(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
08 March 2018 (08.03.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/045104 A1

(51) International Patent Classification:
*A61K 31/4545* (2006.01) *A61K 31/498* (2006.01)
*A61K 31/4725* (2006.01)

(21) International Application Number:
PCT/US2017/049491

(22) International Filing Date:
30 August 2017 (30.08.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/381,087 30 August 2016 (30.08.2016) US

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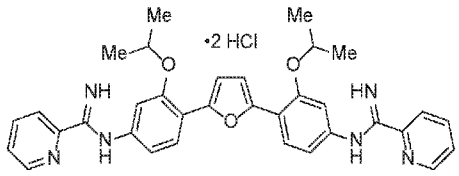
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM,

(54) Title: ANTI-PARASITIC COMPOUNDS

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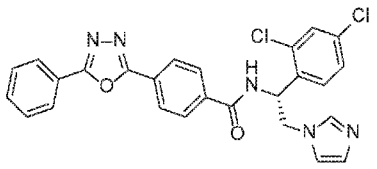


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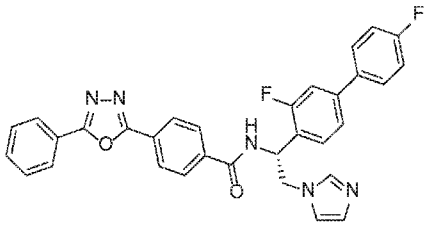


VNI/VNF

FIG. 1 (PRIOR ART)

(57) Abstract: Provided are compounds, methods, and pharmaceutical compositions useful for treatment of parasites, e.g., *Leishmania*. For example, the compound may he represented by Ar—C(=$NR^1$)$NR^2$—A—X—Y—$Het^2$, and pharmaceutically acceptable salts thereof. Ar may be an optionally substituted, aryl or nitrogen-containing heteroaryl. $R^1$ and $R^2$ may independently represent H, optionally substituted $C_1$-$C_6$ alkyl, or optionally substituted $C_3$-$C_6$ cycloalkyl. A may be a bond or an optionally substituted linking moiety comprising 1, 2, or 3 rings. Each ring in the optionally substituted linking moiety may independently be one of: aryl, cycloalkyl, heterocycloalkyl, and heteroaryl. X may be O, S, amide, or a bond. Y may be optionally substituted $C_1$-$C_{14}$ alkyl or optionally substituted $C_2$-$C_{14}$ alkenyl. $Het^2$ may be an optionally substituted five-membered nitrogen-containing heteroaromatic ring comprising 1, 2, or 3 ring heteroatoms.

WO 2018/045104 A1

*[Continued on next page]*

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**(84) Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

**Published:**

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

# ANTI-PARASITIC COMPOUNDS

## CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority from U.S. Provisional Patent Application No.: 62/381,087 filed on August 30, 2016, the entire contents of which are incorporated herein by reference.

## BACKGROUND

[0002] Leishmaniasis is a spectrum of disease that ranges from cutaneous lesions to life-threatening visceral infections caused by sandfly-carried pathogenic *Leishmania* species, of which at least twenty are known. The number of cases of visceral leishmaniasis (VL) was recently estimated as 200,000 to 400,000 per year, with about three times as many cases of cutaneous leishmaniasis (CL). VL may include enlargement of the spleen and liver, anemia, and weight loss, and is usually fatal without effective drug treatment. A vast majority of CL cases occur in Brazil and Peru along with several countries of the Middle East, including Afghanistan, Iran, Iraq, and Syria. In CL, the sandfly bite typically progresses from a papule to a nodule to an ulcerative lesion. Such lesions may self-cure over a period of 2-15 months but may result in a persistent and potentially disfiguring scar. Other manifestations may occur, including diffuse CL (disseminated nodules), leishmaniasis recidivans (recurring infection near a healed lesion), and mucosal leishmaniasis (disfiguring lesions in the mucous membranes of the nose and mouth).

[0003] Despite progress, there are still significant unmet needs in leishmaniasis therapy. Antimonial drugs display serious side effects and high failure rates have prompted their removal as first line treatments against VL on the Indian subcontinent. Liposomal AmB is relatively expensive, limiting its widespread use in developing countries, and is also less effective against Brazilian and East African strains compared to Indian strains. Paromomycin is inexpensive and effective against Indian VL but is less useful against East African VL. Miltefosine is orally available and useful against Indian VL, but is teratogenic in lab animals. A high relapse rate was recently reported for treating VL with miltefosine in Nepal. Injectable antimonials form the basis of most treatment regimens for VL in the New World and are also typically used in the therapy of cutaneous leishmaniasis (CL), either by parenteral or intralesional injection. Miltefosine is recommended for treating CL infections caused by only *L. guyanensis*, *L. panamensis*, and *L. mexicana*, while parenteral pentamidine is a drug of choice for CL caused by *L. guyanensis*. Topical paromomycin is less costly and displays fewer side effects than antimonials but is inferior to these drugs against CL in both the Old World and the New World. The azole antifungal drugs ketoconazole, fluconazole, and itraconazole have all been evaluated in clinical trials against leishmaniasis. While these azoles are orally available and have shown

clinical activity against VL and CL, they lack consistent efficacy. Arylimidamides (AIAs) possess in vitro anti-leishmanial activity and in vivo efficacy in rodent VL models, but higher activity and efficacy is desirable. Studies have shown efficacy for combined application of the AIA DB766 and the azole antifungal posaconazole in vitro. Some anti-leishmanial combinations have been explored in clinical trials, and miltefosine and AmB may be synergistic in mice when given together. However, miltefosine has significant weaknesses, and no oral anti-leishmanial drug combinations exist.

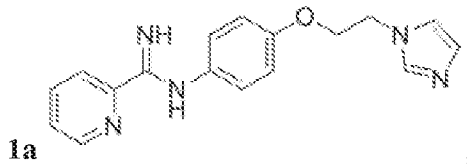
[0004] The present application appreciates that developing treatments for parasite infections such as leishmaniasis may be a challenging endeavor.

## SUMMARY

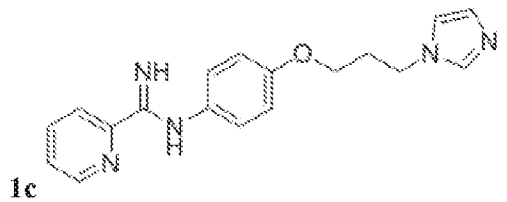
[0005] In one embodiment, a compound is provided, represented by Structural Formula **(Ia)**:

**(Ia)** **Ar**—C(=$NR^1$)$NR^2$—**A**—**X**—**Y**—$\mathbf{Het^2}$

and pharmaceutically acceptable salts thereof. **Ar** may be an optionally substituted aryl or nitrogen-containing heteroaryl. $R^1$ and $R^2$ may independently be H, optionally substituted $C_1$-$C_6$ alkyl, or optionally substituted $C_3$-$C_6$ cycloalkyl. **A** may be a bond or an optionally substituted linking moiety comprising 1, 2, or 3 rings. Each ring in the optionally substituted linking moiety may independently be one of: aryl, cycloalkyl, heterocycloalkyl, and heteroaryl. **X** may be O, S, amide, or a bond. **Y** may be optionally substituted $C_1$-$C_{14}$ alkyl or optionally substituted $C_2$-$C_{14}$ alkenyl, e.g., optionally substituted $C_1$-$C_{10}$ alkyl or optionally substituted $C_2$-$C_{10}$ alkenyl, or optionally substituted $C_1$-$C_8$ alkyl or optionally substituted $C_2$-$C_8$ alkenyl. $\mathbf{Het^2}$ may be an optionally substituted five-membered nitrogen-containing heteroaromatic ring comprising 1, 2, or 3 ring heteroatoms. The compound represented by Structural Formula **(Ia)** may exclude free-base Compounds **1a-f**:




**1a**, **1b**

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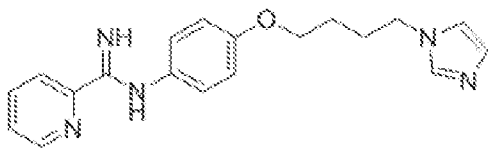
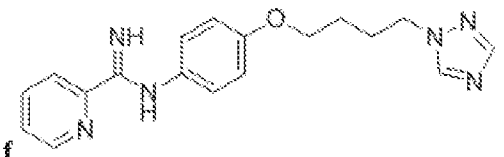
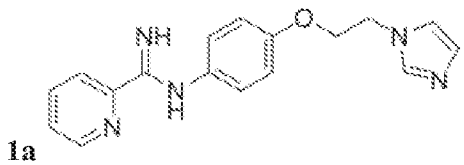
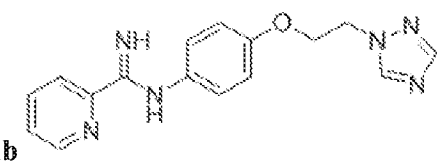
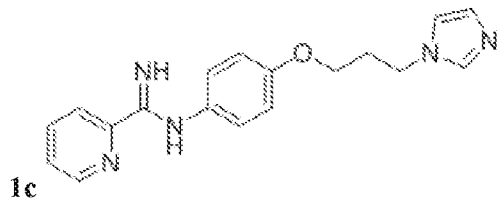
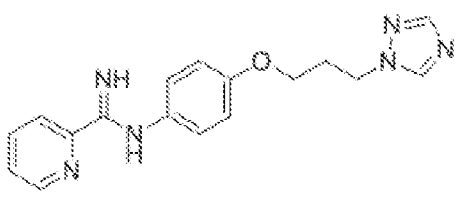

**1e**, and 
**1f**.

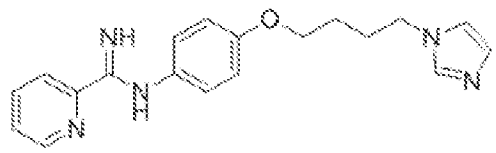
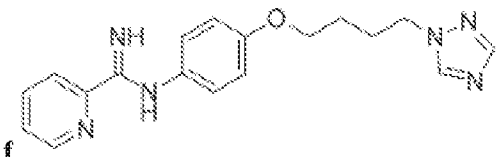
[0006] In another embodiment, a compound is provided, represented by Structural Formula **(I)**:

**(I)** **Het$^1$—C(=NR$^1$)NR$^2$—A—X—Y—Het$^2$**

and pharmaceutically acceptable salts thereof. **Het$^1$** may be an optionally substituted, nitrogen-containing heteroaryl. $R^1$ and $R^2$ may independently be H, optionally substituted $C_1$-$C_6$ alkyl, or optionally substituted $C_3$-$C_6$ cycloalkyl. **A** may be a bond or an optionally substituted linking moiety comprising 1, 2, or 3 rings. Each ring in the optionally substituted linking moiety may independently be one of: aryl, cycloalkyl, heterocycloalkyl, and heteroaryl. **X** may be O, S, amide, or a bond. **Y** may be optionally substituted $C_1$-$C_{10}$ alkyl or optionally substituted $C_2$-$C_{10}$ alkenyl. **Het$^2$** may be an optionally substituted five-membered nitrogen-containing heteroaromatic ring comprising 1, 2, or 3 ring heteroatoms. The compound represented by Structural Formula **(I)** may exclude free-base Compounds **1a-f**:


**1a**, **1b** 


**1c**, **1d** 


**1e**, and **1f**  .

[0007] In one embodiment, a method of anti-parasitic treatment in a subject in need thereof is provided. The method may include providing the subject, the subject being infected by a parasite or at risk of infection by the parasite. The method may include administering a compound to the subject in an amount effective to mitigate infection by the parasite in the subject. The compound may be represented by Structural Formula **(Ia)**:

**(Ia)** **Ar—C(=NR$^1$)NR$^2$—A—X—Y—Het$^2$**

and pharmaceutically acceptable salts thereof. **Ar** may be an optionally substituted aryl or nitrogen-containing heteroaryl. $R^1$ and $R^2$ may independently be H, optionally substituted $C_1$-$C_6$ alkyl, or optionally substituted $C_3$-$C_6$ cycloalkyl. **A** may be a bond or an optionally substituted linking moiety comprising 1, 2, or 3 rings. Each ring in the optionally substituted linking moiety may independently be one of: aryl, cycloalkyl, heterocycloalkyl, and heteroaryl. **X** may be O, S, amide, or a bond. **Y** may be optionally substituted $C_1$-$C_{14}$ alkyl or optionally substituted $C_2$-$C_{14}$ alkenyl, e.g., optionally substituted $C_1$-$C_{10}$ alkyl or optionally substituted $C_2$-$C_{10}$ alkenyl, or optionally substituted $C_1$-$C_8$ alkyl or optionally substituted $C_2$-$C_8$ alkenyl. **$Het^2$** may be an optionally substituted five-membered nitrogen-containing heteroaromatic ring comprising 1, 2, or 3 ring heteroatoms.

[0008] In another embodiment, a method of anti-parasitic treatment in a subject in need thereof is provided. The method may include providing the subject, the subject being infected by a parasite or at risk of infection by the parasite. The method may include administering a compound to the subject in an amount effective to mitigate infection by the parasite in the subject. The compound may be represented by Structural Formula **(I)**:

**(I)** $Het^1$—C(=$NR^1$)$NR^2$—**A**—**X**—**Y**—$Het^2$

and pharmaceutically acceptable salts thereof. **$Het^1$** may be an optionally substituted, nitrogen-containing heteroaryl. $R^1$ and $R^2$ may independently be H, optionally substituted $C_1$-$C_6$ alkyl, or optionally substituted $C_3$-$C_6$ cycloalkyl. **A** may be a bond or an optionally substituted linking moiety comprising 1, 2, or 3 rings. Each ring in the optionally substituted linking moiety may independently be one of: aryl, cycloalkyl, heterocycloalkyl, and heteroaryl. **X** may be O, S, amide, or a bond. **Y** may be optionally substituted $C_1$-$C_{10}$ alkyl or optionally substituted $C_2$-$C_{10}$ alkenyl. **$Het^2$** may be an optionally substituted five-membered nitrogen-containing heteroaromatic ring comprising 1, 2, or 3 ring heteroatoms.

[0009] In one embodiment, a pharmaceutical composition is provided. The pharmaceutical composition may include a pharmaceutically acceptable excipient and a compound represented by Structural Formula **(Ia)**:

**(Ia)** **Ar**—C(=$NR^1$)$NR^2$—**A**—**X**—**Y**—$Het^2$

and pharmaceutically acceptable salts thereof. **Ar** may be an optionally substituted aryl or nitrogen-containing heteroaryl. $R^1$ and $R^2$ may independently be H, optionally substituted $C_1$-$C_6$ alkyl, or optionally substituted $C_3$-$C_6$ cycloalkyl. **A** may be a bond or an optionally substituted linking moiety comprising 1, 2, or 3 rings. Each ring in the optionally substituted linking moiety may independently be one of: aryl, cycloalkyl, heterocycloalkyl, and heteroaryl. **X** may be O, S, amide, or a bond. **Y** may be optionally substituted $C_1$-$C_{14}$ alkyl or optionally substituted $C_2$-$C_{14}$

alkenyl, e.g., optionally substituted $C_1$-$C_{10}$ alkyl or optionally substituted $C_2$-$C_{10}$ alkenyl, or optionally substituted $C_1$-$C_8$ alkyl or optionally substituted $C_2$-$C_8$ alkenyl. **Het**$^2$ may be an optionally substituted five-membered nitrogen-containing heteroaromatic ring comprising 1, 2, or 3 ring heteroatoms.

[0010] In another embodiment, a pharmaceutical composition is provided. The pharmaceutical composition may include a pharmaceutically acceptable excipient and a compound represented by Structural Formula Structural Formula **(I)**:

**(I)** **Het**$^1$—C(=$NR^1$)$NR^2$—**A**—**X**—**Y**—**Het**$^2$

and pharmaceutically acceptable salts thereof. **Het**$^1$ may be an optionally substituted, nitrogen-containing heteroaryl. $R^1$ and $R^2$ may independently be H, optionally substituted $C_1$-$C_6$ alkyl, or optionally substituted $C_3$-$C_6$ cycloalkyl. **A** may be a bond or an optionally substituted linking moiety comprising 1, 2, or 3 rings. Each ring in the optionally substituted linking moiety may independently be one of: aryl, cycloalkyl, heterocycloalkyl, and heteroaryl. **X** may be O, S, amide, or a bond. **Y** may be optionally substituted $C_1$-$C_{10}$ alkyl or optionally substituted $C_2$-$C_{10}$ alkenyl. **Het**$^2$ may be an optionally substituted five-membered nitrogen-containing heteroaromatic ring comprising 1, 2, or 3 ring heteroatoms.

[0011] In one embodiment, a kit for anti-parasite treatment of a subject in need thereof is provided. The kit may include a compound represented by Structural Formula **(I)**:

**(Ia)** **Ar**—C(=$NR^1$)$NR^2$—**A**—**X**—**Y**—**Het**$^2$

[0012] and pharmaceutically acceptable salts thereof. **Ar** may be an optionally substituted aryl or nitrogen-containing heteroaryl. $R^1$ and $R^2$ may independently be H, optionally substituted $C_1$-$C_6$ alkyl, or optionally substituted $C_3$-$C_6$ cycloalkyl. **A** may be a bond or an optionally substituted linking moiety comprising 1, 2, or 3 rings. Each ring in the optionally substituted linking moiety may independently be one of: aryl, cycloalkyl, heterocycloalkyl, and heteroaryl. **X** may be O, S, amide, or a bond. **Y** may be optionally substituted $C_1$-$C_{14}$ alkyl or optionally substituted $C_2$-$C_{14}$ alkenyl, e.g., optionally substituted $C_1$-$C_{10}$ alkyl or optionally substituted $C_2$-$C_{10}$ alkenyl, or optionally substituted $C_1$-$C_8$ alkyl or optionally substituted $C_2$-$C_8$ alkenyl. **Het**$^2$ may be an optionally substituted five-membered nitrogen-containing heteroaromatic ring comprising 1, 2, or 3 ring heteroatoms.

[0013] In another embodiment, a kit for anti-parasite treatment of a subject in need thereof is provided. The kit may include a compound represented by Structural Formula **(I)**:

**(I)** **Het**$^1$—C(=$NR^1$)$NR^2$—**A**—**X**—**Y**—**Het**$^2$

and pharmaceutically acceptable salts thereof, and mixtures thereof with a pharmaceutically acceptable carrier or excipient. **Het**$^1$ may be an optionally substituted, nitrogen-containing

heteroaryl. $R^1$ and $R^2$ may independently be H, optionally substituted $C_1$-$C_6$ alkyl, or optionally substituted $C_3$-$C_6$ cycloalkyl. **A** may be a bond or an optionally substituted linking moiety comprising 1, 2, or 3 rings. Each ring in the optionally substituted linking moiety may independently be one of: aryl, cycloalkyl, heterocycloalkyl, and heteroaryl. **X** may be O, S, amide, or a bond. **Y** may be optionally substituted $C_1$-$C_{10}$ alkyl or optionally substituted $C_2$-$C_{10}$ alkenyl. **Het²** may be an optionally substituted five-membered nitrogen-containing heteroaromatic ring comprising 1, 2, or 3 ring heteroatoms. The kit may include instructions. The instructions may direct a user to provide the subject, the subject being infected by a parasite or at risk of infection by the parasite. The instructions may direct a user to administer the compound or the pharmaceutical composition to the subject in an amount effective to mitigate infection by the parasite in the subject.

## BRIEF DESCRIPTION OF THE DRAWINGS

[0014] The accompanying figures, which are incorporated in and constitute a part of the specification, illustrate example methods and compositions, and are used merely to illustrate example embodiments.

[0015] **FIG. 1** (PRIOR ART) depicts structures of various known compounds.

[0016] **FIG. 2A** is a synthetic scheme for various phenoxyalkyl linker anti-parasitic compounds.

[0017] **FIG. 2B** is a synthetic scheme for various phenoxyalkyl hybrid target compounds substituted *meta* to the arylimidamide group.

[0018] **FIG. 2C** is a synthetic scheme for various phenoxyalkyl hybrid target compounds substituted *ortho* to the arylimidamide group.

[0019] **FIG. 2D** is a synthetic scheme for various phenoxyalkyl hybrid target compounds substituted with pyrrole.

[0020] **FIG. 3A** is a synthetic scheme for various phenyl-unsubstituted diphenylfuran alkyloxy linker hybrid compounds.

[0021] **FIG. 3B** is a synthetic scheme for various phenyl substituted diphenylfuran alkyloxy linker hybrid compounds.

[0022] **FIG. 3C** is a synthetic scheme for various phenyl substituted diphenylfuran alkyloxy linker hybrid compounds.

[0023] **FIG. 3D** is a prophetic synthetic scheme for various diphenylfuran alkyloxy linker hybrid compounds.

[0024] **FIG. 4** is a prophetic synthetic scheme for various alkylamide linker hybrid compounds.

[0025] **FIG. 5A** is a prophetic synthetic scheme for various phenylalkyl linker hybrid compounds **8a** and **8b**.

[0026] **FIG. 5B** is a synthetic scheme for various phenylalkyl linker hybrid compounds.

[0027] **FIG. 6A** is a synthetic scheme for various unsubstituted and substituted biphenyl linker anti-parasitic compounds.

[0028] **FIG. 6B** is a synthetic scheme for various substituted biphenyl linker anti-parasitic compounds.

[0029] **FIG. 6C** is a synthetic scheme for various substituted biphenyl linker anti-parasitic compounds.

[0030] **FIG. 6D** is a synthetic scheme for various substituted biphenyl linker anti-parasitic compounds.

[0031] **FIG. 7A** is a synthetic scheme for various phenyl-piperazinyl-phenyl linker anti-parasitic compounds.

[0032] **FIG. 7B** is a synthetic scheme for various phenyl-piperazinyl linker anti-parasitic compounds.

[0033] **FIG. 8A** is a table reciting $IC_{50}$ values of various phenoxyalkyl linker compounds against *L. donovani*, $CC_{50}$ values against J774 macrophages, and $CC_{50}$ values against HepG2.

[0034] **FIG. 8B** is a table reciting $IC_{50}$ values of various diphenylfuran alkyloxy linker compounds against *L. donovani*, $CC_{50}$ values against J774 macrophages, and $CC_{50}$ values against HepG2.

[0035] **FIG. 8C** is a table reciting $IC_{50}$ values of various biphenyl alkyloxy linker compounds against *L. donovani*, $CC_{50}$ values against J774 macrophages, and $CC_{50}$ values against HepG2.

[0036] **FIG. 8D** is a table reciting $IC_{50}$ values of various piperazinyl linker compounds against *L. donovani* and $CC_{50}$ values against J774 macrophages.

## DETAILED DESCRIPTION

[0037] In various embodiments, a compound is provided, represented by Structural Formula **(Ia)**:

**(Ia)** $\mathbf{Ar—C(=NR^1)NR^2—A—X—Y—Het^2}$

and pharmaceutically acceptable salts thereof. **Ar** may be an optionally substituted aryl or nitrogen-containing heteroaryl. $R^1$ and $R^2$ may independently be H, optionally substituted $C_1$-$C_6$ alkyl, or optionally substituted $C_3$-$C_6$ cycloalkyl. **A** may be a bond or an optionally substituted linking moiety comprising 1, 2, or 3 rings. Each ring in the optionally substituted linking moiety may independently be one of: aryl, cycloalkyl, heterocycloalkyl, and heteroaryl. **X** may be O, S,

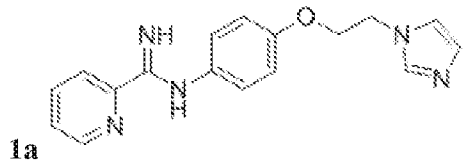
amide, or a bond. **Y** may be optionally substituted $C_1$-$C_{14}$ alkyl or optionally substituted $C_2$-$C_{14}$ alkenyl, e.g., optionally substituted $C_1$-$C_{10}$ alkyl or optionally substituted $C_2$-$C_{10}$ alkenyl, or optionally substituted $C_1$-$C_8$ alkyl or optionally substituted $C_2$-$C_8$ alkenyl. **Het**$^2$ may be an optionally substituted five-membered nitrogen-containing heteroaromatic ring comprising 1, 2, or 3 ring heteroatoms.

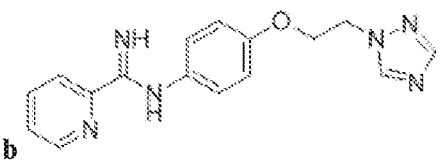
[0038] In some embodiments, a compound is provided, represented by Structural Formula **(I)**:

**(I)** **Het**$^1$—C(=NR$^1$)NR$^2$—**A**—**X**—**Y**—**Het**$^2$

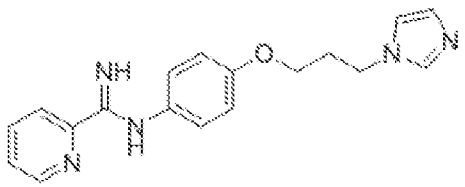
and pharmaceutically acceptable salts thereof. **Het**$^1$ may be an optionally substituted, nitrogen-containing heteroaryl. $R^1$ and $R^2$ may independently be H, optionally substituted $C_1$-$C_6$ alkyl, or optionally substituted $C_3$-$C_6$ cycloalkyl. **A** may be a bond or an optionally substituted linking moiety comprising 1, 2, or 3 rings. Each ring in the optionally substituted linking moiety may independently be one of: aryl, cycloalkyl, heterocycloalkyl, and heteroaryl. **X** may be O, S, amide, or a bond. **Y** may be optionally substituted $C_1$-$C_{14}$ alkyl or optionally substituted $C_2$-$C_{14}$ alkenyl, e.g., optionally substituted $C_1$-$C_{10}$ alkyl or optionally substituted $C_2$-$C_{10}$ alkenyl , or optionally substituted $C_1$-$C_8$ alkyl or optionally substituted $C_2$-$C_8$ alkenyl. **Het**$^2$ may be an optionally substituted five-membered nitrogen-containing heteroaromatic ring comprising 1, 2, or 3 ring heteroatoms.

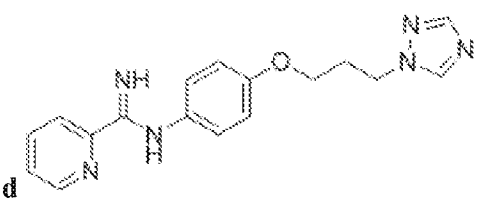
[0039] In several embodiments, the compound represented by Structural Formula **(Ia)** or **(I)** may exclude certain compounds. For example, the compound represented by Structural Formula **(Ia)** or **(I)** may exclude free-base (neutral or non-salt) forms of Compounds **1a-f**, wherein: **Het**$^1$ is unsubstituted pyrid-2-yl; $R^1$ and $R^2$ are each H; **X** is O; **Y** is unbranched, unsubstituted $C_2$-$C_4$ alkyl; and **Het**$^2$ is unsubstituted imidazole-1-yl or unsubstituted 1, 2, 4 triazol-2-yl:



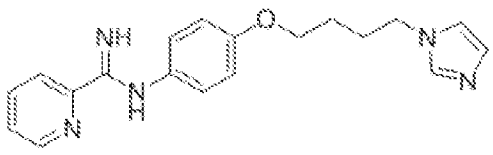

**1a**, 


**1b**,

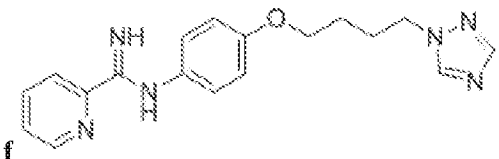



**1c**, 


**1d**,



**1e** , and **1f**

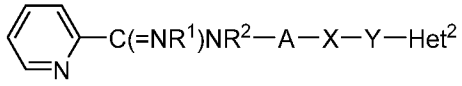


.

[0040] In several embodiments, the compound represented by Structural Formula **(Ia)** or **(I)** may include pharmaceutically acceptable salts of Compounds **1a-f**. The compound represented by Structural Formula **(Ia)** or **(I)** may exclude free-base forms of Compounds **1a-f** and pharmaceutically acceptable salts of Compounds **1a-f**. The compound represented by Structural Formula **(Ia)** or **(I)** may exclude protonated forms of Compounds **1a-f**.

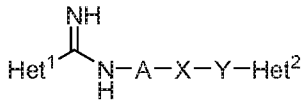
[0041] In some embodiments, the compound represented by Structural Formula **(Ia)** or **(I)** may exclude compounds wherein **Het$^1$** is one of unsubstituted pyridyl and pyrid-2-yl substituted with methyl or ethyl, for example, when: $R^1$ and $R^2$ are each H; **X** is O; **Y** is unbranched, unsubstituted $C_2$-$C_4$ alkyl; and **Het$^2$** is unsubstituted imidazole-1-yl or unsubstituted 1,2,4-triazol-2-yl. In some embodiments, the compound represented by Structural Formula **(Ia)** or **(I)** may exclude compounds wherein one of $R^1$ and $R^2$ is H and the other is methyl or ethyl, for example, when: **Het$^1$** is unsubstituted pyrid-2-yl; **X** is O; **Y** is unbranched, unsubstituted $C_2$-$C_4$ alkyl; and **Het$^2$** is unsubstituted imidazole-1-yl or unsubstituted 1,2,4-triazol-2-yl. In some embodiments, the compound represented by Structural Formula **(Ia)** or **(I)** may exclude compounds wherein **X** is S, for example, when: **Het$^1$** is unsubstituted pyrid-2-yl; $R^1$ and $R^2$ are each H; **Y** is unbranched, unsubstituted $C_2$-$C_4$ alkyl; and **Het$^2$** is unsubstituted imidazole-1-yl or unsubstituted 1,2,4-triazol-2-yl. In some embodiments, the compound represented by Structural Formula **(Ia)** or **(I)** may exclude compounds wherein **Y** is $C_2$-$C_4$ alkyl substituted with methyl or ethyl, unsubstituted or methyl substituted $C_1$-$C_5$ alkyl, or unsubstituted $C_1$-$C_6$ alkyl, for example, when: **Het$^1$** is unsubstituted pyrid-2-yl; $R^1$ and $R^2$ are each H; **X** is O; and **Het$^2$** is unsubstituted imidazole-1-yl or unsubstituted 1,2,4-triazol-2-yl. In some embodiments, the compound represented by Structural Formula **(Ia)** or **(I)** may exclude compounds wherein **Het$^2$** is one of: methyl or ethyl substituted imidazole-1-yl; unsubstituted imidazolyl; methyl or ethyl substituted imidazolyl; methyl or ethyl substituted 1,2,4-triazol-2-yl; unsubstituted 1,2,4-triazolyl; methyl or ethyl substituted 1,2,4-triazolyl; unsubstituted triazolyl; and methyl or ethyl substituted triazolyl; for example, when: **Het$^1$** is unsubstituted pyrid-2-yl; $R^1$ and $R^2$ are each H; **X** is O; and **Y** is unbranched, unsubstituted $C_2$-$C_4$ alkyl.

[0042] In several embodiments, **Het$^1$** may be optionally substituted pyridyl, pyrazinyl, pyrimidinyl, or pyridizinyl. For example, **Het$^1$** may be optionally substituted pyridyl. The compound may be represented by Structural Formula **(II)**:



**(II)**

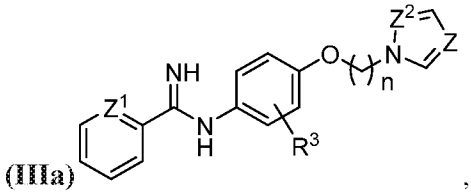
[0043] In several embodiments, the compound may be represented by Structural Formula **(III)**:



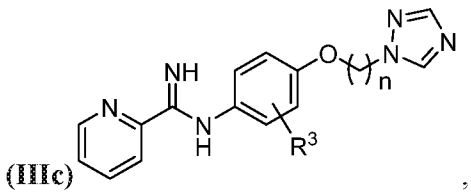
**(III)**

[0044] In various embodiments, each ring in the optionally substituted linking moiety represented by **A** may be independently and optionally substituted by one or more of: hydroxy, halo, and $C_1$-$C_6$ alkoxy. **A** may include an optionally substituted heteroaryl or optionally substituted heterocycloalkyl ring. **A** may include an optionally substituted, oxygen-containing, heteroaryl or heterocycloalkyl ring. **A** may include an optionally substituted furanyl or optionally substituted tetrahydrofuranyl ring. **A** may include optionally substituted 2,5-furanyl. **A** may include one or two optionally substituted phenyl rings. **A** may include optionally substituted 1,4-phenyl. **A** may be optionally substituted 1,4-phenyl. **A** may be optionally substituted phenyl-heteroaryl-phenyl.

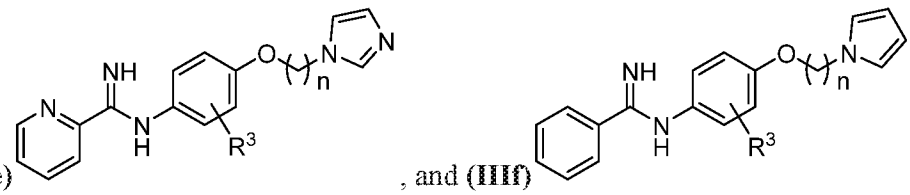
[0045] For example, the compound of Structural Formula **III** may be represented by one of Structural Formulas **(IIIa)-(IIIf)**:



**(IIIa)**, **(IIIb)**,



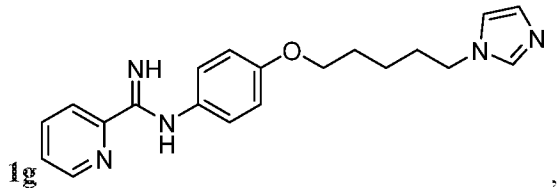
**(IIIc)**, **(IIId)**,

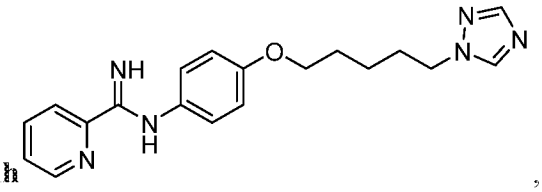


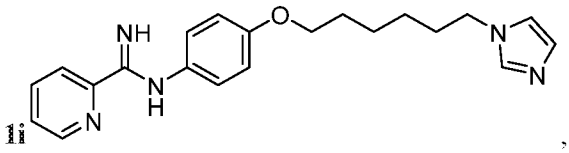
**(IIIe)**, and **(IIIf)**.

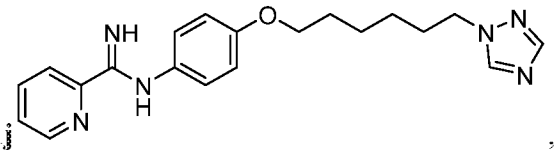
wherein Z, $Z^1$, and $Z^2$ are each independently CH or N, n may be 1-14, e.g., 1-10, and $R^3$ may represent H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy.

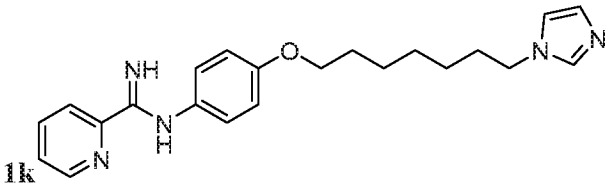
[0046] In some embodiments, the compound may be represented by one of Compounds **1g-1v**, e.g., **1g-1n**:

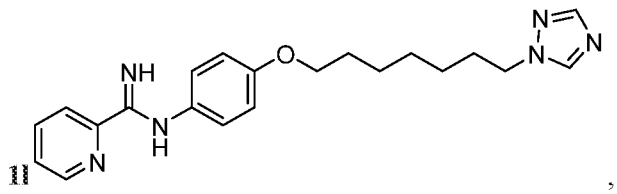

**1g**,

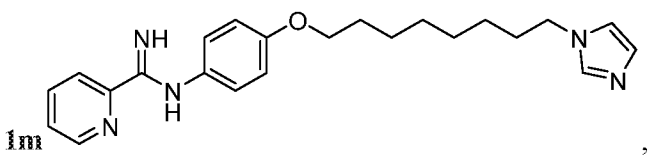

**1h**,

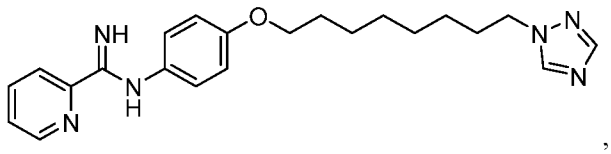

**1i**,

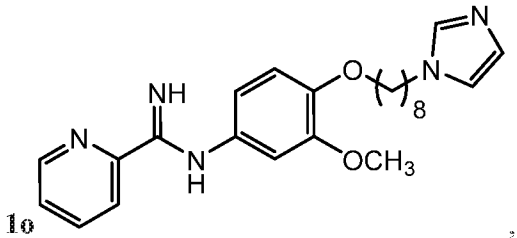

**1j**,

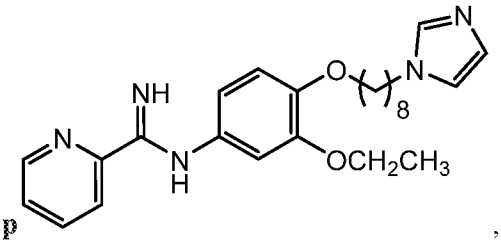

**1k**,

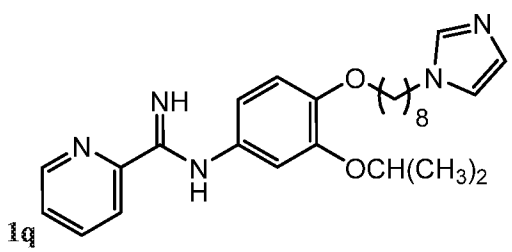

**1l**,

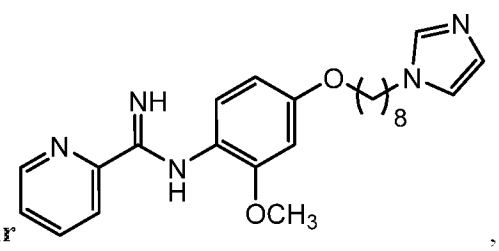

**1m**, **1n**

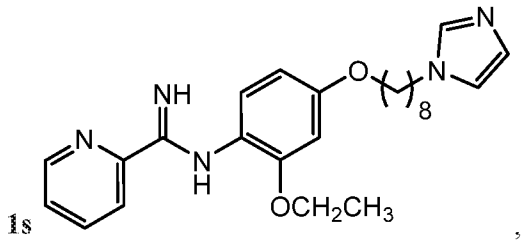

,

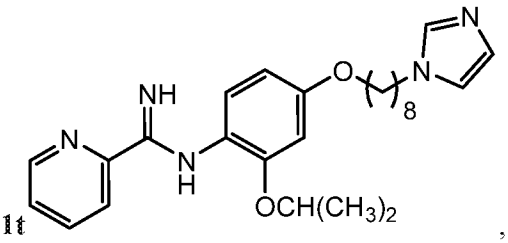

**1o**,


**1p**,

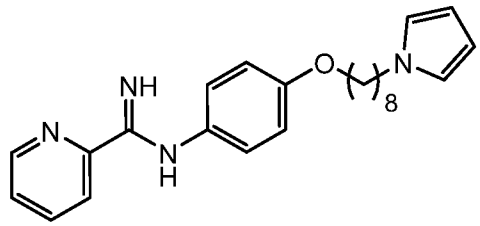

**1q**,

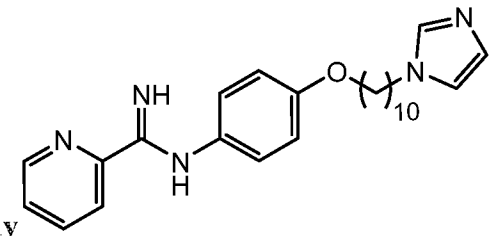

**1r**,




**1s**, 

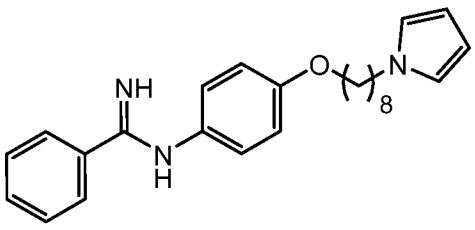

**1t**,




**1u**, and 

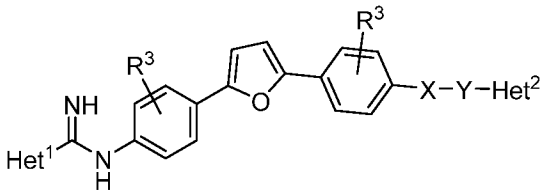

**1v**.

[0047] The compound may be, for example, represented by Structural Formula **(IIIf)** above, e.g., compound **14a**:



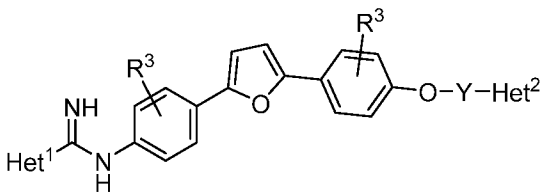

**14a**.

[0048] In some embodiments, the compound may be represented by Structural Formula **(IV)**:




**(IV)**,

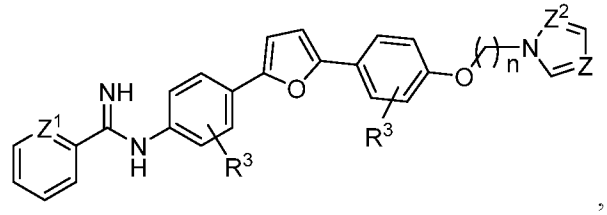
wherein each $\mathbf{R^3}$ may independently represent H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy. For example, the compound may be represented by Structural Formula **(V)**:



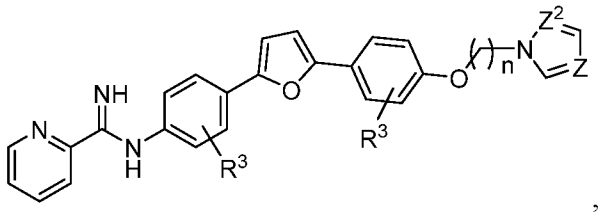

**(V)**.

[0049] In several embodiments, **Y** may include at least 4 linking atoms between **X** and $\mathbf{Het^2}$. **X** may be O or a bond and **Y** may be $C_1$-$C_{14}$, e.g., $C_1$-$C_{10}$ alkyl optionally substituted with one or more of: optionally halogenated $C_1$-$C_8$ alkyl and optionally halogenated aryl.

[0050] For example, the compound may be represented by one of Structural Formulas **(Va)-(Ve)**, wherein each Z, $Z^1$, and $Z^2$ are independently CH or N:



**(Va)**, **(Vb)**



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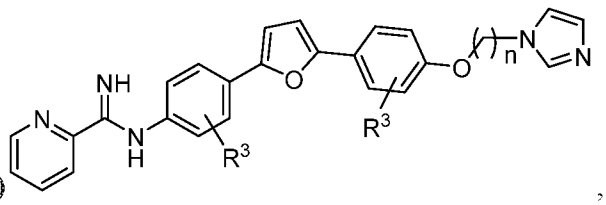
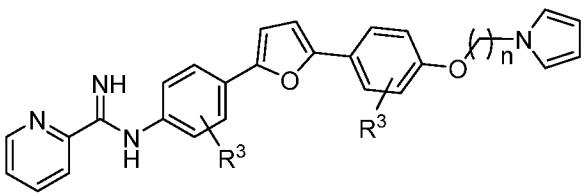
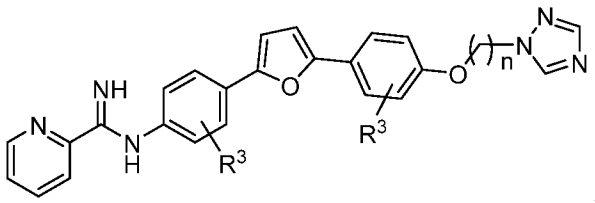


**(Vc)**, **(Vd)**



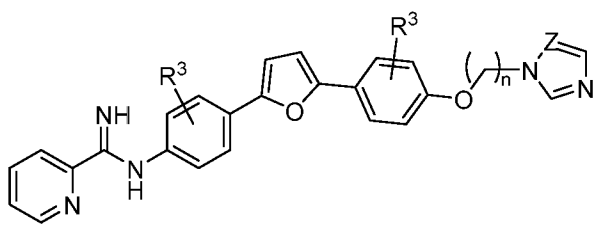
, and **(Ve)**



,

wherein Z, $Z^1$, and $Z^2$ are each independently CH or N, n may be 1-14, e.g., 1-10, and $R^3$ may represent H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy.

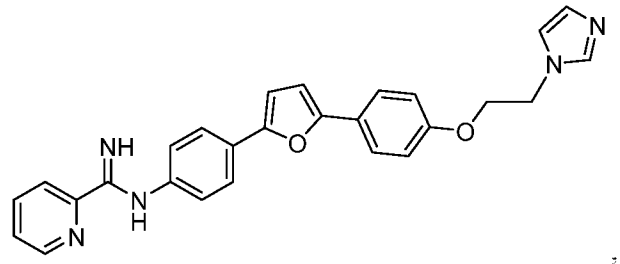
[0051] For example, in some embodiments, the compound may be represented by Structural Formula **(VII)**:



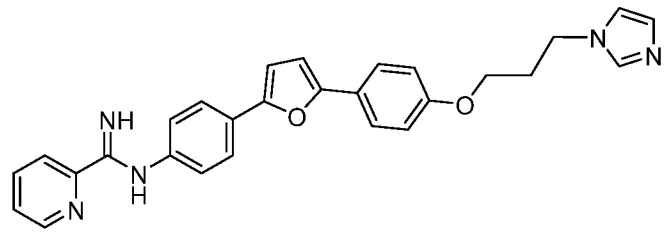
**(VII)**,

wherein: **Z** may be CH or N; each $\mathbf{R^3}$ may independently be H, halogen, optionally halogenated $C_1$-$C_{10}$ alkyl, or optionally halogenated $C_1$-$C_{10}$ alkoxy; and **n** may be an integer from 1 to 10. For example, the compound may be one of Compounds **2a-2h**:

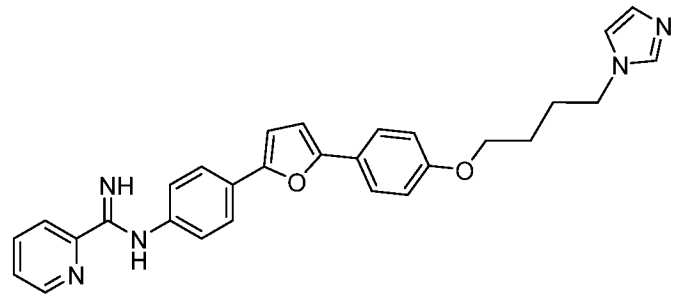
**2a**



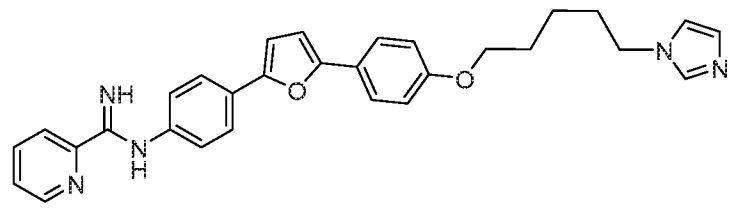
**2b**



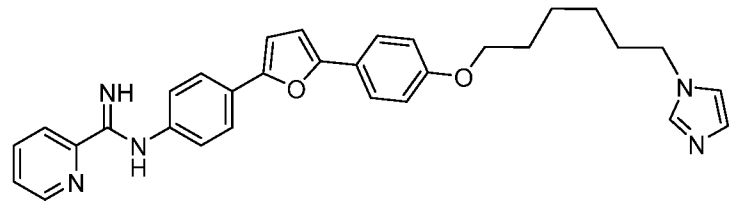
**2c**



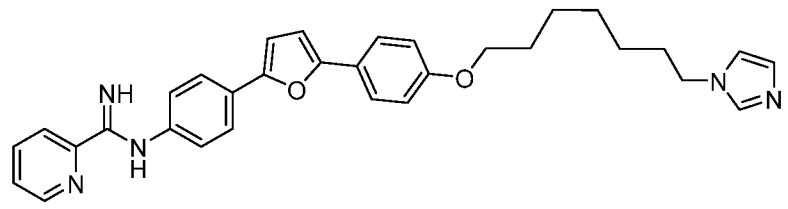
**2d**

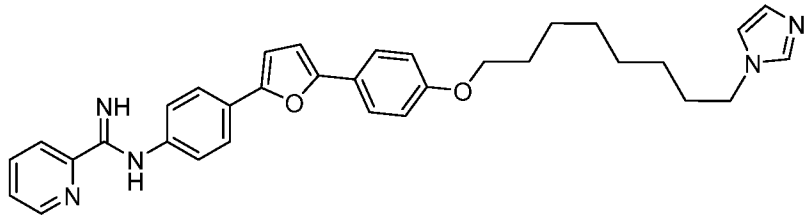


**2e**

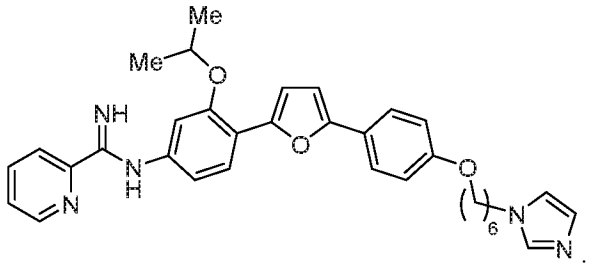


**2f**



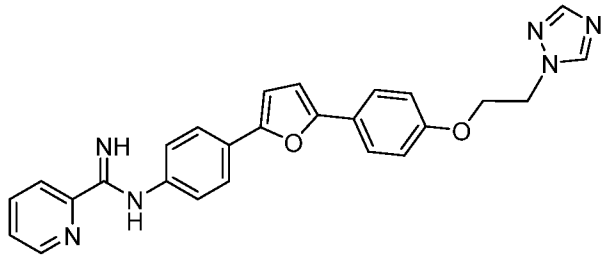


**2g** , and

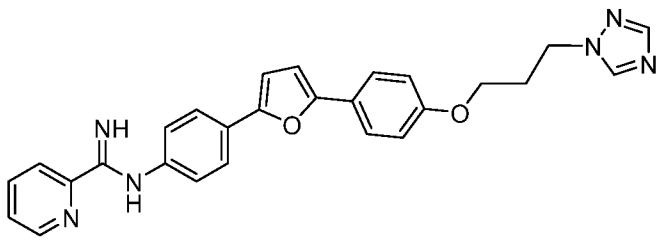


**2h** .

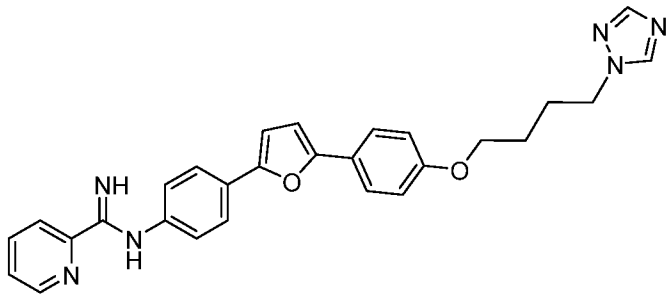
[0052] The compound may be, for example, one of Compounds **3a-3g**:



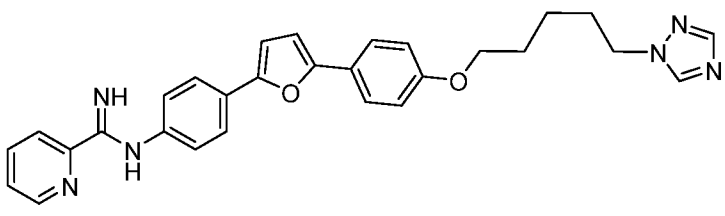
**3a** ,



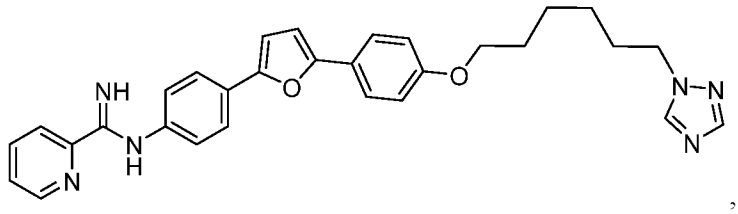
**3b** ,



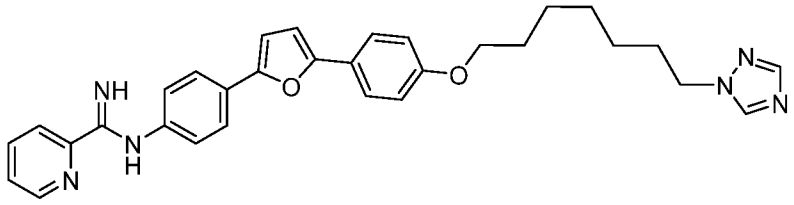
**3c** ,



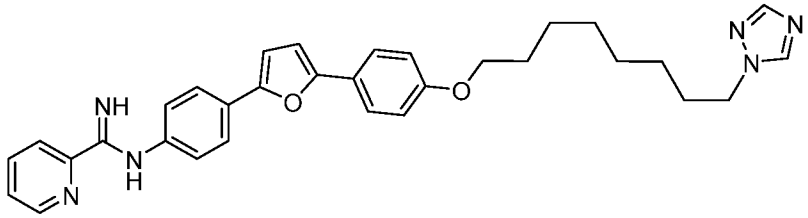
**3d** ,



3e ,

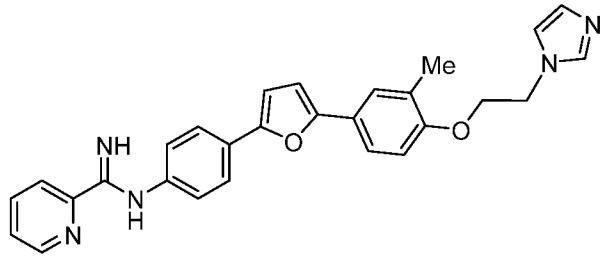


3f , and

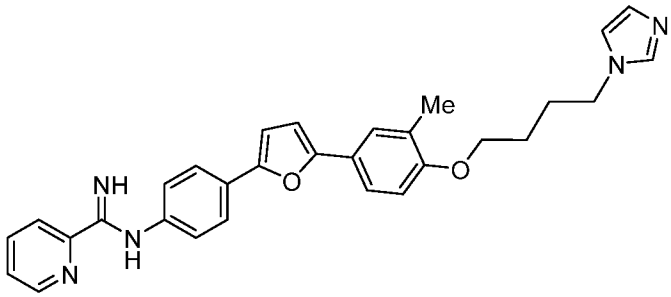


3g .

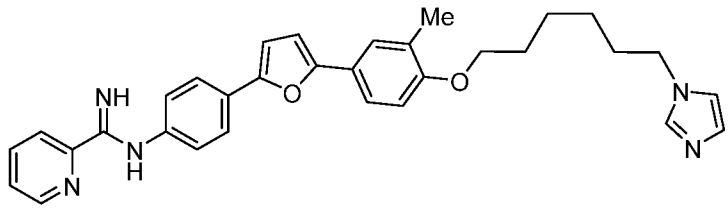
[0053] The compound may be, for example, one of Compounds **4a-4m**, e.g., **4a-4i**:



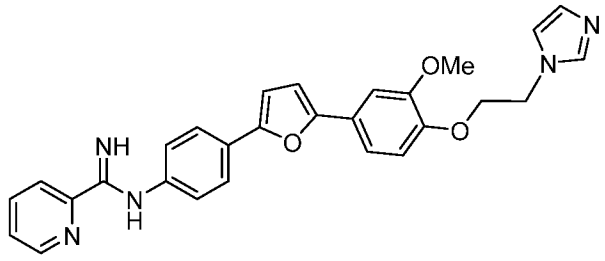
4a ,



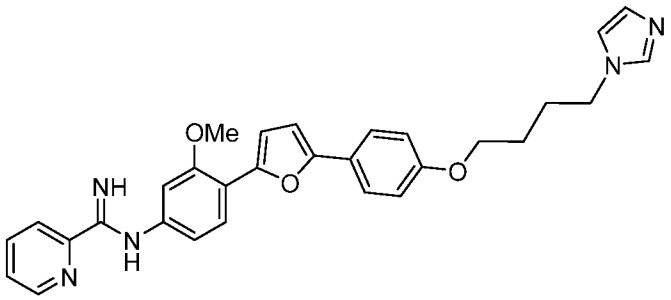
4b ,



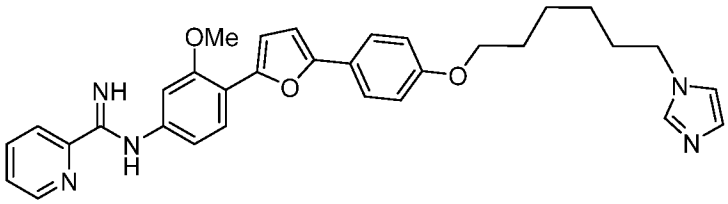
4c .



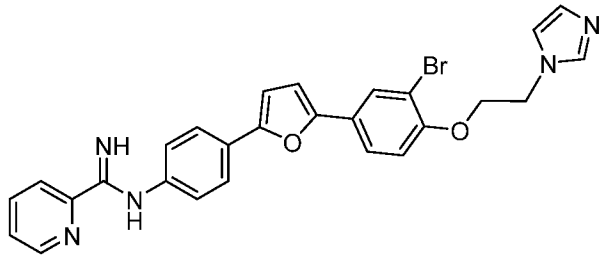
4d ,



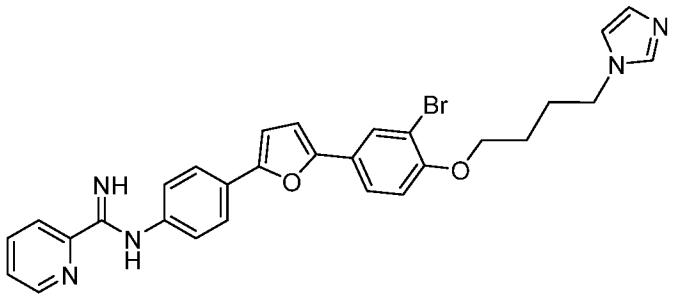
4e ,



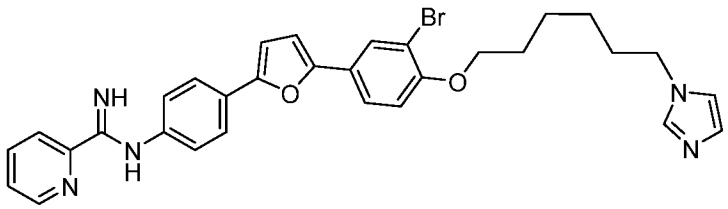
4f ,



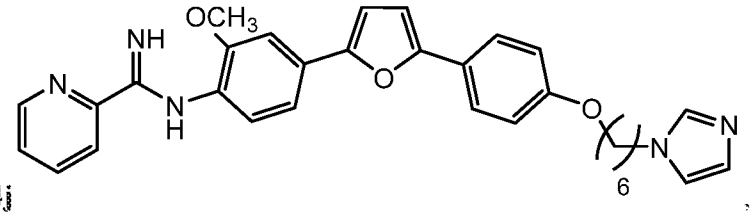
4g ,



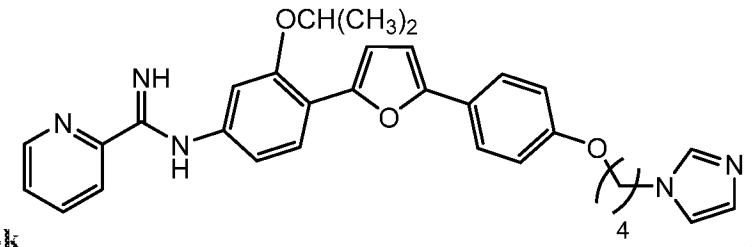
4h ,



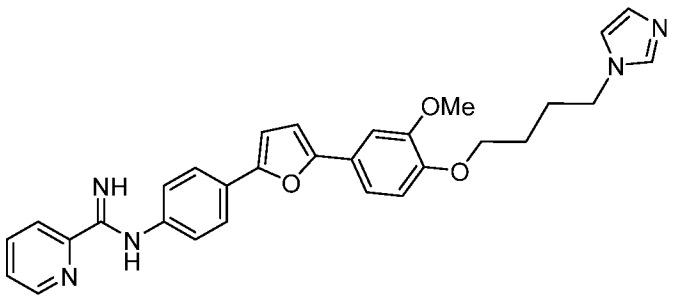
4i ,



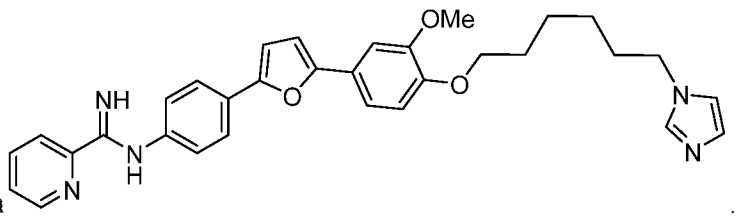

**4j** ,




**4k** ,

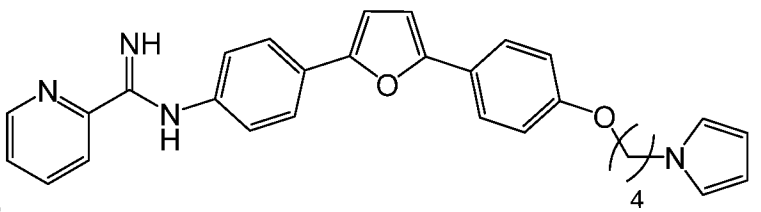



**4l** , and

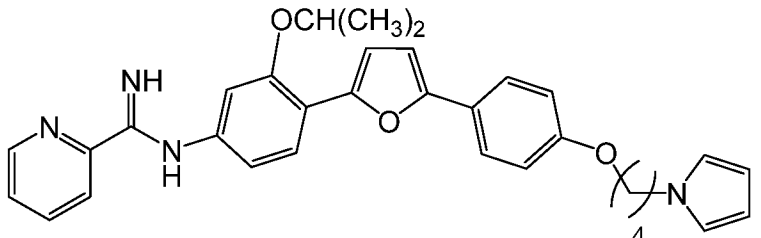



**4m** .

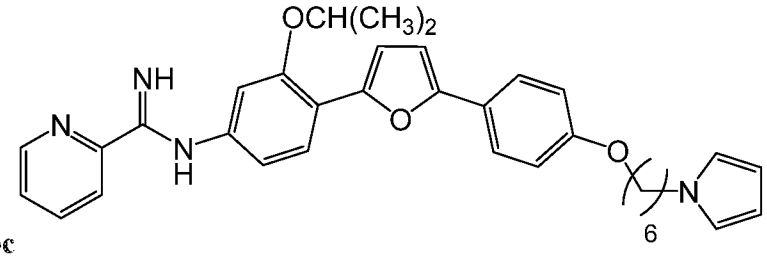
[0054] The compound may be, for example, represented by Structural Formula **(Vd)** above, e.g., one of compounds **13a-13c**:




**13a** ,

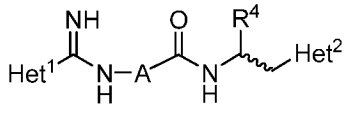



**13b** , and



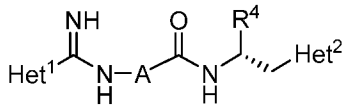
13c

[0055] In various embodiments, the compound may be represented by Structural Formula **(VIa)**:



**(VIa)**

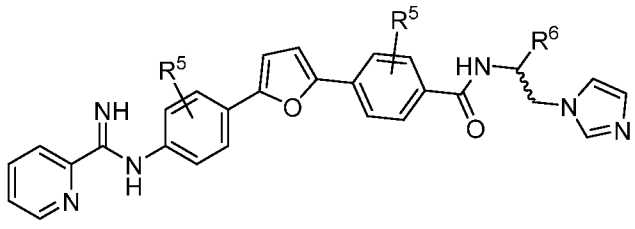
wherein $\mathbf{R^4}$ may be H, optionally halogenated $C_1$-$C_{10}$ alkyl, or optionally halogenated aryl. The compound may be represented by Structural Formula **(VIb)**:



**(VIb)**

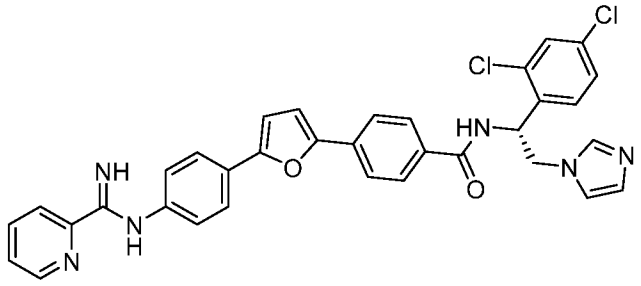
[0056] In some embodiments, $\mathbf{Het^2}$ may include an optionally substituted one of: pyrrole, diazole, thiadiazole, oxadiazole, and triazole. For example, $\mathbf{Het^2}$ may be optionally substituted imidazole or optionally substituted 1, 2, 4 triazole.

[0057] In several embodiments, the compound may be represented by Structural Formula **(VIII)**:

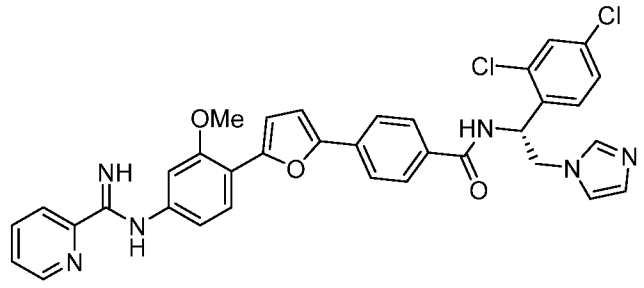


**(VIII)**

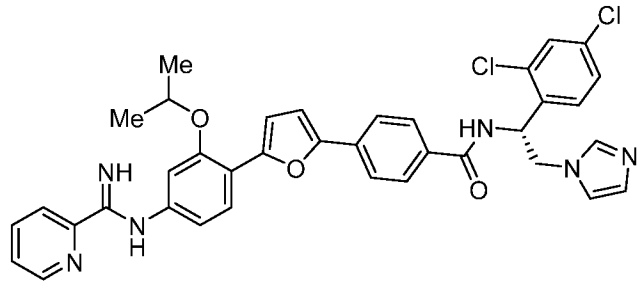
wherein: each $\mathbf{R^5}$ may independently be H, halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy; and $\mathbf{R^6}$ may be H, optionally halogenated $C_1$-$C_6$ alkyl, optionally halogenated phenyl, or optionally halogenated biphenyl. For example, the compound may be one of Compounds **5a-5f**:



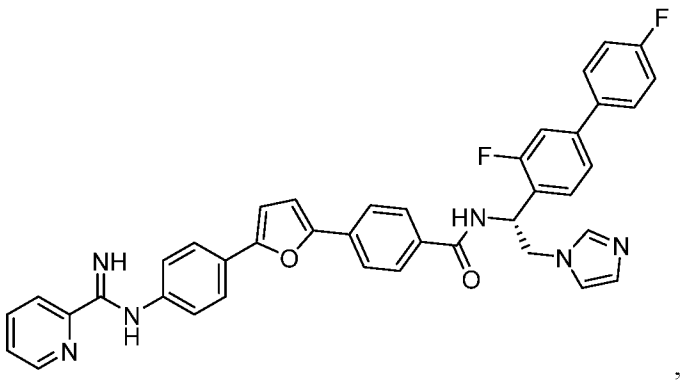
**5a**



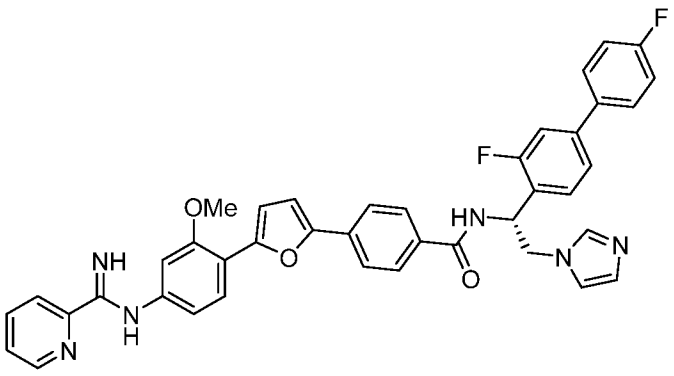
5b ,



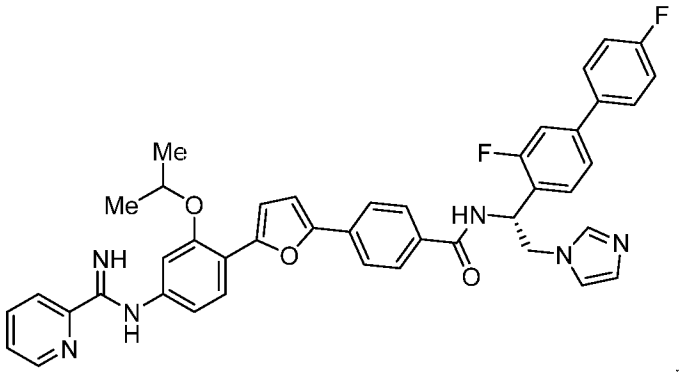
5c ,



5d ,

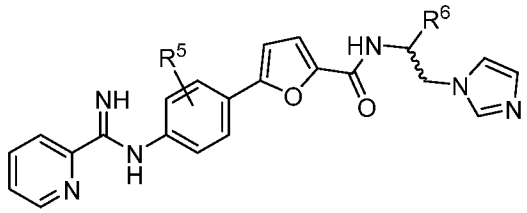


5e , and



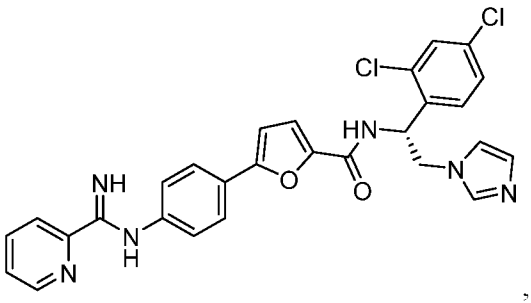
5f

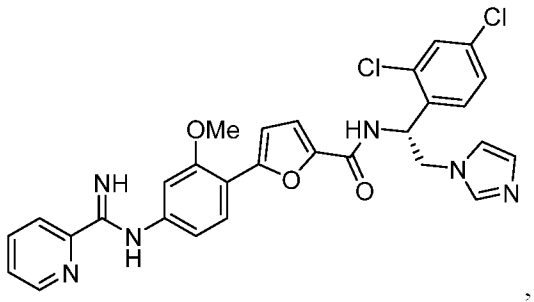
[0058] In various embodiments, the compound may be represented by Structural Formula **(IX)**:



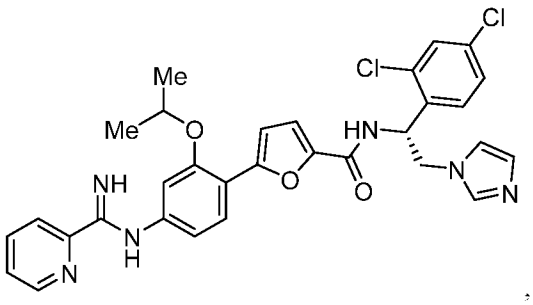
**(IX)**

wherein: each $\mathbf{R^5}$ may independently be H, halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy; and $\mathbf{R^6}$ may be H, optionally halogenated $C_1$-$C_6$ alkyl, optionally halogenated phenyl, or optionally halogenated biphenyl. For example, the compound may be one of Compounds **6a-6f**:

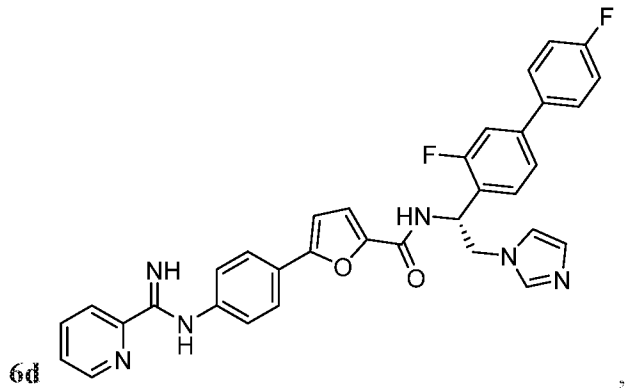


**6a**, 

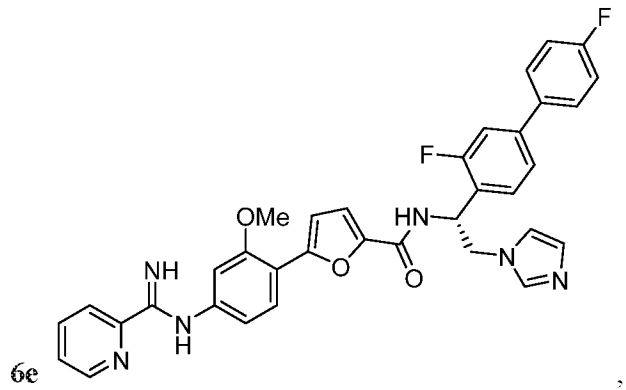
**6b**,



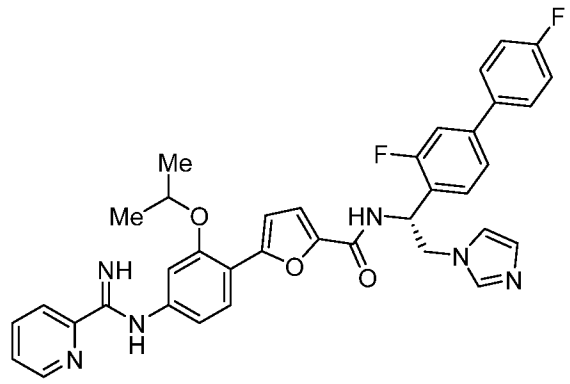
**6c**,



6d

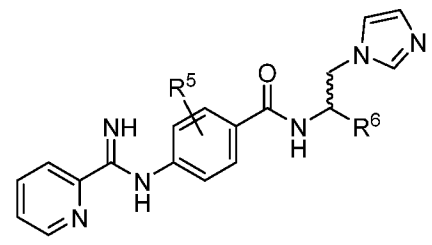


6e , and



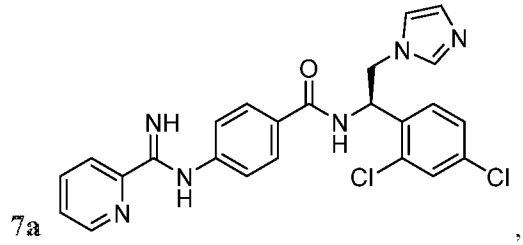
6f

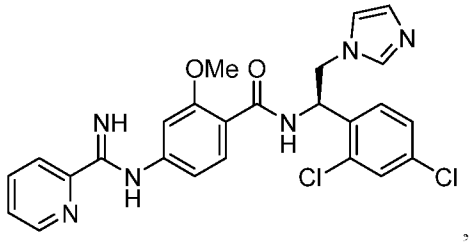
[0059] In some embodiments, the compound may be represented by Structural Formula **(X)**:

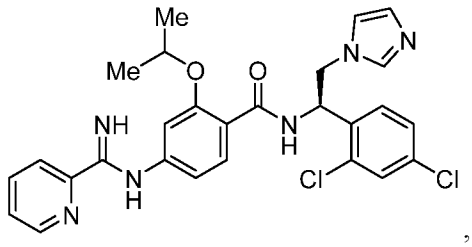


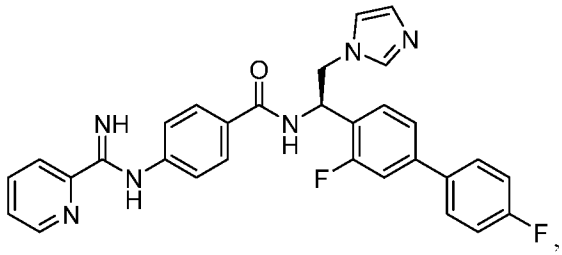
**(X)**

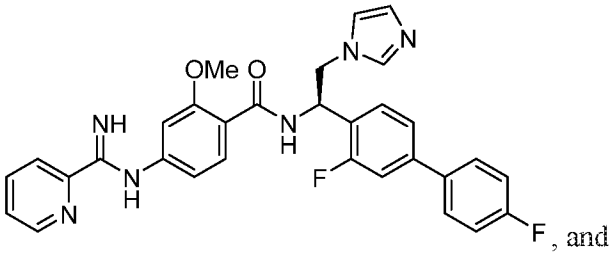
wherein: each $\mathbf{R^5}$ may independently be H, halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy; and $\mathbf{R^6}$ may be H, optionally halogenated $C_1$-$C_6$ alkyl, optionally halogenated phenyl, or optionally halogenated biphenyl. For example, the compound may be one of Compounds **7a-7f**:

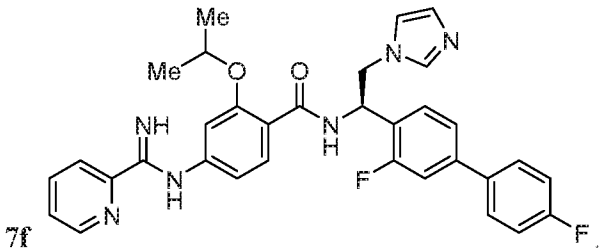

7a


, 7b ,

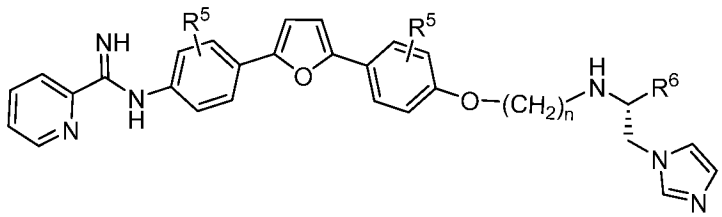

7c


, 7d ,


7e , and


7f .

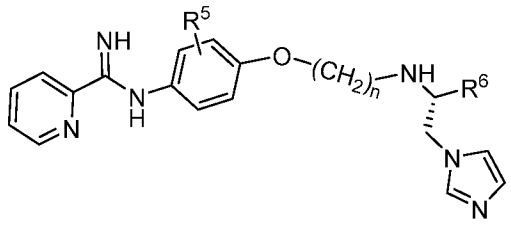
[0060] In several embodiments, the compound may be represented by Structural Formula **(XI)**:



**(XI)**

wherein: each $\mathbf{R^5}$ may independently be H, halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy; and $\mathbf{R^6}$ may be H, optionally halogenated $C_1$-$C_6$ alkyl, optionally halogenated phenyl, or optionally halogenated biphenyl.

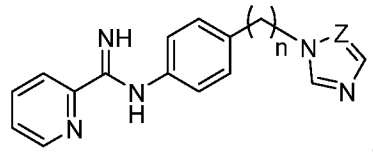
[0061] In several embodiments, the compound may be represented by Structural Formula **(XII)**:



(XII)

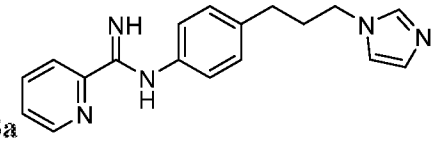
wherein: $R^5$ may independently be H, halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy; and $R^6$ may be H, optionally halogenated $C_1$-$C_6$ alkyl, optionally halogenated phenyl, or optionally halogenated biphenyl.

[0062] In several embodiments of the compound represented by Structural Formula **(Ia)** or **(I)**, **A** may be phenyl and **X** may be a bond. For example, the compound may be represented by Structural Formula **(XIII)**:

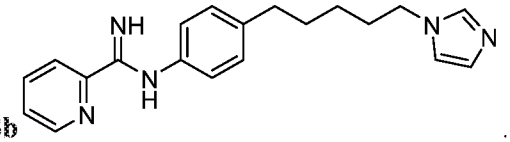


(XIII) ,

wherein **Z** may be CH or N; and **n** may be an integer from 1 to 10. For example, the compound may be one of Compounds **8a-8b**:

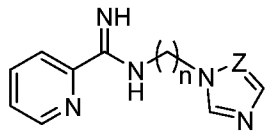


**8a** and



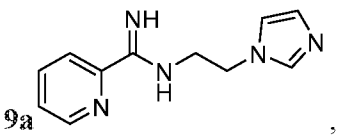
**8b** .

[0063] In several embodiments of the compound represented by Structural Formula **(Ia)** or **(I)**, **A** may be a bond. For example, the compound may be represented by Structural Formula **(XIV)**:

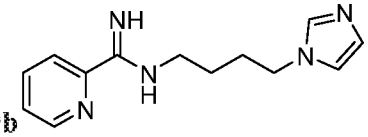


(XIV) ,

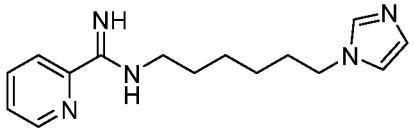
wherein **Z** may be CH or N; and **n** may be an integer from 1 to 10. For example, the compound may be one of Compounds **9a-9d**, e.g., **9a-9c**:



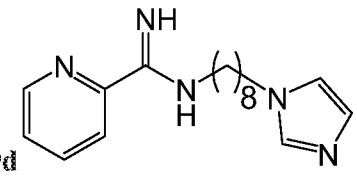
**9a**,



**9b**, **9c**

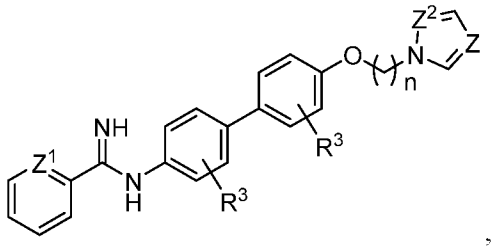


, and



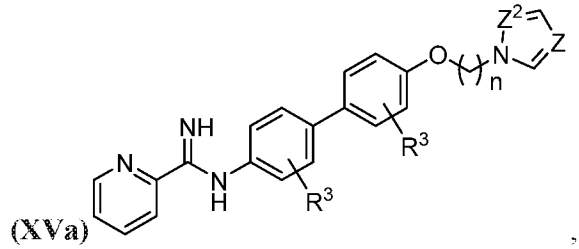
**9d** .

[0064] In several embodiments of the compound represented by Structural Formula **(Ia)** or **(I)**, **A** may be optionally substituted biphenyl. For example, the compound may be represented by Structural Formula **(XV)**:

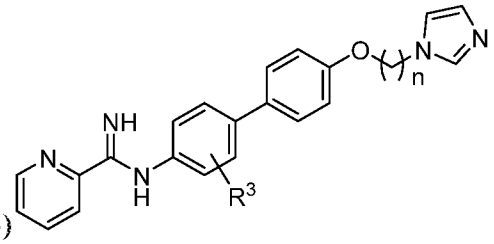


**(XV)** ,

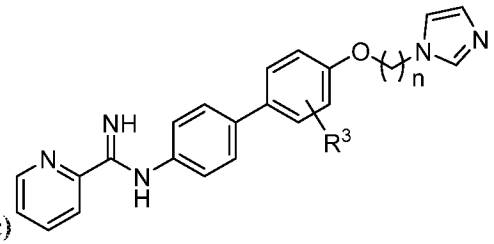
e.g., one of **(XVa)-(XVc)**:



**(XVa)**



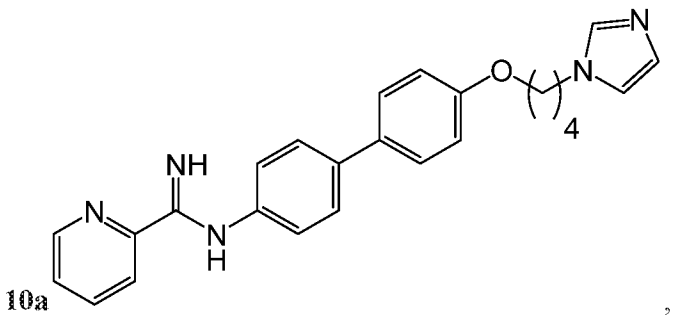
, **(XVb)** ,



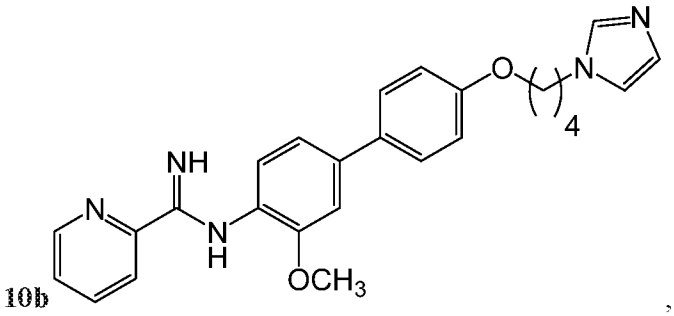
and **(XVc)** .

wherein Z, $Z^1$, and $Z^2$ are each independently CH or N, n may be 1-14, e.g., 1-10, and $R^3$ may represent H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy.

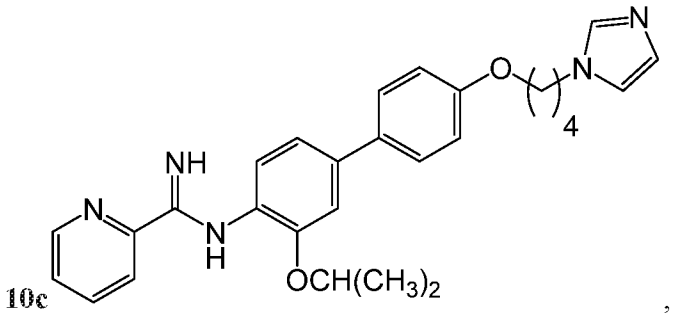
[0065] For example, the compound may be one of Compounds **10a-10n**:



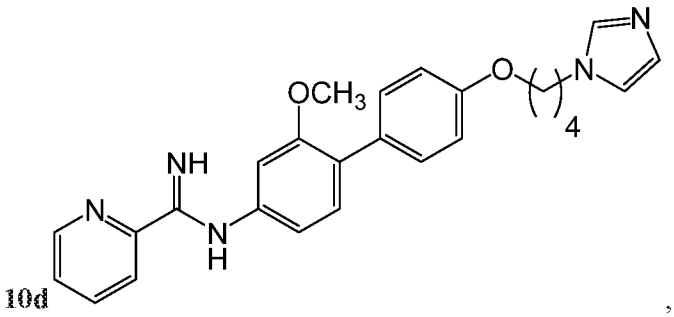
**10a** ,



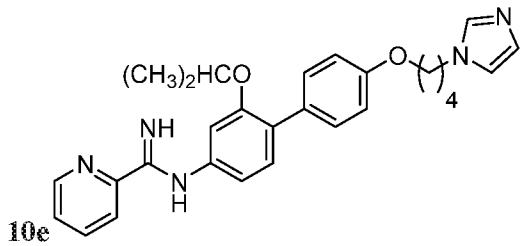

10b ,



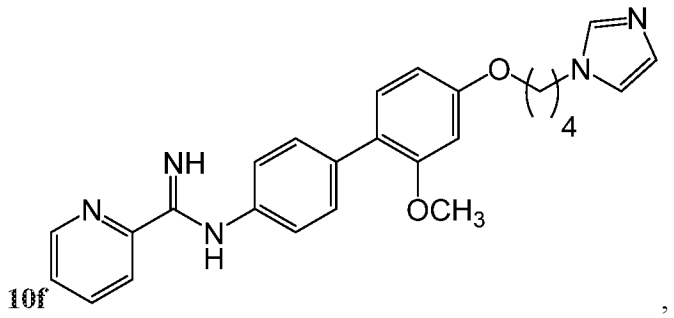

10c ,



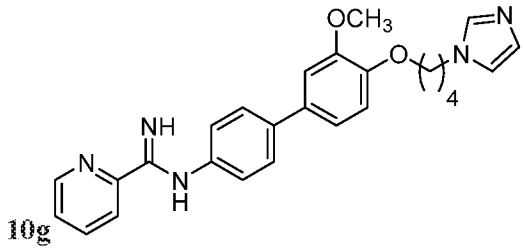

10d ,

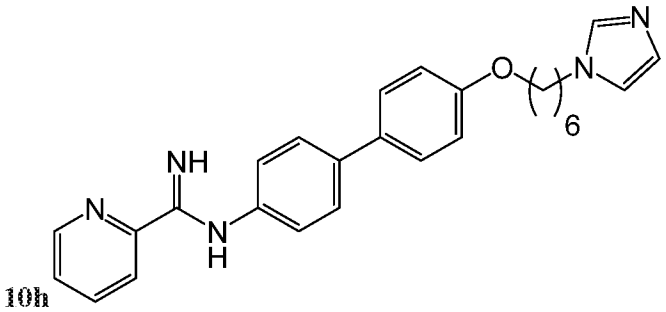


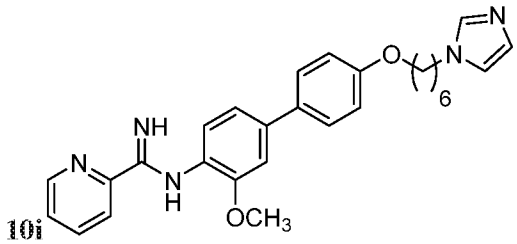

10e ,

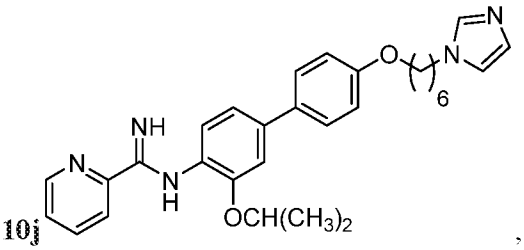
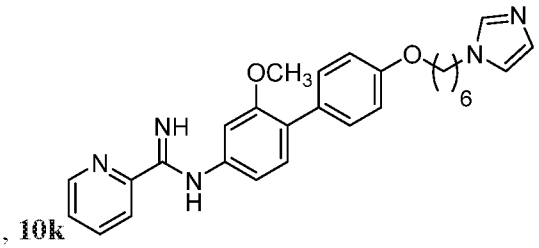


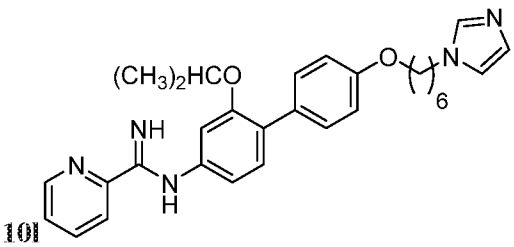
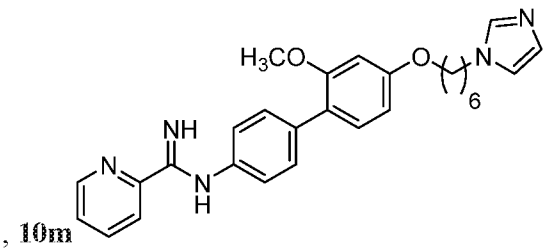

10f ,

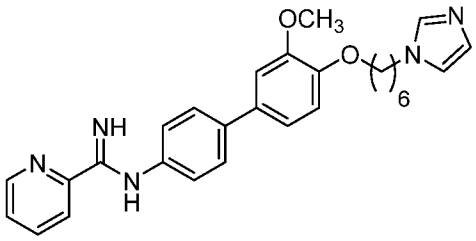

10g ,


10h ,


10i ,

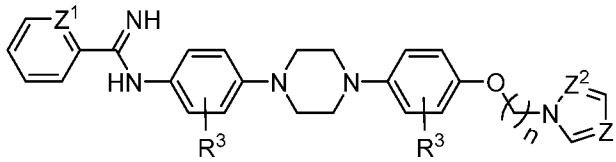

10j , 
10k ,


10l , 
10m , and 10n


,

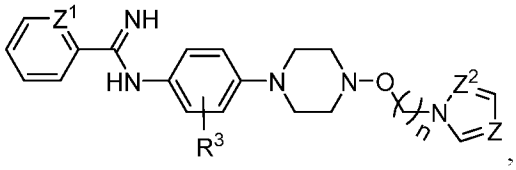
[0066] In several embodiments of the compound represented by Structural Formula **(Ia)** or **(I)**, **A** may be optionally substituted phenyl-piperazinyl-phenyl. For example, the compound may be represented by one of Structural Formulas **(XVI)** and **(XVII)**:

**(XIV)**



and

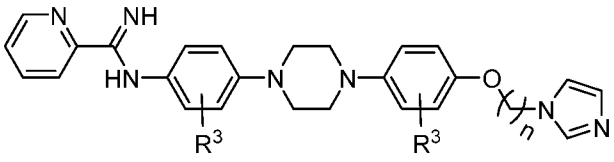
**(XVII)**



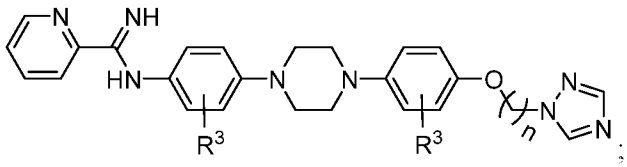
,

For example, the compounds may be represented by one of **(XVIa)-(XVIb)**:

**(XVIa)**



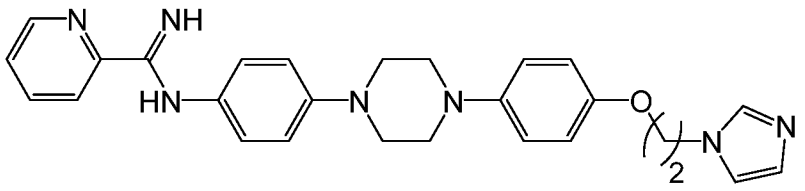
and **(XVIb)**



;

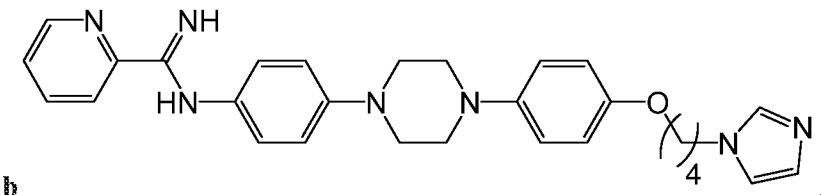
wherein Z, $Z^1$, and $Z^2$ are each independently CH or N, n may be 1-14, e.g., 1-10, and $R^3$ may represent H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy. For example, the compound may be one of Compounds **11a-11d**:

**11a**



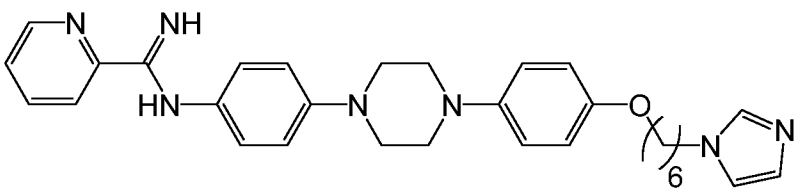
,

**11b**

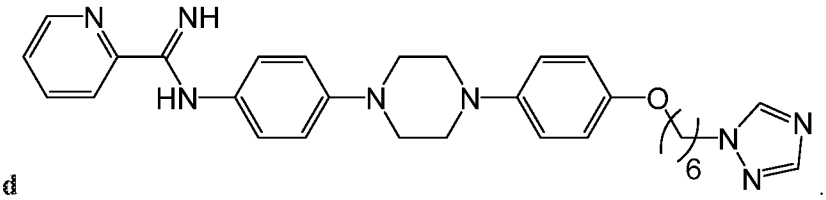


,

**11c**

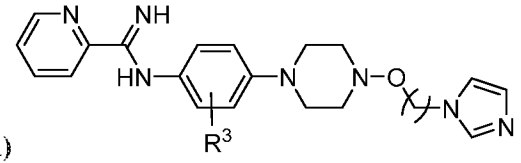


, and

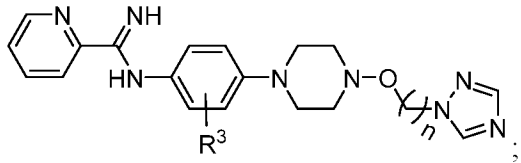


**11d**

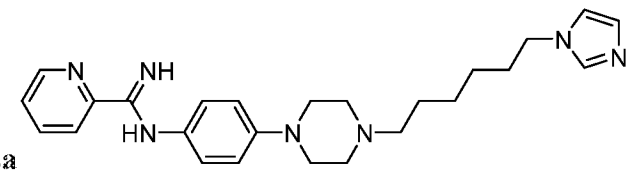
Further, for example, the compounds may be represented by one of **(XVIIa)-(XVIIb)**:



**(XVIIa)** and **(XVIIb)**



wherein Z, $Z^1$, and $Z^2$ are each independently CH or N, n may be 1-14, e.g., 1-10, and $R^3$ may represent H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy. For example, the compound may be Compound **12a**:



**12a**

[0067] In various embodiments, a method of anti-parasitic treatment is provided. The method may include providing a subject that is infected by or at risk of infection by a parasite. The method may include administering a compound to the subject in an amount effective to mitigate infection by the parasite in the subject.

[0068] The compound of the method may be represented by Structural Formula **(Ia)**:

**(Ia)** **Ar**—C(=$NR^1$)$NR^2$—**A**—**X**—**Y**—**$Het^2$**

and pharmaceutically acceptable salts thereof. **Ar** may be an optionally substituted aryl or nitrogen-containing heteroaryl. $R^1$ and $R^2$ may independently be H, optionally substituted $C_1$-$C_6$ alkyl, or optionally substituted $C_3$-$C_6$ cycloalkyl. **A** may be a bond or an optionally substituted linking moiety comprising 1, 2, or 3 rings. Each ring in the optionally substituted linking moiety may independently be one of: aryl, cycloalkyl, heterocycloalkyl, and heteroaryl. **X** may be O, S, amide, or a bond. **Y** may be optionally substituted $C_1$-$C_{14}$ alkyl or optionally substituted $C_2$-$C_{14}$ alkenyl, e.g., optionally substituted $C_1$-$C_{10}$ alkyl or optionally substituted $C_2$-$C_{10}$ alkenyl, or optionally substituted $C_1$-$C_8$ alkyl or optionally substituted $C_2$-$C_8$ alkenyl. **$Het^2$** may be an

optionally substituted five-membered nitrogen-containing heteroaromatic ring comprising 1, 2, or 3 ring heteroatoms.

[0069] The compound of the method may be represented by Structural Formula **(I)**:

**(I)** $\mathbf{Het^1}$—C(=$NR^1$)$NR^2$—**A**—**X**—**Y**—$\mathbf{Het^2}$

and pharmaceutically acceptable salts thereof. $\mathbf{Het^1}$ may be an optionally substituted, nitrogen-containing heteroaryl. $R^1$ and $R^2$ may independently be H, optionally substituted $C_1$-$C_6$ alkyl, or optionally substituted $C_3$-$C_6$ cycloalkyl. **A** may be a bond or an optionally substituted linking moiety comprising 1, 2, or 3 rings. Each ring in the optionally substituted linking moiety may independently be one of: aryl, cycloalkyl, heterocycloalkyl, and heteroaryl. **X** may be O, S, amide, or a bond. **Y** may be optionally substituted $C_1$-$C_{14}$ alkyl or optionally substituted $C_2$-$C_{14}$ alkenyl, e.g., optionally substituted $C_1$-$C_{10}$ alkyl or optionally substituted $C_2$-$C_{10}$ alkenyl, or optionally substituted $C_1$-$C_8$ alkyl or optionally substituted $C_2$-$C_8$ alkenyl. $\mathbf{Het^2}$ may be an optionally substituted five-membered nitrogen-containing heteroaromatic ring comprising 1, 2, or 3 ring heteroatoms.

[0070] In some embodiments, the method may include administering the compound represented by Structural Formula **(Ia)** or **(I)** in the form of any pharmaceutical composition described herein.

[0071] In several embodiments of the method, when the parasite is *L. amazonensis*, the compound represented by Structural Formula **(Ia)** or **(I)** may exclude free-base forms of Compounds **1a-f**. The compound represented by Structural Formula **(Ia)** or **(I)** may exclude protonated forms of Compounds **1a-f**.

[0072] In some embodiments, the subject may be infected by the parasite, and the method may include administering the compound to the subject in an amount effective to mitigate one or more symptoms of infection by the parasite in the subject. Alternatively or in addition, the subject may be at risk of infection by the parasite. The method may include administering the compound to the subject in an amount effective to mitigate infection or re-infection of the subject by the parasite.

[0073] In several embodiments, the parasite may be a kinetoplastid. In various embodiments, the parasite may belong to the genus *Leishmania*. The *Leishmania* parasite may be, for example, one of: *L. aethiopica*, *L. amazonensis*, *L. arabica*, *L. archibaldi*, *L. aristedesi*, *L. Viannia*, *L. braziliensis*, *L. chagasi*, *L. colombiensis*, *L. deanei*, *L. donovani*, *L. enriettii*, *L. equatorensis*, *L. forattinii*, *L. garnhami*, *L. gerbili*, *L. guyanensis*, *L. herreri*, *L. hertigi*, *L. infantum*, *L. killicki*, *L. lainsoni*, *L. major*, *L. mexicana*, *L. naiffi*, *L. panamensis*, *L. peruviana*, *L. pifanoi*, *L. shawi*, *L. tarentolae*, *L. tropica*, *L. turanica*, and *L. venezuelensis*. The subject may

suffer from or may be at risk of one or more of: cutaneous leishmaniasis, mucocutaneous leishmaniasis, and visceral leishmaniasis. The subject may be a human, dog, cat, cow, horse, sheep, pig, bird, amphibian, or fish, e.g., a mammal such as a human.

[0074] In some embodiments, the parasite may belong to the genus *Trypanosoma*. The *Trypanosoma* parasite may be, for example, one of: *T. ambystomae*, *T. avium*, *T. boissoni*, *T. brucei*, *T. cruzi*, *T. congolense*, *T. equinum*, *T. equiperdum*, *T. evansi*, *T. everetti*, *T. hosei*, *T. irwini*, *T. lewisi*, *T. melophagium*, *T. paddae*, *T. parroti*, *T. percae*, *T. rangeli*, *T. rotatorium*, *T. rugosae*, *T. sergenti*, *T. simiae*, *T. sinipercae*, *T. suis*, *T. theileri*, *T. triglae*, and *T. vivax*. The subject may suffer from or may be at risk of one or more of: African trypanosomiasis, sleeping sickness, Chagas disease, nagana, and surra. The subject may be a human, dog, cat, cow, horse, sheep, pig, bird, amphibian, or fish, e.g., a mammal such as a human.

[0075] In several embodiments of the method, when the parasite is *L. amazonensis*, the compound represented by Structural Formula **(Ia)** or **(I)** may exclude free-base forms of Compounds **1a-f**. The compound represented by Structural Formula **(Ia)** or **(I)** may exclude protonated forms of Compounds **1a-f**. Further, for example, the compound represented by Structural Formula **(Ia)** or **(I)** in the method may exclude each of free-base Compounds **1a-f** when the parasite is one of *L. donovani*, *L. amazonensis*, and *L. major*. For example, the method may exclude each of free-base Compounds **1a-f** when the parasite is of the genus *Leishmania*, for example, one of: *L. aethiopica*, *L. amazonensis*, *L. arabica*, *L. archibaldi*, *L. aristedesi*, *L. Viannia*, *L. braziliensis*, *L. chagasi*, *L. colombiensis*, *L. deanei*, *L. donovani*, *L. enriettii*, *L. equatorensis*, *L. forattinii*, *L. garnhami*, *L. gerbili*, *L. guyanensis*, *L. herreri*, *L. hertigi*, *L. infantum*, *L. killicki*, *L. lainsoni*, *L. major*, *L. mexicana*, *L. naiffi*, *L. panamensis*, *L. peruviana*, *L. pifanoi*, *L. shawi*, *L. tarentolae*, *L. tropica*, *L. turanica*, and *L. venezuelensis*. The method may exclude each of free-base Compounds **1a-f** when the subject suffers from visceral leishmaniasis.

[0076] In several embodiments of the method, the compound represented by Structural Formula **(Ia)** or **(I)** may exclude each of free-base Compounds **1a-f** when the parasite is *T. brucei* or *T. cruzi*. For example, the method may exclude each of free-base Compounds **1a-f** when the parasite is of the genus *Trypanosoma*, for example, one of: *T. ambystomae*, *T. avium*, *T. boissoni*, *T. brucei*, *T. cruzi*, *T. congolense*, *T. equinum*, *T. equiperdum*, *T. evansi*, *T. everetti*, *T. hosei*, *T. irwini*, *T. lewisi*, *T. melophagium*, *T. paddae*, *T. parroti*, *T. percae*, *T. rangeli*, *T. rotatorium*, *T. rugosae*, *T. sergenti*, *T. simiae*, *T. sinipercae*, *T. suis*, *T. theileri*, *T. triglae*, and *T. vivax*. In various embodiments of the method, each of the preceding parasite-based exclusions may be independently applied in combination with any of the various embodiments described herein as excluding certain compounds represented by Structural Formula **(Ia)** or **(I)**.

[0077] In some embodiments of the method, the method may incorporate any of the various embodiments described herein for excluding certain compounds represented by Structural Formula **(Ia)** or **(I)**. For example, the compound represented by Structural Formula **(Ia)** or **(I)** may exclude free-base (neutral or non-salt) forms of Compounds **1a-f**. The compound represented by Structural Formula **(Ia)** or **(I)** may include pharmaceutically acceptable salts of Compounds **1a-f**. The compound represented by Structural Formula **(Ia)** or **(I)** may exclude free-base forms of Compounds **1a-f** and pharmaceutically acceptable salts of Compounds **1a-f**. The compound represented by Structural Formula **(Ia)** or **(I)** may exclude protonated forms of Compounds **1a-f**.

[0078] In several embodiments of the method, the compound may include any aspect of the compounds represented by Structural Formulas **(Ia)** or **(I)** as described herein.For example, the compounds of the method may be represented by, as described herein, any one of, or any group of, Structural Formulas: **(I)**, **(Ia)**, **(II)**, **(III)**, **(IIIa)**, **(IIIb)**, **(IIIc)**, **(IIId)**, **(IIIe)**, **(IIIf)**, **(IV)**, **(V)**, **(Va)**, **(Vb)**, **(Vc)**, **(Vd)**, **(Ve)**, **(VIa)**, **(VIb)**, **(VII)**, **(VIII)**, **(IX)**, **(X)**, **(XI)**, **(XII)**, **(XIII)**, **(XIV)**, **(XV)**, **(XVa)**, **(XVb)**, **(XVc)**, **(XVI)**, **(XVIa)**, **(XVIb)**, **(XVII)**, **(XVIIa)**, and **(XVIIb)**. Further, for example, the compound may be any one of, or any group of, as described herein, Compounds: **1a-1v**; **2a-2h**; **3a-3g**; **4a-4m**; **5a-5f**; **6a-6f**; **7a-7f**; **8a-8b**; **9a-9d**; **10a-10n**; **11a-11d**; **12a**; **13a-13c**; and **14a**.

[0079] For example, in some embodiments of the method, the compounds represented by Structural Formulas **(Ia)** or **(I)** may exclude compounds wherein $\mathbf{Het^1}$ is one of unsubstituted pyridyl and pyrid-2-yl substituted with methyl or ethyl, for example, when: $R^1$ and $R^2$ are each H; **X** is O; **Y** is unbranched, unsubstituted $C_2$-$C_{10}$ alkyl; and $\mathbf{Het^2}$ is unsubstituted imidazole-1-yl or unsubstituted 1, 2, 4 triazol-2-yl. In some embodiments, the compound represented by Structural Formula **(Ia)** or **(I)** may exclude compounds wherein one of $R^1$ and $R^2$ is H and the other is methyl or ethyl, for example, when: $\mathbf{Het^1}$ is unsubstituted pyrid-2-yl; **X** is O; **Y** is unbranched, unsubstituted $C_2$-$C_{10}$ alkyl; and $\mathbf{Het^2}$ is unsubstituted imidazole-1-yl or unsubstituted 1, 2, 4 triazol-2-yl. In some embodiments, the compound represented by Structural Formula **(Ia)** or **(I)** may exclude compounds wherein **X** is S, for example, when: $\mathbf{Het^1}$ is unsubstituted pyrid-2-yl; $R^1$ and $R^2$ are each H; **Y** is unbranched, unsubstituted $C_2$-$C_{10}$ alkyl; and $\mathbf{Het^2}$ is unsubstituted imidazole-1-yl or unsubstituted 1, 2, 4 triazol-2-yl. In some embodiments, the compound represented by Structural Formula **(Ia)** or **(I)** may exclude compounds wherein **Y** is $C_2$-$C_4$ alkyl substituted with methyl or ethyl, unsubstituted or methyl substituted $C_1$-$C_5$ alkyl, or unsubstituted $C_1$-$C_6$ alkyl, for example, when: $\mathbf{Het^1}$ is unsubstituted pyrid-2-yl; $R^1$ and $R^2$ are each H; **X** is O; and $\mathbf{Het^2}$ is unsubstituted imidazole-1-yl or unsubstituted 1, 2, 4 triazol-2-yl. In

some embodiments, the compound represented by Structural Formula **(Ia)** or **(I)** may exclude compounds wherein **Het**$^2$ is one of: methyl or ethyl substituted imidazole-1-yl; unsubstituted imidazolyl; methyl or ethyl substituted imidazolyl; methyl or ethyl substituted 1,-2,-4-triazol-2-yl; unsubstituted 1,-2,-4-triazolyl; methyl or ethyl substituted 1,-2,-4-triazolyl; unsubstituted triazolyl; and methyl or ethyl substituted triazolyl; for example, when: **Het**$^1$ is unsubstituted pyrid-2-yl; $R^1$ and $R^2$ are each H; **X** is O; and **Y** is unbranched, unsubstituted $C_2$-$C_4$ alkyl.

[0080] In several embodiments of the method, **Het**$^1$ may be optionally substituted pyridyl, pyrazinyl, pyrimidinyl, or pyridizinyl. For example, **Het**$^1$ may be optionally substituted pyridyl. The compound of the method may be represented by Structural Formula **(II)**. The compound of the method may be represented by Structural Formula **(III)**. In several embodiments of the method, **Y** may include at least 4 linking atoms between **X** and **Het**$^2$. **X** may be O or a bond and **Y** may be $C_1$-$C_{14}$, e.g., $C_1$-$C_{10}$ alkyl optionally substituted with one or more of: optionally halogenated $C_1$-$C_8$ alkyl and optionally halogenated aryl. For example, the compound may be one of Compounds **1a-n**. The compound of the method may be represented by any of Structural Formulas **(IIIa)**, **(IIIb)**, **(IIIc)**, **(IIId)**, **(IIIe)**, and **(IIIf)**, wherein Z, $Z^1$, and $Z^2$ may be each independently CH or N, n may be 1-14, and $R^3$ may be H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy. The compound of the method may be any one of Compounds **1a-1v**. The compound of the method may be any one of Compounds **1a-1n**.

[0081] In various embodiments of the method, each ring in the optionally substituted linking moiety represented by **A** may be independently and optionally substituted by one or more of: hydroxy, halo, and $C_1$-$C_{10}$ , e.g., $C_1$-$C_6$ alkoxy. **A** may include an optionally substituted heteroaryl or optionally substituted heterocycloalkyl ring. **A** may include an optionally substituted, oxygen-containing, heteroaryl or heterocycloalkyl ring. **A** may include an optionally substituted furanyl or optionally substituted tetrahydrofuranyl ring. **A** may include optionally substituted 2,5-furanyl. **A** may include one or two optionally substituted phenyl rings. **A** may include optionally substituted 1,4-phenyl. **A** may be optionally substituted 1,4-phenyl. **A** may be optionally substituted phenyl-heteroaryl-phenyl.

[0082] In some embodiments of the method, the compound may be represented by Structural Formula **(IV)**, wherein each $\mathbf{R}^3$ may independently represent H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy. The compound may be represented by Structural Formula **(V)**. The compound of the method may be represented by any of Structural Formulas **(V)**, **(Va)**, **(Vb)**, **(Vc)**, **(Vd)**, and **(Ve)**, wherein Z, $Z^1$, and $Z^2$ may be each

independently CH or N, n may be 1-14, and $R^3$ may be H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy.

[0083] In various embodiments of the method, the compound may be represented by Structural Formula **(VIa)** wherein $\mathbf{R^4}$ may be H, optionally halogenated $C_1$-$C_8$ alkyl, or optionally halogenated aryl. The compound may be represented by Structural Formula **(VIb)**.

[0084] In some embodiments of the method, $\mathbf{Het^2}$ may include an optionally substituted one of: pyrrole, diazole, thiadiazole, oxadiazole, and triazole. For example, $\mathbf{Het^2}$ may be optionally substituted imidazole or optionally substituted 1, 2, 4 triazole. For example, the compound may be represented by Structural Formula **(VII)**, wherein: **Z** may be CH or N; each $\mathbf{R^3}$ may independently be H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy; and **n** may be an integer from 1 to 10. For example, the compound may be one of Compounds **2a-2g**. The compound may be, for example, one of Compounds **3a-3g**. The compound may be, for example, one of Compounds **4a-4m**, e.g., **4a-4i**. The compound may be, for example, one of Compounds **13a-13c**.

[0085] In several embodiments of the method, the compound may be represented by Structural Formula **(VIII)**, wherein each $\mathbf{R^5}$ may independently be H, halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy, and $\mathbf{R^6}$ may be H, optionally halogenated $C_1$-$C_6$ alkyl, optionally halogenated phenyl, or optionally halogenated biphenyl. For example, the compound may be one of Compounds **5a-5f**. The compound may be represented by Structural Formula **(IX)**, wherein: each $\mathbf{R^5}$ may independently be H, halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy; and $\mathbf{R^6}$ may be H, optionally halogenated $C_1$-$C_6$ alkyl, optionally halogenated phenyl, or optionally halogenated biphenyl. For example, the compound may be one of Compounds **6a-5f**. The compound may be represented by Structural Formula **(X)** wherein: each $\mathbf{R^5}$ may independently be H, halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy; and $\mathbf{R^6}$ may be H, optionally halogenated $C_1$-$C_6$ alkyl, optionally halogenated phenyl, or optionally halogenated biphenyl. For example, the compound may be one of Compounds **7a-7f**.

[0086] In several embodiments of the method, the compound may be represented by Structural Formula **(XI)**, wherein each $\mathbf{R^5}$ may independently be H, halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy; and $\mathbf{R^6}$ may be H, optionally halogenated $C_1$-$C_6$ alkyl, optionally halogenated phenyl, or optionally halogenated biphenyl.

[0087] In several embodiments of the method, the compound may be represented by Structural Formula **(XII)**, wherein each $\mathbf{R^5}$ may independently be H, halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy; and $\mathbf{R^6}$ may be H, optionally halogenated $C_1$-$C_6$ alkyl, optionally halogenated phenyl, or optionally halogenated biphenyl.

[0088] In several embodiments of the method, the compound may be represented by Structural Formula **(Ia)** or **(I)**, wherein **A** may be phenyl and **X** may be a bond. For example, the compound may be represented by Structural Formula **(XIII)**, wherein **Z** may be CH or N; and **n** may be an integer from 1 to 10. For example, the compound may be one of Compounds **8a-8b**.

[0089] In several embodiments of the method, the compound may be represented by Structural Formula **(Ia)** or **(I)**, wherein **A** may be a bond. For example, the compound may be represented by Structural Formula **(XIV)**, wherein **Z** may be CH or N; and **n** may be an integer from 1 to 10. For example, the compound may be one of Compounds **9a-9d**, for example, **9a-9c**.

[0090] In several embodiments of the method, the compound may be represented by Structural Formula **(XV)**, wherein Z, $Z^1$, and $Z^2$ may be each independently CH or N, n may be 1-14, and $R^3$ may be H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy. For example, the compound may be represented by one of Structural Formulas **(XVa)-(XVc)**. For example, the compound may be one of Compounds **10a-10n**.

[0091] In several embodiments of the method, the compound may be represented by one of Structural Formulas **(XVI)** and **(XVII)**, wherein Z, $Z^1$, and $Z^2$ may be each independently CH or N, n may be 1-14, and $R^3$ may be H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy. For example, the compound may be represented by one of Structural Formulas **(XVIa)-(XVIb)**, e.g., the compound may be one of Compounds **11a-11d**.

[0092] In various embodiments, a pharmaceutical composition is provided. The pharmaceutical composition may include a pharmaceutically acceptable carrier or excipient.

[0093] The pharmaceutical composition may include a compound represented by Structural Formula **(Ia)**:

**(Ia)** **Ar**—C(=$NR^1$)$NR^2$—**A**—**X**—**Y**—**$Het^2$**

and pharmaceutically acceptable salts thereof. **Ar** may be an optionally substituted aryl or nitrogen-containing heteroaryl. $R^1$ and $R^2$ may independently be H, optionally substituted $C_1$-$C_6$ alkyl, or optionally substituted $C_3$-$C_6$ cycloalkyl. **A** may be a bond or an optionally substituted linking moiety comprising 1, 2, or 3 rings. Each ring in the optionally substituted linking moiety may independently be one of: aryl, cycloalkyl, heterocycloalkyl, and heteroaryl. **X** may be O, S, amide, or a bond. **Y** may be optionally substituted $C_1$-$C_{14}$ alkyl or optionally substituted $C_2$-$C_{14}$ alkenyl, e.g., optionally substituted $C_1$-$C_{10}$ alkyl or optionally substituted $C_2$-$C_{10}$ alkenyl, or optionally substituted $C_1$-$C_8$ alkyl or optionally substituted $C_2$-$C_8$ alkenyl. **$Het^2$** may be an optionally substituted five-membered nitrogen-containing heteroaromatic ring comprising 1, 2, or 3 ring heteroatoms.

[0094] The pharmaceutical composition may include a compound represented by Structural Formula **(I)**:

**(I)** $\mathbf{Het^1}$—C(=$NR^1$)$NR^2$—**A**—**X**—**Y**—$\mathbf{Het^2}$

and pharmaceutically acceptable salts thereof. $\mathbf{Het^1}$ may be an optionally substituted, nitrogen-containing heteroaryl. $R^1$ and $R^2$ may independently be H, optionally substituted $C_1$-$C_6$ alkyl, or optionally substituted $C_3$-$C_6$ cycloalkyl. **A** may be a bond or an optionally substituted linking moiety comprising 1, 2, or 3 rings. Each ring in the optionally substituted linking moiety may independently be one of: aryl, cycloalkyl, heterocycloalkyl, and heteroaryl. **X** may be O, S, amide, or a bond. **Y** may be optionally substituted $C_1$-$C_{14}$, e.g., $C_1$-$C_{10}$ alkyl or optionally substituted $C_2$-$C_{14}$, e.g., $C_2$-$C_{10}$ alkenyl. $\mathbf{Het^2}$ may be an optionally substituted five-membered nitrogen-containing heteroaromatic ring comprising 1, 2, or 3 ring heteroatoms.

[0095] In several embodiments of the pharmaceutical composition, the compound represented by Structural Formula **(Ia)** or **(I)** may include one of Compounds **1a-f**. In some embodiments, each of Compounds **1a-f** may be in the form of a solid. Additionally or alternatively, each of Compounds **1a-f** may be in the form of a pharmaceutically acceptable salt. Additionally or alternatively, at least a portion of the pharmaceutically acceptable carrier or excipient may be in the form of a solid or gel. Additionally or alternatively, the pharmaceutical composition may be configured for administration in unit dosage form. Additionally or alternatively, the pharmaceutical composition may be configured for administration in the form of one of: a tablet; a capsule; a lozenge; a cream, a spray, a transdermal patch, an aerosol, a suppository, a depot preparation; a suture that is coated or impregnated with one of Compounds **1a-f**; a bandage that is coated or impregnated with one of Compounds **1a-f**; a medical device that is coated or impregnated with one of Compounds **1a-f**; and the like.

[0096] In some embodiments of the pharmaceutical composition, pharmaceutically acceptable salts of Compounds **1a-1f** are included. In some embodiments of the pharmaceutical composition, free-base (neutral) Compounds **1a-f** may be excluded. In some embodiments of the pharmaceutical composition, protonated forms of Compounds **1a-1f** may be excluded. Alternatively or in addition, the pharmaceutical composition may incorporate any of the various embodiments described herein for excluding certain compounds represented by Structural Formula **(Ia)** or **(I)**. For example, the compound represented by Structural Formula **(Ia)** or **(I)** may exclude free-base (neutral or non-salt) forms of Compounds **1a-f**. The compound represented by Structural Formula **(Ia)** or **(I)** may include pharmaceutically acceptable salts of Compounds **1a-f**. The compound represented by Structural Formula **(Ia)** or **(I)** may exclude free-base forms of Compounds **1a-f** and pharmaceutically acceptable salts of Compounds **1a-f**.

The compound represented by Structural Formula **(Ia)** or **(I)** may exclude protonated forms of Compounds **1a-f**.

[0097] In several embodiments of the pharmaceutical composition, the compound may include any aspect of the compounds represented by Structural Formulas **(Ia)** or **(I)** as described herein. For example, the compounds of the pharmaceutical composition may be represented by, as described herein, any one of, or any group of, Structural Formulas: **(I)**, **(Ia)**, **(II)**, **(III)**, **(IIIa)**, **(IIIb)**, **(IIIc)**, **(IIId)**, **(IIIe)**, **(IIIf)**, **(IV)**, **(V)**, **(Va)**, **(Vb)**, **(Vc)**, **(Vd)**, **(Ve)**, **(Via)**, **(VIb)**, **(VII)**, **(VIII)**, **(IX)**, **(X)**, **(XI)**, **(XII)**, **(XIII)**, **(XIV)**, **(XV)**, **(XVa)**, **(XVb)**, **(XVc)**, **(XVI)**, **(XVIa)**, **(XVIb)**, **(XVII)**, **(XVIIa)**, and **(XVIIb)**. Further, for example, the compound may be any one of, or any group of, as described herein, Compounds: **1a-1v**; **2a-2h**; **3a-3g**; **4a-4m**; **5a-5f**; **6a-6f**; **7a-7f**; **8a-8b**; **9a-9d**; **10a-10n**; **11a-11d**; **12a**; **13a-13c**; and **14a**.

[0098] For example, in some embodiments of the pharmaceutical composition, the compounds represented by Structural Formulas **(Ia)** or **(I)** may exclude compounds wherein $\mathbf{Het^1}$ is one of unsubstituted pyridyl and pyrid-2-yl substituted with methyl or ethyl, for example, when: $R^1$ and $R^2$ are each H; **X** is O; **Y** is unbranched, unsubstituted $C_2$-$C_{10}$ alkyl; and $\mathbf{Het^2}$ is unsubstituted imidazole-1-yl or unsubstituted 1, 2, 4 triazol-2-yl. In some embodiments, the compound represented by Structural Formula **(Ia)** or **(I)** may exclude compounds wherein one of $R^1$ and $R^2$ is H and the other is methyl or ethyl, for example, when: $\mathbf{Het^1}$ is unsubstituted pyrid-2-yl; **X** is O; **Y** is unbranched, unsubstituted $C_2$-$C_{10}$ alkyl; and $\mathbf{Het^2}$ is unsubstituted imidazole-1-yl or unsubstituted 1, 2, 4 triazol-2-yl. In some embodiments, the compound represented by Structural Formula **(Ia)** or **(I)** may exclude compounds wherein **X** is S, for example, when: $\mathbf{Het^1}$ is unsubstituted pyrid-2-yl; $R^1$ and $R^2$ are each H; **Y** is unbranched, unsubstituted $C_2$-$C_{10}$ alkyl; and $\mathbf{Het^2}$ is unsubstituted imidazole-1-yl or unsubstituted 1, 2, 4 triazol-2-yl. In some embodiments, the compound represented by Structural Formula **(Ia)** or **(I)** may exclude compounds wherein **Y** is $C_2$-$C_4$ alkyl substituted with methyl or ethyl, unsubstituted or methyl substituted $C_1$-$C_5$ alkyl, or unsubstituted $C_1$-$C_6$ alkyl, for example, when: $\mathbf{Het^1}$ is unsubstituted pyrid-2-yl; $R^1$ and $R^2$ are each H; **X** is O; and $\mathbf{Het^2}$ is unsubstituted imidazole-1-yl or unsubstituted 1, 2, 4 triazol-2-yl. In some embodiments, the compound represented by Structural Formula **(Ia)** or **(I)** may exclude compounds wherein $\mathbf{Het^2}$ is one of: methyl or ethyl substituted imidazole-1-yl; unsubstituted imidazolyl; methyl or ethyl substituted imidazolyl; methyl or ethyl substituted 1,-2,-4-triazol-2-yl; unsubstituted 1,-2,-4-triazolyl; methyl or ethyl substituted 1,-2,-4-triazolyl; unsubstituted triazolyl; and methyl or ethyl substituted triazolyl; for example, when: $\mathbf{Het^1}$ is unsubstituted pyrid-2-yl; $R^1$ and $R^2$ are each H; **X** is O; and **Y** is unbranched, unsubstituted $C_2$-$C_4$ alkyl.

[0099] In several embodiments of the pharmaceutical composition, **Het$^1$** may be optionally substituted pyridyl, pyrazinyl, pyrimidinyl, or pyridizinyl. For example, **Het$^1$** may be optionally substituted pyridyl. The compound of the pharmaceutical composition may be represented by Structural Formula **(II)**. The compound of the pharmaceutical composition may be represented by Structural Formula **(III)**. In several embodiments of the pharmaceutical composition, **Y** may include at least 4 linking atoms between **X** and **Het$^2$**. **X** may be O or a bond and **Y** may be $C_1$-$C_{14}$, e.g., $C_1$-$C_{10}$ alkyl optionally substituted with one or more of: optionally halogenated $C_1$-$C_8$ alkyl and optionally halogenated aryl. For example, the compound may be one of Compounds **1a-n**. The compound of the pharmaceutical composition may be represented by any of Structural Formulas **(IIIa)**, **(IIIb)**, **(IIIc)**, **(IIId)**, **(IIIe)**, and **(IIIf)**, wherein Z, $Z^1$, and $Z^2$ may be each independently CH or N, n may be 1-14, and $R^3$ may be H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy. The compound of the pharmaceutical composition may be any one of Compounds **1a-1v**. The compound of the pharmaceutical composition may be any one of Compounds **1a-1n**.

[00100] In various embodiments of the pharmaceutical composition, each ring in the optionally substituted linking moiety represented by **A** may be independently and optionally substituted by one or more of: hydroxy, halo, and $C_1$-$C_{10}$ , e.g., $C_1$-$C_6$ alkoxy. **A** may include an optionally substituted heteroaryl or optionally substituted heterocycloalkyl ring. **A** may include an optionally substituted, oxygen-containing, heteroaryl or heterocycloalkyl ring. **A** may include an optionally substituted furanyl or optionally substituted tetrahydrofuranyl ring. **A** may include optionally substituted 2,5-furanyl. **A** may include one or two optionally substituted phenyl rings. **A** may include optionally substituted 1,4-phenyl. **A** may be optionally substituted 1,4-phenyl. **A** may be optionally substituted phenyl-heteroaryl-phenyl.

[00101] In some embodiments of the pharmaceutical composition, the compound may be represented by Structural Formula **(IV)**, wherein each **R$^3$** may independently represent H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy. The compound may be represented by Structural Formula **(V)**. The compound of the pharmaceutical composition may be represented by any of Structural Formulas **(V)**, **(Va)**, **(Vb)**, **(Vc)**, **(Vd)**, and **(Ve)**, wherein Z, $Z^1$, and $Z^2$ may be each independently CH or N, n may be 1-14, and $R^3$ may be H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy.

[00102] In various embodiments of the pharmaceutical composition, the compound may be represented by Structural Formula **(VIa)** wherein **R$^4$** may be H, optionally halogenated $C_1$-$C_8$ alkyl, or optionally halogenated aryl. The compound may be represented by Structural Formula **(VIb)**.

[00103] In some embodiments of the pharmaceutical composition, **Het**$^2$ may include an optionally substituted one of: pyrrole, diazole, thiadiazole, oxadiazole, and triazole. For example, **Het**$^2$ may be optionally substituted imidazole or optionally substituted 1, 2, 4 triazole. For example, the compound may be represented by Structural Formula **(VII)**, wherein: **Z** may be CH or N; each $\mathbf{R}^3$ may independently be H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy; and **n** may be an integer from 1 to 10. For example, the compound may be one of Compounds **2a-2g**. The compound may be, for example, one of Compounds **3a-3g**. The compound may be, for example, one of Compounds **4a-4m**, e.g., **4a-4i**. The compound may be, for example, one of Compounds **13a-13c**.

[00104] In several embodiments of the pharmaceutical composition, the compound may be represented by Structural Formula **(VIII)**, wherein each $\mathbf{R}^5$ may independently be H, halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy, and $\mathbf{R}^6$ may be H, optionally halogenated $C_1$-$C_6$ alkyl, optionally halogenated phenyl, or optionally halogenated biphenyl. For example, the compound may be one of Compounds **5a-5f**. The compound may be represented by Structural Formula **(IX)**, wherein: each $\mathbf{R}^5$ may independently be H, halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy; and $\mathbf{R}^6$ may be H, optionally halogenated $C_1$-$C_6$ alkyl, optionally halogenated phenyl, or optionally halogenated biphenyl. For example, the compound may be one of Compounds **6a-5f**. The compound may be represented by Structural Formula **(X)** wherein: each $\mathbf{R}^5$ may independently be H, halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy; and $\mathbf{R}^6$ may be H, optionally halogenated $C_1$-$C_6$ alkyl, optionally halogenated phenyl, or optionally halogenated biphenyl. For example, the compound may be one of Compounds **7a-7f**.

[00105] In several embodiments of the pharmaceutical composition, the compound may be represented by Structural Formula **(XI)**, wherein each $\mathbf{R}^5$ may independently be H, halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy; and $\mathbf{R}^6$ may be H, optionally halogenated $C_1$-$C_6$ alkyl, optionally halogenated phenyl, or optionally halogenated biphenyl.

[00106] In several embodiments of the pharmaceutical composition, the compound may be represented by Structural Formula **(XII)**, wherein each $\mathbf{R}^5$ may independently be H, halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy; and $\mathbf{R}^6$ may be H, optionally halogenated $C_1$-$C_6$ alkyl, optionally halogenated phenyl, or optionally halogenated biphenyl.

[00107] In several embodiments of the pharmaceutical composition, the compound may be represented by Structural Formula **(Ia)** or **(I)**, wherein **A** may be phenyl and **X** may be a bond. For example, the compound may be represented by Structural Formula **(XIII)**, wherein **Z** may be CH or N; and **n** may be an integer from 1 to 10. For example, the compound may be one of Compounds **8a-8b**.

[00108] In several embodiments of the pharmaceutical composition, the compound may be represented by Structural Formula **(Ia)** or **(I)**, wherein **A** may be a bond. For example, the compound may be represented by Structural Formula **(XIV)**, wherein **Z** may be CH or N; and **n** may be an integer from 1 to 10. For example, the compound may be one of Compounds **9a-9d**, for example, **9a-9c**.

[00109] In several embodiments of the pharmaceutical composition, the compound may be represented by Structural Formula **(XV)**, wherein Z, $Z^1$, and $Z^2$ may be each independently CH or N, n may be 1-14, and $R^3$ may be H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy. For example, the compound may be represented by one of Structural Formulas **(XVa)-(XVc)**. For example, the compound may be one of Compounds **10a-10n**.

[00110] In several embodiments of the pharmaceutical composition, the compound may be represented by one of Structural Formulas **(XVI)** and **(XVII)**, wherein Z, $Z^1$, and $Z^2$ may be each independently CH or N, n may be 1-14, and $R^3$ may be H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy. For example, the compound may be represented by one of Structural Formulas **(XVIa)-(XVIb)**. For example, the compound may be one of Compounds **11a-11d**. Further, for example, the compound may be represented by one of Structural Formulas **(XVIIa)-(XVIIb)**, e.g., the compound may be Compound **12a**.

[00111] In various embodiments, a kit for anti-parasite treatment of a subject in need thereof is provided. The kit may include any anti-parasitic compound described herein, for example, the compound represented by Structural Formula **(Ia)**:

**(Ia)** **Ar**—C(=$NR^1$)$NR^2$—**A**—**X**—**Y**—**$Het^2$**

[00112] and pharmaceutically acceptable salts thereof. **Ar** may be an optionally substituted aryl or nitrogen-containing heteroaryl. $R^1$ and $R^2$ may independently be H, optionally substituted $C_1$-$C_6$ alkyl, or optionally substituted $C_3$-$C_6$ cycloalkyl. **A** may be a bond or an optionally substituted linking moiety comprising 1, 2, or 3 rings. Each ring in the optionally substituted linking moiety may independently be one of: aryl, cycloalkyl, heterocycloalkyl, and heteroaryl. **X** may be O, S, amide, or a bond. **Y** may be optionally substituted $C_1$-$C_{14}$ alkyl or optionally substituted $C_2$-$C_{14}$ alkenyl, e.g., optionally substituted $C_1$-$C_{10}$ alkyl or optionally substituted $C_2$-$C_{10}$ alkenyl, or optionally substituted $C_1$-$C_8$ alkyl or optionally substituted $C_2$-$C_8$ alkenyl. **$Het^2$** may be an optionally substituted five-membered nitrogen-containing heteroaromatic ring comprising 1, 2, or 3 ring heteroatoms.

[00113] The kit may include any anti-parasitic compound described herein, for example, the compound represented by Structural Formula **(I)**:

**(I)** $\mathbf{Het^1}$—C(=$NR^1$)$NR^2$—**A**—**X**—**Y**—$\mathbf{Het^2}$

pharmaceutically acceptable salts thereof, and mixtures thereof with a pharmaceutically acceptable carrier or excipient to form a pharmaceutical composition. $\mathbf{Het^1}$ may be an optionally substituted, nitrogen-containing heteroaryl. $R^1$ and $R^2$ may independently be H, optionally substituted $C_1$-$C_6$ alkyl, or optionally substituted $C_3$-$C_6$ cycloalkyl. **A** may be a bond or an optionally substituted linking moiety comprising 1, 2, or 3 rings. Each ring in the optionally substituted linking moiety may independently be one of: aryl, cycloalkyl, heterocycloalkyl, and heteroaryl. **X** may be O, S, amide, or a bond. **Y** may be optionally substituted $C_1$-$C_{14}$, e.g., $C_1$-$C_{10}$ alkyl or optionally substituted $C_2$-$C_{14}$, e.g., $C_2$-$C_{10}$ alkenyl. $\mathbf{Het^2}$ may be an optionally substituted five-membered nitrogen-containing heteroaromatic ring comprising 1, 2, or 3 ring heteroatoms. The kit may include instructions. The instructions may direct a user to provide the subject, the subject being infected by a parasite or at risk of infection by the parasite. The instructions may direct a user to administer the compound or the pharmaceutical composition to the subject in an amount effective to mitigate infection by the parasite in the subject.

[00114] In some embodiments of the kit, the compound represented by Structural Formula **(Ia)** or **(I)** may include any aspect of the anti-parasitic compounds described herein, either alone or as encompassed by any of the methods or pharmaceutical compositions described herein.

[00115] In several embodiments of the kit, the instructions may direct a user to conduct any step or combination of steps described herein for the method.

## EXAMPLES

### Example 1: Design Considerations and Molecular Modeling

[00116] AIAs and antifungal azole drugs each include a nitrogen-containing heterocycle bound to a linear or curved linker. A known target of azole antifungal drugs is the CYP51 enzyme, which participates in sterol biosynthesis. The crystal structure of CYP51 from *L. infantum* has been reported in the form of a bound fluconazole molecule interacting with the heme portion of CYP51 through coordination of a triazole nitrogen with the heme iron atom. Such a structure is consistent with known crystal structures of other CYP51-azole complexes, which also show a complex between the heme iron atom and the azole nitrogen. Although some azoles have been attempted in clinical treatment of leishmaniasis, azoles are less potent against *Leishmania* compared to *T. cruzi* in vitro.

[00117] Recent studies have uncovered inhibitors of kinetoplastid CYP51. The compound VNI (**FIG. 1**) binds with a $K_d$ of 70 nM to *T. cruzi* CYP51 and inhibits the growth of intracellular *T. cruzi* amastigotes by 50% at a concentration of 1.3 nM. (See Villalta, et al. "VNI cures acute and chronic experimental Chagas disease." *J. Infect. Dis.* **2013,** *208*, 504-511, the

entire contents of which are incorporated herein by reference) VNI also treats *T. cruzi* infections in murine models of Chagas disease. VNI has been crystallized with *T. cruzi* CYP51 and also coordinates via its imidazole nitrogen with CYP51 heme iron. A molecule similar to VNI, termed VNI/VNF (**FIG. 1**), is also a known inhibitor of *L. infantum* CYP51, although no studies against *Leishmania* parasites were reported.

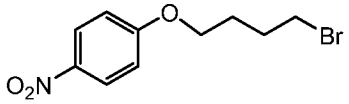
[00118] Preliminary modeling calculations supported the binding of **5a** and **6a** to CYP51. Accordingly, , the anti-parasitic compounds disclosed herein were designed by combining carefully selected AIA fragments and azole fragments. The disclosed anti-parasitic compounds were then synthesized and tested as detailed in the following Examples.

**Example 2A: Synthesis of Phenoxyalkyl Linker Anti-Parasitic Compounds**

[00119] **FIG. 2A** is a synthetic scheme various phenoxyalkyl linker anti-parasitic Compounds **1a-1n** and **1v**. Compounds **1a**, **1b**, **1c**, **1e**, **1f**, **1g**, **1i**, **1m**, and **1v** were made according to **FIG. 2A**. Generally, reagents and conditions for synthesis of compounds according to **FIG. 2A** included: a) α,ω-dibromoalkane, $K_2CO_3$, acetone; b) imidazole or 1,2,4-triazole, $K_2CO_3$, $CH_3CN$; c) $SnCl_2.2H_2O$, EtOAc; d) *S*-(2-naphthylmethyl)-2-pyridylthioimidate hydrobromide, $CH_3CN$/EtOH (1:3), rt.

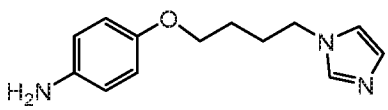
[00120] Details of the representative synthesis of Compound **1e** are as follows.

**1-(4-bromobutoxy)-4-nitrobenzene**




[00121] Reaction of 4-nitrophenol (2.00 g, 14.4 mmol), 1,4-dibromobutane (3.5 mL, 6.33 g, 29.3 mmol), and potassium carbonate (5.96 g, 43.2 mmol) in acetone at reflux afforded 1-(4-bromobutoxy)-4-nitrobenzene as white crystals, yield 1.69 g, 6.15 mmol, 43%; m.p. 39-42 °C. The $^1$H NMR spectrum of this material was consistent with that reported in Narlawar et al., *Journal of Medicinal Chemistry*, **2010**, *53*, 3028-3037.

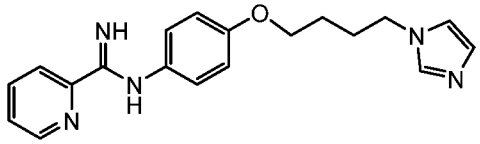
**4-(4-(1H-imidazol-1-yl)butoxy)aniline**




[00122] Reaction of imidazole (0.44 g, 6.43 mmol), 1-(4-bromobutoxy)-4-nitrobenzene (1.20 g, 4.28 mmol), and potassium carbonate (0.89 g, 6.4 mmol) in acetonitrile at reflux afforded 1-[4-(4-nitrophenoxy)butyl]-1H-imidazole as a dark brown solid, yield: 0.67 g, 2.6 mmol, 60%; m.p. 71-74 °C, lit m.p. 67-69 °C. The $^1$H NMR spectrum of this material was consistent with that reported in Salerno et. al, *Bioorganic and Medicinal Chemistry*, **2013**, *21*,

5145-5153. Reaction of 1-[4-(4-nitrophenoxy)butyl]-1H-imidazole (0.10 g, 0.38 mmol) and stannous chloride dihydrate (0.43 g, 1.9 mmol) in ethyl acetate at reflux afforded 4-(4-(1H-imidazol-1-yl)butoxy)aniline as a bright orange powder, yield: 0.046 g, 0.20 mmol, 52%. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 1.57 (quint, *J*= 7.0, 2H), 1.82 (quint, *J*= 7.3, 2H), 3.81 (t, *J*= 6.4, 2H), 4.00 (t, *J*= 7.0, 2H), 4.60 (br, 2H) 6.48 (m, 2H), 6.62 (m, 2H), 6.9 (s, 1H), 7.2 (s, 1H), 7.6 (s, 1H).

***N*-(4-(4-(1*H*-imidazol-1-yl)butoxy)phenyl)picolinimidamide**




[00123] Reaction of 4-(4-(1H-imidazol-1-yl)butoxy)aniline (0.15 g, 0.64 mmol) and *S*-(2-naphthylmethyl)-2-pyridyl thioimidate hydrobromide (0.34 g, 0.95 mmol) in anhydrous acetonitrile (6 mL) and ethanol (20 mL) at room temperature afforded *N*-(4-(4-(1*H*-imidazol-1-yl)butoxy)phenyl)picolinimidamide (**1e**) as a white crystal, yield: 0.0178 g, 0.053 mmol, 9%; m.p. 99-101 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 1.65 (m, 2H), 1.88 (m, 2H), 3.95 (t, *J*= 6.3, 2H), 4.04 (t, *J*= 7.0, 2H), 6.40 (br, 2H), 6.88 (m, 5H), 7.19 (s, 1H), 7.54 (m, 1H), 7.64 (s, 1H), 7.93 (td, $J_1$=7.7, $J_2$=1.68, 1H), 8.30 (d, *J*=7.9, 1H), 8.62 (sd, *J*=4.2, 1H) ppm; $^{13}$C NMR (300 MHz, $CDCl_3$): δ 26.4, 28.1, 46.8, 67.4, 115.5, 118.7, 121.5, 122.6, 125.1, 129.5, 136.8, 137.1, 143.2, 147.8, 151.7, 153.0, 154.8 ppm.

**Example 2B: Synthesis of *meta*-Substituted Phenoxyalkyl Linker Anti-Parasitic Compounds**

[00124] **FIG. 2B** is a synthetic scheme for various phenoxyalkyl hybrid target compounds substituted *meta* to the arylimidamide group, e.g., Compounds **1o-1q**. Generally, reagents and conditions for synthesis of compounds according to **FIG. 2B** included: a) MOMCl, $K_2CO_3$, acetone, 30°C; b) RI, $K_2CO_3$, sealed tube, 80°C; c) HCl, MeOH/$CH_2Cl_2$, rt; d) 1,8-Dibromooctane, $K_2CO_3$, $CH_3CN$, reflux; e) imidazole, $K_2CO_3$, $CH_3CN$, reflux; f) $SnCl_2{\cdot}2H_2O$, EtOAc, reflux; g) *S*-(2-naphthylmethyl)-2-pyridylthioimidate hydrobromide, $CH_3CN$/EtOH (1:3), rt.

**Example 2C: Synthesis of *ortho*-Substituted Phenoxyalkyl Linker Anti-Parasitic Compounds**

[00125] **FIG. 2C** is a synthetic scheme for various phenoxyalkyl hybrid target compounds substituted *ortho* to the arylimidamide group, e.g., Compounds **1r-1t**. Generally, reagents and conditions for synthesis of compounds according to **FIG. 2C** included: a) RI, $K_2CO_3$, sealed tube, 80°C; b) NaOH, DMSO, reflux; c) 1,8-Dibromooctane, $K_2CO_3$, $CH_3CN$,

reflux; d) imidazole, $K_2CO_3$, $CH_3CN$, reflux; e) $SnCl_2{\cdot}2H_2O$, EtOAc, reflux; f) *S*-(2-naphthylmethyl)thioimidate hydrobromide, $CH_3CN$/EtOH, rt..

**Example 2D: Synthesis of Pyrrole-Substituted Phenoxyalkyl Linker Anti-Parasitic Compounds**

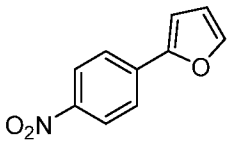
[00126] **FIG. 2D** is a synthetic scheme for various phenoxyalkyl hybrid target compounds substituted with pyrrole, e.g., Compound **1u**. Generally, reagents and conditions for synthesis of Compound **1u** according to **FIG. 2D** included: a) 1,8-dibromooctane, $K_2CO_3$, acetone; b) pyrrole, $K_2CO_3$, $CH_3CN$; c) $SnCl_2{\cdot}2H_2O$, EtOAc; d) *S*-(2-naphthylmethyl)-2-pyridylthioimidate hydrobromide, $CH_3CN$/EtOH (1:3), rt.

**Example 3A: Synthesis of Diphenylfuran Alkyloxy Linker Anti-Parasitic Compounds**

[00127] **FIG. 3A** is a synthetic scheme for various phenyl-unsubstituted diphenylfuran alkyloxy linker hybrid Compounds **2a-2g** and **3a-g**. Compounds **2a-e**, **2g**, **3a-e**, and **3g** were made according to **FIG. 3A**. Compound **2h** was made according to **FIG. 3A**, but starting with 1-bromo-2-oxy(prop-2-yl)-4-nitrobenzene. Generally, reagents and conditions for synthesis of compounds according to **FIG. 3A** included: a) $Pd(PPh_3)_4$, dioxane, 90°C; b) NBS, DMF, rt; c) $K_2CO_3$, acetone, reflux; d) $Pd(PPh_3)_4$, $K_2CO_3$, MeOH, toluene, 80°C; e) azole, NaH, DMF, rt; f) $H_2$, Pd(C), EtOH-EtOAc; g) (i) *S*-(2-naphthylmethyl-2-pyridylthioimidate hydrobromide, EtOH; (ii) NaOH; (iii) ethanolic HCl.

[00128] The synthesis of Compound **2c** is representative, as follows.

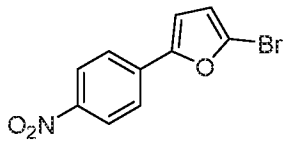
**2-(4-nitrophenyl)furan**




[00129] Tetrakistriphenylphosphine palladium (0.5 mmol) was added to a stirred mixture of the 2-(tributylstannyl) furan (11 mmol) and 1-bromo-4-nitrobenzene (10 mmol) in deaerated dioxane (25 mL) under a nitrogen atmosphere. The vigorously stirred mixture was heated at 90-100 °C for 24 h. The solvent was evaporated under reduced pressure, the resulting solid was partitioned between ethyl acetate (200 mL) and 5 mL of concentrated ammonia to remove the palladium complex, washed with water, passed through celite to remove the catalyst, dried over sodium sulfate and evaporated. Purification by column chromatography on silica gel, using hexanes/ethyl acetate (93/7, v/v) followed by recrystallization from hexanes/ethyl acetate to afford a yellow solid, yield (68 %); m.p. 134-135 °C, (Lit Molander et al. "Scope of the Suzuki–Miyaura Cross-Coupling Reactions of Potassium Heteroaryltrifluoroborates," *J. Org. Chem.* **2009**, *74(3)*, 973–980, the entire teachings of which are incorporated herein by reference),

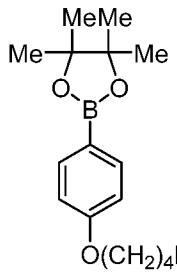
m.p. 131-132 °C; $^1$H NMR (DMSO-$d_6$) δ 6.71 (d, $J$ = 3.6 Hz, 1H), 7.02 (br s, 1H), 7.23 (d, $J$ = 3.6 Hz, 1H), 7.90 (d, $J$ = 8.8 Hz, 2H), 7.98 (d, $J$ = 8.8 Hz, 2H).

**2-bromo-5-(4-nitrophenyl)furan**



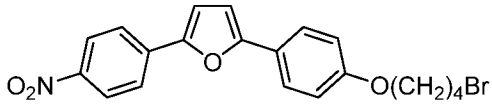

[00130] *N*-bromosuccinimide (2.13 gm, 12 mmol) was added portion-wise to a stirred solution of the previous nitro compound (10 mmol) in dimethylformamide (20 mL). The reaction mixture was stirred at room temperature for 12 h then poured onto cold water, the precipitate was collected and dried. Purification was conducted by column chromatography on silica gel, using hexanes/ethyl acetate (95/5, v/v). Yellow solid, yield 96 %; m.p. 141-143 °C (see Ismail et al., "An efficient synthesis of 5,5′-diaryl-2,2′-bichalcophenes," *Tet Lett* **2006**, *47(5)*, 795-797, the entire teachings of which are incorporated herein by reference); $^1$H NMR (DMSO-$d_6$) δ 6.83 (d, $J$ = 3.6 Hz, 1H), 7.35 (d, $J$ = 3.6 Hz, 1H), 7.90 (d, $J$ = 8.8 Hz, 2H), 8.26 (d, $J$ = 8.8 Hz, 2H); HRMS: m/z calculated for $C_{10}H_7BrNO_3$: 267.9609, found: 267.9602 ($M^+$ +1).

**2-(4-(4-(bromobutoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane**



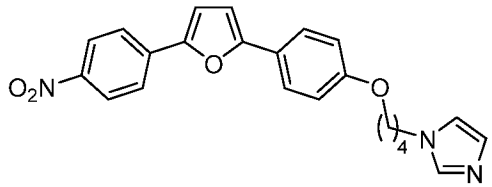

[00131] 1,4-dibromobutane (36 mmol) was added to a solution of the p-hydroxyphenylboronic acid ester (1.32 gm, 6 mmol), dry $K_2CO_3$ (1.65 gm, 12 mmol) and $Cs_2CO_3$ (0.39 gm, 1.2 mmol) in anhydrous dimethylacetamide (15 mL) under a nitrogen atmosphere. Stirring was continued for 12 h and ice water was added and the reaction mixture was filtered and air dried. Purification was performed by column chromatography on silica gel, using hexanes/ethyl acetate (93/7, v/v). White solid (73%) m.p. 112-113 °C, $^1$H NMR (DMSO-$d_6$) δ 1.27 (s, 12 H), 1.82-1.85 (m, 2 H), 1.94-1.98 (m, 2 H), 3.61 (t, $J$ =5.2 Hz, 2 H), 4.01 (t, $J$ =5.2 Hz, 2 H), 6.93 (d, $J$ = 8.4 Hz, 2 H), 7.68 (d, $J$ =8.4 Hz, 2 H).

**2-(4-(4-(bromobutoxy)phenyl)-5-(4-nitrophenyl)furan**



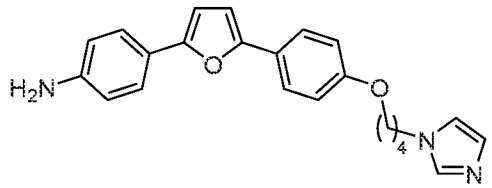
[00132] 2.3 mL deaerated 2 M aqueous solution of $K_2CO_3$ and 2-(4-(bromobutoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.73 mmol) in 5 mL deaerated methanol were added to a stirred solution of 2-bromo-5-(4-nitrophenyl)furan (2.28 mmol), and tetrakistriphenylphosphine palladium (0.114 mmol) in deaerated toluene (25 mL) under a nitrogen atmosphere. The vigorously stirred mixture was warmed to 80 °C for 24 h. The solvent was evaporated under reduced pressure. Purification was carried out by column chromatography on silica gel, using hexanes/ethyl acetate (90/10, v/v). Orange solid, yield (71 %); m.p. 81-83 °C; $^1$HNMR (DMSO-$d_6$) δ 1.84-1.88 (m, 2 H), 1.97-2.00 (m, 2 H), 3.62 (t, $J$ = 6.4 Hz, 2 H), 4.06 (t, $J$ = 6.4 Hz, 2 H), 7.03-7.05 (m, 3 H), 7.40 (d, $J$ = 3.6 Hz, 1 H), 7.80 (d, $J$ =8.4 Hz, 2H), 8.02 (d, $J$ =8.8 Hz, 2H), 8.29 (d, $J$ = 8.8 Hz, 2H).

**1-(4-(4-(5-(4-nitrophenyl)furan-2-yl)phenoxy)butyl)-1*H*-imidazole**



[00133] 2-(4-(4-(bromobutoxy)phenyl)-5-(4-nitrophenyl)furan (2 mmol) was added to a solution of the azole (2 mmol) and NaH (2.5 mmol) in dry DMF (10 mL) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 12 h, then poured on ice-water (50 mL), filtered and dried. Purification was conducted by recrystallization from ethyl acetate/hexanes. Yellow solid, yield (71 %); m.p. 75-78 °C; $^1$HNMR (DMSO-$d_6$) δ 1.66 (br s, 2H), 1.85 (br s, 2H), 4.02-4.05 (m, 4 H), 6.90 (br s, 1H), 7.01-7.04 (m, 3 H), 7.20 (br s, 1H), 7.41 (d, $J$ = 3.6 Hz, 1 H), 7.66 (br s, 1H), 7.79 (d, $J$ = 8.4 Hz, 2 H), 8.02 (d, $J$ = 8.8 Hz, 2H), 8.27 (d, $J$ = 8.4 Hz, 2H); HRMS: m/z calculated for $C_{23}H_{22}N_3O_4$: 404.1610, found: 404.1595 ($M^+$ +1).

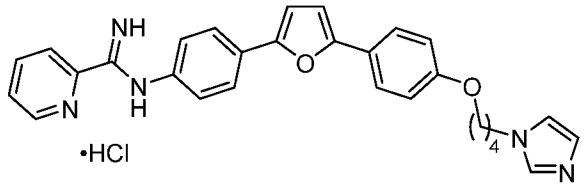
**4-(5-(4-(4-(1*H*-azol-1-yl)butoxy)phenyl)furan-2-yl)aniline**



[00134] Pd/C (10 %) (0.2 gm) was added to a de-aerated solution of 1-(4-(4-(5-(4-nitrophenyl)furan-2-yl)phenoxy)butyl)-1*H*-imidazole (5 mmol) in ethyl acetate/ethanol (60 mL: 20 mL) mixture. Stirring in a Parr hydrogenator under 50 atmosphere until the uptake of hydrogen ceased, the consumption of hydrogen gave a clear solution. The solution was filtrated

through celite, and the filtrate was removed under reduced pressure, the residue formed was used directly in the next step without further purification (the amine is easily oxidized and decomposes on standing). White solid, yield (94 %); m.p. 62-63 °C; $^1$HNMR ($CDCl_3$) δ 1.80 (br s, 2 H), 202-204 (m, 2 H), 3.77 (s, 2 H), 4.00-4.06 (m, 4 H), 6.52 (d, *J* = 3.6 Hz, 1 H), 6.57 (d, *J* = 3.6 Hz, 1 H), 6.74 (d, *J* = 8.4 Hz, 2 H), 6.91 (d, *J* = 8.4 Hz, 2 H), 6.96 (br s, 1 H), 7.09 (br s, 1H), 7.53 (br s, 1H), 7.56 (d, *J* = 8.8 Hz, 2 H), 7.66 (d, *J* = 8.8 Hz, 2 H); HRMS: m/z calculated for $C_{23}H_{24}N_3O_2$: 374.1869, found: 374.1857 ($M^+$ +1).

***N*-(4-(5-(4-(4-(1*H*-imidazol-1-yl)butoxy)phenyl)furan-2-yl)phenyl)picolinimidamide hydrochloride**




[00135] *S*-(2-Naphthylmethyl)-2-pyridyl thioimidate hydrobromide (1.87 mmol) was added to a cooled solution of 4-(5-(4-(4-(1*H*-azol-1-yl)butoxy)phenyl)furan-2-yl)aniline (1.7 mmol) in dry ethanol (30 mL) in an ice bath. The reaction mixture was stirred at room temperature for overnight. After the disappearance of the starting material, the organic solvent was evaporated under reduced pressure to yield a crude oil product. Dry ether (100 mL) was added to the crude material and the mixture was stirred at room temperature for 1 h. The precipitate was filtered and washed with dry ether. The solid was dissolved in ethanol (2 mL); the solution was cooled to 0 °C in an ice bath and 10% NaOH was added until pH reached approximately 10. The free base was extracted with ethyl acetate (3 × 50 mL). The organic layer was washed with distilled water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting suspension was crystallized by adding dry hexanes and then filtered. The free base was suspended in dry ethanol (20 mL) and cooled to 0 °C in an ice bath. Freshly prepared ethanolic HCl solution (2 mL) was added to the suspension and the mixture was stirred at room temperature for overnight. The resulting red solution was concentrated under reduced pressure. The red crude solid was recrystallized twice from dry ethanol and dry ether and filtered. Yellow solid, yield (57 %); m.p. 83-85 °C Dec.; $^1$HNMR (DMSO-$d_6$) δ 1.71 (t, *J* = 6 Hz, 2 H), 1.97-2 (m, 2 H), 4.06 (t, *J* = 6 Hz, 2 H), 4.30 (t, *J* = 6 Hz, 2 H), 6.98 (d, *J* = 3.2 Hz, 1 H), 7.02 (d, *J* = 8.8 Hz, 2 H), 7.19 (d, *J* = 3.2 Hz, 1 H), 7.56 (d, *J* = 8.4 Hz, 2 H), 7.72 (br s, 2 H), 7.78 (d, *J* = 8.4 Hz, 2 H), 7.86 (d, *J* = 8.8 Hz, 2 H), 7.98 (d, *J* = 8 Hz, 1 H), 8.21-8.25 (m, 1 H), 8.51(d, *J* = 7.6 Hz, 1 H), 8.91 (br s, 1H), 9.26 (br s, 1H), 9.37 (s, 1H), 10.15 (s, 1H), 11.91 (s, 1 H); $^{13}$CNMR (DMSO-$d_6$) δ 24.9, 25.9, 47.7, 66.4, 106.2, 108.8, 114.4,

119.3, 121.5, 122.4, 122.9, 123.6, 124.6, 124.8, 125.9, 128, 129.7, 132.6, 134.7, 137.8, 144, 150.5, 157.8, 158.9; HRMS: m/z calculated for $C_{29}H_{28}N_5O_2$: 478.2238, found: 478.2216 (base $M^+$ +1); Anal. Calcd. For $C_{29}H_{27}N_5O_2$. 2 HCl. 1.75 $H_2O$: C, 59.85; H, 5.63; N, 12.03; Found: C, 59.35; H, 5.77; N, 11.83.

**Example 3B: Synthesis of Phenyl-Substituted Diphenylfuran Alkyloxy Linker Anti-Parasitic Compounds**

[00136] **FIG. 3B** is a synthetic scheme for various phenyl substituted diphenylfuran alkyloxy linker hybrid compounds, each of which may be prepared, for example, from a suitably substituted aryl boronate according to **FIG. 3A**. Alternatively, compounds may be prepared from the corresponding phenol and bromoalkyl imidazole, as shown in **FIG. 3B**. The phenol may be prepared from a phenol protected aryl boronate according to **FIG. 3A**, followed by subsequent deprotection.

[00137] Compound **4j** was made according to **FIG. 3B**. Generally, reagents and conditions for synthesis of compounds according to **FIG. 3B** included: a) $Pd(PPh_3)_4$, dioxane, 90°C; b) NBS, DMF, rt; c) $K_2CO_3$, $Cs_2CO_3$, DMA, rt; d) $Pd(PPh_3)_4$, $K_2CO_3$, MeOH, toluene, 80°C; e) imidazole, NaH, DMF, rt; f) $H_2$, Pd(C), EtOH-EtOAc; g) (i) *S*-(2-naphthylmethyl)-2-pyridylthioimidate hydrobromide, EtOH; (ii) NaOH.

**Example 3C: Synthesis of Phenyl-Substituted Diphenylfuran Alkyloxy Linker Anti-Parasitic Compounds**

[00138] **FIG. 3C** is a synthetic scheme for various phenyl substituted diphenylfuran alkyloxy linker hybrid compounds. For example, Compounds **2h**, **4k**, **13b**, and **13c** were made according to **FIG. 3C**. Generally, reagents and conditions for synthesis of compounds according to **FIG. 3C** included: aa) $Pd(PPh_3)_4$, dioxane, 90°C; b) NBS, DMF, rt; c) $K_2CO_3$, $Cs_2CO_3$, DMA, rt; d) $Pd(PPh_3)_4$, $K_2CO_3$, MeOH, toluene, 80°C; e) imidazole, NaH, DMF, rt; f) $H_2$, Pd(C), EtOH-EtOAc; g) (i) *S*-(2-naphthylmethyl-2-pyridylthioimidate hydrobromide, EtOH; (ii) NaOH.

**Example 3D (Prophetic): Synthesis of Diphenylfuran Alkyloxy Linker Anti-Parasitic Compounds**

[00139] **FIG. 3D** is a prophetic synthetic scheme for various diphenylfuran alkyloxy linker hybrid Compounds **4a-i**, each of which may be prepared, for example, from a suitably substituted aryl boronate according to **FIG. 3A**. Alternatively, Compounds **4a-i** may be prepared from the corresponding phenol and bromoalkyl imidazole, as shown in **FIG. 3D**. The phenol may be prepared from a phenol protected aryl boronate according to **FIG. 3A**, followed by subsequent deprotection.

**Example 4 : Synthesis of Alkylamide Linker Anti-Parasitic Compounds**

[00140] **FIG. 4** is a synthetic scheme for various alkylamide linker hybrid Compounds **5a-f**, **6a-f**, and **7a-f**. For example, precursor carboxylic acids were prepared similarly to **FIG. 3A** by a cross-coupling of a benzylalcohol boronate ester with 2-(4-nitrophenyl)furan, nitro reduction, and imidamide formation. Oxidation of the benzyl alcohol provided the carboxylic acid compound shown in **FIG. 4**, and subsequent peptide coupling with the illustrated imidazoyl amine is proposed to afford Compounds **5a** and **5c**.

[00141] Similarly, for example, Compound **6a** may be prepared from 2-(4-nitrophenyl)furan, followed by nitro reduction and imidamide formation. Bromination of the resulting furanyl compound followed by a metal-mediated carboxylation may provide the carboxylic acid shown in **FIG. 4**. Subsequent peptide coupling with the illustrated imidazoyl amine may afford Compound **6a**. Similarly, for example, Compound **7a** may be prepared from a suitable 4-aminobenzoic acid derivative. Imidamide formation may provide the carboxylic acid compound shown in **FIG. 4**, and subsequent peptide coupling with the illustrated imidazoyl amine may provide Compound **6a**.

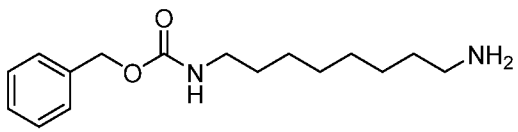
**Example 5A (Prophetic): Synthesis of Phenylalkyl Linker Anti-Parasitic Compounds**

[00142] **FIG. 5A** is a prophetic synthetic scheme for various phenylalkyl linker hybrid Compounds **8a** and **8b**. For example, Compound **8a** and **8b** may be prepared from phenyllithium and the corresponding dibromoalkane, as shown in **FIG. 5A**. Nitration of the resulting alkylaryl bromide followed by displacement of the bromide with imidazole can provide the nitrophenyl alkylimidazole. Subsequent reduction of the nitro group to the amine, followed by amidine synthesis with naphthalene-2-ylmethylpyridine-2-carbimidothioate may provide Compounds **8a** and **8b**.

**Example 5B: Synthesis of Alkyl Linker Anti-Parasitic Compounds**

[00143] **FIG. 5B** is a synthetic scheme for various phenylalkyl linker hybrid Compounds **9a-9d**. The synthesis of Compound **9d** is representative, as follows.

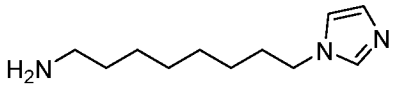
**Benzyl (8-aminooctyl)carbamate**




[00144] Benzyl chloroformate (1 g, 5.86 mmol) was added to 10 equivalents of 1,8-diaminooctane (8.45 g, 58.6 mmol) dissolved in 60 mL dry DCM/EtOH (1:1) in an ice bath. The mixture was allowed to stir for 3 hours at 0 °C and left to stir overnight at room temperature. The mixture was then filtered and partitioned between DCM (100 mL) and water (50 mL) and

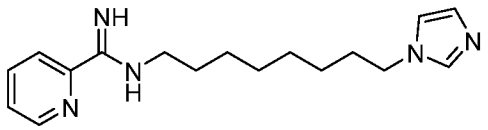
brine (50 mL) then dried over sodium sulfate. The solution was evaporated under reduced pressure and the crude product was purified by column chromatography using DCM/MeOH/TEA (100:6:0.7) as eluent to obtain benzyl (8-aminooctyl)carbamate as a yellow oil, 0.95 g, yield 58%. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.31-1.50 (m, 12 H), 2.68 (t, $J$ = 6.8 Hz, 2H), 3.16-3.22 (m, 2H), 4.78 (br s, 1H), 5.10 (s, 2H), 7.31-7.37 (m, 5H).

**8-(1H-imidazol-1-yl)octan-1-amine**



[00145] Aqueous glyoxal (40%, 0.88 mL, 6.19 mmol), ammonium acetate (0.48 g, 6.19 mmol), and aqueous formaldehyde solution (37% w/v, 0.51 mL, 6.19 mmol) were added to benzyl (8-aminooctyl)carbamate (0.87 g, 3.12 mmol) in methanol (8 mL). The reaction was heated to reflux overnight then the solution was evaporated under reduced pressure. The pH was rendered alkaline by the addition of 2N NaOH and the mixture was extracted with DCM (100 mL). The organic phase was dried over sodium sulfate and the liquid was evaporated under reduced pressure. The product was obtained after column chromatography purification over neutralized silica gel with DCM/MeOH (100:1) as a brown oil of the protected aminoalkyl imidazole, 0.48 g. A dry 25 mL two-necked flask was charged with Pd/C (10%, 0.15 g) and the protected amine (0.48 g, 1.45 mmol) in 20 mL absolute ethanol under nitrogen. The mixture was stirred under 1 atmosphere of hydrogen for 24 hours. The mixture was filtered and ethanol was removed under reduced pressure to obtain the crude product which was purified by column chromatography over silica gel with DCM/MeOH/TEA (100:15:0.1) to obtain 8-(1*H*-imidazol-1-yl)octan-1-amine as a yellow oil, 0.15 g, overall yield 25% from benzyl (8-aminooctyl)carbamate. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.31 (br s, 8H), 1.42-1.46 (m, 2H), 1.76-1.85 (m, 4H), 2.69 (t, $J$ = 6.7 Hz, 2H), 3.93 (t, $J$ = 7 Hz, 2H), 6.91 (t, $J$ = 1.1 Hz, 1H), 7.06 (br t, $J$ = 0.9 Hz, 1H), 7.47 (s, 1H).

**N-(8-(1H-imidazol-1-yl)octyl)picolinimidamide**



[00146] *S*-(2-Naphthylmethyl)-2-pyridyl thioimidate hydrobromide (0.40 g, 1.11 mmol) was added to a cooled solution of 8-(1H-imidazol-1-yl)octan-1-amine (0.1 g, 0.51 mmol) in dry ethanol:acetonitrile (7:3) (10 mL) in an ice bath. The reaction mixture was stirred at room temperature for 48 hours. After the disappearance of the starting material, the organic solvent was evaporated under reduced pressure to yield a crude oil. Dry ether (50 mL) was added to the

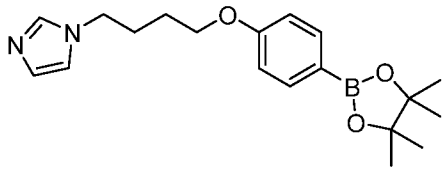
crude material and the mixture was stirred at room temperature overnight. The precipitate was filtered and washed with dry ether. The solid was dissolved in ethanol (2 mL); the solution was cooled to 0 °C in an ice bath and 10% NaOH was added until the pH reached approximately 10. The free base was extracted with ethyl acetate (3 × 25 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting suspension was purified by column chromatography over silica gel using DCM/MeOH/TEA (9.5:1.2:0.6) as eluent then further purified by 5 mL hexanes/diethyl ether (1:1) to yield a buff powder, 0.085 g, 55%. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.28-1.45 (m, 8H), 1.67-1.82 (m, 4H), 3.29 (t, $J$ = 6.9 Hz, 2H), 3.93 (t, $J$ = 7 Hz, 2H), 6.04 (br s, 2H), 6.91 (t, $J$ = 1.2 Hz, 1H), 7.06 (t, $J$ = 1 Hz, 1H), 7.36 (ddd, $J_1$ = 7.6 Hz, $J_2$ = 4.8 Hz, $J_3$ = 1.2 Hz, 1H), 7.48 (br s, 1H), 7.79 (td, $J_1$ = 7.8 Hz, $J_2$ = 1.7, 1H), 8.23 (d, $J$ = 7.8, 1H) 8.55 (ddd, $J_1$ = 4.8 Hz, $J_2$ = 1.7 Hz, $J_3$ = 0.95 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 26.48, 27.19, 28.97, 29.17, 29.44, 31.04, 42.55, 47.00, 118.74, 120.83, 124.85, 129.40, 136.89, 137.06, 147.82, 151.49. HRMS: 300.21707 [M+ $H^+$].

**Example 6A: Synthesis of Unsubstituted and Certain Substituted Biphenyl Linker Anti-Parasitic Compounds**

[00147] **FIG. 6A** is a synthetic scheme for various unsubstituted and substituted biphenyl linker anti-parasitic compounds, which was used to produce Compounds **10a**, **10d**, **10e**, **10h**, **10k**, and **10l**. Biphenyl linkers in these compounds were either unsubstituted or were substituted *meta* to the amidine group. Generally, reagents and conditions for synthesis of compounds according to **FIG. 6A** included: dibromoalkane, $K_2CO_3$, $CH_3CN$, reflux; b) imidazole, $K_2CO_3$, $CH_3CN$, reflux; c) 2-alkoxy-4-nitroiodobenzene, $Pd(dppf)Cl_2$, $K_2CO_3$, DMSO, 100°C; d) $SnCl_2.2H_2O$, EtOAc, reflux; e) *S*-(2-naphthylmethyl)-2-pyridylthioimidate hydrobromide, $CH_3CN$/EtOH (1:3), rt.

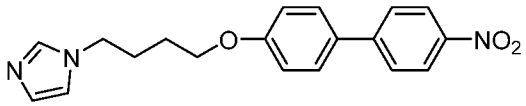
*Synthesis of 2-(4-(4-bromobutoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.*

[00148] Reaction of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (2.00 g, 9.1 mmol), 1,4-dibromobutane (5.42 mL, 9.80 g, 45.4 mmol), and potassium carbonate (2.5 g, 18.2 mmol) was performed in dry acetonitrile under reflux overnight followed by filtration and evaporation of the filtrate under reduced pressure. Purification of the crude product was performed by column chromatography on silica gel using hexane to hexane/ethyl acetate (10:1) to afford a white solid which was further crystallized from methanol to yield the product as a white crystalline solid. Yield 2.42 g (75%), mp = 62-64 °C, lit mp 64-66 °C.[1] The $^1$H NMR spectrum of this material was consistent with the literature report.



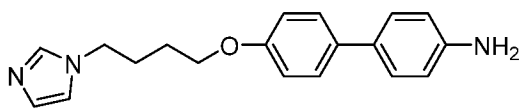
*Synthesis of 1-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)butyl)-1H-imidazole.*

[00149] Reaction of 2-(4-(4-bromobutoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.38 g, 3.9 mmol), imidazole (0.52 g, 7.8 mmol), and potassium carbonate (1.07 g, 7.8 mmol) was performed in dry acetonitrile under reflux overnight followed by filtration and evaporation of the filtrate under reduced pressure. Purification of the crude product was performed by column chromatography on silica gel using DCM: MeOH (25:1) to afford a white solid which was further crystallized from the ethyl acetate/hexane to yield the product as white crystalline solid. Yield 0.75 g (56%), mp=113-115 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ1.35 (s, 12H), 1.78-1.83 (m, 2H), 1.97-2.04 (m, 2H), 4.00-4.06 (m, 4H), 6.88 (d, *J*=6.8 Hz, 2H), 6.95 (s, 1H), 7.09 (s, 1H), 7.51 (s, 1H), 7.76 (d, *J*= 6.8 Hz, 2H).



*Synthesis of 1-(4-((4'-nitro-[1,1'-biphenyl]-4-yl)oxy)butyl)-1H-imidazole.*

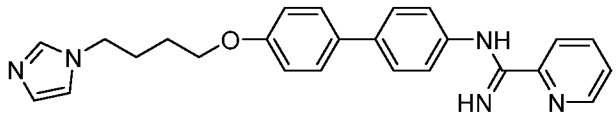
[00150] 1-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)butyl)-1H-imidazole (0.35 g, 1.02 mmol), 4-iodonitrobenzene (0.35 g, 1.4 mmol), and tetrakis(triphenylphosphine)palladium(0) (59 mg, 0.05 mmol) were added to a three necked flask. Degassed dry DMF (10 ml) was added and the flask was purged with nitrogen. Degassed potassium carbonate (1 mL of a 2M aqueous solution) was added and the flask was heated to reflux overnight. The reaction mixture was filtered over celite, then the filtrate was evaporated under reduced pressure and purified by column chromatography on silica gel using hexanes/ethyl acetate (1:3) as the eluent to afford the pure product as a yellow powder, yield 0.25 g (73%), mp=113-115 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ1.82-1.88 (m, 2H), 2.01-2.08 (m, 2H), 4.03-4.09 (m, 4H), 6.97-7.01 (m, 3H), 7.10 (s, 1H), 7.53-7.60 (m, 3H), 7.70 (d, *J*= 8.8 Hz, 2H), 8.28 (d, *J*=8.8 Hz, 2H).



*Synthesis of 4'-(4-(1H-imidazol-1-yl)butoxy)-[1,1'-biphenyl]-4-amine.*

[00151] A mixture of 1-(4-((4'-nitro-[1,1'-biphenyl]-4-yl)oxy)butyl)-1H-imidazole (0.23 g, 0.68 mmol) and tin chloride dihydrate (0.77 g, 3.40 mmol) in ethyl acetate was heated at

reflux overnight. The reaction mixture was cooled, then aqueous sodium hydroxide (2N) was added until the pH reached 11. The product was then extracted with ethyl acetate (25 mL × 3), dried over anhydrous sodium sulfate, filtered over celite, and evaporated under reduced pressure to yield the product as a buff powder which was taken directly to the next step without further purification, yield 0.19 g (91%). $^1$H NMR (300 MHz, $CDCl_3$) δ 1.76-1.85 (m, 2H), 1.97-2.07 (m, 2H), 3.68 (br s, 2H), 3.99-4.07 (m, 4H), 6.74-6.77 (m, 2H), 6.91-6.95 (m, 3H), 7.09 (s, 1H), 7.35-7.38 (m, 2H), 7.45-7.47 (m, 2H), 7.52 (s, 1H).




*Synthesis of N-(4'-(4-(1H-imidazol-1-yl)butoxy)-[1,1'-biphenyl]-4-yl)picolinimidamide.*

[00152] *S*-(2-Naphthylmethyl)-2-pyidyl thioimidate hydrobromide (0.40 g, 1.1 mmol) was added to a cooled solution of 4'-(4-(1H-imidazol-1-yl)butoxy)-[1,1'-biphenyl]-4-amine (0.15 g, 0.48 mmol) in dry ethanol: acetonitrile (7:3, 10 mL) in an ice bath. The reaction mixture was stirred at room temperature for 48 hours. After the disappearance of the starting material, the organic solvent was evaporated under reduced pressure to yield the product as an oil. Dry diethyl ether (100 mL) was added to the crude material and the mixture was stirred at room temperature overnight. The precipitate was filtered and washed with dry diethyl ether. The solid was dissolved in ethanol (2 mL), then the solution was cooled to 0 °C in an ice bath and 10% NaOH was added until pH reached approximately 10. The free base was extracted with ethyl acetate (3 × 25 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting suspension was purified by column chromatography over silica gel (neutralized by washing with trimethylamine) using DCM:MeOH (200:1 to 50:1) as eluent then further purified by crystallization from hexanes/ethyl acetate to yield yellow crystals, 0.135 g (68%). $^1$H NMR (300 MHz, $CDCl_3$) δ 1.80-1.87 (m, 2H), 1.99-2.06 (m, 2H), 4.02-4.09 (m, 4H), 5.91 (brs, 2H), 6.95-6.98 (m, 3H), 7.08-7.10 (m, 3H), 7.42 (ddd, $J_1$=1.1 Hz, $J_2$=4.9 Hz, $J_3$=6.8 Hz, 1H), 7.53-7.60 (m, 5H), 7.84 (td, $J_1$=1.7 Hz, $J_2$=7.7 Hz, 1H), 8.46 (d, $J$=7.7 Hz, 1H), 8.59-8.61 (m, 1H).

**Example 6B: Synthesis of Certain Substituted Biphenyl Linker Anti-Parasitic Compounds**

[00153] **FIG. 6B** is a synthetic scheme for various substituted biphenyl linker anti-parasitic compounds, which was used to produce Compounds **10b**, **10c**, **10i**, and **10j**. Biphenyl linkers in these compounds were substituted *ortho* to the amidine group. Generally, reagents and conditions for synthesis of compounds according to **FIG. 6B** included: a) dibromoalkane, $K_2CO_3$, $CH_3CN$, reflux; b) imidazole, $K_2CO_3$, $CH_3CN$, reflux; c) **23a,b**, $Pd[P(Ph)_3]_4$, $K_2CO_3$,

DMF, 100°C; d) $SnCl_2.2H_2O$, EtOAc, reflux; e) *S*-(2-naphthylmethyl)-2-pyridylthioimidate hydrobromide, $CH_3CN$/EtOH (1:3), rt.

**Example 6C: Synthesis of Certain Substituted Biphenyl Linker Anti-Parasitic Compounds**

[00154] **FIG. 6C** is a synthetic scheme for various substituted biphenyl linker anti-parasitic compounds, which was used to produce Compounds **10f** and **10m**. Biphenyl linkers in these compounds were substituted *meta* to the alkoxy linking group. Generally, reagents and conditions for synthesis of compounds according to **FIG. 6C** included: a) TsCl, $K_2CO_3$, acetone, reflux; b) MeI, $K_2CO_3$, sealed tube, $CH_3CN$, reflux; c) bis(pinocolato)diboron, $Pd(dppf)Cl_2$, AcOK; d) 4-nitro-iodobenzene, $Pd(dppf)Cl_2$, dimethoxyethane/DMF/water (7:3:1), reflux; e) aq NaOH, EtOH/DMSO; f) 1,4-dibromobutane or 1,6-dibromohexane, $K_2CO_3$, $CH_3CN$, reflux; g) imidazole, $K_2CO_3$, $CH_3CN$, reflux; h) $SnCl_2.2H_2O$, EtOAc, reflux; i) *S*-(2-naphthylmethyl)-2-pyridylthioimidate hydrobromide, $CH_3CN$/EtOH (1:3), rt.

**Example 6D: Synthesis of Certain Substituted Biphenyl Linker Anti-Parasitic Compounds**

[00155] **FIG. 6D** is a synthetic scheme for various substituted biphenyl linker anti-parasitic compounds, which was used to produce Compounds **10g** and **10n**. Biphenyl linkers in these compounds were substituted *ortho* to the alkoxy linking group. Generally, reagents and conditions for synthesis of compounds according to **FIG. 6D** included: a) TsCl, acetonitrile, $K_2CO_3$, reflux ; b) Bis(pinacolato)diboron, $Pd(dppf)Cl_2$, AcOK, dioxane, 100°C; c) 1-Iodo-4-nitrobenzene, $Pd[P(Ph)_3]_4$ or $Pd(dppf)Cl_2$, $K_2CO_3$, DME:DMF:$H_2O$ (7:3:1),100°C; d) aq NaOH, EtOH/DMSO; e) dibromoalkane, acetonitrile, $K_2CO_3$, reflux; f) Imidazole, $K_2CO_3$. reflux; g) $SnCl_2.2H_2O$, ethyl acetate, reflux; h) *S*-(2-naphthylmethyl)-2-pyridylthioimidate hydrobromide, $CH_3CN$/EtOH (1:3), rt.

**Example 7A: Synthesis of Phenyl-Piperazinyl-Phenyl Linker Anti-Parasitic Compounds**

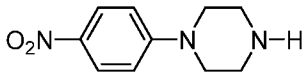
[00156] **FIG. 7A** is a synthetic scheme for various phenyl-piperazinyl-phenyl linker anti-parasitic compounds, which was used to produce Compounds **11a-11d**. Generally, reagents and conditions for synthesis of compounds according to **FIG. 7A** included: a) NMP, DIPEA, 4-chloronitrobenzene; b) α,ω-dihaloalkane, $K_2CO_3$, acetone or $Cs_2CO_3$, DMF; c) imidazole or 1,2,4-triazole, $Cs_2CO_3$, DMF; d) Pd/C, $H_2$, EtOAc/MeOH; e) *S*-(2-naphthylmethyl-2-pyridylthioimidate hydrobromide, $CH_3CN$/EtOH.

**Example 7B: Synthesis of Phenyl-Piperazinyl Linker Anti-Parasitic Compounds**

[00157] **FIG. 7B** is a synthetic scheme for various phenyl-piperazinyl linker anti-parasitic compounds, e.g., corresponding to Structural Formula (**XVII**). Generally, reagents and conditions for synthesis of compounds according to **FIG. 7B** included: a) $K_2CO_3$/DMSO; b) α,ω-dihaloalkane, e.g., 1,6-dibromohexane, $Cs_2CO_3$, DMF; c) imidazole, $Cs_2CO_3$, DMF; d)

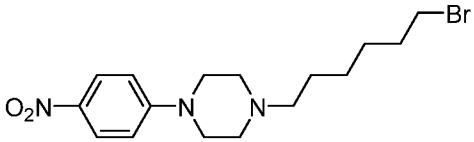
Pd/C, $H_2$, MeOH; e) *S*-(2-naphthylmethyl-2-pyridylthioimidate hydrobromide, $CH_3CN$/EtOH. The synthesis of Compound **12a**, N-(4-(4-(6-(1H-imidazol-1-yl)hexyl)piperazin-1-yl)phenyl)picolinimidamide, is representative, as follows.

***Step 1:*** *Synthesis of 1-(4-nitrophenyl)piperazine*



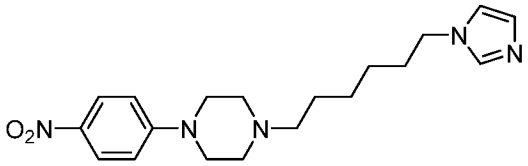
[00158] 4-Chloro nitrobenzene (1.57 g, 10 mmol, 1 eq), piperazine (1.12 g, 13 mmol, 1.3 eq), potassium carbonate (2.07 g, 15 mmol, 1.5 eq) and tetra-N-butyl ammonium iodide (37 mg, 0.1 mmol, 0.01 eq) were added to a reaction vessel, then dimethyl sulfoxide (25 mL) was added under an inert atmosphere. The resulting suspension was heated at 120 °C overnight. The reaction mixture was cooled, diluted with ice water (40 mL), neutralized with 2N hydrochloric acid and then extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with water and brine, dried over $Na_2SO_4$, and concentrated under reduced pressure to yield 1-(4-nitrophenyl)piperazine as a yellow solid. Yield = 1.65 g, 80%; $^1$H NMR ($CDCl_3$, 500 MHz) δ 3.01-3.03 (t, 4H, *J* = 5.15 Hz), 3.37-3.39 (t, 4H, 4.9 Hz), 6.81-6.82 (d, 2H, *J* = 9.3 Hz), 8.11-8.13 (d, 2H, *J* = 9.35 Hz).

***Step 2:*** *Synthesis of 1-(6-bromohexyl)-4-(4-nitrophenyl)piperazine*



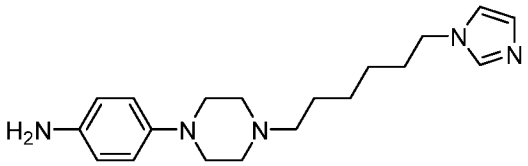
[00159] 1 -(4-nitrophenyl)piperazine (1.03 g, 5 mmol, 1 eq), cesium carbonate (25 mmol, 8.14 g, 5 eq) were added to dry dimethylformamide (25 mL) under an inert atmosphere. To the resulting suspension was added 1,6-dibromohexane (1.02 mL, 6.6 mmol, 1.3 eq) and the mixture was stirred at room temperature for 24 hours. On completion, the reaction mixture was extracted with ethyl acetate (25 mL x 2). The combined organic layers were evaporated under reduced pressure and the resulting liquid was purified by column chromatography using ethyl acetate/hexane (1:1) as an eluent. Fractions containing the main product were combined and evaporated to dryness to give 1-(6-bromohexyl)-4-(4-nitrophenyl)piperazine as a yellow solid. Yield = 550 mg, 30%; $^1$H NMR ($CDCl_3$, 500 MHz) δ 1.37-1.42 (m, 2H), 1.47-1.59 (m, 4H), 1.87-1.93 (m, 2H), 2.40-2.43 (t, 2H, *J*= 7.45 Hz), 2.59-2.61 (t, 4H, *J* = 5.2 Hz), 3.43-3.46 (m, 6H), 6.83-6.86 (d, 2H, *J* = 9.4 Hz), 8.13-8.15 (d, 2H, *J* = 9.4 Hz).

***Step 3:*** *Synthesis of 1-(6-(1H-imidazol-1-yl)hexyl)-4-(4-nitrophenyl)piperazine*



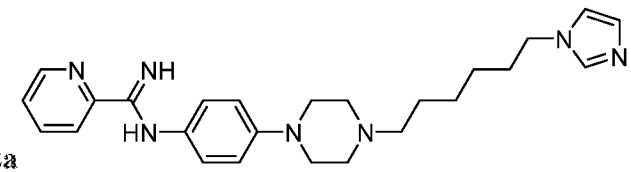
[00160] 1-(6-bromohexyl)-4-(4-nitrophenyl)piperazine (518 mg, 1.4 mmol, 1 eq), *1H*-imidazole (143 mg, 2.1 mmol, 1.5 eq) and cesium carbonate (2.28 g, 7 mmol, 5 eq) were added to a reaction vessel, then dry dimethylformamide (10 mL) was added. The reaction was stirred at 50 °C for 6 hours, then the reaction mixture was cooled to rt, diluted with water and extracted with ethyl acetate. The combined organic layers were concentrated under reduced pressure and purified by column chromatography using dichloromethane/methanol (95:5) as an eluent. Fractions containing the product were combined and evaporated to dryness to give 1-(6-(1H-imidazol-1-yl)hexyl)-4-(4-nitrophenyl)piperazine as a brown solid. Yield = 365 mg, 73%; $^1$H NMR ($CDCl_3$, 500 MHZ) δ 1.31-1.37 (m, 4H), 1.48-1.54 (m, 2H), 1.76-1.82 (m, 2H), 2.34-2.37 (t, 2H, *J* = 7.4 Hz), 2.55-2.57 (t, 4H, *J* = 5.0 Hz), 3.41-3.43 (t, 4H, *J* = 4.9 Hz), 3.92-3.95(t, 2H, *J* = 7.0 Hz), 6.80-6.82 (d, 2H, *J* = 9.3 Hz), 6.9 (s, 1H), 7.05 (s, 1H), 7.46 (s, 1H), 8.10-8.12 (d, 2H, *J* = 9.25 Hz).

***Step 4:*** *4-(4-(6-(1H-imidazol-1-yl)hexyl)piperazin-1-yl)aniline*



[00161] 1-(6-(1H-imidazol-1-yl)hexyl)-4-(4-nitrophenyl)piperazine (322 mg, 0.9 mmol) was dissolved in methanol (30 mL). This mixture was hydrogenated at 40-45 psi using 10% Pd/C as catalyst for 30 minutes in a Parr hydrogenator. The reaction mixture was filtered through a bed of celite and the filtrate was concentrated to give 4-(4-(6-(1H-imidazol-1-yl)hexyl)piperazin-1-yl)aniline as a brown solid. Yield = 275 mg, 93%; $^1$H NMR (DMSO-$d_6$, 500 MHz) δ 1.18-1.24 (m, 2H), 1.26-1.32 (m, 2H), 1.39-1.43 (m, 2H), 1.67-1.73 (m, 2H), 2.25-2.27 (t, 2H, *J* = 7.2 Hz), 2.44 (s, 4H), 2.88 (s, 4H), 3.92-3.95 (t, 2H, *J* = 7.0 Hz), 4.53 (s, 2H), 6.47-6.49 (d, 2H, *J* = 8.55 Hz), 6.66-6.68 (d, 2H, *J* = 8.65 Hz), 6.87 (s, 1H), 7.15 (s, 1H), 7.6 (s, 1H).

***Step 5:*** *Synthesis of N-(4-(4-(6-(1H-imidazol-1-yl)hexyl)piperazin-1-yl)phenyl) picolinimidamide*



**12a**

[00162] *S*-(2-Naphthylmethyl)-2-pyridyl thioimidate hydrobromide (216 mg, 6 mmol, 1.2 eq) was added to an ice cooled solution of 4-(4-(6-(1H-imidazol-1-yl)hexyl)piperazin-1-yl)aniline (164 mg, 0.5 mmol, 1 eq) in a mixture of absolute ethanol/acetonitrile (2:1, 15mL). The resulting mixture was stirred at room temperature for 24 hours. Upon completion of the reaction indicated by TLC, the solvent was evaporated under reduced pressure. To the crude residue was then added dry diethyl ether (50 mL) and the resulting suspension was stirred at room temperature for 6 hours. The separated solid was filtered and washed with dry diethyl ether. The solid was suspended in cold ethanol (5 mL); the mixture was placed in an ice bath and 10% NaOH was added until a pH of approximately 10 was reached. The free base was extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with distilled water, dried over anhydrous $K_2CO_3$, filtered and concentrated under reduced pressure. Dry hexane was added to the resulting suspension, which was then filtered to provide the product as the free base (light yellow solid). Yield = 108 mg, 50%; $^1$H NMR (DMSO-$d_6$, 500 MHZ) δ 1.20-1.26 (m, 2H), 1.28-1.34 (m, 2H), 1.41-1.46 (m, 2H), 1.68-1.74 (m, 2H), 2.27-2.30 (t, 2H, $J$ = 7.2 Hz), 2.49 (s, 4H), 3.07 (s, 4H), 3.93-3.96 (t, 2H, $J$ = 7.1 Hz), 6.36-6.66 (br, 2H), 6.83-6.84 (d, 2H, $J$ = 8.7 Hz), 6.88 (s, 1H), 6.92-6.94 (d, 2H, $J$ = 8.8 Hz), 7.16 (s, 1H), 7.52-7.54 (dd, 1H, $J$ = 5.5, 7.1 Hz), 7.61 (s, 1H), 7.91-7.94 (td, 1H, $J$ = 1.6, 7.8 Hz), 8.29-8.30 (d, 1H, $J$ = 7.9 Hz), 8.61-8.62 (d, 1H, $J$ = 4.5 Hz); $^{13}$C NMR (DMSO-$d_6$, 125 MHz) δ 26.32, 26.63, 26.87, 31.01, 46.35, 49.49, 53.40, 58.25, 117.10, 119.70, 121.57, 122.60, 125.66, 128.74, 137.48, 137.66, 142.34, 147.15, 148.41, 151.94, 152.23; HRMS exact mass of $(M+H)^+$, 432.2876 amu; observed mass of $(M+H)^+$, 432.2878 amu.

**Example 8: Biological Evaluation of Anti-Parasitic Compounds**

[00163] Selected compounds were tested to determine $IC_{50}$ values in an intracellular amastigote assay (*L. donovani*) as follows. Peritoneal macrophages were obtained from CD-1 mice, plated at a density of $10^5$ cells/well in 96-well plates in macrophage medium (RPMI 1640 with Glutamax (Life Technologies, pH=7.4 containing 100 µg/mL streptomycin, 100 U/mL penicillin, and 10% heat-inactivated fetal bovine serum), and permitted to adhere overnight. Macrophages were then infected with *L. donovani* LV82 strain promastigotes at a ratio of five parasites per macrophage. After overnight incubation at 37°C in a humidified atmosphere containing 5% $CO_2$, samples were washed with Hank's Balanced Salt Solution (HBSS), then compounds or the standard drug amphotericin B were added in two-fold serial dilutions in macrophage medium at a final volume of 200 µL/well. Plates were then incubated for three days under the conditions described previously. After incubation, medium was removed and cells were washed with HBSS. Fixation of the cells was then performed using 10% formalin for 30

min. Cells were then permeabilized with 0.1% Triton in PBS, washed with PBS, and stained with 1 μg/mL DAPI for 10 min. Plates were then read using an Array Scan XTI High Content Platform imaging system (Life Technologies) to quantitate macrophage nuclei and parasite nuclei. The data obtained was used to determine the number of parasites per macrophage in each well. A four-parameter curve function available in KaleidaGraph software was then employed to calculate $IC_{50}$ values.

[00164] Selected compounds were tested to determine $IC_{50}$ values in an intracellular amastigote assay (*L. donovani*) and $CC_{50}$ values against J774 macrophages, and selectivity was calculated as $CC_{50}/IC_{50}$ as follows. The cytotoxicity of the compounds on J774 macrophages was evaluated as outlined by Zhu et al. See Zhu, et al., *Bioorg. Med. Chem.* (2015) 23: 5182-5189, the entirety of which is incorporated herein by reference. J774 macrophages were maintained in RPMI + GlutaMAX medium (Gibco) supplemented with 100 U/mL penicillin, 100 μg/mL streptomycin, and 10% fetal bovine serum at 37°C in a humidified 5% $CO_2$ atmosphere. Macrophages were plated at a density of $5 \times 10^3$ cells/well in the presence or absence of serial dilutions of test compounds, vehicle, or podophyllotoxin standard drug in a final volume of 100 μL. After 72 hour incubation under the same conditions described above, 25 μL of a 5 mg/mL solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) in water was added to each well, and the plate was returned to the incubator for 2 hr. A solution of 10% SDS (w/v) in 50% aqueous dimethylformamide was then added to each well, then the plate was incubated for an additional 3-5 h at 37°C. Optical densities for each well were then read at 570 nm using a SpectraMax Plus microplate reader and $CC_{50}$ values were determined as mentioned in the protocol for the intracellular *L. amazonensis* assay.

[00165] The above procedures for J774 macrophages were used with slight modification for HepG2 hepatocellular carcinoma cells. HepG2 cells ($5\times10^3$ in 100 μL) were incubated for 72 h with serial dilutions of compounds in DMEM medium supplemented with 10% fetal bovine serum and antibiotics. MTT was added and absorbance at 570 nm provided an assessment of cell proliferation versus compound concentration, from which $CC_{50}$ against HepG2 was determined in μM. See Werbovetz, K., et al. *Int. J. Toxicol.* **2014**, *33*, 282-287, the entirety of which is incorporated herein by reference.

**Example 8A: Biological Evaluation of Phenoxyalkyl Linker Compounds Against L. Donovani, $CC_{50}$ values against J774 macrophages, and $CC_{50}$ values against HepG2**

[00166] FIG. **8A** is a table demonstrating $IC_{50}$ values in μM against intracellular *L. donovani*, $CC_{50}$ values against J774 macrophages, and $CC_{50}$ values against HepG2 for various phenoxyalkyl linker compounds compared to amphotericin B, podophyllotoxin, and doxorubicin.

**Example 8B: Biological Evaluation of Diphenylfuran Alkyloxy Linker Compounds**

[00167] FIG. **8B** is a table demonstrating $IC_{50}$ values in μM against intracellular *L. donovani*, and $CC_{50}$ values against J774 macrophages, and HepG2 for various diphenylfuran linker compounds compared to amphotericin B, podophyllotoxin, and doxorubicin.

**Example 8C: Biological Evaluation of Biphenyl Alkyloxy Linker Compounds Against L. Donovani, $CC_{50}$ values against J774 macrophages, and $CC_{50}$ values against HepG2**

[00168] FIG. **8C** is a table demonstrating $IC_{50}$ values in μM against intracellular *L. donovani*, $CC_{50}$ values against J774 macrophages, and $CC_{50}$ values against HepG2 for various biphenyl linker compounds compared to amphotericin B, podophyllotoxin, and doxorubicin.

**Example 8F: Biological Evaluation of Phenyl-Piperazinyl-Phenyl Alkyloxy Linker Compounds Against L. donovani, and $CC_{50}$ values against J774 macrophages**

[00169] **FIG. 8D** is a table demonstrating $IC_{50}$ values in μM against intracellular *L. donovani* and $CC_{50}$ values against J774 macrophages for various phenyl-piperazinyl-phenyl linker compounds compared to amphotericin B and podophyllotoxin.

DEFINITIONS

[00170] As used herein, an "alkyl" group includes straight chain and branched chain alkyl groups having a number of carbon atoms, for example, from 1 to 12, 1 to 10, 1 to 8, 1 to 6, or 1 to 4. Examples of straight chain alkyl groups include groups such as methyl, ethyl, *n*-propyl, *n*-butyl, *n*-pentyl, *n*-hexyl, *n*-heptyl, and *n*-octyl groups. Examples of branched alkyl groups include, e.g., isopropyl, iso-butyl, *sec*-butyl, *tert*-butyl, neopentyl, isopentyl, and 2,2-dimethylpropyl groups. Representative substituted alkyl groups may be substituted one or more times with substituents such as those listed above and include, without limitation, haloalkyl (e.g., trifluoromethyl), hydroxyalkyl, thioalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, or carboxyalkyl.

[00171] As used herein, an "alkoxy" group means a hydroxyl group (-OH) in which the bond to the hydrogen atom is replaced by a bond to a carbon atom of a substituted or unsubstituted alkyl group. Examples of linear alkoxy groups include, e.g., methoxy, ethoxy, propoxy, butoxy, pentoxy, or hexoxy. Examples of branched alkoxy groups include, e.g., isopropoxy, *sec*-butoxy, *tert*-butoxy, isopentoxy, or isohexoxy. Examples of cycloalkoxy groups include, e.g., cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, or cyclohexyloxy. Representative substituted alkoxy groups may be substituted one or more times.

[00172] As used herein, a "cycloalkyl" group includes mono-, bi- or tricyclic alkyl groups having from 3 to 12 carbon atoms in each ring, for example, 3 to 10, 3 to 8, or 3 to 4, 5, or 6 carbon atoms. Exemplary monocyclic cycloalkyl groups include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. A cycloalkyl group may have a number of ring carbons of from 3 to 8, 3 to 7, 3 to 6, or 3 to 5. Bi- and tricyclic ring systems may include both bridged cycloalkyl groups and fused rings, e.g., bicyclo[2.1.1]hexane, adamantyl, decalinyl, and the like. Substituted cycloalkyl groups may be substituted one or more times with non-hydrogen and non-carbon groups as defined above. Substituted cycloalkyl groups may include rings that may be substituted with straight or branched chain alkyl groups. Representative substituted cycloalkyl groups may be mono-substituted or substituted more than once, for example, 2,2-, 2,3-, 2,4- 2,5- or 2,6-disubstituted cyclohexyl groups.

[00173] As used herein, a "heterocycloalkyl" ring means an aromatic carbocyclic ring having one or more ring carbon atoms replaced by a heteroatom (e.g., N, S, or O). Non-aromatic heterocyclic rings may have 4, 5, 6, 7, or 8 ring atoms. Examples include oxazolinyl, thiazolinyl, oxazolidinyl, thiazolidinyl, tetrahydrofuranyl, tetrahyrothiophenyl, morpholino, thiomorpholino, pyrrolidinyl, piperazinyl, piperidinyl, thiazolidinyl, and the like.

[00174] As used herein, an "aryl" group means a carbocyclic aromatic hydrocarbon. Aryl groups herein include monocyclic, bicyclic and tricyclic ring systems. Aryl groups include, e.g., phenyl, azulenyl, heptalenyl, biphenyl, fluorenyl, phenanthrenyl, anthracenyl, indenyl, indanyl, pentalenyl, naphthyl, and the like, for example, phenyl, biphenyl, and naphthyl. Aryl groups may contain, for example, 6 to 14, 6 to 12, or 6 to 10 ring carbons. In some embodiments, the aryl groups may be phenyl or naphthyl. Although the phrase "aryl groups" may include groups containing fused rings, such as fused aromatic-aliphatic ring systems (e.g., indanyl or tetrahydronaphthyl), an "aryl" group, unless stated to be substituted or optionally substituted, does not include aryl groups that have other groups, such as alkyl or halo groups, bonded to one of the ring members. Rather, groups such as tolyl may be referred to as substituted aryl groups. Representative substituted aryl groups may be mono-substituted or substituted more than once. For example, monosubstituted aryl groups include, but are not limited to, 2-, 3-, 4-, 5-, or 6-substituted phenyl or naphthyl, which may be substituted with substituents such as those above.

[00175] As used herein, an "aralkyl" group means an alkyl group in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to an aryl group. In some embodiments, aralkyl groups contain 7 to 16 carbon atoms, 7 to 14 carbon atoms, or 7 to 10 carbon atoms. Substituted aralkyl groups may be substituted at the alkyl, the aryl or both the

alkyl and aryl portions of the group. Representative aralkyl groups include, e.g., benzyl and phenethyl groups and fused (cycloalkylaryl)alkyl groups such as 4-indanylethyl. Substituted aralkyls may be substituted one or more times.

[00176] As used herein, a "heteroaryl" group means a carbocyclic aromatic ring having one or more ring carbon atoms replaced by a heteroatom (e.g., N, S, or O). Heteroaryl groups may include, for example, imidazolyl, isoimidazolyl, thienyl, furanyl, pyridyl, pyrimidyl, pyranyl, pyrazolyl, pyrrolyl, pyrazinyl, thiazoyl, isothiazolyl, oxazolyl, isooxazolyl, 1,2,3-trizaolyl, 1,2,4-triazolyl, and tetrazolyl. Heteroaryl groups also include fused polycyclic aromatic ring systems in which a carbocyclic aromatic ring or heteroaryl ring is fused to one or more other heteroaryl rings. Examples of heteroaryl groups may include benzothienyl, benzofuranyl, indolyl, quinolinyl, benzothiazolyl, benzoisothiazolyl, benzooxazolyl, benzoisooxazolyl, benzimidazolyl, quinolinyl, isoquinolinyl and isoindolyl.

[00177] Groups described herein having two or more points of attachment (e.g., divalent, trivalent, or polyvalent) within the compound of the technology may be designated by use of the suffix, "ene." For example, divalent alkyl groups may be alkylene groups, divalent aryl groups may be arylene groups, divalent heteroaryl groups may be heteroarylene groups, and so forth. In particular, certain polymers may be described by use of the suffix "ene" in conjunction with a term describing the polymer repeat unit.

[00178] As used herein, "optionally substituted" means a compound or group that may be substituted or unsubstituted. The term "substituted" refers to an organic group (e.g., an alkyl group) in which one or more bonds to a hydrogen atom contained therein may be replaced by a bond to non-hydrogen or non-carbon atoms. Substituted groups also include groups in which one or more bonds to a carbon or hydrogen atom may be replaced by one or more bonds, including double or triple bonds, to a heteroatom. A substituted group may be substituted with one or more substituents, unless otherwise specified. In some embodiments, a substituted group may be substituted with 1, 2, 3, 4, 5, or 6 substituents.

[00179] Examples of substituent groups include: halogens (F, Cl, Br, and I); hydroxyl; alkoxy, alkenoxy, aryloxy, aralkyloxy, heterocyclooxy, and heterocycloalkoxy groups; carbonyls (oxo); carboxyls; esters; urethanes; oximes; hydroxylamines; alkoxyamines; aralkoxyamines; thiols; sulfides; sulfoxides; sulfones; sulfonyls; sulfonamides; amines; N-oxides; hydrazines; hydrazides; hydrazones; azides; amides; ureas; amidines; guanidines; enamines; imides; isocyanates; isothiocyanates; cyanates; thiocyanates; imines; nitro groups; or nitriles. A "per"-substituted compound or group is a compound or group having all or substantially all substitutable positions substituted with the indicated substituent. For example, 1,6-diiodo

perfluoro hexane indicates a compound of formula $C_6F_{12}I_2$, where all the substitutable hydrogens have been replaced with fluorine atoms.

[00180] In particular, suitable substituents for an alkyl group, cycloalkyl group, heterocycloalkyl group, or an aryl group ring carbon are those which do not substantially interfere with the activity of the disclosed compounds. Examples include -OH, halogen (-Br, -I and -F), $-OR^A$, $-O(CO)R^A$, $-(CO)R^A$, -CN, $-NO_2$, $-CO_2H$, $-SO_3H$, $-NH_2$, $-NHR^A$, $-N(R^AR^B)$, $-(CO)OR^A$, -(CO)H, $-CONH_2$, $-CONHR^A$, $-CON(R^AR^B)$, $-NHCOR^A$, $-NRCOR^A$, $-NHCONH_2$, $-NHCONR^AH$, $-NHCON(R^AR^B)$, $-NR^CCONH_2$, $-NR^CCONR^AH$, $-NR^CCON(R^AR^B)$, $-C(=NH)-NH_2$, $-C(=NH)-NHR^A$, $-C(=NH)-N(R^AR^B)$, $-C(=NR^C)-NH_2$, $-C(=NR^C)-NHR^A$, $-C(=NR^C)-N(R^AR^B)$, $-NH-C(=NH)-NH_2$, $-NH-C(=NH)-NHR^A$, $-NH-C(=NH)-N(R^AR^B)$, $-NH-C(=NR^C)-NH_2$, $-NH-C(=NR^C)-NHR^A$, $-NH-C(=NR^C)-N(R^AR^B)$, $NR^DH-C(=NH)-NH_2$, $-NR^D-C(=NH)-NHR^A$, $-NR^D-C(=NH)-N(R^AR^B)$, $-NR^D-C(=NR^C)NH_2$, $-NR^D-C(=NR^C)-NHR^A$, $-NR^D-C(=NR^C)-N(R^AR^B)$, $-NHNH_2$, $-NHNHR^A$, $-NHR^AR^B$, $-SO_2NH_2$, $-SO_2NHR^A$, $-SO_2NR^AR^B$, $-CH=CHR^A$, $-CH=CR^AR^B$, $-CR^C=CR^AR^B$, $-CR^C=CHR^A$, $-CR^C=CR^B$, $-CCR^A$, -SH, $-SO_kR^A$ (k is 0, 1 or 2) and $-NH-C(=NH)-NH_2$. Each of $R^A$-$R^D$ may independently be an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aryl or substituted aryl group, for example, an alkyl, benzylic or aryl group. Further, $-NR^AR^D$, taken together, may form a substituted or unsubstituted non-aromatic heterocyclic group. A non-aromatic heterocyclic group, benzylic group or aryl group may also have an aliphatic or substituted aliphatic group as a substituent. A substituted aliphatic group may also have a non-aromatic heterocyclic ring, a substituted a non-aromatic heterocyclic ring, benzyl, substituted benzyl, aryl or substituted aryl group as a substituent. A substituted aliphatic, non-aromatic heterocyclic group, substituted aryl, or substituted benzyl group may have more than one substituent.

[00181] Suitable substituents for heteroaryl ring nitrogen atoms having three covalent bonds to other heteroaryl ring atoms may include –OH and $C_1$ to $C_{10}$ alkoxy. Substituted heteroaryl ring nitrogen atoms that have three covalent bonds to other heteroaryl ring atoms are positively charged, which may be balanced by counteranions such as chloride, bromide, formate, acetate and the like. Examples of other suitable counteranions may include counteranions found in the described pharmacologically acceptable salts.

[00182] Suitable substituents for heteroaryl ring nitrogen atoms having two covalent bonds to other heteroaryl ring atoms include alkyl, substituted alkyl (including haloalkyl), phenyl, substituted phenyl, $-S(O)_2$-(alkyl), $-S(O)_2-NH$(alkyl), $-S(O)_2-NH(alkyl)_2$, and the like.

[00183] Also included are pharmaceutically acceptable salts of the compounds described herein. Compounds disclosed herein that possess a sufficiently basic functional group

may react with any of a number of organic or inorganic acids to form a salt. Likewise, compounds disclosed herein that possess a sufficiently acidic functional group may react with any of a number of organic or inorganic bases to form a salt. Acids commonly employed to form acid addition salts from compounds with basic groups may include inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenyl-sulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such salts may include the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, gamma-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate, and the like. Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of the described compounds may include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, and the like.

[00184] An "effective amount" is the quantity of compound in which a beneficial clinical outcome may be achieved when the compound is administered to a subject suffering from the described parasite. A "beneficial clinical outcome" may include one or more of: a reduction in number of parasites in a subject; a reduction in the rate of parasite growth in a subject; a reduction in parasite consumption of a subject's bodily resources; a reduction in biomarkers, toxins, proteins, peptides, and other biomolecules associated with infection of the subject by the parasite; a reduction in inflammatory, allergic, toxic, disfigurement, or other effects on the subject by the parasite; a reduction in the severity of the symptoms associated with the parasite and/or an increase in the longevity or health of the subject compared with the absence of the treatment.

[00185] The precise amount of compound administered to a subject may depend on the species, lifecycle, of the parasitical infection. The precise amount of compound administered to a subject may also depend on the characteristics of the subject, such as general health, age, sex, body weight and tolerance to drugs. A skilled artisan may determine appropriate dosages

depending on these and other factors. Effective amounts of the disclosed compounds typically range between about 1 mg/mm$^2$ per day and about 10 grams/mm$^2$ per day, and preferably between 10 mg/mm$^2$ per day and about 5 grams/mm$^2$.

[00186] The disclosed compounds and pharmaceutical compositions may be administered by any suitable route, including, for example, orally in tablets, pills, gelcaps, lozenges, or suspensions; by parenteral administration. Parenteral administration can include, for example, systemic administration, such as by intramuscular, intravenous, subcutaneous, or intraperitoneal injection. The compounds may also be administered, for example, orally (e.g., dietary); topically, in the form of creams, sprays, patches, and the like; by inhalation (e.g., intrabronchial, intranasal, or oral inhalation of an aerosol formulation, by intranasal drops, and the like); via absorption through mucus membranes (e.g., tissues such as oral, nasal, rectal, vaginal, and the like) via, for example, creams, lozenges, sprays, drops, suppositories, and the like); depot preparations; coatings on sutures, bandages, medical devices, and the like. In some embodiments, oral or parenteral administration are exemplary modes of administration. The disclosed compounds may be administered to the subject in conjunction with an acceptable pharmaceutical carrier as part of a pharmaceutical composition for treatment of infection by the described parasite. Formulation of the compound to be administered may vary according to the route and vehicle of administration selected (e.g., solution for injection, capsule or tablet for ingestion, and the like). Suitable pharmaceutical carriers may contain inert ingredients that do not interact with the described compound. Standard pharmaceutical formulation techniques may be employed, such as those described in Remington's Pharmaceutical Sciences, 22$^{nd}$ ed., Mack Publishing Company, Easton, PA, 2012. Suitable pharmaceutical carriers for parenteral administration may include, for example, sterile water, physiological saline, bacteriostatic saline (e.g., saline containing about 0.9% mg/mL benzyl alcohol, and the like), phosphate-buffered saline, Hank's solution, Ringer's-lactate and the like. Methods for encapsulating compositions (such as in a coating of hard gelatin or cyclodextrin) or tableting compositions are known in the art (Baker, et al., "Controlled Release of Biological Active Agents," John Wiley and Sons, New York, 1986).

[00187] A "subject" may be any animal subject to infection by the described parasites, e.g., the subject may be a mammal, bird, marsupial, fish, or amphibian. For example, the subject may be a mammal, such as a human. The subject may also be a domestic or wild animal in need of veterinary treatment, e.g., companion animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, pigs, horses, and the like), laboratory animals (e.g., rats, mice, guinea pigs, and the like), birds, fish, marsupials, and the like.

[00188] To the extent that the term "includes" or "including" is used in the specification or the claims, it is intended to be inclusive in a manner similar to the term "comprising" as that term is interpreted when employed as a transitional word in a claim. Furthermore, to the extent that the term "or" is employed (e.g., A or B) it is intended to mean "A or B or both." When the applicants intend to indicate "only A or B but not both" then the term "only A or B but not both" will be employed. Thus, use of the term "or" herein is the inclusive, and not the exclusive use. See Bryan A. Garner, A Dictionary of Modern Legal Usage 624 (2d. Ed. 1995). Also, to the extent that the terms "in" or "into" are used in the specification or the claims, it is intended to additionally mean "on" or "onto." To the extent that the term "selectively" is used in the specification or the claims, it is intended to refer to a condition of a component wherein a user of the apparatus may activate or deactivate the feature or function of the component as is necessary or desired in use of the apparatus. To the extent that the term "operatively connected" is used in the specification or the claims, it is intended to mean that the identified components are connected in a way to perform a designated function. To the extent that the term "substantially" is used in the specification or the claims, it is intended to mean that the identified components have the relation or qualities indicated with degree of error as would be acceptable in the subject industry.

[00189] As used in the specification and the claims, the singular forms "a," "an," and "the" include the plural unless the singular is expressly specified. For example, reference to "a compound" may include a mixture of two or more compounds, as well as a single compound.

[00190] As used herein, the term "about" in conjunction with a number is intended to include ± 10% of the number. In other words, "about 10" may mean from 9 to 11. Where the term "about" is used with respect to a number that is an integer, the term "about" may mean ± 10% of the number, or ± 5, ± 4, ± 3, ± 2, or ± 1 of the number.

[00191] As used herein, the terms "optional" and "optionally" mean that the subsequently described circumstance may or may not occur, so that the description includes instances where the circumstance occurs and instances where it does not.

[00192] In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group. As will be understood by one skilled in the art, for any and all purposes, such as in terms of providing a written description, all ranges disclosed herein also encompass any and all possible sub-ranges and combinations of sub-ranges thereof. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves,

thirds, quarters, fifths, tenths, and the like. As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, and the like. As will also be understood by one skilled in the art all language such as "up to," "at least," "greater than," "less than," include the number recited and refer to ranges which can be subsequently broken down into sub-ranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member. For example, a group having 1-3 members refers to groups having 1, 2, or 3 members. Similarly, a group having 1-5 members refers to groups having 1, 2, 3, 4, or 5 members, and so forth. While various aspects and embodiments have been disclosed herein, other aspects and embodiments will be apparent to those skilled in the art.

[00193] As stated above, while the present application has been illustrated by the description of embodiments thereof, and while the embodiments have been described in considerable detail, it is not the intention of the applicants to restrict or in any way limit the scope of the appended claims to such detail. Additional advantages and modifications will readily appear to those skilled in the art, having the benefit of the present application. Therefore, the application, in its broader aspects, is not limited to the specific details, illustrative examples shown, or any apparatus referred to. Departures may be made from such details, examples, and apparatuses without departing from the spirit or scope of the general inventive concept.

CLAIMS

1. A compound, represented by Structural Formula **(Ia)**:

**(Ia)** **Ar**—C(=$NR^1$)$NR^2$—**A**—**X**—**Y**—**$Het^2$**

and pharmaceutically acceptable salts thereof, wherein:

**Ar** is an optionally substituted aryl or nitrogen-containing heteroaryl;

$R^1$ and $R^2$ are independently H, optionally substituted $C_1$-$C_6$ alkyl, or optionally substituted $C_3$-$C_6$ cycloalkyl;

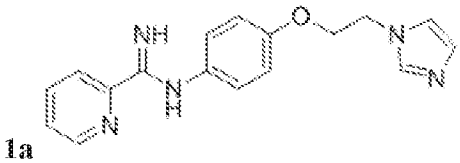
**A** is a bond or an optionally substituted linking moiety comprising 1, 2, or 3 rings, each ring in the optionally substituted linking moiety independently being one of: aryl, cycloalkyl, heterocycloalkyl, and heteroaryl;

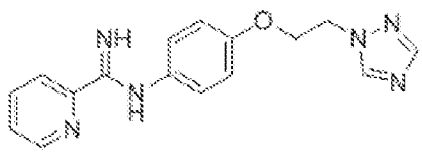
**X** is O, S, amide, or a bond;

**Y** is optionally substituted $C_1$-$C_{14}$ alkyl or optionally substituted $C_2$-$C_{14}$ alkenyl; and

**$Het^2$** is an optionally substituted five-membered nitrogen-containing heteroaromatic ring comprising 1, 2, or 3 ring heteroatoms,

provided that the compound represented by Structural Formula **(Ia)** is not one of free-base Compounds **1a-f**:



**1a**, 

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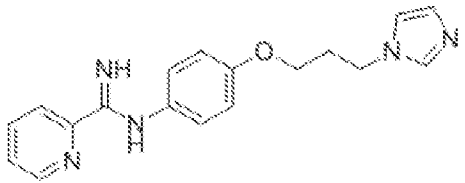
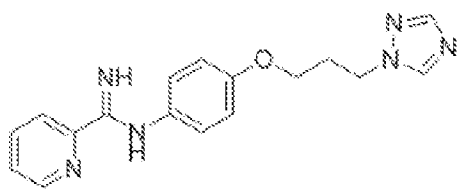
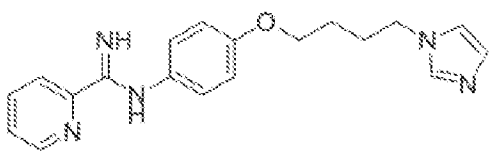
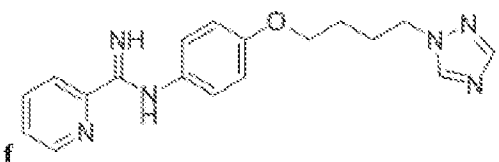


**1c**, 

**1d**,



**1e**, and 

**1f**.

2. The compound of claim 1, represented by Structural Formula **(I)**:

**(I)** **$Het^1$**—C(=$NR^1$)$NR^2$—**A**—**X**—**Y**—**$Het^2$**

and pharmaceutically acceptable salts thereof, wherein:

**$Het^1$** is an optionally substituted, nitrogen-containing heteroaryl;

$R^1$ and $R^2$ are independently H, optionally substituted $C_1$-$C_6$ alkyl, or optionally substituted $C_3$-$C_6$ cycloalkyl;

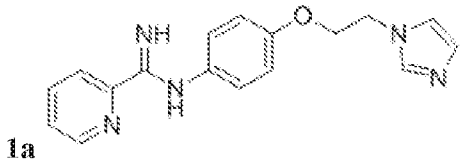
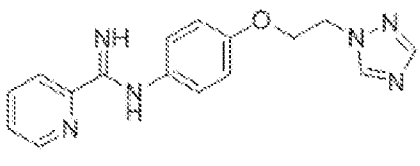
**A** is a bond or an optionally substituted linking moiety comprising 1, 2, or 3 rings, each ring in the optionally substituted linking moiety independently being one of: aryl, cycloalkyl, heterocycloalkyl, and heteroaryl;

**X** is O, S, amide, or a bond;

**Y** is optionally substituted $C_1$-$C_{10}$ alkyl or optionally substituted $C_2$-$C_{10}$ alkenyl; and

**Het$^2$** is an optionally substituted five-membered nitrogen-containing heteroaromatic ring comprising 1, 2, or 3 ring heteroatoms,

provided that the compound represented by Structural Formula **(I)** is not one of free-base Compounds **1a-f**:


**1a**, 
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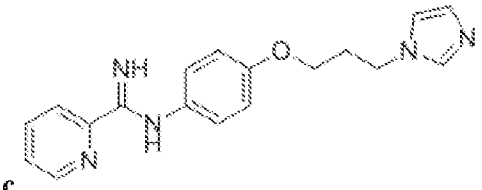
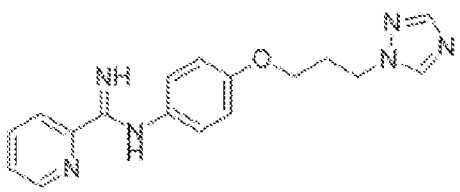

**1c**, 
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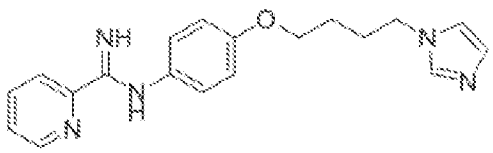
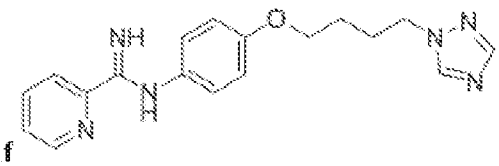
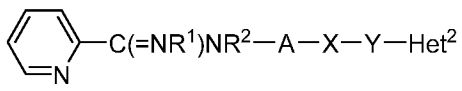

**1e**, and 
**1f**.

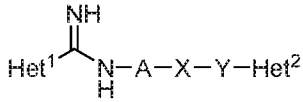
3. The compound of claim 2, wherein **Het$^1$** is optionally substituted pyridyl, pyrazinyl, pyrimidinyl, or pyridizinyl.

4. The compound of claim 2, wherein **Het$^1$** is optionally substituted pyridyl.

5. The compound of claim 1, represented by Structural Formula **(II)**:


**(II)**

6. The compound of claim 1, represented by Structural Formula **(III)**:


**(III)**

7. The compound of claim 2, wherein each ring in the optionally substituted linking moiety represented by **A** is independently and optionally substituted by one or more of: hydroxy, halo, and $C_1$-$C_6$ alkoxy.

8. The compound of claim 2, wherein **A** comprises an optionally substituted heteroaryl or optionally substituted heterocycloalkyl ring.

9. The compound of claim 8, wherein **A** comprises an optionally substituted, oxygen-containing heteroaryl or heterocycloalkyl ring.

10. The compound of claim 9, wherein **A** comprises an optionally substituted furanyl or optionally substituted tetrahydrofuranyl ring.

11. The compound of claim 9, wherein **A** comprises optionally substituted 2,5-furanyl.

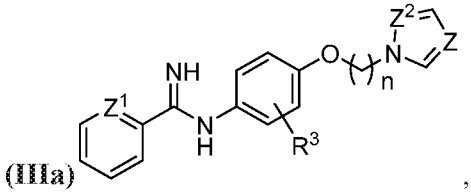
12. The compound of claim 2, wherein **A** comprises one or two optionally substituted phenyl rings.

13. The compound of claim 12, wherein **A** comprises optionally substituted 1,4-phenyl.

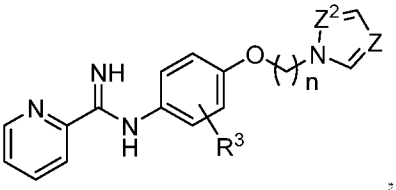
14. The compound of claim 12, wherein **A** is optionally substituted 1,4-phenyl.

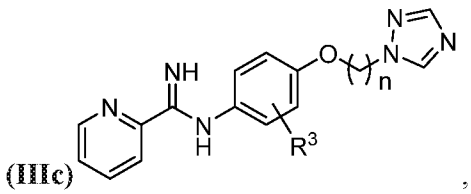
15. The compound of claim 12, wherein **A** is optionally substituted phenyl-heteroaryl-phenyl.

16. The compound of claim 1, represented by one of Structural Formulas **(IIIa)-(IIIf)**:

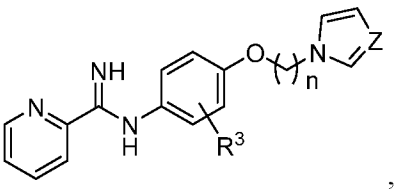

**(IIIa)**

, **(IIIb)**


,


**(IIIc)**

, **(IIId)**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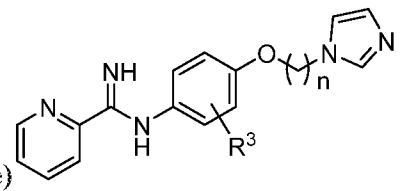
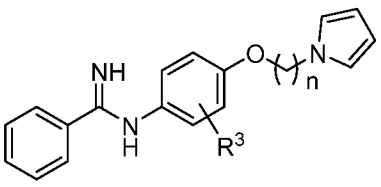
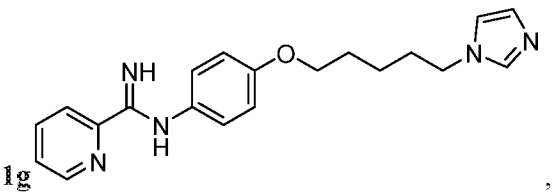

**(IIIe)**

, and **(IIIf)**

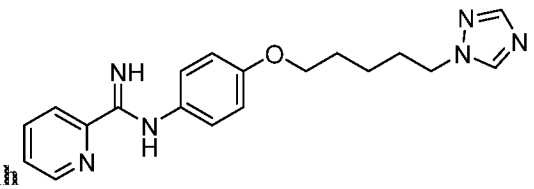

,

wherein Z, $Z^1$, and $Z^2$ are each independently CH or N, n is 1-14, and $R^3$ is H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy.

17. The compound of claim 16, wherein the compound is one of Compounds **1g-1v**:


**1g**

, **1h**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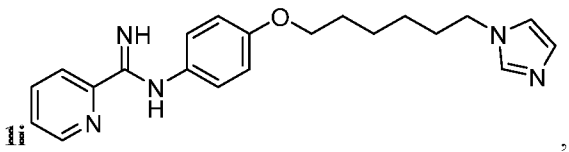
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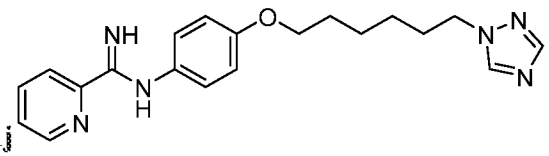
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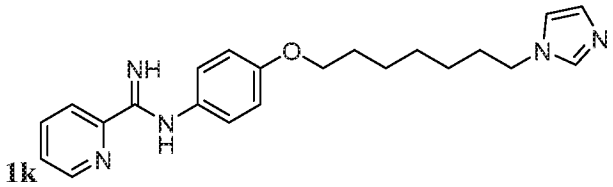
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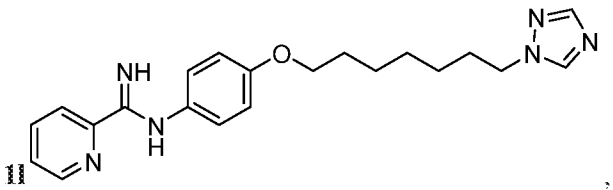
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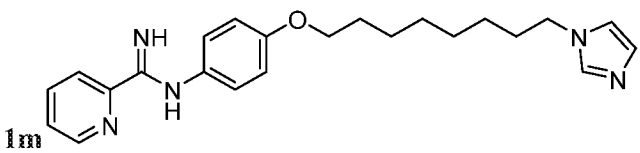
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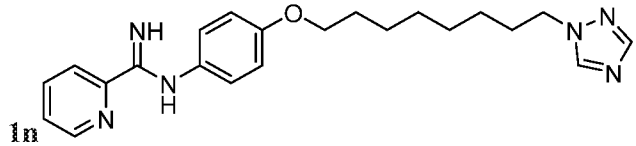
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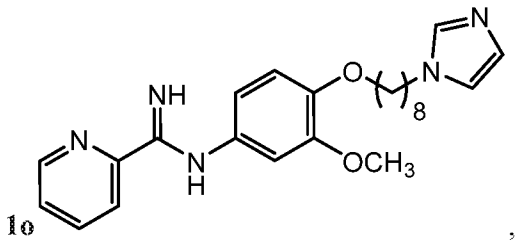
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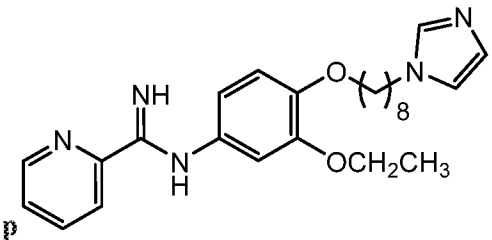
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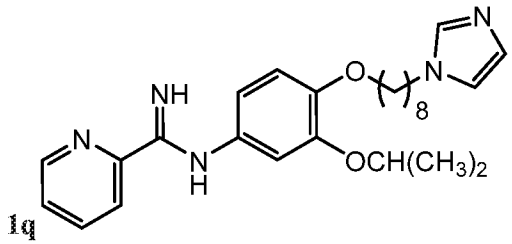
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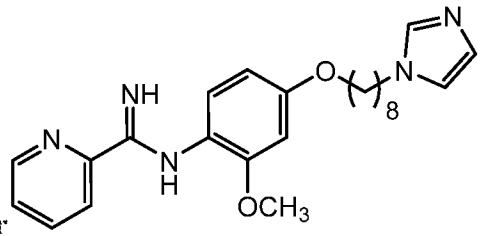
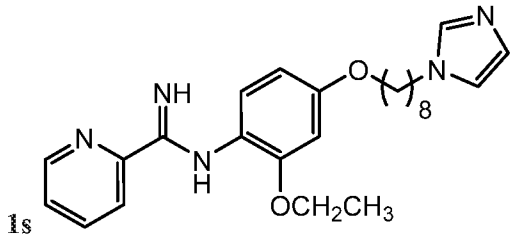
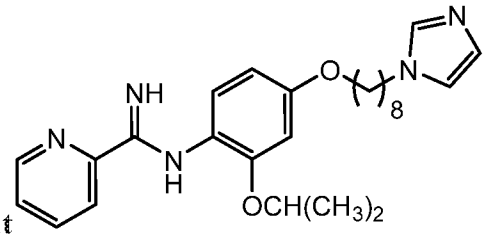
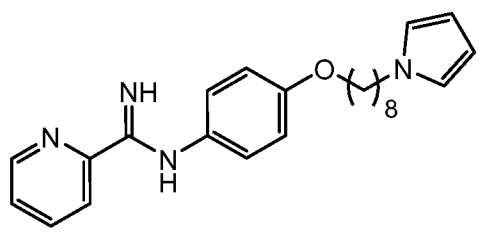
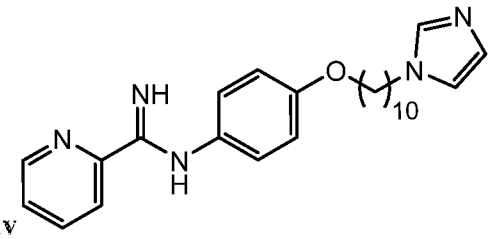

1r,


1s,


1t,

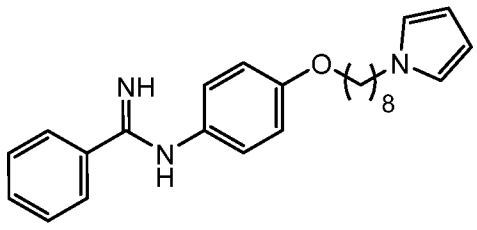



**1u**, and



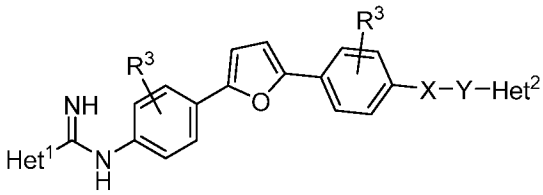

**1v**.

18. The compound of claim 16, wherein the compound is Compound **14a**:




**14a**.

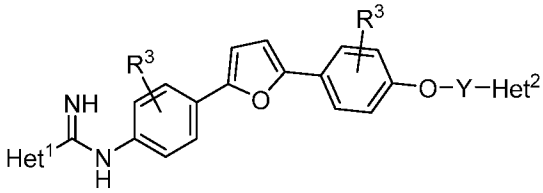
19. The compound of claim 1, represented by Structural Formula **(IV)**:




**(IV)**,

wherein each $\mathbf{R^3}$ is independently H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy.

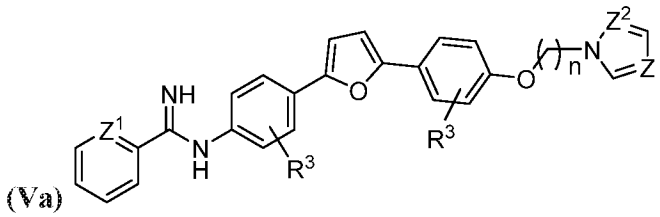
20. The compound of claim 1, represented by Structural Formula **(V)**:



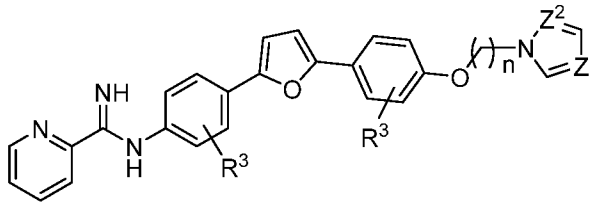

**(V)**,

wherein each $\mathbf{R^3}$ is independently H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy.

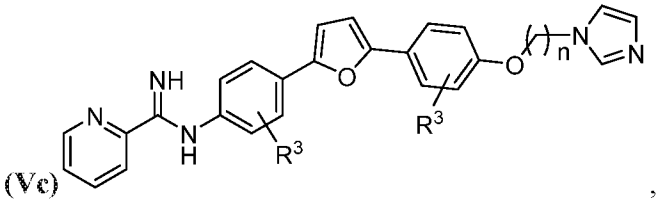
21. The compound of claim 1, represented by one of Structural Formulas **(Va)-(Ve)**:



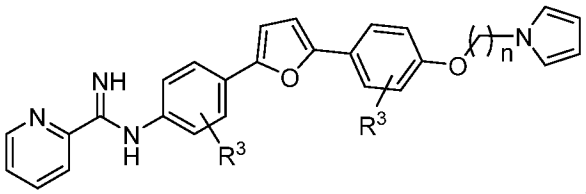
(Va) , (Vb)



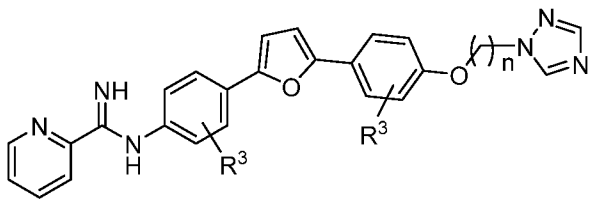
,



(Vc) , (Vd)



, and (Ve)



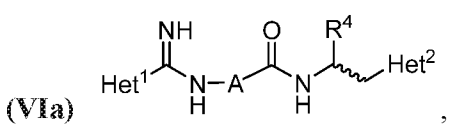
,

wherein Z, $Z^1$, and $Z^2$ are each independently CH or N, n is 1-14, and $R^3$ is H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy.

22. The compound of claim 1, wherein **Y** comprises at least 4 linking atoms between **X** and **Het²**.

23. The compound of claim 1, wherein **X** is O or a bond and **Y** is $C_1$-$C_{12}$ alkyl optionally substituted with one or more of: optionally halogenated $C_1$-$C_8$ alkyl and optionally halogenated aryl.

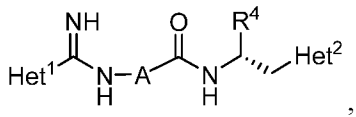
24. The compound of claim 1, represented by Structural Formula **(VIa)**:



**(VIa)** ,

wherein $\mathbf{R^4}$ is H, optionally halogenated $C_1$-$C_8$ alkyl, or optionally halogenated aryl.

25. The compound of claim 1, represented by Structural Formula **(VIb)**:



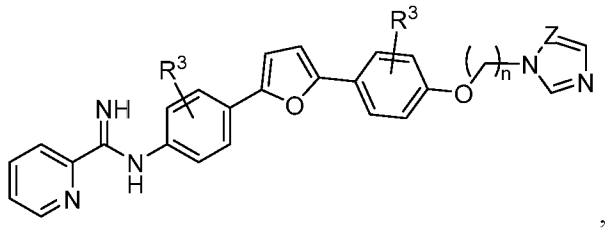

**(VIb)** ,

wherein $\mathbf{R^4}$ is H, optionally halogenated $C_1$-$C_8$ alkyl, or optionally halogenated aryl.

26. The compound of claim 2, wherein $\mathbf{Het^2}$ comprises an optionally substituted one of: pyrrole, diazole, thiadiazole, oxadiazole, and triazole.

27. The compound of claim 26, wherein $\mathbf{Het^2}$ is optionally substituted imidazole or optionally substituted 1, 2, 4 triazole.

28. The compound of claim 1, represented by Structural Formula **(VII)**:




**(VII)** ,

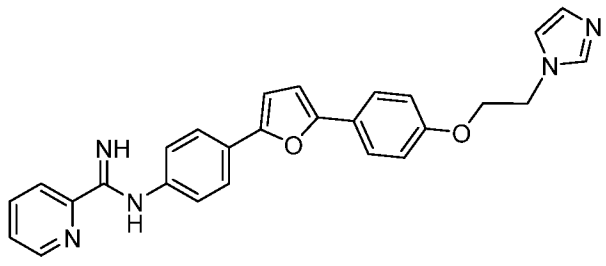
wherein:

**Z** = CH or N;

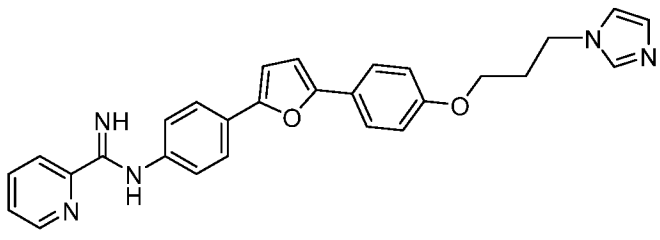
each $\mathbf{R^3}$ is independently H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy; and

**n** is an integer from 1 to 10.

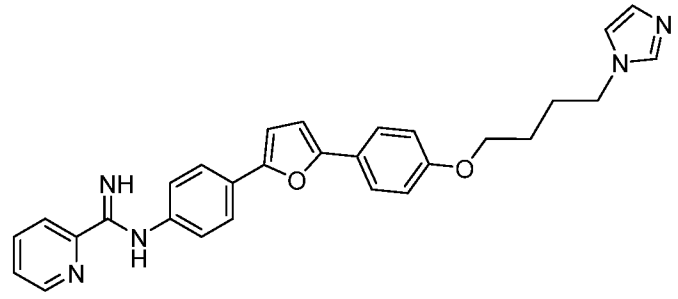
29. The compound of claim 28, wherein the compound is one of Compounds **2a-2h**:



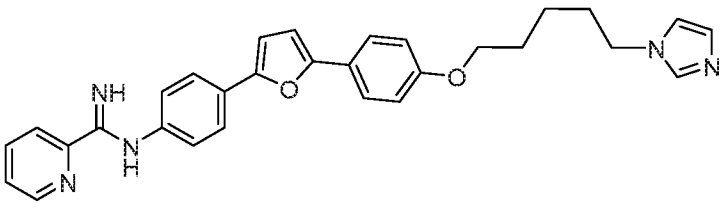

**2a** ,



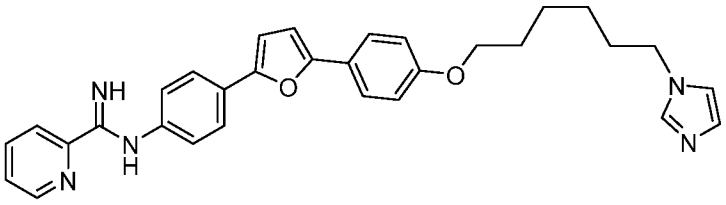

**2b** ,



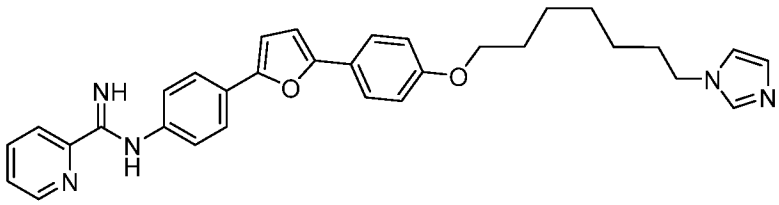
2c ,



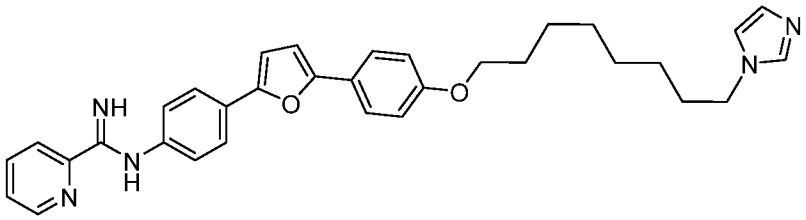
2d ,



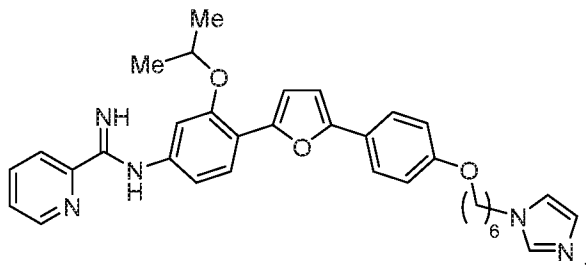
2e ,



2f ,

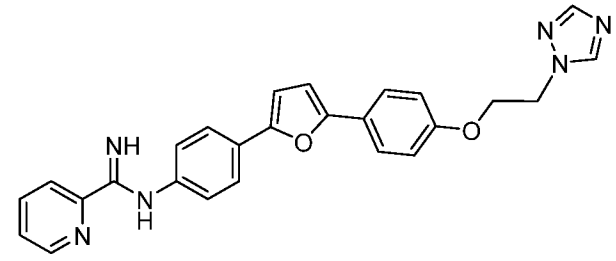


2g ; and

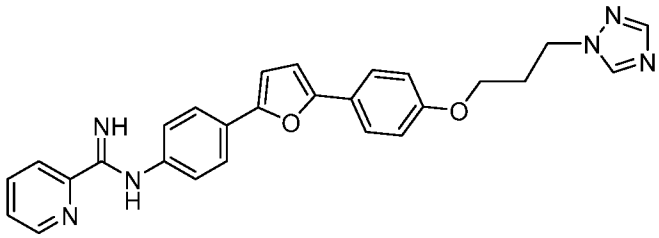


2h .

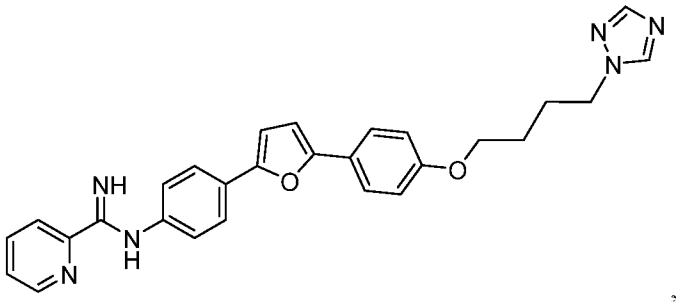
30. The compound of claim 28, wherein the compound is one of Compounds **3a-3g**:



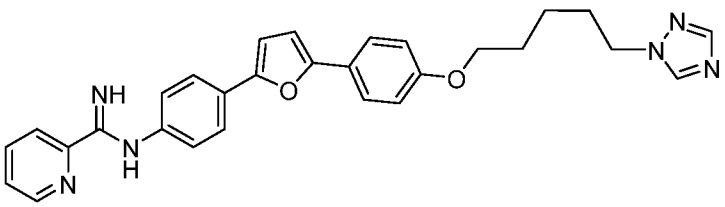
3a ,



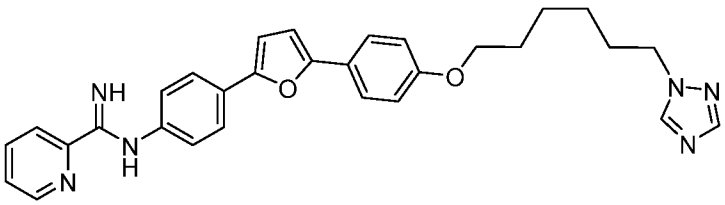
3b ,



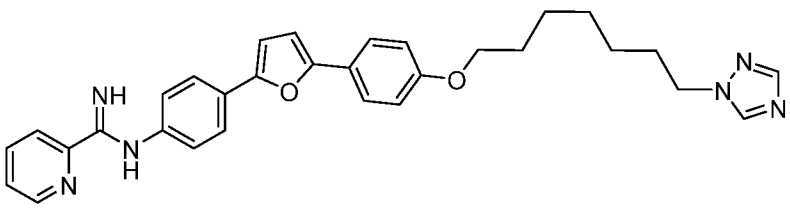
3c ,



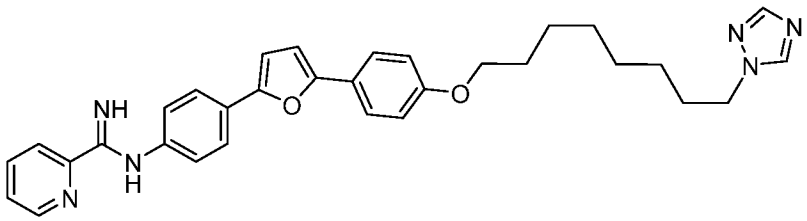
3d ,



3e ,

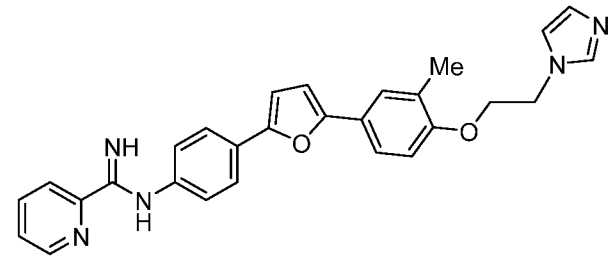


3f , and

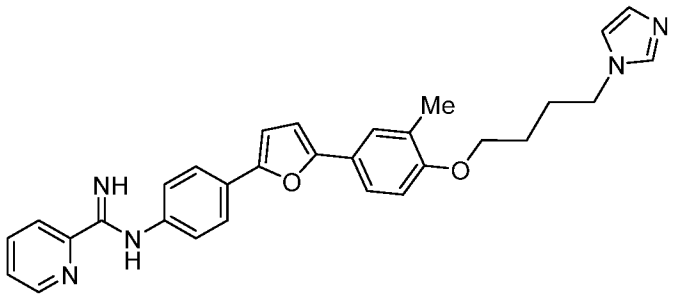


3g .

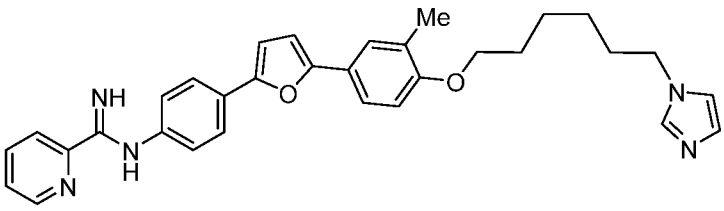
31. The compound of claim 28, wherein the compound is one of Compounds **4a-4m**:



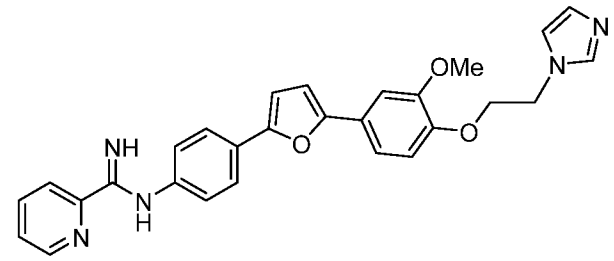
**4a**,



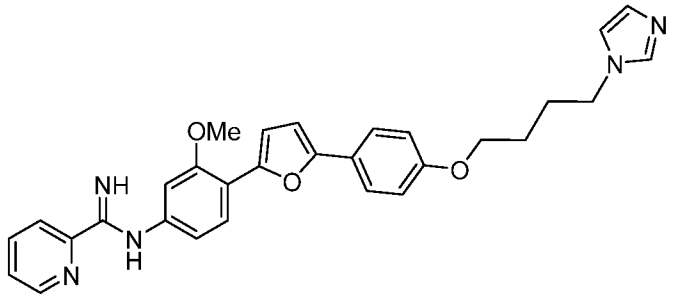
**4b**,



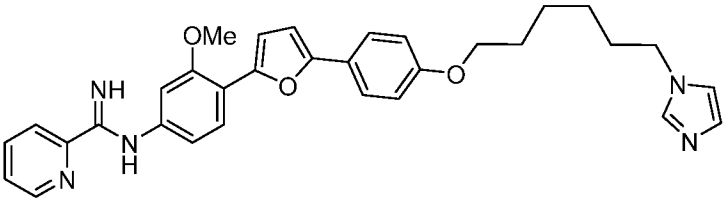
**4c**,



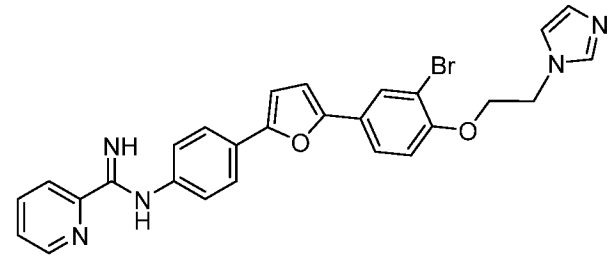
**4d**,



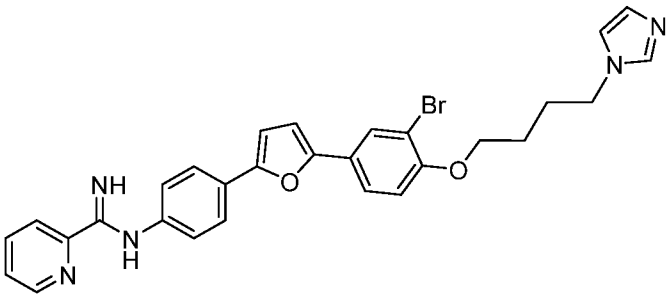
**4e**,



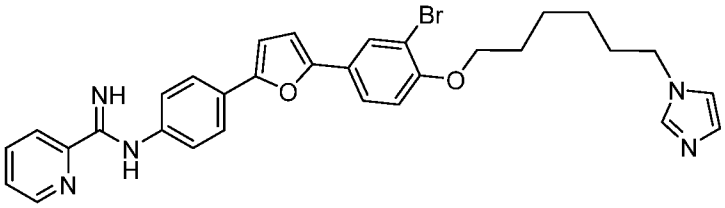
**4f**,



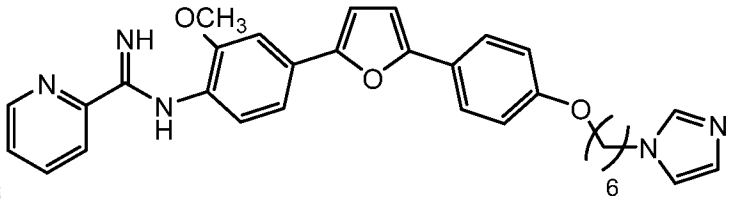
4g ,



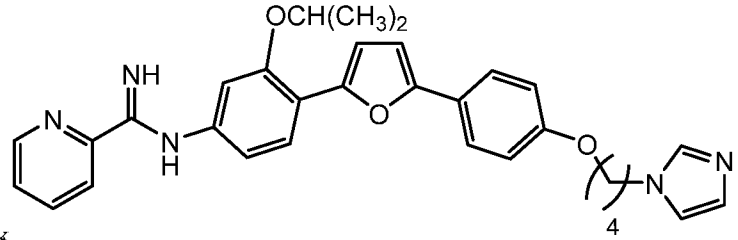
4h ,



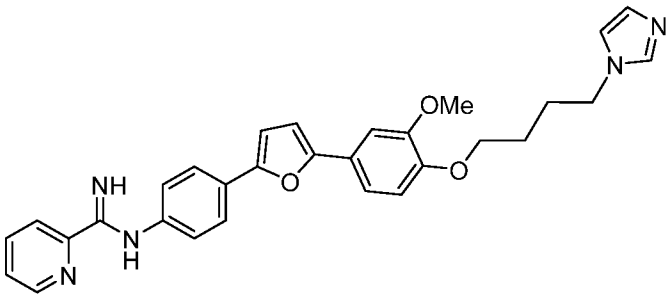
4i ,



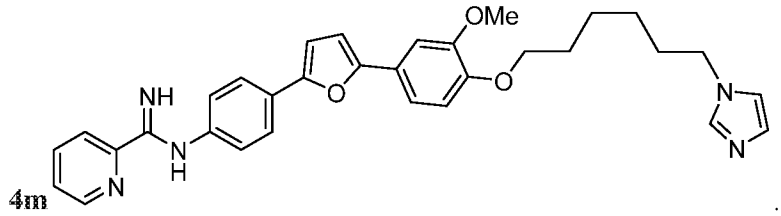
4j ,



4k ,

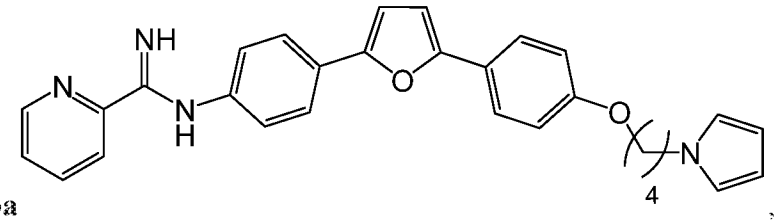


4l , and

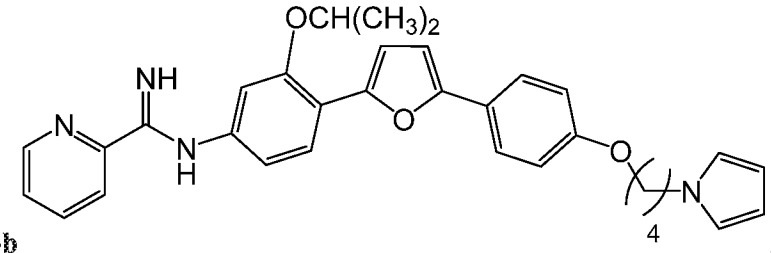



**4m**

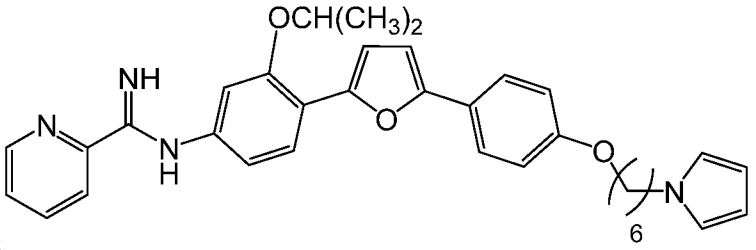
32. The compound of claim 1, wherein the compound is one of Compounds **13a-13c**:




**13a**,

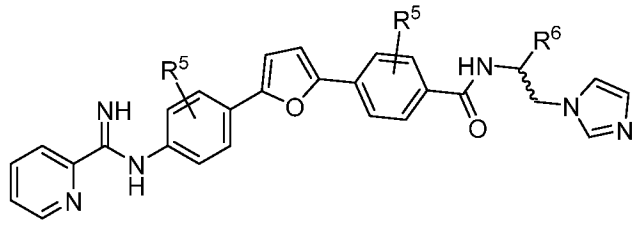



**13b**, and




**13c**.

33. The compound of claim 1, represented by Structural Formula **(VIII)**:



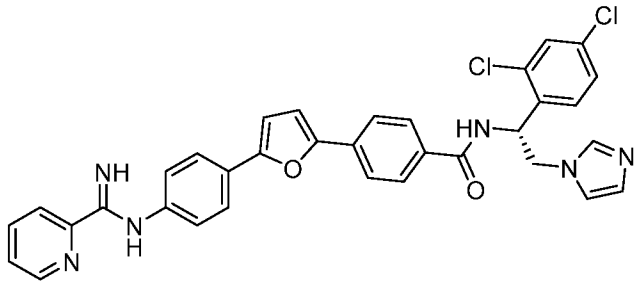

**(VIII)**,

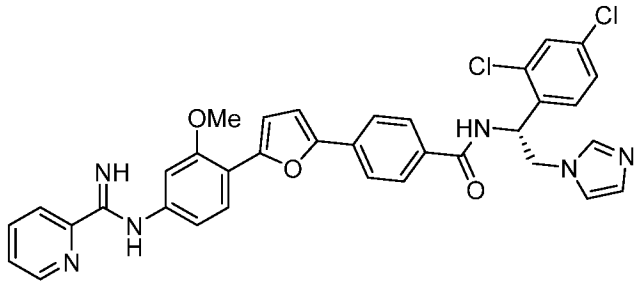
wherein:

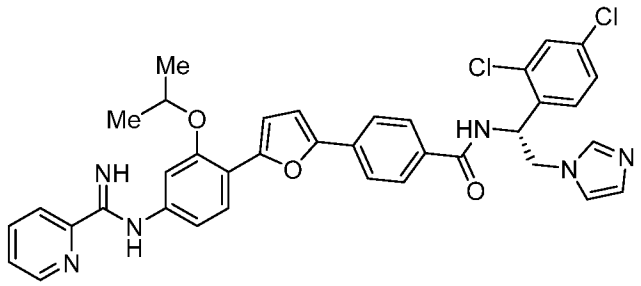
each $\mathbf{R^5}$ is independently H, halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy; and

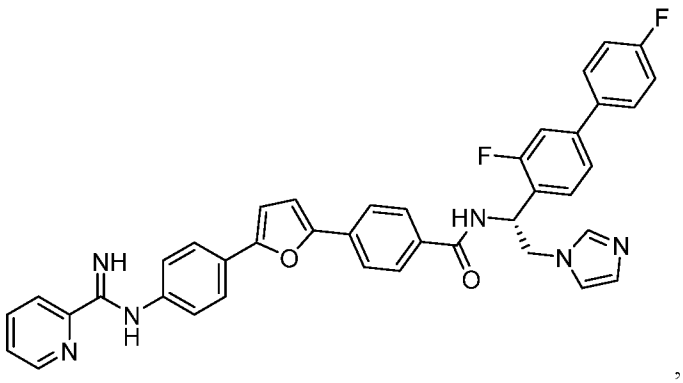
$\mathbf{R^6}$ is H, optionally halogenated $C_1$-$C_6$ alkyl, optionally halogenated phenyl, or optionally halogenated biphenyl.

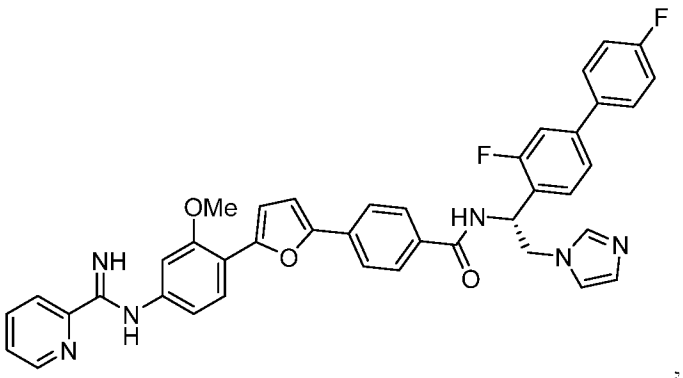
34. The compound of claim 33, wherein the compound is one of Compounds **5a-5f**:

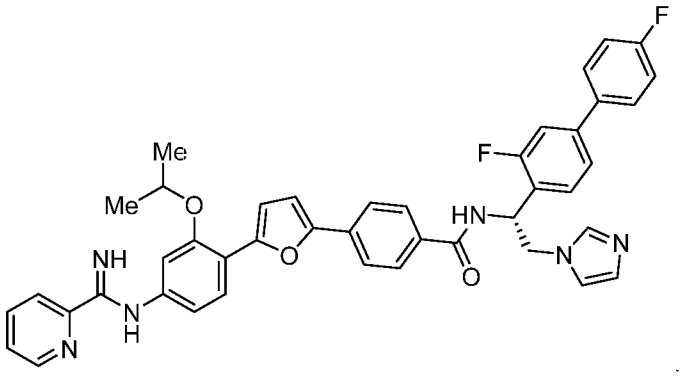
5a  ,

5b  ,

5c  ,

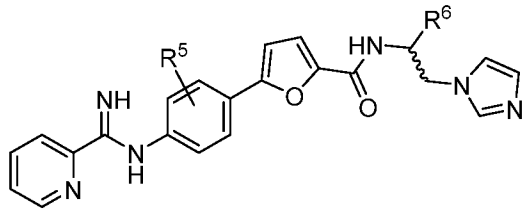
5d  ,

5e  , and



**5f**

35. The compound of claim 1, represented by Structural Formula **(IX)**:



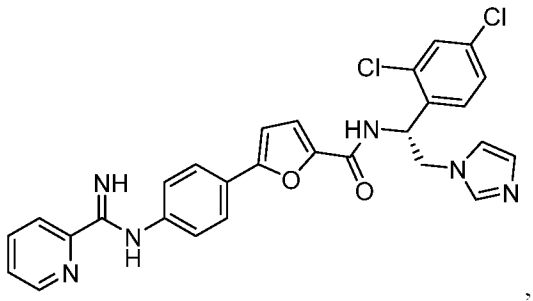
**(IX)**,

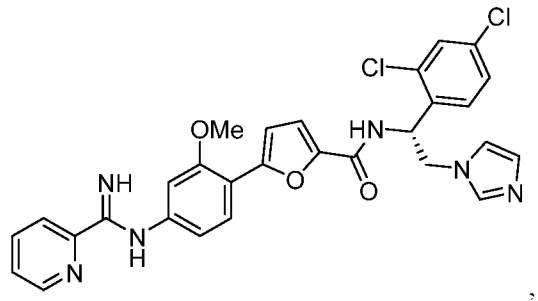
wherein:

each $\mathbf{R^5}$ is independently H, halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy; and

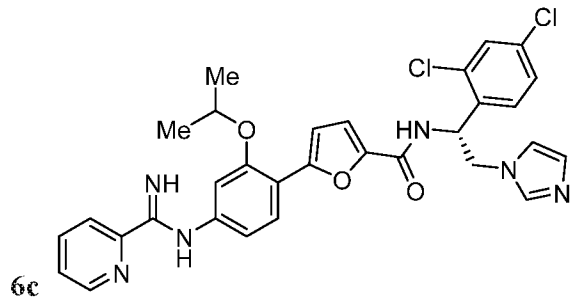
$\mathbf{R^6}$ is H, optionally halogenated $C_1$-$C_6$ alkyl, optionally halogenated phenyl, or optionally halogenated biphenyl.

36. The compound of claim 35, wherein the compound is one of Compounds **6a-6f**:

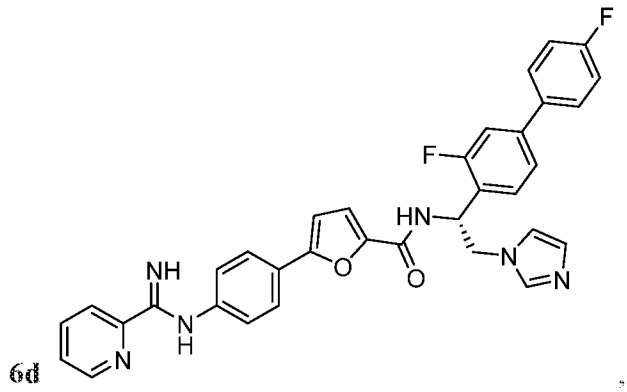


**6a**, 

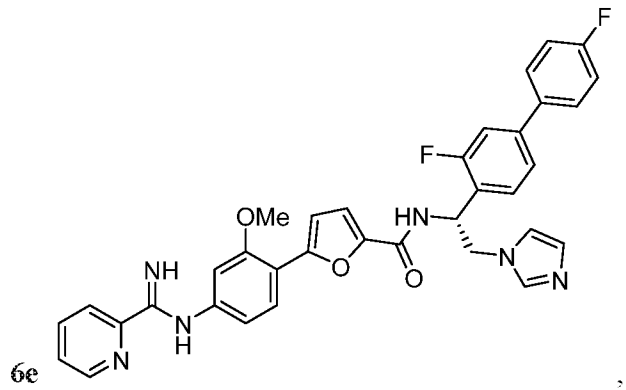
**6b**,



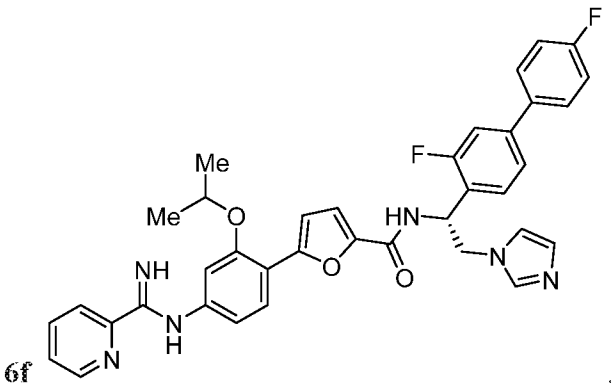
**6c**,



6d ,

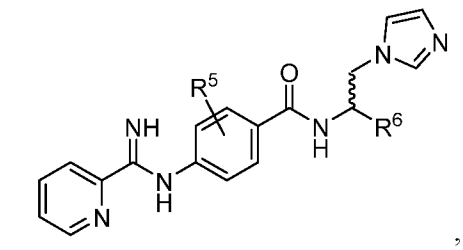


6e , and



6f .

37. The compound of claim 1, represented by Structural Formula (**X**):



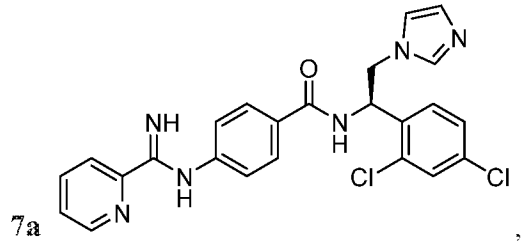
(**X**) ,

wherein:

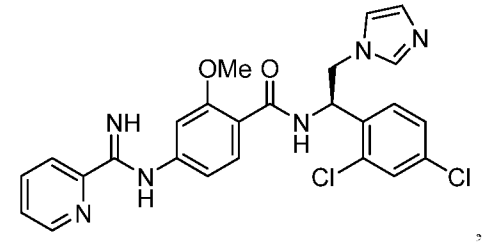
each $\mathbf{R^5}$ is independently H, halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy; and

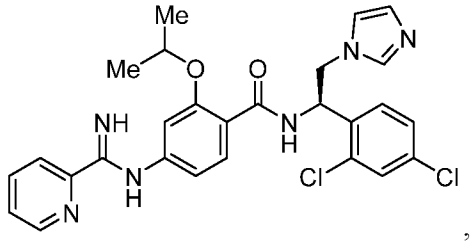
$\mathbf{R^6}$ is H, optionally halogenated $C_1$-$C_6$ alkyl, optionally halogenated phenyl, or optionally halogenated biphenyl.

38. The compound of claim 37, wherein the compound is one of Compounds **7a-7f**:

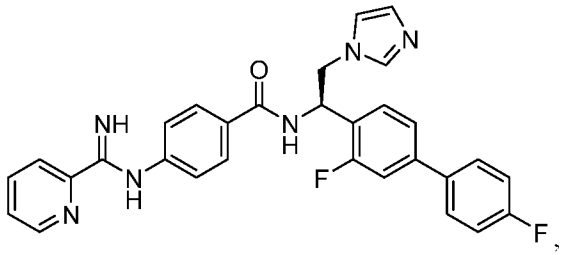

7a

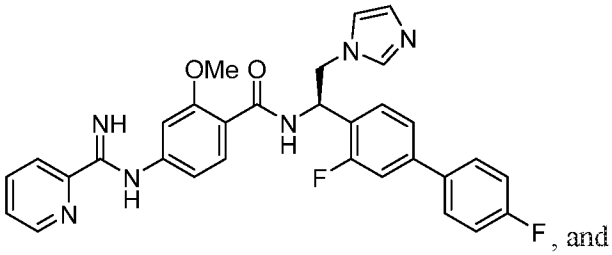
, 7b

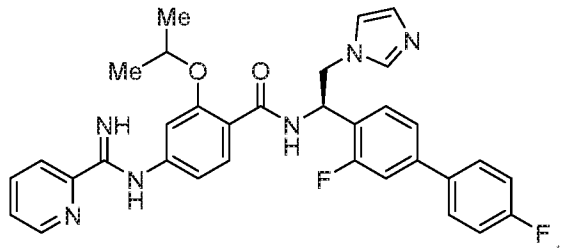

,


7c

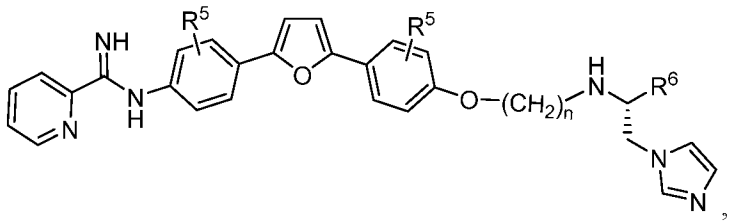
, 7d


,


7e , and


7f .

39. The compound of claim 1, represented by Structural Formula **(XI)**:



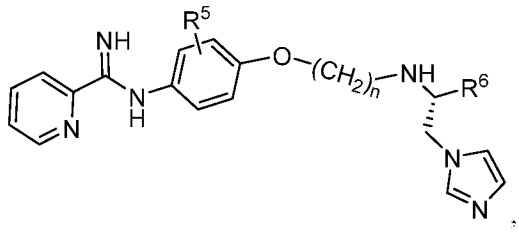
**(XI)**,

wherein:

each $\mathbf{R^5}$ is independently H, halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy; and

$\mathbf{R^6}$ is H, optionally halogenated $C_1$-$C_6$ alkyl, optionally halogenated phenyl, or optionally halogenated biphenyl.

40. The compound of claim 1, represented by Structural Formula **(XII)**:



**(XII)**

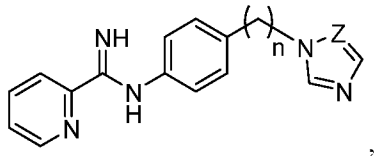
wherein:

each $\mathbf{R^5}$ is independently H, halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy; and

$\mathbf{R^6}$ is H, optionally halogenated $C_1$-$C_6$ alkyl, optionally halogenated phenyl, or optionally halogenated biphenyl.

41. The compound of claim 2, wherein **A** is phenyl and **X** is a bond.

42. The compound of claim 1, represented by Structural Formula **(XIII)**:



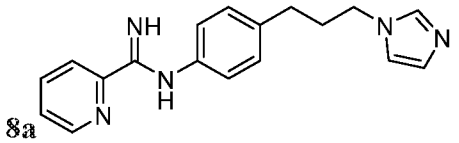
**(XIII)**

wherein:

**Z** = CH or N; and

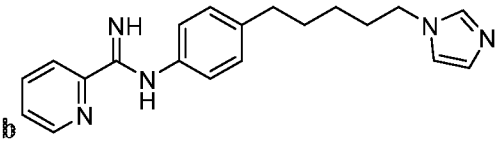
**n** is an integer from 1 to 10.

43. The compound of claim 42, wherein the compound is one of Compounds **8a-8b**:



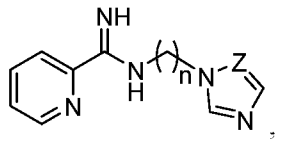
**8a**

and **8b**



44. The compound of claim 2, wherein **A** is a bond.

45. The compound of claim 44, represented by Structural Formula **(XIV)**:



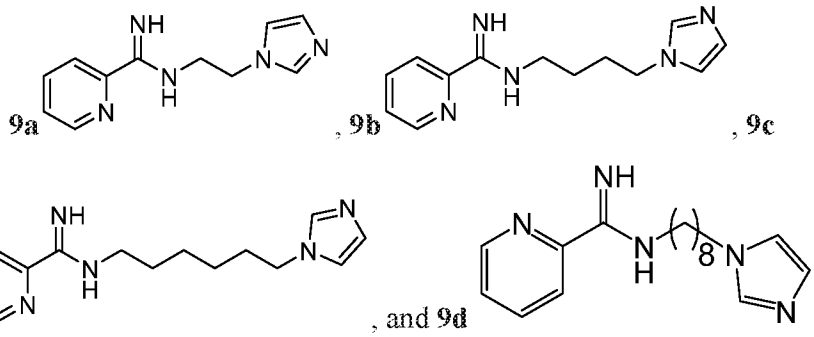
**(XIV)**

wherein:

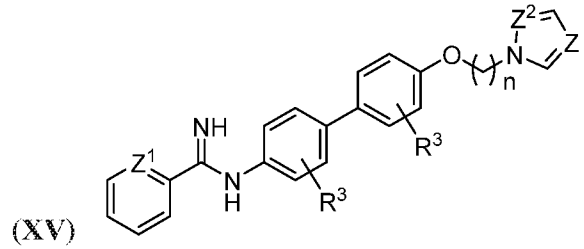
**Z** = CH or N; and

**n** is an integer from 1 to 10.

46. The compound of claim 45, wherein the compound is one of Compounds **9a-9d**:

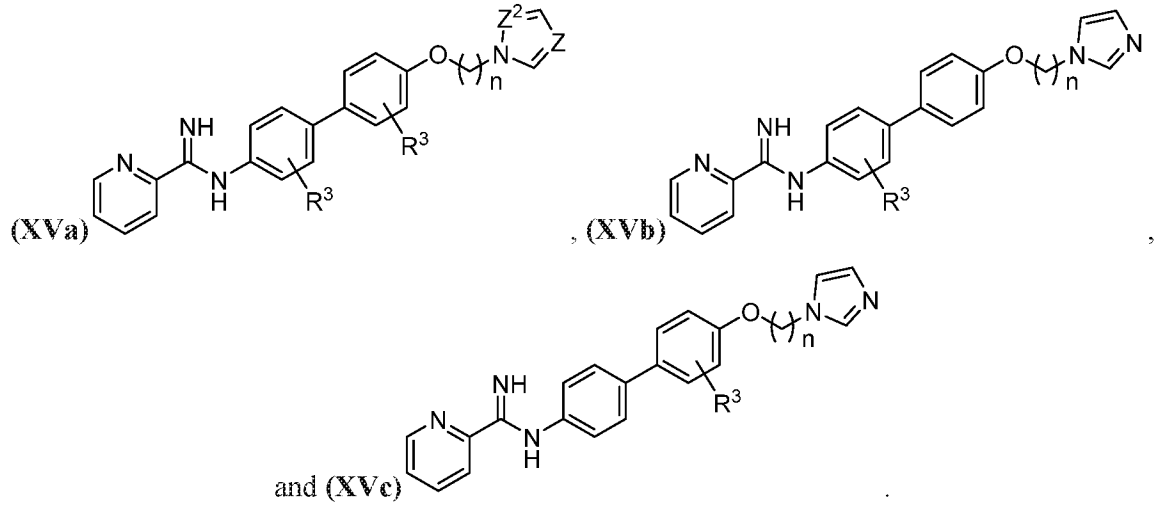



47. The compound of claim 1, represented by Structural Formula **(XV)**:

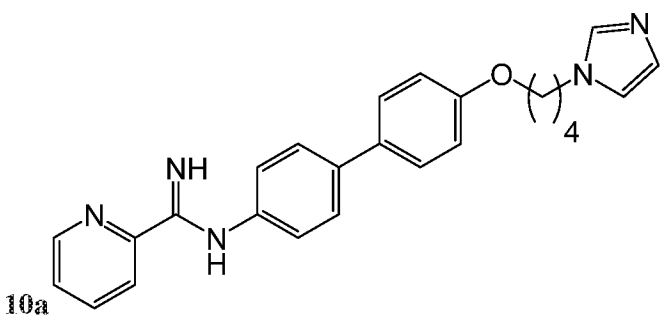


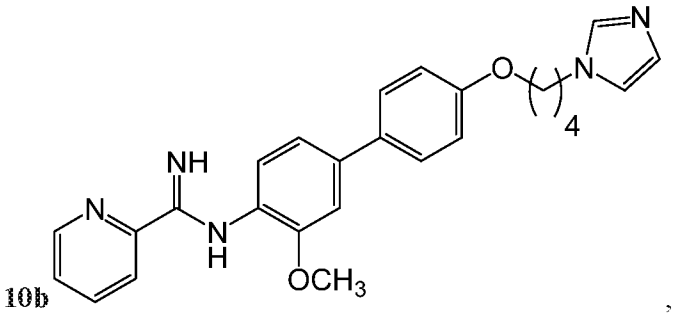

wherein Z, $Z^1$, and $Z^2$ are each independently CH or N, n is 1-14, and $R^3$ is H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy.

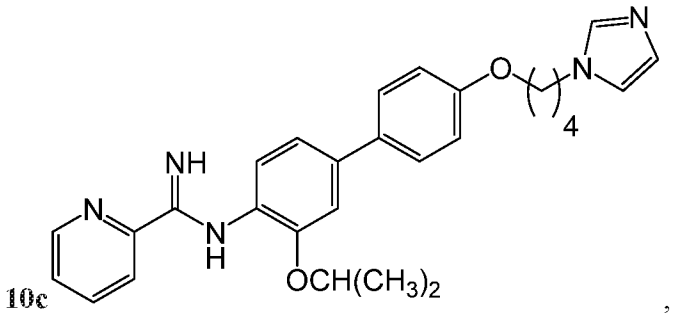
48. The compound of claim 47, represented by one of Structural Formulas **(XVa)-(XVc)**:

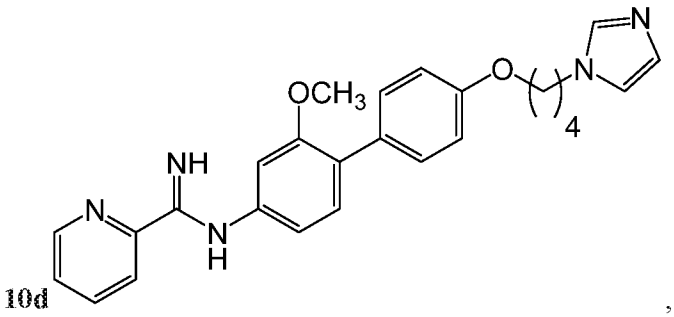


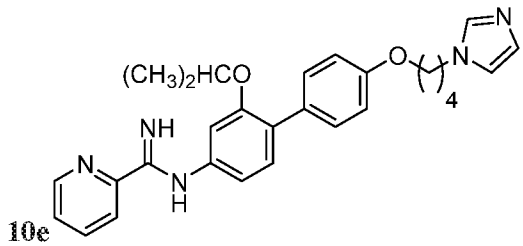

49. The compound of claim 48, wherein the compound is one of Compounds **10a-10m**:

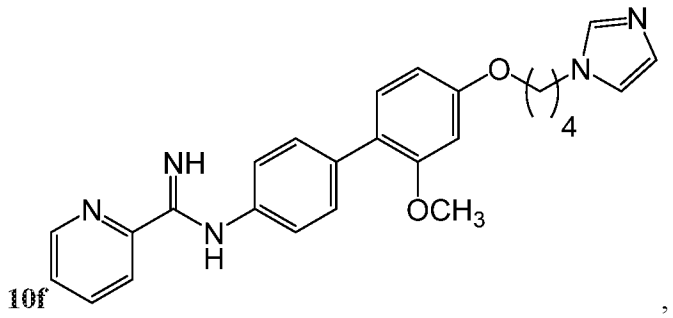


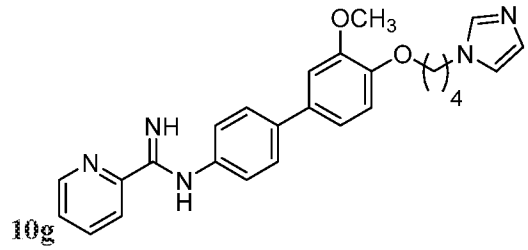

10b ,


10c ,

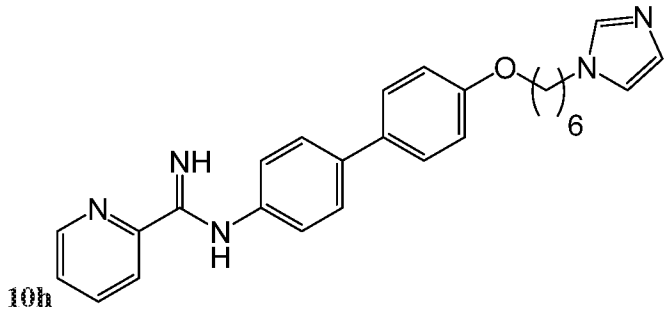

10d ,


10e ,

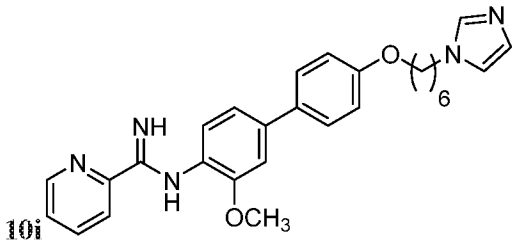

10f ,



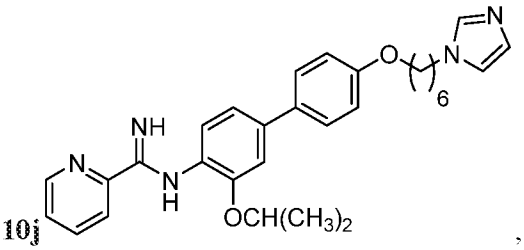
10g ,

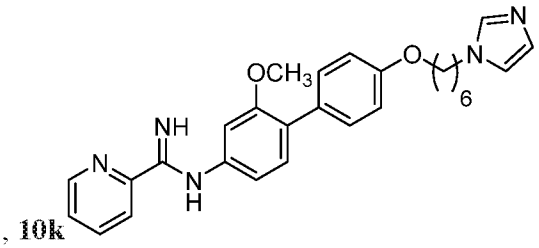


10h ,

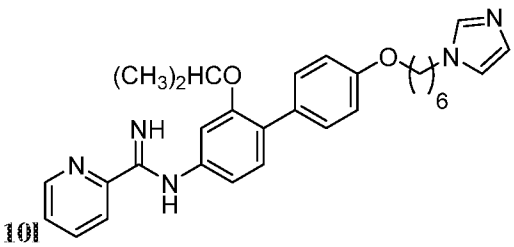


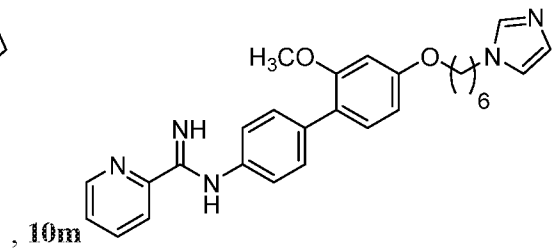
10i ,



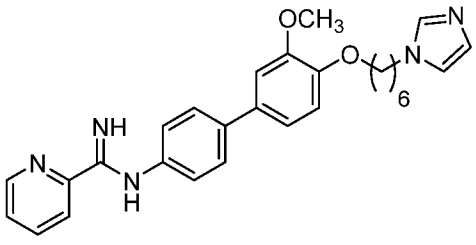
10j , 

10k ,



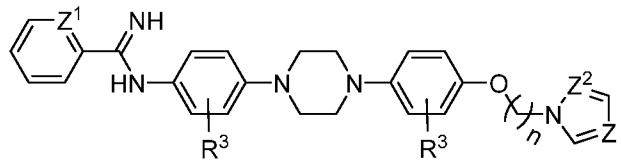
10l , 

10m , and **10n**

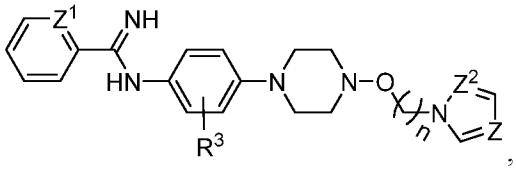


,

50. The compound of claim 1, represented by Structural Formula **(XVI)** and **(XVII)**:



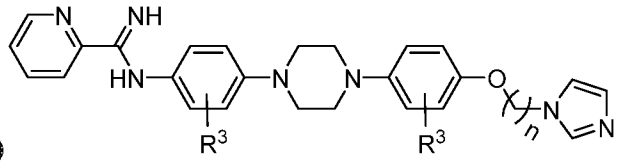
(XIV) and



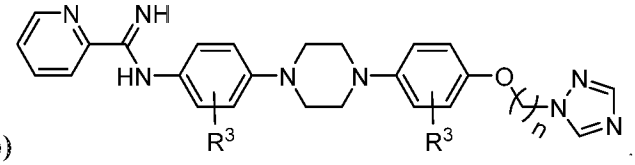
(XVII) ,

wherein Z, $Z^1$, and $Z^2$ are each independently CH or N, n is 1-14, and $R^3$ is H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy.

51. The compound of claim 50, represented by one of Structural Formulas **(XVIa)-(XVIb)**:

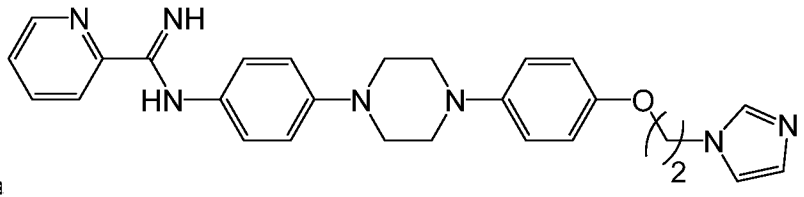


**(XVIa)** , and

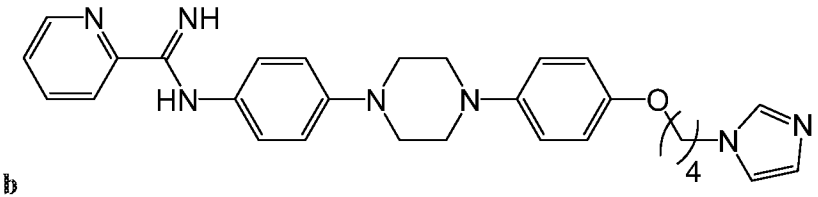


**(XVIb)** .

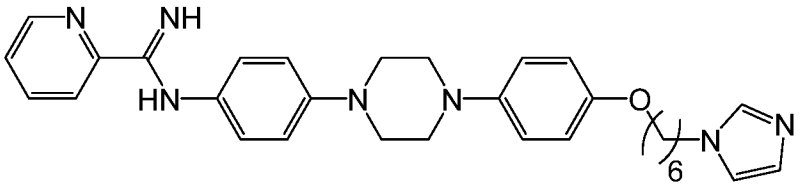
52. The compound of claim 51, wherein the compound is one of Compounds **11a-11d**:



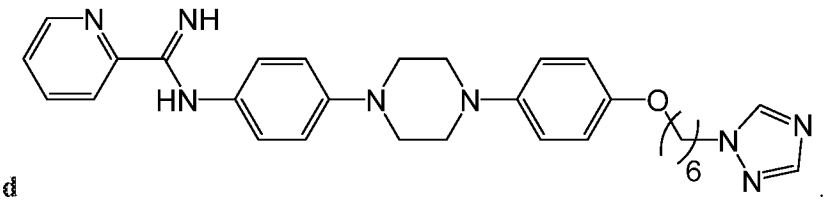
**11a** ,



**11b** ,

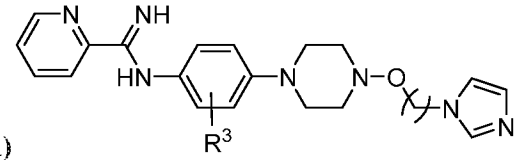


**11c** , and

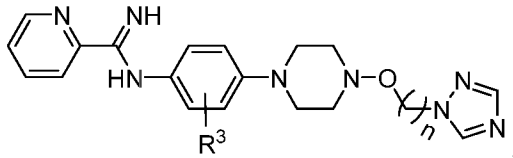


**11d**

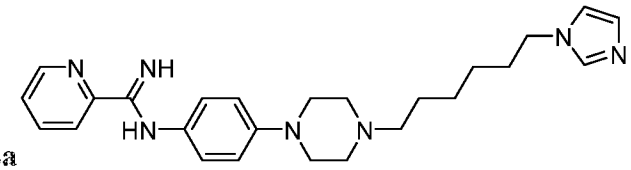
53. The compound of claim 50, represented by one of Structural Formulas **(XVIIa)-(XVIIb)**:



**(XVIIa)** and **(XVIIb)**



54. The compound of claim 53, wherein the compound is Compound **12a**:



**12a**

55. A method of anti-parasitic treatment for a subject in need thereof, comprising:

providing the subject, the subject being infected by a parasite or at risk of infection by the parasite;

administering a compound to the subject in an amount effective to mitigate infection by the parasite in the subject, the compound being represented by Structural Formula **(Ia)**:

**(Ia)** **Ar**—C(=$NR^1$)$NR^2$—**A**—**X**—**Y**—**$Het^2$**

and pharmaceutically acceptable salts thereof, wherein:

**Ar** is an optionally substituted aryl or nitrogen-containing heteroaryl;

$R^1$ and $R^2$ are independently H, optionally substituted $C_1$-$C_6$ alkyl, or optionally substituted $C_3$-$C_6$ cycloalkyl;

**A** is a bond or an optionally substituted linking moiety comprising 1, 2, or 3 rings, each ring in the optionally substituted linking moiety independently being one of: aryl, cycloalkyl, heterocycloalkyl, and heteroaryl;

**X** is O, S, amide, or a bond;

**Y** is optionally substituted $C_1$-$C_{14}$ alkyl or optionally substituted $C_2$-$C_{14}$ alkenyl; and

**$Het^2$** is an optionally substituted five-membered nitrogen-containing heteroaromatic ring comprising 1, 2, or 3 ring heteroatoms.

56. The method of claim 55, comprising:

providing the subject, the subject being infected by the parasite or at risk of infection by the parasite;

administering the compound to the subject in an amount effective to mitigate infection by the parasite in the subject, the compound being represented by Structural Formula **(I)**:

**(I)** $\mathbf{Het^1}$—$C(=NR^1)NR^2$—**A**—**X**—**Y**—$\mathbf{Het^2}$

and pharmaceutically acceptable salts thereof, wherein:

$\mathbf{Het^1}$ is an optionally substituted, nitrogen-containing heteroaryl;

$R^1$ and $R^2$ are independently H, optionally substituted $C_1$-$C_6$ alkyl, or optionally substituted $C_3$-$C_6$ cycloalkyl;

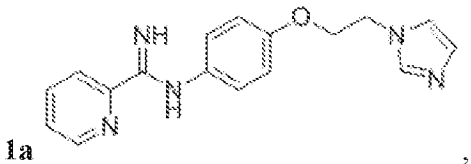
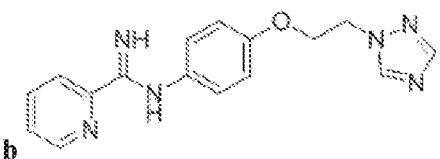
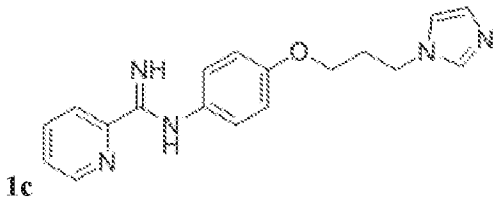
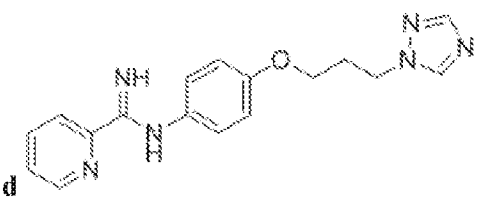
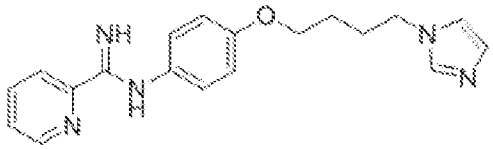
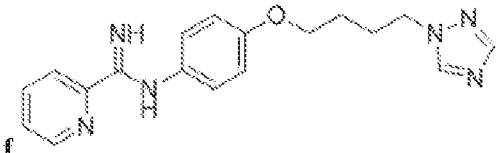
**A** is a bond or an optionally substituted linking moiety comprising 1, 2, or 3 rings, each ring in the optionally substituted linking moiety independently being one of: aryl, cycloalkyl, heterocycloalkyl, and heteroaryl;

**X** is O, S, amide, or a bond;

**Y** is optionally substituted $C_1$-$C_{10}$ alkyl or optionally substituted $C_2$-$C_{10}$ alkenyl; and

$\mathbf{Het^2}$ is an optionally substituted five-membered nitrogen-containing heteroaromatic ring comprising 1, 2, or 3 ring heteroatoms.

57. The method of claim 55, provided that when the parasite is *L. amazonensis*, the compound represented by Structural Formula **(Ia)** is not one of free-base Compounds **1a-f**:


**1a**, 
**1b**, 
**1c**, 
**1d**, 
**1e**, and 
**1f**.

58. The method of claim 55, the subject being infected by the parasite, the method comprising administering the compound to the subject in an amount effective to mitigate one or more symptoms of infection by the parasite in the subject.

59. The method of claim 55, the subject being at risk of infection by the parasite, the method comprising administering the compound to the subject in an amount effective to mitigate infection or re-infection of the subject by the parasite.

60. The method of claim 55, the parasite being a kinetoplastid.

61. The method of claim 60, the parasite comprising at least two distinct cytochrome P450 mediated biosterol synthesis pathways.

62. The method of claim 61, the parasite comprising CYP5122A.

63. The method of claim 61, the parasite comprising CYP51 and CYP5122A.

64. The method of claim 55, the parasite belonging to the genus *Leishmania*.

65. The method of claim 63, the *Leishmania* parasite being one of: *L. aethiopica*, *L. amazonensis*, *L. arabica*, *L. archibaldi*, *L. aristedesi*, *L. Viannia*, *L. braziliensis*, *L. chagasi*, *L. colombiensis*, *L. deanei*, *L. donovani*, *L. enriettii*, *L. equatorensis*, *L. forattinii*, *L. garnhami*, *L. gerbili*, *L. guyanensis*, *L. herreri*, *L. hertigi*, *L. infantum*, *L. killicki*, *L. lainsoni*, *L. major*, *L. mexicana*, *L. naiffi*, *L. panamensis*, *L. peruviana*, *L. pifanoi*, *L. shawi*, *L. tarentolae*, *L. tropica*, *L. turanica*, and *L. venezuelensis*.

66. The method of claim 63, wherein the subject suffers from or is at risk of suffering from one or more of: cutaneous leishmaniasis, mucocutaneous leishmaniasis, and visceral leishmaniasis.

67. The method of claim 55, the parasite being of the genus *Trypanosoma*.

68. The method of claim 67, wherein the *Trypanosoma* parasite is one of: *T. ambystomae*, *T. avium*, *T. boissoni*, *T. brucei*, *T. cruzi*, *T. congolense*, *T. equinum*, *T. equiperdum*, *T. evansi*, *T. everetti*, *T. hosei*, *T. irwini*, *T. lewisi*, *T. melophagium*, *T. paddae*, *T. parroti*, *T. percae*, *T. rangeli*, *T. rotatorium*, *T. rugosae*, *T. sergenti*, *T. simiae*, *T. sinipercae*, *T. suis*, *T. theileri*, *T. triglae*, and *T. vivax*.

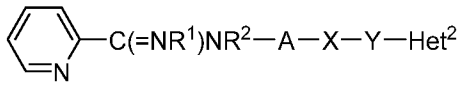
69. The method of claim 67, wherein the subject suffers from or is at risk of suffering from: African trypanosomosis, sleeping sickness, Chagas disease, nagana, and surra.

70. The method of claim 55, wherein the subject is a human, dog, cat, cow, horse, sheep, pig, bird, amphibian, or fish.

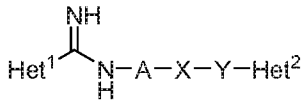
71. The method of claim 56, wherein **Het$^1$** is optionally substituted pyridyl, pyrazinyl, pyrimidinyl, or pyridizinyl.

72. The method of claim 56, wherein **Het$^1$** is optionally substituted pyridyl.

73. The method of claim 55, wherein the compound is represented by Structural Formula **(II)**:

(II) 

74. The method of claim 55, wherein the compound is represented by Structural Formula **(III)**:

(III) 

75. The method of claim 55, wherein each ring in the optionally substituted linking moiety represented by **A** is independently and optionally substituted by one or more of: hydroxy, halo, and $C_1$-$C_6$ alkoxy.

76. The method of claim 55, wherein **A** comprises an optionally substituted heteroaryl or optionally substituted heterocycloalkyl ring.

77. The method of claim 55, wherein **A** comprises an optionally substituted, oxygen-containing, heteroaryl or heterocycloalkyl ring.

78. The method of claim 55, wherein **A** comprises an optionally substituted furanyl or optionally substituted tetrahydrofuranyl ring.

79. The method of claim 55, wherein **A** comprises optionally substituted 2,5-furanyl.

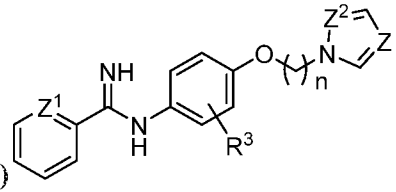
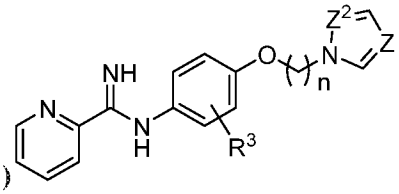
80. The method of claim 55, wherein **A** comprises one or two optionally substituted phenyl rings.

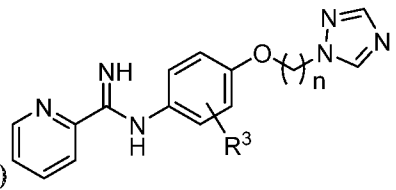
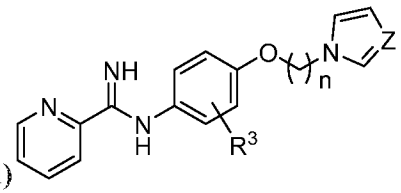
81. The method of claim 55, wherein **A** comprises optionally substituted 1,4-phenyl.

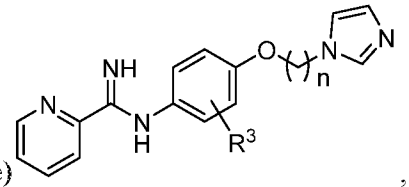
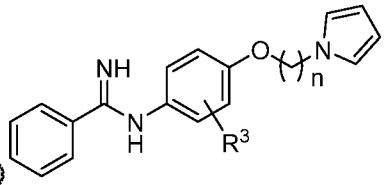
82. The method of claim 55, wherein **A** is optionally substituted 1,4-phenyl.

83. The method of claim 55, wherein **A** is optionally substituted phenyl-heteroaryl-phenyl.

84. The method of claim 55, wherein the compound is represented by one of Structural Formulas **(IIIa)**-**(IIIf)**:

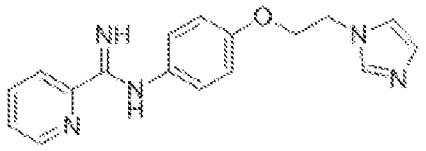
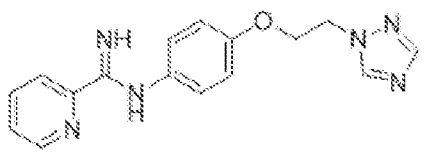
**(IIIa)**  , **(IIIb)**  ,

**(IIIc)**  , **(IIId)**  ,


(IIIe) , and (IIIf) 
,

wherein Z, $Z^1$, and $Z^2$ are each independently CH or N, n is 1-14, and $R^3$ is H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy.

85. The method of claim 84, wherein the compound is one of Compounds **1a-1v**:


**1a** , **1b** 
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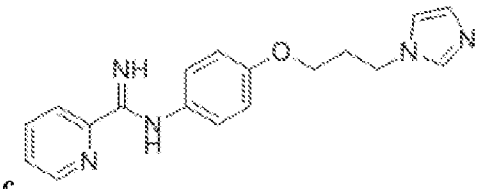
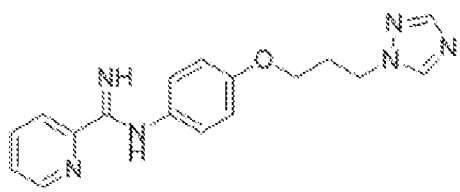

**1c** , **1d** 
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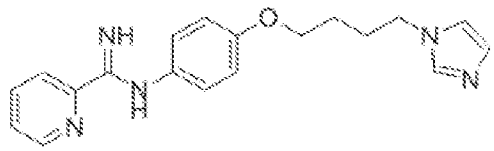
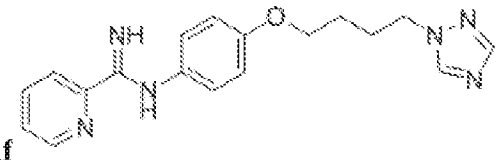

**1e** , **1f** 
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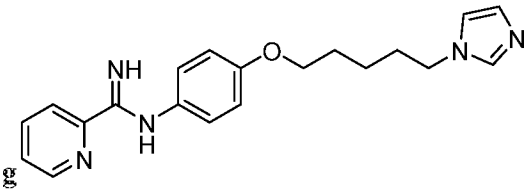
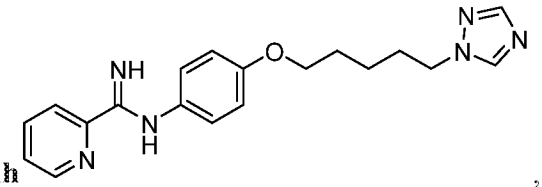

**1g** , **1h** 
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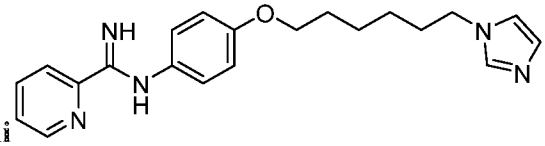
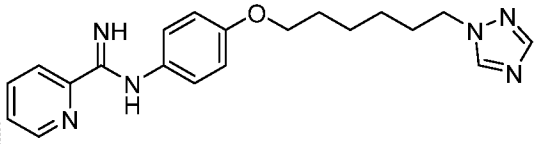

**1i** , **1j** 
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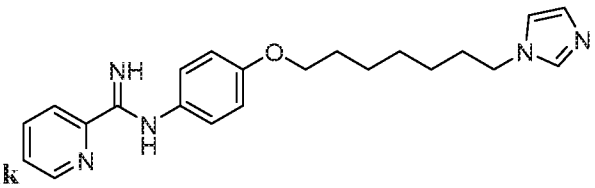
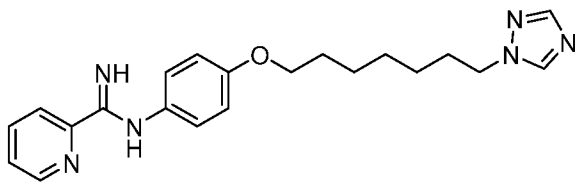

**1k** , **1l**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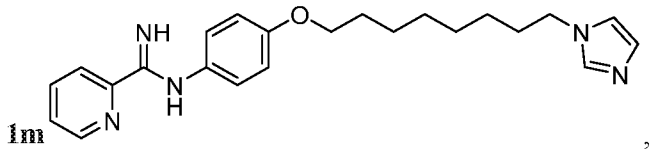
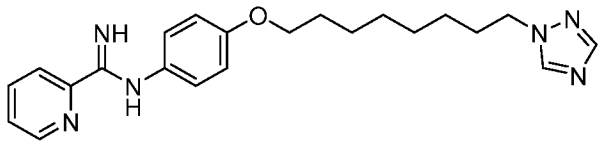
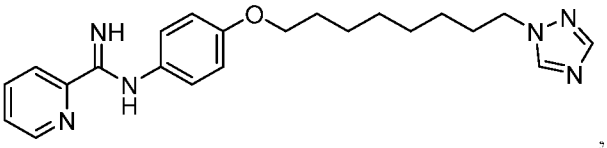



**1m**, **1n**

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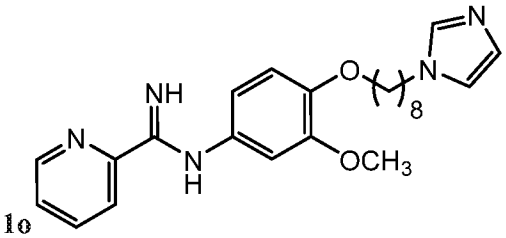
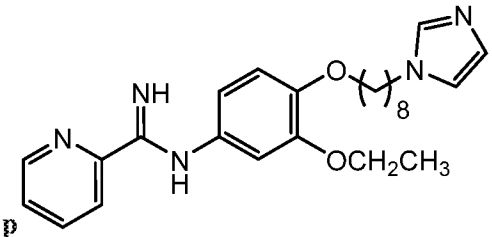



**1o**, **1p**

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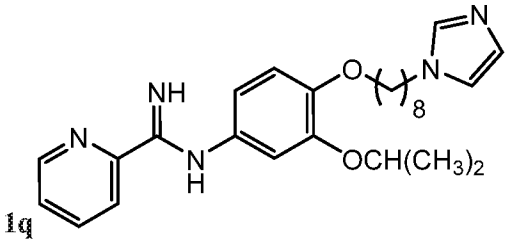
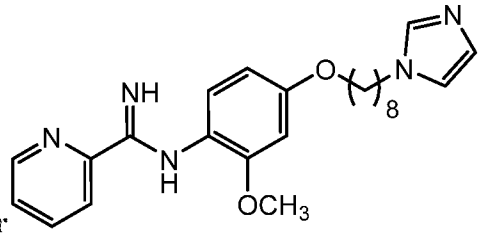



**1q**, **1r**

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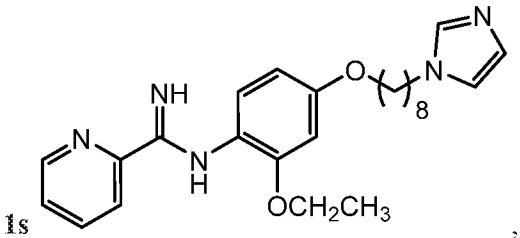
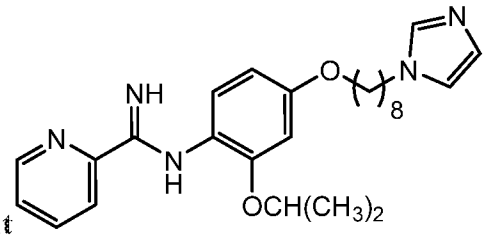



**1s**, **1t**

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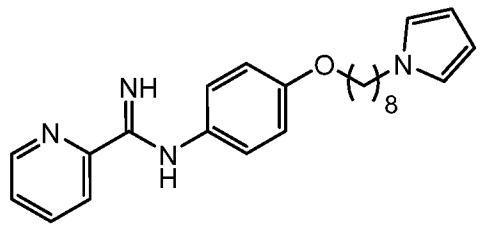
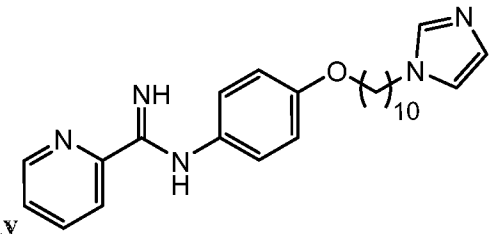
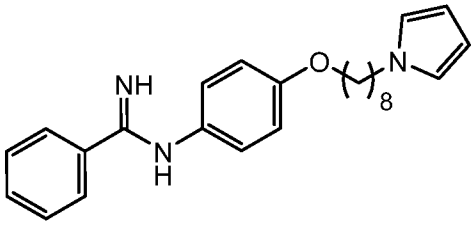



**1u**



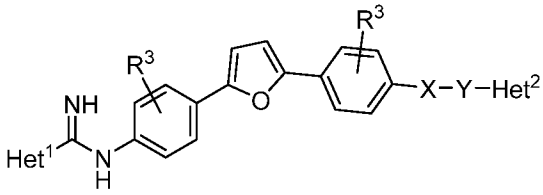

, and **1v**.

86. The method of claim 84, wherein the compound is Compound **14a**:



14a

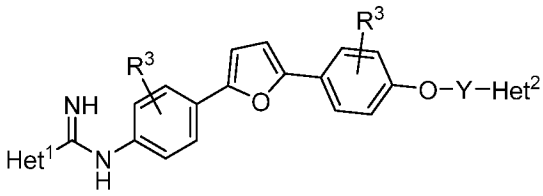
87. The method of claim 55, wherein the compound is represented by Structural Formula **(IV)**:



**(IV)**,

wherein each $\mathbf{R^3}$ is independently H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy.

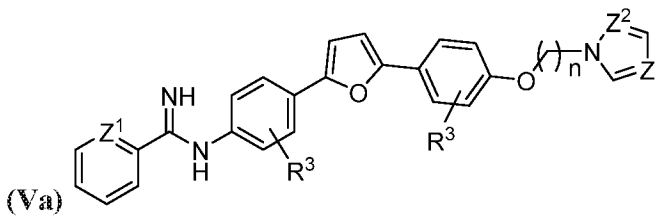
88. The method of claim 55, wherein the compound is represented by Structural Formula **(V)**:



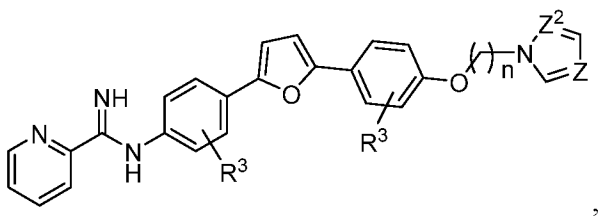
**(V)**,

wherein each $\mathbf{R^3}$ is independently H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy.

89. The method of claim 55, wherein the compound is represented by one of Structural Formulas **(Va)-(Ve)**:



**(Va)**, **(Vb)**



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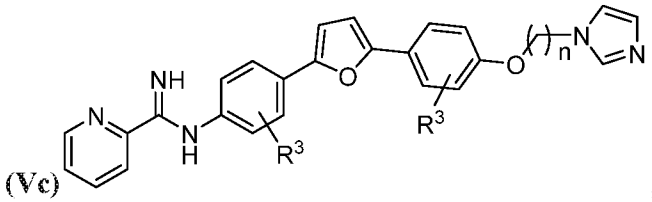
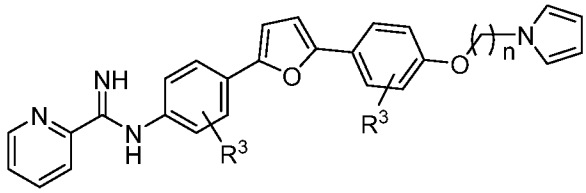
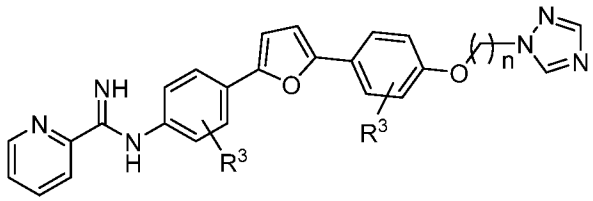


**(Vc)** , **(Vd)**



, and **(Ve)**



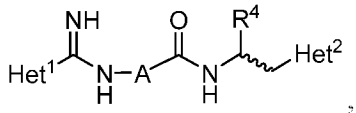
,

wherein Z, $Z^1$, and $Z^2$ are each independently CH or N, n is 1-14, and $R^3$ is H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy.

90. The compound of claim 1, wherein **Y** comprises at least 4 linking atoms between **X** and **Het$^2$**.

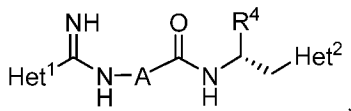
91. The method of claim 55, wherein **X** is O or a bond and **Y** is $C_1$-$C_{12}$ alkyl optionally substituted with one or more of: optionally halogenated $C_1$-$C_8$ alkyl and optionally halogenated aryl.

92. The method of claim 55, wherein the compound is represented by Structural Formula **(VIa)**:

**(VIa)**  ,

wherein **$R^4$** is H, optionally halogenated $C_1$-$C_8$ alkyl, or optionally halogenated aryl.

93. The method of claim 55, wherein the compound is represented by Structural Formula **(VIb)**:

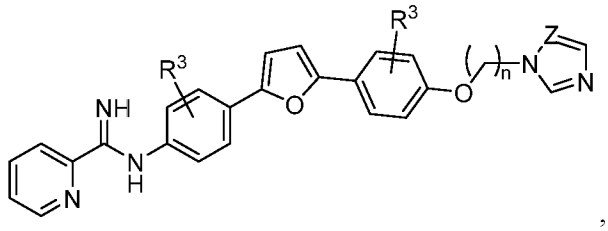
**(VIb)**  ,

wherein **$R^4$** is H, optionally halogenated $C_1$-$C_8$ alkyl, or optionally halogenated aryl.

94. The method of claim 56, wherein **Het$^2$** comprises an optionally substituted one of: pyrrole, diazole, thiadiazole, oxadiazole, and triazole.

95. The method of claim 56, wherein **Het**$^2$ is optionally substituted imidazole or optionally substituted 1, 2, 4 triazole.

96. The method of claim 55, wherein the compound is represented by Structural Formula **(VII)**:

**(VII)** 

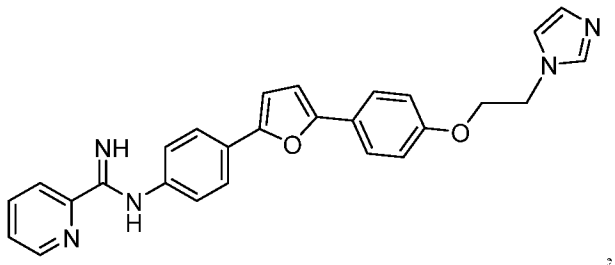
wherein:

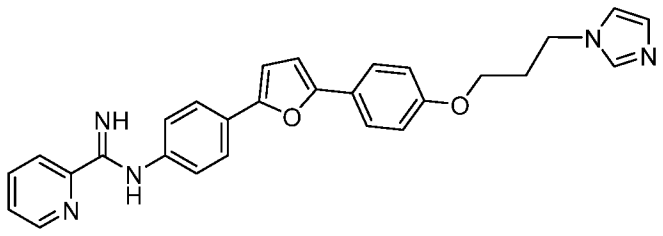
**Z** = CH or N;

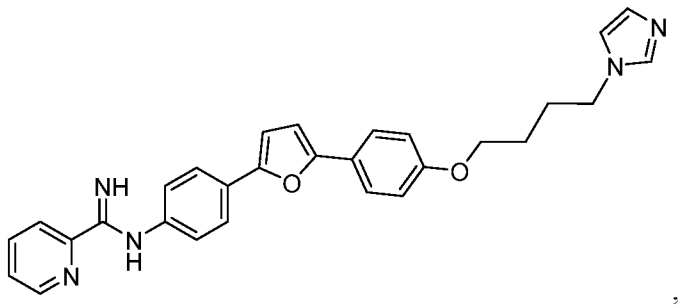
each **R**$^3$ is independently H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy; and

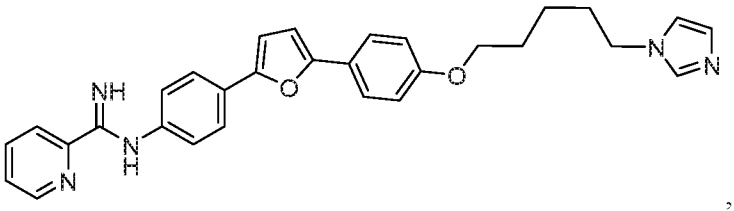
**n** is an integer from 1 to 10.

97. The method of claim 96, wherein the compound is one of Compounds **2a-2h**:

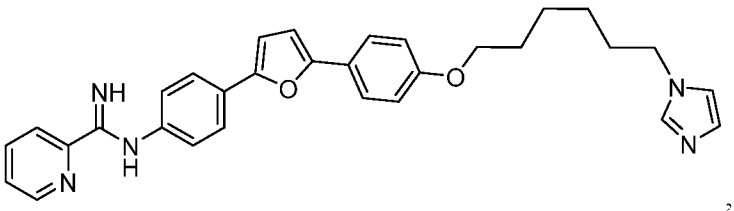
**2a** 

**2b** 

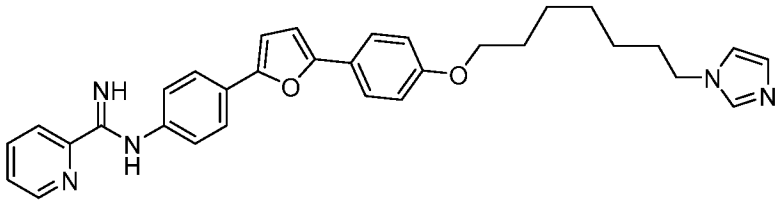
**2c** 



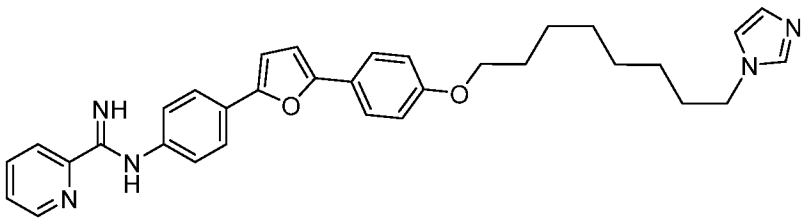
**2d** ,



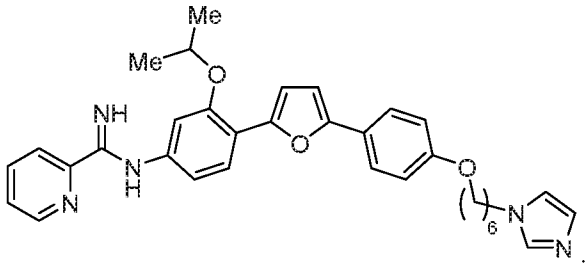
**2e** ,



**2f** ,

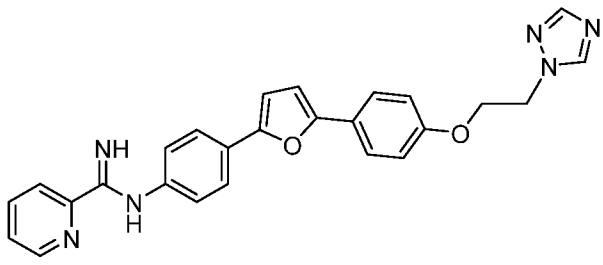


**2g** ; and

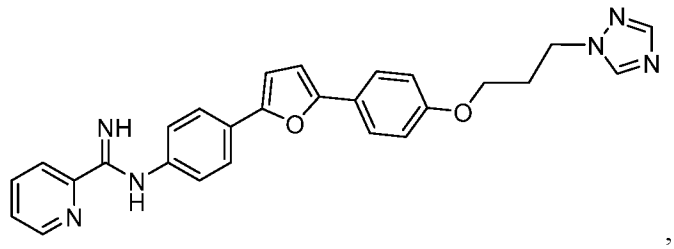


**2h** .

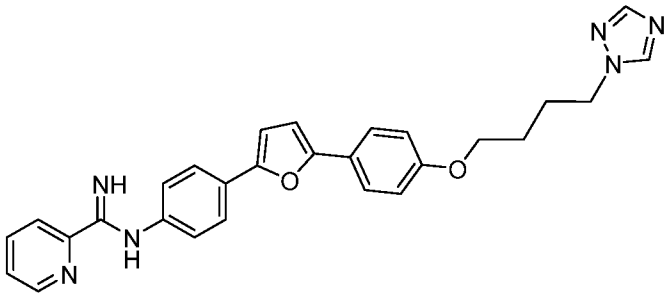
98. The method of claim 96, wherein the compound is one of Compounds **3a-3g**:



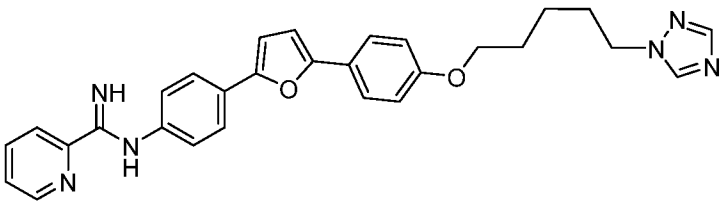
**3a** ,



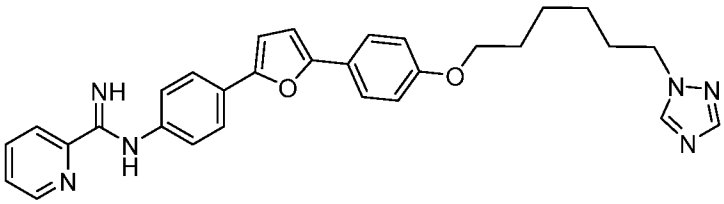
3b ,



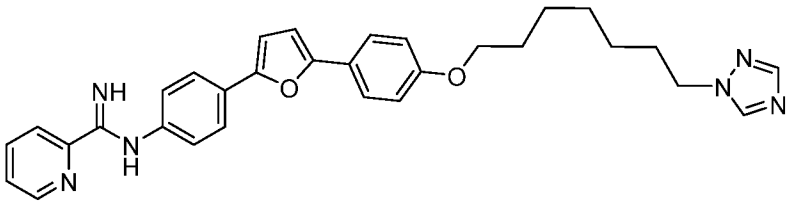
3c ,



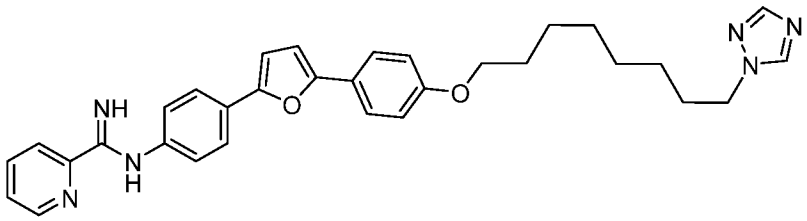
3d ,



3e ,

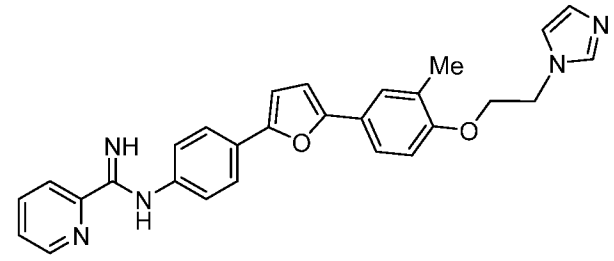


3f , and

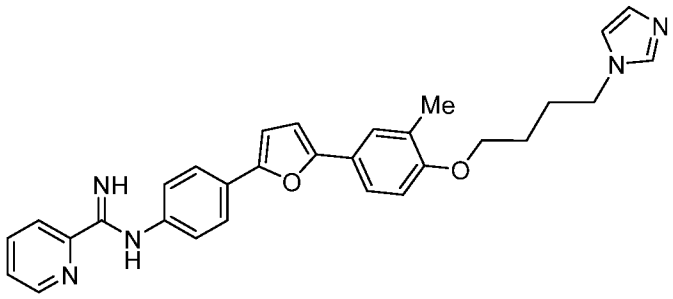


3g .

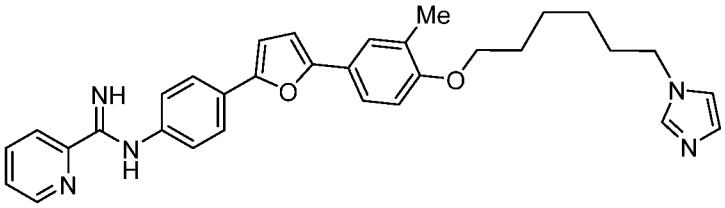
99. The method of claim 96, wherein the compound is one of Compounds **4a-4m**:



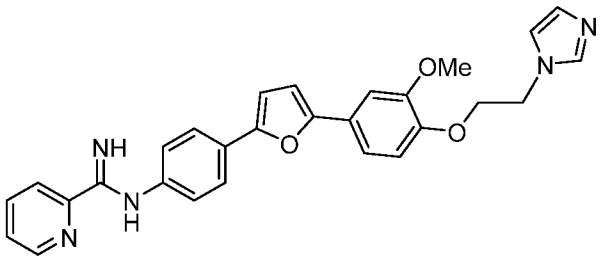
4a ,



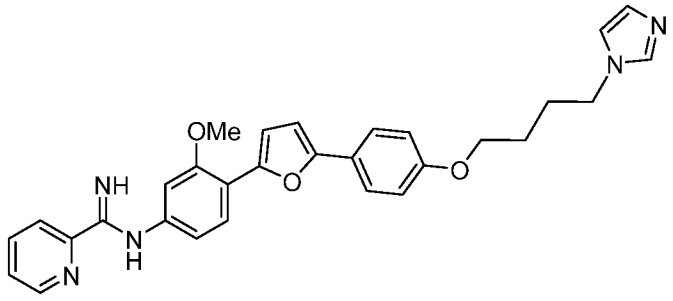
4b ,



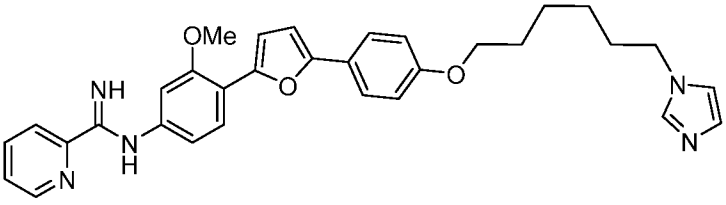
4c ,



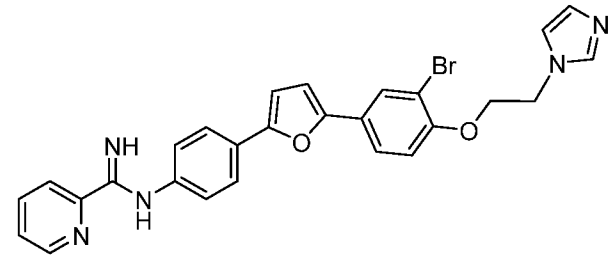
4d ,



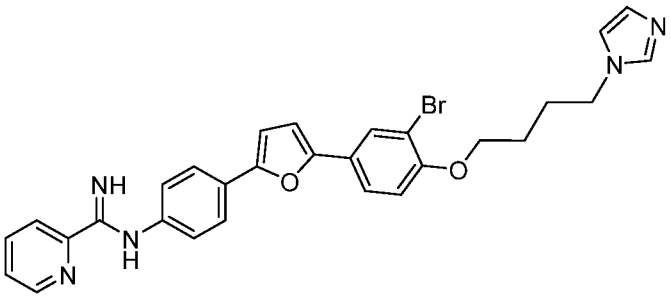
4e ,



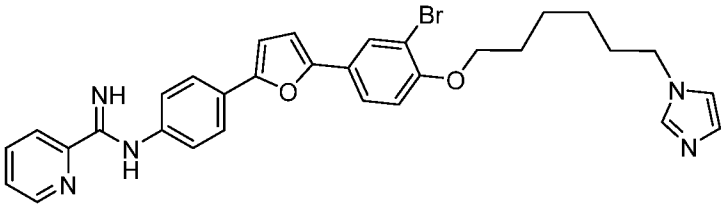
4f ,



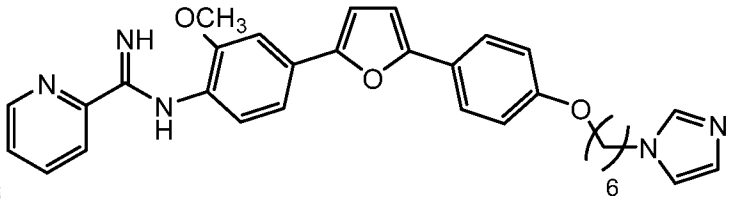
4g ,



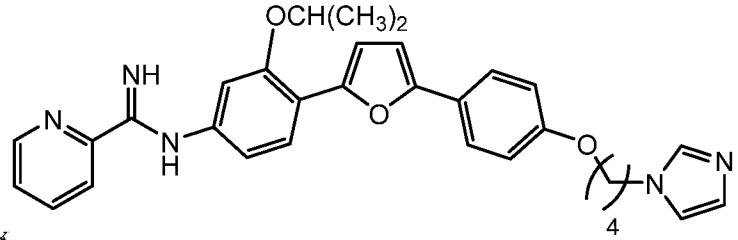
4h ,



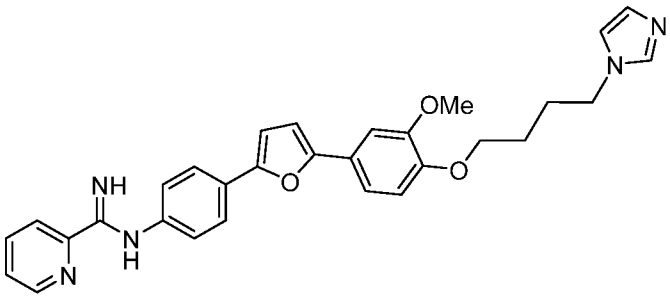
4i ,



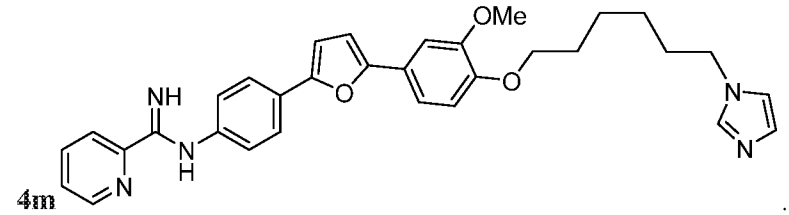
4j ,



4k ,

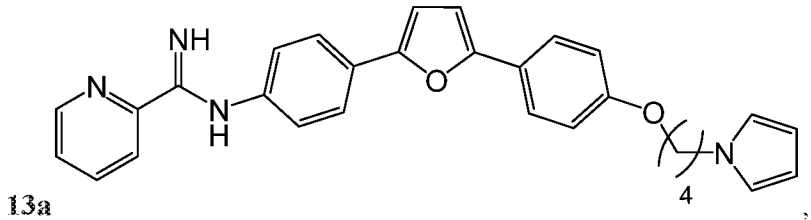


4l , and

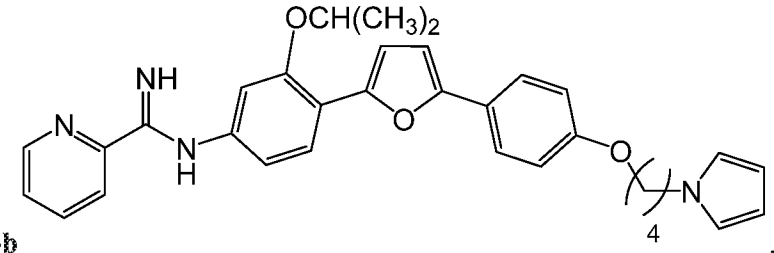



4m

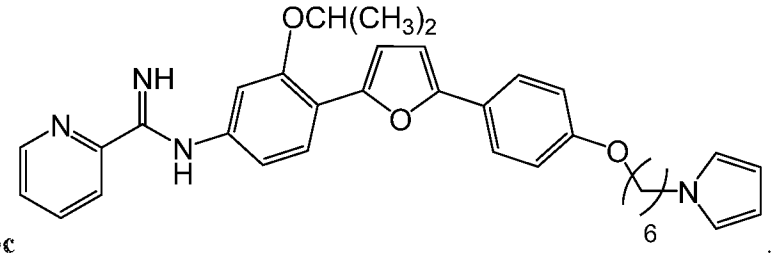
100. The method of claim 55, wherein the compound is one of Compounds **13a-13c**:




**13a**,

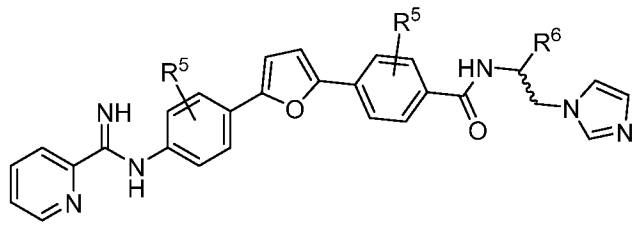



**13b**, and




**13c**.

101. The method of claim 55, wherein the compound is represented by Structural Formula **(VIII)**:



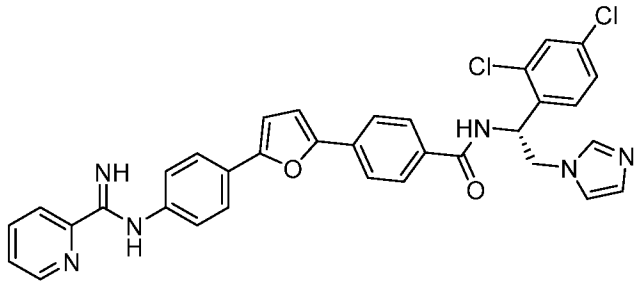

**(VIII)**,

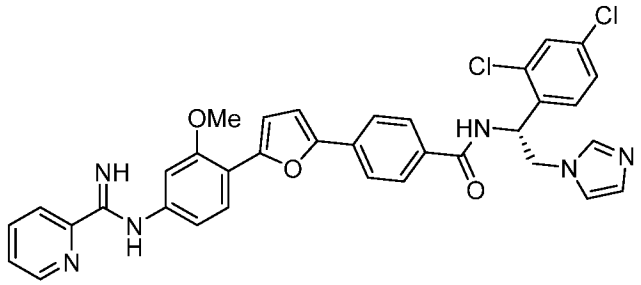
wherein:

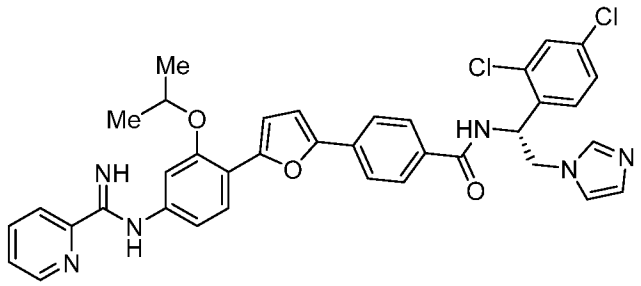
each $\mathbf{R^5}$ is independently H, halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy; and

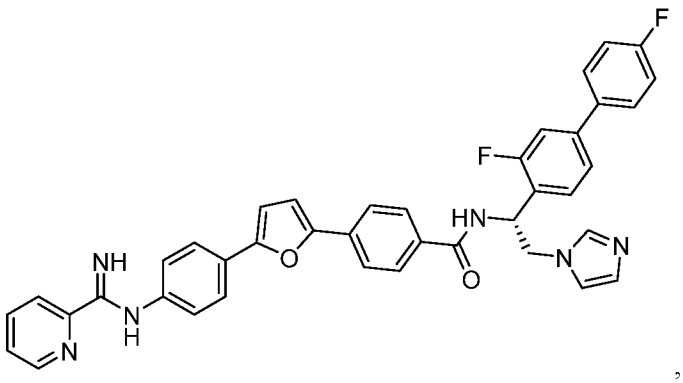
$\mathbf{R^6}$ is H, optionally halogenated $C_1$-$C_6$ alkyl, optionally halogenated phenyl, or optionally halogenated biphenyl.

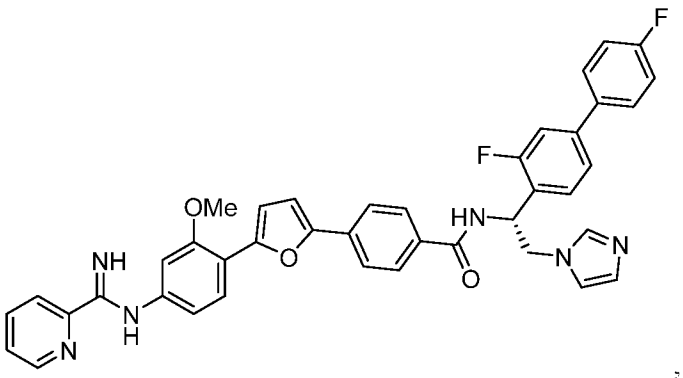
102. The method of claim 101, wherein the compound is one of Compounds **5a-5f**:

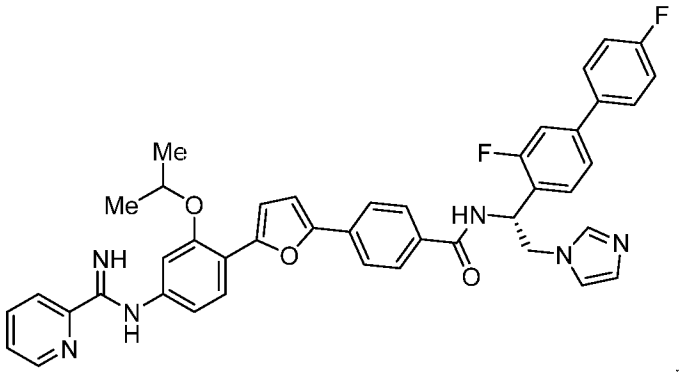
5a  ,

5b  ,

5c  ,

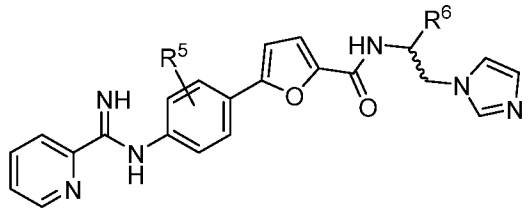
5d  ,

5e  , and



5f

103. The method of claim 55, wherein the compound is represented by Structural Formula **(IX)**:



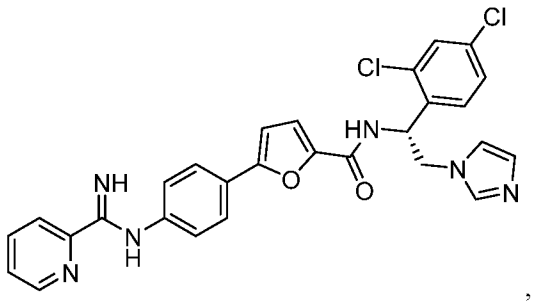
**(IX)**,

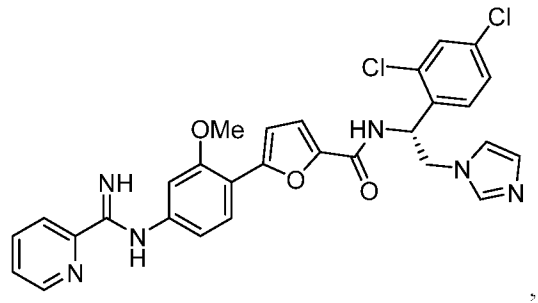
wherein:

each $\mathbf{R^5}$ is independently H, halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy; and

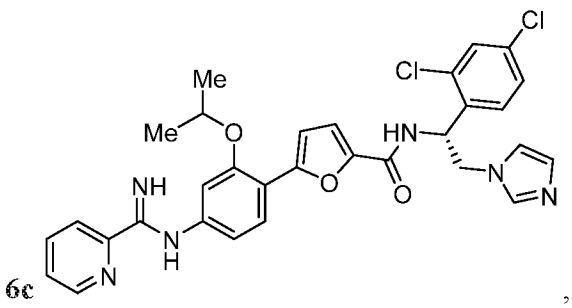
$\mathbf{R^6}$ is H, optionally halogenated $C_1$-$C_6$ alkyl, optionally halogenated phenyl, or optionally halogenated biphenyl.

104. The method of claim 103, wherein the compound is one of Compounds **6a-6f**:

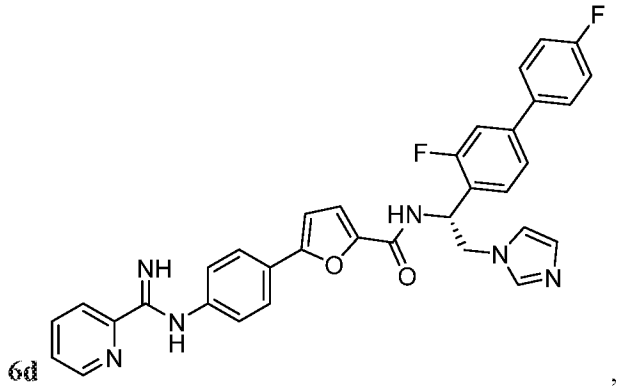


**6a**, 

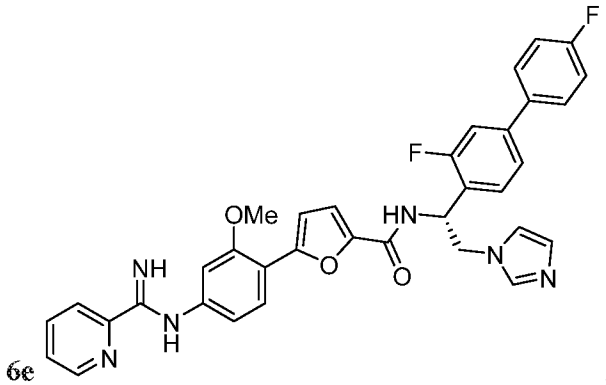
**6b**,



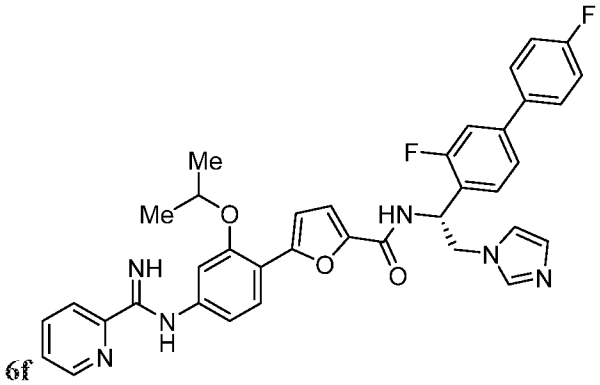
**6c**,



6d ,

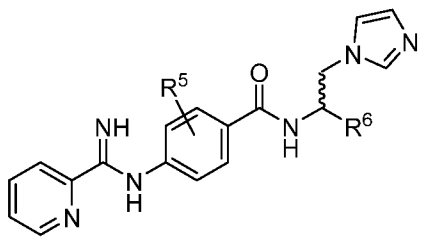


6e , and



6f .

105. The method of claim 55, wherein the compound is represented by Structural Formula **(X)**:



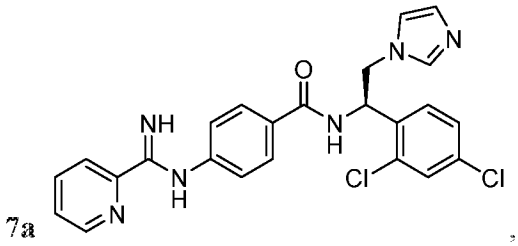
**(X)** ,

wherein:

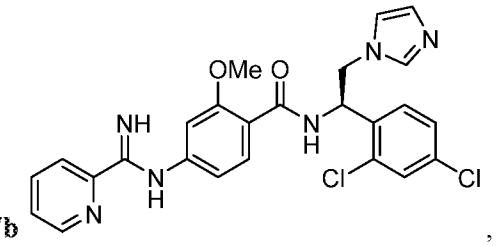
each $\mathbf{R^5}$ is independently H, halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy; and

$\mathbf{R^6}$ is H, optionally halogenated $C_1$-$C_6$ alkyl, optionally halogenated phenyl, or optionally halogenated biphenyl.

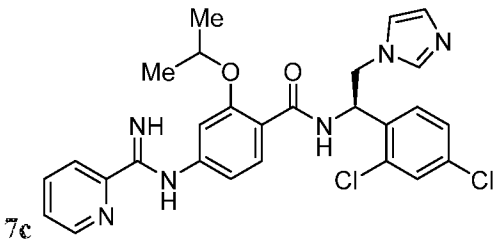
106. The method of claim 105, wherein the compound is one of Compounds **7a-7f**:



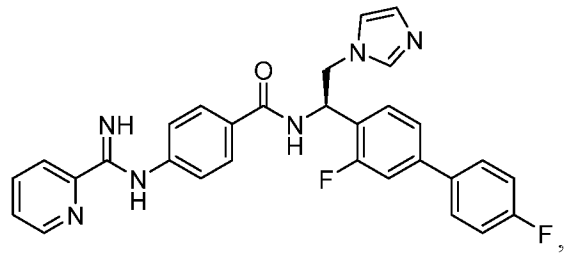
**7a**,



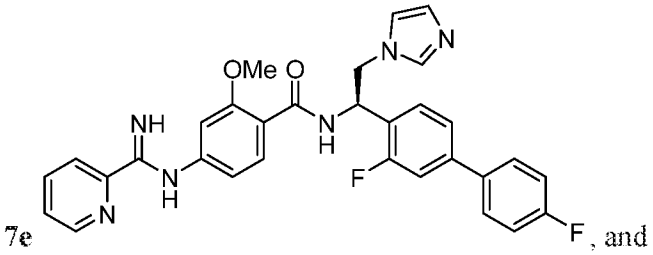
**7b**,



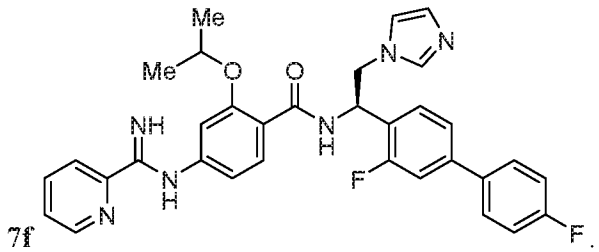
**7c**,



**7d**,

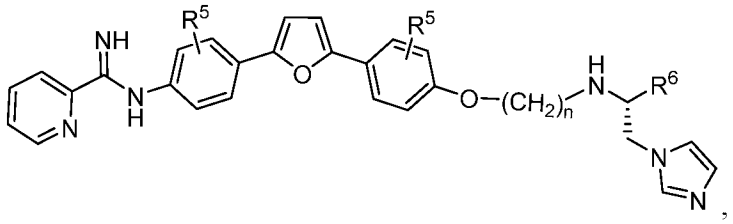


**7e**, and



**7f**.

107. The method of claim 55, wherein the compound is represented by Structural Formula **(XI)**:



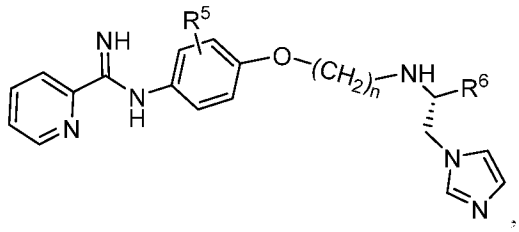
**(XI)**,

wherein:

each $R^5$ is independently H, halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy; and

$R^6$ is H, optionally halogenated $C_1$-$C_6$ alkyl, optionally halogenated phenyl, or optionally halogenated biphenyl.

108. The method of claim 55, wherein the compound is represented by Structural Formula **(XII)**:



**(XII)**

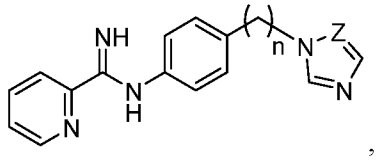
wherein:

each $\mathbf{R^5}$ is independently H, halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy; and

$\mathbf{R^6}$ is H, optionally halogenated $C_1$-$C_6$ alkyl, optionally halogenated phenyl, or optionally halogenated biphenyl.

109. The method of claim 55, wherein **A** is phenyl and **X** is a bond.

110. The method of claim 55, wherein the compound is represented by Structural Formula **(XIII)**:



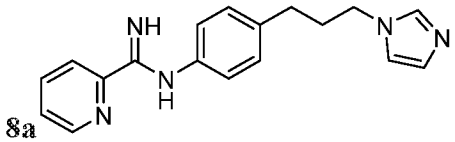
**(XIII)**

wherein:

**Z** = CH or N; and

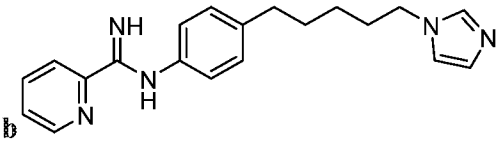
**n** is an integer from 1 to 10.

111. The method of claim 110, wherein the compound is one of Compounds **8a-8b**:



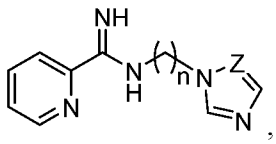
**8a**

and **8b**



112. The method of claim 55, wherein **A** is a bond.

113. The method of claim 112, wherein the compound is represented by Structural Formula **(XIV)**:



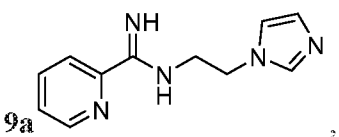
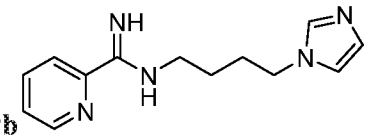
**(XIV)**

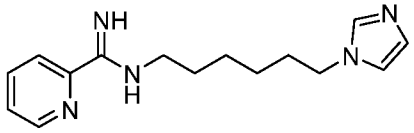
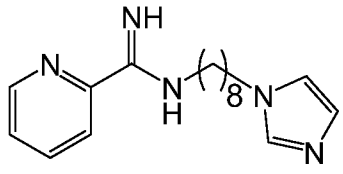
wherein:

**Z** = CH or N; and

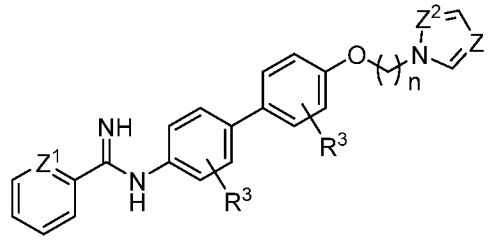
**n** is an integer from 1 to 10.

114. The method of claim 113, wherein the compound is one of Compounds **9a-9d**:


**9a**, 
**9b**, **9c**

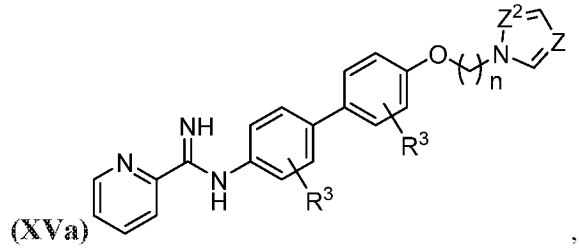
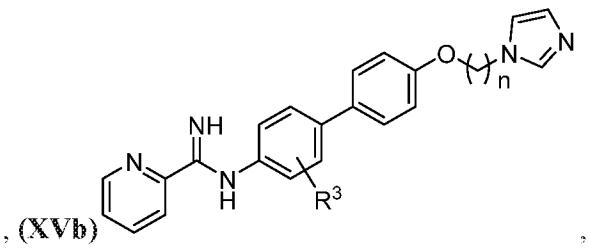

, and 
**9d**..

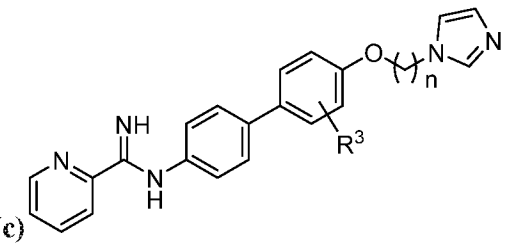
115. The method of claim 55, wherein the compound is represented by Structural Formula **(XV)**:


**(XV)**,

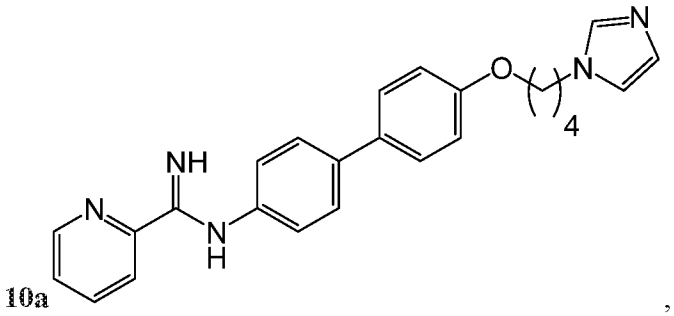
wherein Z, $Z^1$, and $Z^2$ are each independently CH or N, n is 1-14, and $R^3$ is H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy.

116. The method of claim 115, wherein the compound is represented by one of Structural Formulas **(XVa)-(XVc)**:

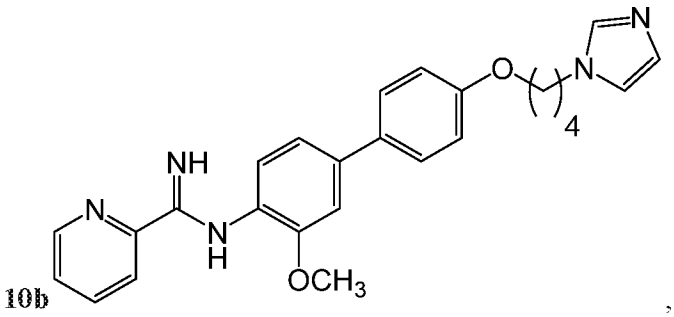

**(XVa)**, 
**(XVb)**,


and **(XVc)**.

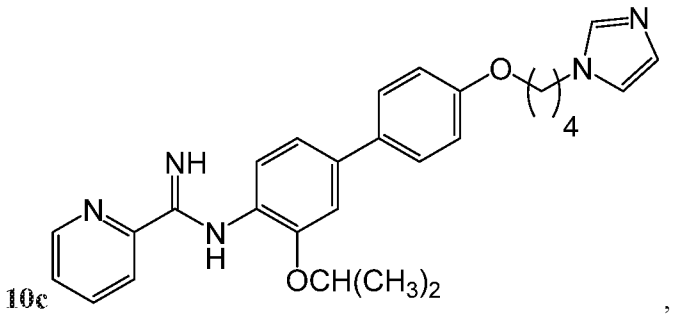
117. The method of claim 116, wherein the compound is one of Compounds **10a-10m**:



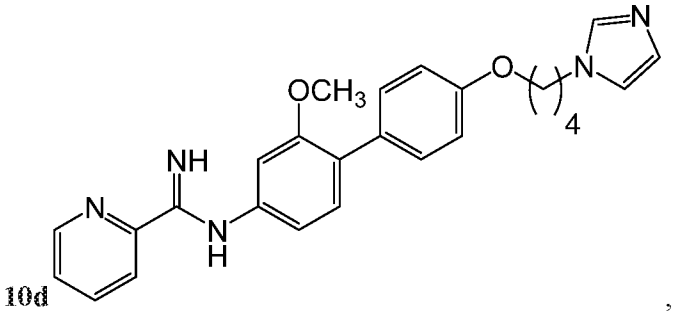
10a ,



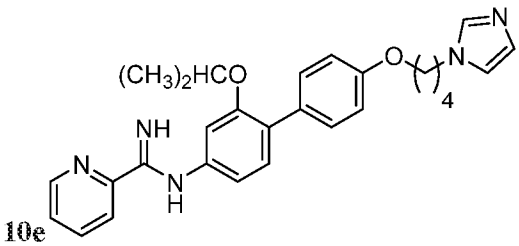
10b ,



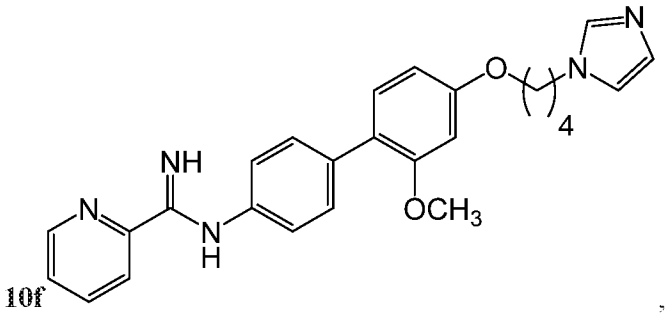
10c ,



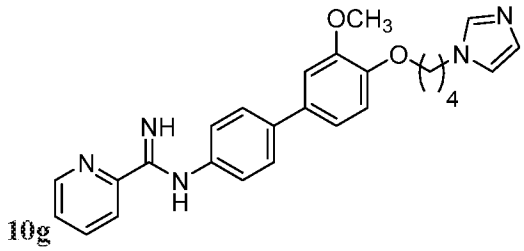
10d ,



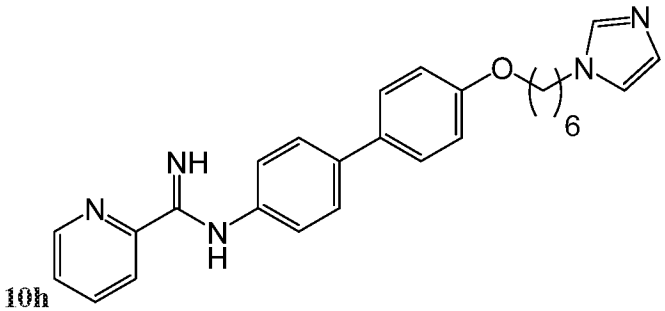
10e ;



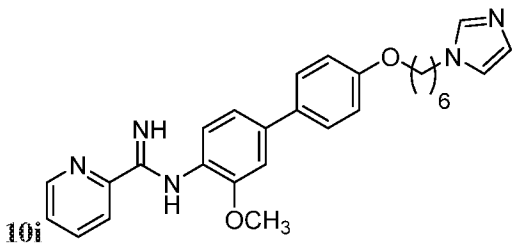
10f ,



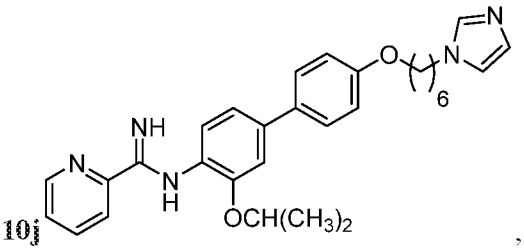
10g ,

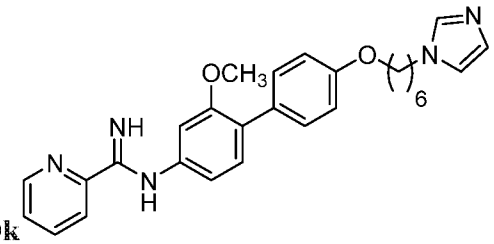


10h ,

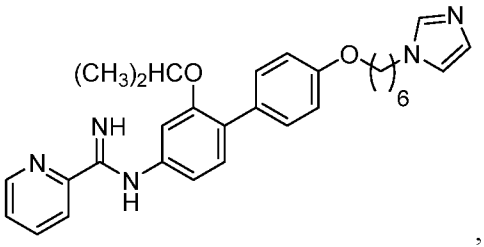


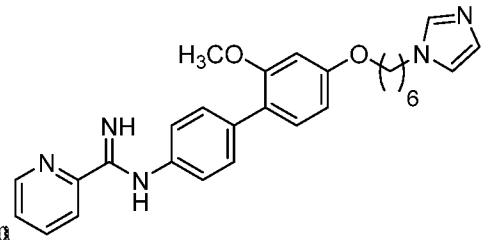
10i ,

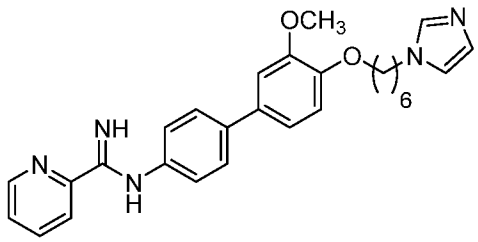


10j , 

10k ,

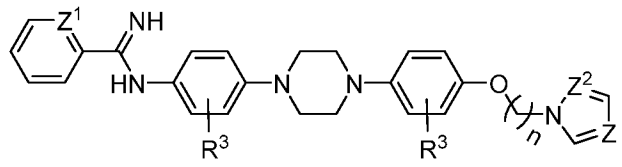


**10l**,  , and **10n**

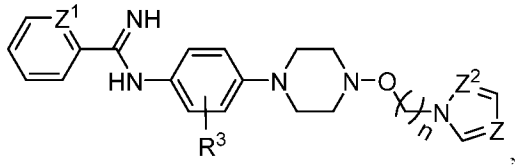


,

118. The method of claim 55, wherein the compound is represented by one of Structural Formulas **(XVI)** and **(XVII)**:



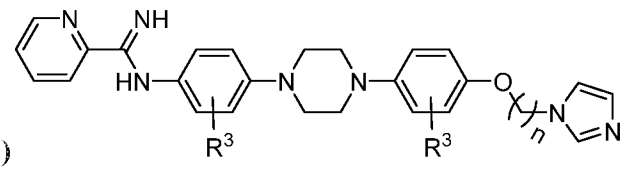
**(XIV)** and



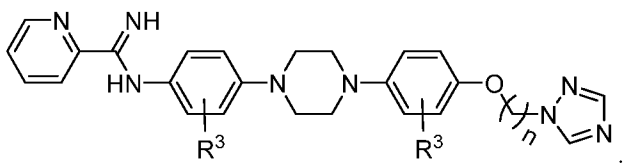
**(XVII)**,

wherein Z, $Z^1$, and $Z^2$ are each independently CH or N, n is 1-14, and $R^3$ is H, halogen, optionally halogenated $C_1$-$C_6$ alkyl, or optionally halogenated $C_1$-$C_6$ alkoxy.

119. The method of claim 118, wherein the compound is represented by one of Structural Formulas **(XVIa)**-**(XVIb)**:

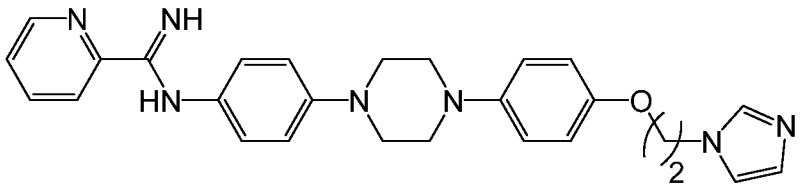


**(XVIa)** and **(XVIb)**

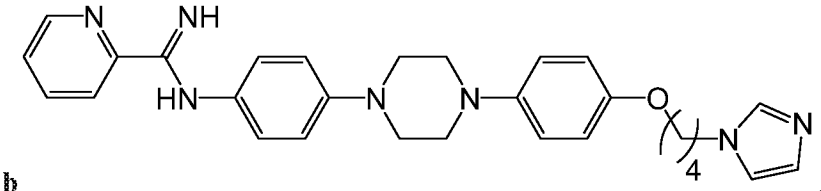


.

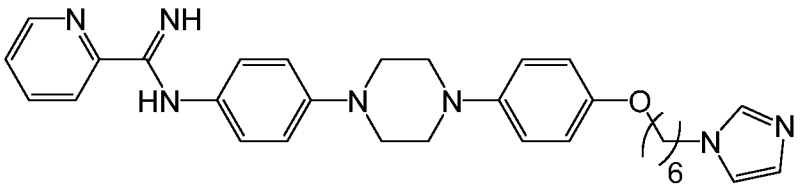
120. The method of claim 119, wherein the compound is one of Compounds **11a-11d**:



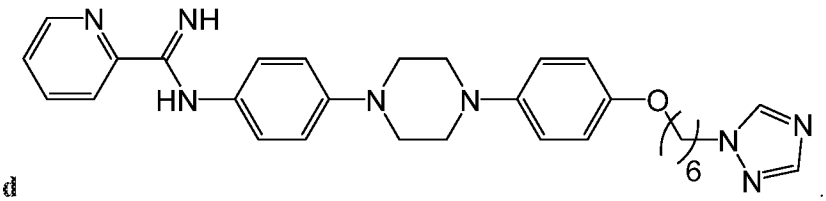
**11a** ,



**11b** ,

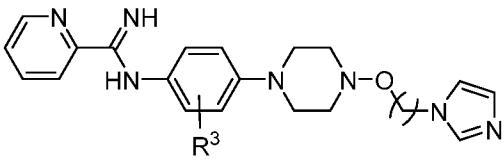


**11c** , and

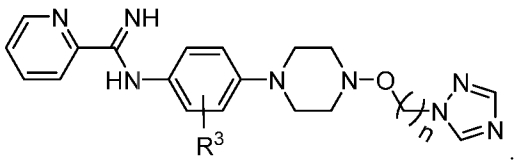


**11d** .

121. The method of claim 55, wherein the compound is represented by one of Structural Formulas **(XVIIa)-(XVIIb)**:

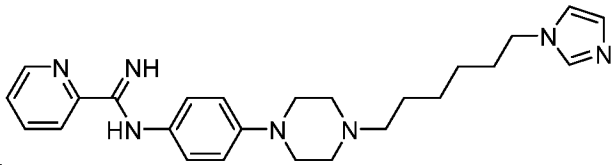


**(XVIIa)** and **(XVIIb)**



.

122. The method of claim 123, wherein the compound is Compound **12a**:



**12a** .

123. A kit for anti-parasite treatment of a subject in need thereof, comprising:

a compound represented by Structural Formula **(I)**:

**(Ia)** **Ar**----C(=$NR^1$)$NR^2$----**A**----**X**----**Y**----**$Het^2$**

pharmaceutically acceptable salts thereof, and mixtures thereof with a pharmaceutically acceptable carrier or excipient, wherein:

**Ar** is an optionally substituted aryl or nitrogen-containing heteroaryl;

$R^1$ and $R^2$ are independently H, optionally substituted $C_1$-$C_6$ alkyl, or optionally substituted $C_3$-$C_6$ cycloalkyl;

**A** is a bond or an optionally substituted linking moiety comprising 1, 2, or 3 rings, each ring in the optionally substituted linking moiety independently being one of: aryl, cycloalkyl, heterocycloalkyl, and heteroaryl;

**X** is O, S, amide, or a bond;

**Y** is optionally substituted $C_1$-$C_{14}$ alkyl or optionally substituted $C_2$-$C_{14}$ alkenyl; and

**$Het^2$** is an optionally substituted five-membered nitrogen-containing heteroaromatic ring comprising 1, 2, or 3 ring heteroatoms; and

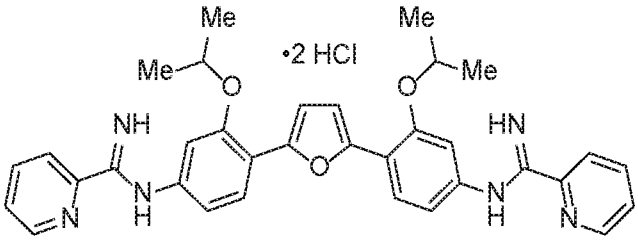
instructions, the instructions directing a user to:

provide the subject, the subject being infected by a parasite or at risk of infection by the parasite; and

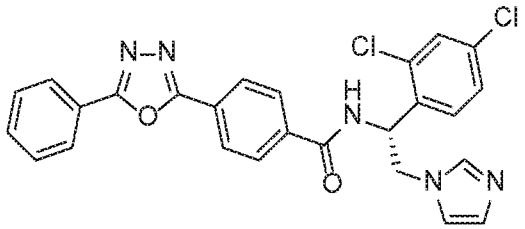
administer the compound or the pharmaceutical composition to the subject in an amount effective to mitigate infection by the parasite in the subject.

124. The kit for anti-parasite treatment of claim 123, the compound being the compound of any of claims 1-54.

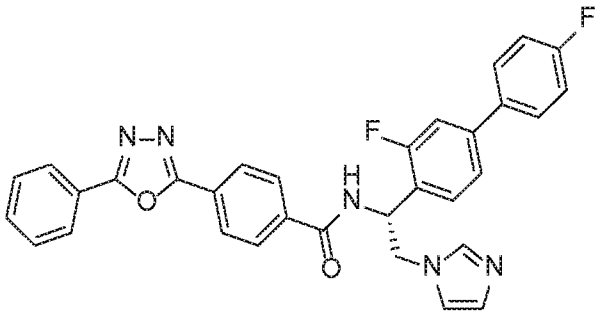
125. The kit for anti-parasite treatment of claim 123, the instructions directing the user to conduct the method of any of claims 55-122.




DB766




VNI




VNI/VNF

FIG. 1 (PRIOR ART)

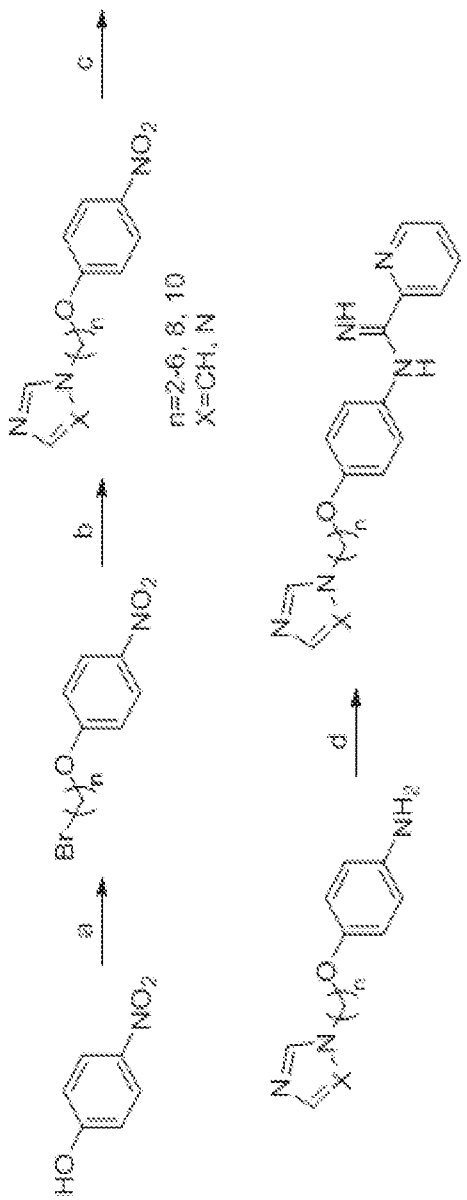



FIG. 2A

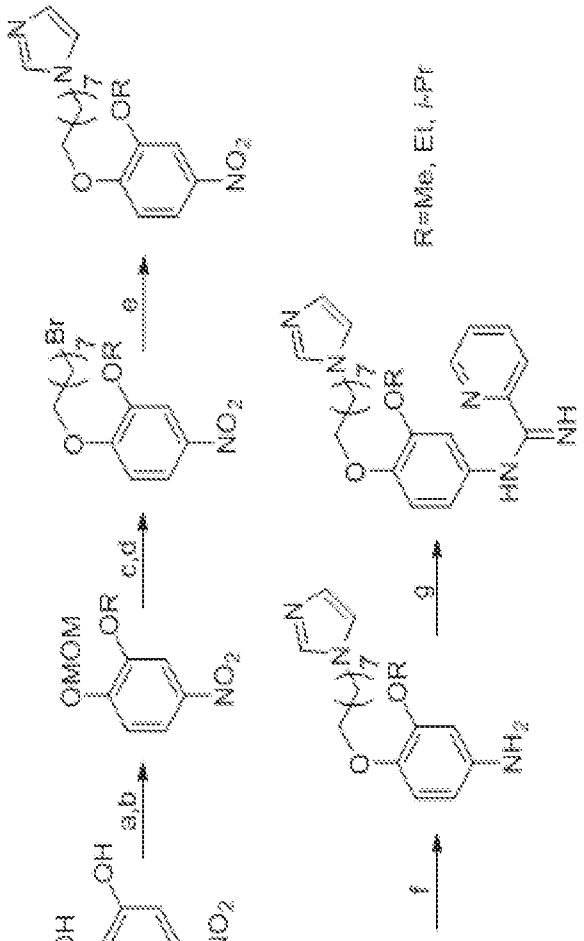



FIG. 2B

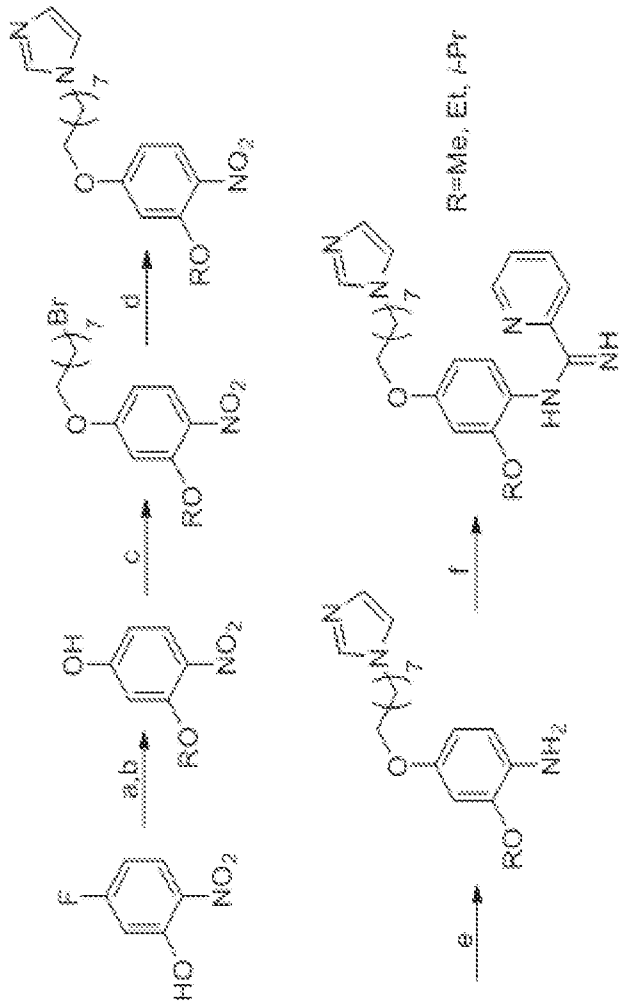



FIG. 2C

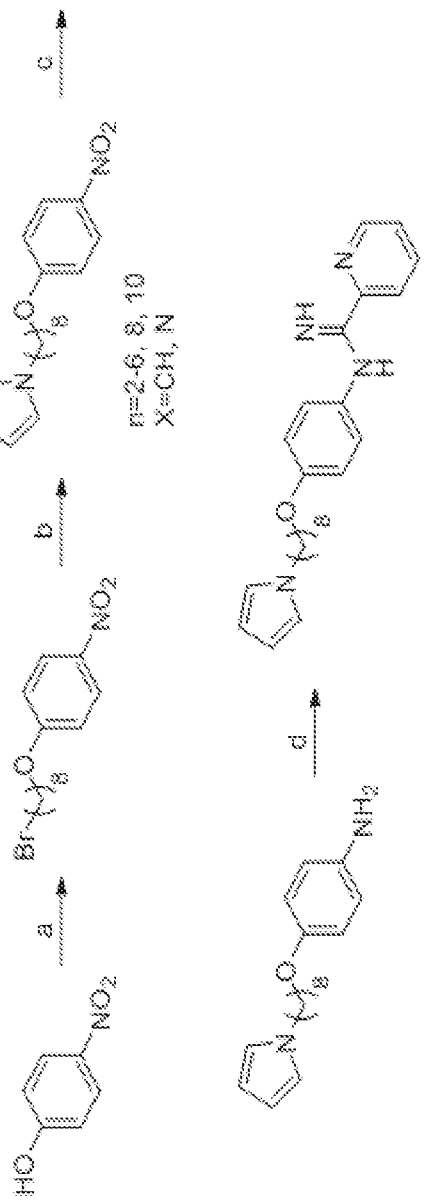



FIG. 2D

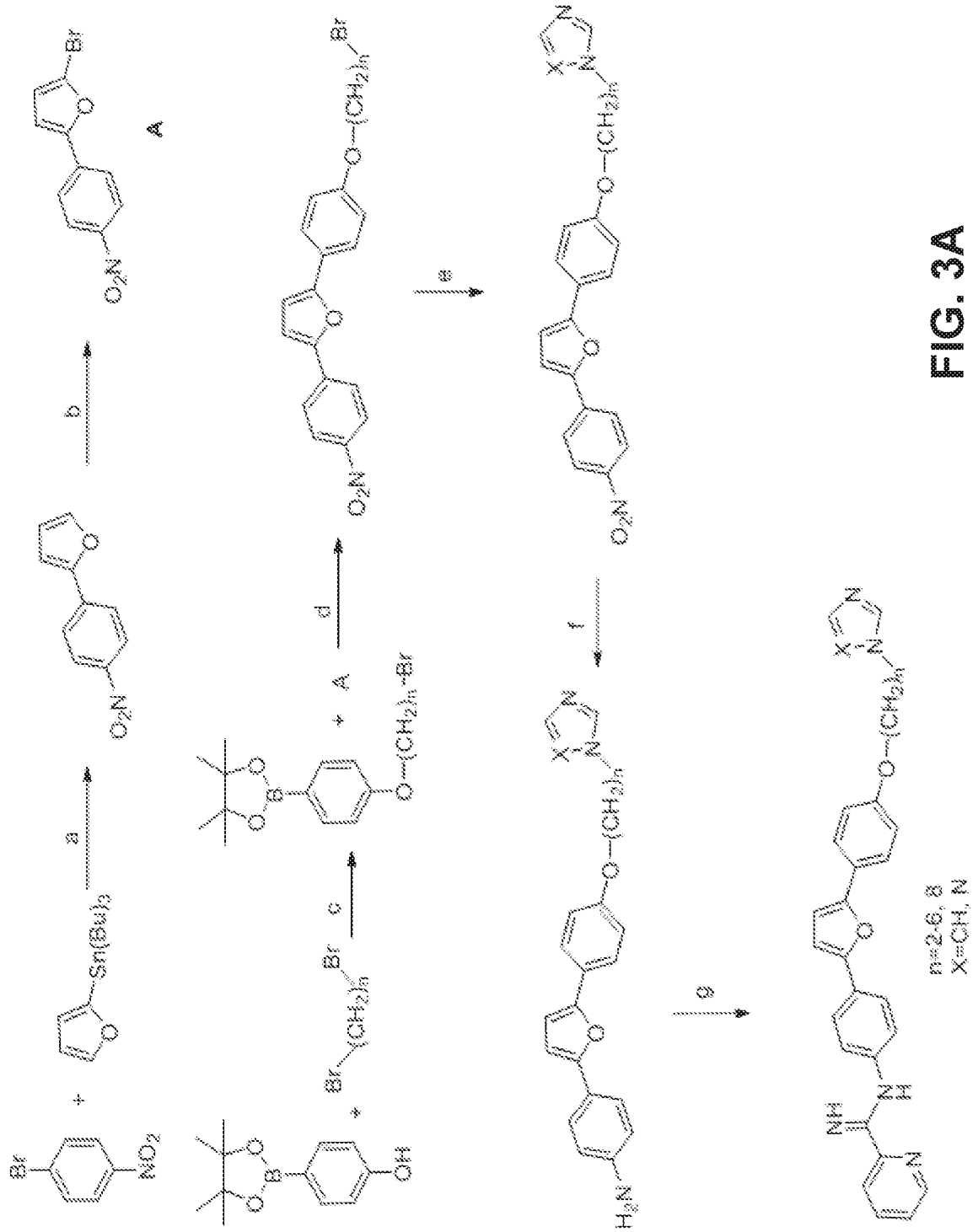


FIG. 3A

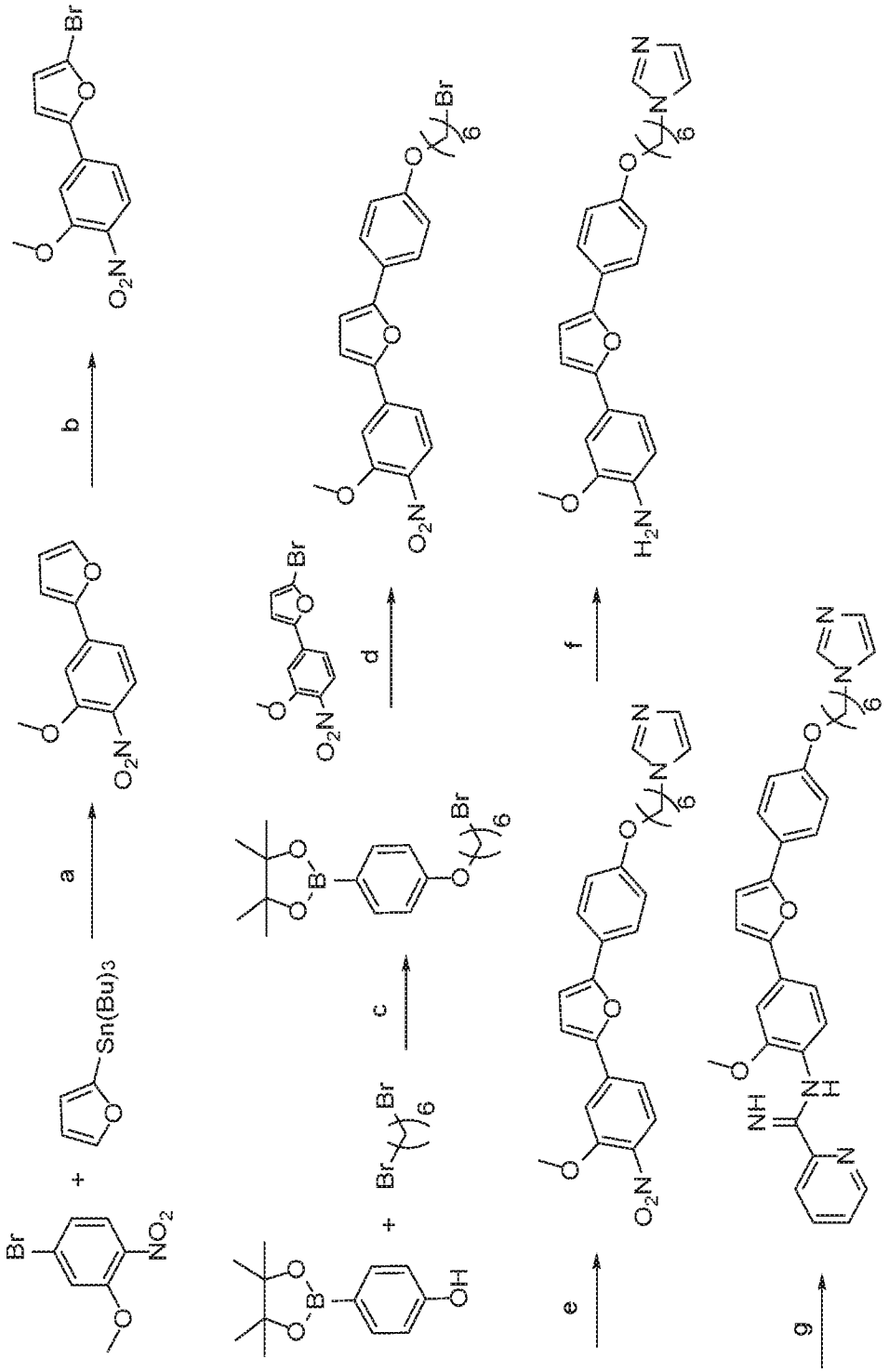



FIG. 3B

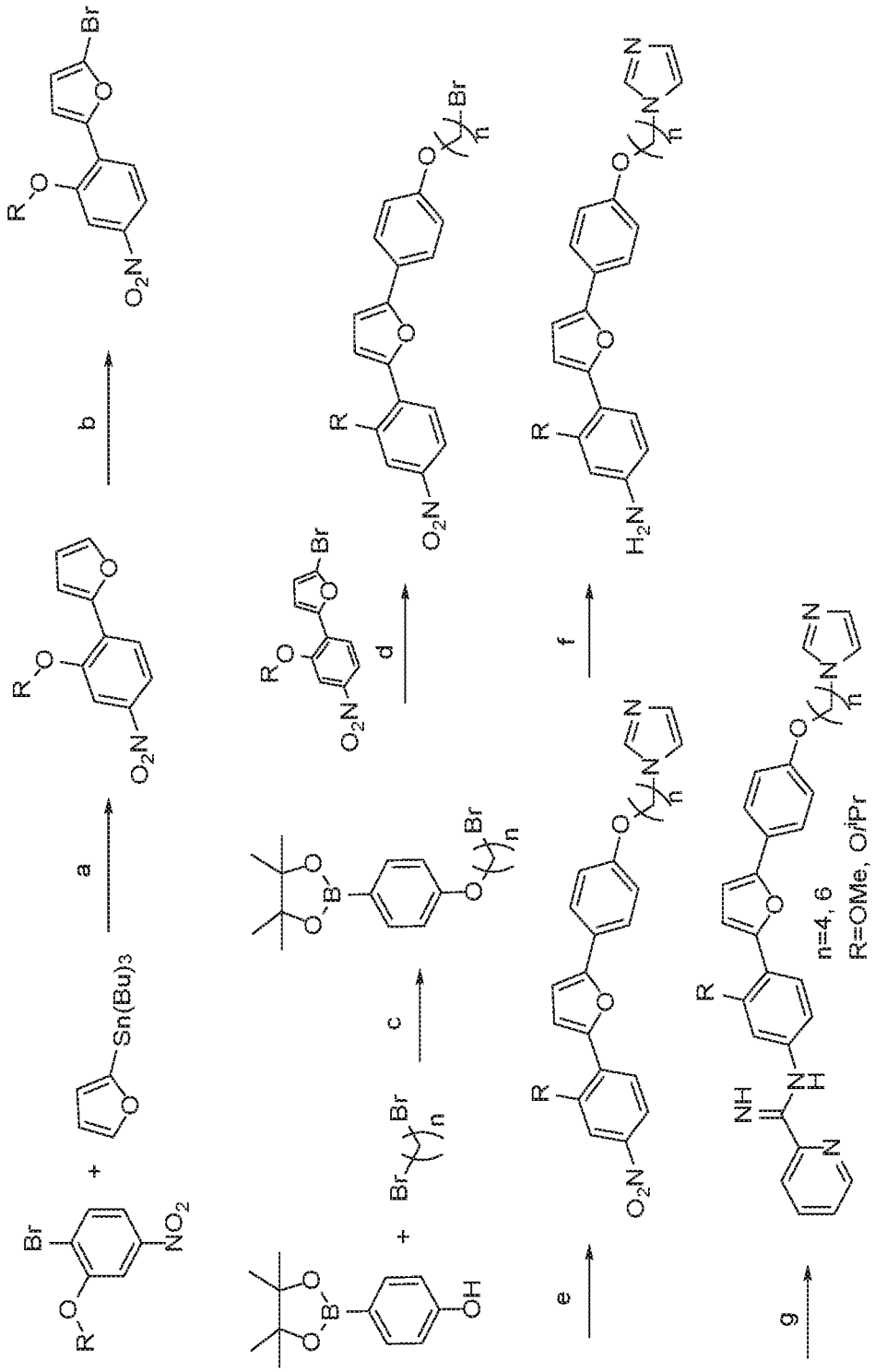



FIG. 3C

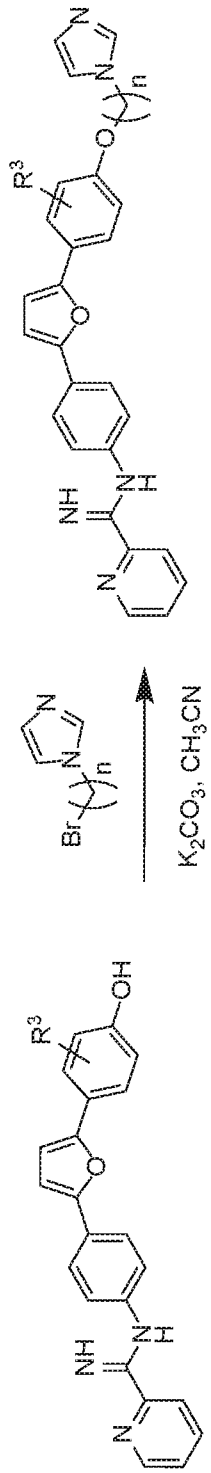
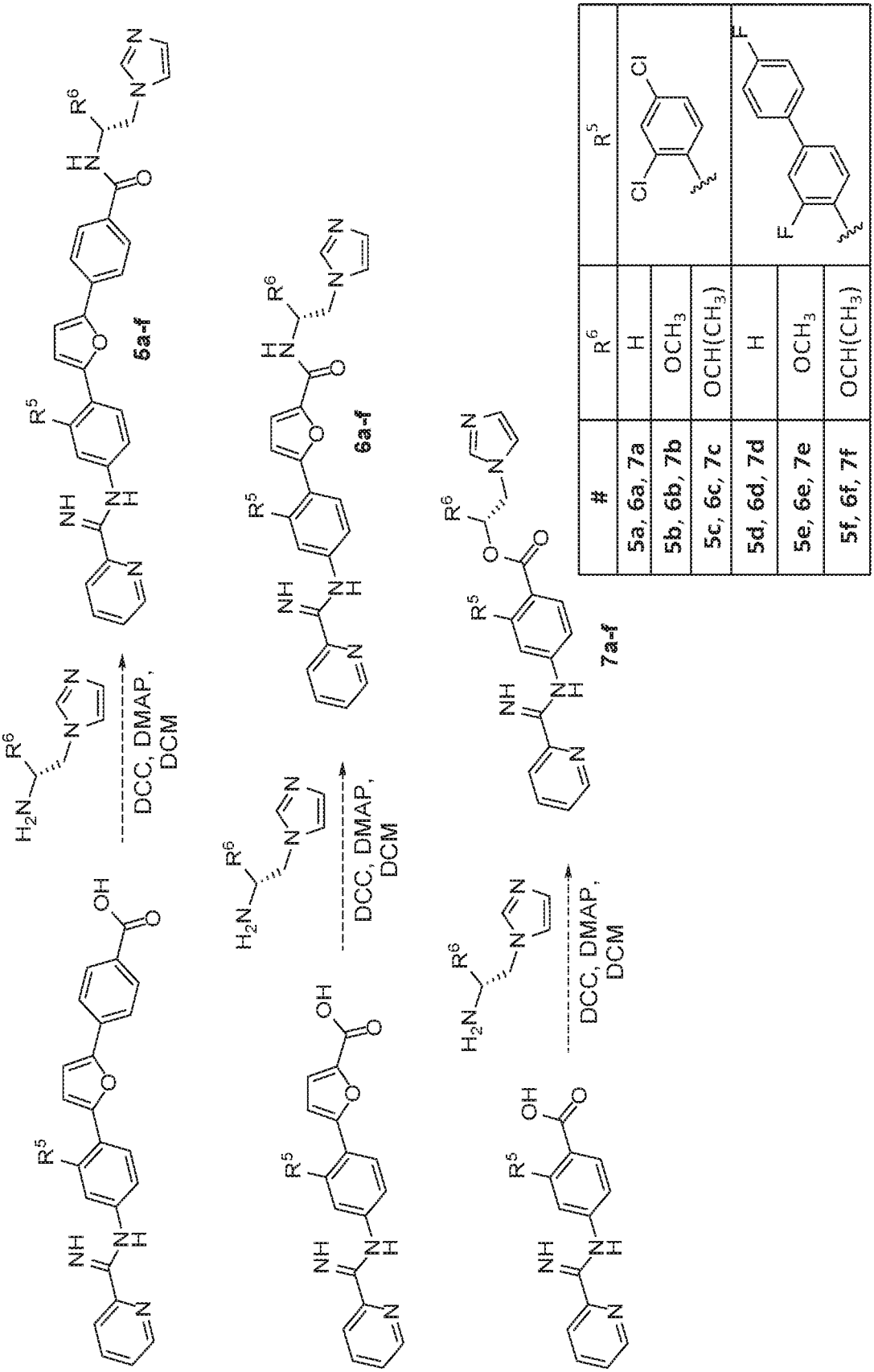
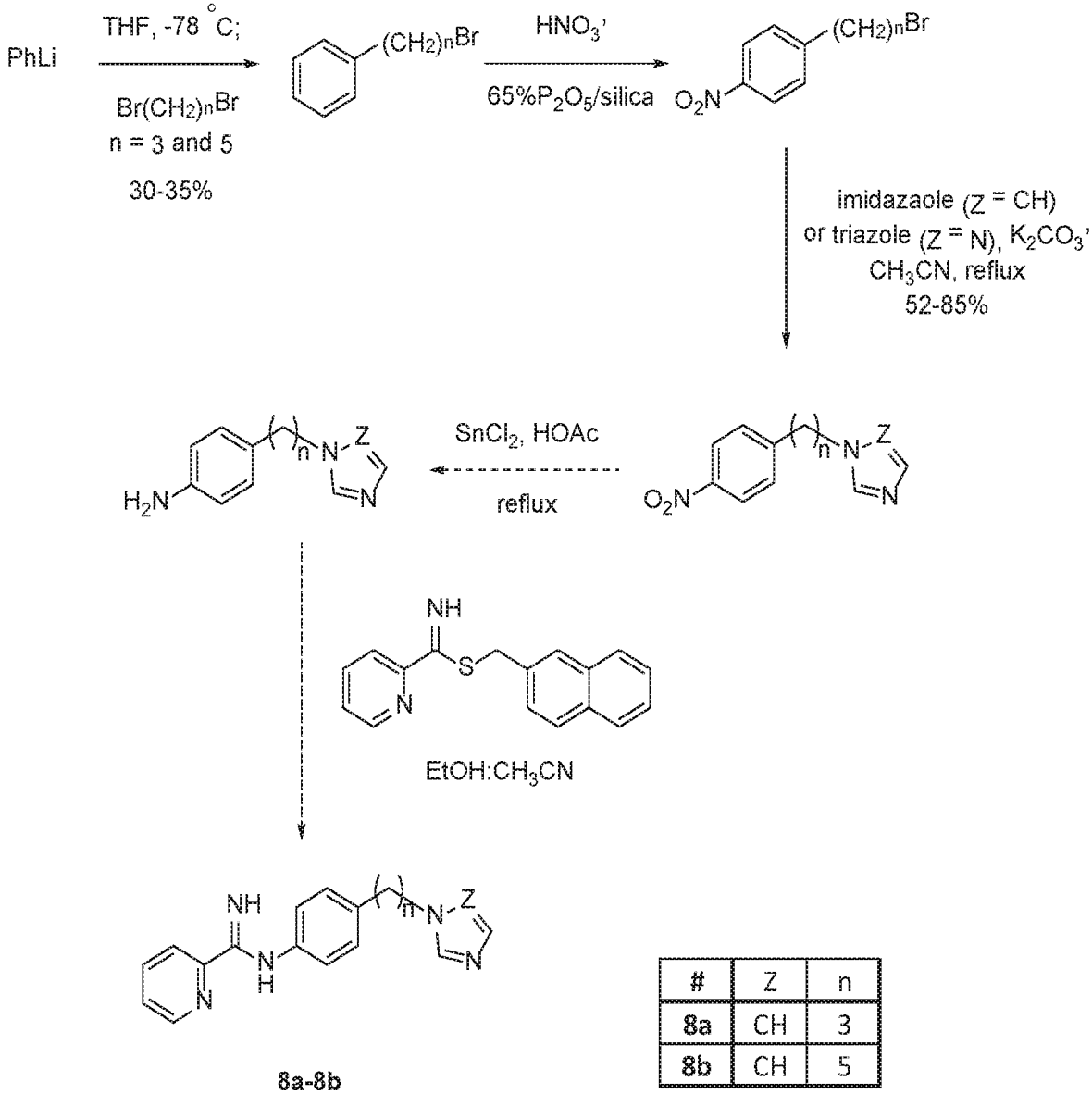



FIG. 3D




| # | $R^6$ | $R^5$ |
|---|---|---|
| 5a, 6a, 7a | H | |
| 5b, 6b, 7b | $OCH_3$ | |
| 5c, 6c, 7c | $OCH(CH_3)$ | |
| 5d, 6d, 7d | H | |
| 5e, 6e, 7e | $OCH_3$ | |
| 5f, 6f, 7f | $OCH(CH_3)$ | |

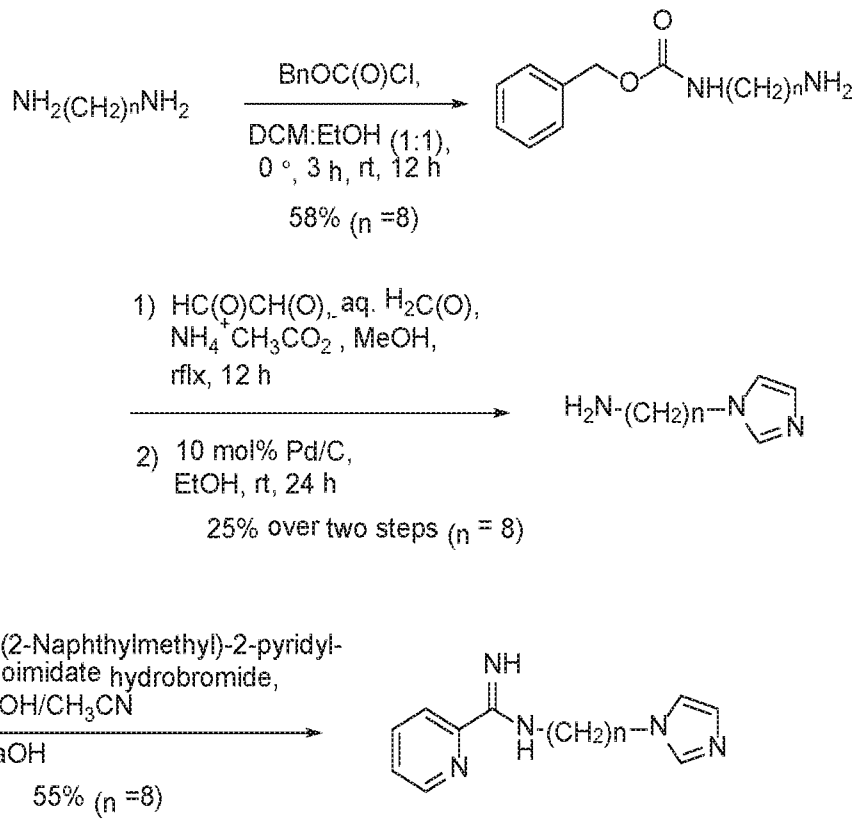
FIG. 4




8a-8b

| # | Z | n |
|---|---|---|
| 8a | CH | 3 |
| 8b | CH | 5 |

FIG. 5A




| # | n |
|---|---|
| 9a | 2 |
| 9b | 4 |
| 9c | 6 |
| 9d | 8 |

FIG. 5B

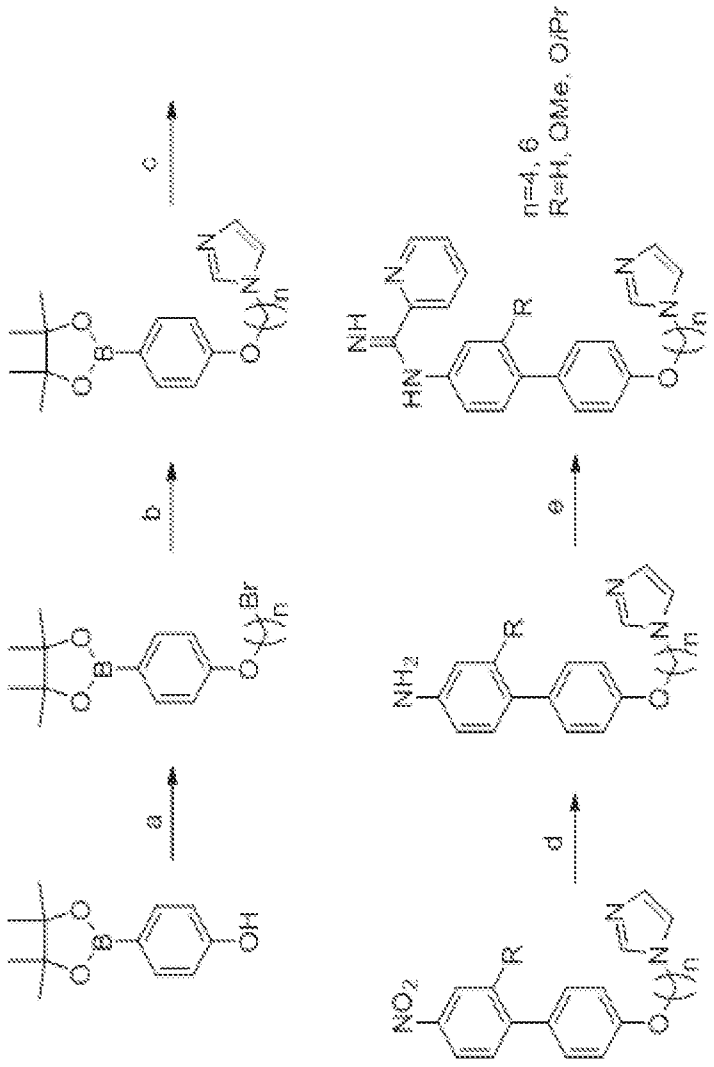



FIG. 6A

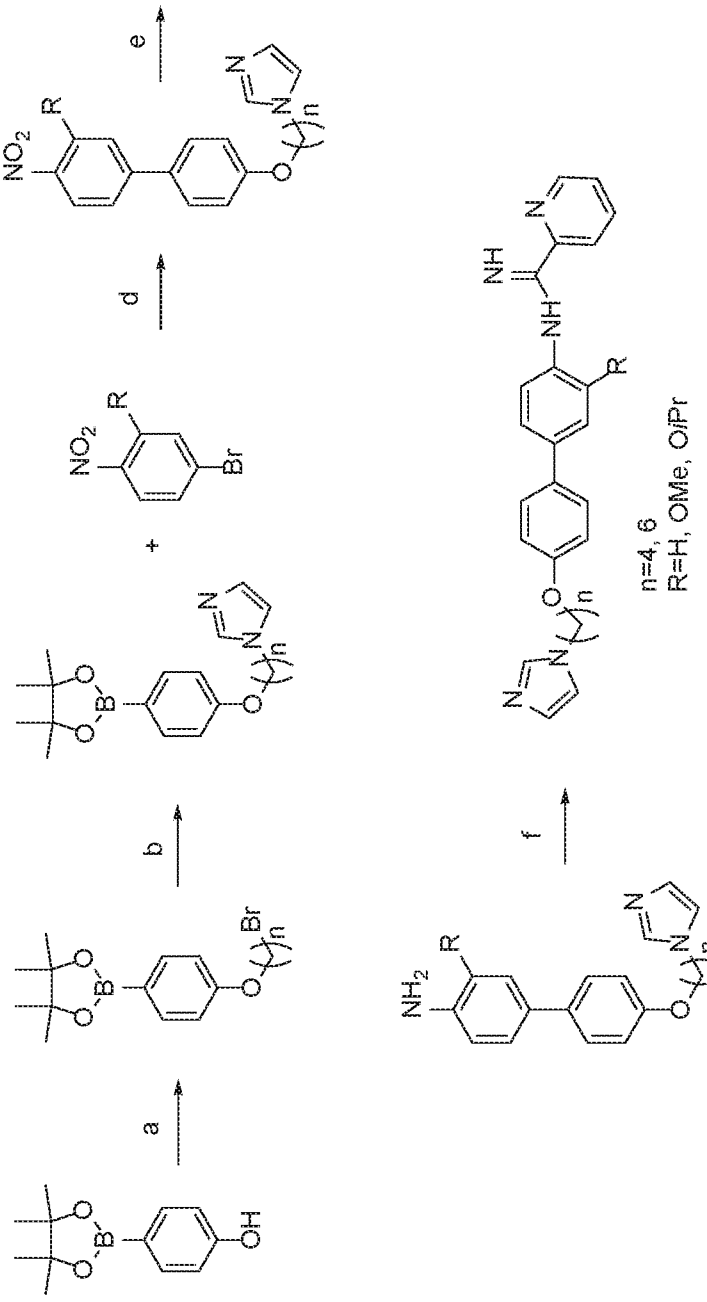



FIG. 6B

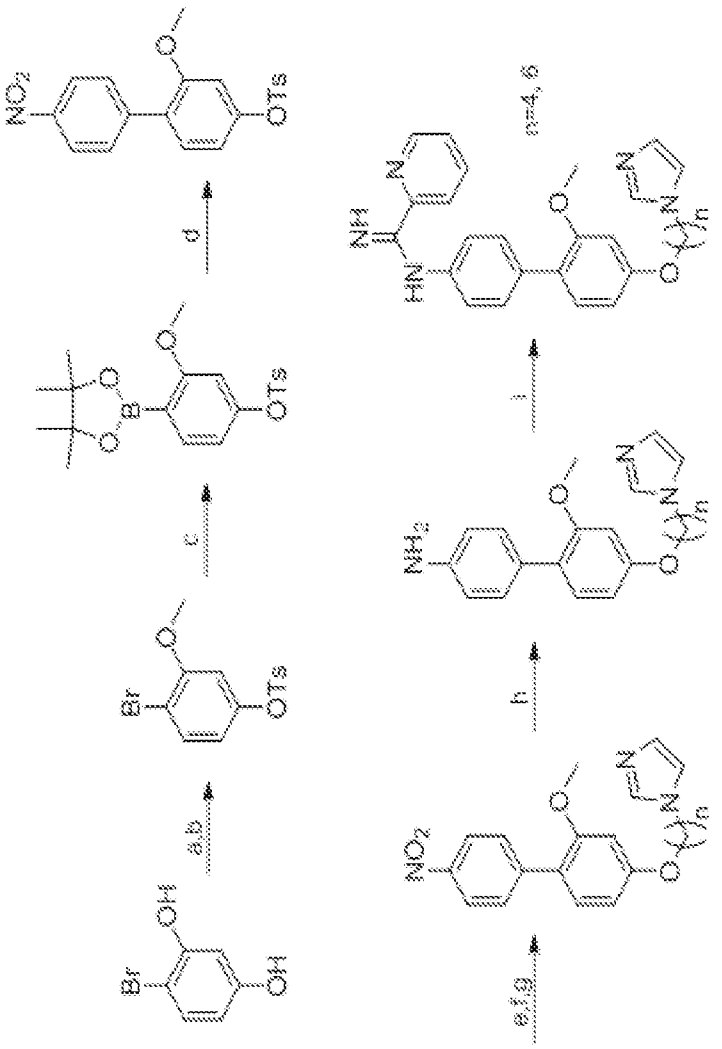



FIG. 6C

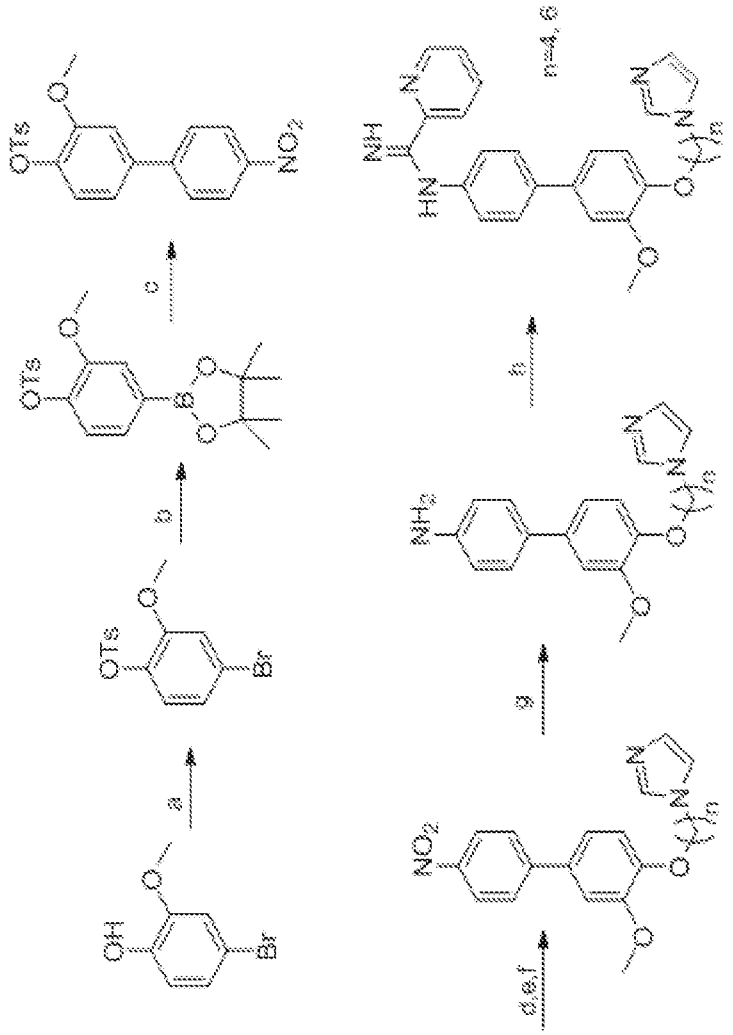

OH
Br
a
OTs
Br
b
OTs
B
O
O
c
OTs
NO2
d,e,f
NO2
O
N
N
n
g
NH2
O
N
N
n
h
NH
HN
N
O
N
N
n
n=4, 6

FIG. 6D

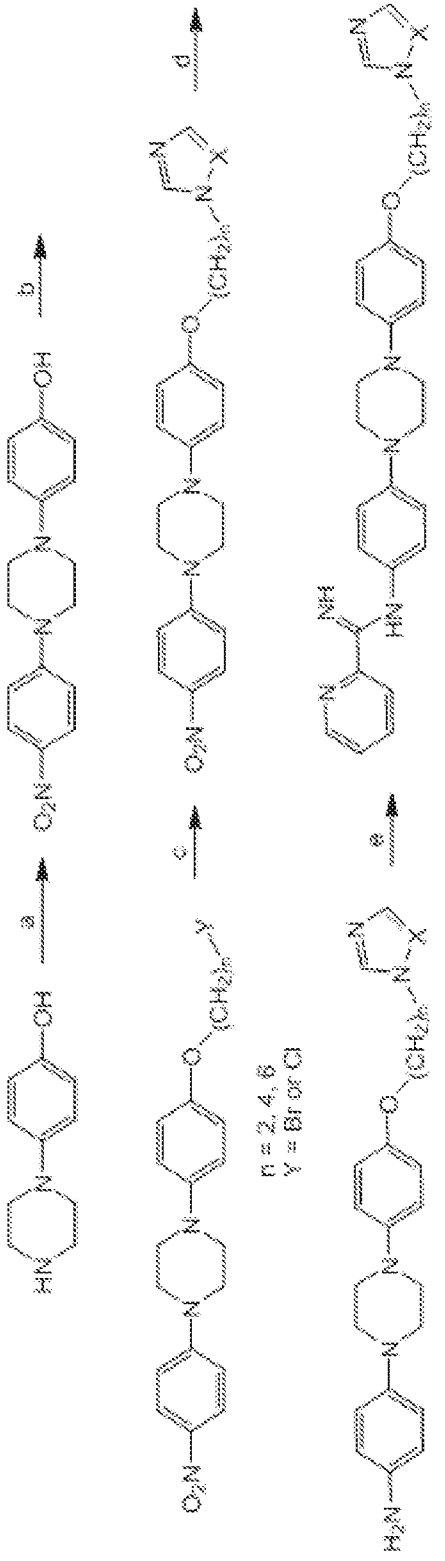



FIG. 7A

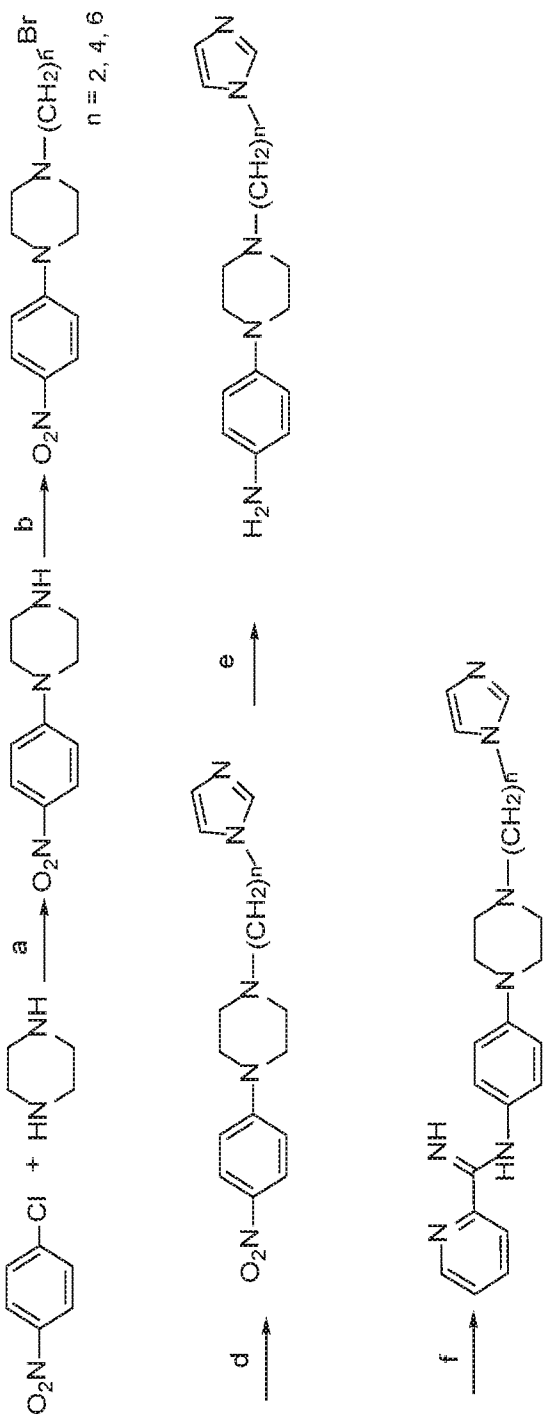



FIG. 7B

| Compound | $IC_{50}$ against *L. donovani* (μM)[a] | $CC_{50}$ against J774 macrophages (μM)[a] | $CC_{50}$ against HepG2 (μM)[a] |
|---|---|---|---|
| **1a** | >50 | >100 | >50 |
| **1b** | >100 | >50 | >100 |
| **1c** | >25 | >100 | >50 |
| **1e** | 18 ± 5 | >50 | 32 ± 6 |
| **1f** | >100 | >100 | >100 |
| **1g** | 13 ± 10 | >50 | 42 ± 7 |
| **1i** | 12 ± 6 | >40 | 20 ± 6 |
| **1m** | 1.0 ± 0.1 | 11 ± 3 | 12 ± 4 |
| **1n** | 13 ± 2 | 36 ± 1[b] | NT |
| **1o** | 2.2 ± 0.6 | 17 ± 2 | 23 ± 4 |
| **1p** | 1.9 ± 0.5 | 9.2 ± 2.2 | 13 ± 0 |
| **1q** | 0.97 ± 0.12 | 8.0 ± 0.7 | 18 ± 2 |
| **1r** | 1.1 ± 0.5 | 10 ± 2 | 16 ± 4 |
| **1s** | 0.78 ± 0.29 | 7.4 ± 1.1 | 12 ± 3 |
| **1t** | 0.58 ± 0.06 | 6.7 ± 0.4 | 12 ± 3 |
| **1u** | 1.7 ± 0.5 | 11 ± 2 | 13 ± 4 |
| **1v** | 1.5 ± 0.6 | 4.9 ± 1.6 | 6.9 ± 1.7 |
| **14a** | 1.3 ± 0.2 | 0.51 ± 0.03[b] | NT |
| **9d** | >25 | NT | NT |
| Amphotericin B | 0.049 ± 0.020 | NT | NT |
| Podophyllotoxin | Not tested | 0.025 ± 0.004 | NT |
| Doxorubicin | Not tested | NT | 0.22 ± 0.0.06 |

[a]Mean ± standard deviation of at least three independent measureme
[b]Mean ± range of two independent measurements
NT = not tested

FIG. 8A

| Compound | $IC_{50}$ against *L. donovani* (μM)[a] | $CC_{50}$ against J774 macrophages (μM)[a] | $CC_{50}$ against HepG2 (μM)[a] |
|---|---|---|---|
| **2a** | NT | >25 | 25 ± 7 |
| **2b** | 2.4 ± 0.1 | 3.1 ± 0.1 | 9.2 ± 4.3 |
| **2c** | 1.4 ± 0.3 | 2.4 ± 0.3 | 6.2 ± 1.6 |
| **2d** | 0.71 ± 0.11 | 2.7 ± 0.8 | 7.9 ± 2.8 |
| **2e** | 2.1 ± 0.9 | 3.1 ± 1.5 | 25 ± 14 |
| **2g** | 1.3 ± 0.2 | 3.6 ± 3.0 | 3.3 ± 1.0 |
| **2h** | 0.16 ± 0.01 | 3.4 ± 0.2 | 6.0 ± 1.3 |
| **3a** | 8.4 ± 2.8 | 18 ± 5 | 10 ± 2 |
| **3b** | 4.7 ± 1.6 | 12 ± 2 | 11 ± 5 |
| **3c** | NT | NT | NT |
| **3d** | 1.5 ± 0.1 | 9.3 ± 3.5 | 14 ± 6 |
| **3e** | 3.8 ± 0.8 | 26 ± 8 | 27 ± 5 |
| **3g** | 2.2 ± 0.5 | >25 | 28 ± 9 |
| **4e** | 0.52 ± 0.33 | 4.1 ± 1.6 | 10 ± 2 |
| **4f** | 2.4 ± 0.9 | 3.3 ± 1.6[b] | 6.6 ± 2.0 |
| **4j** | 0.60 ± 0.14 | 2.2 ± 0.3 | 6.5 ± 0.6 |
| **4k** | 0.22 ± 0.09 | 3.8 ± 1.4 | 7.0 ± 0.1 |
| Amphotericin B | 0.050 ± 0.022 | NT | NT |
| Podophyllotoxin | NT | 0.025 ± 0.004 | NT |
| Doxorubicin | NT | NT | 0.17 ± 0.08 |

[a]Mean ± standard deviation of at least three independent r

[b]Mean ± range of two independent measurements

NT = not tested

FIG. 8B

| Compound | $IC_{50}$ against *L. donovani* (μM)[a] | $CC_{50}$ against J774 macrophages (μM)[a] | $CC_{50}$ against HepG2 (μM)[a] |
|---|---|---|---|
| **10a** | 2.4 ± 0.7 | 13 ± 0[b] | 10 ± 2 |
| **10b** | 0.97 ± 0.07[b] | NT | NT |
| **10c** | 0.40 ± 0.07[b] | NT | NT |
| **10d** | 2.2 ± 0.6 | 9.8 ± 0.4[b] | 13 ± 1 |
| **10f** | 0.45 ± 0.06 | 7.6 ± 3.0 | NT |
| **10h** | 0.68 ± 0.27 | 6.6 ± 3.1[b] | NT |
| **10j** | 0.32 ± 0.01[b] | NT | NT |
| **10k** | 1.2 ± 0.4 | 4.6 ± 1.4[b] | 7.7 ± 1.2 |
| **10l** | 0.15 ± 0.04 | 3.4 ± 0.5 | NT |
| **10m** | 0.19 ± 0.03 | 4.5 ± 1.8 | NT |
| Amphotericin B | 0.049 ± 0.023 | NT | NT |
| Podophyllotoxin | NT | 0.030 ± 0.010 | NT |
| Doxorubicin | NT | NT | 0.24 ± 0.03 |

[a]Mean ± standard deviation of at least three independent measurements

[b]Mean ± range of two independent measurements

NT = not tested

FIG. 8C

| Compound | $IC_{50}$ against *L. donovani* (μM)[a] | $CC_{50}$ against J774 macrophages (μM)[a] |
|---|---|---|
| **11a** | 2.5 ± 0.7 | 25 ± 2 |
| **11b** | 1.9 ± 0.6 | 6.3 ± 1.3 |
| **11c** | 0.47 ± 0.15 | 1.8 ± 0.2 |
| **11d** | NT | NT |
| Amphotericin B | 0.046 ± 0.021 | NT |
| Podophyllotoxin | NT | 0.033 ± 0.010 |

[a]Mean ± standard deviation of at least three independent mea

[b]Mean ± range of two independent measurements

NT = not tested

FIG. 8D

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/49491

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/4545, A61K 31/4725, A61K 31/498 (2017.01)
CPC - A61K 31/4545, A61K 31/4725, A61K 31/498

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
See Search History Document

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 | WO 2009/049846 A1 (Syngenta Participations Ag) 23 April 2009 (23.04.2009); Abstract, p1, p6, p28, p31 | 1, 22-23 |
| A | Sondhi et al. 'Conventional and microwave assisted synthesis of small molecule based biologically active heterocyclic amidine derivatives', European Journal of Medicinal Chemistry, 18 November 2009 (18.11.2009), Vol.45, page902-908; p903, p904 | 1, 22-23 |
| A | WO 2004/113273 A1 (Syngenta Participations Ag) 29 December 2004 (29.12.2004); entire document | 1, 22-23 |
| A | WO 2012/049327 A2 (Syngenta Participations Ag) 19 April 2012 (19.04.2012); entire document | 1, 22-23 |
| A | US 2007/0037814 A1 (Rawson et al.) 15 February 2007 (15.02.2007); entire document | 1, 22-23 |

☐ 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 | Date of mailing of the international search report |
|---|---|
| 17 October 2017 | 27 DEC 2017 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-8300 | Authorized officer:<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/210 (second sheet) (January 2015)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/49491

**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.: 124-125
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 Supplemental Box

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, 22-23

**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/US 17/49491

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 must be paid.

Group I+: Claims 1-54, 90 directed to a compound, represented by Structural Formula (Ia): and pharmaceutically acceptable salts thereof. The compound of formula will be searched to the extent that it encompasses the compound, represented by Structural Formula (Ia): and pharmaceutically acceptable salts thereof, wherein: Ar is an optionally substituted aryl; R1 and R2 are H; A is a bond; X is O; Y is optionally substituted C1-C14 alkyl; and Het2 is an optionally substituted five-membered nitrogen-containing heteroaromatic ring comprising 1 ring heteroatom, provided that the compound represented by Structural Formula (Ia) is not one of free-base Compounds 1a-f. It is believed that claims 1, 22-23 read on this first named invention, and thus these claims will be searched without fee. Applicant is invited to elect additional compounds of claim 1, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass 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. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be the compound, represented by Structural Formula (Ia): and pharmaceutically acceptable salts thereof, wherein; Ar is an optionally substituted nitrogen-containing heteroaryl; R1 and R2 are H; A is an optionally substituted linking moiety comprising 3 rings, each ring in the optionally substituted linking moiety independently being one of: aryl, cycloalkyl, heterocydoalkyl, and heteroaryl; X is O; Y is optionally substituted C1-C14 alkyl; and Het2 is an optionally substituted five-membered nitrogen-containing heteroaromatic ring comprising 3 ring heteroatoms, provided that the compound represented by Structural Formula (Ia) is not one of freebase Compounds 1a-f (i.e., claims 1, 2(in part), 3-4, 5(in part), 6(in part), 7-15, 19(in part), 20(in part), 21(in part), 22-23, 26(in part), 27(in part), 28(in part), 30, 50(in part), 51(in part)).

Group II: claims 55-89, 91-123 directed to a method/kit of anti-parasitic treatment for a subject in need thereof: comprising: a compound being represented by Structural Formula (Ia): and pharmaceutically acceptable salts thereof

The group of inventions listed above 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:

Special Technical Features:

Group I+ includes the technical feature of a unique compound of formula in claim 1 containing the same, which is not required by any other invention of Group I+.

Group II includes the technical feature of a method/kit of anti-parasitic treatment for a subject in need thereof: comprising: a compound being represented by Structural Formula (Ia): and pharmaceutically acceptable salts thereof, not required by Group I+.

Common technical features:

The inventions of Group I+ share the technical feature of compound of formula containing the same.

Groups I+ and II share the technical feature of compound of Structural Formula (Ia) in claim 1.

These shared technical features, however, do not provide a contribution over the prior art, as being obvious over the journal article entitled 'Conventional and microwave assisted synthesis of small molecule based biologically active heterocyclic amidine derivatives' by Sondhi et al. (hereinafter 'Sondhi'). Sondhi teaches a compound, represented by Structural Formula (Ia): wherein: Ar is nitrogen-containing heteroaryl; R1 and R2 are H; A is a bond; X is a bond; Y is C1 alkyl; and Het2 is a five-membered nitrogen-containing heteroaromatic ring comprising 1 ring heteroatom, provided that the compound represented by Structural Formula (Ia) is not one of freebase Compounds 1a-f (p903, Scheme 1. "Compound 3'a"), but does not teach pharmaceutically acceptable salts thereof. However, it would have been obvious to one of ordinary skill in the art to be motivated to formulate the pharmaceutically acceptable salts by routine experimentation, in order to prepare various forms of anti-inflammatory drugs (p904, right col 1st para "Compounds 3a, 3d, 4d and 4e exhibited good anti-inflammatory activity").

As said compound and compositions were known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I+ and II. The inventions of Group I+ and II thus lack unity under PCT Rule 13.

Note: claims 124-125 determined unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).