

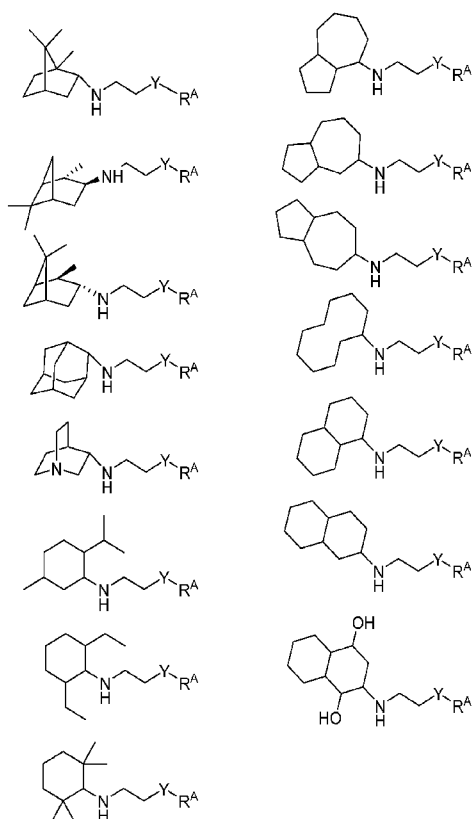


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[Continued on next page]

(54) **Title:** ANTI-MICROBIAL COMPOUNDS AND COMPOSITIONS

Figure 1



(57) **Abstract:** The invention provides a novel compounds and methods of using the compounds. The invention also provides methods of using a variety of compounds to treat infections, such as bacterial or parasitic infections. The compounds can also be used to kill or inhibit the growth of bacteria or parasites. In one embodiment, the compounds are particularly effective for the treatment or inhibition of tuberculosis.



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ANTI-MICROBIAL COMPOUNDS AND COMPOSITIONS

5

RELATED APPLICATIONS

This application claims priority under 35 U.S.C. §119(e) to U.S. Provisional Patent Application No. 61/874,579, filed September 6, 2013, which is incorporated herein by reference.

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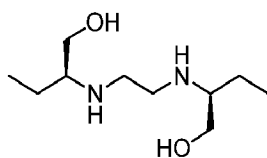
GOVERNMENT SUPPORT

This invention was made with government support under Grant Nos. AI074233, GM65307, and CA158191, each awarded by the National Institutes of Health. The United States Government has certain rights in the invention.

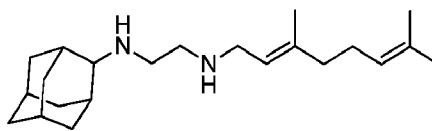
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BACKGROUND OF THE INVENTION

The occurrence of drug resistance is a growing problem. One serious threat is with tuberculosis because there are many millions of individuals infected with *Mycobacterium tuberculosis*, the causative agent of tuberculosis, resulting in ~1-2 million deaths per year. Chemotherapy is lengthy and there is increasing resistance to current antibiotics, in some cases, with complete resistance being found. New drugs and drug leads are thus needed. One of the oldest drugs for tuberculosis treatment is ethambutol (1), an ethylenediamine derivative. In recent work some 74,000 analogs of ethambutol including the ethylenediamine SQ109 (2) (Protopopova et al., *J. Antimicrob. Chemoth.* **2005**,56 (5), 968) and the piperidine SQ609 (Bogatcheva et al., *Bioorg. Med. Chem. Lett.* **2011**,21 (18), 5353) have shown promise.



ethambutol (1)



SQ109 (2)

30

The primary mechanism of action of SQ109 has been proposed to be inhibition of the membrane protein MmpL3, a trehalose monomycolate transporter. There have been no reports of spontaneous resistance to SQ109 but resistance to somewhat similar species involving MmpL3 has been reported, and these MmpL3 mutants have modest cross-resistance to SQ109. A somewhat puzzling observation of these and related results is that mutations appear to occur in widely different spatial positions (based on computer-generated

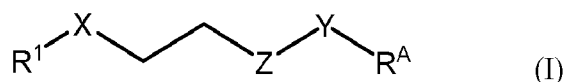
MmpL3 structural models), suggesting, perhaps, additional targets. Moreover, SQ109 has activity against other bacteria (e.g. *Helicobacter pylori*) and yeasts (e.g. *Candida albicans*) that lack the *mmpL3* gene, so in these organisms there must be other targets/mechanisms of action which could also of course be present/operational in *M. tuberculosis*.

5 Accordingly, novel compounds are needed to evaluate the cause of inhibition of various microbes in order to improve current treatment methods. New compounds and methods are also needed for the treatment of infections caused by various microbes and parasites. Compounds are also needed to kill malaria parasites and the organisms that cause tuberculosis to aid the therapeutic treatment of dangerous infections. New compounds and
10 therapeutic methods are also needed to treat infectious diseases because of the rapid rise in drug resistance.

SUMMARY

The invention provides novel compounds that can be used as research tools and anti-
15 infective therapeutic agents. The invention therefor also provides therapeutic methods for treating conditions such as malaria, and bacterial and fungal infections.

Accordingly, the invention provides compounds of Formula I:



wherein

20 X is O, NH, N⁺(Me)₂, S, S(=O), S(=O)₂, or a direct bond;

Y is O, NH, N⁺(Me)₂, S, S(=O), or S(=O)₂;

provided that one of X and Y is NH or N⁺(Me)₂, and X and Y are not both NH;

Z is a direct bond, -CH₂-, or -CH₂-CH₂-; and

R¹ is a (C₆-C₁₀)cycloalkyl, benz-fused cyclohexyl, (C₆-C₁₄)aryl, (C₅-C₉)heterocycle,
25 or (C₅-C₉)heteroaryl group, wherein each group is optionally substituted with a (C₁-C₃)alkoxy group, one to four hydroxyl groups, one or two oxo groups, one to four (C₁-C₃)alkyl groups, or a combination thereof; and

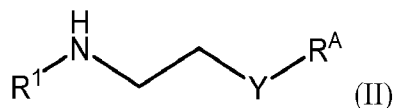
R^A is (C₅-C₁₅)alkyl, (C₅-C₁₅)alkenyl, or phenoxyphenyl(C₁-C₄)alkyl, wherein the alkyl or alkenyl is straight chain or branched;

30 or a salt or solvate thereof.

In one embodiment, X is NH. In another embodiment, X is O or S.

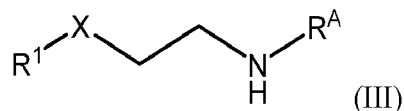
In one embodiment, Y is NH. In another embodiment, Y is O or S.

In some embodiments, the compound of Formula I is a compound of Formula II:



wherein Y is O or S; and R^1 and R^A are as defined for Formula I, or a salt or solvate thereof.

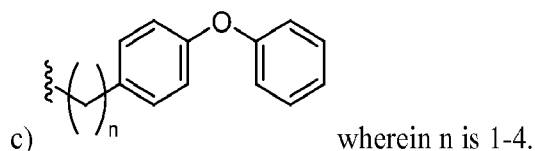
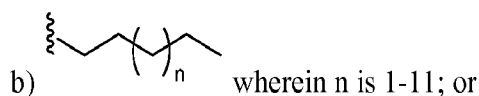
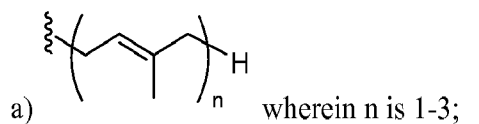
In other embodiments, the compound of Formula I is a compound of Formula III"



5 wherein X is O or S; and R^1 and R^A are as defined for Formula I, or a salt or solvate thereof.

The phenoxy (-OPh) group of the phenoxyphenyl(C₁-C₄)alkyl can be located at an ortho, meta, or para position on the phenyl(C₁-C₄)alkyl group. The phenoxy or phenyl group can be optionally substituted with one or more substituents described below for the term substituted.

10 In some embodiments, R^A is:

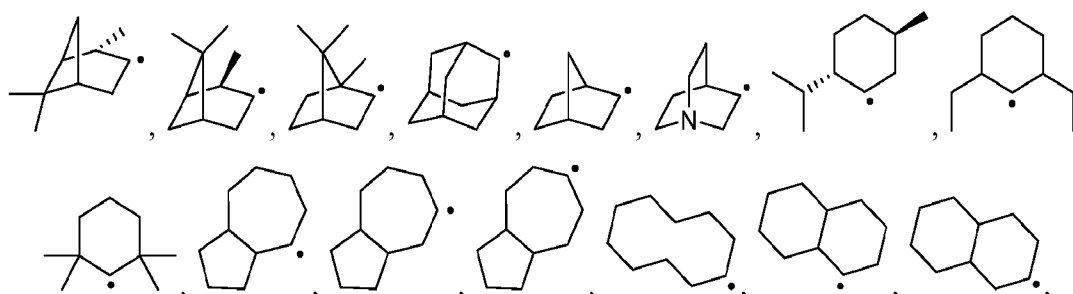


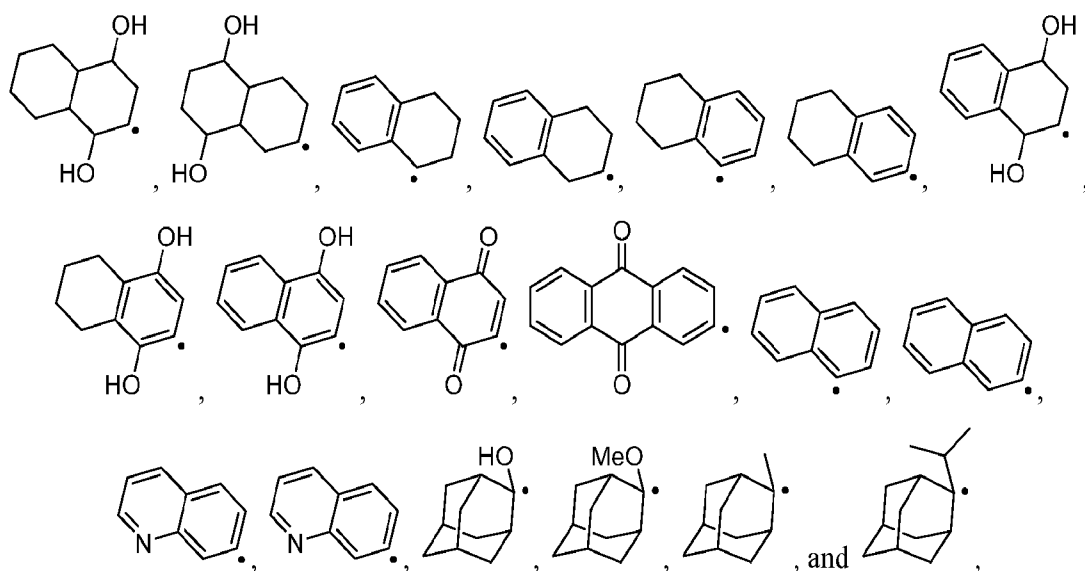
15 In various embodiments, R^A can be a prenyl group, a geranyl group, a farnesyl group, a saturated prenyl group, a saturated geranyl group, or a saturated farnesyl group. These groups can be optionally substituted with one or more substituents described below for the term substituted.

In some embodiments, R^1 is substituted with one or two hydroxyl groups or one or two methoxy groups. R^1 can also be substituted with one, two, three, or four methyl groups.

20 R^1 can further be substituted with one or two oxo groups.

The group R^1 can also be selected from:

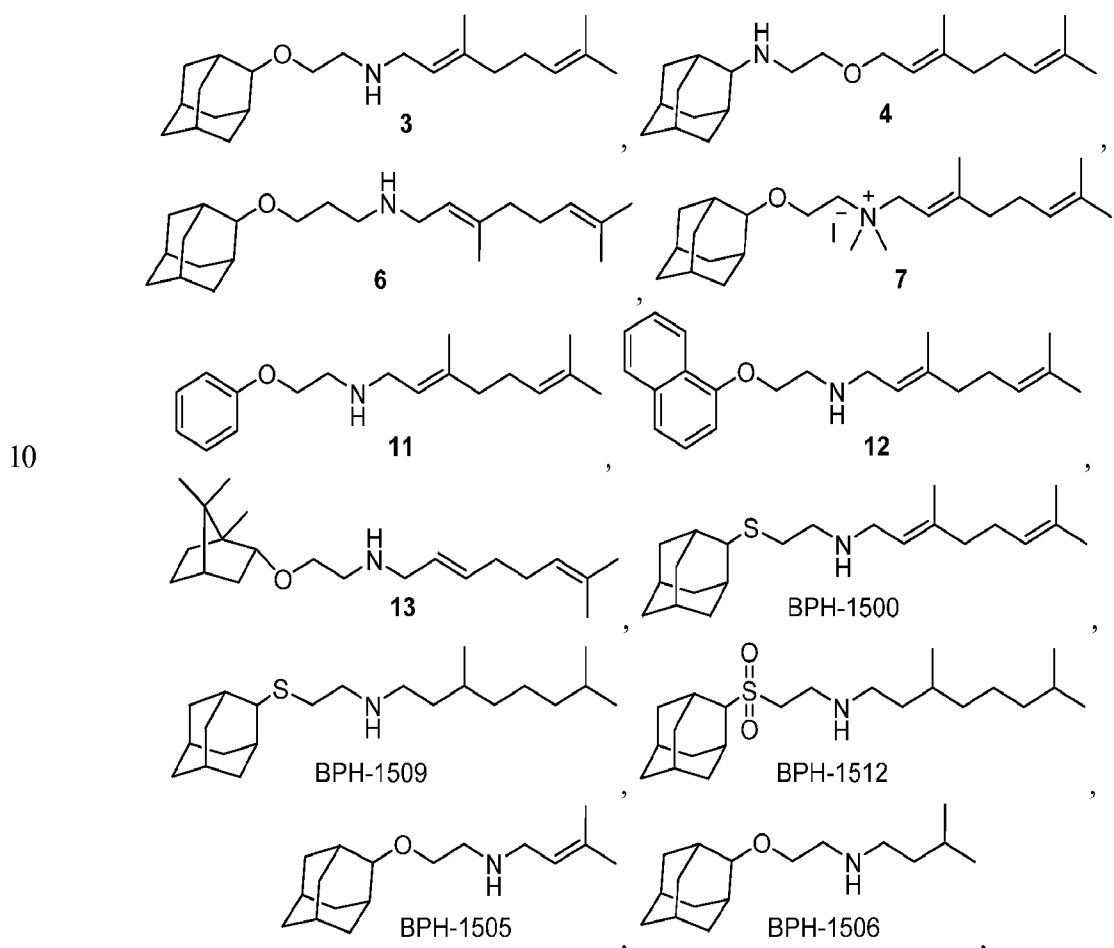


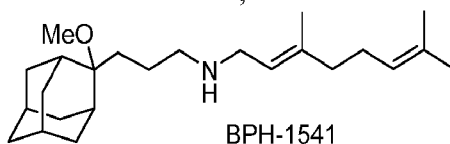
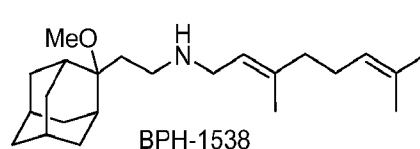
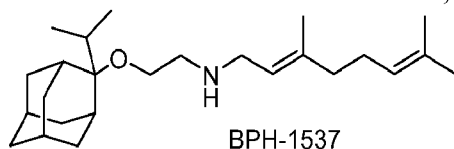
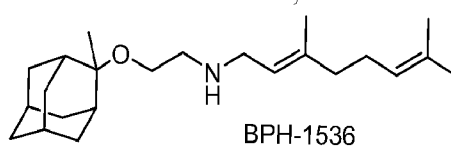
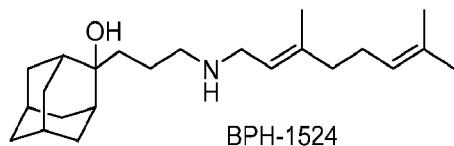
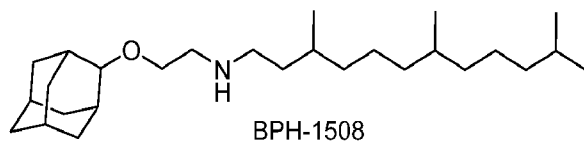
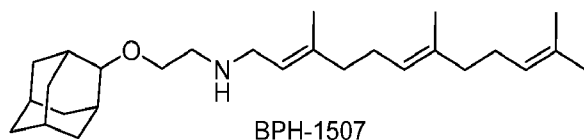


wherein the radical "•" indicates the site of attachment to the group X. The invention

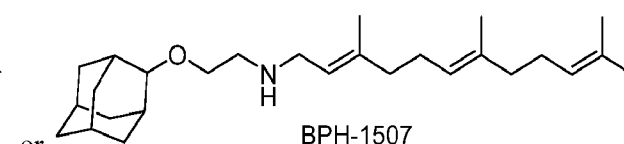
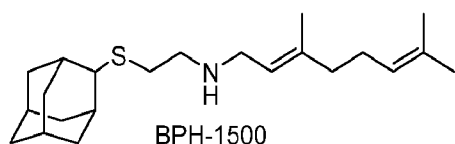
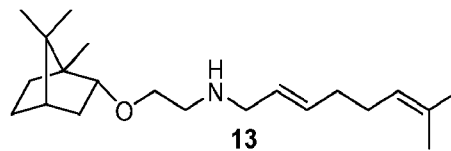
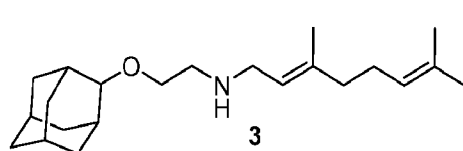
- 5 includes all chiral, enantiomeric, diastereomeric, and racemic forms of the structures illustrated and/or described herein.

In certain specific embodiments, the compound of Formula I is one or more of:



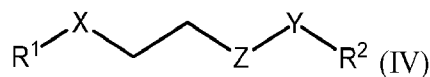


or a salt or solvate thereof. In certain other specific embodiments, the compound of Formula I is:



or a salt or solvate thereof.

The invention also provides a compound of Formula IV:



wherein

X is O, NH, N⁺(Me)₂, S, S(=O), or S(=O)₂;

Y is O, NH, N⁺(Me)₂, S, S(=O), or S(=O)₂, provided that one of X and Y is NH or N⁺(Me)₂, and that X and Y are not both NH;

Z is a direct bond, -CH₂-, or -CH₂-CH₂-; and

R¹ and R² are each independently alkyl, alkenyl, alkoxyalkyl, cycloalkyl, oxygen-containing heterocycle, nitrogen-containing heterocycle, aryl, alkylaryl, heteroaryl, or

alkylheteroaryl, wherein each can be optionally substituted with one or two additional R² groups; or a salt or solvate thereof.

Furthermore, the invention provides compounds of the formulas illustrated in **Figures 1 and 2**, where each compound can also be optionally substituted on carbon with one to five substituent groups. For example, a compound of **Figures 1 and 2** can be substituted with one or more hydroxy, halo, amino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carbonyl, thiocarbonyl, (C₁-C₄)alkyl, or (C₁-C₄)alkoxy groups. The compounds described herein can be an anion, cation, salt or solvate; or a combination thereof.

In some embodiments, R¹, R^A, or both, have a molecular weight of at least about 60 Da, at least about 80 Da, at least about 100 Da, at least about 150 Da, at least about 200 Da, or at least about 250 Da. In various embodiments, R¹, R^A, or both, have a molecular weight of less than about 500 Da, less than about 400 Da, less than about 300 Da, less than about 250 Da, less than about 200 Da, or less than about 150 Da.

The invention also provides pharmaceutical compositions comprising a compound of a formula described herein, or a specific compound described herein, in combination with a pharmaceutically acceptable diluent, excipient, or carrier.

The invention further provides methods of treating or inhibiting a bacterial infection or parasitic infection in a mammal. The method can include administering to a mammal in need of such treatment an effective amount of a compound described herein, wherein the bacterial infection or parasitic infection is treated or inhibited.

The invention yet further provides methods of killing or inhibiting the growth of a bacterium or parasite. The methods can include contacting the bacterial or parasite, *in vitro* or *in vivo*, with an effective amount of a compound described herein, wherein the bacterium or parasite is killed or its growth is inhibited.

The invention additionally provides methods of treating or inhibiting a *Mycobacterium tuberculosis* infection in a mammal. The methods can include administering to a mammal in need of such treatment an effective amount of a compound described herein, wherein the *Mycobacterium tuberculosis* infection is treated or inhibited.

In various embodiments, the compounds can inhibit a biosynthesis pathway of the microbe or parasite. The compounds can also enhance the activity of anti-tubercular drugs such as isoniazid and rifampin. Accordingly, the compounds described herein can be used to provide a drug combination, and combination therapy that includes administering a compound described herein with anti-tubercular drugs such as isoniazid, rifampin, or ethambutol.

Accordingly, in various embodiments, the compounds can be used to treat various infections such as a *Bacillus* infection, a *Candida* infection, an *Enterococcus* infection, an *Escherichia* infection, a *Helicobacter* infection, a *Listeria* infection, a *Mycobacterium* infection, a *Plasmodium* infection, a *Saccharomyces* infection, a *Staphylococcus* infection, or
5 a *Streptococcus* infection.

The invention therefore provides novel compounds of Formula I, intermediates for the synthesis of compounds of Formula I, as well as methods of preparing compounds of Formula I. The invention also provides compounds of Formula I that are useful as intermediates for the synthesis of other useful compounds. The invention provides for the
10 use of compounds of Formula I for the manufacture of medicaments useful for the treatment of bacterial or parasitic infections in a mammal, such as a human.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the specification and are included to further
15 demonstrate certain embodiments or various aspects of the invention. In some instances, embodiments of the invention can be best understood by referring to the accompanying drawings in combination with the detailed description presented herein. The description and accompanying drawings may highlight a certain specific example, or a certain aspect of the invention. However, one skilled in the art will understand that portions of the example or
20 aspect may be used in combination with other examples or aspects of the invention.

Figure 1. Compounds that can be inhibitors, drugs, or active agents, according to various embodiments of the invention where Y and R^A are as defined for Formula I herein.

Figure 2. Compounds that can be inhibitors, drugs, or active agents, according to various embodiments of the invention where X and R^A are as defined for Formula I herein.

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DETAILED DESCRIPTION

The compound SQ109 (*N*-adamantan-2-yl-*N'*-((*E*)-3,7-dimethyl-octa-2,6-dienyl)-ethane-1,2-diamine) is an ethambutol analog and an anti-tubercular drug. Several changes were made to the ethylene diamine backbone and to the non-polar headgroup of SQ109 to
30 provide a series of new compounds with different biological activity. Variations to the backbone included preparing ethanolamines, propanolamines, ethylene glycols, and glycolic amides, among other backbone chains, and conjugating various head and tail groups to the backbones.

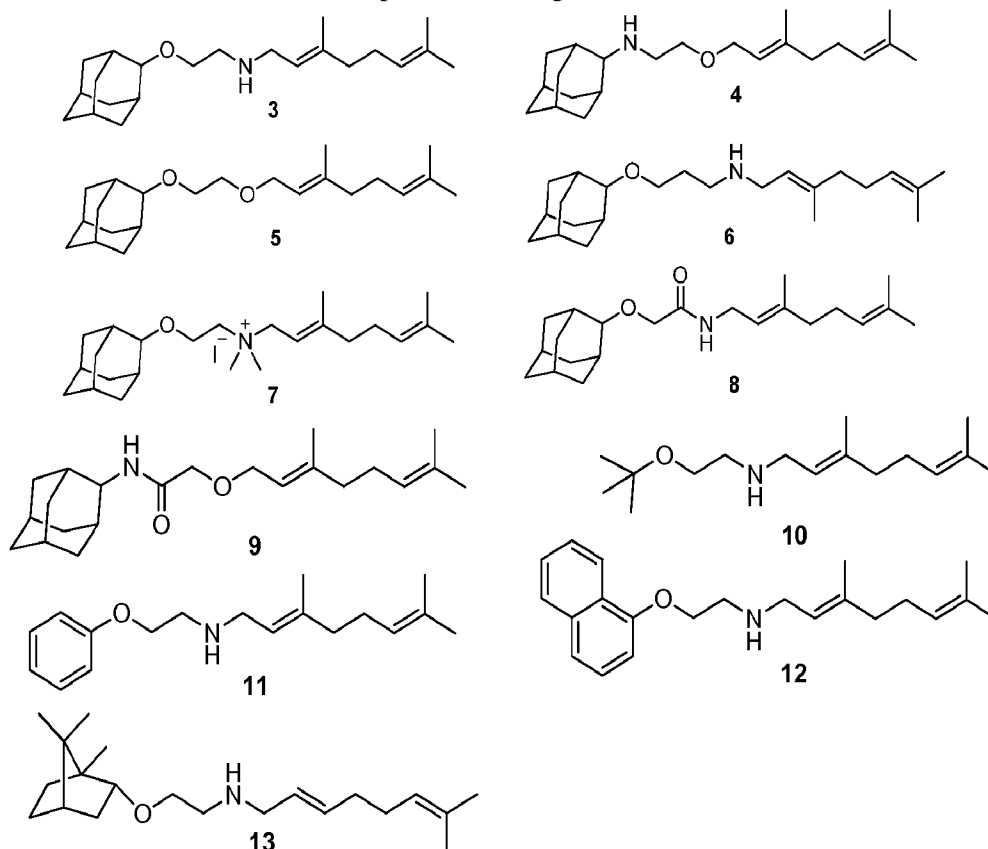
Remarkably, two analogs were significantly more potent than SQ109 against *Mycobacterium tuberculosis* (MIC ~0.02-0.05 µg/mL versus 0.1-0.2 µg/mL). Additionally, several compounds had activity (<1 µg/mL) against the intra-erythrocytic form of the malaria parasite, *Plasmodium falciparum*. There was also a broadly similar pattern of inhibitory activity against bacterial (*M. tuberculosis*, *S. aureus*, and *E. coli*), yeast (*S. cerevisiae*, *Candida albicans*), and protozoan (*P. falciparum*) cell growth. These results indicate that ethanolamine and propanolamine analogs of SQ109 can be effective anti-infectives.

Ethambutol is one of the primary drugs used to treat tuberculosis. One ethylene diamine compound related to ethambutol is SQ109. SQ109 has been found to be more active than ethambutol and is being actively pursued as a new drug lead for treating tuberculosis, and *C. difficile* infections, and certain fungal and yeast infections.

The ethanolamine and propanolamine compounds prepared as described herein were found to have similar or improved activity over the corresponding ethylene diamines. The ethanolamines and propanolamines are also active against the malaria parasite *Plasmodium falciparum*. The invention thus provides potent tuberculosis (TB) and anti-malarial agents. The compounds have also been found to kill malaria parasites and *Toxoplasma gondii* (80% survival in mice), the causative agent of toxoplasmosis.

These observations indicate that the ethanolamine and propanolamine compounds described herein can have activity against a variety of other organisms, such as *Plasmodium falciparum*, the causative agent of the most serious form of malaria. A series of SQ109 analogs was synthesized in which the ethylenediamine fragment was replaced by ethanolamine, choline, propanolamine, ethyleneglycol or glycolic amide moieties. Several side-chain substituted analogs were also prepared. These compounds were then tested against the malaria parasite *Plasmodium falciparum*, the yeasts *Saccharomyces cerevisiae* and *Candida albicans*, as well as the bacteria *S. aureus*, *E. coli*, and *M. tuberculosis*, in evaluate their activity and whether there were patterns of activity amongst these diverse organisms.

In one series of experiments, the compound SQ109 (2) and the 11 compounds (3-13) shown in **Scheme 1** were synthesized. Synthesis and characterization details are provided in Example 1 below. The compounds were then tested against the cells recited above and data was obtained. Growth inhibition results are shown below in **Table 1**.

Scheme 1. Structures of certain compounds investigated.

Four key points were noticed. First, although SQ109 was developed as an ethambutol/ethylene diamine analog, an ethylene diamine moiety is not required for activity; a single protonatable nitrogen suffices. Second, SQ109 as well as several analogs have activity against the intra-erythrocytic form of the malaria parasite *P. falciparum*, with IC_{50} values as low as $\sim 1 \mu\text{g/mL}$. Third, there is a generally similar pattern of activity against this protozoan parasite to that found with the yeasts and bacteria. Fourth, most potent activity is found with *M. tuberculosis*; see **Table 1**.

Table 1. Inhibition of *M. tuberculosis* (Mt), *P. falciparum* (Pf), *S. cerevisiae* (Sc), *C. albicans* (Ca), *S. aureus* (Sa) and *E. coli* (Ec) cell growth by compounds 2-13.

Scheme 1 Compound	Mt ^a	Pf ^b	Sc ^b	Ca ^c	Sa ^d	Ec ^d
2	0.1-0.2	1.0	1.1	+++	>120	2.8
3	0.02-0.05	0.79	1.8	++	8	2.8
4	0.19	0.93	>33	n.d.	>120	4.3
5	NT	7.9	>332	n.d.	n.d.	>332
6	1.6	0.83	2.7	++	8	2.3
7	n.d.	n.d.	15	++	n.d.	37
8	n.d.	6.2	>69	n.d.	>120	>345

9	12	3.8	>69	n.d.	>120	>345
10	6.2	n.d.	n.d.	n.d.	>16	n.d.
11	6.22	n.d.	3.0	n.d.	32	n.d.
12	6.2	n.d.	n.d.	+	8	n.d.
13	0.05	n.d.	0.89	++	8	n.d.

a. MIC, $\mu\text{g/mL}$; b. IC₅₀, $\mu\text{g/mL}$; c. zone of inhibition, mm; d. MIC₉₀, $\mu\text{g/mL}$; n.d. = not determined; NT = not tested

As shown in **Table 1**, SQ109 (**2**) has potent activity against *M. tuberculosis* (Mt) with a MIC₉₀ of ~0.1-0.2 $\mu\text{g/mL}$. Surprisingly, however, the *N*-geranyl-ethanolamines **3** and **13** are more potent, indicating that the presence of the two nitrogen atoms in SQ109 is not essential for activity. In the case of *P. falciparum*, the ethylenediamine **2**, the two ethanolamines (**3**, **4**) as well as the *N*-geranylpropanolamine **6** have the most potent activity (~1 $\mu\text{g/mL}$), while the ethylene glycol (**5**) is less active (7.9 $\mu\text{g/mL}$), as are the glycolic amides **8** and **9** (6.2 $\mu\text{g/mL}$, 3.8 $\mu\text{g/mL}$). This indicates that at least one basic nitrogen is desirable for optimum activity.

A similar pattern of activity was observed with *S. cerevisiae* where the ethylenediamine (**2**), *N*-geranylethanolamines (**3**, **13**) and *N*-geranylpropanolamine (**6**) are most active. The same pattern of activity is also seen with *C. albicans*; **Table 1**. The borneol derivative **13** has the lowest IC₅₀ value, and with the *N*-geranylethanolamines **3** and **13**, activity is higher than with SQ109 (**2**) and about 30× higher than with ethambutol (**1**). The glycolic amides (**8**, **9**) are inactive, as is ethyleneglycol **5**, consistent again with the requirement for at least one protonatable group. These results differ slightly with *P. falciparum* in that **4** is also active.

With *S. aureus* (the MRSA USA300 strain), SQ109 itself had no detectable activity, consistent with the MIC of ~1 mg/mL reported by Onajole et al. (*Med. Chem. Res.*, 20, 1394-1401 (2011)). However, the *N*-geranylethanolamines **3**, **12**, and **13** as well as the *N*-geranylpropanolamine **6**, all had MIC₉₀ values of 8 $\mu\text{g/mL}$, while other analogs were much less active (MIC₉₀ > 32 $\mu\text{g/mL}$). With *E. coli*, activity was weak but SQ109 (**2**), the *N*-geranylethanolamine (**3**), and the *N*-geranylpropanolamine **6** were most active (**Table 1**).

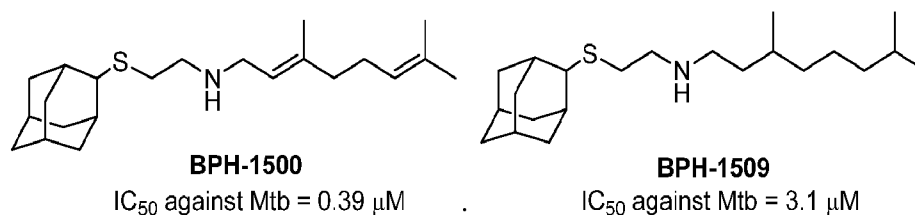
Taken together, these results are of interest because they show that SQ109, currently undergoing clinical trials as an anti-tubercular drug, also has activity against the malaria parasite, *P. falciparum*. Moreover, the ethanolamine and propanolamine analogs are similarly or more active in the malaria parasites than SQ109. They also have a similar pattern of activity in other organism tested. In *M. tuberculosis*, SQ109 inhibits the trehalose

monomycolate transporter but other targets must be involved in the other organisms because MmpL3 is not present. There may also be more than one target in *M. tuberculosis* for these compounds.

Given that cationic geranylamines could be good isosteres for isoprenoid biosynthesis enzymes, the following enzymes were tested for SQ109 inhibition: *M. tuberculosis* *cis*-farnesyl diphosphate synthase (Rv1086); *M. tuberculosis* decaprenyl diphosphate synthase (Rv2361); *P. vivax* geranylgeranyl diphosphate synthase; *S. aureus* and *E. coli* undecaprenyl diphosphate synthases; *S. aureus* farnesyl diphosphate synthase; and *S. aureus* demethylmenaquinone methyl transferase (UbiE). In all cases IC₅₀ values were $\geq 50 \mu\text{M}$, effectively ruling out these enzymes involved in isoprenoid biosynthesis as likely targets.

Overall, these results are of broad, general interest because they show that SQ109, currently in clinical/preclinical testing as a new drug against *M. tuberculosis*, *H. pylori*, *C. glabrata* and *C. difficile*, also has activity against the intra-erythrocytic (red blood cell) form of the malaria parasite. Additionally, the ethanolamine and propanolamine compounds described herein have similar or better activity, while ethylene glycol and glycolamides are generally without activity, indicating that at least one protonatable nitrogen may be necessary for inhibitory activity in these organisms, in certain embodiments. The similar pattern of activity among several bacteria, yeasts and the malaria parasite *P. falciparum* indicates a common or related target, although several *cis*- and *trans*-prenyltransferases can be excluded, based on enzyme inhibition results.

Additional compounds of the formulas described herein that have significant activity against Mtb include BHP-1500 and BHP-1509:



These and other compounds of Formula I are further described in the Examples below.

Definitions

As used herein, the recited terms have the following meanings. All other terms and phrases used in this specification have their ordinary meanings as one of skill in the art would understand. Such ordinary meanings may be obtained by reference to technical dictionaries, such as *Hawley's Condensed Chemical Dictionary* 14th Edition, by R.J. Lewis, John Wiley & Sons, New York, N.Y., 2001.

References in the specification to "one embodiment", "an embodiment", etc., indicate that the embodiment described may include a particular aspect, feature, structure, moiety, or characteristic, but not every embodiment necessarily includes that aspect, feature, structure, moiety, or characteristic. Moreover, such phrases may, but do not necessarily, refer to the same embodiment referred to in other portions of the specification. Further, when a particular aspect, feature, structure, moiety, or characteristic is described in connection with an embodiment, it is within the knowledge of one skilled in the art to affect or connect such aspect, feature, structure, moiety, or characteristic with other embodiments, whether or not explicitly described.

The singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a compound" includes a plurality of such compounds, so that a compound X includes a plurality of compounds X. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for the use of exclusive terminology, such as "solely," "only," and the like, in connection with the recitation of claim elements or use of a "negative" limitation.

The term "and/or" means any one of the items, any combination of the items, or all of the items with which this term is associated. The phrase "one or more" is readily understood by one of skill in the art, particularly when read in context of its usage. For example, one or more substituents on a phenyl ring refers to one to five, or one to four, for example if the phenyl ring is disubstituted.

The term "about" can refer to a variation of $\pm 5\%$, $\pm 10\%$, $\pm 20\%$, or $\pm 25\%$ of the value specified. For example, "about 50" percent can in some embodiments carry a variation from 45 to 55 percent. For integer ranges, the term "about" can include one or two integers greater than and/or less than a recited integer at each end of the range. Unless indicated otherwise herein, the term "about" is intended to include values, e.g., weight percentages, proximate to the recited range that are equivalent in terms of the functionality of the individual ingredient, the composition, or the embodiment.

As will be understood by the skilled artisan, all numbers, including those expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth, are approximations and are understood as being optionally modified in all instances by the term "about." These values can vary depending upon the desired properties sought to be obtained by those skilled in the art utilizing the teachings of the descriptions herein. It is also

understood that such values inherently contain variability necessarily resulting from the standard deviations found in their respective testing measurements.

As will be understood by one skilled in the art, for any and all purposes, particularly in terms of providing a written description, all ranges recited herein also encompass any and all possible sub-ranges and combinations of sub-ranges thereof, as well as the individual values making up the range, particularly integer values. A recited range (e.g., weight percentages or carbon groups) includes each specific value, integer, decimal, or identity within the range. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, or tenths. As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, etc. As will also be understood by one skilled in the art, all language such as "up to", "at least", "greater than", "less than", "more than", "or more", and the like, include the number recited and such terms refer to ranges that can be subsequently broken down into sub-ranges as discussed above. In the same manner, all ratios recited herein also include all sub-ratios falling within the broader ratio. Accordingly, specific values recited for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for radicals and substituents.

One skilled in the art will also readily recognize that where members are grouped together in a common manner, such as in a Markush group, the invention encompasses not only the entire group listed as a whole, but each member of the group individually and all possible subgroups of the main group. Additionally, for all purposes, the invention encompasses not only the main group, but also the main group absent one or more of the group members. The invention therefore envisages the explicit exclusion of any one or more of members of a recited group. Accordingly, provisos may apply to any of the disclosed categories or embodiments whereby any one or more of the recited elements, species, or embodiments, may be excluded from such categories or embodiments, for example, as used in an explicit negative limitation.

The term "alkyl" refers to a branched or unbranched hydrocarbon having, for example, from 1-20 carbon atoms or about 5 to about 15 carbons, and often 1-12, 1-10, 1-8, 1-6, or 1-4 carbon atoms. Examples include, but are not limited to, methyl, ethyl, 1-propyl, 2-propyl (*iso*-propyl), 1-butyl, 2-methyl-1-propyl (*isobutyl*), 2-butyl (*sec*-butyl), 2-methyl-2-propyl (*t*-butyl), 1-pentyl, 2-pentyl, 3-pentyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 3-methyl-1-butyl, 2-methyl-1-butyl, 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-

pentyl, 3-methyl-3-pentyl, 2-methyl-3-pentyl, 2,3-dimethyl-2-butyl, 3,3-dimethyl-2-butyl, hexyl, octyl, decyl, dodecyl, and the like. The alkyl can be unsubstituted or substituted, for example, with a substituent described below. The alkyl can be a branched alkyl, such as saturated isoprene groups of 5, 10, or 15 carbon atoms. The alkyl can be a monovalent hydrocarbon radical, as described and exemplified above, or it can be a divalent hydrocarbon radical (i.e., an alkylene).

The term "alkenyl" refers to a monoradical branched or unbranched partially unsaturated hydrocarbon chain (i.e. a carbon-carbon, sp^2 double bond) preferably having from 2 to 15 carbon atoms, preferably 2 to 6 carbon atoms, and more preferably from 2 to 4 carbon atoms. The "alkenyl" can also be an isoprene moiety, such as a branched alkenyl group of 5, 10, or 15 carbon atoms. Examples include, but are not limited to, ethylene or vinyl, allyl, cyclopentenyl, and 5-hexenyl. The alkenyl can be unsubstituted or substituted as described for alkyl groups.

The term "cycloalkyl" refers to cyclic alkyl groups of, for example, from 3 to 12 carbon atoms having a single cyclic ring or multiple condensed rings. Cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, and the like, or multiple ring structures such as adamantyl, substituted adamantyl, polycyclic compounds such as isopenocamphenyl groups, bornyl groups, and substituted compounds thereof, such as the groups of the compounds illustrated in **Figures 1 and 2**, and the like. The cycloalkyl can be unsubstituted or substituted. The cycloalkyl group can be monovalent or divalent, and can be optionally substituted as described for alkyl groups. The cycloalkyl group can optionally include one or more sites of unsaturation, for example, the cycloalkyl group can include one or more carbon-carbon double bonds, such as, for example, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, and the like.

The term "alkoxy" refers to the group alkyl-O-, where alkyl is as defined herein. Examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like. The alkoxy can be unsubstituted or substituted as described for alkyl groups.

The term "aryl" refers to an aromatic hydrocarbon group derived from the removal of at least one hydrogen atom from a single carbon atom of a parent aromatic ring system. The radical attachment site can be at a saturated or unsaturated carbon atom of the parent ring system. The aryl group can have from 6 to 30 carbon atoms, for example, about 6-14 carbon atoms, or about 6-10 carbon atoms. The aryl group can have a single ring (e.g., phenyl) or multiple

condensed (fused) rings, wherein at least one ring is aromatic (e.g., naphthyl, dihydrophenanthrenyl, fluorenyl, or anthryl). Typical aryl groups include, but are not limited to, radicals derived from benzene, naphthalene, anthracene, biphenyl, and the like. The aryl can be unsubstituted or optionally substituted, as described for alkyl groups.

5 The term "heteroaryl" refers to a monocyclic, bicyclic, or tricyclic ring system containing one, two, or three aromatic rings and containing at least one nitrogen, oxygen, or sulfur atom in an aromatic ring. The heteroaryl can be unsubstituted or substituted, for example, with one or more, and in particular one to three, substituents, as described in the definition of "substituted". Typical heteroaryl groups contain 2-20 carbon atoms or 5-9
10 carbon atoms in the ring skeleton in addition to the one or more heteroatoms. Examples of heteroaryl groups include, but are not limited to, 2H-pyrrolyl, 3H-indolyl, 4H-quinoliziny, acridinyl, benzo[b]thienyl, benzothiazolyl, β -carboline, carbazolyl, chromenyl, cinnoliny, dibenzo[b,d]furanyl, furazanyl, furyl, imidazolyl, imidizolyl, indazolyl, indolisiny, indolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxazolyl,
15 perimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, thiadiazolyl, thianthrenyl, thiazolyl, thienyl, triazolyl, tetrazolyl, and xanthenyl, and dimers thereof. In one embodiment the term "heteroaryl" denotes a monocyclic aromatic ring containing five or six
20 ring atoms containing carbon and 1, 2, 3, or 4 heteroatoms independently selected from non-peroxide oxygen, sulfur, and N(Z) wherein Z is absent or is H, O, alkyl, aryl, or (C₁-C₆)alkylaryl. In some embodiments, heteroaryl denotes an ortho-fused bicyclic heterocycle of about eight to ten ring atoms derived therefrom, particularly a benz-derivative or one derived by fusing a propylene, trimethylene, or tetramethylene diradical thereto.

25 The term "heterocycle" refers to a saturated or partially unsaturated ring system, containing at least one heteroatom selected from the group oxygen, nitrogen, silicon, and sulfur, and optionally substituted with one or more groups as defined for the term "substituted". A heterocycle can be a monocyclic, bicyclic, or tricyclic group. A heterocycle typically has 2 to about 10, or about 5 to about 9 carbon atoms in the ring structure. A
30 heterocycle group also can contain an oxo group (=O) or a thioxo (=S) group attached to the ring. Non-limiting examples of heterocycle groups include 1,3-dihydrobenzofuran, 1,3-dioxolane, 1,4-dioxane, 1,4-dithiane, 2H-pyran, 2-pyrazoline, 4H-pyran, chromanyl, imidazolidinyl, imidazolinyl, indolinyl, isochromanyl, isoindolinyl, morpholinyl, piperazinyl,

piperidinyl, pyrazolidinyl, pyrazolinyl, pyrrolidine, pyrroline, quinuclidine, tetrahydrofuranyl, and thiomorpholine.

By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, and the like. Various combinations of the aforementioned positions are included in the compounds described herein.

By way of example and not limitation, nitrogen bonded heterocycles can be bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β -carboline. In one embodiment, nitrogen bonded heterocycles include 1-aziridyl, 1-azetetyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

The term "substituted" indicates that one or more hydrogen atoms on the group indicated in the expression using "substituted" is replaced with a "substituent". The number referred to by 'one or more' can be apparent from the moiety on which the substituents reside. For example, one or more can refer to, e.g., 1, 2, 3, 4, 5, or 6; in some embodiments 1, 2, or 3; and in other embodiments 1 or 2, and if the substituent is an oxo group, two hydrogen atoms are replaced by the presence of the substituent. The substituent can be one of a selection of indicated groups, or it can be a suitable group recited below or known to those of skill in the art, provided that the substituted atom's normal valency is not exceeded, and that the substitution results in a stable compound. Suitable substituent groups include, e.g., alkyl, alkenyl (e.g., vinyl, or allyl), alkynyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, aroyl, (aryl)alkyl (e.g., benzyl or phenylethyl), heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, alkylcarbonyloxy, amino, alkylamino, dialkylamino, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, difluoromethyl, acylamino, nitro, carboxy,

carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroarylsulfinyl, heteroarylsulfonyl, heterocyclesulfinyl, heterocyclesulfonyl, phosphate, sulfate, hydroxyl amine, hydroxyl (alkyl)amine, and cyano, as well as the moieties illustrated in the schemes and Figures of this disclosure; or combinations thereof. Additionally, suitable

5 substituent groups can be, e.g., -X, -R, -O⁻, -OR, -SR, -S⁻, -NR₂, -NR₃, =NR, -CX₃, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, -NO₂, =N₂, -N₃, -NC(=O)R, -C(=O)R, -C(=O)NRR, -S(=O)₂O⁻, -S(=O)₂OH, -S(=O)₂R, -OS(=O)₂OR, -S(=O)₂NR, -S(=O)R, -OP(=O)(OR)₂, -P(=O)(OR)₂, -OP(=O)(OH)(OR), -P(=O)(OH)(OR), -P(=O)(O⁻)₂, -P(=O)(OH)₂, -C(=O)R, -C(=O)X, -C(S)R, -C(O)OR, -C(O)O⁻, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR,

10 or -C(NR)NRR, where each X is independently a halogen ("halo"): F, Cl, Br, or I; and each R is independently H, alkyl, cycloalkyl, aryl, (aryl)alkyl (e.g., benzyl), heteroaryl, (heteroaryl)alkyl, heterocycle, heterocycle(alkyl), or a protecting group. As would be readily understood by one skilled in the art, when a substituent is keto (=O) or thioxo (=S), or the like, then two hydrogen atoms on the substituted atom are replaced. In some embodiments, one or

15 more substituents above can be excluded from the group of potential values for substituents on the substituted group. The various R groups in the schemes and figures of this disclosure can be one or more of the substituents recited above, thus the listing of certain variables for such R groups (including R¹, R², R^A, etc.) are representative and not exhaustive, and can be supplemented with one or more of the substituents above.

20 Compounds having the substituents described herein can be prepared by using commercially available starting materials having the desired substituents. Many relevant starting materials are commercially available from suppliers such as Acros Organics, Atomax Chemicals, Aurora Fine Chemicals, Orgentis Chemicals, or Sigma-Aldrich, or they can be readily prepared from such compounds using standard synthetic transformations known to

25 those of skill in the art. For example, the substituents can be added to intermediates during the synthetic sequence of preparation.

The term "contacting" refers to the act of touching, making contact, or of bringing to immediate or close proximity, including at the cellular or molecular level, for example, to bring about a physiological reaction, a chemical reaction, or a physical change, e.g., in a

30 solution, in a reaction mixture, *in vitro*, or *in vivo*.

An "effective amount" refers to an amount effective to treat a disease, disorder, and/or condition, or to bring about a recited effect. For example, an effective amount can be an amount effective to reduce the progression or severity of the condition or symptoms being treated. Determination of a therapeutically effective amount is well within the capacity of

persons skilled in the art. The term "effective amount" is intended to include an amount of a compound described herein, or an amount of a combination of compounds described herein, e.g., that is effective to treat or prevent a disease or disorder, or to treat the symptoms of the disease or disorder, in a host. Thus, an "effective amount" generally means an amount that provides the desired effect.

The terms "treating", "treat" and "treatment" include (i) preventing a disease, pathologic or medical condition from occurring (e.g., prophylaxis); (ii) inhibiting the disease, pathologic or medical condition or arresting its development; (iii) relieving the disease, pathologic or medical condition; and/or (iv) diminishing symptoms associated with the disease, pathologic or medical condition. Thus, the terms "treat", "treatment", and "treating" can extend to prophylaxis and can include prevent, prevention, preventing, lowering, stopping or reversing the progression or severity of the condition or symptoms being treated. As such, the term "treatment" can include medical, therapeutic, and/or prophylactic administration, as appropriate.

The terms "inhibit", "inhibiting", and "inhibition" refer to the slowing, halting, or reversing the growth or progression of a disease, infection, condition, or group of cells. The inhibition can be greater than about 20%, 40%, 60%, 80%, 90%, 95%, or 99%, for example, compared to the growth or progression that occurs in the absence of the treatment or contacting.

The term "tuberculosis" refers to disease states usually associated with infections caused by mycobacteria species comprising *M. tuberculosis* complex. The term tuberculosis is also associated with mycobacterial infections caused by other mycobacteria such as *M. avium-intracellulare*, *M. kansari*, *M. fortuitum*, *M. chelonae*, *M. leprae*, *M. africanum*, *M. microti*, *M. avium paratuberculosis*, *M. intracellulare*, *M. scrofulaceum*, *M. xenopi*, *M. marinum*, and *M. ulcerans*. The compounds and compositions described herein can be used to kill or inhibit the growth of these mycobacteria species, and can be used to treat mycobacterial infections caused by these mycobacteria.

The term "solvate" refers to a solid compound that has one or more solvent molecules associated with its solid structure. Solvates can form when a solid compound is crystallized from a solvent, wherein one or more solvent molecules become an integral part of the solid crystalline matrix. The compounds of the formulas described herein can be solvates, for example, ethanol solvates. Another type of a solvate is a hydrate. A "hydrate" likewise refers to a solid compound that has one or more water molecules intimately associated with its solid or crystalline structure at the molecular level. A hydrate is a specific type of a

solvate. Hydrates can form when a compound is solidified or crystallized in water, wherein one or more water molecules become an integral part of the solid crystalline matrix. The compounds of the formulas described herein can be hydrates.

Specific values listed herein for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for radicals and substituents. Generic terms include each of their species. For example, the term halo includes and can explicitly be fluoro, chloro, bromo, or iodo.

As to any compound described herein, which may contain one or more substituents, it is understood, of course, that such compounds or their substituted moieties do not contain any substitution or substitution patterns that are sterically impractical and/or synthetically non-feasible. The total molecular weight of substituents on a single group can be, and will typically be less than about 600, 500, 400, 300, 200, or 100. It will be appreciated that the compounds of the invention can contain asymmetrically substituted carbon atoms, and may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials or by the use of enantioselective catalytic reactions. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a compound are intended as part of this invention.

One diastereomer may display superior activity compared to another. When required, separation of racemic materials can be achieved by high performance liquid chromatography (HPLC) using a chiral column or by a resolution using a resolving agent such as camphonic chloride, as in Thomas J. Tucker et al., *J. Med. Chem.* 1994, 37, 2437-2444. A chiral compound may also be directly synthesized using a chiral catalyst or a chiral ligand; see, for example, Mark A. Huffman et al., *J. Org. Chem.* 1995, 60, 1590-1594.

Recursive Substituents

Selected substituents of the compounds described herein may be present to a recursive degree. In this context, "recursive substituent" means that a substituent may recite another instance of itself. Because of the recursive nature of such substituents, theoretically, a large number may be present in any given claim. One of ordinary skill in the art of medicinal chemistry and organic chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by of example and not limitation, physical properties such as molecular weight, solubility or log P, application properties such as activity against the intended target, and

practical properties such as ease of synthesis. In addition, the compounds of this invention include all stereochemical isomers arising from the substitution of these compounds.

Recursive substituents are an intended aspect of the invention. One of ordinary skill in the art of medicinal and organic chemistry understands the versatility of such substituents.

5 To the degree that recursive substituents are present in a claim of the invention, the total number will be determined as set forth above. In some embodiments, recursive substituents are present only to the extent that the molecular mass of the compound is about 400 to about 1600, about 450 to about 1200, about 500 to about 100, about 600 to about 800. In other
10 embodiments, recursive substituents are present only to the extent that the molecular mass of the compound is less than 2000, less than 1800, less than 1600, less than 1500, less than 1400, less than 1200, less than 1000, less than 900, less than 800, less than 750, less than 700, or less than about 600.

Therapeutic Methods

15 Diagnosis of infections such as mycobacterial infection can be confirmed by the isolation and identification of the pathogen, while conventional diagnosis can be based on sputum smears, chest X-ray examination (CXR), and clinical symptoms. Isolation of mycobacteria on a medium can take as long as four to eight weeks. Species identification can take an additional two weeks. Other techniques for detecting mycobacteria include the
20 polymerase chain reaction (PCR), mycobacterium tuberculosis direct test, or amplified mycobacterium tuberculosis direct test (MTD), and detection assays that utilize radioactive labels.

One diagnostic test used for detecting infections caused by *M. tuberculosis* is the tuberculin skin test. One of two preparations of tuberculin antigens are typically used: old
25 tuberculin (OT), or purified protein derivative (PPD). The antigen preparation can be either injected into the skin intradermally, or can be topically applied and then invasively transported into the skin with the use of a multiprong inoculator (Tine test).

A current standard treatment for tuberculosis caused by drug-sensitive organisms is a six-month regimen consisting of four drugs given for two months, followed by two drugs
30 given for four months. Two important drugs, given throughout the six-month course of therapy, are isoniazid and rifampin. The compounds and compositions described herein can be used in combination with current anti-infective drugs such as isoniazid, rifampin, pyrazinamide, and ethambutol. The compounds and compositions described herein can be administered in doses such as about 1, about 2, about 5, about 7.5, about 10, about 15, about

20, about 25, about 50, about 100, about 200, or about 500 mg/kg, and/or as directed by a clinician.

Pharmaceutical Formulations

5 The compounds described herein can be used to prepare therapeutic pharmaceutical compositions. The compounds may be added to the compositions in the form of a salt or solvate. For example, in cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compounds as salts may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts
10 formed with acids that form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartrate, succinate, benzoate, ascorbate, α -ketoglutarate, and α -glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, halide, sulfate, nitrate, bicarbonate, and carbonate salts.

 Pharmaceutically acceptable salts may be obtained using standard procedures well
15 known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid to provide a physiologically acceptable ionic compound. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example, calcium) salts of carboxylic acids can also be prepared by analogous methods.

 The compounds of the formulas described herein can be formulated as pharmaceutical
20 compositions and administered to a mammalian host, such as a human patient, in a variety of forms. The forms can be specifically adapted to a chosen route of administration, e.g., oral or parenteral administration, by intravenous, intramuscular, topical or subcutaneous routes.

 The compounds described herein may be systemically administered in combination
25 with a pharmaceutically acceptable vehicle, such as an inert diluent or an assimilable edible carrier. For oral administration, compounds can be enclosed in hard or soft shell gelatin capsules, compressed into tablets, or incorporated directly into the food of a patient's diet. Compounds may also be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations typically contain at least 0.1% of active
30 compound. The percentage of the compositions and preparations can vary and may conveniently be from about 1% to about 60%, or about 2% to about 20% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level can be obtained.

 The tablets, troches, pills, capsules, and the like may also contain one or more of the
35 following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as

dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; and a lubricant such as magnesium stearate. A sweetening agent such as sucrose, fructose, lactose or aspartame; or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring, may be added. When the unit dosage form is a capsule, it
5 may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and
10 propyl parabens as preservatives, a dye and flavoring such as cherry or orange flavor. Any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The active compound may be administered intravenously or intraperitoneally by
15 infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can be prepared in glycerol, liquid polyethylene glycols, triacetin, or mixtures thereof, or in a pharmaceutically acceptable oil. Under ordinary conditions of storage and use, preparations may contain a preservative to prevent the growth of microorganisms.

20 Pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions, dispersions, or sterile powders comprising the active ingredient adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. The ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a
25 solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions, or by the use of surfactants. The prevention of the
30 action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thiomersal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers, or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by agents delaying absorption, for example, aluminum monostearate and/or gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in the appropriate solvent with various other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation can include vacuum drying and freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, compounds may be applied in pure form, e.g., when they are liquids. However, it will generally be desirable to administer the active agent to the skin as a composition or formulation, for example, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina, and the like. Useful liquid carriers include water, dimethyl sulfoxide (DMSO), alcohols, glycols, or water-alcohol/glycol blends, in which a compound can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto an affected area using a pump-type or aerosol sprayer.

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses, or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Examples of dermatological compositions for delivering active agents to the skin are known to the art; for example, see U.S. Patent Nos. 4,992,478 (Geria), 4,820,508 (Wortzman), 4,608,392 (Jacquet et al.), and 4,559,157 (Smith et al.). Such dermatological compositions can be used in combinations with the compounds described herein.

Useful dosages of the compounds described herein can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Patent No. 4,938,949 (Borch et al.). The amount of a compound, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular compound or salt selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will be ultimately at the discretion of an attendant physician or clinician.

The compound can be conveniently administered in a unit dosage form, for example, containing 5 to 1000 mg/m², conveniently 10 to 750 mg/m², most conveniently, 50 to 500 mg/m² of active ingredient per unit dosage form. The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations.

The invention provides therapeutic methods of treating infections in a mammal, which involve administering to a mammal having an infection an effective amount of a compound or composition described herein. A mammal includes a primate, human, rodent, canine, feline, bovine, ovine, equine, swine, caprine, bovine and the like. An infection refers to an invasion of body tissues by disease-causing microorganisms, their multiplication and the reaction of body tissues to these microorganisms, and the toxins that they produce. Infections can be caused by microorganisms such as bacteria, yeasts, fungi, and macroparasites.

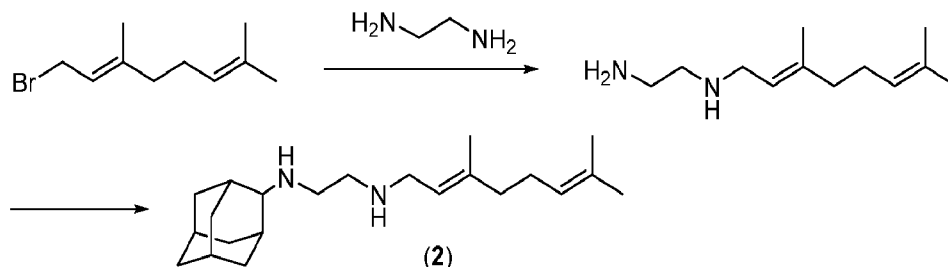
The ability of a compound of the invention to treat an infection may be determined by using assays well known to the art. For example, the design of treatment protocols, toxicity evaluation, data analysis, quantification of cell kill, and the biological significance of the use of transplantable screens are known. In addition, ability of a compound to treat an infection may be determined using the tests described herein, and those described in U.S. Patent Publication No. 2012/0196835 (Oldfield et al.).

The following Examples are intended to illustrate the above invention and should not be construed as to narrow its scope. One skilled in the art will readily recognize that the Examples suggest many other ways in which the invention could be practiced. It should be understood that numerous variations and modifications may be made while remaining within the scope of the invention.

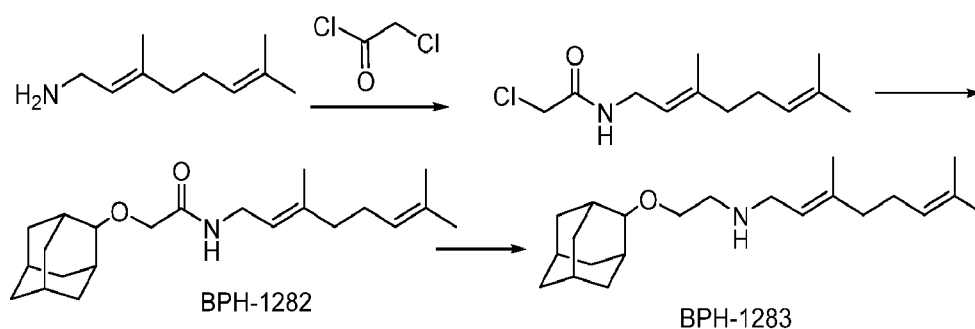
EXAMPLES

Example 1. Compounds and Preparatory Methods

SQ109 (Compound 2) was made by following reported procedure (Onajole et al., *European Journal of Medicinal Chemistry* 45 (2010) 2075–2079); the compound is also commercial available. Compounds 3–13 were prepared by similar procedures or by the procedures described below.



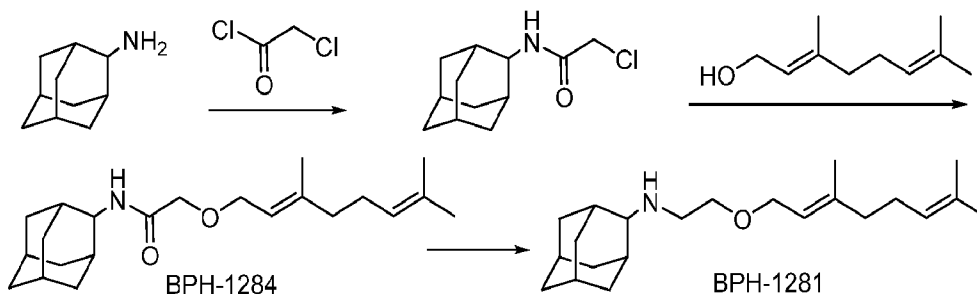
***N*¹-((1*r*,3*r*,5*r*,7*r*)-adamantan-2-yl)-*N*²-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)ethane-1,2-diamine (2).** ¹H NMR (400 MHz, CDCl₃) δ 5.24 (t, *J* = 6.8 Hz, 1H), 5.07 (t, *J* = 7.2 Hz, 1H), 3.21 (d, *J* = 6.8 Hz, 2H), 2.69 (s, 4H), 2.67 (s, 1H), 2.07-1.91 (m, 7H), 1.82-1.68 (m, 7H), 1.65 (s, 3H), 1.61 (s, 3H), 1.57 (s, 3H), 1.47-1.42 (m, 4H).



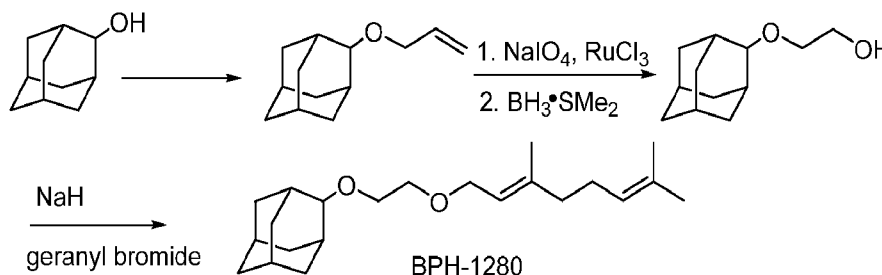
(*E*)-*N*-(2-((1*r*,3*r*,5*r*,7*r*)-adamantan-2-yloxy)ethyl)-3,7-dimethylocta-2,6-dien-1-amine (3). To a stirred solution of geranylamine (153 mg, 1.0 mmol) in CHCl₃ (3 mL), chloroacetyl chloride (167 mg, 1.5 mmol) was added dropwise at 0 °C. Then water (2 mL) was added to the reaction mixture followed by addition of K₂CO₃ (414 mg, 3.0 mmol). A catalytic amount of tetrabutylammonium hydrogensulfate was added to the reaction mixture and stirred for 4 h. After completion of the reaction, as monitored by TLC, the organic layer was separated and dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure. The residual mass was purified by silica gel column chromatography using 25% EtOAc in hexane as eluent to afford pure compound chloroacetamide (183 mg, 80%).

To a solution of 2-adamantanol (210 mg, 1.4 mmol) in dry THF (5 mL) was added NaH (washed and dried from hexane, 46 mg, 2 mmol) at 0 °C with stirring. After stirring 30 min at rt (~23 °C), chloroacetamide (160 mg, 0.7 mmol) was added to the reaction mixture. The stirring was continued for 12 hours at rt, then the reaction was quenched by saturated aqueous NH₄Cl. Upon separation and concentration under reduced pressure, the residue was purified by silica gel column chromatography using 25% EtOAc in hexane as eluent to afford pure compound adamantanyl-oxyacetamide (150 mg, 62%).

To a suspension of LiAlH₄ (27 mg, 0.7 mmol) in dry THF (2 mL) was added adamantanyl-oxyacetamide (120 mg, 0.35 mmol) at rt. Afterward stirring was continued for 20 hours at refluxing temperature, the reaction mixture was cooled with ice-bath and quenched by adding ammonium hydroxide (37%, 0.5 mL). The vigorous stirring was continued for 20 min. Upon separation and concentration under reduced pressure, the residue was purified by silica gel column chromatography (using NH₄OH (37%)/MeOH/EtOAc = 1/5/100 as eluent) to afford pure product (74 mg, 64%). ¹H NMR δ 5.75 (t, J = 6.8 Hz, 1H), 4.98 (s, 1H), 4.45 (d, J = 6.8 Hz, 2H), 3.86 (m, 4H), 3.48 (s, 1H), 3.33 (s, 6H), 2.15 (m, 4H), 1.99-1.46 (m, 14H), 1.87 (s, 3H), 1.65 (s, 3H), 1.57 (s, 3H). Anal. Calcd for C₂₂H₃₇NO·0.25 H₂O: C, 78.63; H, 11.25, N, 4.17. Found: C, 78.29; H, 11.00; N, 4.25.



(1r,3r,5r,7r)-N-(2-(((E)-3,7-dimethylocta-2,6-dien-1-yl)oxy)ethyl)adamantane-2-amine (4). Compound 4 was made by procedure used for compound 3. ¹H NMR δ 5.34 (t, J = 6.8 Hz, 1H), 5.08 (t, J = 7.2 Hz, 1H), 4.00 (d, J = 7.2 Hz, 2H), 3.54 (t, J = 6.4 Hz, 2H), 2.74 (t, J = 6.4 Hz, 2H), 2.69 (s, 1H), 2.10-1.81 (m, 14H), 1.75-1.45 (m, 4H), 1.66 (s, 3H), 1.62 (s, 3H), 1.58 (s, 3H). Anal. Calcd for C₂₂H₃₇NO: C, 79.70; H, 11.25, N, 4.22. Found: C, 79.75; H, 11.28; N, 4.09.

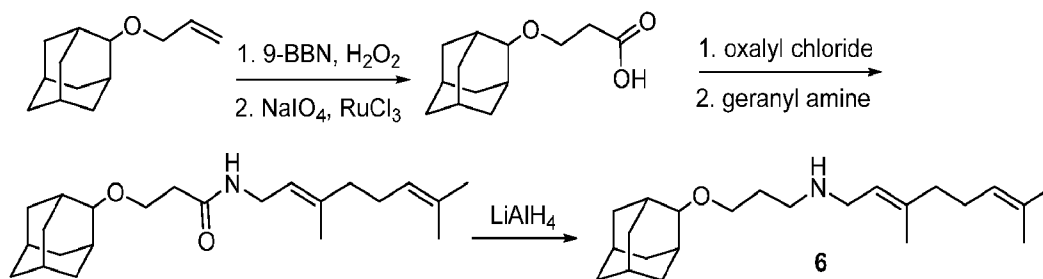


(1r,3r,5r,7r)-2-(2-(((E)-3,7-dimethylocta-2,6-dien-1-yl)oxy)ethoxy)adamantane (5). To the suspension of NaH (washed and dried with hexane 368 mg, 16 mmol) in THF (30 mL) was added 2-admanatanol (1.5 g, 10 mmol) at 0 °C. After stirring was continued for 30 min at rt, the allyl bromide (1.8 g, 15 mmol) was added at 0 °C. After stirring was continued for 3 h at rt, the reaction was quenched by adding saturated aqueous NH₄Cl. Upon separation and

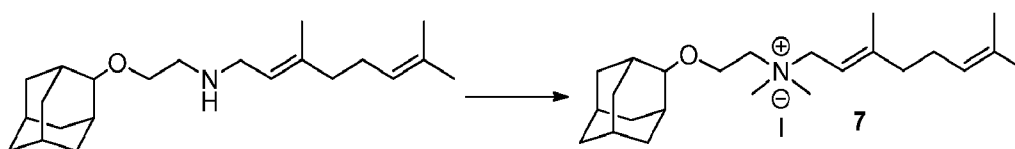
concentration under reduced pressure, the residue was purified by silica gel column chromatography using 5% EtOAc in hexane as eluent to afford pure allyl ether (1.4 g, 75%).

To the suspension of allyl ether (192 mg, 1 mmol) in MeCN/H₂O/CCl₄ (2/3/2, 3.5 mL) was added NaIO₄ (842 mg, 4 mmol), then RuCl₃·H₂O (11 mg, 0.05 mmol). After stirring for 10 h at rt, dichloromethane (4 mL) was added. Separation and concentration of organic phase under reduced pressure gave the crude acid which was reduced by BH₃·SMe₂ to give alcohol.

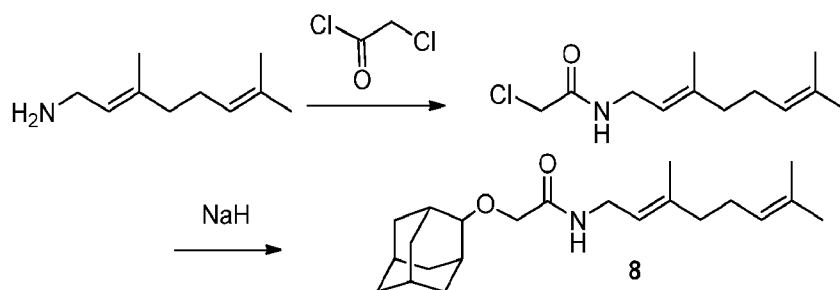
To the solution of alcohol (100 mg, 0.5 mmol) in dry THF (3 mL) was added NaH (washed with hexane, 17 mg, 0.75 mmol). After stirring for 30 min at rt, geranyl bromide (162 mg, 0.75 mmol) was added. After stirring was continued for 10 h at rt, the reaction was quenched with saturated aqueous NH₄Cl. Upon separation and concentration under reduced pressure, the residue was purified by silica gel column chromatography using 5% EtOAc in hexane as eluent to afford pure product (139 mg, 84%). 5.33 (t, J = 6.4 Hz, 1H), 5.07 (t, J = 6.8 Hz, 1H), 4.04 (d, J = 6.4 Hz, 2H), 3.57 (s, 4H), 3.43 (s, 1H). 2.10-1.41 (m, 18H), 1.65 (s, 3H), 1.64 (s, 3H), 1.57 (s, 3H). Anal. Calcd for C₂₂H₃₆NO₂: C, 79.20; H, 10.91. Found: C, 79.04; H, 10.80.



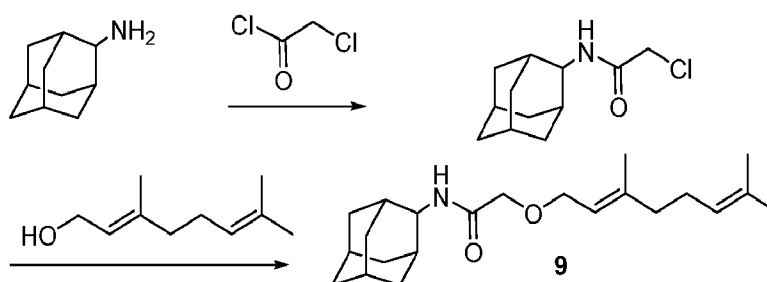
(E)-N-(3-((1r,3r,5r,7r)-adamantan-2-yloxy)propyl)-3,7-dimethylocta-2,6-dien-1-amine (6). Allyl ether was transformed to acid by reported procedure (Carrillo et al., *Tetrahedron* 61(34), 8177-8191, 2005). Acid was transformed to amide and final compound with the same procedure for compound 3 (BPH-1304) H NMR 5.24 (t, J = 6.8 Hz, 1H), 5.07 (t, J = 7.2 Hz, 1H), 3.47 (t, J = 6.0 Hz, 2H), 3.37 (s, 1H), 3.20 (d, J = 6.8 Hz, 2H), 2.70 (t, J = 6.8 Hz, 2H), 2.08-1.97 (m, 8H), 1.82-1.42 (m, 12H), 1.65 (s, 3H), 1.61 (s, 3H), 1.57 (s, 3H). Anal. Calcd for C₂₃H₃₉NO·0.1NH₃·2H₂O: C, 59.13 H, 8.68, N, 2.87. Found: C, 59.08; H, 8.83, N, 2.91.



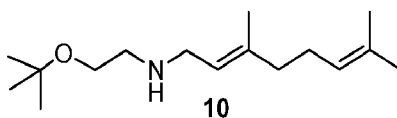
(*E*)-*N*-(2-((1*r*,3*r*,5*r*,7*r*)-adamantan-2-yloxy)ethyl)-*N,N*,3,7-tetramethylocta-2,6-dien-1-aminium iodide (7). To the solution of compound **3** (100 mg, 0.3 mmol) in MeCN (2 mL) was added K₂CO₃ (138 mg, 1 mmol), then MeI (169 mg, 1.4 mmol) at rt. The stirring was continued for 3 days in avoid of light by covering with aluminum foil. The volatile component was removed under reduced pressure and dichloromethane was added. Filtration and concentration of the filtrate gave the product which was purified by thorough wash with hexane, 133 mg (91%). NMR 5.75 (t, *J* = 6.8 Hz, 1H), 4.98 (s, 1H), 4.45 (d, *J* = 6.8 Hz, 2H), 3.86 (m, 4H), 3.48 (s, 1H), 3.33 (s, 6H), 2.15 (m, 4H), 1.99-1.46 (m, 14H), 1.87 (s, 3H), 1.65 (s, 3H), 1.57 (s, 3H). Anal. Calcd for C₂₄H₄₂INO: C, 59.13; H, 8.68, N, 2.87. Found: C, 59.08; H, 8.83; N, 2.91.



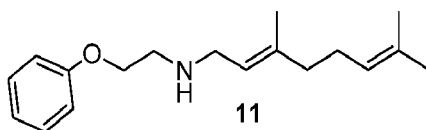
2-((1*r*,3*r*,5*r*,7*r*)-adamantan-2-yloxy)-*N*-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)acetamide (8). Compound **8** was made by the procedure provided for compound **3**. H NMR 6.60 (broad, 1H) 5.18 (t, *J* = 6.8 Hz, 1H), 5.05 (t, *J* = 6.8 Hz, 1H), 3.92 (s, 2H), 3.82 (d, *J* = 6.8 Hz, 2H), 3.43 (s, 1H), 2.12-1.75 (m, 14H), 1.70-1.45 (m, 4H), 1.68 (s, 6H), 1.57 (s, 3H). Anal. Calcd for C₂₂H₃₅NO₂·0.2H₂O: C, 75.49; H, 10.22, N, 4.00. Found: C, 75.71; H, 10.02; N, 3.76.



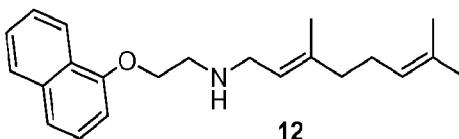
***N*-((1*r*,3*r*,5*r*,7*r*)-adamantan-2-yl)-2-(((*E*)-3,7-dimethylocta-2,6-dien-1-yl)oxy)-acetamide (9).** Compound **9** was made by the procedure provided for compound **3**. 0.71 (broad, 1H), 5.34 (t, *J* = 5.6 Hz, 1H), 5.09 (t, *J* = 5.6 Hz, 1H), 4.12 (m, 1H), 4.09 (d, *J* = 5.6 Hz, 2H), 3.93 (s, 2H), 2.12-1.64 (m, 18H), 1.69 (s, 6H), 1.62 (s, 3H). Anal. Calcd for C₂₂H₃₅NO₂: C, 76.08; H, 10.22, N, 4.03. Found: C, 76.07; H, 10.25; N, 4.24.



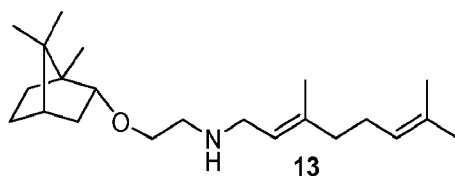
(E)-N-(2-(tert-butoxy)ethyl)-3,7-dimethylocta-2,6-dien-1-amine (10). Compound 10 was made by the procedure provided for compound 3. 5.24 (t, J = 5.6 Hz, 1H), 5.07 (t, J = 6.0 Hz, 1H), 3.46 (t, J = 4.2 Hz, 2H), 3.22 (d, J = 6.4 Hz, 2H), 2.72 (t, J = 4.2 Hz, 2H), 2.06 (m, 2H), 1.99 (m, 2H), 1.66 (s, 1H), 1.62 (s, 3H), 1.58 (s, 3H), 1.17 (s, 9H). Anal. Calcd for $C_{16}H_{31}NO \cdot 0.2NH_3 \cdot 0.5H_2O$: C, 72.29; H, 12.23, N, 6.32. Found: C, 72.02; H, 12.33, N, 6.31.



(E)-3,7-dimethyl-N-(2-phenoxyethyl)octa-2,6-dien-1-amine (11). Compound 11 was made by the procedure provided for compound 3. 7.25 (m, 2H), 6.90 (m, 3H), 5.25 (t, J = 6.8 Hz, 1H), 5.08 (t, J = 6.8 Hz, 1H), 4.09 (t, J = 4.2 Hz, 1H), 3.32 (d, J = 6.8 Hz, 2H), 3.04 (t, J = 4.2 Hz, 2H), 2.10 (m, 2H), 2.05 (m, 2H), 1.66 (s, 3H), 1.64 (s, 3H), 1.58 (s, 3H). HPLC: 96.2% purity (Phenomenex C6-Phenyl 110A. 100x2 mm, 3μm, 204 nm, retention time = 8.80 min).



(E)-3,7-dimethyl-N-(2-(naphthalen-1-yloxy)ethyl)octa-2,6-dien-1-amine (12). Compound 12 was made by the procedure provided for compound 3. 7.72 (m, 3H), 7.41 (t, J = 8.4 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.12 (s, 1H), 5.28 (t, J = 6.8 Hz, 1H), 5.07 (t, J = 6.8 Hz, 1H), 4.18 (t, J = 4.2 Hz, 1H), 3.31 (d, J = 6.8 Hz, 2H), 3.04 (t, J = 4.2 Hz, 2H), 2.09 (m, 2H), 2.01 (m, 2H), 1.66 (s, 3H), 1.65 (s, 3H), 1.58 (s, 3H). HPLC: 95.6% purity (retention time = 9.30 min).



(E)-3,7-dimethyl-N-(2-(((1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)oxy)ethyl)octa-2,6-dien-1-amine (13). Compound 13 was made by the procedure provided for compound 3. 5.20 (t, J = 6.8 Hz, 1H), 5.03 (t, J = 6.4 Hz, 1H), 3.51 (m, 2H), 3.41 (m, 1H), 3.18 (d, J = 6.8 Hz, 2H), 2.67 (m, 2H), 2.08-1.86 (m, 5H), 1.65-1.55 (m, 3H),

1.61 (s, 3H), 1.58 (s, 3H), 1.53 (s, 3H), 1.14 (m, 2H), 0.94 (dd, $J = 3.2$ Hz, 13.2 Hz, 1H), 0.80 (s, 3H), 0.77 (s, 6H). Anal. Calcd for $C_{22}H_{40}ClNO$ (HCl salt): C, 71.41; H, 10.90, N, 3.79. Found: C, 71.16; H, 11.48; N, 3.85.

5 Example 2. Lipophilic Inhibitors of Bacterial and Protozoal Cell Growth

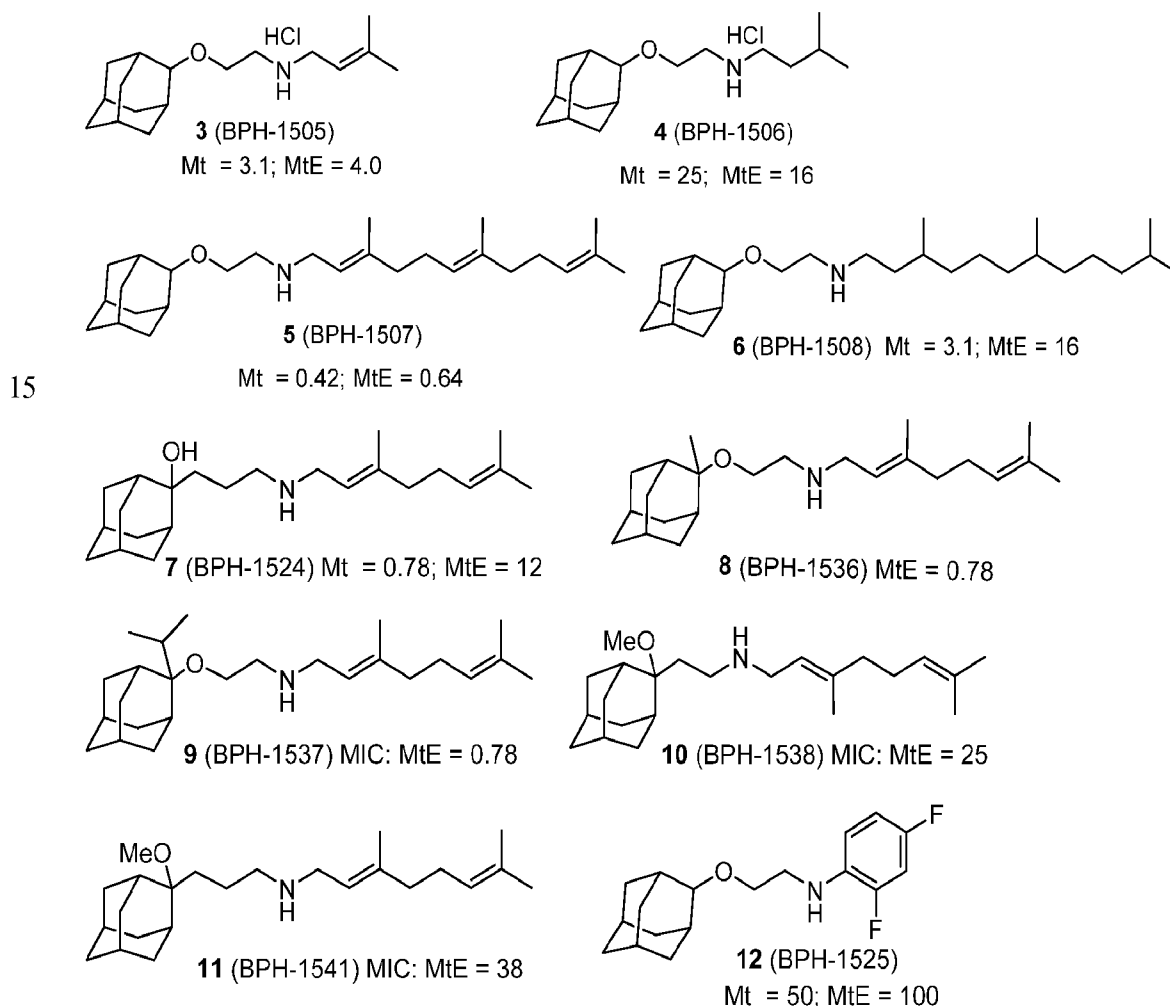
Various oxa- and thia- analogs of SQ109 were prepared and evaluated for their anti-microbial activity. The library included numerous lipophilic, primarily cationic compounds, loosely based on the *Mycobacterium tuberculosis* cell growth inhibitor SQ109, in which the ethylene diamine linker between the adamantyl and geranyl groups was replaced by oxa- or
10 thia- species, and in some cases, the *N*-geranyl group was replaced by another hydrophobic species. Compounds were tested against *Trypanosoma brucei*, *M. tuberculosis* (H37Rv and/or Erdman), *M. smegmatis*, *Bacillus subtilis*, *Escherichia coli*, *Saccharomyces cerevisiae* and two human cell lines (HEK293T and HepG2). The most potent activity was found against *T. brucei* (the causative agent of human African trypanosomiasis), with several
15 SQ109 analogs being more active than was SQ109 (IC_{50} values as low as 10 nM and a therapeutic index of ~300, to be compared with an SQ109 IC_{50} of 240 nM and a TI ~20). Several compounds also had low μ M/high nM activity against one or more other organisms where there may be a requirement for a cationic (or protonatable) center for activity. The most potent inhibition was with alkanolamine and mercaptoethylamine species against *M.*
20 *tuberculosis* with MIC values in the 0.39-0.78 μ g/mL range. In most cases, MIC values as low as ~2 μ g/mL were also seen against the other organisms. Overall, the results are of general interest because they show that various analogs of SQ109 have potent activity against the trypanosomatid parasite, *T. brucei*, and may thus be useful anti-parasitic drug leads.

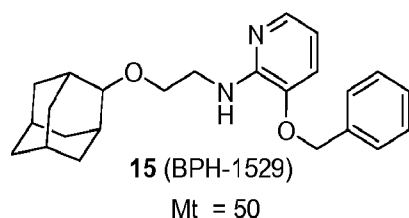
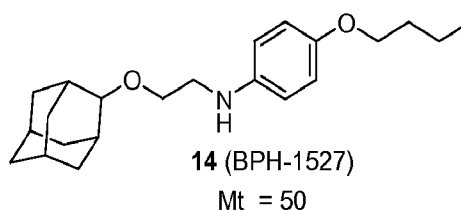
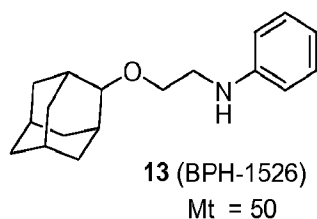
This Example describes the synthesis and evaluation of several types of protonatable
25 SQ109-inspired species that have activity against mycobacteria, as well as against other bacteria, yeasts and protozoa: a) 13 alkanolamine analogs (3-15) of the ethylene diamine linker found in SQ109 and b) 3 thia analogs (16-18) of the ethylene diamine linker. The compounds were tested for cell growth inhibition activity against *Trypanosoma brucei* (the causative agent of human African trypanosomiasis), *M. tuberculosis* (H37Rv and/or Erdman
30 strains) *M. smegmatis*, *Bacillus subtilis*, *Escherichia coli*, *Sacchaormyces cerevisiae* as well as two human cell lines (human embryonic kidney, HEK293T; and HepG2, human hepatocellular carcinoma).

Results and Discussion. We synthesized the two sets of SQ109 analogs shown in Schemes 2.1 (alkanolamines) and 2.2 (thia-analogs). Synthesis and characterization details are provided below.

Alkanolamine-containing compounds. We first synthesized the series of 13 alkanolamine-containing compounds (**3-15**, **Scheme 2.1**) where in each case the adamantane was attached to the hydrophobic side-chain via an alkanolamine linker, or the adamantane contained a 1-OH group and was attached to the adamantane “head-group” via a methylene group (**7**). All compounds were tested against *M. tuberculosis*, *M. smegmatis*, *B. subtilis*, *S. cerevisiae*, *E. coli*, *T. brucei*, HEK293T and HepG2 cells and IC₅₀ (CC₅₀) values are given in **Table 2.1** with the *M. tuberculosis* and *T. brucei* results shown, for convenience, below the structures in **Scheme 2.1**.

Scheme 2.1. Alkanolamine analogs and MIC₉₀ against *Mycobacterium tuberculosis*. Mt = *M. tuberculosis* H37Rv; MtE = *M. tuberculosis* Erdman; values shown are in µg/mL.





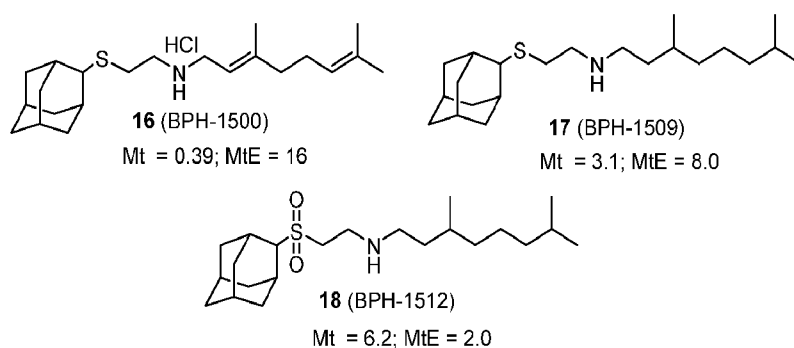
Several compounds with promising activity and interesting structural features were discovered. The most active compound was **5**, an analog of SQ109 (**2**) in which the ethylenediamine nitrogen attached to the adamantane group was replaced by an oxygen, and the geranyl (C₁₀) side-chain by a farnesyl (C₁₅) group. The MIC was 0.39 µg/mL for *M. tuberculosis* H37Rv and 1 µg/mL for *M. tuberculosis* Erdman, **Table 2.1**, to be compared with 0.1-0.2 µg/mL for SQ109 (in both strains). The reduced side-chain species **6** was ~10-20× less active (MIC = 3.1, 16 µg/mL), than was the farnesyl analog. The shorter chain (isopentenyl) ethanolamine analog (**3**) was also less active than was **5**, and reduction again reduced activity further (**4**), as did incorporation of a 1-Me or 1 *i*-Pr group (**8**, **9**). The presence of a 1-OH group (**7**) also resulted in decreased activity (0.8 µg/mL) over that found with SQ109 itself (0.1-0.2 µg/mL). The 1-OH species with a C₃ linker (**7**) had more potent activity than the 1-alkyl substituted species, with an MIC of 780 nM against *M. tuberculosis* H37Rv. Replacement of the isoprenoid side-chains with aromatic groups attached to the ethanolamine (**12-15**) blocked activity. As described in Example 1 above, we found that the analog of **5** containing a geranyl group (Example 1 compound **3**) was even more active than was **2** (MIC 0.02-0.05 µg/mL) while the diether analog of **2** was inactive. These results thus indicate that optimum activity is found with a single nitrogen and the order of activity of these alkanolamines is generally geranyl>>farnesyl>>isopentenyl, and that the reduced side-chain containing species are all less active with respect to the current assays. In the other assays (*B. subtilis*, *E. coli* and *S. cerevisiae*) the most potent cell growth inhibitor (**Table 2.1**) was **5**, the *N*-farnesyl ethanolamine. However, the *mmpL3* gene is absent in these organisms so the target of **5** in these systems cannot be MmpL3.

With the trypanosomatid parasite *T. brucei*, the most active species were **10** (IC₅₀ = 580 nM), **8** (IC₅₀ = 780 nM) and **6** (IC₅₀ = 900 nM) with therapeutic indices, defined as IC₅₀ (HEK293T)/IC₅₀ (*T. brucei*) or IC₅₀ (HepG2)/IC₅₀ (*T. brucei*) of 26, 24 (**10**), 20, 22 (**8**) and

~4-5 (6). For comparison, the IC₅₀ for SQ109 is 240 nM with a TI in the 15-25 range, **Scheme 2.1**, and therefore are less promising than is SQ109 for these microbes. We also tested an SQ109 analog described in Example 1 (BPH-1283) that had potent activity against *M. tuberculosis*, but it was slightly less active and had a worse TI (**Table 2.1**).

5 **Thia-analogs of SQ-109.** We next investigated the 3 thia-analogs of SQ109 (**16-18**) shown in **Scheme 2.2** in which the N attached to adamantane in SQ109 (O in the more active ethanolamine analog) was replaced by a S or SO₂ group (providing different H-bonding possibilities), and in two cases the geranyl group was reduced to the per-hydro species. Several sulfones were also prepared, but were not very stable (at room temperature). Cell growth inhibition results are shown in **Scheme 2.2** and **Table 2.1**.

Scheme 2.2. Mercaptoethylamine analogs and MIC₉₀ against *Mycobacterium tuberculosis*.



Mt = *M. tuberculosis* H37Rv; MIE = *M. tuberculosis* Erdman; values shown are in µg/mL.

15 As can be seen in **Scheme 2.2** and **Table 2.1**, thio-ether **16** has potent activity against *M. tuberculosis* H37Rv with a MIC of 0.39 µg/mL. Thio-ether **16** also has activity against *M. smegmatis* (1.2 µg/mL), *S. cerevisiae* (0.38 µg/mL) and *E. coli* (1.4 µg/mL).

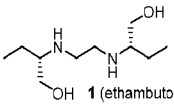
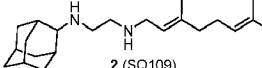
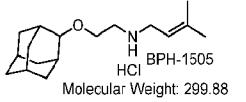
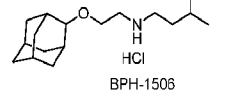
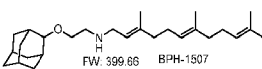
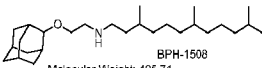
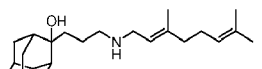
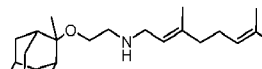
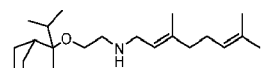
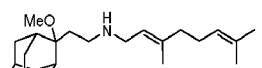
Interestingly, in these organisms, the reduced species was even more active (**Table 2.1**). The sulfone had rather weak activity in all assays. The results in *M. tuberculosis* are consistent with the results found previously for the alkanolamines **5** and **6** in that best activity is found with the unsaturated side-chains. With *T. brucei*, the most active thia-analog was **16** (IC₅₀ = 760 nM; TI 5-9 µM), followed by **17** (IC₅₀ = 1.6 µM; TI 7-9 µM) and **18** (IC₅₀ = 2.3 µM, TI = 4-5 µM). Overall, though, activity is less than with the alkanolamines (best IC₅₀, 20-50 nM).

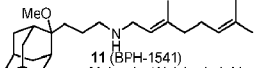
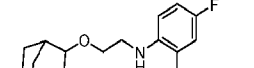
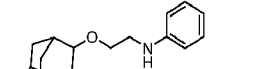
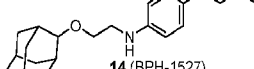
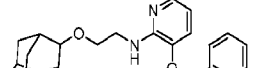
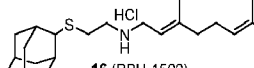
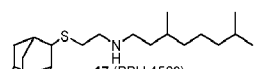
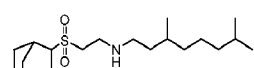
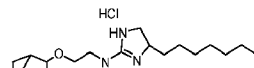
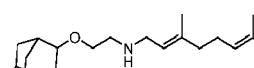
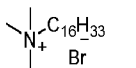
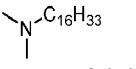
25 Unlike the alkanolamine analogs of SQ109 described in Example 1 above (in which MIC values as low as ~20-50 nM were found against *M. tuberculosis*), none of these new analogs showed improved activity against *M. tuberculosis*, although **5**, **16** and **17** were all more active than was SQ109 against the Gram negative bacterium, *E. coli* (**5**, IC₅₀ = 600 nM; **16**, IC₅₀ = 1.4 µM; **17**, IC₅₀ = 700 nM, versus IC₅₀ = 2.8 µM for SQ109; **Table 2.1**).

The results reported above are of interest because they indicate new routes to the development of analogs of the *M. tuberculosis* growth inhibitor, the ethylene diamine SQ109, currently in clinical trials. We made a broad range of analogs in which diverse hydrophobic side-chain variants were synthesized and tested. Protonatable species had the significant

5 activity and the most potent leads (MIC~0.4-0.5 µg/mL) were found against *M. tuberculosis* and contained ethanolamine or mercaptoethylamine linkers.

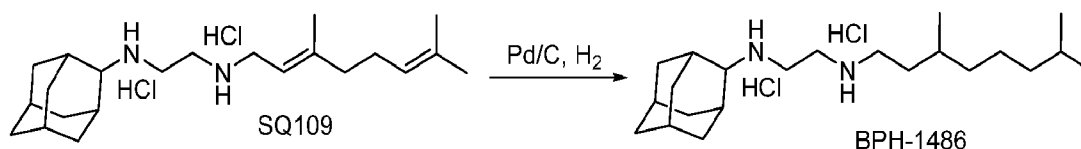
Table 2.1. Growth inhibition of various bacteria and a yeast by SQ109 and its analogs.

compounds	Mt ^a	MtE _b	Ms ^c	Bs ^d	Sc ^e	Ec ^f	Sa ^g	Ba ^h	Lm ⁱ	EP ^j	Sp ^k
1  1 (ethambutol)											
2  2 (SQ109)	0.15	0.5	3.1	7.6	1.1	2.8					
3  BPH-1505 Molecular Weight: 299.88	3.1	4.0		>120	25	9.0					
4  BPH-1506 Molecular Weight: 301.90	25	16		>120	2.1	9.6					
5  BPH-1507 FW: 399.66	0.39	1.0		0.8	0.7	0.6	8	8	8	8	8-50
6  BPH-1508 Molecular Weight: 405.71	3.1	16		3.0	2.8	10	8	8	4	4	8
7  7 (BPH-1524) Molecular Weight: 345.57	0.78	12		2.1	3.2	12	8-50	8-50	8-50	8	8
8  8 (BPH-1536) Molecular Weight: 345.57		0.78	5.8	2.2	4.1	6.2	8-50	8-50	8	8-50	8-50
9  9 (BPH-1537) Molecular Weight: 373.63		0.78	5.7	3.3	4.1	8.0	8-50	8-50	8	8-50	8-50
10  10 (BPH-1538) Molecular Weight: 345.57		25	5.1	2.8	5.1	8.9	8-50	8-50	8	8-50	8-50

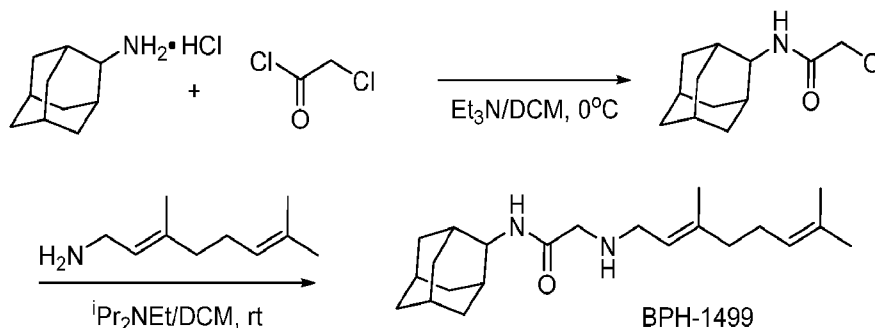
	compounds	Mt ^a	MtE _b	Ms ^c	Bs ^d	Sc ^e	Ec ^f	Sa ^g	Ba ^h	Lm ⁱ	Ef ^j	Sp ^k
11	 11 (BPH-1541) Molecular Weight: 359.60		38	5.2	3.9	6.1	9.2					
12	 12 (BPH-1525) Molecular Weight: 307.38	50	100		>60	>60	>60	>50	>50	>50	>50	>50
13	 13 (BPH-1526) Molecular Weight: 271.40	50			>60	>60	>60	>50	>50	>50	>50	>50
14	 14 (BPH-1527) Molecular Weight: 343.51	50			>60	>60	>60	>50	>50	>50	>50	>50
15	 15 (BPH-1529) Molecular Weight: 378.52	25			>60	>60	>60	>50	>50	>50	>50	>50
16	 16 (BPH-1500) Molecular Weight: 384.06	0.39	16	1.2	1.4	0.38	1.4	8	4	8	8	4
17	 17 (BPH-1509) Molecular Weight: 351.64	3.1	8.0	1.1	0.5	0.1	0.7	8	8-50	8	4	8-50
18	 18 (BPH-1512) Molecular Weight: 383.63	6.25	2.0	4.8	2.3	2.2	2.3	8	8	8	8	8
21	 21 (BPH-1532) Molecular Weight: 398.03	1.6	6.2	1.2	0.38	1.5	2.0	4	4	4	4	4
52	 BPH-1283	0.04		1.6	16	1.8	2.8	8.0	8.0	8.0	4.0	8.0
	 CTAB fw364		50									
	 CDA fw350		>10 0									

a. MIC₉₀, Mt = *M. tuberculosis* H37Rv; b. MIC₉₀, MtE = *M. tuberculosis* Erdman; c. IC₅₀, Ms = *M. Smegmatis*; d. IC₅₀, Bs = *B. subtilis*; e. IC₅₀, Sc = *S. cerevisiae*; f. IC₅₀, Ec = *E. coli*; g. MIC₉₀, Sa = *S. aureus*; h. Ba = MIC₉₀, *B. anthracis*; i. MIC₉₀, Lm = *L. monocytogene*; j. MIC₉₀, Ef = *E. faecalis*; k. MIC₉₀, Sp = *S. pyogenes*.

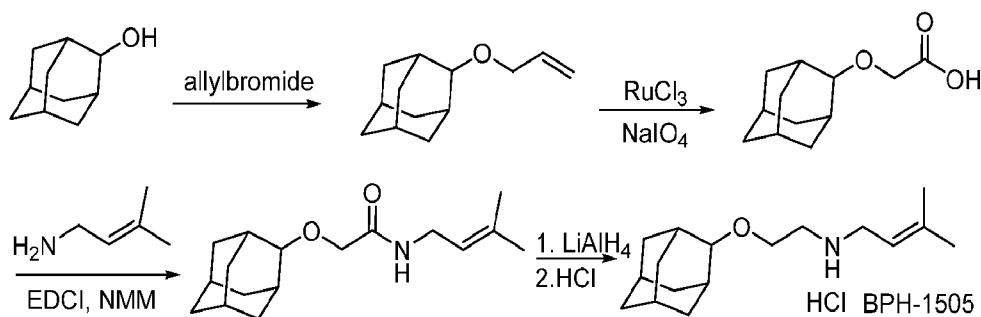
Compounds and Preparatory Methods.



***N*¹-((1*r*,3*r*,5*r*,7*r*)-adamantan-2-yl)-*N*²-((3,7-dimethyloctyl)ethane-1,2-diamine dihydrochloride (BPH-1486).** To the solution of SQ109 (40 mg, 0.1 mmol) in MeOH (3 ml) was added Pd/C (10% by weight, 10 mg) under N₂. The stirring was continued for 5 h at 22 °C after the N₂ was switched to H₂ with hydrogen balloon. The reaction mixture passed through a short Celite pad, then the filtrate was evaporated under reduced pressure to give product as white powder (38 mg, 93%). Purity of the product was determined by qNMR: 92.3%. ¹H NMR (500 MHz, Chloroform-*d*) δ 10.65 (s, 1H), 5.40 (t, *J* = 7.7 Hz, 1H), 5.17 (d, *J* = 7.6 Hz, 2H), 5.04 (s, 1H), 4.39 (s, 2H), 2.73 (s, 3H).



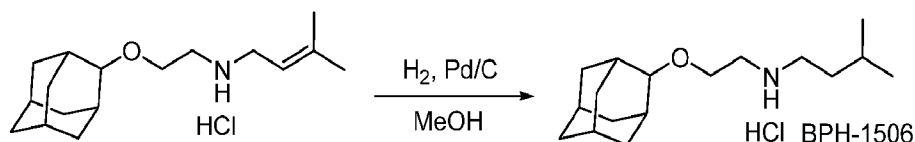
***N*-((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)-2-(((*E*)-3,7-dimethylocta-2,6-dien-1-yl)amino)acetamide (BPH-1499).** To the solution of 2-aminoadamantane hydrochloride (188 mg, 1 mmol) in dry CH₂Cl₂ (5 mL) was added Et₃N (202 mg, 2 mmol) and 2-chloroacetyl chloride (113 mg, 1 mmol) at 0 °C with stirring. The stirring was continued for 1 h at 0 °C and sat. aqueous NH₄Cl (5 mL) was added. The CH₂Cl₂ layer was separated from aqueous phase and evaporation gave the crude 2-chloroacetamide. To the solution of crude 2-chloroacetamide in dry CH₂Cl₂ (5 mL) was added *i*Pr₂NEt (101 mg, 1 mmol) and geranylamine (153 mg, 1 mmol) at 0 °C with stirring. The stirring was continued for 12 h during the raise of temperature of ice bath to rt. The reaction mixture was washed with sat. aqueous NH₄Cl and evaporated with rotary evaporator under reduced pressure to give the residue. The residue was purified by flash chromatography (SiO₂, hexane/ethyl acetate = 4/1) to give the product (246 mg, 71%). Purity of the product was determined by qNMR: 83.06%. ¹H NMR (500 MHz, Chloroform-*d*) δ 9.10 (s, 2H), 8.15 (d, *J* = 7.8 Hz, 1H), 5.41 (s, 1H), 5.04 (s, 1H), 4.07 (d, *J* = 8.1 Hz, 1H), 3.98 (s, 2H), 3.71 (d, *J* = 7.6 Hz, 2H), 2.09-1.57 (m, 18H), 1.75 (s, 3H), 1.68 (s, 3H), 1.59 (s, 3H).



***N*-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)oxy)ethyl)-3-methylbut-2-en-1-amine**

hydrochloride (BPH-1505). To a suspension of NaH (washed with and dried from hexane, 368 mg, 16 mmol) in THF (30 mL) was added 2-adamantananol (1.5 g, 10 mmol) at 0 °C.

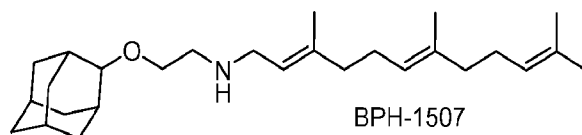
- 5 Stirring was continued for 30 min at 25°C, then allylbromide (1.8 g, 15 mmol) was added. Stirring was continued for 3h at 25°C, then the reaction was quenched by adding sat. aqueous NH₄Cl. Upon separation and concentration under reduced pressure, the residue was purified by silica gel column chromatography using 5% EtOAc in hexane as eluent to afford the allyl ether (1.4 g, 75%). To a suspension of the allyl ether (1.4 g, 7.5 mmol) in MeCN/H₂O/ethyl acetate (1/2/1, 35 mL) was added NaIO₄ (8.42 g, 40 mmol), then RuCl₃·H₂O (110 mg, 0.5 mmol). After stirring for 10 h at 25°C, ethyl acetate (40 mL) was added. Separation and concentration of the organic phase under reduced pressure gave the crude acid (1.3 g, 84%). To the solution of crude acid (210 mg, 1 mmol), isoprenylamine (102 mg, 1.2 mmol), EDCI (228 mg, 1.2 mmol) and HOAT (164 mg, 1.2 mmol) in dry THF/DMF (2 mL/2 mL) was
- 15 added *N*-methylmorpholine (505 mg, 5 mmol) at 0 °C with stirring. The stirring was continued for 2 h at 25°C. The reaction mixture was distributed between sat. aqueous NH₄Cl and hexane. The hexane phase was dried over anhydrous Na₂SO₄ and evaporated with rotary evaporator under reduced pressure to give the residue. Purification of residue with flash chromatography (SiO₂, hexane/ethyl acetate = 10/1) gave the amide (226 mg, yield: 82%).
- 20 To the solution of amide (200 mg, 0.72 mmol) in dry ethyl ether (6 mL) was added LiAlH₄ (76 mg, 2 mmol) under N₂. Stirring was continued for 10 hours at refluxing, the reaction flask cooled in an ice-bath and the reaction was quenched by adding aqueous ammonium hydroxide (37%, 0.2 mL). Vigorous stirring was continued for 20 min. Upon separation and concentration under reduced pressure, the residue was purified by silica gel column
- 25 chromatography (using NH₄OH (37%)/MeOH/EtOAc = 1/5/100 as eluent) to afford the product (134 mg, 71%). The HCl salt was obtained by neutralizing the amine with HCl in toluene in quantitative yield. Purity of the product was determined by qNMR: 98.53%. ¹H NMR (500 MHz, Chloroform-*d*) δ 9.31 (s, 2H), 5.38 (m, 1H), 3.77 (t, *J* = 5.3 Hz, 2H), 3.68 (m, 2H), 3.45 (s, 1H), 3.07 (m, 2H), 1.96-1.40 (m, 20H).



***N*-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)oxy)ethyl)-3-methylbutan-1-amine**

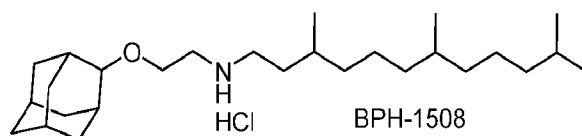
hydrochloride (BPH-1506). To the solution of unsaturated amine (HCl salt, 60 mg, 0.2

5 mmol) in MeOH (4 ml) was added palladium on charcoal (5%, 15 mg) under N₂. The stirring was continued for 1 h at 22 °C after switching the reaction atmosphere from N₂ to H₂ with hydrogen balloon. The reaction mixture passed through a short Celite pad, then the filtrate was evaporated under reduced pressure to give product as white powder. (55 mg, 90%). Purity of the product was determined by qNMR: 93.21%. ¹H NMR (500 MHz, Chloroform-*d*) δ 9.44 (s, 2H), 3.87 (t, *J* = 5.2 Hz, 2H), 3.51 (s, 1H), 3.22 (t, *J* = 5.2 Hz, 2H), 3.15 (dt, *J* = 7.0, 4.0 Hz, 2H), 2.15 – 1.33 (m, 17H), 0.94 (s, 3H), 0.93 (s, 3H).



(2*E*,6*E*)-*N*-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)oxy)ethyl)-3,7,11-trimethyldodeca-

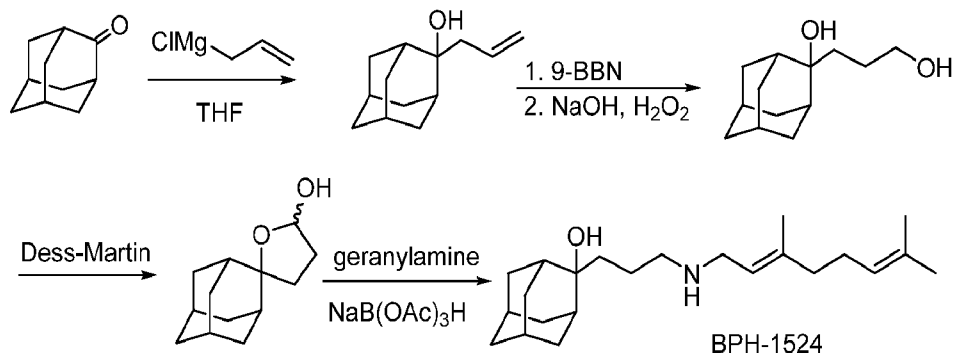
15 **2,6,10-trien-1-amine.** BPH-1507 was made according to the protocol for BPH-1505. Purity of the product was determined by qNMR: 93.77%. ¹H NMR (500 MHz, Chloroform-*d*) δ 5.28 (m, 1H), 5.10 (m, 2H), 3.56 (t, *J* = 5.2 Hz, 2H), 3.43 (s, 1H), 3.28 (d, *J* = 6.8 Hz, 2H), 2.80 (t, *J* = 5.2 Hz, 2H), 2.11-1.45 (m, 22H), 1.65 (s, 3H), 1.65 (s, 3H), 1.0 (s, 6H).



***N*-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)oxy)ethyl)-3,7,11-trimethyldodecan-1-amine**

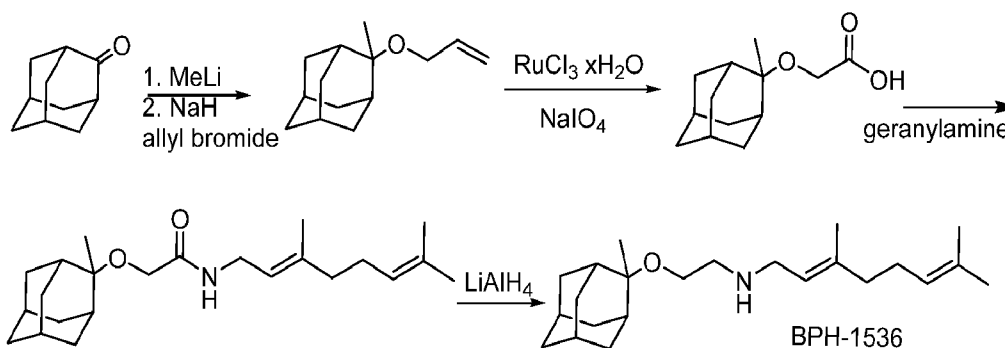
hydrochloride (BPH-1508). BPH-1507 was made according to the protocol for BPH-1506.

Purity of the product was determined by qNMR: 96.42%. ¹H NMR (500 MHz, Chloroform-*d*) δ 9.40 (s, 2H), 3.87 (s, 2H), 3.51 (s, 2H), 3.30 – 3.05 (m, 4H), 2.05 – 0.97 (m, 31H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 6H), 0.84 (d, *J* = 6.6 Hz, 3H).



(1r,3r,5r,7r)-2-(3-(((E)-3,7-Dimethylocta-2,6-dien-1-yl)amino)propyl)adamantan-2-ol.

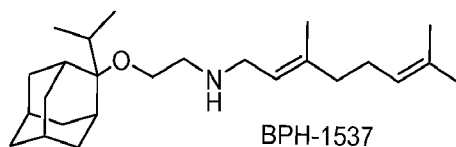
To the solution of 2-adamantanone (300 mg, 2 mmol) in dry THF (7 ml) was added allylmagnesium chloride (2 M in THF, 1.1 mL) dropwise at 0°C with stirring. The stirring was continued for 30min at 0°C and 30min at 25 °C. The reaction mixture was diluted with ethyl acetate and quenched by sat. aqueous NH₄Cl. The organic phase was dried over anhydrous Na₂SO₄ and evaporated with rotary evaporator under reduced pressure to give the crude olefin. To the solution of crude olefin in dry THF (7 mL) was added 9-BBN (0.5 M in THF, 4.4 ml) in a dropwise fashion. The stirring was continued for 30min at 0°C and 1h at 25 °C. The reaction flask was dipped into the ice-bath. To the resulting reaction mixture was added NaOH (3N in H₂O, 3 mL) and H₂O₂ (30% in water, 0.68 mL). The stirring was continued for 30min at 0°C and 1h at 25 °C. The reaction mixture was diluted with ethyl acetate and quenched with sat. aqueous Na₂S₂O₃ at 0°C. The organic phase was dried over Na₂SO₄ and and evaporated with rotary evaporator under reduced pressure to give the crude diol. To the solution of crude diol in DCM (7 mL) was added Dess-Martin periodinane (848 mg) at 0°C. The stirring was continued for 30 min at 0°C and 1h at 25 °C. The reaction residue from reduced-pressure evaporation was submitted to the flash chromatography (SiO₂, hexane/ethyl acetate = 6/1) to give hemiacetal (203 mg, 49%). To the solution of hemiacetal (166 mg, 0.8 mmol) in dry DCM (5 ml) was added geranylamine (122 mg, 0.8 mmol) sodium triacetoxymethylborohydride (424 mg, 2 mmol). The stirring was continued for 12 h at 25 °C. The reaction was quenched by adding sat. aqueous NaHCO₃ (5 mL). The organic phase was dried over anhydrous Na₂SO₄ and evaporated with rotary evaporator under reduced pressure to give the residue. Purification of the residue with flash chromatography (SiO₂, chloroform/methanol = 8/1) to give product (177 mg, 64%). Purity of the product was determined by qNMR: 93.27%. ¹H NMR (500 MHz, Chloroform-*d*) 5.26 (t, *J* = 10.0 Hz, 1H), 5.08 (t, *J* = 10.0 Hz, 1H), 3.26 (d, *J* = 6.9 Hz, 2H), 2.69 (t, *J* = 6.1 Hz, 2H), 2.28 (dd, *J* = 11.8, 3.5 Hz, 2H), 2.09-1.51 (m, 23H), 2.64 (s, 3H), 1.60 (s, 3H).



- (*E*)-3,7-Dimethyl-N-(2-(((1*r*,3*r*,5*r*,7*r*)-2-methyladamantan-2-yl)oxy)ethyl)-octa-2,6-dien-1-amine (BPH-1536).** To the solution of 2-adamantanone (150 mg, 1 mmol) in dry THF (4 mL) was added methyl lithium (1.6 M in diethyl ether, 0.8 mL) dropwise at 0 °C with stirring. The stirring was continued for 30min at 0°C and quenched by sat. aqueous NH₄Cl. The organic phase was separated, dried over anhydrous Na₂SO₄ and evaporated with rotary evaporator under reduced pressure to give the crude alcohol. To the solution of crude alcohol and allylbromide (360 mg, 3 mmol) in dry DMF (3 mL) was added NaH (washed with and dried from hexane, 46 mg) at 0 °C with stirring. The stirring was continued for 1h at 0 °C.
- The reaction mixture was distributed between sat. aqueous NH₄Cl and hexane. The hexane phase was dried over anhydrous Na₂SO₄ and evaporated with rotary evaporator under reduced pressure to give the crude olefin. To the solution of crude olefin in ethyl acetate/MeCN and D.I. water (5 mL/5 mL/5 mL) was added RuCl₃ hydrate (10 mg, 0.05 mmol) and NaIO₄ (428 mg, 2 mmol) at 0 °C. The vigorous stirring was continued for 20 min at 0 °C and 4 h at 25 °C. The organic phase was dried over anhydrous Na₂SO₄ and evaporated with rotary evaporator under reduced pressure to give the crude acid. To the solution of crude acid, geranylamine (153 mg, 1 mmol), EDCI (191 mg, 1 mmol) and HOAT (136 mg, 1 mmol) in dry THF/DMF (2 mL/2 mL) was added *N*-methylmorpholine (505 mg, 5 mmol) at 0°C with stirring. The stirring was continued for 2 h at 25 °C. The reaction mixture was distributed between sat. aqueous NH₄Cl and hexane. The hexane phase was dried over anhydrous Na₂SO₄ and evaporated with rotary evaporator under reduced pressure to give the residue. Purification of residue with flash chromatography (SiO₂, hexane/ethyl acetate = 10/1) gave the amide (147 mg, yield: 41%). To the solution of amide (108 mg, 0.3 mmol) in dry ethyl ether (3 mL) was added LiAlH₄ (38 mg, 1 mmol) under N₂. Stirring was continued for 10 h at refluxing, the reaction flask cooled in an ice-bath and the reaction was quenched by adding aqueous ammonium hydroxide (37%, 0.2 mL). Vigorous stirring was continued for 20 min. Upon separation and concentration under reduced pressure, the residue was purified by silica gel column chromatography (using NH₄OH (37%)/MeOH/EtOAc = 1/5/100 as eluent)

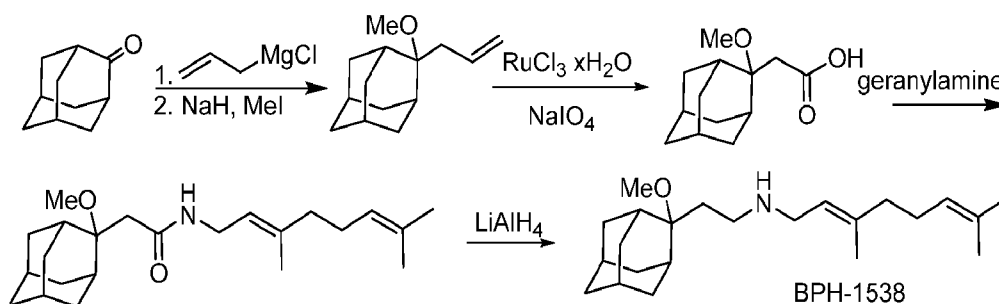
to afford the product (69 mg, 67%). Purity of the product was determined by qNMR: 98.89%. ¹H NMR (500 MHz, Chloroform-*d*) δ 5.27 (t, *J* = 5.9 Hz, 1H), 5.09 (t, *J* = 7.2 Hz, 1H), 3.45 (t, *J* = 5.3 Hz, 2H), 3.26 (d, *J* = 6.8 Hz, 2H), 2.77 (t, *J* = 5.3 Hz, 2H), 2.20 – 1.37 (m, 18H), 1.67 (s, 3H), 1.64 (s, 3H), 1.60 (s, 3H), 1.26 (s, 3H).

5



(*E*)-N-(2-(((1*r*,3*r*,5*r*,7*r*)-2-Isopropyladamantan-2-yl)oxy)ethyl)-3,7-dimethylocta-2,6-dien-1-amine (BPH-1537). BPH-1537 was made according to the protocol for BPH-1536. Purity of the product was determined by qNMR: 98.18%. ¹H NMR (500 MHz, Chloroform-*d*) δ 5.28 ((t, *J* = 5.0 Hz, 1H), 5.10 (t, *J* = 5.0 Hz, 1H), 3.55 (t, *J* = 5.2 Hz, 2H), 3.43 (s, 1H), 3.26 (d, *J* = 6.7 Hz, 2H), 2.79 (t, *J* = 5.2 Hz, 2H), 2.19 – 1.35 (m, 25H), 1.68 (s, 3H), 1.64 (s, 3H), 1.60 (s, 3H).856+.

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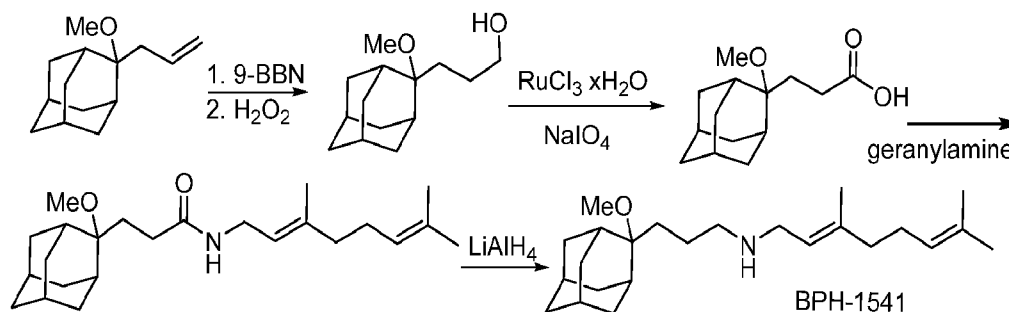


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(*E*)-N-(2-(((1*r*,3*r*,5*r*,7*r*)-2-Methoxyadamantan-2-yl)ethyl)-3,7-dimethylocta-2,6-dien-1-amine (BPH-1538). To the solution of adamantanone (150 mg, 1 mmol) in dry THF (4 ml) was added allylmagnesium chloride (2.0 M in THF, 0.6 mL) dropwise at 0 °C with stirring. The stirring was continued for 30min at 0°C and quenched by sat. aqueous NH₄Cl. The organic phase was separated, dried over anhydrous Na₂SO₄ and evaporated with rotary evaporator under reduced pressure to give the crude alcohol. To the solution of crude alcohol and MeI (426 mg, 3 mmol) in dry DMF (3 mL) was added NaH (washed with and dried from hexane, 46 mg) at 0 °C with stirring. The stirring was continued for 1h at 0°C. The reaction mixture was distributed between sat. aqueous NH₄Cl and hexane. The hexane phase was dried over anhydrous Na₂SO₄ and evaporated with rotary evaporator under reduced pressure to give the crude olefin. The following operation is the same as that for BPH-1536. Purity of the product was determined by qNMR: 90.06%. ¹H NMR (500 MHz, Chloroform-*d*) δ 5.27 (t, *J* = 5.3 Hz, 1H), 5.10 (t, *J* = 5.0 Hz, 1H), 3.23 (d, *J* = 6.8 Hz, 2H), 3.16 (s, 3H), 2.63 (t, *J* = 10.0 Hz, 2H), 2.11-1.4 (m, 18H), 1.68 (s, 3H), 1.64 (s, 3H), 1.60 (s, 3H).

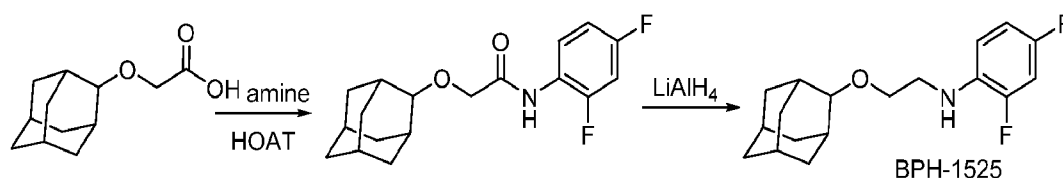
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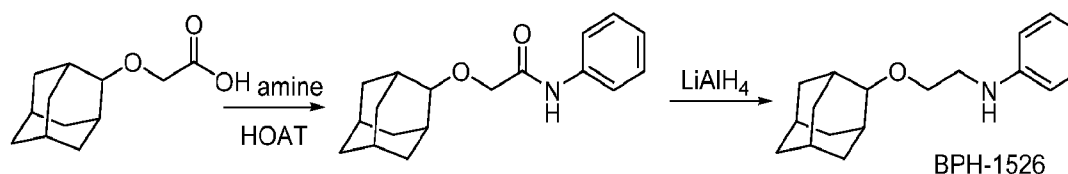
(*E*)-*N*-(3-((1*r*,3*r*,5*r*,7*r*)-2-Methoxyadamantan-2-yl)propyl)-3,7-dimethylocta-2,6-dien-1-amine (BPH-1541). BPH-1541 was made according to the protocol for BPH-1538.

- 5 The only modification is that hydroboration-oxidation of olefin was carried out before sodium periodate oxidation. To the solution of olefin (171 mg, 0.83 mmol) in dry THF (2 mL) was added 9-BBN (0.5 M in THF, 2 mL, 1 mmol) under N₂ at 0 °C. The stirring was continued for 2 h at 0 °C, and then aqueous NaOH (3N, 1 mL) and H₂O₂ (30% in water, 0.18 mL, 1.66 mmol) was added in sequence. The vigorous stirring was continued for 30 min at 0 °C and 1 h at 25 °C, and then ethyl acetate (4 mL) and sat. aqueous Na₂S₂O₃ was added with stirring. The organic phase was separated and evaporated under reduced pressure to give the crude alcohol for next step. Purity of the product was determined by qNMR: 94.07%. ¹H NMR (500 MHz, Chloroform-*d*) δ 5.26 (t, *J* = 5.0 Hz, 1H), 5.10 (t, *J* = 5.0 Hz, 1H), 3.23 (d, *J* = 6.8 Hz, 2H), 3.12 (s, 3H), 2.61 (t, *J* = 7.2 Hz, 2H), 2.11-1.45 (m, 22H), 1.68 (s, 3H), 1.64 (s, 3H), 1.60 (s, 3H).



***N*-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)oxy)ethyl)-2,4-difluoroaniline (BPH-1525).**

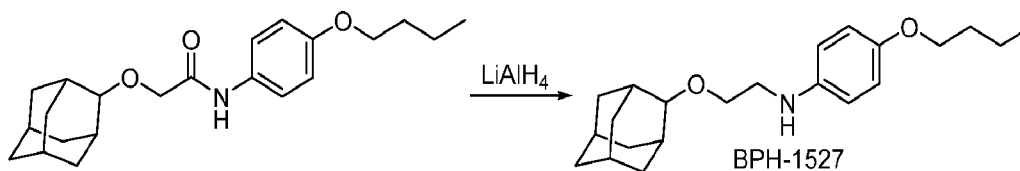
- BPH-1525 was made by the protocol for BPH-1505. Purity of the product was determined by qNMR: 98.05%. ¹H NMR (500 MHz, Chloroform-*d*) 7.76 (m, 1H), 6.93 (m, 2H), 3.7 (t, *J* = 5.2 Hz, 2H), 3.55 (t, *J* = 5.2 Hz, 2H), 3.40 (s, 1H), 1.92-1.41 (m, 14H).



***N*-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)oxy)ethyl)aniline (BPH-1526).** BPH-1526

- was made by the protocol for BPH-1505. Purity of the product was determined by qNMR:

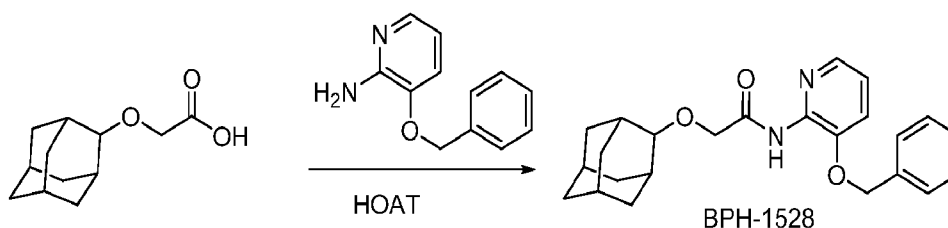
95.01%. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.62 (m, 2H), 7.39 (m, 3H), 3.71 (t, *J* = 5.6 Hz, 2H), 3.50 (t, *J* = 5.5 Hz, 2H), 3.36 (s, 1H), 1.96-1.39 (m, 14H).



5 ***N*-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)oxy)ethyl)-4-butoxyaniline (BPH-1527).**

BPH-1527 was made by the protocol for BPH-1505. Purity of the product was determined by qNMR: 99.45%. ¹H NMR (500 MHz, Chloroform-*d*) δ 6.78 (d, *J* = 8.8 Hz, 2H), 6.62 (d, *J* = 8.8 Hz, 2H), 3.89 (t, *J* = 6.6 Hz, 2H), 3.64 (t, *J* = 5.2 Hz, 2H), 3.44 (m, 1H), 3.24 (t, *J* = 5.2 Hz, 2H), 2.07 – 1.37 (m, 18H), 0.96 (t, *J* = 7.4 Hz, 3H).

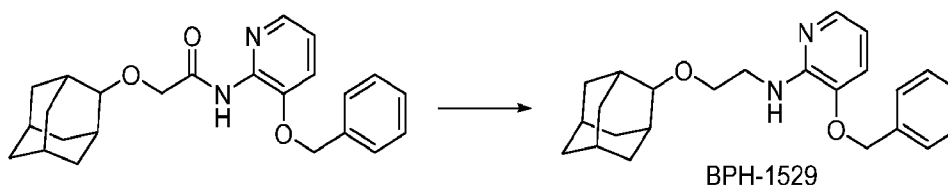
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2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)oxy)-*N*-(3-(benzyloxy)pyridin-2-yl)acetamide (BPH-1528).

BPH-1528 was made by the similar protocol for BPH-1505. Purity of the product was determined by qNMR: 99.79%. ¹H NMR (500 MHz, Chloroform-*d*) δ 9.46 (s, 1H), 8.13 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.42 – 7.32 (m, 4H), 7.22 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.00 (dd, *J* = 8.1, 4.9 Hz, 1H), 4.11 (s, 2H), 3.52 (1H), 1.95 – 1.82 (m, 4H), 1.84 – 1.50 (m, 8H), 1.35 (m, 2H).

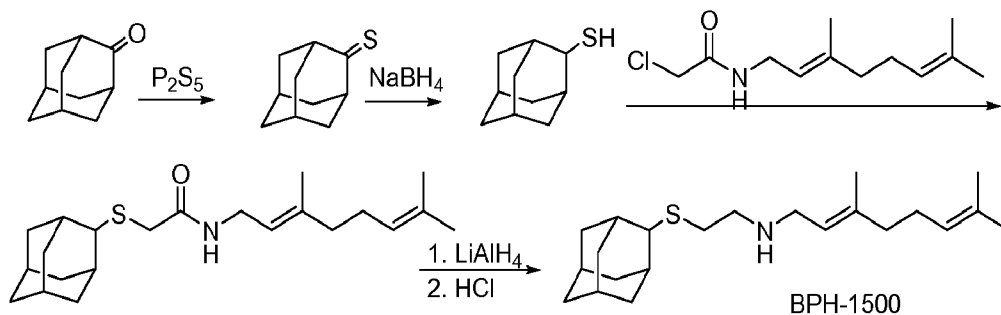
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20 ***N*-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)oxy)ethyl)-3-(benzyloxy)pyridin-2-amine (BPH-1529).**

BPH-1529 was made by the protocol for BPH-1505. Purity of the product was determined by qNMR: 95.36%. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.77 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.41 – 7.33 (m, 2H), 7.24 (d, *J* = 7.8 Hz, 2H), 7.21 – 7.15 (m, 1H), 7.11 (dd, *J* = 7.8, 1.7 Hz, 1H), 6.81 (dd, *J* = 7.8, 4.8 Hz, 1H), 4.64 (s, 2H), 3.48 (dd, *J* = 5.4, 4.1 Hz, 2H), 3.44 (s, 1H), 3.37 (t, *J* = 4.8 Hz, 2H), 2.14 – 1.50 (m, 14H).

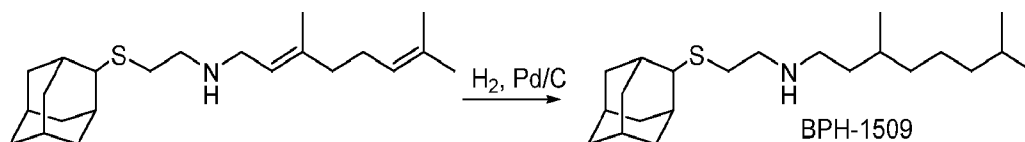
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(E)-N-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)thio)ethyl)-3,7-dimethylocta-2,6-dien-1-amine (BPH-1500). The thio-adamantanol was made according to the reported protocol (Greidan, *Canadian Journal of Chemistry*, 48(22), 3593-7; 1970). To a stirred solution of geranylamine (153 mg, 1.0 mmol) in CHCl_3 (3 mL), chloroacetyl chloride (167 mg, 1.5 mmol) was added drop-wise at 0 °C. Then water (2 mL) was added followed by K_2CO_3 (414 mg, 3.0 mmol). A catalytic amount of tetrabutylammonium hydrogen sulfate was added to the reaction mixture which was then stirred for 4 h. After completion of the reaction, as monitored by TLC, the organic layer was separated and dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residual mass was purified by silica gel column chromatography using 25% EtOAc in hexane as eluent to afford the chloroacetamide (183 mg, 80%).

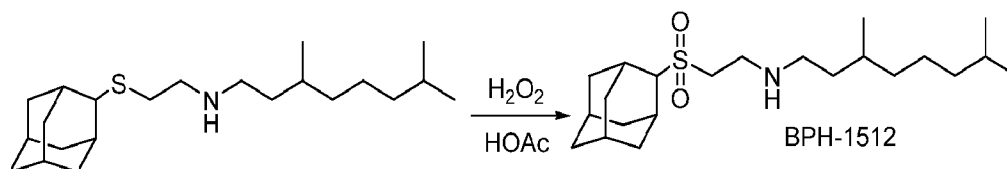
To a solution of 2-(thio)adamantanol (84 mg, 0.5 mmol) in dry THF (3 mL) was added NaH (washed with and dried from hexane, 23 mg, 1 mmol) at 0 °C with stirring. After stirring for 30 min at 22 °C, the chloroacetamide (115 mg, 0.5 mmol) was added. Stirring was continued for 12 h at 22 °C, then the reaction was quenched by adding sat. aqueous NH_4Cl . Upon separation and concentration under reduced pressure, the residue was purified by silica gel column chromatography using 25% EtOAc in hexane as eluent to afford the 2-(adamantan-2-ylthio)acetamide (152 mg, 84%).

To a suspension of LiAlH_4 (38 mg, 1 mmol) in dry THF (2 mL) was added 2-(adamantan-2-ylthio)acetamide (121 mg, 0.33 mmol) at 25 °C. Stirring was continued for 5 h at refluxing, the reaction mixture cooled in an ice-bath and quenched by adding aqueous ammonium hydroxide (37%, 0.3 mL). Vigorous stirring was continued for 20 min. Upon separation and concentration under reduced pressure, the residue was purified by silica gel column chromatography (using NH_4OH (37%)/MeOH/EtOAc = 1/5/100 as eluent) to afford the product (89 mg, 78%). The HCl salt of BPH-1500 was obtained by neutralizing the amine with HCl in toluene with quantitative yield. Purity of the product was determined by qNMR: 91.94%. ^1H NMR (500 MHz, CHCl_3 -*d*) δ 9.60 (s, 2H), 5.41 (m, 1H), 5.04 (m, 1H), 3.65 (m, 2H), 3.02 (m, 5H), 2.26 – 1.36 (m, 27H).

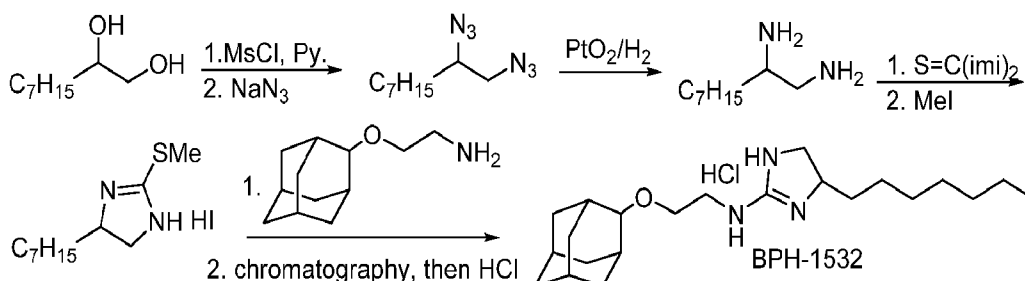


***N*-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)thio)ethyl)-3,7-dimethyloctan-1-amine (BPH-1509).** To the solution of unsaturated amine (30 mg) in MeOH (2 mL) was added
 5 palladium on charcoal (10%, 30 mg) under N₂. The stirring was continued for 1 h at 25 °C after switching the reaction atmosphere from N₂ to H₂ with hydrogen balloon. The filtration and evaporation gave the product (25 mg, 83%). Purity of the product was determined by qNMR: 97.88%. 3.04 (s, 1H), 2.80 (t, *J* = 6.5 Hz, 2H), 2.69 (t, *J* = 6.5 Hz, 2H), 2.62 (m, 2H), 2.16 (d, *J* = 12.7 Hz, 2H), 2.13 (s, 1H), 1.96-1.10 (m, 24H), 0.88-0.86 (m, 9H).

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***N*-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)sulfonyl)ethyl)-3,7-dimethyloctan-1-amine (BPH-1512).** To the solution of thioether (50 mg, 0.14 mmol) in HOAc (1 mL) was added
 15 H₂O₂ (30% in water, 79 mg) at 0 °C with stirring. Ethyl acetate (5 mL) and water (5 mL) was added to the reaction mixture after the stirring was continued for 12 h at 25 °C. Solid NaHCO₃ was added partially until no bubble evolved. The ethyl acetate phase was washed separated, washed with sat. aqueous Na₂S₂O₃, dried over anhydrous Na₂SO₄ and evaporated with rotary evaporator under reduced pressure to give the residue. Purification of residue with
 20 flash chromatography (SiO₂, chloroform/MeOH = 6/1) gave product (30 mg, yield: 57%, purity: 98.68%). Purity of the product was determined by qNMR: 98.68%. ¹H NMR (500 MHz, Chloroform-*d*) δ 3.28 (s, 1H), 3.14 (s, 4H), 2.62 (m, 2H), 2.53 (d, *J* = 3.8 Hz, 2H), 2.46 (dd, *J* = 13.3, 3.2 Hz, 2H), 1.96 (dt, *J* = 11.5, 3.1 Hz, 4H), 1.83-1.02 (m, 18H), 0.86 (m, 9H).



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***N*-(2-(((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-yl)oxy)ethyl)-4-heptyl-4,5-dihydro-1*H*-imidazol-2-amine hydroiodide (BPH-1532).** To the solution of diol (320 mg, 2 mmol) in

dry DCM (6 mL) was added pyridine (480 mg, 6 mmol) and MsCl (342 mg, 3 mmol) at 0 °C with stirring. The stirring was continued for 1 h at 0 °C and quenched by sat. aqueous NaHCO₃. The DCM phase was separated and concentrated to give crude dimesylate. The mixture of the above crude dimesylate and NaN₃ (260 mg, 4 mmol) in DMF (4 mL) was

5 heated at 80 °C for 2 h. The resulting mixture was distributed between hexane and water. The hexane phase was dried over anhydrous Na₂SO₄ and evaporated with rotary evaporator under reduced pressure to give pure enough diazide. The mixture of diazide and PtO₂ (40 mg, 0.1 mmol) in MeOH (4 mL) was stirred under H₂ for 2 h at 25 °C. Filtration and evaporation gave the diamine (227 mg, 72%). To the solution of diamine (227 mg, 1.44 mmol) in dry

10 DCM was added 1,1'-thiocarbonyldiimidazole (356 mg, 2 mmol) at 0°C. The stirring was continued for 2h at 25 °C. The reaction mixture was purified with flash chromatography (SiO₂, hexane/ethyl acetate = 6/1) gave thiourea (216 mg, yield: 75%). The solution of thiourea (216 mg, 1.08 mmol) and MeI (426 mg, 3 mmol) in MeOH (4 mL) was refluxed for 4 h. The solution was evaporated to give methylthio-imidazole pure enough for the next step.

15 The amine (38 mg, 0.2 mmol) and methylthio-imidazole (69 mg, 0.2 mmol) was refluxed in isopropanol (2 mL) for 2 h. The reaction mixture was concentrated and purified with flash chromatography (SiO₂, CHCl₃/MeOH/Et₃N = 100/10/5) gave cyclic guanidine (64 mg, yield: 65%). The HCl salt of cyclic guanidine was obtained by neutralizing it with HCl in toluene. Purity of the product was determined by qNMR: 95.56%. ¹H NMR (500 MHz, Chloroform-

20 *d*) δ 8.99 (s, 1H), 8.42 (d, 1H), 7.05 (d, 1H), 4.51-3.80 (m, 2H), 3.74-3.57 (m, 2H), 3.53 (s, 1H), 3.49-3.10 (m, 3H), 2.09-1.66 (m, 11H), 1.62-1.15 (m, 15H), 0.89 (t, *J* = 5.0 Hz, 1H).

Example 3. Pharmaceutical Dosage Forms

The following formulations illustrate representative pharmaceutical dosage forms that

25 may be used for the therapeutic or prophylactic administration of a compound of a formula described herein, a compound specifically disclosed herein, or a pharmaceutically acceptable salt or solvate thereof (hereinafter referred to as 'Compound X'):

	<u>(i) Tablet 1</u>	<u>mg/tablet</u>
30	'Compound X'	100.0
	Lactose	77.5
	Povidone	15.0
	Croscarmellose sodium	12.0
	Microcrystalline cellulose	92.5
35	Magnesium stearate	<u>3.0</u>
		300.0

	<u>(ii) Tablet 2</u>	<u>mg/tablet</u>
	'Compound X'	20.0
	Microcrystalline cellulose	410.0
	Starch	50.0
5	Sodium starch glycolate	15.0
	Magnesium stearate	<u>5.0</u>
		500.0
	<u>(iii) Capsule</u>	<u>mg/capsule</u>
10	'Compound X'	10.0
	Colloidal silicon dioxide	1.5
	Lactose	465.5
	Pregelatinized starch	120.0
	Magnesium stearate	<u>3.0</u>
15		600.0
	<u>(iv) Injection 1 (1 mg/mL)</u>	<u>mg/mL</u>
	'Compound X' (free acid form)	1.0
	Dibasic sodium phosphate	12.0
20	Monobasic sodium phosphate	0.7
	Sodium chloride	4.5
	1.0 N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
	Water for injection	q.s. ad 1 mL
25	<u>(v) Injection 2 (10 mg/mL)</u>	<u>mg/mL</u>
	'Compound X' (free acid form)	10.0
	Monobasic sodium phosphate	0.3
	Dibasic sodium phosphate	1.1
30	Polyethylene glycol 400	200.0
	0.1 N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
	Water for injection	q.s. ad 1 mL
35	<u>(vi) Aerosol</u>	<u>mg/can</u>
	'Compound X'	20
	Oleic acid	10
	Trichloromonofluoromethane	5,000
	Dichlorodifluoromethane	10,000
40	Dichlorotetrafluoroethane	5,000
	<u>(vii) Topical Gel 1</u>	<u>wt. %</u>
	'Compound X'	5%
	Carbomer 934	1.25%
45	Triethanolamine (pH adjustment to 5-7)	q.s.
	Methyl paraben	0.2%
	Purified water	q.s. to 100g

	<u>(viii) Topical Gel 2</u>	<u>wt. %</u>
	'Compound X'	5%
	Methylcellulose	2%
5	Methyl paraben	0.2%
	Propyl paraben	0.02%
	Purified water	q.s. to 100g
	<u>(ix) Topical Ointment</u>	<u>wt. %</u>
10	'Compound X'	5%
	Propylene glycol	1%
	Anhydrous ointment base	40%
	Polysorbate 80	2%
	Methyl paraben	0.2%
15	Purified water	q.s. to 100g
	<u>(x) Topical Cream 1</u>	<u>wt. %</u>
	'Compound X'	5%
	White bees wax	10%
20	Liquid paraffin	30%
	Benzyl alcohol	5%
	Purified water	q.s. to 100g
	<u>(xi) Topical Cream 2</u>	<u>wt. %</u>
25	'Compound X'	5%
	Stearic acid	10%
	Glyceryl monostearate	3%
	Polyoxyethylene stearyl ether	3%
	Sorbitol	5%
30	Isopropyl palmitate	2 %
	Methyl Paraben	0.2%
	Purified water	q.s. to 100g

These formulations may be prepared by conventional procedures well known in the pharmaceutical art. It will be appreciated that the above pharmaceutical compositions may be varied according to well-known pharmaceutical techniques to accommodate differing amounts and types of active ingredient 'Compound X'. Aerosol formulation (vi) may be used in conjunction with a standard, metered dose aerosol dispenser. Additionally, the specific ingredients and proportions are for illustrative purposes. Ingredients may be exchanged for suitable equivalents and proportions may be varied, according to the desired properties of the dosage form of interest.

While specific embodiments have been described above with reference to the disclosed embodiments and examples, such embodiments are only illustrative and do not

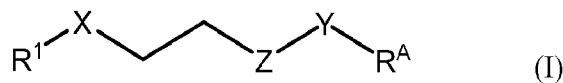
limit the scope of the invention. Changes and modifications can be made in accordance with ordinary skill in the art without departing from the invention in its broader aspects as defined in the following claims.

5 All publications, patents, and patent documents are incorporated by reference herein,
as though individually incorporated by reference. No limitations inconsistent with this
disclosure are to be understood therefrom. The invention has been described with reference
to various specific and preferred embodiments and techniques. However, it should be
understood that many variations and modifications may be made while remaining within the
spirit and scope of the invention.

10

What is claimed is:

1. A compound of Formula I:



wherein

X is O, NH, N⁺(Me)₂, S, S(=O), S(=O)₂, or a direct bond;

Y is O, NH, N⁺(Me)₂, S, S(=O), or S(=O)₂;

provided that one of X and Y is NH, and that X and Y are not both NH;

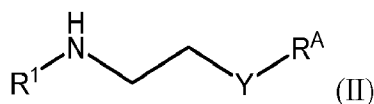
Z is a direct bond, -CH₂-, or -CH₂-CH₂-; and

R¹ is a (C₆-C₁₀)cycloalkyl, benz-fused cyclohexyl, (C₆-C₁₄)aryl, (C₅-C₉)heterocycle, or (C₅-C₉)heteroaryl group, wherein each group is optionally substituted with a (C₁-C₃)alkoxy group, one to four hydroxyl groups, one or two oxo groups, one to four (C₁-C₃)alkyl groups, or a combination thereof; and

R^A is (C₅-C₁₅)alkyl, (C₅-C₁₅)alkenyl, or phenoxyphenyl(C₁-C₄)alkyl, wherein the alkyl or alkenyl is straight chain or branched;

or a salt or solvate thereof.

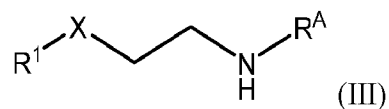
2. The compound of claim 1 wherein X is NH.
3. The compound of claim 1 wherein Y is NH.
4. The compound of claim 1 wherein X is O or S.
5. The compound of claim 1 wherein Y is O or S.
6. The compound of claim 1 wherein the compound is a compound of Formula II:



wherein Y is O or S;

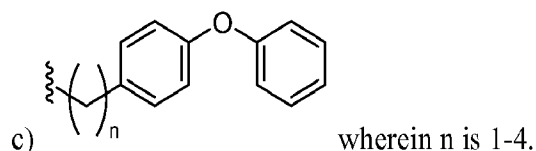
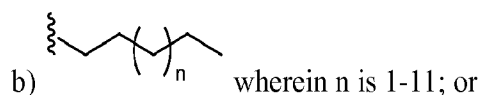
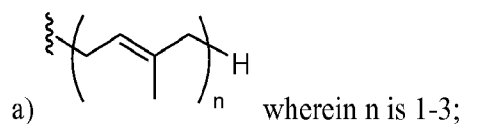
or a salt or solvate thereof.

7. The compound of claim 1 wherein the compound is a compound of Formula III:



wherein X is O or S;
or a salt or solvate thereof.

8. The compound of claim 1 wherein R^A is:



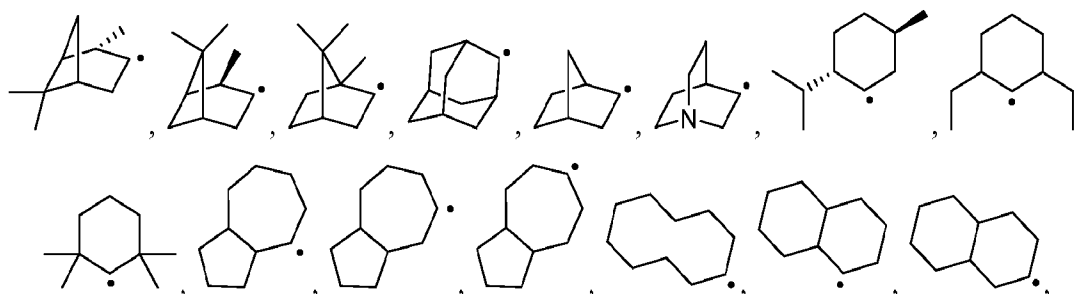
9. The compound of claim 1 wherein R^A is a prenyl group, a geranyl group, a farnesyl group, a saturated prenyl group, a saturated geranyl group, or a saturated farnesyl group.

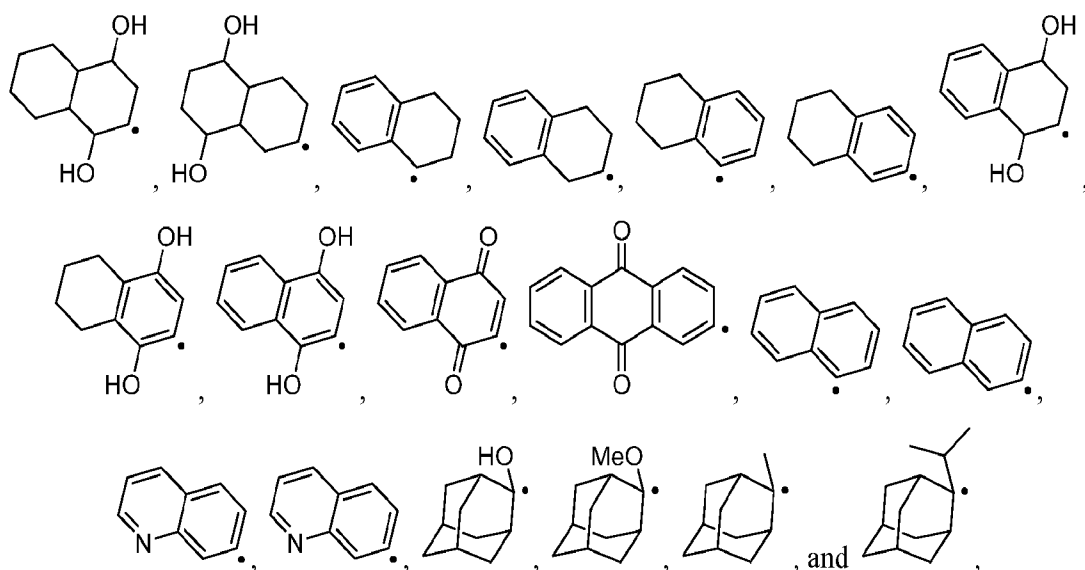
10. The compound of claim 1 wherein R^1 is substituted with one or two hydroxyl groups or one or two methoxy groups.

11. The compound of claim 1 wherein R^1 is substituted with one, two, three, or four methyl groups.

12. The compound of claim 1 wherein R^1 is substituted with one or two oxo groups.

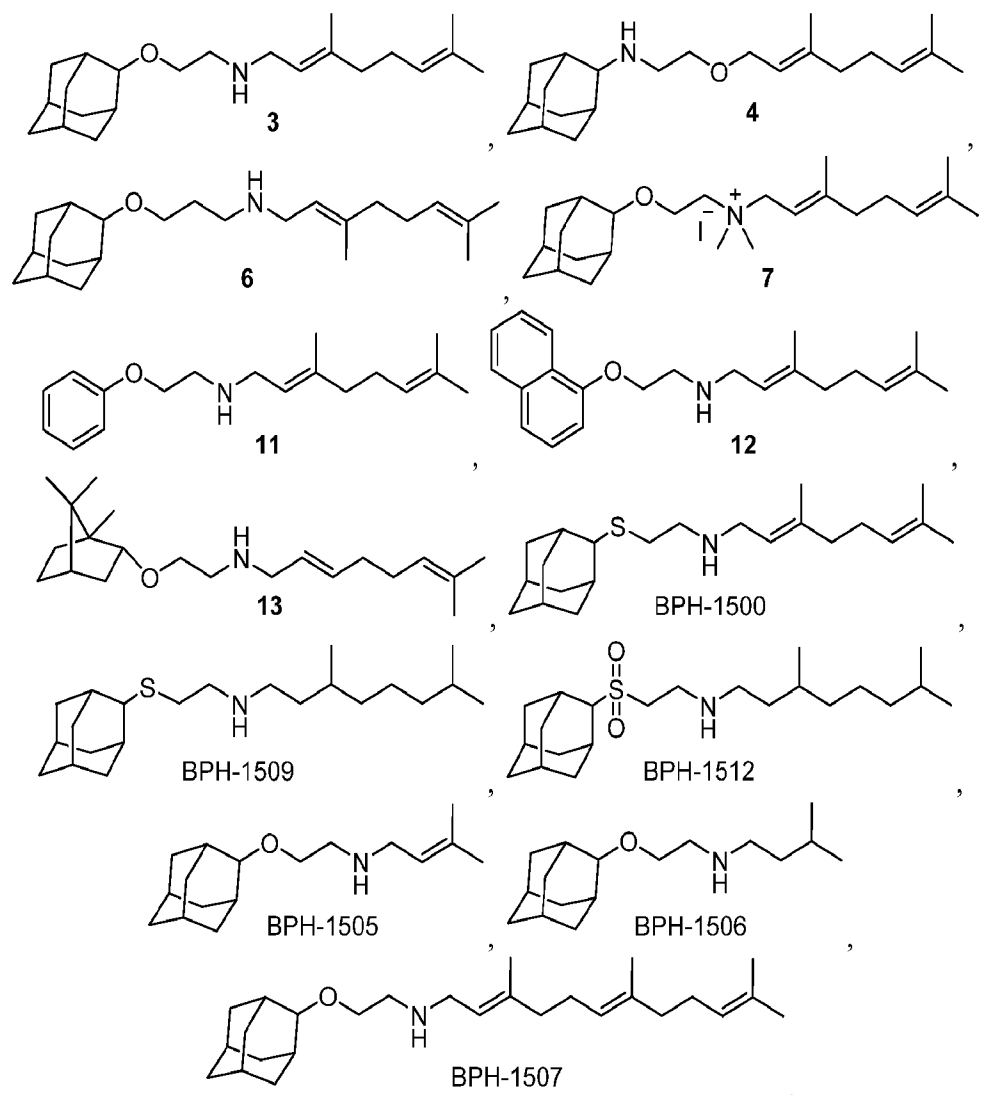
13. The compound of claim 1 wherein R^1 is selected from:

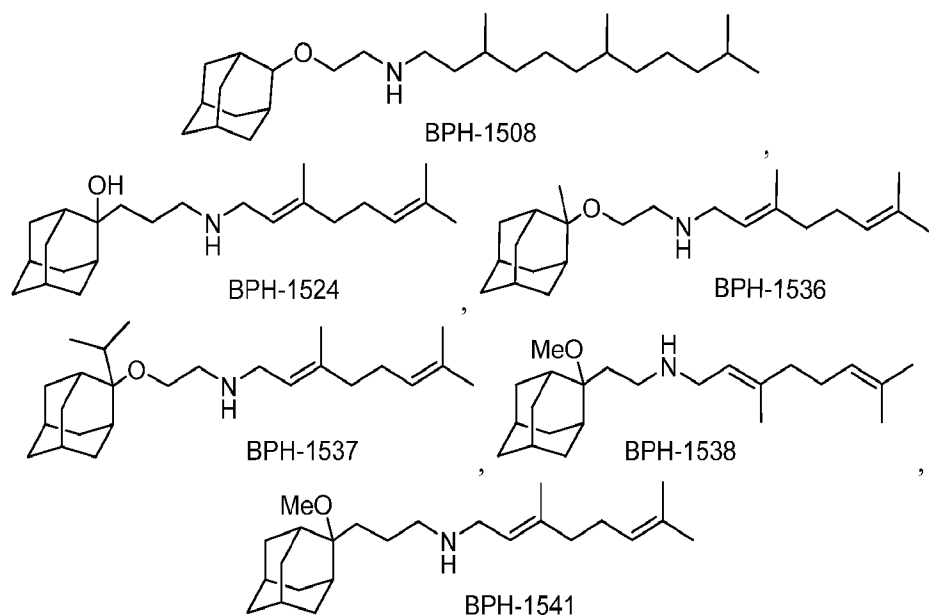




wherein the radical "•" indicates the site of attachment to the group X.

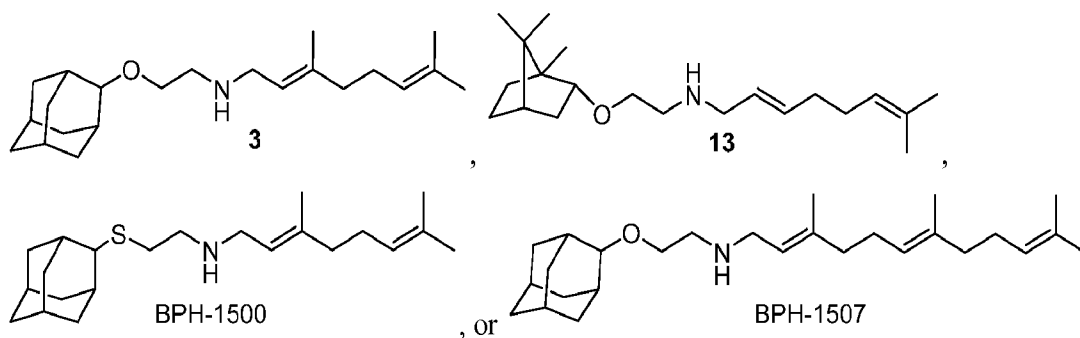
14. The compound of claim 1 wherein the compound is:



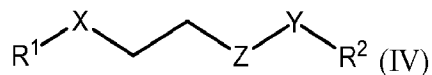


or a salt or solvate thereof.

15. The compound of claim 1 wherein the compound is:



16. A compound of Formula IV:



wherein

X is O, NH, S, S(=O), or S(=O)₂;

Y is O, NH, S, S(=O), or S(=O)₂, provided that one of X and Y is NH and that X and Y are not both NH;

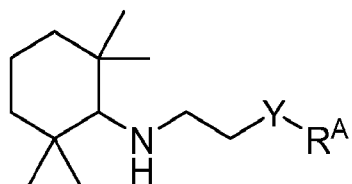
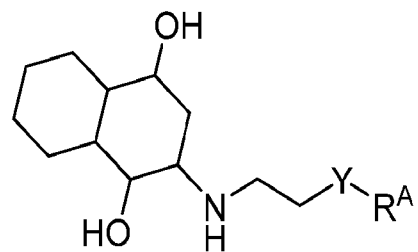
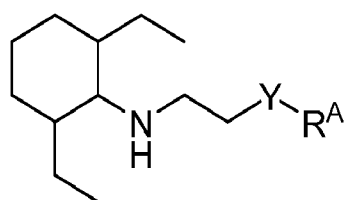
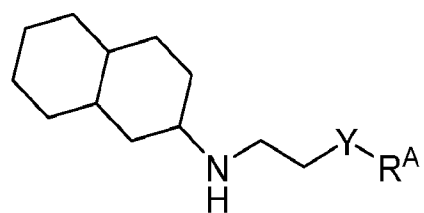
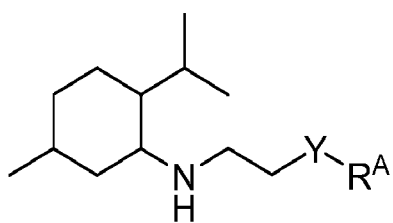
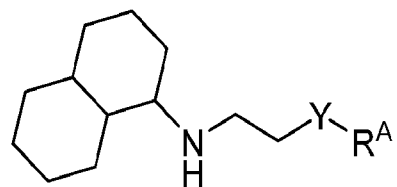
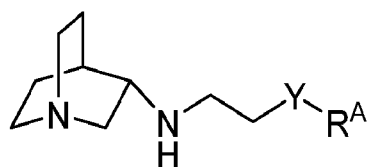
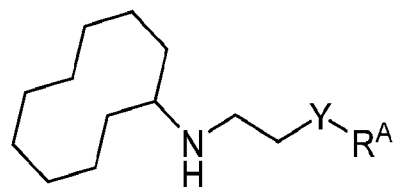
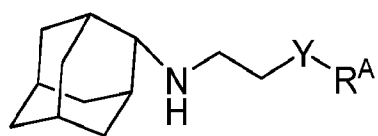
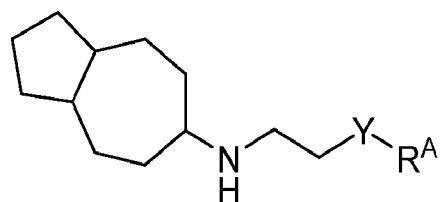
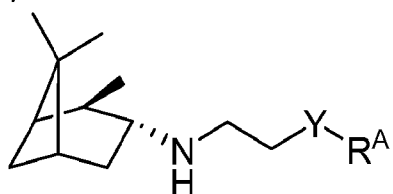
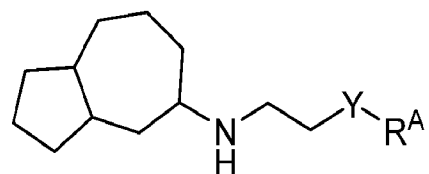
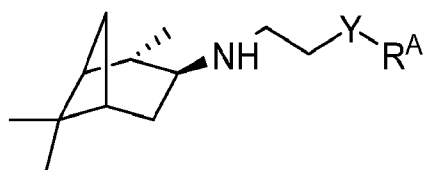
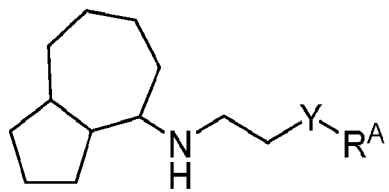
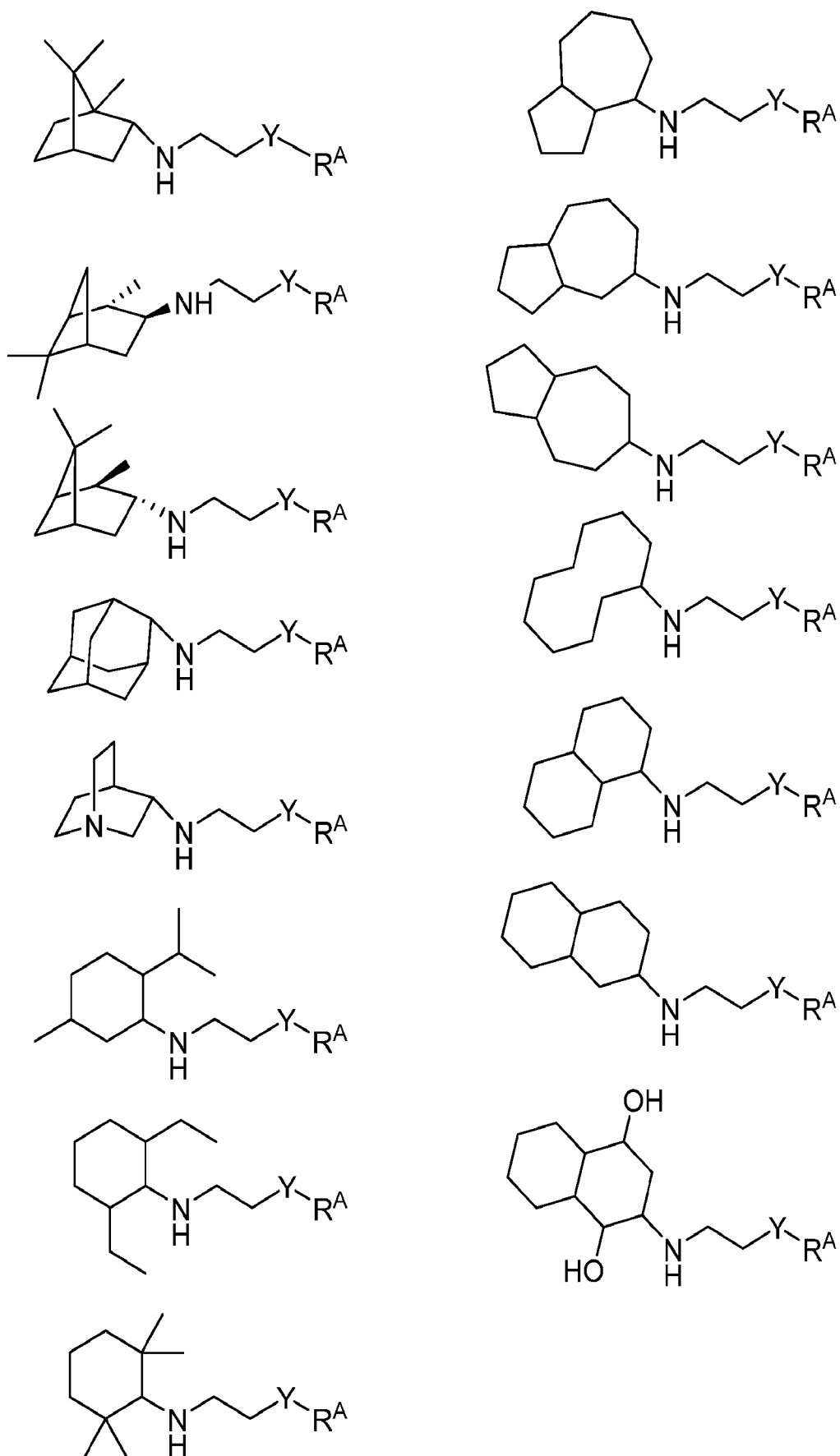
Z is a direct bond, -CH₂-, or -CH₂-CH₂-; and

R¹ and R² are each independently alkyl, alkenyl, alkoxyalkyl, cycloalkyl, oxygen-containing heterocycle, nitrogen-containing heterocycle, aryl, alkylaryl, heterocycle, heteroaryl, or alkylheteroaryl, wherein each can be optionally substituted with one or two additional R² groups;

or a salt or solvate thereof.

17. A pharmaceutical composition comprising a compound of any one of claims 1-16 in combination with a pharmaceutically acceptable diluent or carrier.
18. A method of treating or inhibiting a bacterial infection or parasitic infection in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of any one of claims 1-16, wherein the bacterial infection or parasitic infection is treated or inhibited.
19. A method of killing or inhibiting the growth of a bacterium or parasite comprising contacting the bacterial or parasite with an effective amount of a compound of any one of claims 1-16, wherein the bacterium or parasite is killed or its growth is inhibited.
20. A method of treating or inhibiting a *Mycobacterium tuberculosis* infection in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of any one of claims 1-16, wherein the *Mycobacterium tuberculosis* infection is treated or inhibited.
21. The use of a compound of any one of claims 1-16 for treating or inhibiting a bacterial infection or parasitic infection in a mammal.
22. The use according to claim 21 wherein the infection is a *Bacillus* infection, a *Candida* infection, an *Enterococcus* infection, an *Escherichia* infection, a *Helicobacter* infection, a *Listeria* infection, a *Mycobacterium* infection, a *Plasmodium* infection, a *Saccharomyces* infection, a *Staphylococcus* infection, or a *Streptococcus* infection.
23. The use according to claim 22 wherein the infection is a *Mycobacterium tuberculosis* infection.

Figure 1



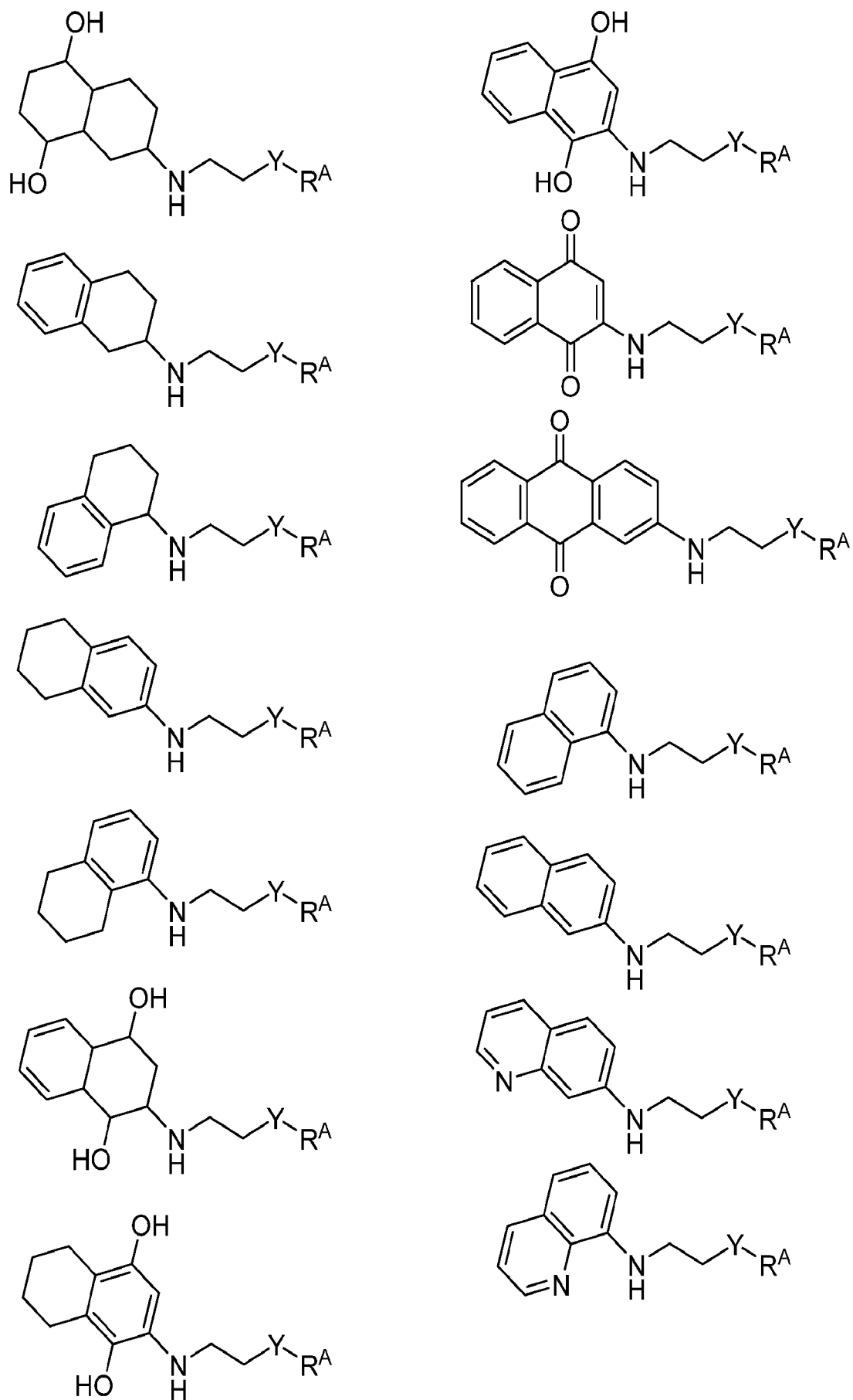
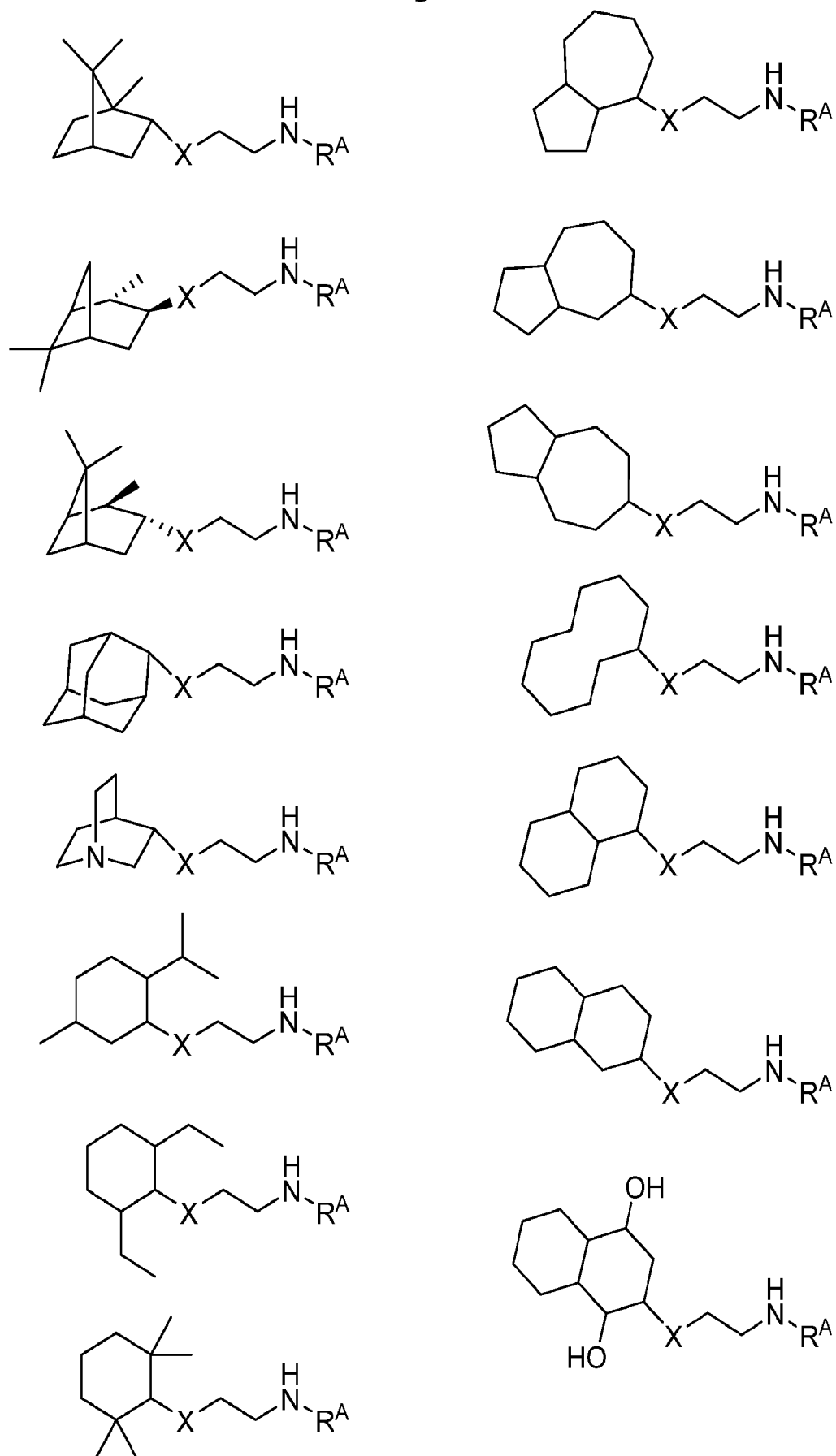
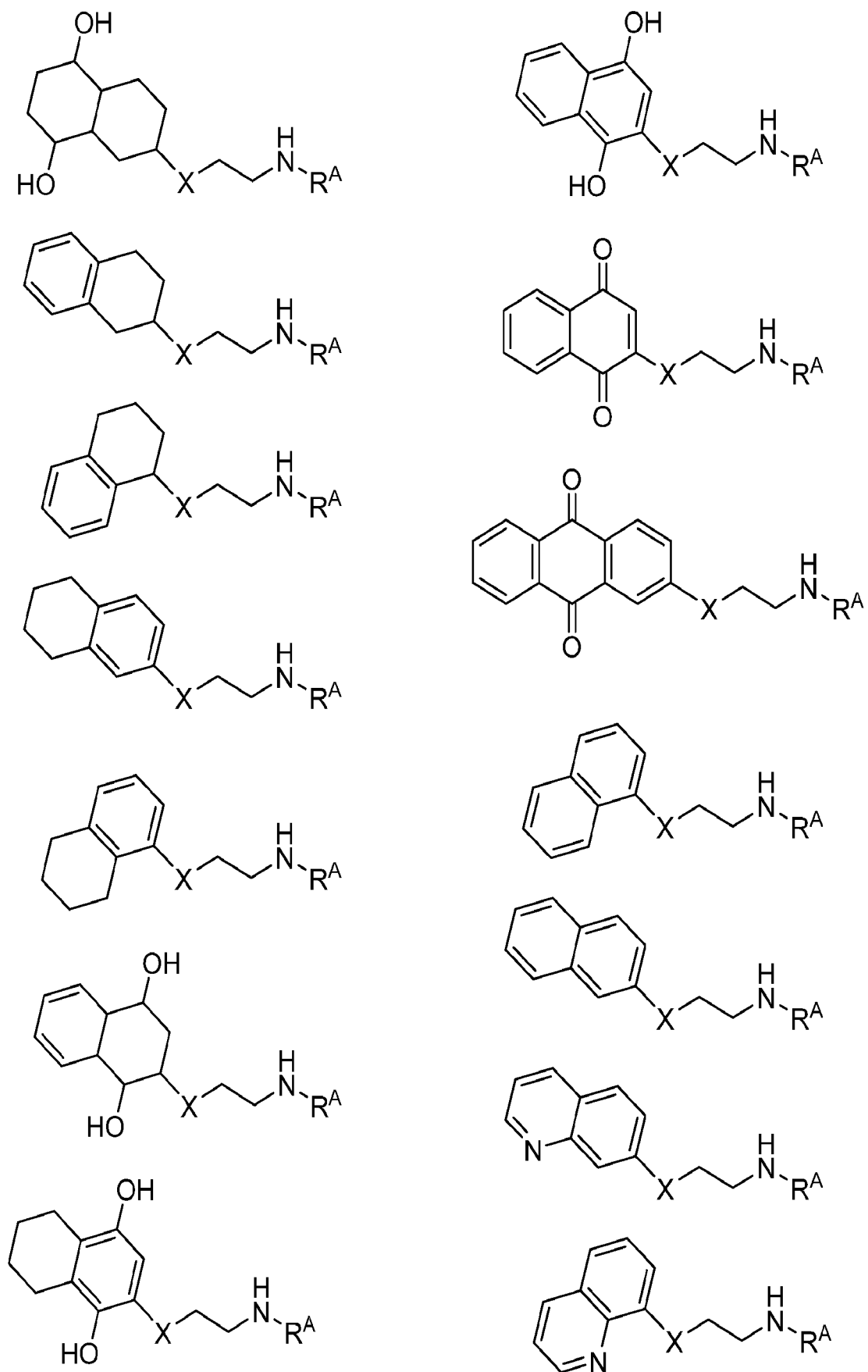
**Figure 1 (cont.)**

Figure 2



**Figure 2 (cont.)**