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(54) Titre : COMPOSES ANTIPALUDEENS
(54) Title: ANTI-MALARIAL COMPOUNDS

(57) **Abrégé/Abstract:**

The present invention provides tricyclic compounds, arylamide compounds, and other compounds, and compositions comprising the same, for treating malaria, and methods of treating malaria comprising administering such compounds to an animal.



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(54) Title: ANTI-MALARIAL COMPOUNDS

(57) Abstract: The present invention provides tricyclic compounds, arylamide compounds, and other compounds, and compositions comprising the same, for treating malaria, and methods of treating malaria comprising administering such compounds to an animal.

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ANTI-MALARIAL COMPOUNDS

Cross-Reference To Related Applications

This application claims priority under 35 U.S.C. §119(e) to U.S. provisional application Serial No. 61/162,467 filed March 23, 2009 and to U.S. provisional application Serial No. 61/083,972 filed July 28, 2008, each of which is incorporated herein by reference in its entirety.

Field of the Invention

The present invention is directed, in part, to tricyclic compounds, arylamide compounds, and other compounds, and compositions comprising the same, for treating malaria, and methods of treating malaria comprising administering such compounds to an animal.

Background of the Invention

World-wide, 41% of the population live in areas where malaria is transmitted, such as parts of Africa, Asia, Middle East, Central and South America, Hispaniola, and Oceania. Each year between 350 and 500 million cases of malaria occur worldwide, and over one million people die, most of them young children in sub-Saharan Africa. In areas of Africa with high malaria transmission, an estimated 990,000 people died of malaria in 1995. In 2002, malaria was the fourth cause of death in children in developing countries. In addition, malaria caused 10.7% of all children's deaths in developing countries.

Antimicrobial peptides (AMPs) represent a component of the innate immune system that provides resistance to a variety of pathogenic bacteria. AMPs have provided new leads for developing antibiotics, because they play a central role in the innate immune system. Some AMPs display very broad spectrum action against bacteria, yeast, fungus, and even viruses. Anti-parasitic activities have also been reported for a number of host defense peptides. The best studied organisms include *Plasmodium*, *Leishmania*, and *Trypanosoma* (Vizioli et al., Trends in Pharmacol., 2002, 18, 475-476; Jacobs et al., Antimicrob. Agents Chemother., 2003, 47, 607-613; and Brand et al., J. Biol. Chem., 2002, 277, 49332-49340), the parasitic agents of malaria, leishmaniasis and Chagas' disease, respectively. Additional protozoan parasites reported to be killed by the host defense peptides are *Cryptosporidium*

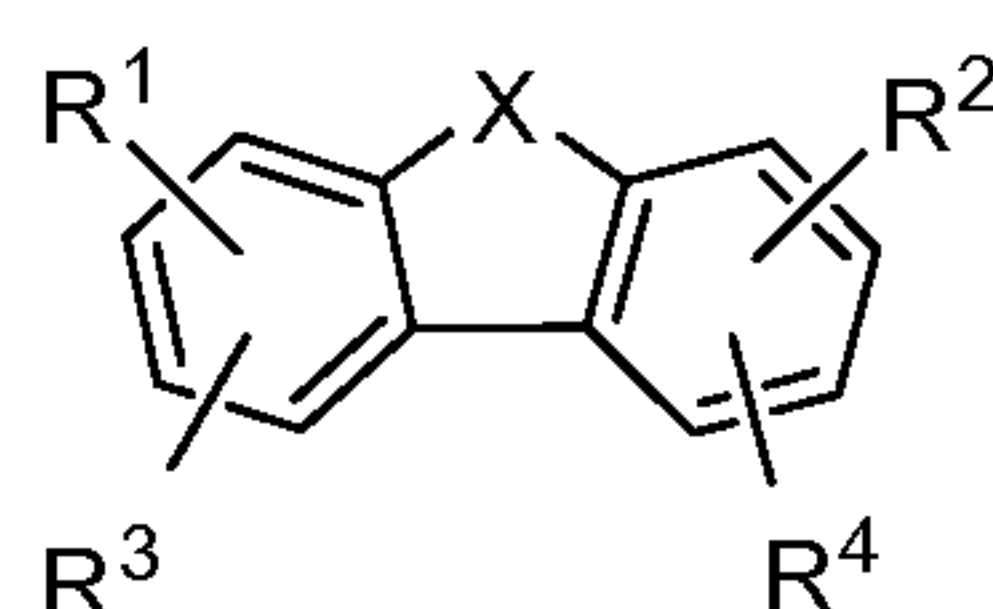
(Giacometti et al., Antimicrob. Agents Chemother., 2000, 44, 3473-3475) and *Giardia* (Aley et al., Infect. Immun., 1994, 62, 5397-5403), human pathogens transmitted in contaminated drinking water. The peptides appear to kill protozoa by interacting with the cytoplasmic membrane causing excessive permeability, lysis and death; a mechanism which is similar to
 5 their mechanism of action against bacteria. Specificity for the parasite versus the host cell can be attributed to differences in phospholipid content and the lack of cholesterol in the protozoan membrane. Because the site of action is at the membrane and not to any specific receptor or intracellular target, the development of resistance to the cytotoxic properties of the antimicrobial peptides is highly unlikely.

10 With regard to anti-malarial activities, natural host defense proteins and their analogs have been shown to inhibit oocyst development of several *Plasmodium* species in various mosquito hosts (Gwadz et al., Infect. Immun., 1989, 57, 2628-2633; and Possani et al., Toxicon, 1998, 36, 1683-1692) and are directly cytotoxic against early sporogonic stages of *Plasmodium* in cell culture (Arrighi et al., Antimicrob. Agents Chemother., 2002, 46,
 15 2104-2110). Furthermore, several antimicrobial peptides have been identified which selectively kill intraerythrocytic parasites (plasmodia life forms growing in red blood cells) by either attacking the infected erythrocyte while sparing normal erythrocytes (Feder et al., J. Biol. Chem., 2000, 275, 4230-4238; and Krugliak et al., Antimicrob. Agents Chemother., 2000, 44, 2442-2451) or interacting with and killing the intracellular parasite without
 20 harming the infected red blood cell (Dagan et al., Antimicrob. Agents Chemother., 2002, 46, 1059-1066; and Efron et al., J. Biol. Chem., 2002, 277, 24067-24072). Recognizing the significant therapeutic limitations of peptides, the development of nonpeptidic mimics of these anti-plasmodia peptides would represent a novel and powerful therapy to combat malaria.

25

Summary of the Invention

The present invention provides compounds of Formula I:



wherein: X is C(R⁷)C(R⁸), C(=O), N(R⁹), O, S, S(=O), or S(=O)₂; R⁷, R⁸, and R⁹ are,
 30 independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, CF₃, or aromatic group; R¹ and R² are,

independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, haloC₁-C₈alkyl, or CN; R³ and R⁴ are, independently, carbocycle(R⁵)(R⁶); each R⁵ and each R⁶ are, independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, CF₃, aromatic group, heterocycle, or the free base or salt form of -(CH₂)_n-NH₂, -(CH₂)_n-NH-(CH₂)_n-NH₂, or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 8; or a pharmaceutically acceptable salt thereof, and compositions comprising the same and a pharmaceutically acceptable carrier.

The present invention also provides methods of treating malaria in an animal comprising administering to the animal a therapeutically effective amount of a compound of Formula I:



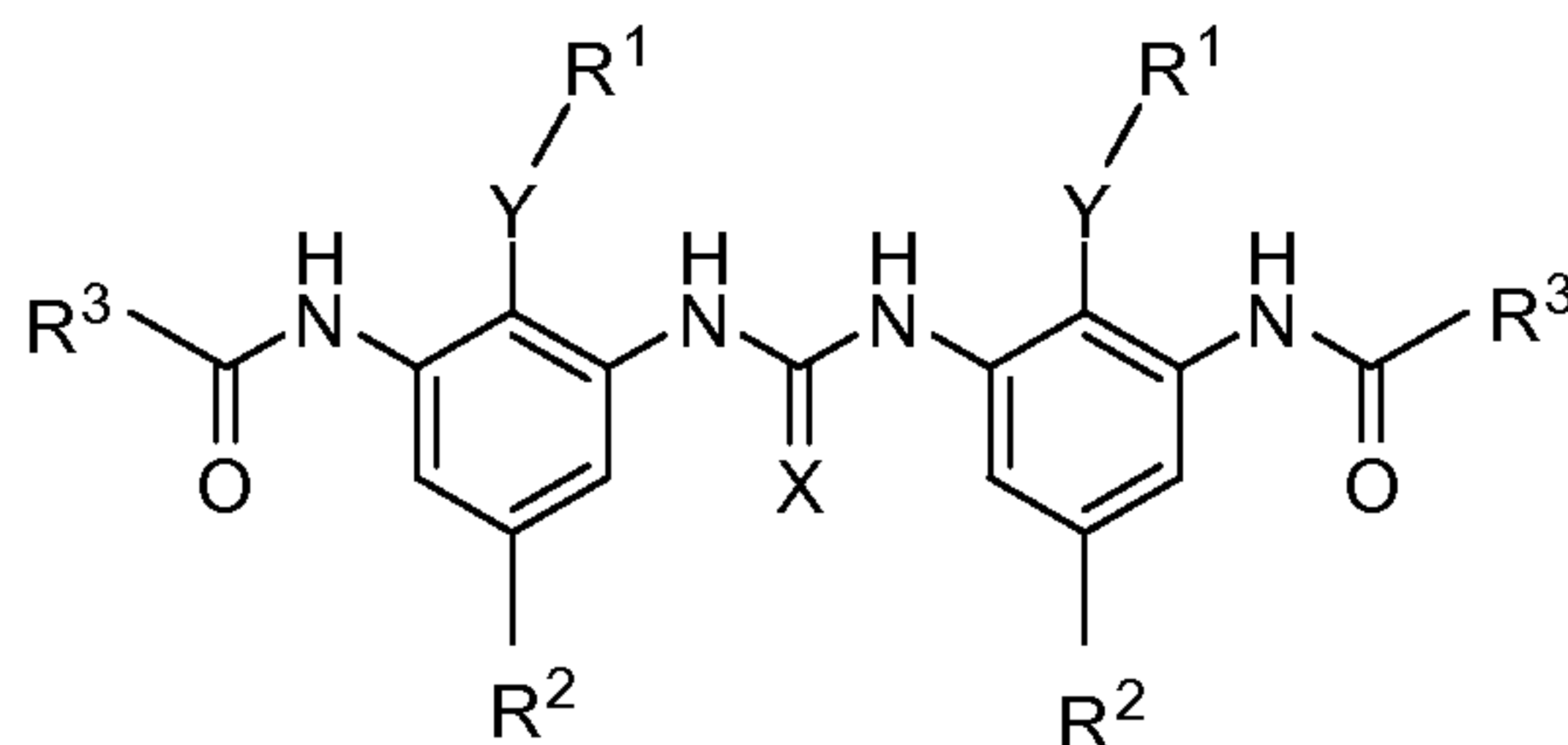
wherein: X is C(R⁷)C(R⁸), C(=O), N(R⁹), O, S, S(=O), or S(=O)₂; R⁷, R⁸, and R⁹ are, independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, CF₃, or aromatic group; R¹ and R² are, independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, haloC₁-C₈alkyl, or CN; R³ and R⁴ are, independently, carbocycle(R⁵)(R⁶); each R⁵ and each R⁶ are, independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, CF₃, aromatic group, heterocycle, or the free base or salt form of -(CH₂)_n-NH₂, -(CH₂)_n-NH-(CH₂)_n-NH₂, or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 8; or a pharmaceutically acceptable salt thereof.

The present invention also provides methods of killing or inhibiting the growth of a *Plasmodium* species comprising contacting the species with an effective amount of a compound of Formula I:



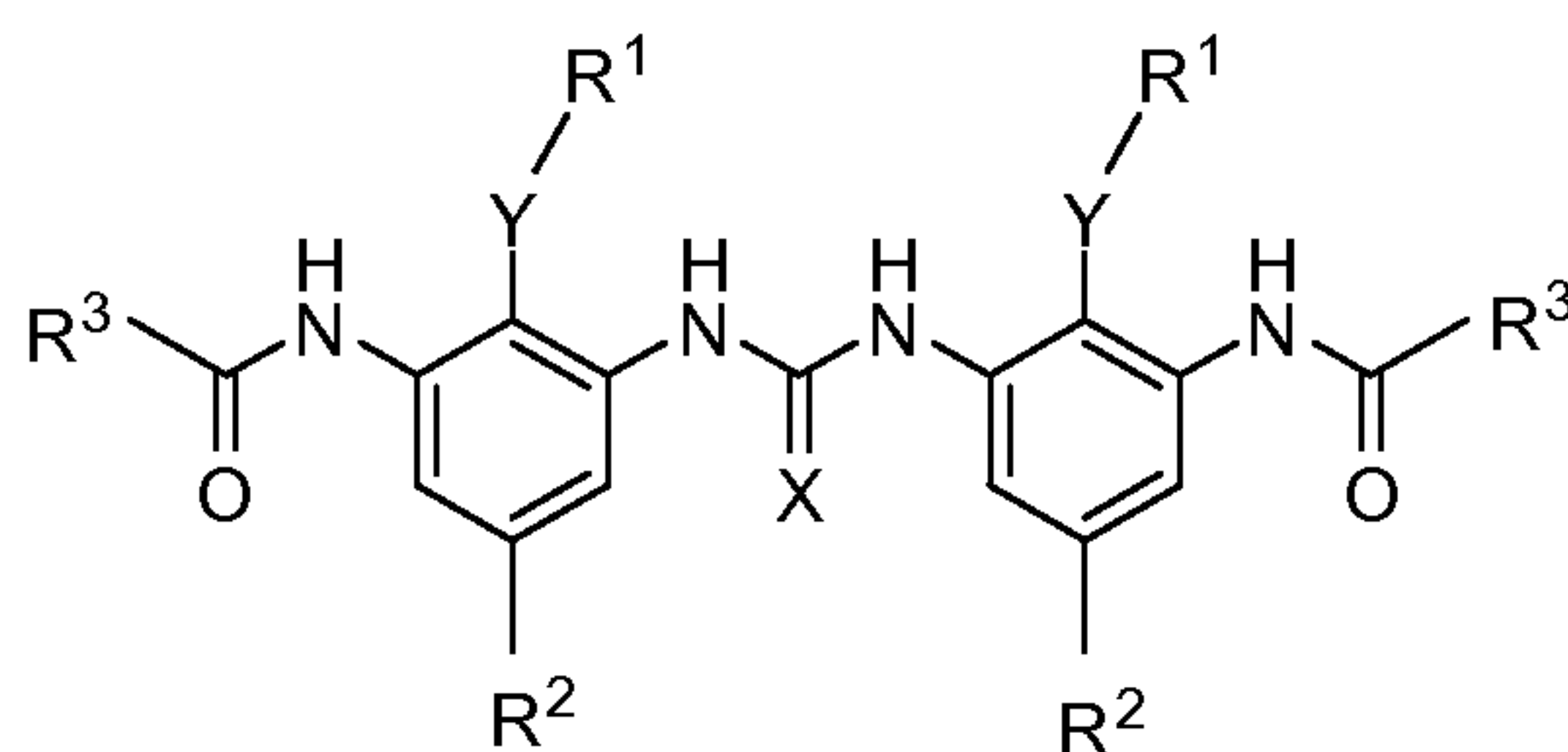
wherein: X is C(R⁷)C(R⁸), C(=O), N(R⁹), O, S, S(=O), or S(=O)₂; R⁷, R⁸, and R⁹ are, independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, CF₃, or aromatic group; R¹ and R² are, independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, haloC₁-C₈alkyl, or CN; R³ and R⁴ are, independently, carbocycle(R⁵)(R⁶); each R⁵ and each R⁶ are, independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, CF₃, aromatic group, heterocycle, or the free base or salt form of -(CH₂)_n-NH₂, -(CH₂)_n-NH-(CH₂)_n-NH₂, or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 8; or a pharmaceutically acceptable salt thereof.

The present invention also provides compounds of Formula II:



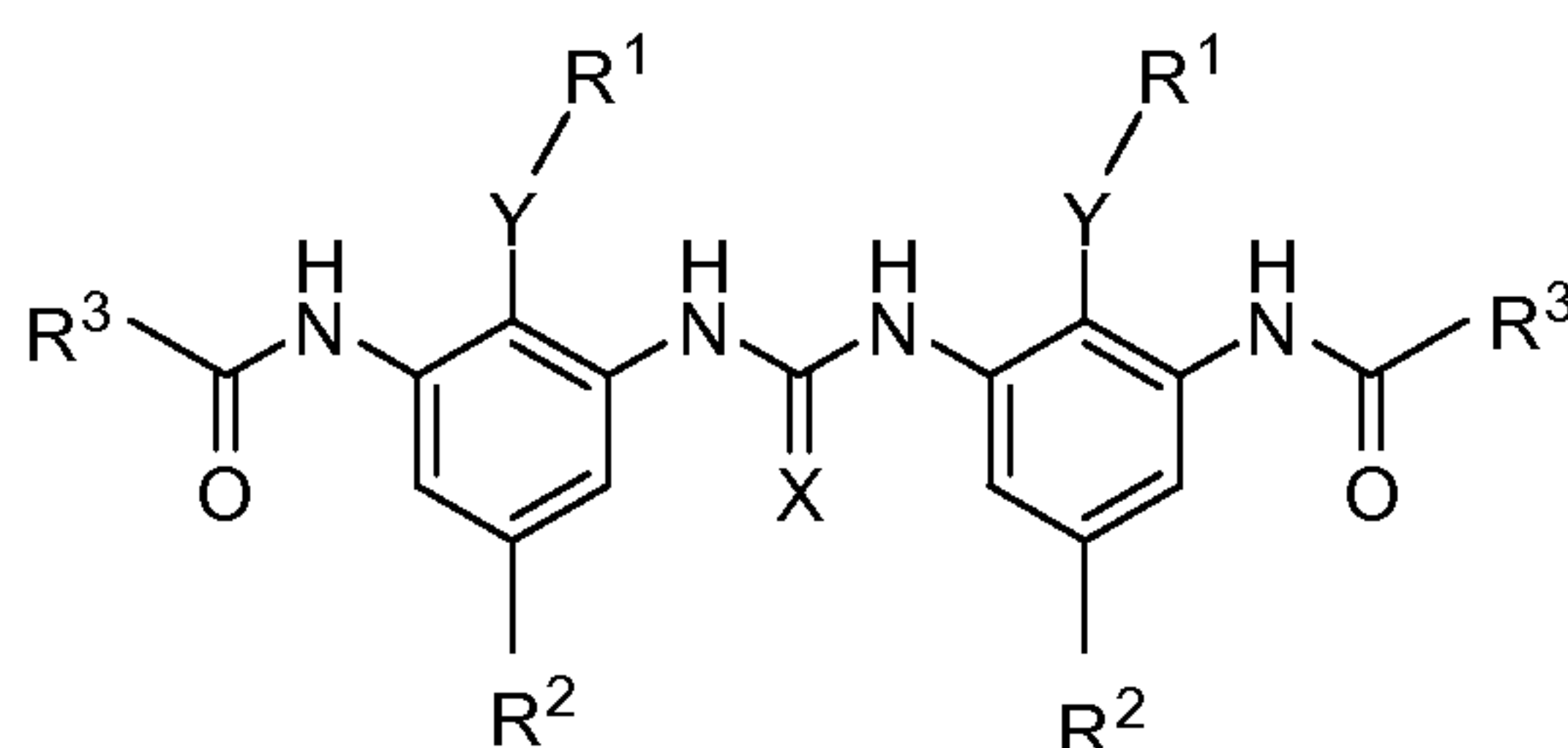
- wherein: X is O or S; each Y is, independently, O, S, or N; each R¹ is, independently, H, 5- or 6-membered heterocycle, or the free base or salt form of $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; or each R¹ is, independently, together with Y a 5- or 6-membered heterocycle; each R² is, independently, H, CF₃, C(CH₃)₃, halo, or OH; and each R³ is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; or a pharmaceutically acceptable salt thereof, and compositions comprising the same and a pharmaceutically acceptable carrier.

The present invention also provides methods of treating malaria in an animal comprising administering to the animal a therapeutically effective amount of a compound of Formula II:



- wherein: X is O or S; each Y is, independently, O, S, or N; each R¹ is, independently, H, 5- or 6-membered heterocycle, or the free base or salt form of $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; or each R¹ is, independently, together with Y a 5- or 6-membered heterocycle; each R² is, independently, H, CF₃, C(CH₃)₃, halo, or OH; and each R³ is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; or a pharmaceutically acceptable salt thereof.

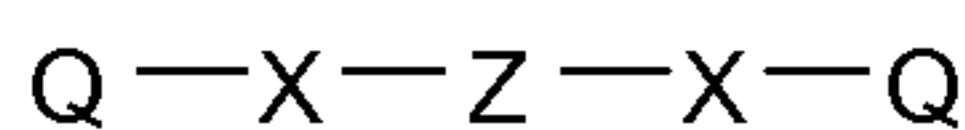
The present invention also provides methods of killing or inhibiting the growth of a *Plasmodium* species comprising contacting the species with an effective amount of a compound of Formula II:

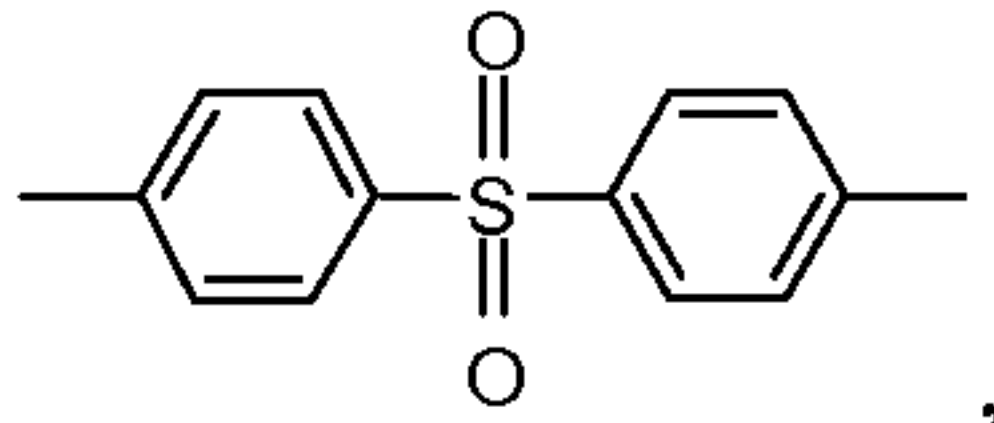
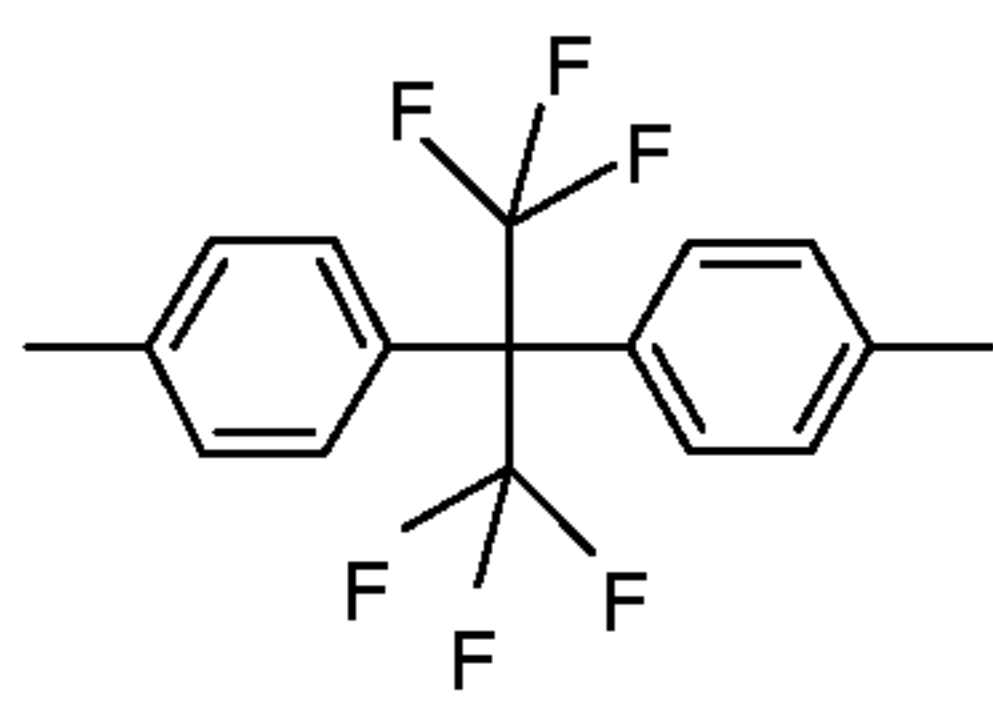


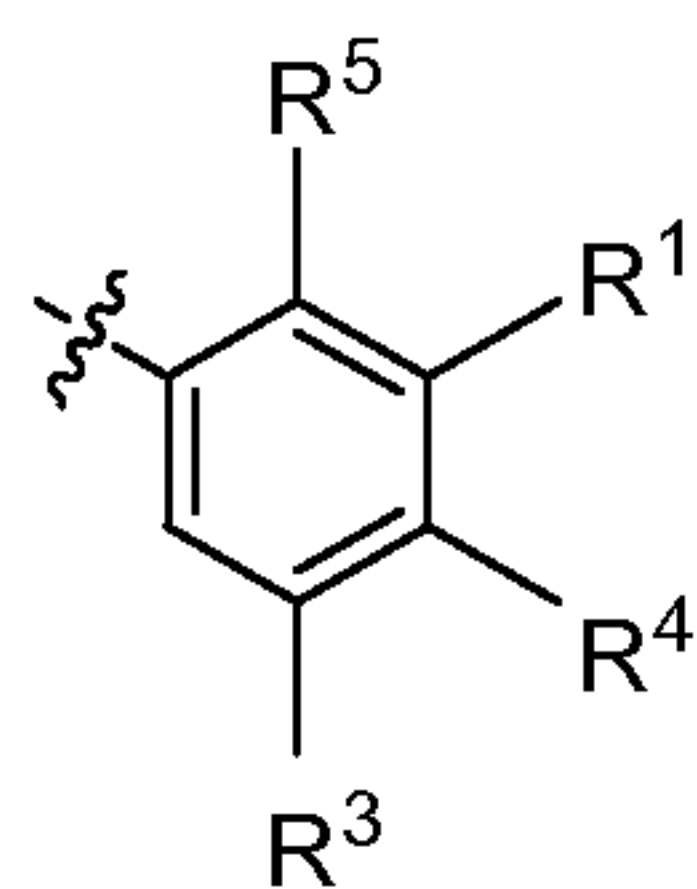
wherein: X is O or S; each Y is, independently, O, S, or N; each R^1 is, independently, H, 5- or 6-membered heterocycle, or the free base or salt form of $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; or each R^1 is, independently, together with Y a 5- or 6-membered heterocycle; each R^2 is, independently, H, CF_3 , $C(CH_3)_3$, halo, or OH; and each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; or a pharmaceutically acceptable salt thereof.

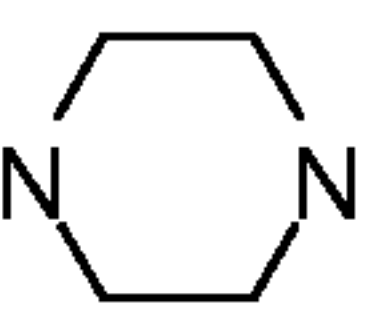
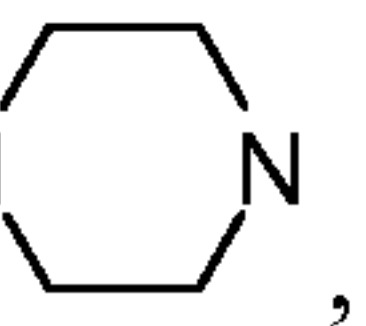
The present invention also provides compounds of Formula III:

10



wherein: Z is , , or phenyl; each Q is, independently,

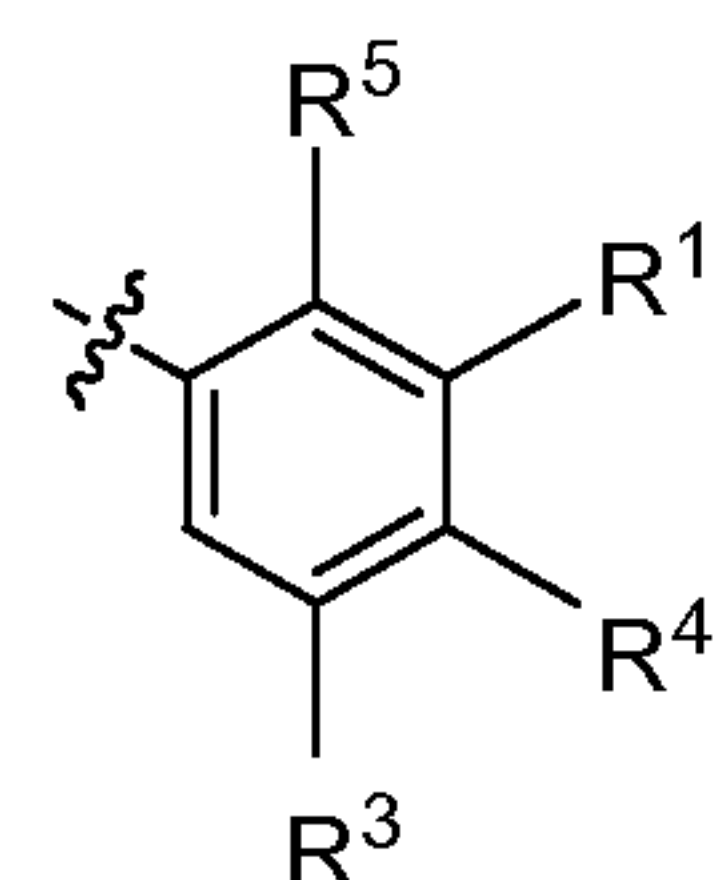
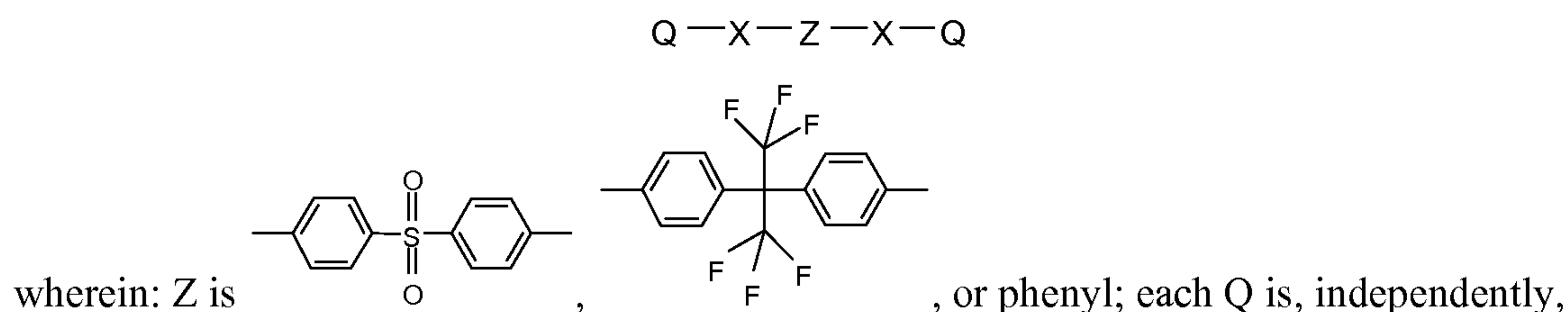


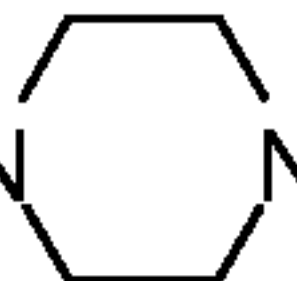
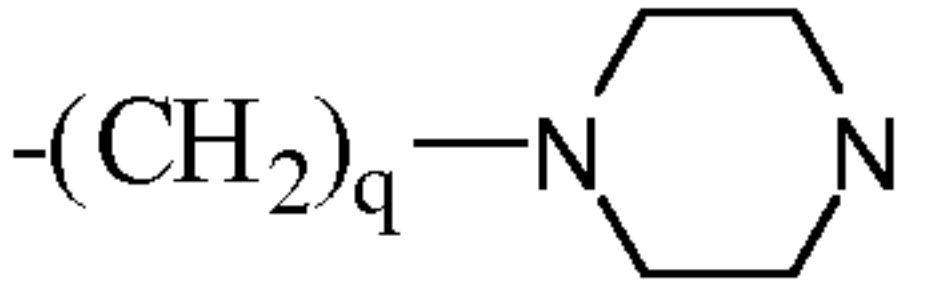
or $-C(=O)-(CH_2)_b-NH-C(=NH)-NH_2$, where each b is, independently, 1 to 4; each X is, independently, O, S, or N; each R^1 is, independently, H, CF_3 , $C(CH_3)_3$, halo, or OH; each R^3 is, independently, H, $-NH-R^2$, $-(CH_2)_r-NH_2$, $-NH_2$, $-NH-(CH_2)_w-NH_2$, or $-(CH_2)_y-N$ , where each r is, independently, 1 or 2, each w is, independently, 1 to 3, and each y is, independently, 1 or 2; each R^2 is, independently, H, or the free base or salt form of $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; each R^4 is, independently, H, $-NH-C(=O)-(CH_2)_p-NH-C(=NH)-NH_2$ or $-(CH_2)_q-N$ , where each p is, independently, 1 to 6, and each q is, independently, 1 or 2; and each R^5 is,

independently, H or CF₃; or a pharmaceutically acceptable salt thereof, and compositions comprising the same and a pharmaceutically acceptable carrier.

The present invention also provides methods of treating malaria in an animal comprising administering to the animal a therapeutically effective amount of a compound of

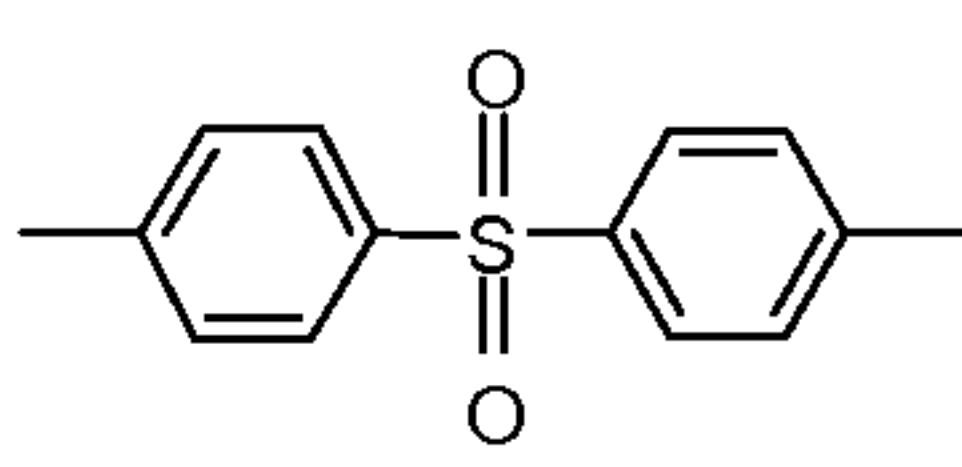
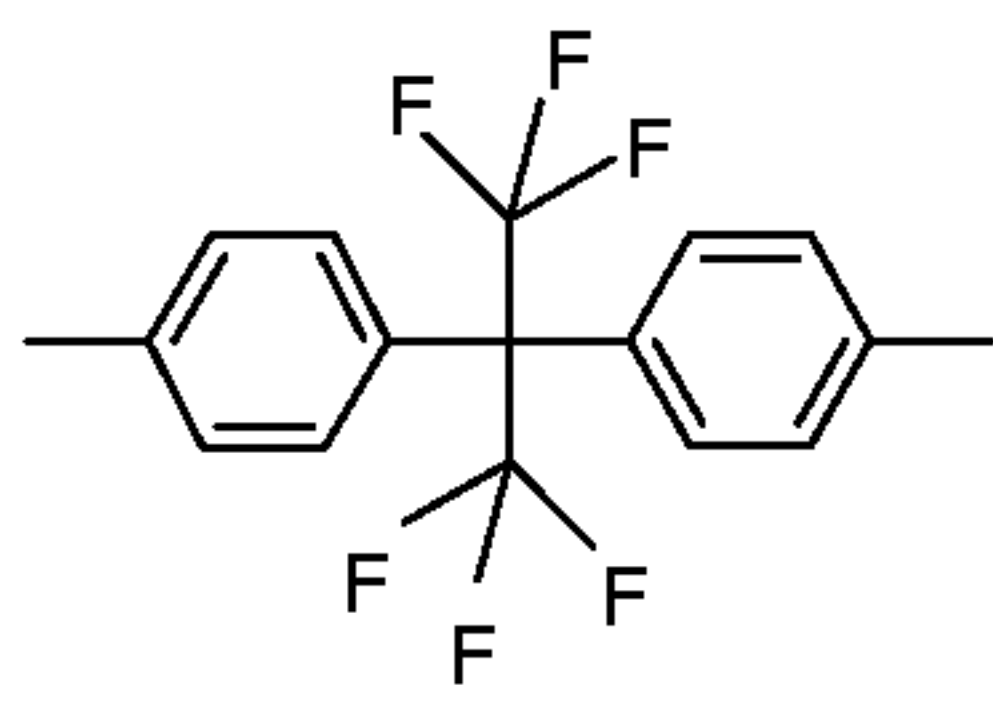
5 Formula III:

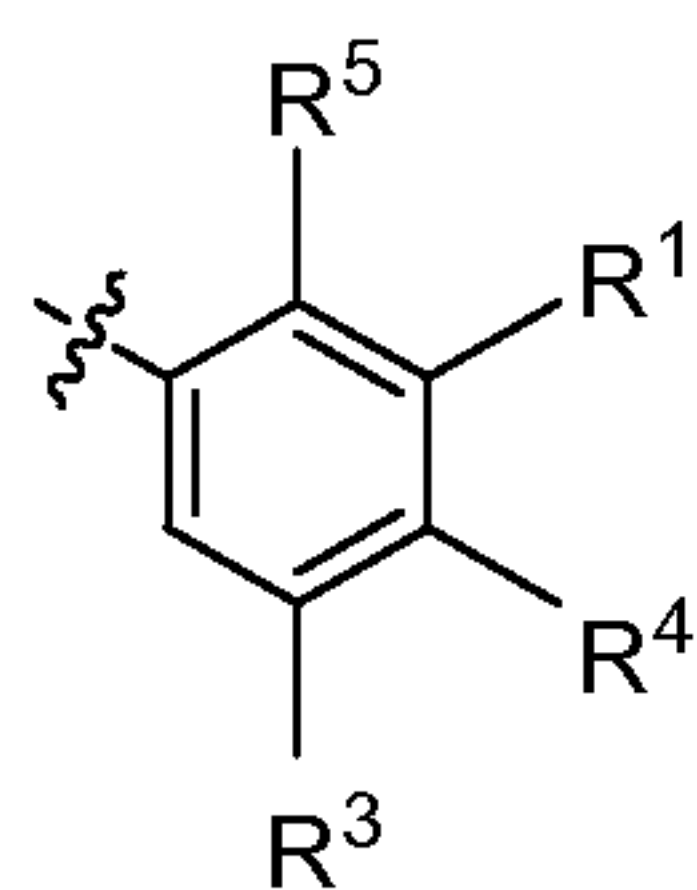


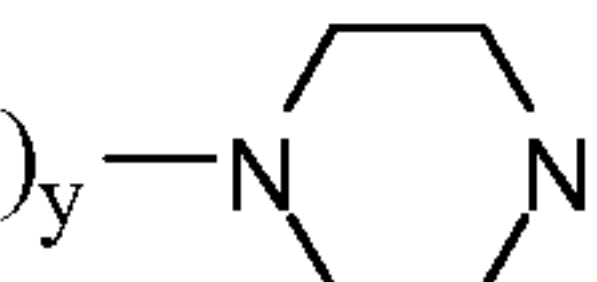
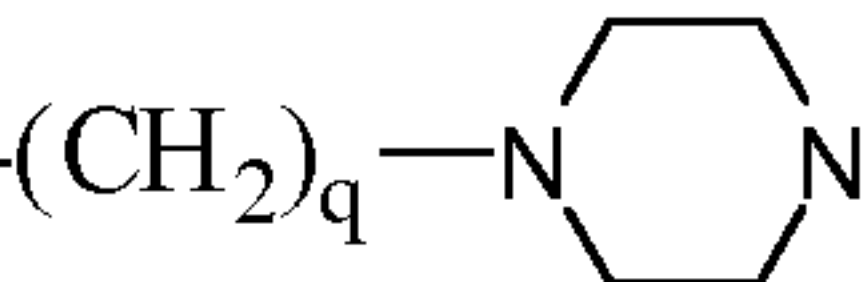
or -C(=O)-(CH₂)_b-NH-C(=NH)-NH₂, where each b is, independently, 1 to 4; each X is, independently, O, S, or N; each R¹ is, independently, H, CF₃, C(CH₃)₃, halo, or
 10 OH; each R³ is, independently, H, -NH-R², -(CH₂)_r-NH₂, -NH₂, -NH-(CH₂)_w-NH₂, or
 -(CH₂)_y-N, where each r is, independently, 1 or 2, each w is, independently, 1 to 3, and each y is, independently, 1 or 2; each R² is, independently, H, or the free base or salt form of -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4;
 each R⁴ is, independently, H, -NH-C(=O)-(CH₂)_p-NH-C(=NH)-NH₂ or ,
 15 where each p is, independently, 1 to 6, and each q is, independently, 1 or 2; and each R⁵ is, independently, H or CF₃, or a pharmaceutically acceptable salt thereof.

The present invention also provides methods of killing or inhibiting the growth of a *Plasmodium* species comprising contacting the species with an effective amount of a compound of Formula III:

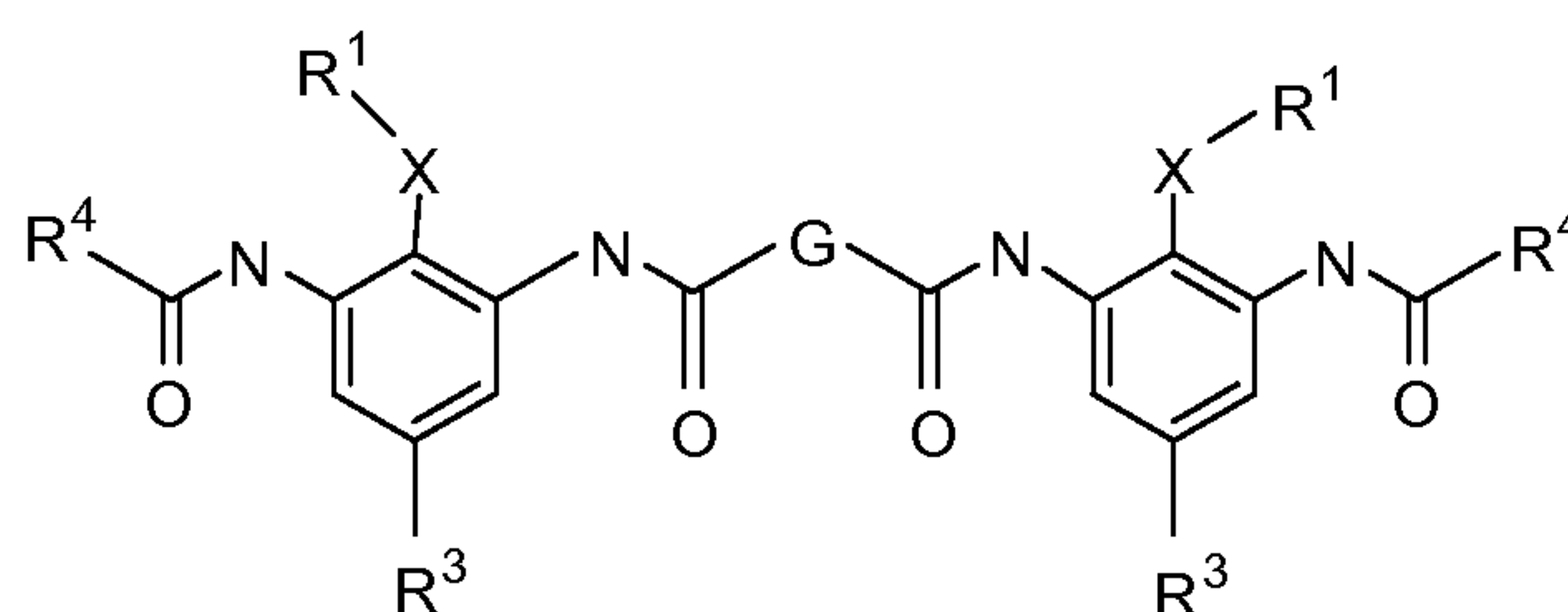


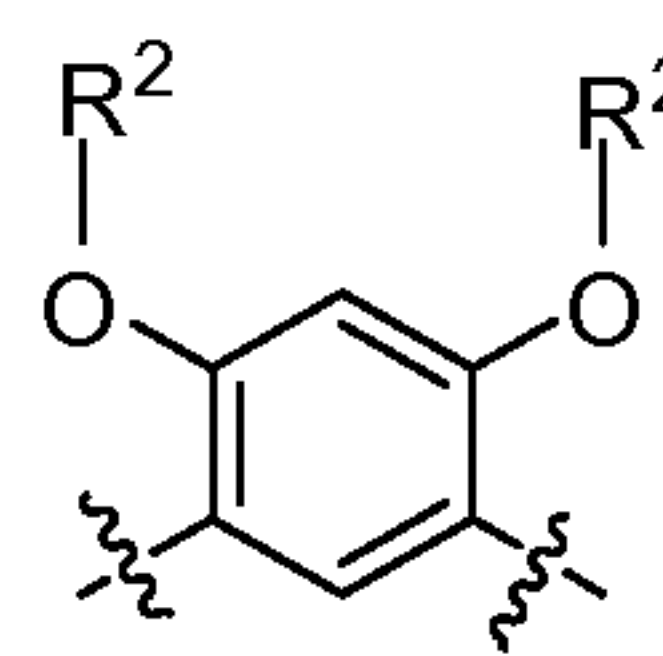
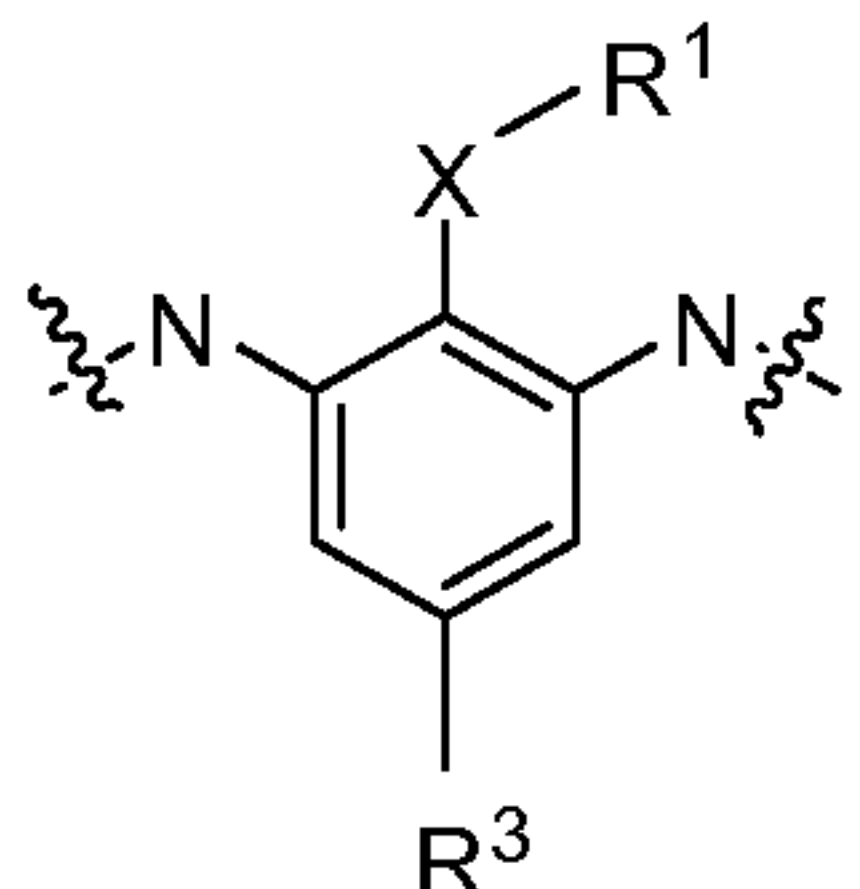
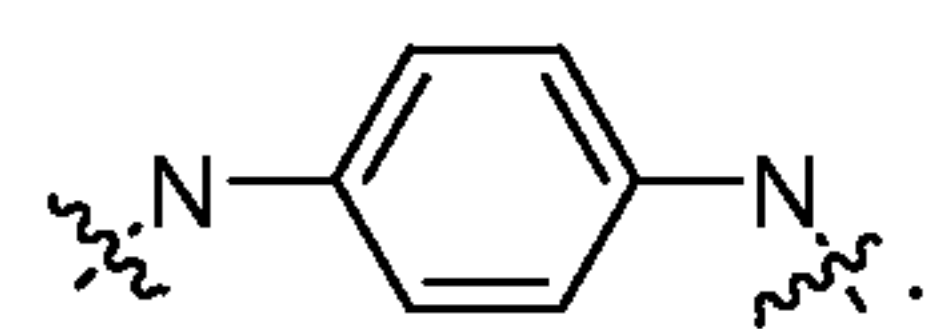
wherein: Z is , , or phenyl; each Q is, independently,

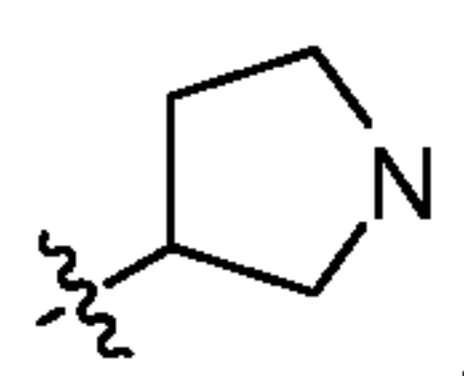


or $-\text{C}(=\text{O})-(\text{CH}_2)_b-\text{NH}-\text{C}(=\text{NH})-\text{NH}_2$, where each b is, independently, 1 to 4; each X is, independently, O, S, or N; each R^1 is, independently, H, CF_3 , $\text{C}(\text{CH}_3)_3$, halo, or OH; each R^3 is, independently, H, $-\text{NH}-\text{R}^2$, $-(\text{CH}_2)_r-\text{NH}_2$, $-\text{NH}_2$, $-\text{NH}-(\text{CH}_2)_w-\text{NH}_2$, or $-(\text{CH}_2)_y-\text{N}$ , where each r is, independently, 1 or 2, each w is, independently, 1 to 3, and each y is, independently, 1 or 2; each R^2 is, independently, H, or the free base or salt form of $-(\text{CH}_2)_n-\text{NH}_2$ or $-(\text{CH}_2)_n-\text{NH}-\text{C}(=\text{NH})\text{NH}_2$, where each n is, independently, 1 to 4; each R^4 is, independently, H, $-\text{NH}-\text{C}(=\text{O})-(\text{CH}_2)_p-\text{NH}-\text{C}(=\text{NH})-\text{NH}_2$ or $-(\text{CH}_2)_q-\text{N}$ , where each p is, independently, 1 to 6, and each q is, independently, 1 or 2; and each R^5 is, independently, H or CF_3 , or a pharmaceutically acceptable salt thereof.

The present invention also provides compounds of Formula IV:

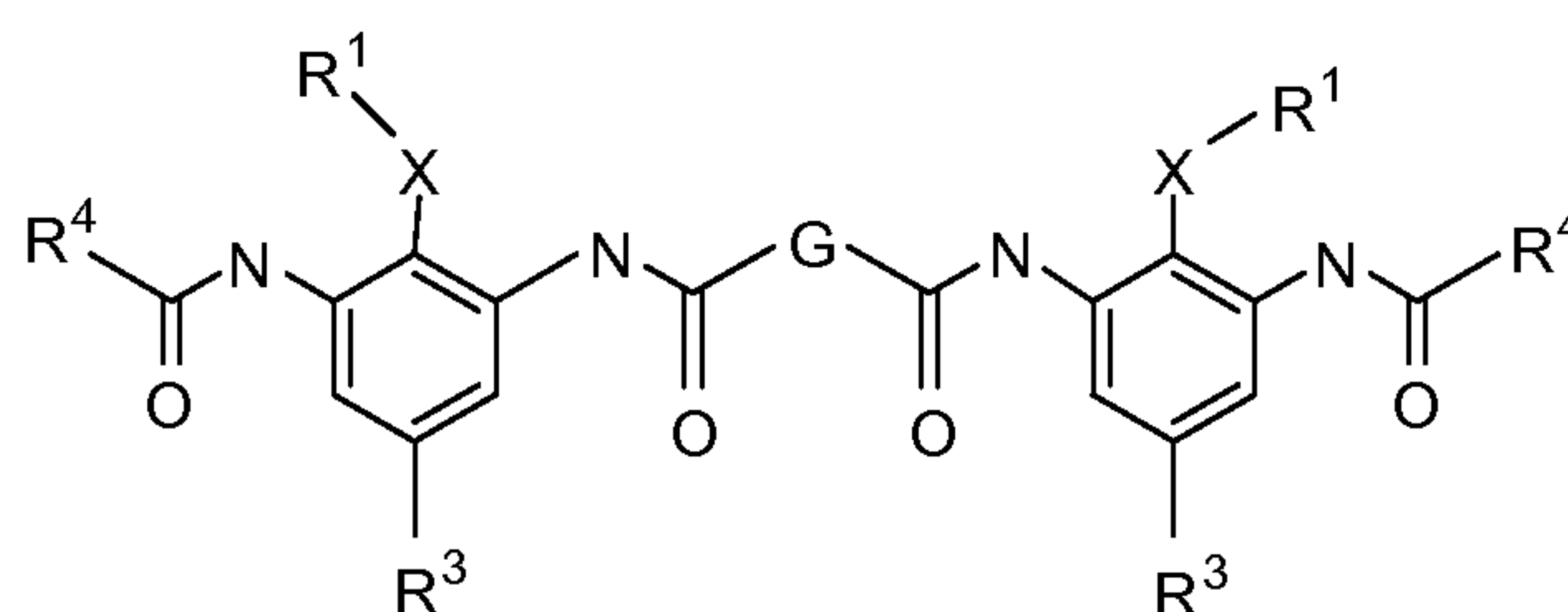


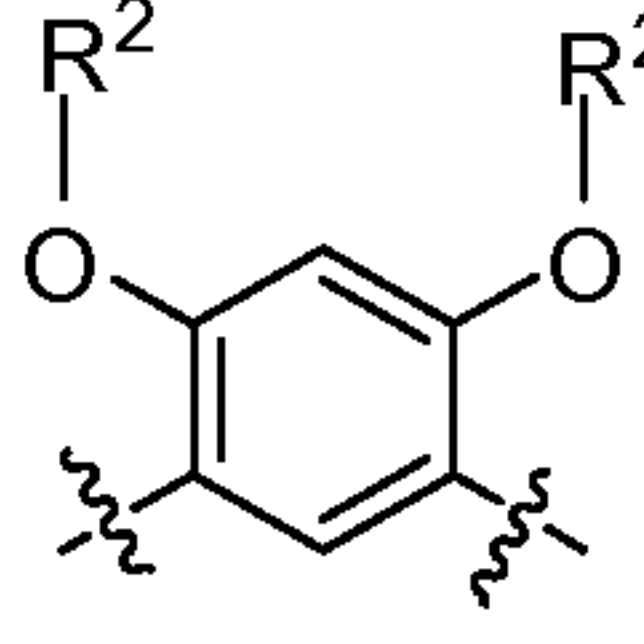
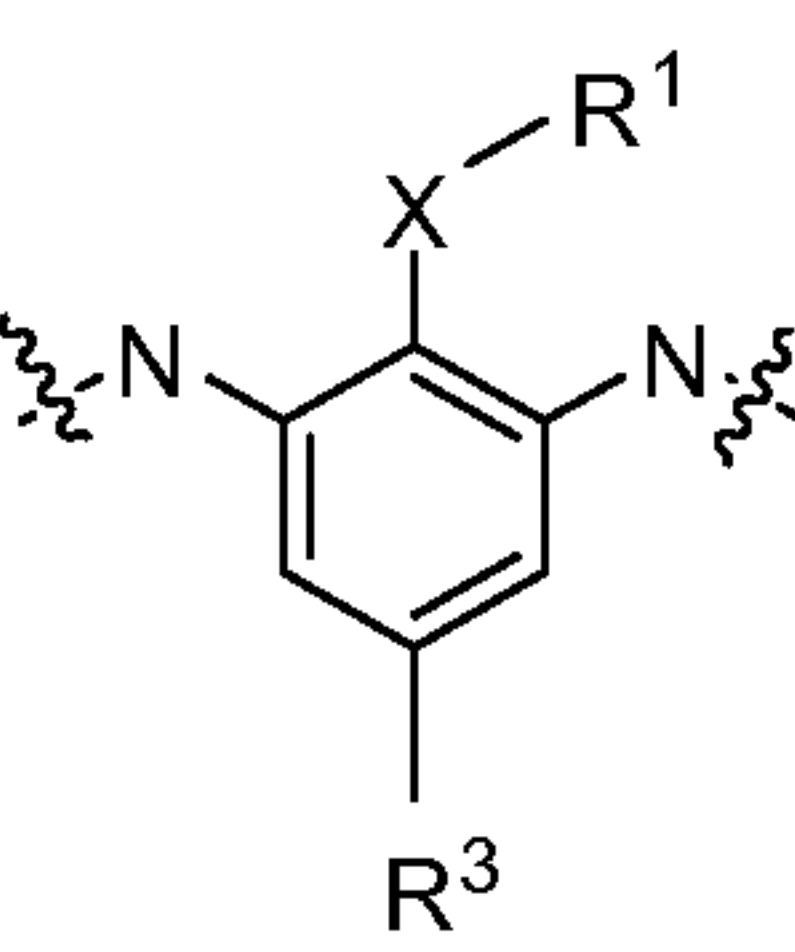
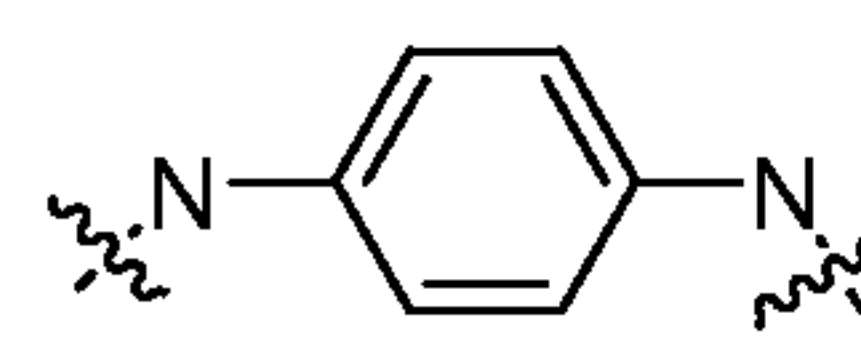
wherein: G is , , or ; each X is, independently,

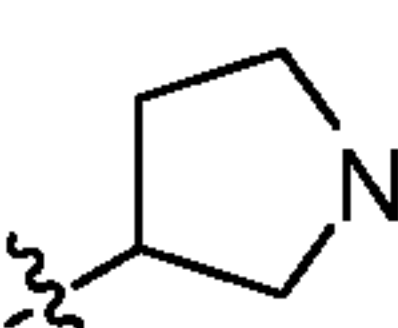
O or S; each R^1 is, independently, , or the free base or salt form of $-(\text{CH}_2)_n-\text{NH}_2$ or $-(\text{CH}_2)_n-\text{NH}-\text{C}(=\text{NH})\text{NH}_2$, where each n is, independently, 1 to 4; each R^2 is, independently, H, C_1-C_8 alkyl, or the free base or salt form of $-(\text{CH}_2)_n-\text{NH}_2$ or $-(\text{CH}_2)_n-\text{NH}-\text{C}(=\text{NH})\text{NH}_2$,

where each n is, independently, 1 to 4; each R^3 is, independently, H, CF_3 , $C(CH_3)_3$, halo, or OH; and each R^4 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4, or a pharmaceutically acceptable salt thereof, and compositions comprising the same and a pharmaceutically acceptable carrier.

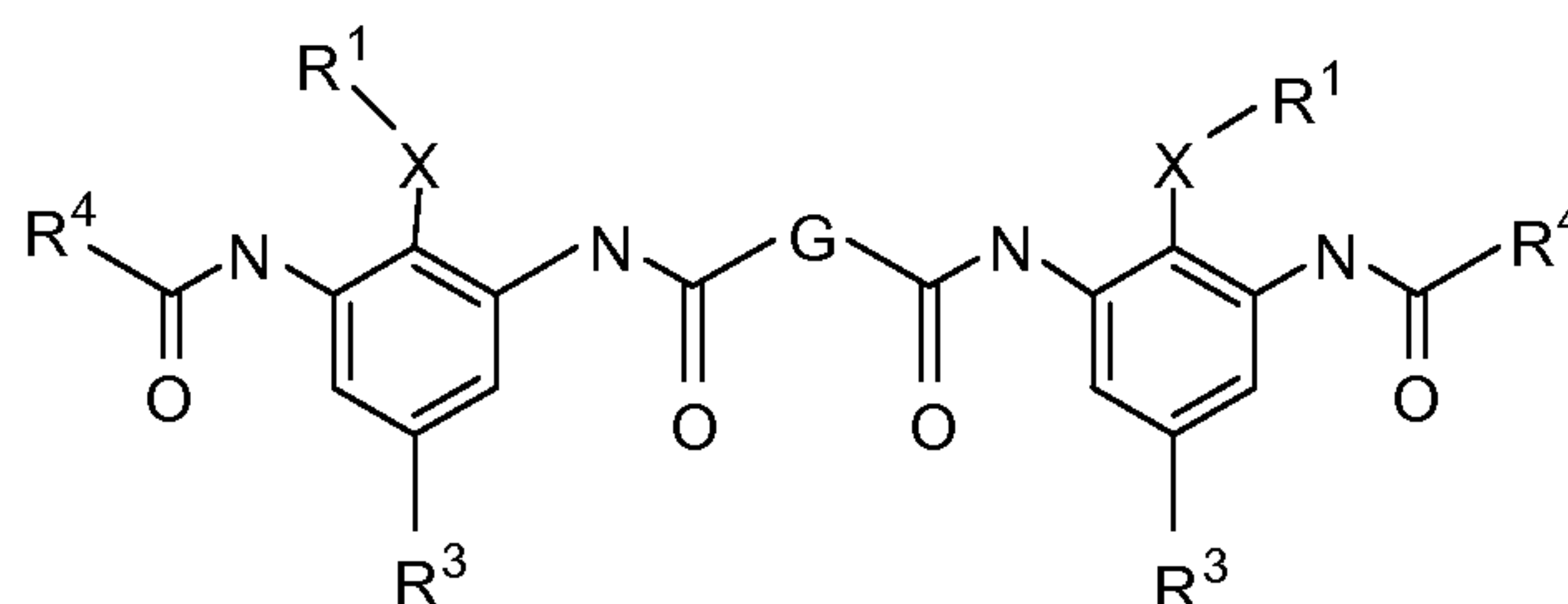
- 5 The present invention also provides methods of treating malaria in an animal comprising administering to the animal a therapeutically effective amount of a compound of Formula IV:

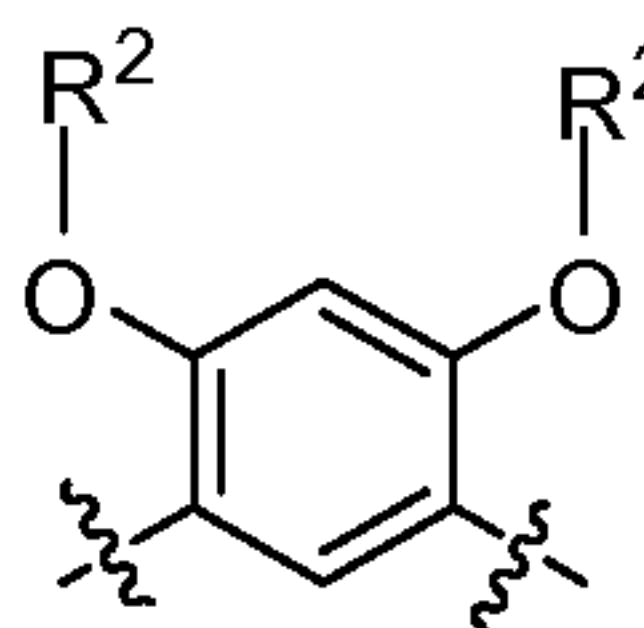
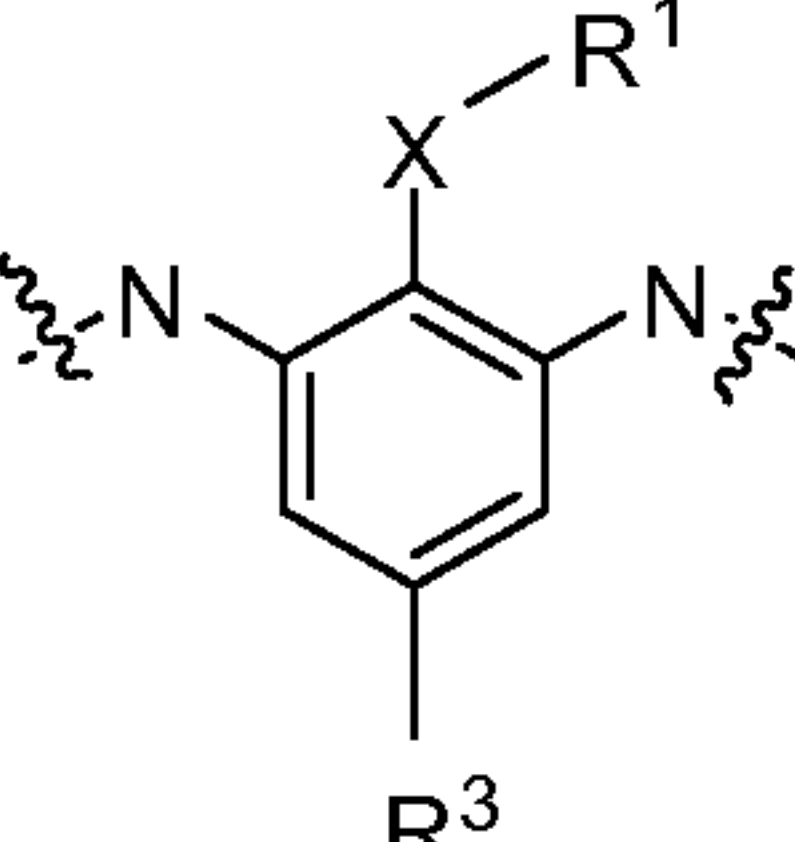
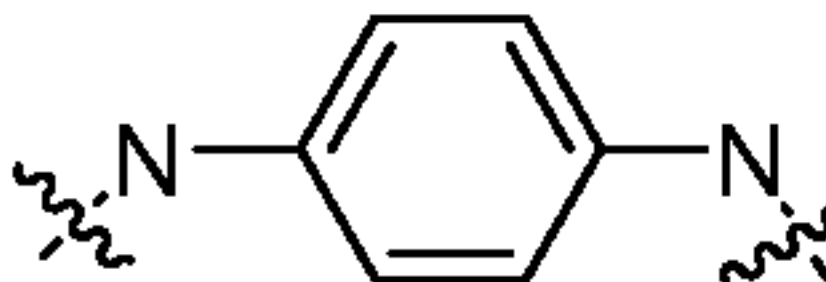


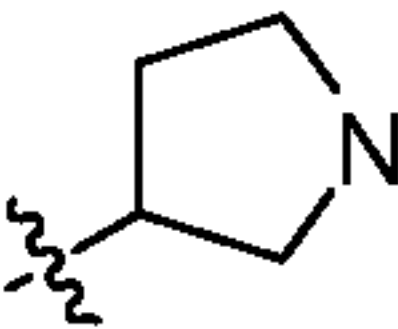
wherein: G is , , or ; each X is, independently,

- 10 O or S; each R^1 is, independently, , or the free base or salt form of $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; each R^2 is, independently, H, C_1 - C_8 alkyl, or the free base or salt form of $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; each R^3 is, independently, H, CF_3 , $C(CH_3)_3$, halo, or OH; and each R^4 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4, or a pharmaceutically acceptable salt thereof.
- 15

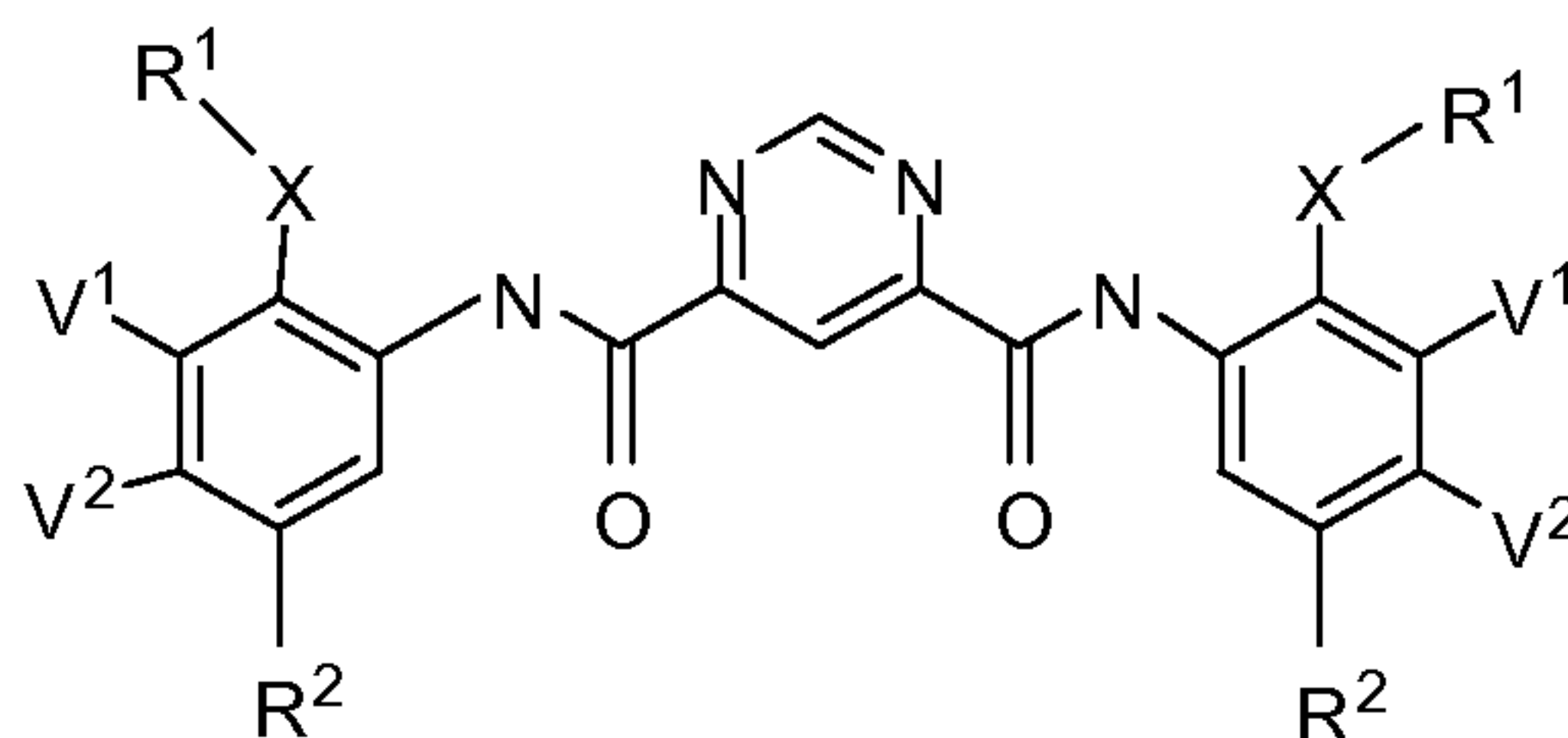
The present invention also provides methods of killing or inhibiting the growth of a *Plasmodium* species comprising contacting the species with an effective amount of a compound of Formula IV:



wherein: G is , , or ; each X is, independently,

O or S; each R¹ is, independently, , or the free base or salt form of -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4; each R² is, independently, H, C₁-C₈alkyl, or the free base or salt form of -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂,
 5 where each n is, independently, 1 to 4; each R³ is, independently, H, CF₃, C(CH₃)₃, halo, or OH; and each R⁴ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4, or a pharmaceutically acceptable salt thereof.

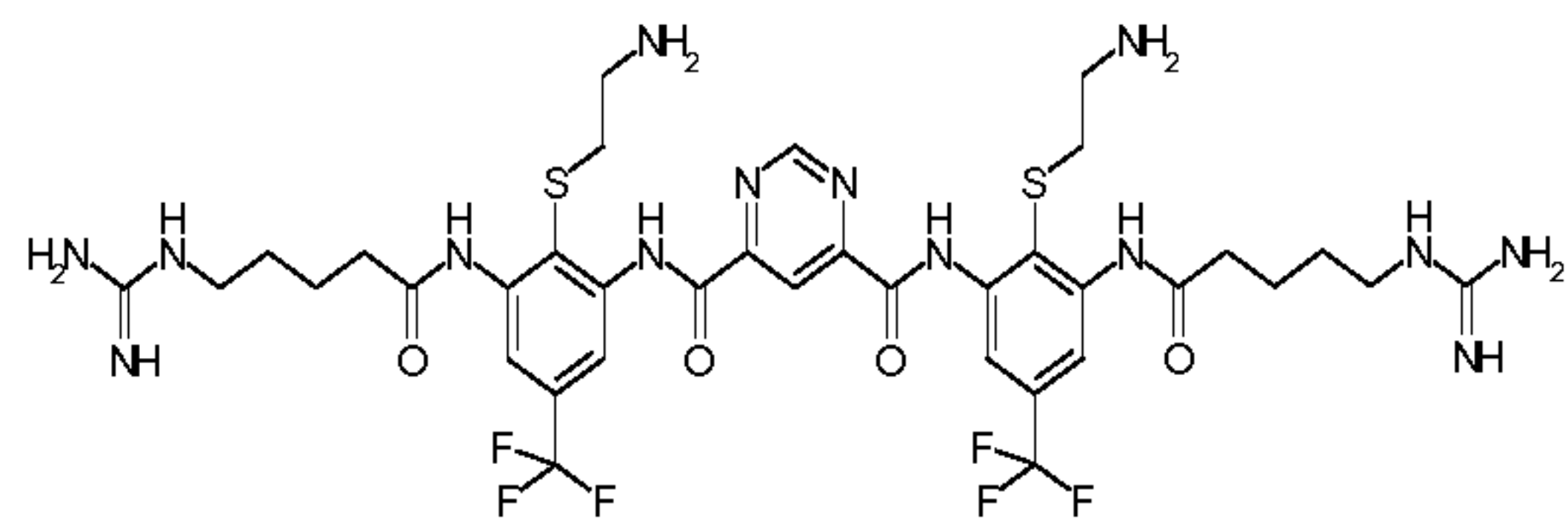
The present invention also provides compounds of Formula V:

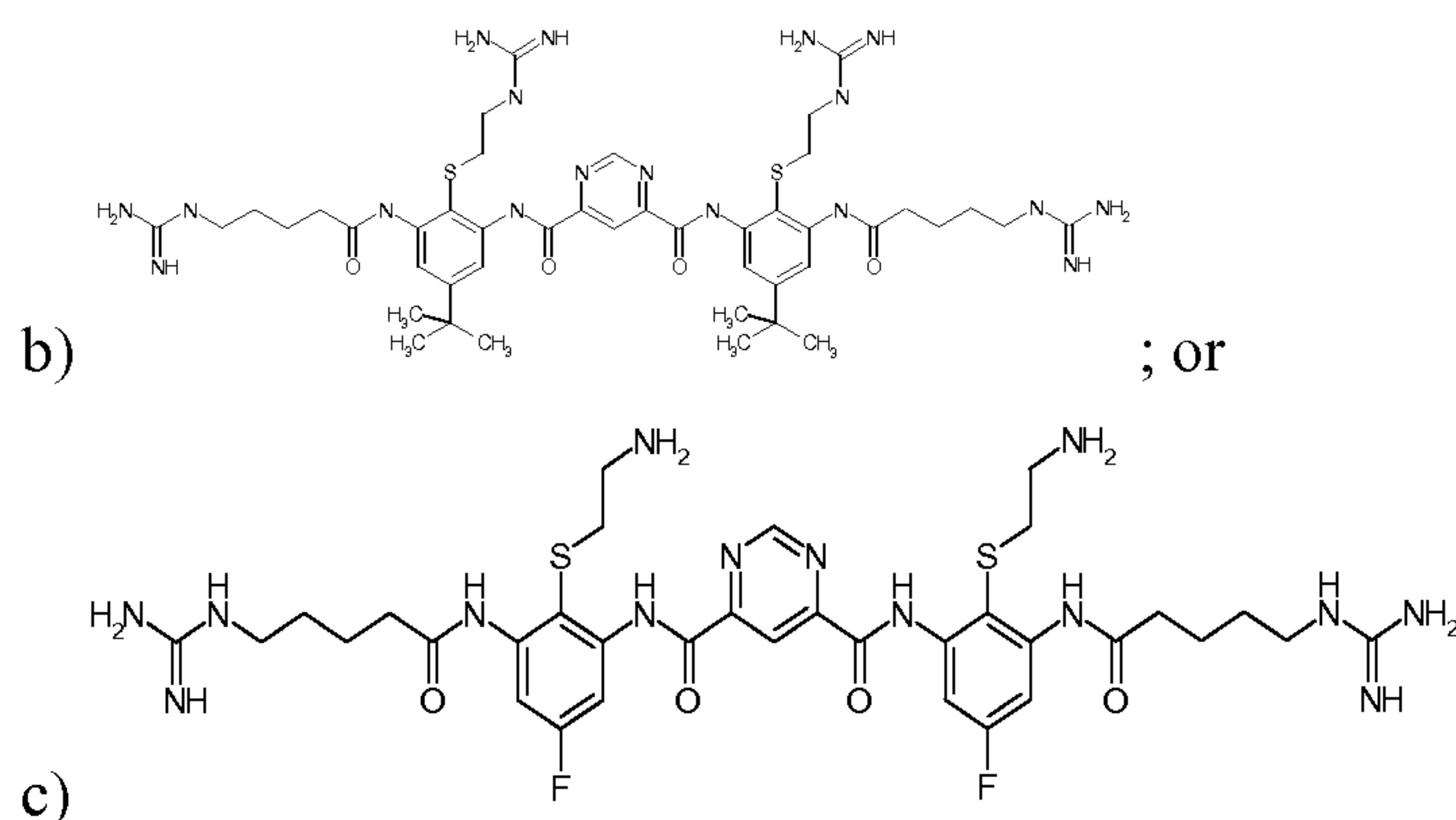


10 wherein: each X is, independently, O, S, or S(=O)₂; each R¹ is, independently, -(CH₂)_n-NH₂, -(CH₂)_n-NH-C(=NH)NH₂, or -(CH₂)_n-NH-C(=O)-R⁴, where each n is, independently, 1 to 4, and each R⁴ is, independently, H, C₁-C₃alkyl, or -(CH₂)_p-NH₂, where each p is, independently, 1 or 2; each R² is, independently, H, halo, CF₃, or C(CH₃)₃; and each V² is H, and each V¹ is, independently, -N-C(=O)-R³, where each R³ is, independently, -(CH₂)_n-NH₂
 15 or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4; or each V¹ is H and each V² is, independently, -S-R⁵, where each R⁵ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4; or a pharmaceutically acceptable salt thereof, and compositions comprising the same and a pharmaceutically acceptable carrier, provided that the compound is not:

20

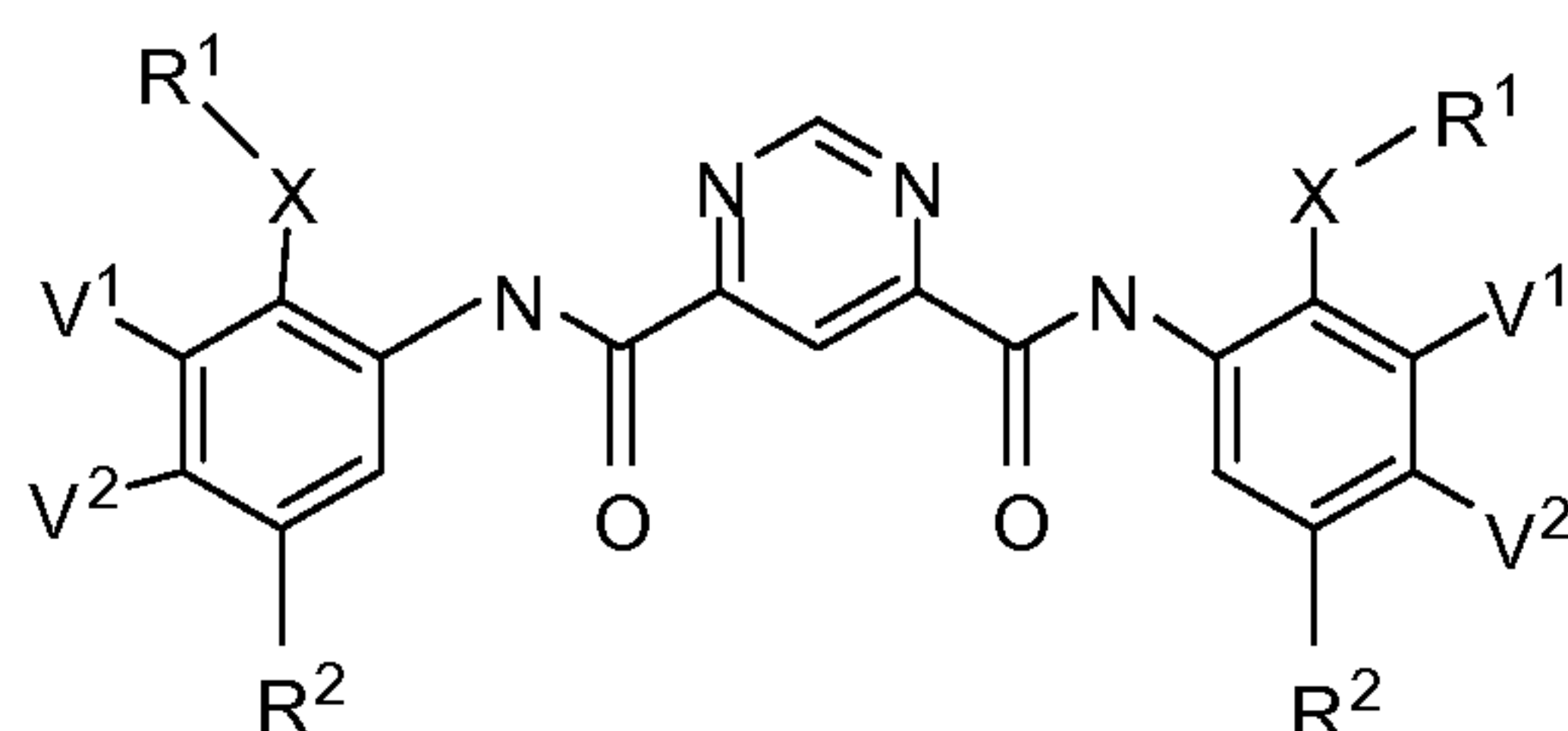
a)





The present invention also provides methods of treating malaria in an animal comprising administering to the animal a therapeutically effective amount of a compound of

5 Formula V:

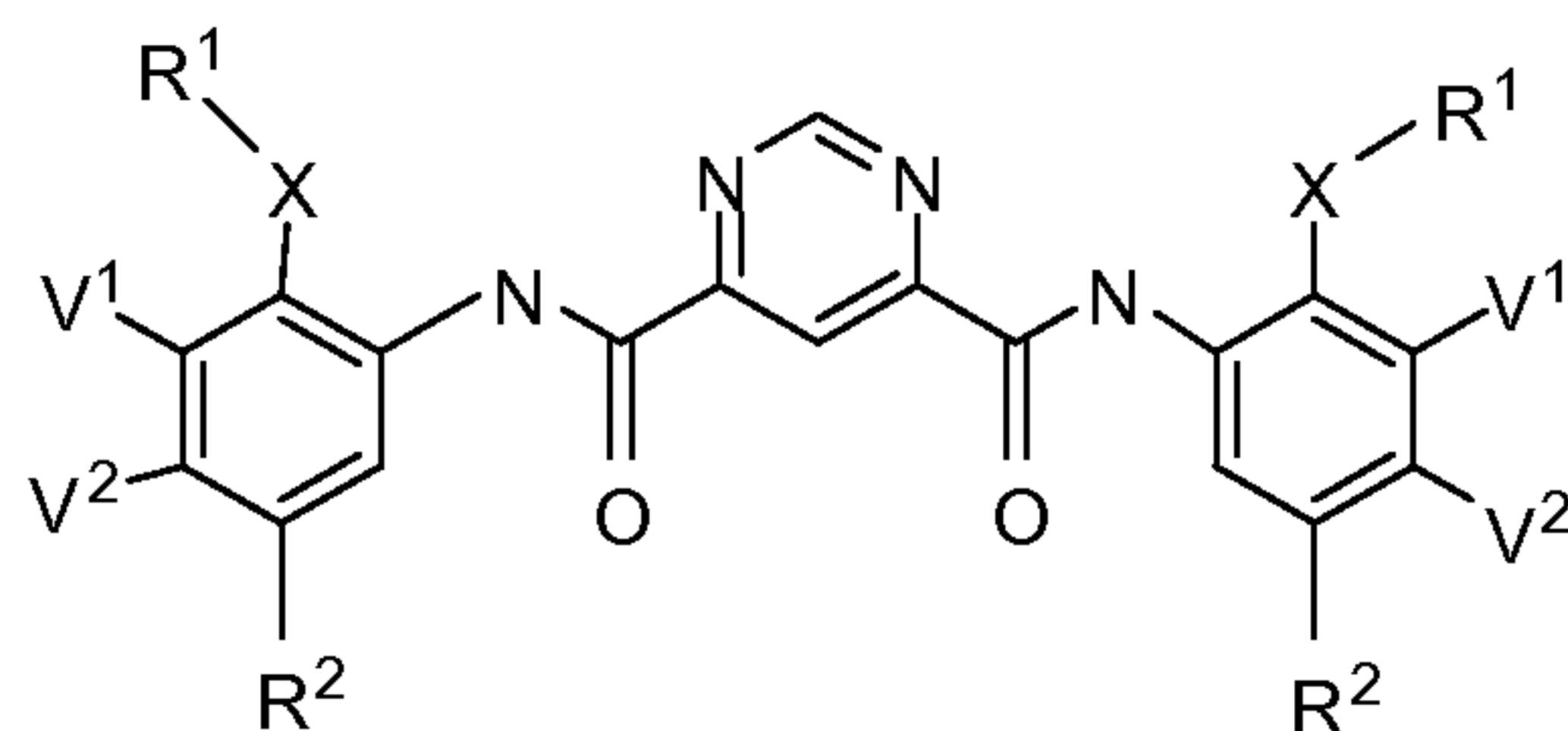


wherein: each X is, independently, O, S, or S(=O)₂; each R¹ is, independently, -(CH₂)_n-NH₂, -(CH₂)_n-NH-C(=NH)NH₂, or -(CH₂)_n-NH-C(=O)-R⁴, where each n is, independently, 1 to 4, and each R⁴ is, independently, H, C₁-C₃alkyl, or -(CH₂)_p-NH₂, where each p is,

10 independently, 1 or 2; each R² is, independently, H, halo, CF₃, or C(CH₃)₃; and each V² is H, and each V¹ is, independently, -N-C(=O)-R³, where each R³ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4; or each V¹ is H and each V² is, independently, -S-R⁵, where each R⁵ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4; or a pharmaceutically

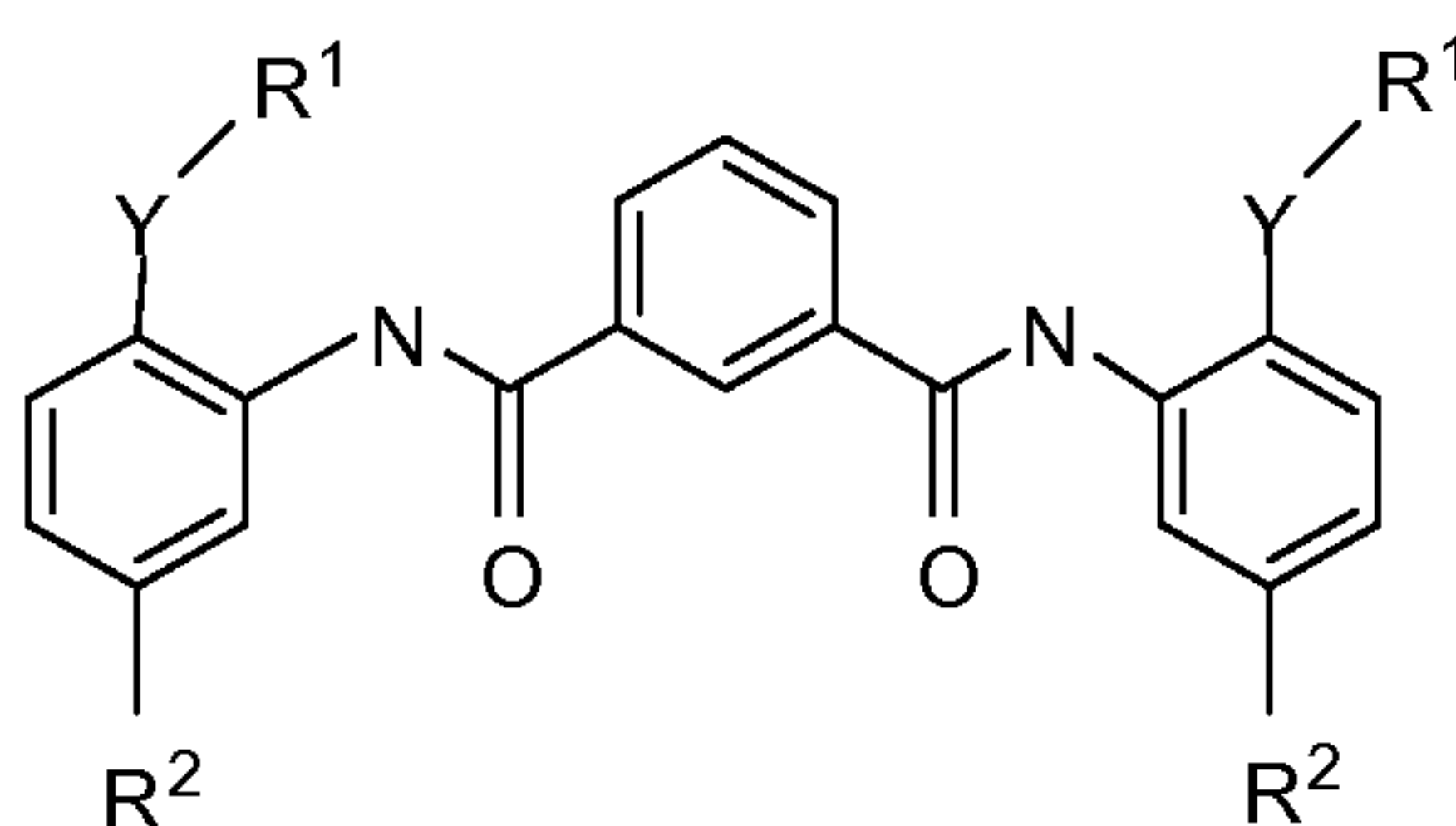
15 acceptable salt thereof.

The present invention also provides methods of killing or inhibiting the growth of a *Plasmodium* species comprising contacting the species with an effective amount of a compound of Formula V:



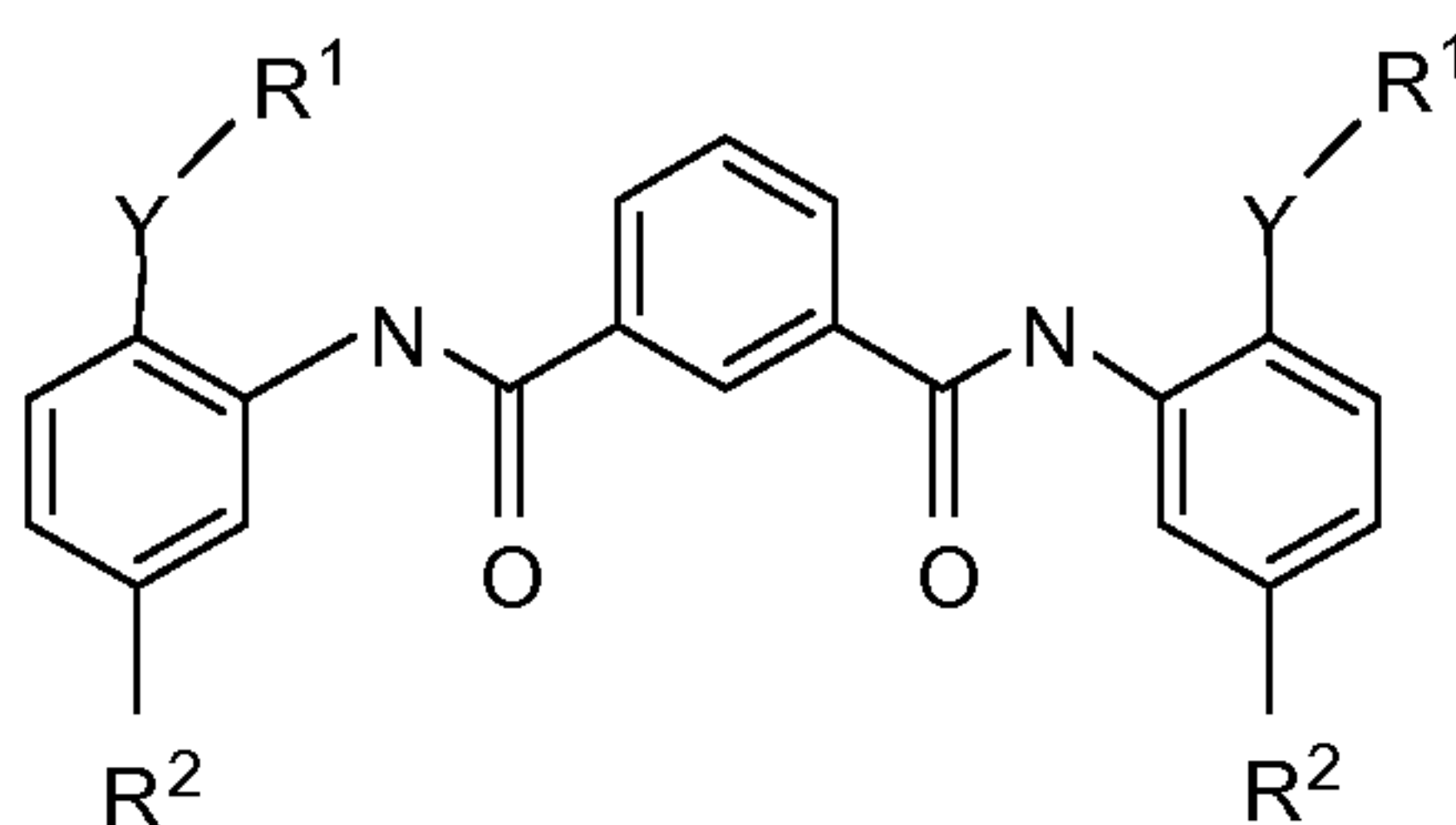
wherein: each X is, independently, O, S, or S(=O)₂; each R¹ is, independently, -(CH₂)_n-NH₂, -(CH₂)_n-NH-C(=NH)NH₂, or -(CH₂)_n-NH-C(=O)-R⁴, where each n is, independently, 1 to 4, and each R⁴ is, independently, H, C₁-C₃alkyl, or -(CH₂)_p-NH₂, where each p is, independently, 1 or 2; each R² is, independently, H, halo, CF₃, or C(CH₃)₃; and each V² is H, and each V¹ is, independently, -N-C(=O)-R³, where each R³ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4; or each V¹ is H and each V² is, independently, -S-R⁵, where each R⁵ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4; or a pharmaceutically acceptable salt thereof.

10 The present invention also provides compounds of Formula VI:



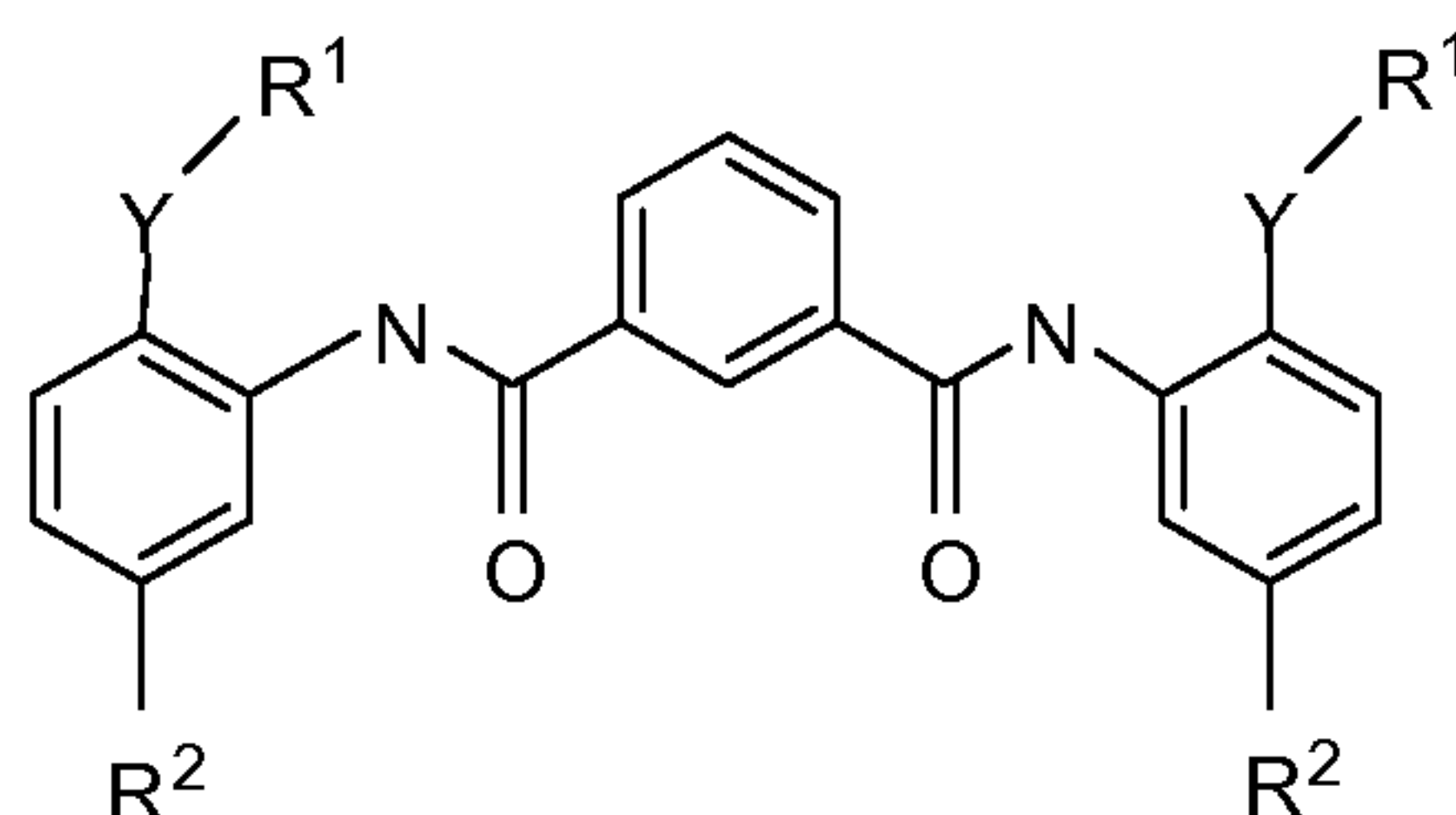
wherein: each Y is, independently, O, S, or NH; each R¹ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4; and each R² is, independently, H, halo, CF₃, or C(CH₃)₃; or a pharmaceutically acceptable salt thereof, and
15 compositions comprising the same and a pharmaceutically acceptable carrier.

The present invention also provides methods of treating malaria in an animal comprising administering to the animal a therapeutically effective amount of a compound of Formula VI:



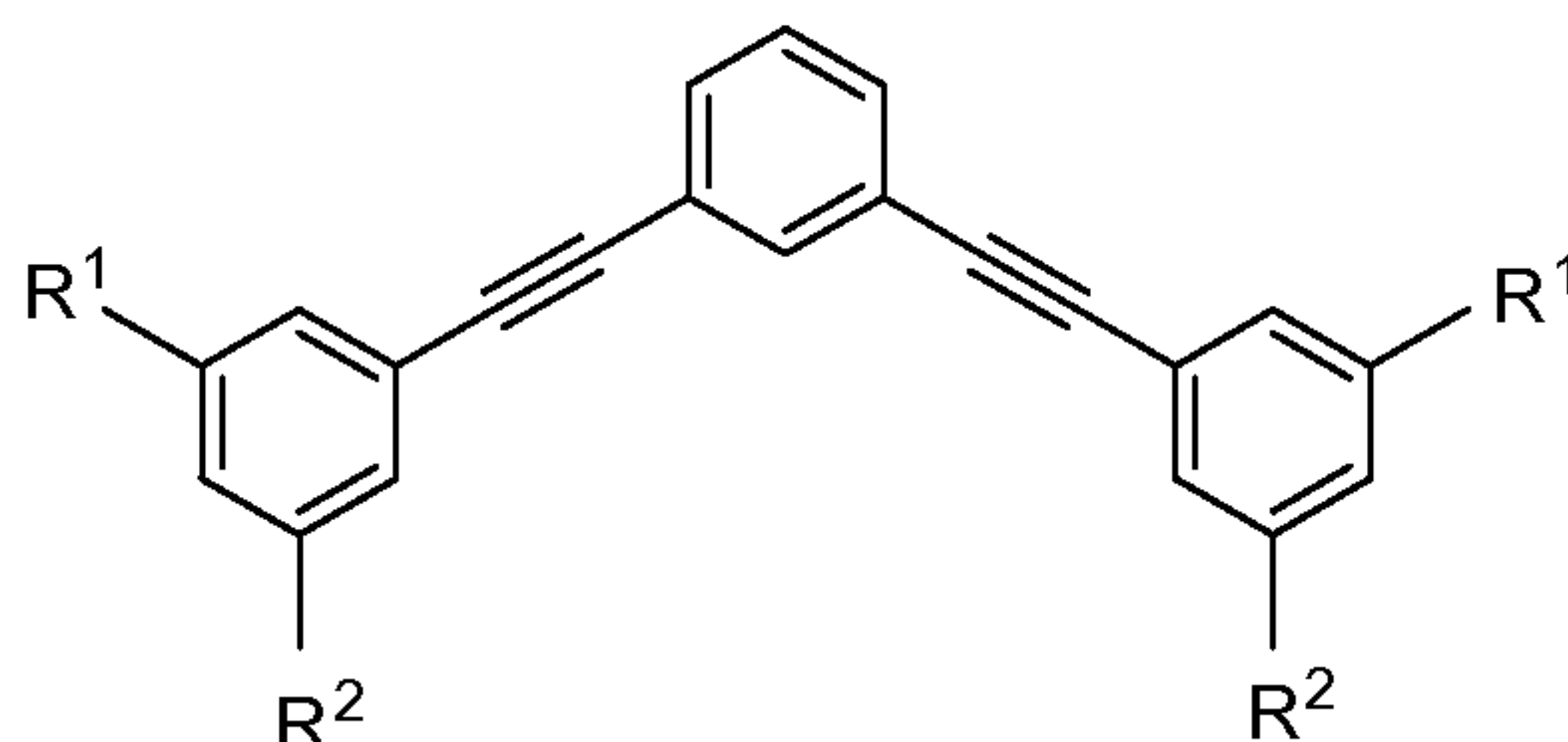
20 wherein: each Y is, independently, O, S, or NH; each R¹ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4; and each R² is, independently, H, halo, CF₃, or C(CH₃)₃; or a pharmaceutically acceptable salt thereof.

The present invention also provides methods of killing or inhibiting the growth of a *Plasmodium* species comprising contacting the species with an effective amount of a
25 compound of Formula VI:



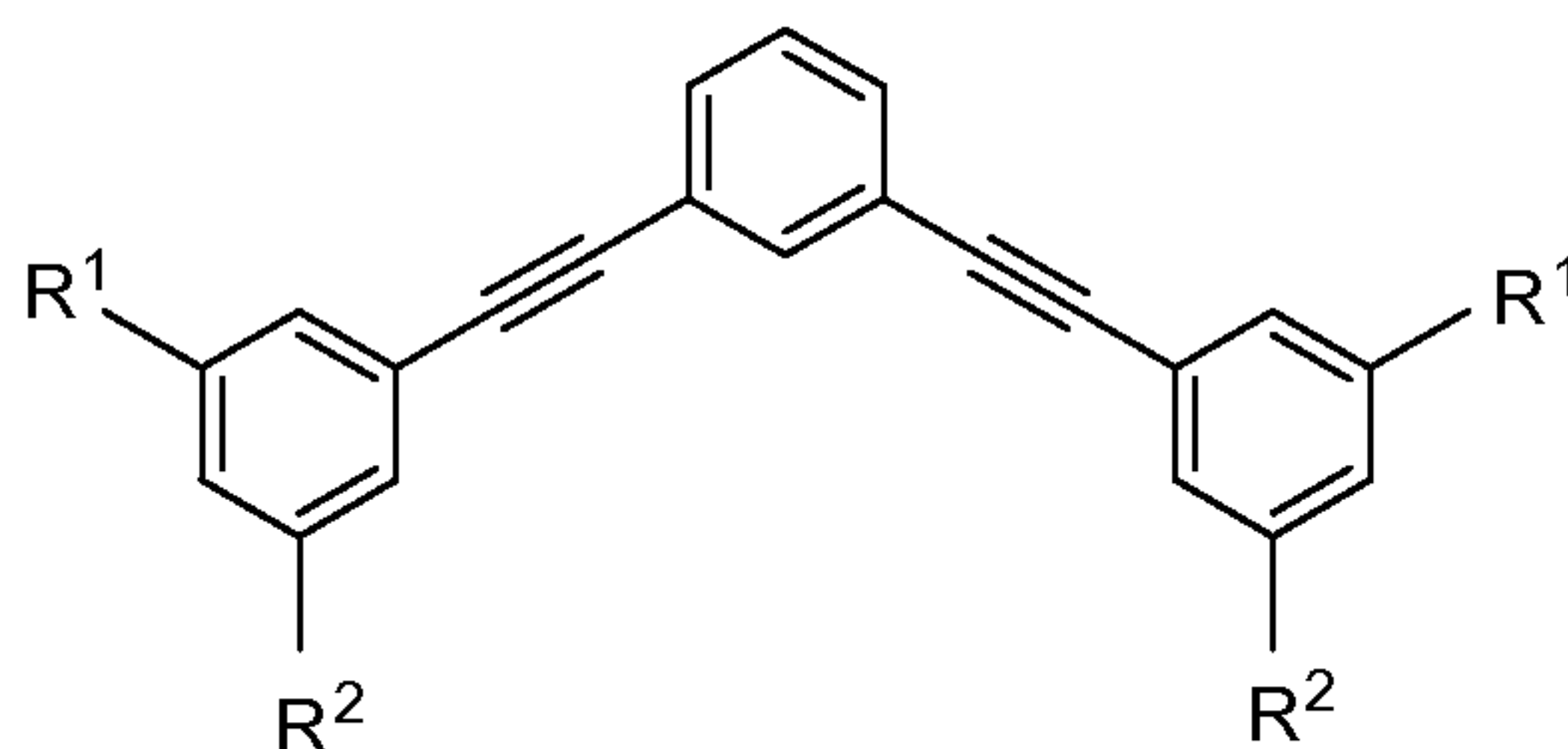
wherein: each Y is, independently, O, S, or NH; each R^1 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; and each R^2 is, independently, H, halo, CF_3 , or $C(CH_3)_3$; or a pharmaceutically acceptable salt thereof.

5 The present invention also provides method of treating malaria in an animal comprising administering to the animal a therapeutically effective amount of a compound of Formula VII:



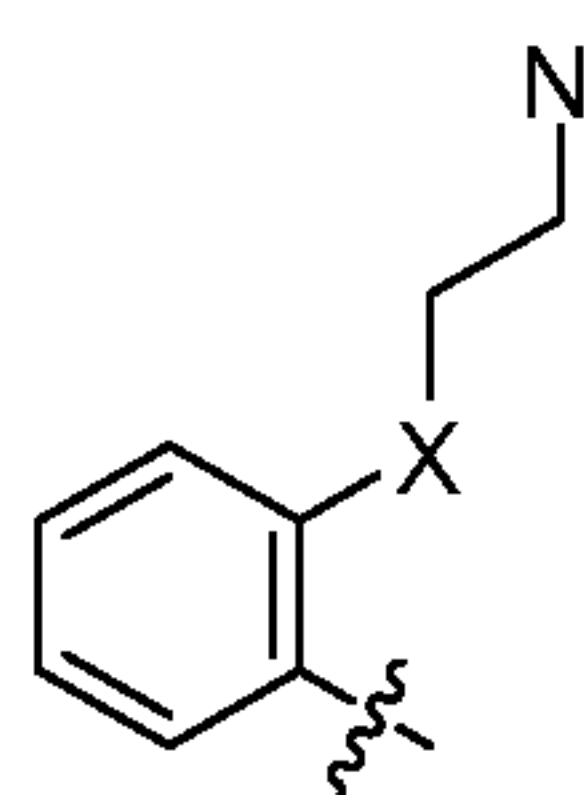
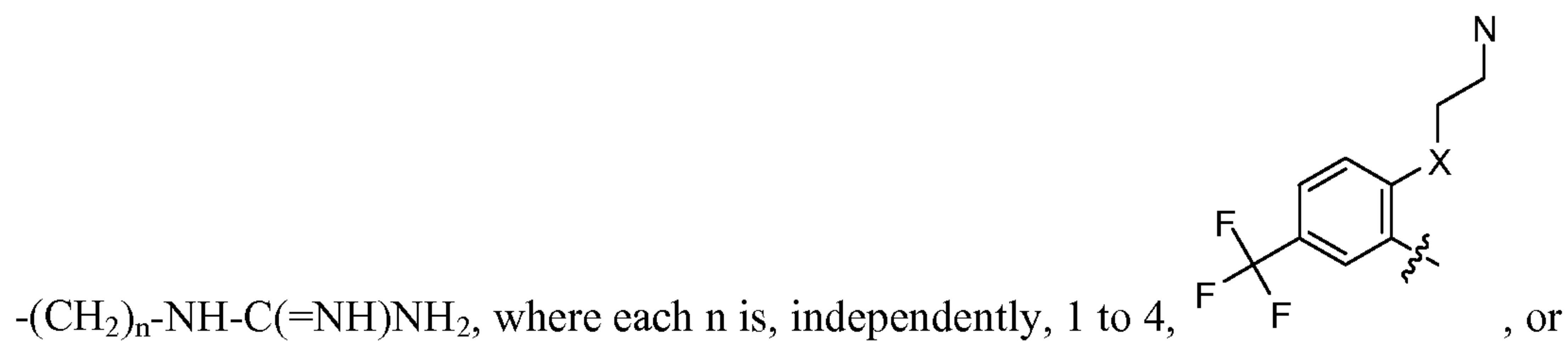
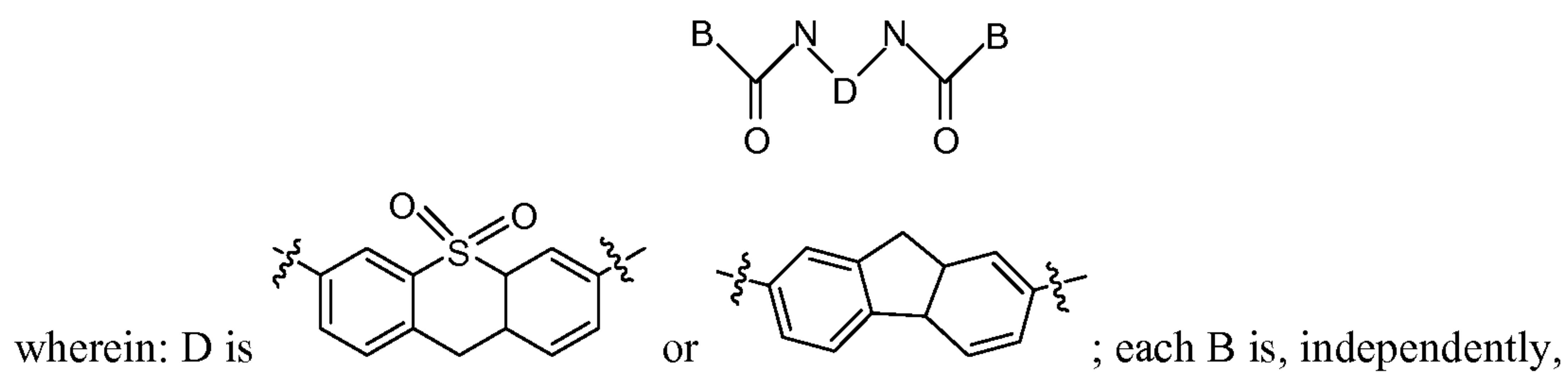
wherein: each R^1 is, independently, H, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, halo, OH, CF_3 , or CN; each
10 R^2 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; or a pharmaceutically acceptable salt thereof.

The present invention also provides methods of killing or inhibiting the growth of a *Plasmodium* species comprising contacting the species with an effective amount of a compound of Formula VII:



15 wherein: each R^1 is, independently, H, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, halo, OH, CF_3 , or CN; each R^2 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; or a pharmaceutically acceptable salt thereof.

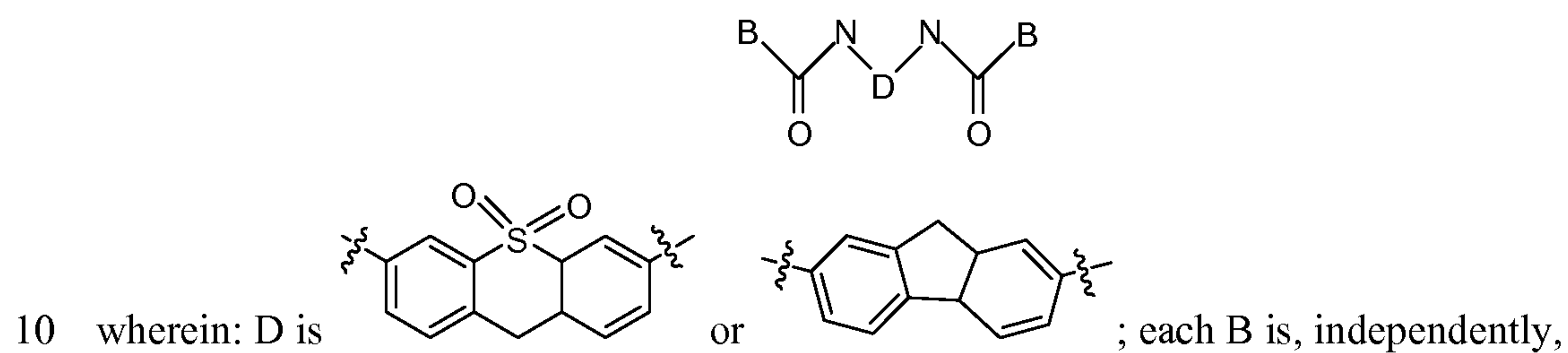
The present invention also provides compounds of Formula VIII:

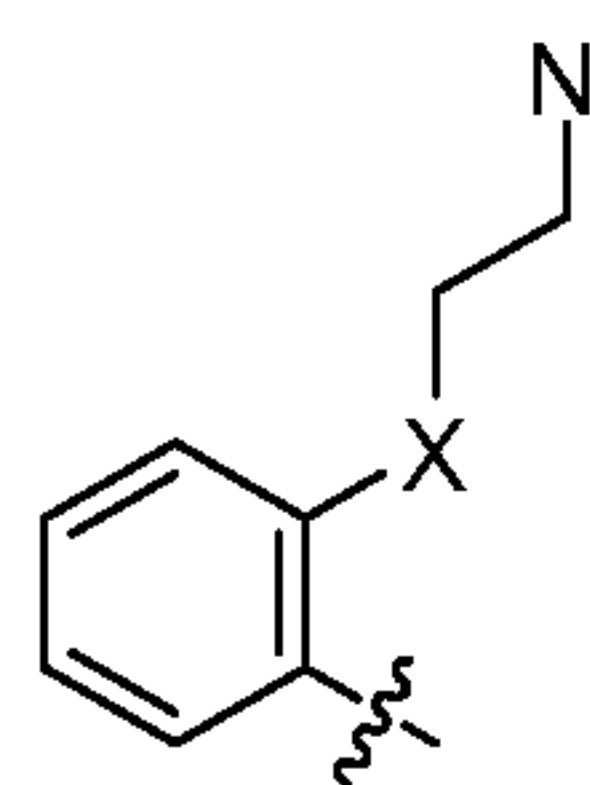
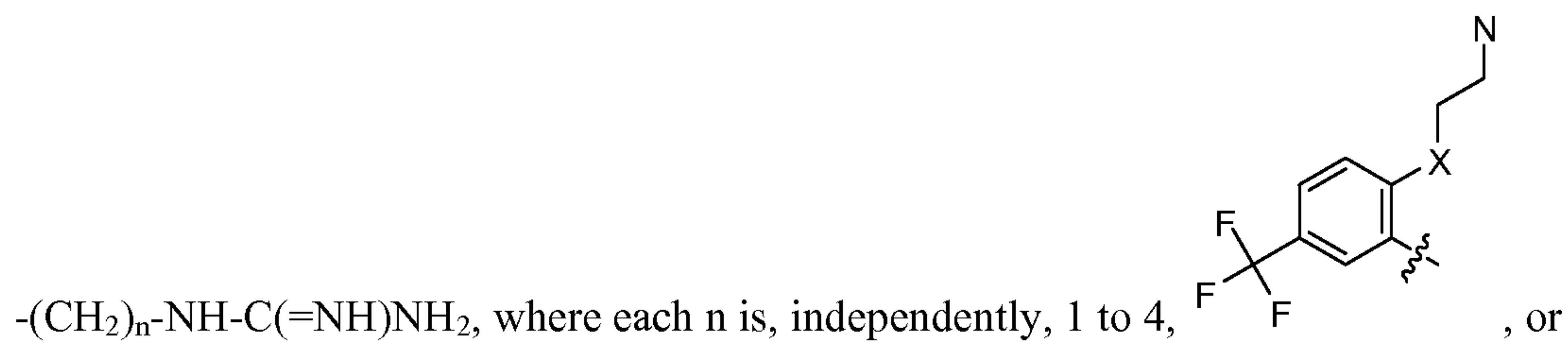


; and each X is, independently, O or S, or a pharmaceutically acceptable salt

5 thereof, and compositions comprising the same and a pharmaceutically acceptable carrier.

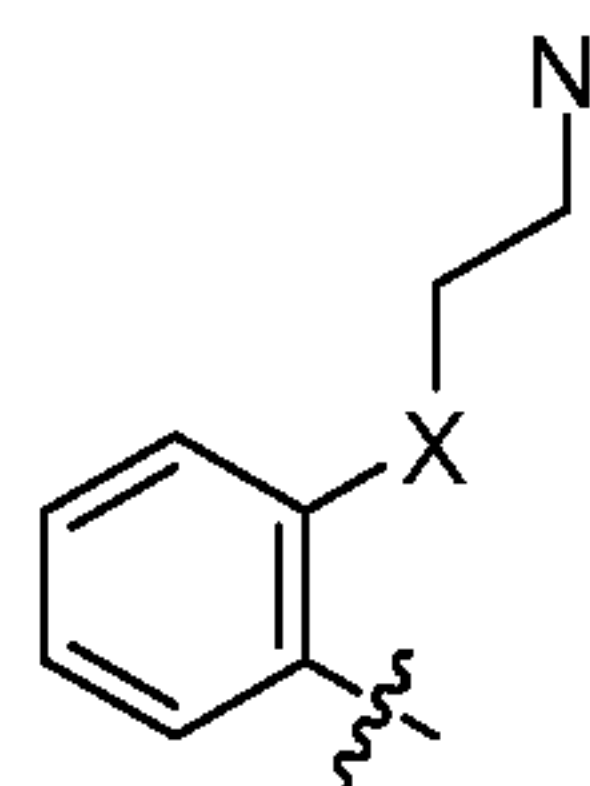
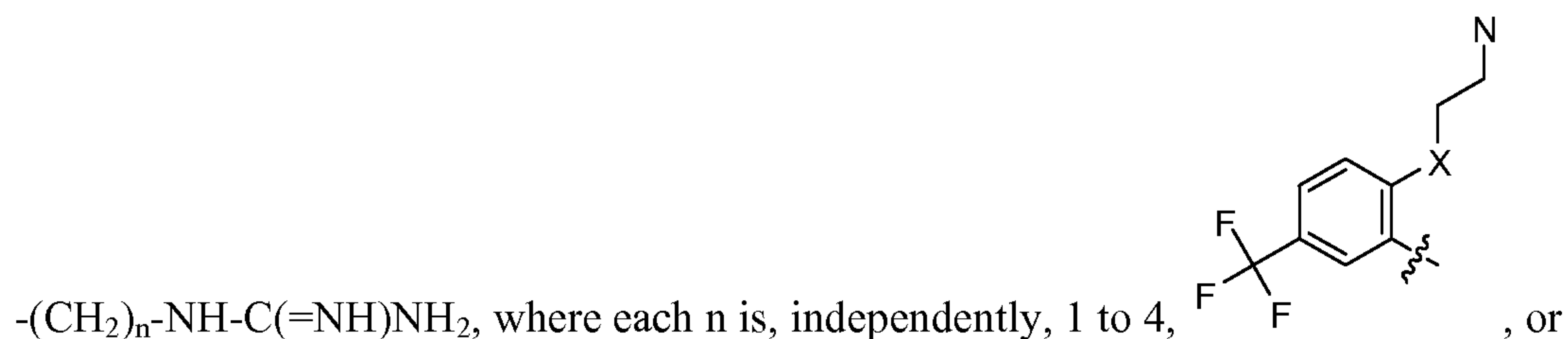
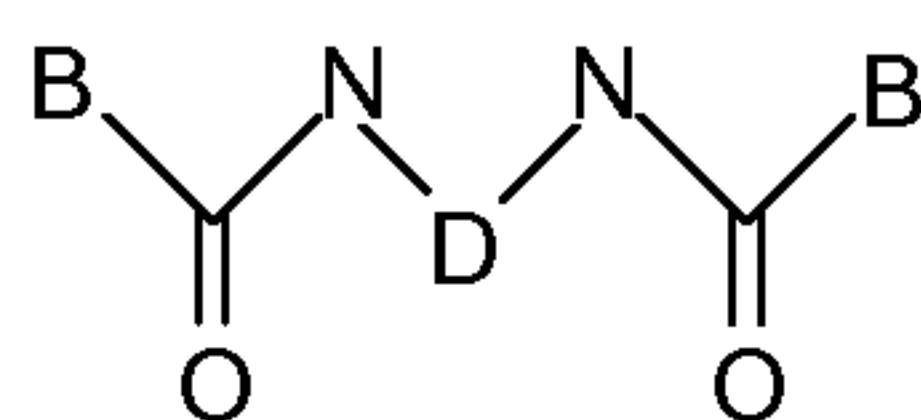
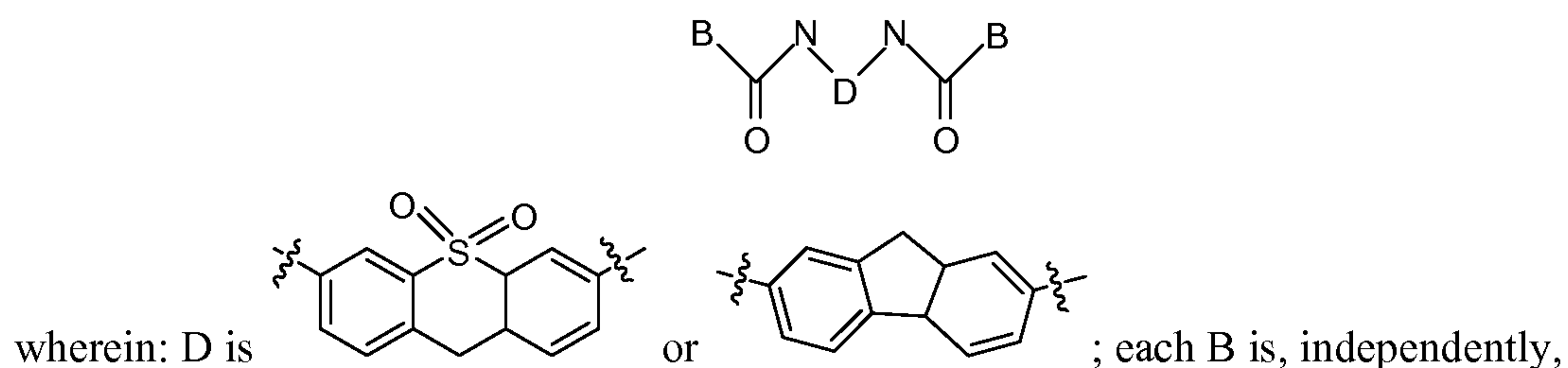
The present invention also provides methods of treating malaria in an animal comprising administering to the animal a therapeutically effective amount of a compound of Formula VIII:





; and each X is, independently, O or S, or a pharmaceutically acceptable salt thereof.

The present invention also provides methods of killing or inhibiting the growth of a *Plasmodium* species comprising contacting the species with an effective amount of a compound of Formula VIII:



; and each X is, independently, O or S, or a pharmaceutically acceptable salt thereof.

Description of Embodiments

Collectively and individually, each of the compounds described herein are also referred to herein as “anti-malarial compounds.”

As used herein and unless otherwise indicated, the term “animal” is intended to include, but not be limited to, humans and non-human vertebrates such as wild, domestic and farm animals.

As used herein and unless otherwise indicated, the term “about” is intended to mean
5 $\pm 5\%$ of the value it modifies. Thus, about 100 means 95 to 105.

As used herein and unless otherwise indicated, the term “alkyl” is intended to include branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, C₁-C₈, as in “C₁-C₈ alkyl” is intended to include groups having 1, 2, 3, 4, 5, 6, 7, or 8 carbons in a linear or branched arrangement.
10 “C₁-C₆ alkyl” is intended to include groups having 1, 2, 3, 4, 5, or 6 carbons in a linear or branched arrangement. “C₁-C₃ alkyl” is intended to include groups having 1, 2, or 3 carbons in a linear or branched arrangement. Examples of alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, i-butyl, 2-methyl-1-propyl, 2-methyl-2-propyl, pentyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl,
15 2,2-dimethyl-1-propyl, isopentyl, neopentyl, hexyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, heptyl, and octyl, or any combination thereof. An alkyl group can be unsubstituted or substituted with one, two, or three suitable substituents. These same alkyl groups can be used in connection with “alkoxy”
20 groups, “haloalkyl” groups, “alkenyl” groups, “alkynyl” groups, and “cycloalkyl” groups as appropriate.

As used herein and unless otherwise indicated, the term “halo” means fluorine, chlorine, bromine, or iodine.

As used herein and unless otherwise indicated, the phrase “5- or 6-membered
25 heterocycle” means a monocyclic ring comprising carbon atoms, hydrogen atoms, and one or more heteroatoms, such as 1 to 3 heteroatoms, independently chosen from nitrogen, oxygen, and sulfur. 5-membered heterocycles include, but are not limited to, thienyl, 2-thienyl, 3-thienyl, furyl, 2-furyl, 3-furyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, and pyrazolinyl.
30 6-membered heterocycles include, but are not limited to, pyranyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, piperidyl, piperazinyl, and morpholinyl. The 5- and 6-membered heterocycles can be unsubstituted or substituted with one, two, or three suitable substituents.

As used herein and unless otherwise indicated, the phrase “carbocycle” means a 5- or 6-membered, saturated or unsaturated cyclic ring, optionally containing O, S, or N atoms as part of the ring. Examples of carbocycles include, but are not limited to, cyclopentyl, cyclohexyl, cyclopenta-1,3-diene, phenyl, and any of the heterocycles recited above.

5 As used herein and unless otherwise indicated, the term “phenyl” means $-C_6H_5$. A phenyl group can be unsubstituted or substituted with one, two, or three suitable substituents.

As used herein and unless otherwise indicated, the phrase “therapeutically effective amount” of a composition or compound is measured by the therapeutic effectiveness of the administered compound, wherein at least one adverse effect is ameliorated or alleviated. The
10 therapeutic effect is dependent upon the disorder being treated or the biological effect desired. As such, the therapeutic effect can be a decrease in the severity of symptoms associated with the disorder and/or inhibition (partial or complete) of progression of the disorder, or improved treatment, healing, prevention or elimination of a disorder, or side-effects. The amount needed to elicit the therapeutic response can be determined based on the
15 age, health, size and sex of the subject. Optimal amounts can also be determined based on monitoring of the subject’s response to treatment.

When administered to a mammal (e.g., to an animal for veterinary use or to a human for clinical use) the anti-malarial compounds described herein can be administered in isolated form. As used herein and unless otherwise indicated, the term “isolated” means that the anti-
20 malarial compounds described herein are separated from other components of either (a) a natural source, such as a plant or cell, such as a bacterial culture, or (b) a synthetic organic chemical reaction mixture, such as by conventional techniques.

As used herein and unless otherwise indicated, the term “purified” means that when isolated, the isolate contains at least 90%, at least 95%, at least 98%, or at least 99% of an
25 anti-malarial compound described herein by weight of the isolate.

As used herein and unless otherwise indicated, the phrase “pharmaceutically acceptable salt(s),” includes, but is not limited to, salts of acidic or basic groups. Compounds that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. Acids that may be used to prepare pharmaceutically acceptable acid
30 addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions including, but not limited to, sulfuric, citric, maleic, acetic, oxalic, hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate,

bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate (i.e.,
 5 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Compounds that include an amino moiety may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above. Compounds that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include, but are not limited to, alkali metal or alkaline earth metal salts and, particularly, calcium,
 10 magnesium, sodium lithium, zinc, potassium, and iron salts.

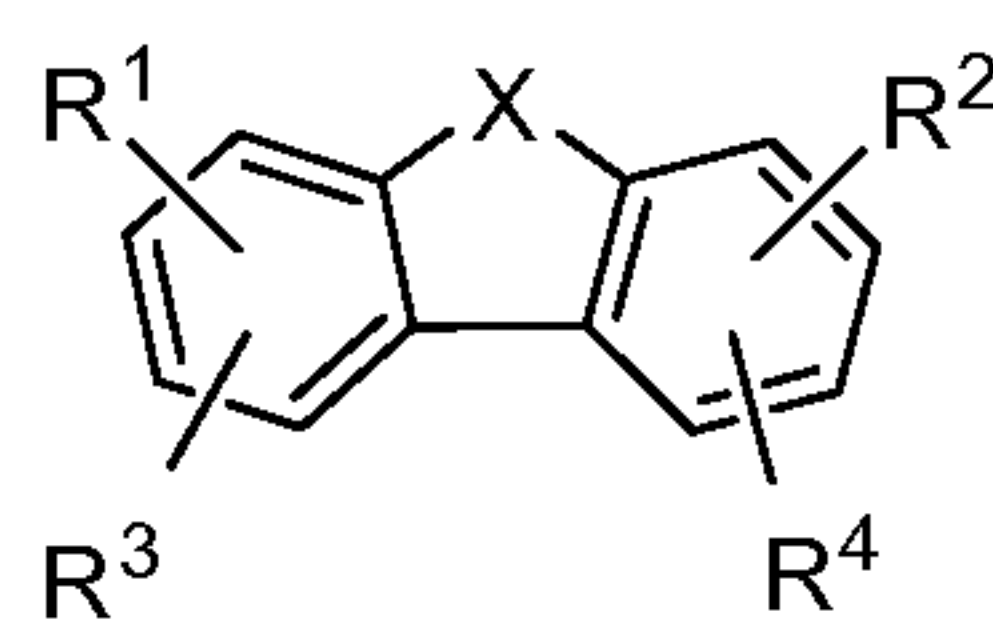
As used herein and unless otherwise indicated, the phrase "suitable substituent" means a group that does not nullify the synthetic or pharmaceutical utility of the anti-malarial compounds described herein or the intermediates useful for preparing them. Examples of suitable substituents include, but are not limited to: (C₁-C₆)alkyl, (C₁-C₆)alkenyl,
 15 (C₁-C₆)alkynyl, (C₅-C₆)aryl, (C₃-C₅)heteroaryl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, (C₅-C₆)aryloxy, -CN, -OH, oxo, halo, -NO₂, -CO₂H, -NH₂, -NH((C₁-C₈)alkyl), -N((C₁-C₈)alkyl)₂, -NH((C₆)aryl), -N((C₅-C₆)aryl)₂, -CHO, -CO((C₁-C₆)alkyl), -CO((C₅-C₆)aryl), -CO₂((C₁-C₆)alkyl), and -CO₂((C₅-C₆)aryl). One of skill in art can readily choose a suitable substituent based on the stability and pharmacological and synthetic activity
 20 of the anti-malarial compounds described herein.

As used herein and unless otherwise indicated, the terms "treatment" or "treating" refers to an amelioration of malaria, or at least one discernible symptom thereof. In another embodiment, "treatment" or "treating" refers to an amelioration of at least one measurable physical parameter, not necessarily discernible by the patient. In yet another embodiment,
 25 "treatment" or "treating" refers to inhibiting the progression of malaria, either physically, e.g., stabilization of a discernible symptom, physiologically, e.g., stabilization of a physical parameter, or both. In yet another embodiment, "treatment" or "treating" refers to delaying the onset of malaria.

In some embodiments, the anti-malarial compound, or composition comprising the
 30 same, are administered to a patient, such as a human, as a preventative measure against malaria. As used herein and unless otherwise indicated, "prevention" or "preventing" refers to a reduction of the risk of acquiring malaria.

The anti-malarial compounds described herein may contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as double-bond isomers (i.e., geometric isomers), enantiomers, or diastereomers. Therefore, the anti-malarial compounds described herein encompass all of the corresponding compound's enantiomers and stereoisomers, that is, both the stereomerically pure form (e.g., geometrically pure, enantiomerically pure, or diastereomerically pure) and enantiomeric and stereoisomeric mixtures. Enantiomeric and stereoisomeric mixtures can be resolved into their component enantiomers or stereoisomers by well known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Enantiomers and stereoisomers can also be obtained from stereomerically- or enantiomerically-pure intermediates, reagents, and catalysts by well known asymmetric synthetic methods.

The present invention provides compounds of Formula I:



wherein:

X is C(R⁷)C(R⁸), C(=O), N(R⁹), O, S, S(=O), or S(=O)₂;

R⁷, R⁸, and R⁹ are, independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, CF₃, or aromatic group;

R¹ and R² are, independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, haloC₁-C₈alkyl, or CN;

R³ and R⁴ are, independently, carbocycle(R⁵)(R⁶);

each R⁵ and each R⁶ are, independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, CF₃, aromatic group, heterocycle, or the free base or salt form of -(CH₂)_n-NH₂,

-(CH₂)_n-NH-(CH₂)_n-NH₂, or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 8;

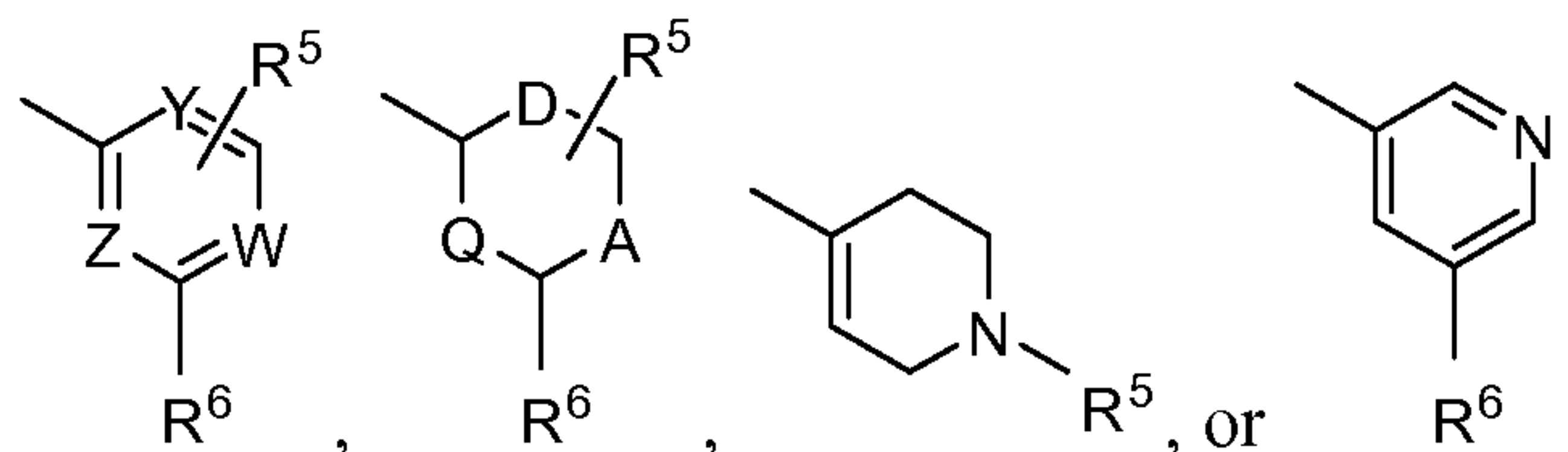
or a pharmaceutically acceptable salt thereof.

In some embodiments, X is N(R⁹), O, S, or S(=O)₂; or X is NH, O, or S; or X is NH or S.

In any of the above embodiments, R¹ and R² are, independently, H, C₁-C₃alkyl,

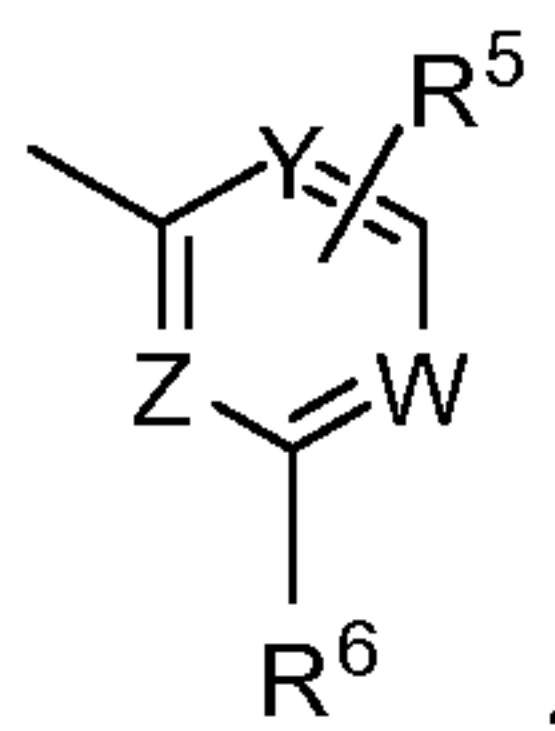
C₁-C₃alkoxy, halo, OH, haloC₁-C₃alkyl, or CN; or R¹ and R² are, independently, H, C₁-C₃alkyl, C₁-C₃alkoxy, halo, or OH; or R¹ and R² are, independently, H, C₁-C₃alkyl, or halo; or R¹ and R² are H.

- In any of the above embodiments, R³ and R⁴ are, independently, carbocycle(R⁵)(R⁶),
 5 where R⁵ and R⁶ can be positioned anywhere on the carbocycle. In any of the above embodiments, R³ and R⁴ are, independently,

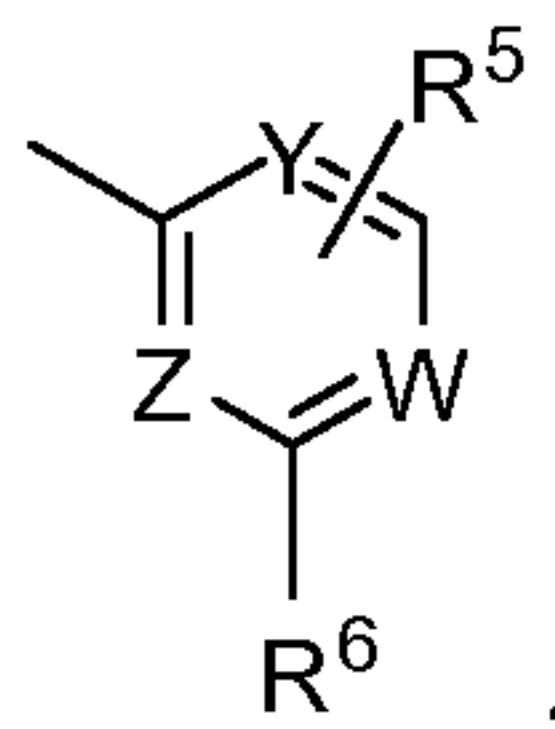


- wherein each W, Y, and Z are, independently, C or N, each A, D, and Q are, independently, C(R¹⁰)C(R¹¹), C(=O), N(R¹²), O, or S, and each R¹⁰, R¹¹, and R¹² are, independently, H,
 10 C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, CF₃, or aromatic group.

In any of the above embodiments, R³ and R⁴ are, independently,



wherein each W, Y, and Z are, independently, C or N; or R³ and R⁴ are, independently,

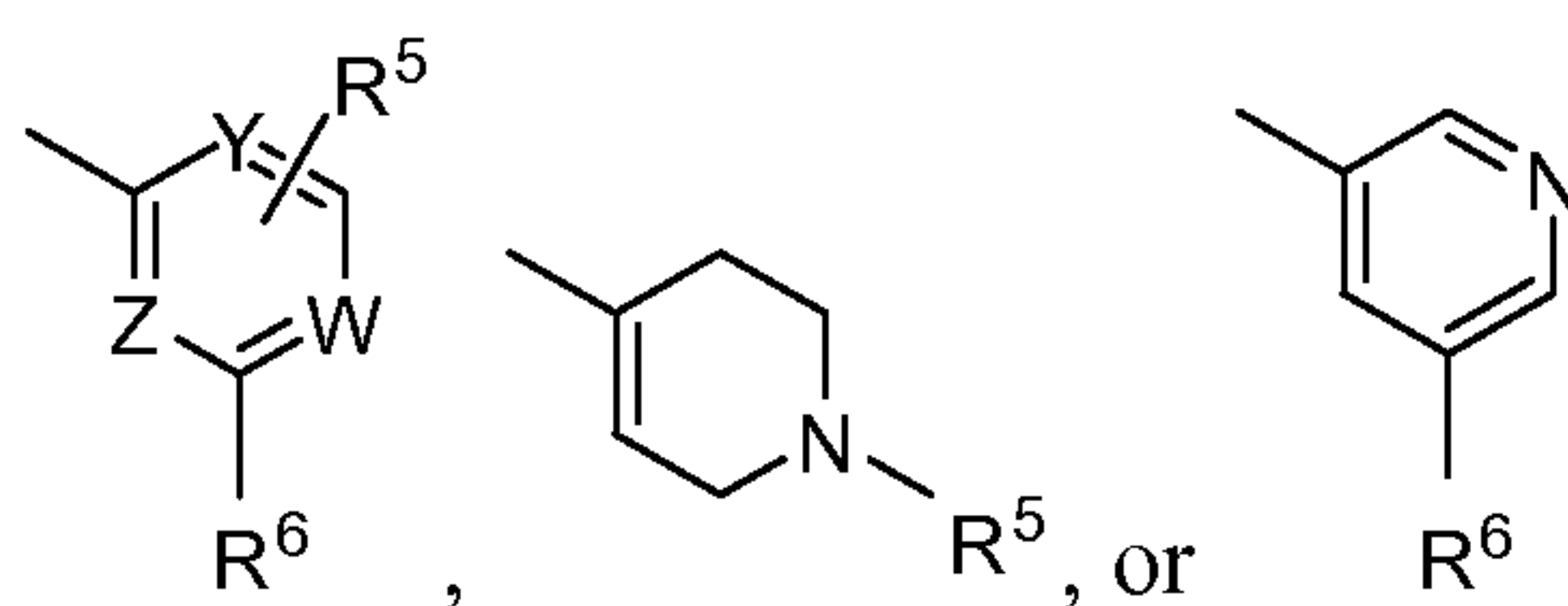


- 15 wherein each W, Y, and Z are C, or each Y and Z are C and each W is N.

- In any of the above embodiments, each R⁵ is, independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, CF₃, or the free base or salt form of -(CH₂)_n-NH₂, -(CH₂)_n-NH-(CH₂)_n-NH₂, or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 8, and each R⁶ is, independently, heterocycle or the free base or salt form of -(CH₂)_n-NH₂,
 20 -(CH₂)_n-NH-(CH₂)_n-NH₂, or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 8; or each R⁵ is, independently, H, C₁-C₃alkyl, C₁-C₃alkoxy, halo, OH, or CF₃, and each R⁶ is, independently, heterocycle or the free base or salt form of -(CH₂)_n-NH₂, where each n is, independently, 1 to 8; or each R⁵ is, independently, H, C₁-C₃alkyl, halo, or OH; and each R⁶ is, independently, heterocycle or the free base or salt form of -(CH₂)_n-NH₂, where each n is,

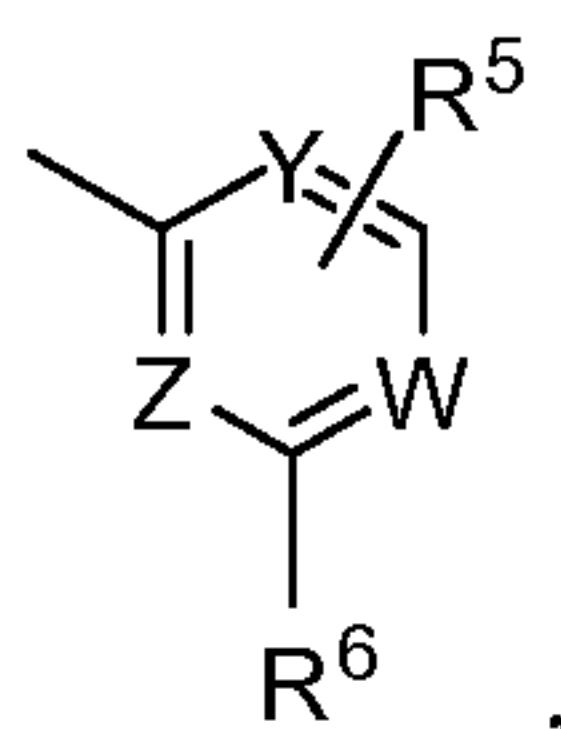
independently, 1 to 4; or each R^5 is, independently, H, C_1 - C_3 alkyl, halo, or OH; and each R^6 is, independently, 6-membered heterocycle or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 3; or each R^5 is, independently, H or halo; and each R^6 is piperazinyl or the free base or salt form of $-(CH_2)_n-NH_2$ where each n is, independently, 1 to 3; or each R^5 is piperazinyl; and each R^6 is, independently, H, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, halo, OH, or CF_3 ; or each R^5 is piperazinyl; and each R^6 is H, C_1 - C_3 alkyl, halo, OH, or CF_3 .

In some embodiments, X is NH, O, S, or $S(=O)_2$; R^1 and R^2 are H; R^3 and R^4 are, independently,



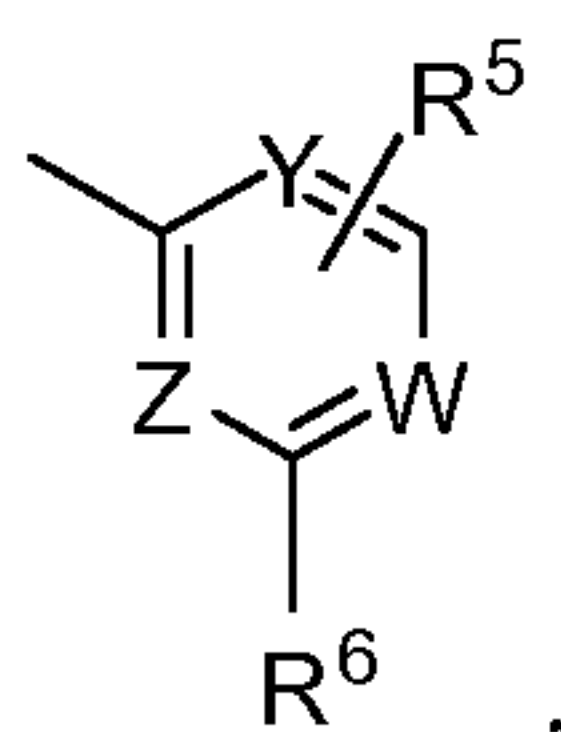
wherein: each W, Y, and Z are, independently, C or N; each R^5 and each R^6 are, independently, H, heterocycle, or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 3.

In some embodiments, X is NH, O, or S; R^1 and R^2 are H; R^3 and R^4 are



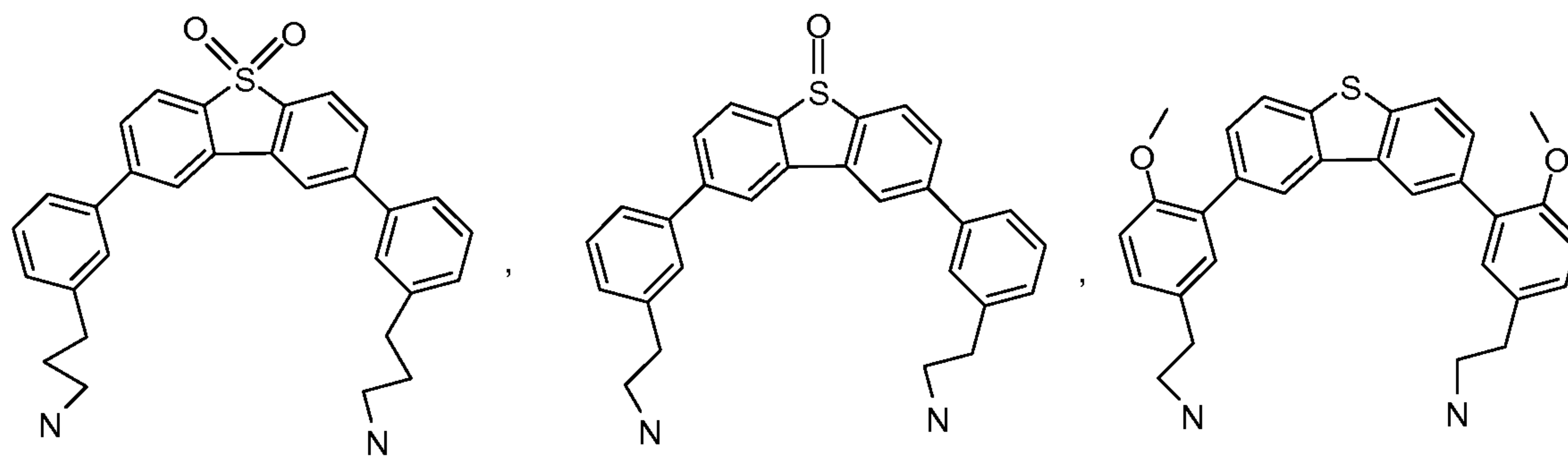
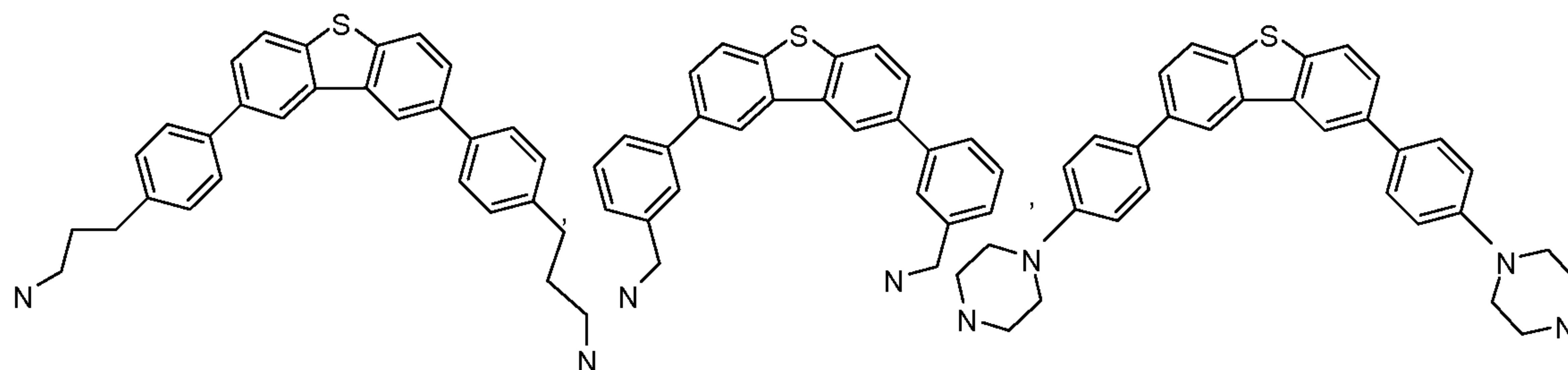
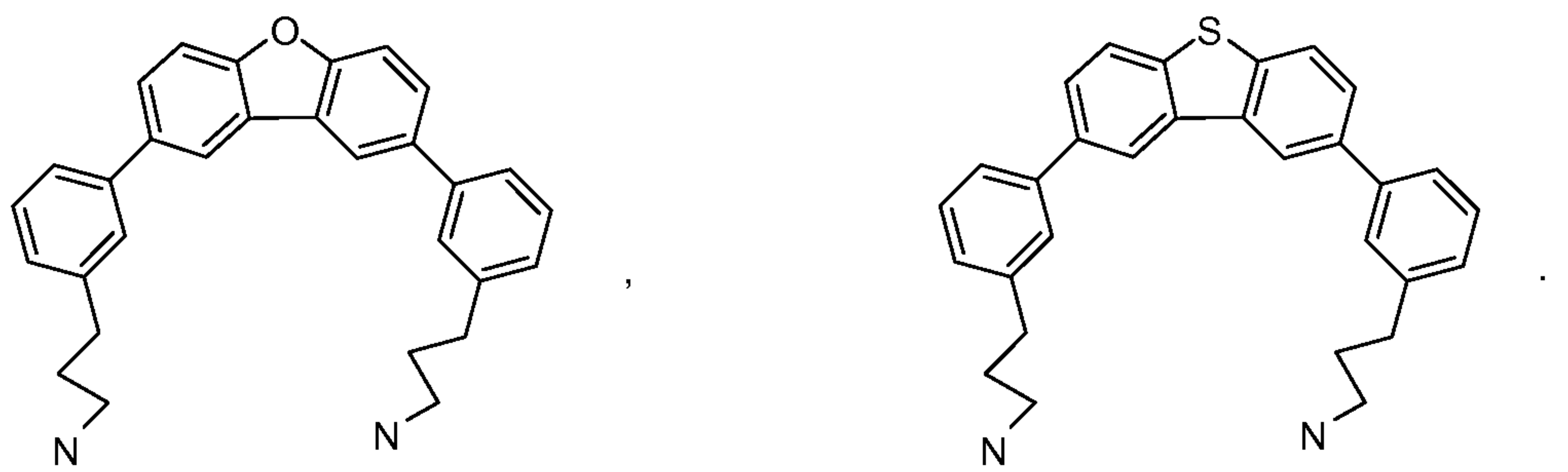
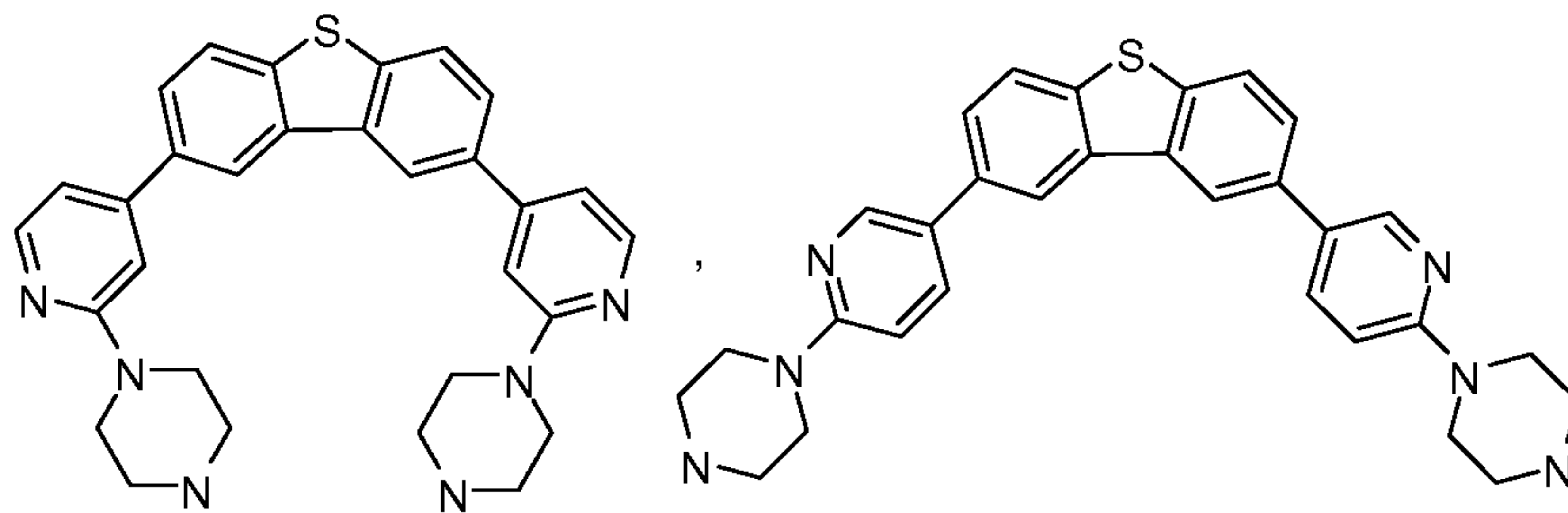
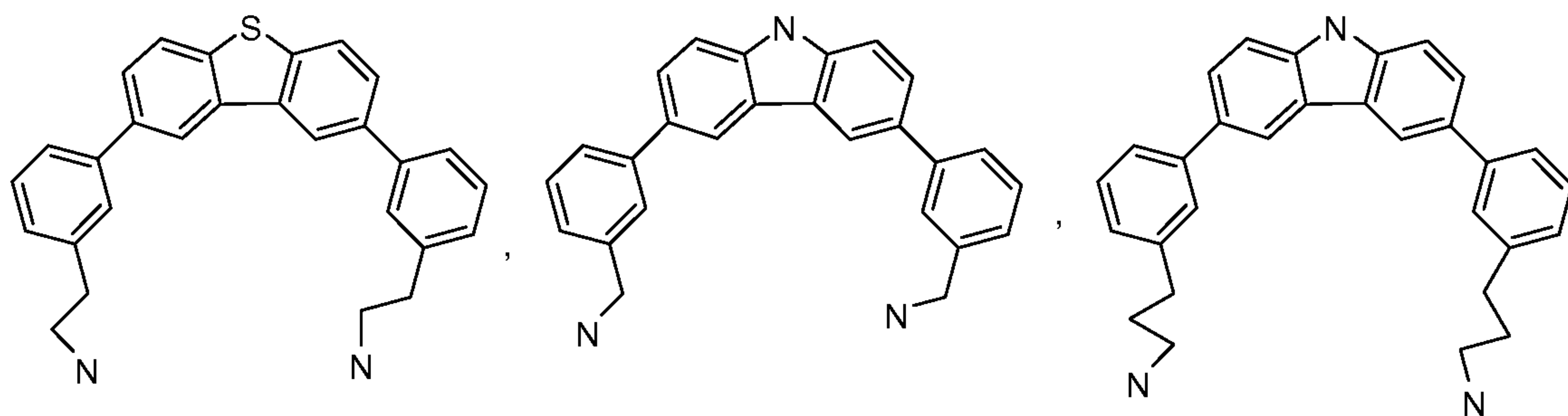
where each Z and Y are C, and each W is N; or each W, Y, and Z are C; each R^5 is, independently, H or halo, and each R^6 is piperazinyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 3; or each R^5 is piperazinyl, and each R^6 is, independently, H, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, halo, OH, or CF_3 .

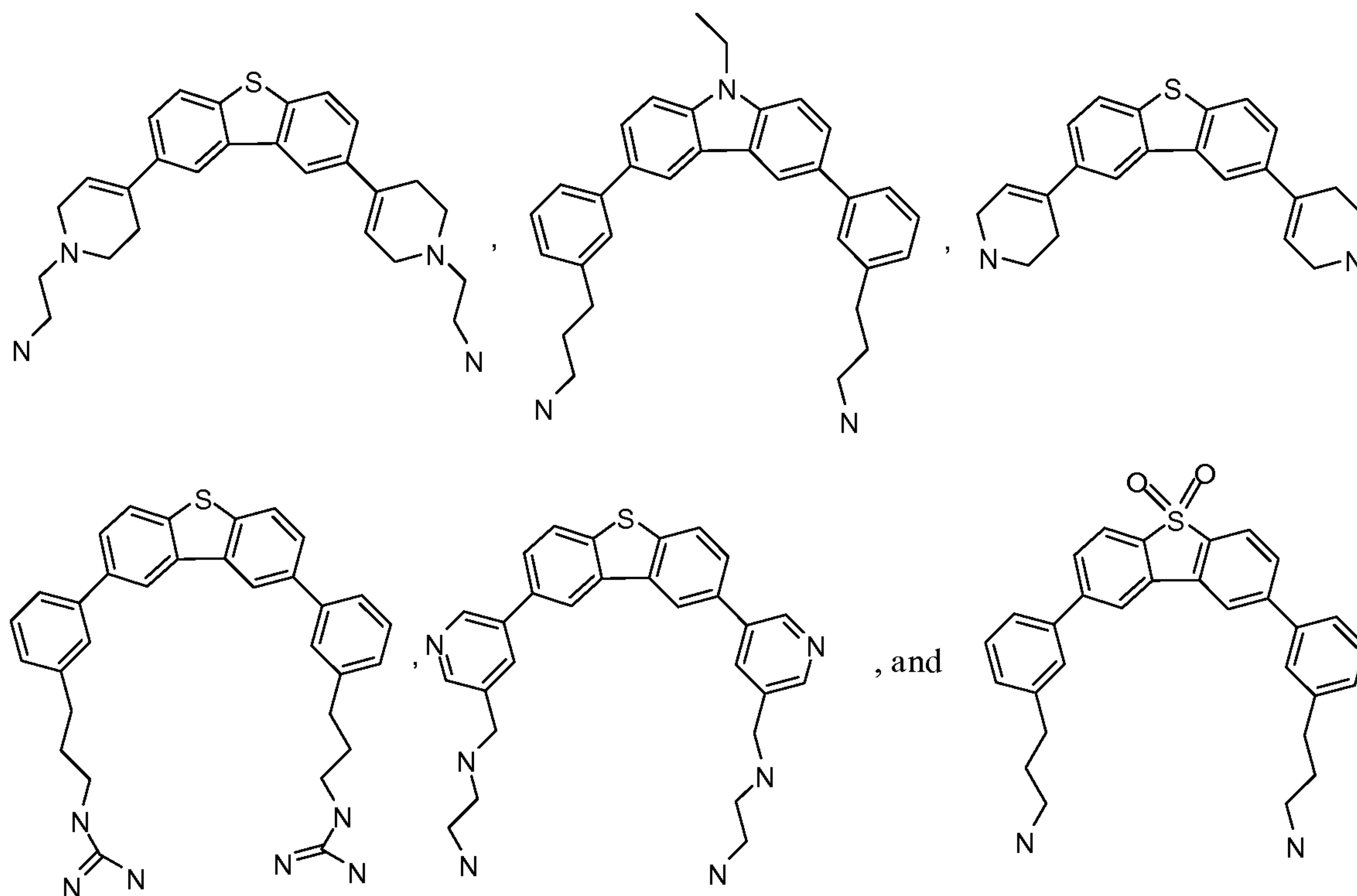
In some embodiments, X is NH, O, or S; R^1 and R^2 are H; R^3 and R^4 are



where each Z and Y are C, and each W is N; or each W, Y, and Z are C; each R^5 is H, and each R^6 is piperazinyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 3; or each R^5 is piperazinyl; and each R^6 is H.

In some embodiments, the compound is chosen from:



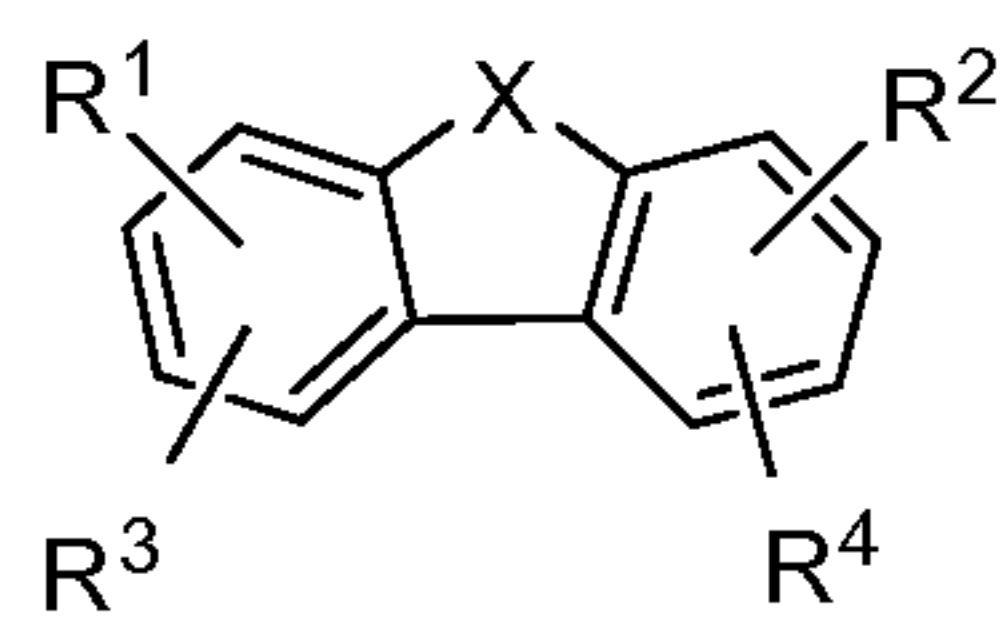


or pharmaceutically acceptable salt thereof.

In some embodiments, any one or more of the above compounds may be excluded
5 from any of the genus of compounds described above.

The present invention also provides compositions comprising one or more of the compounds or salts described above and a pharmaceutically acceptable carrier.

The present invention also provides methods of treating malaria in an animal comprising administering to the animal a therapeutically effective amount of a compound of
10 Formula I:



wherein:

X is C(R⁷)C(R⁸), C(=O), N(R⁹), O, S, S(=O), or S(=O)₂;

R⁷, R⁸, and R⁹ are, independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, CF₃, or
15 aromatic group;

R¹ and R² are, independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, haloC₁-C₈alkyl, or CN;

R³ and R⁴ are, independently, carbocycle(R⁵)(R⁶);

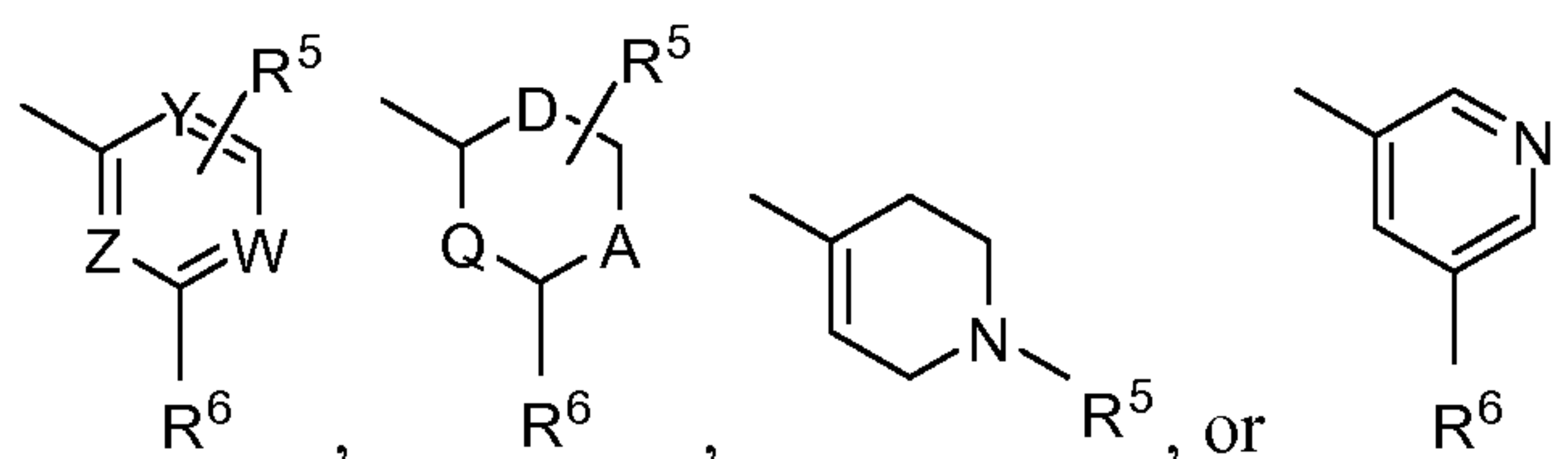
each R^5 and each R^6 are, independently, H, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, halo, OH, CF_3 , aromatic group, heterocycle, or the free base or salt form of $-(CH_2)_n-NH_2$, $-(CH_2)_n-NH-(CH_2)_n-NH_2$, or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 8;

5 or a pharmaceutically acceptable salt thereof.

In some embodiments, X is $N(R^9)$, O, S, or $S(=O)_2$; or X is NH, O, or S; or X is NH or S.

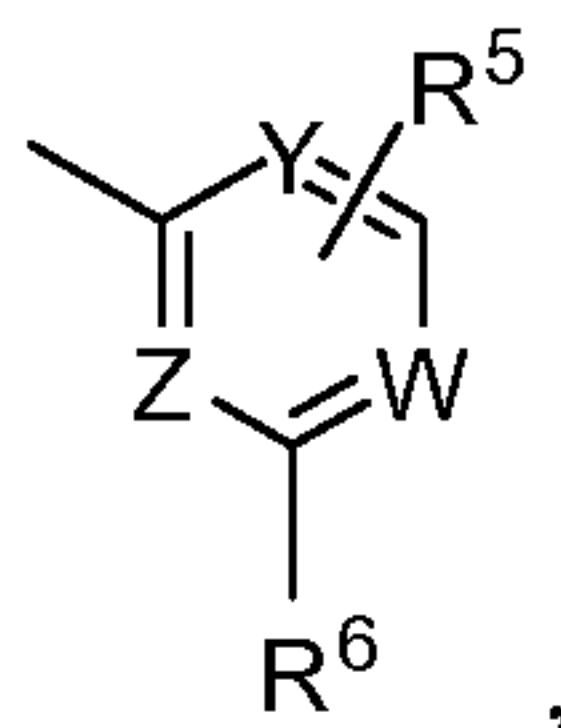
In any of the above embodiments, R^1 and R^2 are, independently, H, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, halo, OH, halo C_1 - C_3 alkyl, or CN; or R^1 and R^2 are, independently, H,
10 C_1 - C_3 alkyl, C_1 - C_3 alkoxy, halo, or OH; or R^1 and R^2 are, independently, H, C_1 - C_3 alkyl, or halo; or R^1 and R^2 are H.

In any of the above embodiments, R^3 and R^4 are, independently,

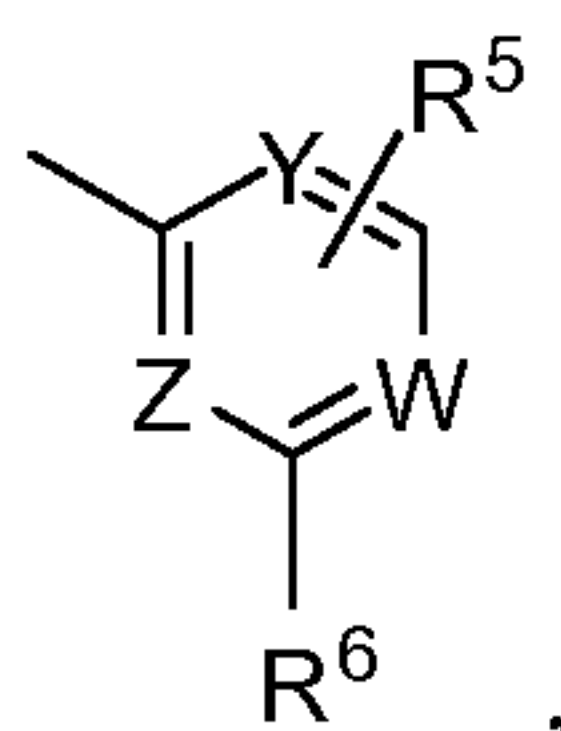


wherein each W, Y, and Z are, independently, C or N, each A, D, and Q are, independently,
15 $C(R^{10})C(R^{11})$, $C(=O)$, $N(R^{12})$, O, or S, and each R^{10} , R^{11} , and R^{12} are, independently, H, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, halo, OH, CF_3 , or aromatic group.

In any of the above embodiments, R^3 and R^4 are, independently,



wherein each W, Y, and Z are, independently, C or N; or R^3 and R^4 are, independently,



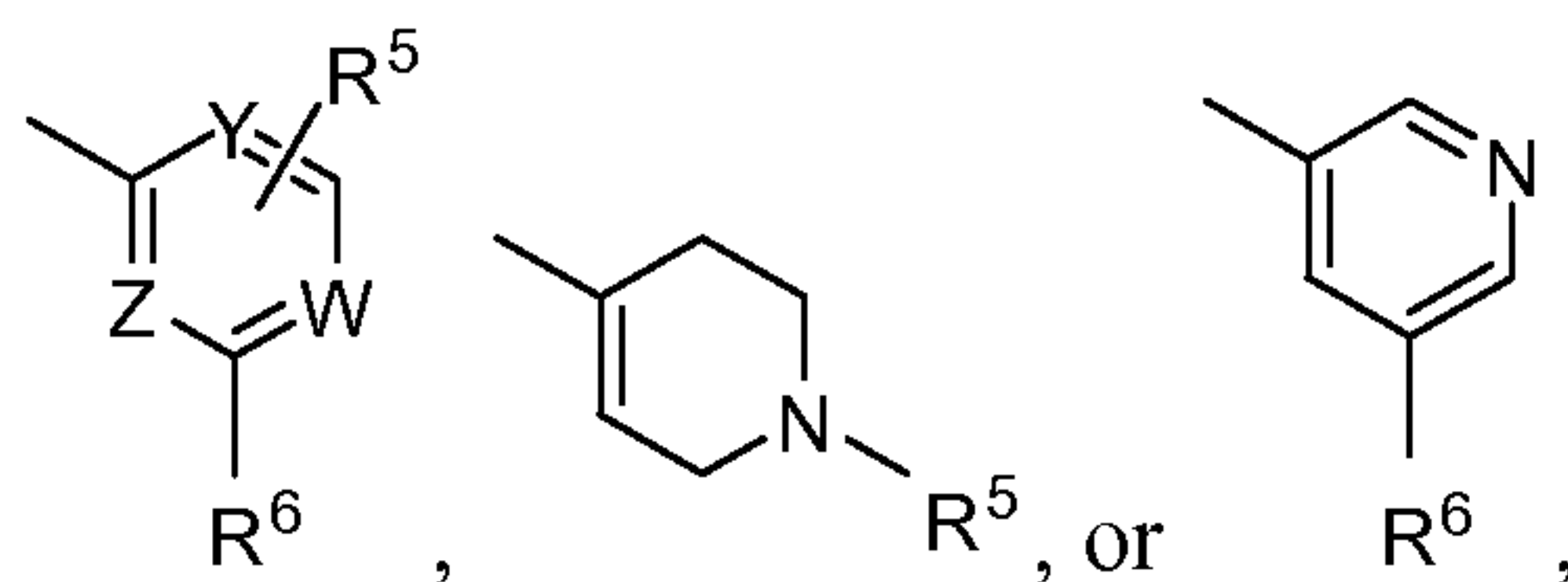
20

wherein each W, Y, and Z are C; or each Y and Z are C and each W is N.

In any of the above embodiments, each R^5 is, independently, H, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, halo, OH, CF_3 , or the free base or salt form of $-(CH_2)_n-NH_2$,

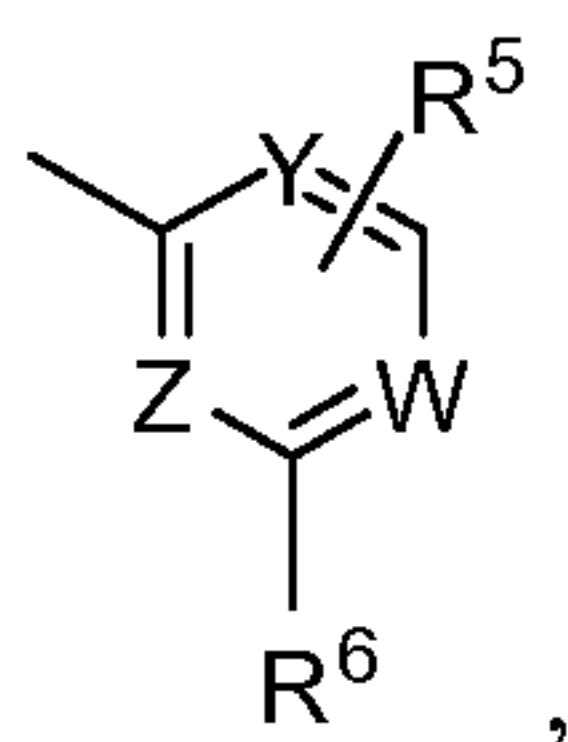
$-(CH_2)_n-NH-(CH_2)_n-NH_2$, or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 8, and each R^6 is, independently, heterocycle or the free base or salt form of $-(CH_2)_n-NH_2$, $-(CH_2)_n-NH-(CH_2)_n-NH_2$, or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 8; or each R^5 is, independently, H, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, halo, OH, or CF_3 , and each R^6 is, independently, heterocycle or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 8; or each R^5 is, independently, H, C_1 - C_3 alkyl, halo, or OH, and each R^6 is, independently, heterocycle or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4; or each R^5 is, independently, H, C_1 - C_3 alkyl, halo, or OH, and each R^6 is, independently, 6-membered heterocycle or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 3; or each R^5 is, independently, H or halo, and each R^6 is piperazinyl or the free base or salt form of $-(CH_2)_n-NH_2$ where each n is, independently, 1 to 3; or each R^5 is piperazinyl, and each R^6 is, independently, H, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, halo, OH, or CF_3 ; or each R^5 is piperazinyl, and each R^6 is H, C_1 - C_3 alkyl, halo, OH, or CF_3 .

In some embodiments, X is NH, O, S, or $S(=O)_2$; R^1 and R^2 are H; R^3 and R^4 are, independently,



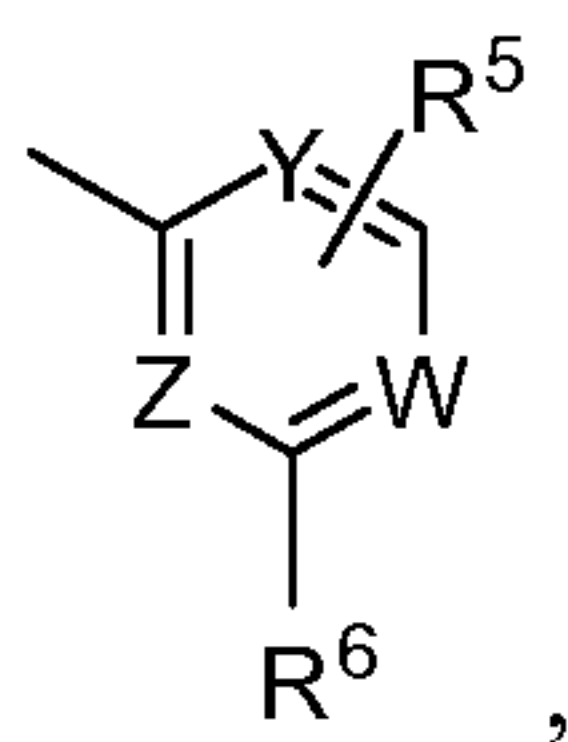
wherein each W, Y, and Z are, independently, C or N; and each R^5 and each R^6 are, independently, H, heterocycle, or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 3.

In some embodiments, X is NH, O, or S; R^1 and R^2 are H; R^3 and R^4 are



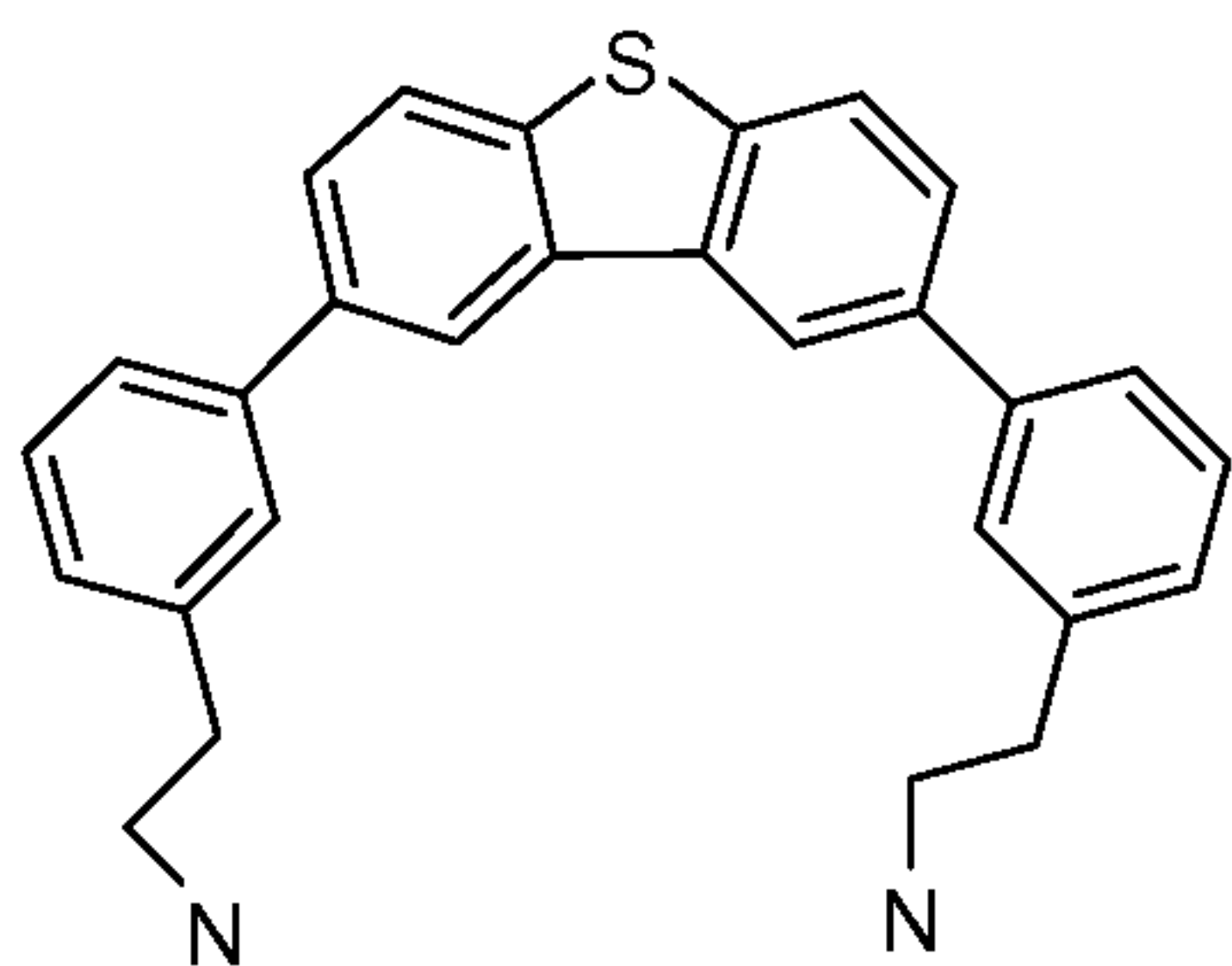
where each Z and Y are C, and each W is N; or each W, Y, and Z are C; each R^5 is, independently, H or halo, and each R^6 is piperazinyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 3; or each R^5 is piperazinyl, and each R^6 is, independently, H, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, halo, OH, or CF_3 .

In some embodiments, X is NH, O, or S; R^1 and R^2 are H; R^3 and R^4 are

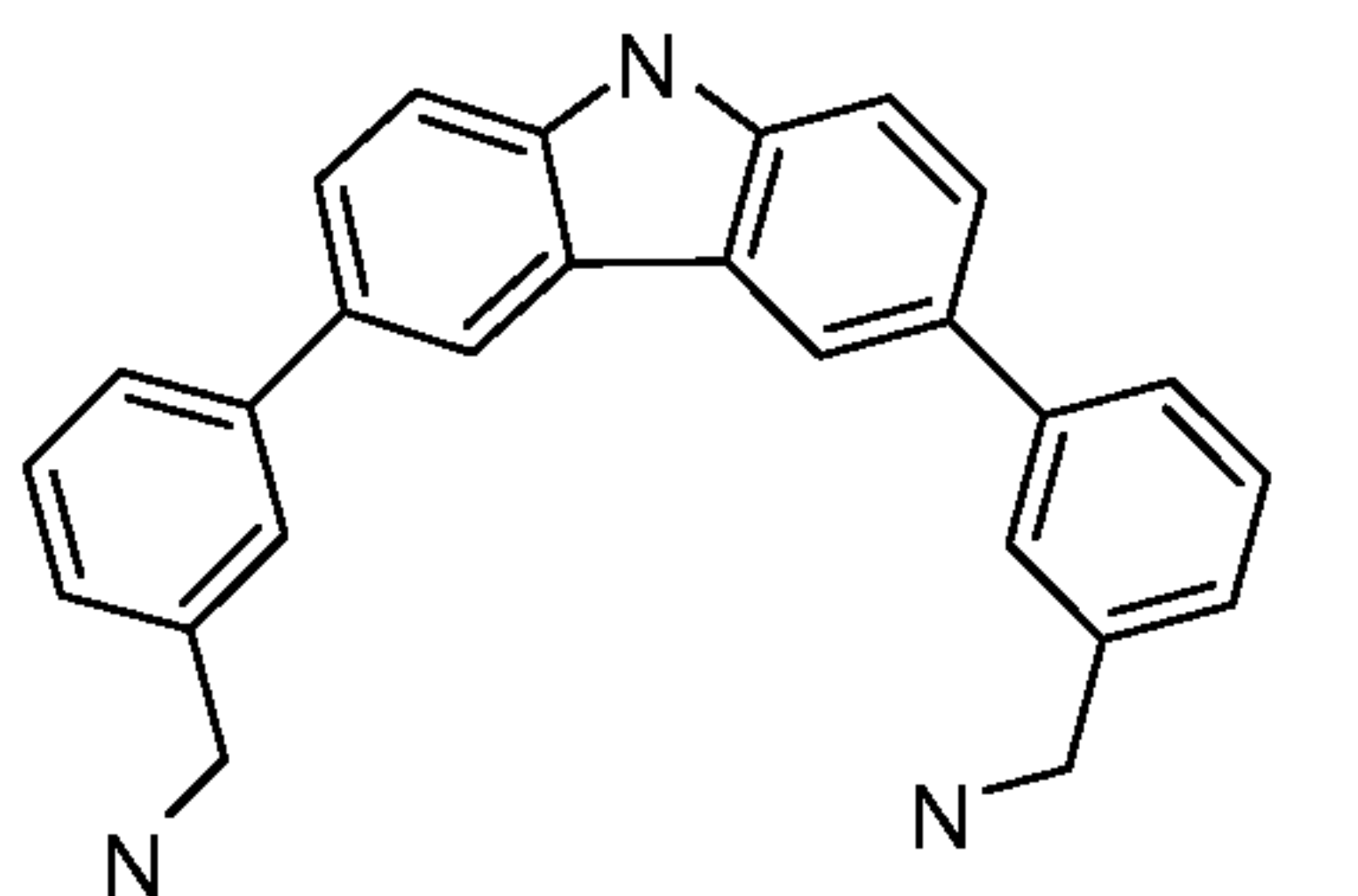


where each Z and Y are C, and each W is N; or each W, Y, and Z are C; each R⁵ is H, and each R⁶ is piperazinyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 3; or each R⁵ is piperazinyl; and each R⁶ is H.

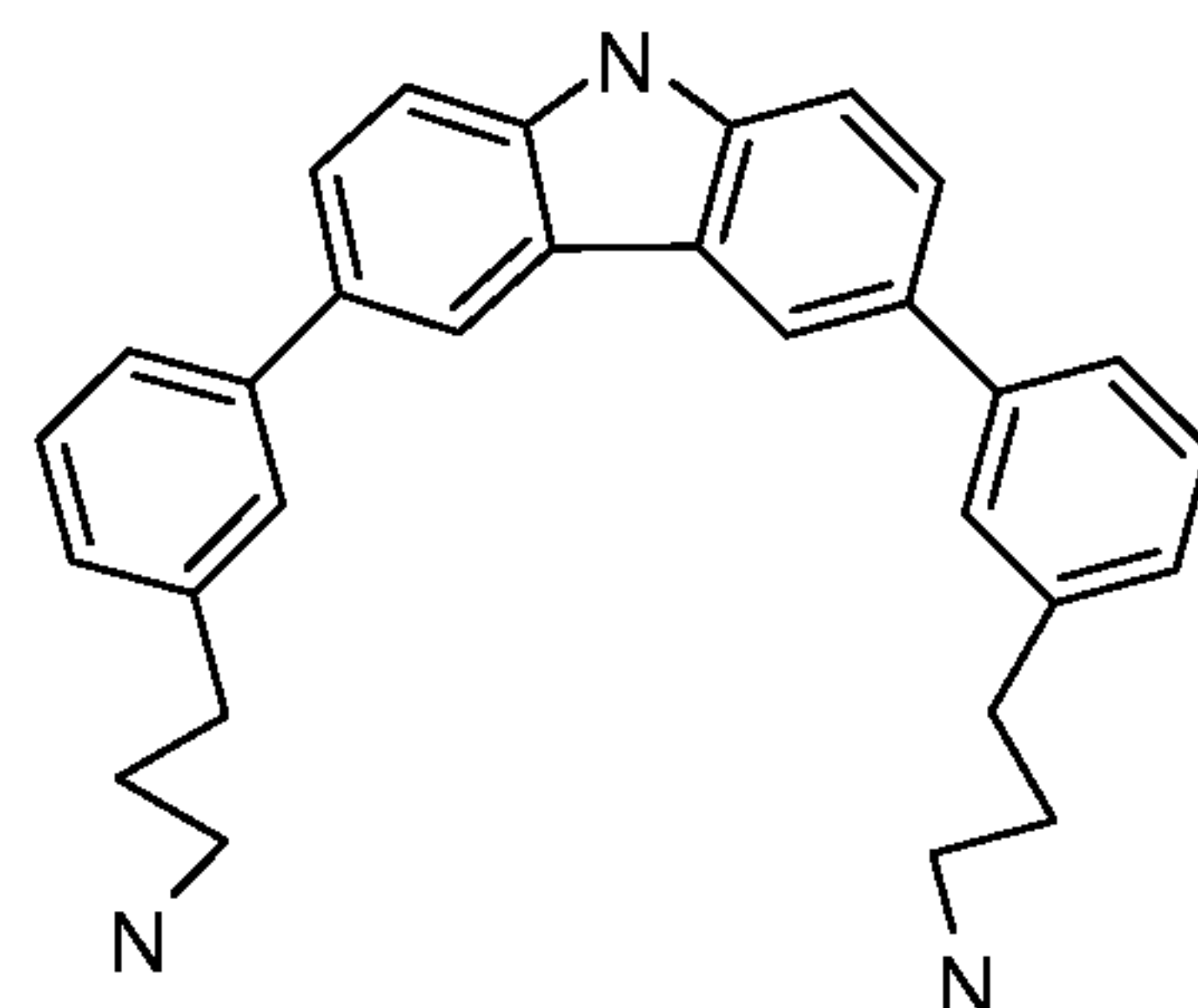
5 In some embodiments, the compound is chosen from:



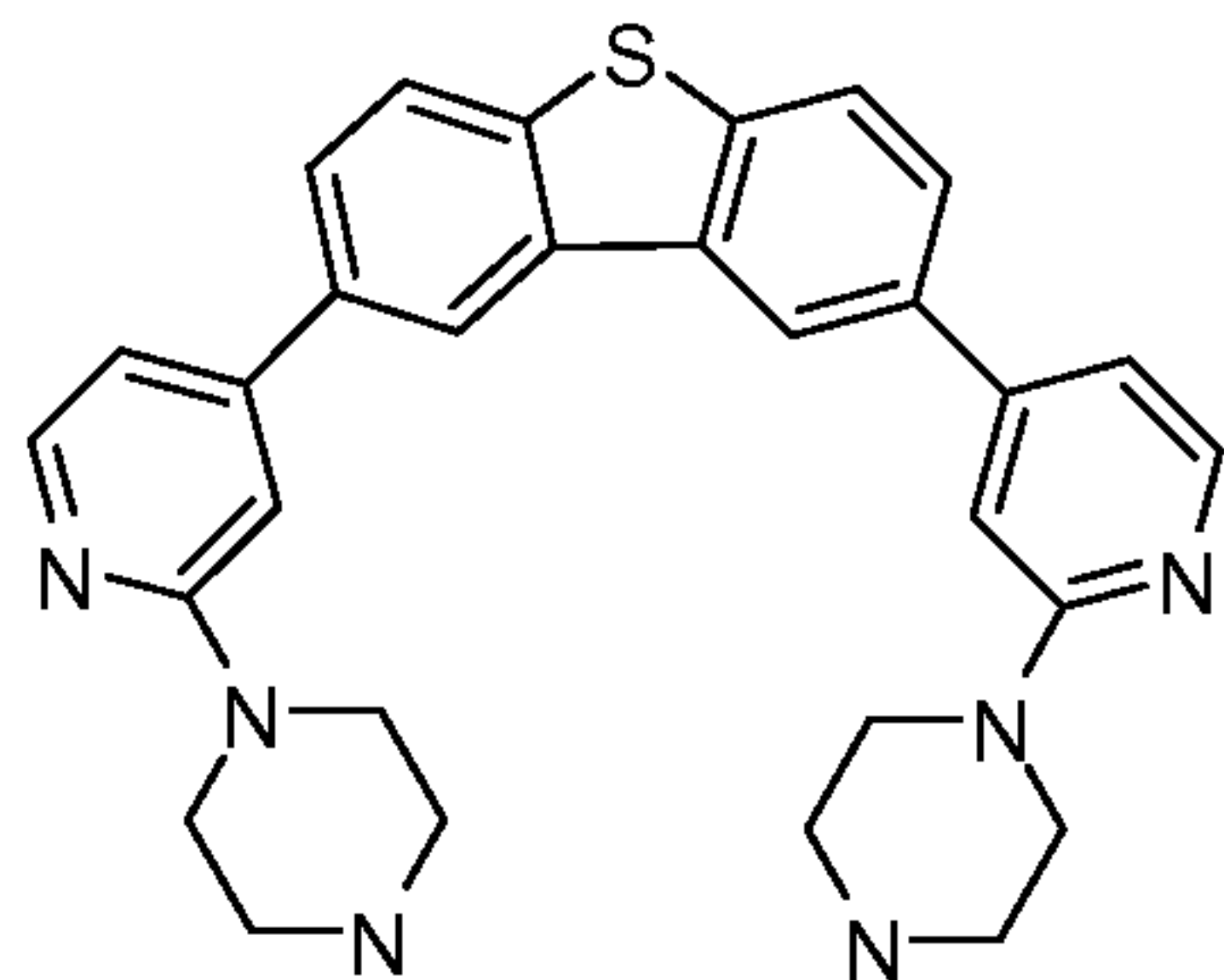
Compound 106



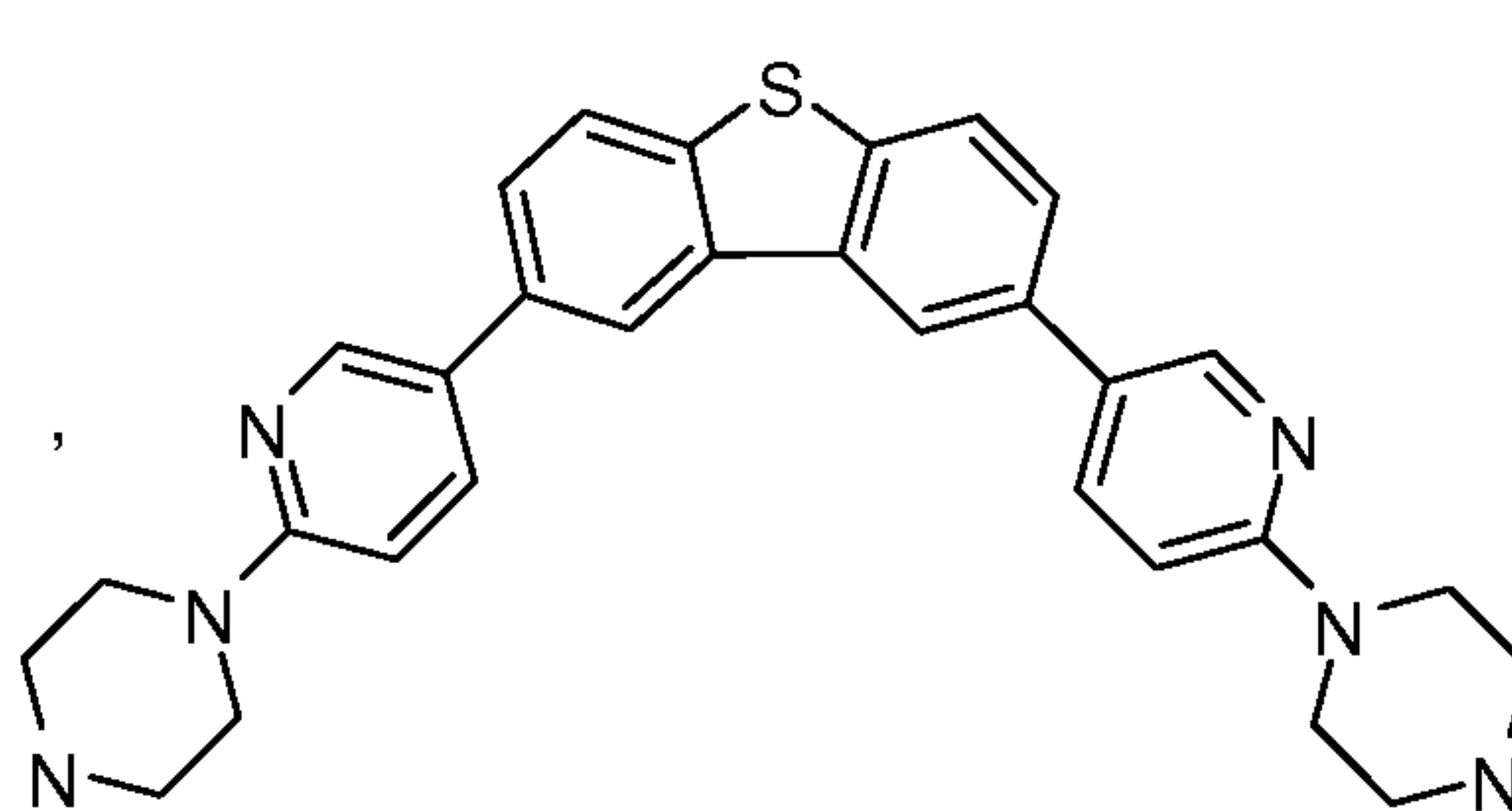
Compound 118



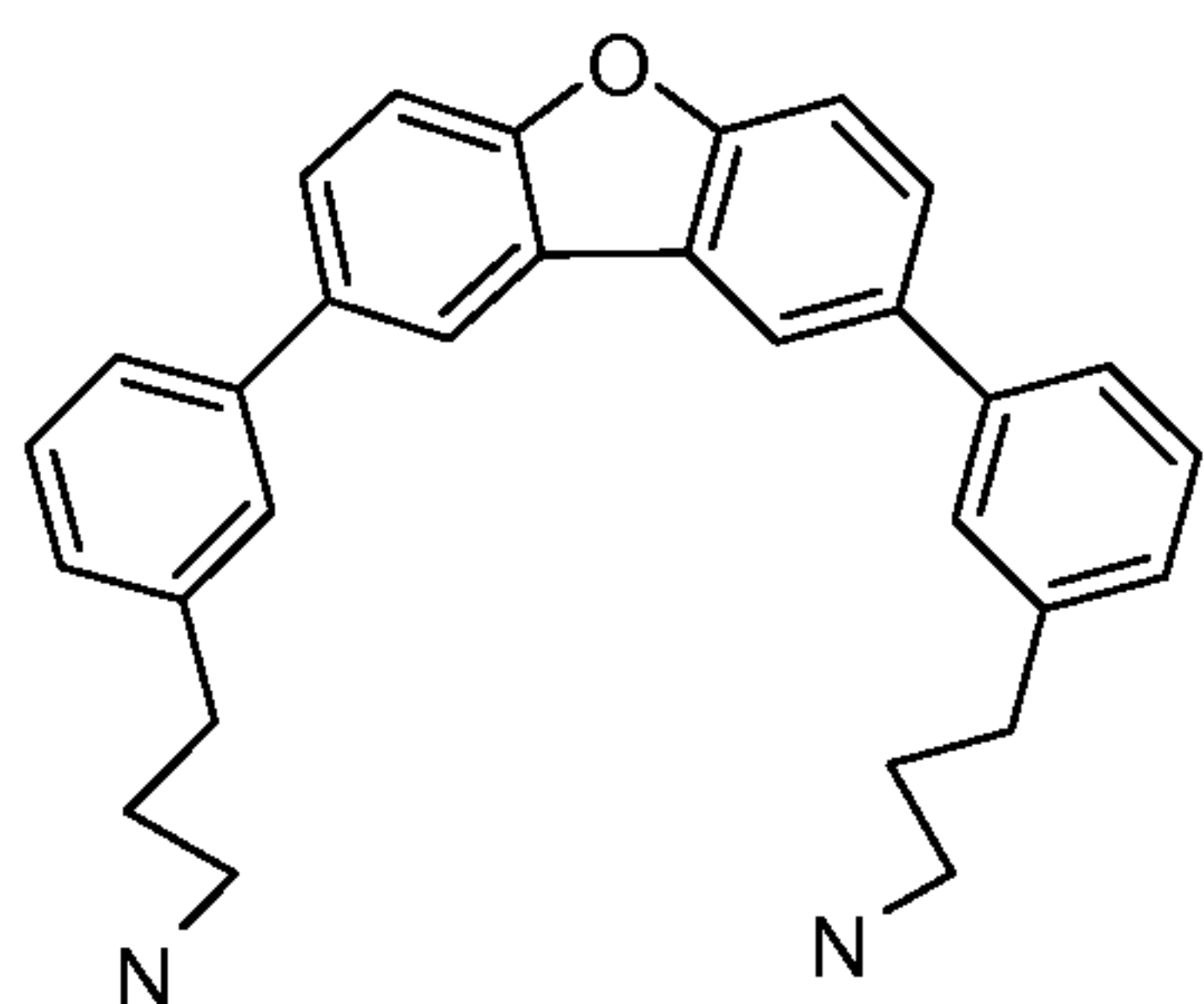
Compound 119



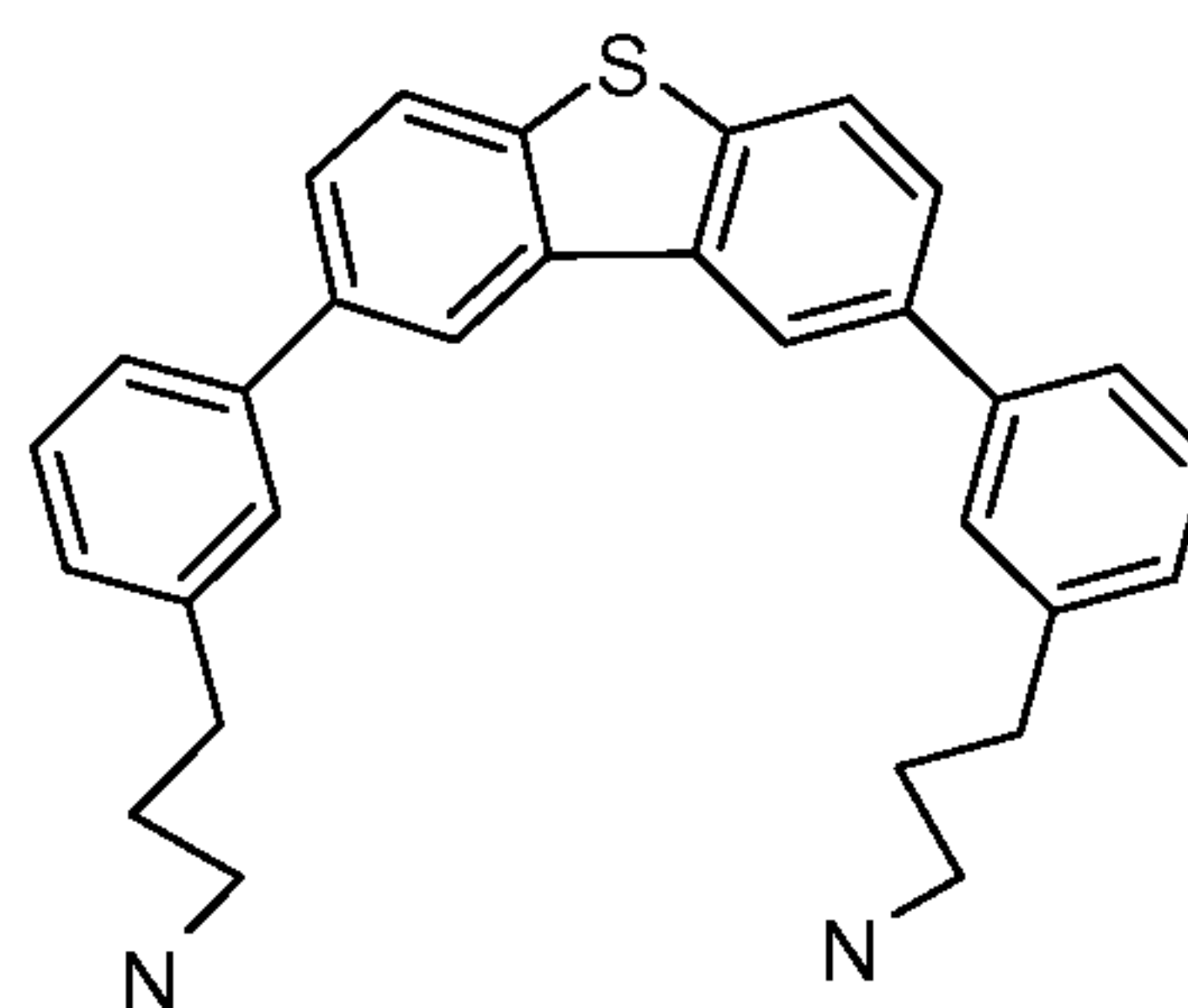
Compound 110



Compound 117

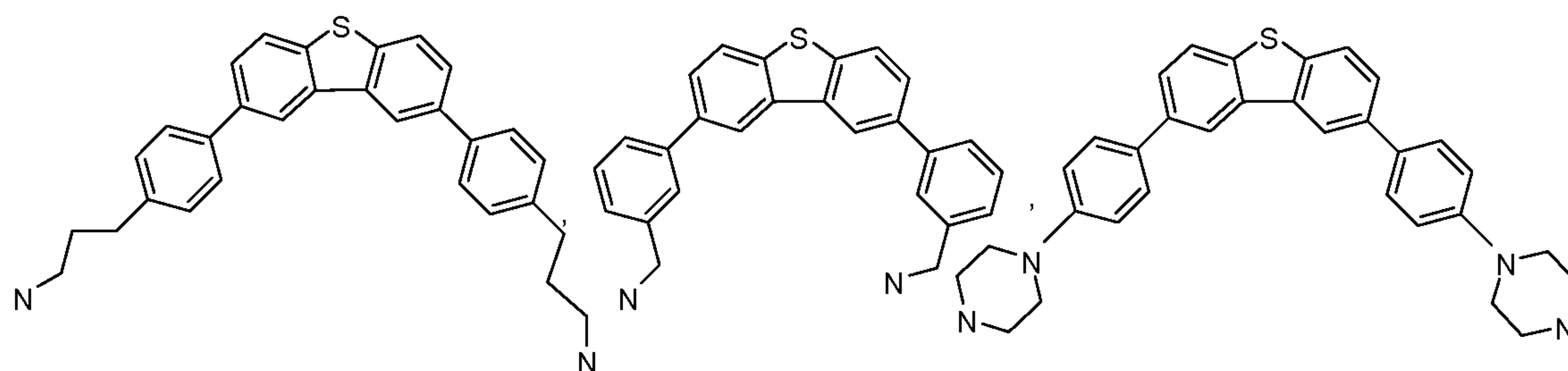


Compound 120



Compound 116

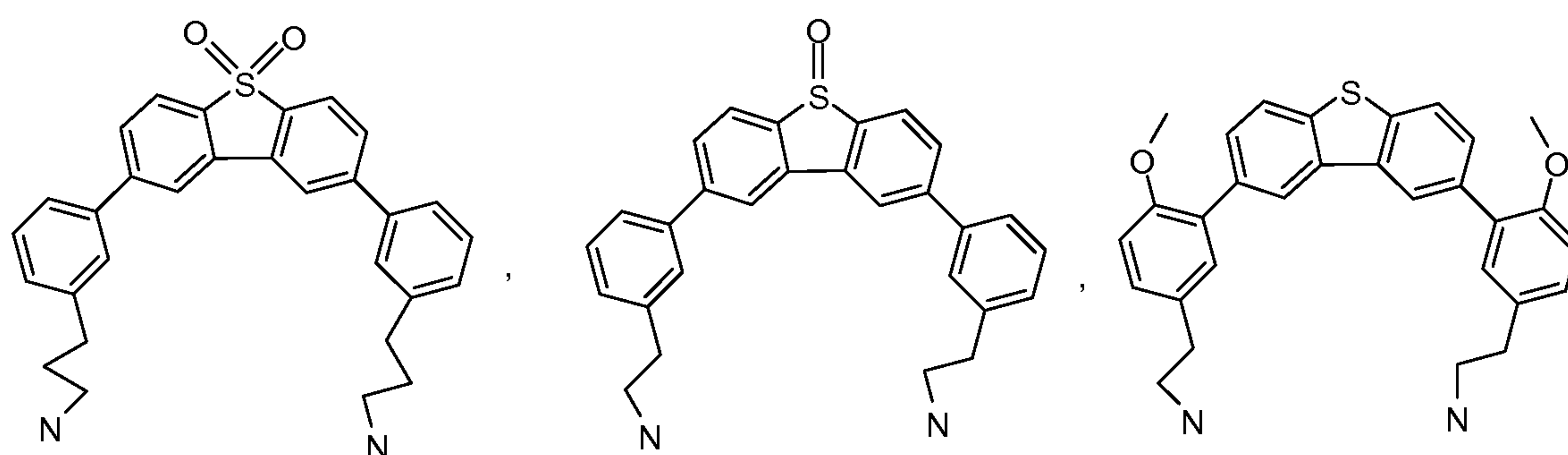
10



Compound 130

Compound 131

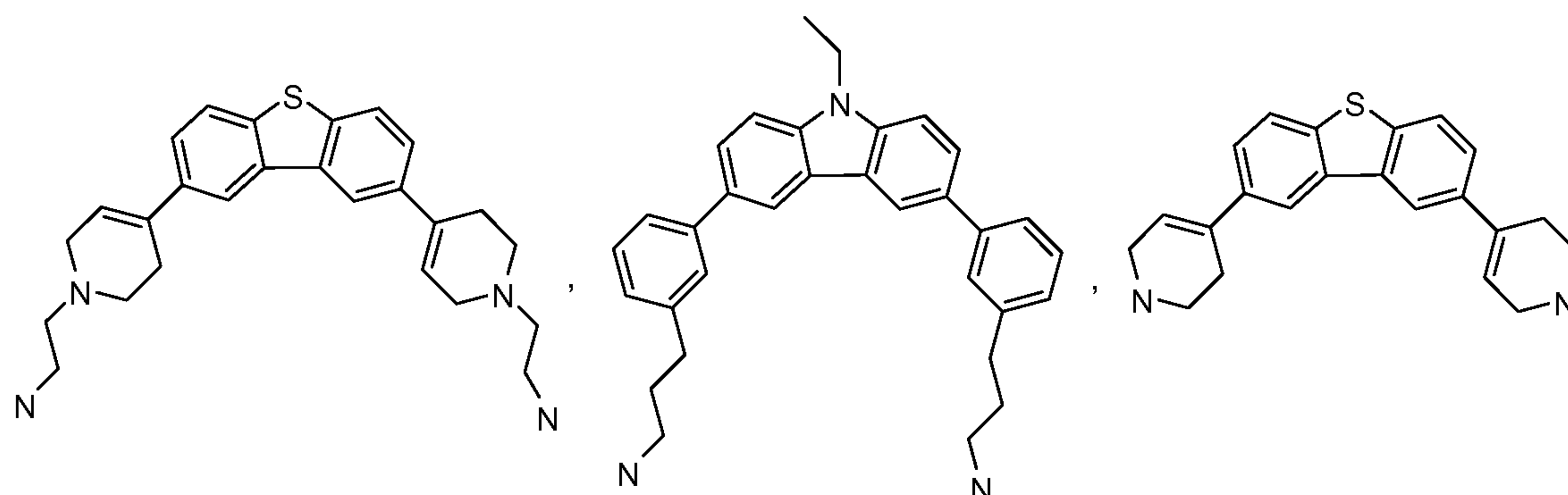
Compound 132



Compound 133

Compound 134

Compound 135

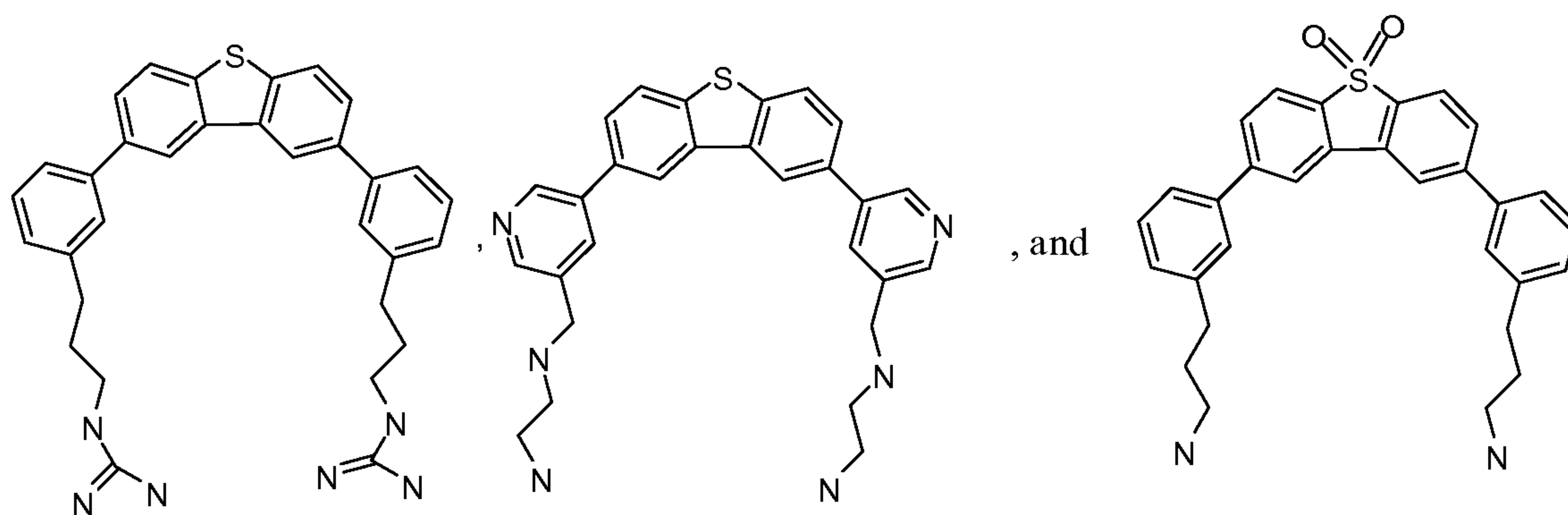


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Compound 136

Compound 137

Compound 138



Compound 139

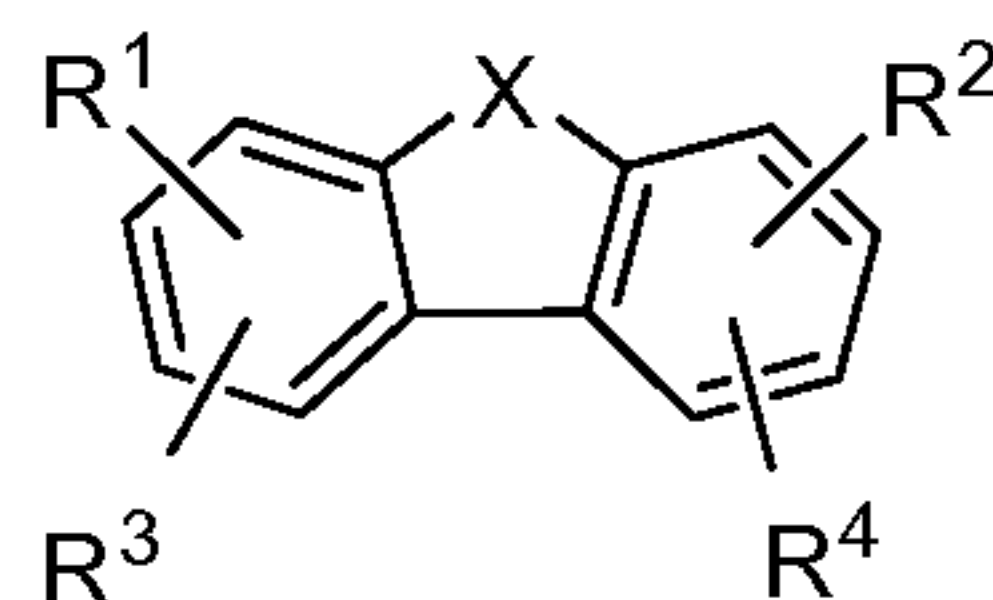
Compound 140

Compound 141

or pharmaceutically acceptable salt thereof.

In any of the above embodiments, the malaria can be chloroquine-sensitive or chloroquine-resistant.

The present invention also provides methods of killing or inhibiting the growth of a *Plasmodium* species comprising contacting the species with an effective amount of a
5 compound of Formula I:



wherein:

X is C(R⁷)C(R⁸), C(=O), N(R⁹), O, S, S(=O), or S(=O)₂;

R⁷, R⁸, and R⁹ are, independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, CF₃, or
10 aromatic group;

R¹ and R² are, independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, haloC₁-C₈alkyl, or CN;

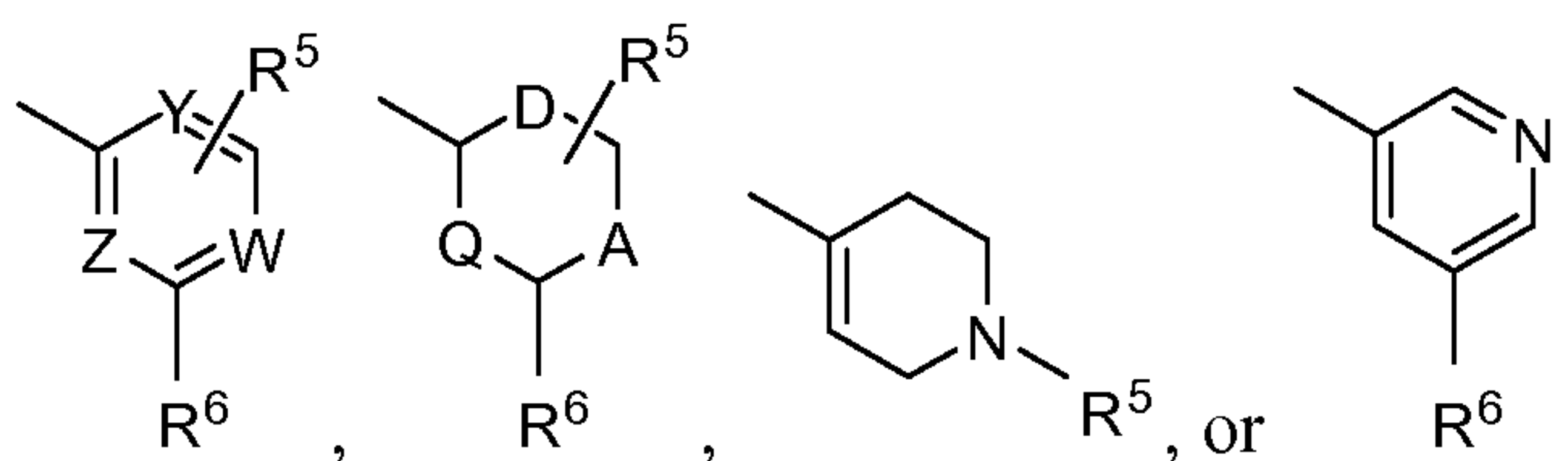
R³ and R⁴ are, independently, carbocycle(R⁵)(R⁶);

each R⁵ and each R⁶ are, independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, CF₃,
15 aromatic group, heterocycle, or the free base or salt form of -(CH₂)_n-NH₂,
-(CH₂)_n-NH-(CH₂)_n-NH₂, or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 8;
or a pharmaceutically acceptable salt thereof.

In some embodiments, X is N(R⁹), O, S, or S(=O)₂; or X is NH, O, or S; or X is NH
20 or S.

In any of the above embodiments, R¹ and R² are, independently, H, C₁-C₃alkyl, C₁-C₃alkoxy, halo, OH, haloC₁-C₃alkyl, or CN; or R¹ and R² are, independently, H, C₁-C₃alkyl, C₁-C₃alkoxy, halo, or OH; or R¹ and R² are, independently, H, C₁-C₃alkyl, or halo; or R¹ and R² are H.

25 In any of the above embodiments, R³ and R⁴ are, independently,

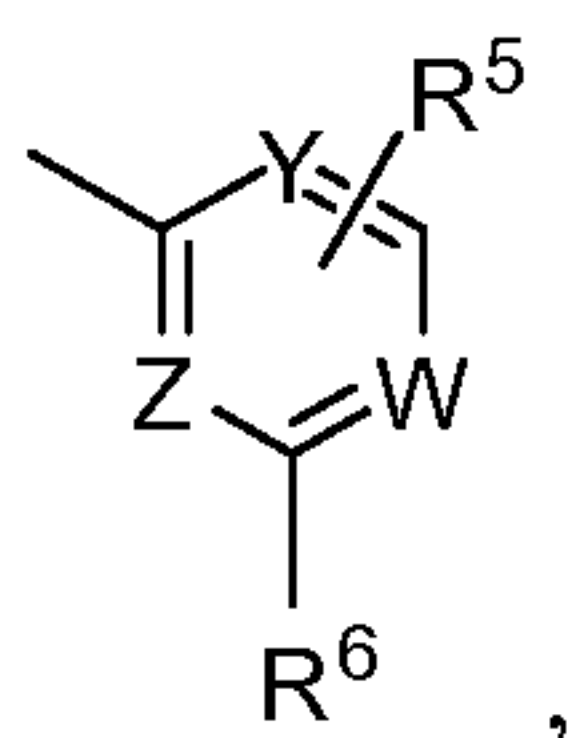


wherein each W, Y, and Z are, independently, C or N, each A, D, and Q are, independently, C(R¹⁰)C(R¹¹), C(=O), N(R¹²), O, or S, and each R¹⁰, R¹¹, and R¹² are, independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, CF₃, or aromatic group.

In any of the above embodiments, R³ and R⁴ are, independently,



wherein each W, Y, and Z are, independently, C or N; or R³ and R⁴ are, independently,

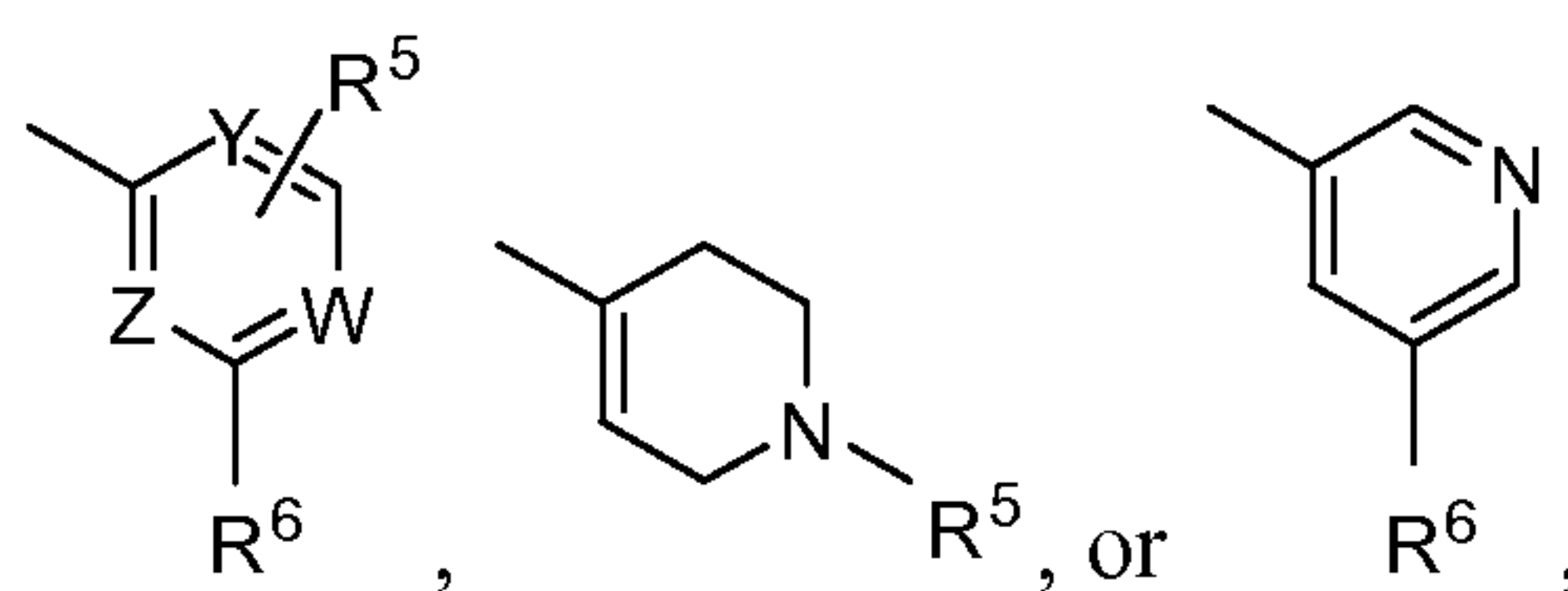


wherein each W, Y, and Z are C; or each Y and Z are C and each W is N.

- In any of the above embodiments, each R⁵ is, independently, H, C₁-C₈alkyl,
- 10 C₁-C₈alkoxy, halo, OH, CF₃, or the free base or salt form of -(CH₂)_n-NH₂, -(CH₂)_n-NH-(CH₂)_n-NH₂, or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 8, and each R⁶ is, independently, heterocycle or the free base or salt form of -(CH₂)_n-NH₂, -(CH₂)_n-NH-(CH₂)_n-NH₂, or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 8; or each R⁵ is, independently, H, C₁-C₃alkyl, C₁-C₃alkoxy, halo, OH, or CF₃, and each R⁶
- 15 is, independently, heterocycle or the free base or salt form of -(CH₂)_n-NH₂, where each n is, independently, 1 to 8; or each R⁵ is, independently, H, C₁-C₃alkyl, halo, or OH, and each R⁶ is, independently, heterocycle or the free base or salt form of -(CH₂)_n-NH₂, where each n is, independently, 1 to 4; or each R⁵ is, independently, H, C₁-C₃alkyl, halo, or OH, and each R⁶ is, independently, 6-membered heterocycle or the free base or salt form of -(CH₂)_n-NH₂,
- 20 where each n is, independently, 1 to 3; or each R⁵ is, independently, H or halo, and each R⁶ is piperazinyl or the free base or salt form of -(CH₂)_n-NH₂ where each n is, independently, 1 to 3; or each R⁵ is piperazinyl, and each R⁶ is, independently, H, C₁-C₃alkyl, C₁-C₃alkoxy, halo, OH, or CF₃; or each R⁵ is piperazinyl, and each R⁶ is H, C₁-C₃alkyl, halo, OH, or CF₃.

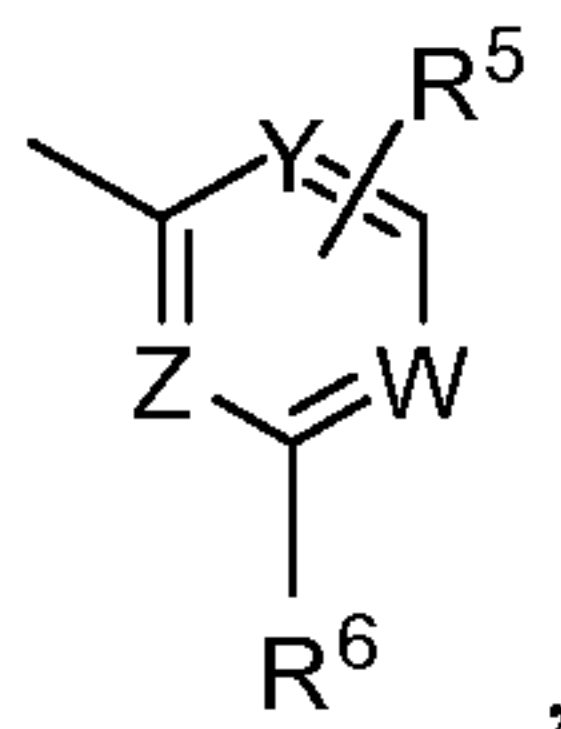
In some embodiments, X is NH, O, S, or S(=O)₂; R¹ and R² are H; R³ and R⁴ are,

25 independently,



wherein each W, Y, and Z are, independently, C or N; and each R^5 and each R^6 are, independently, H, heterocycle, or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 3.

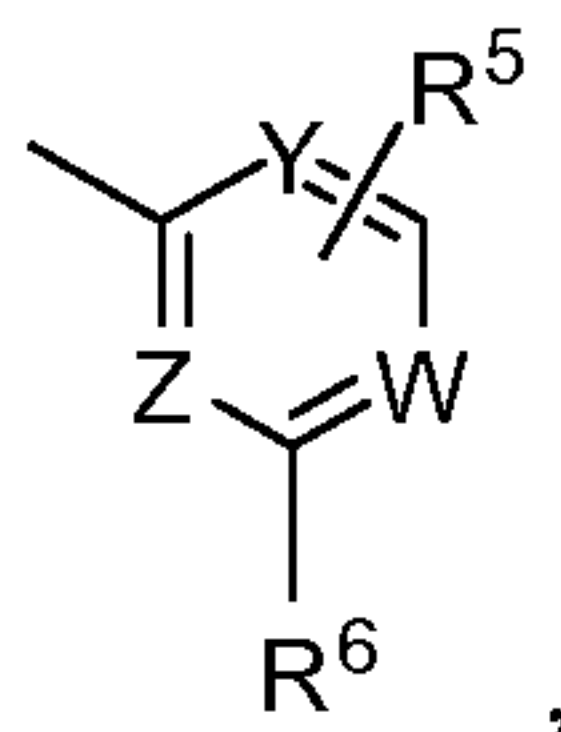
5 In some embodiments, X is NH, O, or S; R^1 and R^2 are H; R^3 and R^4 are



where each Z and Y are C, and each W is N; or each W, Y, and Z are C; each R^5 is, independently, H or halo, and each R^6 is piperazinyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 3; or each R^5 is piperazinyl, and each R^6 is, independently, H, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, halo, OH, or CF_3 .

10

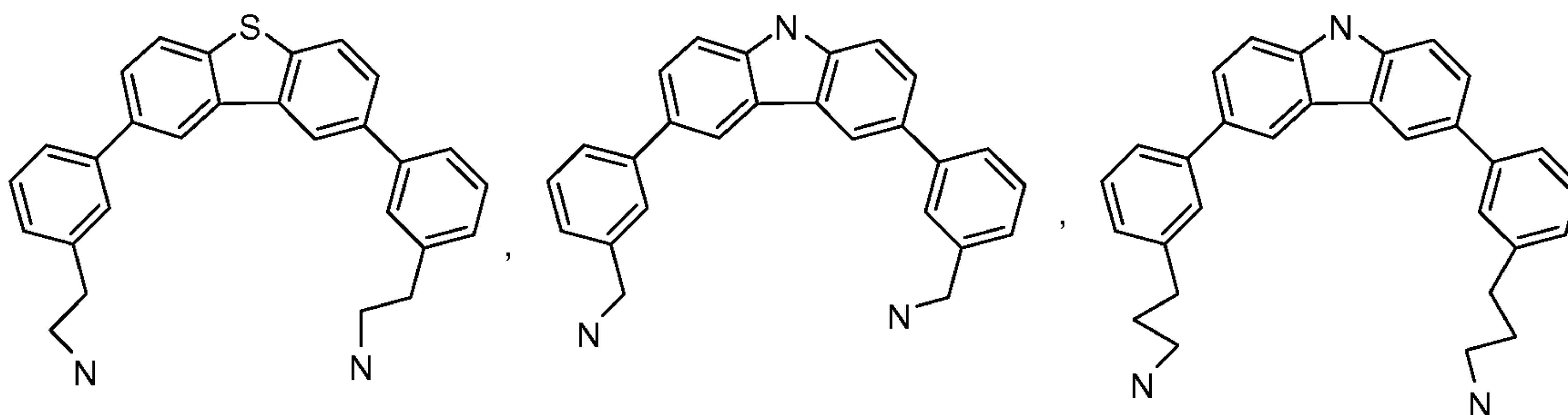
In some embodiments, X is NH, O, or S; R^1 and R^2 are H; R^3 and R^4 are

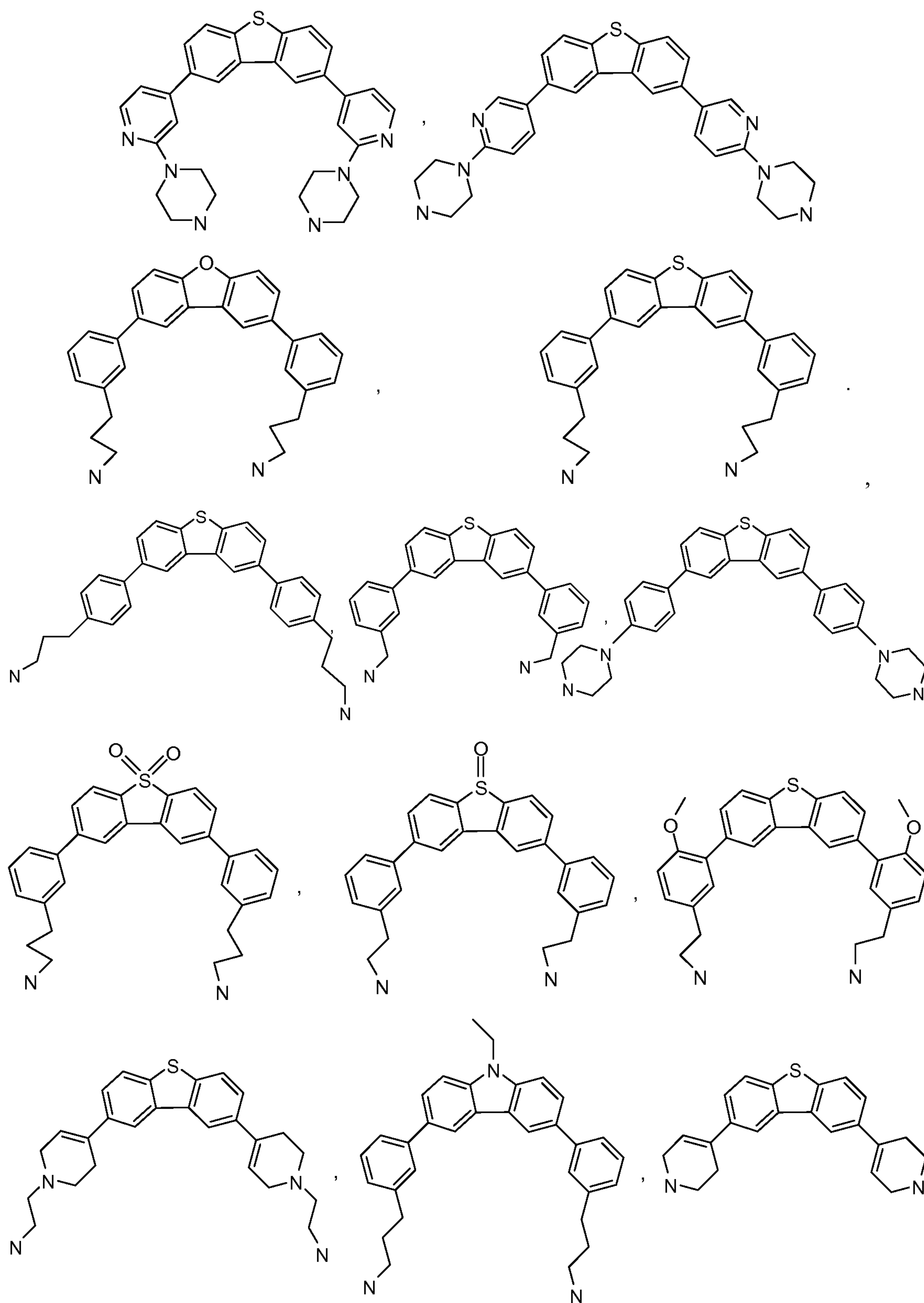


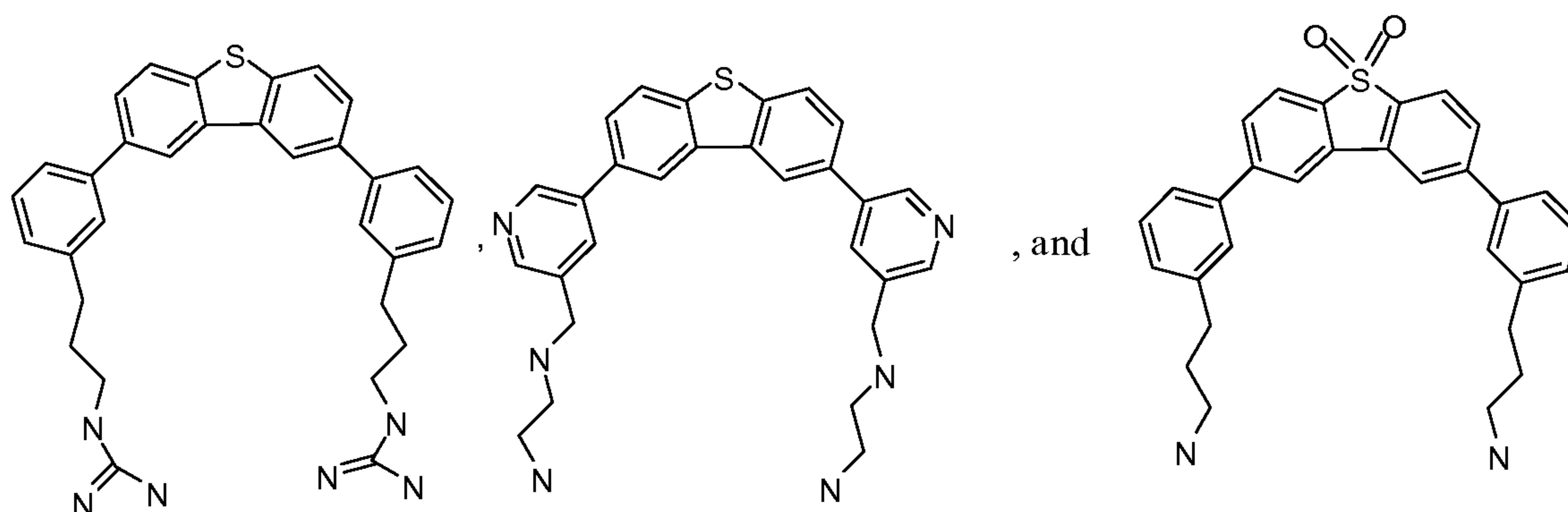
where each Z and Y are C, and each W is N; or each W, Y, and Z are C; each R^5 is H, and each R^6 is piperazinyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is,

15 independently, 1 to 3; or each R^5 is piperazinyl; and each R^6 is H.

In some embodiments, the compound is chosen from:

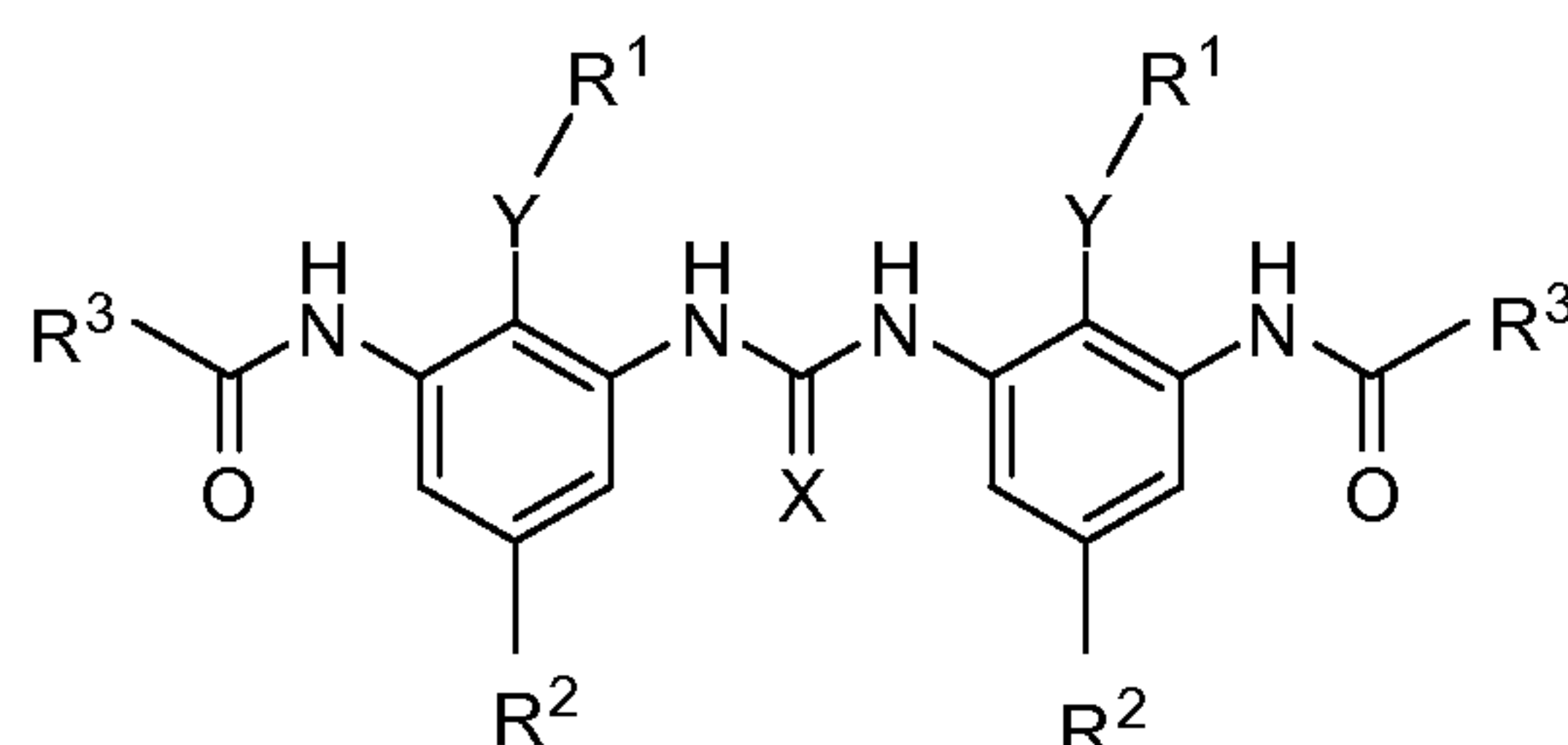






or pharmaceutically acceptable salt thereof.

The present invention also provides compounds of Formula II:



5 wherein:

X is O or S;

each Y is, independently, O, S, or N;

each R^1 is, independently, H, 5- or 6-membered heterocycle, or the free base or salt form of $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; or

10 each R^1 is, independently, together with Y a 5- or 6-membered heterocycle;

each R^2 is, independently, H, CF_3 , $C(CH_3)_3$, halo, or OH; and

each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;

or a pharmaceutically acceptable salt thereof.

15 In some embodiments, X is O.

In any of the above embodiments, each Y is O or S.

In any of the above embodiments, each R^1 is, independently, 5-membered heterocycle or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4; or each R^1 is, independently, 3-pyrrolyl or the free base or salt form of $-(CH_2)_n-NH_2$,

20 where each n is, independently, 1 or 2.

In any of the above embodiments, each R^2 is, independently, CF_3 , $C(CH_3)_3$, or halo.

In any of the above embodiments, each R^3 is, independently,

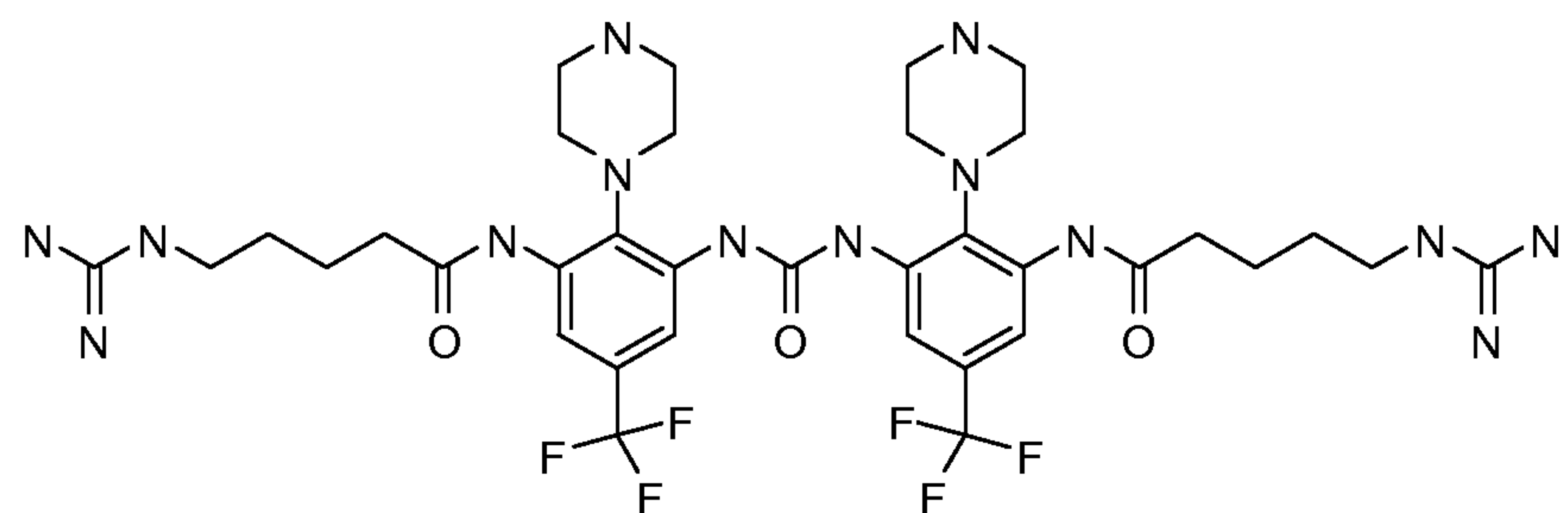
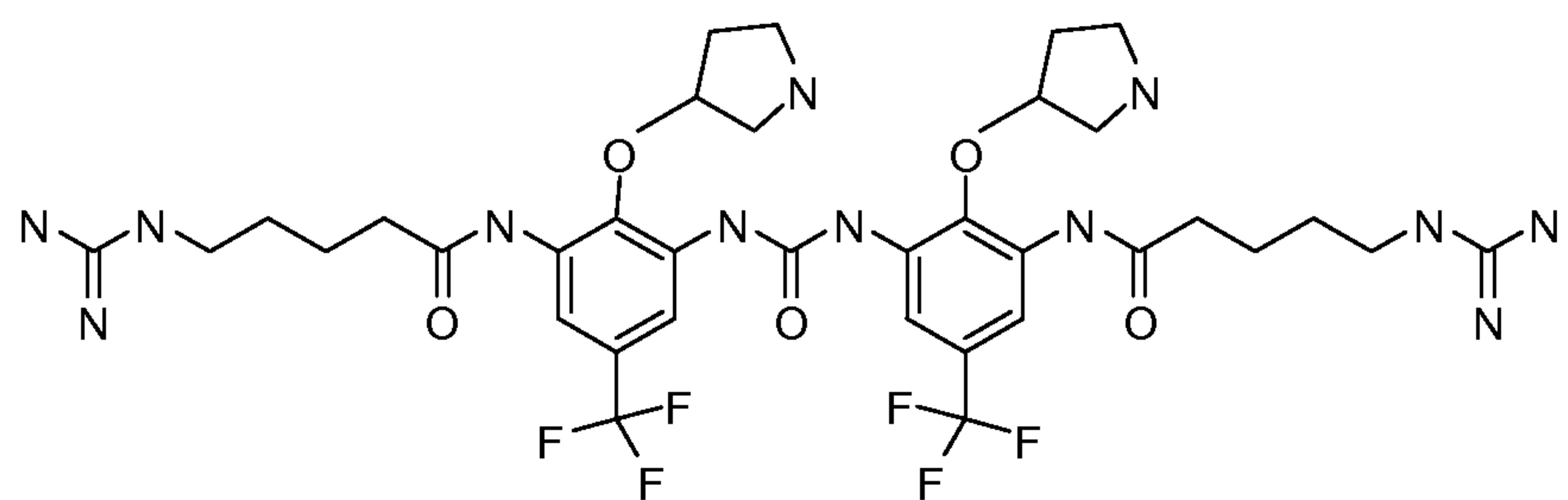
$-(\text{CH}_2)_n\text{-NH-C(=NH)NH}_2$, where each n is, independently, 1 to 4; or each R^3 is $-(\text{CH}_2)_n\text{-NH-C(=NH)NH}_2$, where each n is 4.

In some embodiments, X is O or S; each Y is, independently, O or S; each R^1 is, independently, 5-membered heterocycle, or the free base or salt form of $-(\text{CH}_2)_n\text{-NH}_2$, where
 5 each n is, independently, 1 to 4; each R^2 is, independently, CF_3 or $\text{C}(\text{CH}_3)_3$; and each R^3 is, independently, $-(\text{CH}_2)_n\text{-NH-C(=NH)NH}_2$, where each n is, independently, 1 to 4.

In some embodiments, X is O or S; each Y is O or S; each R^1 is 5-membered heterocycle, or the free base or salt form of $-(\text{CH}_2)_n\text{-NH}_2$, where each n is 1 to 4; each R^2 is CF_3 or $\text{C}(\text{CH}_3)_3$; and each R^3 is $-(\text{CH}_2)_n\text{-NH-C(=NH)NH}_2$, where each n is 1 to 4.

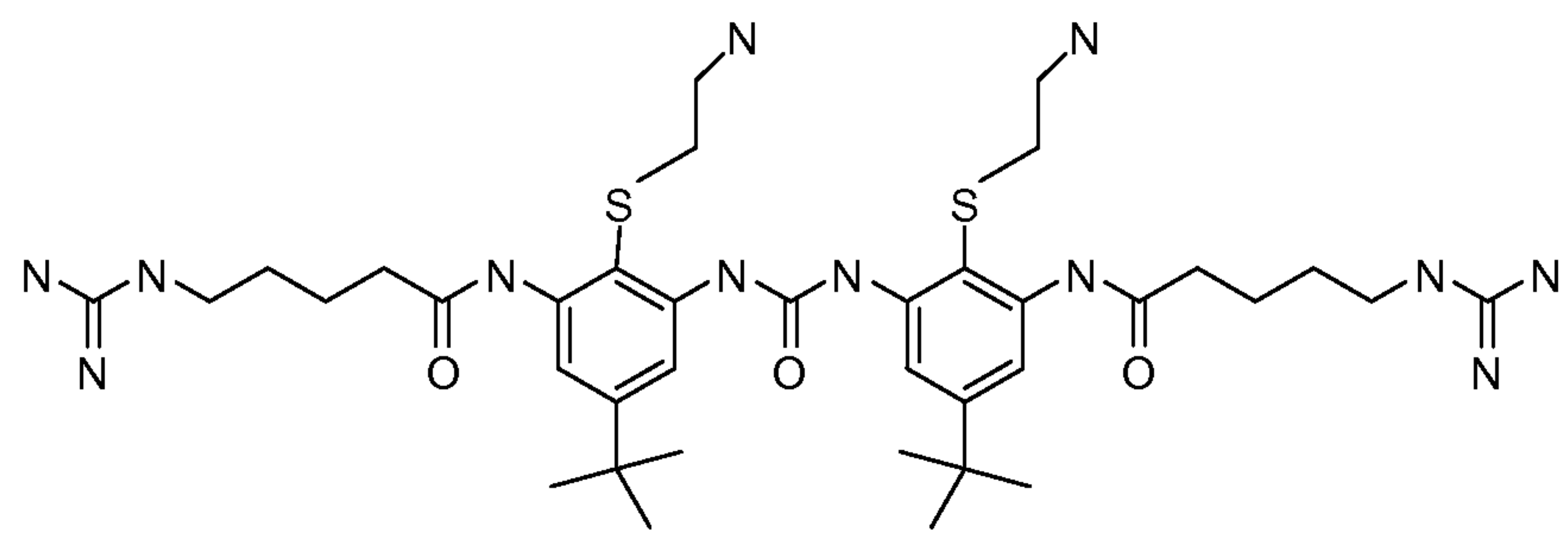
10 In some embodiments, X is O or S; each Y is O or S; each R^1 is 3-pyrrolyl, or the free base or salt form of $-(\text{CH}_2)_n\text{-NH}_2$, where each n is 2; each R^2 is CF_3 or $\text{C}(\text{CH}_3)_3$; and each R^3 is $-(\text{CH}_2)_n\text{-NH-C(=NH)NH}_2$, where each n is 4.

In some embodiments, the compound is chosen from:



15

and

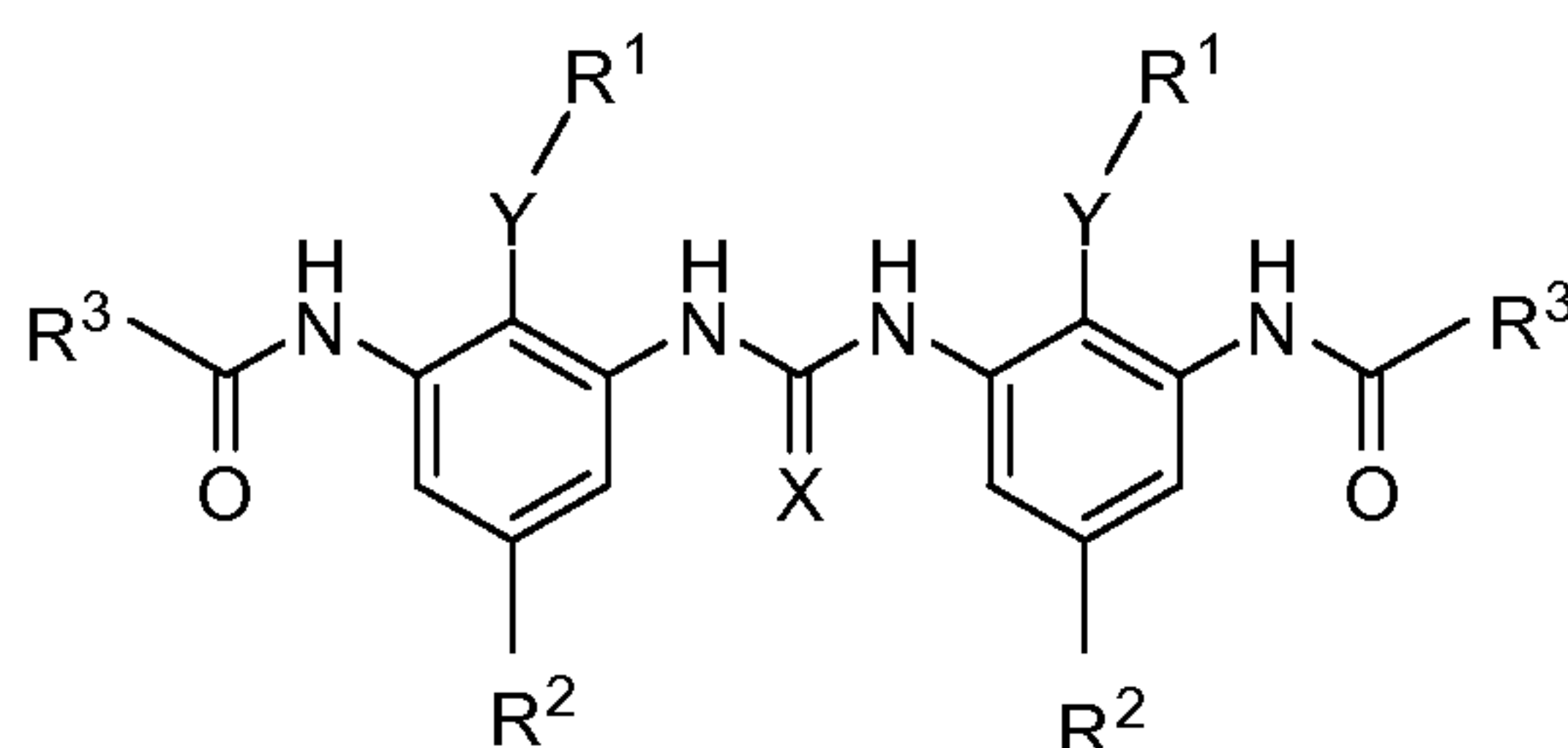


or a pharmaceutically acceptable salt thereof.

In some embodiments, any one or more of the above compounds may be excluded from any of the genus of compounds described above.

The present invention also provides compositions comprising one or more of the compounds or salts described above and a pharmaceutically acceptable carrier.

- 5 The present invention also provides methods of treating malaria in an animal comprising administering to the animal a therapeutically effective amount of a compound of Formula II:



wherein:

- 10 X is O or S;
 each Y is, independently, O, S, or N;
 each R¹ is, independently, H, 5- or 6-membered heterocycle, or the free base or salt form of $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; or
 each R¹ is, independently, together with Y a 5- or 6-membered heterocycle;
 15 each R² is, independently, H, CF₃, C(CH₃)₃, halo, or OH; and
 each R³ is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;
 or a pharmaceutically acceptable salt thereof.

In some embodiments, X is O.

- 20 In any of the above embodiments, each Y is O or S.

In any of the above embodiments, each R¹ is, independently, 5-membered heterocycle or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4; or each R¹ is, independently, 3-pyrrolyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2.

- 25 In any of the above embodiments, each R² is, independently, CF₃, C(CH₃)₃, or halo.

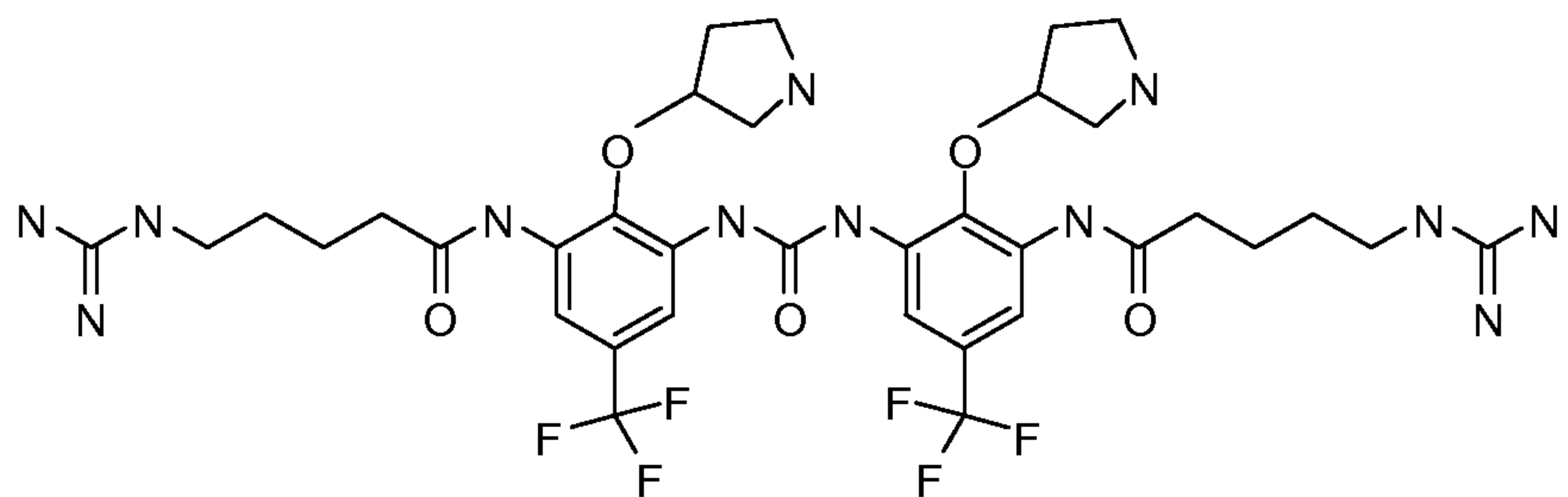
In any of the above embodiments, each R³ is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; or each R³ is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 4.

In some embodiments, X is O or S; each Y is, independently, O or S; each R¹ is, independently, 5-membered heterocycle, or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4; each R² is, independently, CF₃ or C(CH₃)₃; and each R³ is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

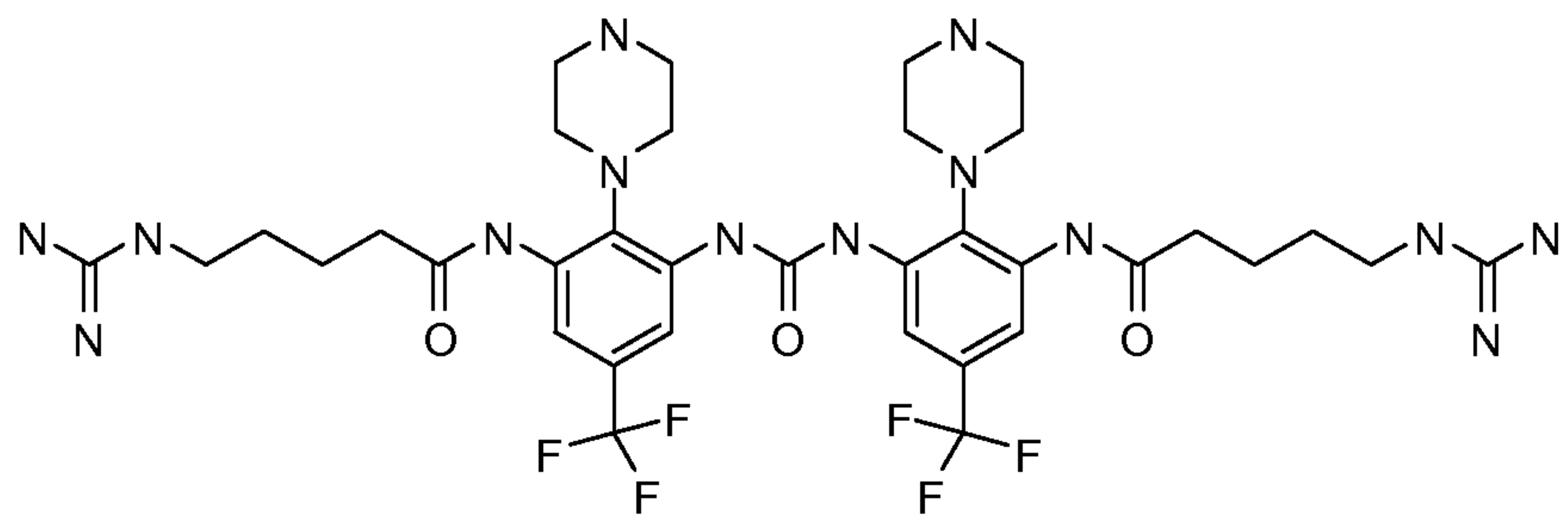
5 In some embodiments, X is O or S; each Y is O or S; each R¹ is 5-membered heterocycle, or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 1 to 4; each R² is CF₃ or C(CH₃)₃; and each R³ is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 to 4.

In some embodiments, X is O or S; each Y is O or S; each R¹ is 3-pyrrolyl, or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2; each R² is CF₃ or C(CH₃)₃; and each
10 R³ is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 4.

In some embodiments, the compound is chosen from:

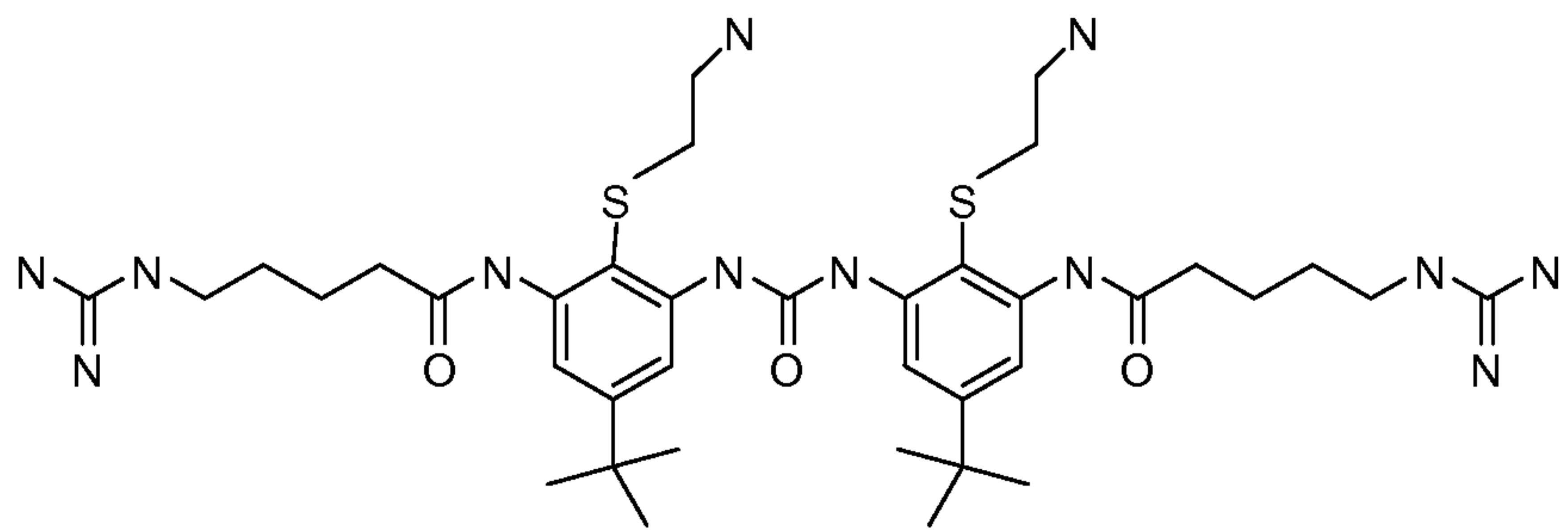


Compound 104



Compound 105

and

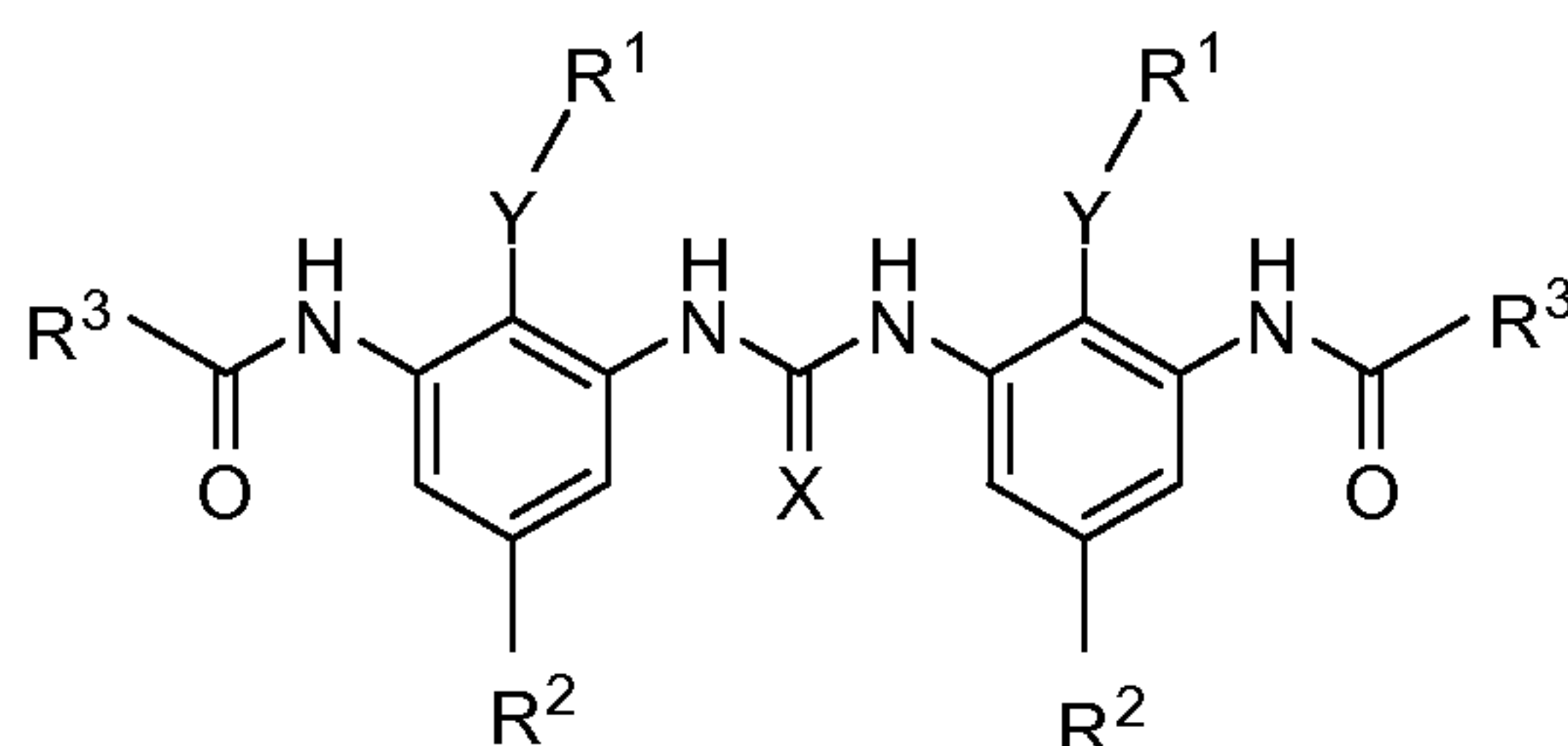


Compound 103

or a pharmaceutically acceptable salt thereof.

In any of the above embodiments, the malaria can be chloroquine-sensitive or chloroquine-resistant.

The present invention also provides methods of killing or inhibiting the growth of a
 5 *Plasmodium* species comprising contacting the species with an effective amount of a compound of Formula II:



wherein:

X is O or S;

10 each Y is, independently, O, S, or N;

each R¹ is, independently, H, 5- or 6-membered heterocycle, or the free base or salt form of $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; or each R¹ is, independently, together with Y a 5- or 6-membered heterocycle;

each R² is, independently, H, CF₃, C(CH₃)₃, halo, or OH; and

15 each R³ is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;

or a pharmaceutically acceptable salt thereof.

In some embodiments, X is O.

In any of the above embodiments, each Y is O or S.

20 In any of the above embodiments, each R¹ is, independently, 5-membered heterocycle or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4; or each R¹ is, independently, 3-pyrrolyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2.

In any of the above embodiments, each R² is, independently, CF₃, C(CH₃)₃, or halo.

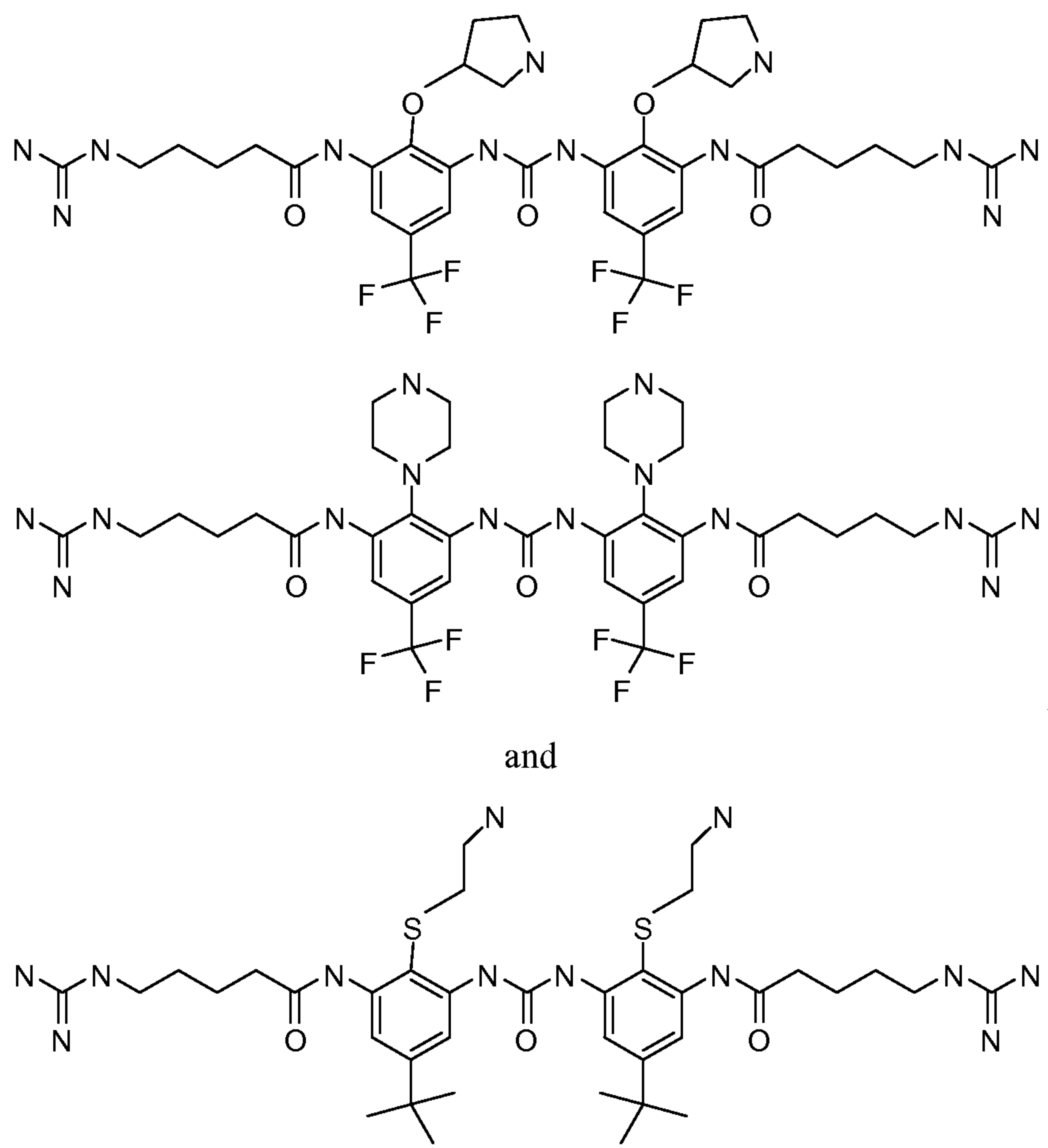
25 In any of the above embodiments, each R³ is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; or each R³ is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 4.

In some embodiments, X is O or S; each Y is, independently, O or S; each R¹ is, independently, 5-membered heterocycle, or the free base or salt form of -(CH₂)_n-NH₂, where each n is, independently, 1 to 4; each R² is, independently, CF₃ or C(CH₃)₃; and each R³ is, independently, -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4.

5 In some embodiments, X is O or S; each Y is O or S; each R¹ is 5-membered heterocycle, or the free base or salt form of -(CH₂)_n-NH₂, where each n is 1 to 4; each R² is CF₃ or C(CH₃)₃; and each R³ is -(CH₂)_n-NH-C(=NH)NH₂, where each n is 1 to 4.

In some embodiments, X is O or S; each Y is O or S; each R¹ is 3-pyrrolyl, or the free base or salt form of -(CH₂)_n-NH₂, where each n is 2; each R² is CF₃ or C(CH₃)₃; and each
10 R³ is -(CH₂)_n-NH-C(=NH)NH₂, where each n is 4.

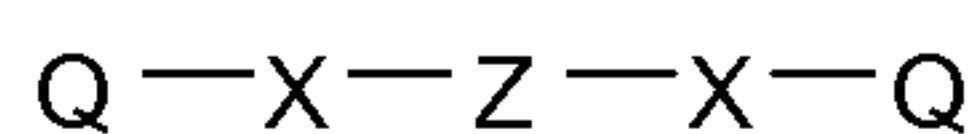
In some embodiments, the compound is chosen from:



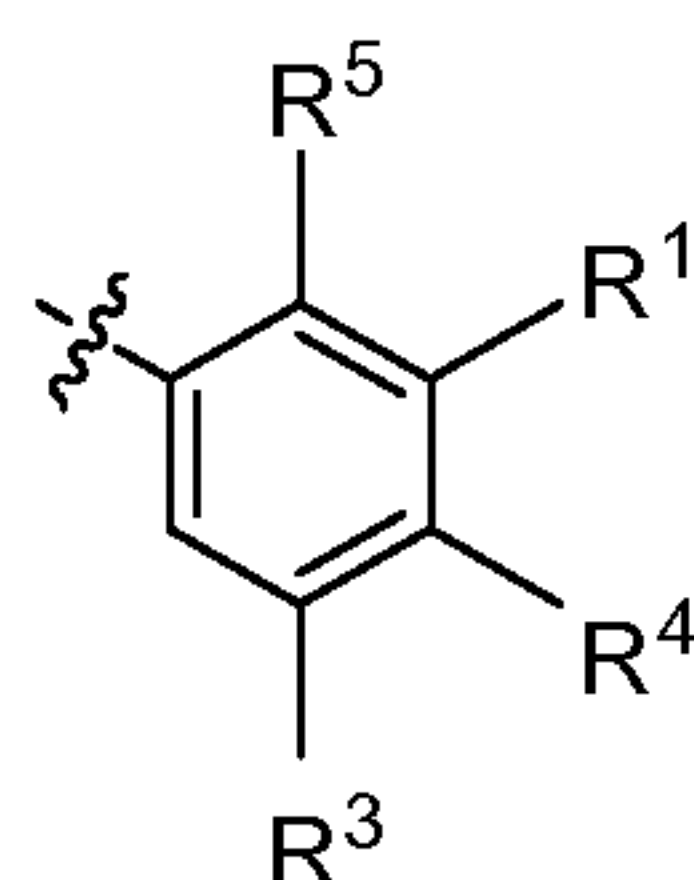
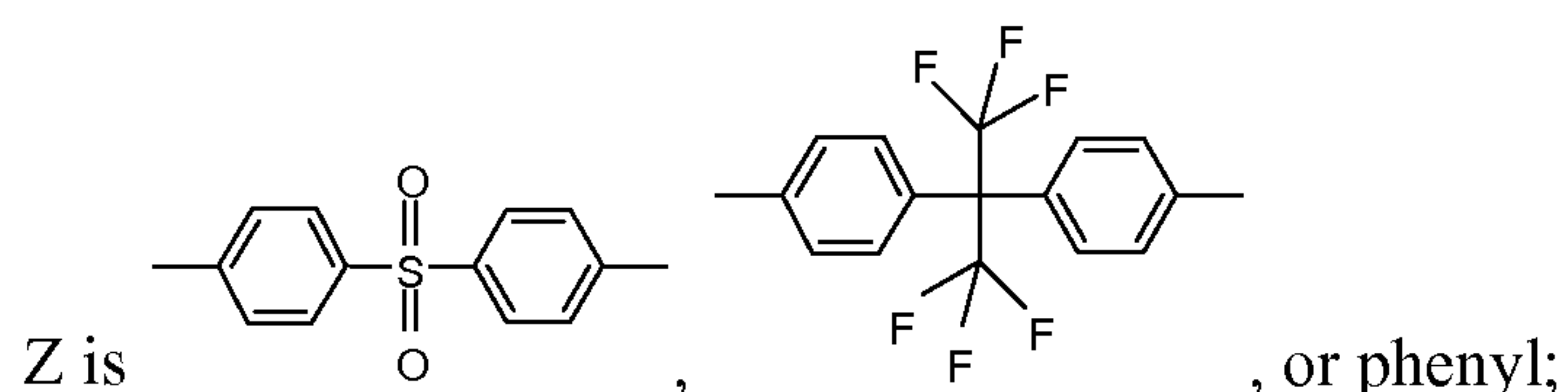
15

or a pharmaceutically acceptable salt thereof.

The present invention also provides compounds of Formula III:



wherein:



each Q is, independently, R^3 or $-C(=O)-(CH_2)_b-NH-C(=NH)-NH_2$, where

each b is, independently, 1 to 4;

5 each X is, independently, O, S, or N;

each R^1 is, independently, H, CF_3 , $C(CH_3)_3$, halo, or OH;

each R^3 is, independently, H, $-NH-R^2$, $-(CH_2)_r-NH_2$, $-NH_2$, $-NH-(CH_2)_w-NH_2$, or

$-(CH_2)_y-N$, where each r is, independently, 1 or 2, each w is, independently, 1 to 3, and each y is, independently, 1 or 2;

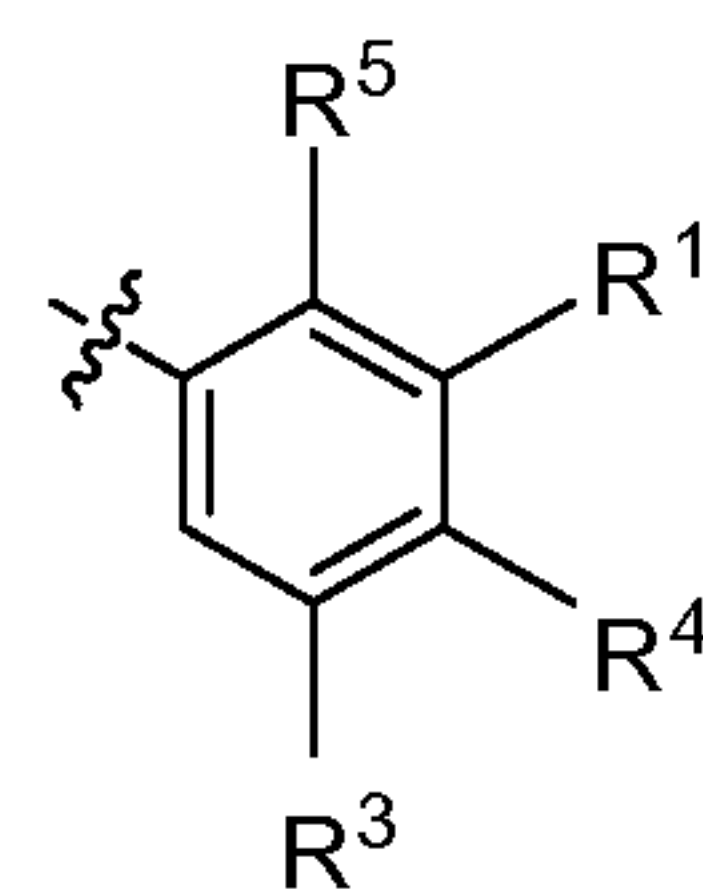
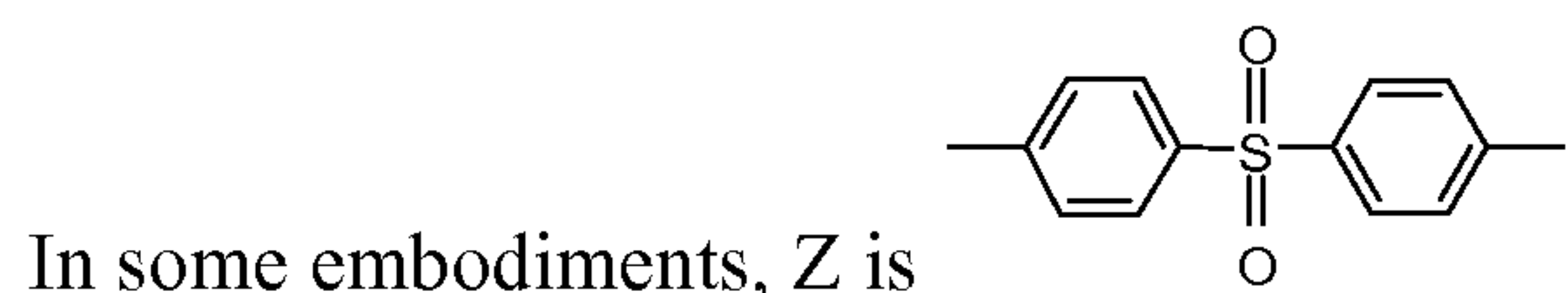
10 each R^2 is, independently, H, or the free base or salt form of $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;

each R^4 is, independently, H, $-NH-C(=O)-(CH_2)_p-NH-C(=NH)-NH_2$ or

$-(CH_2)_q-N$, where each p is, independently, 1 to 6, and each q is, independently, 1 or 2; and

15 each R^5 is, independently, H or CF_3 ;

or a pharmaceutically acceptable salt thereof.



In any of the above embodiments, each Q is, independently,

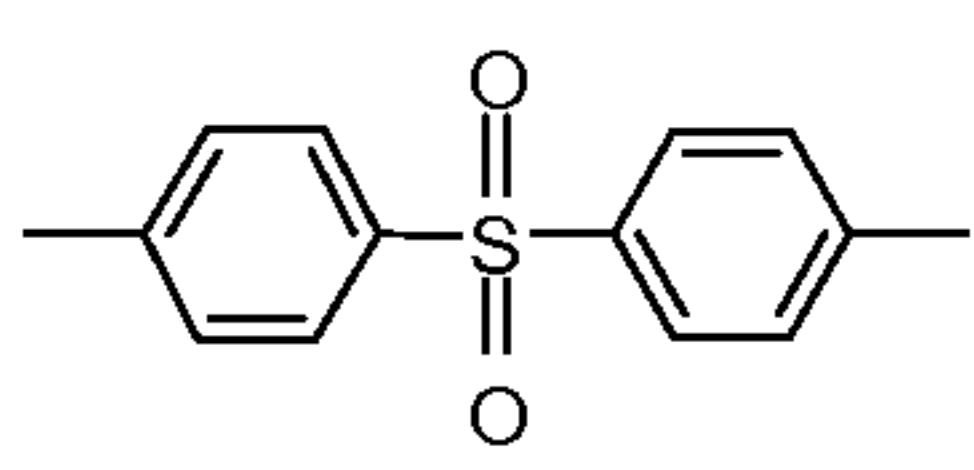
In any of the above embodiments, each X is O.

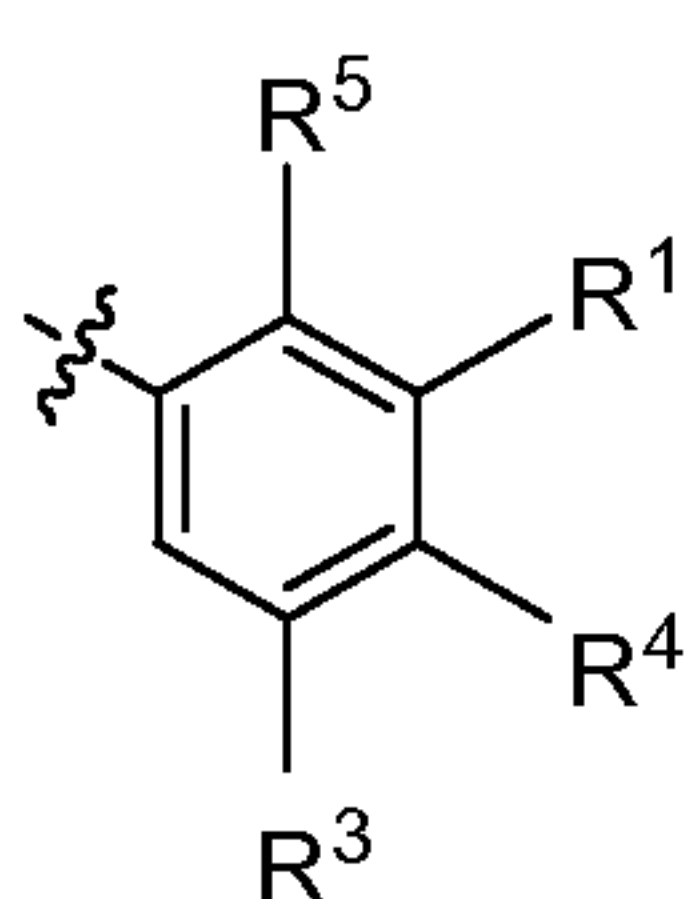
In any of the above embodiments, each R^1 is, independently, H, CF_3 , or halo; or each R^1 is CF_3 .

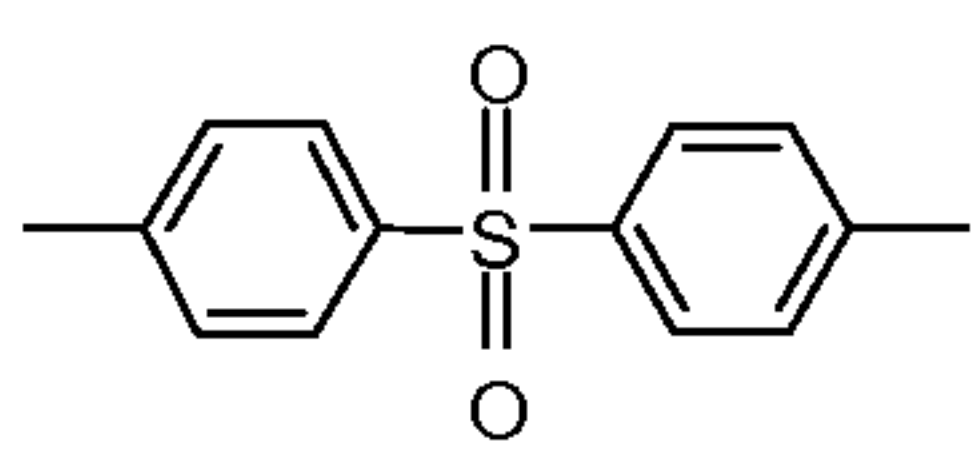
In any of the above embodiments, each R^3 is, independently, $-NH-R^2$.

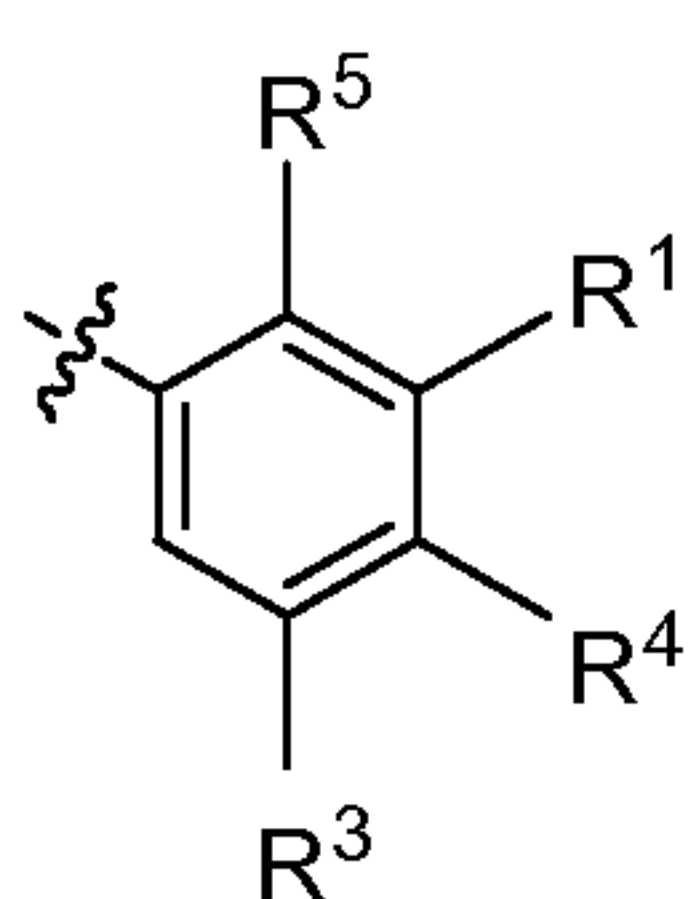
In any of the above embodiments, each R^2 is, independently, H, or the free base or
5 salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4; or each R^2 is, independently, the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2; or each R^2 is the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2.

In any of the above embodiments, each R^4 and each R^5 is H.

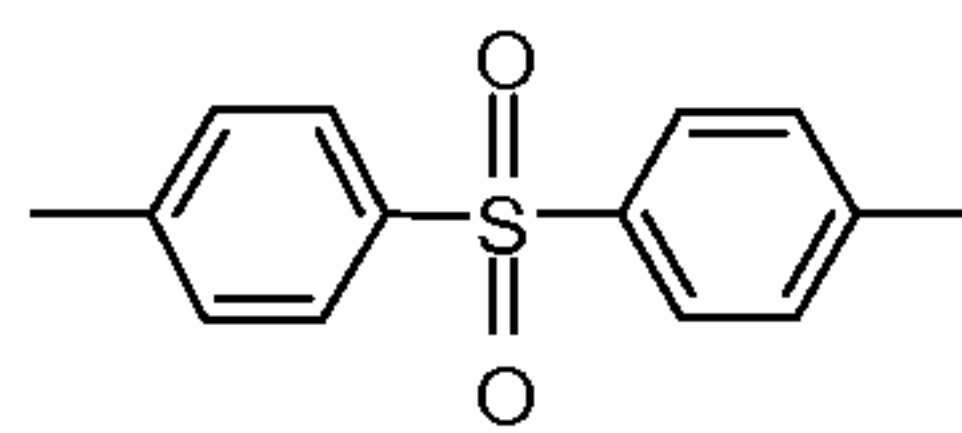
In some embodiments, Z is ; each Q is, independently,

; each X is O or S; each R^1 is, independently, CF_3 , $C(CH_3)_3$, or halo; each R^3 is,
10 independently, $-NH-R^2$; each R^2 is, independently, H, or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4; and each R^4 and each R^5 is H.

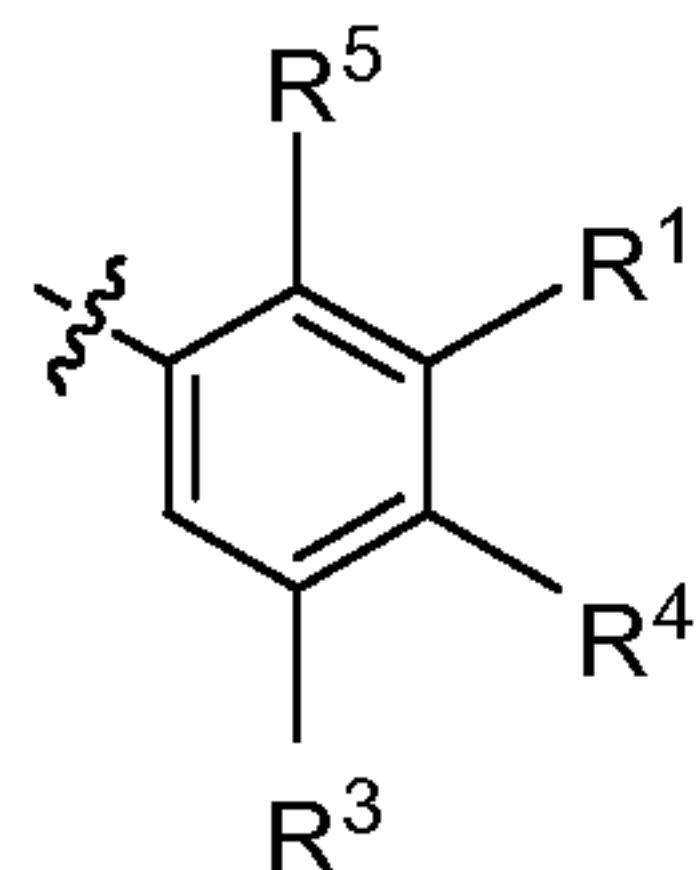
In some embodiments, Z is ; each Q is, independently,

; each X is O; each R^1 is CF_3 , $C(CH_3)_3$, or halo; each R^3 is, independently,
15 $-NH-R^2$; each R^2 is, independently, the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 1 or 2; and each R^4 and each R^5 is H.

In some embodiments, Z is



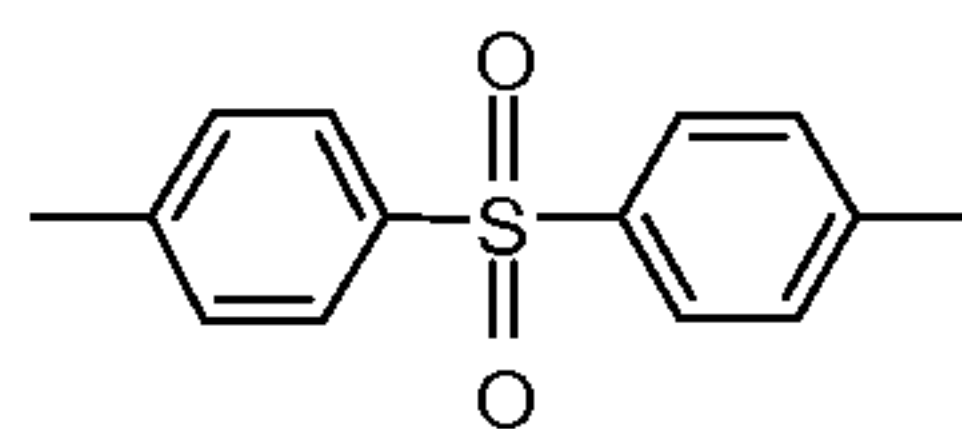
; each Q is, independently,



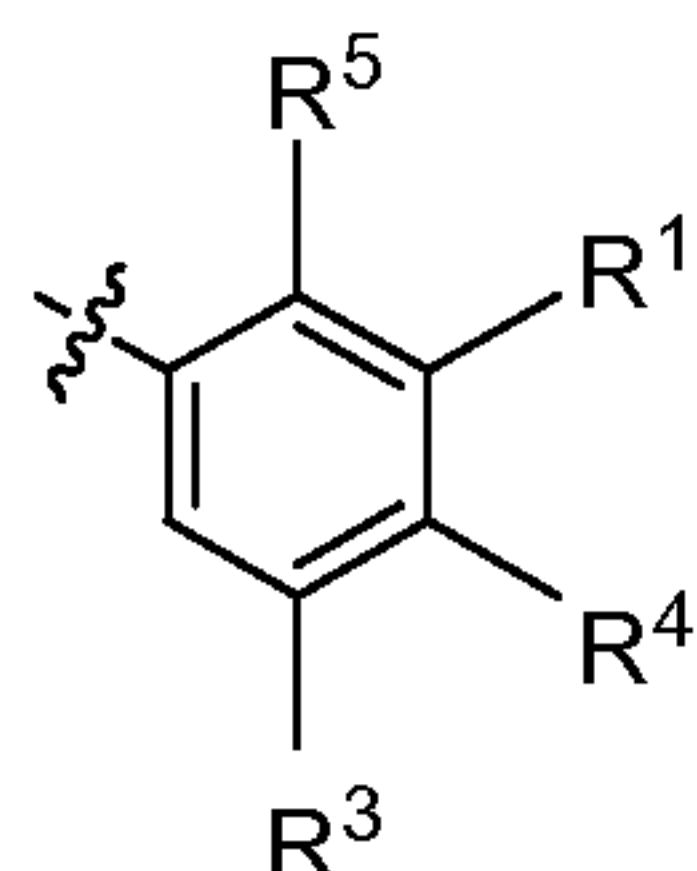
; each X is O; each R^1 is CF_3 or halo; each R^3 is, independently, $-NH-R^2$; each R^2 is the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2; and each R^4 and each R^5 is H.

5

In some embodiments, Z is

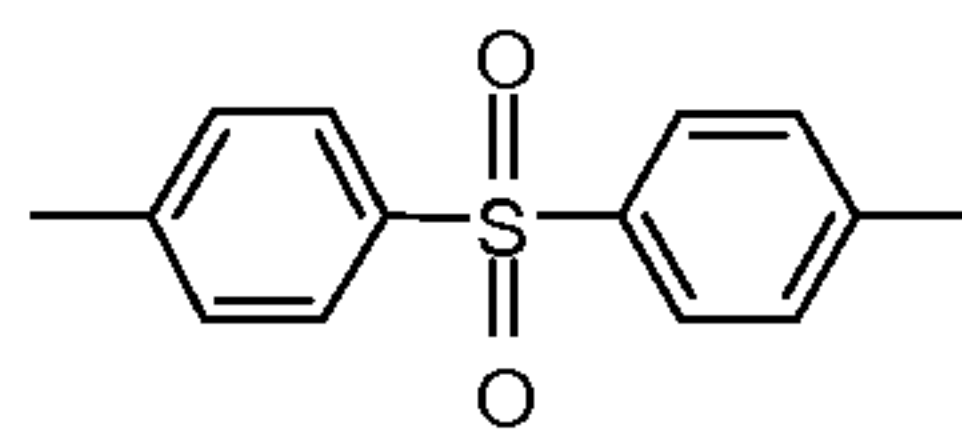


; each Q is, independently,



; each X is, independently, O, or S; each R^1 is, independently, H, or CF_3 ; each R^3 is H; each R^4 is, independently, H or $-NH-C(=O)-(CH_2)_p-NH-C(=NH)-NH_2$, where each p is, independently, 3 or 4; and each R^5 is, independently, H or CF_3 .

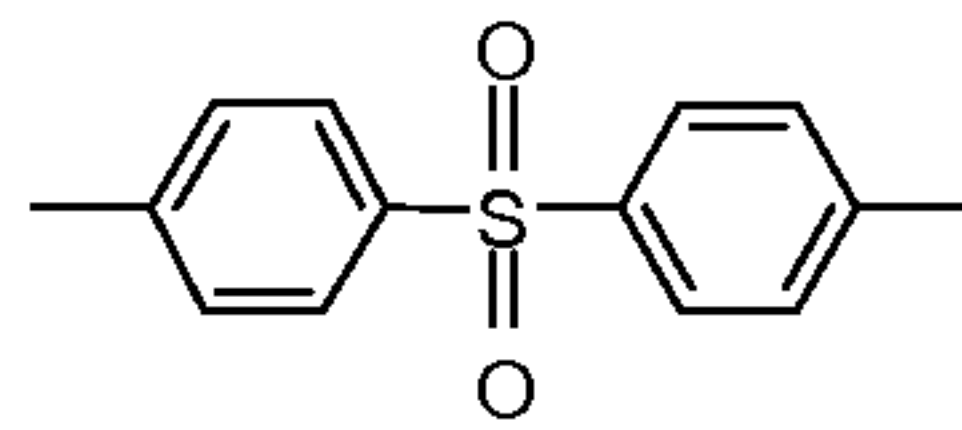
In some embodiments, Z is



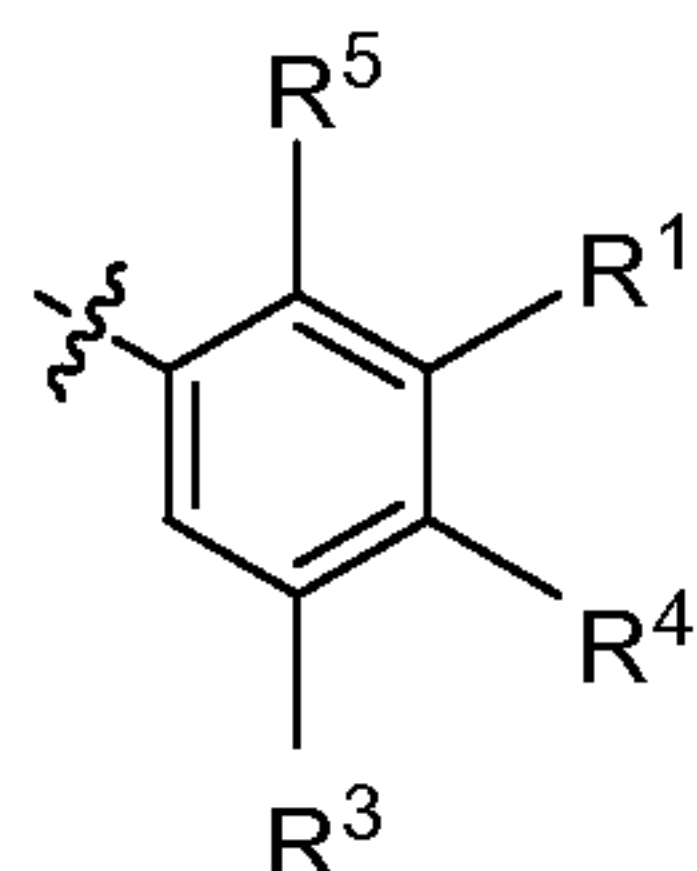
; each Q is, independently,

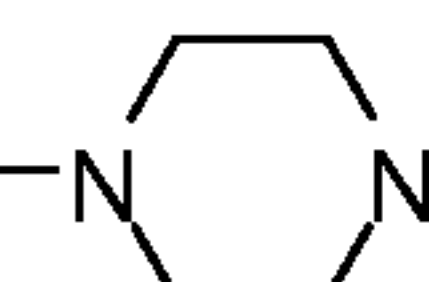
10 $-C(=O)-(CH_2)_b-NH-C(=NH)-NH_2$, where each b is, independently, 3 or 4; and each X is N.

In some embodiments, Z is

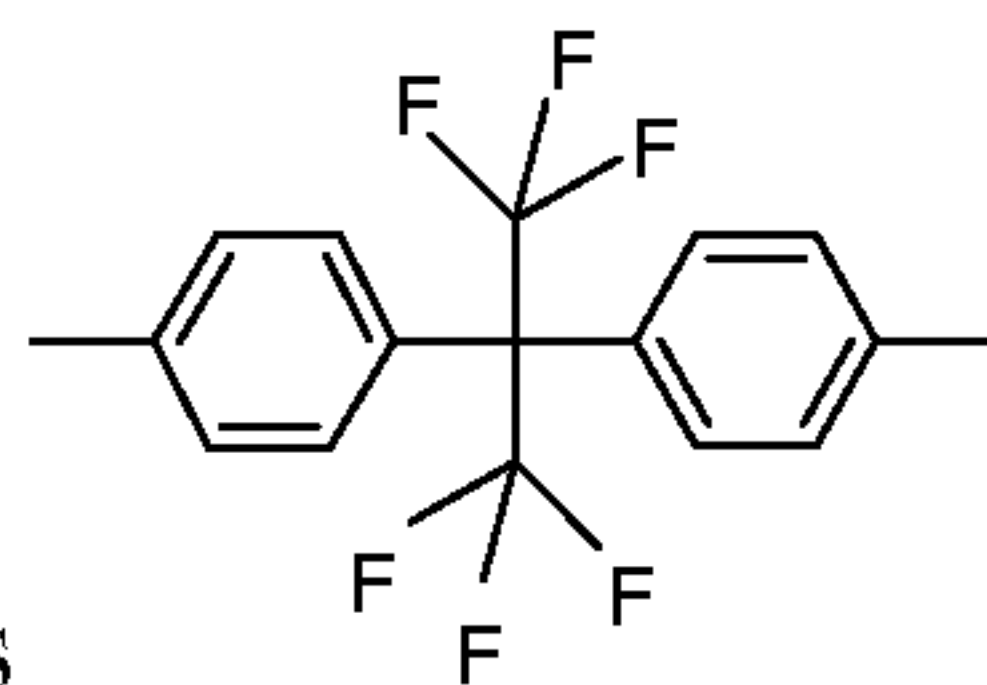


; each Q is, independently,

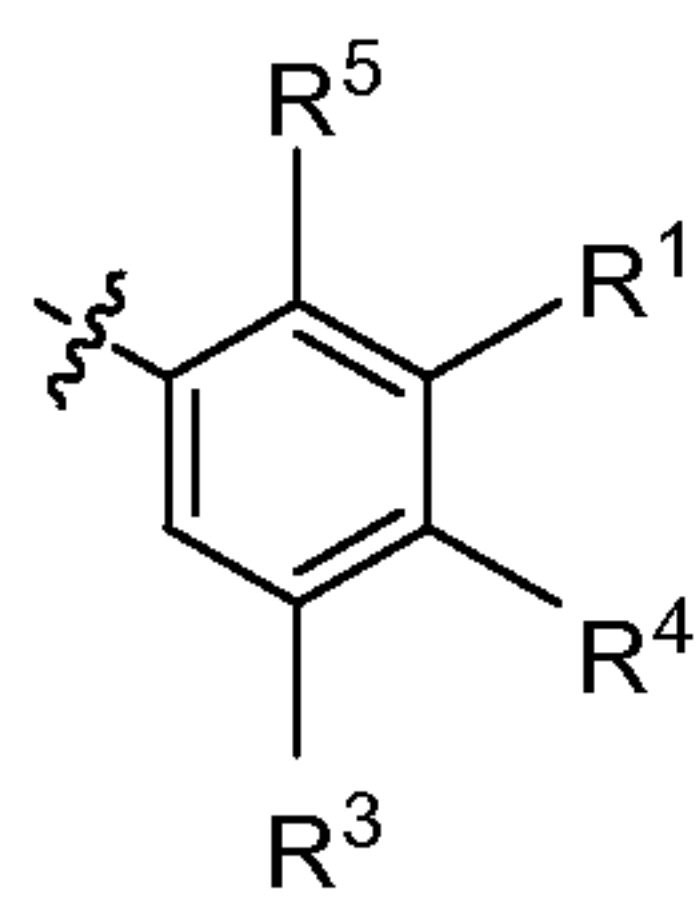


; each X is O or S; each R^1 is, independently, H or CF_3 ; each R^3 is, independently, $-(CH_2)_r-NH_2$, $-NH_2$, $-NH-(CH_2)_w-NH_2$, or $-(CH_2)_y-N$ , where each r is, independently, 1 or 2, each w is, independently, 1 to 3, and each y is, independently, 1 or 2; 15 each R^4 is H; and each R^5 is, independently, H or CF_3 .

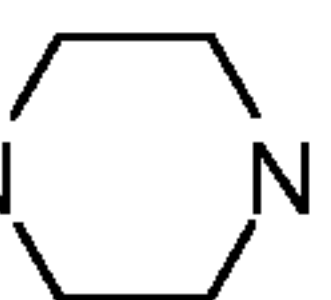
In some embodiments, Z is



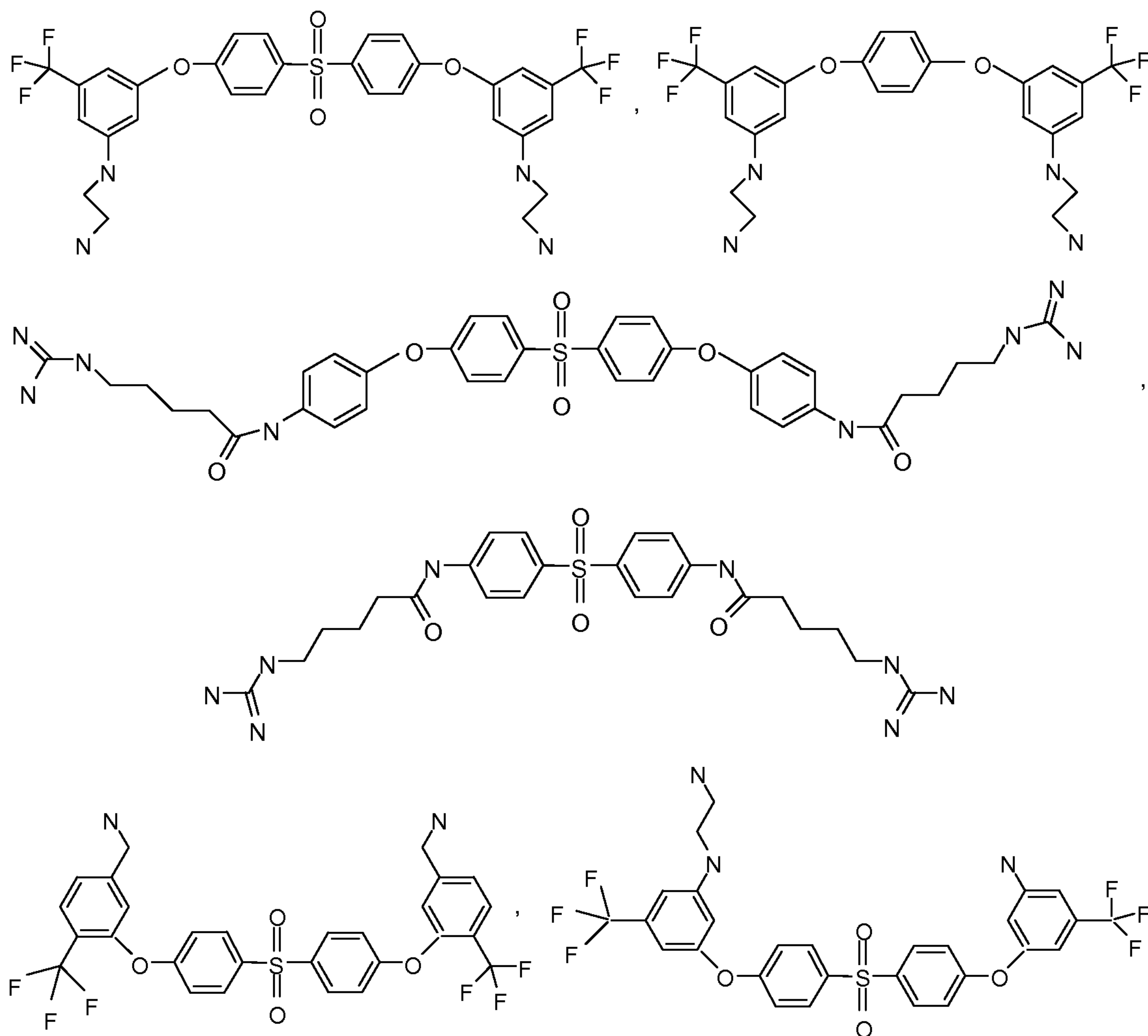
or phenyl; each Q is, independently,

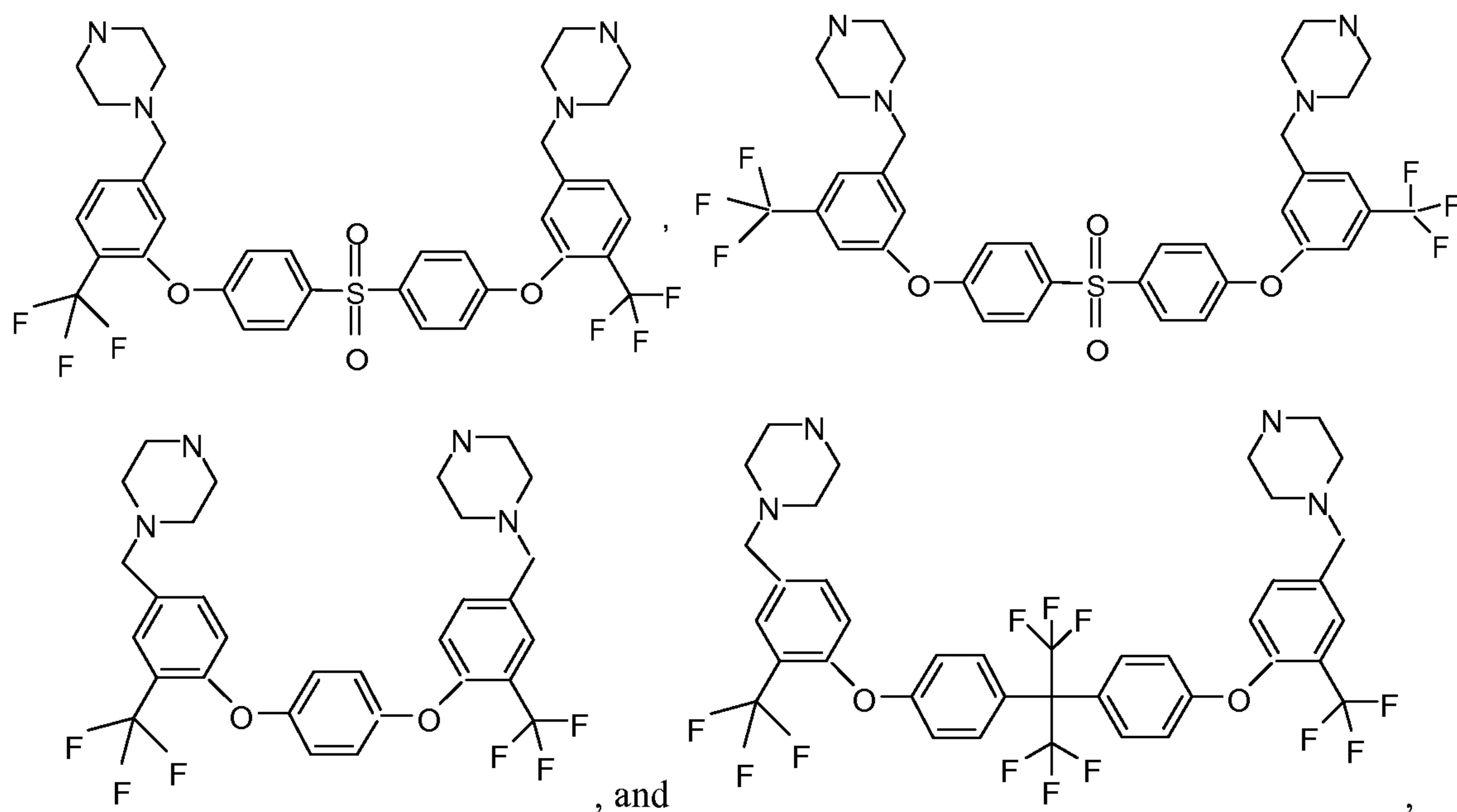


; each X is, independently, O or S; each R¹ is, independently, H or CF₃; each R³

is H; each R⁴ is, independently, $-(CH_2)_q-N$ , where each q is, independently, 1 or 2; and each R⁵ is, independently, H or CF₃.

5 In some embodiments, the compound is chosen from:



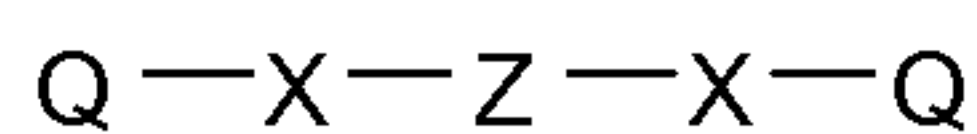


or a pharmaceutically acceptable salt thereof.

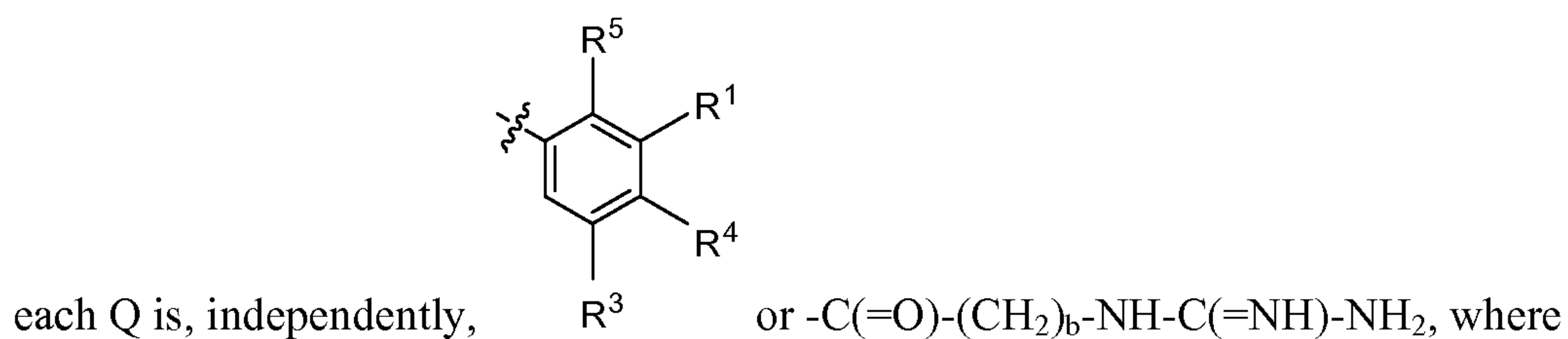
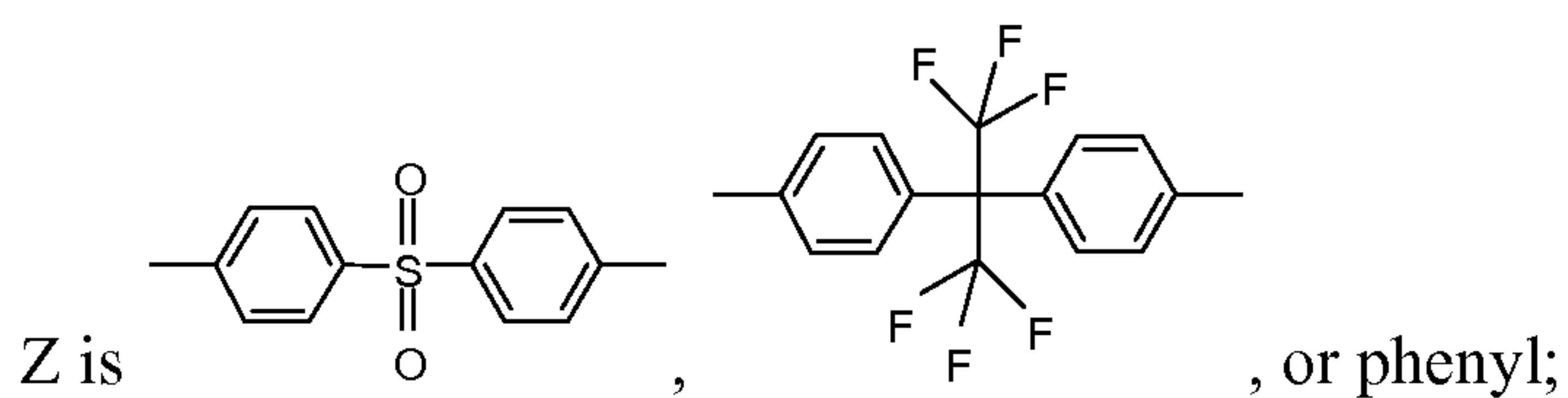
In some embodiments, any one or more of the above compounds may be excluded
 5 from any of the genus of compounds described above.

The present invention also provides compositions comprising one or more of the
 compounds or salts described above and a pharmaceutically acceptable carrier.

The present invention also provides methods of treating malaria in an animal
 comprising administering to the animal a therapeutically effective amount of a compound of
 10 Formula III:



wherein:

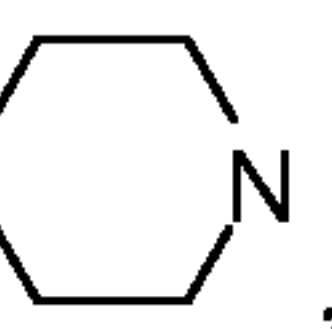


15 each b is, independently, 1 to 4;

each X is, independently, O, S, or N;

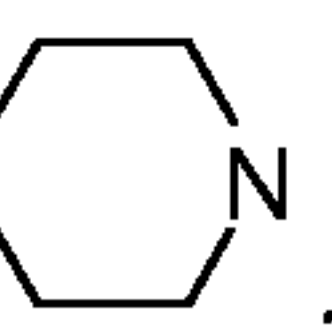
each R^1 is, independently, H, CF_3 , $C(CH_3)_3$, halo, or OH;

each R^3 is, independently, H, $-NH-R^2$, $-(CH_2)_r-NH_2$, $-NH_2$, $-NH-(CH_2)_w-NH_2$, or

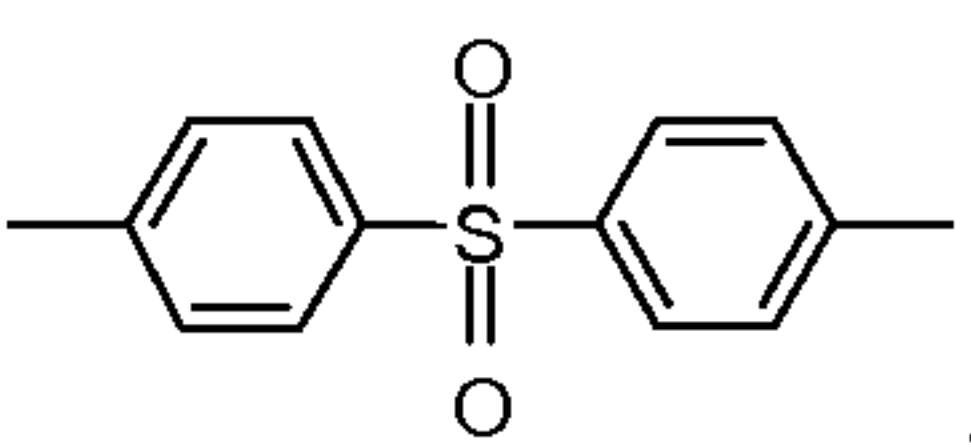
$-(CH_2)_y-N$ , where each r is, independently, 1 or 2, each w is, independently, 1 to 3, and each y is, independently, 1 or 2;

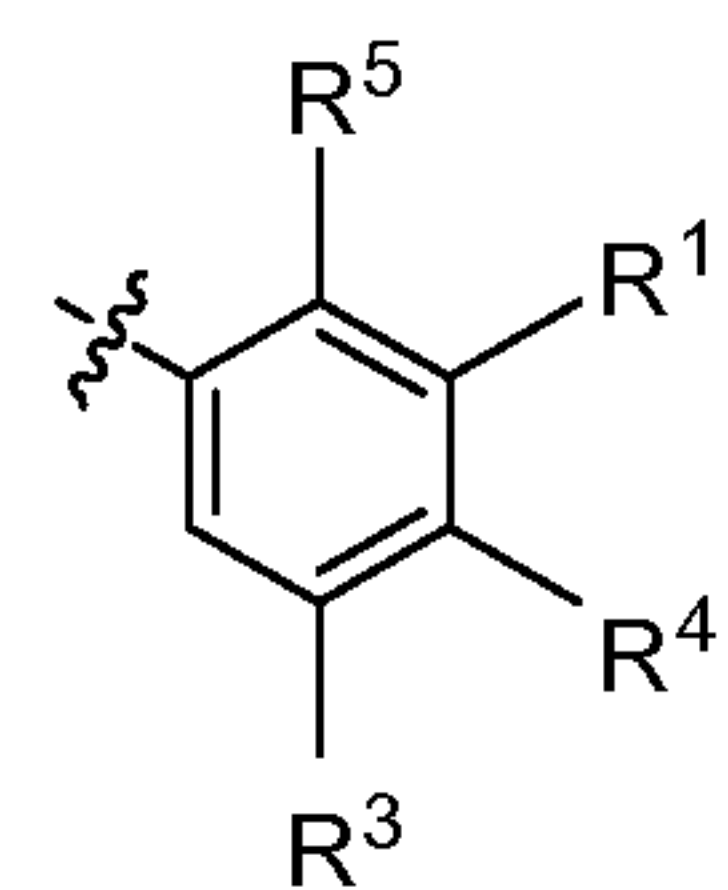
5 each R^2 is, independently, H, or the free base or salt form of $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;

each R^4 is, independently, H, $-NH-C(=O)-(CH_2)_p-NH-C(=NH)-NH_2$ or

$-(CH_2)_q-N$ , where each p is, independently, 1 to 6, and each q is, independently, 1 or 2; and

10 each R^5 is, independently, H or CF_3 ;
or a pharmaceutically acceptable salt thereof.

In some embodiments, Z is .



In any of the above embodiments, each Q is, independently,

In any of the above embodiments, each X is O.

15 In any of the above embodiments, each R^1 is, independently, H, CF_3 , or halo; or each R^1 is CF_3 .

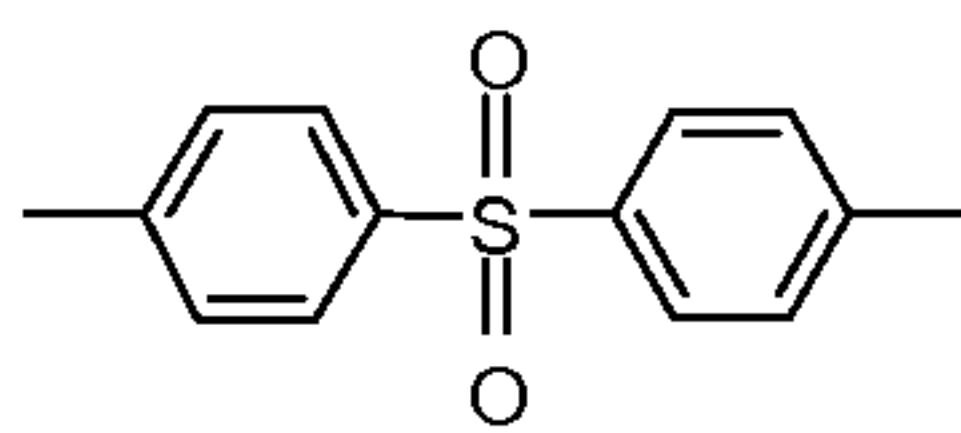
In any of the above embodiments, each R^3 is, independently, $-NH-R^2$.

In any of the above embodiments, each R^2 is, independently, H, or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4; or each R^2 is,

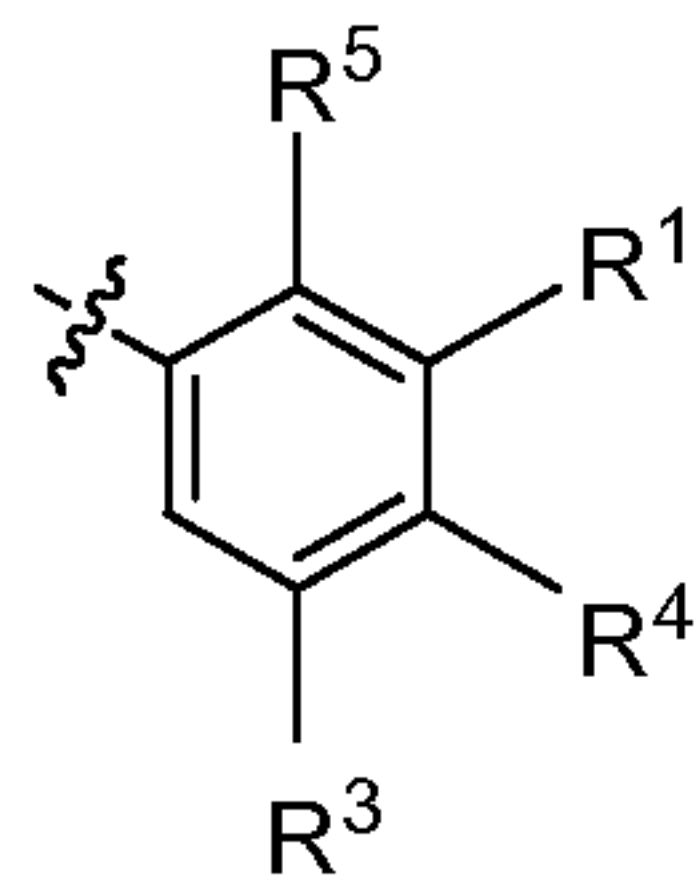
20 independently, the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2; or each R^2 is the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2.

In any of the above embodiments, each R^4 and each R^5 is H.

In some embodiments, Z is



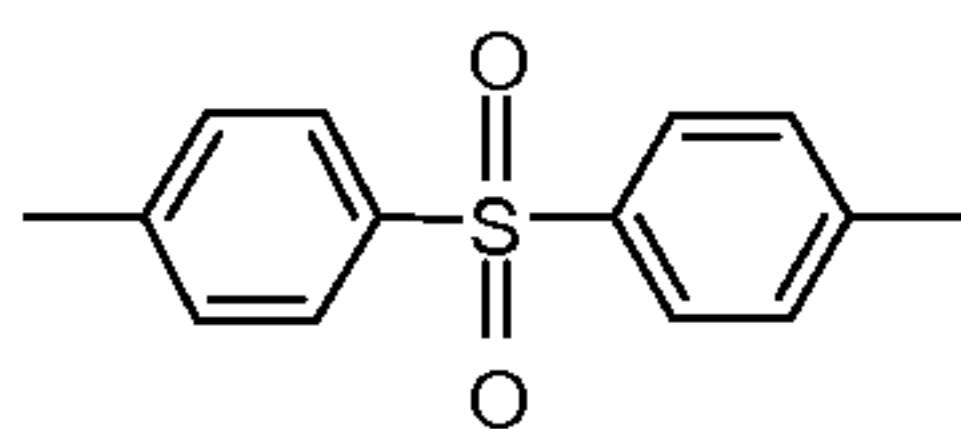
; each Q is, independently,



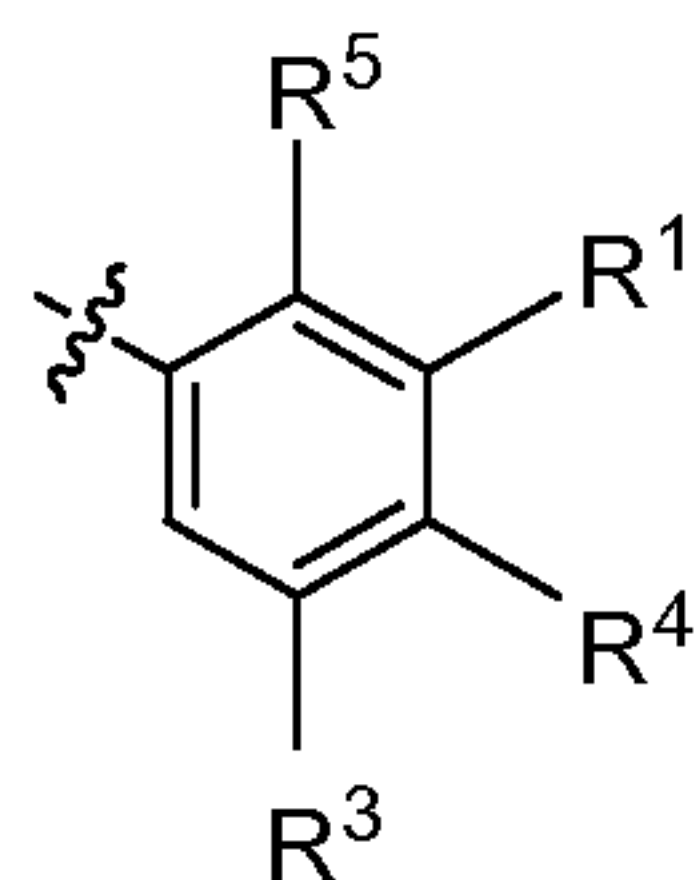
; each X is O or S; each R^1 is, independently, CF_3 , $C(CH_3)_3$, or halo; each R^3 is, independently, $-NH-R^2$; each R^2 is, independently, H, or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4; and each R^4 and each R^5 is H.

5

In some embodiments, Z is

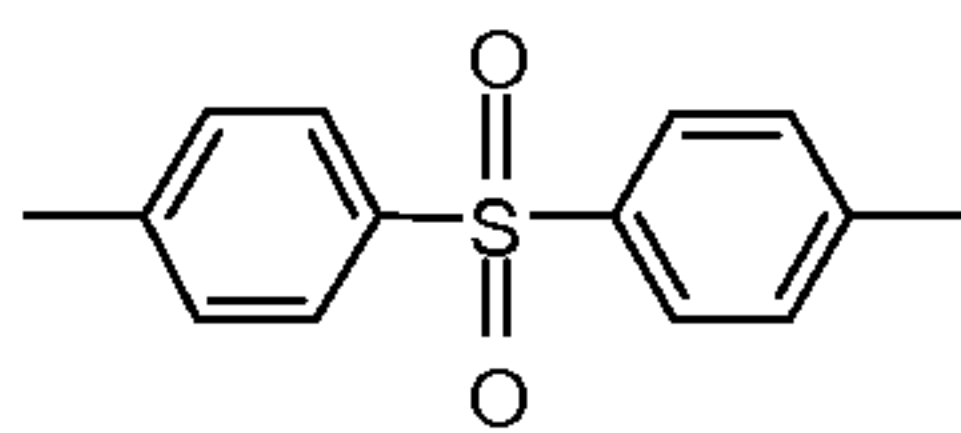


; each Q is, independently,

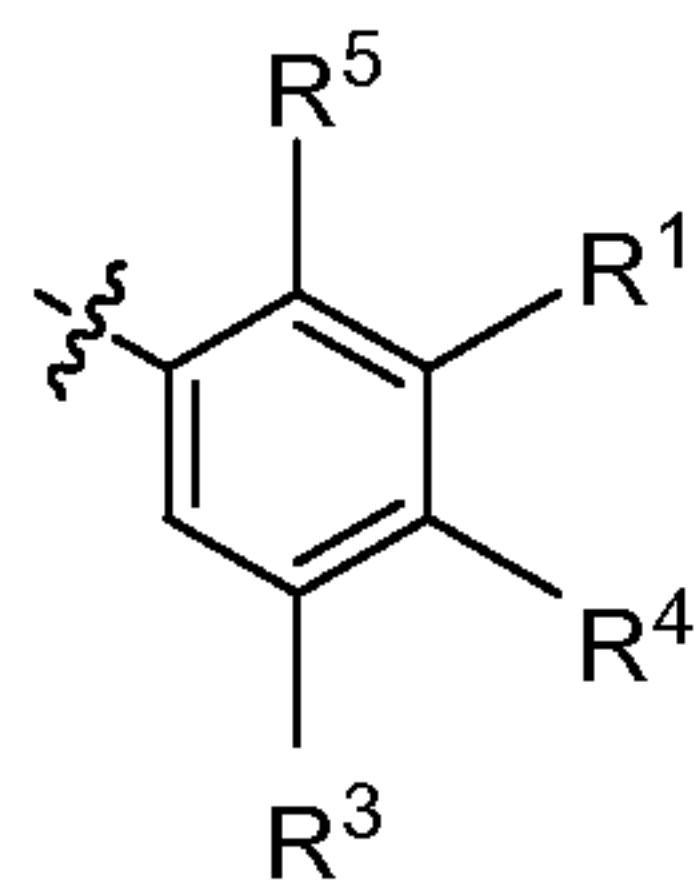


; each X is O; each R^1 is CF_3 , $C(CH_3)_3$, or halo; each R^3 is, independently, $-NH-R^2$; each R^2 is, independently, the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 1 or 2; and each R^4 and each R^5 is H.

In some embodiments, Z is



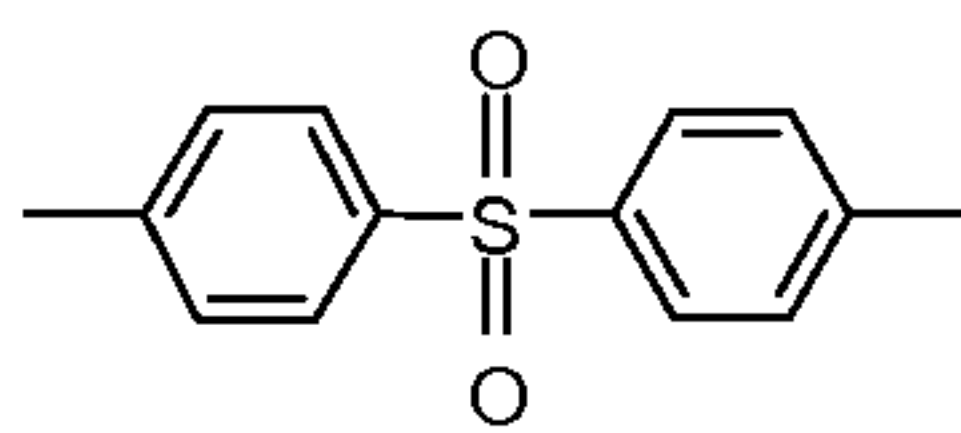
; each Q is, independently,



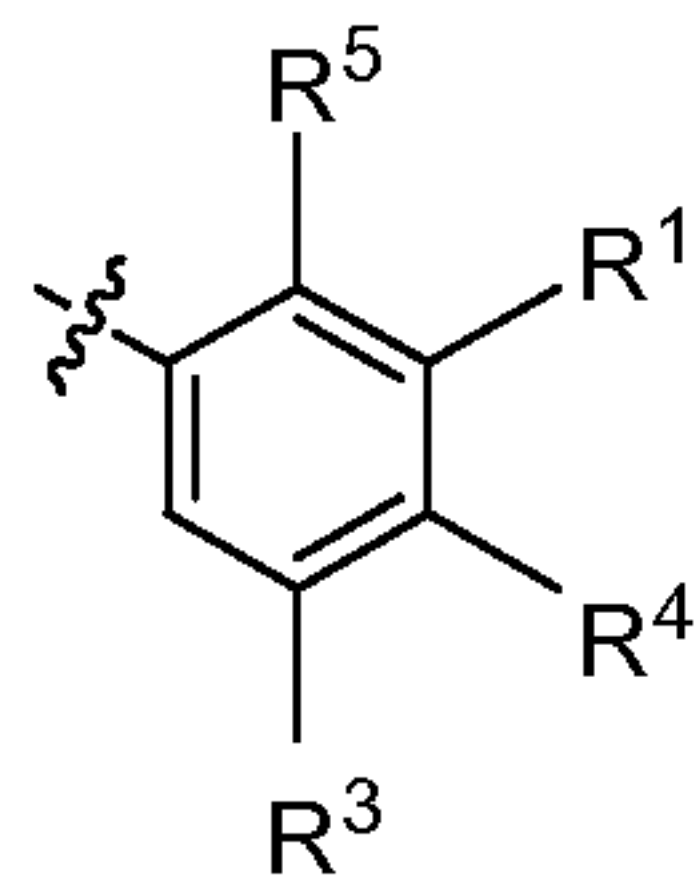
10

; each X is O; each R^1 is CF_3 or halo; each R^3 is, independently, $-NH-R^2$; each R^2 is the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2; and each R^4 and each R^5 is H.

In some embodiments, Z is



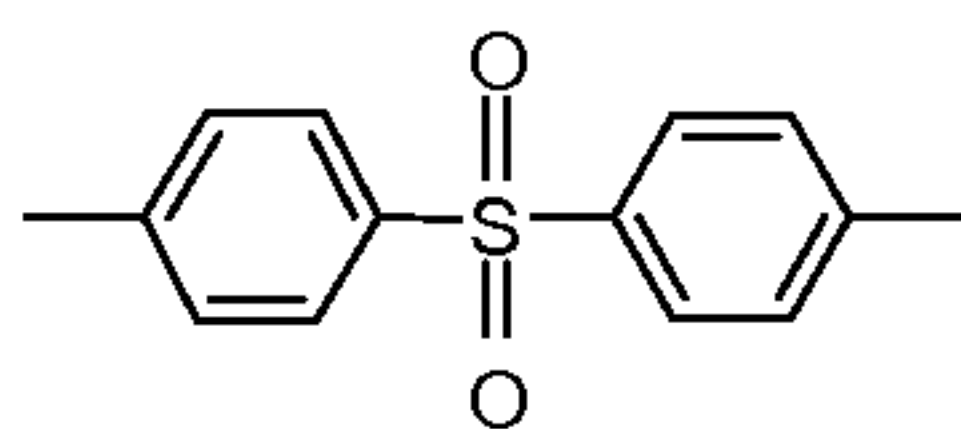
; each Q is, independently,



; each X is, independently, O, or S; each R^1 is, independently, H, or CF_3 ; each R^3 is H; each R^4 is, independently, H or $-NH-C(=O)-(CH_2)_p-NH-C(=NH)-NH_2$, where each p is, independently, 3 or 4; and each R^5 is, independently, H or CF_3 .

5

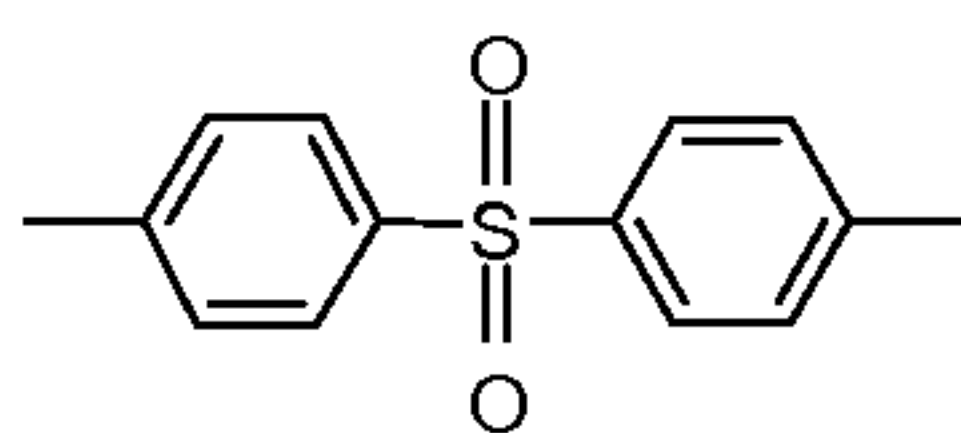
In some embodiments, Z is



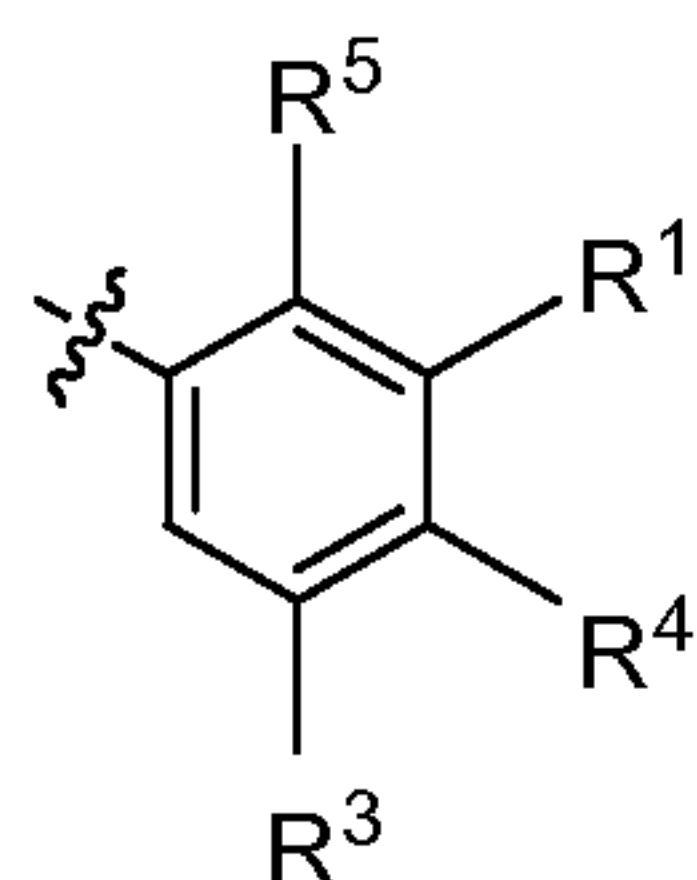
; each Q is, independently,

$-C(=O)-(CH_2)_b-NH-C(=NH)-NH_2$, where each b is, independently, 3 or 4; and each X is N.

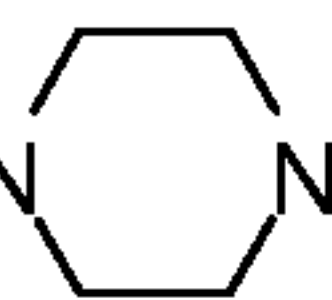
In some embodiments, Z is



; each Q is, independently,

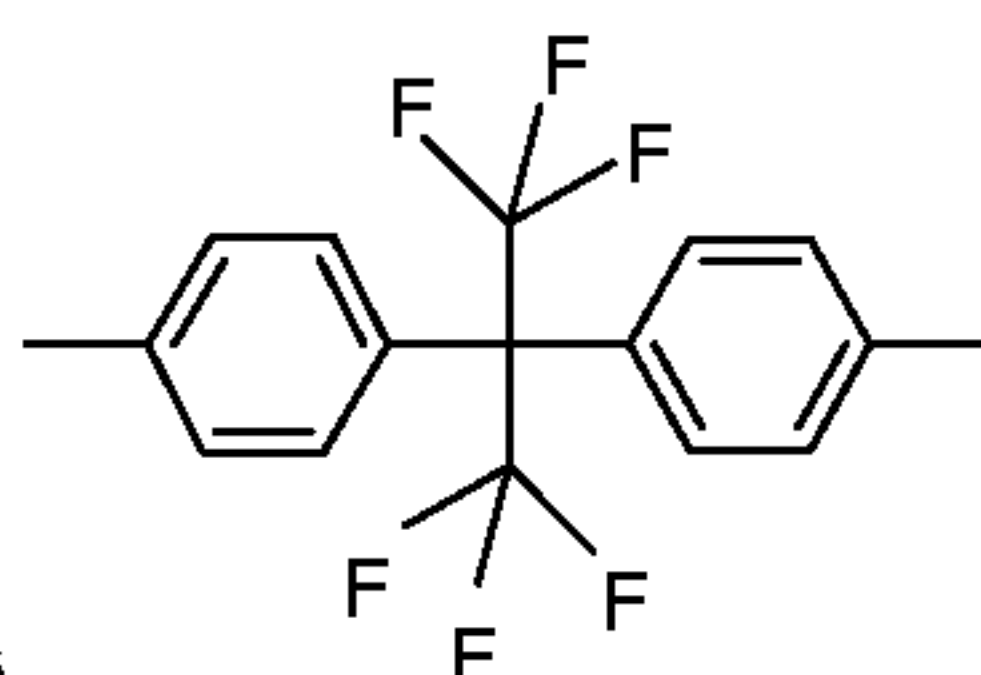


; each X is O or S; each R^1 is, independently, H or CF_3 ; each R^3 is,

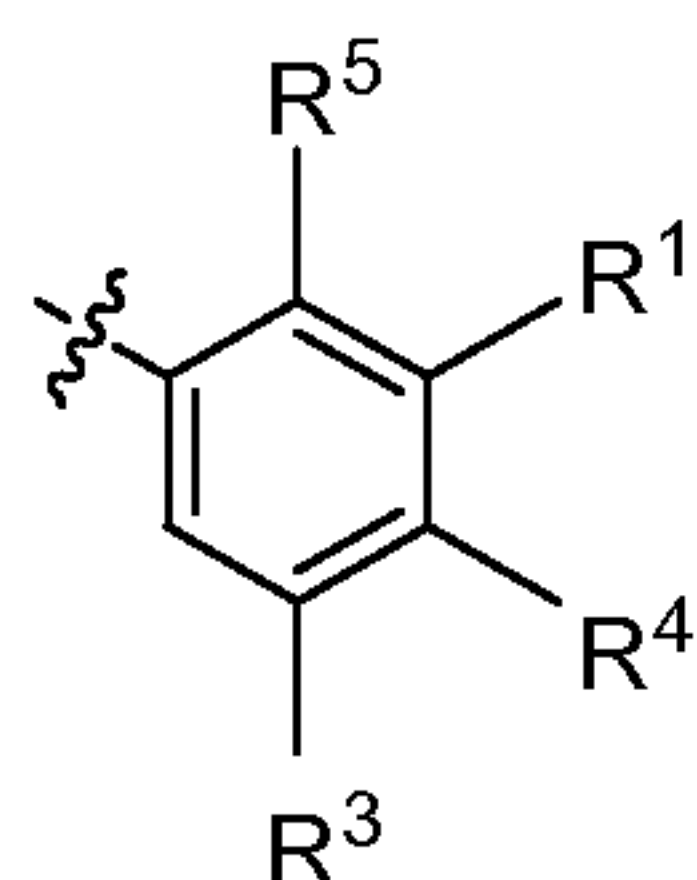
independently, $-(CH_2)_r-NH_2$, $-NH_2$, $-NH-(CH_2)_w-NH_2$, or $-(CH_2)_y-N$ , where each r is,

10 independently, 1 or 2, each w is, independently, 1 to 3, and each y is, independently, 1 or 2; each R^4 is H; and each R^5 is, independently, H or CF_3 .

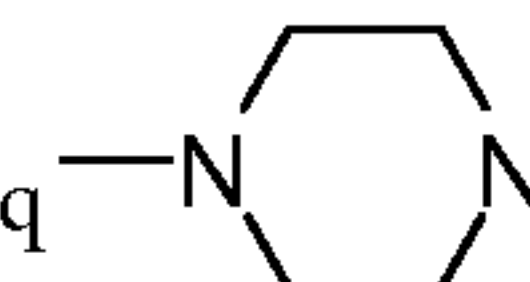
In some embodiments, Z is



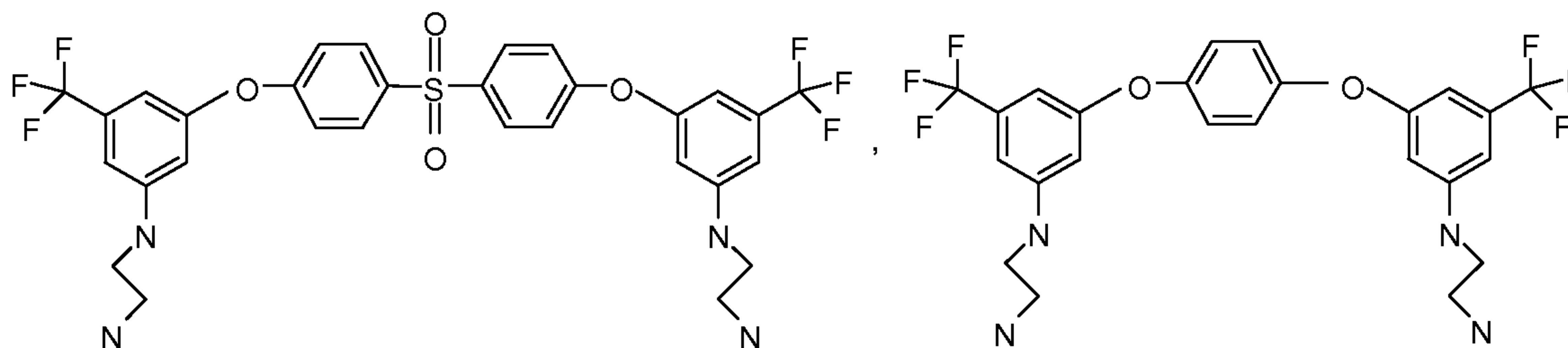
or phenyl; each Q is, independently,



; each X is, independently, O or S; each R^1 is, independently, H or CF_3 ; each R^3

is H; each R^4 is, independently, $-(CH_2)_q-N$ , where each q is, independently, 1 or 2; and each R^5 is, independently, H or CF_3 .

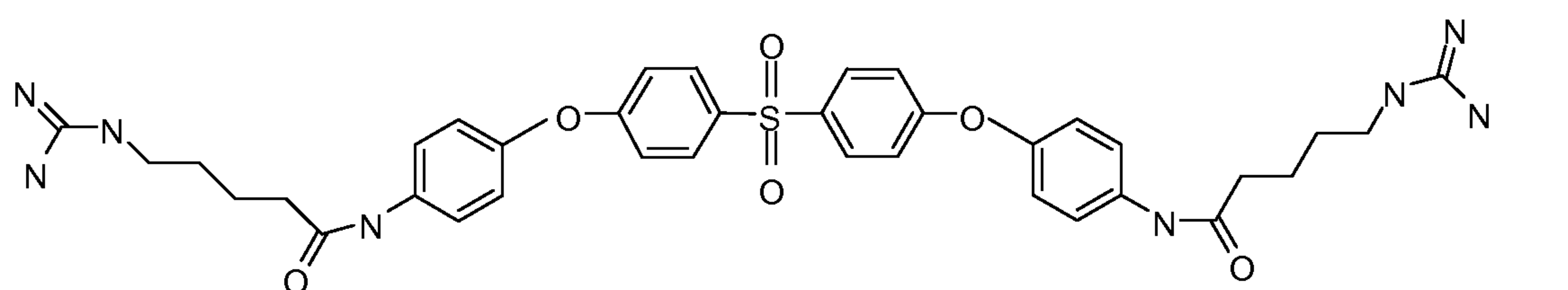
In some embodiments, the compound is chosen from:



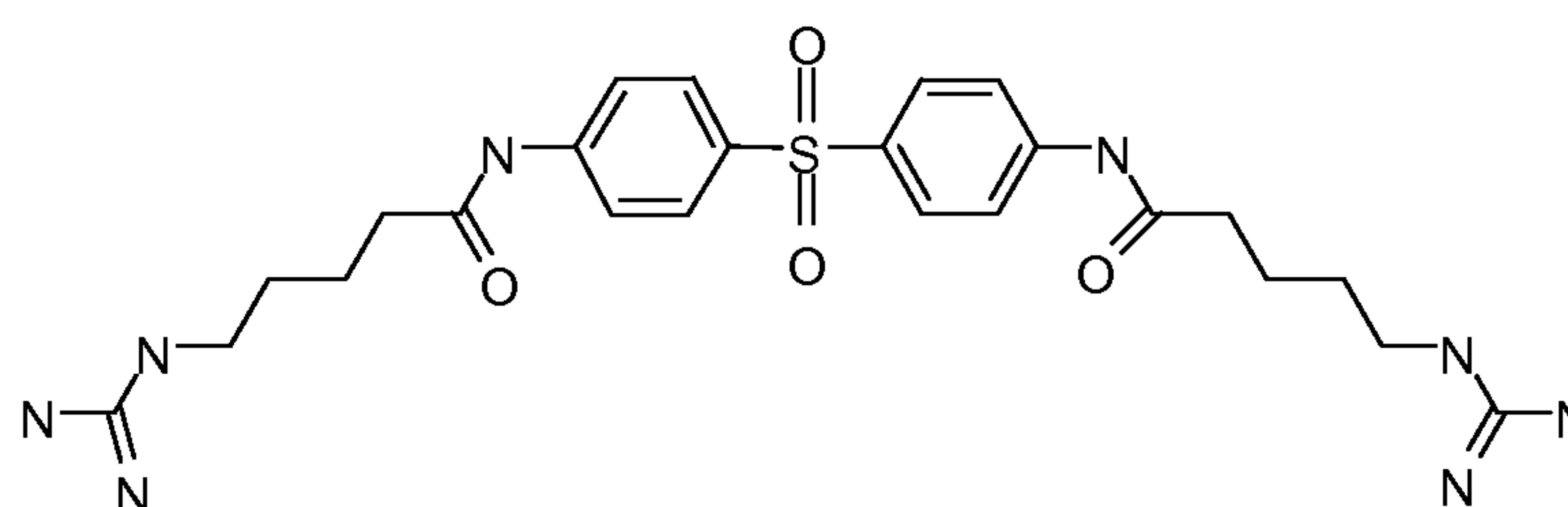
5

Compound 111

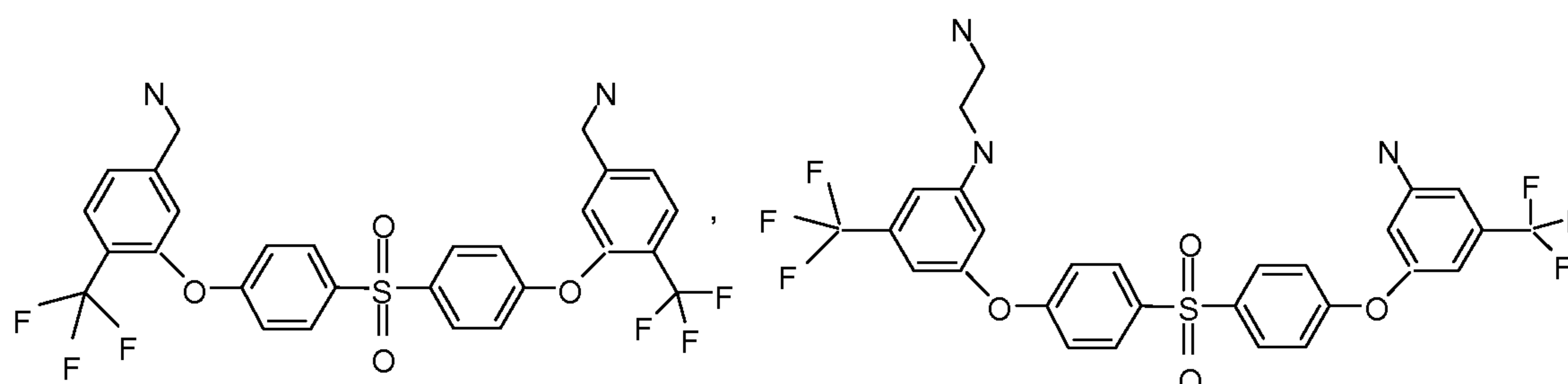
Compound 109



Compound 142



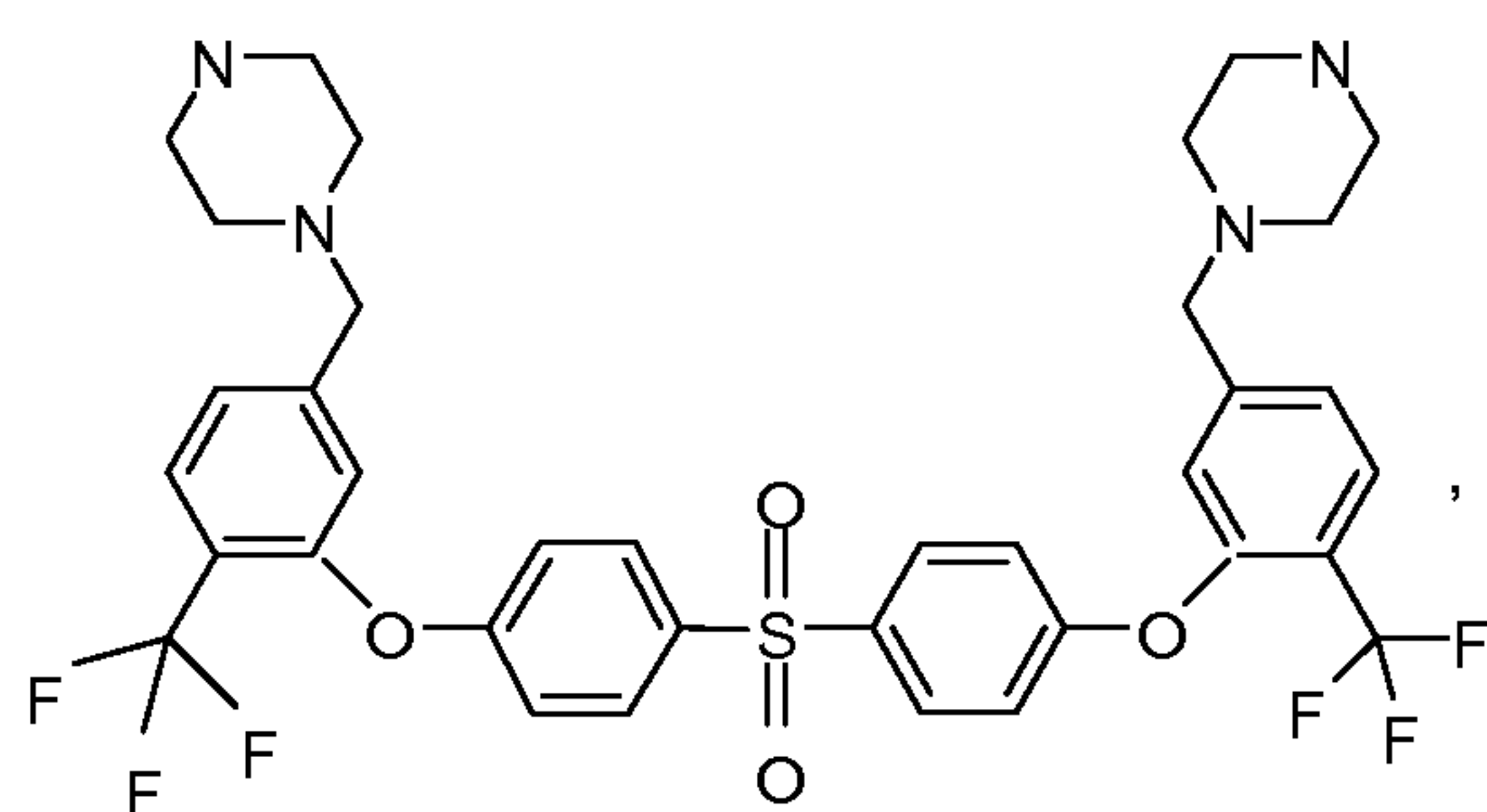
Compound 149



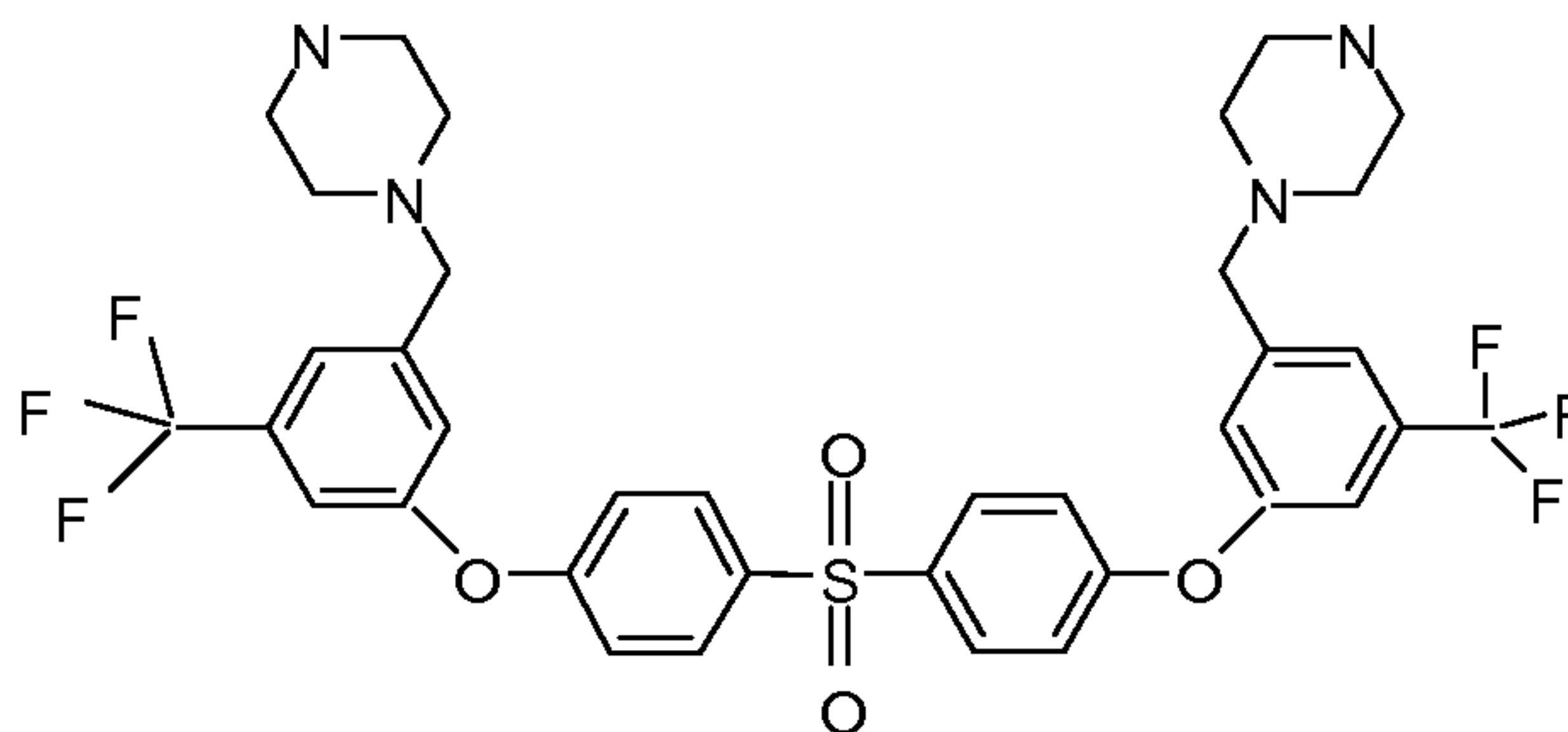
10

Compound 143

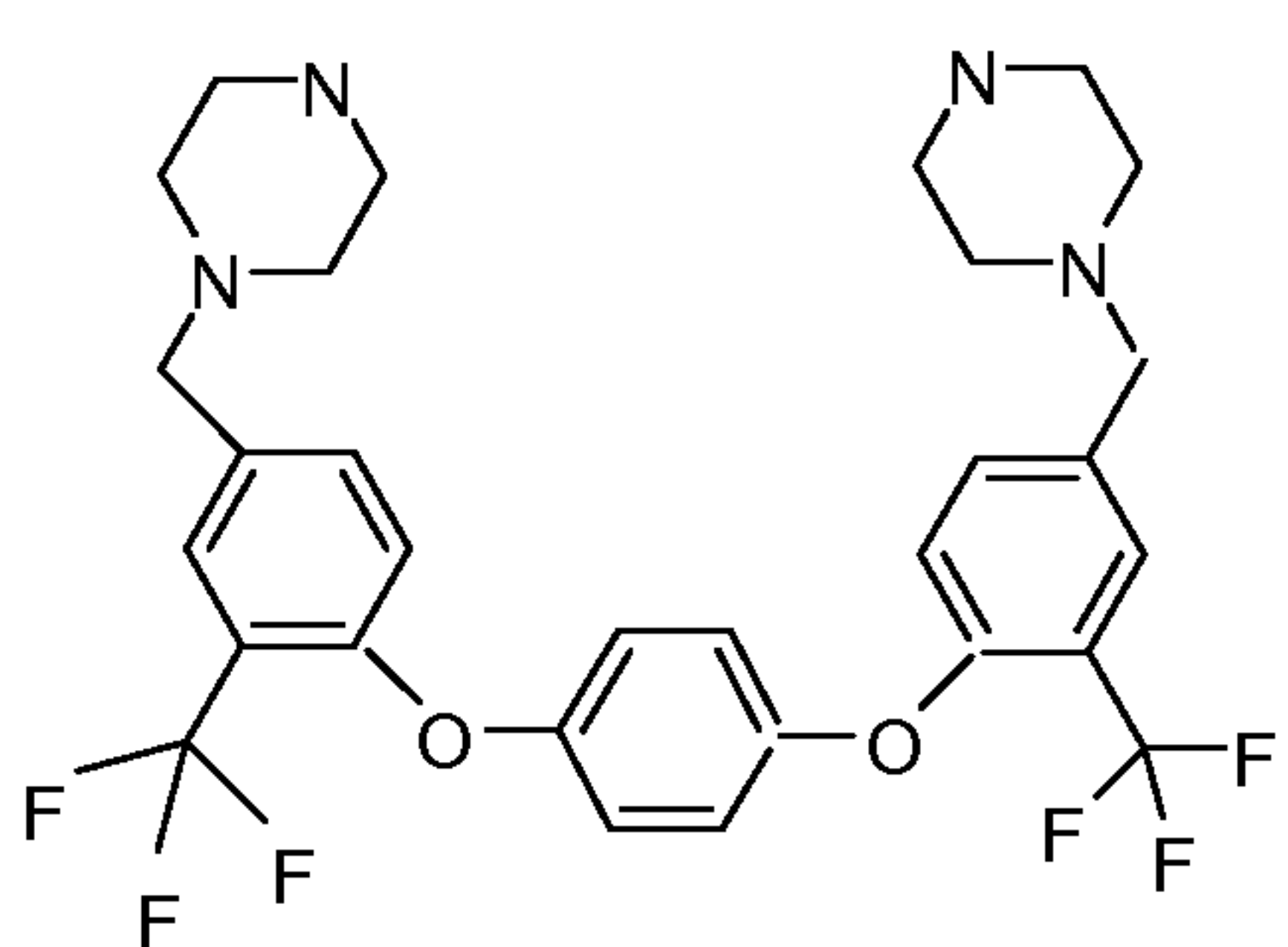
Compound 144



Compound 145

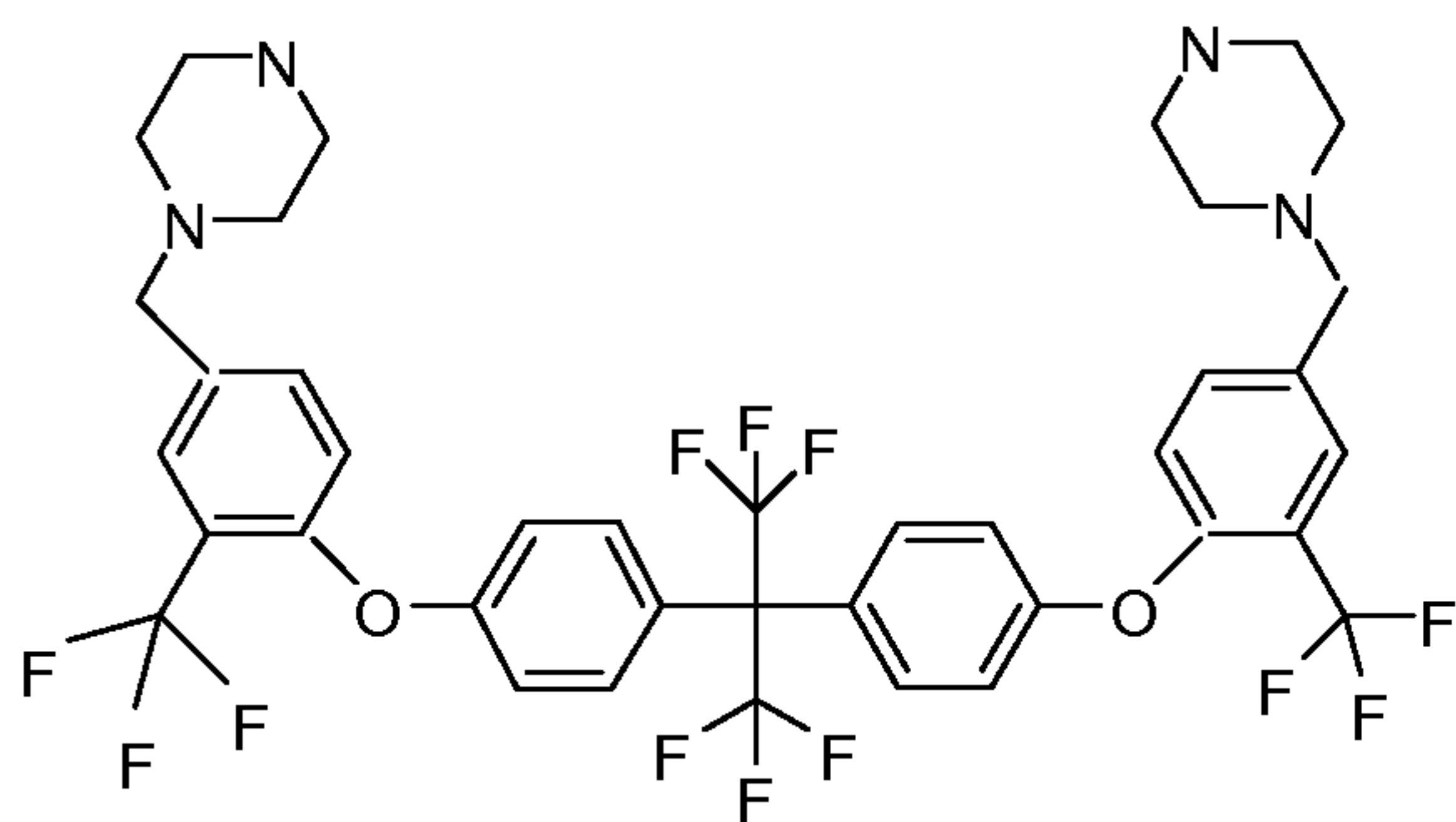


Compound 146



Compound 147

, and



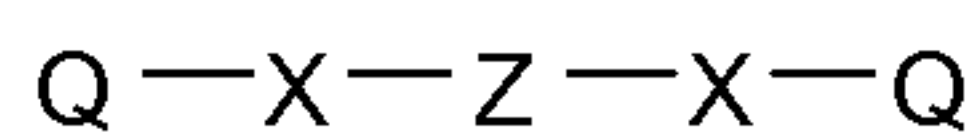
Compound 148

5 or a pharmaceutically acceptable salt thereof.

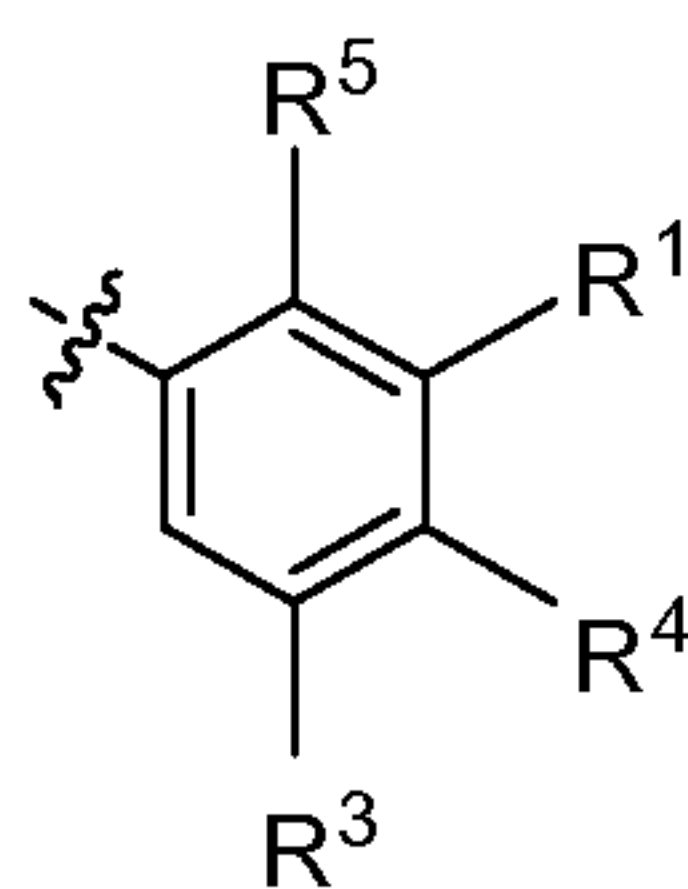
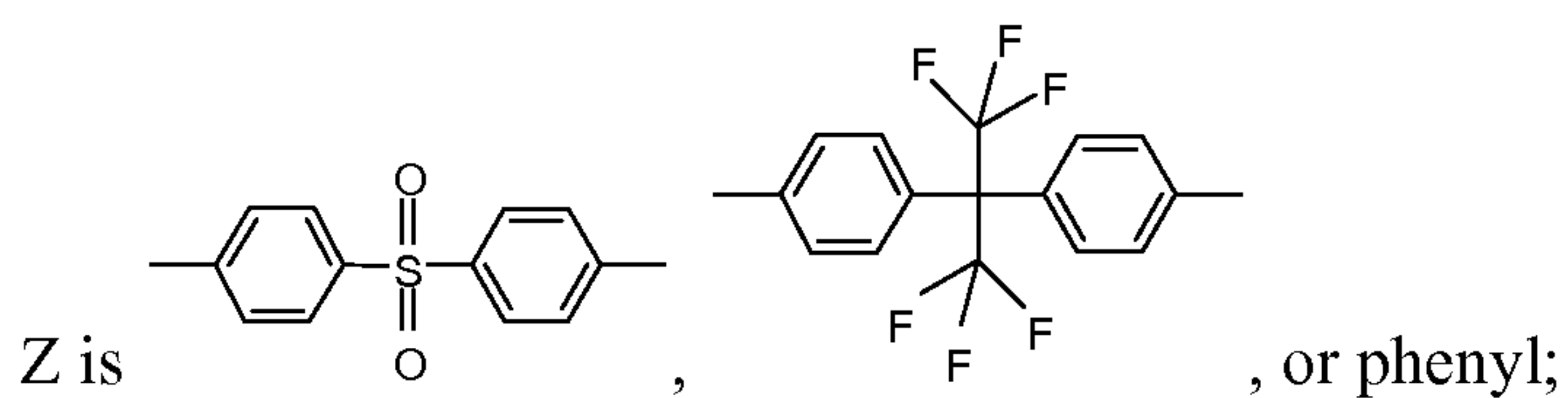
In any of the above embodiments, the malaria can be chloroquine-sensitive or chloroquine-resistant.

The present invention also provides methods of killing or inhibiting the growth of a *Plasmodium* species comprising contacting the species with an effective amount of a

10 compound of Formula III:



wherein:



each Q is, independently,

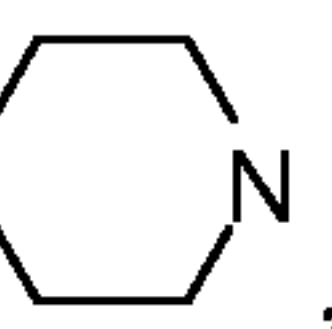
or $-C(=O)-(CH_2)_b-NH-C(=NH)-NH_2$, where

15 each b is, independently, 1 to 4;

each X is, independently, O, S, or N;

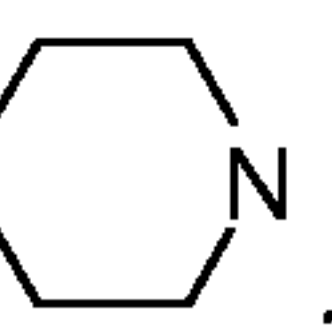
each R^1 is, independently, H, CF_3 , $C(CH_3)_3$, halo, or OH;

each R^3 is, independently, H, $-NH-R^2$, $-(CH_2)_r-NH_2$, $-NH_2$, $-NH-(CH_2)_w-NH_2$, or

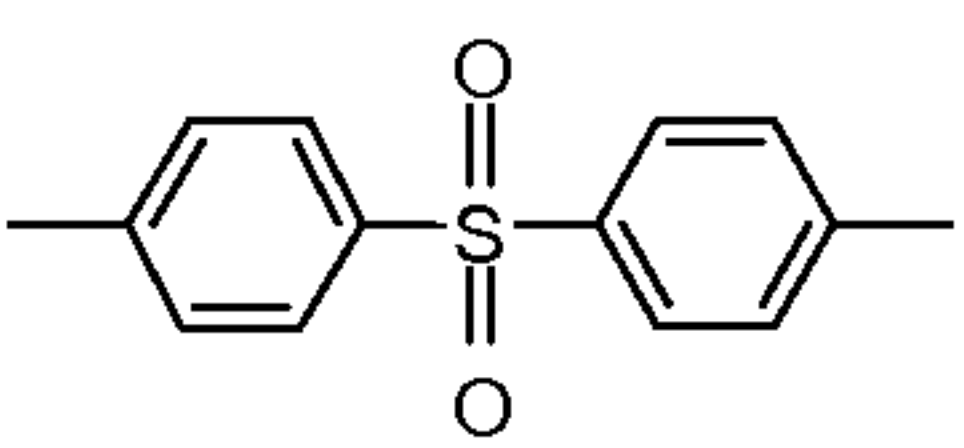
$-(CH_2)_y-N$ , where each r is, independently, 1 or 2, each w is, independently, 1 to 3, and each y is, independently, 1 or 2;

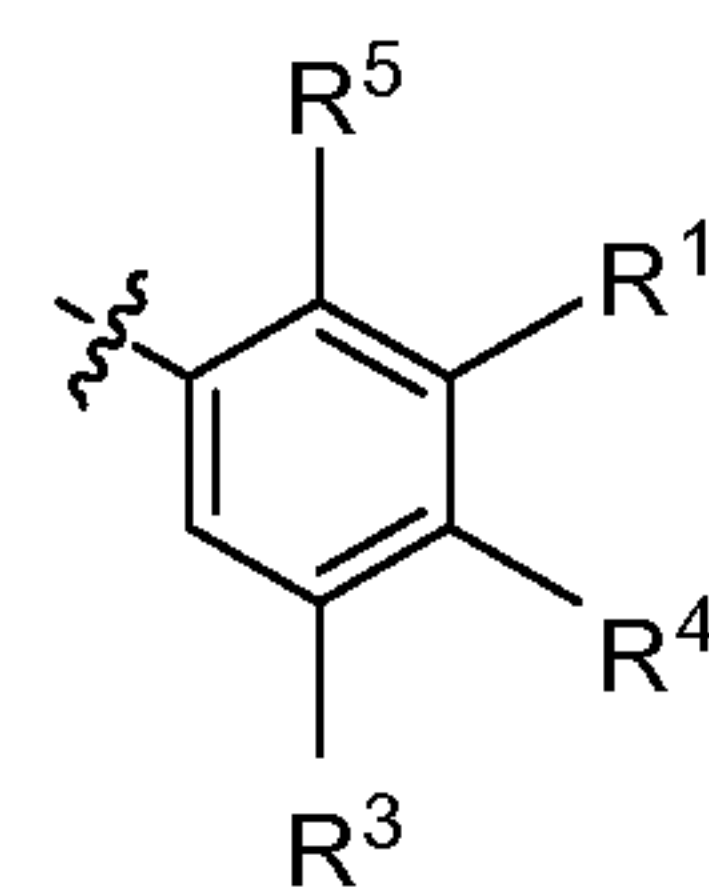
5 each R^2 is, independently, H, or the free base or salt form of $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;

each R^4 is, independently, H, $-NH-C(=O)-(CH_2)_p-NH-C(=NH)-NH_2$ or

$-(CH_2)_q-N$ , where each p is, independently, 1 to 6, and each q is, independently, 1 or 2; and

10 each R^5 is, independently, H or CF_3 ;
or a pharmaceutically acceptable salt thereof.

In some embodiments, Z is .



In any of the above embodiments, each Q is, independently,

In any of the above embodiments, each X is O.

15 In any of the above embodiments, each R^1 is, independently, H, CF_3 , or halo; or each R^1 is CF_3 .

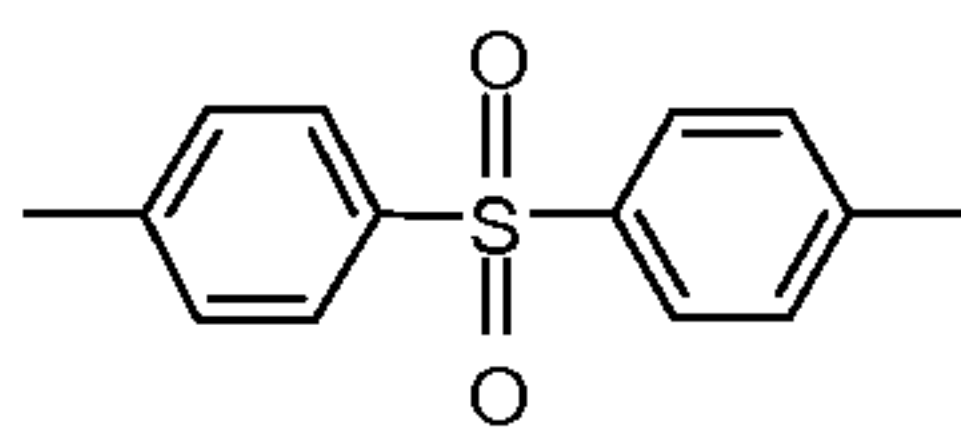
In any of the above embodiments, each R^3 is, independently, $-NH-R^2$.

In any of the above embodiments, each R^2 is, independently, H, or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4; or each R^2 is,

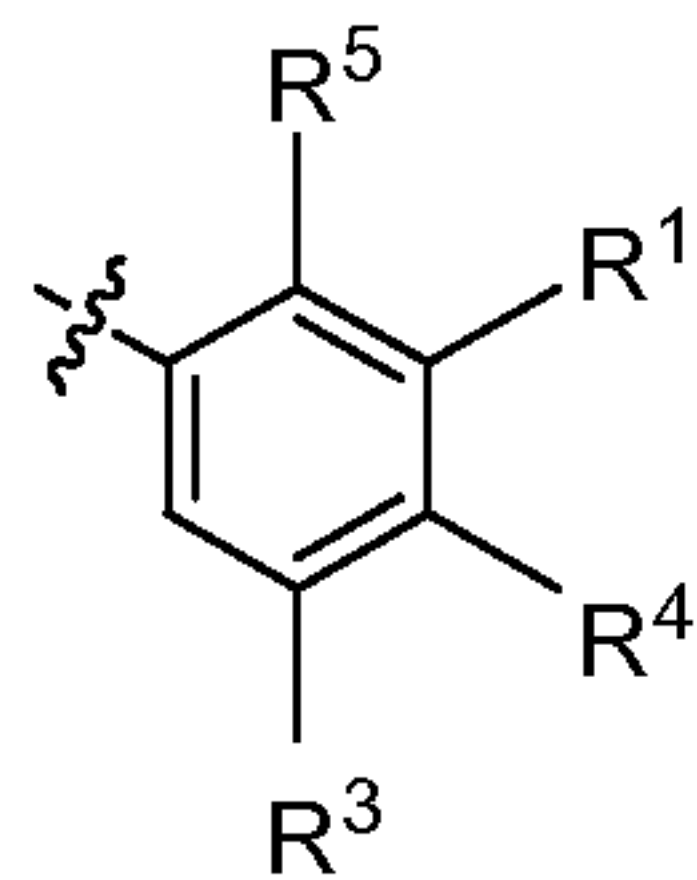
20 independently, the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2; or each R^2 is the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2.

In any of the above embodiments, each R^4 and each R^5 is H.

In some embodiments, Z is



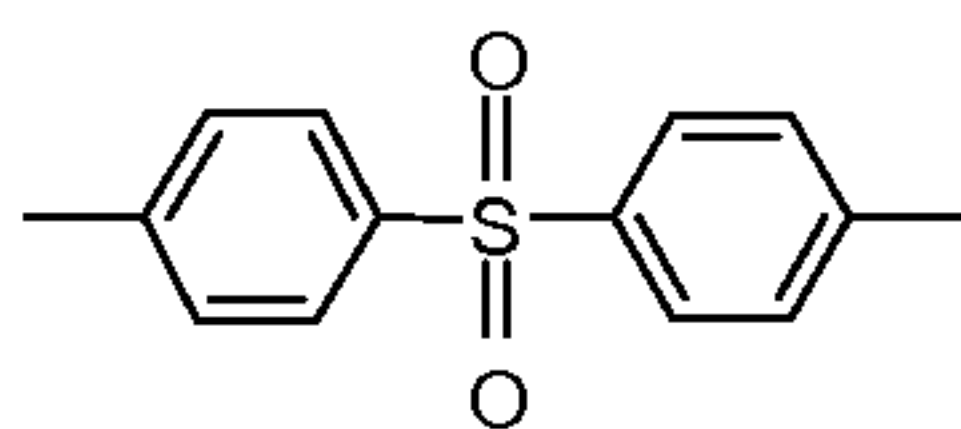
; each Q is, independently,



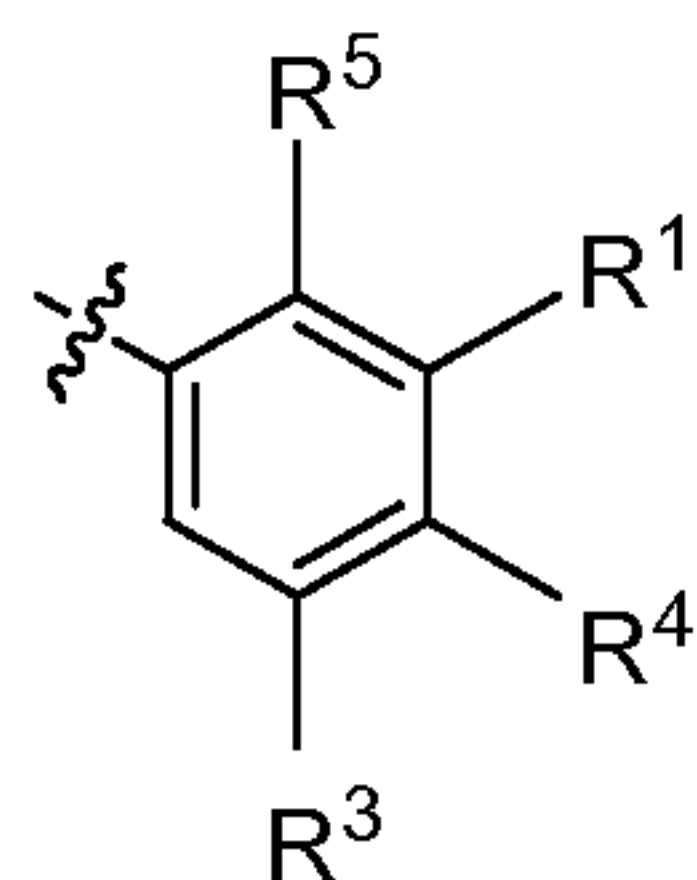
; each X is O or S; each R^1 is, independently, CF_3 , $C(CH_3)_3$, or halo; each R^3 is, independently, $-NH-R^2$; each R^2 is, independently, H, or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4; and each R^4 and each R^5 is H.

5

In some embodiments, Z is

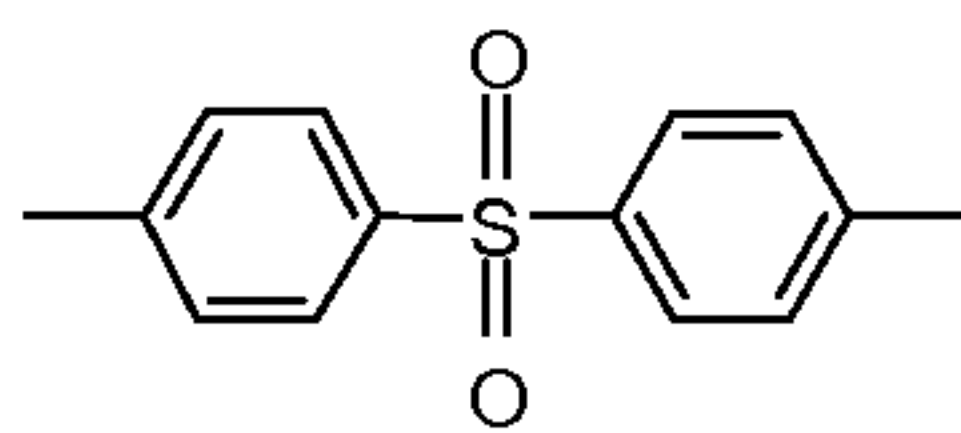


; each Q is, independently,

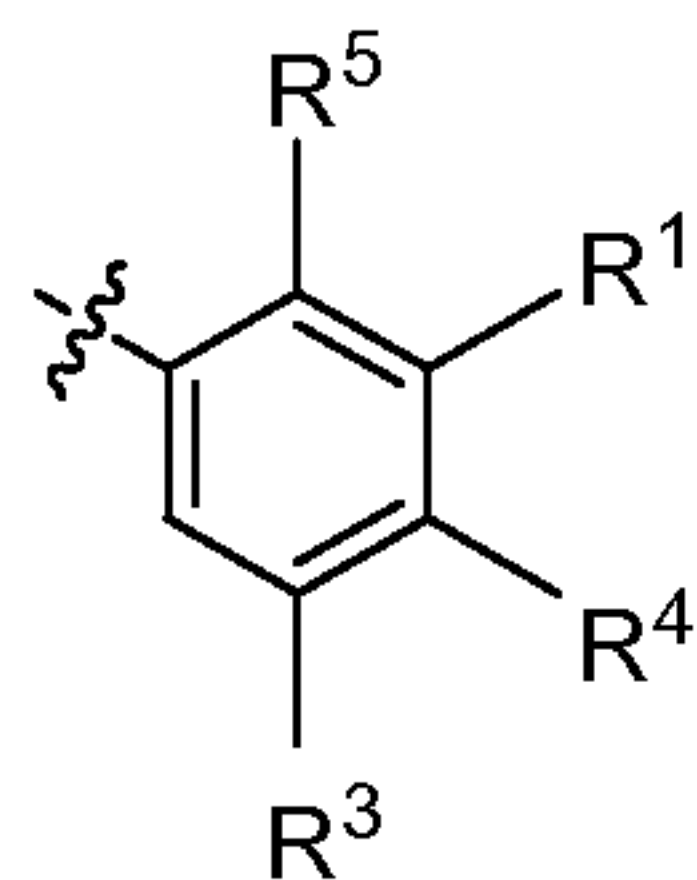


; each X is O; each R^1 is CF_3 , $C(CH_3)_3$, or halo; each R^3 is, independently, $-NH-R^2$; each R^2 is, independently, the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 1 or 2; and each R^4 and each R^5 is H.

In some embodiments, Z is



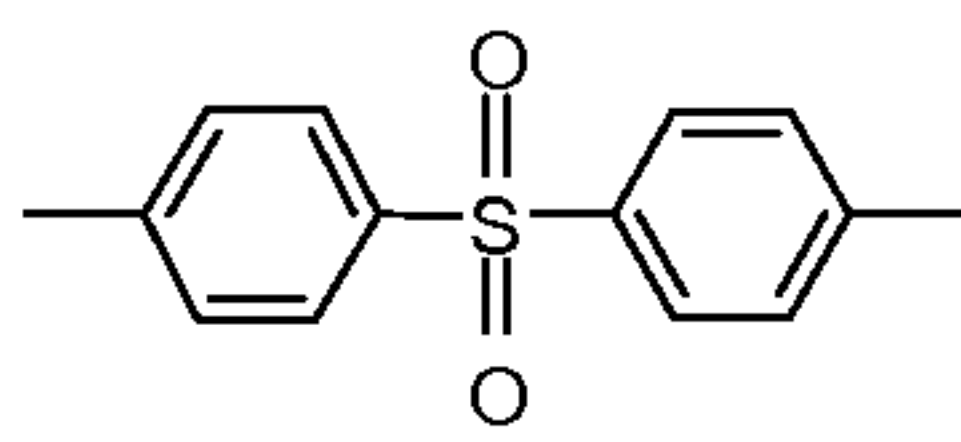
; each Q is, independently,



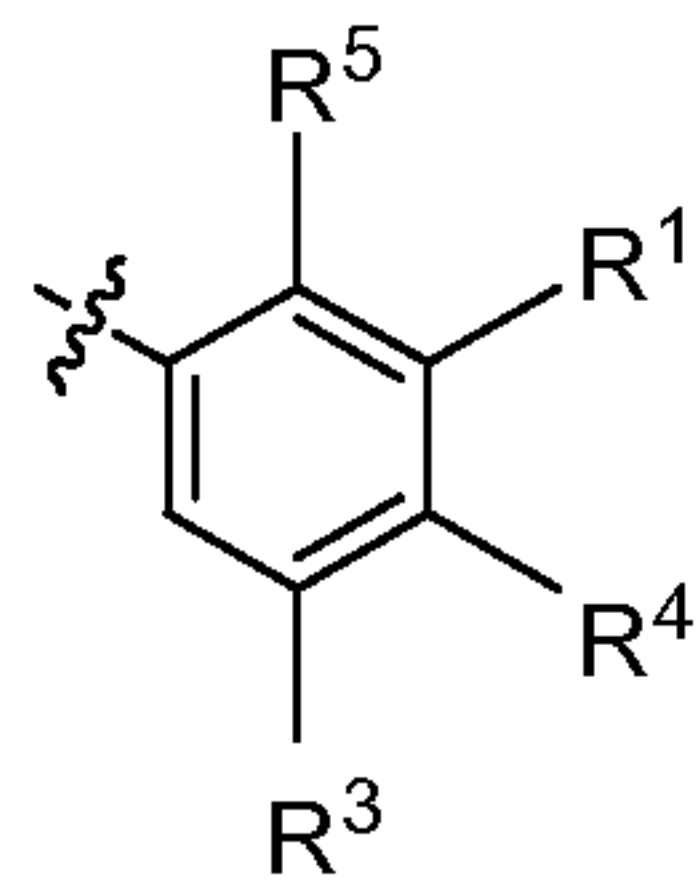
10

; each X is O; each R^1 is CF_3 or halo; each R^3 is, independently, $-NH-R^2$; each R^2 is the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2; and each R^4 and each R^5 is H.

In some embodiments, Z is



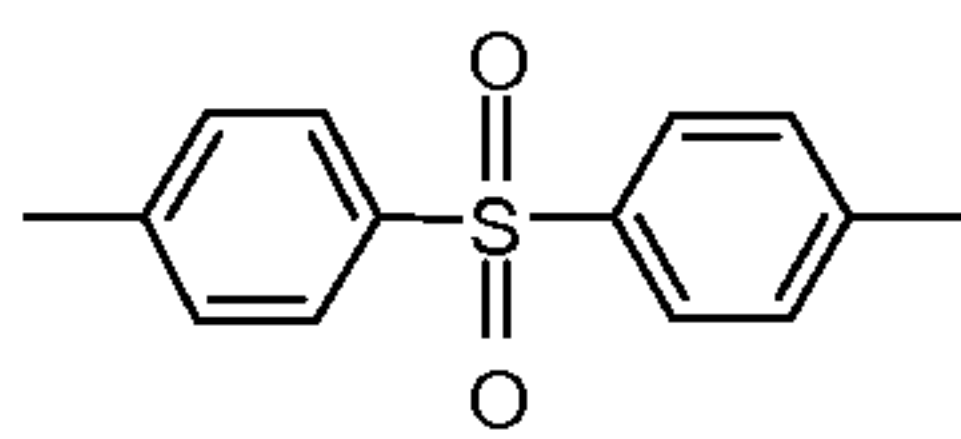
; each Q is, independently,



; each X is, independently, O, or S; each R^1 is, independently, H, or CF_3 ; each R^3 is H; each R^4 is, independently, H or $-NH-C(=O)-(CH_2)_p-NH-C(=NH)-NH_2$, where each p is, independently, 3 or 4; and each R^5 is, independently, H or CF_3 .

5

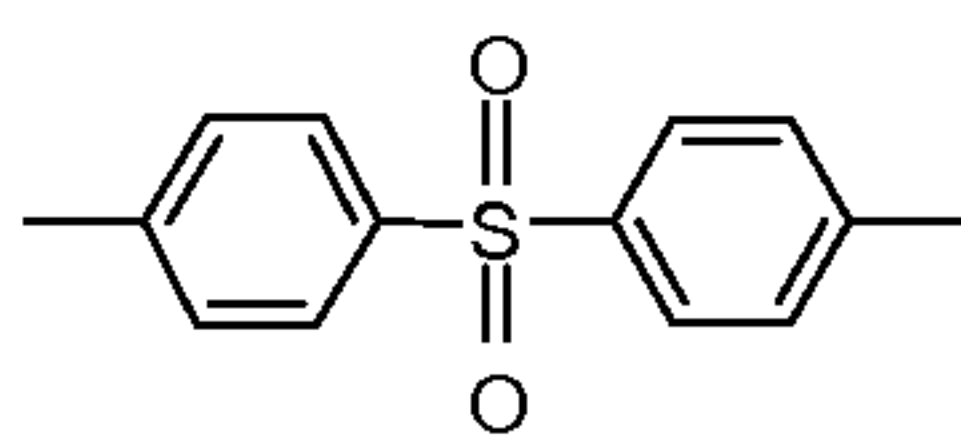
In some embodiments, Z is



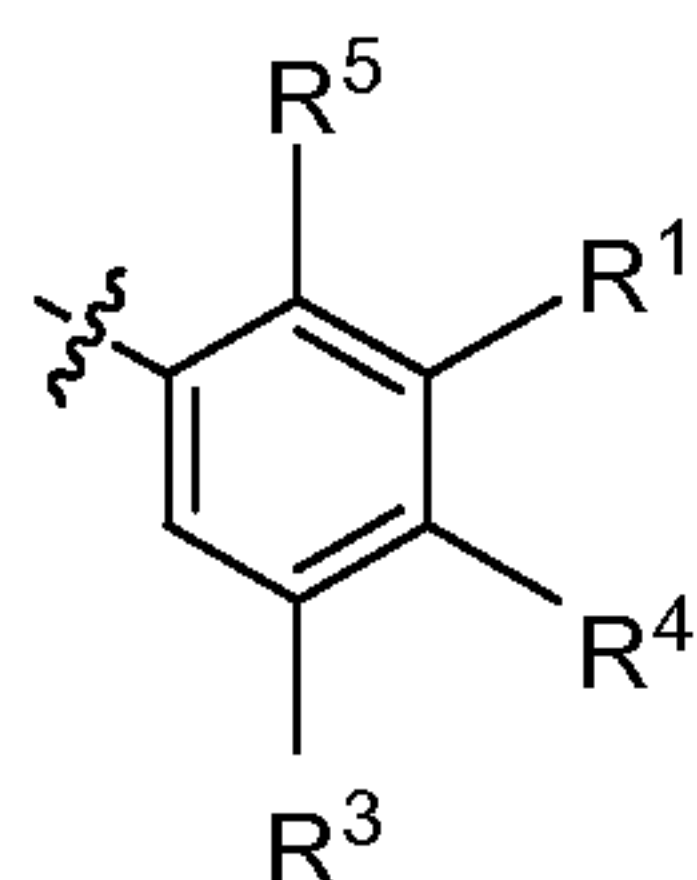
; each Q is, independently,

$-C(=O)-(CH_2)_b-NH-C(=NH)-NH_2$, where each b is, independently, 3 or 4; and each X is N.

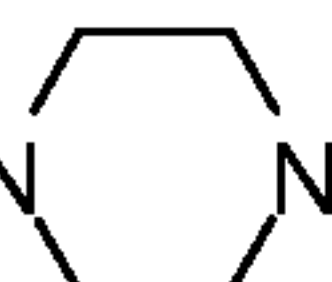
In some embodiments, Z is



; each Q is, independently,

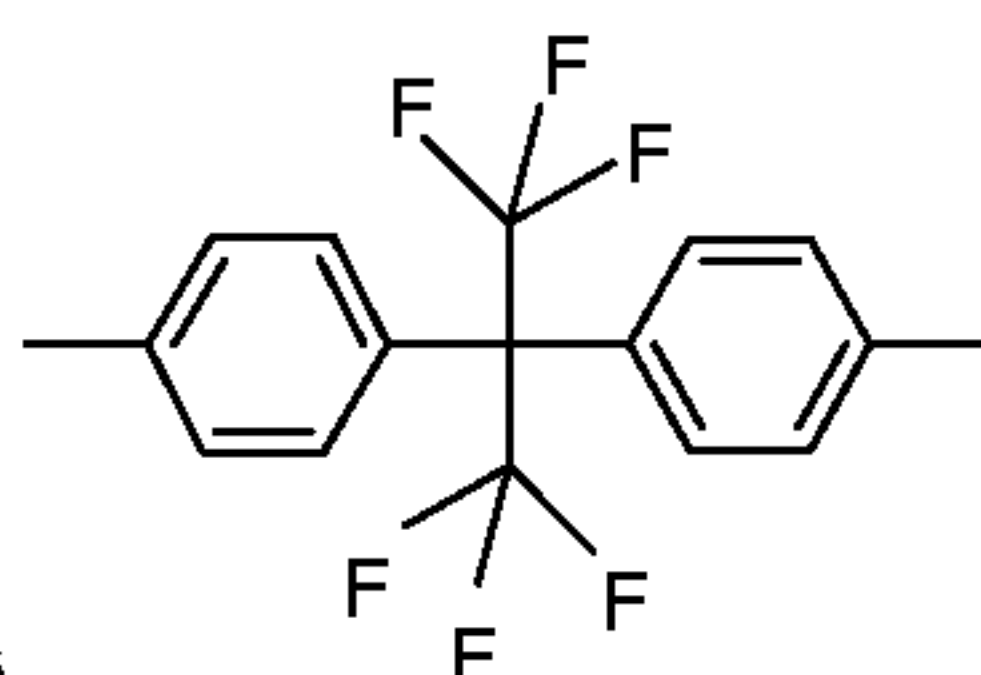


; each X is O or S; each R^1 is, independently, H or CF_3 ; each R^3 is,

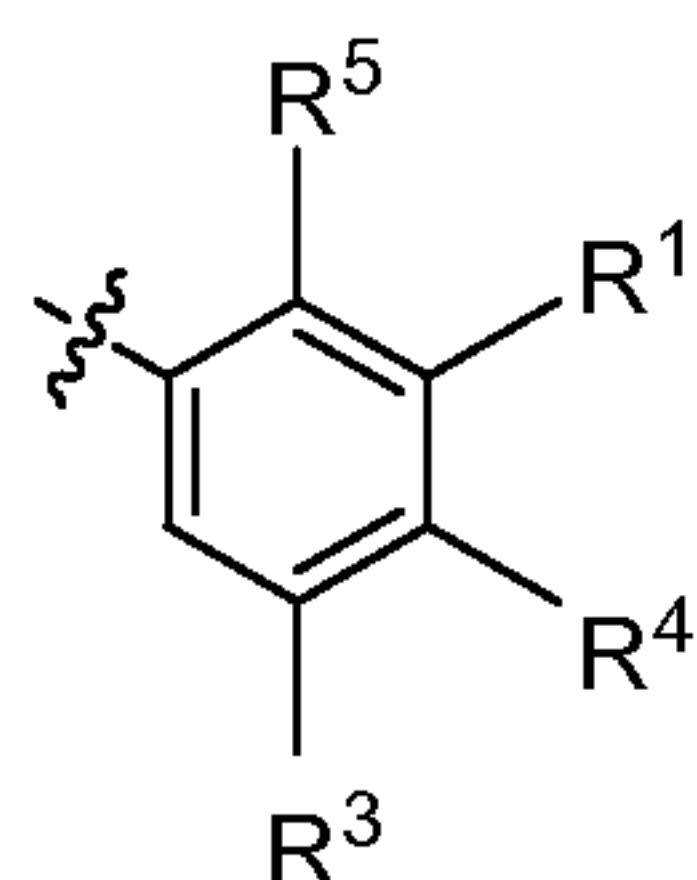
independently, $-(CH_2)_r-NH_2$, $-NH_2$, $-NH-(CH_2)_w-NH_2$, or $-(CH_2)_y-N$ , where each r is,

10 independently, 1 or 2, each w is, independently, 1 to 3, and each y is, independently, 1 or 2; each R^4 is H; and each R^5 is, independently, H or CF_3 .

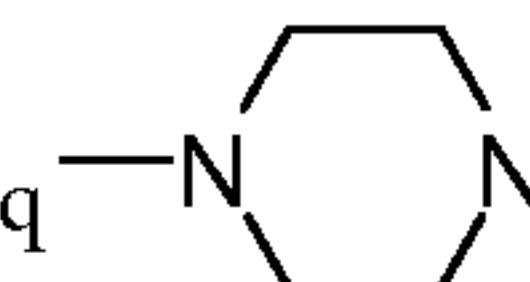
In some embodiments, Z is



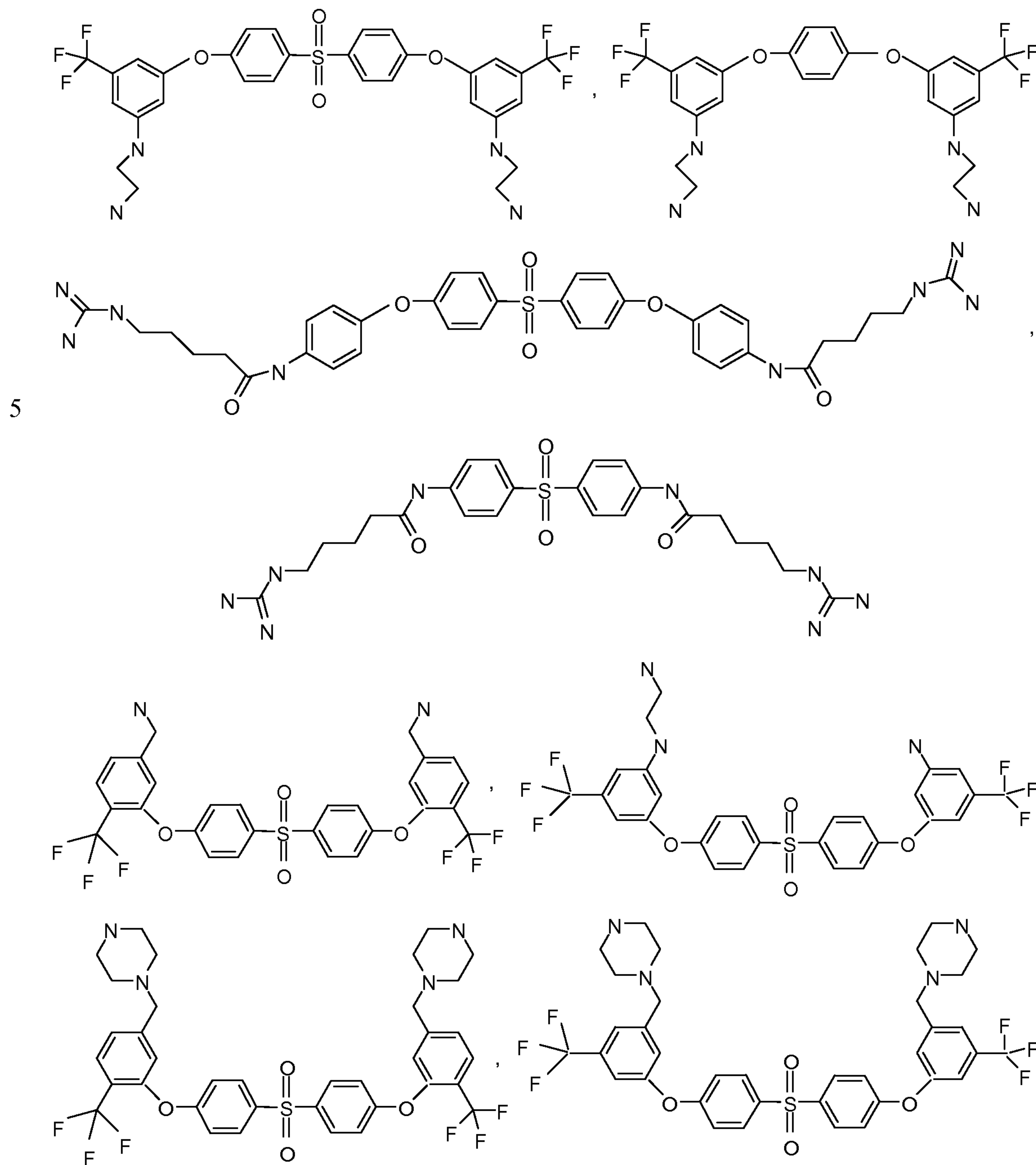
or phenyl; each Q is, independently,

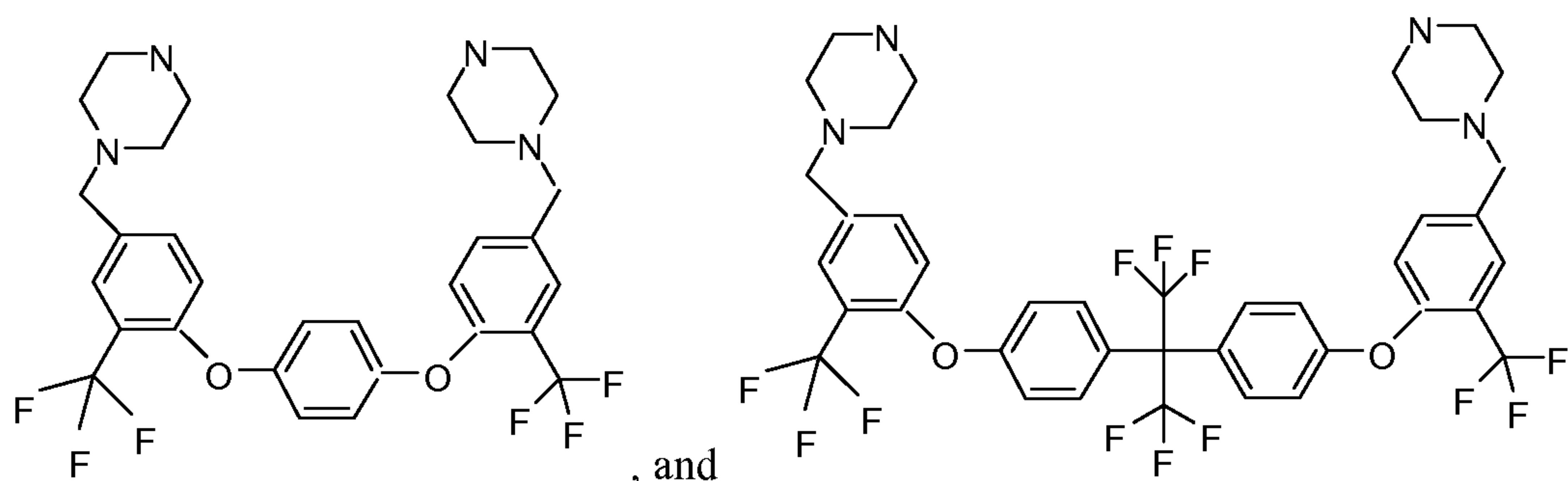


; each X is, independently, O or S; each R^1 is, independently, H or CF_3 ; each R^3

is H; each R^4 is, independently, $-(CH_2)_q-N$ , where each q is, independently, 1 or 2; and each R^5 is, independently, H or CF_3 .

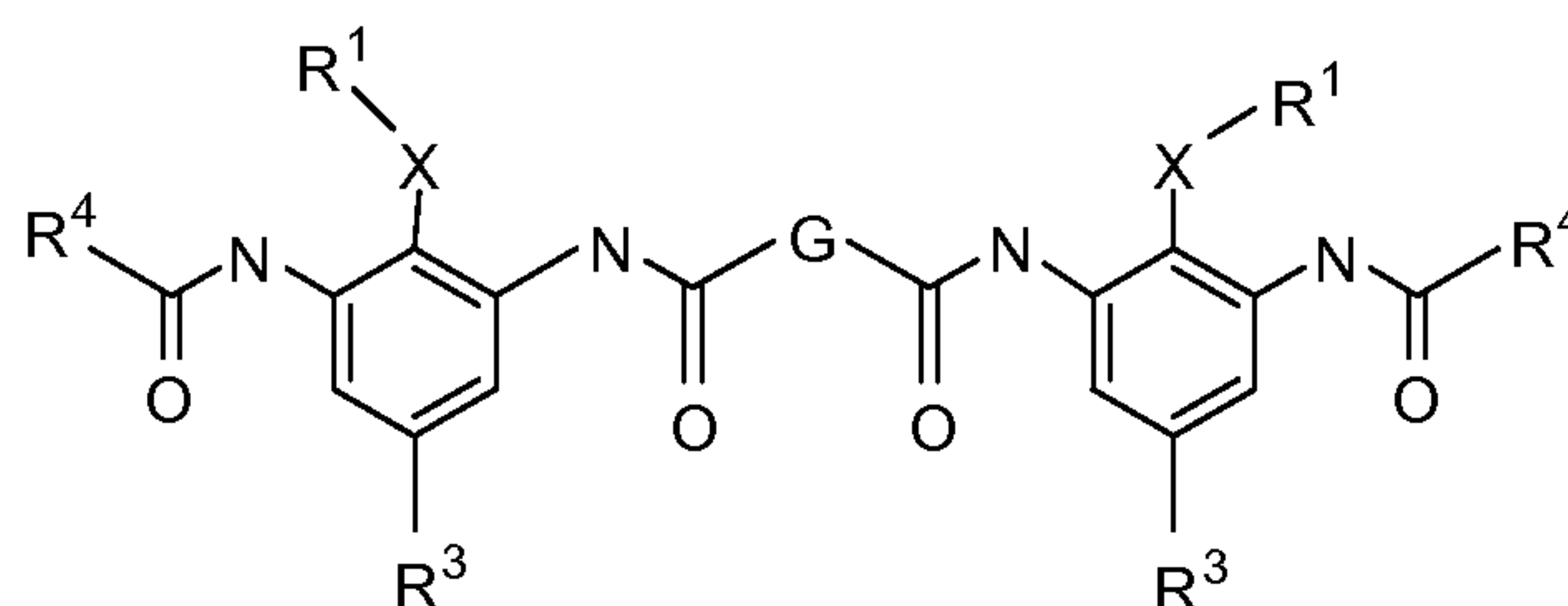
In some embodiments, the compound is chosen from:



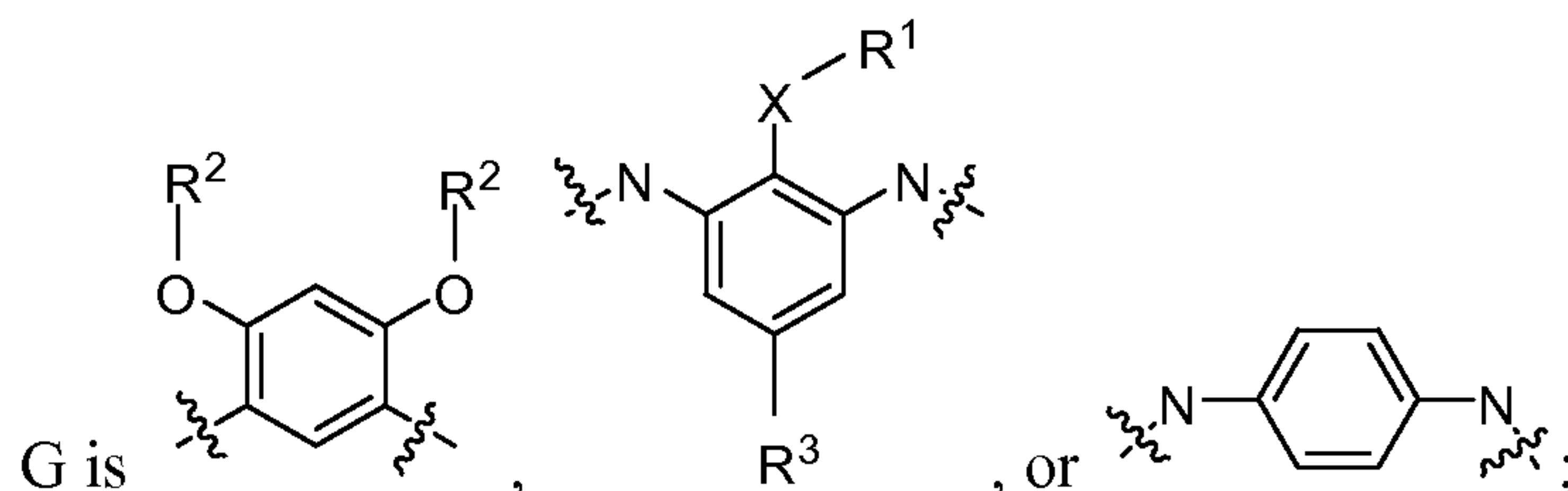


or a pharmaceutically acceptable salt thereof.

The present invention also provides compounds of Formula IV:



5 wherein:



each X is, independently, O or S;

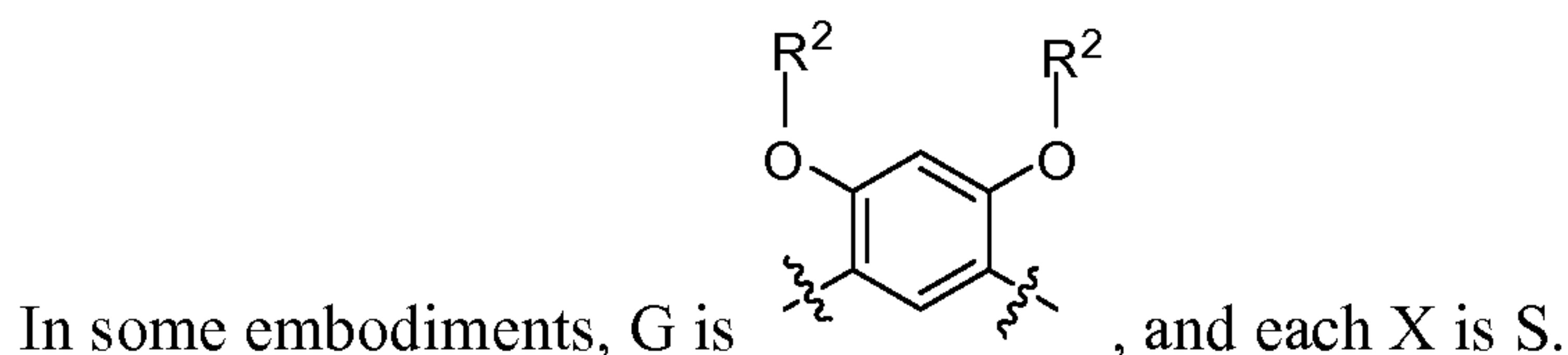
each R¹ is, independently, , or the free base or salt form of $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;

10 each R² is, independently, H, C₁-C₈alkyl, or the free base or salt form of $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;

each R³ is, independently, H, CF₃, C(CH₃)₃, halo, or OH; and

each R⁴ is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;

15 or a pharmaceutically acceptable salt thereof.

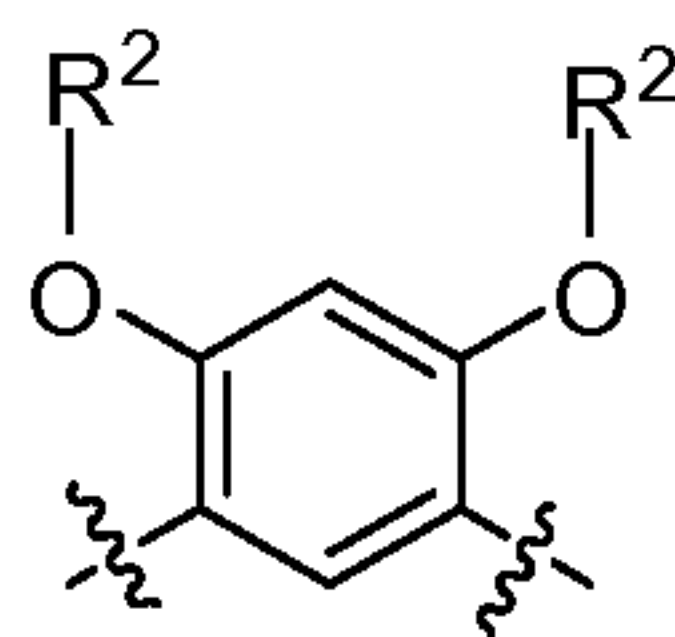


In any of the above embodiments, each R^1 is, independently, the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4; or each R^1 is, independently, the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2; or each R^1 is the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2.

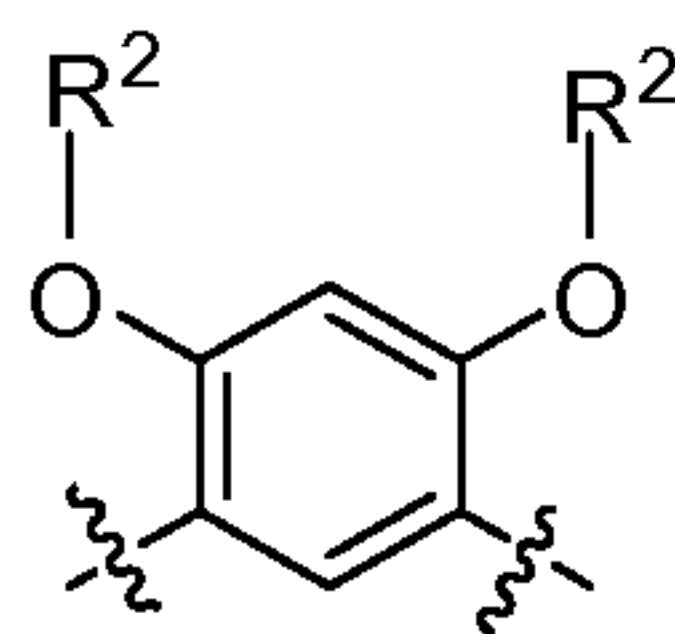
5 In any of the above embodiments, each R^2 is, independently, C_1-C_3 alkyl or the free base or salt form of $-(CH_2)_n-NH_2$ where n is 1 to 4; or each R^2 is, independently, C_1-C_3 alkyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2; or each R^2 is, independently, methyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 2; or each R^2 is methyl or the free base or salt form of $-(CH_2)_n-NH_2$, where
10 each n is 2.

In any of the above embodiments, each R^3 is, independently, CF_3 , $C(CH_3)_3$, or halo; or each R^3 is CF_3 .

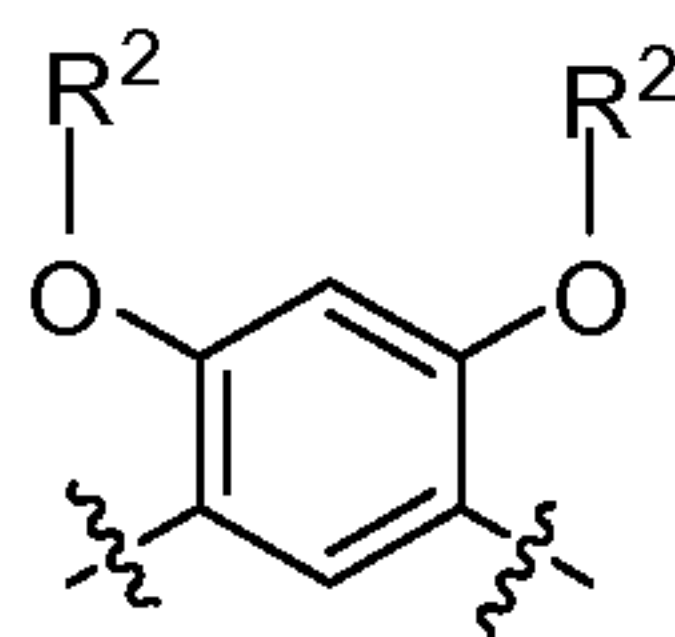
In any of the above embodiments, each R^4 is, independently,
 $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; or each R^4 is
 15 $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 4.

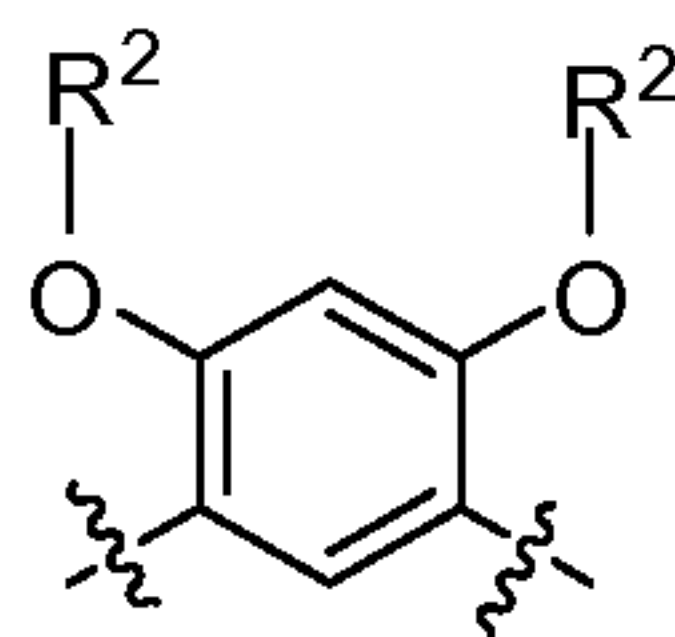


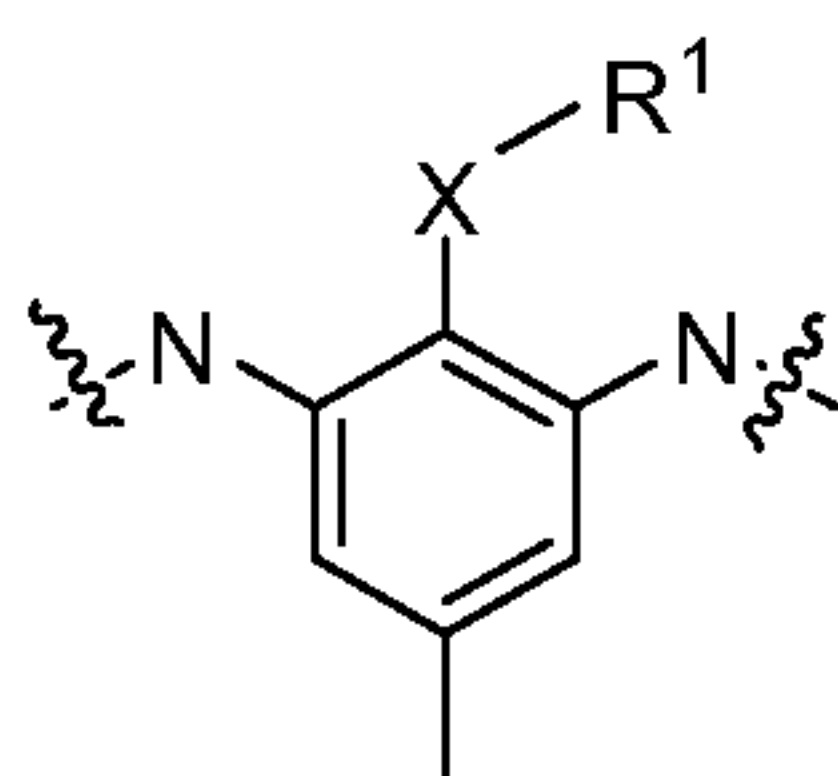
In some embodiments, G is ; each X is S ; each R^1 is, independently, the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2; each R^2 is, independently, C_1-C_8 alkyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2; each R^3 is, independently, CF_3 , $C(CH_3)_3$, or halo; and each R^4 is,
 20 independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 3 or 4.

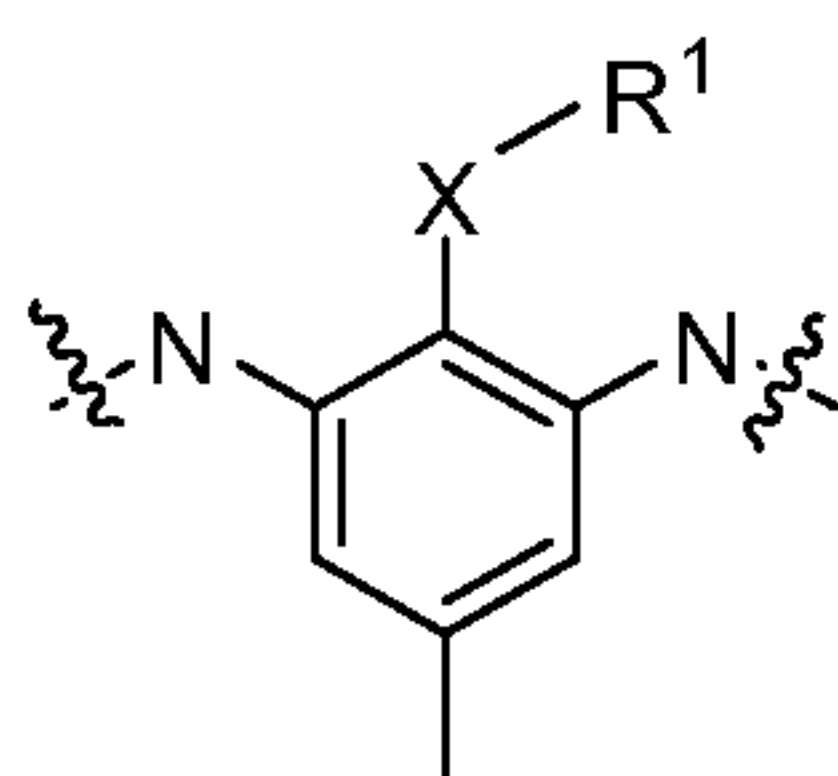


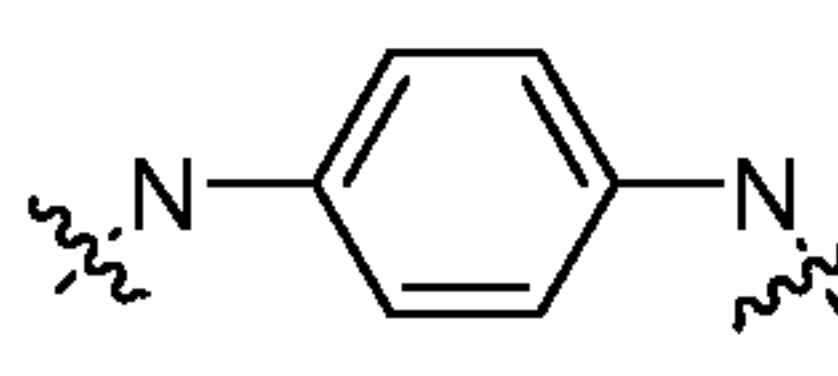
In some embodiments, G is ; each X is S ; each R^1 is the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 1 or 2; each R^2 is, independently, C_1-C_3 alkyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2; each R^3 is, independently, CF_3 or $C(CH_3)_3$; and each R^4 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 3 or 4.

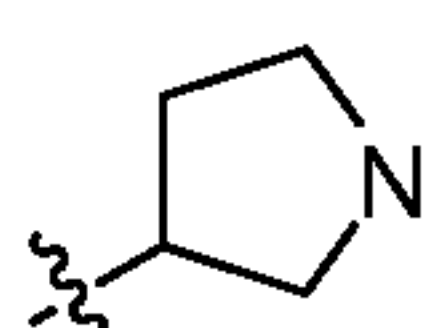


In some embodiments, G is ; each X is S; each R¹ is the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2; each R² is, independently, methyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2; each R³ is, independently, CF₃ or C(CH₃)₃; and each R⁴ is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 4.

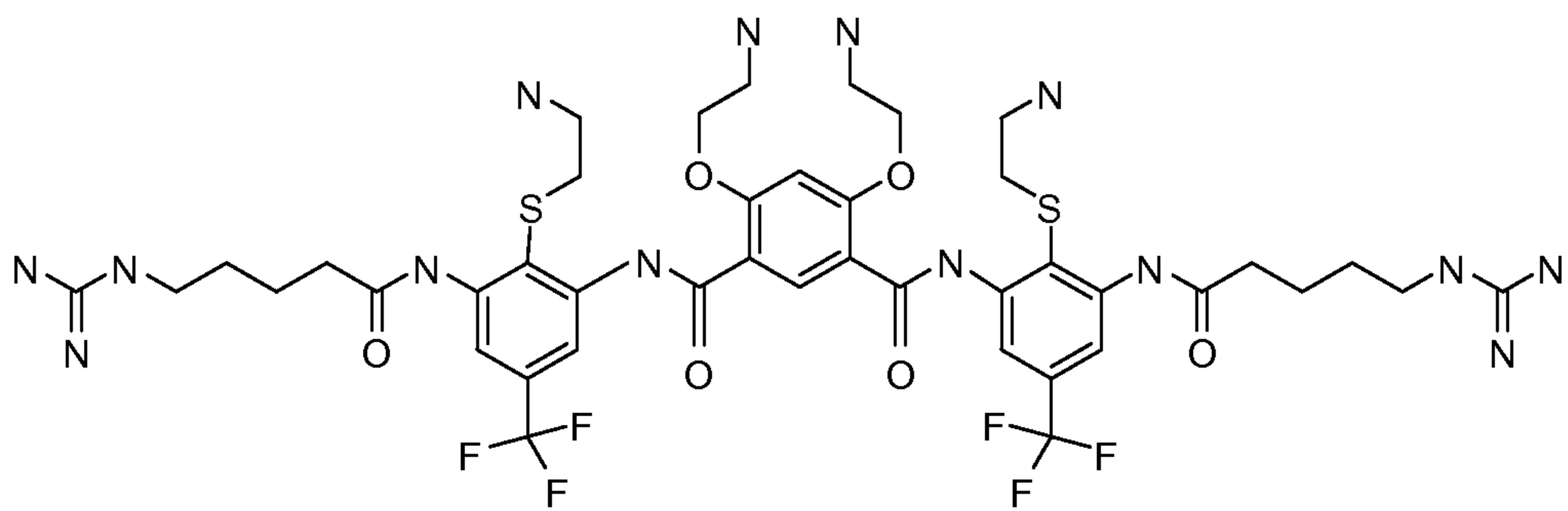


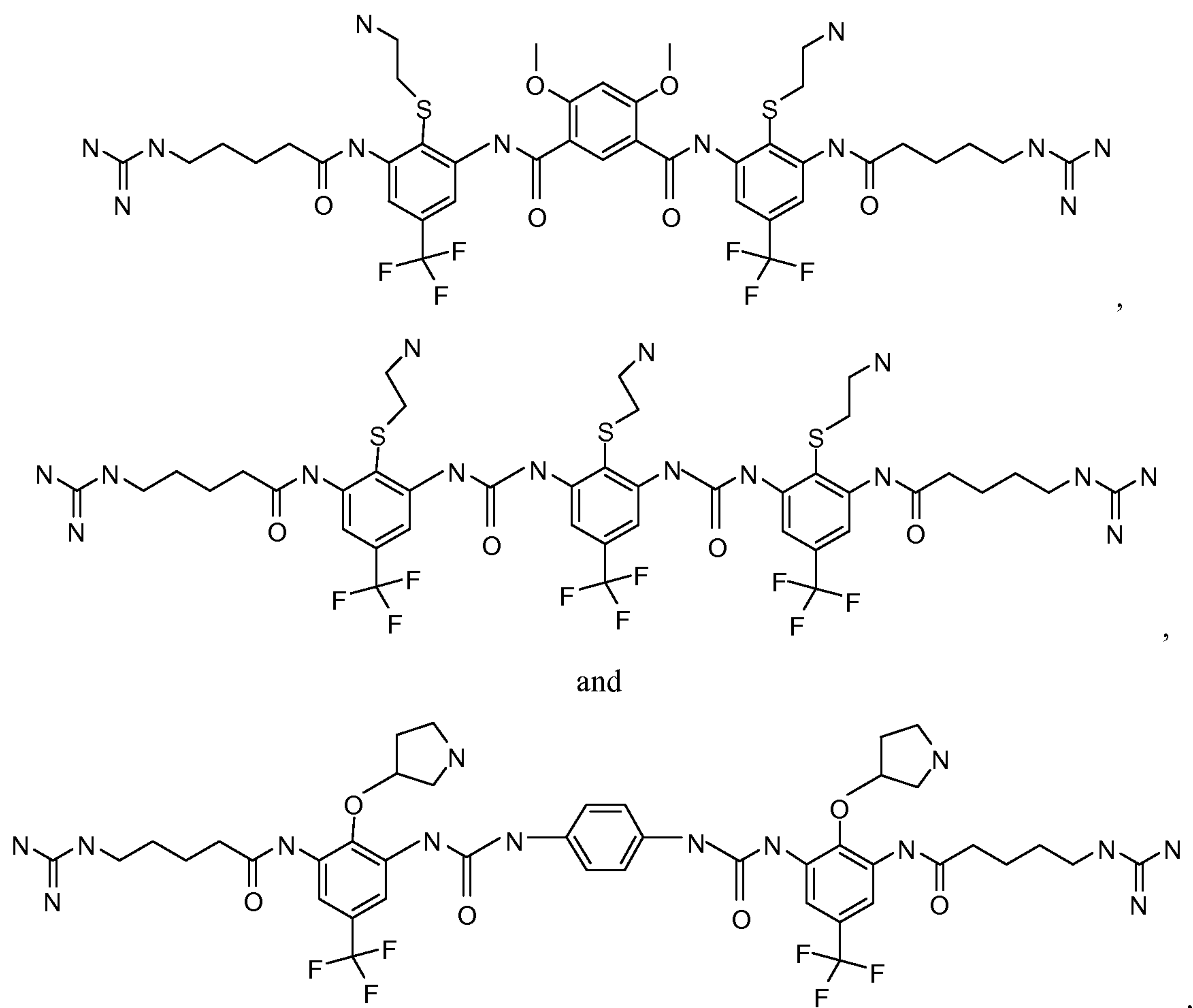
5 In some embodiments, G is ; each X is, independently, O or S; each R¹ is, independently, the free base or salt form of $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; each R³ is, independently, H or CF₃; and each R⁴ is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

10 In some embodiments, G is ; each X is, independently, O or S;

each R¹ is ; each R³ is, independently, H or CF₃; and each R⁴ is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

In some embodiments, the compound is chosen from:



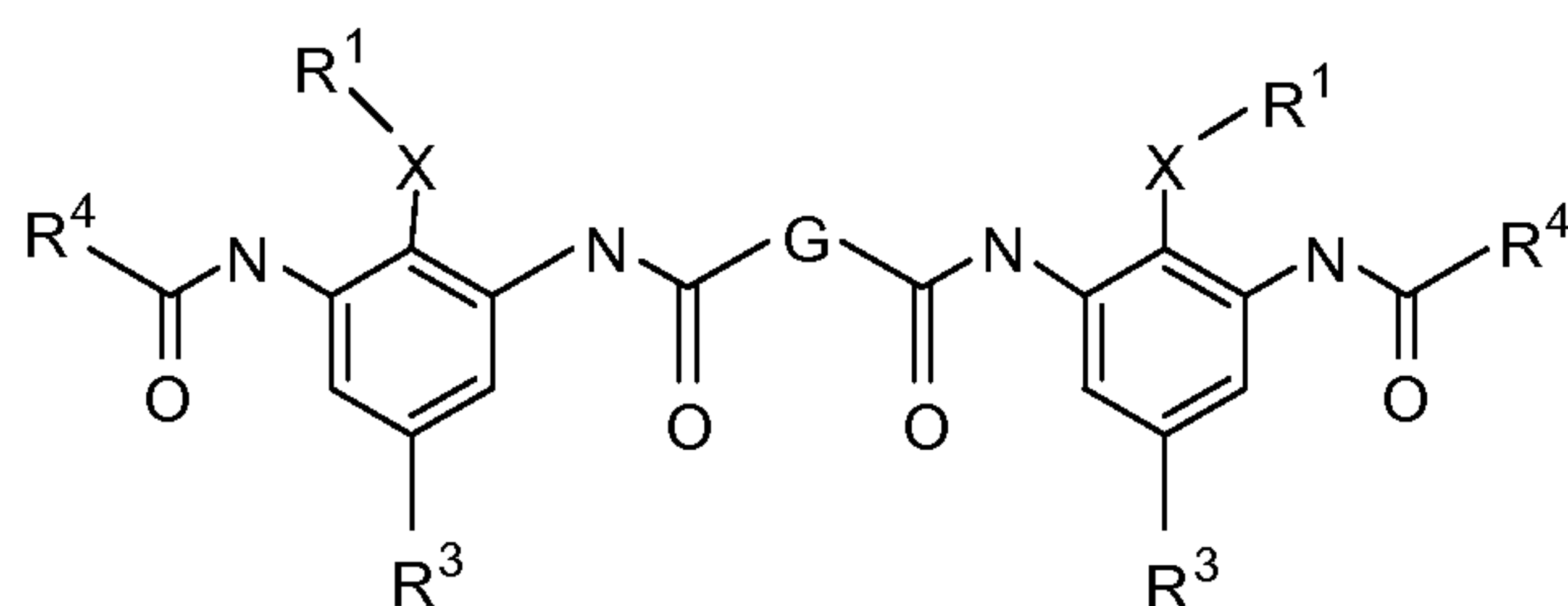


5 or a pharmaceutically acceptable salt thereof.

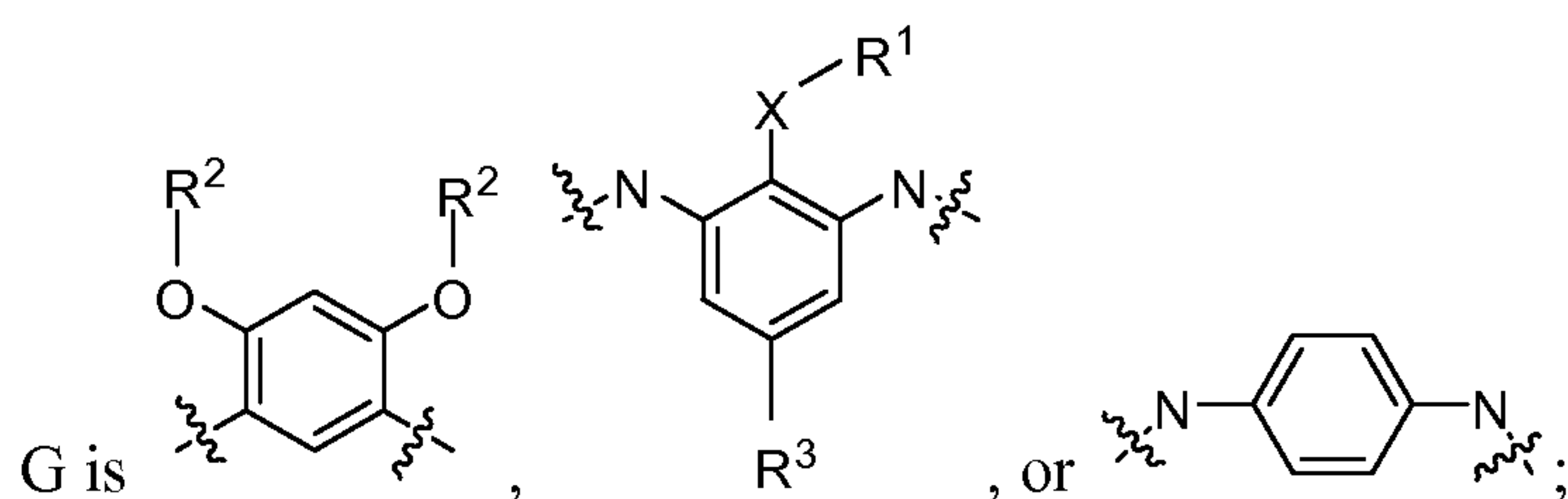
In some embodiments, any one or more of the above compounds may be excluded from any of the genus of compounds described above.

The present invention also provides compositions comprising one or more of the compounds or salts described above and a pharmaceutically acceptable carrier.

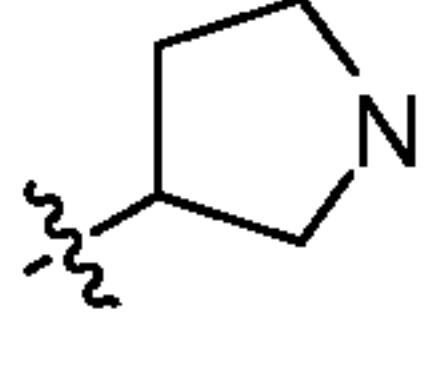
10 The present invention also provides methods of treating malaria in an animal comprising administering to the animal a therapeutically effective amount of a compound of Formula IV:



wherein:



each X is, independently, O or S;

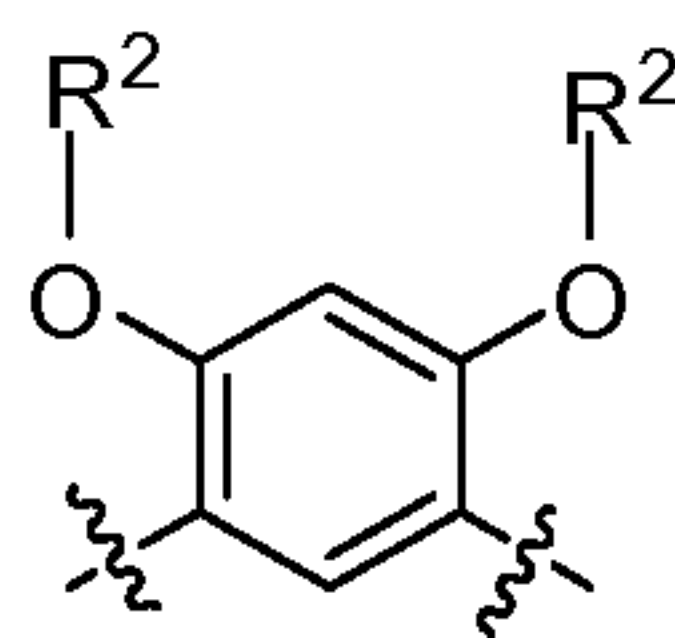
each R¹ is, independently, , or the free base or salt form of -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4;

5 each R² is, independently, H, C₁-C₈alkyl, or the free base or salt form of -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4;

each R³ is, independently, H, CF₃, C(CH₃)₃, halo, or OH; and

each R⁴ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4;

10 or a pharmaceutically acceptable salt thereof.



In some embodiments, G is , and each X is S.

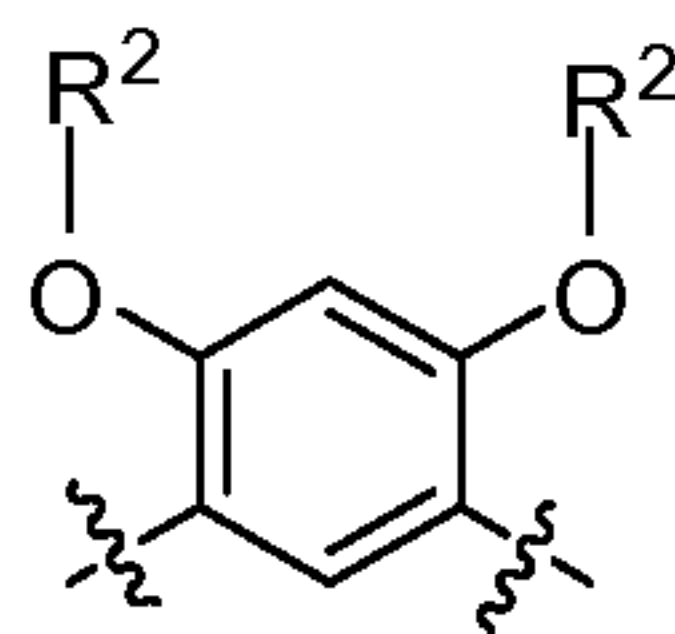
In any of the above embodiments, each R¹ is, independently, the free base or salt form of -(CH₂)_n-NH₂, where each n is, independently, 1 to 4; or each R¹ is, independently, the free base or salt form of -(CH₂)_n-NH₂, where each n is, independently, 1 or 2; or each R¹ is the free base or salt form of -(CH₂)_n-NH₂, where each n is 2.

In any of the above embodiments, each R² is, independently, C₁-C₃alkyl or the free base or salt form of -(CH₂)_n-NH₂ where n is 1 to 4; or each R² is, independently, C₁-C₃alkyl or the free base or salt form of -(CH₂)_n-NH₂, where each n is, independently, 1 or 2; or each R² is, independently, methyl or the free base or salt form of -(CH₂)_n-NH₂, where each n is, independently, 2; or each R² is methyl or the free base or salt form of -(CH₂)_n-NH₂, where each n is 2.

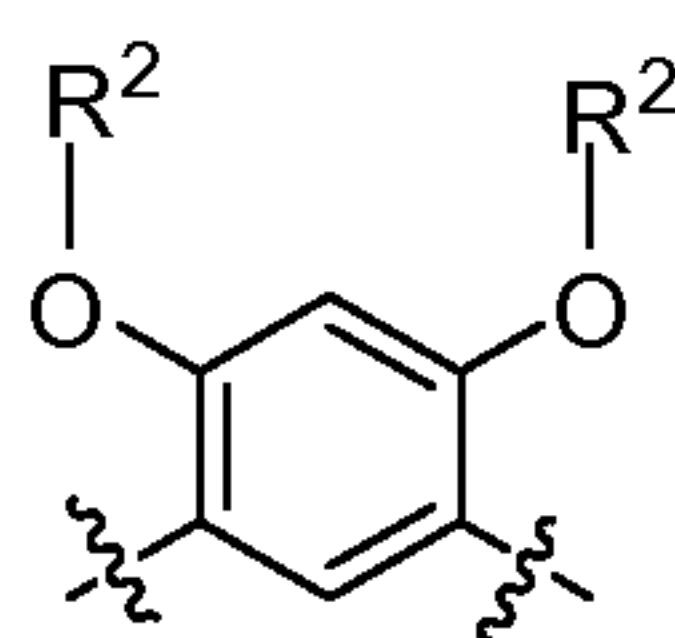
In any of the above embodiments, each R³ is, independently, CF₃, C(CH₃)₃, or halo; or each R³ is CF₃.

In any of the above embodiments, each R⁴ is, independently,
25 -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4; or each R⁴ is

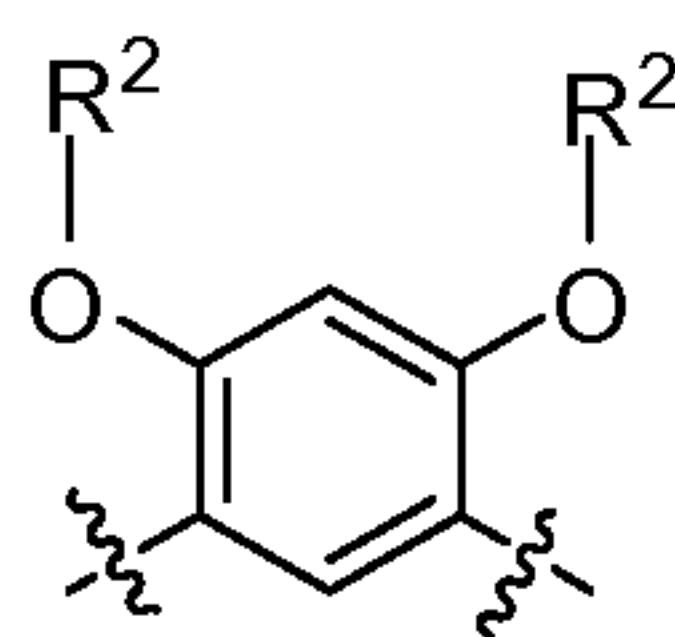
$-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 4.

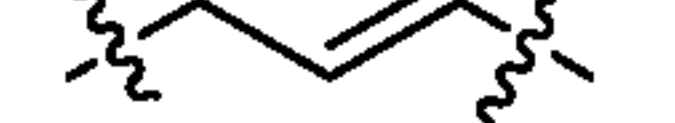


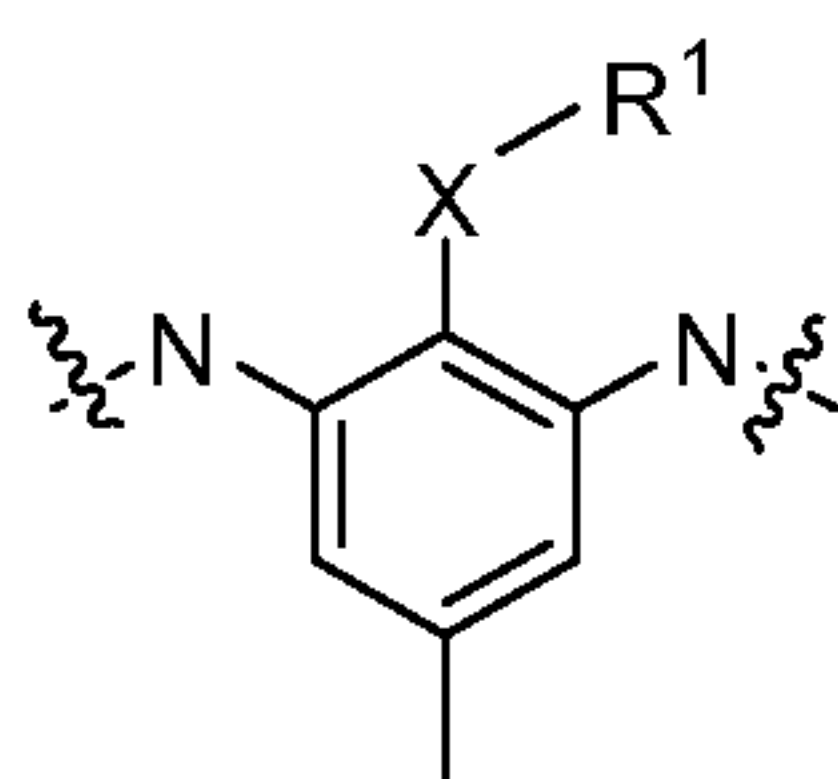
In some embodiments, G is ; each X is S ; each R^1 is, independently, the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2; each R^2 is, independently, C_1 - C_8 alkyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2; each R^3 is, independently, CF_3 , $C(CH_3)_3$, or halo; and each R^4 is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 3 or 4.

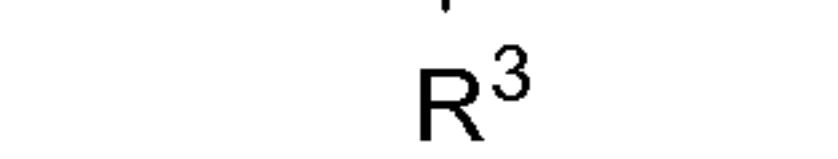


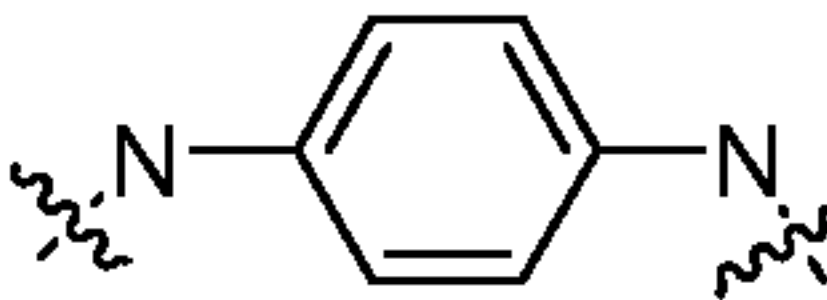
In some embodiments, G is ; each X is S ; each R^1 is the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 1 or 2; each R^2 is, independently, C_1 - C_3 alkyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2; each R^3 is, independently, CF_3 or $C(CH_3)_3$; and each R^4 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 3 or 4.

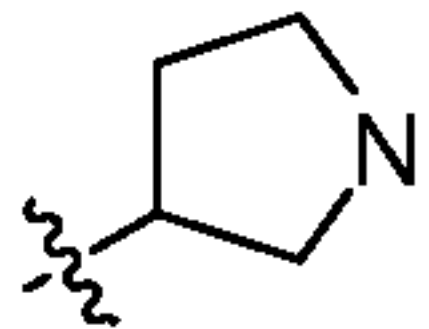


In some embodiments, G is ; each X is S ; each R^1 is the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2; each R^2 is, independently, methyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2; each R^3 is, independently, CF_3 or $C(CH_3)_3$; and each R^4 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 4.

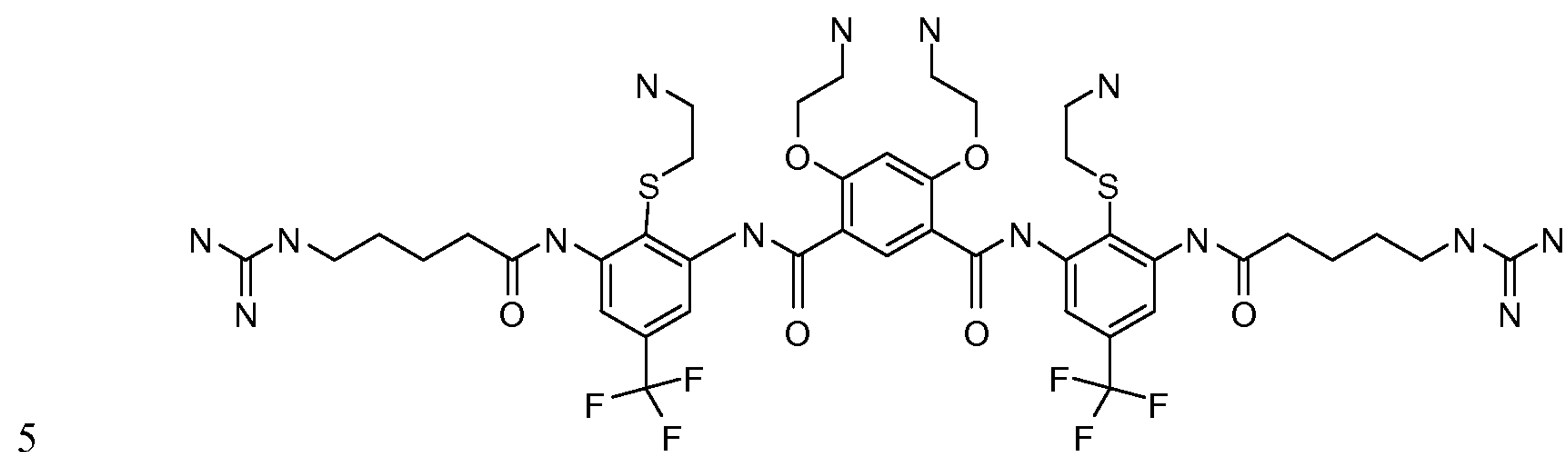


In some embodiments, G is ; each X is, independently, O or S ; each R^1 is, independently, the free base or salt form of $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; each R^3 is, independently, H or CF_3 ; and each R^4 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

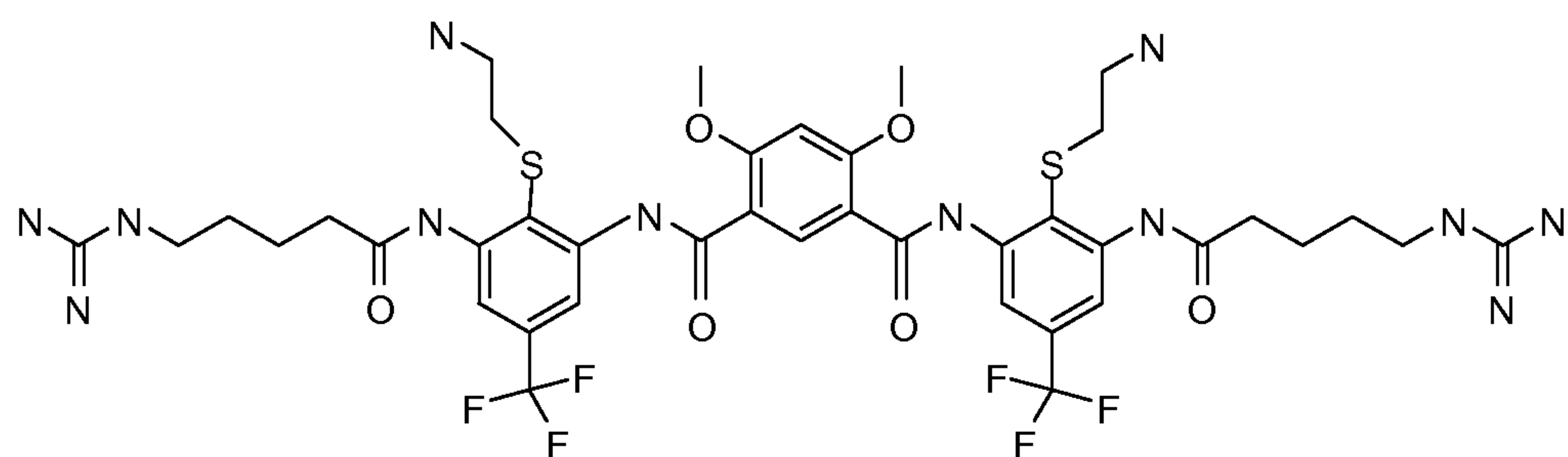
In some embodiments, G is ; each X is, independently, O or S;

each R¹ is ; each R³ is, independently, H or CF₃; and each R⁴ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4.

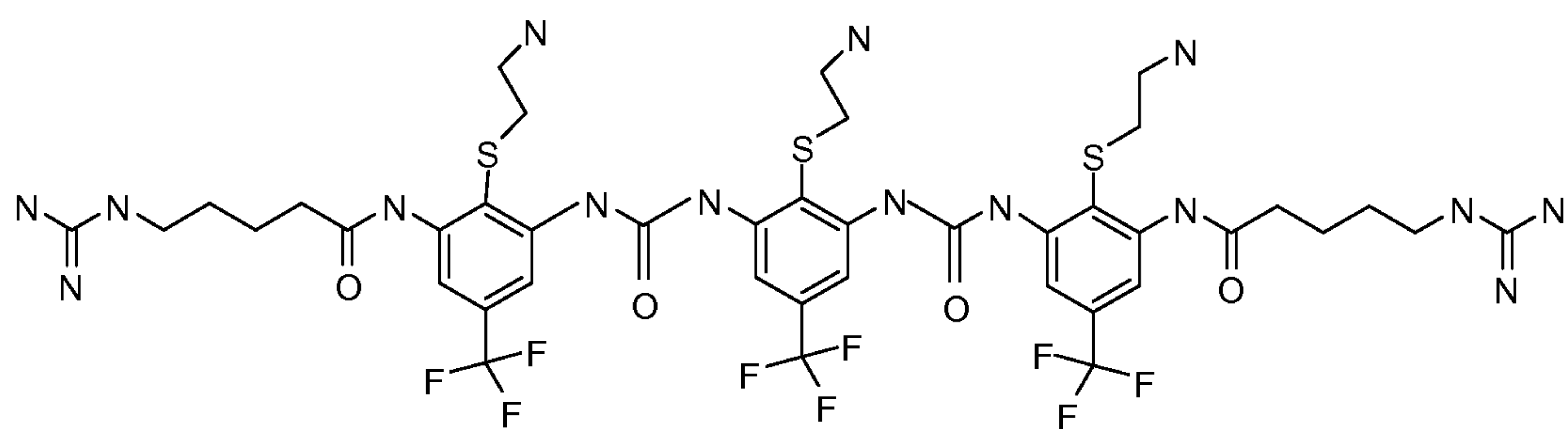
In some embodiments, the compound is chosen from:



Compound 102



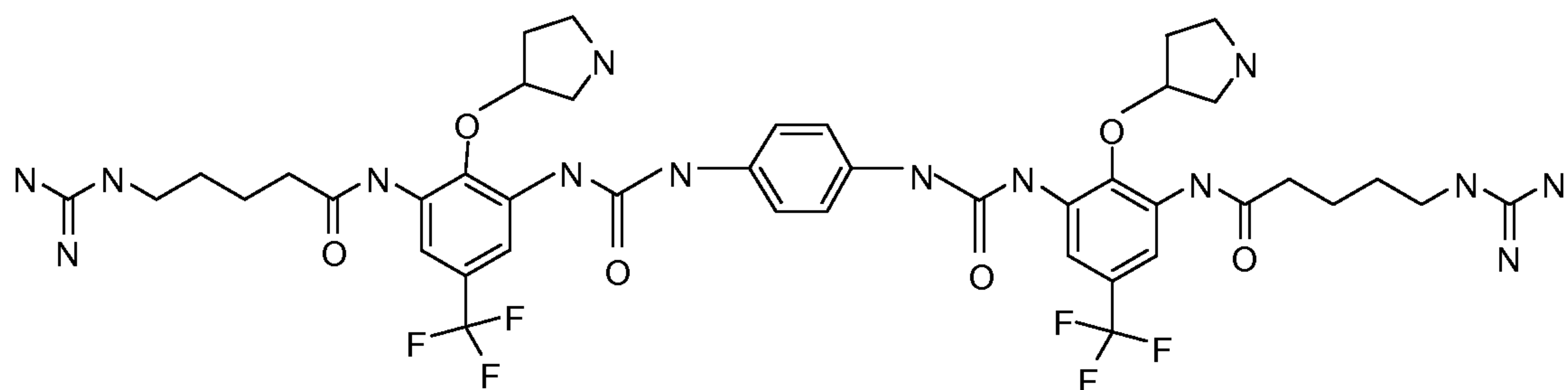
Compound 101



Compound 150

and

10

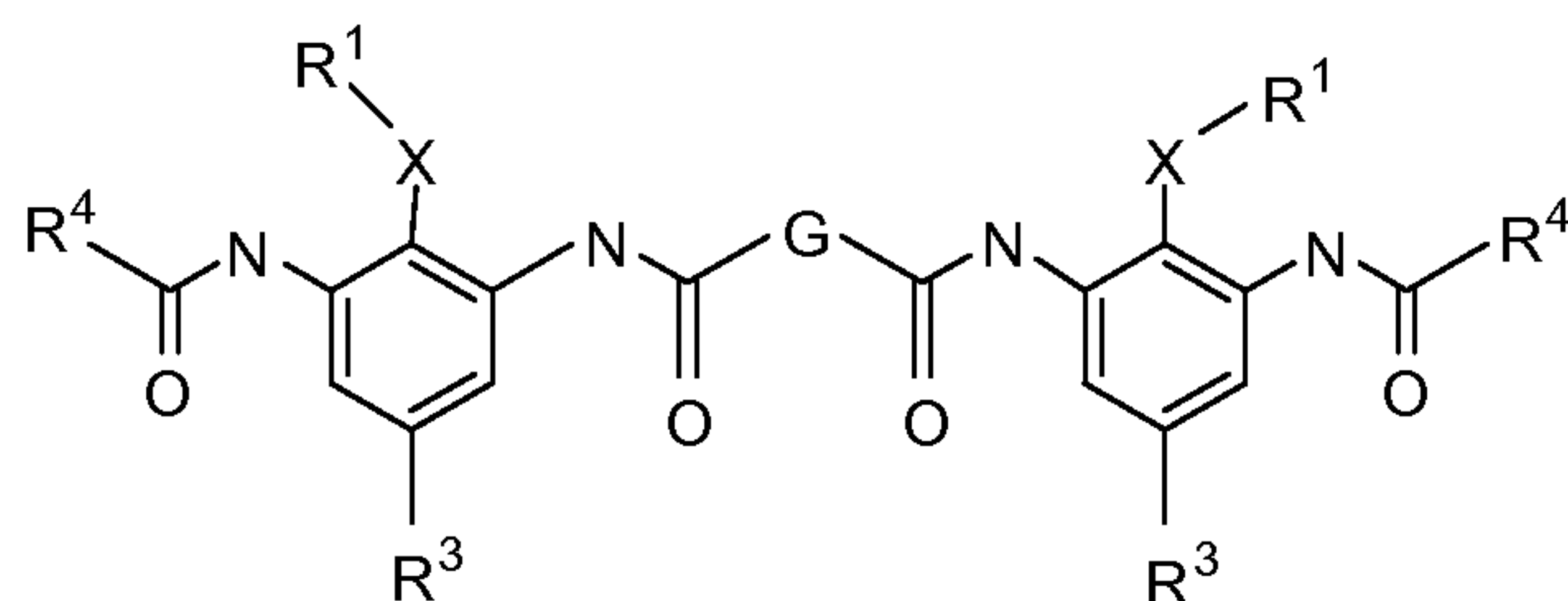


Compound 151

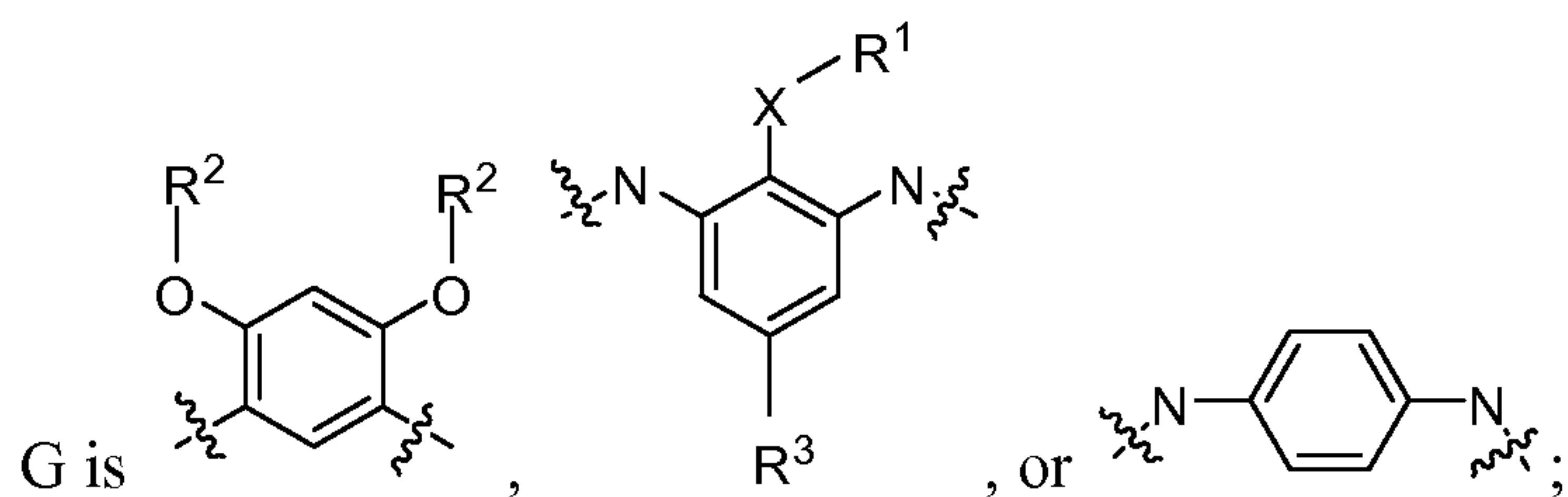
or a pharmaceutically acceptable salt thereof.

In any of the above embodiments, the malaria can be chloroquine-sensitive or
5 chloroquine-resistant.

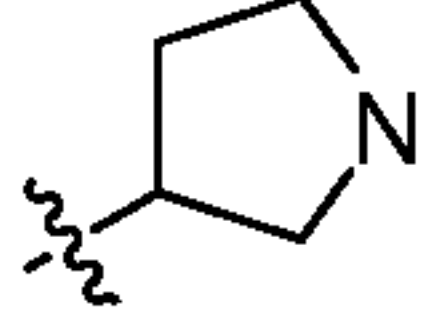
The present invention also provides methods of killing or inhibiting the growth of a *Plasmodium* species comprising contacting the species with an effective amount of a compound of Formula IV:



10 wherein:



each X is, independently, O or S;

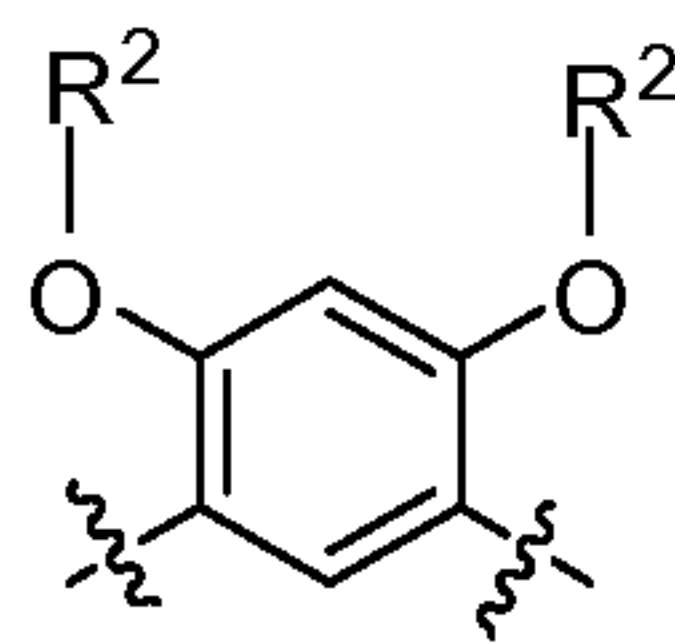
each R¹ is, independently, , or the free base or salt form of -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4;

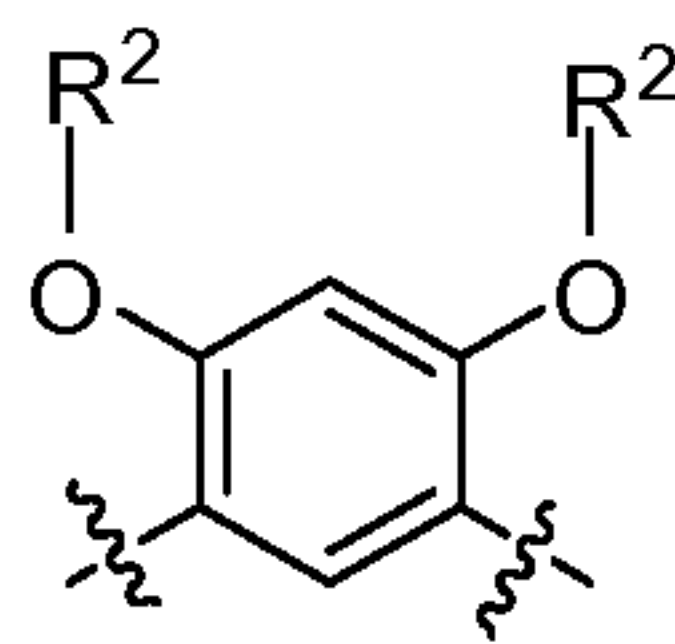
15 each R² is, independently, H, C₁-C₈alkyl, or the free base or salt form of -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4;

each R³ is, independently, H, CF₃, C(CH₃)₃, halo, or OH; and

each R⁴ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4;

or a pharmaceutically acceptable salt thereof.



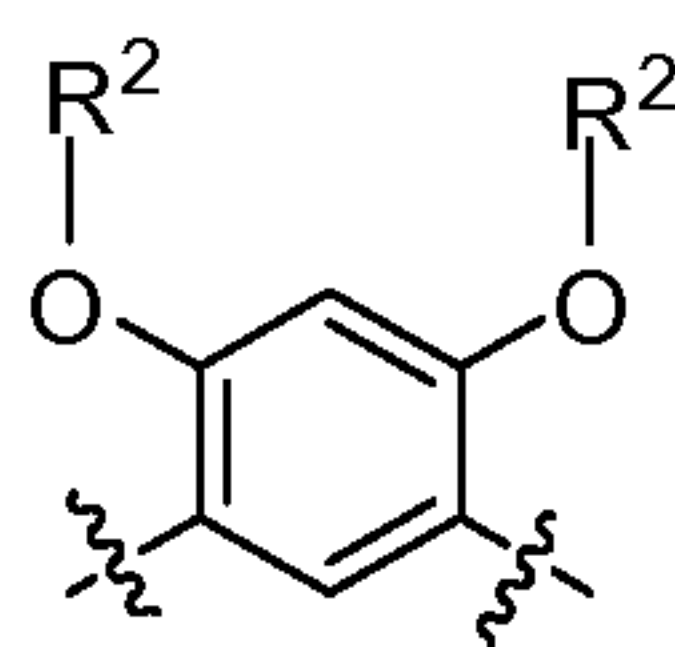
In some embodiments, G is , and each X is S.

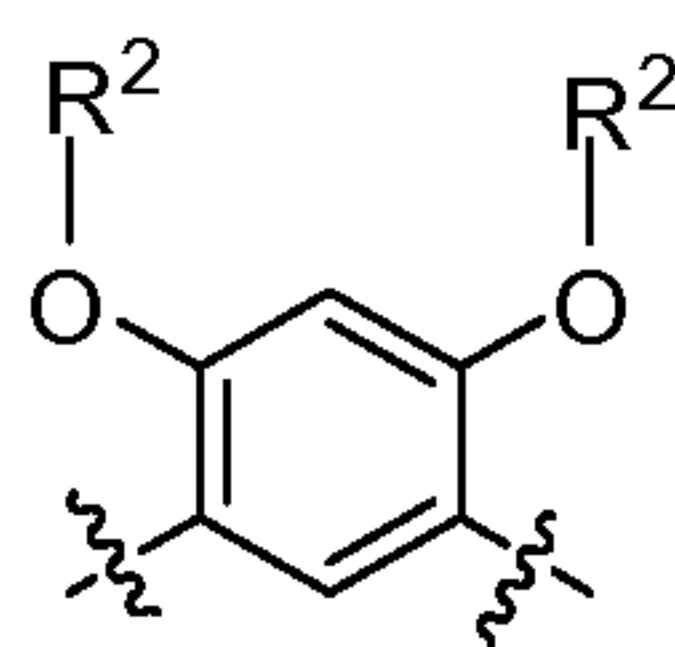
In any of the above embodiments, each R^1 is, independently, the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4; or each R^1 is, independently, the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2; or each R^1 is the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2.

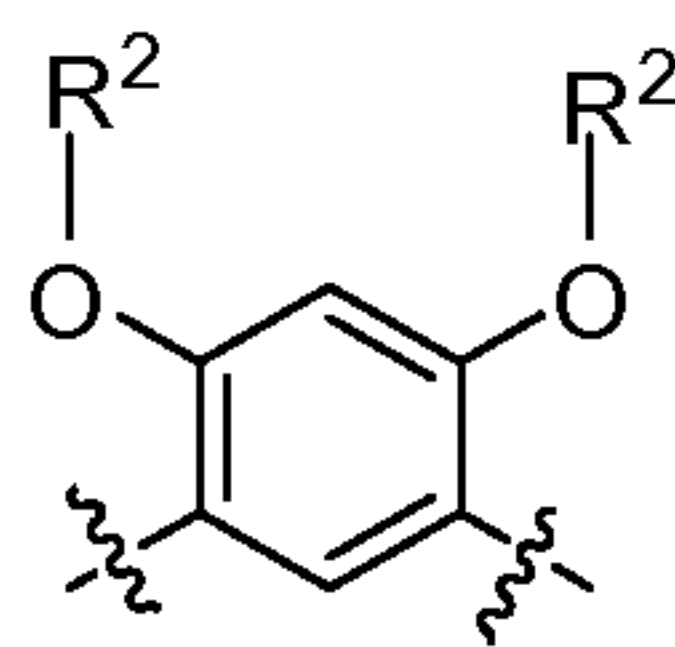
In any of the above embodiments, each R^2 is, independently, C_1 - C_3 alkyl or the free base or salt form of $-(CH_2)_n-NH_2$ where n is 1 to 4; or each R^2 is, independently, C_1 - C_3 alkyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2; or each R^2 is, independently, methyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 2; or each R^2 is methyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2.

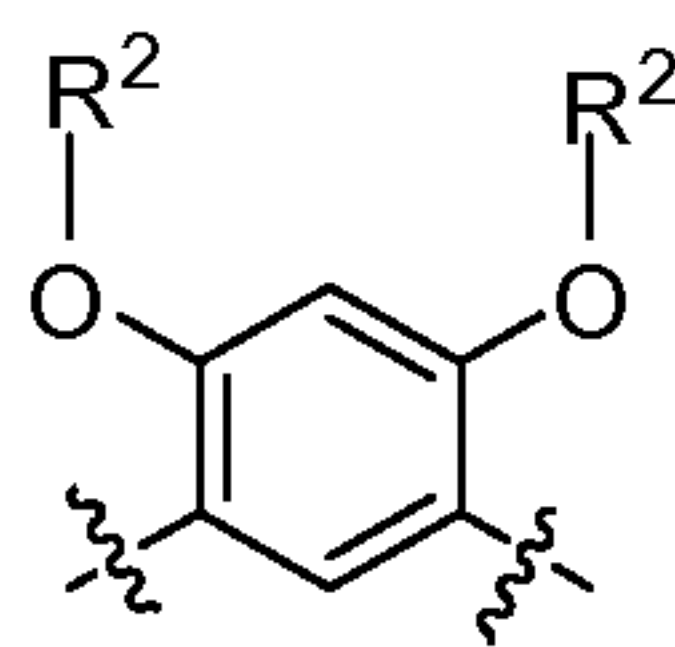
In any of the above embodiments, each R^3 is, independently, CF_3 , $C(CH_3)_3$, or halo; or each R^3 is CF_3 .

In any of the above embodiments, each R^4 is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; or each R^4 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 4.

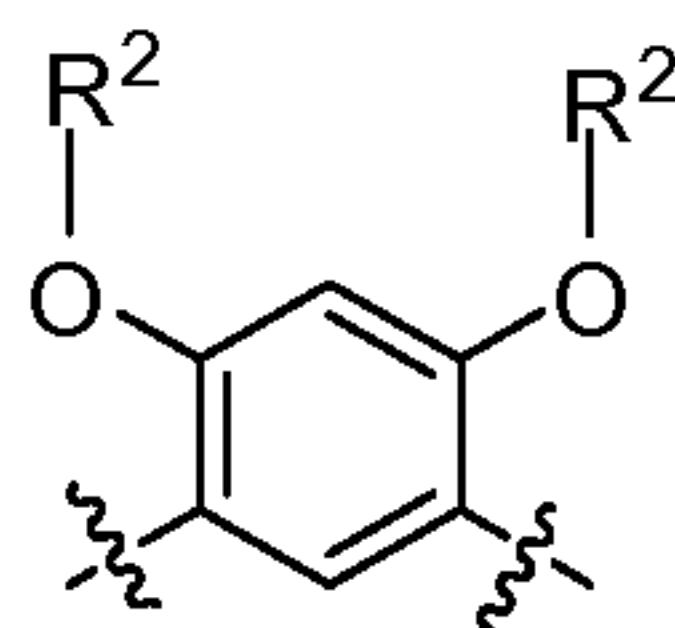


In some embodiments, G is ; each X is S; each R^1 is, independently, the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2; each R^2 is, independently, C_1 - C_8 alkyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2; each R^3 is, independently, CF_3 , $C(CH_3)_3$, or halo; and each R^4 is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 3 or 4.

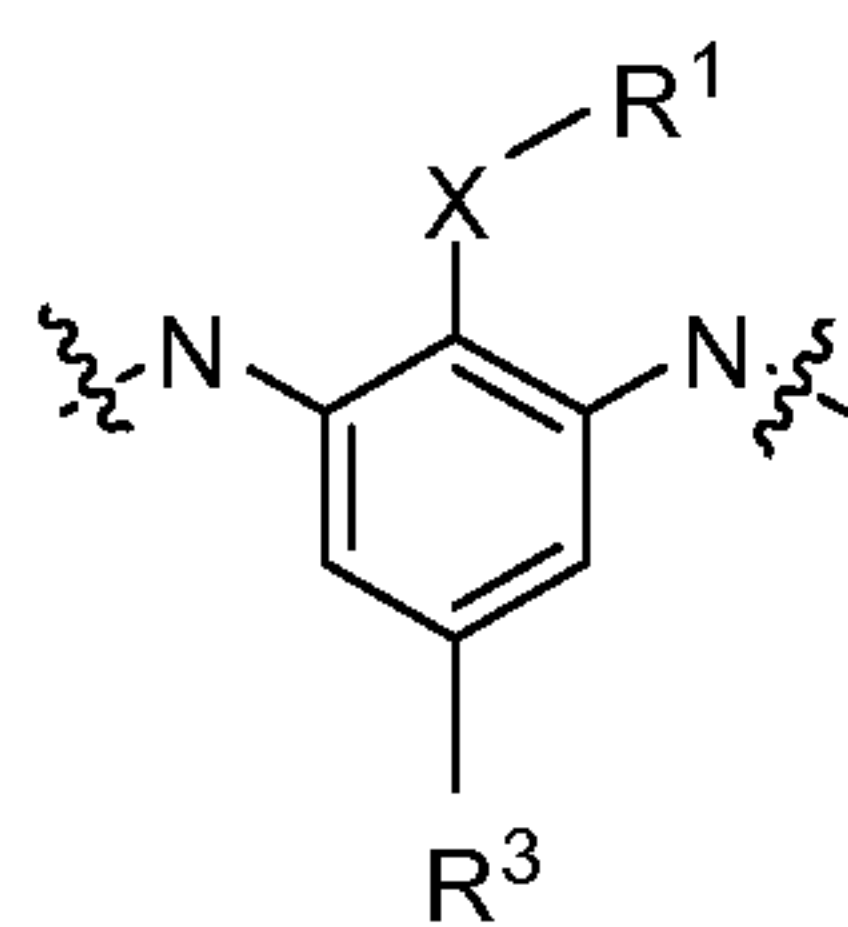


In some embodiments, G is ; each X is S; each R^1 is the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 1 or 2; each R^2 is, independently, C_1 - C_3 alkyl or the

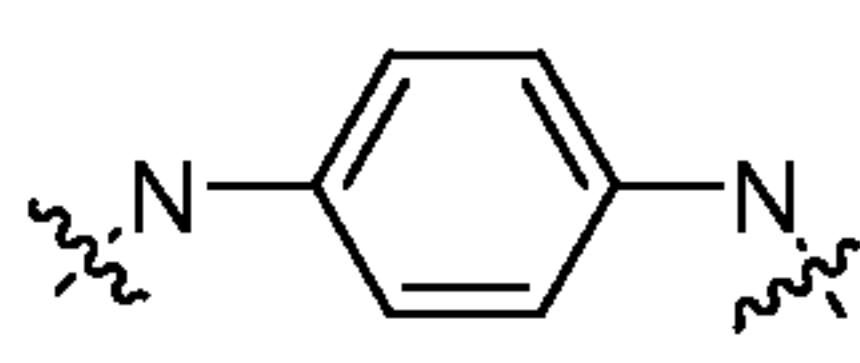
free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2; each R^3 is, independently, CF_3 or $C(CH_3)_3$; and each R^4 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 3 or 4.

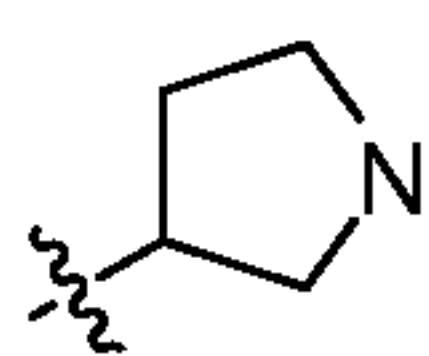


In some embodiments, G is ; each X is S ; each R^1 is the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2; each R^2 is, independently, methyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2; each R^3 is, independently, CF_3 or $C(CH_3)_3$; and each R^4 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 4.

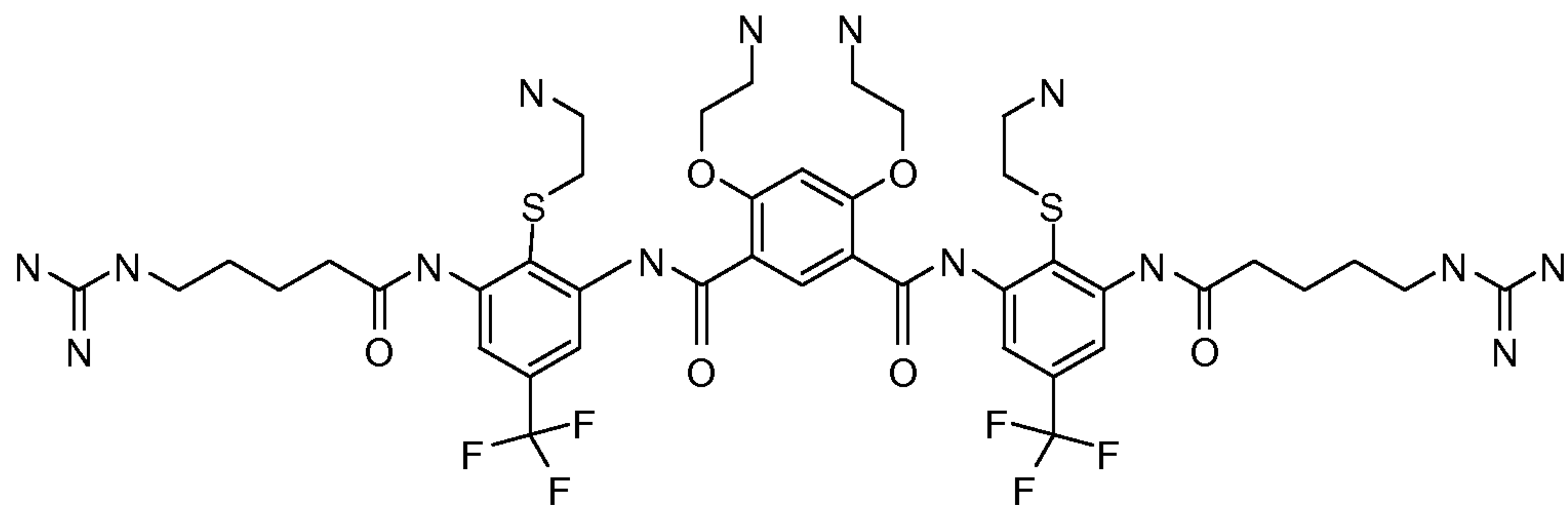


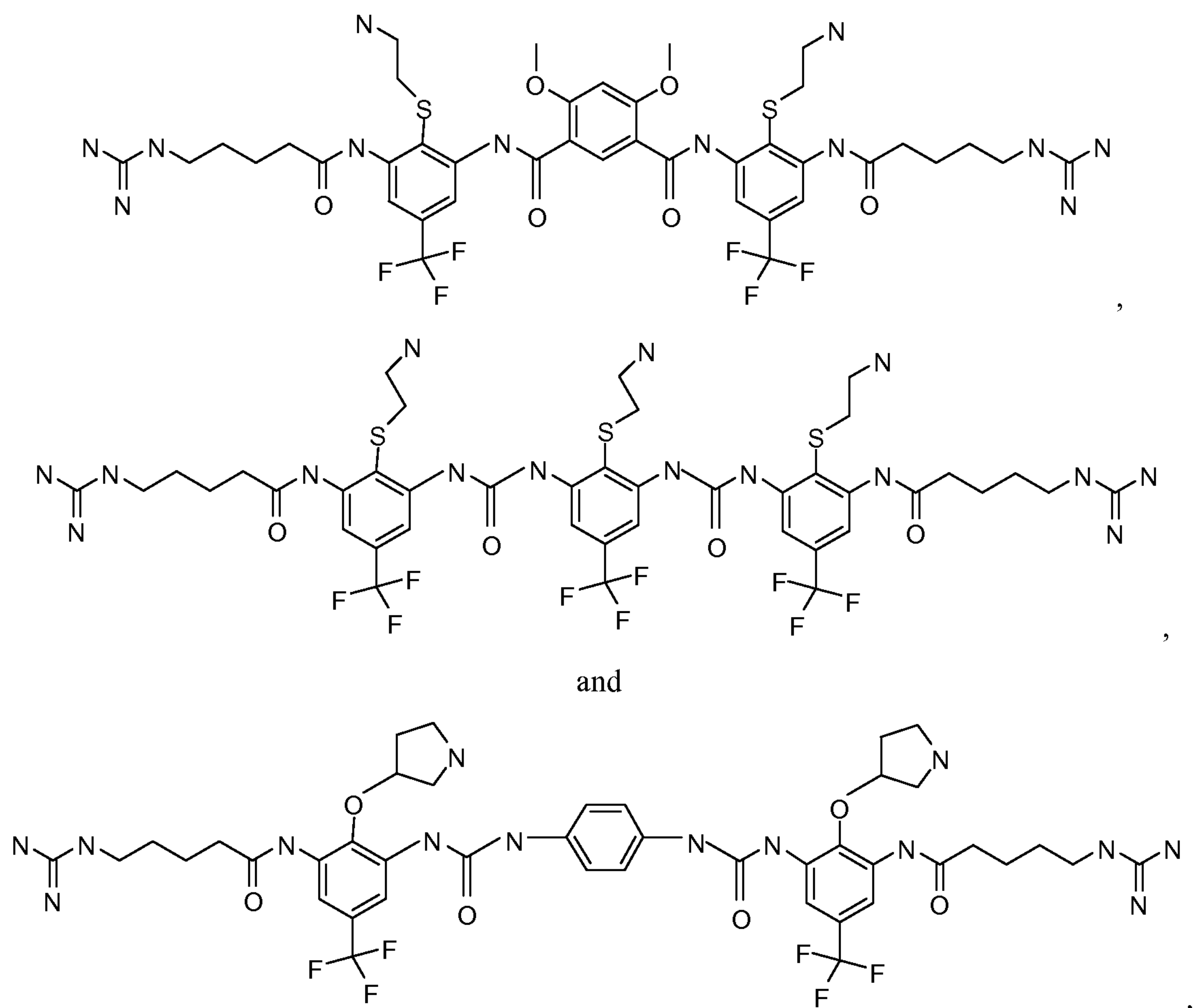
In some embodiments, G is ; each X is, independently, O or S ; each R^1 is, independently, the free base or salt form of $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; each R^3 is, independently, H or CF_3 ; and each R^4 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

In some embodiments, G is ; each X is, independently, O or S ;

each R^1 is ; each R^3 is, independently, H or CF_3 ; and each R^4 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

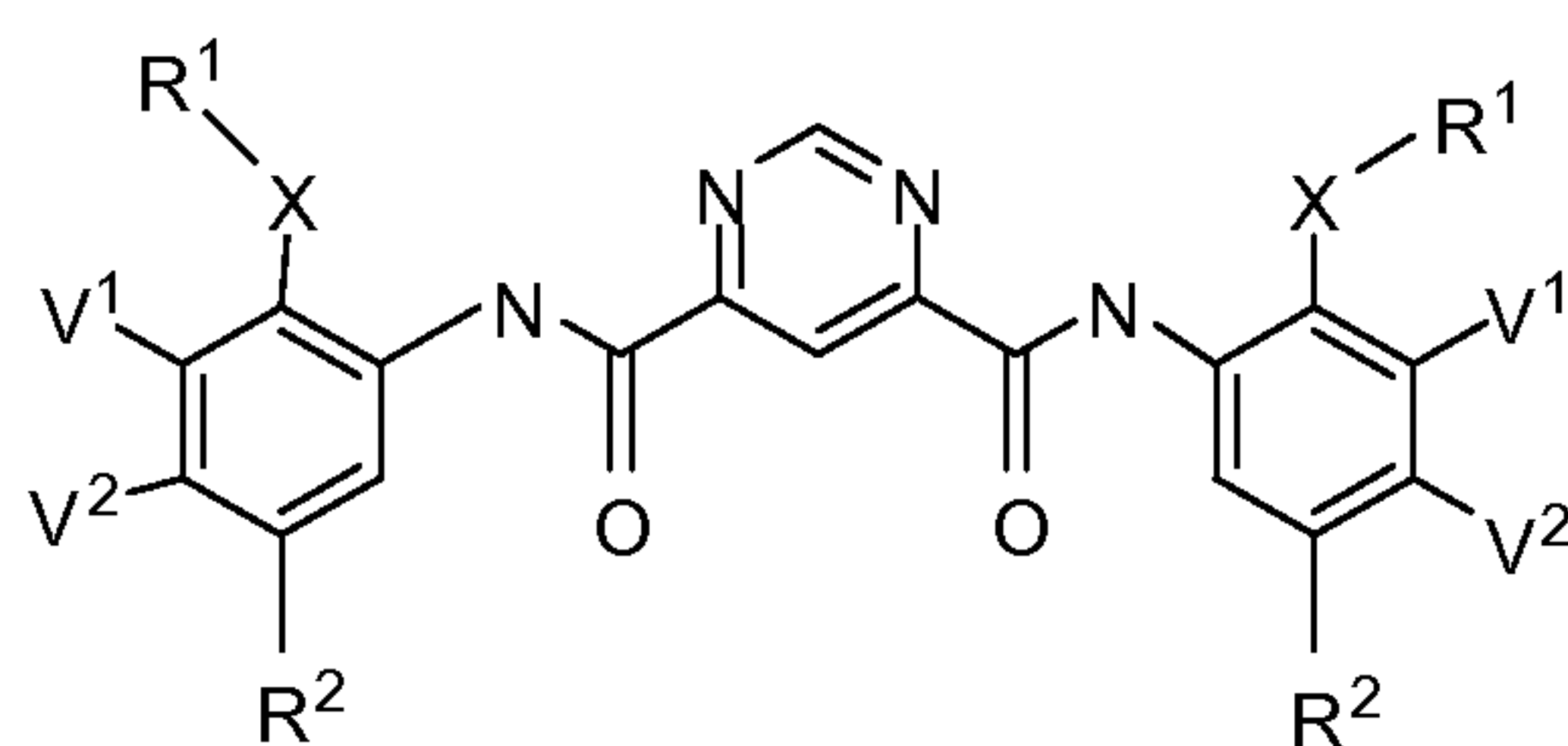
In some embodiments, the compound is chosen from:





5 or a pharmaceutically acceptable salt thereof.

The present invention also provides compounds of Formula V:



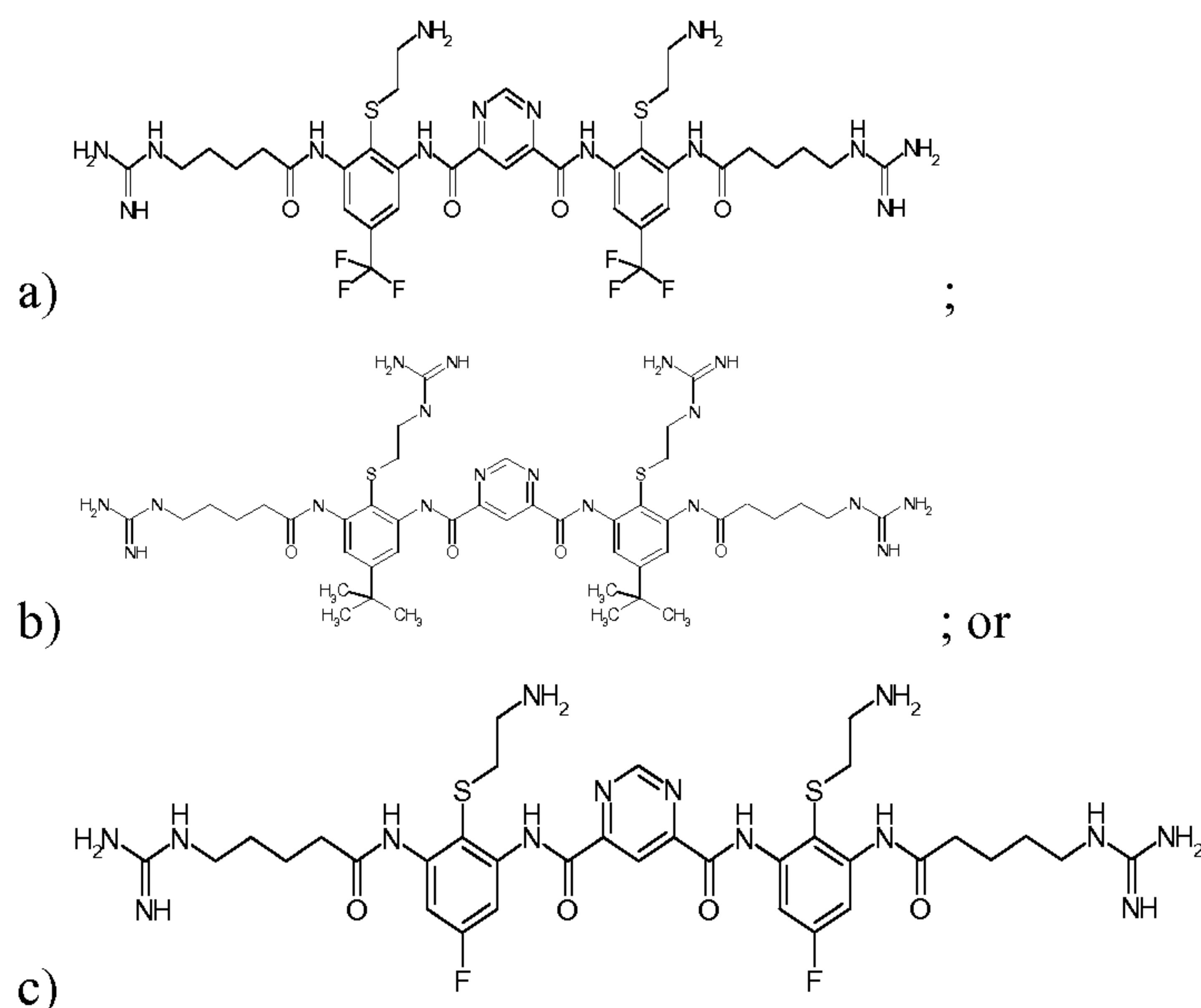
wherein:

- each X is, independently, O, S, or S(=O)₂;
- 10 each R¹ is, independently, -(CH₂)_n-NH₂, -(CH₂)_n-NH-C(=NH)NH₂, or -(CH₂)_n-NH-C(=O)-R⁴, where each n is, independently, 1 to 4, and each R⁴ is, independently, H, C₁-C₃alkyl, or -(CH₂)_p-NH₂, where each p is, independently, 1 or 2;
- each R² is, independently, H, halo, CF₃, or C(CH₃)₃; and

each V^2 is H, and each V^1 is, independently, $-N-C(=O)-R^3$, where each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; or each V^1 is H and each V^2 is, independently, $-S-R^5$, where each R^5 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;

5 or a pharmaceutically acceptable salt thereof;

provided that the compound is not:



10 In some embodiments, each X is S.

In any of the above embodiments, each R^1 is, independently, $-(CH_2)_n-NH_2$, $-(CH_2)_n-NH-C(=NH)NH_2$, or $-(CH_2)_n-NH-C(=O)-R^4$, where each n is, independently, 1 or 2, and each R^4 is, independently, H or methyl; or each R^1 is, independently, $-(CH_2)_n-NH_2$, $-(CH_2)_n-NH-C(=NH)NH_2$, or $-(CH_2)_n-NH-C(=O)-R^4$, where each n is 2 and each R^4 is H; or

15 each R^1 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 2; or each R^1 is $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 2.

In any of the above embodiments, each R^2 is, independently, H, Br, F, Cl, CF_3 , or $C(CH_3)_3$; or each R^2 is Br, F, Cl, CF_3 , or $C(CH_3)_3$.

In any of the above embodiments, each V^2 is H and each V^1 is, independently,

20 $-N-C(=O)-R^3$, where each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; or each V^2 is H and each V^1 is, independently, $-N-C(=O)-R^3$, where each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 or 2; or each V^2 is H and each V^1 is, independently,

-N-C(=O)-R³, where each R³ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is 2; or each V² is H and each V¹ is -N-C(=O)-R³, where each R³ is -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where n is 2.

In any of the above embodiments, each V¹ is H and each V² is, independently,
 5 -S-R⁵, where each R⁵ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4; or each V¹ is H and each V² is, independently, -S-R⁵, where each R⁵ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is 1 or 2; or each V¹ is H and each V² is, independently, -S-R⁵, where each R⁵ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is 2; or each V¹ is H and each V² is
 10 -S-R⁵, where each R⁵ is -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is 2.

In some embodiments, each X is S; each R¹ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4; each R² is, independently, halo, CF₃, or C(CH₃)₃; and each V¹ is H and each V² is, independently, -S-R⁵, where each R⁵ is, independently, -(CH₂)_n-NH₂, where each n is, independently, 1 to 4.

15 In some embodiments, each X is S; each R¹ is, independently, -(CH₂)_n-NH₂, where each n is, independently, 1 or 2; each R² is, independently, CF₃ or C(CH₃)₃; and each V¹ is H and each V² is, independently, -S-R⁵, where each R⁵ is, independently, -(CH₂)_n-NH₂, where each n is, independently, 1 or 2.

In some embodiments, each X is S; each R¹ is -(CH₂)_n-NH₂, where each n is 1 or 2;
 20 each R² is, independently, CF₃ or C(CH₃)₃; and each V¹ is H and each V² is -S-R⁵, where each R⁵ is -(CH₂)_n-NH₂, where each n is 1 or 2.

In some embodiments, each X is O or S; each R¹ is, independently, -(CH₂)_n-NH₂, or -(CH₂)_n-NH-C(=NH)NH₂, or -(CH₂)_n-NH-C(=O)-R⁴, where each n is, independently, 1 to 4, and each R⁴ is, independently, H or methyl; each R² is, independently, halo, CF₃, or C(CH₃)₃;
 25 and each V² is H, and each V¹ is, independently, -N-C(=O)-R³, where each R³ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4.

In some embodiments, each X is S; each R¹ is, independently, -(CH₂)_n-NH-C(=O)-R⁴, where each n is, independently, 1 or 2, and each R⁴ is, independently,
 30 H or methyl; each R² is, independently, halo; and each V² is H, and each V¹ is -N-C(=O)-R³, where each R³ is -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is 4.

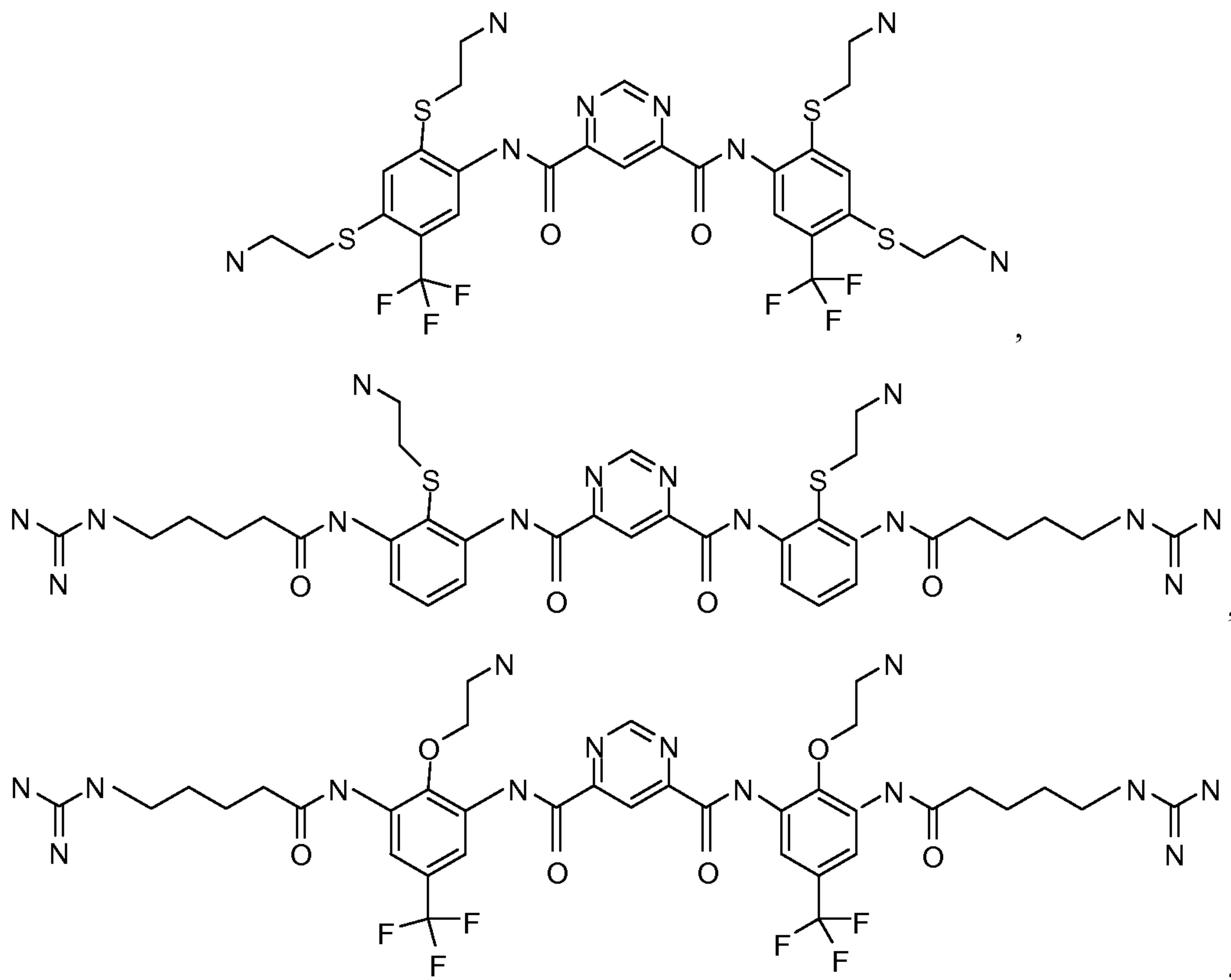
In some embodiments, each X is O or S; each R¹ is, independently, -(CH₂)_n-NH₂ or

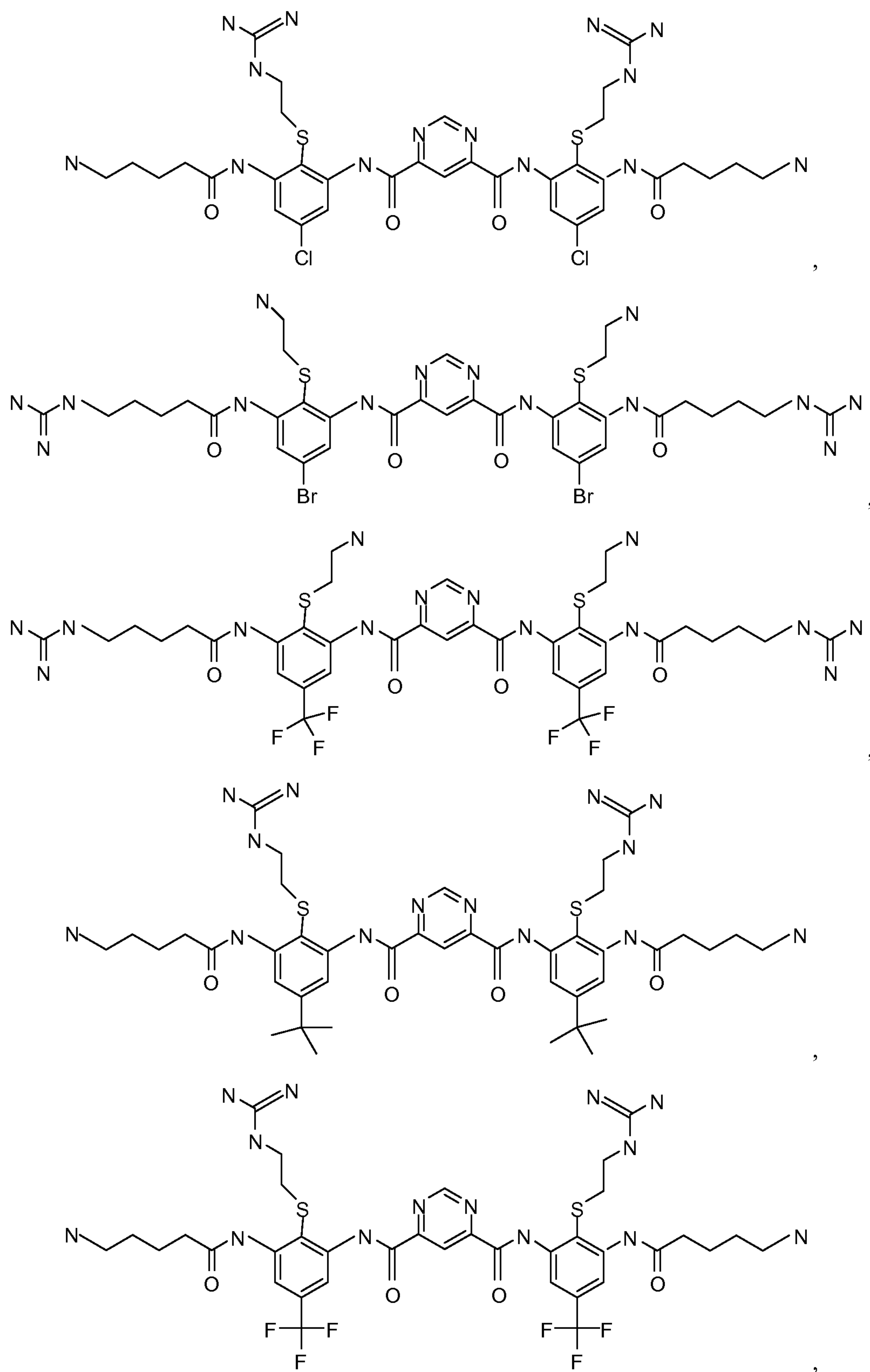
$-(\text{CH}_2)_n\text{-NH-C(=NH)NH}_2$, where each n is, independently, 1 to 4; each R^2 is, independently, halo, CF_3 , or $\text{C(CH}_3)_3$; and each V^2 is H, and each V^1 is, independently, $-\text{N-C(=O)-R}^3$, where each R^3 is, independently, $-(\text{CH}_2)_n\text{-NH}_2$ or $-(\text{CH}_2)_n\text{-NH-C(=NH)NH}_2$, where each n is, independently, 1 to 4.

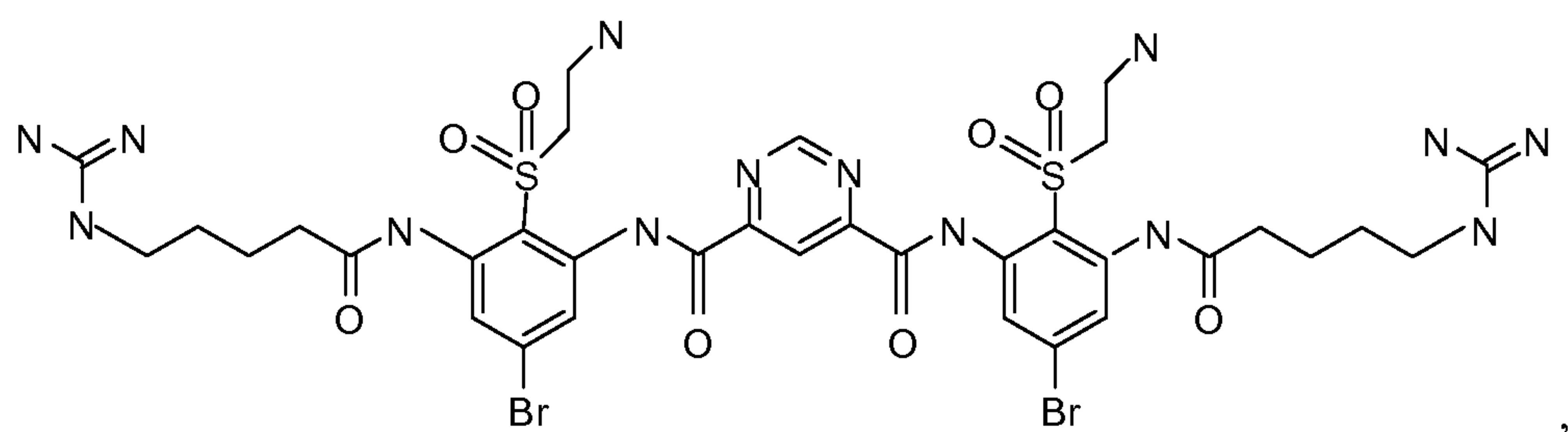
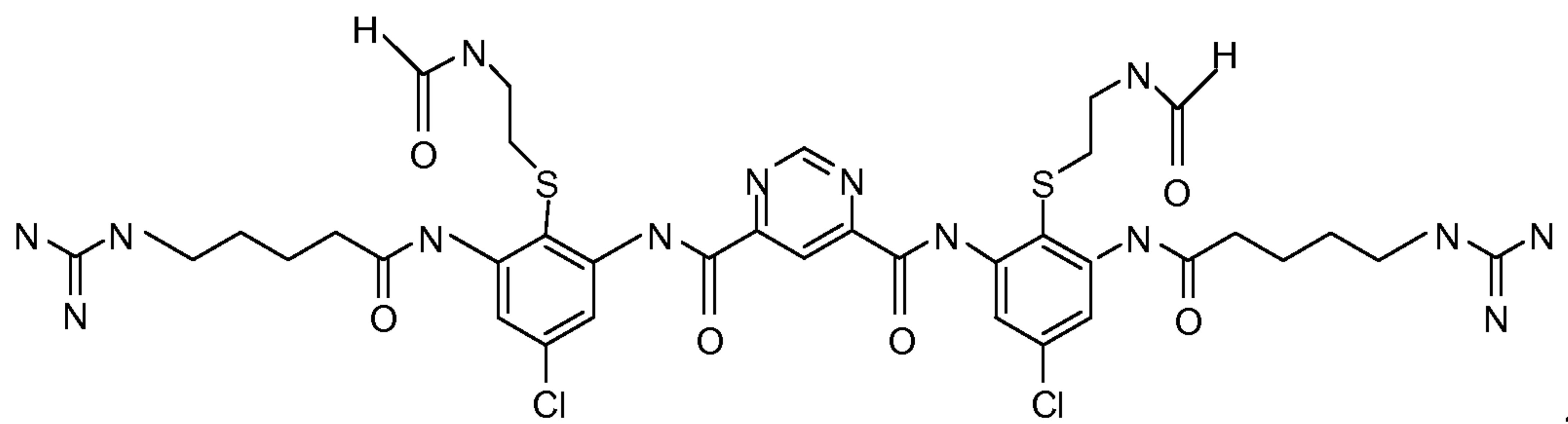
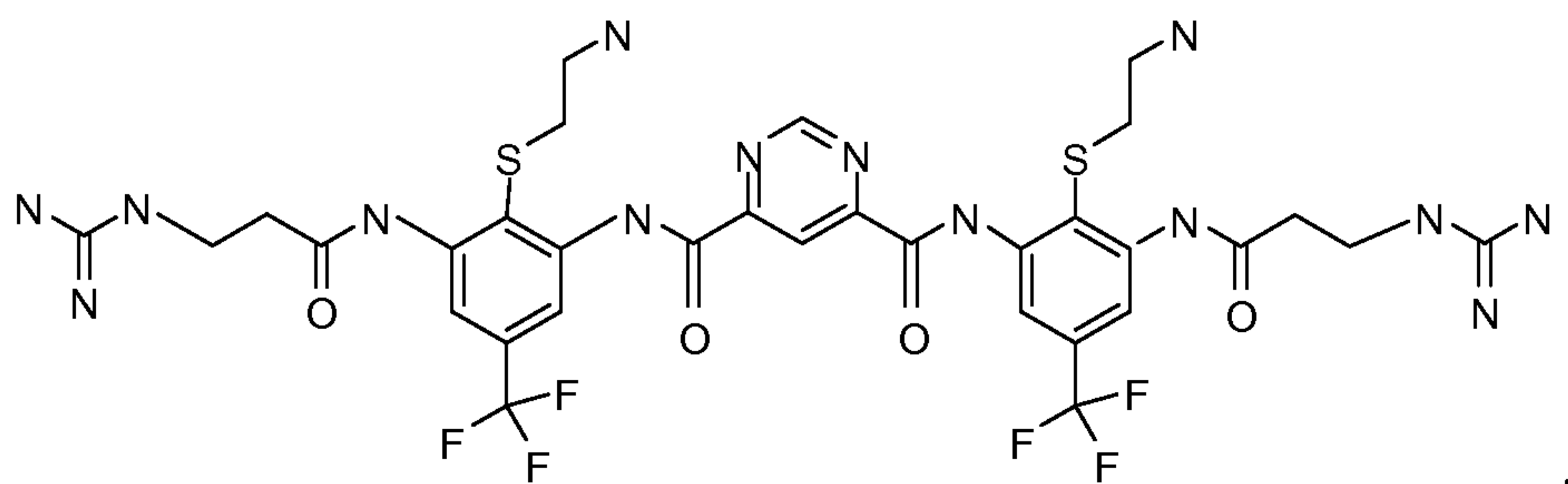
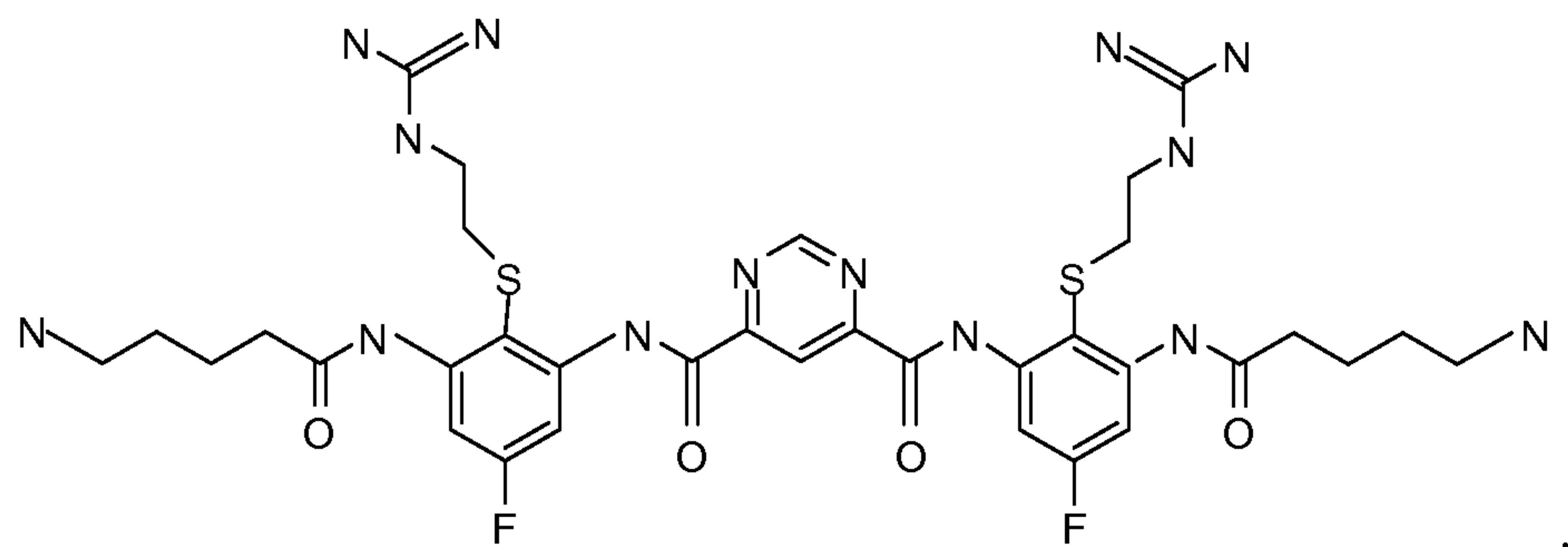
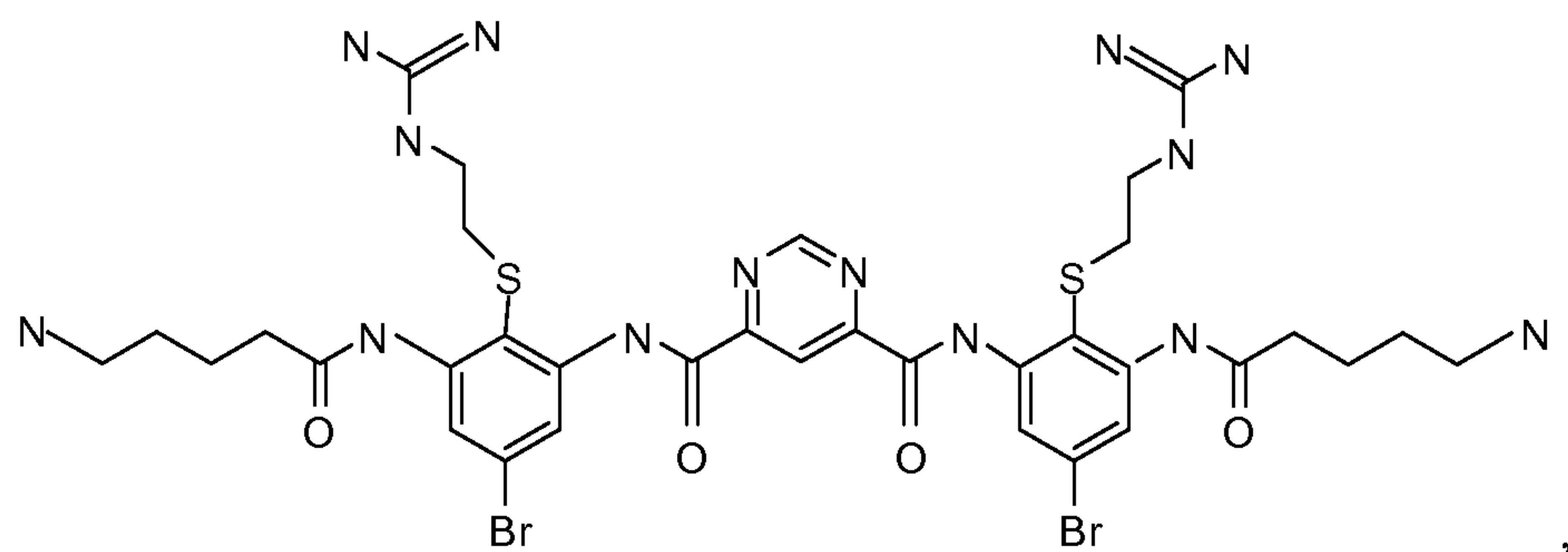
- 5 In some embodiments, each X is O or S; each R^1 is $-(\text{CH}_2)_n\text{-NH}_2$ or $-(\text{CH}_2)_n\text{-NH-C(=NH)NH}_2$, where each n is 1 or 2; each R^2 is halo, CF_3 , or $\text{C(CH}_3)_3$; and each V^2 is H, and each V^1 is $-\text{N-C(=O)-R}^3$, where each R^3 is $-(\text{CH}_2)_n\text{-NH}_2$ or $-(\text{CH}_2)_n\text{-NH-C(=NH)NH}_2$, where each n is 3 or 4.

- 10 In some embodiments, each X is, independently, S or S(=O)_2 ; each R^1 is, independently, $-(\text{CH}_2)_n\text{-NH}_2$ or $-(\text{CH}_2)_n\text{-NH-C(=O)-R}^4$, where each n is, independently, 1 or 2, and each R^4 is, independently, $-(\text{CH}_2)_p\text{-NH}_2$, where each p is, independently, 1 or 2; each R^2 is, independently, halo or CF_3 ; and each V^2 is H, and each V^1 is, independently, $-\text{N-C(=O)-R}^3$, where each R^3 is, independently, $-(\text{CH}_2)_n\text{-NH}_2$ or $-(\text{CH}_2)_n\text{-NH-C(=NH)NH}_2$, where each n is, independently, 3 or 4.

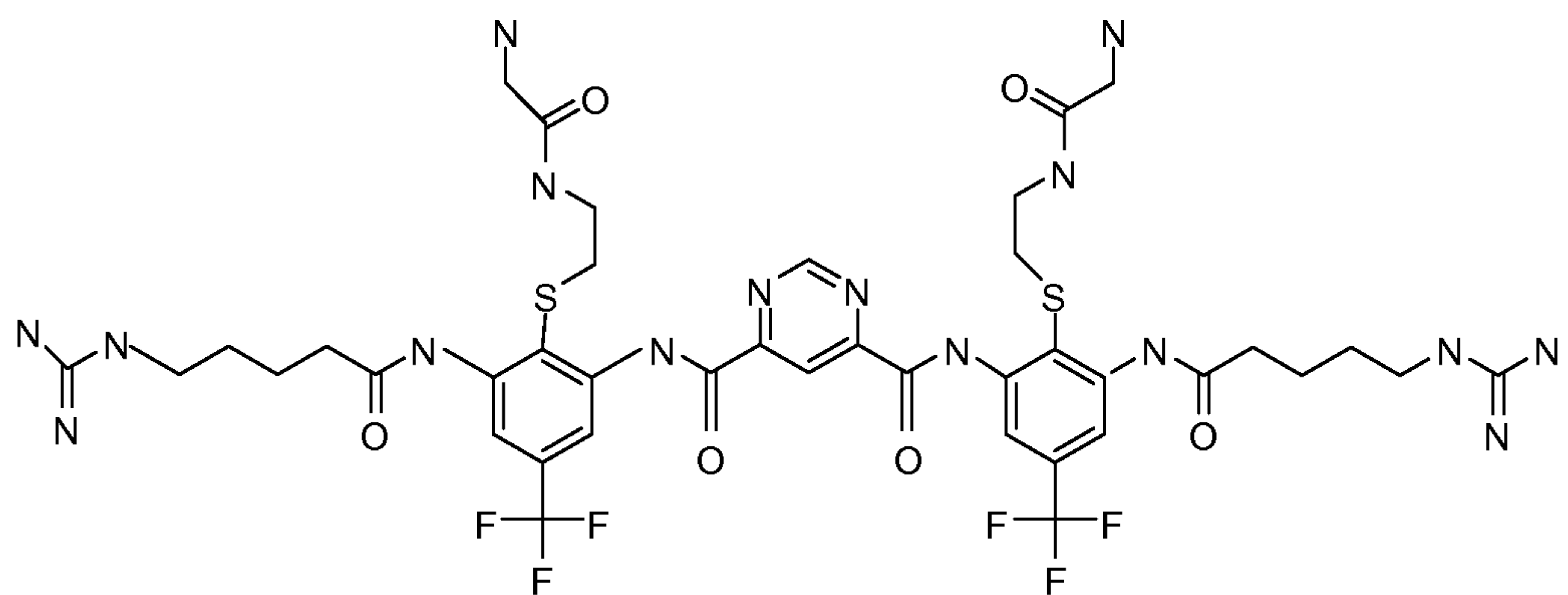
- 15 In some embodiments, the compound is chosen from:







and

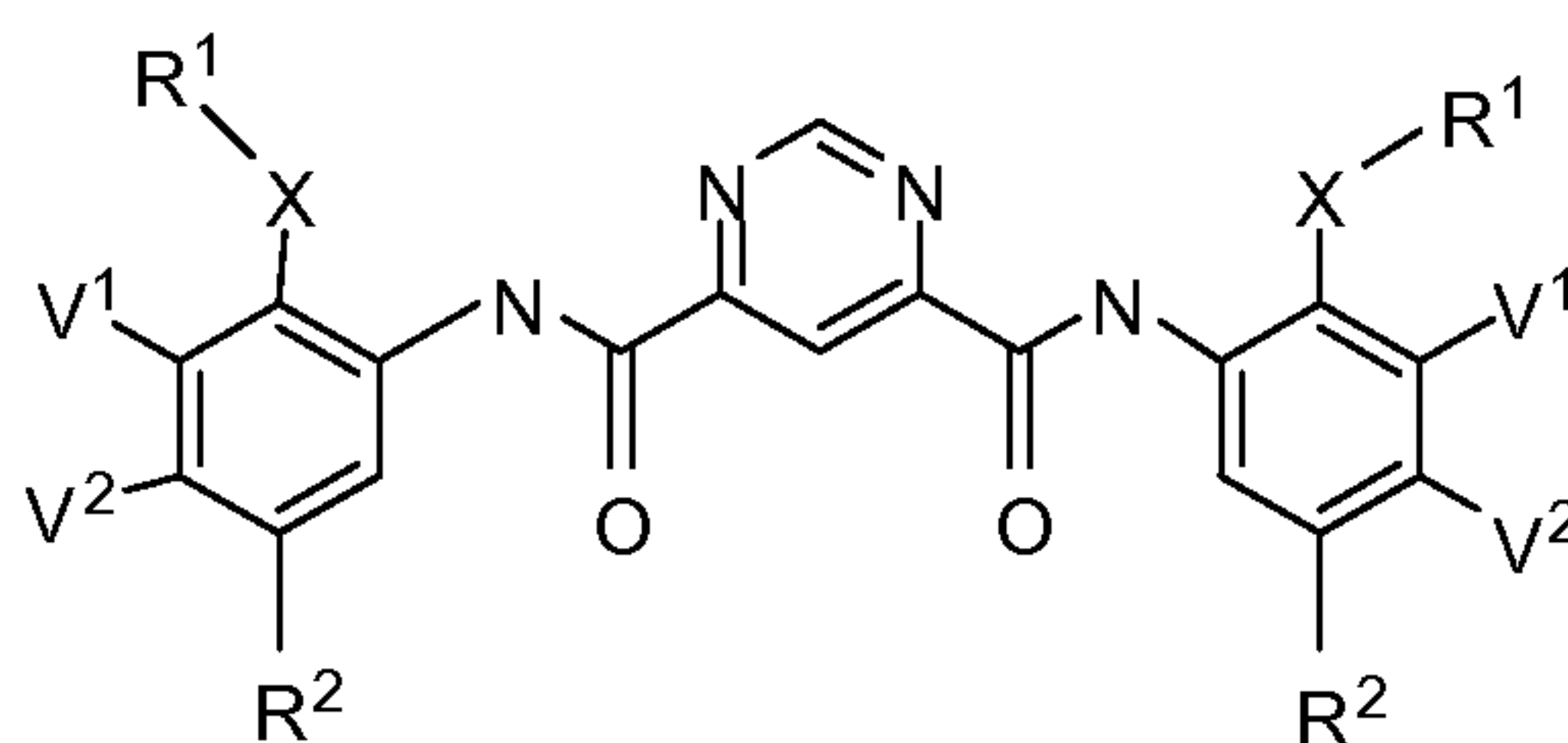


or a pharmaceutically acceptable salt thereof.

In some embodiments, any one or more of the above compounds may be excluded from any of the genus of compounds described above.

5 The present invention also provides compositions comprising one or more of the compounds or salts described above and a pharmaceutically acceptable carrier.

The present invention also provides methods of treating malaria in an animal comprising administering to the animal a therapeutically effective amount of a compound of Formula V:



10

wherein:

each X is, independently, O, S, or S(=O)₂;

each R¹ is, independently, -(CH₂)_n-NH₂, -(CH₂)_n-NH-C(=NH)NH₂, or -(CH₂)_n-NH-C(=O)-R⁴, where each n is, independently, 1 to 4, and each R⁴ is, independently,

15 H, C₁-C₃alkyl, or -(CH₂)_p-NH₂, where each p is, independently, 1 or 2;

each R² is, independently, H, halo, CF₃, or C(CH₃)₃; and

each V² is H, and each V¹ is, independently, -N-C(=O)-R³, where each R³ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4; or each V¹ is H and each V² is, independently, -S-R⁵, where each R⁵ is, independently,

20 -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4;

or a pharmaceutically acceptable salt thereof.

In some embodiments, each X is S.

In any of the above embodiments, each R^1 is, independently, $-(CH_2)_n-NH_2$, $-(CH_2)_n-NH-C(=NH)NH_2$, or $-(CH_2)_n-NH-C(=O)-R^4$, where each n is, independently, 1 or 2, and each R^4 is, independently, H or methyl; or each R^1 is, independently, $-(CH_2)_n-NH_2$, $-(CH_2)_n-NH-C(=NH)NH_2$, or $-(CH_2)_n-NH-C(=O)-R^4$, where each n is 2 and each R^4 is H; or
 5 each R^1 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 2; or each R^1 is $-(CH_2)_n-NH_2$ or, where each n is 2.

In any of the above embodiments, each R^2 is, independently, H, Br, F, Cl, CF_3 , or $C(CH_3)_3$; or each R^2 is Br, F, Cl, CF_3 , or $C(CH_3)_3$.

In any of the above embodiments, each V^2 is H and each V^1 is, independently,
 10 $-N-C(=O)-R^3$, where each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; or each V^2 is H and each V^1 is, independently, $-N-C(=O)-R^3$, where each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 or 2; or each V^2 is H and each V^1 is, independently, $-N-C(=O)-R^3$, where each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$,
 15 where each n is 2; or each V^2 is H and each V^1 is $-N-C(=O)-R^3$, where each R^3 is $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where n is 2.

In any of the above embodiments, each V^1 is H and each V^2 is, independently, $-S-R^5$, where each R^5 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; or each V^1 is H and each V^2 is, independently, $-S-R^5$, where
 20 each R^5 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 or 2; or each V^1 is H and each V^2 is, independently, $-S-R^5$, where each R^5 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 2; or each V^1 is H and each V^2 is $-S-R^5$, where each R^5 is $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 2.

In some embodiments, each X is S; each R^1 is, independently, $-(CH_2)_n-NH_2$ or
 25 $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; each R^2 is, independently, halo, CF_3 , or $C(CH_3)_3$; and each V^1 is H and each V^2 is, independently, $-S-R^5$, where each R^5 is, independently, $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4.

In some embodiments, each X is S; each R^1 is, independently, $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2; each R^2 is, independently, CF_3 or $C(CH_3)_3$; and each V^1 is H
 30 and each V^2 is, independently, $-S-R^5$, where each R^5 is, independently, $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2.

In some embodiments, each X is S; each R^1 is $-(CH_2)_n-NH_2$, where each n is 1 or 2; each R^2 is, independently, CF_3 or $C(CH_3)_3$; and each V^1 is H and each V^2 is $-S-R^5$, where each R^5 is $-(CH_2)_n-NH_2$, where each n is 1 or 2.

In some embodiments, each X is O or S; each R^1 is, independently, $-(CH_2)_n-NH_2$, or
 5 $-(CH_2)_n-NH-C(=NH)NH_2$, or $-(CH_2)_n-NH-C(=O)-R^4$, where each n is, independently, 1 to 4, and each R^4 is, independently, H or methyl; each R^2 is, independently, halo, CF_3 , or $C(CH_3)_3$; and each V^2 is H, and each V^1 is, independently, $-N-C(=O)-R^3$, where each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

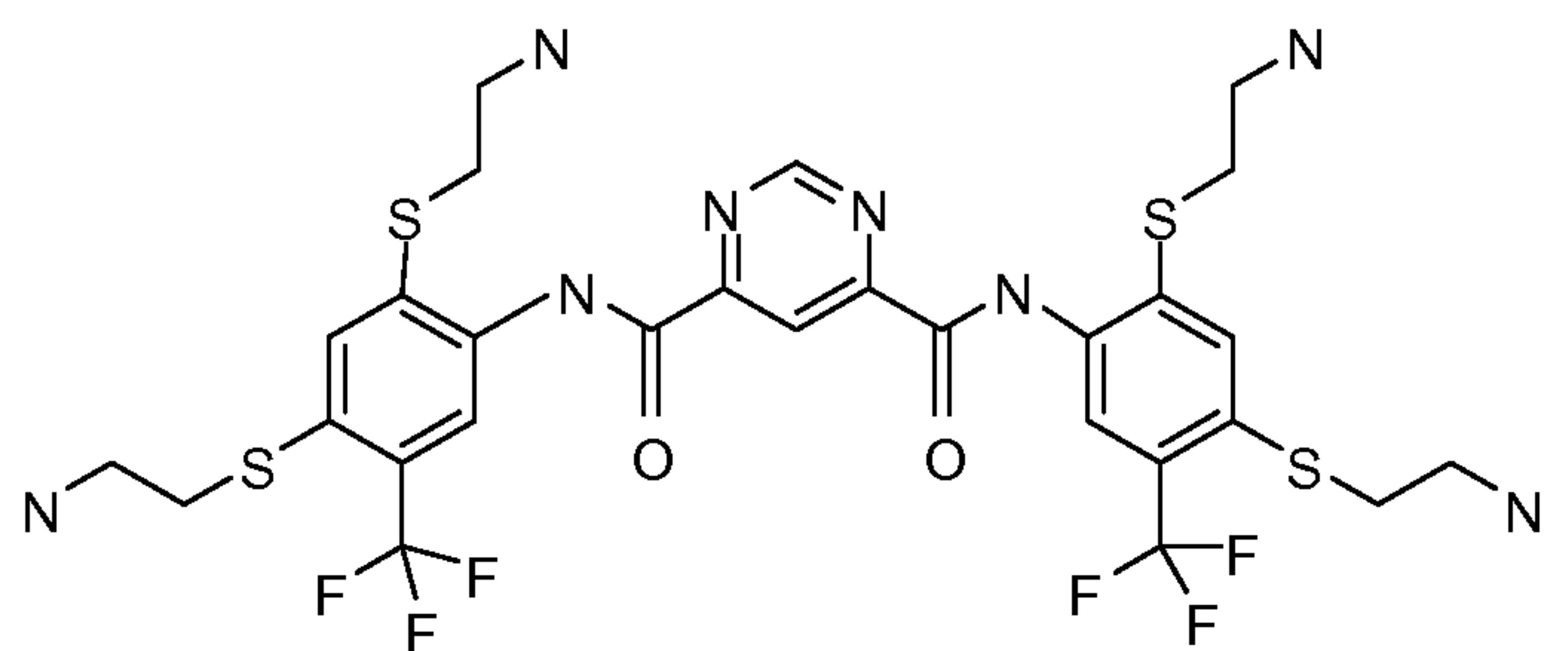
10 In some embodiments, each X is S; each R^1 is, independently, $-(CH_2)_n-NH-C(=O)-R^4$, where each n is, independently, 1 or 2, and each R^4 is, independently, H or methyl; each R^2 is, independently, halo; and each V^2 is H, and each V^1 is $-N-C(=O)-R^3$, where each R^3 is $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 4.

In some embodiments, each X is O or S; each R^1 is, independently, $-(CH_2)_n-NH_2$ or
 15 $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; each R^2 is, independently, halo, CF_3 , or $C(CH_3)_3$; and each V^2 is H, and each V^1 is, independently, $-N-C(=O)-R^3$, where each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

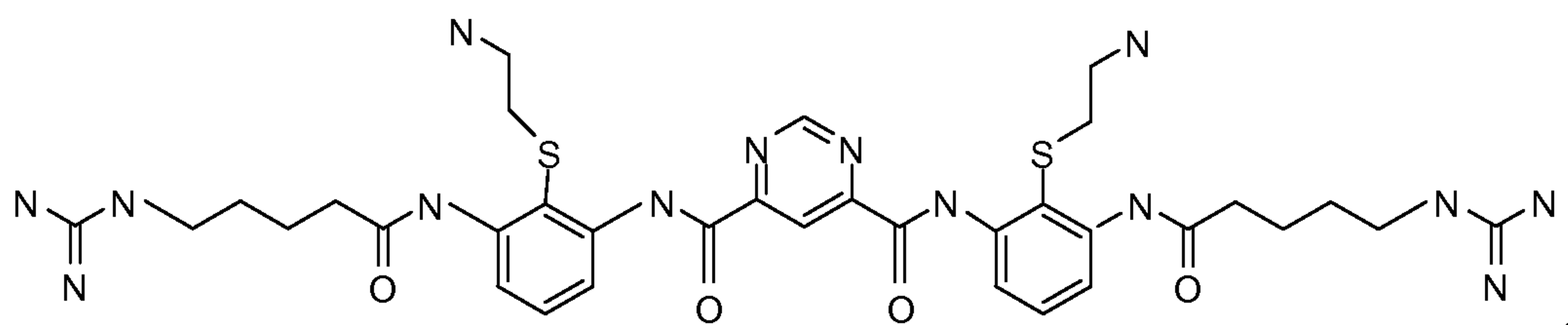
In some embodiments, each X is O or S; each R^1 is $-(CH_2)_n-NH_2$ or
 20 $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 or 2; each R^2 is halo, CF_3 , or $C(CH_3)_3$; and each V^2 is H, and each V^1 is $-N-C(=O)-R^3$, where each R^3 is $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 3 or 4.

In some embodiments, each X is, independently, S or $S(=O)_2$; each R^1 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=O)-R^4$, where each n is, independently, 1 or
 25 2, and each R^4 is, independently, $-(CH_2)_p-NH_2$, where each p is, independently, 1 or 2; each R^2 is, independently, halo or CF_3 ; and each V^2 is H, and each V^1 is, independently, $-N-C(=O)-R^3$, where each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 3 or 4.

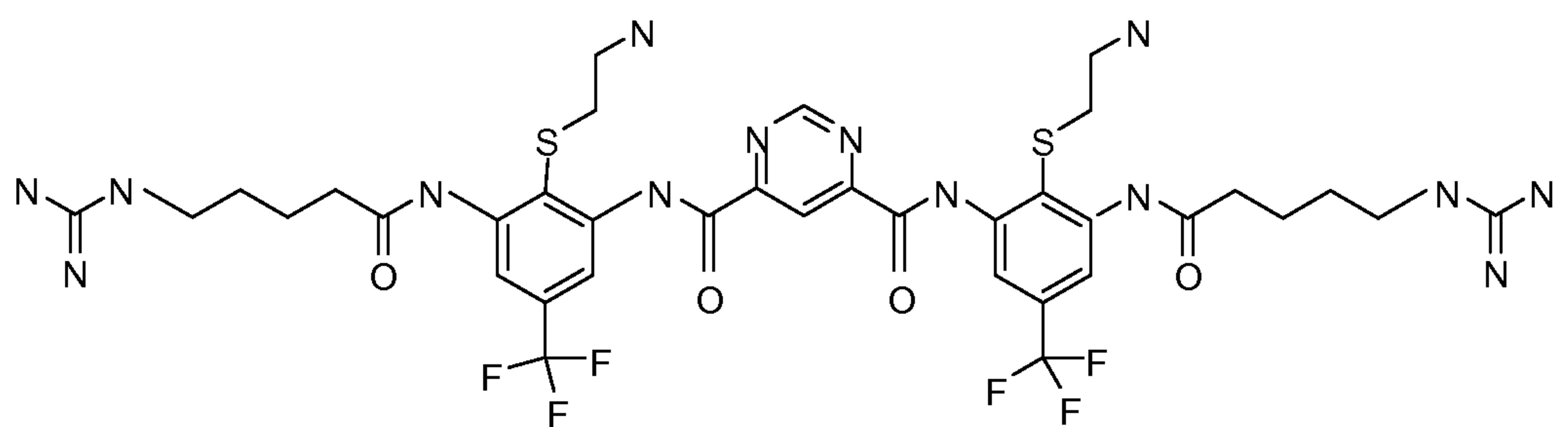
In some embodiments, the compound is chosen from:



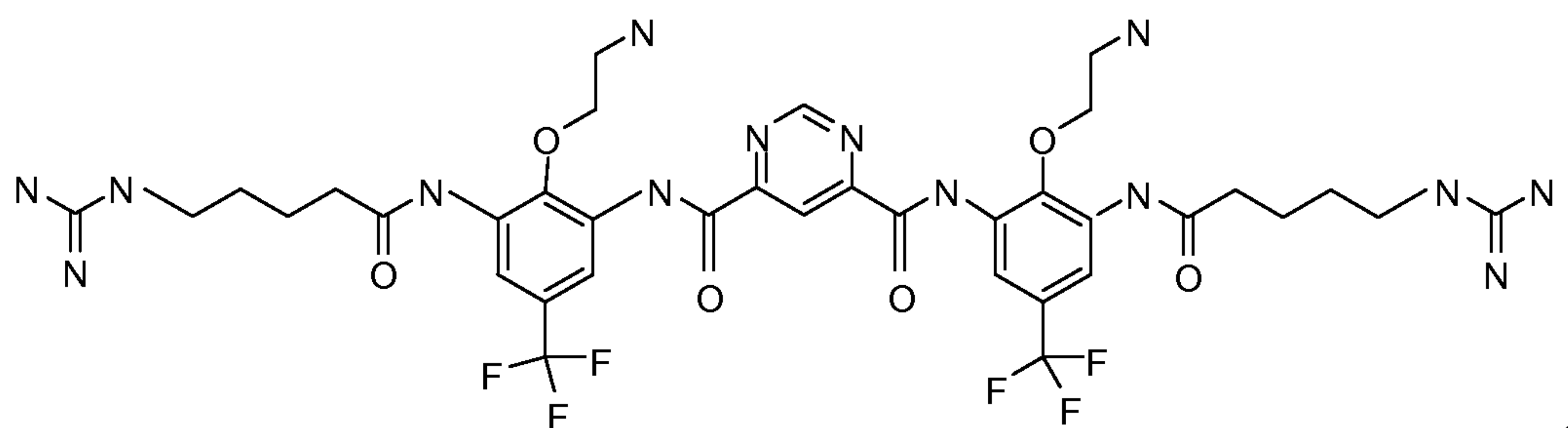
Compound 112



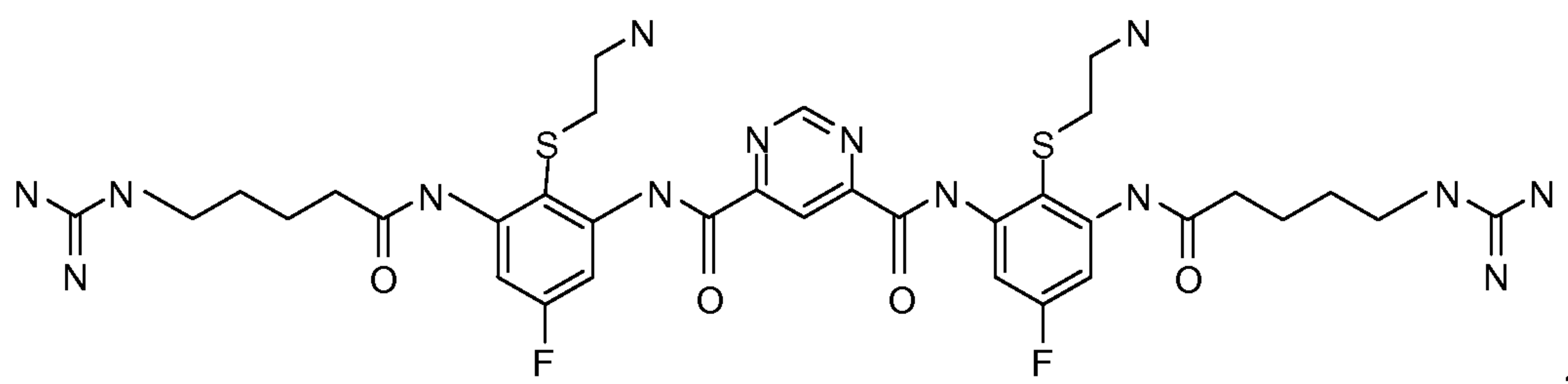
Compound 113



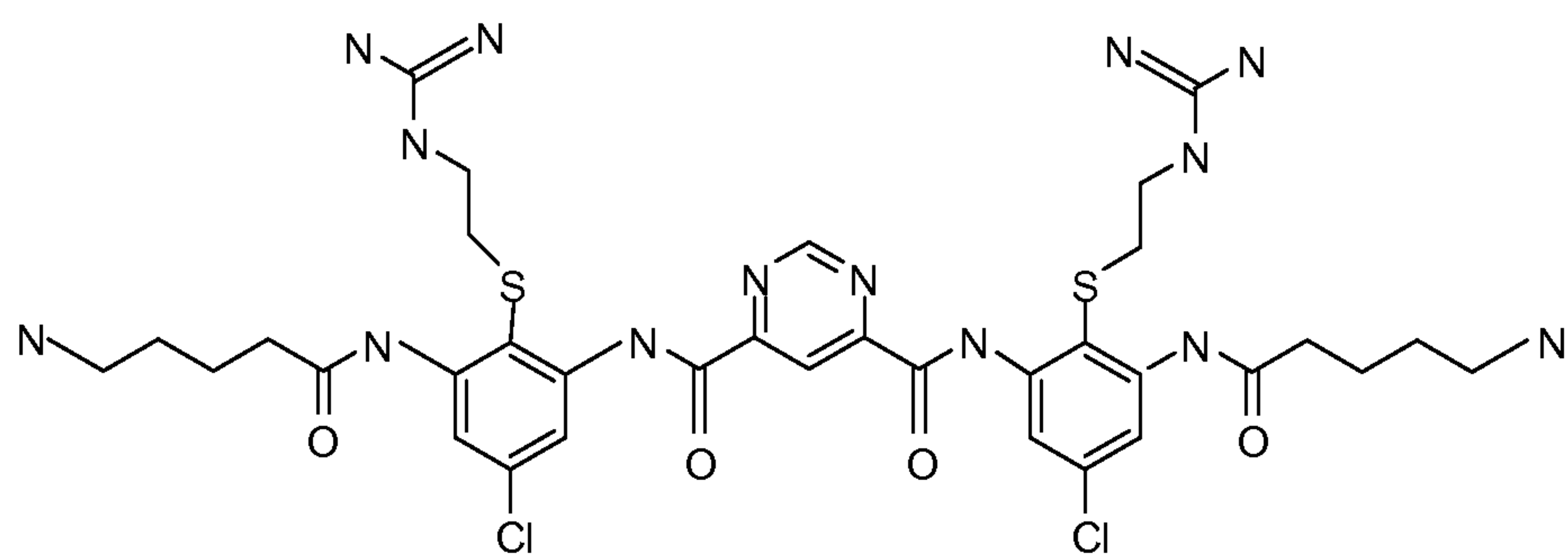
Compound 121



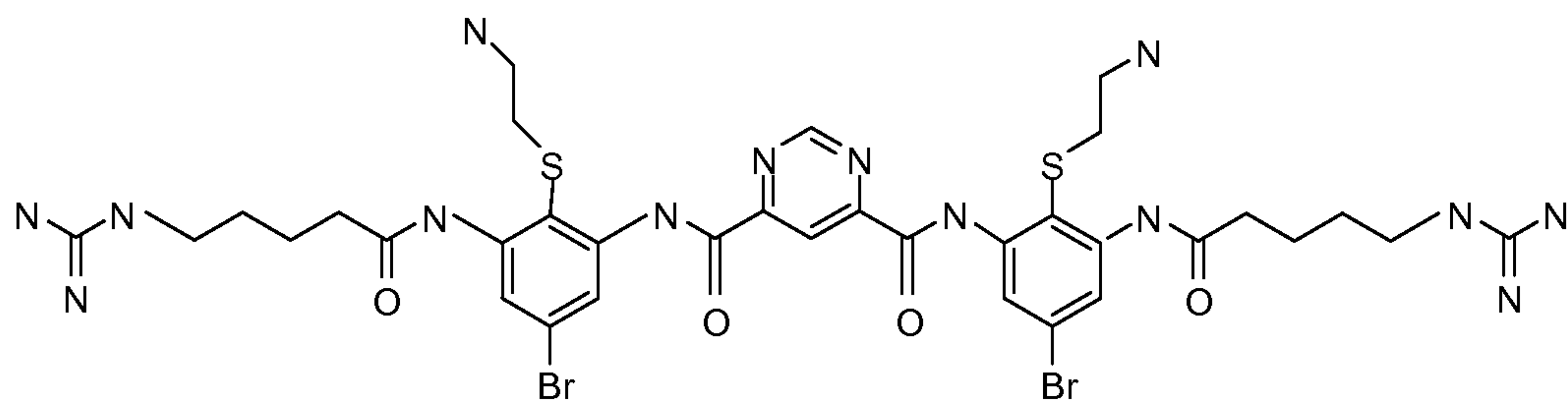
Compound 114



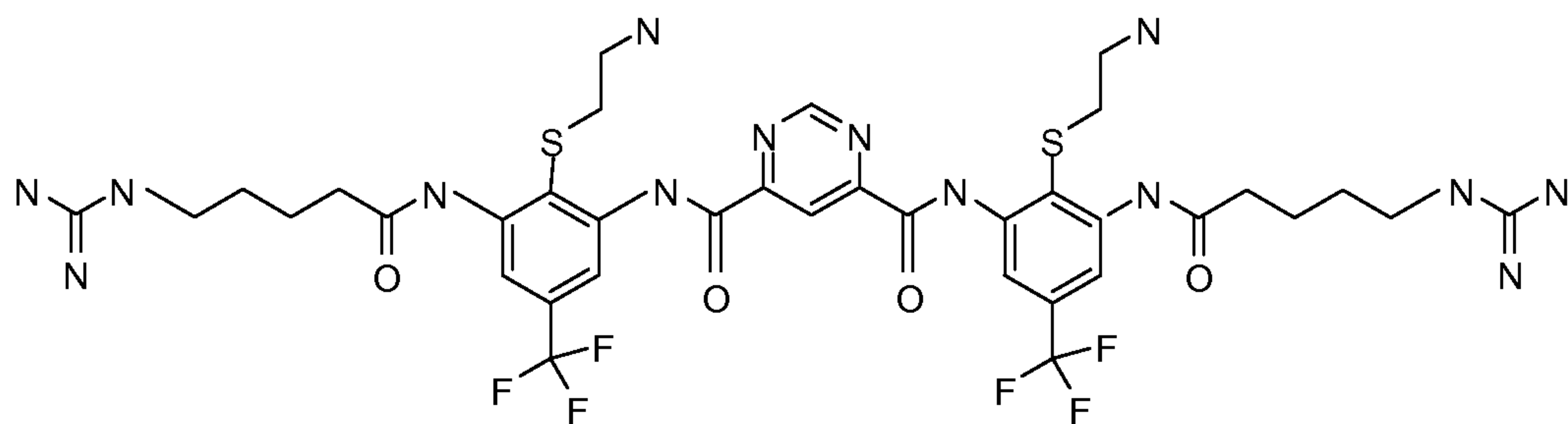
Compound 107



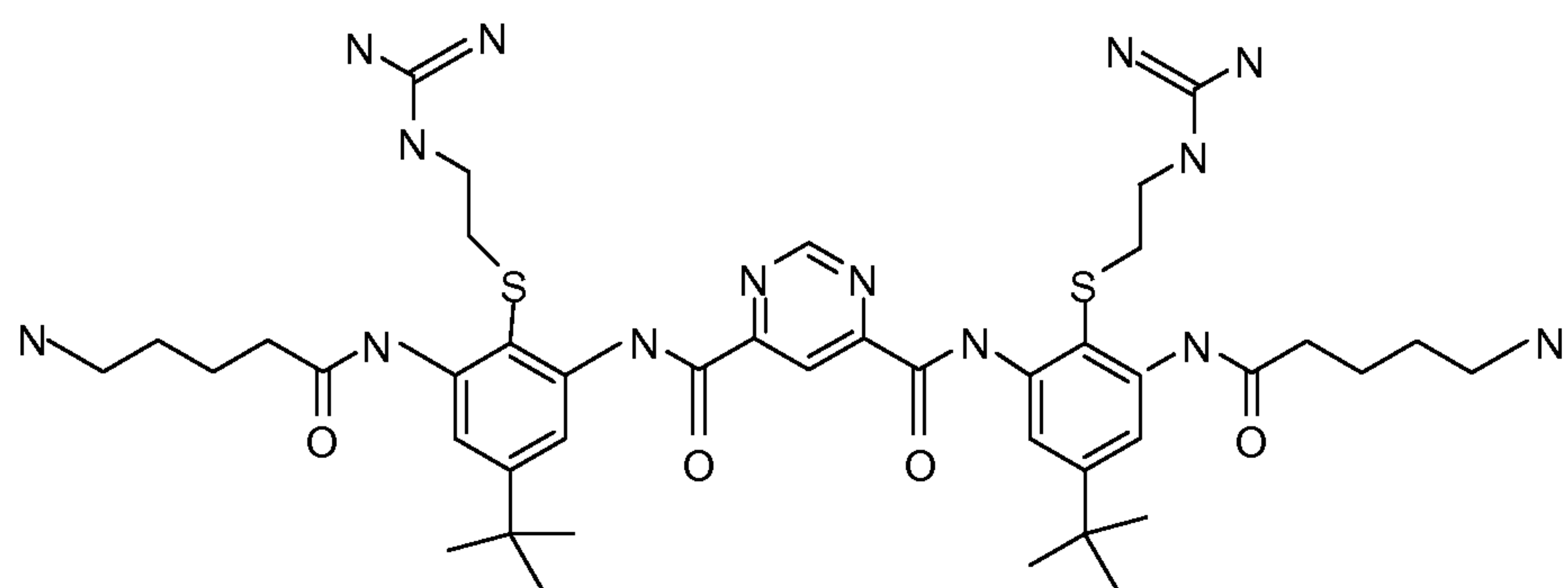
Compound 122



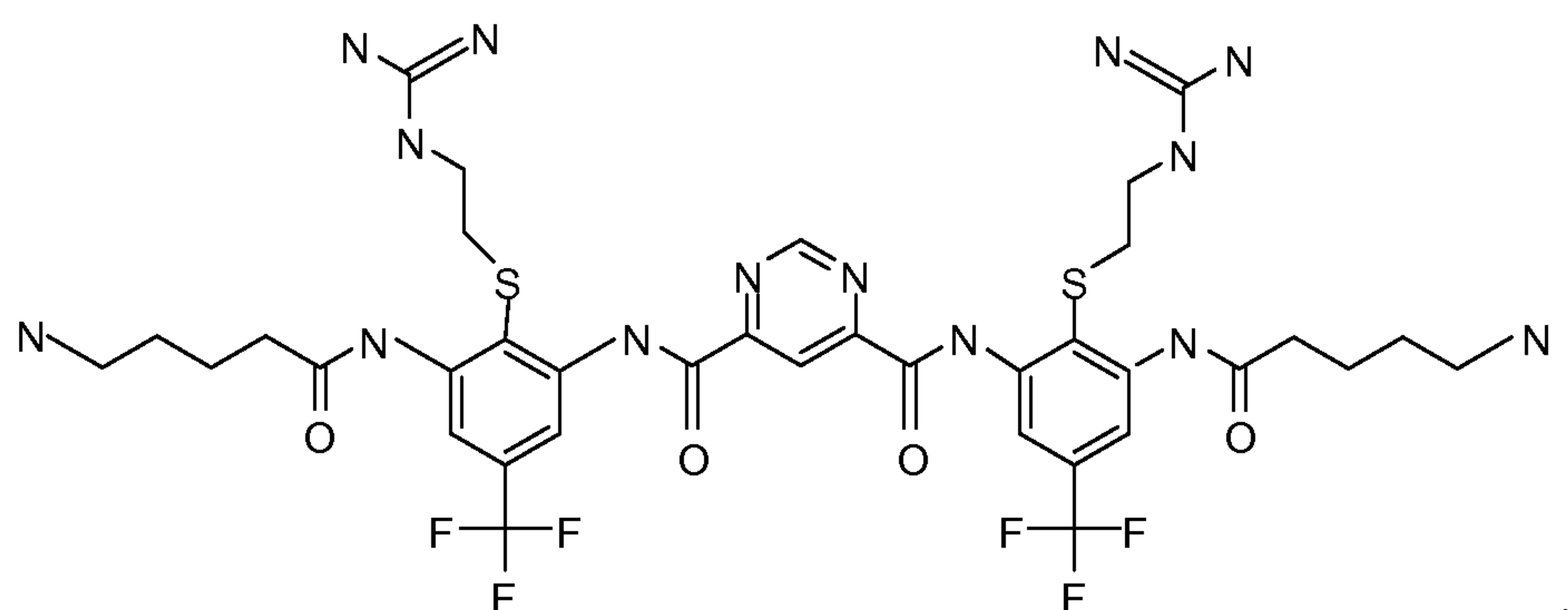
Compound 123



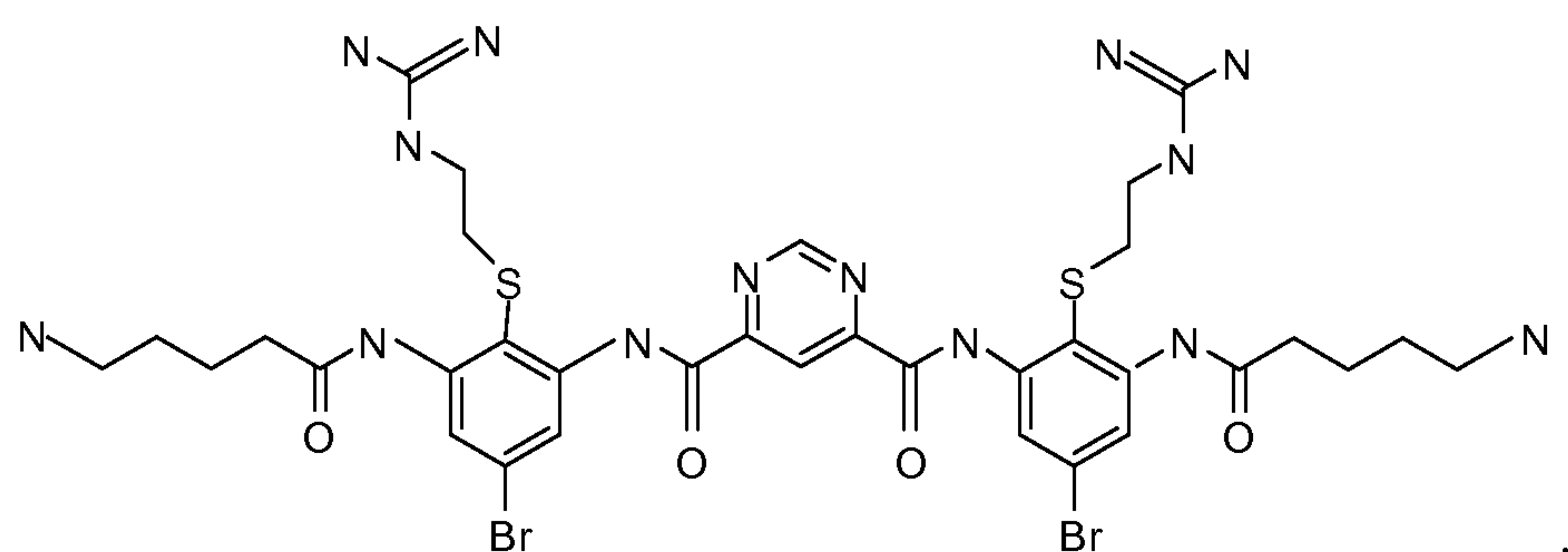
Compound 124



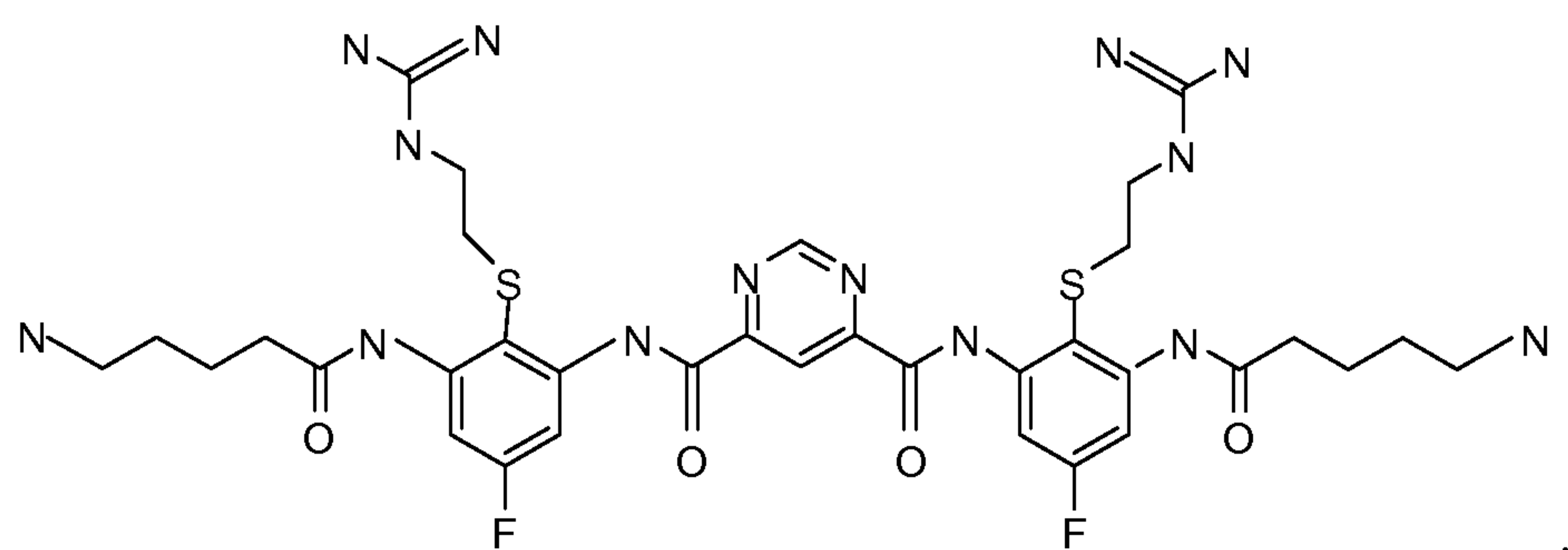
Compound 129



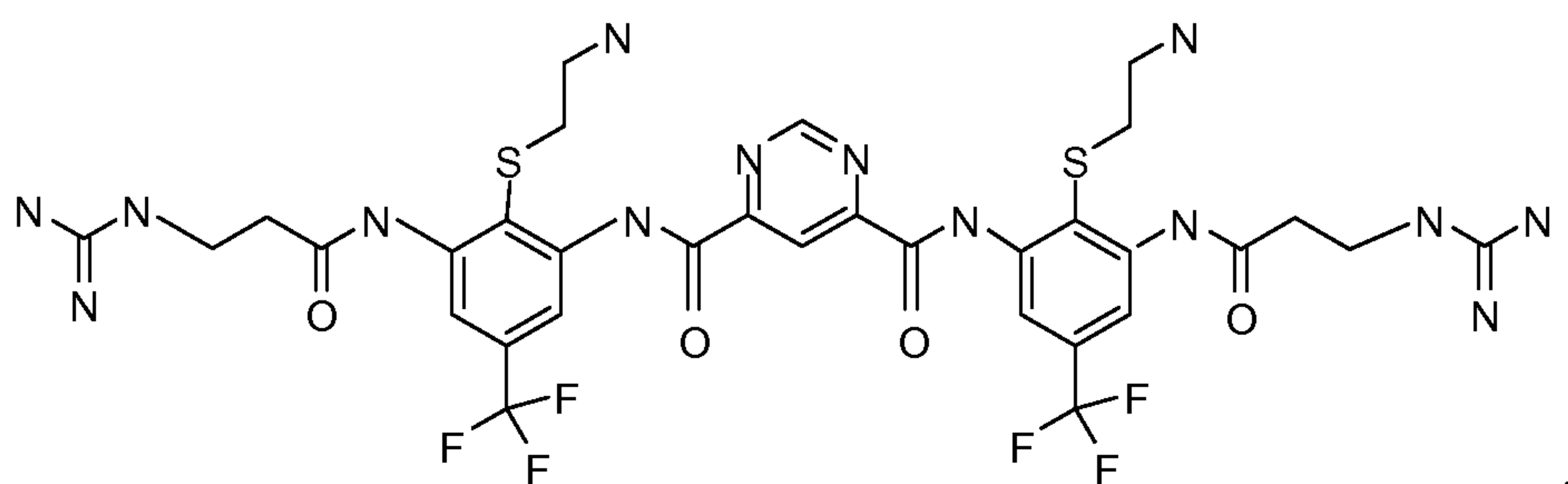
Compound 128



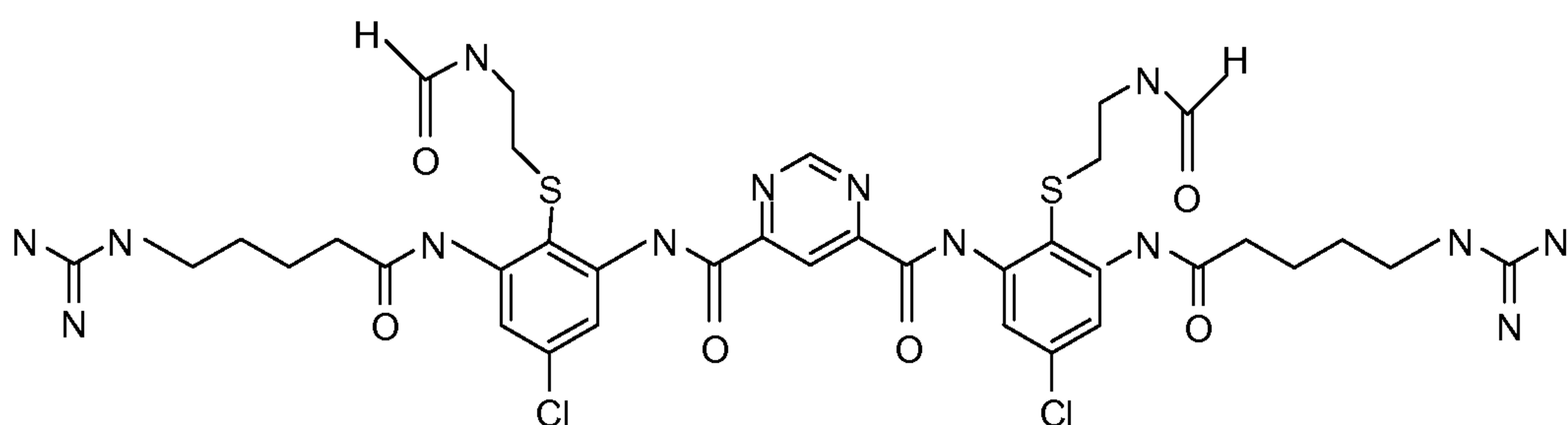
Compound 127



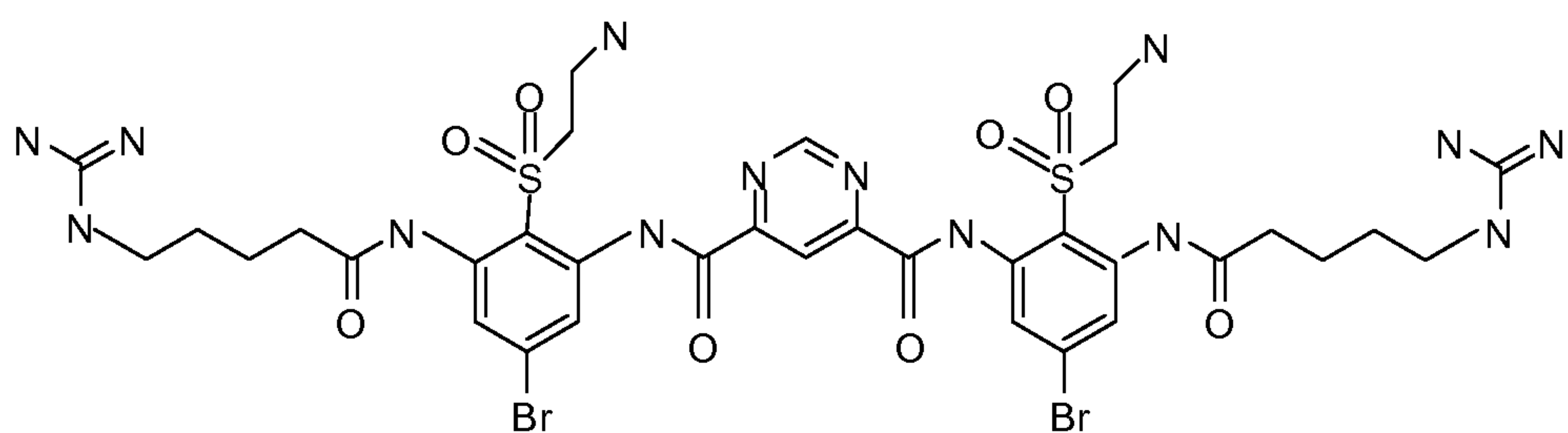
Compound 126



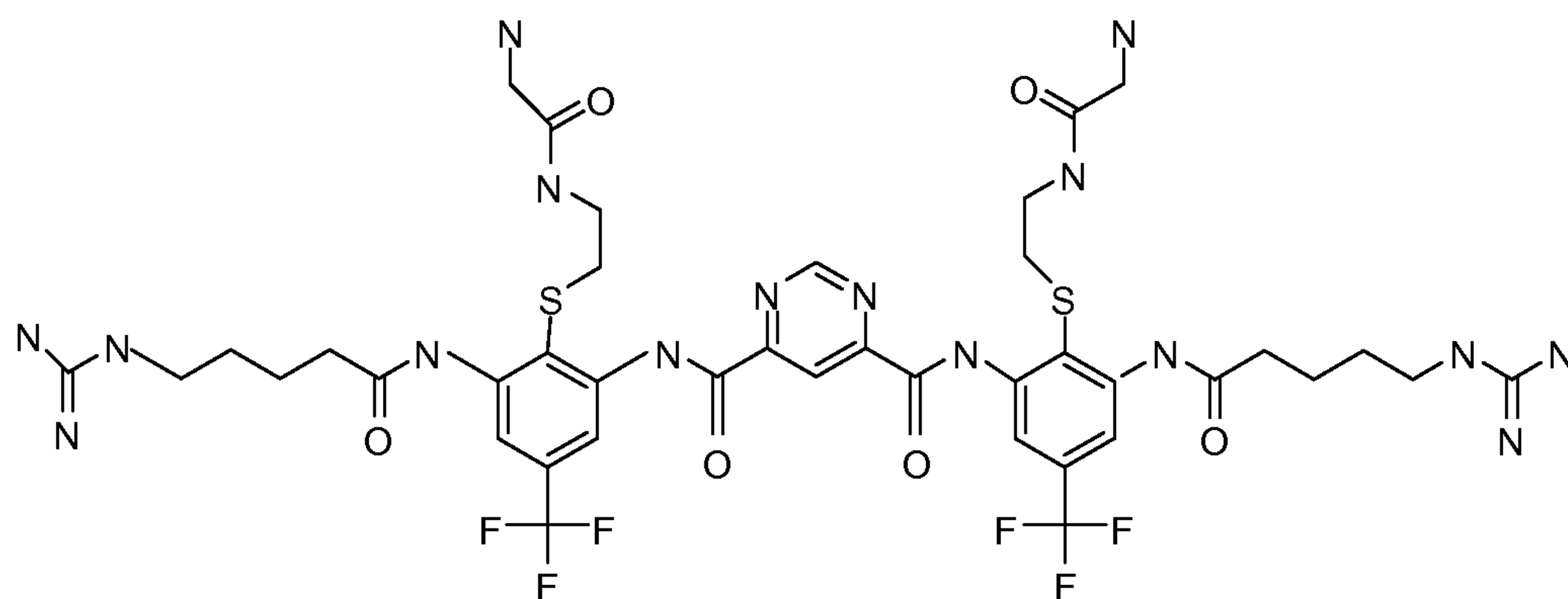
Compound 108



Compound 125



Compound 152, and

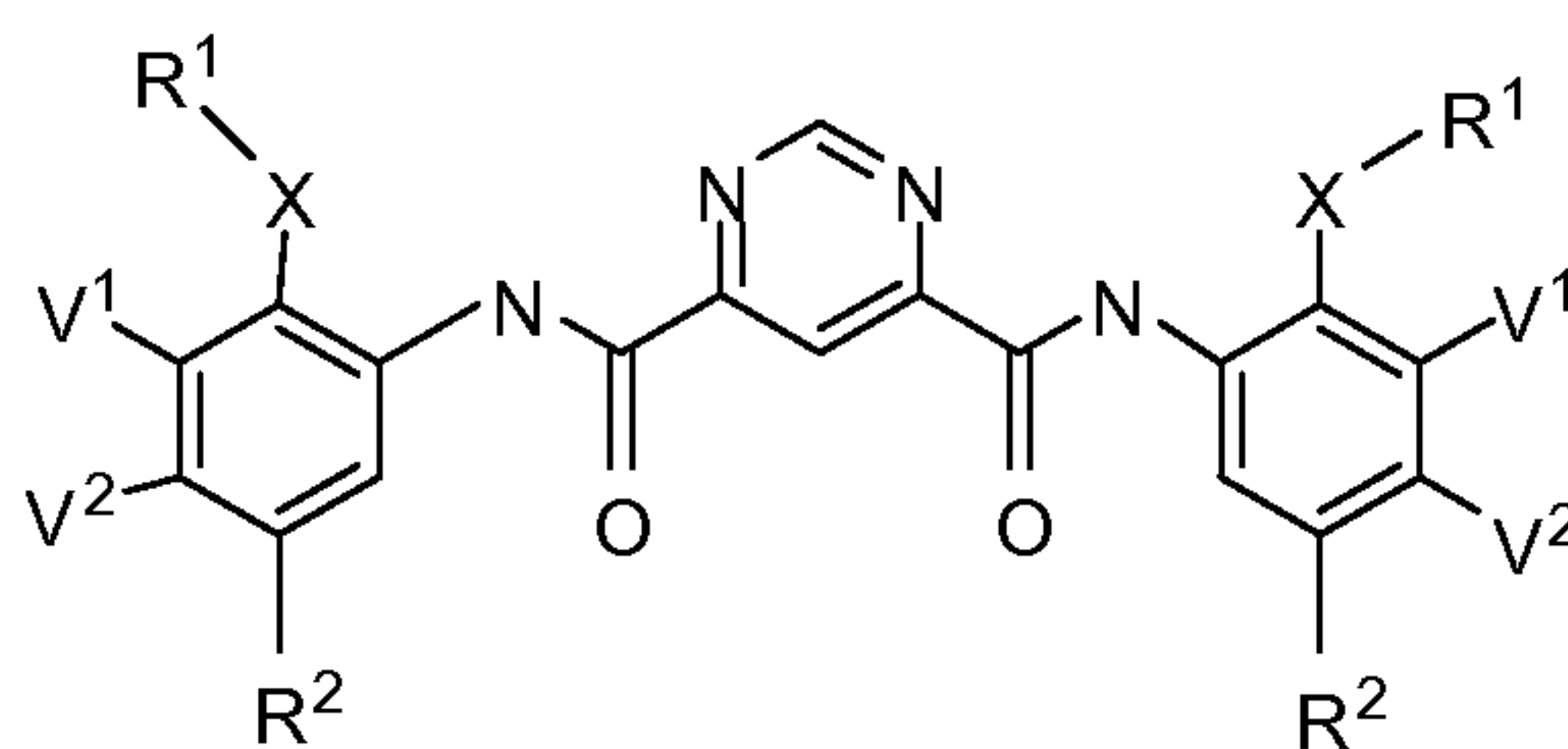


Compound 153

or a pharmaceutically acceptable salt thereof.

In any of the above embodiments, the malaria can be chloroquine-sensitive or chloroquine-resistant.

10 The present invention also provides methods of killing or inhibiting the growth of a *Plasmodium* species comprising contacting the species with an effective amount of a compound of Formula V:



wherein:

each X is, independently, O, S, or S(=O)₂;

each R¹ is, independently, -(CH₂)_n-NH₂, -(CH₂)_n-NH-C(=NH)NH₂, or -(CH₂)_n-NH-C(=O)-R⁴, where each n is, independently, 1 to 4, and each R⁴ is, independently,

5 H, C₁-C₃alkyl, or -(CH₂)_p-NH₂, where each p is, independently, 1 or 2;

each R² is, independently, H, halo, CF₃, or C(CH₃)₃; and

each V² is H, and each V¹ is, independently, -N-C(=O)-R³, where each R³ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4; or each V¹ is H and each V² is, independently, -S-R⁵, where each R⁵ is, independently,

10 -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4;

or a pharmaceutically acceptable salt thereof.

In some embodiments, each X is S.

In any of the above embodiments, each R¹ is, independently, -(CH₂)_n-NH₂, -(CH₂)_n-NH-C(=NH)NH₂, or -(CH₂)_n-NH-C(=O)-R⁴, where each n is, independently, 1 or 2,

15 and each R⁴ is, independently, H or methyl; or each R¹ is, independently, -(CH₂)_n-NH₂, -(CH₂)_n-NH-C(=NH)NH₂, or -(CH₂)_n-NH-C(=O)-R⁴, where each n is 2 and each R⁴ is H; or each R¹ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is 2; or each R¹ is -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is 2.

In any of the above embodiments, each R² is, independently, H, Br, F, Cl, CF₃, or
20 C(CH₃)₃; or each R² is Br, F, Cl, CF₃, or C(CH₃)₃.

In any of the above embodiments, each V² is H and each V¹ is, independently, -N-C(=O)-R³, where each R³ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4; or each V² is H and each V¹ is, independently, -N-C(=O)-R³, where each R³ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂,
25 where each n is, independently, 1 or 2; or each V² is H and each V¹ is, independently, -N-C(=O)-R³, where each R³ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is 2; or each V² is H and each V¹ is -N-C(=O)-R³, where each R³ is -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where n is 2.

In any of the above embodiments, each V¹ is H and each V² is, independently,
30 -S-R⁵, where each R⁵ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4; or each V¹ is H and each V² is, independently, -S-R⁵, where

each R^5 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 or 2; or each V^1 is H and each V^2 is, independently, $-S-R^5$, where each R^5 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 2; or each V^1 is H and each V^2 is $-S-R^5$, where each R^5 is $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 2.

5 In some embodiments, each X is S; each R^1 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; each R^2 is, independently, halo, CF_3 , or $C(CH_3)_3$; and each V^1 is H and each V^2 is, independently, $-S-R^5$, where each R^5 is, independently, $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4.

10 In some embodiments, each X is S; each R^1 is, independently, $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2; each R^2 is, independently, CF_3 or $C(CH_3)_3$; and each V^1 is H and each V^2 is, independently, $-S-R^5$, where each R^5 is, independently, $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2.

In some embodiments, each X is S; each R^1 is $-(CH_2)_n-NH_2$, where each n is 1 or 2; each R^2 is, independently, CF_3 or $C(CH_3)_3$; and each V^1 is H and each V^2 is $-S-R^5$, where
15 each R^5 is $-(CH_2)_n-NH_2$, where each n is 1 or 2.

In some embodiments, each X is O or S; each R^1 is, independently, $-(CH_2)_n-NH_2$, or $-(CH_2)_n-NH-C(=NH)NH_2$, or $-(CH_2)_n-NH-C(=O)-R^4$, where each n is, independently, 1 to 4, and each R^4 is, independently, H or methyl; each R^2 is, independently, halo, CF_3 , or $C(CH_3)_3$; and each V^2 is H, and each V^1 is, independently, $-N-C(=O)-R^3$, where each R^3 is,
20 independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

In some embodiments, each X is S; each R^1 is, independently, $-(CH_2)_n-NH-C(=O)-R^4$, where each n is, independently, 1 or 2, and each R^4 is, independently, H or methyl; each R^2 is, independently, halo; and each V^2 is H, and each V^1 is $-N-C(=O)-R^3$,
25 where each R^3 is $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 4.

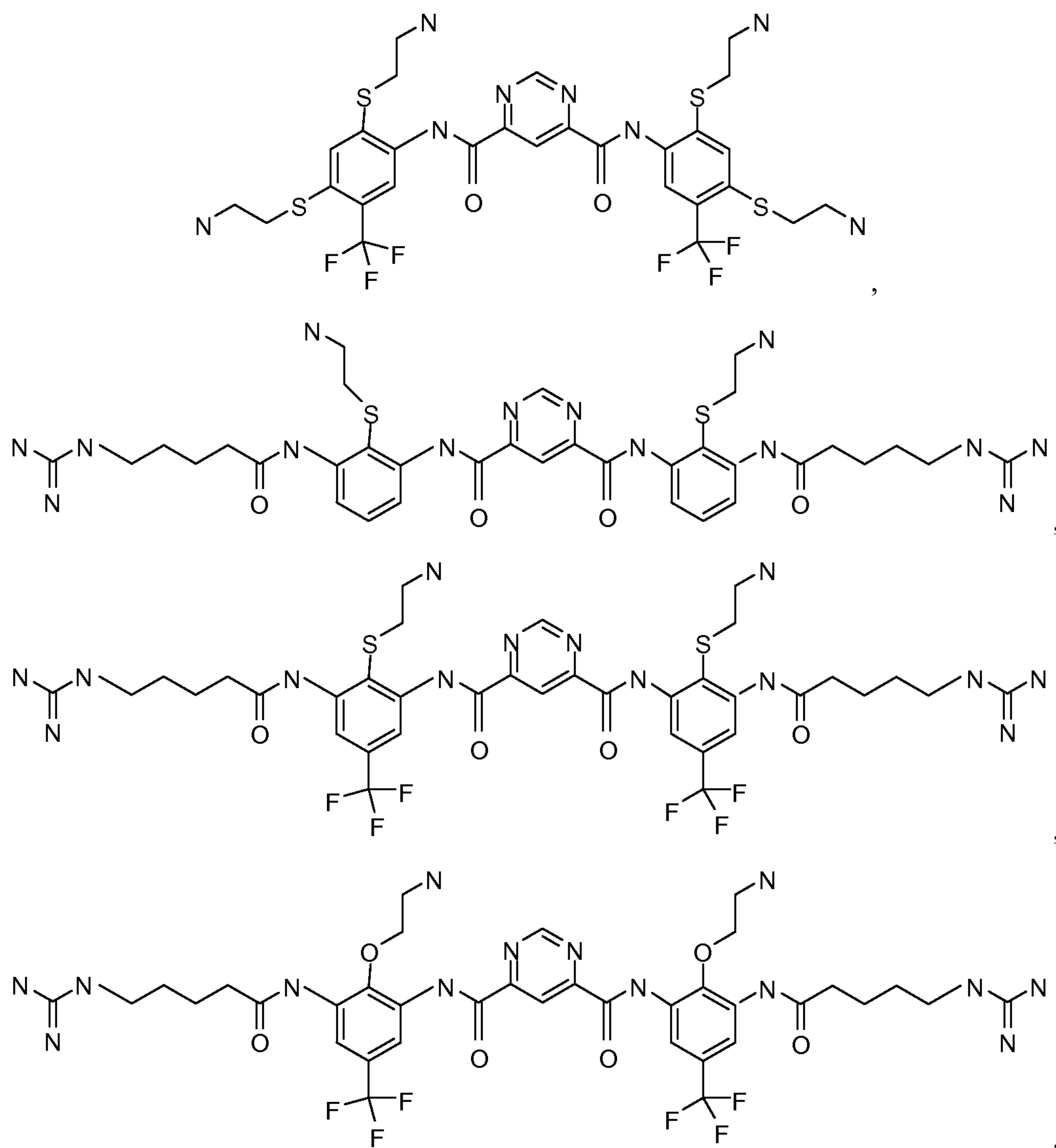
In some embodiments, each X is O or S; each R^1 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; each R^2 is, independently, halo, CF_3 , or $C(CH_3)_3$; and each V^2 is H, and each V^1 is, independently, $-N-C(=O)-R^3$, where each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is,
30 independently, 1 to 4.

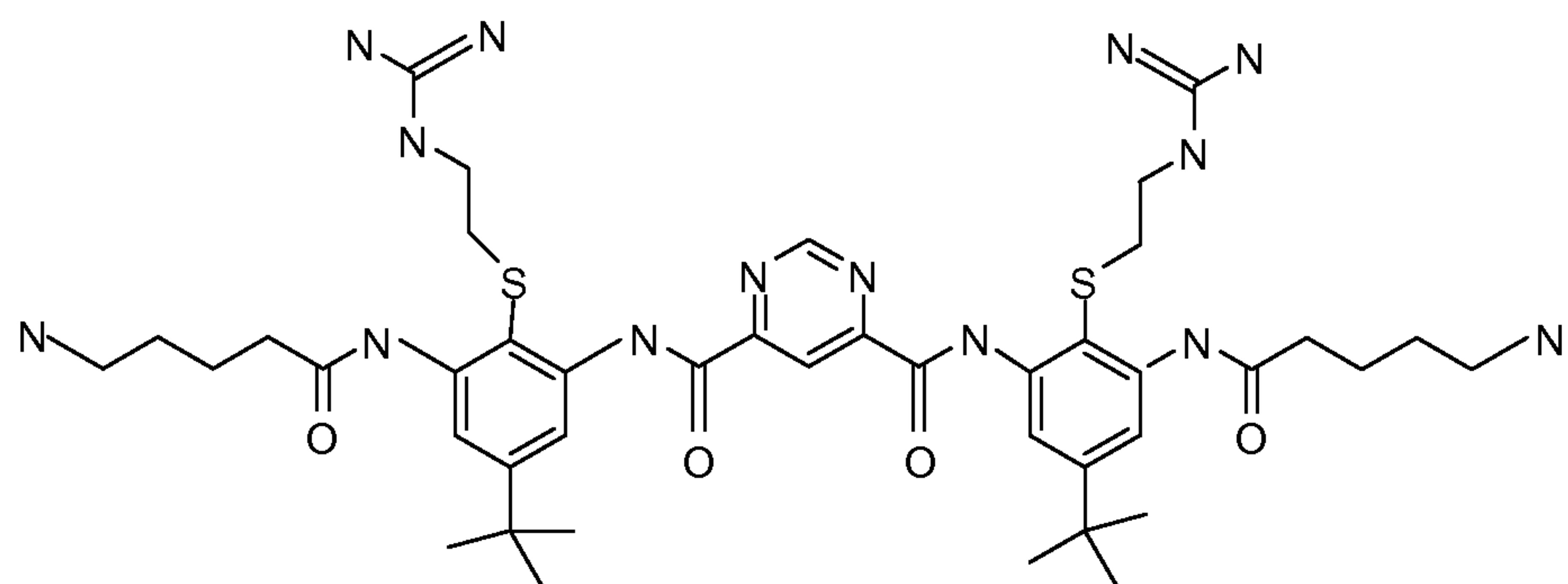
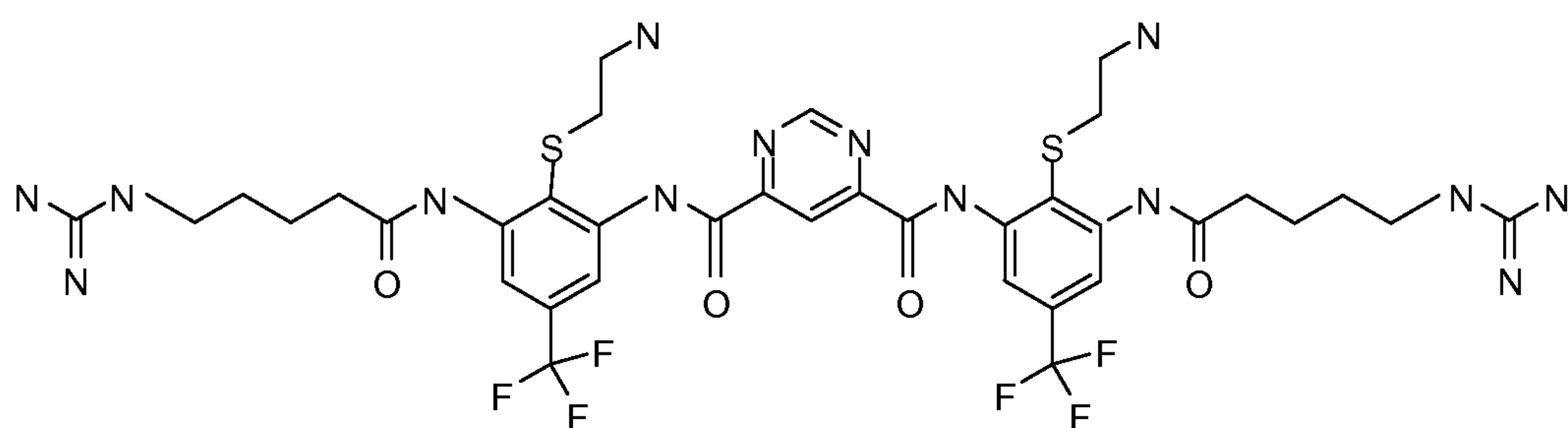
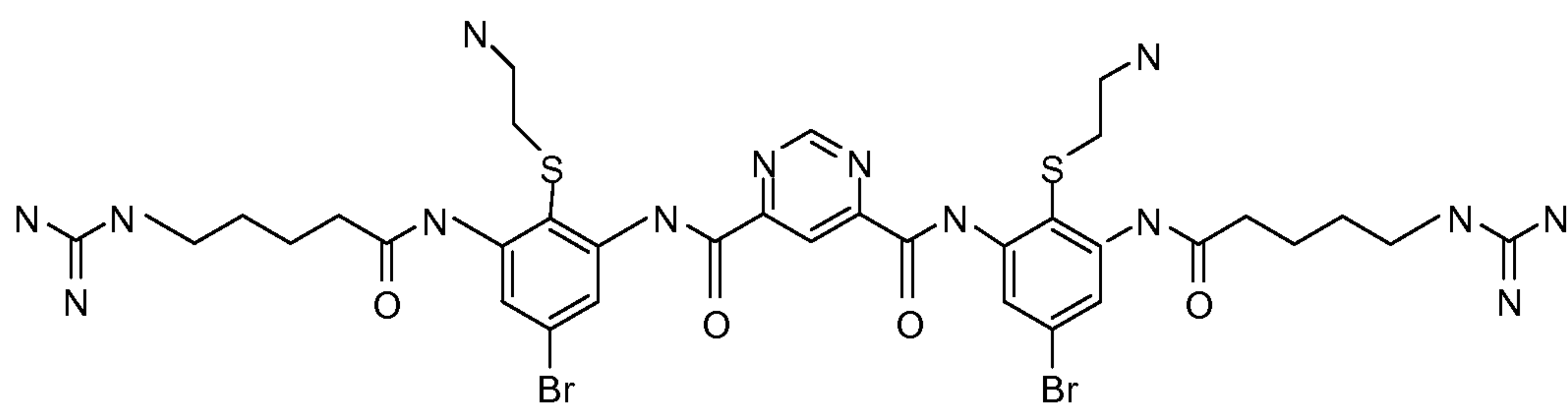
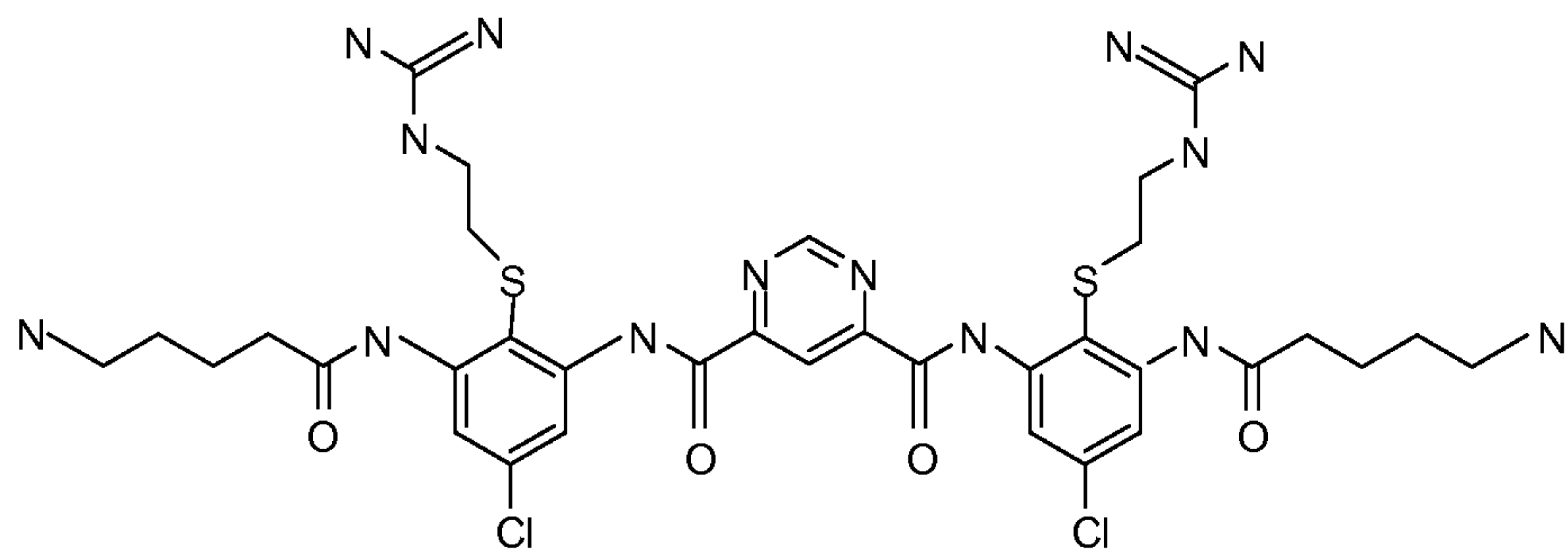
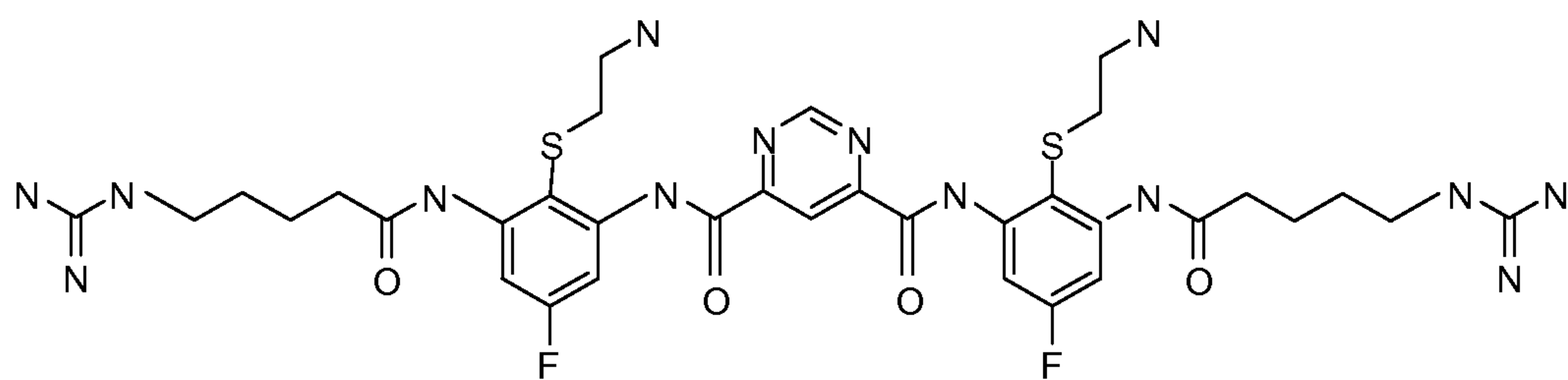
In some embodiments, each X is O or S; each R^1 is $-(CH_2)_n-NH_2$ or

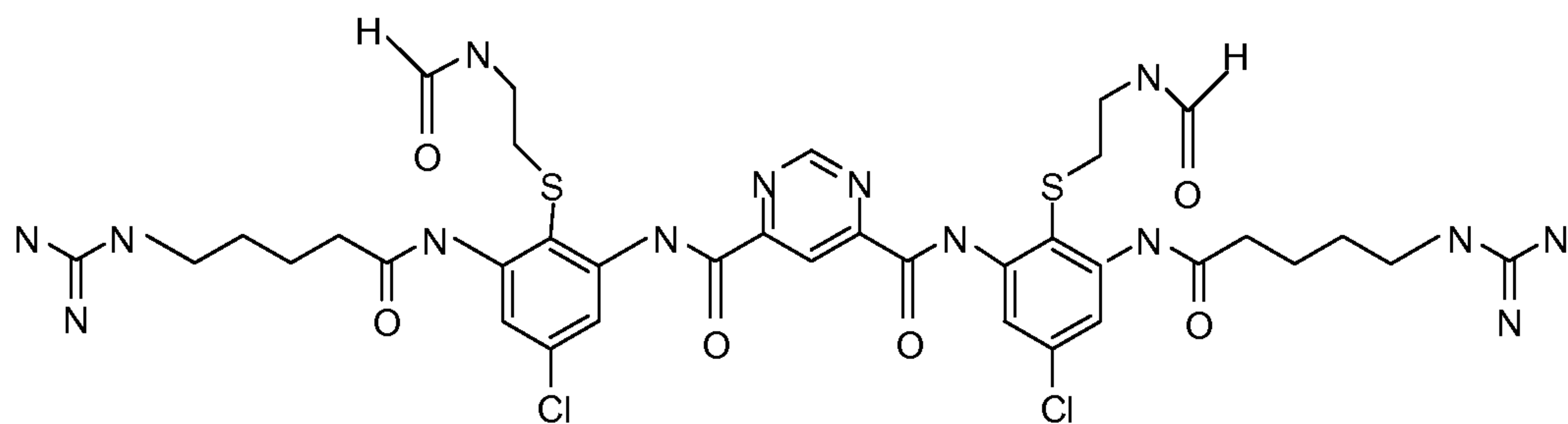
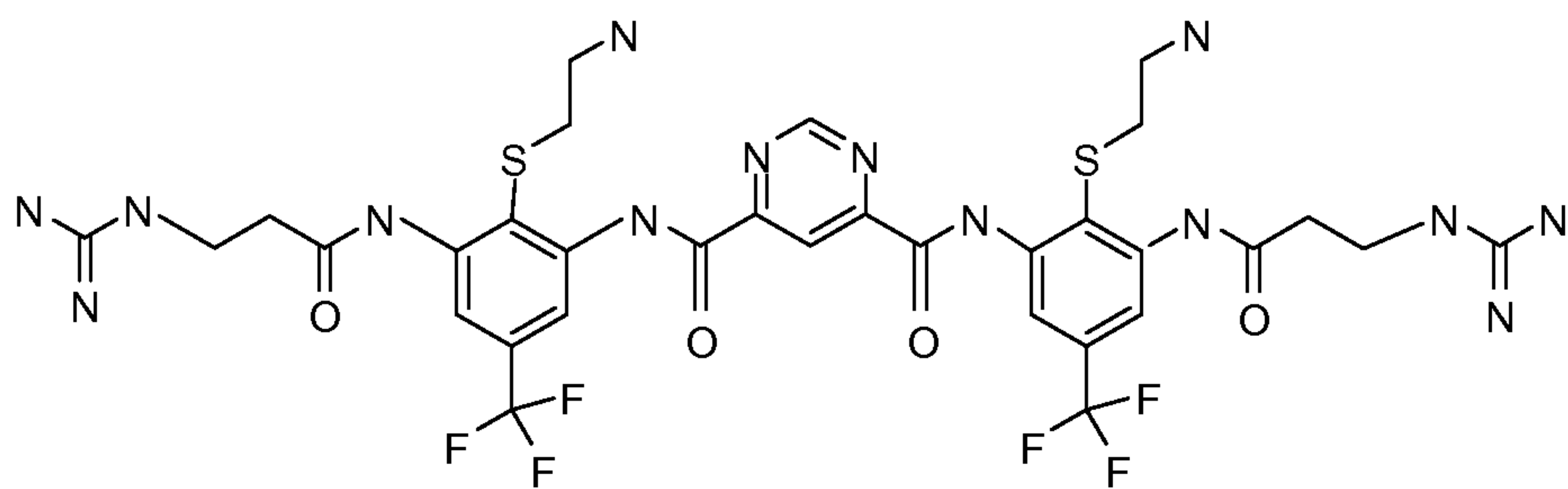
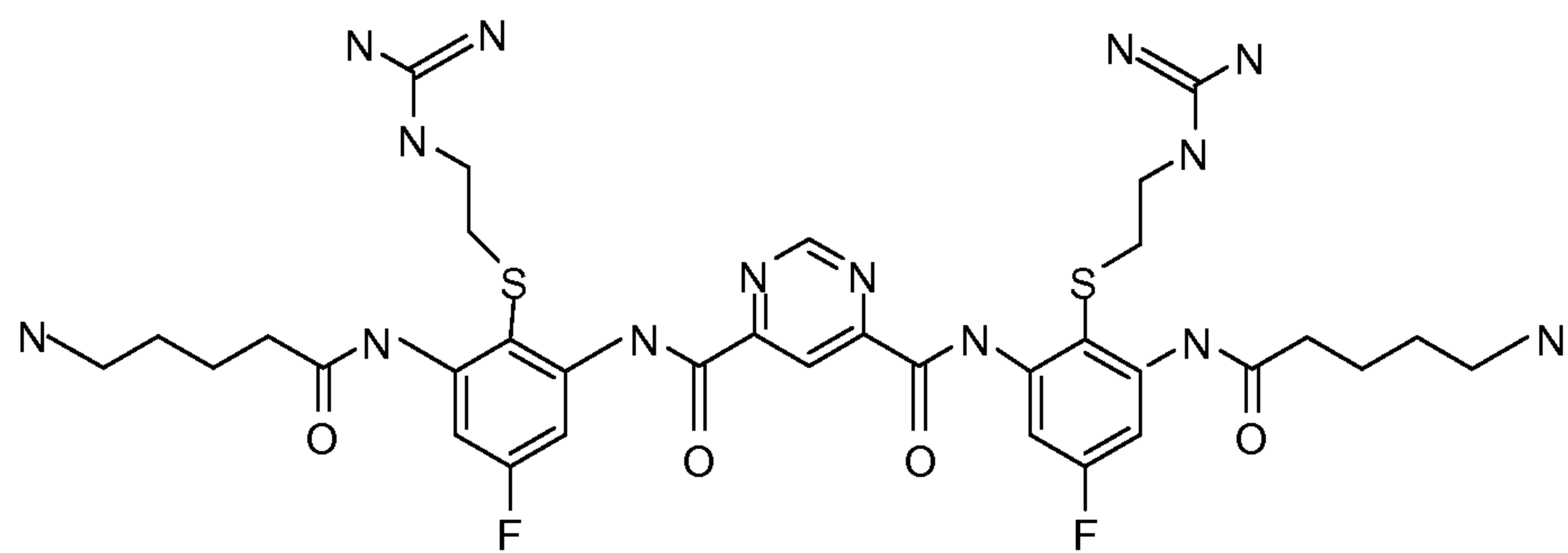
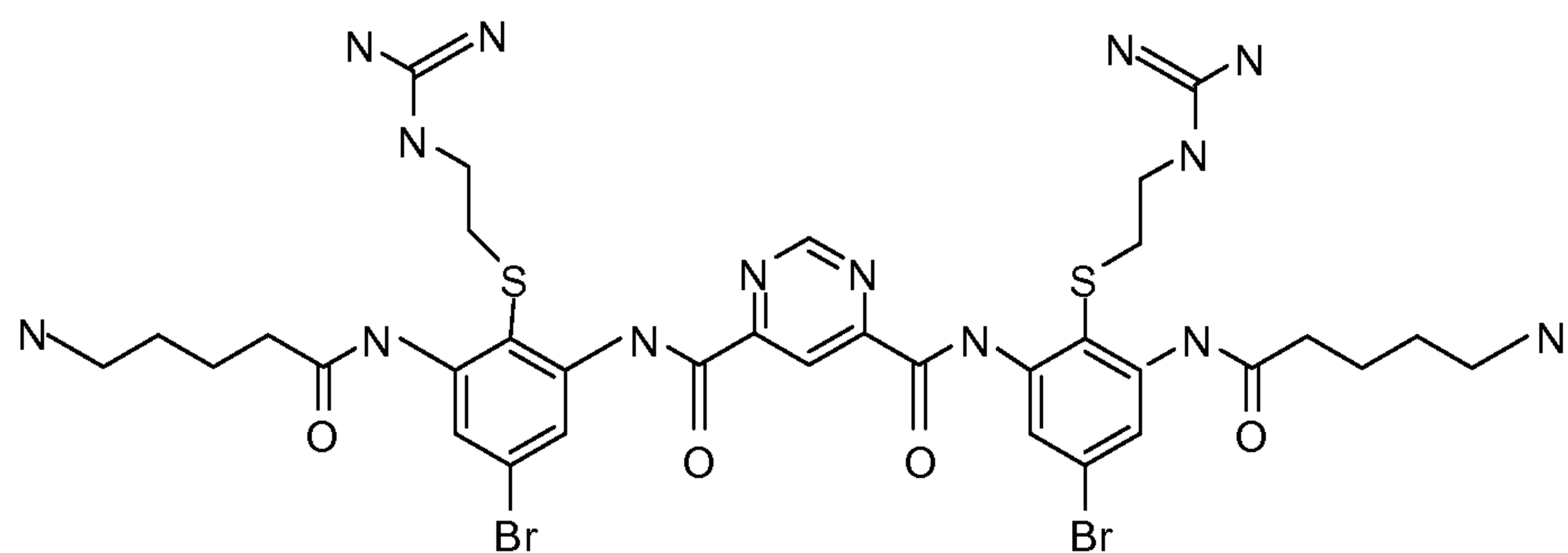
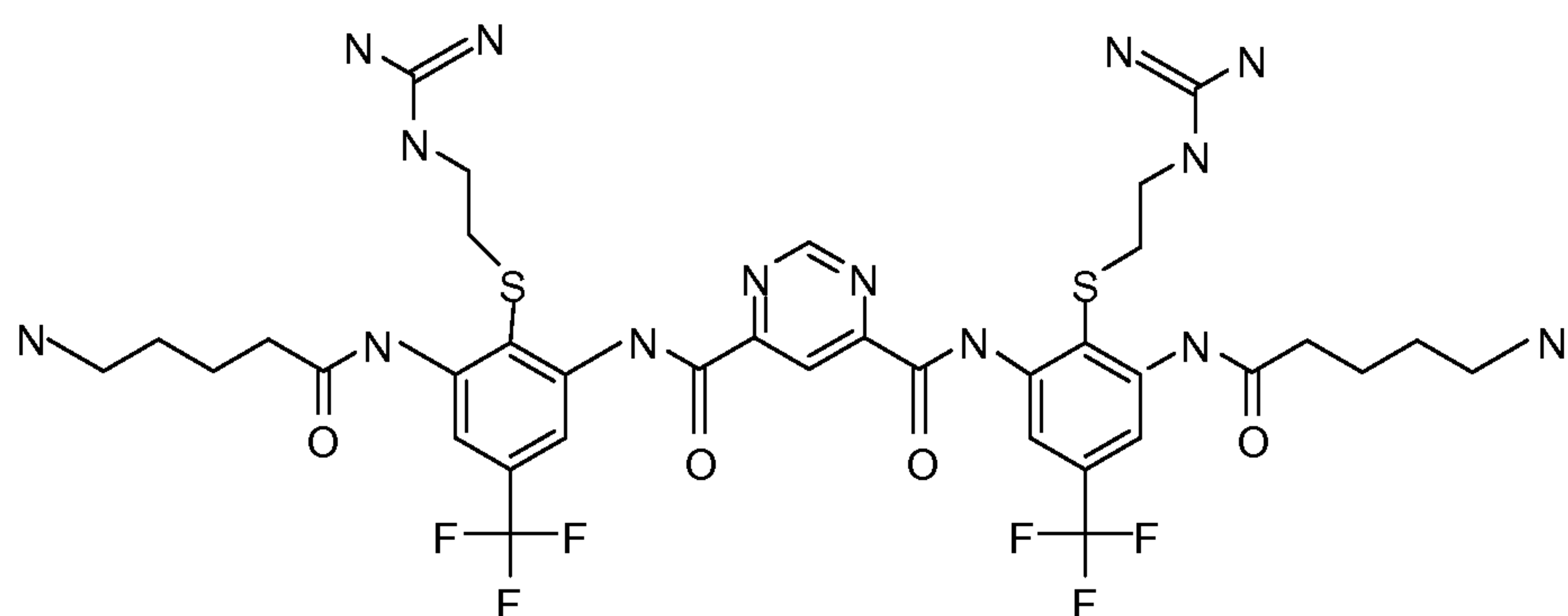
$-(\text{CH}_2)_n\text{-NH-C(=NH)NH}_2$, where each n is 1 or 2; each R^2 is halo, CF_3 , or $\text{C(CH}_3)_3$; and each V^2 is H, and each V^1 is $-\text{N-C(=O)-R}^3$, where each R^3 is $-(\text{CH}_2)_n\text{-NH}_2$ or $-(\text{CH}_2)_n\text{-NH-C(=NH)NH}_2$, where each n is 3 or 4.

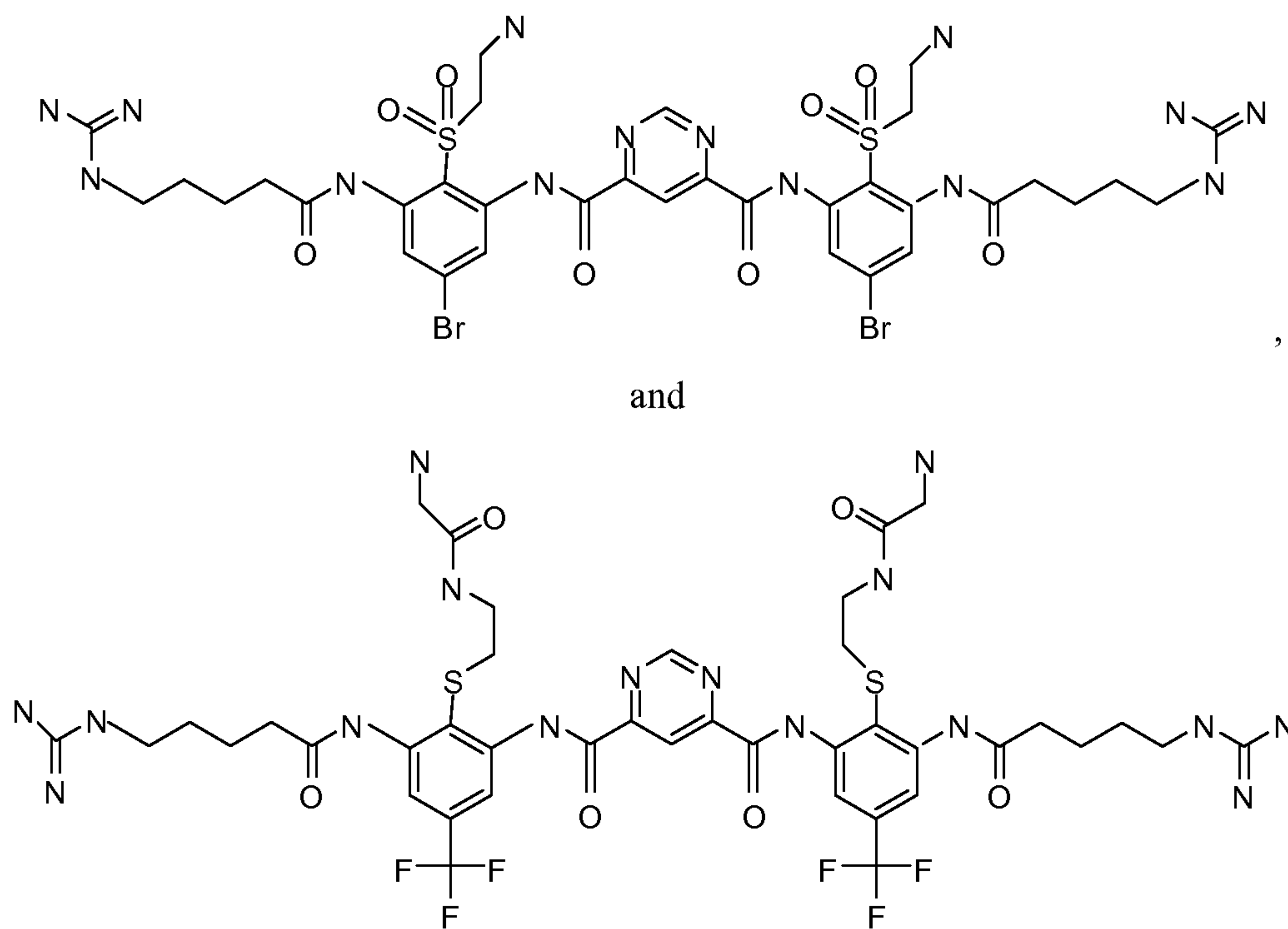
In some embodiments, each X is, independently, S or S(=O)_2 ; each R^1 is, independently, $-(\text{CH}_2)_n\text{-NH}_2$ or $-(\text{CH}_2)_n\text{-NH-C(=O)-R}^4$, where each n is, independently, 1 or 2, and each R^4 is, independently, $-(\text{CH}_2)_p\text{-NH}_2$, where each p is, independently, 1 or 2; each R^2 is, independently, halo or CF_3 ; and each V^2 is H, and each V^1 is, independently, $-\text{N-C(=O)-R}^3$, where each R^3 is, independently, $-(\text{CH}_2)_n\text{-NH}_2$ or $-(\text{CH}_2)_n\text{-NH-C(=NH)NH}_2$, where each n is, independently, 3 or 4.

10 In some embodiments, the compound is chosen from:



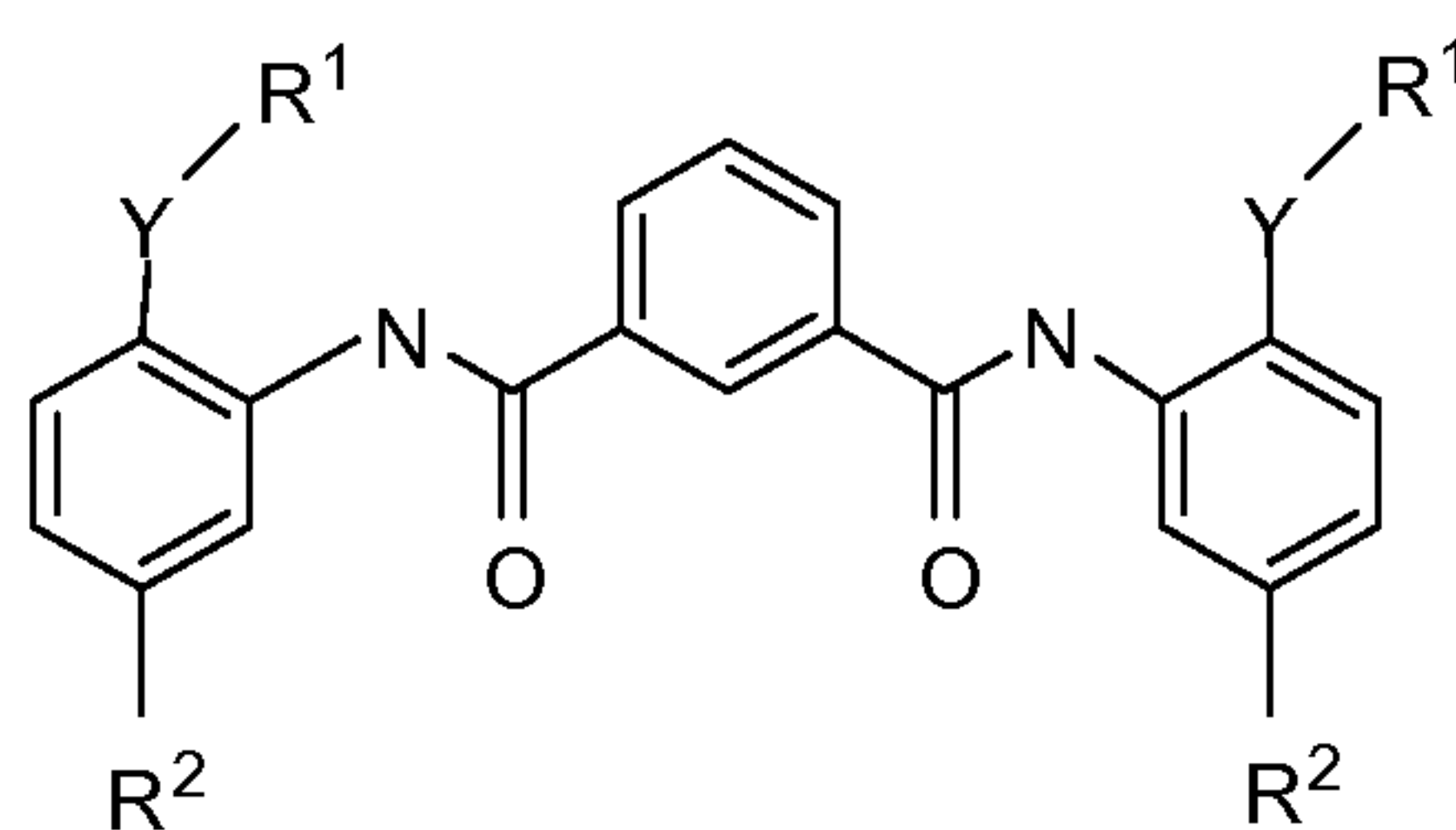






or a pharmaceutically acceptable salt thereof.

5 The present invention also provides compounds of Formula VI:



wherein:

each Y is, independently, O, S, or NH;

each R¹ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n
10 is, independently, 1 to 4; and

each R² is, independently, H, halo, CF₃, or C(CH₃)₃;

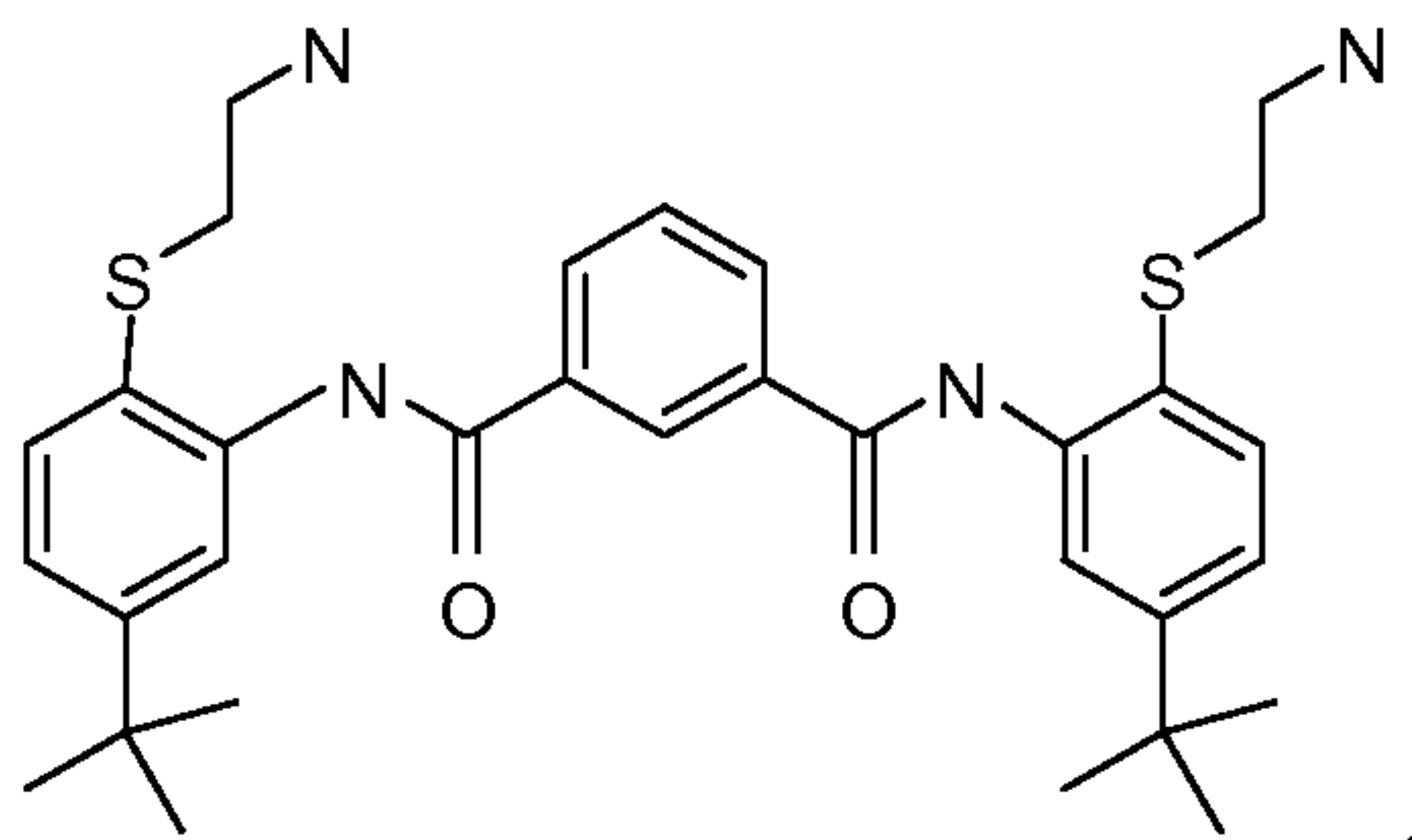
or a pharmaceutically acceptable salt thereof.

In some embodiments, each Y is, independently, O, or S; or each Y is O or S.

In any of the above embodiments, each R¹ is, independently, -(CH₂)_n-NH₂, where
15 each n is, independently, 2 to 4; or each R¹ is -(CH₂)_n-NH₂, where each n is 2 to 4.

In any of the above embodiments, each R² is, independently, halo, CF₃, or C(CH₃)₃;
or each R² is halo, CF₃, or C(CH₃)₃.

In some embodiments, the compound is

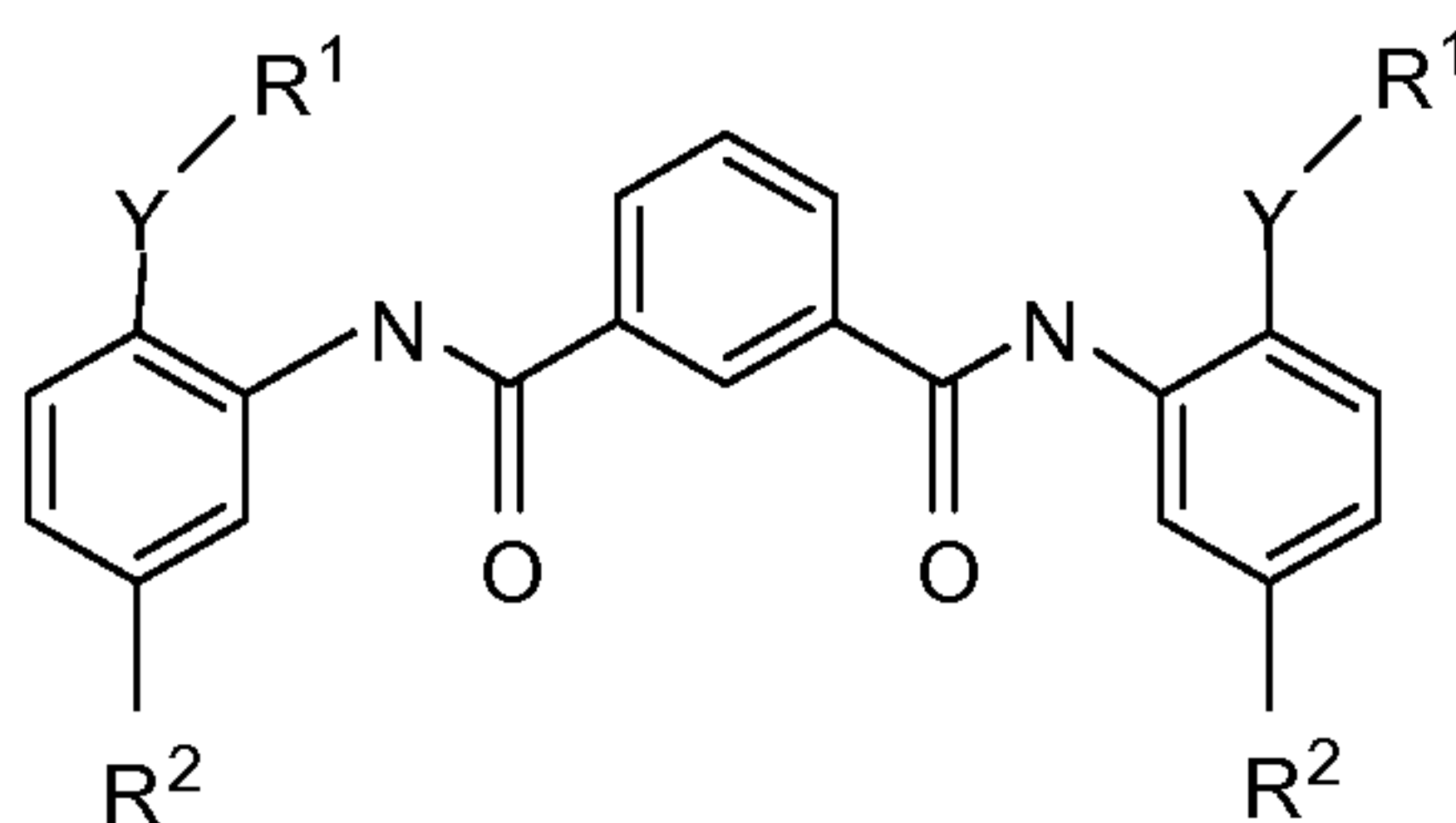


or pharmaceutically acceptable salt thereof.

In some embodiments, any one or more of the above compounds may be excluded
5 from any of the genus of compounds described above.

The present invention also provides compositions comprising one or more of the compounds or salts described above and a pharmaceutically acceptable carrier.

The present invention also provides methods of treating malaria in an animal comprising administering to the animal a therapeutically effective amount of a compound of
10 Formula VI:



wherein:

each Y is, independently, O, S, or NH;

each R¹ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n
15 is, independently, 1 to 4; and

each R² is, independently, H, halo, CF₃, or C(CH₃)₃;

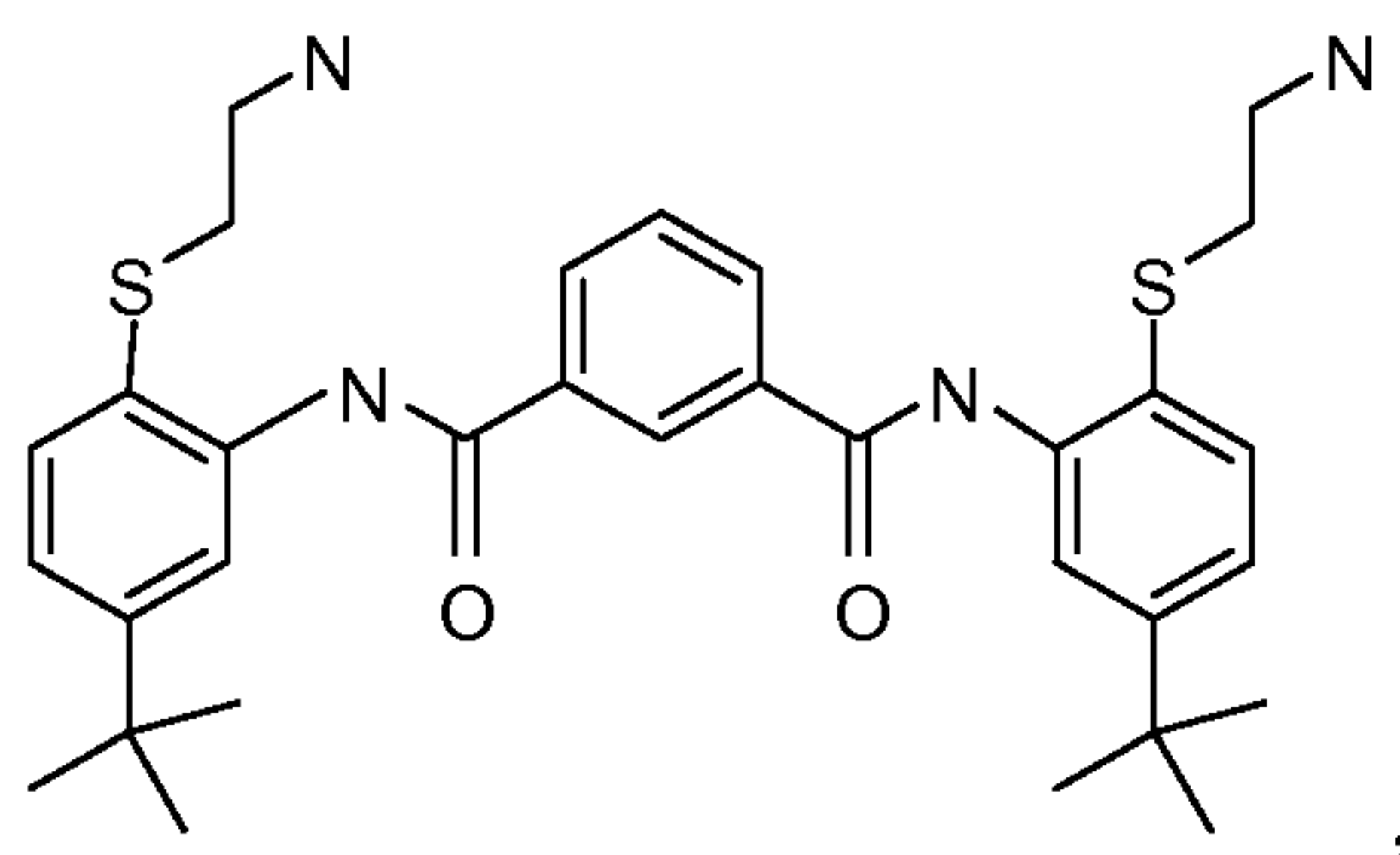
or a pharmaceutically acceptable salt thereof.

In some embodiments, each Y is, independently, O, or S; or each Y is O or S.

In any of the above embodiments, each R¹ is, independently, -(CH₂)_n-NH₂, where
20 each n is, independently, 2 to 4; or each R¹ is -(CH₂)_n-NH₂, where each n is 2 to 4.

In any of the above embodiments, each R² is, independently, halo, CF₃, or C(CH₃)₃;
or each R² is halo, CF₃, or C(CH₃)₃.

In some embodiments, the compound is

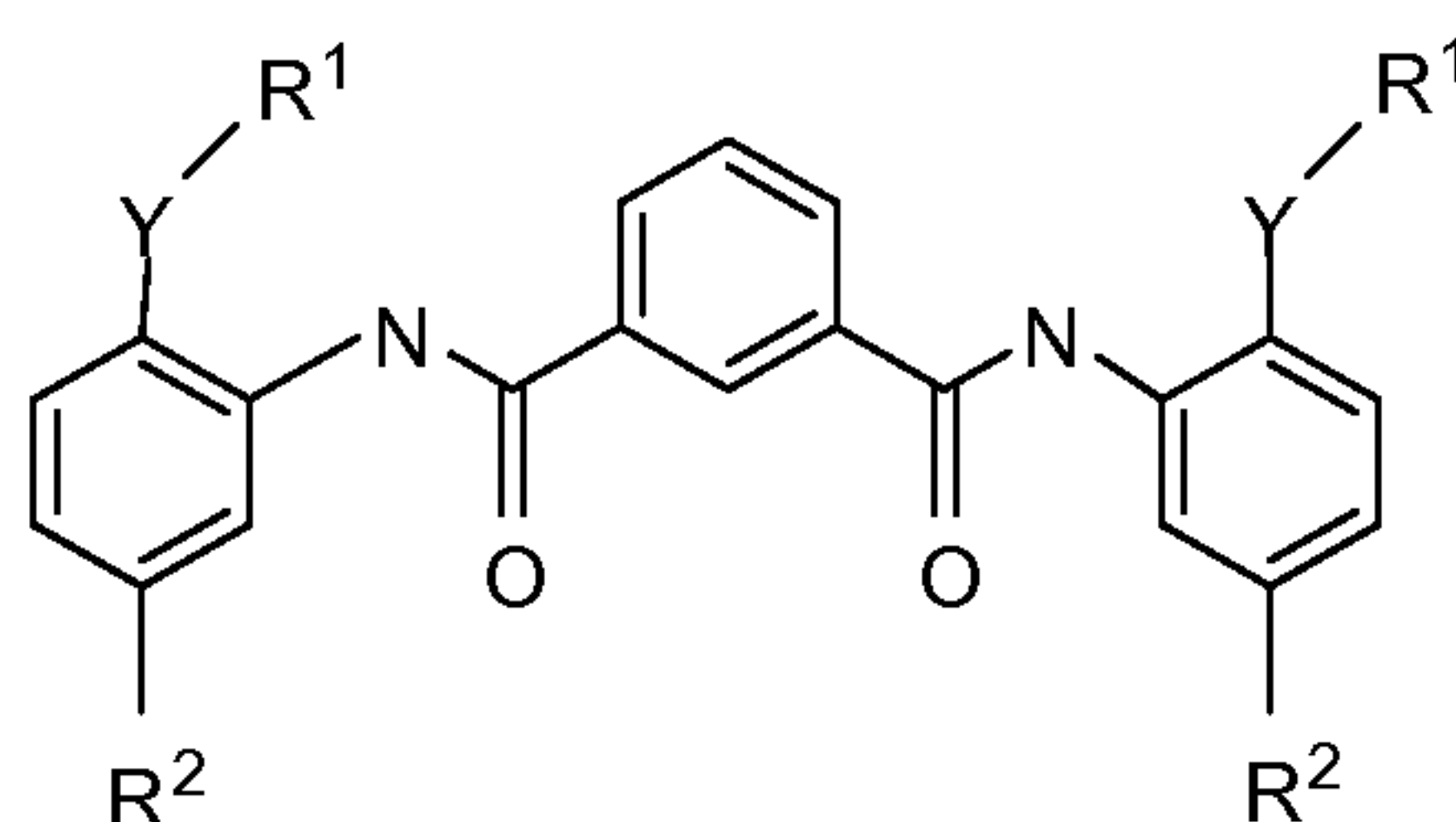


Compound 100

or pharmaceutically acceptable salt thereof.

In any of the above embodiments, the malaria can be chloroquine-sensitive or
5 chloroquine-resistant.

The present invention also provides methods of killing or inhibiting the growth of a *Plasmodium* species comprising contacting the species with an effective amount of a compound of Formula VI:



10 wherein:

each Y is, independently, O, S, or NH;

each R¹ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4; and

each R² is, independently, H, halo, CF₃, or C(CH₃)₃;

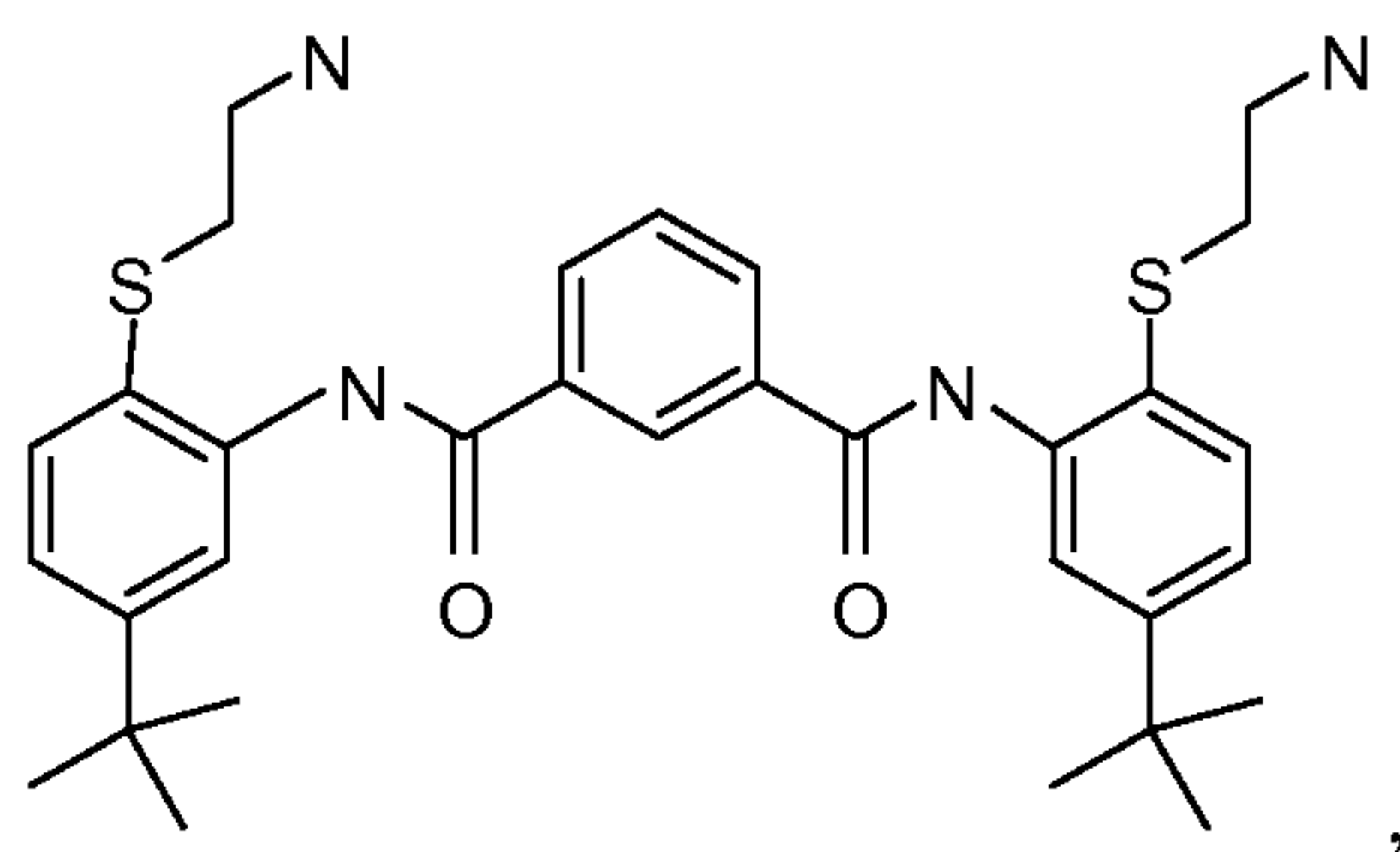
15 or a pharmaceutically acceptable salt thereof.

In some embodiments, each Y is, independently, O, or S; or each Y is O or S.

In any of the above embodiments, each R¹ is, independently, -(CH₂)_n-NH₂, where each n is, independently, 2 to 4; or each R¹ is -(CH₂)_n-NH₂, where each n is 2 to 4.

In any of the above embodiments, each R² is, independently, halo, CF₃, or C(CH₃)₃;
20 or each R² is halo, CF₃, or C(CH₃)₃.

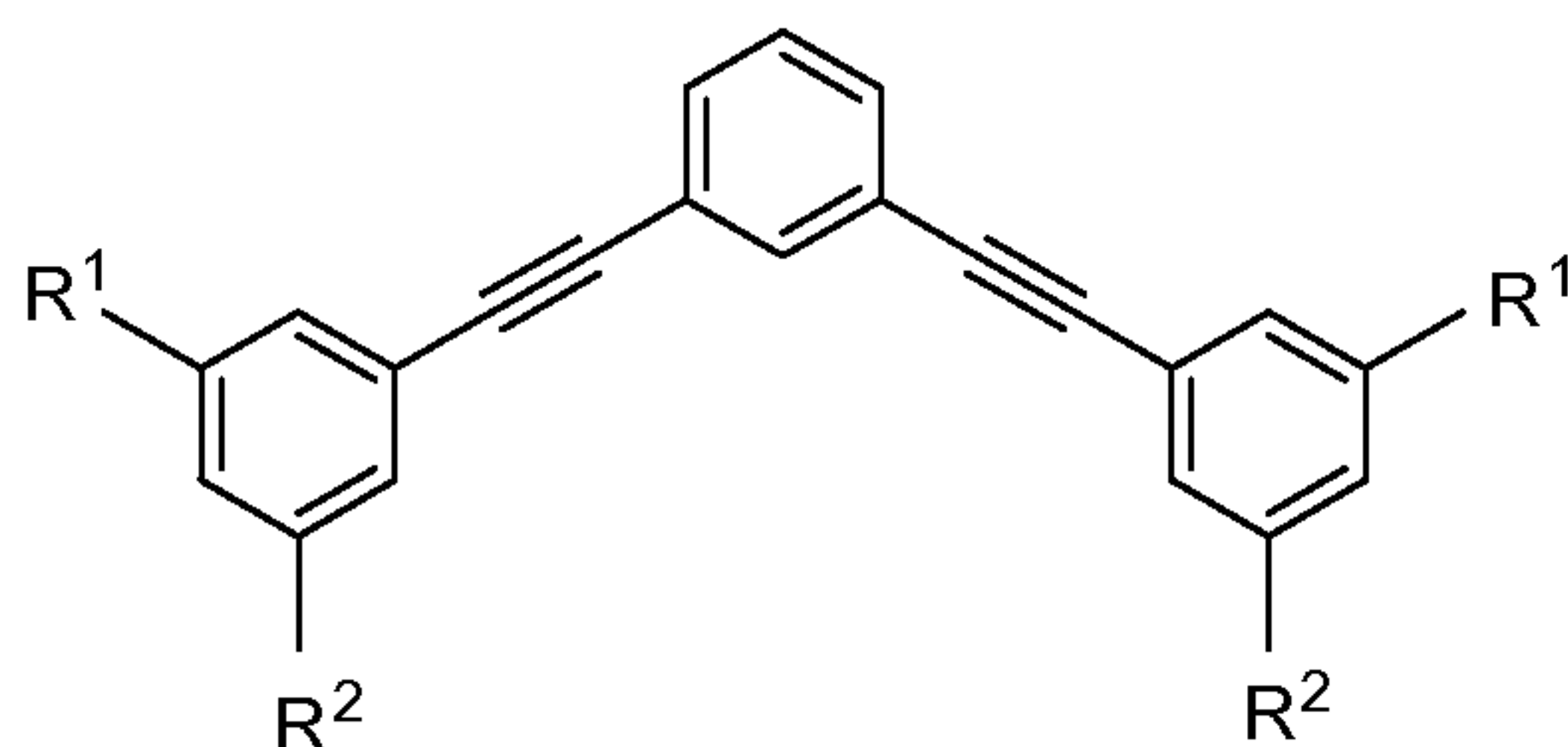
In some embodiments, the compound is



or pharmaceutically acceptable salt thereof.

The present invention also provides methods of treating malaria in an animal comprising administering to the animal a therapeutically effective amount of a compound of

5 Formula VII:



wherein:

each R^1 is, independently, H, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, halo, OH, CF_3 , or CN;

each R^2 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n

10 is, independently, 1 to 4;

or a pharmaceutically acceptable salt thereof.

In some embodiments, each R^1 is, independently, C_1 - C_8 alkyl, halo, OH, CF_3 , or CN; or each R^1 is, independently, C_1 - C_3 alkyl, halo, CF_3 , or CN; or each R^1 is methyl or halo; or each R^1 is Br, F, or Cl.

15 In any of the above embodiments, each R^2 is, independently,

$-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; or each R^2 is

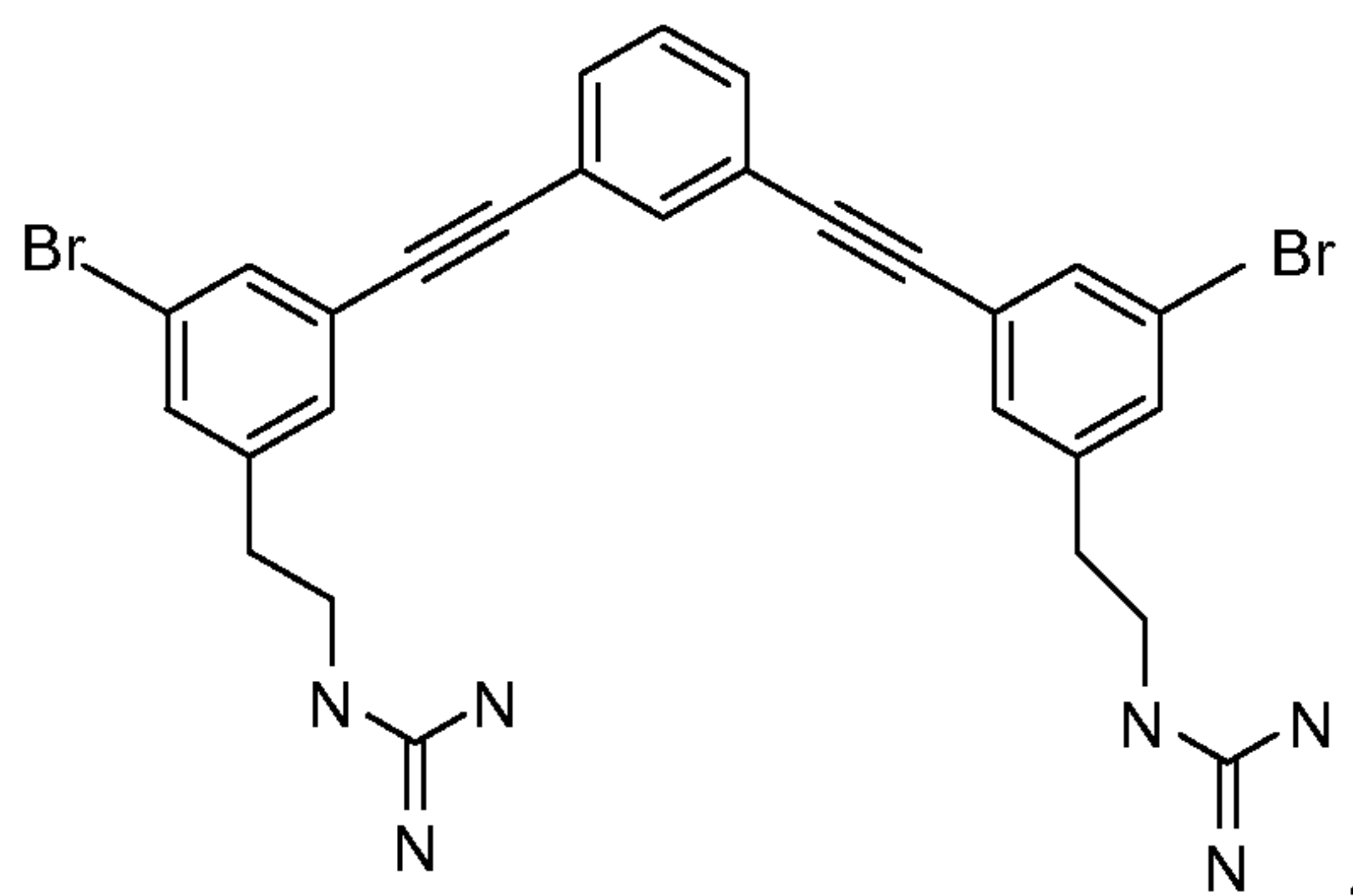
$-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 to 4; or each R^2 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 or 2.

20 In some embodiments, each R^1 is, independently, C_1 - C_8 alkyl, halo, OH, CF_3 , or CN; and each R^2 is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

In some embodiments, each R^1 is, independently, C_1 - C_3 alkyl, halo, CF_3 , or CN; and each R^2 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 to 4.

In some embodiments, each R^1 is methyl or halo; and each R^2 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 or 2.

In some embodiments, the compound is



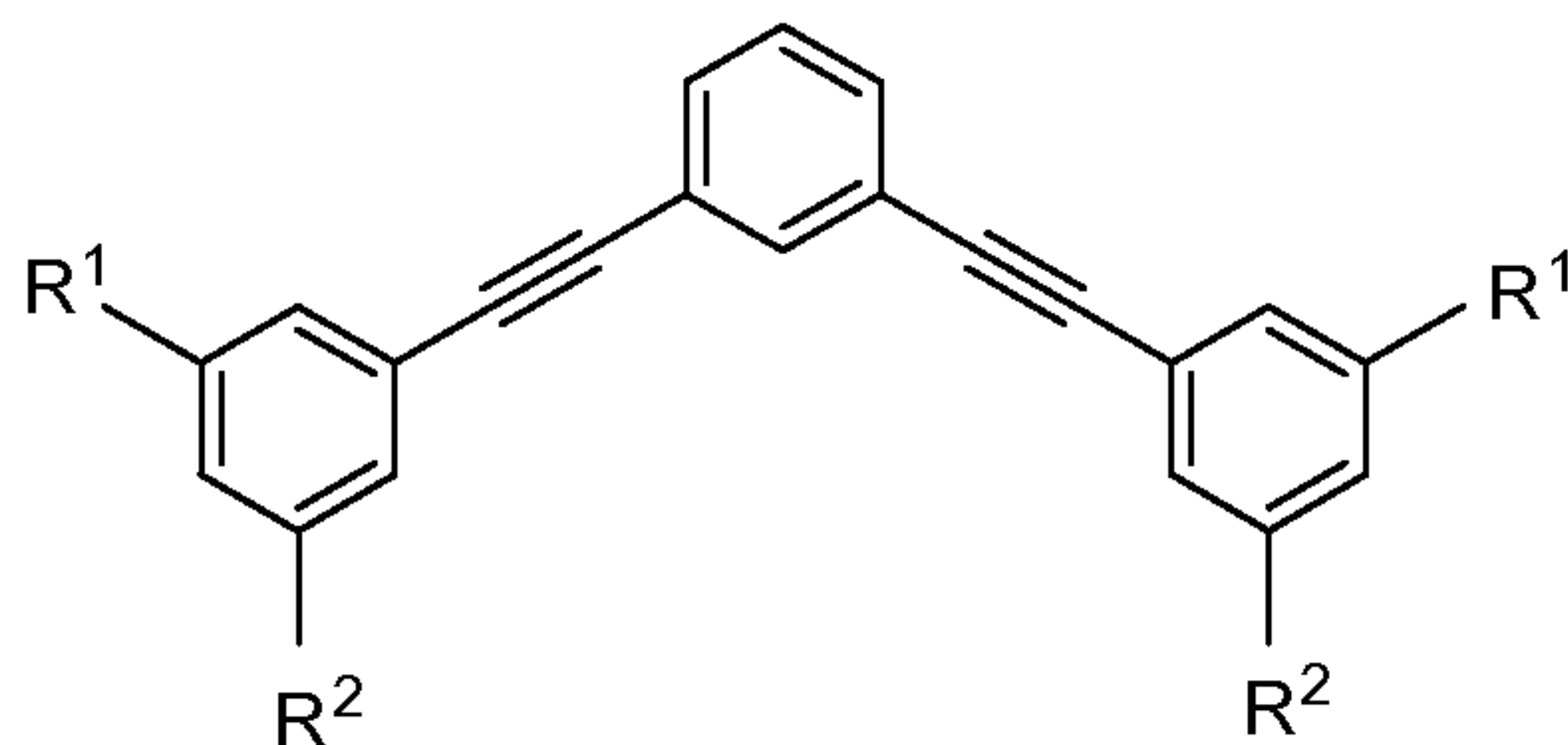
5

Compound 115

or a pharmaceutically acceptable salt thereof.

In any of the above embodiments, the malaria can be chloroquine-sensitive or chloroquine-resistant.

The present invention also provides methods of killing or inhibiting the growth of a
10 *Plasmodium* species comprising contacting the species with an effective amount of a compound of Formula VII:



wherein:

- each R^1 is, independently, H, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, halo, OH, CF_3 , or CN;
15 each R^2 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;
or a pharmaceutically acceptable salt thereof.

In some embodiments, each R^1 is, independently, C_1 - C_8 alkyl, halo, OH, CF_3 , or CN;
or each R^1 is, independently, C_1 - C_3 alkyl, halo, CF_3 , or CN; or each R^1 is methyl or halo; or
20 each R^1 is Br, F, or Cl.

In any of the above embodiments, each R^2 is, independently,
 $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; or each R^2 is

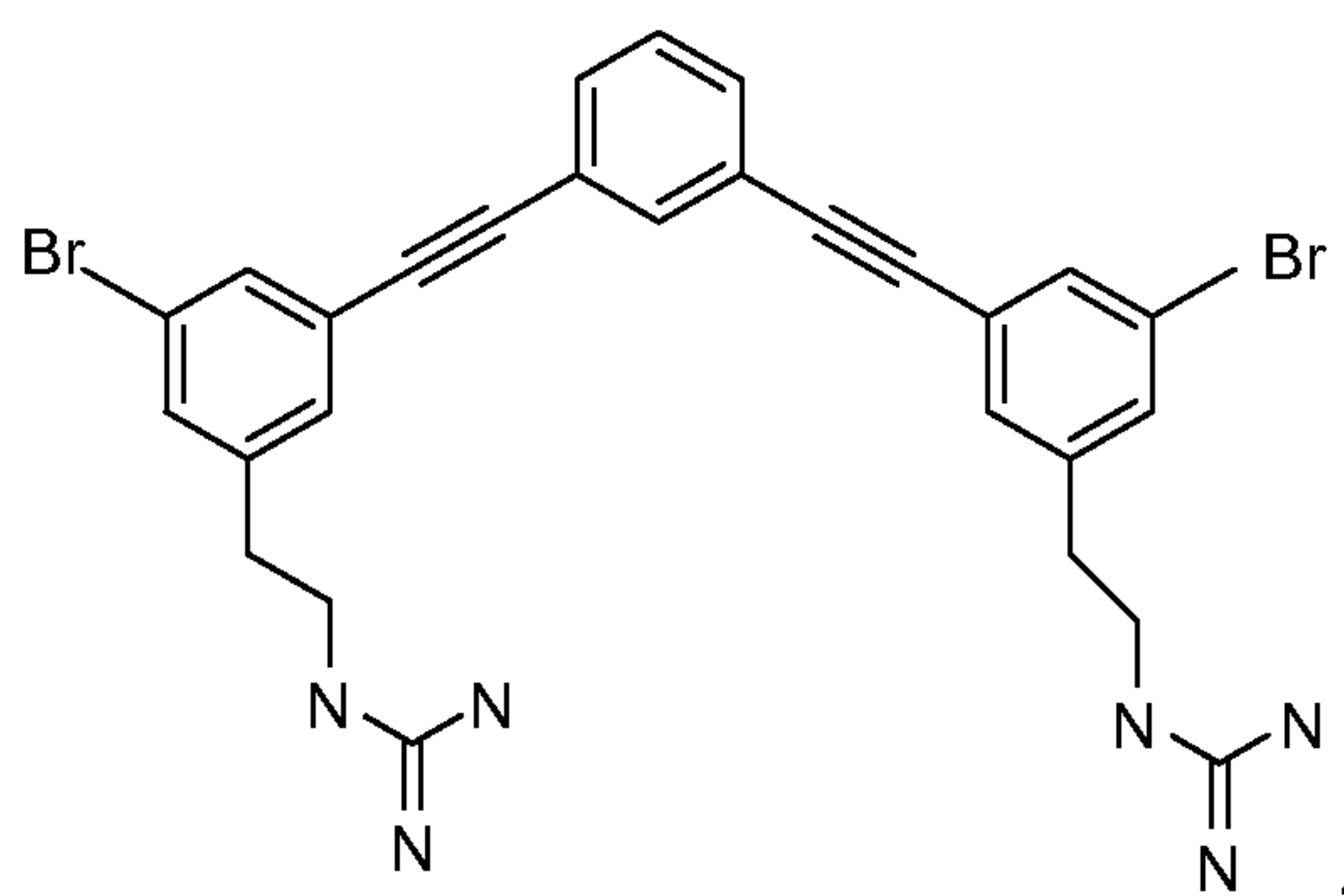
$-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 to 4; or each R^2 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 or 2.

In some embodiments, each R^1 is, independently, C_1 - C_8 alkyl, halo, OH, CF_3 , or CN; and each R^2 is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

In some embodiments, each R^1 is, independently, C_1 - C_3 alkyl, halo, CF_3 , or CN; and each R^2 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 to 4.

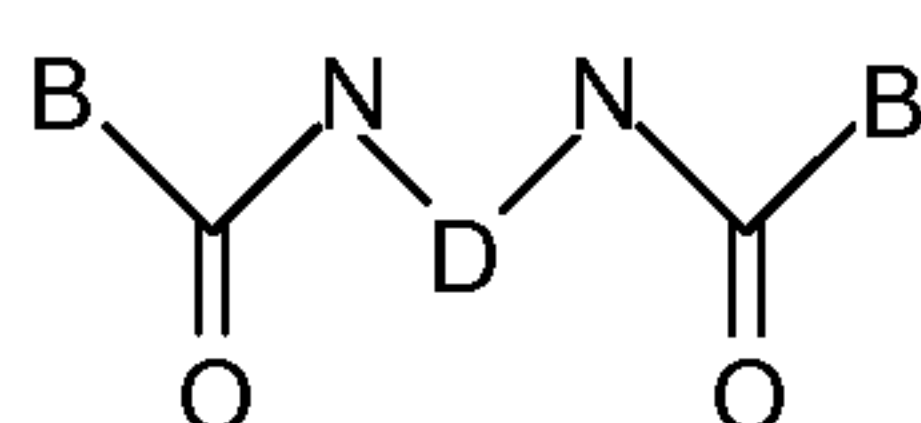
In some embodiments, each R^1 is methyl or halo; and each R^2 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 or 2.

In some embodiments, the compound is

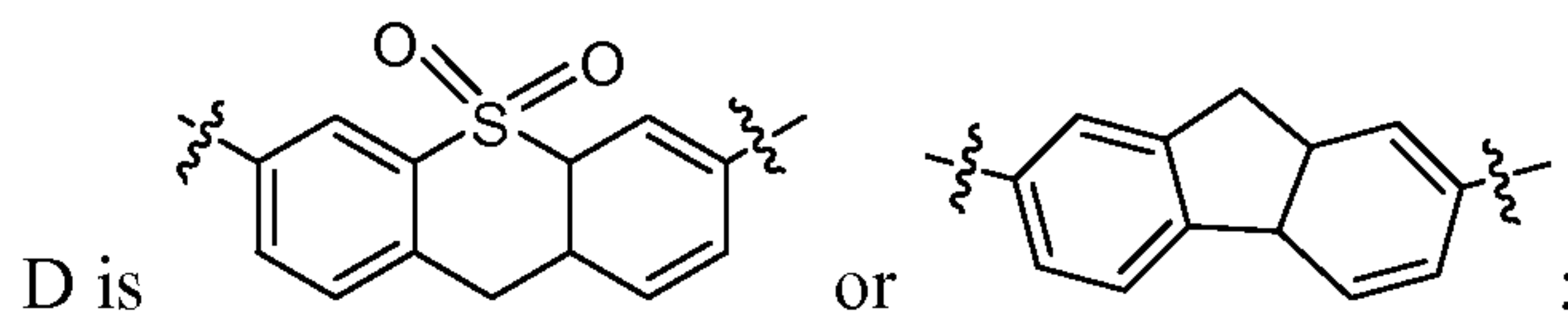


or a pharmaceutically acceptable salt thereof.

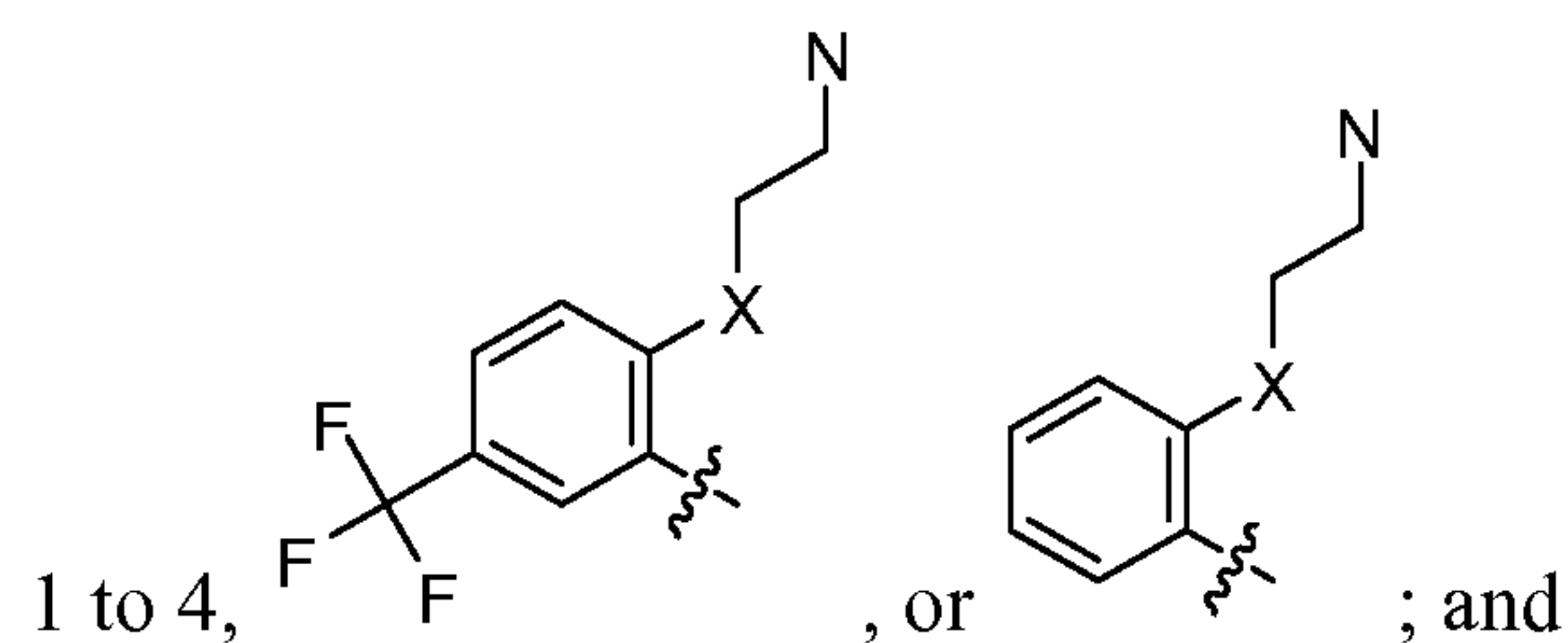
The present invention also provides compounds of Formula VIII:



wherein:

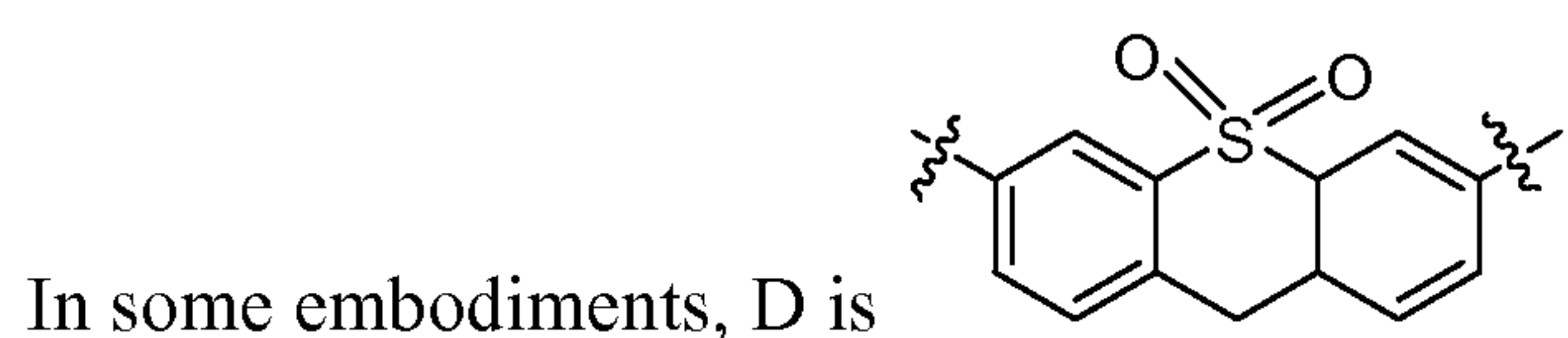


each B is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently,



each X is, independently, O or S;

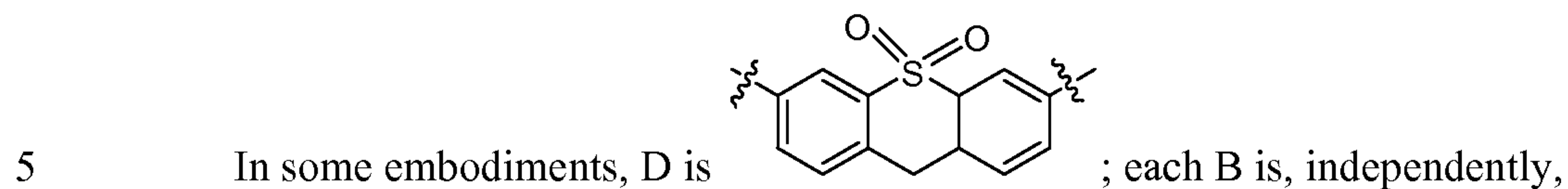
or a pharmaceutically acceptable salt thereof.

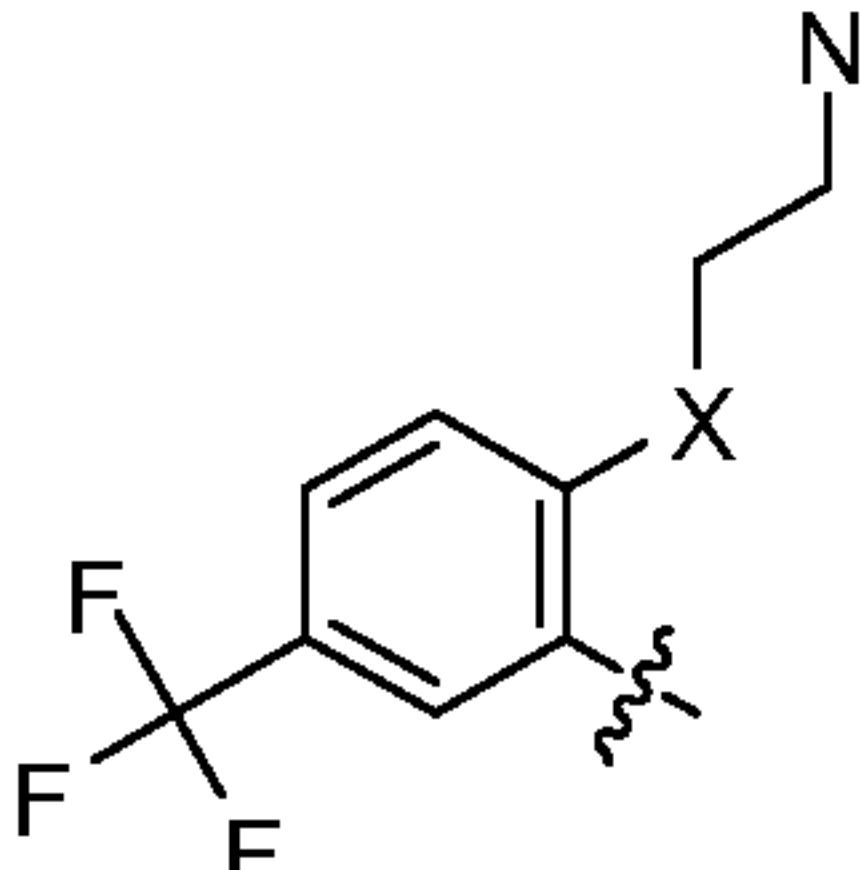


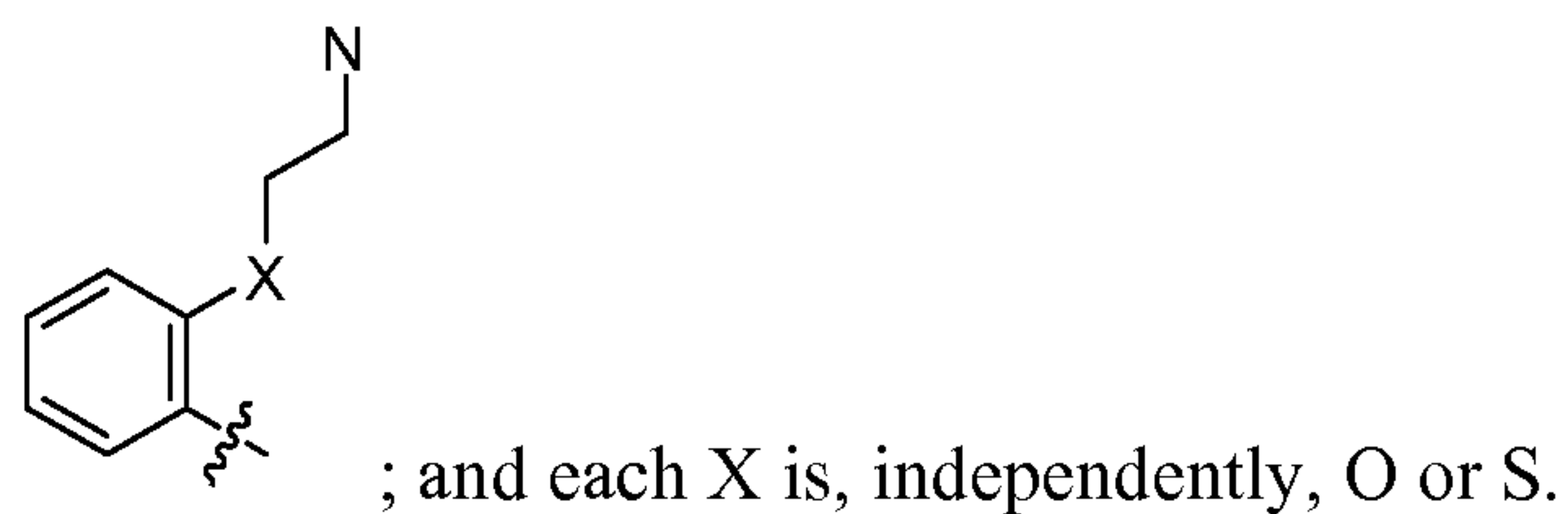
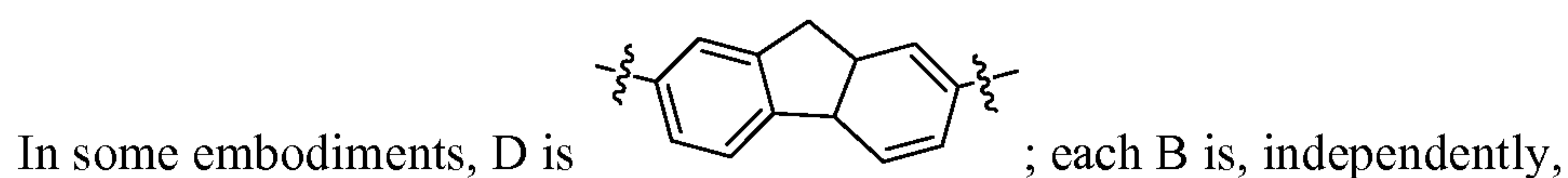
In any of the above embodiments, each B is, independently,

$-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

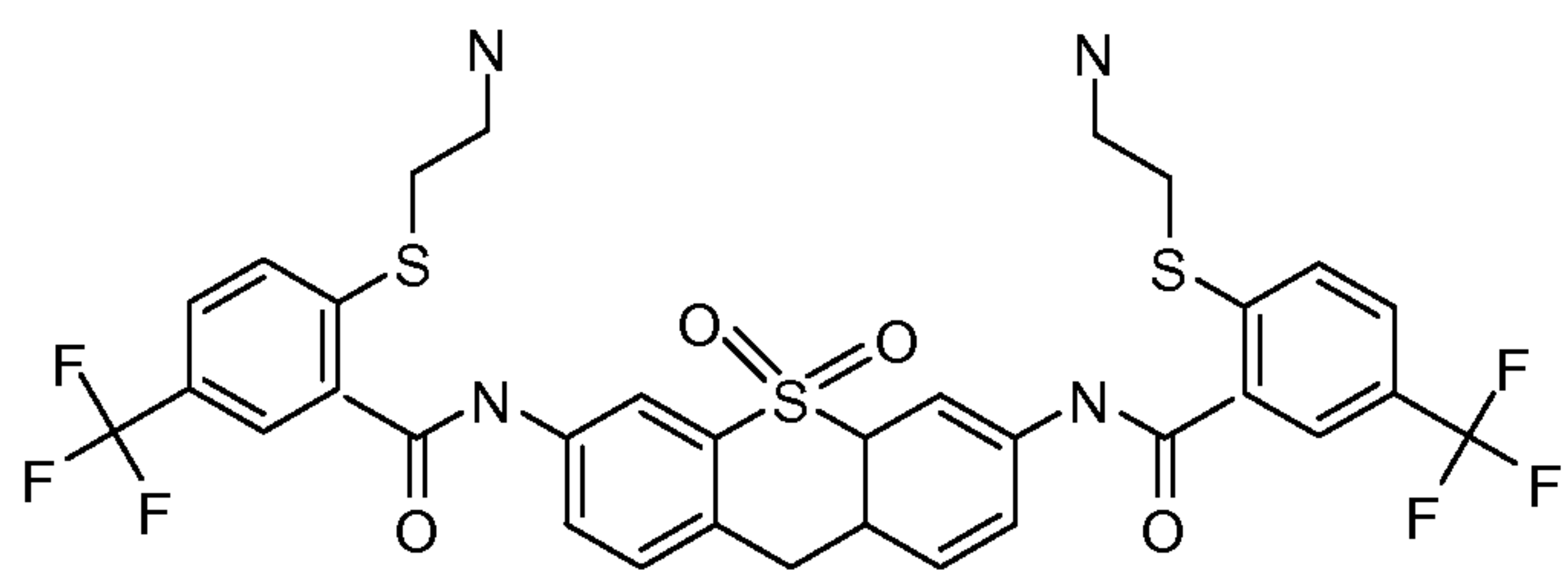
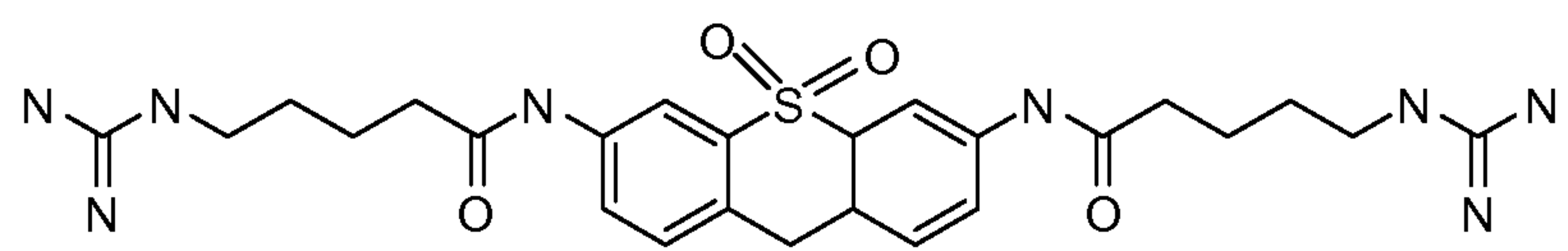
In any of the above embodiments, each X is S.



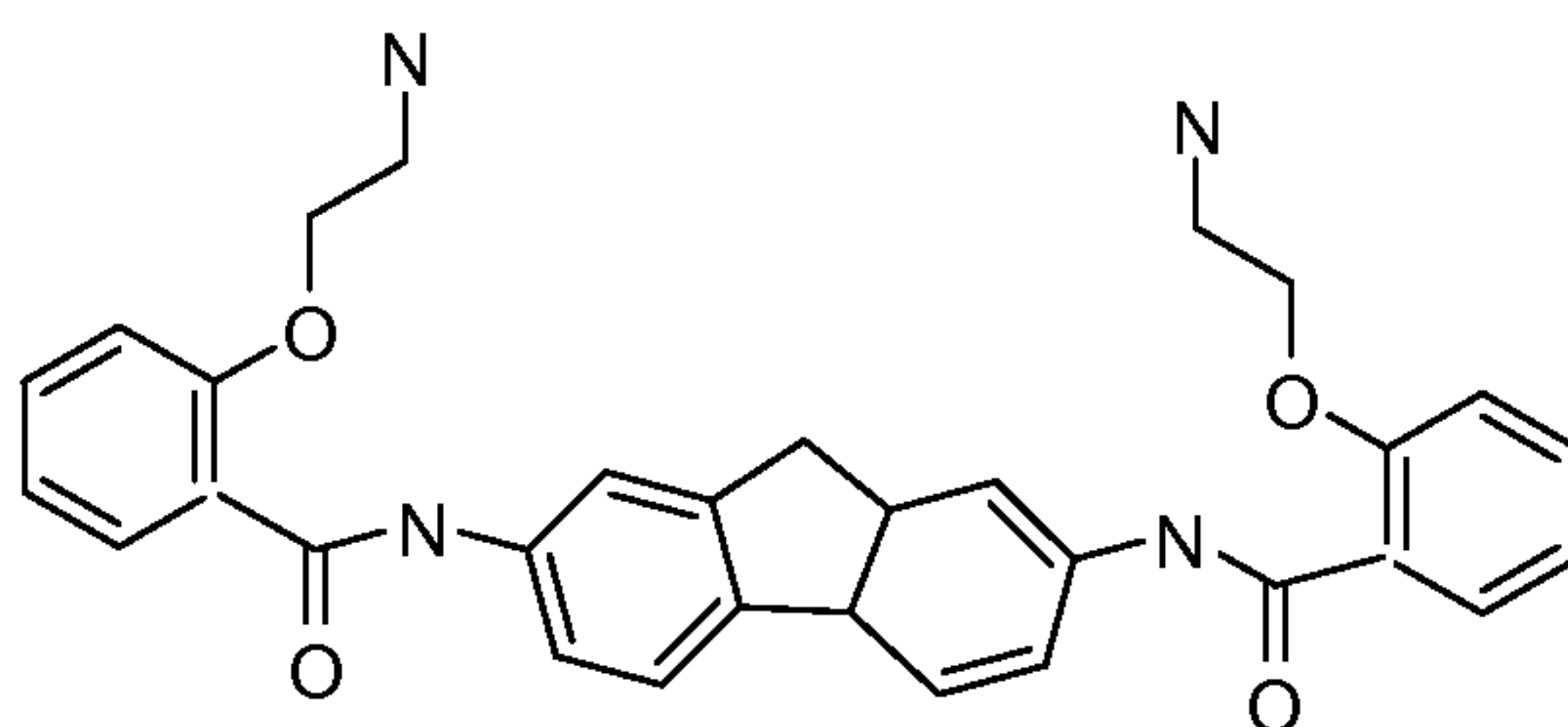
$-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 3 or 4, or ; and each X is S.



10 In some embodiments, the compound is chosen from:



and



or pharmaceutically acceptable salt thereof.

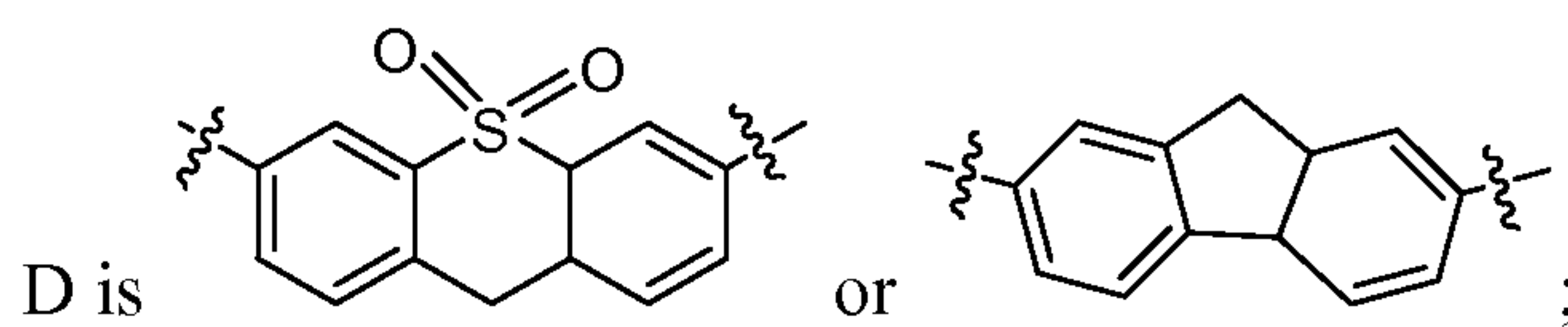
In some embodiments, any one or more of the above compounds may be excluded from any of the genus of compounds described above.

5 The present invention also provides compositions comprising one or more of the compounds or salts described above and a pharmaceutically acceptable carrier.

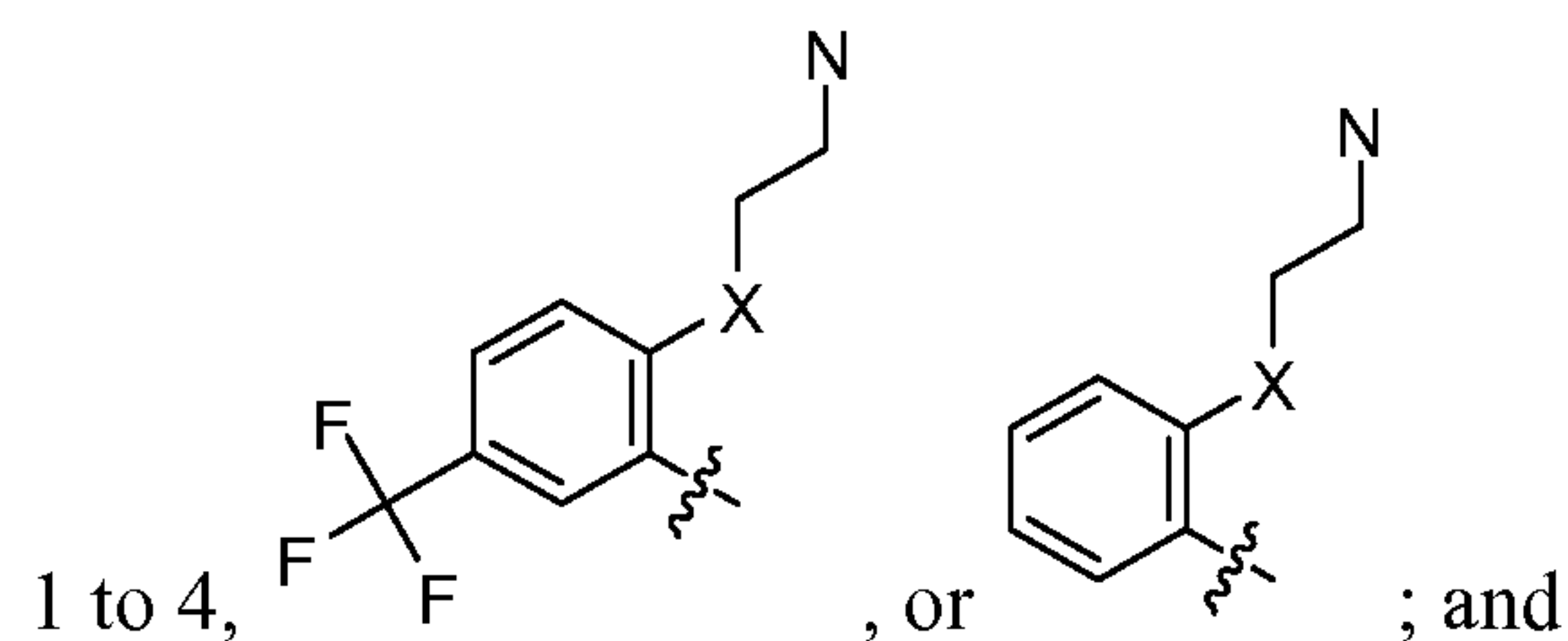
The present invention also provides methods of treating malaria in an animal comprising administering to the animal a therapeutically effective amount of a compound of Formula VIII:



wherein:

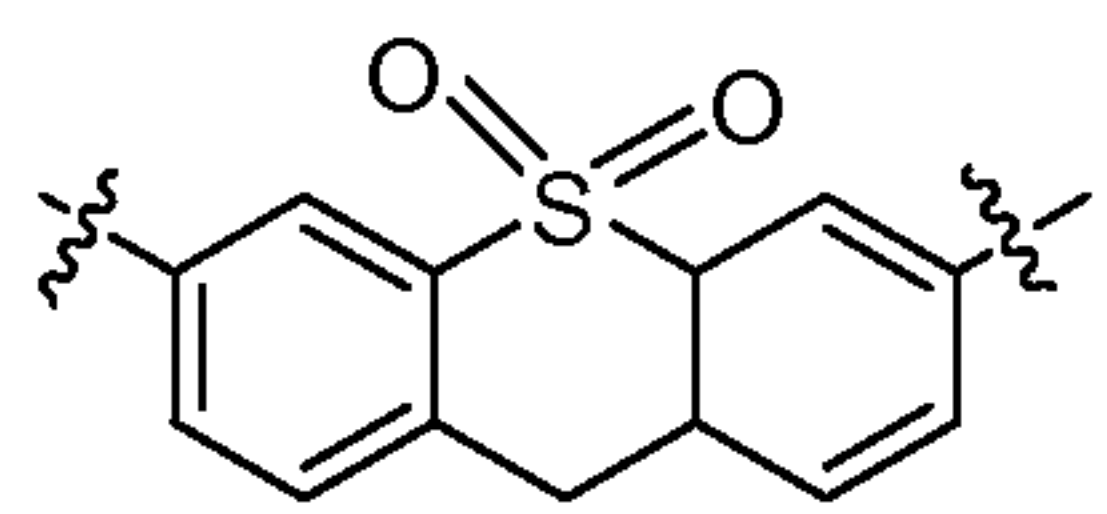


each B is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently,



15 each X is, independently, O or S;

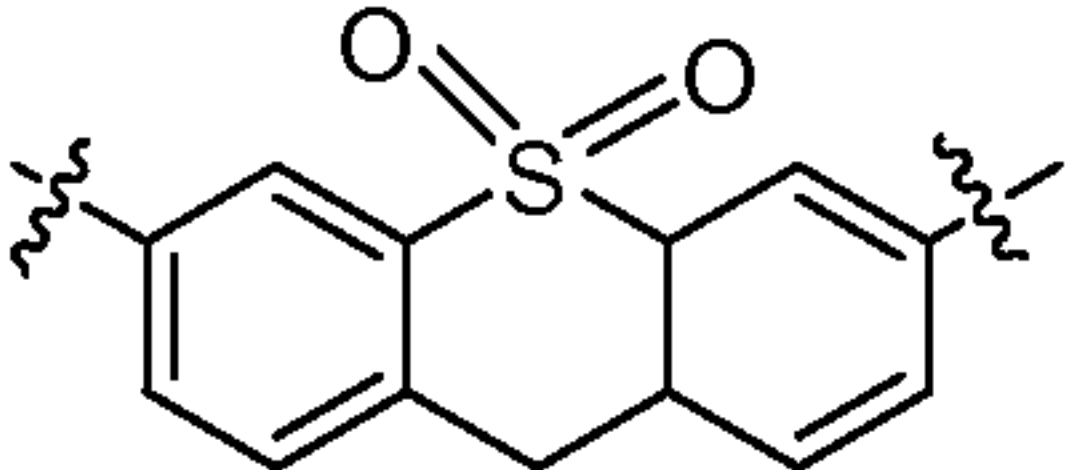
or a pharmaceutically acceptable salt thereof.

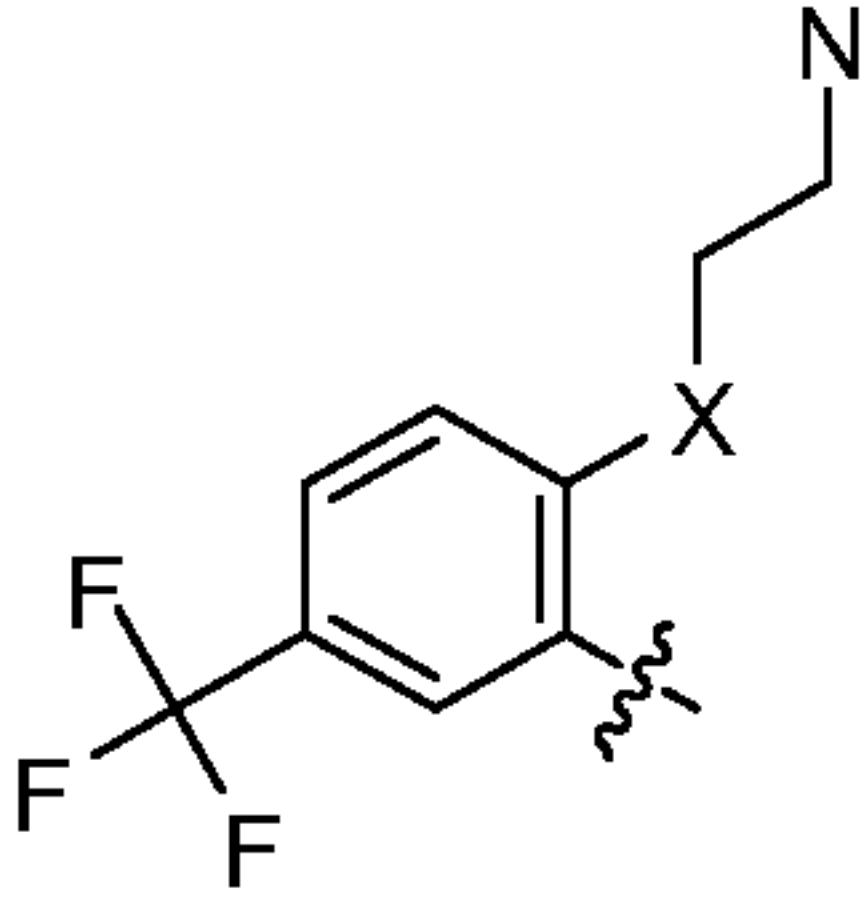


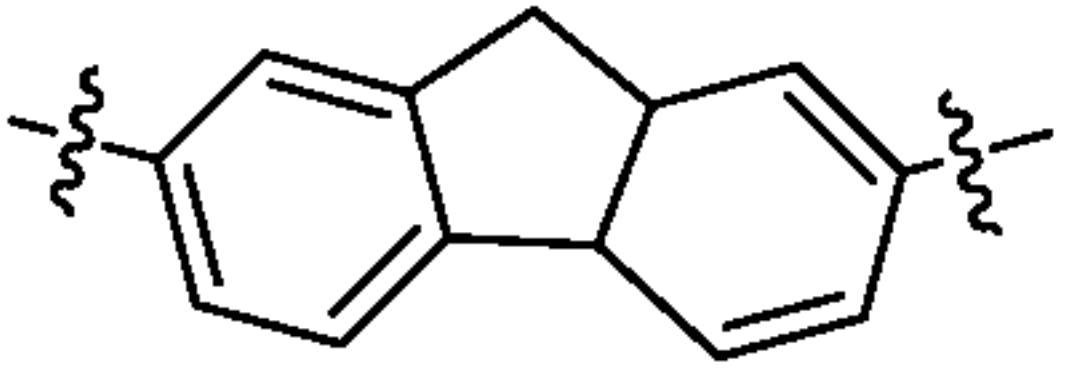
In some embodiments, D is

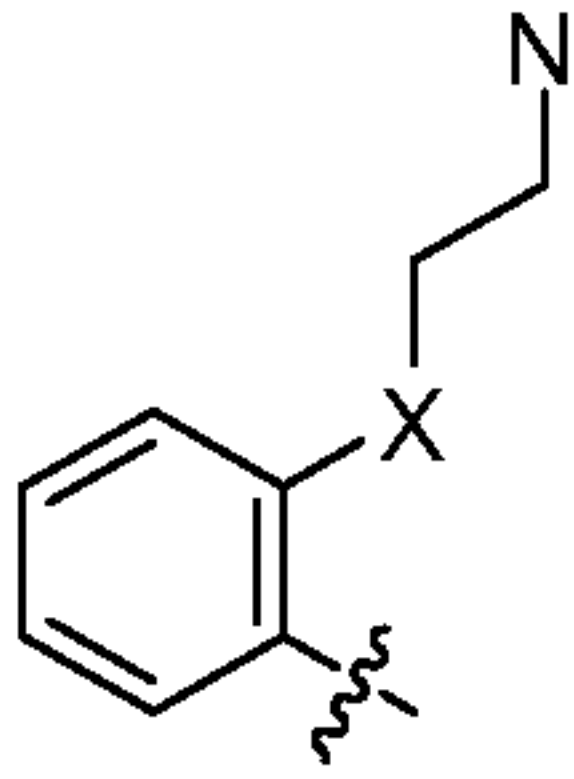
In any of the above embodiments, each B is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

20 In any of the above embodiments, each X is S.

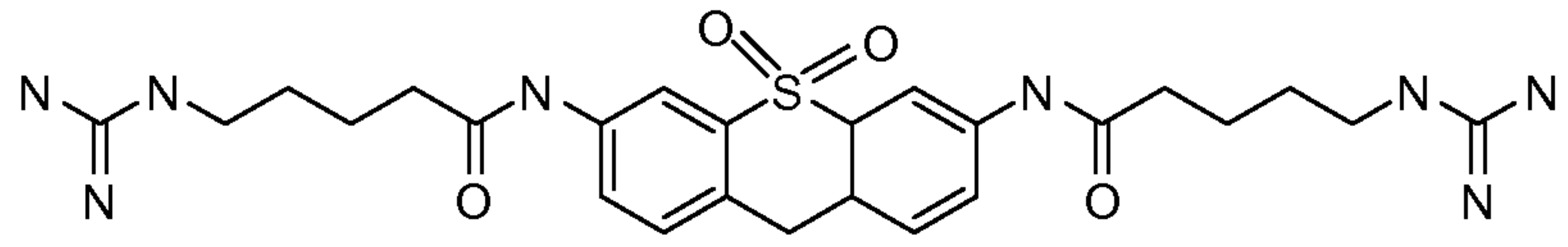
In some embodiments, D is ; each B is, independently,

$-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 3 or 4, or ; and each X is S.

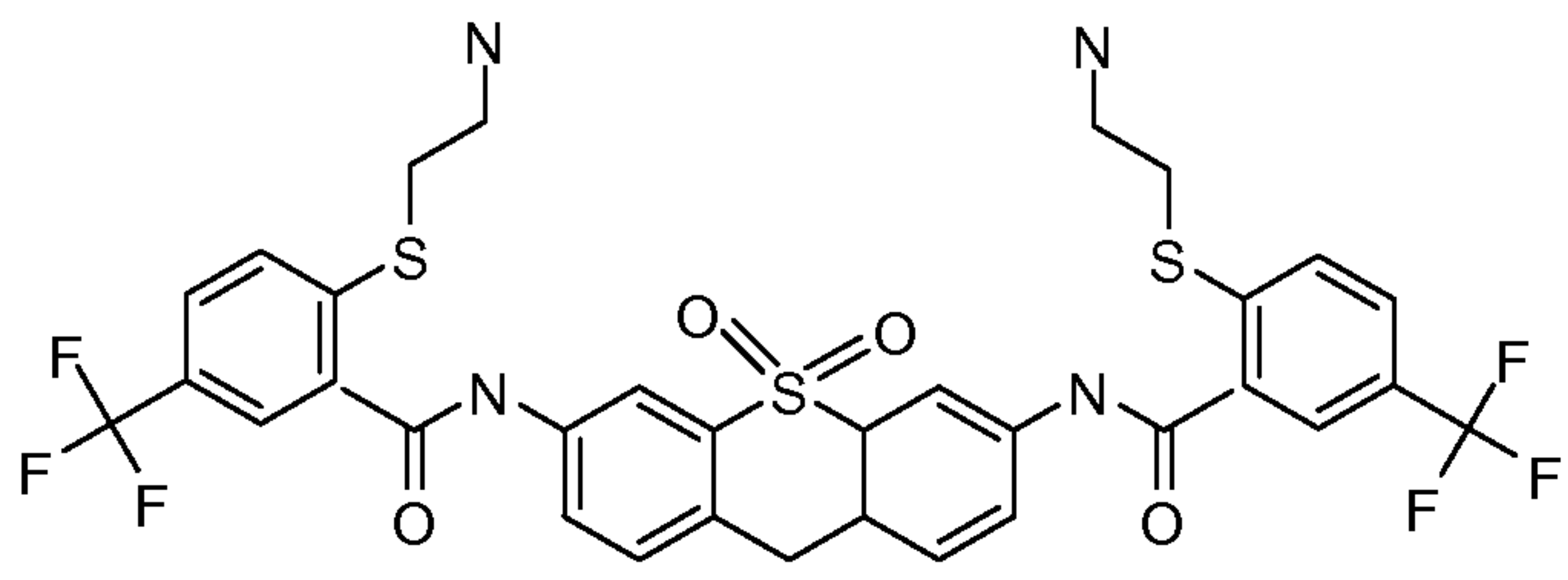
In some embodiments, D is ; each B is, independently,

5 ; and each X is, independently, O or S.

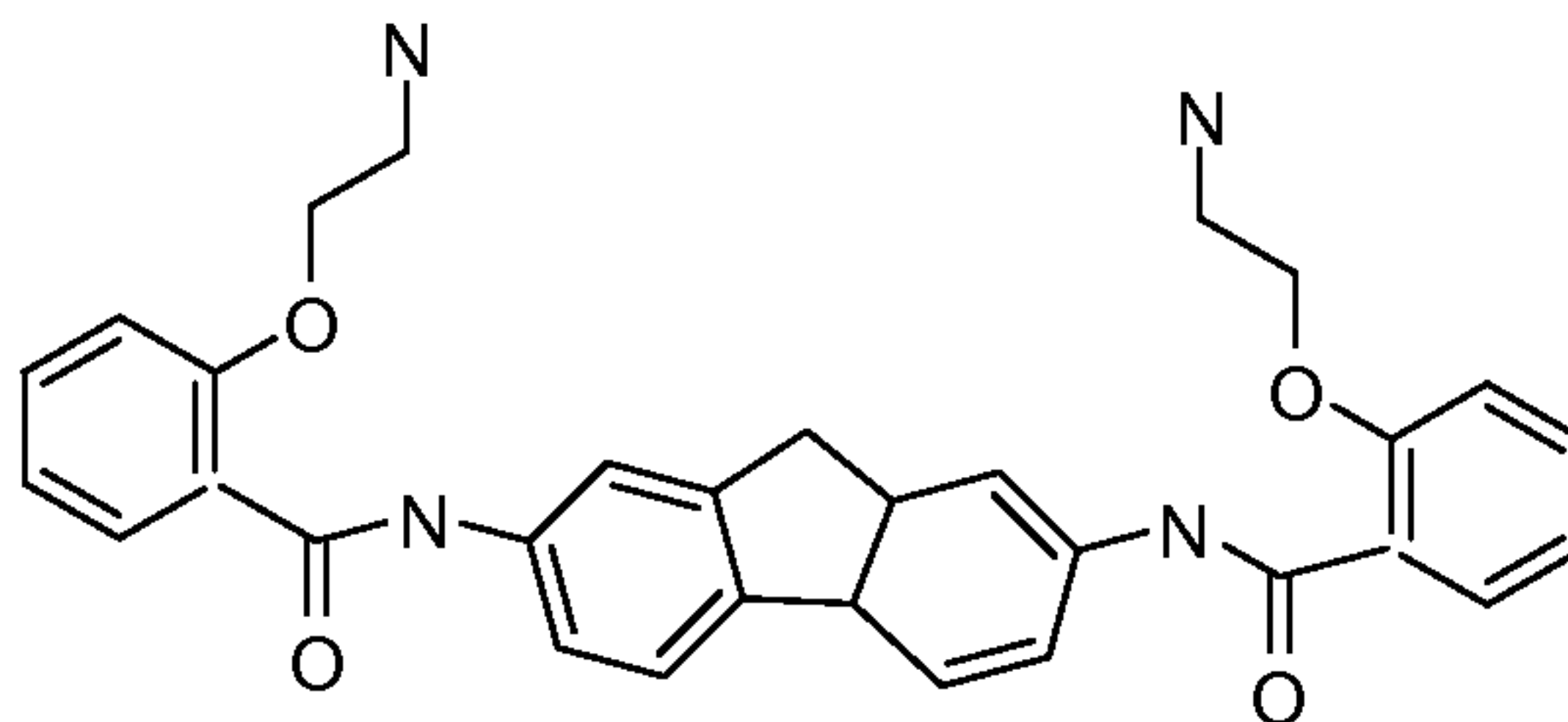
In some embodiments, the compound is chosen from:



Compound 154



Compound 155 and

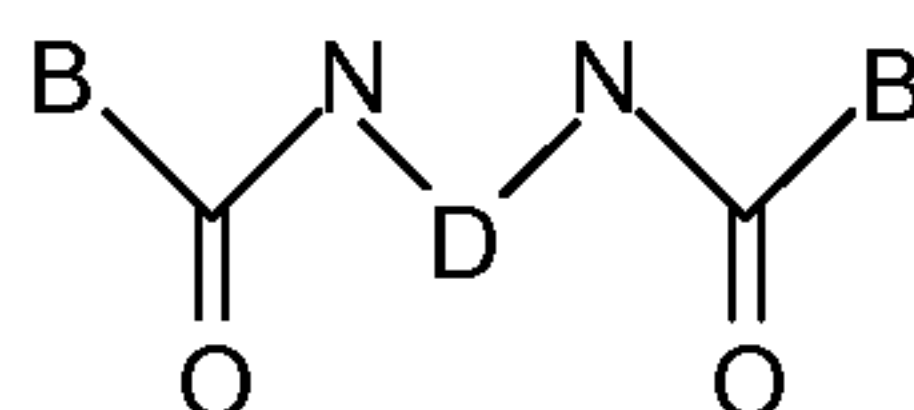


Compound 156

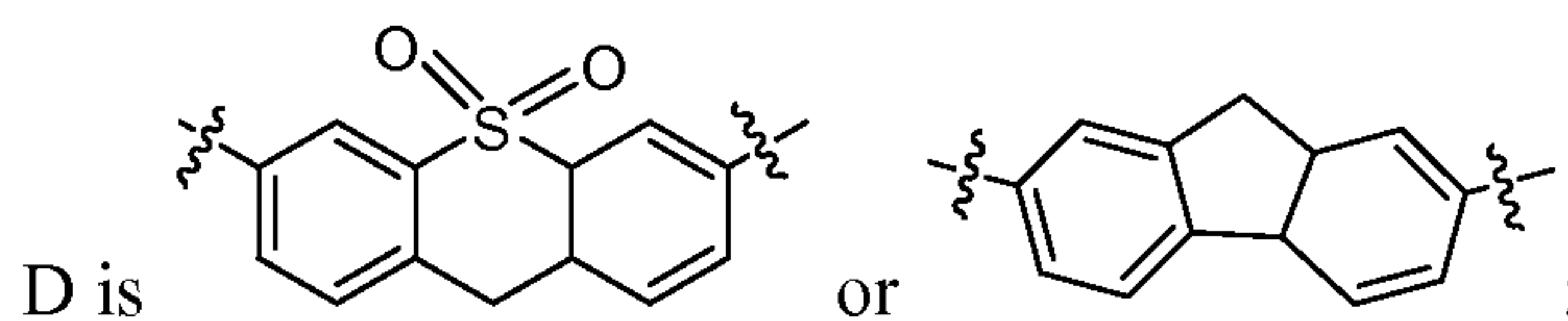
or pharmaceutically acceptable salt thereof.

In any of the above embodiments, the malaria can be chloroquine-sensitive or chloroquine-resistant.

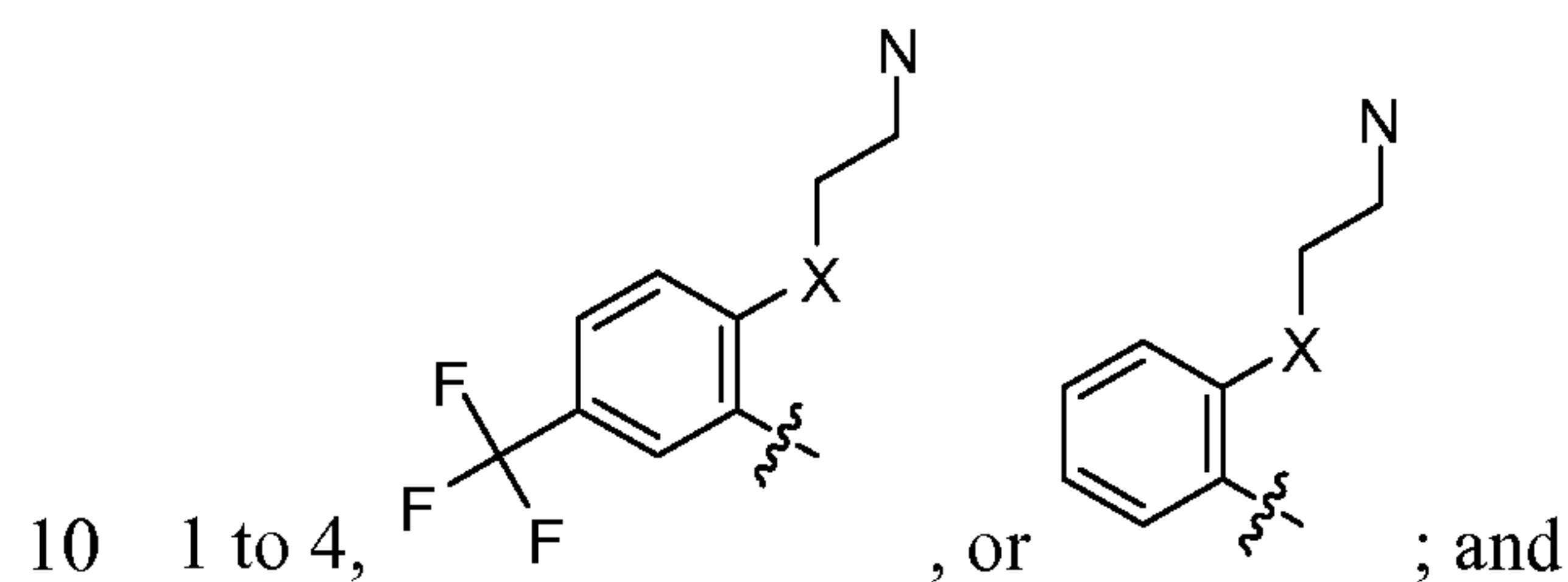
The present invention also provides methods of killing or inhibiting the growth of a *Plasmodium* species comprising contacting the species with an effective amount of a
5 compound of Formula VIII:



wherein:

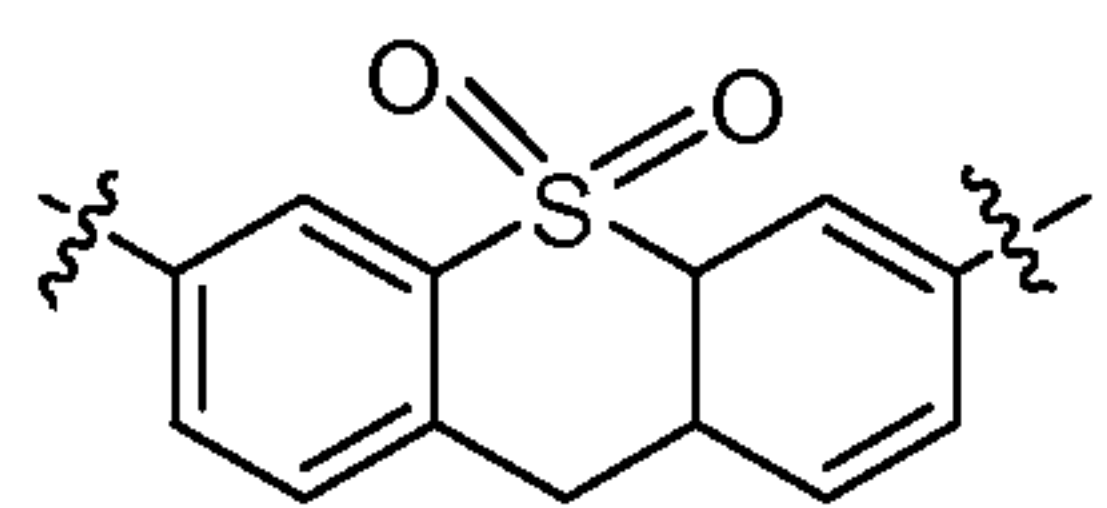


each B is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently,



each X is, independently, O or S;

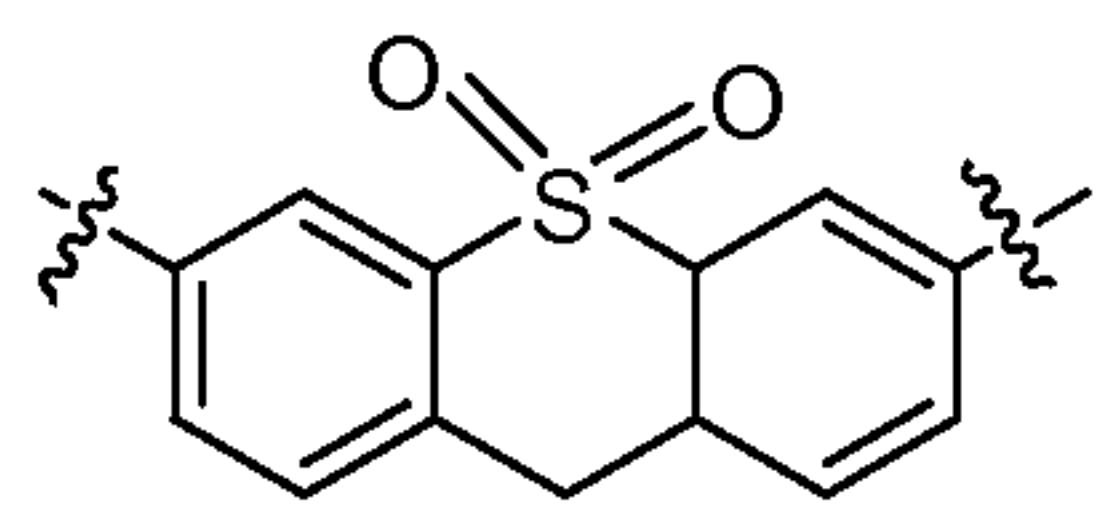
or a pharmaceutically acceptable salt thereof.



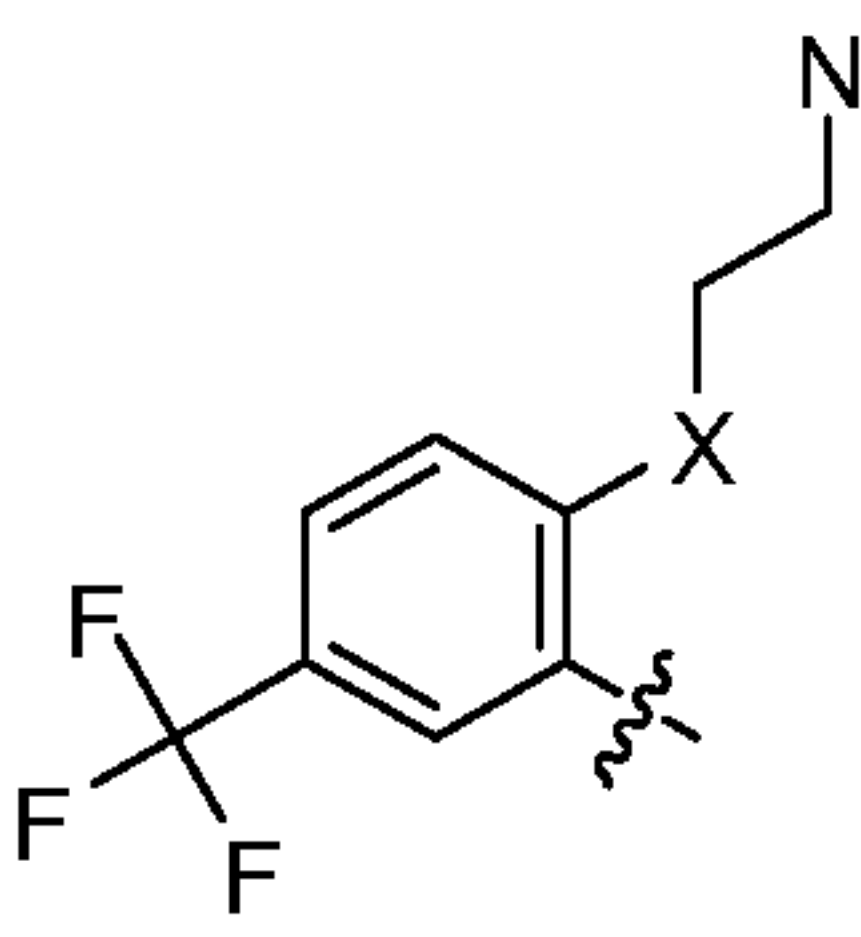
In some embodiments, D is

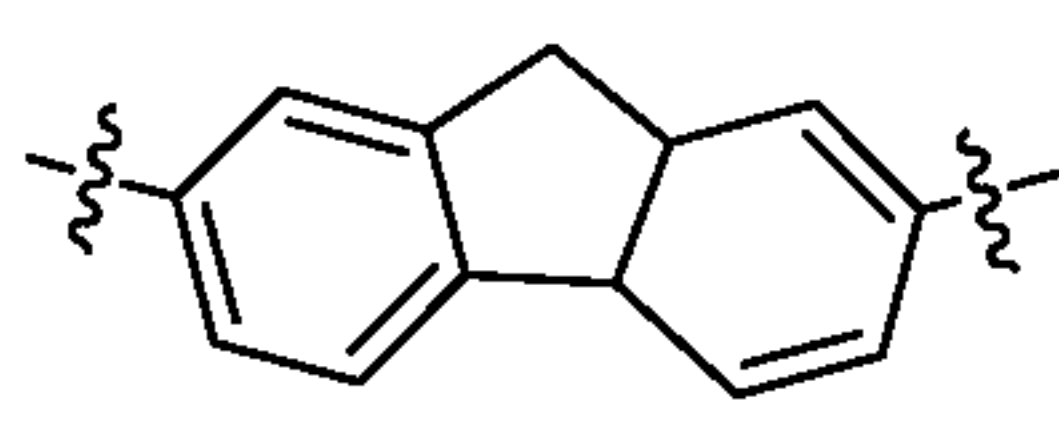
In any of the above embodiments, each B is, independently,
15 $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

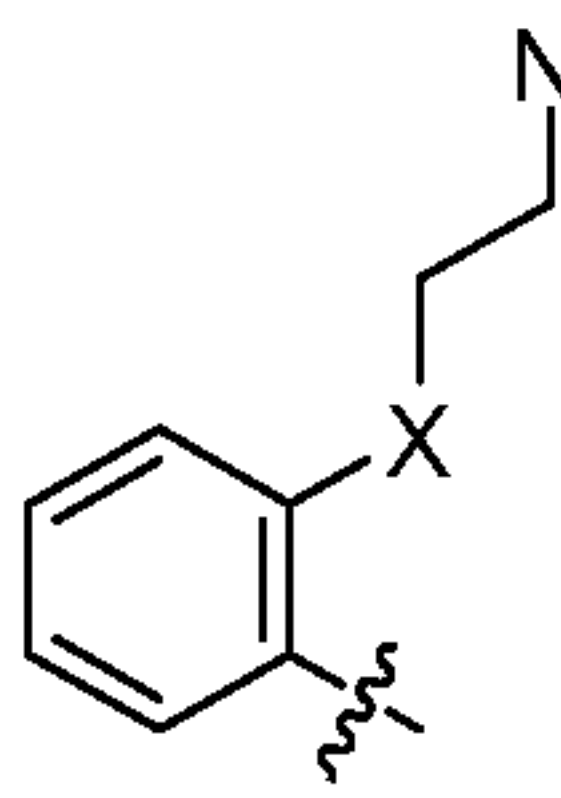
In any of the above embodiments, each X is S.



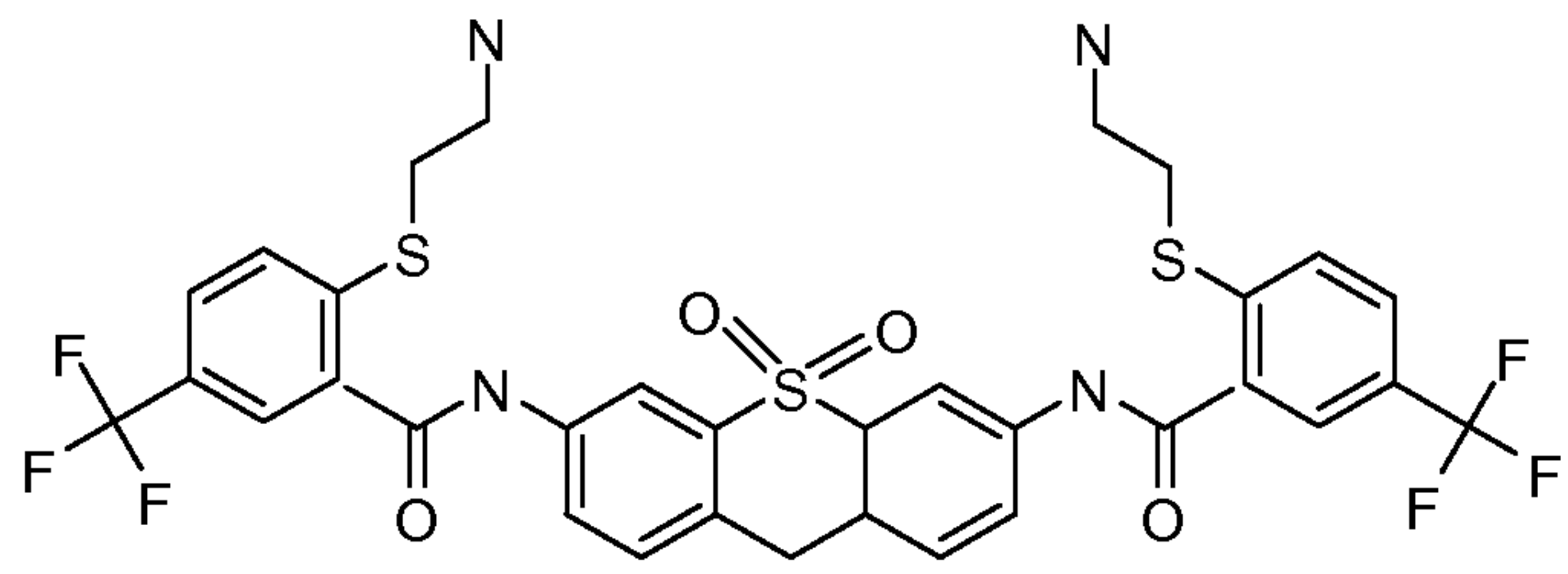
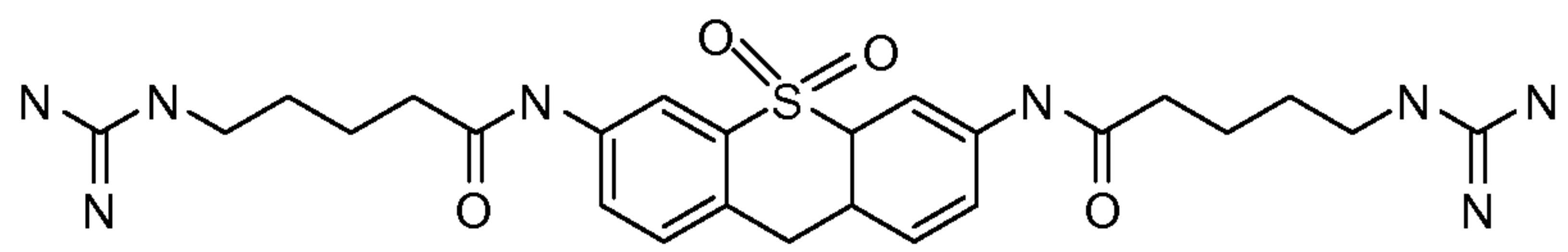
In some embodiments, D is ; each B is, independently,

$-(\text{CH}_2)_n-\text{NH}-\text{C}(=\text{NH})\text{NH}_2$, where each n is, independently, 3 or 4, or ; and each X is S.

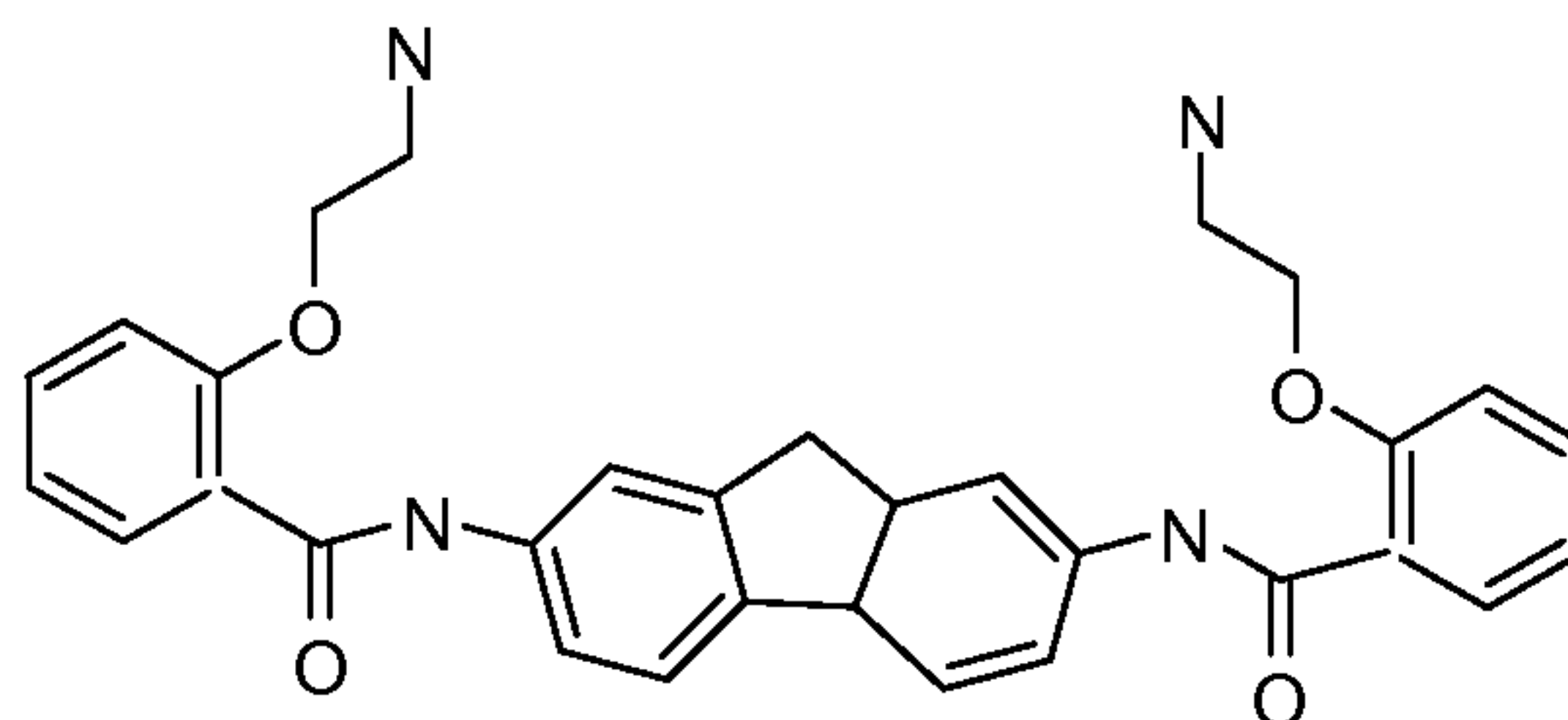
In some embodiments, D is ; each B is, independently,

; and each X is, independently, O or S.

5 In some embodiments, the compound is chosen from:



and



10 or pharmaceutically acceptable salt thereof.

It is to be understood that within any particular Formula, any one embodiment can be combined with any other embodiment(s), as deemed appropriate.

In some embodiments, the anti-malarial compound(s) can be chosen from one or more of the compounds (i.e., genres, sub-genuses, and species) disclosed in U.S. Patent

Application Publication Nos. US 2005/0287108 and/or US 2006/0041023, each of which is incorporated herein by reference in its entirety. The methods described herein can also be carried out using any one or more of the compounds disclosed as a genus, sub-genus, or species of U.S. Patent Application Publication Nos. US 2005/0287108 and/or US
5 2006/0041023.

Some of the compounds of the present invention may be capable of adopting amphiphilic conformations that allow for the segregation of polar and nonpolar regions of the molecule into different spatial regions and provide the basis for a number of uses. For example, some anti-malarial compounds may adopt amphiphilic conformations that are
10 capable of disrupting the integrity of the cell membrane of microorganisms, resulting in the inhibition of growth or the death of, for example, *Plasmodium* species.

The anti-malarial compounds can be useful as anti-malarial agents in a number of applications. For example, anti-malarial compounds can be used therapeutically to treat malaria in animals, including humans and non-human vertebrates such as wild, domestic and
15 farm animals. The malarial infection in an animal can be treated by administering to the animal an effective amount of an anti-malarial compound, or a pharmaceutical composition comprising the same. The anti-malarial compound, or composition thereof, can be administered systemically or topically and can be administered to any body site or tissue.

Although the anti-malarial compounds are suitable, other functional groups can be
20 incorporated into the compound with an expectation of similar results. In particular, thioamides and thioesters are anticipated to have very similar properties. The distance between aromatic rings can impact the geometrical pattern of the compound and this distance can be altered by incorporating aliphatic chains of varying length, which can be optionally substituted or can comprise an amino acid, a dicarboxylic acid or a diamine. The distance
25 between and the relative orientation of monomers within the compounds can also be altered by replacing the amide bond with a surrogate having additional atoms. Thus, replacing a carbonyl group with a dicarbonyl alters the distance between the monomers and the propensity of dicarbonyl unit to adopt an anti arrangement of the two carbonyl moiety and alter the periodicity of the compound. Pyromellitic anhydride represents still another
30 alternative to simple amide linkages which can alter the conformation and physical properties of the compound. Modern methods of solid phase organic chemistry (E. Atherton and R. C. Sheppard, Solid Phase Peptide Synthesis A Practical Approach IRL Press Oxford 1989) now

allow the synthesis of homodisperse compounds with molecular weights approaching 5,000 Daltons. Other substitution patterns are equally effective.

The term “malarialcidal” as used herein means that the compound inhibits, prevents, or destroys the growth or proliferation of a *Plasmodium* species.

5 The anti-malarial compounds can be incorporated into polishes, paints, sprays, or detergents formulated for application to surfaces to inhibit the growth of a *Plasmodium* species thereon. These surfaces include, but are not limited to, surfaces such as, countertops, desks, chairs, laboratory benches, tables, floors, bed stands, tools or equipment, doorknobs, and windows. The anti-malarial compounds can also be incorporated into soaps and hand
10 lotions. The present cleansers, polishes, paints, sprays, soaps, or detergents contain an anti-malarial compound that provides a malarialstatic property to them. The anti-malarial compounds can optionally contain suitable solvent(s), carrier(s), thickeners, pigments, fragrances, deodorizers, emulsifiers, surfactants, wetting agents, waxes, or oils. For example, in some aspects, the anti-malarial compounds can be incorporated into a formulation for
15 external use as a pharmaceutically acceptable skin cleanser, particularly for the surfaces of human hands. Cleansers, polishes, paints, sprays, soaps, hand lotions, and detergents and the like containing the anti-malarial compounds can be useful in homes and institutions, particularly but not exclusively, in hospital settings for the prevention of nosocomial infections.

20 In some aspects, the anti-malarial compounds include derivatives referred to as prodrugs. The expression “prodrug” denotes a derivative of a known direct acting drug, which derivative has enhanced delivery characteristics and therapeutic value as compared to the drug, and is transformed into the active drug by an enzymatic or chemical process.

 It is understood that the present invention encompasses the use, where applicable, of
25 stereoisomers, diastereomers and optical isomers of the anti-malarial compounds, as well as mixtures thereof, for treating malarial infections, an/or killing or inhibiting the growth of a *Plasmodium* species. Additionally, it is understood that stereoisomers, diastereomers, and optical isomers of the anti-malarial compounds, and mixtures thereof, are within the scope of the invention. By way of non-limiting example, the mixture may be a racemate or the mixture
30 may comprise unequal proportions of one particular stereoisomer over the other. Additionally, the anti-malarial compounds can be provided as a substantially pure stereoisomers, diastereomers and optical isomers.

In another aspect, the anti-malarial compounds can be provided in the form of an acceptable salt (i.e., a pharmaceutically acceptable salt) for treating malarial infections, and/or killing or inhibiting the growth of a *Plasmodium* species. Salts can be provided for pharmaceutical use, or as an intermediate in preparing the pharmaceutically desired form of the anti-malarial compounds. One salt that can be considered to be acceptable is the hydrochloride acid addition salt. Hydrochloride acid addition salts are often acceptable salts when the pharmaceutically active agent has an amine group that can be protonated. Since an anti-malarial compound may be polyionic, such as a polyamine, the acceptable salt can be provided in the form of a poly(amine hydrochloride).

10 Polyamides and polyesters that are useful can be prepared by typical condensation polymerization and addition polymerization processes. See, for example, G. Odian, Principles of Polymerization, John Wiley & Sons, Third Edition (1991), M. Steven, Polymer Chemistry, Oxford University Press (1999). Most commonly the polyamides are prepared by (a) thermal dehydration of amine salts of carboxylic acids, (b) reaction of acid chlorides with
15 amines and (c) aminolysis of esters. Methods (a) and (c) are of limited use in polymerizations of aniline derivatives which are generally prepared utilizing acid chlorides. The skilled chemist, however, will recognize that there are many alternative active acylating agents, for example phosphoryl anhydrides, active esters or azides, which may replace an acid chloride and which, depending of the particular polymer being prepared, may be superior to an acid
20 chloride. The acid chloride route is probably the most versatile and has been used extensively for the synthesis of aromatic polyamides.

Homopolymers derived from substituted aminobenzoic acid derivatives can also prepared in a stepwise fashion. A stepwise process comprises coupling an N-protected amino acid to an amine (or hydroxy group) and subsequently removing the amine-protecting group
25 and repeating the process. These techniques have been highly refined for synthesis of specific peptides, allow for the synthesis of specific sequences, and both solid-phase and solution techniques for peptide synthesis are directly applicable to the present invention. An alternative embodiment of the present invention is the corresponding polysulfonamides that can be prepared in analogous fashion by substituting sulfonyl chlorides for carboxylic acid
30 chlorides.

The most common method for the preparation of polyureas is the reaction of diamines with diisocyanates (Yamaguchi, et al., Polym. Bull., 2000, 44, 247). This

exothermic reaction can be carried out by solution techniques or by interfacial techniques. One skilled in organic and polymer chemistry will appreciate that the diisocyanate can be replaced with a variety of other bis-acylating agents e.g., phosgene or N,N'-(diimidazolyl)carbonyl, with similar results. Polyurethanes are prepared by comparable
5 techniques using a diisocyanate and a dialcohol or by reaction of a diamine with a bis-chloroformate.

The syntheses of the anti-malarial compounds can be carried out by routine and/or known methods such as those disclosed in, for example, U.S. Patent Application Publication Nos. US 2005/0287108 and US 2006/0041023, each of which is incorporated herein by
10 reference in its entirety. Numerous pathways are available to incorporate polar and nonpolar side chains. Phenolic groups on the monomer can be alkylated. Alkylation of the commercially available phenol will be accomplished with standard Williamson ether synthesis for the non-polar side chain with ethyl bromide as the alkylating agent. Polar sidechains can be introduced with bifunctional alkylating agents such as BOC-NH(CH₂)₂Br.
15 Alternatively, the phenol group can be alkylated to install the desired polar side chain function by employing the Mitsunobu reaction with BOC-NH(CH₂)₂-OH, triphenyl phosphine, and diethyl acetylenedicarboxylate. Standard conditions for reduction of the nitro groups and hydrolysis of the ester afford the amino acid. With the aniline and benzoic acid in hand, coupling can be effected under a variety of conditions. Alternatively, the hydroxy
20 group of the (di)nitrophenol can be converted to a leaving group and a functionality introduced under nucleophilic aromatic substitution conditions. Other potential scaffolds that can be prepared with similar sequences are methyl 2-nitro-4-hydroxybenzoate and methyl 2-hydroxy-4-nitrobenzoate.

The anti-malarial compounds can also be designed using computer-aided
25 computational techniques, such as *de novo* design techniques, to embody the amphiphilic properties. In general, *de novo* design of anti-malarial compounds is performed by defining a three-dimensional framework of the backbone assembled from a repeating sequence of monomers using molecular dynamics and quantum force field calculations. Next, side groups are computationally grafted onto the backbone to maximize diversity and maintain drug-like
30 properties. The best combinations of functional groups are then computationally selected to produce a cationic, amphiphilic structures. Representative compounds can be synthesized from this selected library to verify structures and test their biological activity. Novel

molecular dynamic and coarse grain modeling programs have also been developed for this approach because existing force fields developed for biological molecules, such as peptides, were unreliable in these oligomer applications (Car, R., and Parrinello, M., Phys. Rev. Lett., 55:2471-2474 (1985); Siepmann, J. I., and Frenkel, D., Mol. Phys. 75:59-70 (1992); Martin, M. G., and Siepmann, J. I., J. Phys. Chem. B 103:4508-4517 (1999); Brooks, B. R., et al., J. Comp. Chem. 4:187-217 (1983)). Several chemical structural series of compounds have been prepared. See, for example, WO 02/100295 A2, which is incorporated herein by reference in its entirety. The anti-malarial compounds can be prepared in a similar manner. Molecular dynamic and coarse grain modeling programs can be used for a design approach. See, for example, U.S. Patent Application No. US 2004-0107056, and U.S. Patent Application No. US 2004-0102941, each of which is incorporated herein by reference in its entirety.

After verifying the suitability of the force field by comparing computed predictions of the structure and thermodynamic properties to molecules that have similar torsional patterns and for which experimental data are available, the fitted torsions can then be combined with bond stretching, bending, one-four, van der Waals, and electrostatic potentials borrowed from the CHARMM (Brooks, B. R., et al., J. Comp. Chem. 4:187-217 (1983)) and TraPPE (Martin, M. G., and Siepmann, J. I., J. Phys. Chem. B 103:4508-4517 (1999); Wick, C. D., et al., J. Phys. Chem. B 104:3093-3104 (2000)) molecular dynamics force fields. To identify conformations that can adopt periodic folding patterns with polar groups and apolar groups lined up on the opposite sides, initial structures can be obtained with the Gaussian package (Frisch, M., et al., Gaussian 98 (revision A.7) Gaussian Inc., Pittsburgh, Pa. 1998). Then, the parallelized plane-wave Car-Parrinello CP-MD (Car, R., and Parrinello, M., Phys. Rev. Lett. 55:2471-2474 (1985)) program, (cf. Röthlisberger, U., et al., J. Chem. Phys. 3692-3700 (1996)) can be used to obtain energies at the minimum and constrained geometries. The conformations of the compounds without side-chains can be investigated in the gas phase. Both MD and MC methods can be used to sample the conformations. The former is useful for global motions of the compound. With biasing techniques (Siepmann, J. I., and Frenkel, D., Mol. Phys. 75:59-70 (1992); Martin, M. G., and Siepmann, J. I., J. Phys. Chem. B 103:4508-4517 (1999); Vlugt, T. J. H., et al. Mol. Phys. 94:727-733 (1998)), the latter allows efficient sampling for compounds with multiple local minimum configurations that are separated by relatively large barriers.

The potential conformations are examined for positions to attach pendant groups that will impart amphiphilic character to the secondary structure. Compounds selected from the gas phase studies with suitable backbone conformations and with side-chains at the optimal positions to introduce amphiphilicity can be further evaluated in a model interfacial
5 system. n-hexane/water can be chosen because it is simple and cheap for calculations while it mimics well the lipid/water bilayer environment. Compound secondary structures that require inter-compound interactions can be identified by repeating the above-mentioned calculations using a periodically repeated series of unit cells of various symmetries (so called variable cell molecular dynamics or Monte Carlo technique) with or without solvent. The results of these
10 calculations can guide the selection of candidates for synthesis.

An example of the design, synthesis, and testing of arylamide polymers and oligomers, a related group of compounds of the invention, is presented in Tew, G. N., et al., Proc. Natl. Acad. Sci. USA 99:5110-5114 (2002), which is incorporated herein by reference in its entirety.

15 The anti-malarial compounds can be synthesized by solid-phase synthetic procedures well known to those of skill in the art. See, for example, Tew et al. (Tew, G. N., et al., Proc. Natl. Acad. Sci. USA 99:5110-5114 (2002)). See also Barany, G., et al., Int. J. Pept. Prot. Res. 30:705-739 (1987); Solid-phase Synthesis: A Practical Guide, Kates, S. A., and Albericio, F., eds., Marcel Dekker, New York (2000); and Dörwald, F. Z., Organic Synthesis
20 on Solid Phase: Supports, Linkers, Reactions, 2nd Ed., Wiley-VCH, Weinheim (2002).

One of skill in the art will recognize that the anti-malarial compounds can be tested for anti-malarial activity by methods well known to those of skill in the art. Any compound found to be active can be purified to homogeneity and re-tested to obtain an accurate IC₅₀.

The anti-malarial compounds can be administered in any conventional manner by
25 any route where they are active. Administration can be systemic, topical, or oral. For example, administration can be, but is not limited to, parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, oral, buccal, or ocular routes, or intravaginally, by inhalation, by depot injections, or by implants. Thus, modes of administration for the anti-malarial compounds (either alone or in combination with other pharmaceuticals) can be, but
30 are not limited to, sublingual, injectable (including short-acting, depot, implant and pellet forms injected subcutaneously or intramuscularly), or by use of vaginal creams, suppositories, pessaries, vaginal rings, rectal suppositories, intrauterine devices, and

transdermal forms such as patches and creams. The selection of the specific route of administration and the dose regimen is to be adjusted or titrated by the clinician according to methods known to the clinician to obtain the desired clinical response.

The amount of any particular anti-malarial compound to be administered is that amount which is therapeutically effective. The dosage to be administered will depend on the characteristics of the subject being treated, e.g., the particular animal treated, age, weight, health, types of concurrent treatment, if any, and frequency of treatments, and can be easily determined by one of skill in the art (e.g., by the clinician). The amount of an anti-malarial compound described herein that will be effective in the treatment of malaria will depend on the nature of the malaria, and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the compositions will also depend on the route of administration, and the seriousness of the disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. However, a suitable dosage range for oral administration is, generally, from about 0.001 milligram to about 200 milligrams per kilogram body weight. In some embodiments, the oral dose is from about 0.01 milligram to 100 milligrams per kilogram body weight, from about 0.01 milligram to about 70 milligrams per kilogram body weight, from about 0.1 milligram to about 50 milligrams per kilogram body weight, from 0.5 milligram to about 20 milligrams per kilogram body weight, or from about 1 milligram to about 10 milligrams per kilogram body weight. In some embodiments, the oral dose is about 5 milligrams per kilogram body weight.

The pharmaceutical compositions and/or formulations containing the anti-malarial compounds and a suitable carrier can be solid dosage forms which include, but are not limited to, tablets, capsules, cachets, pellets, pills, powders and granules; topical dosage forms which include, but are not limited to, solutions, powders, fluid emulsions, fluid suspensions, semi-solids, ointments, pastes, creams, gels and jellies, and foams; and parenteral dosage forms which include, but are not limited to, solutions, suspensions, emulsions, and dry powder; comprising an effective amount of a anti-malarial compound. It is also known in the art that the active ingredients can be contained in such formulations with pharmaceutically acceptable diluents, fillers, disintegrants, binders, lubricants, surfactants, hydrophobic vehicles, water soluble vehicles, emulsifiers, buffers, humectants, moisturizers, solubilizers, preservatives and the like. The means and methods for administration are known

in the art and an artisan can refer to various pharmacologic references for guidance. For example, Modern Pharmaceutics, Banker & Rhodes, Marcel Dekker, Inc. (1979); and Goodman & Gilman's The Pharmaceutical Basis of Therapeutics, 6th Edition, MacMillan Publishing Co., New York (1980) can be consulted.

5 The anti-malarial compounds can be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. The anti-malarial compounds can be administered by continuous infusion subcutaneously over a period of about 15 minutes to about 24 hours. Formulations for injection can be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions can take
10 such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

For oral administration, the anti-malarial compounds can be formulated readily by combining these compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the anti-malarial compounds to be formulated as tablets, pills, dragees,
15 capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by, for example, adding a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, but are not limited to, fillers such as sugars, including, but
20 not limited to, lactose, sucrose, mannitol, and sorbitol; cellulose preparations such as, but not limited to, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and polyvinylpyrrolidone (PVP). If desired, disintegrating agents can be added, such as, but not
25 as sodium alginate.

Dragee cores can be provided with suitable coatings. For this purpose, concentrated sugar solutions can be used, which can optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments can be added to the
30 tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include, but are not limited to, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as, e.g., lactose, binders such as, e.g., starches, and/or lubricants such as, e.g., talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds can be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers can be added. All formulations for oral administration should be in dosages suitable for such administration.

10 For buccal administration, the compositions can take the form of, e.g., tablets or lozenges formulated in a conventional manner.

For administration by inhalation, the anti-malarial compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g.,
15 dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

20 The anti-malarial compounds can also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the anti-malarial compounds can also be formulated as a depot preparation. Such long acting formulations can be
25 administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Depot injections can be administered at about 1 to about 6 months or longer intervals. Thus, for example, the anti-malarial compounds can be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly
30 soluble salt.

In transdermal administration, the anti-malarial compounds can be applied to a plaster, or can be applied by transdermal, therapeutic systems that are consequently supplied to the organism.

The pharmaceutical compositions comprising the anti-malarial compounds also can
5 comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include, but are not limited to, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as, e.g., polyethylene glycols.

In another embodiment, the anti-malarial compounds described herein can be
10 delivered in a vesicle, in particular a liposome (see, Langer, Science, 1990, 249, 1527-1533; Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*).

In yet another embodiment, the anti-malarial compounds described herein can be
15 delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng., 1987, 14, 201; Buchwald et al., Surgery, 1980, 88, 507 Saudek et al., N. Engl. J. Med., 1989, 321, 574). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Fla. (1974); Controlled Drug
20 Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger et al., J. Macromol. Sci. Rev. Macromol. Chem., 1983, 23, 61; see, also Levy et al., Science, 1985, 228, 190; During et al., Ann. Neurol., 1989, 25, 351; Howard et al., J. Neurosurg., 1989, 71, 105). In yet another embodiment, a controlled-release system can be placed in proximity of the target of the anti-malarial compounds described herein, e.g., the
25 liver, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138 (1984)). Other controlled-release systems discussed in the review by Langer, Science, 1990, 249, 1527-1533) may be used.

The anti-malarial compounds can also be administered in combination with other
30 active ingredients such as, for example, antibiotics, including, but not limited to, vancomycin, ciprofloxacin, meropenem, oxacillin, and amikacin. The anti-malarial compounds can also be administered in combination with other anti-malarial compounds such as, for example, any

one or more of artemisinin, quinine, artesunate, sulfadoxine-pyrimethamine, hydroxychloroquine, chloroquine, amodiaquine, pyrimethamine, sulphadoxine, proguanil, mefloquine, atovaquone, primaquine, halofantrine, doxycycline, clindamycin.

Thus, the present invention also provides methods of treating malaria in an animal comprising administering to the animal in need thereof an effective amount of an anti-malarial compound or a salt thereof. The present invention also provides methods of treating malaria in an animal comprising administering to the animal in need thereof a composition comprising an anti-malarial compound, or a salt thereof. The present invention also provides methods of killing or inhibiting the growth of a *Plasmodium* species comprising contacting the species with an effective amount of an anti-malarial compound, or salt thereof. The present invention also provides methods of killing or inhibiting the growth of a *Plasmodium* species comprising contacting the species with a composition comprising an anti-malarial compound, or salt thereof. The present invention also provides methods of killing or inhibiting the growth of a chloroquine-sensitive or chloroquine-resistant *Plasmodium* species comprising contacting the species with an effective amount of an anti-malarial compound, or salt thereof. The present invention also provides methods of killing or inhibiting the growth of a chloroquine-sensitive or chloroquine-resistant *Plasmodium* species comprising contacting the species with a composition comprising an anti-malarial compound, or salt thereof. The present invention also provides methods of disrupting a food vacuole of a *Plasmodium* species comprising contacting the species with an effective amount of an anti-malarial compound, or salt thereof. The present invention also provides methods of disrupting a food vacuole of a *Plasmodium* species comprising contacting the species with a composition comprising an anti-malarial compound, or salt thereof.

An “animal in need thereof” is an animal that has been diagnosed with malaria, an animal who is suspected of having malaria, and/or an animal that is in an environment or will be traveling to an environment in which malaria is prevalent.

The present invention also provides anti-malarial compounds, or a salt thereof, or compositions comprising the same, for use in treating a malarial infection in an animal. The present invention also provides anti-malarial compounds, or a salt thereof, or compositions comprising the same, for use in killing or inhibiting the growth of a *Plasmodium* species. The present invention also provides anti-malarial compounds, or a salt thereof, or compositions comprising the same, for use in preparation of a medicament for treating a malarial infection

in an animal. The present invention also provides anti-malarial compounds, or a salt thereof, or compositions comprising the same, for use in preparation of a medicament for killing or inhibiting the growth of a *Plasmodium* species.

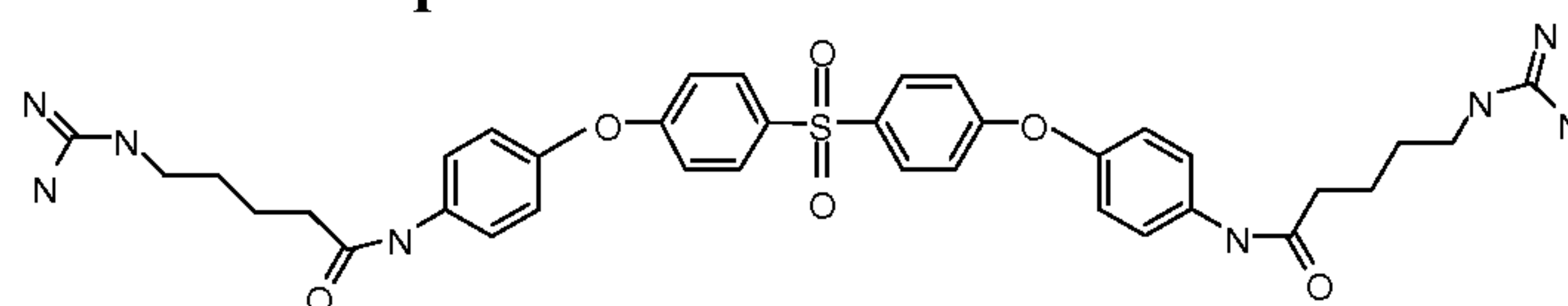
The anti-malarial compounds described herein can be combined with one, two, or
 5 three other anti-malarial compounds described herein to form a cocktail. This cocktail can also include other anti-malarial compounds.

In order that the invention disclosed herein may be more efficiently understood, examples are provided below. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting the invention in any manner.

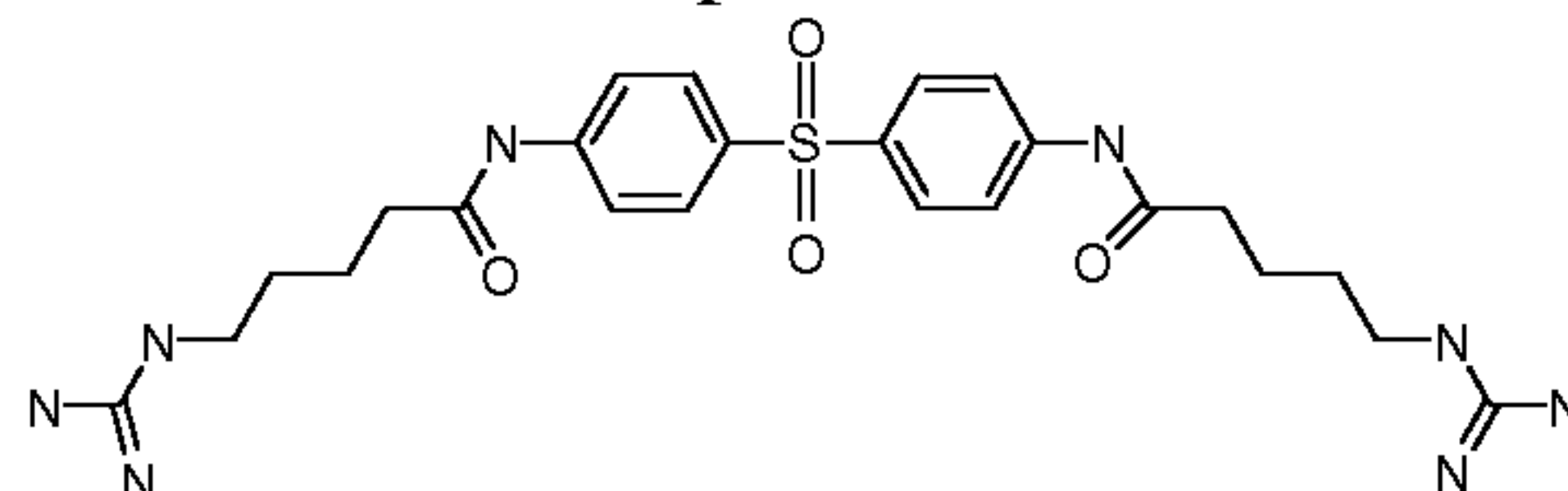
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Examples

Example 1: Synthesis of Compounds 142 and 149

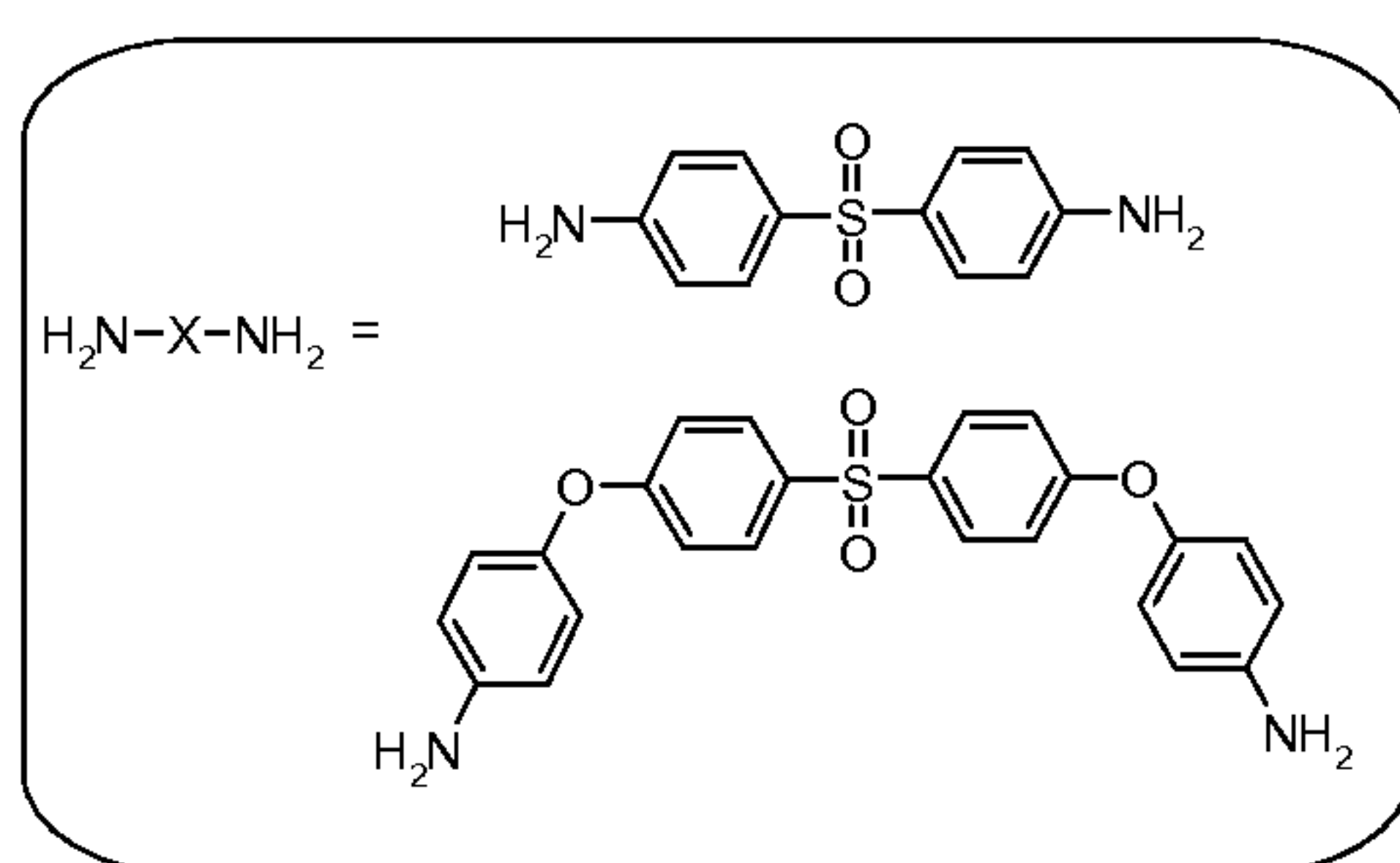
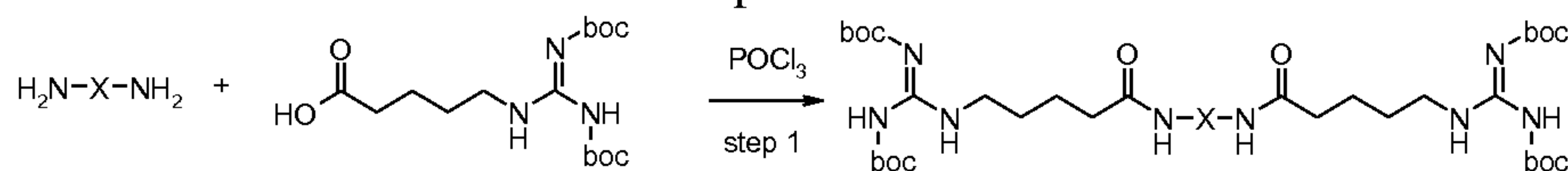


Compound 142



Compound 149

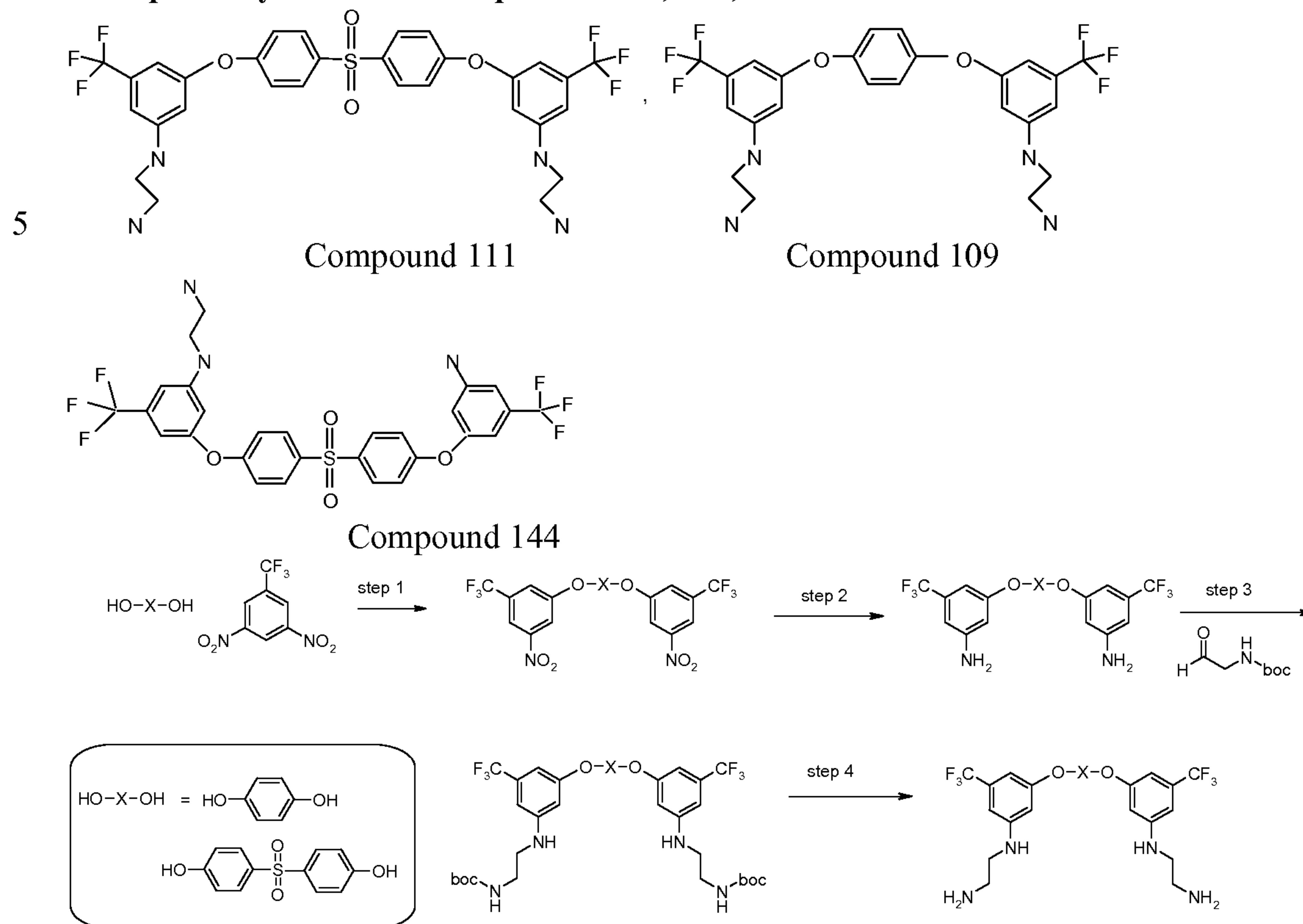
15



Step 1: The diamine (0.1 mmol) and ({[(*tert*-butoxycarbonyl)amino][(*tert*-
 butoxycarbonyl)imino]methyl} amino)pentanoic acid (4 equivalence) were dissolved in 3 mL
 20 of pyridine and cooled to 0°C. The solution was added POCl₃ (4 equiv.) dropwise and stirred
 at 0°C for 1.5 hours. The reaction was quenched with ice water. The solvent was removed on
 a rotovap.

Step 2: The product from step 1 was treated with 50% trifluoroacetic acid (TFA) in dichloromethane (DCM). The product was purified by reverse phase chromatography.

Example 2: Synthesis of Compounds 109, 111, and 144



Step 1: 319.6 mg of 4,4'-dihydroxybiphenyl in 4.0 ml of dimethylformamide (DMF) were sequentially added to 839.0 mg of K_2CO_3 , and 1.3166 g of 3,5-dinitrobenzotrifluoride. The reaction mixture was heated to 125°C with stirring for overnight. TLC analysis indicated the starting material was consumed. The reaction was quenched with water and extracted with ethyl acetate (EtOAc) twice. The organic phase was washed with water, brine and dried with sodium sulfate before being concentrated under reduced pressure. The product was purified by column chromatography with a yield of 865.6 mg (69%).

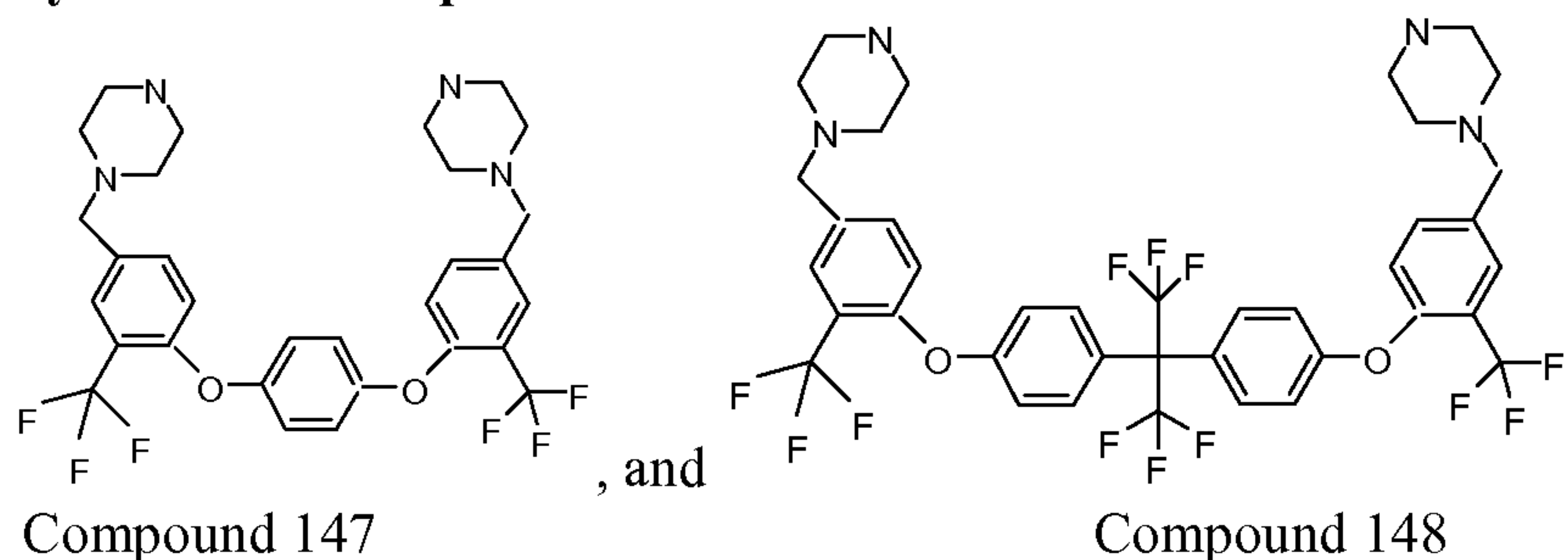
Step 2: 312.3 mg of the product formed in step 1 in 5.0 ml of MeOH was sequentially added to 365.3 mg of NH_4Cl , and 400.2 mg of Zinc dust. The reaction mixture was irradiated under microwave at 115°C for 20 minutes. LCMS analysis indicated the starting material was consumed. The reaction mixture was filtered and concentrated. The residue was quenched with water and extracted with EtOAc twice. The organic phase was

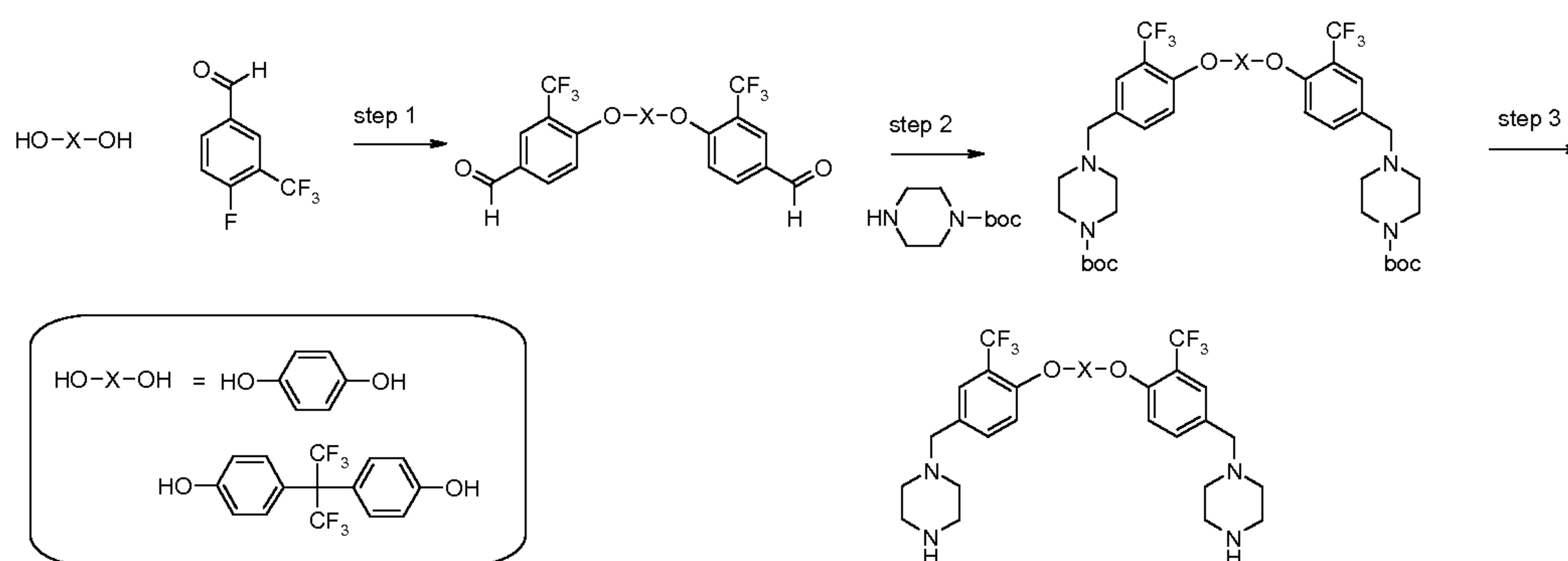
washed with water, brine and dried with sodium sulfate before being concentrated under reduced pressure. The crude product was under high vacuum for 6 hours and was used without further purification.

Step 3: 44.9 mg of diamine formed in step 2 was added to (2-oxo-ethyl)-carbamic acid tert-butyl ester (2 equiv. for compounds 109 and 111, 1 equiv. for compound 144) in 1.5 ml of anhydrous EtOH. The reaction mixture was sequentially added 3 drops of HOAc and 78.6 mg of NaCNBH₃. The reaction mixture was stirred at room temperature overnight. LCMS analysis indicated the starting material was consumed. The reaction mixture was concentrated and the residue was quenched with water and extracted with EtOAc twice. The organic phase was washed with water, brine and dried with sodium sulfate before being concentrated under reduced pressure. The product was purified by column chromatography with a yield of 72.3 mg (97%).

Step 4: 41.3 mg of Boc-protected diamine formed in step 3 in 1.5 ml of DCM was added 1.5 ml of TFA and the reaction mixture was stirred at room temperature for 45 minutes. LCMS analysis indicated the starting material was consumed. The reaction mixture was concentrated and the residue was washed with ether twice. The white powder in 2 ml of ether was further sonicated for 10 minutes. The white solid was then washed with ether twice and was under high vacuum for 12 hours. The yield was 39.6 mg.

20 Example 3: Synthesis of Compounds 148 and 147



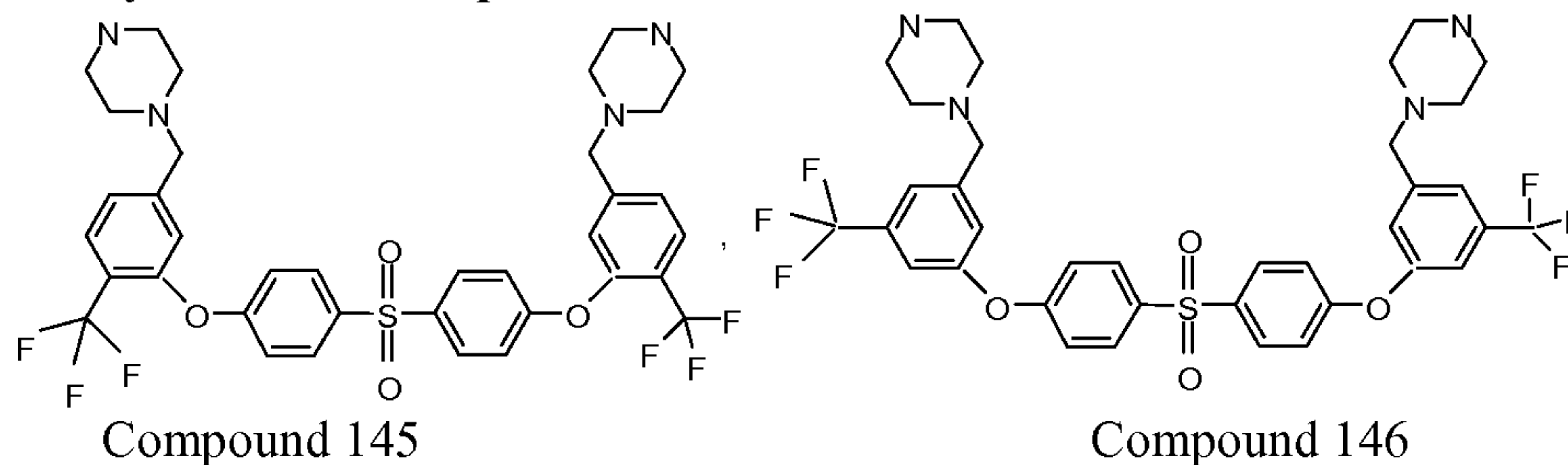


Step 1: 1.1071 g of bis-(4,4-dihydroxypheny)-bis-(trifluoromethyl)-methane in 4.0 ml of DMF were sequentially added 1.36 g of K_2CO_3 , and 1.2777 g of 4-fluoro3-trifluoromethylbenzaldehyde. The reaction mixture was heated to 130°C and stirred for 6 hours. The reaction was quenched with water and extracted with EtOAc twice. The organic phase was washed with water, brine and dried with sodium sulfate before was concentrated under reduced pressure. The product was purified by column chromatography with a yield of 400.0 mg.

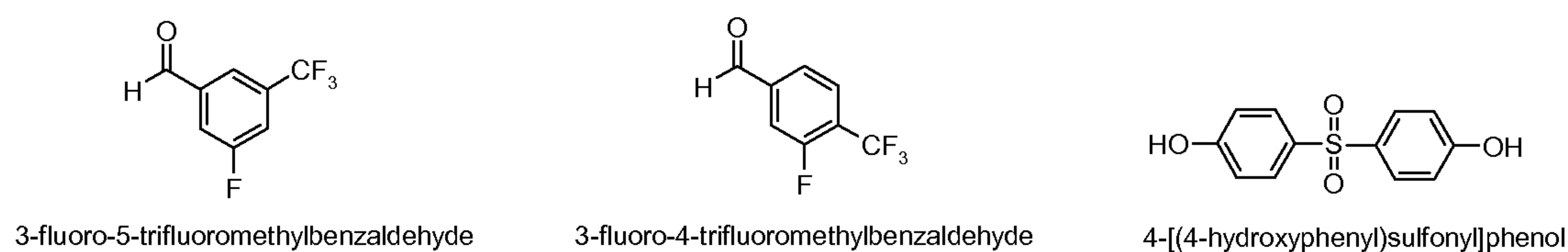
Step 2: 71.4 mg of dialdehyde formed in step 1 in 3.0 ml of dichloroethane was sequentially added 241.8 mg of piperazine-1-carboxylic acid tert-butyl ester, and 257.8 mg of $NaBH(OAc)_3$. The reaction mixture was stirred at room temperature overnight. LCMS analysis indicated the starting material was consumed. The reaction mixture was concentrated and the residue was quenched with Na_2CO_3 solution and extracted with EtOAc twice. The organic phase was washed with water, brine and dried with sodium sulfate before being concentrated under reduced pressure. The product was purified by column chromatography with a yield of 113.7 mg (91%).

Step 3: 73.0 mg of Boc-protected diamine formed in step 2 in 2.0 ml of DCM was added 2.0 ml of TFA and the reaction mixture was stirred at room temperature for 45 minutes. LCMS analysis indicated the starting material was consumed. The reaction mixture was concentrated and the residue was washed with ether twice. The white powder in 2 ml of ether was further sonicated for 10 minutes. The white solid was then washed with ether twice and was under high vacuum for 12 hours. The yield was 70.3 mg.

Example 4: Synthesis of Compounds 145 and 146

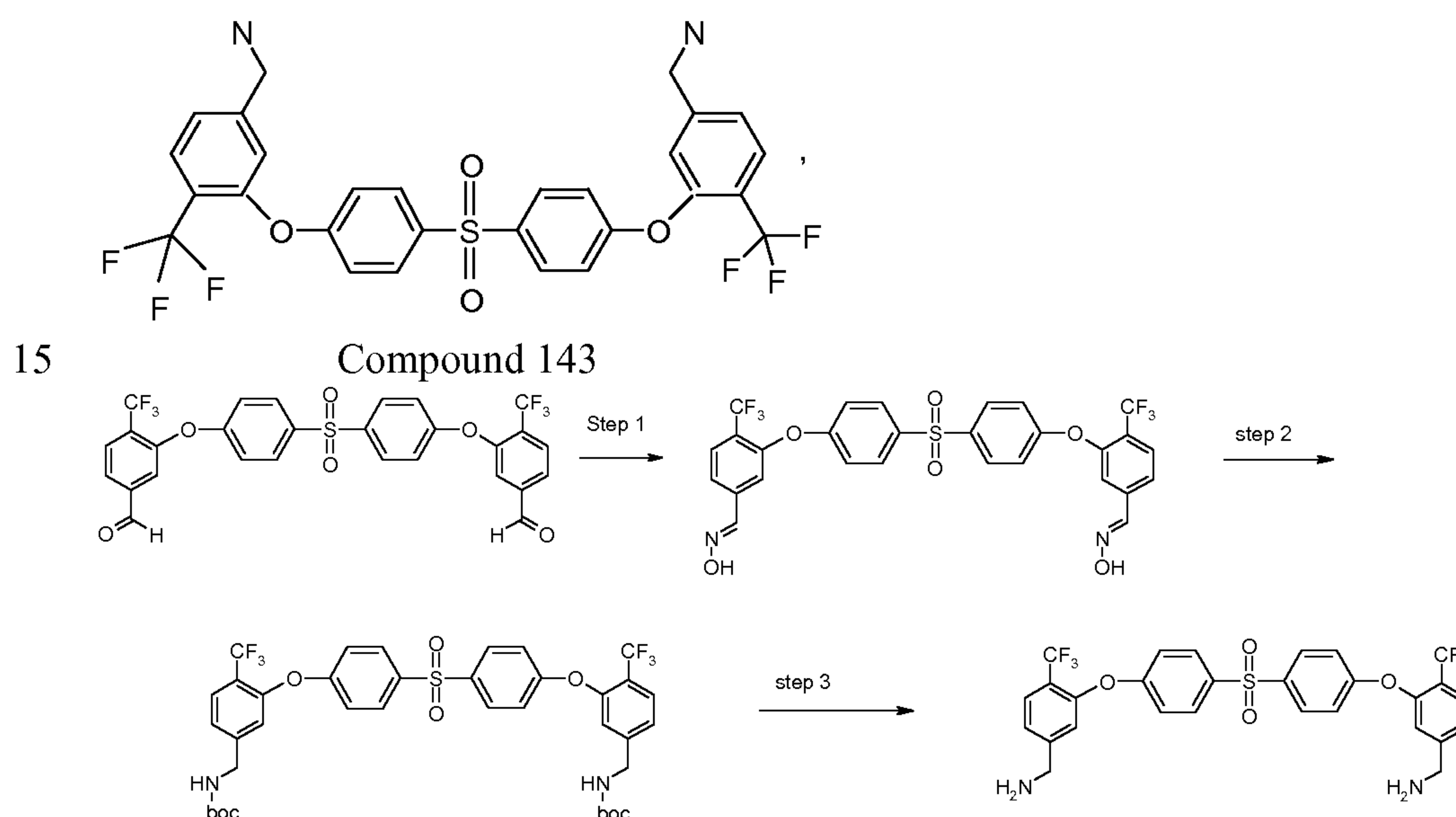


5 Compound 145 was synthesized using a similar procedure for compound 147. The starting materials for step 1 are 4-[(4-hydroxyphenyl)sulfonyl]phenol and 3-fluoro-4-trifluoromethylbenzaldehyde.



Compound 146 was synthesized using a similar procedure for compound 147. The starting materials for step 1 are 4-[(4-hydroxyphenyl)sulfonyl]phenol and 3-fluoro-5-trifluoromethylbenzaldehyde.

Example 5: Synthesis of Compound 143



Step 1: The starting material was made using the same procedure as step 1 of the synthesis of compound 145. 60.6 mg of dialdehyde formed in coupling reaction in 2.0 ml of

EtOH was sequentially added 220.3 mg of $\text{NH}_2\text{OH}\cdot\text{HCl}$, 0.5 ml of water, and 0.1 ml of pyridine. The reaction mixture was irradiated under microwave at 120°C for 30 minutes. LCMS analysis indicated the starting material was consumed. The reaction mixture was concentrated and the residue was quenched with 2 ml of water. The crude product was

5 filtered and used for the next step without further purification.

Step 2: The crude product formed in step 1 above was dissolved in 4 ml of HOAc. Zn dust (321.3 mg) was added in two portions. The resulting mixture was heated at 60°C for 6 hours. The reaction mixture was filtered and concentrated. The residue was charged with 5 ml of tetrahydrofuran (THF), 0.3 ml of triethylamine (TEA) and 100.6 mg of Boc anhydride.

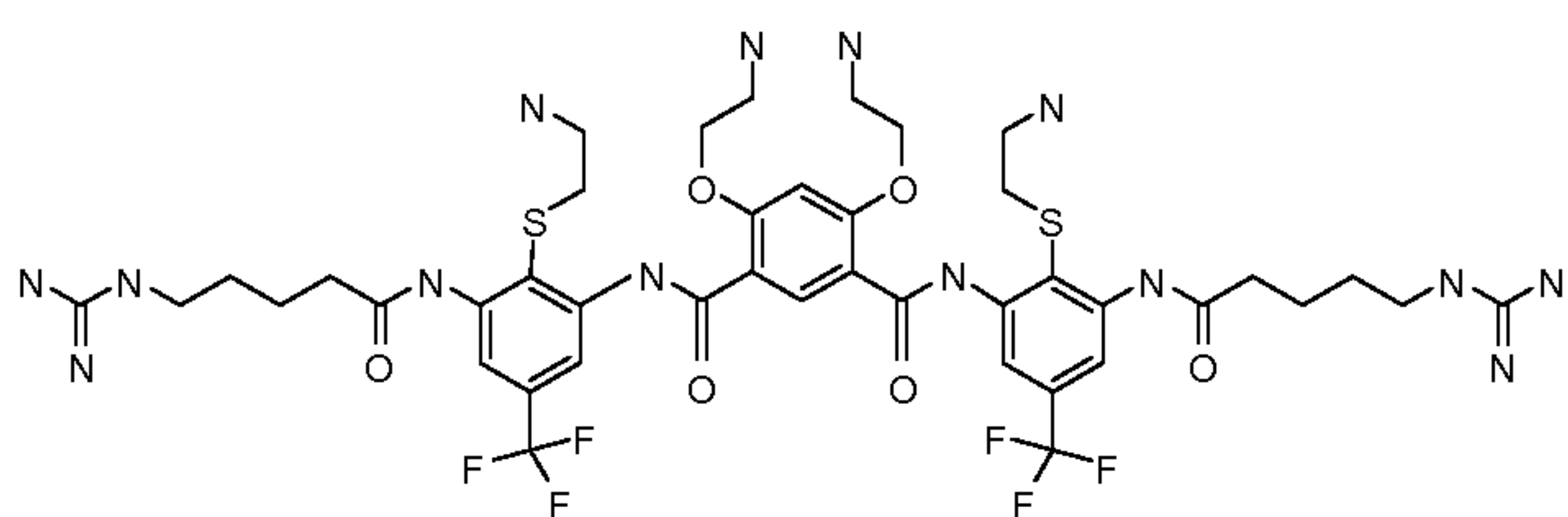
10 The reaction mixture was stirred at room temperature for 4 hours and was quenched with Na_2CO_3 solution and extracted with EtOAc twice. The organic phase was washed with water, brine and dried with sodium sulfate before being concentrated under reduced pressure. The product was purified by column chromatography with a yield of 67.8 mg (82%, two steps).

Step 3: 42.1 mg of Boc-protected diamine formed in step 2 in 2.0 ml of DCM was

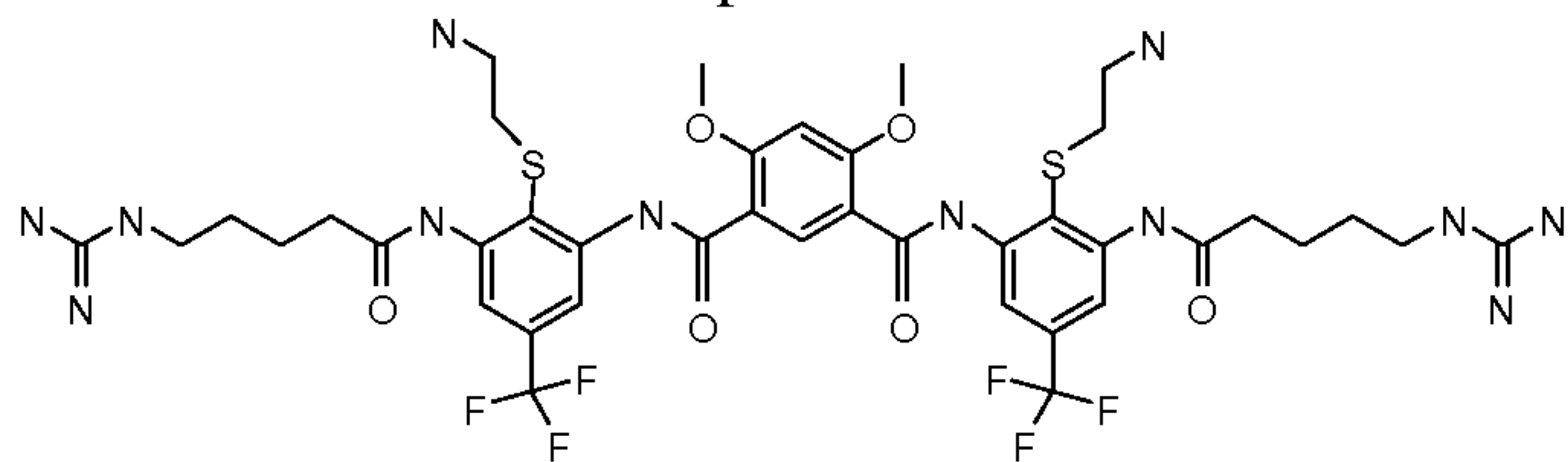
15 added 2.0 ml of TFA and the reaction mixture was stirred at room temperature for 45 minutes. LCMS analysis indicated the starting material was consumed. The reaction mixture was concentrated and the residue was washed with ether twice. The white powder in 2 ml of ether was further sonicated for 10 minutes. The white solid was then washed with ether twice and was under high vacuum for 12 hours. The yield was 30.2 mg.

20

Example 6: Synthesis of Compounds 101, 102, 107, 113, 114, 121, 123, and 124

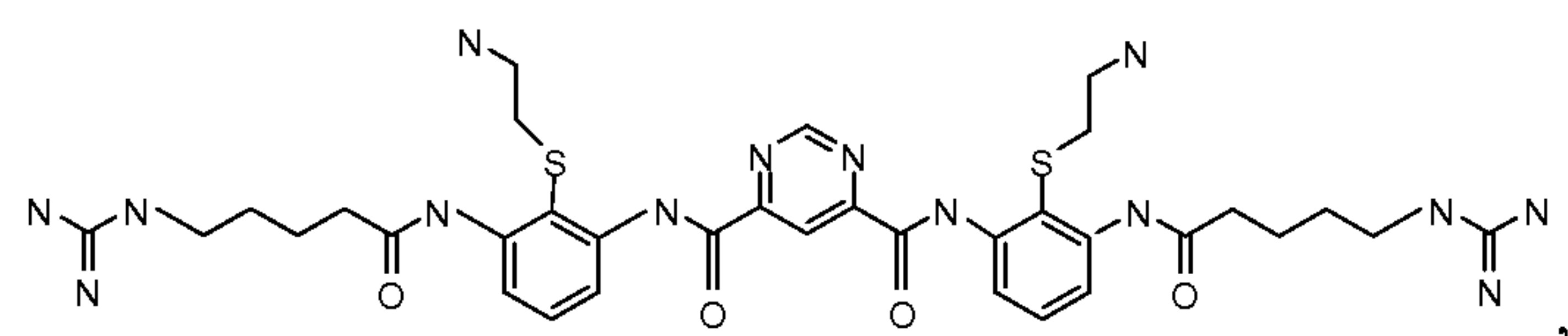


Compound 102

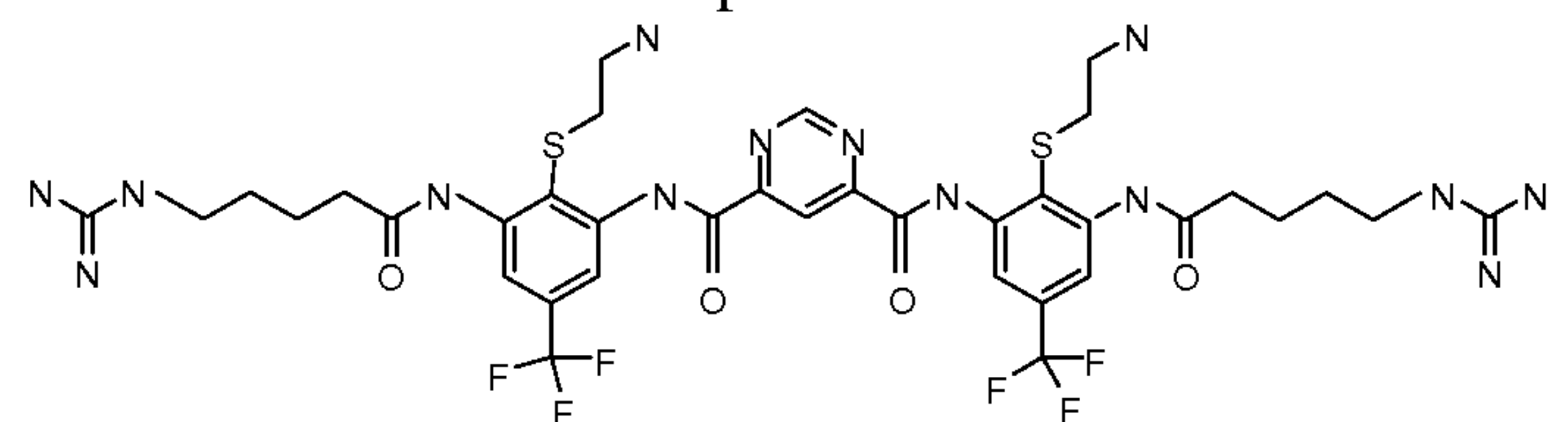


Compound 101

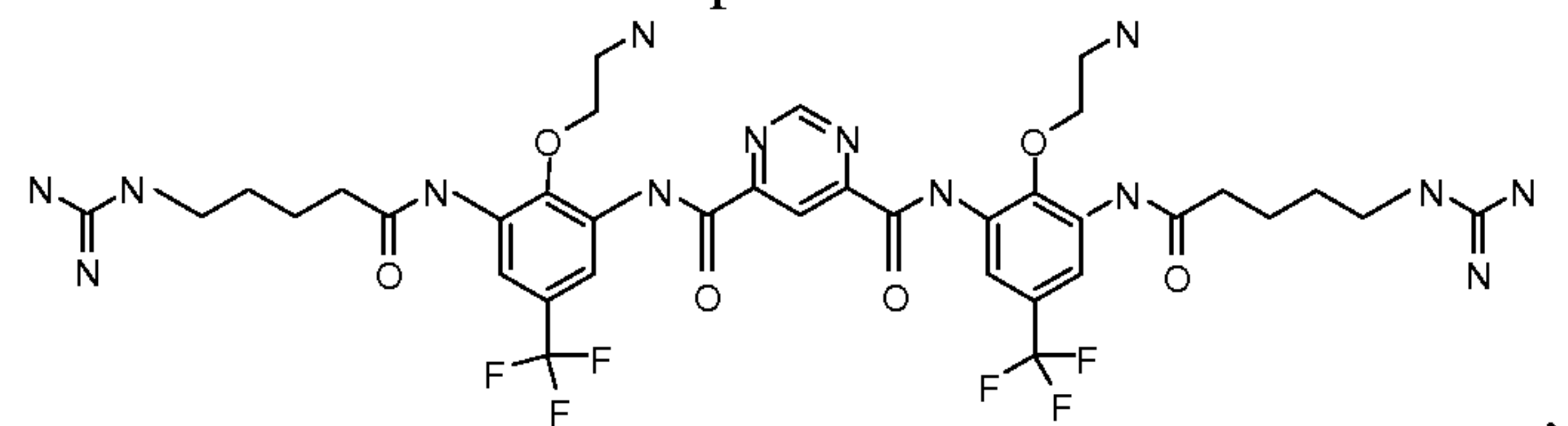
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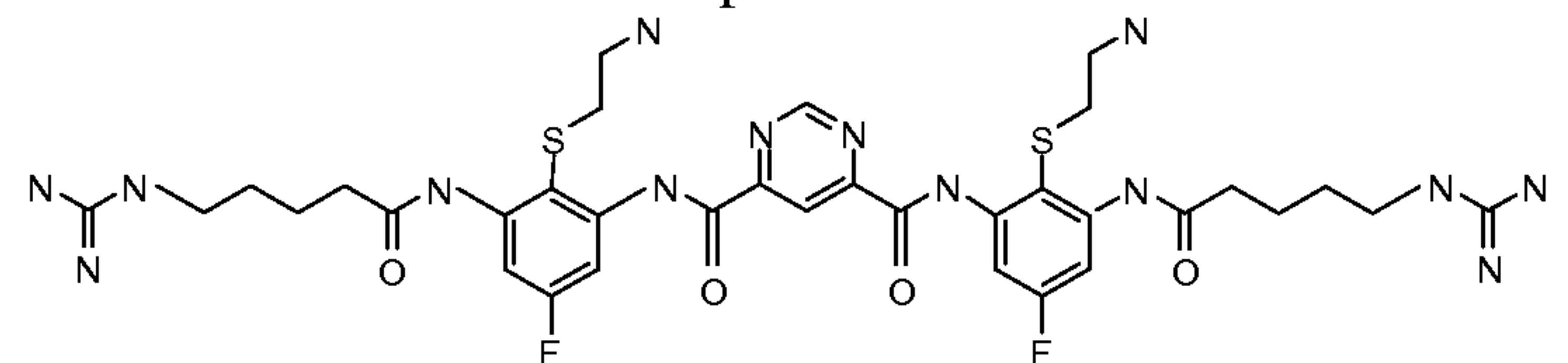
Compound 113



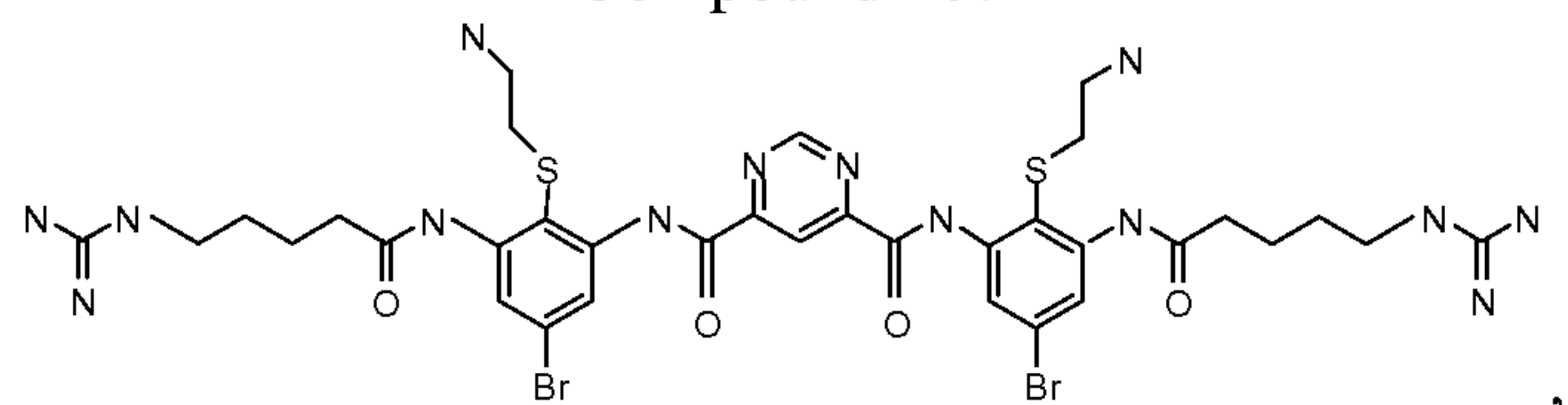
Compound 121



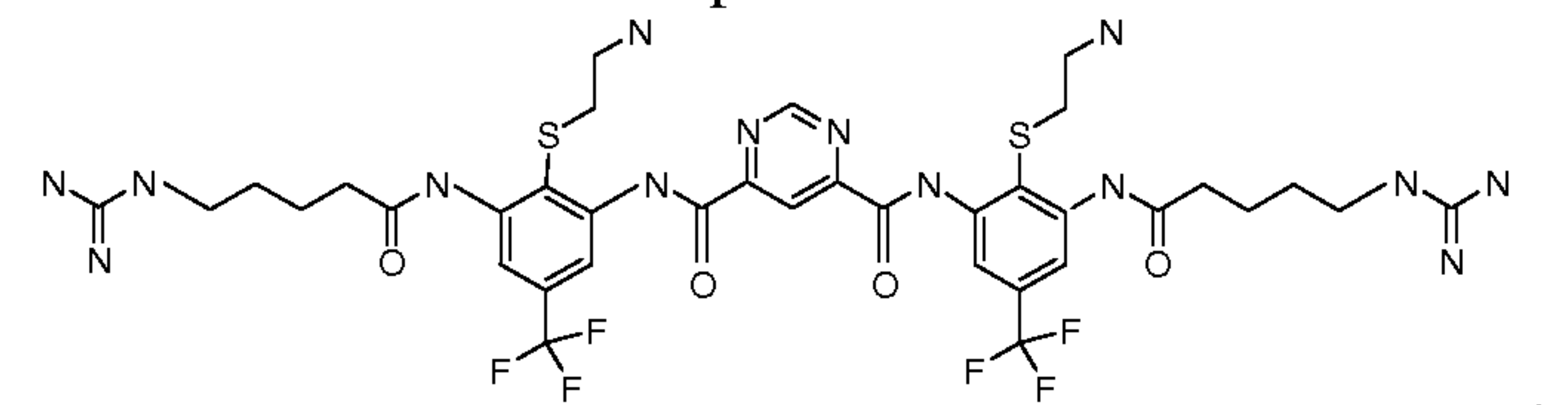
Compound 114



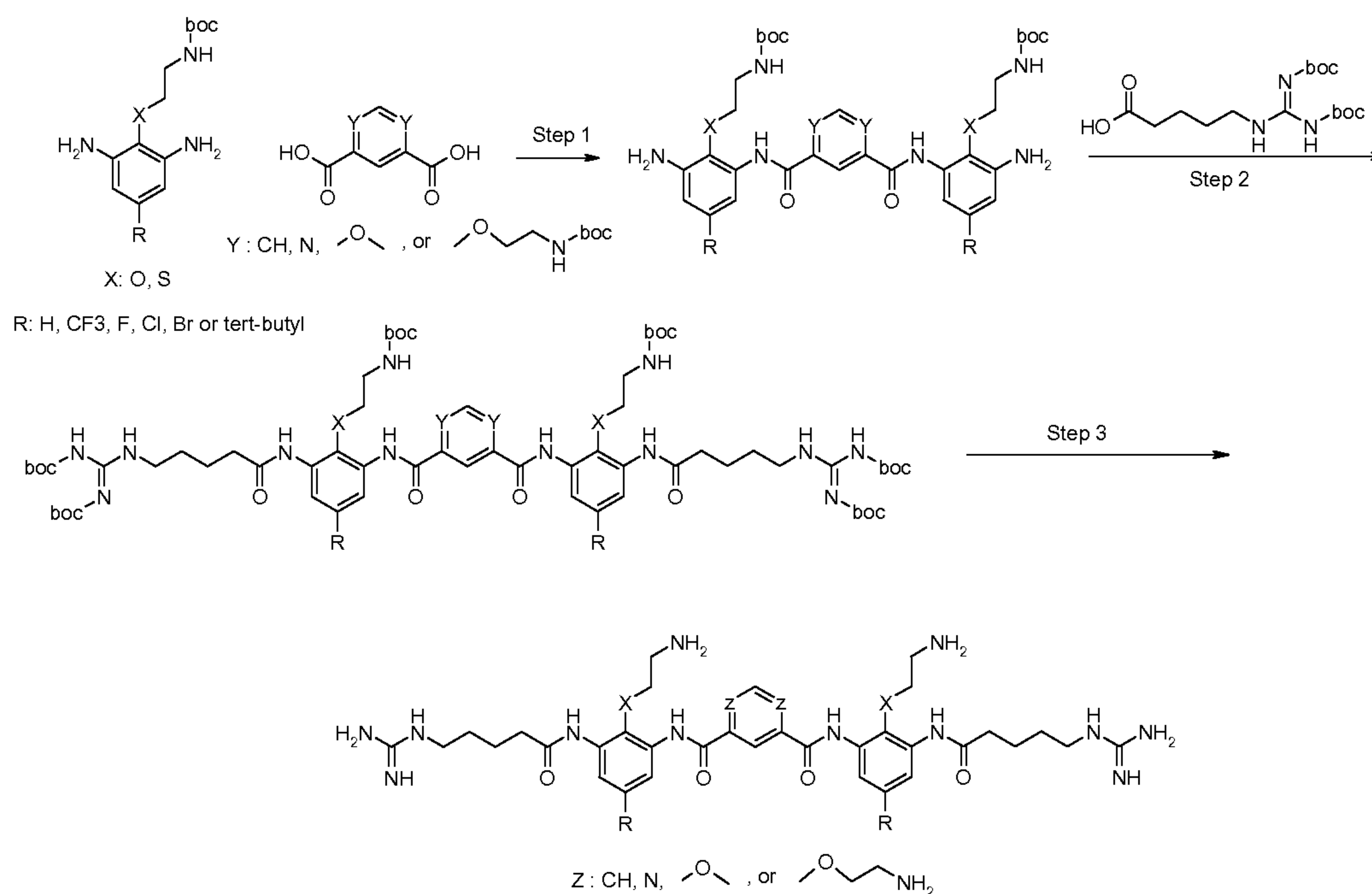
Compound 107



Compound 123



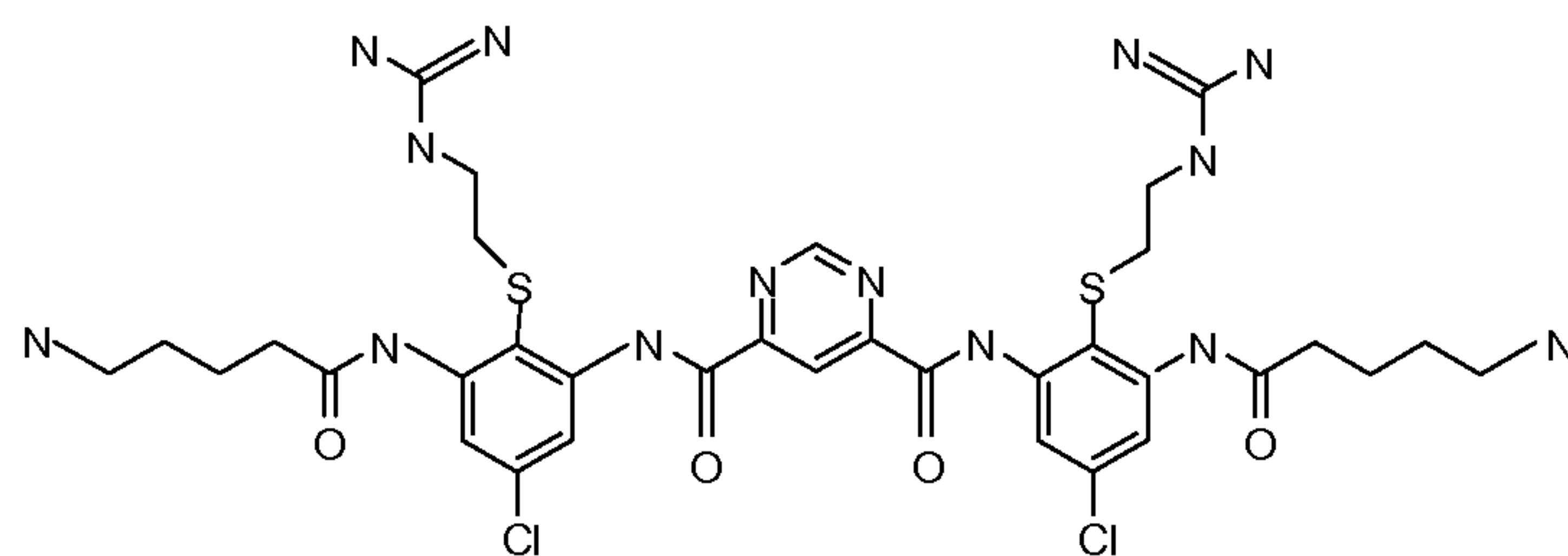
Compound 124



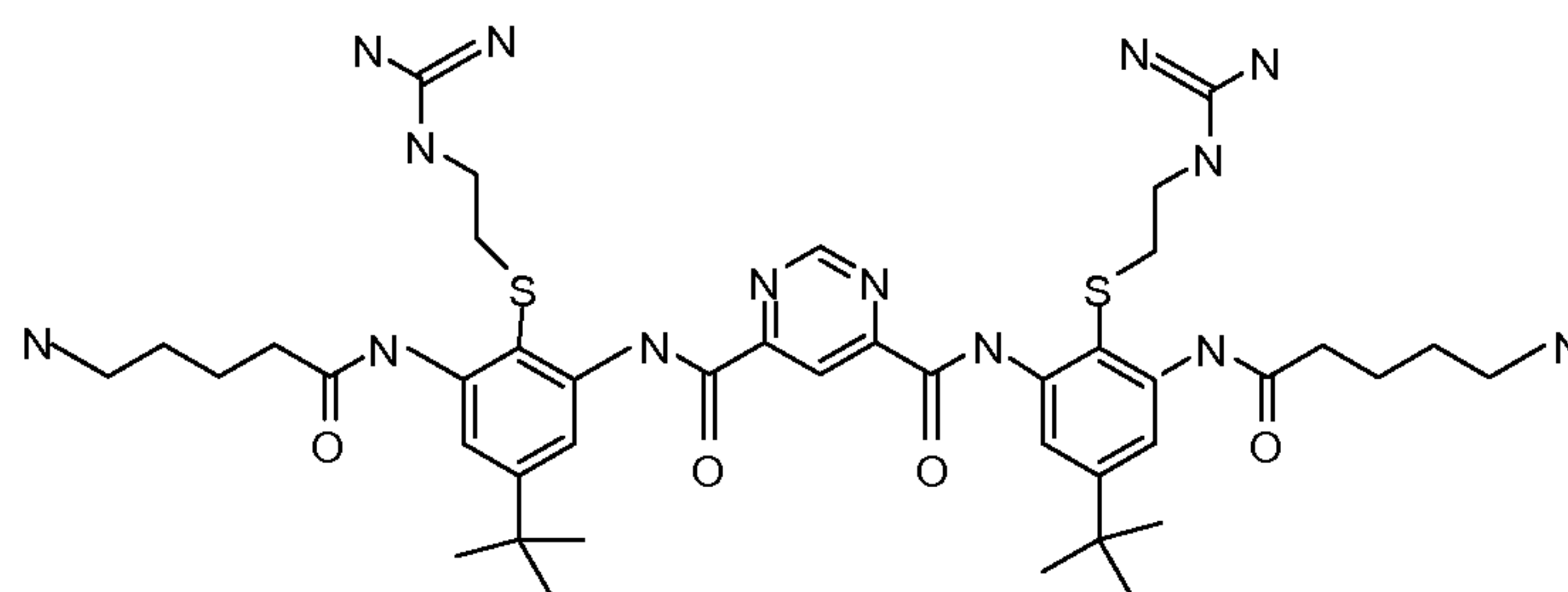
Step 1: Dianiline (0.15 mol) and diacid (0.062 mol) were combined with pyridine (121 mL) and a stir bar in a nitrogen purged 2 L RBF and stirred to a suspension with small
 5 pieces for 15 minutes. Then EDCI (0.185 mol) was added and the mixture was stirred at ambient temperature for 7.5 hours. The reaction was quenched with water (810 mL). The product was purified by column chromatography or trituration using heptane and ethyl acetate.

Step 2: Product from step 1 (0.179 mol) and ($\{[(\text{tert-butoxycarbonyl})\text{amino}][(\text{tert-butoxycarbonyl})\text{imino}]\text{methyl}\}$ amino)pentanoic acid (0.734 mol) were dissolved in 2.1 L
 10 dry pyridine. The solution was cooled to -20°C to 0°C . To the solution, POCl_3 (0.716 mol) was slowly added over 30 minutes. The reaction mixture was stirred for 2 hours at -20°C to 0°C and then it was allowed to warm to room temperature and stirred for another 2 hours. Ice water (8 L) was added to quench the reaction. The precipitated solid was collected and
 15 purified by either column chromatography or trituration.

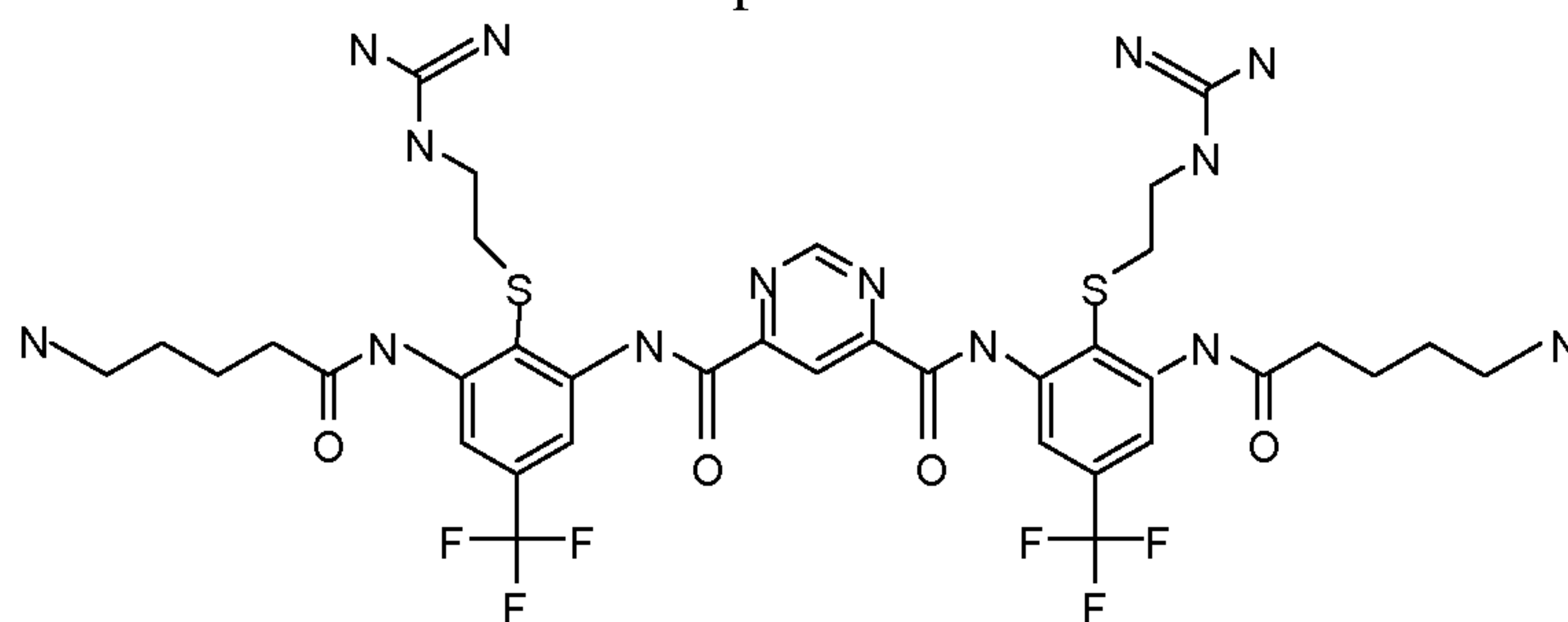
Step 3: Product from step 3 (98.4 mmol) was dissolved in 465 mL of formic acid. The solution was added 246 mL of 4M HCl in dioxane and stirred at room temperature for 10 hours. To this reaction mixture was added 1-butanol (2.5 L). The resulting precipitate was collected by filtration and purified by reverse phase column chromatography.

Example 7: Synthesis of Compounds 122 and 126-129

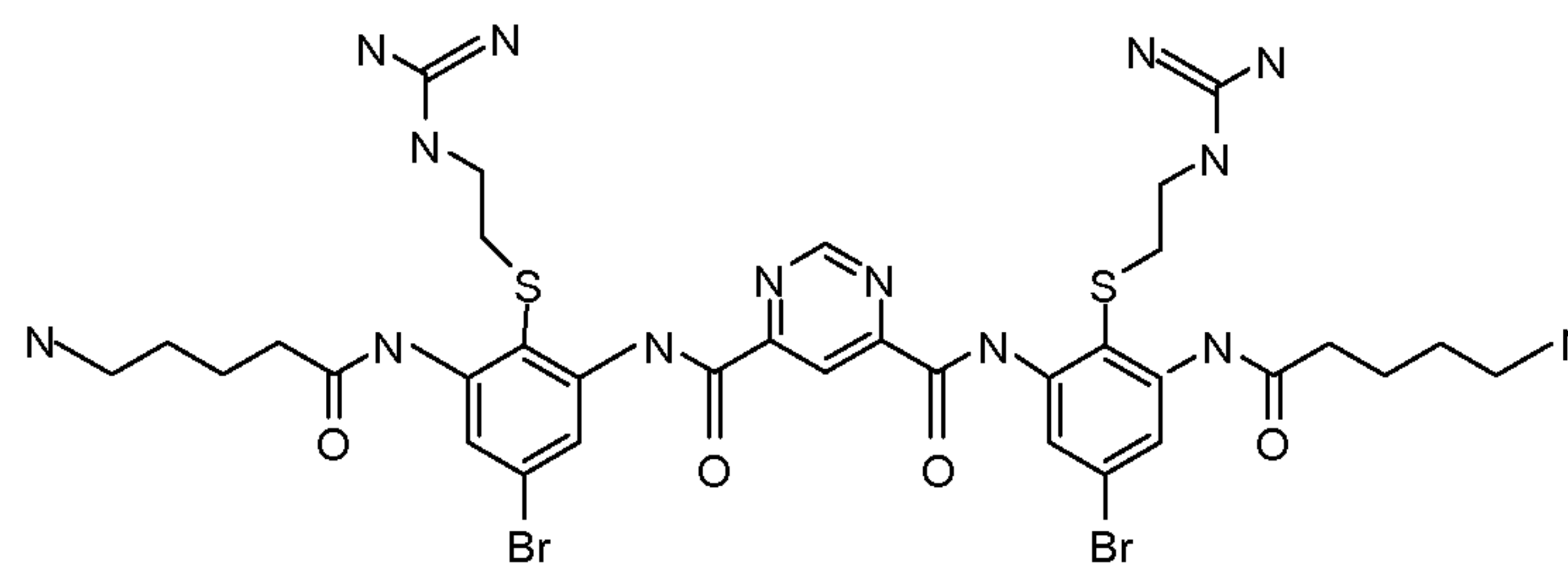
Compound 122



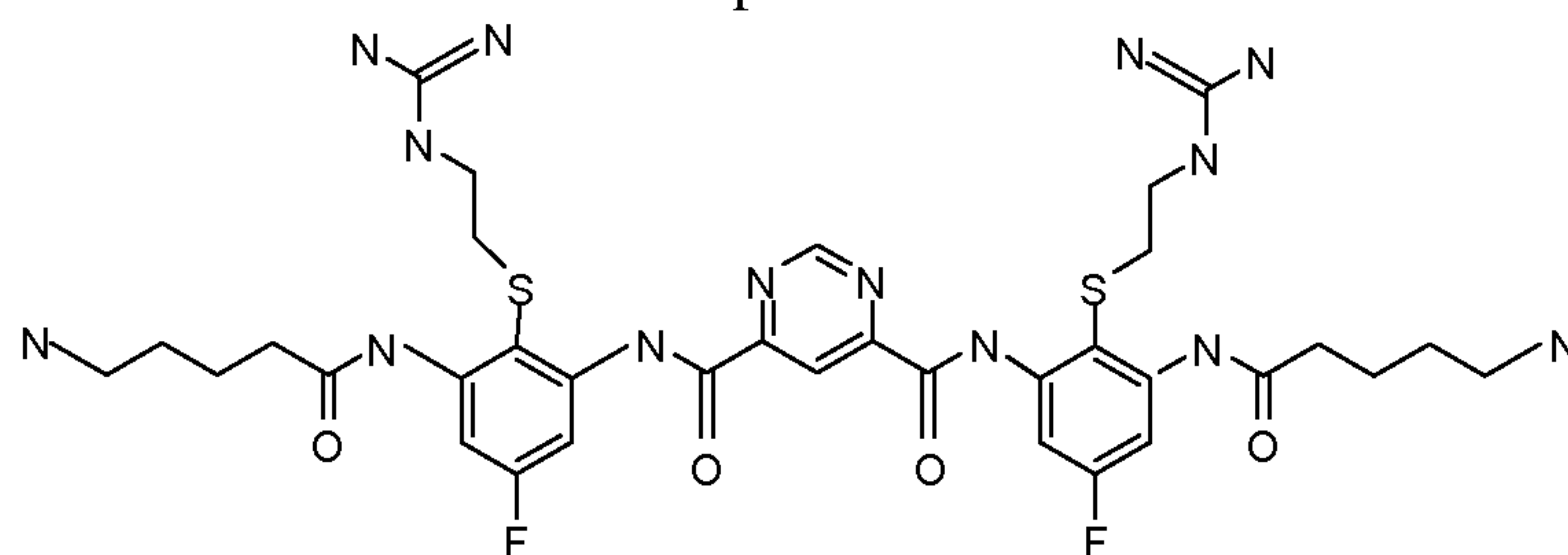
Compound 129



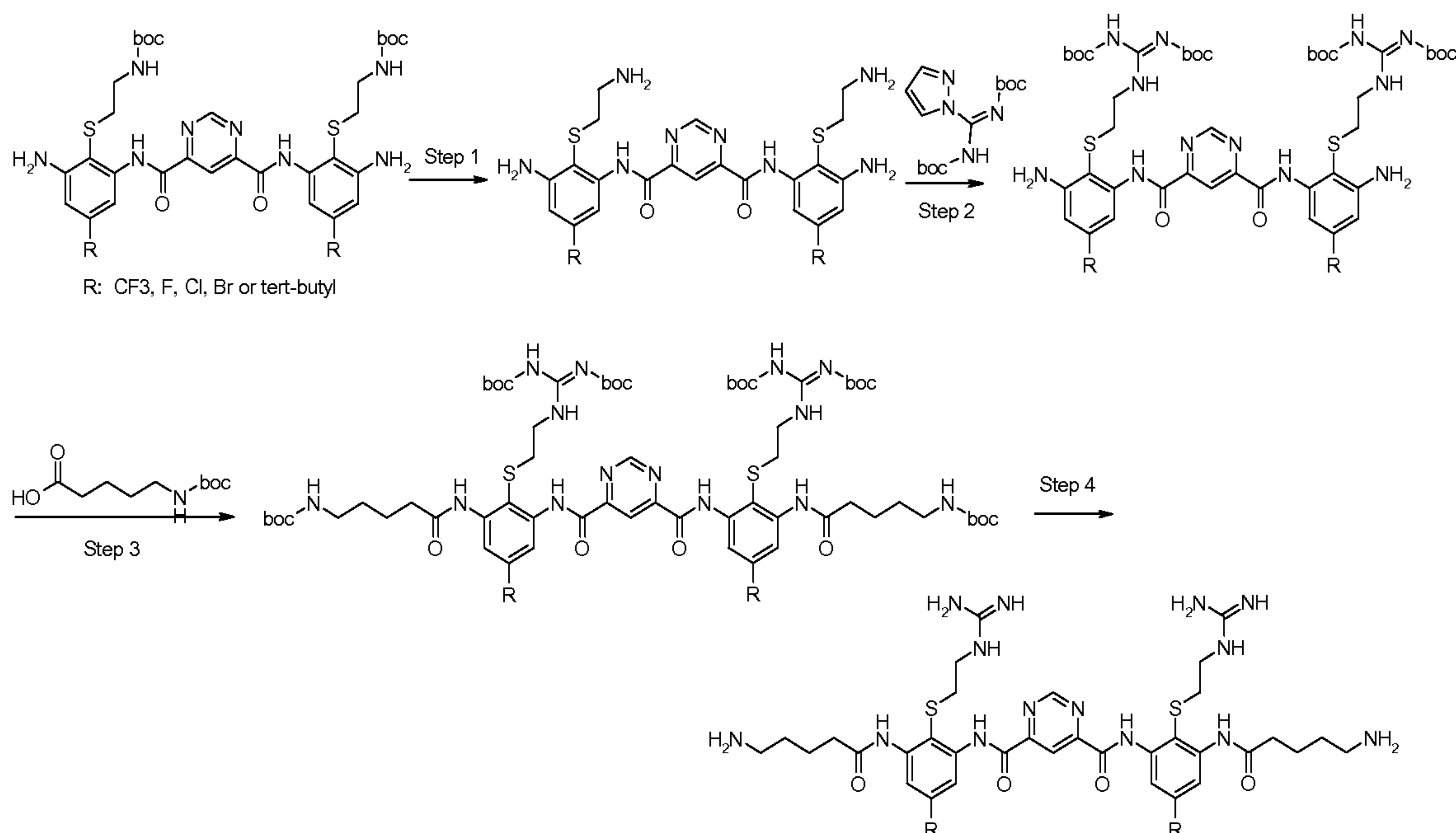
Compound 128



Compound 127



Compound 126



Step 1: The starting diamine is made using similar method as step 1 of common synthesis 2. Diamine was treated with 50% Trifluoroacetic acid in dichloromethane for 2 hours. The resulting solution was concentrated to an oil and triturated with cold diethyl ether.

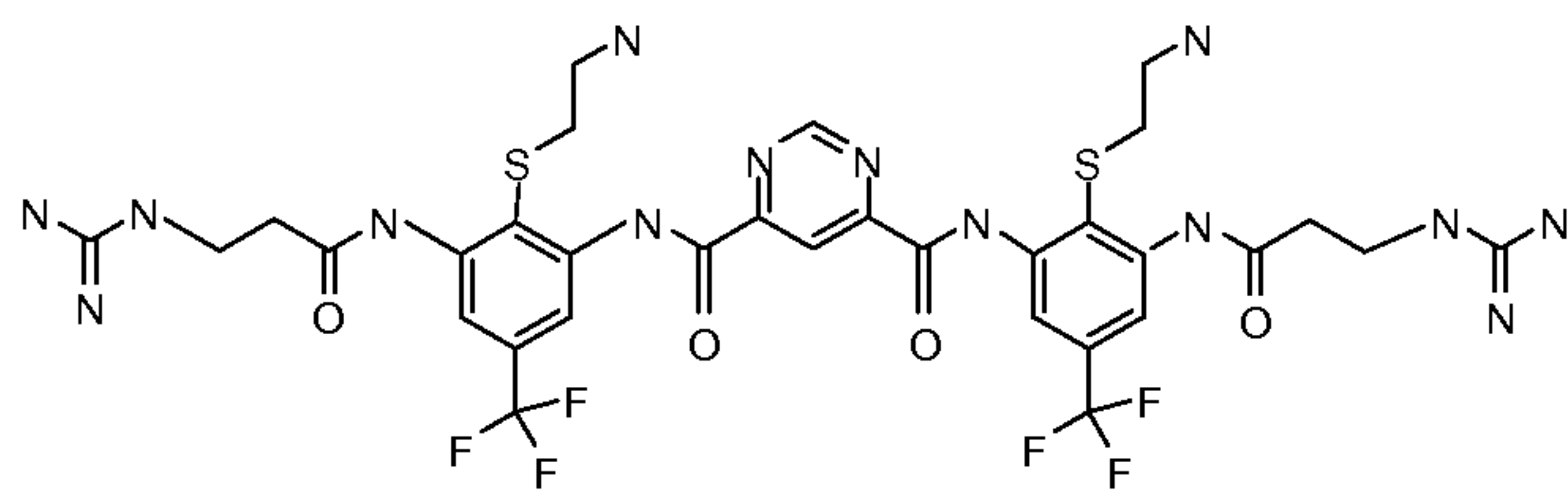
5 The solid was collected by filtration.

Step 2: Product from step 1 (1 mmol) and N,N'-bis-Boc-1-guanylpurazole (2 mmol) were dissolved in 10 mL of methanol followed by 2 equivalence of mL of diisopropylethylamine. The mixture was stirred overnight at room temperature before the solvent was removed by rotovap. The product was purified by column chromatography.

10 Step 3: This step was carried out similar as step 2 of common synthesis 2 using product from step 2 and N-*tert*-butoxycarbonyl-L-proline.

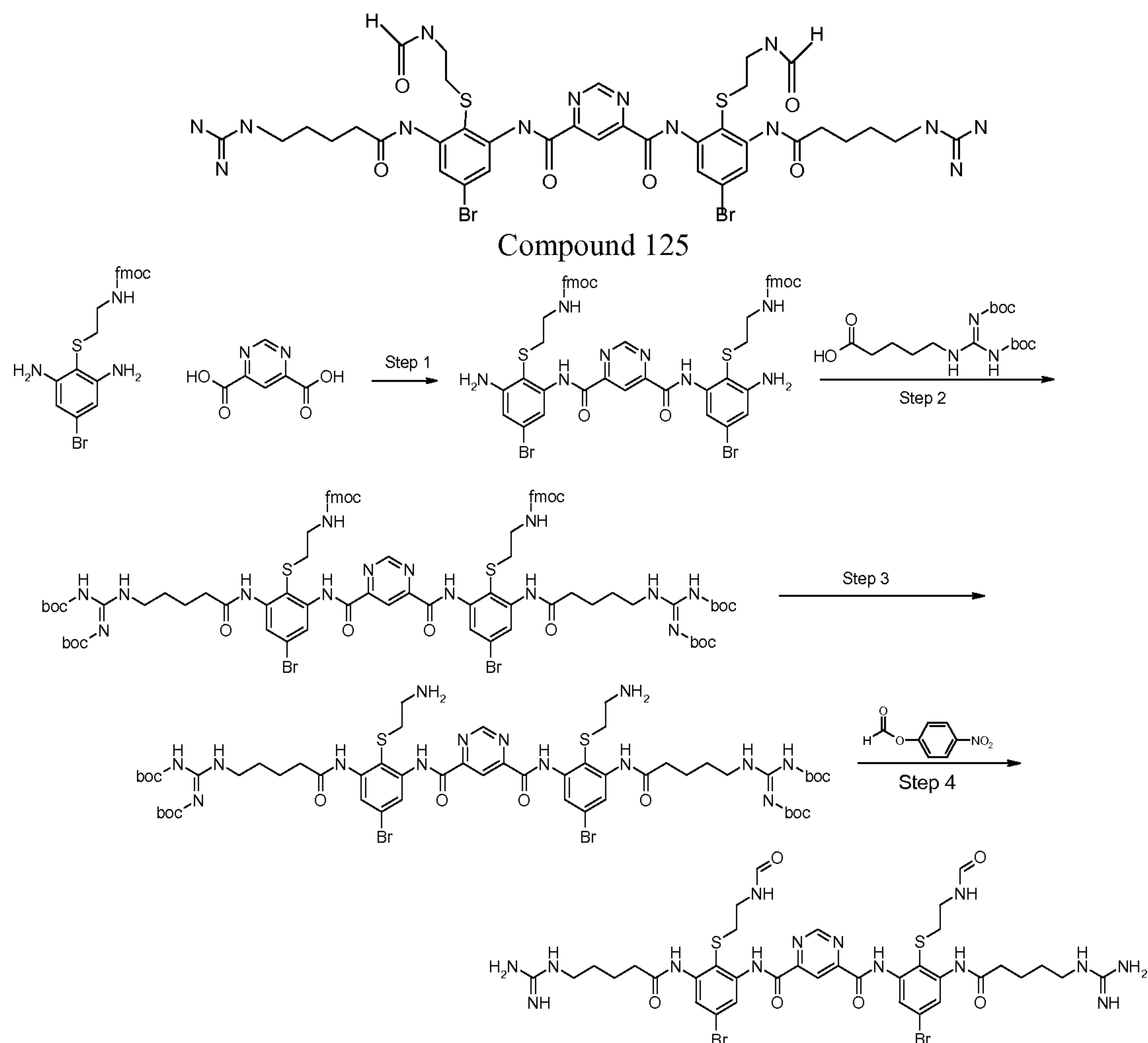
Step 4: This step is the same as step 3 in common synthesis 2.

Example 8: Synthesis of Compound 108



Compound 108

The synthesis is similar as common synthesis 2 except in step 3, ({[*tert*-butoxycarbonyl]amino}[[*tert*-butoxycarbonyl]imino]methyl} amino)propanoic acid was used.

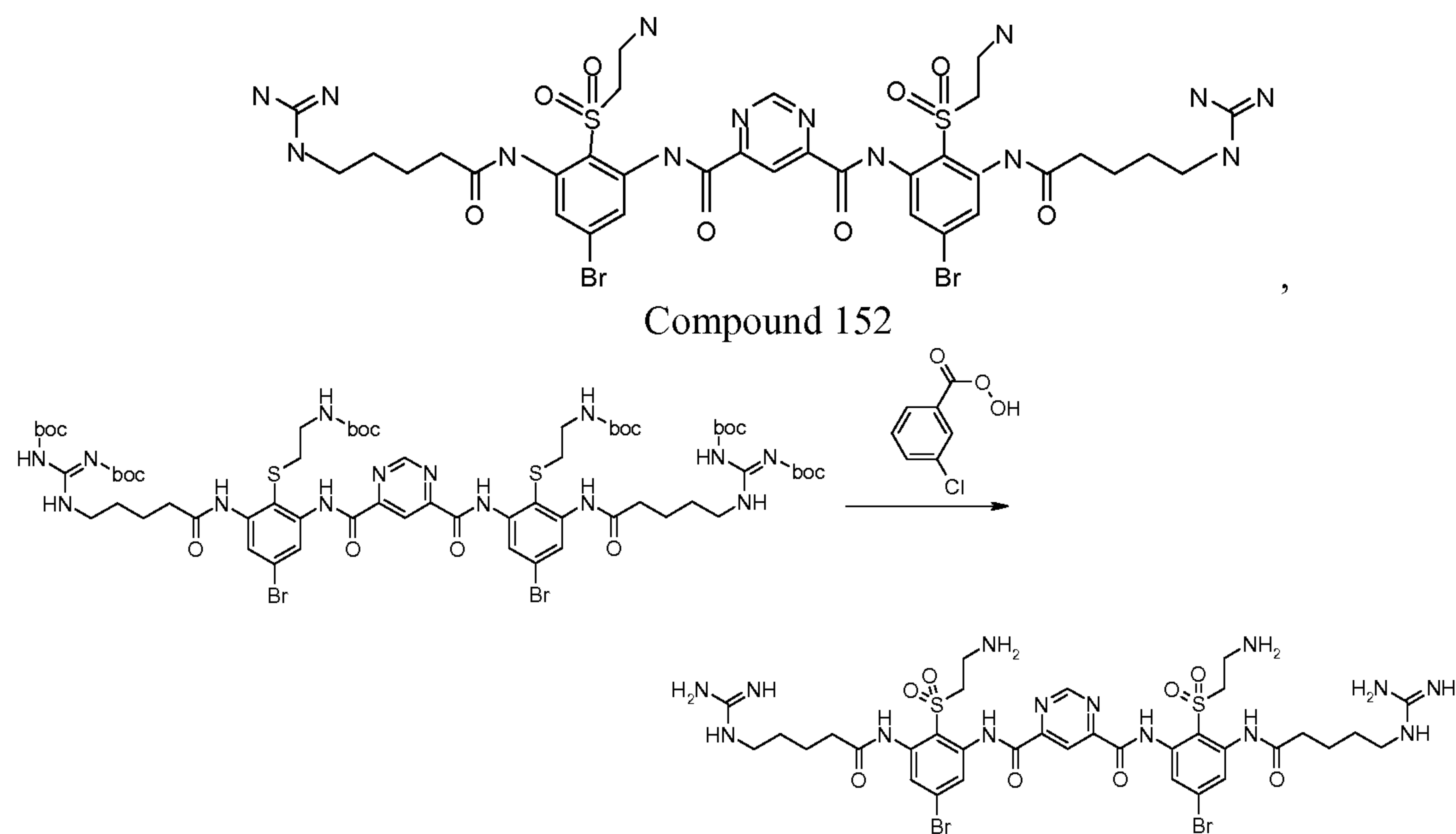
Example 9: Synthesis of Compound 125

5 Step 1 and 2 are similar to step 1 and 2 of the synthesis of compound 101.

Step 3: Product from step 2 was treated with 20% piperidine in DMF. After diluted with ethyl acetate and washed with 10% citric acid and brine, the organic phase was concentrated and triturated with hexane.

10 Step 4: Product from step 3 (0.03 mmol) was mixed with 4-nitrophenyl formate (2 equiv.) in 3 mL of DMF, followed by the addition of DIEA (4 equiv.). The reaction mixture was stirred for 4 hours before was diluted with ethyl acetate. The organic layer was washed with saturated K_2CO_3 , 10% citric acid and water before it was concentrated to a solid. The solid was treated with 50% TFA in DCM and purified by reverse phase column chromatography.

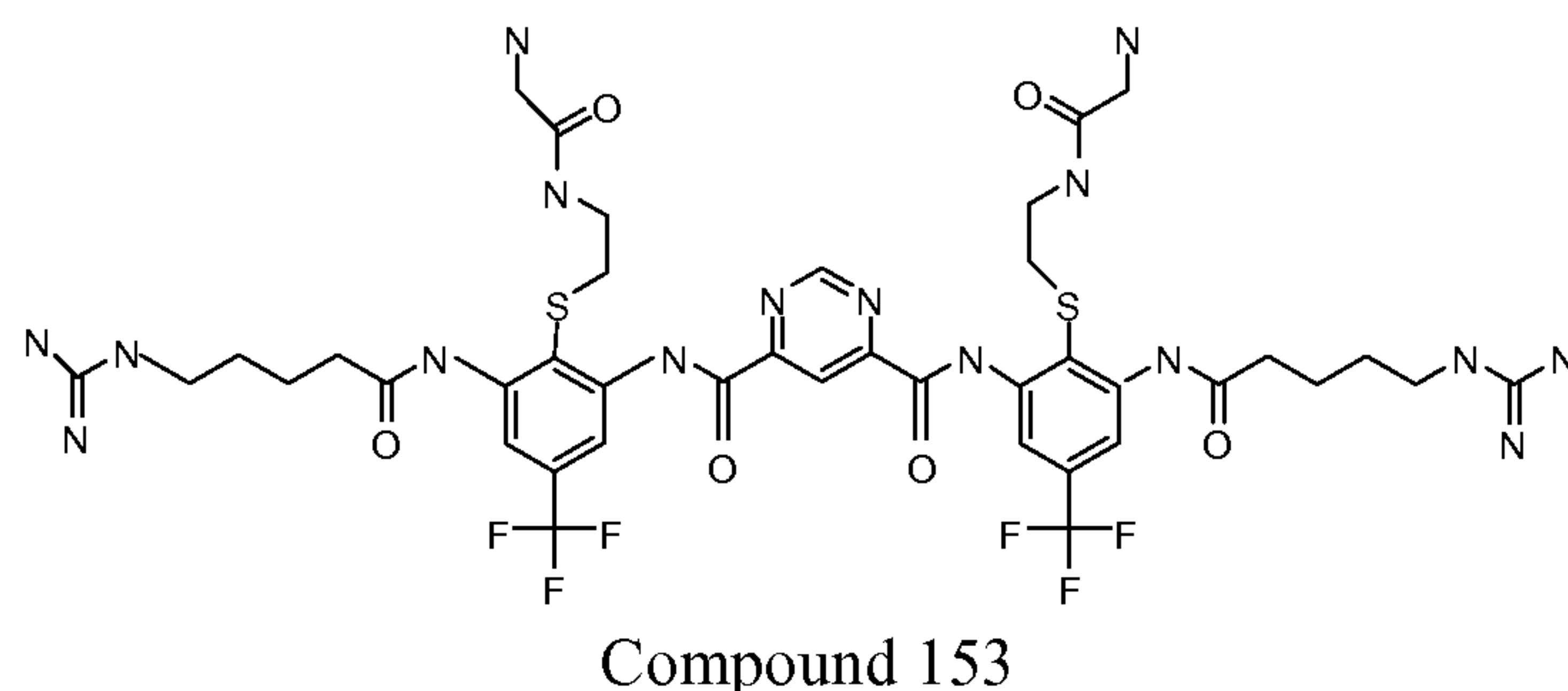
15

Example 10: Synthesis of Compound 152

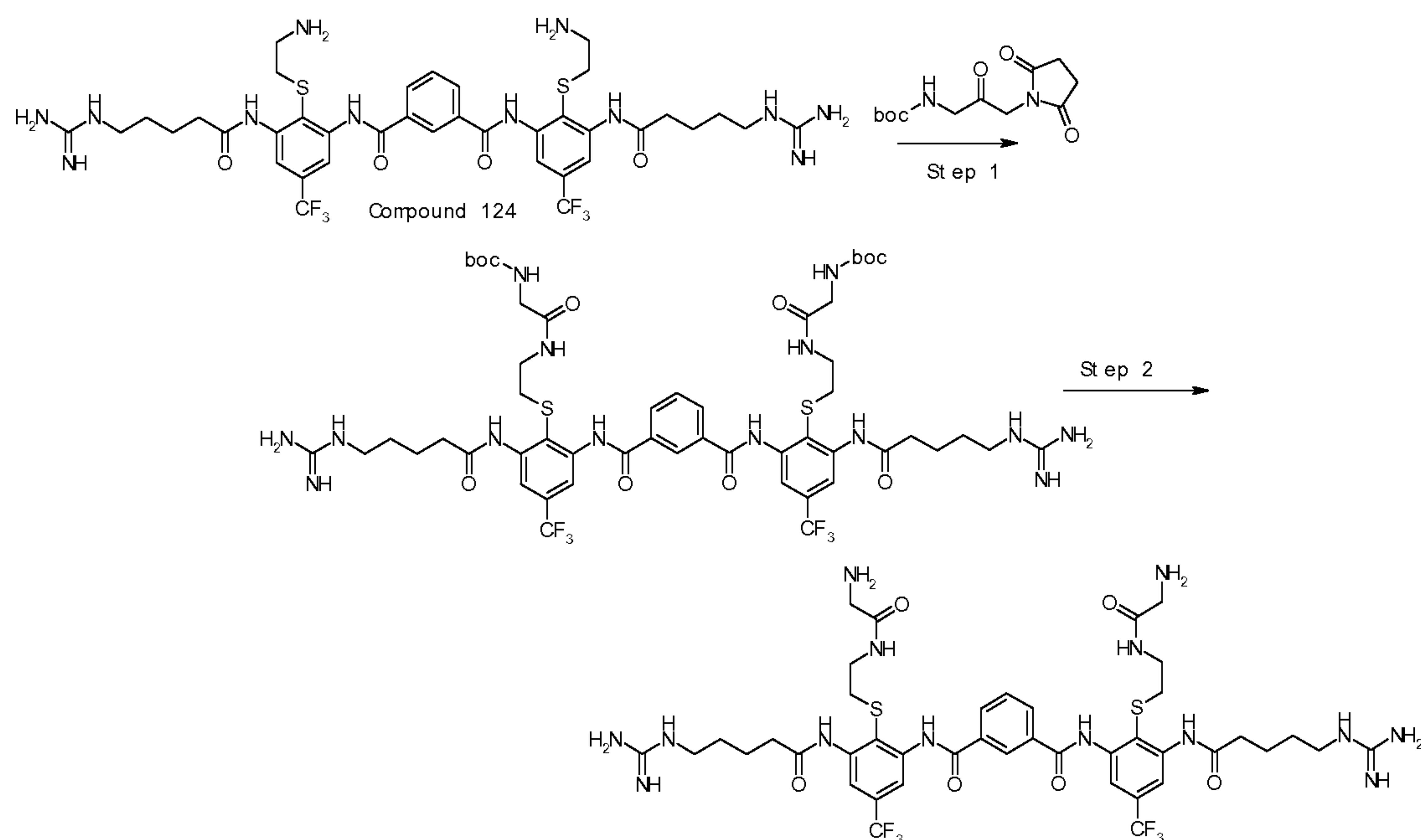
5

The starting material was made from step 1 to 2 in the synthesis of compound 123. The starting Boc-protected amide (0.023 mmol) and 3-chloroperoxybenzoic acid (MCPBA, 42.3 mg) were dissolved in DCM (0.8 mL) and stirred under Ar for 1 hour. The reaction mixture was diluted with DCM and washed with saturated $\text{Na}_2\text{S}_2\text{O}_3$, saturated NaHCO_3 and

10 water. The organic layer was dried and concentrated to a solid. The solid was treated with 50% TFA in DCM. The final product was purified by reverse phase column chromatography.

Example 11: Synthesis of Compound 153

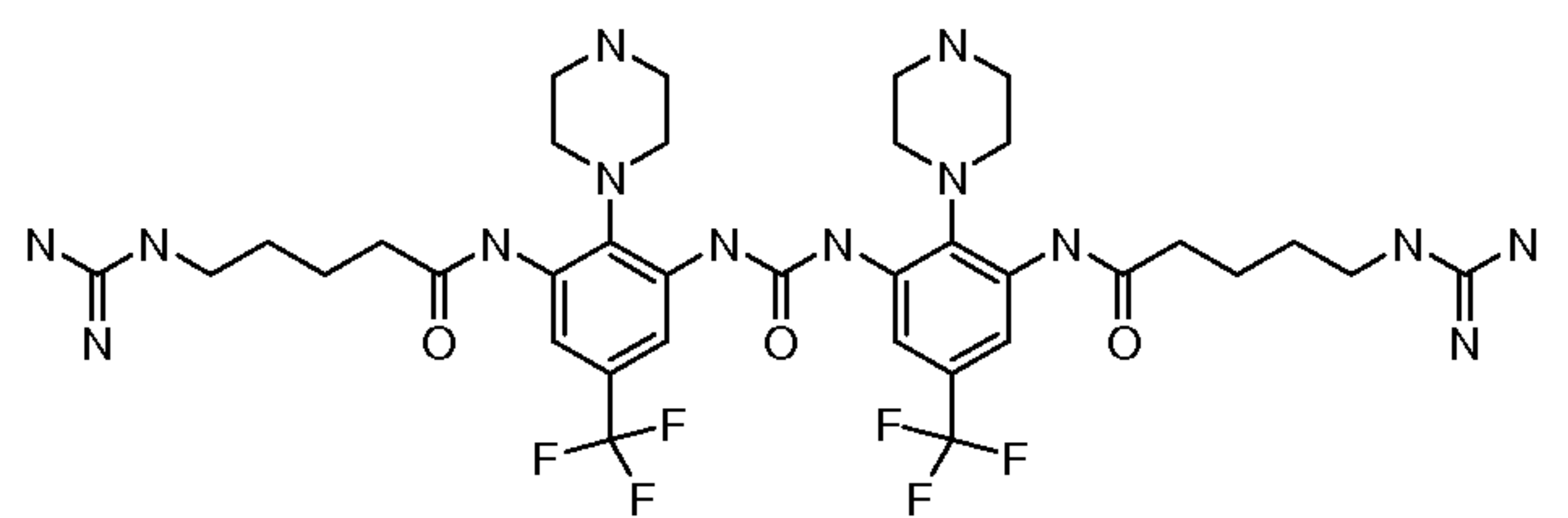
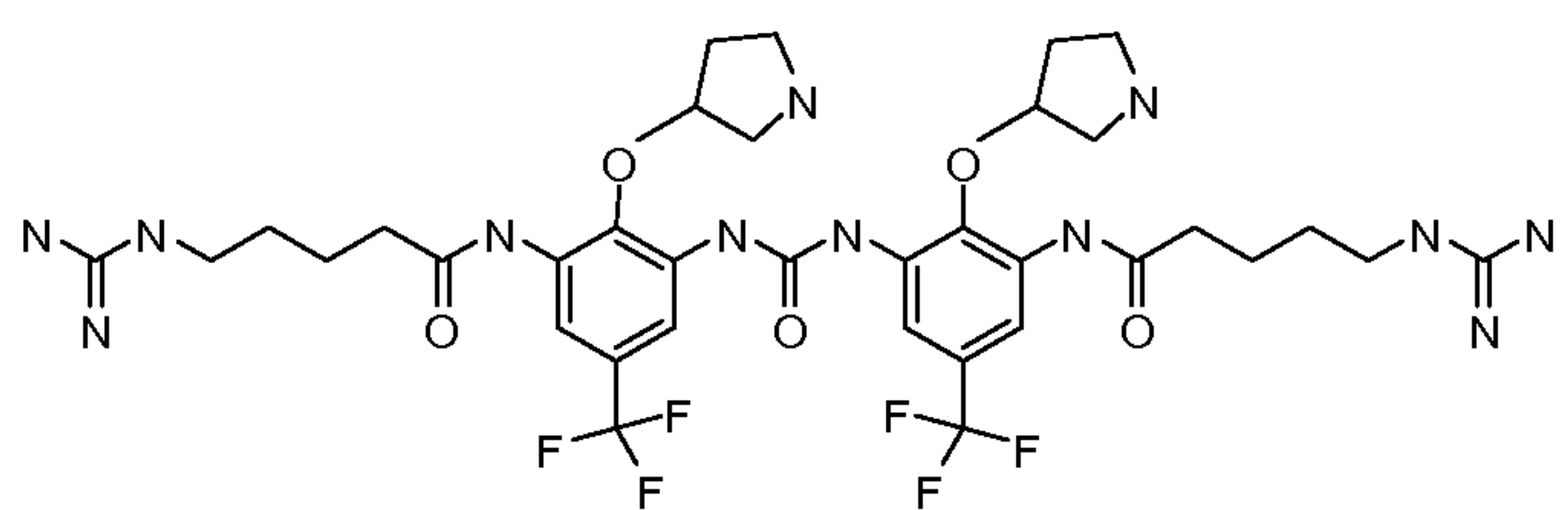
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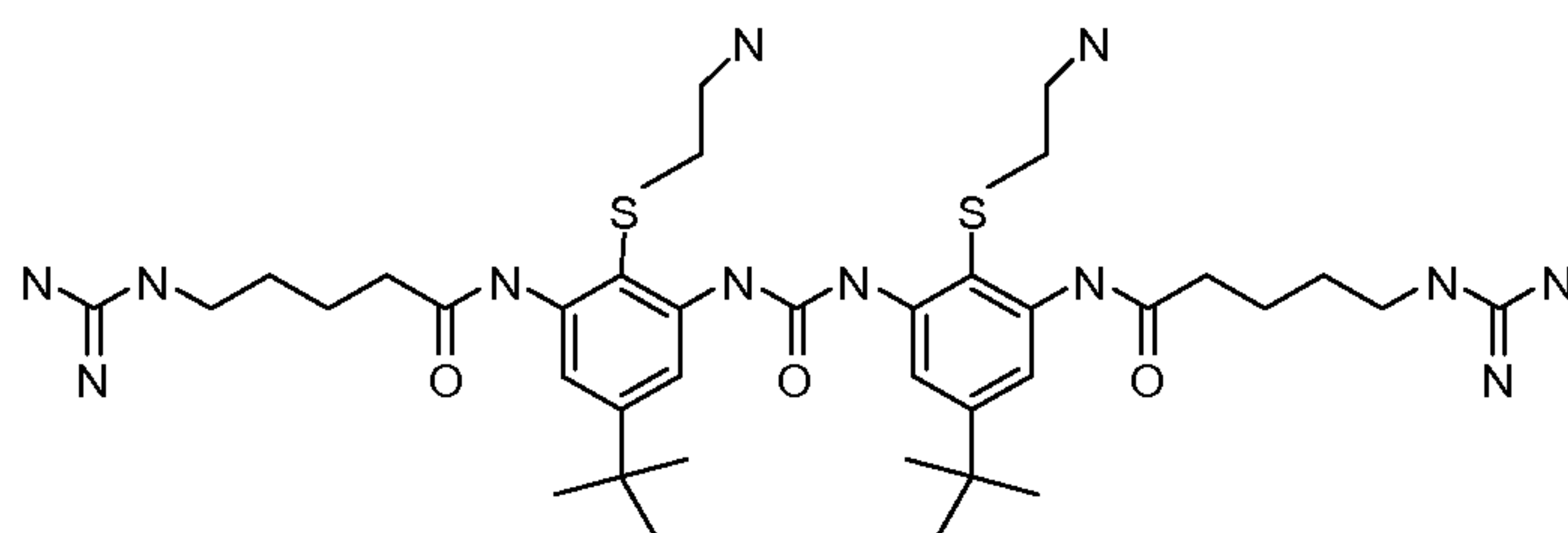


Step 1: Compound 124 (0.29 mmol) was dissolved in 10 mL of water and then was added N-methyl morpholine (NMM, 2.7 equiv.) and 5 mL of DMF. N-Boc-Gly-Osu (2.25 mmol) in 5 mL DMF was added to the solution dropwise. The reaction mixture was stirred at room temperature for 20 minutes before it was concentrated to a solid.

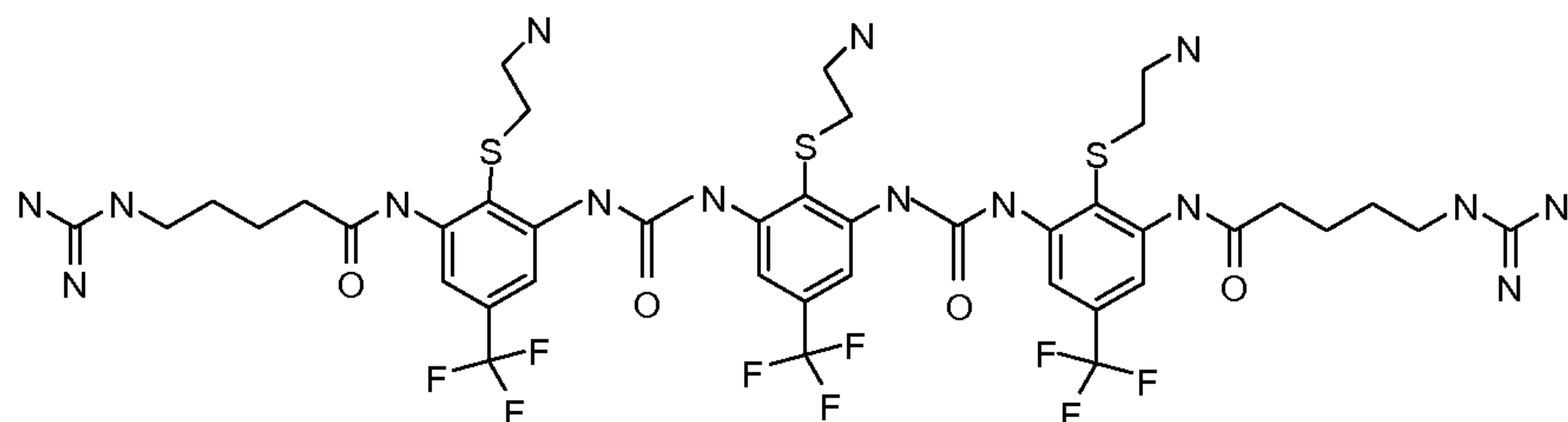
Step 2: The product from step 1 was treated with 4 N HCl in dioxane and purified with reverse phase column chromatography.

10 Example 12: Synthesis of Compounds 103-105 and 150

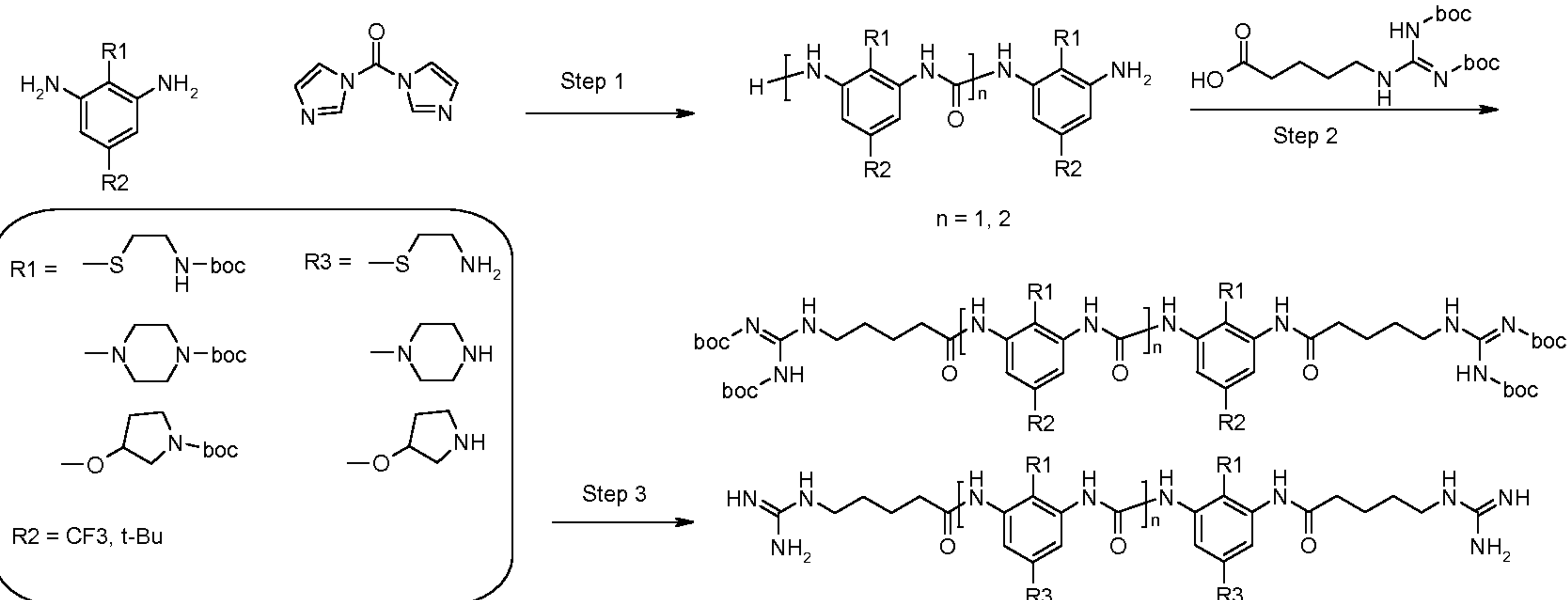




Compound 103



Compound 150

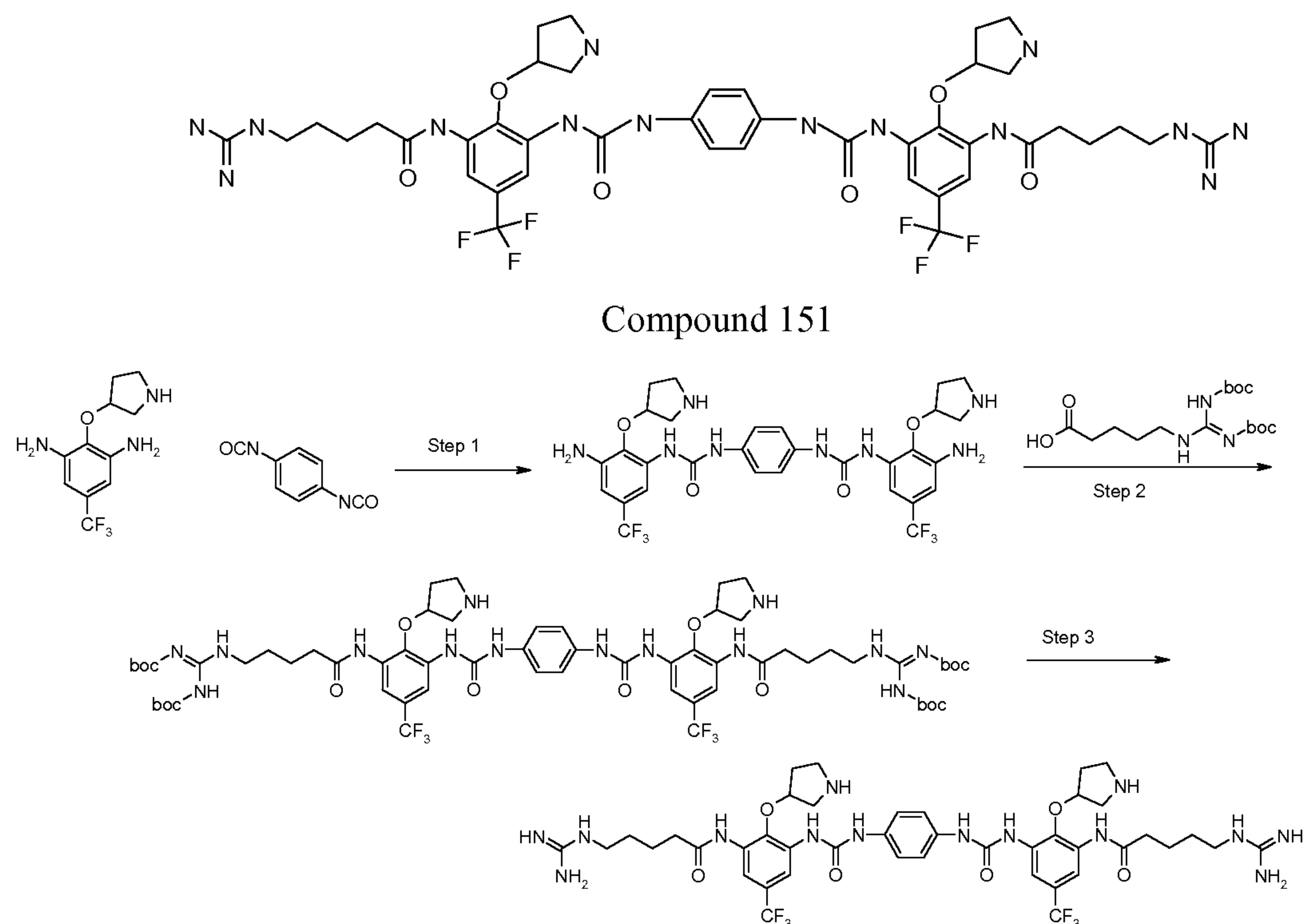


5

Step 1: Bisaniline and carbonyl diimidazole (CDI) were mixed in dry DMSO (with molar ratio bisaniline: CDI = 4:1). The reaction mixture was stirred at 100°C for 24 hours. After it cooled down, water was added to reaction mixture. The precipitate was filtered and dried under vacuum. The crude product was purified with silica gel column with dichloromethane and ethyl acetate as eluents.

Steps 2 and 3 are similar to steps 2 and 3 of the synthetic procedure for compound 101.

15

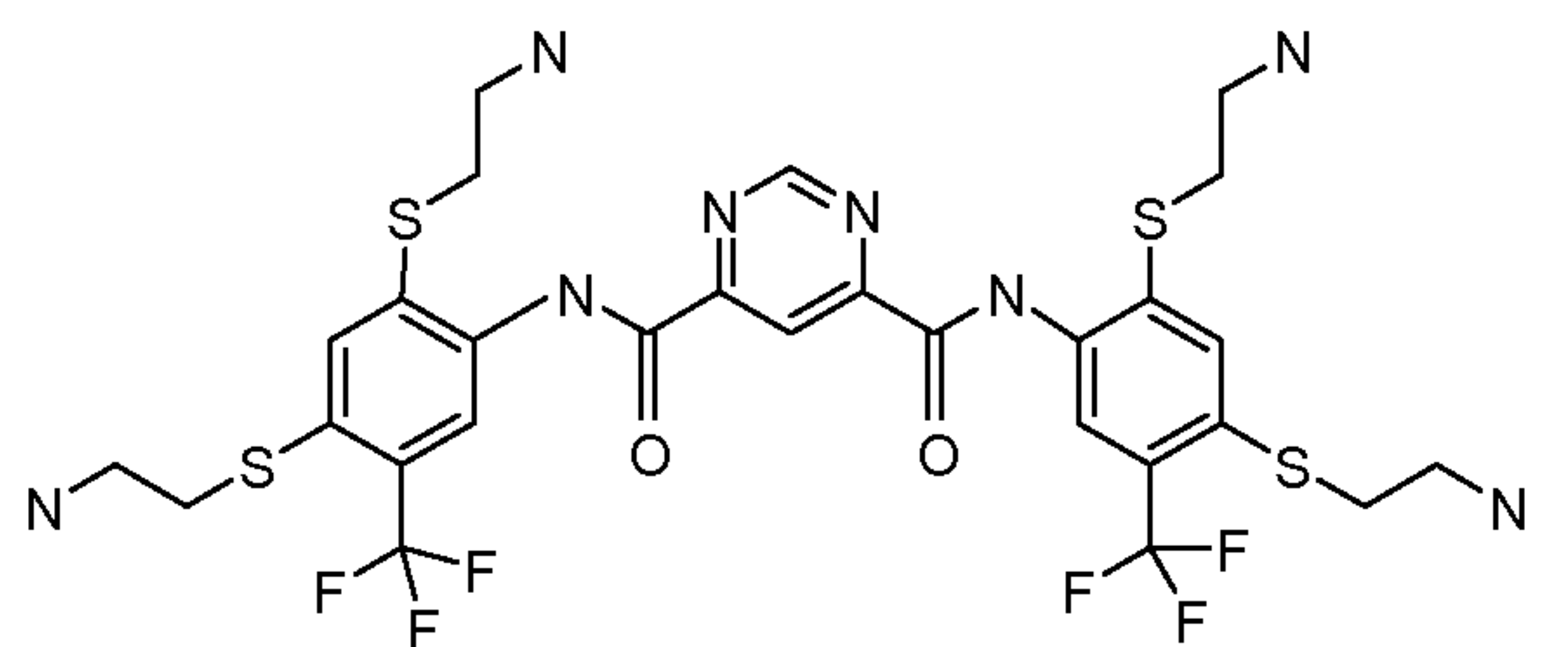
Example 13: Synthesis of Compound 151

5

Step 1: Bisaniline (4 equiv.) and 1, 4-benzenediisocyanate (1 equiv.) were mixed in dry DMSO. The reaction mixture was stirred at 100°C for 24 hours. After it cooled down, water was added to the reaction mixture. The precipitate was filtered and dried under vacuum. The crude product was purified with silica gel column with dichloromethane and ethyl acetate as eluents.

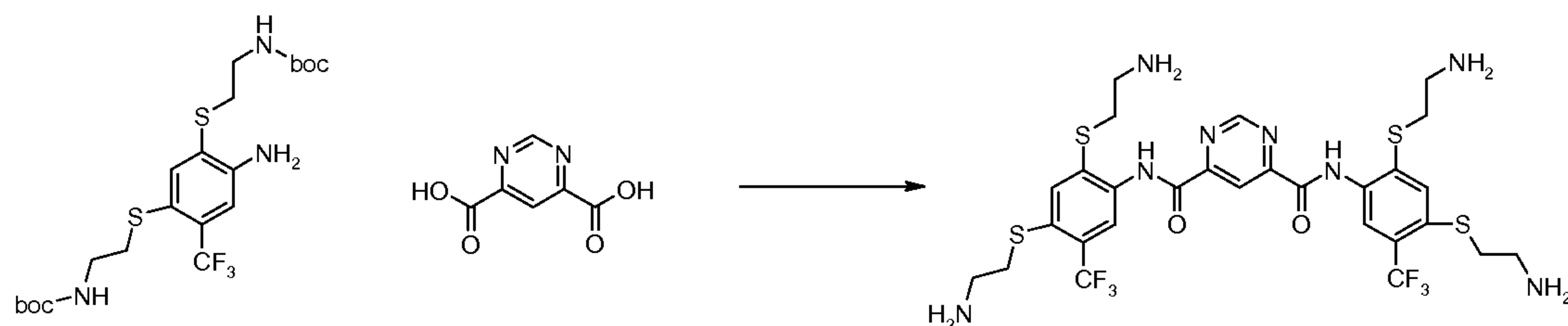
10

Steps 2 and 3 are similar to steps 2 and 3 of the synthetic procedure for compound 101.

Example 14: Synthesis of Compound 112

15

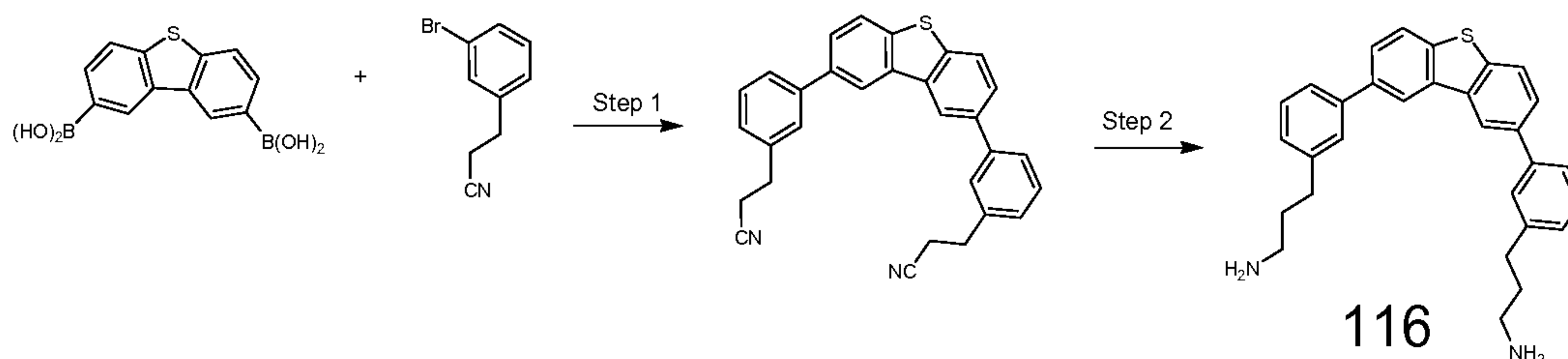
Compound 112



2-Chloro-4,6-dimethoxy-1,3,5-triazine was stirred in anhydrous THF. N-Methylmorpholine was added. The resulting mixture was stirred at room temperature for 30 minutes. Then aniline and pyrimidine-4,6-dicarboxylic acid were added. The mixture was stirred at room temperature for 24 hours. Then the solvent was evaporated completely in vacuum. Water was added and the mixture was stirred for 4 hours. The solid precipitate was collected and purified by silica gel column with dichloromethane and ethyl acetate as eluents. The Boc-protected compound was deprotected using 4N HCl dioxane solution overnight at room temperature to generate the final product.

Example 15: Synthesis of Compound 116

Compound 116 has been synthesized utilizing three synthetic schemes.



Scheme 1

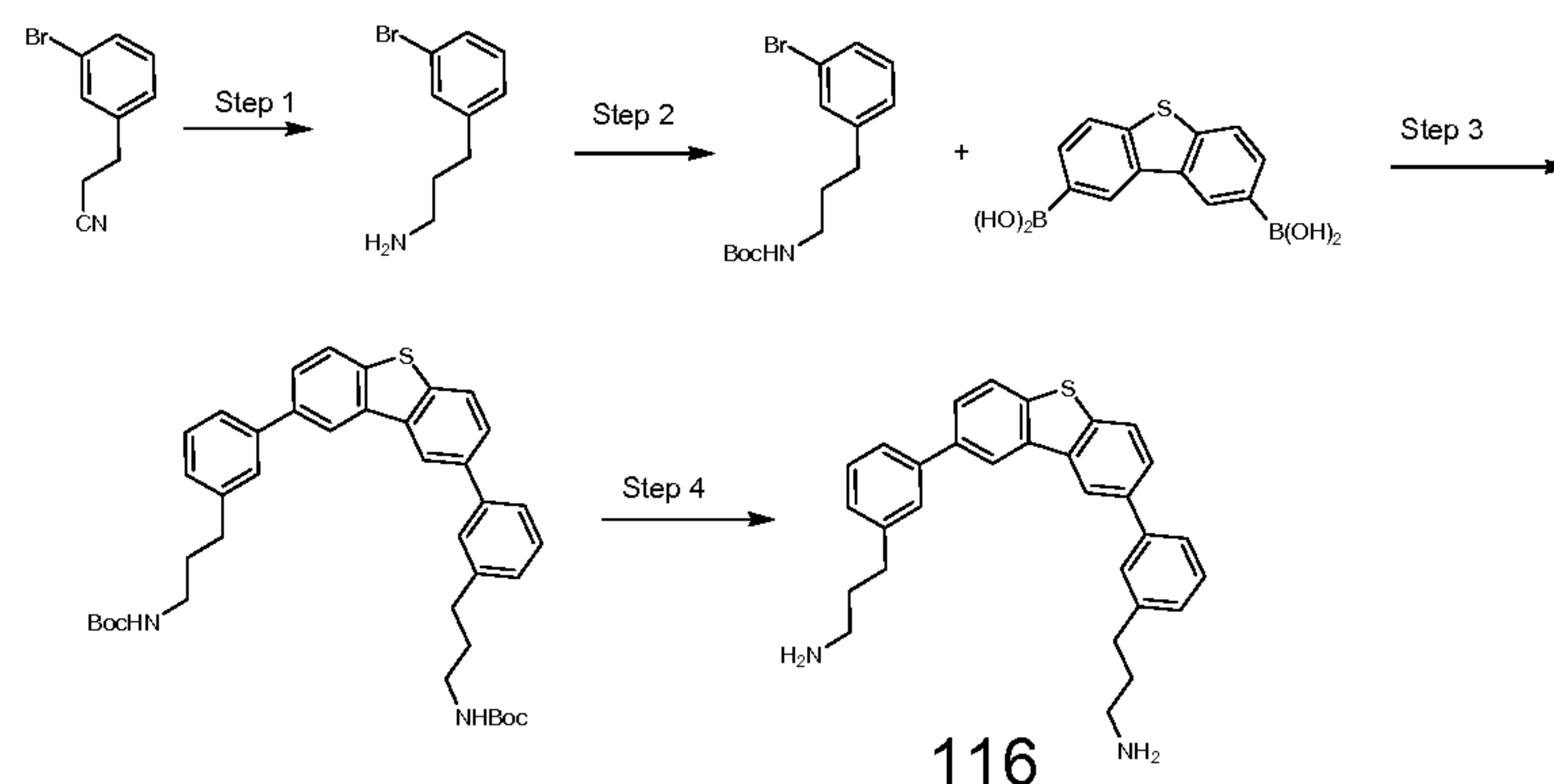
15

Step 1: 8-(dihydroxyboryl)dibenzo[b,d]thiophene-2-ylboronic acid (4 mmol, 1.08 g) and 3-(3-bromophenyl)propanenitrile (8.8 mmol, 1.875g) were added into a microwave tube under Argon. Dioxane (10 mL), Pd(PPh₃)₄ (0.4 mmol, 0.46g) and K₂CO₃ (16 mmol, 4 mL, 4M) were added. The mixture was under microwave irradiation (120°C, 15 minutes) with stirring. Then the reaction was cooled down to room temperature and extracted with EtOAc and brine. The organic layer was dried over NaSO₄ and evaporated under vacuum. The residue was purified with silica column (eluent: EtOAc/hexanes = 1/2, v/v). A yellow solid (1.18 g, 70%) was obtained as product. ¹HNMR was acceptable.

Step 2: 2,8-di(3-phenylpropanenitrile)benzothiophene (1.33 mmol, 0.59g) and platinum oxide hydrate (80 mg) were added into a mixture of MeOH (10 mL)/EtOAc (40mL). HCl (2 mol, 0.5 mL, 4M in dioxane) was added. Hydrogen at 60 psi was introduced

after removal of air. The mixture was shaken over night. Then the hydrogen was removed. The mixture was filtered through celite pad. The filtrate was evaporated under vacuum. The residue was purified by reverse phase HPLC. A white solid (70 mg, 12%) was obtained as product. LC-MS and ^1H NMR were acceptable.

5

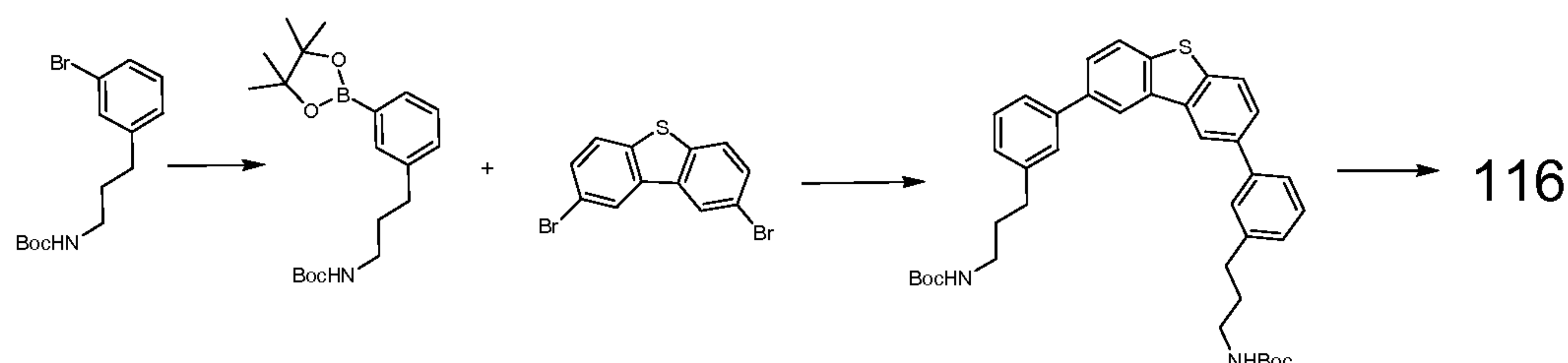


Scheme 2

Step 1, 2 and 3: Synthesis of 2,8-di(tert-butyl 3-phenylpropylcarbamate)

10 benzothiophene. The tert-butyl 3-(3-bromophenyl)propylcarbamate intermediate was synthesized from 3-(3-bromophenyl)propanenitrile by BH_3 reduction and Boc protection. tert-Butyl 3-(3-bromophenyl)propylcarbamate (2.2 mmol, 0.69 g), 8-(dihydroxyboryl) dibenzo[b,d]thiophene-2-ylboronic acid (1 mmol, 0.272 g) were added into a microwave tube under Argon. Dioxane (4 mL), $\text{Pd}(\text{PPh}_3)_4$ (0.1 mmol, 0.115 g) and K_2CO_3 (2 mmol, 2 mL, 15 4M) were added. The mixture was under microwave irradiation (120°C, 15 minutes) with stirring. Then the reaction was cooled down to room temperature and extracted with EtOAc and brine. The organic layer was dried over NaSO_4 and evaporated under vacuum. The residue was purified with silica column (eluent: EtOAc/hexanes = 1/100-1/2, v/v). A yellow solid (1.0 g, 76.9%) was obtained as product. ^1H NMR was acceptable.

20 Step 4: The yellow solid from above reaction was stirred in 10 ml HCl in dioxane (4 M) at room temperature overnight. Then the mixture was filtrated and the cake was washed with ether. The solid was purified by reverse phase column. A white solid (0.376 g, 46.6%) was obtained. LC-MS and ^1H NMR were acceptable.



Scheme 3

Intermediate 2,8-di(tert-butyl 3-phenylpropylcarbamate)benzothiophene was synthesized by Suzuki reaction of 2,8-dibromodibenzothiophene and tert-butyl 3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propylcarbamate, which was obtained from tert-butyl 3-(3-bromophenyl)propylcarbamate. Compound 116 was obtained following similar de-protection reaction condition in route 2.

Example 16: Synthesis of Compound 106

Following similar procedure in route 2 of compound 116, compound 106 was synthesized in 45% overall yield as a white solid.

Example 17: Synthesis of Compounds 110, 117, 118, 119, 131, and 132

Following similar procedure in route 3 of compound 116, compounds 110, 117, 118, 119, 131, and 132 were obtained in 68%, 40%, 20%, 22%, 71%, and 15% overall yield, respectively.

Example 18: Synthesis of Compound 130

Following similar procedure in route 1 of compound 116, compound 130 was obtained in 7% overall yield.

Example 19: Synthesis of Compound 120

2,8-dibromodibenzo[b,d]furan was synthesized by bromination in 29% yield. Following similar procedure in route 3, compound 120 was obtained in 69% after two-step reaction.

Recognizing the significant therapeutic limitations of peptides, a series of non-peptidic mimics of these AMPs (SMAMPs) have been developed that represent a novel and powerful therapy against many microbes including, for example, malaria. A number of small

molecules, sequence-specific oligomers, and polymers SMAMPs have been designed herein that have robust *in vivo* activity against *Staphyococcal aureus* in mouse models, suggesting a novel approach to the development of novel therapeutics. Six of these SMAMPs have been tested and demonstrated to kill *P. falciparum* parasites in culture with a range of IC₅₀s from
5 50 nM to 3 μ M.

The present approach has several advantages. Anti-microbial peptides have remained an effective weapon against bacterial infection over evolutionary time indicating that their mechanism of action thwarts bacterial responses that lead to resistance against toxic substances. This premise is supported by direct experimental data showing that no
10 appreciable resistance to the action of the anti-microbial peptides occurs after multiple serial passages of bacteria in the presence of sub-lethal concentrations of the peptides. Thus, targeting parasite membranes rather than proteins represents a highly innovative and novel approach to treating parasitic diseases and distinguishes the present invention from most others in this field.

15 To more fully evaluate the effects of SMAMP inhibitors on parasite growth through an entire life cycle, cytotoxic/cytostatic growth assays are performed. A synchronized population of parasites can be pulsed with the active SMAMPs for 8 hours during the ring, trophozoite, or schizont stages. The inhibitors can then removed by washing parasites and then parasites can be allowed to finish their cycle. To estimate successful parasite growth, a
20 quantitative growth assay using luciferase expressing parasites can be used. The static effects can be differentiated from toxic effects and the timing of action of these compounds can be determined.

Morphological phenotypes arising from inhibition can be determined. All inhibitors can be evaluated using *P. falciparum* parasites in a culture model of the erythrocytic cycle.
25 Phenotypes for all parasite treatments can be analyzed using Giemsa staining and standard light microscopy. After determining the timing of parasite death, time lapse DIC/fluorescent microscopy can be used to determine that after addition of SMAMPs, the plasma membrane becomes compromised. *P. falciparum* parasites expressing cytoplasmic GFP can be used to allow for the visualization of leakage of cytoplasmic contents after addition of SMAMPs.

30 To investigate the potential for parasites to develop resistance against the antiparasitic activity of the AMP compounds, *P. falciparum* can be serially passaged in 0.25 X EC₅₀, 0.5 X EC₅₀ and the EC₅₀ concentrations of the top three AMP compounds. Resulting

EC₅₀ values can be determined at each passage for each inhibitor. As a control, parallel cultures can also be exposed to 0.5 EC₅₀ concentrations of the antifolate WR99210 and/or pyrimethamine, two well established anti-parasitic agents for which resistance has been reported. If parasites that are resistant to SMAMPs are generated, tiling microarrays (REF) can be used to help determine any genes that contribute to resistance.

SMAMPs can be designed that can be used to probe mechanisms of action and resistance, and compounds that are active *in vivo* can be obtained. A very good correlation between the toxicity to mammalian cells and the overall hydrophobicity of the molecule has been observed. The activity against a particular bacterium has correlated with the overall amphiphilicity of the molecule as well as hydrophobicity, so long as the charge of the molecule was kept constant.

Example 20: Anti-protozoan Activity vs a Malarial Parasite

Seven compounds with diverse structures were screened *in vitro* against the malarial agent *Plasmodium falciparum*. *P. falciparum* is a protozoan parasite and is the infectious agent for the most prevalent and deadly forms of malaria. It accounts for 80% of all human malarial infections and 90% of deaths. More than 120 million clinical cases of malaria and between 1 to 1.5 million deaths occur worldwide every year. There is no vaccine for malaria and current therapies are plagued by rapid resistance which has become endemic in certain regions of the world. Several anti-microbial peptides possess anti-parasitic activities and appear to kill the parasites by interacting with the plasma membrane causing excessive permeability, lysis and death. Specificity for the parasite versus mammalian host cells is attributed to differences in phospholipid content and the lack of cholesterol in the protozoan membrane.

Anti-parasitic activities were measured *in vitro* using a human red blood cell assay. A single *P. falciparum* organism typically infects an erythrocyte and produces 24 progeny within 48 hours following infection. The progeny are released and rapidly infect neighboring red blood cells. The seven compounds (Table 1) were first screened at a single concentration and 6 of the 7 compounds killed *P. falciparum* progeny at a 10 μ M concentration. Four of the active compounds were tested further to determine IC₅₀ and IC₁₀₀ values, or minimum concentrations resulting in 50% and 100% killing, respectively. Observations were also made during the 48 hour incubation period to assess the susceptibility of the parasite during

lifecycle stages inside and outside the host erythrocyte. Two compounds, Compound 116 and Compound 107 possess sub- μM killing activities and Compound 116 potently kills with an IC_{50} of 0.05 μM . Observations made during the infection cycle revealed that only parasitic organisms inside the erythrocyte were visible in the presence of active compounds and no extra-cellular organisms were apparent. Together, these data indicate that the compounds are rapidly killing the protozoa between the time of release and prior to re-infection. One goal of targeting parasite membranes, rather than proteins or metabolic pathways, represents a highly innovative and novel strategy for treating parasitic diseases and distinguishes this approach from most others in this field.

Table 1: Susceptibility of *P. falciparum* to compounds

Compound	% Kill @ 10 μM	IC_{50} (μM)	IC_{100} (μM)
116	100	0.050	0.850
107	100	0.200	0.850
102	100	1.5	3.5
103	100	0.200	1.5
101	100	NT	NT
108	100	NT	NT
102	<10	NT	NT

Example 21: Anti-Malarial Activity

Several compounds were screened in cultures of *P. falciparum* at a concentration of 1.0 or 1.5 μM and showed strong efficacy. Of the compounds tested, Compounds 106 and 107 showed the best results. Compound 106 had an IC_{50} in 3D7 cells of 150 nM with a cytotoxicity of about 40-50 μM in human HepG2 cells. Compound 107 had an IC_{50} in 3D7 cells of 275 nM with a cytotoxicity of about 50-100 μM in human HepG2 cells. Parasite killing generally took place between 6 to 9 hours (data not shown). Neither compound, however, was hemolytic as determined by treatment of uninfected red blood cells using a standard absorbance assay for hemoglobin release (data not shown). In addition, both compounds disrupted food vacuoles as assayed by parasites expressing a marker for the food vacuole (plasmepsin II-YFP), with food vacuole integrity measured by standard fluorescence microscopy.

Example 22: Anti-Malarial Activity

Compounds 106 and 107 were also screened in cultures of *P. falciparum* 3D7 and DD2 and compared to chloroquine. Flow cytometry was used for quantitation of parasitemia using SYOX Green on an LSRII. The results are shown in Table 2.

5

Table 2

Compound	IC ₅₀ (3D7)	IC ₅₀ (DD2)
chloroquine	20 nM	80 nM
Compound 107	275 nM	200 nM
Compound 106	150 nM	100 nM

The DD2 strain of *P. falciparum* is 4 times as resistant to chloroquine as the 3D7 strain. Both Compounds 106 and 107 were effective in strain DD2. Thus, these compounds are effective in chloroquine-sensitive and/or chloroquine-resistant strains.

10

Example 23: Anti-Malarial Activity

Numerous compounds were initially screened using a high throughput quantitative parasite growth assay that makes use of a strain of parasites expressing a cytoplasmic firefly luciferase (obtained from Dr. Kirk Deitsch, Cornell Medical College). These parasites were transfected with a vector containing the firefly luciferase gene using the malarial HRPII promoter. To grow parasites, culture dishes ranging from 96 well plates to 30 ml dishes were used. The 3D7 strain of *P. falciparum* for assays and transfections was primarily used because it has become the standard chloroquine sensitive reference strain and was used for the genome sequencing project. Parasites were cultured in human RBCs under an atmosphere of 5% O₂/7% CO₂/88% N₂ in RPMI 1640 medium supplemented with 25 mM Hepes, 30 mg/L hypoxanthine, 0.225% (w/v) NaHCO₃ and 0.5% (w/v) Albumax II (Life Technologies, Grand Island, NY). Parasite growth was normally synchronized by a combination of serial D-sorbitol treatment for selection of ring stage parasites followed by selective purification of mature schizonts using a Super Macs II magnetic separator (Miltenyi Biotec).

25

A standard luminescent readout was used to measure the growth of parasites. Parasites were grown under normal conditions, lysed in the presence of the luminescence reagents (Bright Glo, Promega) and then measured. To initially test for growth, luciferase expressing parasites were synchronized using serial sorbitol treatments and then parasitemia,

the percentage of RBCs infected with parasites, was adjusted using uninfected RBCs. 100 μ l of total media was used in a 96 well format. Parasitized RBCs were incubated in 96 well plates at 37°C and gassed with 5% CO₂, 5% O₂, 90% N₂. Parasites were allowed to grow for approximately 60 hours, until they successfully divided, ruptured and reinvaded new RBCs.

- 5 At 10-15 hours post invasion, the cells were lysed, and luciferase levels were measured using an Analyst HT luminometer (Molecular Devices). Results are shown in Table 3.

Table 3

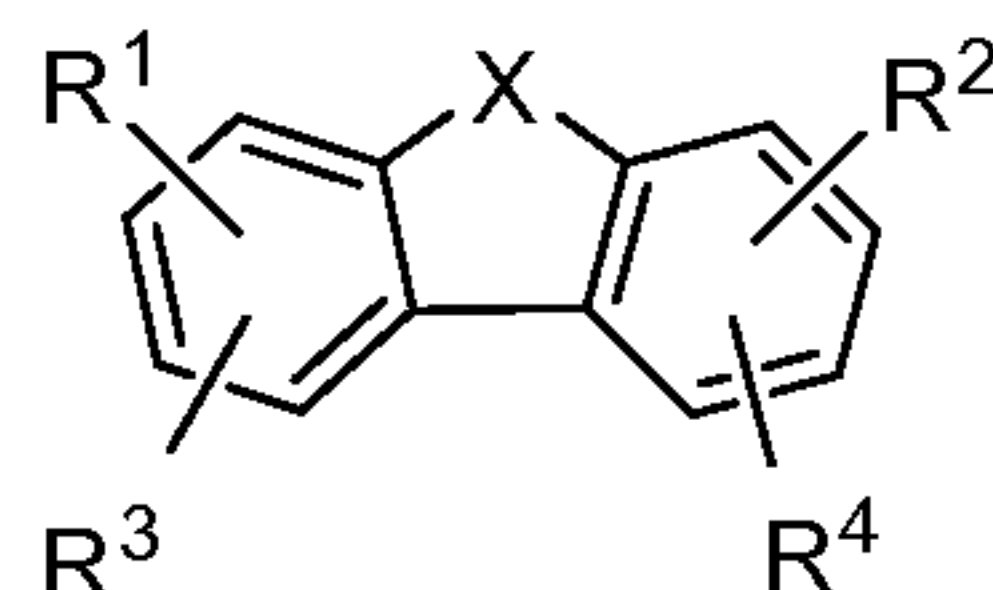
Compound	IC ₅₀ μ M
Artesunate	0.009
Compound 106	1.153
Compound 118	0.364
Compound 119	1.858
Compound 110	0.584
Compound 117	0.301
Compound 104	>10
Compound 111	0.587
Compound 113	0.241
Compound 112	>10
Compound 120	0.604
Compound 121	1.505
Compound 114	>10
Compound 102	5.376
Compound 103	0.783
Compound 107	0.314
Compound 116	0.318
Compound 101	0.308
Compound 122	0.260
Compound 123	1.366
Compound 124	1.582
Compound 129	0.832
Compound 128	1.725

Compound 127	1.765
Compound 126	1.420
Compound 125	0.286
Compound 130	2.559
Compound 131	0.235
Compound 132	0.236
Compound 133	2.028
Compound 134	2.438
Compound 135	0.108
Compound 136	0.958
Compound 137	0.604
Compound 138	0.213
Compound 139	1.169
Compound 140	1.674
Compound 142	0.063
Compound 154	0.200
Compound 149	0.357
Compound 141	1.344
Compound 143	0.258
Compound 144	3.399
Compound 145	0.369
Compound 146	0.127
Compound 155	0.535
Compound 152	0.783
Compound 153	0.925
Compound 150	6.608
Compound 151	2.784
Compound 147	0.221
Compound 148	0.704
Compound 156	0.107

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference (including, but not limited to, journal articles, U.S. and non-U.S. patents, patent application publications, 5 international patent application publications, gene bank accession numbers, and the like) cited in the present application is incorporated herein by reference in its entirety.

What is Claimed is:

1. A compound of Formula I:

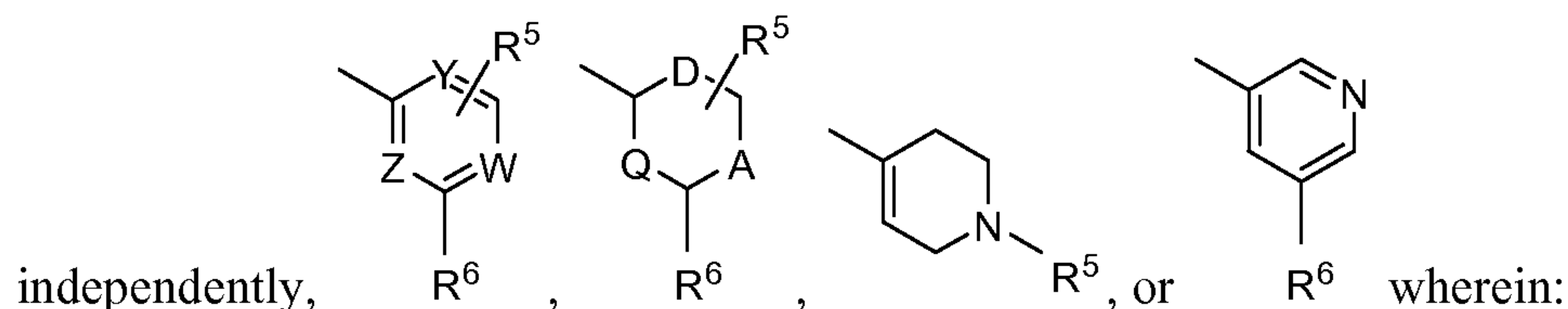


wherein:

- 5 X is C(R⁷)C(R⁸), C(=O), N(R⁹), O, S, S(=O), or S(=O)₂;
 R⁷, R⁸, and R⁹ are, independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, CF₃, or aromatic group;
 R¹ and R² are, independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, haloC₁-C₈alkyl, or CN;
- 10 R³ and R⁴ are, independently, carbocycle(R⁵)(R⁶);
 each R⁵ and each R⁶ are, independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, CF₃, aromatic group, heterocycle, or the free base or salt form of -(CH₂)_n-NH₂, or -(CH₂)_n-NH-(CH₂)_n-NH₂, or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 8;
- 15 or a pharmaceutically acceptable salt thereof.
2. The compound or salt of claim 1 wherein X is N(R⁹), O, S, or S(=O)₂.
3. The compound or salt of claim 1 wherein X is NH, O, or S.
- 20 4. The compound or salt of claim 1 wherein X is NH or S.
5. The compound or salt of any one of claims 1 to 4 wherein R¹ and R² are, independently, H, C₁-C₃alkyl, C₁-C₃alkoxy, halo, OH, haloC₁-C₃alkyl, or CN.
- 25 6. The compound or salt of any one of claims 1 to 4 wherein R¹ and R² are, independently, H, C₁-C₃alkyl, C₁-C₃alkoxy, halo, or OH.
7. The compound or salt of any one of claims 1 to 4 wherein R¹ and R² are,
- 30 independently, H, C₁-C₃alkyl, or halo.

8. The compound or salt of any one of claims 1 to 4 wherein R^1 and R^2 are H.

9. The compound or salt of any one of claims 1 to 8 wherein R^3 and R^4 are,

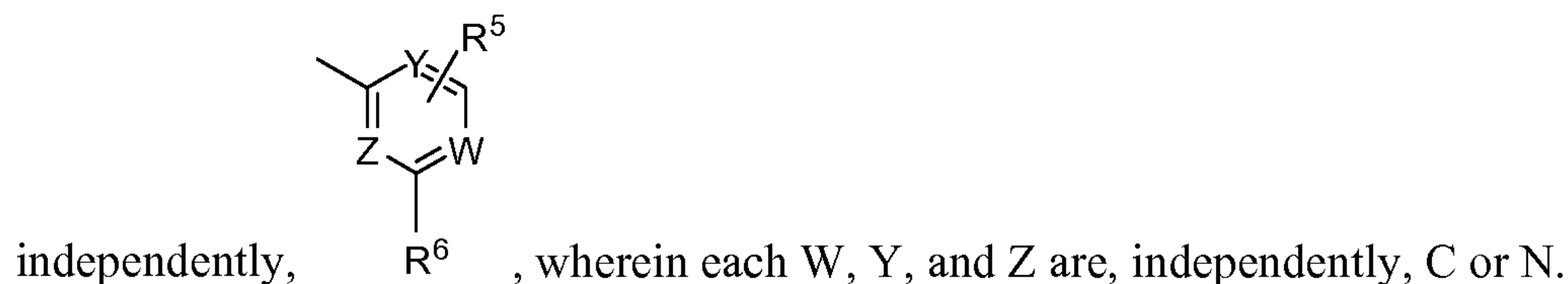


5 each W, Y, and Z are, independently, C or N;

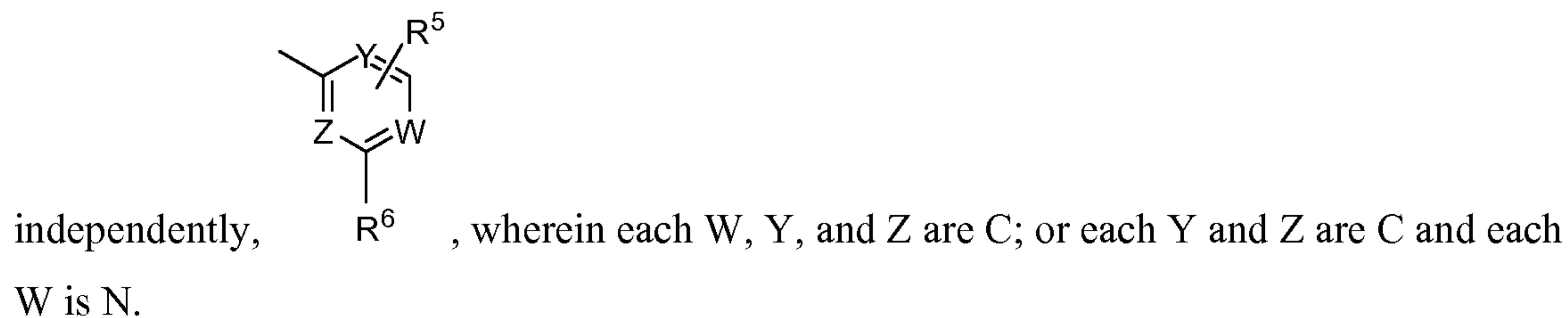
each A, D, and Q are, independently, $C(R^{10})C(R^{11})$, $C(=O)$, $N(R^{12})$, O, or S; and

each R^{10} , R^{11} , and R^{12} are, independently, H, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, halo, OH, CF_3 , or aromatic group.

10 10. The compound or salt of any one of claims 1 to 8 wherein R^3 and R^4 are,



11. The compound or salt of any one of claims 1 to 8 wherein R^3 and R^4 are,



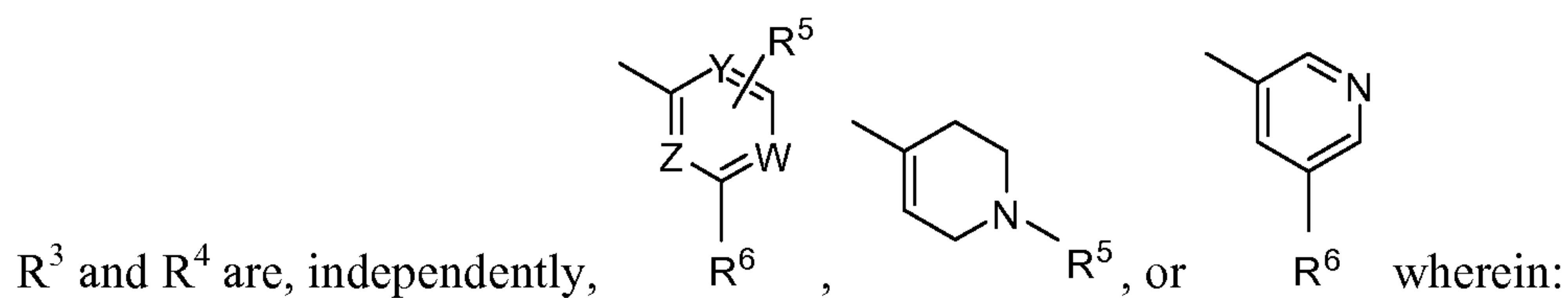
12. The compound or salt of any one of claims 1 to 11 wherein:

each R^5 is, independently, H, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, halo, OH, CF_3 , or the free base or salt form of $-(CH_2)_n-NH_2$, $-(CH_2)_n-NH-(CH_2)_n-NH_2$, or $-(CH_2)_n-NH-C(=NH)NH_2$,

20 where each n is, independently, 1 to 8; and

each R^6 is, independently, heterocycle or the free base or salt form of $-(CH_2)_n-NH_2$, $-(CH_2)_n-NH-(CH_2)_n-NH_2$, or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 8.

13. The compound or salt of any one of claims 1 to 11 wherein:
each R⁵ is, independently, H, C₁-C₃alkyl, C₁-C₃alkoxy, halo, OH, or CF₃; and
each R⁶ is, independently, heterocycle or the free base or salt form of -(CH₂)_n-NH₂,
where each n is, independently, 1 to 8.
- 5
14. The compound or salt of any one of claims 1 to 11 wherein:
each R⁵ is, independently, H, C₁-C₃alkyl, halo, or OH; and
each R⁶ is, independently, heterocycle or the free base or salt form of -(CH₂)_n-NH₂,
where each n is, independently, 1 to 4.
- 10
15. The compound or salt of any one of claims 1 to 11 wherein:
each R⁵ is, independently, H, C₁-C₃alkyl, halo, or OH; and
each R⁶ is, independently, 6-membered heterocycle or the free base or salt form of
-(CH₂)_n-NH₂, where each n is, independently, 1 to 3.
- 15
16. The compound or salt of any one of claims 1 to 11 wherein:
each R⁵ is, independently, H or halo; and
each R⁶ is piperazinyl or the free base or salt form of -(CH₂)_n-NH₂ where each n is,
independently, 1 to 3.
- 20
17. The compound or salt of any one of claims 1 to 11 wherein:
each R⁵ is piperazinyl; and
each R⁶ is, independently, H, C₁-C₃alkyl, C₁-C₃alkoxy, halo, OH, or CF₃.
- 25
18. The compound or salt of any one of claims 1 to 11 wherein:
each R⁵ is piperazinyl; and
each R⁶ is H, C₁-C₃alkyl, halo, OH, or CF₃.
- 30
19. The compound or salt of claim 1 wherein:
X is NH, O, S, or S(=O)₂;
R¹ and R² are H;



each W, Y, and Z are, independently, C or N; and

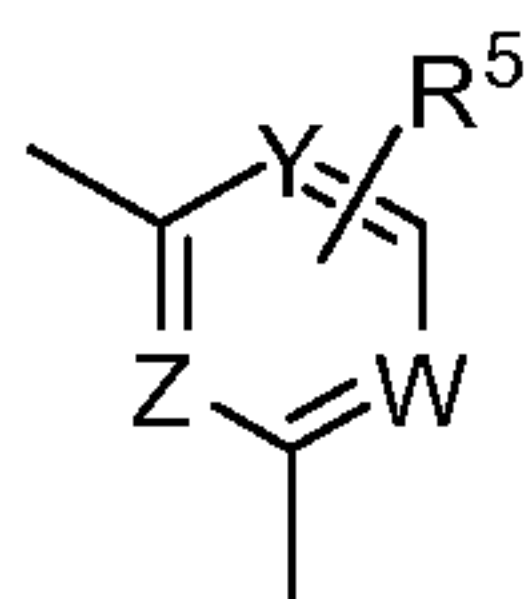
each R^5 and each R^6 are, independently, H, heterocycle, or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 3.

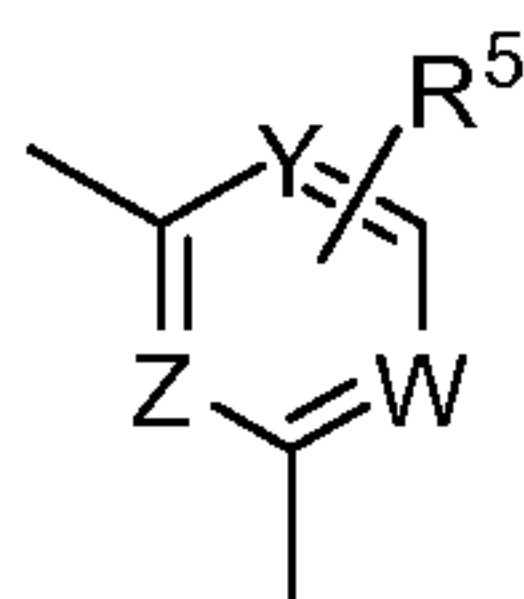
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20. The compound or salt of claim 1 wherein:

X is NH, O, or S;

R^1 and R^2 are H;



R^3 and R^4 are , where each Z and Y are C, and each W is N; or each W,

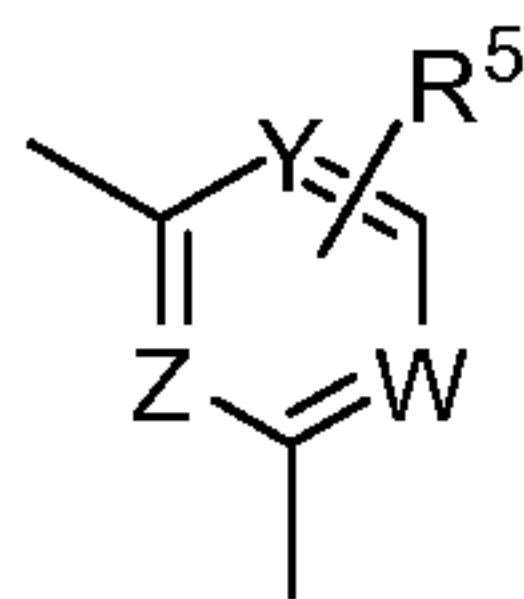
10 Y, and Z are C; and

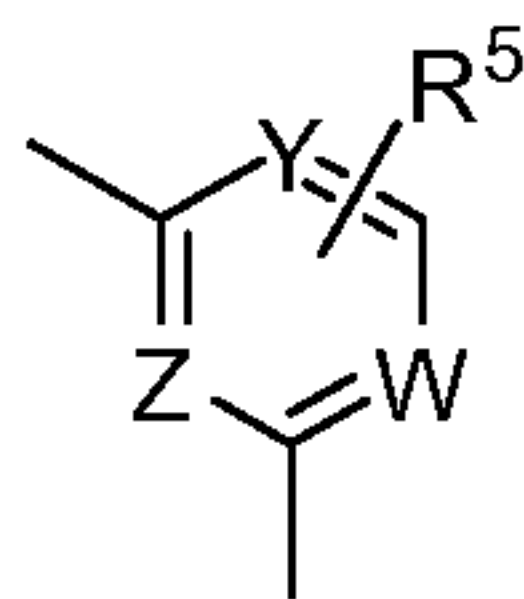
each R^5 is, independently, H or halo, and each R^6 is piperazinyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 3; or each R^5 is piperazinyl, and each R^6 is, independently, H, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, halo, OH, or CF_3 .

15 21. The compound or salt of claim 1 wherein:

X is NH, O, or S;

R^1 and R^2 are H;



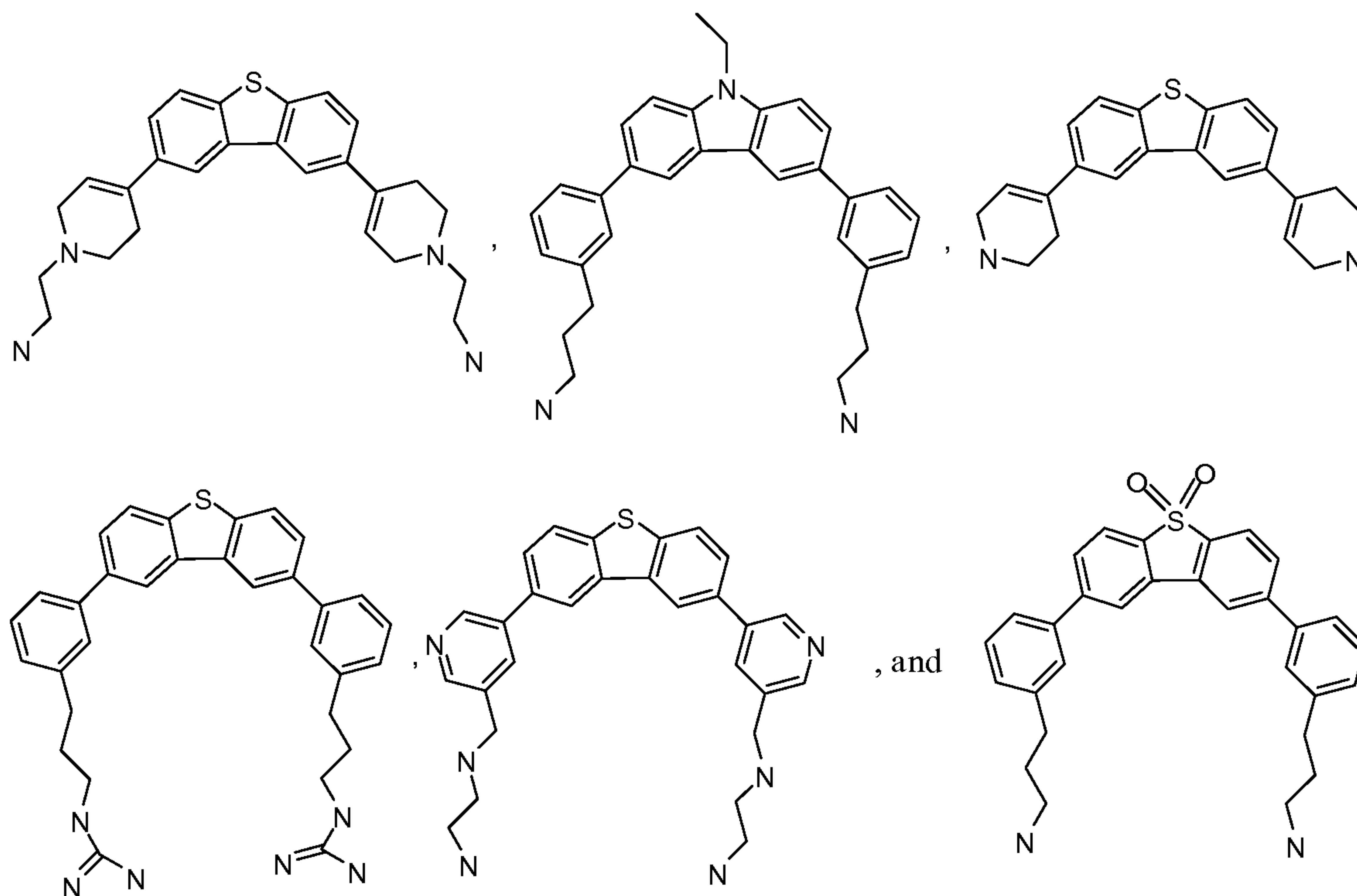
R^3 and R^4 are , where each Z and Y are C, and each W is N; or each W,

Y, and Z are C; and

20 each R^5 is H, and each R^6 is piperazinyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 3; or each R^5 is piperazinyl; and each R^6 is H.

The image displays 15 chemical structures of organic compounds, arranged in five rows of three. The structures are as follows:

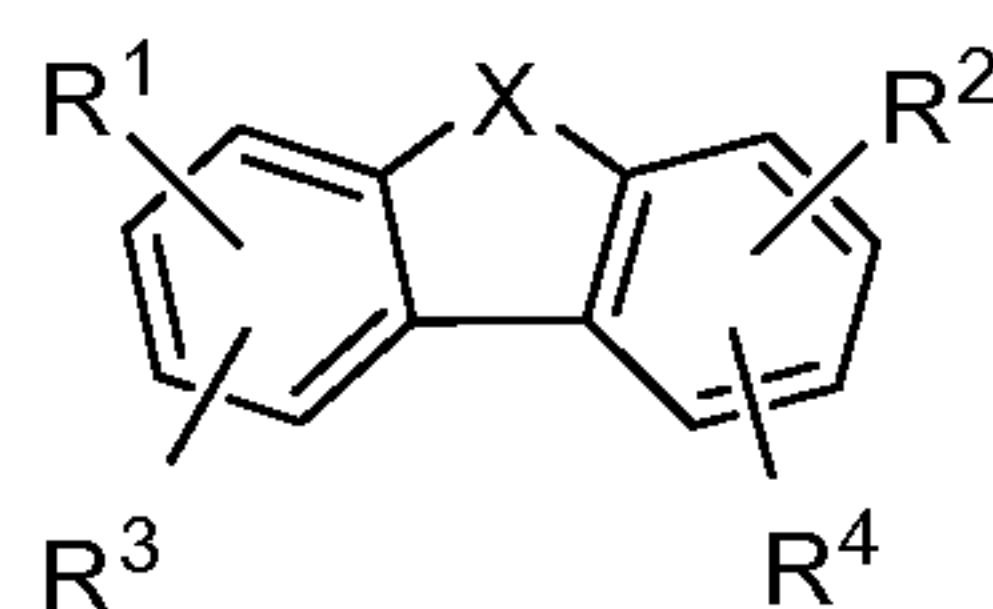
- Row 1:**
 - 1,3-bis(4-(aminomethyl)phenyl)-5-thienylbenzene
 - 1,3-bis(4-(aminomethyl)phenyl)-5-thienylbenzene
 - 1,3-bis(4-(aminomethyl)phenyl)-5-thienylbenzene
- Row 2:**
 - 1,3-bis(4-(aminomethyl)phenyl)-5-thienylbenzene
 - 1,3-bis(4-(aminomethyl)phenyl)-5-thienylbenzene
 - 1,3-bis(4-(aminomethyl)phenyl)-5-thienylbenzene
- Row 3:**
 - 1,3-bis(4-(aminomethyl)phenyl)-5-thienylbenzene
 - 1,3-bis(4-(aminomethyl)phenyl)-5-thienylbenzene
 - 1,3-bis(4-(aminomethyl)phenyl)-5-thienylbenzene
- Row 4:**
 - 1,3-bis(4-(aminomethyl)phenyl)-5-thienylbenzene
 - 1,3-bis(4-(aminomethyl)phenyl)-5-thienylbenzene
 - 1,3-bis(4-(aminomethyl)phenyl)-5-thienylbenzene
- Row 5:**
 - 1,3-bis(4-(aminomethyl)phenyl)-5-thienylbenzene
 - 1,3-bis(4-(aminomethyl)phenyl)-5-thienylbenzene
 - 1,3-bis(4-(aminomethyl)phenyl)-5-thienylbenzene



or pharmaceutically acceptable salt thereof.

23. A composition comprising the compound or salt of any one of claims 1 to 22 and a pharmaceutically acceptable carrier.

24. A method of treating malaria in an animal comprising administering to the animal a therapeutically effective amount of a compound of Formula I:



wherein:

X is C(R⁷)C(R⁸), C(=O), N(R⁹), O, S, S(=O), or S(=O)₂;

R⁷, R⁸, and R⁹ are, independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, CF₃, or aromatic group;

R¹ and R² are, independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, haloC₁-C₈alkyl, or CN;

R³ and R⁴ are, independently, carbocycle(R⁵)(R⁶);

each R^5 and each R^6 are, independently, H, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, halo, OH, CF_3 , aromatic group, heterocycle, or the free base or salt form of $-(CH_2)_n-NH_2$, $-(CH_2)_n-NH-(CH_2)_n-NH_2$, or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 8;

5 or a pharmaceutically acceptable salt thereof.

25. The method of claim 24 wherein X is $N(R^9)$, O, S, or $S(=O)_2$.

26. The method of claim 24 wherein X is NH, O, or S.

10

27. The method of claim 24 wherein X is NH or S.

28. The method of any one of claims 24 to 27 wherein R^1 and R^2 are, independently, H, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, halo, OH, halo C_1 - C_3 alkyl, or CN.

15

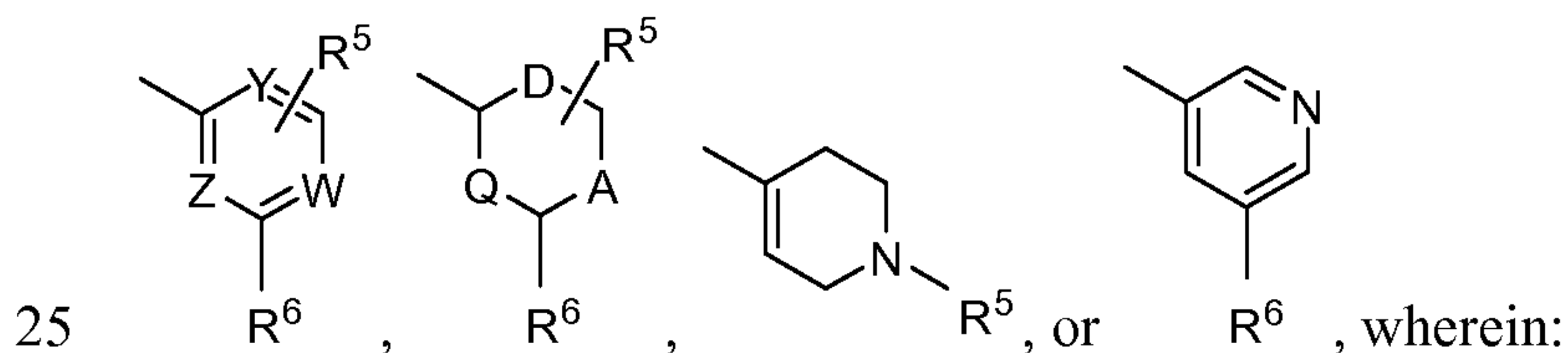
29. The method of any one of claims 24 to 27 wherein R^1 and R^2 are, independently, H, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, halo, or OH.

30. The method of any one of claims 24 to 27 wherein R^1 and R^2 are, independently, H, C_1 - C_3 alkyl, or halo.

20

31. The method of any one of claims 24 to 27 wherein R^1 and R^2 are H.

32. The method of any one of claims 24 to 31 wherein R^3 and R^4 are, independently,



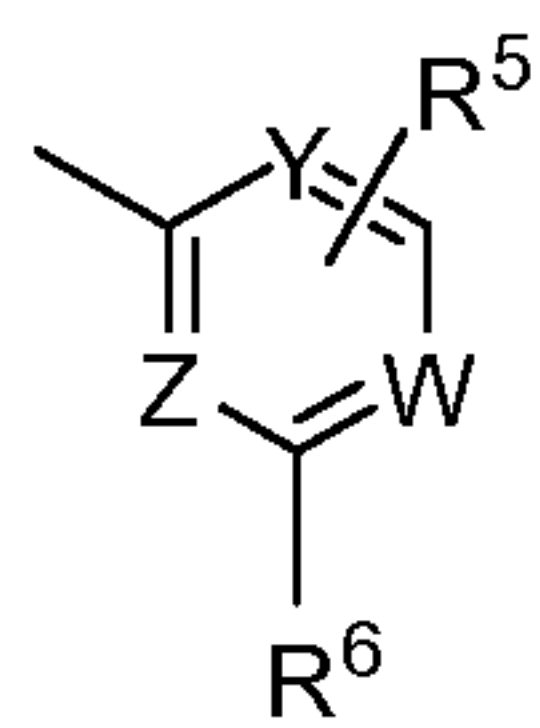
each W, Y, and Z are, independently, C or N;

each A, D, and Q are, independently, $C(R^{10})C(R^{11})$, $C(=O)$, $N(R^{12})$, O, or S; and

each R^{10} , R^{11} , and R^{12} are, independently, H, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, halo, OH, CF_3 , or aromatic group.

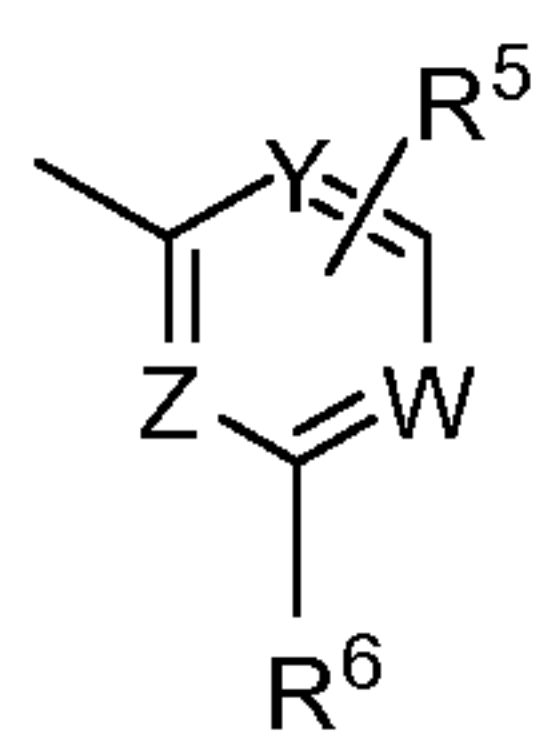
30

33. The method of any one of claims 24 to 31 wherein R^3 and R^4 are, independently,



, wherein each W, Y, and Z are, independently, C or N.

34. The method of any one of claims 24 to 31 wherein R^3 and R^4 are, independently,



5 R^6 , wherein each W, Y, and Z are C; or each Y and Z are C and each W is N.

35. The method of any one of claims 24 to 34 wherein:

each R^5 is, independently, H, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, halo, OH, CF_3 , or the free base or salt form of $-(CH_2)_n-NH_2$, $-(CH_2)_n-NH-(CH_2)_n-NH_2$, or $-(CH_2)_n-NH-C(=NH)NH_2$,

10 where each n is, independently, 1 to 8; and

each R^6 is, independently, heterocycle or the free base or salt form of $-(CH_2)_n-NH_2$, $-(CH_2)_n-NH-(CH_2)_n-NH_2$, or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 8.

15 36. The method of any one of claims 24 to 34 wherein:

each R^5 is, independently, H, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, halo, OH, or CF_3 ; and

each R^6 is, independently, heterocycle or the free base or salt form of $-(CH_2)_n-NH_2$,

where each n is, independently, 1 to 8.

20 37. The method of any one of claims 24 to 34 wherein:

each R^5 is, independently, H, C_1 - C_3 alkyl, halo, or OH; and

each R^6 is, independently, heterocycle or the free base or salt form of $-(CH_2)_n-NH_2$,

where each n is, independently, 1 to 4.

25 38. The method of any one of claims 24 to 34 wherein:

each R^5 is, independently, H, C_1 - C_3 alkyl, halo, or OH; and

each R^6 is, independently, 6-membered heterocycle or the free base or salt form of

-(CH₂)_n-NH₂, where each n is, independently, 1 to 3.

39. The method of any one of claims 24 to 34 wherein:

each R⁵ is, independently, H or halo; and

5 each R⁶ is piperazinyl or the free base or salt form of -(CH₂)_n-NH₂ where each n is, independently, 1 to 3.

40. The method of any one of claims 24 to 34 wherein:

each R⁵ is piperazinyl; and

10 each R⁶ is, independently, H, C₁-C₃alkyl, C₁-C₃alkoxy, halo, OH, or CF₃.

41. The method of any one of claims 24 to 34 wherein:

each R⁵ is piperazinyl; and

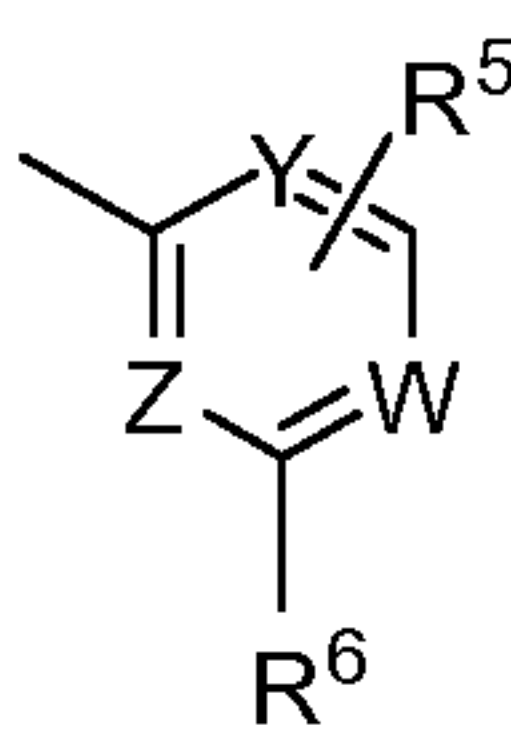
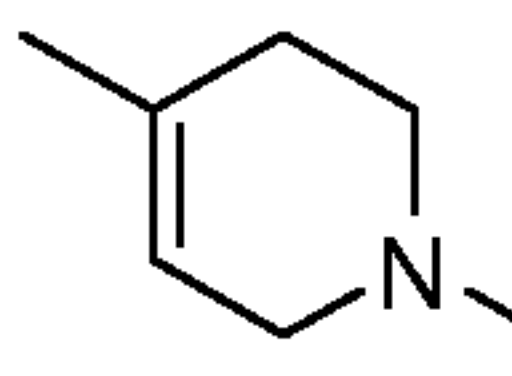
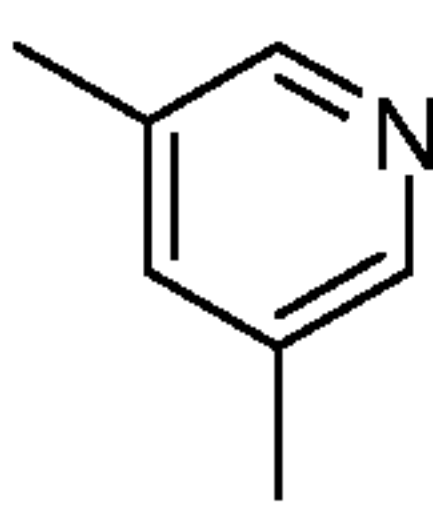
each R⁶ is H, C₁-C₃alkyl, halo, OH, or CF₃.

15

42. The method of claim 24 wherein:

X is NH, O, S, or S(=O)₂;

R¹ and R² are H;

R³ and R⁴ are, independently, , , or , wherein:

20

each W, Y, and Z are, independently, C or N; and

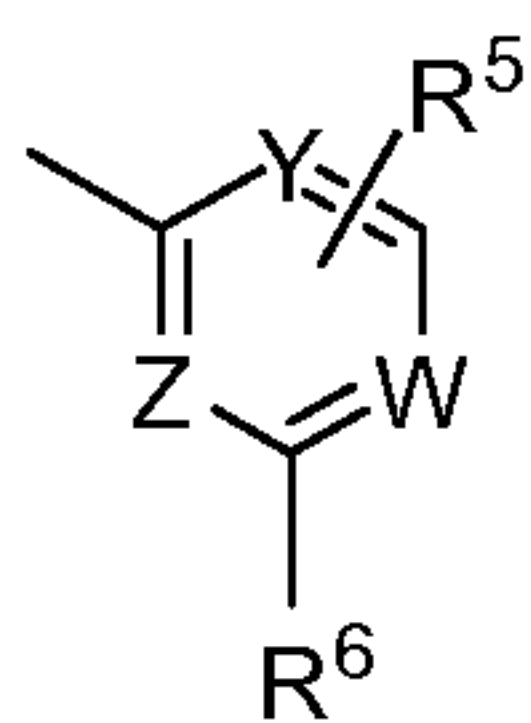
each R⁵ and each R⁶ are, independently, H, heterocycle, or the free base or salt form of -(CH₂)_n-NH₂, where each n is, independently, 1 to 3.

43. The method of claim 24 wherein:

25

X is NH, O, or S;

R¹ and R² are H;



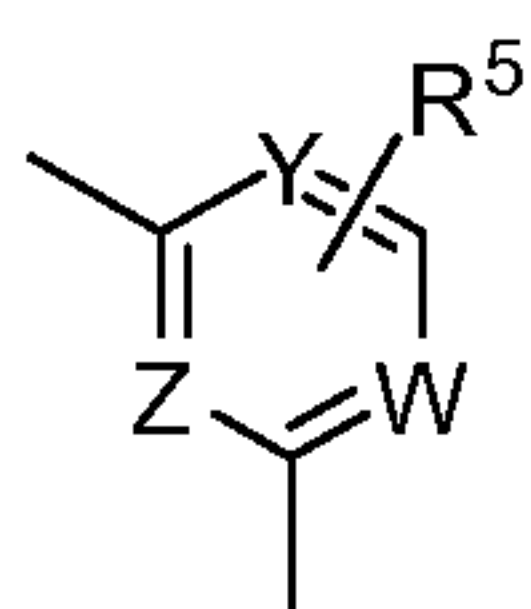
R^3 and R^4 are , where each Z and Y are C, and each W is N; or each W, Y, and Z are C; and

each R^5 is, independently, H or halo, and each R^6 is piperazinyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 3; or each R^5 is piperazinyl, and each R^6 is, independently, H, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, halo, OH, or CF_3 .

44. The method of claim 24 wherein:

X is NH, O, or S;

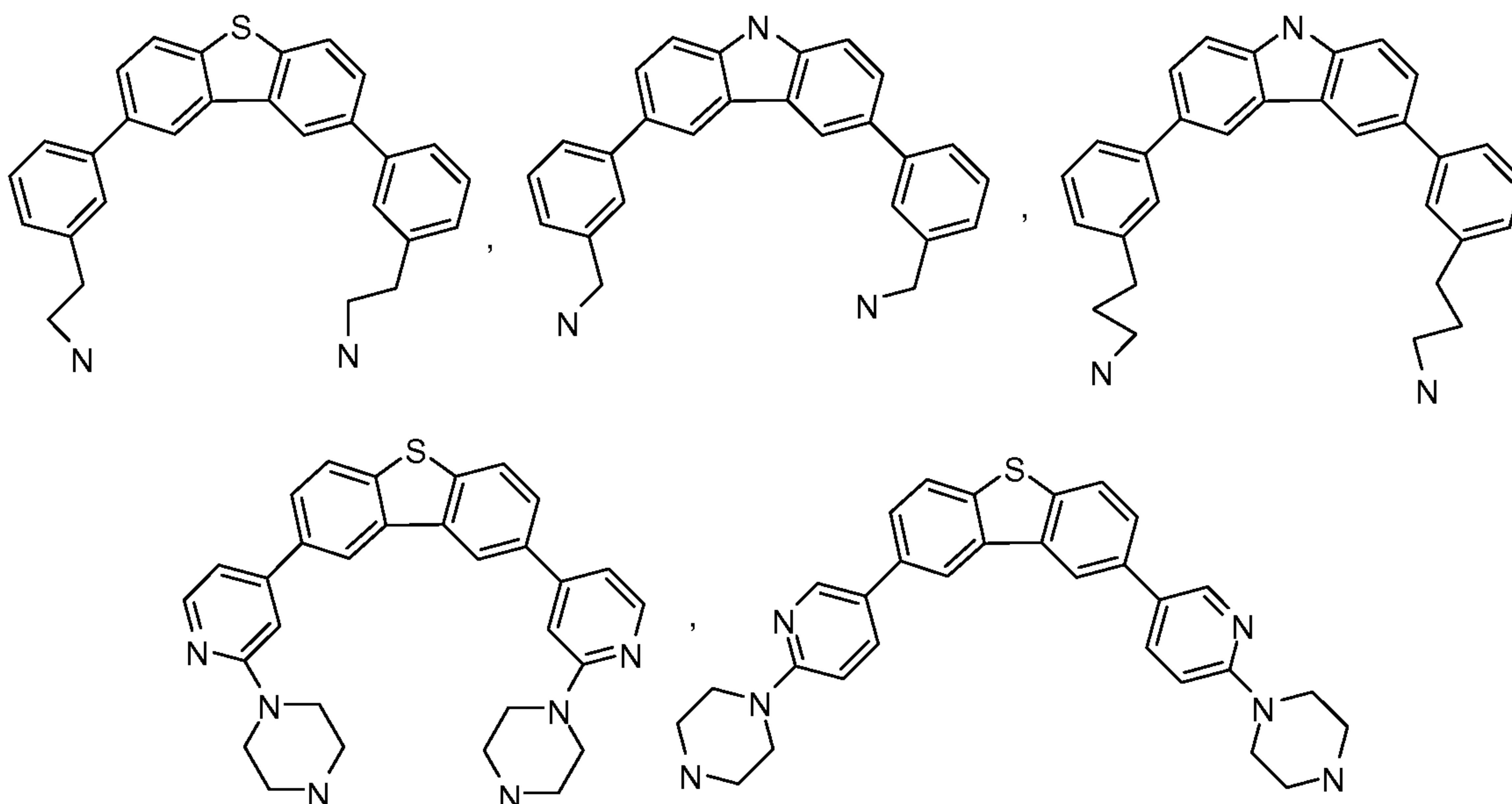
R^1 and R^2 are H;

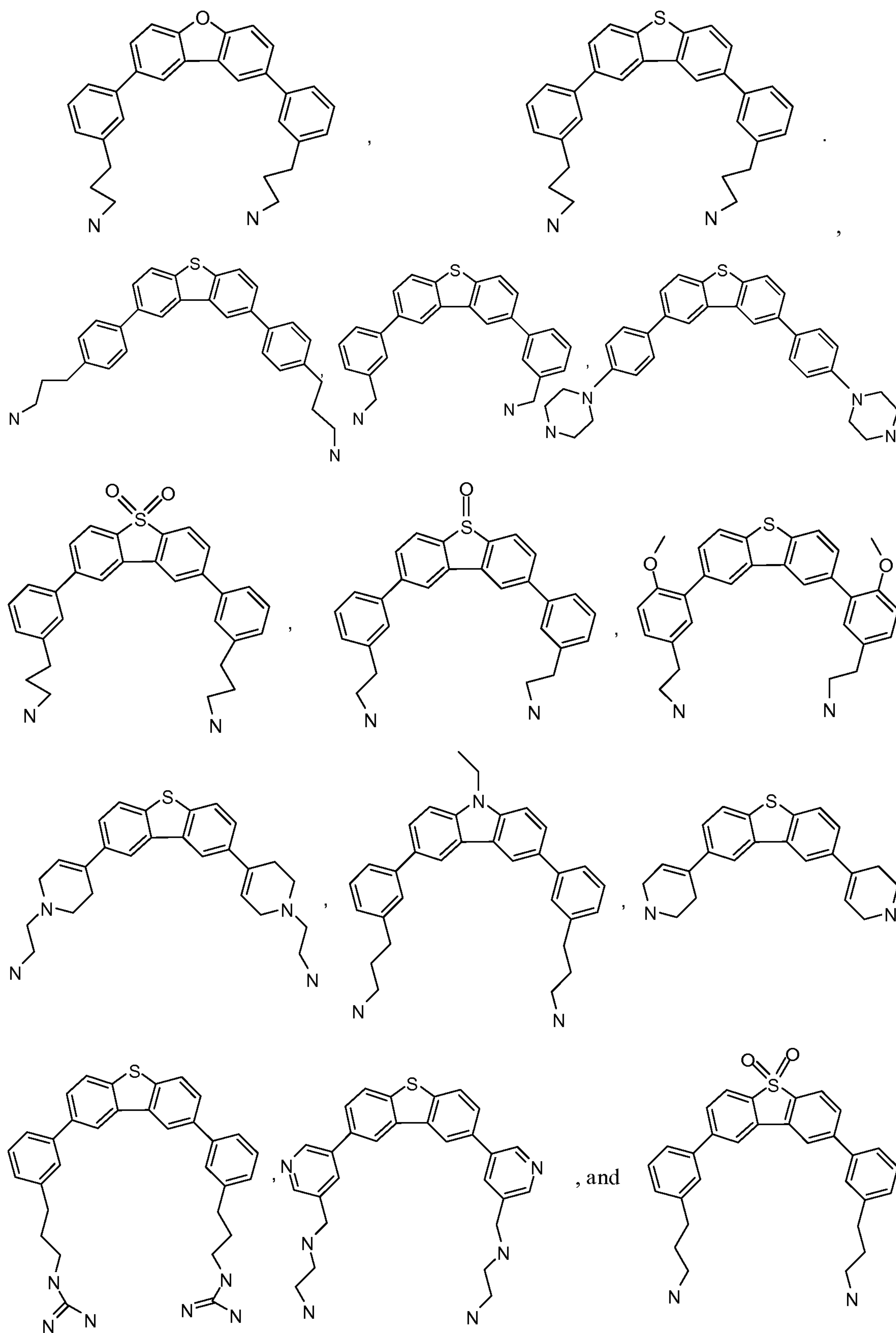


R^3 and R^4 are , where each Z and Y are C, and each W is N; or each W, Y, and Z are C; and

each R^5 is H, and each R^6 is piperazinyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 3; or each R^5 is piperazinyl, and each R^6 is H.

45. The method of claim 24 wherein the compound is chosen from:



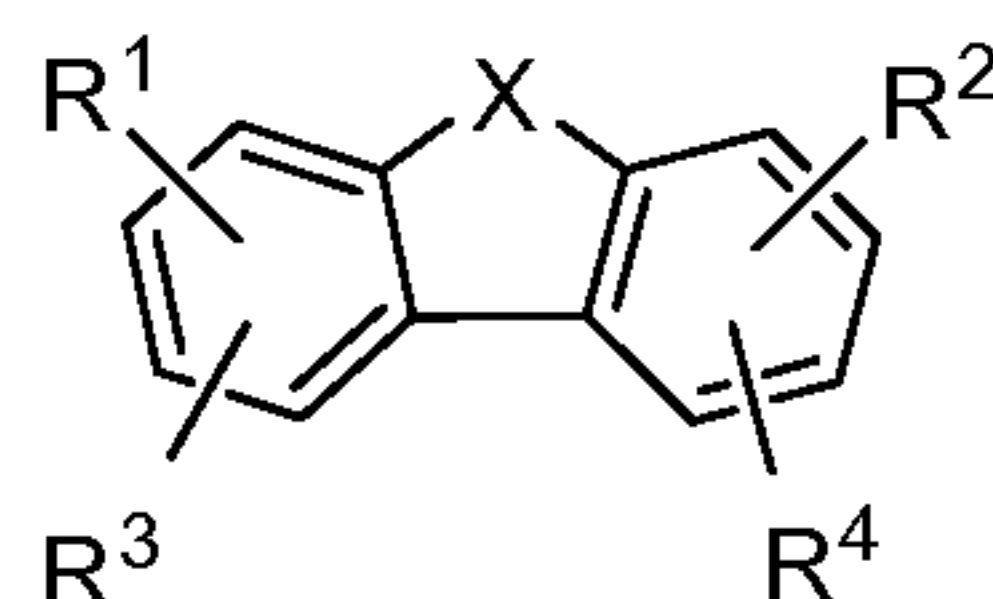


or pharmaceutically acceptable salt thereof.

46. The method of any one of claims 24 to 45 wherein the malaria is chloroquine-sensitive or chloroquine-resistant.

5

47. A method of killing or inhibiting the growth of a *Plasmodium* species comprising contacting the species with an effective amount of a compound of Formula I:



wherein:

10 X is C(R⁷)C(R⁸), C(=O), N(R⁹), O, S, S(=O), or S(=O)₂;

R⁷, R⁸, and R⁹ are, independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, CF₃, or aromatic group;

R¹ and R² are, independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, haloC₁-C₈alkyl, or CN;

15 R³ and R⁴ are, independently, carbocycle(R⁵)(R⁶); and

each R⁵ and each R⁶ are, independently, H, C₁-C₈alkyl, C₁-C₈alkoxy, halo, OH, CF₃, aromatic group, heterocycle, or the free base or salt form of -(CH₂)_n-NH₂, -(CH₂)_n-NH-(CH₂)_n-NH₂, or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 8;

20 or a pharmaceutically acceptable salt thereof.

48. The method of claim 47 wherein X is N(R⁹), O, S, or S(=O)₂.

49. The method of claim 47 wherein X is NH, O, or S.

25

50. The method of claim 47 wherein X is NH or S.

51. The method of any one of claims 47 to 50 wherein R¹ and R² are, independently, H, C₁-C₃alkyl, C₁-C₃alkoxy, halo, OH, haloC₁-C₃alkyl, or CN.

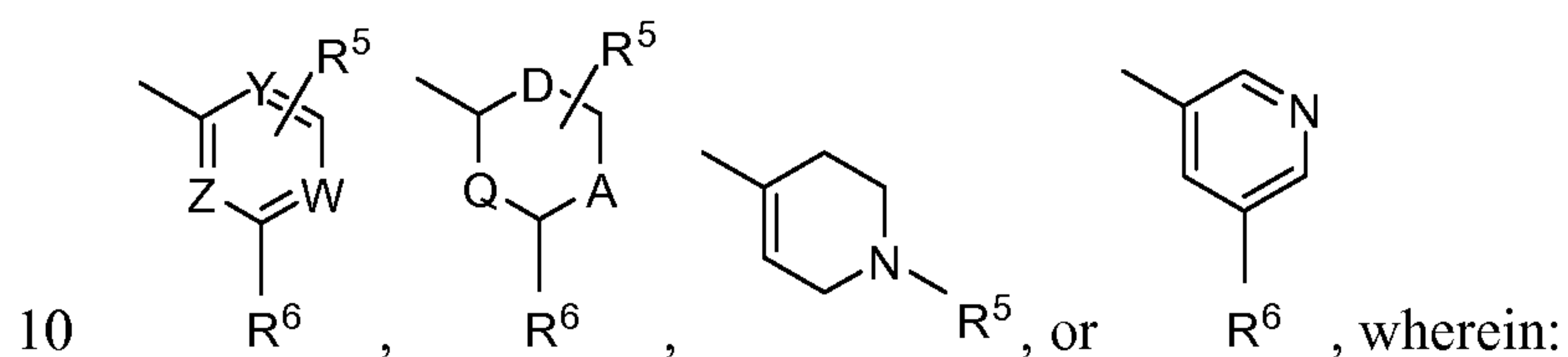
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52. The method of any one of claims 47 to 50 wherein R^1 and R^2 are, independently, H, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, halo, or OH.

53. The method of any one of claims 47 to 50 wherein R^1 and R^2 are, independently, H,
5 C_1 - C_3 alkyl, or halo.

54. The method of any one of claims 47 to 50 wherein R^1 and R^2 are H.

55. The method of any one of claims 47 to 54 wherein R^3 and R^4 are, independently,



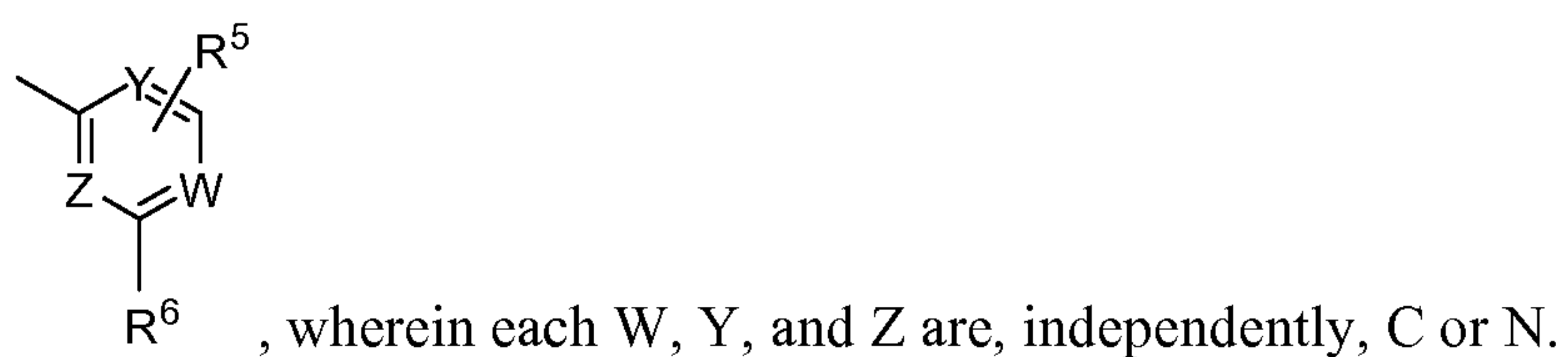
each W, Y, and Z are, independently, C or N;

each A, D, and Q are, independently, $C(R^{10})C(R^{11})$, $C(=O)$, $N(R^{12})$, O, or S; and

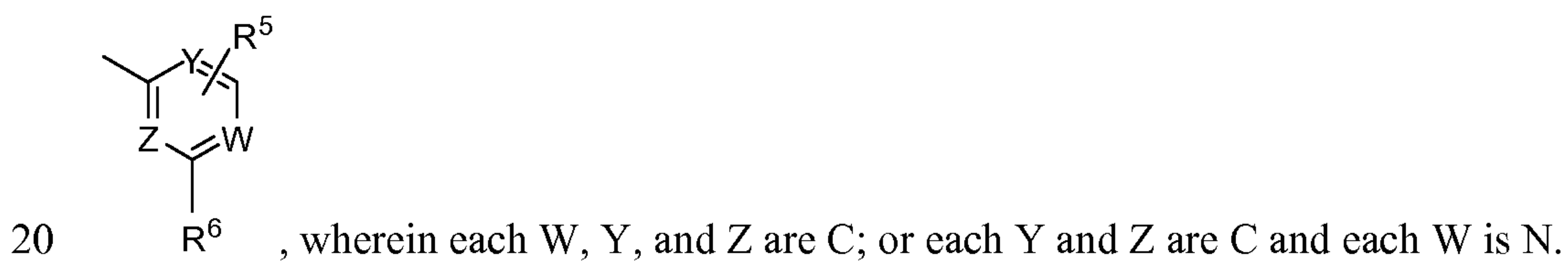
each R^{10} , R^{11} , and R^{12} are, independently, H, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, halo, OH, CF_3 , or aromatic group.

15

56. The method of any one of claims 47 to 54 wherein R^3 and R^4 are, independently,



57. The method of any one of claims 47 to 54 wherein R^3 and R^4 are, independently,



58. The method of any one of claims 47 to 57 wherein:
each R^5 is, independently, H, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, halo, OH, CF_3 , or the free base or salt form of $-(CH_2)_n-NH_2$, $-(CH_2)_n-NH-(CH_2)_n-NH_2$, or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 8; and
5 each R^6 is, independently, heterocycle or the free base or salt form of $-(CH_2)_n-NH_2$, $-(CH_2)_n-NH-(CH_2)_n-NH_2$, or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 8.
59. The method of any one of claims 47 to 57 wherein:
10 each R^5 is, independently, H, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, halo, OH, or CF_3 ; and
each R^6 is, independently, heterocycle or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 8.
60. The method of any one of claims 47 to 57 wherein:
15 each R^5 is, independently, H, C_1 - C_3 alkyl, halo, or OH; and
each R^6 is, independently, heterocycle or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4.
61. The method of any one of claims 47 to 57 wherein:
20 each R^5 is, independently, H, C_1 - C_3 alkyl, halo, or OH; and
each R^6 is, independently, 6-membered heterocycle or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 3.
62. The method of any one of claims 47 to 57 wherein:
25 each R^5 is, independently, H or halo; and
each R^6 is piperazinyl or the free base or salt form of $-(CH_2)_n-NH_2$ where each n is, independently, 1 to 3.
63. The method of any one of claims 47 to 57 wherein:
30 each R^5 is piperazinyl; and
each R^6 is, independently, H, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, halo, OH, or CF_3 .

64. The method of any one of claims 47 to 57 wherein:

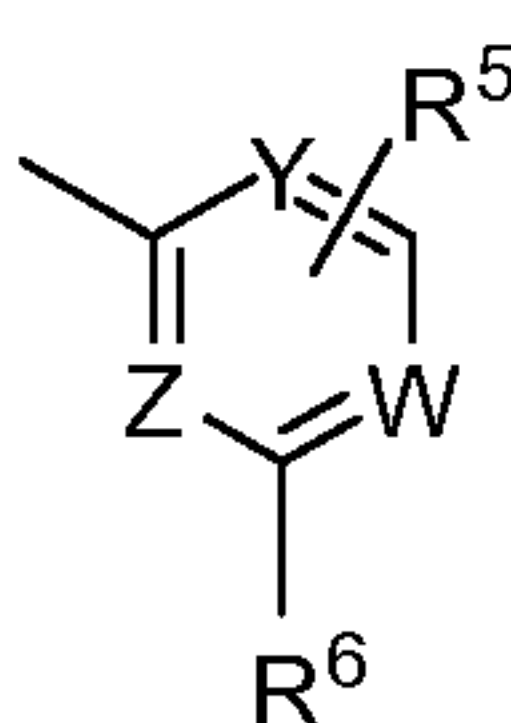
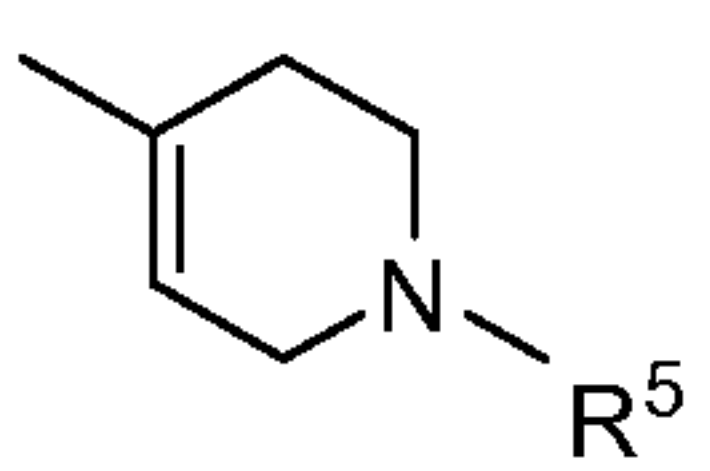
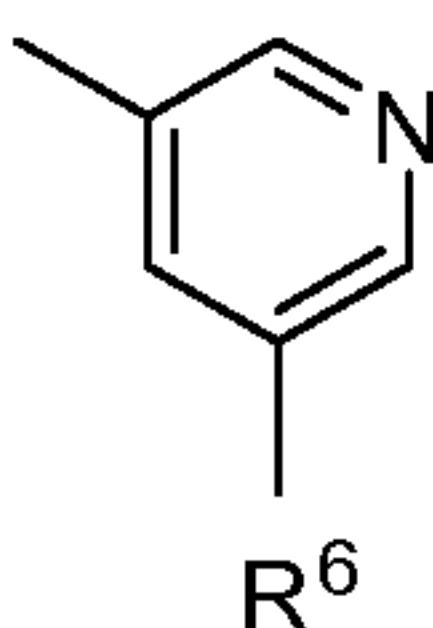
each R^5 is piperazinyl; and

each R^6 is H, C_1 - C_3 alkyl, halo, OH, or CF_3 .

5 65. The method of claim 47 wherein:

X is NH, O, S, or $S(=O)_2$;

R^1 and R^2 are H;

R^3 and R^4 are, independently, , , or , wherein:

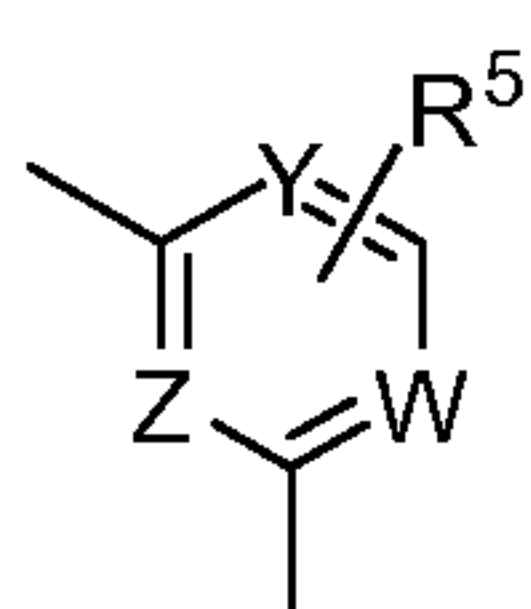
each W, Y, and Z are, independently, C or N; and

10 each R^5 and each R^6 are, independently, H, heterocycle, or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 3.

66. The method of claim 47 wherein:

X is NH, O, or S;

15 R^1 and R^2 are H;

R^3 and R^4 are , where each Z and Y are C, and each W is N; or each W, Y, and Z are C; and

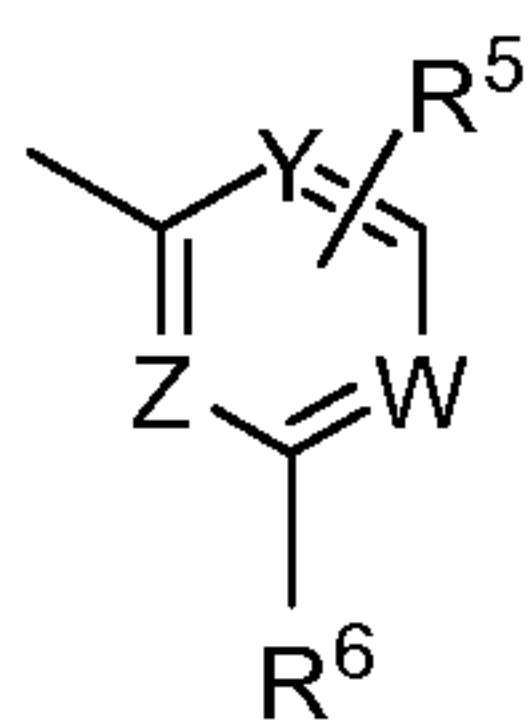
each R^5 is, independently, H or halo, and each R^6 is piperazinyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 3; or each R^5 is piperazinyl,

20 and each R^6 is, independently, H, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, halo, OH, or CF_3 .

67. The method of claim 47 wherein:

X is NH, O, or S;

R^1 and R^2 are H;

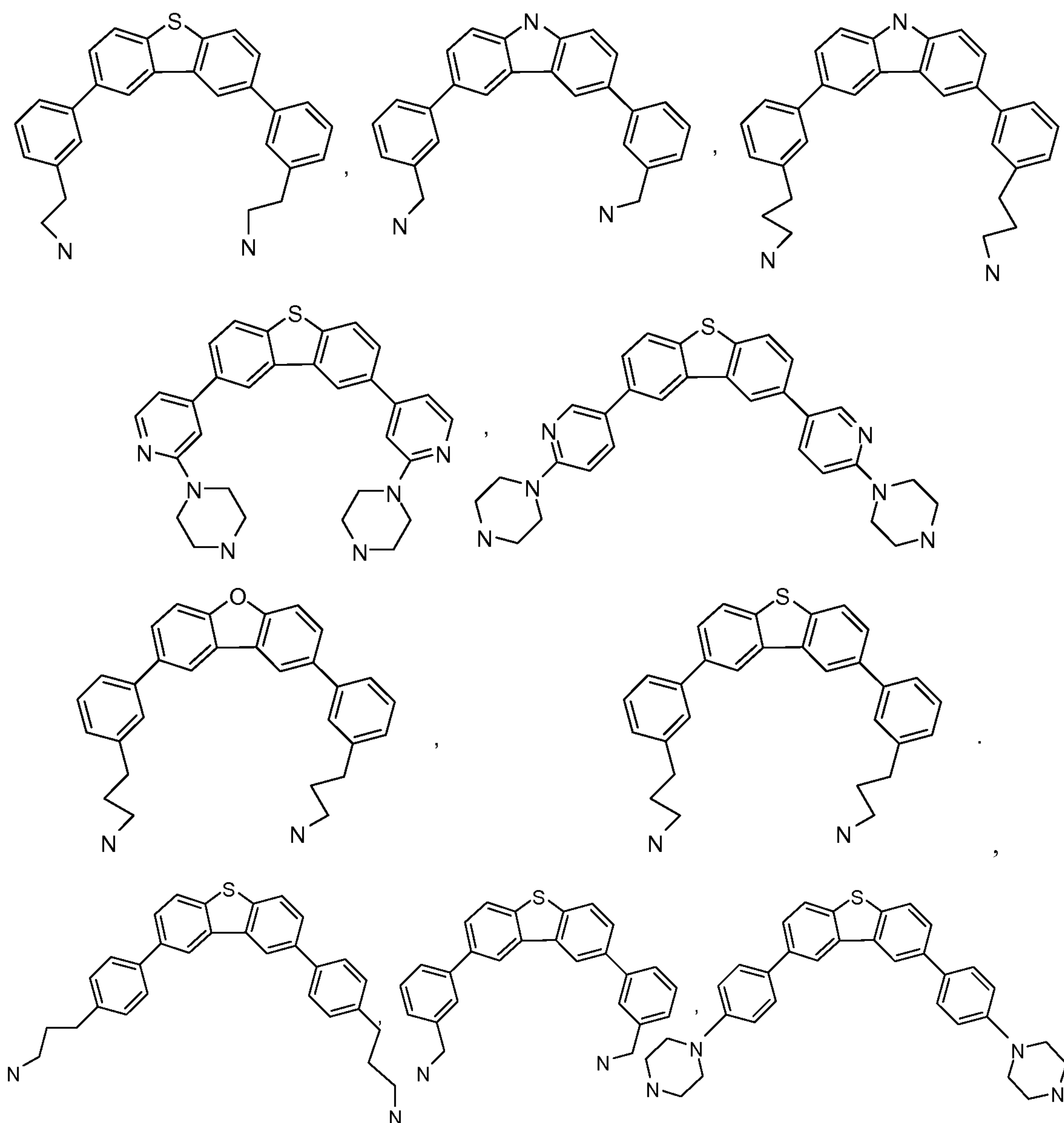


R^3 and R^4 are R^6 , where each Z and Y are C, and each W is N; or each W, Y, and Z are C; and

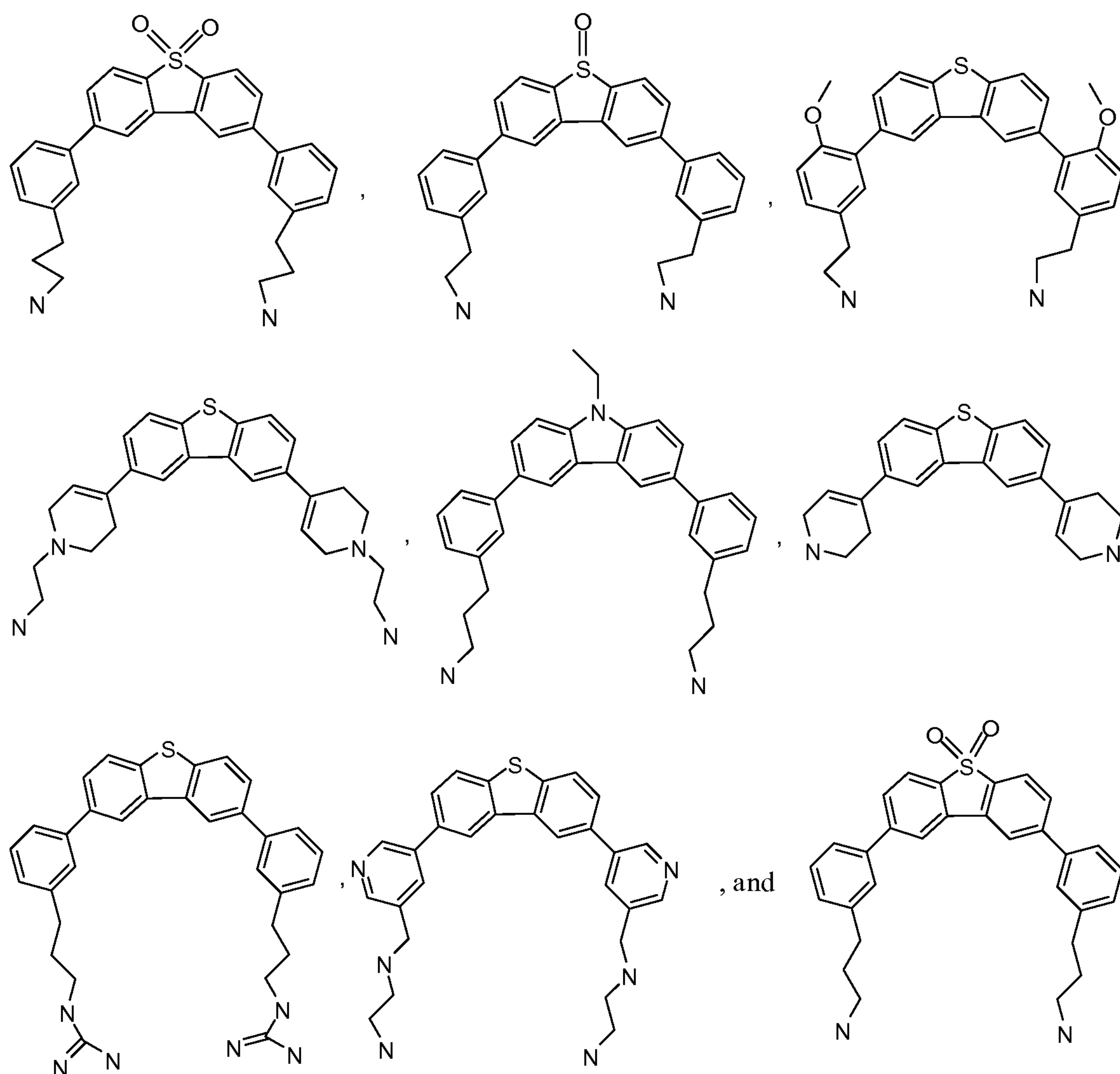
each R^5 is H, and each R^6 is piperazinyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 3; or each R^5 is piperazinyl; and each R^6 is H.

5

68. The method of claim 47 wherein the compound is chosen from:



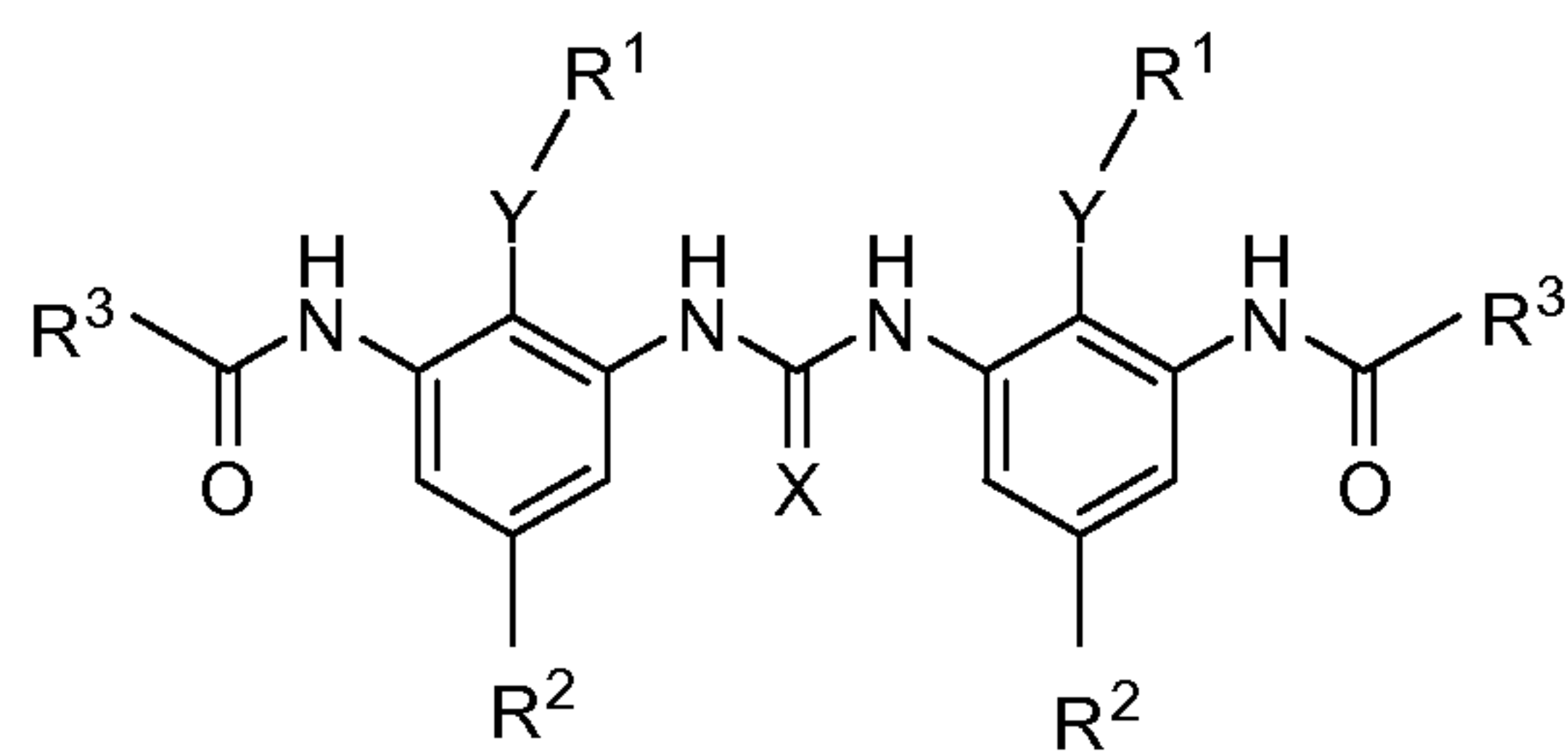
10



or pharmaceutically acceptable salt thereof.

5

69. A compound of Formula II:



wherein:

X is O or S;

10 each Y is, independently, O, S, or N;

each R^1 is, independently, H, 5- or 6-membered heterocycle, or the free base or salt form of $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; or each R^1 is, independently, together with Y a 5- or 6-membered heterocycle;

each R^2 is, independently, H, CF_3 , $C(CH_3)_3$, halo, or OH; and

5 each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;
or a pharmaceutically acceptable salt thereof.

70. The compound or salt of claim 69 wherein X is O.

10

71. The compound or salt of claim 69 or claim 70 wherein Y is O or S.

72. The compound or salt of any one of claims 69 to 71 wherein each R^1 is, independently, 5-membered heterocycle or the free base or salt form of $-(CH_2)_n-NH_2$, where
15 each n is, independently, 1 to 4.

73. The compound or salt of any one of claims 69 to 71 wherein each R^1 is, independently, 3-pyrrolyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2.

20

74. The compound or salt of any one of claims 69 to 73 wherein each R^2 is, independently, CF_3 , $C(CH_3)_3$, or halo.

75. The compound or salt of any one of claims 69 to 74 wherein each R^3 is,
25 independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

76. The compound or salt of any one of claims 69 to 74 wherein each R^3 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 4.

30 77. The compound or salt of claim 69 wherein:
X is O or S;
each Y is, independently, O or S;

each R^1 is, independently, 5-membered heterocycle, or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4;

each R^2 is, independently, CF_3 or $C(CH_3)_3$; and

each R^3 is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is,
5 independently, 1 to 4.

78. The compound or salt of claim 69 wherein:

X is O or S;

each Y is O or S;

10 each R^1 is 5-membered heterocycle, or the free base or salt form of $-(CH_2)_n-NH_2$,
where each n is 1 to 4;

each R^2 is CF_3 or $C(CH_3)_3$; and

each R^3 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 to 4.

15 79. The compound or salt of claim 69 wherein:

X is O or S;

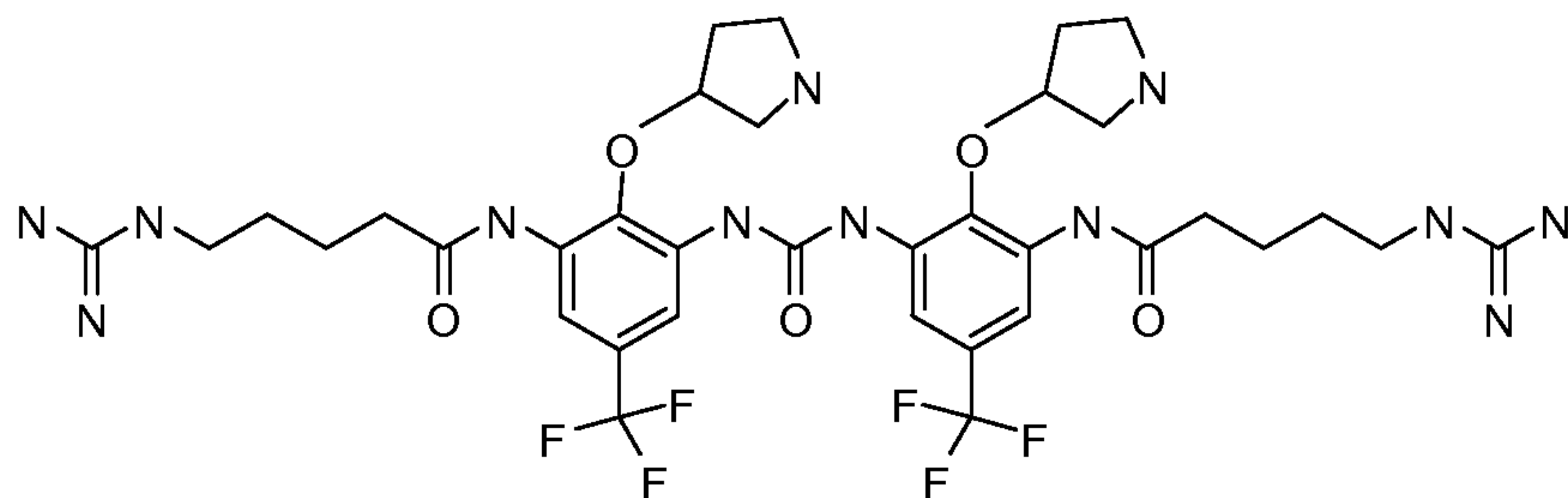
each Y is O or S;

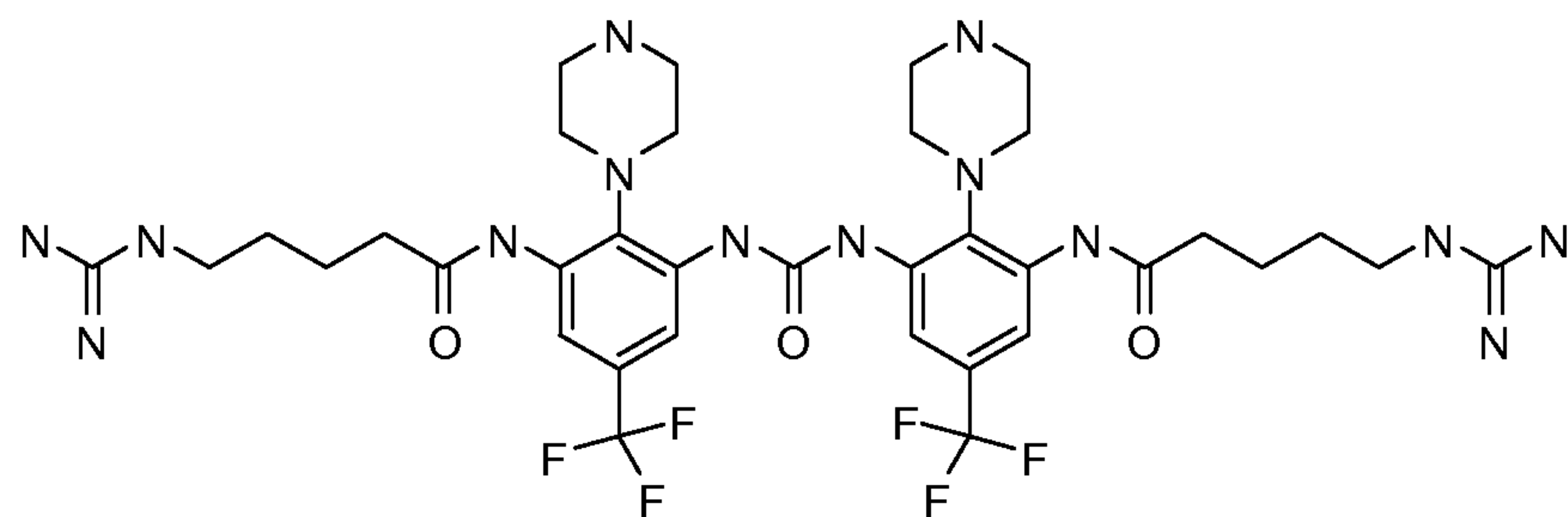
each R^1 is 3-pyrrolyl, or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is
2;

20 each R^2 is CF_3 or $C(CH_3)_3$; and

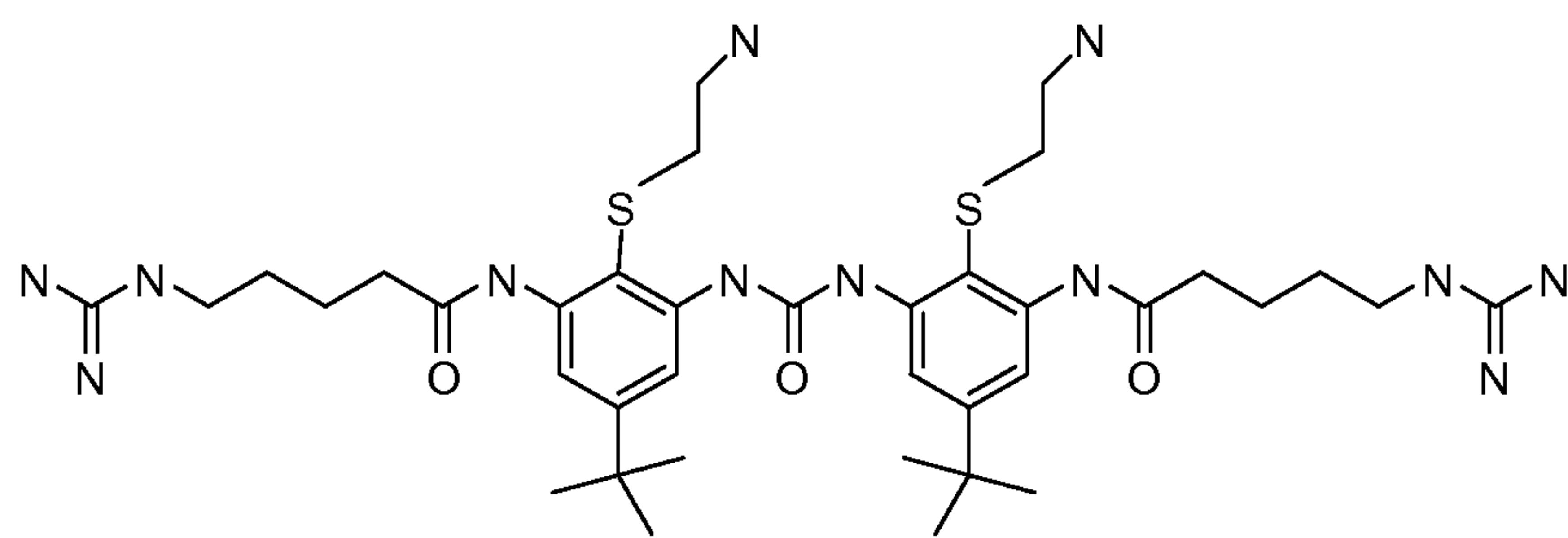
each R^3 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 4.

80. A compound chosen from:





and



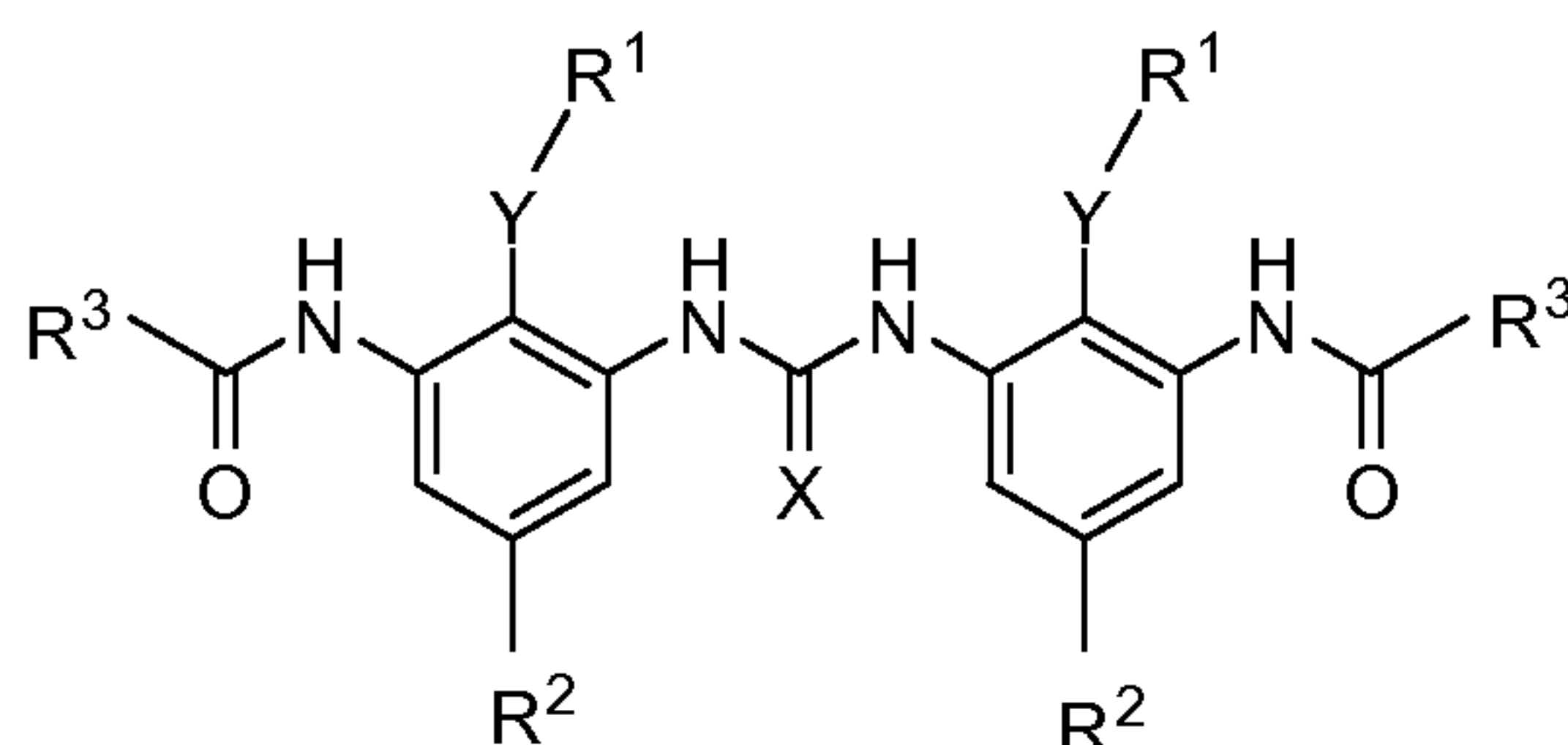
or a pharmaceutically acceptable salt thereof.

5

81. A composition comprising the compound or salt of any one of claims 69 to 80 and a pharmaceutically acceptable carrier.

82. A method of treating malaria in an animal comprising administering to the animal a therapeutically effective amount of a compound of Formula II:

10



wherein:

X is O or S;

each Y is, independently, O, S, or N;

15 each R^1 is, independently, H, 5- or 6-membered heterocycle, or the free base or salt form of $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; or each R^1 is, independently, together with Y a 5- or 6-membered heterocycle;

each R^2 is, independently, H, CF_3 , $C(CH_3)_3$, halo, or OH; and

each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;
or a pharmaceutically acceptable salt thereof.

5 83. The method of claim 82 wherein X is O.

84. The method of claim 82 or claim 83 wherein Y is O or S.

85. The method of any one of claims 82 to 84 wherein each R^1 is, independently,
10 5-membered heterocycle or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4.

86. The method of any one of claims 82 to 84 wherein each R^1 is, independently,
3-pyrrolyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or
15 2.

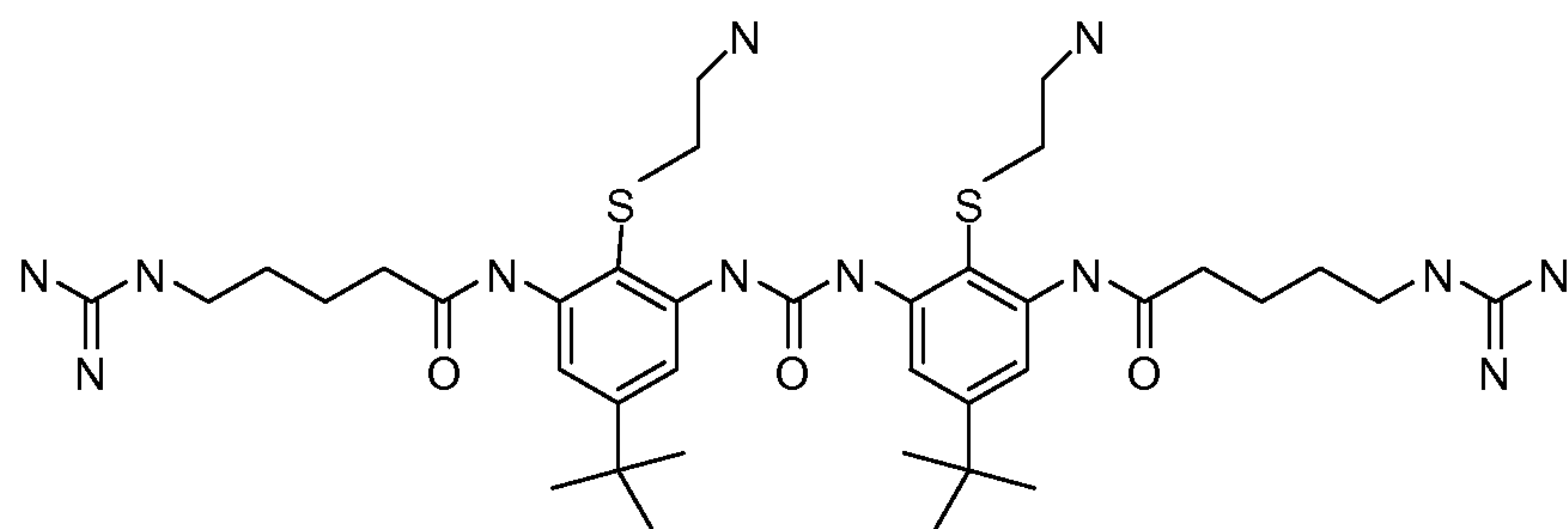
87. The method of any one of claims 82 to 86 wherein each R^2 is, independently, CF_3 , $C(CH_3)_3$, or halo.

20 88. The method of any one of claims 82 to 87 wherein each R^3 is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

89. The method of any one of claims 82 to 87 wherein each R^3 is
 $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 4.

25

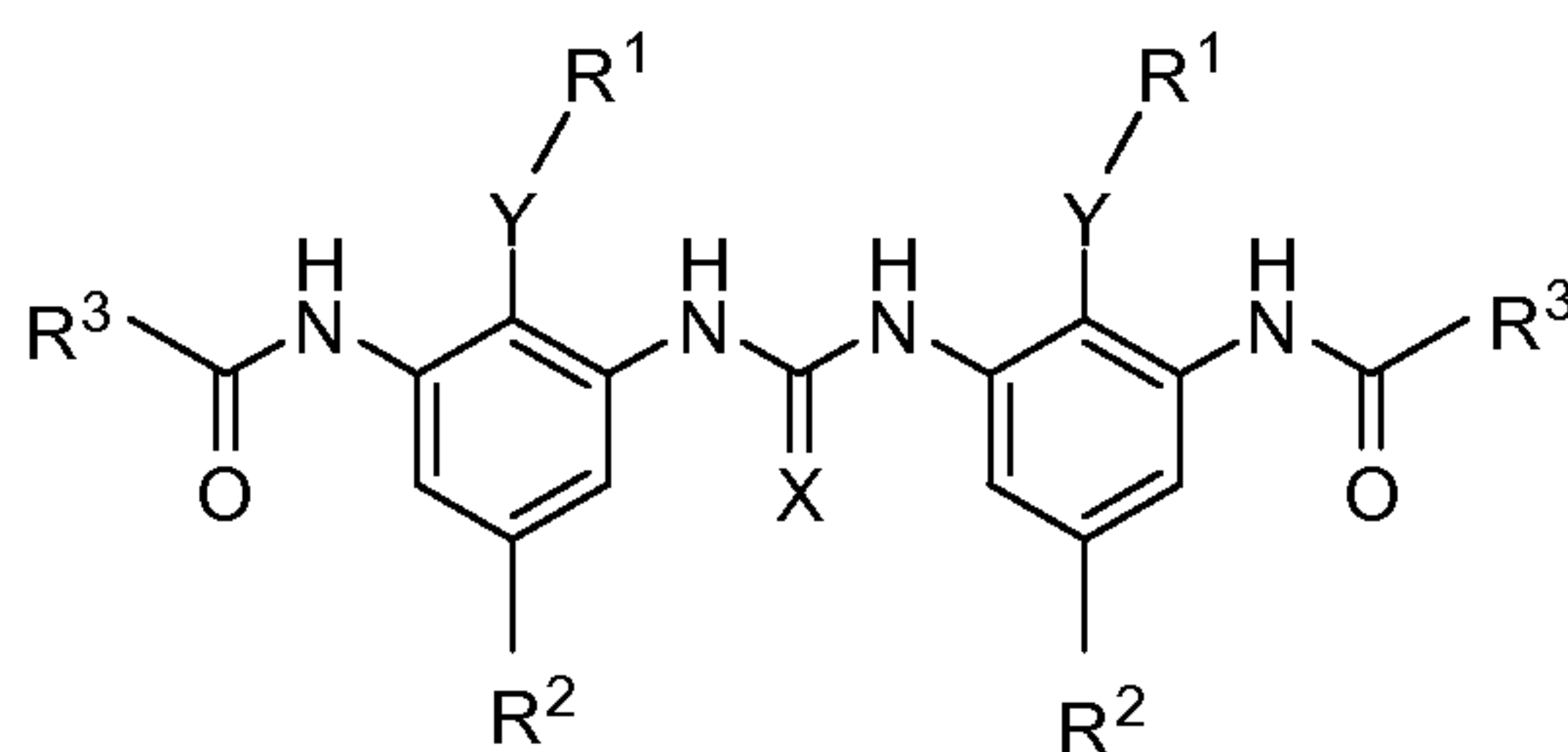
90. The method of claim 82 wherein:
X is O or S;
each Y is, independently, O or S;
each R^1 is, independently, 5-membered heterocycle, or the free base or salt form of
30 $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4;
each R^2 is, independently, CF_3 or $C(CH_3)_3$; and



or a pharmaceutically acceptable salt thereof.

94. The method of any one of claims 82 to 93 wherein the malaria is chloroquine-sensitive or chloroquine-resistant.

95. A method of killing or inhibiting the growth of a *Plasmodium* species comprising contacting the species with an effective amount of a compound of Formula II:



10 wherein:

X is O or S;

each Y is, independently, O, S, or N;

each R¹ is, independently, H, 5- or 6-membered heterocycle, or the free base or salt form of -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4; or

15 each R¹ is, independently, together with Y a 5- or 6-membered heterocycle;

each R² is, independently, H, CF₃, C(CH₃)₃, halo, or OH; and

each R³ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4;

or a pharmaceutically acceptable salt thereof.

20

96. The method of claim 95 wherein X is O.

97. The method of claim 95 or claim 96 wherein Y is O or S.

98. The method of any one of claims 95 to 97 wherein each R^1 is, independently, 5-membered heterocycle or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4.
- 5 99. The method of any one of claims 95 to 97 wherein each R^1 is, independently, 3-pyrrolyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2.
100. The method of any one of claims 95 to 99 wherein each R^2 is, independently, CF_3 ,
10 $C(CH_3)_3$, or halo.
101. The method of any one of claims 95 to 100 wherein each R^3 is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.
- 15 102. The method of any one of claims 95 to 100 wherein each R^3 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 4.
103. The method of claim 95 wherein:
X is O or S;
20 each Y is, independently, O or S;
each R^1 is, independently, 5-membered heterocycle, or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4;
each R^2 is, independently, CF_3 or $C(CH_3)_3$; and
each R^3 is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is,
25 independently, 1 to 4.
104. The method of claim 95 wherein:
X is O or S;
each Y is O or S;
30 each R^1 is 5-membered heterocycle, or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 1 to 4;
each R^2 is CF_3 or $C(CH_3)_3$; and

each R^3 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 to 4.

105. The method of claim 95 wherein:

X is O or S;

5 each Y is O or S;

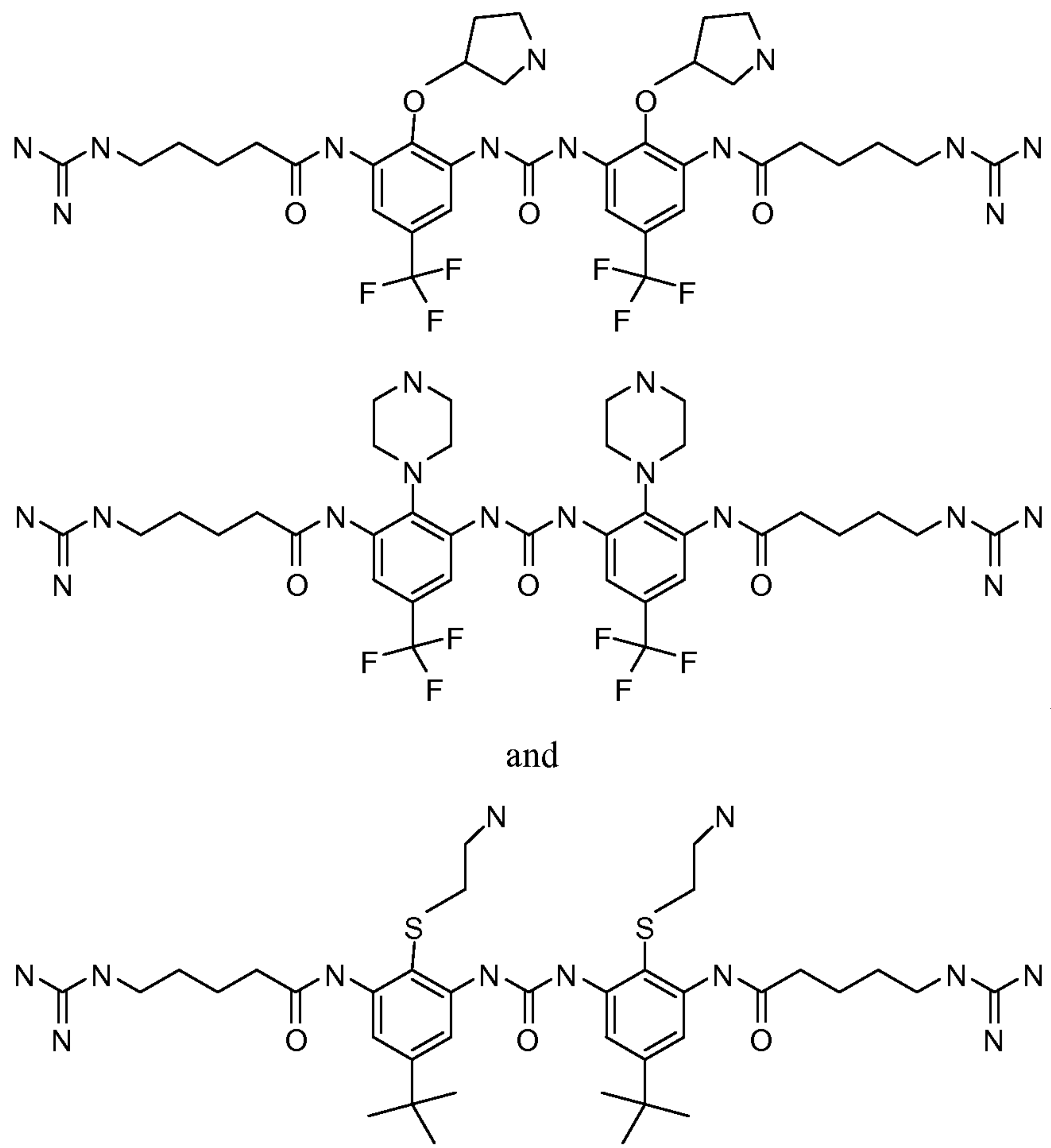
each R^1 is 3-pyrrolyl, or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2;

each R^2 is CF_3 or $C(CH_3)_3$; and

each R^3 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 4.

10

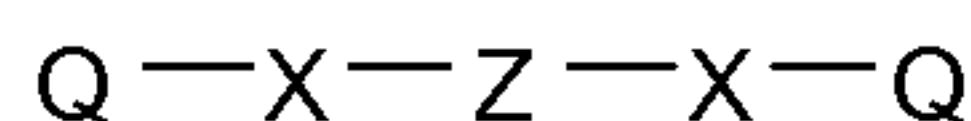
106. The method of claim 95 wherein the compound is chosen from:



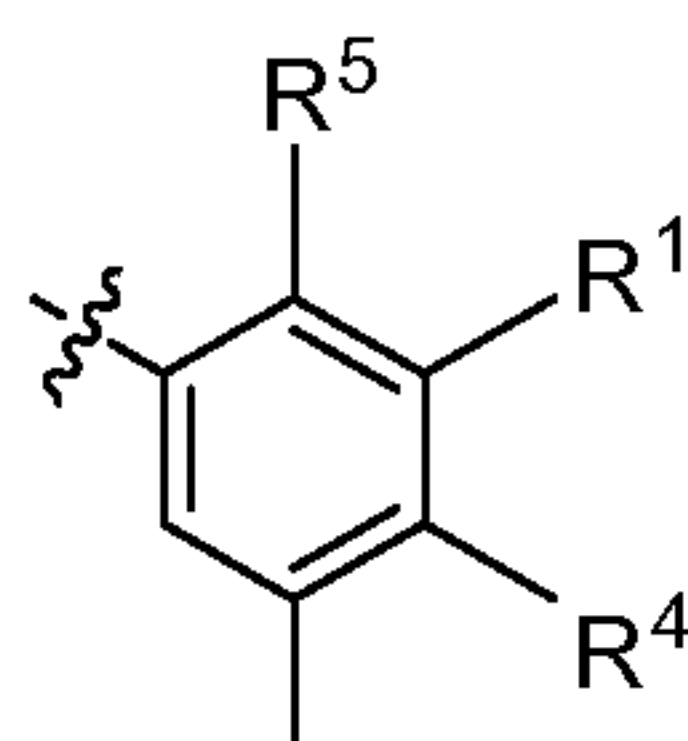
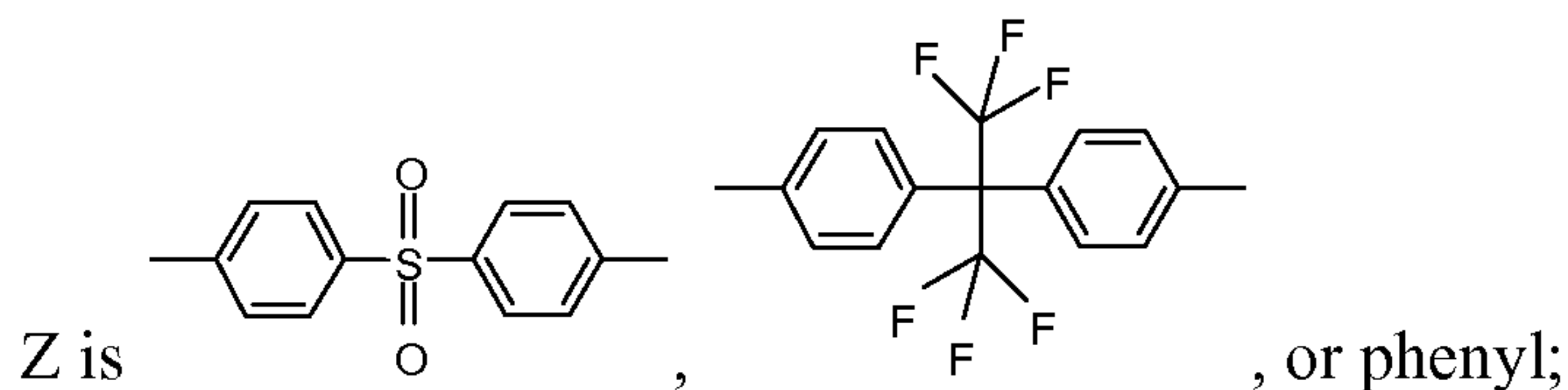
15

or a pharmaceutically acceptable salt thereof.

107. A compound of Formula III:



wherein:



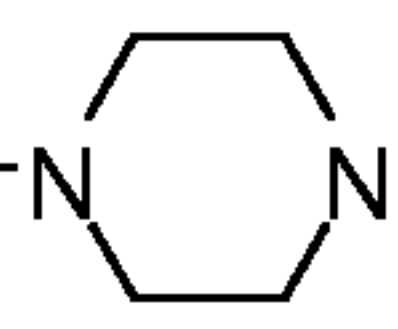
5 each Q is, independently, or $-C(=O)-(CH_2)_b-NH-C(=NH)-NH_2$, where

each b is, independently, 1 to 4;

each X is, independently, O, S, or N;

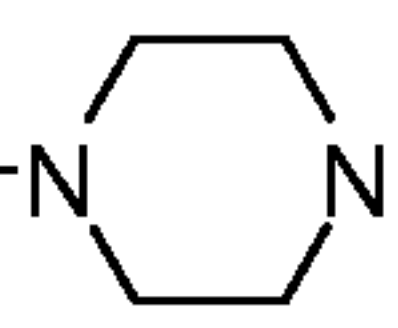
each R^1 is, independently, H, CF_3 , $C(CH_3)_3$, halo, or OH;

each R^3 is, independently, H, $-NH-R^2$, $-(CH_2)_r-NH_2$, $-NH_2$, $-NH-(CH_2)_w-NH_2$, or

10 $-(CH_2)_y-N$ , where each r is, independently, 1 or 2, each w is, independently, 1 to 3, and each y is, independently, 1 or 2;

each R^2 is, independently, H, or the free base or salt form of $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;

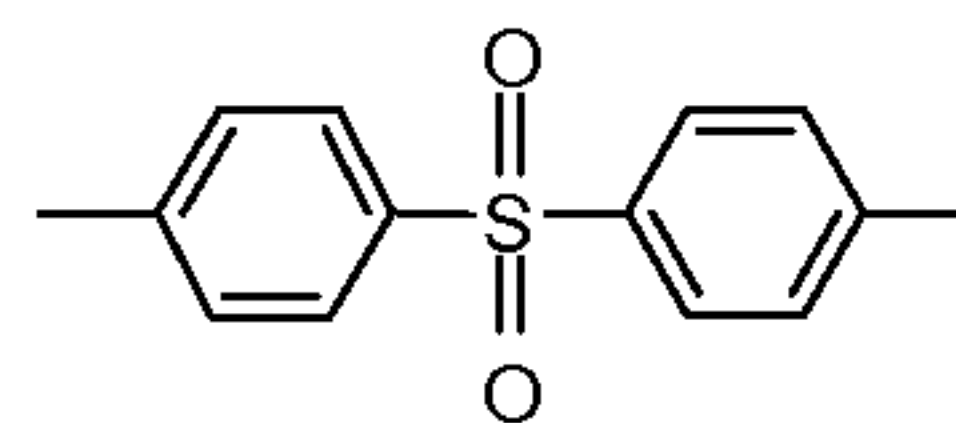
each R^4 is, independently, H, $-NH-C(=O)-(CH_2)_p-NH-C(=NH)-NH_2$ or

15 $-(CH_2)_q-N$ , where each p is, independently, 1 to 6, and each q is, independently, 1 or 2; and

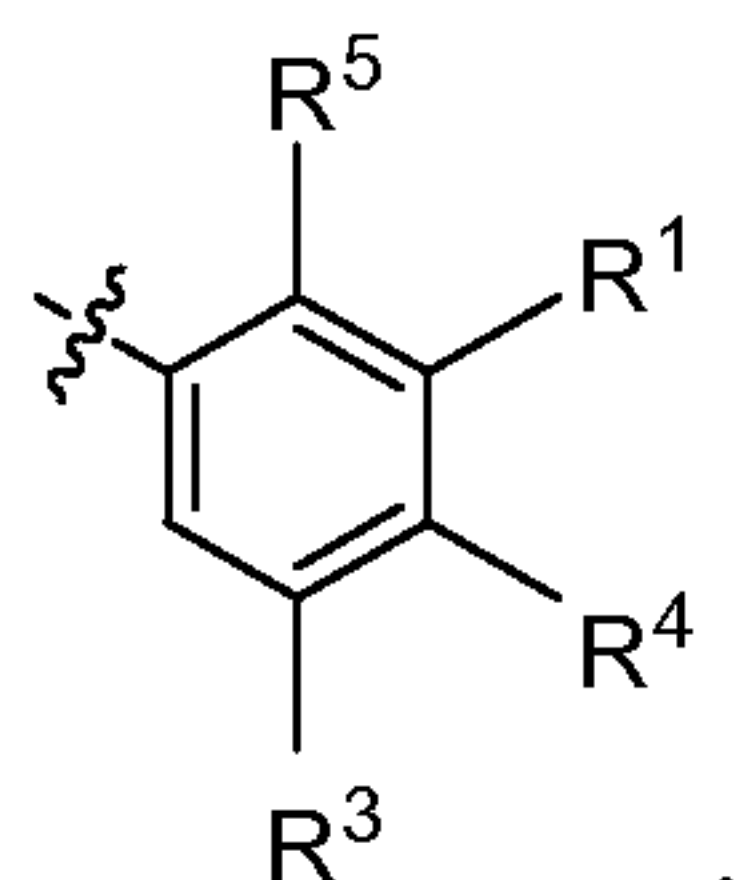
each R^5 is, independently, H or CF_3 ;

or a pharmaceutically acceptable salt thereof.

20 108. The compound or salt of claim 107 wherein Z is



109. The compound or salt of claim 107 or claim 108 wherein each Q is, independently,



110. The compound or salt of any one of claims 107 to 109 wherein each X is O.

5

111. The compound or salt of any one of claims 107 to 110 wherein each R¹ is, independently, H, CF₃, or halo.

112. The compound or salt of any one of claims 107 to 110 wherein each R¹ is CF₃.

10

113. The compound or salt of any one of claims 107 to 112 wherein each R³ is, independently, -NH-R².

114. The compound or salt of any one of claims 107 to 113 wherein each R² is,

15 independently, H, or the free base or salt form of -(CH₂)_n-NH₂, where each n is, independently, 1 to 4.

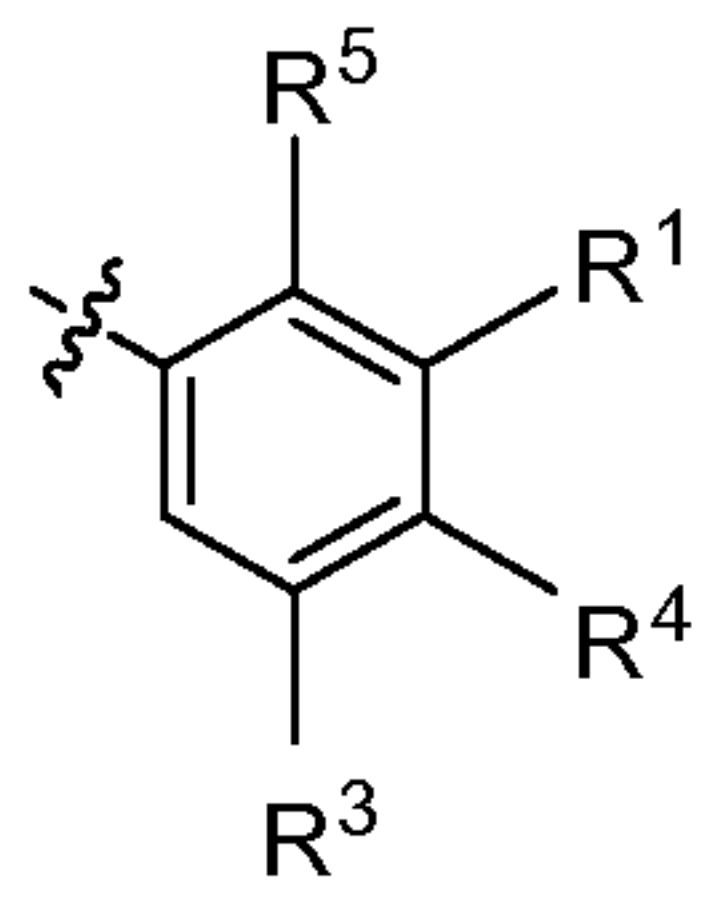
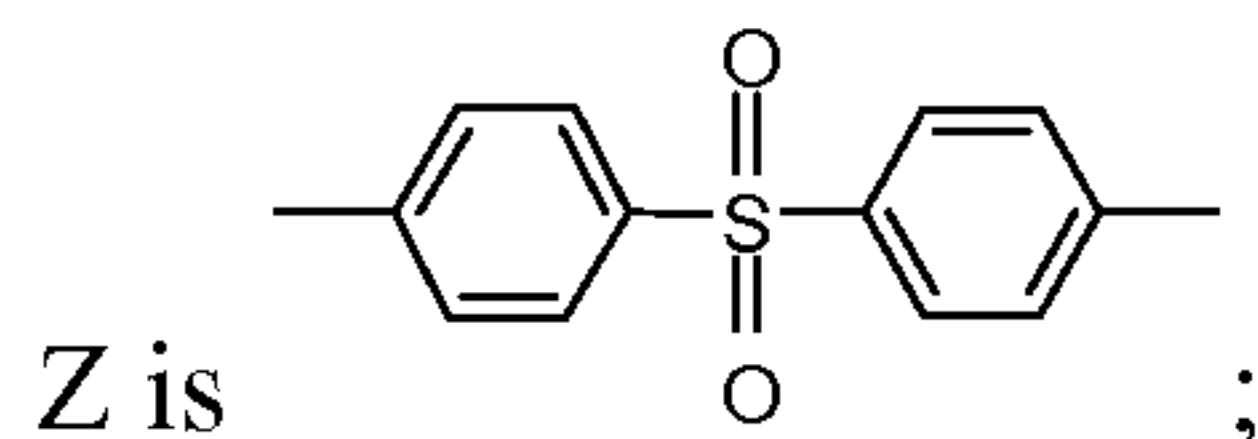
115. The compound or salt of any one of claims 107 to 113 wherein each R² is, independently, the free base or salt form of -(CH₂)_n-NH₂, where each n is, independently, 1

20 or 2.

116. The compound or salt of any one of claims 107 to 113 wherein each R² is the free base or salt form of -(CH₂)_n-NH₂, where each n is 2.

25 117. The compound or salt of any one of claims 107 to 116 wherein each R⁴ and each R⁵ is H.

118. The compound or salt of claim 107 wherein:



each Q is, independently,

each X is O or S;

5 each R¹ is, independently, CF₃, C(CH₃)₃, or halo;

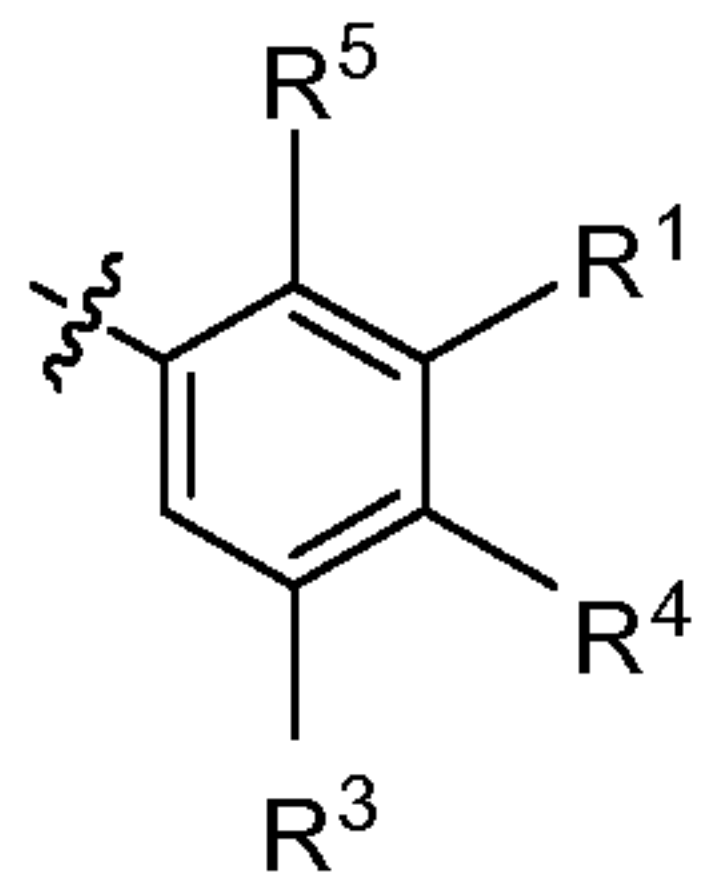
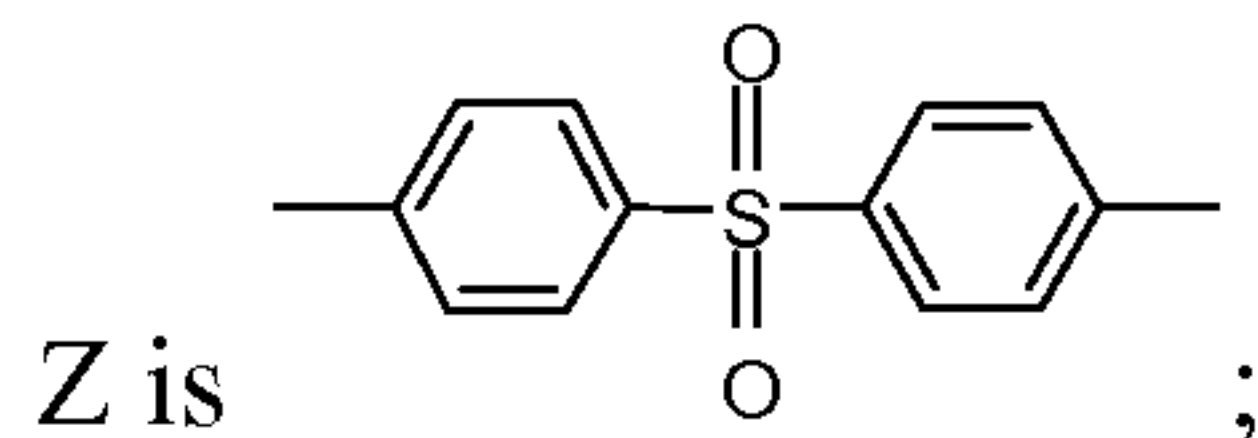
each R³ is, independently, -NH-R²;

each R² is, independently, H, or the free base or salt form of -(CH₂)_n-NH₂, where
each n is, independently, 1 to 4; and

each R⁴ and each R⁵ is H.

10

119. The compound or salt of claim 107 wherein:



each Q is, independently,

each X is O;

15 each R¹ is CF₃, C(CH₃)₃, or halo;

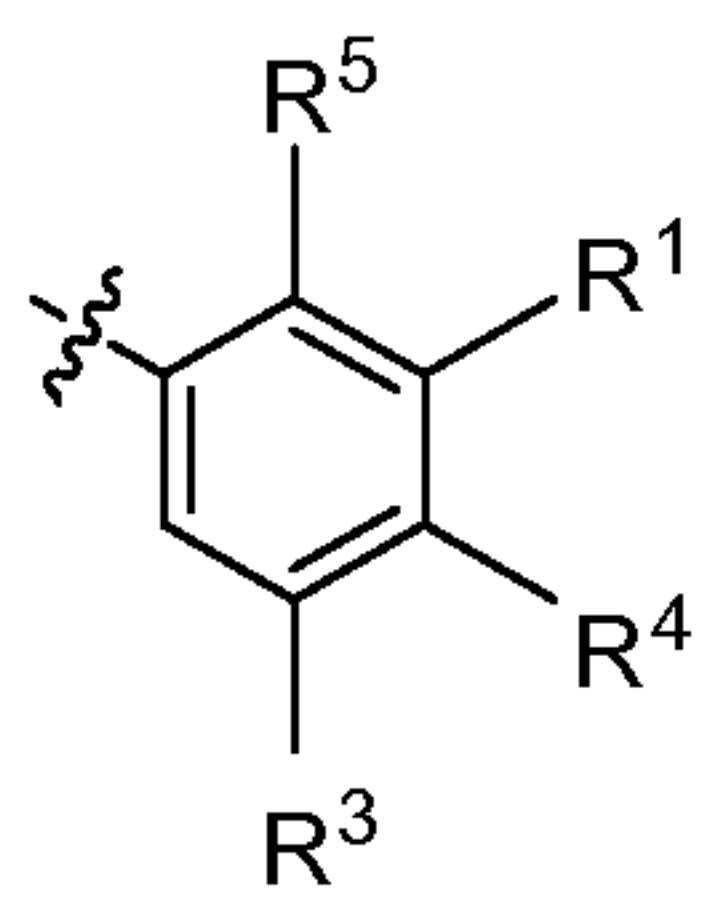
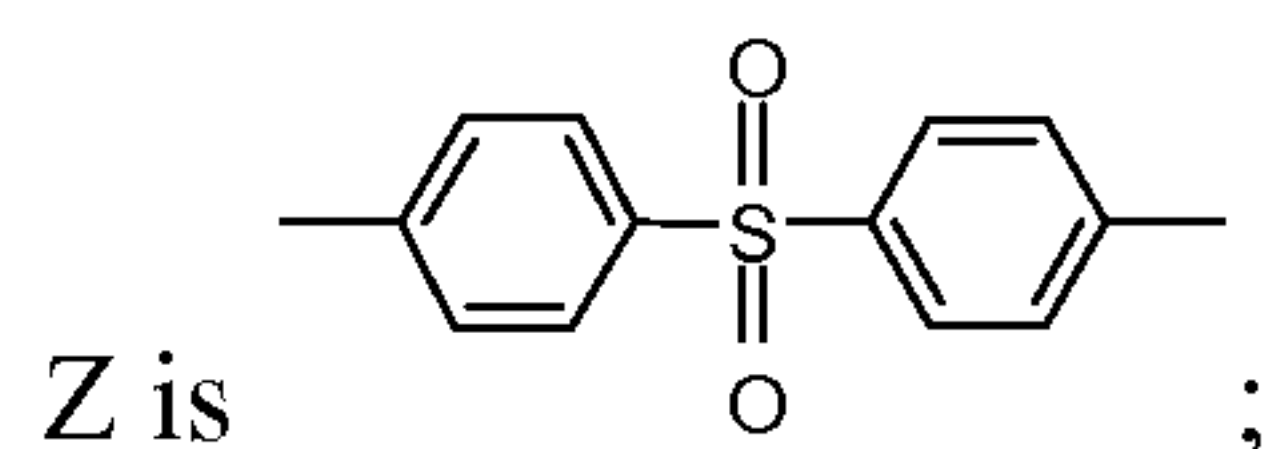
each R³ is, independently, -NH-R²;

each R² is, independently, the free base or salt form of -(CH₂)_n-NH₂, where each n is
1 or 2; and

each R⁴ and each R⁵ is H.

20

120. The compound or salt of claim 107 wherein:



each Q is, independently,

each X is O;

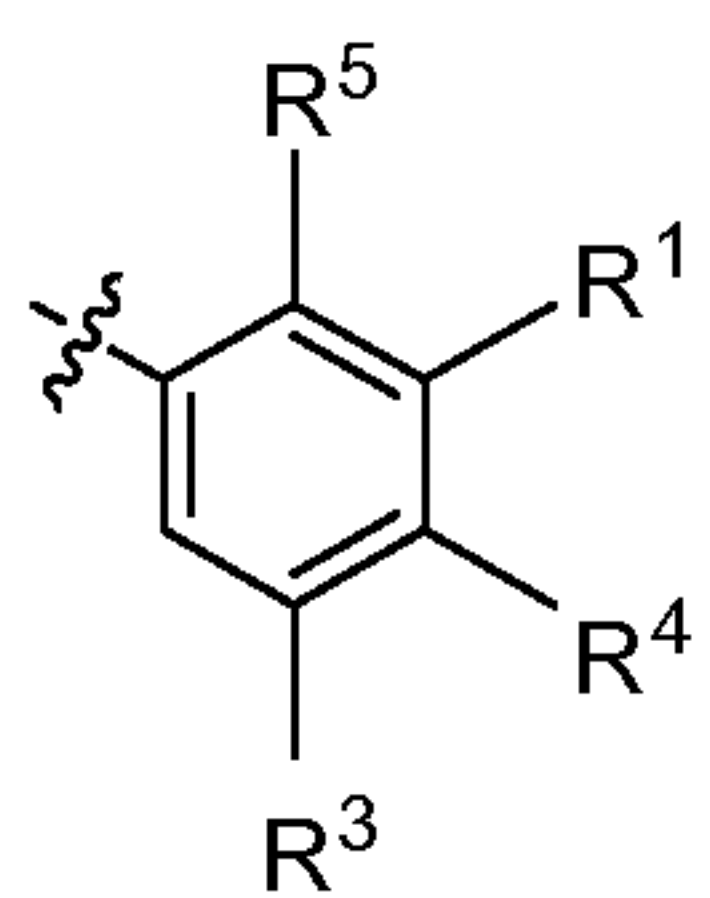
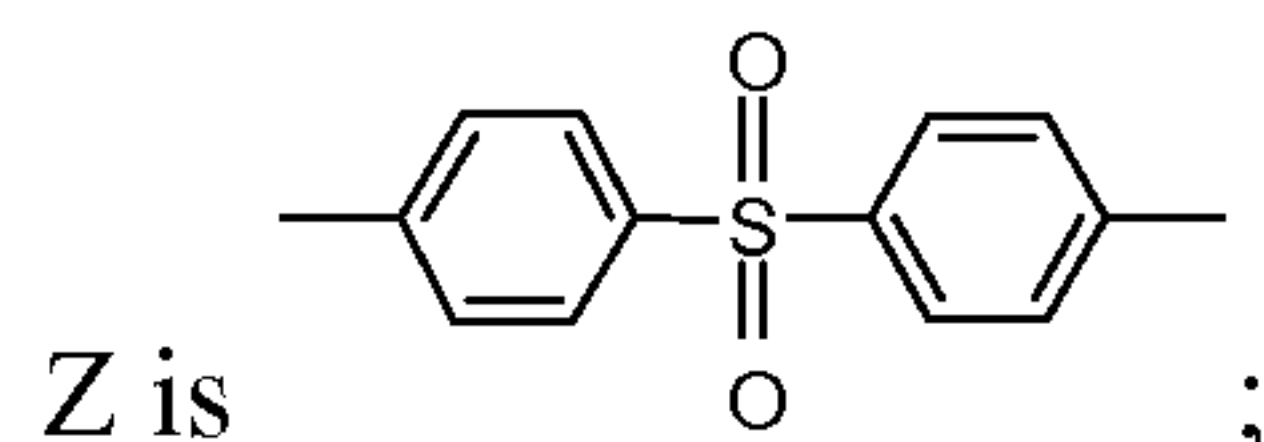
5 each R¹ is CF₃ or halo;

each R³ is, independently, -NH-R²;

each R² is the free base or salt form of -(CH₂)_n-NH₂, where each n is 2; and

each R⁴ and each R⁵ is H.

10 121. The compound or salt of claim 107 wherein:



each Q is, independently,

each X is, independently, O, or S;

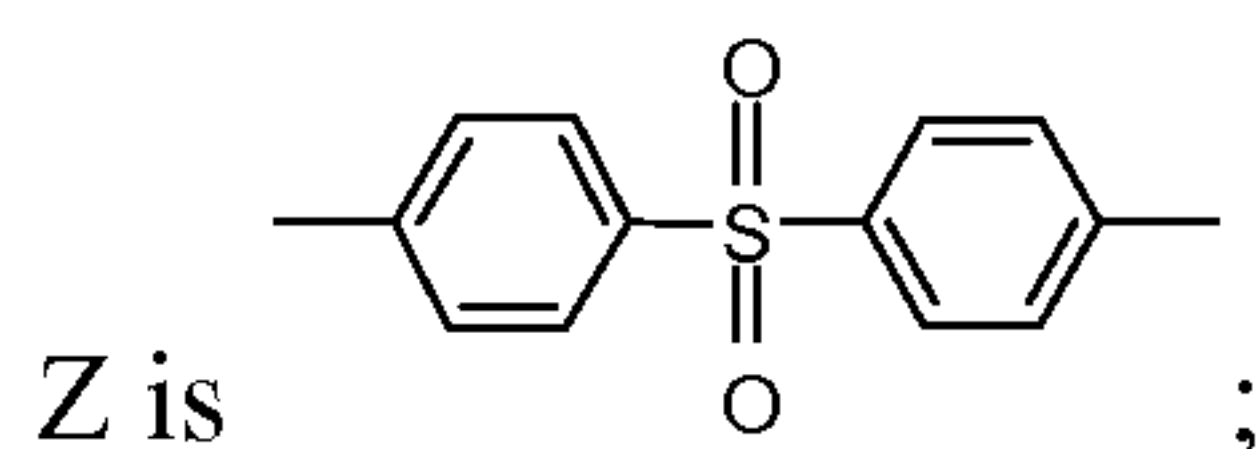
each R¹ is, independently, H, or CF₃;

15 each R³ is H;

each R⁴ is, independently, H or -NH-C(=O)-(CH₂)_p-NH-C(=NH)-NH₂, where each p is, independently, 3 or 4; and

each R⁵ is, independently, H or CF₃.

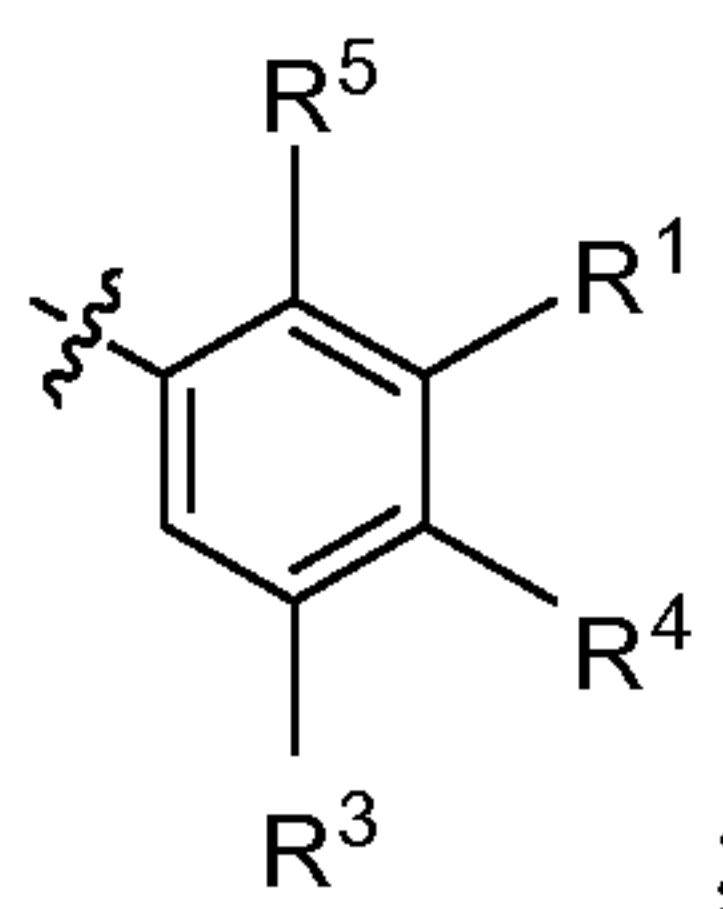
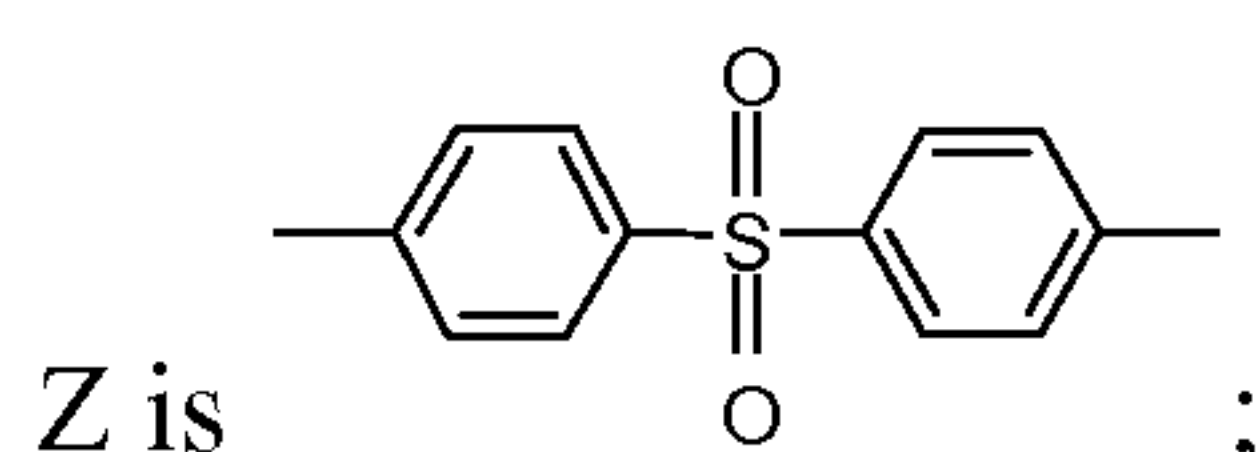
122. The compound or salt of claim 107 wherein:



each Q is, independently, $-\text{C}(=\text{O})-(\text{CH}_2)_b-\text{NH}-\text{C}(=\text{NH})-\text{NH}_2$, where each b is, independently, 3 or 4; and

5 each X is N.

123. The compound or salt of claim 107 wherein:

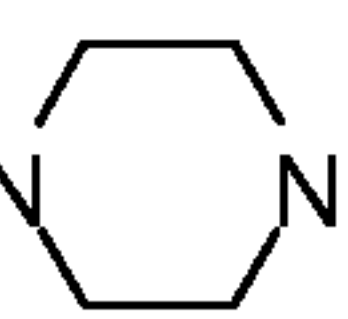


each Q is, independently, ;

10 each X is O or S;

each R^1 is, independently, H or CF_3 ;

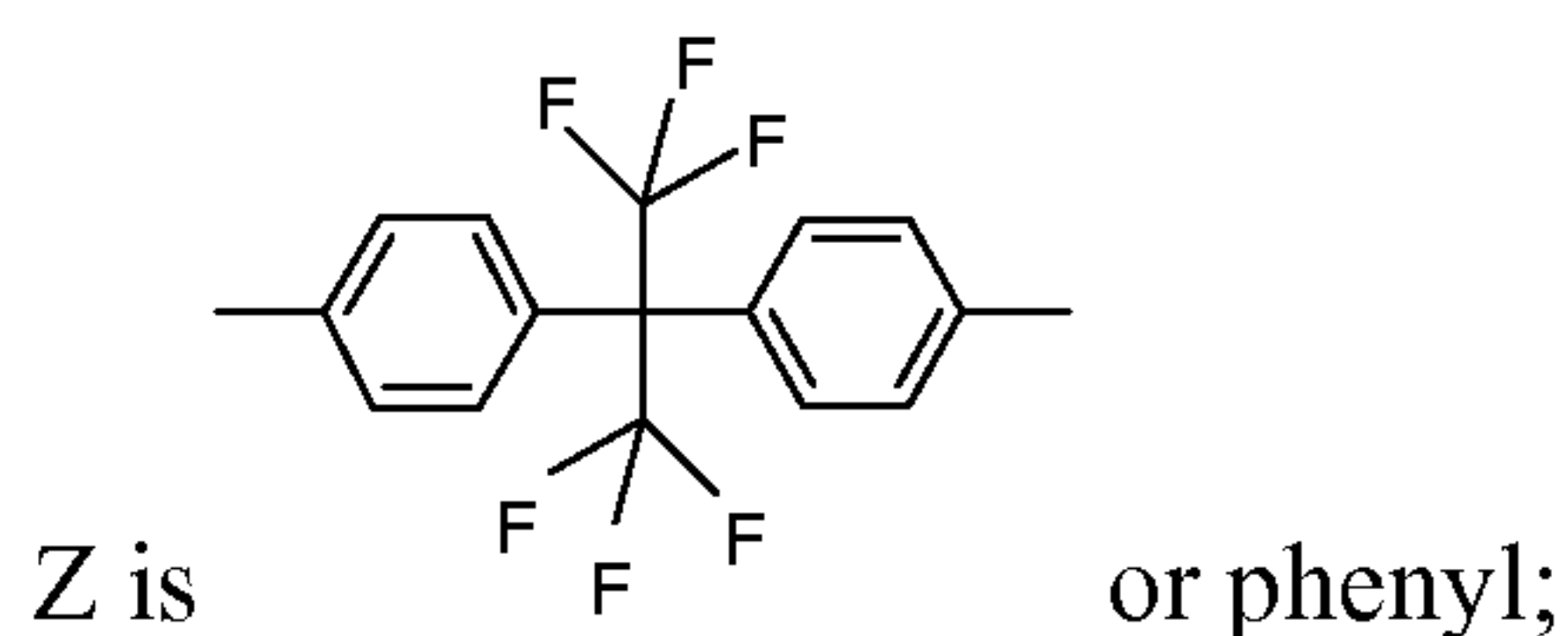
each R^3 is, independently, $-(\text{CH}_2)_r-\text{NH}_2$, $-\text{NH}_2$, $-\text{NH}-(\text{CH}_2)_w-\text{NH}_2$, or

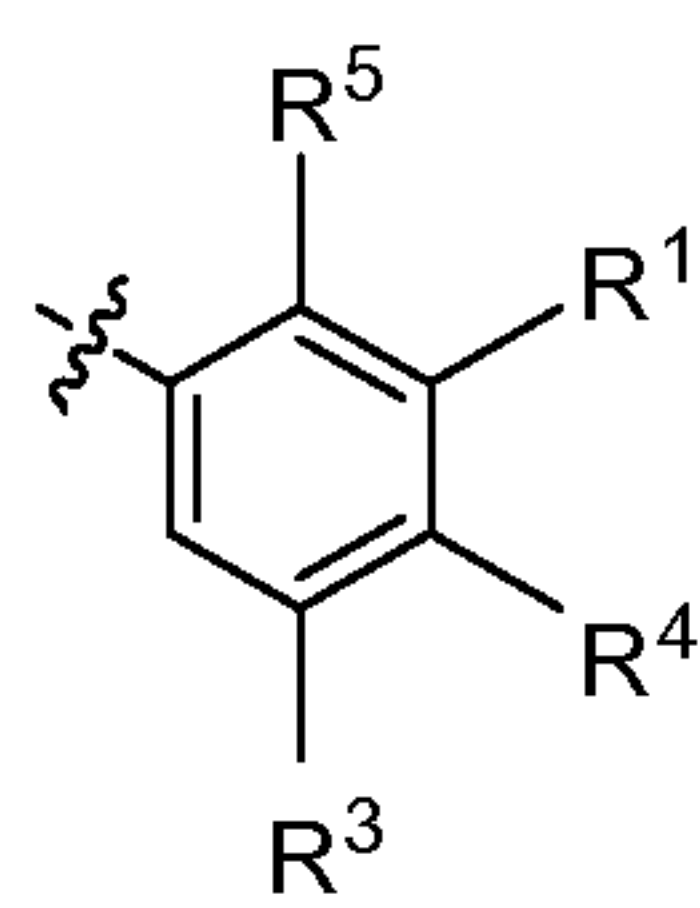
$-(\text{CH}_2)_y-\text{N}$  , where each r is, independently, 1 or 2, each w is, independently, 1 to 3, and each y is, independently, 1 or 2;

15 each R^4 is H; and

each R^5 is, independently, H or CF_3 .

124. The compound or salt of claim 107 wherein:



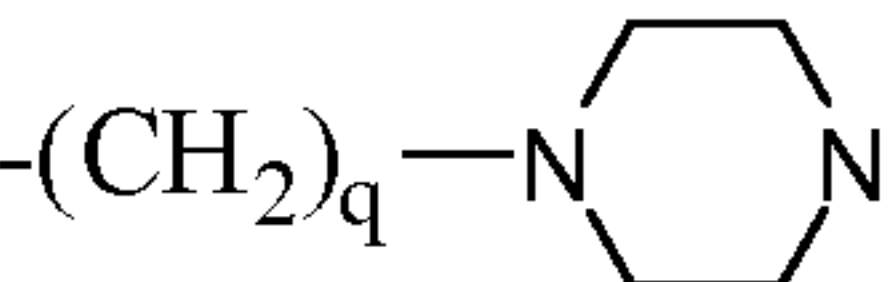


each Q is, independently, ;

each X is, independently, O or S;

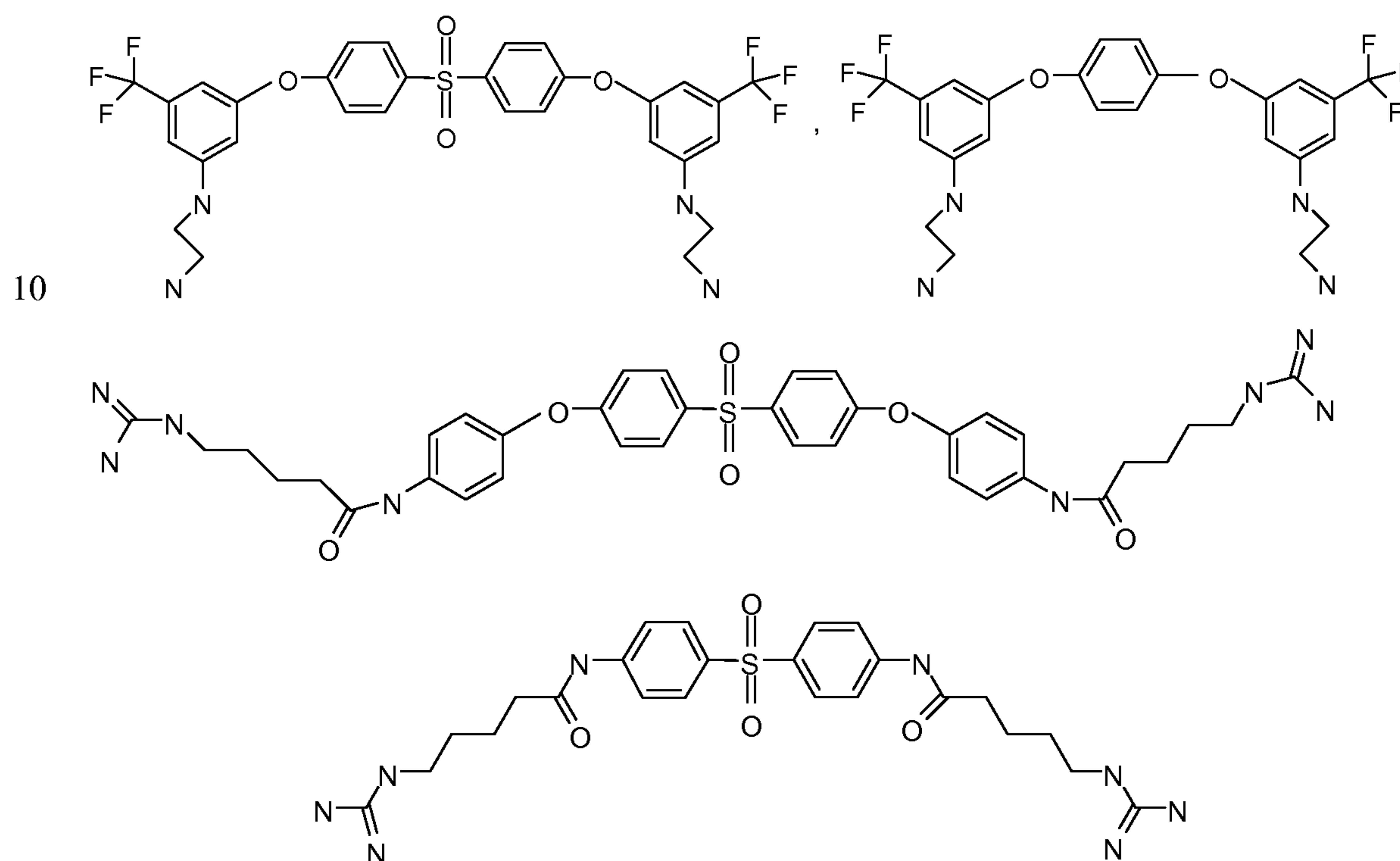
each R¹ is, independently, H or CF₃;

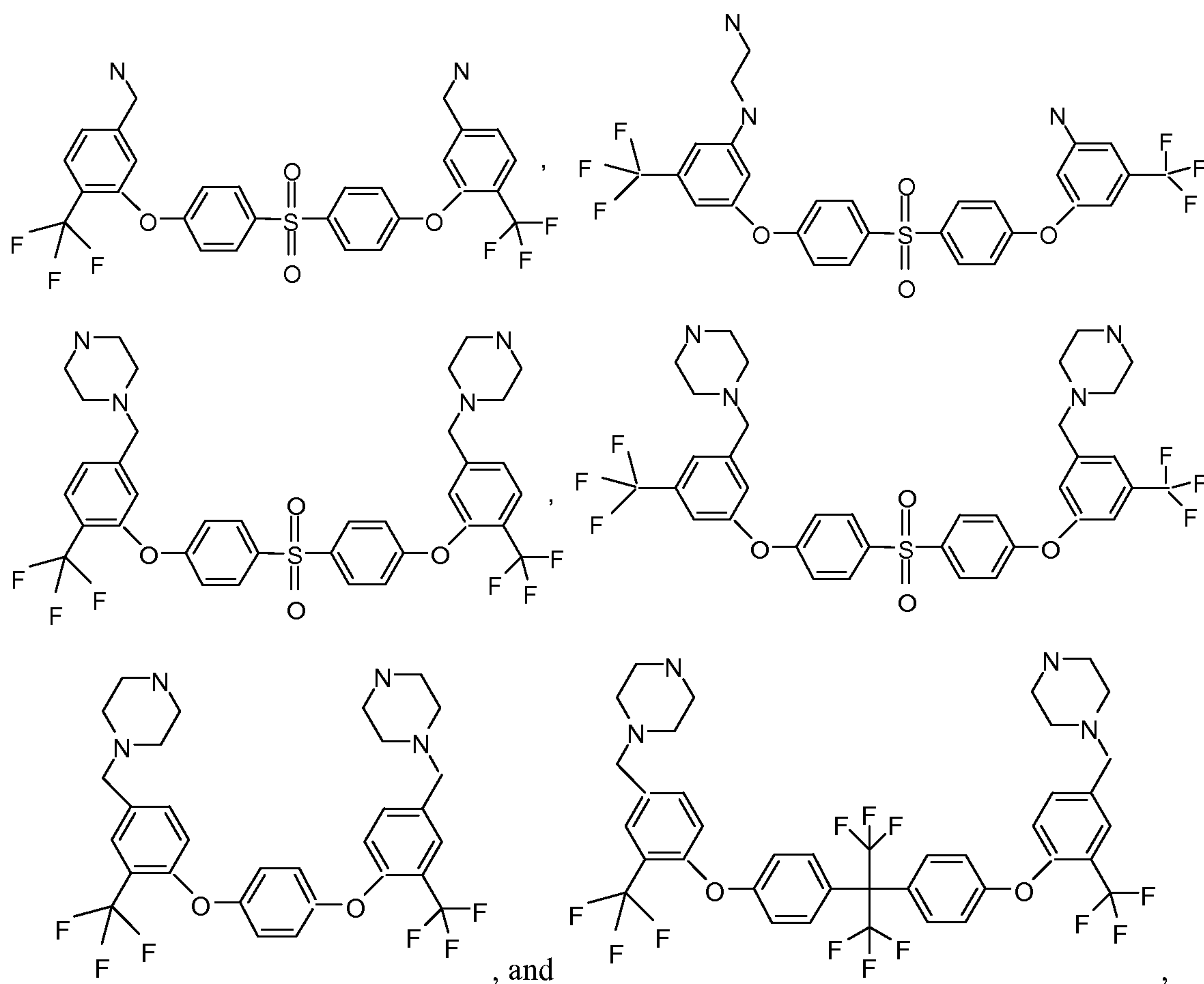
each R³ is H;

5 each R⁴ is, independently, $-(\text{CH}_2)_q-\text{N}$ , where each q is, independently, 1 or 2; and

each R⁵ is, independently, H or CF₃.

125. A compound chosen from:



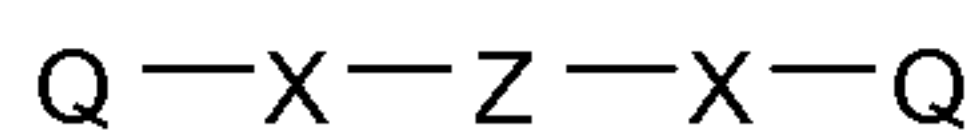


or a pharmaceutically acceptable salt thereof.

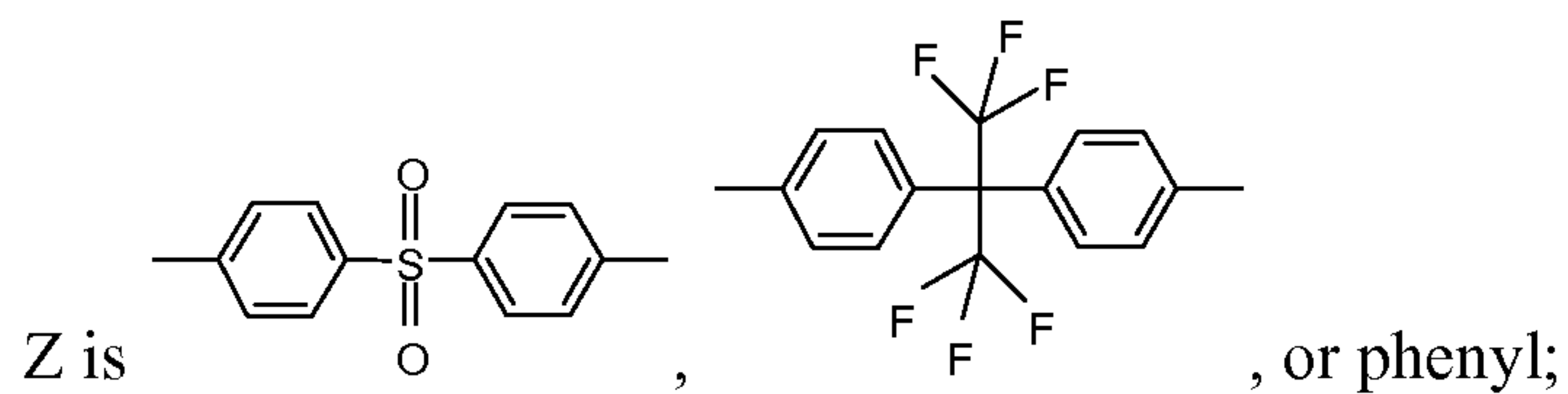
5

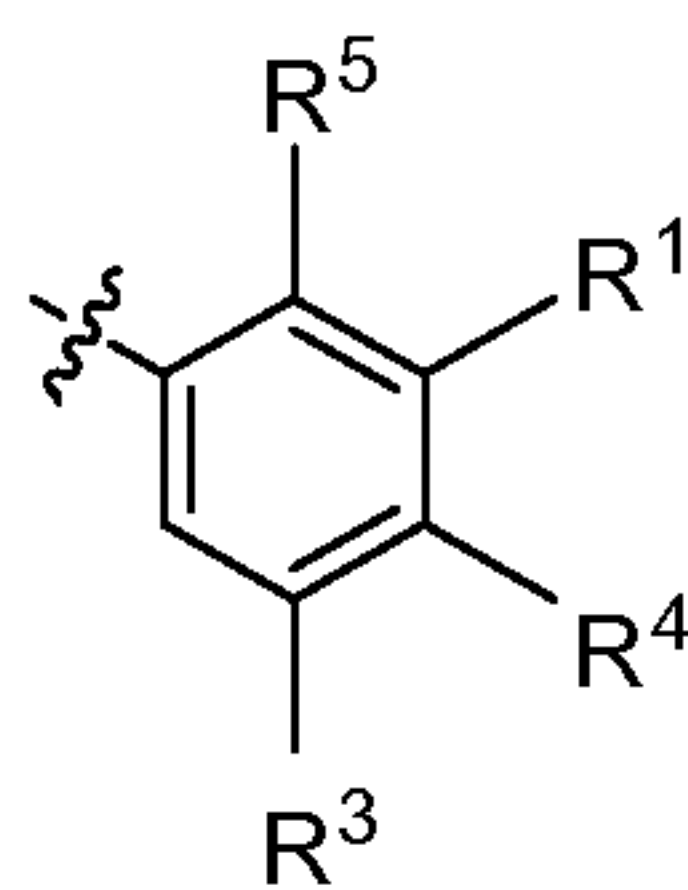
126. A composition comprising the compound or salt of any one of claims 107 to 125 and a pharmaceutically acceptable carrier.

127. A method of treating malaria in an animal comprising administering to the animal a therapeutically effective amount of a compound of Formula III:



wherein:



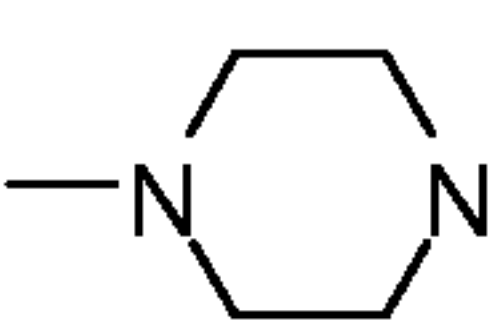


each Q is, independently, or $-\text{C}(=\text{O})-(\text{CH}_2)_b-\text{NH}-\text{C}(=\text{NH})-\text{NH}_2$, where each b is, independently, 1 to 4;

each X is, independently, O, S, or N;

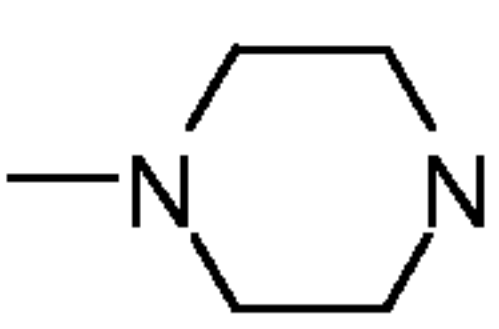
each R¹ is, independently, H, CF₃, C(CH₃)₃, halo, or OH;

5 each R³ is, independently, H, $-\text{NH}-\text{R}^2$, $-(\text{CH}_2)_r-\text{NH}_2$, $-\text{NH}_2$, $-\text{NH}-(\text{CH}_2)_w-\text{NH}_2$, or

$-(\text{CH}_2)_y-\text{N}$  N, where each r is, independently, 1 or 2, each w is, independently, 1 to 3, and each y is, independently, 1 or 2;

each R² is, independently, H, or the free base or salt form of $-(\text{CH}_2)_n-\text{NH}_2$ or $-(\text{CH}_2)_n-\text{NH}-\text{C}(=\text{NH})\text{NH}_2$, where each n is, independently, 1 to 4;

10 each R⁴ is, independently, H, $-\text{NH}-\text{C}(=\text{O})-(\text{CH}_2)_p-\text{NH}-\text{C}(=\text{NH})-\text{NH}_2$ or

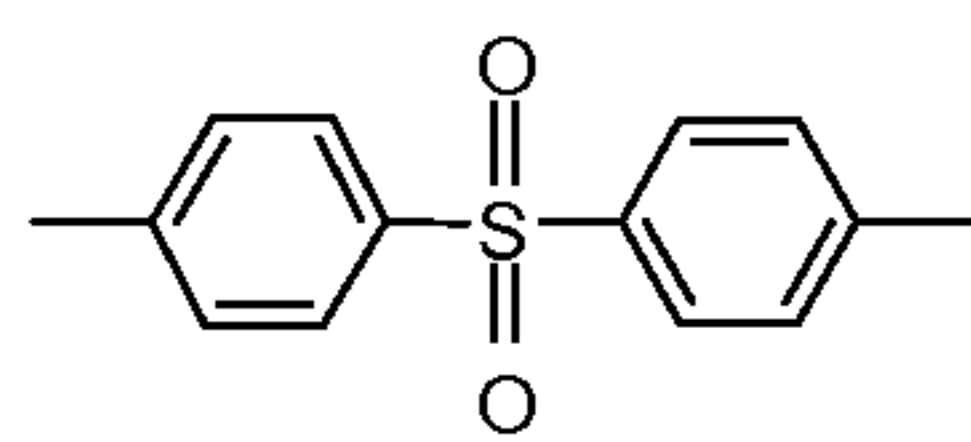
$-(\text{CH}_2)_q-\text{N}$  N, where each p is, independently, 1 to 6, and each q is, independently, 1 or 2; and

each R⁵ is, independently, H or CF₃;

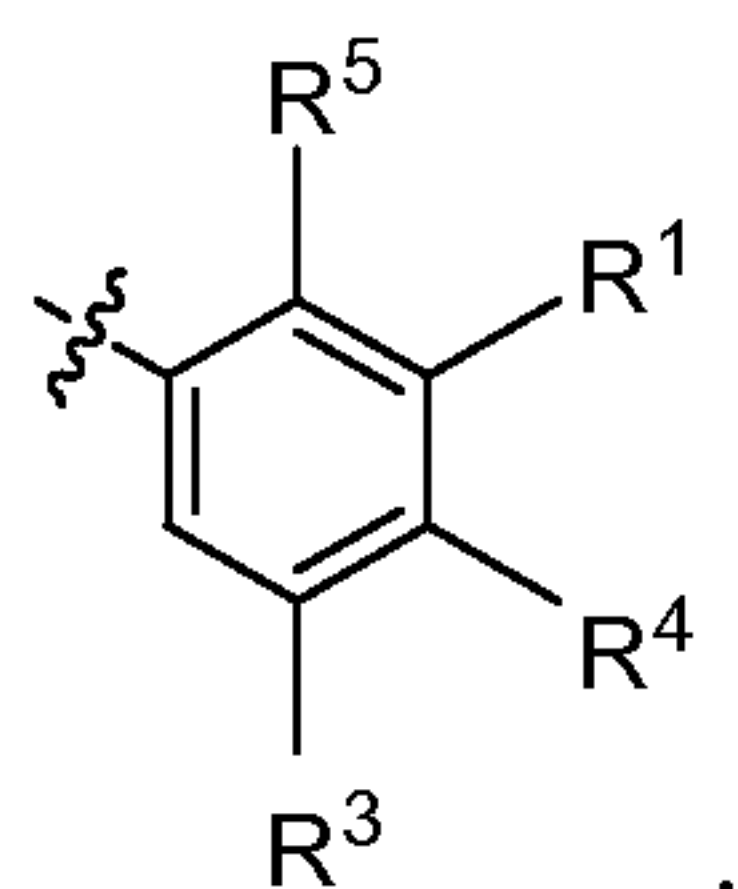
or a pharmaceutically acceptable salt thereof.

15

128. The method of claim 127 wherein Z is



129. The method of claim 127 or claim 128 wherein each Q is, independently,



20

130. The method of any one of claims 127 to 129 wherein each X is O.

131. The method of any one of claims 127 to 130 wherein each R^1 is, independently, H, CF_3 , or halo.

132. The method of any one of claims 127 to 130 wherein each R^1 is CF_3 .

5

133. The method of any one of claims 127 to 132 wherein each R^3 is, independently, - $NH-R^2$.

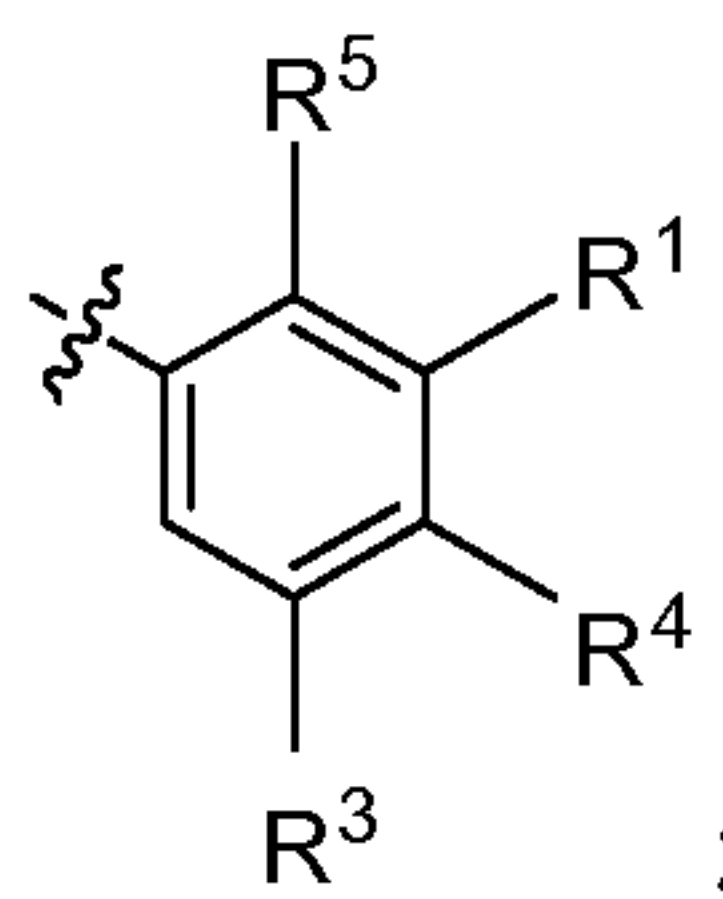
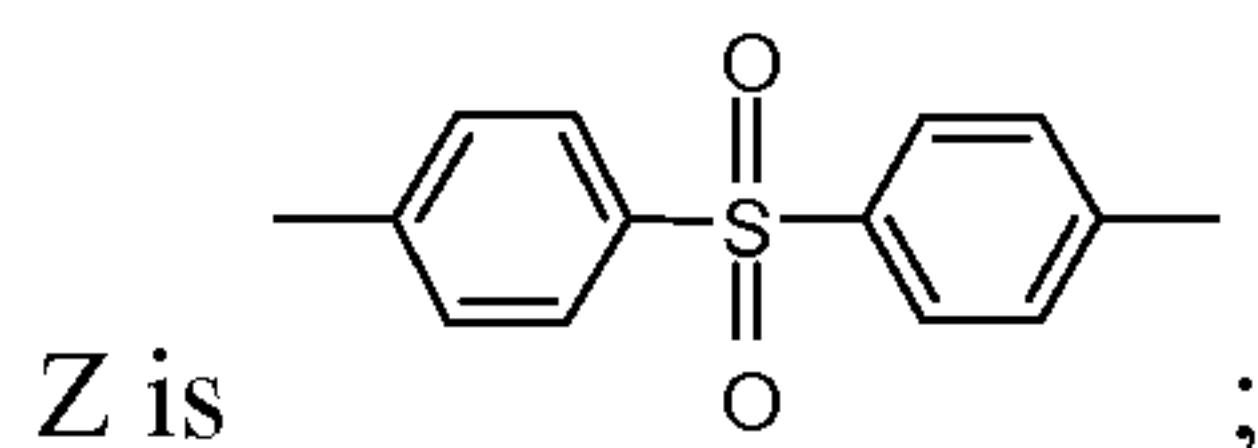
134. The method of any one of claims 127 to 133 wherein each R^2 is, independently, H,
10 or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4.

135. The method of any one of claims 127 to 133 wherein each R^2 is, independently, the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2.

15 136. The method of any one of claims 127 to 133 wherein each R^2 is the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2.

137. The method of any one of claims 127 to 136 wherein each R^4 and each R^5 is H.

20 138. The method of claim 127 wherein:



each Q is, independently, ;

each X is O or S;

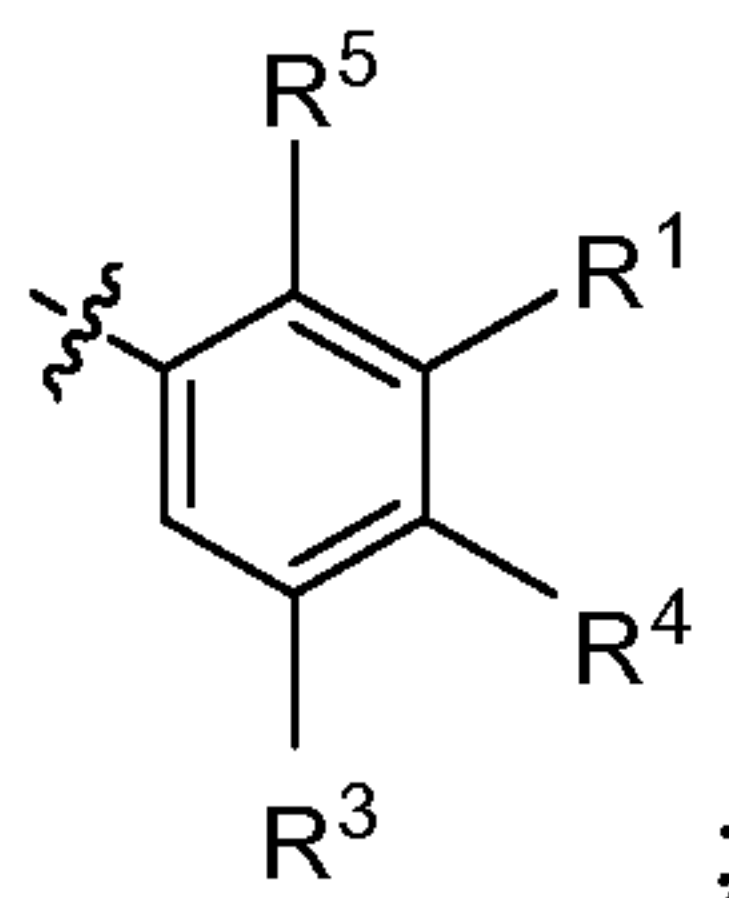
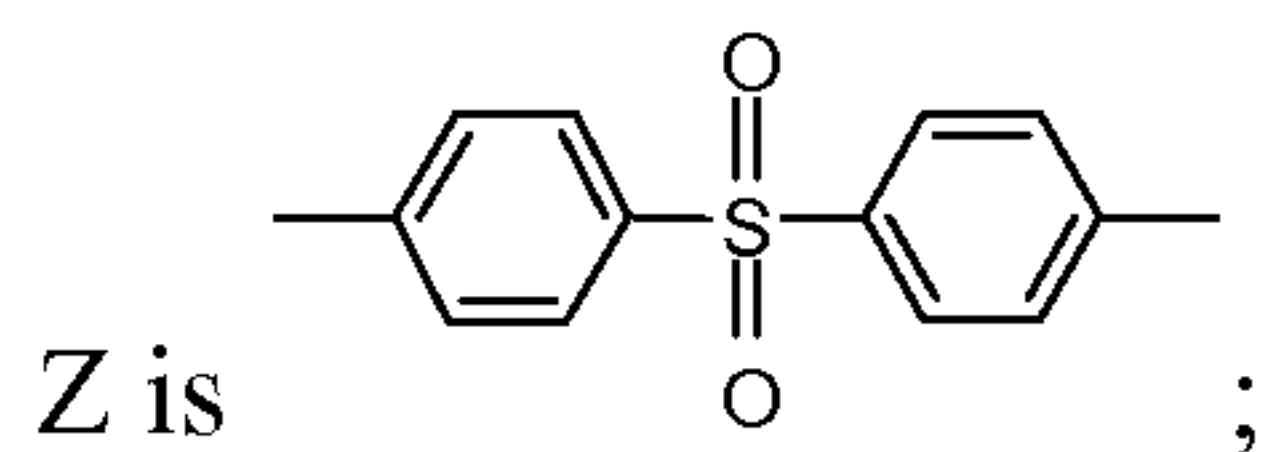
each R^1 is, independently, CF_3 , $C(CH_3)_3$, or halo;

25 each R^3 is, independently, $-NH-R^2$;

each R^2 is, independently, H, or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4; and

each R^4 and each R^5 is H.

139. The method of claim 127 wherein:



5 each Q is, independently,

each X is O;

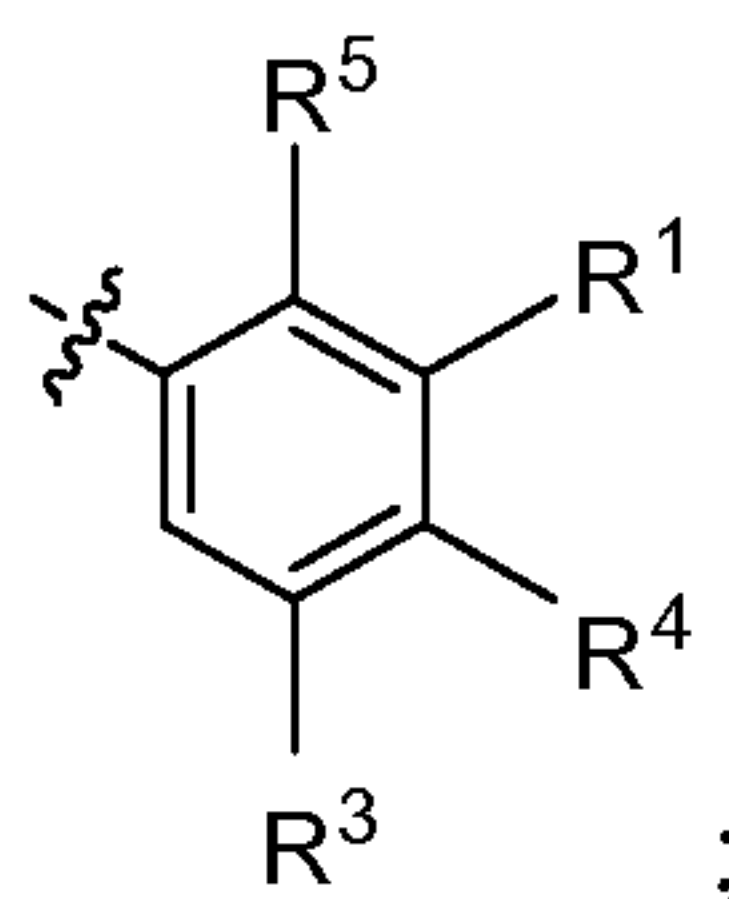
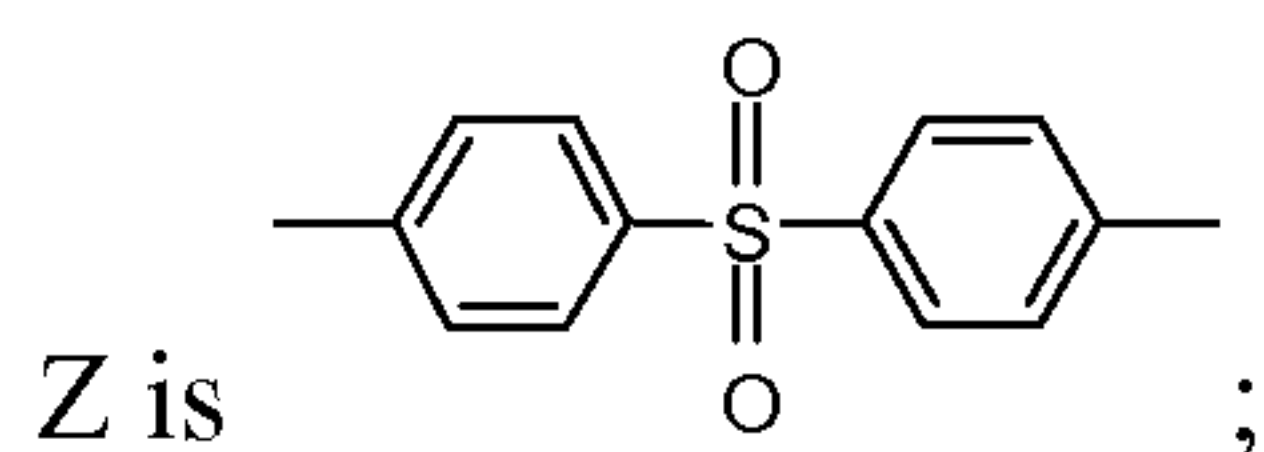
each R^1 is CF_3 , $C(CH_3)_3$, or halo;

each R^3 is, independently, $-NH-R^2$;

each R^2 is, independently, the free base or salt form of $-(CH_2)_n-NH_2$, where each n is
10 1 or 2; and

each R^4 and each R^5 is H.

140. The method of claim 127 wherein:



15 each Q is, independently,

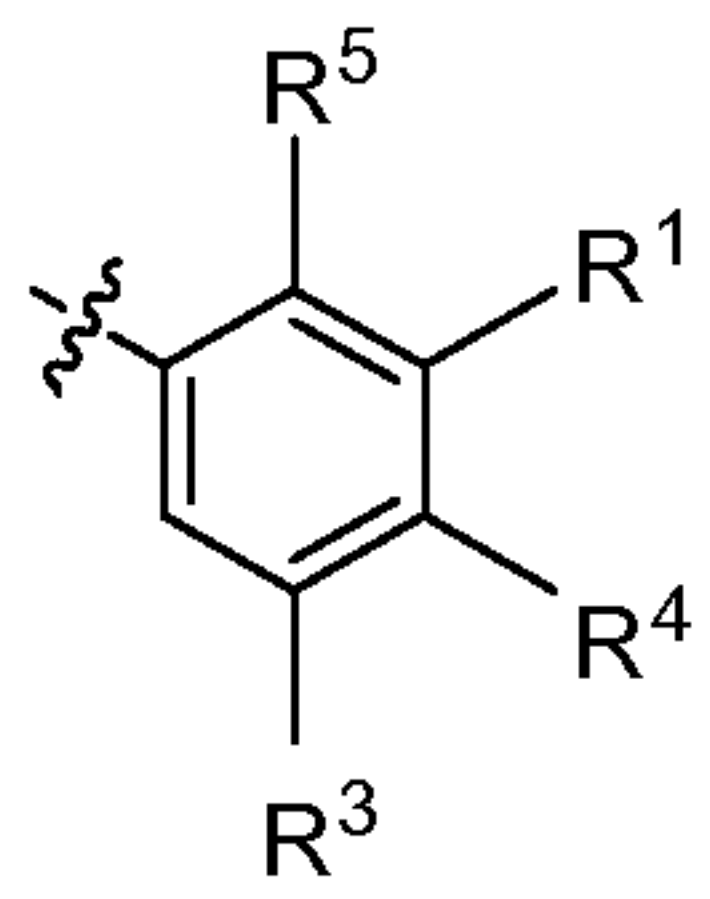
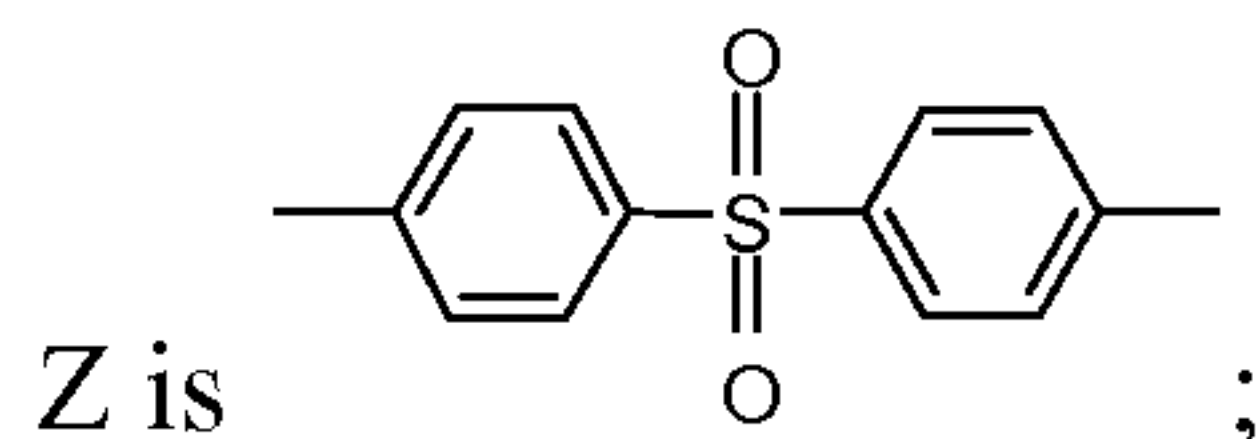
each X is O;

each R^1 is CF_3 or halo;

each R^3 is, independently, $-NH-R^2$;

each R^2 is the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2; and
20 each R^4 and each R^5 is H.

141. The method of claim 127 wherein:



each Q is, independently, ;

each X is, independently, O, or S;

5 each R¹ is, independently, H, or CF₃;

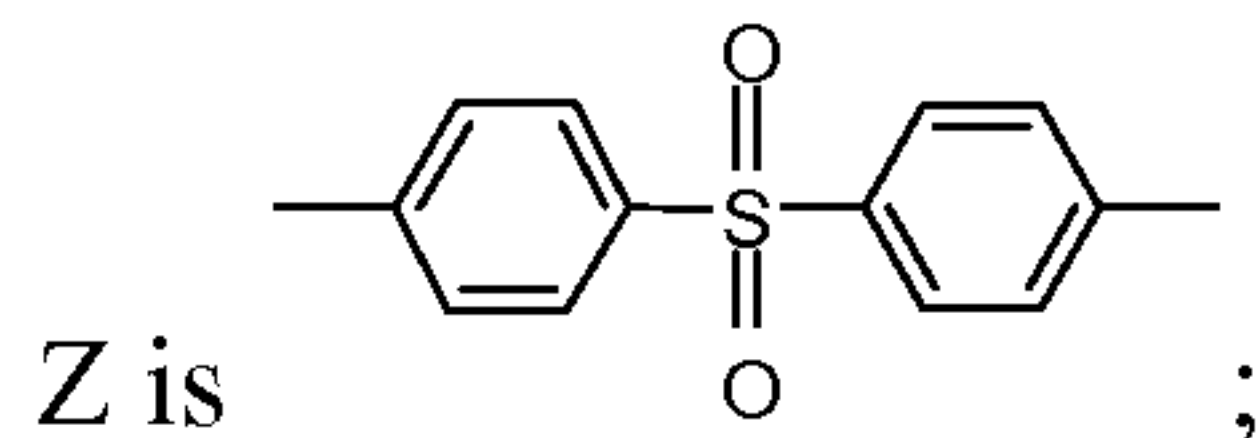
each R³ is H;

each R⁴ is, independently, H or -NH-C(=O)-(CH₂)_p-NH-C(=NH)-NH₂, where each p is, independently, 3 or 4; and

each R⁵ is, independently, H or CF₃.

10

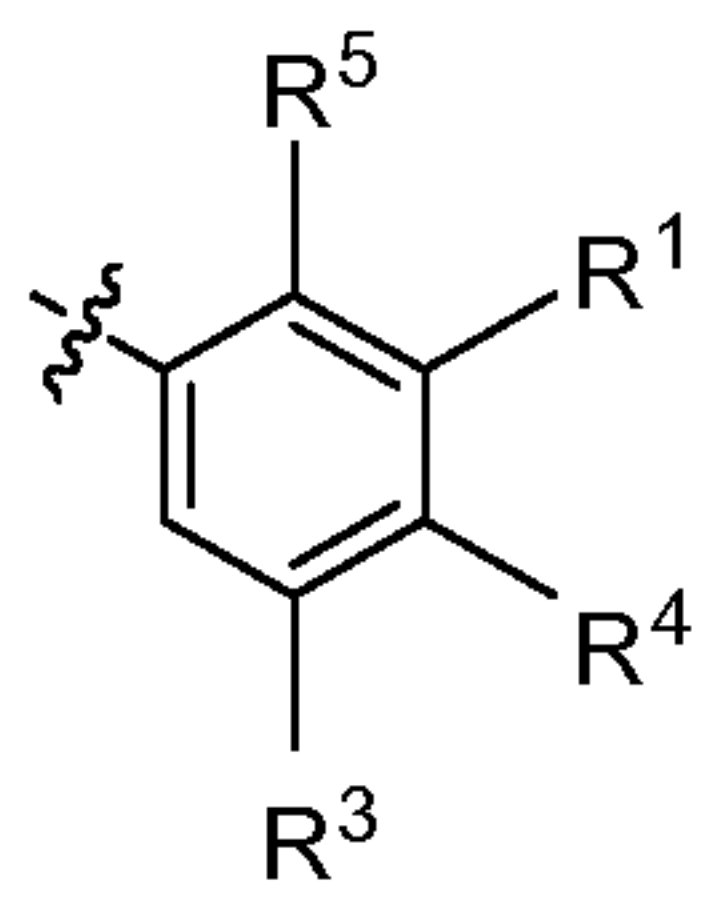
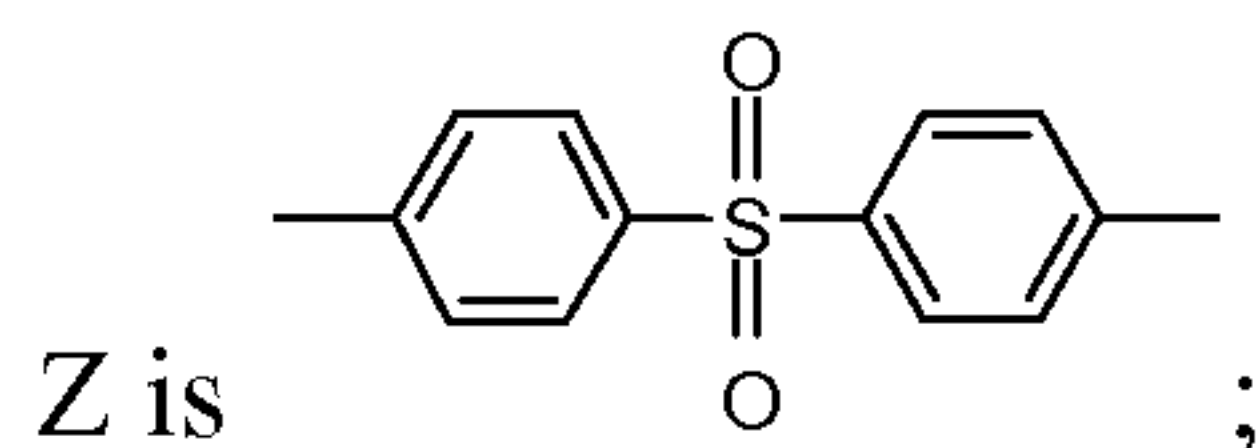
142. The method of claim 127 wherein:



each Q is, independently, -C(=O)-(CH₂)_b-NH-C(=NH)-NH₂, where each b is, independently, 3 or 4; and

15 each X is N.

143. The method of claim 127 wherein:

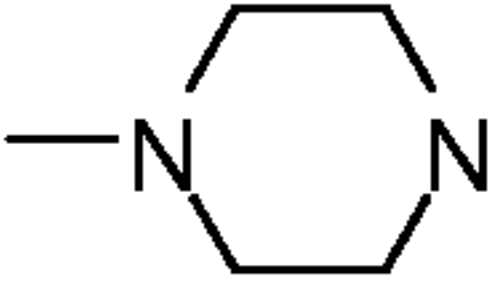


each Q is, independently, ;

each X is O or S;

each R¹ is, independently, H or CF₃;

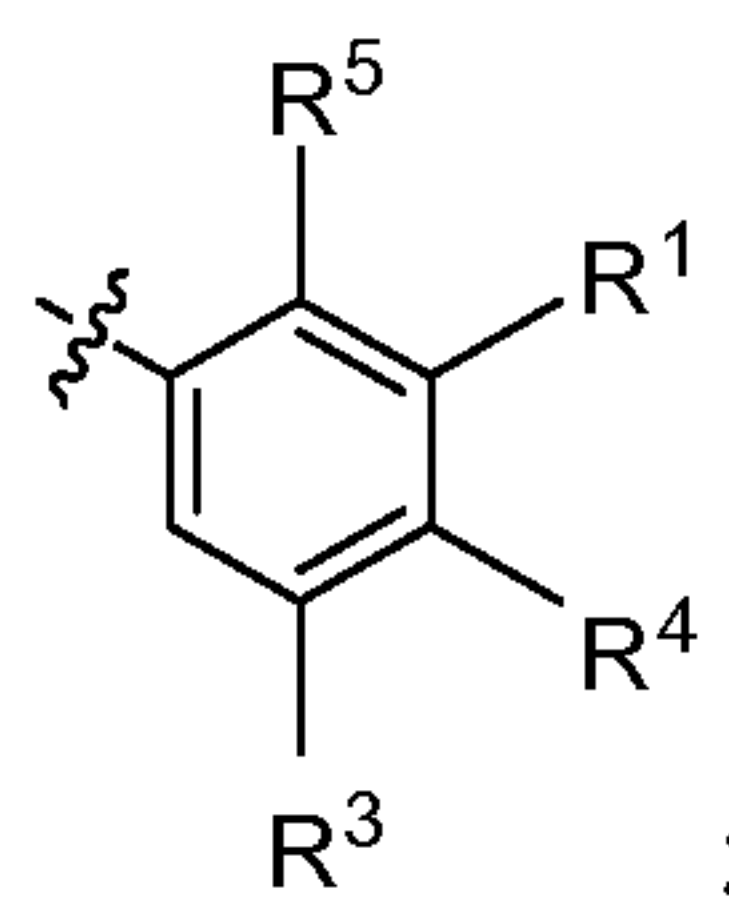
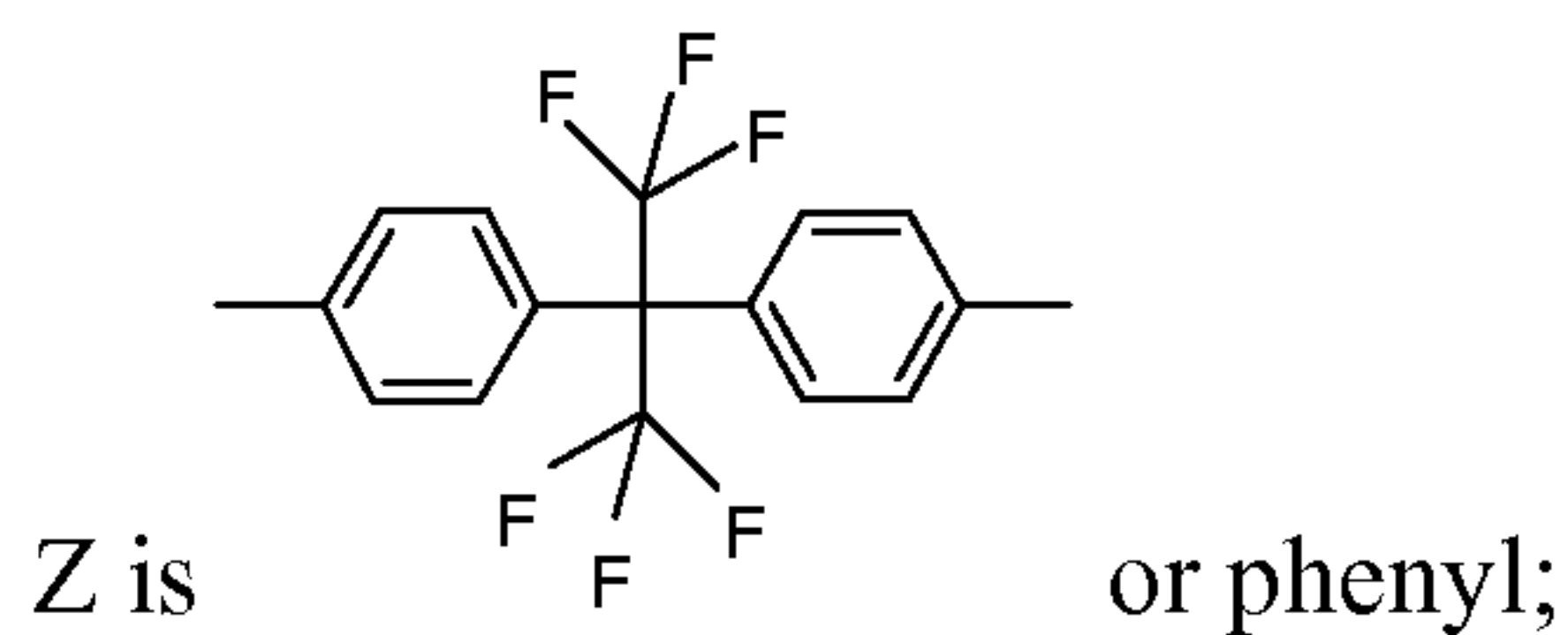
20

each R^3 is, independently, $-(CH_2)_r-NH_2$, $-NH_2$, $-NH-(CH_2)_w-NH_2$, or $-(CH_2)_y-N$ , where each r is, independently, 1 or 2, each w is, independently, 1 to 3, and each y is, independently, 1 or 2;

each R^4 is H; and

5 each R^5 is, independently, H or CF_3 .

144. The method of claim 127 wherein:

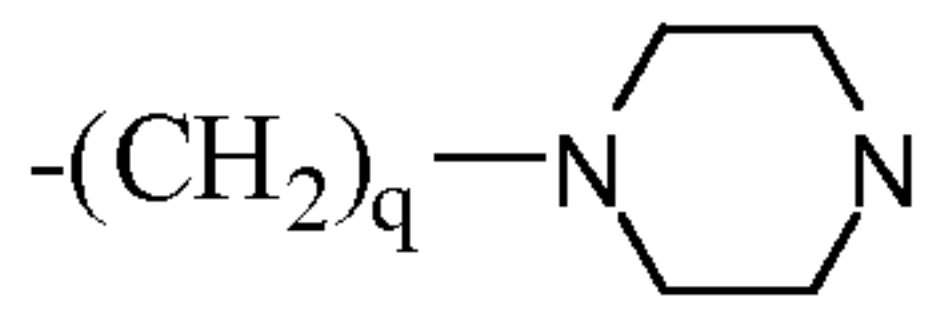


each Q is, independently, ;

10 each X is, independently, O or S;

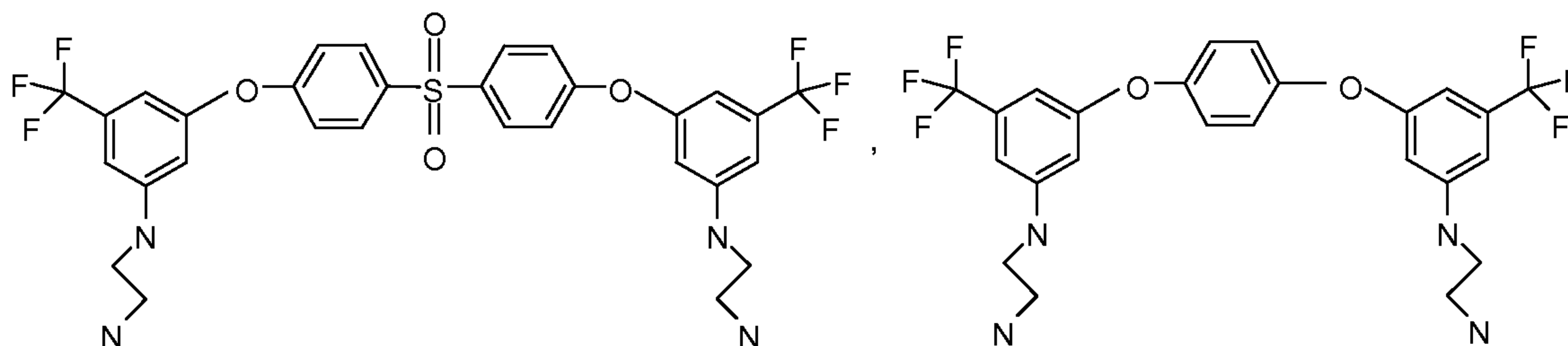
each R^1 is, independently, H or CF_3 ;

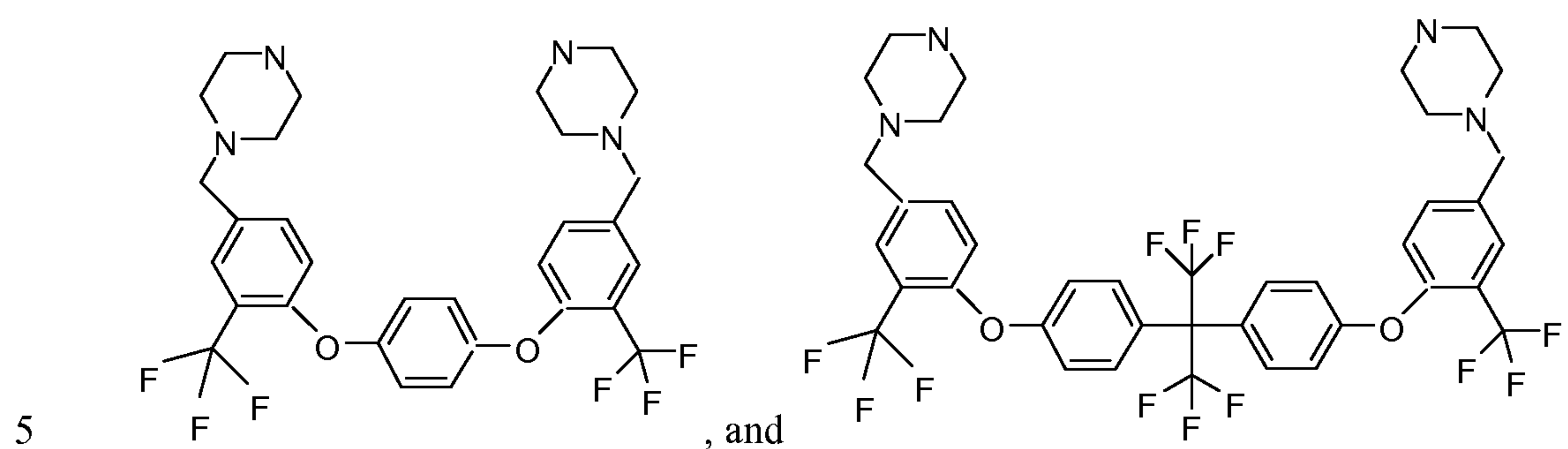
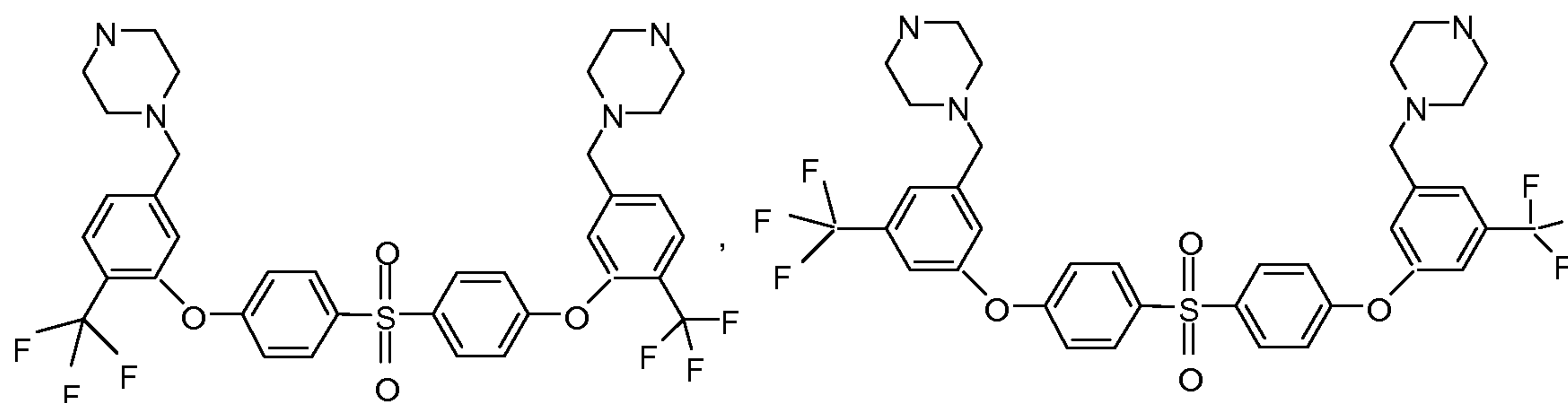
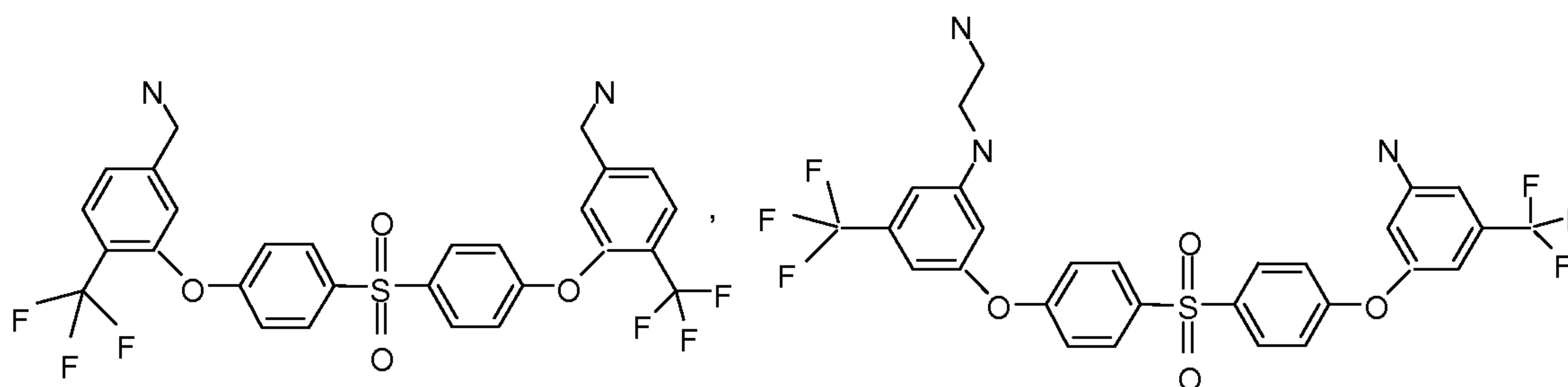
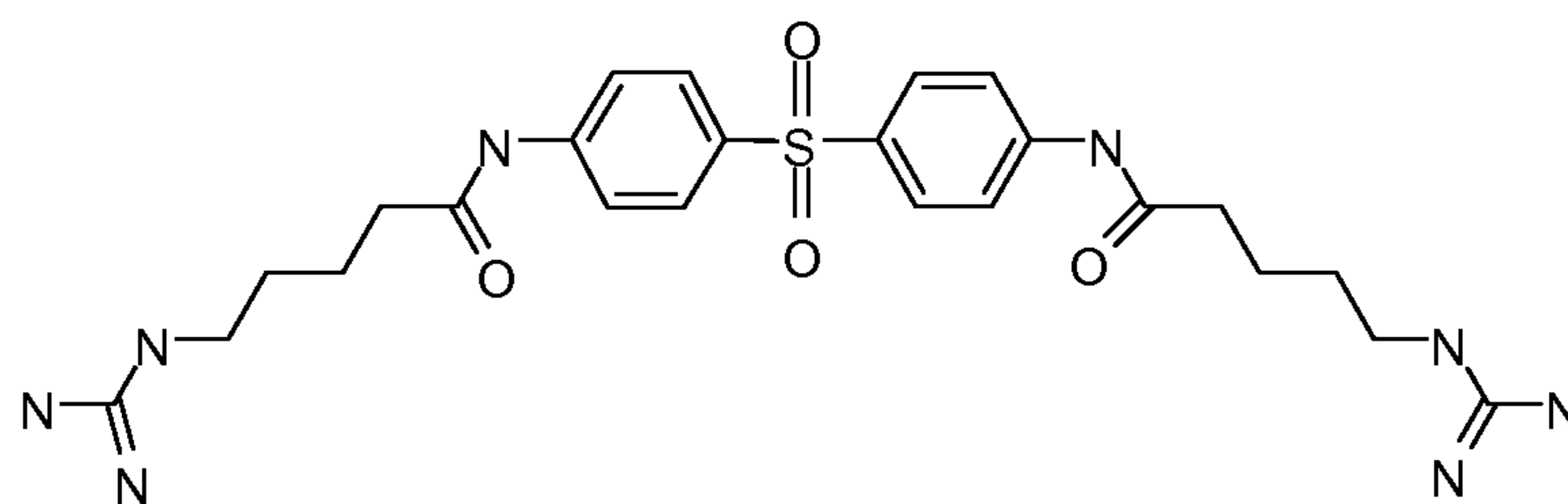
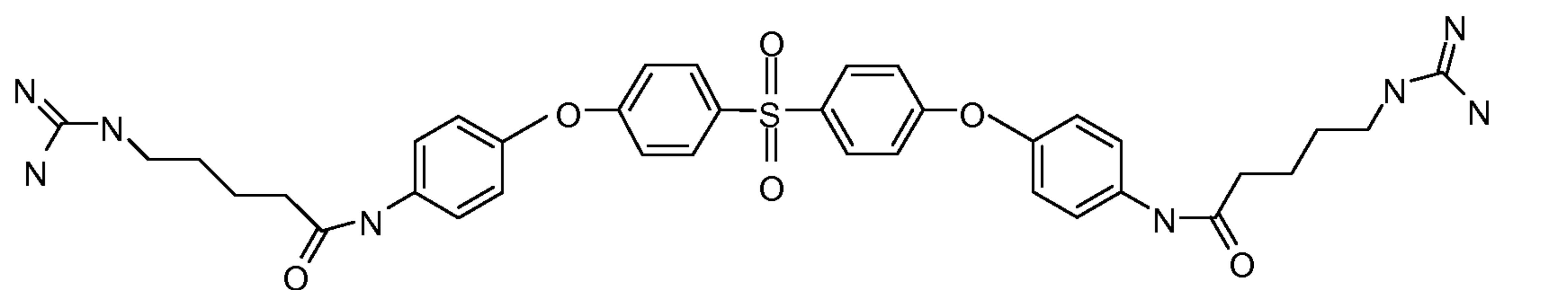
each R^3 is H;

each R^4 is, independently, $-(CH_2)_q-N$ , where each q is, independently, 1 or 2; and

15 each R^5 is, independently, H or CF_3 .

145. The method of claim 127 wherein the compound is chosen from:

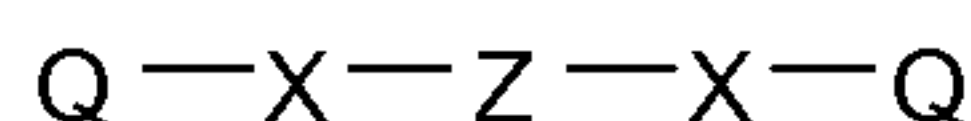




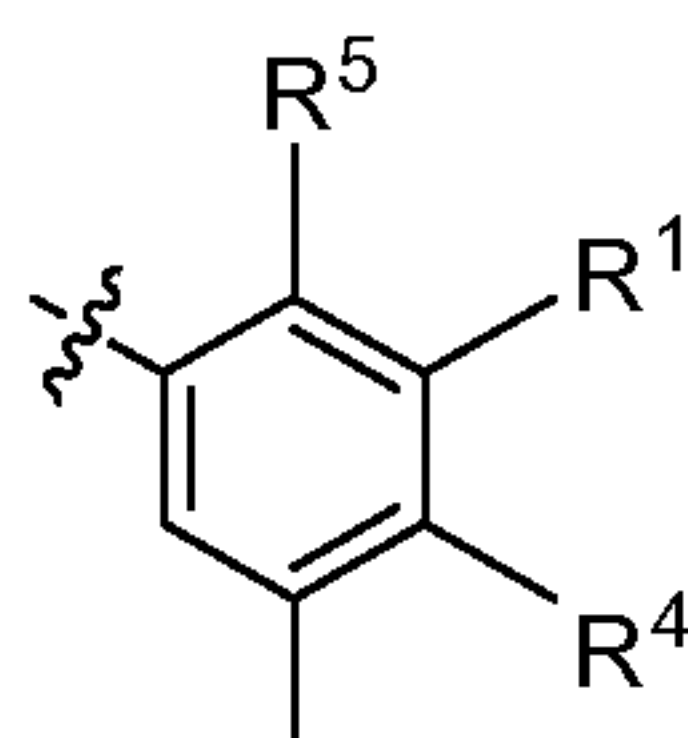
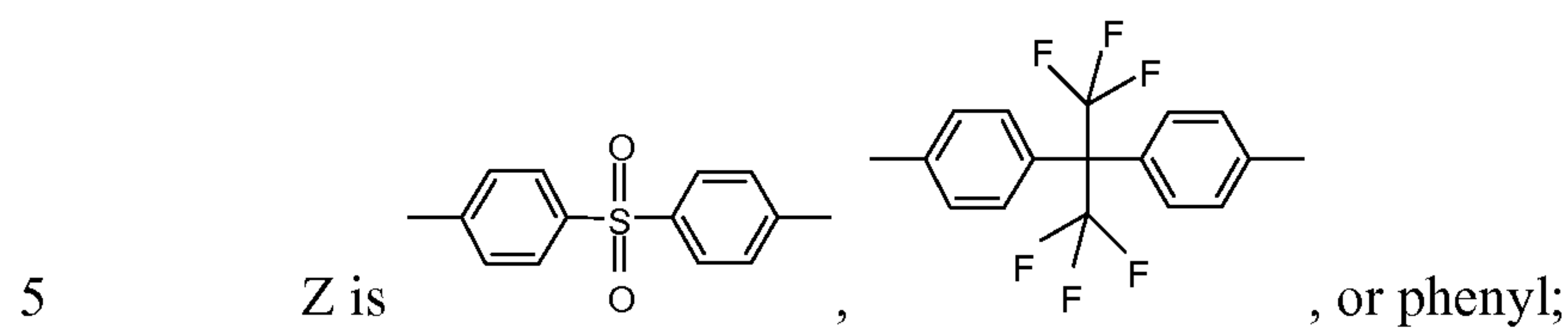
or a pharmaceutically acceptable salt thereof.

146. The method of any one of claims 127 to 145 wherein the malaria is chloroquine-sensitive or chloroquine-resistant.

147. A method of killing or inhibiting the growth of a *Plasmodium* species comprising contacting the species with an effective amount of a compound of Formula III:



wherein:



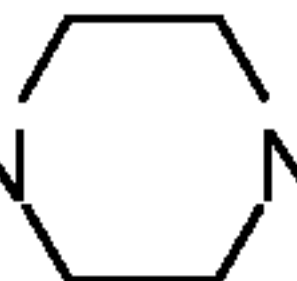
each Q is, independently, or $-C(=O)-(CH_2)_b-NH-C(=NH)-NH_2$, where

each b is, independently, 1 to 4;

each X is, independently, O, S, or N;

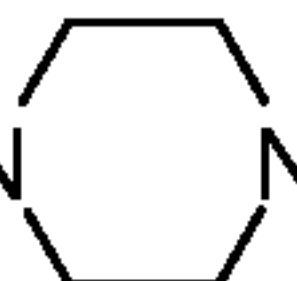
each R^1 is, independently, H, CF_3 , $C(CH_3)_3$, halo, or OH;

10 each R^3 is, independently, H, $-NH-R^2$, $-(CH_2)_r-NH_2$, $-NH_2$, $-NH-(CH_2)_w-NH_2$, or

$-(CH_2)_y-N$ , where each r is, independently, 1 or 2, each w is, independently, 1 to 3, and each y is, independently, 1 or 2;

each R^2 is, independently, H, or the free base or salt form of $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;

15 each R^4 is, independently, H, $-NH-C(=O)-(CH_2)_p-NH-C(=NH)-NH_2$ or

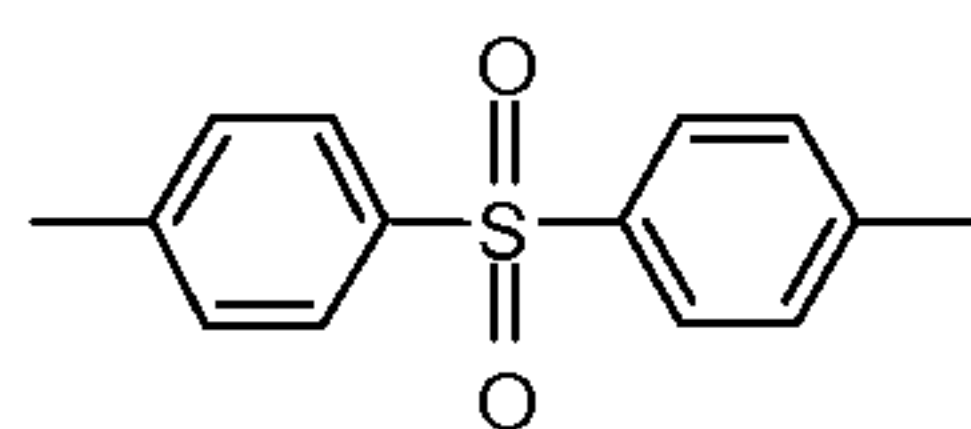
$-(CH_2)_q-N$ , where each p is, independently, 1 to 6, and each q is, independently, 1 or 2; and

each R^5 is, independently, H or CF_3 ;

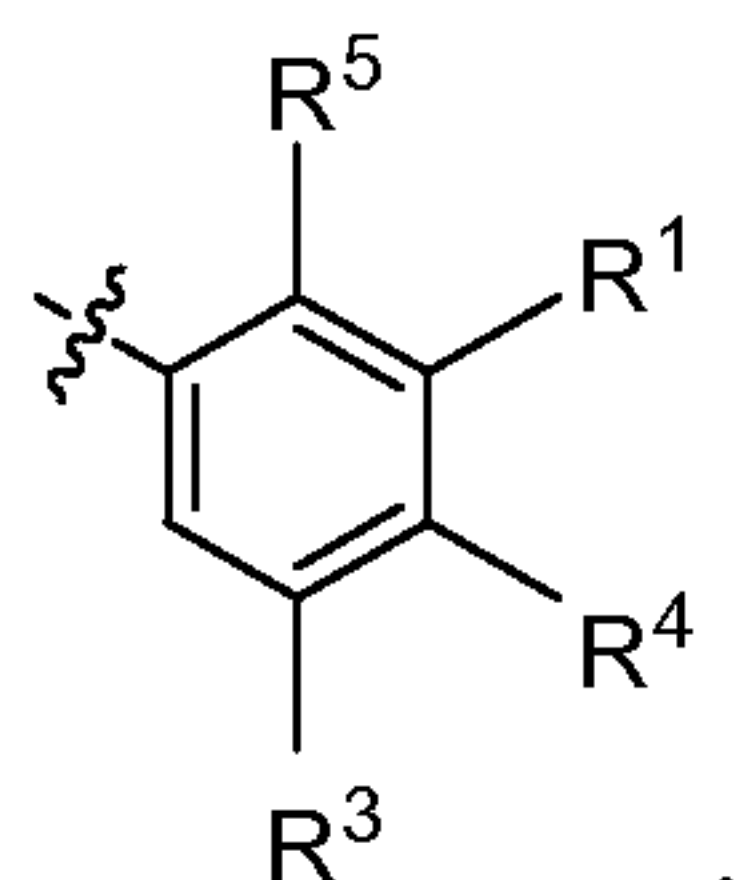
or a pharmaceutically acceptable salt thereof.

20

148. The method of claim 147 wherein Z is



149. The method of claim 147 or claim 148 wherein each Q is, independently,



150. The method of any one of claims 147 to 149 wherein each X is O.

5

151. The method of any one of claims 147 to 150 wherein each R¹ is, independently, H, CF₃, or halo.

152. The method of any one of claims 147 to 150 wherein each R¹ is CF₃.

10

153. The method of any one of claims 147 to 152 wherein each R³ is, independently, -NH-R².

154. The method of any one of claims 147 to 153 wherein each R² is, independently, H,

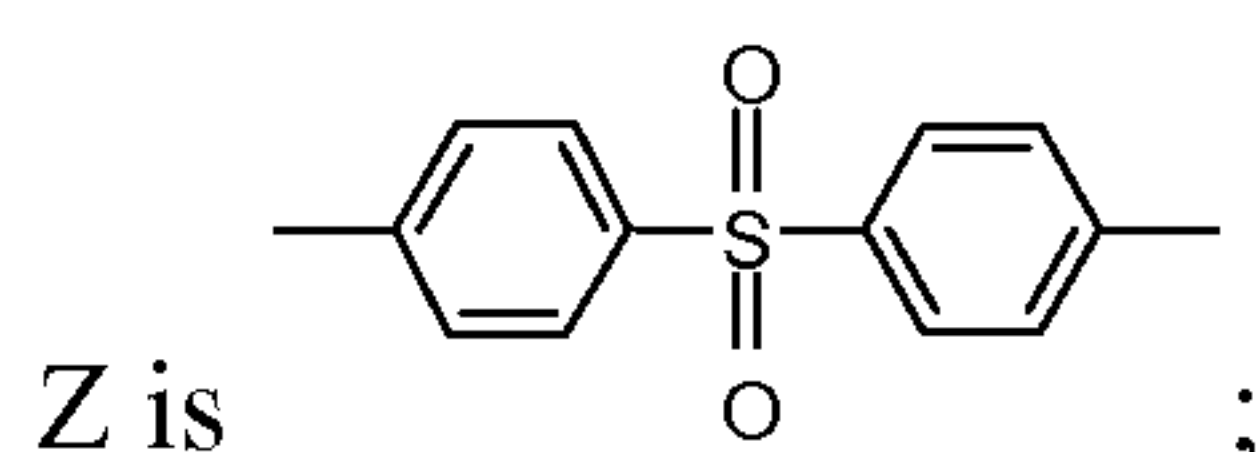
15 or the free base or salt form of -(CH₂)_n-NH₂, where each n is, independently, 1 to 4.

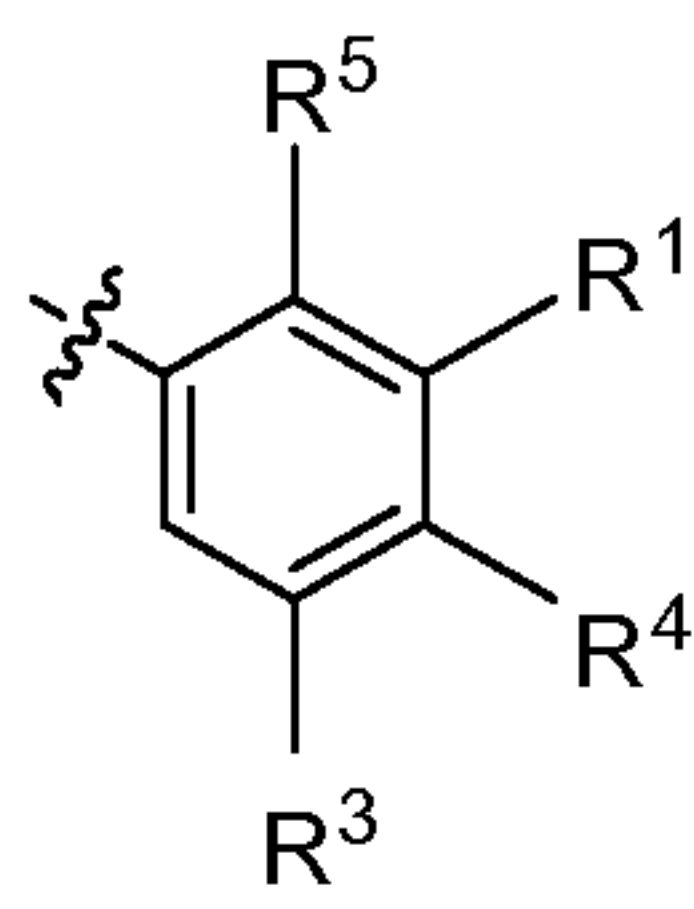
155. The method of any one of claims 147 to 153 wherein each R² is, independently, the free base or salt form of -(CH₂)_n-NH₂, where each n is, independently, 1 or 2.

20 156. The method of any one of claims 147 to 153 wherein each R² is the free base or salt form of -(CH₂)_n-NH₂, where each n is 2.

157. The method of any one of claims 147 to 156 wherein each R⁴ and each R⁵ is H.

25 158. The method of claim 147 wherein:





each Q is, independently, ;

each X is O or S;

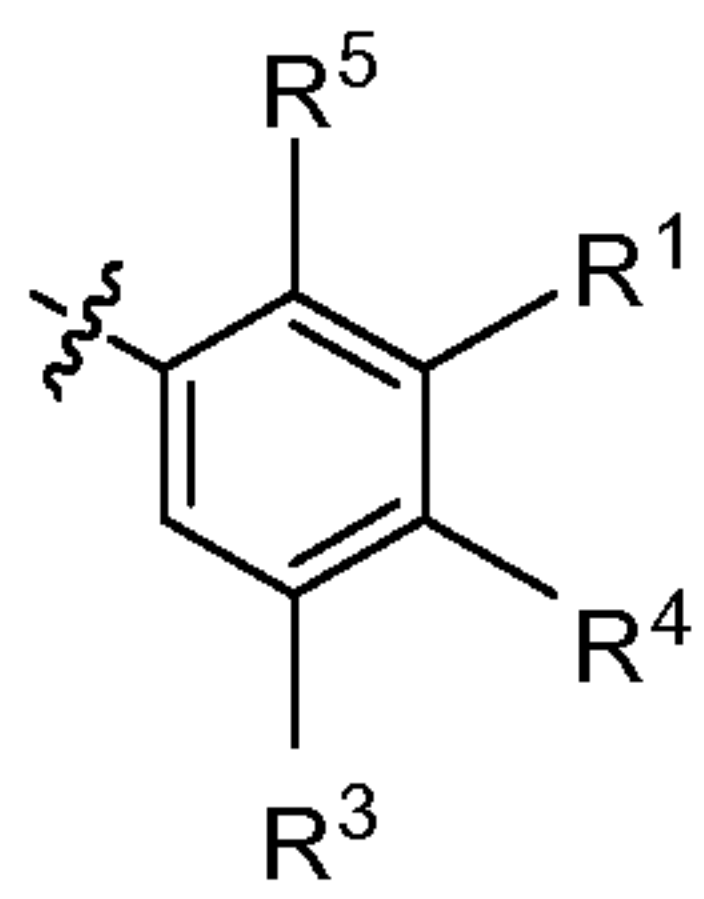
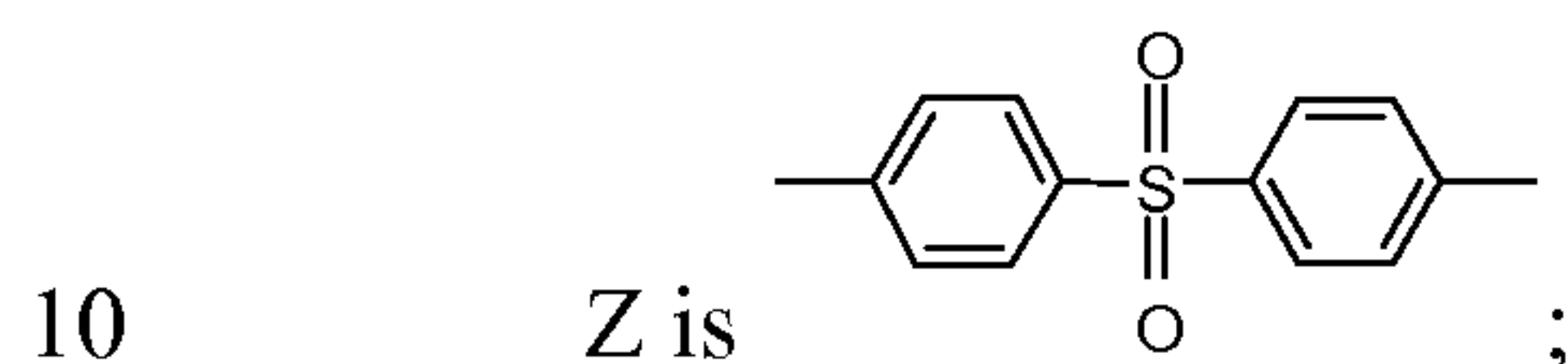
each R¹ is, independently, CF₃, C(CH₃)₃, or halo;

each R³ is, independently, -NH-R²;

5 each R² is, independently, H, or the free base or salt form of -(CH₂)_n-NH₂, where each n is, independently, 1 to 4; and

each R⁴ and each R⁵ is H.

159. The method of claim 147 wherein:



each Q is, independently, ;

each X is O;

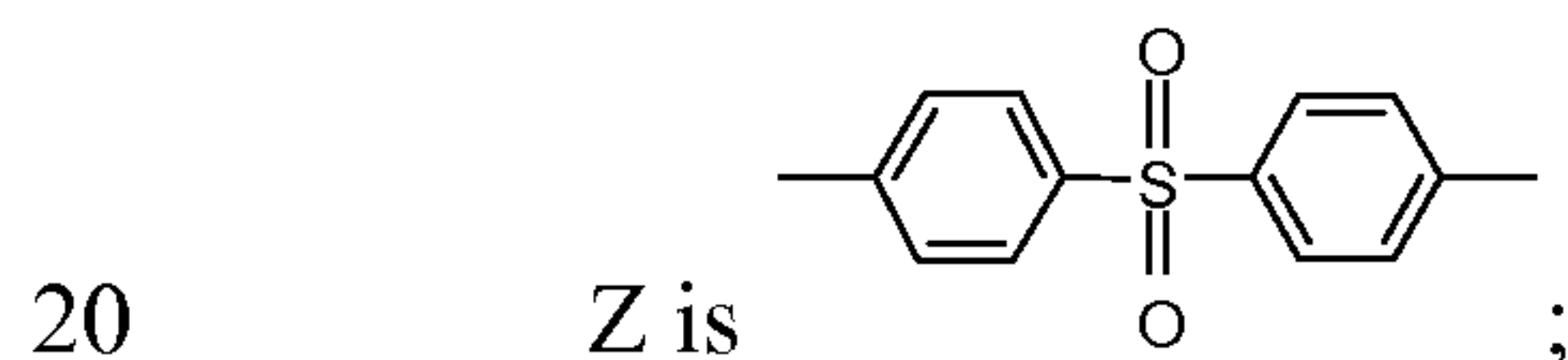
each R¹ is CF₃, C(CH₃)₃, or halo;

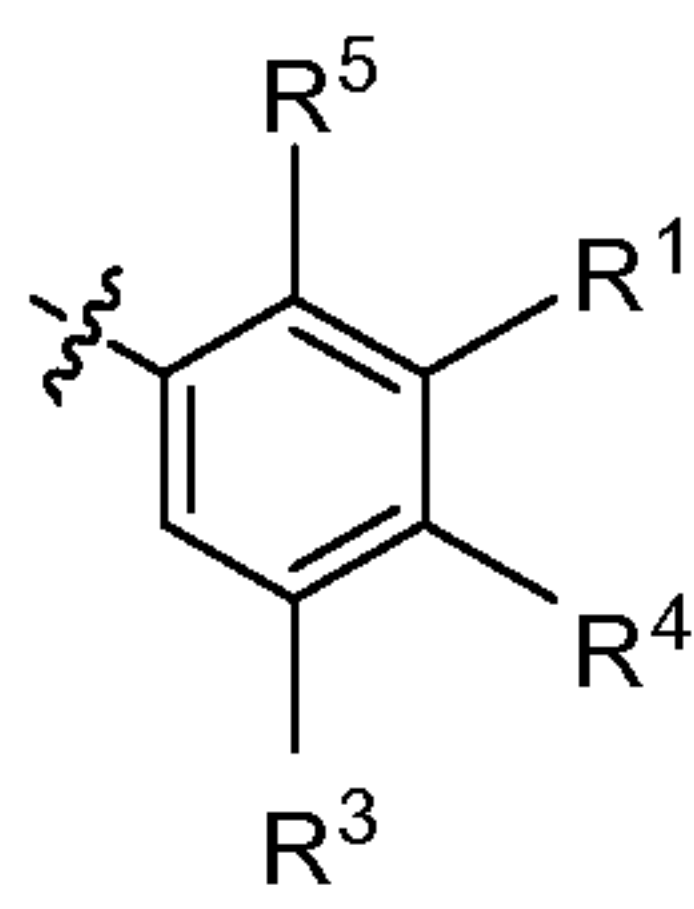
each R³ is, independently, -NH-R²;

15 each R² is, independently, the free base or salt form of -(CH₂)_n-NH₂, where each n is 1 or 2; and

each R⁴ and each R⁵ is H.

160. The method of claim 147 wherein:





each Q is, independently, ;

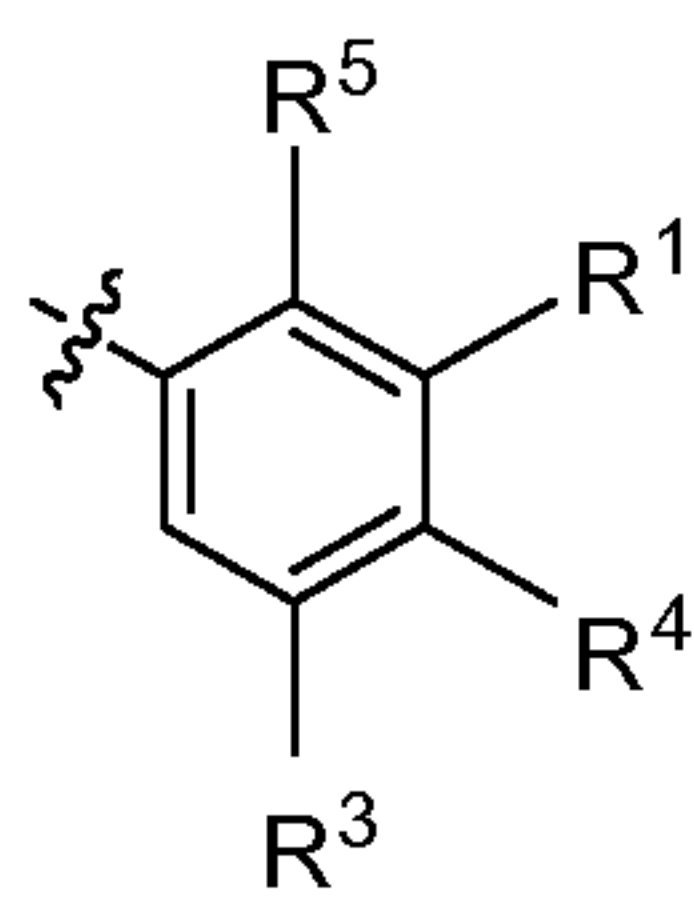
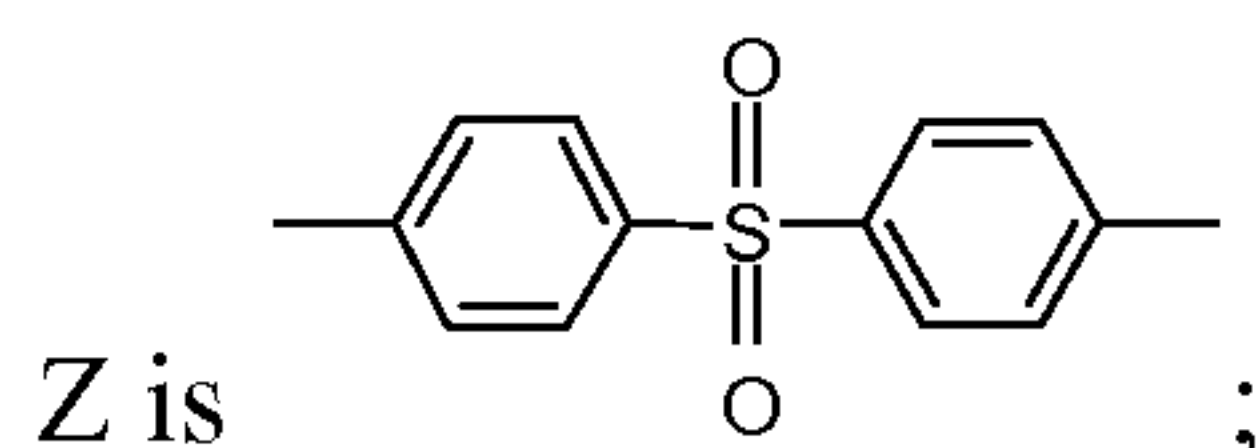
each X is O;

each R¹ is CF₃ or halo;

each R³ is, independently, -NH-R²;

5 each R² is the free base or salt form of -(CH₂)_n-NH₂, where each n is 2; and
each R⁴ and each R⁵ is H.

161. The method of claim 147 wherein:



10 each Q is, independently, ;

each X is, independently, O, or S;

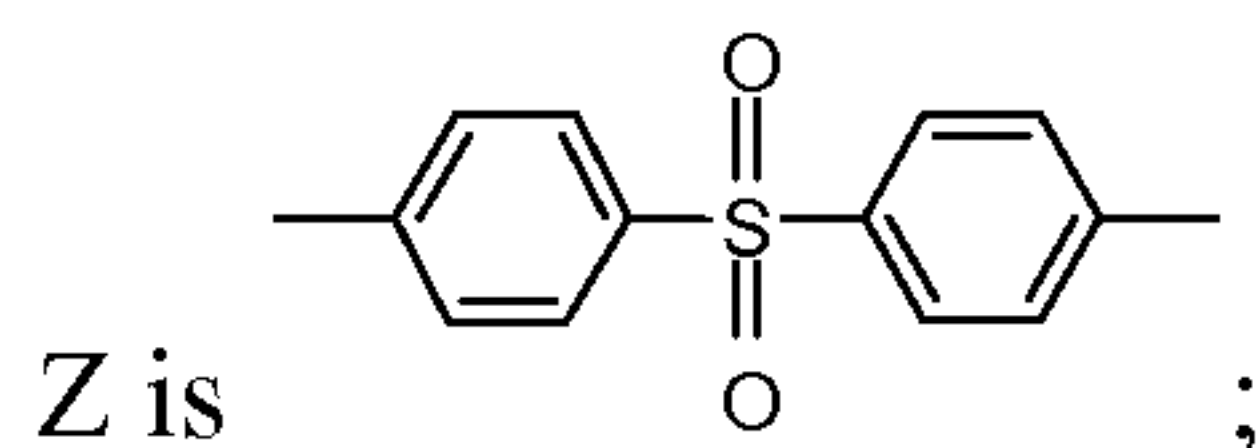
each R¹ is, independently, H, or CF₃;

each R³ is H;

15 each R⁴ is, independently, H or -NH-C(=O)-(CH₂)_p-NH-C(=NH)-NH₂, where each p
is, independently, 3 or 4; and

each R⁵ is, independently, H or CF₃.

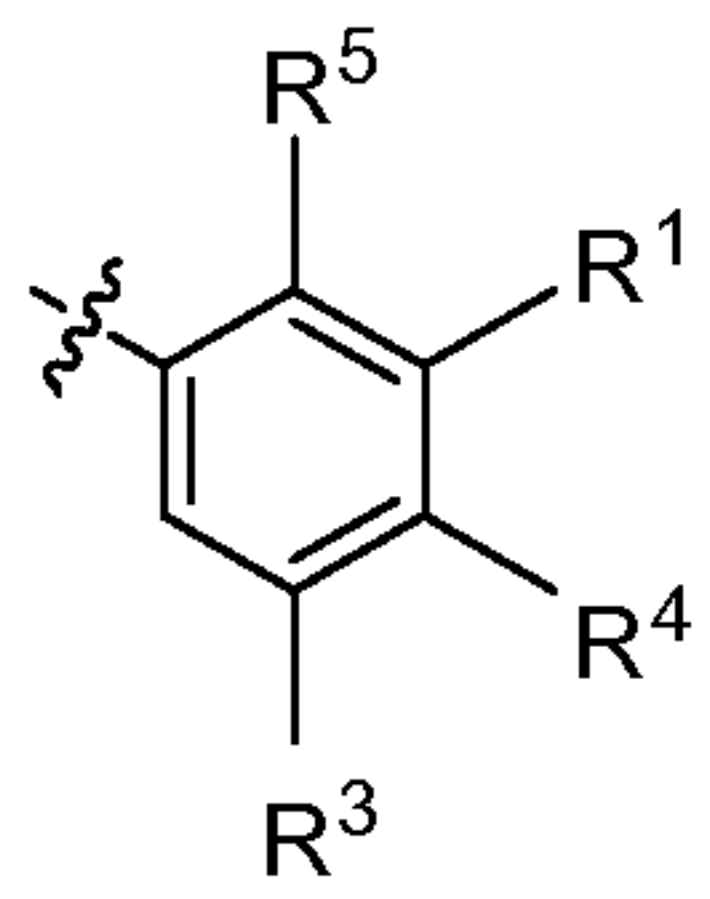
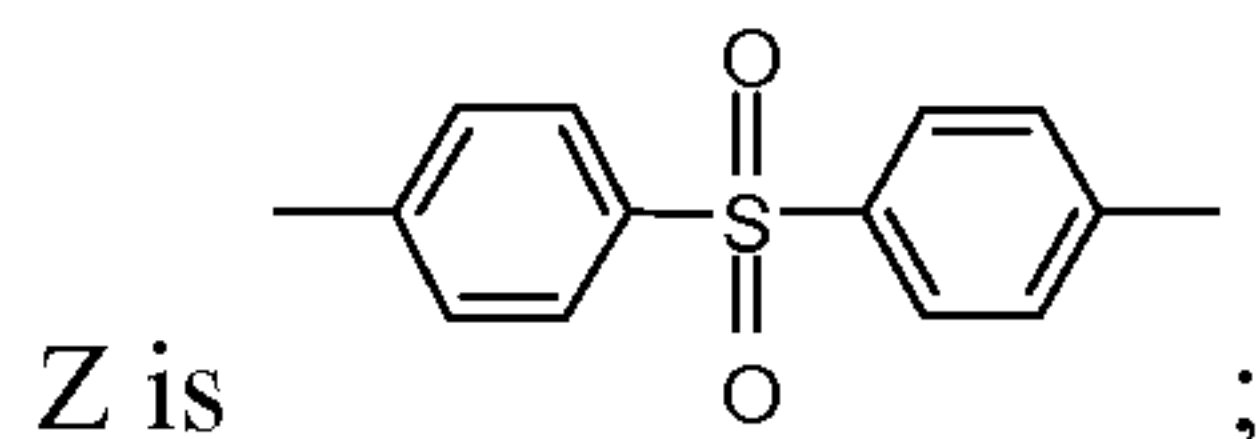
162. The method of claim 147 wherein:



20 each Q is, independently, -C(=O)-(CH₂)_b-NH-C(=NH)-NH₂, where each b is,
independently, 3 or 4; and

each X is N.

163. The method of claim 147 wherein:

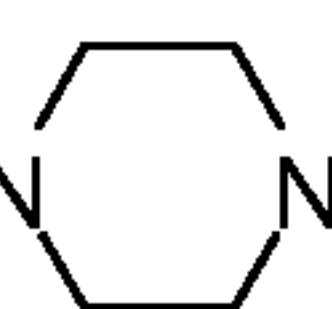


each Q is, independently,

each X is O or S;

5 each R¹ is, independently, H or CF₃;

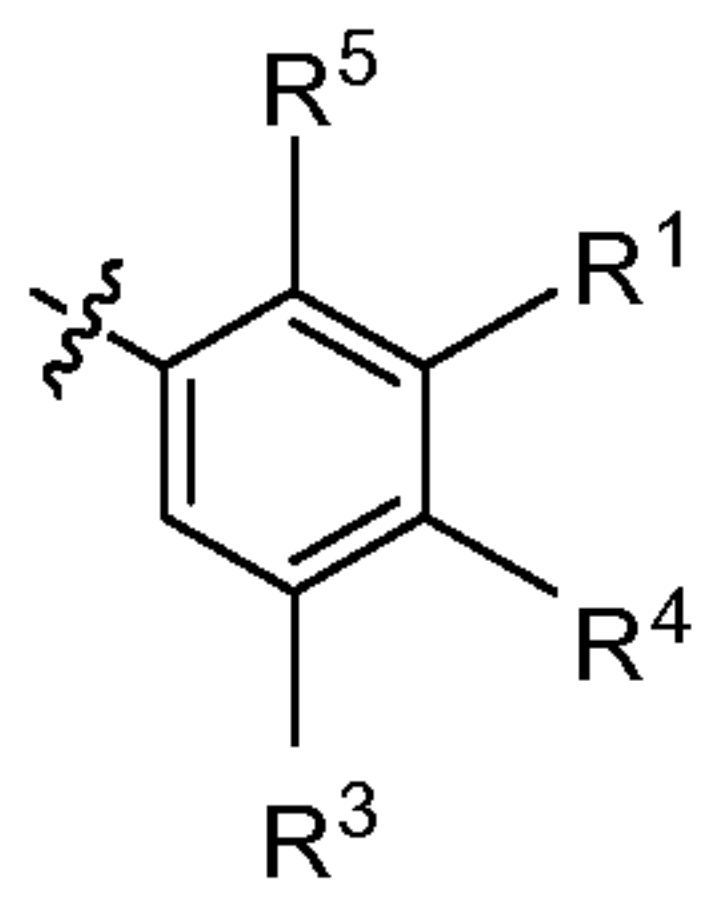
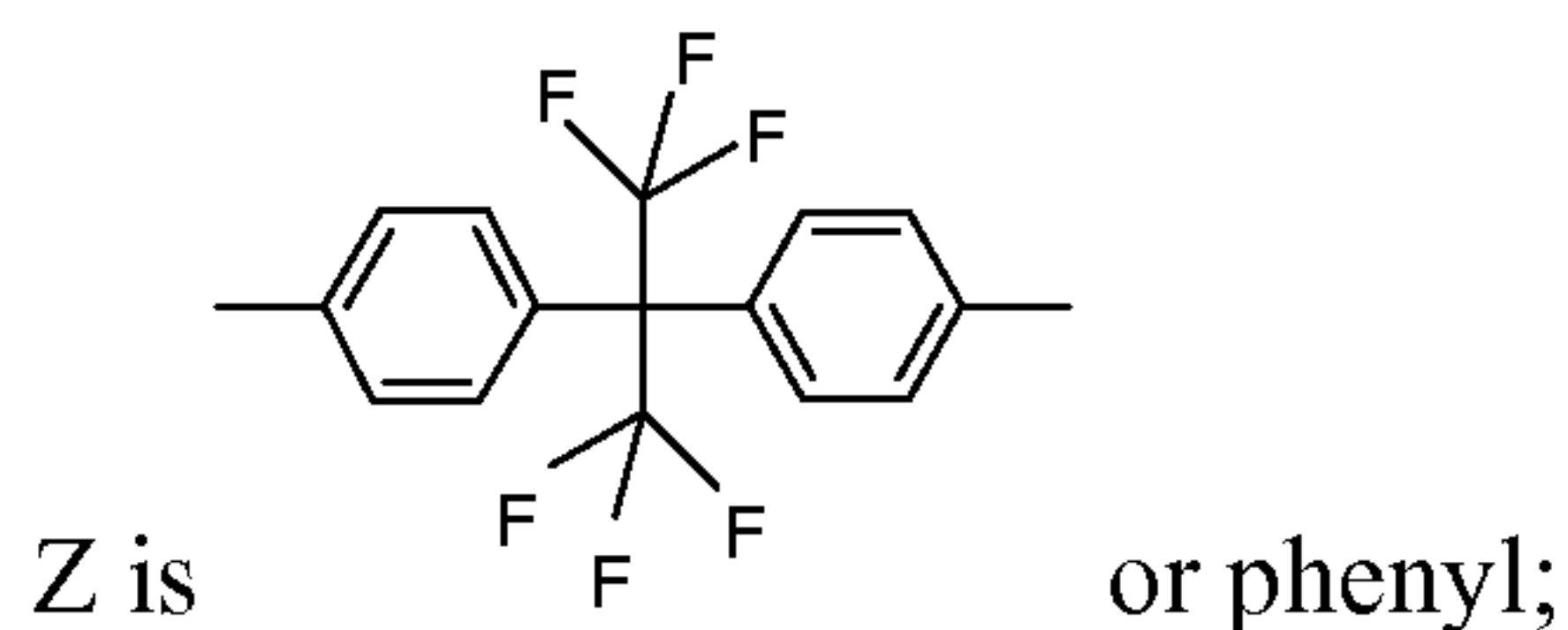
each R³ is, independently, -(CH₂)_r-NH₂, -NH₂, -NH-(CH₂)_w-NH₂, or

-(CH₂)_y-N, where each r is, independently, 1 or 2, each w is, independently, 1 to 3, and each y is, independently, 1 or 2;

each R⁴ is H; and

10 each R⁵ is, independently, H or CF₃.

164. The method of claim 147 wherein:

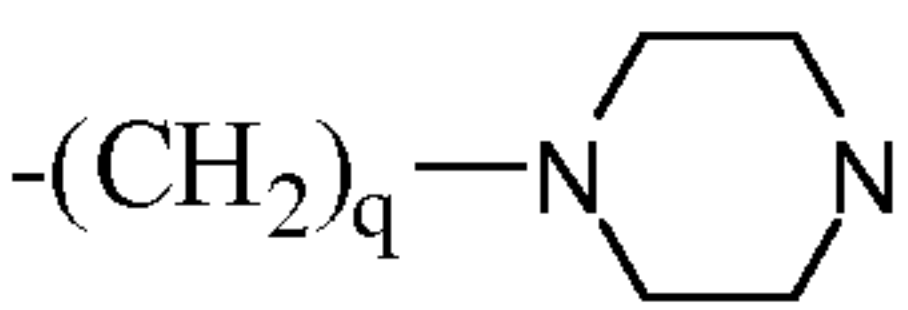


each Q is, independently,

each X is, independently, O or S;

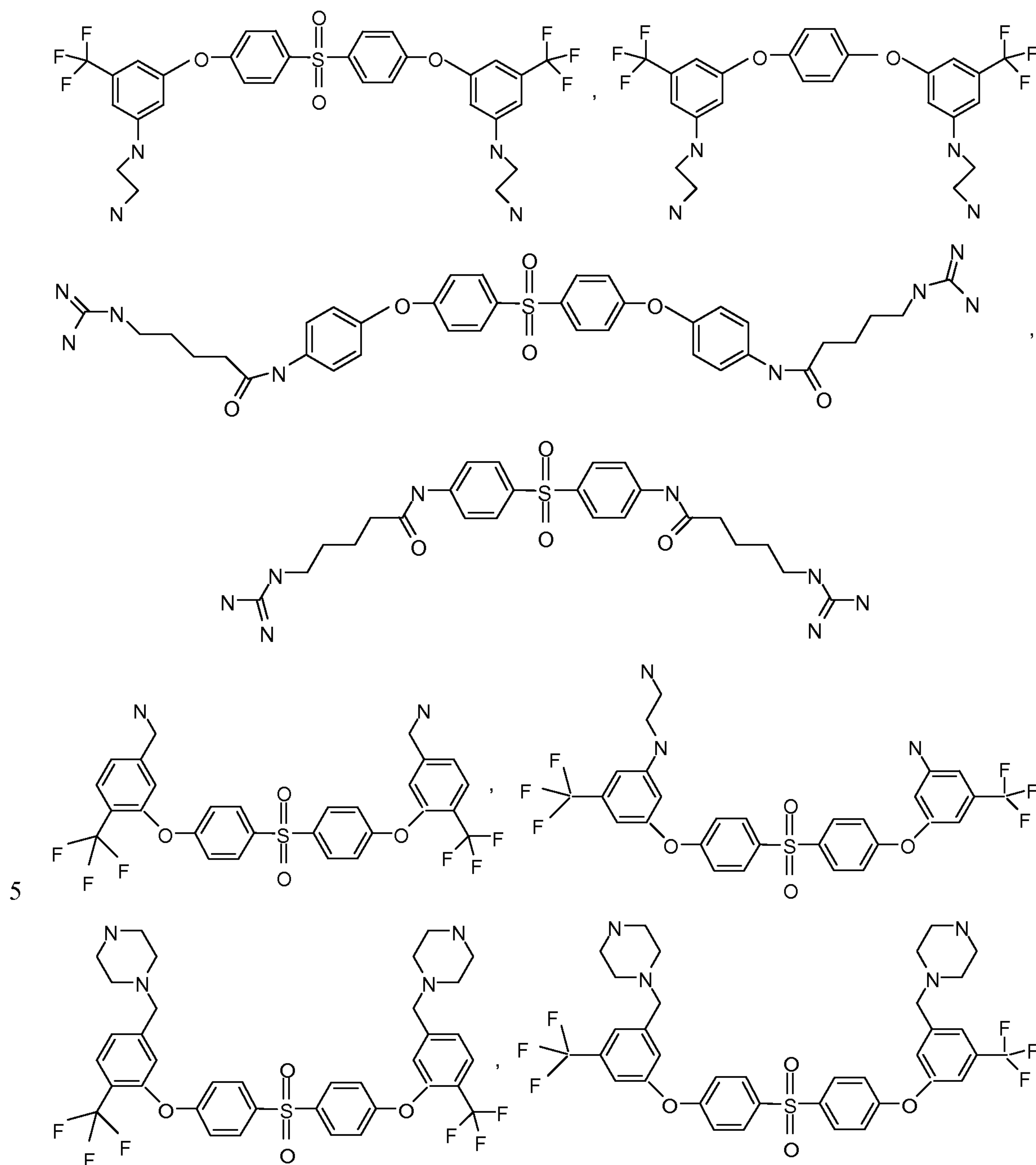
15 each R¹ is, independently, H or CF₃;

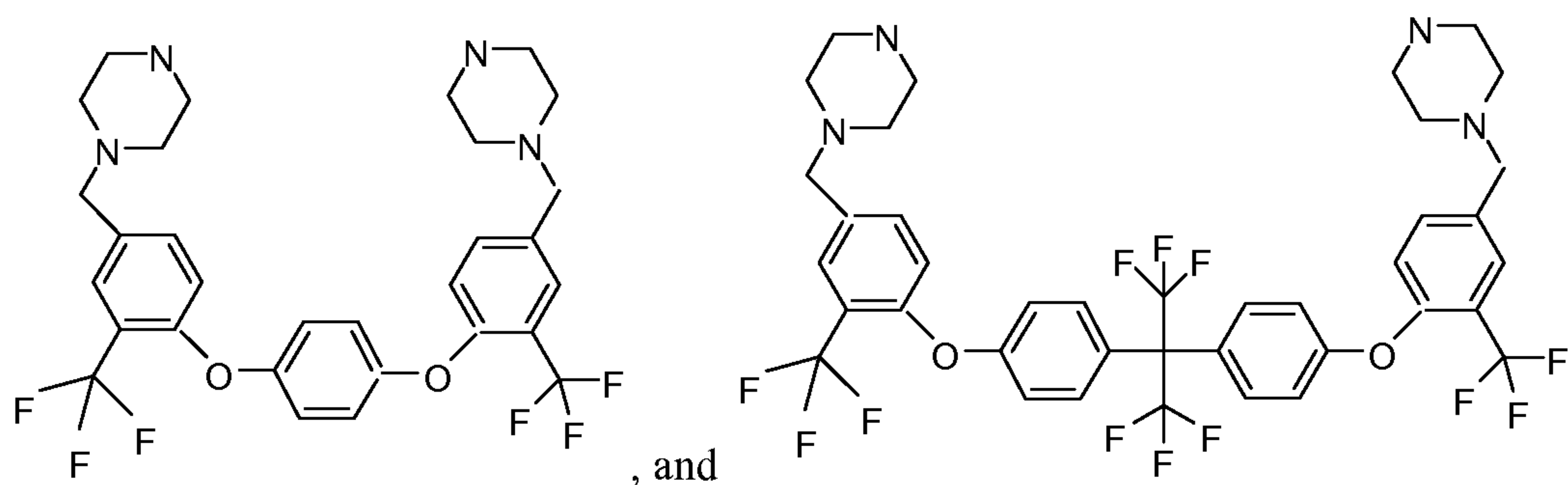
each R³ is H;

each R⁴ is, independently, -(CH₂)_q-N, where each q is, independently, 1 or 2; and

20 each R⁵ is, independently, H or CF₃.

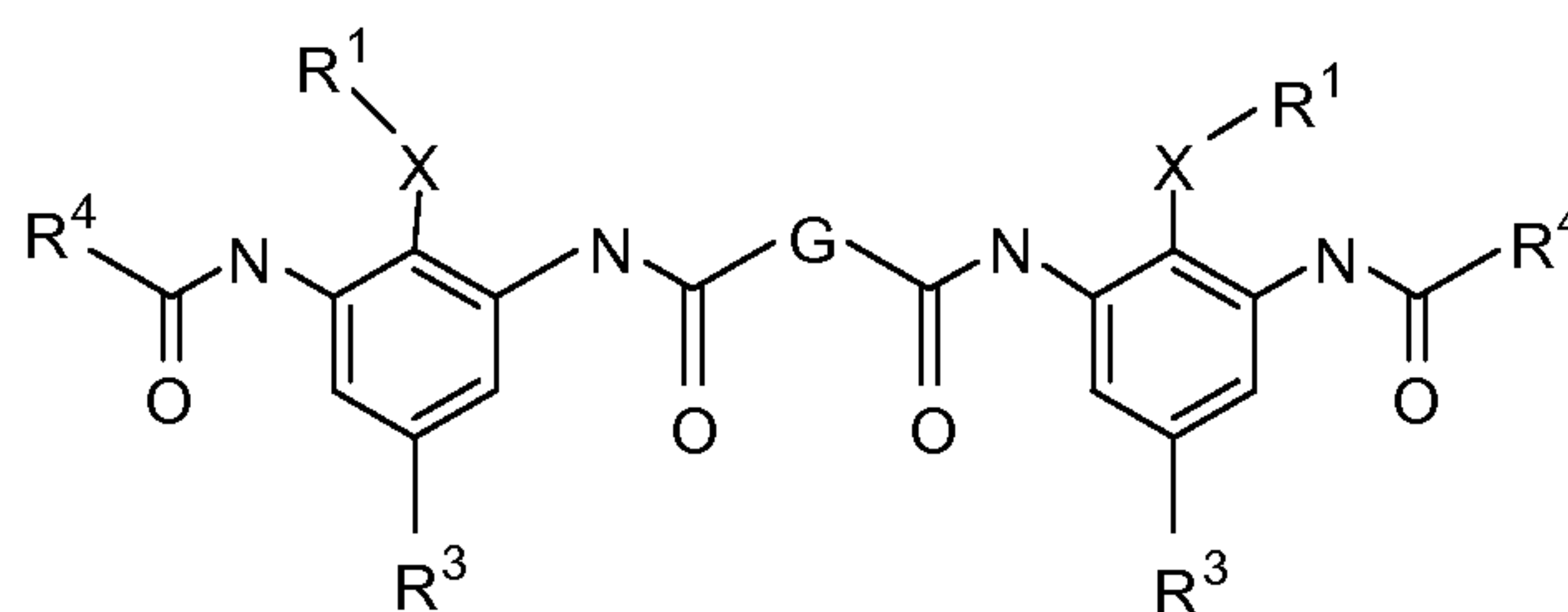
165. The method of claim 147 wherein the compound is chosen from:





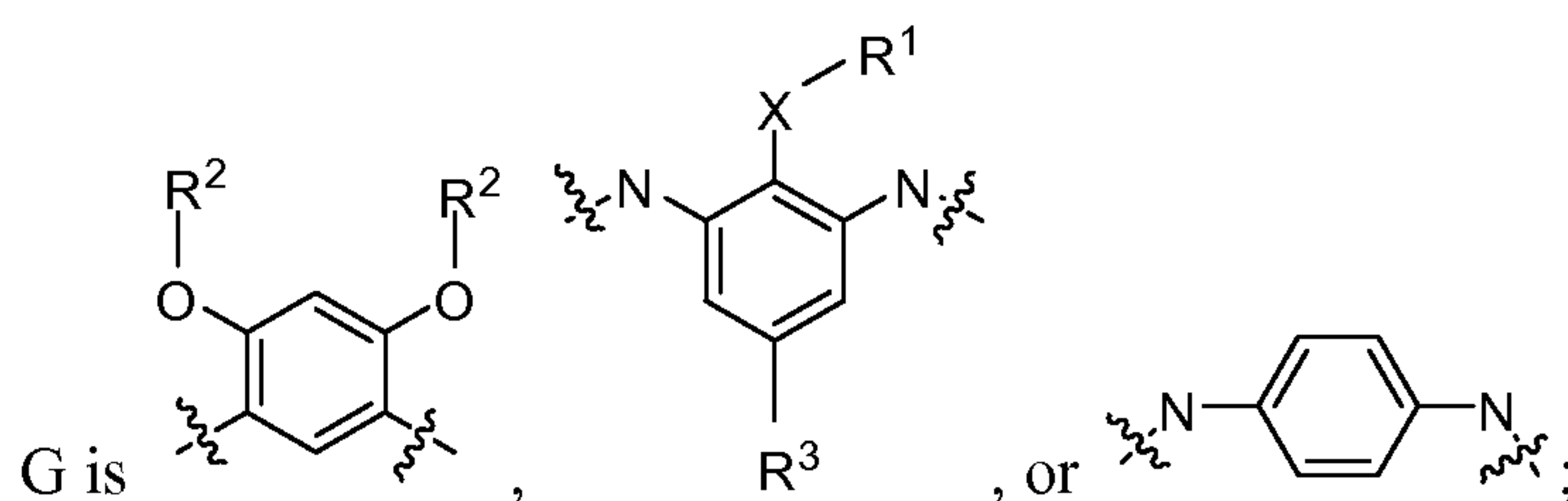
or a pharmaceutically acceptable salt thereof.

166. A compound of Formula IV:



5

wherein:



each X is, independently, O or S;



each R¹ is, independently, , or the free base or salt form of $-(CH_2)_n-NH_2$ or

10 $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;

each R² is, independently, H, C₁-C₈alkyl, or the free base or salt form of

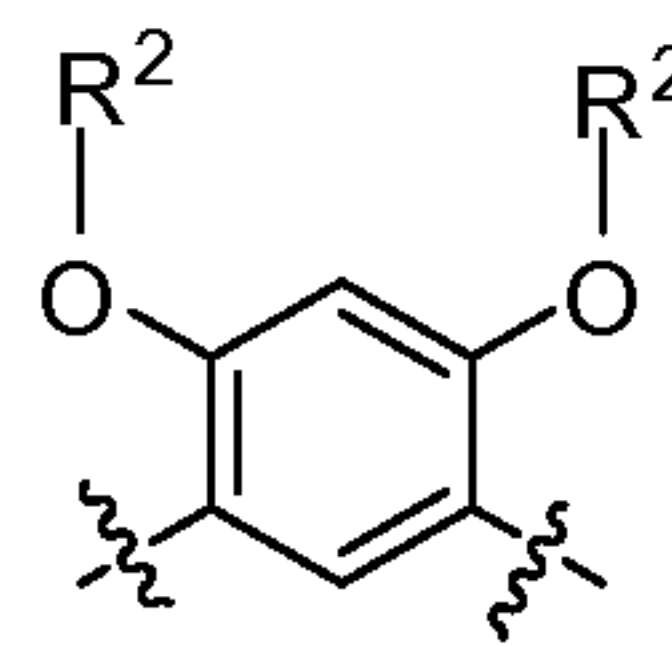
$-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;

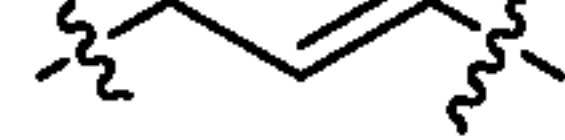
each R³ is, independently, H, CF₃, C(CH₃)₃, halo, or OH; and

each R⁴ is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n

15 is, independently, 1 to 4;

or a pharmaceutically acceptable salt thereof.



167. The compound or salt of claim 166 wherein G is , and each X is S.

168. The compound or salt of claim 166 or claim 167 wherein each R¹ is, independently, the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4.

5

169. The compound or salt of claim 166 or claim 167 wherein each R¹ is, independently, the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2.

170. The compound or salt of claim 166 or claim 167 wherein each R¹ is the free base or
10 salt form of $-(CH_2)_n-NH_2$, where each n is 2.

171. The compound or salt of any one of claims 166 to 170 wherein each R² is, independently, C₁-C₃alkyl or the free base or salt form of $-(CH_2)_n-NH_2$ where n is 1 to 4.

15 172. The compound or salt of any one of claims 166 to 170 wherein each R² is, independently, C₁-C₃alkyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2.

173. The compound or salt of any one of claims 166 to 170 wherein each R² is,
20 independently, methyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 2.

174. The compound or salt of any one of claims 166 to 170 wherein each R² is methyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2.

25

175. The compound or salt of any one of claims 166 to 174 wherein each R³ is, independently, CF₃, C(CH₃)₃, or halo.

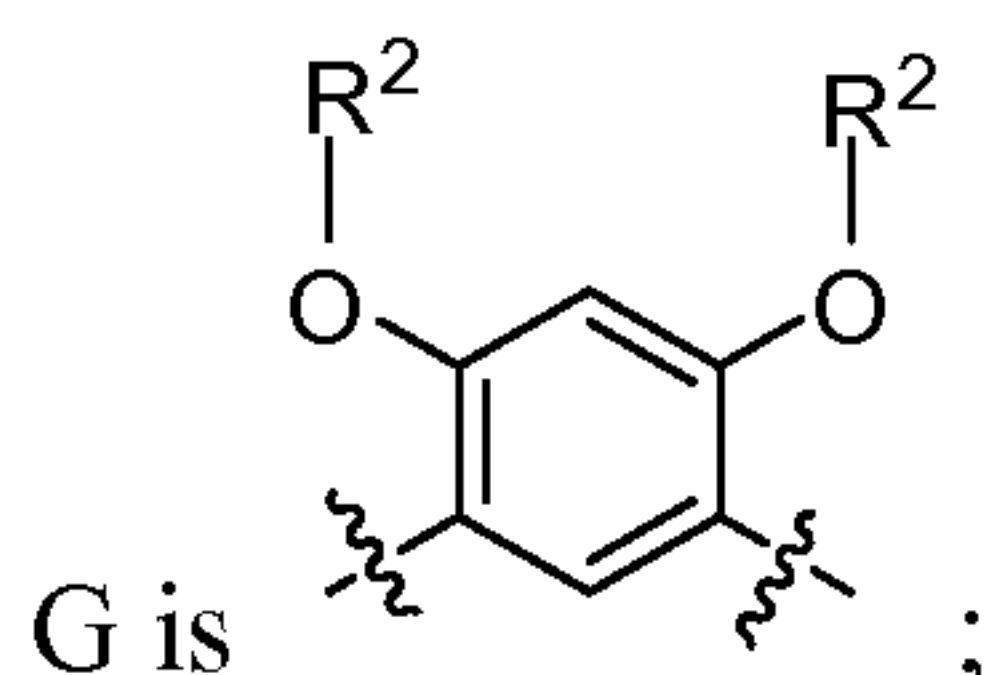
176. The compound or salt of any one of claims 166 to 174 wherein each R³ is CF₃.

30

177. The compound or salt of any one of claims 166 to 176 wherein each R^4 is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

178. The compound or salt of any one of claims 166 to 176 wherein each R^4 is
5 $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 4.

179. The compound or salt of claim 166 wherein:



each X is S ;

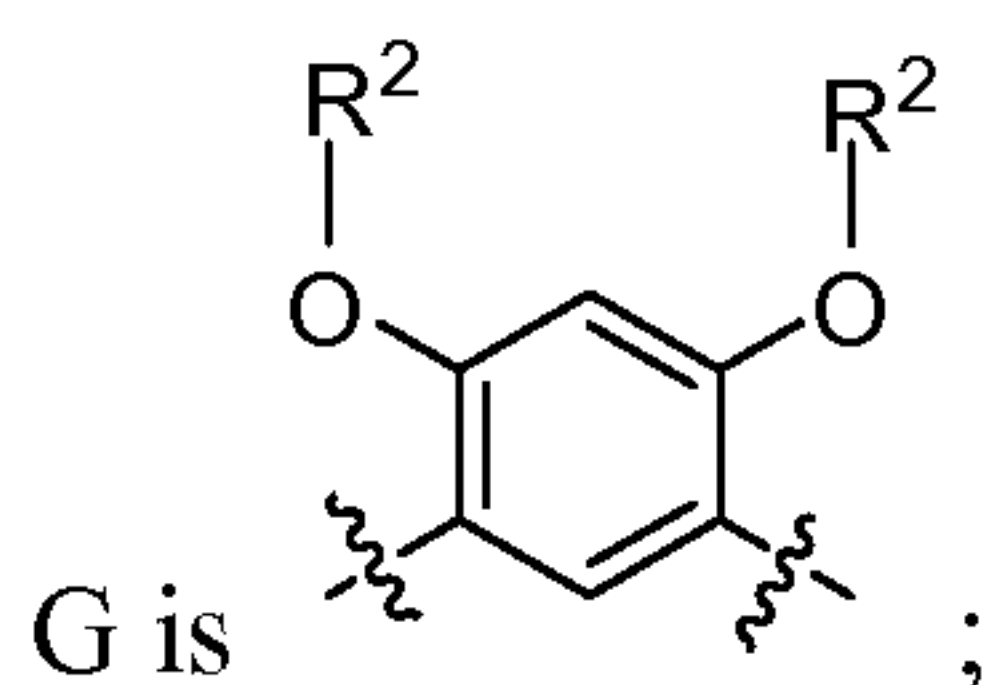
10 each R^1 is, independently, the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2;

each R^2 is, independently, C_1 - C_8 alkyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2;

each R^3 is, independently, CF_3 , $C(CH_3)_3$, or halo; and

15 each R^4 is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 3 or 4.

180. The compound or salt of claim 166 wherein:



20 each X is S ;

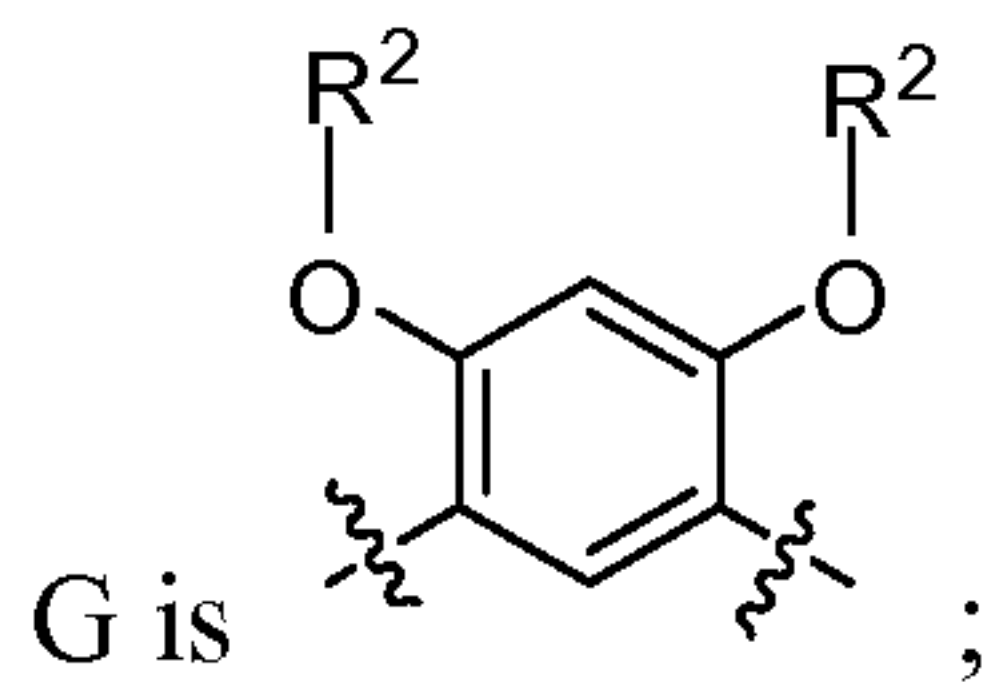
each R^1 is the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 1 or 2;

each R^2 is, independently, C_1 - C_3 alkyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2;

each R^3 is, independently, CF_3 or $C(CH_3)_3$; and

25 each R^4 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 3 or 4.

181. The compound or salt of claim 166 wherein:



each X is S;

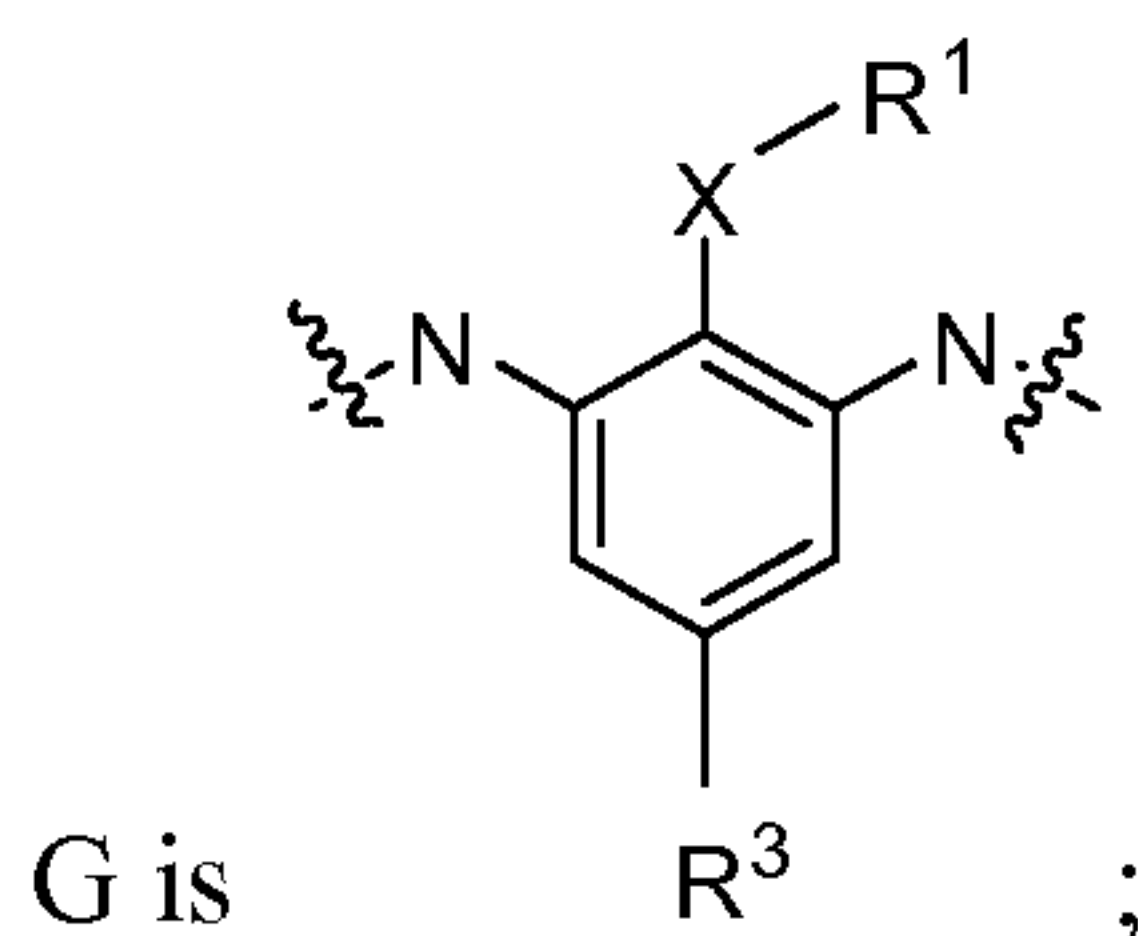
each R¹ is the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2;

5 each R² is, independently, methyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2;

each R³ is, independently, CF₃ or C(CH₃)₃; and

each R⁴ is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 4.

10 182. The compound or salt of claim 166 wherein:



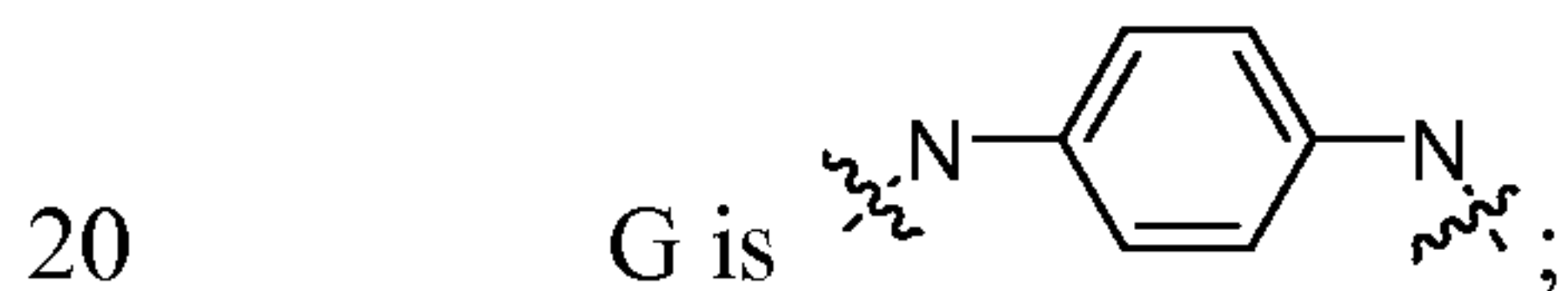
each X is, independently, O or S;

each R¹ is, independently, the free base or salt form of $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;

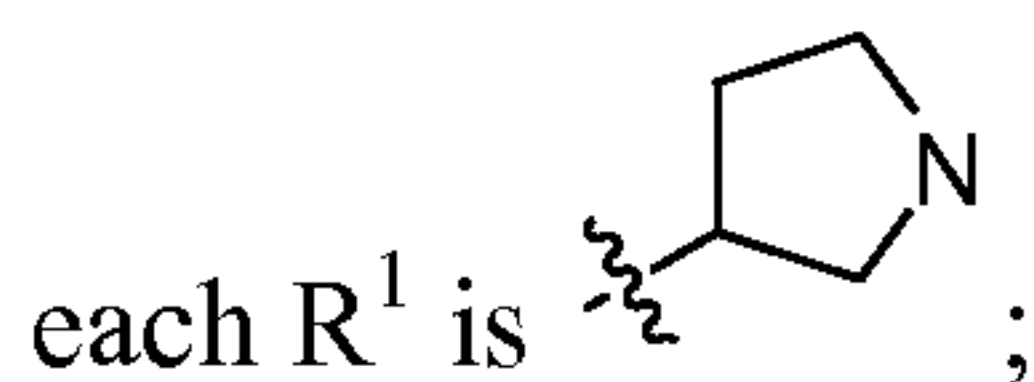
15 each R³ is, independently, H or CF₃; and

each R⁴ is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

183. The compound or salt of claim 166 wherein:



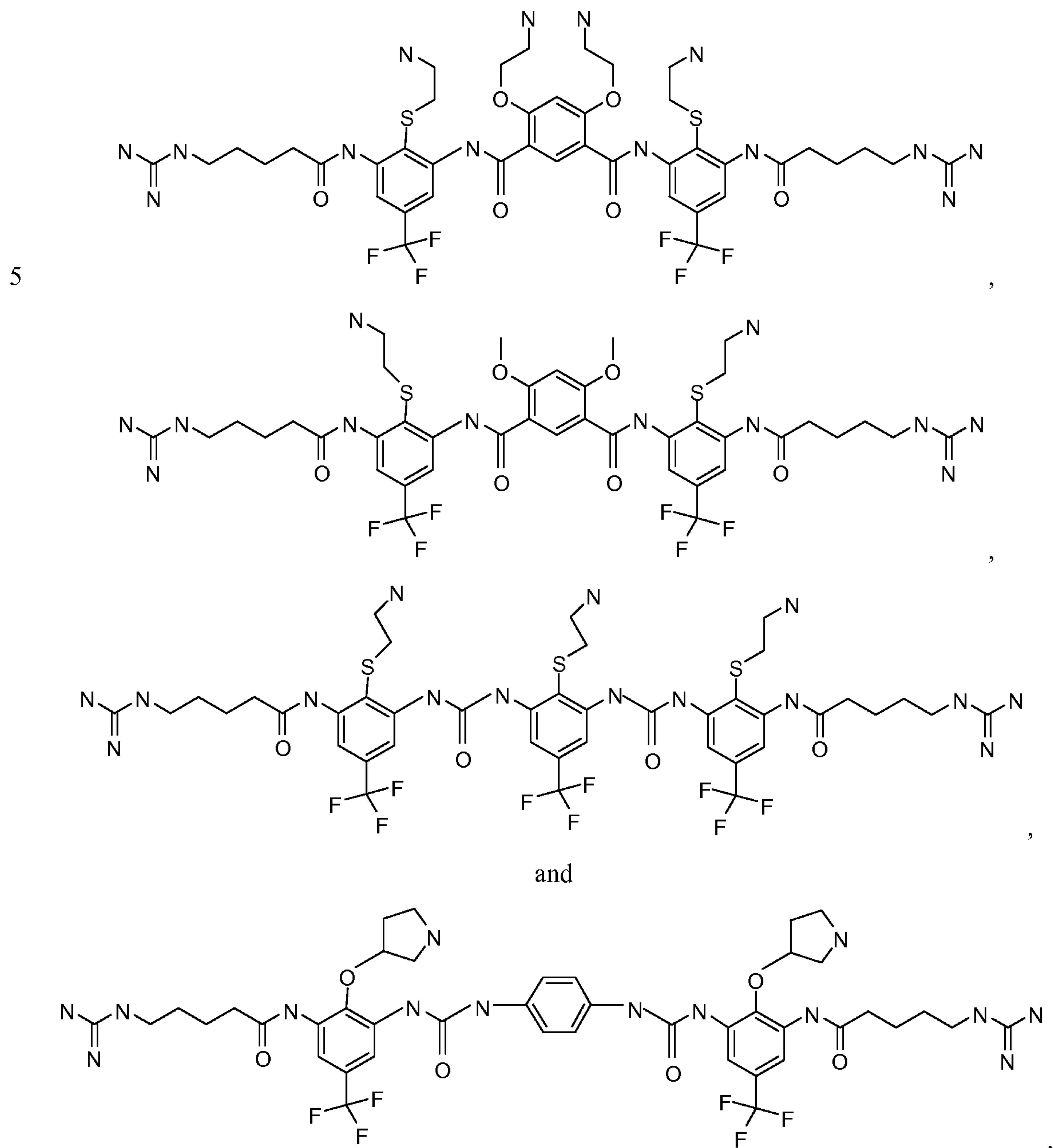
each X is, independently, O or S;



each R³ is, independently, H or CF₃; and

each R^4 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

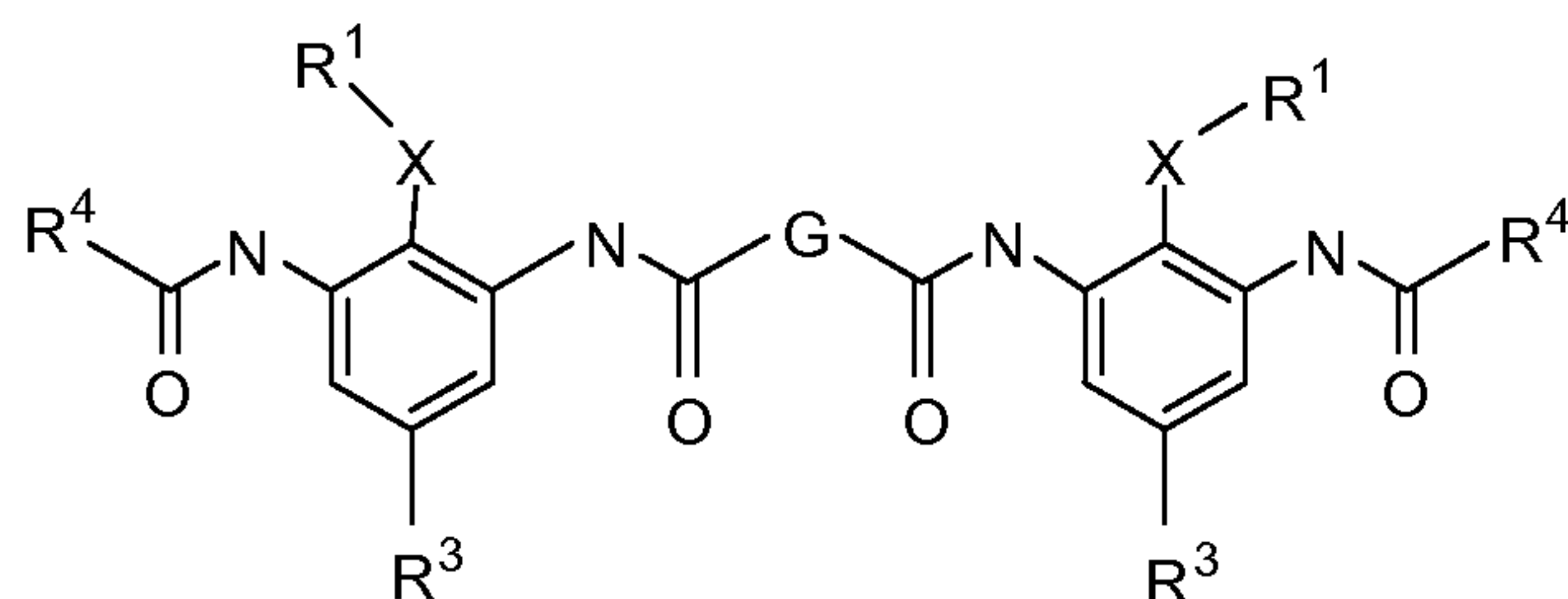
184. A compound chosen from:



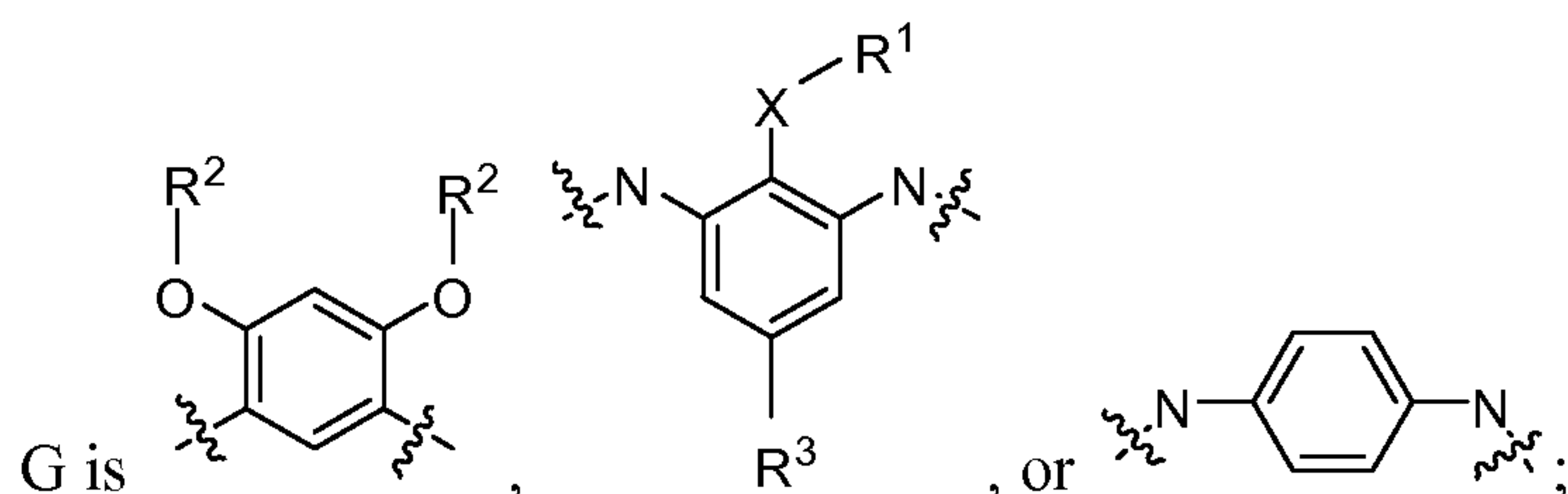
10 or a pharmaceutically acceptable salt thereof.

185. A composition comprising the compound or salt of any one of claims 166 to 184 and a pharmaceutically acceptable carrier.

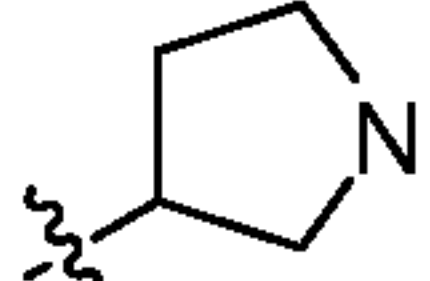
186. A method of treating malaria in an animal comprising administering to the animal a therapeutically effective amount of a compound of Formula IV:



wherein:



each X is, independently, O or S;

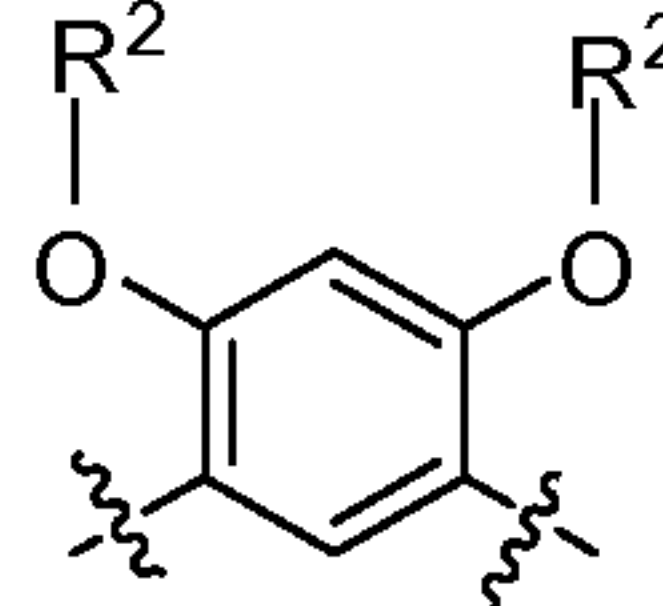
each R^1 is, independently, , or the free base or salt form of $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;

each R^2 is, independently, H, C_1 - C_8 alkyl, or the free base or salt form of $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;

each R^3 is, independently, H, CF_3 , $C(CH_3)_3$, halo, or OH; and

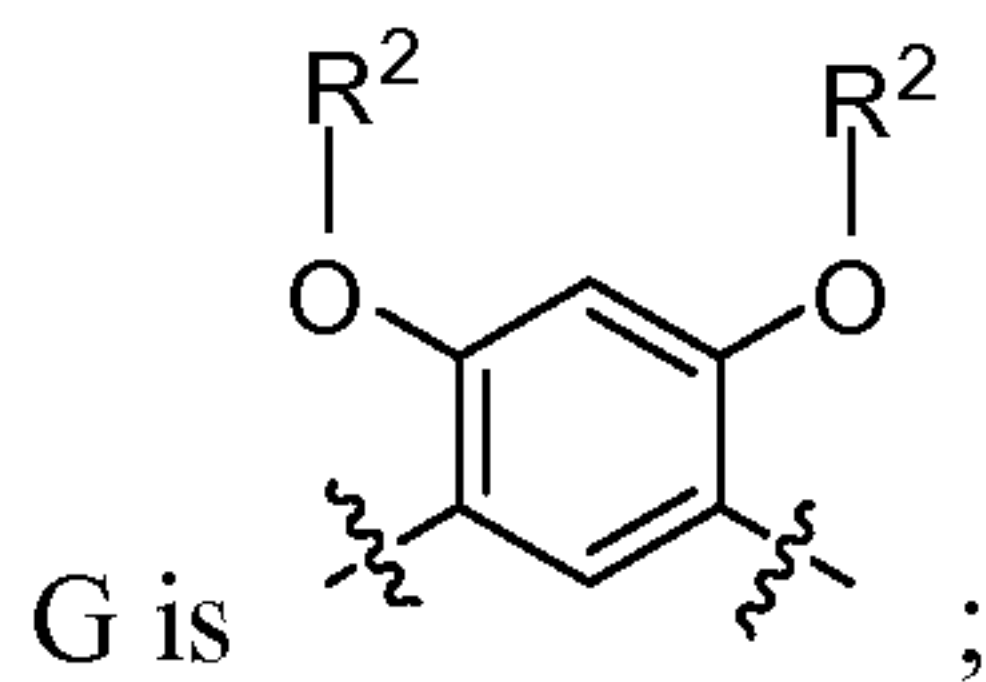
each R^4 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;

or a pharmaceutically acceptable salt thereof.

187. The method of claim 186 wherein G is , and each X is S.

188. The method of claim 186 or claim 187 wherein each R^1 is, independently, the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4.
189. The method of claim 186 or claim 187 wherein each R^1 is, independently, the free
5 base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2.
190. The method of claim 186 or claim 187 wherein each R^1 is the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2.
- 10 191. The method of any one of claims 186 to 190 wherein each R^2 is, independently, C_1 - C_3 alkyl or the free base or salt form of $-(CH_2)_n-NH_2$ where n is 1 to 4.
192. The method of any one of claims 186 to 190 wherein each R^2 is, independently, C_1 - C_3 alkyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or
15 2.
193. The method of any one of claims 186 to 190 wherein each R^2 is, independently, methyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 2.
- 20 194. The method of any one of claims 186 to 190 wherein each R^2 is methyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2.
195. The method of any one of claims 186 to 194 wherein each R^3 is, independently, CF_3 , $C(CH_3)_3$, or halo.
25
196. The method of any one of claims 186 to 194 wherein each R^3 is CF_3 .
197. The method of any one of claims 186 to 196 wherein each R^4 is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.
30
198. The method of any one of claims 186 to 196 wherein each R^4 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 4.

199. The method of claim 186 wherein:



each X is S;

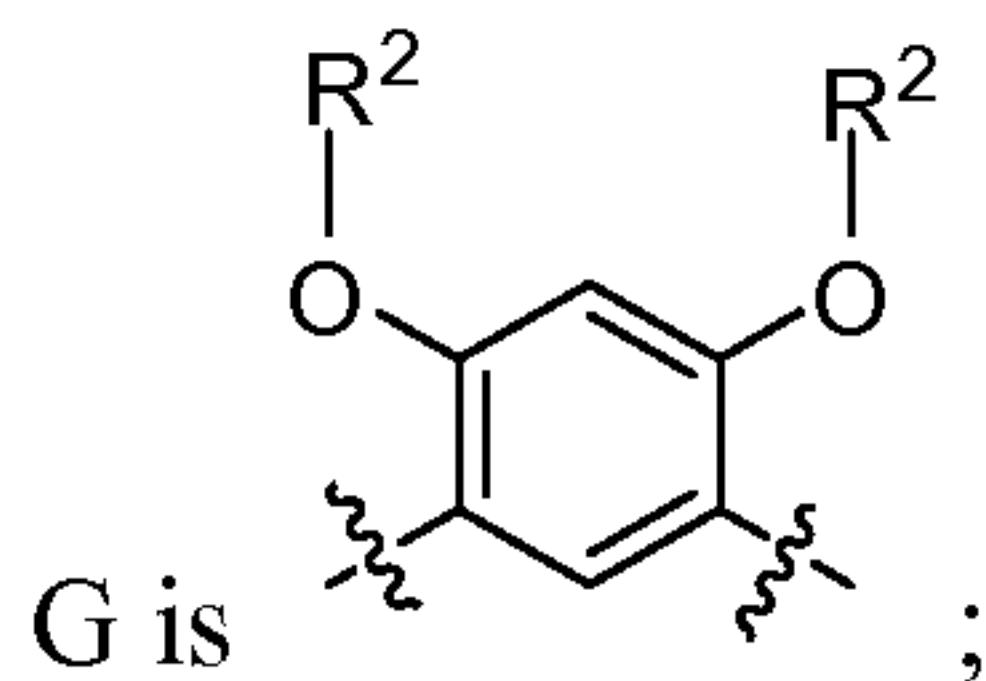
each R¹ is, independently, the free base or salt form of -(CH₂)_n-NH₂, where each n is, independently, 1 or 2;

each R² is, independently, C₁-C₈alkyl or the free base or salt form of -(CH₂)_n-NH₂, where each n is, independently, 1 or 2;

each R³ is, independently, CF₃, C(CH₃)₃, or halo; and

each R⁴ is, independently, -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 3 or 4.

200. The method of claim 186 wherein:



each X is S;

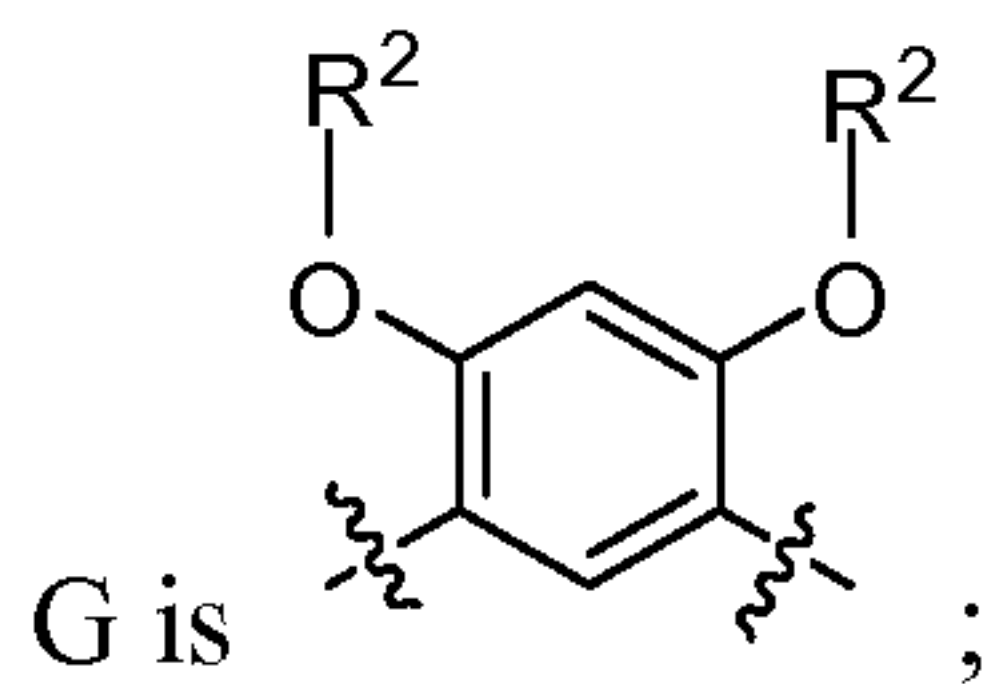
each R¹ is the free base or salt form of -(CH₂)_n-NH₂, where each n is 1 or 2;

each R² is, independently, C₁-C₃alkyl or the free base or salt form of -(CH₂)_n-NH₂, where each n is 2;

each R³ is, independently, CF₃ or C(CH₃)₃; and

each R⁴ is -(CH₂)_n-NH-C(=NH)NH₂, where each n is 3 or 4.

201. The method of claim 186 wherein:



each X is S;

each R¹ is the free base or salt form of -(CH₂)_n-NH₂, where each n is 2;

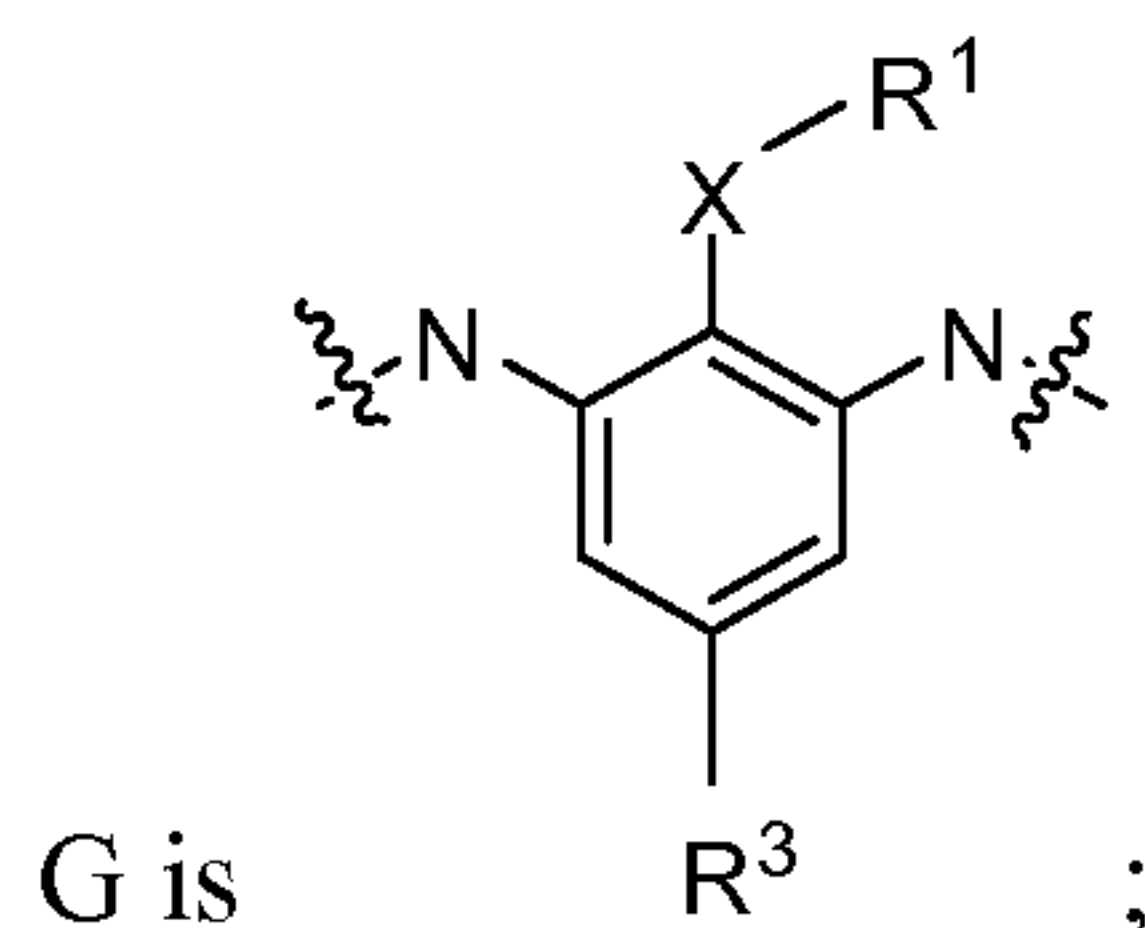
each R^2 is, independently, methyl or the free base or salt form of $-(CH_2)_n-NH_2$,
where each n is 2;

each R^3 is, independently, CF_3 or $C(CH_3)_3$; and

each R^4 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 4.

5

202. The method of claim 186 wherein:



each X is, independently, O or S;

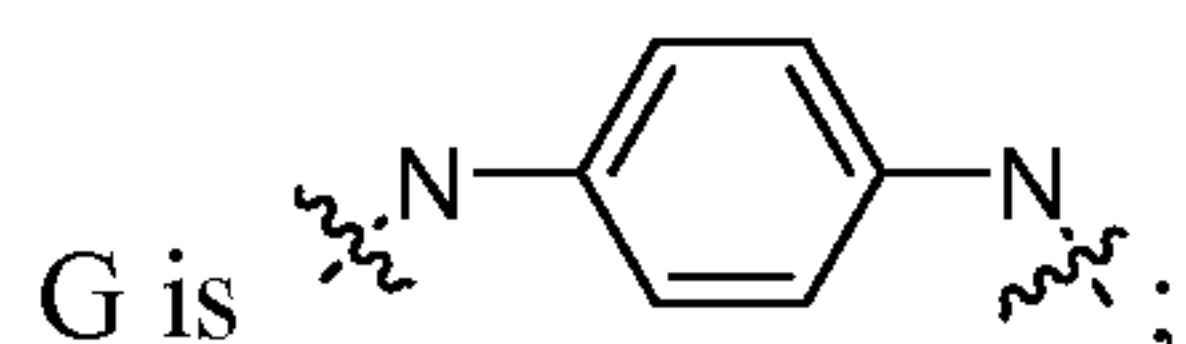
each R^1 is, independently, the free base or salt form of $-(CH_2)_n-NH_2$ or

10 $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;

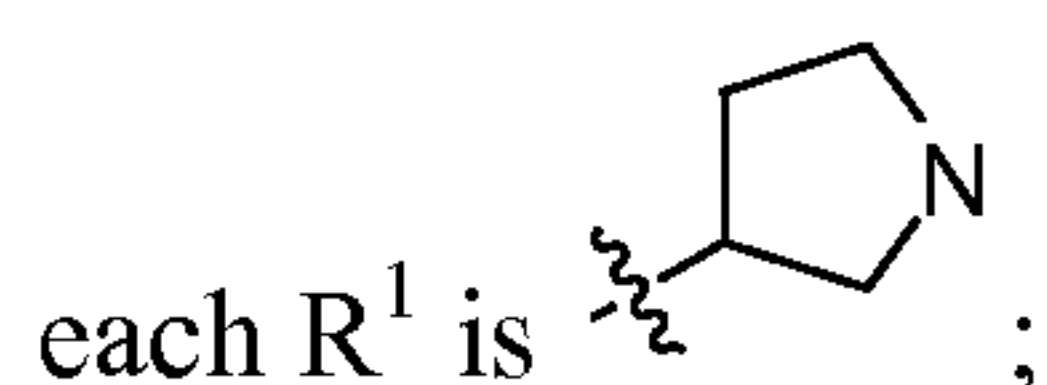
each R^3 is, independently, H or CF_3 ; and

each R^4 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

15 203. The method of claim 186 wherein:



each X is, independently, O or S;

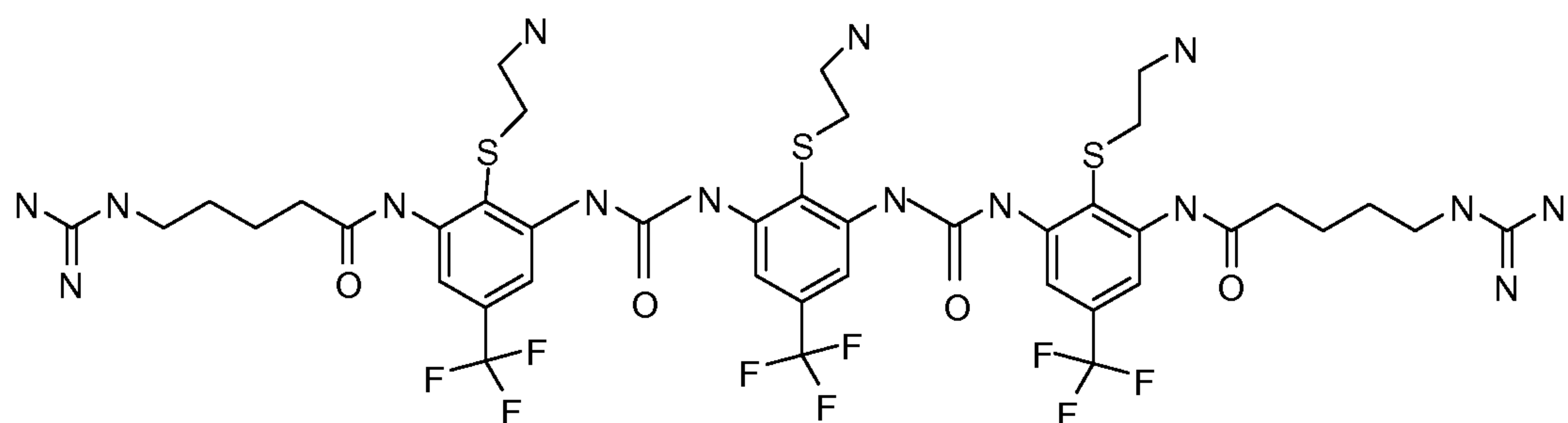
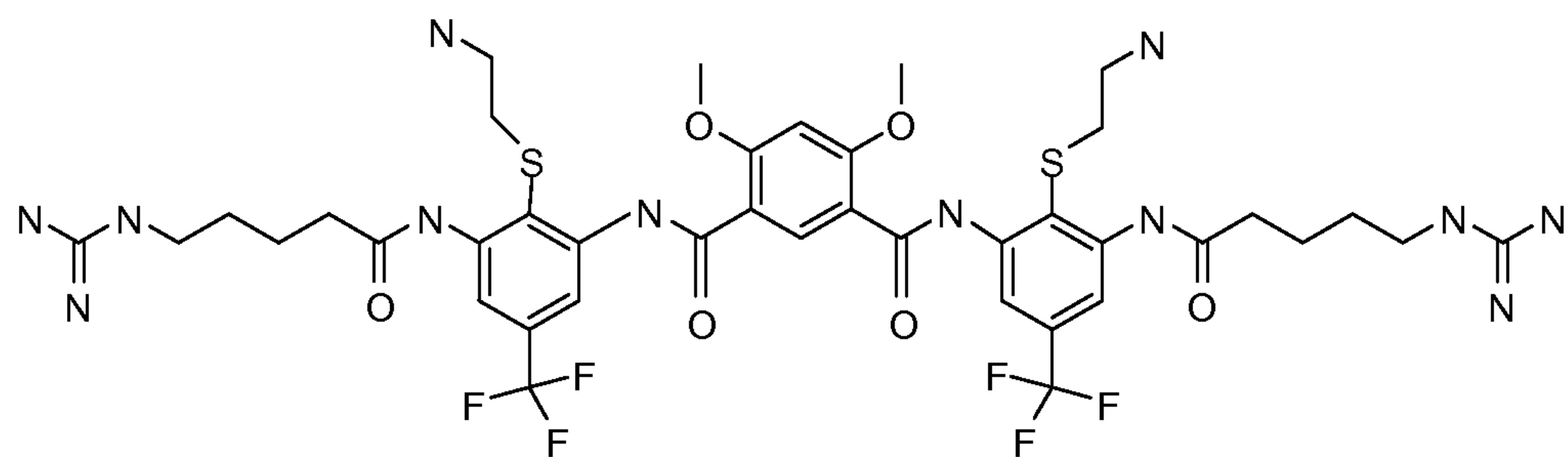
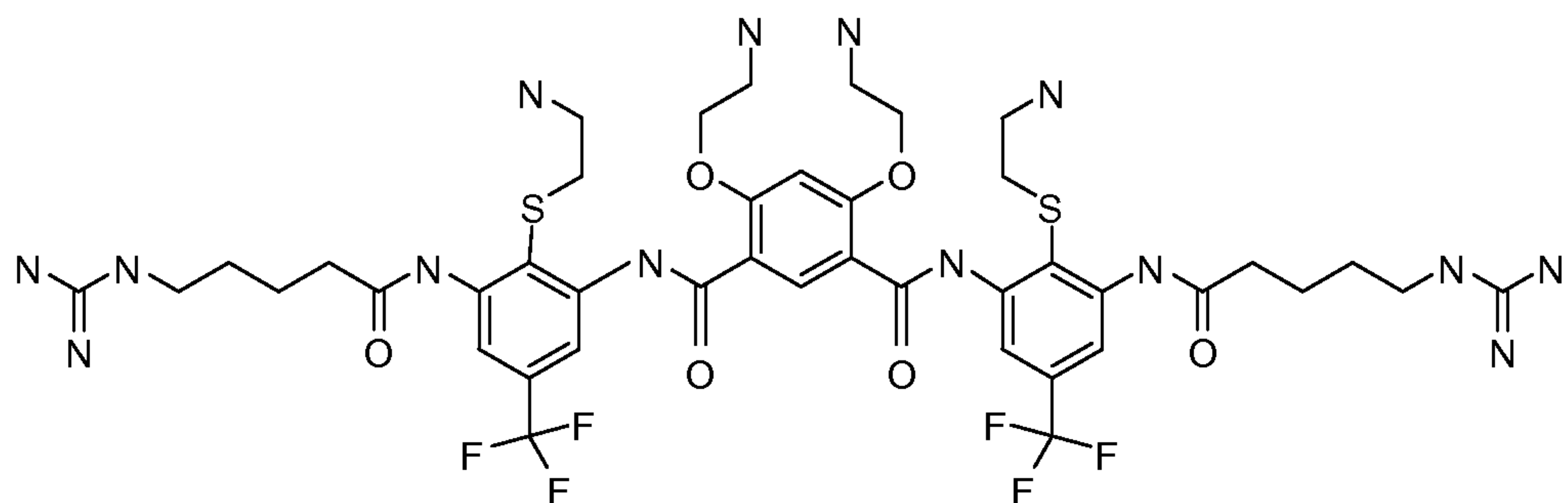


each R^3 is, independently, H or CF_3 ; and

20 each R^4 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

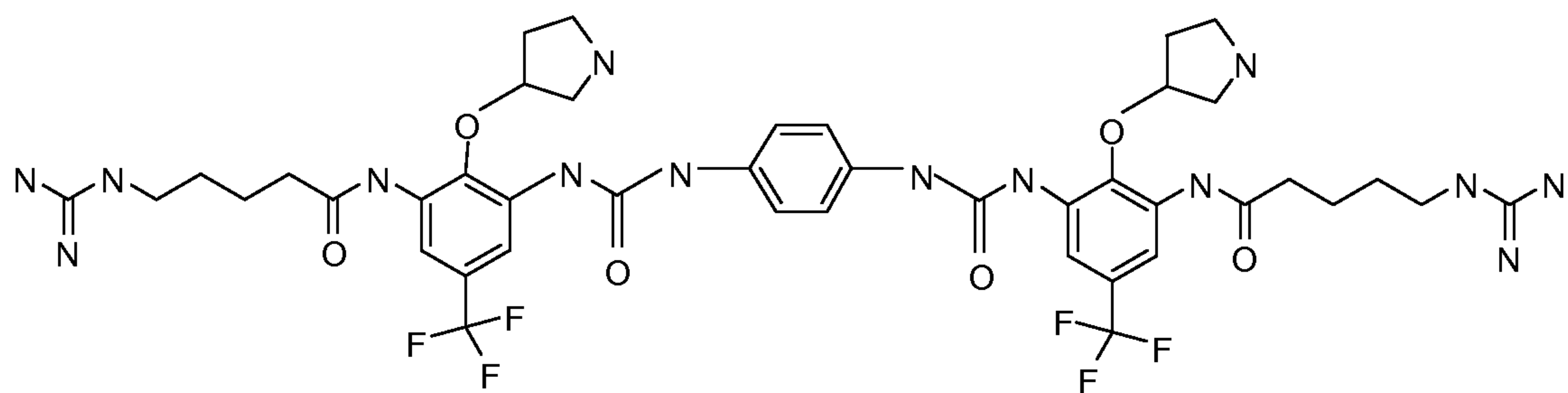
25

204. The method of claim 186 wherein the compound is chosen from:



5

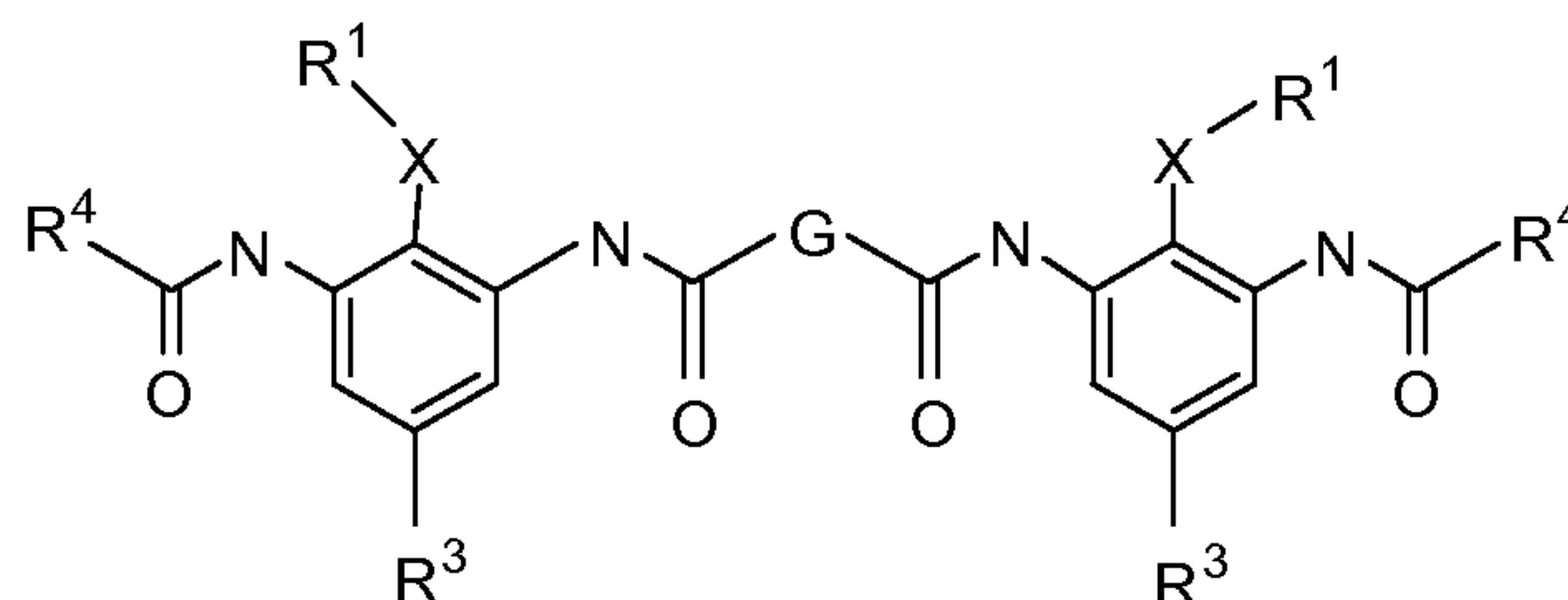
and



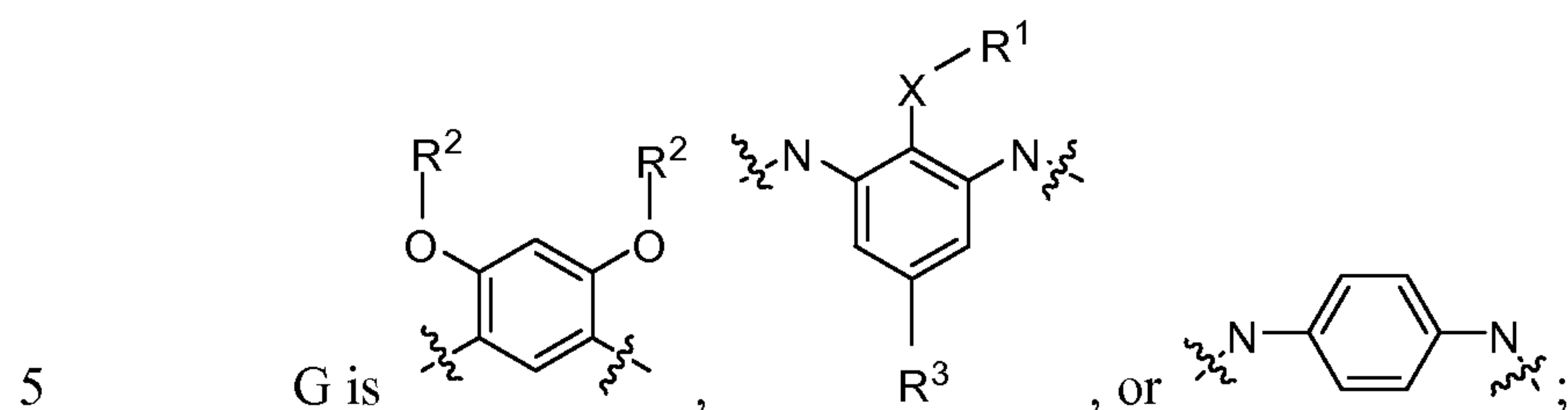
or a pharmaceutically acceptable salt thereof.

205. The method of any one of claims 186 to 204 wherein the malaria is chloroquine-
10 sensitive or chloroquine-resistant.

206. A method of killing or inhibiting the growth of a *Plasmodium* species comprising contacting the species with an effective amount of a compound of Formula IV:



wherein:



each X is, independently, O or S;

each R¹ is, independently, , or the free base or salt form of -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4;

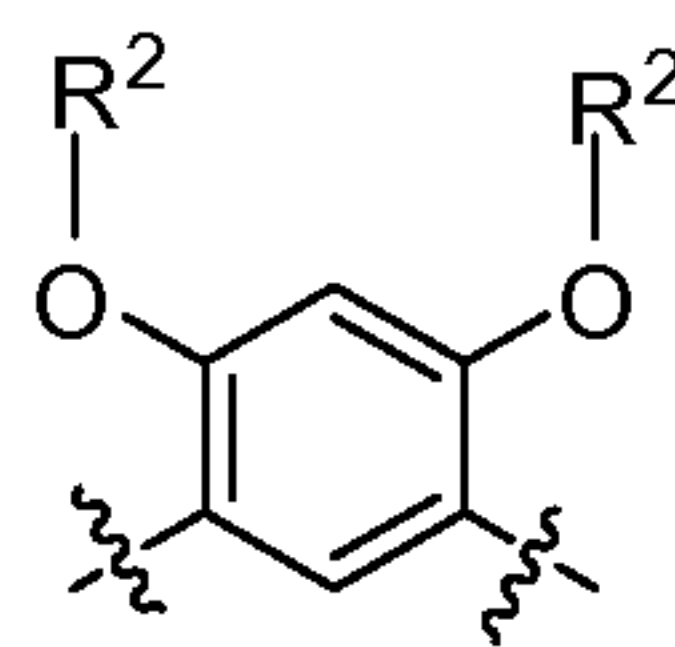
each R² is, independently, H, C₁-C₈alkyl, or the free base or salt form of
10 -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4;

each R³ is, independently, H, CF₃, C(CH₃)₃, halo, or OH; and

each R⁴ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4;

or a pharmaceutically acceptable salt thereof.

15



207. The method of claim 206 wherein G is , and each X is S.

208. The method of claim 206 or claim 207 wherein each R¹ is, independently, the free base or salt form of -(CH₂)_n-NH₂, where each n is, independently, 1 to 4.

20

209. The method of claim 206 or claim 207 wherein each R^1 is, independently, the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2.

210. The method of claim 206 or claim 207 wherein each R^1 is the free base or salt form
5 of $-(CH_2)_n-NH_2$, where each n is 2.

211. The method of any one of claims 206 to 210 wherein each R^2 is, independently, C_1 - C_3 alkyl or the free base or salt form of $-(CH_2)_n-NH_2$ where n is 1 to 4.

10 212. The method of any one of claims 206 to 210 wherein each R^2 is, independently, C_1 - C_3 alkyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2.

213. The method of any one of claims 206 to 210 wherein each R^2 is, independently,
15 methyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is, independently, 2.

214. The method of any one of claims 206 to 210 wherein each R^2 is methyl or the free base or salt form of $-(CH_2)_n-NH_2$, where each n is 2.

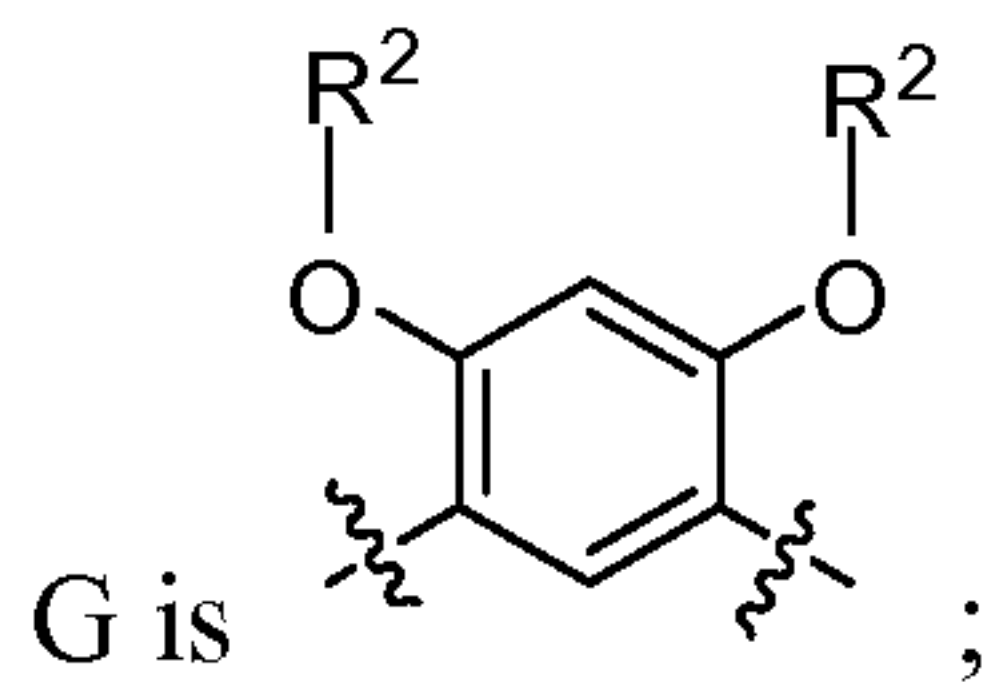
20 215. The method of any one of claims 206 to 214 wherein each R^3 is, independently, CF_3 , $C(CH_3)_3$, or halo.

216. The method of any one of claims 206 to 214 wherein each R^3 is CF_3 .

25 217. The method of any one of claims 206 to 216 wherein each R^4 is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

218. The method of any one of claims 206 to 216 wherein each R^4 is
30 $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 4.

219. The method of claim 206 wherein:



each X is S;

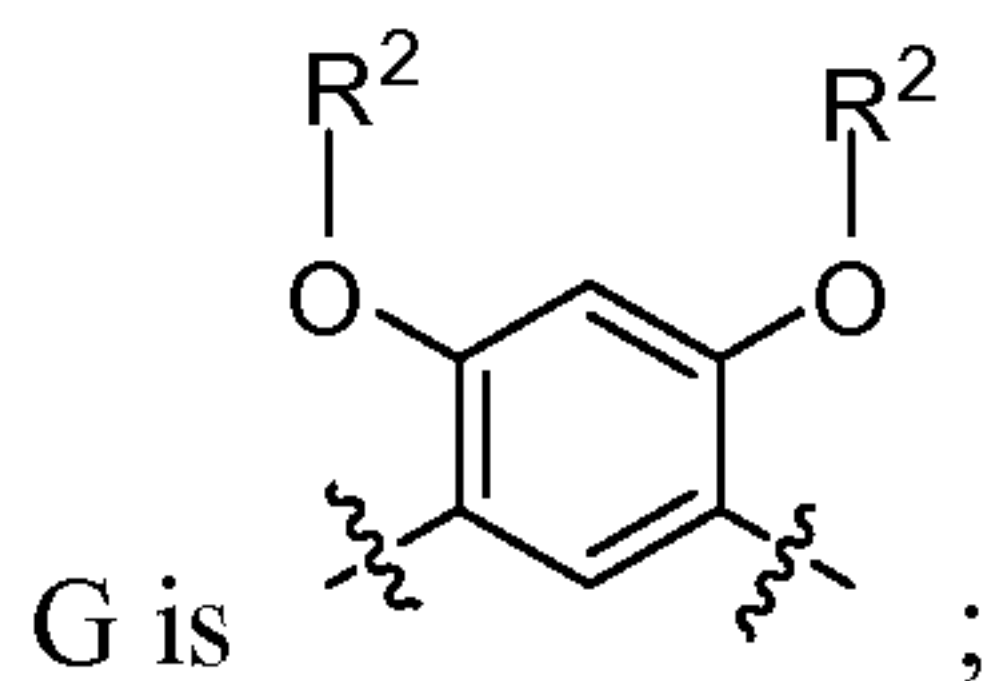
each R¹ is, independently, the free base or salt form of -(CH₂)_n-NH₂, where each n is, independently, 1 or 2;

each R² is, independently, C₁-C₈alkyl or the free base or salt form of -(CH₂)_n-NH₂, where each n is, independently, 1 or 2;

each R³ is, independently, CF₃, C(CH₃)₃, or halo; and

each R⁴ is, independently, -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 3 or 4.

220. The method of claim 206 wherein:



each X is S;

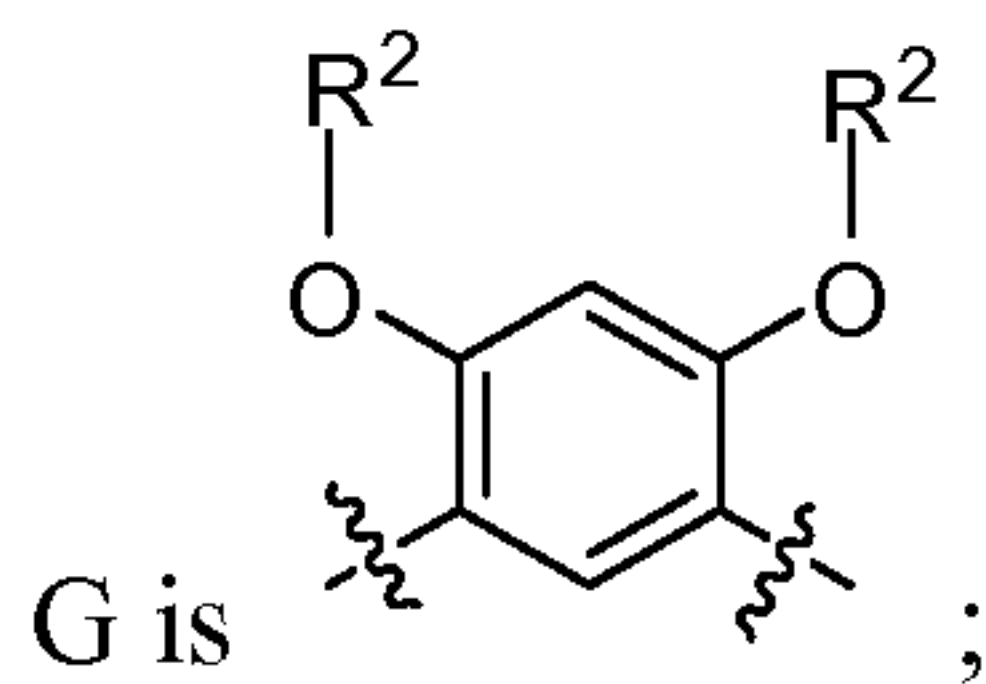
each R¹ is the free base or salt form of -(CH₂)_n-NH₂, where each n is 1 or 2;

each R² is, independently, C₁-C₃alkyl or the free base or salt form of -(CH₂)_n-NH₂, where each n is 2;

each R³ is, independently, CF₃ or C(CH₃)₃; and

each R⁴ is -(CH₂)_n-NH-C(=NH)NH₂, where each n is 3 or 4.

221. The method of claim 206 wherein:



each X is S;

each R¹ is the free base or salt form of -(CH₂)_n-NH₂, where each n is 2;

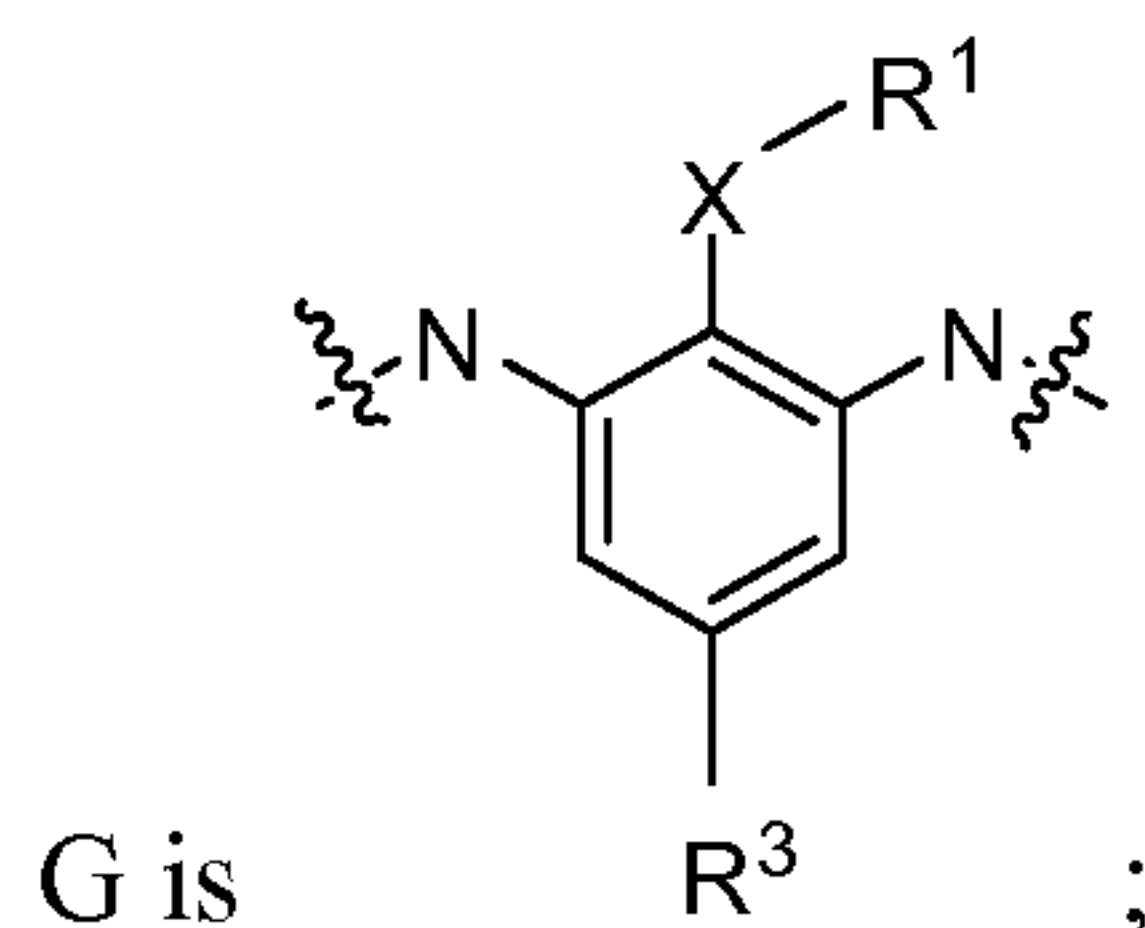
each R^2 is, independently, methyl or the free base or salt form of $-(CH_2)_n-NH_2$,
where each n is 2;

each R^3 is, independently, CF_3 or $C(CH_3)_3$; and

each R^4 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 4.

5

222. The method of claim 206 wherein:



each X is, independently, O or S ;

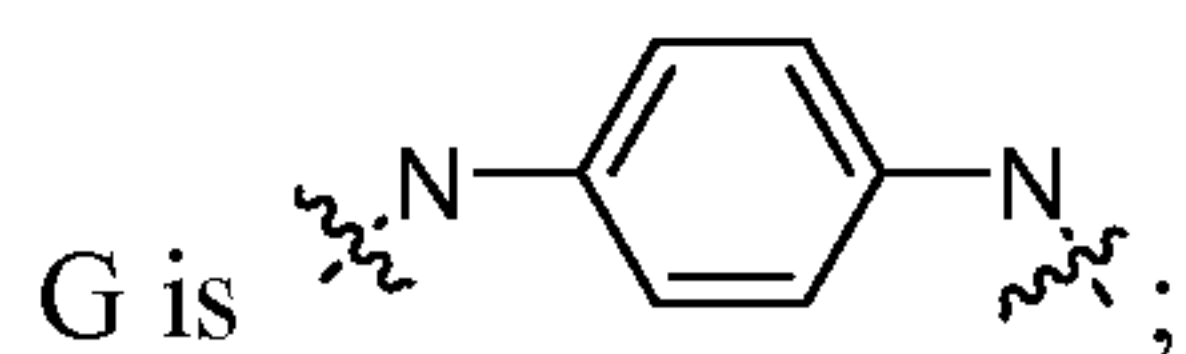
each R^1 is, independently, the free base or salt form of $-(CH_2)_n-NH_2$ or

10 $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;

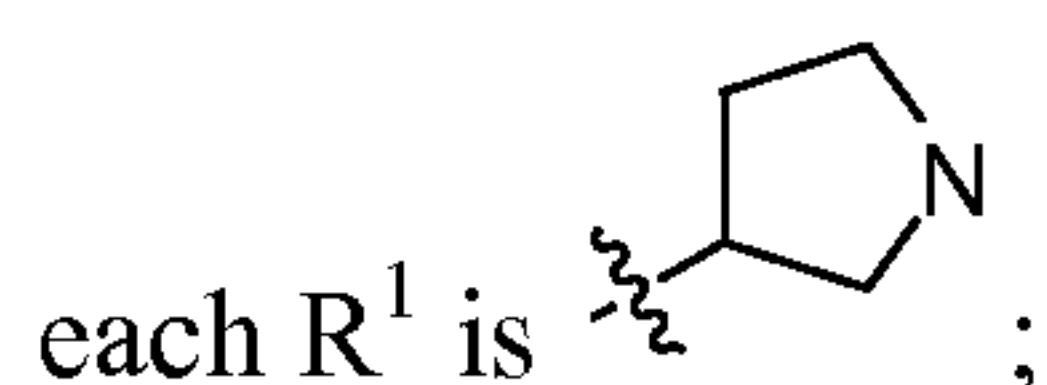
each R^3 is, independently, H or CF_3 ; and

each R^4 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n
is, independently, 1 to 4.

15 223. The method of claim 206 wherein:



each X is, independently, O or S ;

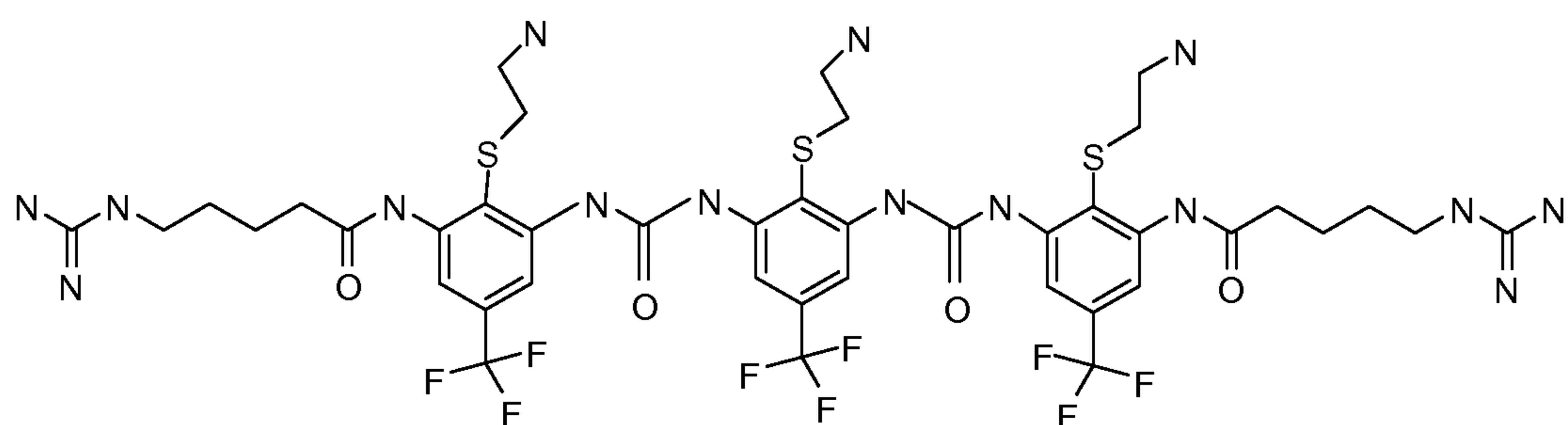
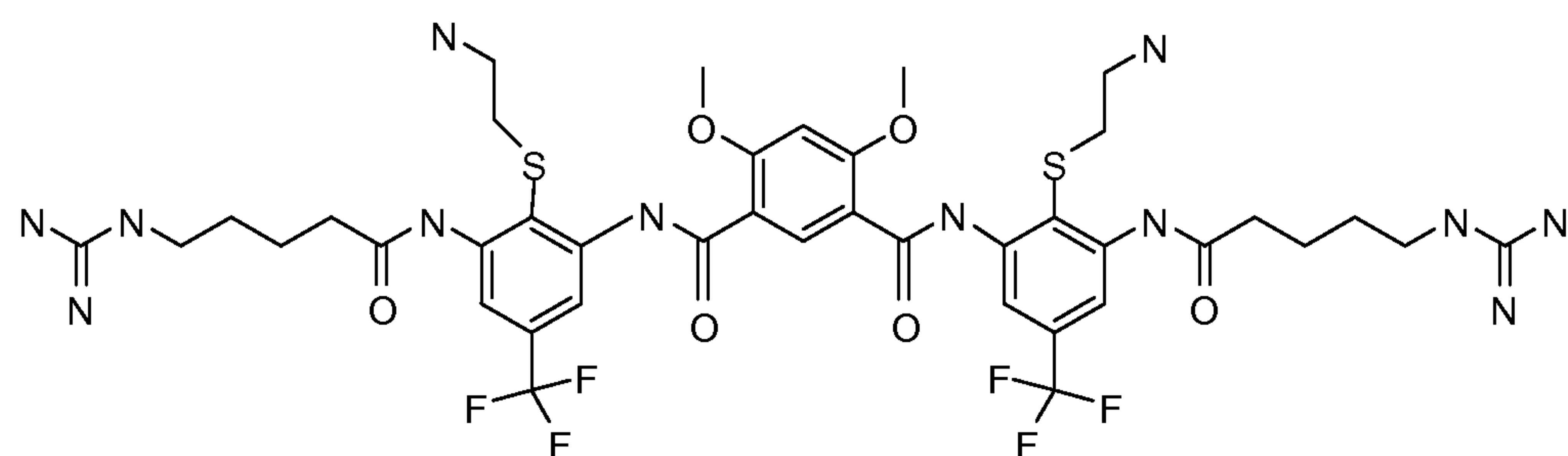
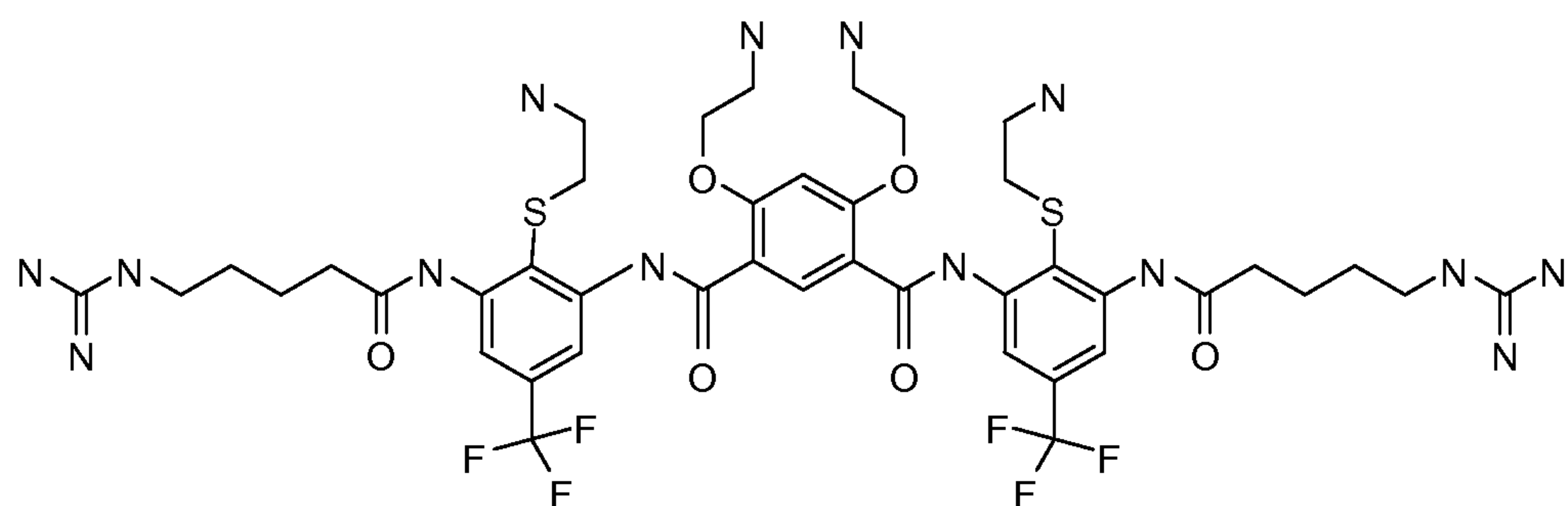


each R^3 is, independently, H or CF_3 ; and

20 each R^4 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n
is, independently, 1 to 4.

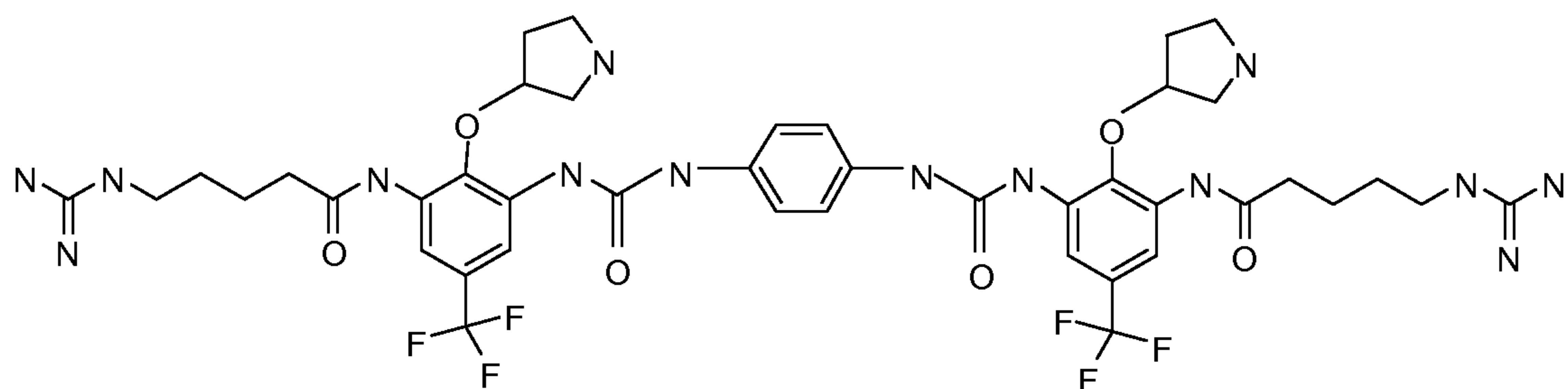
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224. The method of claim 206 wherein the compound is chosen from:



5

and

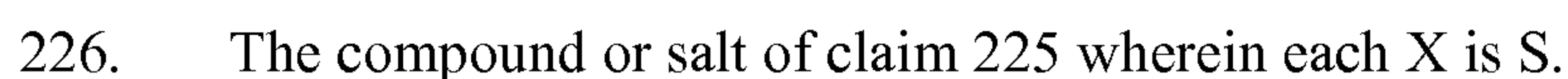


or a pharmaceutically acceptable salt thereof.

10

The chemical structure shows a central pyrimidine ring (a six-membered aromatic heterocycle with two nitrogen atoms) connected via amide bonds to two substituted benzene rings. The pyrimidine ring has nitrogen atoms at positions 1 and 3. The amide bonds are at positions 2 and 6. Each benzene ring is substituted with a group R^1 at the para position (position 4), a group R^2 at the meta position (position 3), and two groups V^1 and V^2 at the ortho positions (positions 2 and 6). The groups V^1 and V^2 are adjacent to each other on the benzene ring.

provided that the compound is not:



227. The compound or salt of claim 225 or claim 226 wherein each R^1 is, independently, $-(CH_2)_n-NH_2$, $-(CH_2)_n-NH-C(=NH)NH_2$, or $-(CH_2)_n-NH-C(=O)-R^4$, where each n is, independently, 1 or 2, and each R^4 is, independently, H or methyl.

5 228. The compound or salt of claim 225 or claim 226 wherein each R^1 is, independently, $-(CH_2)_n-NH_2$, $-(CH_2)_n-NH-C(=NH)NH_2$, or $-(CH_2)_n-NH-C(=O)-R^4$, where each n is 2 and each R^4 is H.

229. The compound or salt of claim 225 or claim 226 wherein each R^1 is, independently,
10 $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 2.

230. The compound or salt of claim 225 or claim 226 wherein each R^1 is $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 2.

15 231. The compound or salt of any one of claims 225 to 230 wherein each R^2 is, independently, H, Br, F, Cl, CF_3 , or $C(CH_3)_3$.

232. The compound or salt of any one of claims 225 to 230 wherein each R^2 is Br, F, Cl, CF_3 , or $C(CH_3)_3$.

20

233. The compound or salt of any one of claims 225 to 232 wherein each V^2 is H and each V^1 is, independently, $-N-C(=O)-R^3$, where each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

25 234. The compound or salt of any one of claims 225 to 232 wherein each V^2 is H and each V^1 is, independently, $-N-C(=O)-R^3$, where each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 or 2.

235. The compound or salt of any one of claims 225 to 232 wherein each V^2 is H and
30 each V^1 is, independently, $-N-C(=O)-R^3$, where each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 2.

236. The compound or salt of any one of claims 225 to 232 wherein each V^2 is H and each V^1 is $-N-C(=O)-R^3$, where each R^3 is $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where n is 2.

5 237. The compound or salt of any one of claims 225 to 232 wherein each V^1 is H and each V^2 is, independently, $-S-R^5$, where each R^5 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

238. The compound or salt of any one of claims 225 to 232 wherein each V^1 is H and
10 each V^2 is, independently, $-S-R^5$, where each R^5 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 or 2.

239. The compound or salt of any one of claims 225 to 232 wherein each V^1 is H and each V^2 is, independently, $-S-R^5$, where each R^5 is, independently, $-(CH_2)_n-NH_2$ or
15 $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 2.

240. The compound or salt of any one of claims 225 to 232 wherein each V^1 is H and each V^2 is $-S-R^5$, where each R^5 is $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 2.

20

241. The compound or salt of claim 225 wherein:
each X is S;
each R^1 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;
25 each R^2 is, independently, halo, CF_3 , or $C(CH_3)_3$; and
each V^1 is H and each V^2 is, independently, $-S-R^5$, where each R^5 is, independently, $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4.

242. The compound or salt of claim 225 wherein:
30 each X is S;
each R^1 is, independently, $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2;
each R^2 is, independently, CF_3 or $C(CH_3)_3$; and

each V^1 is H and each V^2 is, independently, $-S-R^5$, where each R^5 is, independently, $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2.

243. The compound or salt of claim 225 wherein:

5 each X is S;

each R^1 is $-(CH_2)_n-NH_2$, where each n is 1 or 2;

each R^2 is, independently, CF_3 or $C(CH_3)_3$; and

each V^1 is H and each V^2 is $-S-R^5$, where each R^5 is $-(CH_2)_n-NH_2$, where each n is 1 or 2.

10

244. The compound or salt of claim 225 wherein:

each X is O or S;

each R^1 is, independently, $-(CH_2)_n-NH_2$, $-(CH_2)_n-NH-C(=NH)NH_2$, or $-(CH_2)_n-NH-C(=O)-R^4$, where each n is, independently, 1 to 4, and each R^4 is, independently, H or methyl;

15 each R^2 is, independently, halo, CF_3 , or $C(CH_3)_3$; and

each V^2 is H, and each V^1 is, independently, $-N-C(=O)-R^3$, where each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

20 245. The compound or salt of claim 225 wherein:

each X is S;

each R^1 is, independently, $-(CH_2)_n-NH-C(=O)-R^4$, where each n is, independently, 1 or 2, and each R^4 is, independently, H or methyl;

each R^2 is, independently, halo; and

25 each V^2 is H, and each V^1 is $-N-C(=O)-R^3$, where each R^3 is $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 4.

246. The compound or salt of claim 225 wherein:

each X is O or S;

30 each R^1 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;

each R^2 is, independently, halo, CF_3 , or $C(CH_3)_3$; and

each V^2 is H, and each V^1 is, independently, $-N-C(=O)-R^3$, where each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

5 247. The compound or salt of claim 225 wherein:

each X is O or S;

each R^1 is $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 or 2;

each R^2 is halo, CF_3 , or $C(CH_3)_3$; and

each V^2 is H, and each V^1 is $-N-C(=O)-R^3$, where each R^3 is $-(CH_2)_n-NH_2$ or
10 $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 3 or 4.

248. The compound or salt of claim 225 wherein:

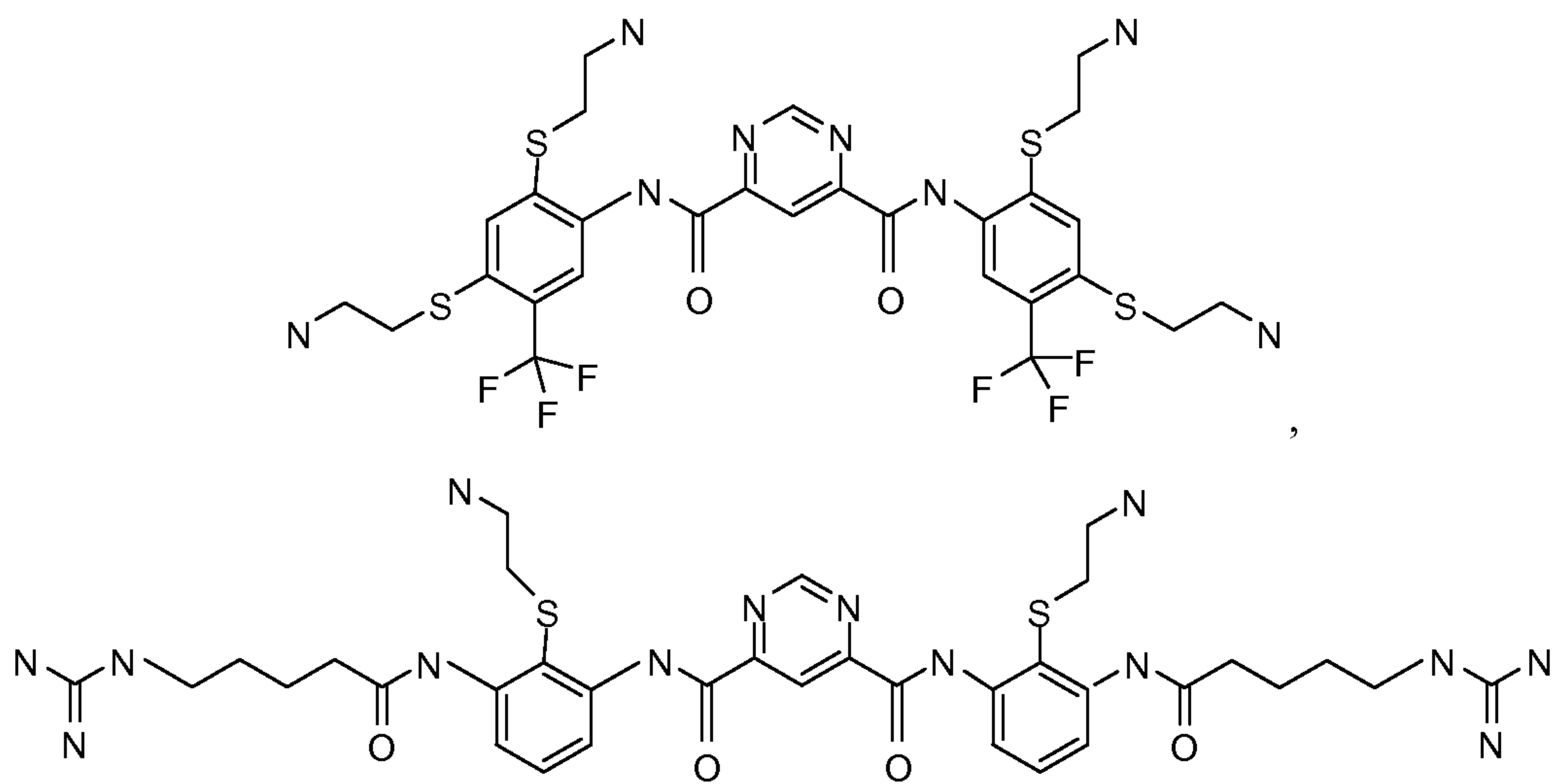
each X is, independently, S or $S(=O)_2$;

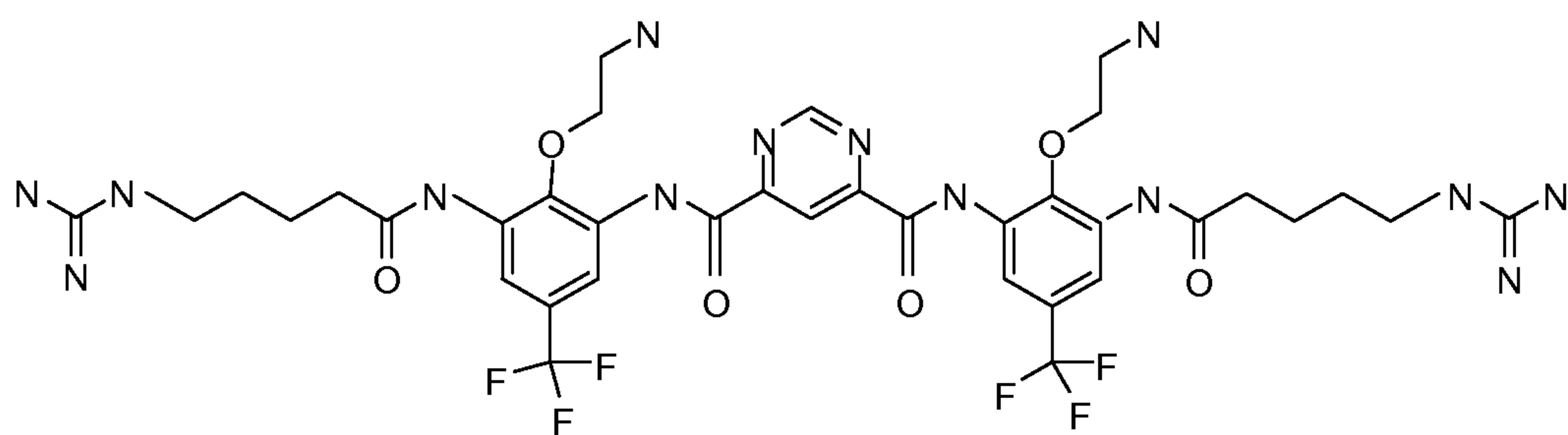
each R^1 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=O)-R^4$, where each n is,
15 independently, 1 or 2, and each R^4 is, independently, $-(CH_2)_p-NH_2$, where each p is,
independently, 1 or 2;

each R^2 is, independently, halo or CF_3 ; and

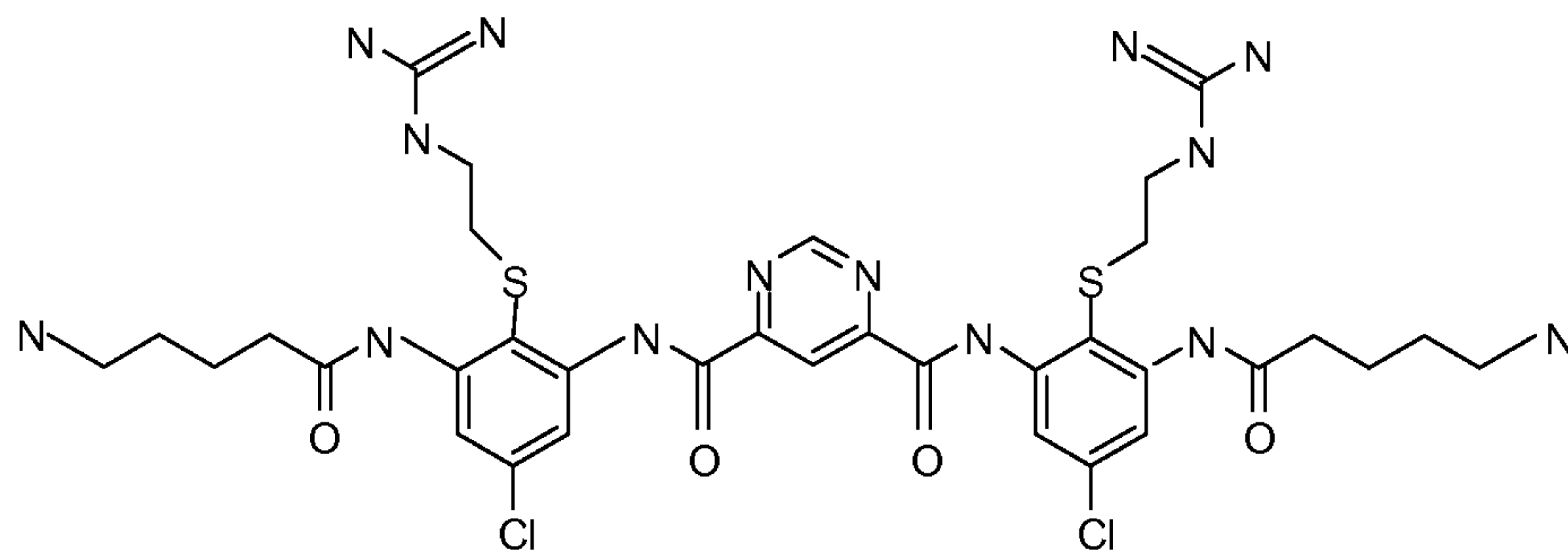
each V^2 is H, and each V^1 is, independently, $-N-C(=O)-R^3$, where each R^3 is,
independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 3
20 or 4.

249. A compound chosen from:

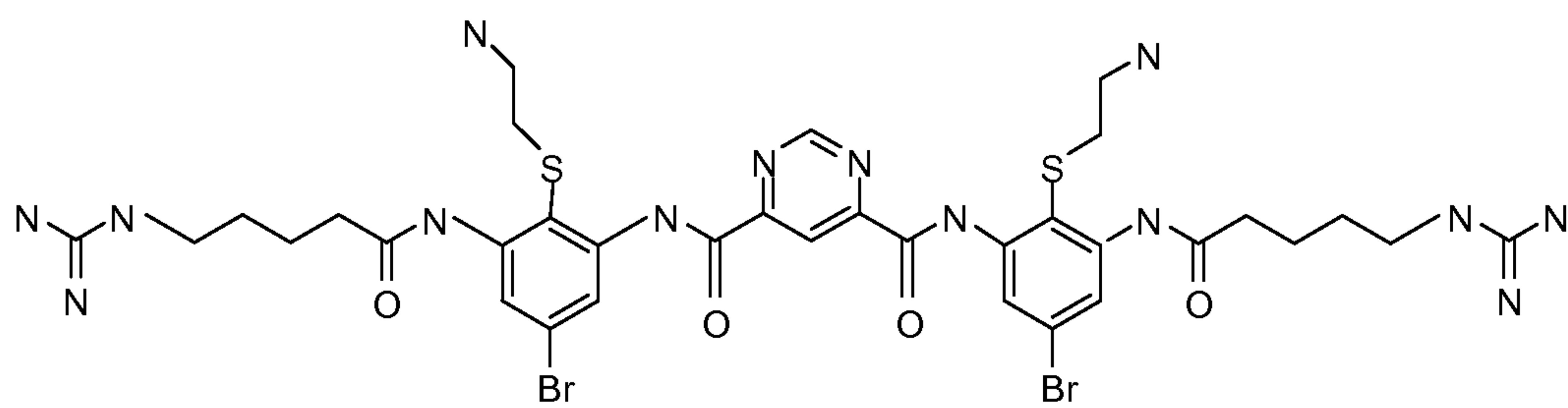




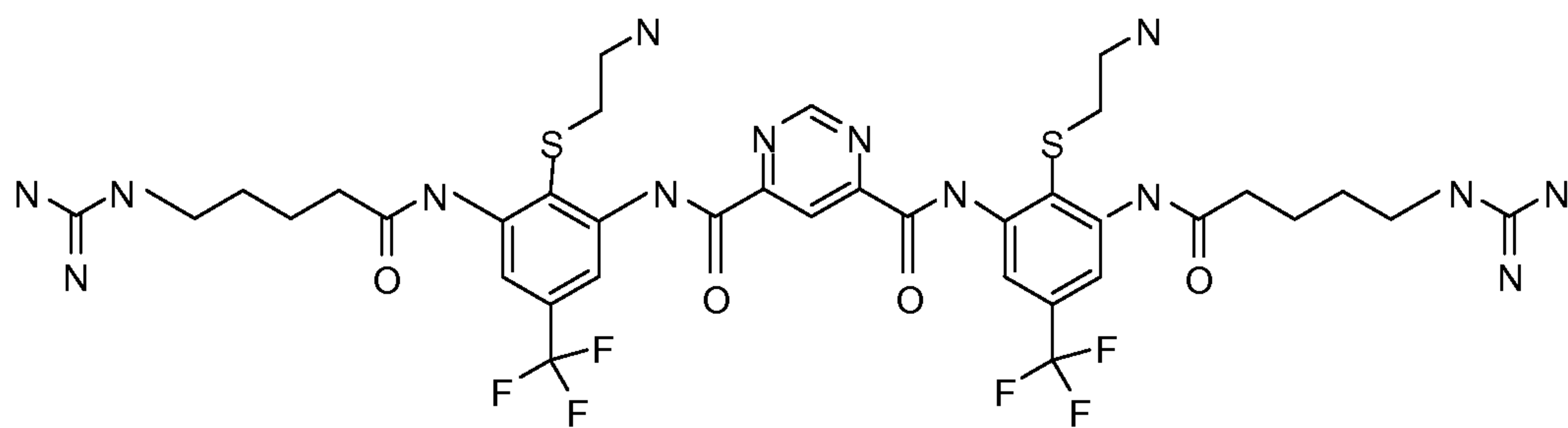
,



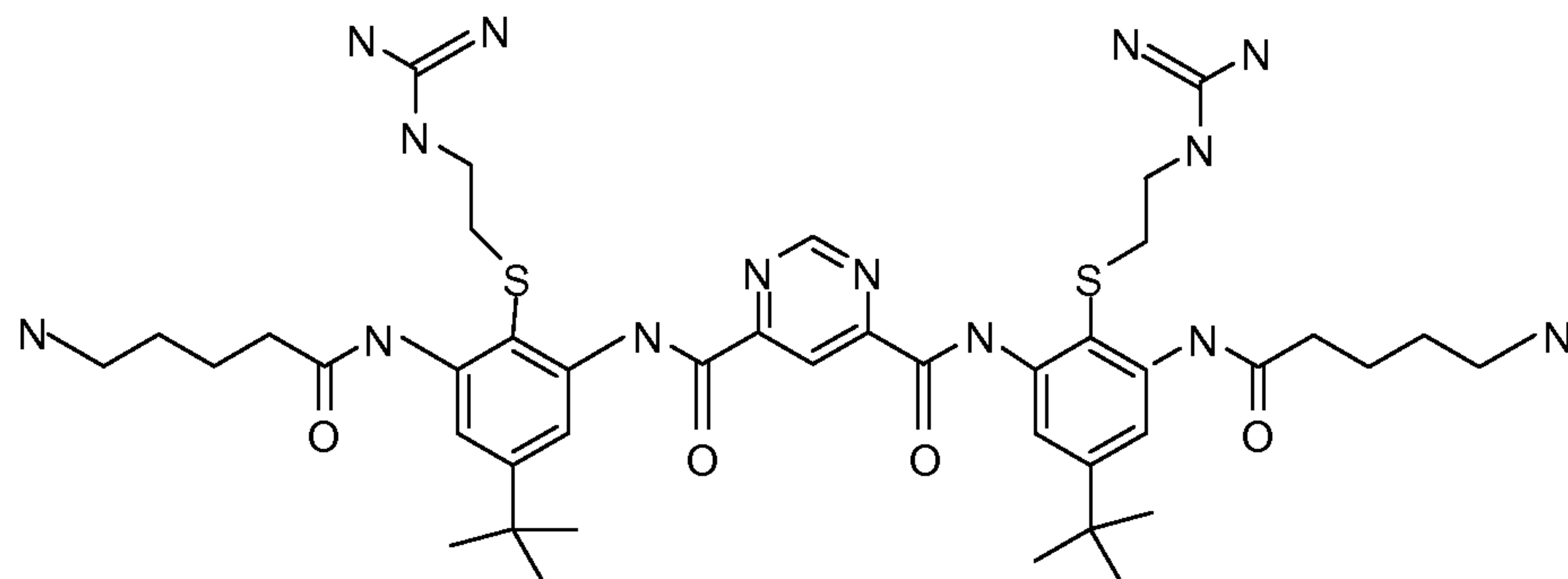
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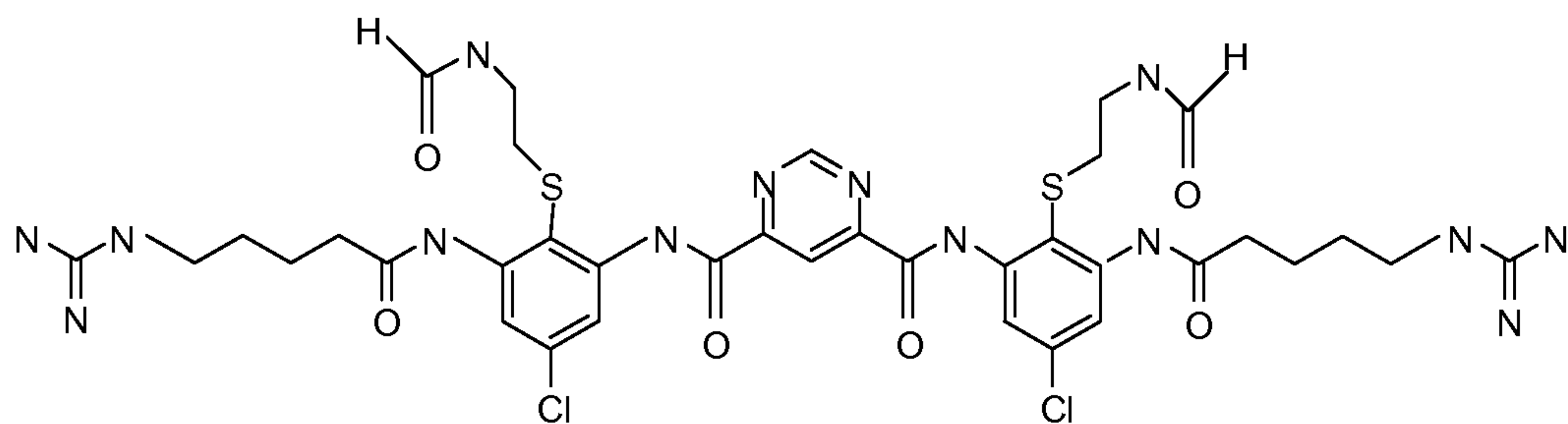
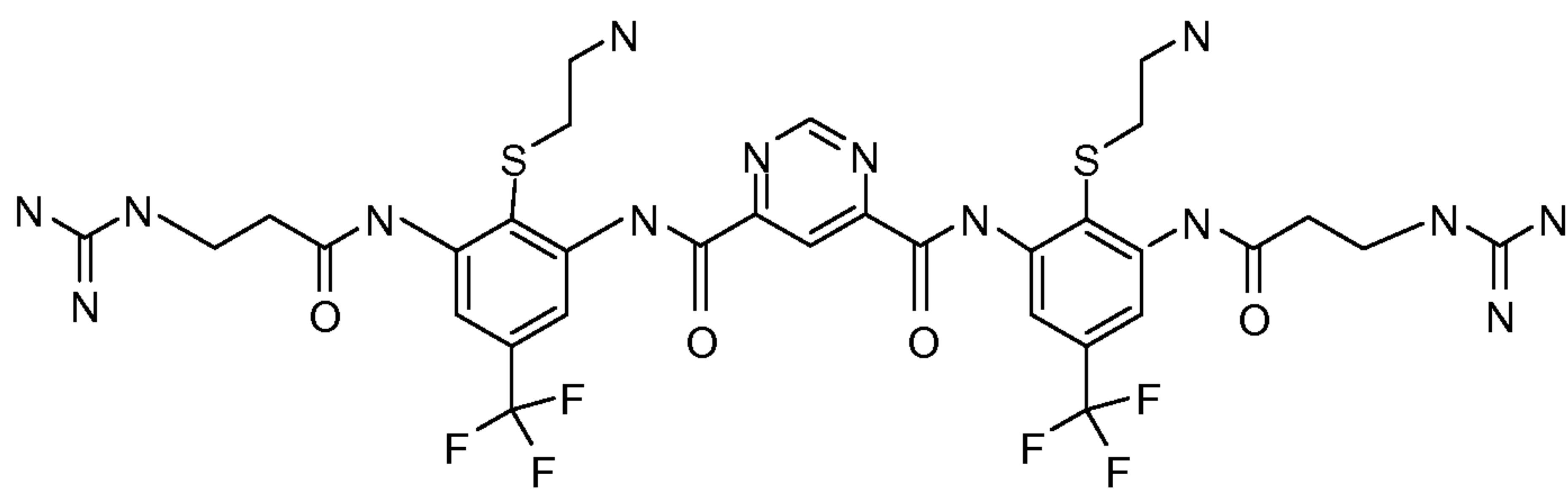
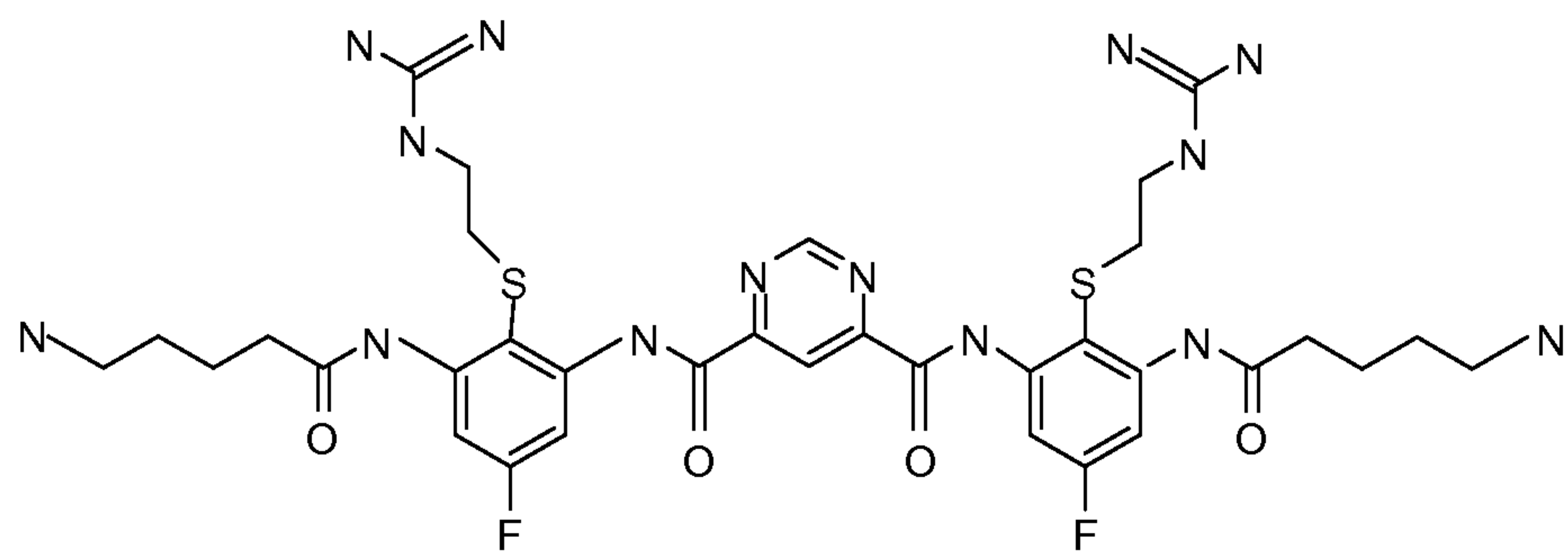
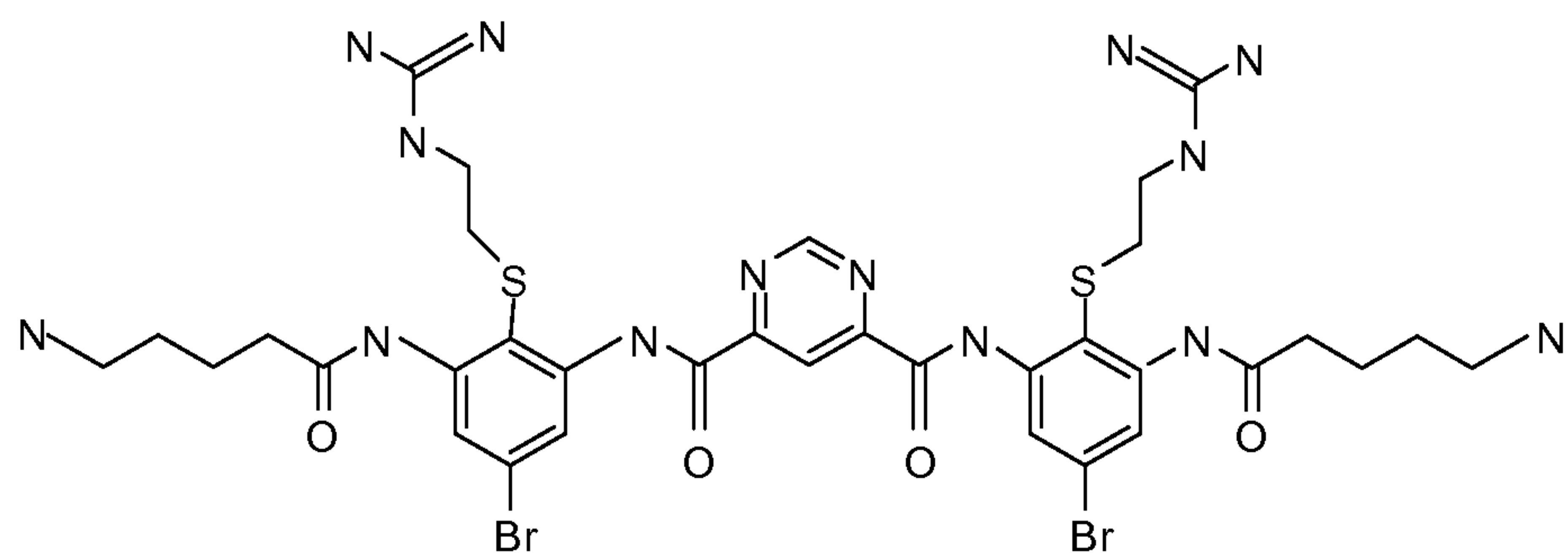
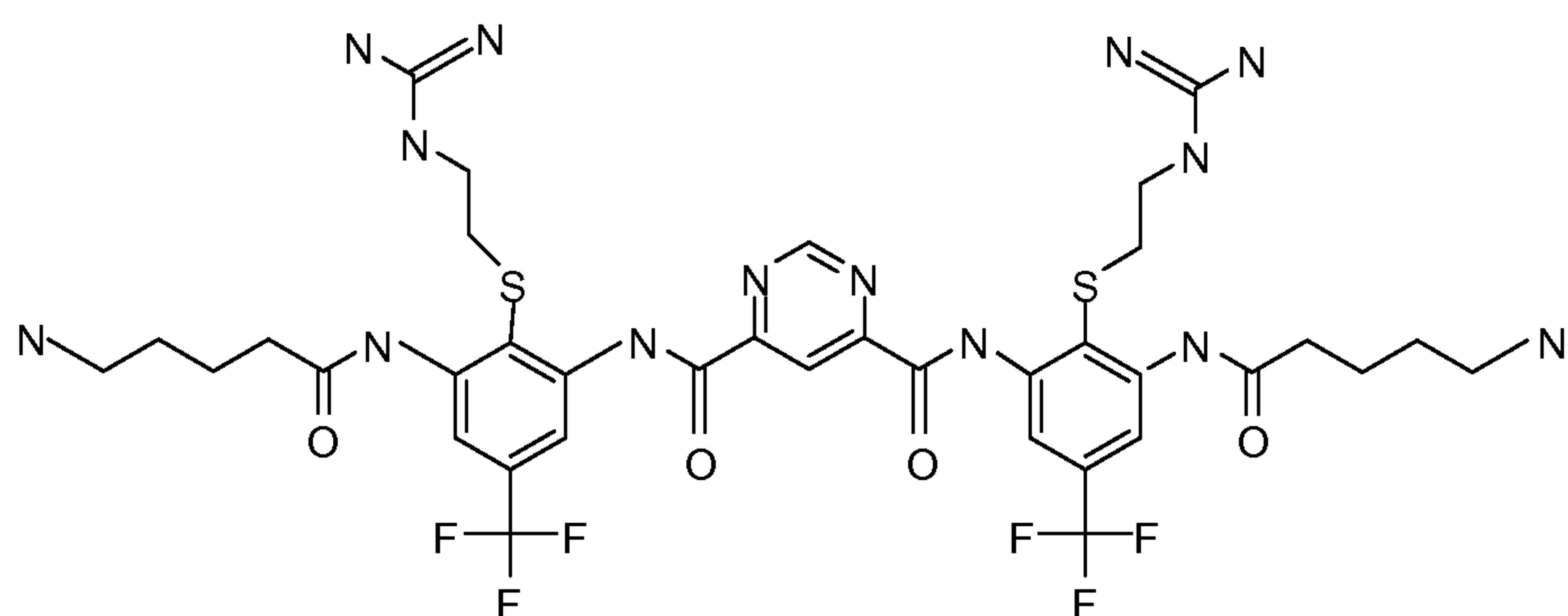
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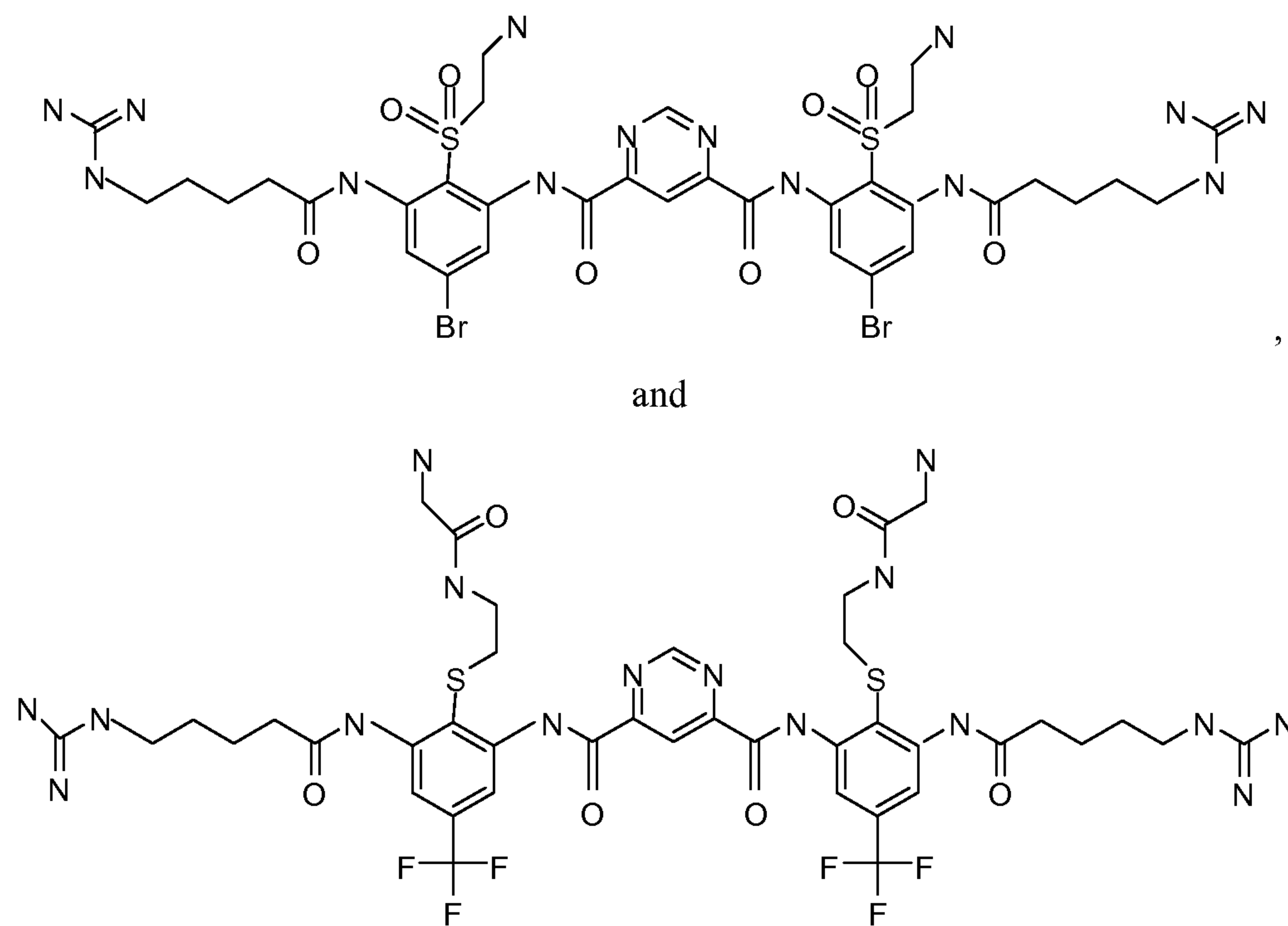


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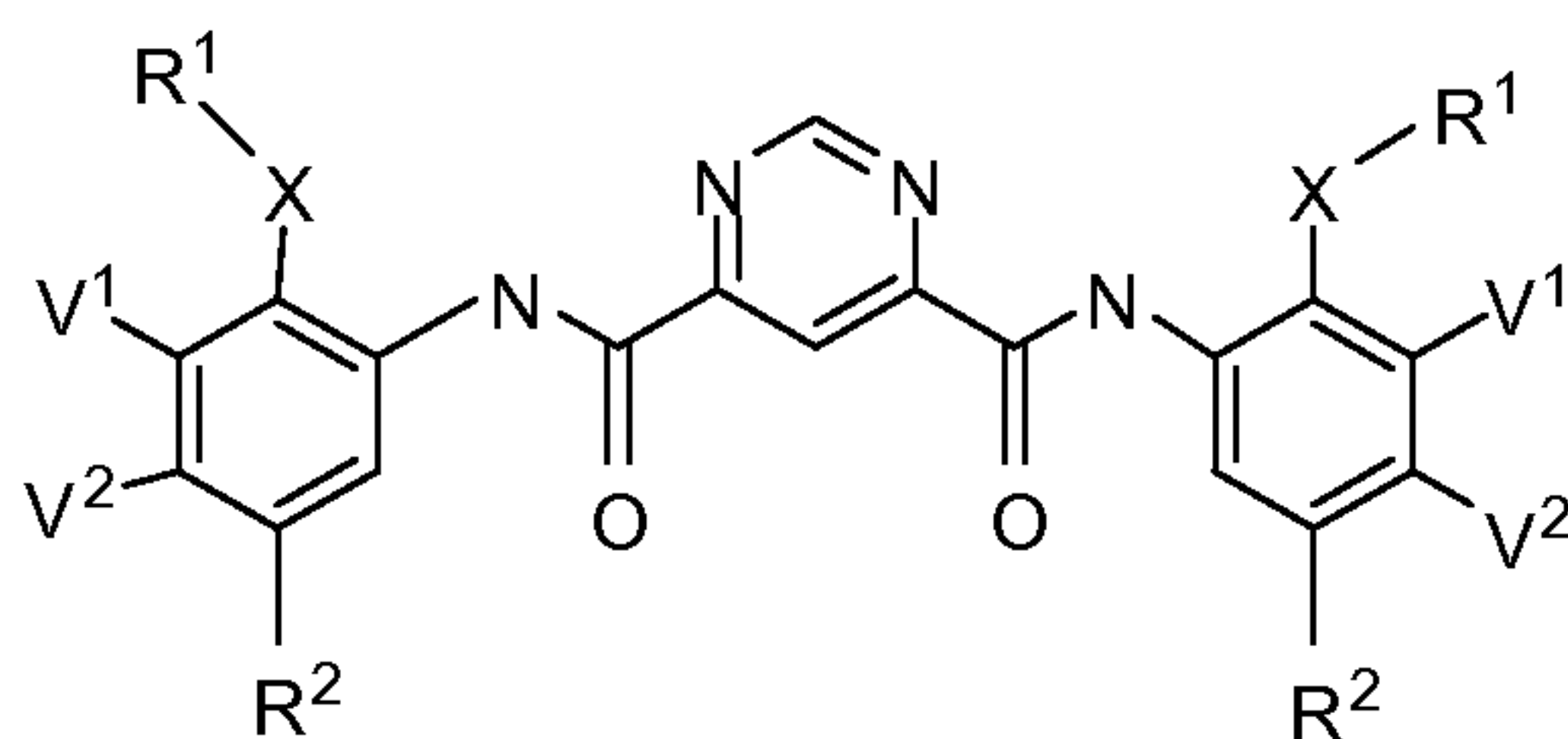


or a pharmaceutically acceptable salt thereof.

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250. A composition comprising the compound or salt of any one of claims 225 to 249 and a pharmaceutically acceptable carrier.

251. A method of treating malaria in an animal comprising administering to the animal a therapeutically effective amount of a compound of Formula V:



wherein:

each X is, independently, O, S, or S(=O)₂;

each R¹ is, independently, -(CH₂)_n-NH₂, -(CH₂)_n-NH-C(=NH)NH₂, or
 15 -(CH₂)_n-NH-C(=O)-R⁴, where each n is, independently, 1 to 4, and each R⁴ is, independently,
 H, C₁-C₃alkyl, or -(CH₂)_p-NH₂, where each p is, independently, 1 or 2;
 each R² is, independently, H, halo, CF₃, or C(CH₃)₃; and

each V^2 is H, and each V^1 is, independently, $-N-C(=O)-R^3$, where each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4; or each V^1 is H and each V^2 is, independently, $-S-R^5$, where each R^5 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;
 5 or a pharmaceutically acceptable salt thereof.

252. The method of claim 251 wherein each X is S.

253. The method of claim 251 or claim 252 wherein each R^1 is, independently, $-(CH_2)_n-NH_2$, $-(CH_2)_n-NH-C(=NH)NH_2$, or $-(CH_2)_n-NH-C(=O)-R^4$, where each n is,
 10 independently, 1 or 2, and each R^4 is, independently, H or methyl.

254. The method of claim 251 or claim 252 wherein each R^1 is, independently, $-(CH_2)_n-NH_2$, $-(CH_2)_n-NH-C(=NH)NH_2$, or $-(CH_2)_n-NH-C(=O)-R^4$, where each n is 2 and each R^4 is H.

15

255. The method of claim 251 or claim 252 wherein each R^1 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 2.

256. The method of claim 251 or claim 252 wherein each R^1 is $-(CH_2)_n-NH_2$ or
 20 $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 2.

257. The method of any one of claims 251 to 256 wherein each R^2 is, independently, H, Br, F, Cl, CF_3 , or $C(CH_3)_3$.

25 258. The method of any one of claims 251 to 256 wherein each R^2 is Br, F, Cl, CF_3 , or $C(CH_3)_3$.

259. The method of any one of claims 251 to 258 wherein each V^2 is H and each V^1 is, independently, $-N-C(=O)-R^3$, where each R^3 is, independently, $-(CH_2)_n-NH_2$ or
 30 $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

260. The method of any one of claims 251 to 258 wherein each V^2 is H and each V^1 is, independently, $-N-C(=O)-R^3$, where each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 or 2.

5 261. The method of any one of claims 251 to 258 wherein each V^2 is H and each V^1 is, independently, $-N-C(=O)-R^3$, where each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 2.

262. The method of any one of claims 251 to 258 wherein each V^2 is H and each V^1 is
10 $-N-C(=O)-R^3$, where each R^3 is $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where n is 2.

263. The method of any one of claims 251 to 258 wherein each V^1 is H and each V^2 is, independently, $-S-R^5$, where each R^5 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

15

264. The method of any one of claims 251 to 258 wherein each V^1 is H and each V^2 is, independently, $-S-R^5$, where each R^5 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 or 2.

20 265. The method of any one of claims 251 to 258 wherein each V^1 is H and each V^2 is, independently, $-S-R^5$, where each R^5 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 2.

266. The method of any one of claims 251 to 258 wherein each V^1 is H and each V^2 is
25 $-S-R^5$, where each R^5 is $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 2.

267. The method of claim 251 wherein:

each X is S;

each R^1 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n
30 is, independently, 1 to 4;

each R^2 is, independently, halo, CF_3 , or $C(CH_3)_3$; and

each V^1 is H and each V^2 is, independently, $-S-R^5$, where each R^5 is, independently, $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4.

268. The method of claim 251 wherein:

- 5 each X is S;
 each R^1 is, independently, $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2;
 each R^2 is, independently, CF_3 or $C(CH_3)_3$; and
 each V^1 is H and each V^2 is, independently, $-S-R^5$, where each R^5 is, independently,
 $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2.

10

269. The method of claim 251 wherein:

- each X is S;
 each R^1 is $-(CH_2)_n-NH_2$, where each n is 1 or 2;
 each R^2 is, independently, CF_3 or $C(CH_3)_3$; and
 15 each V^1 is H and each V^2 is $-S-R^5$, where each R^5 is $-(CH_2)_n-NH_2$, where each n is 1
 or 2.

270. The method of claim 251 wherein:

- each X is O or S;
 20 each R^1 is, independently, $-(CH_2)_n-NH_2$, $-(CH_2)_n-NH-C(=NH)NH_2$, or
 $-(CH_2)_n-NH-C(=O)-R^4$, where each n is, independently, 1 to 4, and each R^4 is, independently,
 H or methyl;
 each R^2 is, independently, halo, CF_3 , or $C(CH_3)_3$; and
 each V^2 is H, and each V^1 is, independently, $-N-C(=O)-R^3$, where each R^3 is,
 25 independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1
 to 4.

271. The method of claim 251 wherein:

- each X is S;
 30 each R^1 is, independently, $-(CH_2)_n-NH-C(=O)-R^4$, where each n is, independently, 1
 or 2, and each R^4 is, independently, H or methyl;
 each R^2 is, independently, halo; and

each V^2 is H, and each V^1 is $-N-C(=O)-R^3$, where each R^3 is $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 4.

272. The method of claim 251 wherein:

5 each X is O or S;

each R^1 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;

each R^2 is, independently, halo, CF_3 , or $C(CH_3)_3$; and

10 each V^2 is H, and each V^1 is, independently, $-N-C(=O)-R^3$, where each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

273. The method of claim 251 wherein:

each X is O or S;

15 each R^1 is $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 or 2;

each R^2 is halo, CF_3 , or $C(CH_3)_3$; and

each V^2 is H, and each V^1 is $-N-C(=O)-R^3$, where each R^3 is $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 3 or 4.

20 274. The method of claim 251 wherein:

each X is, independently, S or $S(=O)_2$;

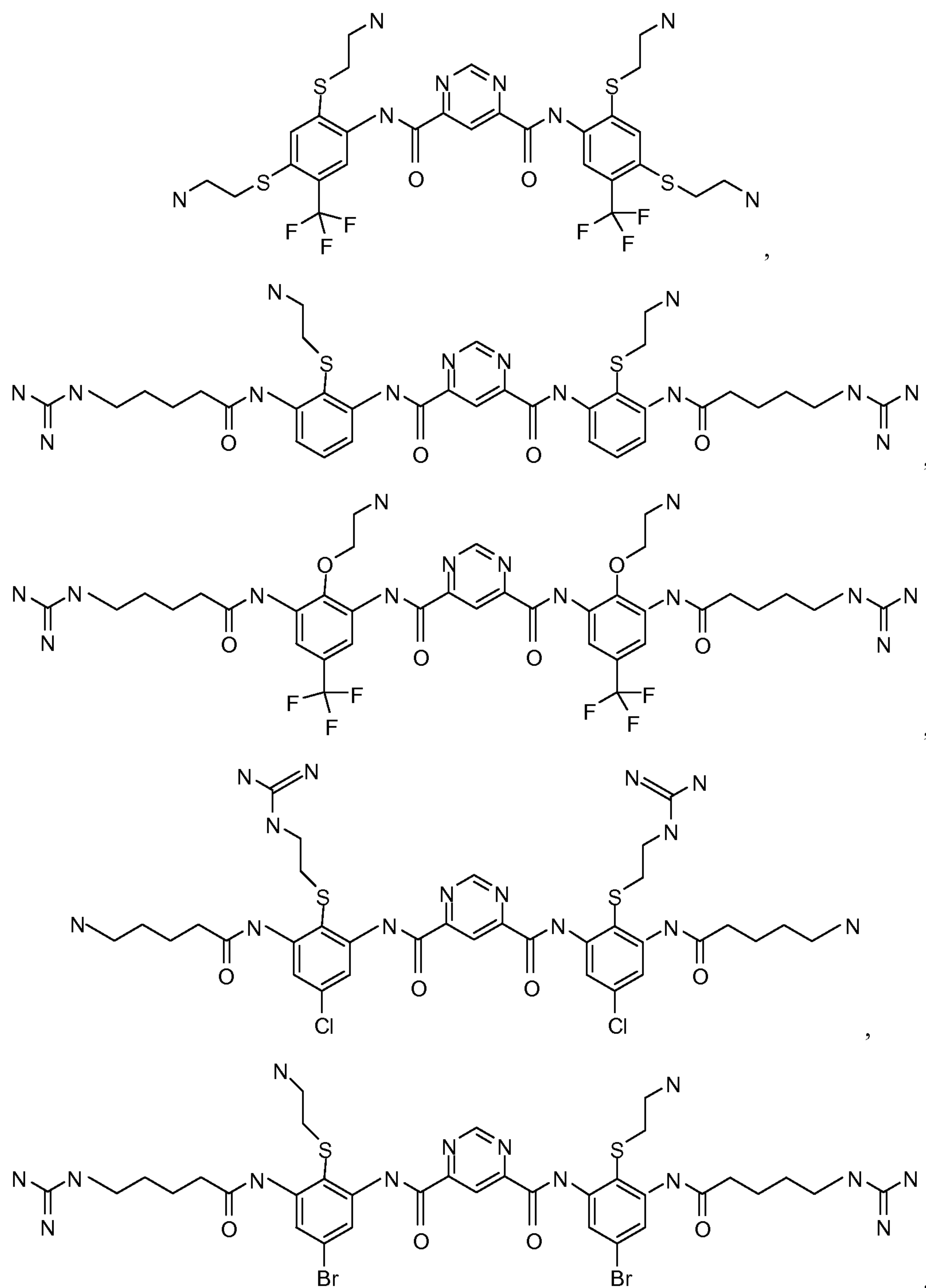
each R^1 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=O)-R^4$, where each n is, independently, 1 or 2, and each R^4 is, independently, $-(CH_2)_p-NH_2$, where each p is, independently, 1 or 2;

25 each R^2 is, independently, halo or CF_3 ; and

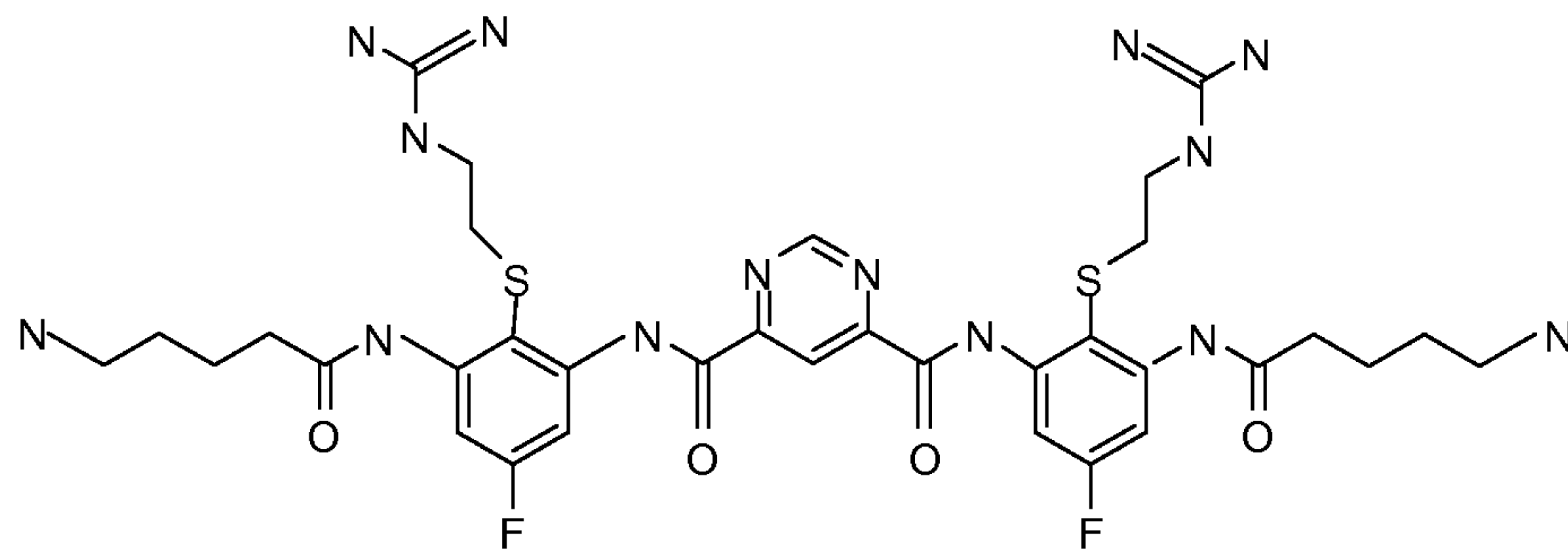
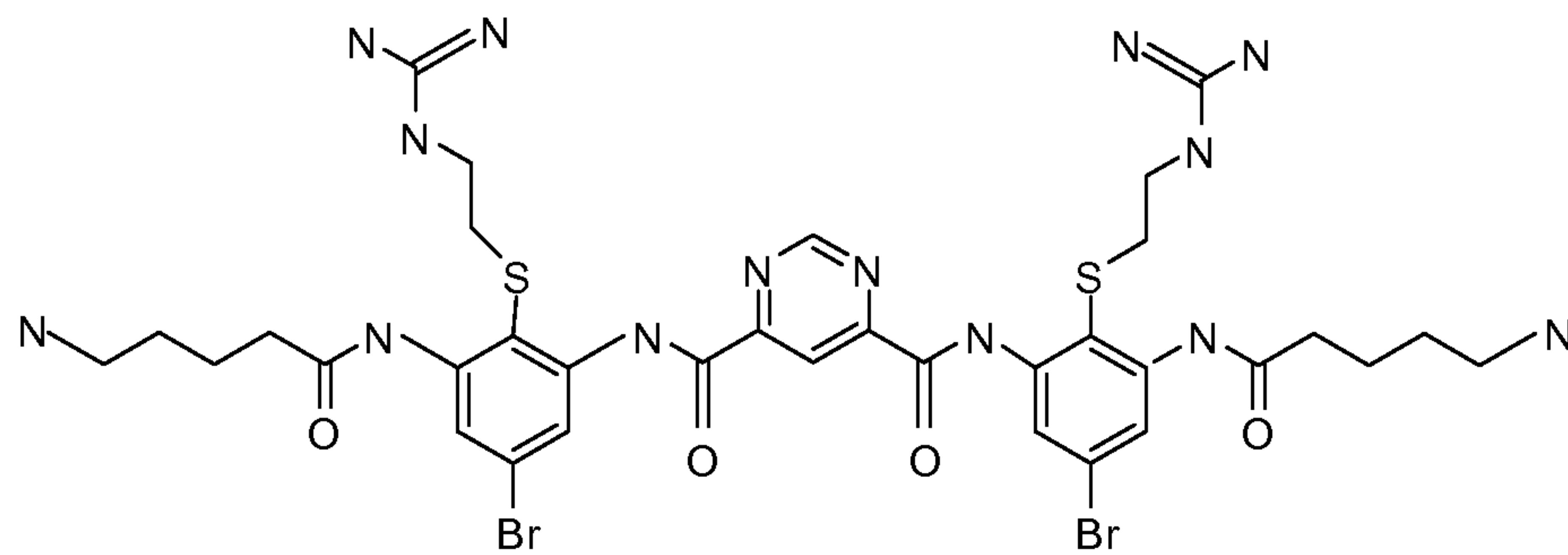
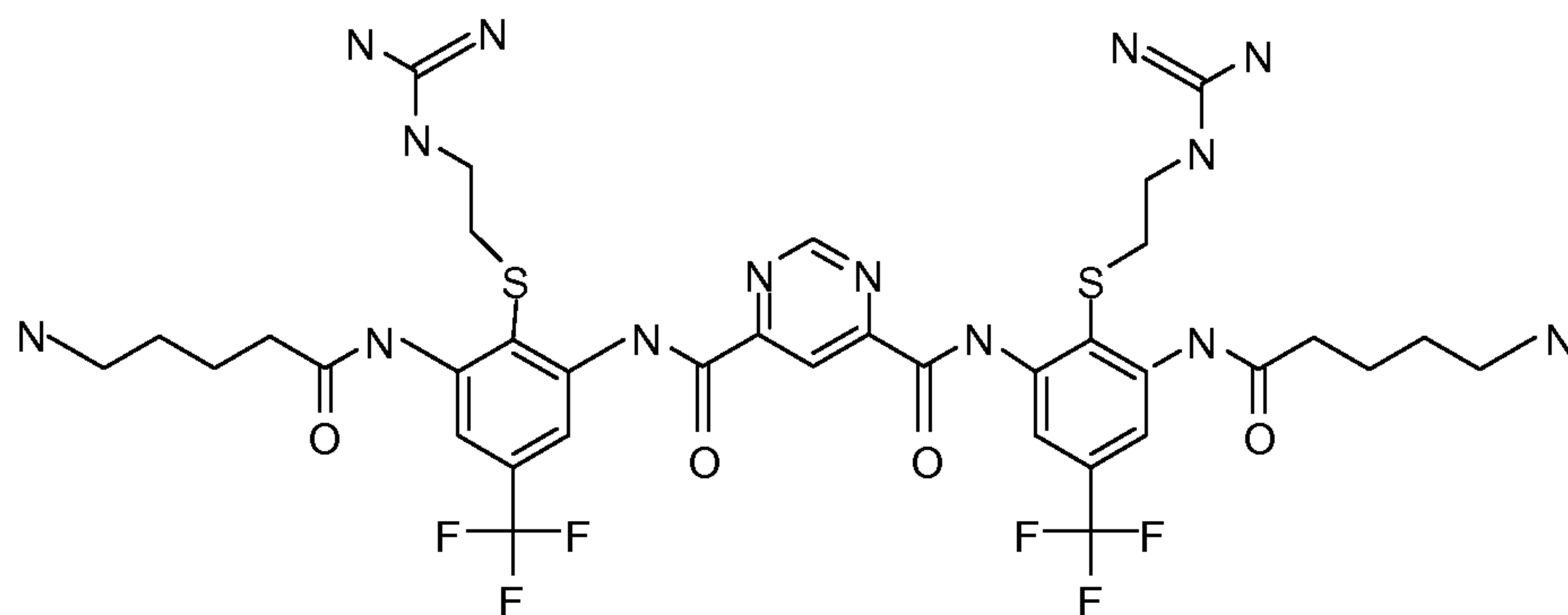
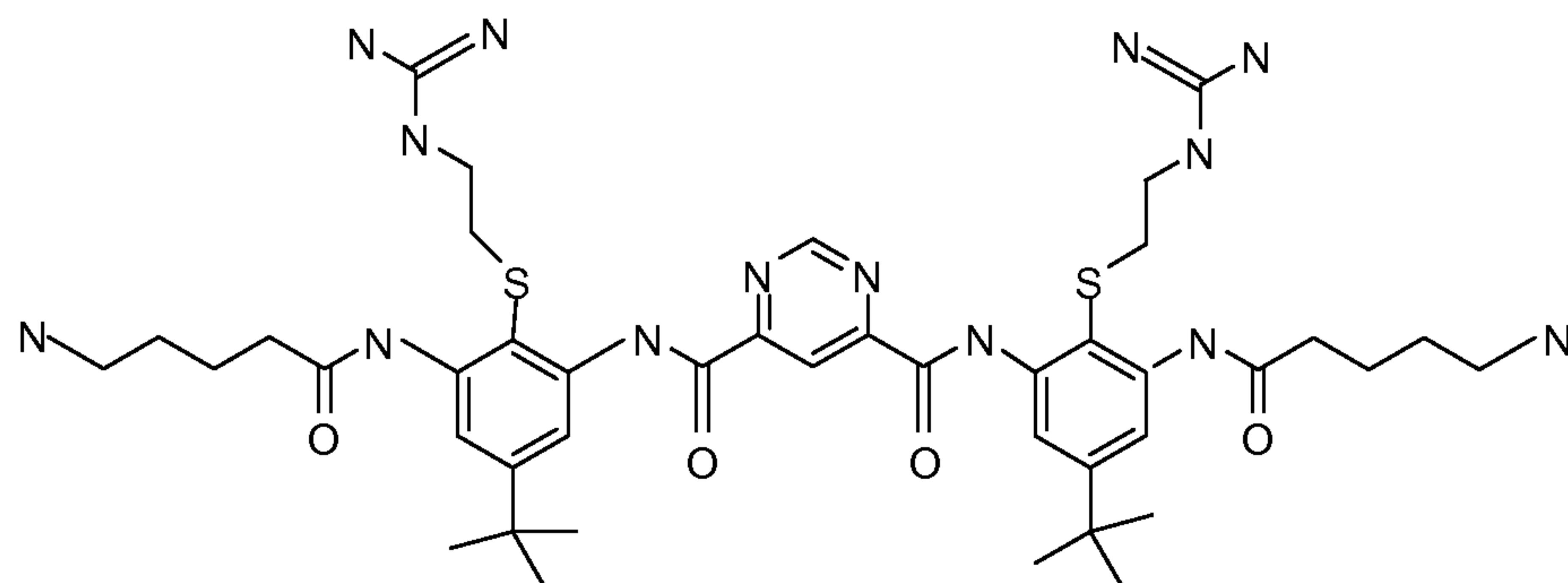
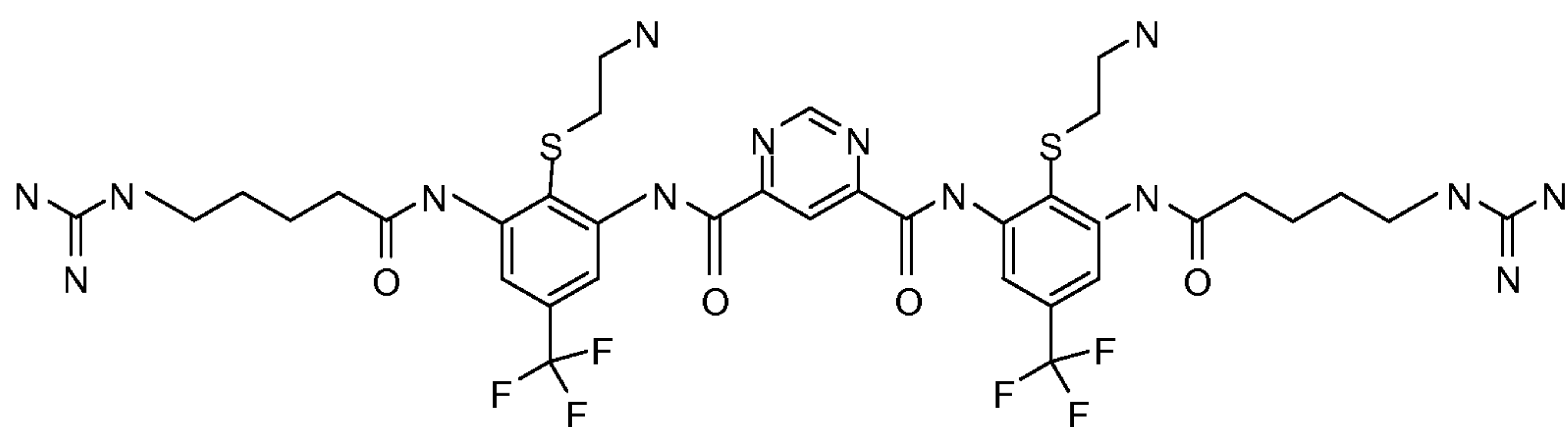
each V^2 is H, and each V^1 is, independently, $-N-C(=O)-R^3$, where each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 3 or 4.

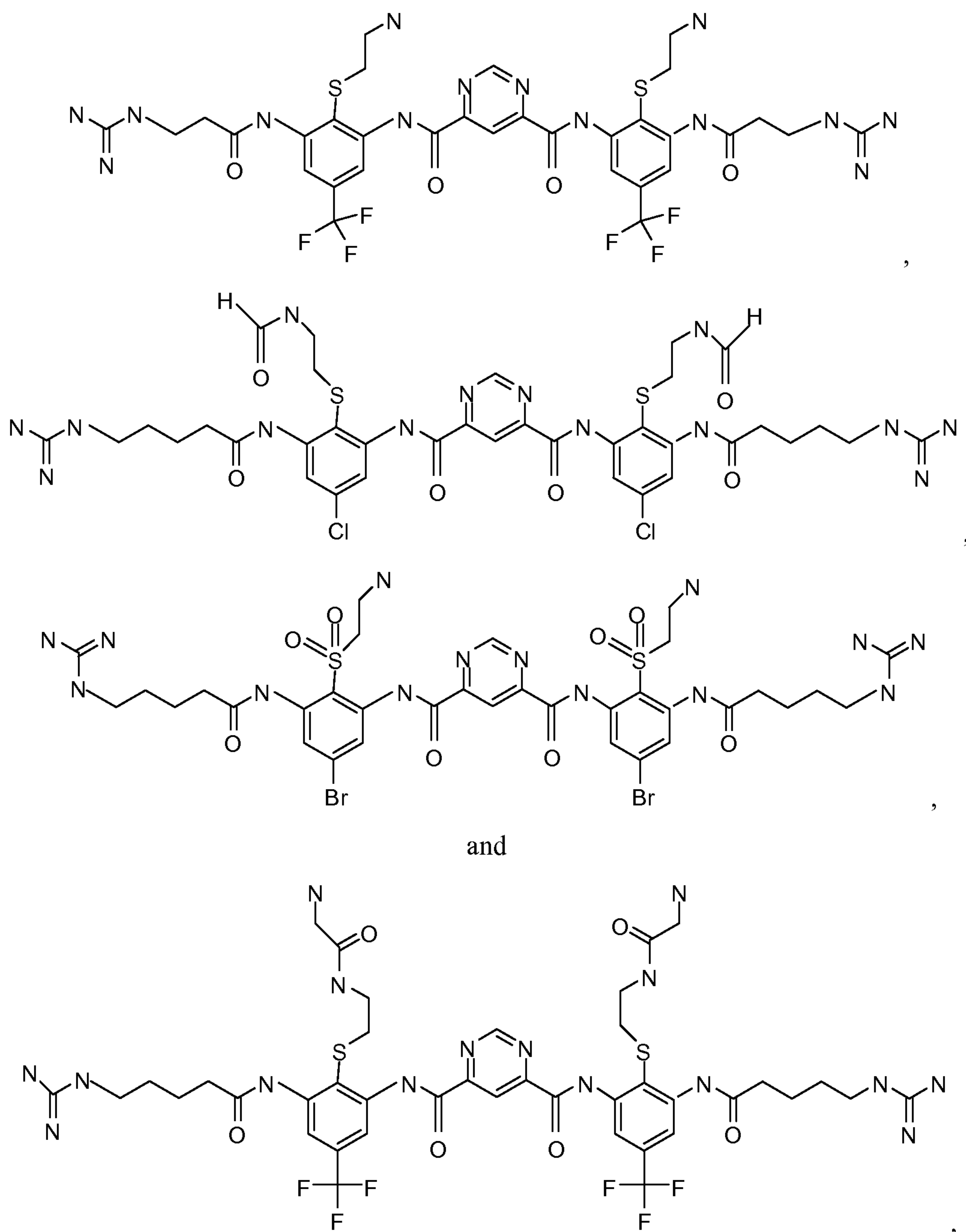
30

275. The method of claim 251 wherein the compound is chosen from:



5

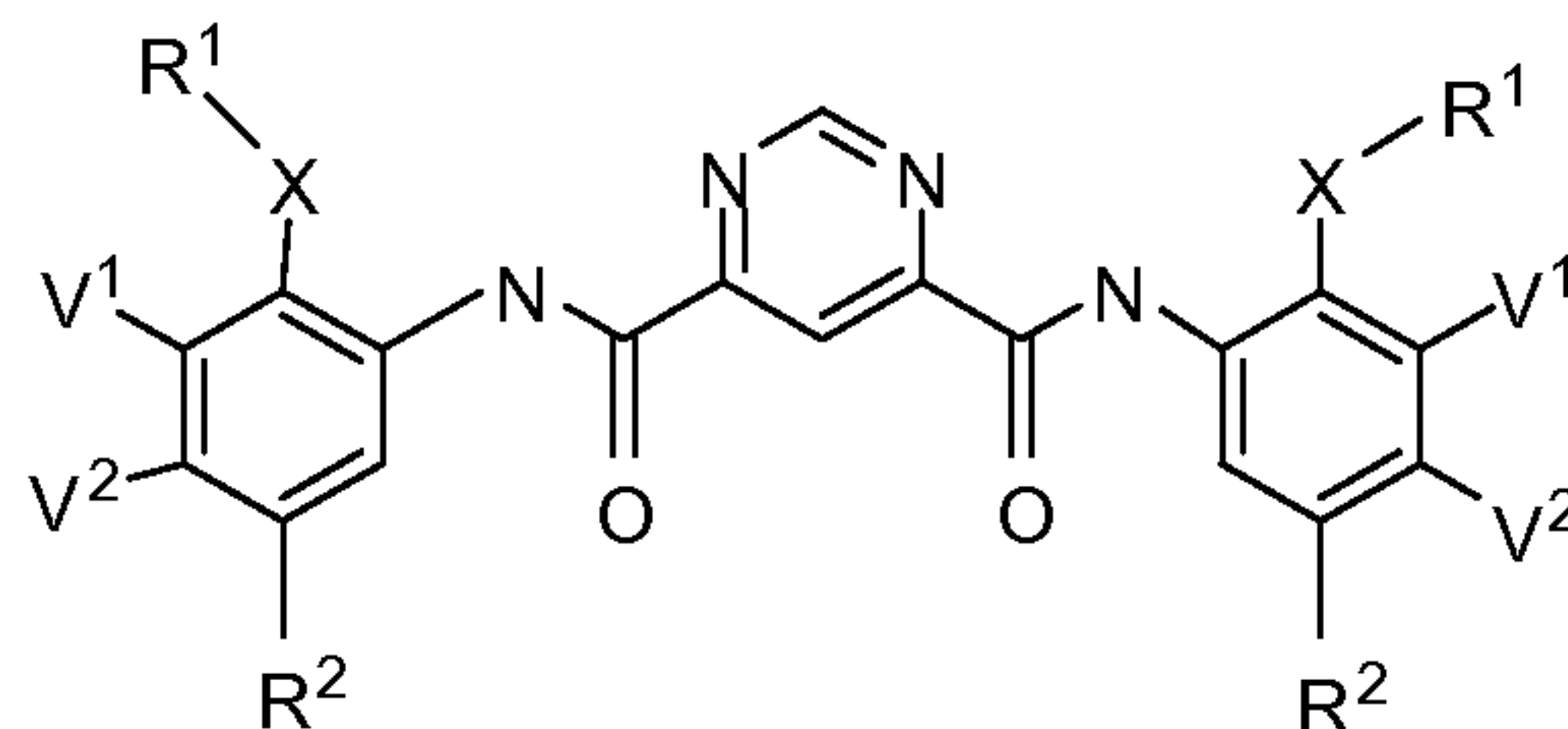




or a pharmaceutically acceptable salt thereof.

276. The method of any one of claims 251 to 275 wherein the malaria is chloroquine-sensitive or chloroquine-resistant.

277. A method of killing or inhibiting the growth of a *Plasmodium* species comprising contacting the species with an effective amount of a compound of Formula V:



wherein:

- 5 each X is, independently, O, S, or S(=O)₂;
 each R¹ is, independently, -(CH₂)_n-NH₂, -(CH₂)_n-NH-C(=NH)NH₂, or
 -(CH₂)_n-NH-C(=O)-R⁴, where each n is, independently, 1 to 4, and each R⁴ is, independently,
 H, C₁-C₃alkyl, or -(CH₂)_p-NH₂, where each p is, independently, 1 or 2;
 each R² is, independently, H, halo, CF₃, or C(CH₃)₃; and
 10 each V² is H, and each V¹ is, independently, -N-C(=O)-R³, where each R³ is,
 independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1
 to 4; or each V¹ is H and each V² is, independently, -S-R⁵, where each R⁵ is, independently,
 -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4;
 or a pharmaceutically acceptable salt thereof.

15

278. The method of claim 277 wherein each X is S.

279. The method of claim 277 or claim 278 wherein each R¹ is, independently,
 -(CH₂)_n-NH₂, -(CH₂)_n-NH-C(=NH)NH₂, or -(CH₂)_n-NH-C(=O)-R⁴, where each n is,
 20 independently, 1 or 2, and each R⁴ is, independently, H or methyl.

280. The method of claim 277 or claim 278 wherein each R¹ is, independently,
 -(CH₂)_n-NH₂, -(CH₂)_n-NH-C(=NH)NH₂, or -(CH₂)_n-NH-C(=O)-R⁴, where each n is 2 and
 each R⁴ is H.

25

281. The method of claim 277 or claim 278 wherein each R¹ is, independently,
 -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is 2.

282. The method of claim 277 or claim 278 wherein each R^1 is $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 2.
283. The method of any one of claims 277 to 282 wherein each R^2 is, independently, H,
5 Br, F, Cl, CF_3 , or $C(CH_3)_3$.
284. The method of any one of claims 277 to 282 wherein each R^2 is Br, F, Cl, CF_3 , or $C(CH_3)_3$.
- 10 285. The method of any one of claims 277 to 284 wherein each V^2 is H and each V^1 is, independently, $-N-C(=O)-R^3$, where each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.
286. The method of any one of claims 277 to 284 wherein each V^2 is H and each V^1 is,
15 independently, $-N-C(=O)-R^3$, where each R^3 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 or 2.
287. The method of any one of claims 277 to 284 wherein each V^2 is H and each V^1 is, independently, $-N-C(=O)-R^3$, where each R^3 is, independently, $-(CH_2)_n-NH_2$ or
20 $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 2.
288. The method of any one of claims 277 to 284 wherein each V^2 is H and each V^1 is $-N-C(=O)-R^3$, where each R^3 is $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where n is 2.
- 25 289. The method of any one of claims 277 to 284 wherein each V^1 is H and each V^2 is, independently, $-S-R^5$, where each R^5 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.
290. The method of any one of claims 277 to 284 wherein each V^1 is H and each V^2 is,
30 independently, $-S-R^5$, where each R^5 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 or 2.

291. The method of any one of claims 277 to 284 wherein each V^1 is H and each V^2 is, independently, $-S-R^5$, where each R^5 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 2.

5 292. The method of any one of claims 277 to 284 wherein each V^1 is H and each V^2 is $-S-R^5$, where each R^5 is $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 2.

293. The method of claim 277 wherein:

each X is S;

10 each R^1 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;

each R^2 is, independently, halo, CF_3 , or $C(CH_3)_3$; and

each V^1 is H and each V^2 is, independently, $-S-R^5$, where each R^5 is, independently, $-(CH_2)_n-NH_2$, where each n is, independently, 1 to 4.

15

294. The method of claim 277 wherein:

each X is S;

each R^1 is, independently, $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2;

each R^2 is, independently, CF_3 or $C(CH_3)_3$; and

20 each V^1 is H and each V^2 is, independently, $-S-R^5$, where each R^5 is, independently, $-(CH_2)_n-NH_2$, where each n is, independently, 1 or 2.

295. The method of claim 277 wherein:

each X is S;

25 each R^1 is $-(CH_2)_n-NH_2$, where each n is 1 or 2;

each R^2 is, independently, CF_3 or $C(CH_3)_3$; and

each V^1 is H and each V^2 is $-S-R^5$, where each R^5 is $-(CH_2)_n-NH_2$, where each n is 1 or 2.

30 296. The method of claim 277 wherein:

each X is O or S;

each R^1 is, independently, $-(CH_2)_n-NH_2$, $-(CH_2)_n-NH-C(=NH)NH_2$, or

$-(\text{CH}_2)_n\text{-NH-C(=O)-R}^4$, where each n is, independently, 1 to 4, and each R^4 is, independently, H or methyl;

each R^2 is, independently, halo, CF_3 , or $\text{C}(\text{CH}_3)_3$; and

each V^2 is H, and each V^1 is, independently, $-\text{N-C(=O)-R}^3$, where each R^3 is,
 5 independently, $-(\text{CH}_2)_n\text{-NH}_2$ or $-(\text{CH}_2)_n\text{-NH-C(=NH)NH}_2$, where each n is, independently, 1 to 4.

297. The method of claim 277 wherein:

each X is S;

10 each R^1 is, independently, $-(\text{CH}_2)_n\text{-NH-C(=O)-R}^4$, where each n is, independently, 1 or 2, and each R^4 is, independently, H or methyl;

each R^2 is, independently, halo; and

each V^2 is H, and each V^1 is $-\text{N-C(=O)-R}^3$, where each R^3 is $-(\text{CH}_2)_n\text{-NH}_2$ or
 $-(\text{CH}_2)_n\text{-NH-C(=NH)NH}_2$, where each n is 4.

15

298. The method of claim 277 wherein:

each X is O or S;

each R^1 is, independently, $-(\text{CH}_2)_n\text{-NH}_2$ or $-(\text{CH}_2)_n\text{-NH-C(=NH)NH}_2$, where each n
 is, independently, 1 to 4;

20 each R^2 is, independently, halo, CF_3 , or $\text{C}(\text{CH}_3)_3$; and

each V^2 is H, and each V^1 is, independently, $-\text{N-C(=O)-R}^3$, where each R^3 is,
 independently, $-(\text{CH}_2)_n\text{-NH}_2$ or $-(\text{CH}_2)_n\text{-NH-C(=NH)NH}_2$, where each n is, independently, 1 to 4.

25 299. The method of claim 277 wherein:

each X is O or S;

each R^1 is $-(\text{CH}_2)_n\text{-NH}_2$ or $-(\text{CH}_2)_n\text{-NH-C(=NH)NH}_2$, where each n is 1 or 2;

each R^2 is halo, CF_3 , or $\text{C}(\text{CH}_3)_3$; and

each V^2 is H, and each V^1 is $-\text{N-C(=O)-R}^3$, where each R^3 is $-(\text{CH}_2)_n\text{-NH}_2$ or
 30 $-(\text{CH}_2)_n\text{-NH-C(=NH)NH}_2$, where each n is 3 or 4.

300. The method of claim 277 wherein:

each X is, independently, S or S(=O)₂;

each R¹ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=O)-R⁴, where each n is, independently, 1 or 2, and each R⁴ is, independently, -(CH₂)_p-NH₂, where each p is,

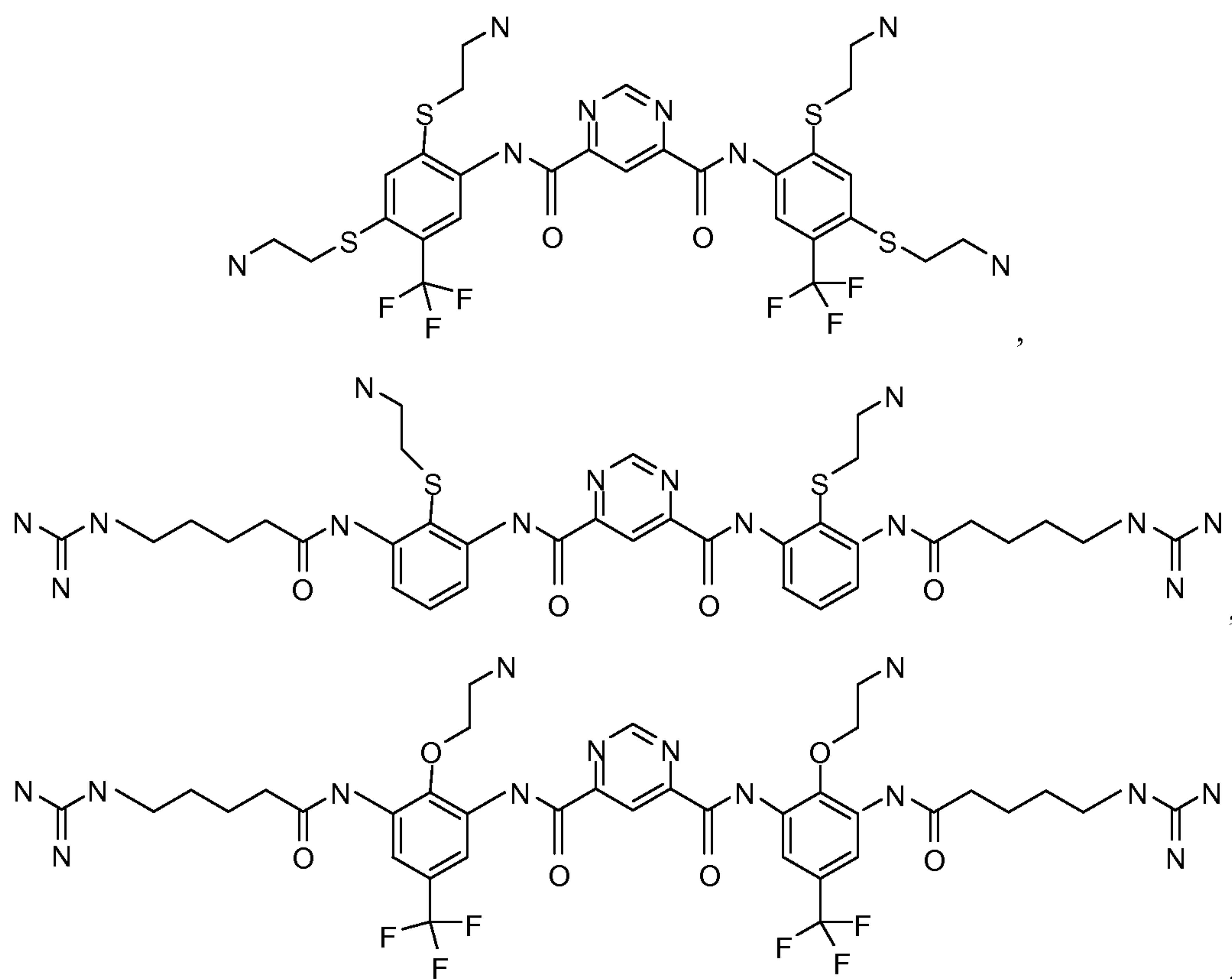
5 independently, 1 or 2;

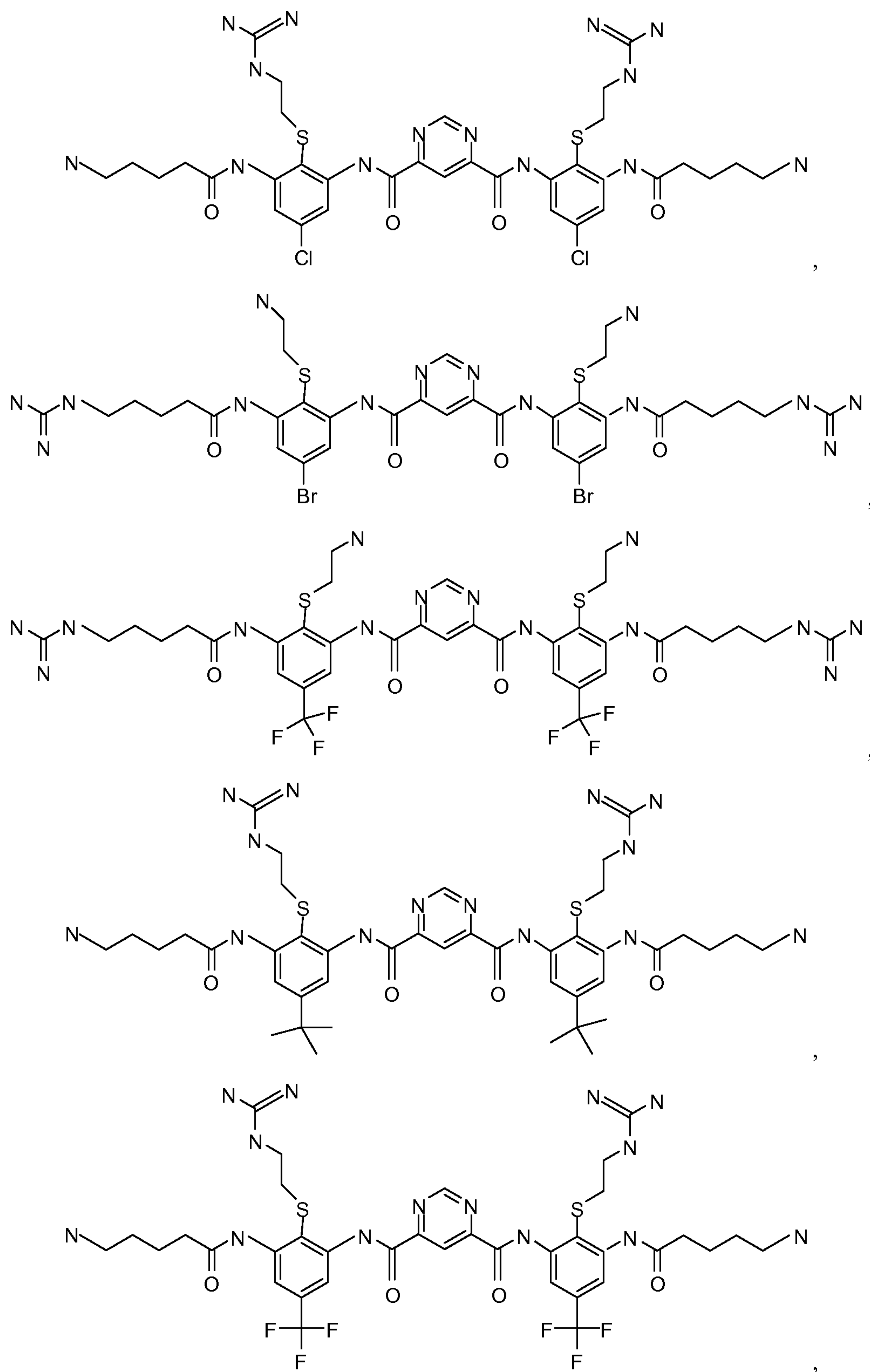
each R² is, independently, halo or CF₃; and

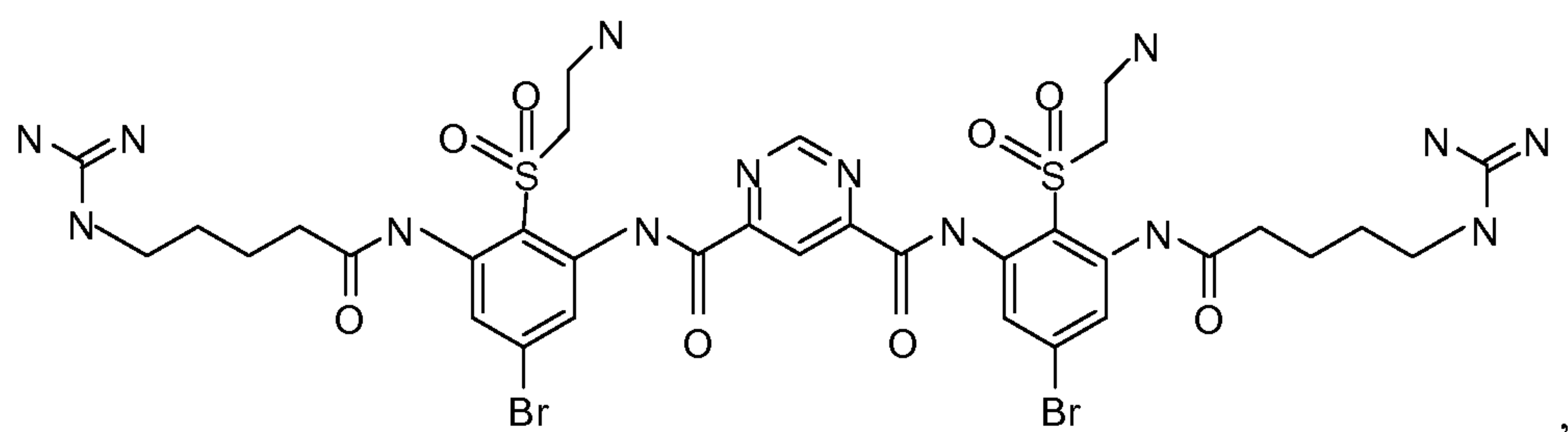
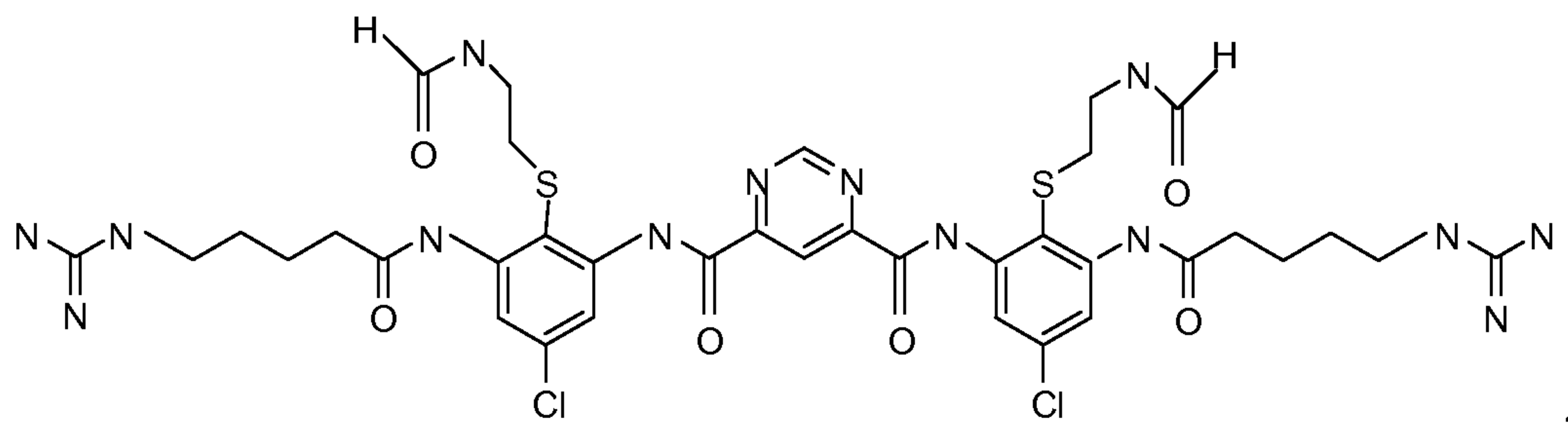
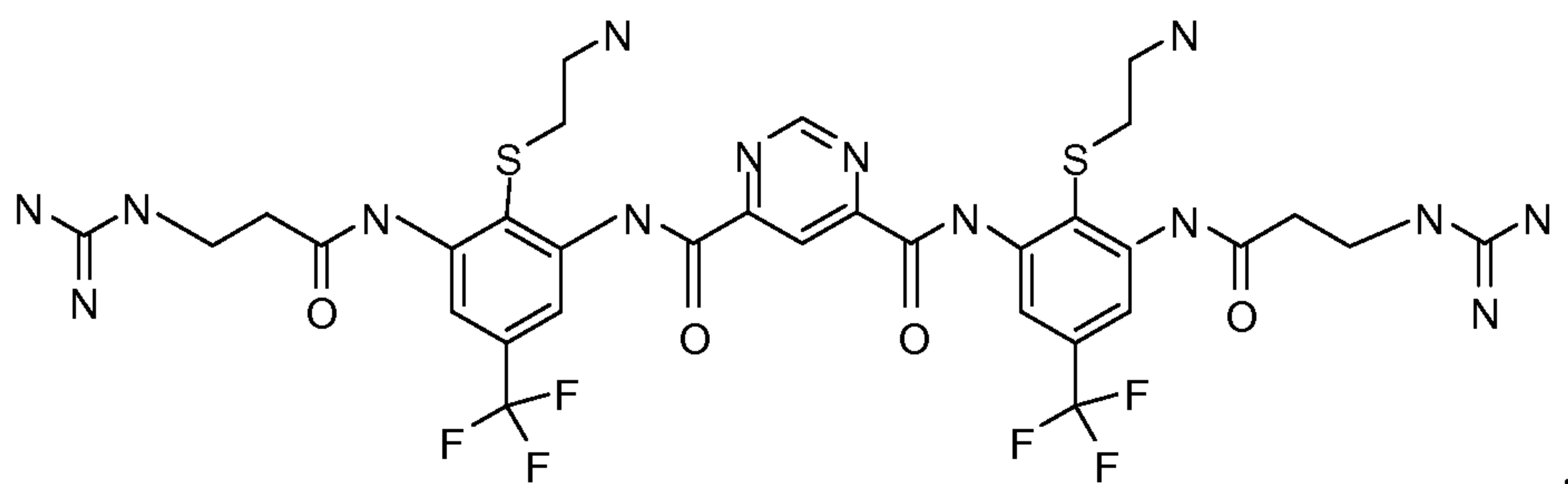
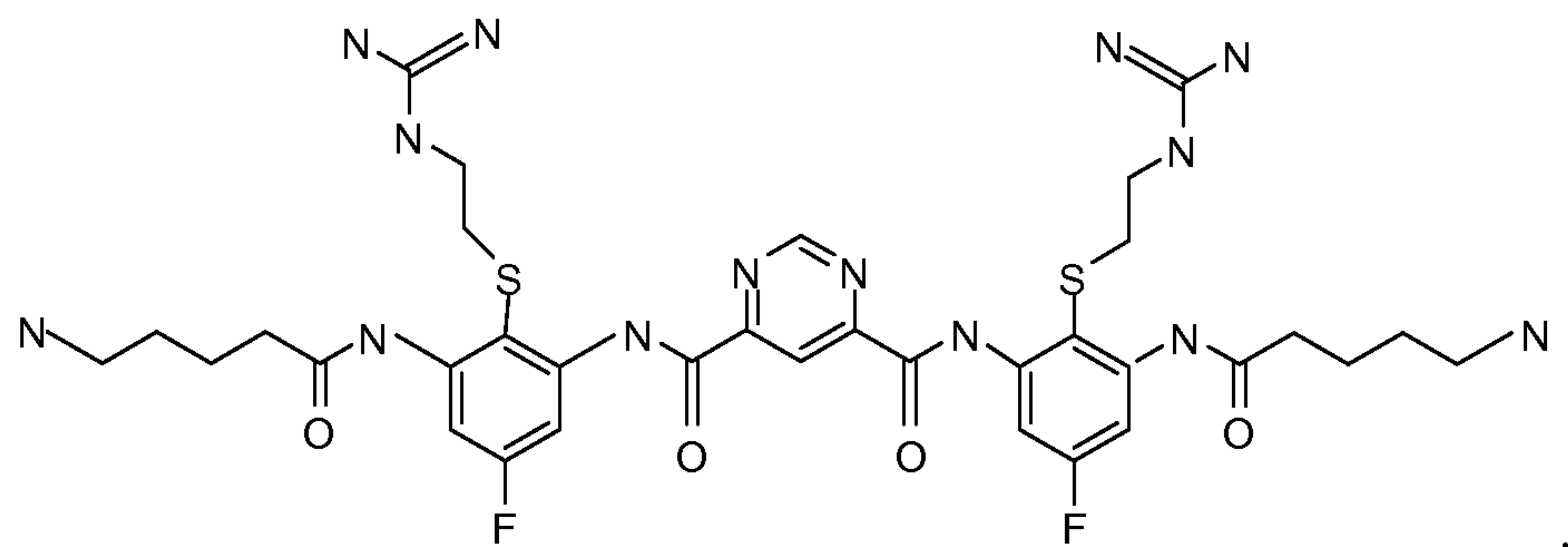
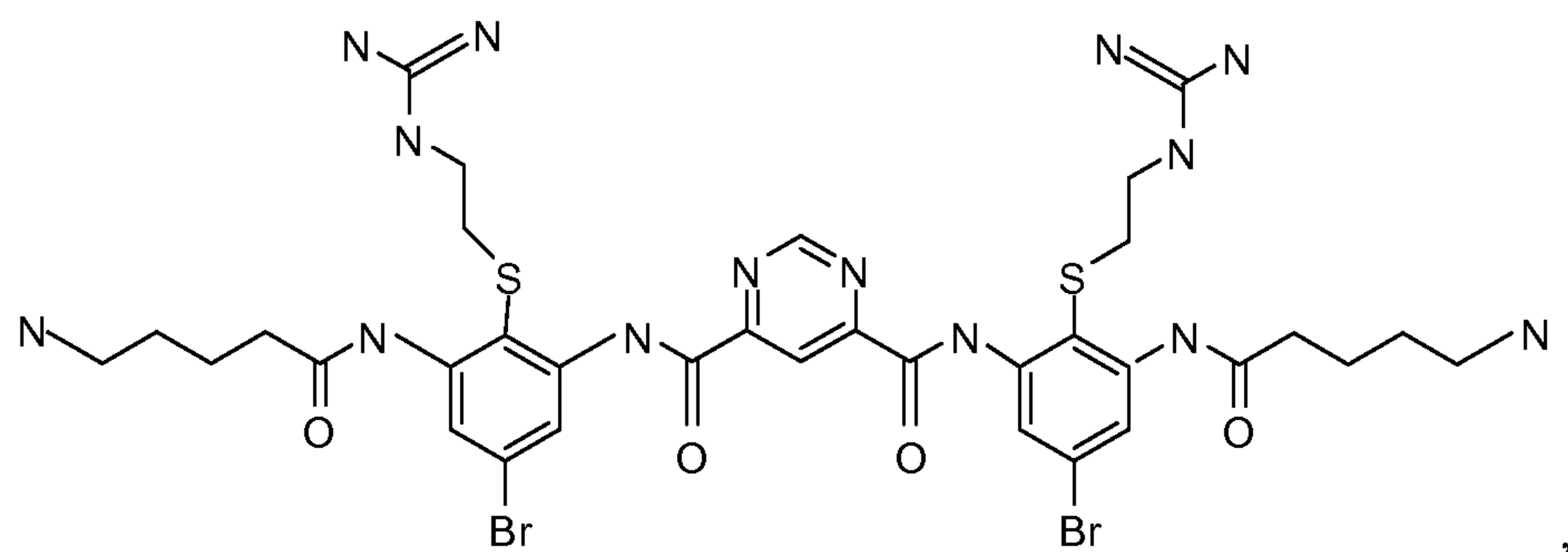
each V² is H, and each V¹ is, independently, -N-C(=O)-R³, where each R³ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 3 or 4.

10

301. The method of claim 277 wherein the compound is chosen from:

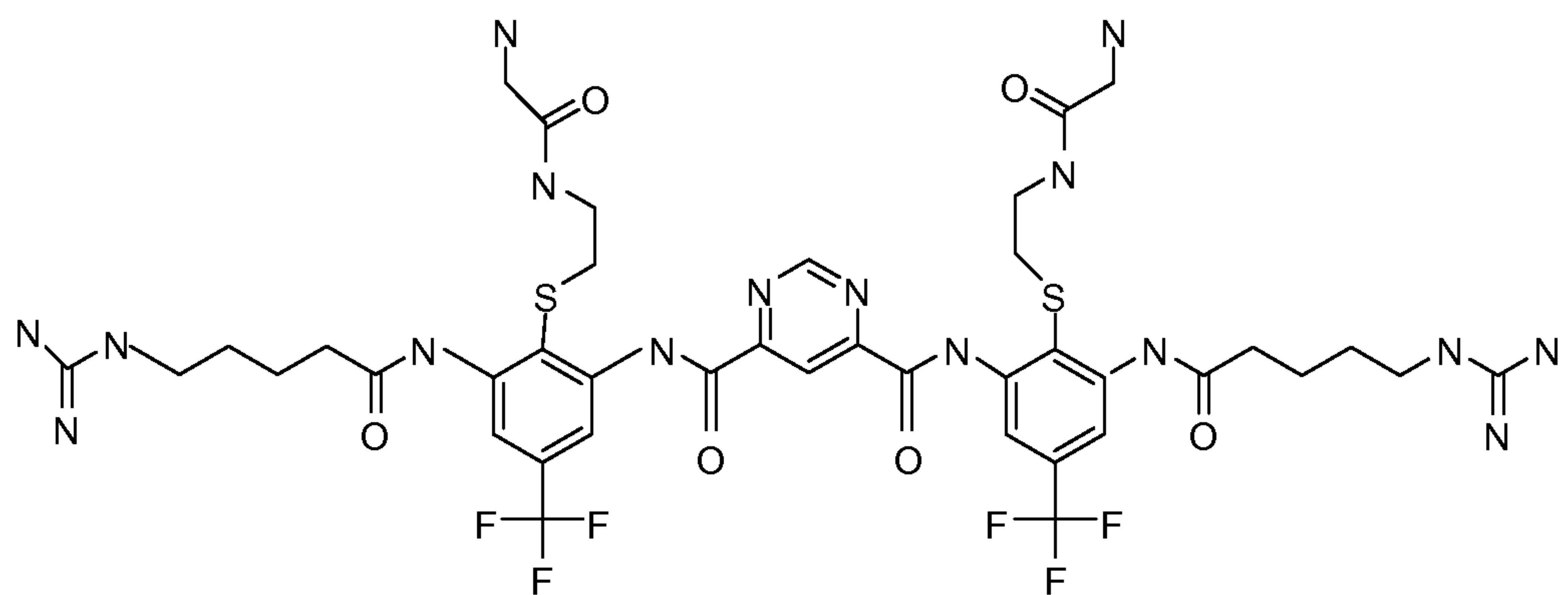






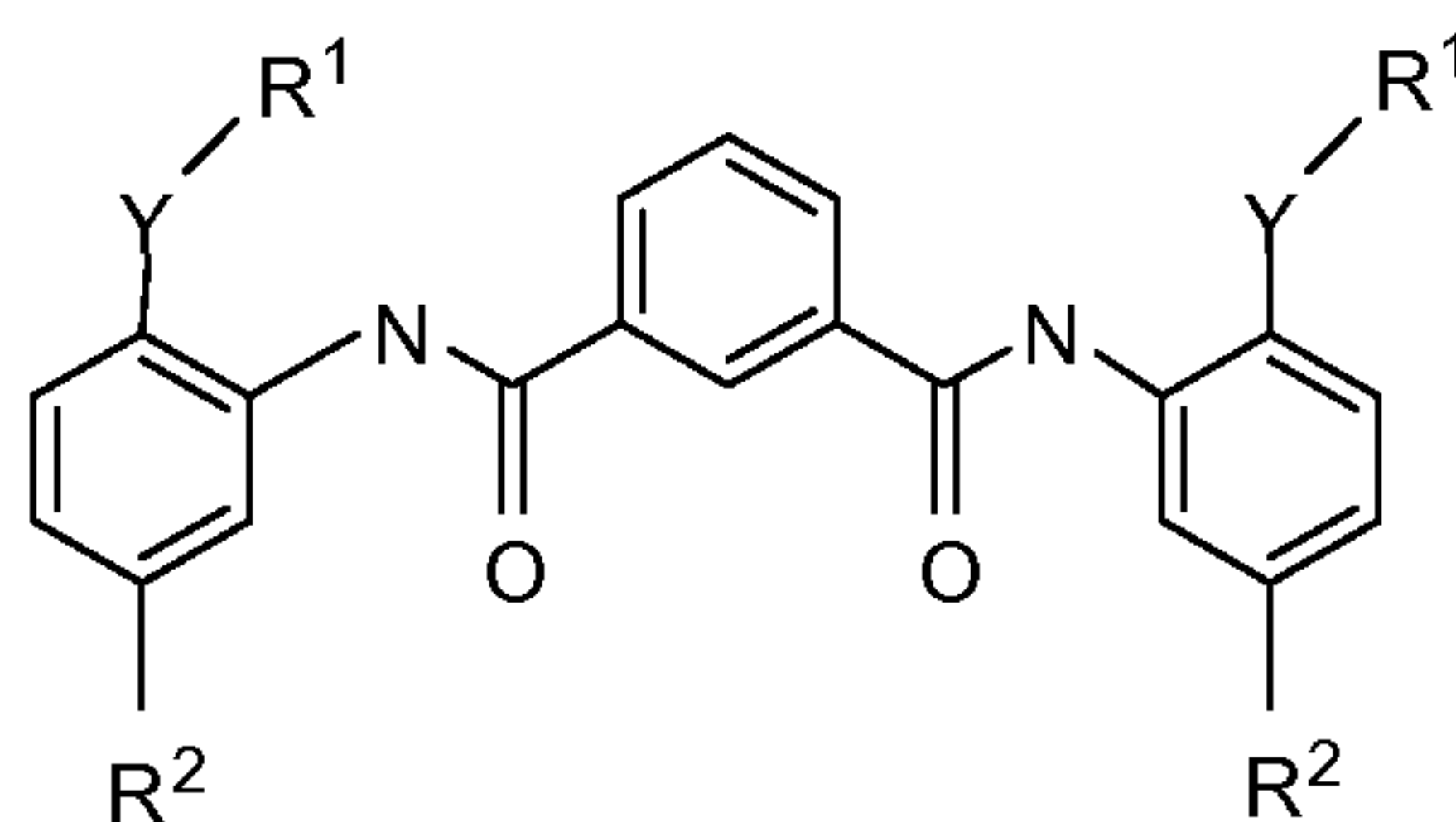
5

and



or a pharmaceutically acceptable salt thereof.

302. A compound of Formula VI:



5

wherein:

each Y is, independently, O, S, or NH;

each R¹ is, independently, -(CH₂)_n-NH₂ or -(CH₂)_n-NH-C(=NH)NH₂, where each n is, independently, 1 to 4; and

10 each R² is, independently, H, halo, CF₃, or C(CH₃)₃;

or a pharmaceutically acceptable salt thereof.

303. The compound or salt of claim 302 wherein each Y is, independently, O, or S.

15 304. The compound or salt of claim 302 wherein each Y is O or S.

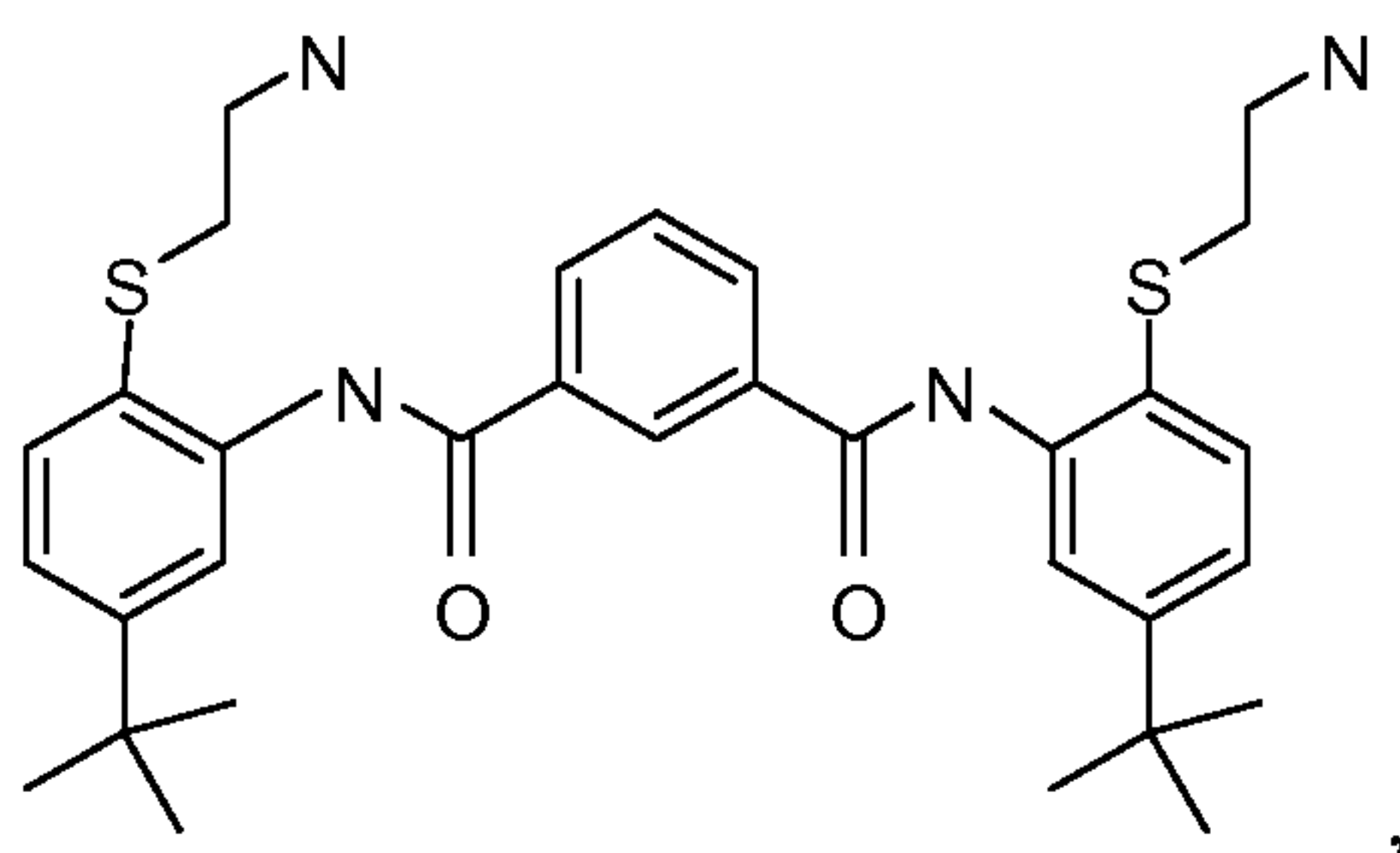
305. The compound or salt of any one of claims 302 to 304 wherein each R¹ is, independently, -(CH₂)_n-NH₂, where each n is, independently, 2 to 4.

20 306. The compound or salt of any one of claims 302 to 304 wherein each R¹ is -(CH₂)_n-NH₂, where each n is 2 to 4.

307. The compound or salt of any one of claims 302 to 306 wherein each R^2 is, independently, halo, CF_3 , or $C(CH_3)_3$.

308. The compound or salt of any one of claims 302 to 306 wherein each R^2 is halo, CF_3 ,
5 or $C(CH_3)_3$.

309. The compound of claim 302 which is

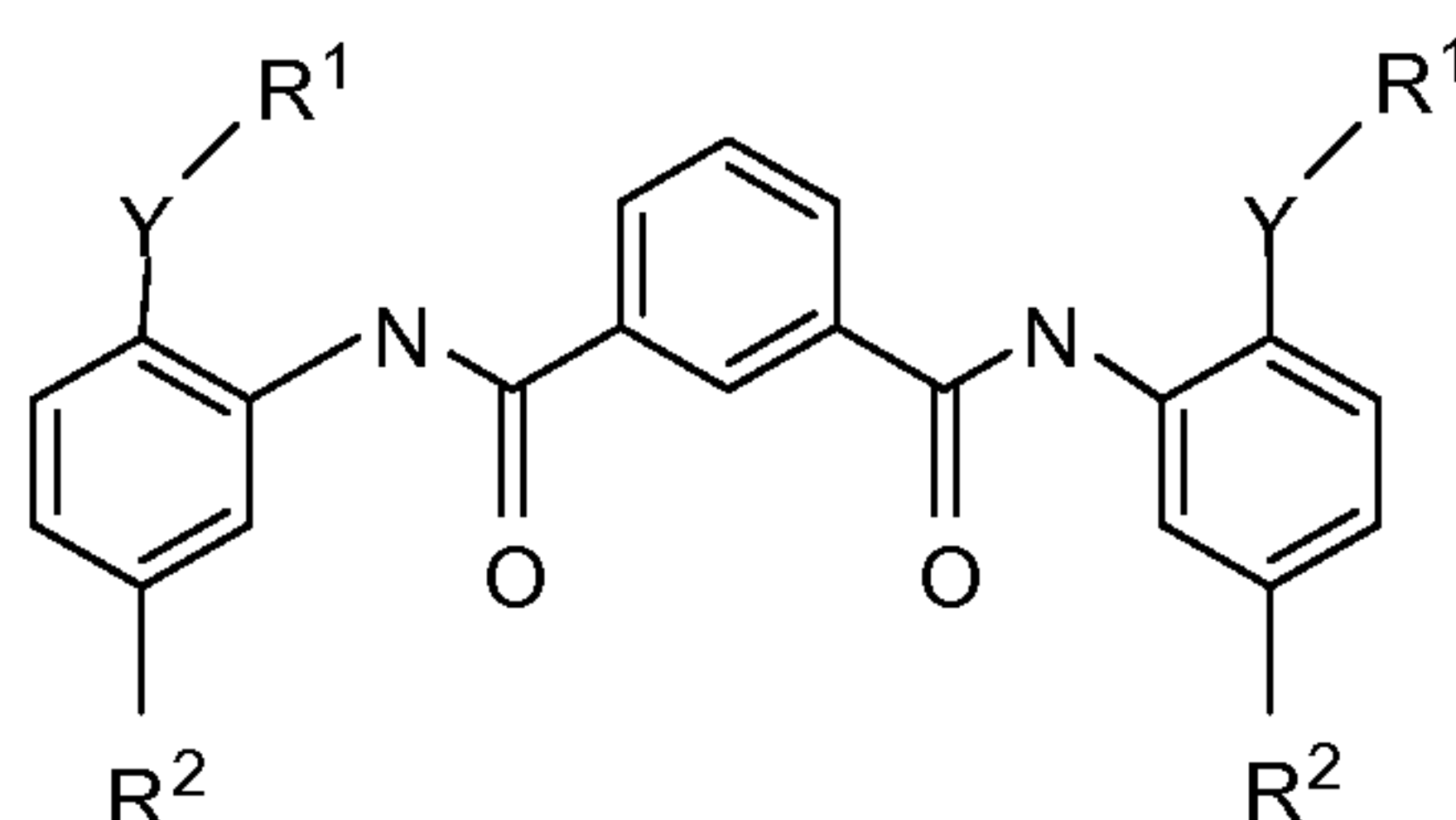


or pharmaceutically acceptable salt thereof.

10

310. A composition comprising the compound or salt of any one of claims 302 to 309 and a pharmaceutically acceptable carrier.

311. A method of treating malaria in an animal comprising administering to the animal a
15 therapeutically effective amount of a compound of Formula VI:



wherein:

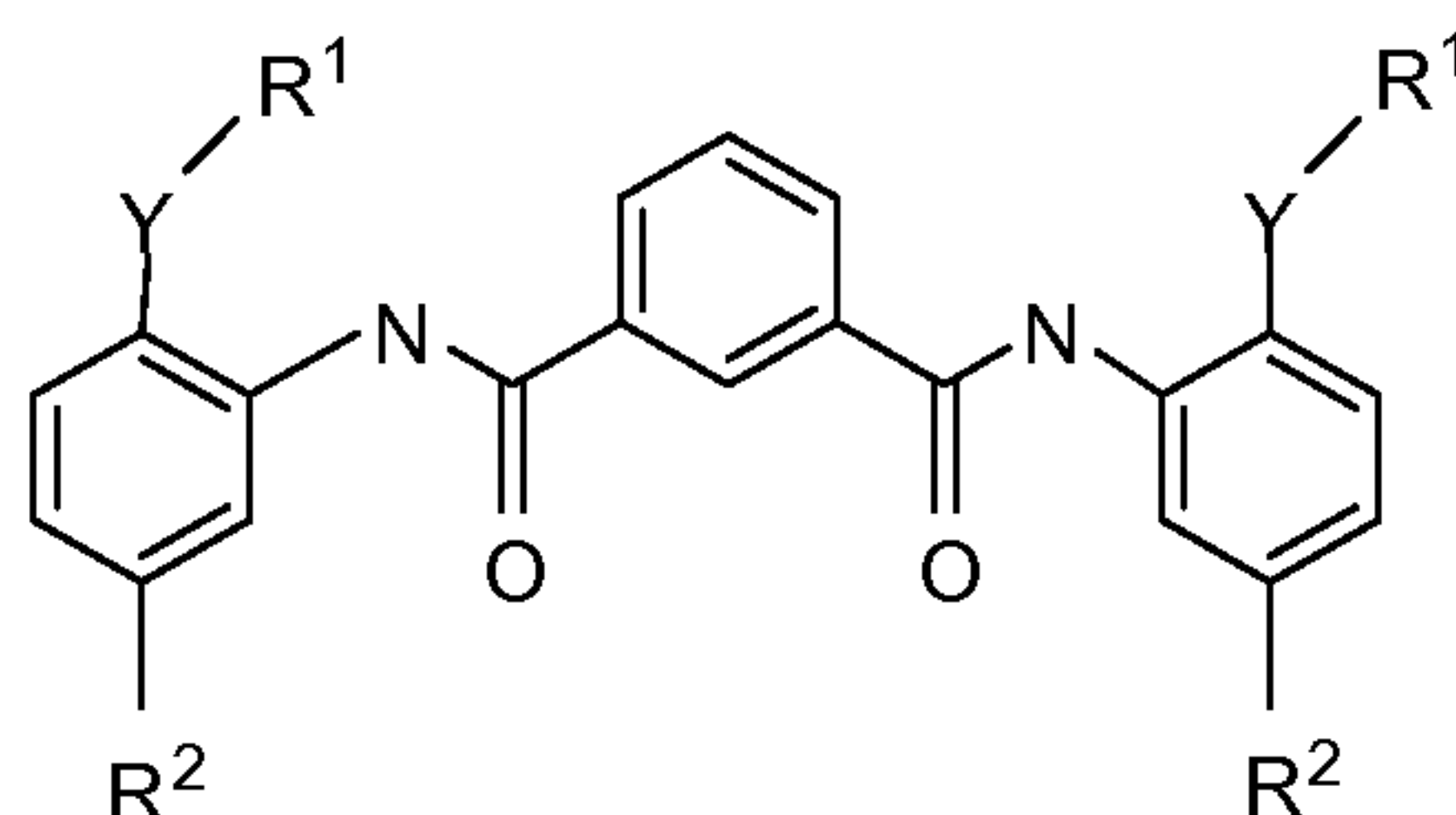
each Y is, independently, O, S, or NH;

each R^1 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n
20 is, independently, 1 to 4; and

each R^2 is, independently, H, halo, CF_3 , or $C(CH_3)_3$;

or a pharmaceutically acceptable salt thereof.

312. The method of claim 311 wherein each Y is, independently, O, or S.



wherein:

each Y is, independently, O, S, or NH;

each R^1 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n
5 is, independently, 1 to 4; and

each R^2 is, independently, H, halo, CF_3 , or $C(CH_3)_3$;

or a pharmaceutically acceptable salt thereof.

321. The method of claim 320 wherein each Y is, independently, O, or S.

10

322. The method of claim 320 wherein each Y is O or S.

323. The method of any one of claims 320 to 322 wherein each R^1 is, independently,
 $-(CH_2)_n-NH_2$, where each n is, independently, 2 to 4.

15

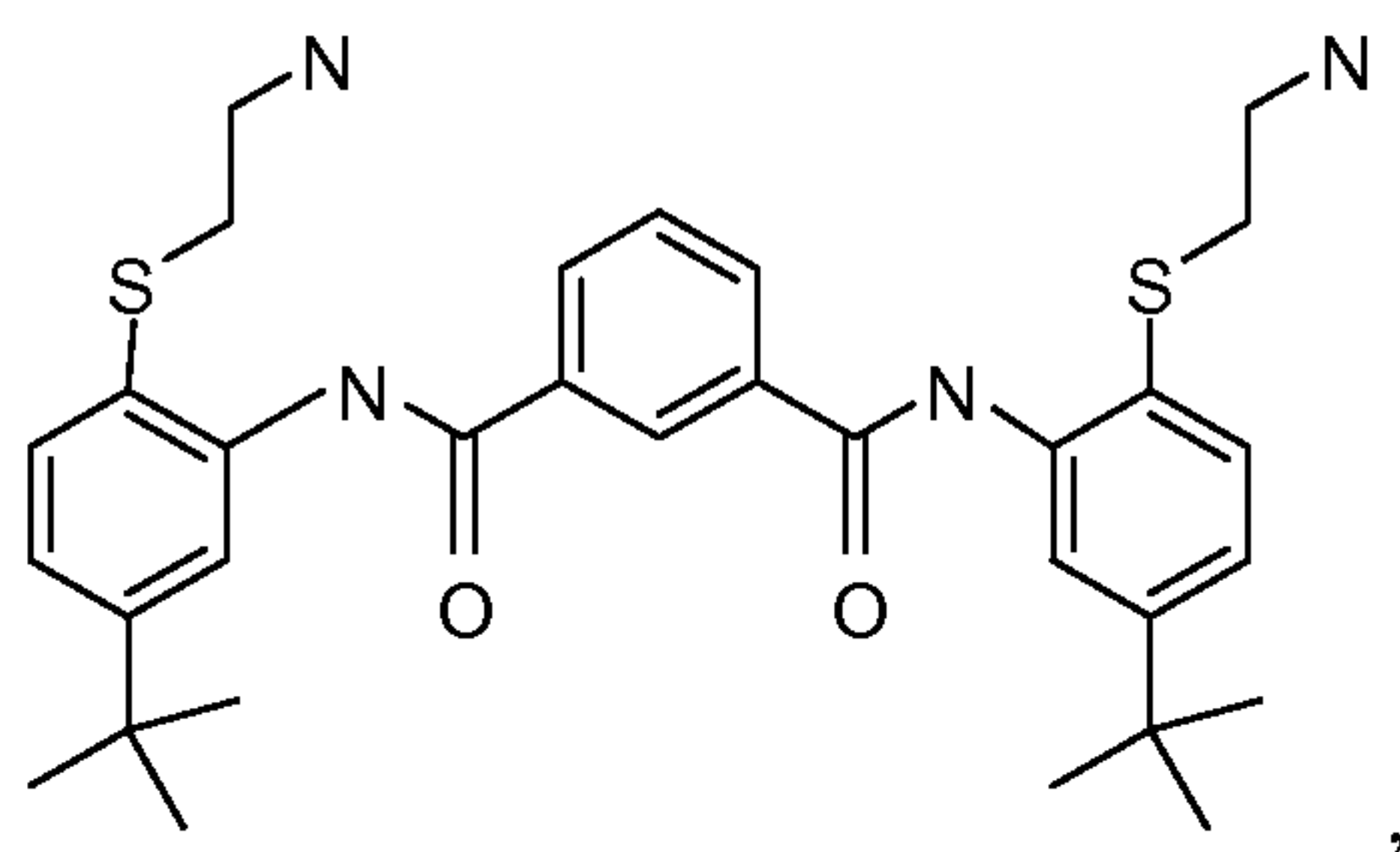
324. The method of any one of claims 320 to 322 wherein each R^1 is $-(CH_2)_n-NH_2$, where
each n is 2 to 4.

325. The method of any one of claims 320 to 324 wherein each R^2 is, independently,

20 halo, CF_3 , or $C(CH_3)_3$.

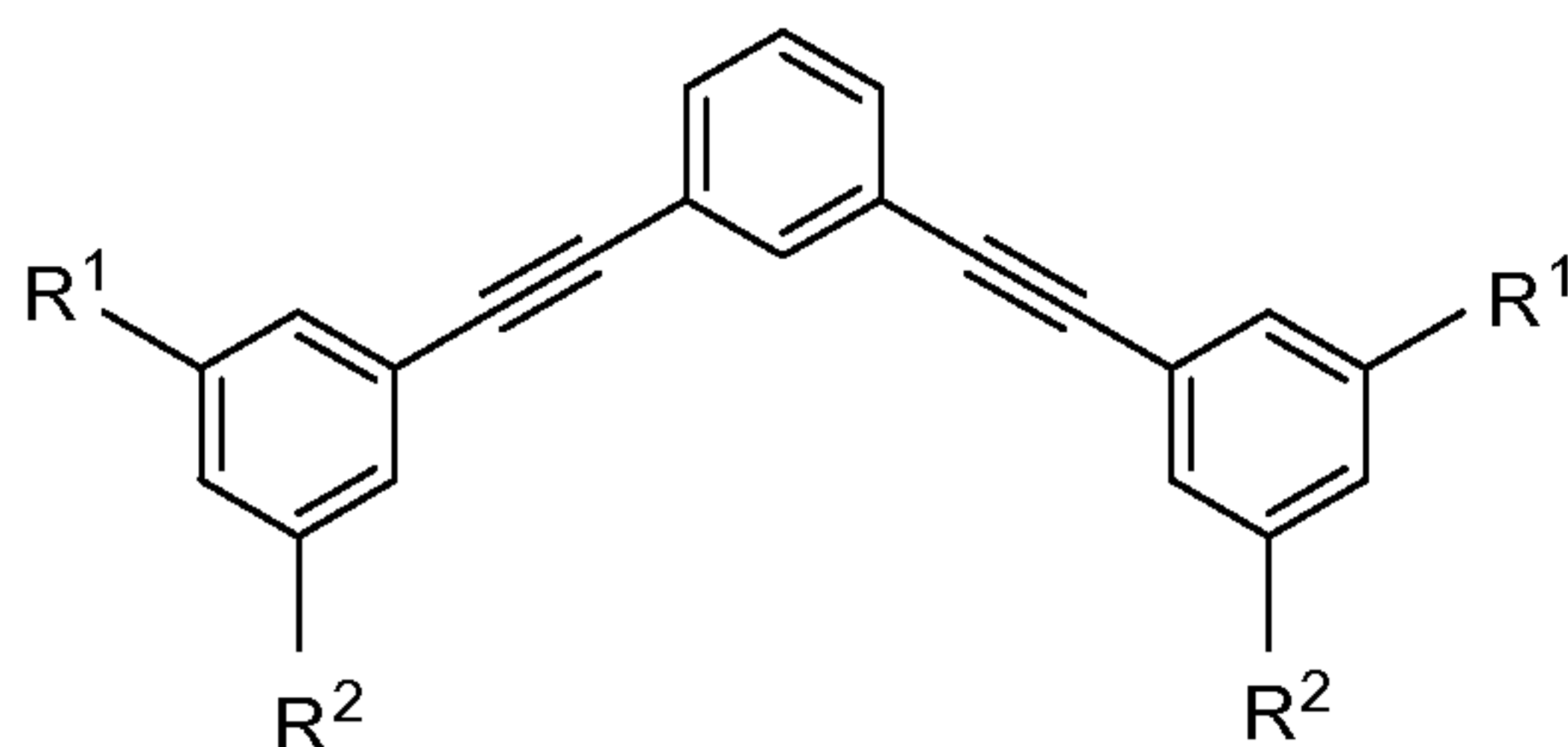
326. The method of any one of claims 320 to 324 wherein each R^2 is halo, CF_3 , or
 $C(CH_3)_3$.

25 327. The method of claim 320 wherein the compound is



or pharmaceutically acceptable salt thereof.

328. A method of treating malaria in an animal comprising administering to the animal a
5 therapeutically effective amount of a compound of Formula VII:



wherein:

each R^1 is, independently, H, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, halo, OH, CF_3 , or CN;

each R^2 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n
10 is, independently, 1 to 4;
or a pharmaceutically acceptable salt thereof.

329. The method of claim 328 wherein each R^1 is, independently, C_1 - C_8 alkyl, halo, OH,
 CF_3 , or CN.

15

330. The method of claim 328 wherein each R^1 is, independently, C_1 - C_3 alkyl, halo, CF_3 ,
or CN.

331. The method of claim 328 wherein each R^1 is methyl or halo.

20

332. The method of claim 328 wherein each R^1 is Br, F, or Cl.

333. The method of any one of claims 328 to 332 wherein each R^2 is, independently,
 $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

334. The method of any one of claims 328 to 332 wherein each R^2 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 to 4.

5 335. The method of any one of claims 328 to 332 wherein each R^2 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 or 2.

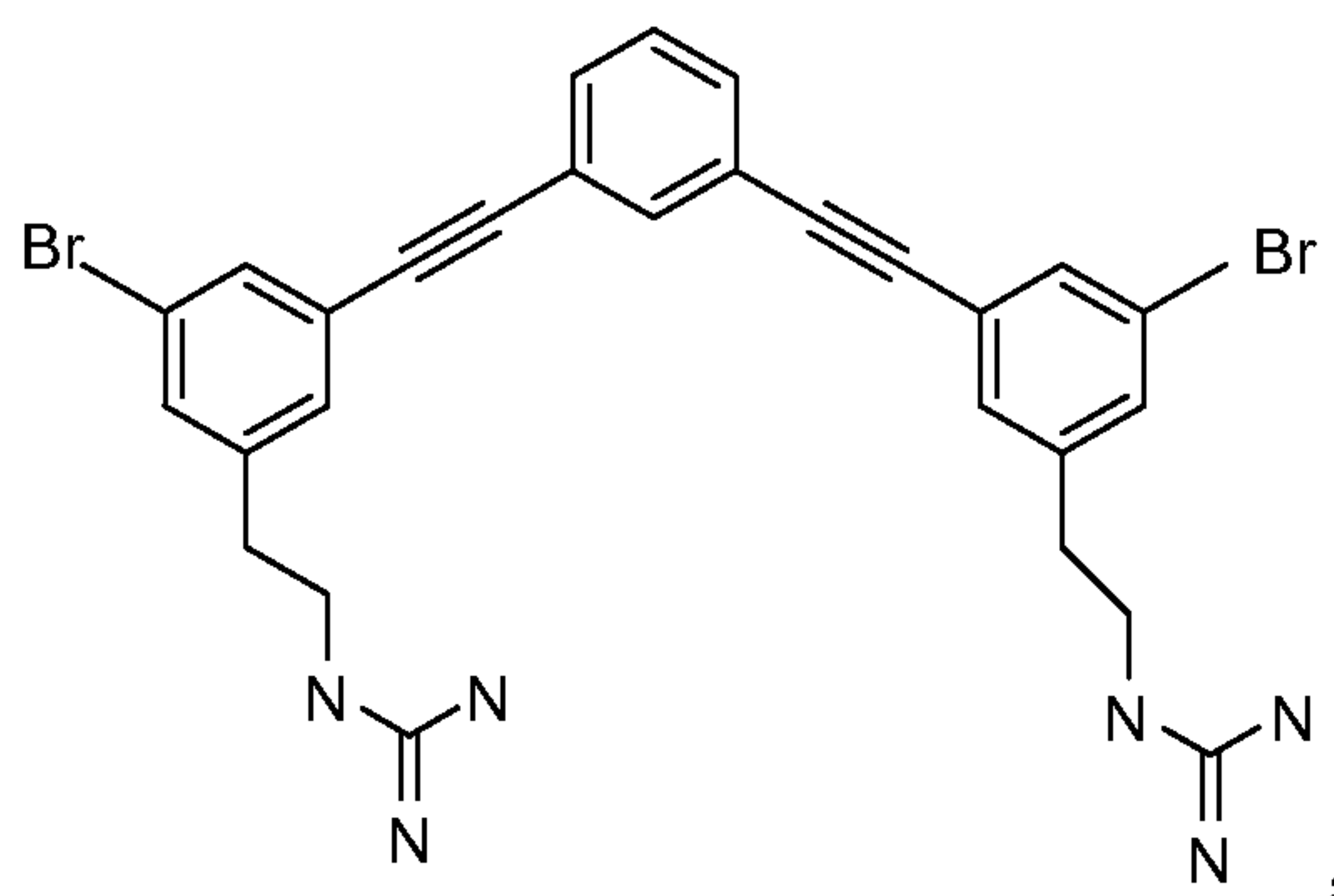
336. The method of claim 328 wherein:
 each R^1 is, independently, C_1 - C_8 alkyl, halo, OH, CF_3 , or CN; and
 10 each R^2 is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

337. The method of claim 328 wherein:
 each R^1 is, independently, C_1 - C_3 alkyl, halo, CF_3 , or CN; and
 15 each R^2 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 to 4.

338. The method of claim 328 wherein:
 each R^1 is methyl or halo; and
 each R^2 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 or 2.

20

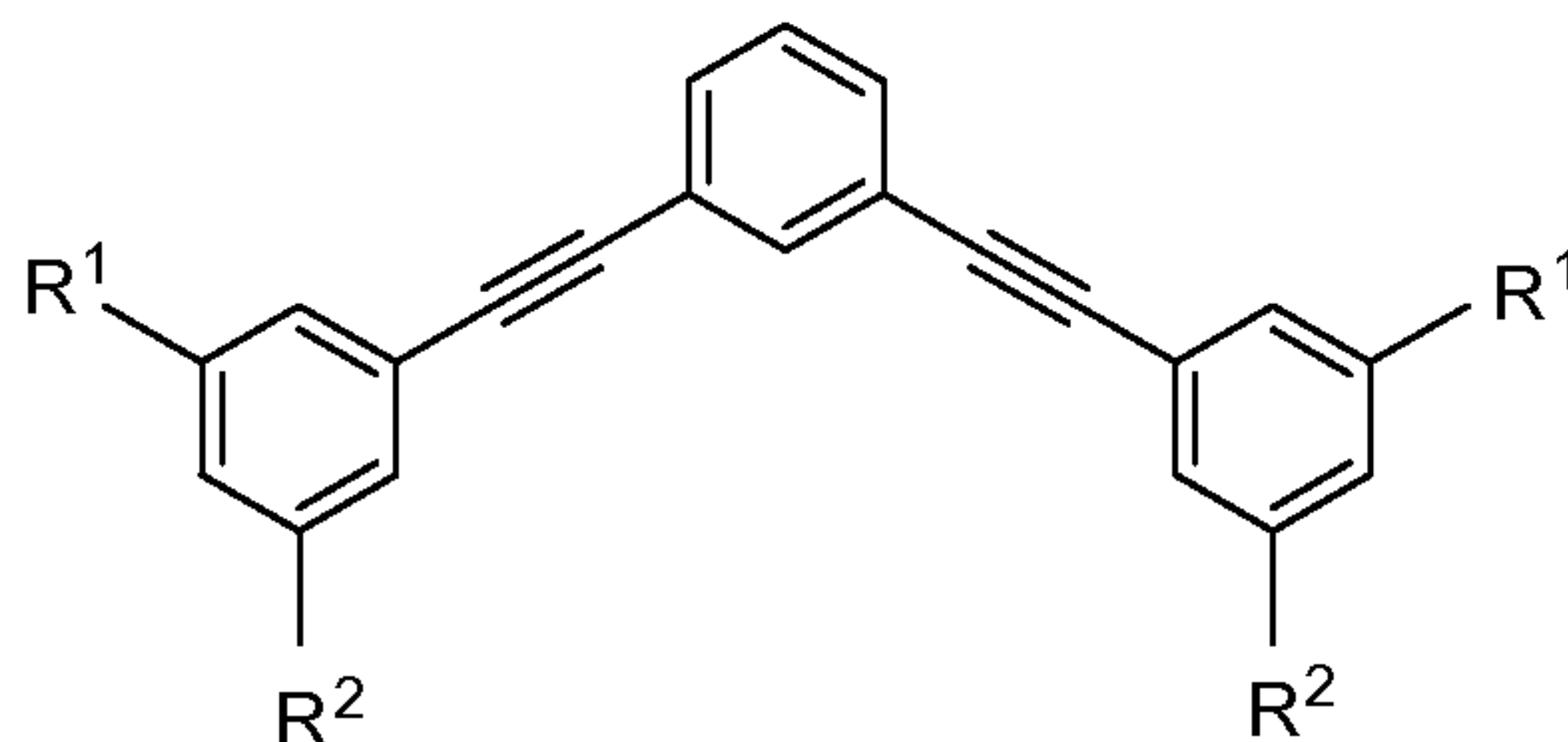
339. The method of claim 328 wherein the compound is



or a pharmaceutically acceptable salt thereof.

25 340. The method of any one of claims 328 to 339 wherein the malaria is chloroquine-sensitive or chloroquine-resistant.

341. A method of killing or inhibiting the growth of a *Plasmodium* species comprising contacting the species with an effective amount of a compound of Formula VII:



5 wherein:

each R^1 is, independently, H, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, halo, OH, CF_3 , or CN; and

each R^2 is, independently, $-(CH_2)_n-NH_2$ or $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4;

or a pharmaceutically acceptable salt thereof.

10

342. The method of claim 341 wherein each R^1 is, independently, C_1 - C_8 alkyl, halo, OH, CF_3 , or CN.

343. The method of claim 341 wherein each R^1 is, independently, C_1 - C_3 alkyl, halo, CF_3 ,

15 or CN.

344. The method of claim 341 wherein each R^1 is methyl or halo.

345. The method of claim 341 wherein each R^1 is Br, F, or Cl.

20

346. The method of any one of claims 341 to 345 wherein each R^2 is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

347. The method of any one of claims 341 to 345 wherein each R^2 is

25 $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 to 4.

348. The method of any one of claims 341 to 345 wherein each R^2 is

$-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 or 2.

349. The method of claim 341 wherein:

each R^1 is, independently, C_1 - C_8 alkyl, halo, OH, CF_3 , or CN; and

each R^2 is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

5

350. The method of claim 341 wherein:

each R^1 is, independently, C_1 - C_3 alkyl, halo, CF_3 , or CN; and

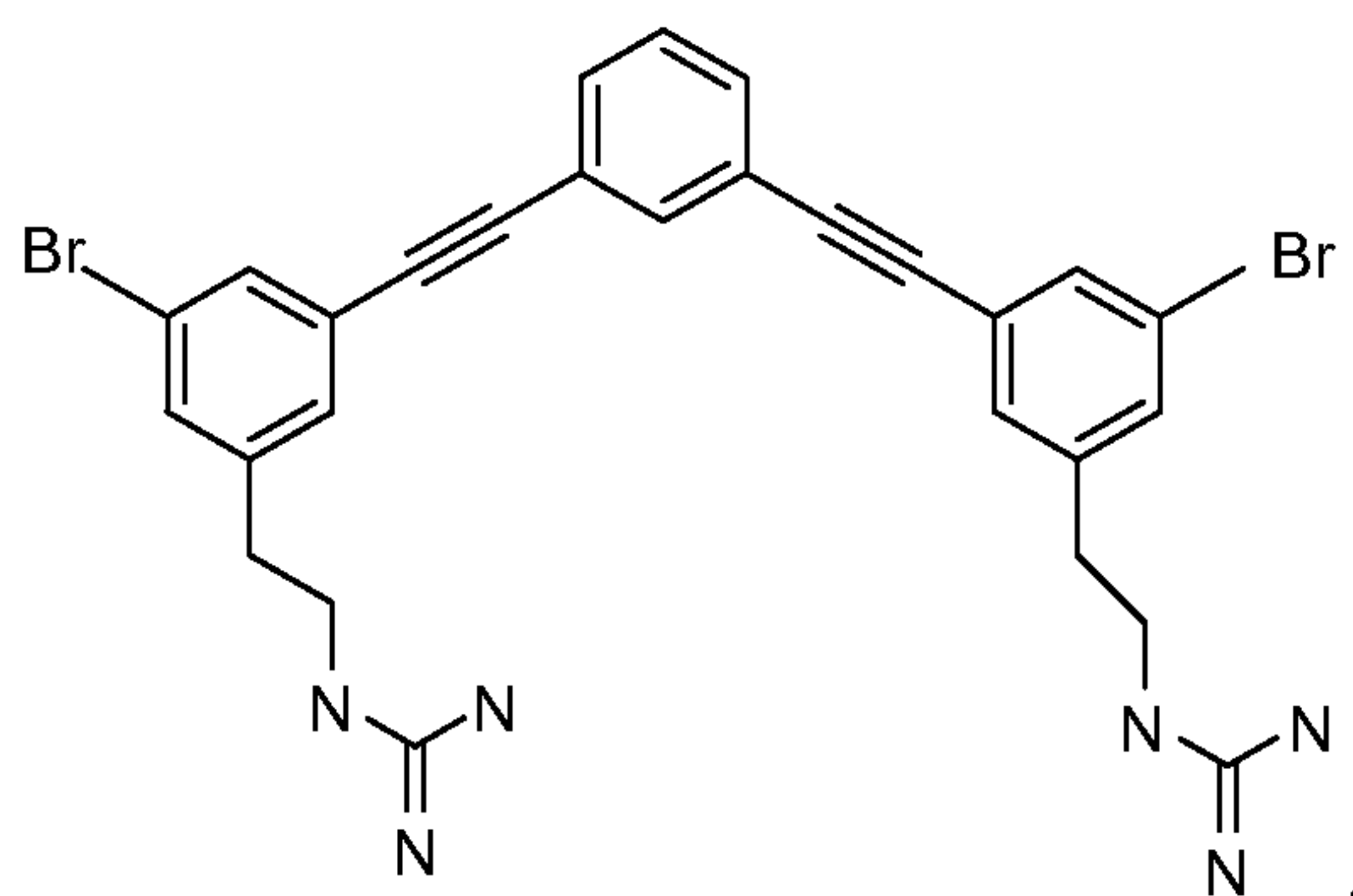
each R^2 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 to 4.

10 351. The method of claim 341 wherein:

each R^1 is methyl or halo; and

each R^2 is $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is 1 or 2.

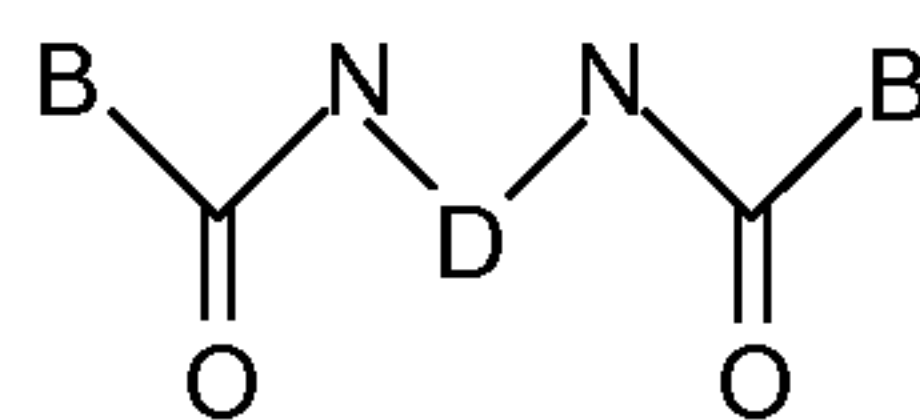
352. The method of claim 341 wherein the compound is



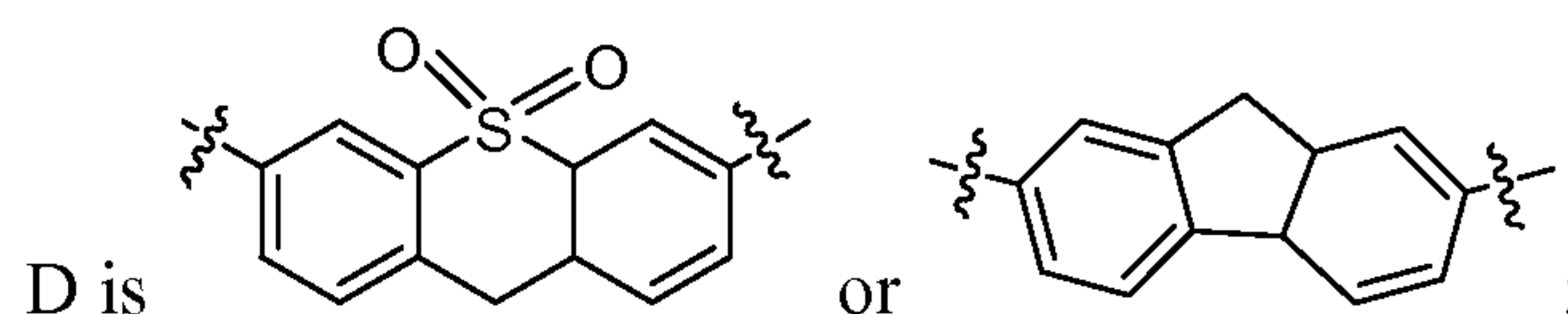
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or a pharmaceutically acceptable salt thereof.

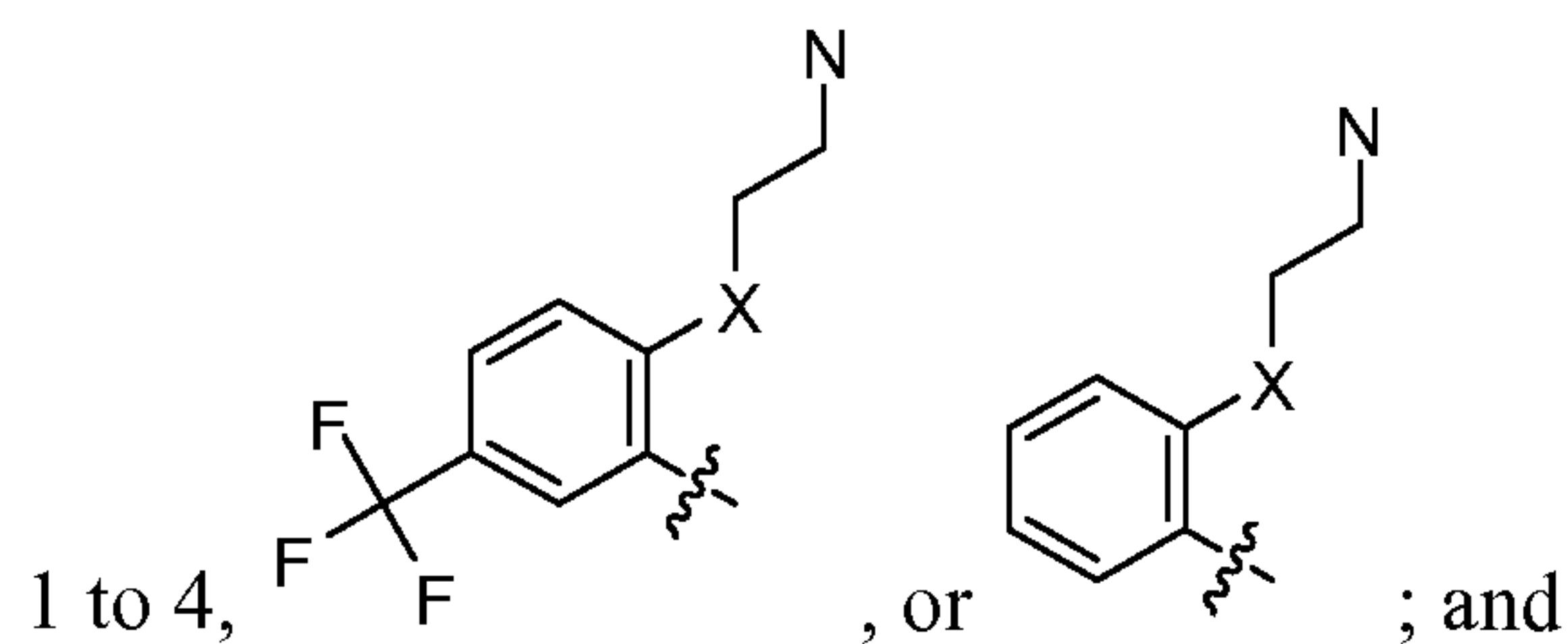
353. A compound of Formula VIII:



20 wherein:



each B is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently,

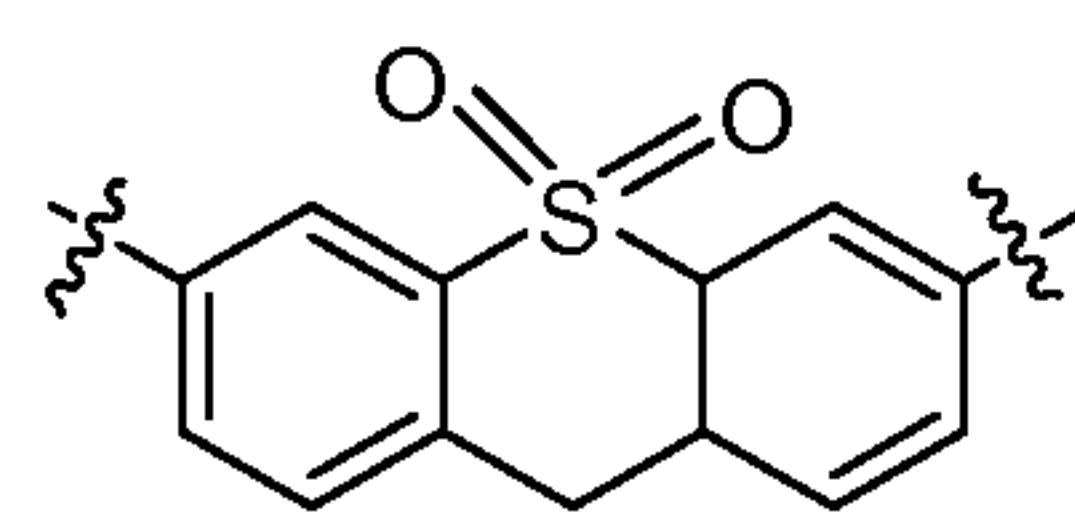


each X is, independently, O or S;

or a pharmaceutically acceptable salt thereof.

5

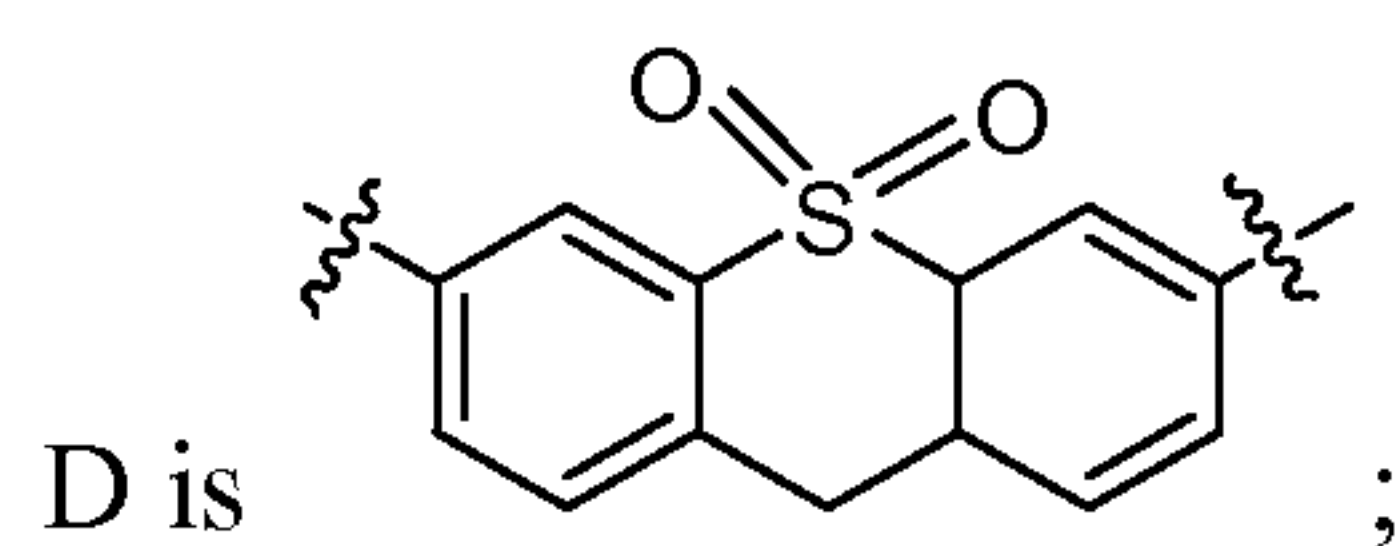
354. The compound or salt of claim 353 wherein D is



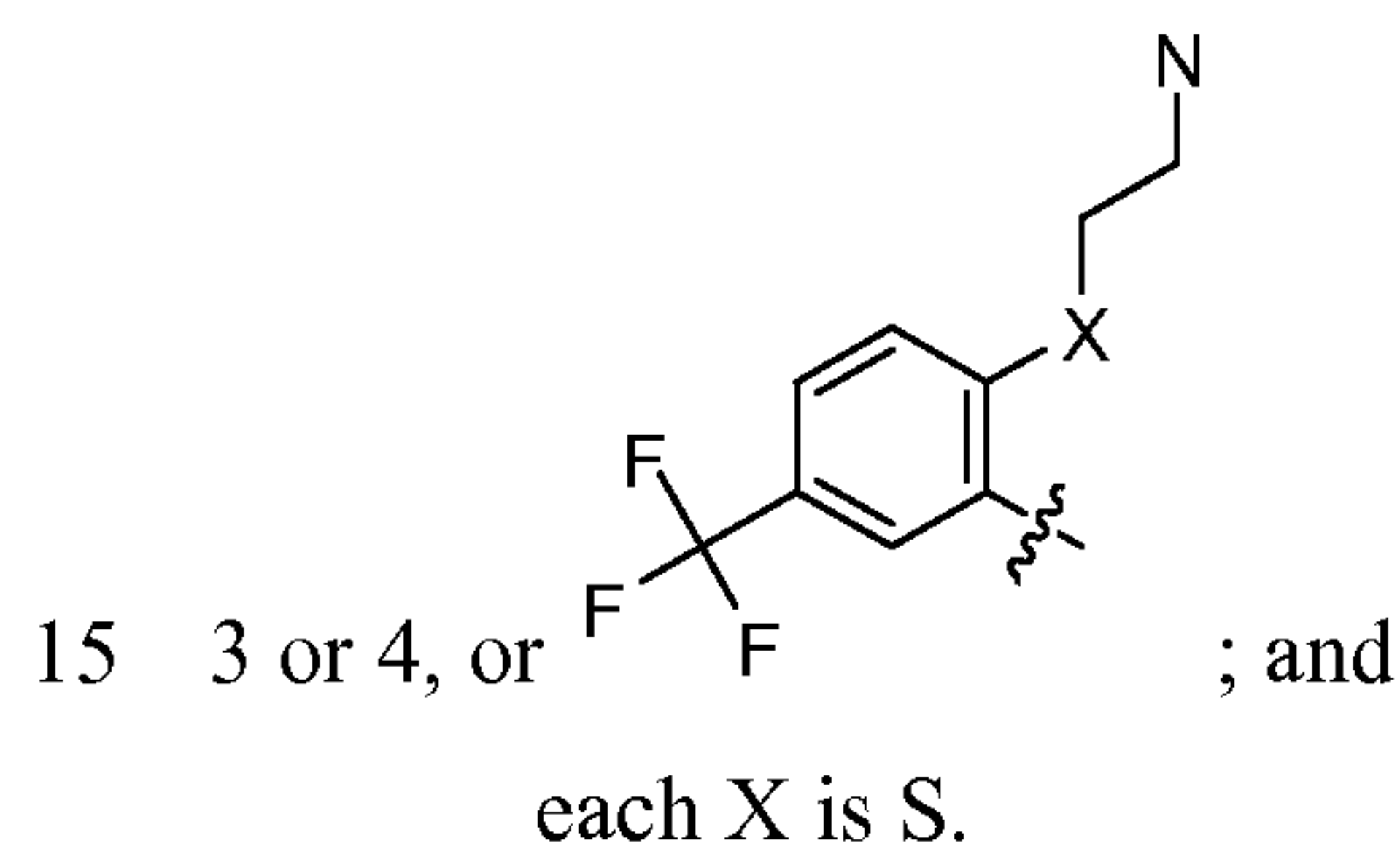
355. The compound or salt of claim 353 or claim 354 wherein each B is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

10 356. The compound or salt of any one of claims 353 to 355 wherein each X is S.

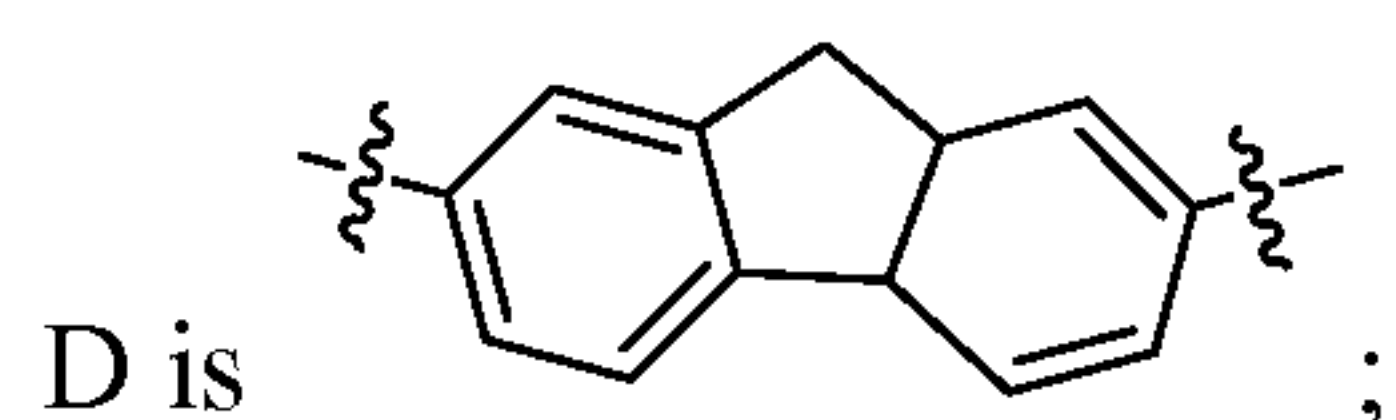
357. The compound or salt of claim 353 wherein:

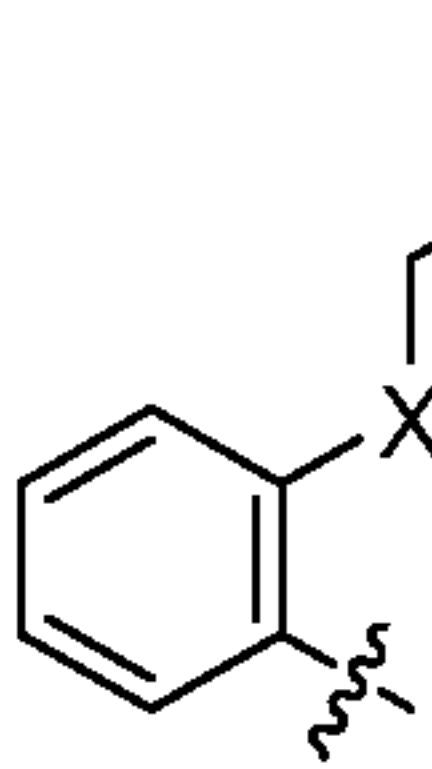


each B is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently,

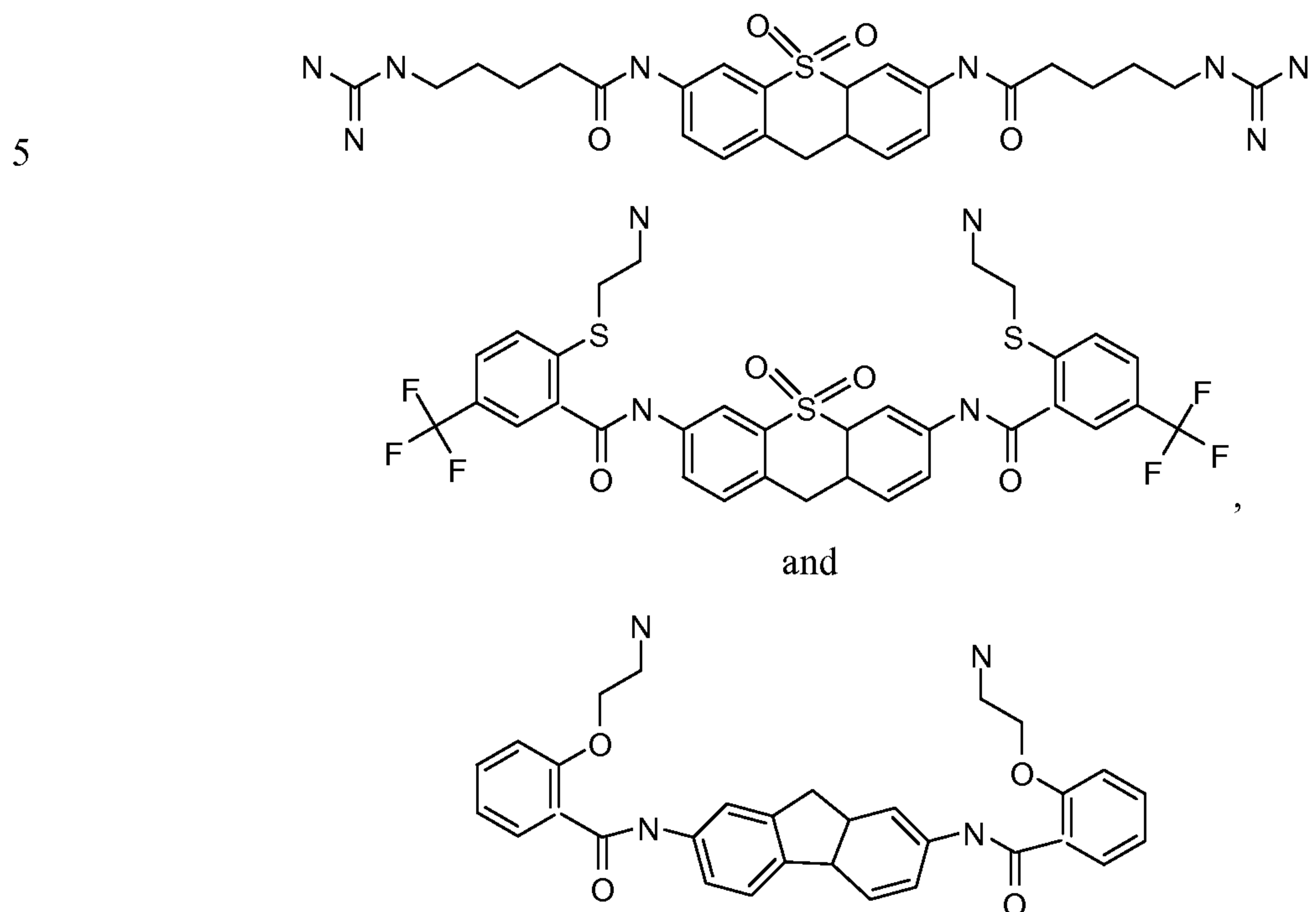


358. The compound or salt of claim 353 wherein:



each B is, independently, ; and
each X is, independently, O or S.

359. A compound chosen from:

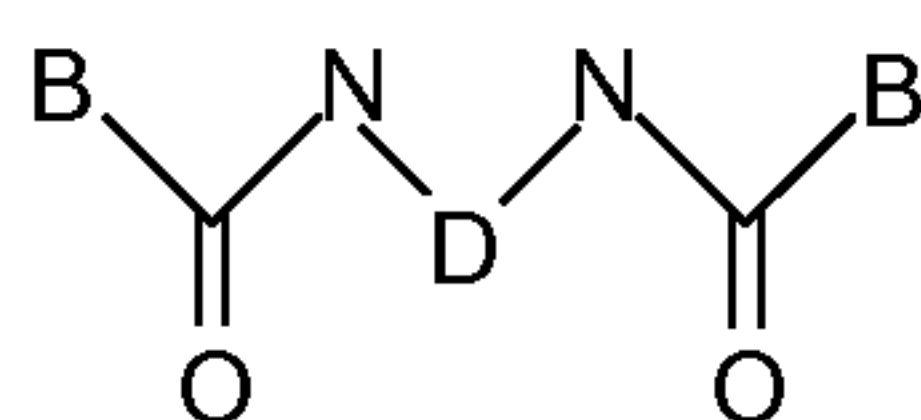


or pharmaceutically acceptable salt thereof.

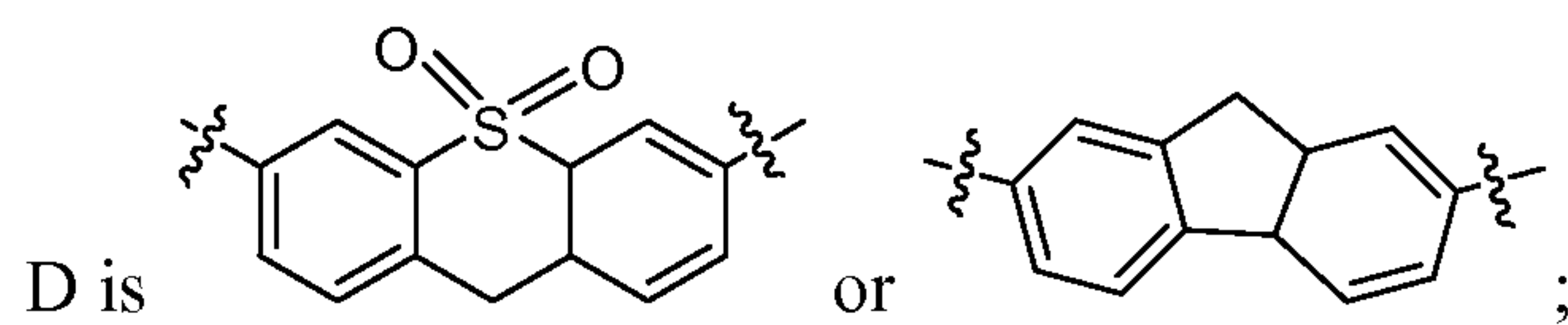
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360. A composition comprising the compound or salt of any one of claims 353 to 359 and a pharmaceutically acceptable carrier.

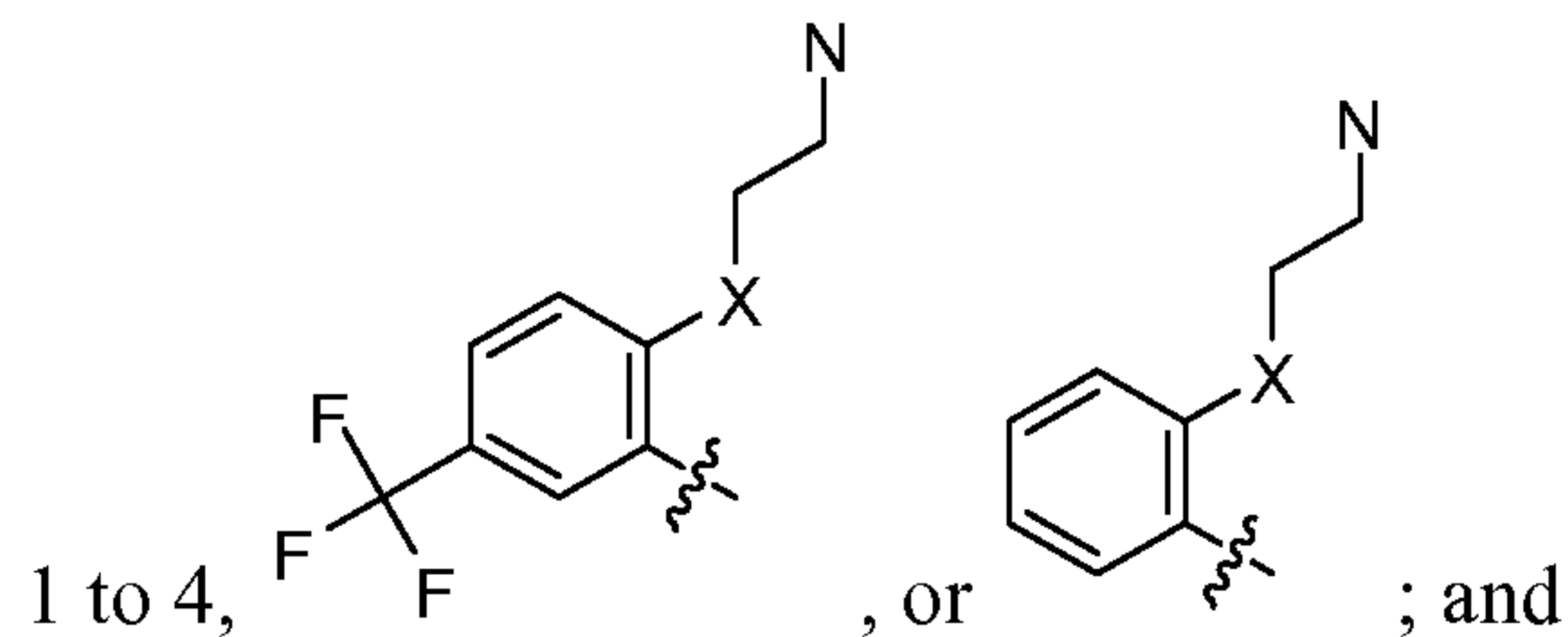
361. A method of treating malaria in an animal comprising administering to the animal a
15 therapeutically effective amount of a compound of Formula VIII:



wherein:



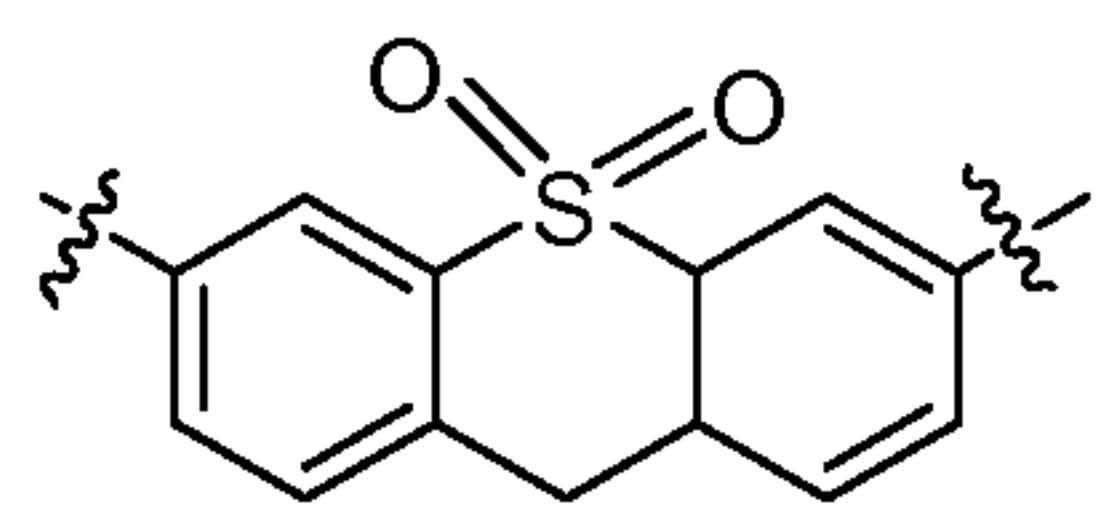
each B is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently,



each X is, independently, O or S;

5 or a pharmaceutically acceptable salt thereof.

362. The method of claim 361 wherein D is

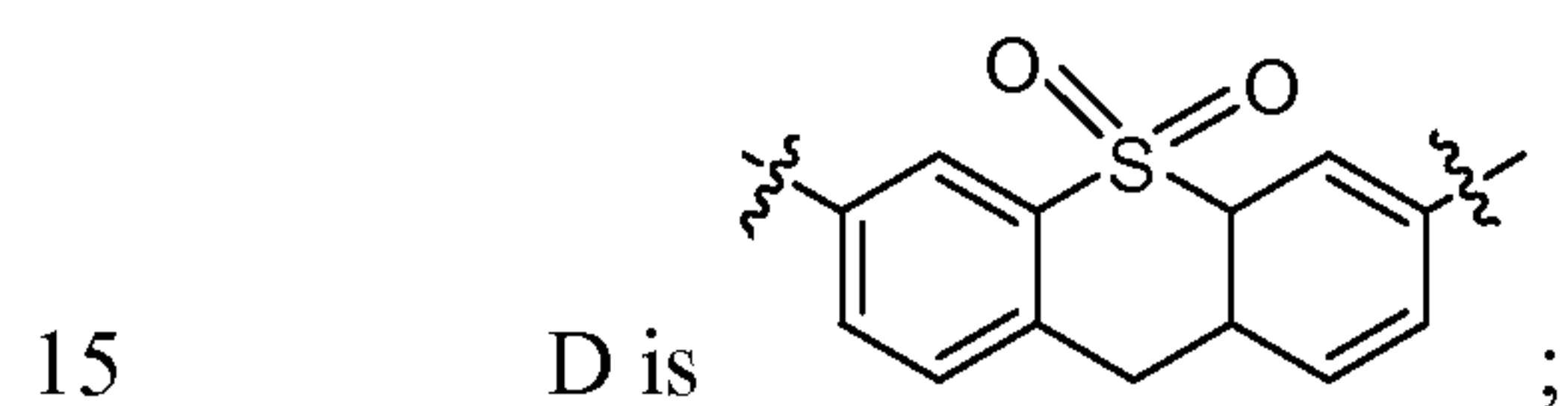


363. The method of claim 361 or claim 362 wherein each B is, independently,

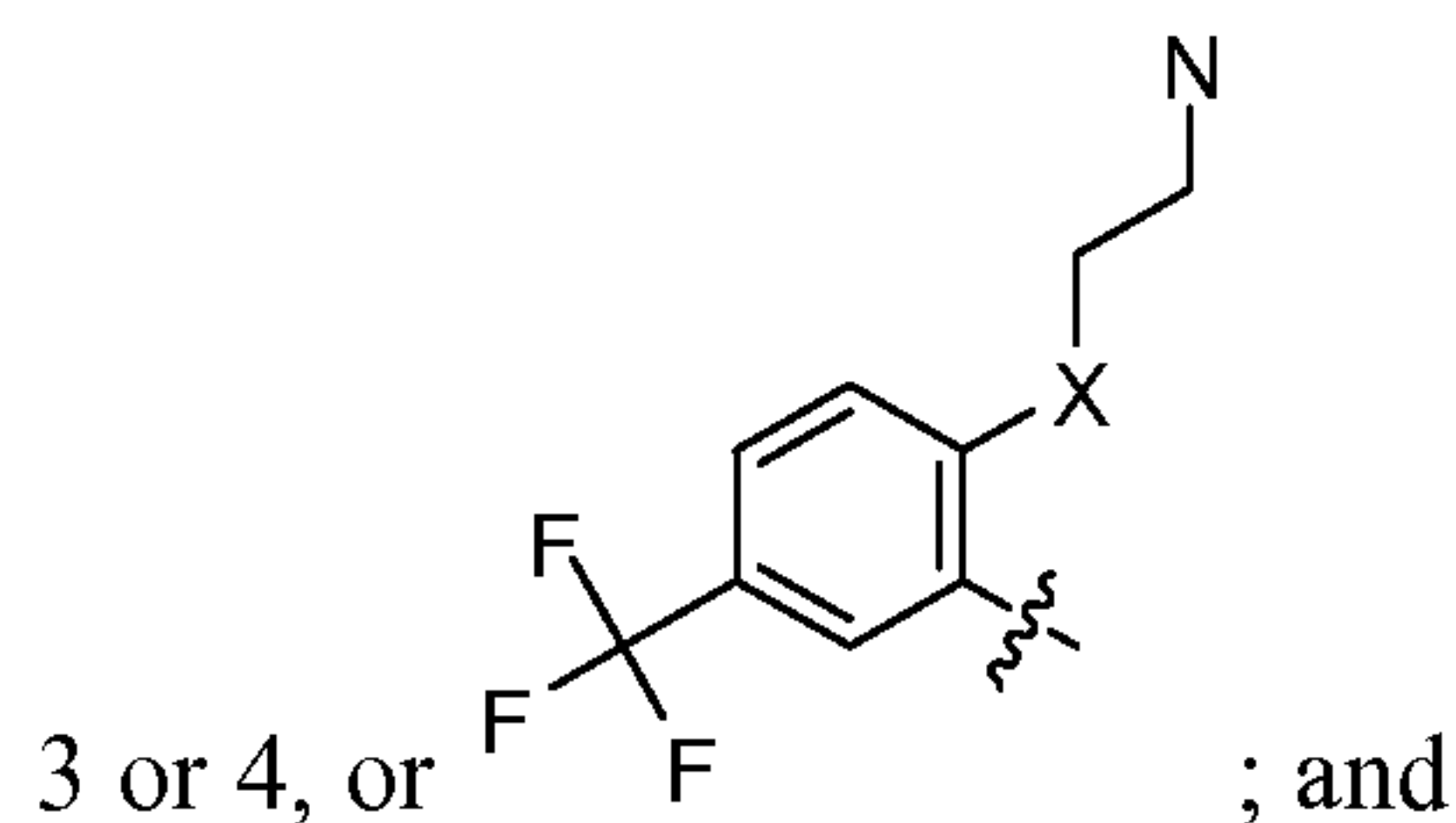
10 $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

364. The method of any one of claims 361 to 363 wherein each X is S.

365. The method of claim 361 wherein:



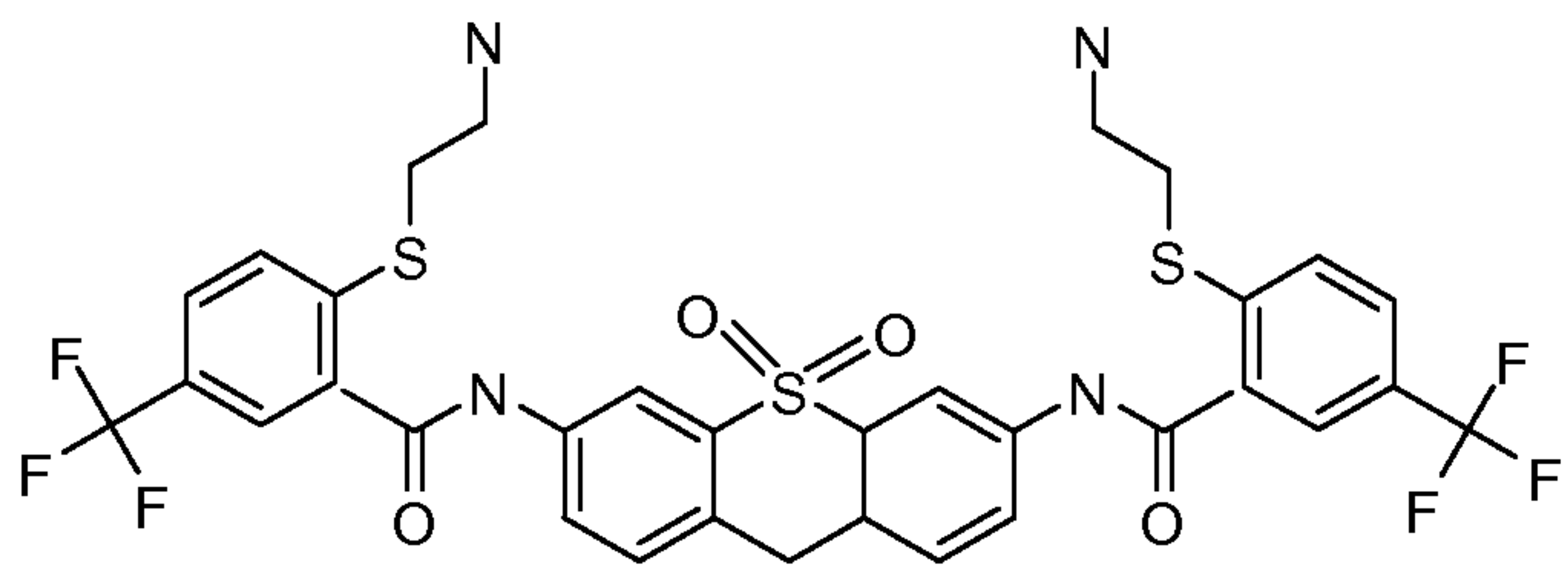
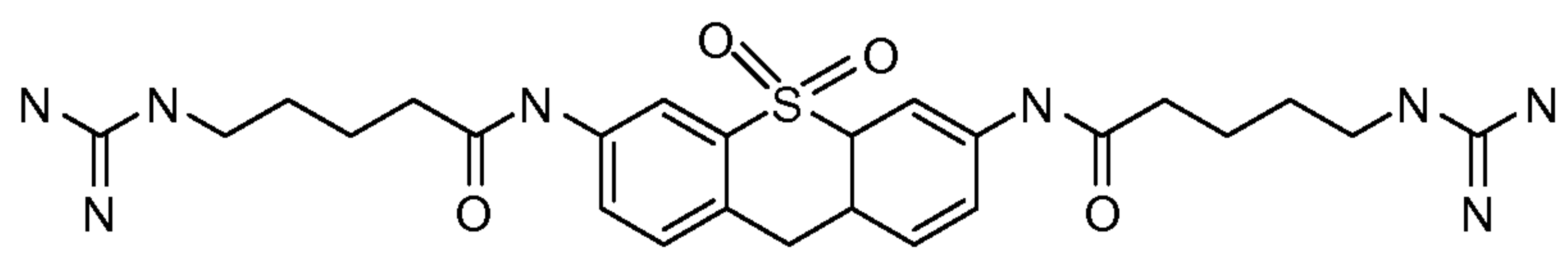
each B is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently,



each X is S.

D is 

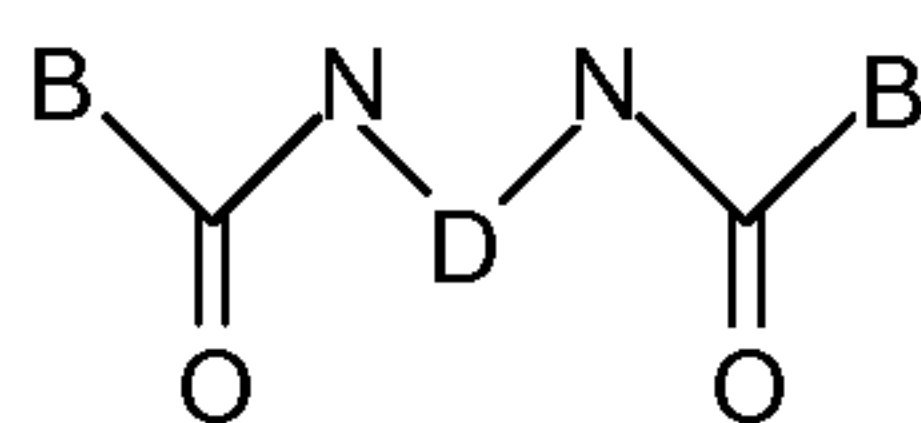
367. The method of claim 361 wherein the compound is chosen from:

O=C(Nc1ccc2c3ccccc3cc2c1)Oc1ccccc1OCCN

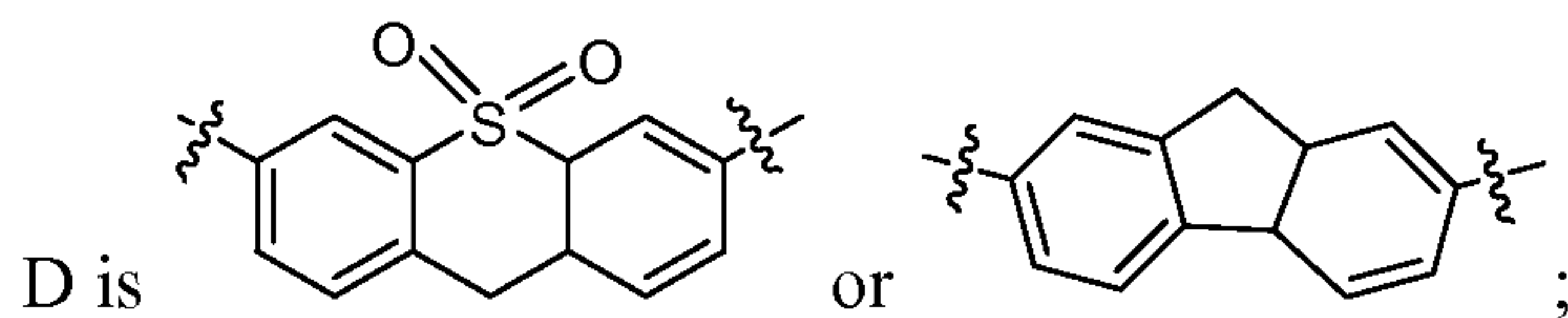
or pharmaceutically acceptable salt thereof.

15

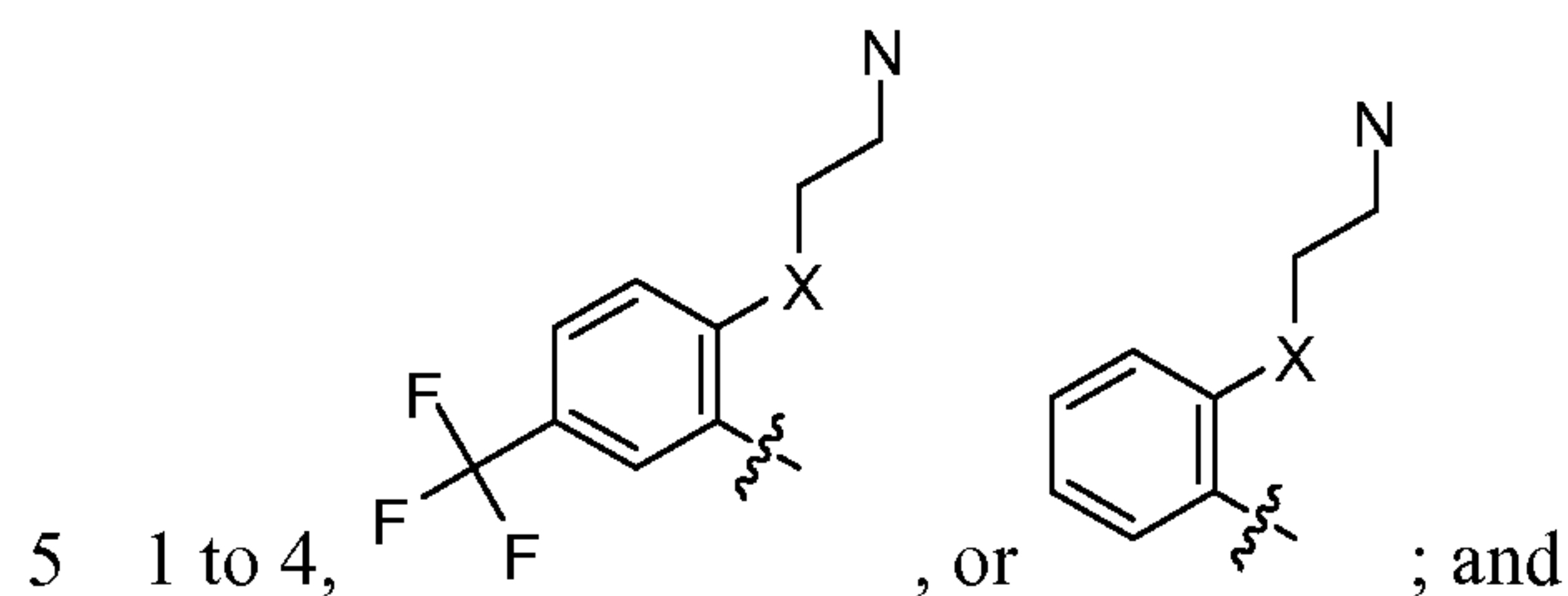
-218-



wherein:



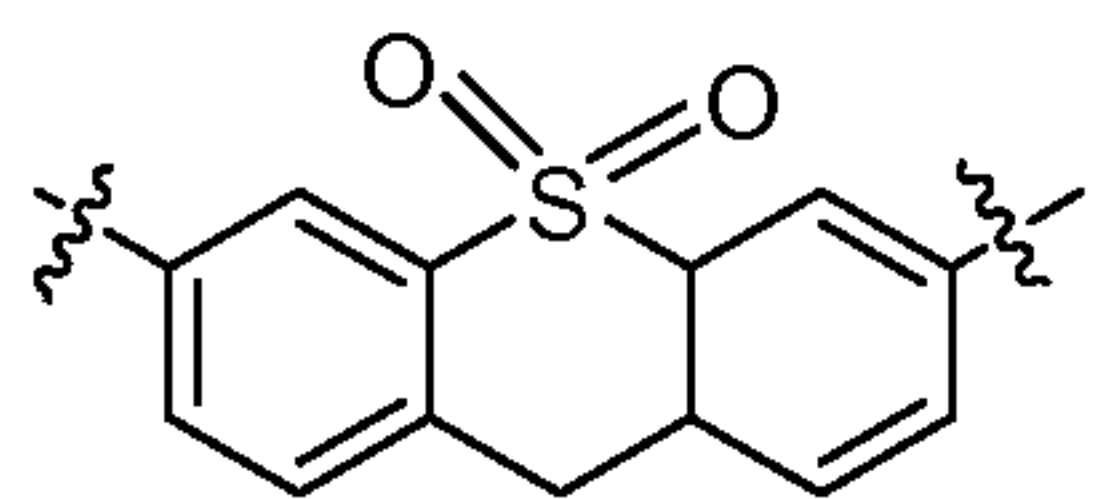
each B is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently,



each X is, independently, O or S;

or a pharmaceutically acceptable salt thereof.

370. The method of claim 369 wherein D is



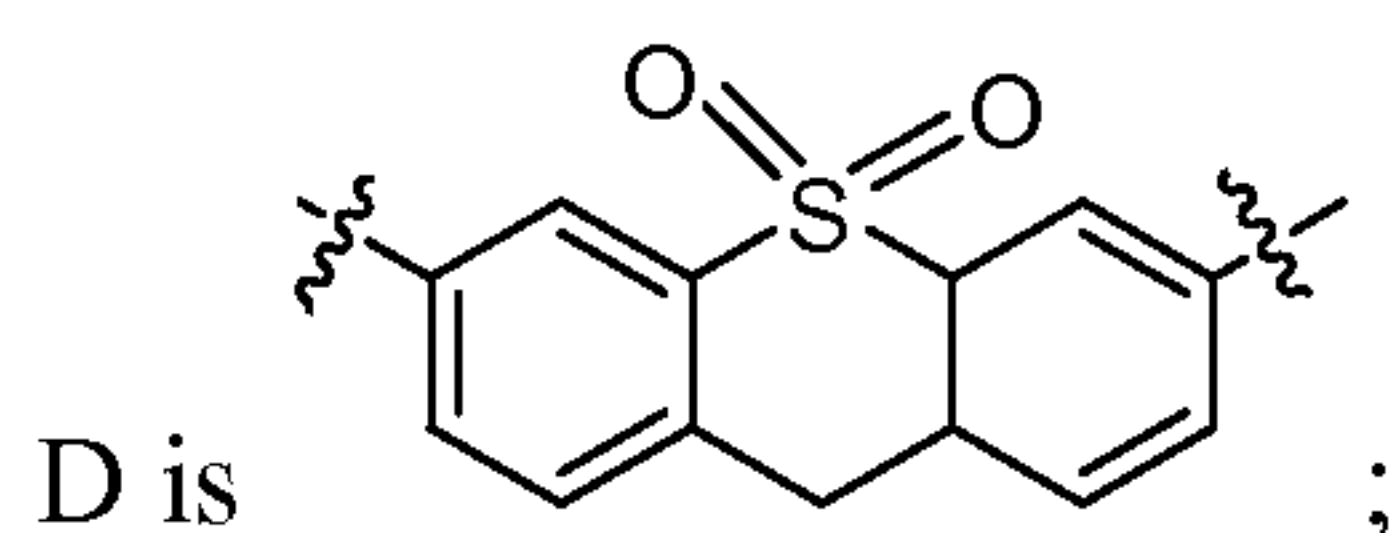
10

371. The method of claim 369 or claim 370 wherein each B is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently, 1 to 4.

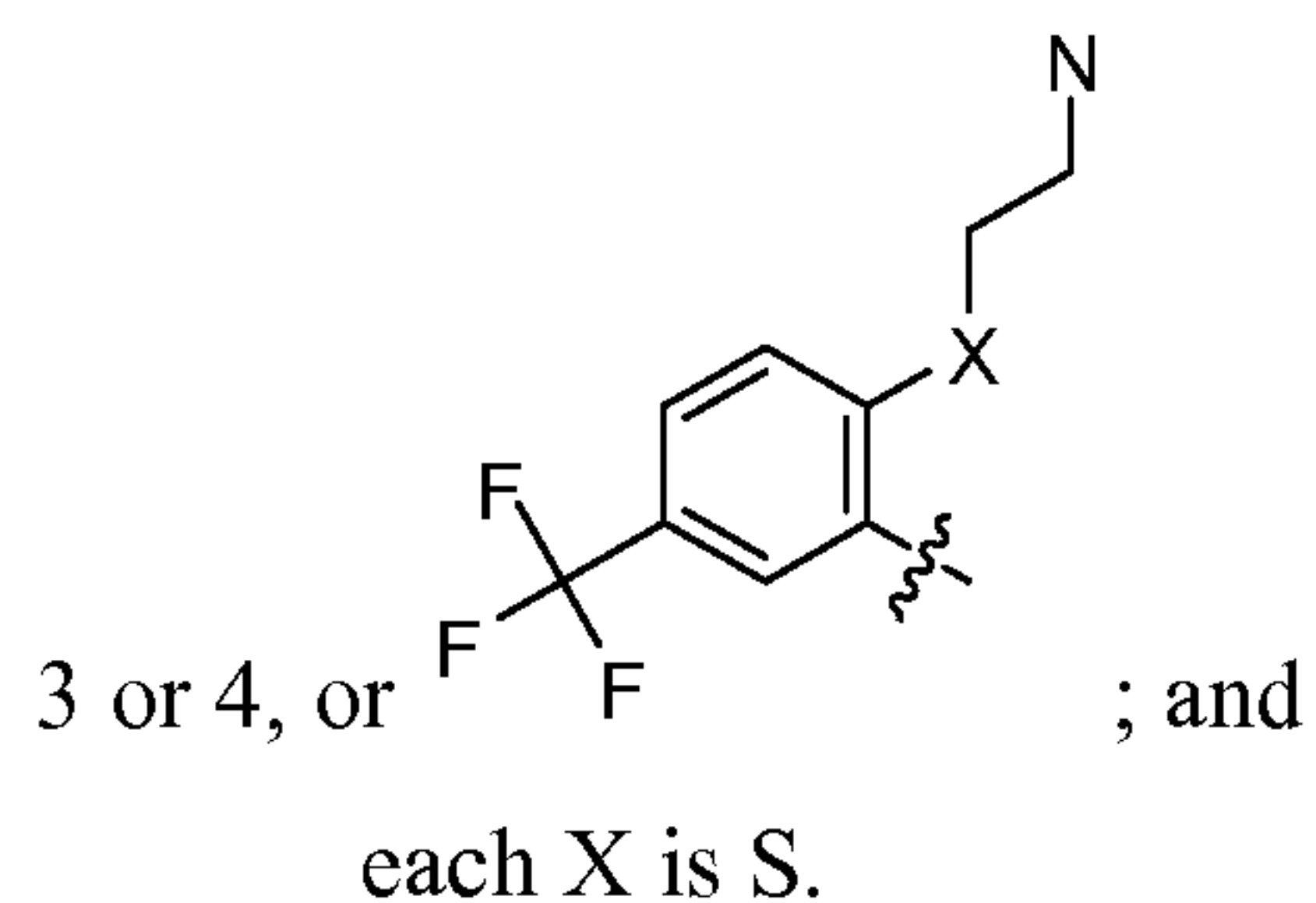
372. The method of any one of claims 369 to 371 wherein each X is S.

15

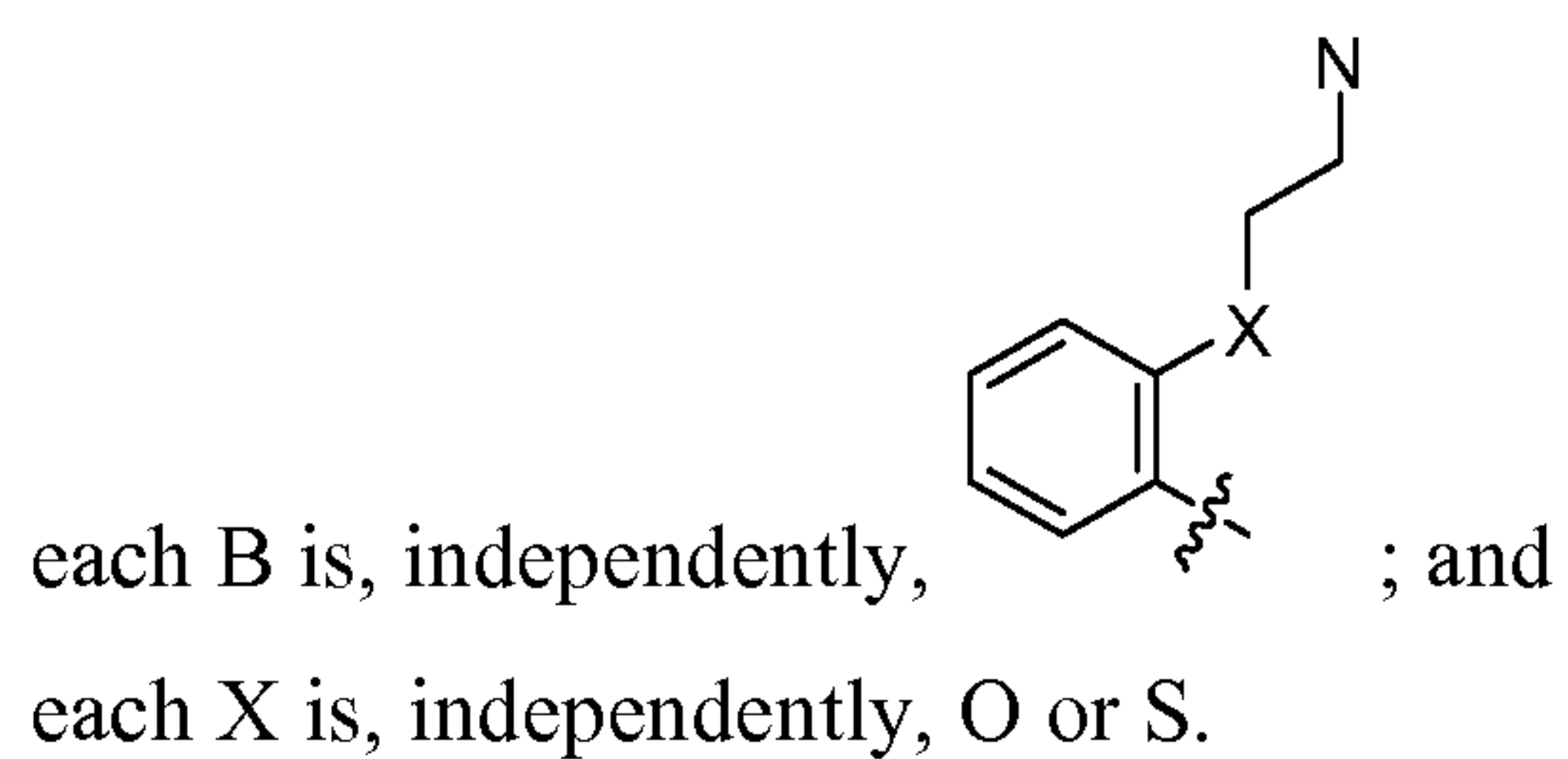
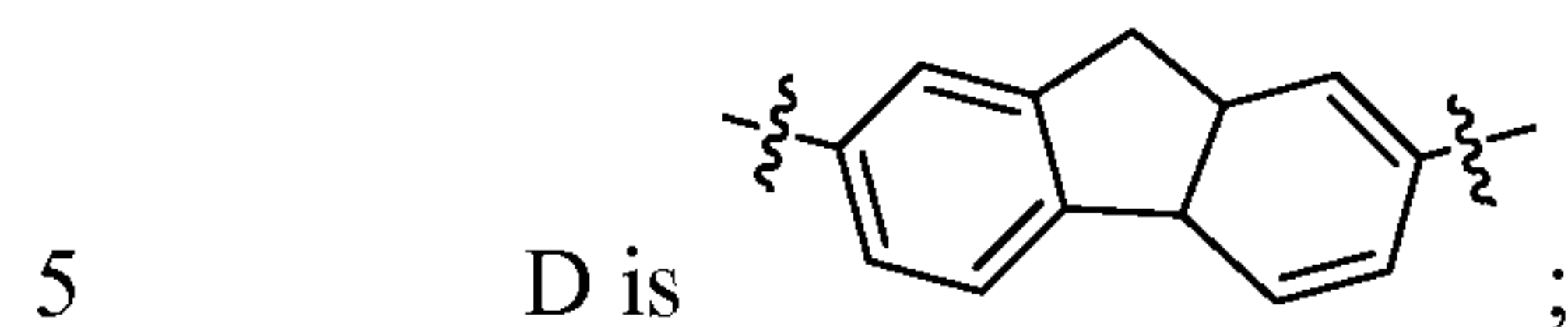
373. The method of claim 369 wherein:



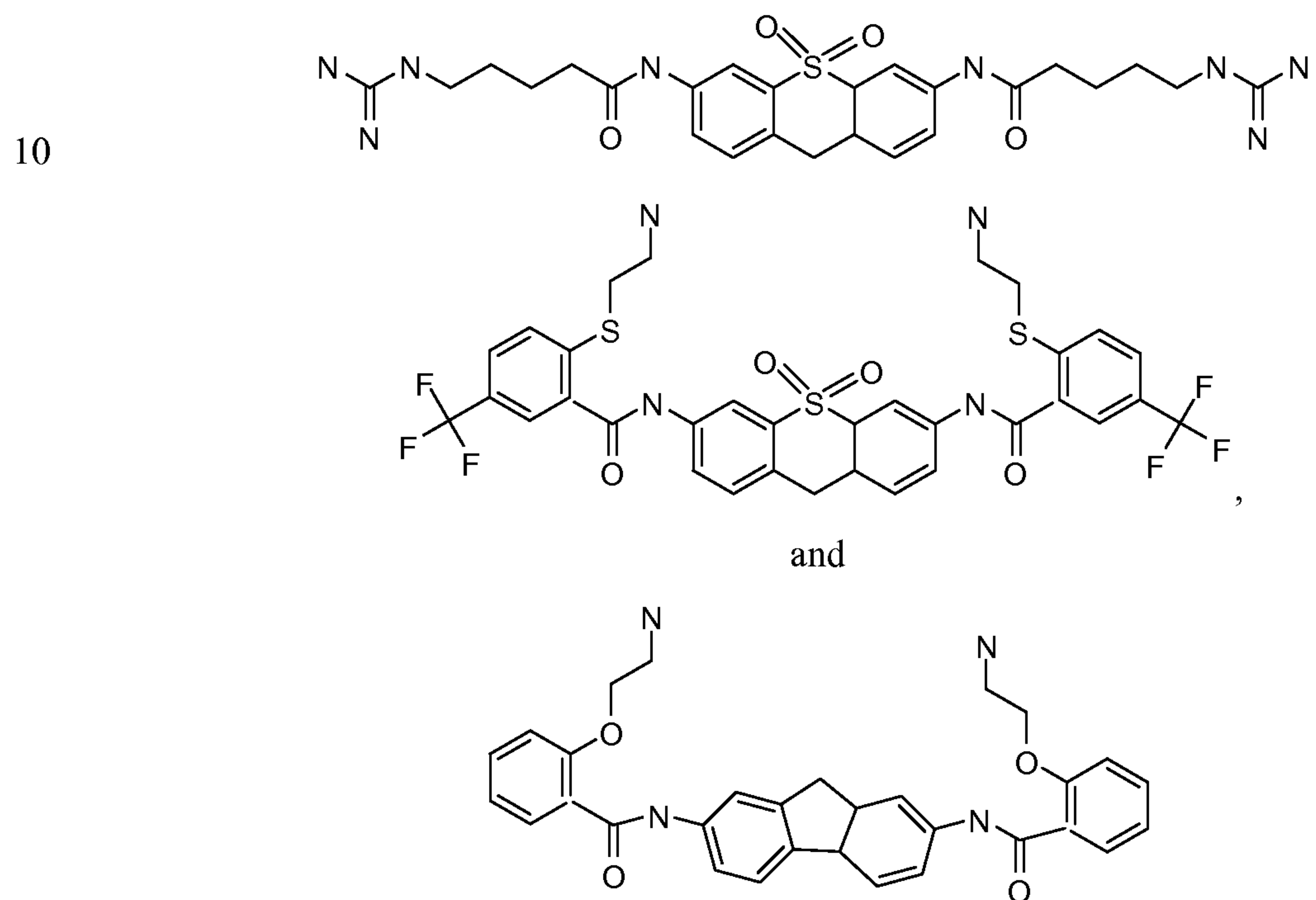
each B is, independently, $-(CH_2)_n-NH-C(=NH)NH_2$, where each n is, independently,



374. The method of claim 369 wherein:



375. The method of claim 369 wherein the compound is chosen from:



or pharmaceutically acceptable salt thereof.