sub>-;  $R_{2B}$  is selected from the  
 20 group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

In some embodiments of Formula XIII, the compound is present in the form of a salt. The salt is typically a pharmaceutically acceptable salt. Most commonly, the salt is a hydrochloride or dihydrochloride salt.

The present disclosure provides a method of inducing cytokine biosynthesis in an animal  
 25 comprising administering to the animal an effective amount of a compound or salt to the animal selected from the group consisting of any one of the above embodiments of Formulas I-XIII.

The present disclosure provides a method of inducing IFN-alpha biosynthesis in an animal by administering to the animal an effective amount of a compound or salt selected from any one of the above embodiments of Formulas I-XIII.

30 The present disclosure provides a method of inducing IFN-gamma biosynthesis in an animal by administering to the animal an effective amount of a compound or salt selected from any one of the above embodiments of Formulas I-XIII.

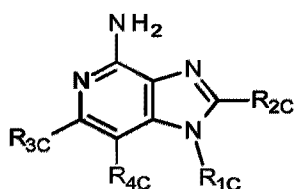
The present disclosure provides a method of inducing TNF-alpha biosynthesis in an animal by administering to the animal an effective amount of a compound or salt selected from any one of the  
 35 above embodiments of Formulas I-XIII.

The present disclosure provides a method of inducing IP-10 biosynthesis in an animal by administering to the animal an effective amount of a compound or salt selected from any one of the above embodiments of Formulas I-XIII.

The present disclosure also provides a method of treating a viral disease in an animal by administering an effective amount of a compound or salt to the animal selected from any one of the above embodiments of Formulas I-XIII.

The present disclosure also provides a method of treating a neoplastic disease in an animal by administering an effective amount of a compound or salt to the animal selected from any one of the above embodiments of Formulas I-XIII.

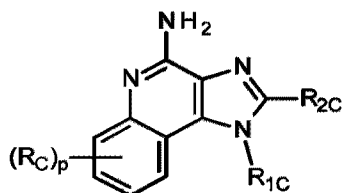
This disclosure provides compounds of the following Formula XIV:



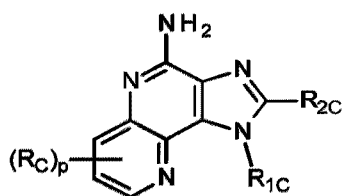
Formula XIV

wherein  $R_{1C}$ ,  $R_{2C}$ ,  $R_{3C}$ , and  $R_{4C}$  are as defined below; and pharmaceutically acceptable salts thereof.

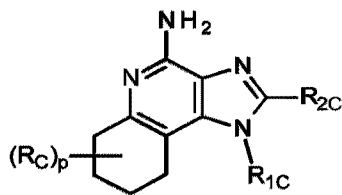
Examples of compounds of Formula XIV are more specifically defined by the following Formulas XV-XVIII:



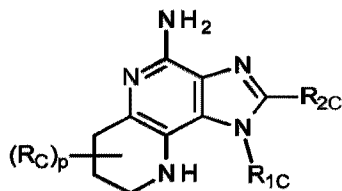
Formula XV



Formula XVI



Formula XVII



Formula XVIII

wherein  $R_C$ ,  $R_{1C}$ ,  $R_{2C}$ , and  $p$  are as defined below; and pharmaceutically acceptable salts thereof.

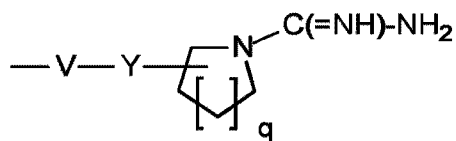
For compounds and salts, such as pharmaceutically acceptable salts, of Formula XIV,  $R_{3C}$  and  $R_{4C}$  are taken together to form a fused benzene ring, a fused pyridine ring, a fused cyclohexene ring, or a fused tetrahydropyridine ring; wherein the fused benzene ring, fused pyridine ring, fused cyclohexene ring, or fused tetrahydropyridine ring is either unsubstituted or substituted by one or more  $R_C$  groups.

For compounds and salts such as pharmaceutically acceptable salts, of Formulas XIV-XVIII:

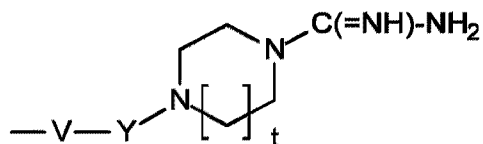
$R_C$  is selected from the group consisting of halogen, hydroxyl, alkyl, alkoxy, haloalkyl, -C(O)-O-alkyl, -C(O)-OCH<sub>2</sub>Ph, -C(O)-O-aryl, amino, alkylamino, and dialkylamino, aryl, arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, heteroarylalkyleneoxy, and heteroaryloxy, wherein the alkyl, aryl, arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, heteroarylalkyleneoxy, and heteroaryloxy groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, haloalkyl, hydroxyl, hydroxyalkylenyl, alkoxyalkylenyl, arylalkyleneoxy, nitrile, amino, alkylamino, and dialkylamino;

$p$  is an integer from 0 to 2;

$R_{1C}$  is selected from the group consisting of



, and



V is selected from the group consisting of a covalent bond, -O-, and -NH-;

Y is selected from the group consisting of alkylene, alkenylene, and alkynylene, wherein any of the alkylene, alkenylene, and alkynylene groups can be optionally interrupted by one or more -O- groups;

$R_{2C}$  is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, -O-alkyl, hydroxyalkylenyl, alkoxyalkylenyl, alkylaminoalkylenyl, hydroxyl, -CH<sub>2</sub>-NH-O-alkyl, and -CH<sub>2</sub>NHC(O)-alkyl;

q is an integer from 0 to 5; and

t is an integer from 1 to 4.

In some embodiments of Formula XIV,  $R_{3C}$  and  $R_{4C}$  are taken together to form a fused benzene ring, a fused pyridine ring, or a fused cyclohexene ring.

In some embodiments of Formula XIV,  $R_{3C}$  and  $R_{4C}$  are taken together to form a fused benzene ring or a fused cyclohexene ring.

In some embodiments of Formula XIV,  $R_{3C}$  and  $R_{4C}$  are taken together to form a fused benzene ring or a fused pyridine ring.

In some embodiments of Formula XIV,  $R_{3C}$  and  $R_{4C}$  are taken together to form a fused benzene ring.

In some embodiments of Formula XIV,  $R_{3C}$  and  $R_{4C}$  are taken together to form a fused benzene ring, a fused pyridine ring, or a fused cyclohexene ring; wherein the fused benzene ring, fused pyridine ring, or fused cyclohexene ring can be either unsubstituted or substituted by one and only one  $R_C$  group.

In some embodiments of Formula XIV,  $R_{3C}$  and  $R_{4C}$  are taken together to form a fused benzene ring or a fused pyridine ring; wherein the fused benzene ring or fused pyridine ring can be either unsubstituted or substituted by one and only one  $R_C$  group.

In some embodiments of Formulas XIV,  $R_C$  is selected from the group consisting of halogen, hydroxy, alkyl, alkoxy, haloalkyl, -C(O)-O-alkyl, -C(O)-O-CH<sub>2</sub>Ph, -C(O)-O-aryl, amino, alkylamino, and dialkylamino.

In some embodiments of Formulas XIV,  $R_C$  is selected from the group consisting of alkyl, aryl, arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, heteroarylalkyleneoxy, and heteroaryloxy, wherein the alkyl, aryl, arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, heteroarylalkyleneoxy, and heteroaryloxy groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl,



alkoxy, halogen, haloalkyl, hydroxy, hydroxyalkylenyl, alkoxyalkylenyl, arylalkyleneoxy, nitrile, amino, alkylamino, and dialkylamino.

In some embodiments of Formulas XIV,  $R_C$  is selected from the group consisting of aryl, arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, heteroarylalkyleneoxy, and heteroaryloxy.

In some embodiments of Formulas XV-XVIII,  $p$  is 0 or 1.

In some embodiments of Formulas XV-XVIII,  $p$  is 0.

In some embodiments of Formulas XIV-XVIII,  $V$  is a covalent bond and  $Y$  is alkylene optionally interrupted by one or more -O- groups.

In some embodiments of Formulas XIV-XVIII, -V-Y- is -O-C<sub>1-7</sub>alkylene- or -C<sub>1-8</sub>alkylene-.

In some embodiments of Formulas XIV-XVIII, -V-Y- is -CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, or -CH<sub>2</sub>CH<sub>2</sub>-O-CH<sub>2</sub>CH<sub>2</sub>-.

In some embodiments of Formulas XIV-XVIII,  $R_{2C}$  is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, alkylaminoalkylenyl, and hydroxyalkylenyl.

In some embodiments of Formulas XIV-XVIII,  $R_{2C}$  is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

In some embodiments of Formulas XIV-XVIII,  $R_{2C}$  is selected from the group consisting of hydrogen, -CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>OCH<sub>3</sub>, -CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, -CH<sub>2</sub>NHCH<sub>3</sub>, -CH<sub>2</sub>NHCH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>NHCH<sub>3</sub>, -CH<sub>2</sub>OH, -CH<sub>2</sub>CH<sub>2</sub>OH, and -CH<sub>2</sub>NHOCH<sub>3</sub>.

In some embodiments of Formulas XIV-XVIII,  $R_{2C}$  is selected from the group consisting of hydrogen, -CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>OCH<sub>3</sub>, -CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, and -CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>.

In some embodiments of Formulas XIV-XVIII,  $q$  is an integer from 1 to 4.

In some embodiments of Formulas XIV-XVIII,  $q$  is 2.

In some embodiments of Formulas XIV-XVIII,  $t$  is 1.

In some embodiments of Formulas XIV-XVIII,  $V$  is selected from the group consisting of a covalent bond and -O-;  $Y$  is alkylene optionally interrupted by one or more -O- groups;  $p$  is 0;  $q$  is an integer from 1 to 2;  $t$  is 1;  $R_{2C}$  is selected from the group consisting of hydrogen, -CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>OCH<sub>3</sub>, -CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, and -CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>.

In some embodiments of Formulas XIV-XVIII, the compound is present in the form of a salt. The salt is typically a pharmaceutically acceptable salt. Most commonly, the salt is a hydrochloride or dihydrochloride salt.

The disclosure also provides a method of inducing cytokine biosynthesis in an animal by administering to the animal an effective amount of a compound or salt selected from the group consisting of any one of the above embodiments of Formula XIV, Formula XV, Formula XVI, Formula XVII, and Formula XVIII.

5 The disclosure also provides a method of inducing cytokine biosynthesis in an animal by administering to the animal an effective amount of a compound or salt selected from the group consisting of any one of the above embodiments of Formula XIV, Formula XV, Formula XVI, Formula XVII, and Formula XVIII; wherein V is a covalent bond, Y is alkylene optionally interrupted by one or more -O- groups, q is 1 or 2, t is 1, and R<sub>2c</sub> is selected from the group consisting of  
10 hydrogen, alkyl and alkoxyalkylenyl.

The disclosure also provides a method of inducing IFN-alpha biosynthesis in an animal by administering to the animal an effective amount of a compound or salt selected from any one of the above embodiments of Formula XIV, Formula XV, Formula XVI, Formula XVII, or Formula XVIII.

15 The disclosure also provides a method of inducing IFN-gamma biosynthesis in an animal by administering to the animal an effective amount of a compound or salt selected from any one of the above embodiments of Formula XIV, Formula XV, Formula XVI, Formula XVII, or Formula XVIII.

The disclosure also provides a method of inducing TNF-alpha biosynthesis in an animal by administering to the animal an effective amount of a compound or salt selected from any one of the above embodiments of Formula XIV, Formula XV, Formula XVI, Formula XVII, or Formula XVIII.

20 The disclosure also provides a method of inducing IP-10 biosynthesis in an animal by administering to the animal an effective amount of a compound or salt selected from any one of the above embodiments of Formula XIV, Formula XV, Formula XVI, Formula XVII, or Formula XVIII.

The disclosure also provides a method for treating a viral disease in an animal by administering to the animal an effective amount of a compound or salt selected from the group  
25 consisting of any one of the above embodiments of Formula XIV, Formula XV, Formula XVI, Formula XVII, and Formula XVIII.

The disclosure also provides a method for treating a neoplastic disease in an animal by administering to the animal an effective amount of a compound or salt selected from the group consisting of any one of the above embodiments of Formula XIV, Formula XV, Formula XVI,  
30 Formula XVII, and Formula XVIII.

The compounds of the disclosure may be synthesized by synthetic routes that include processes analogous to those well known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Sigma-Aldrich Company (St. Louis, MO) or are readily prepared using methods well known to those  
35 of ordinary skill in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, Reagents for Organic Synthesis, v. 1-26, Wiley, New York; Alan R. Katritzky, Otto Meth-Cohn, Charles W. Rees, Comprehensive Organic Functional Group Transformations, v 1-6, Pergamon

Press, Oxford, England, (1995); Barry M. Trost and Ian Fleming, *Comprehensive Organic Synthesis*, v. 1-8, Pergamon Press, Oxford, England, (1991); or Beilsteins Handbuch der Organischen Chemie, 4, Aufl. Ed. Springer-Verlag, Berlin, Germany, including supplements (also available via the Beilstein online database)).

Specifically, the compounds of the disclosure can be prepared using any one of several standard methods for preparing guanidine containing compounds. Several standard methods are known to those of ordinary skill in the art for converting amino groups to guanidines (see Katritzky, *ARKIVOC*, 2005, *iv*, pages 49-87; Zhang, *Chem Commun*, 2015, *51*, pages 254-265; Bernatowicz, *Journal of Organic Chemistry*, 1992, *57*, pages 2497-2502). For example, amine compounds (such as those of Formulas XIX-XXXI) can be reacted with pyrazole-1-carboxamidinium hydrochloride (CAS Number 4023-02-3), or benzotriazole-1-carboxamidinium tosylate (CAS Number 163853-10-9), or triazole-1-carboxamidinium hydrochloride (CAS Number 19503-26-5) to provide the compounds of the disclosure. As a further example, amine compounds (such as those of Formulas XIX-XXXI) can be reacted with N,N'-bis-BOC-pyrazole-1-carboxamidinium (CAS Number 152120-54-2) to form a di-Boc protected guanidine. The BOC protecting groups can be subsequently be removed using standard techniques such as treatment with acid to provide the compounds of the disclosure (see Bernatowicz, *Tetrahedron Letters*, 1993, *34*, pages 3389-3392).

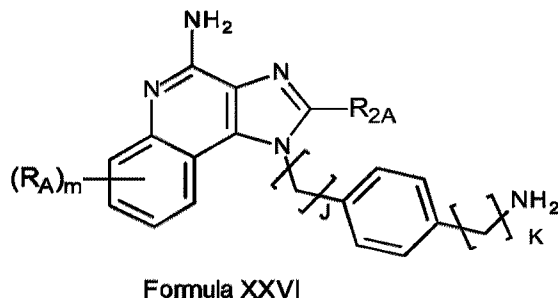
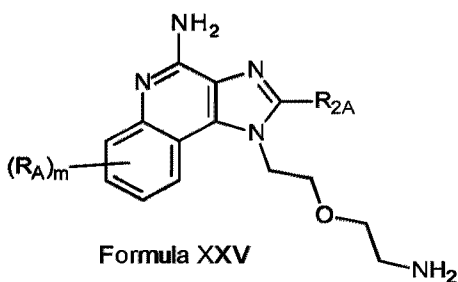
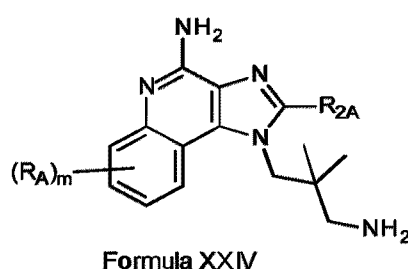
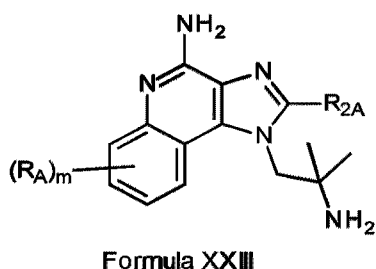
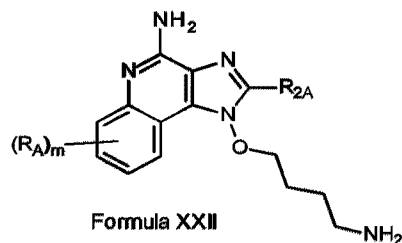
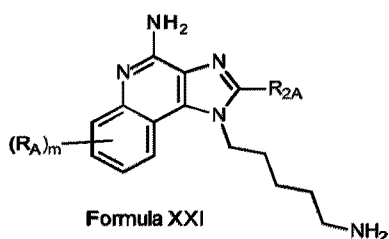
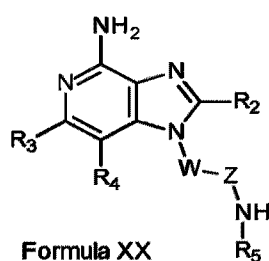
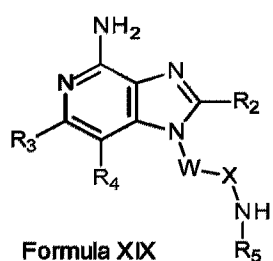
General synthetic methods that are useful for the preparation of the intermediate amines of Formulas XIX-XXXI have been previously described and many of the intermediate amine compounds are known compounds. References for the preparation of the intermediate amine compounds include U.S. Patent Number 7,799,800 (Wightman, see Example 1 Parts A-J), U.S. Patent Number 7,115,622 (Crooks, see Reaction Schemes II,III,V and Examples 1-3,5, 67-69), U.S. Patent Number 7,579,359 (Krepski, see Reaction Schemes VI and VII), U.S. Patent Application 2013/0230578 (Wightman, see Example 1 Parts A-D), U.S Patent Number 7,163,947 (Griesgraber, see Scheme VII and Example 14 Parts A-F), U.S. Patent Number 6,069,149 (Nanba, see Examples 5, 10, 12, 17, 20-21, 28, 33, 39), U.S. Patent Number 8,728,486 (David, see Compound 7c and 7d), U.S. Patent Number 7,968,563 (Kshirsagar), U.S. Patent Number 8,088,790 (Kshirsagar, see Scheme IV, Example 8 Parts A-D, Example 56 Parts A-D, Example 62 Parts A-E), U.S. Patent Number 8,168,802 (Hays), U.S. Patent Number 9,034,336 (Ferguson), U.S. Patent Number 7,884,207 (Stoermer, see Scheme VII, Example 286 Parts A-B, Example 339 Parts A-D).

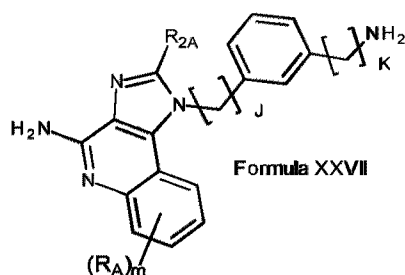
Some examples of intermediate amine compounds that can be converted into the guanidine compounds of the disclosure are shown in Formulas XIX-XXXI, wherein R<sub>2</sub>, R<sub>2A</sub>, R<sub>2B</sub>, R<sub>2C</sub>, R<sub>3</sub>, R<sub>3C</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>5B</sub>, R<sub>4C</sub>, R<sub>A</sub>, R<sub>C</sub>, V, W, X, X<sub>B</sub>, Y, Z, Z<sub>B</sub>, m, J, K, q can be as defined in any of the embodiments above.

In the preparation of the compounds of the disclosure it is understood by one of ordinary skill in the art that it may be necessary to protect a particular functional group while reacting other functional groups of an intermediate compound. The need for such protection will vary depending on

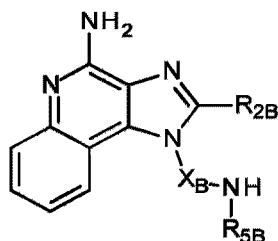
the nature of the particular functional group and the conditions of the particular reaction step. A review of reactions for protecting and deprotecting functional groups can be found in T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, USA, 1991.

Conventional methods and techniques of separation and purification can be used to isolate the IRM compounds used in the formulations of the disclosure. Such techniques may include, for example, all types of chromatography (high performance liquid chromatography (HPLC), column chromatography using common absorbents such as silica gel, and thin layer chromatography), recrystallization, and differential (i.e., liquid-liquid) extraction techniques.

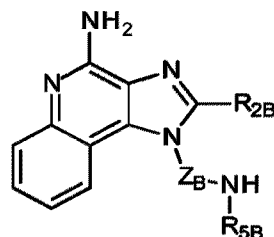




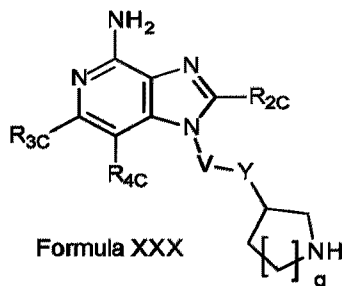
Formula XXVII



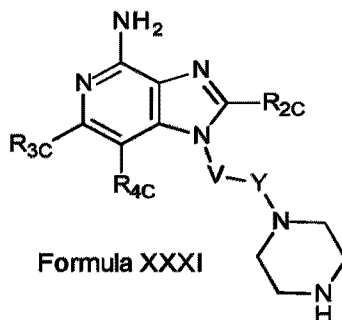
Formula XXVIII



Formula XXIX



Formula XXX



Formula XXXI

5

It is understood that for Formulas I-V and XIII, when “Q” or “Q<sub>B</sub>” is a covalent bond the resulting ring that is formed is a cyclopropane ring; when “Q is -CH<sub>2</sub>-” the resulting ring that is formed is a cyclobutane ring; when “Q is -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-” the resulting ring that is formed is a cyclohexane ring; and when “Q is -CH<sub>2</sub>OCH<sub>2</sub>-” the resulting ring that is formed is a tetrahydropyran ring.

10

When a group (or substituent or variable) is present more than once in any Formula described herein, each group (or substituent or variable) is independently selected, whether explicitly stated or not. For example, for a Formula containing “-X-arylene-X-” each “X” group is independently selected.

15

For simplicity and convenience, it is understood that some of the compounds of the disclosure may be drawn in a certain isomeric form, but in fact all stereoisomers [i.e. configurational isomers (e.g. E,Z isomers), conformational isomers (e.g. rotational isomers), diastereomers, enantiomers] are expressly included within the scope of this disclosure (whether explicitly drawn or not).

Specifically, it is understood that for compounds of Formulas I-XVIII, all stereoisomers [i.e. configurational isomers (e.g. E,Z isomers), conformational isomers (e.g. rotational isomers), diastereomers, enantiomers] are expressly included (whether explicitly drawn or not).

Compounds or salts of the present disclosure may exist in different tautomeric forms, and it is understood that all such forms are expressly included within the scope of this disclosure. Specifically, it is understood that for compounds of Formulas I-XVIII, all tautomers are expressly included (whether explicitly drawn or not).

Prodrugs of the disclosed compounds can also be prepared by attaching to the compounds a functional group that can be cleaved under physiological conditions. Typically a cleavable functional group will be cleaved in vivo by various mechanisms (such as through a chemical (e.g., hydrolysis) or enzymatic transformation) to yield a compound of the disclosure. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella. "Prodrugs as Novel Delivery Systems", vol. 14 of the ACS Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For any of the compounds of Formula I presented herein, each one of the variables R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, Q, W, X, Z in any of the Formula I embodiments can be combined with any one or more of the other variables in any of the Formula I embodiments, as would be understood by one of ordinary skill in the art. Each of the resulting combinations of variables is also an embodiment of the disclosure.

For any of the compounds of Formula II-V presented herein, each one of the variables R, R<sub>1</sub>, R<sub>2</sub>, R<sub>5</sub>, n, Q, W, X, Z in any of the Formula II-V embodiments can be combined with any one or more of the other variables in any of the Formula II-V embodiments, as would be understood by one of ordinary skill in the art. Each of the resulting combinations of variables is also an embodiment of the disclosure.

For any of the compounds of Formula VI-XII presented herein, each one of the variables R<sub>A</sub>, R<sub>2A</sub>, m, J, K in any of the Formula VI-XII embodiments can be combined with any one or more of the other variables in any of the Formula VI-XII embodiments, as would be understood by one of ordinary skill in the art. Each of the resulting combinations of variables is also an embodiment of the disclosure.

For any of the compounds of Formula XIII presented herein, each one of the variables R<sub>1B</sub>, R<sub>2B</sub>, R<sub>3B</sub>, X<sub>B</sub>, Z<sub>B</sub>, Q<sub>B</sub> in any of the Formula XIII embodiments can be combined with any one or more of the other variables in any of the Formula XIII embodiments, as would be understood by one of ordinary skill in the art. Each of the resulting combinations of variables is also an embodiment of the disclosure.

For any of the compounds of Formula XIV presented herein, each one of the variables R<sub>C</sub>, R<sub>1C</sub>, R<sub>2C</sub>, R<sub>3C</sub>, R<sub>4C</sub>, V, Y, q, t in any of the Formula XIV embodiments can be combined with any one or more of the other variables in any of the Formula XIV embodiments, as would be understood by

one of ordinary skill in the art. Each of the resulting combinations of variables is also an embodiment of the disclosure.

For any of the compounds of Formula XV-XVIII presented herein, each one of the variables  $R_C$ ,  $R_{1C}$ ,  $R_{2C}$ ,  $V$ ,  $Y$ ,  $p$ ,  $q$ ,  $t$  in any of the Formula XV-XVIII embodiments can be combined with any one or more of the other variables in any of the Formula XV-XVIII embodiments, as would be understood by one of ordinary skill in the art. Each of the resulting combinations of variables is also an embodiment of the disclosure.

#### Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the disclosure are also contemplated. Pharmaceutical compositions of the disclosure contain a therapeutically effective amount of a compound or salt of the disclosure (described herein) in combination with a pharmaceutically acceptable carrier.

The exact amount of compound or salt used in a pharmaceutical composition of the disclosure will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound or salt, the nature of the carrier, and the intended dosing regimen.

In some embodiments, the compositions of the disclosure will contain sufficient active ingredient or prodrug to provide a dose of about 100 nanograms per kilogram (ng/kg) to about 50 milligrams per kilogram (mg/kg), preferably about 10 micrograms per kilogram ( $\mu\text{g/kg}$ ) to about 5 mg/kg, of the compound or salt to the subject.

In some embodiments, the compositions of the disclosure will contain sufficient active ingredient or prodrug to provide a dose of for example, from about  $0.01 \text{ mg/m}^2$  to about  $5.0 \text{ mg/m}^2$ , computed according to the Dubois method, in which the body surface area of a subject ( $\text{m}^2$ ) is computed using the subject's body weight:  $\text{m}^2 = (\text{wt kg}^{0.425} \times \text{height cm}^{0.725}) \times 0.007184$ , although in some embodiments the methods may be performed by administering a compound or salt or composition in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound to provide a dose of from about  $0.1 \text{ mg/m}^2$  to about  $2.0 \text{ mg/m}^2$  to the subject, for example, a dose of from about  $0.4 \text{ mg/m}^2$  to about  $1.2 \text{ mg/m}^2$ .

A variety of dosage forms may be used to administer the compounds or salts of the disclosure to an animal. Dosage forms that can be used include, for example, tablets, lozenges, capsules, parenteral formulations, creams, ointments, topical gels, aerosol formulations, liquid formulations (e.g. aqueous formulation), transdermal patches, and the like. These dosage forms can be prepared with conventional pharmaceutically acceptable carriers and additives using conventional methods, which generally include the step of bringing the active ingredient into association with the carrier. A preferred dosage form has one or more of the compounds or salts of the disclosure dissolved in an aqueous formulation.

Compounds or salts disclosed herein can induce the production of certain cytokines in experiments performed according to the description of the Examples. These results indicate that the compounds or salts are useful for enhancing the immune response in a number of different ways, making them useful in the treatment of a variety of disorders.

5 The compounds or salts described herein can be administered as the single therapeutic agent in the treatment regimen, or the compounds or salts described herein may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, proteins, peptides, oligonucleotides, antibodies, etc.

10 Compounds or salts described herein can induce the production of cytokines (e.g., IFN-alpha, IFN-gamma, TNF-alpha, IP-10) in experiments performed according to the tests set forth below. These results indicate that the compounds or salts of the disclosure are useful for activating the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders. As such, the compounds or salts of the disclosure (compounds or salts of Formulas I-XVIII) are agonists of cytokine biosynthesis and production, particularly agonists of IFN-alpha, IFN-gamma, 15 TNF-alpha, and IP-10 cytokine biosynthesis and production.

It is believed that one way in which the compounds or salts of the disclosure (Formulas I-XVIII) induce cytokine production is through the activation of Toll-like receptors (TLRs) in the immune system, particularly TLR-7 and/or TLR-8, however other mechanisms may be involved. It is believed that in the immune system pathways (i.e. mechanisms) for cytokine induction, the 20 compounds or salts of the disclosure (Formulas I-XVIII) primarily act as agonists of TLR-7 and/or TLR-8, however other pathways or activities may be involved.

Administration of the compounds or salts described herein can induce the production of interferon-alpha (IFN-alpha), interferon-gamma (IFN-gamma), tumor necrosis factor-alpha (TNF-alpha), and IP-10 in cells. Cytokines whose biosynthesis can be induced by compounds or salts of the 25 disclosure include IFN-alpha, IFN-gamma, TNF-alpha, IP-10, and a variety of other cytokines. Among other effects, these cytokines can inhibit virus production and tumor cell growth, making the compounds or salts useful in the treatment of viral diseases and neoplastic diseases. Accordingly, this disclosure provides a method of inducing cytokine biosynthesis in an animal by administering an effective amount of a compound or salt of the disclosure to the animal. The animal to which the 30 compound or salt is administered for induction of cytokine production may have one or more diseases, disorders, or conditions described below, for example a viral disease or a neoplastic disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

35 In addition to the ability to induce the production of cytokines, compounds or salts described herein can affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds or salts may also



activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. In addition, the compounds or salts may cause proliferation and differentiation of B-lymphocytes.

Conditions for which compounds or salts or compositions identified herein may be used as treatment include, but are not limited to:

Viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpes virus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus, avian influenza), a paramyxovirus (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV), ebolavirus;

Neoplastic diseases such as bladder cancer, cervical dysplasia, actinic keratosis, basal cell carcinoma, cutaneous T-cell lymphoma, mycosis fungoides, Sezary Syndrome, HPV associated head and neck cancer (e.g., HPV positive oropharyngeal squamous cell carcinoma), Kaposi's sarcoma, melanoma, squamous cell carcinoma, renal cell carcinoma, acute myeloid leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, B-cell lymphoma, hairy cell leukemia, esophageal cancer, and other cancers;

$T_H2$ -mediated atopic diseases such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, and Ommen's syndrome;

Diseases associated with wound repair, such as, for example, inhibition of keloid formation and other types of scarring (e.g., enhancing wound healing, including chronic wounds);

Parasitic diseases including but not limited to malaria, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection.

In addition, a compound, salt, or composition described herein may be used as a vaccine adjuvant for use in conjunction with any material that increases either humoral and/or cell mediated immune responses, such as, for example, tumor antigens (e.g. MAGE-3, NY-ESO-1); live viral, bacterial, or parasitic immunogens; inactivated viral, protozoal, fungal, or bacterial immunogens; toxoids; toxins; polysaccharides; proteins; glycoproteins; peptides; cellular vaccines; DNA vaccines; autologous vaccines; recombinant proteins; and the like.

Examples of vaccines that can benefit from use of a compound, salt, or composition identified herein as a vaccine adjuvant include BCG vaccine, cholera vaccine, plague vaccine, typhoid vaccine, hepatitis A vaccine, hepatitis B vaccine, hepatitis C vaccine, influenza A vaccine, influenza B vaccine, parainfluenza vaccine, polio vaccine, rabies vaccine, measles vaccine, mumps vaccine, rubella vaccine, yellow fever vaccine, tetanus vaccine, diphtheria vaccine, hemophilus influenza b vaccine, tuberculosis vaccine, meningococcal and pneumococcal vaccines, adenovirus vaccine, HIV

vaccine, chicken pox vaccine, cytomegalovirus vaccine, dengue vaccine, feline leukemia vaccine, fowl plague vaccine, HSV-1 vaccine and HSV-2 vaccine, hog cholera vaccine, Japanese encephalitis vaccine, respiratory syncytial virus vaccine, rotavirus vaccine, papilloma virus vaccine, yellow fever vaccine, ebola virus vaccine.

5           Compounds, salts, or compositions identified herein may be particularly useful as vaccine adjuvants when used in conjunction with tumor antigens associated with colorectal cancer, head and neck cancer, breast cancer, lung cancer and melanoma.

10           Compounds, salts, or compositions identified herein may be particularly useful in individuals having compromised immune function. For example, compounds, salts, or compositions may be used for treating opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients, and HIV patients.

          One or more of the above diseases or types of diseases, for example, a viral disease or neoplastic disease may be treated in an animal in need thereof (having the disease) by administering a therapeutically effective amount of a compound, salt, or composition to the animal.

15           An animal may also be vaccinated by administering an effective amount of a compound, salt, or composition described herein as a vaccine adjuvant. In one embodiment, a method of vaccinating an animal includes administering an effective amount of a compound, salt, or composition described herein to the animal as a vaccine adjuvant. The vaccine adjuvant can be co-administered with the material that increases one or more of humoral and cell mediated immune responses by including each  
20           in the same composition. Alternatively, the vaccine adjuvant and the material that increases either humoral and/or cell mediated immune responses can be in separate compositions.

          Compounds or salts or compositions identified herein may be particularly useful when an effective amount is administered to an animal to treat bladder cancer, cervical dysplasia, actinic keratosis, basal cell carcinoma, genital warts, herpes virus infection, or cutaneous T-cell lymphoma.  
25           For these conditions, administration of the compound, salt, or composition of the disclosure is preferably topical (i.e. applied directly to the surface of a tumor, a lesion, a wart, or an infected tissue, etc.).

          In one embodiment an effective amount of compound, salt, or composition described herein, such as an aqueous composition, is administered into the bladder of an animal that has at least one  
30           tumor of the bladder by intravesical instillation (e.g., administration using a catheter).

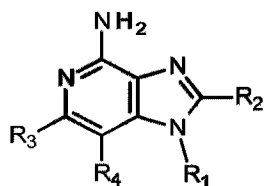
          An amount of a compound or salt effective to induce cytokine biosynthesis will typically cause one or more cell types, such as monocytes, macrophages, dendritic cells, and B-cells to produce an amount of one or more cytokines, such as, for example, IFN-alpha, IFN-gamma, TNF-alpha, and IP-10 that is increased (induced) over a background level of such cytokines. The precise dose will  
35           vary according to factors known in the art but is typically a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 µg/kg to about 5 mg/kg. In other embodiments, the amount can be , for example, from about 0.01 mg/m<sup>2</sup> to about 5.0 mg/m<sup>2</sup>, (computed according to the Dubois method as

described above) although in other embodiments the induction of cytokine biosynthesis may be performed by administering a compound or salt in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound or salt or composition to provide a dose from about 0.1 mg/m<sup>2</sup> to about 2.0 mg/m<sup>2</sup> to the subject, for example, a dose of from about 0.4 mg/m<sup>2</sup> to about 1.2 mg/m<sup>2</sup>.

A method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal can include administering an effective amount of at least one compound or salt described herein to the animal. An effective amount to treat or inhibit a viral infection can be an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but it is normally a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 µg/kg to about 5 mg/kg. An amount of a compound or salt effective to treat a neoplastic condition can be an amount that causes a reduction in tumor size or in the number of tumor foci. The precise amount will vary according to factors known in the art but is typically about 100 ng/kg to about 50 mg/kg, preferably about 10 µg/kg to about 5 mg/kg. In other embodiments, the amount is typically, for example, from about 0.01 mg/m<sup>2</sup> to about 5.0 mg/m<sup>2</sup>, (computed according to the Dubois method as described above) although in some embodiments the induction of cytokine biosynthesis may be performed by administering a compound or salt in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound or salt or composition to provide a dose from about 0.1 mg/m<sup>2</sup> to about 2.0 mg/m<sup>2</sup> to the subject, for example, a dose of from about 0.4 mg/m<sup>2</sup> to about 1.2 mg/m<sup>2</sup>.

## EMBODIMENTS

Embodiment 1 is a compound of Formula (I):



Formula I

wherein:

R<sub>3</sub> and R<sub>4</sub> are taken together to form a fused benzene ring, a fused pyridine ring, a fused cyclohexene ring, or a fused tetrahydropyridine ring; wherein the fused benzene ring, fused pyridine ring, fused

**R is selected from the group consisting of halogen, hydroxyl, alkyl, alkoxy, haloalkyl,**

**arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl,**

**arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl,**

substituted by one or more substituents independently selected from the group consisting of alkyl,

**amino, alkylamino, and dialkylamino;**

**-W-Z-N(R<sub>5</sub>)-C(=NH)-NH<sub>2</sub>, and**



**X is selected from the group consisting of alkylene, alkenylene, and alkynylene, wherein any of the alkylene, alkenylene, and alkynylene groups can be optionally interrupted by one or more -O- groups;**

**-X-arylene-X-**,

-X-arylene-, and

**-X-heteroarylene-;**

hydroxyalkylenyl, alkoxyalkylenyl, alkylaminoalkylenyl, hydroxyl, -CH<sub>2</sub>-NH-O-alkyl, and -

**R<sub>5</sub> is selected from the group consisting of hydrogen, alkyl, arylalkylenyl, alkoxyalkylenyl,**

more substituents independently selected from the group consisting of halogen, hydroxyl, alkoxy, alkyl, haloalkyl, and nitrile;

**-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>-O-CH<sub>2</sub>-, and -OCH<sub>2</sub>-;**

or a pharmaceutically acceptable salt thereof.

Embodiment 2 is the compound or salt of embodiment 1, wherein R<sub>3</sub> and R<sub>4</sub> are taken together to form a fused benzene ring, a fused pyridine ring, or a fused cyclohexene ring.

Embodiment 3 is the compound or salt of any one of the embodiments 1-2, wherein R<sub>3</sub> and R<sub>4</sub> are taken together to form a fused benzene ring, a fused pyridine ring, or a fused cyclohexene ring, and wherein the fused benzene ring, fused pyridine ring, or fused cyclohexene ring is either unsubstituted or substituted by one and only one R group.

Embodiment 4 is the compound or salt of any one of the embodiments 1-3, wherein R<sub>3</sub> and R<sub>4</sub> are taken together to form a fused benzene ring or a fused cyclohexene ring, and wherein the fused benzene ring, or fused cyclohexene ring is either unsubstituted or substituted by one and only one R group.

Embodiment 5 is the compound or salt of any one of the embodiments 1-3, wherein R<sub>3</sub> and R<sub>4</sub> are taken together to form a fused benzene ring or a fused pyridine ring, and wherein the fused benzene ring, or fused pyridine ring is either unsubstituted or substituted by one and only one R group.

Embodiment 6 is the compound or salt of any one of the embodiments 1-5, wherein R is selected from the group consisting of hydroxyl, F, Cl, -CF<sub>3</sub>, -OCF<sub>3</sub>, -O-C<sub>1-6</sub>alkyl, and -C<sub>1-6</sub>alkyl.

Embodiment 7 is the compound or salt of any one of the embodiments 1-5, wherein R is selected from the group consisting of hydroxyl, F, Cl, -CF<sub>3</sub>, -OCH<sub>3</sub>, -OCF<sub>3</sub>, -OCH<sub>2</sub>CH<sub>3</sub>, -OCH(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, and -CH(CH<sub>3</sub>)<sub>2</sub>.

Embodiment 8 is the compound or salt of any one of the embodiments 1-5, wherein R is -C(O)OC<sub>1-4</sub> alkyl.

Embodiment 9 is the compound or salt of any one of the embodiments 1-5, wherein R is selected from the group consisting of

-CO<sub>2</sub>CH<sub>3</sub>, -CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CO<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, -CO<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CO<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CO<sub>2</sub>-CH<sub>2</sub>Ph, and -CO<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>.

Embodiment 10 is the compound or salt of any one of the embodiments 1-9, wherein R<sub>5</sub> is hydrogen, alkyl, or -CH<sub>2</sub>Ph.

Embodiment 11 is the compound or salt of any one of the embodiments 1-10, wherein R<sub>5</sub> is hydrogen, C<sub>1-8</sub> alkyl, or -CH<sub>2</sub>Ph.

Embodiment 12 is the compound or salt of any one of the embodiments 1-11, wherein R<sub>5</sub> is hydrogen or C<sub>1-4</sub> alkyl.

Embodiment 13 is the compound or salt of any one of the embodiments 1-9, wherein R<sub>5</sub> is selected from the group consisting of hydrogen, -CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>3</sub>, -CH(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, -C(CH<sub>3</sub>)<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, cyclopentyl, cyclohexyl, -CH<sub>2</sub>(cyclopentyl), -CH<sub>2</sub>(cyclohexyl), and -CH<sub>2</sub>CH<sub>2</sub>-O-CH<sub>3</sub>.

Embodiment 14 is the compound or salt of any one of the embodiments 1-9, wherein  $R_5$  is selected from the group consisting of hydrogen, alkyl,  $-\text{CH}_2\text{Ph}$ ,  $-\text{CH}_2\text{CH}_2\text{Ph}$ ,  $-\text{CH}_2\text{CH}_2-\text{O}-\text{Ph}$ ,  $-\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_2\text{Ph}$ , and  $-(\text{CH}_2)_{2-6}-\text{O}-(\text{CH}_2)_{1-6}\text{Ph}$ , wherein Ph can be either unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, alkyl, alkoxy, haloalkyl, and nitrile.

Embodiment 15 is the compound or salt of any one of the embodiments 1-14, wherein  $R_1$  is selected from the group consisting of  $-\text{W}-\text{X}-\text{N}(\text{H})-\text{C}(=\text{NH})-\text{NH}_2$ , and  $-\text{W}-\text{Z}-\text{N}(\text{H})-\text{C}(=\text{NH})-\text{NH}_2$ .

Embodiment 16 is the compound or salt of any one of the embodiments 1-15, wherein W is a covalent bond or  $-\text{O}-$ .

Embodiment 17 is the compound or salt of any one of the embodiments 1-16, wherein X is alkylene optionally interrupted by one or more  $-\text{O}-$  groups.

Embodiment 18 is the compound or salt of any one of the embodiments 1-17, wherein X is selected from the group consisting of  $-\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}_2\text{C}(\text{CH}_3)_2-$ ,  $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_2-$ ,  $-(\text{CH}_2)_{2-4}-(\text{OCH}_2\text{CH}_2-)_{1-5}$ , and  $-(\text{CH}_2)_{2-6}-(\text{OCH}_2\text{CH}_2-)_{1-4}$ .

Embodiment 19 is the compound or salt of any one of the embodiments 1-18, wherein Z is  $-\text{C}_{1-5}\text{alkylene-arylene-C}_{1-5}\text{alkylene-}$  or  $-\text{C}_{1-5}\text{alkylene-heteroarylene-C}_{1-5}\text{alkylene-}$ .

Embodiment 20 is the compound or salt of any of the embodiments 1-19, wherein Z is  $-\text{CH}_2\text{-phenylene-CH}_2-$ .

Embodiment 21 is the compound or salt of any one of the embodiments 1-20, wherein  $R_2$  is selected from the group consisting hydrogen, alkyl, alkoxyalkylenyl, alkylaminoalkylenyl, and hydroxyalkylenyl.

Embodiment 22 is the compound or salt of any one of the embodiments 1-21, wherein  $R_2$  is selected from the group consisting of hydrogen,  $-\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{OCH}_3$ ,  $-\text{CH}_2\text{OCH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{OCH}_3$ ,  $-\text{CH}_2\text{NHCH}_3$ ,  $-\text{CH}_2\text{NHCH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{NHCH}_3$ ,  $-\text{CH}_2\text{OH}$ , and  $-\text{CH}_2\text{CH}_2\text{OH}$ .

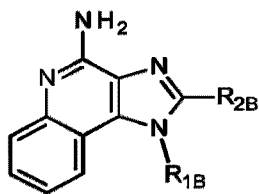
Embodiment 23 is the compound or salt of any one of the embodiments 1-22, wherein  $R_2$  is selected from the group consisting of hydrogen,  $-\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{OCH}_3$ ,  $-\text{CH}_2\text{OCH}_2\text{CH}_3$ , and  $-\text{CH}_2\text{CH}_2\text{OCH}_3$ .

Embodiment 24 is the compound or salt of any one of the embodiments 1-20, wherein  $R_2$  is  $-\text{CH}_2\text{NHOCCH}_3$ ,  $-\text{CH}_2\text{NHC}(\text{O})\text{CH}_3$  or  $-\text{CH}_2\text{NHC}(\text{O})\text{cyclopropyl}$ .

Embodiment 25 is the compound or salt of any one of the embodiments 1-24, wherein the pharmaceutically acceptable salt is hydrochloride.

Embodiment 26 is the compound or salt of any one of the embodiments 1-24, wherein the pharmaceutically acceptable salt is dihydrochloride.

Embodiment 27 is a compound of Formula XIII:



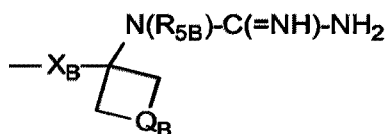
Formula XIII

5

wherein:

$R_{1B}$  is selected from the group consisting of  $-X_B-N(R_{5B})-C(=NH)-NH_2$ ,

$-Z_B-N(R_{5B})-C(=NH)-NH_2$ , and



;

10

$X_B$  is selected from the group consisting of alkylene, alkenylene, and alkynylene, wherein any of the alkylene, alkenylene, and alkynylene groups can be optionally interrupted by one or more -O- groups;

$Z_B$  is selected from the group consisting of

$-X_B$ -arylene- $X_B$ -,

$-X_B$ -heteroarylene- $X_B$ -,

$-X_B$ -arylene-, and

15

$-X_B$ -heteroarylene-;

$R_{2B}$  is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, -O-alkyl, hydroxyalkylenyl, alkoxyalkylenyl, alkylaminoalkylenyl, hydroxyl,  $-CH_2-NH-O$ -alkyl, and  $-CH_2NHC(O)$ -alkyl;

20

$R_{5B}$  is selected from the group consisting of hydrogen, alkyl, arylalkylenyl, alkoxyalkylenyl, aryloxyalkylenyl, benzyloxyalkylenyl, aryl- $(CH_2)_{2-6}$ -O-alkylenyl, and cycloalkylalkylenyl, wherein any of the alkyl, arylalkylenyl, alkoxyalkylenyl, aryloxyalkylenyl, benzyloxyalkylenyl, aryl- $(CH_2)_{2-6}$ -O-alkylenyl, and cycloalkylalkylenyl groups can be either unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, alkoxy, alkyl, haloalkyl, and nitrile;

25

$Q_B$  is selected from the group consisting of a bond,  $-CH_2-$ ,  $-CH_2CH_2-$ ,  $-CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2CH_2CH_2-$ ,  $-CH_2-O-CH_2-$ , and  $-OCH_2-$ ; or a pharmaceutically acceptable salt thereof.

Embodiment 28 is the compound or salt of embodiment 27, wherein  $R_{5B}$  is hydrogen, alkyl, or  $-CH_2Ph$ .

Embodiment 29 is the compound or salt of any one of the embodiments 27-28, wherein  $R_{5B}$  is hydrogen,  $C_{1-8}$  alkyl, or  $-CH_2Ph$ .

Embodiment 30 is the compound or salt of any one of the embodiments 27-29, wherein  $R_{5B}$  is hydrogen or  $C_{1-4}$  alkyl.

5 Embodiment 31 is the compound or salt of embodiment 27, wherein  $R_{5B}$  is selected from the group consisting of hydrogen,  $-CH_3$ ,  $-CH_2CH_3$ ,  $-CH(CH_3)_2$ ,  $-CH_2CH_2CH_3$ ,  $-CH_2CH_2CH_2CH_3$ ,  $-CH_2CH(CH_3)_2$ ,  $-C(CH_3)_3$ ,  $-CH_2CH_2CH_2CH_2CH_3$ ,  $-CH_2CH_2CH(CH_3)_2$ , cyclopentyl, cyclohexyl,  $-CH_2(cyclopentyl)$ ,  $-CH_2(cyclohexyl)$ , and  $-CH_2CH_2-O-CH_3$ .

10 Embodiment 32 is the compound or salt of any one of embodiment 27, wherein  $R_{5B}$  is selected from the group consisting of hydrogen, alkyl,  $-CH_2Ph$ ,  $-CH_2CH_2Ph$ ,  $-CH_2CH_2-O-Ph$ ,  $-CH_2CH_2-O-CH_2Ph$ , and  $-(CH_2)_{2-6}-O-(CH_2)_{1-6}Ph$ , wherein Ph can be either unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, alkyl, alkoxy, and, nitrile.

15 Embodiment 33 is the compound or salt of embodiment 27-32, wherein  $R_{1B}$  is selected from the group consisting of  $-X_B-N(H)-C(=NH)-NH_2$ , and  $-Z_B-N(H)-C(=NH)-NH_2$ .

Embodiment 34 is the compound or salt of any one of the embodiments 27-33, wherein  $X_B$  is alkylene optionally interrupted by one or more  $-O-$  groups.

20 Embodiment 35 is the compound or salt of any one of the embodiments 27-34, wherein  $X_B$  is selected from the group consisting of  $-CH_2CH_2-$ ,  $-CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$ ,  $-CH_2C(CH_3)_2-$ ,  $-CH_2C(CH_3)_2CH_2-$ ,  $-CH_2CH_2-O-CH_2CH_2-$ ,  $-CH_2CH_2-O-CH_2CH_2-O-CH_2CH_2-$ ,  $-(CH_2)_{2-4}-(OCH_2CH_2-)_{1-5}$ , and  $-(CH_2)_{2-6}-(OCH_2CH_2-)_{1-4}$ .

25 Embodiment 36 is the compound or salt of any one of the embodiments 27-34, wherein  $X_B$  is selected from the group consisting of  $-CH_2CH_2-$ ,  $-CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2CH_2CH_2CH_2-$ ,  $-CH_2C(CH_3)_2-$ ,  $-CH_2C(CH_3)_2CH_2-$ .

30 Embodiment 37 is the compound or salt of any one of the embodiments 27-36, wherein  $Z_B$  is  $-C_{1-5}alkylene-arylene-C_{1-5}alkylene-$  or  $-C_{1-5}alkylene-heteroarylene-C_{1-5}alkylene-$ .

Embodiment 38 is the compound or salt of any of the embodiments 27-37, wherein  $Z_B$  is  $-CH_2-phenylene-CH_2-$ .

35 Embodiment 39 is the compound or salt of any one of the embodiments 27-38, wherein  $R_{2B}$  is selected from the group consisting hydrogen, alkyl, alkoxyalkylenyl, alkylaminoalkylenyl, and hydroxyalkylenyl.

Embodiment 40 is the compound or salt of any one of the embodiments 27-39, wherein  $R_{2B}$  is selected from the group consisting of hydrogen,  $-CH_3$ ,  $-CH_2CH_3$ ,



-CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>OCH<sub>3</sub>, -CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>,  
 -CH<sub>2</sub>NHCH<sub>3</sub>, -CH<sub>2</sub>NHCH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>NHCH<sub>3</sub>, -CH<sub>2</sub>OH, and -CH<sub>2</sub>CH<sub>2</sub>OH.

Embodiment 41 is the compound or salt of any one of the embodiments 27-40, wherein R<sub>2B</sub> is selected from the group consisting of hydrogen, -CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>3</sub>,

5 -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>OCH<sub>3</sub>, -CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, and -CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>.

Embodiment 42 is the compound or salt of any one of the embodiments 27-38, wherein R<sub>2B</sub> is -CH<sub>2</sub>NHOCH<sub>3</sub>, -CH<sub>2</sub>NHC(O)CH<sub>3</sub> or -CH<sub>2</sub>NHC(O)cyclopropyl.

Embodiment 43 is the compound or salt of any one of the embodiments 27-42, wherein the pharmaceutically acceptable salt is hydrochloride.

10 Embodiment 44 is the compound or salt of any one of the embodiments 27-42, wherein the pharmaceutically acceptable salt is dihydrochloride.

Embodiment 45 is a method of inducing biosynthesis of IFN-alpha in an animal comprising administering an effective amount of a compound or salt of any one of the embodiments 1-44 to the animal.

15 Embodiment 46 is a method of inducing biosynthesis of IFN-gamma in an animal comprising administering an effective amount of a compound or salt of any one of the embodiments 1-44 to the animal.

Embodiment 47 is a method of inducing biosynthesis of TNF-alpha in an animal comprising administering an effective amount of a compound or salt of any one of the embodiments 1-44 to the animal.

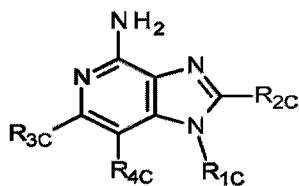
20 Embodiment 48 is a method of inducing biosynthesis of IP-10 in an animal comprising administering an effective amount of a compound or salt of any one of the embodiments 1-44 to the animal.

25 Embodiment 49 is a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of any one of the embodiments 1-44 to the animal.

Embodiment 50 is a pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of embodiment 1 in combination with a pharmaceutically acceptable carrier.

30 Embodiment 51 is a pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of any one of the embodiments 1-44 in combination with a pharmaceutically acceptable carrier.

Embodiment 52 is a compound of Formula XIV:



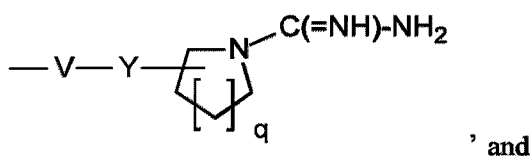
Formula XIV

wherein:

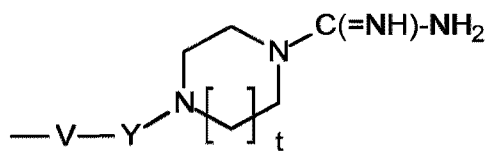
$R_{3C}$  and  $R_{4C}$  are taken together to form a fused benzene ring, a fused pyridine ring, a fused cyclohexene ring, or a fused tetrahydropyridine ring; wherein the fused benzene ring, fused pyridine ring, fused cyclohexene ring, or fused tetrahydropyridine ring is either unsubstituted or substituted by one or more  $R_C$  groups;

$R_C$  is selected from the group consisting of halogen, hydroxyl, alkyl, alkoxy, haloalkylenyl,  $-C(O)-O-$ alkyl,  $-C(O)-OCH_2Ph$ ,  $-C(O)-O-$ aryl, amino, alkylamino, and dialkylamino, aryl, arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, heteroarylalkyleneoxy, and heteroaryloxy, wherein the alkyl, aryl, arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, heteroarylalkyleneoxy, and heteroaryloxy groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, haloalkyl, hydroxyl, hydroxyalkylenyl, alkoxyalkylenyl, arylalkyleneoxy, nitrile, amino, alkylamino, and dialkylamino;

$R_{1C}$  is selected from the group consisting of



, and



;

$V$  is selected from the group consisting of a covalent bond,  $-O-$ , and  $-NH-$ ;

$Y$  is selected from the group consisting of alkylene, alkenylene, and alkynylene, wherein any of the alkylene, alkenylene, and alkynylene groups can be optionally interrupted by one or more  $-O-$  groups;

$R_{2C}$  is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl,  $-O-$ alkyl, hydroxyalkylenyl, alkoxyalkylenyl, alkylaminoalkylenyl, hydroxyl,  $-CH_2-NH-O-$ alkyl, and  $-CH_2NHC(O)-$ alkyl;

$q$  is an integer from 0 to 5;

t is an integer from 1 to 4;

or a pharmaceutically acceptable salt thereof.

Embodiment 53 is the compound or salt of embodiment 52, wherein  $R_{3C}$  and  $R_{4C}$  are taken together to form a fused benzene ring, a fused pyridine ring, or a fused cyclohexene ring.

5 Embodiment 54 is the compound or salt of any one of the embodiments 52-53, wherein  $R_{3C}$  and  $R_{4C}$  are taken together to form a fused benzene ring, a fused pyridine ring, or a fused cyclohexene ring, and wherein the fused benzene ring, fused pyridine ring, or fused cyclohexene ring is either unsubstituted or substituted by one and only one  $R_C$  group.

10 Embodiment 55 is the compound or salt of any one of the embodiments 52-54, wherein  $R_{3C}$  and  $R_{4C}$  are taken together to form a fused benzene ring or a fused cyclohexene ring, and wherein the fused benzene ring, or fused cyclohexene ring is either unsubstituted or substituted by one and only one  $R_C$  group.

15 Embodiment 56 is the compound or salt of any one of the embodiments 52-54, wherein  $R_{3C}$  and  $R_{4C}$  are taken together to form a fused benzene ring or a fused pyridine ring, and wherein the fused benzene ring, or fused pyridine ring is either unsubstituted or substituted by one and only one  $R_C$  group.

Embodiment 57 is the compound or salt of any one of the embodiments 52-56, wherein  $R_C$  is selected from the group consisting of hydroxyl, F, Cl,  $-CF_3$ ,  $-OCF_3$ ,  $-O-C_{1-6}alkyl$ , and  $-C_{1-6}alkyl$ .

20 Embodiment 58 is the compound or salt of any one of the embodiments 52-56,  $R_C$  is selected from the group consisting of hydroxyl, F, Cl,  $-CF_3$ ,  $-OCH_3$ ,  $-OCF_3$ ,  $-OCH_2CH_3$ ,  $-OCH(CH_3)_2$ ,  $-CH_3$ ,  $-CH_2CH_3$ ,  $-CH_2CH_2CH_3$ , and  $-CH(CH_3)_2$ .

Embodiment 59 is the compound or salt of any one of the embodiments 52-56, wherein  $R_C$  is  $-C(O)OC_{1-4}alkyl$ .

25 Embodiment 60 is the compound or salt of any one of the embodiments 52-56, wherein  $R_C$  is selected from the group consisting of  $-CO_2CH_3$ ,  $-CO_2CH_2CH_3$ ,  $-CO_2CH(CH_3)_2$ ,  $-CO_2CH_2CH_2CH_3$ ,  $-CO_2CH_2CH_2CH_2CH_3$ ,  $-CO_2CH_2Ph$ , and  $-CO_2CH_2CH(CH_3)_2$ .

30 Embodiment 61 is the compound or salt of any one of the embodiments 52-60, wherein V is a covalent bond and Y is alkylene optionally interrupted by one or more  $-O-$  groups.

Embodiment 62 is the compound or salt of any one of the embodiments 52-61, wherein  $-V-Y-$  is  $-CH_2-$ ,  $-CH_2CH_2-$ ,  $-CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2CH_2CH_2CH_2-$ , or  $-CH_2CH_2-O-CH_2CH_2-$ .

35 Embodiment 63 is the compound or salt of any one of the embodiments 52-60, wherein  $-V-Y-$  is  $-O-C_{1-7}alkylene-$  or  $-C_{1-8}alkylene-$ .

Embodiment 64 is the compound or salt of any one of the embodiments 52-63, wherein  $R_{2C}$  is selected from the group consisting hydrogen, alkyl, alkoxyalkylenyl, alkylaminoalkylenyl, and hydroxyalkylenyl.

Embodiment 65 is the compound or salt of any one of the embodiments 52-64, wherein  $R_{2C}$  is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

Embodiment 66 is the compound or salt of any one of the embodiments 52-64, wherein  $R_{2C}$  is selected from the group consisting of hydrogen,  $-CH_3$ ,  $-CH_2CH_3$ ,  $-CH_2CH_2CH_3$ ,  $-CH_2CH_2CH_2CH_3$ ,  $-CH_2OCH_3$ ,  $-CH_2OCH_2CH_3$ ,  $-CH_2CH_2OCH_3$ ,  $-CH_2NHCH_3$ ,  $-CH_2NHCH_2CH_3$ ,  $-CH_2CH_2NHCH_3$ ,  $-CH_2OH$ , and  $-CH_2CH_2OH$ .

Embodiment 67 is the compound or salt of any one of the embodiments 52-64, wherein  $R_{2C}$  is selected from the group consisting of hydrogen,  $-CH_3$ ,  $-CH_2CH_3$ ,  $-CH_2CH_2CH_3$ ,  $-CH_2CH_2CH_2CH_3$ ,  $-CH_2OCH_3$ ,  $-CH_2OCH_2CH_3$ , and  $-CH_2CH_2OCH_3$ .

Embodiment 68 is the compound or salt of any one of the embodiments 52-63, wherein  $R_{2C}$  is  $-CH_2NHOCH_3$ ,  $-CH_2NHC(O)CH_3$  or  $-CH_2NHC(O)cyclopropyl$ .

Embodiment 69 is the compound or salt of any one of the embodiments 52-63, wherein  $R_{2C}$  is  $-CH_2NHOCH_3$ .

Embodiment 70 is the compound or salt of embodiment 52, wherein V is selected from the group consisting of a covalent bond and  $-O-$ ; Y is alkylene optionally interrupted by one or more  $-O-$  groups; q is an integer from 1 to 2; t is 1;  $R_{2C}$  is selected from the group consisting of hydrogen,  $-CH_3$ ,  $-CH_2CH_3$ ,  $-CH_2CH_2CH_3$ ,  $-CH_2CH_2CH_2CH_3$ ,  $-CH_2OCH_3$ ,  $-CH_2OCH_2CH_3$ , and  $-CH_2CH_2OCH_3$ .

Embodiment 71 is the compound or salt of any one of the embodiments 52-70, wherein the pharmaceutically acceptable salt is hydrochloride.

Embodiment 72 is the compound or salt of any one of the embodiments 52-70, wherein the pharmaceutically acceptable salt is dihydrochloride.

Embodiment 73 is a pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of any one of the embodiments 52-72 in combination with a pharmaceutically acceptable carrier.

Embodiment 74 is a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of any one of the embodiments 52-72 to the animal.

Embodiment 75 is a method of inducing biosynthesis of IFN-alpha in an animal comprising administering an effective amount of a compound or salt of any one of the embodiments 52-72 to the animal.

Embodiment 76 is a method of inducing biosynthesis of IFN-gamma in an animal comprising administering an effective amount of a compound or salt of any one of the embodiments 52-72 to the animal.

Embodiment 77 is a method of inducing biosynthesis of TNF-alpha in an animal comprising administering an effective amount of a compound or salt of any one of the embodiments 52-72 to the animal.

Embodiment 78 is a method of inducing biosynthesis of IP-10 in an animal comprising administering an effective amount of a compound or salt of any one of the embodiments 52-72 to the animal.

Embodiment 79 is the compound or salt of any one of the embodiments 1-5, wherein R is selected from the group consisting of halogen, hydroxyl, alkyl, alkoxy, haloalkyl, -C(O)-O-alkyl, -C(O)-OCH<sub>2</sub>Ph, -C(O)-O-aryl, amino, alkylamino, and dialkylamino.

Embodiment 80 is the compound or salt of any one of the embodiments 1-5, wherein R is selected from the group consisting of aryl, arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, heteroarylalkyleneoxy, and heteroaryloxy, wherein the alkyl, aryl, arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, heteroaryl alkyleneoxy, and heteroaryloxy groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, haloalkyl, hydroxyl, hydroxyalkylenyl, alkoxyalkylenyl, arylalkyleneoxy, nitrile, amino, alkylamino, and dialkylamino.

Embodiment 81 is the compound or salt of any one of the embodiments 52-56, wherein R<sub>C</sub> is selected from the group consisting of halogen, hydroxyl, alkyl, alkoxy, haloalkyl, -C(O)-O-alkyl, -C(O)-OCH<sub>2</sub>Ph, -C(O)-O-aryl, amino, alkylamino, and dialkylamino.

Embodiment 82 is the compound or salt of any one of the embodiments 52-56, wherein R<sub>C</sub> is selected from the group consisting of aryl, arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, heteroarylalkyleneoxy, and heteroaryloxy, wherein the alkyl, aryl, arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, heteroarylalkyleneoxy, and heteroaryloxy groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, haloalkyl, hydroxyl, hydroxyalkylenyl, alkoxyalkylenyl, arylalkyleneoxy, nitrile, amino, alkylamino, and dialkylamino.

Embodiment 83 is a compound selected from the group consisting of:

- 1-[4-(4-aminoimidazo[4,5-c]quinolin-1-yl)butyl]guanidine;
- 1-[4-(4-amino-2-methyl-imidazo[4,5-c]quinolin-1-yl)butyl]guanidine;
- 1-[4-(4-amino-2-ethyl-imidazo[4,5-c]quinolin-1-yl)butyl]guanidine;
- 1-[4-(4-amino-2-propyl-imidazo[4,5-c]quinolin-1-yl)butyl]guanidine;
- 1-[4-(4-amino-2-butyl-imidazo[4,5-c]quinolin-1-yl)butyl]guanidine;
- 1-[4-(4-amino-2-(2-methoxyethyl)imidazo[4,5-c]quinolin-1-yl)butyl]guanidine;
- 1-[4-(4-amino-2-(ethoxymethyl)imidazo[4,5-c]quinolin-1-yl)butyl]guanidine;
- 1-[4-(4-amino-2-(methoxymethyl)imidazo[4,5-c]quinolin-1-yl)butyl]guanidine;

or a pharmaceutically acceptable salt thereof.

Embodiment 84 is a compound selected from the group consisting of:

1-[3-(4-aminoimidazo[4,5-c]quinolin-1-yl)propyl]guanidine;  
 1-[3-(4-amino-2-methyl-imidazo[4,5-c]quinolin-1-yl)propyl]guanidine;  
 5 1-[3-(4-amino-2-ethyl-imidazo[4,5-c]quinolin-1-yl)propyl]guanidine;  
 1-[3-(4-amino-2-propyl-imidazo[4,5-c]quinolin-1-yl)propyl]guanidine;  
 1-[3-(4-amino-2-butyl-imidazo[4,5-c]quinolin-1-yl)propyl]guanidine;  
 1-[3-(4-amino-2-(2-methoxyethyl)imidazo[4,5-c]quinolin-1-yl)propyl]guanidine;  
 1-[3-(4-amino-2-(ethoxymethyl)imidazo[4,5-c]quinolin-1-yl)propyl]guanidine;  
 10 1-[3-(4-amino-2-(methoxymethyl)imidazo[4,5-c]quinolin-1-yl)propyl]guanidine;  
 or a pharmaceutically acceptable salt thereof.

Embodiment 85 is a compound selected from the group consisting of:

1-[2-(4-aminoimidazo[4,5-c]quinolin-1-yl)ethyl]guanidine;  
 1-[2-(4-amino-2-methyl-imidazo[4,5-c]quinolin-1-yl)ethyl]guanidine;  
 15 1-[2-(4-amino-2-ethyl-imidazo[4,5-c]quinolin-1-yl)ethyl]guanidine;  
 1-[2-(4-amino-2-propyl-imidazo[4,5-c]quinolin-1-yl)ethyl]guanidine;  
 1-[2-(4-amino-2-butyl-imidazo[4,5-c]quinolin-1-yl)ethyl]guanidine;  
 1-[2-(4-amino-2-(2-methoxyethyl)imidazo[4,5-c]quinolin-1-yl)ethyl]guanidine;  
 1-[2-(4-amino-2-(ethoxymethyl)imidazo[4,5-c]quinolin-1-yl)ethyl]guanidine;  
 20 1-[2-(4-amino-2-(methoxymethyl)imidazo[4,5-c]quinolin-1-yl)ethyl]guanidine;  
 or a pharmaceutically acceptable salt thereof.

Embodiment 86 is a compound selected from the group consisting of:

1-[2-[2-(4-aminoimidazo[4,5-c]quinolin-1-yl)ethoxy]ethyl]guanidine;  
 1-[2-[2-(4-amino-2-methyl-imidazo[4,5-c]quinolin-1-yl)ethoxy]ethyl]guanidine;  
 25 1-[2-[2-(4-amino-2-ethyl-imidazo[4,5-c]quinolin-1-yl)ethoxy]ethyl]guanidine;  
 1-[2-[2-(4-amino-2-propyl-imidazo[4,5-c]quinolin-1-yl)ethoxy]ethyl]guanidine;  
 1-[2-[2-(4-amino-2-butyl-imidazo[4,5-c]quinolin-1-yl)ethoxy]ethyl]guanidine;  
 1-[2-[2-(4-amino-2-(2-methoxyethyl)imidazo[4,5-c]quinolin-1-yl)ethoxy]ethyl]guanidine;  
 1-[2-[2-(4-amino-2-(ethoxymethyl)imidazo[4,5-c]quinolin-1-yl)ethoxy]ethyl]guanidine;  
 30 1-[2-[2-(4-amino-2-(methoxymethyl)imidazo[4,5-c]quinolin-1-yl)ethoxy]ethyl]guanidine;  
 or a pharmaceutically acceptable salt thereof.

Embodiment 87 is a compound selected from the group consisting of:

1-[3-[4-aminoimidazo[4,5-c]quinolin-1-yl]-2,2-dimethyl-propyl]guanidine;  
 1-[3-[4-amino-2-methyl-imidazo[4,5-c]quinolin-1-yl]-2,2-dimethyl-propyl]guanidine;  
 35 1-[3-[4-amino-2-ethyl-imidazo[4,5-c]quinolin-1-yl]-2,2-dimethyl-propyl]guanidine;  
 1-[3-[4-amino-2-propyl-imidazo[4,5-c]quinolin-1-yl]-2,2-dimethyl-propyl]guanidine;  
 1-[3-[4-amino-2-butyl-imidazo[4,5-c]quinolin-1-yl]-2,2-dimethyl-propyl]guanidine;

1-[3-[4-amino-2-(2-methoxyethyl)imidazo[4,5-c]quinolin-1-yl]-2,2-dimethyl-propyl]guanidine;  
 1-[3-[4-amino-2-(ethoxymethyl)imidazo[4,5-c]quinolin-1-yl]-2,2-dimethyl-propyl]guanidine;  
 1-[3-[4-amino-2-(methoxymethyl)imidazo[4,5-c]quinolin-1-yl]-2,2-dimethyl-propyl]guanidine;  
 or a pharmaceutically acceptable salt thereof.

5 Embodiment 88 is a compound selected from the group consisting of:

1-[2-(4-amino-imidazo[4,5-c][1,5]naphthyridin-1-yl)ethyl]guanidine;  
 1-[2-(4-amino-2-methyl-imidazo[4,5-c][1,5]naphthyridin-1-yl)ethyl]guanidine;  
 1-[2-(4-amino-2-ethyl-imidazo[4,5-c][1,5]naphthyridin-1-yl)ethyl]guanidine;  
 1-[2-(4-amino-2-propyl-imidazo[4,5-c][1,5]naphthyridin-1-yl)ethyl]guanidine;  
 10 1-[2-(4-amino-2-butyl-imidazo[4,5-c][1,5]naphthyridin-1-yl)ethyl]guanidine;  
 1-[2-(4-amino-2-(2-methoxyethyl)imidazo[4,5-c][1,5]naphthyridin-1-yl)ethyl]guanidine;  
 1-[2-(4-amino-2-(2-ethoxymethyl)imidazo[4,5-c][1,5]naphthyridin-1-yl)ethyl]guanidine;  
 1-[2-(4-amino-2-(2-methoxymethyl)imidazo[4,5-c][1,5]naphthyridin-1-yl)ethyl]guanidine;  
 or a pharmaceutically acceptable salt thereof.

15

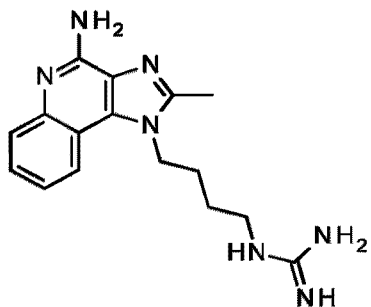
Objects and advantages of the disclosure are further illustrated by the examples provided herein. The particular materials and amounts thereof recited in these examples, as well as other conditions and details, are merely illustrative and are not intended to be limiting. The person of ordinary skill in the art, after carefully reviewing the entirety of this disclosure, will be able to use materials and conditions in addition to those specifically described in the examples.

20

## EXAMPLES

### Example 1

25 1-[4-(4-amino-2-methyl-imidazo[4,5-c]quinolin-1-yl)butyl]guanidine dihydrochloride



30

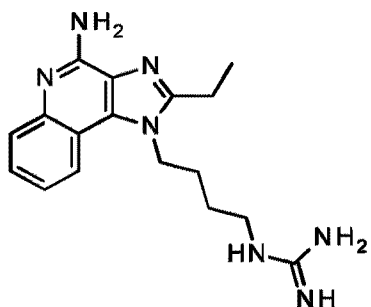
1-(4-aminobutyl)-2-methyl-imidazo[4,5-c]quinolin-4-amine (1.347 g, 5.01 mmol) was suspended in 12 mL of anhydrous N,N-dimethylformamide (DMF) and stirred under a nitrogen

atmosphere. Diisopropylethylamine (0.88 mL, 5.1 mmol) and pyrazole-1-carboxamide hydrochloride (750 mg, 5.12 mmol) were then added and the reaction mixture was stirred for 3 days. The reaction mixture was then concentrated under reduced pressure and the resulting solid was

titrated with acetonitrile to provide an orange powder that was isolated by filtration. Chromatography (SiO<sub>2</sub>, chloroform-methanol-water-acetic acid eluent 80:18:2:0.1 with a gradient to 50:40:10:0.1) gave a foam that was concentrated from 1N hydrochloric acid solution and then from ethanol to provide 1-[4-(4-amino-2-methyl-imidazo[4,5-c]quinolin-1-yl)butyl]guanidine dihydrochloride as a yellow crystalline solid, mp 234-244 °C. <sup>1</sup>H NMR (D<sub>2</sub>O, 500 MHz) 7.81 (d, 8.4 *J* = 8.4 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.52-7.45 (m, 2H), 4.26 (t, *J* = 7.6, 2H), 3.07 (t, *J* = 6.7 Hz, 2H), 2.57 (s, 3H), 1.77 (m, 2H), 1.61 (m, 2H).

#### Example 2

##### 1-[4-(4-amino-2-ethyl-imidazo[4,5-c]quinolin-1-yl)butyl]guanidine hydrochloride

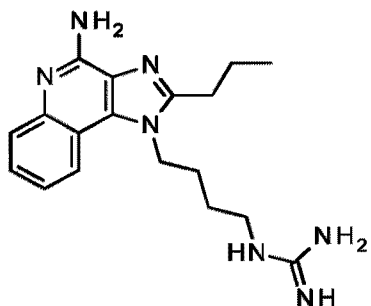


1-(4-aminobutyl)-2-ethyl-imidazo[4,5-c]quinolin-4-amine (1.22 g, 4.49 mmol) was suspended in 10 mL of anhydrous DMF and stirred under a nitrogen atmosphere. Diisopropylethylamine (0.78 mL, 4.5 mmol) and pyrazole-1-carboxamide hydrochloride (658 mg, 4.49 mmol) were then added and the reaction mixture was stirred overnight. The reaction mixture was then concentrated under reduced pressure and the resulting solid was crystallized from acetonitrile/water to provide 1-[4-(4-amino-2-ethyl-imidazo[4,5-c]quinolin-1-yl)butyl]guanidine hydrochloride as off-white crystals, mp 240-242 °C. <sup>1</sup>H NMR (D<sub>2</sub>O, 500 MHz) 7.32 (d, *J* = 8.3 Hz, 1H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 8.1 Hz, 1H), 6.99 (t, *J* = 7.4 Hz, 1H), 3.56 (m, 2H), 2.92 (t, *J* = 6.4 Hz, 2H), 2.50 (quartet, *J* = 7.4 Hz, 2H), 1.41-1.26 (m, 4H), 1.18 (t, *J* = 7.5 Hz, 3H).

#### Example 3

##### 1-[4-(4-amino-2-propyl-imidazo[4,5-c]quinolin-1-yl)butyl]guanidine hydrochloride

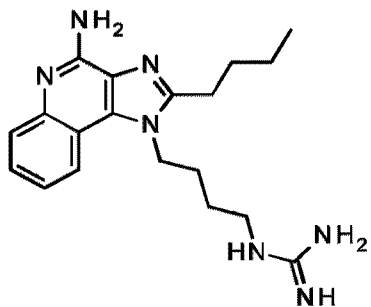




1-(4-(4-amino-2-propyl-imidazo[4,5-c]quinolin-4-amine (1.487 g, 5.01 mmol) was suspended in 12 mL of anhydrous DMF and stirred under a nitrogen atmosphere. Diisopropylethylamine (0.90 mL, 5.2 mmol) and pyrazole-1- carboxamidine hydrochloride (750 mg, 5.12 mmol) were then added and the reaction mixture was stirred for 3 days. The reaction mixture was then concentrated under reduced pressure and the resulting solid was crystallized from acetonitrile to provide 1-[4-(4-amino-2-propyl-imidazo[4,5-c]quinolin-1-yl)butyl]guanidine hydrochloride as off-white crystals, mp 156-158 °C. <sup>1</sup>H NMR (D<sub>2</sub>O, 500 MHz) 7.23 (d, *J* = 8.3 Hz, 1H), 7.17 (t, *J* = 7.4 Hz, 1H), 6.94-6.88 (m, 2H), 3.41 (m, 2H), 2.90 (t, *J* = 6.5 Hz, 2H), 2.32 (t, *J* = 7.4 Hz 2H), 1.47 (m, 2H), 1.35 (m, 2H), 1.11 (m, 2H), 0.88 (t, *J* = 7.0 Hz, 3H).

#### Example 4

1-[4-(4-amino-2-butyl-imidazo[4,5-c]quinolin-1-yl)butyl]guanidine hydrochloride

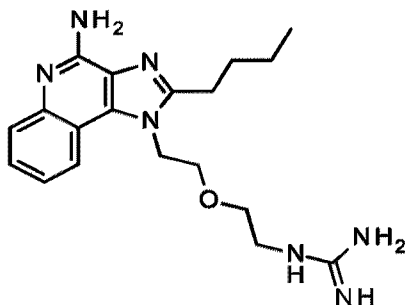


1-(4-(4-amino-2-butyl-imidazo[4,5-c]quinolin-4-amine (2.00 g, 6.43 mmol) was suspended in 14 mL of anhydrous N-methylpyrrolidone and stirred under a nitrogen atmosphere. Diisopropylethylamine (1.12 mL, 6.41 mmol) and pyrazole-1- carboxamidine hydrochloride (939 mg, 6.41 mmol) were then added and the reaction mixture was stirred overnight. The reaction mixture was then concentrated under reduced pressure and the resulting solid was crystallized from acetonitrile/water to provide 1-[4-(4-amino-2-butyl-imidazo[4,5-c]quinolin-1-yl)butyl]guanidine hydrochloride, mp 237-238 °C. <sup>1</sup>H NMR (D<sub>2</sub>O, 500 MHz) 7.32 (d, *J* = 8.2 Hz, 1H), 7.24 (t, *J* = 7.5

Hz, 1H), 7.07 (t,  $J = 8.0$  Hz, 1H), 6.97 (t,  $J = 7.4$  Hz, 1H), 3.54 (m, 2H), 2.94 (t,  $J = 6.4$  Hz, 2H), 2.38 (t,  $J = 7.6$  Hz, 2H), 1.41-1.36 (m, 4H), 1.32-1.22 (m, 4H), 0.88 (t,  $J = 7.3$  Hz, 3H).

#### Example 5

##### 5 1-[2-[2-(4-amino-2-butyl-imidazo[4,5-c]quinolin-1-yl)ethoxy]ethyl]guanidine dihydrochloride

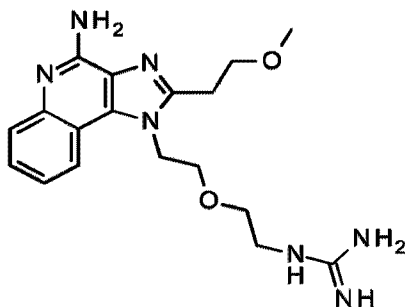


1-[2-(2-aminoethoxy)ethyl]-2-butyl-imidazo[4,5-c]quinolin-4-amine (1.637 g, 5.01 mmol, see  
 10 Example 1 of US7115622) was suspended in 12 mL of anhydrous DMF and stirred under a nitrogen  
 atmosphere. Diisopropylethylamine (0.90 mL, 5.2 mmol) and pyrazole-1- carboxamidine  
 hydrochloride (750 mg, 5.12 mmol) were then added and the reaction mixture was stirred for 3 days.  
 The reaction mixture was then concentrated under reduced pressure. Chromatography (SiO<sub>2</sub>,  
 chloroform-methanol-water-acetic acid eluent 80:18:2:0.1 with a gradient to 50:40:10:0.1) gave a  
 foam. The foam was crystallized from ethanol and the concentrated from 1N hydrochloric acid  
 15 solution followed by ethanol to provide 1-[2-[2-(4-amino-2-butyl-imidazo[4,5-c]quinolin-1-  
 yl)ethoxy]ethyl]guanidine dihydrochloride  
 as a solid, mp 184-188 °C. <sup>1</sup>H NMR (D<sub>2</sub>O, 500 MHz) 8.00 (m, 1H), 7.60 (m, 1H), 7.48-7.44 (m, 2H),  
 4.55 (t,  $J = 5.1$ , 2H), 3.86 (t,  $J = 5.1$ , 2H), 3.39 (t,  $J = 4.7$ , 2H), 2.93-2.88 (m, 4H), 1.81 (m, 2H), 1.47  
 (m, 2H), 0.97 (t,  $J = 7.4$  Hz, 3H).

20

#### Example 6

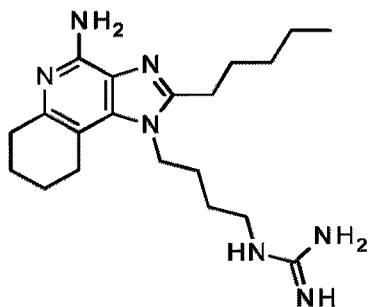
##### 1-[2-[2-[4-amino-2-(2-methoxyethyl)imidazo[4,5-c]quinolin-1-yl]ethoxy]ethyl]guanidine dihydrochloride



1-[2-(2-aminoethoxy)ethyl]-2-(2-methoxyethyl)imidazo[4,5-c]quinolin-4-amine (1.317 g, 4.00 mmol, see Example 3 of US7115622) was suspended in 12 mL of anhydrous DMF and stirred under N<sub>2</sub>. Diisopropylethylamine (0.72 mL, 4.2 mmol) and pyrazole-1- carboxamide hydrochloride (600 mg, 4.09 mmol) were then added and the reaction mixture was stirred for 3 days. The reaction mixture was then concentrated under reduced pressure. Chromatography (SiO<sub>2</sub>, chloroform-methanol-water-acetic acid eluent 80:18:2:0.1 with a gradient to 50:40:10:0.1) gave a foam. The foam was concentrated from 1N hydrochloric acid solution followed by ethanol to give 1-[2-[2-[4-amino-2-(2-methoxyethyl)imidazo[4,5-c]quinolin-1-yl]ethoxy]ethyl]guanidine dihydrochloride as a solid, mp 188-192 °C. <sup>1</sup>H NMR (D<sub>2</sub>O, 500 MHz) 7.99 (m, 1H), 7.61 (m, 1H), 7.49-7.44 (m, 2H), 4.58 (t, *J* = 4.7, 2H), 4.00 (t, *J* = 6.0, 2H), 3.86 (t, *J* = 5.1, 2H), 3.43 (s, 3H), 3.39 (t, *J* = 4.8, 2H), 3.23 (t, *J* = 6.1 Hz, 2H), 2.91 (t, *J* = 4.7 Hz, 2H).

#### Example 7

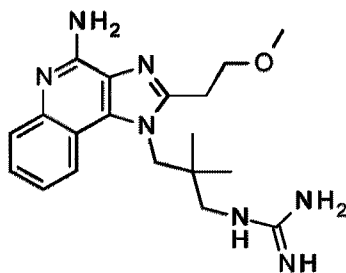
1-[4-(4-amino-2-pentyl-6,7,8,9-tetrahydroimidazo[4,5-c]quinolin-1-yl)butyl]guanidine hydrochloride



1-(4-aminobutyl)-2-pentyl-6,7,8,9-tetrahydroimidazo[4,5-c]quinolin-4-amine (1.260 g, 3.83 mmol) was suspended in 10 mL of anhydrous DMF and stirred under a nitrogen atmosphere. Diisopropylethylamine (0.72 mL, 4.2 mmol) and pyrazole-1- carboxamide hydrochloride (600 mg, 4.09 mmol) were then added and the reaction mixture was stirred for 2 days. The reaction mixture was then concentrated under reduced pressure to provide a gummy solid. Crystallization from acetonitrile-methanol provided 1-[4-(4-amino-2-pentyl-6,7,8,9-tetrahydroimidazo[4,5-c]quinolin-1-yl)butyl]guanidine hydrochloride as tan needles, mp 178-180 °C. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 500 MHz) 4.31 (t, *J* = 7.8, 2H), 3.23 (t, *J* = 6.9, 2H), 3.00 (m, 2H), 2.86 (t, *J* = 7.8, 2H), 2.75 (m, 2H), 1.86-1.83 (m, 4H), 1.69 (m, 2H), 1.47-1.42 (m, 4H), 0.95 (t, *J* = 7.1 Hz, 3H).

#### Example 8

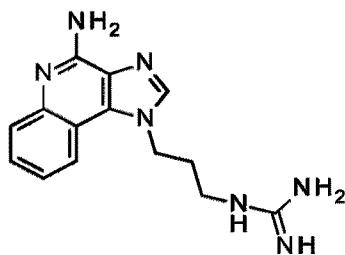
1-[3-[4-amino-2-(2-methoxyethyl)imidazo[4,5-c]quinolin-1-yl]-2,2-dimethyl-propyl]guanidine hydrochloride



1-(3-amino-2,2-dimethyl-propyl)-2-(2-methoxyethyl)imidazo[4,5-c]quinolin-4-amine (1.024 g, 3.15 mmol) was suspended in 10 mL of anhydrous DMF and stirred under a nitrogen atmosphere. Diisopropylethylamine (0.58 mL, 3.3 mmol) and pyrazole-1- carboxamidine hydrochloride (476 mg, 3.25 mmol) were then added and the reaction mixture was stirred for 3 days. The reaction mixture was then concentrated under reduced pressure to give a brown syrup. The syrup was triturated with acetonitrile to give a brown powder which was isolated by filtration. Crystallization from acetonitrile-methanol provided 1-[3-[4-amino-2-(2-methoxyethyl)imidazo[4,5-c]quinolin-1-yl]-2,2-dimethyl-propyl]guanidine hydrochloride as white crystals, mp 246-250 °C. <sup>1</sup>H NMR (D<sub>2</sub>O, 500 MHz) 7.52 (d, *J* = 8.3 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 4.01 (d, *J* = 14.4 Hz, 1H), 3.84 (d, *J* = 14.4 Hz, 1H), 2.95 (d, *J* = 12.4 Hz, 1H), 2.88 (d, *J* = 12.4 Hz, 1H), 2.63 (m, 2H), 1.64 (m, 2H), 1.36 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H), 0.61 (s, 3H), 0.50 (s, 3H).

#### Example 9

1-[3-(4-aminoimidazo[4,5-c]quinolin-1-yl)propyl]guanidine dihydrochloride



1-(3-aminopropyl)imidazo[4,5-c]quinolin-4-amine (560 mg, 2.32 mmol) was dissolved in 10 mL of anhydrous DMF and stirred under a nitrogen atmosphere. N,N'-Bis-BOC-pyrazole-1-carboxamidine (720 mg, 2.32 mmol) was added and the reaction mixture was heated at 70 °C for 90 minutes. The reaction mixture was concentrated under reduced pressure. The resulting material was dissolved in a solution of chloroform (50 mL) and methanol (2 mL) and then washed with water (3x) and finally brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Chromatography [SiO<sub>2</sub>, chloroform/(10% methanol/chloroform saturated with NH<sub>4</sub>OH) eluent] followed by

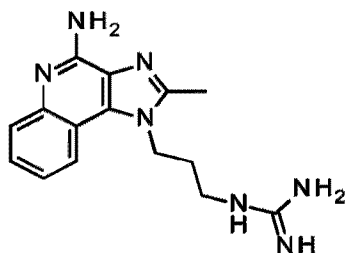
crystallization from acetonitrile yielded 203 mg of tert-butyl-N-[[3-(4-aminoimidazo[4,5-c]quinolin-1-yl)propylamino]-(tert-butoxycarbonylamino)methylene]carbamate.

The BOC protected product was dissolved in 5 mL of 1.25 N HCl in methanol and heated at 70 °C overnight. The mixture was cooled resulting in the precipitation of a solid.

The solid was isolated by filtration, rinsed with a cold methanol and dried under vacuum to provide 75 mg of 1-[3-(4-aminoimidazo[4,5-c]quinolin-1-yl)propyl]guanidine dihydrochloride as a white powder. <sup>1</sup>H NMR (D<sub>2</sub>O, 500 MHz) 8.12 (s, 1H), 7.86 (m, 1H), 7.60 (m, 1H), 7.50-7.44 (m, 2H), 4.47 (t, *J* = 7.1 Hz, 2H), 3.14 (t, *J* = 6.4 Hz, 2H), 2.08 (m, 2H).

#### Example 10

##### 1-[3-(4-amino-2-methyl-imidazo[4,5-c]quinolin-1-yl)propyl]guanidine dihydrochloride



1-(3-aminopropyl)-2-methyl-imidazo[4,5-c]quinolin-4-amine (400 mg, 1.57 mmol) was dissolved in 10 mL of anhydrous DMF and stirred under a nitrogen atmosphere. N,N'-Bis-BOC-pyrazole-1-carboxamidine (490 mg, 1.57 mmol) was added and the reaction mixture was stirred for 3 hours. The reaction mixture was then concentrated under reduced pressure.

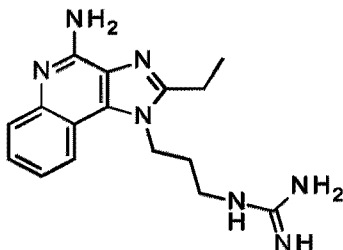
The resulting material was dissolved in 50 mL of chloroform and then washed with water (3x) and finally brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Chromatography [SiO<sub>2</sub>, chloroform/(10% methanol/chloroform saturated with NH<sub>4</sub>OH) eluent] followed by crystallization from acetonitrile yielded 374 mg of tert-butyl-N-[[3-(4-amino-2-methyl-imidazo[4,5-c]quinolin-1-yl)propylamino]-(tert-butoxycarbonylamino)methylene]carbamate.

The BOC protected product was dissolved in 10 mL of 1.25 N HCl in methanol and heated at 70 °C overnight. The mixture was cooled resulting in the precipitation of a solid. The solid was isolated by filtration, rinsed with a cold methanol and dried under vacuum to provide 151 mg of 1-[3-(4-amino-2-methyl-imidazo[4,5-c]quinolin-1-yl)propyl]guanidine

dihydrochloride as a white powder.  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 500 MHz) 7.71 (m, 1H), 7.55 (m, 1H), 7.43-7.37 (m, 2H), 4.23 (m, 2H), 3.18 (t,  $J = 6.4$  Hz, 2H), 2.50 (s, 3H), 1.92 (m, 2H).

#### Example 11

##### 5 1-[3-(4-amino-2-ethyl-imidazo[4,5-c]quinolin-1-yl)propyl]guanidine dihydrochloride

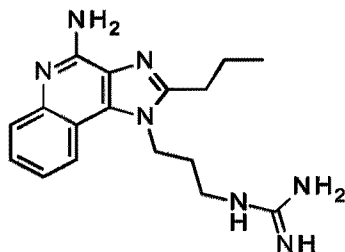


10 1-(3-aminopropyl)-2-ethyl-imidazo[4,5-c]quinolin-4-amine (770 mg, 2.86 mmol) was dissolved 10 mL of anhydrous DMF and stirred under a nitrogen atmosphere. N,N'-Bis-BOC-pyrazole-1-carboximidine (880 mg, 2.84 mmol) was added and the reaction mixture was stirred overnight. The reaction mixture was then concentrated under reduced pressure. The resulting material was dissolved in 50 mL of chloroform and then washed with water (3x) and finally brine. The organic layer was then dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. Chromatography [ $\text{SiO}_2$ , chloroform/(10% methanol/chloroform saturated with  $\text{NH}_4\text{OH}$ ) eluent] followed by crystallization from acetonitrile yielded 561 mg of tert-butyl-N-[[3-(4-amino-2-ethyl-imidazo[4,5-c]quinolin-1-yl)propylamino]-(tert-butoxycarbonylamino)methylene]carbamate.

20 The BOC protected product was dissolved in 10 mL of 1.25 N HCl in methanol and heated at 70 °C overnight. The mixture was cooled resulting in the precipitation of a solid. The solid was isolated by filtration, rinsed with a cold methanol and dried under vacuum to provide 107 mg of 1-[3-(4-amino-2-ethyl-imidazo[4,5-c]quinolin-1-yl)propyl]guanidine dihydrochloride as a white powder.  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 500 MHz) 7.78 (m, 1H), 7.56 (m, 1H), 7.45-7.41 (m, 2H), 4.30 (m, 2H), 3.20 (t,  $J = 6.3$  Hz, 2H), 2.83 (q,  $J = 7.4$  Hz, 2H), 1.96 (m, 25 2H), 1.32 (t,  $J = 7.4$  Hz, 3H).

#### Example 12

##### 1-[3-(4-amino-2-propyl-imidazo[4,5-c]quinolin-1-yl)propyl]guanidine dihydrochloride

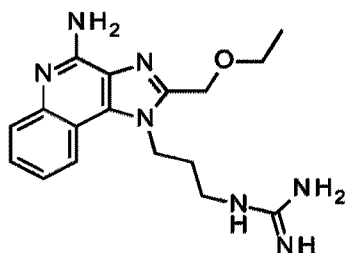


1-(3-aminopropyl)-2-propyl-imidazo[4,5-c]quinolin-4-amine (1.304 g, 4.61 mmol) was dissolved 10 mL of anhydrous DMF and stirred under a nitrogen atmosphere. N,N'-Bis-BOC-pyrazole-1-carboxamide (1.428 mg, 4.61 mmol) was added and the reaction mixture was heated at 50 °C for 2 hours. The reaction mixture was then concentrated under reduced pressure. The resulting material was dissolved in 75 mL of chloroform and then washed with water (3x) and finally brine. The organic layer was then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Chromatography [SiO<sub>2</sub>, chloroform/(10% methanol/chloroform saturated with NH<sub>4</sub>OH) eluent] followed by crystallization from acetonitrile yielded 1.15 g of tert-butyl-N-[[3-(4-amino-2-propyl-imidazo[4,5-c]quinolin-1-yl)propylamino]-(tert-butoxycarbonylamino)methylene]carbamate.

The BOC protected product was dissolved in 15 mL of 1.2 N HCl in methanol and heated at 60 °C overnight. The mixture was cooled resulting in the precipitation of a solid. The solid was isolated by filtration, rinsed with a cold methanol and dried under vacuum to provide 709 mg of 1-[3-(4-amino-2-propyl-imidazo[4,5-c]quinolin-1-yl)propyl]guanidine dihydrochloride as white crystals. <sup>1</sup>H NMR (D<sub>2</sub>O, 500 MHz) 7.70 (m, 1H), 7.54 (m, 1H), 7.44-7.39 (m, 2H), 4.31 (m, 2H), 3.21 (t, *J* = 6.0 Hz, 2H), 2.78 (m, 2H), 1.96 (m, 2H), 1.76 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

### Example 13

1-[3-[4-amino-2-(ethoxymethyl)imidazo[4,5-c]quinolin-1-yl]propyl]guanidine dihydrochloride

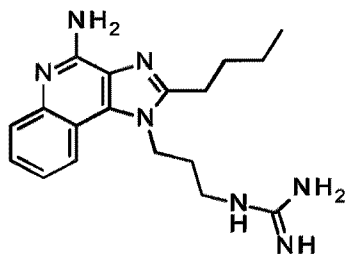


1-(3-aminopropyl)-2-(ethoxymethyl)imidazo[4,5-c]quinolin-4-amine (570 mg, 1.91 mmol) was dissolved in 10 mL of anhydrous DMF and stirred under a nitrogen atmosphere. N,N'-Bis-BOC-pyrazole-1-carboxamidine (590 mg, 1.91 mmol) was added and the reaction mixture was stirred for 3 hours. The reaction mixture was then concentrated under reduced pressure. The resulting material was dissolved in 50 mL of chloroform and then washed with water (3x) and finally brine. The organic layer was then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Chromatography [SiO<sub>2</sub>, chloroform/(10% methanol/chloroform saturated with NH<sub>4</sub>OH) eluent] followed by crystallization from acetonitrile yielded 420 mg of tert-butyl-N-[[3-(4-amino-2-(ethoxymethyl)imidazo[4,5-c]quinolin-1-yl)propylamino]-(tert-butoxycarbonylamino)methylene]carbamate

The BOC protected product was dissolved in 10 mL of 1.2 N HCl in methanol and heated at 60 °C overnight. The mixture was cooled resulting in the precipitation of a solid. The solid was isolated by filtration, rinsed with a cold methanol and dried under vacuum to provide 87 mg of 1-[3-[4-amino-2-(ethoxymethyl)imidazo[4,5-c]quinolin-1-yl]propyl]guanidine dihydrochloride as a white solid. <sup>1</sup>H NMR (D<sub>2</sub>O, 500 MHz) 7.87 (m, 1H), 7.66 (m, 1H), 7.51-7.45 (m, 2H), 4.77 (s, 2H), 4.46 (m, 2H), 3.63 (q, *J* = 7.1 Hz, 2H), 3.29 (t, *J* = 6.3 Hz, 2H), 2.05 (m, 2H), 1.16 (t, *J* = 7.1 Hz, 3H).

#### Example 14

1-[3-(4-amino-2-butyl-imidazo[4,5-c]quinolin-1-yl)propyl]guanidine dihydrochloride



1-(3-aminopropyl)-2-butyl-imidazo[4,5-c]quinolin-4-amine (1.26 g, 4.26 mmol) was dissolved in 10 mL of anhydrous DMF and stirred under a nitrogen atmosphere. N,N'-Bis-BOC-pyrazole-1-carboxamidine (1.32 mg, 4.26 mmol) was added and the reaction mixture was stirred overnight. The reaction mixture was treated with an additional portion of N,N'-bis-BOC-pyrazole-1-carboxamidine and stirring was continued for 24 hours. The reaction mixture was then concentrated under reduced pressure. The resulting material was dissolved in 50 mL of chloroform and then washed with water (3x) and finally brine. The organic layer



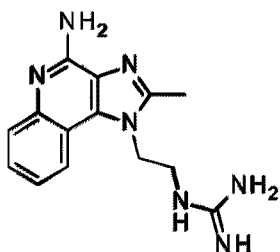
was then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure.

Chromatography [SiO<sub>2</sub>, chloroform/(10% methanol/chloroform saturated with NH<sub>4</sub>OH) eluent] followed by crystallization from acetonitrile yielded 262 mg of tert-butyl-N-[[3-(4-amino-2-butyl-imidazo[4,5-c]quinolin-1-yl)propylamino]-(tert-butoxycarbonylamino)methylene]carbamate.

The BOC protected product was dissolved in 10 mL of 1.2 N HCl in methanol and heated at 70 °C overnight. The mixture was cooled resulting in the precipitation of a solid. The solid was isolated by filtration, rinsed with a cold methanol and dried under vacuum to provide 81 mg of 1-[3-(4-amino-2-butyl-imidazo[4,5-c]quinolin-1-yl)propyl]guanidine dihydrochloride as white crystals. <sup>1</sup>H NMR (D<sub>2</sub>O, 500 MHz) 7.78 (m, 1H), 7.53 (m, 1H), 7.44-7.39 (m, 2H), 4.32 (m, 2H), 3.21 (t, *J* = 6.2 Hz, 2H), 2.79 (t, *J* = 7.8 Hz, 2H), 1.96 (m, 2H), 1.70 (m, 2H), 1.37 (m, 2H), 0.87 (t, *J* = 7.4 Hz, 3H).

#### Example 15

1-[2-(4-amino-2-methyl-imidazo[4,5-c]quinolin-1-yl)ethyl]guanidine dihydrochloride



N'-(3-nitro-4-quinolyl)ethane-1,2-diamine (7.48 g, 32.2 mmol) was dissolved 50 mL of anhydrous DMF and stirred under a nitrogen atmosphere. N,N'-Bis-BOC-pyrazole-1-carboximidine (10.0 g, 32.3 mmol) was added and the reaction mixture was stirred overnight. The reaction mixture was then concentrated under reduced pressure to give a yellow solid. The resulting material was dissolved in 300 mL of dichloromethane and then washed with water (3x) and finally brine. The organic layer was then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting yellow solid was triturated in 100 mL of ethyl acetate, filtered and dried to give 13.5 g tert-butyl-N-[(tert-butoxycarbonylamino)-[2-[(3-nitro-4-quinolyl)amino]ethylamino]methylene]carbamate as a yellow solid.

tert-Butyl-N-[(tert-butoxycarbonylamino)-[2-[(3-nitro-4-quinolyl)amino]ethylamino]methylene]carbamate (5.13 g) was placed in a Parr<sup>TM</sup> reaction vessel and suspended in 200 mL of acetonitrile. Following the addition of 200 mg of 3% Pt

on carbon, the vessel was shaken under 40 PSI of hydrogen pressure for 4 hours. The reaction mixture was filtered through a pad of Celite<sup>TM</sup> and concentrated under reduced pressure to give 4.80 g of tert-butyl-N-[[2-[(3-amino-4-quinolyl)amino]ethylamino]-(tert-butoxycarbonylamino)methylene]carbamate as a light brown foam.

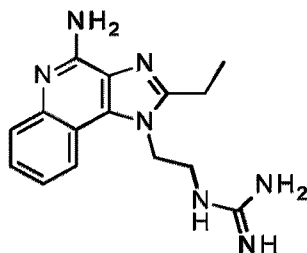
5        tert-Butyl-N-[[2-[(3-amino-4-quinolyl)amino]ethylamino]-(tert-butoxycarbonylamino)methylene]carbamate (2.78 g, 6.26 mmol) was dissolved in 30 mL of dichloromethane and cooled to 0 °C under an atmosphere of nitrogen. Triethylamine (0.87 mL, 6.26 mmol) and acetyl chloride (445 µL, 6.26 mmol) were added and the reaction was stirred overnight. The reaction mixture was then concentrated under reduced pressure. The resulting  
10        material was dissolved in 30 mL of ethanol, treated with 1 mL of triethylamine and heated to reflux for 3 hours. The reaction mixture was then concentrated under reduced pressure. The resulting syrup was dissolved in 50 mL of dichloromethane and then washed with water (3x) and finally brine. The organic layer was then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Chromatography (SiO<sub>2</sub>, 2-20% methanol/ethyl acetate eluent) gave 1.15 g of  
15        tert-butyl-N-[(tert-butoxycarbonylamino)-[2-(2-methylimidazo[4,5-c]quinolin-1-yl)ethylamino]methylene]carbamate as an amber foam.

The foam (1.15 g, 2.46 mmol) was dissolved in 30 mL of dichloromethane and mCPBA (57-86%, 0.74 g) was added. After stirring for 60 minutes, concentrated NH<sub>4</sub>OH solution (10 ML) and p-toluenesulfonyl chloride (516 mg, 2.70 mmol) were added. The resulting reaction  
20        mixture was stirred for 60 minutes, and then sequentially diluted with 25 mL of dichloromethane, washed with water (2x), and washed with brine. The organic layer was then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Chromatography [SiO<sub>2</sub>, chloroform/(10% methanol/chloroform saturated with NH<sub>4</sub>OH) eluent] followed by crystallization from acetonitrile yielded 435 mg of tert-butyl-N-[[2-(4-amino-2-methyl-  
25        imidazo[4,5-c]quinolin-1-yl)ethylamino]-(tert-butoxycarbonylamino)methylene]carbamate as amber crystals.

The BOC protected product was dissolved in 5 mL of 2.5 N HCl in methanol and heated at 70 °C for 4 hours. The mixture was cooled resulting in the precipitation of a solid. The solid was isolated by filtration and crystallized from ethanol and water to provide 151 mg of 1-[2-  
30        (4-amino-2-methyl-imidazo[4,5-c]quinolin-1-yl)ethyl]guanidine dihydrochloride as a white solid. <sup>1</sup>H NMR (D<sub>2</sub>O, 500 MHz) 7.90 (m, 1H), 7.60 (m, 1H), 7.50-7.45 (m, 2H), 4.51 (t, *J* = 5.3 Hz, 2H), 3.60 (t, *J* = 5.3 Hz, 2H), 2.52 (s, 3H).

## Example 16

1-[2-(4-amino-2-ethyl-imidazo[4,5-c]quinolin-1-yl)ethyl]guanidine dihydrochloride



5

tert-butyl-N-[[2-[(3-amino-4-quinolyl)amino]ethylamino]-(tert-butoxycarbonylamino)methylene]carbamate (2.24 g, 5.05 mmol) was dissolved in 15 mL of dichloromethane and cooled to 0 °C under an atmosphere of nitrogen. Triethylamine (702 microliters, 5.05 mmol) and propionyl chloride (441 microliters, 6.26 mmol) were added and the reaction was stirred overnight. The reaction mixture was then concentrated under reduced pressure. The resulting material was dissolved in 20 mL of ethanol, treated with 1 mL of triethylamine and heated to reflux for 3 hours. The reaction mixture was then concentrated under reduced pressure. The resulting syrup was dissolved in 50 mL of dichloromethane and then washed with water (3x) and finally brine. The organic layer was then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Chromatography (SiO<sub>2</sub>, 2-20% methanol/ethyl acetate eluent) gave 0.77 g of tert-butyl-N-[(tert-butoxycarbonylamino)-[2-(2-ethylimidazo[4,5-c]quinolin-1-yl)ethylamino]methylene]carbamate as an amber foam.

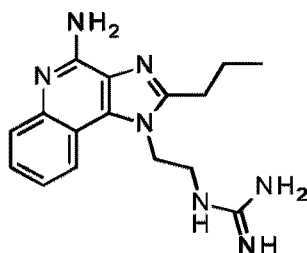
The foam (737 mg, 1.52 mmol) was dissolved in 30 mL of dichloromethane and mCPBA (57-86%, 461 mg) was added. After stirring for 60 minutes, concentrated NH<sub>4</sub>OH solution (10 mL) and p-toluenesulfonyl chloride (319 mg, 1.67 mmol) were added. The resulting reaction mixture was stirred for 60 minutes, and then sequentially diluted with 25 mL of dichloromethane, washed with water (2x) and washed with brine. The organic layer was then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Chromatography [SiO<sub>2</sub>, chloroform/(10% methanol/chloroform saturated with NH<sub>4</sub>OH) eluent] followed by crystallization from hexanes/propyl acetate yielded 424 mg of tert-butyl-N-[2-(4-amino-2-ethyl-imidazo[4,5-c]quinolin-1-yl)ethylamino]-(tert-butoxycarbonylamino)methylene]carbamate as rust-colored crystals.

The BOC protected product was dissolved in 5 mL of 2.5 N HCl in methanol and heated at 70 °C for 4 hours. The mixture was cooled and concentrated under reduced

pressure. The resulting material was dissolved in 10 mL of H<sub>2</sub>O and washed with chloroform (3 x 10 mL). The aqueous portion was concentrated under reduced pressure. The resulting solid was triturated with ethanol and a drop of H<sub>2</sub>O and then filtered to provide 72 mg of 1-[2-(4-amino-2-ethyl-imidazo[4,5-c]quinolin-1-yl)ethyl]guanidine dihydrochloride as an off-white solid. <sup>1</sup>H NMR (D<sub>2</sub>O, 500 MHz) 7.89 (m, 1H), 7.57 (m, 1H), 7.48-7.43 (m, 2H), 4.51 (m, 2H), 3.58 (m, 2H), 2.82 (q, *J* = 7.4 Hz, 2H), 1.34 (t, *J* = 7.4 Hz, 3H).

#### Example 17

1-[2-(4-amino-2-propyl-imidazo[4,5-c]quinolin-1-yl)ethyl]guanidine dihydrochloride



tert-Butyl-N-[[2-[(3-amino-4-quinolyl)amino]ethylamino]-(tert-butoxycarbonylamino)methylene]carbamate (2.17 g, 4.89 mmol) was dissolved in 15 mL of dichloromethane and cooled to 0 °C under an atmosphere of nitrogen. Triethylamine (680 microliters, 4.89 mmol) and butyryl chloride (511 microliters, 4.89 mmol) were added and the reaction was stirred overnight. The reaction mixture was then concentrated under reduced pressure. The resulting material was dissolved in 10 mL of toluene and heated at reflux for 3 hours. The reaction mixture was then concentrated under reduced pressure. The resulting syrup was dissolved in 50 mL of dichloromethane and then washed with water (3x) and finally brine. The organic layer was then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Chromatography (SiO<sub>2</sub>, 2-20% methanol/ethyl acetate eluent) gave 1.05 g of tert-butyl-N-[(tert-butoxycarbonylamino)-[2-(2-propyl-imidazo[4,5-c]quinolin-1-yl)ethylamino]methylene]carbamate as light brown foam.

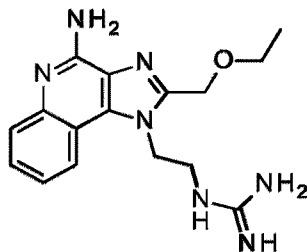
The foam (1.05 g, 2.12 mmol) was dissolved in 20 mL of dichloromethane and mCPBA (57-86%, 639 mg) was added. After stirring for 60 minutes, concentrated NH<sub>4</sub>OH solution (10 mL) and p-toluenesulfonyl chloride (444 mg, 2.33 mmol) were added. The resulting reaction mixture was stirred for 60 minutes, and then sequentially diluted with 50 mL of dichloromethane, washed with water (3x) and washed with brine. The organic layer was then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure.

Chromatography [ $\text{SiO}_2$ , chloroform/(10% methanol/chloroform saturated with  $\text{NH}_4\text{OH}$ ) eluent] followed by crystallization from acetonitrile yielded 380 mg of tert-butyl-N-[[2-(4-amino-2-propyl-imidazo[4,5-c]quinolin-1-yl)ethylamino]-(tert-butoxycarbonylamino)methylene]carbamate as colorless crystals.

The BOC protected product was dissolved in 5 mL of 2.5 N HCl in methanol and heated at 70 °C for 4 hours. The mixture was cooled and concentrated under reduced pressure. The resulting material was crystallized from ethanol and a drop of  $\text{H}_2\text{O}$  to give 204 mg of 1-[2-(4-amino-2-propyl-imidazo[4,5-c]quinolin-1-yl)ethyl]guanidine dihydrochloride as white crystals.  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 500 MHz) 7.83 (m, 1H), 7.54 (m, 1H), 7.45-7.39 (m, 2H), 4.48 (t,  $J = 5.4$  Hz, 2H), 3.56 (t,  $J = 5.4$  Hz, 2H), 2.75 (t,  $J = 7.5$  Hz, 2H), 1.82 (m, 2H), 1.00 (t,  $J = 7.4$  Hz, 3H).

#### Example 18

1-[2-(4-amino-2-(ethoxymethyl)imidazo[4,5-c]quinolin-1-yl)ethyl]guanidine dihydrochloride



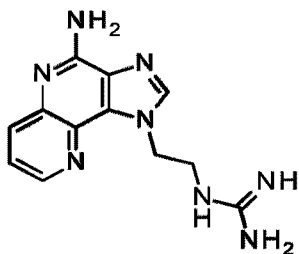
tert-Butyl-N-[[2-[(3-amino-4-quinolyl)amino]ethylamino]-(tert-butoxycarbonylamino)methylene]carbamate (2.35 g, 5.29 mmol) was dissolved in 30 mL of dichloromethane and cooled to 0 °C under an atmosphere of nitrogen. Triethylamine (736 microliters, 5.29 mmol) and ethoxyacetyl chloride (578 microliters, 5.29 mmol) were added and the reaction was stirred overnight. The reaction mixture was then concentrated under reduced pressure. The resulting material was dissolved in 30 mL of ethanol, treated with 1 mL of triethylamine and heated at reflux for 3 hours. The reaction mixture was then concentrated under reduced pressure. The resulting syrup was dissolved in 50 mL of dichloromethane and then washed with water (3x) and finally brine. The organic layer was then dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. Chromatography ( $\text{SiO}_2$ , 2-20% methanol/ethyl acetate eluent) gave 1.28 g of tert-butyl-N-[(tert-butoxycarbonylamino)-[2-(2-(ethoxymethyl)imidazo[4,5-c]quinolin-1-yl)ethylamino]methylene]carbamate as a yellow syrup.

The syrup (1.28 g, 2.50 mmol) was dissolved in 30 mL of dichloromethane and mCPBA (57-86%, 0.75 g) was added. After stirring for 90 minutes, concentrated NH<sub>4</sub>OH solution (10 mL) and p-toluenesulfonyl chloride (524 mg, 2.75 mmol) were added. The resulting reaction mixture was stirred for 2 hours, and then sequentially diluted with 25 mL of dichloromethane, washed with water (2x), and washed with brine. The organic layer was then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Chromatography [SiO<sub>2</sub>, chloroform/(10% methanol/chloroform saturated with NH<sub>4</sub>OH) eluent] followed by crystallization from acetonitrile 524 mg of tert-butyl-N-[[2-(4-amino-2-(ethoxymethyl)imidazo[4,5-c]quinolin-1-yl)ethylamino]-(tert-butoxycarbonylamino)methylene]carbamate as amber needles.

The BOC protected product from the previous reaction was dissolved in 5 mL of 2.5 N HCl in methanol and heated at 70 °C for 4 hours. The mixture was cooled to give a syrup. The syrup was treated with a 5 mL of ethanol and subsequent rapid stirring resulted in the formation of a precipitate which was isolated by filtration to provide 179 mg of 1-[2-(4-amino-2-(ethoxymethyl)imidazo[4,5-c]quinolin-1-yl)ethyl]guanidine dihydrochloride as a white powder. <sup>1</sup>H NMR (D<sub>2</sub>O, 500 MHz) 7.99 (m, 1H), 7.62 (m, 1H), 7.53 (m, 1H), 7.48 (m, 1H), 4.76 (s, 2H), 4.68 (m, 2H), 3.69-3.65 (m, 4H), 1.81 (t, *J* = 7.1 Hz, 3H).

#### Example 19

1-[2-(4-aminoimidazo[4,5-c][1,5]naphthyridin-1-yl)ethyl]guanidine dihydrochloride



1-(2-aminoethyl)imidazo[4,5-c][1,5]naphthyridin-4-amine (387 mg, 1.70 mmol) was dissolved in 5 mL of anhydrous DMF and stirred under a nitrogen atmosphere. N,N'-bis-BOC-pyrazole-1-carboxamide (526 mg, 1.70 mmol) was added and the reaction mixture was stirred overnight. The reaction mixture was then concentrated under reduced pressure. The resulting white solid was triturated with ethyl acetate to give a white powder which was isolated by filtration to give 686 mg of tert-butyl-N-[[2-(4-aminoimidazo[4,5-c][1,5]naphthyridin-1-yl)ethylamino]-(tert-butoxycarbonylamino)methylene]carbamate

as a white powder.

The BOC protected product was dissolved in 10 mL of 2.5 N HCl in methanol and heated to 60 °C overnight. The mixture was cooled resulting in the precipitation of a solid. The solid was isolated by filtration, rinsed with a cold methanol and dried under vacuum to provide 251 mg of 1-[2-(4-aminoimidazo[4,5-c][1,5]naphthyridin-1-yl)ethyl]guanidine dihydrochloride as a white powder. <sup>1</sup>H NMR (D<sub>2</sub>O, 500 MHz) 8.60 (dd, *J* = 1.4, 4.6 Hz, 1H), 8.24 (s, 1H), 7.96 (dd, *J* = 1.4, 8.6 Hz, 1H), 7.59 (dd, *J* = 4.6, 8.6 Hz, 1H), 4.81 (t, *J* = 6.3 Hz, 2H), 3.64 (t, *J* = 6.3 Hz, 2H).

#### Cytokine Induction in Human Cells

Whole blood was obtained from healthy human donors and collected by venipuncture into vacutainer tubes or syringes containing EDTA. Human peripheral blood mononuclear cells (PBMC) were purified from the whole blood by density gradient centrifugation. Histopaque 1077 (15 mL, Sigma, St. Louis, MO) was transferred to 6 X 50 mL sterile polypropylene conical tubes. The Histopaque was overlaid with 15-25 mL of blood diluted 1:2 in Hank's Balanced Salts Solution (HBSS) (Gibco, Life Technology, Grand Island NY). The tubes were then centrifuged at 1370 rpm for 30 minutes at 20 °C, with no brake (400Xg, GH 3.8A Rotor).

The interface (buffy coat) containing the PBMC was collected and placed in a new sterile 50 mL conical polypropylene centrifuge tube. The PBMC were mixed with an equal volume of HBSS (about 20 mL from the interface and about 20 mL of HBSS), and then centrifuged at 1090 rpm, 10 min, 20 °C, with brake (270Xg, GH 3.8A Rotor). After completing centrifugation, the cells were resuspended in 2-3mL ACK Red blood cell lysis buffer (ammonium chloride potassium solution, Gibco, Life Technology) and incubated for 2-5 minutes at 20 °C. Next, HBSS (40 mL) was added to the cells, and the sample was centrifuged at 270Xg for 10 min at 20 °C. The supernatant was decanted, and the cell pellet was resuspended in 5 mL AIM V® Medium (Gibco, Life Technology). Cell aggregates and debris were removed by filtering the cell solution through a BD Falcon 70 micron nylon cell strainer (BD Biosciences, San Jose, CA).

The number of viable cells were determined by counting with a Miltenyi FACS instrument (Miltenyi Biotec Inc., San Diego, CA) or by using a hemacytometer. For determining cell viability with a hemacytometer, the cells were diluted 1/10 in 0.4% trypan blue and HBSS (specifically, 50 microliter of trypan blue + 40 microliter of HBSS + 10 microliter of cell solution were added to a microfuge tube and mixed). Ten microliters of the diluted cells were then applied to the hemacytometer, and the number of viable PBMC were determined by microscopy.

The PBMC sample was then resuspended in 96-well plates at a concentration of  $8 \times 10^5$  cells/well in 0.1 mL of AIM-V medium. Each compound was solubilized in DMSO to create a 3 mM stock solution. The stock solution was then further diluted with AIM-V medium to prepare the serial

dilutions. The diluted compound (100 microliters) was then transferred to the PBMCs to achieve final compound concentrations of 10, 1, 0.1, 0.01, 0.001, 0.0001 micromolar. The plates also had both positive and negative controls. The negative control wells contained only AIM-V medium with no example compound. The positive control wells contained imiquimod serially diluted to concentrations of 10, 1, 0.1, 0.01, 0.001, 0.0001 micromolar. The plates were then cultured at 37°C /5 % CO<sub>2</sub> for 21-24hrs. Cell-free supernatants were harvested by centrifuging the 96-well plates at 2100 rpm, 23°C for 10 minutes. Approximately 160 microliter of the supernatant was then stored in a NUNC 96-well plate, covered with the compression cap and stored at -80°C until the cytokine analysis was done.

IFN-alpha cytokine levels (pg/mL) were measured by ELISA (human IFN- $\alpha$ , pan specific, Mabtech, Cincinnati, OH), IFN-gamma, TNF-alpha, and IP-10 cytokine levels (pg/mL) were measured by multiplex bead assay (magnetic beads, R & D Systems Minneapolis, MN) according to the manufacturer's instructions.

The data was analyzed to determine the minimum effective concentration (MEC) for each compound at which induction of a particular cytokine was observed in the assay. Specifically, the minimum effective concentration of each compound (micromolar) was determined as the lowest concentration of the compound that induced a measured cytokine response at a level (pictograms/mL) that was at least 2X greater than that observed with the negative control wells. The results are presented in Table 1.

Table 1.

Compound	MEC to Induce Cytokine (micromolar)			
	IFN-alpha	IFN-gamma	TNF-alpha	IP-10
Example 1	1	NT	0.001	NT
Example 2	0.1	NT	0.1	0.1
Example 3	0.1	>10	0.1	NT
Example 4	0.01	0.1	0.01	0.01
Example 5	0.01	0.01	0.001	0.001
Example 6	0.01	0.01	0.01	0.01
Example 7	1	>10	1	0.1
Example 8	0.1	0.1	0.1	0.01
imiquimod	10	10	10	10

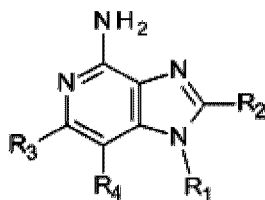
NT = not tested

Various modifications and alterations to this invention will become apparent to those of ordinary skill 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.



CLAIMS:

1. A compound of the Formula (I):



**Formula I**

wherein:

$R_3$  and  $R_4$  are taken together to form a fused benzene ring, a fused pyridine ring, a fused cyclohexene ring, or a fused tetrahydropyridine ring; wherein the fused benzene ring, fused pyridine ring, fused cyclohexene ring, or fused tetrahydropyridine ring is either unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of halogen, hydroxyl, alkyl, alkoxy, haloalkyl,

-C(O)-O-alkyl, -C(O)-OCH<sub>2</sub>Ph, -C(O)-O-aryl, amino, alkylamino, dialkylamino, aryl, arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, heteroarylalkyleneoxy, and heteroaryloxy, wherein the alkyl, aryl, arylalkylenyl, aryloxyalkylenyl, arylalkyleneoxy, aryloxy, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, heteroarylalkyleneoxy, and heteroaryloxy groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, haloalkyl, hydroxyl, hydroxyalkylenyl, alkoxyalkylenyl, arylalkyleneoxy, nitrile, amino, alkylamino, and dialkylamino;

$R_1$  is -W-X-N(H)-C(=NH)-NH<sub>2</sub>;

W is selected from the group consisting of a covalent bond, -O-, and -NH-;

X is selected from the group consisting of -CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>-, -CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-O-CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-O-CH<sub>2</sub>CH<sub>2</sub>-O-CH<sub>2</sub>CH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2-4</sub>-(OCH<sub>2</sub>CH<sub>2</sub>)<sub>1-5</sub>, and -(CH<sub>2</sub>)<sub>2-6</sub>-(OCH<sub>2</sub>CH<sub>2</sub>)<sub>1-4</sub>;

$R_2$  is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, -O-alkyl, hydroxyalkylenyl, alkoxyalkylenyl, alkylaminoalkylenyl, hydroxyl, -CH<sub>2</sub>-NH-O-alkyl, and -CH<sub>2</sub>NHC(O)-alkyl;

wherein

alkyl groups contain from 1 to 14 carbon atoms,

haloalkyl groups are alkyl groups that are substituted by one or more halogen atoms,

aryl groups are selected from the group consisting of phenyl, naphthyl, and biphenyl,

alkylenyl groups contain from 1 to 14 carbon atoms,

alkylene groups contain from 1 to 14 carbon atoms,

heteroaryl groups are a ring or ring system that contains 2 to 12 carbon atoms, 1 to 3 rings, 1 to 4 heteroatoms with O, S, and N as the heteroatoms,

alkenyl groups contain from 2 to 14 carbon atoms,

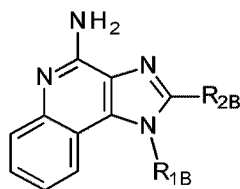
alkynyl groups contain from 2 to 14 carbon atoms,

cycloalkyl groups contain from 3 to 10 ring carbon atoms, and

unless otherwise defined, groups having the prefix "alk-" contain from 1 to 14 carbon atoms,

or a pharmaceutically acceptable salt thereof.

2. The compound or salt of claim 1, wherein  $R_3$  and  $R_4$  are taken together to form a fused benzene ring, a fused pyridine ring, or a fused cyclohexene ring, and wherein the fused benzene ring, fused pyridine ring, or fused cyclohexene ring is either unsubstituted or substituted by one and only one R group.
3. The compound or salt of claim 1 or 2, wherein W is a covalent bond or -O-.
4. The compound or salt of any one of claims 1 to 3, wherein  $R_2$  is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, alkylaminoalkylenyl, and hydroxyalkylenyl.
5. A compound of the Formula XIII:



Formula XIII

wherein:

$R_{1B}$  is selected from the group consisting of -X<sub>B</sub>-N(H)-C(=NH)-NH<sub>2</sub>;

$X_B$  is selected from the group consisting of  $-\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}_2\text{C}(\text{CH}_3)_2-$ ,  $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}_2\text{-O-CH}_2\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}_2\text{-O-CH}_2\text{CH}_2\text{-O-CH}_2\text{CH}_2-$ ,  $-(\text{CH}_2)_{2-4}\text{-(OCH}_2\text{CH}_2\text{)}_{1-5}$ , and  $-(\text{CH}_2)_{2-6}\text{-(OCH}_2\text{CH}_2\text{)}_{1-4}$ ;

$R_{2B}$  is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, -O-alkyl, hydroxyalkylenyl, alkoxyalkylenyl, alkylaminoalkylenyl, hydroxyl,  $-\text{CH}_2\text{-NH-O-alkyl}$ , and  $-\text{CH}_2\text{NHC(O)-alkyl}$ ;

wherein

alkyl groups contain from 1 to 14 carbon atoms,

alkylenyl groups contain from 1 to 14 carbon atoms,

alkenyl groups contain from 2 to 14 carbon atoms,

alkynyl groups contain from 2 to 14 carbon atoms, and

unless otherwise defined, groups having the prefix "alk-" contain from 1 to 14 carbon atoms, or a pharmaceutically acceptable salt thereof.

6. The compound or salt of claim 5, wherein  $R_{2B}$  is selected from the group consisting of hydrogen,  $-\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{OCH}_3$ ,  $-\text{CH}_2\text{OCH}_2\text{CH}_3$ , and  $-\text{CH}_2\text{CH}_2\text{OCH}_3$ .
7. The compound or salt of any one of claims 1 to 6 for use in the treatment of a viral disease or a neoplastic disease in an animal.
8. Use of the compound or salt as defined in any one of claims 1 to 6 for the treatment of a viral disease or a neoplastic disease in an animal.
9. A pharmaceutical composition comprising the compound or salt as defined in any one of claims 1 to 6 in combination with a pharmaceutically acceptable carrier.

