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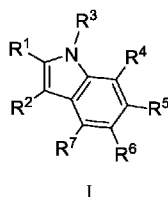
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(54) Title: THERAPEUTIC COMPOUNDS AND METHODS TO TREAT INFECTION



(57) Abstract: Disclosed herein are compounds of formula (I), or a salt thereof and compositions comprising compounds of formula I that exhibit antibacterial activities, when tested alone and/or in combination with a bacterial efflux pump inhibitor. Also disclosed are methods of treating or preventing a bacterial infection in an animal comprising administering to the animal a compound of formula I alone or in combination with the administration of a bacterial efflux pump inhibitor.



THERAPEUTIC COMPOUNDS AND METHODS TO TREAT INFECTION**PRIORITY OF INVENTION**

This application claims priority to United States Provisional Patent Application Number
5 62/586,003 filed November 14, 2017. The entire content of the application referenced above is
hereby incorporated by reference herein.

BACKGROUND OF THE INVENTION

The emergence of Multidrug Resistant (MDR) bacterial pathogens has increased
10 concerns as to the adequacy of current antimicrobials and pathogen treatment methods. The
lethality of pathogens, such as *Pseudomonas aeruginosa*, has often led to treatment methods
that are experimental or would otherwise normally be avoided in standard clinical practice.
The growing threat from MDR pathogens highlights a critical need for additional
antimicrobials. In this connection, there is a pressing need for new antibiotics that exhibit
15 novel mechanisms of action or circumvent conventional mechanisms of resistance.

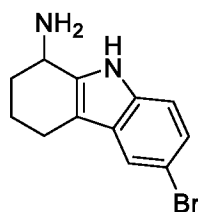
Bacteria have developed several different mechanisms to overcome the action of
antibiotics. These mechanisms of resistance can be specific such as for a molecule or a family of
antibiotics, or the mechanisms can be non-specific. Several mechanisms of resistance can exist
in a single bacterial strain, and those mechanisms may act independently, or they may act
20 synergistically to overcome the action of an antibiotic or a combination of antibiotics. Specific
mechanisms include, for example, degradation of the drug, inactivation of the drug by enzymatic
modification, and alteration of the drug target. Additional mechanisms of drug resistance
include mechanisms in which access of the antibiotic to the target is prevented or reduced by
decreasing the transport of the antibiotic into the cell or by increasing the efflux of the drug from
25 the cell to the outside medium. These mechanisms can lower the concentration of drug at the
target site and allow bacterial survival in the presence of one or more antibiotics that would
otherwise inhibit or kill the bacterial cells. Some bacteria utilize both mechanisms, combining
low permeability of the cell wall (including membranes) with an active efflux of antibiotics. It
has been shown that efflux of antibiotics can be mediated by more than one pump in a single
30 organism and that almost all antibiotics are subject to resistance by this mechanism. For
example, *Pseudomonas aeruginosa* expresses numerous efflux pumps including MexAB-OprM,
MexCD-OprJ, MexEF-OprN, and MexXY-OprA(OprM) which actively efflux various
antibacterial agents.

These multiple resistance mechanisms have become widespread and threaten the clinical
35 utility of antibacterial therapy. The increase in antibiotic resistant strains has been particularly

noted in major hospitals and care centers. The consequences of the increase in resistant strains include, for example higher morbidity and mortality, longer patient hospitalization, and an increase in treatment costs. Accordingly, there is a need for methods and combinations of agents for treating bacterial infections.

5 MreB is a well conserved and essential cytoskeleton-like protein, which represents a bacterial homolog of actin. Studies with various MreB homologs have established that this protein forms dynamic, actin-like helical filaments in an ATP- or GTP-dependent fashion. The filaments are localized within the bacterial cell on the inner surface of the cytoplasmic membrane. MreB protein provides a critical role in the maintenance of cell shape, polar protein
10 localization, and/or chromosome segregation. Because of its essential role in bacterial growth and function, MreB inhibitors represent a novel class of antibacterial agents.

The MreB homolog of *P. aeruginosa* is essential for cell viability as well as maintenance of rod-like cell morphology. CBR-4830 was identified as an effective MreB inhibitor in *P. aeruginosa* while screening libraries of compounds against a *P. aeruginosa* strains with
15 defective efflux transporters.



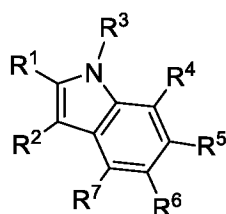
CBR-4830

CBR-4830 is a substrate for the MexAB-OprM efflux transporter present in wild-type *P. aeruginosa*, which limited its efficacy and clinical promise. Thus, there is an ongoing need for
20 antibacterial agents (e.g., MreB inhibitors). There is also a need for antibacterial agents (e.g., MreB inhibitors) that have improved properties such as improved formulation characteristics or lowered toxicity.

SUMMARY OF THE INVENTION

25 Compounds disclose herein exhibit antibacterial activities, when tested alone and/or in combination with a bacterial efflux pump inhibitor.

One embodiment provides a compound of formula I:



R^1 is (C₁-C₁₂)alkyl substituted with one or more (e.g., 1, 2, 3, 4, or 5) or NR^aR^b and wherein the (C₁-C₁₂)alkyl is optionally substituted with one or more (e.g., 1, 2, 3, 4, or 5) halo, hydroxyl, or phenyl wherein the phenyl is optionally substituted independently with one or more (e.g., 1, 2, 3, 4, or 5) halo, cyano, (C₁-C₃)alkyl, or (C₁-C₃)haloalkyl, and R^2 is hydrogen or (C₁-C₈)alkyl optionally substituted with one or more (e.g., 1, 2, 3, 4, or 5) halo, hydroxyl, oxo, or NR^aR^b, or R^1 and R^2 together with the atoms to which they are attached form a 5 or 7-membered carbocycle wherein the carbocycle is substituted with one or more (e.g., 1, 2, 3, 4, or 5) NR^aR^b and wherein the carbocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4, or 5) halo, hydroxyl, NR^aR^b, or (C₁-C₄)alkyl wherein the (C₁-C₄)alkyl is optionally substituted with one or more (e.g., 1, 2, 3, 4, or 5) NR^aR^b;

R^3 is hydrogen or (C₁-C₄)alkyl;

R^4 is hydrogen, halo, cyano, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, or phenyl wherein the phenyl is optionally substituted with one or more (e.g., 1, 2, 3, 4, or 5) halo, (C₁-C₆)haloalkyl, cyano, nitro or (C₁-C₆)haloalkoxy;

R^5 is hydrogen, halo, cyano, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, or phenyl wherein the phenyl is optionally substituted with one or more (e.g., 1, 2, 3, 4, or 5) halo, (C₁-C₆)haloalkyl, cyano, nitro or (C₁-C₆)haloalkoxy;

R^6 is hydrogen, halo, cyano, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, or phenyl wherein the phenyl is optionally substituted with one or more (e.g., 1, 2, 3, 4, or 5) halo, (C₁-C₆)haloalkyl, cyano, nitro or (C₁-C₆)haloalkoxy; and

R^7 is hydrogen, halo, cyano, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, or phenyl wherein the phenyl is optionally substituted with one or more (e.g., 1, 2, 3, 4, or 5) halo, (C₁-C₆)haloalkyl, cyano, nitro or (C₁-C₆)haloalkoxy;

each R^a is independently hydrogen or (C₁-C₆)alkyl wherein the (C₁-C₆)alkyl is optionally substituted with one or more (e.g., 1, 2, 3, 4, or 5) halo, hydroxyl, NR^cR^d, R^g, -C(=O)NR^{e1}R^{e2}, -OR^f, or -O(C₁-C₃)alkyl-R^f;

each R^b is independently hydrogen, or (C₁-C₆)alkyl wherein the (C₁-C₆)alkyl is optionally substituted with one or more (e.g., 1, 2, 3, 4, or 5) halo, hydroxyl, or NR^cR^d;

each R^c is independently hydrogen, (C₁-C₃)alkyl, -C(=O)R^h, phenyl, C₃-C₇carbocycle, or -(C₁-C₆)alkylphenyl wherein the phenyl, C₃-C₇carbocycle, or -(C₁-C₆)alkylphenyl is optionally substituted independently with one or more (e.g., 1, 2, 3, 4, or 5) halo, cyano, (C₁-C₆)alkyl, or (C₁-C₆)haloalkyl;

each R^d is independently hydrogen or (C₁-C₃)alkyl;

each R^{e1} is phenyl optionally substituted independently with one or more (e.g., 1, 2, 3, 4, or 5) halo, cyano, (C₁-C₆)alkyl, or (C₁-C₆)haloalkyl;

each R^{e2} is independently hydrogen or (C₁-C₃)alkyl;

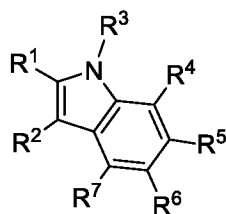
each R^f is phenyl optionally substituted independently with one or more (e.g., 1, 2, 3, 4, or 5) halo, cyano, (C₁-C₆)alkyl, or (C₁-C₆)haloalkyl;

each R^g is independently 5-6 membered heteroaryl, phenyl, or C₃-C₇carbocycle wherein
 5 the 5-6 membered heteroaryl, phenyl, or C₃-C₇carbocycle is optionally substituted independently with one or more (e.g., 1, 2, 3, 4, or 5) halo, cyano, (C₁-C₆)alkyl, or (C₁-C₆)haloalkyl; and

each R^h is independently 5-6 membered heteroaryl, phenyl, or C₃-C₇carbocycle wherein
 the 5-6 membered heteroaryl, phenyl, or C₃-C₇carbocycle is optionally substituted independently with one or more (e.g., 1, 2, 3, 4, or 5) halo, cyano, (C₁-C₆)alkyl, or (C₁-C₆)haloalkyl;

10 or a salt thereof.

One embodiment provides a compound of formula I:



R¹ is (C₁-C₂₀)alkyl substituted with one or more or NR^aR^b and wherein the (C₁-C₂₀)alkyl
 15 is optionally substituted with one or more halo or hydroxyl and R² is hydrogen or (C₁-C₈)alkyl optionally substituted with one or more halo, hydroxyl, oxo, or NR^aR^b, or R¹ and R² together with the atoms to which they are attached form a 5 or 7-membered carbocycle wherein the carbocycle is substituted with one or more or NR^aR^b and wherein the carbocycle is optionally substituted with one or more halo, hydroxyl, NR^aR^b, or (C₁-C₄)alkyl wherein the (C₁-C₄)alkyl is
 20 optionally substituted with one or more NR^aR^b;

R³ is hydrogen or (C₁-C₄)alkyl;

R⁴ is hydrogen, halo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, or phenyl wherein the phenyl is optionally substituted with one or more halo, (C₁-C₆)haloalkyl, nitro or (C₁-C₆)haloalkoxy;

25 R⁵ is hydrogen, halo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, or phenyl wherein the phenyl is optionally substituted with one or more halo, (C₁-C₆)haloalkyl, nitro or (C₁-C₆)haloalkoxy;

R⁶ is hydrogen, halo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, or phenyl wherein the phenyl is optionally substituted with one or more halo, (C₁-C₆)haloalkyl, nitro or (C₁-C₆)haloalkoxy; and
 30

R⁷ is hydrogen, halo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, or phenyl wherein the phenyl is optionally substituted with one or more halo, (C₁-C₆)haloalkyl, nitro or (C₁-C₆)haloalkoxy;

5 each R^a is independently hydrogen or (C₁-C₆)alkyl wherein the (C₁-C₆)alkyl is optionally substituted with one or more halo, hydroxyl, or NR^cR^d;

each R^b is independently hydrogen, (C₁-C₆)alkyl wherein the (C₁-C₆)alkyl is optionally substituted with one or more halo, hydroxyl, or NR^cR^d;

each R^c is independently hydrogen or (C₁-C₃)alkyl; and

each R^d is independently hydrogen or (C₁-C₃)alkyl;

10 or a salt thereof.

One embodiment provides a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof as described herein and a pharmaceutically acceptable excipient.

15 One embodiment provides a compound of formula I or a pharmaceutically acceptable salt thereof as described herein for use in medical therapy.

One embodiment provides a compound of formula I or a pharmaceutically acceptable salt thereof as described herein for the prophylactic or therapeutic treatment of a bacterial infection in an animal (e.g., a mammal such as a human).

20 One embodiment provides a compound of formula I or a pharmaceutically acceptable salt thereof as described herein for the preparation of a medicament for treating a bacterial infection in an animal (e.g., a mammal such as a human).

One embodiment provides a method of treating or preventing a bacterial infection in an animal (e.g., a mammal such as a human) comprising administering to the animal a compound of formula I or a pharmaceutically acceptable salt thereof as described herein.

25 One embodiment provides a method of treating or preventing a bacterial infection in an animal (e.g., a mammal such as a human) comprising administering to the animal a bacterial efflux pump inhibitor and a compound of formula I or a pharmaceutically acceptable salt thereof as described herein.

30 One embodiment provides a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof as described herein, a bacterial efflux pump inhibitor, and a pharmaceutically acceptable vehicle.

One embodiment provides a compound of formula I or a pharmaceutically acceptable salt thereof as described herein, combined with a bacterial efflux pump inhibitor, for use in medical therapy.

One embodiment provides a compound of formula I or a pharmaceutically acceptable salt thereof as described herein, combined with a bacterial efflux pump inhibitor, for the prophylactic or therapeutic treatment of a bacterial infection in an animal (e.g., a mammal such as a human).

5 One embodiment provides the use of a compound of formula I or a pharmaceutically acceptable salt thereof as described herein, combined with a bacterial efflux pump inhibitor, for the preparation of a medicament for treating a bacterial infection in an animal (e.g., a mammal such as a human).

10 One embodiment provides processes and intermediates disclosed herein that are useful for preparing compounds of formula I or salts thereof.

DETAILED DESCRIPTION

The following definitions are used, unless otherwise described: halo or halogen is fluoro, chloro, bromo, or iodo. Alkyl and alkoxy, etc. denote both straight and branched groups but
15 reference to an individual radical such as propyl embraces only the straight chain radical (a branched chain isomer such as isopropyl being specifically referred to).

As used herein, the term "(C_a-C_b)alkyl" wherein a and b are integers refers to a straight or branched chain alkyl radical having from a to b carbon atoms. Thus, when a is 1 and b is 6, for example, the term includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-
20 butyl, n-pentyl and n-hexyl.

The term "aryl" as used herein refers to a single aromatic ring or a multiple condensed ring system wherein the ring atoms are carbon. For example, an aryl group can have 6 to 10 carbon atoms, or 6 to 12 carbon atoms. Aryl includes a phenyl radical. Aryl also includes multiple condensed ring systems (e.g., ring systems comprising 2 rings) having about 9 to 12
25 carbon atoms or 9 to 10 carbon atoms in which at least one ring is aromatic. Such multiple condensed ring systems may be optionally substituted with one or more (e.g., 1 or 2) oxo groups on any cycloalkyl portion of the multiple condensed ring system. It is to be understood that the point of attachment of a multiple condensed ring system, as defined above, can be at any position of the ring system including an aryl or a cycloalkyl portion of the ring. Typical aryl groups
30 include, but are not limited to, phenyl, indenyl, naphthyl, 1, 2, 3, 4-tetrahydronaphthyl, anthracenyl, and the like.

The term "heteroaryl" as used herein refers to a single aromatic ring or a multiple condensed ring system. The term includes single aromatic rings of from about 1 to 6 carbon atoms and about 1-4 heteroatoms selected from the group consisting of oxygen, nitrogen and
35 sulfur in the rings. The sulfur and nitrogen atoms may also be present in an oxidized form

provided the ring is aromatic. Such rings include but are not limited to pyridyl, pyrimidinyl, oxazolyl or furyl. The term also includes multiple condensed ring systems (e.g. ring systems comprising 2 rings) wherein a heteroaryl group, as defined above, can be condensed with one or more heteroaryls (e.g., naphthyridinyl), heterocycles, (e.g., 1, 2, 3, 4-tetrahydronaphthyridinyl), cycloalkyls (e.g., 5,6,7,8-tetrahydroquinolyl) or aryls (e.g. indazolyl) to form a multiple condensed ring system. Such multiple condensed ring systems may be optionally substituted with one or more (e.g., 1 or 2) oxo groups on the cycloalkyl or heterocycle portions of the condensed ring. In one embodiment a monocyclic or bicyclic heteroaryl has 5 to 10 ring atoms comprising 1 to 9 carbon atoms and 1 to 4 heteroatoms. It is to be understood that the point of attachment of a multiple condensed ring system (as defined above for a heteroaryl) can be at any position of the multiple condensed ring system including a heteroaryl, heterocycle, aryl or cycloalkyl portion of the multiple condensed ring system and at any suitable atom of the multiple condensed ring system including a carbon atom and heteroatom (e.g., a nitrogen). Exemplary heteroaryls include but are not limited to pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, thienyl, indolyl, imidazolyl, oxazolyl, thiazolyl, furyl, oxadiazolyl, thiadiazolyl, quinolyl, isoquinolyl, benzothiazolyl, benzoxazolyl, indazolyl, quinoxalyl, quinazolyl, 5,6,7,8-tetrahydroisoquinolyl, benzofuranyl, benzimidazolyl and thianaphthenyl.

The term cycloalkyl, carbocycle, or carbocyclyl includes saturated and partially unsaturated carbocyclic ring systems. In one embodiment the cycloalkyl is a monocyclic carbocyclic ring. Such cycloalkyls include “(C₃-C₇)carbocyclyl” and “(C₃-C₈)cycloalkyl”.

The term “heterocyclyl” or “heterocycle” as used herein refers to a single saturated or partially unsaturated ring or a multiple condensed ring system. The term includes single saturated or partially unsaturated rings (e.g., 3, 4, 5, 6 or 7-membered rings) from about 1 to 6 carbon atoms and from about 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur in the ring. The ring may be substituted with one or more (e.g., 1, 2 or 3) oxo groups and the sulfur and nitrogen atoms may also be present in their oxidized forms. Such rings include but are not limited to azetidiny, tetrahydrofuranyl or piperidinyl. It is to be understood that the point of attachment for a heterocycle can be at any suitable atom of the heterocycle Exemplary heterocycles include, but are not limited to aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, homopiperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydrofuranyl, dihydrooxazolyl, tetrahydropyranyl and tetrahydrothiopyranyl.

The term “haloalkyl” includes an alkyl group as defined herein that is substituted with one or more (e.g., 1, 2, 3, 4, or 5) halo groups (e.g., trifluoromethyl, difluoromethyl etc.). One specific halo alkyl is a “(C₁-C₆)haloalkyl”.

The term “alkoxy” refers to -O(alkyl) and the term “haloalkoxy” refers to an alkoxy that

is substituted with one or more (e.g., 1, 2, 3, 4, or 5) halo (e.g., trifluoromethoxy or pentafluoroethoxy).

Specific values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

Specifically, (C₁-C₆)alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, 3-pentyl, or hexyl; (C₁-C₆)alkoxy can be methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec-butoxy, pentoxy, 3-pentoxy, or hexyloxy.

It is understood that the embodiments provided below are for compounds of formula I and all sub-formulas thereof (e.g., formulas Ia). It is to be understood the two or more embodiments may be combined.

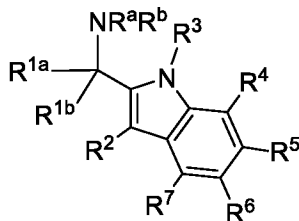
In one embodiment R¹ is (C₁-C₂₀)alkyl substituted with one or more or NR^aR^b and wherein the (C₁-C₂₀)alkyl is optionally substituted with one or more halo or hydroxyl and R² is hydrogen or (C₁-C₈)alkyl optionally substituted with one or more halo, hydroxyl, oxo, or NR^aR^b, or R¹ and R² together with the atoms to which they are attached form a 5 or 7-membered carbocycle wherein the carbocycle is substituted with one or more or NR^aR^b and wherein the carbocycle is optionally substituted with one or more halo, hydroxyl, NR^aR^b, or (C₁-C₄)alkyl wherein the (C₁-C₄)alkyl is optionally substituted with one or more NR^aR^b;

In one embodiment R¹ is (C₁-C₈)alkyl substituted with one NR^aR^b and wherein the (C₁-C₂₀)alkyl is optionally substituted with one or more halo or hydroxyl, and R² is hydrogen or (C₁-C₈)alkyl, or R¹ and R² together with the atoms to which they are attached form a 5 or 7-membered carbocycle wherein the carbocycle is substituted with one NR^aR^b and wherein the carbocycle is optionally substituted with one or more halo, hydroxyl, or (C₁-C₄)alkyl.

In one embodiment R¹ is (C₁-C₈)alkyl substituted with one NR^aR^b and R² is hydrogen, or R¹ and R² together with the atoms to which they are attached form a 5 or 7-membered carbocycle wherein the carbocycle is substituted with one NR^aR^b.

In one embodiment R¹ is (C₁-C₈)alkyl substituted with one NR^aR^b and R² is hydrogen.

In one embodiment the compound of formula I is a compound of formula Ia or a salt thereof:



Ia

R^{1a} is hydrogen or (C₁-C₈)alkyl optionally substituted with one or more halo, hydroxyl, or NR^aR^b and R^2 is hydrogen or (C₁-C₈)alkyl optionally substituted with one or more halo, hydroxyl, oxo, or NR^aR^b , or R^{1a} and R^2 together with the atoms to which they are attached form a 5 or 7-membered carbocycle wherein the carbocycle is optionally substituted with one or more halo, hydroxyl, NR^aR^b , or (C₁-C₄)alkyl wherein the (C₁-C₄)alkyl is optionally substituted with one or more NR^aR^b ; and

R^{1b} is hydrogen or (C₁-C₈)alkyl optionally substituted with one or more halo, hydroxyl, or NR^aR^b .

In one embodiment R^{1a} is hydrogen or (C₁-C₈)alkyl optionally substituted with one or more halo, hydroxyl, or NR^aR^b and R^2 is hydrogen or (C₁-C₈)alkyl optionally substituted with one or more halo, hydroxyl, oxo, or NR^aR^b .

In one embodiment R^{1a} is hydrogen or (C₁-C₈)alkyl optionally substituted with one or more halo, hydroxyl, or NR^aR^b and R^2 is hydrogen or (C₁-C₈)alkyl.

In one embodiment R^{1a} is hydrogen or (C₁-C₈)alkyl optionally substituted with one or more NR^aR^b and R^2 is hydrogen.

In one embodiment R^{1a} is hydrogen, methyl, butyl, or ethylamine.

In one embodiment R^{1a} and R^2 together with the atoms to which they are attached form a 5 or 7-membered carbocycle wherein the carbocycle is optionally substituted with one or more halo, hydroxyl, NR^aR^b , or (C₁-C₄)alkyl wherein the (C₁-C₄)alkyl is optionally substituted with one or more NR^aR^b .

In one embodiment R^{1a} and R^2 together with the atoms to which they are attached form a 5 or 7-membered carbocycle wherein the carbocycle is optionally substituted with one or more NR^aR^b or (C₁-C₄)alkyl wherein the (C₁-C₄)alkyl is optionally substituted with one or more NR^aR^b .

In one embodiment R^{1b} is hydrogen.

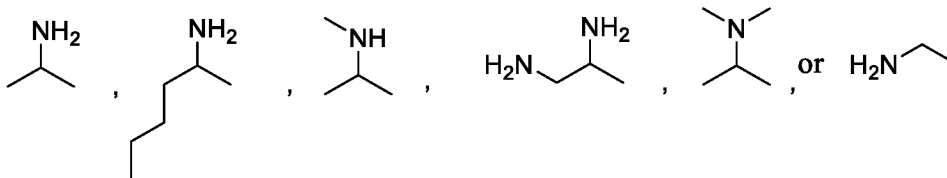
In one embodiment each R^a is independently hydrogen or (C₁-C₆)alkyl.

In one embodiment each R^a is independently hydrogen or methyl.

In one embodiment each R^b is independently hydrogen or (C₁-C₆)alkyl.

In one embodiment each R^b is independently hydrogen or methyl.

In one embodiment R^1 or the moiety $-\text{CH}(\text{NR}^a\text{R}^b)\text{R}^{1a}\text{R}^{1b}$ of formula Ia is:



In one embodiment R^3 is hydrogen or methyl.

In one embodiment R^4 is hydrogen.

In one embodiment R^4 is hydrogen or halo.

In one embodiment R^5 is hydrogen or halo.

In one embodiment R^5 is hydrogen, fluoro, chloro, or bromo.

In one embodiment R^6 is hydrogen, halo, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, or (C₁-C₆)haloalkoxy.

In one embodiment R^6 is hydrogen, fluoro, bromo, trifluoromethyl, methoxy, or trifluoromethoxy.

In one embodiment R^7 is hydrogen or halo.

In one embodiment R^7 is hydrogen or chloro.

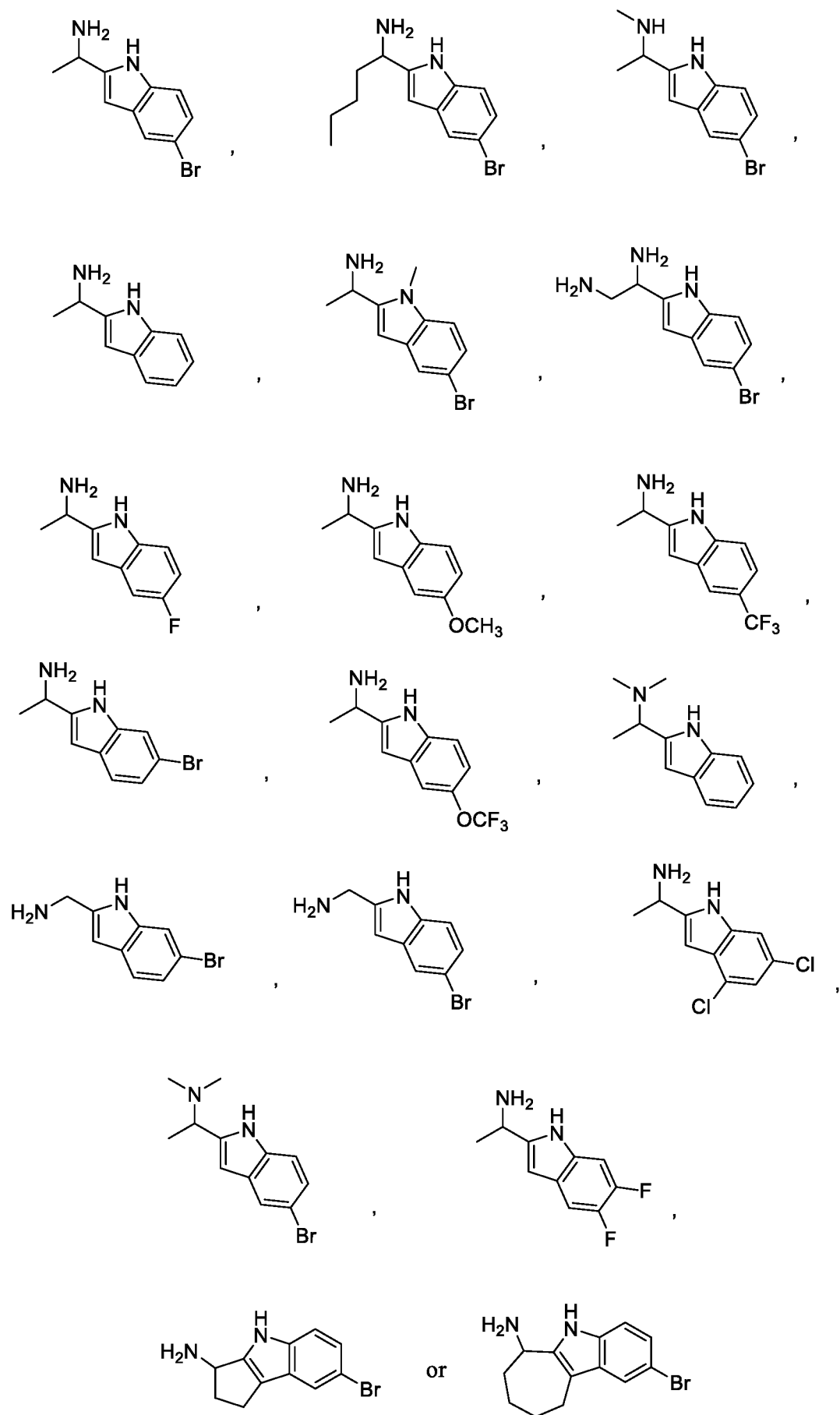
In one embodiment at least one of R^4 , R^5 , R^6 , or R^7 is not hydrogen.

In one embodiment at least two of R^4 , R^5 , R^6 , or R^7 are not hydrogen.

In one embodiment at least one of R^4 , R^5 , R^6 , or R^7 is halo, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, or (C₁-C₆)haloalkoxy.

In one embodiment at least two of R^4 , R^5 , R^6 , or R^7 are halo, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, or (C₁-C₆)haloalkoxy.

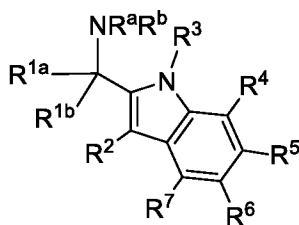
One embodiment provides the compound:



or a salt thereof.

In one embodiment R^1 is (C₁-C₈)alkyl substituted with one NR^aR^b and wherein the (C₁-C₈)alkyl is optionally substituted with one or more halo, hydroxyl or phenyl wherein the phenyl is optionally substituted independently with one or more halo, cyano, (C₁-C₃)alkyl, or (C₁-C₃)haloalkyl, and R^2 is hydrogen or (C₁-C₈)alkyl, or R^1 and R^2 together with the atoms to which they are attached form a 5 or 7-membered carbocycle wherein the carbocycle is substituted with one NR^aR^b and wherein the carbocycle is optionally substituted with one or more halo, hydroxyl, or (C₁-C₄)alkyl.

One embodiment provides a compound of formula Ia:



Ia

wherein: R^{1a} is hydrogen or (C₁-C₈)alkyl optionally substituted with one or more halo, hydroxyl, NR^aR^b , or phenyl wherein the phenyl is optionally substituted independently with one or more halo, cyano, (C₁-C₃)alkyl, or (C₁-C₃)haloalkyl and R^2 is hydrogen or (C₁-C₈)alkyl optionally substituted with one or more halo, hydroxyl, oxo, or NR^aR^b , or R^{1a} and R^2 together with the atoms to which they are attached form a 5 or 7-membered carbocycle wherein the carbocycle is optionally substituted with one or more halo, hydroxyl, NR^aR^b , or (C₁-C₄)alkyl wherein the (C₁-C₄)alkyl is optionally substituted with one or more NR^aR^b ; and

R^{1b} is hydrogen or (C₁-C₈)alkyl optionally substituted with one or more halo, hydroxyl, or NR^aR^b .

In one embodiment R^{1a} is hydrogen or (C₁-C₈)alkyl optionally substituted with one or more halo, hydroxyl, NR^aR^b or phenyl wherein the phenyl is optionally substituted independently with one or more halo, cyano, (C₁-C₃)alkyl, or (C₁-C₃)haloalkyl and R^2 is hydrogen or (C₁-C₈)alkyl optionally substituted with one or more halo, hydroxyl, oxo, or NR^aR^b .

In one embodiment R^{1a} is hydrogen or (C₁-C₈)alkyl optionally substituted with one or more halo, hydroxyl, NR^aR^b or phenyl wherein the phenyl is optionally substituted independently with one or more halo, cyano, (C₁-C₃)alkyl, or (C₁-C₃)haloalkyl and R^2 is hydrogen or (C₁-C₈)alkyl.

In one embodiment R^{1a} is hydrogen or (C₁-C₈)alkyl optionally substituted with one or more NR^aR^b or phenyl wherein the phenyl is optionally substituted independently with one or more halo, cyano, (C₁-C₃)alkyl, or (C₁-C₃)haloalkyl and R^2 is hydrogen.

In one embodiment R^{1a} is hydrogen, methyl, propyl, ethylamine, or phenethyl.

In one embodiment R^{1a} is hydrogen, methyl, butyl, ethylamine, or phenethyl.

In one embodiment R^{1a} and R^2 together with the atoms to which they are attached form a 5 or 7-membered carbocycle.

5 In one embodiment each R^a is independently hydrogen or (C_1-C_6) alkyl wherein the (C_1-C_6) alkyl is optionally substituted with one or more NR^cR^d , R^g , $-C(=O)NR^{e1}R^{e2}$, or $-OR^f$.

In one embodiment each R^c is independently (C_1-C_3) alkyl, or $-C(=O)R^h$.

In one embodiment each R^d is hydrogen.

In one embodiment each R^{e1} is phenyl optionally substituted with one or more halo.

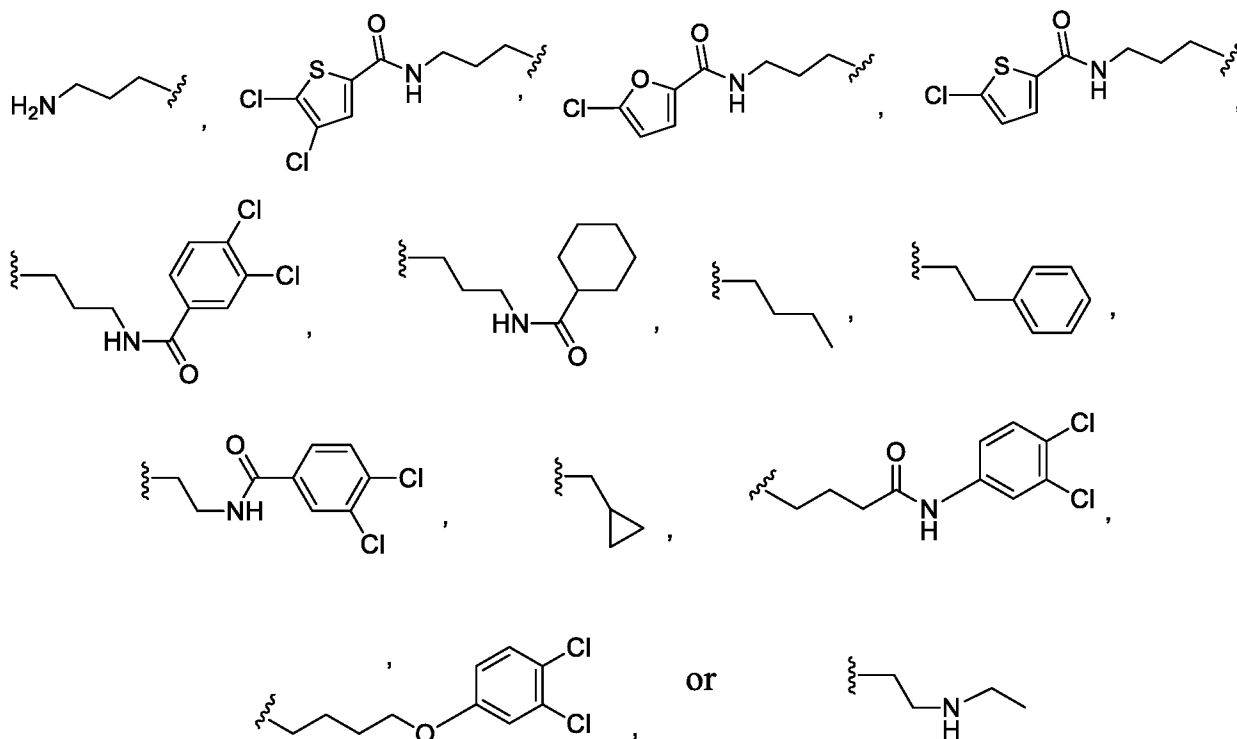
10 In one embodiment each R^{e2} is hydrogen.

In one embodiment each R^f is phenyl optionally substituted with one or more halo.

In one embodiment each R^g is independently phenyl, or C_3-C_7 carbocycle wherein the phenyl or C_3-C_7 carbocycle is independently substituted with one or more halo, cyano, (C_1-C_6) alkyl, or (C_1-C_6) haloalkyl.

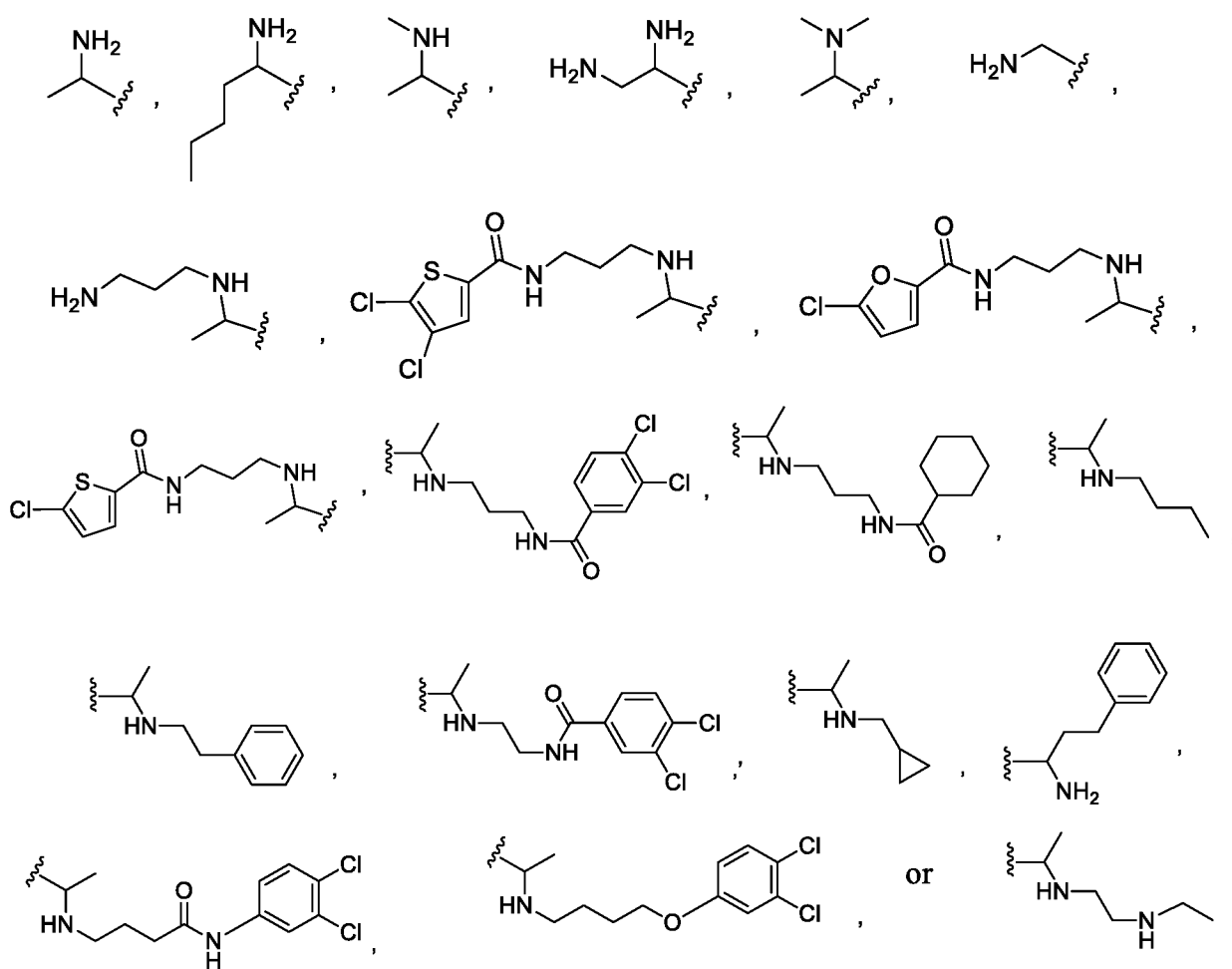
15 In one embodiment each R^h is independently 5-6 membered heteroaryl, phenyl, or C_3-C_7 carbocycle wherein the 5-6 membered heteroaryl, phenyl, or C_3-C_7 carbocycle is independently substituted halo.

In one embodiment each R^a is independently hydrogen, methyl,



20

In one embodiment R^1 , or the moiety $-CH(NR^aR^b)R^{1a}R^{1b}$ of a compound of formula Ia is:



In one embodiment R^4 is hydrogen, halo, (C_1-C_6) haloalkyl, (C_1-C_6) alkoxy, or (C_1-C_6) haloalkoxy.

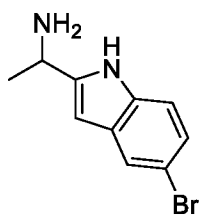
In one embodiment R^4 is hydrogen.

In one embodiment R^5 is hydrogen, halo, (C_1-C_6) haloalkyl, (C_1-C_6) alkoxy, or (C_1-C_6) haloalkoxy.

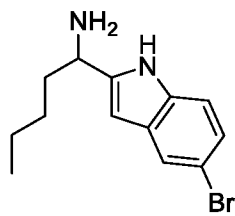
In one embodiment R^6 is hydrogen, fluoro, chloro, bromo, trifluoromethyl, methoxy, or trifluoromethoxy.

In one embodiment R^7 is hydrogen, halo, (C_1-C_6) haloalkyl, (C_1-C_6) alkoxy, or (C_1-C_6) haloalkoxy.

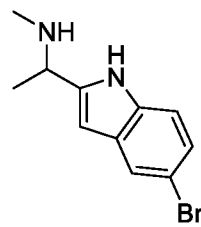
One embodiment provides a compound that is:



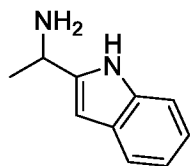
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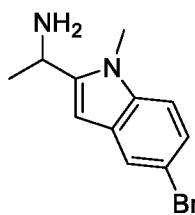
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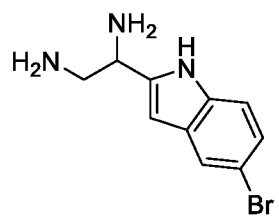
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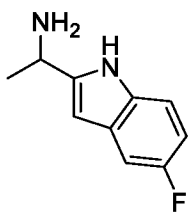
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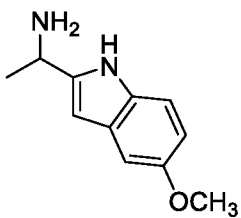
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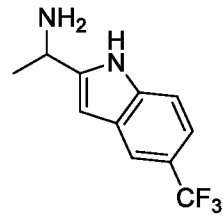
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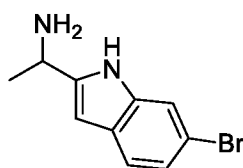
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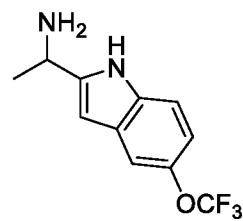
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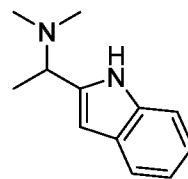
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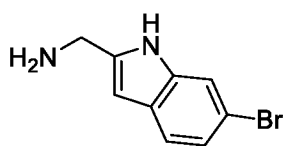
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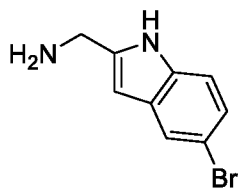
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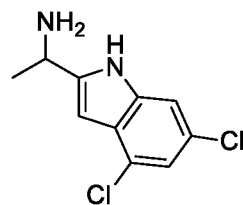
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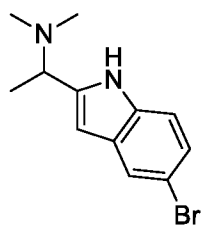
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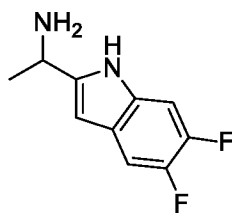
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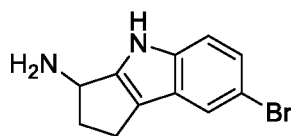
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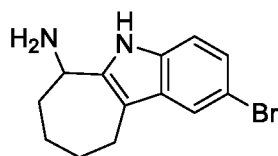
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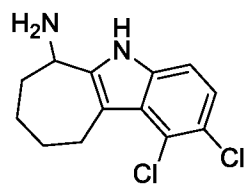
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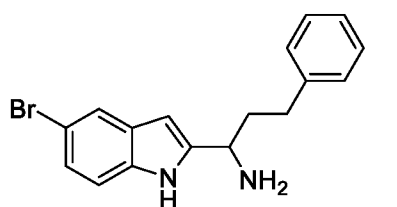
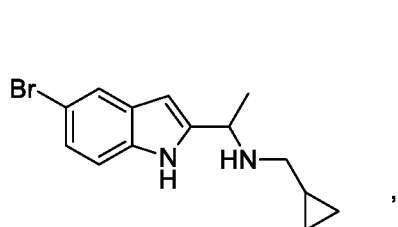
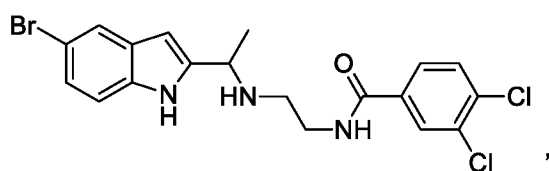
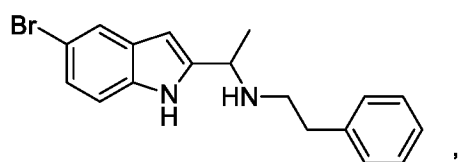
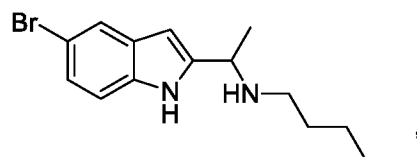
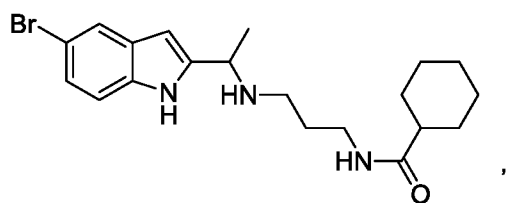
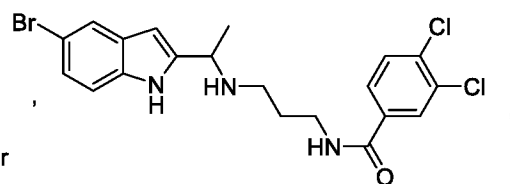
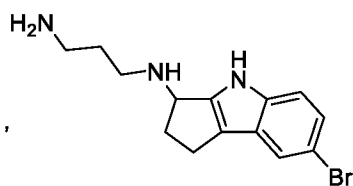
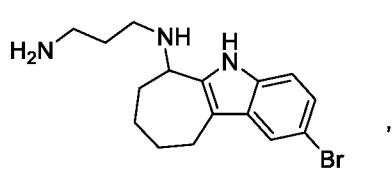
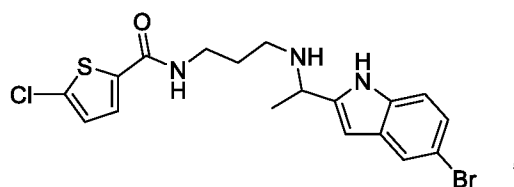
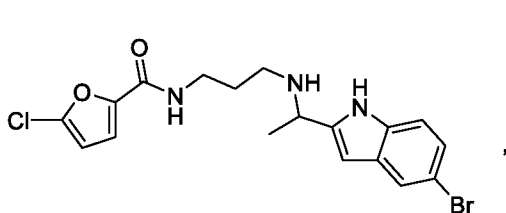
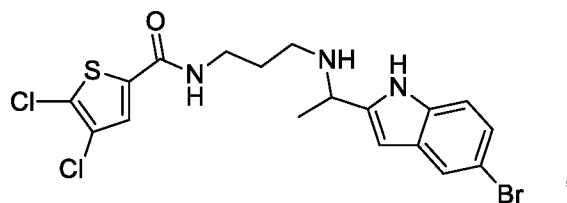
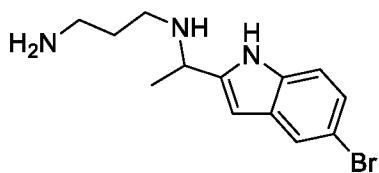
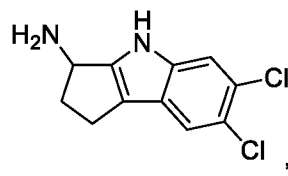
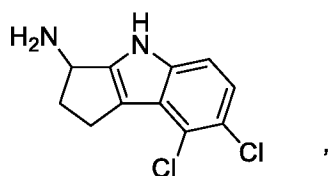
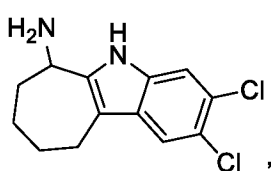
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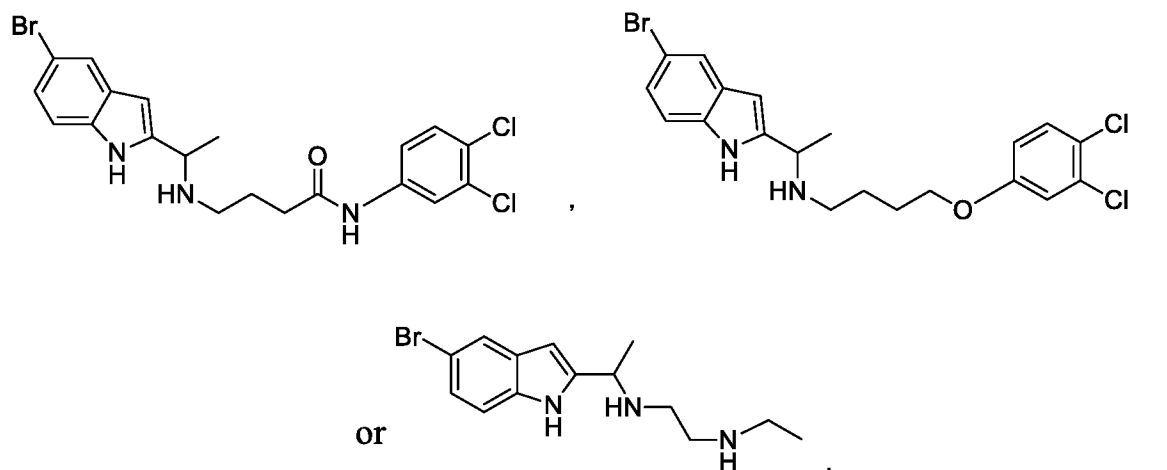


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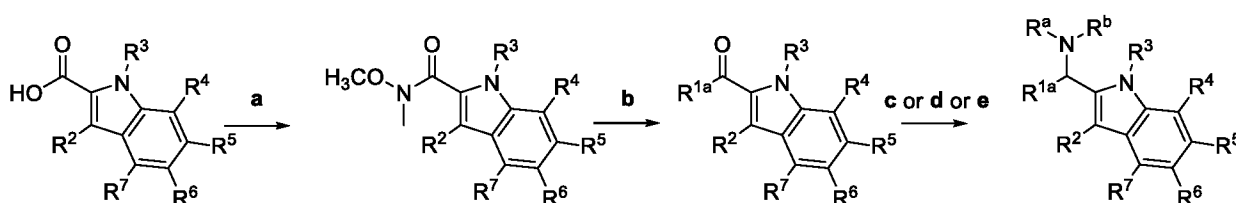


or a salt thereof.

5 Generally, compounds of formula I as well as synthetic intermediates that can be used for preparing compounds of formula I can be prepared as illustrated in the following General Methods and Schemes. It is understood that variable groups shown below (e.g., R) can represent the final corresponding groups present in a compound of formula I or that these groups can represent groups that can be converted to the final corresponding groups present in a compound of formula I at a convenient point in a synthetic sequence. For example, the variable groups can contain one or more protecting groups that can be removed at a convenient point in a synthetic sequence to provide the final corresponding groups in the compound of formula I. The reagents and conditions shown are exemplary and non-limiting. Other reagents and conditions can be used in the general synthetic schemes.

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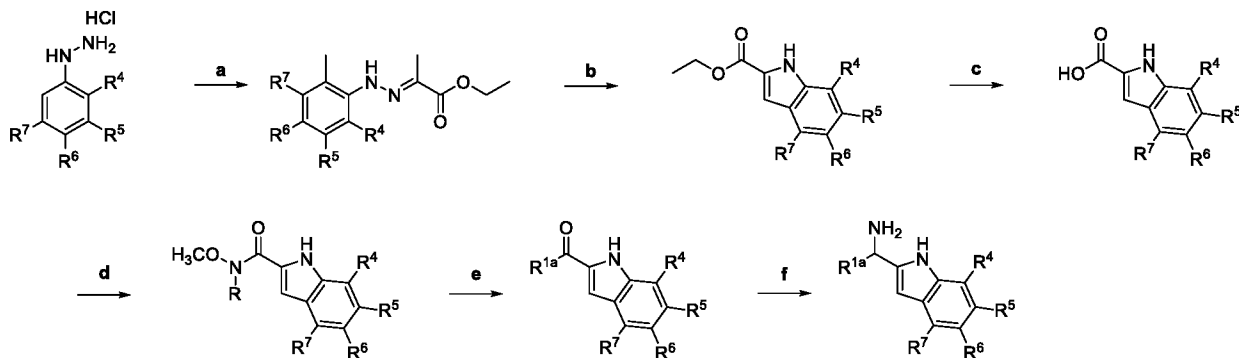
Scheme 1



Reagent and conditions: (a) $\text{CH}_3\text{ONHCH}_3\text{HCl}$, EDC HCl, HOBT, NEt_3 , DMF; (b) R^{1a}Li or R^{1a}MgX , THF, -78°C ; (c) NH_4OAc , NaBH_3CN , EtOH, 60°C (for $\text{R}^a, \text{R}^b = \text{H}$); (d) 2.0 M methylamine in THF, NaBH_3CN , cat. AcOH, EtOH, 60°C (for $\text{R}^a = \text{CH}_3, \text{R}^b = \text{H}$); (e) 2.0 M N,N-dimethylamine in THF, NaBH_3CN , cat. AcOH, EtOH, 60°C (for $\text{R}^a, \text{R}^b = \text{CH}_3$).

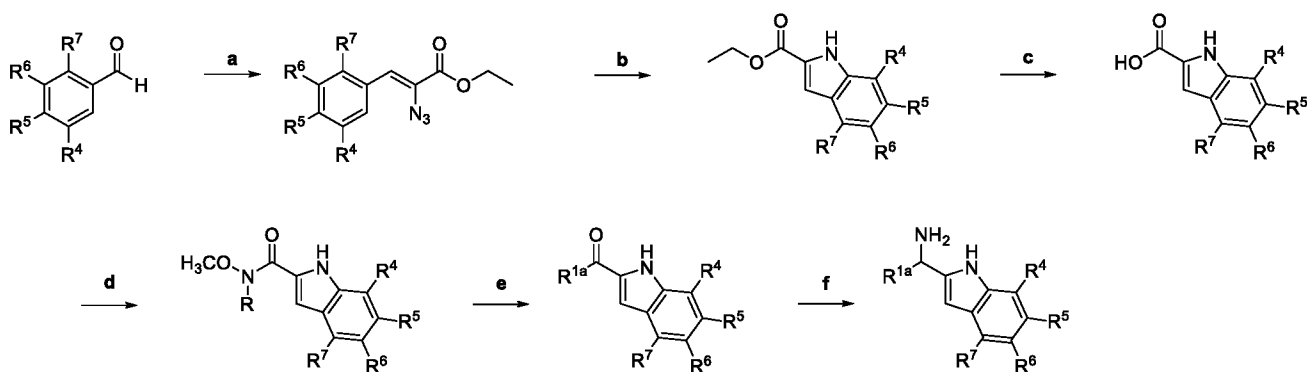
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Scheme 2



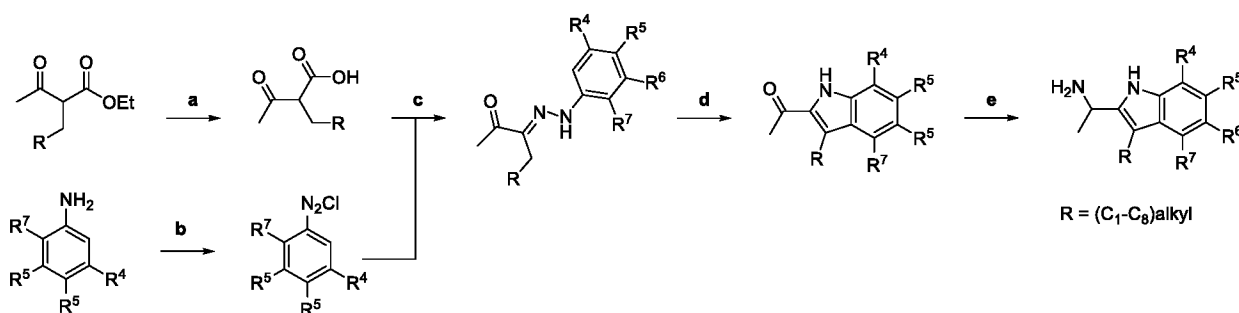
Reagent and conditions: (a) ethyl pyruvate, cat. AcOH, EtOH, reflux; (b) TFA or PPA or *p*-toluenesulfonic acid, toluene, reflux; (c) LiOH, EtOH, reflux; (d) CH₃ONHCH₃ HCl, EDC HCl, HOBt, NEt₃, DMF; (e) R^{1a}Li or R^{1a}MgX, THF, -78 °C; (f) NH₄OAc, NaBH₃CN, EtOH, 60 °C.

Scheme 3



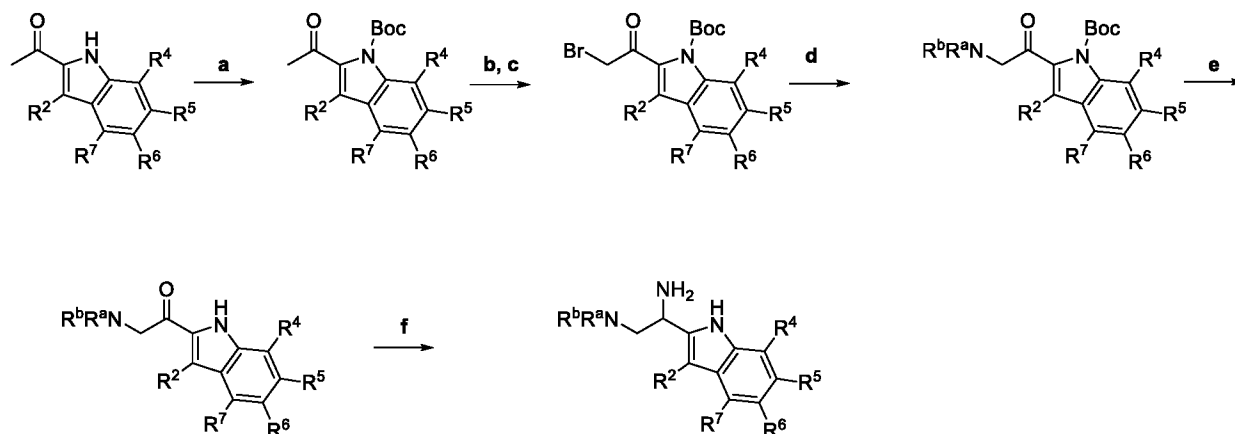
Reagent and conditions: (a) ethyl azidoacetate, NaOEt, EtOH, 0 °C; (b) xylene, reflux; (c) LiOH, EtOH, reflux; (d) CH₃ONHCH₃ HCl, EDC HCl, HOBt, NEt₃, DMF; (e) RLi or RMgX, THF, -78 °C; (f) NH₄OAc, NaBH₃CN, EtOH, 60 °C.

Scheme 4



Reagent and conditions: (a) NaOH, water; (b) NaNO₂, conc. HCl, water, 0 °C; (c) NaOAc, methanol, water, 0 °C; (d) conc. HCl, AcOH, 130 °C; (e) NH₄OAc, NaBH₃CN, EtOH, 60 °C.

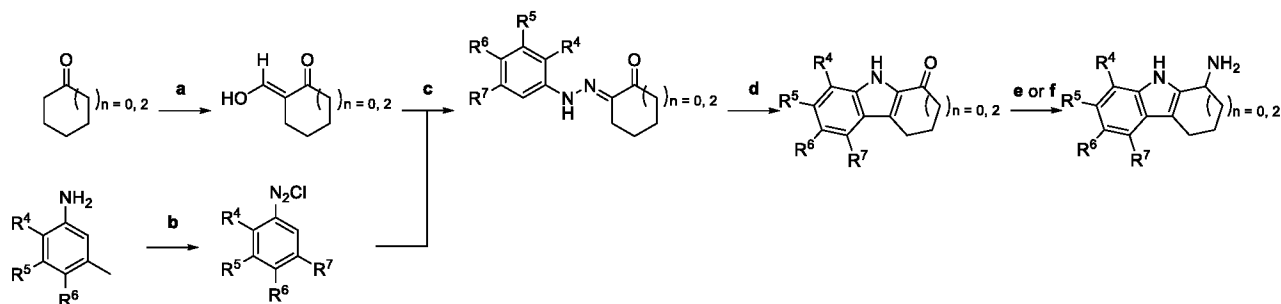
Scheme 5



Reagent and conditions: (a) Boc_2O , DMAP, THF; (b) TMSOTf, DCM, 0°C ; (c) NBS, DCM, 0°C ; (d) $\text{R}^b\text{R}^a\text{N}$, DMF; (e) TFA, DCM; (f) NH_4OAc , NaBH_3CN , EtOH, 60°C .

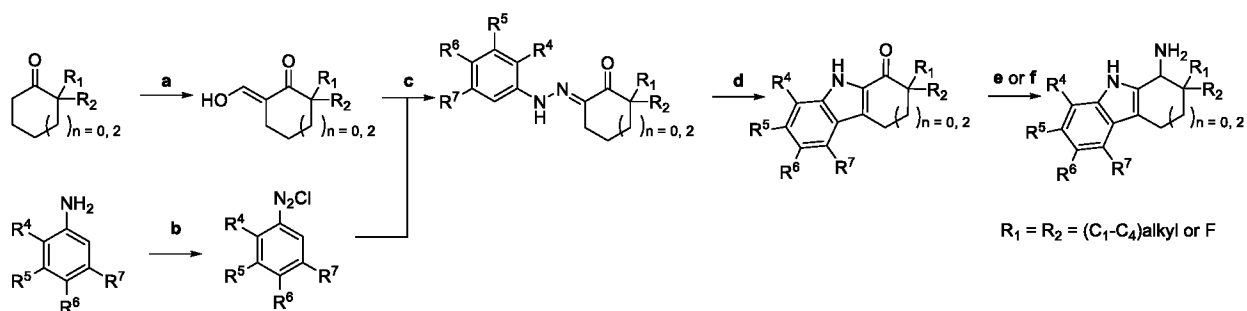
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Scheme 6



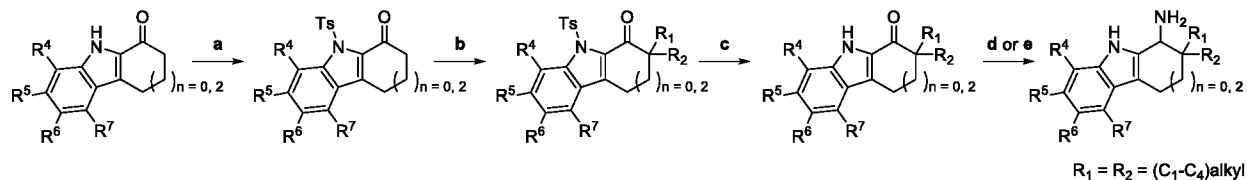
Reagent and conditions: (a) LiHMDS, ethyl formate, THF, 0°C ; (b) NaNO_2 , conc. HCl, water, 0°C ; (c) NaOAc, methanol, water, 0°C ; (d) conc. HCl, AcOH, 130°C ; (e) NH_4OAc , NaBH_3CN , cat. AcOH, EtOH, 60°C (for $n=0$); (f) NH_4OAc , NaBH_3CN , EtOH, 60°C (for $n=2$).

Scheme 7



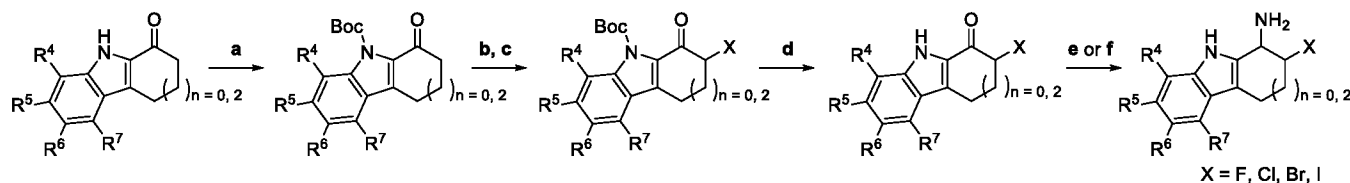
Reagent and conditions: (a) LiHMDS, ethyl formate, THF, 0°C ; (b) NaNO_2 , conc. HCl, water, 0°C ; (c) NaOAc, methanol, water, 0°C ; (d) conc. HCl, AcOH, 130°C ; (e) NH_4OAc , NaBH_3CN , cat. AcOH, EtOH, 60°C (for $n=0$); (f) NH_4OAc , NaBH_3CN , EtOH, 60°C (for $n=2$).

Scheme 8



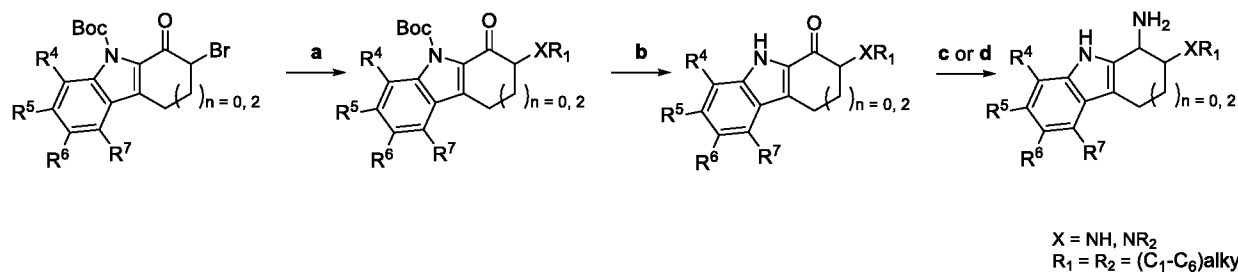
Reagent and conditions: (a) NaH, TsCl, THF; (b) LiHMDS, RX (X = OMs, Cl, Br, I), -78 °C to 0 °C; (c) NaOH, methanol, reflux; (d) NH₄OAc, NaBH₃CN, cat. AcOH, EtOH, 60 °C (for n = 0);
 5 (e) NH₄OAc, NaBH₃CN, EtOH, 60 °C (for n = 2).

Scheme 9



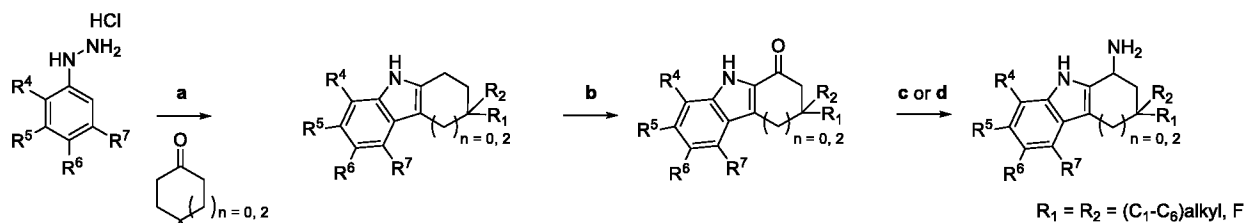
Reagent and conditions: (a) Boc₂O, DMAP, THF; (b) TMSOTf, DCM, 0 °C; (c) Selectfluor,
 10 ACN, 0 °C or NCS, DCM, 0 °C or NBS, DCM, 0 °C or NIS, DCM, 0 °C; (d) TFA, DCM; (e)
 NH₄OAc, NaBH₃CN, cat. AcOH, EtOH, 60 °C (for n = 0); (f) NH₄OAc, NaBH₃CN, EtOH, 60
 °C (for n = 2).

Scheme 10



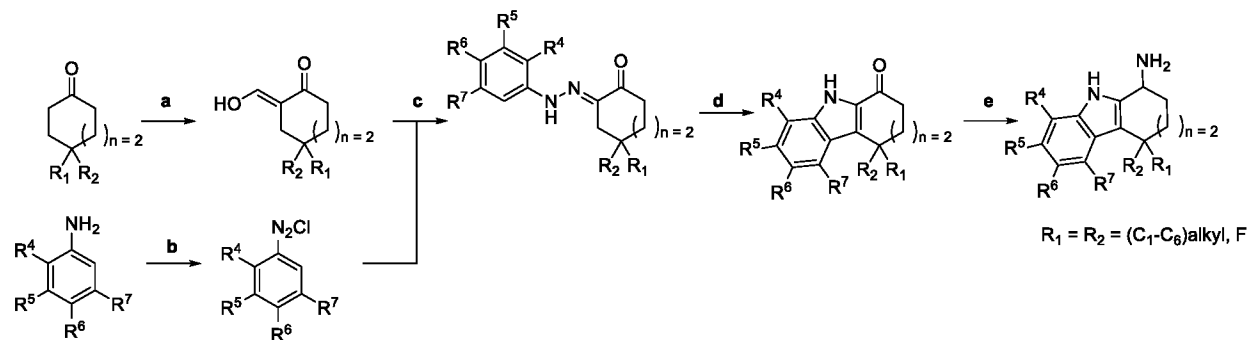
Reagent and conditions: (a) NaOR₁ or NaSR₁ or R₁NH₂ or R₁R₂NH, DMF; (b) TFA, DCM; (c)
 15 NH₄OAc, NaBH₃CN, cat. AcOH, EtOH, 60 °C (for n = 0); (d) NH₄OAc, NaBH₃CN, EtOH, 60
 °C (for n = 2).

Scheme 11



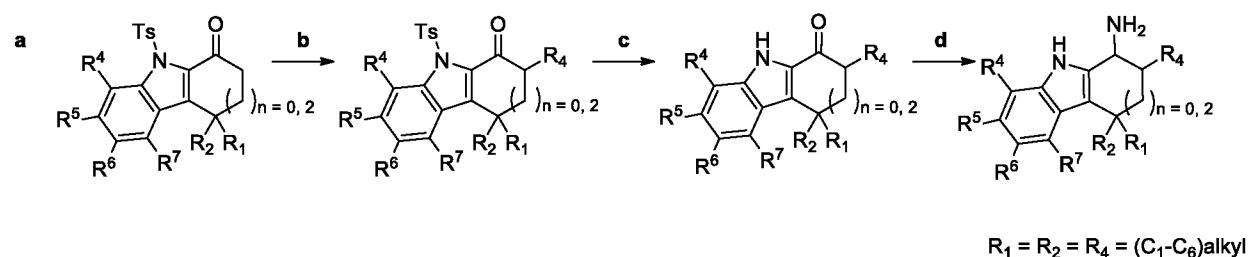
Reagent and conditions: (a) AcOH; (b) periodic acid, EtOH, water; (c) NH₄OAc, NaBH₃CN, cat. AcOH, EtOH, 60 °C (for n = 0); (d) NH₄OAc, NaBH₃CN, EtOH, 60 °C (for n = 2).

Scheme 12



Reagent and conditions: (a) LiHMDS, ethyl formate, THF, 0 °C; (b) NaNO₂, conc. HCl, water, 0 °C; (c) NaOAc, methanol, water, 0 °C; (d) conc. HCl, AcOH, 130 °C; (e) NH₄OAc, NaBH₃CN, EtOH, 60 °C.

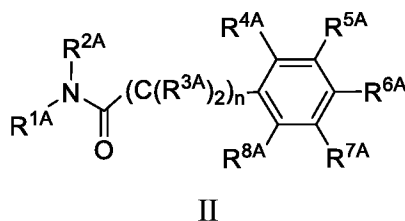
Scheme 13



Reagent and conditions: (a) NaH, TsCl, THF; (b) LiHMDS, RX (X = OMs, Cl, Br, I), -78 °C to 0 °C; (c) NaOH, methanol, reflux; (d) NH₄OAc, NaBH₃CN, EtOH, 60 °C.

Bacterial Efflux Pump Inhibitors

In one embodiment, the bacterial efflux pump inhibitor is a compound of formula II:



or a pharmaceutically acceptable salt thereof, wherein:

R^{1A} is (C₃-C₈)alkyl substituted with two or more groups selected from -NR^{b1}R^{c1}, -NHNH₂, -C(=NR^{a1})(NR^{b1}R^{c1}), -NR^{a1}C(=NR^{a1})(R^{d1}) and -NR^{a1}C(=NR^{a1})(NR^{b1}R^{c1});

R^{2A} is hydrogen or (C₁-C₃)alkyl;

each R^{3A} is independently hydrogen, halo or (C₁-C₄)alkyl;

R^{4A} is hydrogen, halo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₄)haloalkoxy, aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy and (C₁-C₄)haloalkoxy;

5 R^{5A} is hydrogen, halo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₄)haloalkoxy, aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy and (C₁-C₄)haloalkoxy;

10 R^{6A} is hydrogen, halo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₄)haloalkoxy, aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy and (C₁-C₄)haloalkoxy;

15 R^{7A} is hydrogen, halo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₄)haloalkoxy, aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy and (C₁-C₄)haloalkoxy;

20 R^{8A} is hydrogen, halo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₄)haloalkoxy, aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy and (C₁-C₄)haloalkoxy;

each R^{a1} is independently hydrogen or (C₁-C₄)alkyl;

each R^{b1} and R^{c1} is independently hydrogen or (C₁-C₄)alkyl;

R^{d1} is (C₁-C₃)alkyl and

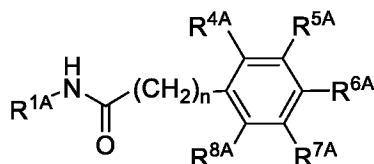
n is 0 or 1.

25 It is to be understood that the embodiments provided below are for compounds of formula II and all sub-formulas thereof (e.g., formulas IIa, IIb, IIc, IId, IId, IIe, IIe, IIe, IIe). It is to be understood the two or more embodiments may be combined.

In one embodiment R^{2A} is hydrogen.

In one embodiment R^{3A} is hydrogen.

30 One embodiment provides a bacterial efflux pump inhibitor which is a compound of formula IIa:



IIa

or a pharmaceutically acceptable salt thereof.

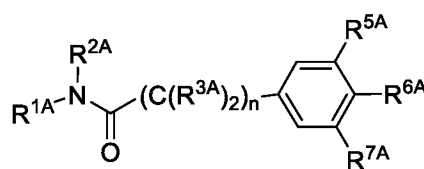
In one embodiment R^{8A} is hydrogen.

In one embodiment R^{4A} is hydrogen, (C₁-C₆)haloalkyl or aryl wherein the aryl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy and (C₁-C₄)haloalkoxy.

In one embodiment R^{4A} is hydrogen, -CF₃ or phenyl.

In one embodiment R^{4A} is hydrogen.

One embodiment provides a bacterial efflux pump inhibitor which is a compound of formula IIb:

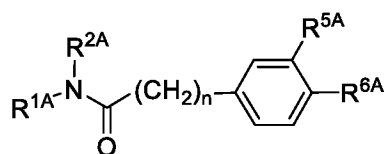


IIb

or a pharmaceutically acceptable salt thereof.

In one embodiment R^{7A} is hydrogen.

One embodiment provides a bacterial efflux pump inhibitor which is a compound of formula IIc:



IIc

or a pharmaceutically acceptable salt thereof.

In one embodiment R^{5A} is halo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₄)haloalkoxy, aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy and (C₁-C₄)haloalkoxy;

In one embodiment R^{5A} is (C₁-C₆)haloalkyl.

In one embodiment R^{5A} is -CF₃.

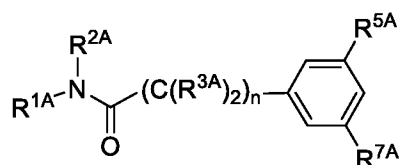
In one embodiment R^{6A} is halo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₄)haloalkoxy, aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy and (C₁-C₄)haloalkoxy;

In one embodiment R^{6A} is (C₁-C₆)haloalkyl.

In one embodiment R^{6A} -CF₃.

In one embodiment R^{6A} is hydrogen.

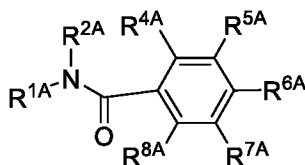
One embodiment provides a bacterial efflux pump inhibitor which is a compound of formula IIc:



IIc

or a pharmaceutically acceptable salt thereof.

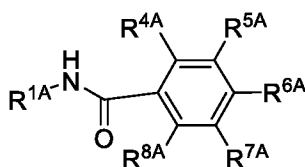
One embodiment provides a bacterial efflux pump inhibitor which is a compound of formula IIe:



IIe

or a pharmaceutically acceptable salt thereof.

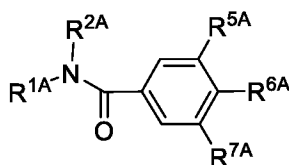
One embodiment provides a bacterial efflux pump inhibitor which is a compound of formula IIc:



IIc

or a pharmaceutically acceptable salt thereof.

One embodiment provides a bacterial efflux pump inhibitor which is a compound of formula IIg:



IIg

or a pharmaceutically acceptable salt thereof.

In one embodiment R^{5A} is halo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₄)haloalkoxy, aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted

with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy and (C₁-C₄)haloalkoxy.

In one embodiment R^{5A} is (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, or aryl wherein the aryl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy and (C₁-C₄)haloalkoxy.

In one embodiment R^{5A} is (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, or phenyl wherein phenyl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy and (C₁-C₄)haloalkoxy.

In one embodiment R^{5A} is *tert*-butyl, -CF₃, phenyl or 4-fluorophenyl.

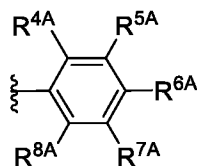
In one embodiment R^{7A} is halo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₄)haloalkoxy, aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy and (C₁-C₄)haloalkoxy.

In one embodiment R^{7A} is (C₁-C₆)alkyl, (C₁-C₆)haloalkyl or aryl wherein the aryl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy and (C₁-C₄)haloalkoxy.

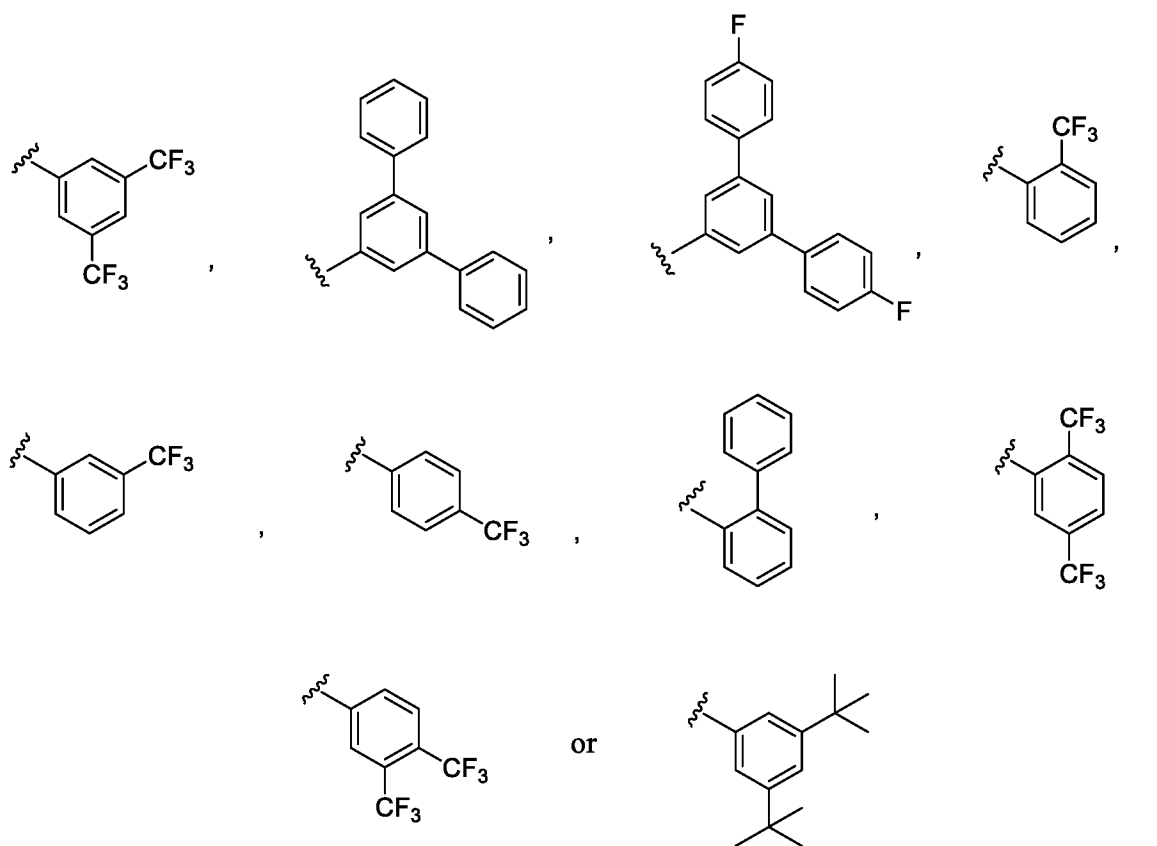
In one embodiment R^{7A} is (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, or phenyl wherein phenyl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) groups independently selected from halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy and (C₁-C₄)haloalkoxy.

In one embodiment R^{7A} is *tert*-butyl, -CF₃, phenyl or 4-fluorophenyl.

In one embodiment the moiety:



of the compound of formula II is:



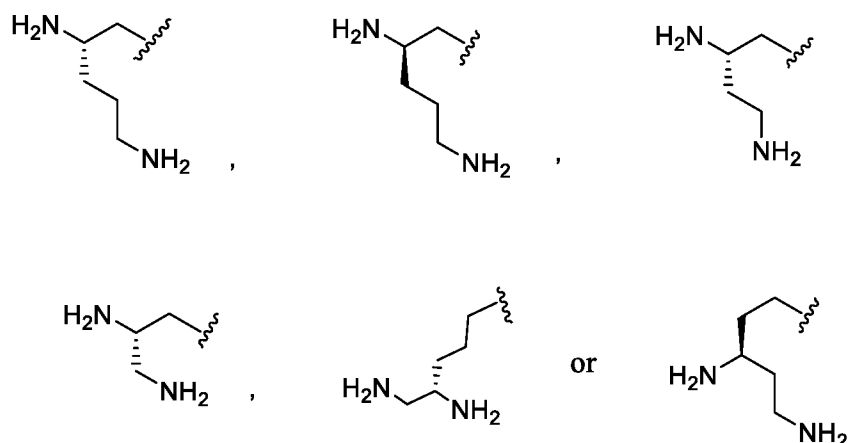
In one embodiment R^{1A} is (C_3-C_8) alkyl substituted with two or more groups
 5 independently selected from $-NR^{b1}R^{c1}$.

In one embodiment R^{1A} is (C_3-C_8) alkyl substituted with two groups independently
 selected from $-NR^{b1}R^{c1}$.

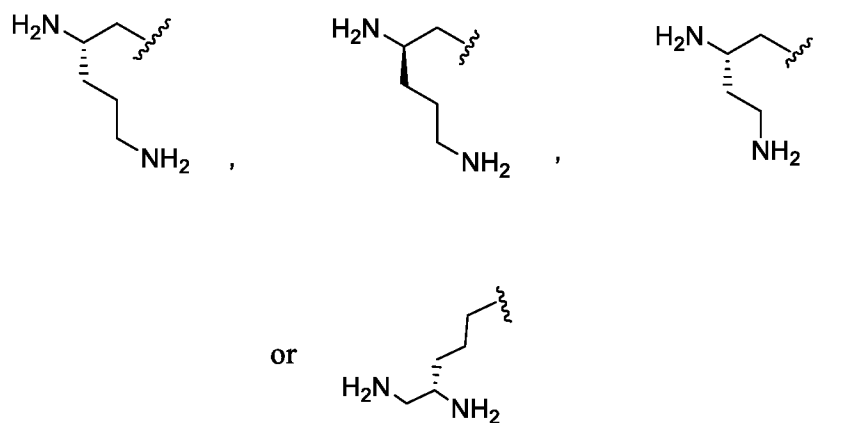
In one embodiment R^{1A} is (C_4-C_5) alkyl substituted with two groups independently
 selected from $-NR^{b1}R^{c1}$.

10 In one embodiment R^{b1} and R^{c1} are each hydrogen.

In one embodiment R^{1A} is:

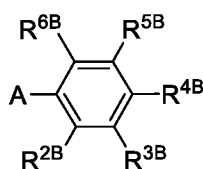


In one embodiment R^{1A} is:



In one embodiment n is 0.

In one embodiment, the bacterial efflux pump inhibitor is a compound of formula III:



III

or a pharmaceutically acceptable salt thereof, wherein:

A is $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}1})-\text{R}^{\text{1B}}$, $-(\text{C}_1-\text{C}_3)\text{alkyl}-\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}1})\text{R}^{\text{1B}}$, $-(\text{C}_1-\text{C}_3)\text{alkyl}-\text{O}-\text{R}^{\text{1B}}$, $-\text{O}-\text{R}^{\text{1B}}$, $-(\text{C}_1-\text{C}_3)\text{alkyl}-\text{N}(\text{R}^{\text{a}1})-\text{R}^{\text{1B}}$, or $-\text{N}(\text{R}^{\text{a}1})-\text{R}^{\text{1B}}$;

each R^{1B} is independently a (C_3-C_7) carbocyclyl, (C_3-C_7) carbocyclyl- (C_1-C_4) alkyl-, 4-7 membered monocyclic heterocyclyl, or 4-7 membered monocyclic heterocyclyl- (C_1-C_4) alkyl-, wherein each (C_3-C_7) carbocyclyl or (C_3-C_7) carbocyclyl- (C_1-C_4) alkyl- is independently substituted with one or more groups selected from the group consisting of Z and $-(\text{C}_1-\text{C}_6)$ alkyl substituted with one or more Z, and wherein each 4-7 membered monocyclic heterocyclyl or 4-7 membered monocyclic heterocyclyl- (C_1-C_4) alkyl- is independently optionally substituted with one or more groups selected from the group consisting of Z and $-(\text{C}_1-\text{C}_6)$ alkyl substituted with one or more Z, wherein each Z is independently selected from the group consisting of $\text{NR}^{\text{b}2}\text{R}^{\text{c}2}$, $-\text{NHNH}_2$, $-\text{C}(=\text{NR}^{\text{a}2})(\text{NR}^{\text{b}2}\text{R}^{\text{c}2})$, $-\text{NR}^{\text{a}2}\text{C}(=\text{NR}^{\text{a}2})(\text{R}^{\text{d}2})$, and $-\text{NR}^{\text{a}2}\text{C}(=\text{NR}^{\text{a}2})(\text{NR}^{\text{b}2}\text{R}^{\text{c}2})$ and wherein each (C_3-C_7) carbocyclyl, (C_3-C_7) carbocyclyl- (C_1-C_4) alkyl-, 4-7 membered monocyclic heterocyclyl, or 4-7 membered monocyclic heterocyclyl- (C_1-C_4) alkyl-, is independently optionally substituted independently with one or more (C_1-C_4) alkyl;

R^{2B} is hydrogen, halo, (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkoxy, aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, $-\text{NO}_2$, $-\text{CN}$, (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, (C_1-C_4) alkoxy and (C_1-C_4) haloalkoxy;

R^{3B} is hydrogen, halo, (C₁-C₆)alkyl, (C₁-C₄)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₄)haloalkoxy, aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, -NO₂, -CN, (C₁-C₆)alkyl, (C₁-C₄)haloalkyl, (C₁-C₆)alkoxy and (C₁-C₄)haloalkoxy;

R^{4B} is hydrogen, halo, (C₁-C₆)alkyl, (C₁-C₄)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₄)haloalkoxy, aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, -NO₂, -CN, (C₁-C₆)alkyl, (C₁-C₄)haloalkyl, (C₁-C₆)alkoxy and (C₁-C₄)haloalkoxy;

R^{5B} is hydrogen, halo, (C₁-C₆)alkyl, (C₁-C₄)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₄)haloalkoxy, aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, -NO₂, -CN, (C₁-C₆)alkyl, (C₁-C₄)haloalkyl, (C₁-C₆)alkoxy and (C₁-C₄)haloalkoxy;

R^{6B} is hydrogen, halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, -NO₂, -CN, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy and (C₁-C₄)haloalkoxy;

each R^{a1} is independently hydrogen, (C₁-C₆)alkyl or (C₃-C₇)carbocyclyl;

each R^{a2} is independently hydrogen, (C₁-C₆)alkyl or (C₃-C₇)carbocyclyl;

each R^{b2} and R^{c2} is independently hydrogen, (C₁-C₆)alkyl or (C₃-C₇)carbocyclyl; and

R^{d2} is (C₁-C₆)alkyl or (C₃-C₇)carbocyclyl.

It is to be understood that the embodiments provided below are for compounds of formula III and all sub-formulas thereof. It is to be understood the two or more embodiments may be combined.

In one embodiment A is -C(=O)N(R^{a1})-R^{1B}, -(C₁-C₃)alkyl-C(=O)N(R^{a1})R^{1B},
 5 -(C₁-C₃)alkyl-O-R^{1B}, or -O-R^{1B}.

In one embodiment A is -C(=O)N(R^{a1})-R^{1B}.

In one embodiment A is -(C₁-C₃)alkyl-C(=O)N(R^{a1})R^{1B}.

In one embodiment R^{a1} is hydrogen.

In one embodiment A is -O-R^{1B}.

10 In one embodiment R^{2B} is hydrogen, halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, or (C₁-C₄)haloalkoxy.

In one embodiment R^{2B} is hydrogen.

In one embodiment R^{3B} is aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, -NO₂, -CN, (C₁-C₆)alkyl, (C₁-C₄)haloalkyl, (C₁-C₆)alkoxy and (C₁-C₄)haloalkoxy.
 15

In one embodiment R^{3B} is phenyl wherein the phenyl is optionally substituted with one or more groups independently selected from halo, $-\text{NO}_2$, $-\text{CN}$, $(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_1\text{-C}_4)\text{haloalkyl}$, $(\text{C}_1\text{-C}_6)\text{alkoxy}$ and $(\text{C}_1\text{-C}_4)\text{haloalkoxy}$.

In one embodiment R^{3B} is 4-fluorophenyl.

5 In one embodiment R^{4B} is hydrogen, halo, $(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_1\text{-C}_4)\text{haloalkyl}$, $(\text{C}_1\text{-C}_6)\text{alkoxy}$, $(\text{C}_1\text{-C}_4)\text{haloalkoxy}$.

In one embodiment R^{4B} is hydrogen.

10 In one embodiment R^{5B} is aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, $-\text{NO}_2$, $-\text{CN}$, $(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_1\text{-C}_4)\text{haloalkyl}$, $(\text{C}_1\text{-C}_6)\text{alkoxy}$ and $(\text{C}_1\text{-C}_4)\text{haloalkoxy}$.

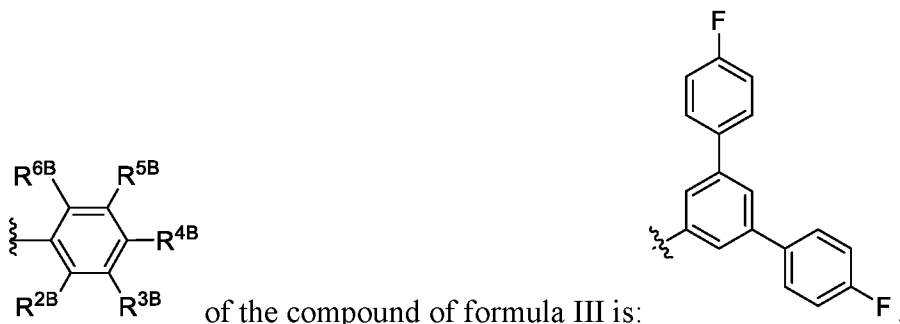
In one embodiment R^{5B} is phenyl wherein the phenyl is optionally substituted with one or more groups independently selected from halo, $-\text{NO}_2$, $-\text{CN}$, $(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_1\text{-C}_4)\text{haloalkyl}$, $(\text{C}_1\text{-C}_6)\text{alkoxy}$ and $(\text{C}_1\text{-C}_4)\text{haloalkoxy}$.

In one embodiment R^{5B} is 4-fluorophenyl.

15 In one embodiment R^{6B} is hydrogen, halo, $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_1\text{-C}_4)\text{haloalkyl}$, $(\text{C}_1\text{-C}_4)\text{alkoxy}$, or $(\text{C}_1\text{-C}_4)\text{haloalkoxy}$.

In one embodiment R^{6B} is hydrogen.

In one embodiment the moiety:



of the compound of formula III is:

20 In one embodiment R^{1B} is a 4-7 membered monocyclic heterocyclyl or 4-7 membered monocyclic heterocyclyl- $(\text{C}_1\text{-C}_4)\text{alkyl}$ -, wherein the 4-7 membered monocyclic heterocyclyl or 4-7 membered monocyclic heterocyclyl- $(\text{C}_1\text{-C}_4)\text{alkyl}$ - is optionally substituted independently with one or more groups selected from the group consisting of Z and $-(\text{C}_1\text{-C}_6)\text{alkyl}$ substituted with one or more Z, wherein each Z is $\text{NR}^{b2}\text{R}^{c2}$ nd wherein the 4-7 membered monocyclic heterocyclyl or 4-7 membered monocyclic heterocyclyl- $(\text{C}_1\text{-C}_4)\text{alkyl}$ - is optionally substituted with one or more $(\text{C}_1\text{-C}_4)\text{alkyl}$.

In one embodiment R^{1B} is a 4-7 membered monocyclic N-heterocyclyl or 4-7 membered monocyclic N-heterocyclyl- $(\text{C}_1\text{-C}_4)\text{alkyl}$ -, wherein the 4-7 membered monocyclic N-heterocyclyl or 4-7 membered monocyclic N-heterocyclyl- $(\text{C}_1\text{-C}_4)\text{alkyl}$ - is optionally substituted

independently with one or more groups selected from the group consisting of Z and $-(C_1-C_6)alkyl$ substituted with one or more Z, wherein each Z is $NR^{b2}R^{c2}$ nd wherein the 4-7 membered monocyclic N-heterocyclyl or 4-7 membered monocyclic N-heterocyclyl- $(C_1-C_4)alkyl$ - is optionally substituted with one or more $(C_1-C_4)alkyl$.

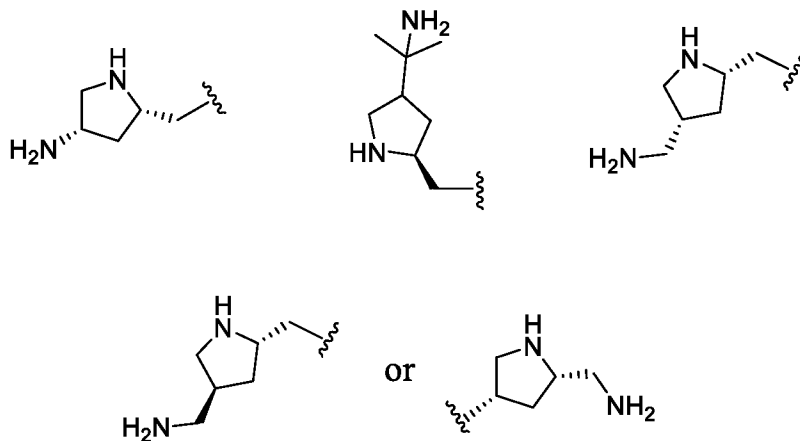
5 In one embodiment R^{1B} is a pyrrolidinyl or pyrrolidinyl- $(C_1-C_4)alkyl$ -, wherein the pyrrolidinyl or pyrrolidinyl- $(C_1-C_4)alkyl$ - is optionally substituted independently with one or more groups selected from the group consisting of Z and $-(C_1-C_6)alkyl$ substituted with one or more Z, wherein each Z is $NR^{b2}R^{c2}$ nd wherein the pyrrolidinyl or pyrrolidinyl- $(C_1-C_4)alkyl$ -is optionally substituted with one or more $(C_1-C_4)alkyl$.

10 In one embodiment R^{1B} is a pyrrolidinyl or pyrrolidinyl- (CH_2) -, wherein the pyrrolidinyl- (CH_2) - is optionally substituted independently with one or more groups selected from the group consisting of Z and $-(C_1-C_6)alkyl$ substituted with one or more Z, wherein each Z is $NR^{b2}R^{c2}$ and wherein the pyrrolidinyl or pyrrolidinyl- $(C_1-C_4)alkyl$ -is optionally substituted with one or more $(C_1-C_4)alkyl$.

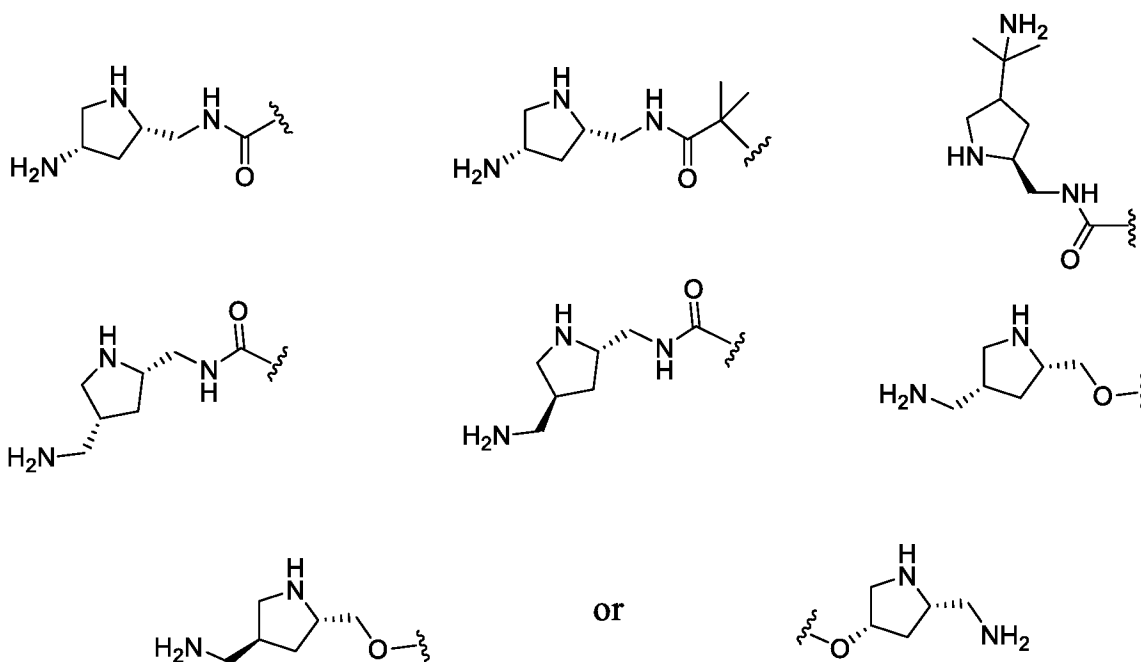
15 In one embodiment R^{1B} is a pyrrolidinyl or pyrrolidinyl- (CH_2) -, wherein the pyrrolidinyl- (CH_2) - is optionally substituted independently with one or more groups selected from the group consisting of Z and $-(C_1-C_4)alkyl$ substituted with one or more Z, wherein each Z is $NR^{b2}R^{c2}$.

In one embodiment each R^{b2} and R^{c2} is hydrogen

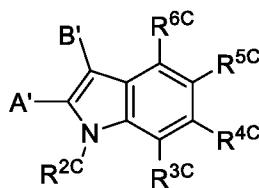
20 In one embodiment R^{1B} is:



In one embodiment A is:



In one embodiment, the bacterial efflux pump inhibitor is a compound of formula IV:



IV

or a pharmaceutically acceptable salt thereof, wherein:

one of A' or B' is -C(=O)N(R^{al})-R^{1C}, -(C₁-C₃)alkyl-C(=O)N(R^{al})R^{1C}, -(C₁-C₃)alkyl-O-R^{1C}, -O-R^{1C}, -(C₁-C₃)alkyl-N(R^{al})-R^{1C}, -N(R^{al})-R^{1C}, or R^{1C} and the other of A' or B' is H, halogen, or (C₁-C₄)alkyl;

each R^{1C} is independently:

(a) (C₁-C₁₄)alkyl substituted with one or more groups selected from the group consisting of -NR^{b2}R^{c2}, -NHNH₂, -C(=NR^{a2})(NR^{b2}R^{c2}), -NR^{a2}C(=NR^{a2})(R^{d2}), and -NR^{a2}C(=NR^{a2})(NR^{b2}R^{c2}); and wherein (C₁-C₁₄)alkyl is optionally substituted independently with one or more halo, (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl; or

(b) (C₃-C₇)carbocyclyl, (C₃-C₇)carbocyclyl-(C₁-C₄)alkyl-, 4-7 membered monocyclic heterocyclyl, or 4-7 membered monocyclic heterocyclyl-(C₁-C₄)alkyl-, wherein each (C₃-C₇)carbocyclyl or (C₃-C₇)carbocyclyl-(C₁-C₄)alkyl- is independently substituted with one or more Z¹ or Z², and wherein each 4-7 membered monocyclic heterocyclyl or 4-7 membered monocyclic heterocyclyl-(C₁-C₄)alkyl- is independently optionally substituted with one or more Z¹ or Z², and wherein any (C₃-C₇)carbocyclyl, (C₃-C₇)carbocyclyl-(C₁-C₄)alkyl-, 4-7 membered

monocyclic heterocyclyl, or 4-7 membered monocyclic heterocyclyl-(C₁-C₄)alkyl- of R¹ is independently optionally substituted independently with one or more halo, (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl;

R^{2C} is hydrogen, (C₁-C₄)alkyl or phenyl(C₁-C₃)alkyl-, wherein the phenyl is optionally substituted with one or more (C₁-C₄)alkyl, -O(C₁-C₄)alkyl, halogen, or -NO₂;

R^{3C} is hydrogen, halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, aryl, or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more
5 groups independently selected from the group consisting of halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, and (C₁-C₄)haloalkoxy;

R^{4C} is hydrogen, halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, aryl, or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl,
10 (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, and (C₁-C₄)haloalkoxy;

R^{5C} is hydrogen, halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, aryl, or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl,
(C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, and (C₁-C₄)haloalkoxy;

R^{6C} is hydrogen, halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, aryl, or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl,
15 (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, and (C₁-C₄)haloalkoxy;

each Z¹ is independently selected from the group consisting of -NR^{b3}R^{c3}, -NHNH₂,
20 -C(=NR^{a3})(NR^{b3}R^{c3}), -NR^{a3}C(=NR^{a3})(R^{d3}), and -NR^{a3}C(=NR^{a3})(NR^{b3}R^{c3});

each Z² is independently -(C₁-C₆)alkyl substituted with one or more Z¹ and optionally substituted with one or more Z³;

each Z³ is independently halo or (C₃-C₇)carbocyclyl;

each R^{a1} is independently hydrogen, (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl;

each R^{a2} is independently hydrogen, (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl;

each R^{b2} and R^{c2} is independently hydrogen, (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl;

R^{d2} is (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl;

25 each R^{a3} is independently hydrogen (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl;

each R^{b3} and R^{c3} is independently hydrogen (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl; and

R^{d3} is (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl.

It is to be understood that the embodiments provided below are for compounds of formula IV and all sub-formulas thereof (e.g., formulas IVa, IVb). It is to be understood the two or more embodiments may be combined.

In one embodiment one of A' or B' is $-C(=O)N(R^{1C})-R^{1C}$ or
 5 $-(C_1-C_3)\text{alkyl}-C(=O)N(R^{1C})R^{1C}$, and the other of A' or B' is H, halogen, or $(C_1-C_6)\text{alkyl}$.

In one embodiment one of A' or B' is $-C(=O)N(R^{1C})-R^{1C}$, and the other of A' or B' is H, halogen, or $(C_1-C_6)\text{alkyl}$.

In one embodiment A' is $-C(=O)N(R^{1C})-R^{1C}$, and B' is H.

In one embodiment B' is $-C(=O)N(R^{1C})-R^{1C}$, and A' is H.

10 In one embodiment one of A' or B' is $-C(=O)N(R^{1C})-R^{1C}$ or $-(C_1-C_3)\text{alkyl}-C(=O)N(R^{1C})R^{1C}$, and the other of A' or B' is H.

In one embodiment one of A' or B' is $-C(=O)N(R^{1C})-R^{1C}$, and the other of A' or B' is H.

In one embodiment R^{2C} is hydrogen, $(C_1-C_4)\text{alkyl}$ or benzyl, wherein benzyl is optionally substituted with one or more $(C_1-C_4)\text{alkyl}$, $-O(C_1-C_4)\text{alkyl}$, halogen or $-\text{NO}_2$.

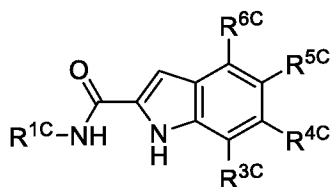
15 In one embodiment R^{1C} is hydrogen.

In one embodiment R^{2C} is hydrogen or $(C_1-C_4)\text{alkyl}$.

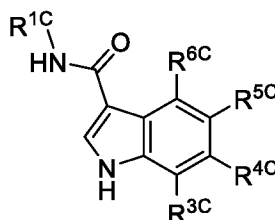
In one embodiment R^{2C} is hydrogen.

In one embodiment R^{2C} is hydrogen, methyl, or 4-fluorobenzyl.

In one embodiment a compound of formula IV is a compound formula IVa or IVb:



IVa



IVb

or a pharmaceutically acceptable salt thereof.

In one embodiment R^{3C} is hydrogen or aryl wherein the aryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-\text{OH}$, $-\text{NO}_2$, $-\text{CN}$,
 25 $(C_1-C_4)\text{alkyl}$, $(C_1-C_4)\text{haloalkyl}$, $(C_1-C_4)\text{alkoxy}$ and $(C_1-C_4)\text{haloalkoxy}$.

In one embodiment R^{3C} is hydrogen or phenyl wherein the phenyl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-\text{OH}$, $-\text{NO}_2$, $-\text{CN}$, $(C_1-C_4)\text{alkyl}$, $(C_1-C_4)\text{haloalkyl}$, $(C_1-C_4)\text{alkoxy}$ and $(C_1-C_4)\text{haloalkoxy}$.

In one embodiment R^{3C} is hydrogen or 4-fluorophenyl.

In one embodiment R^{4C} is hydrogen, aryl, or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, and (C₁-C₄)haloalkoxy.

5 In one embodiment R^{4C} is hydrogen, phenyl, or pyridinyl wherein the phenyl or pyridinyl is optionally substituted with one or more groups independently selected from the group consisting of halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, and (C₁-C₄)haloalkoxy.

10 In one embodiment R^{4C} is hydrogen, 4-nitrophenyl, 4-fluorophenyl, 3,4-difluorophenyl, 4-*t*-butylphenyl, 4-methoxyphenyl, pyridin-4-yl, 4-hydroxyphenyl, 4-chlorophenyl, or 4-cyanophenyl.

In one embodiment R^{5C} is hydrogen or aryl wherein the aryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy and (C₁-C₄)haloalkoxy.

15 In one embodiment R^{5C} is hydrogen or phenyl wherein the phenyl is optionally substituted with one or more groups independently selected from the group consisting of halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy and (C₁-C₄)haloalkoxy.

In one embodiment R^{5C} is hydrogen or 4-fluorophenyl.

20 In one embodiment R^{6C} is hydrogen or aryl wherein the aryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy and (C₁-C₄)haloalkoxy.

In one embodiment R^{6C} is hydrogen or phenyl wherein the phenyl is optionally substituted with one or more groups independently selected from the group consisting of halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy and (C₁-C₄)haloalkoxy.

In one embodiment R^{6C} is hydrogen or 4-fluorophenyl.

In one embodiment R^{1C} is (C₁-C₁₄)alkyl substituted with one or more groups independently selected from -NR^{b2}R^{c2}.

In one embodiment R^{1C} is (C₂-C₁₀)alkyl substituted with one or more groups independently selected from -NR^{b2}R^{c2}.

In one embodiment R^{1C} is (C₁-C₁₄)alkyl substituted with one or more groups independently selected from -NR^{b2}R^{c2}.

In one embodiment R^{1C} is (C₂-C₈)alkyl substituted with two or more groups independently selected from -NR^{b2}R^{c2}.

In one embodiment R^{1C} is (C₄-C₈)alkyl substituted with two or more groups independently selected from -NR^{b2}R^{c2}.

In one embodiment R^{b2} and R^{c2} are each hydrogen.

In one embodiment R^{1C} is a 4-7 membered monocyclic heterocycl-yl-(C₁-C₄)alkyl-, wherein the 4-7 membered monocyclic heterocycl-yl-(C₁-C₄)alkyl- is substituted with one or more groups independently selected from the group consisting of Z and -(C₁-C₆)alkyl substituted with one or more Z, wherein each Z is independently selected from the group consisting of
 5 -NR^{b3}R^{c3}, -NHNH₂, -C(=NR^{a3})(NR^{b3}R^{c3}), -NR^{a3}C(=NR^{a3})(R^{d3}), and -NR^{a3}C(=NR^{a3})(NR^{b3}R^{c3}) and wherein the 4-7 membered monocyclic heterocycl-yl-(C₁-C₄)alkyl- is optionally substituted with one or more (C₁-C₆)alkyl.

In one embodiment R^{1C} is a 4-7 membered monocyclic heterocycl-yl-(C₁-C₄)alkyl-, wherein the 4-7 membered monocyclic heterocycl-yl-(C₁-C₄)alkyl- is substituted with one or
 10 more groups independently selected from the group consisting of Z and (C₁-C₆)alkyl substituted with one or more Z, wherein each Z is independently -NR^{b3}R^{c3} and wherein the 4-7 membered monocyclic heterocycl-yl-(C₁-C₄)alkyl- is optionally substituted with one or more (C₁-C₆)alkyl.

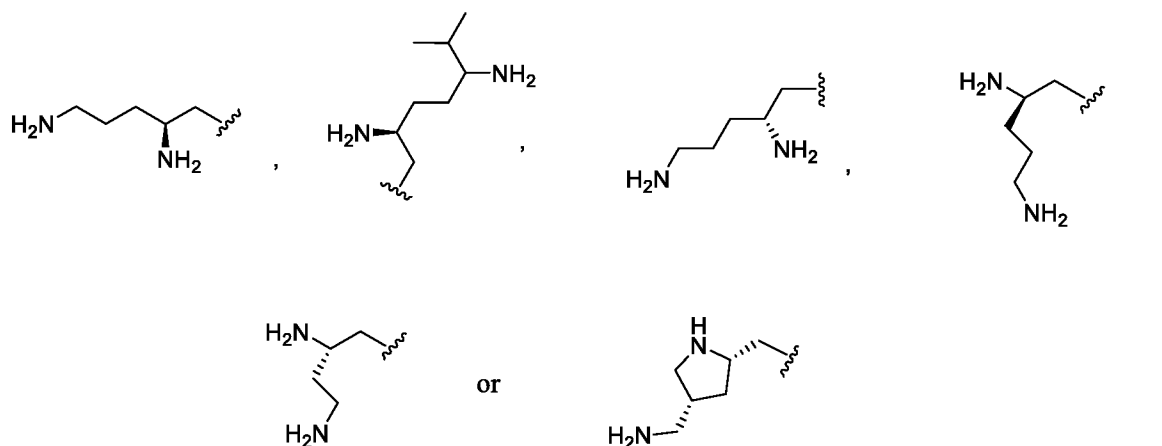
In one embodiment R^{1C} is pyrrolidinyl-(C₁-C₄)alkyl-, wherein the pyrrolidinyl-(C₁-C₄)alkyl- is substituted with one or more groups independently selected from the group
 15 consisting of Z and -(C₁-C₆)alkyl substituted with one or more Z, wherein each Z is independently -NR^{b3}R^{c3} and wherein the pyrrolidinyl-(C₁-C₄)alkyl- is optionally substituted independently with one or more (C₁-C₆)alkyl

In one embodiment R^{1C} is pyrrolidinyl-(CH₂)-, wherein the pyrrolidinyl-(CH₂)- is substituted with one or more groups independently selected from the group consisting of Z and -
 20 (C₁-C₆)alkyl substituted with one or more Z, wherein each Z is independently -NR^{b3}R^{c3} and wherein the pyrrolidinyl-(CH₂)- is optionally substituted independently with one or more (C₁-C₆)alkyl.

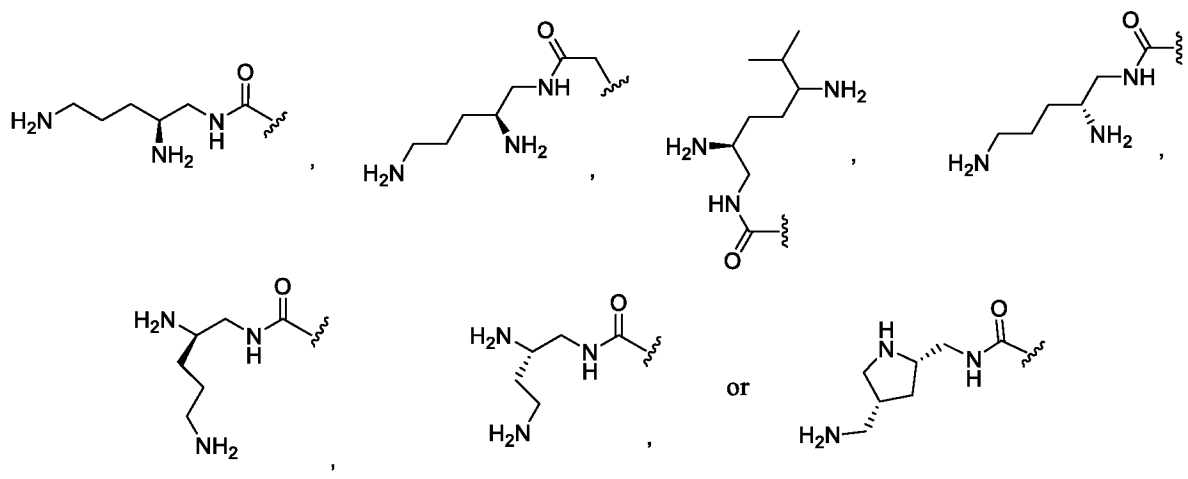
In one embodiment R^{1C} is pyrrolidinyl-(CH₂)-, wherein the pyrrolidinyl-(CH₂)- is substituted on the pyrrolidinyl with an -(C₁-C₆)alkyl substituted with one or more -NR^{b3}R^{c3}.

In one embodiment R^{b3} and R^{c3} are each hydrogen.

In one embodiment R^{1C} is:

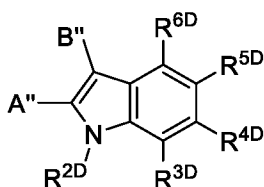


In one embodiment one of A' or B' is:



and the other of A' or B' is H.

In one embodiment, the bacterial efflux pump inhibitor is a compound of formula V:



V

or a pharmaceutically acceptable salt thereof, wherein:

A'' is $-C(=O)N(R^{a1})-R^{1D}$, $-(C_1-C_3)\text{alkyl}-C(=O)N(R^{a1})R^{1D}$, $-(C_1-C_3)\text{alkyl}-O-R^{1D}$, $-O-R^{1D}$, $-(C_1-C_3)\text{alkyl}-N(R^{a1})-R^{1D}$, $-N(R^{a1})-R^{1D}$, or R^{1D} ;

B'' is $(C_2-C_8)\text{alkenyl}$, $(C_2-C_8)\text{alkynyl}$, $(C_1-C_4)\text{haloalkyl}$, $(C_1-C_4)\text{alkoxy}$, $(C_1-C_4)\text{haloalkoxy}$, $(C_3-C_7)\text{carbocyclyl}$, $(C_3-C_7)\text{carbocyclyl}-(C_1-C_4)\text{alkyl-}$, aryl, aryl- $(C_1-C_4)\text{alkyl-}$, heteroaryl, heteroaryl- $(C_1-C_4)\text{alkyl-}$, 3-7 membered-monocyclic-heterocycle, or 3-7 membered-monocyclic-heterocycle- $(C_1-C_4)\text{alkyl-}$ wherein any $(C_3-C_7)\text{carbocyclyl}$, $(C_3-C_7)\text{carbocyclyl}-(C_1-C_4)\text{alkyl-}$, aryl, aryl- $(C_1-C_4)\text{alkyl-}$, heteroaryl, heteroaryl- $(C_1-C_4)\text{alkyl-}$, 3-7 membered-monocyclic-heterocycle, or 3-7 membered-monocyclic-heterocycle- $(C_1-C_4)\text{alkyl-}$ of B'' is optionally substituted with one or more Z^1 groups;

each R^{1D} is independently:

(a) $(C_1-C_{14})\text{alkyl}$ substituted with one or more groups selected from the group consisting of $-NR^{b2}R^{c2}$, $-NHNH_2$, $-C(=NR^{a2})(NR^{b2}R^{c2})$, $-NR^{a2}C(=NR^{a2})(R^{d2})$, and $-NR^{a2}C(=NR^{a2})(NR^{b2}R^{c2})$ and wherein $(C_1-C_{14})\text{alkyl}$ is optionally substituted independently with one or more halo, $(C_1-C_4)\text{alkyl}$ or $(C_3-C_7)\text{carbocyclyl}$; or

(b) $(C_3-C_7)\text{carbocyclyl}$, $(C_3-C_7)\text{carbocyclyl}-(C_1-C_4)\text{alkyl-}$, 4-7 membered monocyclic heterocyclyl, or 4-7 membered monocyclic heterocyclyl- $(C_1-C_4)\text{alkyl-}$, wherein each $(C_3-C_7)\text{carbocyclyl}$ or $(C_3-C_7)\text{carbocyclyl}-(C_1-C_4)\text{alkyl-}$ is independently substituted with one or

more Z^2 or Z^3 , and wherein each 4-7 membered monocyclic heterocyclyl or 4-7 membered monocyclic heterocyclyl-(C₁-C₄)alkyl- is independently optionally substituted with one or more Z^2 or Z^3 , and wherein any (C₃-C₇)carbocyclyl, (C₃-C₇)carbocyclyl-(C₁-C₄)alkyl-, 4-7 membered monocyclic heterocyclyl, or 4-7 membered monocyclic heterocyclyl-(C₁-C₄)alkyl- of R¹ is optionally substituted independently with one or more halo, (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl;

R^{2D} is hydrogen, (C₁-C₄)alkyl or phenyl(C₁-C₃)alkyl-, wherein the phenyl is optionally substituted with one or more (C₁-C₄)alkyl, -O(C₁-C₄)alkyl, halogen, or -NO₂;

R^{3D} is hydrogen, halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, aryl, or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, and (C₁-C₄)haloalkoxy;

R^{4D} is hydrogen, halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, aryl, or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, and (C₁-C₄)haloalkoxy;

R^{5D} is hydrogen, halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, aryl, or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, and (C₁-C₄)haloalkoxy;

R^{6D} is hydrogen, halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, aryl, or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, and (C₁-C₄)haloalkoxy;

each Z¹ is independently halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, or (C₁-C₄)haloalkoxy;

each Z² is independently selected from the group consisting of -NR^{b3}R^{c3}, -NHNH₂, -C(=NR^{a3})(NR^{b3}R^{c3}), -NR^{a3}C(=NR^{a3})(R^{d3}), and -NR^{a3}C(=NR^{a3})(NR^{b3}R^{c3})

each Z³ is independently -(C₁-C₆)alkyl substituted with one or more Z² and optionally substituted with one or more Z⁴;

each Z⁴ is independently halo or (C₃-C₇)carbocyclyl;

each R^{a1} is independently hydrogen, (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl;

each R^{a2} is independently hydrogen, (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl;

each R^{b2} and R^{c2} is independently hydrogen, (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl;

R^{d2} is (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl;

each R^{a3} is independently hydrogen (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl;

each R^{b3} and R^{c3} is independently hydrogen (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl; and R^{d3} is (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl.

It is understood that the embodiments provided below are for compounds of formula V and all sub-formulas thereof (e.g., formulas Va). It is to be understood the two or more embodiments may be combined.

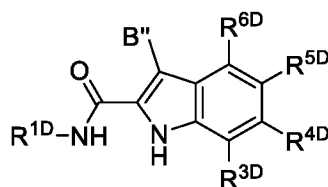
In one embodiment A'' is $-C(=O)N(R^{a1})-R^{1D}$.

In one embodiment R^{a1} is hydrogen.

In one embodiment R^{2D} is hydrogen or (C₁-C₆)alkyl.

In one embodiment R^{2D} is hydrogen.

In one embodiment a compound of formula I is a compound of formula Va:



Va

or a pharmaceutically acceptable salt thereof.

In one embodiment R^{3D} is hydrogen, halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, or (C₁-C₄)haloalkoxy.

In one embodiment R^{3D} is hydrogen.

In one embodiment R^{4D} is hydrogen, aryl, or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, and (C₁-C₄)haloalkoxy.

In one embodiment R^{4D} is phenyl wherein the phenyl is optionally substituted with one or more groups independently selected from the group consisting of halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, and (C₁-C₄)haloalkoxy.

In one embodiment R^{4D} is phenyl wherein the phenyl is optionally substituted with one or more halo.

In one embodiment R^{4D} is 4-fluorophenyl.

In one embodiment R^{5D} is hydrogen, halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, or (C₁-C₄)haloalkoxy.

In one embodiment R^{5D} is hydrogen.

In one embodiment R^{6D} is hydrogen, halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, or (C₁-C₄)haloalkoxy.

In one embodiment R^{6D} is hydrogen.

In one embodiment B'' is (C₃-C₇)carbocyclyl, (C₃-C₇)carbocyclyl-(C₁-C₄)alkyl-, aryl, aryl-(C₁-C₄)alkyl-, heteroaryl, or heteroaryl-(C₁-C₄)alkyl-, wherein any (C₃-C₇)carbocyclyl, (C₃-C₇)carbocyclyl-(C₁-C₄)alkyl-, aryl, aryl-(C₁-C₄)alkyl-, heteroaryl, or heteroaryl-(C₁-C₄)alkyl- of B'' is optionally substituted with one or more Z¹ groups.

In one embodiment B'' is (C₃-C₇)carbocyclyl, aryl, aryl-(C₁-C₄)alkyl-, or heteroaryl wherein any (C₃-C₇)carbocyclyl, aryl, aryl-(C₁-C₄)alkyl-, or heteroaryl, of B'' is optionally substituted with one or more Z¹ groups.

In one embodiment B'' is (C₃-C₇)carbocyclyl, phenyl, phenyl-(C₁-C₄)alkyl-, or 5-6 membered heteroaryl wherein any (C₃-C₇)carbocyclyl, phenyl, phenyl-(C₁-C₄)alkyl-, or 5-6 membered heteroaryl of B'' is optionally substituted with one or more Z¹ groups.

In one embodiment B'' is (C₃-C₇)carbocyclyl, phenyl, phenyl-(C₁-C₄)alkyl-, or 5-6 membered heteroaryl wherein any (C₃-C₇)carbocyclyl, phenyl, phenyl-(C₁-C₄)alkyl-, or 5-6 membered heteroaryl of B'' is optionally substituted with one or more Z¹ groups.

In one embodiment B'' is (C₃-C₇)carbocyclyl, phenyl, phenyl-(C₁-C₄)alkyl-, or 6 membered heteroaryl wherein any (C₃-C₇)carbocyclyl, phenyl, phenyl-(C₁-C₄)alkyl-, or 6 membered heteroaryl of B'' is optionally substituted with one or more Z¹ groups.

In one embodiment B'' is (C₃-C₇)carbocyclyl, phenyl, phenyl-(CH₂)-, or pyridinyl wherein any phenyl, phenyl-(CH₂)-, or pyridinyl of B'' is optionally substituted with one or more Z¹ groups.

In one embodiment each Z¹ is independently halo, -OH, or (C₁-C₄)haloalkyl.

In one embodiment B'' is 4-fluorophenyl, cyclopropyl, benzyl, pyridin-4-yl, 4-hydroxyphenyl, or 4-trifluoromethylphenyl.

In one embodiment R^{1D} is (C₁-C₁₄)alkyl substituted with one or more groups independently selected from -NR^{b2}R^{c2} and wherein the (C₁-C₁₄)alkyl is optionally substituted with one or more (C₃-C₇)carbocyclyl.

In one embodiment R^{1D} is (C₂-C₁₀)alkyl substituted with one or more groups independently selected from -NR^{b2}R^{c2} and wherein the (C₂-C₁₀)alkyl is optionally substituted with one or more (C₃-C₇)carbocyclyl.

In one embodiment R^{1D} is (C₄-C₈)alkyl substituted with two or more groups independently selected from -NR^{b2}R^{c2}.

In one embodiment R^{b2} and R^{c2} are each hydrogen.

In one embodiment R^{1D} is a 4-7 membered monocyclic heterocyclyl-(C₁-C₄)alkyl-, wherein the 4-7 membered monocyclic heterocyclyl-(C₁-C₄)alkyl- is substituted with one or more groups independently selected from the group consisting of Z and -(C₁-C₆)alkyl substituted with one or more Z, wherein each Z is independently selected from the group consisting of

$-\text{NR}^{\text{b}3}\text{R}^{\text{c}3}$, $-\text{NHNH}_2$, $-\text{C}(=\text{NR}^{\text{a}3})(\text{NR}^{\text{b}3}\text{R}^{\text{c}3})$, $-\text{NR}^{\text{a}3}\text{C}(=\text{NR}^{\text{a}3})(\text{R}^{\text{d}3})$, and $-\text{NR}^{\text{a}3}\text{C}(=\text{NR}^{\text{a}3})(\text{NR}^{\text{b}3}\text{R}^{\text{c}3})$ and wherein the 4-7 membered monocyclic heterocyclyl-(C₁-C₄)alkyl- is optionally substituted with one or more (C₁-C₆)alkyl.

In one embodiment R^{1D} is a 4-7 membered monocyclic heterocyclyl-(C₁-C₄)alkyl-, wherein the 4-7 membered monocyclic heterocyclyl-(C₁-C₄)alkyl- is substituted with one or more groups independently selected from the group consisting of Z and (C₁-C₆)alkyl substituted with one or more Z, wherein each Z is independently $-\text{NR}^{\text{b}3}\text{R}^{\text{c}3}$ and wherein the 4-7 membered monocyclic heterocyclyl-(C₁-C₄)alkyl- is optionally substituted with one or more (C₁-C₆)alkyl.

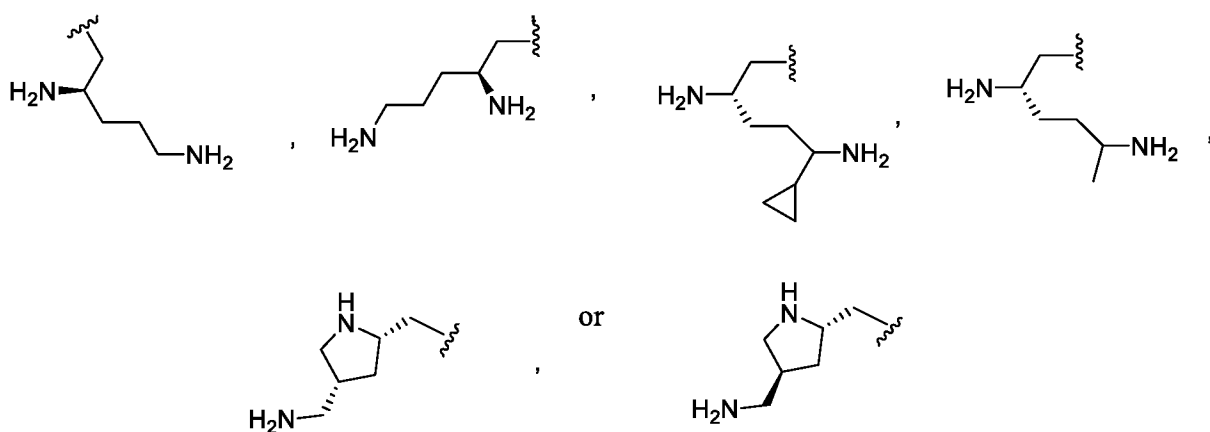
In one embodiment R^{1D} is pyrrolidinyl-(C₁-C₄)alkyl-, wherein the pyrrolidinyl-(C₁-C₄)alkyl- is substituted with one or more groups independently selected from the group consisting of Z and (C₁-C₆)alkyl substituted with one or more Z, wherein each Z is independently $-\text{NR}^{\text{b}3}\text{R}^{\text{c}3}$ and wherein the pyrrolidinyl-(C₁-C₄)alkyl- is optionally substituted independently with one or more (C₁-C₆)alkyl.

In one embodiment R^{1D} is pyrrolidinyl-(CH₂)-, wherein the pyrrolidinyl-(CH₂)- is substituted with one or more groups independently selected from the group consisting of Z and (C₁-C₆)alkyl substituted with one or more Z, wherein each Z is independently $-\text{NR}^{\text{b}3}\text{R}^{\text{c}3}$ and wherein the pyrrolidinyl-(CH₂)- is optionally substituted independently with one or more (C₁-C₆)alkyl.

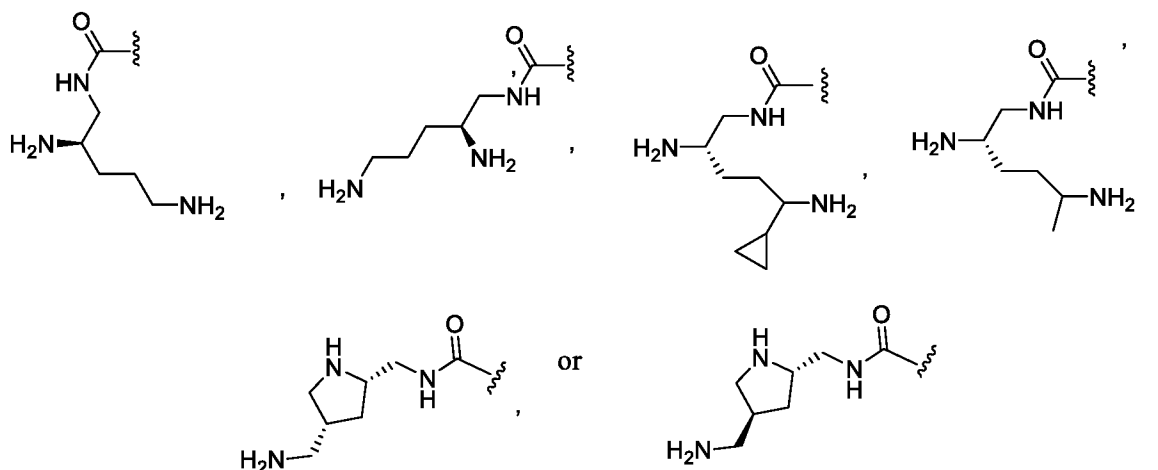
In one embodiment R^{1D} is pyrrolidinyl-(CH₂)-, wherein the pyrrolidinyl-(CH₂)- is substituted on the pyrrolidinyl with (C₁-C₆)alkyl substituted with one or more $-\text{NR}^{\text{b}3}\text{R}^{\text{c}3}$.

In one embodiment $\text{R}^{\text{b}3}$ and $\text{R}^{\text{c}3}$ are each hydrogen.

In one embodiment R^{1D} is:



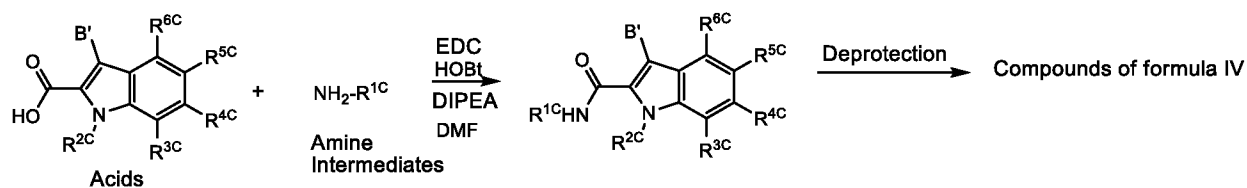
In one embodiment A'' is:



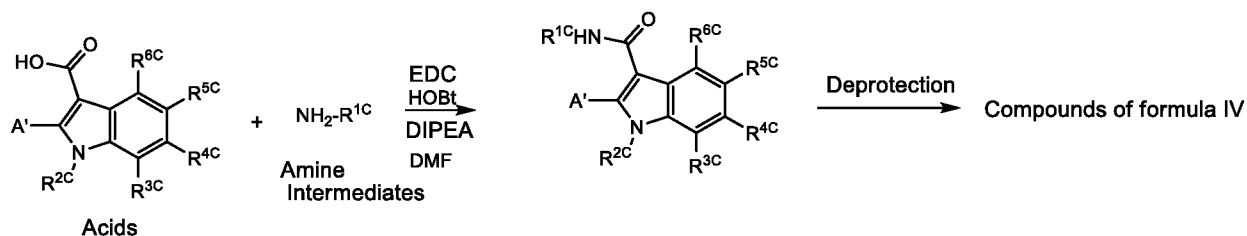
Generally, the bacterial efflux pump inhibitors discussed here can be prepared as illustrated in the following General Methods and Schemes as well as U.S. Patent Application Publication US2016/0271082 which document is hereby incorporated by reference in its entirety. It is understood that variable groups shown below (e.g., R) can represent the final corresponding groups present in a final compound or that these groups can represent groups that can be converted to the final corresponding groups present in a final compound at a convenient point in a synthetic sequence. For example, the variable groups can contain one or more protecting groups that can be removed at a convenient point in a synthetic sequence to provide the final corresponding groups in the final compound. The reagents and conditions shown are exemplary and non-limiting. Other reagents and conditions can be used in the general synthetic schemes.

Schemes 14, 15 and 16 illustrate some general methods for the preparation of substituted 1[H]-indole carboxamides.

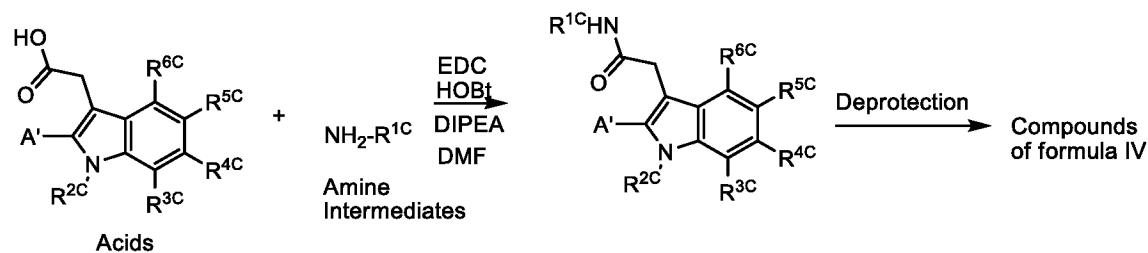
Scheme 14



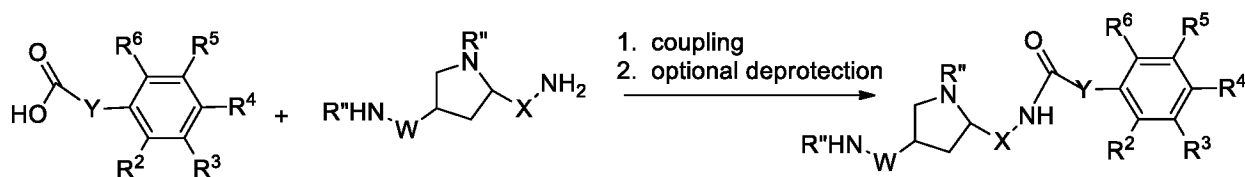
Scheme 15



Scheme 16



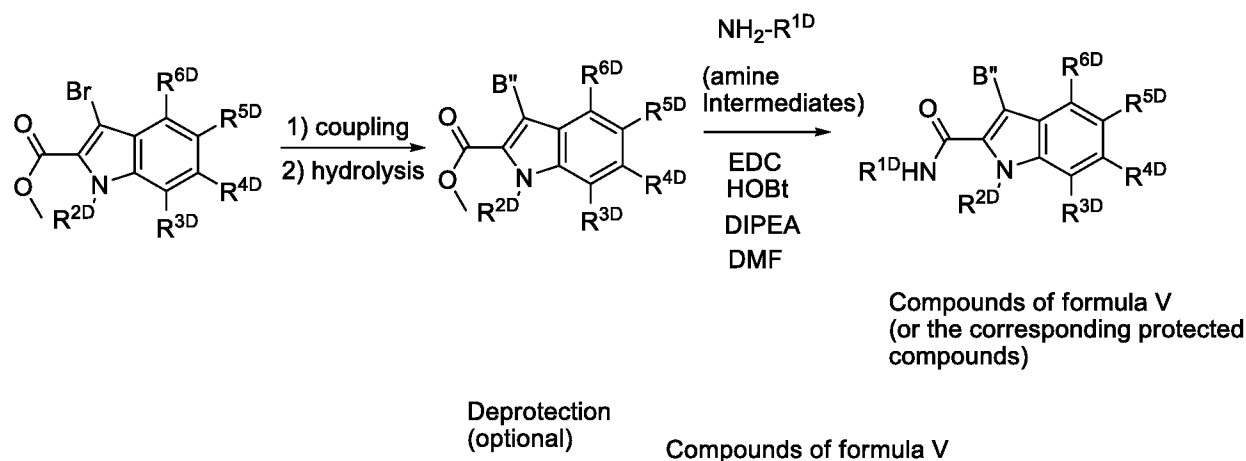
Scheme 17



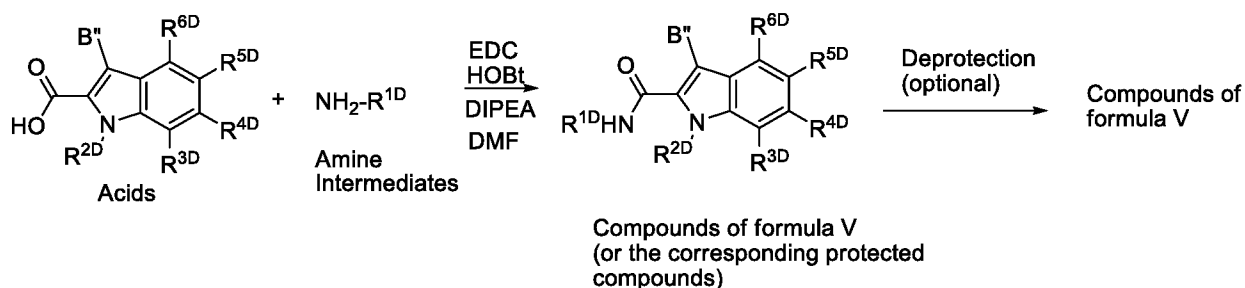
(each R'' is a protecting group, hydrogen or $(\text{C}_1\text{-C}_4)$ alkyl; W is a $-(\text{C}_1\text{-C}_6)$ alkyl or absent; X is $-(\text{C}_1\text{-C}_4)$ alkyl- or absent; and Y is a $-(\text{C}_1\text{-C}_3)$ alkyl- or absent)

Schemes 18 and 19 illustrate some general methods for the preparation of substituted indole carboxamide efflux pump inhibitors.

Scheme 18



Scheme 19



As used herein, the term “minimum inhibitory concentration (MIC)” refers to the lowest concentration of a compound (e.g., an antibiotic) that prevents visible growth of a bacterium. Assays for measuring the MIC of a compound are known in the art, for example, as described herein. As used herein, the term “intrinsic MIC” refers the MIC of a compound (e.g., an antibiotic) for the particular bacterial species that has not been pre-exposed to the compound.

As used herein, the term “sub-inhibitory concentration” refers to a concentration of the antibiotic that does not reduce the visible growth of the bacteria. In certain embodiments, the sub-inhibitory concentration is $\frac{1}{2} \times \text{MIC}$ of the antibiotic. In certain embodiments, the sub-inhibitory concentration of the antibiotic is a concentration that is capable of inducing the expression of one or more efflux pumps in the bacteria.

As used herein, the term “inhibitory concentration” refers to a concentration of the antibiotic that reduces the visible growth of the bacteria. In certain embodiments, this concentration is the intrinsic MIC of the antibiotic.

In certain embodiments the compound of formula I is an effective antibiotic when administered alone.

In certain embodiments, the combination of the compound of formula I and a bacterial efflux pump inhibitor is a synergistic combination.

In certain embodiments, the animal is a non-human animal. For example, in certain embodiments, the animal is a mouse.

5 An efflux pump inhibitor is a compound that interferes with the ability of an efflux pump to export a substrate. The inhibitor may have intrinsic antibacterial properties of its own. The compounds disclosed herein may be useful for treating bacterial infections (e.g., Gram-negative and Gram-positive) when administered with an bacterial efflux pump inhibitor.

In one embodiment the bacterial infection being treated is a Gram-negative bacterial strain infection. In one embodiment the Gram-negative bacterial strain is selected from the group consisting of *Acinetobacter baumannii*, *Acinetobacter calcoaceticus*, *Acinetobacter haemolyticus*, *Acinetobacter lwoffii*, *Actinobacillus actinomycetemcomitans*, *Aeromonas hydrophila*, *Aggregatibacter actinomycetemcomitans*, *Agrobacterium tumefaciens*, *Bacteroides distasonis*, *Bacteroides eggerthii*, *Bacteroides forsythus*, *Bacteroides fragilis*, *Bacteroides ovalis*, *Bacteroides splanchnicus*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Bordetella bronchiseptica*, *Bordetella parapertussis*, *Bordetella pertussis*, *Borrelia burgdorferi*, *Branhamella catarrhalis*, *Burkholderia cepacia*, *Campylobacter coli*, *Campylobacter fetus*, *Campylobacter jejuni*, *Caulobacter crescentus*, *Chlamydia trachomatis*, *Citrobacter diversus*, *Citrobacter freundii*, *Enterobacter aerogenes*, *Enterobacter asburiae*, *Enterobacter cloacae*, *Enterobacter sakazakii*, *Escherichia coli*, *Francisella tularensis*, *Fusobacterium nucleatum*, *Gardnerella vaginalis*, *Haemophilus ducreyi*, *Haemophilus haemolyticus*, *Haemophilus influenzae*, *Haemophilus parahaemolyticus*, *Haemophilus parainfluenzae*, *Helicobacter pylori*, *Kingella denitrificans*, *Kingella indologenes*, *Kingella kingae*, *Kingella oralis*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Klebsiella rhinoscleromatis*, *Legionella pneumophila*, *Listeria monocytogenes*, *Moraxella bovis*, *Moraxella catarrhalis*, *Moraxella lacunata*, *Morganella morganii*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Pantoea agglomerans*, *Pasteurella canis*, *Pasteurella haemolytica*, *Pasteurella multocida*, *Pasteurella tularensis*, *Porphyromonas gingivalis*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia alcalifaciens*, *Providencia rettgeri*, *Providencia stuartii*, *Pseudomonas acidovorans*, *Pseudomonas aeruginosa*, *Pseudomonas alcaligenes*, *Pseudomonas fluorescens*, *Pseudomonas putida*, *Salmonella enteritidis*, *Salmonella paratyphi*, *Salmonella typhi*, *Salmonella typhimurium*, *Serratia marcescens*, *Shigella dysenteriae*, *Shigella flexneri*, *Shigella sonnei*, *Stenotrophomonas maltophilia*, *Veillonella parvula*, *Vibrio cholerae*, *Vibrio parahaemolyticus*, *Yersinia enterocolitica*, *Yersinia intermedia*, *Yersinia pestis* and *Yersinia pseudotuberculosis*.

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In one embodiment the bacterial infection being treated is a Gram-positive bacterial strain infection. In one embodiment the Gram-positive bacterial strain is selected from the group consisting of *Actinomyces naeslundii*, *Actinomyces viscosus*, *Bacillus anthracis*, *Bacillus cereus*, *Bacillus subtilis*, *Clostridium difficile*, *Corynebacterium diphtheriae*, *Corynebacterium ulcerans*, *Enterococcus faecalis*, *Enterococcus faecium*, *Micrococcus luteus*, *Mycobacterium avium*, *Mycobacterium intracellulare*, *Mycobacterium leprae*, *Mycobacterium tuberculosis*, *Propionibacterium acnes*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Staphylococcus hominis*, *Staphylococcus hyicus*, *Staphylococcus intermedius*, *Staphylococcus saccharolyticus*, *Staphylococcus saprophyticus*, *Streptococcus agalactiae*, *Streptococcus mutans*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus salivarius* and *Streptococcus sanguis*.

In one embodiment, the animal is infected with *P. aeruginosa*.

In one embodiment, the animal is infected with *E. coli*.

In one embodiment, the animal is infected with *K. pneumoniae*.

In one embodiment, the animal is infected with *A. baumannii*.

The compositions can, if desired, also contain other active therapeutic agents, such as a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an anti-cancer, an antimicrobial (for example, an aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, a cephalosporin (e.g., cefepime), a fluoroquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an anti-psoriatic, a corticosteroid, an anabolic steroid, a diabetes-related agent, a mineral, a nutritional, a thyroid agent, a vitamin, a calcium-related hormone, an antidiarrheal, an anti-tussive, an anti-emetic, an anti-ulcer, a laxative, an anticoagulant, an erythropoietin (for example, epoetin alpha), a filgrastim (for example, G-CSF, Neupogen), a sargramostim (GM-CSF, Leukine), an immunization, an immunoglobulin, an immunosuppressive (for example, basiliximab, cyclosporine, daclizumab), a growth hormone, a hormone replacement drug, an estrogen receptor modulator, a mydriatic, a cycloplegic, an alkylating agent, an anti-metabolite, a mitotic inhibitor, a radiopharmaceutical, an anti-depressant, an anti-manic agent, an anti-psychotic, an anxiolytic, a hypnotic, a sympathomimetic, a stimulant, donepezil, tacrine, an asthma medication, a beta agonist, an inhaled steroid, a leukotriene inhibitor, a methylxanthine, a cromolyn, an epinephrine or analog thereof, dornase alpha (Pulmozyme), a cytokine, or any combination thereof.

It will be appreciated that compounds of the invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic,

optically-active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase.

When a bond in a compound formula herein is drawn in a non-stereochemical manner (e.g. flat), the atom to which the bond is attached includes all stereochemical possibilities. When a bond in a compound formula herein is drawn in a defined stereochemical manner (e.g. bold, bold-wedge, dashed or dashed-wedge), it is to be understood that the atom to which the stereochemical bond is attached is enriched in the absolute stereoisomer depicted unless otherwise noted. In one embodiment, the compound may be at least 51% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 60% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 80% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 90% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 95 the absolute stereoisomer depicted. In another embodiment, the compound may be at least 99% the absolute stereoisomer depicted.

It will also be appreciated by those skilled in the art that certain compounds of the invention can exist in more than one tautomeric form. For example, a substituent of formula -NH-C(=O)H in a compound of formula (I) could exist in tautomeric form as -N=C(OH)H. The present invention encompasses all tautomeric forms of a compound of formula I as well as mixtures thereof that can exist in equilibrium with non-charged and charged entities depending upon pH, which possess the useful properties described herein

In cases where compounds are sufficiently basic or acidic, a salt of a compound of formula I can be useful as an intermediate for isolating or purifying a compound of formula I. Additionally, administration of a compound of formula I as a pharmaceutically acceptable acid or base salt may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartrate, succinate, fumarate, benzoate, ascorbate, α -ketoglutarate, and α -glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts. Salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording the corresponding anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

Pharmaceutically suitable counterions include pharmaceutically suitable cations and pharmaceutically suitable anions that are well known in the art. Examples of pharmaceutically suitable anions include, but are not limited to those described above (e.g. physiologically acceptable anions) including Cl^- , Br^- , I^- , CH_3SO_3^- , H_2PO_4^- , CF_3SO_3^- , $p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_3^-$, citrate, tartrate, phosphate, malate, fumarate, formate, or acetate.

It will be appreciated by those skilled in the art that a compound of the invention comprising a counterion can be converted to a compound of the invention comprising a different counterion. Such a conversion can be accomplished using a variety of well-known techniques and materials including but not limited to ion exchange resins, ion exchange chromatography and selective crystallization.

The compounds of formula I can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, i.e., orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes. For oral administration the compounds can be formulated as a solid dosage form with or without an enteric coating.

Thus, the present compounds may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent, excipient or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may 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 should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 90% 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 will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the 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; a lubricant such as magnesium stearate; and 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 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 propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, 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, particles, and devices.

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

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, 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 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 action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, 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 the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the 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, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as

compositions or formulations, 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, nanoparticles, and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds 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 the affected area using pump-type or aerosol sprayers.

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.

Useful dosages of the compounds of formula I 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. Pat. No. 4,938,949.

The amount of the compound, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular 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 the attendant physician or clinician.

In general, however, a suitable dose will be in the range of from about 1 to about 500 mg/kg, e.g., from about 5 to about 400 mg/kg of body weight per day, such as 1 to about 250 mg per kilogram body weight of the recipient per day.

The compound is conveniently formulated in unit dosage form; for example, containing 5 to 500 mg, 10 to 400 mg, or 5 to 100 mg of active ingredient per unit dosage form. In one embodiment, the invention provides a composition comprising a compound of the invention formulated in such a unit dosage form.

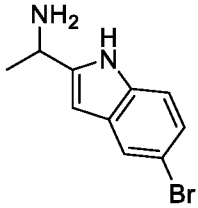
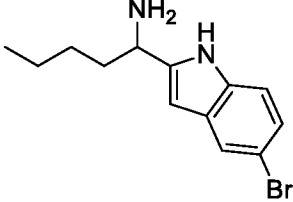
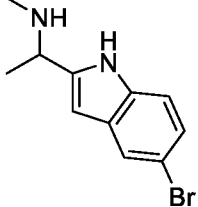
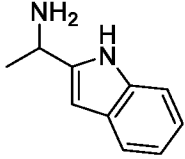
The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations.

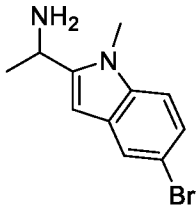
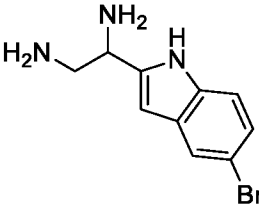
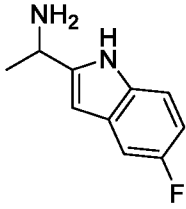
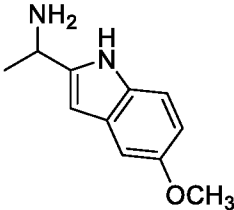
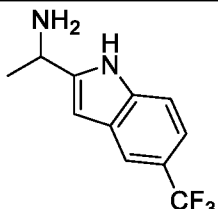
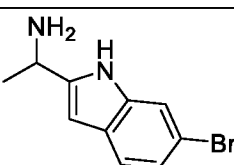
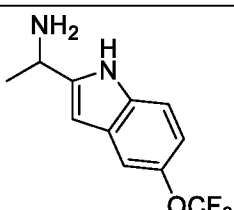
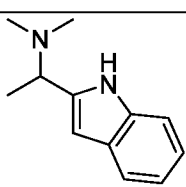
Co-administration of a compound disclosed herein with one or more other active therapeutic agents (e.g., antibacterial agents) generally refers to simultaneous or sequential

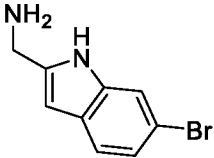
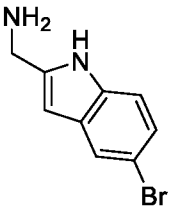
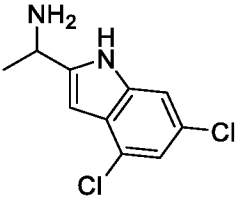
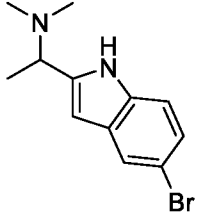
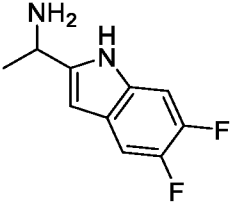
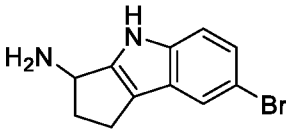
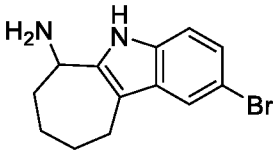
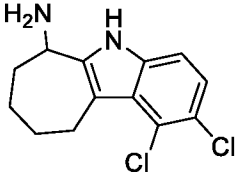
administration of a compound disclosed herein and one or more other active therapeutic agents, such that therapeutically effective amounts of disclosed herein and one or more other active therapeutic agents are both present in the body of the patient.

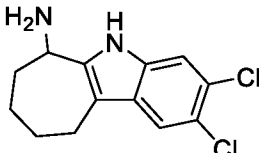
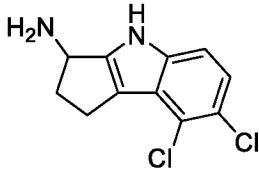
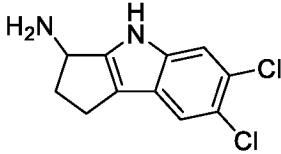
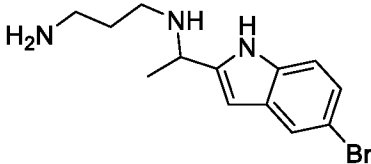
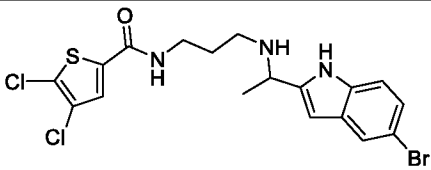
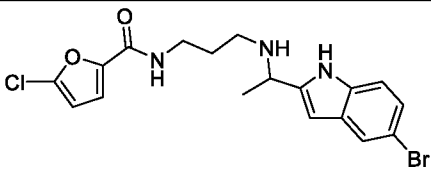
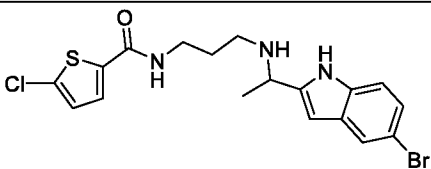
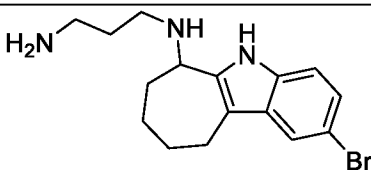
5 The ability of a compound to produce an antibiotic effect can be determined using a method as described in Example 11. Data for representative compounds used in combination with the bacterial efflux pump inhibitor (EPI) N-(((2S,4R)-4-(aminomethyl)pyrrolidin-2-yl)methyl)-6-(4-fluorophenyl)-1*H*-indole-2-carboxamide is shown in Table 1.

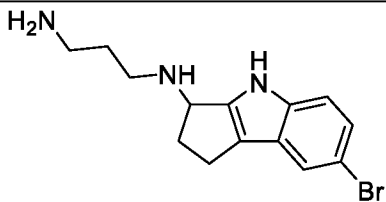
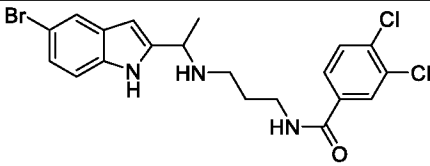
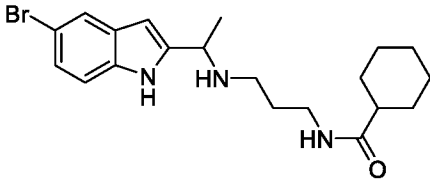
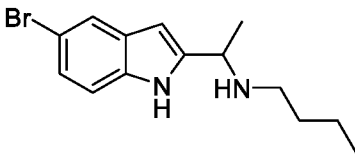
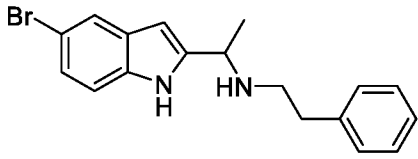
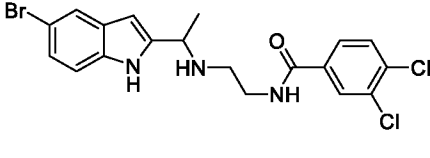
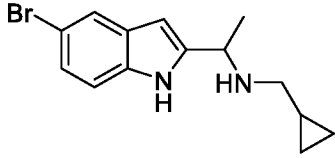
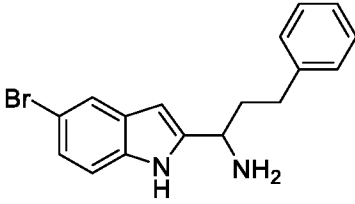
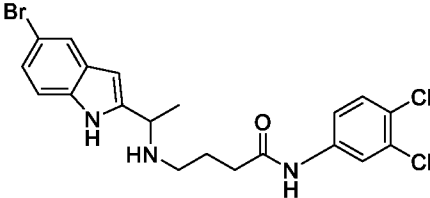
Table 1

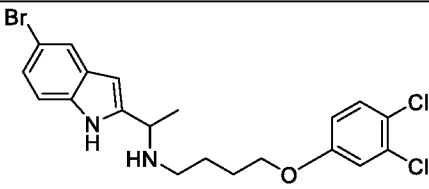
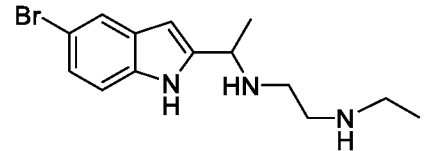
Example	Structure	MIC (wo EPI/ w EPI)	
		<i>P. Aeruginosa</i> PAO1	
		Intrinsic MIC	MIC in the Presence of EPI*
1		128	8
2		>256	64
3		>256	64
4		>256	128

5		>256	64
6		256	128
7		256	16
8		>256	256
9		>256	16
10		>256	32
11		>256	64
12		>256	256

13		64	16
14		128	8
15		256	16
16		256	64
17		256	8
18		128	2
19		128	4
20		32	1

21		256	32
22		32	1
23		64	8
24		64(128)	128
25		>256	16
26		>256	16
27		32(>256)	64
28		64(32)	32

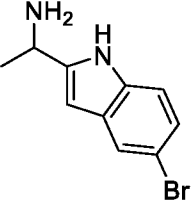
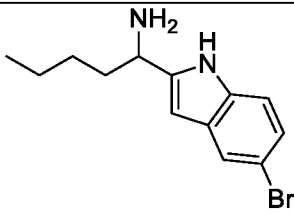
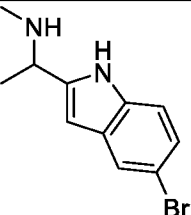
29		64(128)	128
30		>256	32
31		>256	128
32		>256	64
33		>256	32
34		>256	32
35		>256	256
36		>256	32
37		>256	16

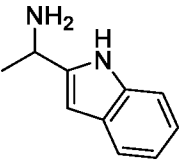
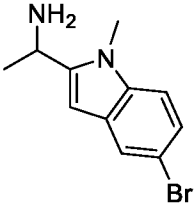
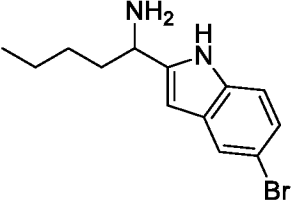
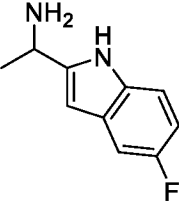
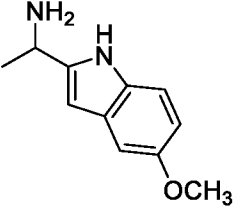
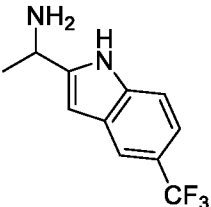
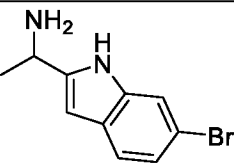
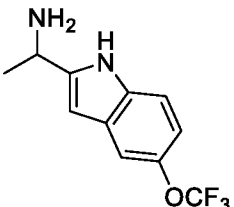
38		>256	16
39		>256	>256

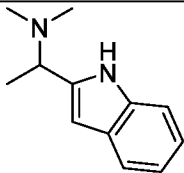
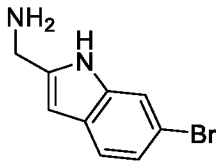
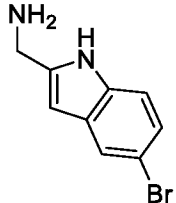
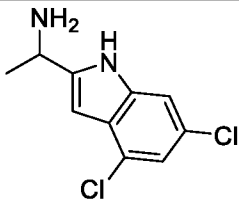
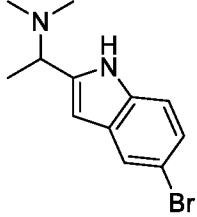
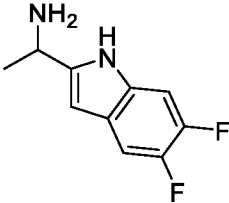
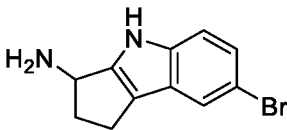
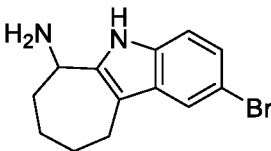
*In the presence of 12.5 µg/ml of N-(((2S,4R)-4-(aminomethyl)pyrrolidin-2-yl)methyl)-6-(4-fluorophenyl)-1H-indole-2-carboxamide.

- 5 The MICs obtained for representative compounds against *E. coli*, *K. pneumoniae* and *A. baumannii* are provided in Table 2.

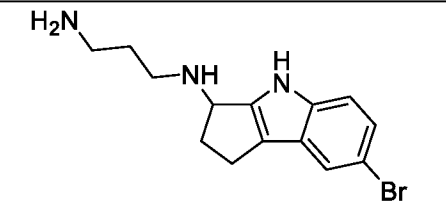
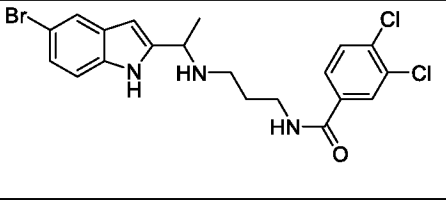
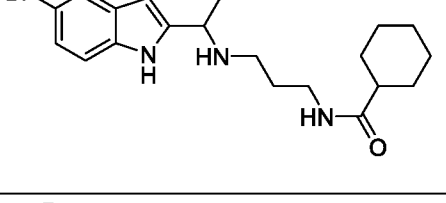
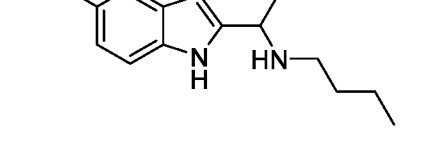
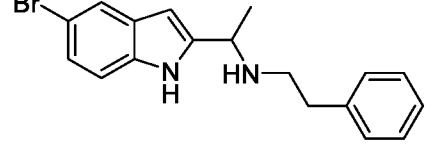
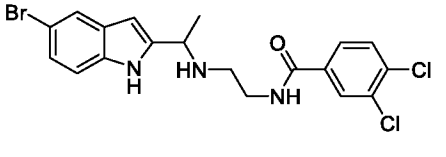
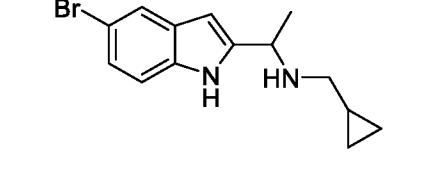
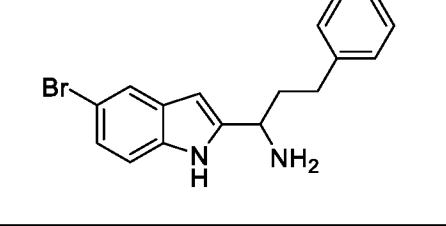
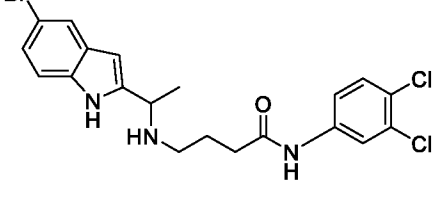
Table 2

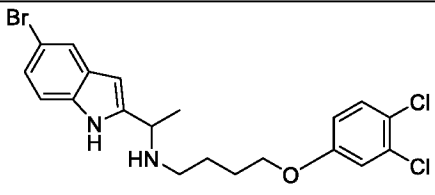
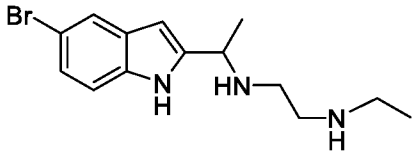
Example	Structure	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>A. baumannii</i>
		ATCC 25922	ATCC 10031	ATCC 19606
		Intrinsic MIC (ug/ml)		
1		128	64	128
2		16	16	32
3		256	128	64

4		>256	>256	>256
5		128	64	128
6		128	64	128
7		>256	>256	>256
8		>256	>256	256
9		128	64	64
10		256	128	128
11		128	64	64

12		>256	>256	>256
13		256	256	128
14		128	64	64
15		128	64	32
16		256	256	128
17		256	128	128
18		32	32	64
19		16	16	16

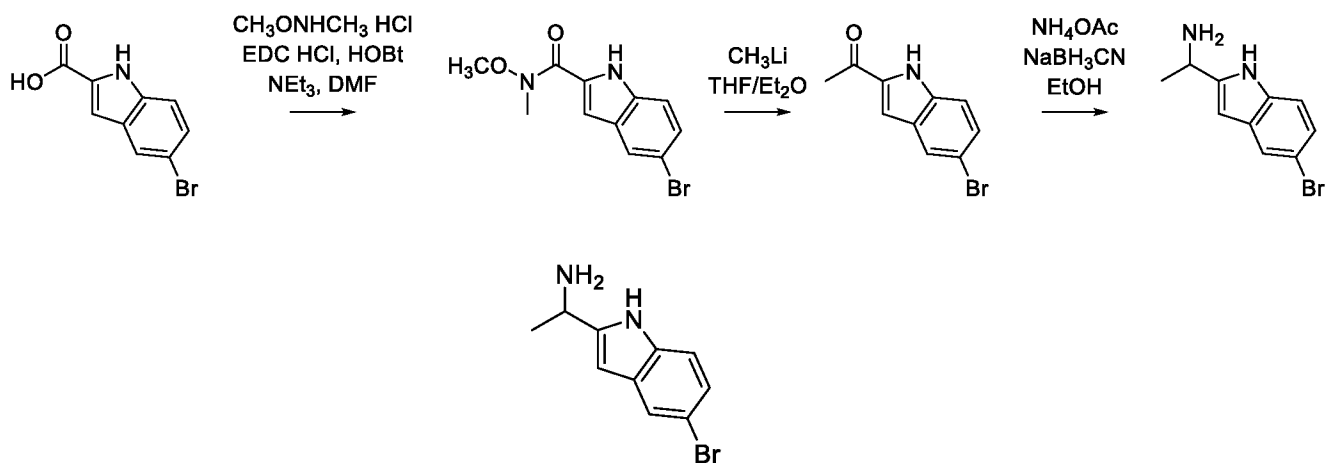
20		8	2	8
21		16	8	16
22		16	8	8
23		16	8	16
24		128	64	256
25		8	1	16
26		64	16	128
27		32	8	32
28		16	8	32

29		64	32	256
30		32	4	64
31		64	16	64
32		32	16	64
33		16	4	32
34		32	4	64
35		128	64	128
36		16	8	32
37		16	4	32

38		16	4	64
39		256	128	256

The invention will now be illustrated by the following non-limiting examples.

5 Example 1. Preparation of 1-(5-bromo-1*H*-indol-2-yl)ethan-1-amine.



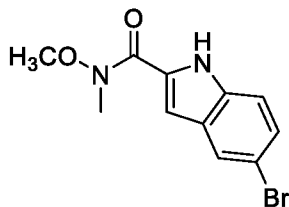
1-(5-Bromo-1*H*-indol-2-yl)ethan-1-amine

10 1-(5-Bromo-1*H*-indol-2-yl)ethan-1-one (95 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol) and sodium cyanoborohydride (126 mg, 2.00 mmol) were dissolved in ethanol (5 mL). The mixture was stirred for overnight at 60 °C. The reaction mixture was diluted with ethyl acetate. The organic layer was washed with 10% NaOH and brine, and it was dried over Na₂SO₄. The organic layer was concentrated under reduced pressure. The residue was purified

15 on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give the product as a yellow oil (32 mg, 33%); ¹H NMR (300 MHz) (DMSO-*d*₆) δ 11.07 (bs, 1H), 7.57 (d, *J* = 2 Hz, 1H), 7.24 (d, *J* = 9 Hz, 1H), 7.08 (dd, *J* = 8 Hz, *J* = 2 Hz, 1H), 6.18 (s, 1H), 4.11-4.04 (m, 1H), 1.34 (d, *J* = 7 Hz, 3H); LC/MS RT = 2.50 (M-H⁺: 237/239).

20 The requisite intermediate was prepared as follows:

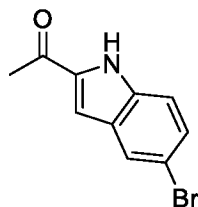
Step 1)



5-Bromo-N-methoxy-N-methyl-1*H*-indole-2-carboxamide

5-Bromo-1*H*-indole-2-carboxylic acid (1.0 g, 4.17 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (611 mg, 6.26 mmol), HOBt (563 mg, 4.17 mmol), EDC hydrochloride (1.68 g, 8.76 mmol) and triethylamine (2.32 mL, 16.68 mmol) were dissolved in anhydrous dimethylformamide (40 mL). The mixture was stirred for overnight at room temperature. The reaction mixture was diluted with ethyl acetate, and the organic layer was washed with water, saturated NH_4Cl , 10% NaOH and brine. The organic layer was dried over Na_2SO_4 , and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give product as a white solid (800 mg, 68%); ^1H NMR (300 MHz) (CDCl_3) δ 9.33 (bs, 1H), 7.83 (s, 1H), 7.38 (dd, $J = 9$ Hz, $J = 1$ Hz, 1H), 7.31 (d, $J = 9$ Hz, 1H), 7.15 (s, 1H), 3.85 (s, 3H), 3.43 (s, 3H).

Step 2)

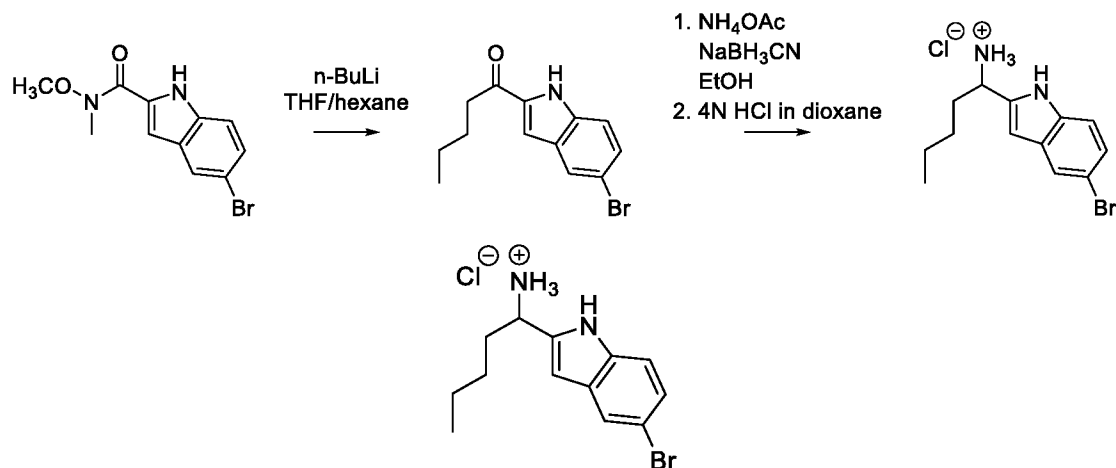


1-(5-Bromo-1*H*-indol-2-yl)ethan-1-one

5-Bromo-N-methoxy-N-methyl-1*H*-indole-2-carboxamide (600 mg, 2.12 mmol) was dissolved in anhydrous tetrahydrofuran (50 mL). The mixture was cooled to -78°C , and, then, a solution of 1.6 M methyllithium in diethyl ether (4.00 mL, 6.36 mmol) was added. The mixture was stirred for 2 hours at -78°C . An additional solution of 1.6 M methyllithium in diethyl ether (4.00 mL, 6.36 mmol) was added. The mixture was stirred for an hour at -78°C . The reaction was stopped by addition of water (10 mL). After removal of the solvent, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with saturated NH_4Cl and brine, and it was dried over Na_2SO_4 . The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give product as

a white solid (344 mg, 68%); ^1H NMR (300 MHz) (CDCl_3) δ 9.19 (bs, 1H), 7.85 (s, 1H), 7.42 (dd, $J = 9$ Hz, $J = 2$ Hz, 1H), 7.31 (d, $J = 8$ Hz, 1H), 7.12 (s, 1H), 2.60 (s, 3H).

Example 2. Preparation of 1-(5-bromo-1*H*-indol-2-yl)pentan-1-aminium chloride.

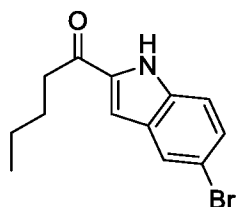


1-(5-Bromo-1*H*-indol-2-yl)pentan-1-aminium chloride

1-(5-Bromo-1*H*-indol-2-yl)pentan-1-one (100 mg, 0.36 mmol), ammonium acetate (277 mg, 3.60 mmol) and sodium cyanoborohydride (113 mg, 1.80 mmol) were dissolved in ethanol (5 mL). The mixture was stirred for overnight at 60 °C. The reaction mixture was diluted with ethyl acetate. The organic layer was washed with 10% NaOH and brine, and it was dried over Na_2SO_4 . The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH_4OH) to give crude 1-(5-bromo-1*H*-indol-2-yl)pentan-1-amine. The crude material was treated with 4N HCl in dioxane, and it was stirred for 15 min at 0 °C. After removal of solvent, it was suspended in ethyl acetate. The resulted suspension was filtered to give the product as a white solid (9 mg, 8%); ^1H NMR (300 MHz) ($\text{DMSO}-d_6$) δ 11.57 (bs, 1H), 8.56 (bs, 3H), 7.73 (s, 1H), 7.35 (d, $J = 9$ Hz, 1H), 7.20 (dd, $J = 8$ Hz, $J = 2$ Hz, 1H), 6.53 (s, 1H), 4.38-4.37 (m, 1H), 1.99-1.92 (m, 2H), 1.30-1.09 (m, 4H), 0.80 (t, $J = 7$ Hz, 3H); LC/MS RT = 2.74 (M-H $^+$:279/281).

The requisite intermediate was prepared as follows:

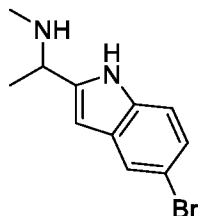
Step 1)



1-(5-Bromo-1*H*-indol-2-yl)pentan-1-one

5-Bromo-N-methoxy-N-methyl-1*H*-indole-2-carboxamide (200 mg, 0.71 mmol) was dissolved in anhydrous tetrahydrofuran (15 mL). The mixture was cooled to -78 °C, and, then, a solution of 2.5 M *n*-butyllithium in hexane (0.71 mL, 1.78 mmol) was added. The mixture was stirred for an hour at -78 °C. The reaction was stopped by addition of water (10 mL). After removal of the solvent, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with saturated NH₄Cl and brine, and it was dried over Na₂SO₄. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give product as a white solid (167 mg, 84%); ¹H NMR (300 MHz) (CDCl₃) δ 9.37 (bs, 1H), 7.84 (s, 1H), 7.42 (dd, *J* = 9 Hz, *J* = 1 Hz, 1H), 7.32 (d, *J* = 9 Hz, 1H), 7.12 (s, 1H), 2.97-2.92 (m, 2H), 1.79-1.72 (m, 2H), 1.47-1.39 (m, 2H), 0.99-0.93 (m, 3H).

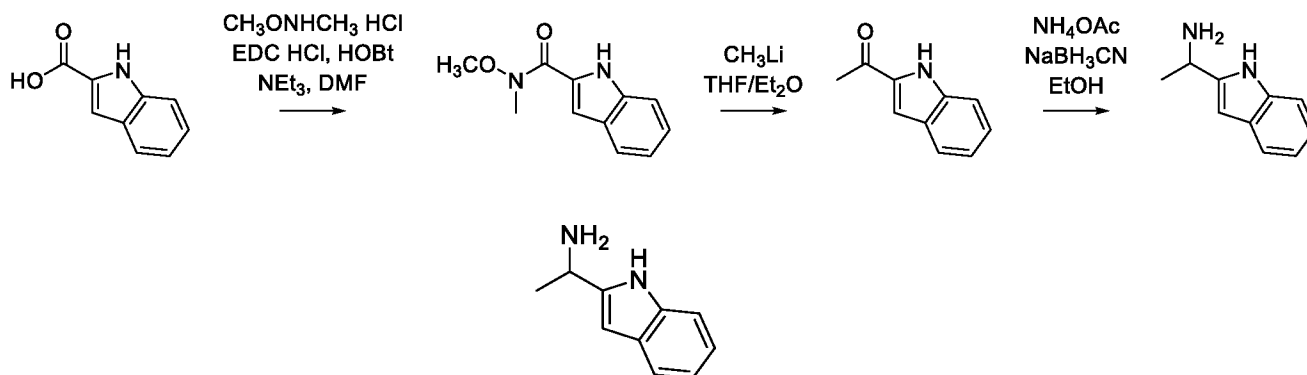
Example 3. Preparation of 1-(5-bromo-1*H*-indol-2-yl)-*N*-methylethan-1-amine.



15 1-(5-Bromo-1*H*-indol-2-yl)-*N*-methylethan-1-amine

To a mixture of 1-(5-bromo-1*H*-indol-2-yl)ethan-1-one (50 mg, 0.21 mmol) in ethanol (5 mL), a solution of 2.0 M methylamine in tetrahydrofuran (1.05 mL, 2.10 mmol) was added. The mixture was treated with catalytic amount of acetic acid, and it was stirred for an hour at 60 °C. Then, the mixture was treated with sodium cyanoborohydride (66 mg, 1.05 mmol), and it was stirred for overnight at 60 °C. The reaction mixture was acidified with 6N HCl, and it was washed with ethyl acetate. Then, the aqueous layer was basified with NaOH, and it was extracted with ethyl acetate. The organic layer was washed with brine, and it was dried over Na₂SO₄. The organic layer was concentrated under reduced pressure, and the residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give the product as a colorless oil (53 mg, 100%); ¹H NMR (300 MHz) (CDCl₃) δ 9.79 (bs, 1H), 7.67 (s, 1H), 7.27-7.26 (m, 2H), 6.41 (s, 1H), 4.35-4.32 (m, 1H), 2.43 (s, 3H), 1.71 (d, *J* = 7 Hz, 3H); LC/MS RT = 2.60 (M-H⁺: 251/253).

Example 4. Preparation of 1-(1*H*-indol-2-yl)ethan-1-amine.

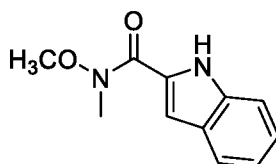
1-(1*H*-Indol-2-yl)ethan-1-amine

5 1-(1*H*-Indol-2-yl)ethan-1-one (100 mg, 0.63 mmol), ammonium acetate (486 mg, 6.30 mmol) and sodium cyanoborohydride (198 mg, 3.15 mmol) were dissolved in ethanol (10 mL). The mixture was stirred for overnight at 60 °C. The reaction mixture was diluted with ethyl acetate. The organic layer was washed with 10% NaOH and brine, and it was dried over Na₂SO₄. The organic layer was concentrated under reduced pressure. The residue was purified
 10 on an ISCO chromatograph (100% dichloromethane followed by 10% methanol/dichloromethane + 0.1% NH₄OH) to give the product as a colorless oil (85 mg, 84%); ¹H NMR (300 MHz) (CD₃OD) δ 7.44 (d, *J* = 8 Hz, 1H), 7.29 (d, *J* = 8 Hz, 1H), 7.03 (t, *J* = 8 Hz, 1H), 6.94 (t, *J* = 7 Hz, 1H), 6.29 (s, 1H), 4.24-4.17 (m, 1H), 1.51 (d, *J* = 7 Hz, 3H); LC/MS RT = 2.19 (M-H⁺: 159).

15

The requisite intermediate was prepared as follows:

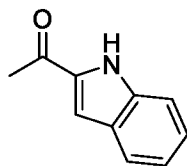
Step 1)

20 N-Methoxy-N-methyl-1*H*-indole-2-carboxamide

1*H*-Indole-2-carboxylic acid (1.0 g, 6.21 mmol), N,O-dimethylhydroxylamine hydrochloride (909 mg, 9.32 mmol), HOBT (839 mg, 6.21 mmol), EDC hydrochloride (2.5 g, 13.04 mmol) and triethylamine (3.46 mL, 24.84 mmol) were dissolved in anhydrous
 25 dimethylformamide (40 mL). The mixture was stirred for overnight at room temperature. The reaction mixture was diluted with ethyl acetate, and the organic layer was washed with water, saturated NH₄Cl, 10% NaOH and brine. The organic layer was dried over Na₂SO₄, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-

30% ethyl acetate/hexane) to give product as a white solid (450 mg, 35%); ^1H NMR (300 MHz) (CDCl_3) δ 9.30 (bs, 1H), 7.70 (d, $J = 8$ Hz, 1H), 7.44 (d, $J = 8$ Hz, 1H), 7.31 (t, $J = 8$ Hz, 1H), 7.25 (s, 1H), 7.14 (t, $J = 8$ Hz, 1H), 3.85 (s, 3H), 3.44 (s, 3H).

5 Step 2)

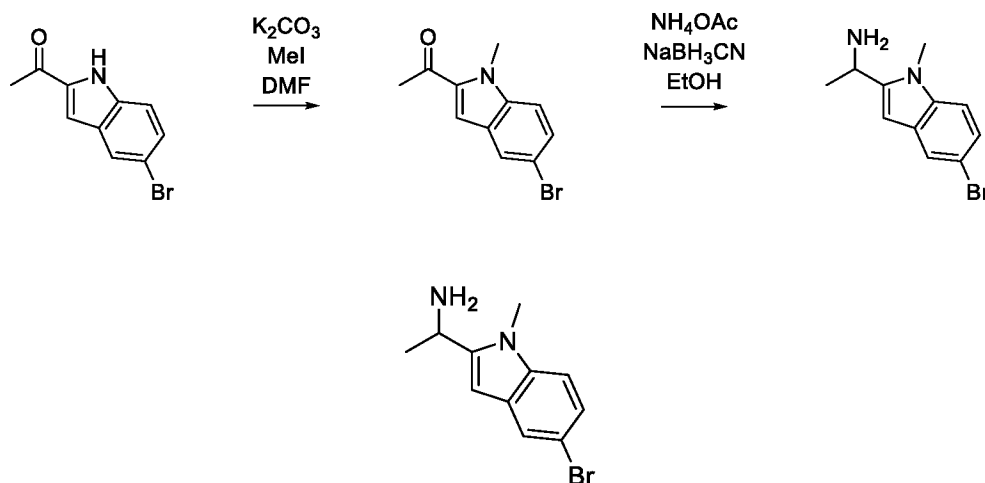


1-(1*H*-Indol-2-yl)ethan-1-one

N-Methoxy-N-methyl-1*H*-indole-2-carboxamide (450 mg, 2.20 mmol) was dissolved in anhydrous tetrahydrofuran (50 mL). The mixture was cooled to -78°C , and, then, a solution of 1.6 M methyllithium in diethyl ether (4.13 mL, 6.60 mmol) was added. The mixture was stirred for 2 hours at -78°C . An additional solution of 1.6 M methyllithium in diethyl ether (4.13 mL, 6.60 mmol) was added. The mixture was stirred for an hour at -78°C . The reaction was stopped by addition of water (10 mL). After removal of the solvent, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with saturated NH_4Cl and brine, and it was dried over Na_2SO_4 . The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give product as a white solid (290 mg, 83%); ^1H NMR (300 MHz) (CDCl_3) δ 9.37 (bs, 1H), 7.72 (d, $J = 8$ Hz, 1H), 7.45 (d, $J = 8$ Hz, 1H), 7.38-7.33 (m, 1H), 7.22-7.14 (m, 2H), 2.62 (s, 3H).

20

Example 5. Preparation of 1-(5-bromo-1-methyl-1*H*-indol-2-yl)ethan-1-amine.



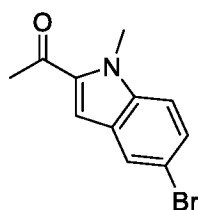
25

1-(5-Bromo-1-methyl-1*H*-indol-2-yl)ethan-1-amine

1-(5-Bromo-1-methyl-1*H*-indol-2-yl)ethan-1-one (91 mg, 0.36 mmol), ammonium acetate (277 mg, 3.60 mmol) and sodium cyanoborohydride (113 mg, 1.80 mmol) were dissolved in ethanol (10 mL). Then, catalytic amount of acetic acid was added. The mixture was stirred for overnight at 60 °C. The reaction mixture was diluted with ethyl acetate. The organic layer was washed with 10% NaOH and brine, and it was dried over Na₂SO₄. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give the product as a white solid (57 mg, 63%); ¹H NMR (300 MHz) (CD₃OD) δ 7.62 (d, *J* = 2 Hz, 1H), 7.28 (d, *J* = 9 Hz, 1H), 7.21 (dd, *J* = 9 Hz, *J* = 2 Hz, 1H), 6.44 (s, 1H), 4.44-4.38 (m, 1H), 3.75 (s, 3H), 1.56 (d, *J* = 7 Hz, 3H); LC/MS RT = 2.49 (M-NH₂⁺:236/238).

The requisite intermediate was prepared as follows:

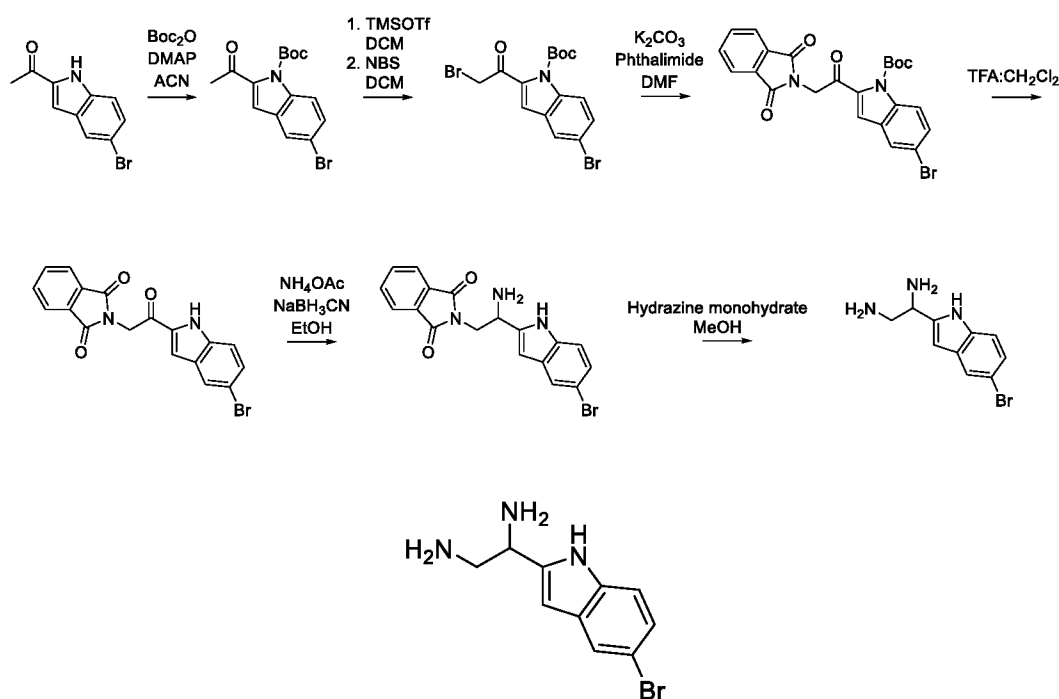
Step 1)



1-(5-Bromo-1-methyl-1*H*-indol-2-yl)ethan-1-one

1-(5-Bromo-1*H*-indol-2-yl)ethan-1-one (100 mg, 0.42 mmol), K₂CO₃ (116 mg, 0.84 mmol) and methyl iodide (52 μL, 0.84 mmol) were dissolved in anhydrous dimethylformamide (5 mL). The mixture was stirred for 3 hours at 60 °C. After the mixture was cooled to room temperature, it was diluted with ethyl acetate. The organic layer was washed with water and brine, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give product as a white solid (91 mg, 86%); ¹H NMR (300 MHz) (CDCl₃) δ 7.82 (d, *J* = 2 Hz, 1H), 7.45 (dd, *J* = 9 Hz, *J* = 2 Hz, 1H), 7.27 (d, *J* = 9 Hz, 1H), 7.20 (s, 1H), 4.05 (s, 3H), 2.61 (s, 3H).

Example 6. Preparation of 1-(5-bromo-1*H*-indol-2-yl)ethane-1,2-diamine.

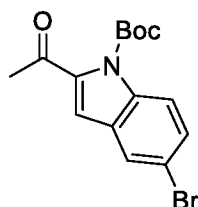


1-(5-Bromo-1*H*-indol-2-yl)ethane-1,2-diamine

2-(2-Amino-2-(5-bromo-1*H*-indol-2-yl)ethyl)isoindoline-1,3-dione (45 mg, 0.12 mmol) and hydrazine monohydrate were dissolved in methanol (5 mL), and it was stirred for overnight at room temperature. The mixture was then refluxed for an hour. The resulted suspension was filtered, and it was excessively washed with methanol. The filtrate was concentrated under reduced pressure, and it was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH_4OH) to give product as a colorless oil (15 mg, 50%); ^1H NMR (300 MHz) (CD_3OD) δ 7.61 (d, $J = 2$ Hz, 1H), 7.24 (d, $J = 8$ Hz, 1H), 7.15 (dd, $J = 8$ Hz, $J = 2$ Hz, 1H), 6.35 (s, 1H), 4.08-4.07 (m, 1H), 3.02 (d, $J = 6$ Hz, 1H), 2.95 (d, $J = 7$ Hz, 1H); LC/MS RT = 2.05 (M-H $^+$: 252/254).

The requisite intermediate was prepared as follows:

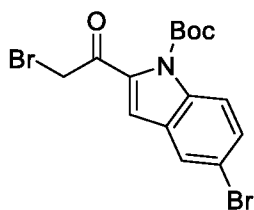
Step 1)



t-Butyl 2-acetyl-5-bromo-1*H*-indole-1-carboxylate

1-(5-Bromo-1*H*-indol-2-yl)ethan-1-one (200 mg, 0.84 mmol), Boc anhydride (367 mg, 1.68 mmol) and DMAP (103 mg, 0.84 mmol) were dissolved in acetonitrile, and it was stirred for 3 hours at room temperature. The reaction mixture was diluted with ethyl acetate, and it was washed with saturated NH₄Cl and brine. The organic layer was dried over Na₂SO₄, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give the product as a colorless oil (219 mg, 77%); ¹H NMR (300 MHz) (CDCl₃) δ 7.93 (d, *J* = 10 Hz, 1H), 7.75 (d, *J* = 2 Hz, 1H), 7.50 (dd, *J* = 9 Hz, *J* = 2 Hz, 1H), 6.97 (s, 1H), 2.56 (s, 3H), 1.62 (s, 9H).

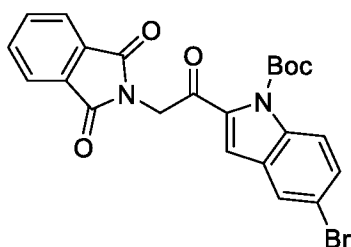
Step 2)



t-Butyl 5-bromo-2-(2-bromoacetyl)-1*H*-indole-1-carboxylate

t-Butyl 2-acetyl-5-bromo-1*H*-indole-1-carboxylate (215 mg, 0.64 mmol), triethylamine (0.45 mL, 3.2 mmol) and trimethylsilyl trifluoromethanesulfonate (0.23 mL, 1.28 mmol) were dissolved in dichloromethane (10 mL), and it was stirred for an hour at 0 °C. The reaction mixture was then diluted with ethyl acetate, and it was washed with saturated NaHCO₃ and brine. The organic layer was dried over Na₂SO₄, and it was concentrated under reduced pressure. The residue was dissolved in dichloromethane (10 mL), and N-bromosuccinimide (114 mg, 0.64) was added at 0 °C. The mixture was stirred for an hour at the temperature. The reaction mixture was then diluted with ethyl acetate, and it was washed with saturated NaHCO₃ and brine. The organic layer was dried over Na₂SO₄, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give the product as a colorless oil (169 mg, 63%); ¹H NMR (300 MHz) (CDCl₃) δ 7.94 (d, *J* = 9 Hz, 1H), 7.77 (d, *J* = 2 Hz, 1H), 7.53 (dd, *J* = 9 Hz, *J* = 2 Hz, 1H), 7.03 (s, 1H), 4.35 (s, 2H), 1.62 (s, 9H).

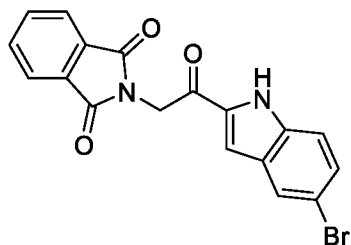
Step 3)



t-Butyl 5-bromo-2-(2-(1,3-dioxoisindolin-2-yl)acetyl)-1*H*-indole-1-carboxylate

To a solution of phthalimide (63 mg, 0.43 mmol) and K₂CO₃ (62 mg, 0.45 mmol) in anhydrous dimethylformamide (10 mL), *t*-butyl 5-bromo-2-(2-bromoacetyl)-1*H*-indole-1-carboxylate (169 mg, 0.41 mmol) was added. The mixture was stirred for 2 hours at room temperature. The reaction mixture was then diluted with ethyl acetate, and it was washed with water and brine. The organic layer was dried over Na₂SO₄, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give the product as a yellow oil (165 mg, 83%); ¹H NMR (300 MHz) (CDCl₃) δ 7.99-7.95 (m, 1H), 7.92-7.87 (m, 2H), 7.79-7.73 (m, 3H), 7.52 (dd, *J* = 9 Hz, *J* = 2 Hz, 1H), 7.27 (s, 1H), 4.97 (s, 2H), 1.58 (s, 9H).

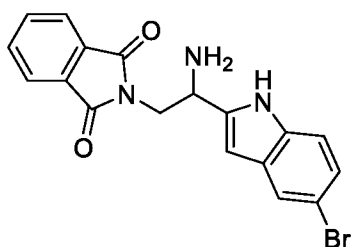
Step 4)



2-(2-(5-bromo-1*H*-indol-2-yl)-2-oxoethyl)isoindoline-1,3-dione

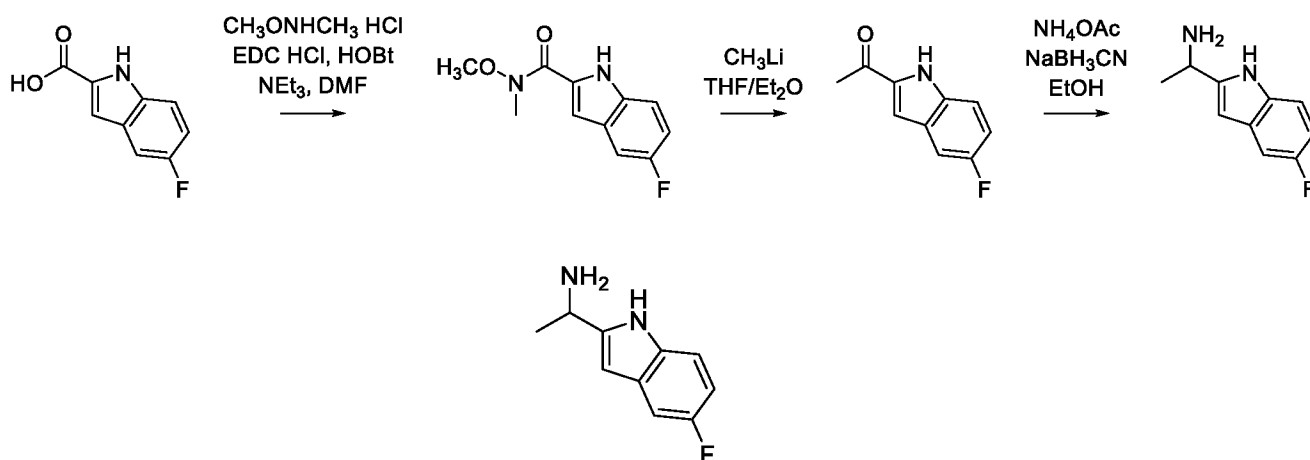
t-Butyl 5-bromo-2-(2-(1,3-dioxoisindolin-2-yl)acetyl)-1*H*-indole-1-carboxylate (165 mg, 0.34 mmol) was dissolved in a mixture of trifluoroacetic acid (1 mL) and dichloromethane (5 mL), and it was stirred for an hour at room temperature. After removal of solvent, it was diluted with ethyl acetate. The organic layer was washed with 10% NaOH and brine, and it was dried over Na₂SO₄. The organic layer was concentrated under reduced pressure, and the residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give the product as a white solid (130 mg, 100%); ¹H NMR (300 MHz) (DMSO-*d*₆) δ 12.13 (bs, 1H), 7.97-7.88 (m, 7H), 7.62 (s, 1H), 5.16 (s, 2H).

Step 5)

2-(2-Amino-2-(5-bromo-1*H*-indol-2-yl)ethyl)isoindoline-1,3-dione

2-(2-(5-Bromo-1*H*-indol-2-yl)-2-oxoethyl)isoindoline-1,3-dione (130 mg, 0.34 mmol), ammonium acetate (262 mg, 3.40 mmol) and sodium cyanoborohydride (107 mg, 1.70 mmol) were dissolved in ethanol (10 mL). The mixture was stirred for overnight at 60°C. The reaction mixture was diluted with ethyl acetate. The organic layer was washed with 10% NaOH and brine, and it was dried over Na₂SO₄. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give the product as a yellow oil 50 mg, 38%); ¹H NMR (300 MHz) (CDCl₃) δ 7.91 (bs, 1H), 7.82-7.79 (m, 2H), 7.72-7.69 (m, 2H), 7.62 (s, 1H), 7.26-7.22 (m, 2H), 6.43 (s, 1H), 4.73-4.69 (m, 1H), 4.13-4.03 (m, 2H).

Example 7. Preparation of 1-(5-fluoro-1*H*-indol-2-yl)ethan-1-amine.

1-(5-Fluoro-1*H*-indol-2-yl)ethan-1-amine

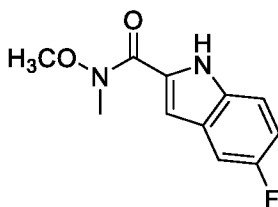
1-(5-Fluoro-1*H*-indol-2-yl)ethan-1-one (100 mg, 0.56 mmol), ammonium acetate (432 mg, 5.60 mmol) and sodium cyanoborohydride (176 mg, 2.80 mmol) were dissolved in ethanol (10 mL). The mixture was stirred for overnight at 60 °C. The reaction mixture was acidified with 6N HCl, and it was washed with ethyl acetate. Then, the aqueous layer was basified with NaOH, and it was extracted with ethyl acetate. The organic layer was washed with brine, and it was dried over Na₂SO₄. The organic layer was concentrated under reduced pressure, and the

residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give the product as a white solid (61 mg, 60%); ¹H NMR (300 MHz) (CD₃OD) δ 7.25-7.21 (m, 1H), 7.10 (d, *J* = 8 Hz, 1H), 6.79 (t, *J* = 8 Hz, 1H), 6.28 (s, 1H), 4.22-4.17 (m, 1H), 1.49 (d, *J* = 6 Hz, 3H); LC/MS RT = 2.33 (M-H⁺: 177).

5

The requisite intermediate was prepared as follows:

Step 1)



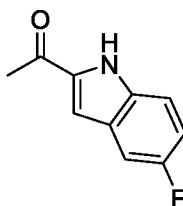
10

5-Fluoro-N-methoxy-N-methyl-1*H*-indole-2-carboxamide

5-Fluoro-1*H*-indole-2-carboxylic acid (1.0 g, 5.58 mmol), N, O-dimethylhydroxylamine hydrochloride (816 mg, 8.37 mmol), HOBt (754 mg, 5.58 mmol), EDC hydrochloride (2.25 g, 11.7 mmol) and triethylamine (3.11 mL, 22.3 mmol) were dissolved in anhydrous dimethylformamide (50 mL). The mixture was stirred for overnight at room temperature. The reaction mixture was diluted with ethyl acetate, and the organic layer was washed with water, saturated NH₄Cl, 10% NaOH and brine. The organic layer was dried over Na₂SO₄, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give product as a white solid (770 mg, 62%); ¹H NMR (300 MHz) (CDCl₃) δ 9.94 (bs, 1H), 7.41-7.36 (m, 1H), 7.32 (dd, *J* = 9 Hz, *J* = 2 Hz, 1H), 7.19 (s, 1H), 7.06 (td, *J* = 9 Hz, *J* = 3 Hz, 1H), 3.85 (s, 3H), 3.46 (s, 3H).

20

Step 2)



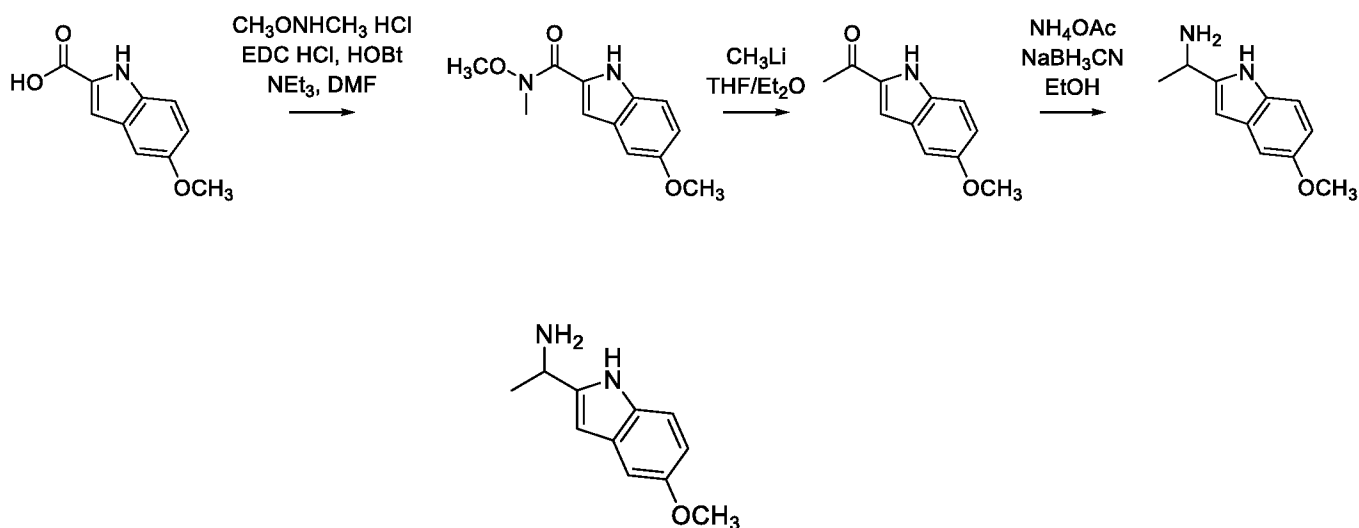
25

1-(5-Fluoro-1*H*-indol-2-yl)ethan-1-one

5-Fluoro-N-methoxy-N-methyl-1*H*-indole-2-carboxamide (300 mg, 1.35 mmol) was dissolved in anhydrous tetrahydrofuran (25 mL). The mixture was cooled to -78 °C, and, then, a

solution of 1.6 M methyllithium in diethyl ether (2.53 mL, 4.05 mmol) was added. The mixture was stirred for 2 hours at -78 °C. The reaction was stopped by addition of water (10 mL). After removal of the solvent, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with saturated NH₄Cl and brine, and it was dried over Na₂SO₄. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give product as a white solid (220 mg, 92%); ¹H NMR (300 MHz) (CDCl₃) δ 9.18 (bs, 1H), 7.39-7.32 (m, 2H), 7.16-7.08 (m, 2H), 2.60 (s, 3H).

Example 8. Preparation of 1-(5-methoxy-1*H*-indol-2-yl)ethan-1-amine.

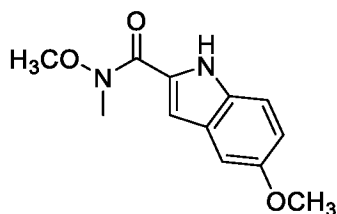


1-(5-Methoxy-1*H*-indol-2-yl)ethan-1-amine

1-(5-Methoxy-1*H*-indol-2-yl)ethan-1-one (100 mg, 0.42 mmol), ammonium acetate (324 mg, 4.20 mmol) and sodium cyanoborohydride (132 mg, 2.10 mmol) were dissolved in ethanol (10 mL). The mixture was stirred for overnight at 60 °C. The reaction mixture was acidified with 6N HCl, and it was washed with ethyl acetate. Then, the aqueous layer was basified with NaOH, and it was extracted with ethyl acetate. The organic layer was washed with brine, and it was dried over Na₂SO₄. The organic layer was concentrated under reduced pressure, and the residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give the product as a white solid (58 mg, 58%); ¹H NMR (300 MHz) (DMSO-d₆) δ 10.66 (bs, 1H), 7.15 (d, *J* = 9 Hz, 1H), 6.90 (d, *J* = 2 Hz, 1H), 6.61 (dd, *J* = 9 Hz, *J* = 2 Hz, 1H), 6.09 (s, 1H), 4.08-4.02 (m, 1H), 3.69 (s, 3H), 1.33 (d, *J* = 6 Hz, 3H); LC/MS RT = 2.17 (M-H⁺: 189).

The requisite intermediate was prepared as follows:

Step 1)



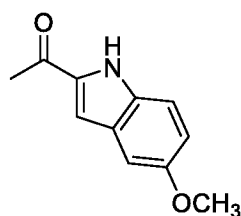
N,5-Dimethoxy-N-methyl-1*H*-indole-2-carboxamide

5

5-Methoxy-1*H*-indole-2-carboxylic acid (1.0 g, 5.23 mmol), N, O-dimethylhydroxylamine hydrochloride (766 mg, 7.85 mmol), HOBt (707 mg, 5.23 mmol), EDC hydrochloride (2.10 g, 10.98 mmol) and triethylamine (2.92 mL, 20.92 mmol) were dissolved in anhydrous dimethylformamide (50 mL). The mixture was stirred for overnight at room temperature. The reaction mixture was diluted with ethyl acetate, and the organic layer was washed with water, saturated NH₄Cl, 10% NaOH and brine. The organic layer was dried over Na₂SO₄, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give product as a white solid (743 mg, 60%); ¹H NMR (300 MHz) (CDCl₃) δ 9.78 (bs, 1H), 7.35 (d, *J* = 9 Hz, 1H), 7.17 (s, 1H), 7.1 (d, *J* = 2 Hz, 1H), 6.98 (dd, *J* = 9 Hz, *J* = 2 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.46 (s, 3H).

15

Step 2)



1-(5-Methoxy-1*H*-indol-2-yl)ethan-1-one

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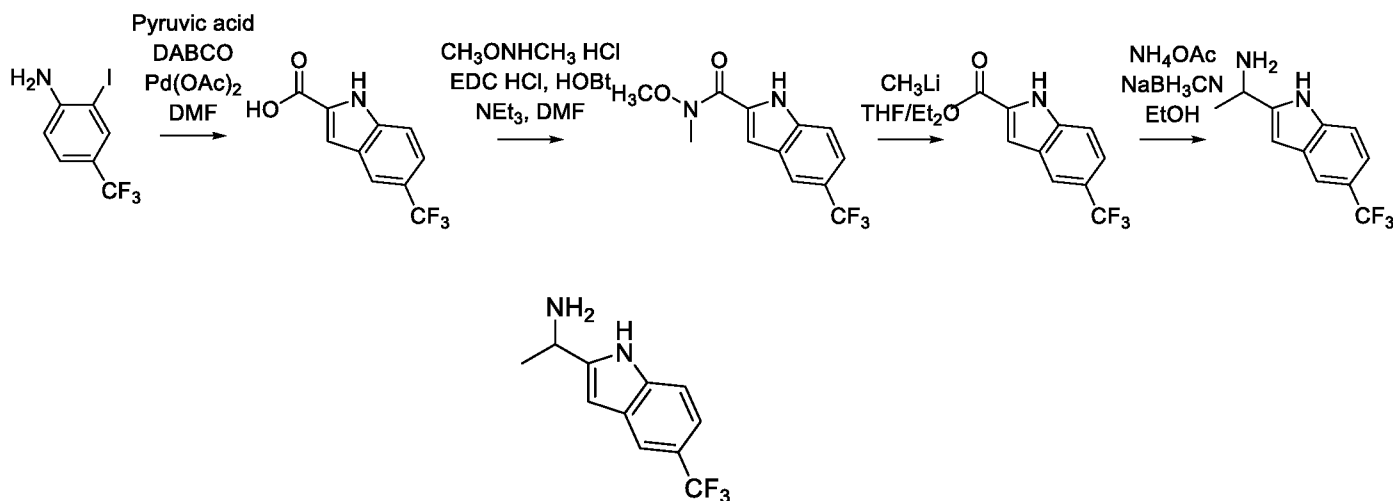
N,5-Dimethoxy-N-methyl-1*H*-indole-2-carboxamide (300 mg, 1.28 mmol) was dissolved in anhydrous tetrahydrofuran (20 mL). The mixture was cooled to -78°C, and, then, a solution of 1.6 M methyllithium in diethyl ether (2.40 mL, 3.84 mmol) was added. The mixture was stirred for 2 hours at -78°C. The reaction was stopped by addition of water (10 mL). After removal of the solvent, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with saturated NH₄Cl and brine, and it was dried over Na₂SO₄. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give product as a white solid (180 mg, 74%); ¹H NMR (300

25

MHz) (CDCl₃) δ 8.91 (bs, 1H), 7.31 (d, J = 9 Hz, 1H), 7.12-7.08 (m, 2H), 7.03 (dd, J = 9 Hz, J = 3 Hz, 1H), 3.85 (s, 3H), 2.58 (s, 3H).

Example 9. Preparation of 1-(5-(trifluoromethyl)-1*H*-indol-2-yl)ethan-1-amine.

5



1-(5-(Trifluoromethyl)-1*H*-indol-2-yl)ethan-1-amine

10

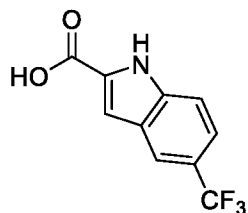
1-(5-Trifluoromethyl-1*H*-indol-2-yl)ethan-1-one (100 mg, 0.44 mmol), ammonium acetate (339 mg, 4.40 mmol) and sodium cyanoborohydride (138 mg, 2.20 mmol) were dissolved in ethanol (10 mL). The mixture was stirred for overnight at 60 °C. The reaction mixture was acidified with 6N HCl, and it was washed with ethyl acetate. Then, the aqueous layer was basified with NaOH, and it was extracted with ethyl acetate. The organic layer was washed with brine, and it was dried over Na₂SO₄. The organic layer was concentrated under reduced pressure, and the residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give the product as a white solid (42 mg, 42%); ¹H NMR (300 MHz) (DMSO-*d*₆) δ 11.34 (bs, 1H), 7.79 (s, 1H), 7.46 (d, J = 9 Hz, 1H), 7.27 (d, J = 8 Hz, 1H), 6.36 (s, 1H), 4.15-4.09 (m, 1H), 1.37 (d, J = 6 Hz, 3H); LC/MS RT = 2.50 (M-H⁺: 227).

20

The requisite intermediate was prepared as follows:

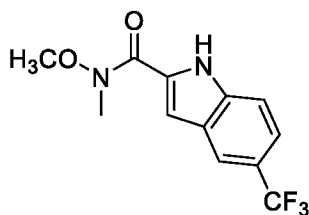
25

Step 1)

5-(Trifluoromethyl)-1*H*-indole-2-carboxylic acid

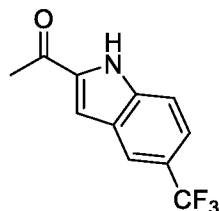
2-Iodo-4-(trifluoromethyl)aniline (1.0 g, 3.48 mmol), pyruvic acid (0.74 mL, 10.44 mmol), DABCO (1.17 g, 10.44 mmol) and Pd(OAc)₂ (79 mg, 0.35 mmol) were dissolved in anhydrous dimethylformamide (10 mL). The mixture was purged with nitrogen, and it was stirred for 4 hours at 110 °C. The reaction mixture was diluted with ethyl acetate, and the organic layer was washed with 1N HCl and brine. The organic layer was dried over Na₂SO₄, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give product as a beige solid (484 mg, 54%); ¹H NMR (300 MHz) (CD₃OD) δ 11.66 (bs, 1H), 7.98 (s, 1H), 7.57 (d, *J* = 9 Hz, 1H), 7.47 (d, *J* = 9 Hz, 1H), 7.26 (s, 1H).

Step 2)

N-Methoxy-N-methyl-5-(trifluoromethyl)-1*H*-indole-2-carboxamide

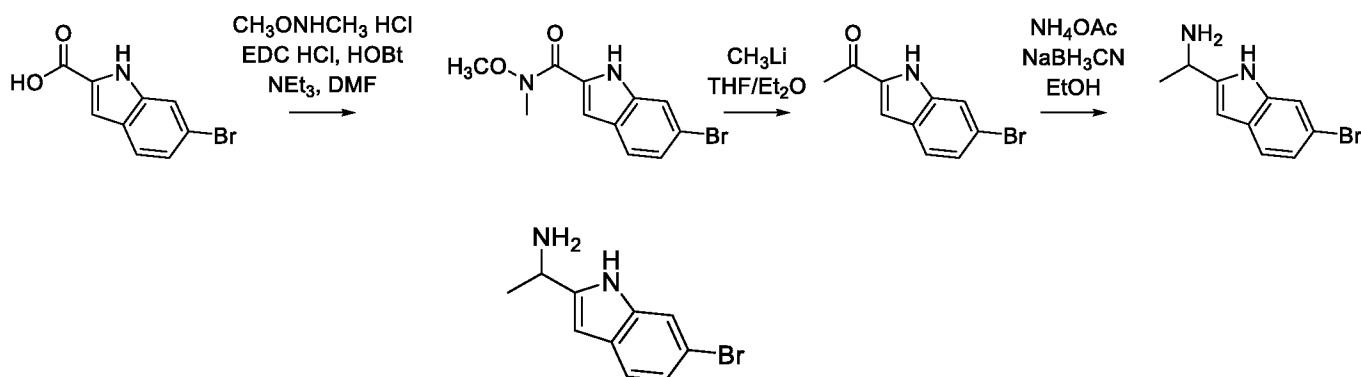
5-(Trifluoromethyl)-1*H*-indole-2-carboxylic acid (484 mg, 2.11 mmol), N, O-dimethylhydroxylamine hydrochloride (309 mg, 3.17 mmol), HOBt (285 mg, 2.11 mmol), EDC hydrochloride (849 mg, 4.43 mmol) and triethylamine (1.18 mL, 8.44 mmol) were dissolved in anhydrous dimethylformamide (50 mL). The mixture was stirred for overnight at room temperature. The reaction mixture was diluted with ethyl acetate, and the organic layer was washed with water, saturated NH₄Cl, 10% NaOH and brine. The organic layer was dried over Na₂SO₄, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give product as a white solid (402 mg, 70%); ¹H NMR (300 MHz) (CDCl₃) δ 9.97 (bs, 1H), 8.01 (s, 1H), 7.53 (m, 2H), 7.32 (s, 1H), 3.86 (s, 3H), 3.45 (s, 3H).

Step 3)

1-(5-(Trifluoromethyl)-1*H*-indol-2-yl)ethan-1-one

5 N-Methoxy-N-methyl-5-(trifluoromethyl)-1*H*-indole-2-carboxamide (300 mg, 1.10 mmol) was dissolved in anhydrous tetrahydrofuran (20 mL). The mixture was cooled to -78 °C, and, then, a solution of 1.6 M methyllithium in diethyl ether (2.06 mL, 3.30 mmol) was added. The mixture was stirred for 2 hours at -78 °C. The reaction was stopped by addition of water (10 mL). After removal of the solvent, the reaction mixture was diluted with ethyl acetate. The
 10 organic layer was washed with saturated NH₄Cl and brine, and it was dried over Na₂SO₄. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give product as a white solid (197 mg, 80%); ¹H NMR (300 MHz) (CDCl₃) δ 9.40 (bs, 1H), 8.03 (s, 1H), 7.59-7.51 (m, 2H), 7.28 (s, 1H), 2.64 (s, 3H).

15 Example 10. Preparation of 1-(6-bromo-1*H*-indol-2-yl)ethan-1-amine.

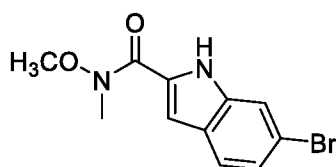
1-(6-Bromo-1*H*-indol-2-yl)ethan-1-amine

20 1-(6-Bromo-1*H*-indol-2-yl)ethan-1-one (100 mg, 0.42 mmol), ammonium acetate (324 mg, 4.20 mmol) and sodium cyanoborohydride (132 mg, 2.10 mmol) were dissolved in ethanol (10 mL). The mixture was stirred for overnight at 60 °C. The reaction mixture was acidified with 6N HCl, and it was washed with ethyl acetate. Then, the aqueous layer was basified with NaOH, and it was extracted with ethyl acetate. The organic layer was washed with brine, and it

was dried over Na₂SO₄. The organic layer was concentrated under reduced pressure, and the residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give the product as a white solid (58 mg, 58%); ¹H NMR (300 MHz) (DMSO-d₆) δ 11.39 (bs, 1H), 8.43 (bs, 2H), 7.58 (s, 1H), 7.49 (d, *J* = 8 Hz, 1H), 7.13 (dd, *J* = 9 Hz, *J* = 2 Hz, 1H), 6.51 (s, 1H), 4.57-4.55 (m, 1H), 1.59 (d, *J* = 7 Hz, 3H); LC/MS RT = 2.43 (M-H⁺: 237/239).

The requisite intermediate was prepared as follows:

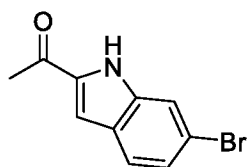
Step 1)



6-Bromo-N-methoxy-N-methyl-1*H*-indole-2-carboxamide

6-Bromo-1*H*-indole-2-carboxylic acid (1.0 g, 4.17 mmol), N, O-dimethylhydroxylamine hydrochloride (611 mg, 6.26 mmol), HOBt (563 mg, 4.17 mmol), EDC hydrochloride (1.68 g, 8.76 mmol) and triethylamine (2.32 mL, 16.68 mmol) were dissolved in anhydrous dimethylformamide (50 mL). The mixture was stirred for overnight at room temperature. The reaction mixture was diluted with ethyl acetate, and the organic layer was washed with water, saturated NH₄Cl, 10% NaOH and brine. The organic layer was dried over Na₂SO₄, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give product as a white solid (327 mg, 28%); ¹H NMR (300 MHz) (CDCl₃) δ 9.62 (bs, 1H), 7.61 (s, 1H), 7.55 (d, *J* = 9 Hz, 1H), 7.26-7.19 (m, 2H), 3.85 (s, 3H), 3.45 (s, 3H).

Step 2)

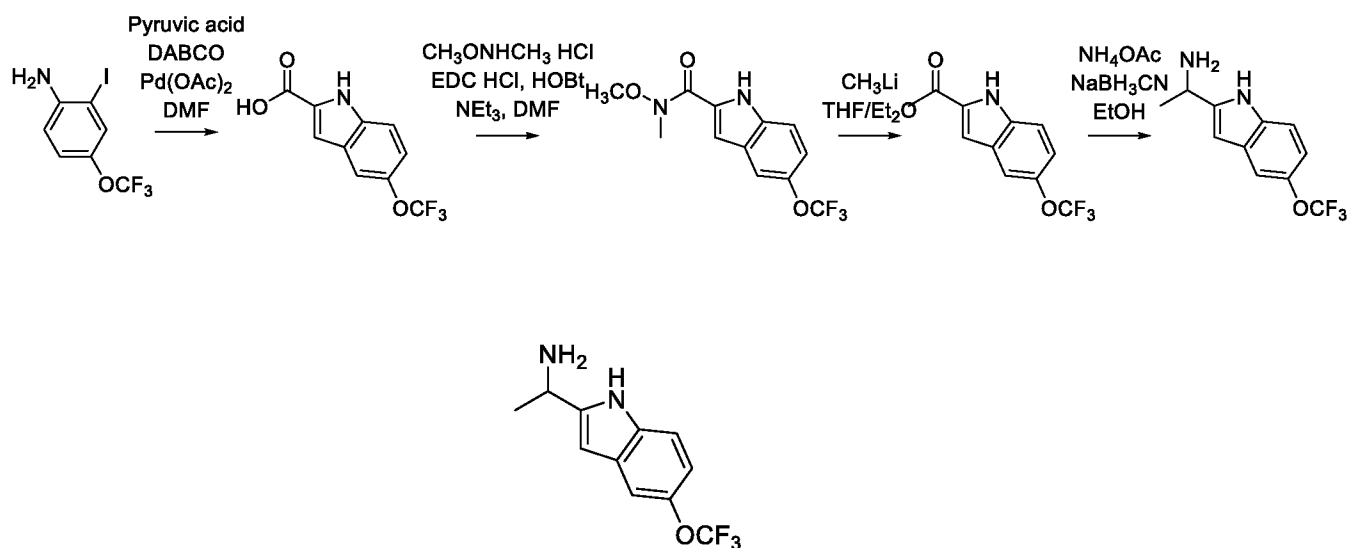


1-(6-Bromo-1*H*-indol-2-yl)ethan-1-one

6-Bromo-N-methoxy-N-methyl-1*H*-indole-2-carboxamide (327 mg, 1.15 mmol) was dissolved in anhydrous tetrahydrofuran (20 mL). The mixture was cooled to -78 °C, and, then, a

solution of 1.6 M methyllithium in diethyl ether (2.16 mL, 3.45 mmol) was added. The mixture was stirred for 2 hours at -78 °C. The reaction was stopped by addition of water (10 mL). After removal of the solvent, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with saturated NH₄Cl and brine, and it was dried over Na₂SO₄. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give product as a white solid (197 mg, 72%); ¹H NMR (300 MHz) (CDCl₃) δ 9.12 (bs, 1H), 7.60-7.56 (m, 2H), 7.27-7.34 (m, 1H), 7.16 (s, 1H), 2.59 (s, 3H).

Example 11. Preparation of 1-(5-(trifluoromethoxy)-1H-indol-2-yl)ethan-1-amine.

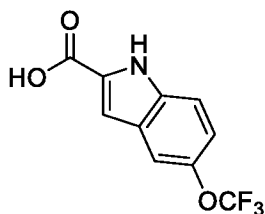


1-(5-(Trifluoromethoxy)-1H-indol-2-yl)ethan-1-amine

1-(5-(Trifluoromethoxy)-1H-indol-2-yl)ethan-1-one (100 mg, 0.41 mmol), ammonium acetate (316 mg, 4.10 mmol) and sodium cyanoborohydride (129 mg, 2.05 mmol) were dissolved in ethanol (10 mL). The mixture was stirred for overnight at 60 °C. The reaction mixture was acidified with 6N HCl, and it was washed with ethyl acetate. Then, the aqueous layer was basified with NaOH, and it was extracted with ethyl acetate. The organic layer was washed with brine, and it was dried over Na₂SO₄. The organic layer was concentrated under reduced pressure, and the residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give the product as a white solid (48 mg, 48%); ¹H NMR (300 MHz) (DMSO-d₆) δ 11.15 (bs, 1H), 7.38 (s, 1H), 7.35 (d, *J* = 9 Hz, 1H), 6.94 (d, *J* = 8 Hz, 1H), 6.27 (s, 1H), 4.14-4.07 (m, 1H), 1.36 (d, *J* = 7 Hz, 3H); LC/MS RT = 2.55 (M-H⁺: 243).

The requisite intermediate was prepared as follows:

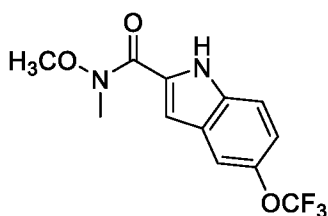
Step 1)



5-(Trifluoromethoxy)-1H-indole-2-carboxylic acid

2-Iodo-4-(trifluoromethoxy)aniline (1.0 g, 3.30 mmol), pyruvic acid (0.70 mL, 9.90 mmol), DABCO (1.11 g, 9.90 mmol) and Pd(OAc)₂ (74 mg, 0.33 mmol) were dissolved in anhydrous dimethylformamide (10 mL). The mixture was purged with nitrogen, and it was stirred for 4 hours at 110 °C. The reaction mixture was diluted with ethyl acetate, and the organic layer was washed with 1N HCl and brine. The organic layer was dried over Na₂SO₄, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give product as a beige solid (592 mg, 73%); ¹H NMR (300 MHz) (DMSO-d₆) δ 12.02 (bs, 1H), 7.64 (s, 1H), 7.49 (d, *J* = 9 Hz, 1H), 7.20 (d, *J* = 6 Hz, 1H), 7.13 (s, 1H).

Step 2)

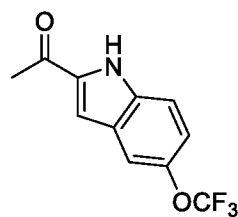


N-Methoxy-N-methyl-5-(trifluoromethoxy)-1H-indole-2-carboxamide

5-(Trifluoromethoxy)-1H-indole-2-carboxylic acid (592 mg, 2.41 mmol), N, O-dimethylhydroxylamine hydrochloride (353 mg, 3.62 mmol), HOBt (326 mg, 2.41 mmol), EDC hydrochloride (970 mg, 5.06 mmol) and triethylamine (1.18 mL, 8.44 mmol) were dissolved in anhydrous dimethylformamide (50 mL). The mixture was stirred for overnight at room temperature. The reaction mixture was diluted with ethyl acetate, and the organic layer was washed with water, saturated NH₄Cl, 10% NaOH and brine. The organic layer was dried over Na₂SO₄, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-70% ethyl acetate/hexane) to give product as a white solid (378 mg, 54%); ¹H

NMR (300 MHz) (CDCl₃) δ 9.33 (bs, 1H), 7.55 (s, 1H), 7.42 (d, J = 9 Hz, 1H), 7.24 (s, 1H), 7.18 (d, J = 9 Hz, 1H), 3.85 (s, 3H), 3.44 (s, 3H).

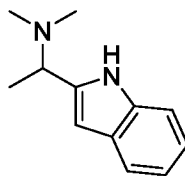
Step 3)



1-(5-(Trifluoromethoxy)-1H-indol-2-yl)ethan-1-one

N-Methoxy-N-methyl-5-(trifluoromethoxy)-1H-indole-2-carboxamide (378 mg, 1.31 mmol) was dissolved in anhydrous tetrahydrofuran (20 mL). The mixture was cooled to -78 °C, and, then, a solution of 1.6 M methyllithium in diethyl ether (2.46 mL, 3.93 mmol) was added. The mixture was stirred for 2 hours at -78 °C. The reaction was stopped by addition of water (10 mL). After removal of the solvent, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with saturated NH₄Cl and brine, and it was dried over Na₂SO₄. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give product as a white solid (259 mg, 81%); ¹H NMR (300 MHz) (CDCl₃) δ 9.35 (bs, 1H), 7.57 (s, 1H), 7.44 (d, J = 9 Hz, 1H), 7.26-7.20 (m, 2H), 2.62 (s, 3H).

Example 12. Preparation of 1-(1H-indol-2-yl)-N,N-dimethylethan-1-amine.

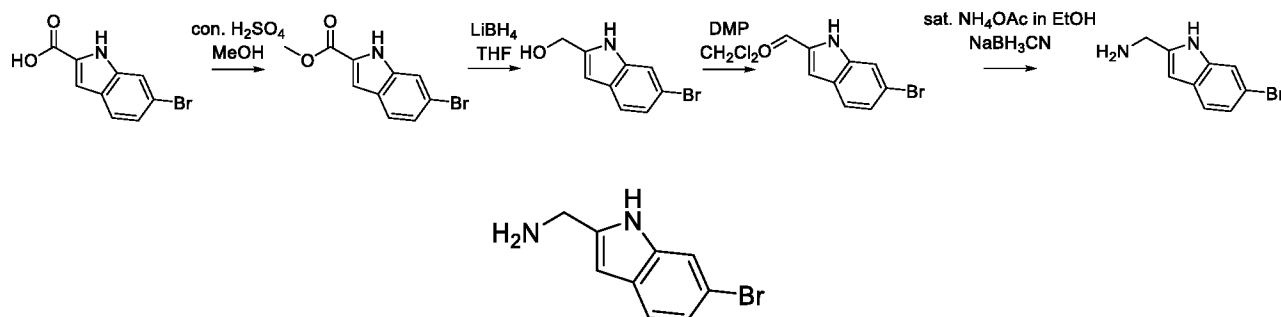


1-(1H-Indol-2-yl)-N,N-dimethylethan-1-amine

1-(5-Bromo-1H-indol-2-yl)-N-methylethan-1-amine (53 mg, 0.21 mmol) and Boc anhydride (92 mg, 0.42 mmol) were dissolved in anhydrous tetrahydrofuran (10 mL), and it was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, and it was washed with water and brine. The organic layer was dried over Na₂SO₄, and it was concentrated under reduced pressure. The crude material was dissolved in anhydrous tetrahydrofuran (10 mL), and lithium aluminum hydride (24 mg, 0.63 mmol) was added. The mixture was stirred for an hour at 50 °C. The reaction was stopped by addition of saturated

sodium sulfate (1 mL), and the resulted suspension was filtered. The filtrate was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give the product as a white solid (6 mg, 15%); LC/MS RT = 2.46 (M+H⁺: 189).

5 Example 13. Preparation of (6-bromo-1*H*-indol-2-yl)methanamine.

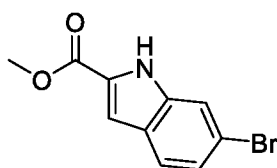


10 (6-Bromo-1*H*-indol-2-yl)methanamine

6-Bromo-1*H*-indole-2-carbaldehyde (51 mg, 0.23 mmol) was dissolved in a solution of saturated ammonium acetate in ethanol (20 mL), and, then, it was treated with sodium cyanoborohydride (43 mg, 0.69 mmol). The mixture was stirred for overnight at room temperature. The reaction mixture was diluted with ethyl acetate, and it was washed with saturated water and brine. The organic layer was dried over Na₂SO₄, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give product as a colorless oil (7 mg, 13%); ¹H NMR (300 MHz) (DMSO-*d*₆) δ 11.12 (bs, 1H), 7.54 (s, 1H), 7.43 (d, *J* = 8 Hz, 1H), 7.07 (d, *J* = 9 Hz, 1H), 6.37 (s, 1H), 3.97 (s, 2H); LC/MS RT = 2.52 (M-H⁺: 223/225).

The requisite intermediate was prepared as follows:

Step 1)

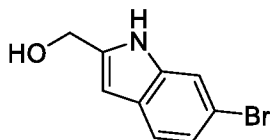


25 Methyl 6-bromo-1*H*-indole-2-carboxylate

6-Bromo-1*H*-indole-2-carboxylic acid (1.0 g, 4.17 mmol) was dissolved in methanol (100 mL), and it was treated with catalytic amount of concentrated sulfuric acid. The mixture

was refluxed overnight. After removal of solvent, it was diluted with ethyl acetate. The organic layer was washed with 10% NaOH and brine, and it was dried over Na₂SO₄. The organic layer was concentrated under reduced pressure, and the residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give product as a pink solid (612 mg, 58%); ¹H NMR (300 MHz) (CDCl₃) δ 9.01 (bs, 1H), 7.59 (s, 1H), 7.55 (d, *J* = 9 Hz, 1H), 7.28-7.24 (m, 1H), 7.19 (s, 1H), 3.96 (s, 3H).

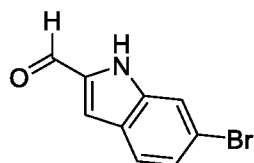
Step 2)



(6-Bromo-1*H*-indol-2-yl)methanol

Methyl 6-bromo-1*H*-indole-2-carboxylate (200 mg, 0.79 mmol) and lithium borohydride (86 mg, 3.95 mmol) were dissolved in anhydrous tetrahydrofuran (10 mL) at 0 °C, and it was stirred for overnight at room temperature. The reaction mixture was diluted with ethyl acetate, and it was washed with saturated NH₄Cl and brine. The organic layer was dried over Na₂SO₄, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give product as a white solid (162 mg, 91 %); ¹H NMR (300 MHz) (CDCl₃) δ 8.42 (bs, 1H), 7.47 (s, 1H), 7.42 (d, *J* = 8 Hz, 1H), 7.20 (dd, *J* = 10 Hz, *J* = 2 Hz, 1H), 6.36 (d, *J* = 1 Hz, 1H), 4.80 (s, 2H).

Step 3)



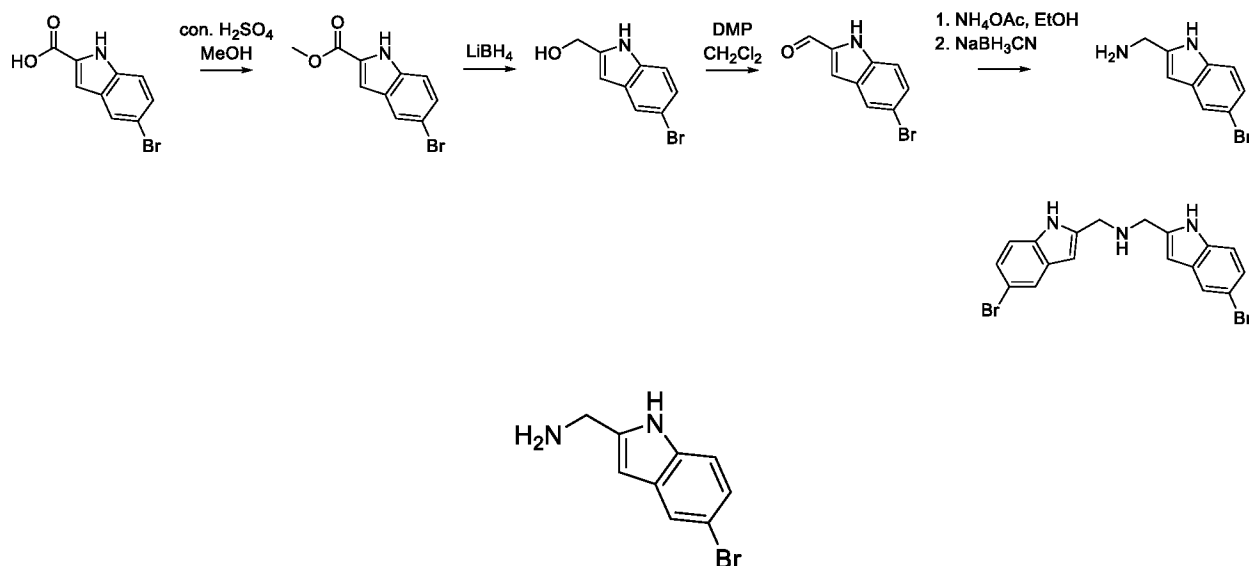
6-Bromo-1*H*-indole-2-carbaldehyde

(6-Bromo-1*H*-indol-2-yl)methanol (80 mg, 0.35 mmol) and Dess-Martin periodinane (178 mg, 0.42 mmol) were dissolved in dichloromethane (10 mL), and it was stirred for 30 minutes at room temperature. The reaction mixture was diluted with ethyl acetate, and it was washed with 10% sodium thiosulfate, saturated NaHCO₃ and brine. The organic layer was dried over Na₂SO₄, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give product as a white solid (78 mg,

100%); ^1H NMR (300 MHz) (CDCl_3) δ 9.86 (s, 1H), 9.23 (bs, 1H), 7.65 (s, 1H), 7.61 (d, $J = 9$ Hz, 1H), 7.29 (d, $J = 9$ Hz, 1H), 7.26-7.25 (m, 1H).

Example 14. Preparation of (5-bromo-1*H*-indol-2-yl)methanamine.

5



(5-Bromo-1*H*-indol-2-yl)methanamine

10

5-Bromo-1*H*-indole-2-carbaldehyde (55 mg, 0.25 mmol) was dissolved in ethanol (25 mL), and it was treated with ammonium acetate (193 mg, 2.50 mmol). The mixture was stirred for an hour at room temperature. Then, sodium cyanoborohydride (79 mg, 1.25 mmol) was added, and it was stirred for 3 hours at room temperature. The reaction mixture was diluted with ethyl acetate, and it was washed with saturated NaHCO_3 and brine. The organic layer was dried over Na_2SO_4 , and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH_4OH) to give (5-bromo-1*H*-indol-2-yl)methanamine as a white solid (26 mg, 46%). ^1H NMR (300 MHz) ($\text{DMSO}-d_6$) δ 11.25 (bs, 1H), 7.72 (d, $J = 2$ Hz, 1H), 7.36 (d, $J = 8$ Hz, 1H), 7.19 (dd, $J = 9$ Hz, $J = 2$ Hz, 1H), 6.46 (s, 1H), 4.11 (s, 2H); LC/MS RT = 2.52 (M-H $^+$: 223/225). along with bis((5-bromo-1*H*-indol-2-yl)methyl)amine as a white solid (26 mg, 49%). ^1H NMR (300 MHz) (CDCl_3) δ 7.65 (s, 2H), 7.26-7.21 (m, 4H), 6.31 (s, 2H), 3.97 (s, 4H); LC/MS RT = 2.97 (M-H $^+$: 430/432/434).

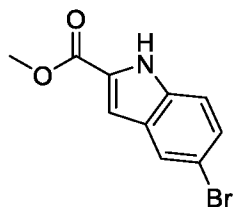
15

20

The requisite intermediate was prepared as follows:

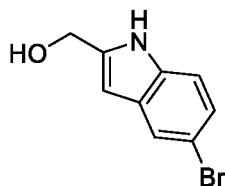
25

Step 1)

Methyl 5-bromo-1*H*-indole-2-carboxylate

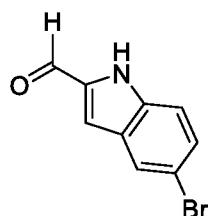
5-Bromo-1*H*-indole-2-carboxylic acid (1.5 g, 6.25 mmol) was dissolved in methanol (100 mL), and it was treated with catalytic amount of concentrated sulfuric acid. The mixture was refluxed overnight. After removal of solvent, it was diluted with ethyl acetate. The organic layer was washed with 10% NaOH and brine, and it was dried over Na₂SO₄. The organic layer was concentrated under reduced pressure, and the residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give product as a white solid (1.19 g, 75%); ¹H NMR (300 MHz) (CDCl₃) δ 8.97 (bs, 1H), 7.83 (s, 1H), 7.40 (dd, *J* = 9 Hz, *J* = 2 Hz, 1H), 7.30 (d, *J* = 9 Hz, 1H), 7.14 (s, 1H), 3.95 (s, 3H).

Step 2)

(5-Bromo-1*H*-indol-2-yl)methanol

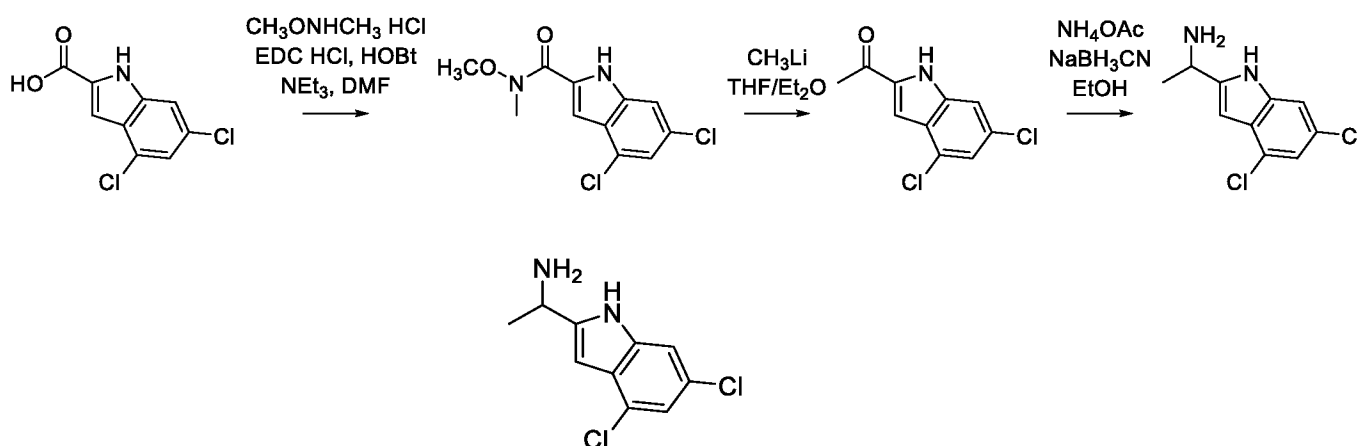
Methyl 5-bromo-1*H*-indole-2-carboxylate (200 mg, 0.79 mmol) and lithium borohydride (86 mg, 3.95 mmol) were dissolved in anhydrous tetrahydrofuran (10 mL) at 0 °C, and it was stirred for overnight at room temperature. The reaction mixture was diluted with ethyl acetate, and it was washed with saturated NH₄Cl and brine. The organic layer was dried over Na₂SO₄, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give product as a white solid (149 mg, 83 %); ¹H NMR (300 MHz) (CDCl₃) δ 8.37 (bs, 1H), 7.69 (s, 1H), 7.28-7.21 (m, 2H), 6.34 (d, *J* = 1 Hz, 1H), 4.84 (s, 2H).

Step 3)

5-Bromo-1*H*-indole-2-carbaldehyde

(5-Bromo-1*H*-indol-2-yl)methanol (100 mg, 0.44 mmol) and Dess-Martin periodinane (280 mg, 0.66 mmol) were dissolved in dichloromethane (10 mL), and it was stirred for 15 minutes at room temperature. The reaction mixture was diluted with ethyl acetate, and it was washed with 10% sodium thiosulfate, saturated NaHCO₃ and brine. The organic layer was dried over Na₂SO₄, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give product as a white solid (55 mg, 56%); ¹H NMR (300 MHz) (CDCl₃) δ 9.85 (s, 1H), 9.05 (bs, 1H), 7.90 (s, 1H), 7.47 (dd, *J* = 9 Hz, *J* = 2 Hz, 1H), 7.34 (d, *J* = 9 Hz, 1H), 7.21 (s, 1H).

Example 15. Preparation of 1-(4,6-dichloro-1*H*-indol-2-yl)ethan-1-amine.

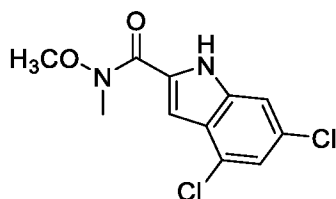
1-(4,6-Dichloro-1*H*-indol-2-yl)ethan-1-amine

1-(4,6-Dichloro-1*H*-indol-2-yl)ethan-1-one (100 mg, 0.44 mmol), ammonium acetate (339 mg, 4.40 mmol) and sodium cyanoborohydride (138 mg, 2.20 mmol) were dissolved in ethanol (10 mL). The mixture was stirred for overnight at 60 °C. The reaction mixture was acidified with 6N HCl, and it was washed with ethyl acetate. Then, the aqueous layer was basified with NaOH, and it was extracted with ethyl acetate. The organic layer was washed with brine, and it was dried over Na₂SO₄. The organic layer was concentrated under reduced pressure, and the residue was purified on an ISCO chromatograph (0-10%

methanol/dichloromethane + 0.1% NH₄OH) to give the product as a white solid (55 mg, 54%); ¹H NMR (300 MHz) (DMSO-d₆) δ 7.32 (s, 1H), 7.06 (s, 1H), 6.27 (s, 1H), 4.12-4.01 (m, 1H), 1.35 (d, *J* = 8 Hz, 3H); LC/MS RT = 2.61 (M-H⁺: 227/229).

5 The requisite intermediate was prepared as follows:

Step 1)



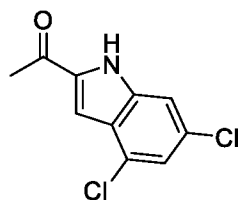
4,6-Dichloro-N-methoxy-N-methyl-1*H*-indole-2-carboxamide

10

4,6-Dichloro-1*H*-indole-2-carboxylic acid (500 mg, 2.17 mmol), N,O-dimethylhydroxylamine hydrochloride (423 mg, 4.34 mmol), HOBt (332 mg, 2.17 mmol), EDC hydrochloride (874 mg, 4.56 mmol) and triethylamine (1.32 mL, 8.68 mmol) were dissolved in anhydrous dimethylformamide (40 mL). The mixture was stirred for overnight at room temperature. The reaction mixture was diluted with ethyl acetate, and the organic layer was washed with water, saturated NH₄Cl, 10% NaOH and brine. The organic layer was dried over Na₂SO₄, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give product as a white solid (505 mg, 85%); ¹H NMR (300 MHz) (DMSO-d₆) δ 12.10 (bs, 1H), 7.45 (d, *J* = 1 Hz, 1H), 7.24 (d, *J* = 1 Hz, 1H), 7.09 (s, 1H), 3.80 (s, 3H), 3.33 (s, 3H).

20

Step 2)



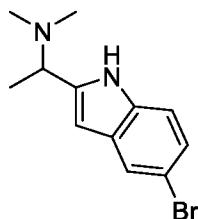
1-(4,6-Dichloro-1*H*-indol-2-yl)ethan-1-one

25

4,6-Dichloro-N-methoxy-N-methyl-1*H*-indole-2-carboxamide (500 mg, 1.83 mmol) was dissolved in anhydrous tetrahydrofuran (25 mL). The mixture was cooled to -78 °C, and, then, a solution of 1.6 M methyllithium in diethyl ether (3.43 mL, 5.49 mmol) was added. The mixture was stirred for 2 hours at -78 °C. The reaction was stopped by addition of water (10 mL). After

removal of the solvent, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with saturated NH_4Cl and brine, and it was dried over Na_2SO_4 . The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give product as a white solid (278 mg, 67%); ^1H NMR (300 MHz) ($\text{DMSO}-d_6$) δ 12.20 (bs, 1H), 7.41 (s, 1H), 7.39 (s, 1H), 7.27 (s, 1H), 2.57 (s, 3H).

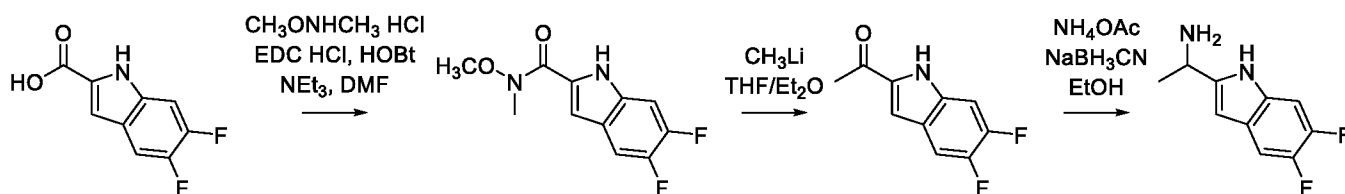
Example 16. Preparation of 1-(5-bromo-1*H*-indol-2-yl)-*N,N*-dimethylethan-1-amine.

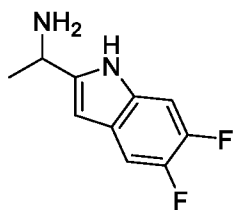


1-(5-Bromo-1*H*-indol-2-yl)-*N,N*-dimethylethan-1-amine

To a mixture of 1-(5-bromo-1*H*-indol-2-yl)ethan-1-one (75 mg, 0.32 mmol) in ethanol (10 mL), a solution of 2.0 M *N,N*-dimethylamine in tetrahydrofuran (1.60 mL, 3.20 mmol) was added. The mixture was treated with catalytic amount of acetic acid followed by sodium cyanoborohydride (101 mg, 1.69 mmol), and it was stirred for overnight at 60 °C. The reaction mixture was acidified with 6N HCl, and it was washed with ethyl acetate. Then, the aqueous layer was basified with NaOH, and it was extracted with ethyl acetate. The organic layer was washed with brine, and it was dried over Na_2SO_4 . The organic layer was concentrated under reduced pressure, and the residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH_4OH) to give the product as a colorless oil (12 mg, 14%); ^1H NMR (300 MHz) (CDCl_3) δ 8.81 (bs, 1H), 7.66 (s, 1H), 7.26-7.20 (m, 2H), 6.24 (s, 1H), 3.82-3.80 (m, 1H), 2.25 (s, 6H), 1.40 (d, J = 7 Hz, 3H); LC/MS RT = 2.62 (M-H⁺: 265/267).

Example 17. Preparation of 1-(5,6-difluoro-1*H*-indol-2-yl)ethan-1-amine.

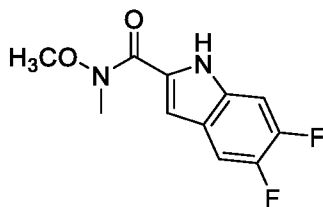


1-(5,6-Difluoro-1*H*-indol-2-yl)ethan-1-amine

1-(5,6-Difluoro-1*H*-indol-2-yl)ethan-1-one (150 mg, 0.77 mmol), ammonium acetate
5 (594 mg, 7.70 mmol) and sodium cyanoborohydride (242 mg, 3.85 mmol) were dissolved in ethanol (10 mL). The mixture was stirred for overnight at 60 °C. The reaction mixture was acidified with 6N HCl, and it was washed with ethyl acetate. Then, the aqueous layer was basified with NaOH, and it was extracted with ethyl acetate. The organic layer was washed with
10 brine, and it was dried over Na₂SO₄. The organic layer was concentrated under reduced pressure, and the residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give the product as a white solid (69 mg, 46%); ¹H NMR (300 MHz) (DMSO-*d*₆) δ 11.49 (bs, 1H), 8.49 (bs, 2H), 7.57-7.50 (m, 1H), 7.44-7.38 (m, 1H), 6.50 (s, 1H), 4.58-4.51 (m, 1H), 1.58 (d, *J* = 6 Hz, 3H); LC/MS RT = 2.47 (M-H⁺: 195).

15 The requisite intermediate was prepared as follows:

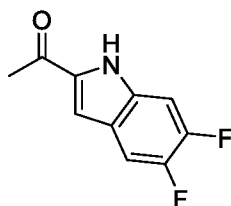
Step 1)

5,6-Difluoro-N-methoxy-N-methyl-1*H*-indole-2-carboxamide

5,6-Difluoro-1*H*-indole-2-carboxylic acid (500 mg, 2.54 mmol), N, O-dimethylhydroxylamine hydrochloride (496 mg, 5.08 mmol), HOBt (389 mg, 2.54 mmol), EDC hydrochloride (1.02 g, 5.33 mmol) and triethylamine (1.54 mL, 10.2 mmol) were dissolved in
25 anhydrous dimethylformamide (20 mL). The mixture was stirred for overnight at room temperature. The reaction mixture was diluted with ethyl acetate, and the organic layer was washed with water, saturated NH₄Cl, 10% NaOH and brine. The organic layer was dried over Na₂SO₄, and it was concentrated under reduced pressure. The residue was purified on an ISCO

chromatograph (0-50% ethyl acetate/hexane) to give product as a white solid (367 mg, 60%); ^1H NMR (300 MHz) (CDCl_3) δ 9.33 (bs, 1H), 7.45-7.38 (m, 1H), 7.23-7.17 (m, 2H), 3.85 (s, 3H), 3.42 (s, 3H).

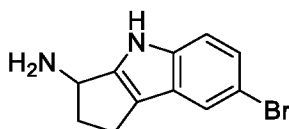
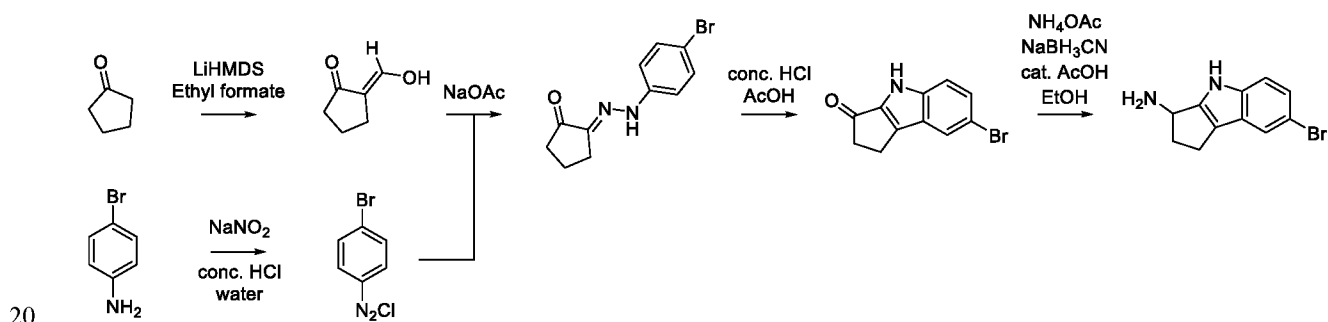
5 Step 2)



1-(5,6-Difluoro-1H-indol-2-yl)ethan-1-one

10 5,6-Difluoro-N-methoxy-N-methyl-1H-indole-2-carboxamide (350 mg, 1.46 mmol) was dissolved in anhydrous tetrahydrofuran (20 mL). The mixture was cooled to -78°C , and, then, a solution of 1.6 M methyllithium in diethyl ether (2.73 mL, 4.38 mmol) was added. The mixture was stirred for 2 hours at -78°C . The reaction was stopped by addition of water (10 mL). After removal of the solvent, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with saturated NH_4Cl and brine, and it was dried over Na_2SO_4 . The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give product as a white solid (207 mg, 73%); ^1H NMR (300 MHz) (CDCl_3) δ 9.24 (bs, 1H), 7.47-7.41 (m, 1H), 7.26-7.14 (m, 2H), 2.58 (s, 3H).

Example 18. Preparation of 7-bromo-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-amine.

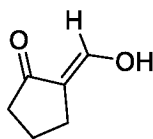


7-Bromo-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-amine

7-Bromo-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (100 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol) and sodium cyanoborohydride (126 mg, 2.00 mmol) were dissolved in ethanol (10 mL). The mixture was stirred for overnight at 60 °C. An additional ammonium acetate (308 mg, 4.00 mmol) and sodium cyanoborohydride (126 mg, 2.00 mmol) along with catalytic amount of acetic acid were added. The mixture was stirred for 5 hours at 85°C. The reaction mixture was acidified with 6N HCl, and it was washed with ethyl acetate. Then, the aqueous layer was basified with NaOH, and it was extracted with ethyl acetate. The organic layer was washed with brine, and it was dried over Na₂SO₄. The organic layer was concentrated under reduced pressure, and the residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give the product as a white solid (17 mg, 17%); ¹H NMR (300 MHz) (CD₃OD) δ 7.48 (d, *J* = 1 Hz, 1H), 7.22 (d, *J* = 9 Hz, 1H), 7.12 (dd, *J* = 9 Hz, *J* = 2 Hz, 1H), 4.43-4.41 (m, 1H), 2.94-2.83 (m, 2H), 2.78-2.62 (m, 1H), 2.21-2.12 (m, 1H); LC/MS RT = 2.57 (M-H⁺: 249/251).

The requisite intermediate was prepared as follows:

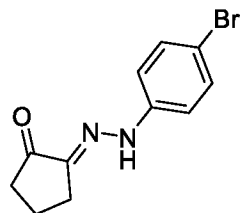
Step 1)



5 (*E*)-2-(Hydroxymethylene)cyclopentan-1-one

Cyclopentanone (2.21 mL, 25 mmol) was dissolved in anhydrous tetrahydrofuran (10 mL), and it was cooled to 0 °C. A solution of 1.0 M LiHMDS in tetrahydrofuran (30 mL, 30 mmol) was slowly added, and it was stirred for 5 minutes at the temperature. Ethyl formate (2.42 mL, 30 mmol) was slowly added, and it was stirred for 2 hours at the temperature. The reaction mixture was diluted with ethyl acetate, and it was washed with 6N HCl and brine. The organic layer was dried over Na₂SO₄, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give product as a white solid (772 mg, 28%); ¹H NMR (300 MHz) (CDCl₃) δ 7.21 (s, 1H), 2.56-2.51 (m, 2H), 2.43-2.37 (m, 2H), 2.01-1.94 (m, 2H).

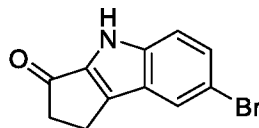
Step 2)



(*E*)-2-(2-(4-Bromophenyl)hydrazineylidene)cyclopentan-1-one

To a solution of 4-bromoaniline (1.07 g, 6.23 mmol) in concentrated hydrochloric acid (2 mL), a solution of sodium nitrite (430 mg, 6.23 mmol) in water (4 mL) was added slowly at 0 °C. The mixture was stirred for 30 minutes at the temperature. In a separate round bottom flask, 5 (*E*)-2-(hydroxymethylene)cyclopentan-1-one (700 mg, 6.23 mmol) was dissolved in methanol (12 mL). To the mixture, a solution of sodium acetate (1.28 g, 15.58 mmol) in water (5 mL) was added slowly at 0 °C. The mixture was stirred for 20 minutes at the temperature. Then, the 10 freshly prepared diazonium salt solution was slowly added. The mixture was stirred for additional 30 minutes at the temperature, and the formed yellow suspension was filtered to give the product as a yellow solid (1.47 g, 89%); ¹H NMR (300 MHz) (DMSO-*d*₆) δ 10.03 (s, 1H), 7.42 (d, *J* = 9 Hz, 2H), 7.19 (d, *J* = 9 Hz, 2H), 2.65-2.60 (m, 2H), 2.34-2.29 (m, 2H), 1.99-1.95 (m, 2H).

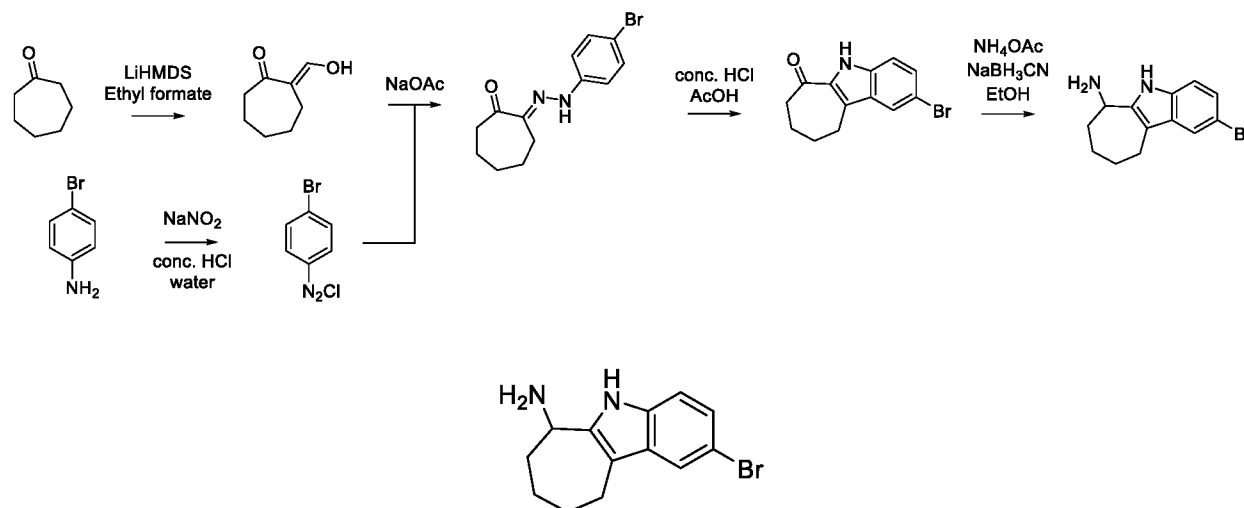
Step 3)



7-Bromo-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one

(*E*)-2-(2-(4-Bromophenyl)hydrazineylidene)cyclopentan-1-one (1.47 g, 5.50 mmol) was dissolved in a mixture of concentrated hydrochloric acid (2 mL) and acetic acid (8 mL), and it was stirred for 30 minutes at 130 °C. The resulting dark brown suspension was diluted with ethyl acetate, and it was washed with 10% NaOH and brine. The organic layer was dried over Na₂SO₄, and it was concentrated under reduced pressure. The residue was purified on an ISCO 20 chromatograph (0-20% ethyl acetate/hexane) to give product as a beige solid (116 mg, 8%); ¹H NMR (300 MHz) (CDCl₃) δ 8.80 (bs, 1H), 7.87 (d, *J* = 2 Hz, 1H), 7.48 (dd, *J* = 9 Hz, *J* = 2 Hz, 1H), 7.35 (d, *J* = 9 Hz, 1H), 3.10-3.07 (m, 2H), 3.03-3.00 (m, 2H).

Example 19. Preparation of 2-Bromo-5,6,7,8,9,10-hexahydrocyclohepta[*b*]indol-6-amine.

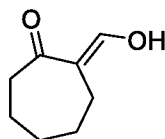


5 2-Bromo-5,6,7,8,9,10-hexahydrocyclohepta[*b*]indol-6-amine

2-Bromo-7,8,9,10-tetrahydrocyclohepta[*b*]indol-6(5*H*)-one (100 mg, 0.36 mmol), ammonium acetate (277 mg, 3.60 mmol) and sodium cyanoborohydride (113 mg, 1.80 mmol) were dissolved in ethanol (10 mL). The mixture was stirred for overnight at 60 °C. The reaction mixture was acidified with 6N HCl, and it was washed with ethyl acetate. Then, the aqueous layer was basified with NaOH, and it was extracted with ethyl acetate. The organic layer was washed with brine, and it was dried over Na₂SO₄. The organic layer was concentrated under reduced pressure, and the residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give the product as a white solid (34 mg, 34%);
 15 ¹H NMR (300 MHz) (CD₃OD) δ 10.76 (bs, 1H), 7.51 (d, *J* = 2 Hz, 1H), 7.24 (d, *J* = 8 Hz, 1H), 7.03 (dd, *J* = 8 Hz, *J* = 2 Hz, 1H), 4.01-3.97 (m, 1H), 2.86-2.81 (m, 1H), 2.58-2.56 (m, 1H), 1.99-1.84 (m, 2H), 1.71-1.50 (m, 4H); LC/MS RT = 2.57 (M-H⁺: 277/279).

The requisite intermediate was prepared as follows:

20 Step 1)

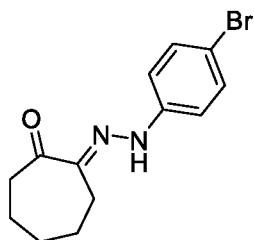


(*E*)-2-(Hydroxymethylene)cycloheptan-1-one

25 Cycloheptanone (2.95 mL, 25 mmol) was dissolved in anhydrous tetrahydrofuran (10 mL), and it was cooled to 0 °C. A solution of 1.0 M LiHMDS in tetrahydrofuran (30 mL, 30

mmol) was slowly added, and it was stirred for 5 minutes at the temperature. Ethyl formate (2.42 mL, 30 mmol) was slowly added, and it was stirred for 2 hours at the temperature. The reaction mixture was diluted with ethyl acetate, and it was washed with 6N HCl and brine. The organic layer was dried over Na₂SO₄. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give product as a colorless oil (1.30 g, 37%); ¹H NMR (300 MHz) (CDCl₃) δ 7.59 (d, *J* = 9 Hz, 1H), 2.51-2.47 (m, 2H), 2.23-2.19 (m, 2H), 1.73-1.54 (m, 6H).

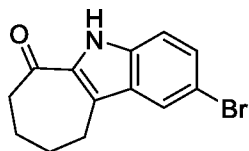
Step 2)



(*E*)-2-(2-(4-Bromophenyl)hydrazineylidene)cycloheptan-1-one

To a solution of 4-bromoaniline (1.60 g, 9.30 mmol) in concentrated hydrochloric acid (2 mL), a solution of sodium nitrite (642 mg, 9.30 mmol) in water (4 mL) was added slowly at 0 °C. The mixture was stirred for 30 minutes at the temperature. In a separate round bottom flask, (*E*)-2-(hydroxymethylene)cycloheptan-1-one (1.30 g, 9.30 mmol) was dissolved in methanol (12 mL). To the mixture, a solution of sodium acetate (1.91 g, 23.3 mmol) in water (5 mL) was added slowly at 0 °C. The mixture was stirred for 20 minutes at the temperature. Then, the freshly prepared diazonium salt solution was slowly added. The mixture was stirred for additional 30 minutes at the temperature, and the formed yellow suspension was filtered to give the product as a yellow solid (2.17 g, 79%); ¹H NMR (300 MHz) (DMSO-*d*₆) δ 13.27 (s, 1H), 7.43 (d, *J* = 9 Hz, 2H), 7.23 (d, *J* = 9 Hz, 2H), 2.62-2.56 (m, 4H), 1.68 (m, 6H).

Step 3)

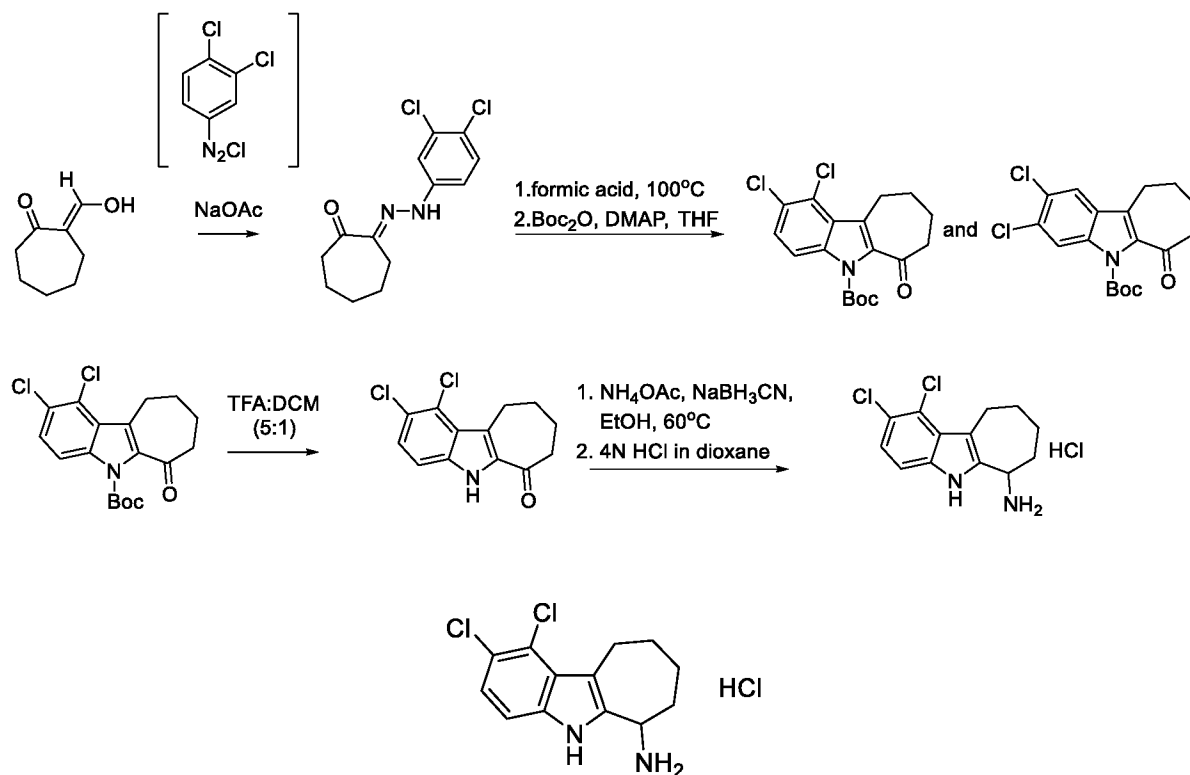


2-Bromo-7,8,9,10-tetrahydrocyclohepta[*b*]indol-6(5*H*)-one

(*E*)-2-(2-(4-Bromophenyl)hydrazineylidene)cycloheptan-1-one (2.17 g, 7.35 mmol) was dissolved in a mixture of concentrated hydrochloric acid (2 mL) and acetic acid (8 mL), and it

was stirred for 30 minutes at 130 °C. The resulting dark brown suspension was diluted with ethyl acetate, and it was washed with 10% NaOH and brine. The organic layer was dried over Na₂SO₄, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give product as a yellow solid (472 mg, 23%);
 5 ¹H NMR (300 MHz) (CDCl₃) δ 8.90 (bs, 1H), 7.79 (s, 1H), 7.41 (dd, *J* = 9 Hz, *J* = 2 Hz, 1H), 7.26-7.23 (m, 1H), 3.11-3.07 (m, 2H), 2.86-2.82 (m, 2H), 2.11-1.99 (m, 4H).

Example 20. Preparation of 1,2-dichloro-5,6,7,8,9,10-hexahydrocyclohepta[*b*]indol-6-amine.



1,2-Dichloro-5,6,7,8,9,10-hexahydrocyclohepta[*b*]indol-6-amine hydrochloric acid

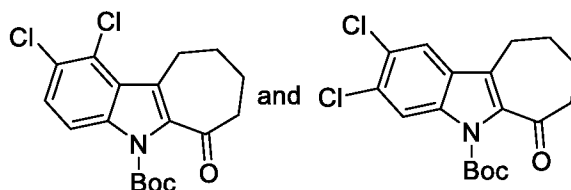
15 1,2-Dichloro-7,8,9,10-tetrahydrocyclohepta[*b*]indol-6(5*H*)-one (99 mg, 0.37 mmol), ammonium acetate (285 mg, 3.70 mmol) and sodium cyanoborohydride (116 mg, 1.85 mmol) were dissolved in ethanol (10 mL). The reaction mixture was stirred for overnight at 60 °C. After removal of solvent, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with 10% sodium hydroxide and brine, and it was dried over sodium sulfate.
 20 The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give product as a white solid. The solid was then treated with 4N hydrochloric acid in dioxane, and it was stirred for 30 minutes at room temperature. The white suspension was concentrated under reduced pressure,

and the resulting residue was suspended in ethyl acetate. The suspension was filtered to give hydrochloric acid salt of product as a white solid (42 mg, 37%); ^1H NMR (300 MHz) ($\text{DMSO}-d_6$) δ 11.65 (bs, 1H), 8.42 (bs, 3H), 7.37 (d, $J = 8$ Hz, 1H), 7.25 (d, $J = 9$ Hz, 1H), 4.58 (m, 1H), 3.65-3.60 (m, 2H), 3.12-2.98 (m, 2H), 1.97-1.89 (m, 4H); LC/MS RT = 2.90 (M-H $^-$: 267/269).

5

The requisite intermediate was prepared as follows:

Step 1)



tert-Butyl 1,2-dichloro-6-oxo-7,8,9,10-tetrahydrocyclohepta[*b*]indole-5(6*H*)-carboxylate and

10

tert-Butyl 2,3-dichloro-6-oxo-7,8,9,10-tetrahydrocyclohepta[*b*]indole-5(6*H*)-carboxylate

To a solution of 3,4-dichloroaniline (1.53 g, 9.42 mmol) in concentrated hydrochloric acid (10 mL), a solution of sodium nitrite (650 mg, 9.42 mmol) in water (20 mL) was added slowly at 0 °C. The mixture was stirred for 30 minutes at the temperature. In a separate round bottom flask, (E)-2-(hydroxymethylene)cycloheptan-1-one (1.32 g, 9.42 mmol) was dissolve in methanol (12 mL). To the mixture, a solution of sodium acetate (1.93 g, 23.55 mmol) in water (5 mL) was added slowly at 0 °C. The mixture was stirred for 20 minutes at 0 °C. Then, the freshly prepared diazonium salt solution was slowly added. The mixture was stirred for additional 30 minutes at 0 °C.. The reaction mixture was diluted with ethyl acetate, and the organic layer was washed with saturated sodium bicarbonate followed brine. The organic layer was concentrated under reduced pressure and the resulted dark brown oil was carried next step without further purification.

20

The residue was dissolved in formic acid (10 mL), and it was stirred for 2 hours at 100 °C. The resulting dark brown suspension was diluted with ethyl acetate, and it was washed with 10% NaOH and brine. The organic layer was dried over sodium sulfate, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give a mixture of two regioisomers, 1,2-dichloro-7,8,9,10-tetrahydrocyclohepta[*b*]indol-6(5*H*)-one and 2,3-dichloro-7,8,9,10-tetrahydrocyclohepta[*b*]indol-6(5*H*)-one as a beige solid (212 mg, 8%).

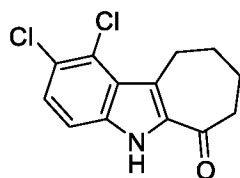
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30

To a solution of a mixture of the two regioisomers (212 mg, 0.79 mmol) in tetrahydrofuran (10 mL), boc anhydride (345 mg, 1.58 mmol) and DAMP (89 mg, 0.79 mmol) were added. The reaction mixture was stirred for 3 hours. The reaction mixture was diluted with ethyl acetate, and it was washed with saturated ammonium chloride, followed by brine.

- 5 The organic layer was dried over sodium sulfate, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give *tert*-butyl 1,2-dichloro-6-oxo-7,8,9,10-tetrahydrocyclohepta[*b*]indole-5(6*H*)-carboxylate (152 mg, 49%). ¹H NMR (300 MHz) (CDCl₃) δ 7.93 (d, *J* = 9 Hz, 1H), 7.41 (d, *J* = 9 Hz, 1H), 3.42-3.38 (m, 2H), 2.87-2.83 (m, 2H), 1.97-1.95 (m, 4H), 1.55 (s, 9H). along with *tert*-butyl 2,3-
- 10 dichloro-6-oxo-7,8,9,10-tetrahydrocyclohepta[*b*]indole-5(6*H*)-carboxylate (59 mg, 20%). ¹H NMR (300 MHz) (CDCl₃) δ 8.20 (s, 1H), 7.62 (s, 1H), 2.91 (m, 2H), 2.85 (m, 2H), 2.02-1.98 (m, 4H), 1.57 (s, 9H).

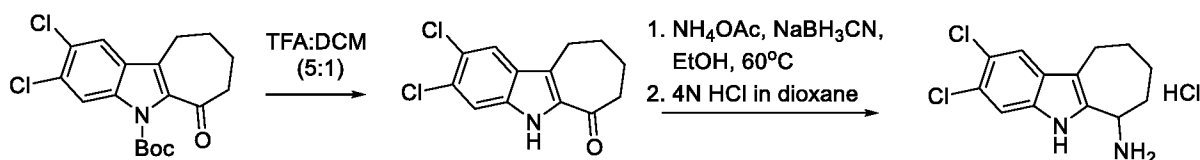
Step 2)

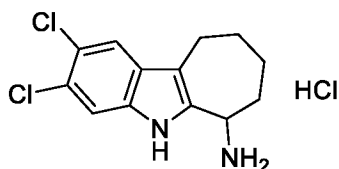


15 1,2-Dichloro-7,8,9,10-tetrahydrocyclohepta[*b*]indol-6(5*H*)-one

- To a solution of *tert*-butyl 1,2-dichloro-6-oxo-7,8,9,10-tetrahydrocyclohepta[*b*]indole-5(6*H*)-carboxylate (152 mg, 0.41 mmol) in dichloromethane (5 mL), trifluoroacetic acid (1 mL)
- 20 was added. The reaction mixture was stirred for an hour at room temperature. After removal of solvent, the mixture was diluted with ethyl acetate, and it was washed with 10% sodium hydroxide and brine. The organic layer was dried over sodium sulfate, and it was concentrated under reduced pressure to give product as a white solid (99 mg, 90%); ¹H NMR (300 MHz) (CDCl₃) δ 9.08 (bs, 1H), 7.35 (d, *J* = 9 Hz, 1H), 7.20 (d, *J* = 9 Hz, 1H), 3.58-3.54 (m, 2H), 2.87-
- 25 2.83 (m, 2H), 2.11-2.04 (m, 2H), 1.99-1.91 (m, 2H).

Example 21. Preparation of 2,3-dichloro-5,6,7,8,9,10-hexahydrocyclohepta[*b*]indol-6-amine.

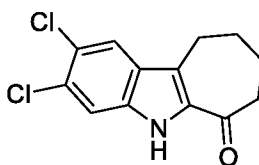


2,3-Dichloro-5,6,7,8,9,10-hexahydrocyclohepta[*b*]indol-6-amine hydrochloric acid

5 2,3-Dichloro-7,8,9,10-tetrahydrocyclohepta[*b*]indol-6(5*H*)-one (100 mg, 0.37 mmol), ammonium acetate (285 mg, 3.70 mmol) and sodium cyanoborohydride (116 mg, 1.85 mmol) were dissolved in ethanol (10 mL). The reaction mixture was stirred for overnight at 60 °C. After removal of solvent, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with 10% sodium hydroxide and brine, and it was dried over sodium sulfate. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give product as a white solid. The solid was then treated with 4N hydrochloric acid in dioxane, and it was stirred for 30 minutes at room temperature. The white suspension was concentrated under reduced pressure, and the resulting residue was suspended in ethyl acetate. The suspension was filtered to give hydrochloric acid salt of product as a white solid (76 mg, 67%); ¹H NMR (300 MHz) (DMSO-*d*₆) δ 11.36 (bs, 1H), 8.44 (bs, 3H), 7.78 (s, 1H), 7.62 (s, 1H), 4.56 (m, 1H), 3.55-3.26 (m, 2H), 2.89-2.71 (m, 4H), 1.93-1.76 (m, 2H); LC/MS RT = 2.91 (M-H⁺: 267/269).

The requisite intermediate was prepared as follows:

20 Step 1)

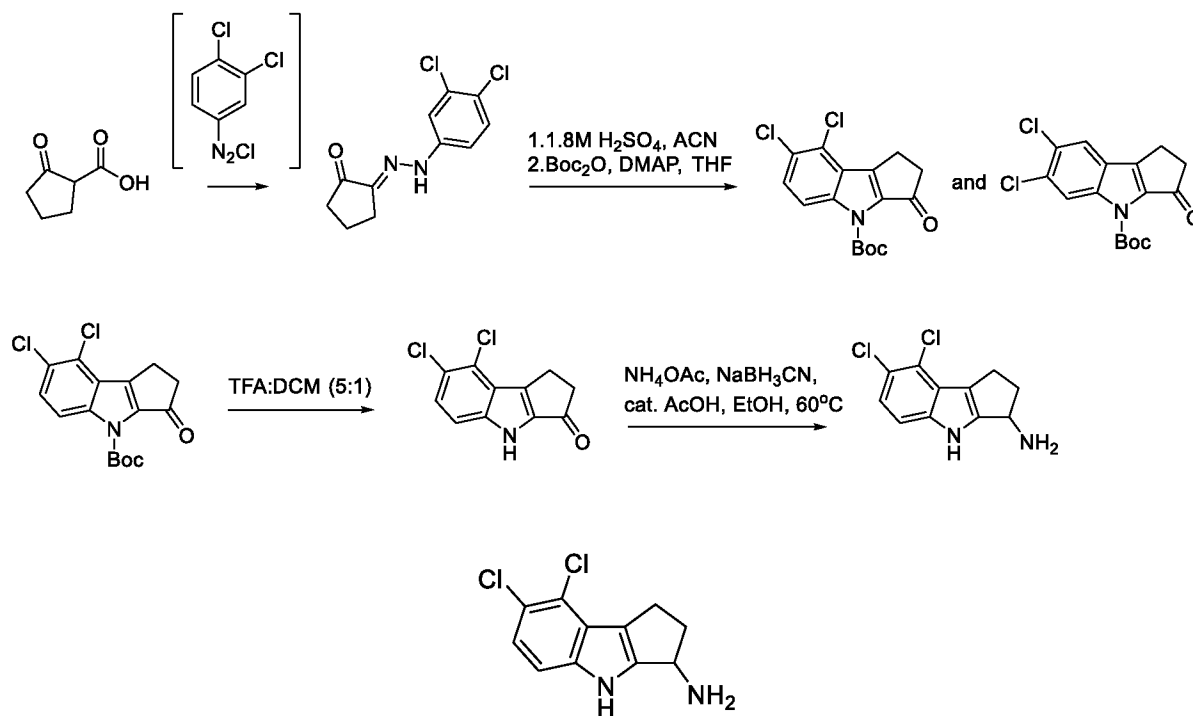
2,3-Dichloro-7,8,9,10-tetrahydrocyclohepta[*b*]indol-6(5*H*)-one

To a solution of *tert*-butyl 2,3-dichloro-6-oxo-7,8,9,10-tetrahydrocyclohepta[*b*]indole-5(6*H*)-carboxylate (943 mg, 2.64 mmol) in dichloromethane (25 mL), trifluoroacetic acid (5 mL) was added. The reaction mixture was stirred for 2 hours at room temperature. After removal of solvent, the mixture was diluted with ethyl acetate, and it was washed with 10% sodium hydroxide and brine. The organic layer was dried over sodium sulfate, and it was concentrated under reduced pressure to give product as a white solid (675 mg, 95%); ¹H NMR

(300 MHz) (CDCl_3) δ 8.90 (bs, 1H), 7.74 (s, 1H), 7.48 (s, 1H), 3.10-3.06 (m, 2H), 2.87-2.83 (m, 2H), 2.11-2.05 (m, 2H), 2.01-1.99 (m, 2H).

Example 22. Preparation of 7,8-dichloro-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-amine.

5



7,8-Dichloro-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-amine

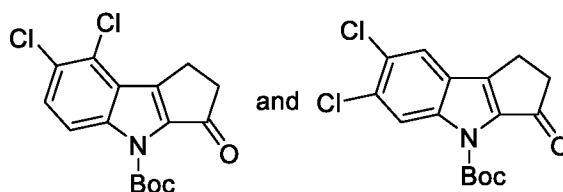
10

7,8-Dichloro-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (100 mg, 0.42 mmol), ammonium acetate (647 mg, 8.40 mmol) and sodium cyanoborohydride (132 mg, 2.10 mmol) were dissolved in ethanol (10 mL). The reaction mixture was stirred for overnight at 60 °C. After removal of solvent, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with 10% sodium hydroxide and brine, and it was dried over sodium sulfate. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH_4OH) to give product as a white solid (41 mg, 41%); ^1H NMR (300 MHz) (MeOD) δ 7.22 (d, $J = 9$ Hz, 1H), 7.09 (d, $J = 9$ Hz, 1H), 4.47-4.44 (m, 1H), 3.16-3.07 (m, 1H), 2.95-2.83 (m, 2H), 2.24-2.16 (m, 1H); LC/MS RT = 2.74 (M-H⁻: 239/241).

20

The requisite intermediate was prepared as follows:

Step 1)



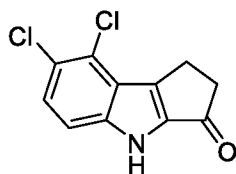
tert-Butyl 7,8-dichloro-3-oxo-2,3-dihydrocyclopenta[*b*]indole-4(1*H*)-carboxylate and *tert*-Butyl 6,7-dichloro-3-oxo-2,3-dihydrocyclopenta[*b*]indole-4(1*H*)-carboxylate

5 To a suspension of 3,4-dichloroaniline (8.10 g, 50.00 mmol) in water (30 mL), concentrated hydrochloric acid (12.5 mL) was slowly added at 0°C. Then, a solution of sodium nitrite (3.45 g, 50.00 mmol) in water (35 mL) was slowly added at 0 °C. The mixture was stirred for 30 minutes at 0 °C. This freshly prepared diazonium salt solution was slowly added to a solution of 2-oxocyclopentane-1-carboxylic acid (6.40 g, 50.00 mmol) in concentrated
10 hydrochloric acid (4.58 mL). The mixture was stirred for additional 30 minutes at 0 °C to give a yellow suspension. The suspension was filtered to give intermediate, (E)-2-(2-(3,4-dichlorophenyl)hydrazineylidene)cyclopentan-1-one, as an orange solid.

The intermediate was then dissolved in acetonitrile (50 mL), and 1.8M sulfuric acid was
15 added. The reaction mixture was stirred for overnight at 75 °C. The resulting dark brown suspension was diluted with ethyl acetate, and it was washed with 10% NaOH and brine. The organic layer was dried over sodium sulfate, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give a mixture of two regioisomers, 7,8-dichloro-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one and 6,7-
20 dichloro-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one as a dark brown solid (493 mg, 10%).

To a solution of a mixture of the two regioisomers (493 mg, 2.05 mmol) in tetrahydrofuran (25 mL), boc anhydride (895 mg, 4.10 mmol) and DAMP (230 mg, 2.05 mmol) were added. The reaction mixture was stirred for 3 hours. The reaction mixture was diluted
25 with ethyl acetate, and it was washed with saturated ammonium chloride, followed by brine. The organic layer was dried over sodium sulfate, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give *tert*-butyl 7,8-dichloro-3-oxo-2,3-dihydrocyclopenta[*b*]indole-4(1*H*)-carboxylate (121 mg, 17%). ¹H NMR (300 MHz) (CDCl₃) δ 8.15 (d, *J* = 9 Hz, 1H), 7.48 (d, *J* = 9 Hz, 1H), 3.26-3.22 (m, 2H), 3.02-2.99 (m, 2H), 1.68 (s, 9H). along with *tert*-butyl 6,7-dichloro-3-oxo-2,3-
30 dihydrocyclopenta[*b*]indole-4(1*H*)-carboxylate (160 mg, 23%). ¹H NMR (300 MHz) (CDCl₃) δ 8.47 (s, 1H), 7.73 (s, 1H), 3.01-3.00 (m, 4H), 1.69 (s, 9H).

Step 2)



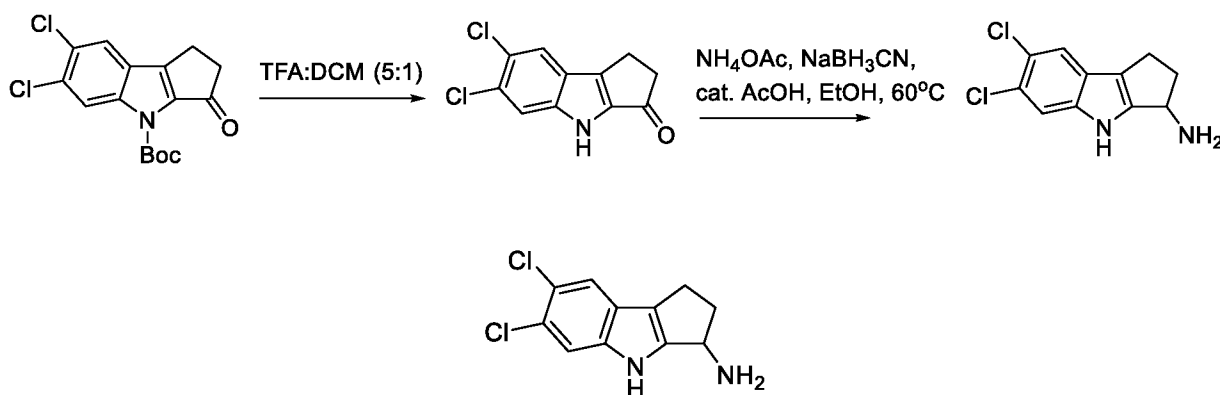
7,8-Dichloro-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one

5

To a solution of *tert*-butyl 7,8-dichloro-3-oxo-2,3-dihydrocyclopenta[*b*]indole-4(1*H*)-carboxylate (121 mg, 0.36 mmol) in dichloromethane (5 mL), trifluoroacetic acid (1 mL) was added. The reaction mixture was stirred for an hour at room temperature. After removal of solvent, the mixture was diluted with ethyl acetate, and it was washed with 10% sodium hydroxide and brine. The organic layer was dried over sodium sulfate, and it was concentrated under reduced pressure to give product as a white solid (27 mg, 31%); ¹H NMR (300 MHz) (CDCl₃) δ 9.61 (bs, 1H), 7.41 (d, *J* = 9 Hz, 1H), 7.36 (d, *J* = 9 Hz, 1H), 3.35-3.32 (m, 2H), 3.09-3.03 (m, 2H).

10

15 Example 23. Preparation of 6,7-dichloro-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-amine.



20

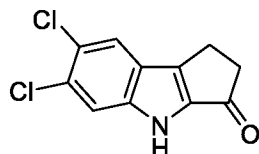
6,7-Dichloro-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-amine

6,7-Dichloro-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (148 mg, 0.62 mmol), ammonium acetate (956 mg, 12.4 mmol) and sodium cyanoborohydride (195 mg, 3.1 mmol) were dissolved in ethanol (20 mL). The reaction mixture was stirred for overnight at 60 °C. After removal of solvent, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with 10% sodium hydroxide and brine, and it was dried over sodium sulfate. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give product as a white

solid (93 mg, 62%); ^1H NMR (300 MHz) (MeOD) δ 7.46 (s, 1H), 7.45 (s, 1H), 4.43-4.39 (m, 1H), 2.93-2.79 (m, 2H), 2.71-2.61 (m, 1H), 2.21-2.12 (m, 1H); LC/MS RT = 2.74 (M-H $^+$: 239/241).

5 The requisite intermediate was prepared as follows:

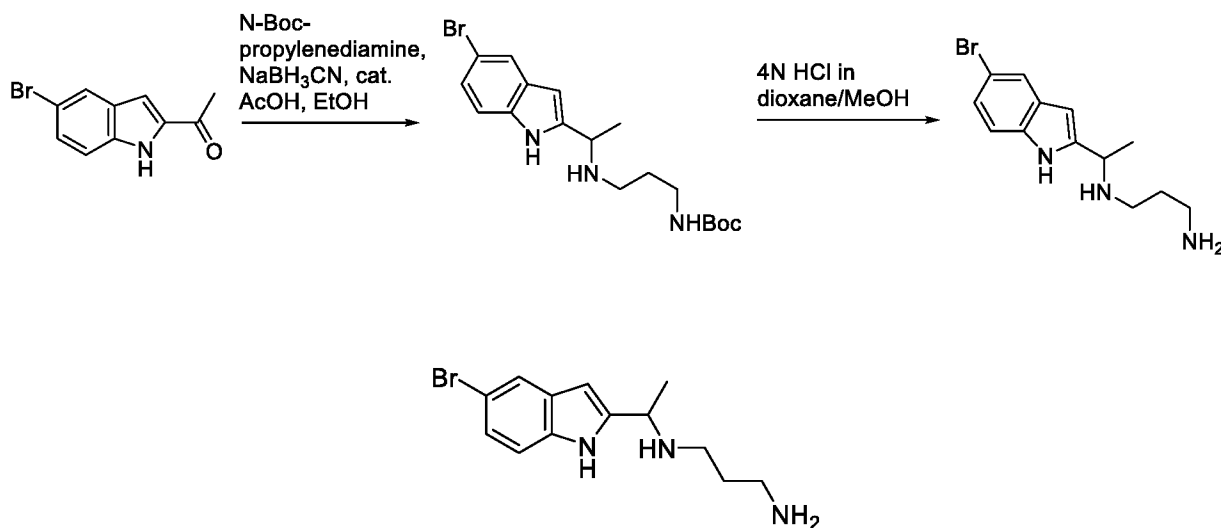
Step 1)



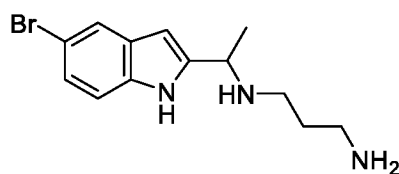
6,7-Dichloro-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one

10 To a solution of *tert*-butyl 6,7-dichloro-3-oxo-2,3-dihydrocyclopenta[*b*]indole-4(1*H*)-carboxylate (571 mg, 1.68 mmol) in dichloromethane (25 mL), trifluoroacetic acid (5 mL) was added. The reaction mixture was stirred for an hour at room temperature. After removal of solvent, the mixture was diluted with ethyl acetate, and it was washed with 10% sodium hydroxide and brine. The organic layer was dried over sodium sulfate, and it was concentrated
15 under reduced pressure to give product as a white solid (148 mg, 37%); ^1H NMR (300 MHz) (DMSO- d_6) δ 11.98 (bs, 1H), 8.06 (s, 1H), 7.64 (s, 1H), 3.02-2.99 (m, 2H), 2.90-2.87 (m, 2H).

Example 24. Preparation of N¹-(1-(5-bromo-1*H*-indol-2-yl)ethyl)propane-1,3-diamine.



N¹-(1-(5-Bromo-1*H*-indol-2-yl)ethyl)propane-1,3-diamine

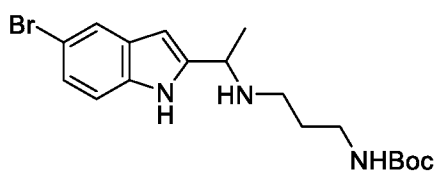


N¹-(1-(5-Bromo-1H-indol-2-yl)ethyl)propane-1,3-diamine

To a solution of *tert*-butyl (3-((1-(5-bromo-1H-indol-2-yl)ethyl)amino)propyl)carbamate (817 mg, 2.06 mmol) in methanol (3 mL), 4N HCl in dioxane (6 mL, 24 mmol) was added. The reaction mixture was stirred for an hour at room temperature. After removal of solvent, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with 10% sodium hydroxide and brine, and it was dried over sodium sulfate. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give the product as colorless oil (332 mg, 54%); ¹H NMR (300 MHz) (CDCl₃) δ 9.22 (bs, 1H), 7.65 (s, 1H), 7.26-7.20 (m, 3H), 6.24 (s, 1H), 4.05-4.01 (m, 1H), 2.83-2.54 (m, 4H), 1.67-1.60 (m, 2H), 1.45 (d, *J* = 6 Hz, 3H); LC/MS RT = 2.49 (M+H⁺: 296/298).

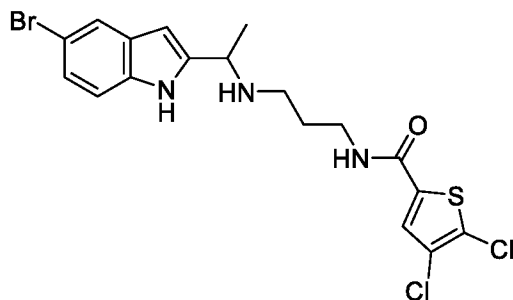
The requisite intermediate was prepared as follows:

Step 1)

*tert*-Butyl (3-((1-(5-bromo-1H-indol-2-yl)ethyl)amino)propyl)carbamate

1-(5-Bromo-1H-indol-2-yl)ethan-1-one (500 mg, 2.10 mmol), N-boc propylenediamine (1.10 g, 6.30 mmol) and sodium cyanoborohydride (314 mg, 10.50 mmol) were dissolved in ethanol (20 mL). Catalytic amount of acetic acid was added. The reaction mixture was stirred for overnight at 60 °C. After removal of solvent, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with 10% sodium hydroxide and brine, and it was dried over sodium sulfate. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give the product as colorless oil (817 mg, 99%); ¹H NMR (300 MHz) (CDCl₃) δ 9.50 (bs, 1H), 7.68 (s, 1H), 7.37-7.26 (m, 3H), 6.43 (s, 1H), 5.04 (m, 1H), 4.35-4.33 (m, 1H), 3.30-3.28 (m, 2H), 2.80-2.76 (m, 2H), 1.85-1.80 (m, 2H), 1.75 (d, *J* = 7 Hz, 3H), 1.46 (s, 9H).

Example 25. Preparation of N-(3-((1-(5-bromo-1*H*-indol-2-yl)ethyl)amino)propyl)-4,5-dichlorothiophene-2-carboxamide.



N-(3-((1-(5-Bromo-1*H*-indol-2-yl)ethyl)amino)propyl)-4,5-dichlorothiophene-2-carboxamide

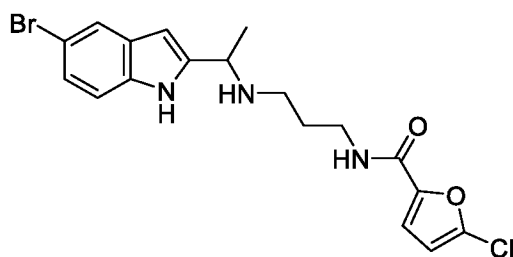
5

4,5-Dichlorothiophene-2-carboxylic acid (162 mg, 0.82 mmol), EDC hydrochloric acid (157 mg, 0.82 mmol), HOBt (55 mg, 0.41 mmol) and DIPEA (0.23 mL, 1.26 mmol) were dissolved in DMF (5 mL). After 5 minutes of stirring, N¹-(1-(5-bromo-1*H*-indol-2-yl)ethyl)propane-1,3-diamine (120 mg, 0.41 mmol) was added, and it was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, and it was washed with 1N hydrochloric acid, 10% sodium hydroxide and brine. The organic layer was dried over sodium sulfate. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give the product as a white solid (63 mg, 32%); ¹H NMR (300 MHz) (CDCl₃) δ 8.88 (bs, 1H), 7.64 (s, 1H), 7.26-7.12 (m, 3H), 7.06 (bs, 1H), 6.26 (s, 1H), 4.04-3.98 (m, 1H), 3.65-3.58 (m, 1H), 3.49-3.40 (m, 1H), 2.75-2.69 (m, 1H), 2.63-2.57 (m, 1H) 1.74-1.68 (m, 2H), 1.49 (d, *J* = 7 Hz, 3H); LC/MS RT = 3.05 (M+H⁺: 474/476/478).

15

Example 26. Preparation of N-(3-((1-(5-bromo-1*H*-indol-2-yl)ethyl)amino)propyl)-4,5-dichlorothiophene-2-carboxamide.

20



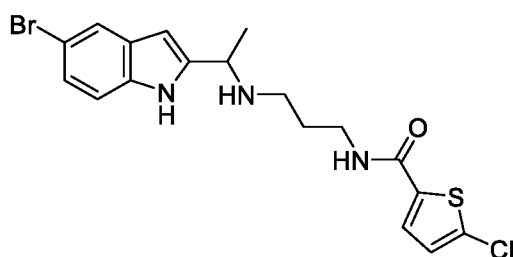
N-(3-((1-(5-Bromo-1*H*-indol-2-yl)ethyl)amino)propyl)-5-chlorofuran-2-carboxamide

25

5-Chlorofuran-2-carboxylic acid (120 mg, 0.82 mmol), EDC hydrochloric acid (157 mg, 0.82 mmol), HOBt (55 mg, 0.41 mmol) and DIPEA (0.23 mL, 1.26 mmol) were dissolved in

DMF (5 mL). After 5 minutes of stirring, N¹-(1-(5-bromo-1*H*-indol-2-yl)ethyl)propane-1,3-diamine (120 mg, 0.41 mmol) was added, and it was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, and it was washed with 1N hydrochloric acid, 10% sodium hydroxide and brine. The organic layer was dried over sodium sulfate. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give the product as a white solid (54 mg, 31%); ¹H NMR (300 MHz) (CDCl₃) δ 9.02 (bs, 1H), 7.63 (s, 1H), 7.18 (m, 2H), 7.11 (d, *J* = 3 Hz, 1H), 7.05 (bs, 1H), 6.32 (d, *J* = 3 Hz, 1H), 6.24 (s, 1H), 4.03-3.98 (m, 1H), 3.76-3.69 (m, 1H), 3.51-3.35 (m, 1H), 2.73-2.68 (m, 1H), 2.60-2.54 (m, 1H), 1.72-1.69 (m, 2H), 1.49 (d, *J* = 6 Hz, 3H); LC/MS RT = 2.95 (M+H⁺: 424/426/428).

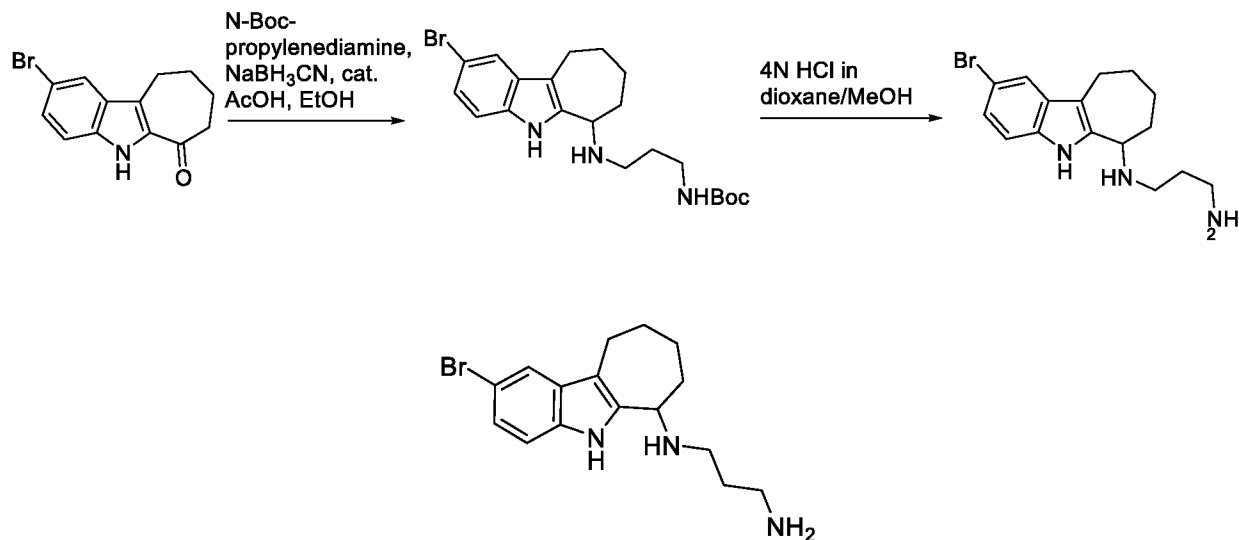
Example 27. Preparation of N-(3-((1-(5-bromo-1*H*-indol-2-yl)ethyl)amino)propyl)-5-chlorothiophene-2-carboxamide.



N-(3-((1-(5-Bromo-1*H*-indol-2-yl)ethyl)amino)propyl)-5-chlorothiophene-2-carboxamide

5-Chlorothiophene-2-carboxylic acid (249 mg, 1.53 mmol), EDC hydrochloric acid (196 mg, 1.02 mmol), HOBt (69 mg, 0.51 mmol) and DIPEA (0.27 mL, 1.53 mmol) were dissolved in DMF (2 mL). After 5 minutes of stirring, N¹-(1-(5-bromo-1*H*-indol-2-yl)ethyl)propane-1,3-diamine (150 mg, 0.51 mmol) was added, and it was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, and it was washed with 1N hydrochloric acid, 10% sodium hydroxide and brine. The organic layer was dried over sodium sulfate. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give the product as a white solid (29 mg, 13%); ¹H NMR (300 MHz) (CDCl₃) δ 9.07 (bs, 1H), 7.64 (s, 1H), 7.26-7.06 (m, 2H), 6.79-6.78 (m, 2H), 6.26 (s, 1H), 4.05-4.00 (m, 1H), 3.66-3.60 (m, 1H), 3.51-3.39 (m, 1H), 2.75-2.71 (m, 1H), 2.62-2.54 (m, 1H), 1.73-1.70 (m, 2H), 1.51 (d, *J* = 7 Hz, 3H); LC/MS RT = 3.05 (M+H⁺: 440/442/444).

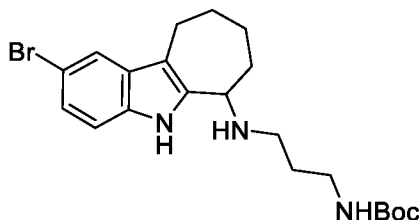
Example 28. Preparation of N¹-(2-bromo-5,6,7,8,9,10-hexahydrocyclohepta[*b*]indol-6-yl)propane-1,3-diamine.



N¹-(2-Bromo-5,6,7,8,9,10-hexahydrocyclohepta[*b*]indol-6-yl)propane-1,3-diamine

To a solution of *tert*-butyl (3-((2-bromo-5,6,7,8,9,10-hexahydrocyclohepta[*b*]indol-6-yl)amino)propyl)carbamate (614 mg, 1.41 mmol) in methanol (3 mL), 4N HCl in dioxane (6 mL, 24 mmol) was added. The reaction mixture was stirred for 1.0 hour at room temperature. After removal of solvent, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with 10% sodium hydroxide and brine, and it was dried over sodium sulfate. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give the product as yellow oil (202 mg, 43%); ¹H NMR (300 MHz) (CDCl₃) δ 10.02 (bs, 1H), 7.58 (s, 1H), 7.15-7.14 (m, 2H), 3.87-3.83 (m, 1H), 2.96-2.75 (m, 6H), 2.63-2.51 (m, 1H), 2.12-2.02 (m, 2H), 1.94-1.88 (m, 1H), 1.74-1.62 (m, 4H); LC/MS RT = 2.52 (M+H⁺: 336/338).

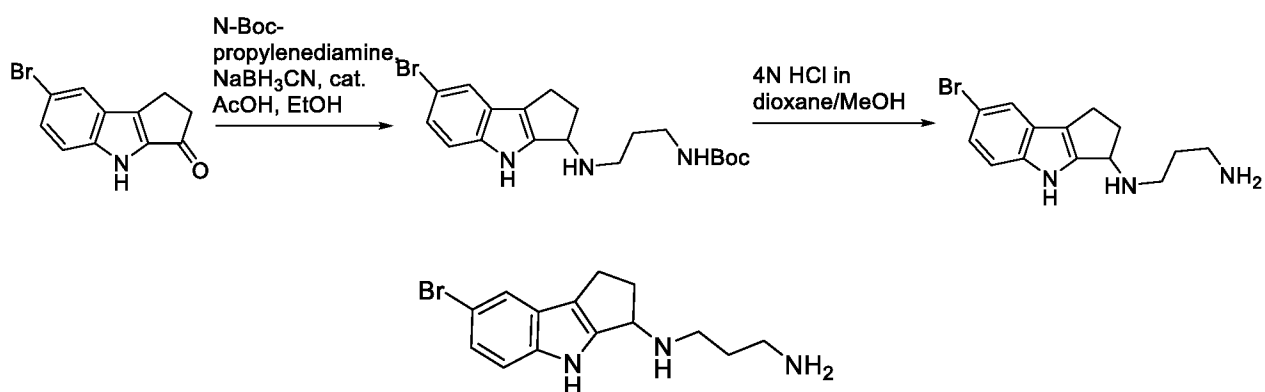
The requisite intermediate was prepared as follows:
Step 1)



tert-Butyl (3-((2-bromo-5,6,7,8,9,10-hexahydrocyclohepta[*b*]indol-6-yl)amino)propyl)carbamate

2-Bromo-7,8,9,10-tetrahydrocyclohepta[*b*]indol-6(5*H*)-one (500 mg, 1.80 mmol), N-boc propylenediamine (941 mg, 5.40 mmol) and sodium cyanoborohydride (566 mg, 9.00 mmol) were dissolved in ethanol (20 mL). Catalytic amount of acetic acid was added. The reaction mixture was stirred for overnight at 60 °C. After removal of solvent, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with 10% sodium hydroxide and brine, and it was dried over sodium sulfate. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give the product as yellow oil (614 mg, 78%); ¹H NMR (300 MHz) (CDCl₃) δ 9.51 (bs, 1H), 7.61 (s, 1H), 7.36-7.25 (m, 2H), 5.14-5.12 (m, 1H), 4.62-4.61 (m, 1H), 3.25-2.80 (m, 6H), 2.45-2.43 (m, 1H), 2.12-1.82 (m, 7H), 1.39 (s, 9H); LC/MS RT = 3.13 (M+H⁺: 436/438).

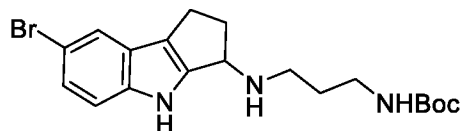
Example 29. Preparation of N¹-(7-bromo-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)propane-1,3-diamine.



To a solution of *tert*-butyl (3-((7-bromo-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)amino)propyl)carbamate (817 mg, 2.00 mmol) in methanol (3 mL), 4N HCl in dioxane (6 mL, 24 mmol) was added. The reaction mixture was stirred for an hour at room temperature. After removal of solvent, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with 10% sodium hydroxide and brine, and it was dried over sodium sulfate. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give the product as a white solid (616 mg, 100%); ¹H NMR (300 MHz) (CDCl₃) δ 9.25 (bs, 1H), 7.58 (s, 1H), 7.26-7.18 (m, 2H), 4.37-4.33 (m, 1H), 2.88-2.65 (m, 8H), 2.12-2.04 (m, 1H), 2.04-1.97 (m, 2H); LC/MS RT = 2.50 (M+H⁺: 308/310).

The requisite intermediate was prepared as follows:

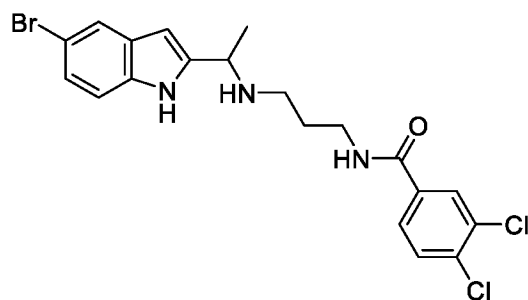
Step 1)



5 *tert*-Butyl (3-((7-bromo-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)amino)propyl)carbamate

7-Bromo-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (500 mg, 2.00 mmol), N-boc propylenediamine (1.05 g, 6.00 mmol) and sodium cyanoborohydride (628 mg, 10.00 mmol) were dissolved in ethanol (20 mL). Catalytic amount of acetic acid was added. The reaction mixture was stirred for overnight at 60 °C. After removal of solvent, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with 10% sodium hydroxide and brine, and it was dried over sodium sulfate. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give the product as a foamy yellow solid (817 mg, 100%); ¹H NMR (300 MHz) (CDCl₃) δ 9.16 (bs, 1H), 7.63 (s, 1H), 7.33-7.32 (m, 2H), 5.07-5.03 (m, 1H), 4.83 (m, 1H), 3.26-3.24 (m, 2H), 3.04-2.85 (m, 5H), 2.60-2.54 (m, 1H), 1.98-1.96 (m, 2H), 1.39 (s, 9H); LC/MS RT = 3.08 (M+H⁺: 408/410).

Example 30. Preparation of N-(3-((1-(5-bromo-1*H*-indol-2-yl)ethyl)amino)propyl)-3,4-dichlorobenzamide.

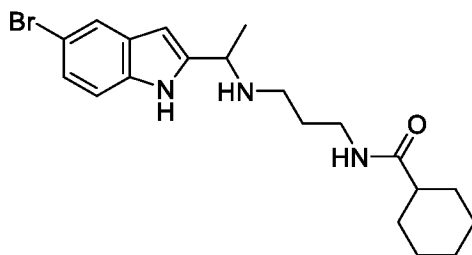


N-(3-((1-(5-Bromo-1*H*-indol-2-yl)ethyl)amino)propyl)-3,4-dichlorobenzamide

3,4-Dichlorobenzoic acid (32 mg, 0.17 mmol), EDC hydrochloric acid (65 mg, 0.34 mmol), HOBt (23 mg, 0.17 mmol) and DIPEA (0.09 mL, 0.51 mmol) were dissolved in dichloromethane (5 mL). After 5 minutes of stirring, N¹-(1-(5-bromo-1*H*-indol-2-yl)ethyl)propane-1,3-diamine (50 mg, 0.17 mmol) was added, and it was stirred overnight at

room temperature. The reaction mixture was diluted with ethyl acetate, and it was washed with 1N hydrochloric acid, 10% sodium hydroxide and brine. The organic layer was dried over sodium sulfate. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give the product as colorless oil (14 mg, 18%); ¹H NMR (300 MHz) (CDCl₃) δ 9.97 (bs, 1H), 7.88 (d, *J* = 2 Hz, 1H), 7.64 (s, 1H), 7.53 (dd, *J* = 8 Hz, *J* = 2 Hz, 2H), 7.42 (d, *J* = 8 Hz, 1H), 7.25-7.18 (m, 2H), 4.35-4.28 (m, 1H), 3.63-3.48 (m, 2H), 2.81-2.69 (m, 2H), 1.94-1.90 (m, 2H), 1.72 (d, *J* = 7 Hz, 3H); LC/MS RT = 3.12 (M+H⁺: 468/470/472).

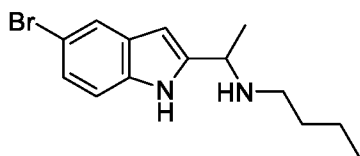
Example 31. Preparation of N-(3-((1-(5-bromo-1*H*-indol-2-yl)ethyl)amino)propyl)-cyclohexanecarboxamide



N-(3-((1-(5-Bromo-1*H*-indol-2-yl)ethyl)amino)propyl)cyclohexanecarboxamide

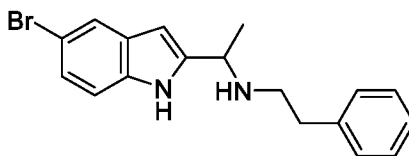
Cyclohexane carboxylic acid (22 mg, 0.17 mmol), EDC hydrochloric acid (65 mg, 0.34 mmol), HOBt (23 mg, 0.17 mmol) and DIPEA (0.09 mL, 0.51 mmol) were dissolved in dichloromethane (5 mL). After 5 minutes of stirring, N¹-(1-(5-bromo-1*H*-indol-2-yl)ethyl)propane-1,3-diamine (50 mg, 0.17 mmol) was added, and it was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, and it was washed with 1N hydrochloric acid, 10% sodium hydroxide and brine. The organic layer was dried over sodium sulfate. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give the product as colorless oil (55 mg, 80%); ¹H NMR (300 MHz) (CDCl₃) δ 9.28 (bs, 1H), 7.64 (d, *J* = 2 Hz, 1H), 7.26 (d, *J* = 9 Hz, 1H), 7.19 (dd, *J* = 8 Hz, *J* = 2 Hz, 1H), 6.23 (d, *J* = 1 Hz, 1H), 5.68 (bs, 1H), 4.00-3.96 (m, 1H), 3.54-3.47 (m, 1H), 3.27-3.20 (m, 1H), 2.62-2.54 (m, 1H), 2.49-2.41 (m, 1H), 2.04-2.00 (m, 1H), 1.79-1.57 (m, 6H), 1.47 (d, *J* = 7 Hz, 3H), 1.38-1.14 (m, 6H); LC/MS RT = 2.88 (M+H⁺: 406/408).

Example 32. Preparation of N-(1-(5-bromo-1*H*-indol-2-yl)ethyl)butan-1-amine.

N-(1-(5-Bromo-1*H*-indol-2-yl)ethyl)butan-1-amine

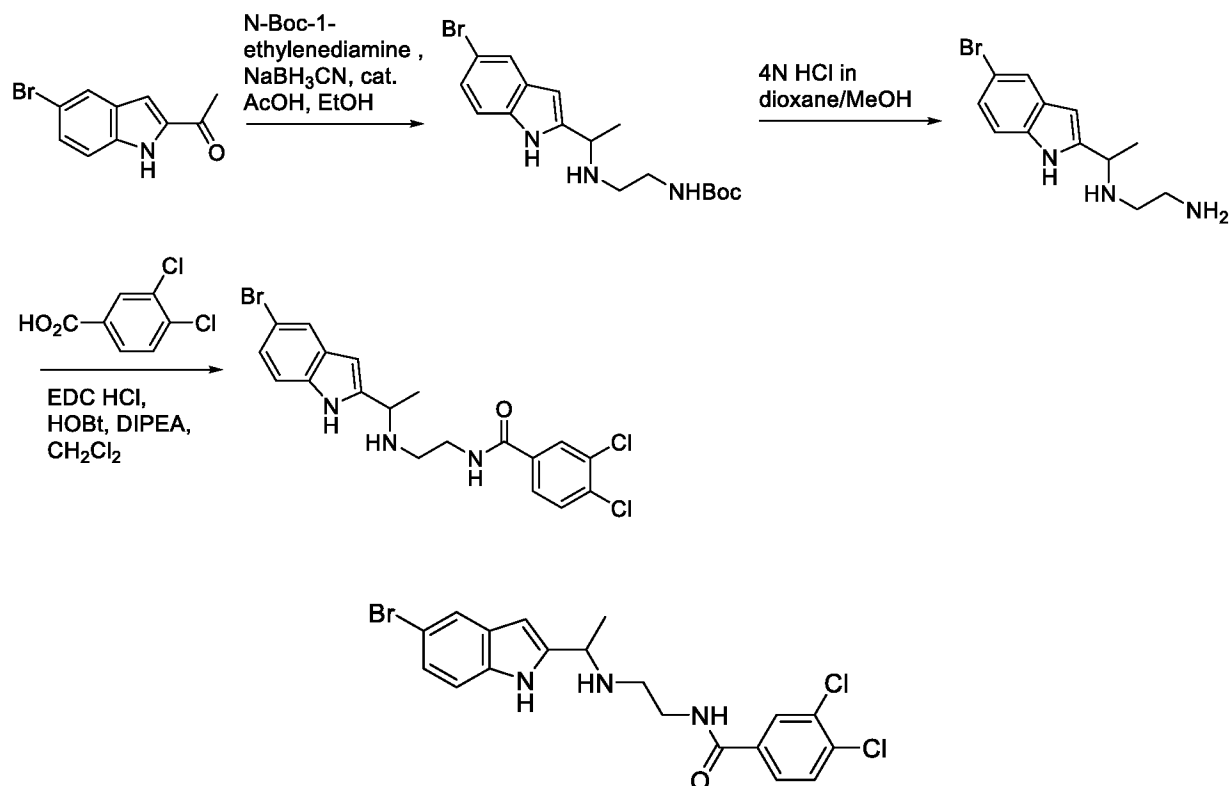
1-(5-Bromo-1*H*-indol-2-yl)ethan-1-one (100 mg, 0.42 mmol), *n*-butylamine (0.42 mL, 4.20 mmol) and sodium cyanoborohydride (132 mg, 2.10 mmol) were dissolved in ethanol (50 mL). Catalytic amount of acetic acid was added. The reaction mixture was stirred for overnight at 60 °C. After removal of solvent, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with 10% sodium hydroxide and brine, and it was dried over sodium sulfate. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give the product as colorless oil (94 mg, 76%); ¹H NMR (300 MHz) (CDCl₃) δ 8.83 (bs, 1H), 7.67 (s, 1H), 7.26-7.23 (m, 2H), 6.29 (s, 1H), 4.14-4.07 (m, 1H), 2.64-2.50 (m, 2H), 1.51 (d, *J* = 7 Hz, 3H), 1.47-1.44 (m, 2H), 1.36-1.29 (m, 2H), 0.89 (t, *J* = 7 Hz, 3H); LC/MS RT = 2.79 (M+H⁺: 295/297).

Example 33. Preparation of 1-(5-bromo-1*H*-indol-2-yl)-*N*-phenethylethan-1-amine.

1-(5-Bromo-1*H*-indol-2-yl)-*N*-phenethylethan-1-amine

1-(5-Bromo-1*H*-indol-2-yl)ethan-1-one (100 mg, 0.42 mmol), phenethylamine (0.53 mL, 4.20 mmol) and sodium cyanoborohydride (132 mg, 2.10 mmol) were dissolved in ethanol (50 mL). A catalytic amount of acetic acid was added. The reaction mixture was stirred for overnight at 60 °C. After removal of solvent, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with 10% sodium hydroxide and brine, and it was dried over sodium sulfate. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give the product as colorless oil (47 mg, 33%); ¹H NMR (300 MHz) (CDCl₃) δ 8.41 (bs, 1H), 7.63 (d, *J* = 2 Hz, 1H), 7.34-7.11 (m, 6H), 7.10 (d, *J* = 9 Hz, 1H), 6.21 (d, *J* = 2 Hz, 1H), 4.06-4.00 (m, 1H), 2.92-2.84 (m, 1H), 2.79-2.71 (m, 3H), 1.40 (d, *J* = 7 Hz, 3H); LC/MS RT = 3.02 (M+H⁺: 343/345).

Example 34. Preparation of N-(2-((1-(5-bromo-1*H*-indol-2-yl)ethyl)amino)ethyl)-3,4-dichlorobenzamide.

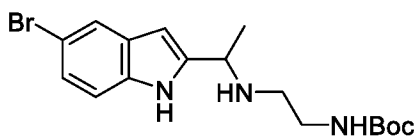


N-(2-((1-(5-Bromo-1*H*-indol-2-yl)ethyl)amino)ethyl)-3,4-dichlorobenzamide

3,4-Dichlorobenzoic acid (66 mg, 0.35 mmol), EDC hydrochloric acid (134 mg, 0.70 mmol), HOBT (47 mg, 0.35 mmol) and DIPEA (0.19 mL, 1.05 mmol) were dissolved in dichloromethane (10 mL). After 5 minutes of stirring, N¹-(1-(5-bromo-1*H*-indol-2-yl)ethyl)ethane-1,2-diamine (100 mg, 0.35 mmol) was added, and it was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, and it was washed with 1N hydrochloric acid, 10% sodium hydroxide and brine. The organic layer was dried over sodium sulfate. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give the product as colorless oil (38 mg, 24%); ¹H NMR (300 MHz) (CDCl₃) δ 8.81 (bs, 1H), 7.83 (s, 1H), 7.65 (s, 1H), 7.49-7.46 (m, 2H), 7.23-7.13 (m, 2H), 6.49 (bs, 1H), 6.27 (s, 1H), 4.11-4.05 (m, 1H), 3.54-3.44 (m, 2H), 2.91-2.72 (m, 2H), 1.48 (d, *J* = 7 Hz, 3H); LC/MS RT = 3.04 (M+H⁺: 454/456/458).

The requisite intermediate was prepared as follows:

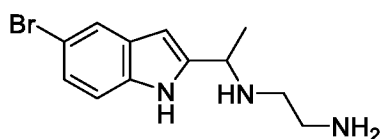
Step 1)



tert-Butyl (2-((1-(5-bromo-1*H*-indol-2-yl)ethyl)amino)ethyl)carbamate

1-(5-Bromo-1*H*-indol-2-yl)ethan-1-one (300 mg, 1.26 mmol), N-boc-1-ethylenediamine
 5 (0.59 mL, 3.78 mmol) and sodium cyanoborohydride (396 mg, 6.30 mmol) were dissolved in ethanol (10 mL). A catalytic amount of acetic acid was added. The reaction mixture was stirred for overnight at 60 °C. After removal of solvent, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with 10% sodium hydroxide and brine, and it was dried over sodium sulfate. The organic layer was concentrated under reduced pressure. The residue
 10 was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane) to give the product as colorless oil (482 mg, 100%); ¹H NMR (300 MHz) (CDCl₃) δ 9.33 (bs, 1H), 7.67 (s, 1H), 7.30-7.26 (m, 2H), 6.39 (d, *J* = 2 Hz, 1H), 5.10 (m, 1H), 4.39-4.35 (m, 1H), 3.30-3.28 (m 2H), 2.88-2.86 (m, 2H), 1.66 (d, *J* = 6 Hz, 3H), 1.44 (s, 9H).

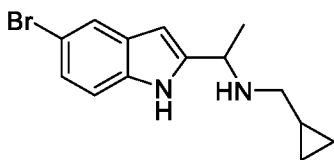
15 Step 2)



N¹-(1-(5-Bromo-1*H*-indol-2-yl)ethyl)ethane-1,2-diamine

To a solution of *tert*-butyl (2-((1-(5-bromo-1*H*-indol-2-yl)ethyl)amino)ethyl)carbamate
 20 (482 mg, 1.26 mmol) in methanol (2 mL), 4N HCl in dioxane (4 mL, 16 mmol) was added. The reaction mixture was stirred for an hour at room temperature. After removal of solvent, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with 10% sodium hydroxide and brine, and it was dried over sodium sulfate. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-
 25 10% methanol/dichloromethane + 0.1% NH₄OH) to give the product as colorless oil (351 mg, 99%); ¹H NMR (300 MHz) (CDCl₃) δ 9.09 (bs, 1H), 7.65 (s, 1H), 7.20-7.19 (m, 2H), 6.24 (s, 1H), 4.07-4.01 (m, 1H), 2.82-2.67 (m, 3H), 2.58-2.51 (m, 1H), 1.46 (d, *J* = 6 Hz, 3H).

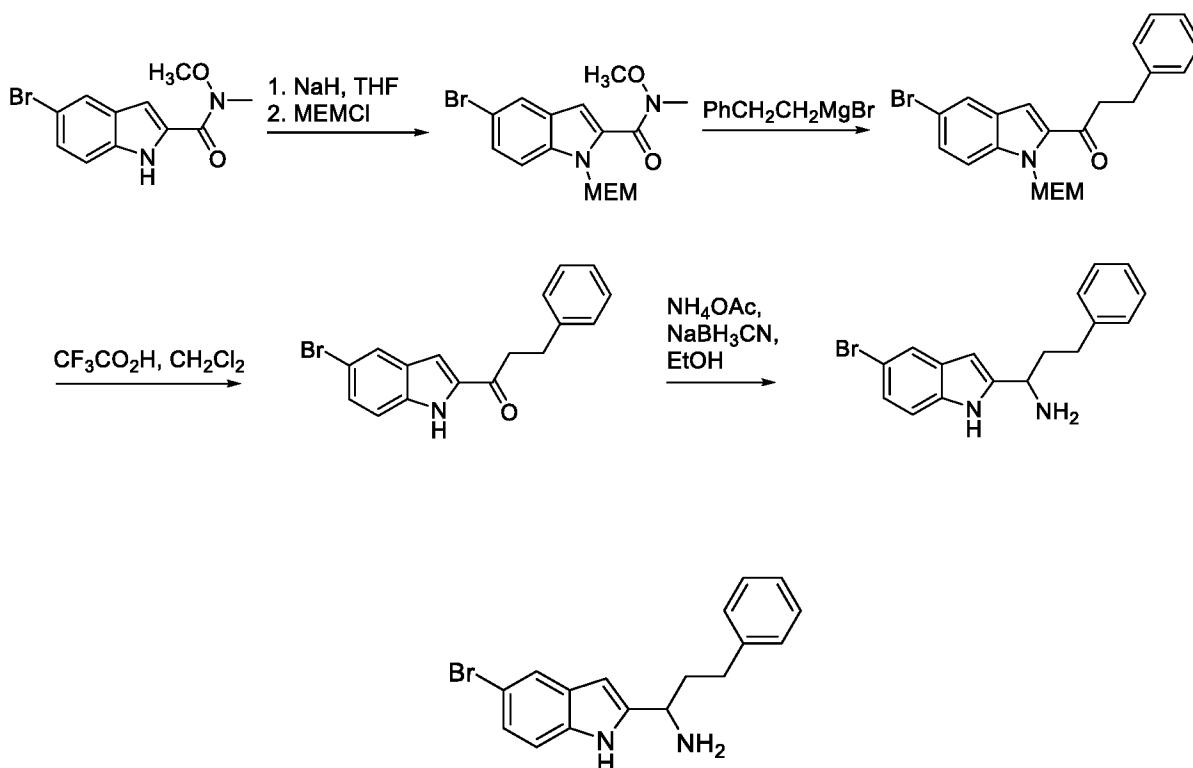
Example 35. Preparation of 1-(5-bromo-1*H*-indol-2-yl)-*N*-(cyclopropylmethyl)ethan-1-amine.



1-(5-Bromo-1*H*-indol-2-yl)-*N*-(cyclopropylmethyl)ethan-1-amine

To a solution of 1-(5-bromo-1*H*-indol-2-yl)ethan-1-one (190 mg, 0.80 mmol) in ethanol (10 mL), cyclopropanemethylamine hydrochloride (452 mg, 4.20 mmol), sodium cyanoborohydride (132 mg, 2.19 mmol), and DIPEA (0.73 mL, 4.20 mmol) were added. The reaction mixture was stirred for 60 °C for 24 hours. The mixture was diluted with ethyl acetate, and the organic layer was washed with 10% sodium hydroxide, saturated ammonium chloride, and brine. The organic layer was then dried over sodium sulfate, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (10% methanol/dichloromethane + 1% NH₄OH) to give product as colorless oil (30 mg, 24%); ¹H NMR (300 MHz, CDCl₃) δ 9.34 (bs, 1H), 7.70 (s, 1H), 7.33-7.24 (m, 2H), 6.48 (s, 1H), 4.62-4.55 (m, 1H), 2.71-2.57 (m, 2H), 1.84 (d, *J* = 6 Hz, 3H), 1.11-1.04 (m, 1H), 0.71-0.64 (m, 1H), 0.31-0.26 (m, 1H); LC/MS RT = 2.88 (M+H⁺: 293/295).

Example 36. Preparation of 1-(5-bromo-1*H*-indol-2-yl)-3-phenylpropan-1-amine.

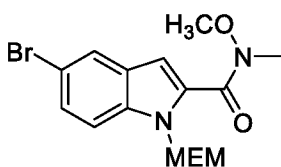


1-(5-Bromo-1*H*-indol-2-yl)-3-phenylpropan-1-amine

To a solution of 1-(5-bromo-1*H*-indol-2-yl)-3-phenylpropan-1-one (50 mg, 0.15 mmol) in ethanol (10 mL), ammonium acetate (115 mg, 1.50 mmol) and sodium cyanoborohydride (47 mg, 0.75 mmol) were added. The reaction mixture was stirred for overnight at 60 °C. After removal of solvent, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with 10% sodium hydroxide and brine, and it was then dried over sodium sulfate. The organic layer was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-10% methanol/dichloromethane + 0.1% NH₄OH) to give product as colorless oil (47 mg, 96%); ¹H NMR (300 MHz) (CDCl₃) δ 8.87 (bs, 1H), 7.62 (s, 1H), 7.24-7.15 (m, 5H), 7.08 (d, *J* = 7 Hz, 2H), 6.40 (s, 1H), 4.24 (m, 1H), 2.52-2.46 (m, 2H), 2.29-2.26 (m, 2H); LC/MS RT = 3.00 (M-H⁺: 327/329).

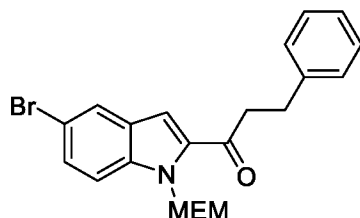
The requisite intermediate was prepared as follows:

Step 1)

5-Bromo-N-methoxy-1-((2-methoxyethoxy)methyl)-N-methyl-1*H*-indole-2-carboxamide

To a solution of 5-bromo-N-methoxy-N-methyl-1*H*-indole-2-carboxamide (100 mg, 0.35 mmol) in tetrahydrofuran (10 mL), sodium hydride (60% dispersed in oil, 28 mg, 0.70 mmol) was added at 0 °C. Then MEM chloride (79 μL, 0.70 mmol) was added at 0 °C. The reaction mixture was stirred for an hour at 0 °C. The mixture was quenched with water, and it was diluted with ethyl acetate. The organic layer was washed with saturated ammonium chloride and brine. The organic layer was dried over sodium sulfate, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-50% ethyl acetate/hexane) to give product as colorless oil (121 mg, 93%); ¹H NMR (300 MHz) (CDCl₃) δ 7.74 (s, 1H), 7.46-7.40 (m, 2H), 7.03 (s, 1H), 5.86 (s, 2H), 3.66 (s, 3H), 3.64-3.51 (m, 2H), 3.44-3.38 (m, 5H), 3.30 (m, 3H).

Step 2)

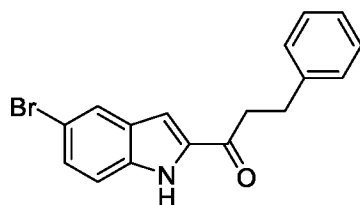


1-(5-Bromo-1-((2-methoxyethoxy)methyl)-1*H*-indol-2-yl)-3-phenylpropan-1-one

5 To a solution of 5-bromo-N-methoxy-1-((2-methoxyethoxy)methyl)-N-methyl-1*H*-indole-2-carboxamide (657 mg, 1.77 mmol) in tetrahydrofuran (20 mL), 1.0M phenylethyl magnesium bromide (8.85 mL, 8.85 mmol) was added at 0 °C. The reaction mixture was stirred for an hour at 0°C. After the mixture was quenched with water, it was poured onto ethyl acetate. The organic layer was washed with saturated ammonium chloride and brine. The organic layer
10 was then dried over sodium sulfate, and it was concentrated under reduced pressure. The resulting residue was purified on an ISCO chromatograph (0-20% ethyl acetate/hexane) to give product as colorless oil (509 mg, 69%); ¹H NMR (300 MHz) (CDCl₃) δ 7.79 (s, 1H), 7.47-7.46 (m, 2H), 7.31-7.21 (m, 6H), 6.07 (s, 2H), 3.57-3.54 (m, 2H), 3.45-3.42 (m, 2H), 3.30-3.31 (m, 5H), 3.11-3.05 (m, 2H).

15

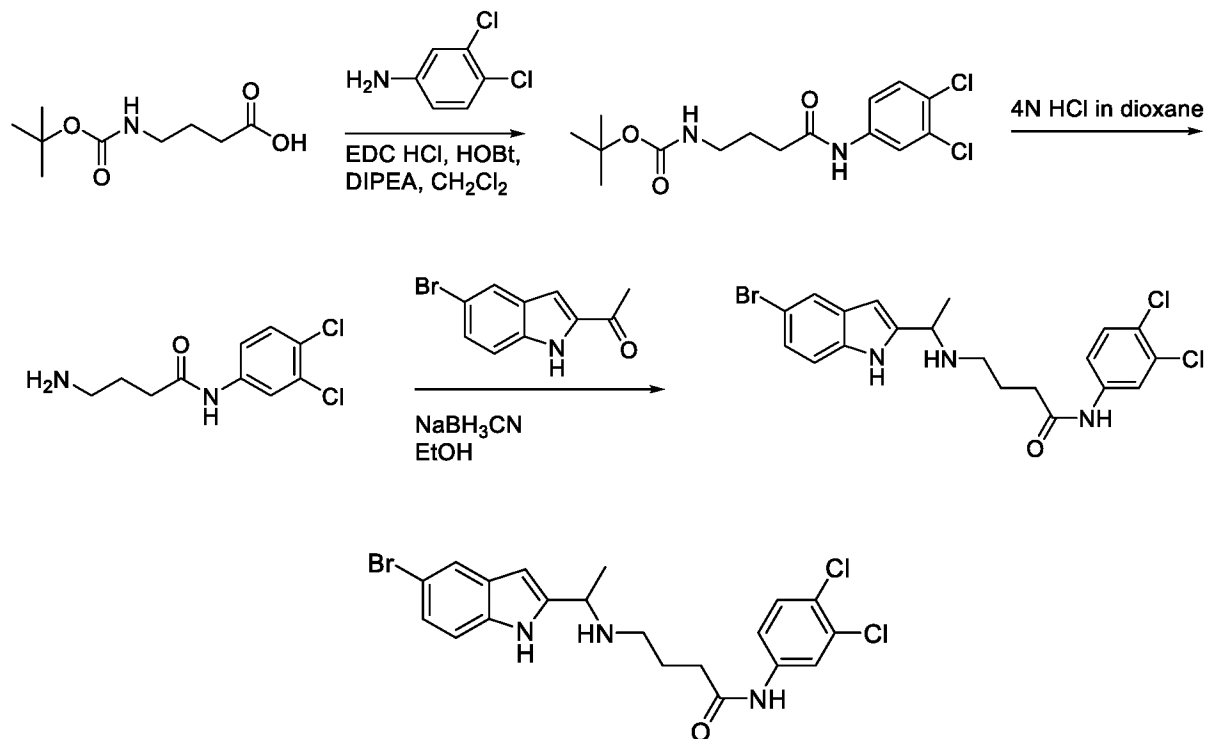
Step 3)



1-(5-Bromo-1*H*-indol-2-yl)-3-phenylpropan-1-one

20 To a solution of 1-(5-bromo-1-((2-methoxyethoxy)methyl)-1*H*-indol-2-yl)-3-phenylpropan-1-one (250 mg, 0.60 mmol) in dichloromethane (2 mL), trifluoroacetic acid (2 mL) was added at room temperature. The reaction mixture was stirred for 30 minutes at room temperature. After removal of solvent, it was diluted with ethyl acetate. The organic layer was washed with 10% sodium hydroxide followed by brine. The organic layer was dried over
25 sodium sulfate, and it was concentrated under reduced pressure. The resulting residue was purified on an ISCO chromatograph (0-10% ethyl acetate/hexane) to give product as a white solid (51 mg, 26%); ¹H NMR (300 MHz) (CDCl₃) δ 9.21 (bs, 1H), 7.83 (s, 1H), 7.42 (dd, *J* = 9 Hz, *J* = 2 Hz, 1H), 7.33-7.22 (m, 6H), 7.10 (s, 1H), 3.31-3.26 (m, 2H), 3.13-3.08 (m, 2H).

Example 37. Preparation of 4-((1-(5-bromo-1*H*-indol-2-yl)ethyl)amino)-*N*-(3,4-dichlorophenyl)butanamide.

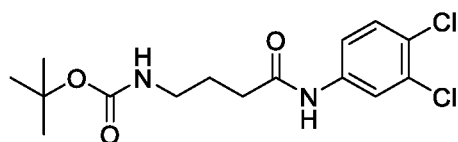


4-((1-(5-Bromo-1*H*-indol-2-yl)ethyl)amino)-*N*-(3,4-dichlorophenyl)butanamide

To a solution of 1-(5-bromo-1*H*-indol-2-yl)ethan-1-one (243 mg, 1.02 mmol) in ethanol (10 mL), 4-amino-*N*-(3,4-dichlorophenyl)butanamide (253 mg, 1.02 mmol) and sodium cyanoborohydride (320 mg, 5.10 mmol) were added. The reaction mixture was stirred for 60 °C for 24 hours. The mixture was diluted with ethyl acetate, and the organic layer was washed with 10% sodium hydroxide, saturated ammonium chloride, and brine. The organic layer was then dried over sodium sulfate, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (10% methanol/dichloromethane + 1% NH₄OH) to give product as colorless oil (73 mg, 15%); ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.30 (bs, 1H), 10.25 (bs, 1H), 8.00-7.99 (m, 1H), 7.72 (s, 1H), 7.60-7.55 (m, 1H), 7.49-7.44 (m, 1H), 7.38-7.36 (m, 1H), 7.23-7.21 (m, 1H), 6.48 (s, 1H), 4.33 (m, 1H), 2.76-2.60 (m, 2H), 2.42 (m, 2H), 1.84 (m, 2H), 1.57 (m, 3H).

The requisite intermediate was prepared as follows:

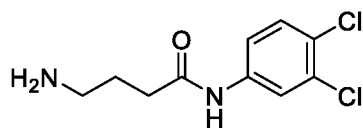
Step 1)



tert-Butyl (4-((3,4-dichlorophenyl)amino)-4-oxobutyl)carbamate

To a solution of 4-((*tert*-butoxy carbonyl)amino)butanoic acid (1.0 g, 4.9 mmol) in dichloromethane (50 mL), EDC hydrochloric acid (1.98 g, 10.3 mmol), HOBt (665 mg, 4.9 mmol) and DIPEA (1.80 mL, 10.33 mmol) were added. After the mixture stirred for 5 minutes, 3,4-dichloroaniline (797 mg, 4.92 mmol) was added. The mixture was then stirred for overnight at room temperature. The mixture was then diluted with dichloromethane, and the organic layer was washed with 1N hydrochloric acid, 10% sodium hydroxide, saturated ammonium chloride and brine. The organic layer was then dried over sodium sulfate, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give product as a white solid (757 mg, 44%); ¹H NMR (300 MHz, CDCl₃) δ 9.47 (bs, 1H), 7.92 (s, 1H), 7.48 (d, *J* = 9 Hz, 1H), 7.37 (d, *J* = 9 Hz, 1H), 4.87 (m, 1H), 3.27-3.24 (m, 2H), 2.41-2.37 (m, 2H), 1.89-1.87 (m, 2H), 1.49 (s, 9H).

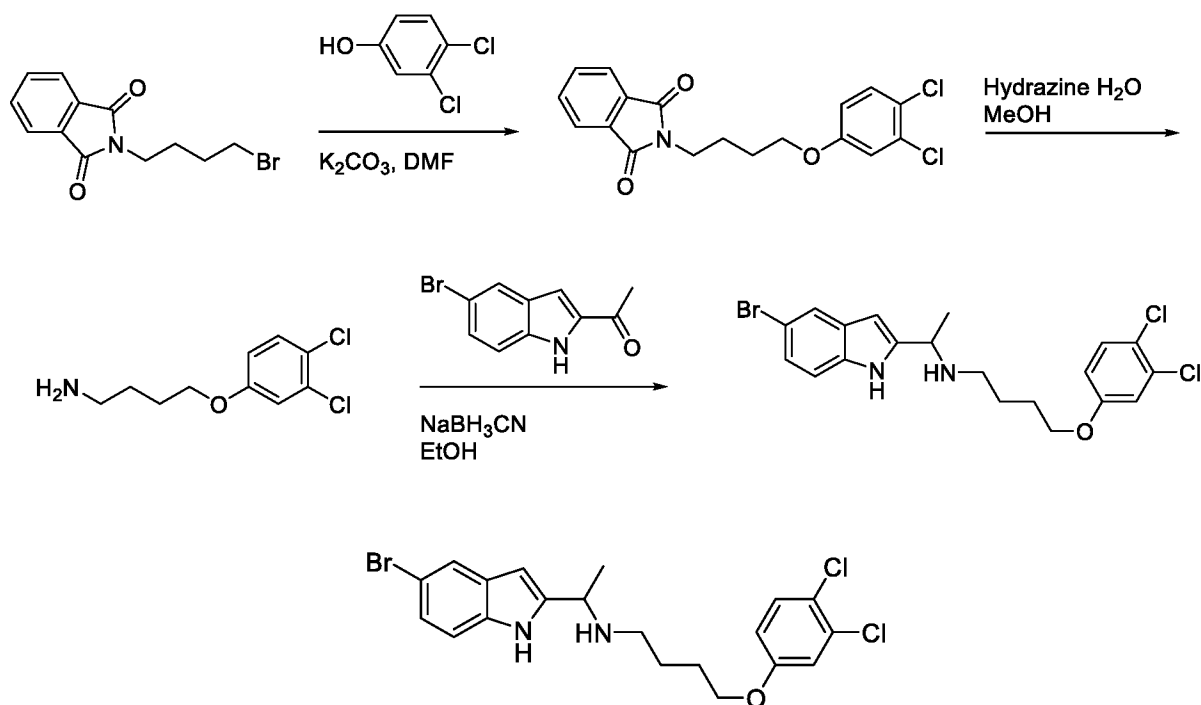
Step2)



4-Amino-*N*-(3,4-dichlorophenyl)butanamide

To a solution of *tert*-butyl (4-((3,4-dichlorophenyl)amino)-4-oxobutyl)carbamate (500 mg, 1.44 mmol) in methanol (0.36 mL), 4N hydrochloric acid (3.60 mL, 14.40 mmol) was added. The reaction mixture was stirred for 2 hours at room temperature. The mixture was diluted with ethyl acetate, and the organic layer was washed with 10% sodium hydroxide saturated ammonium chloride and brine. The organic layer was then dried over sodium sulfate, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane followed by 10% methanol/dichloromethane + 1% NH₄OH) to give product as colorless oil (253 mg, 71%); ¹H NMR (300 MHz, CDCl₃) δ 9.85 (bs, 1H), 7.78 (d, *J* = 2 Hz, 1H), 7.38-7.32 (m, 2H), 2.90-2.86 (m, 2H), 2.54-2.49 (m, 2H), 1.80-1.84 (m, 2H), 1.64 (bs, 2H).

Example 38. Preparation of *N*-(1-(5-bromo-1*H*-indol-2-yl)ethyl)-4-(3,4-dichlorophenoxy)butan-1-amine.



N-(1-(5-Bromo-1*H*-indol-2-yl)ethyl)-4-(3,4-dichlorophenoxy)butan-1-amine

5

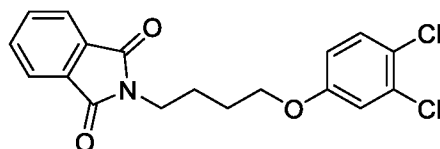
To a solution of 1-(5-bromo-1*H*-indol-2-yl)ethan-1-one (190 mg, 0.80 mmol) in ethanol (10 mL), 4-(3,4-dichlorophenoxy)butan-1-amine (187 mg, 0.80 mmol) and sodium cyanoborohydride (251 mg, 4.00 mmol) were added. The reaction mixture was stirred for 60 °C for 24 hours. The mixture was diluted with ethyl acetate, and the organic layer was washed with 10% sodium hydroxide, saturated ammonium chloride and brine. The organic layer was then dried over sodium sulfate, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (10% methanol/dichloromethane + 1% NH₄OH) to give product as colorless oil (47 mg, 13%); ¹H NMR (300 MHz, CDCl₃) δ 9.11 (bs, 1H), 7.71 (s, 1H), 7.31-7.28 (m, 3H), 6.91 (s, 1H), 6.62 (d, *J* = 9 Hz, 1H), 6.44 (s, 1H), 4.11-4.39 (m, 1H), 3.87 (m, 2H), 2.78 (m, 2H), 1.81 (m, 4H), 1.72 (d, *J* = 7 Hz, 3H).

10

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The requisite intermediate was prepared as follows:

Step 1)

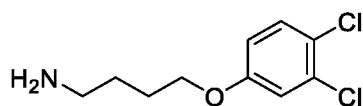


2-(4-(3,4-Dichlorophenoxy)butyl)isoindoline-1,3-dione

20

To a solution of 2-(4-bromobutyl)isoindoline-1,3-dione (500 mg, 1.77 mmol) in DMF (5 mL), 3,4-dichlorophenol (289 mg, 1.77 mmol) and potassium carbonate (245 mg, 1.77 mmol) were added. The reaction mixture was stirred for 5 hours at room temperature. The mixture was diluted with ethyl acetate, the organic layer was washed with water and brine. The organic layer was then dried over sodium sulfate, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-30% ethyl acetate/hexane) to give product as colorless oil (545 mg, 84%); ¹H NMR (300 MHz, CDCl₃) δ 7.89-7.86 (m, 2H), 7.76-7.73 (m, 2H), 7.29 (d, *J* = 9 Hz, 1H), 6.98 (d, *J* = 3 Hz, 1H), 6.75 (dd, *J* = 9 Hz, *J* = 3 Hz, 1H), 4.00-3.96 (m, 2H), 3.81-3.77 (m, 2H), 1.89-1.87 (m, 4H).

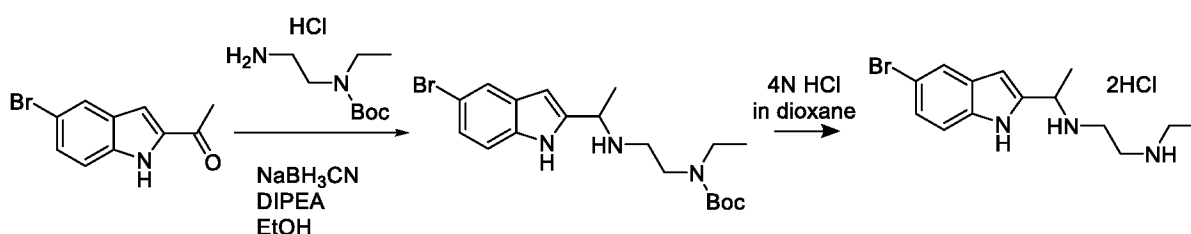
Step 2)

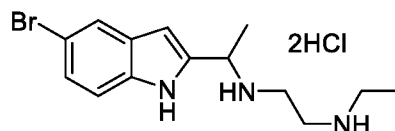


4-(3,4-Dichlorophenoxy)butan-1-amine

To a solution of 2-(4-(3,4-dichlorophenoxy)butyl)isoindoline-1,3-dione (545 mg, 1.50 mmol) in methanol (15 mL), hydrazine monohydrate (0.15 mL, 3.00 mmol) was added at room temperature. The reaction mixture was stirred for 2 hours at 60 °C. The white suspension was formed, and the suspension was filtered. The suspension was concentrated under reduced pressure, and the residue was diluted with ethyl acetate. The organic layer was washed with 10% sodium hydroxide and brine. The organic layer was then dried over sodium sulfate, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph (0-100% ethyl acetate/hexane followed by 10% methanol/dichloromethane + 1% NH₄OH) to give product as colorless oil (187 mg, 53%); ¹H NMR (300 MHz, CDCl₃) δ 7.31 (d, *J* = 9 Hz, 1H), 6.99 (d, *J* = 3 Hz, 1H), 6.75 (dd, *J* = 9 Hz, *J* = 3 Hz, 1H), 3.97-3.92 (m, 2H), 2.80-2.75 (m, 2H), 1.85-1.80 (m, 2H), 1.66-1.58 (m, 2H), 1.23 (bs, 2H).

Example 39. Preparation of N-(1-(5-bromo-1*H*-indol-2-yl)ethyl)-4-(3,4-dichlorophenoxy)butan-1-amine.



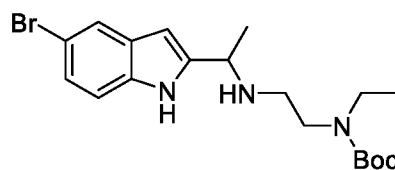


N¹-(1-(5-Bromo-1*H*-indol-2-yl)ethyl)-N²-ethylethane-1,2-diamine hydrochloric acid

5 To a solution of *tert*-butyl (2-((1-(5-bromo-1*H*-indol-2-yl)ethyl)amino)ethyl)(ethyl)carbamate (67 mg, 0.16 mmol) in methanol (0.04 mL), 4*N* hydrochloric acid in dioxane (0.4 mL, 1.6 mmol) was added. The reaction mixture was stirred for 2 hours at room temperature. The mixture was then concentrated under reduced pressure, and the residue was suspended in ethyl acetate. The suspension was filtered to give product as a
 10 white solid (47 mg, 77%); ¹H NMR (300 MHz, D₂O) δ 7.77 (s, 1H), 7.35-7.30 (m, 2H), 6.63 (s, 1H), 3.31-3.24 (m, 5H), 3.01-2.95 (m, 2H), 1.74-1.68 (m, 3H), 1.18-1.09 (m, 3H).

The requisite intermediate was prepared as follows:

Step 1)



tert-Butyl (2-((1-(5-bromo-1*H*-indol-2-yl)ethyl)amino)ethyl)(ethyl)carbamate

To a solution of 1-(5-bromo-1*H*-indol-2-yl)ethan-1-one (105 mg, 0.44 mmol) in ethanol (10 mL), *tert*-butyl (2-aminoethyl)(ethyl)carbamate hydrochloric acid (100 mg, 0.44 mmol),
 20 sodium cyanoborohydride (138 mg, 2.20 mmol), and DIPEA (76 μL, 0.44 mmol) were added. The reaction mixture was stirred for 60 °C for 48 hours. The reaction mixture was diluted with ethyl acetate, and the organic layer was washed with 10% sodium hydroxide, saturated ammonium chloride, and brine. The organic layer was then dried over sodium sulfate, and it was concentrated under reduced pressure. The residue was purified on an ISCO chromatograph
 25 (10% methanol/dichloromethane + 1% NH₄OH) to give product as colorless oil (67 mg, 37%); ¹H NMR (300 MHz, CDCl₃) δ 9.41 (bs, 1H), 7.67 (s, 1H), 7.23 (m, 2H), 6.29 (s, 1H), 4.15-4.11 (m, 1H), 3.51-3.21 (m, 5H), 2.77 (m, 2H), 2.38 (m, 2H), 1.51 (s, 9H), 1.38 (t, *J* = 7 Hz, 3H).

Example 40. Description of General Test Methods.

Intrinsic MIC assays

MIC assays were conducted in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines for broth microdilution. A 96-well plate containing cation-adjusted Mueller-Hinton (CAMH broth with 2-fold serial dilution of compounds was inoculated with log-phase bacterial at 5×10^5 CFU/mL. The final volume in each well was 100 μ L. Each compound was tested in duplicate. The microtiter plates were incubated in an aerobic environment for 18 hours at 37 °C. Then the bacterial growth was tested by reading the plate with a VersaMax plate reader (Molecular Devices, Inc.) at 600 nm. The MIC was defined as the lowest compound concentration that inhibited 90% of bacteria growth.

The intrinsic MIC of the experimental EPIs was tested with the method described. The 2-fold serial dilution begins with 100 μ g/mL of tested compound in the first column of the 96-well plates. The following Gram-negative bacterial strains were included in these assays:

Escherichia coli ATCC 25922

Klebsiella pneumoniae ATCC 13883 and ATCC 10031

Pseudomonas aeruginosa ATCC 27853.

Pseudomonas aeruginosa PAO1

Acinetobacter baumannii ATCC 19606

MIC Assays in the presence of a Bacterial Efflux Inhibitor

The EPI assay for the purposes of these studies represents a MIC assay in which the MIC of the antibiotic against the bacteria is tested in the presence of an experimental efflux pump inhibitor (EPI). The highest concentration of the EPI present in the assay typically is $\frac{1}{2}$ of the intrinsic MIC of the compound. If the intrinsic MIC of the EPI is greater than 100 μ g/mL, the EPI assay was tested with 50 μ g/mL. Using serial dilutions of the EPI, its enhancement of antibiotic activity was then evaluated. The relative EPI activity was decided by comparing the MIC of the antibiotic in the presence of the EPI compound with the intrinsic MIC of the antibiotic alone. For comparative purposes, we generally used EPIs at concentration of 12.5 and 6.25 μ g/ml against varying concentration of our test antibiotic.

Example 41. The following can illustrate representative pharmaceutical dosage forms, containing a compound of formula I, II, III, IV or V ('Compound X') or a pharmaceutically acceptable salt thereof, for therapeutic or prophylactic use in humans. The tablets can optionally comprise an enteric coating.

	<u>(i) Tablet 1</u>	<u>mg/tablet</u>
	Compound X=	100.0
	Lactose	77.5
	Povidone	15.0
5	Croscarmellose sodium	12.0
	Microcrystalline cellulose	92.5
	Magnesium stearate	<u>3.0</u>
		300.0
10	<u>(ii) Tablet 2</u>	<u>mg/tablet</u>
	Compound X=	20.0
	Microcrystalline cellulose	410.0
	Starch	50.0
	Sodium starch glycolate	15.0
15	Magnesium stearate	<u>5.0</u>
		500.0
	<u>(iii) Capsule</u>	<u>mg/capsule</u>
	Compound X=	10.0
20	Colloidal silicon dioxide	1.5
	Lactose	465.5
	Pregelatinized starch	120.0
	Magnesium stearate	<u>3.0</u>
		600.0
25	<u>(iv) Injection 1 (1 mg/mL)</u>	<u>mg/mL</u>
	Compound X= (free acid form)	1.0
	Dibasic sodium phosphate	12.0
	Monobasic sodium phosphate	0.7
30	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
35	<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
	Polyethylene glycol 400	200.0
40	1.0 N Sodium hydroxide solution	
	(pH adjustment to 7.0-7.5)	q.s.
	Water for injection	q.s. ad 1 mL
	<u>(vi) Aerosol</u>	<u>mg/can</u>
45	Compound X=	20.0
	Oleic acid	10.0
	Trichloromonofluoromethane	5,000.0
	Dichlorodifluoromethane	10,000.0
	Dichlorotetrafluoroethane	5,000.0
50		

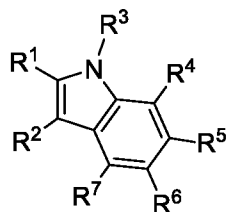
The above formulations may be obtained by conventional procedures well known in the pharmaceutical art.

5 All publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. 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.

CLAIMS

We claim:

1. A compound of formula I:



R^1 is (C_1-C_{12}) alkyl substituted with one or more NR^aR^b and wherein the (C_1-C_{12}) alkyl is optionally substituted with one or more halo, hydroxyl, or phenyl wherein the phenyl is optionally substituted independently with one or more halo, cyano, (C_1-C_3) alkyl, or (C_1-C_3) haloalkyl, and R^2 is hydrogen or (C_1-C_8) alkyl optionally substituted with one or more halo, hydroxyl, oxo, or NR^aR^b , or R^1 and R^2 together with the atoms to which they are attached form a 5 or 7-membered carbocycle wherein the carbocycle is substituted with one or more NR^aR^b and wherein the carbocycle is optionally substituted with one or more halo, hydroxyl, NR^aR^b , or (C_1-C_4) alkyl wherein the (C_1-C_4) alkyl is optionally substituted with one or more NR^aR^b ;

R^3 is hydrogen or (C_1-C_4) alkyl;

R^4 is hydrogen, halo, cyano, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_1-C_6) alkoxy, (C_1-C_6) haloalkoxy, or phenyl wherein the phenyl is optionally substituted with one or more halo, (C_1-C_6) haloalkyl, cyano, nitro or (C_1-C_6) haloalkoxy;

R^5 is hydrogen, halo, cyano, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_1-C_6) alkoxy, (C_1-C_6) haloalkoxy, or phenyl wherein the phenyl is optionally substituted with one or more halo, (C_1-C_6) haloalkyl, cyano, nitro or (C_1-C_6) haloalkoxy;

R^6 is hydrogen, halo, cyano, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_1-C_6) alkoxy, (C_1-C_6) haloalkoxy, or phenyl wherein the phenyl is optionally substituted with one or more halo, (C_1-C_6) haloalkyl, cyano, nitro or (C_1-C_6) haloalkoxy; and

R^7 is hydrogen, halo, cyano, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_1-C_6) alkoxy, (C_1-C_6) haloalkoxy, or phenyl wherein the phenyl is optionally substituted with one or more halo, (C_1-C_6) haloalkyl, cyano, nitro or (C_1-C_6) haloalkoxy;

each R^a is independently hydrogen or (C_1-C_6) alkyl wherein the (C_1-C_6) alkyl is optionally substituted with one or more halo, hydroxyl, NR^cR^d , R^g , $-C(=O)NR^{e1}R^{e2}$, $-OR^f$, or $-O(C_1-C_3)alkyl-R^f$;

each R^b is independently hydrogen, or (C_1-C_6) alkyl wherein the (C_1-C_6) alkyl is optionally substituted with one or more halo, hydroxyl, or NR^cR^d ;

each R^c is independently hydrogen, (C₁-C₃)alkyl, -C(=O)R^h, phenyl, C₃-C₇carbocycle, or -(C₁-C₆)alkylphenyl wherein the phenyl, C₃-C₇carbocycle, or -(C₁-C₆)alkylphenyl is optionally substituted independently with one or more halo, cyano, (C₁-C₆)alkyl, or (C₁-C₆)haloalkyl;

each R^d is independently hydrogen or (C₁-C₃)alkyl;

each R^{e1} is phenyl optionally substituted independently with one or more halo, cyano, (C₁-C₆)alkyl, or (C₁-C₆)haloalkyl;

each R^{e2} is independently hydrogen or (C₁-C₃)alkyl;

each R^f is phenyl optionally substituted independently with one or more halo, cyano, (C₁-C₆)alkyl, or (C₁-C₆)haloalkyl;

each R^g is independently 5-6 membered heteroaryl, phenyl, or C₃-C₇carbocycle wherein the 5-6 membered heteroaryl, phenyl, or C₃-C₇carbocycle is optionally substituted independently with one or more halo, cyano, (C₁-C₆)alkyl, or (C₁-C₆)haloalkyl; and

each R^h is independently 5-6 membered heteroaryl, phenyl, or C₃-C₇carbocycle wherein the 5-6 membered heteroaryl, phenyl, or C₃-C₇carbocycle is optionally substituted independently with one or more halo, cyano, (C₁-C₆)alkyl, or (C₁-C₆)haloalkyl;

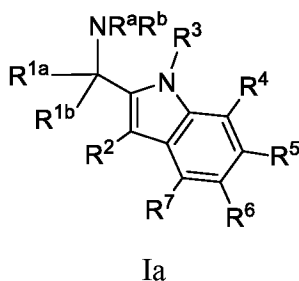
or a salt thereof.

2. The compound of claim 1, wherein R¹ is (C₁-C₈)alkyl substituted with one NR^aR^b and wherein the (C₁-C₈)alkyl is optionally substituted with one or more halo, hydroxyl or phenyl wherein the phenyl is optionally substituted independently with one or more halo, cyano, (C₁-C₃)alkyl, or (C₁-C₃)haloalkyl, and R² is hydrogen or (C₁-C₈)alkyl, or R¹ and R² together with the atoms to which they are attached form a 5 or 7-membered carbocycle wherein the carbocycle is substituted with one NR^aR^b and wherein the carbocycle is optionally substituted with one or more halo, hydroxyl, or (C₁-C₄)alkyl.

3. The compound of claim 1, wherein R¹ is (C₁-C₈)alkyl substituted with one NR^aR^b and R² is hydrogen, or R¹ and R² together with the atoms to which they are attached form a 5 or 7-membered carbocycle wherein the carbocycle is substituted with one NR^aR^b.

4. The compound of claim 1, wherein R¹ is (C₁-C₈)alkyl substituted with one NR^aR^b and R² is hydrogen.

5. The compound of claim 1, that is a compound of formula Ia:



R^{1a} is hydrogen or (C₁-C₈)alkyl optionally substituted with one or more halo, hydroxyl, NR^aR^b , or phenyl wherein the phenyl is optionally substituted independently with one or more halo, cyano, (C₁-C₃)alkyl, or (C₁-C₃)haloalkyl and R^2 is hydrogen or (C₁-C₈)alkyl optionally substituted with one or more halo, hydroxyl, oxo, or NR^aR^b , or R^{1a} and R^2 together with the atoms to which they are attached form a 5 or 7-membered carbocycle wherein the carbocycle is optionally substituted with one or more halo, hydroxyl, NR^aR^b , or (C₁-C₄)alkyl wherein the (C₁-C₄)alkyl is optionally substituted with one or more NR^aR^b ; and

R^{1b} is hydrogen or (C₁-C₃)alkyl optionally substituted with one or more halo, hydroxyl, or NR^aR^b .

6. The compound of claim 5, wherein R^{1a} is hydrogen or (C₁-C₈)alkyl optionally substituted with one or more halo, hydroxyl, NR^aR^b or phenyl wherein the phenyl is optionally substituted independently with one or more halo, cyano, (C₁-C₃)alkyl, or (C₁-C₃)haloalkyl and R^2 is hydrogen or (C₁-C₈)alkyl optionally substituted with one or more halo, hydroxyl, oxo, or NR^aR^b .

7. The compound of claim 5, wherein R^{1a} is hydrogen or (C₁-C₈)alkyl optionally substituted with one or more halo, hydroxyl, NR^aR^b or phenyl wherein the phenyl is optionally substituted independently with one or more halo, cyano, (C₁-C₃)alkyl, or (C₁-C₃)haloalkyl and R^2 is hydrogen or (C₁-C₈)alkyl.

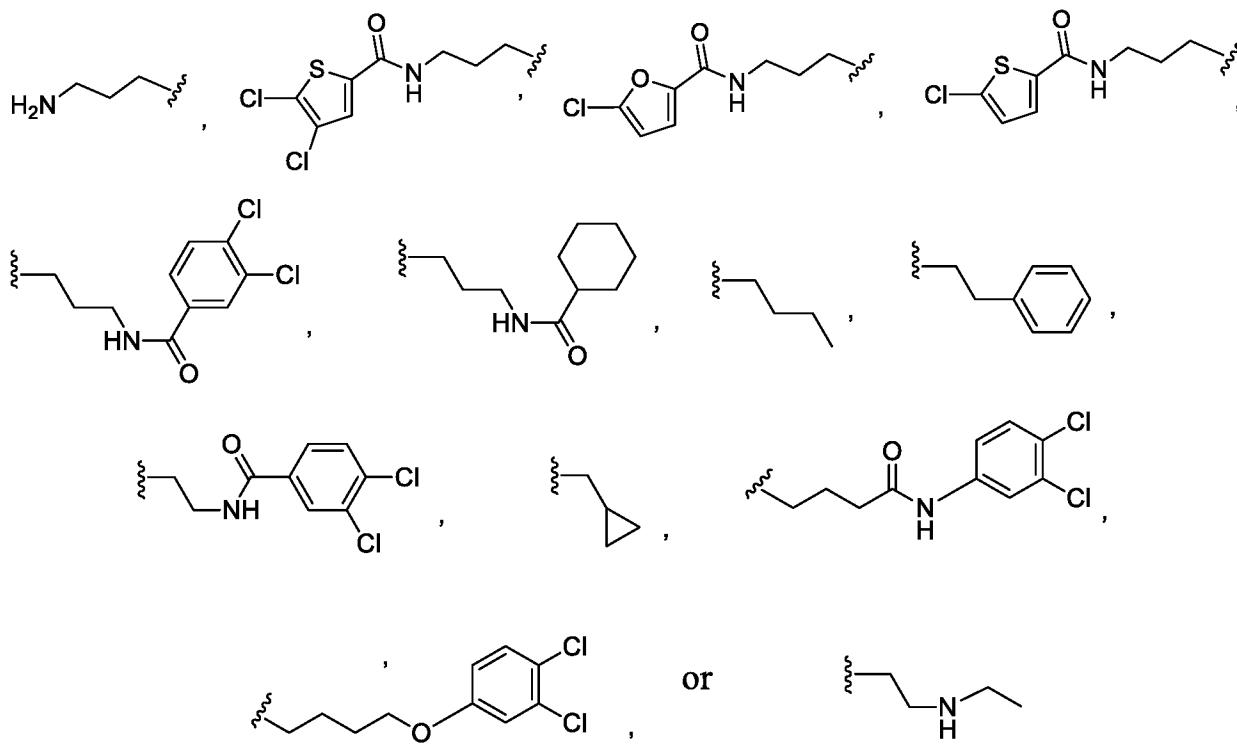
8. The compound of claim 5, wherein R^{1a} is hydrogen or (C₁-C₈)alkyl optionally substituted with one or more NR^aR^b or phenyl wherein the phenyl is optionally substituted independently with one or more halo, cyano, (C₁-C₃)alkyl, or (C₁-C₃)haloalkyl and R^2 is hydrogen.

9. The compound of claim 5, wherein R^{1a} is hydrogen, methyl, butyl, ethylamine, or phenethyl.

10. The compound of claim 5, wherein R^{1a} and R^2 together with the atoms to which they are attached form a 5 or 7-membered carbocycle wherein the carbocycle is optionally substituted with one or more halo, hydroxyl, NR^aR^b , or (C_1-C_4) alkyl wherein the (C_1-C_4) alkyl is optionally substituted with one or more NR^aR^b .
11. The compound of claim 5, wherein R^{1a} and R^2 together with the atoms to which they are attached form a 5 or 7-membered carbocycle wherein the carbocycle is optionally substituted with one or more NR^aR^b or (C_1-C_4) alkyl wherein the (C_1-C_4) alkyl is optionally substituted with one or more NR^aR^b .
12. The compound of claim 5, wherein R^{1a} and R^2 together with the atoms to which they are attached form a 5 or 7-membered carbocycle.
13. The compound of any one of claims 5-12, wherein R^{1b} is hydrogen.
14. The compound of any one of claims 1-13, wherein each R^a is independently hydrogen or (C_1-C_6) alkyl wherein the (C_1-C_6) alkyl is optionally substituted with one or more NR^cR^d , R^g , $-C(=O)NR^{e1}R^{e2}$, or $-OR^f$.
15. The compound of any one of claims 1-14, wherein each R^c is independently (C_1-C_3) alkyl, or $-C(=O)R^h$.
16. The compound of any one of claims 1-15, wherein each R^d is hydrogen.
17. The compound of any one of claims 1-16, wherein each R^{e1} is phenyl optionally substituted with one or more halo.
18. The compound of any one of claims 1-17, wherein each R^{e2} is hydrogen.
19. The compound of any one of claims 1-18, wherein each R^f is phenyl optionally substituted with one or more halo.
20. The compound of any one of claims 1-19, wherein each R^g is independently phenyl, or C_3-C_7 carbocycle wherein the phenyl or C_3-C_7 carbocycle is independently substituted with one or more halo, cyano, (C_1-C_6) alkyl, or (C_1-C_6) haloalkyl.

21. The compound of any one of claims 1-20, wherein each R^h is independently 5-6 membered heteroaryl, phenyl, or C_3 - C_7 carbocycle wherein the 5-6 membered heteroaryl, phenyl, or C_3 - C_7 carbocycle is independently substituted halo.

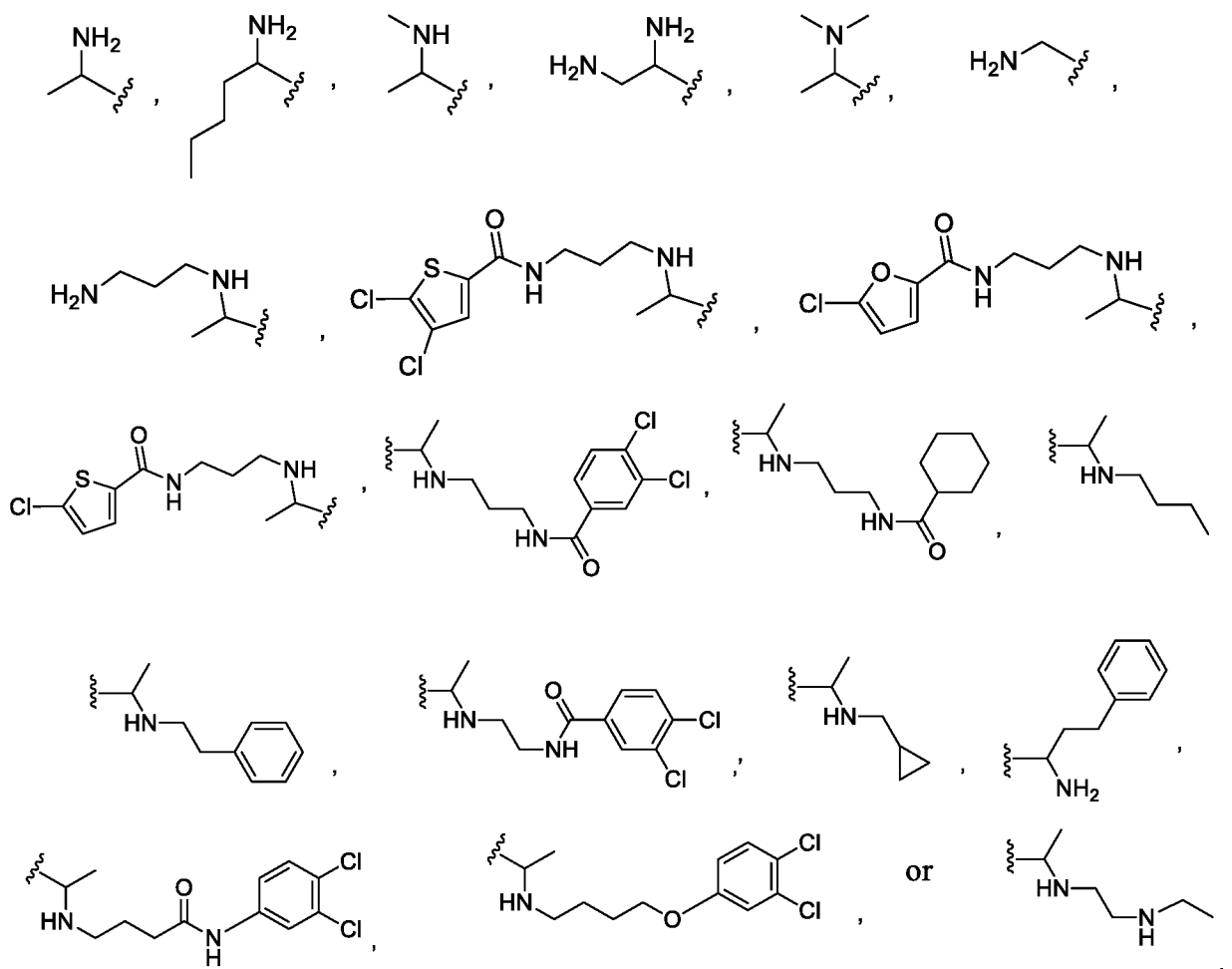
22. The compound of any one of claims 1-12, wherein each R^a is independently hydrogen, methyl,



23. The compound of any one of claims 1-22, wherein each R^b is independently hydrogen or (C_1-C_6) alkyl.

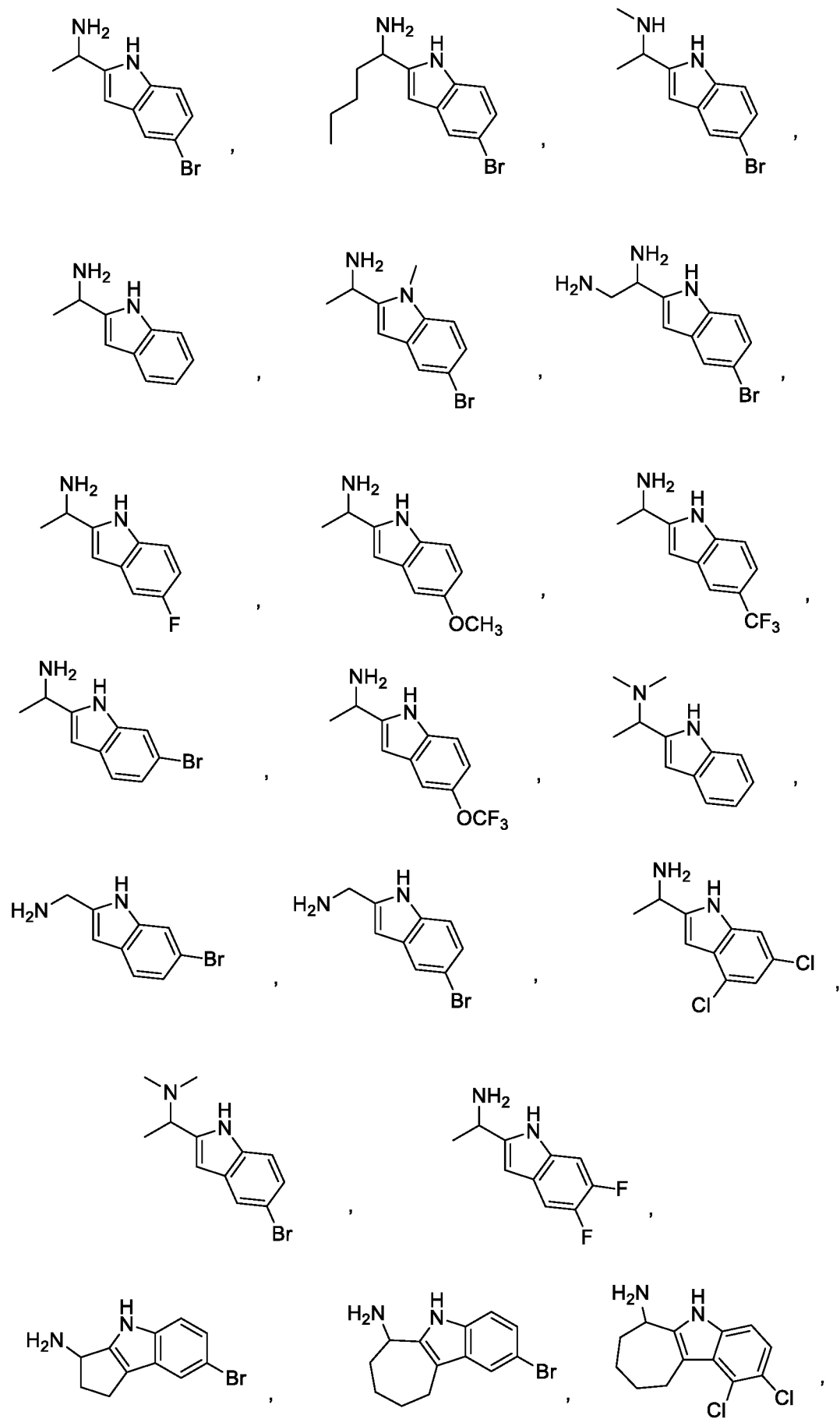
24. The compound of any one of claims 1-22, wherein each R^b is independently hydrogen or methyl.

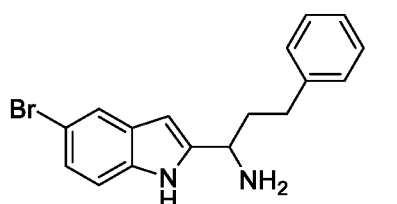
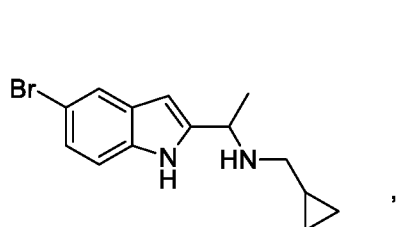
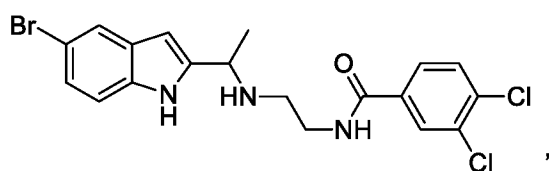
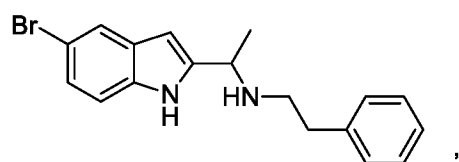
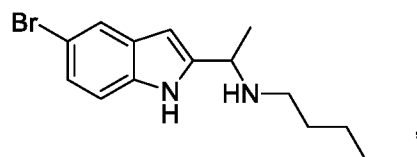
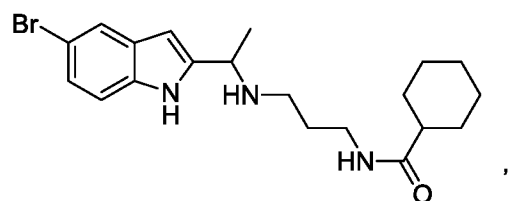
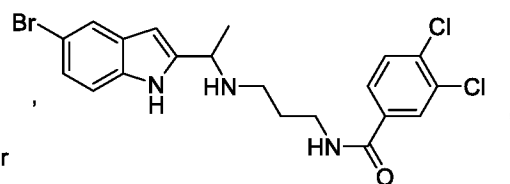
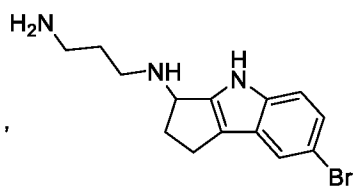
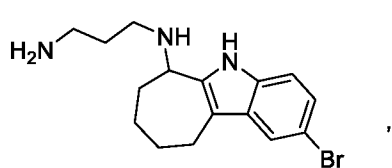
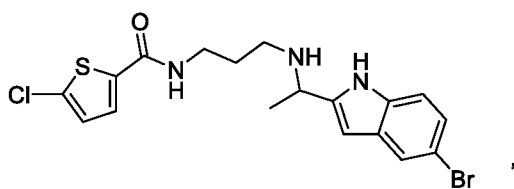
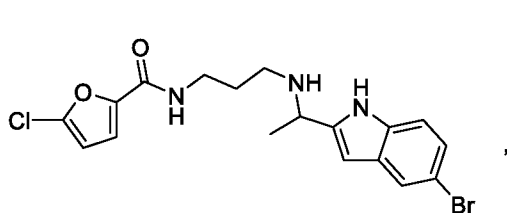
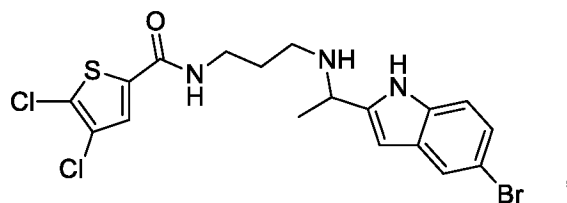
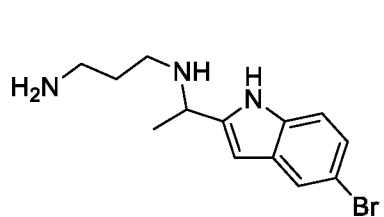
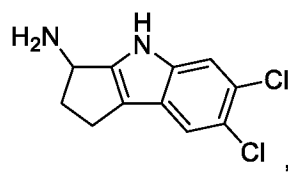
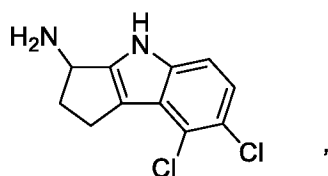
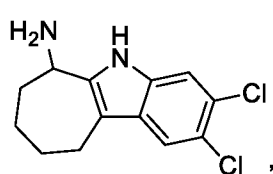
25. The compound of claim 1 wherein R^1 , or the compound of claim 5 wherein the moiety $-CH(NR^aR^b)R^{1a}R^{1b}$ of formula Ia is:

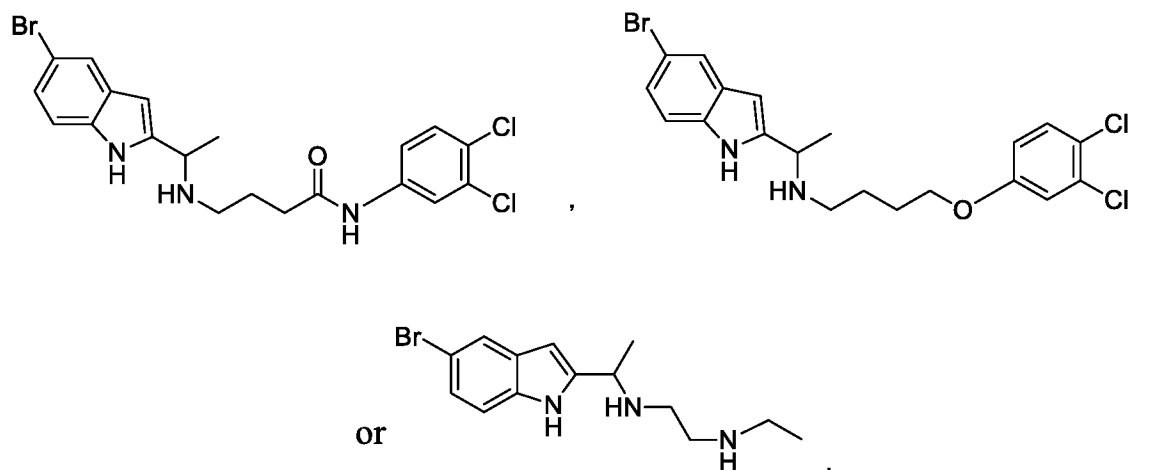


26. The compound of any one of claims 1-25, wherein R^3 is hydrogen or methyl.
27. The compound of any one of claims 1-26, wherein R^4 is hydrogen, halo, $(\text{C}_1\text{-C}_6)\text{haloalkyl}$, $(\text{C}_1\text{-C}_6)\text{alkoxy}$, or $(\text{C}_1\text{-C}_6)\text{haloalkoxy}$.
28. The compound of any one of claims 1-26, wherein R^4 is hydrogen or halo.
29. The compound of any one of claims 1-26, wherein R^4 is hydrogen.
30. The compound of any one of claims 1-29, wherein R^5 is hydrogen, halo, $(\text{C}_1\text{-C}_6)\text{haloalkyl}$, $(\text{C}_1\text{-C}_6)\text{alkoxy}$, or $(\text{C}_1\text{-C}_6)\text{haloalkoxy}$.
31. The compound of any one of claims 1-29, wherein R^5 is hydrogen or halo.
32. The compound of any one of claims 1-29, wherein R^5 is hydrogen, fluoro, chloro, or bromo.

33. The compound of any one of claims 1-32, wherein R^6 is hydrogen, halo, (C_1-C_6) haloalkyl, (C_1-C_6) alkoxy, or (C_1-C_6) haloalkoxy.
34. The compound of any one of claims 1-33, wherein R^6 is hydrogen, fluoro, chloro, bromo, trifluoromethyl, methoxy, or trifluoromethoxy.
35. The compound of any one of claims 1-34, wherein R^7 is hydrogen, halo, (C_1-C_6) haloalkyl, (C_1-C_6) alkoxy, or (C_1-C_6) haloalkoxy.
36. The compound of any one of claims 1-34, wherein R^7 is hydrogen or halo.
37. The compound of any one of claims 1-34, wherein R^7 is hydrogen or chloro.
38. The compound of any one of claims 1-37, wherein at least one of R^4 , R^5 , R^6 , or R^7 is not hydrogen.
39. The compound of any one of claims 1-37, wherein at least two of R^4 , R^5 , R^6 , or R^7 are not hydrogen.
40. The compound of any one of claims 1-39, wherein at least one of R^4 , R^5 , R^6 , or R^7 is halo, (C_1-C_6) haloalkyl, (C_1-C_6) alkoxy, or (C_1-C_6) haloalkoxy.
41. The compound of any one of claims 1-39, wherein at least two of R^4 , R^5 , R^6 , or R^7 are halo, (C_1-C_6) haloalkyl, (C_1-C_6) alkoxy, or (C_1-C_6) haloalkoxy.
42. The compound of claim 1 that is:







or a salt thereof.

43. A pharmaceutical composition comprising a compound as described in any one of claims 1-42 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

44. A compound as described in any one of claims 1-42 or a pharmaceutically acceptable salt thereof, for use in medical therapy.

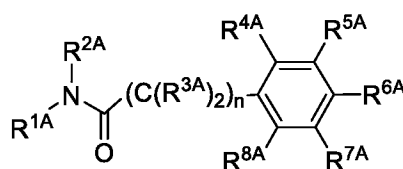
45. A compound as described in any one of claims 1-42 or a pharmaceutically acceptable salt thereof, for the prophylactic or therapeutic treatment of a bacterial infection in an animal.

46. The use of a compound as described in any one of claims 1-42 or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for treating a bacterial infection in an animal.

47. A method of treating or preventing a bacterial infection in an animal comprising administering to the animal a compound as described in any one of claims 1-42 or a pharmaceutically acceptable salt thereof.

48. A method of treating or preventing a bacterial infection in an animal comprising administering to the animal a bacterial efflux pump inhibitor and a compound as described in any one of claims 1-42 or a pharmaceutically acceptable salt thereof.

49. The method of claim 48, wherein the bacterial efflux pump inhibitor is a compound of formula II:



II

or a pharmaceutically acceptable salt thereof, wherein:

R^{1A} is (C₃-C₈)alkyl substituted with two or more groups selected from $-NR^{b1}R^{c1}$, $-NHNH_2$, $-C(=NR^{a1})(NR^{b1}R^{c1})$, $-NR^{a1}C(=NR^{a1})(R^{d1})$ and $-NR^{a1}C(=NR^{a1})(NR^{b1}R^{c1})$;

R^{2A} is hydrogen or (C₁-C₃)alkyl;

each R^{3A} is independently hydrogen, halo or (C₁-C₄)alkyl;

R^{4A} is hydrogen, halo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₄)haloalkoxy, aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy and (C₁-C₄)haloalkoxy;

R^{5A} is hydrogen, halo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₄)haloalkoxy, aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy and (C₁-C₄)haloalkoxy;

R^{6A} is hydrogen, halo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₄)haloalkoxy, aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy and (C₁-C₄)haloalkoxy;

R^{7A} is hydrogen, halo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₄)haloalkoxy, aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy and (C₁-C₄)haloalkoxy;

R^{8A} is hydrogen, halo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₄)haloalkoxy, aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy and (C₁-C₄)haloalkoxy;

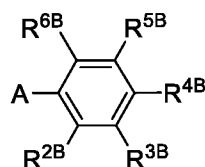
each R^{a1} is independently hydrogen or (C₁-C₄)alkyl;

each R^{b1} and R^{c1} is independently hydrogen or (C₁-C₄)alkyl;

R^{d1} is (C₁-C₃)alkyl and

n is 0 or 1.

50. The method of claim 48, wherein the bacterial efflux pump inhibitor is a compound of formula III:



III

or a pharmaceutically acceptable salt thereof, wherein:

A is $-C(=O)N(R^{a1})-R^{1B}$, $-(C_1-C_3)alkyl-C(=O)N(R^{a1})R^{1B}$, $-(C_1-C_3)alkyl-O-R^{1B}$, $-O-R^{1B}$, $-(C_1-C_3)alkyl-N(R^{a1})-R^{1B}$, or $-N(R^{a1})-R^{1B}$;

each R^{1B} is independently a $(C_3-C_7)carbocyclyl$, $(C_3-C_7)carbocyclyl-(C_1-C_4)alkyl-$, 4-7 membered monocyclic heterocyclyl, or 4-7 membered monocyclic heterocyclyl- $(C_1-C_4)alkyl-$, wherein each $(C_3-C_7)carbocyclyl$ or $(C_3-C_7)carbocyclyl-(C_1-C_4)alkyl-$ is independently substituted with one or more groups selected from the group consisting of Z and $-(C_1-C_6)alkyl$ substituted with one or more Z, and wherein each 4-7 membered monocyclic heterocyclyl or 4-7 membered monocyclic heterocyclyl- $(C_1-C_4)alkyl-$ is independently optionally substituted with one or more groups selected from the group consisting of Z and $-(C_1-C_6)alkyl$ substituted with one or more Z, wherein each Z is independently selected from the group consisting of $NR^{b2}R^{c2}$, $-NHNH_2$, $-C(=NR^{a2})(NR^{b2}R^{c2})$, $-NR^{a2}C(=NR^{a2})(R^{d2})$, and $-NR^{a2}C(=NR^{a2})(NR^{b2}R^{c2})$ and wherein each $(C_3-C_7)carbocyclyl$, $(C_3-C_7)carbocyclyl-(C_1-C_4)alkyl-$, 4-7 membered monocyclic heterocyclyl, or 4-7 membered monocyclic heterocyclyl- $(C_1-C_4)alkyl-$, is independently optionally substituted independently with one or more $(C_1-C_4)alkyl$;

R^{2B} is hydrogen, halo, $(C_1-C_4)alkyl$, $(C_1-C_4)haloalkyl$, $(C_1-C_4)alkoxy$, $(C_1-C_4)haloalkoxy$, aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, $-NO_2$, $-CN$, $(C_1-C_4)alkyl$, $(C_1-C_4)haloalkyl$, $(C_1-C_4)alkoxy$ and $(C_1-C_4)haloalkoxy$;

R^{3B} is hydrogen, halo, $(C_1-C_6)alkyl$, $(C_1-C_4)haloalkyl$, $(C_1-C_6)alkoxy$, $(C_1-C_4)haloalkoxy$, aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, $-NO_2$, $-CN$, $(C_1-C_6)alkyl$, $(C_1-C_4)haloalkyl$, $(C_1-C_6)alkoxy$ and $(C_1-C_4)haloalkoxy$;

R^{4B} is hydrogen, halo, $(C_1-C_6)alkyl$, $(C_1-C_4)haloalkyl$, $(C_1-C_6)alkoxy$, $(C_1-C_4)haloalkoxy$, aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, $-NO_2$, $-CN$, $(C_1-C_6)alkyl$, $(C_1-C_4)haloalkyl$, $(C_1-C_6)alkoxy$ and $(C_1-C_4)haloalkoxy$;

R^{5B} is hydrogen, halo, (C₁-C₆)alkyl, (C₁-C₄)haloalkyl, (C₁-C₆)alkoxy, (C₁-C₄)haloalkoxy, aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, -NO₂, -CN, (C₁-C₆)alkyl, (C₁-C₄)haloalkyl, (C₁-C₆)alkoxy and (C₁-C₄)haloalkoxy;

R^{6B} is hydrogen, halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, -NO₂, -CN, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy and (C₁-C₄)haloalkoxy;

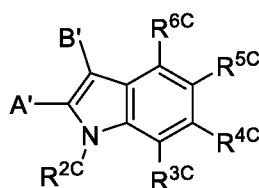
each R^{a1} is independently hydrogen, (C₁-C₆)alkyl or (C₃-C₇)carbocyclyl;

each R^{a2} is independently hydrogen, (C₁-C₆)alkyl or (C₃-C₇)carbocyclyl;

each R^{b2} and R^{c2} is independently hydrogen, (C₁-C₆)alkyl or (C₃-C₇)carbocyclyl; and

R^{d2} is (C₁-C₆)alkyl or (C₃-C₇)carbocyclyl.

51. The method of claim 48, wherein the bacterial efflux pump inhibitor is a compound of formula IV:



IV

or a pharmaceutically acceptable salt thereof, wherein:

one of A' or B' is -C(=O)N(R^{a1})-R^{1C}, -(C₁-C₃)alkyl-C(=O)N(R^{a1})R^{1C}, -(C₁-C₃)alkyl-O-R^{1C}, -O-R^{1C}, -(C₁-C₃)alkyl-N(R^{a1})-R^{1C}, -N(R^{a1})-R^{1C}, or R^{1C} and the other of A' or B' is H, halogen, or (C₁-C₄)alkyl;

each R^{1C} is independently:

(a) (C₁-C₁₄)alkyl substituted with one or more groups selected from the group consisting of -NR^{b2}R^{c2}, -NHNH₂, -C(=NR^{a2})(NR^{b2}R^{c2}), -NR^{a2}C(=NR^{a2})(R^{d2}), and -NR^{a2}C(=NR^{a2})(NR^{b2}R^{c2}); and wherein (C₁-C₁₄)alkyl is optionally substituted independently with one or more halo, (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl; or

(b) (C₃-C₇)carbocyclyl, (C₃-C₇)carbocyclyl-(C₁-C₄)alkyl-, 4-7 membered monocyclic heterocyclyl, or 4-7 membered monocyclic heterocyclyl-(C₁-C₄)alkyl-, wherein each (C₃-C₇)carbocyclyl or (C₃-C₇)carbocyclyl-(C₁-C₄)alkyl- is independently substituted with one or more Z¹ or Z², and wherein each 4-7 membered monocyclic heterocyclyl or 4-7 membered monocyclic heterocyclyl-(C₁-C₄)alkyl- is independently optionally substituted with one or more Z¹ or Z², and wherein any (C₃-C₇)carbocyclyl, (C₃-C₇)carbocyclyl-(C₁-C₄)alkyl-, 4-7 membered

monocyclic heterocyclyl, or 4-7 membered monocyclic heterocyclyl-(C₁-C₄)alkyl- of R¹ is independently optionally substituted independently with one or more halo, (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl;

R^{2C} is hydrogen, (C₁-C₄)alkyl or phenyl(C₁-C₃)alkyl-, wherein the phenyl is optionally substituted with one or more (C₁-C₄)alkyl, -O(C₁-C₄)alkyl, halogen, or -NO₂;

R^{3C} is hydrogen, halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, aryl, or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, and (C₁-C₄)haloalkoxy;

R^{4C} is hydrogen, halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, aryl, or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, and (C₁-C₄)haloalkoxy;

R^{5C} is hydrogen, halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, aryl, or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, and (C₁-C₄)haloalkoxy;

R^{6C} is hydrogen, halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, aryl, or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, and (C₁-C₄)haloalkoxy;

each Z¹ is independently selected from the group consisting of -NR^{b3}R^{c3}, -NHNH₂, -C(=NR^{a3})(NR^{b3}R^{c3}), -NR^{a3}C(=NR^{a3})(R^{d3}), and -NR^{a3}C(=NR^{a3})(NR^{b3}R^{c3});

each Z² is independently -(C₁-C₆)alkyl substituted with one or more Z¹ and optionally optionally substituted with one or more Z³;

each Z³ is independently halo or (C₃-C₇)carbocyclyl;

each R^{a1} is independently hydrogen, (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl;

each R^{a2} is independently hydrogen, (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl;

each R^{b2} and R^{c2} is independently hydrogen, (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl;

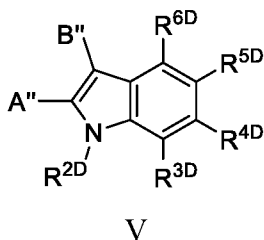
R^{d2} is (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl;

each R^{a3} is independently hydrogen (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl;

each R^{b3} and R^{c3} is independently hydrogen (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl; and

R^{d3} is (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl.

52. The method of claim 48, wherein the bacterial efflux pump inhibitor is a compound of formula V:



or a pharmaceutically acceptable salt thereof, wherein:

A'' is -C(=O)N(R^{1D})-R^{1D}, -(C₁-C₃)alkyl-C(=O)N(R^{1D})-R^{1D}, -(C₁-C₃)alkyl-O-R^{1D}, -O-R^{1D}, -(C₁-C₃)alkyl-N(R^{1D})-R^{1D}, -N(R^{1D})-R^{1D}, or R^{1D};

B'' is (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, (C₃-C₇)carbocyclyl, (C₃-C₇)carbocyclyl-(C₁-C₄)alkyl-, aryl, aryl-(C₁-C₄)alkyl-, heteroaryl, heteroaryl-(C₁-C₄)alkyl-, 3-7 membered-monocyclic-heterocycle, or 3-7 membered-monocyclic-heterocycle-(C₁-C₄)alkyl- wherein any (C₃-C₇)carbocyclyl, (C₃-C₇)carbocyclyl-(C₁-C₄)alkyl-, aryl, aryl-(C₁-C₄)alkyl-, heteroaryl, heteroaryl-(C₁-C₄)alkyl-, 3-7 membered-monocyclic-heterocycle, or 3-7 membered-monocyclic-heterocycle-(C₁-C₄)alkyl- of B'' is optionally substituted with one or more Z¹ groups;

each R^{1D} is independently:

(a) (C₁-C₁₄)alkyl substituted with one or more groups selected from the group consisting of -NR^{b2}R^{c2}, -NHNH₂, -C(=NR^{a2})(NR^{b2}R^{c2}), -NR^{a2}C(=NR^{a2})(R^{d2}), and -NR^{a2}C(=NR^{a2})(NR^{b2}R^{c2}) and wherein (C₁-C₁₄)alkyl is optionally substituted independently with one or more halo, (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl; or

(b) (C₃-C₇)carbocyclyl, (C₃-C₇)carbocyclyl-(C₁-C₄)alkyl-, 4-7 membered monocyclic heterocyclyl, or 4-7 membered monocyclic heterocyclyl-(C₁-C₄)alkyl-, wherein each (C₃-C₇)carbocyclyl or (C₃-C₇)carbocyclyl-(C₁-C₄)alkyl- is independently substituted with one or more Z² or Z³, and wherein each 4-7 membered monocyclic heterocyclyl or 4-7 membered monocyclic heterocyclyl-(C₁-C₄)alkyl- is independently optionally substituted with one or more Z² or Z³, and wherein any (C₃-C₇)carbocyclyl, (C₃-C₇)carbocyclyl-(C₁-C₄)alkyl-, 4-7 membered monocyclic heterocyclyl, or 4-7 membered monocyclic heterocyclyl-(C₁-C₄)alkyl- of R¹ is optionally substituted independently with one or more halo, (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl;

R^{2D} is hydrogen, (C₁-C₄)alkyl or phenyl(C₁-C₃)alkyl-, wherein the phenyl is optionally substituted with one or more (C₁-C₄)alkyl, -O(C₁-C₄)alkyl, halogen, or -NO₂;

R^{3D} is hydrogen, halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, aryl, or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more

groups independently selected from the group consisting of halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, and (C₁-C₄)haloalkoxy;

R^{4D} is hydrogen, halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, aryl, or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, and (C₁-C₄)haloalkoxy;

R^{5D} is hydrogen, halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, aryl, or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, and (C₁-C₄)haloalkoxy;

R^{6D} is hydrogen, halo, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, aryl, or heteroaryl wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, and (C₁-C₄)haloalkoxy;

each Z¹ is independently halo, -OH, -NO₂, -CN, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, or (C₁-C₄)haloalkoxy;

each Z² is independently selected from the group consisting of -NR^{b3}R^{c3}, -NHNH₂, -C(=NR^{a3})(NR^{b3}R^{c3}), -NR^{a3}C(=NR^{a3})(R^{d3}), and -NR^{a3}C(=NR^{a3})(NR^{b3}R^{c3})

each Z³ is independently -(C₁-C₆)alkyl substituted with one or more Z² and optionally optionally substituted with one or more Z⁴;

each Z⁴ is independently halo or (C₃-C₇)carbocyclyl;

each R^{a1} is independently hydrogen, (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl;

each R^{a2} is independently hydrogen, (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl;

each R^{b2} and R^{c2} is independently hydrogen, (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl;

R^{d2} is (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl;

each R^{a3} is independently hydrogen (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl;

each R^{b3} and R^{c3} is independently hydrogen (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl; and

R^{d3} is (C₁-C₄)alkyl or (C₃-C₇)carbocyclyl.

53. The method of any one of claims 45-52, wherein the animal is infected with bacteria.

54. The method of any one of claims 45-53, wherein the bacterial infection is a Gram-negative bacterial strain infection.

55. The method of claim 42, wherein the Gram-negative bacterial strain is selected from the group consisting of *Acinetobacter baumannii*, *Acinetobacter calcoaceticus*, *Acinetobacter haemolyticus*, *Acinetobacter lwoffii*, *Actinobacillus actinomycetemcomitans*, *Aeromonas hydrophilia*, *Aggregatibacter actinomycetemcomitans*, *Agrobacterium tumefaciens*, *Bacteroides distasonis*, *Bacteroides eggerthii*, *Bacteroides forsythus*, *Bacteroides fragilis*, *Bacteroides ovalus*, *Bacteroides splanchnicus*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Bordetella bronchiseptica*, *Bordetella parapertussis*, *Bordetella pertussis*, *Borrelia burgdorferi*, *Branhamella catarrhalis*, *Burkholderia cepacia*, *Campylobacter coli*, *Campylobacter fetus*, *Campylobacter jejuni*, *Caulobacter crescentus*, *Chlamydia trachomatis*, *Citrobacter diversus*, *Citrobacter freundii*, *Enterobacter aerogenes*, *Enterobacter asburiae*, *Enterobacter cloacae*, *Enterobacter sakazakii*, *Escherchia coli*, *Francisella tularensis*, *Fusobacterium nucleatum*, *Gardnerella vaginalis*, *Haemophilus ducreyi*, *Haemophilus haemolyticus*, *Haemophilus influenzae*, *Haemophilus parahaemolyticus*, *Haemophilus parainfluenzae*, *Helicobacter pylori*, *Kingella denitrificans*, *Kingella indologenes*, *Kingella kingae*, *Kingella oralis*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Klebsiella rhinoscleromatis*, *Legionella pneumophila*, *Listeria monocytogenes*, *Moraxella bovis*, *Moraxella catarrhalis*, *Moraxella lacunata*, *Morganella morganii*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Pantoea agglomerans*, *Pasteurella canis*, *Pasteurella haemolytica*, *Pasteurella multocida*, *Pasteurella tularensis*, *Porphyromonas gingivalis*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia alcalifaciens*, *Providencia rettgeri*, *Providencia stuartii*, *Pseudomonas acidovorans*, *Pseudomonas aeruginosa*, *Pseudomonas alcaligenes*, *Pseudomonas fluorescens*, *Pseudomonas putida*, *Salmonella enteritidis*, *Salmonella paratyphi*, *Salmonella typhi*, *Salmonella typhimurium*, *Serratia marcescens*, *Shigella dysenteriae*, *Shigella jlexneri*, *Shigella sonnei*, *Stenotrophomonas maltophilia*, *Veillonella parvula*, *Vibrio cholerae*, *Vibrio parahaemolyticus*, *Yersinia enterocolitica*, *Yersinia intermedia*, *Yersinia pestis* and *Yersinia pseudotuberculosis*.

56. The method of any one of claims 45-53, wherein the bacterial infection is a Gram-positive bacterial strain infection.

57. The method of claim 56, wherein the Gram-positive bacterial strain is selected from the group consisting of *Actinomyces naeshundii*, *Actinomyces viscosus*, *Bacillus anthracis*, *Bacillus cereus*, *Bacillus subtilis*, *Clostridium difficile*, *Corynebacterium diphtheriae*, *Corynebacterium ulcerans*, *Enterococcus faecalis*, *Enterococcus faecium*, *Micrococcus luteus*, *Mycobacterium avium*, *Mycobacterium intracellulare*, *Mycobacterium leprae*, *Mycobacterium tuberculosis*,

Propionibacterium acnes, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Staphylococcus hominis*, *Staphylococcus hyicus*, *Staphylococcus intermedius*, *Staphylococcus saccharolyticus*, *Staphylococcus saprophyticus*, *Streptococcus agalactiae*, *Streptococcus mutans*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus salivarius* and *Streptococcus sanguis*.

58. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof of as described in any one of claims 1-42, a bacterial efflux pump inhibitor, and a pharmaceutically acceptable vehicle.

59. The pharmaceutical composition of claim 58, wherein the bacterial efflux pump inhibitor is a compound or a pharmaceutically acceptable salt thereof of as described in any one of claims 49-52.

60. A compound or a pharmaceutically acceptable salt thereof as described in any one of claims 1-42, combined with a bacterial efflux pump inhibitor, for use in medical therapy.

61. A compound or a pharmaceutically acceptable salt thereof as described in any one of claims 1-42, combined with a bacterial efflux pump inhibitor, for the prophylactic or therapeutic treatment of a bacterial infection in an animal.

62. The compound of claim 60 or 61, wherein the bacterial efflux pump inhibitor is a compound or a pharmaceutically acceptable salt thereof of as described in any one of claims 49-52.

63. The use of a compound or a pharmaceutically acceptable salt thereof as described in any one of claims 1-42, combined with a bacterial efflux pump inhibitor, for the preparation of a medicament for treating a bacterial infection in an animal.

64. The use of claim 63, wherein the bacterial efflux pump inhibitor is a compound or a pharmaceutically acceptable salt thereof of as described in any one of claims 49-52.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2018/060816

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 14-21, 23, 24, 26-41, 43-64
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Extra Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-9, 13

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2018/060816

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07D 405/04; A61K 45/06; C07D 209/42; C12Q 1/18 (2019.01)

CPC - C07D 405/04; A61K 45/06; C07D 209/42; C12Q 1/18 (2019.02)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

USPC - 546/201; 514/323; 514/338; 514/339; 546/275.1 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PUBCHEM, SID 275115126, Available date: 24 December 2015 [retrieved 11 December 2018]. Retrieved from the Internet:<URL: http://pubchem.ncbi.nlm.nih.gov/substance/275115126/version/1#section=Top >. entire document	1-9, 13
P, X	US 2017/0368116 A1 (UNITED STATES OF AMERICA AS REPRESENTED BY THE SECRETARY OF THE NAVY) 28 December 2017 (28.12.2017) entire document	1-9, 13
P, X	WO 2018/165611 A1 (RUTGERS THE STATE UNIVERSITY OF NEW JERSEY et al) 13 September 2018 (13.09.2018) entire document	1-9, 13

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

04 February 2019

Date of mailing of the international search report

19 FEB 2019

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
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PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2018/060816

Continued from Box No. III Observations where unity of invention is lacking

Claims 1-9 and 13 have been analyzed subject to the restriction that claims read on a compound of formula I: R1 is C1 alkyl, substituted with one NRaRb, and wherein the C1 alkyl is not further substituted, R2 is hydrogen; R3 is hydrogen; R4 is hydrogen; R5 is hydrogen; R6 is hydrogen; R7 is hydrogen; each Ra is independently hydrogen; and each Rb is independently hydrogen.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-13, 22, 25, and 42 are drawn to compounds of formula I, or a salt thereof.

The first invention of Group I+ is restricted to a compound of formula I: R1 is C1 alkyl, substituted with one NRaRb, and wherein the C1 alkyl is not further substituted, R2 is hydrogen; R3 is hydrogen; R4 is hydrogen; R5 is hydrogen; R6 is hydrogen; R7 is hydrogen; each Ra is independently hydrogen; and each Rb is independently hydrogen. It is believed that claims 1-9 and 13 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound of formula I: R1 is C1 alkyl, substituted with one NRaRb, and wherein the C1 alkyl is not further substituted, R2 is hydrogen; R3 is hydrogen; R4 is hydrogen; R5 is hydrogen; R6 is hydrogen; R7 is hydrogen; each Ra is independently unsubstituted C1 alkyl; and each Rb is independently hydrogen. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables R1, R2, R3, R4, R5, R6, R7, and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features of a compound of formula I or a salt thereof, these shared technical features do not represent a contribution over the prior art as disclosed by Substance Record for SID 275115126 to PubChem.

Substance Record for SID 275115126 to PubChem teaches a compound of formula I: R1 is C1 alkyl substituted with one NRaRb; R2 is hydrogen; R3 is hydrogen; R4 is hydrogen; R5 is hydrogen; R6 is hydrogen; R7 is hydrogen; Ra is hydrogen; and Rb is hydrogen (Pg. 3; ...see shown structure...).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.