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(71) Applicant: **NEOCULI PTY LTD** [AU/AU]; 4/25-37
Hungtingdale Road, Burwood, Victoria 3125 (AU).

(72) Inventors: **PAGE, Stephen**; 55 Campbell Street, New-
town, New South Wales 2042 (AU). **STEVENS, Andrew**;
3/10 Longerenong Street, Farrer, Australian Capital Territ-
ory 2607 (AU). **MCCLUSKEY, Adam**; 405 Warners
Road, Charlestown, New South Wales 2290 (AU). **KEEN-**

AN, Martine; Epichem Pty Ltd, Murdoch University Cam-
pus, 70 South Street, Murdoch, Western Australia 6150
(AU). **ABRAHAM, Rebecca**; School of Animal and
Veterinary Science, The University of Adelaide, Adelaide,
South Australia 5005 (AU).

(74) Agent: **WRAYS**; Ground Floor, 56 Ord Street, West Perth,
Western Australia 6005 (AU).

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(54) Title: METHODS FOR TREATING PROTOZOAN INFECTIONS

(57) Abstract: The invention provides compounds of Formula (I), and their use in methods for treating or preventing a protozoan infection in a subject using a compound of Formula (I). The invention also provides the use of a compound of Formula (I) in the manufacture of a medicament for the treatment of a protozoan infection in a subject. The invention further provides a medical device when used in a method of treating or preventing a protozoan infection in a subject and to a medical device comprising the composition of the invention.



METHODS FOR TREATING PROTOZOAN INFECTIONS**TECHNICAL FIELD**

[0001] This invention relates to compounds of Formula I and their use in methods for treating or preventing a protozoan infection in a subject using a compound of Formula I, the use of a compound of Formula I in the manufacture of a medicament for the treatment of a protozoan infection in a subject, and medical devices when used in a method of treating or preventing a protozoan infection in a subject.

BACKGROUND ART

[0002] Giardiasis, amoebiasis and cryptosporidiosis are the most common protozoal parasitic diseases of the human intestinal tract and common causes of enteric disease in non-human animal species as well. Different drugs have been used for the management of these diseases, but many have a significant failure rate in clearing parasites from the intestine and many are associated with a high incidence of undesirable side effects, which often leads to use being contraindicated in certain circumstances. There is a need in the art for an improved treatment which would require one or very few dosings, would be associated with a very high level of clearance of the target protozoal agent, would kill intestinal cysts (to reduce environmental contamination and the reservoir of reinfection), be associated with no or only mild and well tolerated adverse effects, have no pre-existing resistance, be safe for use in pregnant and lactating humans and other species and/or be suitable for use as a preventive medication.

[0003] Many existing antiprotozoal agents, especially those for the treatment of giardiasis, have suboptimal intrinsic efficacy. For metronidazole giardia curative rates may be high, but have also been reported as low as 60% (measured by clearance of the protozoan) in human adult and paediatric patients when it is administered for 5 - 10 days. Both metronidazole and tinidazole have been reported to have a median efficacy of approximately 89%. The newer anti-giardial agent, nitazoxanide has demonstrated an overall response rate of 75% (measured by clearance of the protozoan), ranging between 64 and 94%.

[0004] To improve compliance it is highly desirable that the dosage regimen is simple and of short duration. As outlined above, the duration of dosing with metronidazole is most commonly 5-10 days, leaving many opportunities for missed treatments, poor compliance and reduced efficacy or treatment failure.

[0005] Acquired resistance by giardia to the available treatments is widely experienced and an increasing cause of treatment failure. This is not surprising as the majority of currently recommended antiprotozoal agents have been in use for many decades. A review of

antiprotozoal agents approved by the FDA between 1987 and 2013 (Kesselheim, A. S. and J. J. Darrow (2014). "Drug Development and FDA Approval, 1938-2013." *New England Journal of Medicine* 370(26): e39) discloses only 7 new agents for all protozoan diseases (mefloquine in 1989, eflornithine in 1990, halofantrine and atovaquone in 1992, nitazoxanide in 2002, tinidazole in 2004 and the combination of artemether and lumefantrine in 2009). Amongst these agents, only nitazoxanide and tinidazole are used for giardia treatment, and both have median efficacies less than 90%.

[0006] Frequently it is the profile of adverse effects that limits the use of antiprotozoal agents. There is a diversity of adverse effects of currently available antiprotozoal agents. For example, side effects for the widely used metronidazole include metallic taste, nausea, headache, vertigo, leukopaenia, insomnia and irritability. Less frequently, CNS toxicity has been reported especially with high doses, and alcohol consumption is not recommended when taking metronidazole because of the possibility of developing a reaction similar to that of disulfiram. Metronidazole has been shown to be mutagenic in bacteria; based on animal studies, the drug has been carcinogenic at high doses and over long periods. For quinacrine adverse effects include headache, nausea, vomiting and a bitter taste, resulting in poor compliance. Yellow discolouration of the skin, urine and sclerae may also follow its administration. Blue or black pigmentation of the nails, urticaria and exfoliative dermatitis can also occur. Other side effects reported are haemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD)-deficiency, toxic psychosis and exacerbation of psoriasis. Quinacrine, in common with other antiprotozoal agents, is able to cross the placenta and reach the foetus, contraindicating its use during pregnancy due to a possible link with birth deformities. Other serious side effects described have included psychiatric disturbances.

[0007] For the treatment of Cryptosporidia and amoebiasis caused by *Entamoeba histolytica* the limitations on available treatments are even more limited than with giardia, with no consistently effective and specific treatment for Cryptosporidia (Cabada, M. M. and A. C. White, Jr. (2010). "Treatment of cryptosporidiosis: do we know what we think we know?" *Curr Opin Infect Dis* 23(5): 494-499).

[0008] There is an unmet clinical need for antiprotozoan agents with novel mechanisms of action to supplement and/or replace currently available antiprotozoan agents, the efficacy of which is increasingly undermined by antiprotozoan resistance mechanisms. There additionally remains a need for alternative antiprotozoan agents in the treatment of infection by multi-resistant protozoa. However, as reported by the Pharmaceutical Research and Manufacturers of America in their 2013 report "Medicines in Development for Infectious Diseases" no novel antiprotozoan agents and few line extensions are being developed that offer promising results over existing treatments.

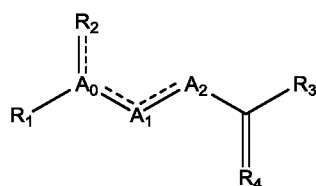
[0009] It is an object of the present invention to overcome at least one of the failings of the prior art.

[0010] The discussion of the background art set out above is intended to facilitate an understanding of the present invention only. The discussion is not an acknowledgement or admission that any of the material referred to is or was part of the common general knowledge as at the priority date of the application.

SUMMARY OF INVENTION

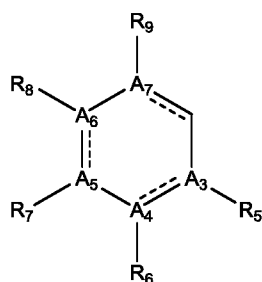
[0011] According to one aspect of the invention, there is a method of treating or preventing a protozoan colonisation or infection in a subject, the method including the step of administering a therapeutically effective amount of a compound of Formula I or stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof to the subject, wherein the protozoan infection is caused by a protozoan agent.

[0012] In one embodiment of the invention, the compound of Formula I, is:

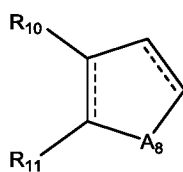


Formula I

[0013] In another embodiment of the invention, R_1 is H, cycloalkyl, Formula II, or Formula III;

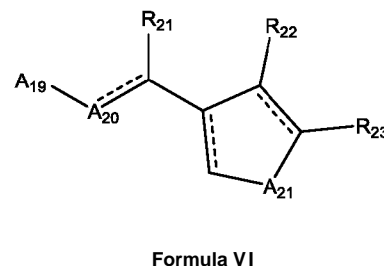
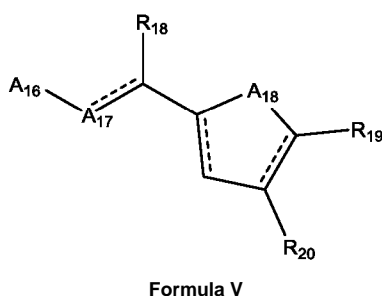
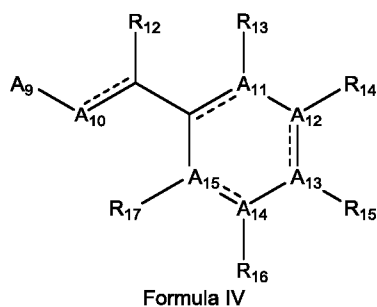


Formula II



Formula III

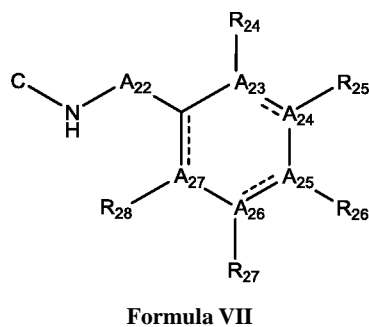
[0014] In another embodiment of the invention, R_3 is selected from the group consisting of : H; NH_2 ; NHNH_2 ; $\text{O-CH}_2\text{-CH}_3$; NH-C(=O)-phenyl ; N-CH-chlorophenyl ; NH-chlorophenyl ; $\text{NH-CH}_2\text{-chlorophenyl}$; $\text{NH-N-CH-cycloalkyl}$; N and R_4 is CH-N-CH-CCl - and R_4 is bonded to R_3 ; Formula IV; Formula V; and Formula VI;



[0015] In another embodiment of the invention, A_0 is N, C, CH, or A_0 is C and A_0 is bonded to R_4 to form a triazole ring.

[0016] In another embodiment, R_4 is CH-N-CH-CCI-. Preferably, R_4 is bonded to R_3 when R_3 is N.

[0017] In another embodiment of the invention, A_3 is N, C, NH, $-(CH)_2-N-$, $-(C_6H_5)C-CH-N-$, or Formula VII;



[0018] In another embodiment of the invention, A_2 is N, C, NH, N-C(O)-phenyl or Formula VII, or $(CH_2)_n$, wherein n is an integer between 1 and 3, inclusive.

[0019] In another embodiment of the invention, $A_3, A_4, A_5, A_6, A_7, A_8, A_n, A_{12}, A_{13}, A_{14}, A_{15}, A_{16}, A_{17}, A_{18}, A_{19}, A_{20}, A_{21}, A_{23}, A_{24}, A_{25}, A_{26}$ and A_{27} are independently C, O, N, NH, S.

[0020] In another embodiment of the invention, A_9 is C, O, N, NH, N-C(O)-O-CH₂-CH₃, N-C(O)-O-CH(CH₃)₂, N-C(O)-NH-CH₂-CH₃, N-C(O)-NH-CH₂-phenyl, N-C(O)-CH₂-CH₂-CH₂-CH₂-CH₂-CH₃, N-C(O)-CH₂-furan-2-yl.

[0021] In another embodiment of the invention, A_{10} is C, NH, $-N-(CH)_2-$, $-N-CH-C(C_6H_5)-$.

[0022] In another embodiment of the invention, A_{22} is $-CH(CH_3)-$, $-N-CH-$, $-N-C(CH_3)-$, $N-C(CH_2OH)-$.

[0023] In another embodiment of the invention, R_2 is H, COOH, CH₂NH₂, CH₂OH, CH₂NHNH₂, methyl, ethyl, propyl, butyl, pentyl, heptyl, cyclopentyl, CH₂(Cyclohexyl), (CH₂)₂(cyclopentyl), or

Formula VII and R_2 are R_4 are bonded together to form a pyrimidine, pyrazine or triazine ring, or R_2 and R_9 are bonded together to form a pyrrolidinyl oxindole ring.

[0024] In another embodiment of the invention, R_4 is H_2 , N, NH, O, S, or R_4 and A_0 are bonded together to form a triazole ring, or R_4 is N and R_4 and R_2 are bonded together to form a pyrimidine ring.

[0025] In another embodiment of the invention, R_7 is H, Cl, Br, F, OH, CH_3 , OCH_3 , SCH_3 , CN, CCH, CF_3 , OCF_3 , SCF_3 , NO_2 , butyl, f-butyl, dimethylamino, phenyl, n-propyl, l-propyl, $-NH-C(O)-CH_3$, $-(CH)_2-COOH$, piperazin-1-yl, or R_7 and R_8 are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring.

[0026] In another embodiment of the invention, R_6 , R_8 , R_{14} , R_{16} , R_{25} and R_{27} are independently H, OH, Cl, F, Br, CH_3 , CN, OCH_3 , COOH, NO_2 , CF_3 , R_8 and R_7 bond together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring, or benzene ring, R_{14} and R_{15} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, R_8 and R_9 are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R_{14} and R_{13} are bonded together to form a substituted or unsubstituted saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring.

[0027] In another embodiment of the invention, R_5 , R_9 , R_{17} , R_{24} and R_{28} are independently H, O, OH, Cl, F, Br, NH_2 , CH_3 , CF_3 , OCH_3 , CN, NO_2 , phenyl, $-NH-CH(OH)-CH_3$, $-NH-C(O)-CH_3$, or R_9 and R_8 are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R_{13} and R_{14} are bonded together to form a substituted or unsubstituted saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring.

[0028] In another embodiment of the invention, R_{10} , R_n , R_{19} , R_{20} , R_{22} and R_{23} are independently H, Cl, or Br, or R_{10} and R_{11} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R_{19} and R_{20} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R_{22} and R_{23} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring

[0029] In another embodiment of the invention, R_{12} , R_{18} and R_{21} are independently H, COOH, CH_2NH_2 , CH_2OH , methyl, ethyl, propyl, butyl, cyclopentyl, or R_{12} and R_{13} are bonded together to form a pyrrolidinyl oxindole ring.

[0030] In another embodiment of the invention, R_{15} and R_{26} are independently H, Cl, Br, F, OH, CH_3 , OCH_3 , SCH_3 , CN, CF_3 , OCF_3 , SCF_3 , NO_2 , CCH, n-butyl, f-butyl, dimethylamino, phenyl, n-propyl, /-propyl, $-NH-C(=O)-CH_3$, $-(CH_2)_2-COOH$, piperazin-1-yl, or R_{15} and R_{14} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, and

[0031] In another embodiment of the invention, "— " is a double bond or a single bond.

[0032] In another embodiment of the invention, the compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, is selected from the compounds presented in Figure 1.

[0033] In another embodiment of the invention, the compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof comprises the following features:

wherein A_0 is C;

wherein A_1 is N; or Formula VII;

wherein A_2 is N; or NH;

wherein $A_3, A_4, A_6, A_7, A_n, A_{12}, A_{14}, A_{15}$, are N; or C;

wherein $A_5, A_{13}, A_{23}, A_{24}, A_{25}, A_{26}$ and A_{27} are C;

wherein A_8 and A_{21} are S;

wherein A_9 is NH;

wherein A_{10} is N;

wherein A_{22} is $-N-CH-$; $-N-C(CH_3)-$; or $-N-C(CH_2OH)-$;

wherein R_1 is H; Formula II; Formula III; cycloalkyl;

wherein R_2 is H; methyl; ethyl; CH_2NHNH_2 ; CH_2OH ; butyl; cyclopentyl; or Formula VII and R_2 is bonded to R_4 , to form a pyrimidine ring;

wherein R_3 is NH_2 ; Formula IV; Formula V; Formula VI; NH_2 , $NH-N-CH-cycloalkyl$; or $O-CH_2-CH_3$;

wherein R_4 is NH; O; S; or R_4 is N and R_4 and R_2 are bonded together to form a pyrimidine ring;

wherein R_7 is H; F; Cl; CF_3 ; methyl; R_7 and R_8 are bonded together to form an unsubstituted, benzene ring; OH; f-butyl; phenyl; dimethylamino; /-propyl; n-propyl; CN; CCH; n-butyl; SCH_3 ; R_7 and R_8 are bonded together to form an unsubstituted, unsaturated heterocyclic ring; OCH_3 ; Br; OCF_3 ; piperazin-1-yl; or SCF_3 ;

wherein R_6, R_8, R_{14} , and R_{16} are independently H; OH; F; OCH_3 ; CF_3 ; methyl; Cl; CN; Br; R_8 and R_7 are bonded together to form an unsubstituted, benzene ring; R_8 and R_7 are bonded together to form an unsubstituted, unsaturated heterocyclic ring; R_{14} and R_{15} are

bonded together to form an unsubstituted, benzene ring; or R_{14} and R_{15} are bonded together to form an unsubstituted, unsaturated heterocyclic ring;

wherein R_5 , R_9 , R_{13} , and R_{17} are independently H; OH; NH_2 ; Cl; F; OCH_3 ; OH; $-NH-CH(OH)-CH_3$;

wherein R_{12} is H; methyl; ethyl; CH_2OH ; or cyclopentyl;

wherein R_{15} is H; F; Cl; CF_3 ; methyl; R_7 and R_8 are bonded together to form an unsubstituted, benzene ring; OH; *i*-butyl; phenyl; dimethylamino; *l*-propyl; *n*-propyl; CN; CCH; *n*-butyl; SCH_3 ; R_{15} and R_{14} are bonded together to form an unsubstituted, unsaturated heterocyclic ring; OCH_3 ; Br; OCF_3 ; piperazin-1-yl; or SCF_3 ;

wherein R_{24} and R_{28} are independently H; OH; or Cl;

wherein R_{25} and R_{27} are independently H; or OH;

wherein R_{26} is H; CH_3 ; Br; Cl; OH; dimethylamino; $-O-P(0)(OEt)_2$; CF_3 ; or F; and

wherein "—" is independently a single or a double bond.

[0034] In another embodiment of the invention, the compound is selected from the group comprising: NCL008; NCL009; NCL023; NCL025; NCL026; NCL028; NCL029; NCL036; NCL037; NCL039; NCL040; NCL050; NCL061; NCL062; NCL064; NCL065; NCL068; NCL075; NCL076; NCL078; NCL079; NCL080; NCL081; NCL084; NCL085; NCL086; NCL088; NCL089; NCL090; NCL092; NCL094; NCL095; NCL097; NCL098; NCL099; NCL101; NCL104; NCL105; NCL106; NCL108; NCL111; NCL112; NCL114; NCL115; NCL116; NCL118; NCL119; NCL121; NCL122; NCL123; NCL124; NCL125; NCL126; NCL130; NCL131; NCL132; NCL133; NCL135; NCL136; NCL137; NCL138; NCL139; NCL140; NCL141; NCL144; NCL145; NCL146; NCL147; NCL148; NCL150; NCL152; NCL153; NCL154; NCL156; NCL157; NCL158; NCL159; NCL161; NCL162; NCL164; NCL165; NCL166; NCL167; NCL168; NCL169; NCL170; NCL171; NCL172; NCL173; NCL174; NCL176; NCL177; NCL178; NCL179; NCL180; NCL181; NCL183; NCL184; NCL185; NCL186; NCL187; NCL188; NCL189; NCL190; NCL193; NCL194; NCL195; NCL196; NCL197; NCL198; NCL199; NCL200; NCL201; NCL202; NCL203; NCL204; NCL205; NCL206; NCL207; NCL208; NCL209; NCL210; NCL211; NCL212; NCL213; NCL215; NCL216; NCL217; NCL218; NCL219; NCL220; NCL221; NCL222; NCL223; NCL223; NCL224; NCL225; NCL226; NCL227; NCL228; NCL229; NCL230; NCL231; NCL232; NCL233; NCL234; NCL235; NCL236; NCL237; NCL238; NCL239; NCL240; NCL241; NCL242; NCL243; NCL244; NCL245; NCL246; NCL247; NCL248; NCL249; NCL250; NCL251; NCL252; NCL253; NCL254; NCL255; NCL256; NCL257; NCL258; NCL259; NCL260; NCL261; NCL262; NCL263; NCL264; NCL265; NCL266; NCL267; NCL268; NCL269; NCL270; NCL271; NCL272; NCL273; NCL274; and NCL275.

[0035] In another embodiment of the invention, the compound is selected from the group comprising: NCL028; NCL040; NCL062; NCL078; NCL079; NCL080; NCL081; NCL084; NCL088; NCL089; NCL097; NCL099; NCL123; NCL146; NCL157; NCL158; NCL177; NCL179;

NCL188; NCL193; NCL195; NCL196; NCL197; NCL199; NCL202; NCL204; NCL205; NCL215; NCL216; NCL217; NCL219; NCL221 ; NCL245 and NCL246.

[0036] In a preferred embodiment of the invention, the compound is selected from the group comprising: NCL062; NCL078; NCL079; NCL080; NCL081 ; NCL084; NCL089; NCL097; NCL099; NCL157; NCL158; NCL179; NCL188; NCL193; NCL195; NCL196; NCL199; NCL204; NCL216; NCL217; NCL219; NCL221 ; NCL245 and NCL246.

[0037] In an even more preferred embodiment of the invention, the compound is selected from the group comprising: NCL062; NCL089; NCL097; NCL099; NCL157; NCL179; NCL188; NCL193; NCL195; NCL196; NCL216; NCL219; and NCL221 .

[0038] In an even more preferred embodiment of the invention, the compound is selected from the group comprising: NCL062; NCL097; NCL099; NCL157; NCL179; NCL188; NCL195; and NCL196.

[0039] In another embodiment of the invention, the compound is a chloride salt.

[0040] In another embodiment of the invention, the compound is a compound selected from the group comprising: NCL812 and NCL062. In another embodiment of the invention, the compound is not a compound selected from the group comprising: NCL812 and NCL062. For example, the compound is NCL099.

[0041] In another embodiment of the invention, the compound is a compound selected from the group comprising: NCL020, NCL021 , NCL024, NCL035, NCL072, NCL077, NCL107, NCL109, NCL134, NCL143, NCL143, NCL151 , NCL155 and NCL160. In another embodiment of the invention, the compound is not a compound selected from the group comprising: NCL020, NCL021 , NCL024, NCL035, NCL072, NCL077, NCL107, NCL109, NCL134, NCL143, NCL143, NCL151 , NCL155 and NCL160. For example, the compound is NCL099.

[0042] In another embodiment of the invention, the subject is an animal most preferably selected from the group comprising: human, canine, feline, bovine, ovine, caprine, porcine, avian, piscine and equine species.

[0043] In another embodiment of the invention, the compound is administered to the subject in a dose in the range of 0.1 mg/kg to 250 mg/kg bodyweight.

[0044] In another embodiment of the invention, the protozoan agent is selected from the group of protozoa genera comprising: Acanthamoeba, Babesia, Balamuthia, Balantidium, Besnoitia , Blastocystis, Chilomastix, Cochlosoma, Cryptosporidium, Cyclospora, Cystoisospora, Cytauxzoon, Dientamoeba, Eimeria, Endolimax, Entamoeba, Giardia, Haemoproteus,

Hammondia Hartmannella, Hepatozoon, Hexamita, Histomonas, Isospora, Leishmania (including subgenus Viannia), Leucocytozoon, Naegleria, Neospora, Pentatrachomonas, Plasmodium (including subgenera Plasmodium (Bennettinia) (birds); Plasmodium (Giovannolaia) (birds); Plasmodium (Haemamoeba) (birds); Plasmodium (Huffia) (birds); Plasmodium (Laverania) (higher primates, includes Plasmodium falciparum); Plasmodium (Novyella) (birds); Plasmodium (Paraplasmodium) (lizards); Plasmodium (Plasmodium) (higher primates, includes Plasmodium brasilianum, cynomolgi, inui, knowlesi, malariae); Plasmodium (Sauramoeba) (lizards); Plasmodium (Vinckeia)), Sappinia, Sarcocystis, Tetratrachomonas, Theileria, Toxoplasma, Trichomonas, Tritrichomonas, Trypanosoma (Subgenera Duttonella, Herpetosoma, Nannomonas, Schizotrypanum, Trypanozoon), Tyzzeria and Wenyonella.

[0045] In another embodiment of the invention, the protozoan agent is selected from the group of protozoa listed in Table 1 (see below).

[0046] In another embodiment of the invention, the protozoan agent is a resistant protozoa.

[0047] In another embodiment of the invention, the infection or colonisation is caused by a mixture of at least two protozoan agents.

[0048] In another embodiment of the invention, the protozoan agent is resistant to one or more compounds selected from the group listed in Table 2 (see below).

[0049] In another embodiment of the invention, the protozoan agent is resistant to the compound when the protozoan agent is exposed to the compound at a concentration range selected from the following: 0.001 µg/mL - 10,000 µg/mL; 0.01 µg/mL - 1000 µg/mL; 0.10 µg/mL - 100 µg/mL; and 1 µg/mL - 50 µg/mL.

[0050] In another embodiment of the invention, the protozoan infection or colonisation in the subject is a zoonosis.

[0051] In another embodiment of the invention, the protozoan infection or colonisation in the subject substantially causes an indication selected from the group comprising: Trypanosomosis (caused by the order, Kinetoplastorida of the family, Trypanosamidae); Amboebiasis (caused by the subphylum, Sarcodina, of the order, Amoebozoa, of the family Endamoebidae); Babesiosis (caused by the class, Piroplasmida, of the family, Babesiidae); Balantidiosis (caused by the phylum, Ciliophora, of the order, Trichostomatorida, of the family Balantidiidae); Chagas Disease (caused by the order, Kinetoplastorida, of the family, Trypanosomatidae); Cryptosporidiosis (caused by the subclass, Coccidea, of the family, Cryptosporidiidae); Giardiasis (caused by the class, Zoomastigophora, of the order, Diplomonadida, of the family, Diplomonadida, including Giardia lamblia); Leishmaniasis (caused by the class,

Zoomastigophora, of the family, Trypanosomatidae, of the genus, Leishmania); Malaria (caused by the genus, Plasmodium, including *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*); Sarcocystosis (caused by the subclass, Coccidia, of the order Eucoccidiorida, of the family Sarcocystidae); Toxoplasmosis (cause by the subclass, Coccidia, of the order, Eucoccidiorida, of the family, Sarcocystidae, including *Toxoplasma gondii*); Cyclosporiasis (caused by the species, *Cyclospora cayetanensis*); Infections caused by free-living Amoebae (caused by *Naegleria*, *Acanthamoeba* and/or *Balamuthia*); Malaria in Non-human Primates (caused by the genus, Plasmodium); Microsporidiosis (caused by *Enterocytozoon bieneusi*, *Encephalitozoon intestinalis* and/or *E. cuniculi*); Atypical Human Trypanosomosis (*T. lewisi*, *T. evansi*, *T. brucei*, *T. vivax*, and/or *T. congolense*); Trichomoniasis (caused by *Trichomonas vaginalis*); Amoebic dysentery (caused by *Entamoeba histolyticum*); and Acanthamoebiasis (caused by *Acanthamoeba*).

[0052] In another embodiment of the invention, the therapeutically effective amount of compound of Formula I, or a therapeutically acceptable salt thereof, is administered to the subject by oral administration.

[0053] In another embodiment of the invention, the therapeutically effective amount of compound of Formula I, or a therapeutically acceptable salt thereof, is administered to the subject together with a second antimicrobial agent selected from the group consisting of compounds listed in Table 2 (see below).

[0054] In another embodiment of the invention, the therapeutically effective amount of compound of Formula I, or a therapeutically acceptable salt thereof, is administered to the subject by parenteral administration.

[0055] In another embodiment of the invention, the therapeutically effective amount of compound of Formula I, or a therapeutically acceptable salt thereof, is administered to the subject by topical administration.

[0056] In a further aspect of the invention, the invention is a antiprotozoan pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I, or a therapeutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient or carrier.

[0057] In a further aspect of the invention, the invention is a antiprotozoan veterinary composition comprising a therapeutically effective amount of a compound of Formula I, or a therapeutically acceptable salt thereof, and optionally a veterinary acceptable excipient or carrier.

[0058] In another embodiment of the invention, the composition comprises a further antimicrobial agent selected from the group listed in Table 2 (see below).

[0059] In another embodiment of the invention, the composition is adapted for oral administration.

[0060] In another embodiment of the invention, the composition is adapted for parenteral administration.

[0061] In another embodiment of the invention, the composition is adapted for topical administration.

[0062] In a further aspect of the invention, the invention is the use of a compound of Formula I, or a therapeutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a protozoan colonisation or infection in a subject. In another embodiment of the invention, the use comprises administering a therapeutically effective amount of compound of Formula I, or a therapeutically acceptable salt thereof, to the subject. In another embodiment of the invention, the compound of Formula I is administered to the subject in a dose in the range of 0.1 mg/kg to 250 mg/kg body weight. In one preferred embodiment, the compound is administered to the subject in a dose in the range selected from the group consisting of: 0.1 mg/kg to 100 mg/kg body weight; 0.1 mg/kg to 50 mg/kg body weight; 1 mg/kg to 20 mg/kg body weight; 1 mg/kg to 10 mg/kg body weight; and 2 mg/kg to 5 mg/kg body weight. In one preferred embodiment, the compound is administered to the subject at a dose that achieves within 1 hour a compound plasma concentration range selected from the group consisting of: 0.0^μg/ml - 100^μg/ml; 0.^μg/ml - 10Mg/ml; ^μg/ml - 8^μg/ml. Preferably, after 1 hour, the dose achieves a compound plasma concentration above 8^μg/ml. Preferably, after 7 hours, the dose achieves a compound plasma concentration above 8^μg/ml. Preferably, after 24 hours, the dose achieves a compound plasma concentration above 8^μg/ml.

[0063] In one preferred embodiment, the compound is administered to the subject at a frequency selected from the group consisting of: every 30 minutes; every hour; every 2 hours; every 3 hours; every 4 hours; every 5 hours; every 6 hours; every 8 hours; every 12 hours; once daily; every 2 days; once weekly; twice weekly; once every 2 weeks; once monthly; once every 2 months; once every 3 months; once every 4 months; once every 5 months; once every 6 months; once every year; once every 2 years; and once.

[0064] In another embodiment of the invention, the medicament is administered to the subject by oral administration. In another embodiment of the invention, the medicament is administered to the subject by parenteral administration. In another embodiment of the invention, the medicament is administered to the subject by topical administration.

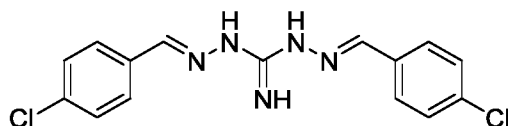
[0065] In a further aspect of the invention, the invention is a medical device when used in a method of treating or preventing a protozoan colonisation or infection in the subject, wherein the medical device comprises the composition of the invention. In another embodiment of the invention, the medical device is in a form selected from the group comprising: a plaster, a bandage, a dressing or implant applied to a protozoan colonisation or infection in a subject.

[0066] In a further aspect of the invention, the invention is a method of killing protozoa, the method including the step of contacting the protozoa with a compound of Formula I, or a therapeutically acceptable salt thereof.

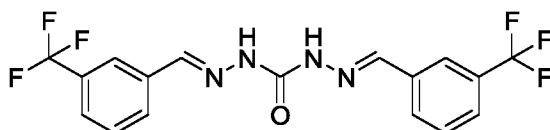
[0067] In a further aspect of the invention, the invention is the use of a compound of Formula I, or a therapeutically acceptable salt thereof, to kill protozoa, said use comprising the step of contacting the protozoa with a compound of Formula I, or a therapeutically acceptable salt thereof.

[0068] In a further aspect of the invention, the invention is a method, a composition, device or a use, substantially as described herein with reference to the accompanying Examples and Figures.

[0069] In a preferred aspect of the invention, the compound of Formula I is robenidine (also referenced in this specification as NCL812 and also known as 1,3-bis[(E)-(4-chlorophenyl)methyleneamino]guanidine), which has a structure as follows:

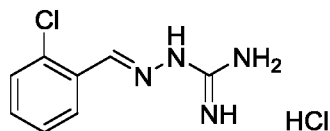


[0070] In one preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_7 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_8, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_7, R_9, R_{12}, R_{13}, R_{15}, R_{16}, R_{17}$ are H; R_4 is O; R_e and R_{14} are CF_3 ; and "—" in Formula I between A_0 and A_1 , all Formula II and all Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL101):

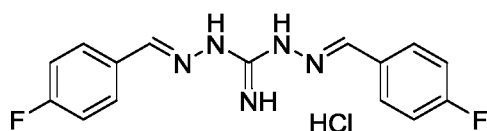


[0071] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof,

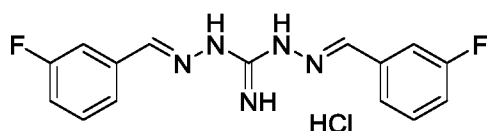
wherein R_1 is Formula II; R_3 is NH_2 ; A_1 is N and A_2 is NH; $A_0, A_3, A_4, A_5, A_6,$ and A_7 are C; $R_2, R_5, R_6, R_7,$ and R_8 are H; R_4 is NH; R_9 is Cl; and "—" in Formula I between A_0 and A_1 and all Formula II "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL015):



[0072] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and $A_{15},$ are C; $R_2, R_5, R_6, R_8, R_9, R_{12}, R_{13}, R_{14}, R_{16}, R_{17}$ are H; R_4 is NH; R_7 and R_{15} are F; and "—" in Formula I between A_0 and $A_1,$ all Formula II and all Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL021):

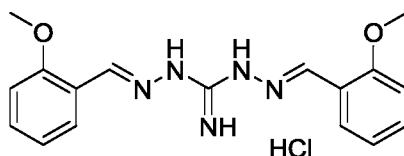


[0073] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and $A_{15},$ are C; $R_2, R_5, R_6, R_7, R_9, R_{12}, R_{13}, R_{15}, R_{16}, R_{17}$ are H; R_4 is NH; R_8 and R_{14} are F; and "—" in Formula I between A_0 and $A_1,$ all Formula II and all Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL023):

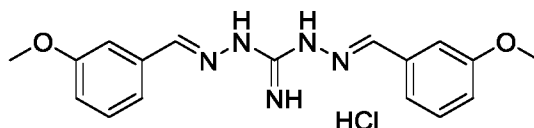


[0074] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and $A_{15},$ are C; $R_2, R_5, R_6, R_7, R_8, R_{12}, R_{14}, R_{15}, R_{16}, R_{17}$ are H; R_4 is NH; R_9 and R_{13} are OCH_3 ; and "—" in Formula I between A_0 and $A_1,$ all Formula II and all Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL028):

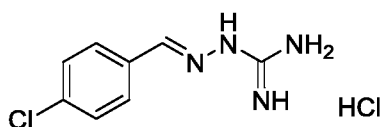
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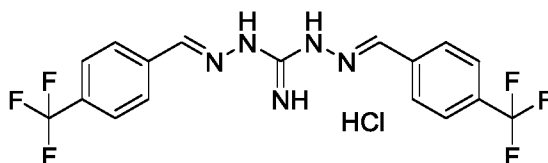
[0075] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_n, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_7, R_9, R_{12}, R_{13}, R_{15}, R_{16}, R_{17}$ are H; R_4 is NH; R_8 and R_{14} are OCH_3 ; and "—" in Formula I between A_0 and A_i , all Formula II and all Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL029):



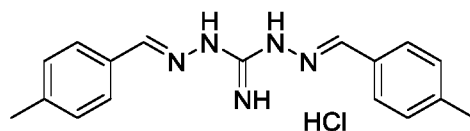
[0076] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is NH_2 ; A_1 is N; A_2 is NH; A_0, A_3, A_4, A_5, A_6 , and A_7 are C; R_2, R_5, R_6, R_8 and R_9 are H; R_4 is NH; R_7 is Cl; and "—" in Formula I between A_0 and A_i , and all Formula II "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL030):



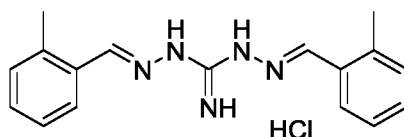
[0077] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_n, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_8, R_9, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}$ are H; R_4 is NH; R_7 and R_{15} are CF_3 ; and "—" in Formula I between A_0 and A_i , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL035):



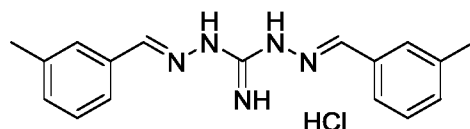
[0078] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_n, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_8, R_9, R_{12}, R_{13}, R_{14}, R_{16}, R_{17}$ are H; R_4 is NH; R_7 and R_{15} are methyl; and "—" in Formula I between A_0 and A_i , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL038):



[0079] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_7, R_8, R_{12}, R_{14}, R_{15}, R_{16}, R_{17}$ are H; R_4 is NH; R_9 and R_{13} are methyl; and "—" in Formula I between A_0 and A_i , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL039):

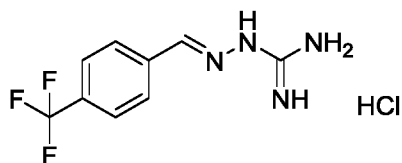


[0080] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_n, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_7, R_9, R_{12}, R_{13}, R_{15}, R_{16}$ and R_{17} are H; R_4 is NH; R_8 and R_{14} are methyl; and "—" in Formula I between A_0 and A_i , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL040):

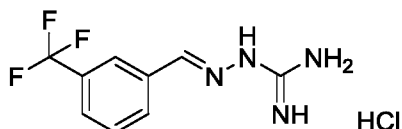


[0081] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is NH_2 ; A_1 is N; A_2 is NH; $A_0, A_3, A_4, A_5, A_6, A_7$ are C; $R_2, R_5, R_6, R_8,$ and R_9 are H; R_4 is NH; R_7 is CF_3 ; and "—" in Formula I between A_0 and A_i , and all Formula

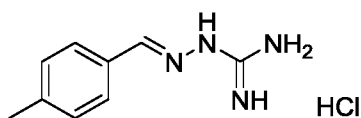
||"—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL041):



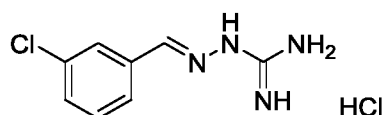
[0082] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is NH_2 ; A_1 is N; A_2 is NH; A_0 , A_3 , A_4 , A_5 , A_6 , and A_7 are C; R_2 , R_5 , R_6 , R_7 , and R_9 are H; R_4 is NH; R_8 is CF_3 ; and"—" in Formula I between A_0 and A_i , and all Formula II"—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL043):



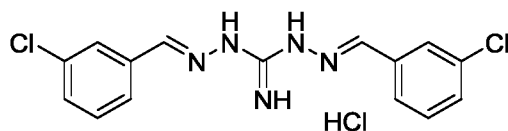
[0083] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is NH_2 ; A_1 is N; A_2 is NH; A_0 , A_3 , A_4 , A_5 , A_6 , and A_7 are C; R_2 , R_5 , R_6 , R_8 , and R_9 are H; R_4 is NH; R_7 is methyl; and"—" in Formula I between A_0 and A_i , and all Formula II"—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL044):



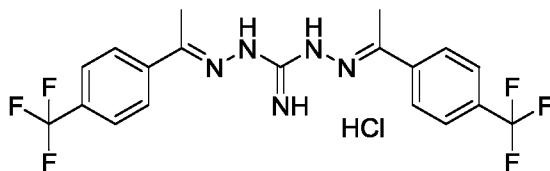
[0084] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is NH_2 ; A_1 is N; A_2 is NH; A_0 , A_3 , A_4 , A_5 , A_6 , and A_7 are C; R_2 , R_5 , R_6 , R_7 , and R_9 are H; R_4 is NH; R_8 is Cl; and"—" in Formula I between A_0 and A_i , and all Formula II"—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL052):



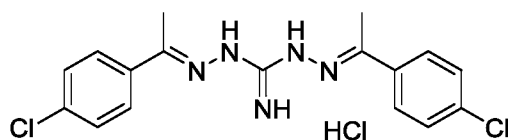
[0085] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_7, R_8, R_{12}, R_{13}, R_{15}, R_{16}, R_{17}$ are H; R_4 is NH; R_8 and R_{14} are Cl; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL054):



[0086] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; R_2 and R_{12} are methyl; $R_5, R_6, R_7, R_8, R_{13}, R_{14}, R_{16}, R_{17}$ are H; R_4 is NH; R_7 and R_{15} are CF_3 ; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL061):

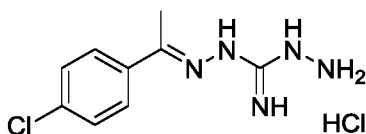


[0087] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; R_2 and R_{12} are methyl; $R_5, R_6, R_7, R_8, R_{13}, R_{14}, R_{16}$ and R_{17} are H; R_4 is NH; R_7 and R_{15} are Cl; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL062):

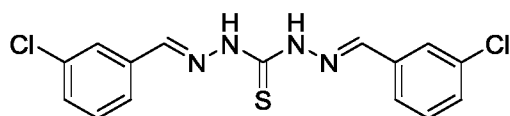


[0088] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is $NHNH_2$; A_1 is N; A_2 is NH; $A_0, A_3, A_4, A_5, A_6, A_7$ are C; R_2 is

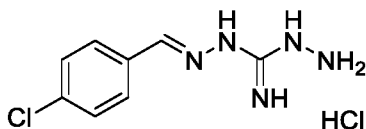
methyl, R_5 , R_6 , R_e and R_9 are H; R_4 is NH; R_7 is Cl; and "—" in Formula I between A_0 and A_i , and all Formula II "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL069):



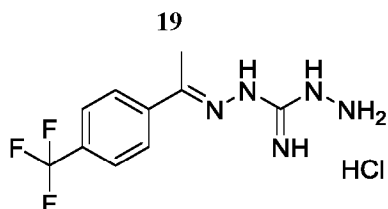
[0089] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; A_0 , A_3 , A_4 , A_5 , A_6 , A_7 , A_n , A_{12} , A_{13} , A_{14} and A_{15} , are C; R_2 , R_5 , R_6 , R_7 , R_9 , R_{12} , R_{13} , R_{15} , R_{16} , and R_{17} are H; R_4 is S; R_8 and R_{14} are Cl; and "—" in Formula I between A_0 and A_i , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL070):



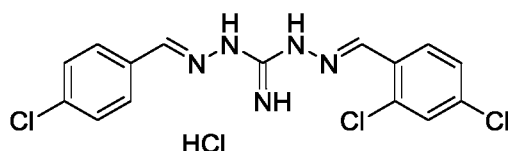
[0090] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is NH_2 ; A_1 is N; A_2 is NH; A_0 , A_3 , A_4 , A_5 , A_6 , and A_7 are C; R_2 , R_5 , R_6 , R_8 , and R_9 are H; R_4 is NH; R_7 is Cl; and "—" in Formula I between A_0 and A_i , and all Formula II "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL072):



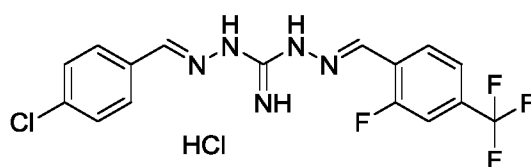
[0091] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is $NHNH_2$; A_1 is N; A_2 is NH; A_0 , A_3 , A_4 , A_5 , A_6 and A_7 are C; R_2 is methyl; R_5 , R_6 , R_8 , and R_9 are H; R_4 is NH; R_7 is CF_3 ; and "—" in Formula I between A_0 and A_i , and all Formula II "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL073):



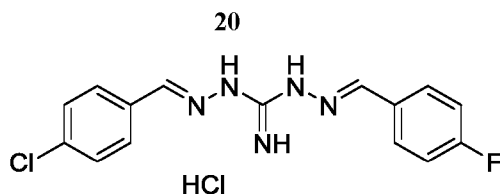
[0092] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_8, R_9, R_{12}, R_{13}, R_{14}$, and R_{16} are H; R_4 is NH; R_7, R_{15} and R_{17} are Cl; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL074):



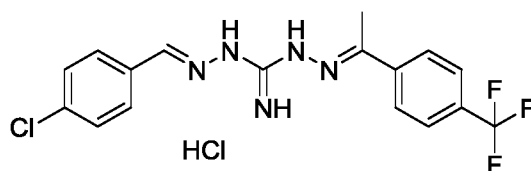
[0093] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_n, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_e, R_g, R_{12}, R_{13}, R_{14}$, and R_{16} are H; R_4 is NH; R_7 is Cl; R_{15} is CF_3 ; R_{17} is F; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL078):



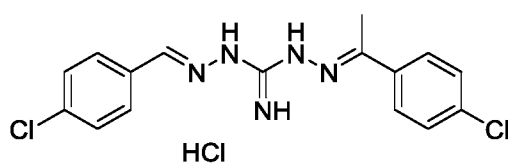
[0094] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_n, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_e, R_g, R_{12}, R_{13}, R_{14}, R_{1e}$ and R_{17} are H; R_4 is NH; R_7 is Cl; R_{15} is F; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL079):



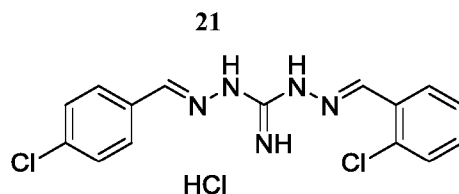
[0095] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_8, R_9, R_{13}, R_{14}, R_{16}$ and R_{17} are H; R_4 is NH; R_7 is Cl; R_{12} is methyl; R_{15} is CF_3 ; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL080):



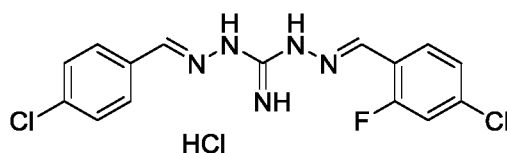
[0096] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_8, R_9, R_{13}, R_{14}, R_{16}$ and R_{17} are H; R_4 is NH; R_7 and R_{15} are Cl; R_{12} is methyl; and "—" in Formula I A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL081):



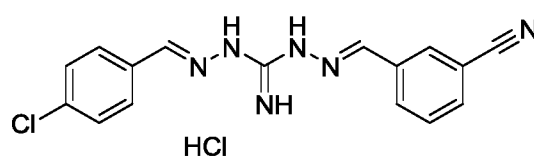
[0097] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_8, R_9, R_{12}, R_{13}, R_{14}, R_{15}$, and R_{16} are H; R_4 is NH; R_7 and R_{17} are Cl; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL082):



[0098] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_n, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_8, R_9, R_{12}, R_{13}, R_{14}$, and R_{16} are H; R_4 is NH; R_7 and R_{15} are Cl; R_{17} is F; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL084):

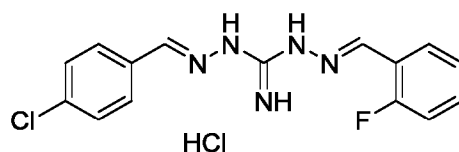


[0099] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_n, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_8, R_9, R_{12}, R_{13}, R_{15}, R_{16}$, and R_{17} are H; R_4 is NH; R_7 is Cl; R_{14} is CN; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL086):

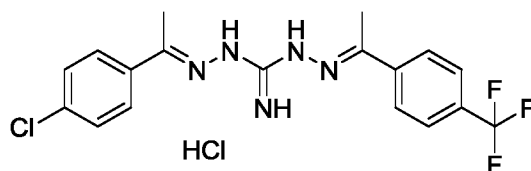


[001 00] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_8, R_9, R_{12}, R_{13}, R_{14}, R_{15}$, and R_{16} are H; R_4 is NH; R_7 is Cl; R_{17} is F; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL088):

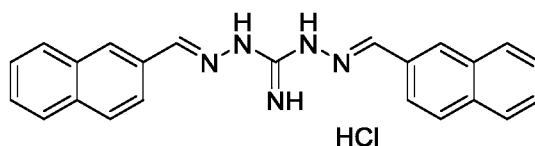
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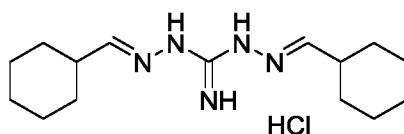
[00101] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_n, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; R_2 and R_{12} are methyl; $R_5, R_6, R_8, R_9, R_{13}, R_{14}, R_{16}$, and R_{17} are H; R_4 is NH; R_7 is Cl; R_{15} is CF_3 ; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL089):



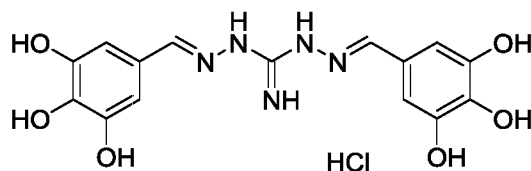
[00102] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_n, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_9, R_{12}, R_{13}, R_{16}$, and R_{17} are H; R_4 is NH; R_7 and R_8 are bonded together to form an unsubstituted, benzene ring; R_{14} and R_{15} are bonded together to form an unsubstituted, benzene ring; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL093):



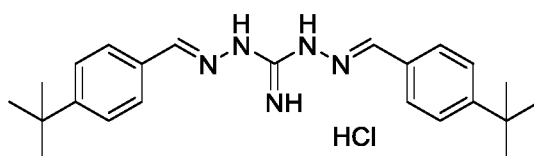
[00103] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein A_0 is C; A_1 is N; A_2 is NH; R_1 is cyclohexyl; R_3 is NH-N-CH-cyclohexyl; R_4 is NH; R_2 is H; and "—" in Formula I between A_0 and A_1 is a double bond. An example of a compound of this embodiment of the invention includes (NCL094):



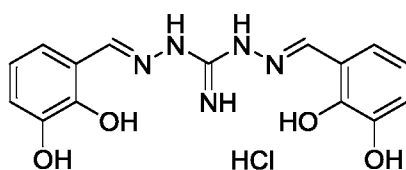
[00104] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_9, R_{12}, R_{13}$ and R_{17} are H; R_4 is NH; $R_6, R_7, R_8, R_{14}, R_{15}$, and R_{16} are OH; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL097):



[00105] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_9, R_{12}, R_{13}, R_{14}, R_{16}$ and R_{17} are H; R_4 is NH; R_7 and R_{15} are t-butyl; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL099):

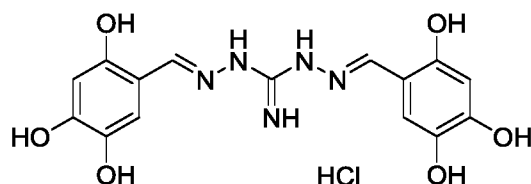


[00106] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_7, R_8, R_9, R_{12}, R_{13}, R_{14}$, and R_{15} are H; R_4 is NH; R_5, R_6, R_{16} , and R_{17} are OH; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL101):

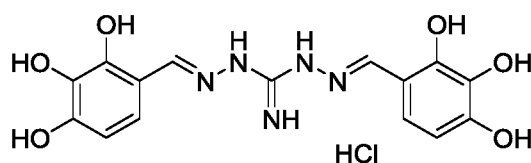


[00107] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof,

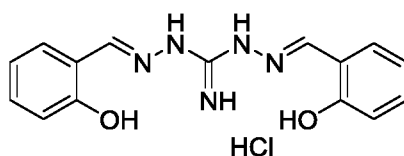
wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_n, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_8, R_{12}, R_{i4}$, and R_{17} are H; R_4 is NH; $R_6, R_7, R_9, R_{i3}, R_{i5}$, and R_{16} are OH; and "—" in Formula I between A_0 and A_i , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL104):



[00108] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_n, A_{12}, A_{i3}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_e, R_{12}, R_{ie}$, and R_{17} are H; R_4 is NH; $R_7, R_8, R_9, R_{13}, R_{14}$, and R_{15} are OH; and "—" in Formula I between A_0 and A_i , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL097):

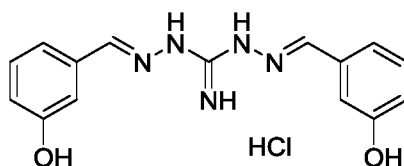


[00109] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_n, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_6, R_7, R_8, R_9, R_{i2}, R_{i3}, R_{i4}, R_{15}$, and R_{16} are H; R_4 is NH; R_5 and R_{17} are OH; and "—" in Formula I between A_0 and A_i , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL107):

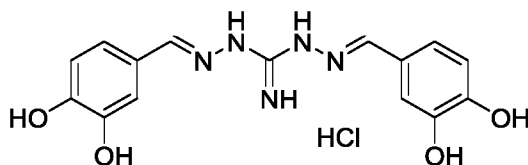


[00110] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_n, A_{12}, A_{i3}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_7, R_8, R_9, R_{12}, R_{13}, R_{i4}, R_{15}$, and R_{17} are H; R_4 is

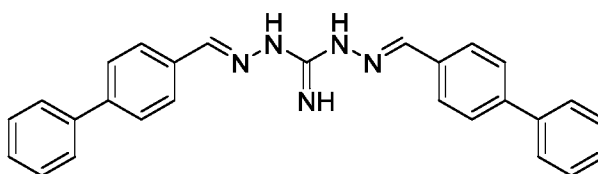
NH; R_6 and R_{16} are OH; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL1 08):



[001 11] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_8, R_9, R_{12}, R_{13}, R_{14}$, and R_{17} are H; R_4 is NH; R_6, R_7, R_{15} , and R_{16} are OH; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL1 11):

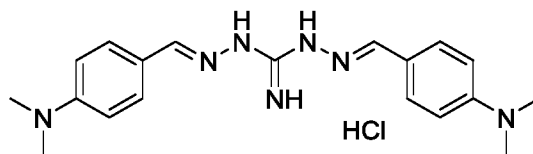


[001 12] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_8, R_9, R_{12}, R_{13}, R_{14}, R_{16}$, and R_{17} are H; R_4 is NH; R_7 and R_{15} are phenyl; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL1 12):

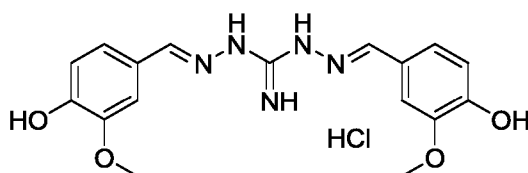


[001 13] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_8, R_9, R_{12}, R_{13}, R_{14}, R_{16}$, and R_{17} are H; R_4 is NH; R_7 and R_{15} are dimethylamino; and "—" in Formula I between A_0 and A_1 , all Formula II and

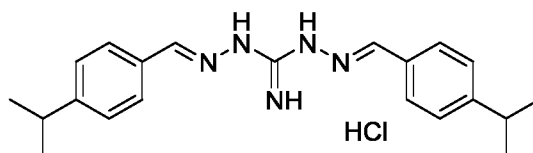
Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL1 13):



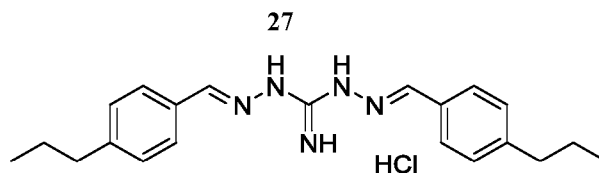
[001 14] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_8, R_9, R_{12}, R_{13}, R_{14}$, and R_{17} are H; R_4 is NH; R_6 and R_{16} are OCH_3 ; R_7 and R_{15} are OH; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL1 17):



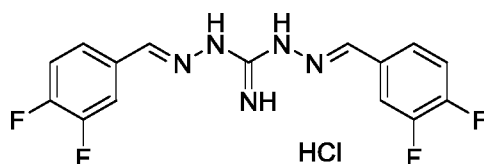
[001 15] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_8, R_9, R_{12}, R_{13}, R_{14}, R_{16}$, and R_{17} are H; R_4 is NH; R_7 and R_{15} are *l*-propyl; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL1 20):



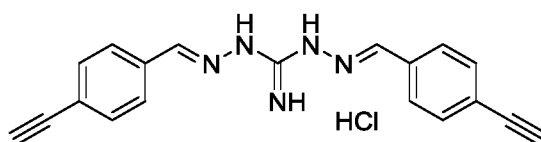
[001 16] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_8, R_9, R_{12}, R_{13}, R_{14}, R_{16}$, and R_{17} are H; R_4 is NH; R_7 and R_{15} are *n*-propyl; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL1 21):



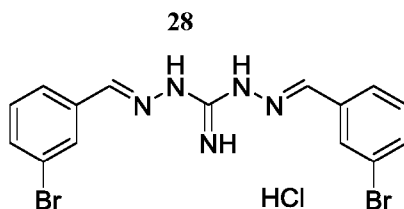
[001 17] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_8, R_9, R_{12}, R_{13}, R_{14}$, and R_{17} are H; R_4 is NH; R_6, R_7, R_{15} , and R_{16} are F; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL1 23):



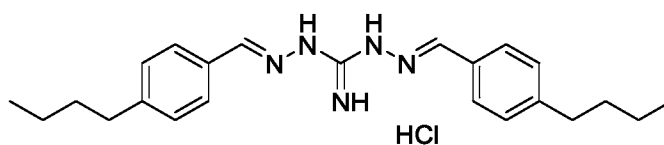
[001 18] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_8, R_9, R_{12}, R_{13}, R_{14}, R_{16}$, and R_{17} are H; R_4 is NH; R_7 and R_{15} are CCH; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL1 26):



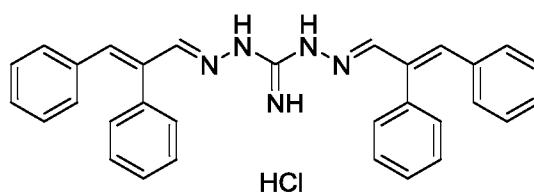
[001 19] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_7, R_8, R_9, R_{12}, R_{13}, R_{14}, R_{15}$, and R_{17} are H; R_4 is NH; R_6 and R_{16} are Br; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL1 31):



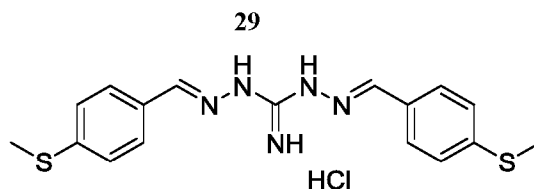
[001 20] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_8, R_9, R_{12}, R_{13}, R_{14}, R_{16}$, and R_{17} are H; R_4 is NH; R_7 and R_{15} are butyl; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL1 36):



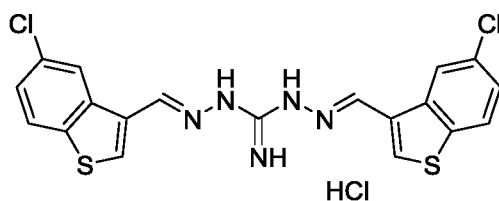
[001 21] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 is $-(C_6H_5)-CH-N-$ and A_{10} is $-N-CH-C(C_6H_5)-$; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_7, R_8, R_9, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}$, and R_{17} are H; R_4 is NH; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL1 38):



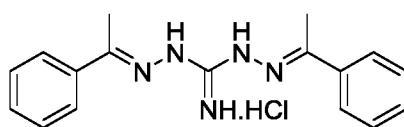
[001 22] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_8, R_9, R_{12}, R_{13}, R_{14}, R_{16}$, and R_{17} are H; R_4 is NH; R_7 and R_{15} are CH_3S ; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL1 40):



[00123] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula III; R_3 is Formula VI; A_0 is C; R_2 and R_{2i} are H; A_1 and A_{20} are N; A_2 and A_{19} are NH; A_8 and A_{21} are S; R_4 is NH; R_{10} and R_{11} are bonded together to form a substituted benzene ring; R_{22} and R_{23} are bonded together to form a substituted benzene ring; and "—" in Formula I between A_0 and A_i , and all Formula III and Formula VI "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL141):

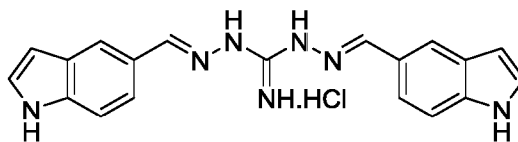


[00124] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_8, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; R_2 and R_{12} are methyl; $R_5, R_6, R_7, R_8, R_9, R_{13}, R_{14}, R_{15}, R_{16}$, and R_{17} are H; R_4 is NH; and "—" in Formula I between A_0 and A_i , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL143):

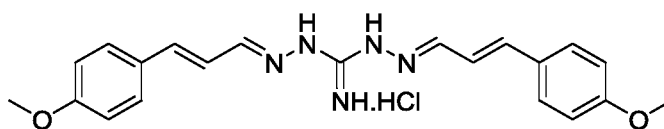


[00125] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_9, R_{12}, R_{13}, R_{16}$, and R_{17} are H; R_4 is NH; R_7 and R_8 are bonded together to form an unsubstituted, heterocyclic ring; R_{14} and R_{15} are bonded together to form an unsubstituted, unsaturated heterocyclic ring; and "—" in Formula I between A_0 and A_i , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL146):

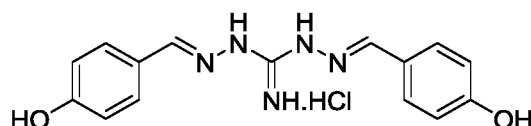
30



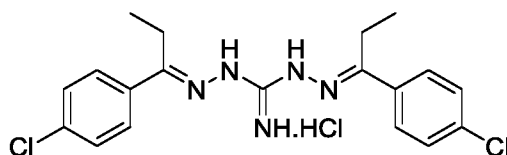
[00126] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 is $-(CH)_2-N-$ and A_{10} is $-N-(CH)_2-$; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_e, R_9, R_{i2}, R_{i3}, R_{i4}, R_{i6}$, and R_{i7} are H; R_4 is NH; R_7 and R_{15} are OCH_3 ; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL150):



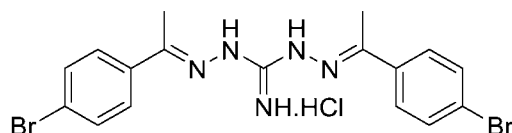
[00127] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_e, R_g, R_{i2}, R_{i3}, R_{i4}, R_{i6}$, and R_{i7} are H; R_4 is NH; R_7 and R_{15} are OH; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL151):



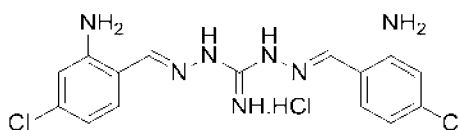
[00128] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; R_2 and R_{12} are ethyl; $R_5, R_6, R_8, R_9, R_{13}, R_{14}, R_{16}$, and R_{17} are H; R_4 is NH; R_7 and R_{15} are Cl; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL153):



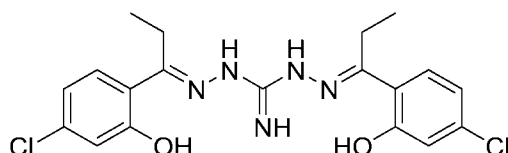
[001 29] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; R_2 and R_{12} are methyl; $R_5, R_6, R_8, R_9, R_{13}, R_{14}, R_{16}$, and R_{17} are H; R_4 is NH; R_7 and R_{15} are Br; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL1 55):



[001 30] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_6, R_8, R_{12}, R_{14}, R_{16}$, and R_{17} are H; R_4 is NH; R_7 and R_{15} are Cl; R_9 and R_{13} are NH_2 ; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL1 57):

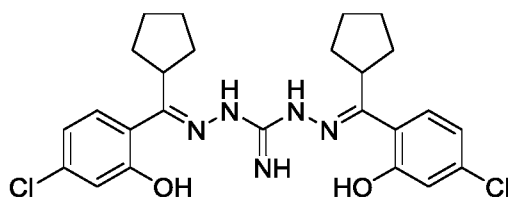


[001 31] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; R_2 and R_{12} are ethyl; R_5 and R_{17} are OH; $R_6, R_8, R_9, R_{13}, R_{14}$, and R_{16} are H; R_4 is NH; R_7 and R_{15} are Cl; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL1 58):

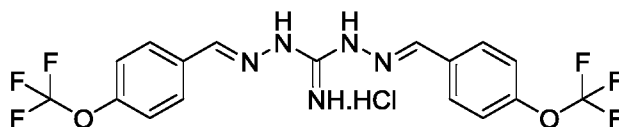


[001 32] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; R_2 and R_{12} are cyclopentyl; R_5 and R_{17} are OH; $R_6, R_8,$

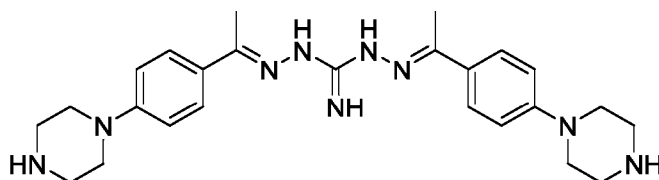
R₉, R₁₃, R₁₄, and R₁₆ are H; R₄ is NH; R₇ and R₁₅ are Cl; and "—" in Formula I between A₀ and A₁, all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL159):



[00133] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R₁ is Formula II; R₃ is Formula IV; A₁ and A₁₀ are N; A₂ and A₉ are NH; A₀, A₃, A₄, A₅, A₆, A₇, A₁₁, A₁₂, A₁₃, A₁₄ and A₁₅, are C; R₂, R₅, R_e, R_e, R₉, R₁₂, R₁₃, R₁₄, R_{1e} and R₁₇ are H; R₄ is NH; R₇ and R₁₅ are OCF₃; and "—" in Formula I between A₀ and A₁, all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL160):

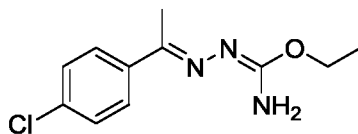


[00134] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R₁ is Formula II; R₃ is Formula IV; A₁ and A₁₀ are N; A₂ and A₉ are NH; A₀, A₃, A₄, A₅, A₆, A₇, A₁₁, A₁₂, A₁₃, A₁₄ and A₁₅, are C; R₂ and R₁₂ are methyl; R₅, R₆, R_e, R_g, R₁₃, R₁₄, R_{1e} and R₁₇ are H; R₄ is NH; R₇ and R₁₅ are piperazin-1-yl; and "—" in Formula I between A₀ and A₁, all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL161):

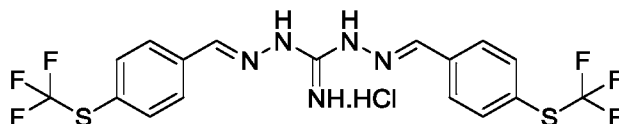


[00135] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R₁ is Formula II; R₃ is 0-CH₂-CH₃; A₁ is N; A₂ is NH; A₀, A₃, A₄, A₅, A₆ and A₇ are C; R₂ is methyl; R₅, R₆, R₈, and R₉ are H; R₄ is NH; R₇ is Cl; and "—" in Formula I between A₀ and A₁,

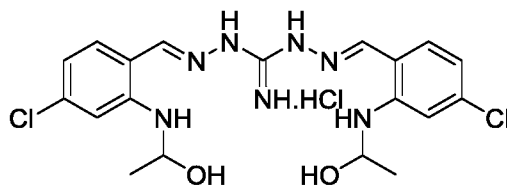
and all Formula II "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL162):



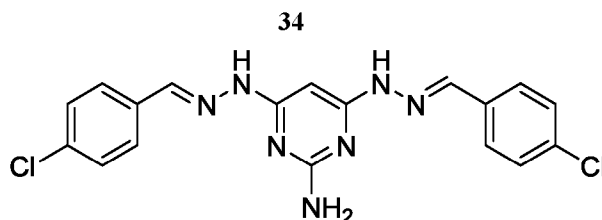
[00136] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_n, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_5, R_e, R_e, R_9, R_{12}, R_{13}, R_{i4}, R_{ie}$ and R_{17} are H; R_4 is NH; R_7 and R_{15} are SCF_3 ; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL166):



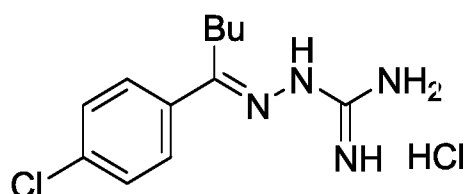
[00137] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_n, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_6, R_8, R_9, R_{12}, R_{13}, R_{i4}$, and R_{16} are H; R_4 is NH; R_7 and R_{15} are Cl; R_5 and R_{17} are $-NH-CH(OH)-CH_3$; and "—" in Formula I between A_0 and A_1 , all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL168):



[00138] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein A_0 is C; R_1 is H; A_2 and R_4 are N; R_3 is NH_2 ; A_1 is Formula VII; R_2 is Formula VII and R_2 is bonded to R_4 , forming a pyrimidine ring; "—" in Formula I between R_2 and A_0 , and between A_1 and A_2 are double bonds; A_{22} is $-N-CH-$; R_{24}, R_{25}, R_{27} and R_{28} are H; $A_{23}, A_{24}, A_{25}, A_{26}$ and A_{27} are C; and R_{26} is Cl. An example of a compound of this embodiment of the invention includes (NCL179):



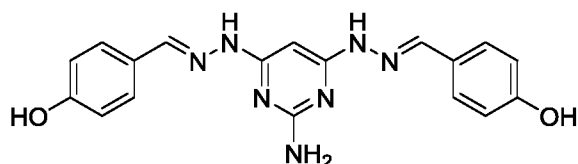
[00139] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is NH_2 ; A_1 is N; A_2 and R_4 are NH; A_0 , A_3 , A_4 , A_5 , A_6 , and A_7 are C; R_5 , R_6 , R_8 , and R_9 are H; R_2 is butyl; R_7 is Cl; and "—" in Formula I between A_0 and A_i , and all Formula II "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL188):



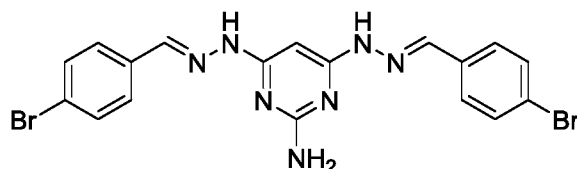
[00140] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein A_0 is C; R_1 is H; A_2 and R_4 are N; R_3 is NH_2 ; A_1 is Formula VII; R_2 is Formula VII and R_2 is bonded to R_4 , forming a pyrimidine ring; "—" in Formula I between R_2 and A_0 , and between A_1 and A_2 are double bonds; A_{22} is -N-CH-; R_{24} , R_{25} , R_{27} and R_{28} are H; A_{23} , A_{24} , A_{25} , A_{26} and A_{27} are C; and R_{26} is CH_3 . An example of a compound of this embodiment of the invention includes (NCL195):



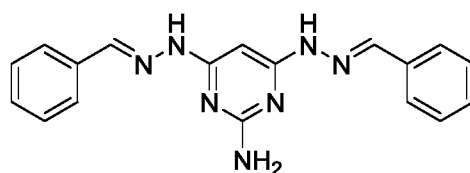
[00141] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein A_0 is C; R_1 is H; A_2 and R_4 are N; R_3 is NH_2 ; A_1 is Formula VII; R_2 is Formula VII and R_2 is bonded to R_4 , forming a pyrimidine ring; "—" in Formula I between R_2 and A_0 , and between A_1 and A_2 are double bonds; A_{22} is -N-CH-; R_{24} , R_{25} , R_{27} and R_{28} are H; A_{23} , A_{24} , A_{25} , A_{26} and A_{27} are C; and R_{26} is OH. An example of a compound of this embodiment of the invention includes (NCL196):



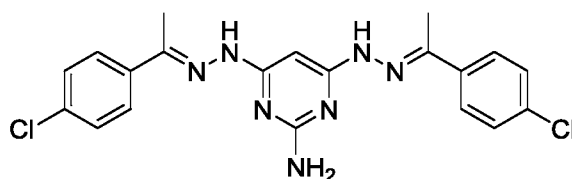
[00142] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein A_0 is C; R_1 is H; A_2 and R_4 are N; R_3 is NH_2 ; A_1 is Formula VII; R_2 is Formula VII and R_2 is bonded to R_4 , forming a pyrimidine ring; "—" in Formula I between R_2 and A_0 , and between A_1 and A_2 are double bonds; A_{22} is -N-CH-; R_{24} , R_{25} , R_{27} and R_{28} are H; A_{23} , A_{24} , A_{25} , A_{26} and A_{27} are C; and R_{26} is Br. An example of a compound of this embodiment of the invention includes (NCL193):



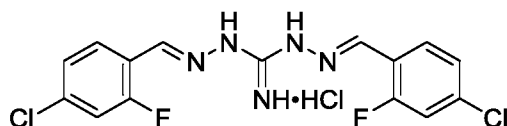
[00143] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein A_0 is C; R_1 is H; A_2 and R_4 are N; R_3 is NH_2 ; A_1 is Formula VII; R_2 is Formula VII and R_2 is bonded to R_4 , forming a pyrimidine ring; "—" in Formula I between R_2 and A_0 , and between A_1 and A_2 are double bonds; A_{22} is -N-CH-; R_{24} , R_{25} , R_{26} , R_{27} and R_{28} are H; and A_{23} , A_{24} , A_{25} , A_{26} and A_{27} are C. An example of a compound of this embodiment of the invention includes (NCL199):



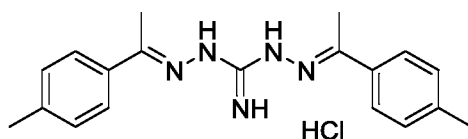
[00144] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein A_0 is C; R_1 is H; A_2 and R_4 are N; R_3 is NH_2 ; A_1 is Formula VII; R_2 is Formula VII and R_2 is bonded to R_4 , forming a pyrimidine ring; "—" in Formula I between R_2 and A_0 , and between A_1 and A_2 are double bonds; A_{22} is -N-C(CH_3)-; R_{24} , R_{25} , R_{27} and R_{28} are H; A_{23} , A_{24} , A_{25} , A_{26} and A_{27} are C; and R_{26} is Cl. An example of a compound of this embodiment of the invention includes (NCL204):



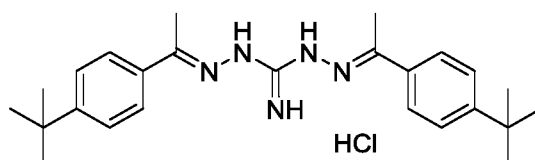
[00145] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; $R_2, R_6, R_8, R_9, R_{12}, R_{13}, R_{14}$, and R_{16} are H; R_4 is NH; R_7 and R_{15} are Cl; R_5 and R_{17} are F; and "—" in Formula I between A_0 and A-i, all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL216):



[00146] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; R_2 and R_{12} are methyl; $R_5, R_6, R_8, R_9, R_{13}, R_{14}, R_{16}$ and R_{17} are H; R_4 is NH; R_7 and R_{15} are CH_3 ; and "—" in Formula I between A_0 and A-i, all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL217):

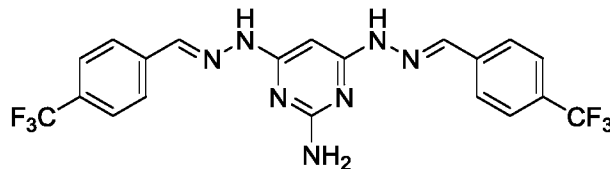


[00147] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R_1 is Formula II; R_3 is Formula IV; A_1 and A_{10} are N; A_2 and A_9 are NH; $A_0, A_3, A_4, A_5, A_6, A_7, A_{11}, A_{12}, A_{13}, A_{14}$ and A_{15} , are C; R_2 and R_{12} are methyl; $R_5, R_6, R_8, R_9, R_{13}, R_{14}, R_{16}$ and R_{17} are H; R_4 is NH; R_7 and R_{15} are t-butyl; and "—" in Formula I between A_0 and A-i, all Formula II and Formula IV "—" are double bonds. An example of a compound of this embodiment of the invention includes (NCL219):



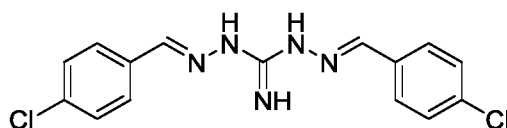
[00148] In another preferred embodiment of the invention, the compound is a compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein A_0 is C; R_1 is H; A_2 and R_4 are N; R_3 is NH_2 ; A_1 is Formula VII; R_2 is Formula VII and R_2

is bonded to R₄, forming a pyrimidine ring; "—" in Formula I between R₂ and A₀, and between A₁ and A₂ are double bonds; A₂₂ is -N-CH-; R₂₄, R₂₅, R₂₇ and R₂₈ are H; A₂₃, A₂₄, A₂₅, A₂₆ and A₂₇ are C; and R₂₆ is CF₃. An example of a compound of this embodiment of the invention includes (NCL221):



[00149] In another aspect of the invention, the invention is a compound selected from the list of compounds presented in Figure 1. In one preferred embodiment, the compound is a compound selected from the following compounds: NCL231 to NCL275. In a further aspect, the invention is a composition comprising a compound of the invention. In yet a further aspect, the invention is a pharmaceutical composition comprising a compound of the invention together with an pharmaceutically acceptable excipient and/or carrier. In yet a further aspect, the invention is a veterinary composition comprising a compound of the invention together with an acceptable excipient and/or carrier.

[00150] Terms used herein will have their customary meanings in the art unless specified. As used herein, the term robenidine, NCL812 (also known as 1,3-bis[(£)-(4-chlorophenyl)methyleneamino]guanidine) refers to a compound having the following chemical structure:



[00151] Preferably, the protozoan agent is selected from the group of genera, sub-genera and species listed in **Table 1**.

Table 1

<p>Acanthamoeba (Scientific classification: Eukaryota; Amoebozoa; Discosea; Longamoebia; Centramoebida; Acanthamoebidae) including <i>Acanthamoeba astronxis</i>, <i>Acanthamoeba castellanii</i>, <i>Acanthamoeba comandoni</i>, <i>Acanthamoeba culbertsoni</i>, <i>Acanthamoeba divionensis</i>, <i>Acanthamoeba echinulata</i>, <i>Acanthamoeba griffini</i>, <i>Acanthamoeba hatchetti</i>, <i>Acanthamoeba healyi</i>, <i>Acanthamoeba jacobsi</i>, <i>Acanthamoeba lenticulata</i>, <i>Acanthamoeba lugdunensis</i>, <i>Acanthamoeba mauritaniensis</i>, <i>Acanthamoeba palestinesis</i>, <i>Acanthamoeba paradiionensis</i>, <i>Acanthamoeba pearcei</i>, <i>Acanthamoeba polyphaga</i>, <i>Acanthamoeba pustulosa</i>, <i>Acanthamoeba quina</i>, <i>Acanthamoeba rhyodes</i>, <i>Acanthamoeba royreba</i>, <i>Acanthamoeba stvensoni</i>, <i>Acanthamoeba terricola</i>, <i>Acanthamoeba triangularis</i>, <i>Acanthamoeba tubiashi</i>, <i>Acanthamoeba sp.</i>, and unclassified <i>Acanthamoeba</i>.</p>

<p>Babesia (Scientific classification: Eukaryota; Alveolata; Apicomplexa; Aconoidasida; Piroplasmida; Babesiidae) including <i>Babesia bennetti</i>, <i>Babesia bicornis</i>, <i>Babesia bigemina</i>, <i>Babesia cf. bigemina</i>, <i>Babesia bovis</i>, <i>Babesia cf. bovis</i>, <i>Babesia caballi</i>, <i>Babesia canis</i> (and subspecies <i>Babesia canis canis</i>, <i>Babesia canis rossii</i> and <i>Babesia canis vogeli</i>), <i>Babesia capreoli</i>, <i>Babesia conradae</i>, <i>Babesia crassa</i>, <i>Babesia cf. crassa</i> GU184, <i>Babesia divergens</i>, <i>Babesia cf. divergens</i>, <i>Babesia cf. divergens</i> AdL5, <i>Babesia duncani</i>, <i>Babesia equi</i>, <i>Babesia felis</i>, <i>Babesia cf. felis</i>, <i>Babesia gibsoni</i>, <i>Babesia hongkongensis</i>, <i>Babesia kiwiensis</i>, <i>Babesia lengau</i>, <i>Babesia leo</i>, <i>Babesia major</i>, <i>Babesia microti</i>, <i>Babesia cf. microti</i>, <i>Babesia cf. microti</i> MES-2012, <i>Babesia motasi</i>, <i>Babesia muratovi</i>, <i>Babesia occultans</i>, <i>Babesia odocoilei</i>, <i>Babesia cf. odocoilei</i>, <i>Babesia orientalis</i>, <i>Babesia cf. orientalis</i>, <i>Babesia ovata</i>, <i>Babesia ovis</i>, <i>Babesia poelea</i>, <i>Babesia rodhaini</i>, <i>Babesia vesperuginis</i>, <i>Babesia vitalii</i>, <i>Babesia sp. 'venatorum'</i>, and unclassified <i>Babesia</i>.</p>
<p>Balamuthia (Scientific classification: Eukaryota; Amoebozoa; Discosea; Longamoebia; Centramoebida; Balamuthiidae) including <i>Balamuthia mandrillaris</i></p>
<p>Balantidium (Scientific classification: Eukaryota; Alveolata; Ciliophora; Intramacronucleata; Litostomatea; Trichostomatia; Vestibuliferida; Balantidiidae) including <i>Balantidium cf. coli</i>, <i>Balantidium ctenopharyngodoni</i> and <i>Balantidium entozoon</i>.</p>
<p>Besnoitia (Scientific classification: Eukaryota; Alveolata; Apicomplexa; Conoidasida; Coccidia; Eucoccidiorida; Eimeriorina; Sarcocystidae) including, <i>Besnoitia akodoni</i>, <i>Besnoitia bennetti</i>, <i>Besnoitia besnoiti</i>, <i>Besnoitia caprae</i>, <i>Besnoitia darlingi</i>, <i>Besnoitia jellisoni</i>, <i>Besnoitia neotomofelis</i>, <i>Besnoitia oryctofelisi</i>, and <i>Besnoitia tarandi</i>.</p>
<p>Blastocystis (Scientific classification: Eukaryota; Stramenopiles) including <i>Blastocystis cycluri</i>, <i>Blastocystis geocheloni</i>, <i>Blastocystis hominis</i>, <i>Blastocystis lapemi</i>, <i>Blastocystis pythoni</i>, <i>Blastocystis ratti</i>, and <i>Blastocystis sp.</i> Subtypes.</p>
<p>Chilomastix (Scientific classification: Eukaryota; Fornicata; Retortamonadidae) including <i>Chilomastix caulleryi</i>, <i>Chilomastix mesnili</i> and <i>Chilomastix wenrichi</i>.</p>
<p>Cochlosoma (Scientific classification: Eukaryota; Parabasalia; Trichomonadida; Trichomonadidae) including <i>Cochlosoma anatis</i>.</p>
<p>Cryptosporidium (Scientific classification: Eukaryota; Alveolata; Apicomplexa; Conoidasida; Coccidia; Eucoccidiorida; Eimeriorina; Cryptosporidiidae) including <i>Cryptosporidium andersoni</i>, <i>Cryptosporidium baileyi</i>, <i>Cryptosporidium bovis</i>, <i>Cryptosporidium canis</i>, <i>Cryptosporidium cf. bovis</i> G2, <i>Cryptosporidium cf. bovis</i> G3, <i>Cryptosporidium cf. bovis</i> G4, <i>Cryptosporidium cf. bovis</i> G7, <i>Cryptosporidium cf. molnari</i>, <i>Cryptosporidium cf. parvum</i>, <i>Cryptosporidium cf. suis</i>, <i>Cryptosporidium cuniculus</i>, <i>Cryptosporidium erinacei</i>, <i>Cryptosporidium fayeri</i>, <i>Cryptosporidium felis</i>, <i>Cryptosporidium fragile</i>, <i>Cryptosporidium galli</i>, <i>Cryptosporidium hominis</i>, <i>Cryptosporidium macropodum</i>, <i>Cryptosporidium meleagridis</i>, <i>Cryptosporidium molnari</i>, <i>Cryptosporidium muris</i>, <i>Cryptosporidium parvum</i>, <i>Cryptosporidium parvum</i> mouse genotype, <i>Cryptosporidium ryanae</i>, <i>Cryptosporidium saurophilum</i>, <i>Cryptosporidium scrofarum</i>, <i>Cryptosporidium serpentis</i>, <i>Cryptosporidium struthionis</i>, <i>Cryptosporidium suis</i>, <i>Cryptosporidium tyzzeri</i>, <i>Cryptosporidium ubiquitousum</i>, <i>Cryptosporidium viatorum</i>, <i>Cryptosporidium wrairi</i>, <i>Cryptosporidium xiaoi</i>, and unclassified <i>Cryptosporidium</i>.</p>
<p>Cyclospora (Scientific classification: Eukaryota; Alveolata; Apicomplexa; Conoidasida; Coccidia; Eucoccidiorida; Eimeriorina; Eimeriidae) including <i>Cyclospora cayetanensis</i>, <i>Cyclospora cercopitheci</i>, <i>Cyclospora colobi</i>, <i>Cyclospora papionis</i>, and <i>Cyclospora sp.</i></p>
<p>Cystoisospora (Scientific classification: Eukaryota; Alveolata; Apicomplexa; Conoidasida; Coccidia; Eucoccidiorida; Eimeriorina; Sarcocystidae) including <i>Cystoisospora belli</i>, <i>Cystoisospora felis</i>, <i>Cystoisospora ohioensis</i>, <i>Cystoisospora cf. ohioensis</i>, <i>Cystoisospora rivolta</i>, <i>Cystoisospora suis</i>, and <i>Cystoisospora timoni</i>.</p>
<p>Cytauxzoon (Scientific classification: Eukaryota; Alveolata; Apicomplexa; Aconoidasida; Piroplasmida; Theileriidae) including <i>Cytauxzoon felis</i>, <i>Cytauxzoon manul</i> and unclassified <i>Cytauxzoon</i>.</p>
<p>Dientamoeba (Scientific classification: Eukaryota; Parabasalia; Tritrichomonadida; Dientamoebidae) including <i>Dientamoeba fragilis</i>.</p>
<p>Eimeria (Scientific classification: Eukaryota; Alveolata; Apicomplexa; Conoidasida; Coccidia; Eucoccidiorida; Eimeriorina; Eimeriidae) including <i>Eimeria acervulina</i>, <i>Eimeria adenoides</i>, <i>Eimeria ahsata</i>, <i>Eimeria alabamensis</i>, <i>Eimeria albigulae</i>, <i>Eimeria alorani</i>, <i>Eimeria anguillae</i>, <i>Eimeria anseris</i>, <i>Eimeria antrozoi</i>, <i>Eimeria apionodes</i>, <i>Eimeria arizonensis</i>, <i>Eimeria arloingi</i>, <i>Eimeria arnyi</i>, <i>Eimeria auburnensis</i>, <i>Eimeria auritusi</i>, <i>Eimeria banffensis</i>, <i>Eimeria bovis</i>, <i>Eimeria brunetti</i>, <i>Eimeria bukidnonensis</i>, <i>Eimeria burdai</i>, <i>Eimeria cahiriniensis</i>, <i>Eimeria callospermophili</i>, <i>Eimeria canadensis</i>, <i>Eimeria catronensis</i>, <i>Eimeria caviae</i>, <i>Eimeria chaetodipi</i>, <i>Eimeria chinchillae</i>, <i>Eimeria chobotari</i>, <i>Eimeria coecicola</i>, <i>Eimeria crandallis</i>, <i>Eimeria cylindrica</i>, <i>Eimeria cylindrospora</i>, <i>Eimeria daviesae</i>, <i>Eimeria dipodomysis</i>, <i>Eimeria disperse</i>, <i>Eimeria ellipsoidalis</i>, <i>Eimeria exigua</i>, <i>Eimeria falciformis</i>, <i>Eimeria faurei</i>, <i>Eimeria flavescens</i>, <i>Eimeria furonis</i>, <i>Eimeria gallopavonis</i>, <i>Eimeria gruis</i>, <i>Eimeria hermani</i>, <i>Eimeria hessei</i>, <i>Eimeria intestinalis</i>, <i>Eimeria irresidua</i>, <i>Eimeria krijgsmanni</i>, <i>Eimeria laeae</i>, <i>Eimeria lancasterensis</i>, <i>Eimeria langebarteli</i>, <i>Eimeria leucisci</i>, <i>Eimeria</i></p>

leucopi, <i>Eimeria macropodis</i> , <i>Eimeria macusaniensis</i> , <i>Eimeria magna</i> , <i>Eimeria maxima</i> , <i>Eimeria media</i> , <i>Eimeria meleagridis</i> , <i>Eimeria mitis</i> , <i>Eimeria mivati</i> , <i>Eimeria cf. mivati</i> , <i>Eimeria myoxi</i> , <i>Eimeria nafuko</i> , <i>Eimeria necatrix</i> , <i>Eimeria nemethi</i> , <i>Eimeria nieschulzi</i> , <i>Eimeria ontarioensis</i> , <i>Eimeria onychomysis</i> , <i>Eimeria ovinoidalis</i> , <i>Eimeria papillata</i> , <i>Eimeria pavonina</i> , <i>Eimeria percae</i> , <i>Eimeria perforans</i> , <i>Eimeria peromysci</i> , <i>Eimeria phalacrocoraxae</i> , <i>Eimeria pilarensis</i> , <i>Eimeria piriformis</i> , <i>Eimeria polita</i> , <i>Eimeria porci</i> , <i>Eimeria praecox</i> , <i>Eimeria pragensis</i> , <i>Eimeria quokka</i> , <i>Eimeria ranae</i> , <i>Eimeria reedi</i> , <i>Eimeria reichenowi</i> , <i>Eimeria rioarribaensis</i> , <i>Eimeria rutili</i> , <i>Eimeria scabra</i> , <i>Eimeria scholtzsecki</i> , <i>Eimeria separata</i> , <i>Eimeria setonicis</i> , <i>Eimeria sevilletensis</i> , <i>Eimeria siliculiformis</i> , <i>Eimeria sinensis</i> , <i>Eimeria stiedai</i> , <i>Eimeria subepithelialis</i> , <i>Eimeria subspherica</i> , <i>Eimeria telekii</i> , <i>Eimeria tenella</i> , <i>Eimeria cf. tenggilingi</i> L12_Ros, <i>Eimeria trichosuri</i> , <i>Eimeria tropidura</i> , <i>Eimeria variabilis</i> , <i>Eimeria vejdvovskiyi</i> , <i>Eimeria vermiformis</i> , <i>Eimeria vilasi</i> , <i>Eimeria weybridgei</i> , <i>Eimeria wyomingensis</i> , <i>Eimeria zuernii</i> , and unclassified <i>Eimeria</i> .
Endolimax (Scientific classification: Eukaryota; Amoebozoa; Archamoebae; Entamoebidae) including <i>Endolimax nana</i> and <i>Endolimax piscium</i> .
Entamoeba (Scientific classification: Eukaryota; Amoebozoa; Archamoebae; Entamoebidae) including <i>Entamoeba bangladeshi</i> , <i>Entamoeba bovis</i> , <i>Entamoeba chattoni</i> , <i>Entamoeba coli</i> , <i>Entamoeba dispar</i> , <i>Entamoeba ecuadoriensis</i> , <i>Entamoeba equi</i> , <i>Entamoeba gingivalis</i> , <i>Entamoeba hartmanni</i> , <i>Entamoeba histolytica</i> , <i>Entamoeba insolita</i> , <i>Entamoeba invadens</i> , <i>Entamoeba moshkovskii</i> , <i>Entamoeba muris</i> , <i>Entamoeba nuttalli</i> , <i>Entamoeba polecki</i> , <i>Entamoeba ranarum</i> , <i>Entamoeba struthionis</i> , <i>Entamoeba suis</i> , and <i>Entamoeba terrapinae</i> .
Giardia (Scientific classification: Eukaryota; Fornicata; Diplomonadida; Hexamitidae; Giardiae) including <i>Giardia ardeae</i> , <i>Giardia intestinalis</i> (synonyms <i>Giardia duodenalis</i> and <i>Giardia lamblia</i>) (and various assemblages), <i>Giardia microti</i> , <i>Giardia muris</i> , <i>Giardia psittaci</i> and unclassified <i>Giardia</i> .
Haemoproteus (Scientific classification: Eukaryota; Alveolata; Apicomplexa; Aconoidasida; Haemosporida) including <i>Haemoproteus balmorali</i> , <i>Haemoproteus belopolskyi</i> , <i>Haemoproteus chelodinae</i> , <i>Haemoproteus coatneyi</i> , <i>Haemoproteus columbae</i> , <i>Haemoproteus danilewskyi</i> , <i>Haemoproteus elani</i> , <i>Haemoproteus enucleator</i> , <i>Haemoproteus fringillae</i> , <i>Haemoproteus hirundinis</i> , <i>Haemoproteus homobelopolskyi</i> , <i>Haemoproteus iwa</i> , <i>Haemoproteus jenniae</i> , <i>Haemoproteus kopki</i> , <i>Haemoproteus lanii</i> , <i>Haemoproteus magnus</i> , <i>Haemoproteus majoris</i> , <i>Haemoproteus mesnili</i> , <i>Haemoproteus micronuclearis</i> , <i>Haemoproteus minutus</i> , <i>Haemoproteus motacillae</i> , <i>Haemoproteus multipigmentatus</i> , <i>Haemoproteus nucleofascialis</i> , <i>Haemoproteus pallidulus</i> , <i>Haemoproteus pallidus</i> , <i>Haemoproteus parabelopolskyi</i> , <i>Haemoproteus paranucleophilus</i> , <i>Haemoproteus passeris</i> , <i>Haemoproteus pastoris</i> , <i>Haemoproteus payevskiyi</i> , <i>Haemoproteus picae</i> , <i>Haemoproteus pyodactylis</i> , <i>Haemoproteus sacharovi</i> , <i>Haemoproteus sanguinis</i> , <i>Haemoproteus sylvae</i> , <i>Haemoproteus synnii</i> , <i>Haemoproteus tartakovskyi</i> , <i>Haemoproteus turtur</i> , <i>Haemoproteus vacuolatus</i> , and unclassified <i>Haemoproteus</i> .
Hammondia (Scientific classification: Eukaryota; Alveolata; Apicomplexa; Conoidasida; Coccidia; Eucoccidiorida; Eimeriorina; Sarcocystidae) including <i>Hammondia hammondi</i> , <i>Hammondia heydorni</i> , <i>Hammondia truffittae</i> and <i>Hammondia</i> sp. Fox-2000.
Hartmannella (Scientific classification: Eukaryota; Amoebozoa; Tubulinea; Euamoebida; Tubulinida; Hartmannellidae) including <i>Hartmannella abertawensis</i> , <i>Hartmannella cantabrigiensis</i> , <i>Hartmannella cf. vermiformis</i> [now known as <i>Vermamoeba vermiformis</i>], and <i>Hartmannella</i> sp.
Hepatozoon (Scientific classification: Eukaryota; Alveolata; Apicomplexa; Conoidasida; Coccidia; Eucoccidiorida; Adeleorina; Hepatozoidae) including <i>Hepatozoon americanum</i> , <i>Hepatozoon ayorgbor</i> , <i>Hepatozoon canis</i> , <i>Hepatozoon catesbiana</i> , <i>Hepatozoon cf. catesbiana</i> , <i>Hepatozoon clamatae</i> , <i>Hepatozoon cf. clamatae</i> , <i>Hepatozoon erhardovae</i> , <i>Hepatozoon felis</i> , <i>Hepatozoon seychellensis</i> , <i>Hepatozoon sipedon</i> , <i>Hepatozoon tuatarae</i> , <i>Hepatozoon ursi</i> , and unclassified <i>Hepatozoon</i> .
Hexamita (Scientific classification: Eukaryota; Fornicata; Diplomonadida; Hexamitidae; Hexamitinae) including <i>Hexamita inflata</i> , <i>Hexamita nelsoni</i> and <i>Hexamita</i> sp.
Histomonas (Scientific classification: Eukaryota; Parabasalia; Tritrichomonadida; Dientamoebidae) including <i>Histomonas meleagridis</i> and <i>Histomonas</i> sp.
Isospora (Scientific classification: Eukaryota; Alveolata; Apicomplexa; Conoidasida; Coccidia; Eucoccidiorida; Eimeriorina; Eimeriidae) including <i>Isospora anthochaerae</i> , <i>Isospora gryphoni</i> , <i>Isospora hypoleuca</i> , <i>Isospora insularius</i> , <i>Isospora lesouefi</i> , <i>Isospora orlovi</i> , <i>Isospora peromysis</i> , and <i>Isospora robini</i> .
Leishmania (Scientific classification: Eukaryota; Euglenozoa; Kinetoplastida; Trypanosomatidae; Leishmaniinae) including subgenus <i>Leishmania</i> (including <i>Leishmania aethiopia</i> species complex, <i>Leishmania aristidesi</i> , <i>Leishmania deanei</i> , <i>Leishmania donovani</i> species complex, <i>Leishmania hertigi</i> , <i>Leishmania major</i> species complex, <i>Leishmania major x donovani</i> , <i>Leishmania mexicana</i> species complex, <i>Leishmania tropica</i> species complex, lizard <i>Leishmania</i> (<i>Leishmania adleri</i> , <i>Leishmania gymnodactyli</i> , <i>Leishmania hoogstraali</i> , <i>Leishmania tarentolae</i> , <i>Leishmania</i> sp. NC29/Iran/2007), subgenus <i>Viannia</i> (including <i>Leishmania braziliensis</i> species complex, <i>Leishmania garnhami</i> , <i>Leishmania guyanensis</i> species complex, <i>Leishmania lainsoni</i> species complex, <i>Leishmania lindenbergi</i> , <i>Leishmania naiffi</i> species complex, <i>Leishmania utingensis</i> , and unclassified <i>Leishmania</i>).

<p>Leucocytozoon (Scientific classification: Eukaryota; Alveolata; Apicomplexa; Aconoidasida; Haemosporida) including <i>Leucocytozoon buteonis</i>, <i>Leucocytozoon caulleryi</i>, <i>Leucocytozoon dubreuilii</i>, <i>Leucocytozoon fringillinarum</i>, <i>Leucocytozoon gentili</i>, <i>Leucocytozoon lovati</i>, <i>Leucocytozoon macleani</i>, <i>Leucocytozoon majoris</i>, <i>Leucocytozoon quynzae</i>, <i>Leucocytozoon sabrazei</i>, <i>Leucocytozoon schoutedeni</i>, <i>Leucocytozoon simondi</i>, <i>Leucocytozoon squamatus</i>, <i>Leucocytozoon toddi</i>, <i>Leucocytozoon ziemanni</i>, <i>Leucocytozoon sp.</i>, and unclassified <i>Leucocytozoon</i>.</p>
<p>Naegleria (Scientific classification: Eukaryota; Heterolobosea; Schizopyrenida; Vahlkampfiidae) including <i>Naegleria americana</i>, <i>Naegleria andersoni</i>, <i>Naegleria angularis</i>, <i>Naegleria antarctica</i>, <i>Naegleria arctica</i>, <i>Naegleria australiensis</i>, <i>Naegleria cf. australiensis</i>, <i>Naegleria canariensis</i>, <i>Naegleria carteri</i>, <i>Naegleria chilensis</i>, <i>Naegleria clarki</i>, <i>Naegleria dobsoni</i>, <i>Naegleria dunnebackei</i>, <i>Naegleria endoi</i>, <i>Naegleria fowleri</i>, <i>Naegleria fultoni</i>, <i>Naegleria galeacystis</i>, <i>Naegleria gallica</i>, <i>Naegleria gruberi</i>, <i>Naegleria cf. gruberi</i>, <i>Naegleria indonesiensis</i>, <i>Naegleria italica</i>, <i>Naegleria jadini</i>, <i>Naegleria jamiesoni</i>, <i>Naegleria laresi</i>, <i>Naegleria lovaniensis</i>, <i>Naegleria mexicana</i>, <i>Naegleria minor</i>, <i>Naegleria morgansensis</i>, <i>Naegleria neoantarctica</i>, <i>Naegleria neochilensis</i>, <i>Naegleria neodobsoni</i>, <i>Naegleria neopolaris</i>, <i>Naegleria pagei</i>, <i>Naegleria paradobsoni</i>, <i>Naegleria peruana</i>, <i>Naegleria philippinensis</i>, <i>Naegleria polaris</i>, <i>Naegleria pringsheimi</i>, <i>Naegleria pussardi</i>, <i>Naegleria robinsoni</i>, <i>Naegleria schusteri</i>, <i>Naegleria spitzbergeniensis</i>, <i>Naegleria tenerifensis</i>, <i>Naegleria tihangensis</i>, <i>Naegleria sp.</i>, and unclassified <i>Naegleria</i>.</p>
<p>Neospora (Scientific classification: Eukaryota; Alveolata; Apicomplexa; Conoidasida; Coccidia; Eucoccidiorida; Eimeriorina; Sarcocystidae) including <i>Neospora caninum</i>, <i>Neospora hughesi</i> and <i>Neospora sp.</i></p>
<p>Pentatrachomonas (Scientific classification: Eukaryota; Parabasalia; Trichomonadida; Trichomonadidae) including <i>Pentatrachomonas hominis</i>.</p>
<p>Plasmodium (Scientific classification: Eukaryota; Alveolata; Apicomplexa; Aconoidasida; Haemosporida) including <i>Plasmodium ovale</i>, <i>Plasmodium simiovale</i>, <i>Plasmodium simium</i>, <i>Plasmodium vivax</i>, and subgenera <i>Plasmodium</i> (<i>Bennettinia</i>) (birds); <i>Plasmodium</i> (<i>Giovannolaia</i>) (birds); <i>Plasmodium</i> (<i>Haemamoeba</i>) (birds); <i>Plasmodium</i> (<i>Huffia</i>) (birds); <i>Plasmodium</i> (<i>Laverania</i>) (higher primates, includes <i>Plasmodium falciparum</i>); <i>Plasmodium</i> (<i>Novyella</i>) (birds); <i>Plasmodium</i> (<i>Paraplasmodium</i>) (lizards); <i>Plasmodium</i> (<i>Plasmodium</i>) (higher primates, includes <i>Plasmodium brasilianum</i>, <i>Plasmodium cynomolgi</i>, <i>Plasmodium inui</i>, <i>Plasmodium knowlesi</i>, <i>Plasmodium malariae</i>]; <i>Plasmodium</i> (<i>Sauramoeba</i>) (lizards); and <i>Plasmodium</i> (<i>Vinckeia</i>).</p>
<p>Sappinia (Scientific classification: Eukaryota; Amoebozoa; Discosea; Longamoebia; Thecamoebida) including <i>Sappinia diploidea</i>, <i>Sappinia pedata</i> and <i>Sappinia sp.</i></p>
<p>Sarcocystis (Scientific classification: Eukaryota; Alveolata; Apicomplexa; Conoidasida; Coccidia; Eucoccidiorida; Eimeriorina; Sarcocystidae) including <i>Sarcocystis albifronsi</i>, <i>Sarcocystis alces</i>, <i>Sarcocystis alceslatrans</i>, <i>Sarcocystis anasi</i>, <i>Sarcocystis arctica</i>, <i>Sarcocystis arieticanis</i>, <i>Sarcocystis atheridis</i>, <i>Sarcocystis aucheniae</i>, <i>Sarcocystis buffalonis</i>, <i>Sarcocystis calchasi</i>, <i>Sarcocystis campestris</i>, <i>Sarcocystis canis</i>, <i>Sarcocystis capracanis</i>, <i>Sarcocystis capreolicanis</i>, <i>Sarcocystis cf. clethrionomyelaphis JH-2013</i>, <i>Sarcocystis columbae</i>, <i>Sarcocystis cornixi</i>, <i>Sarcocystis cruzi</i>, <i>Sarcocystis cf. cruzi</i>, <i>Sarcocystis dasypi</i>, <i>Sarcocystis disperse</i>, <i>Sarcocystis elongata</i>, <i>Sarcocystis falcatala</i>, <i>Sarcocystis cf. falcatala</i>, <i>Sarcocystis fayeri</i>, <i>Sarcocystis felis</i>, <i>Sarcocystis cf. felis WACF-2013</i>, <i>Sarcocystis fusiformis</i>, <i>Sarcocystis gallotiae</i>, <i>Sarcocystis gigantea</i>, <i>Sarcocystis gracilis</i>, <i>Sarcocystis grueneri</i>, <i>Sarcocystis hardangeri</i>, <i>Sarcocystis hirsuta</i>, <i>Sarcocystis hjorti</i>, <i>Sarcocystis hominis</i>, <i>Sarcocystis lacertae</i>, <i>Sarcocystis lamacanis</i>, <i>Sarcocystis lindsayi</i>, <i>Sarcocystis miescheriana</i>, <i>Sarcocystis moulei</i>, <i>Sarcocystis mucosa</i>, <i>Sarcocystis muris</i>, <i>Sarcocystis nesbitti</i>, <i>Sarcocystis neurona</i> [agent of equine protozoal myeloencephalitis (EPM)], <i>Sarcocystis cf. neurona</i>, <i>Sarcocystis neurona-like</i> protozoan, <i>Sarcocystis ovalis</i>, <i>Sarcocystis oviformis</i>, <i>Sarcocystis ramphastosi</i>, <i>Sarcocystis rangi</i>, <i>Sarcocystis rangiferi</i>, <i>Sarcocystis rileyi</i>, <i>Sarcocystis rodentifelis</i>, <i>Sarcocystis scandinavica</i>, <i>Sarcocystis silva</i>, <i>Sarcocystis sinensis</i>, <i>Sarcocystis singaporensis</i>, <i>Sarcocystis sui hominis</i>, <i>Sarcocystis taeniata</i>, <i>Sarcocystis tarandi</i>, <i>Sarcocystis tarandivulpes</i>, <i>Sarcocystis tenella</i>, <i>Sarcocystis truncata</i>, <i>Sarcocystis turdusi</i>, <i>Sarcocystis wobeseri</i>, <i>Sarcocystis zamani</i>, <i>Sarcocystis zuoi</i>, and unclassified <i>Sarcocystis</i>.</p>
<p>Tetratrachomonas (Scientific classification: Eukaryota; Parabasalia; Trichomonadida; Trichomonadidae) including <i>Tetratrachomonas brumpti</i>, <i>Tetratrachomonas buttrei</i>, <i>Tetratrachomonas gallinarum</i>, <i>Tetratrachomonas limacis</i>, <i>Tetratrachomonas prowazeki</i>, <i>Tetratrachomonas undula</i>, and unclassified <i>Tetratrachomonas</i>.</p>
<p>Theileria (Scientific classification: Eukaryota; Alveolata; Apicomplexa; Aconoidasida; Piroplasmida; Theileriidae) including <i>Theileria annae</i>, <i>Theileria annulata</i>, <i>Theileria annulata strain Ankara</i>, <i>Theileria bicornis</i>, <i>Theileria brachyuri</i>, <i>Theileria buffeli</i>, <i>Theileria cf. buffeli A MEC-2013</i>, <i>Theileria cf. buffeli B</i>, <i>Theileria cf. buffeli C</i>, <i>Theileria cf. buffeli MC-2012</i>, <i>Theileria capreoli</i>, <i>Theileria cervi</i>, <i>Theileria equi</i>, <i>Theileria fuliginosus</i>, <i>Theileria lestoquardi</i>, <i>Theileria cf. lestoquardi</i> (Atbara), <i>Theileria cf. lestoquardi G4</i>, <i>Theileria cf. lestoquardi G6</i>, <i>Theileria luwenshuni</i>, <i>Theileria mutans</i>, <i>Theileria cf. mutans 3</i>, <i>Theileria cf. mutans A MEC-2013</i>, <i>Theileria cf. mutans B MEC-2013</i>, <i>Theileria cf. mutans C MEC-2013</i>, <i>Theileria orientalis</i>, <i>Theileria orientalis complex isolate 9172</i>, <i>Theileria orientalis complex isolate 9196</i>, <i>Theileria orientalis strain Shintoku</i>, <i>Theileria ovis</i>, <i>Theileria cf. ovis G4</i>, <i>Theileria cf. ovis G6</i>, <i>Theileria parva</i>, <i>Theileria parva bovis</i>, <i>Theileria parva lawrencei</i>, <i>Theileria parva parva</i>, <i>Theileria parva strain Muguga</i>, <i>Theileria penicillata</i>, <i>Theileria separata</i>, <i>Theileria sergenti</i>, <i>Theileria sinensis</i>, <i>Theileria cf. sinensis</i>, <i>Theileria cf. sinensis MC-2012</i>, <i>Theileria taurotragi</i>, <i>Theileria uilenbergi</i>, <i>Theileria velifera</i>, <i>Theileria cf. velifera A</i>, <i>Theileria cf. velifera A MEC-2013</i>, <i>Theileria cf. velifera B</i>, <i>Theileria cf. velifera B MEC-2013</i>, <i>Theileria cf. velifera (Syncerus caffer)</i>, <i>Theileria</i></p>

youngi, Theileria sp., and unclassified Theileria.
Toxoplasma (Scientific classification: Eukaryota; Alveolata; Apicomplexa; Conoidasida; Coccidia; Eucoccidiorida; Eimeriorina; Sarcocystidae) including <i>Toxoplasma gondii</i> .
Trichomonas (Scientific classification: Eukaryota; Parabasalia; Trichomonadida; Trichomonadidae) including <i>Trichomonas canistomae</i> , <i>Trichomonas equibuccalis</i> , <i>Trichomonas gallinae</i> , <i>Trichomonas stableri</i> , <i>Trichomonas tenax</i> , and <i>Trichomonas vaginalis</i> .
Tritrichomonas (Scientific classification: Eukaryota; Parabasalia; Tritrichomonadida; Tritrichomonadidae) including <i>Tritrichomonas augusta</i> , <i>Tritrichomonas foetus</i> , <i>Tritrichomonas mobilensis</i> , <i>Tritrichomonas muris</i> , <i>Tritrichomonas nonconforma</i> , and <i>Tritrichomonas suis</i> .
Trypanosoma (Scientific classification: Eukaryota; Euglenozoa; Kinetoplastida; Trypanosomatidae) including Subgenus <i>Duttonella</i> (<i>Trypanosoma vivax</i> and <i>Trypanosoma</i> sp. T78), Subgenus <i>Herpetosoma</i> (<i>Trypanosoma blanchardi</i> , <i>Trypanosoma lewisi</i> , <i>Trypanosoma rabinowitschae</i> , <i>Trypanosoma rangeli</i> , <i>Trypanosoma</i> sp. SJP-201 1), Subgenus <i>Nannomonas</i> (<i>Trypanosoma congolense</i> , <i>Trypanosoma simiae</i> , <i>Trypanosoma simiae</i> Tsavo, <i>Trypanosoma</i> sp. Fly9), Subgenus <i>Schizotrypanum</i> (<i>Trypanosoma cruzi</i> , <i>Trypanosoma dionisii</i> , <i>Trypanosoma erneyi</i> , <i>Trypanosoma vespertilionis</i>), <i>Trypanosoma</i> with unspecified subgenus (<i>Trypanosoma avium</i> , <i>Trypanosoma</i> cf. <i>avium</i> TRM-2012, <i>Trypanosoma bennetti</i> , <i>Trypanosoma binneyi</i> , <i>Trypanosoma boissoni</i> , <i>Trypanosoma caninum</i> , <i>Trypanosoma carassii</i> , <i>Trypanosoma cascavelli</i> , <i>Trypanosoma cervi</i> , <i>Trypanosoma chattoni</i> , <i>Trypanosoma chelodinae</i> , <i>Trypanosoma cobitis</i> , <i>Trypanosoma conorhini</i> , <i>Trypanosoma copemani</i> , <i>Trypanosoma corvi</i> , <i>Trypanosoma culicavium</i> , <i>Trypanosoma cyclops</i> , <i>Trypanosoma danilewskyi</i> , <i>Trypanosoma desterrensis</i> , <i>Trypanosoma everetti</i> , <i>Trypanosoma evotomys</i> , <i>Trypanosoma fallisi</i> , <i>Trypanosoma gallinarum</i> , <i>Trypanosoma godfreyi</i> , <i>Trypanosoma granulorum</i> , <i>Trypanosoma grayi</i> , <i>Trypanosoma grosi</i> , <i>Trypanosoma hastatus</i> , <i>Trypanosoma irwini</i> , <i>Trypanosoma kuseli</i> , <i>Trypanosoma leeuwenhoekii</i> , <i>Trypanosoma livingstonei</i> , <i>Trypanosoma mega</i> , <i>Trypanosoma melophagium</i> , <i>Trypanosoma microti</i> , <i>Trypanosoma minasense</i> , <i>Trypanosoma murmanensis</i> , <i>Trypanosoma musculi</i> , <i>Trypanosoma nabiasi</i> , <i>Trypanosoma neveulemairei</i> , <i>Trypanosoma nudigobii</i> , <i>Trypanosoma ophiocephali</i> , <i>Trypanosoma otospermophili</i> , <i>Trypanosoma percae</i> , <i>Trypanosoma pestanai</i> , <i>Trypanosoma pleuronectidium</i> , <i>Trypanosoma ralphi</i> , <i>Trypanosoma ranarum</i> , <i>Trypanosoma rotatorium</i> , <i>Trypanosoma scelopori</i> , <i>Trypanosoma siniperca</i> , <i>Trypanosoma terrestris</i> , <i>Trypanosoma theileri</i> , <i>Trypanosoma therezieni</i> , <i>Trypanosoma triglae</i> , <i>Trypanosoma varani</i>), Subgenus <i>Trypanozoon</i> (<i>Trypanosoma brucei</i> , <i>Trypanosoma</i> cf. <i>brucei</i> Msubugwe, <i>Trypanosoma equiperdum</i> , <i>Trypanosoma evansi</i> , and unclassified <i>Trypanosoma</i>).
Tyzzeria (Scientific classification: Eukaryota; Alveolata; Apicomplexa; Conoidasida; Coccidia; Eucoccidiorida; Eimeriorina; Eimeriidae) species.
Wenyonella (Scientific classification: Eukaryota; Alveolata; Apicomplexa; Conoidasida; Coccidia; Eucoccidiorida; Eimeriorina; Eimeriidae) species.

BRIEF DESCRIPTION OF THE DRAWINGS

[00152] Further features of the present invention are more fully described in the following description of several non-limiting embodiments thereof. This description is included solely for the purposes of exemplifying the present invention. It should not be understood as a restriction on the broad summary, disclosure or description of the invention as set out above. The description will be made with reference to the accompanying drawings in which:

Figure 1 presents the chemical name and chemical structure of the compounds NCL001 to NCL230;

Figure 2 is a graph illustrating the activity of NCL099 against *Giardia duodenalis*;

Figure 3 is a graph illustrating the effect of NCL812 and metronidazole on the adherence of *Giardia duodenalis* trophozoites;

Figure 4 is a graph illustrating the activity of NCL812 against *Giardia duodenalis*;

Figure 5 is a graph illustrating the activity of NCL062 against *Giardia duodenalis*;

Figure 6 is a graph illustrating the activity of Metronidazole against *Giardia duodenalis*;

Figure 7 is a graph illustrating the erythrocyte lysis based on n-fold minimum inhibitory concentration;

Figure 8 presents photographs demonstrating changes in the ultrastructure of Giardia trophozoites exposed to NCL812. A-B: control 0.1 % DMSO, C: metronidazole control, D-G: NCL812 exposed trophozoites (1hr);

Figure 9 is a graph illustrating the cumulative release of NCL812 and NCL099 from Formulation B according to example 7;

Figure 10 is a graph illustrating the activity of NCL compounds at 10 μ M against *T. brucei* (black) and *L. donovani* (grey);

Figure 11 is a table illustrating the physicochemical and metabolic characteristics of nine NCL compounds;

Figure 12 is a graph illustrating the plasma concentration versus time profiles for NCL026, NCL195, NCL259 and NCL812; and

Figure 13 is a graph illustrating the plasma concentrations of NCL195 in male Swiss outbred mice following IP administration at an average dose of 43 mg/kg.

DESCRIPTION OF EMBODIMENTS

General

[00153] Before describing the present invention in detail, it is to be understood that the invention is not limited to particular exemplified methods or compositions disclosed herein. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments of the invention only, and is not intended to be limiting.

[00154] All publications referred to herein, including patents or patent applications, are incorporated by reference in their entirety. However, applications that are mentioned herein are referred to simply for the purpose of describing and disclosing the procedures, protocols, and reagents referred to in the publication which may have been used in connection with the invention. The citation of any publications referred to herein is not to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

[00155] In addition, the carrying out of the present invention makes use of, unless otherwise indicated, conventional microbiological techniques within the skill of the art. Such conventional techniques are known to the skilled worker.

[00156] As used herein, and in the appended claims, the singular forms "a", "an", and "the" include the plural unless the context clearly indicates otherwise.

[00157] Unless otherwise indicated, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any materials and methods similar to, or equivalent to, those described herein may be used to carry out the present invention, the preferred materials and methods are herein described.

[00158] The invention described herein may include one or more ranges of values (e.g. size, concentration, dose etc). A range of values will be understood to include all values within the range, including the values defining the range, and values adjacent to the range that lead to the same or substantially the same outcome as the values immediately adjacent to that value which define the boundary of the range.

[00159] The pharmaceutical or veterinary compositions of the invention may be administered in a variety of unit dosages depending on the method of administration, target site, physiological state of the patient, and other medicaments administered. For example, unit dosage form suitable for oral administration include solid dosage forms such as powder, tablets, pills, and capsules, and liquid dosage forms, such as elixirs, syrups, solutions and suspensions. The active ingredients may also be administered parenterally in sterile liquid dosage forms. Gelatin capsules may contain the active ingredient and inactive ingredients such as powder carriers, glucose, lactose, sucrose, mannitol, starch, cellulose or cellulose derivatives, magnesium stearate, stearic acid, sodium saccharin, talcum, magnesium carbonate, and the like.

[00160] The phrase "therapeutically effective amount" as used herein refers to an amount sufficient to inhibit protozoan growth associated with a protozoan infection or colonisation. That is, reference to the administration of the therapeutically effective amount of a compound of Formula I according to the methods or compositions of the invention refers to a therapeutic effect in which substantial protozoacidal or protozoastatic activity causes a substantial inhibition of protozoan infection. The term "therapeutically effective amount" as used herein, refers to a sufficient amount of the composition to provide the desired biological, therapeutic, and/or prophylactic result. The desired results include elimination of protozoan infection or colonisation or reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. An effective amount in any individual case may be

determined by one of ordinary skill in the art using routine experimentation. In relation to a pharmaceutical or veterinary composition, effective amounts can be dosages that are recommended in the modulation of a diseased state or signs or symptoms thereof. Effective amounts differ depending on the composition used and the route of administration employed. Effective amounts are routinely optimized taking into consideration pharmacokinetic and pharmacodynamic characteristics as well as various factors of a particular patient, such as age, weight, gender, etc and the area affected by disease or disease causing microbes.

[00161] As referred to herein, the terms "treatment" or "treating" refers to the full or partial removal of the symptoms and signs of the condition. For example, in the treatment of a protozoan infection or colonisation, the treatment completely or partially removes the signs of the infection. Preferably in the treatment of infection, the treatment reduces or eliminates the infecting protozoan pathogen leading to microbial cure.

[00162] As referred to herein, the term "protozoa" refers to members of a large domain of eukaryotic unicellular microorganisms. Typically a few micrometres in length, protozoa have a number of shapes, ranging from spheres to rods and spirals and can be present as individual cells or present in linear chains or clusters of variable numbers and shape. Preferably the terms "protozoa" and its adjectives "protozoan" "protozoal" refer to protozoa. The terms may refer to an antiprotozoal-sensitive strain or an antiprotozoal-resistant strain.

[00163] Referred to herein, the term "resistant protozoa" refers a protozoa isolate that demonstrates resistance to anyone of the following antimicrobial agents listed in **Table 2**.

Table 2 : Antimicrobial agents

Chemical Class	Examples
4-aminoquinoline	Amodiaquine, chloroquine, hydroxychloroquine, piperazine (bis-4-aminoquinoline)
8-aminoquinoline	Bulaquine, pamaquine, Primaquine, tafenoquine
Acetamide	Thiolutin
Acridine dye	Acriflavine, mepacrine (quinacrine)
Alkylphosphocholine	Miltefosine
Allylamine	Terbinafine
Aminoglycosides	Paromomycin
Aminophenanthridium	Homidium, isometamidium chloride,
Aminopyridine antimalarials	MMV390048
Antimonials, pentavalent	Sodium stibogluconate, meglumine antimoniate
Arsenicals (trivalent & pentavalent)	Acetarsol (5+), arsthinol (3+), carbarsone (5+), difetarzone (5+), glycoarsol (5+), melarsomine (3+), melarsoprol (3+), nitarzone (5+), oxophenarsine (3+), roxarsone (5+), tryparsamide (5+)
Arylaminoalcohol	Halofantrine, lumefantrine, quinine/quinidine
Azo naphthalene dyes	Trypan blue, trypan red
Azoles (triazoles and imidazoles)	Albaconazole, itraconazole, ketoconazole, posoconazole, ravuconazole
Benzamide	Zoxamide
Benzenediol	Resveratrol
Benzimidazoles and probenzimidazoles	Albendazole, fenbendazole, febantel, mebendazole, omeprazole
Bicyclohexylammonium	Fumagillin
Carbamate	Disulfiram

Cinnamamido adenosine	Puromycin
Coumarin	Flocoumafen
Diamidines	Amicarbalide, diminazene diacetate, imidocarb dipropionate, pafuramide, pentamidine isethionate, phenamidine isethionate, propamidine, stilbamidine
Dichloroacetamide	Clefamide, Etofamide, Teclozan
Dichloroacetamide	Diloxanide furoate
Difluoromethylornithine	Eflornithine
Dihydrofolate reductase/thymidylate synthase inhibitors	Diaveridine, ormetoprim, pyrimethamine, trimethoprim
Dihydroorotate dehydrogenase (DHODH) inhibitors	
Dinitroaniline	Trifluralin, oryzalin
Dinitrocarbanilide + pyrimidinol	Nicarbazin
Dithiocarbamate	Thiram
Ethoxybenzoic acid	Ethopabate
Fluoroquinolones	Ciprofloxacin, enrofloxacin, marbofloxacin
Guanidines	Chlorproguanil, cycloguanil, lauroguadine, proguanil, Robenidine
Halogenated 8-hydroxyquinoline	Iodoquinol, chlorquinaldol, tilbroquinol, broxyquinoline, diiodohydroxyquinoline, cloquinol
Hydroxyoxo-cyclohexenecarbaldehyde oxime	Sethoxydim, tralkoxydim, alloxydim, clethodim and cycloxydim
Hydroxyquinolones	Buquinolate, decoquinolate, nequinolate
Imidazolopiperazine	Kaf1 56
Isoquinoline	Emetine/dehydroemetine
Lincosamides	Clindamycin, lincomycin
Macrolides	Azithromycin, clarithromycin, erythromycin, roxithromycin, spiramycin
Methylquinolinium	Quinapyramine, quinuronium sulfate
Miscellaneous	Pyridaben
Naphthoquinones	Atovaquone, buparvaquone, parvaquone
Naphthyridine	Pyronaridine
Nitrobenzamides	Aklomide, dinitolmide
Nitrofurans	Nifurtimox, furaltodone, furazolidone, nifuratel, nifuroxime, nifursol
Nitroimidazoles	Azanidazole, benznidazole, carnidazole, dimetridazole, fexnidazole, ipronidazole, metronidazole, nimorazole, ornidazole, propenidazole, ronidazole, satranidazole, secnidazole, ternidazole, tinidazole
Nitrothiazoles	Nitazoxanide, aminitrozole (nithiamide), forminitrazole, niridazole, tenonitrozole
Organometallic antiprotozoal	Auranofin, ferroquine
Oxaborole (including benzoxaboroles)	SCYX-71 58
Phenoxyphenol	Triclosan
phenylsulfamide	Tolyfluanid
Phosphonic acid derivative	Fosmidomycin
Phosphonomethylglycine	Glyphosate
Phosphoramidothioic acid	Amiprofos-methyl
Polyene	Amphotericin B, mepartricin, hachimycin, Hamycin
Polyether ionophores	Laidlomycin, lasalocid, maduramicin, monensin, narasin, salinomycin, semduramicin
Polypeptide	Bacitracin (zinc, methylene disalicylate), cecropins, cyclosporins, dermaseptin, magainins, tachyplesin, thiostrepton
Polysulfonated naphthylamine	Suramin
Propylphosphonic acid	Fosmidomycin
Purinamine	Arprinocid
Pyrazolopyran	
Pyrazolopyrimidine	Allopurinol
Pyridinols	Clopidol
Pyrimidine	Fenarimol
Pyrrolidinediol	Anisomycin
Quinazolinone	Febrifugine, halofuginone
Quinoline	Mefloquine, nequinolate (methyl benzoquate), quinfamidine, tiliquinol
Quinoxaline	Carbadox
Rifamycin	Rifaximin
Spiroindolone	KAE609 (formerly NITD609), cipargamin

Strobilurin	Fluacrypyrim, azoxystrobin, trifloxystrobin, dimoxystrobin
Sulfonamides	Sulfadiazine, sulfadimethoxine, sulfadoxine, sulfaguandine, sulfamethazine (sulfadimidine), sulfamethoxazole, sulfanitran, sulfaquinoxaline, sulfamethoxypyrazine, cyazofamid
Sulphone	Dapsone
Tetracyclines	Chlortetracycline, doxycycline, oxytetracycline, tetracycline, tigecycline
Tetraoxanes	
Thiamine analogs	Amprolium
Thiophenone	Thiolactomycin
Translation elongation factor 2 (eEF2) inhibitor	DDD1 07498
Triazine	Clazuril, diclazuril, ponazuril, toltrazuril
Triazole	Bitertanol
Trioxane (sesquiterpene lactones, artemisinins)	Artemether, artesunate, dihydroartemisinin, artemotil, artemisinin, arteether, artemisone
Trioxolane (including ozonides)	Arterolane, OZ277, OZ439

[00164] Pharmaceutically and veterinary acceptable salts include salts which retain the biological effectiveness and properties of the compounds of the present disclosure and which are not biologically or otherwise undesirable. In many cases, the compounds disclosed herein are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto. Acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases, include by way of example only, sodium, potassium, lithium, ammonium, calcium and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, such as by way of example only, alkyl amines, dialkyl amines, trialkyl amines, substituted alkyl amines, di(substituted alkyl) amines, tri(substituted alkyl) amines, alkenyl amines, dialkenyl amines, trialkenyl amines, substituted alkenyl amines, di(substituted alkenyl) amines, tri(substituted alkenyl) amines, cycloalkyl amines, di(cycloalkyl) amines, tri(cycloalkyl) amines, substituted cycloalkyl amines, disubstituted cycloalkyl amines, trisubstituted cycloalkyl amines, cycloalkenyl amines, di(cycloalkenyl) amines, tri(cycloalkenyl) amines, substituted cycloalkenyl amines, disubstituted cycloalkenyl amines, trisubstituted cycloalkenyl amines, aryl amines, diaryl amines, triaryl amines, heteroaryl amines, diheteroaryl amines, triheteroaryl amines, heterocyclic amines, diheterocyclic amines, triheterocyclic amines, mixed di- and tri-amines where at least two of the substituents on the amine are different and are selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic, and the like. Also included are amines where the two or three substituents, together with the amino nitrogen, form a heterocyclic or heteroaryl group.

[00165] Pharmaceutically and veterinary acceptable acid addition salts may be prepared from inorganic and organic acids. The inorganic acids that can be used include, by way of example only, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. The organic acids that can be used include, by way of example only, acetic acid,

propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like.

[00166] The pharmaceutically or veterinary acceptable salts of the compounds useful in the present disclosure can be synthesized from the parent compound, which contains a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa. (1985), p. 1418, the disclosure of which is hereby incorporated by reference. Examples of such acceptable salts are the iodide, acetate, phenyl acetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate, γ -hydroxybutyrate, β -hydroxybutyrate, butyne-1,4-dioate, hexyne-1,4-dioate, hexyne-1,6-dioate, caproate, caprylate, chloride, cinnamate, citrate, decanoate, formate, fumarate, glycollate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, nitrate, oxalate, phthalate, terephthalate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propiolate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, sulfate, bisulfate, pyrosulfate, sulfite, bisulfite, sulfonate, benzenesulfonate, p-bromophenylsulfonate, chlorobenzenesulfonate, propanesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, methanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, p-toluenesulfonate, xylenesulfonate, tartarate, and the like.

[00167] The pharmaceutical or veterinary compositions of the invention may be formulated in conventional manner, together with other pharmaceutically acceptable excipients if desired, into forms suitable for oral, parenteral, or topical administration. The modes of administration may include parenteral, for example, intramuscular, subcutaneous and intravenous administration, oral administration, topical administration and direct administration to sites of infection such as intraocular, intraaural, intrauterine, intranasal, intramammary, intraperitoneal, intralesional, etc.

[00168] The pharmaceutical or veterinary compositions of the invention may be formulated for oral administration. Traditional inactive ingredients may be added to provide desirable colour, taste, stability, buffering capacity, dispersion, or other known desirable features. Examples include red iron oxide, silica gel, sodium laurel sulphate, titanium dioxide, edible white ink, and the like. Conventional diluents may be used to make compressed tablets.

Both tablets and capsules may be manufactured as sustained-release compositions for the continual release of medication over a period of time. Compressed tablets may be in the form of sugar coated or film coated tablets, or enteric-coated tablets for selective disintegration in the gastrointestinal tract. Liquid dosage forms for oral administration may contain colouring and/or flavouring to increase patient compliance. As an example, the oral formulation comprising compounds of the invention may be a tablet comprising any one, or a combination of, the following excipients: calcium hydrogen phosphate dehydrate, microcrystalline cellulose, lactose, hydroxypropyl methyl cellulose, and talc.

[00169] The compositions described herein may be in the form of a liquid formulation. Examples of preferred liquid compositions include solutions, emulsions, injection solutions, solutions contained in capsules. The liquid formulation may comprise a solution that includes a therapeutic agent dissolved in a solvent. Generally, any solvent that has the desired effect may be used in which the therapeutic agent dissolves and which can be administered to a subject. Generally, any concentration of therapeutic agent that has the desired effect can be used. The formulation in some variations is a solution which is unsaturated, a saturated or a supersaturated solution. The solvent may be a pure solvent or may be a mixture of liquid solvent components. In some variations the solution formed is an *in situ* gelling formulation. Solvents and types of solutions that may be used are well known to those versed in such drug delivery technologies.

[00170] The composition described herein may be in the form of a liquid suspension. The liquid suspensions may be prepared according to standard procedures known in the art. Examples of liquid suspensions include micro-emulsions, the formation of complexing compounds, and stabilising suspensions. The liquid suspension may be in undiluted or concentrated form. Liquid suspensions for oral use may contain suitable preservatives, antioxidants, and other excipients known in the art functioning as one or more of dispersion agents, suspending agents, thickening agents, emulsifying agents, wetting agents, solubilising agents, stabilising agents, flavouring and sweetening agents, colouring agents, and the like. The liquid suspension may contain glycerol and water.

[00171] The composition described herein may be in the form of an oral paste. The oral paste may be prepared according to standard procedures known in the art.

[00172] The composition is described herein may be in the form of a liquid formulation for injection, such as intra-muscular injection, and prepared using methods known in the art. For example, the liquid formulation may contain polyvinylpyrrolidone K30 and water.

[00173] The composition is described herein may be in the form of topical preparations. The topical preparation may be in the form of a lotion or a cream, prepared using methods

known in the art. For example, a lotion may be formulated with an aqueous or oily base and may include one or more excipients known in the art, functioning as viscosity enhancers, emulsifying agents, fragrances or perfumes, preservative agents, chelating agents, pH modifiers, antioxidants, and the like. For example, the topical formulation comprising one or more compounds of the invention may be a gel comprising anyone, or a combination of, the following excipients: PEG 8000, PEG 4000, PEG 200, glycerol, propylene glycol. The NCL812 compound may further be formulated into a solid dispersion using SoluPlus (BASF, www.soluplus.com) and formulated with anyone, or a combination of, the following excipients: PEG 8000, PEG 4000, PEG 200, glycerol, and propylene glycol.

[00174] For aerosol administration, the composition of the invention is provided in a finely divided form together with a non-toxic surfactant and a propellant. The surfactant is preferably soluble in the propellant. Such surfactants may include esters or partial esters of fatty acids.

[00175] The compositions of the invention may alternatively be formulated for delivery by injection. As an example, the compound is delivered by injection by any one of the following routes: intravenous, intramuscular, intradermal, intraperitoneal, and subcutaneous.

[00176] The compositions of the invention may alternatively be formulated using nanotechnology drug delivery techniques such as those known in the art. Nanotechnology-based drug delivery systems have the advantage of improving bioavailability, patient compliance and reducing side effects.

[00177] The formulation of the composition of the invention includes the preparation of nanoparticles in the form of nanosuspensions or nanoemulsions, based on compound solubility. Nanosuspensions are dispersions of nanosized drug particles prepared by bottom-up or top-down technology and stabilised with suitable excipients. This approach may be applied to the compounds of the invention which can have poor aqueous and lipid solubility, in order to enhance saturation solubility and improve dissolution characteristics. An example of this technique is set out in Sharma and Garg (2010) (Pure drug and polymer-based nanotechnologies for the improved solubility, stability, bioavailability, and targeting of anti-HIV drugs. *Advanced Drug Delivery Reviews*, 62: p. 491-502). Saturation solubility will be understood to be a compound-specific constant that depends on temperature, properties of the dissolution medium, and particle size (<1-2 μm).

[00178] The composition of the invention may be provided in the form of a nanosuspension. For nanosuspensions, the increase in the surface area may lead to an increase in saturation solubility. Nanosuspensions are colloidal drug delivery systems, consisting of particles below 1 μm . Compositions of the invention may be in the form of nanosuspensions including nanocrystalline suspensions, solid lipid nanoparticles (SLNs),

polymeric nanoparticles, nanocapsules, polymeric micelles and dendrimers. Nanosuspensions may be prepared using a top-down approach where larger particles may be reduced to nanometre dimensions by a variety of techniques known in the art including wet-milling and high-pressure homogenisation. Alternatively, nanosuspensions may be prepared using a bottom-up technique where controlled precipitation of particles may be carried out from solution.

[00179] The composition of the invention may be provided in the form of a nanoemulsion. Nanoemulsions are typically clear oil-in-water or water-in-oil biphasic systems, with a droplet size in the range of 100-500 nm, and with compounds of interest present in the hydrophobic phase. The preparation of nanoemulsions may improve the solubility of the compounds of the invention described herein, leading to better bioavailability. Nanosized suspensions may include agents for electrostatic or steric stabilisation such as polymers and surfactants. Compositions in the form of SLNs may comprise biodegradable lipids such as triglycerides, steroids, waxes and emulsifiers such as soybean lecithin, egg lecithin, and poloxamers. The preparation of a SLN preparation may involve dissolving/dispersing drug in melted lipid followed by hot or cold homogenisation. If hot homogenisation is used, the melted lipidic phase may be dispersed in an aqueous phase and an emulsion prepared. This may be solidified by cooling to achieve SLNs. If cold homogenisation is used, the lipidic phase may be solidified in liquid nitrogen and ground to micron size. The resulting powder may be subjected to high-pressure homogenisation in an aqueous surfactant solution.

[00180] The Compounds of Formula I as described herein may be dissolved in oils/liquid lipids and stabilised into an emulsion formulation. Nanoemulsions may be prepared using high- and low-energy droplet reduction techniques. High-energy methods may include high-pressure homogenisation, ultrasonication and microfluidisation. If the low-energy method is used, solvent diffusion and phase inversion will generate a spontaneous nanoemulsion. Lipids used in nanoemulsions may be selected from the group comprising triglycerides, soybean oil, safflower oil, and sesame oil. Other components such as emulsifiers, antioxidants, pH modifiers and preservatives may also be added.

[00181] The composition may be in the form of a controlled-release formulation and may include a degradable or non-degradable polymer, hydrogel, organogel, or other physical construct that modifies the release of the compound. It is understood that such formulations may include additional inactive ingredients that are added to provide desirable colour, stability, buffering capacity, dispersion, or other known desirable features. Such formulations may further include liposomes, such as emulsions, foams, micelles, insoluble monolayers, liquid crystals, phospholipid dispersions, lamellar layers and the like. Liposomes for use in the invention may

be formed from standard vesicle-forming lipids, generally including neutral and negatively charged phospholipids and a sterol, such as cholesterol.

[00182] The formulations of the invention may have the advantage of increased solubility and/or stability of the compounds, particularly for those formulations prepared using nanotechnology techniques. Such increased stability and/or stability of the compounds of Formula I may improve bioavailability and enhance drug exposure for oral and/or parenteral dosage forms.

[00183] Throughout this specification, unless the context requires otherwise, the word "comprise" or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

EXAMPLES

EXAMPLE 1: Preparation of NCL812 analogues.

Materials and Methods

NCL812

[00184] Analytical grade NCL812 with a defined potency of 960 mg/g (i.e. 96%) was obtained. The powder was stored in a sealed sample container out of direct sunlight and at room temperature at the study site. Aliquots (1 mL) of stock solution (containing 25.6 mg/mL of NCL812 in DMSO) were prepared and stored at -80°C and defrosted immediately before use.

Synthesising and Testing of NCL812 Analogues

[00185] Analogues NCL001 to NCL275, as identified in Figure 1, were synthesised using standard methods in the art. As an example, the methods used to manufacture compounds NCL097; NCL157; NCL179; NCL188; NCL195; and NCL196 are as follows:

NCL 097 (2,2'-bis[(3,4,5-trihydroxyphenyl)methylene]carbonimidic dihydrazide hydrochloride)

[00186] A suspension of 3,4,5-trihydroxybenzaldehyde (412.0 mg, 2.673 mmol, 2.21 eq.) and *N,N'*-diaminoguanidine hydrochloride (152.0 mg, 1.211 mmol) in EtOH (5 mL) was subjected to microwave irradiation (150 W) at 100 °C for 10 min. The reaction was then allowed to cool to ambient temperature. The resulting precipitate was collected and washed with chilled EtOH (5 mL) and Et₂O (5 mL) to afford the carbonimidicdihydrazide (369.0 mg, 77%) as a pale brown solid. M.P. 292°C (Decomp.). ¹H NMR (300 MHz, DMSO-d₆) δ 9.06 (br s, 6H), 8.25 - 8.01

(m, 4H), 6.83 (s, 4H). ^{13}C NMR (75 MHz, DMSO-d₆) δ 152.2, 149.7, 146.2, 136.5, 123.7, 107.4. LRMS(ESI⁺): 361 .95 [M + 1]⁺.

NCL157 (2,2'-bis[(2-amino-4-chlorophenyl)methylene]carbonimidic dihydrazide hydrochloride)

[00187] *Synthesis of 2-amino-4-chloro-N-methoxy-N-methylbenzamide.* To a solution of 2-amino-4-chlorobenzoic acid (5.6691 g, 33.041 mmol), *N,N*-dimethylhydroxylamine hydrochloride (5.7504 g, 58.954 mmol, 1.78 eq.), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (7.7925 g, 40.649 mmol, 1.23 eq.) and *N*-hydroxybenzotriazole hydrate (5.2371 g, 38.793 mmol (anhydrous basis), 1.17 eq.) in DMF (100 mL) was added diisopropylethylamine (18.0 mL, 13.4 g, 104 mmol, 3.15 eq.) and the brown solution stirred at ambient temperature for 7 h. The reaction was then concentrated *in vacuo* before dilution with 1M NaOH (100 mL) and extracting with CH₂Cl₂ (3 * 100 mL) The combined organic extracts were washed with 1M HCl (100 mL) before drying over MgSO₄ and concentrating *in vacuo* to afford a brown syrup. This oil was then further dried at 60 °C under high vacuum to afford the crude Weinreb amide (7.021 g, 99%) as a brown syrup that crystallised on standing. The crude material was used without further purification. ^1H NMR (400 MHz, CDCl₃) δ 7.24 (d, *J* = 8.4 Hz, 1H), 6.62 (d, *J* = 18 Hz, 1H), 6.54 (dd, *J* = 8.4, 1.9 Hz, 1H), 4.75 (s, 2H), 3.48 (s, 3H), 3.24 (s, 3H). ^{13}C NMR (101 MHz, CDCl₃) δ 169.2, 148.4, 137.1, 130.6, 116.6, 116.1, 115.0, 61.1, 34.0.

[00188] *Synthesis of 2-amino-4-chlorobenzaldehyde.* Crude 2-amino-4-chloro-*N*-methoxy-*N'*-methylbenzamide (751.1 mg, 3.532 mmol) was broken up into ca. 120 mg batches and each dissolved in THF (10 mL) and cooled to 0 °C before LiAlH₄ (2M in THF, 0.5 mL) was added to each and the solutions stirred for 16 h, allowing the reactions to achieve room temperature. The reactions were quenched with saturated NH₄Cl (1 mL) before being combined, diluted with saturated NaHCO₃ (160 mL) and extracted with CHCl₃ (2 x 150 mL, 1 x 75 mL). The combined organics were dried over MgSO₄ and concentrated *in vacuo* to afford the crude benzaldehyde (463.3 mg, 85%) as yellow/orange crystals. The material was used without further purification. ^1H (400 MHz, CD₃OD) 9.77 (d, *J* = 0.7 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 1H), 6.83 - 6.71 (m, 1H), 6.63 (dd, *J* = 8.4, 1.9 Hz, 1H). ^{13}C NMR (101 MHz, CD₃OD) δ 194.6, 153.0, 142.5, 138.4, 118.3, 116.8, 116.1.

[00189] *Synthesis of 2,2'-bis[(2-amino-4-chlorophenyl)methylene]carbonimidic dihydrazide hydrochloride.* A suspension of 2-amino-4-chlorobenzaldehyde (128.0 mg, 0.823 mmol, 1.78 eq.) and *N,N'*-diaminoguanidine hydrochloride (58.0 mg, 0.462 mmol) in EtOH (2 mL) was subjected to microwave irradiation (100 W) at 60°C for 5 minutes. Most solvent was then removed *in vacuo*, EtOH (1 mL) was added and the flask was transferred to the freezer to effect crystallisation. The resulting precipitate was collected and washed with EtOH (1 mL) to afford the carbonimidicdihydrazide (21.0 mg, 13%) as a pale yellow solid. ^1H NMR (400 MHz,

DMSO-*d*₆) δ 11.71 (br s, 2H), 8.40 (s, 2H), 8.37 (s, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 2.0 Hz, 2H), 6.73 (br s, 4H), 6.59 (dd, *J* = 8.3, 2.0 Hz, 2H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 152.1, 151.5, 148.9, 136.0, 134.7, 115.1, 114.5, 112.8.

NCL179 (4,6-bis(2-(4-chlorobenzylidene)hydrazinyl)pyrimidin-2-amine)

[00190] A suspension of 2-amino-4,6-dihydrazinylpyrimidine (67.3 mg, 0.434 mmol) and 4-chlorobenzaldehyde (198.8 mg, 1.414 mmol, 3.26 eq.) in EtOH (25 mL) was heated at reflux for 16 h. After this time, the condenser was removed and the solution concentrated to approximately 1 mL and the resulting precipitate filtered hot and washed with Et₂O (10 mL) to afford the aminopyrimidine (42.8 mg, 25%) as an off-white amorphous powder. M.P. 275 °C (Decomp.). ¹H NMR (400 MHz, DMSO) δ 10.70 (s, 2H), 8.02 (s, 2H), 7.67 (d, *J* = 8.4 Hz, 4H), 7.52 (d, *J* = 8.4 Hz, 4H), 6.28 (s, 1H), 5.85 (s, 2H). ¹³C NMR (101 MHz, DMSO) δ 162.8, 162.6, 138.8, 134.1, 133.1, 128.9, 127.6, 73.5.

NCL188 ((*E*)-2-(1-(4-chlorophenyl)pentylidene)hydrazine-1-carboximidamide hydrochloride)

[00191] A suspension of 1-(4-chlorophenyl)pentanone (1.8319 g, 9.3146 mmol, 1.95 eq.) and aminoguanidine hydrochloride (527.6 mg, 4.773 mmol) in EtOH (15 mL) was heated at 65 °C for 16 h. The crude was cooled to ambient temperature before being diluted with Et₂O (60 mL) and cooled to 0 °C to precipitate unreacted aminoguanidine hydrochloride (174.5 mg). The mother liquors were then concentrated *in vacuo* and the residue dissolved in Et₂O (20 mL). The solution was then boiled and hexanes (10 mL) added to afford the caboximidamide as a cream solid. ¹H NMR (400 MHz, DMSO) δ 11.54 (s, 1H), 7.99 (d, *J* = 8.7 Hz, 2H), 7.90 (s, 3H), 7.47 (d, *J* = 8.6 Hz, 2H), 2.91 - 2.82 (m, 2H), 1.48 - 1.32 (m, 4H), 0.89 - 0.84 (m, 3H). ¹³C NMR (101 MHz, DMSO) δ 156.2, 153.8, 134.8, 134.4, 128.7, 128.4, 28.1, 26.6, 22.0, 13.8

NCL195 (4,6-bis(2-((*E*)-4-methylbenzylidene)hydrazinyl)pyrimidin-2-amine)

[00192] A suspension of 2-amino-4,6-dihydrazinopyrimidine (58.9 mg, 0.380 mmol) and 4-methylbenzaldehyde (0.10 mL, 100 mg, 0.832 mmol, 2.19 eq.) in EtOH (4 mL) was heated at reflux for 16 h. The reaction mixture was cooled to ambient temperature before collecting the pellet-like precipitate, washing with Et₂O (20 mL). The 'pellets' were then crushed and the solid further washed with Et₂O (10 mL) to afford the pyrimidine (85.8 mg, 63%) as a white 'fluffy' powder. M.P. 274-276 °C. ¹H NMR (400 MHz, DMSO) δ 10.51 (s, 2H), 8.00 (s, 2H), 7.54 (d, *J* = 8.0 Hz, 4H), 7.26 (d, *J* = 7.9 Hz, 4H), 6.26 (s, 1H), 5.77 (s, 2H), 2.34 (s, 6H). ¹³C NMR (101 MHz, DMSO) δ 162.8, 162.6, 140.1, 138.4, 132.5, 129.4, 126.0, 73.3, 21.0.

NCL196 (4',4'-((*iE*,*rE*)-((2-aminopyrimidine-4,6-diyl)bis(hydrazin-2-yl-1-ylidene))bis(methanylylidene))diphenol)

[00193] A suspension of 2-amino-4,6-dihydrazino-pyrimidine (70.4 mg, 0.454 mmol) and 4-hydroxybenzaldehyde (140.3 mg, 1.149 mmol, 2.53 eq.) in EtOH (3 mL) was heated at reflux for 16 h. The reaction mixture was cooled to ambient temperature before collecting the precipitate, washing with Et₂O (25 mL), to afford the pyrimidine (91.4 mg, 55%) as an off-white powder. MP. 298 °C (Decomp.). ¹H NMR (400 MHz, DMSO) δ 10.31 (s, 2H), 9.74 (s, 2H), 7.94 (s, 2H), 7.48 (d, J = 8.6 Hz, 4H), 6.83 (d, J = 8.6 Hz, 4H), 6.20 (s, 1H), 5.70 (s, 2H). ¹³C (101 MHz, DMSO) δ 162.7, 162.5, 158.3, 140.5, 127.7, 126.3, 115.7, 73.0.

EXAMPLE 2: Giardia Adherence Assay

[00194] *Aim.* The aim of this study was to determine the anti-giardial activity of NCL099 and NCL812.

[00195] *Methods.* Giardia strain WB was grown until confluent (grown and maintained in TYI-S-33 medium with 10% foetal bovine serum). For the assay, media of a confluent culture was replaced with fresh TYI-S-33 medium. Cultures were then cold shocked (on ice) for 40 minutes to detach trophozoites. The cell density of the cultures was adjusted to 1 x 10⁶ cells/ml and 1 ml was added to each well of a 24 well plate already containing 1 ml of diluted compounds (see below). A coverslip was placed in the bottom of each well and the assay was incubated in an anaerobic environment (candle jar) for 2.5 hours at 37°C. After incubation the coverslips were removed, air-dried and stained with Diff-Quik (a Romanowski stain variant). Coverslips were mounted onto glass slides using polymount. Images at 10x magnification were taken at 5 random locations per coverslip. Dotcount freeware was used to count the number of cells per image and this data was analysed using GraphPad Prism v6. Stock solutions of compounds were prepared in DMSO at 25.6 mg/ml. Compounds were diluted 1:100 in TYI-S-33 medium. A 1:2 serial dilution was then performed in TYI-S-33 medium in 24 well plates.

[00196] *Results.* The results of this study are presented in Figures 2 to 3. Figure 2 shows the activity of NCL099 against *Giardia duodenalis in vitro*. A significant decrease in the number of adherent cells was observed at NCL099 concentrations of 11 µg/ml (P=0.0099), 38 µg/ml (P=0.001) and 128 µg/ml (P=<0.0001) compared to the control (Figure 2). An increase in activity was seen as the concentration of NCL099 increased. Figure 3 shows the activity of NCL812 and metronidazole against *Giardia duodenalis in vitro*. A significant decreases in the number of adherent trophozoites is seen for both metronidazole (P=0.0002) and NCL812 (P=<0.0001). The samples were exposed for 5 hours not 2.5 hours.

[00197] *Conclusion.* This study demonstrates that NCL099 and NCL812 inhibit the ability of *Giardia* cells to adhere to a surface therefore limiting the ability of this pathogen to cause disease (as adherence is necessary to cause disease).

EXAMPLE 3: Resazurin Reduction Assay

[00198] *Aim.* To determine the activity of NCL812 and NCL062 against *Giardia duodenalis in vitro*

[00199] *Methods.* *Giardia* trophozoites were grown until confluent. The media was replaced with fresh media and they were cold shocked for 40 minutes (as above). Cells were diluted to a concentration of ~ 500 000 cells/ml and 100 μ I were added to each well of the assay plate (except media only control). The assay was incubated in an anaerobic environment (candle jar) for 42 hours at 37°C. Alamarblue™ was added to a concentration of 10% and the samples incubated in an anaerobic environment for a further 6 hours. After incubation the absorbance of each sample was read at 570 and 630 nm. The percent reduction of resazurin (Alamarblue™) was calculated and data was analysed with GraphPad Prism v6 software. Assay set-up: the assay was performed in 96 well plates in a total volume of 200 μ I. 100 μ I of NCL812 or NCL062 (concentration of 25.6 mg/ml in DMSO) or metronidazole (concentration 5 mg/ml in DMSO) stock was added to 9.9 ml of TYI-S-33 medium, then serially diluted 1:2 in the same medium. Cells were added as above.

[00200] *Results.* The results are shown in Figures 4 to 6. All three compounds tested (NCL812, NCL062 and metronidazole) showed a reduction in the metabolic activity of the trophozoites (indicated by a decreased percentage of reduction of resazurin). Both NCL compounds showed greater activity when compared to metronidazole.

[00201] *Conclusion.* Both NCL812 and NCL062 show inhibitory activity towards *Giardia duodenalis* trophozoites *in vitro*.

EXAMPLE 4: Erythrocyte haemolysis assay

[00202] *Aim.* The aim of this study was to determine the *in vitro* toxicity of NCL812, NCL099 and NCL062 against mammalian cells.

[00203] *Methods.* Whole sheep blood was obtained from Thermofisher scientific. The red blood cells were separated from other blood components via centrifugation at 1500 g for 10 minutes and washed with saline 3 times. Erythrocytes were diluted to a concentration of ~1x 10¹⁰ cells/ml in saline. 50 μ I of NCL compounds diluted in DMSO (see below) were added to 1.5 ml Eppendorf tubes and 500 μ I of diluted red blood cells were added to each tube. Erythrocytes were incubated with compounds for 30 minutes at 37°C with gentle shaking (75 rpm). After incubation cells were placed on ice for 5 minutes then centrifuged at 1500 rpm for 10 minutes to

pellet cells. The supernatant was removed and serially diluted in saline. Absorbance of the supernatant and dilutions were recorded at 550 nm. Sample lysis was compared relative to cells lysed 100% in distilled water and analysed using GraphPad Prism v6 software.

[00204] *Results.* The results of this study are presented in Figure 7 (NCL062 tested from 1 to 128 Mg/ml, NCL812 tested from 2 to 256 µg/ml, NCL099 tested from 8 to 1024 Mg/ml). Figure 7 shows the amount of erythrocyte lysis as a percentage of the positive control (100% lysed blood cells in water) at various concentrations.

[00205] *Conclusion.* This study demonstrates that the concentration required of each compound to cause a toxic effect in mammalian cells (erythrocytes) is much higher than the concentration required to effect protozoal cells (giardia). This study also demonstrates that NCL099 appears to have greater selectivity for bacterial and protozoal cells than mammalian cells when compared to NCL812 and NCL062.

EXAMPLE 5: Transmission Electron Microscopy Study

[00206] *Aim.* To determine the effect that NCL812 has on the ultrastructure of *Giardia duodenalis*.

[00207] *Methods.* *Giardia* WB strain was grown until confluent (same as above) and old media was replaced with fresh media containing 6 µg/ml NCL812, 25 µg/ml metronidazole or 0.1 % DMSO (control). Samples were incubated at 37°C for 1 hour (NCL treated) or 4 hours (Metronidazole and DMSO control) then cold shocked to detach trophozoites. Treated samples were centrifuged at 900 x g for 10 minutes and washed twice with cold saline. Final cell pellet was resuspended in pre-cooled fixative (1.25% gluteraldehyde, 4% paraformaldehyde in PBS with 4% sucrose, pH 7.2) and left overnight. Samples were post-fixed in 2% osmium tetroxide solution for 1 hour and dehydrated through a graded ethanol series (70 - 100%). Samples were embedded in epoxy resin and stained with uranyl acetate and lead citrate before viewing on an FEI Tecnai G2 Spirit Transmission Electron Microscope.

[00208] *Results.* The results of this study are shown in Figure 8. This figure shows the severe change in the ultrastructure of the NCL treated trophozoites (D-G) compared to the controls (A-C). Development of vacuoles and disintegration of the cytoplasmic membrane is observed.

Conclusion. NCL812 causes significant changes in to the ultrastructure of *Giardia duodenalis*.

EXAMPLE 6: Formulations of Compounds

[00209] The following formulations were prepared using standard methods in the art.

Formulation A - Topical Formulation - PEG-based Gel with compounds of the invention

4.0g PEG 4000;
3.5g PEG 200;
0.6g propylene glycol;
1.9g water; and
0.204g of Compound (for example, NCL099)

[00210] PEG 4000, PEG 200 and propylene glycol were mixed and heated to 150 °C and until all solid crystals were dissolved. Compound was added to water and sonicated for 30 minutes until fully suspended. The Compound solution and gel solutions were mixed and allowed to cool and solidify. Formulation A will likely demonstrate acceptable viscosity, ease of skin application, uniform suspension and consistent and fine texture.

Formulation B - Topical Formulation - PEG-based Gel with compounds of the invention

3.0g PEG 4000;
1.0g PEG 8000;
3.0g PEG 200;
1.0g propylene glycol;
1.9g water; and
0.202g of Compound (for example, NCL099)

[0021 1] PEG 4000, PEG 8000, PEG 200 and propylene glycol were mixed and heated to 150 °C and until all solid crystals were dissolved. Compound (for example, NCL099) was added to water and sonicated for 30 minutes until fully suspended. The Compound solution and gel solutions were mixed and allowed to cool and solidify. Formulation B demonstrated acceptable viscosity, ease of skin application, uniform suspension and consistent and fine texture.

Formulation C - Topical Formulation - PEG-based Gel with Compound-Soluplus

2.5g PEG 4000;
4.0g PEG 200;
2.5g propylene glycol;
1.0g water; and
1.8g solid dispersion of Compound-SoluPlus.

[00212] Soluplus was purchased from BASF (www.soluplus.com). Compound-SoluPlus was prepared using standard methods in the art. PEG 4000, PEG 200, Compound-SoluPlus and propylene glycol were mixed and heated to 150 °C and until all solid crystals were dissolve. Water was added and then the solution was sonicated. The solution was allowed to cool and solidify. Formulation C demonstrated acceptable viscosity, ease of skin application, uniform suspension and consistent and fine texture.

Formulation D - Tablet Formulation

30mg Calcium hydrogen phosphate dehydrate;
80mg Microcrystalline cellulose;
50mg Lactose;
8mg Hydroxypropyl methyl cellulose
1.5mg Talc
10mg of compound (for example NCL099)

[00213] The excipients were weighed and mixed for 5 minutes. The mixture was fed into a feed hopper of a tablet press machine and the machine was operated according to standard procedures in the art. Formulation D demonstrated acceptable tablet hardness, disintegration and friability.

Formulation E - Oral Suspension

2.0 ml Glycerol;
1.5ml Absolute ethanol;
600mg NCL812; and
To 60ml Vehicle (Ora Sweet and Ora Plus, 1:1).

[00214] NCL 812 powder was sieved through a 75 μm sieve. 600 mg of sieved NCL 812 was mixed with 2.0 ml glycerol and 1.5 ml absolute ethanol. The mixture was placed in a mortar and manually milled until all NCL 812 was suspended uniformly. The suspension was sonicated for 30 minutes. Vehicle (55 ml of Ora Sweet and Ora Plus mixture) was then added to the suspension and milled for another 10 minutes. Volume was made up with the Ora plus and Ora sweet mixture to 60 ml by transferring to a measuring cylinder

[00215] Formulation E demonstrated acceptable suspension and demonstrated acceptable short term stability.

Formulation F - Intramuscular Injection

20mg/ml Polyvinylpyrrolidone K30 (PVPK30);
0.09mg/ml NCL812; and
50ml water.

[00216] Two percent of w/v PVP K30 solution was prepared by the addition of 1.0 g of PVP K30 to 50 ml of MilliQ water. The solution was then placed in a sonicator for 30 minutes to equilibrate and 4.5 mg of NCL 812 was added to the PVP solution and placed on an incubator shaker at a maximum speed of 10 rpm over a period of 24 hours, with controlled temperature of $25\pm 1^\circ\text{C}$. Solution was transferred to 5 ml vials and checked for clarity, appearance, pH and short-term stability. The pH of solution was 7.25.

Formulation F demonstrated acceptable transparency and short term stability.

EXAMPLE 7: Release of NCL812 and NCL099 from Formulation B.

[00217] *Aim:* The objective of this study was to measure the release of NCL812 and NCL099 from Formulation B prepared in Example 6.

[00218] *Method:* Franz diffusion cells were utilized to quantify the release rate of NCL 812 and NCL099 from its topical formulations. Five millilitres of absolute ethanol, which was chosen as the desired release medium, was loaded into the receptor chamber. Temperature of the receptor fluid was kept constant, at $32\pm 1^{\circ}\text{C}$ using a water jacket. Acetyl cellulose membranes, with pore size of $0.45\ \mu\text{m}$ (Pall Corporation) was selected and placed between donor and receptor chamber. Followed by that, a number of test samples (Formulation B) was loaded into the donor chamber. One millilitre of receptor fluid was collected at regular time intervals of 0.25, 0.50, 0.75, 1, 2, 3, 4, 5, 6, 7, 8 and 24 hours through the sampling port. One millilitre of fresh absolute ethanol was immediately returned to the receptor chamber. UV-HPLC was utilized to analyse the content of the receptor fluids attained.

[00219] *Results and Conclusion:* Figure 9 presents the cumulative release of NCL812 and NCL099 over time. This study demonstrates that Formulation B provides an acceptable release profile for NCL812 and NCL099.

EXAMPLE 8: NMR Spectroscopy Lists of Compounds NCL812, NCL001-NCL275

[00220] NMR Spectroscopy was performed on compounds NCL812, NCL001-NCL275 using standard methods in the art. The lists of the NMR spectroscopy are presented in Table 3.

Table 3: NMR Spectroscopy Lists of Compounds NCL812, NCL001-NCL275

NCL Code	NMR
NCL812	¹ H NMR (400 MHz, DMSO) δ 12.04 (br. s, 2H), 8.48 (br. s, 1H), 8.37 (br. s, 2H), 7.97 (d, J = 8.6 Hz, 4H), 7.57 (d, J = 8.6 Hz, 4H)
NCL001	¹ H NMR (400 MHz, DMSO) δ 10.84 (br. s, 2H), 8.17 (br. s, 2H), 7.77 (d, J = 8.2 Hz, 4H), 7.50 (d, J = 8.6 Hz, 4H)
NCL002	¹ H NMR (400 MHz, DMSO) δ 11.06 (s, 2H), 8.58 (br. s, 2H), 8.17 (br. s, 2H), 7.50 - 7.52 (m, 2H), 7.41 - 7.45 (m, 4H)
NCL003	¹ H NMR (400 MHz, DMSO) δ 10.71 (s, 2H), 8.17 (br. s, 2H), 7.73 - 7.88 (m, 4H), 7.28 (t, J = 8.8 Hz, 4H)
NCL004	¹ H NMR (400 MHz, DMSO) δ 10.89 (br. s, 2H), 8.19 (br. s, 2H), 7.65 (br. s, 2H), 7.43 - 7.56 (m, 4H), 7.19 - 7.27 (m, 2H)
NCL005	¹ H NMR (400 MHz, DMSO) δ 10.94 (br. s, 2H), 8.43 (br. s, 2H), 8.10 (br. s, 2H), 7.39 - 7.52 (m, 2H), 7.21 - 7.35 (m, 4H)
NCL006	¹ H NMR (400 MHz, DMSO) δ 10.50 (s, 2H), 8.11 (br. s, 2H), 7.68 (d, J = 8.6 Hz, 4H), 6.99 (d, J = 8.6 Hz, 4H), 3.80 (s, 6H)
NCL007	¹ H NMR (400 MHz, DMSO) δ 11.10 (br. s, 2H), 8.24 (br. s, 2H), 7.81 - 8.03 (m, 8H)
NCL008	¹ H NMR (400 MHz, DMSO) δ 11.24 (br. s, 2H), 8.51 (br. s, 2H), 8.18 - 8.29 (m, 2H), 7.90 (d, J = 7.4 Hz, 2H), 7.80 (t, J = 7.6 Hz, 2H), 7.59 (t, J = 7.0 Hz, 2H)
NCL009	¹ H NMR (400 MHz, DMSO) δ 11.02 (s, 2H), 8.26 (br. s, 4H), 8.07 (d, J = 7.8 Hz, 2H), 7.85 (d, J = 7.8 Hz, 2H), 7.65 (t, J = 7.8 Hz, 2H)
NCL010	¹ H NMR (400 MHz, DMSO) δ 10.74 (br. s, 2H), 8.15 (br. s, 2H), 7.25 - 7.39 (m, 6H), 6.94-7.01 (m, 2H), 3.82 (s, 6H)
NCL011	¹ H NMR (400 MHz, DMSO) δ 11.02 (s, 2H), 8.28 (br. s, 2H), 8.13 (s, 2H), 8.04 (d, J = 7.4 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H), 7.68 (t, J = 8.0 Hz, 2H)
NCL012	¹ H NMR (400 MHz, DMSO) δ 11.04 (br. s, 2H), 8.27 (br. s, 2H), 7.97 (d, J = 7.8 Hz, 4H), 7.80 (d, J = 8.2 Hz, 4H)
NCL013	¹ H NMR (400 MHz, DMSO) δ 11.22 (br. s, 2H), 8.55 (br. s, 2H), 8.35 (d, J = 7.0 Hz, 2H), 7.73 - 7.82 (m, 4H), 7.57 - 7.65 (m, 2H)
NCL014	¹ H NMR (400 MHz, DMSO) δ 10.30 (s, 1H), 7.81 (s, 1H), 7.76 (d, J = 8.6 Hz, 2H), 7.43 (d, J = 8.6 Hz, 2H), 6.53 (br. s, 2H)
NCL015	¹ H NMR (400 MHz, DMSO) δ 12.02 (br. s, 1H), 8.55 (s, 1H), 8.27-8.33 (m, 1H), 7.79 (br. s, 3H), 7.51 - 7.56 (m, 1H), 7.39 - 7.51 (m, 2H)
NCL016	¹ H NMR (400 MHz, DMSO) δ 11.98 (br. s, 1H), 8.39 (s, 1H), 8.19-8.26 (m, 1H), 7.80 (br. s, 3H), 7.46 - 7.58 (m, 1H), 7.20 - 7.38 (m, 2H)
NCL017	¹ H NMR (400 MHz, DMSO) δ 11.79 (br. s, 1H), 8.17 (s, 1H), 7.87 (d, J = 9.8 Hz, 1H), 7.71 (br. s, 3H), 7.62 (d, J = 7.4 Hz, 1H), 7.45 - 7.54 (m, 1H), 7.25-7.32 (m, 1H)
NCL018	¹ H NMR (400 MHz, DMSO) δ 10.66 (s, 2H), 8.47 (br. s, 2H), 7.91-8.00 (m, 2H), 7.19 - 7.32 (m, 6H), 2.42 (s, 6H)
NCL019	¹ H NMR (400 MHz, DMSO) δ 10.68 (br. s, 2H), 8.15 (br. s, 2H), 7.57 (s, 2H), 7.52 (d, J = 7.4 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.21 (d, J = 7.4 Hz, 2H), 2.36 (s, 6H)
NCL020	¹ H NMR (400 MHz, DMSO) δ 12.37 (br. s, 2H), 8.83 (br. s, 2H), 8.63 (br. s, 2H), 8.39 - 8.44 (m, 2H), 7.55 - 7.60 (m, 2H), 7.44 - 7.55 (m, 4H)
NCL021	¹ H NMR (400 MHz, DMSO) δ 12.11 (br. s, 1H), 8.52 (br. s, 2H), 8.40 (br. s, 2H), 8.02 (t, J = 8.6, 4H), 7.35 (t, J = 8.8 Hz, 4H)
NCL022	¹ H NMR (400 MHz, DMSO) δ 12.19 (br. s, 2H), 8.65 (br. s, 2H), 8.58 (br. s, 1H), 8.34 (t, J = 7.6 Hz, 2H), 7.51 - 7.60 (m, 2H), 7.34 (t, J = 8.2 Hz, 4H)
NCL023	¹ H NMR (400 MHz, DMSO) δ 12.08 (br. s, 2H), 8.38 (br. s, 2H), 7.92-8.00 (m, 2H), 7.65-7.71 (m, 2H), 7.50 - 7.58 (m, 2H), 7.29 - 7.37 (m, 2H)
NCL024	¹ H NMR (400 MHz, DMSO) δ 12.32 (br. s, 2H), 8.67 (br. s, 2H), 8.44 (br. s, 2H), 8.15 (d, J = 8.6 Hz, 4H), 7.98 (d, J = 8.6 Hz, 4H)
NCL025	¹ H NMR (400 MHz, DMSO) δ 8.75 (br. s, 2H), 8.50 (d, J = 8.2 Hz, 2H), 7.97 (d, J = 7.4 Hz, 2H), 7.85 (t, J = 7.6 Hz, 2H), 7.68 (t, J = 7.6 Hz, 2H)

NCL026	1H NMR (400 MHz, DMSO-d₆) δ 12.26 (br. s, 1H), 8.66 (br. s, 1H), 8.55 (s, 2H), 8.43 (br. s, 2H), 8.21 (d, J = 7.8 Hz, 2H), 7.94 (d, J = 7.8 Hz, 2H), 7.71 (t, J = 7.8 Hz, 2H)
NCL027	1H NMR (400 MHz, DMSO-d₆) δ 11.78 (br. s, 2H), 8.31 (br. s, 3H), 7.87 (d, J = 8.6 Hz, 4H), 7.04 (d, J = 8.6 Hz, 4H), 3.83 (s, 6H)
NCL028	1H NMR (400 MHz, DMSO-d₆) δ 12.00 (br. s, 2H), 8.75 (br. s, 2H), 8.39 (br. s, 2H), 8.22 (d, J = 6.7 Hz, 2H), 7.44 - 7.52 (m, 2H), 7.14 (d, J = 8.2 Hz, 2H), 7.05 (t, J = 7.6 Hz, 2H)
NCL029	1H NMR (400 MHz, DMSO-d₆) δ 11.98 (br. s, 2H), 8.48 (br. s, 2H), 8.36 (br. s, 2H), 7.56 (s, 2H), 7.35 - 7.49 (m, 4H), 7.04-7.10 (m, 2H), 3.84 (s, 6H)
NCL030	1H NMR (400 MHz, DMSO-d₆) δ 11.83 (br. s, 1H), 8.16 (s, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.75 (br. s, 1H), 7.53 (d, J = 8.2 Hz, 2H)
NCL031	1H NMR (400 MHz, DMSO-d₆) δ 11.91 (br. s, 1H), 8.22 (s, 1H), 8.09 (d, J = 8.2 Hz, 2H), 7.93 (d, J = 8.2 Hz, 2H)
NCL032	1H NMR (400 MHz, DMSO-d₆) δ 12.12 (s, 1H), 8.48 (s, 1H), 8.38 (d, J = 7.8 Hz, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.86 (br. s, 2H), 7.80 (t, J = 7.8 Hz, 2H), 7.64 (t, J = 7.6 Hz, 1H)
NCL033	1H NMR (400 MHz, DMSO-d₆) δ 11.93 (s, 1H), 8.50 (s, 1H), 8.20 (s, 1H), 8.14 (d, J = 7.8 Hz, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.66 (t, J = 7.8 Hz, 1H)
NCL034	1H NMR (400 MHz, DMSO-d₆) δ 11.87 (br. s, 1H), 8.48 (s, 1H), 8.09 (d, J = 7.8 Hz, 1H), 7.70 (br. s, 2H), 7.38 - 7.49 (m, 1H), 7.11 (d, J = 8.6 Hz, 1H), 7.01 (t, J = 7.4 Hz, 1H), 3.9 (s, 3H)
NCL035	1H NMR (400 MHz, DMSO-d₆) δ 12.32 (br. s, 2H), 8.69 (br. s, 2H), 8.49 (br. s, 2H), 8.18 (d, J = 7.8 Hz, 4H), 7.86 (d, J = 8.2 Hz, 4H)
NCL036	1H NMR (400 MHz, DMSO-d₆) δ 12.51 (br. s, 1H), 8.80 (br. s, 2H), 8.72 (br. s, 1H), 8.59 (d, J = 7.8 Hz, 2H), 7.78 - 7.91 (m, 4H), 7.71 (t, J = 8.0 Hz, 2H)
NCL037	1H NMR (400 MHz, DMSO-d₆) δ 12.28 (br. s, 2H), 8.70 (br. s, 2H), 8.50 (br. s, 2H), 8.38 (s, 2H), 8.22 (d, J = 7.8 Hz, 2H), 7.85 (d, J = 7.8 Hz, 2H), 7.74 (t, J = 7.8 Hz, 2H)
NCL038	1H NMR (400 MHz, DMSO-d₆) δ 11.92 (br. s, 2H), 8.41 (br. s, 2H), 8.36 (br. s, 2H), 7.83 (d, J = 8.2 Hz, 4H), 7.31 (d, J = 7.8 Hz, 4H), 2.37 (s, 6H)
NCL039	1H NMR (400 MHz, DMSO-d₆) δ 11.99 (br. s, 2H), 8.73 (br. s, 2H), 8.41 (br. s, 2H), 8.19 (d, J = 7.8 Hz, 2H), 7.37 (t, J = 8.0 Hz, 2H), 7.30 (t, J = 7.8 Hz, 4H), 2.46 (s, 6H)
NCL040	1H NMR (400 MHz, DMSO-d₆) δ 11.97 (br. s, 2H), 8.44 (br. s, 2H), 8.37 (br. s, 2H), 7.76 (s, 2H), 7.71 (d, J = 7.8 Hz, 2H), 7.38 (t, J = 7.8 Hz, 2H), 7.31 (d, J = 7.8 Hz, 2H), 2.38 (s, 6H)
NCL041	1H NMR (400 MHz, DMSO-d₆) δ 11.94 (s, 1H), 8.25 (s, 1H), 8.11 (d, J = 7.8 Hz, 2H), 7.71 - 7.91 (m, 4H)
NCL042	1H NMR (400 MHz, DMSO-d₆) δ 12.04 (s, 1H), 8.46 - 8.56 (m, 2H), 7.70 - 7.93 (m, 5H), 7.66 (t, J = 7.8 Hz, 1H)
NCL043	1H NMR (400 MHz, DMSO-d₆) δ 11.88 (s, 1H), 8.33 (s, 1H), 8.26 (s, 1H), 8.14 (d, J = 7.8 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.69 (t, J = 7.8 Hz, 1H)
NCL044	1H NMR (400 MHz, DMSO-d₆) δ 11.71 (br. s, 1H), 8.13 (s, 1H), 7.76 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 7.8 Hz, 2H), 2.35 (s, 3H)
NCL045	1H NMR (400 MHz, DMSO-d₆) δ 11.69 (br. s, 1H), 8.45 (s, 1H), 8.06 (d, J = 7.4 Hz, 1H), 7.67 (br. s, 2H), 7.30 - 7.39 (m, 1H), 7.20 - 7.29 (m, 2H), 2.42 (s, 3H)
NCL046	1H NMR (400 MHz, DMSO-d₆) δ 11.64 (br. s, 1H), 8.12 (s, 1H), 7.53 - 7.77 (m, 4H), 7.34 (t, J = 7.8 Hz, 1H), 7.27 (d, J = 7.8 Hz, 1H), 2.35 (s, 3H)
NCL047	1H NMR (400 MHz, DMSO-d₆) δ 10.47 (s, 1H), 8.23 (s, 1H), 8.16 - 8.21 (m, 1H), 7.42 - 7.50 (m, 1H), 7.30 - 7.40 (m, 2H), 6.57 (br. s, 2H)
NCL048	1H NMR (400 MHz, DMSO-d₆) δ 10.40 (s, 1H), 8.08 - 8.15 (m, 1H), 8.05 (s, 1H), 7.34 - 7.44 (m, 1H), 7.17 - 7.28 (m, 2H), 6.54 (br. s, 2H)
NCL049	1H NMR (400 MHz, DMSO-d₆) δ 10.51 (s, 1H), 7.93 (d, J = 8.2 Hz, 1H), 7.86 (s, 1H), 7.83 (d, J = 8.2 Hz, 1H), 6.63 (br. s, 2H)
NCL050	1H NMR (400 MHz, DMSO-d₆) δ 10.66 (s, 1H), 8.13 (d, J = 8.0 Hz, 1H), 8.11 (s, 1H), 7.85 (d, J = 7.4 Hz, 1H), 7.71 (t, J = 7.8 Hz, 1H), 7.52 (t, J = 7.0 Hz, 1H), 6.60 (br. s, 2H)

N ^o L051	1H NMR (400 MHz, DMSO) δ 10.43 (s, 1H), 8.37 (s, 1H), 7.98 (d, J = 7.8 Hz, 1H), 7.84 (s, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H)
N ^o CL052	1H NMR (400 MHz, DMSO) δ 11.95 (s, 1H), 8.16 (s, 1H), 8.10 (s, 1H), 7.80 (br. s, 2H), 7.76 (d, J = 7.0 Hz, 1H), 7.40 - 7.55 (m, 2H)
N ^o CL ^o 53	1H NMR (400 MHz, DMSO) δ 11.88 (s, 1H), 8.17 (s, 1H), 7.95 (dd, J = 8.8, 5.7 Hz, 2H), 7.76 (br. s, 1H), 7.30 (t, J = 9.0 Hz, 2H)
N ^o CL ^o 54	1H NMR (400 MHz, DMSO) δ 12.17 (br. s, 2H), 8.61 (br. s, 2H), 8.39 (br. s, 2H), 8.16 (s, 2H), 7.83 (d, J = 7.0 Hz, 2H), 7.45 - 7.61 (m, 4H)
N ^o CL055	1H NMR (400 MHz, DMSO) δ 10.34 (s, 1H), 7.93 (s, 1H), 7.80 (s, 1H), 7.54 - 7.67 (m, 1H), 7.32 - 7.46 (m, 2H), 6.58 (br. s, 1H)
NCL056	1H NMR (400 MHz, DMSO) δ 10.23 (s, 1H), 7.82 (s, 1H), 7.78 (dd, J = 8.8, 5.7 Hz, 2H), 7.21 (t, J = 8.8 Hz, 1H), 6.49 (br. s, 2H)
NCL057	1H NMR (400 MHz, DMSO) δ 10.33 (s, 1H), 7.82 (s, 1H), 7.71 (d, J = 9.8 Hz, 1H), 7.35 - 7.53 (m, 2H), 7.10 - 7.23 (m, 1H), 6.57 (br. s, 1H)
N ^o CL058	1H NMR (400 MHz, DMSO) δ 10.08 (s, 1H), 7.78 (s, 1H), 7.65 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 8.6 Hz, 2H), 6.40 (br. s, 2H), 3.78 (s, 3H)
N ^o CL ^o 59	1H NMR (400 MHz, DMSO) δ 10.23 (s, 1H), 7.80 (s, 1H), 7.34 (s, 1H), 7.29 (t, J = 7.8 Hz, 1H), 7.21 (d, J = 7.8 Hz, 1H), 6.91 (dd, J = 7.8, 2.0 Hz, 1H), 6.51 (br. s, 2H), 3.79 (s, 3H)
N ^o CL ^o 6 ^o	1H NMR (400 MHz, DMSO) δ 10.56 (s, 1H), 8.41 (d, J = 7.8 Hz, 1H), 8.19 (br. s, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.54 (t, J = 7.8 Hz, 1H), 6.62 (br. s, 2H)
N ^o CL ^o 61	1H NMR (400 MHz, DMSO) δ 11.71 (br. s, 2H), 8.91 (br. s, 1H), 8.28 (d, J = 7.8 Hz, 4H), 7.82 (d, J = 8.2 Hz, 4H), 2.49 (br. s, 6H)
N ^o CL062	1H NMR (400 MHz, DMSO) δ 11.68 (br. s, 2H), 8.78 (br. s, 1H), 8.10 (d, J = 8.6 Hz, 4H), 7.52 (d, J = 8.6 Hz, 4H), 2.43 (s, 6H)
N ^o CL ^o 63	1H NMR (400 MHz, DMSO) δ 7.99 (br. s, 4H), 7.83 (d, J = 7.8 Hz, 6H)
N ^o CL ^o 64	1H NMR (400 MHz, DMSO) δ 7.94 (d, J = 7.8 Hz, 4H), 7.84 (t, J = 7.6 Hz, 4H), 7.64 (t, J = 7.6 Hz, 4H)
N ^o CL ^o 65	1H NMR (400 MHz, DMSO) δ 12.20 (br. s, 1H), 11.86 (br. s, 1H), 8.65 (br. s, 1H), 8.50 (br. s, 1H), 8.03-8.27 (m, 3H), 7.90 (d, J = 7.8 Hz, 2H), 7.68 (t, J = 7.6 Hz, 2H)
NCL ^o 66	1H NMR (400 MHz, DMSO) δ 7.43 - 7.67 (m, 7H), 7.23 - 7.34 (m, 2H)
N ^o CL ^o 67	1H NMR (400 MHz, DMSO) δ 10.40 (s, 1H), 8.16 (s, 1H), 7.98 (d, J = 7.4 Hz, 1H), 7.90 (s, 1H), 7.67 (d, J = 7.3 Hz, 1H), 7.60 (t, J = 7.4 Hz, 1H)
N ^o CL ^o 68	1H NMR (400 MHz, DMSO) δ 8.47 (br. s, 1H), 8.18 (d, J = 7.8 Hz, 3H), 8.07 (d, J = 8.6 Hz, 2H), 7.85 (d, J = 7.8 Hz, 2H), 7.53 (d, J = 8.6 Hz, 2H), 2.40 (s, 3H)
NCL ^o 69	1H NMR (400 MHz, DMSO) δ 9.44 (br. s, 1H), 8.03 (d, J = 8.2 Hz, 2H), 7.94 (br. s, 2H), 7.48 (d, J = 8.6 Hz, 2H), 2.31 (s, 3H)
N ^o CL070	1H NMR (400 MHz, DMSO) δ 8.12 (br. s, 1H), 7.71 (br. s, 3H), 7.49 (br. s, 6H)
N ^o CL ^o 71	1H NMR (400 MHz, DMSO) δ 11.43 (s, 1H), 8.40 (s, 1H), 8.15 (br. s, 1H), 8.10 (d, J = 7.4 Hz, 1H), 7.95 (br. s, 1H), 7.37 (t, J = 7.8 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 6.95 (t, J = 7.4 Hz, 1H), 3.82 (s, 3H)
N ^o CL ^o 72	1H NMR (400 MHz, DMSO) δ 7.91 (br. d, J = 8.2 Hz, 3H), 7.52 (d, J = 8.6 Hz, 2H)
N ^o CL ^o 73	1H NMR (400 MHz, DMSO) δ 9.51 (br. s, 1H), 8.22 (d, J = 8.3 Hz, 2H), 8.01 (br. s, 2H), 7.77 (d, J = 8.3 Hz, 2H), 2.36 (s, 3H)
NCL074	1H NMR (400 MHz, DMSO) δ 12.46 (br. s, 1H), 8.79 (br. s, 1H), 8.66 (br. s, 2H), 8.46 (d, J = 8.2 Hz, 2H), 7.99 (d, J = 7.0 Hz, 2H), 7.77 (br. s, 1H), 7.58 (d, J = 6.7 Hz, 3H)
N ^o CL075	1H NMR (400 MHz, DMSO) δ 8.48 (br. s, 1H), 8.26 (d, J = 7.4 Hz, 2H), 8.19 (d, J = 7.4 Hz, 2H), 7.75-7.93 (m, 4H), 2.46 (s, 3H)
N ^o CL ^o 76	1H NMR (400 MHz, DMSO) δ 8.53 (br. s, 2H), 8.29 - 8.46 (m, 2H), 7.99 (d, J = 7.8 Hz, 2H), 7.83 (d, J = 7.8 Hz, 2H), 7.57 (d, J = 7.8 Hz, 2H), 7.31 (d, J = 7.8 Hz, 2H), 2.37 (s, 3H)

N C ₀ -77	¹ H NMR (400 MHz, DMSO) δ 12.28 (br. s, 1H), 8.67 (br. s, 1H), 8.49 (br. s, 1H), 8.42 (br. s, 1H), 8.18 (d, J = 7.8 Hz, 2H), 8.00 (d, J = 8.2 Hz, 2H), 7.86 (d, J = 8.2 Hz, 2H), 7.58 (d, J = 7.8 Hz, 2H)
N ^F L ^o 78	¹ H NMR (400 MHz, DMSO) δ 12.33 (br. s, 1H), 8.74 (br. s, 2H), 8.58 (t, J = 7.6 Hz, 1H), 8.42 (br. s, 1H), 8.00 (d, J = 8.2 Hz, 2H), 7.87 (d, J = 10.2 Hz, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.58 (d, J = 8.2 Hz, 2H)
N C ₀ -79	¹ H NMR (400 MHz, DMSO) δ 12.08 (br. s, 1H), 8.54 (br. s, 1H), 8.39 (br. s, 2H), 7.93 - 8.09 (m, 4H), 7.57 (d, J = 8.2 Hz, 2H), 7.35 (t, J = 8.6 Hz, 2H)
N ^o L ^o 80	¹ H NMR (400 MHz, DMSO) δ 12.04 (br. s, 1H), 11.36 (br. s, 1H), 8.40 (br. s, 1H), 8.25 (d, J = 8.2 Hz, 2H), 8.00 (d, J = 7.0 Hz, 2H), 7.82 (d, J = 7.4 Hz, 2H), 7.57 (d, J = 6.7 Hz, 2H), 2.44 (s, 3H)
N ^o L ^o 81	¹ H NMR (400 MHz, DMSO) δ 8.39 (br. s, 1H), 8.07 (d, J = 8.6 Hz, 2H), 7.99 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 8.6 Hz, 2H), 2.39 (s, 3H)
N ^o L ^o 82	¹ H NMR (400 MHz, DMSO) δ 12.40 (br. s, 1H), 8.84 (br. s, 1H), 8.63 (br. s, 2H), 8.42 (d, J = 7.8 Hz, 2H), 7.99 (d, J = 8.6 Hz, 2H), 7.58 (d, J = 8.2 Hz, 3H), 7.43 - 7.54 (m, 2H)
N ^o L ^o 83	¹ H NMR (400 MHz, DMSO) δ 12.30 (br. s, 1H), 8.64 (br. s, 2H), 8.41 (br. s, 2H), 8.17 (s, 1H), 7.99 (d, J = 8.6 Hz, 2H), 7.82 (d, J = 6.7 Hz, 1H), 7.45 - 7.64 (m, 4H)
N C ₀ -84	¹ H NMR (400 MHz, DMSO) δ 12.38 (br. s, 1H), 8.64 (br. s, 2H), 8.30 - 8.50 (m, 2H), 7.99 (d, J = 8.6 Hz, 2H), 7.62 (d, J = 10.4, 1.4 Hz, 1H), 7.57 (d, J = 8.6 Hz, 2H), 7.46 (d, J = 8.6 Hz, 1H)
N C ₀ -85	¹ H NMR (400 MHz, DMSO) δ 8.77 (br. s, 1H), 8.68 (br. s, 2H), 8.52 (d, J = 8.2 Hz, 1H), 8.46 (br. s, 1H), 7.92 - 8.06 (m, 3H), 7.84 (t, J = 7.6 Hz, 1H), 7.68 (t, J = 7.6 Hz, 1H), 7.58 (d, J = 8.2 Hz, 2H)
N ^o L ^o 86	¹ H NMR (400 MHz, DMSO) δ 12.39 (br. s, 1H), 8.68 (br. s, 2H), 8.57 (s, 1H), 8.43 (br. s, 2H), 8.21 (d, J = 7.4 Hz, 1H), 8.00 (d, J = 8.2 Hz, 2H), 7.94 (d, J = 7.0 Hz, 1H), 7.70 (t, J = 7.2 Hz, 1H), 7.58 (d, J = 7.8 Hz, 2H)
N ^o L ^o 87	¹ H NMR (400 MHz, DMSO) δ 8.71 (br. s, 2H), 8.48 (br. s, 1H), 8.43 (br. s, 1H), 8.16 (d, J = 8.2 Hz, 2H), 7.99 (t, J = 8.0 Hz, 4H), 7.58 (d, J = 8.6 Hz, 2H)
N C ₀ -88	¹ H NMR (400 MHz, DMSO) δ 12.33 (br. s, 1H), 8.68 (br. s, 1H), 8.61 (br. s, 2H), 8.42 (br. s, 1H), 8.35 (t, J = 7.4 Hz, 1H), 7.99 (d, J = 8.2 Hz, 2H), 7.49 - 7.64 (m, 3H), 7.27 - 7.41 (m, 2H)
N ^F L ^o 89	¹ H NMR (400 MHz, DMSO) δ 11.45 (br. s, 1H), 8.76 - 8.94 (m, 1H), 8.11 (d, J = 8.0 Hz, 4H), 7.53 (d, J = 8.0 Hz, 4H), 2.42 (br. s, 6H)
N C ₀ -90	¹ H NMR (400 MHz, DMSO) δ 10.60 (br. s, 1H), 8.68 (s, 1H), 8.09 (br. s, 1H), 7.95 (br. s, 4H), 7.32 - 7.71 (m, 10H)
N C ₀ -91	¹ H NMR (400 MHz, DMSO) δ 9.61 (br. s, 1H), 8.19 (d, J = 6.3 Hz, 2H), 7.90 (br. s, 2H), 7.56 - 7.73 (m, 2H), 7.26 - 7.40 (m, 2H)
N C ₀ -92	¹ H NMR (400 MHz, DMSO) δ 12.38 (br. s, 1H), 7.82 - 7.94 (m, 2H), 7.18 - 7.63 (m, 7H), 4.39 (br. s, 2H)
N C ₀ -93	¹ H NMR (300 MHz, DMSO) δ 8.64 (s, 4H), 8.35 - 8.24 (m, 4H), 8.06 - 7.93 (m, 6H), 7.64 - 7.54 (m, 4H)
N C ₀ -94	¹ H NMR (300 MHz, CDCl ₃) δ 7.16 (d, J = 4.7 Hz, 2H), 6.10 (br. s, 3H), 2.27 - 2.14 (m, 2H), 1.84 - 1.61 (m, 10H), 1.37 - 1.13 (m, 10H)
N ^o L ^o 95	¹ H NMR (300 MHz, DMSO) δ 8.39 (s, 2H), 8.36 - 8.11 (m, 4H), 7.78 (s, 2H), 7.12 (d, J = 1.4 Hz, 2H)
N C ₀ -96	¹ H NMR (300 MHz, MeOD) δ 8.08 (d, J = 8.2 Hz, 2H), 7.61 - 7.53 (m, 4H), 7.45 - 7.30 (m, 6H), 7.17 - 6.97 (m, 4H)
¹ H NMR (300 MHz, DMSO) δ 9.06 (br. s, 6H), 8.25 - 8.01 (m, 4H), 6.83 (s, 4H)	
¹³ C NMR (75 MHz, DMSO) δ 152.2, 149.7, 146.2, 136.5, 123.7, 107.4	

NCL 998	1H NMR (300 MHz, DMSO) δ 8.65 (s, 2H), 8.53 (s, 2H), 8.40 (s, 2H), 8.24 (d, J = 7.3 Hz, 2H), 8.09 – 7.98 (m, 2H), 7.62 (t, J = 7.7 Hz, 2H).
NCL 086	1H NMR (300 MHz, DMSO) δ 8.56 – 8.32 (m, 4H), 7.85 (d, J = 8.3 Hz, 4H), 7.49 (d, J = 8.3 Hz, 4H), 1.31 (s, 18H). 13C NMR (75 MHz, DMSO) δ 153.7, 152.7, 148.8, 130.7, 127.8, 125.6, 34.7, 31.0.
NCL 100	1H NMR (300 MHz, DMSO) δ 12.39 (br s, 2H), 8.55 (s, 2H), 8.46 (s, 2H), 8.01 – 7.88 (m, 4H), 7.55 – 7.41 (m, 6H).
NCL 101	1H NMR (300 MHz, DMSO) δ 12.06 (br s, 2H), 9.71 (br s, 2H), 9.21 (br s, 2H), 8.70 (s, 2H), 8.30 (s, 2H), 7.50 (d, J = 7.9 Hz, 2H), 6.90 (d, J = 7.7 Hz, 2H), 6.70 (t, J = 7.7 Hz, 2H).
NCL 102	1H NMR (300 MHz, DMSO) δ 12.86 (br s, 2H), 8.89 (s, 2H), 8.77 (s, 2H), 8.52 (d, J = 7.9 Hz, 2H), 8.11 (d, J = 8.1 Hz, 2H), 7.91 – 7.78 (m, 2H), 7.77 – 7.65 (m, 2H).
NCL 103	1H NMR (300 MHz, DMSO) δ 11.81 (br s, 2H), 10.32 – 9.85 (m, 4H), 8.52 (s, 2H), 8.12 (s, 2H), 7.85 (d, J = 8.4 Hz, 2H), 6.43 (s, 2H), 6.33 (d, J = 8.5 Hz, 2H).
NCL 104	1H NMR (300 MHz, DMSO) δ 11.72 (br s, 2H), 9.78 (br s, 2H), 9.45 (s, 2H), 8.48 (s, 2H), 8.34 (br s, 2H), 8.04 (s, 2H), 7.33 (s, 2H), 6.44 (s, 2H).
NCL 105	1H NMR (300 MHz, DMSO) δ 11.75 (br s, 2H), 9.71 (br s, 2H), 9.15 (br s, 2H), 8.86 – 8.40 (m, 4H), 8.13 (s, 2H), 7.33 (d, J = 8.6 Hz, 2H), 6.42 (d, J = 8.6 Hz, 2H).
NCL 106	1H NMR (300 MHz, DMSO) δ 9.12 (br s, 4H), 8.29 (s, 2H), 8.20 (s, 2H), 7.10 (s, 2H), 6.93 (s, 2H), 3.84 (s, 6H).
NCL 107	1H NMR (300 MHz, DMSO) δ 12.19 (s, 2H), 10.25 (s, 2H), 8.70 (s, 2H), 8.34 (s, 2H), 8.06 (d, J = 7.8 Hz, 2H), 7.35 – 7.23 (m, 2H), 7.00 (d, J = 8.2 Hz, 2H), 6.87 (t, J = 7.5 Hz, 2H).
NCL 108	1H NMR (300 MHz, DMSO) δ 8.00 (s, 2H), 7.26 – 7.08 (m, 6H), 6.98 – 6.43 (m, 4H).
NCL 109	1H NMR (300 MHz, DMSO) δ 8.60 (d, J = 1.2 Hz, 2H), 8.33 – 8.19 (m, 4H), 8.15 (d, J = 8.0 Hz, 2H), 7.74 – 7.61 (m, 2H), 7.12 (s, 2H).
NCL 110	1H NMR (300 MHz, DMSO) δ 8.85 (s, 2H), 8.58 (s, 2H), 8.31 (d, J = 8.7 Hz, 4H), 8.23 (d, J = 8.9 Hz, 4H).
NCL 111	1H NMR (300 MHz, DMSO) δ 11.80 (br s, 2H), 10.30 – 9.80 (m, 4H), 8.52 (s, 2H), 8.12 (s, 2H), 7.84 (d, J = 8.6 Hz, 2H), 6.42 (d, J = 1.8 Hz, 2H), 6.33 (d, J = 8.6 Hz, 2H).
NCL 112	1H NMR (300 MHz, DMSO) δ 12.48 (br s, 2H), 8.62 (s, 2H), 8.51 (s, 2H), 8.04 (d, J = 7.5 Hz, 4H), 7.85 – 7.69 (m, 8H), 7.54 – 7.36 (m, 6H).
NCL 113	1H NMR (400 MHz, DMSO) δ 11.92 (br s, 2H), 8.24 (s, 2H), 8.16 (s, 2H), 7.71 (d, J = 8.9 Hz, 4H), 6.74 (d, J = 8.9 Hz, 4H), 2.98 (s, 12H).
NCL 114	1H NMR (400 MHz, DMSO) δ 12.67 (br s, 2H), 8.81 (s, 2H), 8.40 (s, 2H), 8.06 (d, J = 1.8 Hz, 4H), 7.68 (t, J = 1.8 Hz, 2H).
NCL 115	1H NMR (400 MHz, DMSO) δ 12.09 (br s, 2H), 8.44 (s, 2H), 8.34 (s, 2H), 7.63 (d, J = 1.4 Hz, 2H), 7.33 (dd, J = 8.3, 1.6 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 3.86 (s, 6H), 3.81 (s, 6H).
NCL 116	1H NMR (400 MHz, DMSO) δ 12.27 (br s, 2H), 8.49 (s, 2H), 8.44 – 8.27 (m, 4H), 7.57 – 7.44 (m, 10H), 7.41 – 7.33 (m, 6H).
NCL 117	1H NMR (400 MHz, DMSO) δ 9.77 (br s, 2H), 8.36 (s, 2H), 8.29 (s, 2H), 7.58 (d, J = 1.5 Hz, 2H), 7.23 (dd, J = 8.1, 1.2 Hz, 2H), 6.87 (d, J = 8.1 Hz, 2H), 3.86 (s, 6H).
NCL 118	1H NMR (400 MHz, DMSO) δ 12.83 (br s, 2H), 8.76 (s, 2H), 8.69 (s, 2H), 8.31 – 8.21 (m, 2H), 7.45 – 7.31 (m, 4H).
NCL 118	1H NMR (400 MHz, DMSO) δ 12.13 (br s, 2H), 10.35 (s, 2H), 8.39 (s, 2H), 7.85 (d, J = 8.7 Hz, 4H), 7.72 (d, J = 8.6 Hz, 4H), 2.08 (s, 6H).
NCL 118	1H NMR (400 MHz, DMSO) δ 8.62 – 8.29 (m, 4H), 7.85 (d, J = 8.2 Hz, 4H), 7.33 (d, J = 8.2 Hz, 4H), 2.98 – 2.87 (m, 2H), 1.21 (d, J = 6.9 Hz, 12H).
NCL 121	1H NMR (400 MHz, DMSO) δ 8.60 – 8.30 (m, 4H), 7.84 (d, J = 8.1 Hz, 4H), 7.28 (d, J = 8.1 Hz, 4H), 2.59 (t, J = 7.5 Hz, 4H), 1.64 – 1.54 (m, 4H), 0.88 (t, J = 7.3 Hz, 6H).
NCL 122	1H NMR (400 MHz, DMSO) δ 8.56 (s, 2H), 8.42 (d, J = 2.0 Hz, 2H), 8.38 (s, 2H), 8.09 (dd, J = 8.7, 2.0 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H).

- N CL 12^g ¹H NMR (400 MHz, DMSO) δ 8.68 (s, 2H), 8.43 (s, 2H), 8.28 – 8.16 (m, 2H), 7.77 – 7.64 (m, 2H), 7.58 – 7.46 (m, 2H).
¹³C NMR (101 MHz, DMSO) δ 153.0, 150.8 (dd, J = 250.6, 13.0 Hz), 149.9 (dd, J = 245.9, 13.2 Hz), 146.6, 131.2 (dd, J = 6.4, 3.4 Hz), 126.0 (dd, J = 6.4, 2.8 Hz), 117.8 (d, J = 17.7 Hz), 115.7 (d, J = 18.5 Hz).
- N CL 124 ¹H NMR (400 MHz, DMSO) δ 10.84 (br s, 2H), 9.29 (s, 2H), 8.80 (d, J = 8.6 Hz, 2H), 8.43 (s, 2H), 7.94 (d, J = 9.0 Hz, 2H), 7.87 (d, J = 7.9 Hz, 2H), 7.64 – 7.56 (m, 2H), 7.43 – 7.38 (m, 2H), 7.34 (d, J = 8.9 Hz, 2H).
- N CL 125 ¹H NMR (400 MHz, DMSO) δ 9.21 (br s, 2H), 8.42 – 8.17 (m, 4H), 7.43 (d, J = 1.9 Hz, 2H), 7.25 (dd, J = 8.4, 1.9 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H), 3.83 (s, 6H).
- N CL 126 ¹H NMR (400 MHz, DMSO) δ 12.27 (br s, 2H), 8.58 (s, 2H), 8.42 (s, 2H), 7.96 (d, J = 8.3 Hz, 4H), 7.58 (d, J = 8.2 Hz, 4H), 4.39 (s, 2H).
- N CL 127 ¹H NMR (400 MHz, DMSO) δ 12.84 (br s, 2H), 8.84 (s, 2H), 8.74 (s, 2H), 8.46 (d, J = 8.6 Hz, 2H), 7.71 (d, J = 1.6 Hz, 2H), 7.54 (dd, J = 8.6, 1.2 Hz, 2H).
- N CL 12^h ¹H NMR (400 MHz, DMSO) δ 8.64 (s, 2H), 8.36 (s, 2H).
- N CL 12ⁱ ¹H NMR (400 MHz, DMSO) δ 8.84 (s, 2H), 8.69 (s, 2H), 8.41 (dd, J = 7.8, 1.7 Hz, 2H), 7.70 (dd, J = 8.0, 1.0 Hz, 2H), 7.48 (t, J = 7.3 Hz, 2H)*, 7.44 – 7.37 (m, 2H)*.
- N CL 13^g ¹H NMR (400 MHz, DMSO) δ 8.66 (s, 2H), 8.37 (s, 2H), 7.79 (d, J = 1.6 Hz, 2H), 7.68 – 7.62 (m, 2H), 3.92 (s, 6H), 3.78 (s, 6H).
- N CL 131 ¹H NMR (400 MHz, DMSO) δ 12.45 (br s, 2H), 8.68 (s, 2H), 8.41 (s, 2H), 8.29 (s, 2H), 7.87 (d, J = 7.8 Hz, 2H), 7.70 – 7.63 (m, 2H), 7.44 (t, J = 7.9 Hz, 2H).
- N CL 13^g ¹H NMR (400 MHz, DMSO) δ 12.69 (br s, 2H), 8.61 (s, 4H), 7.34 (dd, J = 9.0, 2.8 Hz, 2H), 7.22 (td, J = 8.6, 2.9 Hz, 2H), 7.03 (dd, J = 8.8, 4.6 Hz, 2H), 5.29 (s, 4H).
- N CL 133 ¹H NMR (400 MHz, DMSO) δ 12.51 (br s, 2H), 8.49 – 8.28 (m, 4H), 8.16 (s, 2H), 7.35 (s, 2H).
- N CL 13^h ¹H NMR (400 MHz, DMSO) δ 12.42 (br s, 2H), 8.60 (s, 2H), 8.42 (s, 2H), 7.91 (d, J = 8.5 Hz, 4H), 7.69 (d, J = 8.5 Hz, 4H).
- N CL 135 ¹H NMR (400 MHz, DMSO) δ 12.24 (br s, 2H), 8.66 (s, 2H), 8.49 (br s, 2H), 7.79 (s, 2H), 7.24 (s, 2H), 3.88 (s, 6H), 3.85 (s, 6H).
- N CL 136 ¹H NMR (400 MHz, DMSO) δ 12.21 (br s, 2H), 8.44 (s, 2H), 8.39 (s, 2H), 7.83 (d, J = 8.2 Hz, 4H), 7.30 (d, J = 8.2 Hz, 4H), 2.63 (t, J = 7.7 Hz, 4H), 1.61 – 1.52 (m, 4H), 1.36 – 1.26 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H).
- N CL 137 ¹H NMR (400 MHz, DMSO) δ 12.94 (br s, 2H), 8.68 (s, 2H), 8.33 (s, 2H), 7.60 (d, J = 7.9 Hz, 4H)*, 7.49 (dd, J = 8.7, 7.4 Hz, 2H)*.
- N CL 138 ¹H NMR (400 MHz, DMSO) δ 12.12 (br s, 2H), 8.21 (s, 2H), 7.97 (s, 2H), 7.54 – 7.47 (m, 6H), 7.42 – 7.36 (m, 6H), 7.31 – 7.21 (m, 8H), 6.84 (d, J = 9.8 Hz, 2H).
- N CL 139 ¹H NMR (400 MHz, DMSO) δ 12.65 (br s, 2H), 9.63 (d, J = 1.8 Hz, 2H), 8.88 – 8.58 (m, 6H), 8.13 – 8.01 (m, 4H), 7.88 – 7.79 (m, 2H), 7.68 (t, J = 7.4 Hz, 2H).
- N CL 140 ¹H NMR (400 MHz, DMSO) δ 12.17 (br s, 2H), 8.46 (s, 2H), 8.37 (s, 2H), 7.86 (d, J = 8.2 Hz, 4H), 7.34 (d, J = 8.2 Hz, 4H), 2.53 (s, 6H).
- N CL 141 ¹H NMR (400 MHz, DMSO) δ 8.66 (s, 2H), 8.60 (d, J = 1.9 Hz, 2H), 8.52 (br s, 2H), 8.49 (s, 2H), 8.09 (d, J = 8.6 Hz, 2H), 7.50 (dd, J = 8.6, 2.0 Hz, 2H).
- N CL 142 ¹H NMR (400 MHz, DMSO) δ 8.80 (s, 2H), 7.41 – 7.20 (m, 12H), 5.56 (s, 2H), 3.79 (d, J = 3.4 Hz, 4H).
- N CL 143 ¹H NMR (400 MHz, DMSO) δ 11.91 (br s, 2H), 8.66 (br s, 2H), 8.10 – 8.00 (m, 4H), 7.51 – 7.41 (m, 6H), 2.45 (s, 6H).
- N CL 144 ¹H NMR (400 MHz, DMSO) δ 12.36 (br s, 2H), 8.38 – 8.23 (m, 4H), 7.16 (d, J = 3.5 Hz, 2H), 6.82 (d, J = 3.5 Hz, 2H).
- N CL 145 ¹H NMR (400 MHz, DMSO) δ 12.41 (br s, 2H), 8.41 – 8.21 (m, 4H), 7.20 (d, J = 3.5 Hz, 2H), 6.73 (d, J = 3.5 Hz, 2H).
- ⁿ CL 14^e ¹H NMR (400 MHz, DMSO) δ 11.97 (br s, 2H), 11.45 (s, 2H), 8.47 (s, 2H), 8.30 (s, 2H), 8.02 (s, 2H), 7.80 (dd, J = 8.6, 0.9 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 7.45 – 7.40 (m, 2H), 6.53 (s, 2H).
¹³C NMR (101 MHz, DMSO) δ 152.4, 150.6, 137.4, 127.6, 126.7, 124.5, 121.8, 120.3, 111.9, 102.0.

NCL 147	¹ H NMR (400 MHz, DMSO) δ 13.09 (br s, 2H), 9.97 (s, 2H), 9.01 (s, 2H), 8.73 (s, 2H), 8.19 - 8.09 (m, 4H), 7.95 - 7.84 (m, 4H).
NCL 148	¹ H NMR (400 MHz, DMSO) δ 12.44 (s, 4H), 8.60 (s, 2H), 8.44 (s, 2H), 7.99 (d, J = 8.3 Hz, 4H), 7.81 (d, J = 8.3 Hz, 4H), 7.63 (d, J = 16.0 Hz, 2H), 6.66 (d, J = 16.0 Hz, 2H).
NCL 149	¹ H NMR (400 MHz, DMSO) δ 8.75 (d, J = 6.1 Hz, 4H), 8.68 (s, 2H), 8.47 (s, 2H), 8.07 (d, J = 6.1 Hz, 4H).
NCL 150	¹ H NMR (400 MHz, DMSO) δ 12.10 (br s, 2H), 8.23 - 8.07 (m, 4H), 7.55 (d, J = 8.7 Hz, 4H), 7.13 (d, J = 16.0 Hz, 2H), 6.99 (d, J = 8.7 Hz, 4H), 6.81 (dd, J = 16.0, 9.4 Hz, 2H), 3.79 (s, 6H).
NCL 151	¹ H NMR (400 MHz, DMSO) δ 11.92 (br s, 2H), 10.13 (br s, 2H), 8.28 (s, 4H), 7.75 (d, J = 8.5 Hz, 4H), 6.86 (d, J = 8.5 Hz, 4H).
NCL 152	¹ H NMR (400 MHz, DMSO) δ 12.08 (br s, 2H), 9.35 (s, 2H), 8.66 (s, 2H), 8.48 (s, 2H), 7.67 (d, J = 7.2 Hz, 2H), 7.25 (d, J = 7.2 Hz, 2H), 6.88 (t, J = 7.6 Hz, 2H), 2.23 (s, 6H).
NCL 153	¹ H NMR (400 MHz, DMSO) δ 11.68 (s, 2H), 8.78 (s, 2H), 8.09 (d, J = 8.4 Hz, 4H), 7.52 (d, J = 8.6 Hz, 4H), 2.92 (q, J = 7.5 Hz, 4H), 1.12 (i, J = 7.4 Hz, 6H).
NCL 154	¹ H NMR (400 MHz, DMSO) δ 12.09 (s, 2H), 8.69 (s, 2H), 8.07 (d, J = 8.6 Hz, 4H), 7.50 (d, J = 8.6 Hz, 4H), 3.01 - 2.88 (m, 4H), 1.49 - 1.39 (m, 8H), 0.88 (t, J = 6.6 Hz, 6H).
NCL 155	¹ H NMR (400 MHz, DMSO) δ 11.63 (s, 2H), 8.76 (s, 2H), 8.01 (d, J = 8.6 Hz, 4H), 7.65 (d, J = 8.6 Hz, 4H), 2.41 (s, 6H).
NCL 156	¹ H NMR (400 MHz, DMSO) δ 12.18 (s, 2H), 8.71 (s, 2H), 8.08 (d, J = 8.0 Hz, 4H), 7.50 (d, J = 8.3 Hz, 4H), 3.01 - 2.87 (m, 4H), 1.58 - 1.46 (m, 4H), 1.01 (t, J = 7.1 Hz, 6H).
NCL 157	¹ H NMR (400 MHz, DMSO) δ 11.71 (br s, 2H), 8.40 (s, 2H), 8.37 (s, 2H), 7.29 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 2.0 Hz, 2H), 6.73 (br s, 4H), 6.59 (dd, J = 8.3, 2.0 Hz, 2H). ¹³ C NMR (101 MHz, DMSO) δ 152.1, 151.5, 148.9, 136.0, 134.7, 115.1, 114.5, 112.8.
NCL 158	¹ H NMR (400 MHz, DMSO) δ 13.03 (br s, 1H), 10.49 (br s, 1H), 9.35 (br s, 1H), 7.24 (d, J = 7.6 Hz, 2H), 7.11 - 6.61 (m, 6H), 2.5 (Contains CH ₂ groups determined by COSY, however eclipsed by solvent signal), 0.93 (s, 6H). ¹³ C NMR (101 MHz, DMSO) δ 157.8, 155.4, 152.9, 134.4, 130.1, 118.7, 115.6, 29.9, 10.8. 'COSY' was used to determine that the signal due to the methylene protons appears under the DMSO signal. Line broadening is apparent in the ¹³ C-NMR (due to tautomerisation effects) making carbon allocation difficult.
NCL 159	¹ H NMR (400 MHz, DMSO) δ 12.69 (br s, 1H), 10.44 (br s, 1H), 9.15 (br s, 1H), 7.21 (s, 2H), 7.09 - 6.60 (m, 6H), 2.98 (p, J = 7.7 Hz, 2H), 1.84 - 1.01 (m, 16H).
NCL 160	¹ H NMR (400 MHz, DMSO) δ 12.49 (br s, 2H), 8.65 (s, 2H), 8.49 (s, 2H), 8.10 (d, J = 8.7 Hz, 4H)*, 7.47 (d, J = 8.3 Hz, 4H)*.
NCL 161	¹ H NMR (400 MHz, DMSO) δ 7.73 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 3.22 - 3.13 (m, 4H), 2.99 - 2.86 (m, 4H), 2.24 (s, 3H).
NCL162	¹ H NMR (400 MHz, CDCl ₃) δ 7.76 - 7.70 (m, 2H), 7.35 - 7.30 (m, 2H), 4.99 (s, 2H), 4.34 (q, J = 7.1 Hz, 2H), 2.39 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H).
NCL 163	¹ H NMR (400 MHz, DMSO) δ 13.88 (s, 1H), 13.21 (s, 1H), 11.50 (s, 2H), 9.70 (s, 2H), 7.70 (s, 2H), 7.43 (t, J = 7.7 Hz, 2H), 7.14 (t, J = 7.5 Hz, 2H), 7.00 (d, J = 7.8 Hz, 2H).
NCL164	¹ H NMR (400 MHz, DMSO) δ 10.85 (s, 2H), 9.38 (s, 2H), 8.64 (s, 3H), 7.90 (s, 3H), 7.34 (d, J = 8.5 Hz, 2H), 7.19 (s, 3H), 6.83 (d, J = 2.1 Hz, 2H), 6.57 (dd, J = 8.5, 2.1 Hz, 2H).
NCL155	¹ H NMR (400 MHz, DMSO) δ 10.87 (br s, 1H), 8.77 (br s, 3H), 7.61-7.44 (m, 8H), 7.40 (br s, 3H), 7.27 (br s, 3H), 4.07 (br s, 2H).
NCL166	¹ H NMR (400 MHz, DMSO) δ 12.70 (br s, 2H), 8.75 (br s, 2H), 8.55 (br s, 2H), 8.13 (d, J = 8.2 Hz, 4H), 7.81 (d, J = 8.1 Hz, 4H).
NCL167	¹ H NMR (400 MHz, DMSO) δ 14.09 (s, 1H), 8.12 (d, J = 6.9 Hz, 2H), 7.97 (dd, J = 6.4, 3.0 Hz, 2H), 7.56 (ddd, J = 8.2, 6.7, 2.9 Hz, 7H).

¹ H NMR (400 MHz, DMSO) δ 11.86 (br s, 2H), 8.42 (br s, 4H), 7.35 (d, J = 6.8 Hz, 4H), 6.75 (s, 2H), 6.67 (d, J = 7.9 Hz, 2H), 3.44 (d, J = 6.9 Hz, 2H)*, 1.24 (t, J = 5.3 Hz, 6H). *Signal partly eclipsed by H ₂ O in DMSO	NCL168
¹ H NMR (400 MHz, DMSO) δ 12.29 (s, 2H), 10.29 (s, 2H), 8.55 (s, 2H), 8.45 (s, 2H), 8.13 (d, J = 8.5 Hz, 2H), 7.71 (s, 2H), 7.35 (dd, J = 8.5, 1.8 Hz, 2H), 2.12 (s, 6H).	N _C -170
¹ H NMR (400 MHz, DMSO) δ 11.63 (s, 2H), 9.84 (s, 2H), 8.46 (s, 2H), 8.02 (s, 2H), 7.74 (d, J = 8.3 Hz, 2H), 6.30 (d, J = 7.4 Hz*, 2H), 6.17 (s, 2H), 2.94 (s, 12H). *Poorly resolved doublet gives reduced coupling constant.	N _C -171
¹ H NMR (400 MHz, DMSO) δ 12.00 (s, 2H), 8.92 (s, 2H), 8.64 (dd, J = 4.7, 0.6 Hz, 2H), 8.57 (d, J = 8.1 Hz, 2H), 7.89 (td, J = 8.0, 1.6 Hz, 2H), 7.50 – 7.41 (m, 2H), 2.52 (s, 6H).	N _C -172
¹ H NMR (400 MHz, DMSO) δ 11.49 (br s, 2H), 10.62 (br s, 2H), 8.55 (br s, 2H), 7.59 (d, J = 8.3 Hz, 2H), 6.98 (d, J = 1.9 Hz, 2H), 6.92 (dd, J = 8.4, 2.0 Hz, 2H), 2.37 (s, 6H).	N _C -176
¹ H NMR (400 MHz, DMSO) δ 12.02 (s, 2H), 10.81 (s, 2H), 8.63 (s, 2H), 8.38 (s, 2H), 8.12 (d, J = 8.3 Hz, 2H), 7.13 – 6.84 (m, 4H).	N _C -174
¹ H NMR (400 MHz, DMSO) δ 12.63 (br s, 2H), 8.90 (d, J = 2.1 Hz, 2H), 8.74 (s, 2H), 8.56 – 8.42 (m, 4H), 7.66 (d, J = 8.4 Hz, 2H).	N _C -175
¹ H NMR (400 MHz, DMSO) δ 11.94 (br s, 2H), 8.44 (s, 2H), 8.36 (s, 2H), 8.07 (dd, J = 4.8, 1.7 Hz, 2H), 7.72 (dd, J = 7.6, 1.4 Hz, 2H), 7.19 (s, 4H), 6.67 (dd, J = 7.5, 4.9 Hz, 2H).	N _C -178
¹ H NMR (400 MHz, DMSO) δ 8.67 (s, 2H), 7.97 (s, 4H), 7.50 (d, J = 8.6 Hz, 4H), 4.81 (s, 4H).	N _C -177
¹ H NMR (400 MHz, DMSO) δ 10.17 (s, 2H), 8.24 (s, 1H), 7.83 (d, J = 8.6 Hz, 4H), 7.50 (d, J = 8.6 Hz, 4H), 6.97 (s, 1H), 2.32 (s, 6H).	N _C -178
¹ H NMR (400 MHz, DMSO) δ 10.70 (s, 2H), 8.02 (s, 2H), 7.67 (d, J = 8.4 Hz, 4H), 7.52 (d, J = 8.4 Hz, 4H), 6.28 (s, 1H), 5.85 (s, 2H).	N _C -179
¹³ C NMR (101 MHz, DMSO) δ 162.8, 162.6, 138.8, 134.1, 133.1, 128.9, 127.6, 73.5.	N _C -179
¹ H NMR (400 MHz, DMSO) δ 10.62 (s, 2H), 8.22 (d, J = 0.9 Hz, 1H), 7.82 – 7.74 (m, 4H), 7.53 – 7.47 (m, 4H), 6.93 (d, J = 0.6 Hz, 1H), 5.85 (t, J = 5.3 Hz, 2H), 4.74 (d, J = 5.2 Hz, 4H).	N _C -180
¹ H NMR (400 MHz, DMSO) δ 11.20 (s, 2H), 8.17 (s, 1H), 8.09 (s, 2H), 7.72 (d, J = 7.4 Hz, 4H), 7.54 (d, J = 7.6 Hz, 4H), 6.83 (s, 1H).	N _C -181
¹ H NMR (400 MHz, CDCl ₃) δ 7.44 – 7.19 (m, 6H), 5.67 (s, 1H), 5.42 (s, 1H), 5.06 (s, 2H), 4.95 – 4.63 (m, 1H), 1.52 (d, J = 6.8 Hz, 3H).	N _C -192
¹ H NMR (400 MHz, CDCl ₃) δ 8.28 (s, 1H), 7.43 – 7.13 (m, 10H), 6.19 (s, 1H), 5.94 (s, 1H), 4.95 – 4.48 (m, 2H), 1.56 (d, J = 6.8 Hz, 4H), 1.50 (d, J = 6.5 Hz, 2H).	N _C -186
¹ H NMR (400 MHz, MeOD) δ 7.44 – 7.04 (m, 10H), 5.26 – 4.53 (m, 7H), 1.51 – 1.35 (m, 6H).	N _C -184
¹ H NMR (400 MHz, DMSO) δ 11.54 (s, 1H), 7.99 (d, J = 8.7 Hz, 2H), 7.90 (s, 3H), 7.47 (d, J = 8.6 Hz, 2H), 2.91 – 2.82 (m, 2H), 1.48 – 1.32 (m, 4H), 0.89 – 0.84 (m, 3H).	N _C -188
¹³ C NMR (101 MHz, DMSO) δ 156.2, 153.8, 134.8, 134.4, 128.7, 128.4, 28.1, 26.6, 22.0, 13.8.	N _C -188
¹ H NMR (400 MHz, DMSO) δ 11.42 (s, 1H), 8.06 (d, J = 8.7 Hz, 3H), 8.01 – 7.71 (m, 5H), 7.53 (d, J = 8.7 Hz, 3H), 4.90 (s, 2H), 3.69 (br s, 3H).	N _C -190
¹ H NMR (400 MHz, DMSO) δ 11.51 (s, 1H), 8.85 (s, 3H), 7.99 (d, J = 8.6 Hz, 7H), 7.46 (d, J = 8.6 Hz, 4H), 2.35 (s, 3H).	N _C -191
¹ H NMR (400 MHz, DMSO) δ 11.65 (s, 1H), 8.21 (s, 4H), 7.82 (dd, J = 7.6, 1.9 Hz, 2H), 7.53 – 7.39 (m, 3H).	N _C -198
¹ H NMR (400 MHz, DMSO) δ 10.71 (s, 2H), 8.00 (s, 2H), 7.66 (d, J = 8.5 Hz, 4H), 7.60 (d, J = 8.6 Hz, 4H), 6.27 (s, 1H), 5.86 (s, 2H).	N _C -198
¹³ C NMR (101 MHz, DMSO) δ 162.7, 162.6, 138.8, 134.5, 131.8, 127.9, 121.7, 73.5.	N _C -198
¹ H NMR (400 MHz, DMSO) δ 12.01 (br s, 1H), 10.84 (s, 2H), 9.98 (br s, 1H), 9.79 (br s, 1H), 7.96 (br s, 3H), 7.79 (br s, 2H), 7.67 – 7.37 (m, 6H), 5.37 (br s, 1H).	N _C -194

NCL195	<p>¹H NMR (400 MHz, DMSO) δ 10.51 (s, 2H), 8.00 (s, 2H), 7.54 (d, J = 8.0 Hz, 4H), 7.26 (d, J = 7.9 Hz, 4H), 6.26 (s, 1H), 5.77 (s, 2H), 2.34 (s, 6H).</p> <p>¹³C NMR (101 MHz, DMSO) δ 162.8, 162.6, 140.1, 138.4, 132.5, 129.4, 126.0, 73.3, 21.0.</p>
NCL196	<p>¹H NMR (400 MHz, CDCl₃) δ 10.31 (s, 2H), 9.74 (s, 2H), 7.94 (s, 2H), 7.48 (d, J = 8.6 Hz, 4H), 6.83 (d, J = 8.6 Hz, 4H), 6.20 (s, 1H), 5.70 (s, 2H).</p> <p>¹³C NMR (101 MHz, CDCl₃) δ 162.7, 162.5, 158.3, 140.5, 127.7, 126.3, 115.7, 73.0.</p>
NCL197	<p>¹H NMR (400 MHz, DMSO) δ 10.51 (s, 2H), 9.55 (s, 2H), 7.95 (s, 2H), 7.22 (t, J = 7.9 Hz, 2H), 7.11 - 7.04 (m, 4H), 6.76 (d, J = 8.4 Hz, 2H), 6.23 (s, 1H), 5.80 (s, 2H).</p> <p>¹³C NMR (101 MHz, DMSO) δ 162.8, 162.6, 157.7, 140.4, 136.4, 129.9, 117.4, 116.1, 112.4, 73.3.</p>
NCL199	<p>¹H NMR (400 MHz, DMSO) δ 10.60 (s, 2H), 8.04 (s, 2H), 7.66 (d, J = 7.5 Hz, 4H), 7.45 (t, J = 7.1 Hz, 4H), 7.40 - 7.34 (m, 2H), 6.30 (s, 1H), 5.82 (s, 2H).</p> <p>¹³C NMR (101 MHz, DMSO) δ 163.3, 163.1, 140.5, 135.7, 129.3, 129.2, 126.5, 73.9.</p>
NCL200	<p>¹H NMR (400 MHz, DMSO) δ 10.51 (s, 2H), 8.02 (s, 2H), 7.58 (d, J = 8.3 Hz, 4H), 7.47 (d, J = 8.3 Hz, 4H), 6.25 (s, 1H), 5.77 (s, 2H), 1.31 (s, 18H).</p>
NCL201	<p>¹H NMR (400 MHz, DMSO) δ 10.19 (s, 2H), 7.91 (s, 2H), 7.47 (d, J = 8.8 Hz, 4H), 6.77 (d, J = 8.9 Hz, 4H), 6.16 (s, 1H), 5.63 (s, 2H).</p>
NCL202	<p>¹H NMR (600 MHz, DMSO) δ 13.43 (s, 1H), 11.45 (s, 2H), 10.28 (br. s, 1H), 9.47 (s, 1H), 8.38 (s, 2H), 7.71 (dd, J = 7.7, 1.3 Hz, 1H), 7.67 (br d, J = 7.0 Hz, 2H), 7.53 - 7.48 (m, 1H), 7.23 - 7.23 (m, 2H), 7.03 - 6.98 (m, 2H), 6.96 - 6.90 (m, 4H), 6.56 (br s, 1H).</p> <p>*Due to tautomers and rotamers associated with proximity of the phenol to the hydrazone >17 protons are observed.</p> <p>¹³C NMR (151 MHz, DMSO) δ 167.7, 163.2, 162.6, 156.7*, 141.4*, 135.3, 133.9, 131.0, 130.5, 120.7*, 119.95, 119.8, 118.9, 117.6, 116.7, 116.6*.</p> <p>*Line broadening due to tautomers and rotamers made signals difficult to assign.</p>
NCL203	<p>¹H NMR (400 MHz, DMSO) δ 12.60 - 10.94 (m, 3H), 7.79 - 7.39 (m, 3H), 2.25 (s, 2H), 1.82 - 1.59 (m, 10H), 1.35 - 1.15 (m, 10H).</p>
NCL204	<p>¹H NMR (400 MHz, DMSO) δ 9.58 (d, J = 7.6 Hz, 2H), 7.82 (s, 4H), 7.50 (s, 4H), 6.45 (d, J = 9.6 Hz, 1H), 5.75 (s, 2H), 2.28 (d, J = 9.3 Hz, 6H).</p> <p>¹³C NMR (101 MHz, DMSO) δ 163.48, 162.11, 143.34, 137.68, 132.88, 128.34, 127.16, 75.15, 13.01.</p>
NCL205	<p>¹H NMR (600 MHz, DMSO) δ 10.92 (s, 2H), 8.42 (s, 2H), 7.98 (d, J = 7.5 Hz, 2H), 7.50 (d, J = 7.8 Hz, 2H), 7.44 (t, J = 7.4 Hz, 2H), 7.38 (t, J = 7.3 Hz, 2H), 6.35 (s, 1H), 5.95 (s, 2H).</p> <p>¹³C NMR (151 MHz, DMSO) δ 162.75, 162.68, 136.0, 132.4, 132.0, 130.1, 129.9, 127.6, 126.2, 73.7.</p>
NCL206	<p>¹H NMR (400 MHz, DMSO) δ 10.75 (s, 2H), 8.09 (s, 2H), 7.52 (d, J = 8.1 Hz, 4H), 7.24 (d, J = 8.0 Hz, 4H), 6.71 (s, 1H), 2.33 (s, 6H).</p>
NCL207	<p>¹H NMR (400 MHz, DMSO) δ 11.43 (s, 2H), 11.05 (s, 2H), 8.31 (s, 2H), 7.42 (s, 2H), 7.29 - 7.18 (m, 2H), 6.89 (t, J = 7.7 Hz, 4H), 6.74 (s, 2H).</p>
NCL208	<p>¹H NMR (400 MHz, DMSO) δ 9.63 (s, 2H), 7.82 (d, J = 8.5 Hz, 4H), 7.46 (d, J = 8.5 Hz, 4H), 6.73 (s, 2H), 2.29 (s, 6H).</p>
NCL209	<p>¹H NMR (400 MHz, DMSO) δ 10.75 (s, 2H), 9.55 (s, 2H), 8.04 (s, 2H), 7.21 (t, J = 7.8 Hz, 2H), 7.06 (s, 2H), 7.02 (d, J = 7.6 Hz, 2H), 6.84 - 6.57 (m, 4H).</p>
NCL210	<p>¹H NMR (400 MHz, DMSO) δ 11.16 (s, 2H), 8.22 (s, 2H), 7.85 (d, J = 8.3 Hz, 4H), 7.80 (d, J = 8.5 Hz, 4H), 6.92 (s, 2H).</p>
NCL211	<p>¹H NMR (400 MHz, DMSO) δ 10.56 (s, 2H), 9.78 (s, 2H), 8.02 (s, 2H), 7.45 (d, J = 8.6 Hz, 4H), 6.80 (d, J = 8.6 Hz, 4H), 6.62 (s, 2H).</p>
NCL212	<p>¹H NMR (400 MHz, DMSO) δ 10.94 (s, 2H), 8.10 (s, 2H), 7.67 - 7.60 (m, 4H), 7.61 - 7.54 (m, 4H), 6.80 (s, 2H).</p>
NCL213	<p>¹H NMR (400 MHz, DMSO) δ 10.23 (br s, 2H), 7.27 (s, 2H), 2.27 - 1.98 (m, 2H), 1.78 - 1.42 (m, 10H), 1.33 - 1.00 (m, 10H).</p>

NCL21*	¹ H NMR (400 MHz, DMSO) δ 10.84 (s, 2H), 8.14 (s, 2H), 7.63 (d, J = 7.4 Hz, 4H), 7.46 – 7.33 (m, 3H), 6.76 (s, 2H).
NCL21#	¹ H NMR (600 MHz, DMSO) δ 12.06 (s, 2H), 8.72 (s, 2H), 7.97 (t, J = 8.4 Hz, 2H), 7.56 (dd, J = 11.1, 1.9 Hz, 2H), 7.38 (dd, J = 8.5, 1.9 Hz, 2H), 2.42 (d, J = 2.9 Hz, 6H).
NCL216	¹ H NMR (400 MHz, DMSO) δ 12.43 (br s, 2H), 8.66 (br s, 2H), 8.38 (t, J = 8.3 Hz, 2H), 7.61 (dd, J = 10.5, 1.9 Hz, 2H), 7.45 (dd, J = 8.6, 1.6 Hz, 2H). ¹³ C NMR (101 MHz, DMSO) δ 160.7 (d, J = 254.5 Hz), 152.8*, 140.8*, 136.3 (d, J = 10.8 Hz), 128.5, 125.3, 120.2 (d, J = 10.0 Hz), 116.7 (d, J = 24.7 Hz).
	*Broad signals
NCL217	¹ H NMR (400 MHz, DMSO) δ 11.66 (s, 2H), 8.61 (s, 2H), 7.94 (d, J = 8.2 Hz, 4H), 7.25 (d, J = 8.1 Hz, 4H), 2.41 (s, 6H), 2.35 (s, 6H).
NCL218	¹³ C NMR (101 MHz, DMSO) δ 154.0, 153.3, 139.7, 133.9, 129.0, 127.0, 21.0, 14.9.
NCL219	¹ H NMR (400 MHz, DMSO) δ 10.73 (s, 2H), 8.05 (s, 2H), 7.70 (d, J = 8.58 Hz, 4H), 7.31 – 7.27 (m, 4H), 6.24 (s, 1H), 5.92 (s, 2H), 4.17 (dq, J = 7.06, 8.70 Hz, 8H), 1.28 (td, J = 1.01, 7.05 Hz, 12H).
NCL220	¹ H NMR (400 MHz, DMSO) δ 11.74 (s, 2H), 8.60 (s, 2H), 7.95 (d, J = 8.6 Hz, 4H), 7.45 (d, J = 8.6 Hz, 4H), 2.42 (s, 6H), 1.31 (s, 18H).
NCL221	¹³ C NMR (101 MHz, DMSO) δ 154.1, 153.3, 152.6, 134.0, 126.8, 125.0, 34.5, 31.0, 14.9.
NCL222	¹ H NMR (400 MHz, DMSO) δ 10.61 (s, 2H), 8.03 (s, 2H), 7.70 (dd, J = 8.7, 5.6 Hz, 4H), 7.29 (t*, J = 8.9 Hz, 4H), 6.27 (s, 1H), 5.82 (s, 2H).
NCL223	¹ H NMR (600 MHz, DMSO) δ 10.89 (s, 2H), 8.11 (s, 2H), 7.86 (d, J = 8.2 Hz, 4H), 7.81 (d, J = 8.4 Hz, 4H), 6.34 (s, 1H), 5.94 (s, 2H).
NCL224	¹ H NMR (400 MHz, DMSO) δ 10.76 (s, 2H), 7.99 (s, 2H), 7.70 (td, J = 1.7, 9.2 Hz, 2H), 7.54 – 7.41 (m, 4H), 6.30 (s, 1H), 5.87 (s, 2H).
NCL225	¹ H NMR (400 MHz, DMSO) δ 10.48 (s, 2H), 10.07 (s, 2H), 7.98 (s, 2H), 7.65 (d, J = 8.7 Hz, 4H), 7.58 (d, J = 8.7 Hz, 4H), 6.24 (s, 1H), 5.76 (s, 2H), 2.07 (s, 6H).
NCL226	¹ H NMR (400 MHz, DMSO) δ 8.36 (s, 1H), 7.96 – 7.90 (m, 2H), 7.86 (s, 1H), 7.79 – 7.73 (m, 2H), 7.54 – 7.47 (m, 6H), 4.26 (q, J = 7.1 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H).
NCL227	¹ H NMR (400 MHz, DMSO) δ 8.35 (s, 1H), 7.98 – 7.91 (m, 2H), 7.87 (s, 1H), 7.79 – 7.74 (m, 2H), 7.51 (dd, J = 2.8, 8.5 Hz, 6H), 3.99 (d, J = 6.5 Hz, 2H), 1.95 (hept, J = 6.7 Hz, 1H), 0.93 (d, J = 6.7 Hz, 6H).
NCL228	¹ H NMR (400 MHz, DMSO) δ 10.95 (s, 1H), 9.18 (t, J = 5.6 Hz, 1H), 8.38 (d, J = 10.1 Hz, 2H), 8.32 (s, 1H), 7.99 – 7.92 (m, 2H), 7.83 (d, J = 8.5 Hz, 2H), 7.57 – 7.46 (m, 5H), 3.30 – 3.20 (m, 2H), 1.14 (t, J = 7.2 Hz, 3H).
NCL229	¹ H NMR (400 MHz, DMSO) δ 11.00 (s, 1H), 9.68 (s, 1H), 8.52 (s, 1H), 8.41 (s, 1H), 8.32 (s, 1H), 8.01 – 7.80 (m, 4H), 7.56 – 7.46 (m, 4H), 7.36 (d, J = 6.00 Hz, 4H), 7.30 – 7.21 (m, 1H), 4.56 – 4.33 (m, 2H).
NCL230	¹ H NMR (400 MHz, DMSO) δ 10.95 (s, 1H), 9.22 (t, J = 5.6 Hz, 1H), 8.40 (s, 1H), 8.34 (s, 1H), 7.98 – 7.90 (m, 2H), 7.87 – 7.80 (m, 2H), 7.55 – 7.48 (m, 4H), 3.22 (q, J = 6.6 Hz, 2H), 1.56 – 1.46 (m, 2H), 1.39 – 1.25 (m, 6H), 0.88 (t, J = 6.6 Hz, 3H).
NCL231	¹ H NMR (400 MHz, DMSO) δ 10.98 (s, 1H), 9.60 (s, 1H), 8.54 (s, 1H), 8.40 (s, 1H), 8.30 (s, 1H), 8.01 – 7.89 (m, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.64 – 7.59 (m, 1H), 7.54 – 7.47 (m, 4H), 6.42 (dd, J = 1.8, 3.3 Hz, 1H), 6.31 (m, 1H), 4.44 (d, J = 5.5 Hz, 2H).

NCL230	¹ H NMR (400 MHz, DMSO) δ 10.41 (s, 2H), 7.98 (s, 2H), 7.59 (d, J = 8.9 Hz, 4H), 7.02 (d, J = 8.9 Hz, 4H), 6.23 (s, 1H), 5.73 (s, 2H), 3.80 (s, 6H).
NCL231	¹ H NMR (400 MHz, DMSO) δ 7.71 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 3.3 Hz, 2H), 6.07 (s, 2H), 5.78 (s, 2H), 2.22 (s, 3H), 1.28 (s, 9H). ¹³ C NMR (101 MHz, DMSO) δ 159.03, 149.99, 147.94, 137.04, 125.31, 124.70, 34.22, 31.09, 13.59.
NCL232	¹ H NMR (400 MHz, DMSO) δ 7.96 (s, 1H), 7.57 (d, J = 7.2 Hz, 2H), 7.34 (d, J = 7.3 Hz, 2H), 5.91 (s, 2H), 5.53 (s, 2H), 1.28 (s, 9H). ¹³ C NMR (101 MHz, DMSO) δ 180.25, 150.33, 143.29, 134.17, 126.01, 125.10, 34.35, 31.08.
NCL233	¹ H NMR (400 MHz, DMSO) δ 11.52 (s, 1H), 7.99 (d, J = 8.7 Hz, 2H), 7.89 (s, 4H), 7.46 (d, J = 8.7 Hz, 2H), 2.90 - 2.78 (m, 2H), 1.53 - 1.37 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H). ¹³ C NMR (101 MHz, DMSO) δ 156.12, 153.60, 134.76, 134.39, 128.69, 128.38, 28.39, 19.40, 13.60.
NCL234	¹ H NMR (400 MHz, DMSO) δ 11.42 (s, 1H), 8.00 (d, J = 8.7 Hz, 2H), 7.86 (s, 4H), 7.48 (d, J = 8.7 Hz, 2H), 2.85 (q, J = 7.6 Hz, 2H), 1.06 (t, J = 7.6 Hz, 3H). ¹³ C NMR (101 MHz, DMSO) δ 156.03, 154.70, 134.44, 134.38, 128.64, 128.42, 20.07, 10.69.
NCL235	¹ H NMR (400 MHz, DMSO) δ 8.25 (s, 1H), 8.22 (t, J = 8.5 Hz, 1H), 7.50 (d, J = 10.5 Hz, 1H), 7.42 (s, 4H), 7.34 (d, J = 8.4 Hz, 1H). OR ¹ H NMR (400 MHz, DMSO) δ 8.31 - 8.15 (m, 2H), 7.73 - 7.14 (m, 6H). ¹³ C NMR (101 MHz, DMSO) δ 160.16 (d, J = 253.3 Hz), 157.07, 136.99 (d, J = 4.2 Hz), 134.83 (d, J = 10.7 Hz), 128.07 (d, J = 3.6 Hz), 125.08 (d, J = 3.2 Hz), 121.22 (d, J = 10.0 Hz), 116.45 (d, J = 24.8 Hz).
NCL236	¹ H NMR (400 MHz, DMSO) δ 11.36 (s, 1H), 7.95 - 7.64 (m, 5H), 7.53 (d, J = 10.9 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 2.33 (s, 3H). ¹³ C NMR (101 MHz, DMSO) δ 159.90 (d, J = 252.9 Hz), 156.21, 148.64, 134.88 (d, J = 1C.8 Hz), 131.48 (d, J = 3.9 Hz), 125.07 (d, J = 11.4 Hz), 124.74 (d, J = 3.3 Hz), 116.79 (d, J = 26.3 Hz), 17.80 (d, J = 6.1 Hz).
NCL237	¹ H NMR (400 MHz, DMSO) δ 14.38 (s, 1H), 7.30 (d, J = 8.6 Hz, 1H), 6.73 - 6.66 (m, 2H), 6.39 (s, 2H), 6.27 (s, 2H), 2.57 (d, J = 7.3 Hz, 2H), 1.63 - 1.46 (m, 5H), 1.32 (s, 1H), 1.13 - 0.97 (m, 3H), 0.89 - 0.77 (m, 2H). ¹³ C NMR (101 MHz, DMSO) δ 160.62, 158.15, 152.94, 134.16, 130.52, 124.27, 119.53, 116.22, 44.10, 36.13, 32.45, 25.98, 25.57.
NCL238	¹ H NMR (400 MHz, DMSO) δ 10.92 (s, 2H), 8.61 (d, J = 1.7 Hz, 2H), 8.14 (dd, J = 8.3, 2.0 Hz, 2H), 8.05 (s, 2H), 7.59 (d, J = 8.3 Hz, 2H), 6.30 (s, 1H), 5.93 (s, 2H). ¹³ C NMR (101 MHz, DMSO) δ 162.67, 162.59, 149.65, 147.85, 135.86, 130.63, 124.61, 73.64.
NCL239	¹ H NMR (400 MHz, DMSO) δ 10.82 (s, 2H), 8.80 (d, J = 1.6 Hz, 2H), 8.54 (dd, J = 4.7, 1.5 Hz, 2H), 8.11 - 8.03 (m, 4H), 7.46 (dd, J = 7.9, 4.8 Hz, 2H), 6.33 (s, 1H), 5.91 (s, 2H). ¹³ C NMR (101 MHz, DMSO) δ 162.74, 162.62, 149.41, 147.69, 137.19, 132.57, 131.02, 123.96, 73.55.
NCL240	¹ H NMR (600 MHz, DMSO) δ 10.91 (s, 2H), 8.60 - 8.53 (m, 2H), 8.10 (s, 2H), 7.94 (d, J = 7.7 Hz, 2H), 7.87 (t, J = 7.3 Hz, 2H), 7.38 - 7.30 (m, 2H), 6.35 (s, 1H), 5.94 (br s, 2H). ¹³ C NMR (151 MHz, DMSO) δ 162.7*, 154.0, 149.4, 140.8, 136.7, 123.2, 119.1, 73.7* *2D NMR analysis suggests that the signals for the two quaternary carbons of the pyrimidine core both occur at 162.7 ppm.
NCL241	¹ H NMR (400 MHz, DMSO) δ 11.03 (s, 2H), 8.62 (d, J = 3.3 Hz, 4H), 8.01 (s, 2H), 7.60 (d, J = 3.2 Hz, 4H), 6.38 (s, 1H), 6.00 (s, 2H). ¹³ C NMR (101 MHz, DMSO) δ 162.71, 162.69, 150.18, 142.21, 137.53, 120.15, 73.96.

NCL242	<p>¹H NMR (400 MHz, DMSO) δ 10.61 (s, 2H), 10.42 (s, 1H), 9.78 (s, 1H), 9.08 (s, 1H), 8.87 (s, 1H), 8.84 (s, 2H), 8.20 (s, 2H), 7.08 (d, J = 2.5 Hz, 1H), 6.93 (d, J = 2.5 Hz, 2H), 6.89 - 6.76 (m, 2H), 6.71 (d, J = 8.7 Hz, 2H), 6.64 (dd, J = 8.7, 2.7 Hz, 2H), 5.91 (s, 1H), 5.84 (s, 2H).</p> <p>¹³C NMR (101 MHz, DMSO) δ 162.66, 162.18, 151.58, 149.94, 149.88, 149.08, 140.17, 120.97, 120.39, 118.32, 117.43, 117.23, 116.73, 115.04, 112.60, 72.69.</p>
NCL243	<p>¹H NMR (400 MHz, DMSO) δ 10.25 (s, 2H), 9.18 (s, 4H), 7.87 (s, 2H), 7.11 (d, J = 1.4 Hz, 2H), 6.90 (dd, J = 8.1, 1.4 Hz, 2H), 6.78 (d, J = 8.1 Hz, 2H), 6.14 (s, 1H), 5.69 (s, 2H).</p> <p>¹³C NMR (101 MHz, DMSO) δ 163.16, 162.89, 147.24, 146.03, 141.55, 127.12, 119.30, 116.24, 113.09, 73.36.</p>
NCL244	<p>¹H NMR (400 MHz, DMSO) δ 10.71 (s, 3H), 9.95 (s, 3H), 9.30 (s, 3H), 8.96 (s, 1H), 8.26 (s, 2H), 7.13 (d, J = 7.7 Hz, 1H), 7.01 (d, J = 7.4 Hz, 2H), 6.95 (d, J = 7.6 Hz, 1H), 6.86 - 6.74 (m, 3H), 6.71 (t, J = 7.7 Hz, 2H), 5.95 (s, 1H), 5.85 (s, 2H).</p> <p>¹³C NMR (101 MHz, DMSO) δ 163.39, 162.70, 162.18, 147.40, 145.67, 144.80, 140.68, 121.27, 120.58, 119.43, 119.18, 118.88, 118.44, 117.96, 116.00, 72.75.</p>
NCL245	<p>¹H NMR (400 MHz, DMSO) δ 10.75 (s, 2H), 8.83 - 8.78 (m, 2H), 8.74 (s, 2H), 8.05 - 8.00 (m, 2H), 7.98 (d, J = 8.2 Hz, 2H), 7.92 (d, J = 7.0 Hz, 2H), 7.67 - 7.53 (m, 6H), 6.51 (s, 1H), 5.92 (s, 2H).</p> <p>¹³C NMR (101 MHz, DMSO) δ 162.94, 162.74, 139.74, 133.69, 130.51, 129.90, 129.25, 128.84, 126.93, 126.11, 125.99, 125.60, 123.98, 73.45.</p>
NCL246	<p>¹H NMR (400 MHz, DMSO) δ 10.55 (s, 2H), 7.87 (d, J = 9.2 Hz, 2H), 7.59 (d, J = 7.4 Hz, 4H), 7.37 (t, J = 7.5 Hz, 4H), 7.29 (t, J = 7.3 Hz, 2H), 7.01 (dd, J = 16.1, 9.3 Hz, 2H), 6.84 (d, J = 16.0 Hz, 2H), 6.13 (s, 1H), 5.78 (s, 2H).</p> <p>¹³C NMR (101 MHz, DMSO) δ 162.52, 142.73, 136.42, 135.24, 128.76, 128.19, 126.69, 126.04, 73.35.</p>
NCL247	<p>¹H NMR (400 MHz, DMSO) δ 10.20 (s, 2H), 9.00 (s, 4H), 8.43 (s, 2H), 7.80 (s, 2H), 6.59 (s, 4H), 6.07 (s, 1H), 5.67 (s, 2H).</p>
NCL248	<p>¹H NMR (400 MHz, DMSO) δ 8.73 (s, 1H), 8.66 (d, J = 8.2 Hz, 1H), 8.00 (d, J = 7.2 Hz, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.60 - 7.44 (m, 3H), 5.95 (s, 2H), 5.58 (s, 2H).</p> <p>¹³C NMR (101 MHz, DMSO) δ 160.68, 142.16, 133.59, 132.18, 130.24, 128.52, 127.94, 126.48, 125.77, 125.58, 125.02, 124.11.</p>
NCL249	<p>¹H NMR (400 MHz, DMSO) δ 7.82 (d, J = 9.5 Hz, 1H), 7.47 (d, J = 7.5 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.23 (t, J = 7.3 Hz, 1H), 6.95 (dd, J = 16.0, 9.5 Hz, 1H), 6.72 (d, J = 16.0 Hz, 1H), 4.38 (s, 4H).</p>
NCL250	<p>¹H NMR (400 MHz, DMSO) δ 8.34 (s, 2H), 7.78 - 7.65 (m, 4H), 7.54 - 7.43 (m, 4H), 3.87 (s, 4H).</p> <p>¹³C NMR (101 MHz, DMSO) δ 160.85, 135.20, 134.84, 129.44, 128.77, 60.70.</p>
NCL251	<p>¹H NMR (400 MHz, DMSO) δ 8.35 (s, 2H), 7.79 - 7.70 (m, 4H), 7.55 - 7.45 (m, 4H), 3.60 (d, J = 0.9 Hz, 4H), 1.67 (t, J = 2.7 Hz, 4H).</p> <p>¹³C NMR (101 MHz, DMSO) δ 159.49, 135.06, 134.98, 129.42, 128.74, 60.20, 28.25.</p>
NCL252	<p>¹H NMR (400 MHz, CDC13) δ 8.26 (s, 2H), 7.71 - 7.60 (m, 4H), 7.42 - 7.33 (m, 4H), 3.71 (td, J = 6.8, 1.1 Hz, 4H), 2.10 (p, J = 6.8 Hz, 2H).</p> <p>¹³C NMR (101 MHz, CDC13) δ 160.00, 136.54, 134.74, 129.25, 128.90, 59.16, 31.90.</p>
NCL253	<p>¹H NMR (400 MHz, DMSO) δ 7.89 (s, 1H), 7.47 (d, J = 8.7 Hz, 2H), 6.67 (d, J = 8.8 Hz, 2H), 5.71 (s, 2H), 5.25 (s, 2H), 2.91 (s, 6H).</p>
NCL254	<p>¹H NMR (400 MHz, DMSO) δ 11.30 (s, 1H), 7.98 (d, J = 8.7 Hz, 2H), 7.80 (s, 4H), 7.47 (d, J = 8.7 Hz, 2H), 2.99 - 2.68 (m, 2H), 1.68 - 1.13 (m, 6H), 0.84 (t, J = 7.2 Hz, 3H).</p> <p>¹³C NMR (101 MHz, DMSO) δ 156.06, 153.87, 134.79, 134.40, 128.68, 128.41, 30.95, 26.63, 25.60, 21.95, 13.86.</p>

NCL255	<p>¹H NMR (400 MHz, DMSO) δ 10.69 (s, 2H), 8.09 (s, 2H), 7.77 (s, 8H), 7.71 (d, J = 7.5 Hz, 4H), 7.47 (t, J = 7.6 Hz, 4H), 7.37 (t, J = 7.3 Hz, 2H), 6.42 (s, 1H), 5.87 (s, 2H).</p> <p>¹³C NMR (101 MHz, DMSO) δ 162.80, 162.64, 140.22, 139.71, 139.48, 134.31, 128.97, 127.64, 127.05, 126.66, 126.55, 73.49.</p>
NCL256	<p>¹H NMR (400 MHz, DMSO) δ 10.47 (s, 4H), 9.81 (s, 2H), 8.14 (s, 2H), 7.29 (d, J = 8.4 Hz, 2H), 6.40 - 6.24 (m, 4H), 5.78 (s, 3H).</p>
NCL257	<p>¹H NMR (400 MHz, DMSO) δ 11.73 (s, 1H, Isomer A), 10.65 (s, 1H, Isomer A), 8.99 (s, 1H, Isomer A), 8.75 (d, J = 8.6 Hz, 1H, Isomer A), 7.92 (d, J = 8.9 Hz, 1H, Isomer A masking a signal from Isomer B), 7.85 (d, J = 7.7 Hz, 1H, Isomer A), 7.73 - 7.50 (m, 5H, Isomers A & B), 7.39 (t, J = 7.6 Hz, 1H, Isomer A masking a signal from Isomer B), 7.24 (d, J = 8.9 Hz, 1H, Isomer A).</p> <p>¹H NMR (400 MHz, DMSO) δ 12.88 (s, 1H, Isomer B), 9.99 (s, 1H, Isomer B), 8.65 (d, J = 8.8 Hz, 1H, Isomer B), 8.07 - 8.01 (m, 2H, Isomer B), 7.95 (d, J = 9.0 Hz, 1H, Isomer B), 7.47 - 7.42 (m, 1H), 7.30 (d, J = 8.8 Hz, 1H, Isomer B), 7.29 (d, J = 9.0 Hz, 1H, Isomer B). Masked signals are identified in Isomer A NMR.</p> <p>¹³C NMR (101 MHz, DMSO) δ 157.22, 154.74, 146.77, 133.32, 131.19, 128.61, 128.20, 128.07, 124.17, 123.58, 118.12, 109.69.</p>
NCL258	<p>¹H NMR (400 MHz, DMSO) δ 7.33 (s, 8H), 3.64 (s, 4H), 2.42 (s, 4H), 1.42 (s, 4H).</p> <p>¹³C NMR (101 MHz, DMSO) δ 140.20, 130.86, 129.64, 127.95, 52.14, 48.53, 27.32.</p>
NCL259	<p>¹H NMR (400 MHz, DMSO) δ 11.37 (s, 1H), 7.98 (d, J = 8.6 Hz, 2H), 7.84 (s, 4H), 7.46 (d, J = 8.6 Hz, 2H), 2.83 (d, J = 7.1 Hz, 2H), 1.69 - 1.43 (m, 6H), 1.08 (s, 5H).</p> <p>¹³C NMR (101 MHz, DMSO) δ 156.02, 153.02, 135.35, 134.32, 128.84, 128.33, 35.79, 33.41, 31.97, 25.65.</p>
NCL260	<p>¹H NMR (400 MHz, CDCl₃) δ 7.25 (d, J = 8.3 Hz, 4H), 7.21 (d, J = 8.4 Hz, 4H), 3.70 (s, 4H), 2.70 (s, 4H).</p>
NCL261	<p>¹H NMR (400 MHz, DMSO) δ 12.09 (s, 1H), 8.34 (s, 1H), 8.24 - 8.17 (m, 2H), 7.96 (dd, J = 8.8, 4.6 Hz, 3H), 7.83 (s, 4H), 7.61 - 7.54 (m, 2H).</p> <p>¹³C NMR (101 MHz, DMSO) δ 155.42, 146.87, 133.90, 132.70, 131.23, 129.46, 128.35, 128.31, 127.81, 127.35, 126.82, 123.04.</p>
NCL262	<p>¹H NMR (400 MHz, DMSO) δ 9.98 (s, 2H), 7.42 - 7.07 (m, 12H), 5.97 (d, J = 25.2 Hz, 1H), 5.59 (s, 2H), 2.79 (t, J = 7.6 Hz, 4H), 2.57 - 2.44 (m, 4H).</p> <p>¹³C NMR (101 MHz, DMSO) δ 162.74, 162.47, 143.11, 141.15, 128.40, 128.27, 125.86, 72.62, 33.61, 32.43.</p>
NCL263	<p>¹H NMR (400 MHz, DMSO) δ 12.15 (s, 1H), 8.47 (t, J = 7.6 Hz, 1H), 8.40 (s, 1H), 7.90 (s, 4H), 7.81 (d, J = 10.4 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H).</p>
NCL264	<p>¹H NMR (400 MHz, DMSO) δ 10.78 (s, 2H), 8.23 (s, 2H), 8.10 - 7.87 (m, 10H), 7.56 (s, 4H), 6.46 (s, 1H), 5.88 (s, 2H).</p> <p>¹³C NMR (101 MHz, DMSO) δ 162.83, 162.67, 140.09, 133.19, 133.12, 133.00, 128.45, 128.08, 127.76, 126.96, 126.67, 126.53, 122.37, 73.63.</p>
NCL265	<p>¹H NMR (400 MHz, DMSO) δ 7.78 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 8.7 Hz, 2H), 5.85 (s, 2H), 5.45 (s, 2H), 2.90 - 2.74 (m, 2H), 1.49 - 1.33 (m, 2H), 1.33 - 1.11 (m, 8H), 0.84 (t, J = 6.9 Hz, 3H).</p> <p>¹³C NMR (101 MHz, DMSO) δ 160.12, 149.95, 138.11, 131.48, 127.92, 127.10, 31.31, 29.43, 28.69, 26.44, 25.86, 22.07, 13.96.</p>
NCL265	<p>¹H NMR (400 MHz, DMSO) δ 7.77 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 8.7 Hz, 2H), 5.85 (s, 2H), 5.43 (s, 2H), 2.90 - 2.77 (m, 2H), 1.82 - 1.65 (m, 3H), 1.62 - 1.28 (m, 6H), 1.21 - 1.00 (m, 2H).</p> <p>¹³C NMR (101 MHz, DMSO) δ 160.07, 150.06, 138.09, 131.49, 127.96, 127.08, 39.95, 32.79, 32.22, 25.17, 24.86.</p>

NCL267	¹ H NMR (400 MHz, DMSO) δ 11.62 (s, 1H), 8.58 (s, 1H), 8.06 (d, J = 4.7 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H). ¹³ C NMR (101 MHz, DMSO) δ 152.2, 145.5, 141.3, 133.8, 133.4, 132.6, 128.8, 128.2.
NCL268	¹ H NMR (400 MHz, DMSO) δ 11.49 (s, 1H), 8.54 (s, 1H), 8.03 (s, 2H), 7.62 (d, J = 7.6 Hz, 2H), 7.24 (d, J = 7.4 Hz, 2H), 2.33 (s, 3H). ¹³ C NMR (101 MHz, DMSO) δ 152.4, 145.5, 142.9, 139.2, 132.1, 131.7, 129.4, 128.7, 126.6, 21.0.
NCL269	¹ H NMR (400 MHz, DMSO) δ 11.66 (s, 1H), 10.89 (br s, 1H), 8.23 (d, J = 7.8 Hz, 1H), 7.97 (d, J = 2.4 Hz, 1H), 7.51 (br s, 3H), 7.42 (d, J = 8.0 Hz, 1H), 7.22 – 7.14 (m, 1H), 7.14 – 7.06 (m, 1H), 2.39 (s, 3H). ¹³ C NMR (101 MHz, DMSO) δ 155.6, 151.9, 137.2, 129.5, 124.2, 122.8, 122.3, 120.6, 113.8, 111.7, 15.9.
NCL270	¹ H NMR (400 MHz, DMSO) δ 11.71 (s, 2H), 11.33 (br s, 2H), 8.33 (d, J = 7.8 Hz, 2H), 8.05 (d, J = 2.7 Hz, 2H), 7.83 (br s, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.24 – 7.18 (m, 2H), 7.18 – 7.12 (m, 2H), 2.50 (s, 6H, obscured by DMSO-d ₆). ¹³ C NMR (101 MHz, DMSO) δ 153.2, 153.0, 137.2, 129.8, 124.2, 122.8, 122.4, 120.6, 113.7, 111.8, 15.9.
NCL271	¹ H NMR (400 MHz, DMSO) δ 12.23 (br s, 2H), 8.68 (br s, 2H), 8.06 (d, J = 8.7 Hz, 4H), 7.50 (d, J = 8.7 Hz, 4H), 3.03 – 2.86 (m, 4H), 1.52 – 1.36 (m, 8H), 1.34 – 1.23 (m, 4H), 0.84 (t, J = 7.3 Hz, 6H). ¹³ C NMR (101 MHz, DMSO) δ 155.7, 154.4, 134.6, 128.9, 128.4, 30.9, 27.2, 25.8, 22.0, 13.9.
NCL272	¹ H NMR (400 MHz, DMSO) δ 12.28 (br s, 2H), 8.68 (br s, 2H), 8.06 (d, J = 8.5 Hz, 4H), 7.50 (d, J = 8.5 Hz, 4H), 3.04 – 2.86 (m, 4H), 1.53 – 1.35 (m, 8H), 1.32 – 1.14 (m, 12H), 0.83 (t, J = 6.7 Hz, 6H). ¹³ C NMR (101 MHz, DMSO) δ 155.6, 154.3, 134.6 (2 × C)*, 128.9, 128.4, 31.2, 28.6, 28.5, 27.1, 26.1, 22.0, 13.9. *Determined using 2D NMR analysis.
NCL273	¹ H NMR (400 MHz, Acetone) δ 13.20 (br s, 2H), 8.19 (br s, 2H), 7.96 (d, J = 8.6 Hz, 4H), 7.46 (d, J = 8.7 Hz, 4H), 3.14 – 3.05 (m, 4H), 2.15 (dt, J = 15.5, 7.8 Hz, 2H), 1.88 – 1.78 (m, 4H), 1.67 – 1.46 (m, 12H), 1.31 – 1.17 (m, 4H). ¹³ C NMR (101 MHz, Acetone) δ 157.7, 156.6, 156.2, 136.1, 129.5, 129.4, 40.9, 33.3, 33.1, 28.4, 25.8.
NOL274	¹ H NMR (400 MHz, DMSO) δ 11.99 (s, 2H), 11.64 (s, 2H), 8.50 (br s, 4H), 8.10 (s, 2H), 8.02 (s, 2H), 7.44 (d, J = 7.3 Hz, 2H), 7.36 (d, J = 7.0 Hz, 2H).
NCL275	¹ H NMR (400 MHz, DMSO) δ 11.51 (br s, 2H), 8.77 (br s, 2H), 8.10 – 7.90 (m, 4H), 7.54 (d, J = 8.3 Hz, 4H), 4.81 (br s, 4H), 3.59 (q, J = 6.8 Hz, 4H), 1.20 – 1.03 (m, 6H).

EXAMPLE 9: Antigiardial activity of NCL analogues 231 - 247 and NCL219.

[00221] *Aim:* The objective of this study was to determine the activity of NCL219, and NCL231 - NCL247 against *Giardia duodenalis in vitro* using the Resazurin Reduction Assay.

[00222] *Methods:* *Giardia* trophozoites were grown until confluent. The media was replaced with fresh media and cold shocked for 40 minutes. Compounds were prepared in DMSO and serially diluted 2-fold in DMSO starting at with a 1/100 dilution of the stock (e.g. 128 mg/ml stock starting dilution would be 128 µg/ml). 2 µl of dilutions were added to the appropriate wells and 198 µl of TYI-S-33 media added to each well. Cells were diluted to a concentration of ~ 500 000 cells/ml and 100 µl were added to each well of the assay plate (except media only control). The assay was incubated in an anaerobic environment (candle jar) for 5 hours at 37°C. The media was removed and replaced with 100 µl of warm PBS then Alamarblue™ added to a concentration of 10%. The samples were incubated in an anaerobic environment until colour development. After incubation, the absorbance of each sample was read at 570 and 630 nm. The percent reduction of resazurin (Alamarblue™) was calculated (using the formula below) and data was analysed with GraphPad Prism v6 software. The formula used to calculate percent reduction of Alamarblue was $((E_{\text{oxi } 630} \times A_{570}) - (E_{\text{oxi } 570} \times A_{630})) / ((E_{\text{red } 570} \times C_{630}) - (E_{\text{red } 630} \times C_{570})) \times 100$, Where: $E_{\text{oxi } 630} = 34798$, $E_{\text{oxi } 570} = 80586$, A_{570} = absorbance at 570nm, A_{630} = absorbance at 630 nm, $E_{\text{red } 570} = 155677$, $E_{\text{red } 630} = 5494$, C_{630} = absorbance of negative control well at 630 nm and C_{570} = absorbance of negative control well at 570 nm.

[00223] *Results and Conclusions:* Three of the compounds tested in this assay showed excellent inhibitory activity towards *Giardia duodenalis in vitro*, NCL245 (9.6 µM), NCL246 (5.4 µM) and NCL219 (1.03 µM). The results are presented in Table 4.

Table 4

NCL code	[Stock] (mg/ml)	<i>S. aureus</i> ATCC 29213 (µg/ml)	<i>Giardia</i> WB (µg/ml)	<i>Giardia</i> WB (µM)
NCL231	25.6	32.00	9.6	41.24
NCL232	12.8	64, 32	20	93.48
NCL233	25.6	64, 32	68	247.3
NCL234	25.6	64.00	>64*	0
NCL235	25.6	128	>64*	NC
NCL236	25.6	16	>64*	NC
NCL237	25.6	4,8	22.8 ^	NC
NCL238	6.4	>64	>64*	NC
NCL239	12.8	32	111	334
NCL240	25.6	>128	~30	~91.73

NCL241	25.6	> 128	-30	-91 .29
NCL242	25.6	> 128	32	-60.33
NCL243	25.6	> 128	639	1754
NCL244	25.6	16	>64*	NC
NCL245	25.6	8	4	9.591
NCL246	25.6	8	2	5.446
NCL247	25.6	> 128	40	92.87
NCL219	10.0	> 100	0.4	1.030

*IC50 could not be calculated

^1 repeat only

IC50 after 5 hours, MIC after 24 hours, NC - not converged

EXAMPLE 10: Anti-trypanosomatid activity of NCL analogues

[00224] *Background:* Trypanosomatids cause significant human morbidity and mortality with an estimated 1.3 million new cases per year resulting in -30 000 deaths occurring due to *Leishmania* sp. alone. In addition to this Trypanosomatids, such as *Trypanosoma brucei* (endemic to Africa), cause significant morbidity and mortality to humans (upto 66 million people affected) as well as significant losses in the livestock industry (known as nagana). Currently the chemotherapy available for these organisms is limited and has unwanted toxic side effects. In this study, we looked at the *in vitro* efficacy of 20 chemical analogues from the NCL series (see Table 5 for details) against the procyclic stage of *T. brucei* and the promastigote stage of *Leishmania donovani*. Analogues that showed promising *in vitro* activity against either of the parasites were tested *in vitro* for selectivity against a mouse macrophage cell line (ATCC RAW 264.7).

[00225] *Aim:* The objective of this study was to: (1) evaluate the *in vitro* antiparasitic activity of 20 structurally related aminoguanidines (from the NCL series) against *T. brucei* and *L. donovani*; and (2) determine the selectivity of these compounds for parasites over mammalian cell.

[00226] *Methods:* Antimicrobial agents (Table 5) were all dissolved in DMSO to a final concentration of 10 mM. Pentamidine (Sigma) was used as a positive control and prepared as the NCL compounds

Table 5.

Scaffold 1		
Compound	R	R'
NCL024	4-CN	H
NCL026	3-CN	H
NCL028	2-OCH ₃	H
NCL062	4-Cl	CH ₃
NCL099	4-C(CH ₃) ₃	H
NCL113	4-N(CH ₃) ₂	H
NCL166	4-SCF ₃	H
NCL171	2-OH, 4-N(CH ₃) ₂	H
NCL219	4-C(CH ₃) ₃	CH ₃
NCL812	4-Cl	H

Scaffold 2	
Compound	R
NCL195	4-CH ₃
NCL197	5-OH
NCL201	4-N(CH ₃) ₂

Scaffold 3		
Compound	R	R'
NCL041	H	4-CF ₃
NCL042	H	2-CF ₃
NCL052	H	3-Cl
NCL191	CH ₃	4-Cl
NCL231	CH ₃	4-C(CH ₃) ₃

[00227] *L. donovani* Screening. Procyclic promastigotes from exponentially growing cultures maintained in DME-L+ Bob additions were used for all assays. Compounds were initially screened for activity at 10 μ M. Compounds were diluted in culture media to a final volume of 10 μ M in 96 well plates. Promastigotes were diluted to a density of $\sim 8 \times 10^5$ cells/ml then added to the assay plate resulting in a final cell density of 4×10^5 cells/ml in 96 well plates. Cells were incubated for 96 hrs at 27°C before the addition of Alamarblue (thermofisher). Fluorescence was read at excitation 530nm and Emission 590nm. Compounds that showed inhibitory activity at 10 μ M were further investigated to determine IC₅₀ values. Compounds were serially diluted in thirds, in a 96 well plate, in cell growth media so that concentrations ranged from 0.005 to 10 μ M and promastigotes added to a final concentration of 1×10^6 cells/ml. Cells were incubated at 27°C for 72 hours before the addition of alamar blue. Fluorescence was measured as above.

[00228] *T. brucei* screening. Procyclic promastigotes from exponentially growing cells maintained SDM-79 medium were used in all assays. Compounds were initially screened at 10 μ M for activity. Compounds were diluted in culture media to a concentration of 20 μ M and added to a 96 well plate, after addition of promastigotes (final concentration 4×10^5 cells/ml) compound concentration was 10 μ M. Cells were incubated for 48 hrs at 27°C before the addition of alamar blue and fluorescence measurement as described above. Compounds that showed inhibition at 10 μ M were further characterised to determine IC₅₀ values. Compounds were serially diluted in thirds in culture media resulting in final concentrations ranging from 0.004 - 10 μ M. Promastigotes were added at a final concentration of 4×10^5 cells/ml. Cells were

incubated at 27°C for 48 hours before addition of alamar blue. In addition promastigotes, at a concentration of 8×10^5 were exposed to NCL026 for 1.5 hours before removal of the drug via centrifugation at 5000 rpm for 7 minutes and resuspension of cells in culture media. Cells were incubated for 96 hours at 27°C and observed daily for metabolic activity (alamar blue assay) and morphological changes. A control culture was exposed to DMSO instead of NCL026.

[00229] Cell toxicity assays. Mouse macrophages (RAW 264.7) were grown in RPMI1640 media supplemented with L-glutamine and 10% foetal calf serum. Cells were trypsinised when 80% confluent and subcultured every 3-4 days. For cytotoxicity assays cells were diluted to a final cell concentration of 2×10^4 cells/ml and 198 μ l added to each well of a 96 well plate. Cells were incubated in a humidified incubator for 2 hours at 37°C 5% CO₂ before the addition of NCL compounds (2 μ l/well, previously diluted in DMSO). Camptothecin, triton X and DMSO only were used as controls. Cells were exposed to the compounds for 24 hours. The metabolic activity of the cells was determined using the WST-1 assay system (Roche Life Science). The supernatant was removed, 100 μ l of PBS with 10% WST-1 was added to each well and incubated for 1 hr before reading absorbance at 450nm. The selectivity index of the compounds was determined by dividing the IC₅₀ of macrophages by the IC₅₀ against parasites. IC₅₀ was determined via graphpad prism software.

[00230] *Results:* Robenidine and 19 structural analogues were screened for activity against the procyclic promastigote stage of *L. donovani* and *T. brucei* at 10 μ M. Of the compounds tested 70% showed a $\geq 90\%$ reduction of metabolic activity in *L. donovani* while 15% showed a similar reduction of metabolic activity in *T. brucei* (see Figure 10). The procyclic stage of *T. brucei* and the promastigote stage of *L. donovani* were exposed to the compounds for 48 or 96 hrs respectively before the effect was measured using a resazurin dye. Assays were repeated in triplicate. P = pentamidine. Error \pm SD.

[00231] Of those compounds active against *L. donovani* NCL026, NCL028, NCL041, NCL042, NCL062, NCL099, NCL195, NCL201, NCL219 and NCL246 had the greatest activity inhibiting the parasite 100%. Against *T. brucei* NCL026, NCL062, and NCL246 had the greatest inhibitory effect. NCL026, NCL062 and NCL246 were very effective against both species of parasites. Further investigation of a selection of compounds that had activity against the parasites was completed to determine the IC₅₀ values. The IC₅₀ value was determined for NCL028, NCL099, NCL166, NCL201, NCL245, NCL246 and NCL812 against *L. donovani*. The IC₅₀ ranged from 0.37 μ M (NCL028) to 6.48 μ M (NCL245 and NCL246). The IC₅₀ value was determined against *T. brucei* with the 6 most effective analogues NCL024, NCL026, NCL062, NCL171, NCL195 and NCL246. Of these analogues NCL026, NCL171 and NCL195 were the most effective with IC₅₀ values of 1.7, 1.4 and 1.5 μ M respectively. The highest IC₅₀ value

determined was 4.2 μM for NCL246. A recovery assay to determine the ability of *T. brucei* to recover after a short exposure to NCL026 was performed. After 1.5 hrs of exposure to the for select periods of time to determine the GI_{50} or IC_{50} . The selectivity index (SI) was determined by dividing the GI_{50} of macrophages by the IC_{50} of parasites. An $\text{SI} \geq 10$ is considered selective for the parasite. Assays were repeated in triplicate. Error \pm SD. Based on this assay the selectivity of the compounds ranged from 0.57 to 27.9. It is generally considered that a selectivity index <10 is relatively unselective while a selectivity index >10 is considered selective for the parasite. Based on this convention only one compound (NCL171) could be considered relatively selective for *T. brucei* while 4 compounds were highly selective for *L. donovani in vitro* (NCL028, NCL 099, NCL1 13 and NCL219).

Table 6

Compound	GI_{50} macrophage (μM)	<i>T. brucei</i>		<i>L. donovani</i>	
		IC_{50} (MM)	SI	IC_{50} (MM)	SI
NCL 024	12.74 \pm 2.79	3.35 \pm 0.1 1	3.79	-	-
NCL 026	9.60 \pm 0.99	1.68 \pm 0.63	5.71	2.5 \pm 0.13	3.84
NCL 028	8.10 \pm 2.76	-	-	0.29 \pm 0.05	27.9
NCL 062	7.15 \pm 1 .27	4.04 \pm 0.83	1.75	-	-
NCL 099	7.66 \pm 0.56	-	-	0.37 \pm 0.04	20.7
NCL 113	12.90 \pm 3.49	-	-	0.92 \pm 0.06	14
NCL 166	9.46 \pm 0.05	-	-	3.23 \pm 1 .00	2.78
NCL 171	12.50 \pm 3.61	1.37 \pm 0.03	9.14	-	-
NCL 195	5.78 \pm 0.33	1.46 \pm 0.76	3.79	-	-
NCL 201	12.28 \pm 2.06	-	-	2.92 \pm 0.22	4.23
NCL 2 19	19.26 \pm 3.77	-	-	0.80 \pm 0.1 0	24.08
NCL 245	3.7 \pm 0.71	-	-	7.1 7 \pm 2.05	0.57
NCL 246	13.83 \pm 0.07	4.1 8 \pm 0.37	3.31	6.72 \pm 2.99	2.06
NCL 812	14.85 \pm 1 .34	-	-	2.9 \pm 0.24	5.12

[00232] *Conclusion.* This study demonstrated that several of the compounds tested showed high inhibitory activity against either *L. donovani* or *T. brucei in vitro*. Based on the *in vitro* selectivity index, NCL171 appears to be the most promising against *T. brucei* while NCL028, NCL099 and NCL219 appear to be the most promising against *L. donovani*.

EXAMPLE 11: The physicochemical and metabolic properties of NCL026, NCL028, NCL099, NCL171, NCL177, NCL195, NCL217, NCL259 and NCL812.

[00233] *Aim:* The objective of this study was to evaluate the physicochemical and metabolic properties of NCL026, NCL028, NCL099, NCL171, NCL177, NCL195, NCL217, NCL259 and NCL812.

[00234] The physicochemical and metabolic characteristics of the nine compounds were assessed using a combination of *in silico* and experimental techniques and the results have been summarised in Figure 11.

[00235] Calculated physicochemical parameters for each compound were generally within the limits normally associated with compounds having "drug-like" properties. The polar surface area values of NCL026 and NCL171 are however, approaching the upper limit recommended for good membrane permeability, reflecting the relatively high number of heteroatoms within these two structures. All of the compounds demonstrated low kinetic solubilities under neutral pH conditions, except for NCL259 which was more moderate. Most of the compounds showed greater solubility under acidic conditions (pH 2) suggesting an increase in ionisation at low pH. Measured partition coefficient values were relatively high at pH 7.4, with LogD_{7.4} values ranging from 3.6 to >5.3. LogD values were lower under acidic conditions (pH 3), however would still be considered to be moderate to high (2.8 to 4.9). The observed pH dependent solubility and partition coefficient results are consistent with the basic characteristics of the compounds predicted by their structures. The metabolic stability of the nine compounds were evaluated in both human and mouse liver microsomes. Five of the compounds, NCL026, NCL177, NCL195, NCL259 and NCL812, showed low rates of degradation in both species of liver microsomes (EH values <0.3). NCL099, NCL171 and NCL217 showed intermediate to high rates of degradation (EH values 0.49 to 0.88) with degradation rates for each compound being broadly comparable between species. NCL028 showed a low rate of degradation in human liver microsomes and a high rate of degradation in mouse liver microsomes which may suggest a significant difference in metabolism between species for this compound. There was no measurable degradation of any of the compounds in control (non-cofactor) incubations in either species suggesting that there was no major cofactor independent metabolism contributing to their overall rates of metabolism.

Experimental Methods

Calculated physicochemical parameters using ChemAxon JChem software

[00236] Theoretical physicochemical values for each compound were calculated using the ChemAxon chemistry cartridge via JChem for Excel software. Parameters calculated and a brief explanation of their relevance is given below.

[00237] Molecular Weight (MW): Ideally, MW should be less than 500 for good membrane permeability.

[00238] Polar Surface Area (PSA): Calculated using a simplified 2-dimensional modelling approach, which has been validated against a more sophisticated 3-dimensional modelling strategy. The value has been calculated at pH =7.4, which takes ionisation of the molecule into account. It is usually accepted that PSA values of less than approximately 120 Å^2 will provide acceptable oral drug absorption and membrane permeability.

[00239] Freely Rotating Bonds: Number of single bonds that are not in a ring or constrained system and are not bound to a hydrogen atom. FRB should be less than or equal to 10 for good membrane permeability (See D. Veber et al, J. Med. Chem. 2002, 45, 2615-2623).

[00240] H Bond Donor / Acceptors: Number of hydrogen bond donors and acceptors gives an indication of the hydrogen bonding capacity of the molecule which is inversely related to membrane permeability. Ideally, the number of H-Bond donors should be less than 5 and the number of H-Bond acceptors should be less than 10.

[00241] pKa: Basic physicochemical measure of the acidity of a compound. In the context of drug development, the values themselves only indicate whether ionisation is likely to be relevant at physiological conditions.

Solubility Estimates using Nephelometry

[00242] Compound in DMSO was spiked into either pH 6.5 phosphate buffer or 0.01 M HCl (approx. pH 2.0) with the final DMSO concentration being 1%. Samples were then analysed via Nephelometry to determine a solubility range. (See C. D. Bevan and R. S. Lloyd, Anal. Chem. 2000, 72, 1781-1787).

LogD Measurement

[00243] Partition coefficient values (LogD) of the test compounds were estimated by correlation of their chromatographic retention properties against the characteristics of a series of standard compounds with known partition coefficient values. The method employed is a gradient HPLC based derivation of the method developed by Lombardo (See F. Lombardo *et al*, J. Med. Chem. 2001 , 44, 2490-2497).

Microsomal Stability

[00244] Incubation methods: The metabolic stability assay was performed by incubating each test compound (at 1 μ M) with human and mouse liver microsomes (Xenotech, Lot# 1210057 and 131021 1, respectively) at 37°C and 0.4 mg/mL protein concentration. The metabolic reaction was initiated by the addition of an NADPH-regenerating system (i.e. NADPH is the cofactor required for CYP450-mediated metabolism) and quenched at various time points over a 60 minute incubation period by the addition of acetonitrile containing diazepam as internal standard. Control samples (containing no NADPH) were included (and quenched at 2, 30 and 60 minutes) to monitor for potential degradation in the absence of cofactor. Analytical conditions: Instrument: Waters Micromass Xevo G2 QTOF coupled to a Waters Acquity UPLC; Detection: Positive electrospray ionisation under MSE mode; Cone Voltage 30 V; Column: Ascentis Express Amide column (50 x 2.1 mm, 2.7 μ m); LC conditions: Gradient cycle time: 4 minutes; Injection volume: 5 μ L; Flow rate: 0.4 mL/min; Mobile phase: Acetonitrile-water gradient with 0.05% formic acid Metabolite; Identification: A metabolite screen was not included in this study, however, since data was acquired using MSE mode, which allows for the simultaneous acquisition of low and high collision energy MS spectra, a post-hoc metabolite search may be conducted at a later date if warranted.

[00245] Calculations: Test compound concentration versus time data were fitted to an exponential decay function to determine the first-order rate constant for substrate depletion. In cases where clear deviation from first-order kinetics was evident, only the initial linear portion of the profile was utilised to determine the degradation rate constant (k). Using standard methods in the art, each substrate depletion rate constant was then used to calculate: [1] a degradation half-life, [2] an *in vitro* intrinsic clearance value (CL_{int}, *in vitro*); [3] a predicted *in vivo* hepatic intrinsic clearance value (CL_{int}); [4] a predicted *in vivo* blood clearance value (CL_{blood}); and [5] a predicted *in vivo* hepatic extraction ratio (E_H). The following scaling parameters were assumed in the above calculations (Table 7).

Table 7

Species	Liver mass (g liver/kg body weight)	Microsomal protein (mg/g liver mass)	Hepatic blood flow (Q) (mL/minute/kg body weight)
Human ^a	25.7	32	20.7
Mouse ^a	54.9	47	120

^a Ring et al. (2011) *Journal of Pharmaceutical Sciences*, 100:4090-4 110.

[00246] Predictions of *in vivo* hepatic extraction ratios: The microsome-predicted hepatic extraction ratios (EH) obtained based on the relative rates of test compound degradation *in vitro*, were used to classify compounds as low (< 0.3), intermediate (0.3 - 0.7), high (0.7 - 0.95) or very high (> 0.95) extraction compounds.

[00247] *Results:* The physicochemical and metabolic characteristics of the nine compounds were assessed using a combination of *in silico* and experimental techniques and the results have been summarised in Figure 11.

EXAMPLE 12: Exposure of NCL026, NCL195, NCL259 and NCL812 in male Swiss outbred mice following IV administration

[00248] *Aim:* The objective of this study was to evaluate the systemic exposure of NCL026, NCL195, NCL259 and NCL812 in male Swiss outbred mice after IV administration at 5 mg/kg.

[00249] *Methods:* The systemic exposures of NCL026, NCL195, NCL259 and NCL812 were studied in nonfasted male Swiss outbred mice weighing 26.2 - 32.1 g. Mice had access to food and water *ad libitum* throughout the pre- and post-dose sampling period. Each compound was administered IV via a bolus injection into the tail vein (vehicle 20% (v/v) DMSO in PEG400, 1 mL/kg dose volume, n=8 mice per compound). Following administration, blood samples were collected at 5, 15, 30, 120, 240 and 480 min postdose (n = 2 mice per time point for each compound). A maximum of two samples were obtained from each mouse, with samples being taken either via submandibular bleed (approximately 120 µL; conscious sampling) or terminal cardiac puncture (0.6 mL; while mice were anaesthetised using inhaled Isoflurane). No urine samples were collected as mice were housed in bedded cages during the study. Blood was collected directly into polypropylene Eppendorf tubes containing heparin as anticoagulant, and stabilisation cocktail (containing Complete® (a protease inhibitor cocktail with EDTA) and potassium fluoride) to minimise the potential for *ex vivo* degradation of the test compounds in blood/plasma samples. Once collected, blood samples were centrifuged immediately, supernatant plasma was removed, and stored at -80°C until analysis by LC-MS using methods standard in the art.

[00250] Each compound was administered in a vehicle composed of 20% (v/v) DMSO in PEG400. Formulations were prepared by dissolving the compounds in DMSO prior to addition of PEG400. Formulations were not filtered prior to dosing and were administered to mice within 2.5 h of preparation. The average measured concentration of each compound in aliquots (n=2) of their respective formulations was 4.58, 4.31, 5.26 and 5.25 mg/mL for NCL026, NCL195, NCL259 and NCL812, respectively. The dose administered to each mouse was calculated on the basis of the measured concentration in the IV formulation, the dose volume and individual mouse body weight. Plasma concentration versus time data were analysed using non-compartmental methods (WinNonlin Version 6.3.0.395). Standard calculations for each pharmacokinetic parameter were calculated using standard methods in the art.

[00251] One mouse dosed with NCL812 exhibited abnormal behaviour (frantic, hyperactive) commencing a few minutes after dosing; this mouse was anaesthetised and blood was collected at 15 min post-dose. No other animals in this study appeared to exhibit any adverse reactions or compound-related side effects. There was evidence of haemolysis observed in plasma samples however this is likely to be attributable to the solvents used in the IV formulations (20% (v/v) DMSO in PEG400) which were required because of the limited solubility of the test compounds in aqueous formulation vehicles.

[00252] *Results:* The plasma concentration versus time profiles for NCL026, NCL195, NCL259 and NCL812 are shown in Figure 12. The pharmacokinetic parameters are presented in Table 8. All compounds exhibited moderate-to-long apparent terminal elimination half-lives.

Table 8

	NCL026	NCL195	NCL259	NCL812
Measured dose (mg/kg)	4.8	4.4	5.4	5.3
Apparent $t_{1/2}$ (h)	1.5	2.4	2.9	8.2 ^b
Plasma CL (mL/min/kg)	100.6	16.3	56.0 ^a	9.5 ^b
Plasma V_{SS} (L/kg)	6.9	2.6	12.8 ^a	5.9 ^b
AUC_{0-inf} (h*μM)	2.5	12.5	5.5 ^a	27.9 ^b

^a Plasma concentration at time zero could not be determined by log-linear regression of the first two measurements, and was therefore set to the first observed measurement. As such, AUC from 0 to 5 min (and therefore AUC_{0-inf}) will be underestimated and parameters calculated based on AUC₀₋₅ are approximations only.

^b Terminal elimination phase was not well defined, value is an approximation only.

EXAMPLE 13: Exposure of NCL195 in male Swiss outbred mice following IP administration.

[00253] *Aim:* The objective of this study was to obtain a preliminary indication of the plasma exposure of NCL195 following IP administration at a target dose of 50 mg/kg.

[00254] *Methods:* The formulation was prepared by dissolving solid NCL195 in DMSO (to 20% (v/v) of the final volume) before adding PEG400, yielding a clear yellow solution that was dosed to mice within 30 minutes of preparation. The measured concentration of NCL195 in the final formulation was 21.9 mg/mL, resulting in a mean administered dose of 43 mg/kg. Following administration, blood samples were collected up to 24 h post-dose (n = 2 mice per time point). A maximum of two samples were obtained from each mouse, with samples being taken either via submandibular bleed (approximately 120 μ L; conscious sampling) or terminal cardiac puncture (0.6 mL; while mice were anaesthetised using inhaled Isoflurane). No urine samples were collected as mice were housed in bedded cages during the study. Blood was collected directly into polypropylene Eppendorf tubes containing heparin as anticoagulant and stabilisation cocktail (containing Complete® (a protease inhibitor cocktail), potassium fluoride and EDTA) to minimise the potential for *ex vivo* degradation of NCL195 in blood/plasma samples. Once collected, blood samples were centrifuged immediately, supernatant plasma was removed, and stored in -20°C until analysis by LCMS using standard methods in the art.

[00255] *Results:* No adverse reactions or compound-related side effects were observed in any of the mice following IP administration of NCL195 at a dose of 43 mg/kg. The plasma concentration-time profile (Figure 13) indicates that NCL195 was rapidly absorbed after dosing. For the duration of the initial 7.5 h post-dose period, plasma concentrations remained above 3 - 4 μ g/mL, however concentrations fell to 0.2 - 0.5 μ g/mL between 7.5 and 24 h post-dose. Assuming that a 2-fold increase in dose would result in a proportional increase in NCL195 exposure, the present data suggests that IP administration of NCL195 at 100 mg/kg (as a solution formulation) would result in at least 7.5 hours of exposure at a plasma concentration >8 μ g/mL.

EXAMPLE 14: Activity of NCL Analogues against *Trypanosoma cruzi*

[00256] *Background:* Chagas' disease, also known as American trypanosomiasis, is a potentially life-threatening illness caused by the protozoan parasite *Trypanosoma cruzi* (*T. cruzi*). *T. cruzi* is transmitted when the infected faeces of the triatomine vector are inoculated through a bite site or through an intact mucous membrane of the mammalian host. Vectorborne transmission is limited to areas of North America, Central America, and South America. Both in endemic and in nonendemic areas, other infection routes include transfusion, organ and bone marrow transplantation, and congenital transmission. Outbreaks attributed to contaminated food or drink have been reported in northern South America, where transmission cycles involving wild vector populations and mammalian reservoir hosts are prominent. Infection is lifelong in the absence of effective treatment. The most important consequence of *T. cruzi* infection is cardiomyopathy, which occurs in 20 to 30% of infected persons. The World Health Organisation

estimates that in 2015 about 6 million to 7 million people are infected worldwide, mostly in Latin America.

[00257] There are only two drugs, the nitrofuran nifurtimox and the nitroimidazole benznidazole, with established efficacy against *T. cruzi* infection. However, each of these agents have significant limitations in effectiveness and safety.

[00258] In patients with acute Chagas' disease and in those with early congenital Chagas' disease, both benznidazole and nifurtimox reduce the severity of symptoms, shorten the clinical course of illness, and reduce the duration of parasitaemia; but cure rates in the acute phase are only in the order of 80 to 90%.

[00259] Studies of benznidazole involving children with chronic *T. cruzi* infection have revealed cure rates of only around 60%, on the basis of conversion to negative serologic test results 3 to 4 years after treatment.

[00260] Nifurtimox use is associated with gastrointestinal side effects (anorexia, weight loss, nausea, and vomiting) in up to 70% of patients. Neurologic toxic effects include irritability, insomnia, disorientation, and tremors. Rare but more serious side effects include paraesthesias, polyneuropathy, and peripheral neuritis.

[00261] Benznidazole use is frequently associated with dermatological adverse effects, usually mild rashes that respond to antihistamines. However, severe or exfoliative dermatitis or dermatitis associated with fever and lymphadenopathy prompt immediate interruption of treatment. A dose-dependent peripheral neuropathy occurring late in the course of therapy necessitates immediate cessation of treatment. Although bone marrow suppression is rare its occurrence prompts immediate interruption of treatment.

[00262] The absence of safe and effective treatments has led to Chagas' disease being classified as a neglected parasitic infection with major public health implications. The global cost of Chagas' disease has been estimated at more than US\$7billion (Lee, B. Y., K. M. Bacon, M. E. Bottazzi and P. J. Hotez (2013). "Global economic burden of Chagas disease: a computational simulation model." The Lancet Infectious Diseases **13**(4): 342-348) and there remains a desperate and continuing need to identify and develop improved treatments.

[00263] *Aim and Methods:* In an endeavour to identify new agents for the treatment of Chagas' disease, the biological activity of robenidine and 79 analogues against *Trypanosoma cruzi* was assessed in an *in vitro* screening assay according to the methods described by

Keenan et al (Keenan, M., M. J. Abbott, P. W. Alexander, T. Armstrong, W. M. Best, B. Berven, A. Botero, J. H. Chaplin, S. A. Charman, E. Chatelain, T. W. von Geldern, M. Kerfoot, A. Khong, T. Nguyen, J. D. McManus, J. Morizzi, E. Ryan, I. Scandale, R. A. Thompson, S. Z. Wang and K. L. White (2012). "Analogues of fenarimol are potent inhibitors of *Trypanosoma cruzi* and are efficacious in a murine model of Chagas disease." Journal of medicinal chemistry **55**(9): 4189-4204), Buckner and associates (Buckner, F. S., C. L. Verlinde, A. C. La Flamme and W. C. Van Voorhis (1996). "Efficient technique for screening drugs for activity against *Trypanosoma cruzi* using parasites expressing beta-galactosidase." Antimicrobial Agents and Chemotherapy **40**(11): 2592-2597) and by Van Voorhis and Eisen (Van Voorhis, W. C. and H. Eisen (1989). "FI-160. A surface antigen of *Trypanosoma cruzi* that mimics mammalian nervous tissue." The Journal of Experimental Medicine **169**(3): 641-652).

[00264] *In vitro T cruzi* Assay for Determination of IC₅₀.

[00265] The *T cruzi* assay uses Tulahuen trypomastigotes expressing the β -galactosidase gene. The parasites were maintained *in vitro* by serial passage in L6 cells. Briefly, L6 cells were plated into 96 well, flat-bottom tissue culture plates and incubated at 37°C in 5% CO₂ for 24 h to allow cells to adhere. *T cruzi* trypomastigotes were then added at a multiplicity of infection of 3, and plates were incubated for a further 48 h to allow infection to establish. All steps were carried out using RPMI media 1640 (without phenol red) supplemented with 10% Foetal Bovine Serum (FBS, Bovogen). Extracellular trypomastigotes were then removed and NCL compounds were added in seven-point serial dilutions performed in triplicate. Benznidazole (Epichem Pty Ltd.) was included as a control. After 96 h of incubation with the compounds, the colorimetric agent, chlorophenol red-fl-D-galactopyranoside (CPRG, Roche) was added with 0.3% v/v Nonidet P-40. After 4-6 h, a colour change following catabolisation of the reagent by viable *T cruzi* was observed and absorbance was read at 530 nm using a Dynex microplate reader. The % inhibition was calculated by the following equation: %inhibition = 100 - [(7. *cruzi* with compound - compound only)/(7. *cruzi* only - media only)] × 100. For each compound, % inhibition values were used to generate a standard curve from which the IC₅₀ was calculated. Each assay was performed at least twice, and the average was used.

[00266] *Results:* The value of the IC₅₀ of 80 NCL compounds is presented in Table 9.

Table 9

<i>Trypanosoma cruzi</i> activity	
Compound	IC ₅₀ μM
NCL026	1.4

NCL089	3.0
NCL042	4.9
NCL080	7.8
NCL036	8.3

NCL039	9.9
NCL024	12
NCL028	13
NCL027	14

NCL041	14
NCL086	14
NCL052	15
NCL075	15
NCL021	16
NCL037	16
NCL038	16
NCL040	16
NCL043	16
NCL083	16
NCL087	17
NCL030	18
NCL023	19
NCL029	19
NCL054	19
NCL076	19
NCL088	19
NCL025	20
NCL035	20
NCL081	20
NCL085	20
NCL015	21
NCL082	22
NCL084	22

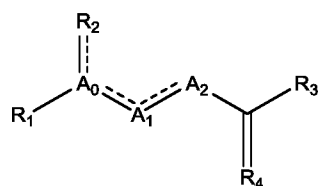
NCL016	24
NCL020	24
NCL073	24
NCL045	29
NCL046	32
NCL074	33
NCL002	38
NCL044	39
NCL072	46
NCL022	49
NCL053	49
NCL010	50
NCL034	53
NCL004	56
NCL017	56
NCL032	58
NCL019	61
NCL031	69
NCL033	80
NCL007	82
NCL003	83
NCL077	> 10
NCL078	> 10
NCL079	> 10

NCL812	> 11
NCL011	> 11
NCL005	>33
NCL018	>33
NCL001	> 100
NCL006	> 100
NCL008	> 100
NCL009	> 100
NCL012	> 100
NCL013	> 100
NCL014	> 100
NCL047	> 100
NCL048	> 100
NCL049	> 100
NCL050	> 100
NCL051	> 100
NCL055	> 100
NCL056	> 100
NCL057	> 100
NCL058	> 100
NCL059	> 100
NCL060	> 100
NCL071	> 100

[00267] *Conclusion:* Notably, 6 compounds had an IC₅₀ of less than 10 μ M while 30 compounds had IC₅₀ values less than or equal to 20 μ M. The NCL series provides a rich source of agents with activity against *Trypanosoma cruzi*.

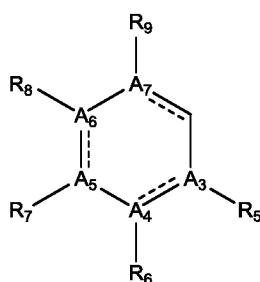
CLAIMS

1. A method of treating or preventing a protozoan colonisation or infection in a subject, the method including the step of administering a therapeutically effective amount of a compound of Formula I or stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof to the subject, wherein the protozoan infection is caused by a protozoan agent, wherein Formula I is:

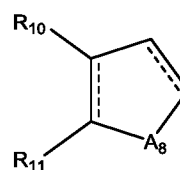


Formula I

wherein R_1 is H, cycloalkyl, Formula II, or Formula III;

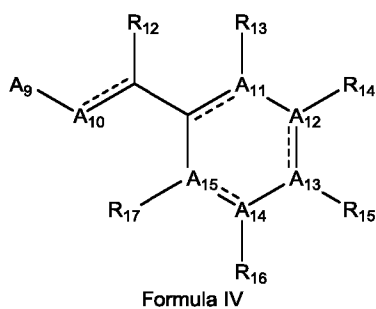


Formula II

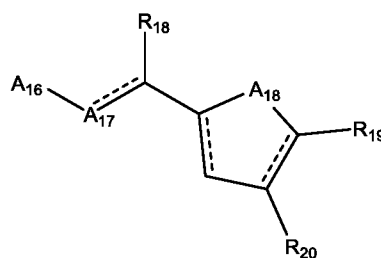


Formula III

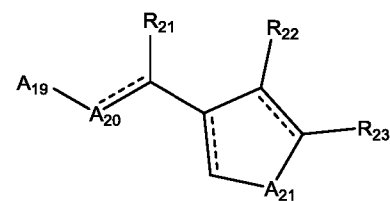
wherein R_3 is selected from the group consisting of: H; NH_2 ; $NHNH_2$; $O-CH_2-CH_3$; $NH-C(0)$ -phenyl; $NH-CH$ -chlorophenyl; NH -chlorophenyl; $NH-CH_2$ -chlorophenyl; $NH-N-CH$ -cycloalkyl; N and R_4 is $CH-N-CH-CCI-$ and R_4 is bonded to R_3 ; Formula IV; Formula V; and Formula VI;



Formula IV



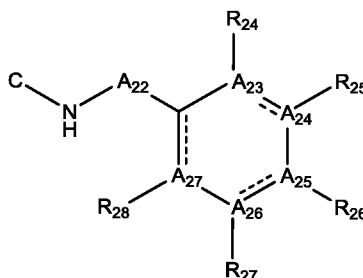
Formula V



Formula VI

wherein A_0 is N, C, CH, or A_0 is C and A_0 is bonded to R_4 to form a triazole ring;

wherein A_1 is N, C, NH, $-(CH)_2-N-$, $-(C_6H_5)C-CH-N-$, or Formula VII;



Formula VII

A_2 is N, C, NH, N-C(0)-phenyl or Formula VII, or $(CH_2)_n$ wherein n is an integer between 1 and 3, inclusive;

wherein $A_3, A_4, A_5, A_6, A_7, A_8, A_{11}, A_{12}, A_{13}, A_{14}, A_{15}, A_{16}, A_{17}, A_{18}, A_{19}, A_{20}, A_{21}, A_{23}, A_{24}, A_{25}, A_{26}$ and A_{27} are independently C, O, N, NH, S;

wherein A_9 is C, O, N, NH, N-C(0)-O-CH₂-CH₃, N-C(0)-O-CH(CH₃)₂, N-C(0)-NH-CH₂-CH₃, N-C(0)-NH-CH₂-phenyl, N-C(0)-CH₂-CH₂-CH₂-CH₂-CH₂-CH₃, N-C(O)-CH₂-furan-2-yl;

wherein A_{10} is C, NH, $-N-(CH)_2-$, $-N-CH-C(C_6H_5)-$;

wherein A_{22} is $-CH(CH_3)-$, $-N-CH-$, $-N-C(CH_3)-$, $N-C(CH_2OH)-$;

R_2 is H, COOH, CH₂NH₂, CH₂OH, CH₂NHNH₂, methyl, ethyl, propyl, butyl, pentyl, heptyl, cyclopentyl, CH₂(Cyclohexyl), $(CH_2)_2$ (cyclopentyl) or Formula VII and R_2 and R_9 are bonded together to form a pyrimidine, pyrazine or triazine ring, or R_2 and R_9 are bonded together to form a pyrrolidinyl oxindole ring;

wherein R_4 is H₂, N, NH, O, S, or R_4 and A_0 are bonded together to form a triazole ring, or R_4 is N and R_4 and R_2 are bonded together to form a pyrimidine ring;

wherein R_7 is H, Cl, Br, F, OH, CH₃, OCH₃, SCH₃, CN, CCH, CF₃, OCF₃, SCF₃, NO₂, butyl, f-butyl, dimethylamino, phenyl, n-propyl, *l*-propyl, $-NH-C(0)-CH_3$, $-(CH)_2-COOH$, piperazin-1-yl, or R_7 and R_8 are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring;

wherein R_6 , R_8 , R_{14} , R_{16} , R_{25} and R_{27} are independently H, OH, Cl, F, Br, CH_3 , CN, OCH_3 , COOH, NO_2 , CF_3 , R_8 and R_7 bond together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring, or benzene ring, R_{14} and R_{15} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, R_8 and R_9 are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R_{14} and R_{13} are bonded together to form a substituted or unsubstituted saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring;

wherein R_5 , R_9 , R_{17} , R_{24} and R_{28} are independently H, O, OH, Cl, F, Br, NH_2 , CH_3 , CF_3 , OCH_3 , CN, NO_2 , phenyl, $-NH-CH(OH)-CH_3$, $-NH-C(=O)-CH_3$, or R_9 and R_8 are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R_{13} and R_{14} are bonded together to form a substituted or unsubstituted saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring;

wherein R_{10} , R_n , R_{19} , R_{20} , R_{22} and R_{23} are independently H, Cl, or Br, or R_{10} and R_{11} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R_{19} and R_{20} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R_{22} and R_{23} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring;

wherein R_{12} , R_{18} and R_{21} are independently H, COOH, CH_2NH_2 , CH_2OH , methyl, ethyl, propyl, butyl, cyclopentyl, or R_{12} and R_{13} are bonded together to form a pyrrolidinyl oxindole ring;

wherein R_{15} and R_{26} are independently H, Cl, Br, F, OH, CH_3 , OCH_3 , SCH_3 , CN, CF_3 , OCF_3 , SCF_3 , NO_2 , CCH, n-butyl, f-butyl, dimethylamino, phenyl, n-propyl, i-propyl, $-NH-C(=O)-CH_3$, $-(CH_2)_2-COOH$, piperazin -1-yl, or R_{15} and R_{14} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring; and

wherein "— " is a double bond or a single bond.

2. The method of claim 1, wherein the compound of Formula 1, or a stereoisomer, tautomer, pharmaceutically acceptable salt, free base, or prodrug thereof, is selected from the group consisting of:

2,2'-bis[(4-chlorophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL812);
2,2'-bis[(4-chlorophenyl)methylene]carbonic dihydrazide (NCL001);
2,2'-bis[(2-chlorophenyl)methylene]carbonic dihydrazide (NCL002);
2,2'-bis[(4-fluorophenyl)methylene]carbonic dihydrazide (NCL003);
2,2'-bis[(3-fluorophenyl)methylene]carbonic dihydrazide (NCL004);
2,2'-bis[(2-fluorophenyl)methylene]carbonic dihydrazide (NCL005);
2,2'-bis[(4-methoxyphenyl)methylene]carbonic dihydrazide (NCL006);
2,2'-bis[(4-cyanophenyl)methylene]carbonic dihydrazide (NCL007);
2,2'-bis[(2-cyanophenyl)methylene]carbonic dihydrazide (NCL008);
2,2'-bis[(3-cyanophenyl)methylene]carbonic dihydrazide (NCL009);
2,2'-bis[(3-methoxyphenyl)methylene]carbonic dihydrazide (NCL010);
2,2'-bis[[3-(trifluoromethyl)phenyl]methylene]carbonic dihydrazide (NCL011);
2,2'-bis[[4-(trifluoromethyl)phenyl]methylene]carbonic dihydrazide (NCL012);
2,2'-bis[[2-(trifluoromethyl)phenyl]methylene]carbonic dihydrazide (NCL013);
2-[(4-chlorophenyl)methylene]hydrazinecarboxamide (NCL014);
2-[(2-chlorophenyl)methylene]hydrazinecarboximidamide hydrochloride (NCL015);
2-[(2-fluorophenyl)methylene]hydrazinecarboximidamide hydrochloride (NCL016);
2-[(3-fluorophenyl)methylene]hydrazinecarboximidamide hydrochloride (NCL017);
2,2'-bis[(2-methylphenyl)methylene]carbonic dihydrazide (NCL018);
2,2'-bis[(3-methylphenyl)methylene]carbonic dihydrazide (NCL019);
2,2'-bis[(2-chlorophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL020);
2,2'-bis[(4-fluorophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL021);
2,2'-bis[(2-fluorophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL022);
2,2'-bis[(3-fluorophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL023);
2,2'-bis[(4-cyanophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL024);
2,2'-bis[(2-cyanophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL025);
2,2'-bis[(3-cyanophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL026);
2,2'-bis[(4-methoxyphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL027);
2,2'-bis[(2-methoxyphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL028);
2,2'-bis[(3-methoxyphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL029);
2-[(4-chlorophenyl)methylene]hydrazinecarboximidamide hydrochloride (NCL030);
2-[(4-cyanophenyl)methylene]hydrazinecarboximidamide hydrochloride (NCL031);
2-[(2-cyanophenyl)methylene]hydrazinecarboximidamide hydrochloride (NCL032);

2-[(3-cyanophenyl)methylene]hydrazinecarboximidamide hydrochloride (NCL033);
2-[(2-methoxyphenyl)methylene]hydrazinecarboximidamide hydrochloride (NCL034);
2,2'-bis[[4-(trifluoromethyl)phenyl]methylene]carbonimidic dihydrazide hydrochloride (NCL035);
2,2'-bis[[2-(trifluoromethyl)phenyl]methylene]carbonimidic dihydrazide hydrochloride (NCL036);
2,2'-bis[[3-(trifluoromethyl)phenyl]methylene]carbonimidic dihydrazide hydrochloride (NCL037);
2,2'-bis[(4-methylphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL038);
2,2'-bis[(2-methylphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL039);
2,2'-bis[(3-methylphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL040);
2-[[4-(trifluoromethyl)phenyl]methylene]hydrazinecarboximidamide hydrochloride (NCL041);
2-[[2-(trifluoromethyl)phenyl]methylene]hydrazinecarboximidamide hydrochloride (NCL042);
2-[[3-(trifluoromethyl)phenyl]methylene]hydrazinecarboximidamide hydrochloride (NCL043);
2-[(4-methylphenyl)methylene]hydrazinecarboximidamide hydrochloride (NCL044);
2-[(2-methylphenyl)methylene]hydrazinecarboximidamide hydrochloride (NCL045);
2-[(3-methylphenyl)methylene]hydrazinecarboximidamide hydrochloride (NCL046);
2-[(2-chlorophenyl)methylene]hydrazinecarboxamide (NCL047);
2-[(2-fluorophenyl)methylene]hydrazinecarboxamide (NCL048);
2-[(4-cyanophenyl)methylene]hydrazinecarboxamide (NCL049);
2-[(2-cyanophenyl)methylene]hydrazinecarboxamide (NCL050);
2-[(3-cyanophenyl)methylene]hydrazinecarboxamide (NCL051);
2-[(3-chlorophenyl)methylene]hydrazinecarboximidamide hydrochloride (NCL052);
2-[(4-fluorophenyl)methylene]hydrazinecarboximidamide hydrochloride (NCL053);
2,2'-bis[(3-chlorophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL054);
2-[(3-chlorophenyl)methylene]hydrazinecarboxamide (NCL055);
2-[(4-fluorophenyl)methylene]hydrazinecarboxamide (NCL056);
2-[(3-fluorophenyl)methylene]hydrazinecarboxamide (NCL057);
2-[(4-methoxyphenyl)methylene]hydrazinecarboxamide (NCL058);
2-[(3-methoxyphenyl)methylene]hydrazinecarboxamide (NCL059);
2-[[2-(trifluoromethyl)phenyl]methylene]hydrazinecarboxamide (NCL060);
2,2'-bis[1-[4-(trifluoromethyl)phenyl]ethylidene]carbonimidic dihydrazide hydrochloride (NCL061);
2,2'-bis[1-(4-chlorophenyl)ethylidene]carbonimidic dihydrazide hydrochloride (NCL062);

2,2'-bis[4-(trifluoromethyl)phenyl]methylene}carbonothioic dihydrazide (NCL063);
2,2'-bis[(2-cyanophenyl)methylene]carbonothioic dihydrazide (NCL064);
2,2'-bis[(3-cyanophenyl)methylene]carbonothioic dihydrazide (NCL065);
2,2'-bis[(3-fluorophenyl)methylene]carbonothioic dihydrazide (NCL066);
2-[[3-(trifluoromethyl)phenyl]methylene}hydrazinecarboxamide (NCL067);
2-[1-(4-chlorophenyl)ethylidene]-2X1-[4-(trifluoromethyl)phenyl]methylene}carbonimidic dihydrazide hydrochloride (NCL068);
2-[1-(4-chlorophenyl)ethylidene]carbonimidic dihydrazide hydrochloride (NCL069);
2,2'-bis[(3-chlorophenyl)methylene]carbonothioic dihydrazide (NCL070);
2-[(2-methoxyphenyl)methylene]hydrazinecarbothioamide (NCL071);
2-[(4-chlorophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL072);
2-[[1-(4-trifluoromethyl)phenyl]ethylidene}carbonimidic dihydrazide hydrochloride (NCL073);
2-[(2,4-dichlorophenyl)methylene]-2'-[(4-chlorophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL074);
2-{1-[4-(trifluoromethyl)phenyl]ethylidene}-2'-[[4-(trifluoromethyl)phenyl]methylene}carbonimidic dihydrazide hydrochloride (NCL075);
2-[(4-chlorophenyl)methylene]-2'-[(4-methylphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL076);
2-[(4-chlorophenyl)methylene]-2X[4-(trifluoromethyl)phenyl]methylene}carbonimidic dihydrazide hydrochloride (NCL077);
2-[[2-fluoro-4-(trifluoromethyl)phenyl]methylene]-2'-[(4-chlorophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL078);
2-[(4-chlorophenyl)methylene]-2'-[(4-fluorophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL079);
2-{1-[4-(trifluoromethyl)phenyl]ethylidene}-2'-[(4-chlorophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL080);
2-[1-(4-chlorophenyl)ethylidene]-2'-[(4-chlorophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL081);
2-[(2-chlorophenyl)methylene]-2'-[(4-chlorophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL082);
2-[(3-chlorophenyl)methylene]-2'-[(4-chlorophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL083);
2-[(2-fluoro-4-chlorophenyl)methylene]-2'-[(4-chlorophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL084);
2-[(2-cyanophenyl)methylene]-2'-[(4-chlorophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL085);

- 2-[(3-cyanophenyl)methylene]-2'-[(4-chlorophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL086);
- 2-[(4-chlorophenyl)methylene]-2'-[(4-cyanophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL087);
- 2-[(2-fluorophenyl)methylene]-2'-[(4-chlorophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL088);
- 2-[1-(4-chlorophenyl)ethylidene]-2X1-[4-(trifluoromethyl)phenyl]ethylidene}carbonimidic dihydrazide hydrochloride (NCL089);
- N-benzoyl-1-benzoyl-2-[(2-chlorophenyl)methylene]hydrazinecarboximidamide hydrochloride (NCL090);
- N-(4-chlorophenyl)-3-[4-(trifluoromethyl)phenyl]-1 H-1 ,2,4-triazol-5-amine (NCL091);
- N-(4-chlorobenzyl)-3-(4-chlorophenyl)-1 H-1 ,2,4-triazol-5-amine (NCL092);
- 2,2'-bis(2-naphthalenylmethylene)carbonimidic dihydrazide hydrochloride (NCL093);
- 2,2'-bis(cyclohexylmethylene)carbonimidic dihydrazide hydrochloride (NCL094);
- 2,2'-bis(3-furanylmethylene)carbonimidic dihydrazide hydrochloride (NCL095);
- 2,2'-bis(3-phenyl-2-propenylidene)carbonimidic dihydrazide hydrochloride (NCL096);
- 2,2'-bis[(3,4,5-trihydroxyphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL097);
- 2,2'-bis[(3-carboxyphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL098);
- 2,2'-bis[[4-(1 ,1-dimethylethyl)phenyl]methylene}carbonimidic dihydrazide hydrochloride (NCL099);
- 2,2'-bis(phenylmethylene)carbonimidic dihydrazide hydrochloride (NCL100);
- 2,2'-bis[(2,3-dihydroxyphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL101);
- 2,2'-bis[(2-nitrophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL102);
- 2,2'-bis[(2,4-dihydroxyphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL103);
- 2,2'-bis[(2,4,5-trihydroxyphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL104);
- 2,2'-bis[(2,3,4-trihydroxyphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL105);
- 2,2'-bis[(4,5-dihydroxy-3-methoxyphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL1 06);
- 2,2'-bis[(2-hydroxyphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL107);
- 2,2'-bis[(3-hydroxyphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL108);
- 2,2'-bis[(3-nitrophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL109);
- 2,2'-bis[(4-nitrophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL1 10);

- 2,2'-bis[(3,4-dihydroxyphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL1 11);
- 2,2'-bis[(1,1'-biphenyl]-4-ylmethylene)carbonimidic dihydrazide hydrochloride (NCL1 12);
- 2,2'-bis[4-(dimethylamino)phenyl]methylene}carbonimidic dihydrazide hydrochloride (NCL1 13);
- 2,2'-bis[(3,5-dichlorophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL1 14);
- 2,2'-bis[(3,4-dimethoxyphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL 115);
- 2,2'-bis[(1,1'-biphenyl]-2-ylmethylene)carbonimidic dihydrazide hydrochloride (NCL 116);
- 2,2'-bis[(4-hydroxy-3-methoxyphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL 117);
- 2,2'-bis[(2,5-fluorophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL 118);
- 2,2'-bis[(4-acetamidophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL 119);
- 2,2'-bis[[4-(1-methylethyl)phenyl]methylene}carbonimidic dihydrazide hydrochloride (NCL 120);
- 2,2'-bis[(4-propylphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL 121);
- 2,2'-bis[(4-hydroxy-3-nitrophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL 122);
- 2,2'-bis[(3,4-difluorophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL123);
- 2,2'-bis[(2-hydroxy-1-naphthalenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL 124);
- 2,2'-bis[(3-hydroxy-4-methoxyphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL 125);
- 2,2'-bis[(3-ethynylphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL 126);
- 2,2'-bis[(2,4-dichlorophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL 127);
- 2,2'-bis[(2,3,4,5,6-pentafluorophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL 128);
- 2,2'-bis[(2-bromophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL 129);
- 2,2'-bis[(3-bromo-4,5-dimethoxyphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL 130);
- 2,2'-bis[(3-bromophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL 131);
- 2,2'-bis[(4-chloro-6-fluoro-2H-1-benzopyran-3-yl)methylene]carbonimidic dihydrazide hydrochloride (NCL 132);
- 2,2'-bis[(4-bromo-2-furanyl)methylene]carbonimidic dihydrazide hydrochloride (NCL

- 133);
- 2,2'-bis[(4-bromophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL 134);
- 2,2'-bis[(2-bromo-4,5-dimethoxyphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL 135);
- 2,2'-bis[(4-butylphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL 136);
- 2,2'-bis[(2,6-dichlorophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL 137);
- 2,2'-bis(2,3-diphenyl-2-propenylidene)carbonimidic dihydrazide hydrochloride (NCL 138);
- 2,2'-bis(3-quinolinylmethylene)carbonimidic dihydrazide hydrochloride (NCL 139);
- 2,2'-bis[[4-(methylsulfanyl)phenyl]methylene]carbonimidic dihydrazide hydrochloride (NCL 140);
- 2,2'-bis[(5-chlorobenzo[b]thien-3-yl)methylene]carbonimidic dihydrazide hydrochloride (NCL 141);
- 1,3-bis(benzylamino)guanidine hydrochloride NCL 142);
- 2,2'-bis[1-phenylethylidene]carbonimidic dihydrazide hydrochloride (NCL 143);
- 2,2'-bis[(5-bromo-2-furanyl)methylene]carbonimidic dihydrazide hydrochloride (NCL 144);
- 2,2'-bis[(5-chloro-2-furanyl)methylene]carbonimidic dihydrazide hydrochloride (NCL 145);
- 2,2'-bis(1 H-indol-5-ylmethylene)carbonimidic dihydrazide hydrochloride (NCL 146);
- 2,2'-bis(2-quinoxalinylmethylene)carbonimidic dihydrazide hydrochloride (NCL 147);
- 2,2'-bis[[4-(carboxypropenyl)phenyl]methylene]carbonimidic dihydrazide hydrochloride (NCL 148);
- 2,2'-Bis(4-pyridinylmethylene)Carbonimidic dihydrazide hydrochloride (NCL 149);
- 2,2'-bis[3-(4-methoxyphenyl)-2-propenylidene]carbonimidic dihydrazide hydrochloride (NCL 150);
- 2,2'-bis[(4-hydroxyphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL 151);
- 2,2'-bis[(2-hydroxy-3-methylphenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL 152);
- 2,2'-bis[1-(4-chlorophenyl)propylidene]carbonimidic dihydrazide hydrochloride (NCL 153);
- 2,2'-bis[1-(4-chlorophenyl)pentylidene]carbonimidic dihydrazide hydrochloride (NCL 154);
- 2,2'-bis[1-(4-bromophenyl)ethylidene]carbonimidic dihydrazide hydrochloride (NCL 155);
- 2,2'-bis[1-(4-chlorophenyl)butylidene]carbonimidic dihydrazide hydrochloride (NCL 156);
- 2,2'-bis[(2-amino-4-chlorophenyl)methylene]carbonimidic dihydrazide hydrochloride (NCL 157);

- 2,2'-bis[1-(2-hydroxy-4-chlorophenyl)propylidene]carbonimidic dihydrazide hydrochloride (NCL 158);
- 2,2'-bis[(2-hydroxy-4-chlorophenyl)(cyclopentyl)methylene]carbonimidic dihydrazide hydrochloride (NCL 159);
- 2,2'-bis[[4-(trifluoromethoxy)phenyl]methylene]carbonimidic dihydrazide hydrochloride (NCL 160);
- 2,2'-bis[1-(4-piperazinylphenyl)ethylidene]carbonimidic dihydrazide hydrochloride (NCL 161);
- ethyl (E)-N'-((E)-1-(4-chlorophenyl)ethylidene)carbamohydrate (NCL 162);
- 2,2'-bis(2-Oxo-1,2-dihydro-3H-indol-3-ylidene)carbonimidic dihydrazide hydrochloride (NCL 163);
- 2,2'-bis[1-(2-amino-4-chlorophenyl)ethylidene]carbonimidic dihydrazide hydrochloride (NCL 164);
- 2,2'-bis(1-phenyl-2-aminoethylidene)carbonimidic dihydrazide trihydrochloride (NCL 165);
- 2,2'-bis[[4-(trifluoromethylsulfanyl)phenyl]methylene]carbonimidic dihydrazide hydrochloride (NCL 166);
- 2,2'-bis(phenylcarboxymethylene)carbonimidic dihydrazide hydrochloride (NCL 167);
- 2,2'-bis[[2-(1-hydroxyethylamino)-4-chlorophenyl]methylene]carbonimidic dihydrazide hydrochloride (NCL 168);
- 2,2'-bis[(2-amino-4-chlorophenyl)methylene]carbonimidic dihydrazide (NCL 169);
- 2,2'-bis[(2-acetamido-4-chlorophenyl)methylene]carbonimidic dihydrazide (NCL 170);
- 2,2'-bis[[4-(dimethylamino)-2-hydroxyphenyl]methylene]carbonimidic dihydrazide (NCL 171);
- 2,2'-Bis[1-(2-pyridinyl)ethylidene]Carbonimidic dihydrazide hydrochloride (NCL 172);
- 2,2'-bis[1-(4-chloro-2-hydroxyphenyl)ethylidene]carbonimidic dihydrazide hydrochloride (NCL 173);
- 2,2'-bis(4-chloro-2-hydroxyphenylmethylene)carbonimidic dihydrazide hydrochloride (NCL 174);
- 2,2'-Bis(4-chloropyridin-3-ylmethylene)Carbonimidic dihydrazide hydrochloride (NCL 175);
- 2,2'-Bis(2-aminopyridin-3-ylmethylene)Carbonimidic dihydrazide hydrochloride (NCL 176);
- 2,2'-bis[1-(4-chlorophenyl)-2-hydroxyethylidene]carbonimidic dihydrazide hydrochloride (NCL 177);
- 4,6-bis(2-((E)-1-(4-chlorophenyl)ethylidene)hydrazinyl)pyrimidine (NCL 178);
- 4,6-bis(2-((E)-4-chlorobenzylidene)hydrazinyl)pyrimidin-2-amine (NCL 179);

(2Z,2'Z)-2,2'-(pyrimidine-4,6-diylbis(hydrazin-2-yl-1-ylidene))bis(2-(4-chloro phenyl)ethan-1-ol) (NCL 180);

4,6-bis(2-((E)-4-chlorobenzylidene)hydrazinyl)pyrimidine (NCL 181);

6-chloro-N4-(1-phenylethyl)pyrimidine-2,4-diamine (NCL 182);

N4,N6-bis(1-phenylethyl)pyrimidine-4,6-diamine (NCL 183);

N4,N6-bis(1-phenylethyl)pyrimidine-2,4,6-triamine (NCL 184);

4,6-bis(2-((E)-1-(4-chlorophenyl)ethylidene)hydrazinyl)pyrimidine hydrochloride (NCL 185);

N2,N5-bis(1-(4-chlorophenyl)ethyl)pyrazine-2,5-diamine (NCL 186);

4,6-bis(2-((E)-4-chlorobenzylidene)hydrazinyl)pyrimidine hydrochloride (NCL 187);

(E)-2-(1-(4-chlorophenyl)pentylidene)hydrazine-1-carboximidamide hydrochloride (NCL 188);

(2Z,2'Z)-2,2'-(pyrimidine-4,6-diylbis(hydrazin-2-yl-1-ylidene))bis(2-(4-chlorophenyl)ethan-1-ol) hydrochloride (NCL 189);

(Z)-2-(1-(4-chlorophenyl)-2-hydrazinylethylidene)hydrazine-1-carboximidamide hydrochloride (NCL 190);

(E)-2-(1-(4-chlorophenyl)ethylidene)hydrazine-1-carboximidamide hydrochloride (NCL 191);

(Z)-2-(2-carbamimidoylhydrazono)-2-phenylacetic acid hydrochloride (NCL 192);

4,6-bis(2-((E)-4-bromobenzylidene)hydrazinyl)pyrimidin-2-amine (NCL193);

N',N''-(2-aminopyrimidine-4,6-diyl)di(benzohydrazide) (NCL194);

4,6-bis(2-((E)-4-methylbenzylidene)hydrazinyl)pyrimidin-2-amine (NCL195);

4,4'-((1 E,1'E)-((2-aminopyrimidine-4,6-diyl)bis(hydrazin-2-yl-1-ylidene))bis(methanylylidene))diphenol (NCL196);

3,3'-((1 E,1'E)-((2-aminopyrimidine-4,6-diyl)bis(hydrazin-2-yl-1-ylidene))bis(methanylylidene))diphenol (NCL197);

4,6-bis(2-((E)-4-(tert-butyl)benzylidene)hydrazinyl)pyrimidin-2-amine dihydrochloride (NCL198);

4,6-bis(2-((E)-benzylidene)hydrazinyl)pyrimidin-2-amine (NCL199);

4,6-bis(2-((E)-4-(tert-butyl)benzylidene)hydrazinyl)pyrimidin-2-amine (NCL200);

4,4'-((1 E,1'E)-((2-aminopyrimidine-4,6-diyl)bis(hydrazin-2-yl-1-ylidene))bis(methanylylidene))bis(N,N-dimethylaniline) (NCL201);

2,2'-((1 E,1'E)-((2-aminopyrimidine-4,6-diyl)bis(hydrazin-2-yl-1-ylidene))bis(methanylylidene))diphenol (NCL202);

4,6-bis(2-((E)-cyclohexylmethylene)hydrazinyl)pyrimidin-2-amine dihydrochloride (NCL203);

4,6-bis(2-((E)-1-(4-chlorophenyl)ethylidene)hydrazinyl)pyrimidin-2-amine (NCL204);

4,6-bis(2-((E)-2-chlorobenzylidene)hydrazinyl)pyrimidin-2-amine (NCL205);
4,6-bis(2-((E)-4-methylbenzylidene)hydrazinyl)-1,3,5-triazin-2-amine (NCL206);
2,2'-((1 E,rE)-((6-amino-1,3,5-triazine-2,4-diyl)bis(hydrazin-2-yl-1-ylidene))bis(methanylylidene))diphenol (NCL207);
4,6-bis(2-((E)-1-(4-chlorophenyl)ethylidene)hydrazinyl)-1,3,5-triazin-2-amine (NCL208);
3,3'-((1 E,1'E)-((6-amino-1,3,5-triazine-2,4-diyl)bis(hydrazin-2-yl-1-ylidene))bis(methanylylidene))diphenol (NCL209);
4,6-bis(2-((E)-4-(trifluoromethyl)benzylidene)hydrazinyl)-1,3,5-triazin-2-amine (NCL210);
4,4'-((1 E,rE)-((6-amino-1,3,5-triazine-2,4-diyl)bis(hydrazin-2-yl-1-ylidene))bis(methanylylidene))diphenol (NCL211);
4,6-bis(2-((E)-4-bromobenzylidene)hydrazinyl)-1,3,5-triazin-2-amine (NCL212);
4,6-bis(2-((E)-cyclohexylmethylene)hydrazinyl)-1,3,5-triazin-2-amine (NCL213);
4,6-bis(2-((E)-benzylidene)hydrazinyl)-1,3,5-triazin-2-amine (NCL214);
2,2'-bis[1-(4-chloro-2-fluorophenyl)ethylidene]carbonimidic dihydrazide hydrochloride (NCL215);
N',2-bis((E)-4-chloro-2-fluorobenzylidene)hydrazine-1-carboximidhydrazide hydrochloride (NCL216);
N',2-bis((E)-1-(p-tolyl)ethylidene)hydrazine-1-carboximidhydrazide hydrochloride (NCL217);
4-((E)-(2-(2-amino-6-(2-((E)-4-((diethoxyphosphoryl)oxy)benzylidene)hydrazinyl)pyrimidin-4-yl)hydrazono)methyl)phenyl diethyl phosphate (NCL218);
2,2'-bis{1-[4-(t-butyl)phenyl]ethylidene}carbonimidic dihydrazide hydrochloride (NCL219);
4,6-bis(2-((E)-4-fluorobenzylidene)hydrazinyl)pyrimidin-2-amine (NCL220);
4,6-bis(2-((E)-4-(trifluoromethyl)benzylidene)hydrazinyl)pyrimidin-2-amine (NCL221);
4,6-bis(2-((E)-3,4-difluorobenzylidene)hydrazinyl)pyrimidin-2-amine (NCL222);
N,N'-(((1 E,1'E)-((2-aminopyrimidine-4,6-diyl)bis(hydrazin-2-yl-1-ylidene))bis(methanylylidene))bis(4,1-phenylene))diacetamide (NCL223);
ethyl 2-((E)-4-chlorobenzylidene)-1-((E)-N'-((E)-4-chlorobenzylidene)carbamo-hydrazonoyl)hydrazine-1-carboxylate (NCL224);
isobutyl 2-((E)-4-chlorobenzylidene)-1-((E)-N'-((E)-4-chlorobenzylidene)carbamo-hydrazonoyl)hydrazine-1-carboxylate (NCL225);
2-((E)-4-chlorobenzylidene)-1-((E)-N'-((E)-4-chlorobenzylidene)carbamo-hydrazonoyl)-N-ethylhydrazine-1-carboxamide (NCL226);
N-benzyl-2-((E)-4-chlorobenzylidene)-1-((E)-N'-((E)-4-chlorobenzylidene)carbamo-hydrazonoyl)hydrazine-1-carboxamide (NCL227);
2-((E)-4-chlorobenzylidene)-1-((E)-N'-((E)-4-chlorobenzylidene)carbamo-hydrazonoyl)-N-

hexylhydrazine-1-carboxamide (NCL228);
2-((E)-4-chlorobenzylidene)-1-((E)-N'-((E)-4-chlorobenzylidene)carbamohydrazoneyl)-N-(furan-2-ylmethyl)hydrazine-1-carboxamide (NCL229);
4,6-bis(2-((E)-4-methoxybenzylidene)hydrazinyl)pyrimidin-2-amine (NCL230);
(E)-2-(1-(4-(tert-butyl)phenyl)ethylideneamino)guanidine (NCL231);
(E)-2-(4-(tert-butyl)benzylideneamino)guanidine (NCL232);
(E)-2-(1-(4-chlorophenyl)butylidene)hydrazine-1-carboximidamide hydrochloride (NCL233);
(E)-2-(1-(4-chlorophenyl)propylidene)hydrazine-1-carboximidamide (NCL234);
(E)-2-(4-chloro-2-fluorobenzylidene)hydrazine-1-carboximidamide (NCL235);
(E)-2-(1-(4-chloro-2-fluorophenyl)ethylidene)hydrazine-1-carboximidamide (NCL236);
(E)-2-(1-(4-chloro-2-hydroxyphenyl)-2-cyclohexylethylideneamino)guanidine (NCL237);
4,6-bis(2-((E)-(6-chloropyridin-3-yl)methylene)hydrazinyl)pyrimidin-2-amine (NCL238);
4,6-bis(2-((E)-pyridin-3-ylmethylene)hydrazinyl)pyrimidin-2-amine (NCL239);
4,6-bis(2-((E)-pyridin-2-ylmethylene)hydrazinyl)pyrimidin-2-amine (NCL240);
4,6-bis(2-((E)-pyridin-4-ylmethylene)hydrazinyl)pyrimidin-2-amine (NCL241);
4,6-bis(2-((E)-2,5-dihydroxybenzylidene)hydrazinyl)pyrimidin-2-aminium 2-formyl-4-hydroxyphenolate (NCL242);
4,6-bis(2-((E)-3,4-dihydroxybenzylidene)hydrazinyl)pyrimidin-2-amine (NCL243);
4,6-bis(2-((E)-2,3-dihydroxybenzylidene)hydrazinyl)pyrimidin-2-aminium 2-formyl-6-hydroxyphenolate (NCL244);
4,6-bis(2-((E)-naphthalen-1-ylmethylene)hydrazinyl)pyrimidin-2-amine (NCL245);
4,6-bis(2-((1 E,2E)-3-phenylallylidene)hydrazinyl)pyrimidin-2-amine (NCL246);
4,6-bis(2-((E)-3,4,5-trihydroxybenzylidene)hydrazinyl)pyrimidin-2-amine (NCL247);
(E)-2-(naphthalen-1-ylmethylideneamino)guanidine (NCL248);
(E)-2-((E)-3-phenylallylideneamino)guanidine (NCL249);
(1 E,1'E)-N,N'-(ethane-1,2-diyl)bis(1-(4-chlorophenyl)methanimine) (NCL250);
(1 E,1'E)-N,N'-(butane-1,4-diyl)bis(1-(4-chlorophenyl)methanimine) (NCL251);
(1 E,1'E)-N,N'-(propane-1,3-diyl)bis(1-(4-chlorophenyl)methanimine) (NCL252);
(E)-2-(4-(dimethylamino)benzylideneamino)guanidine (NCL253);
(E)-2-(1-(4-chlorophenyl)hexylidene)hydrazine-1-carboximidamide hydrochloride (NCL254);
4,6-bis(2-((E)-[1 J'-biphenyl]-4-ylmethylene)hydrazinyl)pyrimidin-2-amine (NCL255);
4,6-bis(2-((E)-2,4-dihydroxybenzylidene)hydrazinyl)pyrimidin-2-amine (NCL256);
(E)-2-((2-hydroxynaphthalen-1-yl)methylene)hydrazine-1-carboximidamide hydrochloride (NCL257);
N1,N4-bis(4-chlorobenzyl)butane-1,4-diamine (NCL258);

(E)-2-(1-(4-chlorophenyl)-2-cyclohexylethylidene)hydrazine-1-carboximidamide hydrochloride (NCL259);
N1,N2-bis(4-chlorobenzyl)ethane-1,2-diamine (NCL260);
(E)-2-(naphthalen-2-ylmethylene)hydrazine-1-carboximidamide hydrochloride (NCL261);
4,6-bis(2-((E)-3-phenylpropylidene)hydrazinyl)pyrimidin-2-amine (NCL262);
(E)-2-(2-fluoro-4-(trifluoromethyl)benzylidene)hydrazine-1-carboximidamide hydrochloride (NCL263);
4,6-bis(2-((E)-naphthalen-2-ylmethylene)hydrazinyl)pyrimidin-2-amine (NCL264);
(E)-2-(1-(4-chlorophenyl)-octylideneamino)guanidine (NCL265);
(E)-2-(1-(4-chlorophenyl)-3-cyclopentylpropylideneamino)guanidine (NCL266);
(E)-4-chloro-6-(2-(4-chlorobenzylidene)hydrazinyl)pyrimidin-2-amine (NCL267);
(E)-4-chloro-6-(2-(4-methylbenzylidene)hydrazinyl)pyrimidin-2-amine (NCL268);
(Z)-2-(1-(1H-indol-3-yl)ethylidene)hydrazinecarboximidamide (NCL269);
2,2'-Bis(1-(1H-indol-3-yl)ethylidene)hydrazidecarboximidamide (NCL270);
2,2'-Bis(1-(4-chlorophenyl)hexylidene)hydrazidecarboximidamide (NCL271);
2,2'-Bis(1-(4-chlorophenyl)octylidene)hydrazidecarboximidamide (NCL272);
2,2'-Bis(1-(4-chlorophenyl)-3-cyclopentylpropylidene)hydrazidecarboximidamide (NCL273);
2,2'-Bis((1H-indol-3-yl)methylene)hydrazine carboximidamide (NCL274); and
2,2'-Bis(1-(4-chlorophenyl)-2-ethoxyethylidene)hydrazidecarboximidamide (NCL275).

3. The method of any one of the preceding claims, wherein the compound of Formula I, or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof comprises the following features:

wherein A_0 is C;

wherein A_1 is N; or Formula VII;

wherein A_2 is N; or NH;

wherein $A_3, A_4, A_6, A_7, A_{11}, A_{12}, A_{14}, A_{15}$, are N; or C;

wherein $A_5, A_{13}, A_{23}, A_{24}, A_{25}, A_{26}$ and A_{27} are C;

wherein A_8 and A_{21} are S;

wherein A_9 is NH;

wherein A_{10} is N;

wherein A_{22} is -N-CH-; -N-C(CH₃)-; or -N-C(CH₂OH)-;

wherein R_1 is H; Formula II; Formula III; cycloalkyl;

wherein R_2 is H; methyl; ethyl; CH₂NHNH₂; CH₂OH; butyl; cyclopentyl; or Formula VII and R_2 is bonded to R_4 , to form a pyrimidine ring;

wherein R_3 is NH₂; Formula IV; Formula V; Formula VI; NH₂, NH-N-CH-cycloalkyl; or O-CH₂-CH₃;

wherein R_4 is NH; O; S; or R_4 is N and R_4 and R_2 are bonded together to form a pyrimidine ring;

wherein R_7 is H; F; Cl; CF₃; methyl; R_7 and R_8 are bonded together to form an unsubstituted, benzene ring; OH; *t*-butyl; phenyl; dimethylamino; *l*-propyl; *n*-propyl; CN; CCH; *n*-butyl; SCH₃; R_7 and R_8 are bonded together to form an unsubstituted, unsaturated heterocyclic ring; OCH₃; Br; OCF₃; piperazin-1-yl; or SCF₃;

wherein R_6 , R_8 , R_{14} , and R_{16} are independently H; OH; F; OCH₃; CF₃; methyl; Cl; CN; Br; R_8 and R_7 are bonded together to form an unsubstituted, benzene ring; R_8 and R_7 are bonded together to form an unsubstituted, unsaturated heterocyclic ring; R_{14} and R_{15} are bonded together to form an unsubstituted, benzene ring; or R_{14} and R_{15} are bonded together to form an unsubstituted, unsaturated heterocyclic ring;

wherein R_5 , R_9 , R_{13} , and R_{17} are independently H; OH; NH₂; Cl; F; OCH₃; OH; -NH-CH(OH)-CH₃;

wherein R_{12} is H; methyl; ethyl; CH₂OH; or cyclopentyl;

wherein R_{15} is H; F; Cl; CF₃; methyl; R_7 and R_8 are bonded together to form an unsubstituted, benzene ring; OH; *t*-butyl; phenyl; dimethylamino; *l*-propyl; *n*-propyl; CN; CCH; *n*-butyl; SCH₃; R_{15} and R_{14} are bonded together to form an unsubstituted, unsaturated heterocyclic ring; OCH₃; Br; OCF₃; piperazin-1-yl; or SCF₃;

wherein R_{24} and R_{28} are independently H; OH; or Cl;

wherein R_{25} and R_{27} are independently H; or OH;

wherein R_{26} is H; CH_3 ; Br; Cl; OH; dimethylamino; $-O-P(O)(OEt)_2$; CF_3 ; or F; and

wherein "—" is independently a single or a double bond.

4. The method according to any one of the preceding claims, wherein the compound is selected from the group comprising: NCL008; NCL009; NCL023; NCL025; NCL026; NCL028; NCL029; NCL036; NCL037; NCL039; NCL040; NCL050; NCL061; NCL062; NCL064; NCL065; NCL068; NCL075; NCL076; NCL078; NCL079; NCL080; NCL081; NCL084; NCL085; NCL086; NCL088; NCL089; NCL090; NCL092; NCL094; NCL095; NCL097; NCL098; NCL099; NCL101; NCL104; NCL105; NCL106; NCL108; NCL111; NCL112; NCL114; NCL115; NCL116; NCL118; NCL119; NCL121; NCL122; NCL123; NCL124; NCL125; NCL126; NCL130; NCL131; NCL132; NCL133; NCL135; NCL136; NCL137; NCL138; NCL139; NCL140; NCL141; NCL144; NCL145; NCL146; NCL147; NCL148; NCL150; NCL152; NCL153; NCL154; NCL156; NCL157; NCL158; NCL159; NCL161; NCL162; NCL164; NCL165; NCL166; NCL167; NCL168; NCL169; NCL170; NCL171; NCL172; NCL173; NCL174; NCL176; NCL177; NCL178; NCL179; NCL180; NCL181; NCL183; NCL184; NCL185; NCL186; NCL187; NCL188; NCL189; NCL190; NCL193; NCL194; NCL195; NCL196; NCL197; NCL198; NCL199; NCL200; NCL201; NCL202; NCL203; NCL204; NCL205; NCL206; NCL207; NCL208; NCL209; NCL210; NCL211; NCL212; NCL213; NCL215; NCL216; NCL217; NCL218; NCL219; NCL220; NCL221; NCL222; NCL223; NCL224; NCL225; NCL226; NCL227; NCL228; NCL229; NCL230; NCL231; NCL232; NCL233; NCL234; NCL235; NCL236; NCL237; NCL238; NCL239; NCL240; NCL241; NCL242; NCL243; NCL244; NCL245; NCL246; NCL247; NCL248; NCL249; NCL250; NCL251; NCL252; NCL253; NCL254; NCL255; NCL256; NCL257; NCL258; NCL259; NCL260; NCL261; NCL262; NCL263; NCL264; NCL265; NCL266; NCL267; NCL268; NCL269; NCL270; NCL271; NCL272; NCL273; NCL274; and NCL275.
5. The method according to any one of the preceding claims, wherein the compound is selected from the group comprising: NCL028; NCL040; NCL062; NCL078; NCL079; NCL080; NCL081; NCL084; NCL088; NCL089; NCL097; NCL099; NCL123; NCL146; NCL157; NCL158; NCL177; NCL179; NCL188; NCL193; NCL195; NCL196; NCL197; NCL199; NCL202; NCL204; NCL205; NCL215; NCL216; NCL217; NCL219; NCL221; NCL245 and NCL246.
6. The method according to any one of the preceding claims, wherein the compound is selected from the group comprising: NCL062; NCL078; NCL079; NCL080; NCL081; NCL084; NCL089; NCL097; NCL099; NCL157; NCL158; NCL179; NCL188; NCL193;

NCL195; NCL196; NCL199; NCL204; NCL216; NCL217; NCL219; NCL221 ; NCL245 and NCL246.

7. The method according to any one of the preceding claims, wherein the compound is selected from the group comprising: NCL062; NCL089; NCL097; NCL099; NCL157; NCL179; NCL188; NCL193; NCL195; NCL196; NCL216; NCL219; and NCL221 .
8. The method according to any one of the preceding claims, wherein the compound is selected from the group comprising: NCL062; NCL097; NCL099; NCL157; NCL179; NCL188; NCL195; and NCL196.
9. The method according to any one of the preceding claims, wherein the compound is a chloride salt.
10. The method according to any one of the preceding claims, wherein the compound is not a compound selected from the group comprising: NCL812 and NCL062.
11. The method according to any one of the preceding claims, wherein the subject is an animal most preferably selected from the group comprising: human, canine, feline, bovine, ovine, caprine, porcine, avian, piscine and equine species.
12. The method according to any one of the preceding claims, wherein the compound is administered to the subject in a dose in the range of 0.1 mg/kg to 250 mg/kg bodyweight.
13. The method according to any one of the preceding claims, wherein the protozoan agent is selected from the group of protozoa genera comprising: Acanthamoeba, Babesia, Balamuthia, Balantidium, Besnoitia , Blastocystis, Chilomastix, Cochlosoma, Cryptosporidium, Cyclospora, Cystoisospora, Cytauxzoon, Dientamoeba, Eimeria, Endolimax, Entamoeba, Giardia, Haemoproteus, Hammondia, Hartmannella, Hepatozoon, Hexamita, Histomonas, Isospora, Leishmania (including subgenus Viannia), Leucocytozoon, Naegleria, Neospora , Pentatrichomonas, Plasmodium (including subgenera Plasmodium (Bennettinia) (birds); Plasmodium (Giovannolaia) (birds); Plasmodium (Haemamoeba) (birds); Plasmodium (Huffia) (birds); Plasmodium (Laverania) (higher primates, includes Plasmodium falciparum); Plasmodium (Novyella) (birds); Plasmodium (Paraplasmodium) (lizards); Plasmodium (Plasmodium) (higher primates, includes Plasmodium brasilianum, cynomolgi, inui, knowlesi, malariae); Plasmodium (Sauramoeba) (lizards); Plasmodium (Vinckeia)), Sappinia, Sarcocystis, Tetratrichomonas, Theileria, Toxoplasma, Trichomonas, Tritrichomonas, Trypanosoma (Subgenera Duttonella, Herpetosoma, Nannomonas, Schizotrypanum, Trypanozoon), Tyzzeria and Wenyonella.

14. The method according to any one of the preceding claims, wherein the infection or colonisation is caused by a mixture of at least two protozoan agents.
15. The method according to any one of the preceding claims, wherein the protozoan agent is resistant to one or more compounds selected from the group comprising:

Chemical Class	Examples
4-aminoquinoline	Amodiaquine, chloroquine, hydroxychloroquine, piperazine (bis-4-aminoquinoline)
8-aminoquinoline	Bulaquine, pamaquine, Primaquine, tafenoquine
Acetamide	Thiolutin
Acridine dye	Acriflavine, mepacrine (quinacrine)
Alkylphosphocholine	Miltefosine
Allylamine	Terbinafine
Aminoglycosides	Paromomycin
Aminophenanthridium	Homidium, isometamidium chloride,
Aminopyridine antimalarials	MMV390048
Antimonials, pentavalent	Sodium stibogluconate, meglumine antimoniate
Arsenicals (trivalent & pentavalent)	Acetarsol (5+), arsthinol (3+), carbarsone (5+), difetarsone (5+), glycoarsol (5+), melarsomine (3+), melarsoprol (3+), nitarson (5+), oxophenarsine (3+), roxarsone (5+), tryparsamide (5+)
Arylaminoalcohol	Halofantrine, lumefantrine, quinine/quinidine
Azo naphthalene dyes	Trypan blue, trypan red
Azoles (triazoles and imidazoles)	Albaconazole, itraconazole, ketoconazole, posoconazole, ravuconazole
Benzamide	Zoxamide
Benzenediol	Resveratrol
Benzimidazoles and probenzimidazoles	Albendazole, fenbendazole, febantel, mebendazole, omeprazole
Bicyclohexylammonium	Fumagillin
Carbamate	Disulfiram
Cinnamamido adenosine	Puromycin
Coumarin	Flocoumafen
Diamidines	Amicarbalide, diminazene diacetate, imidocarb dipropionate, pafuramidine, pentamidine isethionate, phenamidine isethionate, propamidine, stilbamidine
Dichloroacetamide	Clefamide, Etofamide, Teclozan
Dichloroacetamide	Diloxanide furoate
Difluoromethylornithine	Eflornithine
Dihydrofolate reductase/thymidylate synthase inhibitors	Diaveridine, ormetoprim, pyrimethamine, trimethoprim
Dihydroorotate dehydrogenase (DHODH) inhibitors	
Dinitroaniline	Trifluralin, oryzalin
Dinitrocarbanilide + pyrimidinol	Nicarbazin
Dithiocarbamate	Thiram
Ethoxybenzoic acid	Ethopabate
Fluoroquinolones	Ciprofloxacin, enrofloxacin, marbofloxacin
Guanidines	Chlorproguanil, cycloproguanil, lauroguanidine, proguanil, Robenidine
Halogenated 8-hydroxyquinoline	Iodoquinol, chlorquinaldol, tilbroquinol, broxyquinoline, diiodohydroxyquinoline, cloquinol
Hydroxyoxo-cyclohexenecarbaldehyde oxime	Sethoxydim, tralkoxydim, alloxymid, clethodim and cycloxydim
Hydroxyquinolones	Buquinolate, decoquinolate, nequinolate
Imidazolopiperazine	Kaf1 56
Isoquinoline	Emetine/dehydroemetine
Lincosamides	Clindamycin, lincomycin
Macrolides	Azithromycin, clarithromycin, erythromycin, roxithromycin, spiramycin
Methylquinolinium	Quinapyramine, quinuronium sulfate
Miscellaneous	Pyridaben
Naphthoquinones	Atovaquone, buparvaquone, parvaquone

Naphthyridine	Pyronaridine
Nitrobenzamides	Aklomide, dinitolmide
Nitrofurans	Nifurtimox, furaltodone, furazolidone, nifuratel, nifuroxime, nifursol
Nitroimidazoles	Azanidazole, benznidazole, carnidazole, dimetridazole, fexnidazole, ipronidazole, metronidazole, nimorazole, ornidazole, propenidazole, ronidazole, satranidazole, secnidazole, ternidazole, tinidazole
Nitrothiazoles	Nitazoxanide, aminitrozole (nithiamide), forminitrazole, nirdazole, tenonitrozole
Organometallic antiprotozoal	Auranofin, ferroquine
Oxaborole (including benzoxaboroles)	SCYX-71 58
Phenoxyphenol	Triclosan
phenylsulfamide	Tolyfluanid
Phosphonic acid derivative	Fosmidomycin
Phosphonomethylglycine	Glyphosate
Phosphoramidothioic acid	Amipprofos-methyl
Polyene	Amphotericin B, mepartricin, hachimycin, Hamycin
Polyether ionophores	Laidlomycin, lasalocid, maduramicin, monensin, narasin, salinomycin, semduramicin
Polypeptide	Bacitracin (zinc, methylene disalicylate), cecropins, cyclosporins, dermaseptin, magainins, tachyplesin, thiostrepton
Polysulfonated naphthylamine	Suramin
Propylphosphonic acid	Fosmidomycin
Purinamine	Arprinocid
Pyrazolopyran	
Pyrazolopyrimidine	Allopurinol
Pyridinols	Clopidol
Pyrimidine	Fenarimol
Pyrrolidinediol	Anisomycin
Quinazolinone	Febrifugine, halofuginone
Quinoline	Mefloquine, nequinatate (methyl benzoquate), quinfamide, tiliquinol
Quinoxaline	Carbadox
Rifamycin	Rifaximin
Spiroindolone	KAE609 (formerly NITD609), cipargamin
Strobilurin	Fluacrypyrim, azoxystrobin, trifloxystrobin, dimoxystrobin
Sulfonamides	Sulfadiazine, sulfadimethoxine, sulfadoxine, sulfaguandine, sulfamethazine (sulfadimidine), sulfamethoxazole, sulfanitran, sulfaquinoxaline, sulfamethoxyypyrazine, cyazofamid
Sulphone	Dapsone
Tetracyclines	Chlortetracycline, doxycycline, oxytetracycline, tetracycline, tigecycline
Tetraoxanes	
Thiamine analogs	Amprolium
Thiophenone	Thiolactomycin
Translation elongation factor 2 (eEF2) inhibitor	DDD1 07498
Triazine	Clazuril, diclazuril, ponazuril, toltrazuril
Triazole	Bitertanol
Trioxane (sesquiterpene lactones, artemisinins)	Artemether, artesunate, dihydroartemisinin, artemotil, artemisinin, arteether, artemisone
Trioxolane (including ozonides)	Arterolane, OZ277, OZ439

16. The method according to claim 15 wherein the protozoan agent is resistant to the compound when the protozoan agent is exposed to the compound at a concentration range selected from the following: 0.001 $\mu\text{g/mL}$ - 10,000 $\mu\text{g/mL}$; 0.01 $\mu\text{g/mL}$ - 1000 $\mu\text{g/mL}$; 0.10 $\mu\text{g/mL}$ - 100 $\mu\text{g/mL}$; and 1 $\mu\text{g/mL}$ - 50 $\mu\text{g/mL}$.
17. The method according to any one of the preceding claims, wherein the protozoan infection or colonisation in the subject is a zoonosis.

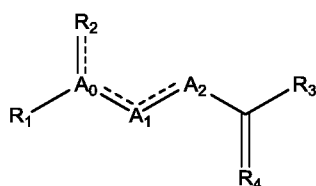
18. The method according to any one of the preceding claims, wherein the protozoan infection or colonisation in the subject substantially causes an indication selected from the group comprising: Trypanosomosis (caused by the order, Kinetoplastorida of the family, Trypanosamidae); Amboebiasis (caused by the subphylum, Sarcodina, of the order, Amoebidorida, of the family Endamoebidae); Babesiosis (caused by the class, Piroplasmida, of the family, Babesiidae); Balantidiosis (caused by the phylum, Ciliphora, of the order, Trichostomatorida, of the family Balantidiidae); Chagas Disease (caused by the order, Kinetoplastorida, of the family, Trypanosomatidae); Cryptosporidiosis (caused by the subclass, Coccidea, of the family, Cryptosporidiidae); Giardiosis (caused by the class, Zoomastigophora, of the order, Diplomonadida, of the family, Diplomonadida, including *Giardia lamblia*); Leishmaniasis (caused by the class, Zoomastigophora, of the family, Trypanosomatidae, of the genus, *Leishmania*); Malaria (caused by the genus, *Plasmodium*, including *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*); Sarcocystosis (caused by the subclass, Coccidia, of the order Eucoccidiorida, of the family Sarcocystidae); Toxoplasmosis (caused by the subclass, Coccidia, of the order, Eucoccidiorida, of the family, Sarcocystidae, including *Toxoplasma gondii*); Cyclosporiasis (caused by the species, *Cyclospora cayetanensis*); Infections caused by free-living Amoebae (caused by *Naegleria*, *Acanthamoeba* and/or *Balamuthia*); Malaria in Non-human Primates (caused by the genus, *Plasmodium*); Microsporidiosis (caused by *Enterocytozoon bienersi*, *Encephalitozoon intestinalis* and/or *E. cuniculi*); Atypical Human Trypanosomosis (*T. lewisi*, *T. evansi*, *T. brucei*, *T. vivax*, and/or *T. congolense*); Trichomoniasis (caused by *Trichomonas vaginalis*); Amoebic dysentery (caused by *Entamoeba histolyticum*); and Acanthamoebiasis (caused by *Acanthamoeba*).
19. The method according to any one of the preceding claims, wherein the therapeutically effective amount of compound of Formula I, or a therapeutically acceptable salt thereof, is administered to the subject by oral administration.
20. The method according to any one of the preceding claims, wherein the therapeutically effective amount of compound of Formula I, or a therapeutically acceptable salt thereof, is administered to the subject together with a second antimicrobial agent selected from the group consisting of:

Chemical Class	Examples
4-aminoquinoline	Amodiaquine, chloroquine, hydroxychloroquine, piperazine (bis-4-aminoquinoline)
8-aminoquinoline	Bulaquine, pamaquine, Primaquine, tafenoquine
Acetamide	Thiolutin
Acridine dye	Acriflavine, mepacrine (quinacrine)
Alkylphosphocholine	Miltefosine

Allylamine	Terbinafine
Aminoglycosides	Paromomycin
Aminophenanthridium	Homidium, isometamidium chloride,
Aminopyridine antimalarials	MMV390048
Antimonials, pentavalent	Sodium stibogluconate, meglumine antimoniate
Arsenicals (trivalent & pentavalent)	Acetarsol (5+), arsthinol (3+), carbarsone (5+), difetarsone (5+), glycobiarsol (5+), melarsomine (3+), melarsoprol (3+), nitarson (5+), oxophenarsine (3+), roxarsone (5+), tryparsamide (5+)
Arylaminoalcohol	Halofantrine, lumefantrine, quinine/quinidine
Azo naphthalene dyes	Trypan blue, trypan red
Azoles (triazoles and imidazoles)	Albaconazole, itraconazole, ketoconazole, posoconazole, ravuconazole
Benzamide	Zoxamide
Benzenediol	Resveratrol
Benzimidazoles and probenzimidazoles	Albendazole, fenbendazole, febantel, mebendazole, omeprazole
Bicyclohexylammonium	Fumagillin
Carbamate	Disulfiram
Cinnamamido adenosine	Puromycin
Coumarin	Flocoumafen
Diamidines	Amicarbalide, diminazene diacetate, imidocarb dipropionate, pafuramidine, pentamidine isethionate, phenamidine isethionate, propamidine, stilbamidine
Dichloroacetamide	Clefamide, Etofamide, Teclozan
Dichloroacetamide	Diloxanide furoate
Difluoromethylornithine	Eflornithine
Dihydrofolate reductase/thymidylate synthase inhibitors	Diaveridine, ormetoprim, pyrimethamine, trimethoprim
Dihydroorotate dehydrogenase (DHODH) inhibitors	
Dinitroaniline	Trifluralin, oryzalin
Dinitrocarbanilide + pyrimidinol	Nicarbazin
Dithiocarbamate	Thiram
Ethoxybenzoic acid	Ethopabate
Fluoroquinolones	Ciprofloxacin, enrofloxacin, marbofloxacin
Guanidines	Chloroproguanil, cycloguanil, lauroguadine, proguanil, Robenidine
Halogenated 8-hydroxyquinoline	Iodoquinol, chlorquinaldol, tilbroquinol, broxyquinoline, diiodohydroxyquinoline, clioquinol
Hydroxyoxo-cyclohexenecarbaldehyde oxime	Sethoxydim, tralkoxydim, alloxydim, clethodim and cycloxydim
Hydroxyquinolones	Buquinolate, decoquinolate, nequinolate
Imidazolopiperazine	Kaf1 56
Isoquinoline	Emetine/dehydroemetine
Lincosamides	Clindamycin, lincomycin
Macrolides	Azithromycin, clarithromycin, erythromycin, roxithromycin, spiramycin
Methylquinolinium	Quinapyramine, quinuronium sulfate
Miscellaneous	Pyridaben
Naphthoquinones	Atovaquone, buparvaquone, parvaquone
Naphthyridine	Pyronaridine
Nitrobenzamides	Aklomide, dinitolmide
Nitrofurans	Nifurtimox, furaltodone, furazolidone, nifuratel, nifuroxime, nifursol
Nitroimidazoles	Azanidazole, benznidazole, carnidazole, dimetridazole, fexnidazole, ipronidazole, metronidazole, nimorazole, ornidazole, propenidazole, ronidazole, satranidazole, secnidazole, ternidazole, tinidazole
Nitrothiazoles	Nitazoxanide, aminitrozole (nithiamide), forminitrazole, niridazole, tenonitrozole
Organometallic antiprotozoal	Auranofin, ferroquine
Oxaborole (including benzoxaboroles)	SCYX-71 58
Phenoxyphenol	Triclosan
phenylsulfamide	Tolyfluanid
Phosphonic acid derivative	Fosmidomycin
Phosphonomethylglycine	Glyphosate
Phosphoramidothioic acid	Amipprofos-methyl

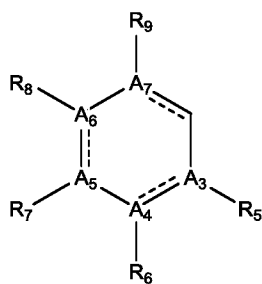
Polyene	Amphotericin B, mepartricin, hachimycin, Hamycin
Polyether ionophores	Laidlomycin, lasalocid, maduramicin, monensin, narasin, salinomycin, semduramicin
Polypeptide	Bacitracin (zinc, methylene disalicylate), cecropins, cyclosporins, dermaseptin, magainins, tachyplesin, thiostrepton
Polysulfonated naphthylamine	Suramin
Propylphosphonic acid	Fosmidomycin
Purinamine	Arprinocid
Pyrazolopyran	
Pyrazolopyrimidine	Allopurinol
Pyridinols	Clopidol
Pyrimidine	Fenarimol
Pyrrolidinediol	Anisomycin
Quinazolinone	Febrifugine, halofuginone
Quinoline	Mefloquine, nequinatate (methyl benzoquate), quinfamide, tiliquinol
Quinoxaline	Carbadox
Rifamycin	Rifaximin
Spiroindolone	KAE609 (formerly NITD609), cipargamin
Strobilurin	Fluacrypyrim, azoxystrobin, trifloxystrobin, dimoxystrobin
Sulfonamides	Sulfadiazine, sulfadimethoxine, sulfadoxine, sulfaguandine, sulfamethazine (sulfadimidine), sulfamethoxazole, sulfanitran, sulfaquinoxaline, sulfamethoxypyrazine, cyazofamid
Sulphone	Dapsone
Tetracyclines	Chlortetracycline, doxycycline, oxytetracycline, tetracycline, tigecycline
Tetraoxanes	
Thiamine analogs	Amprolium
Thiophenone	Thiolactomycin
Translation elongation factor 2 (eEF2) inhibitor	DDD1 07498
Triazine	Clazuril, diclazuril, ponazuril, toltrazuril
Triazole	Bitertanol
Trioxane (sesquiterpene lactones, artemisinins)	Artemether, artesunate, dihydroartemisinin, artemotil, artemisinin, arteether, artemisone
Trioxolane (including ozonides)	Arterolane, OZ277, OZ439

21. The method according to any one of the preceding claims, wherein the therapeutically effective amount of compound of Formula I, or a therapeutically acceptable salt thereof, is administered to the subject by parenteral administration.
22. The method according to any one of the preceding claims, wherein the therapeutically effective amount of compound of Formula I, or a therapeutically acceptable salt thereof, is administered to the subject by topical administration.
23. An antiprotozoan pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I, or a therapeutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient or carrier, wherein Formula I is:

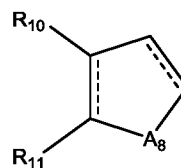


Formula I

wherein R_1 is H, cycloalkyl, Formula II, or Formula III;

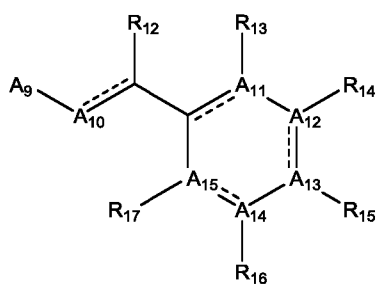


Formula II

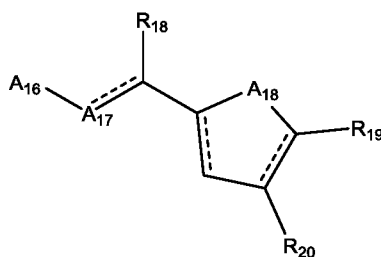


Formula III

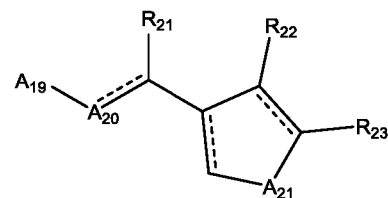
wherein R_3 is selected from the group consisting of: H; NH_2 ; NHNH_2 ; $0\text{-CH}_2\text{-CH}_3$; NH-C(=O)-phenyl ; $\text{NH-CH-chlorophenyl}$; NH-chlorophenyl ; $\text{NH-CH-chlorophenyl}$; $\text{NH-N-CH-cycloalkyl}$; N and R_4 is CH-N-CH-CCI- and R_4 is bonded to R_3 ; Formula IV; Formula V; and Formula VI;



Formula IV



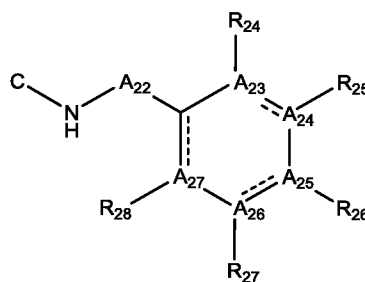
Formula V



Formula VI

wherein A_0 is N, C, CH, or A_0 is C and A_0 is bonded to R_4 to form a triazole ring;

wherein A, is N, C, NH, $-(\text{CH})_2\text{-N-}$, $-(\text{C}_6\text{H}_5)\text{C-CH-N-}$, or Formula VII;



Formula VII

A_2 is N, C, NH, N-C(0)-phenyl or Formula VII, or $(CH_2)_n$ wherein n is an integer between 1 and 3, inclusive;

wherein $A_3, A_4, A_5, A_6, A_7, A_8, A_{11}, A_{12}, A_{13}, A_{14}, A_{15}, A_{16}, A_{17}, A_{18}, A_{19}, A_{20}, A_{21}, A_{23}, A_{24}, A_{25}, A_{26}$ and A_{27} are independently C, O, N, NH, S;

wherein A_9 is C, O, N, NH, N-C(0)-O-CH₂-CH₃, N-C(0)-O-CH(CH₃)₂, N-C(0)-NH-CH₂-CH₃, N-C(0)-NH-CH₂-phenyl, N-C(0)-CH₂-CH₂-CH₂-CH₂-CH₂-CH₃, N-C(O)-CH₂-furan-2-yl;

wherein A_{10} is C, NH, -N-(CH)₂-, -N-CH-C(C₆H₅)₂-;

wherein A_{22} is -CH(CH₃)-, -N-CH-, -N-C(CH₃)-, N-C(CH₂OH)-;

R_2 is H, COOH, CH₂NH₂, CH₂OH, CH₂NHNH₂, methyl, ethyl, propyl, butyl, pentyl, heptyl, cyclopentyl, CH₂(Cyclohexyl), (CH₂)₂(cyclopentyl) or Formula VII and R_2 and R_4 are bonded together to form a pyrimidine, pyrazine or triazine ring, or R_2 and R_9 are bonded together to form a pyrrolidinyl oxindole ring;

wherein R_4 is H₂, N, NH, O, S, or R_4 and A_6 are bonded together to form a triazole ring, or R_4 is N and R_4 and R_2 are bonded together to form a pyrimidine ring;

wherein R_7 is H, Cl, Br, F, OH, CH₃, OCH₃, SCH₃, CN, CCH, CF₃, OCF₃, SCF₃, NO₂, butyl, f-butyl, dimethylamino, phenyl, n-propyl, /-propyl, -NH-C(0)-CH₃, -(CH)₂-COOH, piperazin-1-yl, or R_7 and R_8 are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring;

wherein $R_6, R_8, R_{14}, R_{16}, R_{25}$ and R_{27} are independently H, OH, Cl, F, Br, CH₃, CN, OCH₃, COOH, NO₂, CF₃, R_8 and R_7 bond together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring, or benzene ring, R_{14} and R_{15} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, R_8 and R_9 are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R_{14} and R_{13} are bonded together to form a substituted or unsubstituted saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring;

wherein R_5 , R_9 , R_{17} , R_{24} and R_{28} are independently H, O, OH, Cl, F, Br, NH_2 , CH_3 , CF_3 , OCH_3 , CN, NO_2 , phenyl, $-NH-CH(OH)-CH_3$, $-NH-C(=O)-CH_3$, or R_9 and R_8 are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R_{13} and R_{14} are bonded together to form a substituted or unsubstituted saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring;

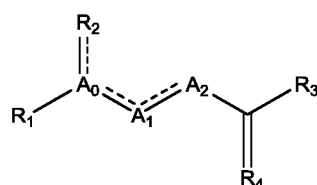
wherein R_{10} , R_n , R_{19} , R_{20} , R_{22} and R_{23} are independently H, Cl, or Br, or R_{10} and R_{11} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R_{19} and R_{20} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R_{22} and R_{23} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring;

wherein R_{12} , R_{18} and R_{21} are independently H, COOH, CH_2NH_2 , CH_2OH , methyl, ethyl, propyl, butyl, cyclopentyl, or R_{12} and R_{13} are bonded together to form a pyrrolidinyl oxindole ring;

wherein R_{15} and R_{26} are independently H, Cl, Br, F, OH, CH_3 , OCH_3 , SCH_3 , CN, CF_3 , OCF_3 , SCF_3 , NO_2 , CCH, n-butyl, f-butyl, dimethylamino, phenyl, n-propyl, /-propyl, $-NH-C(=O)-CH_3$, $-(CH_2)_2-COOH$, piperazin-1-yl, or R_{15} and R_{14} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring; and

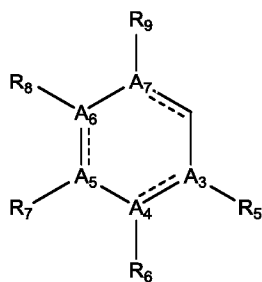
wherein "— " is a double bond or a single bond.

24. An antiprotozoan veterinary composition comprising a therapeutically effective amount of a compound of Formula I, or a therapeutically acceptable salt thereof, and optionally a veterinary acceptable excipient or carrier, wherein Formula I is:

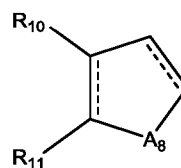


Formula I

wherein R_1 is H, cycloalkyl, Formula II, or Formula III;

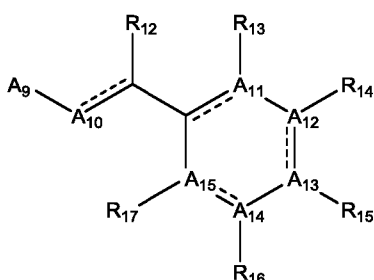


Formula II

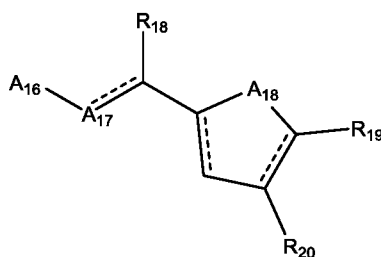


Formula III

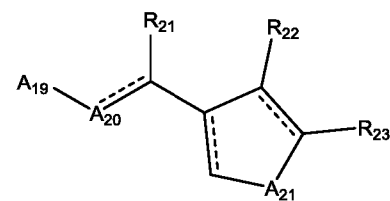
wherein R_3 is selected from the group consisting of: H; NH_2 ; $NHNH_2$; $O-CH_2-CH_3$; $NH-C(0)$ -phenyl; $NH-CH$ -chlorophenyl; NH -chlorophenyl; $NH-CH_2$ -chlorophenyl; $NH-N-CH$ -cycloalkyl; N and R_4 is $CH-N-CH-CCI-$ and R_4 is bonded to R_3 ; Formula IV; Formula V; and Formula VI;



Formula IV



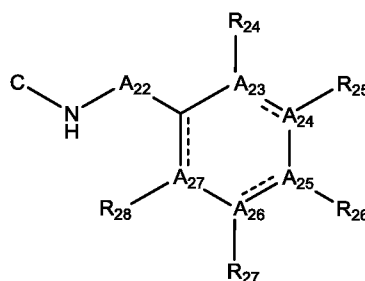
Formula V



Formula VI

wherein A_0 is N, C, CH, or A_0 is C and A_0 is bonded to R_4 to form a triazole ring;

wherein A, is N, C, NH, $-(CH)_2-N-$, $-(C_6H_5)C-CH-N-$, or Formula VII;



Formula VII

A_2 is N, C, NH, $N-C(0)$ -phenyl or Formula VII, or $(CH_2)_n$ wherein n is an integer between 1 and 3, inclusive;

wherein $A_3, A_4, A_5, A_6, A_7, A_8, A_{11}, A_{12}, A_{13}, A_{14}, A_{15}, A_{16}, A_{17}, A_{18}, A_{19}, A_{20}, A_{21}, A_{23}, A_{24}, A_{25}, A_{26}$ and A_{27} are independently C, O, N, NH, S;

wherein A_9 is C, O, N, NH, N-C(O)-O-CH₂-CH₃, N-C(O)-O-CH(CH₃)₂, N-C(O)-NH-CH₂-CH₃, N-C(O)-NH-CH₂-phenyl, N-C(O)-CH₂-CH₂-CH₂-CH₂-CH₂-CH₃, N-C(O)-CH₂-furan-2-yl;

wherein A_{10} is C, NH, -N-(CH)₂-, -N-CH-C(C₆H₅)₂-;

wherein A_{22} is -CH(CH₃)-, -N-CH-, -N-C(CH₃)-, N-C(CH₂OH)-;

R_2 is H, COOH, CH₂NH₂, CH₂OH, CH₂NHNH₂, methyl, ethyl, propyl, butyl, pentyl, heptyl, cyclopentyl, CH₂(Cyclohexyl), (CH₂)₂(cyclopentyl) or Formula VII and R_2 and R_4 are bonded together to form a pyrimidine, pyrazine or triazine ring, or R_2 and R_9 are bonded together to form a pyrrolidinyl oxindole ring;

wherein R_4 is H₂, N, NH, O, S, or R_4 and A_0 are bonded together to form a triazole ring, or R_4 is N and R_4 and R_2 are bonded together to form a pyrimidine ring;

wherein R_7 is H, Cl, Br, F, OH, CH₃, OCH₃, SCH₃, CN, CCH, CF₃, OCF₃, SCF₃, NO₂, butyl, f-butyl, dimethylamino, phenyl, n-propyl, /-propyl, -NH-C(O)-CH₃, -(CH)₂-COOH, piperazin-1-yl, or R_7 and R_8 are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring;

wherein $R_6, R_8, R_{14}, R_{16}, R_{25}$ and R_{27} are independently H, OH, Cl, F, Br, CH₃, CN, OCH₃, COOH, NO₂, CF₃, R_8 and R_7 bond together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring, or benzene ring, R_{14} and R_{15} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, R_8 and R_9 are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R_{14} and R_{13} are bonded together to form a substituted or unsubstituted saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring;

wherein R_5, R_9, R_{17}, R_{24} and R_{28} are independently H, O, OH, Cl, F, Br, NH₂, CH₃, CF₃, OCH₃, CN, NO₂, phenyl, -NH-CH(OH)-CH₃, -NH-C(O)-CH₃, or R_9 and R_8 are bonded together to form a substituted or unsubstituted, saturated or

unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R₁₃ and R₁₄ are bonded together to form a substituted or unsubstituted saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring;

wherein R₁₀, R_n, R₁₉, R₂₀, R₂₂ and R₂₃ are independently H, Cl, or Br, or R₁₀ and R₁₁ are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R₁₉ and R₂₀ are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R₂₂ and R₂₃ are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring;

wherein R₁₂, R₁₈ and R_{2i} are independently H, COOH, CH₂NH₂, CH₂OH, methyl, ethyl, propyl, butyl, cyclopentyl, or R₁₂ and R₁₃ are bonded together to form a pyrrolidinyloxindole ring;

wherein R₁₅ and R₂₆ are independently H, Cl, Br, F, OH, CH₃, OCH₃, SCH₃, CN, CF₃, OCF₃, SCF₃, NO₂, CCH, n-butyl, f-butyl, dimethylamino, phenyl, n-propyl, l-propyl, -NH-C(=O)-CH₃, -(CH₂)₂-COOH, piperazin-1-yl, or R₁₅ and R₁₄ are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring; and

wherein "— " is a double bond or a single bond.

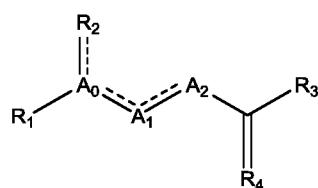
25. The composition according to either claim 23 or claim 24, wherein the composition comprises a further antimicrobial agent selected from the group comprising:

Chemical Class	Examples
4-aminoquinoline	Amodiaquine, chloroquine, hydroxychloroquine, piperazine (bis-4-aminoquinoline)
8-aminoquinoline	Bulaquine, pamaquine, Primaquine, tafenoquine
Acetamide	Thiolutin
Acridine dye	Acriflavine, mepacrine (quinacrine)
Alkylphosphocholine	Miltefosine
Allylamine	Terbinafine
Aminoglycosides	Paromomycin
Aminophenanthridium	Homidium, isometamidium chloride,
Aminopyridine antimalarials	MMV390048
Antimonials, pentavalent	Sodium stibogluconate, meglumine antimoniate
Arsenicals (trivalent & pentavalent)	Acetarsol (5+), arsthinol (3+), carbarsone (5+), difetarsone (5+), glycobarsol (5+), melarsomine (3+), melarsoprol (3+), nitarosone (5+), oxophenarsine (3+), roxarsone (5+), tryparsamide (5+)
Arylaminoalcohol	Halofantrine, lumefantrine, quinine/quinidine
Azo naphthalene dyes	Trypan blue, trypan red
Azoles (triazoles and imidazoles)	Albaconazole, itraconazole, ketoconazole, posaconazole, ravuconazole
Benzamide	Zoxamide
Benzenediol	Resveratrol

Benzimidazoles and probenzimidazoles	Albendazole, fenbendazole, febantel, mebendazole, omeprazole
Bicyclohexylammonium	Fumagillin
Carbamate	Disulfiram
Cinnamamido adenosine	Puromycin
Coumarin	Flocoumafen
Diamidines	Amicarbalide, diminazene diacetate, imidocarb dipropionate, pafuramidine, pentamidine isethionate, phenamidine isethionate, propamidine, stilbamidine
Dichloroacetamide	Clefamide, Etofamide, Teclozan
Dichloroacetamide	Diloxanide furoate
Difluoromethylornithine	Eflornithine
Dihydrofolate reductase/thymidylate synthase inhibitors	Diaveridine, ormetoprim, pyrimethamine, trimethoprim
Dihydroorotate dehydrogenase (DHODH) inhibitors	
Dinitroaniline	Trifluralin, oryzalin
Dinitrocarbanilide + pyrimidinol	Nicarbazin
Dithiocarbamate	Thiram
Ethoxybenzoic acid	Ethopabate
Fluoroquinolones	Ciprofloxacin, enrofloxacin, marbofloxacin
Guanidines	Chlorproguanil, cycloguanil, lauroguadine, proguanil, Robenidine
Halogenated 8-hydroxyquinoline	Iodoquinol, chlorquinaldol, tilbroquinol, broxyquinoline, diiodohydroxyquinoline, clioquinol
Hydroxyoxo-cyclohexenecarbaldehyde oxime	Sethoxydim, tralkoxydim, alloxydim, clethodim and cycloxydim
Hydroxyquinolones	Buquinolate, decoquinate, nequinolate
Imidazolopiperazine	Kaf1 56
Isoquinoline	Emetine/dehydroemetine
Lincosamides	Clindamycin, lincomycin
Macrolides	Azithromycin, clarithromycin, erythromycin, roxithromycin, spiramycin
Methylquinolinium	Quinapyramine, quinuronium sulfate
Miscellaneous	Pyridaben
Naphthoquinones	Atovaquone, buparvaquone, parvaquone
Naphthyridine	Pyronaridine
Nitrobenzamides	Aklomide, dinitolmide
Nitrofurans	Nifurtimox, furaltodone, furazolidone, nifuratel, nifuroxime, nifursol
Nitroimidazoles	Azanidazole, benznidazole, carnidazole, dimetridazole, fexnidazole, ipronidazole, metronidazole, nimorazole, ornidazole, propenidazole, ronidazole, satranidazole, secnidazole, ternidazole, tinidazole
Nitrothiazoles	Nitazoxanide, aminitrozole (nithiamide), forminitrazole, niridazole, tenonitrozole
Organometallic antiprotozoal	Auranofin, ferroquine
Oxaborole (including benzoxaboroles)	SCYX-71 58
Phenoxyphenol	Triclosan
phenylsulfamide	Tolylfluanid
Phosphonic acid derivative	Fosmidomycin
Phosphonomethylglycine	Glyphosate
Phosphoramidothioic acid	Amipprofos-methyl
Polyene	Amphotericin B, mepartricin, hachimycin, Hamycin
Polyether ionophores	Laidlomycin, lasalocid, maduramicin, monensin, narasin, salinomycin, semduramicin
Polypeptide	Bacitracin (zinc, methylene disalicylate), cecropins, cyclosporins, dermaseptin, magainins, tachyplesin, thiostrepton
Polysulfonated naphthylamine	Suramin
Propylphosphonic acid	Fosmidomycin
Purinamine	Arprinocid
Pyrazolopyran	
Pyrazolopyrimidine	Allopurinol
Pyridinols	Clopidol
Pyrimidine	Fenarimol
Pyrrolidinediol	Anisomycin
Quinazolinone	Febrifugine, halofuginone

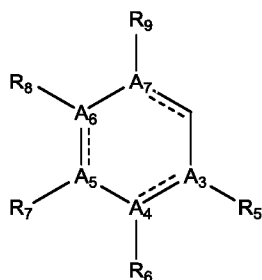
Quinoline	Mefloquine, nequinatate (methyl benzoquate), quinfamidine, tiliquinol
Quinoxaline	Carbadox
Rifamycin	Rifaximin
Spiroindolone	KAE609 (formerly NITD609), cipargamin
Strobilurin	Fluacrypyrim, azoxystrobin, trifloxystrobin, dimoxystrobin
Sulfonamides	Sulfadiazine, sulfadimethoxine, sulfadoxine, sulfaguandine, sulfamethazine (sulfadimidine), sulfamethoxazole, sulfanitran, sulfaquinoxaline, sulfamethoxyprazine, cyazofamid
Sulphone	Dapsone
Tetracyclines	Chlortetracycline, doxycycline, oxytetracycline, tetracycline, tigecycline
Tetraoxanes	
Thiamine analogs	Amprolium
Thiophenone	Thiolactomycin
Translation elongation factor 2 (eEF2) inhibitor	DDD1 07498
Triazine	Clazuril, diclazuril, ponazuril, toltrazuril
Triazole	Bitertanol
Trioxane (sesquiterpene lactones, artemisinins)	Artemether, artesunate, dihydroartemisinin, artemotil, artemisinin, arteether, artemisone
Trioxolane (including ozonides)	Arterolane, OZ277, OZ439

26. The composition according to either claim 24 or claim 25, wherein the composition is adapted for oral administration.
27. The composition according to either claim 24 or claim 25, wherein the composition is adapted for parenteral administration.
28. The composition according to either claim 24 or claim 25, wherein the composition is adapted for topical administration.
29. Use of a compound of Formula I, or a therapeutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a protozoan colonisation or infection in a subject, wherein Formula I is:

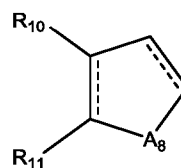


Formula I

wherein R_1 is H, cycloalkyl, Formula II, or Formula III;

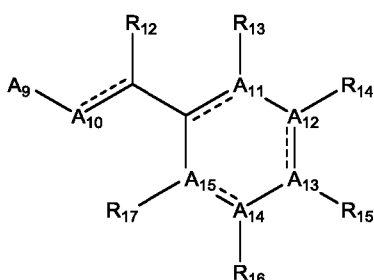


Formula II

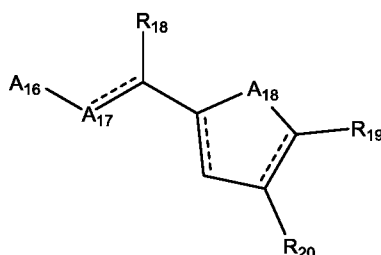


Formula III

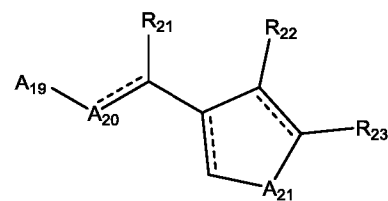
wherein R_3 is selected from the group consisting of: H; NH_2 ; $NHNH_2$; $O-CH_2-CH_3$; $NH-C(0)$ -phenyl; $NH-CH$ -chlorophenyl; NH -chlorophenyl; $NH-CH_2$ -chlorophenyl; $NH-N-CH$ -cycloalkyl; N and R_4 is $CH-N-CH-CCI-$ and R_4 is bonded to R_3 ; Formula IV; Formula V; and Formula VI;



Formula IV



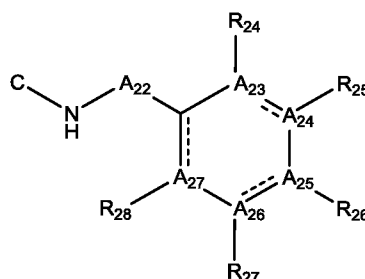
Formula V



Formula VI

wherein A_0 is N, C, CH, or A_0 is C and A_0 is bonded to R_4 to form a triazole ring;

wherein A, is N, C, NH, $-(CH)_2-N-$, $-(C_6H_5)C-CH-N-$, or Formula VII;



Formula VII

A_2 is N, C, NH, $N-C(0)$ -phenyl or Formula VII, or $(CH_2)_n$ wherein n is an integer between 1 and 3, inclusive;

wherein $A_3, A_4, A_5, A_6, A_7, A_8, A_{11}, A_{12}, A_{13}, A_{14}, A_{15}, A_{16}, A_{17}, A_{18}, A_{19}, A_{20}, A_{21}, A_{23}, A_{24}, A_{25}, A_{26}$ and A_{27} are independently C, O, N, NH, S;

wherein A_9 is C, O, N, NH, N-C(O)-O-CH₂-CH₃, N-C(O)-O-CH(CH₃)₂, N-C(O)-NH-CH₂-CH₃, N-C(O)-NH-CH₂-phenyl, N-C(O)-CH₂-CH₂-CH₂-CH₂-CH₂-CH₃, N-C(O)-CH₂-furan-2-yl;

wherein A_{10} is C, NH, -N-(CH)₂-, -N-CH-C(C₆H₅)₂-;

wherein A_{22} is -CH(CH₃)-, -N-CH-, -N-C(CH₃)-, N-C(CH₂OH)-;

R_2 is H, COOH, CH₂NH₂, CH₂OH, CH₂NHNH₂, methyl, ethyl, propyl, butyl, pentyl, heptyl, cyclopentyl, CH₂(Cyclohexyl), (CH₂)₂(cyclopentyl) or Formula VII and R_2 and R_4 are bonded together to form a pyrimidine, pyrazine or triazine ring, or R_2 and R_9 are bonded together to form a pyrrolidinyl oxindole ring;

wherein R_4 is H₂, N, NH, O, S, or R_4 and A_0 are bonded together to form a triazole ring, or R_4 is N and R_4 and R_2 are bonded together to form a pyrimidine ring;

wherein R_7 is H, Cl, Br, F, OH, CH₃, OCH₃, SCH₃, CN, CCH, CF₃, OCF₃, SCF₃, NO₂, butyl, f-butyl, dimethylamino, phenyl, n-propyl, /-propyl, -NH-C(O)-CH₃, -(CH)₂-COOH, piperazin-1-yl, or R_7 and R_8 are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring;

wherein $R_6, R_8, R_{14}, R_{16}, R_{25}$ and R_{27} are independently H, OH, Cl, F, Br, CH₃, CN, OCH₃, COOH, NO₂, CF₃, R_8 and R_7 bond together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring, or benzene ring, R_{14} and R_{15} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, R_8 and R_9 are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R_{14} and R_{13} are bonded together to form a substituted or unsubstituted saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring;

wherein R_5, R_9, R_{17}, R_{24} and R_{28} are independently H, O, OH, Cl, F, Br, NH₂, CH₃, CF₃, OCH₃, CN, NO₂, phenyl, -NH-CH(OH)-CH₃, -NH-C(O)-CH₃, or R_9 and R_8 are bonded together to form a substituted or unsubstituted, saturated or

unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R_{13} and R_{14} are bonded together to form a substituted or unsubstituted saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring;

wherein R_{10} , R_n , R_{19} , R_{20} , R_{22} and R_{23} are independently H, Cl, or Br, or R_{10} and R_{11} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R_{19} and R_{20} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R_{22} and R_{23} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring;

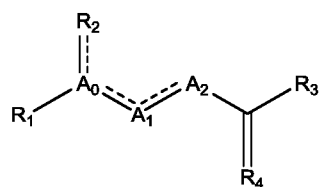
wherein R_{12} , R_{18} and R_{2i} are independently H, COOH, CH_2NH_2 , CH_2OH , methyl, ethyl, propyl, butyl, cyclopentyl, or R_{12} and R_{13} are bonded together to form a pyrrolidinyloxindole ring;

wherein R_{15} and R_{26} are independently H, Cl, Br, F, OH, CH_3 , OCH_3 , SCH_3 , CN, CF_3 , OCF_3 , SCF_3 , NO_2 , CCH, n-butyl, f-butyl, dimethylamino, phenyl, n-propyl, l-propyl, $-NH-C(=O)-CH_3$, $-(CH_2)_2-COOH$, piperazin-1-yl, or R_{15} and R_{14} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring; and

wherein "—" is a double bond or a single bond.

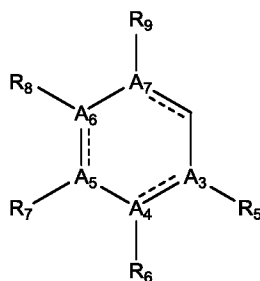
30. The use according to claim 29, wherein the use comprises administering a therapeutically effective amount of compound of Formula I, or a therapeutically acceptable salt thereof, to the subject.
31. The use according to any one of claims 29 to 30, wherein the compound of Formula I is administered to the subject in a dose in the range of 0.1 mg/kg to 250 mg/kg body weight.
32. The use according to any one of claims 29 to 31, wherein the medicament is administered to the subject by oral administration.
33. The use according to any one of claims 29 to 31, wherein the medicament is administered to the subject by parenteral administration.
34. The use according to any one of claims 29 to 31, wherein the medicament is administered to the subject by topical administration.

35. A medical device when used in a method of treating or preventing a protozoan colonisation or infection in the subject, wherein the medical device comprises the composition according to any one of claims 23 to 28.
36. The medical device according to claim 35, wherein the medical device is in a form selected from the group comprising: a plaster, a bandage, a dressing or implant applied to a protozoan colonisation or infection in a subject.
37. A method of killing protozoa, the method including the step of contacting the protozoa with a compound of Formula I, or a therapeutically acceptable salt thereof, wherein Formula I is:

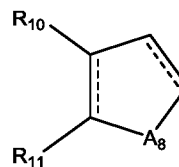


Formula I

wherein R_1 is H, cycloalkyl, Formula II, or Formula III;

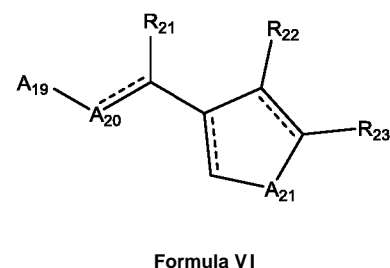
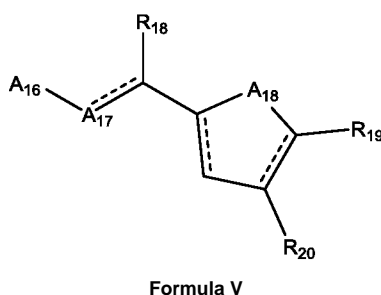
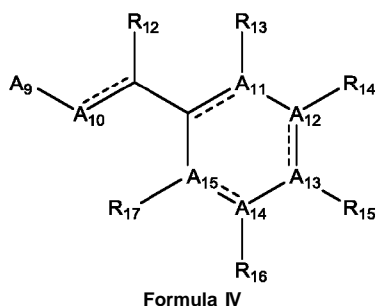


Formula II



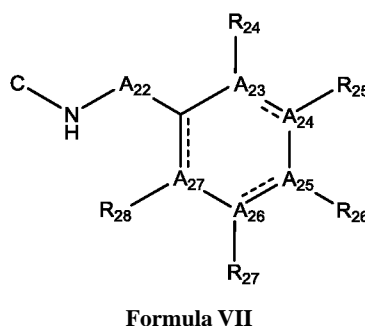
Formula III

wherein R_3 is selected from the group consisting of: H; NH_2 ; $NHNH_2$; $O-CH_2-CH_3$; $NH-C(0)$ -phenyl; $NH-CH$ -chlorophenyl; NH -chlorophenyl; $NH-CH_2$ -chlorophenyl; $NH-N-CH$ -cycloalkyl; N and R_4 is $CH-N-CH-CCI-$ and R_4 is bonded to R_3 ; Formula IV; Formula V; and Formula VI;



wherein A₀ is N, C, CH, or A₀ is C and A₀ is bonded to R₄ to form a triazole ring;

wherein A₁ is N, C, NH, -(CH)₂-N-, -(C₆H₅)C-CH-N-, or Formula VII;



A₂ is N, C, NH, N-C(0)-phenyl or Formula VII, or (CH₂)_n wherein n is an integer between 1 and 3, inclusive;

wherein A₃, A₄, A₅, A₆, A₇, A₈, A_n, A₁₂, A₁₃, A₁₄, A₁₅, A₁₆, A₁₇, A₁₈, A₁₉, A₂₀, A₂₁, A₂₃, A₂₄, A₂₅, A₂₆ and A₂₇ are independently C, O, N, NH, S;

wherein A₉ is C, O, N, NH, N-C(0)-O-CH₂-CH₃, N-C(0)-O-CH(CH₃)₂, N-C(0)-NH-CH₂-CH₃, N-C(0)-NH-CH₂-phenyl, N-C(0)-CH₂-CH₂-CH₂-CH₂-CH₂-CH₃, N-C(0)-CH₂-furan-2-yl;

wherein A₁₀ is C, NH, -N-(CH)₂-, -N-CH-C(C₆H₅)-;

wherein A₂₂ is -CH(CH₃)-, -N-CH-, -N-C(CH₃)-, N-C(CH₂OH)-;

R₂ is H, COOH, CH₂NH₂, CH₂OH, CH₂NHNH₂, methyl, ethyl, propyl, butyl, pentyl, heptyl, cyclopentyl, CH₂(Cyclohexyl), (CH₂)₂(cyclopentyl) or Formula VII and R₂ and R₉ are bonded together to form a pyrimidine, pyrazine or triazine ring, or R₂ and R₉ are bonded together to form a pyrrolidinyloxindole ring;

wherein R_4 is H_2 , N, NH, O, S, or R_4 and A_0 are bonded together to form a triazole ring, or R_4 is N and R_4 and R_2 are bonded together to form a pyrimidine ring;

wherein R_7 is H, Cl, Br, F, OH, CH_3 , OCH_3 , SCH_3 , CN, CCH, CF_3 , OCF_3 , SCF_3 , NO_2 , butyl, f-butyl, dimethylamino, phenyl, n-propyl, /-propyl, $-NH-C(=O)-CH_3$, $-(CH)_2-COOH$, piperazin-1-yl, or R_7 and R_8 are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring;

wherein R_6 , R_8 , R_{14} , R_{16} , R_{25} and R_{27} are independently H, OH, Cl, F, Br, CH_3 , CN, OCH_3 , COOH, NO_2 , CF_3 , R_8 and R_7 bond together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring, or benzene ring, R_{14} and R_{15} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, R_8 and R_9 are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R_{14} and R_{13} are bonded together to form a substituted or unsubstituted saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring;

wherein R_5 , R_9 , R_{17} , R_{24} and R_{28} are independently H, O, OH, Cl, F, Br, NH_2 , CH_3 , CF_3 , OCH_3 , CN, NO_2 , phenyl, $-NH-CH(OH)-CH_3$, $-NH-C(=O)-CH_3$, or R_9 and R_8 are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R_{13} and R_{14} are bonded together to form a substituted or unsubstituted saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring;

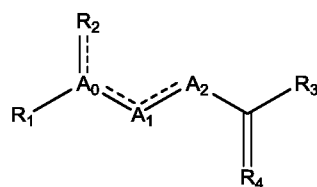
wherein R_{10} , R_n , R_{19} , R_{20} , R_{22} and R_{23} are independently H, Cl, or Br, or R_{10} and R_{11} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R_{19} and R_{20} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R_{22} and R_{23} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring;

wherein R_{12} , R_{18} and R_{21} are independently H, COOH, CH_2NH_2 , CH_2OH , methyl, ethyl, propyl, butyl, cyclopentyl, or R_{12} and R_{13} are bonded together to form a pyrrolidinyl oxindole ring;

wherein R_{15} and R_{26} are independently H, Cl, Br, F, OH, CH_3 , OCH_3 , SCH_3 , CN, CF_3 , OCF_3 , SCF_3 , NO_2 , CCH, n-butyl, f-butyl, dimethylamino, phenyl, n-propyl, /-propyl, $-NH-C(=O)-CH_3$, $-(CH_2)_2-COOH$, piperazin-1-yl, or R_{15} and R_{14} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring; and

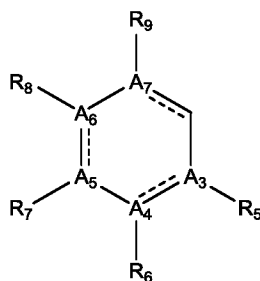
wherein "— " is a double bond or a single bond.

38. Use of a compound of Formula I, or a therapeutically acceptable salt thereof, to kill protozoa, said use comprising the step of contacting the protozoa with a compound of Formula I, or a therapeutically acceptable salt thereof, wherein Formula I is:

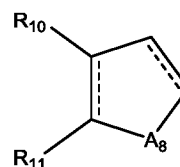


Formula I

wherein R_1 is H, cycloalkyl, Formula II, or Formula III;

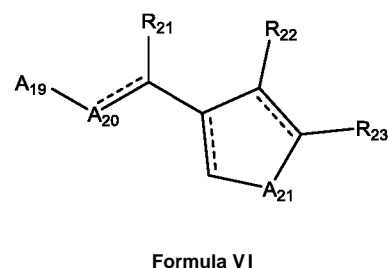
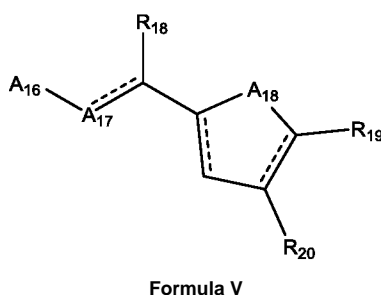
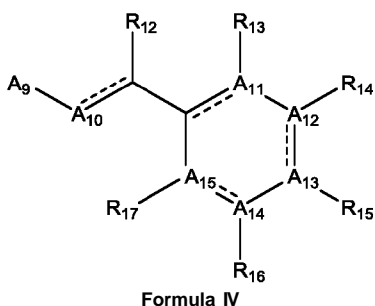


Formula II



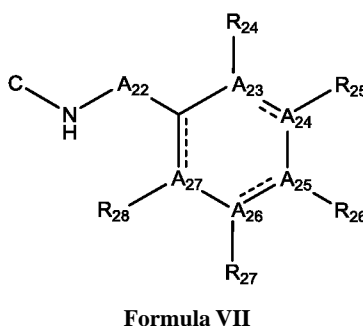
Formula III

wherein R_3 is selected from the group consisting of: H; NH_2 ; $NHNH_2$; $O-CH_2-CH_3$; $NH-C(=O)$ -phenyl; $NH-CH$ -chlorophenyl; NH -chlorophenyl; $NH-CH_2$ -chlorophenyl; $NH-N-CH$ -cycloalkyl; N and R_4 is $CH-N-CH-CCI-$ and R_4 is bonded to R_3 ; Formula IV; Formula V; and Formula VI;



wherein A_0 is N, C, CH, or A_0 is C and A_0 is bonded to R_4 to form a triazole ring;

wherein A, is N, C, NH, $-(CH)_2-N-$, $-(C_6H_5)C-CH-N-$, or Formula VII;



A_2 is N, C, NH, N-C(0)-phenyl or Formula VII, or $(CH_2)_n$ wherein n is an integer between 1 and 3, inclusive;

wherein $A_3, A_4, A_5, A_6, A_7, A_8, A_n, A_{12}, A_{13}, A_{14}, A_{15}, A_{16}, A_{17}, A_{18}, A_{19}, A_{20}, A_{21}, A_{23}, A_{24}, A_{25}, A_{26}$ and A_{27} are independently C, O, N, NH, S;

wherein A_9 is C, O, N, NH, N-C(0)-O-CH₂-CH₃, N-C(0)-O-CH(CH₃)₂, N-C(0)-NH-CH₂-CH₃, N-C(0)-NH-CH₂-phenyl, N-C(0)-CH₂-CH₂-CH₂-CH₂-CH₂-CH₃, N-C(O)-CH₂-furan-2-yl;

wherein A_{10} is C, NH, $-N-(CH)_2-$, $-N-CH-C(C_6H_5)-$;

wherein A_{22} is $-CH(CH_3)-$, $-N-CH-$, $-N-C(CH_3)-$, $N-C(CH_2OH)-$;

R_2 is H, COOH, CH₂NH₂, CH₂OH, CH₂NHNH₂, methyl, ethyl, propyl, butyl, pentyl, heptyl, cyclopentyl, CH₂(Cyclohexyl), $(CH_2)_2$ (cyclopentyl) or Formula VII and R_2 are R_4 are bonded together to form a pyrimidine, pyrazine or triazine ring, or R_2 and R_9 are bonded together to form a pyrrolidiny oxindole ring;

wherein R_4 is H_2 , N, NH, O, S, or R_4 and A_0 are bonded together to form a triazole ring, or R_4 is N and R_4 and R_2 are bonded together to form a pyrimidine ring;

wherein R_7 is H, Cl, Br, F, OH, CH_3 , OCH_3 , SCH_3 , CN, CCH, CF_3 , OCF_3 , SCF_3 , NO_2 , butyl, f-butyl, dimethylamino, phenyl, n-propyl, /-propyl, $-NH-C(=O)-CH_3$, $-(CH)_2-COOH$, piperazin-1-yl, or R_7 and R_8 are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring;

wherein R_6 , R_8 , R_{14} , R_{16} , R_{25} and R_{27} are independently H, OH, Cl, F, Br, CH_3 , CN, OCH_3 , COOH, NO_2 , CF_3 , R_8 and R_7 bond together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring, or benzene ring, R_{14} and R_{15} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, R_8 and R_9 are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R_{14} and R_{13} are bonded together to form a substituted or unsubstituted saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring;

wherein R_5 , R_9 , R_{17} , R_{24} and R_{28} are independently H, O, OH, Cl, F, Br, NH_2 , CH_3 , CF_3 , OCH_3 , CN, NO_2 , phenyl, $-NH-CH(OH)-CH_3$, $-NH-C(=O)-CH_3$, or R_9 and R_8 are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R_{13} and R_{14} are bonded together to form a substituted or unsubstituted saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring;

wherein R_{10} , R_n , R_{19} , R_{20} , R_{22} and R_{23} are independently H, Cl, or Br, or R_{10} and R_{11} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R_{19} and R_{20} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring, or R_{22} and R_{23} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring;

wherein R_{12} , R_{18} and R_{21} are independently H, COOH, CH_2NH_2 , CH_2OH , methyl, ethyl, propyl, butyl, cyclopentyl, or R_{12} and R_{13} are bonded together to form a pyrrolidinyl oxindole ring;

wherein R_{15} and R_{26} are independently H, Cl, Br, F, OH, CH_3 , OCH_3 , SCH_3 , CN, CF_3 , OCF_3 , SCF_3 , NO_2 , CCH, n-butyl, f-butyl, dimethylamino, phenyl, n-propyl, *l*-propyl, $-NH-C(=O)-CH_3$, $-(CH_2)_2-COOH$, piperazin-1-yl, or R_{15} and R_{14} are bonded together to form a substituted or unsubstituted, saturated or unsaturated aliphatic ring, heterocyclic ring or benzene ring; and

wherein "— " is a double bond or a single bond.

39. A compound selected from the list of compounds consisting of:

- (E)-2-(1-(4-(tert-butyl)phenyl)ethylideneamino)guanidine (NCL231);
 (E)-2-(4-(tert-butyl)benzylideneamino)guanidine (NCL232);
 (E)-2-(1-(4-chlorophenyl)butylidene)hydrazine-1-carboximidamide hydrochloride (NCL233);
 (E)-2-(1-(4-chlorophenyl)propylidene)hydrazine-1-carboximidamide (NCL234);
 (E)-2-(4-chloro-2-fluorobenzylidene)hydrazine-1-carboximidamide (NCL235);
 (E)-2-(1-(4-chloro-2-fluorophenyl)ethylidene)hydrazine-1-carboximidamide (NCL236);
 (E)-2-(1-(4-chloro-2-hydroxyphenyl)-2-cyclohexylethylideneamino)guanidine (NCL237);
 4,6-bis(2-((E)-(6-chloropyridin-3-yl)methylene)hydrazinyl)pyrimidin-2-amine (NCL238);
 4,6-bis(2-((E)-pyridin-3-ylmethylene)hydrazinyl)pyrimidin-2-amine (NCL239);
 4,6-bis(2-((E)-pyridin-2-ylmethylene)hydrazinyl)pyrimidin-2-amine (NCL240);
 4,6-bis(2-((E)-pyridin-4-ylmethylene)hydrazinyl)pyrimidin-2-amine (NCL241);
 4,6-bis(2-((E)-2,5-dihydroxybenzylidene)hydrazinyl)pyrimidin-2-aminium 2-formyl-4-hydroxyphenolate (NCL242);
 4,6-bis(2-((E)-3,4-dihydroxybenzylidene)hydrazinyl)pyrimidin-2-amine (NCL243);
 4,6-bis(2-((E)-2,3-dihydroxybenzylidene)hydrazinyl)pyrimidin-2-aminium 2-formyl-6-hydroxyphenolate (NCL244);
 4,6-bis(2-((E)-naphthalen-1-ylmethylene)hydrazinyl)pyrimidin-2-amine (NCL245);
 4,6-bis(2-((1 E,2E)-3-phenylallylidene)hydrazinyl)pyrimidin-2-amine (NCL246);
 4,6-bis(2-((E)-3,4,5-trihydroxybenzylidene)hydrazinyl)pyrimidin-2-amine (NCL247);
 (E)-2-(naphthalen-1-ylmethylideneamino)guanidine (NCL248);
 (E)-2-((E)-3-phenylallylideneamino)guanidine (NCL249);
 (1 E,1'E)-N,N'-(ethane-1,2-diyl)bis(1-(4-chlorophenyl)methanimine) (NCL250);
 (1 E,1'E)-N,N'-(butane-1,4-diyl)bis(1-(4-chlorophenyl)methanimine) (NCL251);
 (1 E,1'E)-N,N'-(propane-1,3-diyl)bis(1-(4-chlorophenyl)methanimine) (NCL252);
 (E)-2-(4-(dimethylamino)benzylideneamino)guanidine (NCL253);
 (E)-2-(1-(4-chlorophenyl)hexylidene)hydrazine-1-carboximidamide hydrochloride (NCL254);

4,6-bis(2-((E)-[1,1'-biphenyl]-4-ylmethylene)hydrazinyl)pyrimidin-2-amine (NCL255);
4,6-bis(2-((E)-2,4-dihydroxybenzylidene)hydrazinyl)pyrimidin-2-amine (NCL256);
(E)-2-((2-hydroxynaphthalen-1-yl)methylene)hydrazine-1-carboximidamide hydrochloride (NCL257);
N1,N4-bis(4-chlorobenzyl)butane-1,4-diamine (NCL258);
(E)-2-(1-(4-chlorophenyl)-2-cyclohexylethylidene)hydrazine-1-carboximidamide hydrochloride (NCL259);
N1,N2-bis(4-chlorobenzyl)ethane-1,2-diamine (NCL260);
(E)-2-(naphthalen-2-ylmethylene)hydrazine-1-carboximidamide hydrochloride (NCL261);
4,6-bis(2-((E)-3-phenylpropylidene)hydrazinyl)pyrimidin-2-amine (NCL262);
(E)-2-(2-fluoro-4-(trifluoromethyl)benzylidene)hydrazine-1-carboximidamide hydrochloride (NCL263);
4,6-bis(2-((E)-naphthalen-2-ylmethylene)hydrazinyl)pyrimidin-2-amine (NCL264);
(E)-2-(1-(4-chlorophenyl)-octylideneamino)guanidine (NCL265);
(E)-2-(1-(4-chlorophenyl)-3-cyclopentylpropylideneamino)guanidine (NCL266);
(E)-4-chloro-6-(2-(4-chlorobenzylidene)hydrazinyl)pyrimidin-2-amine (NCL267);
(E)-4-chloro-6-(2-(4-methylbenzylidene)hydrazinyl)pyrimidin-2-amine (NCL268);
(Z)-2-(1-(1H-indol-3-yl)ethylidene)hydrazinecarboximidamide (NCL269);
2,2'-Bis(1-(1H-indol-3-yl)ethylidene)hydrazidecarboximidamide (NCL270);
2,2'-Bis(1-(4-chlorophenyl)hexylidene)hydrazidecarboximidamide (NCL271);
2,2'-Bis(1-(4-chlorophenyl)octylidene)hydrazidecarboximidamide (NCL272);
2,2'-Bis(1-(4-chlorophenyl)-3-cyclopentylpropylidene)hydrazidecarboximidamide (NCL273);
2,2'-Bis((1H-indol-3-yl)methylene)hydrazine carboximidamide (NCL274); and
2,2'-Bis(1-(4-chlorophenyl)-2-ethoxyethylidene)hydrazidecarboximidamide (NCL275).

40. A composition comprising the compound of claim 39.
41. A method, a composition, compound, device or a use, substantially as described herein with reference to the accompanying Examples and Figures.

Figure 1

NCL COMPOUND CODE	COMPOUND NAME	STRUCTURE
NCL812	2,2'-bis[(4-chlorophenyl)methylene]carbonimidic dihydrazide hydrochloride	
NCL001	2,2'-bis[(4-chlorophenyl)methylene]carbonic dihydrazide	
NCL002	2,2'-bis[(2-chlorophenyl)methylene]carbonic dihydrazide	
NCL003	2,2'-bis[(4-fluorophenyl)methylene]carbonic dihydrazide	
NCL004	2,2'-bis[(3-fluorophenyl)methylene]carbonic dihydrazide	
NCL005	2,2'-bis[(2-fluorophenyl)methylene]carbonic dihydrazide	
NCL006	2,2'-bis[(4-methoxyphenyl)methylene]carbonic dihydrazide	
NCL007	2,2'-bis[(4-cyanophenyl)methylene]carbonic dihydrazide	
NCL008	2,2'-bis[(2-cyanophenyl)methylene]carbonic dihydrazide	

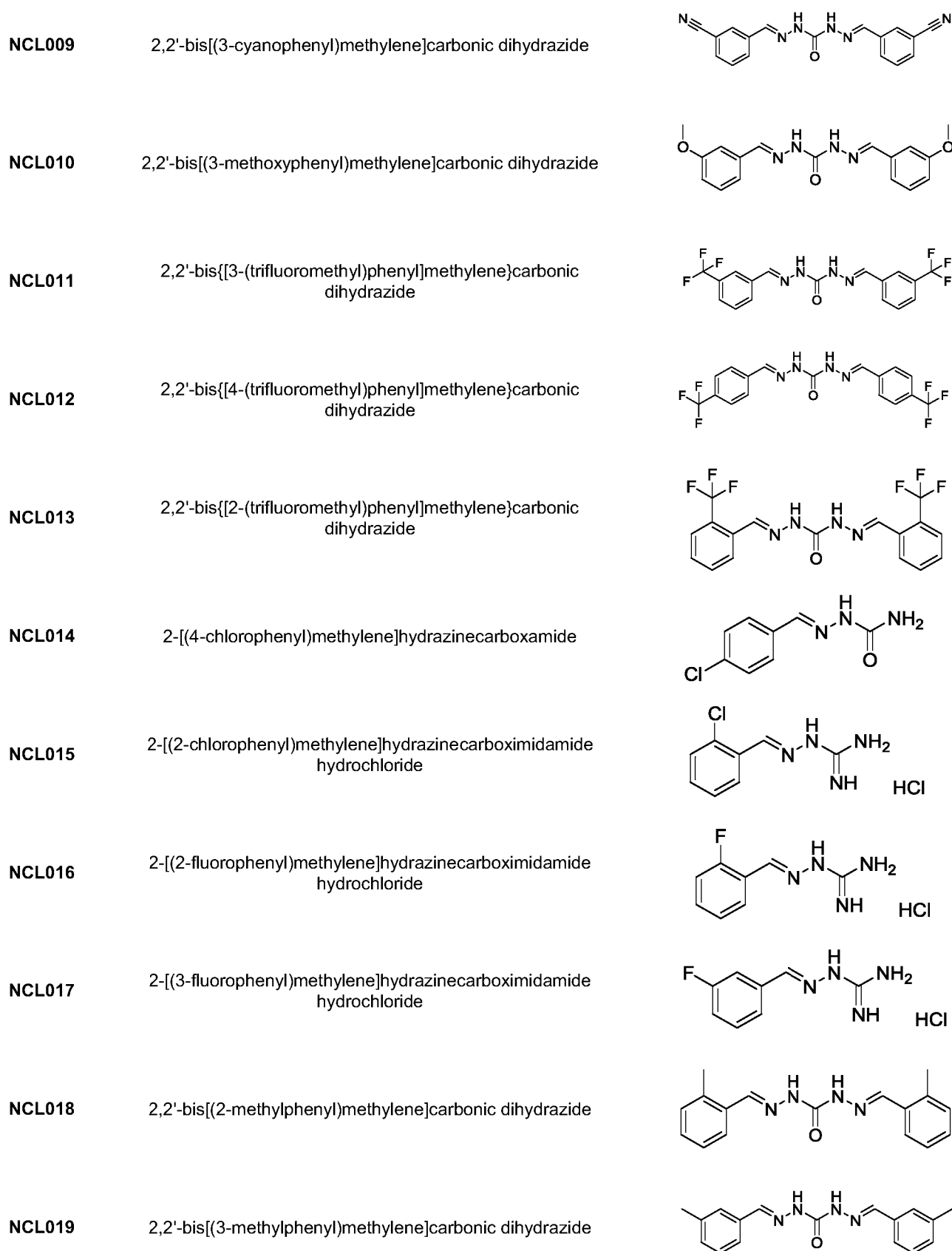


Figure 1 continued

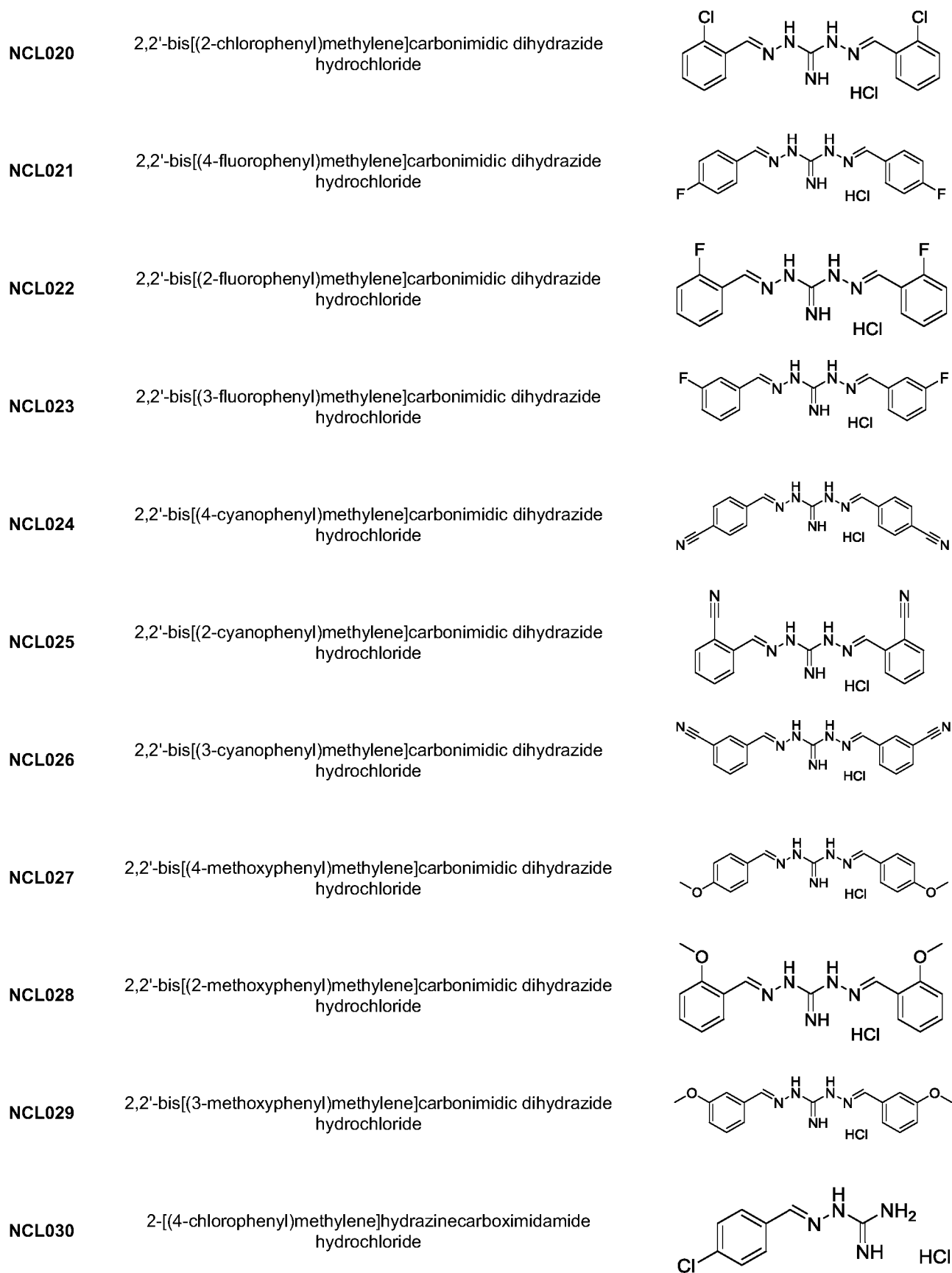


Figure 1 continued

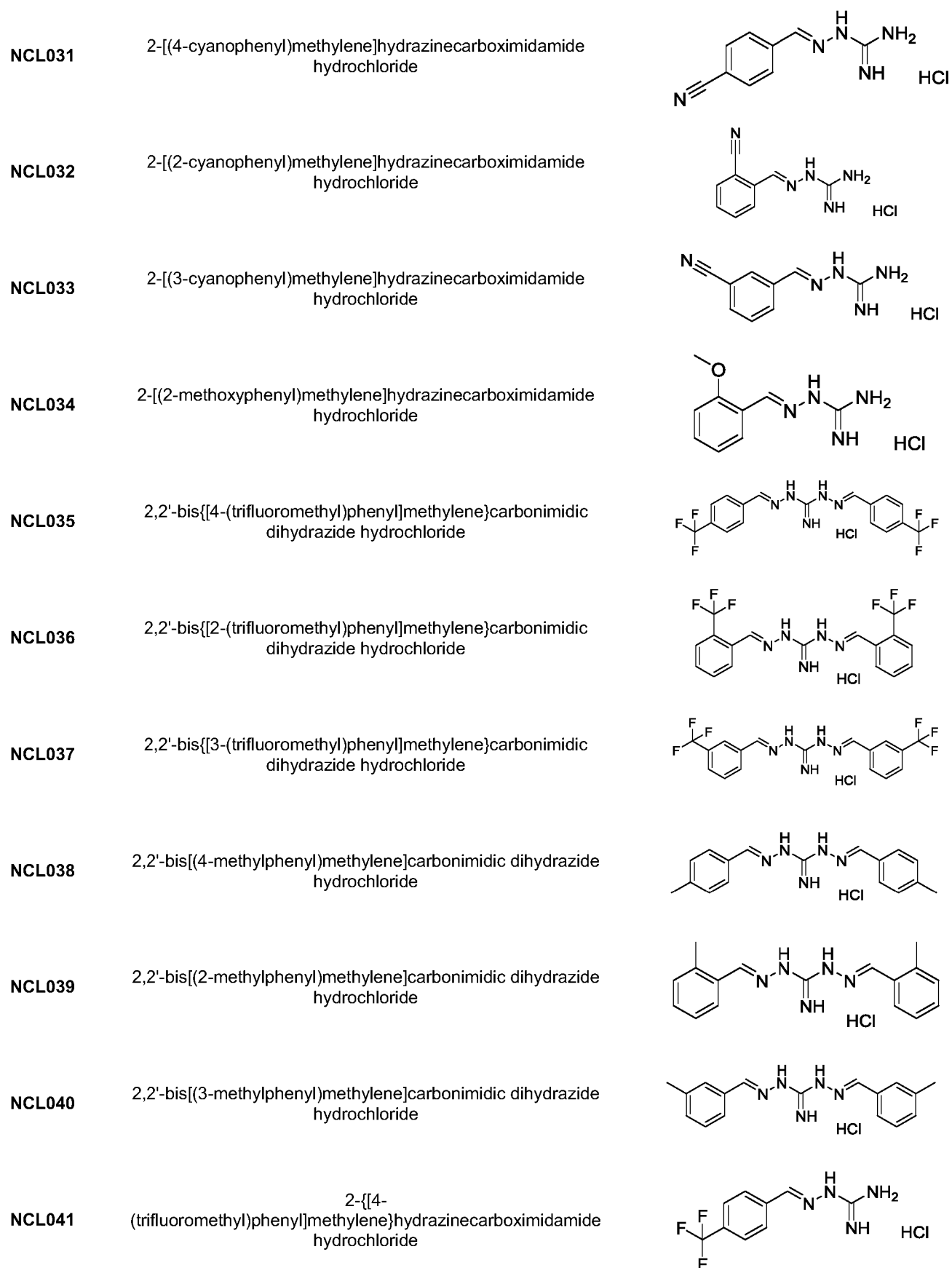


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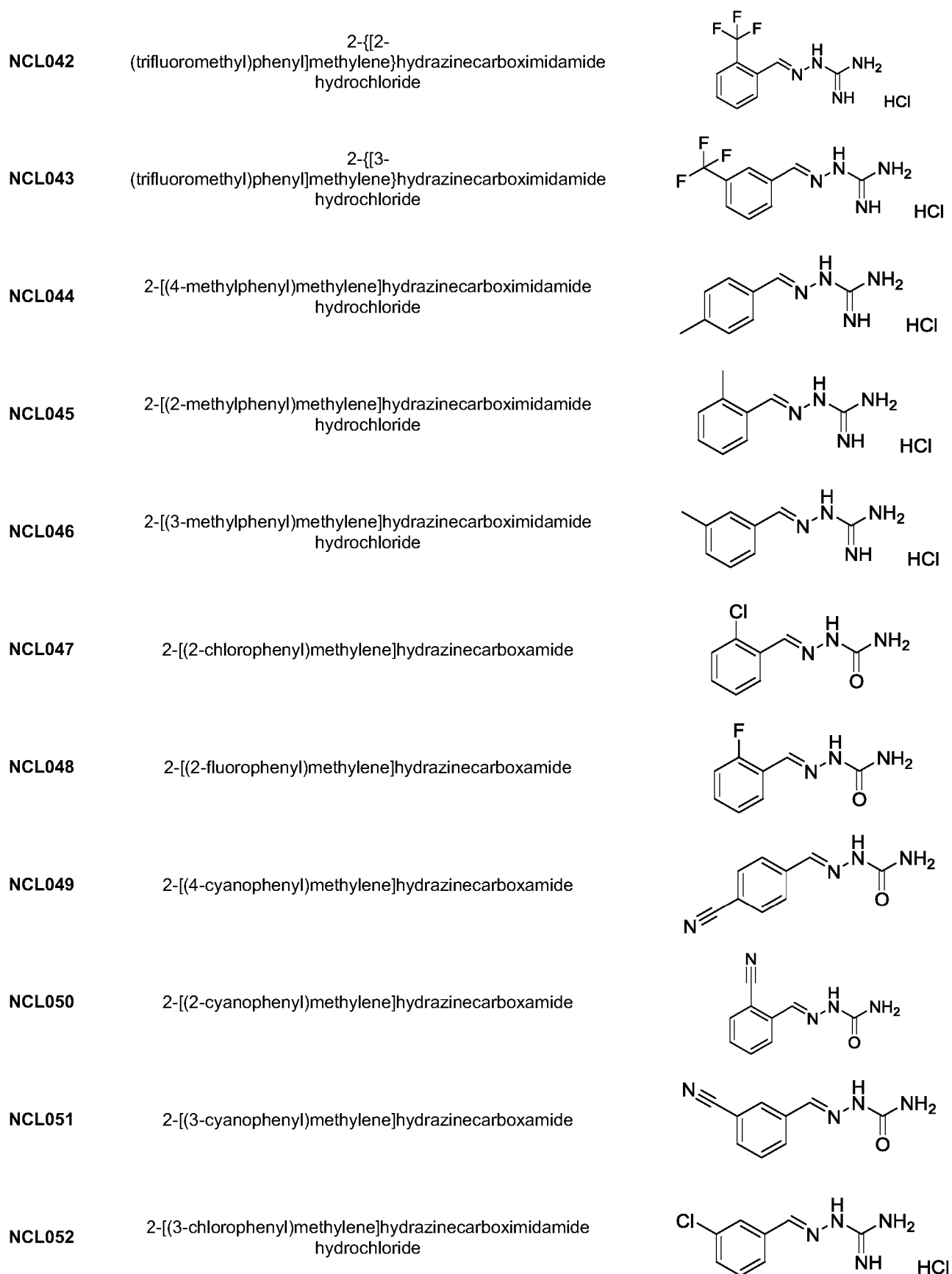


Figure 1 continued

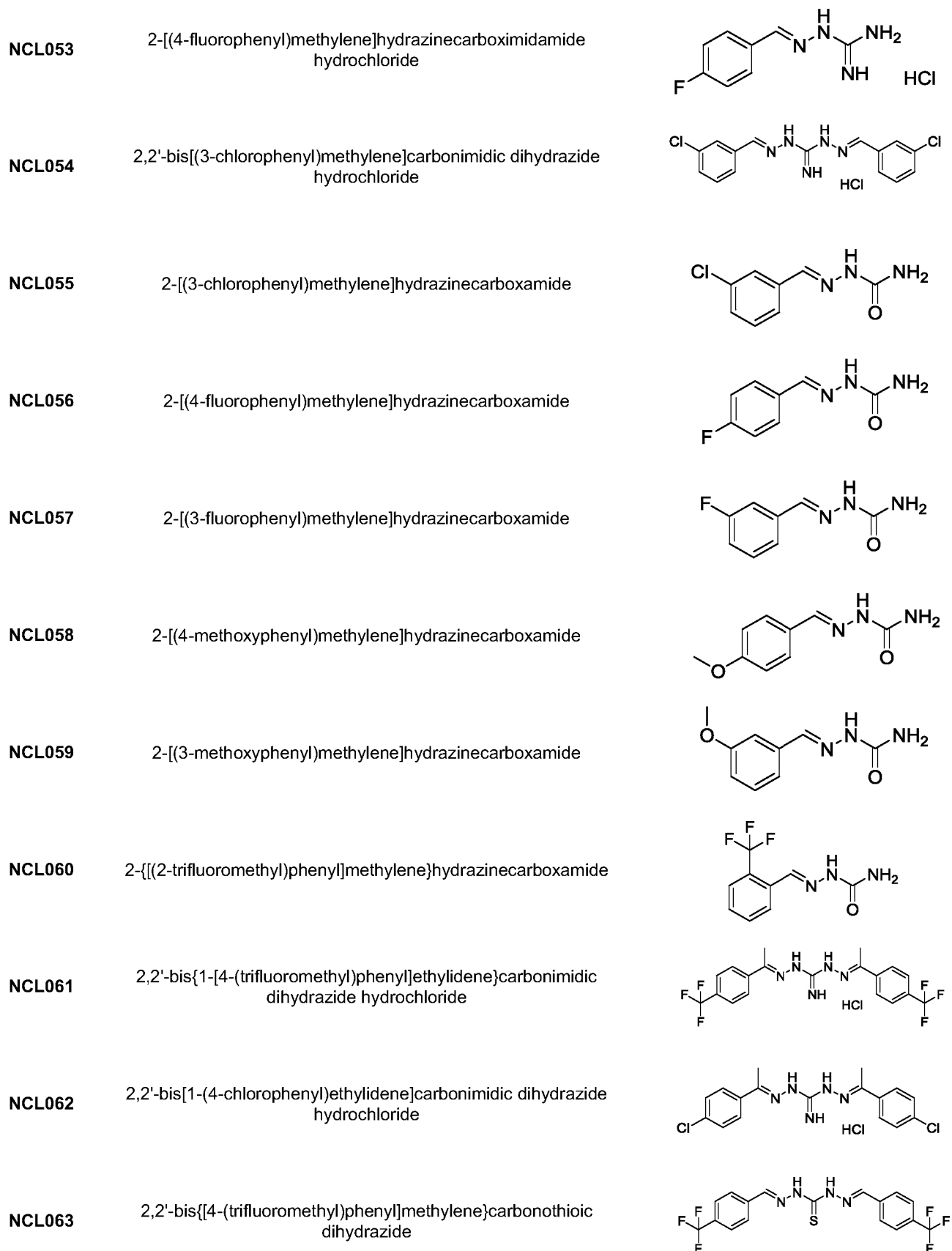


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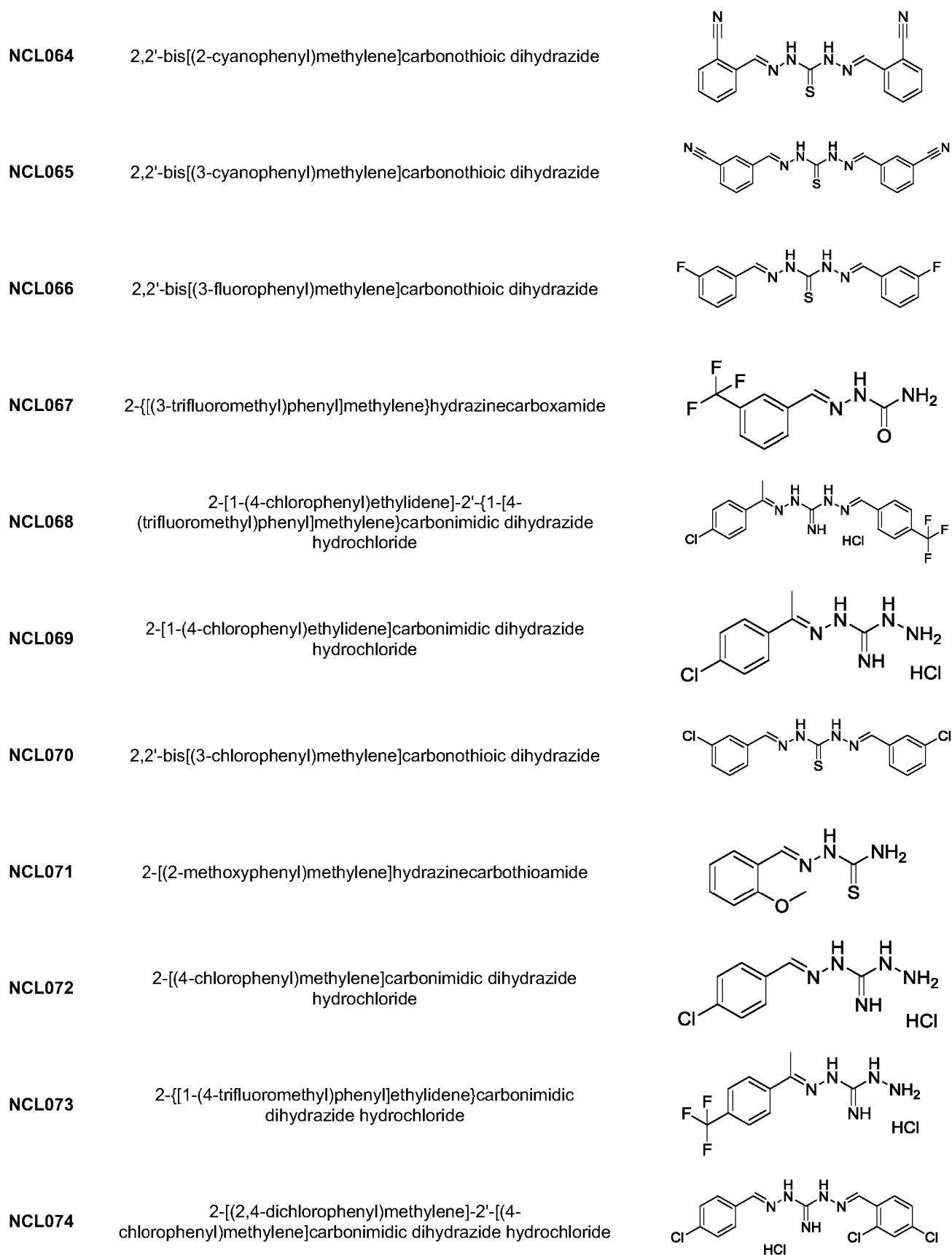


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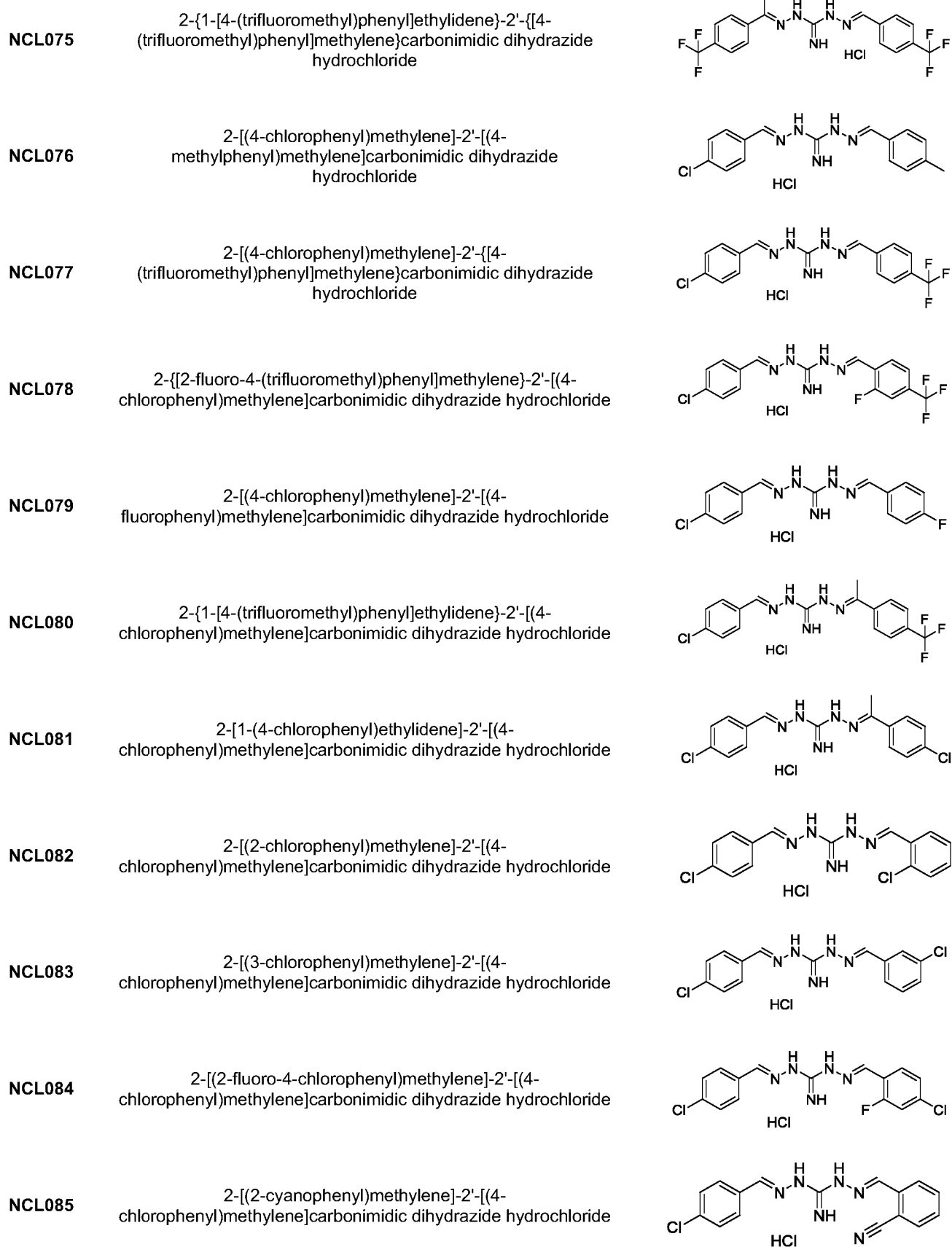


Figure 1 continued

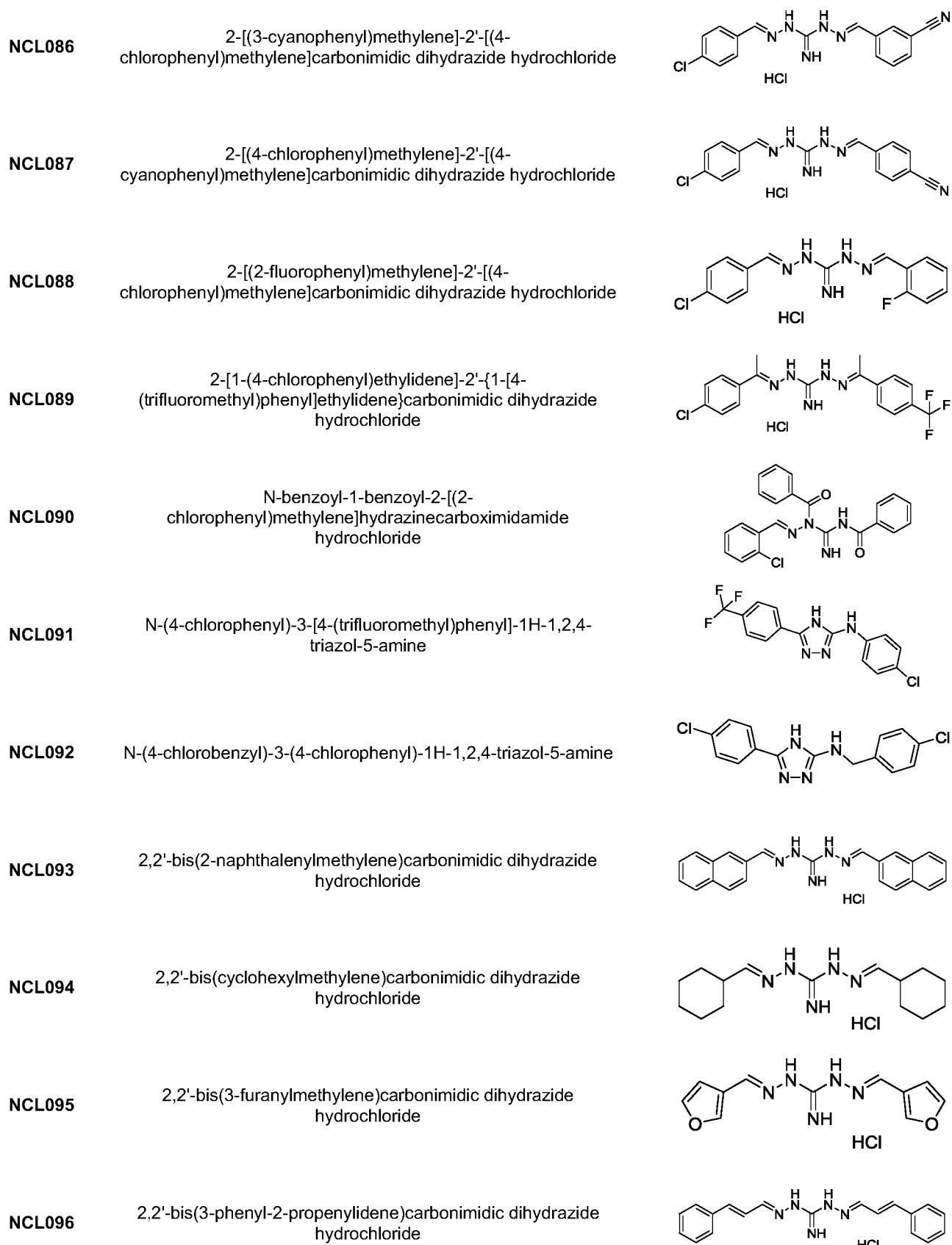


Figure 1 continued

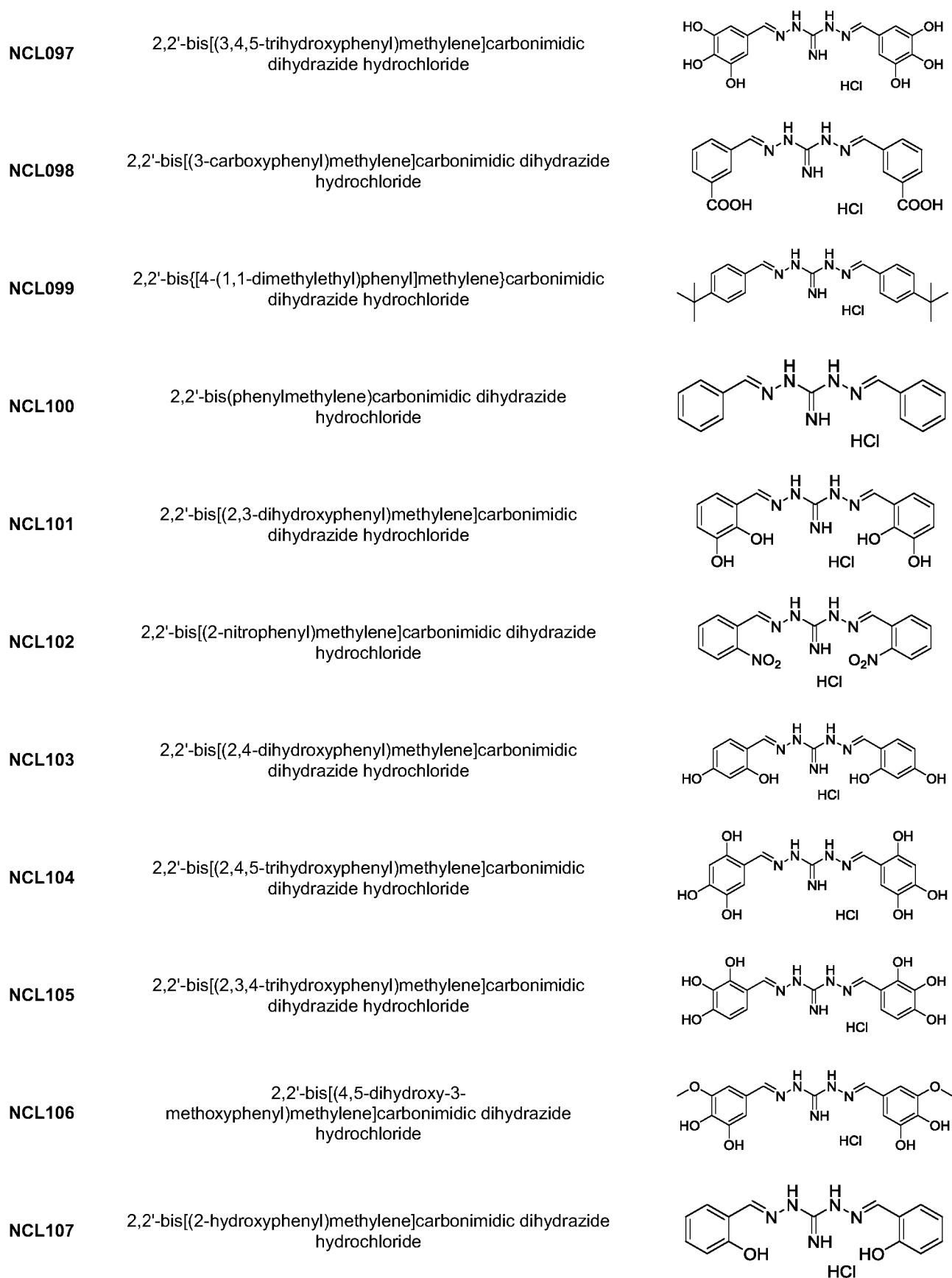


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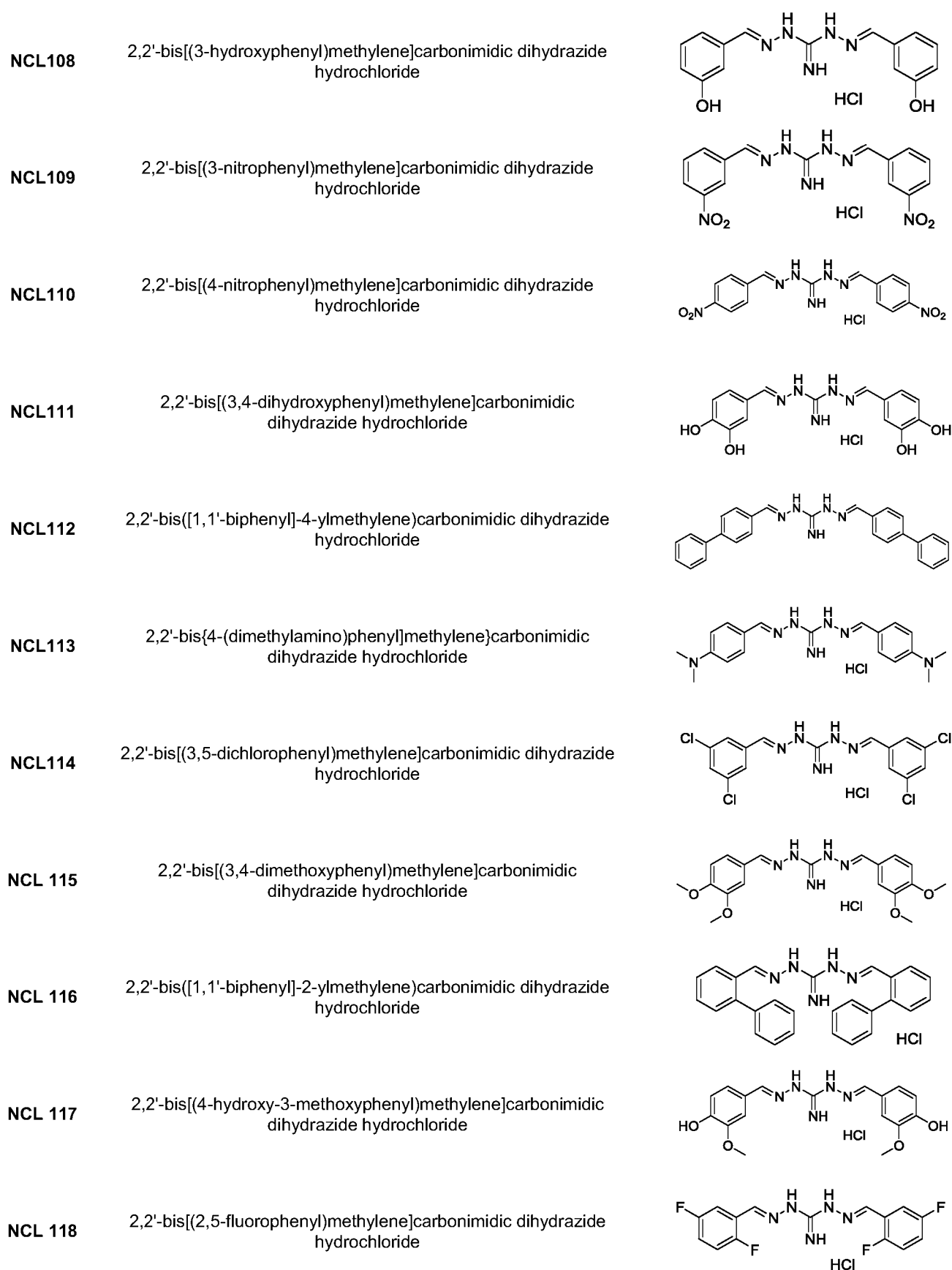


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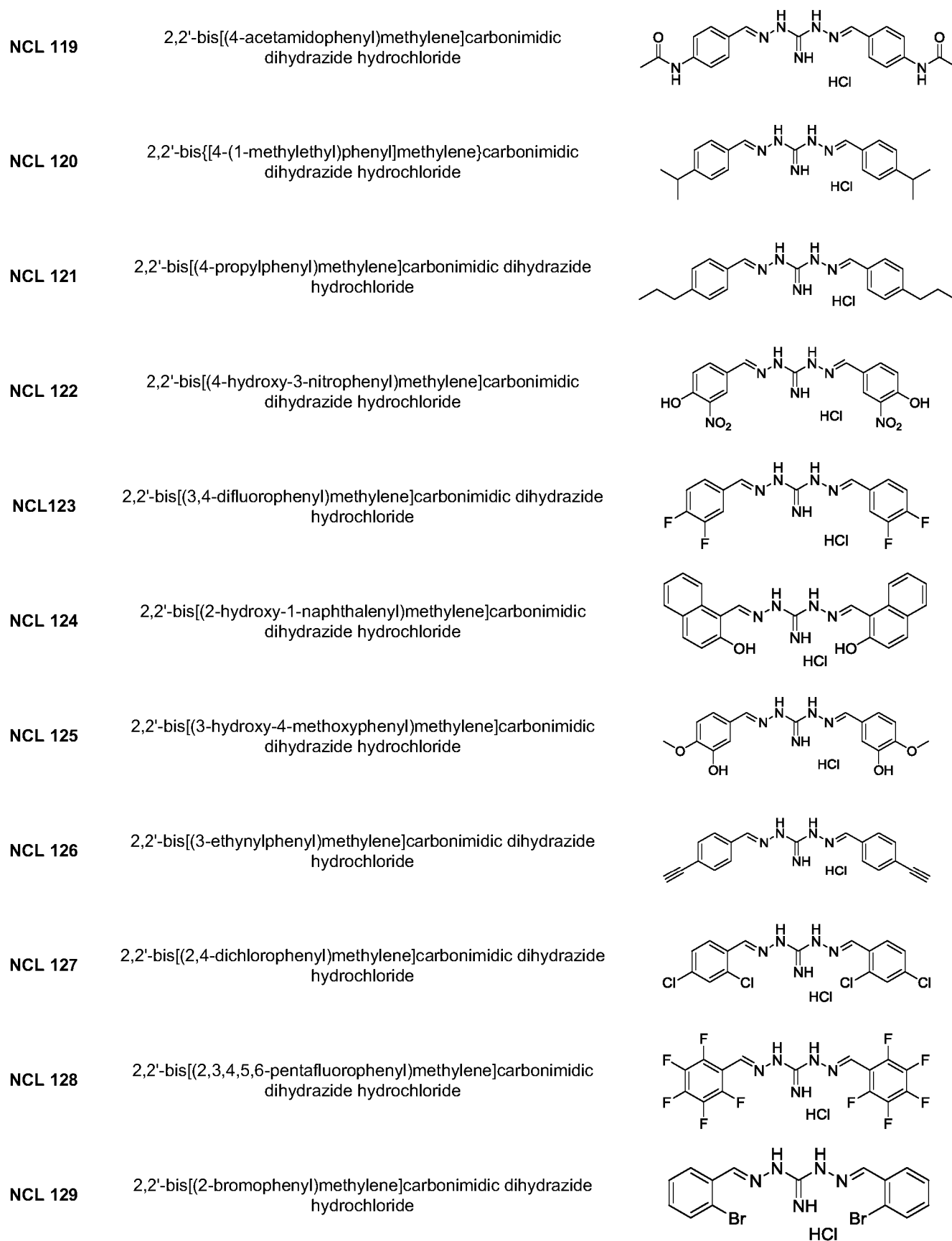


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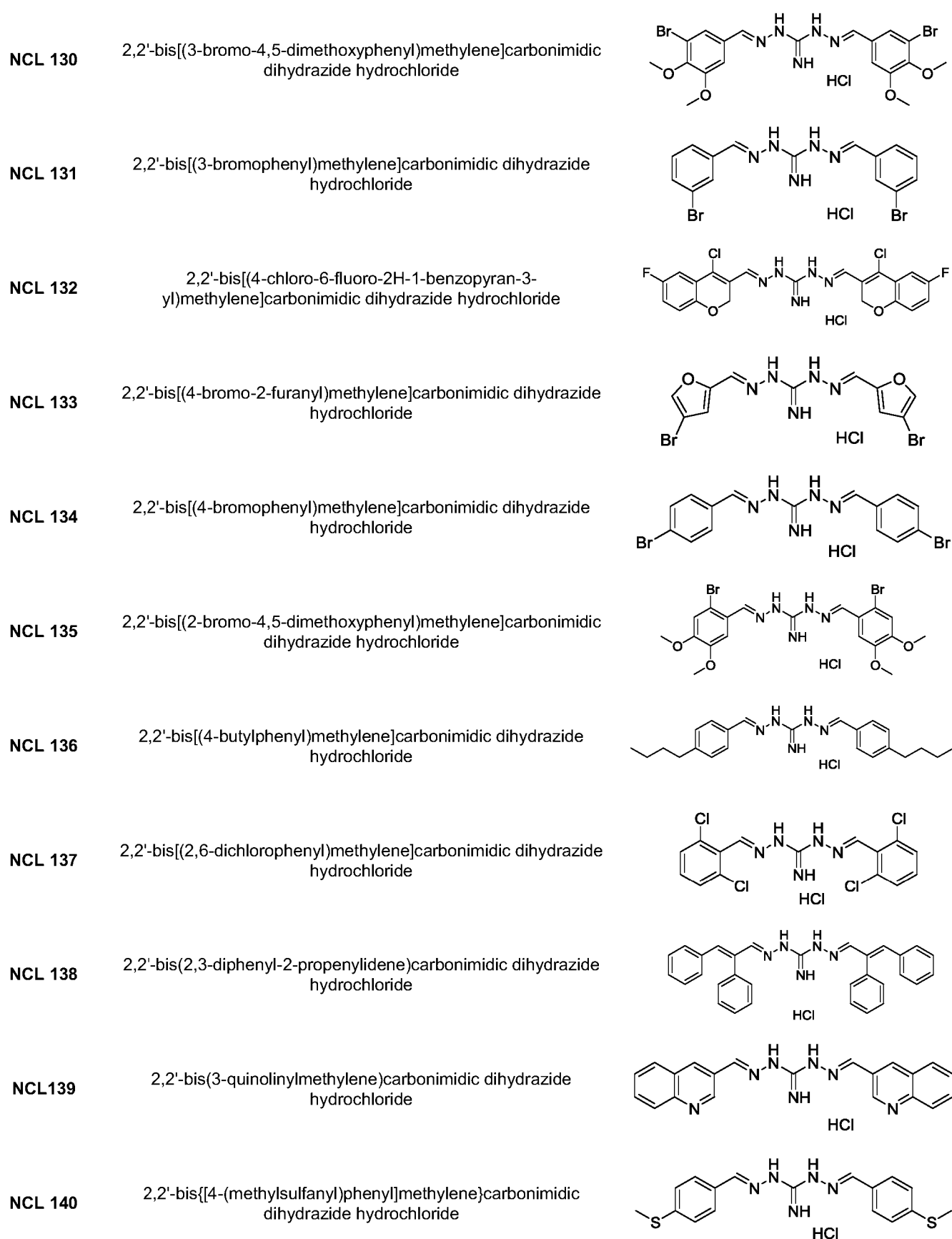


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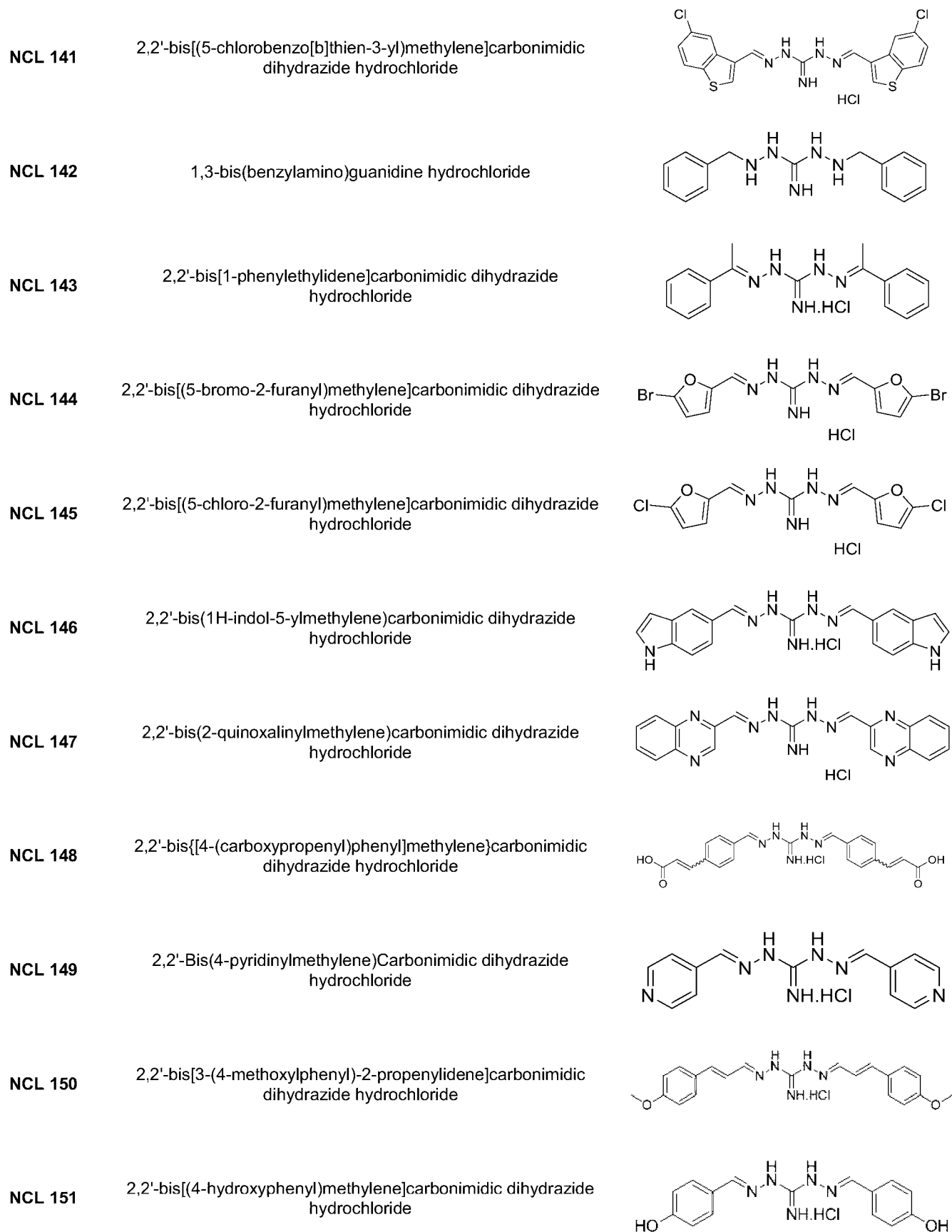


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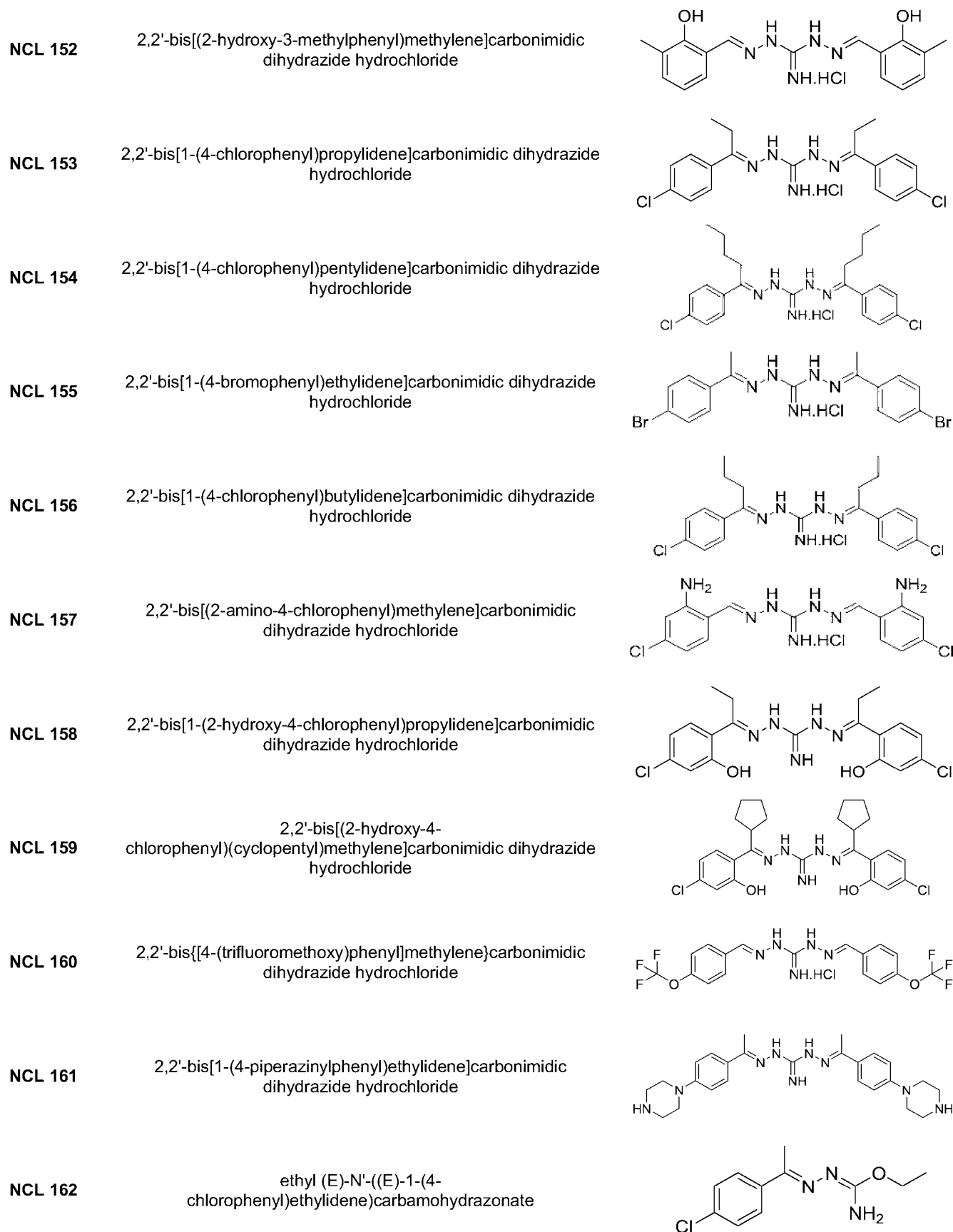


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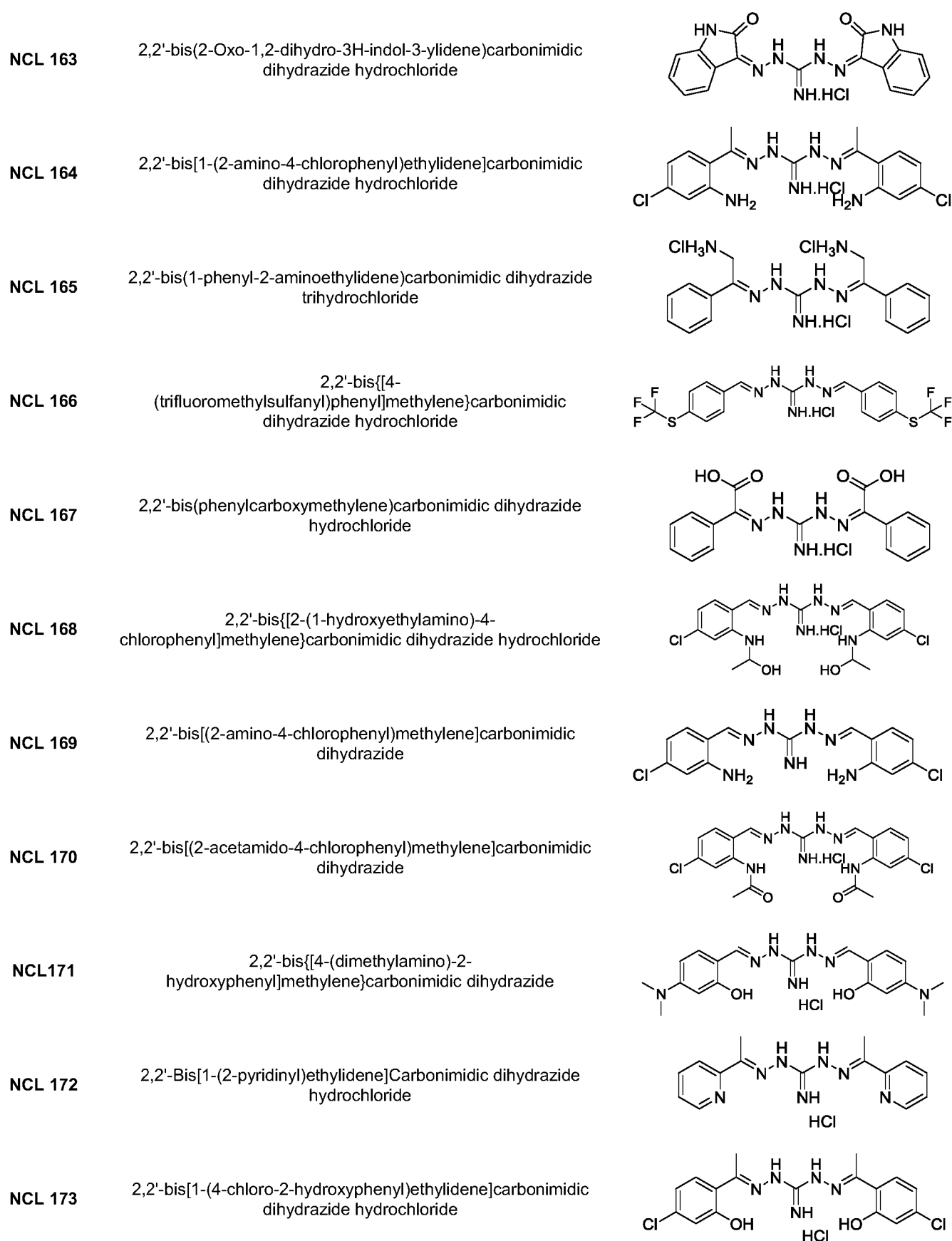


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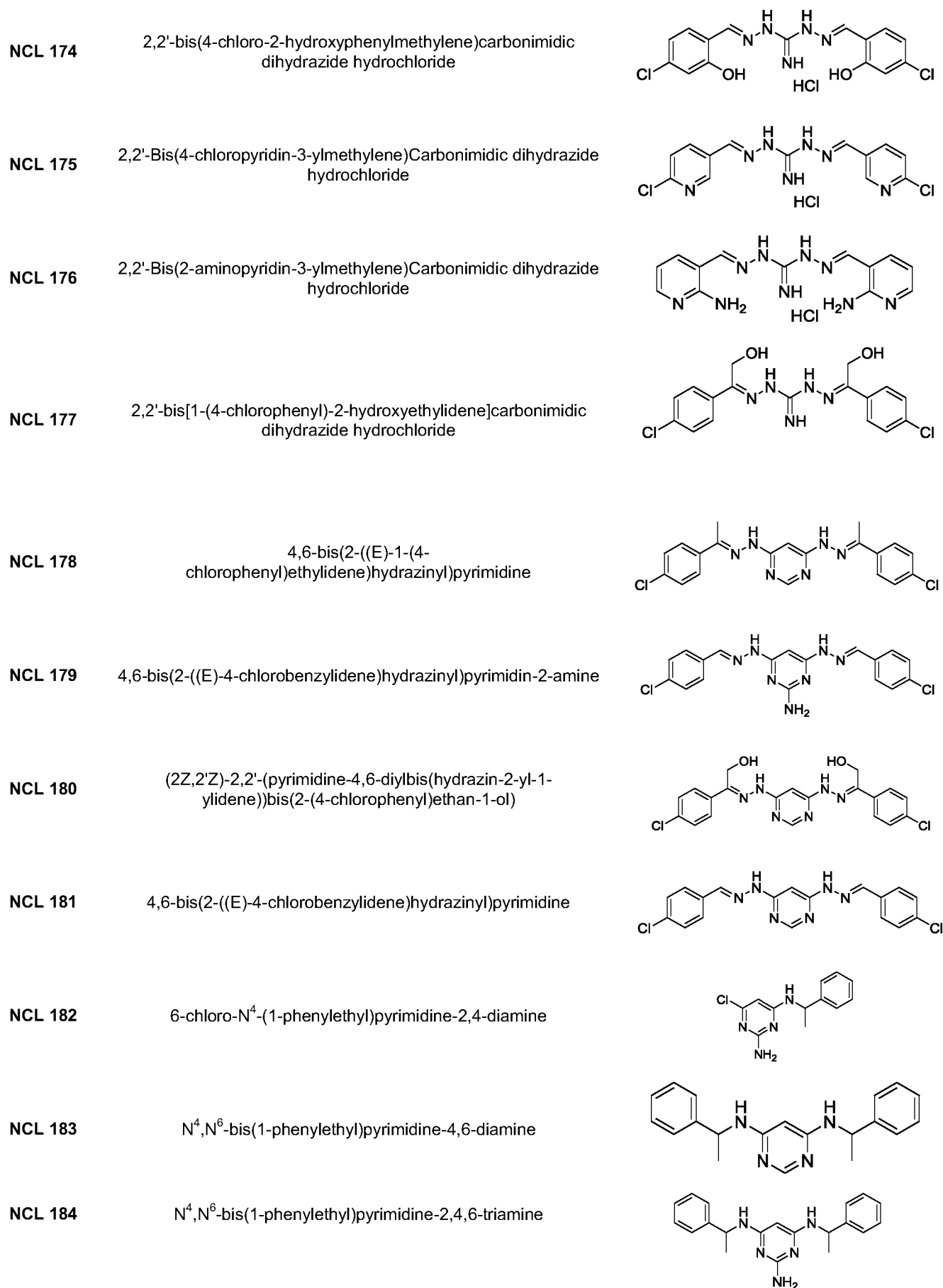


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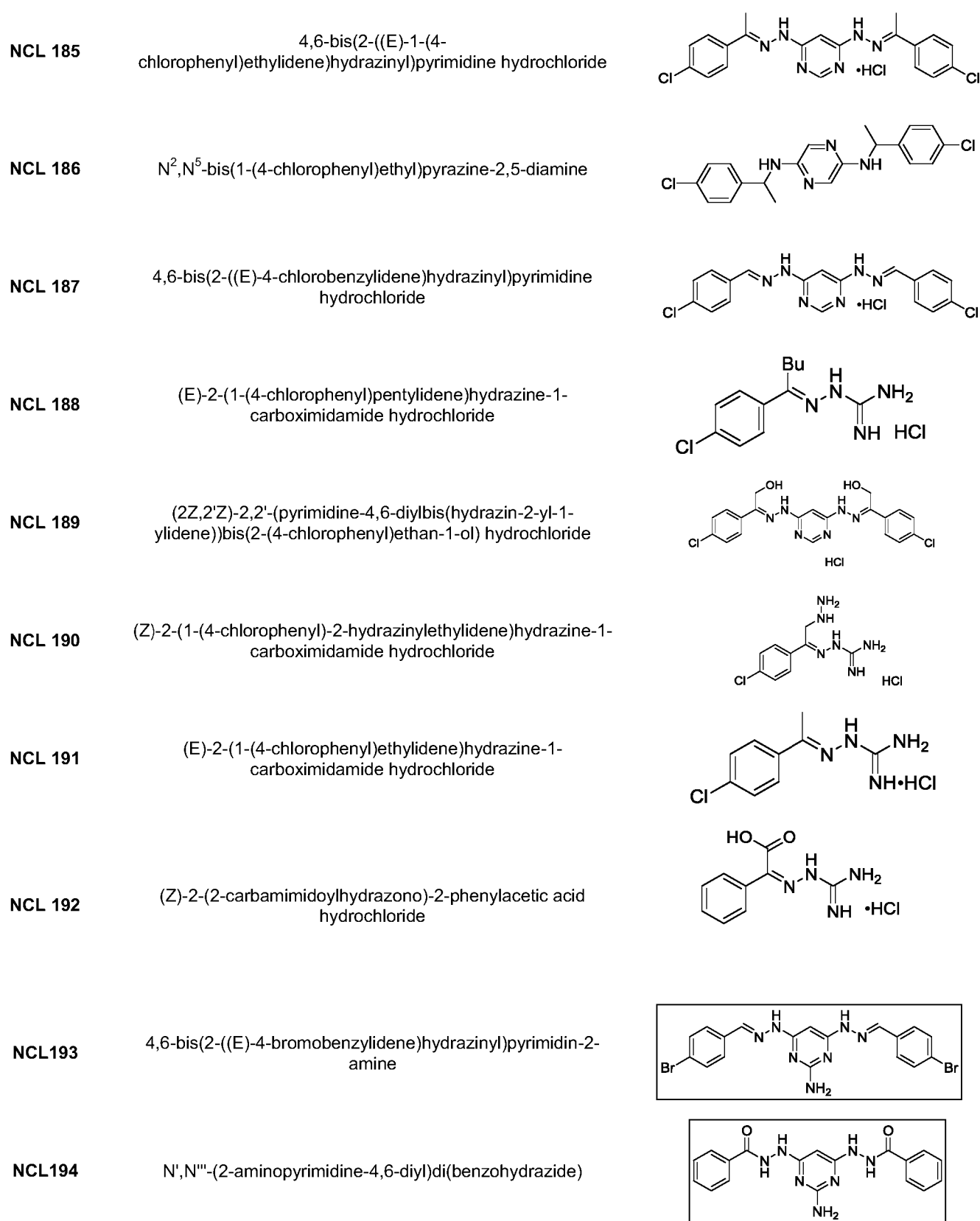


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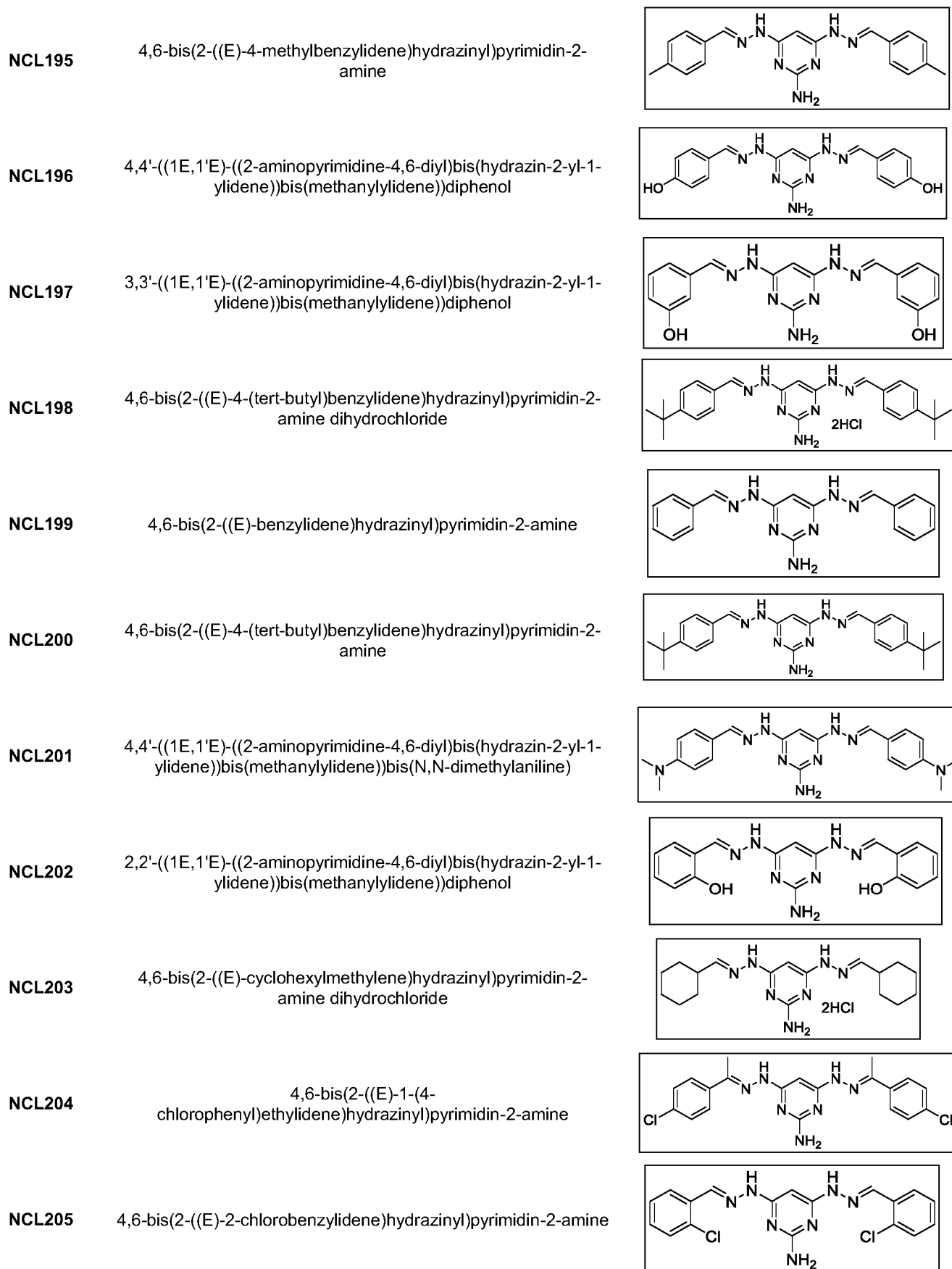


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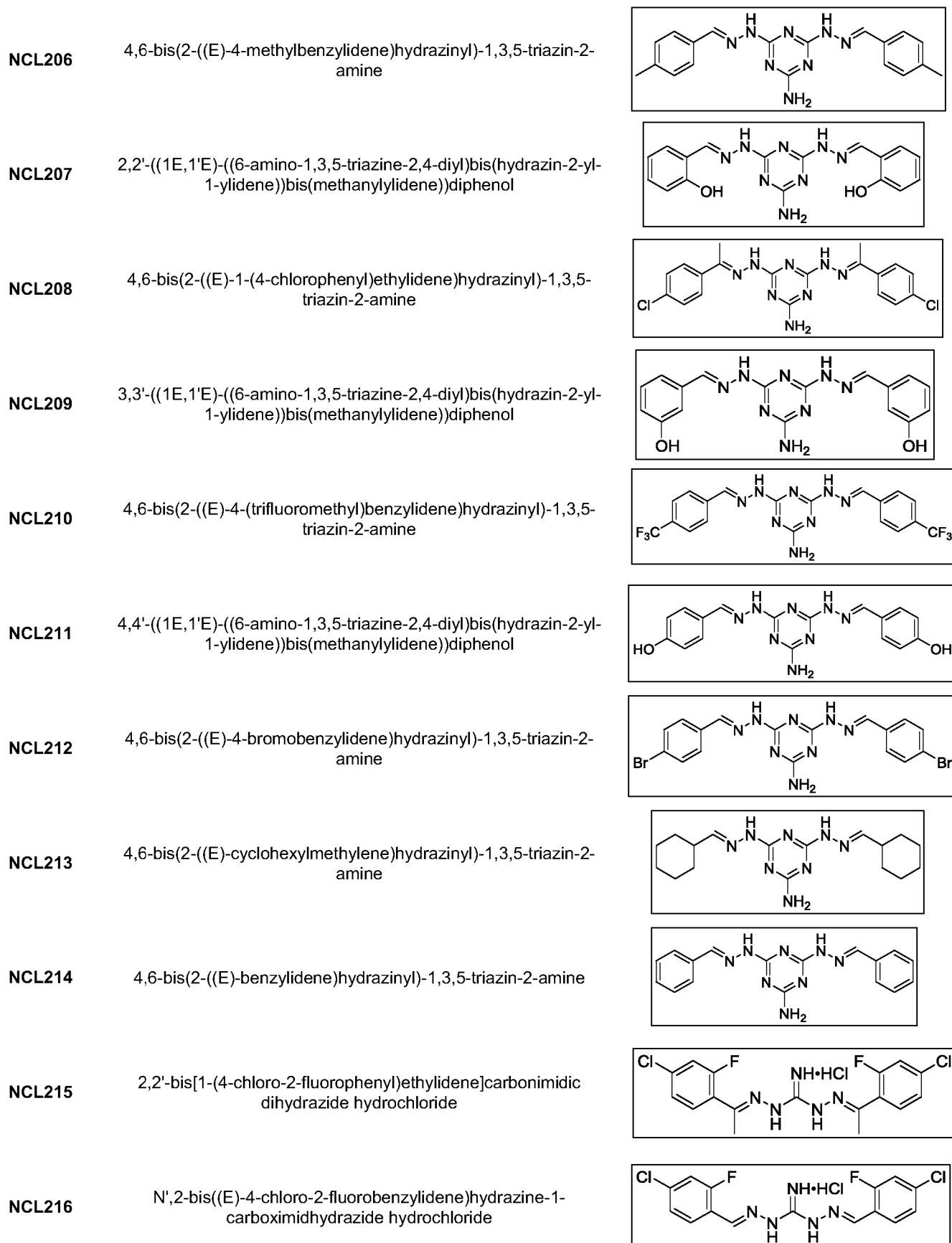
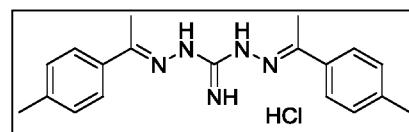


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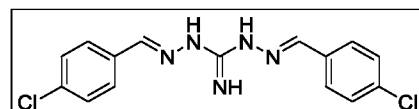
NCL217

N',2-bis((E)-1-(p-tolyl)ethylidene)hydrazine-1-carboximidhydrazide hydrochloride



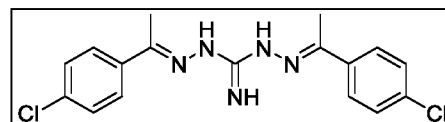
NCL812FB

As Previous



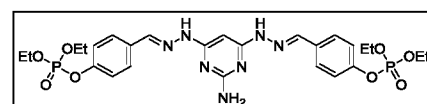
NCL062FB

As Previous



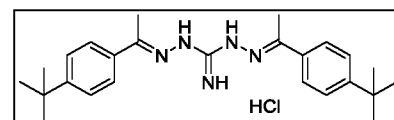
NCL218

4-((E)-(2-(2-amino-6-(2-((E)-4-((diethoxyphosphoryl)oxy)benzylidene)hydrazinyl)pyrimidin-4-yl)hydrazono)methyl)phenyl diethyl phosphate



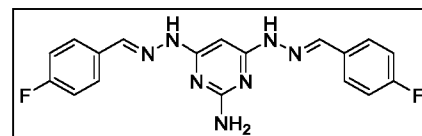
NCL219

2,2'-bis{1-[4-(t-butyl)phenyl]ethylidene}carbonimidic dihydrazide hydrochloride



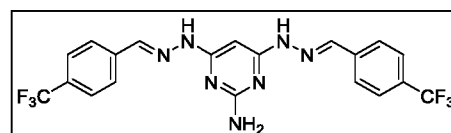
NCL220

4,6-bis(2-((E)-4-fluorobenzylidene)hydrazinyl)pyrimidin-2-amine



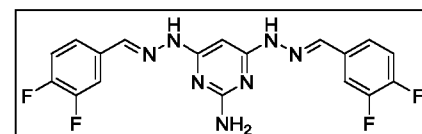
NCL221

4,6-bis(2-((E)-4-(trifluoromethyl)benzylidene)hydrazinyl)pyrimidin-2-amine



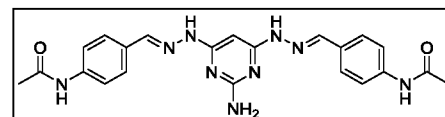
NCL222

4,6-bis(2-((E)-3,4-difluorobenzylidene)hydrazinyl)pyrimidin-2-amine



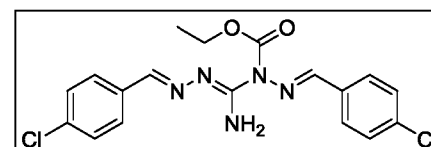
NCL223

N,N'-(((1E,1'E)-((2-aminopyrimidine-4,6-diyl)bis(hydrazin-2-yl-1-ylidene))bis(methanylylidene))bis(4,1-phenylene))diacetamide



NCL224

ethyl 2-((E)-4-chlorobenzylidene)-1-((E)-N'-((E)-4-chlorobenzylidene)carbamohydrazonoyl)hydrazine-1-carboxylate



NCL225

isobutyl 2-((E)-4-chlorobenzylidene)-1-((E)-N'-((E)-4-chlorobenzylidene)carbamohydrazonoyl)hydrazine-1-

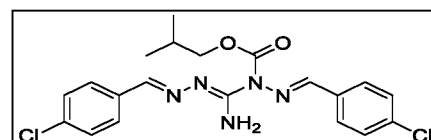


Figure 1 continued

carboxylate

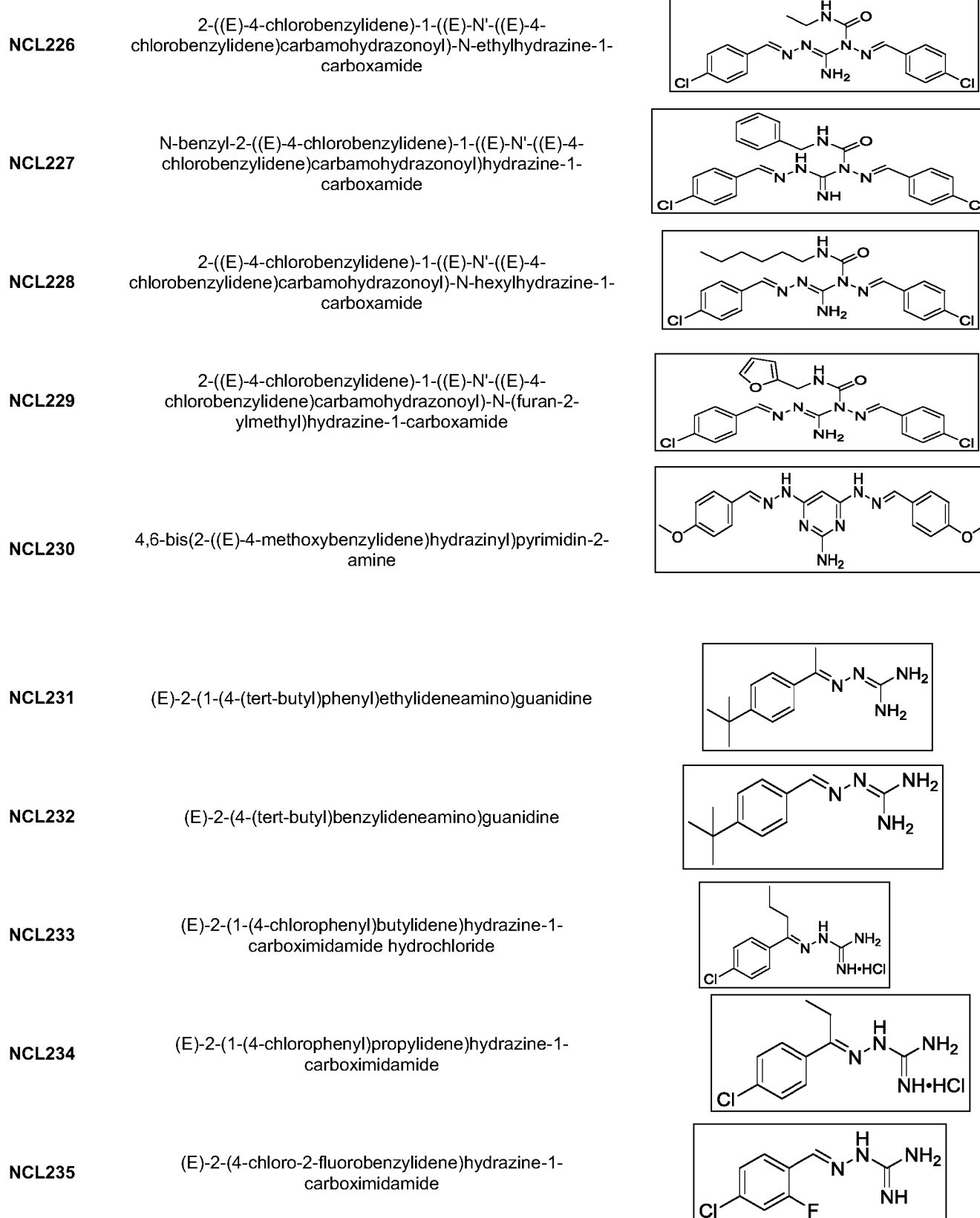


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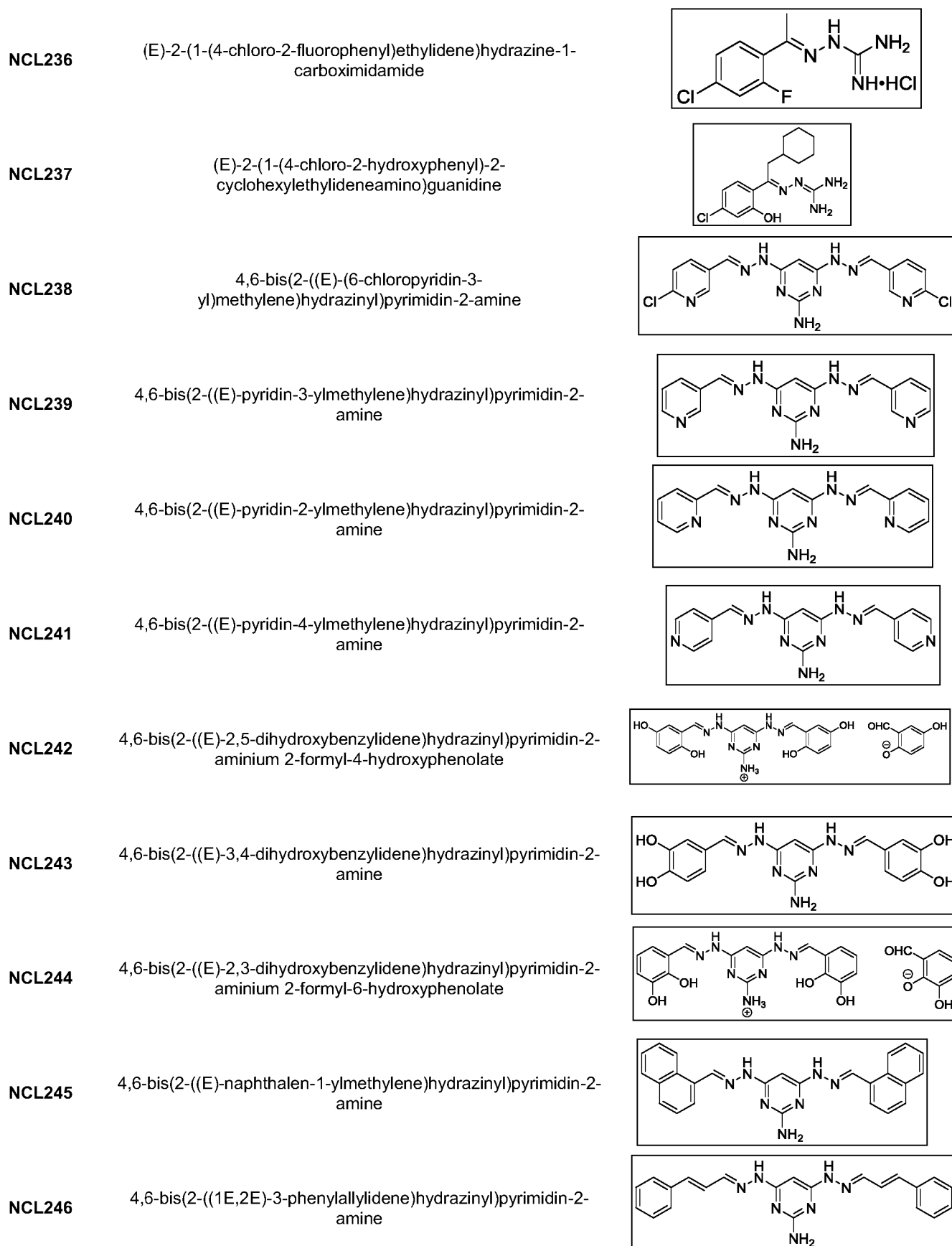


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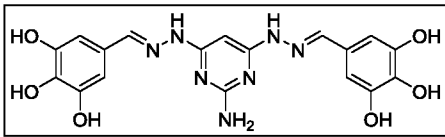
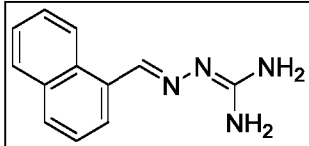
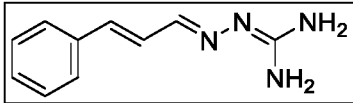
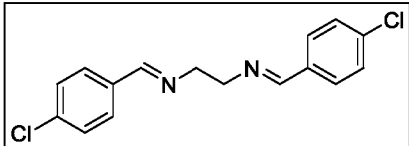
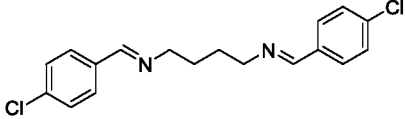
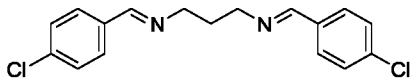
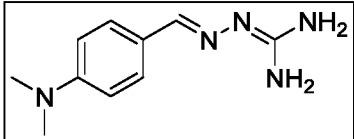
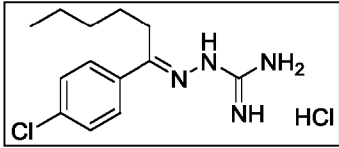
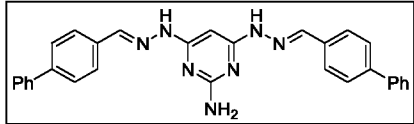
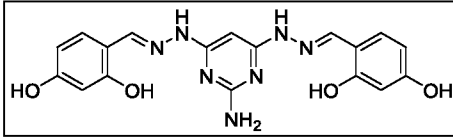
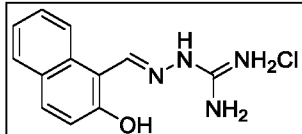
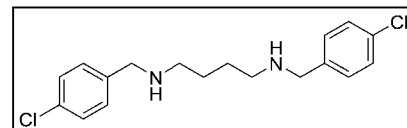
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NCL248	(E)-2-(naphthalen-1-ylmethylideneamino)guanidine	
NCL249	(E)-2-((E)-3-phenylallylideneamino)guanidine	
NCL250	(1E,1'E)-N,N'-(ethane-1,2-diyl)bis(1-(4-chlorophenyl)methanimine)	
NCL251	(1E,1'E)-N,N'-(butane-1,4-diyl)bis(1-(4-chlorophenyl)methanimine)	
NCL252	(1E,1'E)-N,N'-(propane-1,3-diyl)bis(1-(4-chlorophenyl)methanimine)	
NCL253	(E)-2-(4-(dimethylamino)benzylideneamino)guanidine	
NCL254	(E)-2-(1-(4-chlorophenyl)hexylidene)hydrazine-1-carboximidamide hydrochloride	
NCL255	4,6-bis(2-((E)-[1,1'-biphenyl]-4-ylmethylene)hydrazinyl)pyrimidin-2-amine	
NCL256	4,6-bis(2-((E)-2,4-dihydroxybenzylidene)hydrazinyl)pyrimidin-2-amine	
NCL257	(E)-2-((2-hydroxynaphthalen-1-yl)methylene)hydrazine-1-carboximidamide hydrochloride	

Figure 1 continued

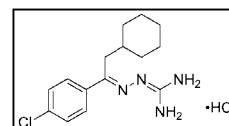
NCL258

N1,N4-bis(4-chlorobenzyl)butane-1,4-diamine



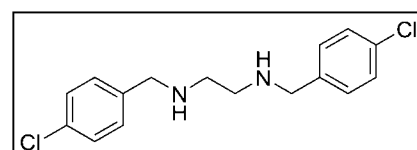
NCL259

(E)-2-(1-(4-chlorophenyl)-2-cyclohexylethylidene)hydrazine-1-carboximidamide hydrochloride



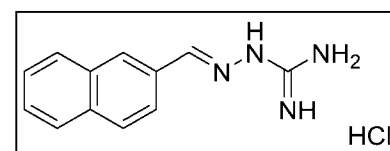
NCL260

N1,N2-bis(4-chlorobenzyl)ethane-1,2-diamine



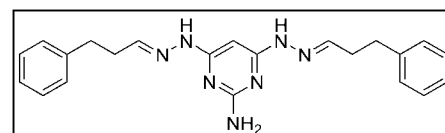
NCL261

(E)-2-(naphthalen-2-ylmethylene)hydrazine-1-carboximidamide hydrochloride



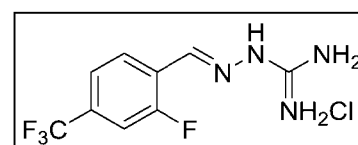
NCL262

4,6-bis(2-((E)-3-phenylpropylidene)hydrazinyl)pyrimidin-2-amine



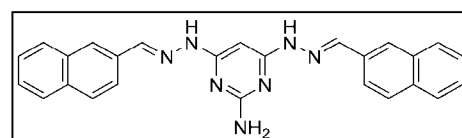
NCL263

(E)-2-(2-fluoro-4-(trifluoromethyl)benzylidene)hydrazine-1-carboximidamide hydrochloride



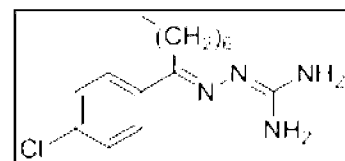
NCL264

4,6-bis(2-((E)-naphthalen-2-ylmethylene)hydrazinyl)pyrimidin-2-amine



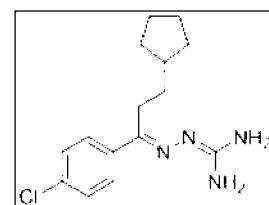
NCL265

(E)-2-(1-(4-chlorophenyl)-octylideneamino)guanidine



NCL266

(E)-2-(1-(4-chlorophenyl)-3-cyclopentylpropylideneamino)guanidine



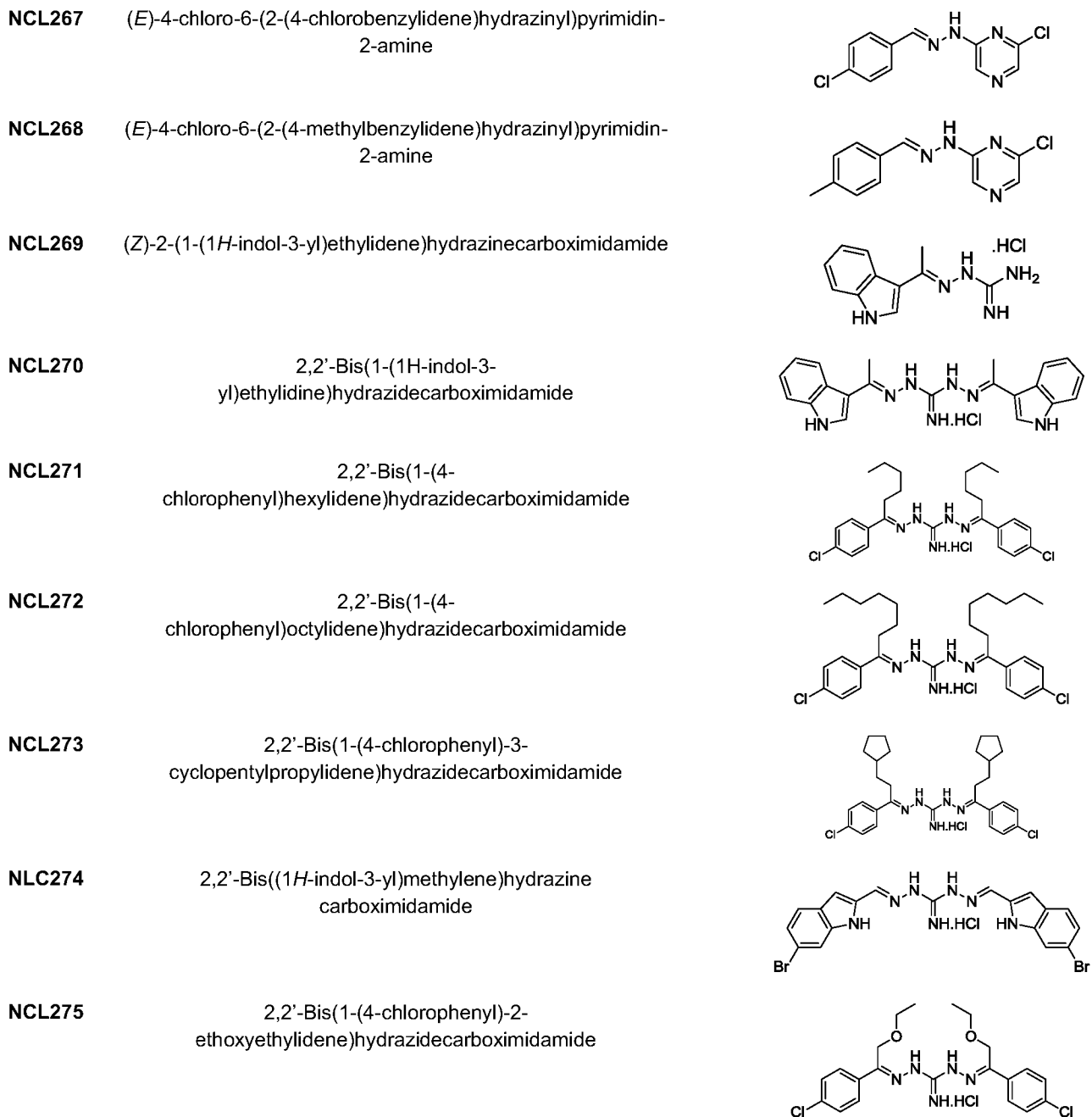


Figure 1 continued

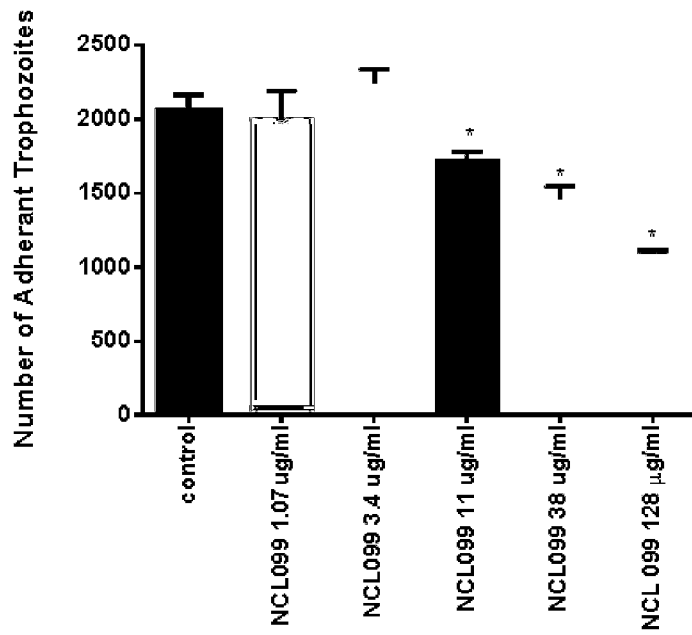


Figure 2

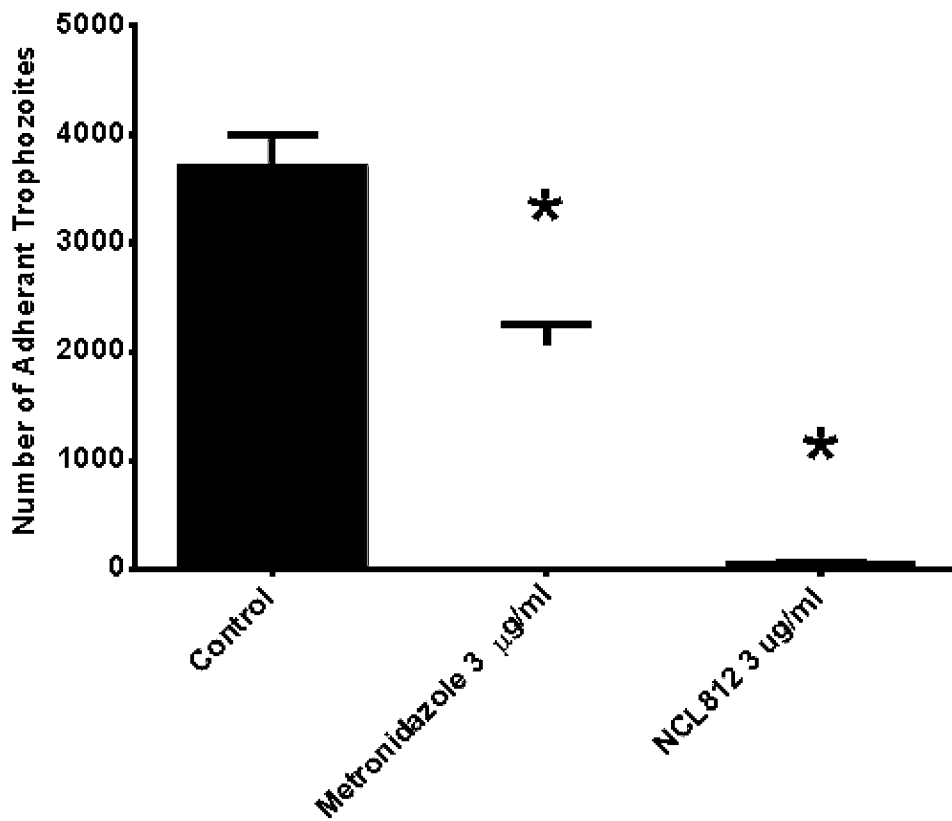


Figure 3

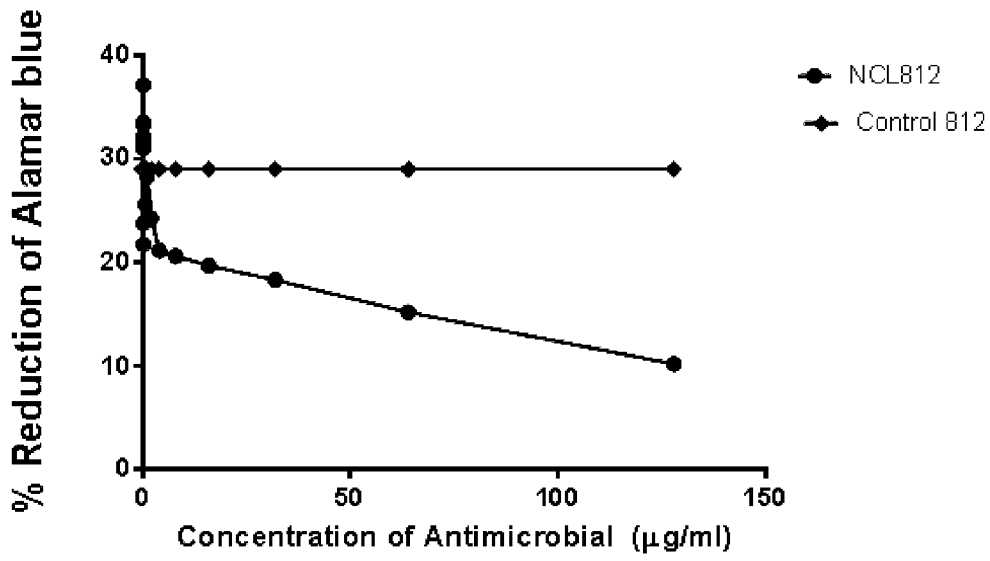


Figure 4

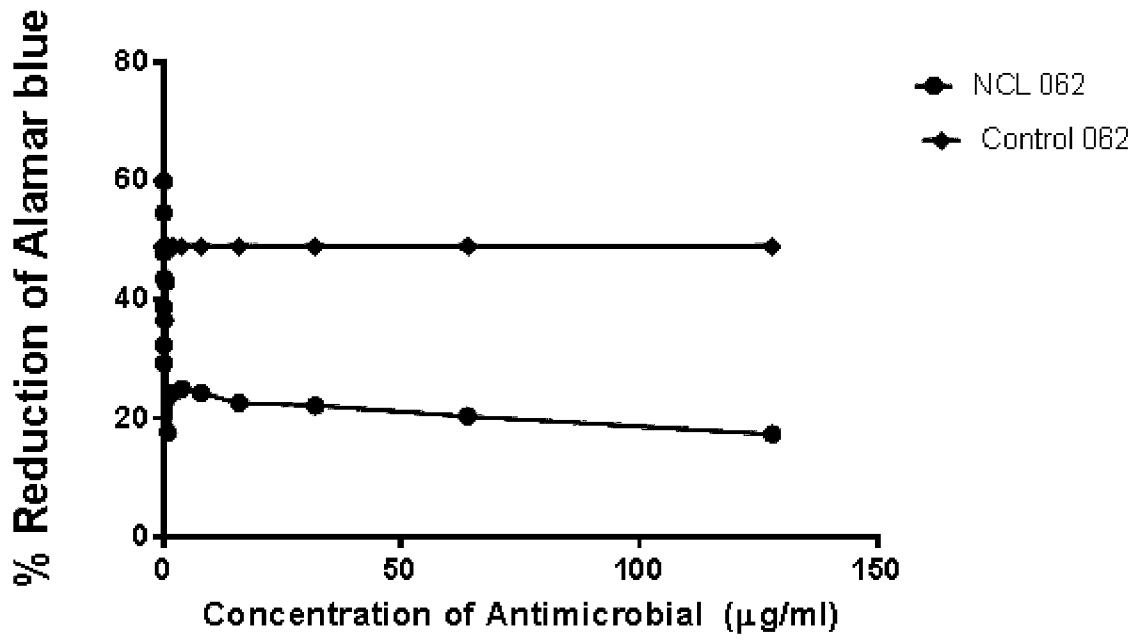


Figure 5

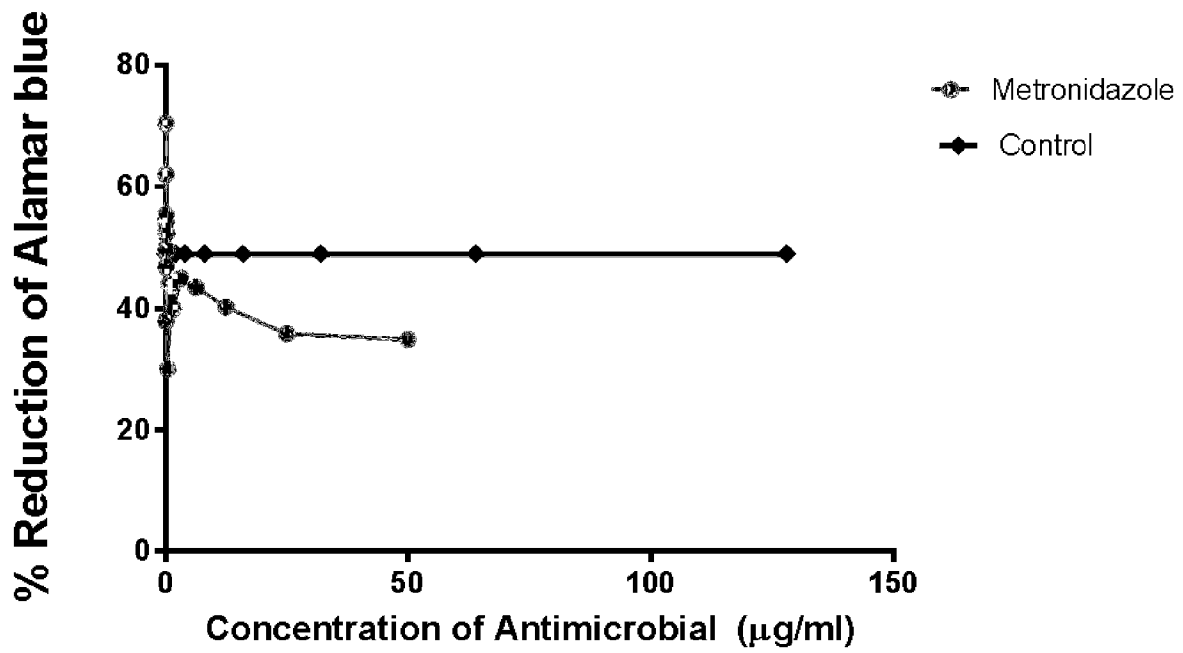


Figure 6

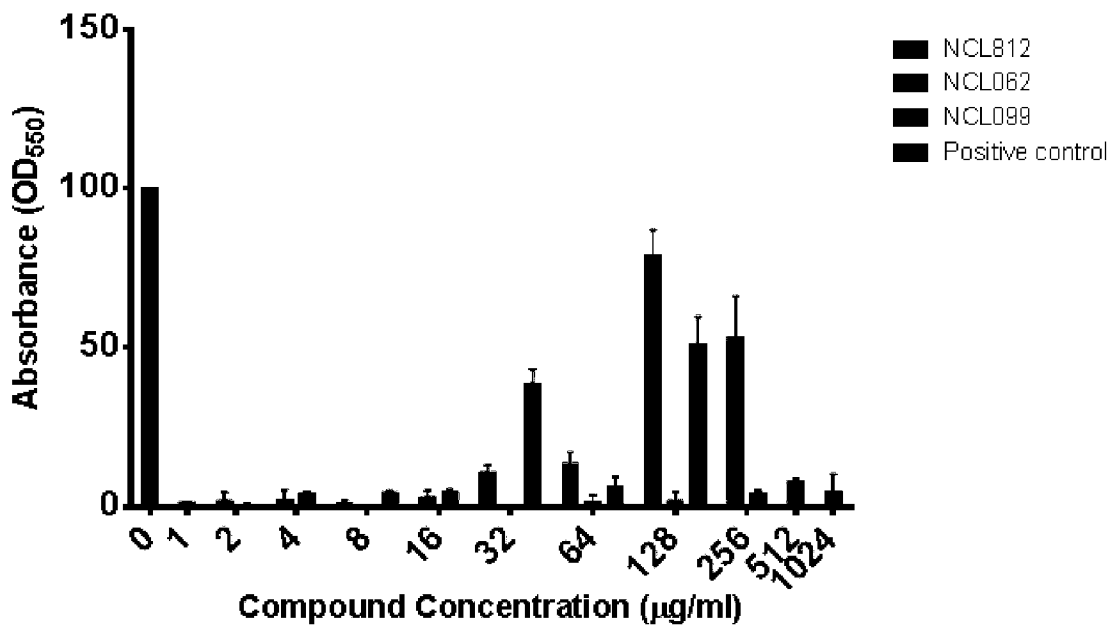


Figure 7

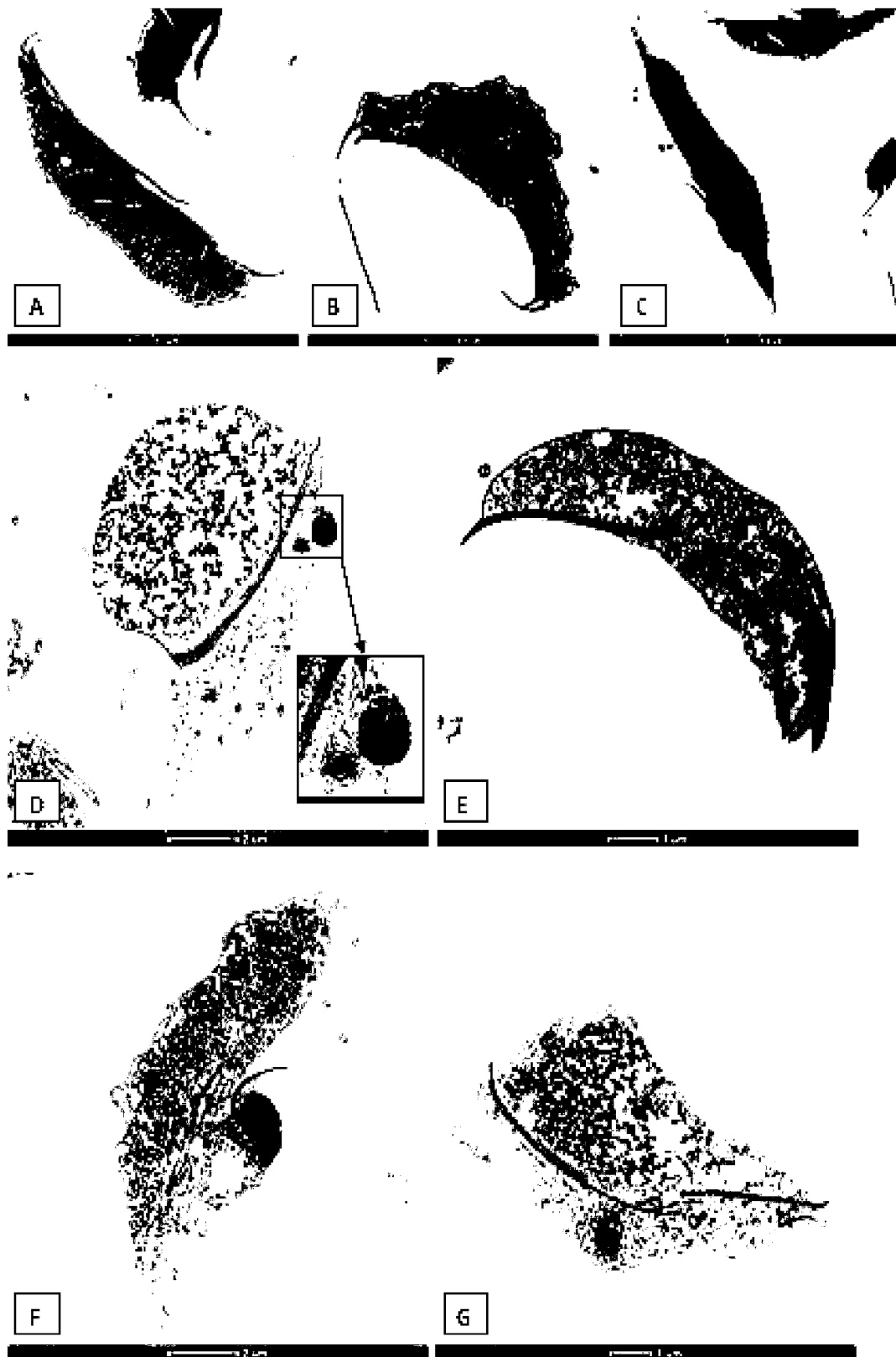


Figure 8

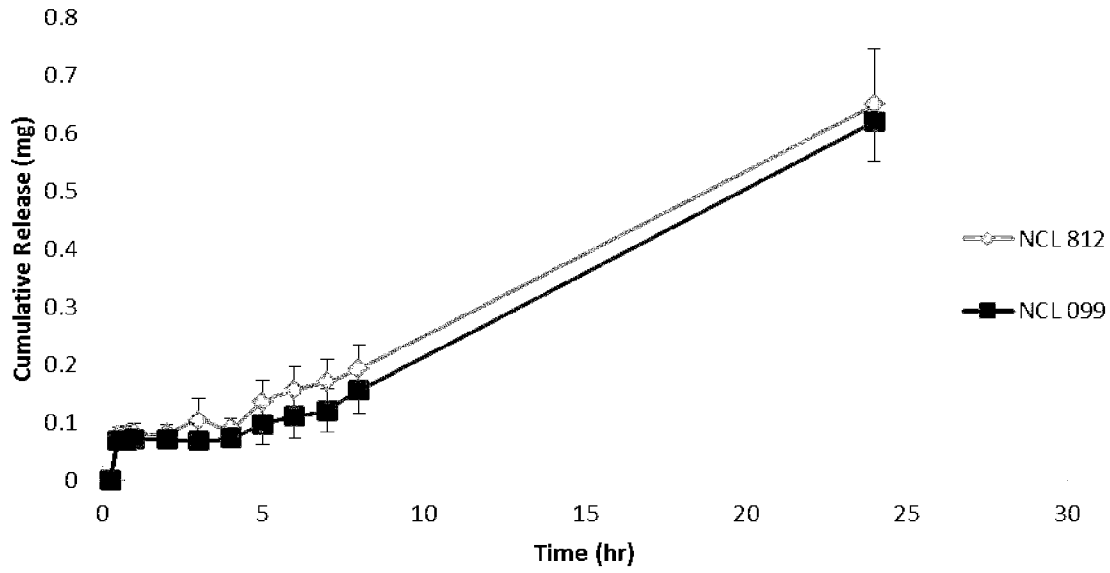


Figure 9

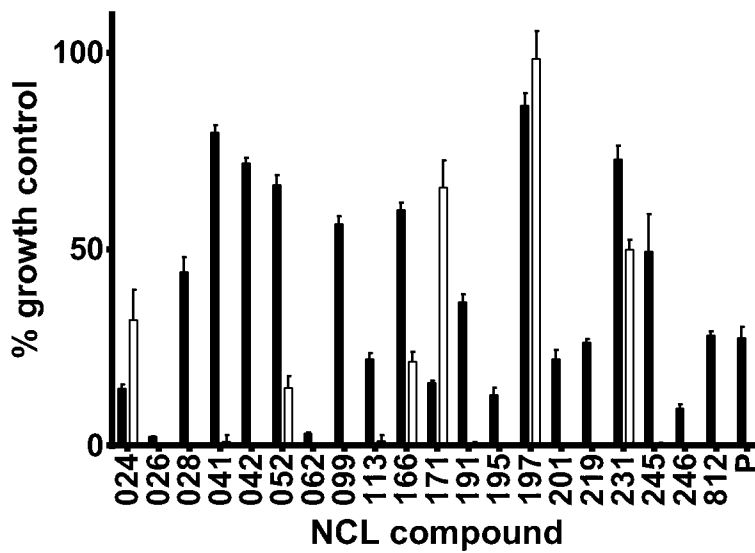


Figure 10


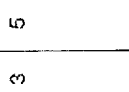

Compound Details			Physicochemical Parameters								Metabolism Parameters						
Compound	Batch	Structure	MW	PSA (Å ²)	FRB	# H-Bond		pKa	LogD			Solubility (µg/mL)		Species	T _{1/2} (min)	CL _{int} (µL/min/mg protein)	E _H
						Don	Acc		pH 3.0	pH 7.4	pH 2.0	pH 6.5					
NCL026	AS5099		315.33	120.2	4	3	7	4.8 – imine (bold) 1.2 – amine (italic)	2.8	3.6	1.6 – 3.1	< 1.6	Human	>247	<7	<0.22	
NCL028	AS5098		325.37	91.1	6	3	9	5.2 – imine (bold) 1.5 – amine (italic)	3.3	4.2	12.5 – 25	1.6 – 3.1	Human	234	7	0.23	
NCL099	AS5096		377.53	72.6	6	3	5	5.1 – imine (bold) 2.4 – amine (italic)	4.9	> 5.3	< 1.6	< 1.6	Human	20	89	0.78	
													Mouse	6	276	0.86	
													Mouse	25	70	0.60	

Figure 11

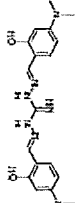
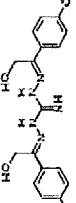
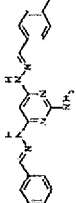
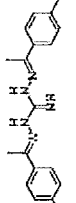
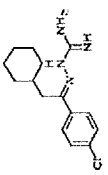
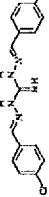
Compound Details			Physicochemical Parameters										Metabolism Parameters			
Compound	Batch	Structure	MW	PSA (Å²)	FRB	# H-Bond		pKa	LogD		Solubility (µg/mL)		Species	T _{1/2} (min)	CL _{int} (µL/min/mg protein)	E _H
						Don	Acc		pH 3.0	pH 7.4	pH 2.0	pH 6.5				
NCL171	AS2102		383.45	119.6	6	5	11	6.8 / 6.0 – dimethyl amines	3.2	4.0	ND ^a	< 1.6	Human	9	188	0.88
NCL177	AS5088		394.26	113.1	6	5	9	4.0 – imine (bold)	3.2	4.0	25 – 50	< 1.6	Human	>247	<7	<0.22
NCL195	AS5087		359.43	100.5	6	4	7	4.9 / 4.3 – amines (bold)	3.7	4.3	3.1 – 6.3	< 1.6	Human	>247	<7	<0.22
NCL217	AS5073		321.42	72.6	4	3	5	2.2 – pyrimidine (fatic)	3.9	5.1	3.1 – 6.3	< 1.6	Mouse	>247	<7	<0.13
								5.5 – imine (bold)					Human	71	24	0.49
								2.1 – amine (fatic)					Mouse	14	122	0.72

Figure 11 continued.

Compound Details			Physicochemical Parameters							Metabolism Parameters						
Compound	Batch	Structure	MW	PSA (Å ²)	FRB	# H-Bond		pKa	LogD		Solubility (µg/mL)		Species	T _{1/2} (min)	CL _{int} (µL/min/mg protein)	E _H
						Don	Acc		pH 3.0	pH 7.4	pH 2.0	pH 6.5				
NCL259	AS5072		292.81	76.0	4	4	4	8.6 – imine (bold) 1.4 – amine (italic)	3.4	4.6	> 100	6.3 - 12.5	Human	>247	<7	<0.22
NCL812	AS5086		334.20	72.6	4	3	5	5.0 – imine (bold) 1.2 – amine (italic)	3.7	4.5	6.3 - 12.5	< 1.6	Human	>247	<7	<0.22
													Mouse	>247	<7	<0.13

^a Solubility value could not be determined, as the nephelometry results were inconclusive.

Figure 11 continued.

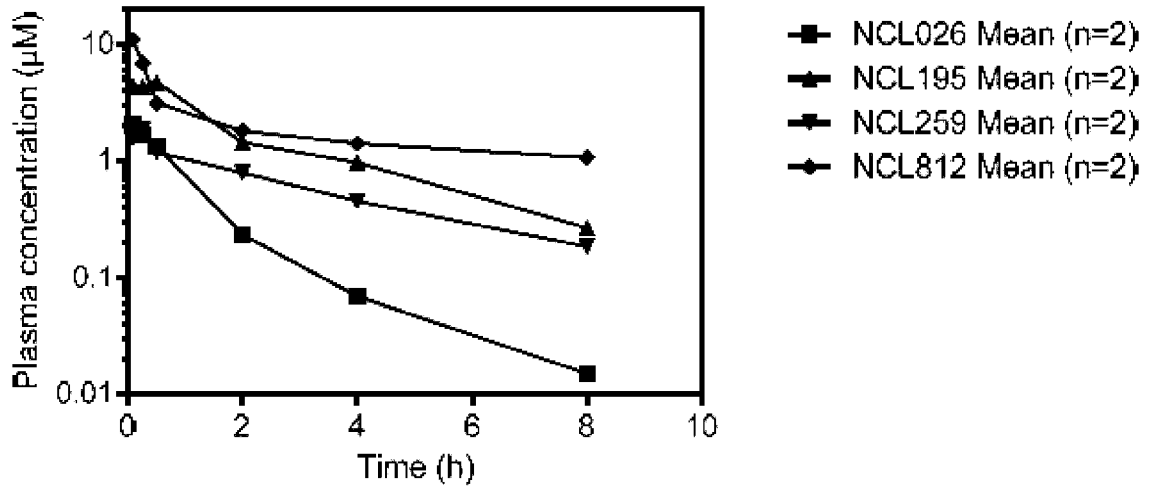


Figure 12

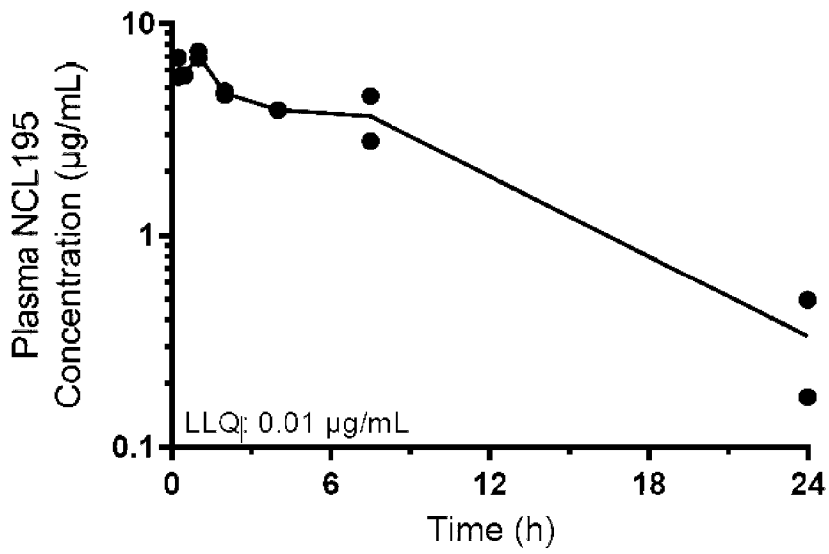


Figure 13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2015/000527

A. CLASSIFICATION OF SUBJECT MATTER [See Supplemental Sheet]		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) STN: Chemical Abstract Registry and CAplus. Substructure search based on compounds of Formula I, and molecular formula and name searches of compounds NCL23 1-NCL275 PatentScope and Espacenet: Inventor and Applicant Search		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C <input checked="" type="checkbox"/> See patent family annex		
* "A"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed	
Date of the actual completion of the international search 17 November 2015	Date of mailing of the international search report 17 November 2015	
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustrialia.gov.au		Authorised officer Ben Harris AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. 0262832272

INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT/AU2015/000527
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3992446 A (TOMCUFCIK) 16 November 1976 see Tables I and II col. 10-12; column 12 lines 22-26	1-3, 9-14, 17-38
X	GB 1304164 A (AMERICAN CYANAMID COMPANY) 24 January 1973 see Table I and lines 1-38 page 2	1-3, 9, 11-13, 19, 23-24, 26, 29-32 and 37-38
X	WO 1994/006280 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 31 March 1994 see compound 197A page 19 and 30; page 27 line 9 to page 28 line 7; page 27 line 9 to page 28 line 30, examples 14-17 pages 35-38, and claim 12	1, 3, 10-13, 18-19, 21, 23-24, 26-27, 29-33 and 37-38
X	US 3897563 A (KULSA et al.) 29 July 1975 see Examples 1-10 col. 5-8; col. 5 lines 16-62; claim 1	1, 3, 9-13, 19-20, 23-26, 29-32 and 37-38
X	US 4310541 A (WANG et al.) 12 January 1982 see col. 4 lines 26-44; col. 3 lines 9-49; col. 4 line 45 to col. 5 line 31	1, 3, 10-13, 18-19, 23-24, 26, 29-32 and 37-38
X	US 4015016 A (LIVAK et al.) 29 March 1977 see col. 4 line 65 to col. 5 line 24, and col. 6 line 53 to col. 7 line 41; col. 8 line 6 to col. 10 line 22; Example 8-1 1 col. 10-17	1, 3, 9-13, 19-20, 23-26, 29-32 and 37-38
X	US 3795692 A (KULSA P. et al.) 05 March 1974 see col. 4 lines 30-52; col. 4 line 54 to col. 5 line 27; col. 1 line 53-63 and col. 3 lines 52-55	1, 3, 9-13, 19-20, 23-26, 29-32 and 37-38
X	GB 1256723 A (AMERICAN CYANAMID COMPANY) 15 December 1971 see Tables I and II pages 4-6; page 6 lines 2-24	1-3, 9-13, 19-21, 23-27, 29-33 and 37-38
X	CAS Registry Number 936347-46-5, STN Entry Date 01 June 2007 Whole document	39
X	CAS Registry Number 7147-21-9, STN Entry Date 16 November 1984 Whole document	39

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

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

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

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

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

See Supplemental Box for Details

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-38 (in part) and 39-40 (in full)

Remark on Protest

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

Supplemental Box**Continuation of: Box III**

The international Application does not comply with the requirement of unity of invention because it does not relate to one invention so linked as to form a single inventive concept.

This authority has found that there are different inventions based on the following features that separate the claims into distinct groups:

Invention 1: Claims 1-40 (in part) are directed toward compounds of Formula I wherein R₃ is selected from Formula IV, V or VI or -N=C-chlorophenyl; and R₄ and is not bonded together with R₂ or A₀; compositions thereof and use in the treatment of bacterial infection.

Invention 2: Claims 1-40 (in part) are directed toward compounds of Formula I wherein R₃ is selected from H, NH₂, NHNH₂, OCH₂CH₃, substituted NH group; and R₄ and is not bonded together with R₂ or A₀; compositions thereof and use in the treatment of bacterial infection.

Invention 3: Claims 1-40 (in part) are directed toward compounds of Formula I wherein R₄ and R₂ together form a pyrimidine, pyrazine or triazine ring; or wherein R₄ and A₀ together form a triazole.

Invention 4: Claims 1-40 (in part) are directed towards compounds of Formula I wherein R₃ is N and R₄ is CH-N-CH-CC1- and is bound to R₃, forming a 2-chloropyrazine.

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

The compounds within the groups of inventions, as above, are all linked by the feature that they are all compounds of Formula (I) which are useful for the treatment of bacterial infections. However said feature cannot be a special technical feature for the requirements of unity of invention as it does not make a contribution over the prior art as they are already disclosed in D1.

D1: US 3992446 A (TOMCUFCIK) 16 November 1976

D1 discloses compounds of Formula I; feedstock comprising these compounds; and their use for the treatment of *Eimeria* protozoan (see Tables I and II col. 10-12).

Therefore in view of D1 the groups of compounds, as above, do not contain a special technical feature which makes a contribution over the prior art and as such does not meet the requirements of unity *a posteriori*.

It is considered that the search and examination for the additional inventions would require more than negligible additional search and examination effort over that of the first invention.

This opinion has been restricted to claims 1-38 in part, where they relate to the first invention, and claims 39-40 in full.

Supplemental Box - IPC Marks

A61K 31/155 (2006.01)

A61K 31/4045 (2006.01)

A61K 31/4192 (2006.01)

A61K 31/341 (2006.01)

A61K 31/381 (2006.01)

A61K 31/498 (2006.01)

A61K 31/44 (2006.01)

A61K 31/137 (2006.01)

C07C 279/02 (2006.01)

C07C 241/04 (2006.01)

C07C 281/08 (2006.01)

C07C 337/08 (2006.01)

C07C 281/18 (2006.01)

C07D 249/14 (2006.01)

C07O 407/12 (2006.01)

C07D 403/12 (2006.01)

C07D 409/12 (2006.01)

C07D 401/12 (2006.01)

C07D 241/20 (2006.01)

C07C 211/27 (2006.01)

C07C 275/68 (2006.01)

C07C 251/24 (2006.01)

A61P 33/02 (2006.01)

A61P 33/04 (2006.01)

A61P 33/06 (2006.01)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/AU2015/000527

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
US 3992446 A	16 November 1976	US 3992446 A	16 Nov 1976
		US 3901944 A	26 Aug 1975
		US 3941825 A	02 Mar 1976
GB 1304164 A	24 January 1973	GB 1304164 A	24 Jan 1973
		FR 2122362 A2	01 Sep 1972
		FR 2122362 B2	22 Mar 1974
		NL 71005 15 A	18 Jul 1972
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		EP 0817624 B1	02 Oct 2002
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		US 3897563 A	29 Jul 1975
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		BE 735375 A	30 Dec 1969
		CA 927394 A	29 May 1973
		CS 170139 B2	27 Aug 1976

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/AU2015/000527

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		DE 1933 112 A1	08 Jan 1970
		DE 1933 112 B2	26 Sep 1974
		DK 129448 B	14 Oct 1974
		ES 368955 A1	16 Jul 1971
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		FR 2012054 B1	12 Jan 1973
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		PH 9607 A	19 Jan 1976
		PL 89014 B1	30 Oct 1976
		PL 89704 B1	31 Dec 1976
		SE 370396 B	14 Oct 1974
		YU 167269 A	30 Jun 1976
		YU 33388 B	31 Dec 1976
		YU 223474 A	31 Aug 1976
		YU 33444 B	28 Feb 1977
		YU 223574 A	31 Aug 1976
		YU 33445 B	28 Feb 1977

End of Annex