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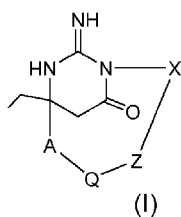
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(57) Abstract: The present disclosure is directed to compounds of Formula I: (I) and methods of treatment of Plasmodium infections comprising administering to a subject in need thereof a compound of Formula I, or a pharmaceutically acceptable salt thereof.



WO 2024/258769 A1

ANTIMALARIAL AGENTS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is an International Patent Application of International Patent Application No. PCT/CN2023/100293, filed June 14, 2023, which is incorporated by reference in its entirety herein.

FIELD

[0002] The present disclosure relates to compounds of Formula I, or pharmaceutically acceptable salts thereof, useful for the treatment of Plasmodium infections. More specifically, the present disclosure relates to compounds of Formula I, or pharmaceutically acceptable salts thereof, useful for the treatment of malaria.

BACKGROUND

[0003] Malaria is a major disease in humans, with several hundred million infections and over 450,000 deaths each year. The most lethal form of malaria is caused by Plasmodium falciparum. This protozoan parasite is responsible for almost all malarial deaths, with most occurring in Africa. P. falciparum has a complex life cycle starting in the Anopheles mosquito vector when sporozoite forms are injected into the human host during a blood feed. These sporozoites migrate to the liver and invade hepatocytes in which they develop to form thousands of liver merozoites that egress into the blood where they invade erythrocytes to commence the asexual cycle of the parasite responsible for the symptoms of malaria. The parasite develops within the protected niche of the red cell to form 16-32 merozoites that, once mature, egress from the host cell to invade new red blood cells. Some of these parasites differentiate to form gametocytes, the sexual form of the parasite. These can be taken up by the mosquito where male and female gametes form, fuse and differentiate into oocysts on the mosquito midgut extracellular matrix. Sporozoites form within the oocyst and upon egress migrate to the salivary gland for delivery to the next host during blood feeding for perpetuation and survival of the parasite.

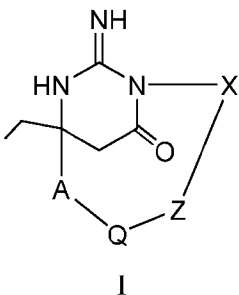
[0004] Other forms of malaria include a relapsing form of malaria caused by P. vivax which is responsible for significant morbidity, can cause virulent forms of this disease with some deaths and is mainly a problem outside Africa. P. knowlesi is found in South East Asia and is a zoonotic parasite that normally infects long-tailed macaques but has been shown to infect humans in Malaysian Borneo.

[0005] Artemisinin combined with partner drugs have become a mainstay in the treatment and control of malaria. However, due to the increasing threat of artemisinin-based combination therapy (ACT) drug resistance, the development of new antimalarials with novel targets that inhibit multiple steps in the parasite life cycle is an urgent priority for the malaria control field. Such novel antimalarials, as monotherapies or ACT partner drugs, could make strides towards malaria elimination as there is a reduced likelihood of parasites with preexisting resistance mutations being present in the parasite population.

[0006] Currently, aspartic acid proteases are prime targets for drug development: the HIV aspartic acid protease has been successfully targeted with a drug in clinical use; inhibitors that target human renin, BACE1 and gamma-secretase have been or are in clinical development. In the antimalarial drug space, *P. falciparum* aspartic acid proteases plasmepsin X and IX (PMX and PMIX) have been identified as potential targets since inhibitors block parasite egress and invasion of the host cell and prevent maturation of some rhoptry and micronemal proteins required for this process (Pino P, Caldelari R, Mukherjee B, Vahokoski J, Klages N, Maco B, et al. A multistage antimalarial targets the plasmepsins IX and X essential for invasion and egress. Science. 2017;358(6362):522-8.)

SUMMARY

[0007] The present disclosure is directed to compounds of Formula I:



wherein A, Q, X, and Z are described below.

[0008] Also described herein are methods of treatment of Plasmodium infections comprising administering to a subject in need thereof a compound of Formula I, or a pharmaceutically acceptable salt thereof. Also described herein are methods of treatment of Plasmodium infections comprising administering to a subject in need thereof a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0009] Also described herein are methods of treatment of malaria comprising administering to a subject in need thereof a compound of Formula I, or a pharmaceutically acceptable salt thereof.

[0010] The present disclosure further provides the use of compositions, including pharmaceutical compositions, comprising one or more compounds of the disclosure (e.g., one compound of the disclosure), or a tautomer thereof, or a pharmaceutically acceptable salt or solvate of said compound(s) and/or said tautomer(s), optionally together with one or more additional therapeutic agents, optionally in an acceptable (e.g., pharmaceutically acceptable) carrier or diluent, for the treatment of malaria.

[0011] Moreover, the present disclosure provides methods for the use of pharmaceutical compositions comprising one or more of said compounds in the free form or in pharmaceutically acceptable salt form, together with one or more customary pharmaceutical excipient(s), for the treatment of Plasmodium infections, the treatment of malaria, the inhibition of plasmepsin X, or the dual inhibition of plasmepsin X and plasmepsin IX. Methods for the use of combinations of the compounds or salts of the disclosure together with one or more additional pharmaceutically active agents are also provided.

[0012] The present disclosure further provides methods for the inhibition of plasmepsin X, or the dual inhibition of plasmepsin X and plasmepsin IX activity and of treatment, prevention, amelioration and/or delaying onset of diseases or disorders in which the inhibition of plasmepsin X and/or plasmepsin IX has or may have a therapeutic effect, e.g., malaria.

[0013] The present disclosure further provides methods for the inhibition of *P. falciparum* aspartic acid proteases. The present disclosure further provides methods for blocking *P. falciparum* growth by inhibiting plasmepsin X. The present disclosure further provides methods for blocking *P. falciparum* growth by inhibiting both PMX and Plasmepsin IX.

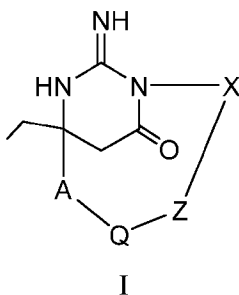
[0014] The present disclosure further provides methods for the treatment of malaria by inhibiting plasmepsin X. The present disclosure further provides methods for the treatment of malaria by inhibiting both PMX and Plasmepsin IX.

[0015] These and other embodiments of the disclosure, which are described in detail below or will become clear to those of ordinary skill in the art, are included within the scope of the disclosure.

[0016] The summary of the technology described above is non-limiting and other features and advantages of the technology will be apparent from the following detailed description, and from the claims.

DETAILED DESCRIPTION

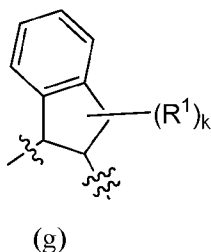
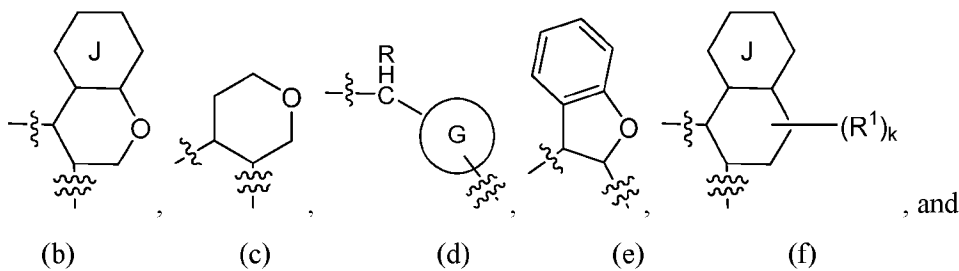
[0017] Described herein are compounds having the structural Formula I:



wherein A is a straight or branched, saturated or unsaturated (C₃-C₁₀)alkylene, comprising at least one -CH₂- group, wherein one or more additional -CH₂- groups in A are optionally and independently replaced with a moiety selected from the group consisting of O, S, NR, CONR, NRCO, SO₂, and SO₂NR and wherein one or more of the hydrogens along A can be replaced with a group independently selected from hydroxyl, halogen and C₁₋₃ haloalkyl;

X is selected from:

(a) straight or branched, saturated or unsaturated (C₃-C₁₀)alkylene,



wherein the single \sim represents point of attachment to nitrogen atom of the tetrahydropyrimidinyl ring and the double \approx represents point of attachment to Z;

J is a six membered aryl or heteroaryl selected from phenyl, pyridyl, pyrimidinyl, pyridazinyl, and pyrazinyl, said phenyl, pyridyl, pyrimidinyl, pyridazinyl, and pyrazinyl unsubstituted or substituted with 1 to 3 groups independently selected from R;

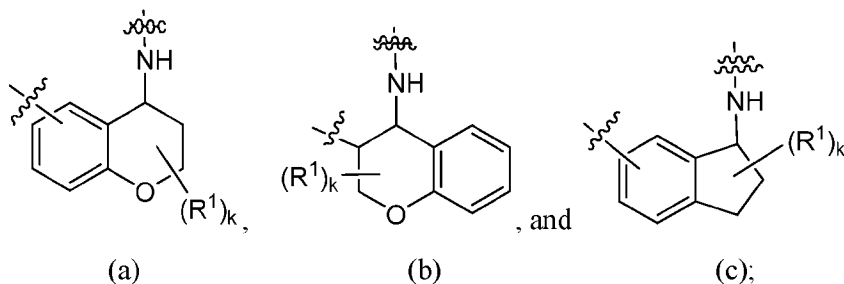
G is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, bicyclobutanyl, bicyclopentanyl, bicyclohexyl, bicycloheptyl, bicyclononyl, pyridyl, pyrimidinyl,

benzylpyrimidinyl, pyrazolyl, imidazolyl, said groups optionally substituted with 1 to 3 groups of R;

R is hydrogen, halogen, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, -OhaloC₁-C₆alkyl, C₁-C₆alkylOH, C₁-C₆alkoxy, COC₁-C₆alkyl, C₁-C₆alkylO-C₁-C₆alkyl, heteroaryl, or COOC₁-C₆alkyl;

Z is a bond, -(CH₂)_pC(O)(CH₂)_p-, -phenyl-, -heteroaryl-, said phenyl and heteroaryl optionally substituted with 1 to 3 groups of R;

Q is selected from:



wherein the single \sim represents point of attachment to A and the double \approx represents point of attachment to Z;

R¹ is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, oxo, COOC₁-C₆alkyl, C₁-C₆alkylCOOC₁-C₆alkyl, C₃-C₆cycloalkyl, C₁-C₆alkylC₃-C₆cycloalkyl, C₁-C₆alkyl, -C₁-C₆alkylOhaloC₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R²)(R³), N(R²)(R³) or C₁-C₆alkylN(R²)(R³);

R² is hydrogen, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, COC₁-C₆alkyl or COOC₁-C₆alkyl;

R³ is hydrogen, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, COC₁-C₆alkyl or COOC₁-C₆alkyl;

k is an integer from 0 to 4; and

p is an integer independently selected from 0 to 4;

or a pharmaceutically acceptable salt thereof.

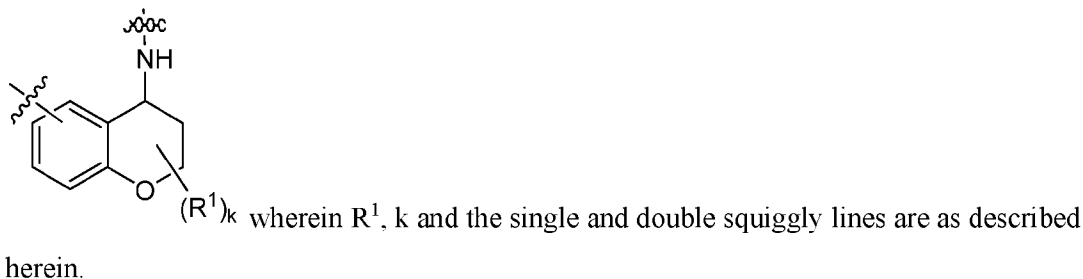
[0018] An embodiment of Formula I is realized when A is a straight or branched, saturated or unsaturated (C₃-C₆)alkylene. A subembodiment of aspect of the disclosure is realized when A is a straight or branched, saturated or unsaturated C₃-alkylene. A subembodiment of aspect of the disclosure is realized when A is a straight or branched, saturated or unsaturated C₄-alkylene. A subembodiment of aspect of the disclosure is realized when A is a straight or branched, saturated or unsaturated C₅-alkylene. A subembodiment of aspect of the disclosure is realized when A is a straight or branched, saturated or unsaturated C₆-alkylene. Another subembodiment is realized when A is a straight or branched, saturated or unsaturated (C₃-C₁₀)alkylene, wherein one or more additional -CH₂- groups in A are optionally and independently replaced with a moiety selected from the group consisting of O, S, NR, CONR, NRCO, SO₂, and SO₂NR and wherein one or more of the hydrogens along A can be replaced with a group independently selected from hydroxyl, halogen and C₁₋₃ haloalkyl. In another embodiment, A is selected from -(CH₂)₆-, -(CH₂)₄-, -(CH₂)₃-, and -(CH₂)₂-CH=CH-.

[0019] Another embodiment of Formula I is realized when each R¹ is independently selected from halogen, CN, OH, C₁-C₆alkoxy-, -COOH, oxo, -COOC₁-C₆alkyl, C₃-C₆cycloalkyl, C₁-C₆alkyl, -haloC₁-C₆alkyl, and C₁-C₆alkylOH. A subembodiment of this aspect of the disclosure is realized when each R¹ is independently selected from halogen, OH, C₁-C₆alkoxy, C₁-C₆alkyl, -C₁-haloC₁-C₆alkyl, and C₁-C₆alkylOH. In a further subembodiment, each R¹ is independently selected from OH, methyl and trifluoromethyl. In one class, R¹ is OH. In another class, each R¹ is independently selected from OH and methyl. In another class R¹ is methyl. In still another class, R¹ is trifluoromethyl.

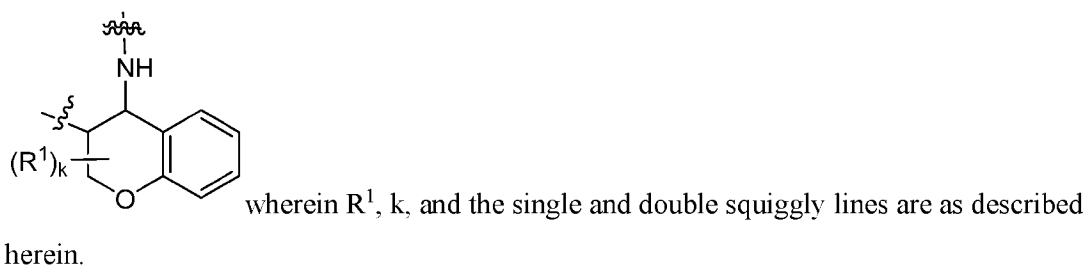
[0020] Another embodiment of Formula I is realized when R is selected from hydrogen, halogen, C₁-C₆alkylCOOH, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, and C₁-C₆alkoxy. A subembodiment of this aspect of the disclosure is realized when R is selected from hydrogen, CH₂COOH, (CH₂)₂COOH, CH(CH₃)COOH, CH₃, CH₂CH₃, (CH₂)₂OCH₃, (CH₂)₃OCH₃, (CH₂)₂OCH₂CH₃, (CH₂)₃OCH₂CH₃, CH₂F, CHF₂, CF₃, (CH₂)₂OH, C₁-C₆alkyl-O-C₁-C₆alkyl, and (CH₂)₃OH. Another subembodiment of this aspect of the disclosure is realized when R is hydrogen. Another subembodiment of this aspect of the disclosure is realized when R is selected from hydrogen, methyl, CH₂COOH, (CH₂)₂COOH, and CH(CH₃)COOH. Another subembodiment of this aspect of the disclosure is realized when R is selected from hydrogen, CH₃, CH₂CH₃, (CH₂)₂OCH₃, (CH₂)₃OCH₃, (CH₂)₂OCH₂CH₃, (CH₂)₃OCH₂CH₃. Another subembodiment of this aspect of the disclosure is realized when R is selected from hydrogen, methyl, (CH₂)₂OCH₃, (CH₂)₃OCH₃, (CH₂)₂OCH₂CH₃, (CH₂)₃OCH₂CH₃. Another

subembodiment of this aspect of the disclosure is realized when R is hydrogen, methyl, or $(\text{CH}_2)_2\text{OCH}_3$. Still another aspect is realized when R is hydrogen or $(\text{CH}_2)_2\text{OCH}_3$. Yet another aspect of this disclosure is realized when R is hydrogen or $(\text{CH}_2)_2\text{OCH}_3$. Another subembodiment of this aspect of the disclosure is realized when R is $(\text{CH}_2)_2\text{OCH}_3$. Another subembodiment of this aspect of the disclosure is realized when R is CH_2F , CHF_2 , CF_3 .

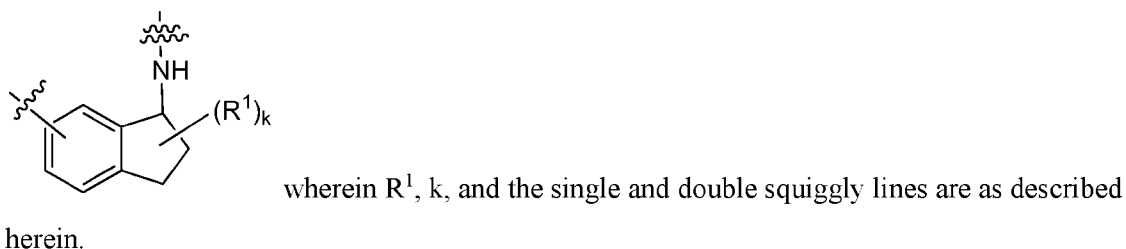
[0021] Another embodiment of Formula I is realized when Q is:



[0022] Another embodiment of Formula I is realized when Q is:



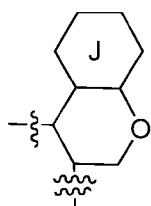
[0023] Another embodiment of Formula I is realized when Q is:



[0024] Another embodiment of Formula I is realized when Z is a bond. Another embodiment of Formula I is realized when Z is $-\text{C}(\text{O})(\text{CH}_2)_p-$. Another embodiment of Formula I is realized when Z is $-\text{C}(\text{O})-$ wherein p is 0. Yet another embodiment of Formula I is realized when Z is $-\text{C}(\text{O})(\text{CH}_2)_2-$. Still another embodiment of Formula (I) is realized when Z is $-\text{C}(\text{O})(\text{CH}_2)_3-$. And still another embodiment of Formula (I) is realized when Z is $-\text{C}(\text{O})(\text{CH}_2)-$. Another embodiment of Formula I is realized when Z is -phenyl-, optionally substituted with 1 to 3 groups of R. Another embodiment of Formula I is realized when Z is -heteroaryl-, optionally substituted with 1 to 3 groups of R.

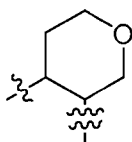
[0025] Another embodiment of Formula I is realized when X is a straight or branched, saturated or unsaturated (C₃-C₁₀)alkylene. A subembodiment of this aspect is realized when X is a straight or branched, saturated or unsaturated (C₃-C₆)alkylene. Another subembodiment of this aspect is realized when X is a straight or branched, saturated or unsaturated (C₃-C₄)alkylene.

[0026] Another embodiment of Formula I is realized when X is

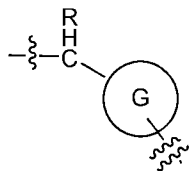


and J is as described herein. A subembodiment of this aspect of the disclosure is realized when J is a fused phenyl ring unsubstituted or substituted with 1 to 3 groups independently selected from R. Another subembodiment of this aspect of the disclosure is realized when J is selected from fused pyridyl, fused pyrimidinyl, fused pyridazinyl, and fused pyrazinyl, said pyridyl, pyrimidinyl, pyridazinyl, and pyrazinyl unsubstituted or substituted with 1 to 3 groups independently selected from R. Another subembodiment of this aspect of the disclosure is realized when J is fused pyridyl, wherein said pyridyl is unsubstituted or substituted with 1 to 3 groups independently selected from R. Another subembodiment of this aspect of the disclosure is realized when J is fused pyrimidinyl, said pyrimidinyl, unsubstituted or substituted with 1 to 3 groups independently selected from R. Another subembodiment of this aspect of the disclosure is realized when J is fused pyridazinyl, said pyridazinyl unsubstituted or substituted with 1 to 3 groups independently selected from R. Another subembodiment of this aspect of the disclosure is realized when J is fused pyrazinyl, said pyrazinyl unsubstituted or substituted with 1 to 3 groups independently selected from R.

[0027] Another embodiment of Formula I is realized when X is

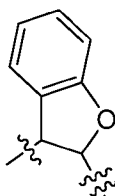


[0028] Another embodiment of Formula I is realized when X is



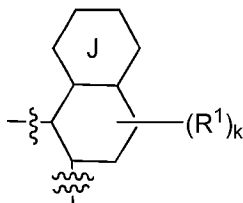
. A subembodiment of this aspect of this disclosure is realized when G is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclobutanyl, bicyclopentanyl, bicyclohexyl, bicycloheptyl, bicyclononanyl, said cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclobutanyl, bicyclopentanyl, bicyclohexyl, bicycloheptyl, and bicyclononanyl, unsubstituted or substituted with 1 to 3 groups of R. A subembodiment of this aspect of this disclosure is realized when G is selected from unsubstituted or substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and bicyclopentanyl. Another subembodiment of this aspect of the disclosure is realized when G is phenyl, said phenyl unsubstituted or substituted with 1 to 3 groups of R. Another subembodiment of this aspect of the disclosure is realized when G is pyridyl, said pyridyl unsubstituted or substituted with 1 to 3 groups of R. Another subembodiment of this aspect of the disclosure is realized when G is pyrimidinyl, said pyrimidinyl unsubstituted or substituted with 1 to 3 groups of R. Another subembodiment of this aspect of the disclosure is realized when G is benzylpyrimidinyl, said benzylpyrimidinyl unsubstituted or substituted with 1 to 3 groups of R. Another subembodiment of this aspect of the disclosure is realized when G is pyrazolyl, said pyrazolyl unsubstituted or substituted with 1 to 3 groups of R. Another subembodiment of this aspect of the disclosure is realized when G is imidazolyl, said imidazolyl unsubstituted or substituted with 1 to 3 groups of R. In yet another aspect of this disclosure, G is cyclopropyl, cyclobutyl, bicyclopentanyl, pyridyl, phenyl, or trifluoromethyl-phenyl.

[0029] Another embodiment of Formula I is realized when X is



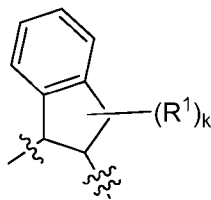
(e)

[0030] Another embodiment of Formula I is realized when X is



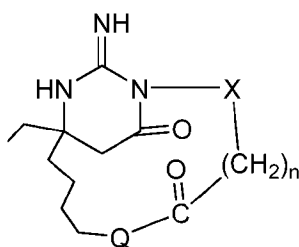
(f)

[0031] Another embodiment of Formula I is realized when X is



(g)

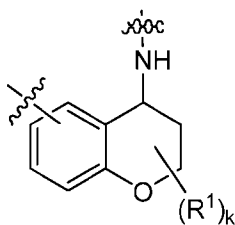
[0032] The present disclosure is also directed to a compound of Formula II:



II

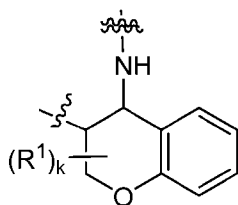
wherein Q, X and n are as defined herein.

[0033] Another embodiment of Formula II is realized when Q is:



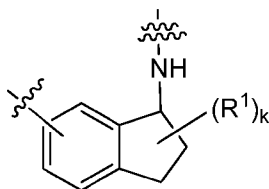
wherein k is an integer between zero and 4, and each R^1 is independently selected from halogen, OH, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, $-C_1$ -halo C_1 - C_6 alkyl, and C_1 - C_6 alkylOH. In a subclass of this embodiment, each R^1 is independently selected from OH, C_1 - C_6 alkyl, and halo- C_1 - C_6 alkyl. In a further subclass, each R^1 is independently selected from OH, methyl and trifluoromethyl.

[0034] Another embodiment of Formula II is realized when Q is:



wherein k is an integer between zero and 4, and R¹ is selected from hydrogen, halogen, OH, C₁-C₆alkoxy, C₁-C₆alkyl, -C₁-haloC₁-C₆alkyl, and C₁-C₆alkylOH. In one aspect of this embodiment, k is zero.

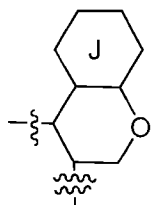
[0035] Another embodiment of Formula II is realized when Q is:



wherein k is an integer between zero and four, and R¹ is selected from hydrogen, halogen, OH, C₁-C₆alkoxy, C₁-C₆alkyl, -C₁-haloC₁-C₆alkyl, and C₁-C₆alkylOH. In one aspect of this embodiment, k is zero. In another aspect of this embodiment, k is one and R¹ is hydroxy.

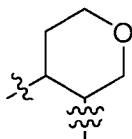
[0036] Another embodiment of Formula II is realized when X is a straight or branched, saturated or unsaturated (C₃-C₆)alkylene.

[0037] Another embodiment of Formula II is realized when X is

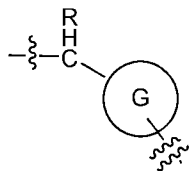


and J is selected from phenyl, pyridyl, pyrimidinyl, said phenyl, pyridyl, and pyrimidinyl, unsubstituted or substituted with 1 to 3 groups independently selected from R. Another embodiment of Formula II is realized when J is unsubstituted or substituted phenyl. In a particular embodiment of Formula II, J is phenyl. Another embodiment of Formula II is realized when J is unsubstituted or substituted pyridyl. Another embodiment of Formula II is realized when J is unsubstituted or substituted pyrimidinyl.

[0038] Another embodiment of Formula II is realized when X is

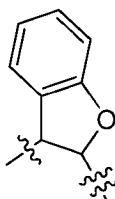


[0039] Another embodiment of Formula II is realized when X is



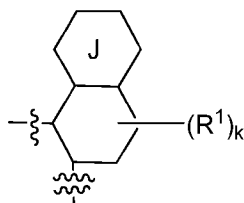
. A subembodiment of this aspect of this disclosure is realized when G is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclobutanyl, bicyclopentanyl, phenyl, pyridyl, pyrimidinyl, benzylpyrimidinyl, pyrazolyl, and imidazolyl said cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclobutanyl, bicyclopentanyl, phenyl, pyridyl, pyrimidinyl, benzylpyrimidinyl, pyrazolyl, and imidazolyl unsubstituted or substituted with 1 to 3 groups of R. Another subembodiment of this aspect of this disclosure is realized when G is selected from cyclopropyl, cyclobutyl, bicyclobutanyl, bicyclopentanyl, phenyl, pyridyl, pyrimidinyl, benzylpyrimidinyl, said cyclopropyl, cyclobutyl, bicyclobutanyl, bicyclopentanyl, phenyl, pyridyl, pyrimidinyl, and benzylpyrimidinyl, unsubstituted or substituted with 1 to 3 groups of R. Another subembodiment of this aspect of this disclosure is realized when G is selected from unsubstituted or substituted cyclopropyl. Another subembodiment of this aspect of this disclosure is realized when G is selected from unsubstituted or substituted cyclobutyl. Another subembodiment of this aspect of this disclosure is realized when G is selected from unsubstituted or substituted bicyclobutanyl. Another subembodiment of this aspect of this disclosure is realized when G is selected from unsubstituted or substituted bicyclopentanyl. Another subembodiment of this aspect of this disclosure is realized when G is selected from unsubstituted or substituted phenyl. Another subembodiment of this aspect of this disclosure is realized when G is selected from unsubstituted or substituted pyridyl. Another subembodiment of this aspect of this disclosure is realized when G is selected from unsubstituted or substituted pyrimidinyl. Another subembodiment of this aspect of this disclosure is realized when G is selected from unsubstituted or substituted benzylpyrimidinyl.

[0040] Another embodiment of Formula II is realized when X is



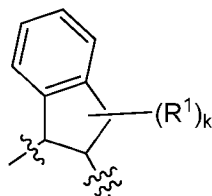
(e)

[0041] Another embodiment of Formula II is realized when X is



(f)

[0042] Another embodiment of Formula II is realized when X is



(g)

[0043] Another embodiment of Formula II is realized when R is selected from hydrogen, halogen, C₁-C₆alkylCOOH, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, and C₁-C₆alkoxy. Another embodiment of Formula II is realized when R is selected from hydrogen, CH₂COOH, (CH₂)₂COOH, CH(CH₃)COOH, CH₃, CH₂CH₃, (CH₂)₂OCH₃, (CH₂)₃OCH₃, (CH₂)₂OCH₂CH₃, (CH₂)₃OCH₂CH₃, CH₂F, CHF₂, CF₃, -OCH₂F, -OCHF₂, -OCF₃, (CH₂)₂OH, (CH₂)₃OH, and pyridyl. In an aspect of this embodiment of Formula II, R is selected from hydrogen, methyl, and (CH₂)₂OCH₃.

[0044] Another embodiment of Formula II is realized when n is 0. Another embodiment of Formula II is realized when n is 1. Another embodiment of Formula II is realized when n is 2. Another embodiment of Formula II is realized when n is 3.

[0045] In each of the various embodiments of the disclosure, in the compounds used in the methods herein, each variable (including those in each of Formulae I- II, and the various embodiments thereof) it shall be understood that each variable is to be selected independently of the others unless otherwise indicated.

[0046] In each of the various embodiments of the disclosure, the compounds described herein, including those in each of Formulae I-II and the various embodiments thereof, may exist in different forms of the compounds such as, for example, any solvates, hydrates, stereoisomers, and tautomers of said compounds and of any pharmaceutically acceptable salts thereof.

Definitions and Abbreviations:

[0047] The terms used herein have their ordinary meaning and the meaning of such terms is independent at each occurrence thereof. That notwithstanding and except where stated otherwise, the following definitions apply throughout the specification and claims. Chemical names,

common names and chemical structures may be used interchangeably to describe that same structure. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Hence the definition of “alkyl” applies to “alkyl” as well as the “alkyl” portion of “hydroxyalkyl”, “haloalkyl”, arylalkyl, alkylaryl, “alkoxy” etc.

[0048] It shall be understood that, in the various embodiments of the disclosure described herein, any variable not explicitly defined in the context of the embodiment is as defined in Formula I.

[0049] In the various embodiments described herein, each variable is selected independently of the others unless otherwise indicated.

[0050] “Drug resistant” means, in connection with a Plasmodium parasite strain, a Plasmodium species which is no longer susceptible to at least one previously effective drug; which has developed the ability to withstand attack by at least one previously effective drug. A drug resistant strain may relay that ability to withstand to its progeny. Said resistance may be due to random genetic mutations in the bacterial cell that alters its sensitivity to a single drug or to different drugs.

[0051] “Patient” includes both human and non-human animals. Non-human animals include those research animals and companion animals such as mice, rats, primates, monkeys, chimpanzees, great apes, dogs, and house cats.

[0052] “Pharmaceutical composition” (or “pharmaceutically acceptable composition”) means a composition suitable for administration to a patient. Such compositions may contain the neat compound (or compounds) of the disclosure or mixtures thereof, or salts, solvates, prodrugs, isomers, or tautomers thereof, and one or more pharmaceutically acceptable carriers or diluents. The term “pharmaceutical composition” is also intended to encompass both the bulk composition and individual dosage units comprised of one or more (e.g., two) pharmaceutically active agents such as, for example, a compound of the present disclosure and an additional agent selected from the lists of the additional agents described herein, along with any pharmaceutically inactive excipients. The bulk composition and each individual dosage unit can contain fixed amounts of the afore-said “more than one pharmaceutically active agents”. The bulk composition is material that has not yet been formed into individual dosage units. An illustrative dosage unit is an oral dosage unit such as tablets, pills and the like. Similarly, the herein-described method of treating a patient by administering a pharmaceutical composition of the present disclosure is also intended to encompass the administration of the afore-said bulk composition and individual dosage units.

[0053] "Halogen" and "halo" mean fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

[0054] "Alkylenes," by itself or as part of another substituent means a divalent hydrocarbon chain radical having the stated number of carbon atoms. For example, -(C₁-C₅)alkylene, would include, e.g., -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂CH₂CH₂CH₂-, -CH₂CH(CH₃)CH₂- or -CH₂CH₂CH₂CH₂CH₂-. A straight alkylenes means a divalent straight hydrocarbon chain radical having the stated number of carbon atoms. A branched alkylenes means a divalent branched hydrocarbon chain radical having the stated number of carbon atoms. A saturated alkylenes means a divalent saturated hydrocarbon chain radical having the stated number of carbon atoms. An unsaturated alkylenes means a divalent hydrocarbon chain radical having the stated number of carbon atoms and one or more double or triple covalent bonds within the chain. A cycloalkylene means a divalent hydrocarbon chain radical having the stated number of carbon atoms and a cycloalkyl moiety within the chain.

[0055] "Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

[0056] "Haloalkyl" means an alkyl as defined above wherein one or more hydrogen atoms on the alkyl is replaced by a halo group defined above.

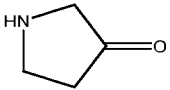
[0057] "Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl. "Monocyclic aryl" means phenyl.

[0058] "Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 12 carbon atoms, preferably about 3 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 10 ring atoms. The cycloalkyl can be optionally substituted with one or more substituents, which may be the same or different, as described herein. Monocyclic cycloalkyl refers to monocyclic versions of the cycloalkyl moieties described herein. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl,


cyclopentyl, cyclohexyl, cycloheptyl and the like. Multicyclic cycloalkyls refers to multicyclic, including bicyclic, rings that include a non-aromatic ring. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like. In certain embodiments, a non-aromatic ring is fused to an aromatic ring.

[0059] The term "heteroaryl" refers to an aromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms for monocyclic, 1-6 heteroatoms for bicyclic, or 1-9 heteroatoms for tricyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S for monocyclic, bicyclic, or tricyclic, respectively). Non-limiting examples of heteroaryls are pyridyl, pyrazolyl, pyrimidinyl, furanyl, oxazolyl, triazolyl, oxadiazolyl, and thiophenyl. The heteroaryl groups herein described may also contain fused rings that share a common carbon-carbon bond.

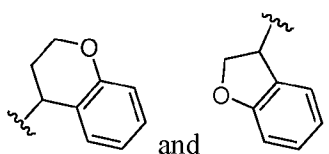
[0060] "Heterocycloalkyl" (or "heterocyclyl") means a non-aromatic, saturated or partially saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any -NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protections are also considered part of this disclosure. The heterocyclyl can be optionally substituted by one or more substituents, which may be the same or different, as described herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Thus, the term "oxide," when it appears in a definition of a variable in a general structure described herein, refers to the corresponding N-oxide, S-oxide, or S,S-dioxide. "Heterocyclyl" also includes rings wherein =O replaces two available hydrogens on the same carbon atom (i.e., heterocyclyl includes rings having a carbonyl group in the ring). Such =O groups may be referred to herein as

"oxo." An example of such a moiety is pyrrolidinone (or pyrrolidone): . As used herein, the term "monocyclic heterocycloalkyl" refers to monocyclic versions of the heterocycloalkyl moieties described herein and include a 4- to 7-membered monocyclic heterocycloalkyl groups comprising from 1 to 4 ring heteroatoms, said ring heteroatoms being

independently selected from the group consisting of N, N-oxide, O, S, S-oxide, S(O), and S(O)₂. The point of attachment to the parent moiety is to any available ring carbon or ring heteroatom. Non-limiting examples of monocyclic heterocycloalkyl groups include piperidyl, oxetanyl, pyrrolyl, piperaziny, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, beta lactam, gamma lactam, delta lactam, beta lactone, gamma lactone, delta lactone, and pyrrolidinone, and oxides thereof. A non-limiting example of a

monocyclic heterocycloalkyl group include the moiety: .

Non-limiting examples of multicyclic heterocycloalkyl groups include, bicyclic heterocycloalkyl groups. Specific examples include, but are not limited to,



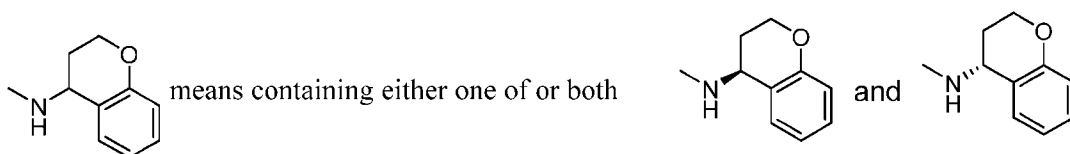
[0061] "Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.


[0062] The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.


[0063] The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

[0064] When a variable appears more than once in a group, e.g., R₈ in -N(R₈)₂, or a variable appears more than once in a structure presented herein, the variables can be the same or different at each occurrence.

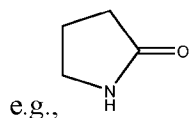
[0065] A solid line —, as a bond generally indicates a mixture of, or either of, the possible isomers, e.g., containing (R)- and (S)-stereochemistry. For example:



[0066] The wavy line , as used herein shown crossing a line representing a chemical bond, indicates a point of attachment to the rest of the compound. Lines drawn into the ring

systems, such as, for example  indicates that the indicated line (bond) may be attached to any of the substitutable ring atoms.

[0067] "Oxo" is defined as an oxygen atom that is double bonded to a ring carbon in a cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, or another ring described herein,



[0068] In this specification, where there are multiple oxygen and/or sulfur atoms in a ring system, there cannot be any adjacent oxygen and/or sulfur present in said ring system.

[0069] As well known in the art, a bond drawn from a particular atom wherein no moiety is depicted at the terminal end of the bond indicates a methyl group bound through that bond to the atom, unless stated otherwise. For example:



[0070] In another embodiment, the compounds useful in the methods of the disclosure, and/or compositions comprising them useful in said methods, are present in isolated and/or purified form. The term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being isolated from a synthetic process (e.g., from a reaction mixture), or natural source or combination thereof. Thus, the term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer) after being obtained from a purification process or processes described herein or well known to the skilled artisan (e.g., chromatography, recrystallization and the like), in sufficient purity to be suitable for in vivo or medicinal use and/or characterizable by standard analytical techniques described herein or well known to the skilled artisan.

[0071] It shall be understood that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

[0072] When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene et al., *Protective Groups in Organic Synthesis* (1991), Wiley, New York.

[0073] Another embodiment provides prodrugs and/or solvates of the compounds of the disclosure. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. The term "prodrug" means a compound (e.g., a drug precursor) that is transformed in vivo to yield a compound of the disclosure or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g., by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

[0074] For example, if a compound useful in the methods of the disclosure or a pharmaceutically acceptable salt thereof, contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, (C1-C8)alkyl, (C2-C12)alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C1-C2)alkylamino(C2-C3)alkyl (such as β -dimethylaminoethyl), carbamoyl-(C1-C2)alkyl, N,N-di (C1-C2)alkylcarbamoyl-(C1-C2)alkyl and piperidino-, pyrrolidino- or morpholino(C2-C3)alkyl, and the like.

[0075] Similarly, if a compound used in the methods of the disclosure contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C1-C6)alkanoyloxymethyl, 1-((C1-C6)alkanoyloxy)ethyl, 1-methyl-1-((C1-C6)alkanoyloxy)ethyl, (C1-

C6)alkoxycarbonyloxymethyl, N-(C1-C6)alkoxycarbonylaminomethyl, succinoyl, (C1-C6)alkanoyl, α -amino(C1-C4)alkanyl, arylacyl and α -aminoacyl, or α -aminoacyl- α -aminoacyl, where each α -aminoacyl group is independently selected from the naturally occurring L-amino acids, P(O)(OH)₂, -P(O)(O(C1-C6)alkyl)₂ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

[0076] If a compound used in the methods of the disclosure incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C1-C10)alkyl, (C3-C7) cycloalkyl, benzyl, or R-carbonyl is a natural α -aminoacyl or natural α -aminoacyl, -C(OH)C(O)OY₁ wherein Y₁ is H, (C1-C6)alkyl or benzyl, -C(OY₂)Y₃ wherein Y₂ is (C1-C4) alkyl and Y₃ is (C1-C6)alkyl, carboxy (C1-C6)alkyl, amino(C1-C4)alkyl or mono-N- or di-N,N-(C1-C6)alkylaminoalkyl, -C(Y₄)Y₅ wherein Y₄ is H or methyl and Y₅ is mono-N- or di-N,N-(C1-C6)alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

[0077] One or more compounds used in the methods of the disclosure may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the disclosure embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of the disclosure with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances, the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H₂O.

[0078] One or more compounds used in the methods of the disclosure may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example M. Caira et al., J. Pharmaceutical Sci., 1993, 3, 601-611, describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder et al., AAPS PharmSciTech., 5(1), article 12 (2004); and A. L. Bingham et al., Chem. Commun., 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated

by standard methods. Analytical techniques such as, for example I. R. spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

[0079] "Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition used in the methods of the present disclosure effective in inhibiting the above-noted diseases or enzyme activity and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

[0080] Another embodiment provides pharmaceutically acceptable salts of the compounds to be used in the methods of the disclosure. Thus, reference to a compound used in the methods of the disclosure herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of the disclosure contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds used in the methods of the disclosure may be formed, for example, by reacting a compound of the disclosure with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

[0081] Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like.

[0082] Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl et al., Camille G. (eds.) Handbook of Pharmaceutical Salts. Properties, Selection and Use. (2002) Zurich: Wiley-VCH; S. Berge et al., Journal of Pharmaceutical Sciences (1977) 66(1) 1-19; P. Gould, International J. of Pharmaceutics (1986) 33 201-217; Anderson et al., The Practice of Medicinal Chemistry (1996), Academic Press, New York; and in The Orange Book (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

[0083] Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g., methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g., decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g., benzyl and phenethyl bromides), and others.

[0084] All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the disclosure and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the disclosure.

[0085] Another embodiment provides pharmaceutically acceptable esters of the compounds used in the methods of the disclosure. Such esters include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C1-4alkyl, or C1-4alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C1-20 alcohol or reactive derivative thereof, or by a 2,3-di (C6-24)acyl glycerol.

[0086] As mentioned herein, another embodiment provides tautomers of the compounds of the disclosure to be used in the methods herein, and salts, solvates, esters and prodrugs of said tautomers. It shall be understood that all tautomeric forms of such compounds are within the scope of the compounds used in the methods of the disclosure. For example, all keto-enol and imine-enamine forms of the compounds, when present, are included in the disclosure.

[0087] The compounds used in the methods of the disclosure may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds used in the methods of the disclosure as well as mixtures thereof, including racemic mixtures, form part of the present disclosure. In addition, the present disclosure embraces use of all geometric and positional isomers. For example, if a compound used in the methods of the disclosure incorporates a double bond or a fused ring, both the cis-

and trans-forms, (E) and (Z) forms, as well as mixtures, are embraced within the scope of the disclosure.

[0088] Another embodiment provides for diastereomeric mixtures and individual enantiomers of the compounds used in the methods of the disclosure. Diastereomeric mixtures can be separated into their individual diastereomers based on their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds used in the methods of the disclosure may be atropisomers (e.g., substituted biaryls) and are considered as part of this disclosure. Enantiomers can also be separated by use of chiral HPLC column.

[0089] All stereoisomers (for example, geometric isomers, optical isomers and the like) of the compounds used in the methods of the disclosure (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated as embodiments within the scope of this disclosure, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). (For example, if a compound of the disclosure incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the disclosure. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the methods of the disclosure).

[0090] Individual stereoisomers of the compounds of the disclosure may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present disclosure can have the S or R configuration as defined by the IUPAC 1974 Recommendations. The use of the terms "salt", "solvate", "ester", "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

[0091] Another embodiment provides isotopically-labelled compounds to be used in the methods the disclosure. Such compounds are identical to those recited herein, but for the fact that

one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as 2H , 3H , 13C , 14C , 15N , 18O , 17O , 31P , 32P , 35S , 18F , and 36Cl , respectively.

[0092] Certain isotopically-labelled compounds of the disclosure (e.g., those labeled with 3H and 14C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., 3H) and carbon-14 (i.e., 14C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., 2H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances.

[0093] Isotopically labelled compounds of the disclosure can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples hereinbelow, by substituting an appropriate isotopically labelled reagent for a non-isotopically labelled reagent.

[0094] In the compounds used in the methods of the disclosure, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present disclosure is meant to include all suitable isotopic variations of the compounds of the disclosure. For example, different isotopic forms of hydrogen (H) include protium (1H) and deuterium (2H). The presence of deuterium in the compounds of the disclosure is indicated by "D". Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing in vivo half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds of the disclosure can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the schemes and examples herein using appropriate isotopically-enriched reagents and/or intermediates.

[0095] Polymorphic forms of the compounds used in the methods of the disclosure, and of the salts, solvates, esters and prodrugs of the compounds of the disclosure, are intended to be included in the present disclosure.

Methods of Treatment

[0096] The present disclosure is directed to methods of treatment of Plasmodium infections comprising administering to a subject in need thereof a compound described herein, or a pharmaceutically acceptable salt thereof. More specifically, the methods of the disclosure comprise administration of a compound of Formula I, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compounds of Formula I, or a pharmaceutically acceptable salt thereof, are administered in the form of a pharmaceutical composition, further comprising a pharmaceutically acceptable carrier or excipient.

[0097] The present disclosure provides a method for treating a Plasmodium infection, or for treating malaria, or for inhibiting plasmepsin X which comprises administering to a subject in need of such treatment a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, said compound having the structural Formula I described in the Summary of the Disclosure. In some embodiments, the compounds of Formula I, or pharmaceutically acceptable salts thereof, are administered with a pharmaceutically acceptable carrier, as a pharmaceutical composition. Also provided herein are various embodiments of these methods, as described, *infra*.

[0098] The disclosure also relates to the use of a compound of Formulae I - II or a pharmaceutically acceptable salt thereof for inhibiting plasmepsin X activity, for treating a Plasmodium infection, or for treating malaria. The disclosure further relates to the use of a compound of Formulae I - II or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for inhibiting plasmepsin X activity, for treating a Plasmodium infection, or for treating malaria. The compounds of Formulae I - II or pharmaceutically acceptable salts thereof described in any of the embodiments of the disclosure herein are useful for any of the uses above.

[0099] The present disclosure provides a method for treating a Plasmodium infection, or for treating malaria, or for inhibiting plasmepsin IX which comprises administering to a subject in need of such treatment a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, said compound having the structural Formula I described in the Summary of the Disclosure. In some embodiments, the compounds of Formula I, or pharmaceutically acceptable salts thereof, are administered with a pharmaceutically acceptable carrier, as a pharmaceutical composition. Also provided herein are various embodiments of these methods, as described, *infra*.

[0100] The disclosure also relates to the use of a compound of Formulae I - II or a pharmaceutically acceptable salt thereof for inhibiting plasmepsin IX activity, for treating a

Plasmodium infection, or for treating malaria. The disclosure further relates to the use of a compound of Formulae I - II or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for inhibiting plasmepsin IX activity, for treating a Plasmodium infection, or for treating malaria. The compounds of Formulae I - II or pharmaceutically acceptable salts thereof described in any of the embodiments of the disclosure herein are useful for any of the uses above.

[0101] The present disclosure provides a method for treating a Plasmodium infection, or for treating malaria, or for inhibiting plasmepsin X and plasmepsin IX which comprises administering to a subject in need of such treatment a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, said compound having the structural Formula I described in the Summary of the Disclosure. In some embodiments, the compounds of Formula I, or pharmaceutically acceptable salts thereof, are administered with a pharmaceutically acceptable carrier, as a pharmaceutical composition. Also provided herein are various embodiments of these methods, as described, *infra*.

[0102] The disclosure also relates to the use of a compound of Formulae I - II or a pharmaceutically acceptable salt thereof for inhibiting plasmepsin X and plasmepsin IX activity, for treating a Plasmodium infection, or for treating malaria. The disclosure further relates to the use of a compound of Formulae I - II or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for inhibiting plasmepsin X and plasmepsin IX activity, for treating a Plasmodium infection, or for treating malaria. The compounds of Formulae I - II or pharmaceutically acceptable salts thereof described in any of the embodiments of the disclosure herein are useful for any of the uses above.

[0103] The methods of the present disclosure are useful for treating malaria in that they inhibit the onset, growth, or progression of the condition, ameliorate the symptoms of the condition, cause regression of the condition, cure the condition, or otherwise improve the general well-being of a subject afflicted with, or at risk of, contracting the condition. Thus, in accordance with the presently disclosed subject matter, the terms “treat”, “treating”, and grammatical variations thereof, as well as the phrase “method of treating”, are meant to encompass any desired therapeutic intervention, including but not limited to a method for treating an existing infection in a subject of infection, such as in a subject that has been exposed to a parasite as disclosed herein.

[0104] Embodiments of the disclosure also include one or more of the compounds of Formulae I - II or a pharmaceutically acceptable salt thereof I for use in, (ii) for use as a medicament or composition for, or (iii) for use in the preparation of a medicament for: (a)

therapy (e.g., of the human body); (b) medicine; (c) inhibition of parasite/Plasmodium growth, (d) treatment or prophylaxis of infection by Plasmodium species; (e) reduction of the progression, onset or severity of pathological symptoms associated with Plasmodium infection and/or reduction of the likelihood of severe Plasmodium infection or, (f) treatment, prophylaxis of, or delay in the onset, severity, or progression of Plasmodium -associated disease(s), including, but not limited to: malaria.

[0105] Accordingly, another embodiment provides methods for the treatment of malaria or for the treatment of Plasmodium infection, comprising administration of combinations comprising an amount of at least one compound of Formulae I - II, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, and an effective amount of one or more additional agents described below. In certain embodiments, described herein are methods for the treatment of malaria or for the treatment of Plasmodium infection, comprising administration of combinations comprising an amount of at least one compound of Formulae I - II, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, and an effective amount of one or more additional anti-malarial agents. In certain embodiments, described herein are methods for the treatment of malaria by inhibition of plasmepsin X, IX and at least one other mechanism, comprising administration of combinations comprising an amount of at least one compound of Formulae I - II, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, and an effective amount of one or more additional anti-malarial agents, wherein the additional anti-malarial agents act through a different mechanism than inhibiting plasmepsin IX or plasmepsin X. The pharmacological properties of the compounds of Formulae I - II, or a pharmaceutically acceptable salt thereof may be confirmed by several pharmacological assays.

Dosage and Administration

[0106] Another embodiment provides suitable dosages and dosage forms of the compounds used in the methods of the disclosure. Suitable doses for administering compounds used in the methods of the disclosure to patients may readily be determined by those skilled in the art, e.g., by an attending physician, pharmacist, or other skilled worker, and may vary according to patient health, age, weight, frequency of administration, use with other active ingredients, and/or indication for which the compounds are administered. Doses may range from about 0.001 to 500 mg/kg of body weight/day of the compound of the disclosure. In one embodiment, the dosage is from about 0.01 to about 25 mg/kg of body weight/day of a compound of the disclosure, or a pharmaceutically acceptable salt or solvate of said compound. In another embodiment, the quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1

mg to about 100 mg, in specific embodiments from about 1 mg to about 50 mg, in specific embodiments from about 1 mg to about 25 mg, according to the particular application. In another embodiment, a typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 500 mg/day, in specific embodiments 1 mg/day to 200 mg/day, in two to four divided doses.

[0107] As discussed above, the amount and frequency of administration of the compounds of the disclosure and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated.

[0108] Liquid form preparations include solutions, suspensions and emulsions. As an example, may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

[0109] Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g., nitrogen.

[0110] Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

[0111] Another embodiment provides for use of compositions comprising a compound of Formulae I - II, or a pharmaceutically acceptable salt thereof formulated for transdermal delivery. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

[0112] Another embodiment provides for use of compositions comprising a compound of Formulae I - II, or a pharmaceutically acceptable salt thereof formulated for subcutaneous delivery. Another embodiment provides for use of compositions suitable for oral delivery. In some embodiments, it may be advantageous for the pharmaceutical preparation comprising one or more compounds of Formulae I - II, or a pharmaceutically acceptable salt thereof to be prepared in a unit dosage form. In such forms, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose. Each of the foregoing alternatives is considered as included in the various embodiments of the disclosure.

[0113] When used in combination with one or more additional therapeutic agents ("combination therapy"), the compounds used in the methods of this disclosure, i.e., the compounds of Formulae I - II, may be administered together or sequentially. When administered sequentially, compounds of the disclosure may be administered before or after the one or more additional therapeutic agents, as determined by those skilled in the art or patient preference.

[0114] If formulated as a fixed dose, such combination products employ the compounds of Formulae I - II, or a pharmaceutically acceptable salt thereof within the dosage range described herein and the other pharmaceutically active agent or treatment within its dosage range.

Combination Therapy

[0115] Another embodiment provides for methods of treatment using pharmaceutically acceptable compositions comprising a compound of the disclosure, either as the neat chemical or optionally further comprising additional ingredients. Such compositions are contemplated for preparation and use alone or in combination therapy. For preparing pharmaceutical compositions from the compounds of the disclosure, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g., magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), *Remington's Pharmaceutical Sciences*, 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

[0116] Non-limiting examples of additional drugs and active agents useful in combination therapies for the treatment of malaria, include the following: Coartem® (Novartis International AG, Basel, Switzerland; artemether + lumefantrine), Eurartesim® (Sigma-Tau Pharmaceuticals, Inc., Rome, Italy; dihydroartemisinin-piperaquine), Pyramax® (Shin Poong Pharmaceutical Co., Ltd., Seoul, Korea; pyronaridine-artesunate), ASAQ Winthrop® (Sanofi SA (Gentilly, France)/DNDi (Geneva, Switzerland); artesunate + amodiaquine), ASMQ (Cipla Limited (Mumbai, India)/DNDi, artesunate + mefloquine), SPAQ-CO™ (Guilin Pharmaceutical Co., Ltd. (Shanghai), amodiaquine + sulfadoxine, pyrimethamine), Artesun® (Guilin Pharmaceutical, artesunate), artemether, artesunate, dihydroartemisinin, lumefantrine, amodiaquine, mefloquine, piperaquine, quinine, chloroquine, atovaquone and proguanil and sulfadoxine-pyrimethamine, Tafenoquine (Glaxosmithkline), OZ439/PQP (Sanofi), OZ439/FQ (Sanofi), KAE609 (Novartis),

KAF156 (Novartis), DSM265 (NIH/Takeda), and MK-4815 (Merck & Co., Inc., Powles et al., *Antimicrobial Agents and Chemotherapy* 56(5): 2414–2419(2012)). Selection of such additional active ingredients will be according to the diseases or disorders present for which treatment is desired, as determined by the attending physician or other health care provider.

[0117] Thus, the disclosure also provides methods of using the compounds of Formulae I-II, or a pharmaceutically acceptable salt thereof to inhibit plasmepsin X, plasmepsin IX or plasmepsin X and IX, to treat Plasmodium infection or treat malaria wherein the method further comprises administering to a subject in need thereof, one or more additional anti-malarial agents. In some embodiments, the one or more additional anti-malarial agents are selected from the group consisting of: artemether, lumefantrine, dihydroartemisinin, piperaquine, pyronaridine, artesunate, amodiaquine, mefloquine, sulfadoxine, pyrimethamine, lumefantrine, quinine, chloroquine, atovaquone, and proguanil.

EXAMPLES

The meanings of the abbreviations in Examples are shown below.

ACN = MeCN = CH₃CN = acetonitrile

Boc = tert-butyloxycarbonyl

Boc₂O = di-tert-butyl dicarbonate

Cbz = carboxybenzyl

CCl₄ = carbontetrachloride

Celite = diatomaceous earth

Conc. = concentrated

DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCE = 1,2-dichloroethane

DCM = dichloromethane

DIAD = Diisopropyl azodicarboxylate

DMAP = 4-dimethylaminopyridine

DMF = N,N-Dimethylformamide

DMSO = dimethyl sulfoxide

DPPA = diphenylphosphoryl azide

EDCI = EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

Et₂O = diethyl ether

EtOAc = ethyl acetate

EtOH = ethanol

2nd Grubbs = [1,3-BIS(2,4,6-trimethylphenyl)imidazolidin-2-ylidene](chloro)(phenylmethylidene)ruthenium, tricyclohexylphosphane or Grubbs Catalyst® 2nd Generation, Grubbs Catalyst® M2a (C848)

h = hours

H₂ = hydrogen

HCl = hydrochloric acid

HPLC = high performance liquid chromatography

HG-II = (1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(o-isopropoxyphenylmethylene)ruthenium

H₃PO₄ = phosphoric acid

HOAc = acetic acid

IPA = isopropyl alcohol

iPrOH = isopropyl alcohol

LCMS or LC/MS = Liquid chromatography–mass spectrometry

LHMDS = LiHMDS = lithium bis(trimethylsilyl)amide

Mg = magnesium

min = minutes

Me = methyl

MeCN = Acetonitrile

MeOH = CH₃OH = methanol

MgSO₄ = Magnesium sulfate

MnO₂ = manganese dioxide

N₂ = nitrogen

NaBH₄ = sodium borohydrate

NaOH = sodium hydroxide

Na₂SO₄ = sodium sulfate

NaBH₃CN = sodium borohydride

NH₃H₂O = ammonia water ammonium hydroxide

NH₄OAc = Ammonium acetate

Pd-C = Palladium on carbon

Pd(OH)₂ = Palladium hydroxide on carbon

Pet.ether = Petroleum Ether

PPh₃ = Triphenylphosphine

r. t. = room temperature

SFC = Supercritical Fluid Chromatography

SiO₂ = silica

TFA = trifluoroacetic acid

THF = tetrahydrofuran

TMS = Trimethylsilyl

TMSOK = potassium trimethylsilylanolate

TLC = thin layer chromatography

ZnBr₂ – zinc (II) bromide

1 Standard atmosphere [atm] = 101325 pascal [Pa] = 14.6959488 psi

The meanings of the abbreviations in the nuclear magnetic resonance spectra are shown below:

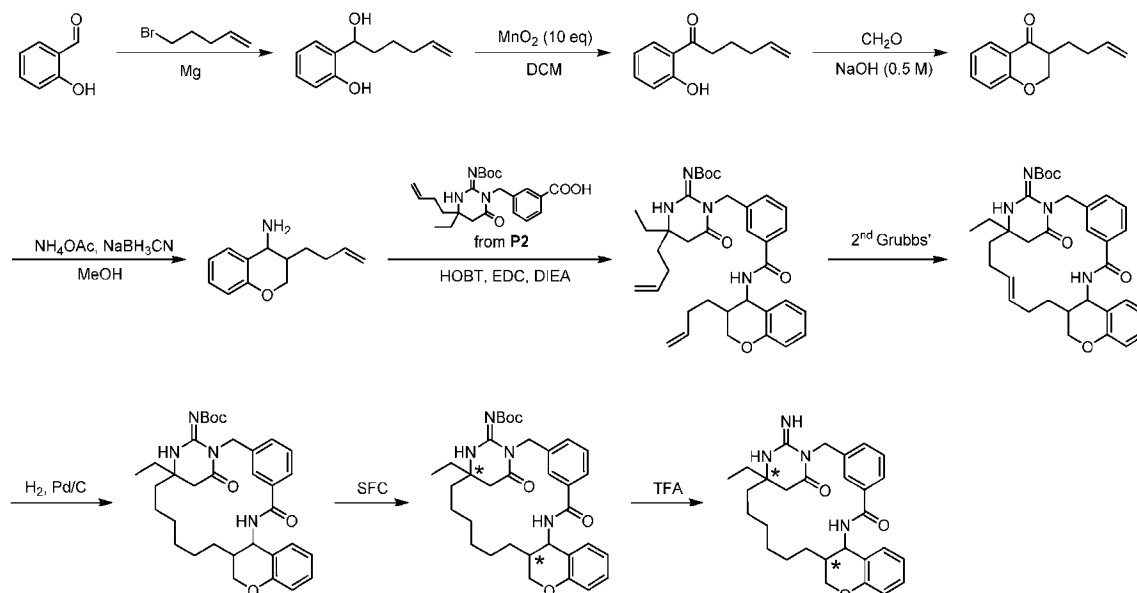
s = singlet, d = doublet, dd = double doublet, dt = double triplet, ddd = double doublet, Sept = septet, t = triplet, m = multiplet, br = broad, brs = broad singlet, q = quartet

J = coupling constant, and Hz = hertz.

[0118] Several methods for preparing the compounds of this disclosure are described in the following Schemes and Examples. Starting materials and intermediates were purchased commercially from common catalog sources or were made using known procedures, or as otherwise illustrated. Some frequently applied routes to the compounds of Formula I are described in the Schemes that follow. In some cases, the order of carrying out the reaction steps in the schemes may be varied to facilitate the reaction or to avoid unwanted reaction products.

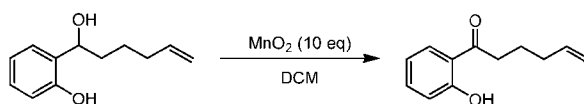
EXAMPLES

[0119] The following examples are meant to be illustrative and should not be construed as further limiting. The contents of the figures and all references, patents, and published patent applications cited throughout this application are expressly incorporated herein by reference.

EXAMPLE 1**Step 1:**

[0120] To a flask under an atmosphere of argon was added magnesium (1.393 g, 57.3 mmol) followed by anhydrous THF (40 mL). To initiate the Grignard reaction, a few drops of the 5-bromopent-1-ene (7.32 g, 49.1 mmol) was added. The reaction mixture was then refluxed (70 °C) for 1 h. After cooling to -50°C, 2-hydroxybenzaldehyde (2 g, 16.38 mmol) in THF (10 mL) was added to the reaction mixture. The reaction was monitored by TLC. After stirring at -50°C for 1 h the reaction mixture was quenched with HCl (1M, 20 mL), diluted with EtOAc (50 mL), and then washed with water (50 mL). The organic layer was dried over MgSO₄ and filtered through CELITE. The filtrate was concentrated, and the resulting residue was purified by flash silica gel chromatography (ISCO®; Agela® Flash Column Silica-CS(4 g), Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 30 mL/min). The desired fractions were concentrated to yield 2-(1-hydroxyhex-5-en-1-yl)phenol.

¹H NMR (400 MHz, chloroform-d) δ 7.93 (s, 1H), 7.16 (t, *J* = 7.67 Hz, 1H), 6.93 (d, *J* = 7.34 Hz, 1H), 6.79-6.88 (m, 2H), 5.72-5.82 (m, 1H), 4.92-5.03 (m, 2H), 4.83 (t, *J* = 6.85 Hz, 1H), 2.65 (s, 1H), 2.08 (q, *J* = 7.09 Hz, 2H), 1.75-1.99 (m, 2H), 1.36-1.60 (m, 2H) ppm.

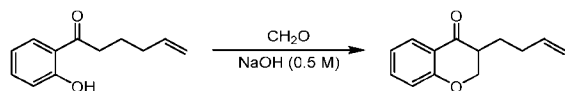
Step 2: Preparation of 1-(2-hydroxyphenyl)hex-5-en-1-one

[0121] To a solution of 2-(1-hydroxyhex-5-en-1-yl)phenol (2.0 g, 10.40 mmol) in DCM (15 mL) was added manganese(IV) oxide (9.04 g, 104 mmol) followed by MgSO₄ (200 mg). The reaction mixture was then stirred at 25 °C. After 3 hours the reaction mixture was filtered, and the filtrate was concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; Agela® Flash Column Silica-CS(4 g), Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 30 mL/min). The desired fractions were concentrated to yield 1-(2-hydroxyphenyl)hex-5-en-1-one.

MS (ESI) *m/z*: 191.1 (**M+H**)⁺

¹H NMR (400 MHz, CDCl₃) δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.73 (t, *J* = 8.5 Hz, 1H), 7.25 (d, *J* = 8.5 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 6.05-6.15 (m, 1H), 5.26-5.35 (m, 2H), 3.21-3.30 (m, 2H), 2.39-2.49 (m, 2H), 2.08-2.19 (m, 2H) ppm.

Step 3: Preparation of 3-(but-3-en-1-yl) chroman-4-one

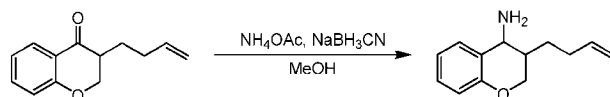


[0122] A mixture of 1-(2-hydroxyphenyl)hex-5-en-1-one (550 mg, 2.89 mmol), formaldehyde (235 mg, 2.89 mmol) and 0.5 N NaOH (12 mL) was stirred at 25 °C. After 10 hours, the reaction mixture acidified with 6 N HCl to pH 4, and the mixture was stirred at room temperature for 1 hour. Then the reaction mixture was diluted with EtOAc (20 mL) and washed with water (20 mL). The organic layer was dried over MgSO₄ and filtered through CELITE. The filtrate was concentrated, and the resulting residue was purified by prep-TLC (SiO₂, Ethyl acetate/Petroleum ether =10:1) to give 3-(but-3-en-1-yl) chroman-4-one.

MS (ESI) *m/z*: 203.0 (**M+H**)⁺

¹H NMR (400 MHz, CDCl₃) δ 8.14 (d, *J* = 7.5 Hz, 1H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 8.5 Hz, 1H), 6.02-6.08 (m, 1H), 5.25-5.34 (m, 2H), 4.75-7.78 (m, 1H), 4.49-4.57 (m, 1H), 2.93-2.96 (m, 1H), 2.41-2.48 (m, 2H), 2.24-2.28 (m, 1H), 1.81-1.84 (m, 1H) ppm.

Step 4: Preparation of 3-(but-3-en-1-yl)chroman-4-amine



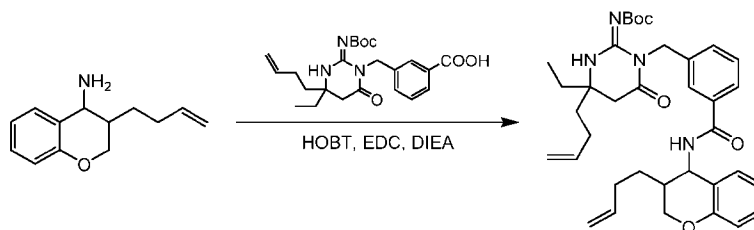
[0123] NH₄OAc (1143 mg, 14.83 mmol) was added to a stirred mixture of 3-(but-3-en-1-yl)chroman-4-one (250 mg, 1.236 mmol) and 4 Å molecular sieves (500 mg) in MeOH (30 mL)

at 25 °C. After 30 minutes NaBH₃CN (311 mg, 4.94 mmol) was added. The mixture was stirred at 90 °C and followed by LC/MS. After 10 hours the mixture was filtered, and filtrate was concentrated. The resulting crude residue was diluted with water (20 mL) and washed with EtOAc (3 x 25 mL). The combined organics were dried over anhydrous Na₂SO₄, filtered and concentrated. The resulting residue was purified by prep-HPLC (TFA). The desired fractions were concentrated to yield 3-(but-3-en-1-yl)chroman-4-amine.

MS (ESI) *m/z*: 187.0 (**M+H**)⁺

¹H NMR (400 MHz, methanol-*d*₄) δ 7.26-7.37 (m, 2H), 6.99 (q, *J* = 7.50 Hz, 1H), 6.83-6.92 (m, 1H), 5.76-5.96 (m, 1H), 4.96-5.18 (m, 2H), 3.97-4.59 (m, 3H), 2.06-2.44 (m, 3H), 1.40-1.68 (m, 2H) ppm.

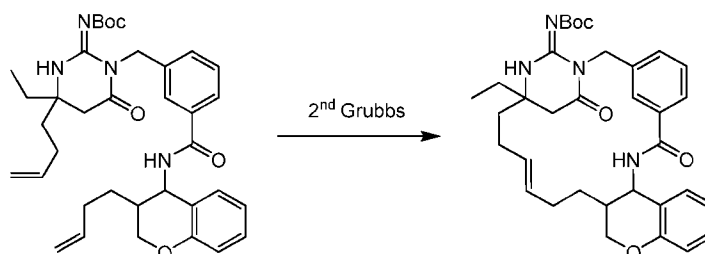
Step 5: Preparation of tert-butyl (4-(but-3-en-1-yl)-1-(3-((3-(but-3-en-1-yl)chroman-4-yl)carbamoyl)benzyl)-4-ethyl-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate



[0124] To a solution of 3-((4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)methyl)benzoic acid (116 mg, 0.270 mmol) (crude), EDC (104 mg, 0.540 mmol), 1H-benzo[d][1,2,3]triazol-1-ol (73.0 mg, 0.540 mmol) and 3-(but-3-en-1-yl)chroman-4-amine (71.4 mg, 0.351 mmol) in THF (5 mL) was added DIEA (0.189 mL, 1.080 mmol). The reaction was stirred at 25 °C and followed by LC/MS. After 2 hours the reaction mixture was quenched with water (10 mL), and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The resulting residue was purified by prep-TLC Pet.ether/EtOAc = 2:1 to yield tert-butyl (4-(but-3-en-1-yl)-1-(3-((3-(but-3-en-1-yl)chroman-4-yl)carbamoyl)benzyl)-4-ethyl-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate.

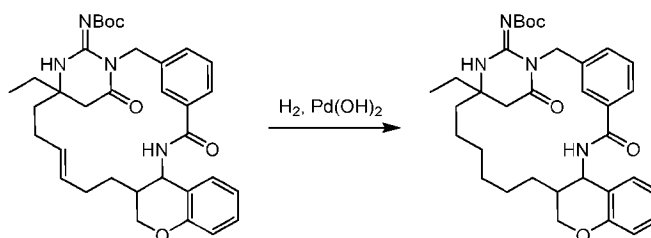
MS (ESI) *m/z*: 615.4 (**M+H**)⁺

Step 6: Preparation of tert-butyl ((12E,9E)-14-ethyl-16,4-dioxo-11,12,13,14,15,16-hexahydro-5-aza-1(1,4)-pyrimidina-6(4,3)-chromana-3(1,3)-benzenacyclododecaphan-9-en-12-ylidene)carbamate



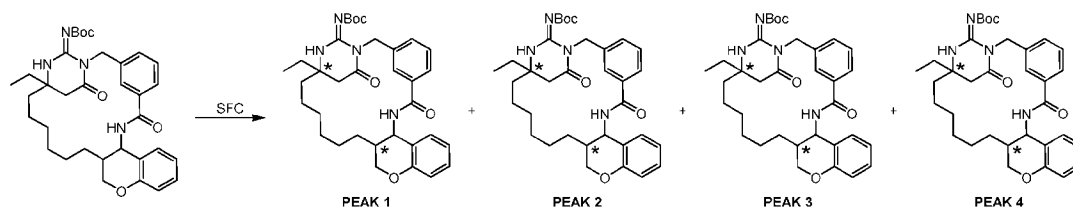
[0125] To a solution of tert-butyl (4-(but-3-en-1-yl)-1-(3-((3-(but-3-en-1-yl)chroman-4-yl)carbamoyl)benzyl)-4-ethyl-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate (140 mg, 0.228 mmol) in DCM (300 mL) was added [1,3-bis(2,4,6-trimethylphenyl)imidazolidin-2-ylidene](chloro)(phenylmethylidene)ruthenium, tricyclohexylphospane (37.1 mg, 0.046 mmol). The reaction was stirred at 25 °C and followed by LC/MS. After 20 hours the reaction mixture was concentrated. The resulting residue was purified by prep-TLC (Pet. ether/EtOAc = 2:1) to yield tert-butyl ((12E,9E)-14-ethyl-16,4-dioxo-11,12,13,14,15,16-hexahydro-5-aza-1(1,4)-pyrimidina-6(4,3)-chromana-3(1,3)-benzenacyclododecaphan-9-en-12-ylidene)carbamate. **MS (ESI) m/z : 587.3 (M+H)⁺**

Step 7: Preparation of tert-butyl (E)-(14-ethyl-16,4-dioxo-11,12,13,14,15,16-hexahydro-5-aza-1(1,4)-pyrimidina-6(4,3)-chromana-3(1,3)-benzenacyclododecaphane-12-ylidene)carbamate



[0126] To a solution of tert-butyl ((12E,9E)-14-ethyl-16,4-dioxo-11,12,13,14,15,16-hexahydro-5-aza-1(1,4)-pyrimidina-6(4,3)-chromana-3(1,3)-benzenacyclododecaphan-9-en-12-ylidene)carbamate (120 mg, 0.205 mmol) in MeOH (30 mL) was added dihydroxypalladium (28.7 mg, 0.020 mmol). The reaction was stirred at 25 °C under an atmosphere of hydrogen (15 psi) and followed by LC/MS. After 2 hours the reaction mixture was filtered, and the filtrate was concentrated to yield tert-butyl (E)-(14-ethyl-16,4-dioxo-11,12,13,14,15,16-hexahydro-5-aza-1(1,4)-pyrimidina-6(4,3)-chromana-3(1,3)-benzenacyclododecaphane-12-ylidene)carbamate. **MS (ESI) m/z : 589.4 (M+H)⁺**

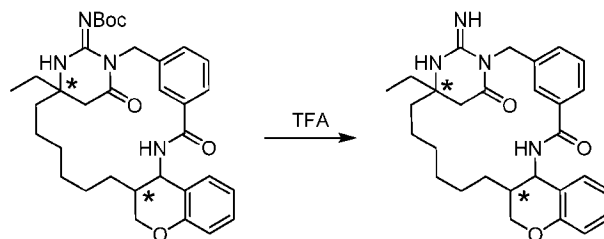
Step 8: Preparation of tert-butyl (E)-(14-ethyl-16,4-dioxo-11,12,13,14,15,16-hexahydro-5-aza-1(1,4)-pyrimidina-6(4,3)-chromana-3(1,3)-benzenacyclododecaphane-12-ylidene)carbamate (PEAK 3)



[0127] Tert-butyl (E)-(14-ethyl-16,4-dioxo-11,12,13,14,15,16-hexahydro-5-aza-1(1,4)-pyrimidina-6(4,3)-chromana-3(1,3)-benzenacyclododecaphane-12-ylidene)carbamate (100 mg, 0.170 mmol) was separated by SFC (Instrument SFC-14 Method Column DAICEL CHIRALPAK AD-H(250mm X 30mm; 5 μ m): Condition 0.1%NH₃H₂O IPA Begin B 30% End B 30%; 100%B; FlowRate(50 mL/min) 50) to yield tert-butyl (E)-(14-ethyl-16,4-dioxo-11,12,13,14,15,16-hexahydro-5-aza-1(1,4)-pyrimidina-6(4,3)-chromana-3(1,3)-benzenacyclododecaphane-12-ylidene)carbamate (PEAK 1), tert-butyl (E)-(14-ethyl-16,4-dioxo-11,12,13,14,15,16-hexahydro-5-aza-1(1,4)-pyrimidina-6(4,3)-chromana-3(1,3)-benzenacyclododecaphane-12-ylidene)carbamate (PEAK 2), tert-butyl (E)-(14-ethyl-16,4-dioxo-11,12,13,14,15,16-hexahydro-5-aza-1(1,4)-pyrimidina-6(4,3)-chromana-3(1,3)-benzenacyclododecaphane-12-ylidene)carbamate (PEAK 3), and tert-butyl (E)-(14-ethyl-16,4-dioxo-11,12,13,14,15,16-hexahydro-5-aza-1(1,4)-pyrimidina-6(4,3)-chromana-3(1,3)-benzenacyclododecaphane-12-ylidene)carbamate (PEAK 4).

MS (ESI) m/z: 589.4 (M+H)⁺

Step 9: Preparation of 14-ethyl-12-imino-11,12,13,14,15,16-hexahydro-5-aza-1(1,4)-pyrimidina-6(4,3)-chromana-3(1,3)-benzenacyclododecaphane-16,4-dione



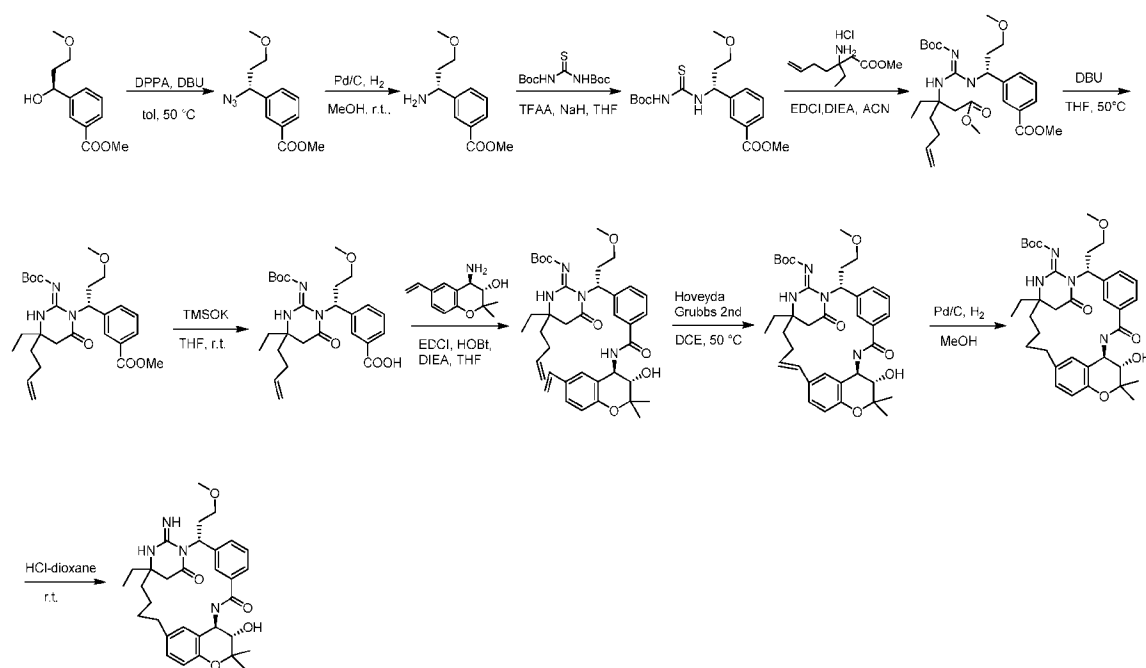
[0128] To a mixture of tert-butyl (E)-(14-ethyl-16,4-dioxo-11,12,13,14,15,16-hexahydro-5-aza-1(1,4)-pyrimidina-6(4,3)-chromana-3(1,3)-benzenacyclododecaphane-12-ylidene)carbamate (Example 1, Step 8, PEAK 3) (20 mg, 0.034 mmol) in DCM (3 mL) was added TFA (1 mL), and the mixture was stirred at 28 °C. The reaction was followed by LC/MS. After 1 hour the reaction

mixture was concentrated. The resulting residue was then purified by HPLC (Column Boston Green ODS 150 x 30 mm; 5 μ m; Condition water (0.1%TFA)-ACN, Begin B 30, End B 60, Gradient Time (10 min), 100%B Hold Time (2 min); Flow Rate (25 mL/min). The desired fractions were concentrated to yield 14-ethyl-12-imino-11,12,13,14,15,16-hexahydro-5-aza-1(1,4)-pyrimidina-6(4,3)-chromana-3(1,3)-benzenacyclododecaphane-16,4-dione.

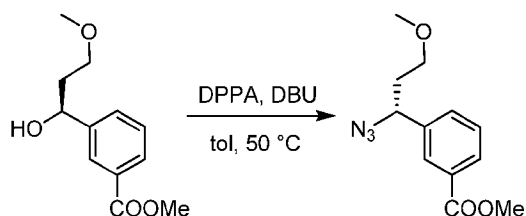
MS (ESI) m/z : 489.3(M+H)⁺

¹H NMR (500MHz, methanol-d₄) δ 8.64 (d, J = 9.0 Hz, 1H), 7.88 - 7.79 (m, 2H), 7.66 (d, J = 8.0 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.22 - 7.15 (m, 1H), 6.94 (dt, J = 1.0, 7.5 Hz, 1H), 6.82 (dd, J = 1.0, 8.0 Hz, 1H), 5.81 (d, J = 16.0 Hz, 1H), 5.53 (dd, J = 5.5, 9.0 Hz, 1H), 4.59 (d, J = 16.0 Hz, 1H), 4.19 - 4.12 (m, 1H), 4.05 (dd, J = 9.0, 11.0 Hz, 1H), 3.05 (d, J = 16.5 Hz, 1H), 2.85 (d, J = 16.5 Hz, 1H), 2.33 - 2.23 (m, 1H), 1.75 (q, J = 7.5 Hz, 2H), 1.60 - 1.43 (m, 4H), 1.43 - 1.35 (m, 1H), 1.34 - 1.11 (m, 7H), 0.99 (t, J = 7.5 Hz, 3H) ppm.

EXAMPLE 2



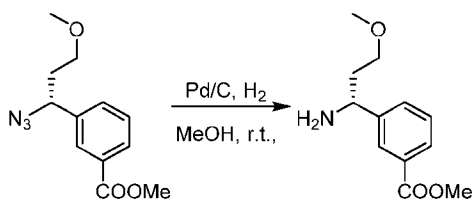
Step1: Preparation of methyl (R)-3-(1-azido-3-methoxypropyl) benzoate



[0129] To a solution of methyl (S)-3-(1-hydroxy-3-methoxypropyl)benzoate (2 g, 8.92 mmol) in toluene (20 mL) was added DBU (4.03 mL, 26.8 mmol) and diphenylphosphinyl azide (5.08 mL, 26.8 mmol) under N₂ atmosphere. Then the mixture was stirred at 50°C, and followed by LC/MS. After 16 hours the reaction mixture was quenched with water (20 mL), and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 15% EtOAc/Pet. ether gradient @ 40 mL/min). The desired fractions were concentrated to yield methyl (R)-3-(1-azido-3-methoxypropyl) benzoate.

¹H NMR (400 MHz, chloroform-d) δ 7.96-8.12 (m, 2H), 7.41-7.58 (m, 2H), 4.76 (dd, *J* = 6.0, 8.4 Hz, 1H), 3.94 (s, 3H), 3.51 (ddd, *J* = 4.8, 7.6, 9.6 Hz, 1H), 3.28-3.41 (m, 4H), 1.91-2.13 (m, 2H) ppm.

Step 2: Preparation of methyl (R)-3-(1-amino-3-methoxypropyl)benzoate

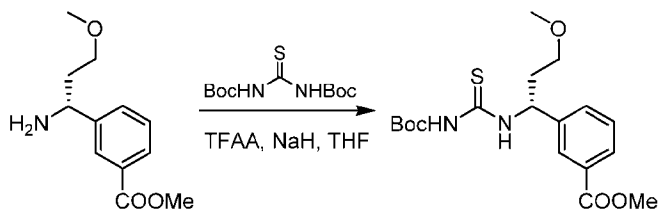


[0130] To a flask was containing methyl (R)-3-(1-azido-3-methoxypropyl)benzoate (1.3 g, 5.22 mmol) in MeOH (13 mL) was added 10% Pd/C (0.555 g, 0.522 mmol). The reaction mixture was stirred under an atmosphere of H₂ (balloon) at 25°C. Followed by LC/MS. After 10 hours the reaction mixture was filtered (CELITE) and the filtrate was concentrated to yield the crude product methyl (R)-3-(1-amino-3-methoxypropyl)benzoate, which was used without further purification.

MS (ESI) *m/z*: 224.1 (M+H⁺)

¹H NMR (400 MHz, chloroform-d) δ 8.01 (s, 1H), 7.88-7.96 (m, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.37-7.47 (m, 1H), 4.17 (t, *J* = 6.8 Hz, 1H), 3.92 (s, 3H), 3.41-3.46 (m, 1H), 3.28-3.37 (m, 4H), 1.88-1.99 (m, 2H) ppm.

Step 3: Preparation of methyl (R)-3-(11,11-dimethyl-9-oxo-7-thioxo-2,10-dioxo-6,8-diazadodecan-5-yl)benzoate

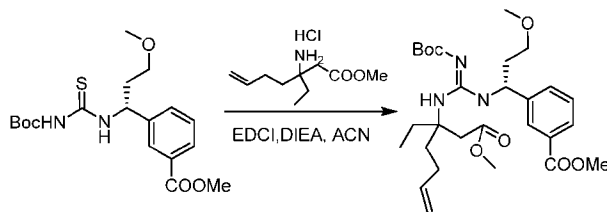


[0131] To a solution of N,N-bis(boc)thiourea (1.324 g, 4.79 mmol) in THF (10 mL) was added sodium hydride (0.383g, 9.58 mmol) at 0°C under an atmosphere of N₂ in portions. After 20 min at this temperature 2,2,2-trifluoroacetic anhydride (0.844 mL, 5.99 mmol) in THF (2 mL) was added dropwise. The mixture was stirred at 0°C for another 20 min. Then a solution of methyl (R)-3-(1-amino-3-methoxypropyl)benzoate (1.07 g, 4.79 mmol) in THF (10 mL) was added dropwise at 0°C. The reaction mixture was stirred at 25 °C and followed by LC/MS. After 16 hours the reaction mixture was quenched with water (30 mL), and extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 40g SepaFlash® Silica Flash Column, Eluent of 30% EtOAc/Pet. ether gradient @ 50 mL/min). The desired fractions were concentrated to yield methyl (R)-3-(11,11-dimethyl-9-oxo-7-thioxo-2,10-dioxa-6,8-diazadodecan-5-yl)benzoate.

MS (ESI) m/z 383.1 (M+H⁺)

¹H NMR (500 MHz, chloroform-d) δ 10.53 (br d, $J = 7.5$ Hz, 1H), 7.92-7.98 (m, 2H), 7.87 (s, 1H), 7.50 (d, $J = 7.5$ Hz, 1H), 7.41-7.45 (m, 1H), 5.66-5.75 (m, 1H), 3.90-3.93 (m, 3H), 3.36-3.40 (m, 1H), 3.27-3.34 (m, 4H), 2.09-2.25 (m, 2H), 1.50 (s, 9H) ppm.

Step 4: Preparation of methyl 3-((5R,Z)-9-(but-3-en-1-yl)-7-((tert-butoxycarbonyl)imino)-9-ethyl-11-oxo-2,12-dioxa-6,8-diazatridecan-5-yl)benzoate

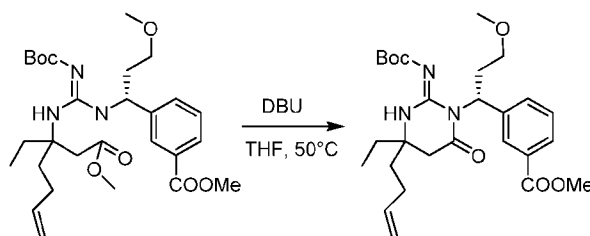


[0132] To a solution of methyl (R)-3-(11,11-dimethyl-9-oxo-7-thioxo-2,10-dioxa-6,8-diazadodecan-5-yl)benzoate (1.6 g, 4.18 mmol), EDCI (2.406 g, 12.55 mmol) and methyl 3-amino-3-ethylhept-6-enoate hydrochloride (1.206 g, 5.44 mmol) in MeCN (20 mL) was added DIEA (4.47 mL, 25.10 mmol). The reaction mixture was stirred at 25°C under N₂ atmosphere and followed by LC/MS. After 16 hours the reaction mixture was quenched with

water (40 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated to yield the crude product methyl 3-((5R,Z)-9-(but-3-en-1-yl)-7-((tert-butoxycarbonyl)imino)-9-ethyl-11-oxo-2,12-dioxo-6,8-diazatridecan-5-yl)benzoate, which was used without further purification.

MS (ESI) m/z 534.2 (M+H⁺)

Step 5: Preparation of methyl 3-((1R)-1-((E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-3-methoxypropyl)benzoate

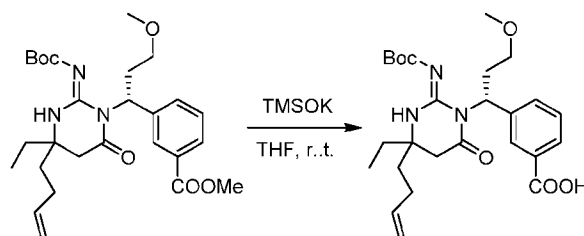


[0133] To a solution of methyl 3-((5R,Z)-9-(but-3-en-1-yl)-7-((tert-butoxycarbonyl)imino)-9-ethyl-11-oxo-2,12-dioxo-6,8-diazatridecan-5-yl)benzoate (2.2 g, 4.12 mmol) in THF (22 mL) was added DBU (3.11 mL, 20.61 mmol). The reaction mixture was stirred at 50°C, and followed by LC/MS. After 16 hours the reaction mixture was concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 15%EtOAc/Pet.ether gradient @ 50mL/min). The desired fractions were concentrated to yield methyl 3-((1R)-1-((E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-3-methoxypropyl)benzoate.

MS (ESI) m/z 502.2 (M+H⁺)

¹H NMR (400 MHz, chloroform-*d*) δ 8.05 (s, 1 H), 7.82 (d, *J* = 7.6 Hz, 1 H), 7.51-7.64 (m, 1 H), 7.26-7.30 (m, 1 H), 6.30-6.34 (m, 1H), 5.60-5.71 (m, 1H), 4.83-5.02 (m, 2H), 3.82 (s, 3 H), 3.33-3.46 (m, 2 H), 3.22 (s, 3 H), 2.67-2.80 (m, 1 H), 2.35-2.51 (m, 3 H), 1.90-1.96 (m, 2 H), 1.58-1.59 (m, 4 H), 1.43 (d, *J* = 2.0 Hz, 9 H), 0.81-0.89 (m, 3 H) ppm.

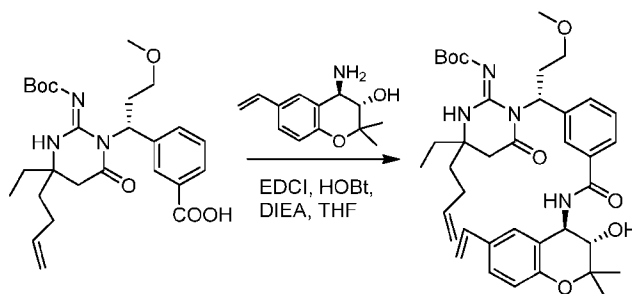
Step 6: Preparation of compound 3-((1R)-1-((E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-3-methoxypropyl)benzoic acid



[0134] To a solution of methyl 3-((1R)-1-((E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-3-methoxypropyl)benzoate (250 mg, 0.498 mmol) in THF (5 mL) was added potassium trimethylsilanolate (384 mg, 2.99 mmol) at 25°C under N₂ atmosphere. The reaction mixture was stirred at 25°C and followed by LC/MS. After 40 min, H₃PO₄ (0.1 g/mL in THF) was added to adjust pH to about 6~7. Then the reaction mixture was quenched with water (20 mL), and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated to yield crude product 3-((1R)-1-((E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-3-methoxypropyl)benzoic acid, which was used without further purification.

MS (ESI) *m/z* 488.2 (**M+H**⁺)

Step 7: Preparation of tert-butyl ((E)-4-(but-3-en-1-yl)-4-ethyl-1-((R)-1-(3-(((3S,4R)-3-hydroxy-2,2-dimethyl-6-vinylchroman-4-yl)carbamoyl)phenyl)-3-methoxypropyl)-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate



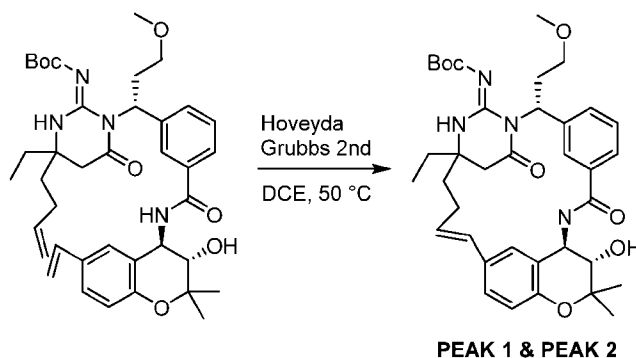
[0135] To a solution of 3-((1R)-1-((E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-3-methoxypropyl)benzoic acid (220 mg, 0.451 mmol), EDC (432 mg, 2.256 mmol), 1H-benzo[d][1,2,3]triazol-1-ol (183 mg, 1.354 mmol) and (3S,4R)-4-amino-2,2-dimethyl-6-vinylchroman-3-ol (119 mg, 0.541 mmol) in THF (6 mL) was added DIEA (0.630 mL, 3.61 mmol). The reaction mixture was stirred at 25°C, and followed by LC/MS. After 16 hours the reaction mixture was quenched with water (10 mL), and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried

over anhydrous Na₂SO₄, filtered and concentrated. The resulting residue was purified by prep-TLC (Pet. ether/EtOAc=2:1) to yield tert-butyl ((E)-4-(but-3-en-1-yl)-4-ethyl-1-((R)-1-(3-(((3S,4R)-3-hydroxy-2,2-dimethyl-6-vinylchroman-4-yl)carbamoyl)phenyl)-3-methoxypropyl)-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate.

MS (ESI) *m/z* 689.5 (**M+H**⁺)

¹H NMR (400 MHz, chloroform-*d*) δ 7.97 (s, 1 H), 7.65-7.69 (m, 2H), 7.40-7.42 (m, 1H), 7.31-7.34 (m, 1H), 6.85 (d, *J* = 8.4 Hz, 1 H), 6.61-6.68 (m, 1 H), 6.53-6.57 (m, 1H), 6.40-6.43 (m, 1H), 5.69-5.80 (m, 1 H), 5.61 (d, *J* = 17.6 Hz, 1 H), 5.23 (t, *J* = 8.0 Hz, 1 H), 5.15 (d, *J* = 10.8 Hz, 1 H), 4.96-5.08 (m, 2 H), 4.57 (br s, 1 H), 3.79 (dd, *J* = 9.2, 2.4 Hz, 1 H), 3.41-3.54 (m, 2 H), 3.29 (s, 3 H), 2.80 (br s, 1 H), 2.42-2.62 (m, 3 H), 2.00-2.04 (m, 1 H), 1.60-1.75 (m, 4 H), 1.52 (s, 3 H), 1.46 (s, 9 H), 1.32 (s, 3 H), 0.87-0.94 (m, 3 H) ppm.

Step 8: Preparation of compound tert-butyl ((12E,63S,64R,2R,7E)-14-ethyl-63-hydroxy-2-(2-methoxyethyl)-62,62-dimethyl-16,4-dioxo-11,12,13,14,15,16-hexahydro-5-aza-1(1,4)-pyrimidina-6(4,6)-chromana-3(1,3)-benzenacyclodecaphan-7-en-12-ylidene)carbamate



[0136] To a solution of tert-butyl ((E)-4-(but-3-en-1-yl)-4-ethyl-1-((R)-1-(3-(((3S,4R)-3-hydroxy-2,2-dimethyl-6-vinylchroman-4-yl)carbamoyl)phenyl)-3-methoxypropyl)-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate (250 mg, 0.363 mmol) in DCE (200 mL) was added (1,3-dimesitylimidazolidin-2-ylidene)(2-isopropoxybenzylidene)ruthenium(VI) chloride (22.74 mg, 0.036 mmol). The reaction mixture was stirred at 50°C under N₂ atmosphere and followed by LC/MS. After 16 hours the reaction mixture was concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 15%EtOAc/Pet.ether gradient @ 30mL/min). The desired fractions were concentrated to yield tert-butyl ((12E,63S,64R,2R,7E)-14-ethyl-63-hydroxy-2-(2-methoxyethyl)-62,62-dimethyl-16,4-dioxo-11,12,13,14,15,16-hexahydro-5-aza-1(1,4)-pyrimidina-6(4,6)-chromana-3(1,3)-benzenacyclodecaphan-7-en-12-ylidene)carbamate (PEAK 1) and tert-butyl

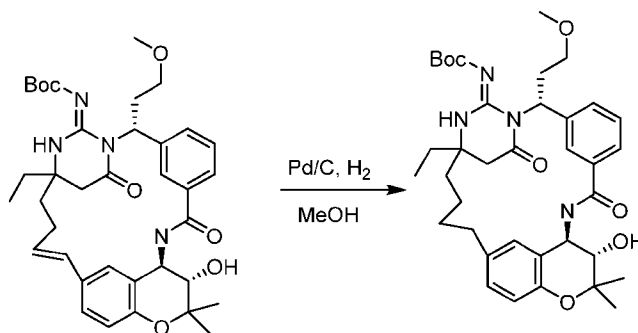
((12E,63S,64R,2R,7E)-14-ethyl-63-hydroxy-2-(2-methoxyethyl)-62,62-dimethyl-16,4-dioxo-11,12,13,14,15,16-hexahydro-5-aza-1(1,4)-pyrimidina-6(4,6)-chromana-3(1,3)-benzenacyclodecaphan-7-en-12-ylidene)carbamate (PEAK 2).

MS (ESI) m/z : 661.2 ($M+H^+$)

PEAK 1: 1H NMR (400 MHz, chloroform- d) δ 7.88 (d, $J = 7.6$ Hz, 1 H), 7.69 (d, $J = 8.0$ Hz, 1 H), 7.39-7.43 (m, 1 H), 7.21-7.27 (m, 2 H), 6.93-7.00 (m, 1 H), 6.66-6.73 (m, 1 H), 6.26-6.40 (m, 2 H), 6.07-6.14 (m, 1 H), 5.83-5.93 (m, 1 H), 5.08-5.16 (m, 1 H), 3.55-3.71 (m, 1 H), 3.31-3.40 (m, 2 H), 3.20-3.23 (m, 3 H), 3.15-3.19 (m, 1 H), 2.80-2.96 (m, 1 H), 2.48-2.56 (m, 1 H), 2.34 - 2.48 (m, 2 H), 2.15-2.23 (m, 1 H), 1.44-1.47 (m, 4 H), 1.32 (s, 6 H), 1.17-1.30 (m, 9 H), 0.86-0.94 (m, 3 H) ppm.

PEAK 2: 1H NMR (500 MHz, chloroform- d) δ 7.93-8.01 (m, 2 H), 7.74 (d, $J = 8.0$ Hz, 1 H), 7.50 (t, $J = 8.0$ Hz, 1 H), 7.21 (s, 1 H), 6.95-7.05 (m, 1 H), 6.71 (d, $J = 8.5$ Hz, 1 H), 6.54 (br d, $J = 8.5$ Hz, 1 H), 6.27-6.38 (m, 2 H), 5.80-5.88 (m, 1 H), 5.19 (t, $J = 9.0$ Hz, 1 H), 3.60-3.68 (m, 2 H), 3.43-3.51 (m, 2 H), 3.27 (s, 3 H), 2.78-2.86 (m, 1 H), 2.70 (d, $J = 16.5$ Hz, 1 H), 2.45 - 2.57 (m, 2 H), 2.23 - 2.40 (m, 2 H), 1.56-1.62 (m, 6 H), 1.32 (s, 4 H), 1.20 (s, 9 H), 0.95 (t, $J = 7.5$ Hz, 3 H) ppm.

Step 9: Preparation of compound tert-butyl ((63S,64R,2R,E)-14-ethyl-63-hydroxy-2-(2-methoxyethyl)-62,62-dimethyl-16,4-dioxo-11,12,13,14,15,16-hexahydro-5-aza-1(1,4)-pyrimidina-6(4,6)-chromana-3(1,3)-benzenacyclodecaphane-12-ylidene)carbamate

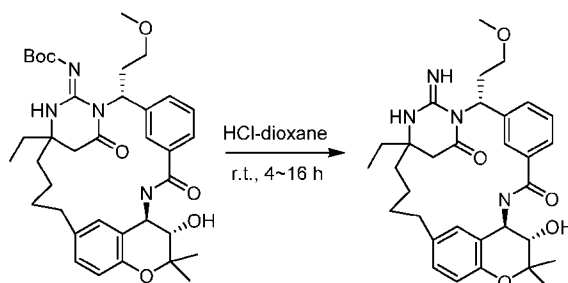


[0137] To a solution of tert-butyl ((12E,63S,64R,2R,7E)-14-ethyl-63-hydroxy-2-(2-methoxyethyl)-62,62-dimethyl-16,4-dioxo-11,12,13,14,15,16-hexahydro-5-aza-1(1,4)-pyrimidina-6(4,6)-chromana-3(1,3)-benzenacyclodecaphan-7-en-12-ylidene)carbamate (Example 2 Step 8 PEAK 2) (30 mg, 0.045 mmol) in MeOH (2 mL) was added 10% Pd/C (4.83 mg, 4.54 μ mol). The reaction mixture was degassed and backfilled with H₂ (3x). The resulting mixture was stirred at 25 °C for 5 min under a hydrogen atmosphere (15 psi), and the reaction

was followed by LC/MS. After 15 min, the reaction mixture was filtered, and the filtrate was concentrated to yield tert-butyl ((63S,64R,2R,E)-14-ethyl-63-hydroxy-2-(2-methoxyethyl)-62,62-dimethyl-16,4-dioxo-11,12,13,14,15,16-hexahydro-5-aza-1(1,4)-pyrimidina-6(4,6)-chromana-3(1,3)-benzenacyclodecaphane-12-ylidene)carbamate, which was used without further purification.

MS (ESI) m/z : 663.4 (M+H⁺)

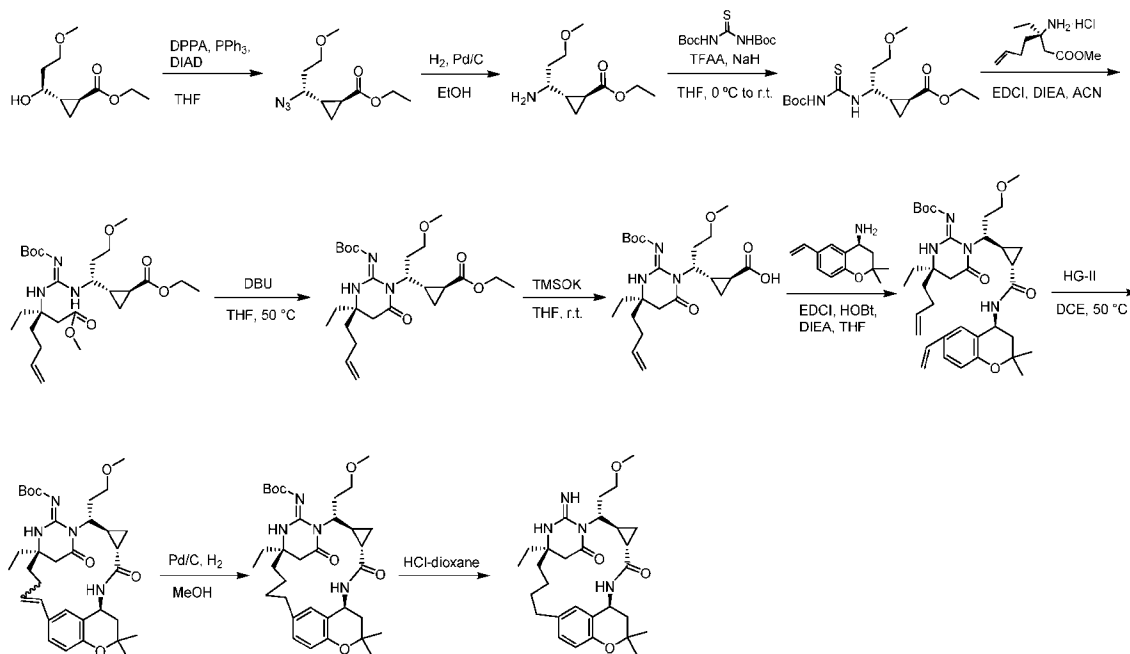
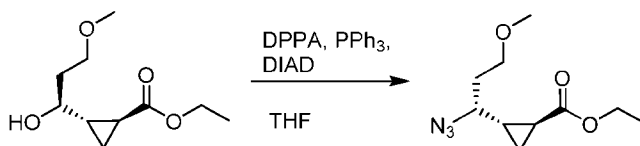
Step 10: Preparation of (63S,64R,2R)-14-ethyl-63-hydroxy-12-imino-2-(2-methoxyethyl)-62,62-dimethyl-11,12,13,14,15,16-hexahydro-5-aza-1(1,4)-pyrimidina-6(4,6)-chromana-3(1,3)-benzenacyclodecaphane-16,4-dione



[0138] A solution of tert-butyl ((63S,64R,2R,E)-14-ethyl-63-hydroxy-2-(2-methoxyethyl)-62,62-dimethyl-16,4-dioxo-11,12,13,14,15,16-hexahydro-5-aza-1(1,4)-pyrimidina-6(4,6)-chromana-3(1,3)-benzenacyclodecaphane-12-ylidene)carbamate (30 mg, 0.045 mmol) in 4N HCl-dioxane (4 ml) was stirred at 25 °C. Followed by LC/MS. After 4 hours the reaction mixture was concentrated. The resulting residue was purified by reverse preparative HPLC (Column Boston Green ODS 150 x 30mm; 5 μ m): Condition water (TFA)-ACN Begin B 30 End B 50 Gradient Time (10 min); 100%B Hold Time (2 min) Flow Rate(25 ml/min). The desired fractions were concentrated to yield (63S,64R,2R)-14-ethyl-63-hydroxy-12-imino-2-(2-methoxyethyl)-62,62-dimethyl-11,12,13,14,15,16-hexahydro-5-aza-1(1,4)-pyrimidina-6(4,6)-chromana-3(1,3)-benzenacyclodecaphane-16,4-dione.

MS (ESI) m/z 563.3 (M+H⁺)

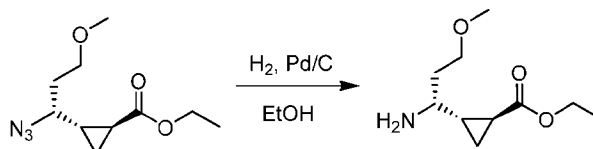
¹H NMR (400 MHz, methanol-*d*₄) δ 7.95 (d, $J = 7.6$ Hz, 1 H), 7.85 (d, $J = 8.0$ Hz, 1 H), 7.64 (s, 1 H), 7.57 (t, $J = 7.6$ Hz, 1 H), 7.05 (s, 1 H), 6.93 (dd, $J = 8.4, 1.6$ Hz, 1 H), 6.67 (d, $J = 8.4$ Hz, 1 H), 5.19-5.30 (m, 2 H), 4.92 - 4.95 (m, 1 H), 3.81 (d, $J = 9.6$ Hz, 1 H), 3.63 (dd, $J = 8.0, 3.2$ Hz, 2 H), 3.40 (s, 3 H), 2.85-2.99 (m, 2 H), 2.72-2.81 (m, 1 H), 2.39 - 2.48 (m, 2 H), 1.70 - 1.80 (m, 2 H), 1.55 - 1.68 (m, 2 H), 1.48 (s, 3 H), 1.17 - 1.32 (m, 7 H), 0.92 (t, $J = 7.6$ Hz, 3 H) ppm.

EXAMPLE 3**Step 1: Preparation of ethyl (1S,2S)-2-((R)-1-azido-3-methoxypropyl)cyclopropane-1-carboxylate**

[0139] To a solution of triphenylphosphine (5.84 g, 22.25 mmol), ethyl (1S,2S)-2-((S)-1-hydroxy-3-methoxypropyl)cyclopropane-1-carboxylate (3 g, 14.83 mmol) in THF (60 mL) was added diphenylphosphinyl azide (5.41 g, 22.25 mmol) and DIAD (4.33 mL, 22.25 mmol) under N₂ atmosphere at 0 °C. The reaction mixture was stirred at 15 °C, and followed by LC/MS. After 16 hours the reaction mixture was concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0-8% EtOAc/Pet. ether gradient @ 60 mL/min). The desired fractions were concentrated to yield ethyl (1S,2S)-2-((R)-1-azido-3-methoxypropyl)cyclopropane-1-carboxylate.

¹H NMR (400 MHz, chloroform-d) δ 4.15 (q, *J* = 7.2 Hz, 2H), 3.47-3.50 (m, 2H), 3.34 (s, 3H), 3.06-3.10 (m, 1H), 1.79-1.96 (m, 2H), 1.72-1.74 (m, 1H), 1.58-1.64 (m, 1H), 1.20-1.33 (m, 4H), 0.88-0.90 (m, 1H) ppm.

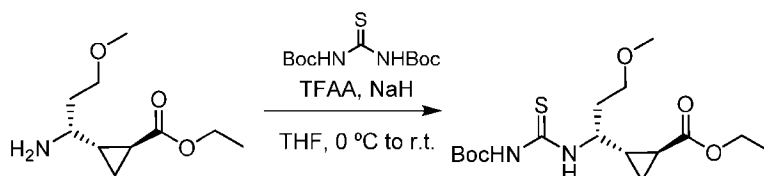
Step 2: Preparation of ethyl (1S,2S)-2-((R)-1-amino-3-methoxypropyl)cyclopropane-1-carboxylate



[0140] To a solution of ethyl (1S,2S)-2-((R)-1-azido-3-methoxypropyl)cyclopropane-1-carboxylate (2.8 g, 12.32 mmol) in EtOH (50 mL) was added 10% Pd/C (1.311 g, 1.232 mmol). The reaction mixture was degassed and backfilled with H₂ (3x). The resulting mixture was stirred at 15 °C under H₂ atmosphere (15 psi). After 4 hours the catalyst was filtered off and the filtrate was concentrated to yield ethyl (1S,2S)-2-((R)-1-amino-3-methoxypropyl)cyclopropane-1-carboxylate, which was used without further purification.

¹H NMR (500 MHz, methanol-d₄) δ 4.10 (dd, *J* = 1.5, 7.0 Hz, 2H), 3.46-3.56 (m, 2H), 2.23-2.32 (m, 1H), 1.72-1.81 (m, 2H), 1.57-1.66 (m, 1H), 1.33-1.42 (m, 1H), 1.24 (t, *J* = 7.0 Hz, 3H), 1.10-1.15 (m, 1H), 0.87-0.89 (m, 1H).

Step 3: Preparation of ethyl (1S,2S)-2-((R)-11,11-dimethyl-9-oxo-7-thioxo-2,10-dioxo-6,8-diazadodecan-5-yl)cyclopropane-1-carboxylate



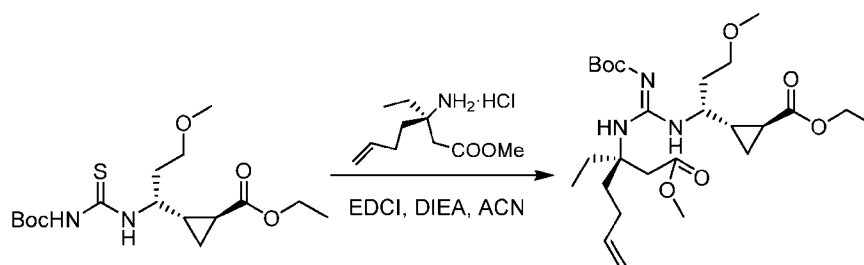
[0141] To a solution of N,N-bis(boc)thiourea (3.57 g, 12.92 mmol) in THF (40 mL) was added sodium hydride (1.033 g, 25.8 mmol) at 0 °C in portions under N₂ atmosphere. After 1hr at 0 °C, 2,2,2-trifluoroacetic anhydride (2.323 mL, 16.15 mmol) in THF (10 mL) was added dropwise. The mixture was stirred at 0 °C for 1 h. Then a solution of ethyl (1S,2S)-2-((R)-1-amino-3-methoxypropyl)cyclopropane-1-carboxylate (2.6 g, 12.92 mmol) in THF (10 mL) was added dropwise at 0 °C. The mixture was stirred at 15 °C, and the reaction was followed by LC/MS. After 12 hours the reaction mixture was quenched with saturated aqueous NH₄Cl (20 mL) and water (30 mL), then extracted with EtOAc (3 x 60 mL). The combined organic layers were washed with brine (80 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The resulting residue was then purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 10% EtOAc gradient @ 50 mL/min). The desired fractions were

concentrated to yield ethyl (1S,2S)-2-((R)-11,11-dimethyl-9-oxo-7-thioxo-2,10-dioxo-6,8-diazadodecan-5-yl)cyclopropane-1-carboxylate.

MS (ESI) m/z 361.2 (M+H⁺)

¹H NMR (400 MHz, chloroform-d) δ 9.96 (br d, $J = 8.4$ Hz, 1H), 7.80 (s, 1H), 4.32-4.44 (m, 1H), 4.07-4.20 (m, 2H), 3.49-3.65 (m, 2H), 3.36 (s, 3H), 1.98-2.06 (m, 1H), 1.90-1.98 (m, 2H), 1.60-1.67 (m, 1H), 1.49 (s, 9H), 1.19-1.30 (m, 4H), 0.87-0.96 (m, 1H).

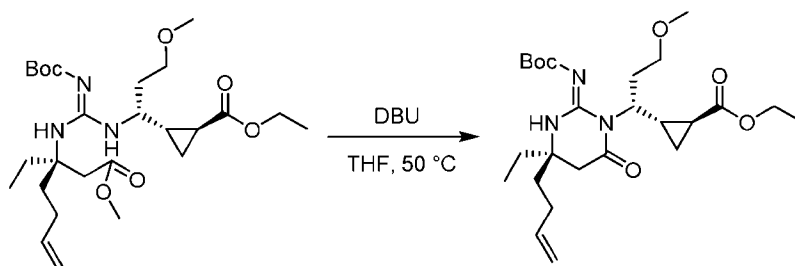
Step 4: Preparation of ethyl (1S,2S)-2-((5R,9R,Z)-9-(but-3-en-1-yl)-7-((tert-butoxycarbonyl)imino)-9-ethyl-11-oxo-2,12-dioxo-6,8-diazatridecan-5-yl)cyclopropane-1-carboxylate



[0142] To a solution of methyl (R)-3-amino-3-ethylhept-6-enoate hydrochloride (517 mg, 2.330 mmol), 3-(((ethylimino)methylene)amino)-N,N-dimethylpropan-1-amine hydrochloride (745 mg, 3.88 mmol) and N-ethyl-N-isopropylpropan-2-amine (1.729 mL, 9.71 mmol) in MeCN (25 mL) was added ethyl (1S,2S)-2-((R)-11,11-dimethyl-9-oxo-7-thioxo-2,10-dioxo-6,8-diazadodecan-5-yl)cyclopropane-1-carboxylate (700 mg, 1.942 mmol). The mixture was stirred at 20°C under N₂ atmosphere, and the reaction was followed by LC/MS. After 16 hours the reaction mixture was quenched with water (30 mL), and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to yield the crude product ethyl (1S,2S)-2-((5R,9R,Z)-9-(but-3-en-1-yl)-7-((tert-butoxycarbonyl)imino)-9-ethyl-11-oxo-2,12-dioxo-6,8-diazatridecan-5-yl)cyclopropane-1-carboxylate, which was used without further purification.

MS (ESI) m/z 512.4 (M+H⁺)

Step 5: Preparation of ethyl (1S,2S)-2-((R)-1-((R,E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-3-methoxypropyl)cyclopropane-1-carboxylate

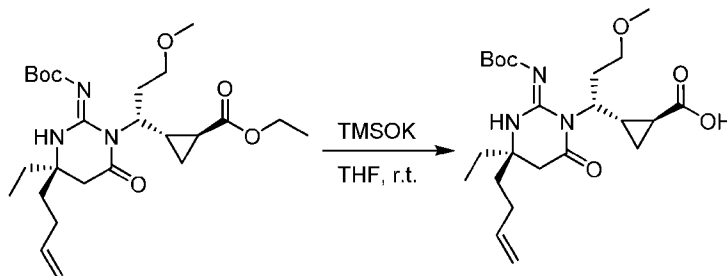


[0143] To a solution of ethyl (1S,2S)-2-((5R,9R,Z)-9-(but-3-en-1-yl)-7-((tert-butoxycarbonyl)imino)-9-ethyl-11-oxo-2,12-dioxo-6,8-diazatridecan-5-yl)cyclopropane-1-carboxylate (980 mg, 1.915 mmol) in THF (20 mL) was added DBU (1.444 mL, 9.58 mmol). The reaction mixture was stirred at 50 °C, and followed by LC/MS. After 16 hours the reaction mixture was quenched with water (20 mL), and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 20g SepaFlash® Silica Flash Column, Eluent of 15% EtOAc/Pet.ether gradient @ 35mL/min). The desired fractions were concentrated to yield ethyl (1S,2S)-2-((R)-1-((R,E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-3-methoxypropyl)cyclopropane-1-carboxylate.

MS (ESI) *m/z* 480.3 (**M+H**⁺)

¹H NMR (400 MHz, chloroform-*d*) δ 10.01 (br s, 1H), 5.75-5.82 (m, 1H), 4.96-5.10 (m, 2H), 4.36-4.48 (m, 1H), 3.99-4.17 (m, 3H), 3.32-3.48 (m, 2H), 3.26 (s, 3H), 2.49-2.66 (m, 3H), 2.18-2.43 (m, 2H), 2.06-2.13 (m, 2H), 1.55-1.74 (m, 5H), 1.47 (br d, *J* = 9.6 Hz, 9H), 1.29-1.30 (m, 1H), 1.20 (t, *J* = 7.2 Hz, 3H), 0.96-1.03 (m, 1H), 0.89-0.95 (m, 3H) ppm.

Step 6: Preparation of (1S,2S)-2-(can-1-((R,E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-3-methoxypropyl)cyclopropane-1-carboxylic acid

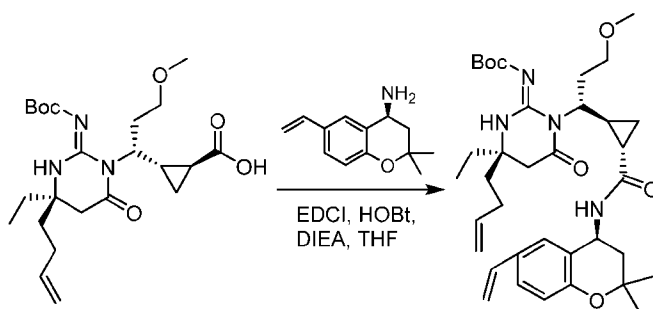


[0144] To a solution of ethyl (1S,2S)-2-((R)-1-((R,E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-3-methoxypropyl)cyclopropane-1-carboxylate (250 mg, 0.521 mmol) in THF (10 mL) was added

potassium trimethylsilanolate (535 mg, 4.17 mmol) at 20°C under N₂ atmosphere. The reaction mixture was stirred at 20°C, and followed by LC/MS. After 1.5 hours added H₃PO₄ (0.1 g/mL in THF) to adjust pH to about 7~8. Then the reaction mixture was quenched with water (20 mL), and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to yield the crude product (1*S*,2*S*)-2-((*R*)-1-((*R*,*E*)-4-(but-3-en-1-yl)-2-((*tert*-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2*H*)-yl)-3-methoxypropyl)cyclopropane-1-carboxylic acid, which was used without further purification.

MS (ESI) m/z 452.3 (M+H⁺)

Step 7: Preparation of tert-butyl ((*R*,*E*)-4-(but-3-en-1-yl)-1-((*R*)-1-((1*S*,2*S*)-2-(((*S*)-2,2-dimethyl-6-vinylchroman-4-yl)carbamoyl)cyclopropyl)-3-methoxypropyl)-4-ethyl-6-oxotetrahydropyrimidin-2(1*H*)-ylidene)carbamate

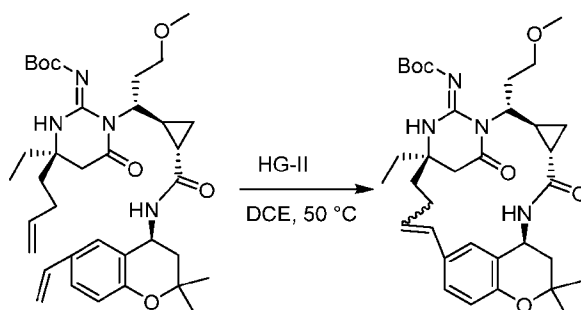


[0145] To a solution of (1*S*,2*S*)-2-((*R*)-1-((*R*,*E*)-4-(but-3-en-1-yl)-2-((*tert*-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2*H*)-yl)-3-methoxypropyl)cyclopropane-1-carboxylic acid (130 mg, 0.288 mmol), EDC (276 mg, 1.439 mmol), 1*H*-benzo[*d*][1,2,3]triazol-1-ol (78 mg, 0.576 mmol) and (*S*)-2,2-dimethyl-6-vinylchroman-4-amine (88 mg, 0.432 mmol) in THF (6 mL) was added DIEA (0.401 mL, 2.303 mmol). The reaction mixture was stirred at 15°C and followed by LC/MS. After 16 hours the reaction mixture was quenched with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated. The resulting residue was purified by prep-TLC (Pet. ether/EtOAc=1:1) to yield tert-butyl ((*R*,*E*)-4-(but-3-en-1-yl)-1-((*R*)-1-((1*S*,2*S*)-2-(((*S*)-2,2-dimethyl-6-vinylchroman-4-yl)carbamoyl)cyclopropyl)-3-methoxypropyl)-4-ethyl-6-oxotetrahydropyrimidin-2(1*H*)-ylidene)carbamate.

MS (ESI) m/z 637.4 (M+H⁺)

¹H NMR (400 MHz, chloroform-d) δ 9.90 (br s, 1H), 7.24-7.26 (m, 1H), 7.10 (s, 1H), 6.74 (d, J = 8.4 Hz, 1H), 6.70-6.72 (m, 1H), 5.53-5.68 (m, 2H), 5.34-5.36 (m, 2H), 5.13 (br d, J = 10.8 Hz, 1H), 4.89-4.93 (m, 2H), 4.38-4.41 (m, 1H), 3.34-3.61 (m, 2H), 3.28 (s, 3H), 2.52-2.54 (m, 1H), 2.29-2.50 (m, 2H), 2.08-2.23 (m, 2H), 1.89 (br s, 1H), 1.62-1.73 (m, 2H), 1.52-1.60 (m, 3H), 1.47 (s, 9H), 1.43 (s, 3H), 1.29 (s, 3H), 1.25-1.27 (m, 2H), 0.97 (br s, 1H), 0.86 (br t, J = 7.2 Hz, 3H).

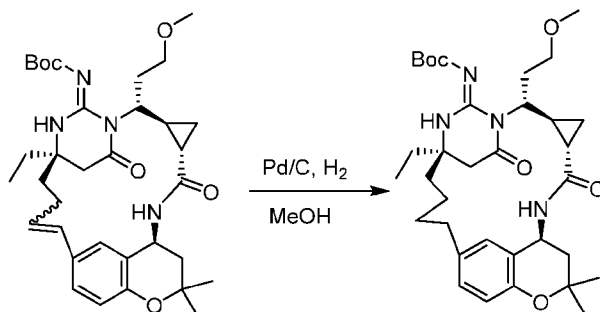
Step 8: Preparation of tert-butyl ((1a*S*,2*R*,6*R*,16a*S*,18a*S*,22*E*)-6-ethyl-2-(2-methoxyethyl)-15,15-dimethyl-4,18-dioxo-1a,2,5,6,7,8,15,16,16a,17,18,18a-dodecahydro-1*H*,4*H*-6,3-(epiminomethano)-11,13-ethenocyclopropa[*c*]pyrano[4,3-*g*][1,6]diazacycloheptadecin-22-ylidene)carbamate



[0146] To a solution of tert-butyl ((*R*,*E*)-4-(but-3-en-1-yl)-1-((*R*)-1-((1*S*,2*S*)-2-(((*S*)-2,2-dimethyl-6-vinylchroman-4-yl)carbamoyl)cyclopropyl)-3-methoxypropyl)-4-ethyl-6-oxotetrahydropyrimidin-2(1*H*)-ylidene)carbamate (180 mg, 0.283 mmol) in DCE (35 mL) was added (1,3-dimesitylimidazolidin-2-ylidene)(2-isopropoxybenzylidene)ruthenium(VI) chloride (35.4 mg, 0.057 mmol). The reaction was stirred at 50°C under N₂ atmosphere and followed by LC/MS. After 16 hours the reaction mixture was concentrated. The resulting residue was purified by Prep-TLC (Pet. ether/EtOAc/EtOH = 8:3:1) to yield tert-butyl ((1a*S*,2*R*,6*R*,16a*S*,18a*S*,22*E*)-6-ethyl-2-(2-methoxyethyl)-15,15-dimethyl-4,18-dioxo-1a,2,5,6,7,8,15,16,16a,17,18,18a-dodecahydro-1*H*,4*H*-6,3-(epiminomethano)-11,13-ethenocyclopropa[*c*]pyrano[4,3-*g*][1,6]diazacycloheptadecin-22-ylidene)carbamate.

MS (ESI) m/z 609.4 ($M+H^+$)

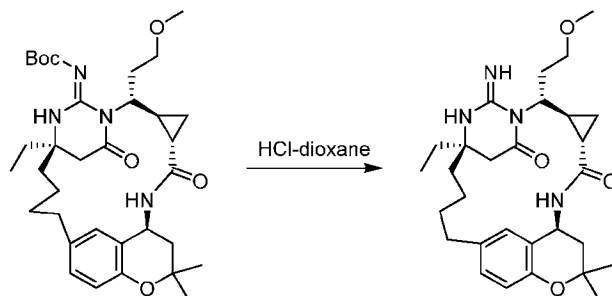
Step 9: Preparation of tert-butyl ((1a*S*,2*R*,6*R*,16a*S*,18a*S*,*E*)-6-ethyl-2-(2-methoxyethyl)-15,15-dimethyl-4,18-dioxo-1a,2,5,6,7,8,9,10,15,16,16a,17,18,18a-tetradecahydro-1*H*,4*H*-6,3-(epiminomethano)-11,13-ethenocyclopropa[*c*]pyrano[4,3-*g*][1,6]diazacycloheptadecin-22-ylidene)carbamate



[0147] To a solution of tert-butyl ((1aS,2R,6R,16aS,18aS,22E)-6-ethyl-2-(2-methoxyethyl)-15,15-dimethyl-4,18-dioxo-1a,2,5,6,7,8,15,16,16a,17,18,18a-dodecahydro-1H,4H-6,3-(epiminomethano)-11,13-ethenocyclopropa[c]pyrano[4,3-g][1,6]diazacycloheptadecin-22-ylidene)carbamate (50 mg, 0.082 mmol) in MeOH (2 mL) was added 10% Pd/C (17.48 mg, 0.016 mmol). The reaction mixture was degassed and backfilled with H₂ (3x). The resulting mixture was stirred under a hydrogen atmosphere (15 psi) at 20°C, and the reaction was followed by LC/MS. After 2 hours the catalyst was filtered off, and the filtrate was concentrated to give tert-butyl ((1aS,2R,6R,16aS,18aS,E)-6-ethyl-2-(2-methoxyethyl)-15,15-dimethyl-4,18-dioxo-1a,2,5,6,7,8,9,10,15,16,16a,17,18,18a-tetradecahydro-1H,4H-6,3-(epiminomethano)-11,13-ethenocyclopropa[c]pyrano[4,3-g][1,6]diazacycloheptadecin-22-ylidene)carbamate, which was used without further purification.

MS (ESI) *m/z* 611.4 (M+H⁺)

Step 10: Preparation of (1aS,2R,6R,16aS,18aS)-6-ethyl-22-imino-2-(2-methoxyethyl)-15,15-dimethyl-1,1a,2,5,6,7,8,9,10,15,16,16a,17,18a-tetradecahydro-4H,18H-6,3-(epiminomethano)-11,13-ethenocyclopropa[c]pyrano[4,3-g][1,6]diazacycloheptadecine-4,18-dione



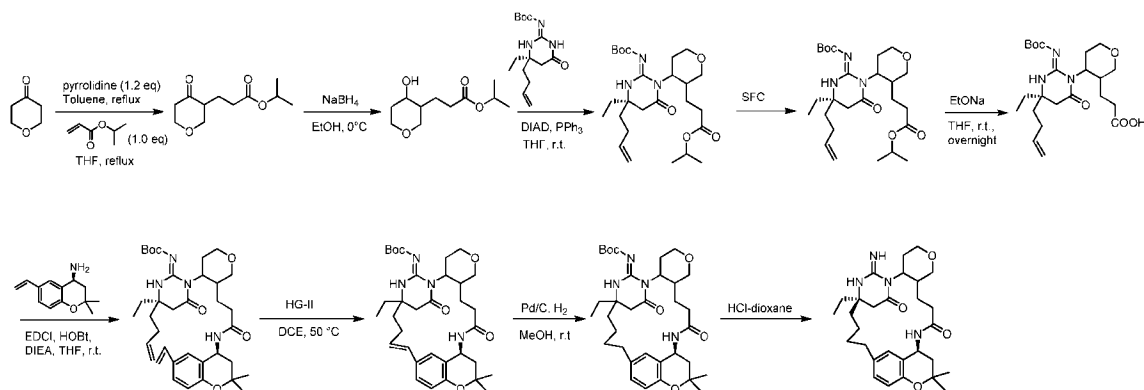
[0148] A solution of tert-butyl ((1aS,2R,6R,16aS,18aS,E)-6-ethyl-2-(2-methoxyethyl)-15,15-dimethyl-4,18-dioxo-1a,2,5,6,7,8,9,10,15,16,16a,17,18,18a-tetradecahydro-1H,4H-6,3-(epiminomethano)-11,13-ethenocyclopropa[c]pyrano[4,3-g][1,6]diazacycloheptadecin-22-ylidene)carbamate (48 mg, 0.079 mmol) in HCl-dioxane (5 mL) was stirred at 25°C. The

reaction was followed by LC/MS. After 10 hours the reaction mixture was concentrated. The resulting residue was purified by reverse preparative HPLC (Column Boston Green ODS 150 x 30mm; 5 μ m: Condition water (0.01%TFcanACN Begin B 32 End B 52 Gradient Time (10 min); 100%B Hold Time (2 min) Flow Rate (25 mL/min). The desired fractions were concentrated to yield (1aS,2R,6R,16aS,18aS)-6-ethyl-22-imino-2-(2-methoxyethyl)-15,15-dimethyl-1,1a,2,5,6,7,8,9,10,15,16,16a,17,18a-tetradecahydro-4H,18H-6,3-(epiminomethano)-11,13-ethenocyclopropa[c]pyrano[4,3-g][1,6]diazacycloheptadecine-4,18-dione.

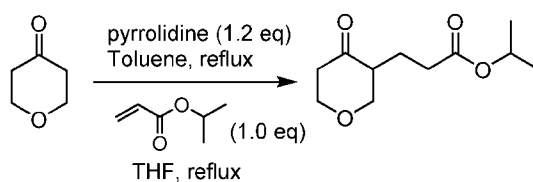
MS (ESI) m/z 511.3 ($M+H^+$)

1H NMR (500 MHz, methanol- d_4) δ 6.93 (dd, $J = 2.0, 8.5$ Hz, 1H), 6.83 (d, $J = 1.5$ Hz, 1H), 6.65 (d, $J = 8.0$ Hz, 1H), 5.16-5.27 (m, 1H), 3.44-3.51 (m, 1H), 3.34-3.41 (m, 2H), 3.31 (s, 3H), 2.96 (d, $J = 16.0$ Hz, 1H), 2.73 (d, $J = 16.0$ Hz, 1H), 2.46-2.67 (m, 4H), 2.10-2.12 (m, 1H), 2.04-2.07 (m, 1H), 1.70-1.86 (m, 5H), 1.55-1.68 (m, 3H), 1.41 (s, 3H), 1.34-1.40 (m, 2H), 1.26 (s, 3H), 1.22-1.24 (m, 1H), 0.99 (t, $J = 7.5$ Hz, 3H), 0.89-0.91 (m, 1H) ppm.

EXAMPLE 4



Step 1: Preparation of isopropyl 3-(4-oxotetrahydro-2H-pyran-3-yl)propanoate



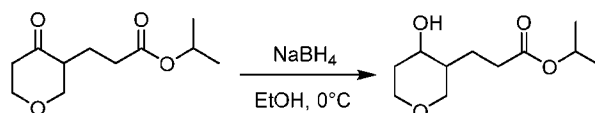
[0149] Tetrahydro-4H-pyran-4-one (6 g, 59.9 mmol) and pyrrolidine (5.11 g, 71.9 mmol) in toluene (80 mL) were refluxed at 130 °C using a Dean & Stark apparatus. After 6 h the solvent and excess pyrrolidine were removed under reduced pressure and the crude enamine was dissolved in THF (60 mL). Then isopropyl acrylate (8.21 g, 71.9 mmol) was added followed by

heating to 90 °C for 4 hours. The solvent was then removed under reduced pressure and the crude product was diluted with EtOAc. The organic phase was washed with dilute HCl and brine. The organic layer was then dried over anhydrous sodium sulfate, filtered and concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO; 80 g Agela Silica Flash Column, Eluent of 15% EtOAc/Pet.ether gradient @ 50 mL/min). The desired fractions were concentrated to yield isopropyl 3-(4-oxotetrahydro-2H-pyran-3-yl)propanoate.

MS (ESI) m/z 215.4 ($M+H^+$)

1H NMR (400 MHz, chloroform- d) δ 4.96-5.03 (m, 1H), 4.12-4.25 (m, 2H), 3.69-3.79 (m, 1H), 3.41 (dd, $J = 10.0, 11.2$ Hz, 1H), 2.54-2.66 (m, 2H), 2.23-2.46 (m, 3H), 2.02-2.12 (m, 1H), 1.46-1.56 (m, 1H), 1.22 (d, $J = 6.4$ Hz, 6H) ppm.

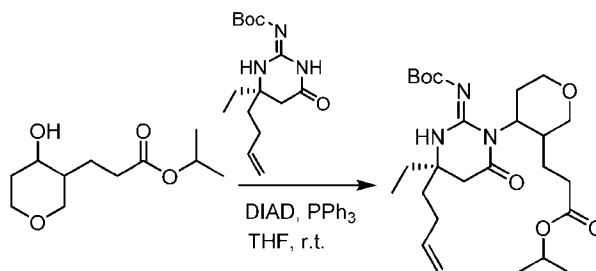
Step 2: Preparation of isopropyl 3-(4-hydroxytetrahydro-2H-pyran-3-yl)propanoate



[0150] A 100 mL round-bottom flask was charged with isopropyl 3-(4-oxotetrahydro-2H-pyran-3-yl)propanoate (2 g, 9.33 mmol), which was dissolved in MeOH (25 mL). The solution was stirred at 0 °C under N₂ atmosphere. Then NaBH₄ (0.706 g, 18.67 mmol) was added in portions. After addition, the reaction mixture was stirred at 30 °C for 1 h. TLC showed the reaction was complete. The mixture was quenched with water (30 mL) slowly under N₂ atmosphere at 0 °C, then the solution was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO; 20 g Agela Silica Flash Column, Eluent of 30% EtOAc/Pet.ether gradient @ 30 mL/min). The desired fractions were concentrated to yield isopropyl 3-(4-hydroxytetrahydro-2H-pyran-3-yl)propanoate.

1H NMR (400 MHz, chloroform- d) δ 4.96-5.08 (m, 1H), 3.93-4.00 (m, 1H), 3.76-3.93 (m, 1H), 3.55-3.70 (m, 1H), 3.35-3.53 (m, 1H), 3.05 (dd, $J = 10.0, 11.6$ Hz, 1H), 2.31-2.44 (m, 2H), 1.90-2.02 (m, 1H), 1.67-1.77 (m, 2H), 1.43-1.60 (m, 2H), 1.24 (d, $J = 6.4$ Hz, 6H) ppm.

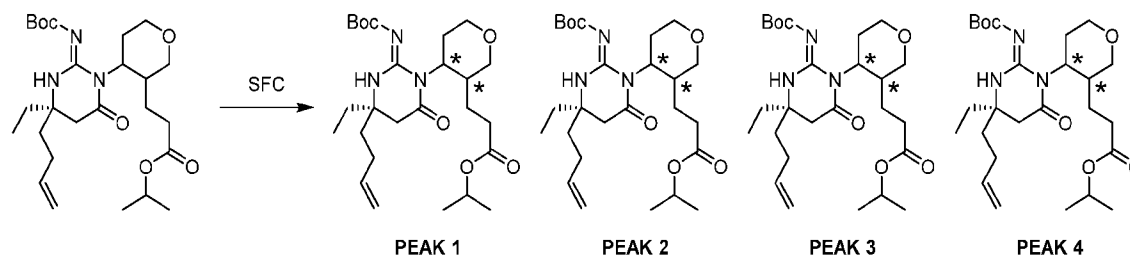
Step 3: Preparation of isopropyl 3-(4-((R,E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)tetrahydro-2H-pyran-3-yl)propanoate.



[0151] To a solution of isopropyl 3-(4-hydroxytetrahydro-2H-pyran-3-yl)propanoate (1.3 g, 6.01 mmol), tert-butyl (R,E)-(4-(but-3-en-1-yl)-4-ethyl-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate (1.598 g, 5.41 mmol) and Ph₃P (3.15 g, 12.02 mmol) in THF (60 mL) was added DIAD (2.337 mL, 12.02 mmol) dropwise at 0 °C under N₂ atmosphere. The reaction mixture was then stirred at 30 °C. Followed by LC/MS. After 12 hours the reaction mixture was concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO; 80 g Agela Silica Flash Column, Eluent of 15% EtOAc/Pet.ether gradient @ 50 mL/min), then repurified by Prep-HPLC (condition: 0.1% FA, 75% ACN in water). The desired fractions were concentrated to afford isopropyl 3-(4-((R,E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)tetrahydro-2H-pyran-3-yl)propanoate.

MS (ESI) m/z 494.4 ($M+H^+$)

Step 4: SFC Chiral Separation of isopropyl 3-(4-((R,E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)tetrahydro-2H-pyran-3-yl)propanoate.

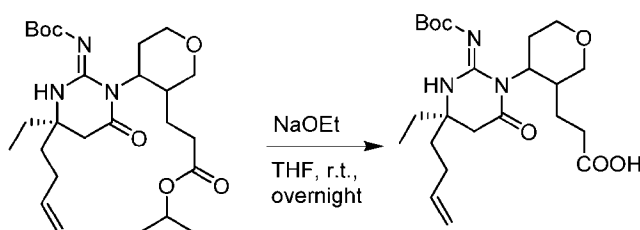


[0152] Isopropyl 3-(4-((R,E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)tetrahydro-2H-pyran-3-yl)propanoate (700 mg, 1.418 mmol) was separated by SFC (Instrument SFC-16 Method SFC Column Phenomenex-Cellulose-2 (250mm x 30mm; 10 μ m): Condition Neu-M EtOH Begin B 20 End B 20 Gradient Time (18 min); 100%B Hold ime (1 min); Flow Rate (60 mL/min); 80 Injections. The desired fractions were concentrated to product isopropyl 3-(4-((R,E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-

4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)tetrahydro-2H-pyran-3-yl)propanoate (PEAK 1, Rt = 2.347), isopropyl 3-(4-((R,E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)tetrahydro-2H-pyran-3-yl)propanoate (mixture of PEAK 2 & PEAK 3) and isopropyl 3-((3S,4S)-4-((R,E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)tetrahydro-2H-pyran-3-yl)propanoate (PEAK 4, Rt = 3.591).

MS (ESI) m/z 494.8 (M+H⁺)

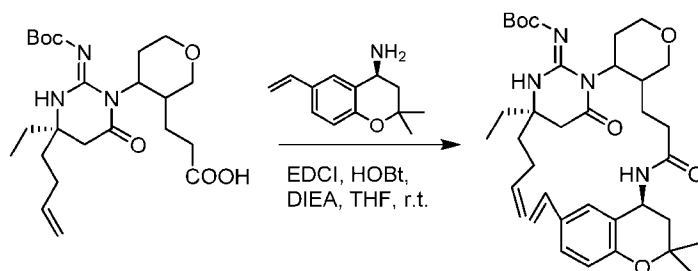
Step 5: Preparation of 3-(4-((R,E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)tetrahydro-2H-pyran-3-yl)propanoic acid



[0153] A solution of isopropyl 3-(4-((R,E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)tetrahydro-2H-pyran-3-yl)propanoate (160 mg, 0.324 mmol) in THF (3 mL) was added sodium ethoxide (132 mg, 1.945 mmol). The reaction was stirred at 30 °C. Followed by LC/MS. After 3 hours, added H₃PO₄ (0.1 g/mL in THF) to adjust pH to about 6~7, then the reaction mixture was diluted with water (5 ml) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 ml), dried over anhydrous Na₂SO₄, filtered and concentrated to yield 3-(4-((R,E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)tetrahydro-2H-pyran-3-yl)propanoic acid. which was used without further purification.

MS (ESI) m/z 452.3 (M+H⁺)

Step 6: Preparation of tert-butyl ((4R,E)-4-(but-3-en-1-yl)-1-(3-(3-(((S)-2,2-dimethyl-6-vinylchroman-4-yl)amino)-3-oxopropyl)tetrahydro-2H-pyran-4-yl)-4-ethyl-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate

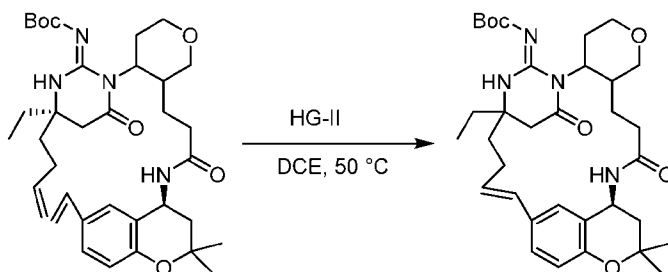


[0154] To a solution of 3-(4-((R,E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)tetrahydro-2H-pyran-3-yl)propanoic acid (150 mg, 0.332 mmol), EDC (127 mg, 0.664 mmol), (S)-2,2-dimethyl-6-vinylchroman-4-amine (67.5 mg, 0.332 mmol) and 1H-benzo[d][1,2,3]triazol-1-ol (90 mg, 0.664 mmol) in THF (5 ml) was added DIEA (0.290 ml, 1.661 mmol). The reaction was stirred at 30 °C. Followed by LC/MS. After 12 hours the reaction mixture was quenched with water (5 ml), and extracted with EtOAc (3 x 7 mL). The combined organic layers were washed with brine (7 ml), dried over anhydrous Na₂SO₄, filtered and concentrated. The resulting residue was purified by prep-TLC (SiO₂, PE:EA = 1:1) to yield tert-butyl ((4R,E)-4-(but-3-en-1-yl)-1-(3-(3-(((S)-2,2-dimethyl-6-vinylchroman-4-yl)amino)-3-oxopropyl)tetrahydro-2H-pyran-4-yl)-4-ethyl-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate.

MS (ESI) *m/z* 637.4 (M+H⁺)

¹H NMR (400 MHz, chloroform-*d*) δ 10.03 (br s, 1 H), 7.24 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.17 (s, 1 H), 6.73 (d, *J* = 8.4 Hz, 1 H), 6.56-6.60 (m, 1 H), 5.67-5.92 (m, 2 H), 5.51-5.61 (m, 1 H), 5.22-5.30 (m, 1 H), 5.02 - 5.13 (m, 2 H), 4.97-4.99 (m, 1 H), 4.90 (br s, 1 H), 3.94 - 4.04 (m, 2 H), 3.44-3.46 (m, 1 H), 3.14-3.16 (m, 1 H), 2.57-2.66 (m, 1 H), 2.49-2.56 (m, 1 H), 2.28-2.38 (m, 1 H), 2.16-2.21 (m, 1 H), 2.05-2.16 (m, 3 H), 1.77-1.87 (m, 2 H), 1.68-1.77 (m, 2 H), 1.49-1.68 (m, 5 H), 1.42-1.43 (m, 13 H), 1.32 (s, 3 H), 0.91 (t, *J* = 7.6 Hz, 2 H) ppm.

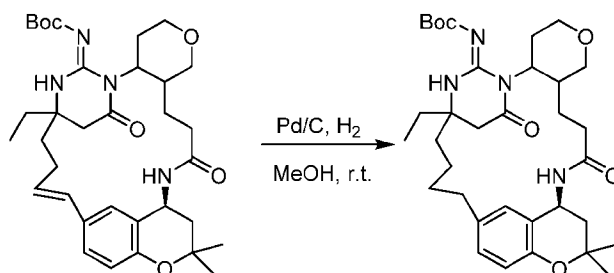
Step 7: Preparation of tert-butyl ((8R,11E,18aS,26E)-8-ethyl-17,17-dimethyl-6,20-dioxo-4,4a,7,8,9,10,17,18,18a,19,20,21,22,22a-tetradecahydro-1H,3H,6H-8,5-(epiminomethano)-13,15-ethenodipyran[4,3-b:4',3'-h][1,7]diazacyclooctadecin-26-ylidene)carbamate



[0155] To a solution of tert-butyl ((4R,E)-4-(but-3-en-1-yl)-1-(3-(3-(((S)-2,2-dimethyl-6-vinylchroman-4-yl)amino)-3-oxopropyl)tetrahydro-2H-pyran-4-yl)-4-ethyl-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate (140 mg, 0.220 mmol) in DCE (50 ml) was added (1,3-dimesitylimidazolidin-2-ylidene)(2-isopropoxybenzylidene)ruthenium(VI) chloride (13.78 mg, 0.022 mmol). The reaction was stirred at 50 °C with N₂ continuously bubbling through the solution. After 3 hours the reaction mixture was filtered, and the filtrate was concentrated. The resulting residue was then purified by Prep-TLC (Pet. ether/EtOAc = 1:1.5) to yield tert-butyl ((8R,11E,18aS,26E)-8-ethyl-17,17-dimethyl-6,20-dioxo-4,4a,7,8,9,10,17,18,18a,19,20,21,22,22a-tetradecahydro-1H,3H,6H-8,5-(epiminomethano)-13,15-ethenodipyrano[4,3-b:4',3'-h][1,7]diazacyclooctadecin-26-ylidene)carbamate.

MS (ESI) m/z 609.4 (M+H⁺)

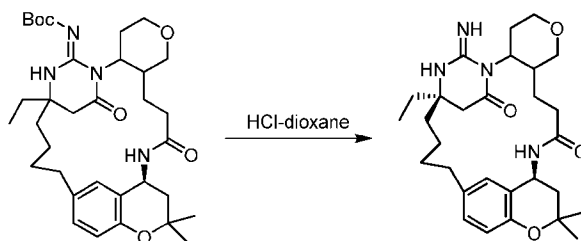
Step 8: Preparation of tert-butyl ((8R,18aS,E)-8-ethyl-17,17-dimethyl-6,20-dioxo-4,4a,7,8,9,10,11,12,17,18,18a,19,20,21,22,22a-hexadecahydro-1H,3H,6H-8,5-(epiminomethano)-13,15-ethenodipyrano[4,3-b:4',3'-h][1,7]diazacyclooctadecin-26-ylidene)carbamate



[0156] To a solution of tert-butyl ((8R,11E,18aS,26E)-8-ethyl-17,17-dimethyl-6,20-dioxo-4,4a,7,8,9,10,17,18,18a,19,20,21,22,22a-tetradecahydro-1H,3H,6H-8,5-(epiminomethano)-13,15-ethenodipyrano[4,3-b:4',3'-h][1,7]diazacyclooctadecin-26-ylidene)carbamate (105 mg, 0.172 mmol) in MeOH (6 mL) was added Pd/C (18.35 mg, 0.017 mmol). The reaction mixture was degassed and backfilled with H₂ (3x). The resulting mixture was stirred under an atmosphere of H₂ (15 psi) at 25 °C. Followed by LC/MS. After ~10 minutes the reaction mixture was filtered. The filtrate was concentrated yield tert-butyl ((8R,18aS,E)-8-ethyl-17,17-dimethyl-6,20-dioxo-4,4a,7,8,9,10,11,12,17,18,18a,19,20,21,22,22a-hexadecahydro-1H,3H,6H-8,5-(epiminomethano)-13,15-ethenodipyrano[4,3-b:4',3'-h][1,7]diazacyclooctadecin-26-ylidene)carbamate, which was used without further purification.

MS (ESI) m/z 611.4 (M+H⁺)

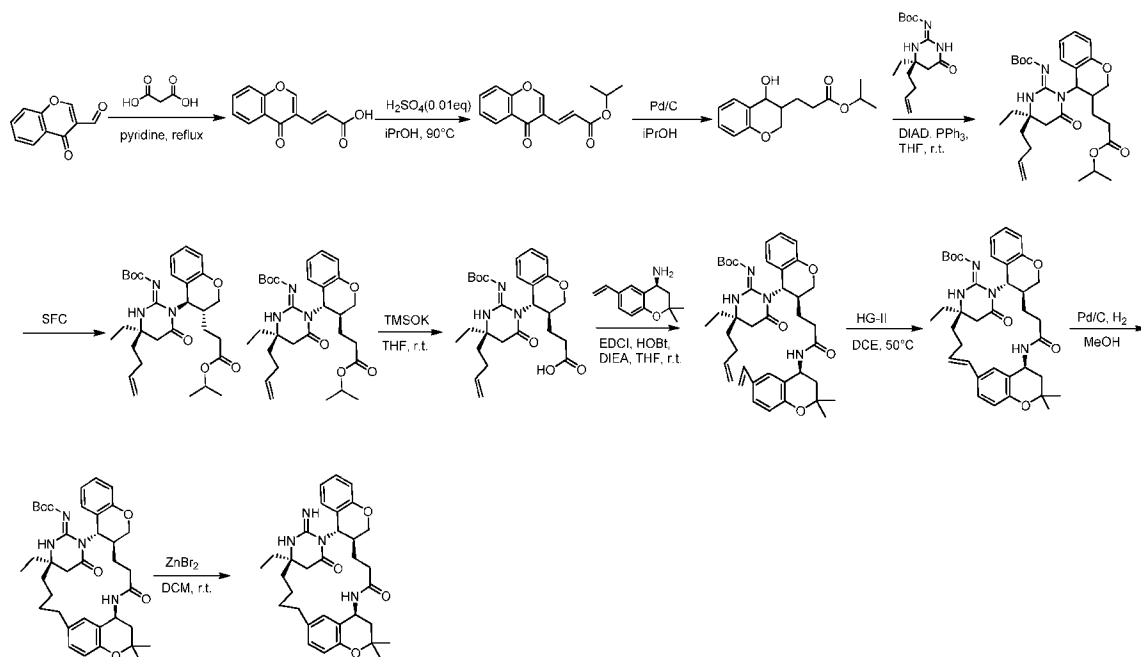
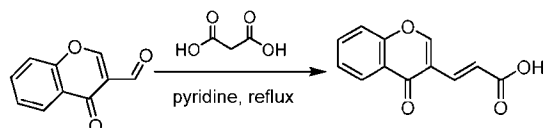
Step 9: Preparation of (18aS)-8-ethyl-26-imino-17,17-dimethyl-3,4,4a,7,8,9,10,11,12,17,18,18a,19,21,22,22a-hexadecahydro-1H,6H,20H-8,5-(epiminomethano)-13,15-ethenodipyrano[4,3-b:4',3'-h][1,7]diazacyclooctadecine-6,20-dione.



[0157] A solution of tert-butyl ((18aS,E)-8-ethyl-17,17-dimethyl-6,20-dioxo-4,4a,7,8,9,10,11,12,17,18,18a,19,20,21,22,22a-hexadecahydro-1H,3H,6H-8,5-(epiminomethano)-13,15-ethenodipyrano[4,3-b:4',3'-h][1,7]diazacyclooctadecine-26-ylidene)carbamate (100 mg, 0.164 mmol) in 4N HCl in dioxane (3 mL) was stirred at 25 °C. The reaction was followed by LC/MS. After 4 hours the reaction mixture was concentrated. The resulting residue was then purified by HPLC (Column Boston Prime C18 150 x 40mm; 5µm: Condition water(0.1%TFA)-ACN Begin B 30 End B 50 Gradient Time (10 min); 100%B Hold Time (1 min); Flow Rate(25 ml/min). The desired fractions were concentrated to yield (18aS)-8-ethyl-26-imino-17,17-dimethyl-3,4,4a,7,8,9,10,11,12,17,18,18a,19,21,22,22a-hexadecahydro-1H,6H,20H-8,5-(epiminomethano)-13,15-ethenodipyrano[4,3-b:4',3'-h][1,7]diazacyclooctadecine-6,20-dione.

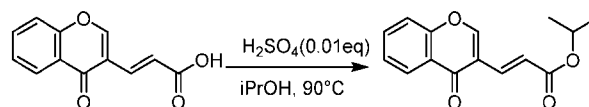
MS (ESI) m/z 511.3 ($M+H^+$)

1H NMR (400 MHz, METHANOL- d_4) δ 6.99 (s, 1 H), 6.89 (dd, $J = 8.4, 1.6$ Hz, 1 H), 6.60 (d, $J = 8.4$ Hz, 1 H), 5.10-5.22 (m, 1 H), 4.05-4.08 (m, 1 H), 3.99-4.02 (m, 1 H), 3.79-3.81 (m, 1 H), 3.47-3.52 (m, 1 H), 3.01-3.20 (m, 2 H), 2.92 (d, $J = 16.4$ Hz, 1 H), 2.66-2.78 (m, 2 H), 2.44-2.65 (m, 2 H), 2.26 - 2.38 (m, 1 H), 2.12-2.21 (m, 1 H), 2.00-2.03 (m, 1 H), 1.81 - 1.93 (m, 2 H), 1.62 - 1.80 (m, 7 H), 1.39 - 1.52 (m, 4 H), 1.30 - 1.38 (m, 2 H), 1.26 (s, 3 H), 0.95 (t, $J = 7.6$ Hz, 3 H) ppm.

EXAMPLE 5**Step 1: Preparation of (E)-3-(4-oxo-4H-chromen-3-yl)acrylic acid**

[0158] A mixture of 4-oxo-4H-chromene-3-carbaldehyde (9 g, 51.7 mmol) and malonic acid (10.76 g, 103 mmol) in pyridine (150 mL) was heated to 120 °C. TLC showed a new spot. The reaction mixture was adjusted to pH = 1 with aqueous 6N HCl at 0 °C, resulting in a large amount of precipitate. The mixture was then filtered, and the filter cake was dried under vacuum to afford (E)-3-(4-oxo-4H-chromen-3-yl)acrylic acid which was used without further purification.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.88 (s, 1 H), 8.14 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.82 - 7.89 (m, 1 H), 7.71 (d, *J* = 8.4 Hz, 1 H), 7.55 (t, *J* = 7.6 Hz, 1 H), 7.43 (d, *J* = 16 Hz, 1 H), 7.12 (d, *J* = 16 Hz, 1 H) ppm.

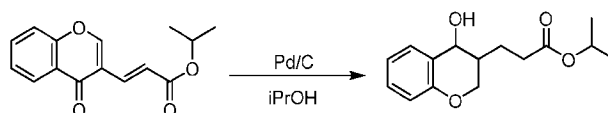
Step 2: Preparation of isopropyl (E)-3-(4-oxo-4H-chromen-3-yl)acrylate

[0159] To a solution of (E)-3-(4-oxo-4H-chromen-3-yl) acrylic acid (11 g, 50.9 mmol) in iPrOH (150 mL) was added H₂SO₄ (0.027 mL, 0.509 mmol), and stirred at 90 °C for 16 h under

an atmosphere of N₂. TLC showed a new spot. After cooling, the mixture was diluted with a saturated solution of aqueous NaHCO₃, adjusted pH to 7 and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, and filtered. The solvent was evaporated under reduced pressure to yield the crude product, which was used in the next step without any further purification.

¹H NMR (400 MHz, chloroform-*d*) δ 8.32 (dd, *J* = 8.0, 1.2 Hz, 1 H), 8.16 (s, 1 H), 7.72-7.75 (m, 1 H), 7.47 - 7.55 (m, 2 H), 7.41 - 7.47 (m, 1 H), 7.27-7.30 (m, 1 H), 5.13-5.21 (m, 1 H), 1.34 (d, *J* = 6.4 Hz, 6 H) ppm.

Step 3: Preparation of isopropyl 3-(4-hydroxychroman-3-yl)propanoate

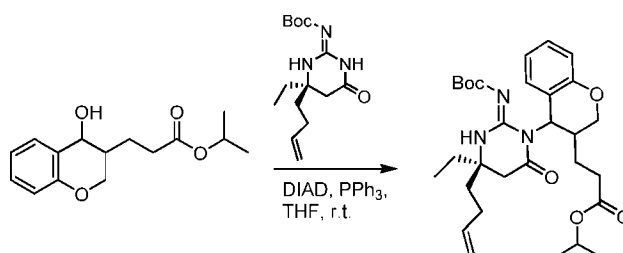


[0160] To a solution of isopropyl (E)-3-(4-oxo-4H-chromen-3-yl)acrylate (6 g, 23.23 mmol) in iPrOH (100 mL) was added 10% Pd/C (2.472 g, 2.323 mmol) at 25°C under an atmosphere of H₂ (50 psi), and followed by LC/MS. After 24 hours the catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to give isopropyl 3-(4-hydroxychroman-3-yl)propanoate which was used in the next step without further purification.

MS (ESI) *m/z* 265.3 (M+H⁺)

¹H NMR (400 MHz, chloroform-*d*) δ 7.19 - 7.29 (m, 1 H), 7.09 - 7.17 (m, 1 H), 6.80 - 6.90 (m, 1 H), 6.75-6.77 (m, 1 H), 4.86 - 5.03 (m, 1 H), 4.36 - 4.58 (m, 1 H), 4.18-4.20 (m, 0.5 H), 3.93 - 3.99 (m, 1.5 H), 2.38-2.42 (m, 1 H), 1.81 - 1.91 (m, 2 H), 1.46 - 1.72 (m, 2 H), 1.14 - 1.18 (m, 6 H) ppm.

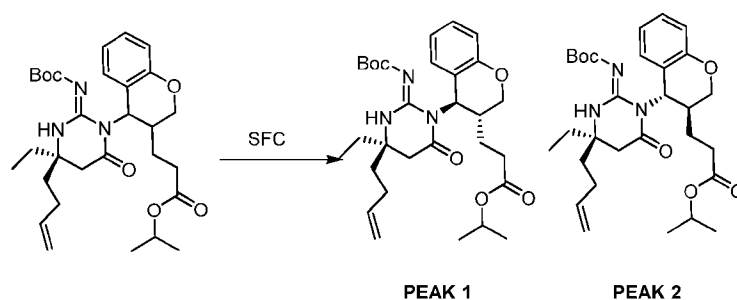
Step 4: Preparation of isopropyl 3-(4-((R,E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chroman-3-yl)propanoate



[0161] To a solution of isopropyl 3-(4-hydroxychroman-3-yl)propanoate (1 g, 3.78 mmol), Ph₃P (1.985 g, 7.57 mmol), tert-butyl (R,E)-4-(but-3-en-1-yl)-4-ethyl-6-

oxotetrahydropyrimidin-2(1H)-ylidene)carbamate (1.006 g, 3.40 mmol) in THF (20 mL) was added DIAD (1.125 mL, 5.67 mmol) at 20 °C under N₂ atmosphere. The reaction was stirred at 20 °C and followed by LC/MS. After 16 hours the reaction mixture was concentrated and the resulting residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 5-15% EtOAc/Pet. ether gradient @ 35 mL/min). The desired fractions were concentrated to yield isopropyl 3-(4-((R,E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chroman-3-yl)propanoate which was then separated by SFC chiral separation.

Step 5: Preparation of isopropyl 3-((3S,4S)-4-((R,E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chroman-3-yl)propanoate (PEAK 2)



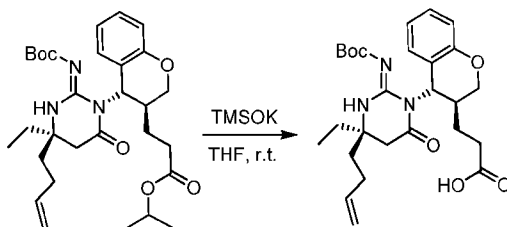
[0162] Chiral Separation: isopropyl 3-(4-((R,E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chroman-3-yl)propanoate (600 mg). was separated by SFC1 (Column: DAICEL CHIRALCEL OD-H(250mm x 30mm, 5 μm): Condition 0.1%NH₃H₂O EtOH Begin B 20% End B 20%; Gradient Time 10 min; 100%B Hold Time 10 min; Flow Rate 70 mL/min. (180 Injections). The desired fractions were concentrated to yield isopropyl 3-((3R,4R)-4-((R,E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chroman-3-yl)propanoate (PEAK 1) and isopropyl 3-((3S,4S)-4-((R,E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chroman-3-yl)propanoate (PEAK 2).

MS (ESI) *m/z*: 542.3 (**M+H⁺**)

¹H NMR (400 MHz, chloroform-*d*) δ 7.07 (t, *J* = 7.2 Hz, 1 H), 6.85-6.91 (m, 1 H), 6.76-6.84 (m, 2 H), 6.18 (br d, *J* = 9.6 Hz, 1 H), 5.81-5.83 (m, 1 H), 5.02-5.12 (m, 2 H), 4.95-5.02 (m, 1 H), 4.33-4.37 (m, 1 H), 3.86 (t, *J* = 10.8 Hz, 1 H), 2.83-2.99 (m, 1 H), 2.40-2.70 (m, 4 H), 2.29-2.31 (m, 1 H), 2.08-2.17 (m, 2 H), 1.81 - 1.92 (m, 1 H), 1.67-1.72 (m, 4 H), 1.50 (s, 9 H), 1.22 (d, *J* = 6.4 Hz, 6 H), 0.98 (t, *J* = 7.6 Hz, 3 H) ppm.

¹H NMR (400 MHz, chloroform-*d*) δ 7.04-7.12 (m, 1 H), 6.75-6.91 (m, 3 H), 6.18 (br d, $J = 10.0$ Hz, 1 H), 5.80-5.82 (m, 1 H), 4.92-5.14 (m, 3 H), 4.35 (dd, $J = 11.2, 3.6$ Hz, 1 H), 3.86 (t, $J = 10.8$ Hz, 1 H), 2.90-2.93 (m, 1 H), 2.51-2.68 (m, 2 H), 2.39-2.48 (m, 1 H), 2.25-2.35 (m, 1 H), 2.07-2.17 (m, 2 H), 1.68-1.90 (m, 6 H), 1.50 (s, 9 H), 1.22 (d, $J = 6.4$ Hz, 6 H), 0.99 (t, $J = 7.6$ Hz, 3 H) ppm.

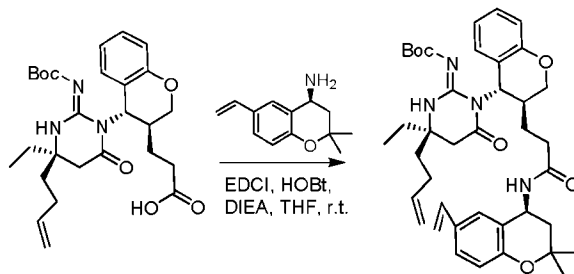
Step 6: Preparation of 3-((3S,4S)-4-((R,E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chroman-3-yl)propanoic acid



[0163] To a solution of isopropyl 3-((3S,4S)-4-((R,E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chroman-3-yl)propanoate (PEAK 2). (190 mg, 0.351 mmol) in THF (4 mL) was added potassium trimethylsilanolate (270 mg, 2.105 mmol). The reaction mixture was stirred at 20 °C, and followed by LC/MS. After 1 hour the reaction mixture was adjusted to pH ~6 with H₃PO₄/H₂O (0.1 g/mL). The mixture was quenched with water (2 mL), then extracted with EtOAc (3 x 2 mL). The combined organic layers were washed with brine (2 mL), then dried over anhydrous Na₂SO₄, then filtered and concentrated to afford 3-((3S,4S)-4-((R,E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chroman-3-yl)propanoic acid, which was used without further purification.

MS (ESI) m/z : 500.4 ($M+H^+$)

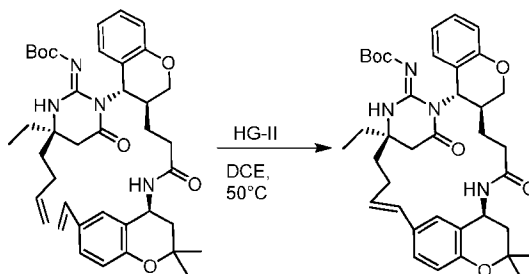
Step 7: Preparation of tert-butyl ((R,E)-4-(but-3-en-1-yl)-1-((3S,4S)-3-(3-(((S)-2,2-dimethyl-6-vinylchroman-4-yl)amino)-3-oxopropyl)chroman-4-yl)-4-ethyl-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate.



[0164] To a solution of 3-((3S,4S)-4-((R,E)-4-(but-3-en-1-yl)-2-((tert-butoxycarbonyl)imino)-4-ethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chroman-3-yl)propanoic acid, (170 mg, 0.340 mmol), EDC (326 mg, 1.701 mmol), 1H-benzo[d][1,2,3]triazol-1-ol (138 mg, 1.021 mmol) and (S)-2,2-dimethyl-6-vinylchroman-4-amine (0.346 mL, 0.340 mmol) in THF (5 mL) was added DIEA (0.475 mL, 2.72 mmol). The reaction was stirred at 20 °C, and followed by LC/MS. After 16 hours the reaction mixture was quenched with water (5 mL) then extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), then dried over anhydrous Na₂SO₄, filtered and concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 30% EtOAc/Pet.ether gradient @ 60 mL/min). The desired fractions were concentrated to afford tert-butyl ((R,E)-4-(but-3-en-1-yl)-1-((3S,4S)-3-(3-(((S)-2,2-dimethyl-6-vinylchroman-4-yl)amino)-3-oxopropyl)chroman-4-yl)-4-ethyl-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate.

MS (ESI) *m/z*: 685.4 (**M+H⁺**)

Step 8: Preparation of tert-butyl ((4aS,8aS,14bS,15R,18R,21E,28E)-18-ethyl-3,3-dimethyl-6,16-dioxo-4,4a,5,6,7,8,8a,14b,17,18,19,20-dodecahydro-3H,9H,16H-18,15-(epiminomethano)-1,23-ethenochromeno[4,3-b]pyrano[4,3-h][1,7]diazacyclooctadecin-28-ylidene)carbamate

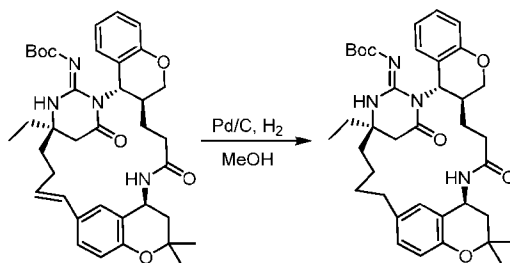


[0165] To a solution of tert-butyl tert-butyl ((R,E)-4-(but-3-en-1-yl)-1-((3S,4S)-3-(3-(((S)-2,2-dimethyl-6-vinylchroman-4-yl)amino)-3-oxopropyl)chroman-4-yl)-4-ethyl-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate (195 mg, 0.285 mmol) in DCE (80 mL) was added (1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(o-isopropoxyphenylmethylene)ruthenium (17.84 mg, 0.028 mmol). The reaction was stirred at 50 °C for 8 hours while bubbled with N₂ continuously. The reaction was followed by LC/MS. After 8 hours the reaction mixture was concentrated. The resulting residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 30% EtOAc/Pet.ether gradient @ 60 mL/min). The desired fractions were concentrated to afford tert-butyl ((4aS,8aS,14bS,15R,18R,21E,28E)-18-ethyl-3,3-dimethyl-6,16-dioxo-

4,4a,5,6,7,8,8a,14b,17,18,19,20-dodecahydro-3H,9H,16H-18,15-(epiminomethano)-1,23-ethenochromeno[4,3-b]pyrano[4,3-h][1,7]diazacyclooctadecin-28-ylidene)carbamate.

MS (ESI) m/z : 657.4 ($M+H^+$)

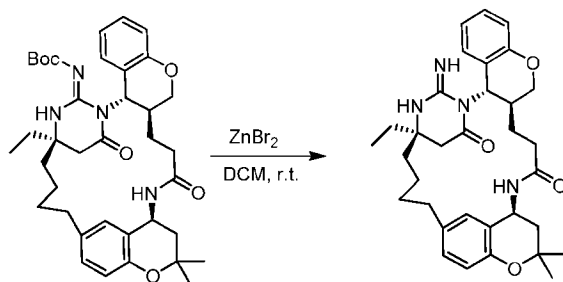
Step 9: Preparation of tert-butyl ((4aS,8aS,14bS,15R,18R,E)-18-ethyl-3,3-dimethyl-6,16-dioxo-4,4a,5,6,7,8,8a,14b,17,18,19,20,21,22-tetradecahydro-3H,9H,16H-18,15-(epiminomethano)-1,23-ethenochromeno[4,3-b]pyrano[4,3-h][1,7]diazacyclooctadecin-28-ylidene)carbamate



[0166] To a solution of tert-butyl ((4aS,8aS,14bS,15R,18R,21E,28E)-18-ethyl-3,3-dimethyl-6,16-dioxo-4,4a,5,6,7,8,8a,14b,17,18,19,20-dodecahydro-3H,9H,16H-18,15-(epiminomethano)-1,23-ethenochromeno[4,3-b]pyrano[4,3-h][1,7]diazacyclooctadecin-28-ylidene)carbamate (70 mg, 0.107 mmol) in MeOH (2 mL) was added 10% Pd-C (11.34 mg, 10.66 μ mol) under N₂ atmosphere. The mixture was degassed and backfilled with H₂ (3x). The resulting mixture was stirred under an atmosphere of H₂ (15 psi) at 20 °C, and followed by LC/MS. After ~30 minutes the reaction mixture was filtered and filtrate was concentrated to yield tert-butyl ((4aS,8aS,14bS,15R,18R,E)-18-ethyl-3,3-dimethyl-6,16-dioxo-4,4a,5,6,7,8,8a,14b,17,18,19,20,21,22-tetradecahydro-3H,9H,16H-18,15-(epiminomethano)-1,23-ethenochromeno[4,3-b]pyrano[4,3-h][1,7]diazacyclooctadecin-28-ylidene)carbamate which was used without further purification.

MS (ESI) m/z : 659.4 ($M+H^+$)

Step 10: Preparation of (4aS,8aS,14bS,15R,18R)-18-ethyl-28-imino-3,3-dimethyl-3,4,4a,5,7,8,8a,14b,17,18,19,20,21,22-tetradecahydro-6H,9H,16H-18,15-(epiminomethano)-1,23-ethenochromeno[4,3-b]pyrano[4,3-h][1,7]diazacyclooctadecine-6,16-dione.



[0167] A mixture of tert-butyl ((4a*S*,8a*S*,14b*S*,15*R*,18*R*,*E*)-18-ethyl-3,3-dimethyl-6,16-dioxo-4,4a,5,6,7,8,8a,14b,17,18,19,20,21,22-tetradecahydro-3*H*,9*H*,16*H*-18,15-(epiminomethano)-1,23-ethenochromeno[4,3-*b*]pyrano[4,3-*h*][1,7]diazacyclooctadecin-28-ylidene)carbamate (60 mg, 0.091 mmol) and zinc(II) bromide (205 mg, 0.911 mmol) in DCM (2 mL) was stirred at 20 °C. The reaction was followed by LC/MS. After 16 hours the reaction mixture was concentrated. The resulting residue was then purified by reverse preparative HPLC (Instrument e.g., Method Phase separation Column Welch Xtimate C18 150 x 25mm x 5µm: Condition water(0.1%TFA)-ACN Begin B 26 End B 56 Gradient Time (11min); 100%B Hold Time 2 min; Flow Rate(25 mL/min). The desired fractions were concentrated to yield (4a*S*,8a*S*,14b*S*,15*R*,18*R*)-18-ethyl-28-imino-3,3-dimethyl-3,4,4a,5,7,8,8a,14b,17,18,19,20,21,22-tetradecahydro-6*H*,9*H*,16*H*-18,15-(epiminomethano)-1,23-ethenochromeno[4,3-*b*]pyrano[4,3-*h*][1,7]diazacyclooctadecine-6,16-dione.

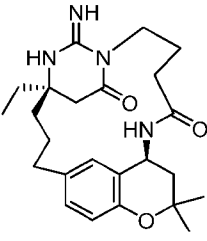
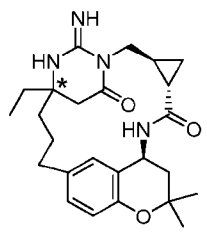
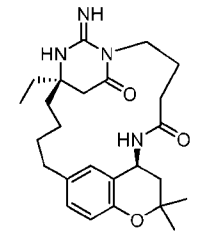
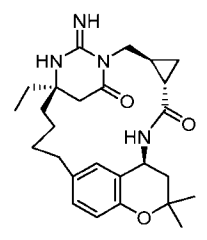
MS (ESI) *m/z*: 559.3 (**M+H⁺**)

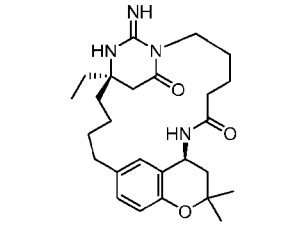
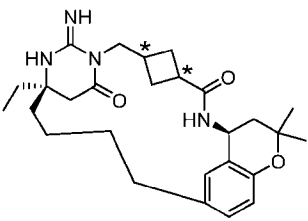
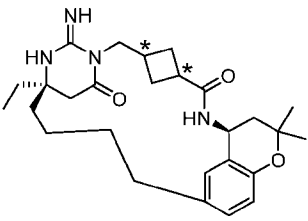
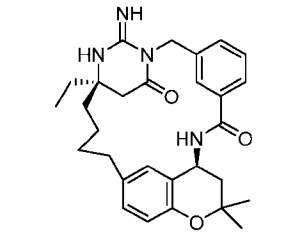
¹H NMR (400 MHz, methanol-*d*₄) δ 7.10-7.17 (m, 1H), 7.01-7.09 (m, 2H), 6.79-6.93 (m, 3H), 6.60 (d, *J* = 8.4 Hz, 1H), 5.23 (d, *J* = 10.4 Hz, 1H), 5.15-5.18 (m, 1H), 4.45 (dd, *J* = 3.6, 11.2 Hz, 1H), 3.92 (t, *J* = 11.2 Hz, 1H), 3.31 (td, *J* = 1.6, 3.2 Hz, 2H), 3.17-3.28 (m, 1H), 2.67-2.90 (m, 3H), 2.49-2.51 (m, 1H), 2.33-2.44 (m, 1H), 2.20-2.32 (m, 1H), 1.91-2.15 (m, 3H), 1.69-1.83 (m, 4H), 1.54-1.68 (m, 3H), 1.42 (s, 3H), 1.28-1.40 (m, 2H), 1.27 (s, 3H), 0.95 (t, *J* = 7.6 Hz, 3H) ppm.

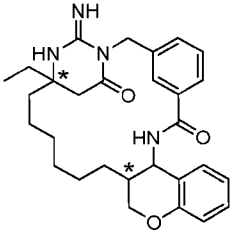
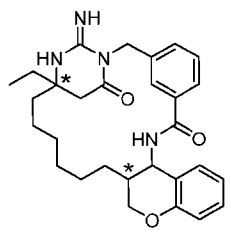
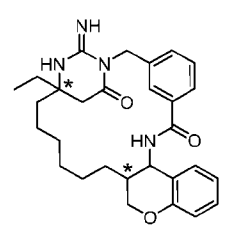
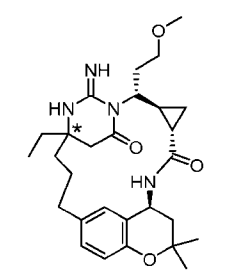
[0168] The compounds in Table 1 were prepared in an analogous fashion to that described for Example 1 through Example 5. The isomers were separated by preparative HPLC or/and preparative chiral SFC.

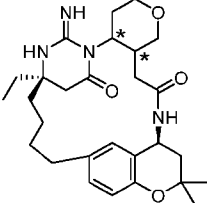
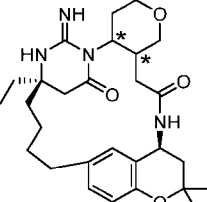
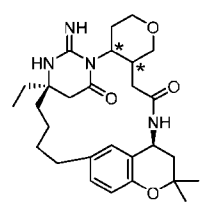
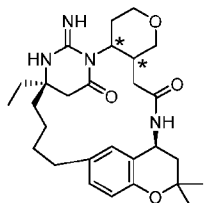
[0169] The asterisk (*) in a chemical structure drawing indicates the location of a chiral center.

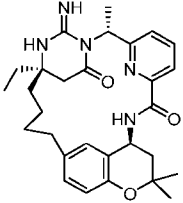
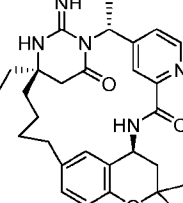
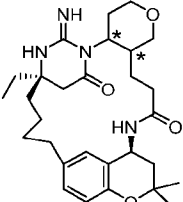
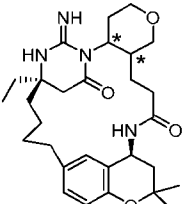
TABLE 1

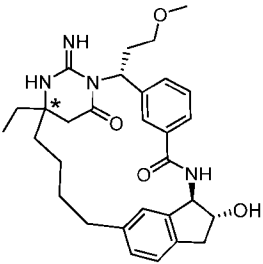
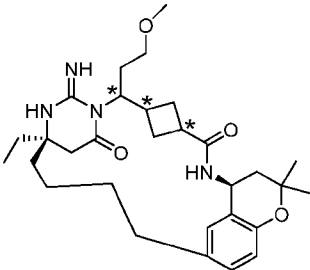
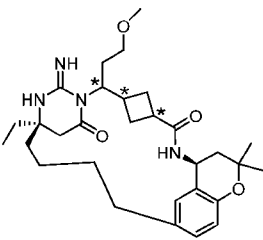
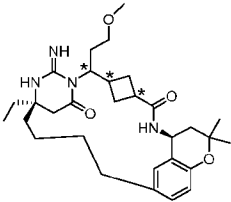
Example	Structure	MS Observed	Chemical Name
6		427.2	(5R,14S)-5-ethyl-7-imino-16,16-dimethyl-17-oxa-6,8,13-triazatetracyclo[12.6.2.25,8.018,22]tetracos-1(21),18(22),19-triene-12,23-dione
7		439.2	(1S,4S,6S)-11-ethyl-9-imino-20,20-dimethyl-19-oxa-2,8,10-triazapentacyclo[13.6.2.28,11.04,6.018,22]pentacos-15(23),16,18(22)-triene-3,25-dione
8		441.3	(6R,15S)-6-ethyl-8-imino-17,17-dimethyl-18-oxa-7,9,14-triazatetracyclo[13.6.2.26,9.019,23]pentacos-1(22),19(23),20-triene-13,24-dione
9		453.2	(1S,4S,6S,11R)-11-ethyl-9-imino-21,21-dimethyl-20-oxa-2,8,10-triazapentacyclo[14.6.2.28,11.04,6.019,23]hexacos-16(24),17,19(23)-triene-3,26-dione

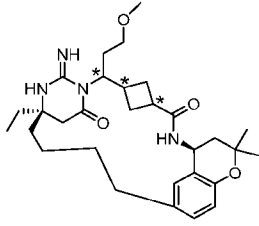
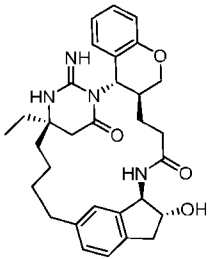
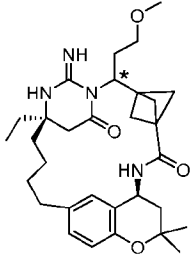
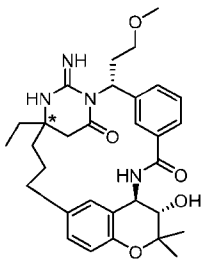
10		455.3	(6R,16S)-6-ethyl-8-imino-18,18-dimethyl-19-oxa-7,9,15-triazatetracyclo[14.6.2.26,9.020,24]hexacosa-1(23),20(24),21-triene-14,25-dione
11		467.2	(1S,11R)-11-ethyl-9-imino-21,21-dimethyl-20-oxa-2,8,10-triazapentacyclo[14.6.2.28,11.14,6.019,23]heptacosa-16(24),17,19(23)-triene-3,26-dione
12		467.2	(1S,11R)-11-ethyl-9-imino-21,21-dimethyl-20-oxa-2,8,10-triazapentacyclo[14.6.2.28,11.14,6.019,23]heptacosa-16(24),17,19(23)-triene-3,26-dione
13		489.2	(1S,13R)-13-ethyl-11-imino-23,23-dimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.210,13.14,8.021,25]nonacosa-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione

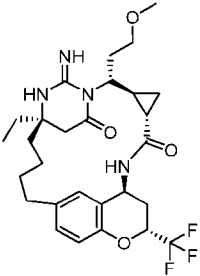
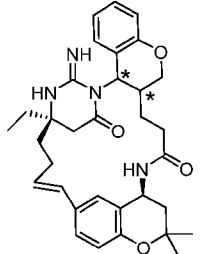
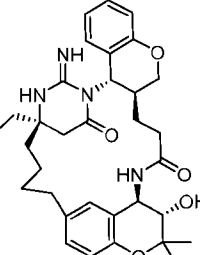
14		489.3	26-ethyl-28-imino-17-oxa-1,9,27-triazapentacyclo[24.2.2.13,7.010,19.011,16]hentriaconta-3,5,7(31),11(16),12,14-hexaene-8,29-dione
15		489.3	26-ethyl-28-imino-17-oxa-1,9,27-triazapentacyclo[24.2.2.13,7.010,19.011,16]hentriaconta-3,5,7(31),11(16),12,14-hexaene-8,29-dione
16		489.3	26-ethyl-28-imino-17-oxa-1,9,27-triazapentacyclo[24.2.2.13,7.010,19.011,16]hentriaconta-3,5,7(31),11(16),12,14-hexaene-8,29-dione
17		497.2	(1S,4S,6S,7R)-11-ethyl-9-imino-7-(2-methoxyethyl)-20,20-dimethyl-19-oxa-2,8,10-triazapentacyclo[13.6.2.28,11.04,6.018,22]pentacosa-15(23),16,18(22)-triene-3,25-dione

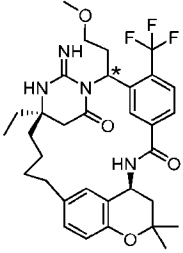
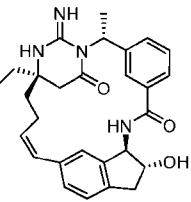
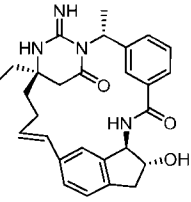
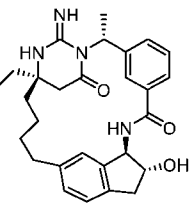
18		497.3	(1S,14R)-14-ethyl-12-imino-24,24-dimethyl-7,23-dioxo-2,11,13-triazapentacyclo[17.6.2.211,14.05,10.022,26]nonacos-19(27),20,22(26)-triene-3,29-dione
19		497.3	(1S,14R)-14-ethyl-12-imino-24,24-dimethyl-7,23-dioxo-2,11,13-triazapentacyclo[17.6.2.211,14.05,10.022,26]nonacos-19(27),20,22(26)-triene-3,29-dione
20		497.3	(1S,14R)-14-ethyl-12-imino-24,24-dimethyl-7,23-dioxo-2,11,13-triazapentacyclo[17.6.2.211,14.05,10.022,26]nonacos-19(27),20,22(26)-triene-3,29-dione
21		497.3	(19S)-5-ethyl-7-imino-21,21-dimethyl-12,22-dioxo-6,8,18-triazapentacyclo[17.6.2.25,8.09,14.023,27]nonacos-1(26),23(27),24-triene-17,28-dione

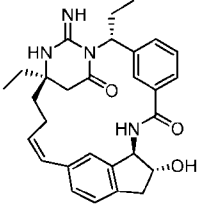
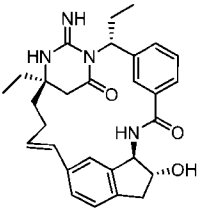
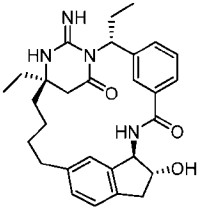
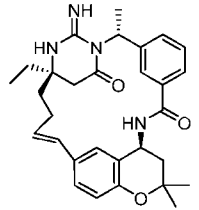
22		504.4	(1S,9R,13R)-13-ethyl-11-imino-9,23,23-trimethyl-22-oxa-2,10,12,29-tetrazapentacyclo[16.6.2.210,13.14,8.021,25]nonacos-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione
23		504.2	(1S,9R,13R)-13-ethyl-11-imino-9,23,23-trimethyl-22-oxa-2,5,10,12-tetrazapentacyclo[16.6.2.210,13.14,8.021,25]nonacos-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione
24		511.3	(6R,20S)-6-ethyl-8-imino-22,22-dimethyl-13,23-dioxo-7,9,19-triazapentacyclo[18.6.2.26,9.010,15.024,28]triacont-1(27),24(28),25-triene-18,29-dione
25		511.3	(6R,20S)-6-ethyl-8-imino-22,22-dimethyl-13,23-dioxo-7,9,19-triazapentacyclo[18.6.2.26,9.010,15.024,28]triacont-1(27),24(28),25-triene-18,29-dione

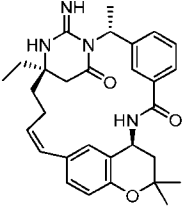
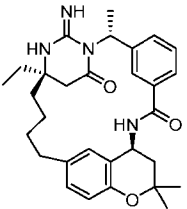
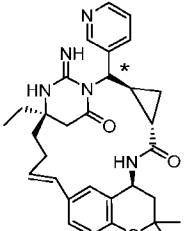
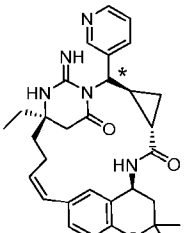
26		519.2	(1R,9R,23R)-13-ethyl-23-hydroxy-11-imino-9-(2-methoxyethyl)-2,10,12-triazapentacyclo[16.5.2.2]octacos-4,6,8(28),18(25),19,21(24)-hexaene-3,27-dione
27		525.3	(1S,11R)-11-ethyl-9-imino-7-(2-methoxyethyl)-21,21-dimethyl-20-oxa-2,8,10-triazapentacyclo[14.6.2.28,11.14,6.0]heptacos-16(24),17,19(23)-triene-3,26-dione
28		525.3	(1S,11R)-11-ethyl-9-imino-7-(2-methoxyethyl)-21,21-dimethyl-20-oxa-2,8,10-triazapentacyclo[14.6.2.28,11.14,6.0]heptacos-16(24),17,19(23)-triene-3,26-dione
29		525.3	(1S,11R)-11-ethyl-9-imino-7-(2-methoxyethyl)-21,21-dimethyl-20-oxa-2,8,10-triazapentacyclo[14.6.2.28,11.14,6.0]heptacos-16(24),17,19(23)-triene-3,26-dione

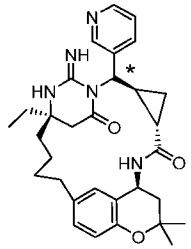
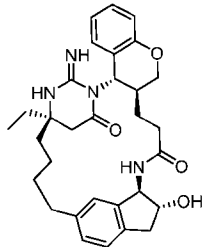
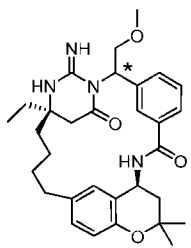
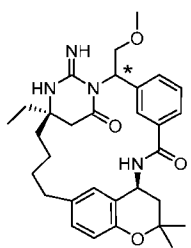
30		525.3	(1S,11R)-11-ethyl-9-imino-7-(2-methoxyethyl)-21,21-dimethyl-20-oxa-2,8,10-triazapentacyclo[14.6.2.28,11.14,6.0]heptacosane-16(24),17,19(23)-triene-3,26-dione
31		531.3	(6R,10S,19S,24R,25R)-6-ethyl-25-hydroxy-8-imino-17-oxa-7,9,23-triazahexacyclo[22.5.2.26,9.010,19.011,16.0]trtriacontane-1(30),11(16),12,14,27(31),28-hexaene-22,32-dione
32		537.3	(1S,11R)-11-ethyl-9-imino-7-(2-methoxyethyl)-21,21-dimethyl-20-oxa-2,8,10-triazahexacyclo[14.6.2.28,11.14,6.14,6.0]octacosane-16(24),17,19(23)-triene-3,26-dione
33		549.3	(1R,9R,23S)-13-ethyl-23-hydroxy-11-imino-9-(2-methoxyethyl)-22,22-dimethyl-21-oxa-2,10,12-triazapentacyclo[15.6.2.2]octacosane-4,6,8(28),17(25),18,20(24)-hexaene-3,27-dione

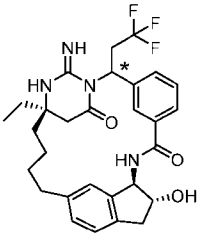
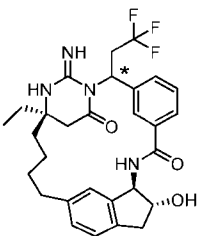
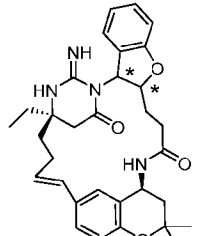
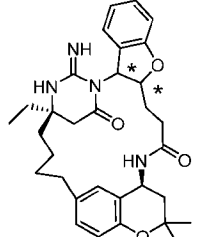
34		551.3	(1S,4S,6S,7R,11R,21R)-11-ethyl-9-imino-7-(2-methoxyethyl)-21-(trifluoromethyl)-20-oxa-2,8,10-triazapentacyclo[14.6.2.28,11.04,6.019,23]hexacosahexaene-16(24),17,19(23)-triene-3,26-dione
35		557.3	(2E,6R,24S)-6-ethyl-8-imino-26,26-dimethyl-17,27-dioxo-7,9,23-triazahexacyclo[22.6.2.26,9.010,19.011,16.028,32]tetratriacontahexaene-1(31),2,11(16),12,14,28(32),29-heptaene-22,33-dione
36		575.3	(6R,10S,19S,24R,25S)-6-ethyl-25-hydroxy-8-imino-26,26-dimethyl-17,27-dioxo-7,9,23-triazahexacyclo[22.6.2.26,9.010,19.011,16.028,32]tetratriacontahexaene-1(31),11(16),12,14,28(32),29-hexaene-22,33-dione

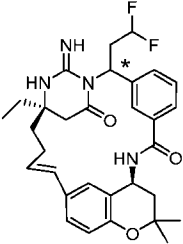
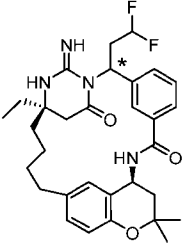
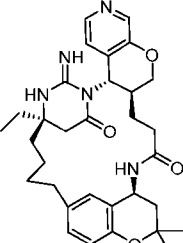
37		615.3	(1S,13R)-13-ethyl-11-imino-9-(2-methoxyethyl)-23,23-dimethyl-7-(trifluoromethyl)-22-oxa-2,10,12-triazapentacyclo[16.6.2.2]10,13,14,8.021,25]nonacos-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione
38		473.2	(1R,9R,13R,16Z,23R)-13-ethyl-23-hydroxy-11-imino-9-methyl-2,10,12-triazapentacyclo[16.5.2.2]10,13,14,8.021,24]octacos-4,6,8(28),16,18(25),19,21(24)-heptaene-3,27-dione
39		473.2	(1R,9R,13R,16E,23R)-13-ethyl-23-hydroxy-11-imino-9-methyl-2,10,12-triazapentacyclo[16.5.2.2]10,13,14,8.021,24]octacos-4,6,8(28),16,18(25),19,21(24)-heptaene-3,27-dione
40		475.2	(1R,9R,13R,23R)-13-ethyl-23-hydroxy-11-imino-9-methyl-2,10,12-triazapentacyclo[16.5.2.2]10,13,14,8.021,24]octacos-4,6,8(28),18(25),19,21(24)-hexaene-3,27-dione

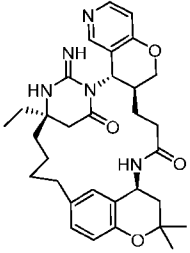
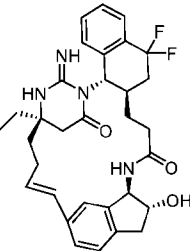
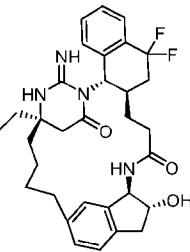
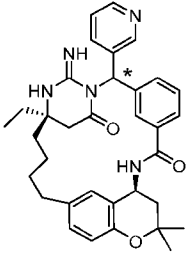
41		487.2	(1R,9R,13R,16Z,23R)-9,13-diethyl-23-hydroxy-11-imino-2,10,12-triazapentacyclo[16.5.2.2]octacosane-14,8,0,21,24]octacosane-4,6,8(28),16,18(25),19,21(24)-heptaene-3,27-dione
42		487.2	(1R,9R,13R,16E,23R)-9,13-diethyl-23-hydroxy-11-imino-2,10,12-triazapentacyclo[16.5.2.2]octacosane-14,8,0,21,24]octacosane-4,6,8(28),16,18(25),19,21(24)-heptaene-3,27-dione
43		489.2	(1R,9R,13R,23R)-9,13-diethyl-23-hydroxy-11-imino-2,10,12-triazapentacyclo[16.5.2.2]octacosane-14,8,0,21,24]octacosane-4,6,8(28),18(25),19,21(24)-hexaene-3,27-dione
44		501.3	(1S,9R,13R,16E)-13-ethyl-11-imino-9,23,23-trimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2]nonacosane-14,8,0,21,25]nonacosane-4,6,8(29),16,18(26),19,21(25)-heptaene-3,28-dione

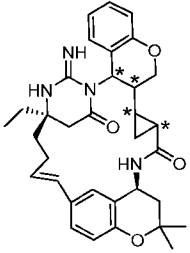
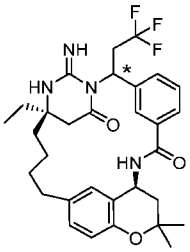
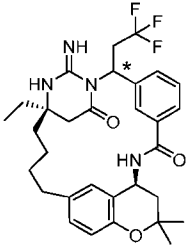
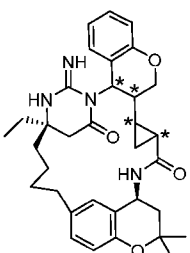
45		501.3	(1S,9R,13R,16Z)-13-ethyl-11-imino-9,23,23-trimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.210,13.14,8.021,25]nonacos-4,6,8(29),16,18(26),19,21(25)-heptaene-3,28-dione
46		503.3	(1S,9R,13R)-13-ethyl-11-imino-9,23,23-trimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.210,13.14,8.021,25]nonacos-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione
47		528.3	(1S,4S,6S,11R,14E)-11-ethyl-9-imino-21,21-dimethyl-7-(3-pyridyl)-20-oxa-2,8,10-triazapentacyclo[14.6.2.28,11.04.6.019,23]hexacos-14,16(24),17,19(23)-tetraene-3,26-dione
48		528.3	(1S,4S,6S,11R,14Z)-11-ethyl-9-imino-21,21-dimethyl-7-(3-pyridyl)-20-oxa-2,8,10-triazapentacyclo[14.6.2.28,11.04.6.019,23]hexacos-14,16(24),17,19(23)-tetraene-3,26-dione

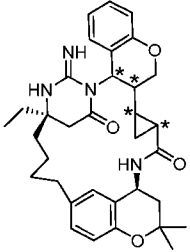
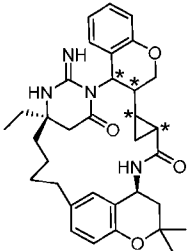
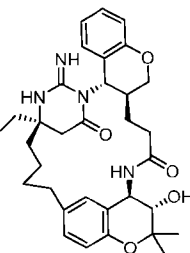
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50		531.3	(6R,10S,19S,24R,25R)-6-ethyl-25-hydroxy-8-imino-17-oxa-7,9,23-triazahexacyclo[22.5.2.26,9.010,19.011,16.027,31]tritriaconta-1(30),11(16),12,14,27(31),28-hexaene-22,32-dione
51		533.3	(1S,13R)-13-ethyl-11-imino-9-(methoxymethyl)-23,23-dimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.210,13.14,8.021,25]nonacos-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione
52		533.3	(1S,13R)-13-ethyl-11-imino-9-(methoxymethyl)-23,23-dimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.210,13.14,8.021,25]nonacos-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione

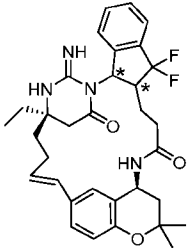
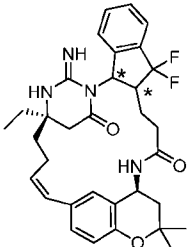
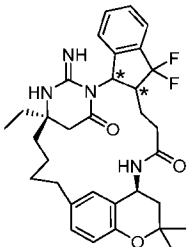
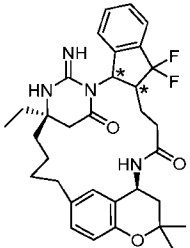
53		543.2	(1R,13R,23R)-13-ethyl-23-hydroxy-11-imino-9-(2,2,2-trifluoroethyl)-2,10,12-triazapentacyclo[16.5.2.210,13.14,8.021,24]octacos-4,6,8(28),18(25),19,21(24)-hexaene-3,27-dione
54		543.2	(1R,13R,23R)-13-ethyl-23-hydroxy-11-imino-9-(2,2,2-trifluoroethyl)-2,10,12-triazapentacyclo[16.5.2.210,13.14,8.021,24]octacos-4,6,8(28),18(25),19,21(24)-hexaene-3,27-dione
55		543.3	(1S,18R,21E)-18-ethyl-16-imino-28,28-dimethyl-7,27-dioxa-2,15,17-triazahexacyclo[21.6.2.215,18.06,14.08,13.026,30]tritriaconta-8(13),9,11,21,23(31),24,26(30)-heptaene-3,33-dione
56		545.3	(1S,18R)-18-ethyl-16-imino-28,28-dimethyl-7,27-dioxa-2,15,17-triazahexacyclo[21.6.2.215,18.06,14.08,13.026,30]tritriaconta-8(13),9,11,23(31),24,26(30)-hexaene-3,33-dione

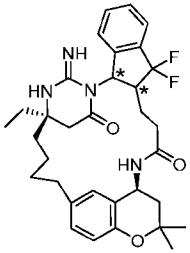
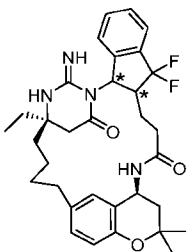
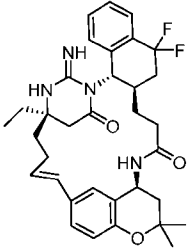
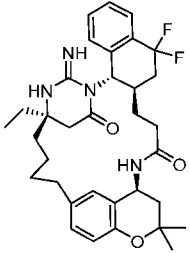
57		551.3	(1S,13R,16E)-9-(2,2-difluoroethyl)-13-ethyl-11-imino-23,23-dimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.2]10,13.14,8.021,25]nonacosane-4,6,8(29),16,18(26),19,21(25)-heptaene-3,28-dione
58		553.3	(1S,13R)-9-(2,2-difluoroethyl)-13-ethyl-11-imino-23,23-dimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.2]10,13.14,8.021,25]nonacosane-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione
59		560.1	(6R,10S,19S,24S)-6-ethyl-8-imino-26,26-dimethyl-17,27-dioxa-7,9,14,23-tetrazahexacyclo[22.6.2.26.9.0]10,19.011,16.028,32]tetratriaconta-1(31),11(16),12,14,28(32),29-hexaene-22,33-dione

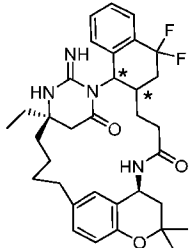
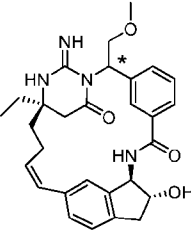
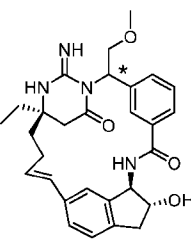
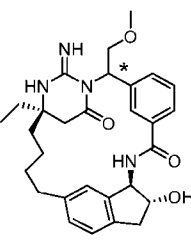
60		560.3	(6R,10S,19S,24S)-6-ethyl-8-imino-26,26-dimethyl-17,27-dioxa-7,9,13,23-tetrahexacyclo[22.6.2.26,9.010,19.011,16.028,32]tetratriacontan-1(31),11(16),12,14,28(32),29-hexaene-22,33-dione
61		563.3	(2E,6R,10S,19R,24R,25R)-6-ethyl-17,17-difluoro-25-hydroxy-8-imino-7,9,23-triazahexacyclo[22.5.2.26,9.010,19.011,16.027,31]tritiacontan-1(30),2,11(16),12,14,27(31),28-heptaene-22,32-dione
62		565.3	(6R,10S,19R,24R,25R)-6-ethyl-17,17-difluoro-25-hydroxy-8-imino-7,9,23-triazahexacyclo[22.5.2.26,9.010,19.011,16.027,31]tritiacontan-1(30),11(16),12,14,27(31),28-hexaene-22,32-dione
63		566.3	(1S,13R)-13-ethyl-11-imino-23,23-dimethyl-9-(3-pyridyl)-22-oxa-2,10,12-triazapentacyclo[16.6.2.210,13.14,8.021,25]nonacosan-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione

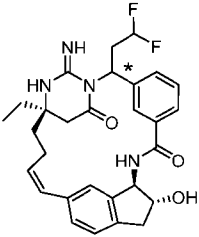
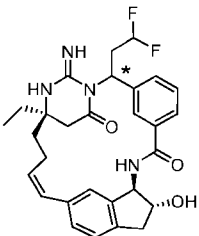
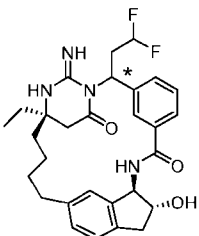
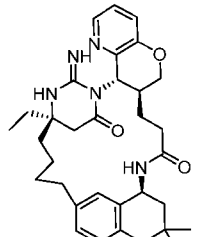
64		569.3	(1S,20R,23E)-20-ethyl-18-imino-30,30-dimethyl-9,29-dioxa-2,17,19-triazaheptacyclo[23.6.2.217,20.04,6.07,16.010,15.028,32]penta-triaconta-10(15),11,13,23,25(33),26,28(32)-heptaene-3,35-dione
65		571.3	(1S,13R)-13-ethyl-11-imino-23,23-dimethyl-9-(2,2,2-trifluoroethyl)-22-oxa-2,10,12-triazapentacyclo[16.6.2.210,13.14,8.021,25]nonacosa-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione
66		571.2	(1S,13R)-13-ethyl-11-imino-23,23-dimethyl-9-(2,2,2-trifluoroethyl)-22-oxa-2,10,12-triazapentacyclo[16.6.2.210,13.14,8.021,25]nonacosa-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione
67		571.3	(1S,20R)-20-ethyl-18-imino-30,30-dimethyl-9,29-dioxa-2,17,19-triazaheptacyclo[23.6.2.217,20.04,6.07,16.010,15.028,32]penta-triaconta-10(15),11,13,25(33),26,28(32)-hexaene-3,35-dione

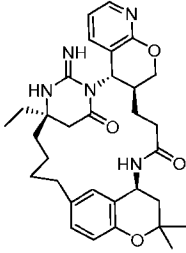
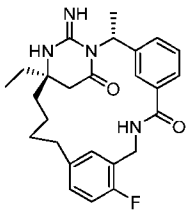
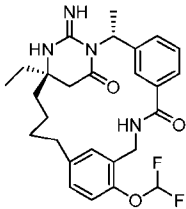
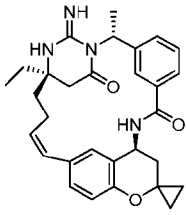
68		571.3	(1S,20R)-20-ethyl-18-imino-30,30-dimethyl-9,29-dioxo-2,17,19-triazaheptacyclo[23.6.2.217,20.04,6.07,16.010,15.028,32]penta-10(15),11,13,25(33),26,28(32)-hexaene-3,35-dione
69		571.3	(1S,20R)-20-ethyl-18-imino-30,30-dimethyl-9,29-dioxo-2,17,19-triazaheptacyclo[23.6.2.217,20.04,6.07,16.010,15.028,32]penta-10(15),11,13,25(33),26,28(32)-hexaene-3,35-dione
70		575.3	(6R,10S,19S,24R,25S)-6-ethyl-25-hydroxy-8-imino-26,26-dimethyl-17,27-dioxo-7,9,23-triazaheptacyclo[22.6.2.26,9.010,19.011,16.028,32]tetra-1(31),11(16),12,14,28(32),29-hexaene-22,33-dione

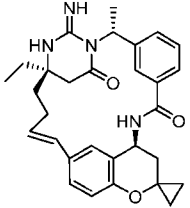
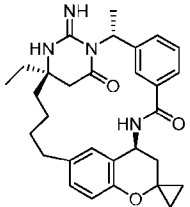
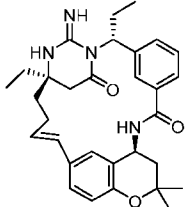
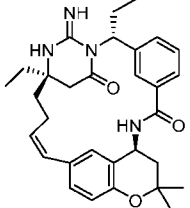
71		577.3	(1S,18R,21E)-18-ethyl-7,7-difluoro-16-imino-28,28-dimethyl-27-oxa-2,15,17-triazahexacyclo[21.6.2.215,18.06,14.08,13.026,30]tritriaconta-8(13),9,11,21,23(31),24,26(30)-heptaene-3,33-dione
72		577.3	(1S,18R,21Z)-18-ethyl-7,7-difluoro-16-imino-28,28-dimethyl-27-oxa-2,15,17-triazahexacyclo[21.6.2.215,18.06,14.08,13.026,30]tritriaconta-8(13),9,11,21,23(31),24,26(30)-heptaene-3,33-dione
73		579.3	(1S,18R)-18-ethyl-7,7-difluoro-16-imino-28,28-dimethyl-27-oxa-2,15,17-triazahexacyclo[21.6.2.215,18.06,14.08,13.026,30]tritriaconta-8(13),9,11,23(31),24,26(30)-hexaene-3,33-dione
74		579.3	(1S,18R)-18-ethyl-7,7-difluoro-16-imino-28,28-dimethyl-27-oxa-2,15,17-triazahexacyclo[21.6.2.215,18.06,14.08,13.026,30]tritriaconta-8(13),9,11,23(31),24,26(30)-hexaene-3,33-dione

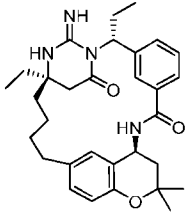
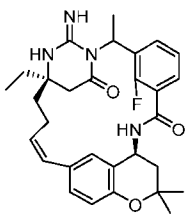
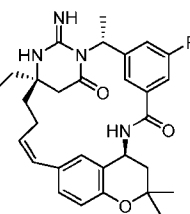
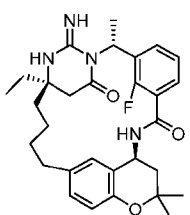
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76		579.3	(1S,18R)-18-ethyl-7,7-difluoro-16-imino-28,28-dimethyl-27-oxa-2,15,17-triazahexacyclo[21.6.2.215,18.06,14.08,13.026,30]tritriacontan-8(13),9,11,23(31),24,26(30)-hexaene-3,33-dione
77		591.3	(2E,6R,10S,19R,24S)-6-ethyl-17,17-difluoro-8-imino-26,26-dimethyl-27-oxa-7,9,23-triazahexacyclo[22.6.2.26,9.010,19.011,16.028,32]tetracontan-1(31),2,11(16),12,14,28(32),29-heptaene-22,33-dione
78		593.3	(6R,10S,19R,24S)-6-ethyl-17,17-difluoro-8-imino-26,26-dimethyl-27-oxa-7,9,23-triazahexacyclo[22.6.2.26,9.010,19.011,16.028,32]tetracontan-1(31),11(16),12,14,28(32),29-hexaene-22,33-dione

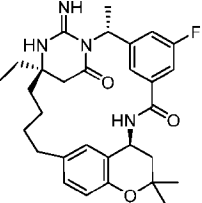
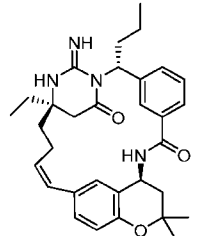
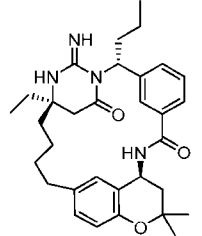
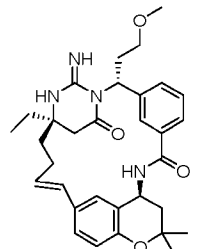
79		593.3	(6R,24S)-6-ethyl-17,17-difluoro-8-imino-26,26-dimethyl-27-oxa-7,9,23-triazahexacyclo[22.6.2.26,9.010,19.011,16.028,32]tetratriacontata-1(31),11(16),12,14,28(32),29-hexaene-22,33-dione
80		503.2	(1R,13R,16Z,23R)-13-ethyl-23-hydroxy-11-imino-9-(methoxymethyl)-2,10,12-triazapentacyclo[16.5.2.210,13.14,8.021,24]octacosaa-4,6,8(28),16,18(25),19,21(24)-heptaene-3,27-dione
81		503.3	(1R,13R,16E,23R)-13-ethyl-23-hydroxy-11-imino-9-(methoxymethyl)-2,10,12-triazapentacyclo[16.5.2.210,13.14,8.021,24]octacosaa-4,6,8(28),16,18(25),19,21(24)-heptaene-3,27-dione
82		505.2	(1R,13R,23R)-13-ethyl-23-hydroxy-11-imino-9-(methoxymethyl)-2,10,12-triazapentacyclo[16.5.2.210,13.14,8.021,24]octacosaa-4,6,8(28),18(25),19,21(24)-hexaene-3,27-dione

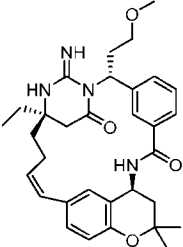
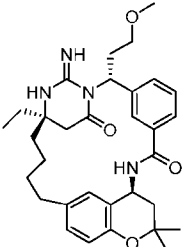
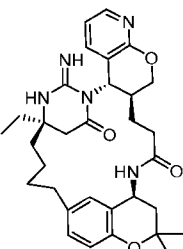
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84		523.2	(1R,13R,16Z,23R)-9-(2,2-difluoroethyl)-13-ethyl-23-hydroxy-11-imino-2,10,12-triazapentacyclo[16.5.2.210,13.14,8.021,24]octacos-4,6,8(28),16,18(25),19,21(24)-heptaene-3,27-dione
85		525.2	(1R,13R,23R)-9-(2,2-difluoroethyl)-13-ethyl-23-hydroxy-11-imino-2,10,12-triazapentacyclo[16.5.2.210,13.14,8.021,24]octacos-4,6,8(28),18(25),19,21(24)-hexaene-3,27-dione
86		560.3	(6R,10S,19S,24S)-6-ethyl-8-imino-26,26-dimethyl-17,27-dioxa-7,9,12,23-tetrahexacyclo[22.6.2.26,9.010,19.011,16.028,32]tetratriaconta-1(31),11(16),12,14,28(32),29-hexaene-22,33-dione

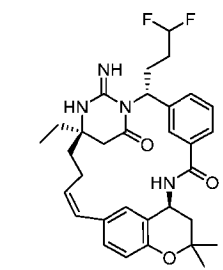
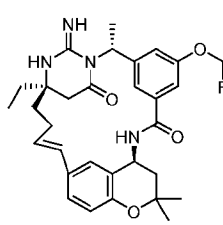
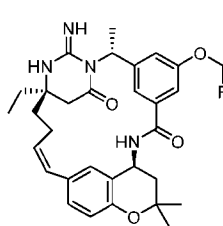
87		560.3	(6R,10S,19S,24S)-6-ethyl-8-imino-26,26-dimethyl-17,27-dioxa-7,9,15,23-tetrazahexacyclo[22.6.2.26,9.010,19.011,16.028,32]tetratriaconta-1(31),11(16),12,14,28(32),29-hexaene-22,33-dione
88		451.2	(2R,20R)-20-ethyl-12-fluoro-22-imino-2-methyl-1,9,21-triazatetracyclo[18.2.2.13,7.111,15]hexacosatriene-3(26),4,6,11,13,15(25)-hexaene-8,23-dione
89		499.2	(2R,20R)-12-(difluoromethoxy)-20-ethyl-22-imino-2-methyl-1,9,21-triazatetracyclo[18.2.2.13,7.111,15]hexacosatriene-3(26),4,6,11,13,15(25)-hexaene-8,23-dione
90		499.3	(1S,9R,13R,16Z)-13-ethyl-11-imino-9-methyl-spiro[22-oxa-2,10,12-triazapentacyclo[16.6.2.210,13,14,8.021,25]nonacosatriene-4,6,8(29),16,18(26),19,21(25)-heptaene-23,1'-cyclopropane]-3,28-dione

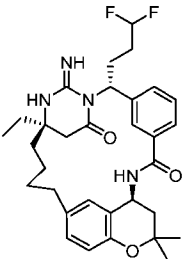
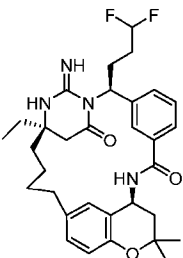
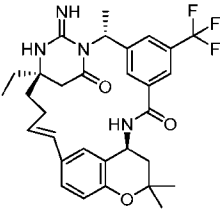
91		499.3	(1S,9R,13R,16E)-13-ethyl-11-imino-9-methyl-spiro[22-oxa-2,10,12-triazapentacyclo[16.6.2.2]nonacos-4,6,8(29),16,18(26),19,21(25)-heptaene-23,1'-cyclopropane]-3,28-dione
92		501.2	(1S,9R,13R)-13-ethyl-11-imino-9-methyl-spiro[22-oxa-2,10,12-triazapentacyclo[16.6.2.2]nonacos-4,6,8(29),18(26),19,21(25)-hexaene-23,1'-cyclopropane]-3,28-dione
93		515.3	(1S,9R,13R,16E)-9,13-diethyl-11-imino-23,23-dimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.2]nonacos-4,6,8(29),16,18(26),19,21(25)-heptaene-3,28-dione
94		515.3	(1S,9R,13R,16Z)-9,13-diethyl-11-imino-23,23-dimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.2]nonacos-4,6,8(29),16,18(26),19,21(25)-heptaene-3,28-dione

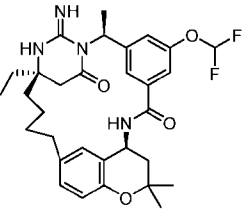
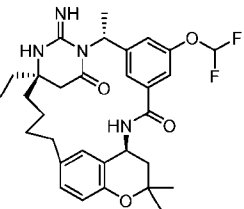
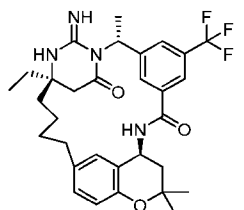
95		517.3	(1S,9R,13R)-9,13-diethyl-11-imino-23,23-dimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.2]nonacos-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione
96		519.3	(1S,13R,16Z)-13-ethyl-29-fluoro-11-imino-9,23,23-trimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.2]nonacos-4,6,8(29),16,18(26),19,21(25)-heptaene-3,28-dione
97		519.3	(1S,9R,13R,16Z)-13-ethyl-6-fluoro-11-imino-9,23,23-trimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.2]nonacos-4,6,8(29),16,18(26),19,21(25)-heptaene-3,28-dione
98		521.3	(1S,9R,13R)-13-ethyl-29-fluoro-11-imino-9,23,23-trimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.2]nonacos-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione

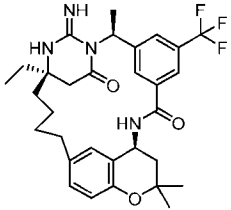
99		521.3	(1S,9R,13R)-13-ethyl-6-fluoro-11-imino-9,23,23-trimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.210,13.14,8.021,25]nonacos-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione
100		529.3	(1S,9R,13R,16Z)-13-ethyl-11-imino-23,23-dimethyl-9-propyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.210,13.14,8.021,25]nonacos-4,6,8(29),16,18(26),19,21(25)-heptaene-3,28-dione
101		531.3	(1S,9R,13R)-13-ethyl-11-imino-23,23-dimethyl-9-propyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.210,13.14,8.021,25]nonacos-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione
102		545.3	(1S,9R,13R,16E)-13-ethyl-11-imino-9-(2-methoxyethyl)-23,23-dimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.210,13.14,8.021,25]nonacos-4,6,8(29),16,18(26),19,21(25)-heptaene-3,28-dione

103		545.3	(1S,9R,13R,16Z)-13-ethyl-11-imino-9-(2-methoxyethyl)-23,23-dimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.210,13.14,8.021,25]nonacos-4,6,8(29),16,18(26),19,21(25)-heptaene-3,28-dione
104		547.3	(1S,9R,13R)-13-ethyl-11-imino-9-(2-methoxyethyl)-23,23-dimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.210,13.14,8.021,25]nonacos-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione
105		560.3	(6R,10S,19S,24S)-6-ethyl-8-imino-26,26-dimethyl-17,27-dioxa-7,9,15,23-tetrazahexacyclo[22.6.2.26,9.010,19.011,16.028,32]tetratriaconta-1(31),11(16),12,14,28(32),29-hexaene-22,33-dione

106		565.3	(1S,9R,13R,16Z)-9-(3,3-difluoropropyl)-13-ethyl-11-imino-23,23-dimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.2]10,13,14,8.0.21,25]nonacos-4,6,8(29),16,18(26),19,21(25)-heptaene-3,28-dione
107		567.2	(1S,9R,13R,16E)-6-(difluoromethoxy)-13-ethyl-11-imino-9,23,23-trimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.2]10,13,14,8.0.21,25]nonacos-4,6,8(29),16,18(26),19,21(25)-heptaene-3,28-dione
108		567.3	(1S,9R,13R,16Z)-6-(difluoromethoxy)-13-ethyl-11-imino-9,23,23-trimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.2]10,13,14,8.0.21,25]nonacos-4,6,8(29),16,18(26),19,21(25)-heptaene-3,28-dione

109		567.3	(1S,9R,13R)-9-(3,3-difluoropropyl)-13-ethyl-11-imino-23,23-dimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.2]10,13.14,8.021,25]nonacos-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione
110		567.3	(1S,9S,13R)-9-(3,3-difluoropropyl)-13-ethyl-11-imino-23,23-dimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.2]10,13.14,8.021,25]nonacos-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione
111		569.2	(1S,9R,13R,16E)-13-ethyl-11-imino-9,23,23-trimethyl-6-(trifluoromethyl)-22-oxa-2,10,12-triazapentacyclo[16.6.2.2]10,13.14,8.021,25]nonacos-4,6,8(29),16,18(26),19,21(25)-heptaene-3,28-dione

112		569.3	<p>(1S,9S,13R)-6-(difluoromethoxy)-13-ethyl-11-imino-9,23,23-trimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.2]10,13.14,8.021,25]nonacosane-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione</p>
113		569.2	<p>(1S,9R,13R)-6-(difluoromethoxy)-13-ethyl-11-imino-9,23,23-trimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.2]10,13.14,8.021,25]nonacosane-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione</p>
114		571.3	<p>(1S,9R,13R)-13-ethyl-11-imino-9,23,23-trimethyl-6-(trifluoromethyl)-22-oxa-2,10,12-triazapentacyclo[16.6.2.2]10,13.14,8.021,25]nonacosane-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione</p>

115		571.3	(1S,9S,13R)-13-ethyl-11-imino-9,23,23-trimethyl-6-(trifluoromethyl)-22-oxa-2,10,12-triazapentacyclo[16.6.2.210,13.14,8.021,25]nonacosa-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione
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[0170] Additional compounds of the disclosure are selected from:

(4aS,8aS,14bS,15R,18R)-18-ethyl-28-imino-3,3-dimethyl-3,4,4a,5,7,8,8a,14b,17,18,19,20,21,22-tetradecahydro-6H,9H,16H-18,15-(epiminomethano)-1,23-ethenochromeno[4,3-b]pyrano[4,3-h][1,7]diazacyclooctadecine-6,16-dione,

(1S,13R)-13-ethyl-11-imino-23,23-dimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.210,13.14,8.021,25]nonacosa-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione,

(1S,9R,13R)-13-ethyl-11-imino-9,23,23-trimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.210,13.14,8.021,25]nonacosa-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione,

(1S,13R)-13-ethyl-11-imino-9-(methoxymethyl)-23,23-dimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.210,13.14,8.021,25]nonacosa-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione,

(1S,9R,13R)-13-ethyl-11-imino-9-methyl-spiro[22-oxa-2,10,12-triazapentacyclo[16.6.2.210,13.14,8.021,25]nonacosa-4,6,8(29),18(26),19,21(25)-hexaene-23,1'-cyclopropane]-3,28-dione,

(1S,9R,13R)-9,13-diethyl-11-imino-23,23-dimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.210,13.14,8.021,25]nonacosa-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione,

(1S,9R,13R)-13-ethyl-29-fluoro-11-imino-9,23,23-trimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.210,13.14,8.021,25]nonacosa-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione,

(1S,9R,13R)-13-ethyl-6-fluoro-11-imino-9,23,23-trimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.210,13.14,8.021,25]nonacosa-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione,

(1S,9R,13R)-13-ethyl-11-imino-9-(2-methoxyethyl)-23,23-dimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.210,13.14,8.021,25]nonacosa-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione, and

(1S,9R,13R)-6-(difluoromethoxy)-13-ethyl-11-imino-9,23,23-trimethyl-22-oxa-2,10,12-triazapentacyclo[16.6.2.210,13.14,8.021,25]nonacosa-4,6,8(29),18(26),19,21(25)-hexaene-3,28-dione, or a pharmaceutically acceptable salt thereof.

Assessing antiparasite potency in a parasite LDH growth assay (Parasite Assay)

[0171] The parasite stock was maintained at 4% haematocrit in RPMI-Hepes media buffered with sodium bicarbonate and supplemented with 5% heat inactivated human serum and 0.5% albumax.

Approximately 42 hours prior to the potency assay being set up, parasites were synchronized with 5% sorbitol to select for ring stage parasites. On the day of assay set up, a blood smear of the parasite culture was Giemsa stained and counted. The parasitemia was adjusted to 0.7% rings and the haematocrit was diluted to 2% in RPMI-Hepes media buffered with sodium bicarbonate and supplemented with 5% heat inactivated human serum and 0.5% albumax. 30µl of diluted parasites were then added into 10µl of media + compound in pre-prepared Greiner TC assay plates. Parasite assay plates were placed in gassed humidified boxes in single layer and allowed to incubate at 37°C for 72 hours. After 72 hours growth, assay plates were sealed with parafilm and frozen flat, in single file at -80°C overnight. On the following day, assay plates were allowed to thaw at room temperature for 4 hours and an LDH assay is performed to measure parasite growth.

Assay EC₅₀ results are shown in Table 2.

Table 2

Example	EC₅₀ (nM)
1	21.9
2	0.3
3	0.3
4	0.9
5	0.4
6	12.0
7	18.4
8	0.8
9	12.5
10	4.1
11	7.4

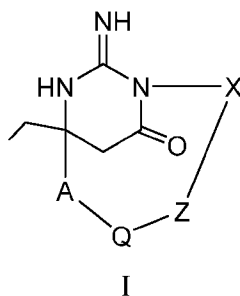
12	1.8
13	0.4
14	27.6
15	35.5
16	70.3
17	0.4
18	17.4
19	0.7
20	7.4
21	49.4
22	14.0
23	0.7
24	7.4
25	199.7
26	5.6
27	1.3
28	20.5
29	0.4
30	41.9
31	4.2
32	0.4
33	0.4
34	0.9
35	12.0
36	0.7
37	110.0
38	0.5
39	44.0
40	1.3
41	0.7
42	24.8
43	1.0
44	14.5
45	0.5
46	0.4
47	2.0
48	6.2
49	1.7
50	4.1

51	77.9
52	0.4
53	0.4
54	11.5
55	73.3
56	0.5
57	14.0
58	0.4
59	0.8
60	1.0
61	65.4
62	1.0
63	18.0
64	51.8
65	0.4
66	92.0
67	0.3
68	51.0
69	0.6
70	0.7
71	18.5
72	2.8
73	0.9
74	27.5
75	4.6
76	1.9
77	29.2
78	0.5
79	2.0
80	1.3
81	37.3
82	1.4
83	0.6
84	13.5
85	0.7
86	0.4
87	0.6
88	7.9
89	1.8

90	0.6
91	34.5
92	0.3
93	20.5
94	0.5
95	0.3
96	0.3
97	0.4
98	0.3
99	0.4
100	0.7
101	1.1
102	27.5
103	0.6
104	0.2
105	0.6
106	0.7
107	23.5
108	0.6
109	0.6
110	62.2
111	35.0
112	4.3
113	0.5
114	0.7
115	37.0

WHAT IS CLAIMED IS:

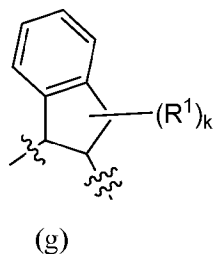
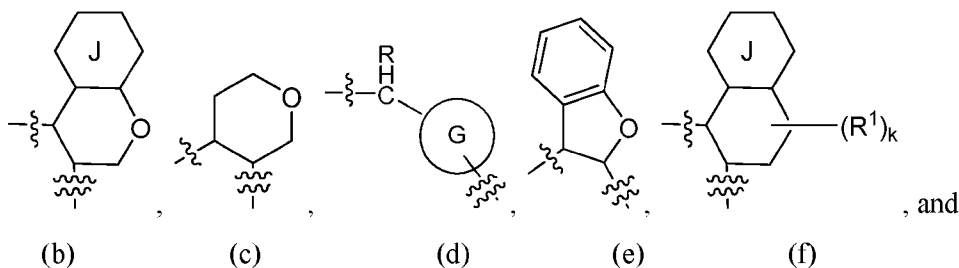
1. A compound having the structural Formula I:



wherein A is a straight or branched, saturated or unsaturated (C₃-C₁₀)alkylene, comprising at least one -CH₂- group, wherein one or more additional -CH₂- groups in A are optionally and independently replaced with a moiety selected from the group consisting of O, S, NR, CONR, NRCO, SO₂, and SO₂NR and wherein one or more of the hydrogens along A can be replaced with a group independently selected from hydroxyl, halogen and C₁₋₃ haloalkyl;

X is selected from:

- (a) straight or branched, saturated or unsaturated (C₃-C₁₀)alkylene,



wherein the single represents point of attachment to nitrogen atom of the tetrahydropyrimidinyl ring and the double represents point of attachment to Z;

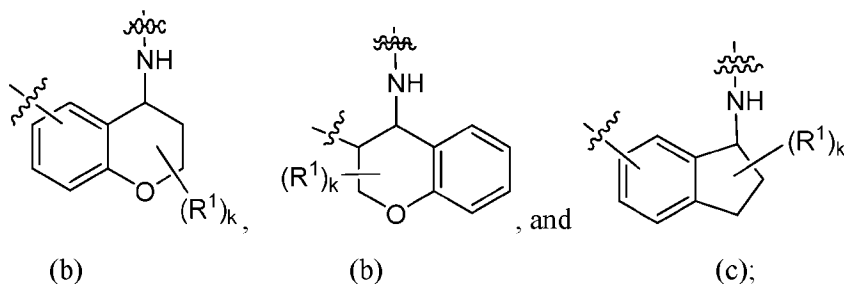
J is a six membered aryl or heteroaryl selected from phenyl, pyridyl, pyrimidinyl, pyridazinyl, and pyrazinyl, said phenyl, pyridyl, pyrimidinyl, pyridazinyl, and pyrazinyl unsubstituted or substituted with 1 to 3 groups independently selected from R;

G is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, bicyclobutanyl, bicyclopentanyl, bicyclohexyl, bicycloheptyl, bicyclononyl, pyridyl, pyrimidinyl, benzylpyrimidinyl, pyrazolyl, imidazolyl, said groups optionally substituted with 1 to 3 groups of R;

R is hydrogen, halogen, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, -OhaloC₁-C₆alkyl, C₁-C₆alkylOH, C₁-C₆alkoxy, COC₁-C₆alkyl, C₁-C₆alkylO-C₁-C₆alkyl, heteroaryl, or COOC₁-C₆alkyl;

Z is a bond, -(CH₂)_pC(O)(CH₂)_p-, -phenyl-, -C₁₋₁₀ heteroaryl-, said phenyl and heteroaryl optionally substituted with 1 to 3 groups of R;

Q is selected from:



wherein the single \sim represents point of attachment to A and the double \approx represents point of attachment to Z;

R¹ is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, oxo, COOC₁-C₆alkyl, C₁-C₆alkylCOOC₁-C₆alkyl, C₃-C₆cycloalkyl, C₁-C₆alkylC₃-C₆cycloalkyl, C₁-C₆alkyl, -C₁-C₆alkylOhaloC₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R²)(R³), N(R²)(R³) or C₁-C₆alkylN(R²)(R³);

R² is hydrogen, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, COC₁-C₆alkyl or COOC₁-C₆alkyl;

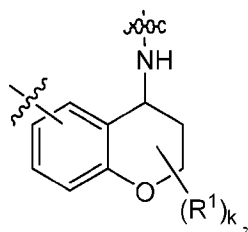
R³ is hydrogen, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, COC₁-C₆alkyl or COOC₁-C₆alkyl;

k is an integer from 0 to 4; and

p is an integer independently selected from 0 to 4;
or a pharmaceutically acceptable salt thereof.

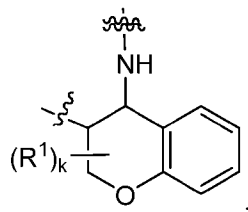
2. The compound according to Claim 1 wherein when A is a straight or branched, saturated or unsaturated (C₃-C₆)alkylene, or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 1 wherein Q is:



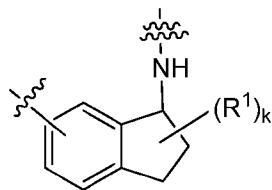
or a pharmaceutically acceptable salt thereof.

4. The compound according to claim 1 wherein Q is:



or a pharmaceutically acceptable salt thereof.

5. The compound according to claim 1 wherein Q is:



or a pharmaceutically acceptable salt thereof.

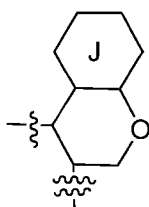
6. The compound according to any one of claims 1-5 wherein Z is a bond, or a pharmaceutically acceptable salt thereof.

7. The compound according to any one of claims 1-5 wherein Z is -C(O)(CH₂)_p-, or a pharmaceutically acceptable salt thereof.

8. The compound according to any one of claims 1-5 wherein Z is selected from -phenyl- and -C₃₋₁₀ heteroaryl, optionally substituted with 1 to 3 groups of R, or a pharmaceutically acceptable salt thereof.

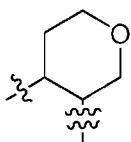
9. The compound according to any one of claims 1-8 wherein X is a straight or branched, saturated or unsaturated (C₃-C₁₀)alkylene, or a pharmaceutically acceptable salt thereof.

10. The compound according to any one of claims 1-8 wherein X is



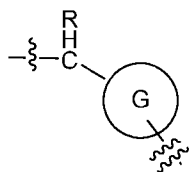
and J is a fused aromatic ring selected from phenyl, pyridyl, pyrimidinyl, pyridazinyl, and pyrazinyl, said phenyl, pyridyl, pyrimidinyl, pyridazinyl, and pyrazinyl unsubstituted or substituted with 1 to 3 groups selected from R, or a pharmaceutically acceptable salt thereof.

11. The compound according to any one of claims 1-8 wherein X is



, or a pharmaceutically acceptable salt thereof.

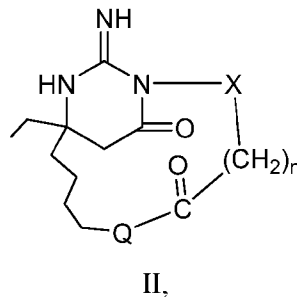
12. The compound according to any one of claims 1-8 wherein X is



wherein G is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclobutanyl, bicyclopentanyl, bicyclohexyl, bicycloheptyl, bicyclononanyl, said cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclobutanyl, bicyclopentanyl, bicyclohexyl,

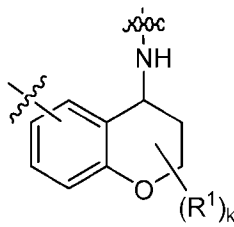
bicycloheptyl, and bicyclononyl, unsubstituted or substituted with 1 to 3 groups of R, or a pharmaceutically acceptable salt thereof.

13. The compound according to any one of claims 1-5 and 9-12 represented by structural Formula II:



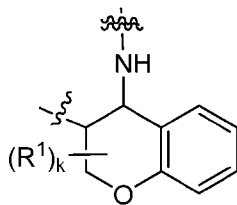
wherein n is an integer from 0 to 4,
or a pharmaceutically acceptable salt thereof.

14. The compound according to claim 13 wherein Q is:



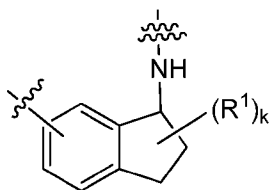
wherein R^1 is selected from hydrogen, halogen, OH, C₁-C₆alkoxy, C₁-C₆alkyl, -C₁-haloC₁-C₆alkyl, and C₁-C₆alkylOH, or a pharmaceutically acceptable salt thereof.

15. The compound according to claim 14 wherein Q is:



wherein R^1 is selected from hydrogen, halogen, OH, C₁-C₆alkoxy, C₁-C₆alkyl, -C₁-haloC₁-C₆alkyl, and C₁-C₆alkylOH, or a pharmaceutically acceptable salt thereof.

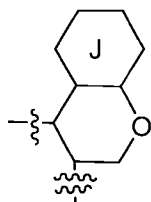
16. The compound according to claim 14 wherein Q is:



wherein R^1 is selected from hydrogen, halogen, OH, C₁-C₆alkoxy, C₁-C₆alkyl, -C₁-haloC₁-C₆alkyl, and C₁-C₆alkylOH, or a pharmaceutically acceptable salt thereof.

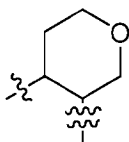
17. The compound according to claim 14 wherein X is a straight or branched, saturated or unsaturated (C₃-C₆)alkylene, or a pharmaceutically acceptable salt thereof.

18. The compound according to claim 14 wherein X is

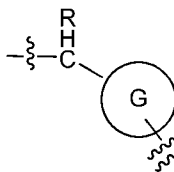


and J is selected from phenyl, pyridyl, pyrimidinyl, said phenyl, pyridyl, and pyrimidinyl, unsubstituted or substituted with 1 to 3 groups selected from R, or a pharmaceutically acceptable salt thereof.

19. The compound according to claim 14 wherein X is



20. The compound according to claim 14 wherein X is

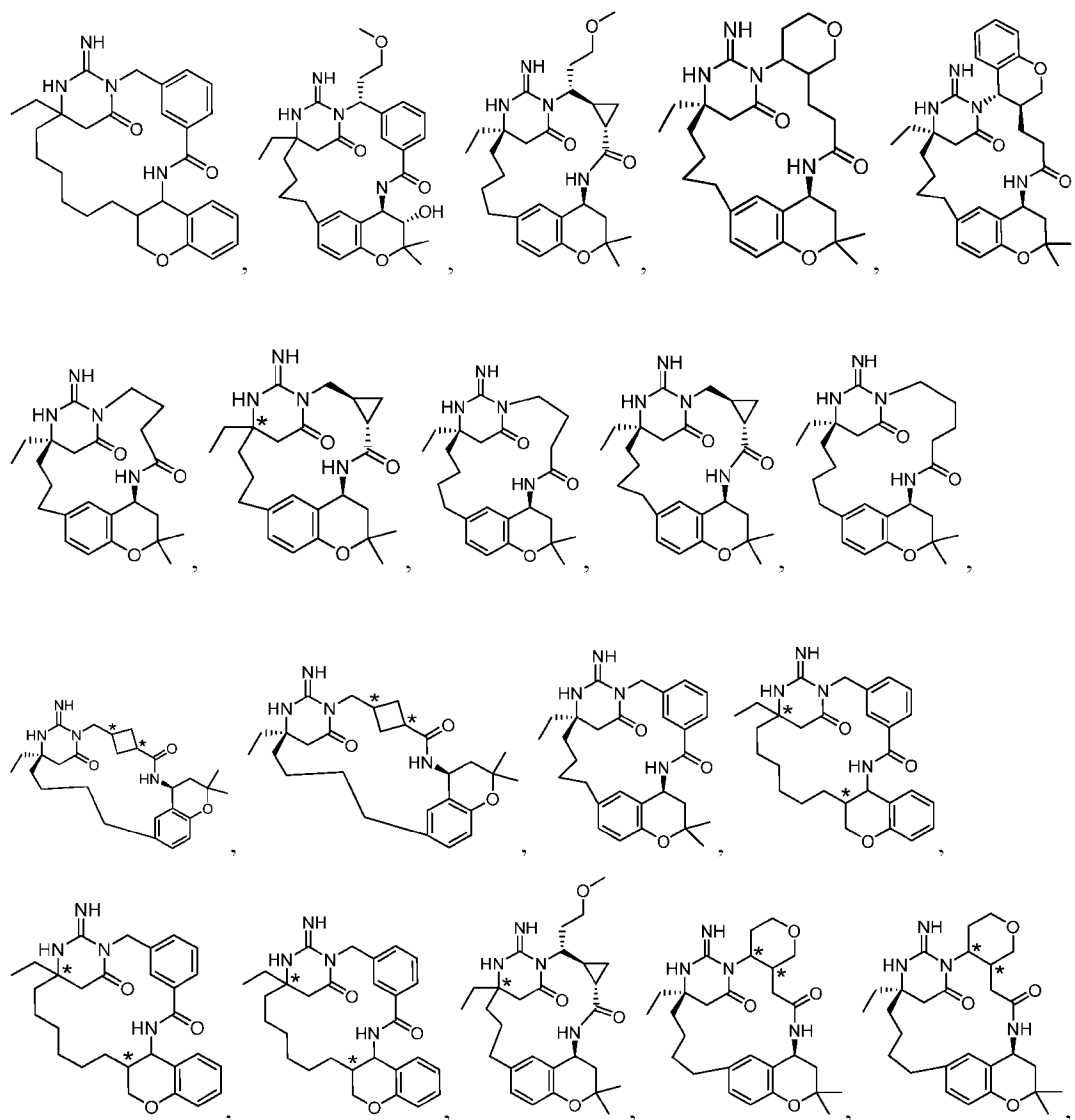


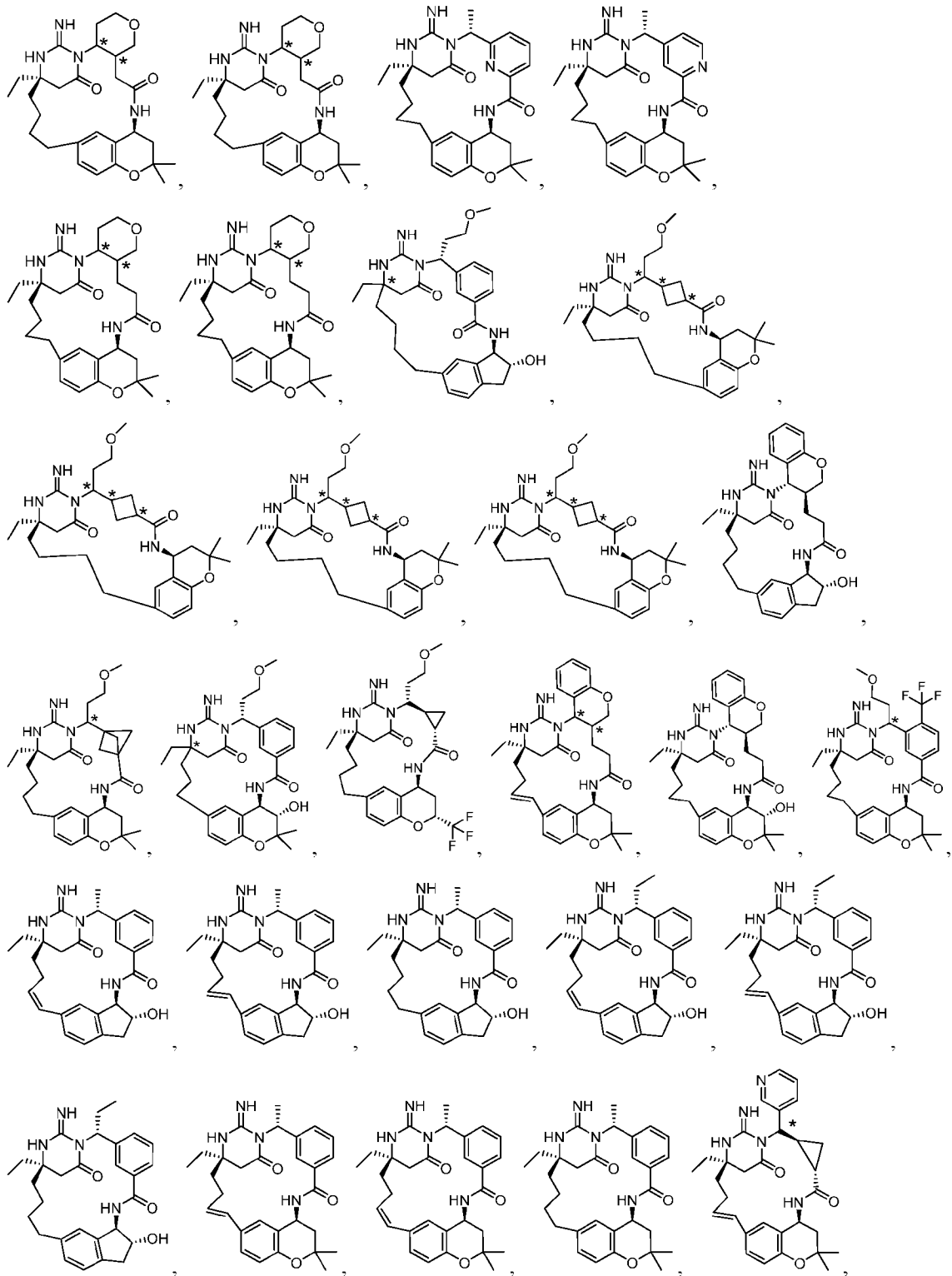
wherein G is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclobutanyl, bicyclopentyl, phenyl, pyridyl, pyrimidinyl, benzylpyrimidinyl, pyrazolyl, and imidazolyl said cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclobutanyl, bicyclopentyl,

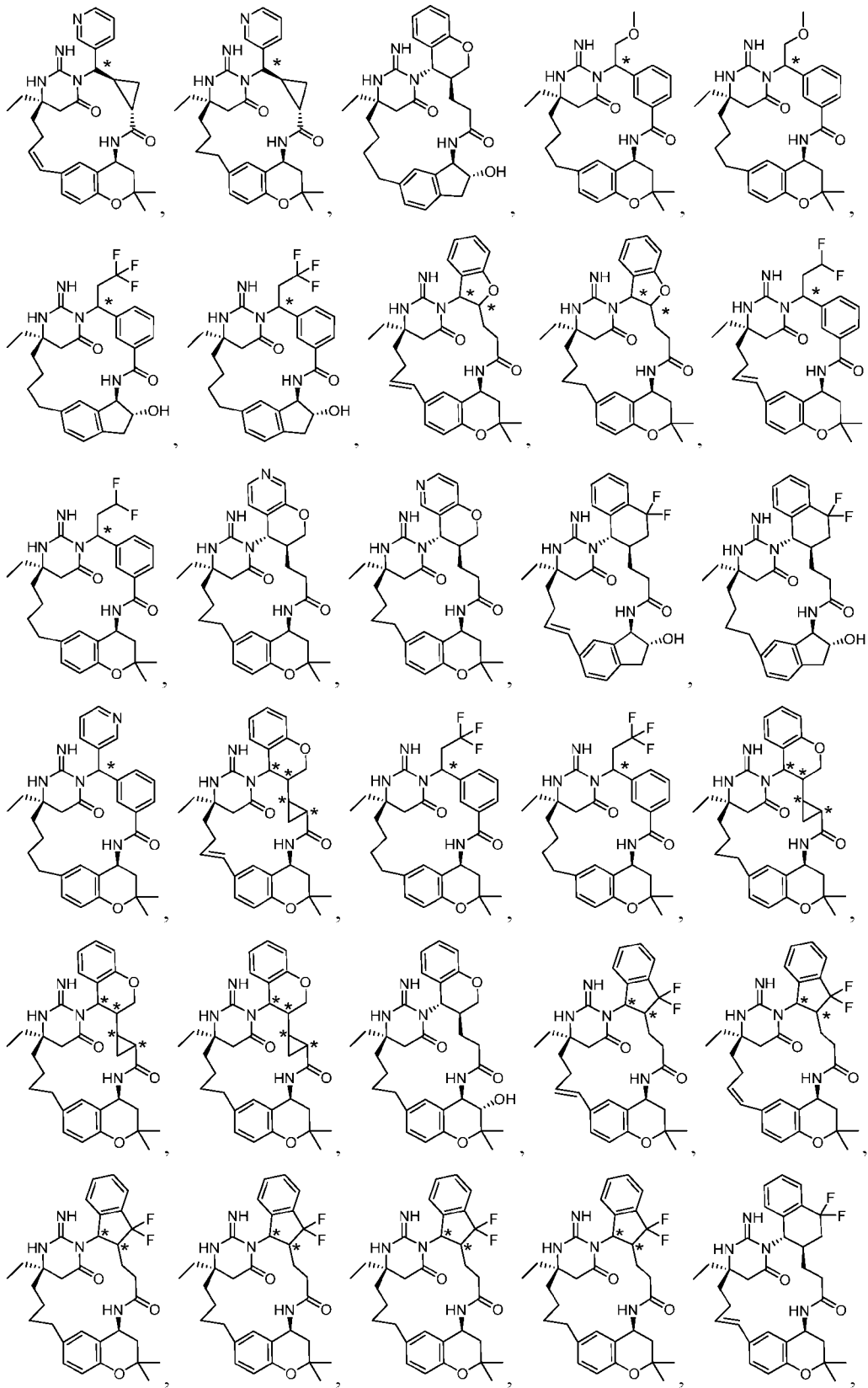
phenyl, pyridyl, pyrimidinyl, benzylpyrimidinyl, pyrazolyl, and imidazolyl unsubstituted or substituted with 1 to 3 groups of R, or a pharmaceutically acceptable salt thereof.

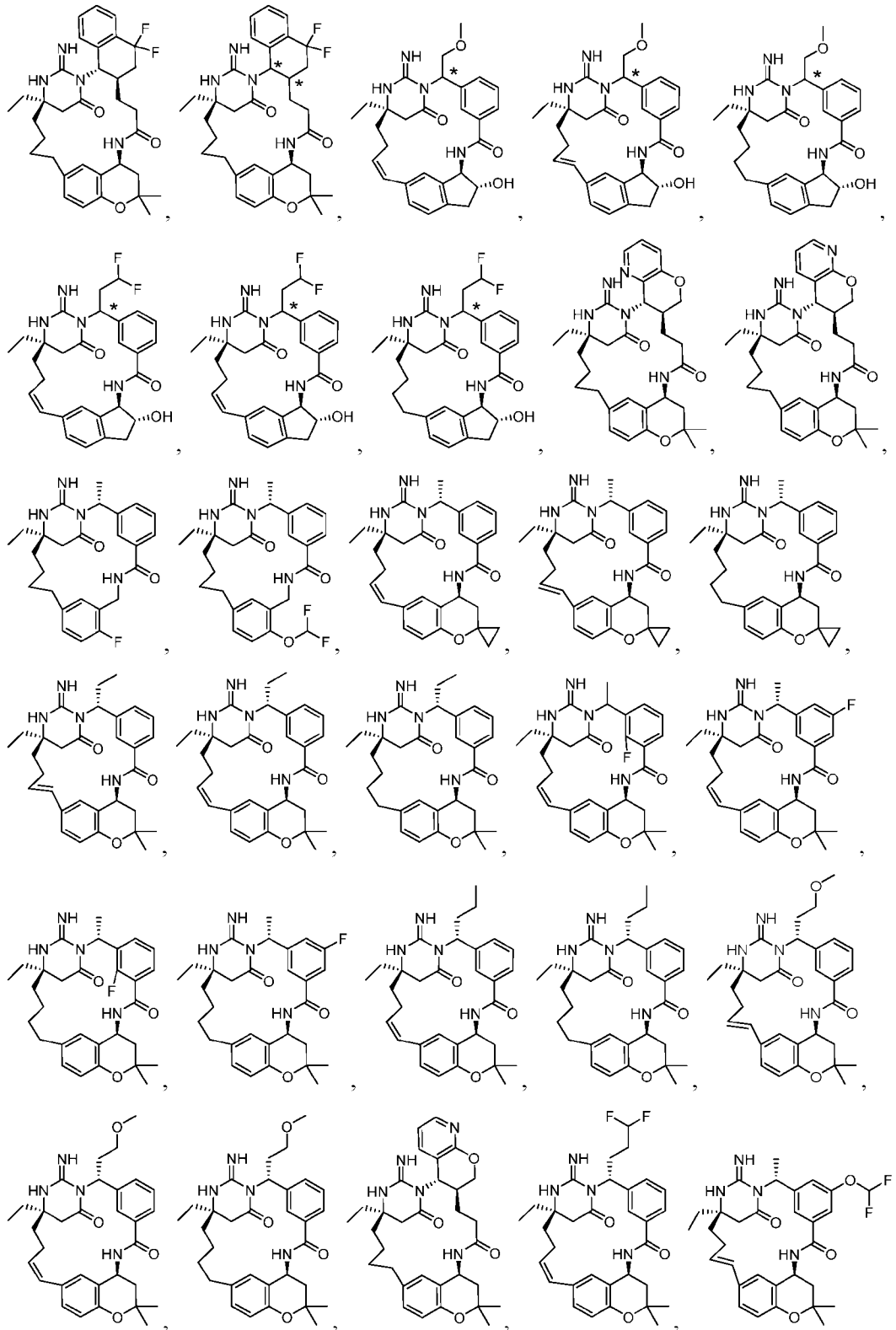
21. The compound according to any one of claims 1-20 wherein R is selected from hydrogen, CH_2COOH , $(\text{CH}_2)_2\text{COOH}$, $\text{CH}(\text{CH}_3)\text{COOH}$, CH_3 , CH_2CH_3 , $(\text{CH}_2)_2\text{OCH}_3$, $(\text{CH}_2)_3\text{OCH}_3$, $(\text{CH}_2)_2\text{OCH}_2\text{CH}_3$, $(\text{CH}_2)_3\text{OCH}_2\text{CH}_3$, CH_2F , CHF_2 , CF_3 , $(\text{CH}_2)_2\text{OH}$, and $(\text{CH}_2)_3\text{OH}$, or a pharmaceutically acceptable salt thereof.

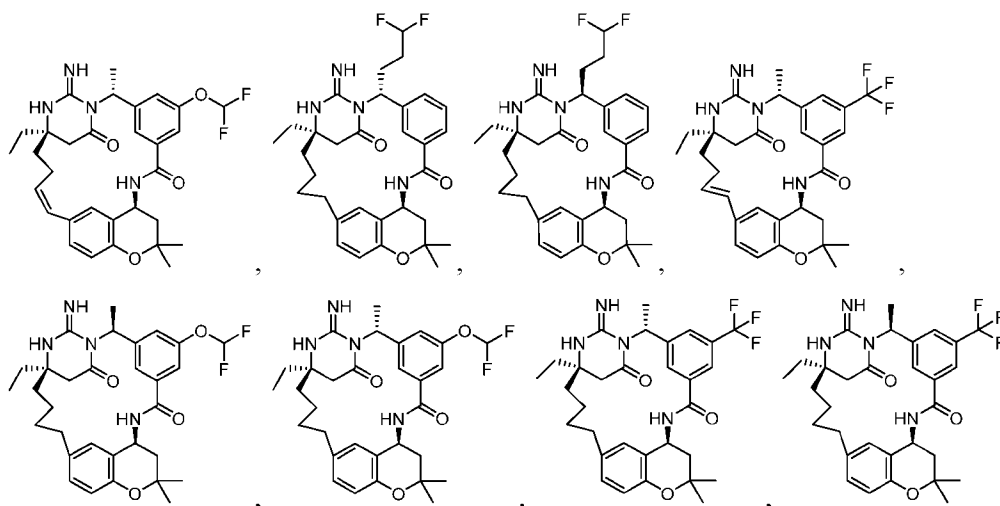
22. A compound selected from:











or a pharmaceutically acceptable salt thereof.

23. A method for treating a *Plasmodium* infection, or for treating malaria, which comprises administering to a subject in need of such treatment a therapeutically effective amount of a compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof.

24. A method for inhibiting plasmepsin X which comprises administering to a subject in need of such treatment a therapeutically effective amount of a compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof.

25. A method for inhibiting plasmepsin IX which comprises administering to a subject in need of such treatment a therapeutically effective amount of a compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof.

26. A method for dual inhibition of plasmepsin X and plasmepsin IX which comprises administering to a subject in need of such treatment a therapeutically effective amount of a compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof.

27. The use of a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-22 to treat a *Plasmodium* infection, or malaria in a patient in need thereof.

28. The use of a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-22 to inhibit plasmepsin X in a patient in need thereof.

29. The use of a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-22 to inhibit plasmepsin IX in a patient in need thereof.

30. The use of a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-22 to inhibit plasmepsin IX and plasmepsin X, in a patient in need thereof.

31. A pharmaceutical composition comprising a compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

32. A pharmaceutical composition comprising a compound of any one of claims 1-22 and a pharmaceutically acceptable carrier.

33. A method for treating a *Plasmodium* infection, or for treating malaria, comprising administration of a compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, and an effective amount of one or more additional anti-malarial agents.

34. A method for the treatment of malaria by inhibition of plasmepsin X, IX and at least one other mechanism, comprising administration of a compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, and an effective amount of one additional anti-malarial agent, wherein the additional anti-malarial agent acts through a mechanism other than inhibiting plasmepsin IX or plasmepsin X.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/033203

A. CLASSIFICATION OF SUBJECT MATTER		
IPC: <i>C07D 491/18</i> (2024.01); <i>A61P 33/06</i> (2024.01); <i>C07D 491/08</i> (2024.01) CPC: <i>C07D 491/18</i> ; <i>C07D 491/08</i> ; <i>A61P 33/06</i>		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) See Search History Document		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched See Search History Document		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) See Search History Document		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2020/0230140 A1 (MERCK SHARP & DOHME CORP et al.) 23 July 2020 (23.07.2020) entire document	1-3, 6
A	US 2010/0113359 A1 (GANT et al.) 06 May 2010 (06.05.2010) entire document	1-3, 6
A	US 2020/0283416 A1 (UCB BIOPHARMA SPRL) 10 September 2020 (10.09.2020) entire document	1-3, 6
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
<p>* Special categories of cited documents:</p> <p>“A” document defining the general state of the art which is not considered to be of particular relevance</p> <p>“D” document cited by the applicant in the international application</p> <p>“E” earlier application or patent but published on or after the international filing date</p> <p>“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)</p> <p>“O” document referring to an oral disclosure, use, exhibition or other means</p> <p>“P” document published prior to the international filing date but later than the priority date claimed</p> <p>“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</p> <p>“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</p> <p>“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</p> <p>“&” document member of the same patent family</p>		
Date of the actual completion of the international search 23 July 2024 (23.07.2024)		Date of mailing of the international search report 20 September 2024 (20.09.2024)
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300		Authorized officer MATOS TAINA Telephone No. 571-272-4300

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

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

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

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

3. Claims Nos.: **9-21, 23-34**
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:

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

Group I+: claims 1-8 and 22 are drawn to compounds having the structural Formula I, and a compound or pharmaceutically acceptable salt thereof.

The first invention of Group I+ is restricted to a compound having the structural Formula I: wherein A is a straight, saturated C3 alkylene, wherein A is -CH₂CH₂CH₂-; X is straight, saturated C3 alkylene, wherein X is -CH₂CH₂CH₂-; Z is a bond; and Q is the first shown structure, wherein the single squiggle line represents point of attachment to A and the double squiggle line represents point of attachment to Z, R1 is absent, and k is 0; or a pharmaceutically acceptable salt thereof; and a compound or a pharmaceutically acceptable salt thereof. The first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Specifically, the first named invention was selected based on the first listed element for each of the variables presented in the claims (A, X, Z, Q – claim 1). It is believed that claims 1-3 and 6 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound having the structural Formula I: wherein A is a straight, saturated C3 alkylene, wherein A is -CH₂CH₂CH₂-; X is straight, saturated C3 alkylene, wherein X is -CH₂CH₂CH₂-; Z is a bond; and Q is the second shown structure, wherein the single squiggle line represents point of attachment to A and the double squiggle line represents point of attachment to Z, R1 is absent, and k is 0; or a pharmaceutically acceptable salt thereof; and a compound or a pharmaceutically acceptable salt thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the “+” group(s) will result in only the first claimed invention to be searched/examined.

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

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

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables A, X, Z, and Q, and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features of a compound having the core structural Formula I or a pharmaceutically acceptable salt thereof; and a compound or a pharmaceutically acceptable salt thereof, these shared technical features do not represent a contribution over the prior art as disclosed by US 2020/0230140 A1 to Merck Sharp & Dohme Corp. et al.

US 2020/0230140 A1 to Merck Sharp & Dohme Corp. et al. teach a compound having the core structural Formula I or a pharmaceutically acceptable salt thereof (Para. [0342], Compound No. 1, see shown structure); and a compound or a pharmaceutically acceptable salt thereof (Para. [0342], Compound No. 1, see shown structure).

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

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.: **1-3, 6**

- 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.