

ANTIMALARIAL AGENTS

FIELD OF THE INVENTION

5 The present invention relates to compounds of Formula (I') and (I), or pharmaceutically acceptable salts thereof, useful for the treatment of *Plasmodium* infections. More specifically, the present invention relates to compounds of Formula (I') and (I), or pharmaceutically acceptable salts thereof, useful for the treatment of *Plasmodium* infections, more particularly for the treatment of malaria.

BACKGROUND OF THE INVENTION

10 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
15 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
20 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
25 blood feeding for perpetuation and survival of the parasite.

 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
30 Malaysian Borneo.

 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

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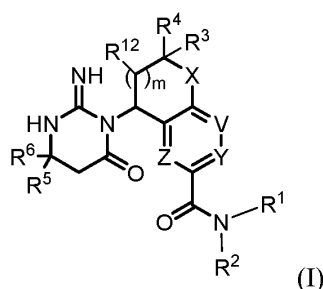
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The present invention



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The present invention is directed to compounds of Formula (I):



wherein X, V, Y, Z, R¹, R², R³, R⁴, R⁵, R⁶ and R¹² are described below.

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

Also described herein are methods of treatment of malaria comprising administering to a subject in need thereof a compound of Formula (I') and (I), or a pharmaceutically acceptable salt thereof.

The present invention further provides the use of compositions, including pharmaceutical compositions, comprising one or more compounds of the invention (e.g., one compound of the invention), 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.

Moreover, the present invention 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 invention together with one or more additional pharmaceutically active agents are also provided.

The present invention 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.

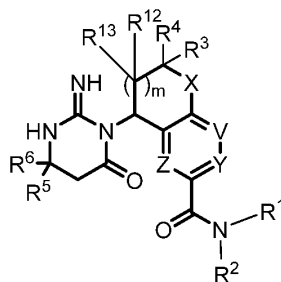
The present invention further provides methods for the inhibition of *P. falciparum* aspartic acid proteases. The present invention further provides methods for blocking *P. falciparum* growth by inhibiting plasmepsin X. The present invention further provides methods for blocking *P. falciparum* growth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

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

These and other embodiments of the invention, 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 invention.

DETAILED DESCRIPTION OF THE INVENTION

Described herein are compounds having the structural Formula (I'):



(I')

or a pharmaceutically acceptable salt thereof, wherein:

X is a bond, C(R¹⁴)₂, O, S, SO, SO₂ or NH;

Y is CR⁹ or N, wherein when Y is N, Z is CR¹¹ and V is CR¹⁰;

V is CR¹⁰ or N, wherein when V is N, Z is CR¹¹ and Y is CR⁹;

Z is CR¹¹ or N, wherein when Z is N, V is CR¹⁰ and Y is CR⁹;

R¹ is a heterocycloalkyl, C₃-C₁₂cycloalkyl, aryl, C₁-C₆alkylaryl or when taken with R², and the nitrogen which they are bonded, forms nitrogen-containing ring, wherein the heterocycloalkyl, C₃-

C₁₂cycloalkyl, aryl, C₁-C₆alkylaryl or nitrogen-containing ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, CN, OH, C₁-C₆alkoxy,

- C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, oxo, COOC₁-C₆alkyl, C₁-C₆alkylCOOC₁-C₆alkyl, C₃-C₆cycloalkyl, C₁-C₆alkylC₃-C₆cycloalkyl, aryl, C₁-C₆alkyl, C₁-C₆alkylOhaloC₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) and C₁-C₆alkylN(R⁷)(R⁸);
- R² is hydrogen, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl or C₁-C₆alkylOH or when taken with R¹, and the nitrogen which they are bonded, forms a nitrogen-containing ring, wherein the nitrogen-containing ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, oxo, COOC₁-C₆alkyl, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) and C₁-C₆alkylN(R⁷)(R⁸);
- 10 R³ is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸), C₁-C₆alkylN(R⁷)(R⁸), C₁-C₆alkyl(OCH₂CH₂)_nN(R⁷)(R⁸) or C₁-C₆alkylOhaloC₁-C₆alkyl or when taken with R⁴ forms a C₃-C₆cycloalkyl or C₃-C₆heterocycloalkyl;
- R⁴ is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, 15 C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸), C₁-C₆alkylN(R⁷)(R⁸), C₁-C₆alkyl(OCH₂CH₂)_nN(R⁷)(R⁸) or C₁-C₆alkylOhaloC₁-C₆alkyl or when taken with R³ forms a C₃-C₆cycloalkyl or C₃-C₆heterocycloalkyl;
- R⁵ is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) or C₁-C₆alkylN(R⁷)(R⁸) or when taken with R⁶ forms a C₃-C₆cycloalkyl or C₃-C₆heterocycloalkyl;
- 20 R⁶ is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) or C₁-C₆alkylN(R⁷)(R⁸) or when taken with R⁵ forms a C₃-C₆cycloalkyl or C₃-C₆heterocycloalkyl;
- R⁷ is hydrogen, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, COC₁-C₆alkyl or COOC₁-C₆alkyl;
- 25 R⁸ is hydrogen, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, COC₁-C₆alkyl or COOC₁-C₆alkyl;
- R⁹ is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) or C₁-C₆alkylN(R⁷)(R⁸);
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R¹⁰ is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) or C₁-C₆alkylN(R⁷)(R⁸);

R¹¹ is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) or C₁-C₆alkylN(R⁷)(R⁸);

R¹² is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) or C₁-C₆alkylN(R⁷)(R⁸);

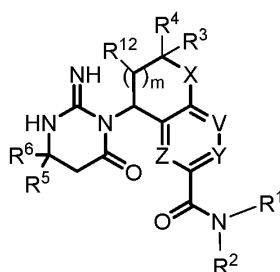
R¹³ is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) or C₁-C₆alkylN(R⁷)(R⁸);

each occurrence of R¹⁴ is independently selected from the group consisting of hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) and C₁-C₆alkylN(R⁷)(R⁸);

n is 1, 2, 3 or 4; and

m is 0, 1 or 2.

Also described herein are compounds having the structural Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

X is CH₂, O, S, SO, SO₂ or NH;

Y is CR⁹ or N, wherein when Y is N, Z is CR¹¹ and V is CR¹⁰;

V is CR¹⁰ or N, wherein when V is N, Z is CR¹¹ and Y is CR⁹;

Z is CR¹¹ or N, wherein when Z is N, V is CR¹⁰ and Y is CR⁹;

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- R¹ is a heterocycloalkyl, C₃-C₁₂cycloalkyl, aryl, C₁-C₆alkylaryl or when taken with R², and the nitrogen which they are bonded, forms nitrogen-containing ring, wherein the heterocycloalkyl, C₃-C₁₂cycloalkyl, aryl, C₁-C₆alkylaryl or nitrogen-containing ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, oxo, COOC₁-C₆alkyl, C₁-C₆alkylCOOC₁-C₆alkyl, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) and C₁-C₆alkylN(R⁷)(R⁸);
- R² is hydrogen, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl or C₁-C₆alkylOH or when taken with R¹, and the nitrogen which they are bonded, forms a nitrogen-containing ring, wherein the nitrogen-containing ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, oxo, COOC₁-C₆alkyl, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) and C₁-C₆alkylN(R⁷)(R⁸);
- R³ is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) or C₁-C₆alkylN(R⁷)(R⁸) or when taken with R⁴ forms a C₃-C₆cycloalkyl or C₃-C₆heterocycloalkyl;
- R⁴ is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) or C₁-C₆alkylN(R⁷)(R⁸) or when taken with R³ forms a C₃-C₆cycloalkyl or C₃-C₆heterocycloalkyl;
- R⁵ is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) or C₁-C₆alkylN(R⁷)(R⁸) or when taken with R⁶ forms a C₃-C₆cycloalkyl or C₃-C₆heterocycloalkyl;
- R⁶ is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) or C₁-C₆alkylN(R⁷)(R⁸) or when taken with R⁵ forms a C₃-C₆cycloalkyl or C₃-C₆heterocycloalkyl;
- R⁷ is hydrogen, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl or C₁-C₆alkylOH;
- R⁸ is hydrogen, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl or C₁-C₆alkylOH;
- R⁹ is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) or C₁-C₆alkylN(R⁷)(R⁸);

R¹⁰ is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) or C₁-C₆alkylN(R⁷)(R⁸);

R¹¹ is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) or C₁-C₆alkylN(R⁷)(R⁸);

R¹² is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) or C₁-C₆alkylN(R⁷)(R⁸); and

m is 0, 1 or 2.

In the embodiments described herein, X is a bond, C(R¹⁴)₂, O, S, SO, SO₂ or NH. In certain embodiments described herein X is a bond. In certain embodiments, X is C(R¹⁴)₂, wherein R¹⁴ is discussed in further detail below. In certain embodiments, X is a bond, CH₂, CH(CH₃), C(CH₃)₂, O, CH(OCH₃), SO₂ or CF₂. In other embodiments X is CH₂, O, S, SO, SO₂ or NH. In certain embodiments, X is CH₂. In the embodiments described herein, X is O. In the embodiments described herein, X is S. In the embodiments described herein, X is SO. In the embodiments described herein, X is SO₂. In the embodiments described herein, X is NH. In the embodiments described herein, X is O or SO₂.

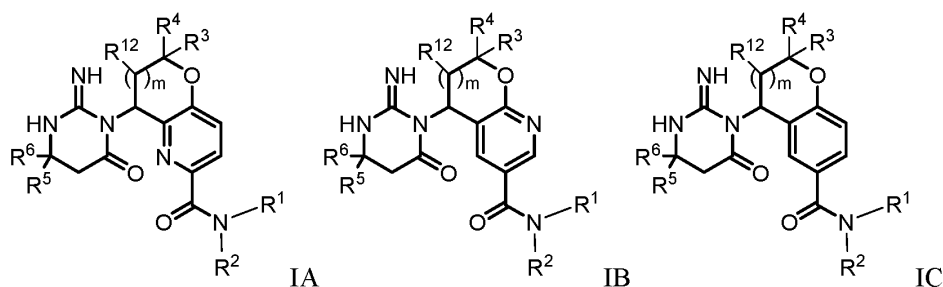
In the embodiments described herein, Y is CR⁹ or N. In certain embodiments, Y is CR⁹, wherein R⁹ is discussed in detail below. In certain embodiments, Y is N. In certain embodiments, Y is CH. In certain embodiments, wherein when Y is N, Z is CR¹¹ and V is CR¹⁰.

In the embodiments described herein, V is CR¹⁰ or N. In certain embodiments, V is CR¹⁰, R¹⁰ are discussed in detail below. In certain embodiments, V is N. In certain embodiments, V is CH. In certain embodiments, wherein when V is N, Z is CR¹¹ and Y is CR⁹.

In the embodiments described herein, Z is CR¹¹ or N. In certain embodiments, Z is CR¹¹, R¹¹ are discussed in detail below. In certain embodiments, Z is CH. In certain embodiments, Z is N. In certain embodiments, wherein when Z is N, V is CR¹⁰ and Y is CR⁹.

In certain embodiments, X is O, Y and V are each CH and Z is N. In certain embodiments, X is O, Y and Z are each CH and V is N. In certain embodiments, X is O and V, Y and Z are all simultaneously CH.

These embodiments are represented as Formulas IA -IC:

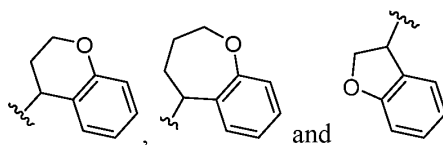


In the embodiments described herein, R^1 is a heterocycloalkyl, C_3 - C_{12} cycloalkyl, aryl, C_1 - C_6 alkylaryl or when taken with R^2 , and the nitrogen which they are bonded, forms nitrogen-containing ring, wherein the heterocycloalkyl, C_3 - C_{12} cycloalkyl, aryl, C_1 - C_6 alkylaryl or nitrogen-containing ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, CN, OH, C_1 - C_6 alkoxy, C_1 - C_6 alkylOC $_1$ - C_6 alkyl, C_1 - C_6 alkylCOOH, COOH, oxo, COOC $_1$ - C_6 alkyl, C_1 - C_6 alkylCOOC $_1$ - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 alkyl C_3 - C_6 cycloalkyl, aryl, C_1 - C_6 alkyl, C_1 - C_6 alkylOhalo C_1 - C_6 alkyl, halo C_1 - C_6 alkyl, C_1 - C_6 alkylOH, CON(R^7)(R^8), N(R^7)(R^8) and C_1 - C_6 alkylN(R^7)(R^8).

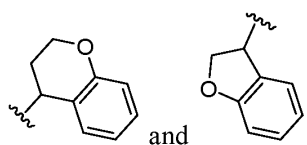
In the embodiments described herein, R^1 is a heterocycloalkyl, C_3 - C_{12} cycloalkyl, aryl, C_1 - C_6 alkylaryl or when taken with R^2 , and the nitrogen which they are bonded, forms nitrogen-containing ring, wherein the heterocycloalkyl, C_3 - C_{12} cycloalkyl, aryl, C_1 - C_6 alkylaryl or nitrogen-containing ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, CN, OH, C_1 - C_6 alkoxy, C_1 - C_6 alkylOC $_1$ - C_6 alkyl, C_1 - C_6 alkylCOOH, COOH, oxo, COOC $_1$ - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 alkyl, halo C_1 - C_6 alkyl, C_1 - C_6 alkylOH, CON(R^7)(R^8), N(R^7)(R^8) and C_1 - C_6 alkylN(R^7)(R^8).

In certain embodiments, R^1 is a bicyclic ring. In certain embodiments, R^1 is a bicyclic heterocycloalkyl, bicyclic C_3 - C_{12} cycloalkyl, bicyclic aryl or when taken with R^2 and the nitrogen to which they are bonded, forms a bicyclic nitrogen-containing ring. In certain embodiments, R^1 is a bicyclic heterocycloalkyl, bicyclic C_3 - C_{12} cycloalkyl, bicyclic aryl or when taken with R^2 and the nitrogen to which they are bonded, forms a bicyclic nitrogen-containing ring, wherein one of the rings is a benzene ring. In certain embodiments, R^1 is a bicyclic heterocycloalkyl, bicyclic C_3 - C_{12} cycloalkyl, C_1 - C_6 alkylphenyl or when taken with R^2 and the nitrogen to which they are bonded, forms a bicyclic nitrogen-containing ring, wherein one of the rings of the bicyclic heterocycloalkyl, bicyclic C_3 - C_{12} cycloalkyl or when taken with R^2 and the nitrogen to which they are bonded, is a benzene ring.

In certain embodiments, R^1 is a heterocycloalkyl. Non-limiting examples of monocyclic heterocycloalkyl groups include piperidyl, oxetanyl, pyrrolyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, *beta* lactam, *gamma* lactam, *delta* lactam, *beta* lactone, *gamma* lactone, *delta* lactone, and pyrrolidinone, and
 5 oxides thereof. Non-limiting examples of bicyclic heterocycloalkyl groups include, but are not limited to,

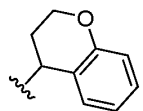


Non-limiting examples of bicyclic heterocycloalkyl groups include, but are not limited to,

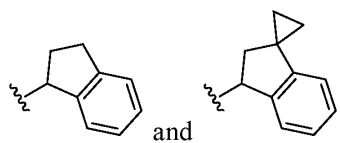


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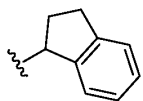
In certain embodiments, R^1 is



In certain embodiments, R^1 is a C_3 - C_{12} cycloalkyl. In certain embodiments, the
 15 cycloalkyl is a monocyclic cycloalkyl. Suitable examples of cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In certain embodiments, the cycloalkyl is a bicyclic cycloalkyl. Suitable examples of cycloalkyls include, but are not limited to:



Suitable examples of cycloalkyls include, but are not limited to:

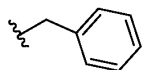


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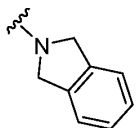
In certain embodiments, R^1 is an aryl ring. Suitable examples of aryls include, but

are not limited to, monocyclic aryl groups such as, phenyl and bicyclic aryl groups such as naphthyl.

In certain embodiments, R^1 is a C₁-C₆alkylaryl ring. Suitable examples of C₁-C₆alkylaryls include, but are not limited to:



5 In certain embodiments, R^1 is taken with R^2 and forms a nitrogen-containing ring. Suitable examples of nitrogen-containing rings include, but are not limited to, aziridinyl, aziriny, azetidiny, azete, indoline, pyrrolidinyl, pyrrolyl, piperidinyl and pyridinyl. In certain embodiments, R^1 is taken with R^2 and forms a nitrogen-containing ring, wherein the nitrogen-containing ring is an indoline. In certain embodiments, R^1 is taken with R^2 and forms a nitrogen-containing ring, wherein
10 the nitrogen-containing ring is:



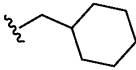
In certain embodiments, R^1 is unsubstituted. In other embodiments, R^1 is substituted with 1 to 5 substituents independently selected from the group consisting of halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, oxo, COOC₁-C₆alkyl, C₁-C₆alkylCOOC₁-C₆alkyl, C₃-C₆cycloalkyl, C₁-C₆alkylC₃-C₆cycloalkyl, aryl, C₁-C₆alkyl, C₁-C₆alkylOhaloC₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R^7)(R^8), N(R^7)(R^8) and C₁-C₆alkylN(R^7)(R^8). In other embodiments, R^1 is substituted with 1 to 5 substituents independently selected from the group consisting of halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, oxo, COOC₁-C₆alkyl, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R^7)(R^8), N(R^7)(R^8) and C₁-C₆alkylN(R^7)(R^8).
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In certain embodiments, R^1 is substituted with 1 substituent. In certain embodiments, R^1 is substituted with 2 substituents. In certain embodiments, R^1 is substituted with 3 substituents. In certain embodiments, R^1 is substituted with 4 substituents. In certain embodiments, R^1 is substituted with 5 substituents.

25 In certain embodiments, R^1 is substituted with halogen. Examples of suitable halogens include chlorine, bromine, fluorine and iodine. In certain embodiments, R^1 is substituted with CN. In certain embodiments, R^1 is substituted with OH. In certain embodiments, R^1 is substituted with an oxo group. In certain embodiments, R^1 is substituted with C₁-C₆alkoxy. Suitable

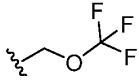
alkoxys include, but are not limited to, methoxy, ethoxy, *n*-propoxy, isopropoxy and *n*-butoxy. In certain embodiments, R¹ is substituted with C₁-C₆alkyloxy. In certain embodiments, R¹ is substituted with C₁-C₆alkylCOOH. In certain embodiments, R¹ is substituted with COOH. In certain embodiments, R¹ is substituted with C₁-C₆alkylCOOC₁-C₆alkyl.

5 In certain embodiments, R¹ is substituted with C₃-C₆cycloalkyl. Suitable examples of cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In certain embodiments, R¹ is substituted with C₁-C₆alkylC₃-C₆cycloalkyl. Suitable examples of

cycloalkyls include, but are not limited to . In certain embodiments, R¹ is substituted with aryl. Suitable examples of cycloalkyls include, but are not limited to, phenyl.

10 In certain embodiments, R¹ is substituted with C₁-C₆alkyl. Examples of C₁-C₆alkyl groups can include but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, sec-butyl, tert-butyl, *n*-pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, *n*-hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl and 1-ethyl-1-methylpropyl.

In certain embodiments, R¹ is substituted with C₁-C₆alkylOhaloC₁-C₆alkyl. Suitable

examples of haloalkyls include, but are not limited to, .

In certain embodiments, R¹ is substituted with haloC₁-C₆alkyl. Suitable examples of haloalkyls include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 1,2-difluoroethyl and 2,2-difluoroethyl. In certain embodiments, R¹ is substituted with C₁-C₆alkylOH. Examples of suitable alcohols include, but are not limited to, methanol, ethanol, propanol, butanol and iso-butanol. In certain embodiments, R¹ is substituted with CON(R⁷)(R⁸). In certain embodiments, R¹ is substituted with N(R⁷)(R⁸). In certain embodiments, R¹ is substituted with C₁-C₆alkylN(R⁷)(R⁸), wherein R⁷ and R⁸ will be described in detail below.

25 In certain embodiments, R¹ is substituted with 1 to 4 substituents selected independently from the group consisting of bromine, fluorine, chlorine, methyl, OH, halogen, CN oxo, methoxymethyl, COOCH₂CH₃ and trifluoromethyl.

In certain embodiments described herein, R² is hydrogen, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl or C₁-C₆alkylOH or when taken with R¹, and the

nitrogen which they are bonded, forms a nitrogen-containing ring, wherein the nitrogen-containing ring is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) and C₁-C₆alkylN(R⁷)(R⁸).

In certain embodiments, R² is hydrogen. In certain embodiments, R² is C₁-C₆alkylCOOH. In certain embodiments, R² is COOH. In certain embodiments, R² is C₃-C₆cycloalkyl. Suitable examples of cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In certain embodiments, R² is C₁-C₆alkyl. Examples of C₁-C₆alkyl groups can include but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, n-hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl and 1-ethyl-1-methylpropyl.

In certain embodiments, R² is haloC₁-C₆alkyl. Suitable examples of haloalkyls include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 1,2-difluoroethyl and 2,2-difluoroethyl. In certain embodiments, R² is C₁-C₆alkylOH. Examples of suitable alcohols include, but are not limited to, methanol, ethanol, propanol, butanol and isobutanol.

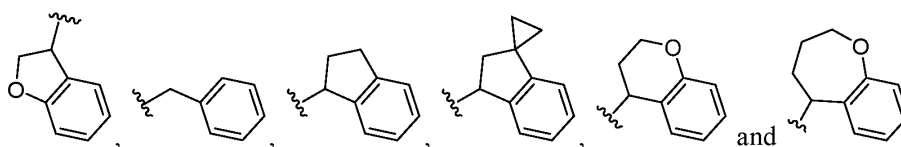
In certain embodiments, R² is taken with R¹ and forms a nitrogen-containing ring. Suitable examples of nitrogen-containing rings include, but are not limited to, aziridinyl, azirinyl, azetidiny, azete, indoline, pyrrolidinyl, pyrrolyl, piperidinyl and pyridinyl. In certain embodiments, R² is taken with R¹ and forms an indoline.

In certain embodiments, the nitrogen-containing ring is unsubstituted. In other embodiments, the nitrogen-containing ring is substituted with 1 to 5 substituents independently selected from the group consisting of halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) and C₁-C₆alkylN(R⁷)(R⁸). In certain embodiments, the nitrogen-containing ring is substituted with 1 substituent. In certain embodiments, the nitrogen-containing ring is substituted with 2 substituents. In certain embodiments, the nitrogen-containing ring is substituted with 3 substituents. In certain embodiments, the nitrogen-containing ring is substituted with 4 substituents. In certain embodiments, the nitrogen-containing ring is substituted with 5 substituents.

In certain embodiments, the nitrogen-containing ring is substituted with halogen. Examples of suitable halogens include chlorine, bromine, fluorine and iodine. In certain embodiments, the nitrogen-containing ring is substituted with CN. In certain embodiments, the nitrogen-containing ring is substituted with OH. In certain embodiments, the nitrogen-containing ring is substituted with alkoxy. Suitable alkoxys include, but are not limited to, methoxy, ethoxy, *n*-propoxy, isopropoxy and *n*-butoxy. In certain embodiments, the nitrogen-containing ring is substituted with C₁-C₆alkylalkoxy. In certain embodiments, the nitrogen-containing ring is substituted with C₁-C₆alkylCOOH. In certain embodiments, the nitrogen-containing ring is substituted with COOH.

In certain embodiments, the nitrogen-containing ring is substituted with C₃-C₆cycloalkyl. Suitable examples of cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In certain embodiments, the nitrogen-containing ring is substituted with C₁-C₆alkyl. Examples of C₁-C₆alkyl groups can include but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, sec-butyl, tert-butyl, *n*-pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, *n*-hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl and 1-ethyl-1-methylpropyl. In certain embodiments, R¹ is substituted with haloC₁-C₆alkyl. Suitable examples of haloalkyls include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 1,2-difluoroethyl and 2,2-difluoroethyl. In certain embodiments, R¹ is substituted with C₁-C₆alkylOH. Examples of suitable alcohols include, but are not limited to, methanol, ethanol, propanol, butanol and iso-butanol. In certain embodiments, the nitrogen-containing ring is substituted with CON(R⁷)(R⁸). In certain embodiments, the nitrogen-containing ring is substituted with N(R⁷)(R⁸). In certain embodiments, the nitrogen-containing ring is substituted with C₁-C₆alkylN(R⁷)(R⁸), wherein R⁷ and R⁸ will be described in detail below.

In certain embodiments, R¹ is selected from the group consisting of:



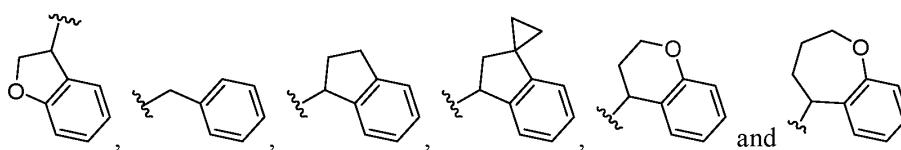
wherein R¹ is unsubstituted or substituted with 1 to 5 substituents selected from the group consisting of halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, oxo,

COOC₁₋₆alkyl, C₃₋₆cycloalkyl, C₁₋₆alkylC₃₋₆cycloalkyl, aryl, C₁₋₆alkyl, haloC₁₋₆alkyl, C₁₋₆alkylOhaloC₁₋₆alkyl, C₁₋₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) and C₁₋₆alkylN(R⁷)(R⁸);

R⁷ is hydrogen, C₁₋₆alkylCOOH, COOH, C₃₋₆cycloalkyl, C₁₋₆alkyl, haloC₁₋₆alkyl or C₁₋₆alkylOH; and

- 5 R⁸ is hydrogen, C₁₋₆alkylCOOH, COOH, C₃₋₆cycloalkyl, C₁₋₆alkyl, haloC₁₋₆alkyl or C₁₋₆alkylOH.

In certain embodiments, R² is hydrogen and R¹ is selected from the group consisting of:



- 10 wherein R¹ is unsubstituted or substituted with 1 to 5 substituents selected from the group consisting of methyl, OH, NH₂, CH₂OH, methoxy, fluorine, phenyl, cyclohexyl, chlorine, trifluoromethyl, CH₂cyclohexyl, CH₂OCHF₂ and COOCH₂CH₃.

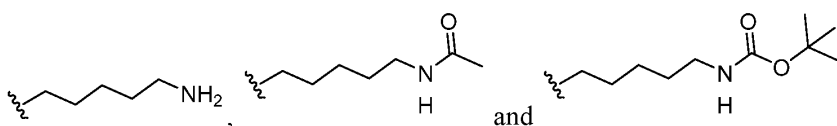
- With regard to the compounds described herein, R³ is hydrogen, halogen, CN, OH, C₁₋₆alkoxy, C₁₋₆alkylOC₁₋₆alkyl, C₁₋₆alkylCOOH, COOH, C₃₋₆cycloalkyl, C₁₋₆alkyl, haloC₁₋₆alkyl, C₁₋₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸), C₁₋₆alkylN(R⁷)(R⁸), C₁₋₆alkyl(OCH₂CH₂)_nN(R⁷)(R⁸) or C₁₋₆alkylOhaloC₁₋₆alkyl or when taken with R⁴ forms a C₃₋₆cycloalkyl or C₃₋₆heterocycloalkyl. In certain embodiments of the compounds described herein, R³ is hydrogen, halogen, CN, OH, C₁₋₆alkoxy, C₁₋₆alkylOC₁₋₆alkyl, C₁₋₆alkylCOOH, COOH, C₃₋₆cycloalkyl, C₁₋₆alkyl, haloC₁₋₆alkyl, C₁₋₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) or C₁₋₆alkylN(R⁷)(R⁸) or when taken with R⁴ forms a C₃₋₆cycloalkyl or C₃₋₆heterocycloalkyl. In certain embodiments, R³ is hydrogen. In certain embodiments, R³ is halogen. Suitable halogens include fluorine, chlorine, bromine, and iodine. In certain embodiments, R³ is CN. In certain embodiments, R³ is OH.

- In certain embodiments, R³ is C₁₋₆alkoxy. Suitable alkoxys include, but are not limited to, methoxy, ethoxy, *n*-propoxy, isopropoxy and *n*-butoxy. In certain embodiments, R³ is C₁₋₆alkylOC₁₋₆alkyl. In certain embodiments, R³ is COOH. In certain embodiments, R³ is C₁₋₆alkylCOOH. In certain embodiments, R³ is C₃₋₆cycloalkyl. Suitable examples of cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In certain embodiments, R³ is C₁₋₆alkyl. Examples of C₁₋₆alkyl groups can include but are not limited to,

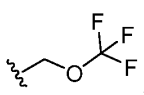
methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, n-hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-

5 methylpropyl and 1-ethyl-1-methylpropyl. In certain embodiments, R^3 is haloC₁-C₆alkyl. Suitable examples of haloalkyls include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 1,2-difluoroethyl and 2,2-difluoroethyl. In certain embodiments, R^3 is C₁-C₆alkylOH. Examples of suitable alcohols include, but are not limited to, methanol, ethanol, propanol, butanol and iso-butanol. In certain embodiments, R^3 is CON(R⁷)(R⁸). Suitable examples of N(R⁷)(R⁸)

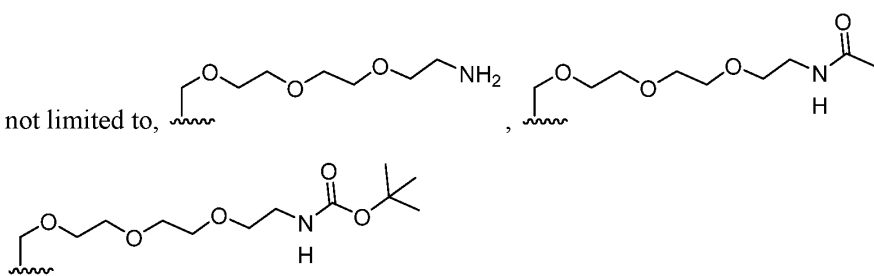
10 include, but are not limited to, CONH₂ and CON(CH₃)₂. In certain embodiments, R^3 is N(R⁷)(R⁸). Suitable examples of N(R⁷)(R⁸) include, but are not limited to, NH₂ and N(CH₃)₂. In certain embodiments, R^3 is C₁-C₆alkylN(R⁷)(R⁸). Suitable examples of C₁-C₆alkylN(R⁷)(R⁸) include, but

are not limited to, . R^7 and R^8 are discussed in further detail below.

15 In certain embodiments, R^3 is C₁-C₆alkylOhaloC₁-C₆alkyl. Suitable examples of

haloalkyls include, but are not limited to, .

In certain embodiments, R^3 is C₁-C₆alkyl(OCH₂CH₂)_nN(R⁷)(R⁸). R^7 , R^8 and n are discussed in detail below. Suitable examples of C₁-C₆alkyl(OCH₂CH₂)_nN(R⁷)(R⁸) include, but are

not limited to, .

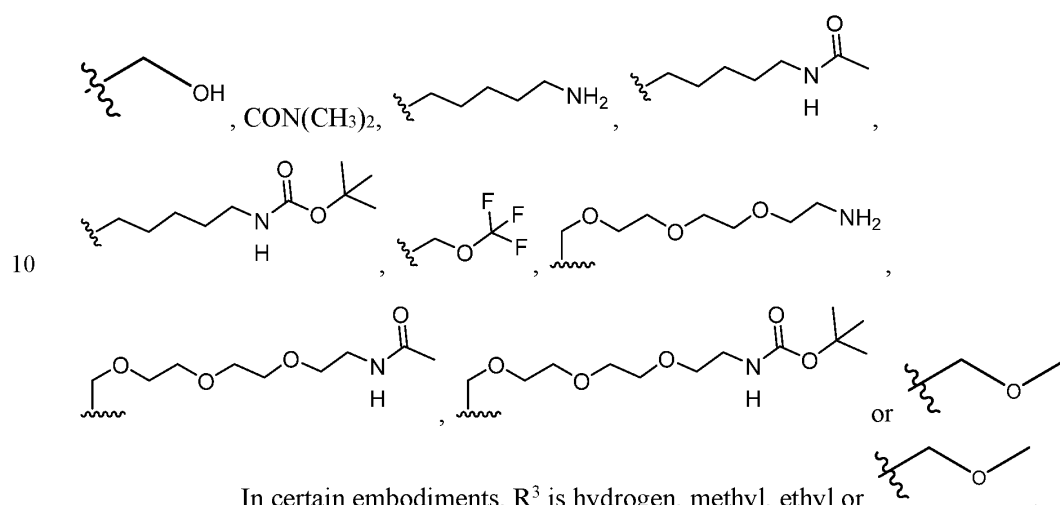
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With regard to the compounds described herein, n is 1, 2, 3 or 4. In certain embodiments, n is 1. In certain embodiments, n is 2. In certain embodiments, n is 3. In certain embodiments, n is 4.

In certain embodiments, R^3 is taken with R^4 and forms a C₃-C₆cycloalkyl or C₃-

C₆heterocycloalkyl. In certain embodiments, R³ is taken with R⁴ and forms a C₃-C₆cycloalkyl. Suitable examples of cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In certain embodiments, R³ is taken with R⁴ and forms a C₃-C₆heterocycloalkyl. Suitable examples of heterocycloalkyls include, but are not limited to, piperidyl, oxetanyl, pyrrolyl, piperazinyl, 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.

In certain embodiments, R³ is hydrogen, fluorine, methyl, ethyl, OH, methoxy,

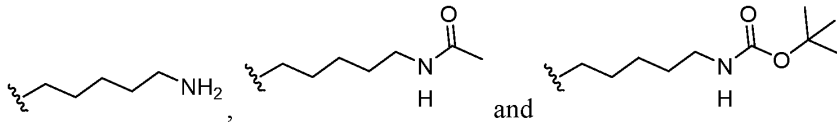


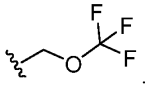
In certain embodiments, R³ is hydrogen, methyl, ethyl or

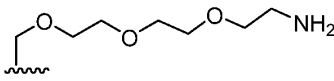
In certain embodiments, R³ is taken with R⁴ to form oxetanyl.

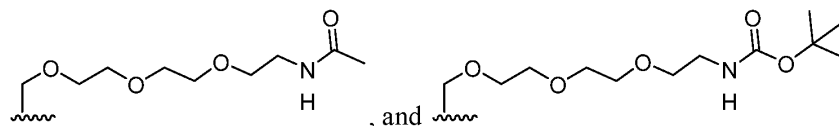
With regard to the compounds described herein, R⁴ is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸), C₁-C₆alkylN(R⁷)(R⁸), C₁-C₆alkyl(OCH₂CH₂)_nN(R⁷)(R⁸) or C₁-C₆alkylOhaloC₁-C₆alkyl or when taken with R³ forms a C₃-C₆cycloalkyl or C₃-C₆heterocycloalkyl. In certain embodiments of the compounds described herein, R⁴ is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) or C₁-C₆alkylN(R⁷)(R⁸) or when taken with R³ forms a C₃-C₆cycloalkyl or C₃-C₆heterocycloalkyl. In certain embodiments, R⁴ is hydrogen. In certain embodiments, R⁴ is halogen. Suitable halogens include fluorine, chlorine, bromine, or iodine. In certain embodiments, R⁴ is CN. In certain embodiments, R⁴ is OH.

In certain embodiments, R^4 is C_1 - C_6 alkoxy. Suitable alkoxys include, but are not limited to, methoxy, ethoxy, *n*-propoxy, isopropoxy and *n*-butoxy. In certain embodiments, R^4 is C_1 - C_6 alkylOC $_1$ - C_6 alkyl. In certain embodiments, R^4 is COOH. In certain embodiments, R^4 is C_1 - C_6 alkylCOOH. In certain embodiments, R^4 is C_3 - C_6 cycloalkyl. Suitable examples of cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In certain embodiments, R^4 is C_1 - C_6 alkyl. Examples of C_1 - C_6 alkyl groups can include but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, sec-butyl, tert-butyl, *n*-pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, *n*-hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl and 1-ethyl-1-methylpropyl. In certain embodiments, R^4 is halo C_1 - C_6 alkyl. Suitable examples of haloalkyls include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 1,2-difluoroethyl and 2,2-difluoroethyl. In certain embodiments, R^4 is C_1 - C_6 alkylOH. Examples of suitable alcohols include, but are not limited to, methanol, ethanol, propanol, butanol and iso-butanol. In certain embodiments, R^4 is $CON(R^7)(R^8)$. Suitable examples of $N(R^7)(R^8)$ include, but are not limited to, $CONH_2$ and $CON(CH_3)_2$. In certain embodiments, R^4 is $N(R^7)(R^8)$. Suitable examples of $N(R^7)(R^8)$ include, but are not limited to, NH_2 and $N(CH_3)_2$. In certain embodiments, R^4 is C_1 - C_6 alkyl $N(R^7)(R^8)$. Suitable examples of C_1 - C_6 alkyl $N(R^7)(R^8)$ include, but

are not limited to,  and R^8 are discussed in further detail below.

In certain embodiments, R^4 is C_1 - C_6 alkylOhalo C_1 - C_6 alkyl. Suitable examples of haloalkyls include, but are not limited to, .

In certain embodiments, R^4 is C_1 - C_6 alkyl $(OCH_2CH_2)_nN(R^7)(R^8)$. R^7 , R^8 are discussed in detail below and n is discussed above. Suitable examples of C_1 - C_6 alkyl $(OCH_2CH_2)_nN(R^7)(R^8)$ include, but are not limited to, .



In certain embodiments, R^4 is taken with R^3 and forms a C₃-C₆cycloalkyl or C₃-C₆heterocycloalkyl. In certain embodiments, R^4 is taken with R^3 and forms a C₃-C₆cycloalkyl. Suitable examples of cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In certain embodiments, R^4 is taken with R^3 and forms a C₃-C₆heterocycloalkyl. Suitable examples of heterocycloalkyls include, but are not limited to, piperidyl, oxetanyl, pyrrolyl, piperazinyl, 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.

In certain embodiments, R^4 is hydrogen or methyl. In certain embodiments, R^4 is hydrogen, methyl, ethyl or . In certain embodiments, R^4 is taken with R^3 to form oxetanyl. In certain embodiments, R^3 and R^4 are both hydrogen, methyl or ethyl.

In certain embodiments, R^3 is hydrogen and R^4 is hydrogen, methyl, ethyl or .

With regard to the compounds described herein, R^5 is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R^7)(R^8), N(R^7)(R^8) or C₁-C₆alkylN(R^7)(R^8) or when taken with R^6 forms a C₃-C₆cycloalkyl or C₃-C₆heterocycloalkyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, R^5 is halogen. Suitable halogens include fluorine, chlorine, bromine, or iodine. In certain embodiments, R^5 is CN. In certain embodiments, R^5 is OH.

In certain embodiments, R^5 is C₁-C₆alkoxy. Suitable alkoxys include, but are not limited to, methoxy, ethoxy, *n*-propoxy, isopropoxy and *n*-butoxy. In certain embodiments, R^5 is C₁-C₆alkylOC₁-C₆alkyl. In certain embodiments, R^5 is COOH. In certain embodiments, R^5 is C₁-C₆alkylCOOH. In certain embodiments, R^5 is C₃-C₆cycloalkyl. Suitable examples of cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In certain embodiments, R^5 is C₁-C₆alkyl. Examples of C₁-C₆alkyl groups can include but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, sec-butyl, tert-butyl, *n*-pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, *n*-hexyl,

isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl and 1-ethyl-1-methylpropyl. In certain embodiments, R⁵ is haloC₁-C₆alkyl. Suitable examples of haloalkyls include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 1,2-difluoroethyl and 2,2-difluoroethyl. In certain embodiments, R⁵ is C₁-C₆alkylOH. Examples of suitable alcohols include, but are not limited to, methanol, ethanol, propanol, butanol and iso-butanol. In certain embodiments, R⁵ is CON(R⁷)(R⁸). In certain embodiments, R⁵ is N(R⁷)(R⁸). In certain embodiments, R⁵ is C₁-C₆alkylN(R⁷)(R⁸). R⁷ and R⁸ are discussed in detail below.

In certain embodiments, R⁵ is taken with R⁶ and forms a C₃-C₆cycloalkyl or C₃-C₆heterocycloalkyl. In certain embodiments, R⁵ is taken with R⁶ and forms a C₃-C₆cycloalkyl. Suitable examples of cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In certain embodiments, R⁵ is taken with R⁶ and forms a C₃-C₆heterocycloalkyl. Suitable examples of heterocycloalkyls include, but are not limited to, piperidyl, oxetanyl, pyrrolyl, piperazinyl, 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.

In certain embodiments, R⁵ is methyl, ethyl or *t*-butyl.

With regard to the compounds described herein, R⁶ is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) or C₁-C₆alkylN(R⁷)(R⁸) or when taken with R⁵ forms a C₃-C₆cycloalkyl or C₃-C₆heterocycloalkyl. In certain embodiments, R⁶ is hydrogen. In certain embodiments, R⁶ is halogen. Suitable halogens include fluorine, chlorine, bromine, or iodine. In certain embodiments, R⁶ is CN. In certain embodiments, R⁶ is OH.

In certain embodiments, R⁶ is C₁-C₆alkoxy. Suitable alkoxys include, but are not limited to, methoxy, ethoxy, *n*-propoxy, isopropoxy and *n*-butoxy. In certain embodiments, R⁶ is C₁-C₆alkylOC₁-C₆alkyl. In certain embodiments, R⁶ is COOH. In certain embodiments, R⁶ is C₁-C₆alkylCOOH. In certain embodiments, R⁶ is C₃-C₆cycloalkyl. Suitable examples of cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In certain embodiments, R⁶ is C₁-C₆alkyl. Examples of C₁-C₆alkyl groups can include but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, sec-butyl, tert-butyl, *n*-pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, *n*-hexyl,

isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl and 1-ethyl-1-methylpropyl. In certain embodiments, R⁶ is haloC₁-C₆alkyl. Suitable examples of haloalkyls include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 1,2-difluoroethyl and 2,2-difluoroethyl. In certain embodiments, R⁶ is C₁-C₆alkylOH. Examples of suitable alcohols include, but are not limited to, methanol, ethanol, propanol, butanol and iso-butanol. In certain embodiments, R⁶ is CON(R⁷)(R⁸). In certain embodiments, R⁶ is N(R⁷)(R⁸). In certain embodiments, R⁶ is C₁-C₆alkylN(R⁷)(R⁸). R⁷ and R⁸ are discussed in detail below.

In certain embodiments, R⁶ is taken with R⁵ and forms a C₃-C₆cycloalkyl or C₃-C₆heterocycloalkyl. In certain embodiments, R⁶ is taken with R⁵ and forms a C₃-C₆cycloalkyl. Suitable examples of cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In certain embodiments, R⁶ is taken with R⁵ and forms a C₃-C₆heterocycloalkyl. Suitable examples of heterocycloalkyls include, but are not limited to, piperidyl, oxetanyl, pyrrolyl, piperazinyl, 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.

In certain embodiments, R⁶ is methyl, ethyl or *t*-butyl.

With regard to the compounds described herein, R⁷ is hydrogen, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, COC₁-C₆alkyl or COOC₁-C₆alkyl. In certain embodiments, R⁷ is hydrogen, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl or C₁-C₆alkylOH.

In certain embodiments, R⁷ is hydrogen. In certain embodiments, R⁷ is C₁-C₆alkylCOOH. In certain embodiments, R⁷ is COOH. In certain embodiments, R⁷ is C₃-C₆cycloalkyl. Suitable examples of cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In certain embodiments, R⁷ is C₁-C₆alkyl. Examples of C₁-C₆alkyl groups can include but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, n-hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl and 1-ethyl-1-methylpropyl. In certain embodiments, R⁷ is haloC₁-C₆alkyl. Suitable examples of haloalkyls include, but are not

limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 1,2-difluoroethyl and 2,2-difluoroethyl. In certain embodiments, R⁷ is C₁-C₆alkylOH. Examples of suitable alcohols include, but are not limited to, methanol, ethanol, propanol, butanol and iso-butanol.

In certain embodiments, R⁷ is COC₁-C₆alkyl. Suitable examples include, but are not limited to, COCH₃. In certain embodiments, R⁷ is COOC₁-C₆alkyl. Suitable examples include, but are not limited to, COOCH₃.

With regard to the compounds described herein, R⁸ is hydrogen, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, COC₁-C₆alkyl or COOC₁-C₆alkyl. In certain embodiments, R⁸ is hydrogen, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl or C₁-C₆alkylOH.

In certain embodiments, R⁸ is hydrogen. In certain embodiments, R⁸ is C₁-C₆alkylCOOH. In certain embodiments, R⁸ is COOH. In certain embodiments, R⁸ is C₃-C₆cycloalkyl. Suitable examples of cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In certain embodiments, R⁸ is C₁-C₆alkyl. Examples of C₁-C₆alkyl groups can include but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, n-hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl and 1-ethyl-1-methylpropyl. In certain embodiments, R⁸ is haloC₁-C₆alkyl. Suitable examples of haloalkyls include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 1,2-difluoroethyl and 2,2-difluoroethyl. In certain embodiments, R⁸ is C₁-C₆alkylOH. Examples of suitable alcohols include, but are not limited to, methanol, ethanol, propanol, butanol and iso-butanol.

In certain embodiments, R⁸ is COC₁-C₆alkyl. Suitable examples include, but are not limited to, COCH₃. In certain embodiments, R⁸ is COOC₁-C₆alkyl. Suitable examples include, but are not limited to, COOCH₃.

With regard to the compounds described herein, R⁹ is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸) and N(R⁷)(R⁸). In certain embodiments, R⁹ is hydrogen. In certain embodiments, R⁹ is halogen. Suitable halogens include fluorine, chlorine, bromine, or iodine. In certain embodiments, R⁹ is CN. In certain embodiments, R⁹ is OH.

In certain embodiments, R⁹ is C₁-C₆alkoxy. Suitable alkoxys include, but are not

limited to, methoxy, ethoxy, *n*-propoxy, isopropoxy and *n*-butoxy. In certain embodiments, R⁹ is C₁-C₆alkylOC₁-C₆alkyl. In certain embodiments, R⁹ is COOH. In certain embodiments, R⁹ is C₁-C₆alkylCOOH. In certain embodiments, R⁹ is C₃-C₆cycloalkyl. Suitable examples of cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In certain

5 embodiments, R⁹ is C₁-C₆alkyl. Examples of C₁-C₆alkyl groups can include but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, sec-butyl, tert-butyl, *n*-pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, *n*-hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-

10 methylpropyl and 1-ethyl-1-methylpropyl. In certain embodiments, R⁹ is haloC₁-C₆alkyl. Suitable examples of haloalkyls include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 1,2-difluoroethyl and 2,2-difluoroethyl. In certain embodiments, R⁹ is C₁-C₆alkylOH. Examples of suitable alcohols include, but are not limited to, methanol, ethanol, propanol, butanol and iso-butanol. In certain embodiments, R⁹ is CON(R⁷)(R⁸). In certain embodiments, R⁹ is

15 N(R⁷)(R⁸). In certain embodiments, R⁹ is C₁-C₆alkylN(R⁷)(R⁸).

With regard to the compounds described herein, R¹⁰ is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸) and N(R⁷)(R⁸). In certain embodiments, R¹⁰ is hydrogen. In certain embodiments, R¹⁰ is halogen. Suitable halogens include fluorine, chlorine,

20 bromine, or iodine. In certain embodiments, R¹⁰ is CN. In certain embodiments, R¹⁰ is OH.

In certain embodiments, R¹⁰ is C₁-C₆alkoxy. Suitable alkoxys include, but are not limited to, methoxy, ethoxy, *n*-propoxy, isopropoxy and *n*-butoxy. In certain embodiments, R¹⁰ is C₁-C₆alkylOC₁-C₆alkyl. In certain embodiments, R¹⁰ is COOH. In certain embodiments, R¹⁰ is C₁-C₆alkylCOOH. In certain embodiments, R¹⁰ is C₃-C₆cycloalkyl. Suitable examples of cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In certain

25 embodiments, R¹⁰ is C₁-C₆alkyl. Examples of C₁-C₆alkyl groups can include but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, sec-butyl, tert-butyl, *n*-pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, *n*-hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-

30 methylpropyl and 1-ethyl-1-methylpropyl. In certain embodiments, R¹⁰ is haloC₁-C₆alkyl. Suitable examples of haloalkyls include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl,

2-fluoroethyl, 1,2-difluoroethyl and 2,2-difluoroethyl. In certain embodiments, R^{10} is C_1 - C_6 alkylOH. Examples of suitable alcohols include, but are not limited to, methanol, ethanol, propanol, butanol and iso-butanol. In certain embodiments, R^{10} is $CON(R^7)(R^8)$. In certain embodiments, R^{10} is $N(R^7)(R^8)$. In certain embodiments, R^{10} is C_1 - C_6 alkylN(R^7)(R^8).

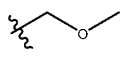
5 With regard to the compounds described herein, R^{11} is hydrogen, halogen, CN, OH, C_1 - C_6 alkoxy, C_1 - C_6 alkylOC $_1$ - C_6 alkyl, C_1 - C_6 alkylCOOH, COOH, C_3 - C_6 cycloalkyl, C_1 - C_6 alkyl, halo C_1 - C_6 alkyl, C_1 - C_6 alkylOH, $CON(R^7)(R^8)$ and $N(R^7)(R^8)$. In certain embodiments, R^{11} is hydrogen. In certain embodiments, R^{11} is halogen. Suitable halogens include fluorine, chlorine, bromine, or iodine. In certain embodiments, R^{11} is CN. In certain embodiments, R^{11} is OH.

10 In certain embodiments, R^{11} is C_1 - C_6 alkoxy. Suitable alkoxy groups include, but are not limited to, methoxy, ethoxy, *n*-propoxy, isopropoxy and *n*-butoxy. In certain embodiments, R^{11} is C_1 - C_6 alkylOC $_1$ - C_6 alkyl. In certain embodiments, R^{11} is COOH. In certain embodiments, R^{11} is C_1 - C_6 alkylCOOH. In certain embodiments, R^{11} is C_3 - C_6 cycloalkyl. Suitable examples of cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In certain
15 embodiments, R^{11} is C_1 - C_6 alkyl. Examples of C_1 - C_6 alkyl groups can include but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, sec-butyl, tert-butyl, *n*-pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, *n*-hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-
20 methylpropyl and 1-ethyl-1-methylpropyl. In certain embodiments, R^{11} is halo C_1 - C_6 alkyl. Suitable examples of haloalkyls include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 1,2-difluoroethyl and 2,2-difluoroethyl. In certain embodiments, R^{11} is C_1 - C_6 alkylOH. Examples of suitable alcohols include, but are not limited to, methanol, ethanol, propanol, butanol and iso-butanol. In certain embodiments, R^{11} is $CON(R^7)(R^8)$. In certain embodiments, R^{11} is
25 $N(R^7)(R^8)$. In certain embodiments, R^{11} is C_1 - C_6 alkylN(R^7)(R^8).

With regard to the compounds described herein, R^{12} is hydrogen, halogen, CN, OH, C_1 - C_6 alkoxy, C_1 - C_6 alkylOC $_1$ - C_6 alkyl, C_1 - C_6 alkylCOOH, COOH, C_3 - C_6 cycloalkyl, C_1 - C_6 alkyl, halo C_1 - C_6 alkyl, C_1 - C_6 alkylOH, $CON(R^7)(R^8)$, $N(R^7)(R^8)$ or C_1 - C_6 alkylN(R^7)(R^8). In certain
30 embodiments, R^{12} is hydrogen. In certain embodiments, R^{12} is halogen. Suitable halogens include fluorine, chlorine, bromine, or iodine. In certain embodiments, R^{12} is CN. In certain embodiments, R^{12} is OH.

In certain embodiments, R^{12} is C_1 - C_6 alkoxy. Suitable alkoxy groups include, but are

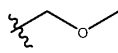
not limited to, methoxy, ethoxy, *n*-propoxy, isopropoxy and *n*-butoxy. In certain embodiments, R¹² is C₁-C₆alkylOC₁-C₆alkyl. In certain embodiments, R¹² is COOH. In certain embodiments, R¹² is C₁-C₆alkylCOOH. In certain embodiments, R¹² is C₃-C₆cycloalkyl. Suitable examples of cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In certain embodiments, R¹² is C₁-C₆alkyl. Examples of C₁-C₆alkyl groups can include but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, sec-butyl, tert-butyl, *n*-pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, *n*-hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl and 1-ethyl-1-methylpropyl. In certain embodiments, R¹² is haloC₁-C₆alkyl. Suitable examples of haloalkyls include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 1,2-difluoroethyl and 2,2-difluoroethyl. In certain embodiments, R¹² is C₁-C₆alkylOH. Examples of suitable alcohols include, but are not limited to, methanol, ethanol, propanol, butanol and iso-butanol. In certain embodiments, R¹² is CON(R⁷)(R⁸). In certain
 15 embodiments, R¹² is N(R⁷)(R⁸). In certain embodiments, R¹² is C₁-C₆alkylN(R⁷)(R⁸).

In certain embodiments, R¹² is hydrogen, methyl, ethyl, methoxy, OH or .

With regard to the compounds described herein, R¹³ is hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) or C₁-C₆alkylN(R⁷)(R⁸). In certain
 20 embodiments, R¹³ is hydrogen. In certain embodiments, R¹³ is halogen. Suitable halogens include fluorine, chlorine, bromine, or iodine. In certain embodiments, R¹³ is CN. In certain embodiments, R¹³ is OH.

In certain embodiments, R¹³ is C₁-C₆alkoxy. Suitable alkoxy groups include, but are not limited to, methoxy, ethoxy, *n*-propoxy, isopropoxy and *n*-butoxy. In certain embodiments, R¹³ is C₁-C₆alkylOC₁-C₆alkyl. In certain embodiments, R¹³ is COOH. In certain embodiments, R¹³ is C₁-C₆alkylCOOH. In certain embodiments, R¹³ is C₃-C₆cycloalkyl. Suitable examples of cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In certain embodiments, R¹³ is C₁-C₆alkyl. Examples of C₁-C₆alkyl groups can include but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, sec-butyl, tert-butyl, *n*-pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, *n*-hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-
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dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl and 1-ethyl-1-methylpropyl. In certain embodiments, R^{13} is haloC₁-C₆alkyl. Suitable examples of haloalkyls include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 1,2-difluoroethyl and 2,2-difluoroethyl. In certain embodiments, R^{13} is C₁-C₆alkylOH. Examples of suitable alcohols include, but are not limited to, methanol, ethanol, propanol, butanol and iso-butanol. In certain embodiments, R^{13} is CON(R⁷)(R⁸). In certain embodiments, R^{13} is N(R⁷)(R⁸). In certain embodiments, R^{13} is C₁-C₆alkylN(R⁷)(R⁸).

In certain embodiments, R^{13} is hydrogen, methyl, ethyl, methoxy, OH or .

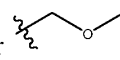
In certain embodiments, wherein m is 1 or 2, R^{12} and R^{13} are independently selected from the group consisting of hydrogen, halogen, OH, C₁-C₆alkylOH, C₁-C₆alkylalkoxy and C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkyl.

With regard to the compounds described herein, each occurrence of R^{14} is selected from the group consisting of hydrogen, halogen, CN, OH, C₁-C₆alkoxy, C₁-C₆alkylOC₁-C₆alkyl, C₁-C₆alkylCOOH, COOH, C₃-C₆cycloalkyl, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkylOH, CON(R⁷)(R⁸), N(R⁷)(R⁸) or C₁-C₆alkylN(R⁷)(R⁸). In certain embodiments, R^{14} is hydrogen. In certain embodiments, R^{14} is halogen. Suitable halogens include fluorine, chlorine, bromine, or iodine. In certain embodiments, R^{14} is CN. In certain embodiments, R^{14} is OH.

In certain embodiments, R^{14} is C₁-C₆alkoxy. Suitable alkoxy groups include, but are not limited to, methoxy, ethoxy, *n*-propoxy, isopropoxy and *n*-butoxy. In certain embodiments, R^{14} is C₁-C₆alkylOC₁-C₆alkyl. In certain embodiments, R^{14} is COOH. In certain embodiments, R^{14} is C₁-C₆alkylCOOH. In certain embodiments, R^{14} is C₃-C₆cycloalkyl. Suitable examples of cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In certain embodiments, R^{14} is C₁-C₆alkyl. Examples of C₁-C₆alkyl groups can include but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, sec-butyl, tert-butyl, *n*-pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, *n*-hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl and 1-ethyl-1-methylpropyl. In certain embodiments, R^{14} is haloC₁-C₆alkyl. Suitable examples of haloalkyls include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 1,2-difluoroethyl and 2,2-difluoroethyl. In certain embodiments, R^{14} is C₁-C₆alkylOH. Examples of suitable alcohols include, but are not limited to, methanol, ethanol,

propanol, butanol and iso-butanol. In certain embodiments, R^{14} is $\text{CON}(R^7)(R^8)$. In certain embodiments, R^{14} is $\text{N}(R^7)(R^8)$. In certain embodiments, R^{14} is $\text{C}_1\text{-C}_6\text{alkylN}(R^7)(R^8)$.

In certain embodiments, wherein X is $\text{C}(R^{14})_2$, R^{14} is independently selected from the group consisting of hydrogen, halogen, OH, $\text{C}_1\text{-C}_6\text{alkylOH}$, $\text{C}_1\text{-C}_6\text{alkylalkoxy}$, $\text{C}_1\text{-C}_6\text{alkylOC}_1\text{-C}_6\text{alkyl}$ and $\text{C}_1\text{-C}_6\text{alkyl}$.

In certain embodiments, R^{14} is hydrogen, methyl, ethyl, methoxy, OH or .

With regard to the compounds described herein, m is 0, 1 or 2. In certain embodiments, m is 0. In certain embodiments, m is 1. In certain embodiments, m is 2.

In certain embodiments, m is 1 and X is O.

In certain embodiments, m is 1 and X is CH_2 .

In certain embodiments, m is 0 and X is O.

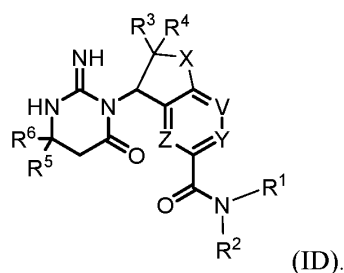
In certain embodiments, m is 1 and X is SO_2 .

In certain embodiments, m is 0 and X is $\text{C}(R^{14})_2$, wherein each occurrence of R^{14} is independently selected from the group consisting of hydrogen, halogen, OH, $\text{C}_1\text{-C}_6\text{alkoxy}$ and $\text{C}_1\text{-C}_6\text{alkyl}$.

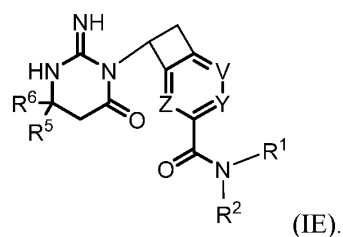
In certain embodiments, m is 1 and X is $\text{C}(R^{14})_2$, wherein each occurrence of R^{14} is independently selected from the group consisting of hydrogen, halogen, OH, $\text{C}_1\text{-C}_6\text{alkoxy}$ and $\text{C}_1\text{-C}_6\text{alkyl}$.

For example, in certain embodiments of Formula (I'), (I), (IA), (IB), and (IC), m is 1.

In the following formula (ID), m is 0:



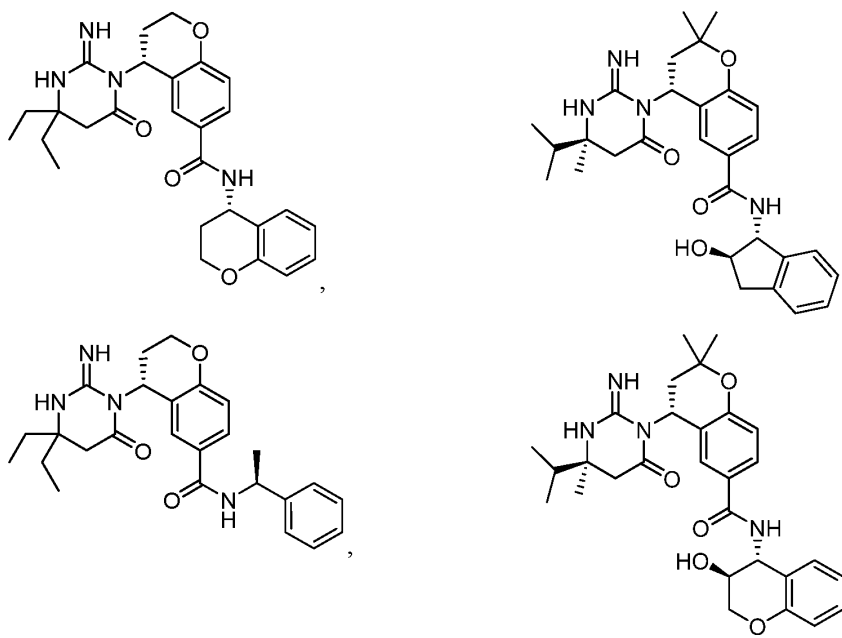
For example, in certain embodiments X is a bond and m is 0, as shown in Formula (IE)

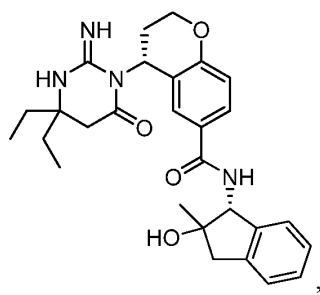
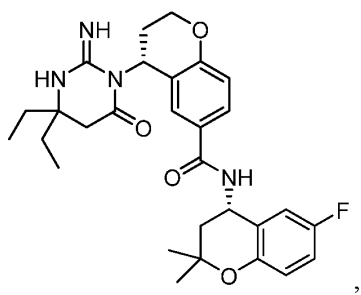
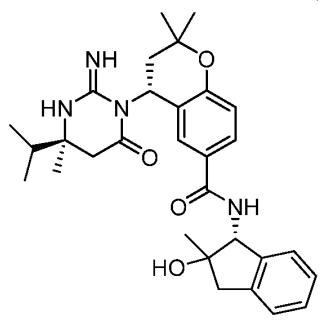
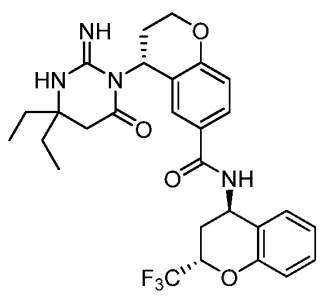
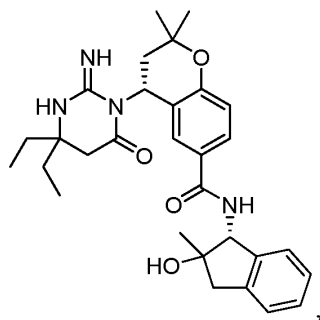
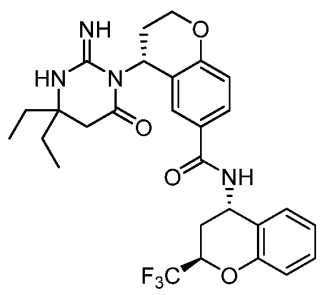
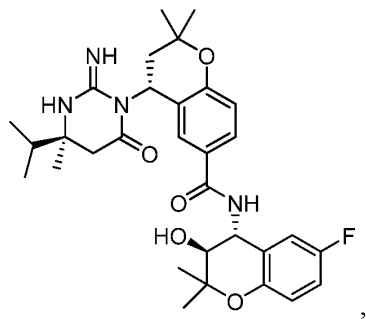
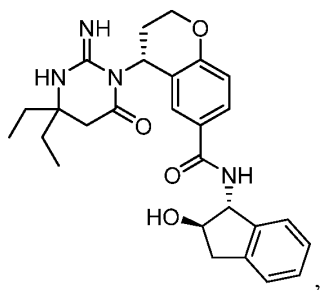


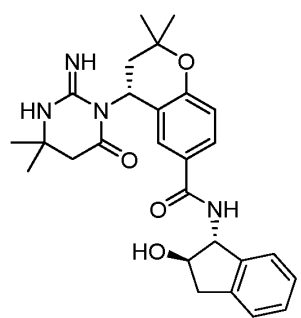
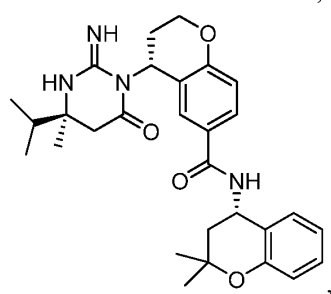
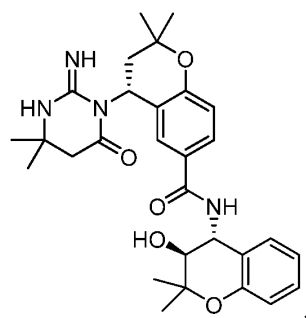
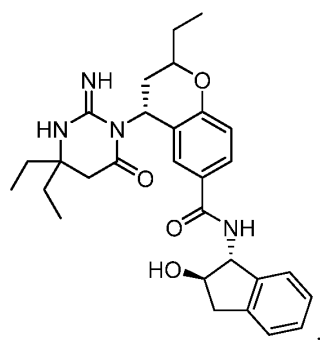
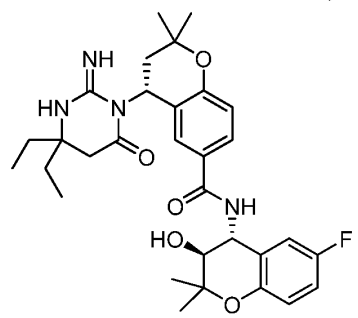
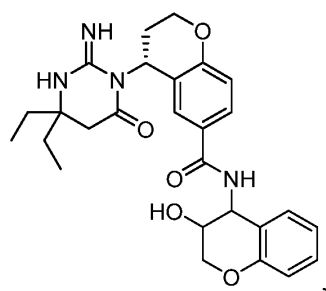
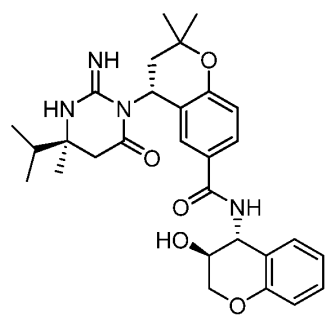
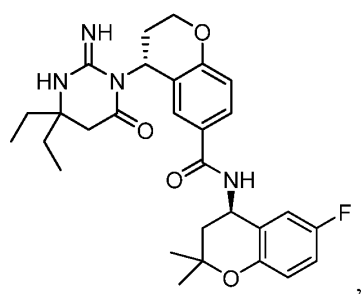
In each of the various embodiments of the invention, in the compounds used in the methods herein, each variable (including those in each of Formula (I'), (I), (IA), (IB), (IC), (ID) and (IE), and the various embodiments thereof) it shall be understood that each variable is to be selected independently of the others unless otherwise indicated.

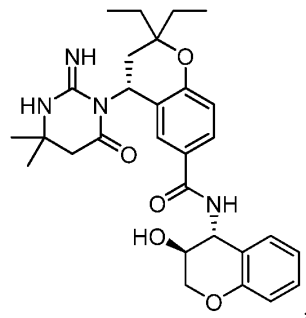
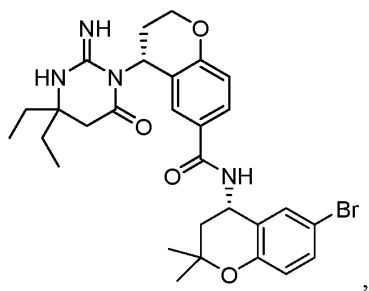
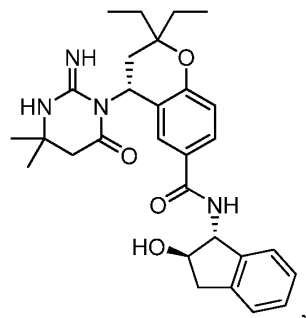
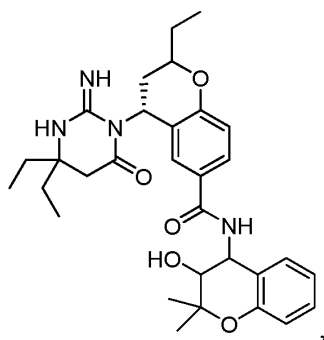
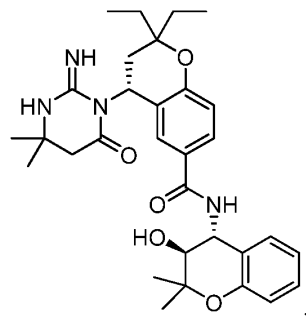
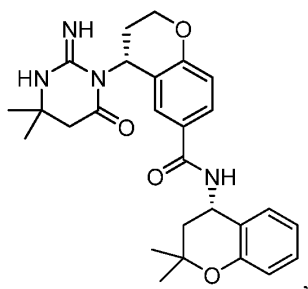
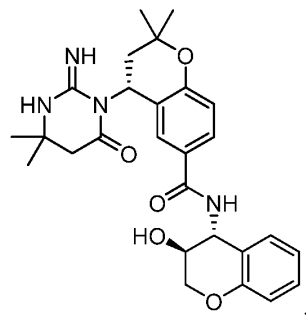
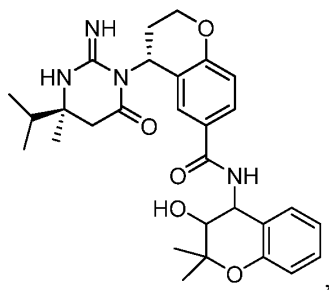
In each of the various embodiments of the invention, the compounds described herein, including those in each of Formula (I'), (I), (IA), (IB), (IC), (ID) and (IE) and the various embodiments thereof, may exist in different forms of the compounds such as, for example, any solvates, hydrates, stereoisomers, and tautomers of said compounds and of any pharmaceutically acceptable salts thereof.

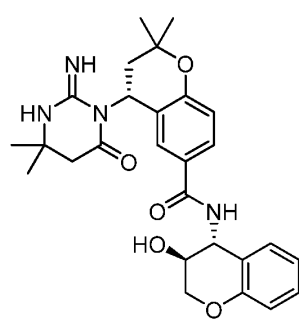
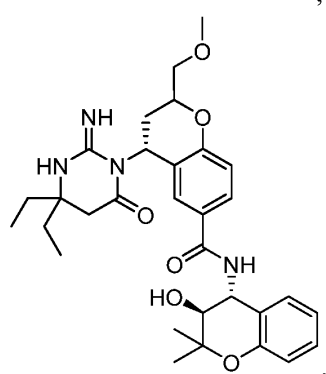
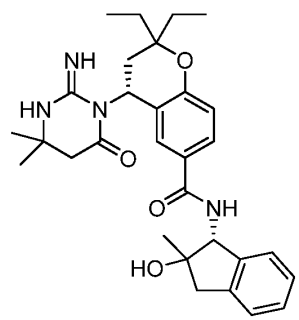
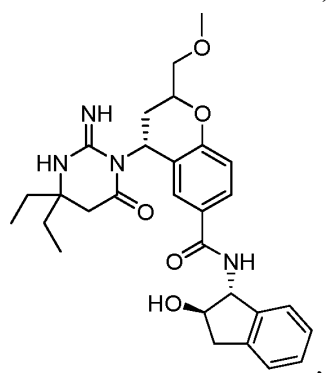
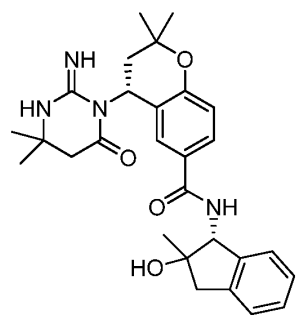
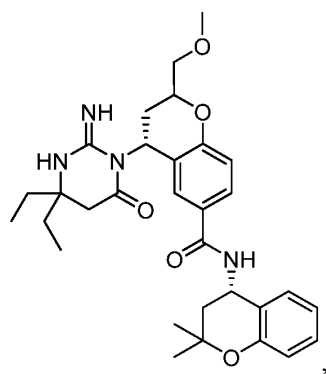
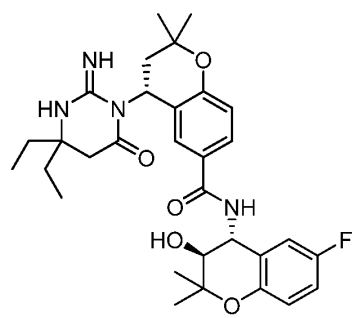
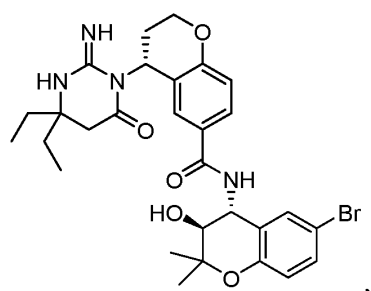
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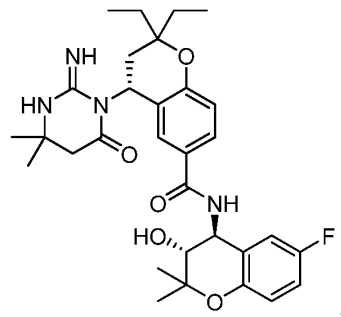
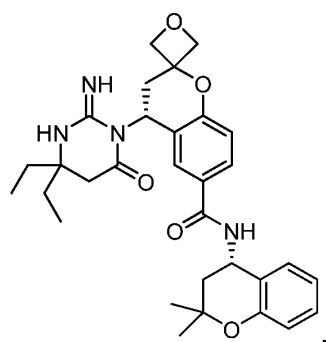
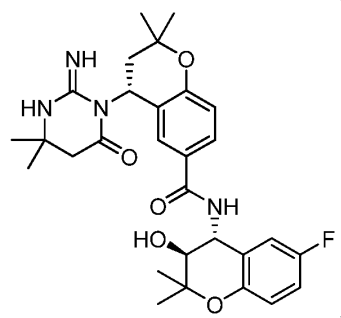
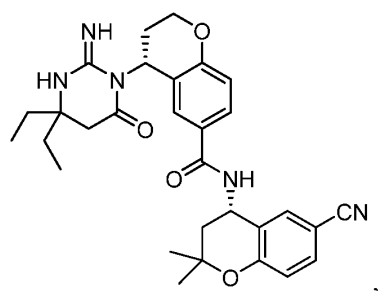
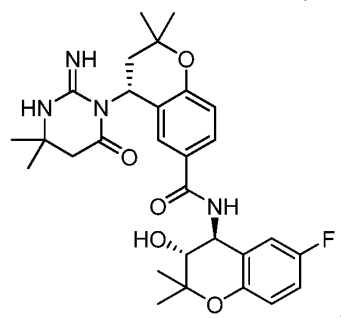
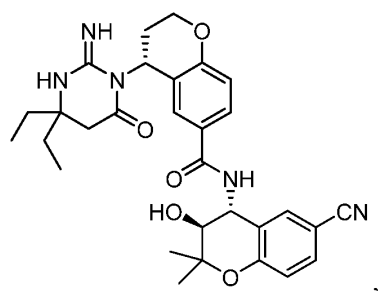
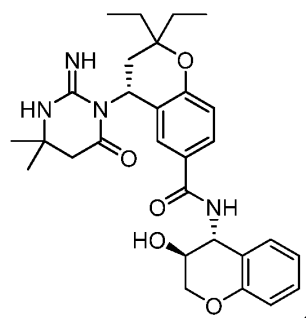
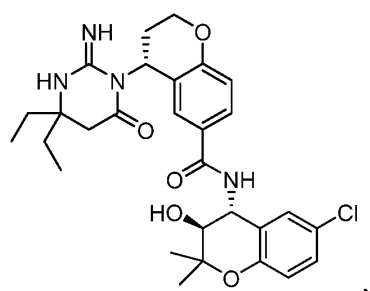


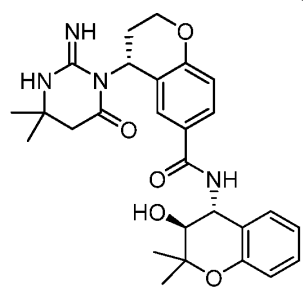
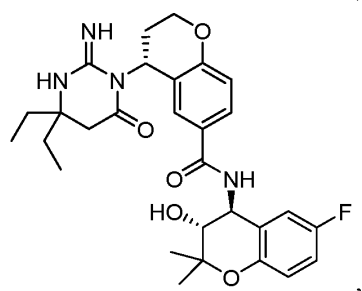
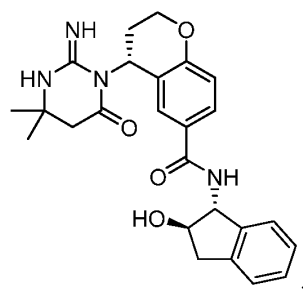
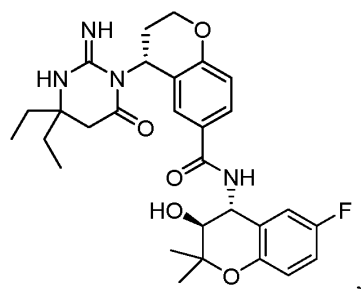
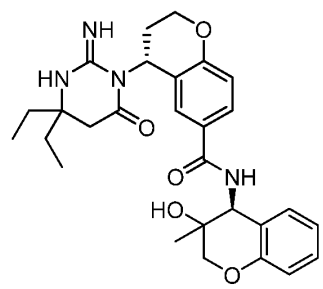
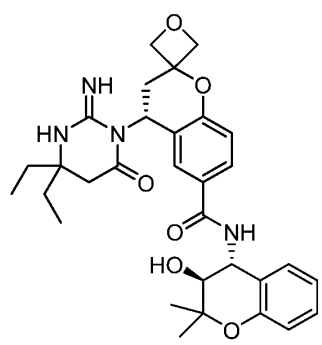
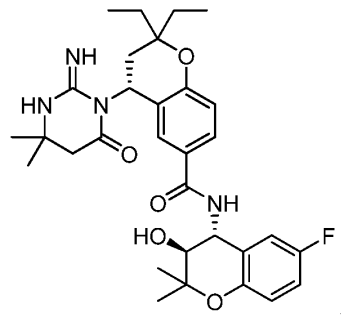
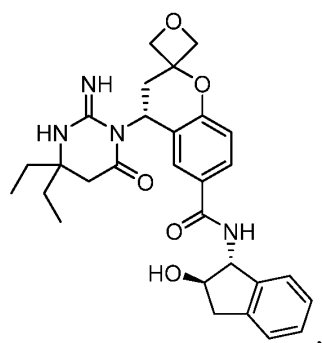


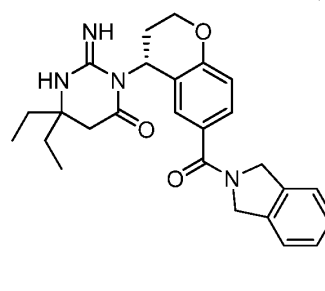
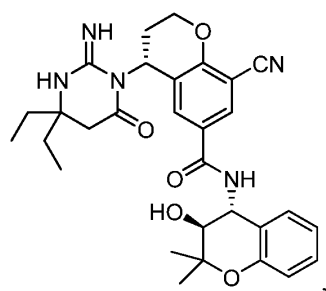
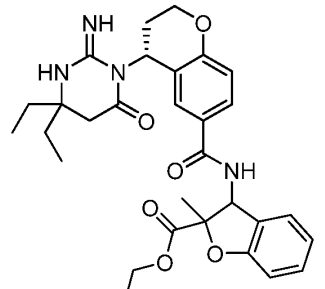
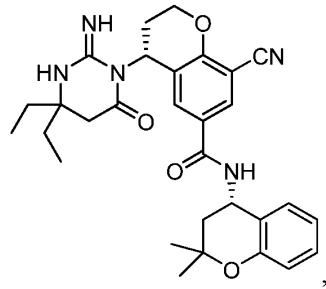
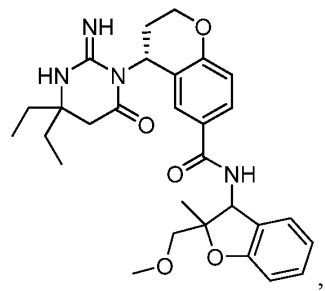
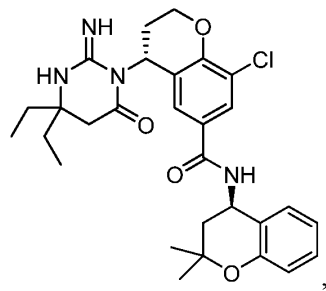
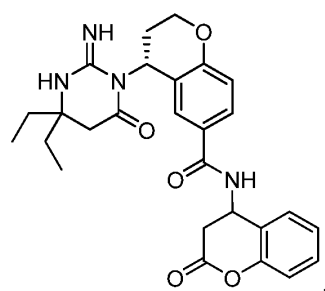
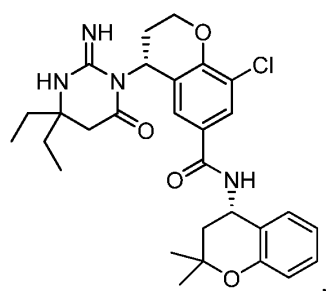


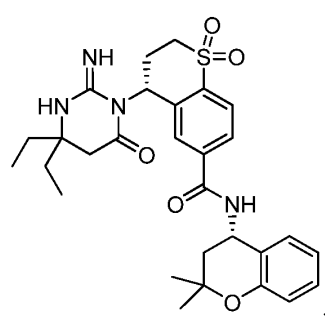
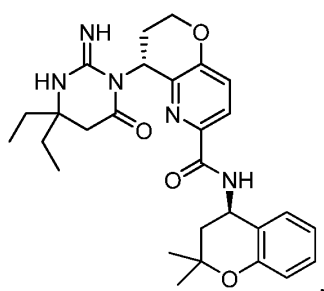
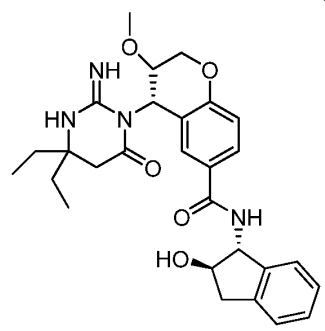
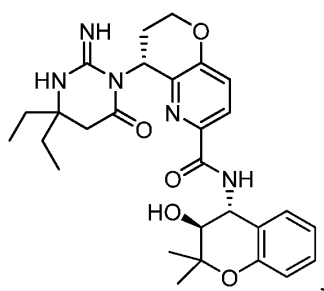
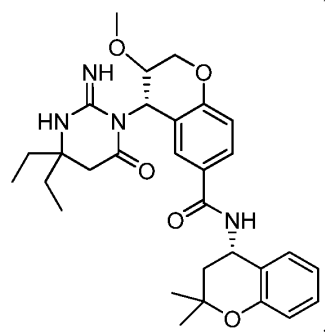
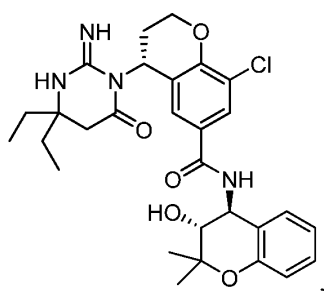
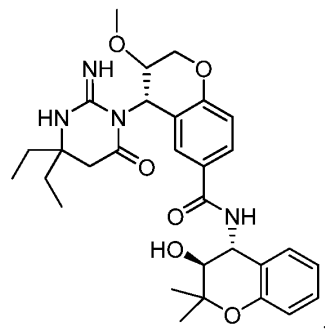
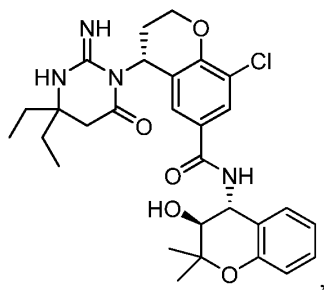


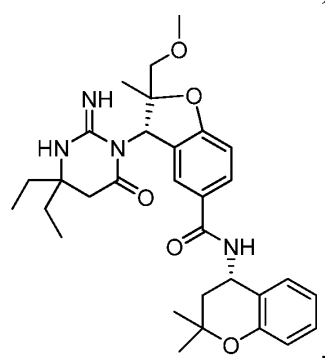
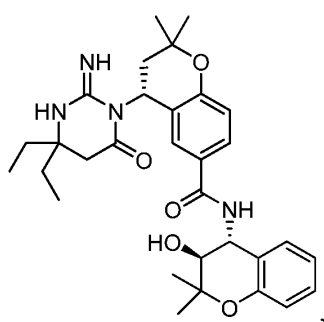
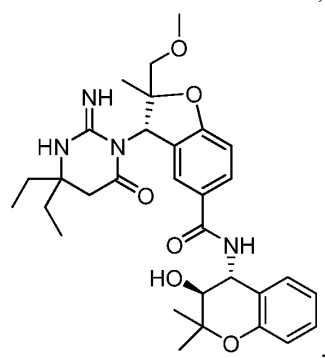
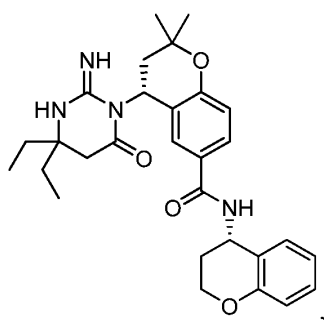
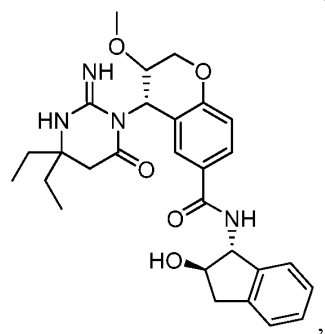
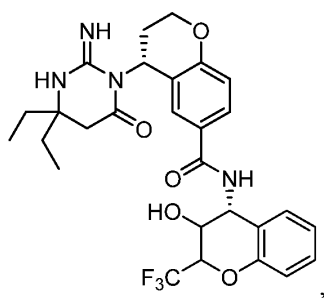
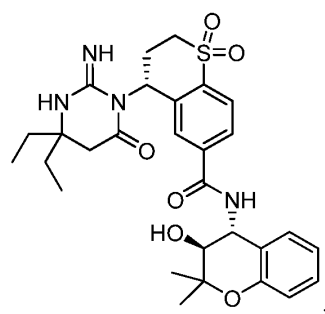
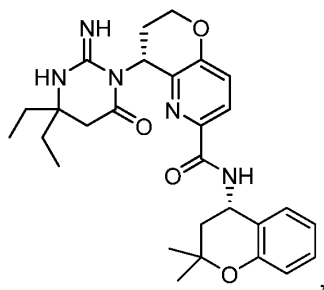


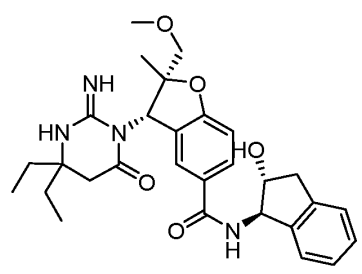
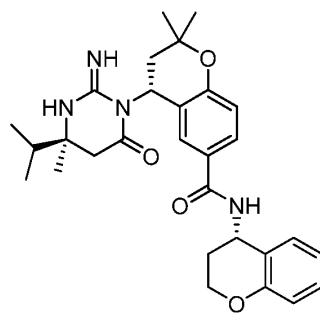
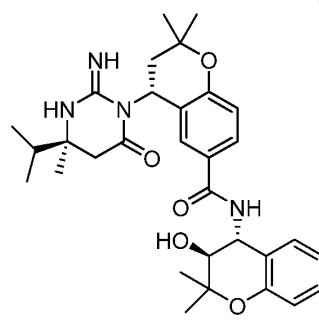
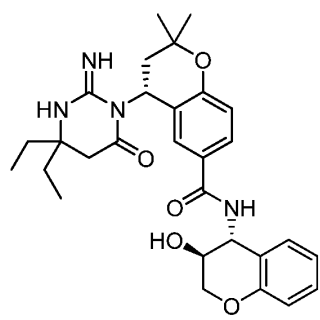
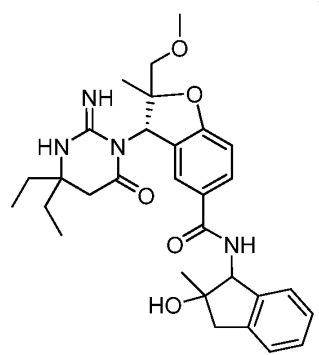
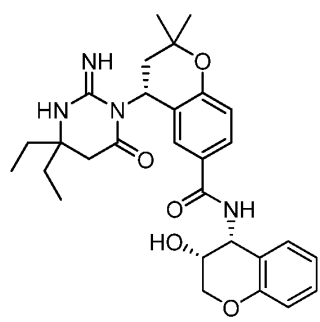
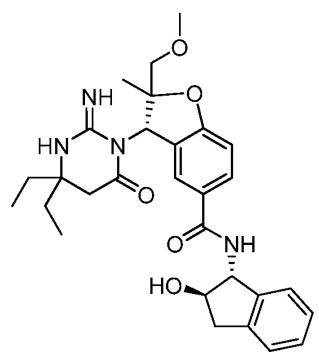
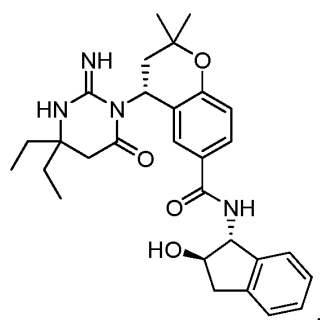


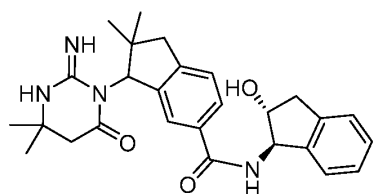
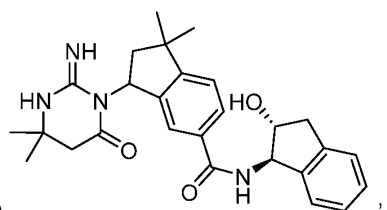
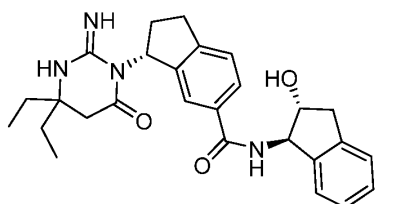
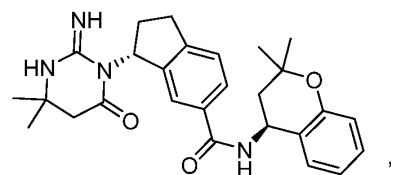
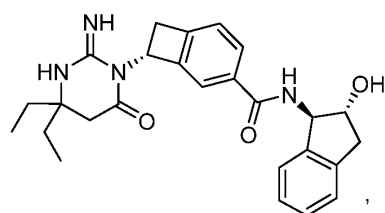
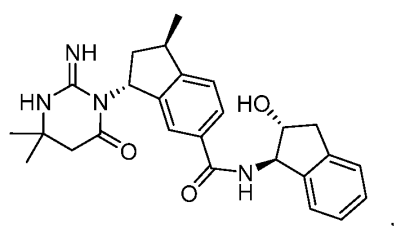
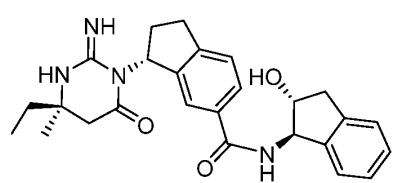
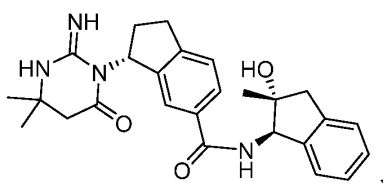
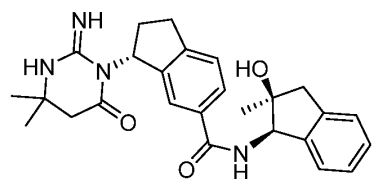
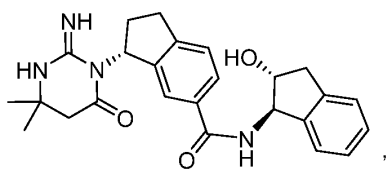


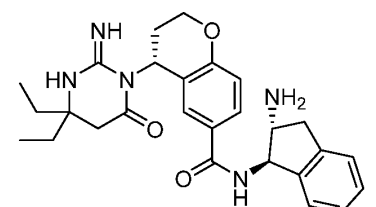
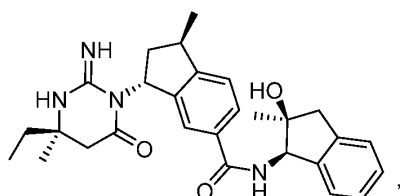
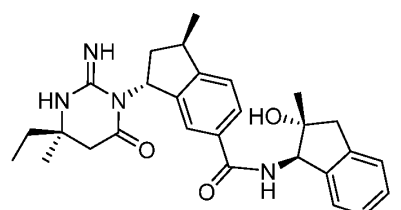
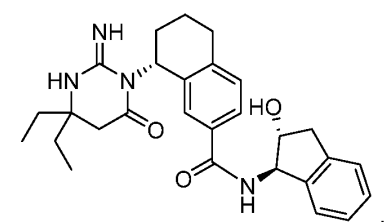
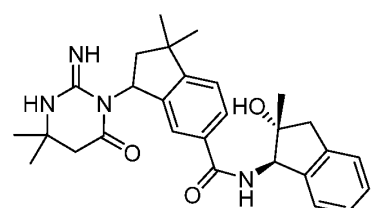
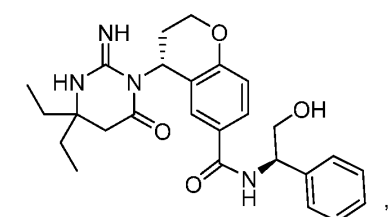
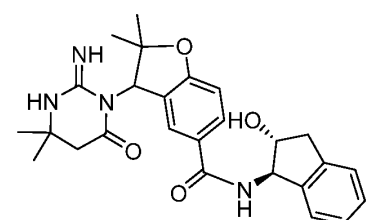
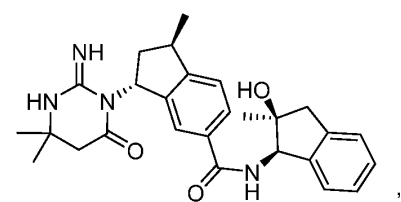
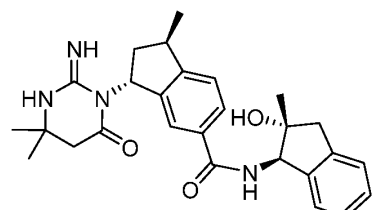
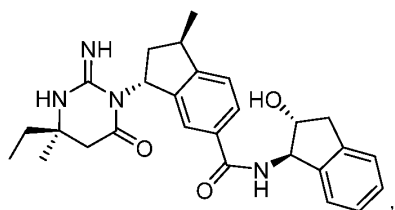


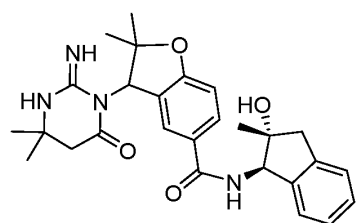
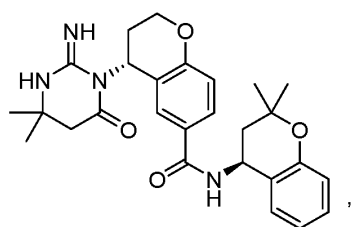
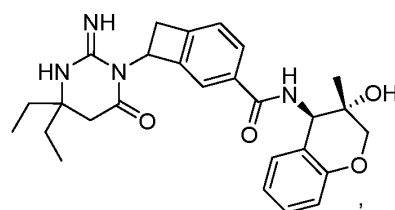
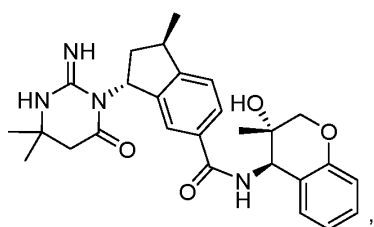
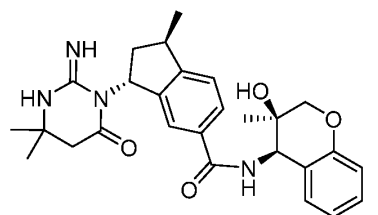
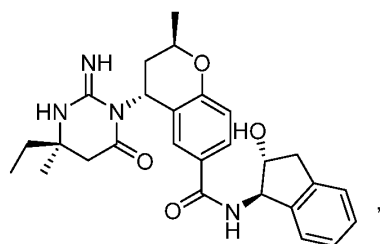
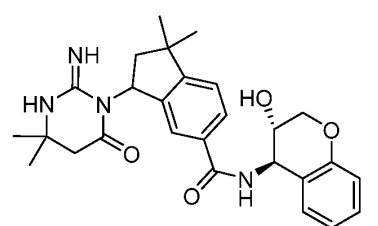
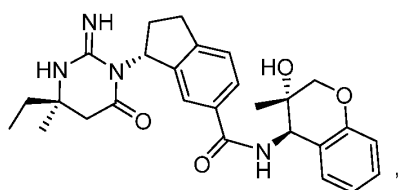
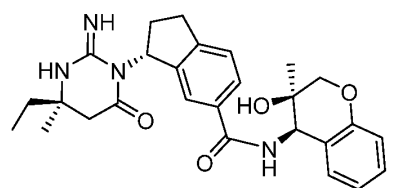
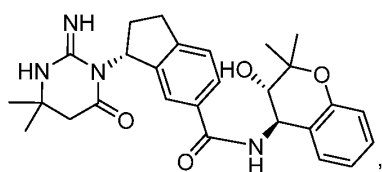


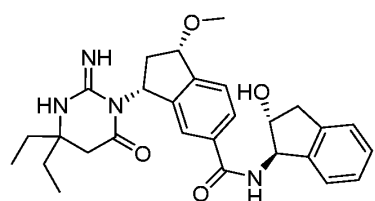
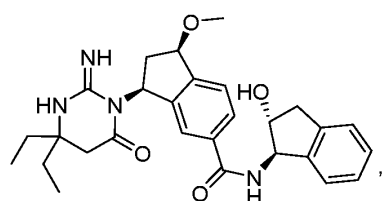
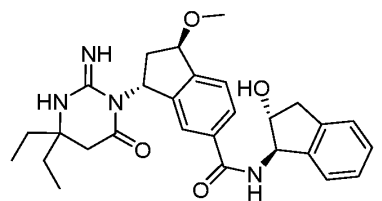
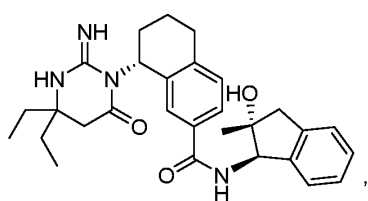
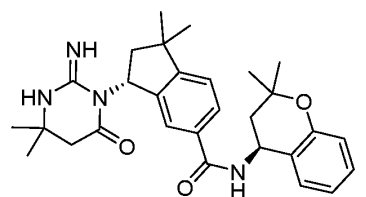
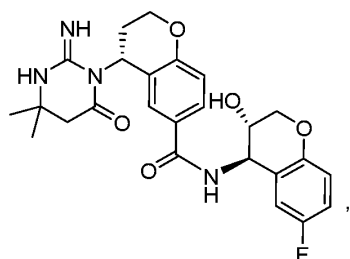
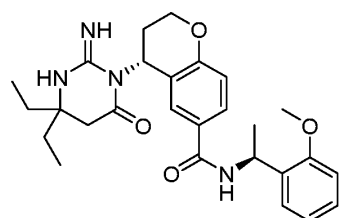
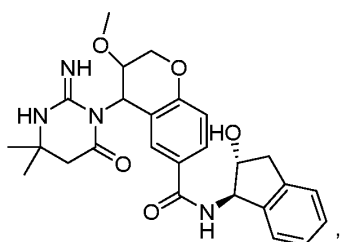
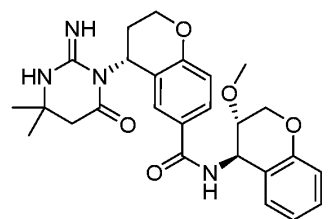
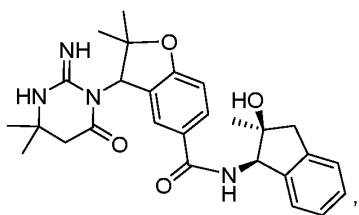


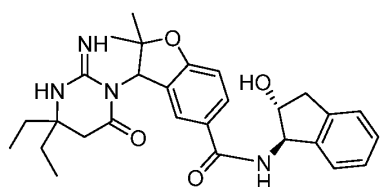
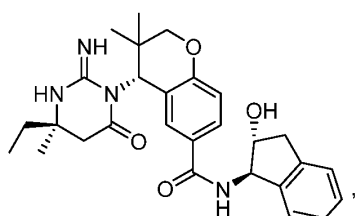
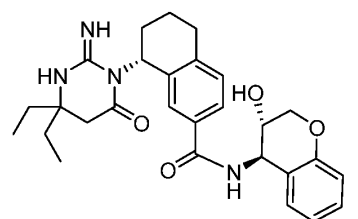
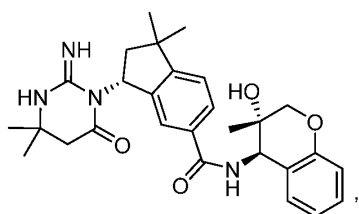
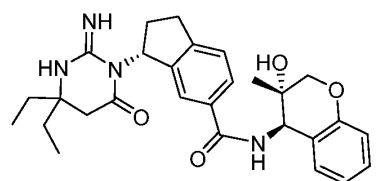
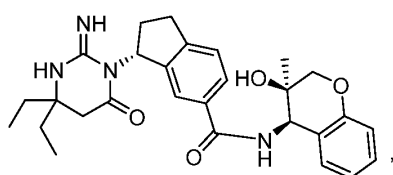
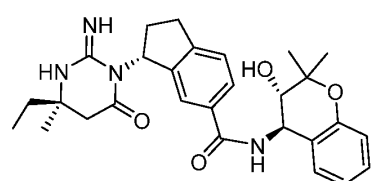
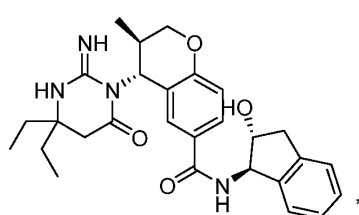
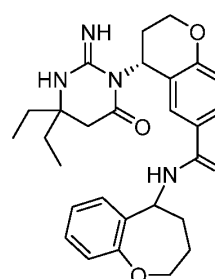
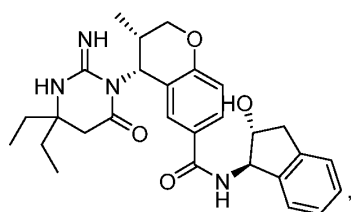


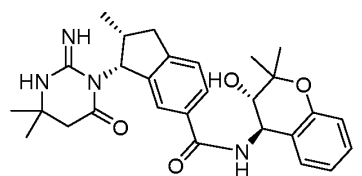
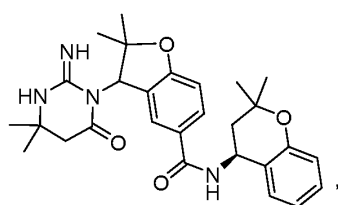
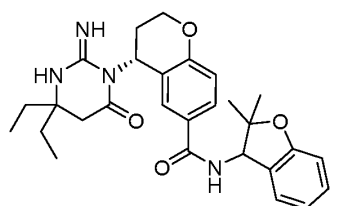
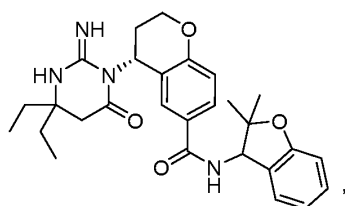
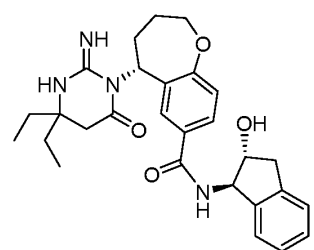
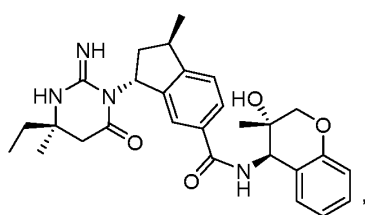
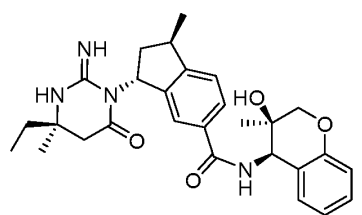
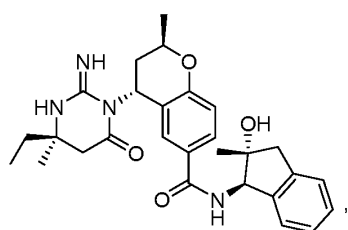
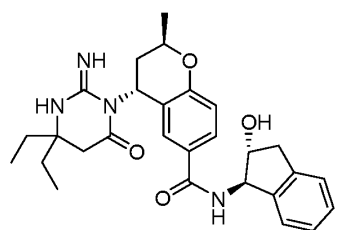
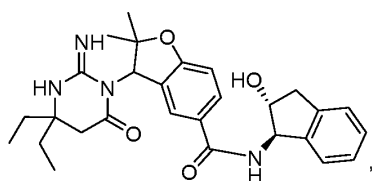


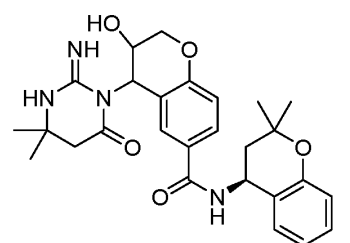
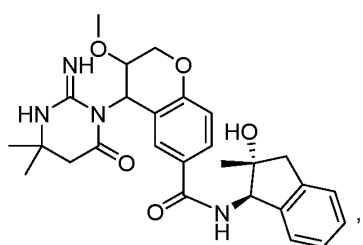
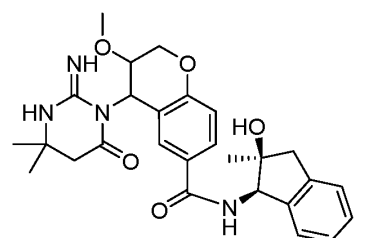
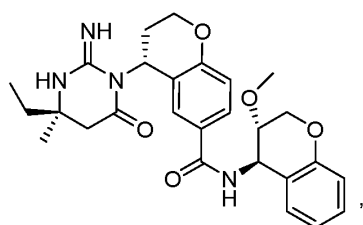
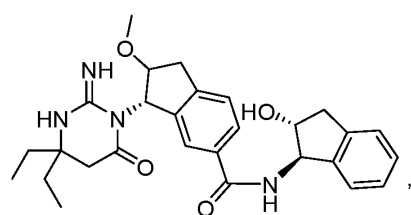
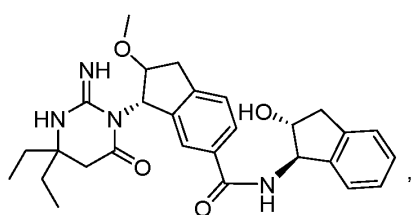
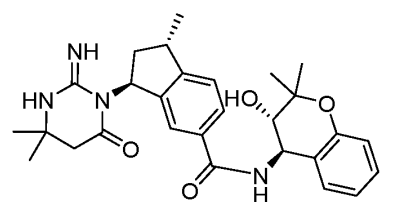
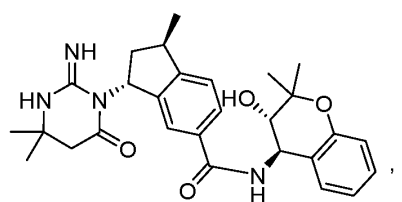
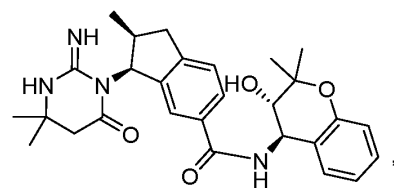
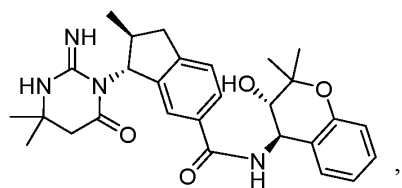


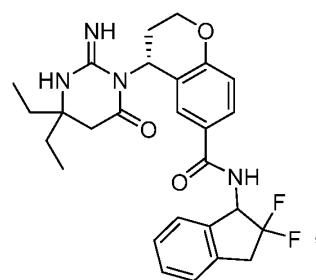
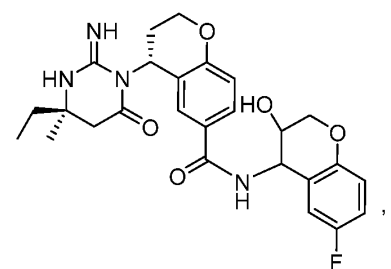
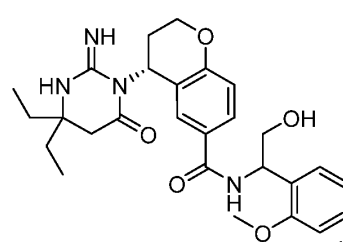
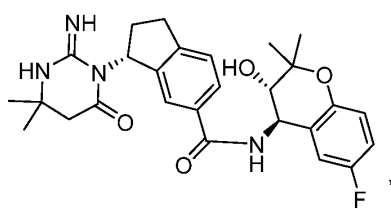
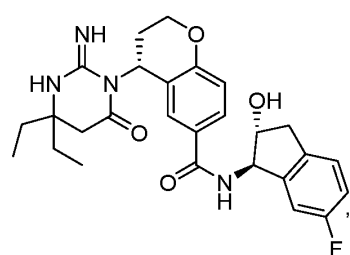
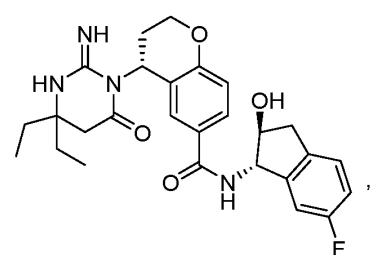
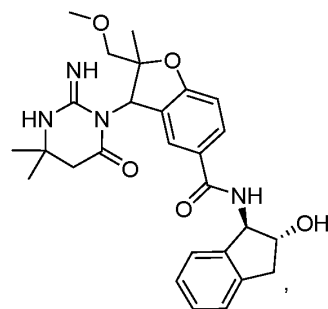
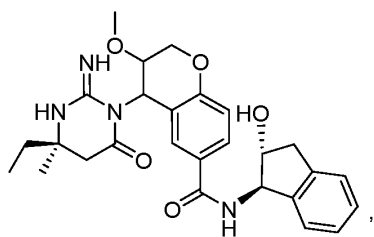


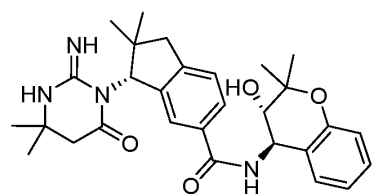
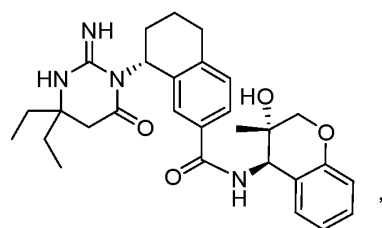
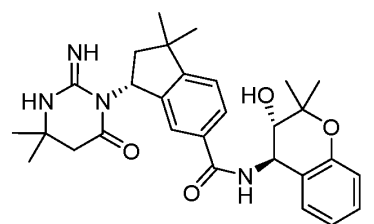
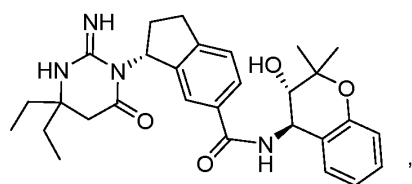
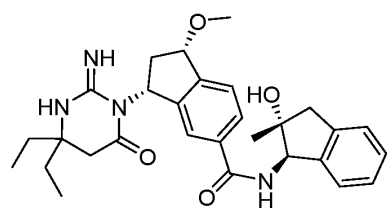
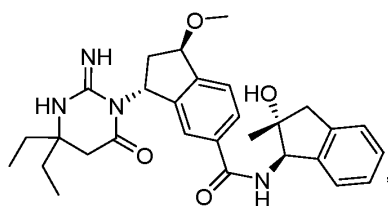
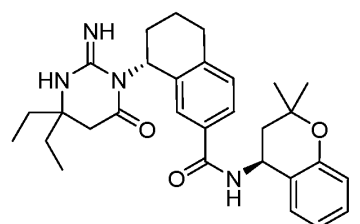
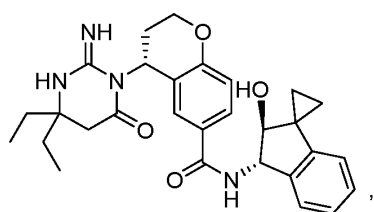
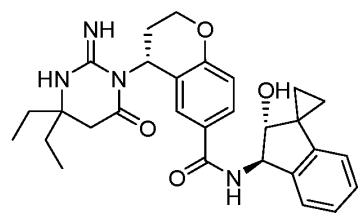
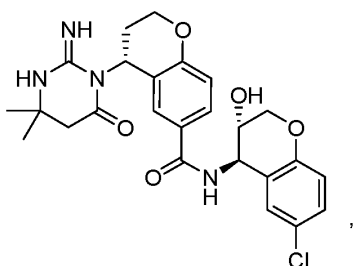


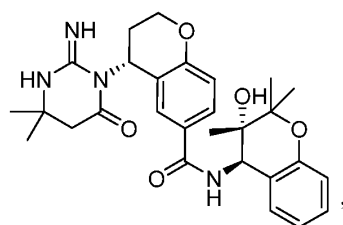
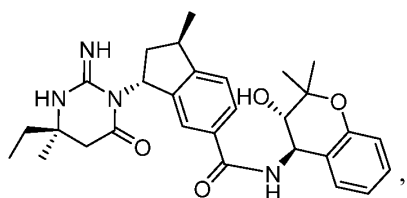
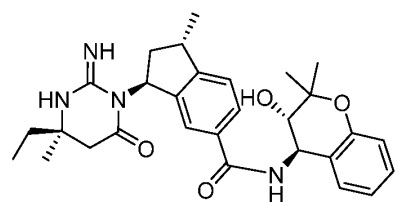
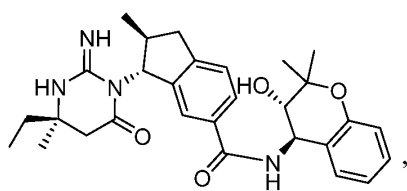
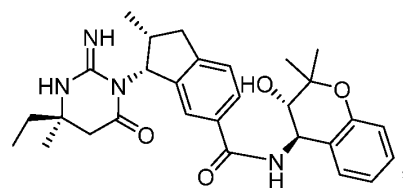
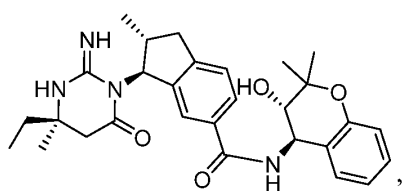
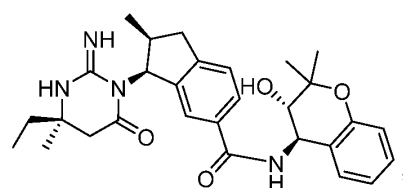
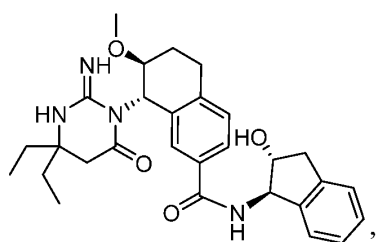
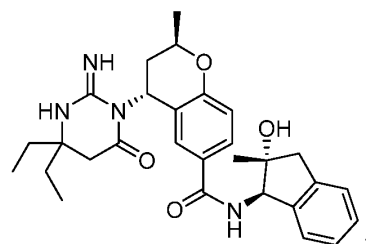
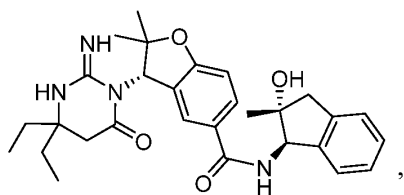


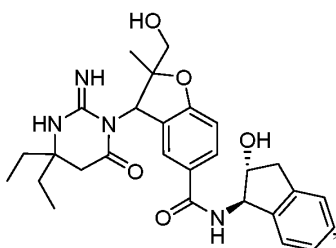
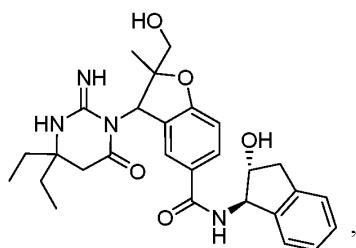
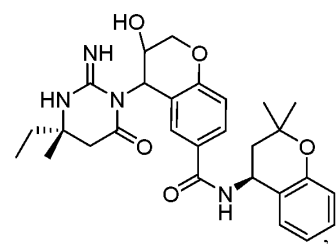
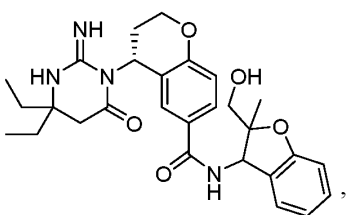
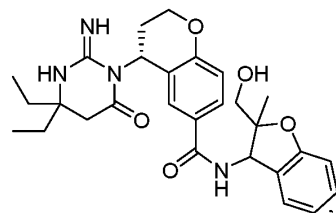
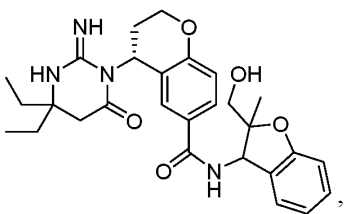
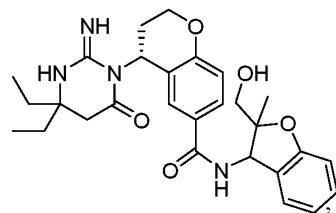
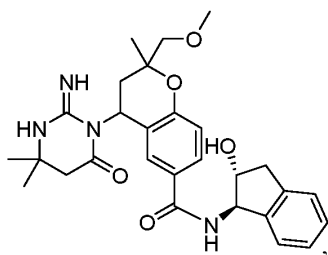
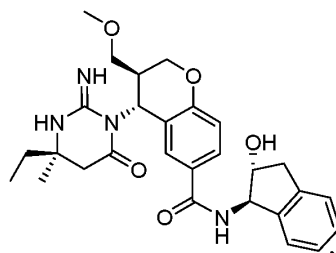
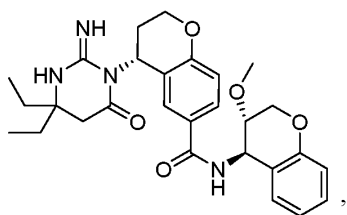


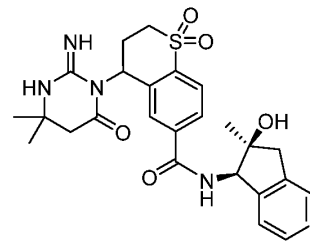
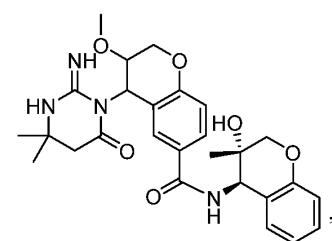
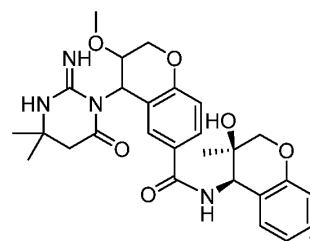
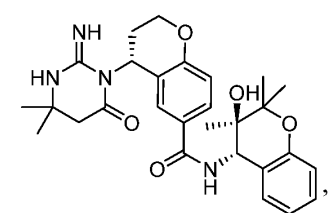
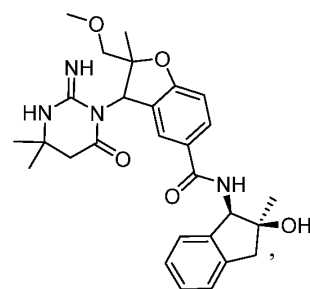
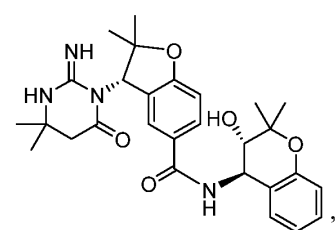
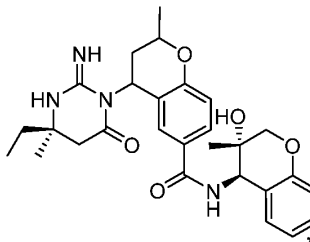
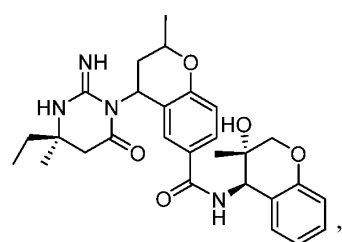
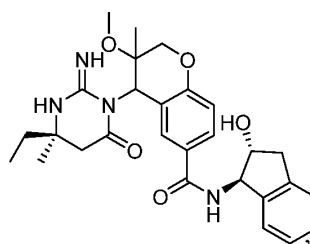
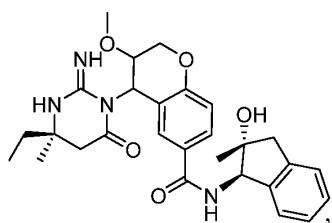


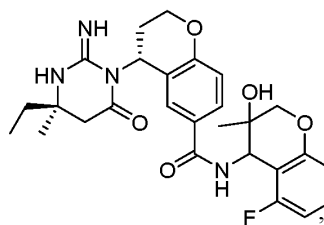
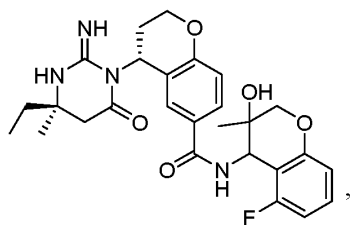
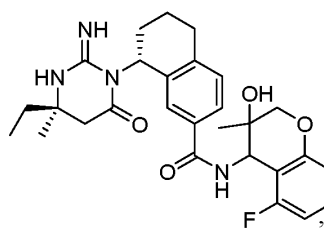
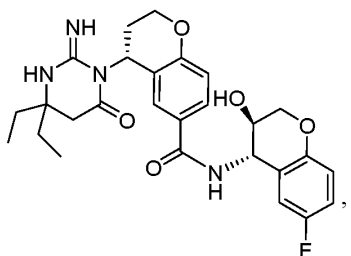
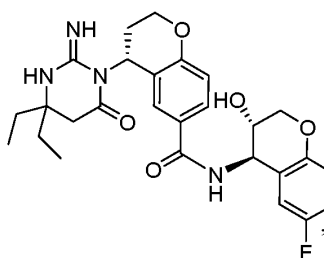
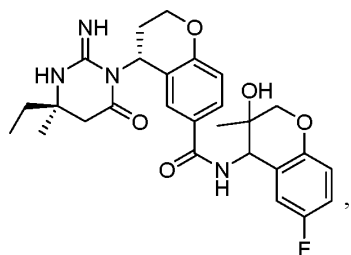
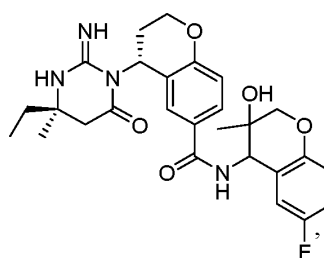
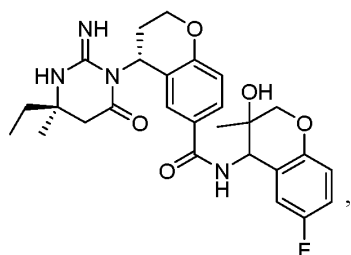
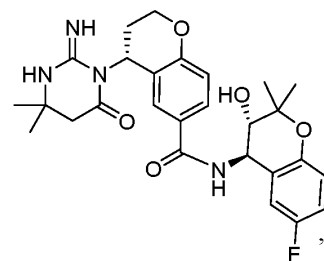
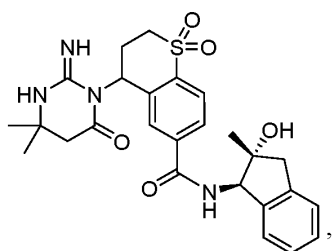


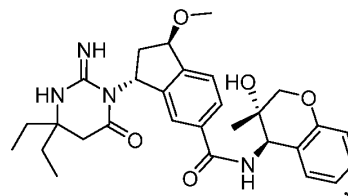
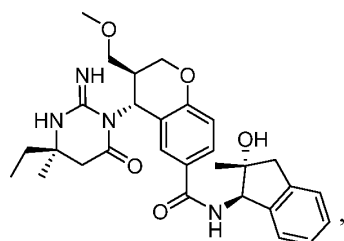
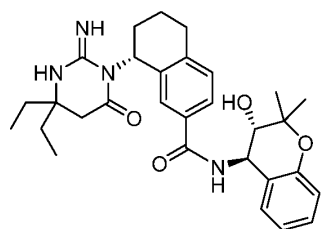
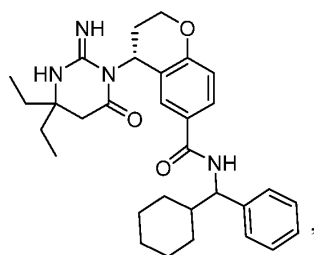
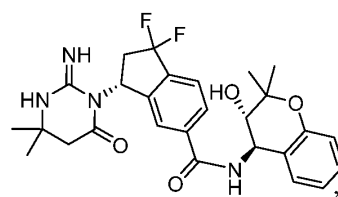
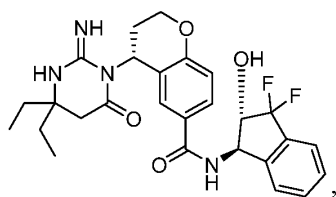
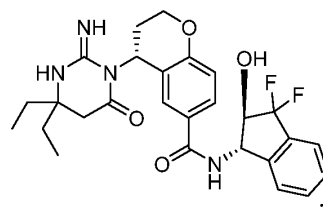
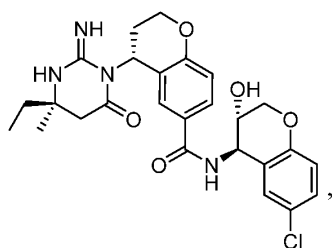
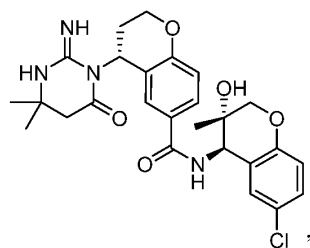
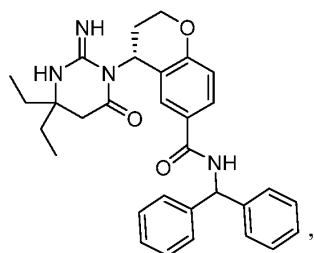


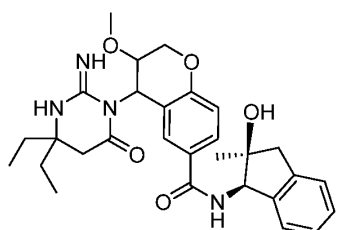
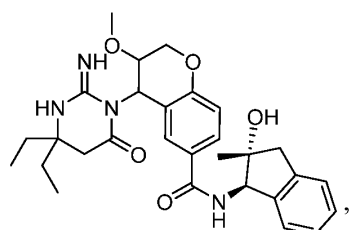
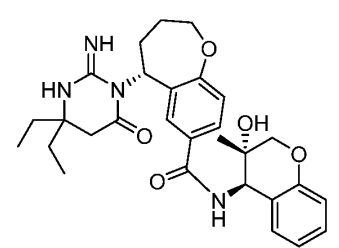
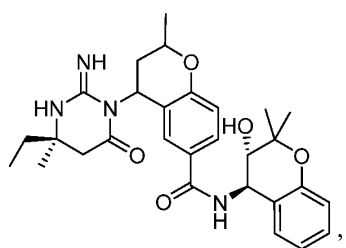
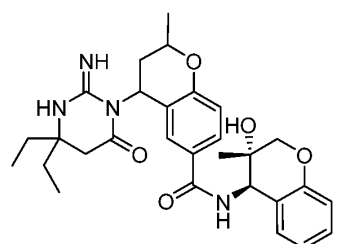
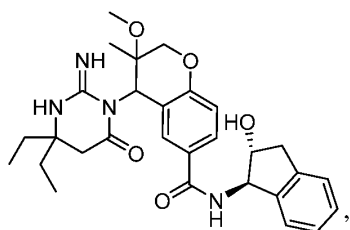
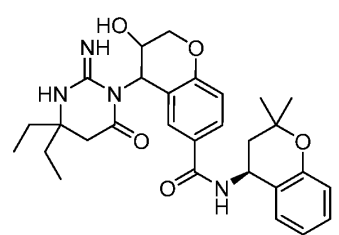
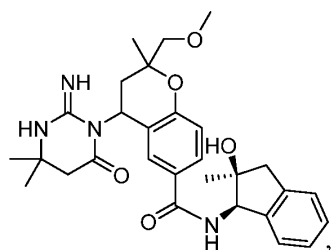
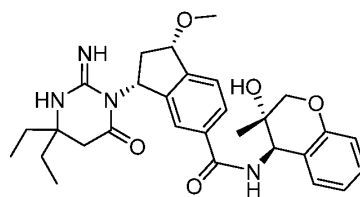
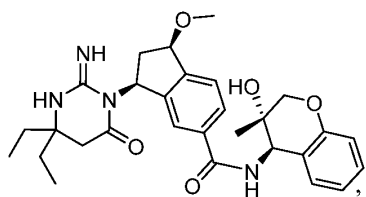


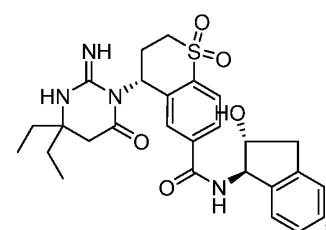
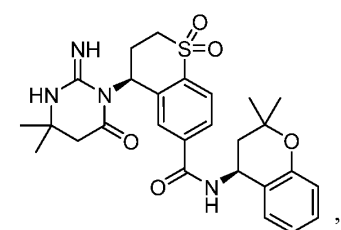
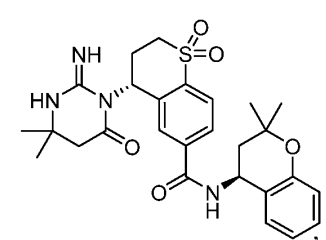
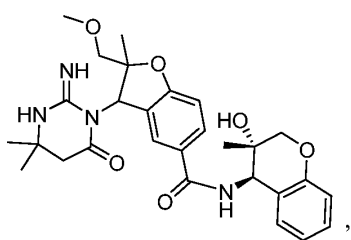
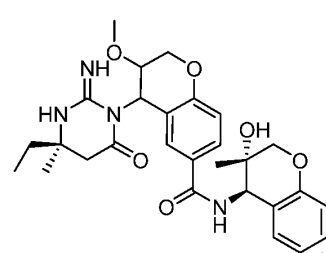
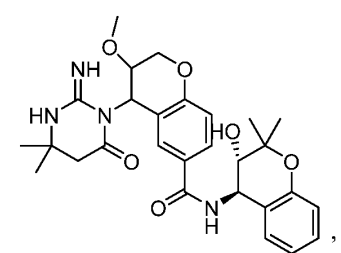
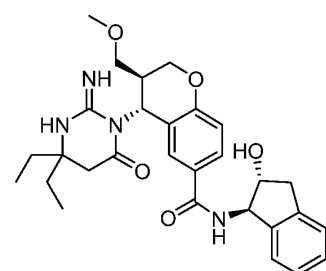
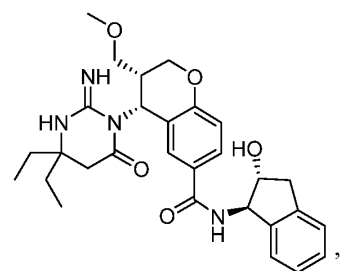
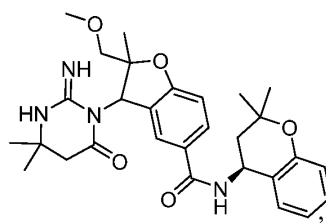
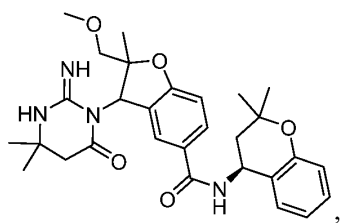


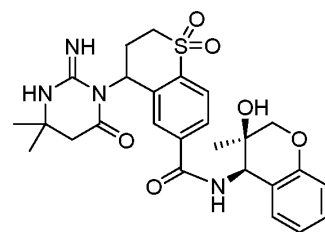
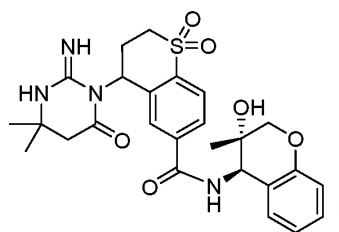
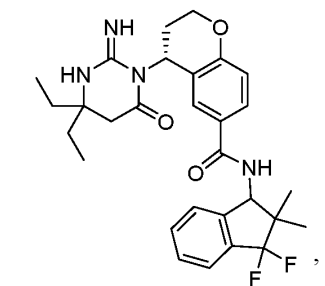
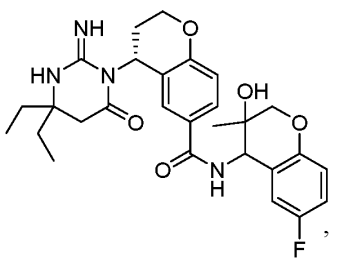
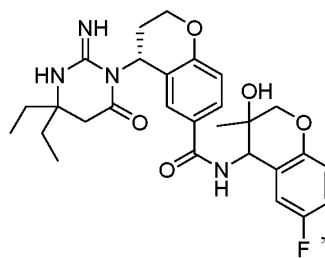
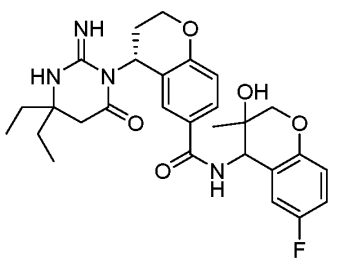
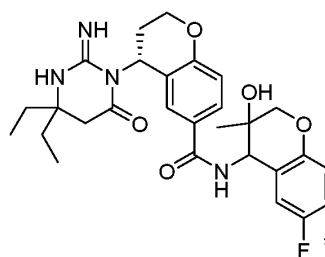
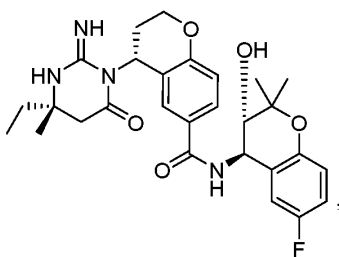
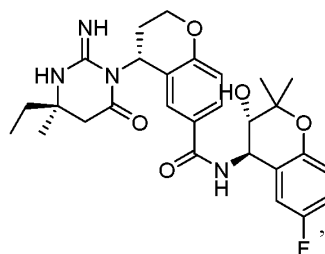
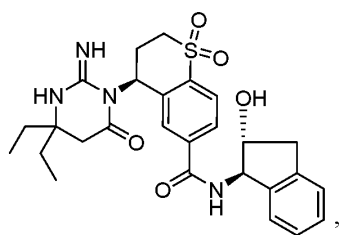


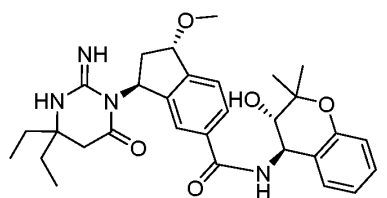
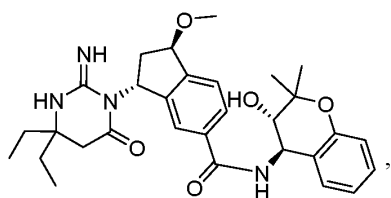
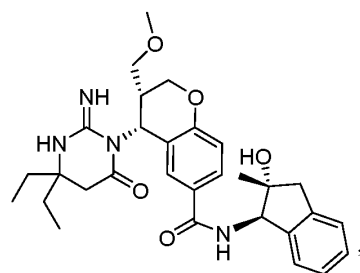
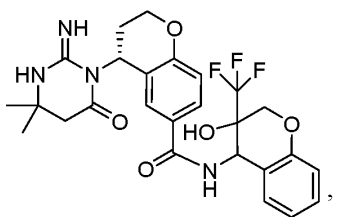
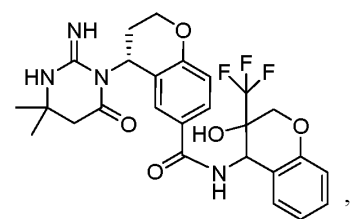
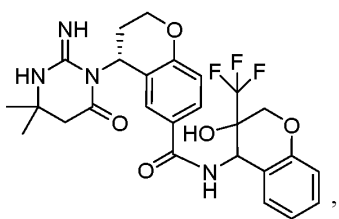
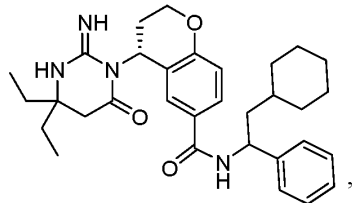
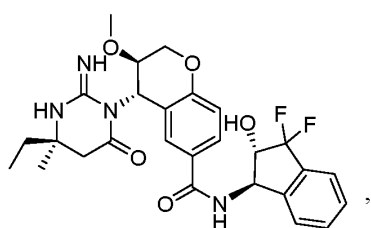
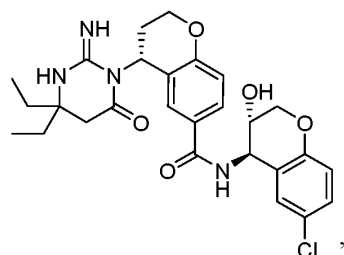
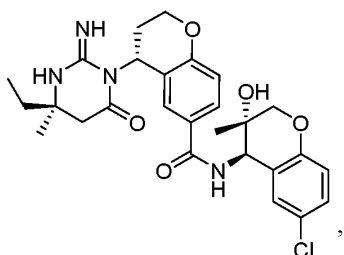


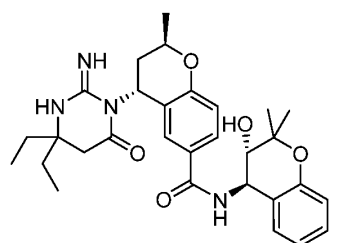
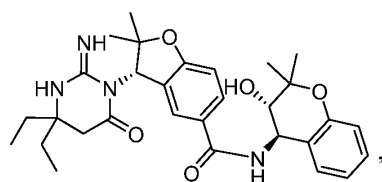
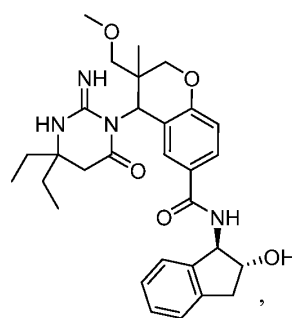
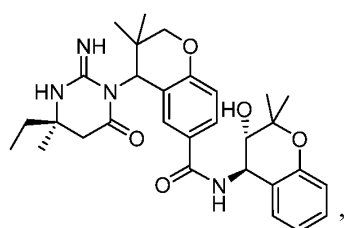
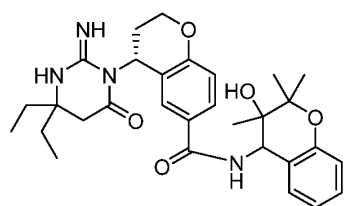
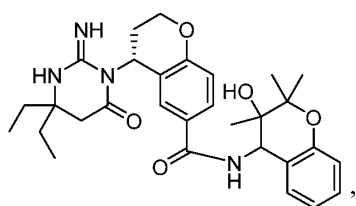
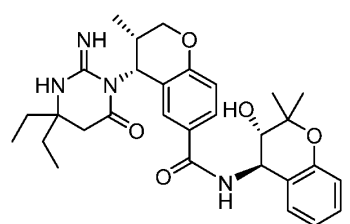
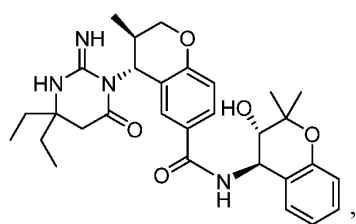
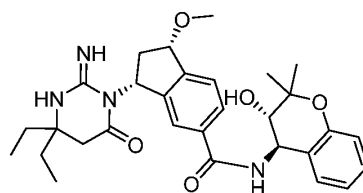
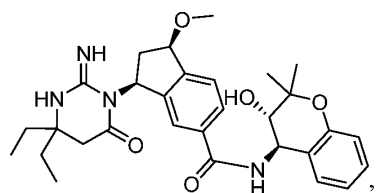


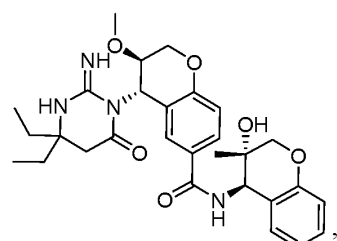
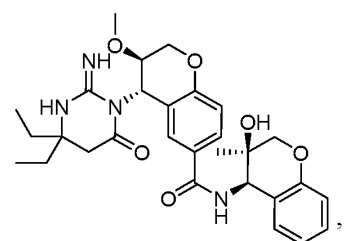
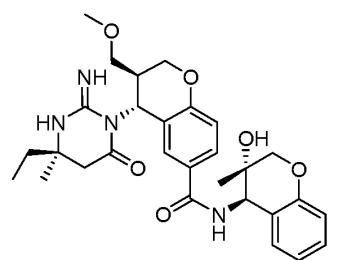
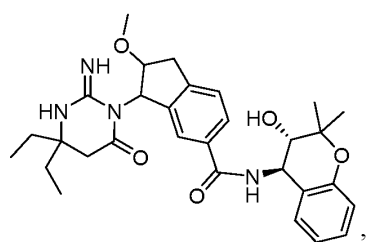
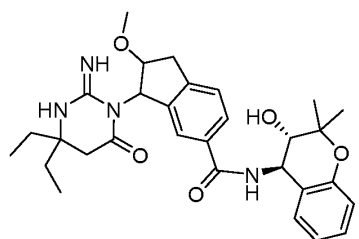
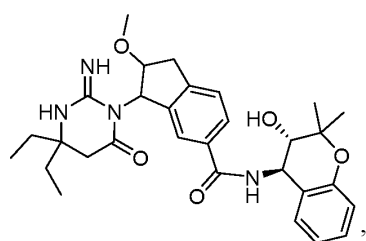
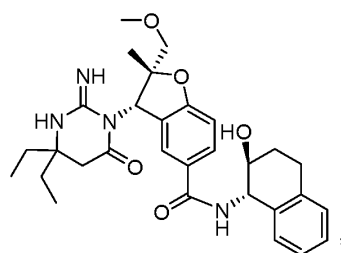
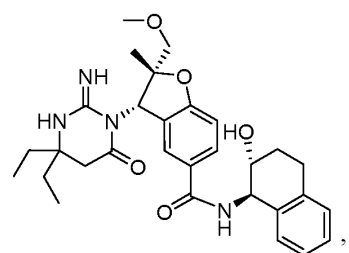
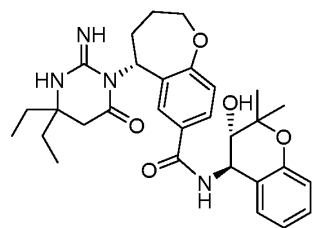
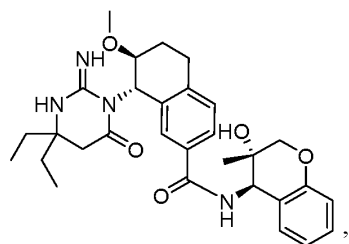


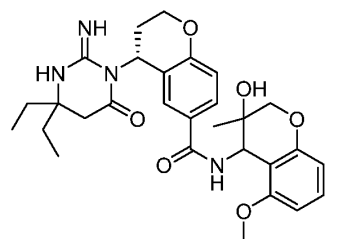
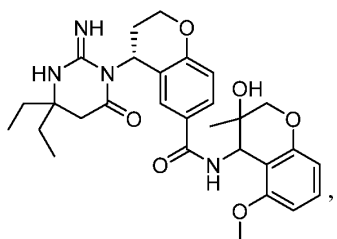
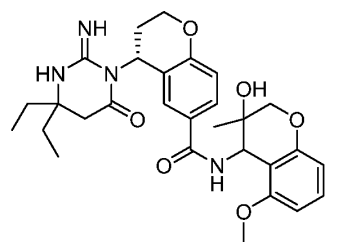
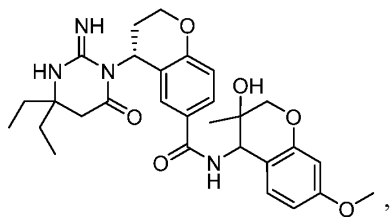
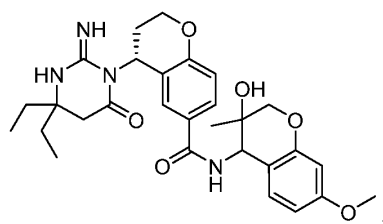
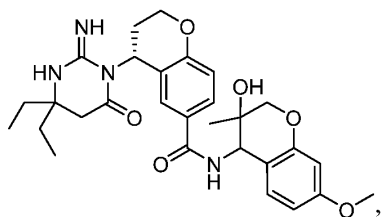
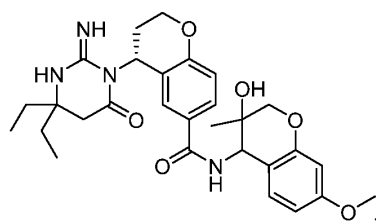
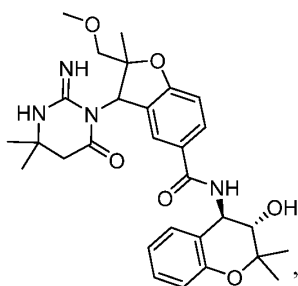
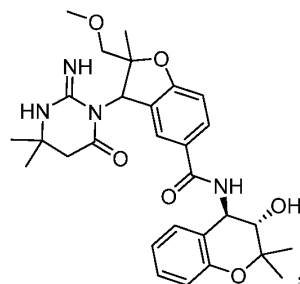
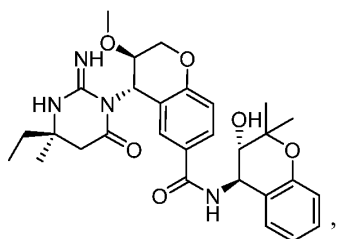


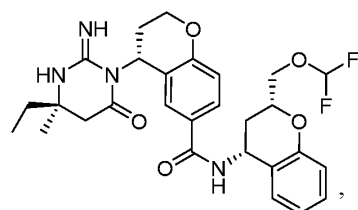
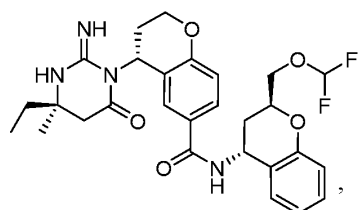
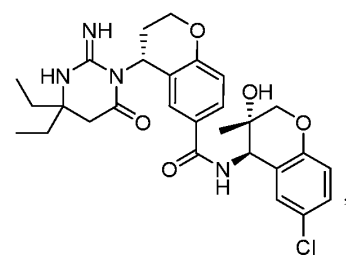
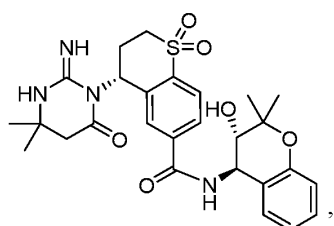
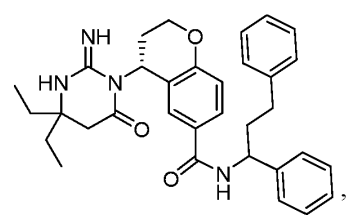
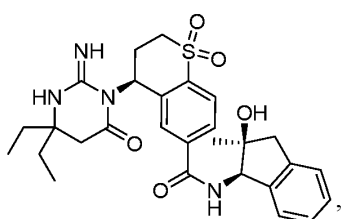
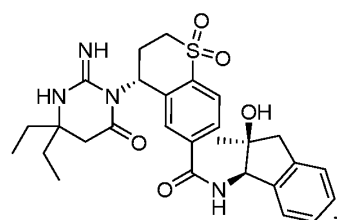
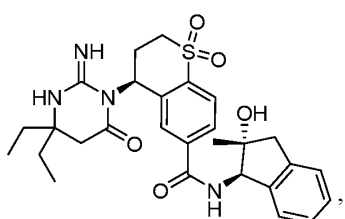
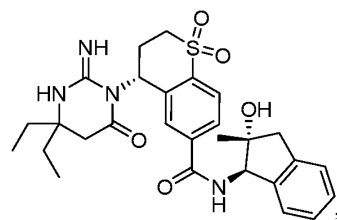
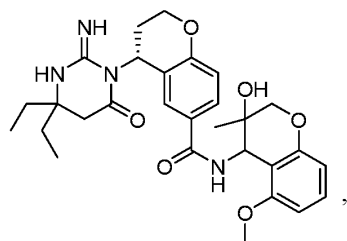


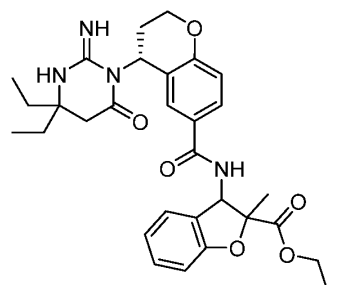
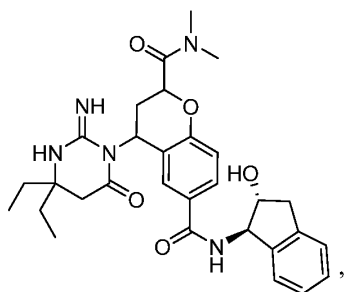
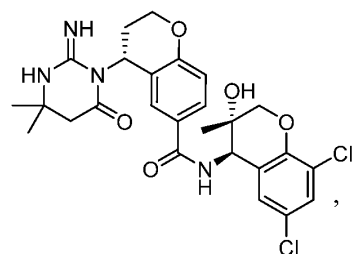
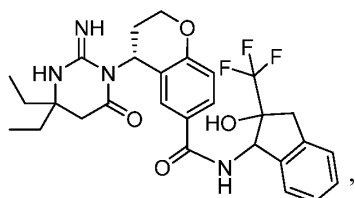
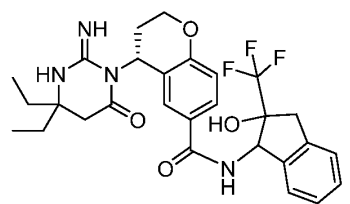
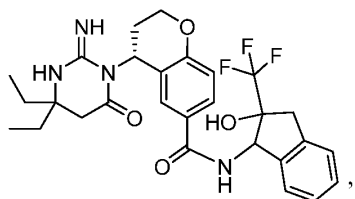
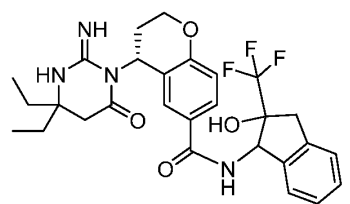
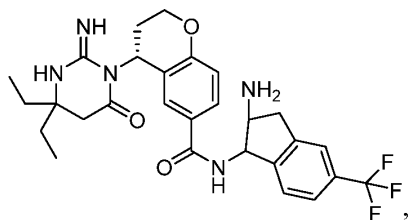
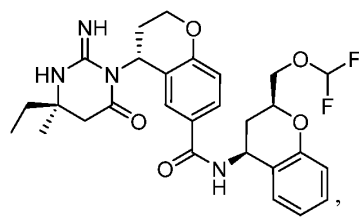
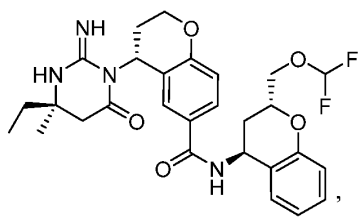


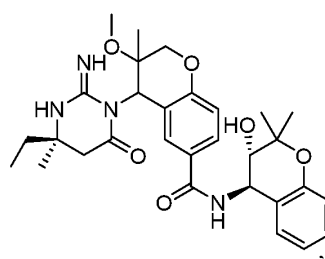
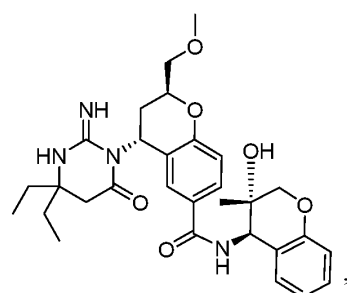
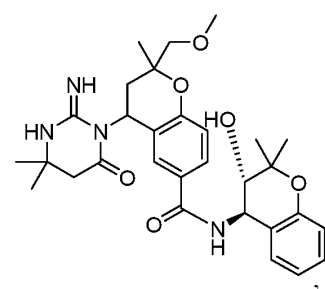
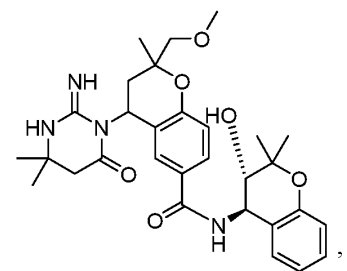
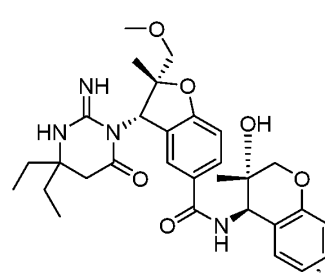
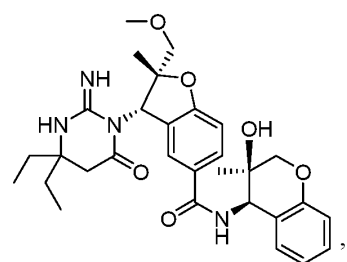
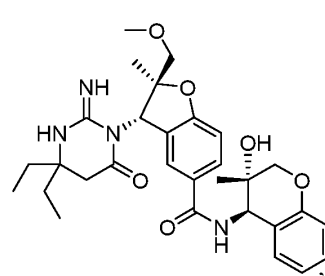
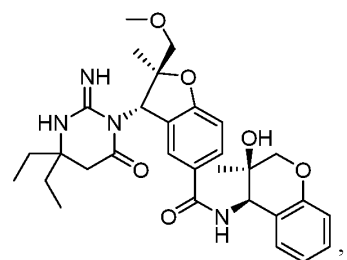
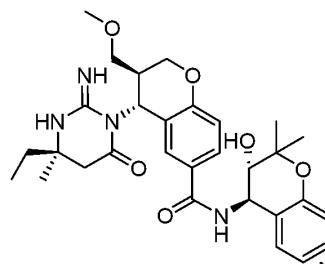
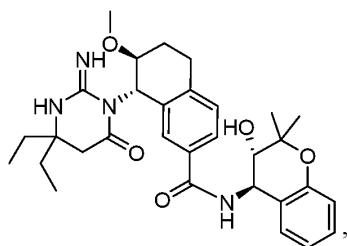


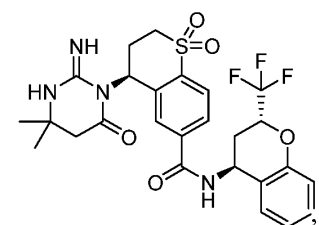
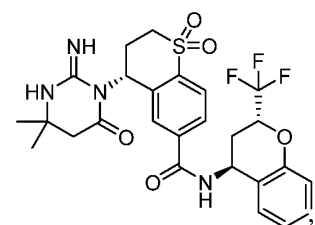
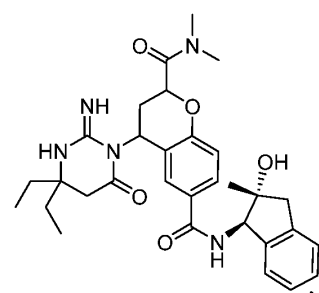
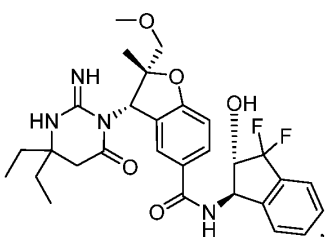
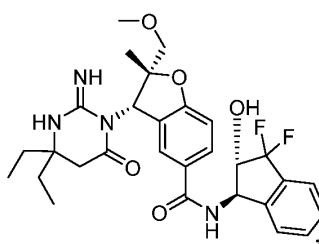
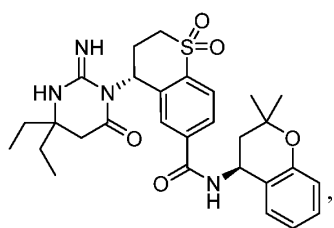
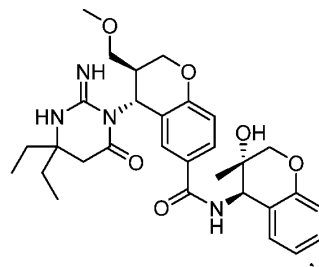
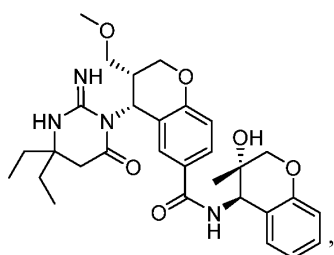
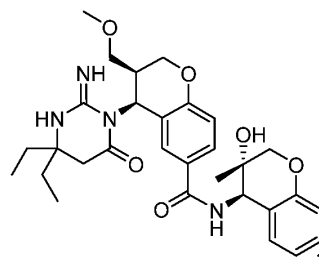
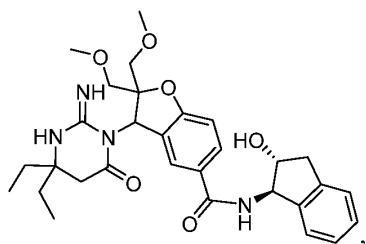


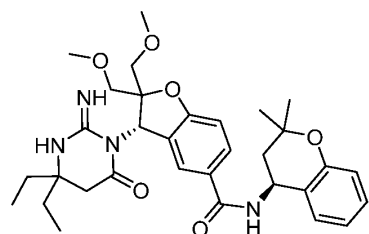
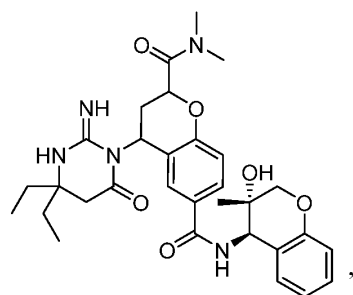
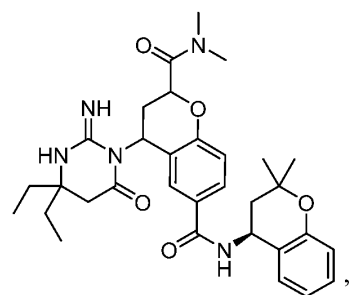
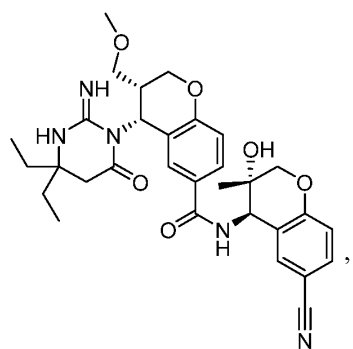
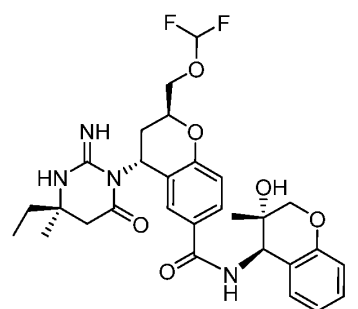
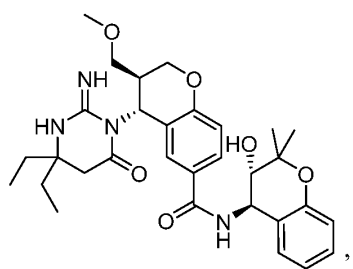
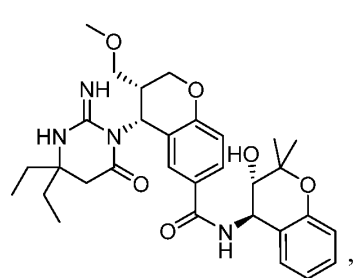
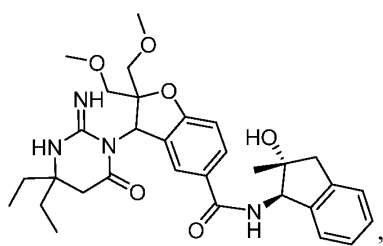
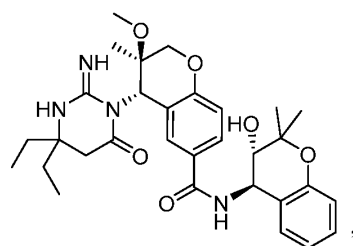
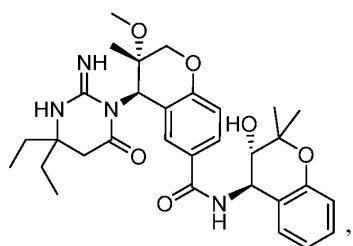


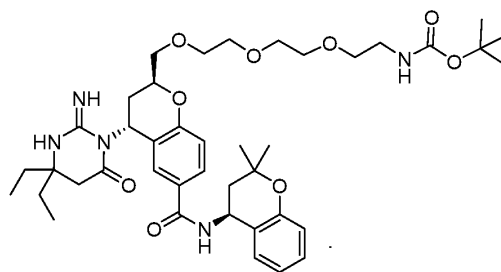
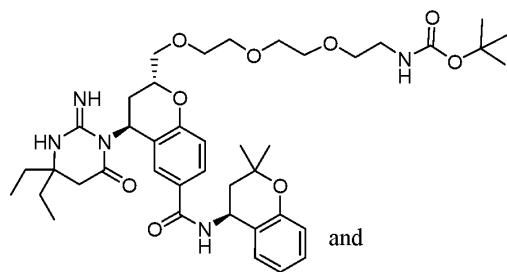
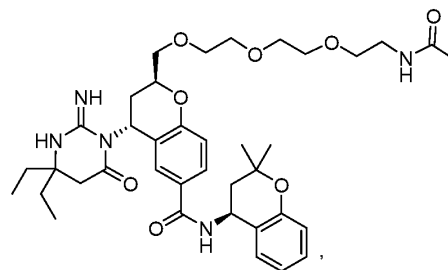
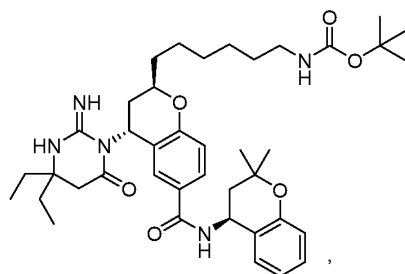
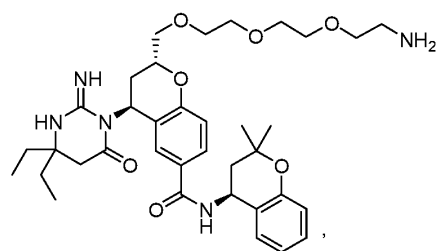
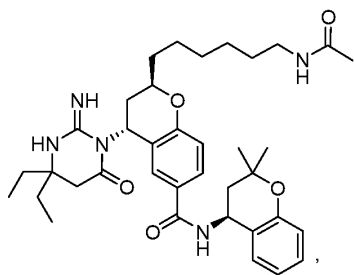
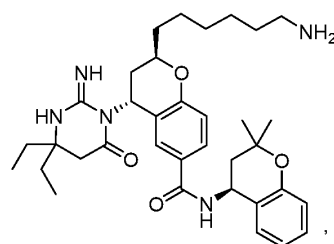
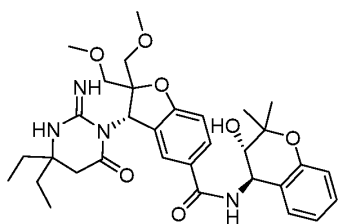
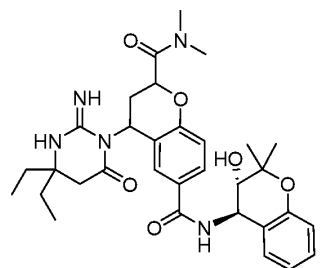
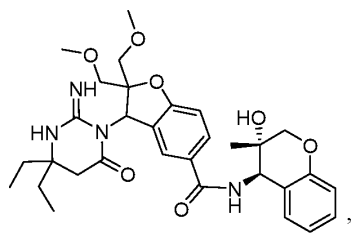




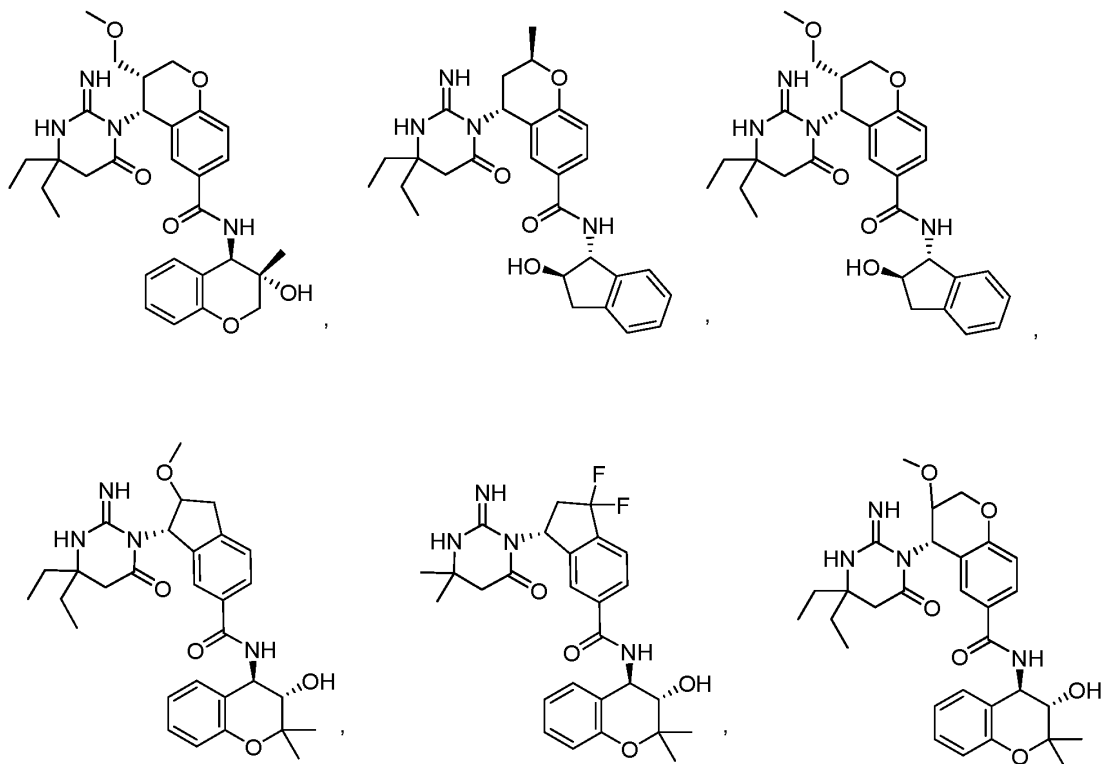


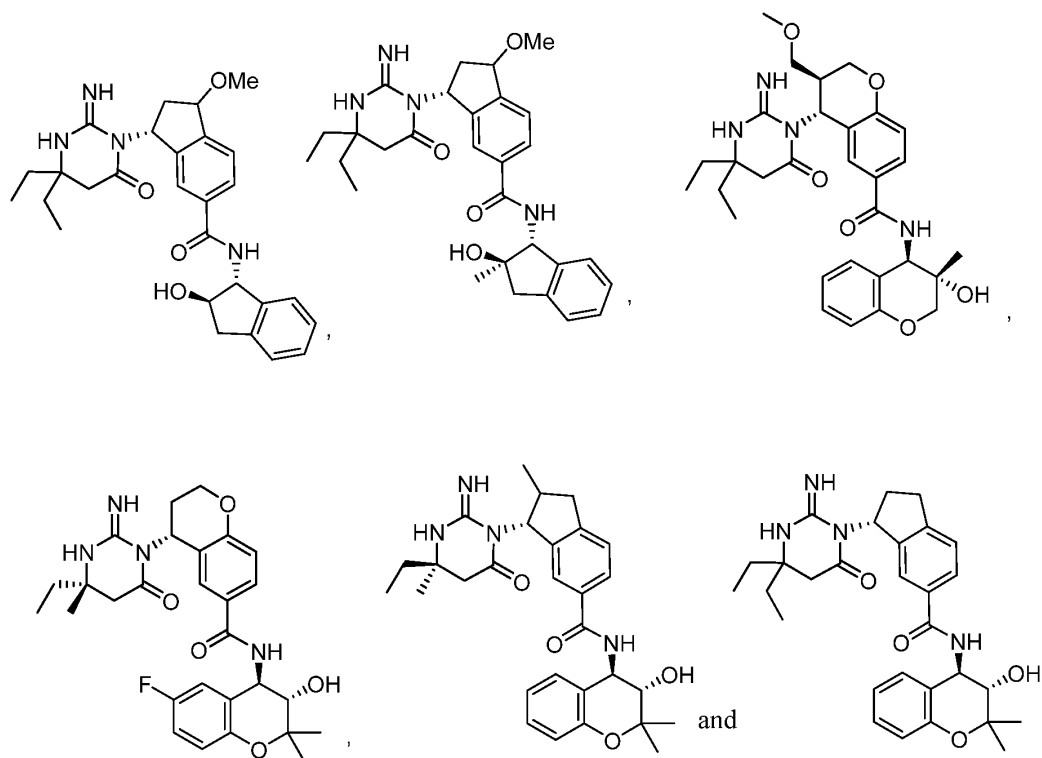




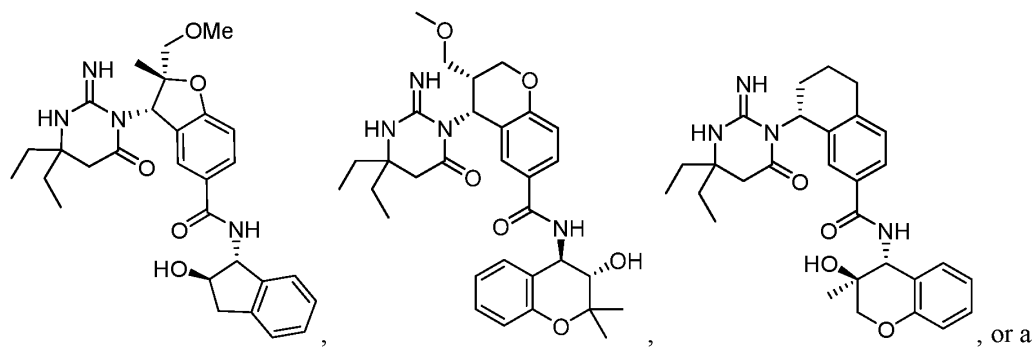


In certain embodiments, the compound is selected from the group consisting of



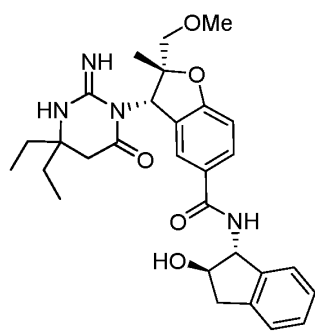


In other embodiments, the compound is selected from the group consisting of



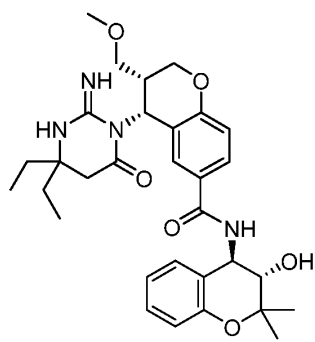
5 pharmaceutically acceptable salt thereof.

In certain embodiments described herein, the compound has the formula:



, or a pharmaceutically acceptable salt thereof.

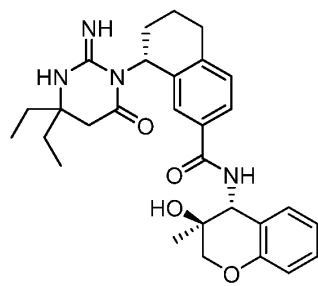
In certain embodiments described herein, the compound has the formula:



, or a pharmaceutically acceptable salt thereof.

5

In certain embodiments described herein, the compound has the formula:



, or a pharmaceutically acceptable salt thereof.

Definitions and Abbreviations:

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.

It shall be understood that, in the various embodiments of the invention described herein, any variable not explicitly defined in the context of the embodiment is as defined in Formula (I').

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

“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.

“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.

“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 invention 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 invention 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 invention is also intended to encompass the administration of the afore-said bulk composition and individual dosage units.

“Halogen” and “halo” mean fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

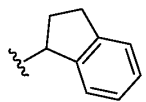
"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. 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.

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

"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.

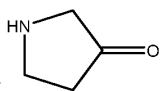
"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 12 carbon atoms, preferably about 3 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 10 ring atoms. The cycloalkyl can be optionally substituted with one or more substituents, which 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. Further non-limiting examples of cycloalkyl include the following:



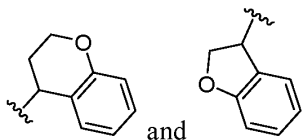
"Heterocycloalkyl" (or "heterocyclyl") means a non-aromatic, saturated or partially saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an

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 invention. 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,



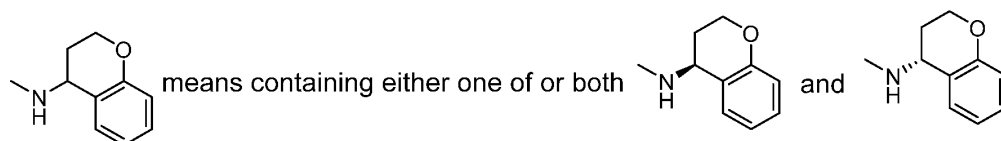
"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, *n*-propoxy, isopropoxy and *n*-butoxy. The bond to the parent moiety is through the ether oxygen.

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.

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

When a variable appears more than once in a group, e.g., R^8 in $-N(R^8)_2$, or a variable appears more than once in a structure presented herein, the variables can be the same or different.

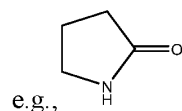
A solid line —, as a bond generally indicates a mixture of, or either of, the possible isomers, e.g., containing (R)- and (S)-stereochemistry. For example:



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.

"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,



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.

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:



5 In another embodiment, the compounds useful in the methods of the invention, 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
10 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
15 vivo or medicinal use and/or characterizable by standard analytical techniques described herein or well known to the skilled artisan.

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.

20 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.

25 Another embodiment provides prodrugs and/or solvates of the compounds of the invention. 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 invention 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.

For example, if a compound useful in the methods of the invention 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.

Similarly, if a compound used in the methods of the invention 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.

If a compound used in the methods of the invention 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, $-C(OH)C(O)OY^1$ wherein Y^1 is H, (C₁-C₆)alkyl or benzyl, $-C(OY^2)Y^3$ wherein Y^2 is (C₁-C₄) alkyl and Y^3 is (C₁-C₆)alkyl, carboxy (C₁-C₆)alkyl, amino(C₁-C₄)alkyl or mono-N- or di-N,N-(C₁-C₆)alkylaminoalkyl, $-C(Y^4)Y^5$ wherein Y^4 is H or methyl and Y^5 is mono-N- or di-N,N-(C₁-C₆)alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

5 One or more compounds used in the methods of the invention 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 invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of the invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent
10 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.

15 One or more compounds used in the methods of the invention 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.*,
20 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
25 the crystals as a solvate (or hydrate).

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

30 Another embodiment provides pharmaceutically acceptable salts of the compounds to be used in the methods of the invention. Thus, reference to a compound used in the methods of the invention 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 invention 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 invention may be formed, for example, by reacting a compound of the invention 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.

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. 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.

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.

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

Another embodiment provides pharmaceutically acceptable esters of the compounds used in the methods of the invention. 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, phenoxyethyl), 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.

As mentioned herein, another embodiment provides tautomers of the compounds of the invention 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 invention. For example, all keto-enol and imine-enamine forms of the compounds, when present, are included in the invention.

The compounds used in the methods of the invention 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 invention as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention embraces use of all geometric and positional isomers. For example, if a compound used in the methods of the invention 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 invention.

Another embodiment provides for diastereomeric mixtures and individual enantiomers of the compounds used in the methods of the invention. 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 invention may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the compounds used in the methods of the invention (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 invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). (For example, if a compound of the invention 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 invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the methods of the invention).

Individual stereoisomers of the compounds of the invention 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 invention 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.

Another embodiment provides isotopically-labelled compounds to be used in the methods the invention. 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 invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively.

Certain isotopically-labelled compounds of the invention (e.g., those labeled with ^3H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^3H) and carbon-14 (i.e., ^{14}C) 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.

Isotopically labelled compounds of the invention 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.

In the compounds used in the methods of the invention, 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 invention is meant to include all suitable isotopic variations of the compounds of the invention. For example, different isotopic forms of hydrogen (H) include protium (^1H) and deuterium (^2H). The presence of deuterium in the compounds of the invention 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 invention 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.

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

Methods of Treatment

The present invention 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 invention comprise administration of a compound of Formula (I') or (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the compounds of Formula (I') or (I), or a pharmaceutically acceptable salt thereof, are administered in the form of a pharmaceutical composition, further comprising a pharmaceutically acceptable carrier or excipient.

The present invention 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') or (I) described in the Summary of the Invention. In some embodiments, the compounds of Formula (I') or (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*.

The invention also relates to the use of a compound of Formula (I'), (I), (IA), (IB), (IC), (ID) or (IE) or a pharmaceutically acceptable salt thereof for inhibiting plasmepsin X activity, for treating a *Plasmodium* infection, or for treating malaria. The invention further relates to the use of a compound of Formula (I'), (I), (IA), (IB), (IC), (ID) or (IE) 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 Formula (I'), (I), (IA), (IB), (IC), (ID) or (IE) or pharmaceutically acceptable salts thereof described in any of the embodiments of the invention herein are useful for any of the uses above.

The present invention 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') or (I) described in the Summary of the Invention. In some embodiments, the compounds of Formula (I') or (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*.

The invention also relates to the use of a compound of Formula (I'), (I), (IA), (IB), (IC), (ID) or (IE) or a pharmaceutically acceptable salt thereof for inhibiting plasmepsin IX activity, for treating a *Plasmodium* infection, or for treating malaria. The invention further relates to the use of a compound of Formula (I'), (I), (IA), (IB), (IC), (ID) or (IE) 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 Formula (I'), (I), (IA), (IB), (IC), (ID) or (IE) or pharmaceutically acceptable salts thereof described in any of the embodiments of the invention herein are useful for any of the uses above.

The present invention 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') or (I) described in the Summary of the Invention. In some embodiments, the compounds of Formula (I') or (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*.

The invention also relates to the use of a compound of Formula (I'), (I), (IA), (IB), (IC), (ID) or (IE) or a pharmaceutically acceptable salt thereof for inhibiting plasmepsin X and plasmepsin IX activity, for treating a *Plasmodium* infection, or for treating malaria. The invention further relates to the use of a compound of Formula (I'), (I), (IA), (IB), (IC), (ID) or (IE) 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 Formula (I'), (I), (IA), (IB), (IC), (ID) or (IE) or pharmaceutically acceptable salts thereof described in any of the embodiments of the invention herein are useful for any of the uses above.

The methods of the present invention 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.

Embodiments of the invention also include one or more of the compounds of Formula (I'), (I), (IA), (IB), (IC), (ID) or (IE) 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.

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 Formula (I'), (I), (IA), (IB), (IC), (ID) or (IE), 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 Formula (I'), (I), (IA), (IB), (IC), (ID) or (IE), 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 Formula (I'), (I), (IA), (IB), (IC), (ID) or (IE), 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 Formula (I'), (I), (IA), (IB), (IC), (ID) or (IE), or a pharmaceutically acceptable salt thereof may be confirmed by several pharmacological assays. Certain assays are exemplified herein.

20 Dosage and Administration

Another embodiment provides suitable dosages and dosage forms of the compounds used in the methods of the invention. Suitable doses for administering compounds used in the methods of the invention 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 invention. In one embodiment, the dosage is from about 0.01 to about 25 mg/kg of body weight/day of a compound of the invention, 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.

As discussed above, the amount and frequency of administration of the compounds of the invention 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.

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.

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.

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.

Another embodiment provides for use of compositions comprising a compound of Formula (I'), (I), (IA), (IB), (IC), (ID) or (IE), 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.

Another embodiment provides for use of compositions comprising a compound of Formula (I'), (I), (IA), (IB), (IC), (ID) or (IE), 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 Formula (I'), (I), (IA), (IB), (IC), (ID) or (IE), 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 invention.

When used in combination with one or more additional therapeutic agents ("combination therapy"), the compounds used in the methods of this invention, i.e. the compounds

of Formula (I'), (I), (IA), (IB), (IC), (ID) or (IE), may be administered together or sequentially. When administered sequentially, compounds of the invention may be administered before or after the one or more additional therapeutic agents, as determined by those skilled in the art or patient preference.

5 If formulated as a fixed dose, such combination products employ the compounds of Formula (I'), (I), (IA), (IB), (IC), (ID) or (IE), 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

10 Another embodiment provides for methods of treatment using pharmaceutically acceptable compositions comprising a compound of the invention, 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 invention, inert, pharmaceutically acceptable carriers
15 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
20 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.

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,
25 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
30 + 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.

Thus, the invention also provides methods of using the compounds of Formula (I'), (I), (IA), (IB), (IC), (ID) or (IE), 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

ACN = acetonitrile

AcOEt = ethylacetate

Bu₃P= Bis(tri-tert-butylphosphine)palladium(0)

DCM = dichloromethane

DIAD= Diisopropyl azodicarboxylate

DIEA= N, N-Diisopropylethylamine, or Hünig's base

DMF = N,N-Dimethylformamide

DMP= Dess–Martin periodinane

DMSO = dimethyl sulfoxide

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

EtOAc = ethyl acetate

h = hours

HOBt= Hydroxybenzotriazole

LCMS=Liquid chromatography–mass spectrometry

LHMDS = LiHMDS= lithium bis(trimethylsilyl)amide

LiAlH₄=lithium aluminum hydride

min = minutes

Me = methyl

MeOH= CH₃OH=methanol

NaBH₄ = sodium borohydride

Na₂SO₄= sodium sulfate

NH₄Cl= Ammonium chloride

5 Pd(dppf)Cl₂ = [1,1'-Bis(diphenylphosphino)ferrocene]palladium(II) dichloride

SFC = Supercritical Fluid Chromatography

TBAF= tetra-n-butylammonium fluoride

TEA= triethylamine

TFA = trifluoroacetic acid

10 THF= tetrahydrofuran

TMS = Trimethylsilyl

CDCl₃ = heavy chloroform

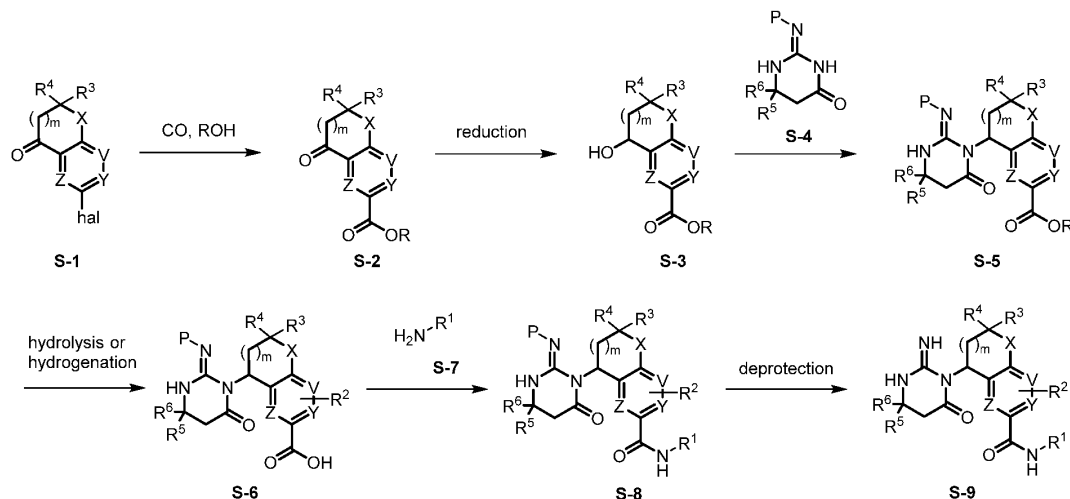
CD₃OD = heavy methanol

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

15 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 double doublet, sept = septet, t = triplet, m = multiplet, br = broad, brs = broad singlet, q = quartet, J = coupling constant and Hz = hertz.

Several methods for preparing the compounds of this disclosure are described in the following Schemes and Examples. Starting materials and intermediates were purchased
20 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') or (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. An asterisk (*) may
25 be used in a chemical structure drawing that indicates the location of a chiral center.

SCHEME 1



- Intermediate compounds of Formula **S-2**, in which hal is a halogen such as Cl, Br and I, are prepared from **S-1** after carbonylation in the presence of an alcohol. Ketone reduction in **S-2** can be performed racemically using a hydride source such as NaBH₄ or LiAlH₄ or stereoselectivity using catalytic asymmetric hydrogenation or biocatalysis (ketoreductases) to yield alcohols **S-3**. Treatment of **S-3** with N-protected iminopyrimidone **S-4** (WO2017142825) under Mitsunobu conditions gives intermediates **S-5**. Alternatively, alcohol in intermediates **S-3** could be transformed into a leaving group such as a mesylate, tosylate or halogen which can be displaced with iminopyrimidones **S-4** to give intermediates **S-5**. Acid or base catalyzed hydrolysis or hydrogenation of the **S-5** ester followed by coupling with amines **S-7** provides intermediates **S-8** which after protecting group removal yields the products of Formula **S-9**.

- Reactions sensitive to moisture or air were performed inside a glove-box or under nitrogen or argon using anhydrous solvents and reagents. The progress of reactions was determined by either analytical thin layer chromatography (TLC) usually performed with pre-coated TLC plates or liquid chromatography-mass spectrometry (LC/MS).

- Typically, the analytical LC-MS system used consisted of a Waters ZQ™ platform with electrospray ionization in positive ion detection mode with an Agilent 1100 series HPLC with autosampler. The column was commonly a Waters Xterra MS C18, 3.0 × 50 mm, 5 μm or a Waters Acquity UPLC® BEH C18 1.0 × 50 mm, 1.7 μm. The flow rate was 1 mL/min, and the injection volume was 10 μL. UV detection was in the range 210–400 nm. The mobile phase consisted of solvent A (water plus 0.05% TFA) and solvent B (MeCN plus 0.05% TFA) with a gradient of 100%

solvent A for 0.7 min changing to 100% solvent B over 3.75 min, maintained for 1.1 min, then reverting to 100% solvent A over 0.2 min.

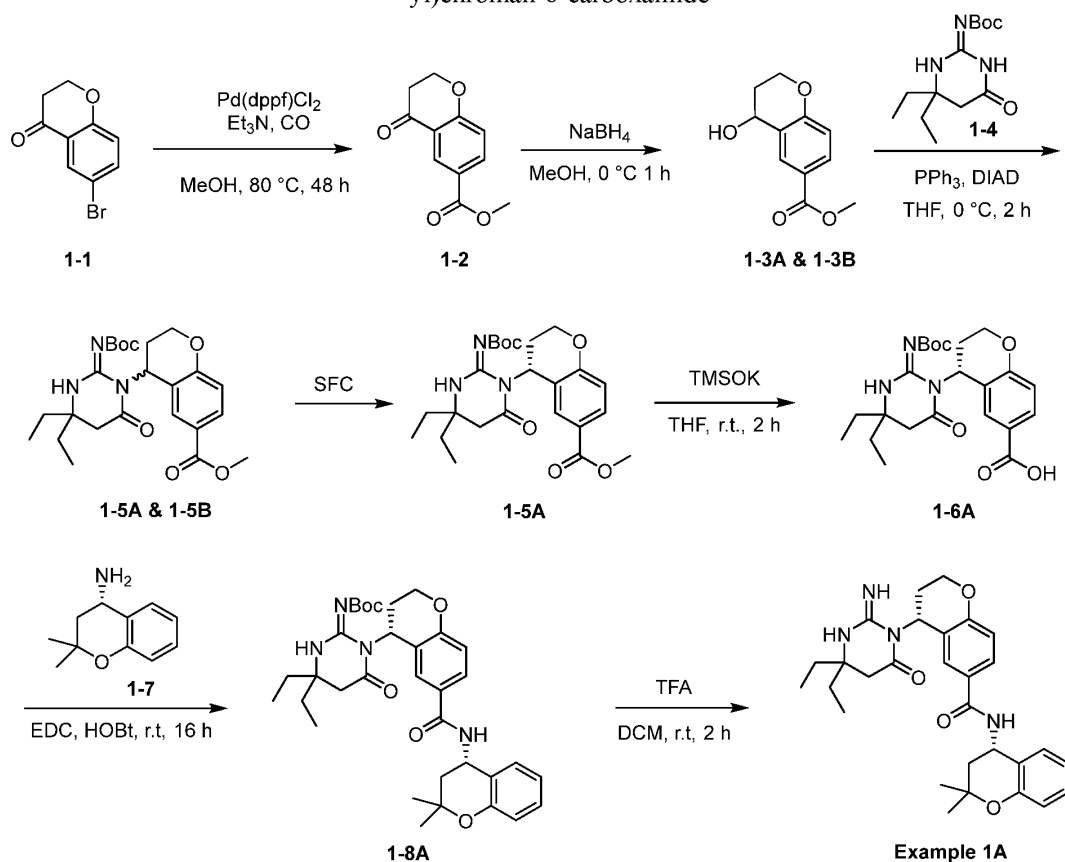
Preparative HPLC purifications were usually performed using either a mass spectrometry directed system or a non-mass guided system. Usually they were performed on a Waters Chromatography Workstation configured with LC-MS System consisting of: Waters ZQ™ single quad MS system with Electrospray Ionization, Waters 2525 Gradient Pump, Waters 2767 Injecto /Collector, Waters 996 PDA Detector, the MS Conditions of: 150-750 amu, Positive Electrospray, Collection Triggered by MS, and a Waters SUNFIRE® C-18 5-micron, 30 mm (id) x 100 mm column. The mobile phases consisted of mixtures of acetonitrile (10-100%) in water containing 0.1% TFA. Flow rates were maintained at 50 mL/min, the injection volume was 1800 µL, and the UV detection range was 210–400 nm. An alternate preparative HPLC system used was a Gilson Workstation consisting of: Gilson GX-281 Injector/Collector, Gilson UV/VIS-155 Detector, Gilson 333 and 334 Pumps, and either a Phenomenex Gemini-NX C-18 5-micron, 50 mm (id) x 250 mm column or a Waters XBridge™ C-18 5-micron OBD™, 30 mm (id) x 250 mm column. The mobile phases consisted of mixtures of acetonitrile (0-75%) in water containing 5mmol (NH₄)HCO₃. Flow rates were maintained at 50 mL/min for the Waters Xbridge™ column and 90 mL/min for the Phenomenex Gemini column. The injection volume ranged from 1000-8000 µL, and the UV detection range was 210–400 nm. Mobile phase gradients were optimized for the individual compounds. Reactions performed using microwave irradiation were normally carried out using an Emrys Optimizer manufactured by Personal Chemistry, or an Initiator manufactured by Biotage. Concentration of solutions was carried out on a rotary evaporator under reduced pressure. Flash chromatography was usually performed using either a Biotage® Flash Chromatography apparatus (Dyax Corp.), an ISCO CombiFlash® Rf apparatus, or an ISCO CombiFlash® Companion XL on silica gel (32-63 µM, 60 Å pore size) in pre-packed cartridges of the size noted. ¹H NMR spectra were acquired at 500 MHz spectrometers in CDCl₃ solutions unless otherwise noted. Chemical shifts were reported in parts per million (ppm). Tetramethylsilane (TMS) was used as internal reference in CDCl₃ solutions, and residual CH₃OH peak or TMS was used as internal reference in CD₃OD solutions. Coupling constants (J) were reported in hertz (Hz). Chiral analytical chromatography was most commonly performed on one of CHIRALPAK® AS, CHIRALPAK® AD, CHIRALCEL® OD, CHIRALCEL® IA, or CHIRALCEL® OJ columns (250x4.6 mm) (Daicel Chemical Industries, Ltd.) with noted percentage of either ethanol in hexane (%Et/Hex) or isopropanol in heptane (%IPA/Hep) as isocratic solvent systems. Chiral preparative chromatography was conducted on one of CHIRALPAK AS, of CHIRALPAK AD, CHIRALCEL® OD, CHIRALCEL® IA, CHIRALCEL® OJ columns (20x250 mm) (Daicel Chemical Industries, Ltd.) with desired isocratic solvent systems identified on chiral analytical chromatography or by supercritical fluid (SFC) conditions.

It is understood that a chiral center in a compound may exist in the "*S*" or "*R*" stereo-configuration, or as a mixture of both. Within a molecule, each bond drawn as a straight line from a chiral center includes both the (*R*) and (*S*) stereoisomers as well as mixtures thereof.

5

EXAMPLE 1A

4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2*H*)-yl)-*N*-((*S*)-2,2-dimethylchroman-4-yl)chroman-6-carboxamide



10

Step A: methyl 4-oxochroman-6-carboxylate **1-2**

Pd(dppf)Cl₂ (11.28 g, 15.41 mmol) and triethylamine (64.5 mL, 462 mmol) were added to a solution of 6-bromochroman-4-one **1-1** (35 g, 154 mmol) in MeOH (120 mL) at 25 °C. The solution was stirred at 80 °C for 48 h under CO atmosphere (50 psi). The reaction mixture was cooled to room temperature, then concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; Agela® Flash Column Silica-

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CS(120 g), Eluent of 10% Ethyl acetate/petroleum ether gradient @55 mL/min) to give methyl 4-oxochroman-6-carboxylate **1-2**.

MS (ESI) m/z : 248.1 ($M+41+H^+$)

1H NMR (400 MHz, CD_3OD) δ 8.49 (d, $J = 2.0$ Hz, 1 H), 8.12 (dd, $J = 8.8, 2.0$ Hz, 1 H), 7.08 (d, $J = 8.8$ Hz, 1 H), 4.60 - 4.65 (m, 2 H), 3.89 (s, 3 H), 2.85 (t, $J = 6.4$ Hz, 2 H).

Step B: methyl 4-hydroxychroman-6-carboxylate **1-3A & 1-3B**.

Sodium borohydride (3.03 g, 80 mmol) at 0 °C was added in portions to a solution of methyl 4-oxochroman-6-carboxylate **1-2** (15 g, 72.7 mmol) in MeOH (100 mL). Then the mixture was stirred at 0 °C for 1 h. Then the mixture was quenched by addition of saturated NH_4Cl (50 mL), then concentrated under reduced pressure to give a residue, added water (100 mL), extracted with EtOAc (50 mL*2). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure, which was purified by flash silica gel chromatography (ISCO®; Agela® Flash Column Silica-CS (40 g), Eluent of 0~22% Ethyl acetate/petroleum ether gradient @50 mL/min) to give methyl 4-hydroxychroman-6-carboxylate **1-3A & 1-3B**.

MS (ESI) m/z : 209.0 ($M+H^+$).

1H NMR (400MHz, chloroform- d) δ 8.03 (d, $J=2.0$ Hz, 1H), 7.86 (dd, $J=2.0, 8.8$ Hz, 1H), 6.85 (d, $J=8.8$ Hz, 1H), 4.82 (s, 1H), 4.41 - 4.24 (m, 2H), 3.87 (s, 3H), 2.20 - 2.05 (m, 3H).

Step C: (*E*)-methyl 4-(2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chroman-6-carboxylate **1-5A & 1-5B**.

DIAD (18.86 mL, 96 mmol) was added dropwise to a solution of (*Z*)-tert-butyl (4,4-diethyl-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate **1-4** (12.94 g, 48.0 mmol), methyl 4-hydroxychroman-6-carboxylate **1-3A & 1-3B** (10 g, 48.0 mmol) and triphenylphosphine (25.2 g, 96 mmol) in THF (50 mL) at 0 °C under N_2 atmosphere. The mixture was stirred at 0 °C for 2 h. The reaction was quenched by water (60 mL) and extracted with ethyl acetate (50 mL*2). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; Agela® Flash Column Silica-CS(40 g), Eluent of 0~25% Ethyl acetate/petroleum ether gradient @50 mL/min) to give (*E*)-methyl 4-(2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chroman-6-carboxylate **1-5A & 1-5B**.

MS (ESI) m/z : 460.2 ($M+H^+$).

1H NMR (500MHz, chloroform- d) δ 7.75 (dd, $J = 2.0, 8.5$ Hz, 1H), 7.60 (s, 1H), 6.82 (d, $J = 8.5$ Hz, 1H), 6.37 (dd, $J = 7.0, 10.1$ Hz, 1H), 4.43 (m, 1H), 4.22 (m, 1H), 3.85 - 3.78 (m, 3H), 2.84 - 2.70

(m, 1H), 2.62 - 2.44 (m, 2H), 2.11 - 2.03 (m, 1H), 1.79 - 1.59 (m, 5H), 1.50 (s, 9H), 1.02 - 0.89 (m, 6H)

Step D: of methyl 4-(2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chroman-6-carboxylate **1-5A**

Methyl 4-(2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chroman-6-carboxylate **1-5A** (6.5 g, 14.14 mmol) was purified by SFC on (Instrument SFC 5, Method Column DAICEL CHIRALCEL OD(250mm*50mm,10um), Condition 0.1% aqNH₃ MeOH, begin B 40%, end B 40%, FlowRate(mL/min) 200, Injections 150) to afford methyl 4-(2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chroman-6-carboxylate **1-5A** (Rt=6.460min).

MS (ESI) *m/z*: 460.2 (M+H⁺).

1-5A: ¹H NMR (500MHz, chloroform-d) δ 10.10 (s, 1H), 7.75 (dd, *J*=2.0, 8.5 Hz, 1H), 7.61 (s, 1H), 6.83 (d, *J*=8.5 Hz, 1H), 6.45 - 6.31 (m, 1H), 4.51 - 4.39 (m, 1H), 4.25 - 4.20 (m, 1H), 3.82 (s, 3H), 2.82 - 2.70 (m, 1H), 2.61 - 2.48 (m, 2H), 2.11 - 2.03 (m, 1H), 1.79 - 1.61 (m, 4H), 1.51 (s, 9H), 1.03 - 0.90 (m, 6H)

Step E: 4-(2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chroman-6-carboxylic acid **1-6A**

Potassium trimethylsilanolate (1.842 g, 14.36 mmol) was added to a solution of methyl 4-(2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chroman-6-carboxylate **1-5A** (2.2 g, 4.79 mmol) in THF (35 mL). The reaction was stirred at 22 °C for 1 h. The solution of 4-(2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chroman-6-carboxylic acid **1-6A** was used for next step directly without any further manipulation or purification.

MS (ESI) *m/z*: 446.1 (M+H⁺)

Step F: tert-butyl (1-(6-(((*S*)-2,2-dimethylchroman-4-yl)carbamoyl)chroman-4-yl)-4,4-diethyl-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate **1-8A**

DIEA (3.14 mL, 17.96 mmol) was added to a solution of 4-(2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chroman-6-carboxylic acid **1-6A** (2.0 g, 4.49 mmol), EDC (1.721 g, 8.98 mmol), 1*H*-benzo[d][1,2,3]triazol-1-ol **7** (1.213 g, 8.98 mmol) and (*S*)-2,2-dimethylchroman-4-amine (1.591 g, 8.98 mmol) in THF (35 mL). The reaction was stirred at 22 °C for 5 h. The mixture was quenched with water (10 mL), and extracted with EtOAc (30 mL * 3). The organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo to afford crude product, which was purified by flash silica gel

chromatography (ISCO®; Agela® Flash Column Silica-CS(40 g), Eluent of 0~26% AcOEt/petroleum ether gradient @50 mL/min) to give tert-butyl (1-(6-(((S)-2,2-dimethylchroman-4-yl)carbamoyl)chroman-4-yl)-4,4-diethyl-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate **1-8A**.

5 MS (ESI) m/z : 605.4 ($M+H^+$)

1H NMR (400MHz, chloroform- d) δ 10.10 (s, 1H), 7.51 (s, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.25 - 7.22 (m, 1H), 7.16 (t, J = 7.6 Hz, 1H), 6.92 - 6.75 (m, 3H), 6.48 - 6.34 (m, 1H), 6.07 (d, J = 8.8 Hz, 1H), 5.53 - 5.39 (m, 1H), 4.44 (d, J = 11.2 Hz, 1H), 4.20 (t, J = 11.2 Hz, 1H), 2.83 - 2.67 (m, 1H), 2.58 - 2.46 (m, 2H), 2.27 (m, 1H), 2.07 (m, 1H), 1.84 - 1.56 (m, 7H), 1.50 (s, 9H), 1.43 (s, 3H), 1.35 (s, 3H), 0.92 (m, 6H)

Step G: 4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((S)-2,2-dimethylchroman-4-yl)chroman-6-carboxamide **Example 1A**

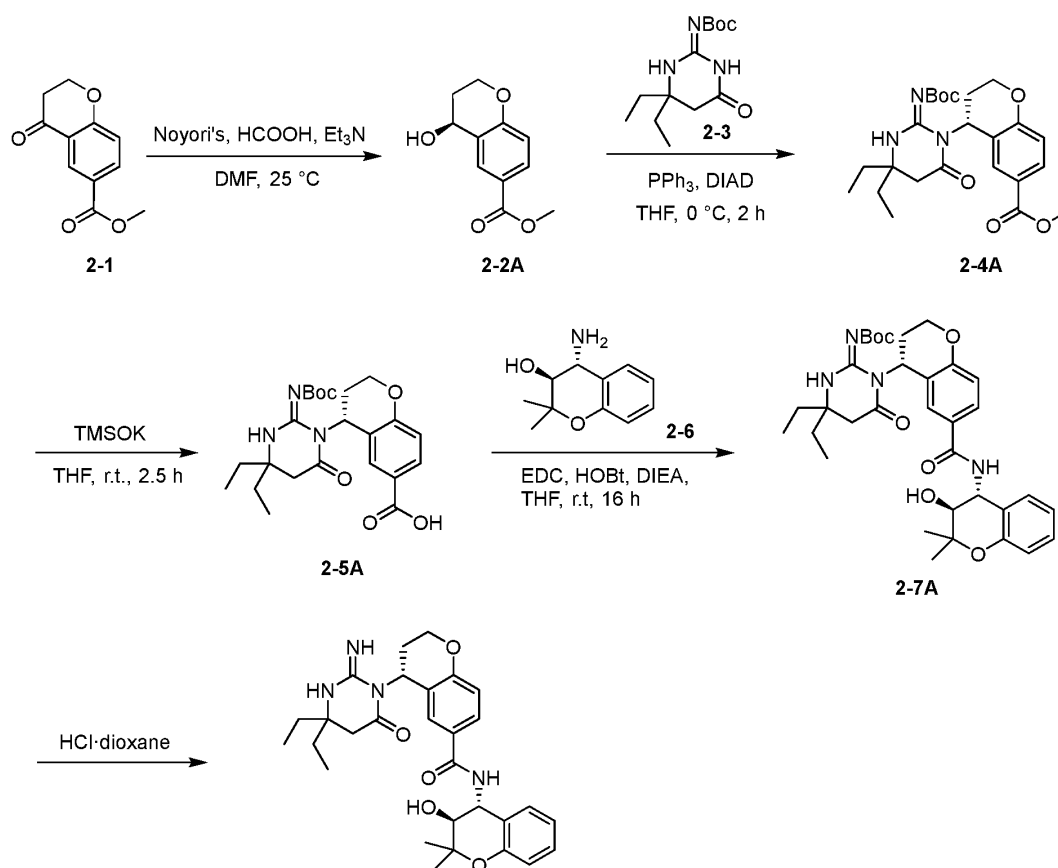
A solution of tert-butyl (1-(6-(((S)-2,2-dimethylchroman-4-yl)carbamoyl)chroman-4-yl)-4,4-diethyl-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate **1-8A** (2.4 g, 3.97 mmol) in DCM (15 mL) and TFA (3 mL) was stirred at 20 °C for 2 h. The mixture was concentrated in vacuo to give the crude product which was purified by Prep-HPLC (0.1% TFA) (Instrument EG Method Column Waters XSELECT C18 150*30mm*5um Condition water (0.1%TFA)-ACN Begin B 22 End B 55 Gradient Time(min) 11 100%B Hold Time(min) 2 FlowRate(mL/min) 25 Injections 10) to afford 4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((S)-2,2-dimethylchroman-4-yl)chroman-6-carboxamide **Example 1A**.

MS (ESI) m/z : 505.3 ($M+H^+$)

1H NMR (400MHz, methanol- d_4) δ 8.54 (d, J =8.8 Hz, 1H), 7.70 (d, J =8.0 Hz, 1H), 7.64 (s, 1H), 7.18 - 7.08 (m, 2H), 6.90 (d, J =8.4 Hz, 1H), 6.83 (t, J =7.2 Hz, 1H), 6.74 (d, J =8.0 Hz, 1H), 5.54 - 5.38 (m, 1H), 4.57 - 4.44 (m, 1H), 4.22 (t, J =10.8 Hz, 1H), 2.93 - 2.67 (m, 3H), 2.27 - 2.17 (m, 1H), 2.12 - 2.10 (m, 1H), 2.10 - 2.00 (m, 1H), 1.83 - 1.63 (m, 4H), 1.44 (s, 3H), 1.34 (s, 3H), 0.98 - 0.93 (m, 6H)

EXAMPLE 2A

4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2*H*)-yl)-*N*-((3*S*,4*R*)-3-hydroxy-2,2-dimethylchroman-4-yl)chroman-6-carboxamide



Example 2A

5

Step A: (*S*)-methyl 4-hydroxychroman-6-carboxylate **2-2A**

A solution of formic acid (30 g, 652 mmol) and triethylamine (120 g, 1186 mmol) in DMF (320 mL) was stirred for 15 min, then methyl 4-oxochroman-6-carboxylate **2-1** (40 g, 194 mmol) and (*S,S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethanediamine(chloro)([*l*-cymene)ruthenium(II) (1.234 g, 1.940 mmol) were added, and the mixture was stirred for 10 h at 25 °C. The mixture was diluted with water (300 mL), and extracted with EtOAc (250 mL*3). The organic layers were washed with brine (300 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; Agela® Flash Column Silica-CS (150 g),

Eluent of 0~30% Ethyl acetate/petroleum ether gradient @65 mL/min) to afford (*S*)-methyl 4-hydroxychroman-6-carboxylate **2-2A**.

MS (ESI) *m/z*: 209.0 (*M*+*H*⁺)

¹H NMR (500 MHz, chloroform-*d*) δ 8.02 (s, 1H), 7.84 (d, *J*=8.50 Hz, 1H), 6.83 (d, *J*=8.0 Hz, 1H),
5 4.81 (q, *J*=4.0 Hz, 1H), 4.26-4.39 (m, 2H), 3.85 (s, 3H), 2.59 (d, *J*=4.0 Hz, 1H), 2.02-2.15 (m, 2H).

Step B: methyl 4-(2-((*tert*-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2*H*)-yl)chroman-6-carboxylate **2-4A**

(*E*)-diisopropyl diazene-1,2-dicarboxylate (34.0 mL, 173 mmol) was added dropwise
10 to a solution of (*Z*)-*tert*-butyl (4,4-diethyl-6-oxotetrahydropyrimidin-2(1*H*)-ylidene)carbamate **2-3**
(40 g, 149 mmol), methyl 4-hydroxychroman-6-carboxylate **2-2A** (30 g, 144 mmol) and
triphenylphosphine (48 g, 183 mmol) in THF (500 mL) at 0 °C under N₂ atmosphere. Then the
mixture was stirred at 25 °C for 3 h. The mixture was concentrated in vacuo, then purified by flash
silica gel chromatography (ISCO®; Agela® Flash Column Silica-CS(150 g), Eluent of 0~5%
15 AcOEt/DCM gradient @65 mL/min) to give methyl 4-(2-((*tert*-butoxycarbonyl)imino)-4,4-diethyl-
6-oxotetrahydropyrimidin-1(2*H*)-yl)chroman-6-carboxylate **2-4A**.

MS (ESI) *m/z*: 460.2 (*M*+*H*⁺).

¹H NMR (400 MHz, chloroform-*d*) δ 10.48-10.83 (m, 1H), 7.78 (d, *J*=8.8 Hz, 1H), 7.60 (s, 1H),
6.85 (d, *J*=8.8 Hz, 1H), 5.93-6.04 (m, 1H), 4.43 (d, *J*=11.2 Hz, 1H), 4.18 (t, *J*=11.2 Hz, 1H), 3.82 (s,
20 3H), 2.72-2.77 (m, 1H), 2.51-2.56 (m, 2H), 2.04-2.08 (m, 1H), 1.60-1.70 (m, 4H), 1.49 (s, 9H),
0.90-0.99 (m, 6H).

Step C: (*R*)-4-(2-((*tert*-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2*H*)-yl)chroman-6-carboxylic acid **2-5A**

25 Potassium trimethylsilanolate (7.54 g, 58.8 mmol) was added to a solution of (*R*)-
methyl 4-(2-((*tert*-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2*H*)-yl)chroman-
6-carboxylate **2-4A** (9.0 g, 19.59 mmol) in THF (300 mL). The reaction was stirred at 22 °C for 2.5
h. The solution of (*R*)-4-(2-((*tert*-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-
1(2*H*)-yl)chroman-6-carboxylic acid **2-5A** was used for next step directly without any further
30 manipulation or purification.

MS (ESI) *m/z*: 446.0 (*M*+*H*⁺)

Step D: *tert*-butyl (4,4-diethyl-1-((*R*)-6-(((3*S*,4*R*)-3-hydroxy-2,2-dimethylchroman-4-yl)carbamoyl)chroman-4-yl)-6-oxotetrahydropyrimidin-2(1*H*)-ylidene)carbamate **2-7A**

35 DIEA (13.69 mL, 78 mmol) was added to a solution of (*R*)-4-(2-((*tert*-
butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2*H*)-yl)chroman-6-carboxylic acid

2-5A (8.73 g, 19.60 mmol), EDC (9.39 g, 49.0 mmol), 1*H*-benzo[d][1,2,3]triazol-1-ol (5.30 g, 39.2 mmol) and (3*S*,4*R*)-4-amino-2,2-dimethylchroman-3-ol **2-6** (4.54 g, 23.51 mmol) in THF (300 mL). The reaction was stirred at 22 °C for 16 h. The mixture was quenched with water (80 mL), and extracted with EtOAc (80 mL x 3). The organic layers were washed with brine (100 mL), dried
5 over Na₂SO₄, filtered, and concentrated in vacuo to afford crude product as colorless oil, which was purified by flash silica gel chromatography (ISCO®; Agela® Flash Column Silica-CS(150 g), Eluent of 0~30% Ethyl acetate/petroleum ether gradient @65 mL/min) to give tert-butyl (4,4-diethyl-1-((*R*)-6-(((3*S*,4*R*)-3-hydroxy-2,2-dimethylchroman-4-yl)carbamoyl)chroman-4-yl)-6-oxotetrahydropyrimidin-2(1*H*)-ylidene)carbamate **2-7A**.

10 MS (ESI) *m/z*: 621.3 (M+H⁺)

¹H NMR (500 MHz, chloroform-*d*) δ 10.12 (br, 1H), 7.55 (s, 1H), 7.36-7.43 (m, 1H), 7.25-7.27 (m, 1H), 7.18-7.23 (m, 1H), 6.94 (dt, *J*=1.0, 7.5 Hz, 1H), 6.80-6.87 (m, 2H), 6.34-6.43 (m, 2H), 5.11-5.12 (m, 1H), 4.84 (s, 1H), 4.39-4.49 (m, 1H), 4.23 (dt, *J*=2.0, 11.5 Hz, 1H), 3.73 (d, *J*=8.0 Hz, 1H), 2.68-2.83 (m, 1H), 2.45-2.56 (m, 2H), 2.05-2.09 (m, 1H), 1.60-1.74 (m, 4H), 1.49-1.50 (m, 12H),
15 1.28 (s, 3H), 0.90-0.98 (m, 6H).

Step E: 4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2*H*)-yl)-N-(((3*S*,4*R*)-3-hydroxy-2,2-dimethylchroman-4-yl)chroman-6-carboxamide **Example 2A**

A solution of tert-butyl (4,4-diethyl-1-(6-(((3*S*,4*R*)-3-hydroxy-2,2-dimethylchroman-4-yl)carbamoyl)chroman-4-yl)-6-oxotetrahydropyrimidin-2(1*H*)-ylidene)carbamate **2-7A** (14 g, 22.55 mmol) in HCl-dioxane (4M) (200 mL) was stirred at 25 °C for 10 h. The mixture was concentrated in vacuo. The crude was purified by Prep-HPLC (Instrument ACSSH-PrepL-K2 Method Column YMC-Triart Prep C18 250*50mm*10um Condition water (0.1%TFA)-ACN Begin
20 B 20 End B 50 Gradient Time (min) 25 100%B Hold Time (min) 3 FlowRate (mL/min) 120) to afford 4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2*H*)-yl)-N-(((3*S*,4*R*)-3-hydroxy-2,2-dimethylchroman-4-yl)chroman-6-carboxamide **Example 2A**.

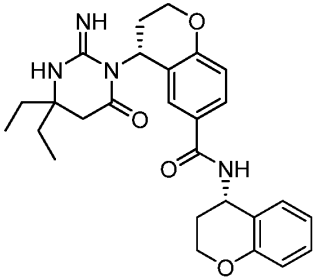
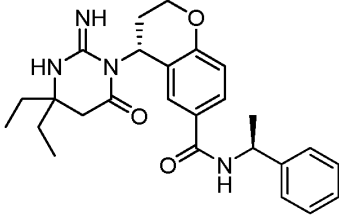
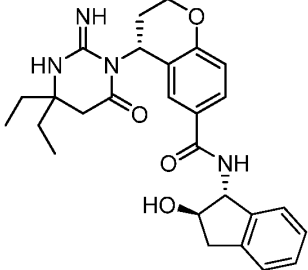
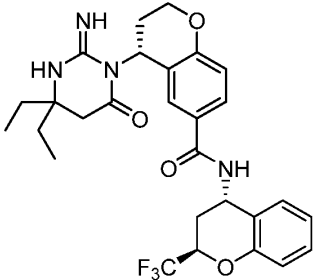
25 MS (ESI) *m/z* 521.3 (M+H⁺)

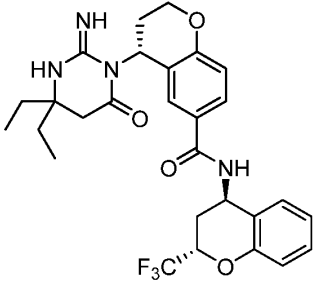
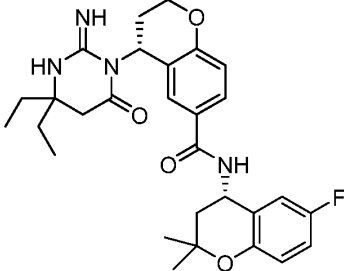
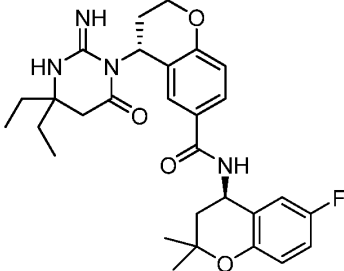
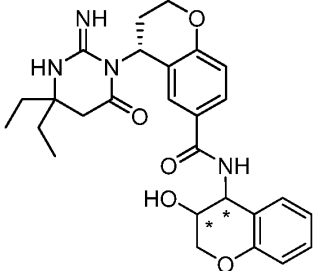
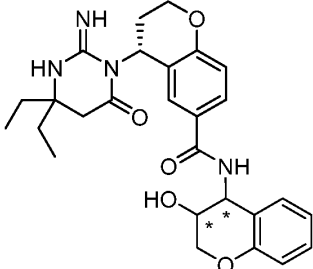
¹H NMR (400 MHz, methanol-*d*₄) δ 8.56 (d, *J*=8.8 Hz, 1H), 7.72 (d, *J*=8.4 Hz, 1H), 7.66 (s, 1H), 7.06-7.14 (m, 2H), 6.89 (d, *J*=8.4 Hz, 1H), 6.80-6.85 (m, 1H), 6.74 (d, *J*=8.0 Hz, 1H), 5.30-5.88 (m, 1H), 5.22 (t, *J*=8.8 Hz, 1H), 4.49 (td, *J*=3.6, 11.6 Hz, 1H), 4.21 (t, *J*=10.8 Hz, 1H), 3.75 (d, *J*=9.6 Hz, 1H), 2.65-2.87 (m, 3H), 2.16-2.24 (m, 1H), 1.62-1.81 (m, 4H), 1.46 (s, 3H), 1.24 (s, 3H), 0.91-0.98 (m, 6H).
30

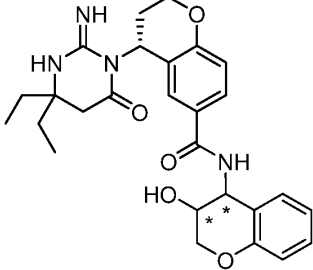
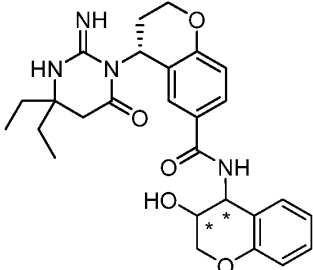
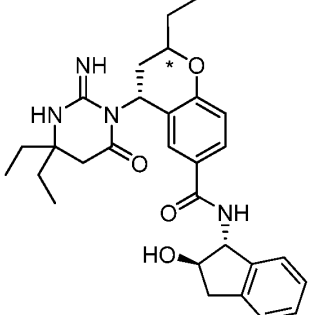
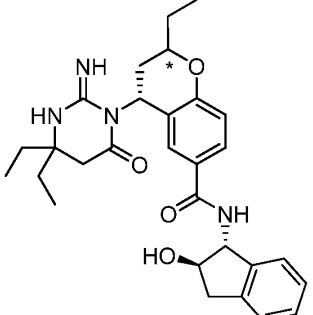
The compounds in Table 1-4 were prepared in an analogous fashion to that described in Scheme 1 and the experimentals described herein. The isomers were separated by preparative HPLC or/and preparative chiral SFC.

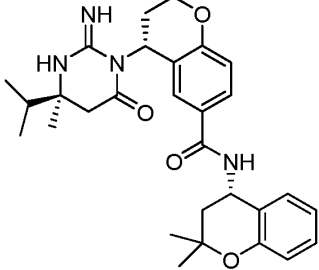
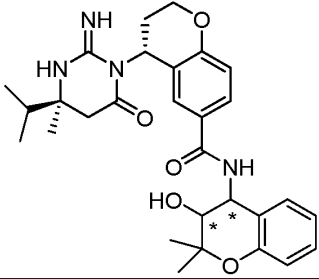
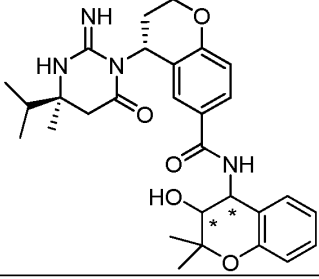
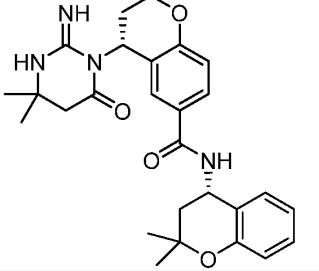
TABLE 1

5

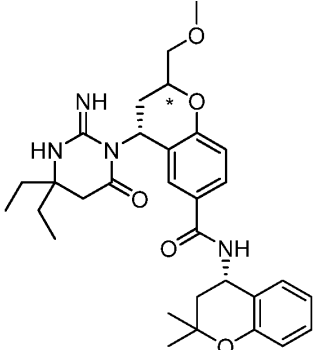
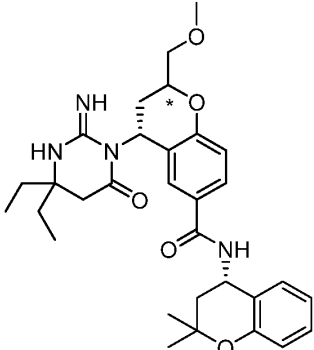
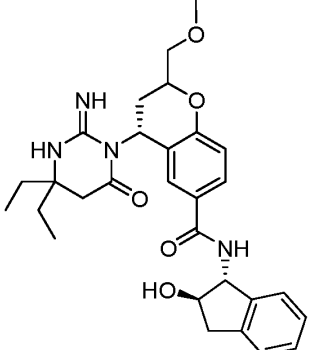
Example	Structure	LC/MS (M+1) ⁺	Name
3A		477.5	(R)-N-((S)-chroman-4-yl)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)chromane-6-carboxamide
4A		449.2	(R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((S)-1-phenylethyl)chromane-6-carboxamide
5A		477.3	(R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)chromane-6-carboxamide
6A		545.2	(R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((2R,4S)-2-(trifluoromethyl)chroman-4-yl)chromane-6-carboxamide

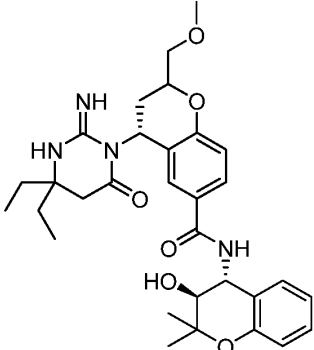
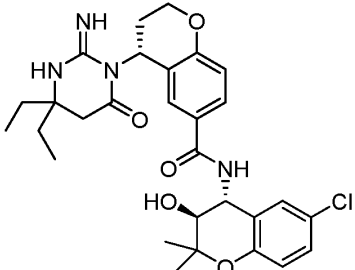
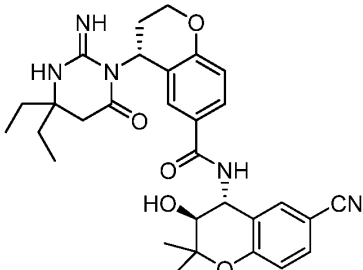
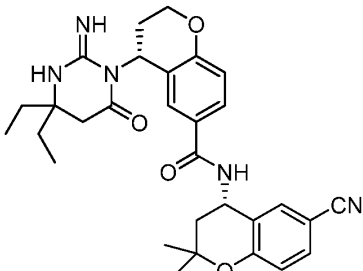
6B		545.2	(R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((2S,4R)-2-(trifluoromethyl)chroman-4-yl)chromane-6-carboxamide
7A		523.2	(R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((S)-6-fluoro-2,2-dimethylchroman-4-yl)chromane-6-carboxamide
7B		523.2	(R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((R)-6-fluoro-2,2-dimethylchroman-4-yl)chromane-6-carboxamide
8A		493.3	(4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-(3-hydroxychroman-4-yl)chromane-6-carboxamide
8B		493.3	(4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-(3-hydroxychroman-4-yl)chromane-6-carboxamide

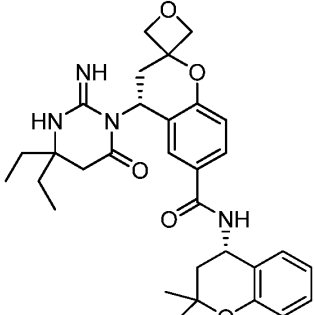
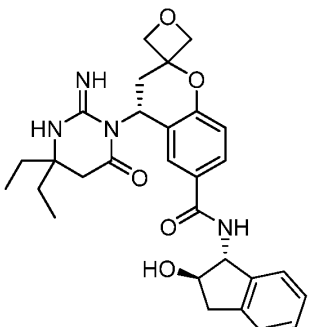
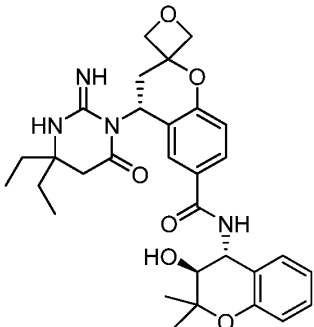
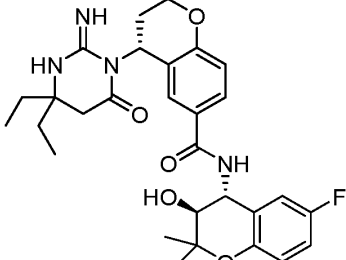
8C		493.1	(4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-(3-hydroxychroman-4-yl)chromane-6-carboxamide
8D		493.3	(4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-(3-hydroxychroman-4-yl)chromane-6-carboxamide
9A		505.3	(4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-2-ethyl-N-((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)chromane-6-carboxamide
9B		505.3	(4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-2-ethyl-N-((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)chromane-6-carboxamide

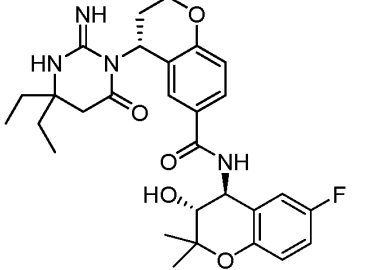
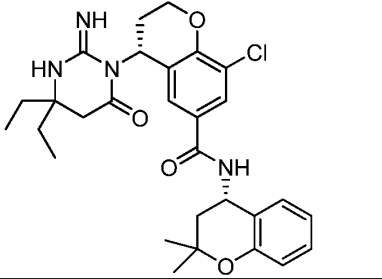
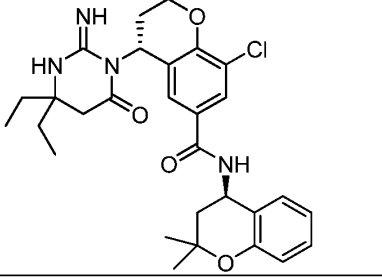
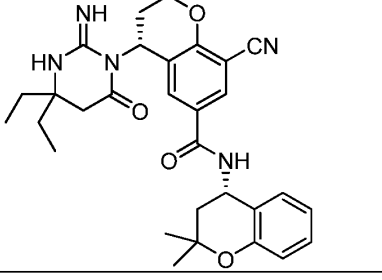
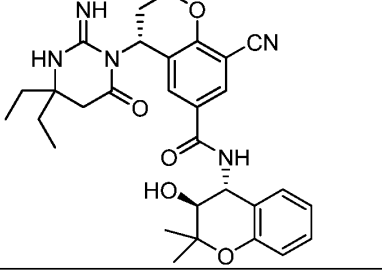
10A		505.3	(R)-N-((S)-2,2-dimethylchroman-4-yl)-4-((S)-2-imino-4-isopropyl-4-methyl-6-oxotetrahydropyrimidin-1(2H)-yl)chromane-6-carboxamide
11A		521.4	(4R)-N-(3-hydroxy-2,2-dimethylchroman-4-yl)-4-((S)-2-imino-4-isopropyl-4-methyl-6-oxotetrahydropyrimidin-1(2H)-yl)chromane-6-carboxamide
11B		521.3	(4R)-N-(3-hydroxy-2,2-dimethylchroman-4-yl)-4-((S)-2-imino-4-isopropyl-4-methyl-6-oxotetrahydropyrimidin-1(2H)-yl)chromane-6-carboxamide
12A		477.3	(R)-N-((S)-2,2-dimethylchroman-4-yl)-4-(2-imino-4,4-dimethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chromane-6-carboxamide

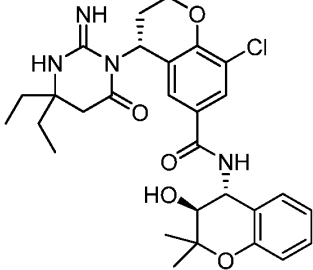
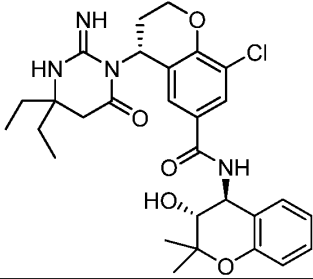
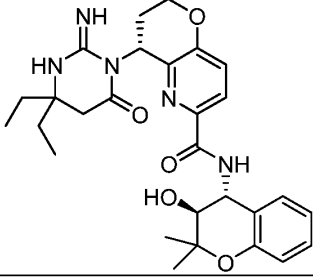
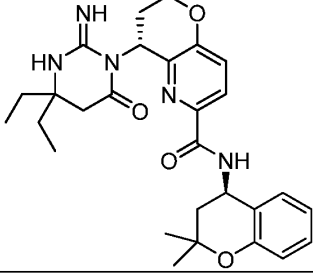
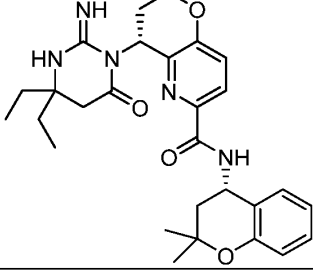
13A		549.3	(4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-2-ethyl-N-(3-hydroxy-2,2-dimethylchroman-4-yl)chromane-6-carboxamide
13B		549.3	(4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-2-ethyl-N-(3-hydroxy-2,2-dimethylchroman-4-yl)chromane-6-carboxamide
14A		583.1, 585.2	(R)-N-((S)-6-bromo-2,2-dimethylchroman-4-yl)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)chromane-6-carboxamide
15A		599.2, 601.3	(R)-N-((3S,4R)-6-bromo-3-hydroxy-2,2-dimethylchroman-4-yl)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)chromane-6-carboxamide

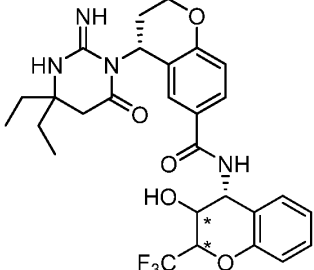
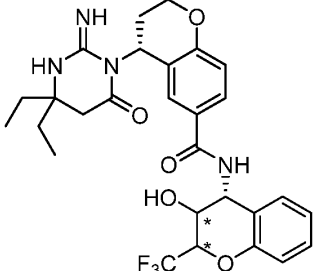
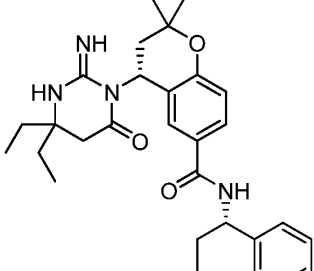
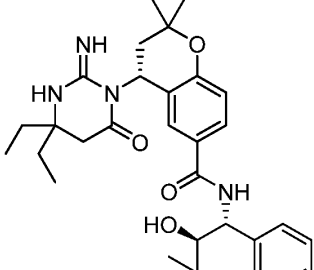
16A		549.3	(4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((S)-2,2-dimethylchroman-4-yl)-2-(methoxymethyl)chromane-6-carboxamide
16B		549.3	(4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((S)-2,2-dimethylchroman-4-yl)-2-(methoxymethyl)chromane-6-carboxamide
17A		521.3	(4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-2-(methoxymethyl)chromane-6-carboxamide

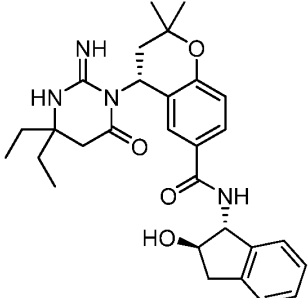
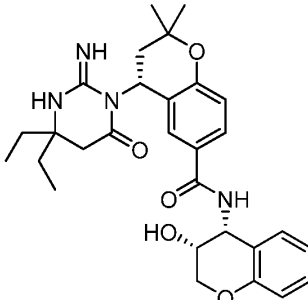
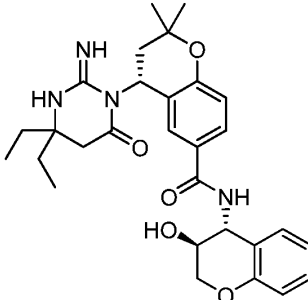
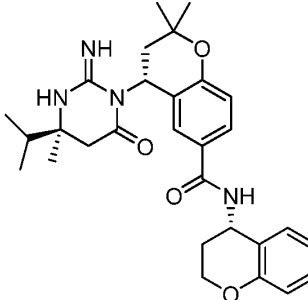
18A		565.3	(4R)-4-(4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((3S,4R)-3-hydroxy-2,2-dimethylchroman-4-yl)-2-(methoxymethyl)chromane-6-carboxamide
19A		555.2, 557.3	(R)-N-((3S,4R)-6-chloro-3-hydroxy-2,2-dimethylchroman-4-yl)-4-(4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)chromane-6-carboxamide
20A		546.3	(R)-N-((3S,4R)-6-cyano-3-hydroxy-2,2-dimethylchroman-4-yl)-4-(4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)chromane-6-carboxamide
21A		530.3	(R)-N-((S)-6-cyano-2,2-dimethylchroman-4-yl)-4-(4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)chromane-6-carboxamide

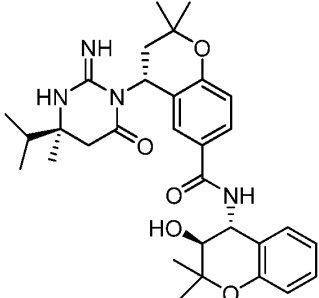
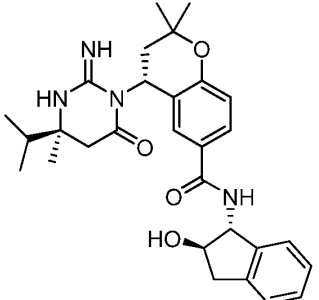
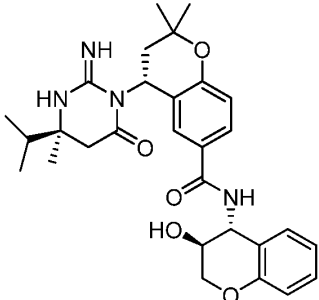
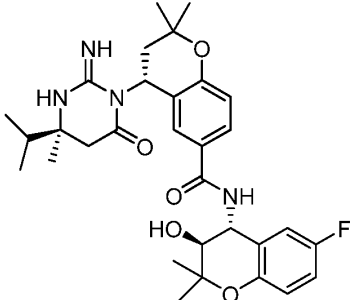
22A		547.4	(R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((S)-2,2-dimethylchroman-4-yl)spiro[chromane-2,3'-oxetane]-6-carboxamide
23A		519.2	(R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)spiro[chromane-2,3'-oxetane]-6-carboxamide
24A		563.3	(R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((3S,4R)-3-hydroxy-2,2-dimethylchroman-4-yl)spiro[chromane-2,3'-oxetane]-6-carboxamide
25A		539.3	(R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((3S,4R)-6-fluoro-3-hydroxy-2,2-dimethylchroman-4-yl)chromane-6-carboxamide

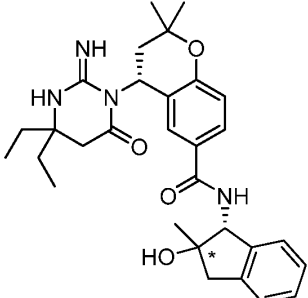
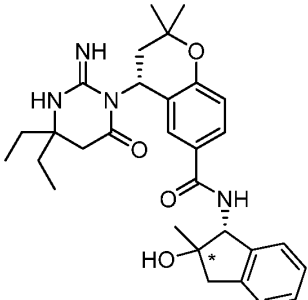
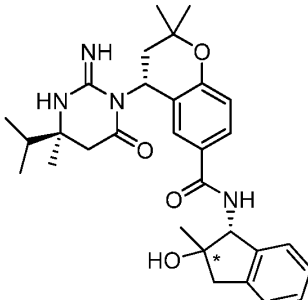
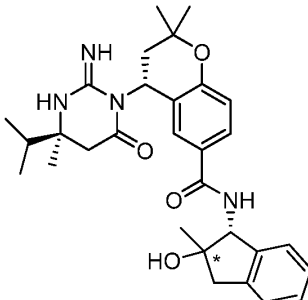
25B		539.3	(R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((3R,4S)-6-fluoro-3-hydroxy-2,2-dimethylchroman-4-yl)chromane-6-carboxamide
26A		539.3, 541.3	(R)-8-chloro-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((S)-2,2-dimethylchroman-4-yl)chromane-6-carboxamide
26B		539.2, 541.3	(R)-8-chloro-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((R)-2,2-dimethylchroman-4-yl)chromane-6-carboxamide
27A		530.3	(R)-8-cyano-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((S)-2,2-dimethylchroman-4-yl)chromane-6-carboxamide
28A		546.3	(R)-8-cyano-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((3S,4R)-3-hydroxy-2,2-dimethylchroman-4-yl)chromane-6-carboxamide

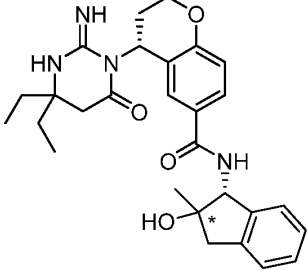
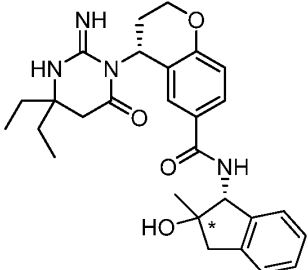
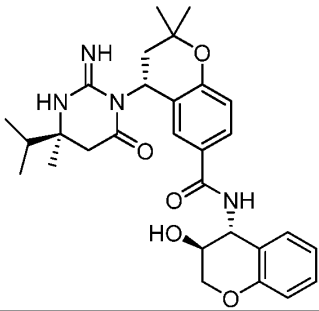
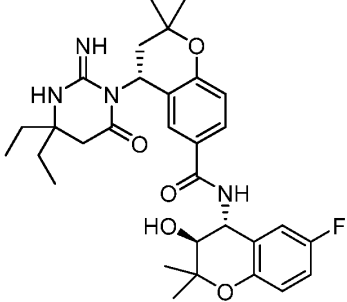
29A		555.3, 557.3	(R)-8-chloro-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((3S,4R)-3-hydroxy-2,2-dimethylchroman-4-yl)chromane-6-carboxamide
29B		555.3, 557.3	(R)-8-chloro-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((3R,4S)-3-hydroxy-2,2-dimethylchroman-4-yl)chromane-6-carboxamide
30A		522.3	(R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((3S,4R)-3-hydroxy-2,2-dimethylchroman-4-yl)-3,4-dihydro-2H-pyranopyridine-6-carboxamide
31A		506.3	(R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((R)-2,2-dimethylchroman-4-yl)-3,4-dihydro-2H-pyranopyridine-6-carboxamide
31B		506.3	(R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((S)-2,2-dimethylchroman-4-yl)-3,4-dihydro-2H-pyranopyridine-6-carboxamide

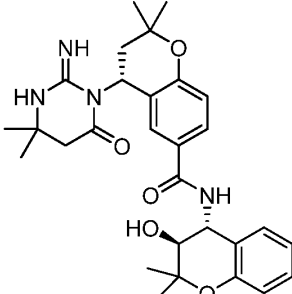
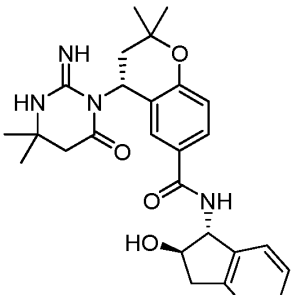
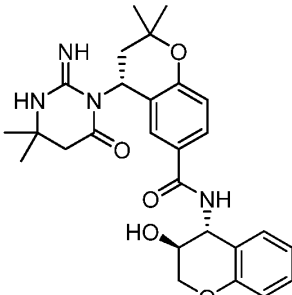
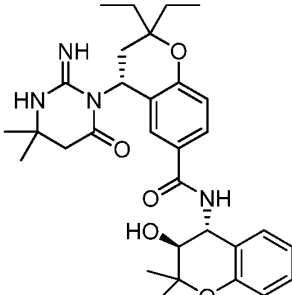
32A		561.3	(4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((4R)-3-hydroxy-2-(trifluoromethyl)chroman-4-yl)chromane-6-carboxamide
32B		561.3	(4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((4R)-3-hydroxy-2-(trifluoromethyl)chroman-4-yl)chromane-6-carboxamide
33A		505.3	(R)-N-((S)-chroman-4-yl)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-2,2-dimethylchromane-6-carboxamide
34A		549.3	(R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((3S,4R)-3-hydroxy-2,2-dimethylchroman-4-yl)-2,2-dimethylchromane-6-carboxamide

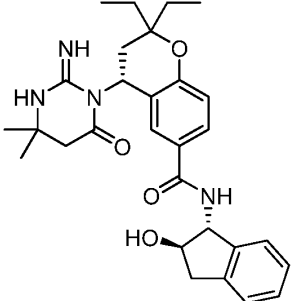
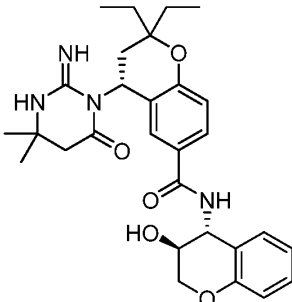
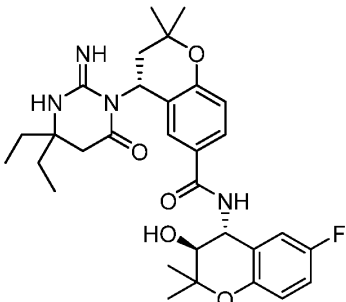
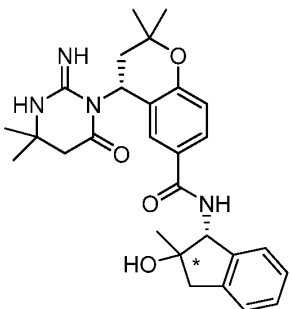
35A		505.3	(R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-2,2-dimethylchromane-6-carboxamide
36A		521.3	(R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((3R,4R)-3-hydroxychroman-4-yl)-2,2-dimethylchromane-6-carboxamide
36B		521.6	(R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((3S,4R)-3-hydroxychroman-4-yl)-2,2-dimethylchromane-6-carboxamide
37A		521.2	(R)-N-((S)-chroman-4-yl)-4-((S)-2-imino-4-isopropyl-4-methyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2,2-dimethylchromane-6-carboxamide

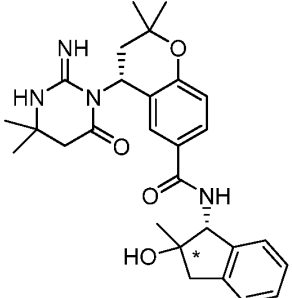
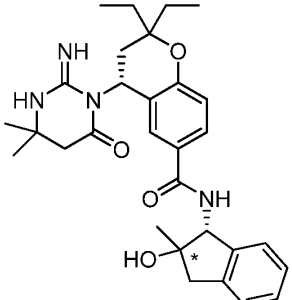
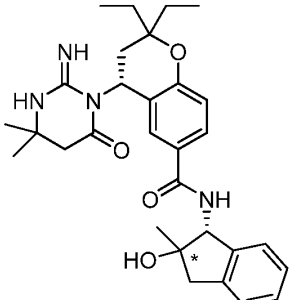
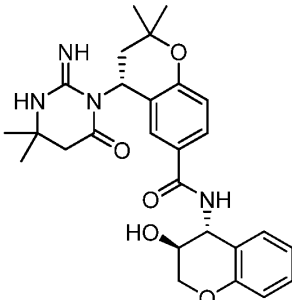
38A		549.3	(R)-N-((3S,4R)-3-hydroxy-2,2-dimethylchroman-4-yl)-4-((S)-2-imino-4-isopropyl-4-methyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2,2-dimethylchromane-6-carboxamide
39A		505.3	(R)-N-((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-4-((S)-2-imino-4-isopropyl-4-methyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2,2-dimethylchromane-6-carboxamide
40A		521.3	(R)-N-((3S,4R)-3-hydroxychroman-4-yl)-4-((S)-2-imino-4-isopropyl-4-methyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2,2-dimethylchromane-6-carboxamide
41A		567.3	(R)-N-((3S,4R)-6-fluoro-3-hydroxy-2,2-dimethylchroman-4-yl)-4-((S)-2-imino-4-isopropyl-4-methyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2,2-dimethylchromane-6-carboxamide

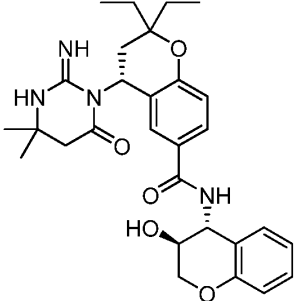
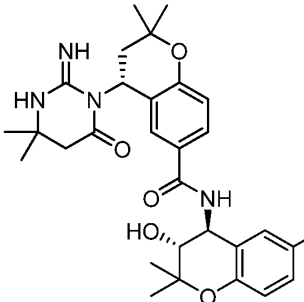
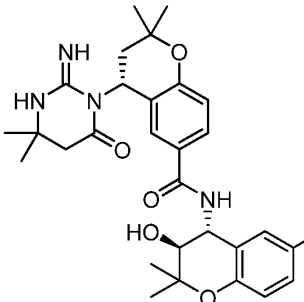
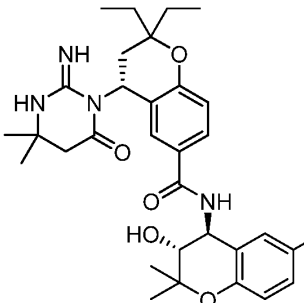
42A		519.3	(4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((1R)-2-hydroxy-2-methyl-2,3-dihydro-1H-inden-1-yl)-2,2-dimethylchromane-6-carboxamide
42B		519.2	(4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((1R)-2-hydroxy-2-methyl-2,3-dihydro-1H-inden-1-yl)-2,2-dimethylchromane-6-carboxamide
43A		519.2	(4R)-N-((1R)-2-hydroxy-2-methyl-2,3-dihydro-1H-inden-1-yl)-4-((S)-2-imino-4-isopropyl-4-methyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2,2-dimethylchromane-6-carboxamide
43B		519.2	(4R)-N-((1R)-2-hydroxy-2-methyl-2,3-dihydro-1H-inden-1-yl)-4-((S)-2-imino-4-isopropyl-4-methyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2,2-dimethylchromane-6-carboxamide

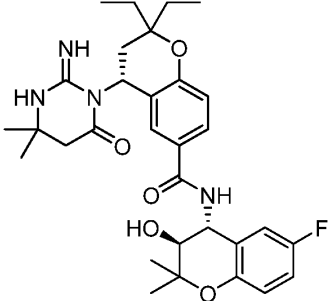
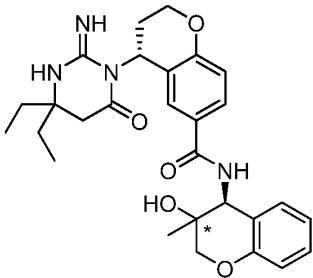
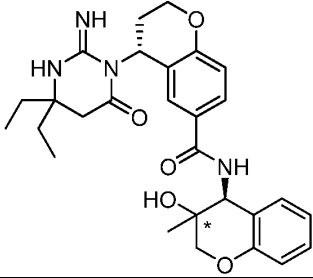
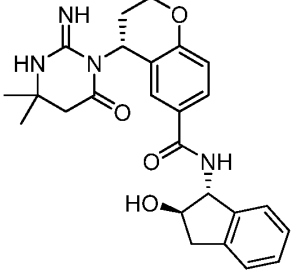
44A		491.2	(4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((1R)-2-hydroxy-2-methyl-2,3-dihydro-1H-inden-1-yl)chromane-6-carboxamide
44B		491.2	(4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((1R)-2-hydroxy-2-methyl-2,3-dihydro-1H-inden-1-yl)chromane-6-carboxamide
45A		521.2	(R)-N-((3S,4R)-3-hydroxychroman-4-yl)-4-((S)-2-imino-4-isopropyl-4-methyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2,2-dimethylchromane-6-carboxamide
46A		567.3	(R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((3S,4R)-6-fluoro-3-hydroxy-2,2-dimethylchroman-4-yl)-2,2-dimethylchromane-6-carboxamide

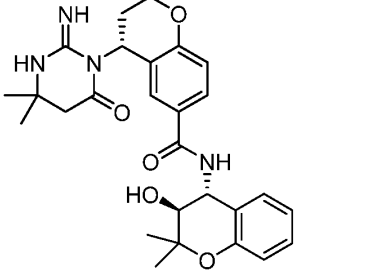
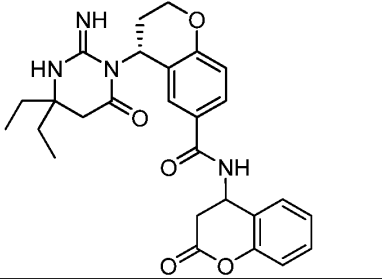
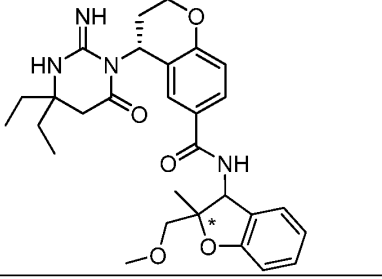
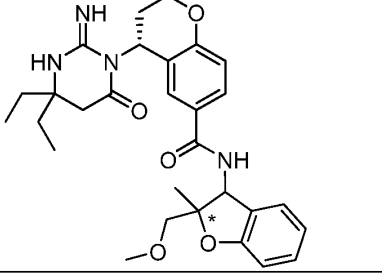
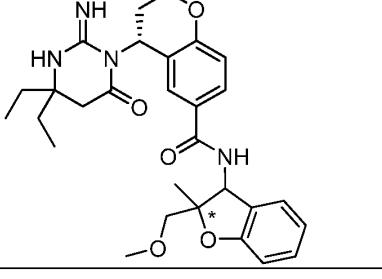
47A		521.3	(R)-N-((3S,4R)-3-hydroxy-2,2-dimethylchroman-4-yl)-4-(2-imino-4,4-dimethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2,2-dimethylchromane-6-carboxamide
48A		477.3	(R)-N-((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-4-(2-imino-4,4-dimethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2,2-dimethylchromane-6-carboxamide
49A		493.3	(R)-N-((3S,4R)-3-hydroxychroman-4-yl)-4-(2-imino-4,4-dimethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2,2-dimethylchromane-6-carboxamide
50A		549.3	(R)-2,2-diethyl-N-((3S,4R)-3-hydroxy-2,2-dimethylchroman-4-yl)-4-(2-imino-4,4-dimethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chromane-6-carboxamide

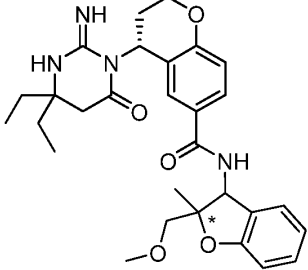
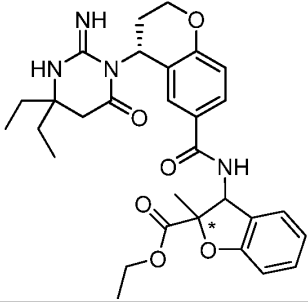
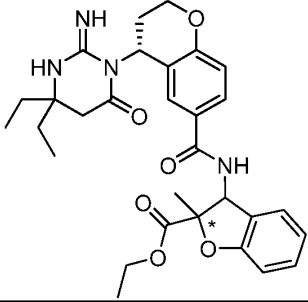
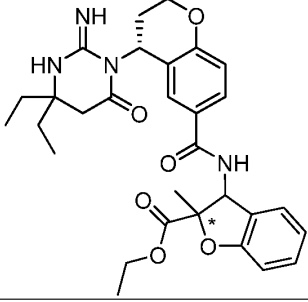
51A		505.3	(R)-2,2-diethyl-N-((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-4-(2-imino-4,4-dimethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chromane-6-carboxamide
52A		521.3	(R)-2,2-diethyl-N-((3S,4R)-3-hydroxychroman-4-yl)-4-(2-imino-4,4-dimethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chromane-6-carboxamide
53A		567.4	(R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((3S,4R)-6-fluoro-3-hydroxy-2,2-dimethylchroman-4-yl)-2,2-dimethylchromane-6-carboxamide
54A		491.3	(4R)-N-((1R)-2-hydroxy-2-methyl-2,3-dihydro-1H-inden-1-yl)-4-(2-imino-4,4-dimethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2,2-dimethylchromane-6-carboxamide

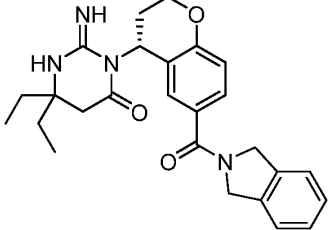
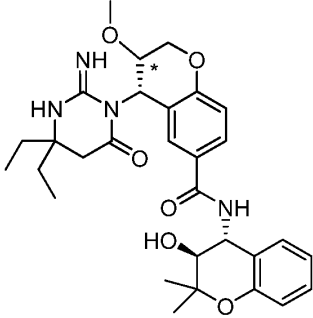
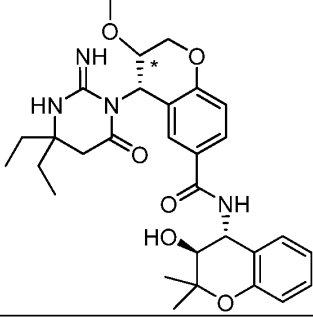
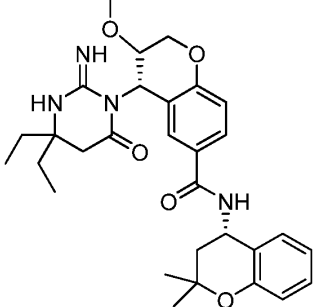
54B		491.6	(4R)-N-((1R)-2-hydroxy-2-methyl-2,3-dihydro-1H-inden-1-yl)-4-(2-imino-4,4-dimethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2,2-dimethylchromane-6-carboxamide
55A		519.3	(4R)-2,2-diethyl-N-((1R)-2-hydroxy-2-methyl-2,3-dihydro-1H-inden-1-yl)-4-(2-imino-4,4-dimethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chromane-6-carboxamide
55B		519.4	(4R)-2,2-diethyl-N-((1R)-2-hydroxy-2-methyl-2,3-dihydro-1H-inden-1-yl)-4-(2-imino-4,4-dimethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chromane-6-carboxamide
56A		493.2	(R)-N-((3S,4R)-3-hydroxychroman-4-yl)-4-(2-imino-4,4-dimethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2,2-dimethylchromane-6-carboxamide

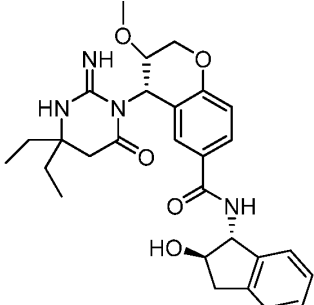
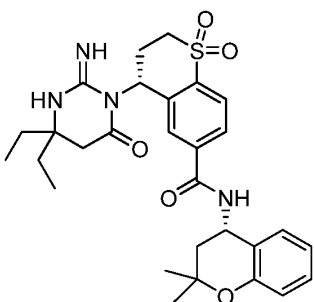
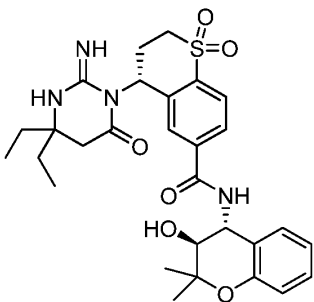
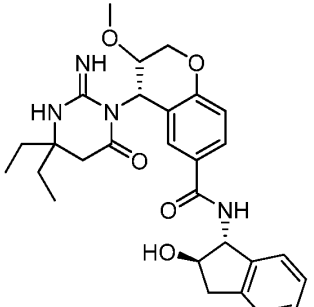
57A		521.3	(R)-2,2-diethyl-N-((3S,4R)-3-hydroxychroman-4-yl)-4-(2-imino-4,4-dimethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chromane-6-carboxamide
58A		539.3	(R)-N-((3R,4S)-6-fluoro-3-hydroxy-2,2-dimethylchroman-4-yl)-4-(2-imino-4,4-dimethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2,2-dimethylchromane-6-carboxamide
58B		539.3	(R)-N-((3S,4R)-6-fluoro-3-hydroxy-2,2-dimethylchroman-4-yl)-4-(2-imino-4,4-dimethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2,2-dimethylchromane-6-carboxamide
59A		567.3	(R)-2,2-diethyl-N-((3R,4S)-6-fluoro-3-hydroxy-2,2-dimethylchroman-4-yl)-4-(2-imino-4,4-dimethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chromane-6-carboxamide

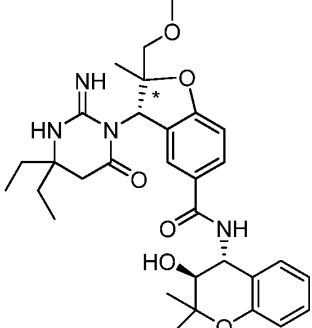
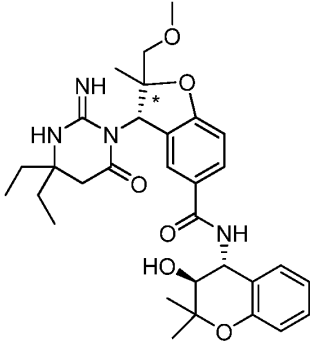
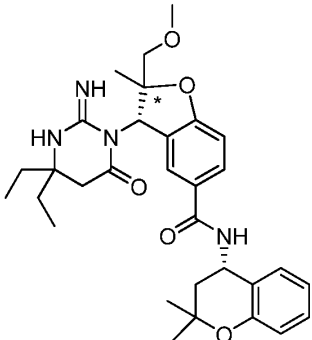
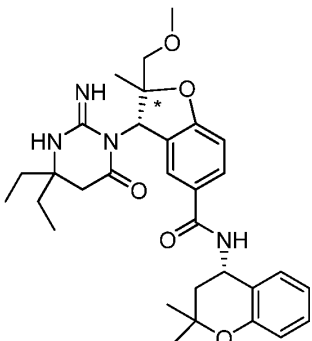
59B		567.3	(R)-2,2-diethyl-N-((3S,4R)-6-fluoro-3-hydroxy-2,2-dimethylchroman-4-yl)-4-(2-imino-4,4-dimethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chromane-6-carboxamide
60A		507.2	(4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((4S)-3-hydroxy-3-methylchroman-4-yl)chromane-6-carboxamide
60B		507.3	(4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((4S)-3-hydroxy-3-methylchroman-4-yl)chromane-6-carboxamide
61A		449.3	(R)-N-((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-4-(2-imino-4,4-dimethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chromane-6-carboxamide

62A		493.3	(R)-N-((3S,4R)-3-hydroxy-2,2-dimethylchroman-4-yl)-4-(2-imino-4,4-dimethyl-6-oxotetrahydropyrimidin-1(2H)-yl)chromane-6-carboxamide
63A		491.3	(4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-(2-oxochroman-4-yl)chromane-6-carboxamide
64A		521.3	(4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-(2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-3-yl)chromane-6-carboxamide
64B		521.3	(4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-(2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-3-yl)chromane-6-carboxamide
64C		521.3	(4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-(2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-3-yl)chromane-6-carboxamide

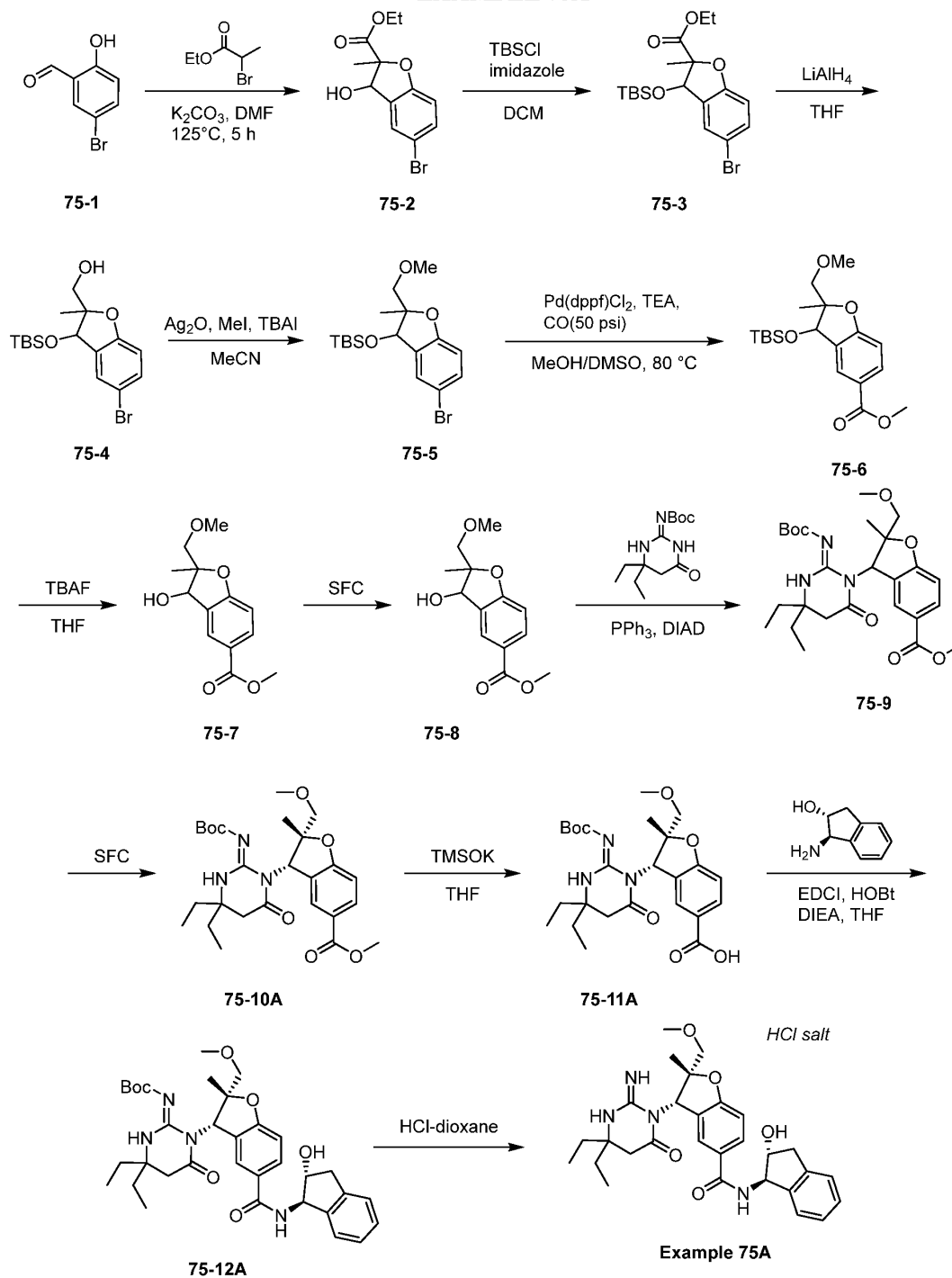
64D		521.3	(4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-(2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-3-yl)chromane-6-carboxamide
65A		549.3	ethyl 3-((R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)chromane-6-carboxamido)-2-methyl-2,3-dihydrobenzofuran-2-carboxylate
65B		549.3	ethyl 3-((R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)chromane-6-carboxamido)-2-methyl-2,3-dihydrobenzofuran-2-carboxylate
65C		549.3	ethyl 3-((R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)chromane-6-carboxamido)-2-methyl-2,3-dihydrobenzofuran-2-carboxylate

66A		447.3	(R)-6,6-diethyl-2-imino-3-(6-(isoindoline-2-carbonyl)chroman-4-yl)tetrahydropyrimidin-4(1H)-one
67A		551.3	(3R,4S)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((3S,4R)-3-hydroxy-2,2-dimethylchroman-4-yl)-3-methoxychromane-6-carboxamide
67B		551.3	(3R,4S)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((3S,4R)-3-hydroxy-2,2-dimethylchroman-4-yl)-3-methoxychromane-6-carboxamide
68A		535.3	(3R,4S)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((S)-2,2-dimethylchroman-4-yl)-3-methoxychromane-6-carboxamide

69A		507.3	(3R,4S)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-3-methoxychromane-6-carboxamide
70A		553.3	(R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((S)-2,2-dimethylchroman-4-yl)thiochromane-6-carboxamide 1,1-dioxide
71A		569.3	(R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((3S,4R)-3-hydroxy-2,2-dimethylchroman-4-yl)thiochromane-6-carboxamide 1,1-dioxide
72A		507.3	(3R,4S)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-3-methoxychromane-6-carboxamide

73A		565.3	(2S,3S)-3-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((3S,4R)-3-hydroxy-2,2-dimethylchroman-4-yl)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxamide
73B		565.2	(2S,3S)-3-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((3S,4R)-3-hydroxy-2,2-dimethylchroman-4-yl)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxamide
74A		549.2	(2S,3S)-3-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((S)-2,2-dimethylchroman-4-yl)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxamide
74B		549.2	(2S,3S)-3-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((S)-2,2-dimethylchroman-4-yl)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxamide

EXAMPLE 75A



Step A: ethyl 5-bromo-3-hydroxy-2-methyl-2,3-dihydrobenzofuran-2-carboxylate **75-2**

Ethyl 2-bromopropanoate (270 g, 1492 mmol) and K₂CO₃ (413 g, 2985 mmol) were added to a solution of 5-bromo-2-hydroxybenzaldehyde **75-1** (300 g, 1492 mmol) in DMF (3 L). The mixture was stirred at 125 °C for 5 h. The mixture was diluted with water (5000 mL) and
5 extracted with EtOAc (2000 mL*3). The organic layers were washed with brine (2000 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, petroleum ether: EtOAc=20:1-5:1) to afford product ethyl 5-bromo-3-hydroxy-2-methyl-2,3-dihydrobenzofuran-2-carboxylate **75-2**.

¹H NMR (400 MHz, chloroform-d) δ 7.45 (d, *J*=1.6 Hz, 1H), 7.34 (dd, *J*=2.0, 8.4 Hz, 1H), 6.79 (d, *J*=8.4 Hz, 1H), 5.27 (s, 1H), 4.12-4.20 (m, 2H), 2.42-2.44 (m, 1H), 1.64 (s, 3H), 1.22 (t, *J*=7.2 Hz, 3H).
10

Step B: ethyl 5-bromo-3-((tert-butyldimethylsilyl)oxy)-2-methyl-2,3-dihydrobenzofuran-2-carboxylate **75-3**

15 Ethyl 5-bromo-3-hydroxy-2-methyl-2,3-dihydrobenzofuran-2-carboxylate **75-2** (300 g, 996 mmol) in DCM (3000 mL) was added to chlorotrimethylsilane (70 g, 644 mmol) and 1H-imidazole (60 g, 881 mmol). The mixture was stirred at 25 °C for 10 h under N₂ atmosphere. Water (3000 mL) was added to the mixture, and the mixture was extracted with DCM (500 mL*2). The organic layers were washed with brine (1000 mL), dried over Na₂SO₄, filtered and concentrated in
20 vacuo, then purified by flash column (petroleum ether/EtOAc=50:1) to give the product ethyl 5-bromo-3-((tert-butyldimethylsilyl)oxy)-2-methyl-2,3-dihydrobenzofuran-2-carboxylate **75-3**.

¹H NMR (400 MHz, chloroform-d) δ 7.26-7.35 (m, 2H), 6.78 (d, *J*=8.4 Hz, 1H), 5.35 (s, 1H), 4.14-4.23 (m, 2H), 1.60 (s, 3H), 1.22-1.27 (m, 3H), 0.93 (s, 9H), 0.18 (s, 6H)

25 Step C: (5-bromo-3-((tert-butyldimethylsilyl)oxy)-2-methyl-2,3-dihydrobenzofuran-2-yl)methanol **75-4**

LiAlH₄ (64.0 g, 1685 mmol) was added to a solution of ethyl 5-bromo-3-((tert-butyldimethylsilyl)oxy)-2-methyl-2,3-dihydrobenzofuran-2-carboxylate **75-3** (350 g, 843 mmol) in THF (3000 mL), in portions at 0 °C for 30 min. Then the mixture was stirred at 27 °C for another
30 30 min. The mixture was quenched with water (100 mL), diluted with EtOAc (5000 mL), dried over anhydrous Na₂SO₄ and MgSO₄, filtered and concentrated to afford product (5-bromo-3-((tert-butyldimethylsilyl)oxy)-2-methyl-2,3-dihydrobenzofuran-2-yl)methanol **75-4**. The product was used for the next step without purification.

¹H NMR (400 MHz, chloroform-d) δ 7.27-7.32 (m, 2H), 6.60-6.70 (m, 1H), 5.23 (s, 1H), 3.55-3.66
35 (m, 2H), 1.77-1.86 (m, 1H), 1.35 (s, 3H), 0.93 (s, 9H), 0.21 (s, 3H), 0.16 (s, 3H).

Step D: ((5-bromo-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-3-yl)oxy)(tert-butyl)dimethylsilane **75-5**

- Iodomethane (968.150 g, 6821 mmol) and TBAI (20 g, 54.1 mmol) was added to a solution of (5-bromo-3-((tert-butyl)dimethylsilyl)oxy)-2-methyl-2,3-dihydrobenzofuran-2-yl)methanol **75-4** (270 g, 723 mmol) and monosilver(I) monosilver(III) monooxide (335 g, 1446 mmol) in MeCN (2.0 L) at 27 °C. The mixture was stirred at 50 °C for 15 h under N₂ atmosphere. The mixture was filtered and concentrated. The residue was purified by flash column (SiO₂, petroleum ether/EtOAc = 100:1) to afford product ((5-bromo-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-3-yl)oxy)(tert-butyl)dimethylsilane **75-5**.
- ¹H NMR (500 MHz, chloroform-d) δ 7.20-7.29 (m, 2H), 6.63 (d, *J*=8.5 Hz, 1H), 5.14 (s, 1H), 3.14-3.46 (m, 5H), 1.34 (s, 3H), 0.89 (s, 9H), 0.07-0.19 (m, 6H).

Step E: methyl 3-((tert-butyl)dimethylsilyl)oxy)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxylate **75-6**.

- Pd(dppf)Cl₂ (18.9 g, 25.8 mmol) and triethylamine (131 g, 1291 mmol) was added to a solution of ((5-bromo-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-3-yl)oxy)(tert-butyl)dimethylsilane **75-5** (100 g, 258 mmol) in MeOH (1000 mL) and DMSO (500 mL). The mixture was stirred at 80 °C for 12 h under 50 psi CO atmosphere. The mixture was filtered and concentrated. The residue was added water (500 mL), and extracted with EtOAc (300 mL x 2). The organic layers were washed with brine (300 mL), dried over Na₂SO₄, filtered and concentrated in vacuo, then purified by flash column (petroleum ether/EtOAc = 100:0 to 10:1) to afford product methyl 3-((tert-butyl)dimethylsilyl)oxy)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxylate **75-6**.
- ¹H NMR (500 MHz, chloroform-d) δ 7.91-7.99 (m, 2H), 6.79 (d, *J*=9.5 Hz, 1H), 5.21 (s, 1H), 3.87 (s, 3H), 3.41-3.46 (m, 1H), 3.36 (s, 3H), 3.32-3.35 (m, 1H), 1.41 (s, 3H), 0.92 (s, 9H), 0.22 (s, 3H), 0.17 (s, 3H).

Step F: methyl 3-hydroxy-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxylate **75-7**.

- TBAF (355 mL, 355 mmol) was added to a solution of methyl 3-((tert-butyl)dimethylsilyl)oxy)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxylate **75-6** (65 g, 177 mmol) in THF (100 mL). The mixture was stirred at 27 °C for 0.5 hours. The mixture was diluted with water (200 mL) and extracted with EtOAc (100 mL x 3). The organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, petroleum ether: EtOAc = 10:1 to 3:1) to afford product methyl 3-hydroxy-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxylate **75-7**.

¹H NMR (400 MHz, chloroform-d) δ 8.04 (d, $J=2.0$ Hz, 1H), 7.90 (dd, $J=2.0, 8.5$ Hz, 1H), 6.78 (d, $J=8.5$ Hz, 1H), 5.08 (s, 1H), 3.85 (s, 3H), 3.30-3.47 (m, 5H), 2.61 (br, 1H), 1.49 (s, 3H).

Step G: methyl (2S,3R)-3-hydroxy-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxylate **75-8 (P1)** and methyl (2R,3S)-3-hydroxy-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxylate **75-8 (P2)**

The methyl 3-hydroxy-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxylate **75-7** (40 g, 159 mmol) was purified by SFC (SFC-7 Method Column DAICEL CHIRALPAK AD (250mm x 50mm, 10um). Condition 0.1% NH₃H₂O IPA Begin B 25% End B 25%. Gradient time (min) 100%B Hold Time(min) FlowRate (mL/min) 200) to give methyl (2S,3R)-3-hydroxy-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxylate **75-8 (P1)** (Rt=3.450) and methyl (2R,3S)-3-hydroxy-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxylate **75-8 (P2)** (Rt=3.951).

75-8 (P1): MS (ESI) m/z 253.1 (M+H⁺)

¹H NMR (400 MHz, chloroform-d) δ 8.04 (s, 1H), 7.91 (dd, $J=2.0, 8.5$ Hz, 1H), 6.78 (d, $J=8.5$ Hz, 1H), 5.07 (d, $J=4.5$ Hz, 1H), 3.84 (s, 3H), 3.27-3.46 (m, 5H), 2.47 (br, $J=7.5$ Hz, 1H), 1.47 (s, 3H).

75-8 (P2): MS (ESI) m/z 253.1 (M+H⁺)

¹H NMR (400 MHz, chloroform-d) δ 8.01 (d, $J=1.2$ Hz, 1H), 7.87 (dd, $J=1.6, 8.4$ Hz, 1H), 6.76 (d, $J=8.4$ Hz, 1H), 5.05 (s, 1H), 3.82 (s, 3H), 3.39-3.46 (m, 1H), 3.28-3.33 (m, 4H), 2.74 (br, 1H), 1.46 (s, 3H).

Step H: methyl 3-(2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxylate **75-9**

DIAD (10.58 mL, 54.4 mmol) was added dropwise to a solution of tert-butyl (4,4-diethyl-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate (11 g, 40.8 mmol), methyl (2S,3R)-3-hydroxy-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxylate **75-8** (10 g, 39.6 mmol) and triphenylphosphine (14 g, 53.4 mmol) in THF (150 mL), at 25 °C under N₂ atmosphere. Then the mixture was stirred at 27 °C for 2h. The mixture was concentrated and added EtOAc (100 mL) to dissolved and added pet. ether slowly to white solid appear. The mixture filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, petroleum ether: EtOAc: DCM=100:10:1-100:10:10) to afford product methyl 3-(2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxylate **75-9**.

MS (ESI) m/z : 504.2 (M+H⁺)

¹H NMR (400 MHz, chloroform-d) δ 9.78-10.08 (m, 1H), 7.87-7.99 (m, 1H), 7.68-7.79 (m, 1H), 6.79-6.89 (m, 1H), 6.44-6.47 (m, 1H), 3.83-3.84 (m, 3H), 3.52-3.58 (m, 2H), 3.40 (s, 3H), 2.45-2.49 (m, 2H), 1.57-1.68 (m, 4H), 1.35-1.54 (m, 11H), 0.89-0.98 (m, 6H).

- 5 Step I: (2R,3S)-methyl 3-(2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxylate **75-10A** and methyl 3-(2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxylate **75-10B**

- 10 The methyl 3-(2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxylate **75-9** (25.5 g, 50.6 mmol) was purified by SFC (Instrument SFC-17 Method Column DAICEL CHIRALPAK AD-H (250mm x 30mm, 5 μ m), Condition 0.1% NH₃H₂O IPA Begin B 30% End B 30% Gradient Time (min) 100%B Hold Time (min) FlowRate (mL/min) 60 Injections 100) to give (2R,3S)-methyl 3-(2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxylate **75-10A (P1)** (9.0 g, 17.87 mmol, 35.3% yield) (R_t=1.869) as a colorless oil and methyl 3-(2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxylate **75-10B (P2)**.

75-10A (P1): MS (ESI) m/z 504.3 (M+H⁺)

- 20 ¹H NMR (500 MHz, chloroform-d) δ 10.00 (s, 1H), 7.93 (dd, J =1.5, 8.5 Hz, 1H), 7.76 (s, 1H), 6.84 (d, J =8.5 Hz, 1H), 6.44 (s, 1H), 3.84 (s, 3H), 3.54 (s, 2H), 3.39 (s, 3H), 2.45 (s, 2H), 1.58-1.64 (m, 4H), 1.50-1.54 (m, 12H), 0.91-0.94 (m, 6H).

75-10B (P2): MS (ESI) m/z 504.3 (M+H⁺)

- 25 ¹H NMR (500 MHz, chloroform-d) δ 9.91 (s, 1H), 7.91 (dd, J =1.5, 8.5 Hz, 1H), 7.71 (s, 1H), 6.83 (d, J =8.5 Hz, 1H), 6.47 (s, 1H), 3.83 (s, 3H), 3.53-3.59 (m, 2H), 3.40 (s, 3H), 2.50 (s, 2H), 1.60-1.66 (m, 4H), 1.51 (s, 9H), 1.37 (s, 3H), 0.90-0.97 (m, 6H).

Step J: (2R,3S)-3-(2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxylic acid **75-11A**

- 30 Potassium trimethylsilanolate (5.60 g, 43.7 mmol) was added to a solution of (2R,3S)-methyl 3-(2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxylate **75-10A** (5.5 g, 10.92 mmol) in THF (100 mL). The reaction was stirred at 27 °C for 1 h under N₂ atmosphere. The solution of (2R,3S)-3-(2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2-

(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxylic acid **75-11A** was used for next step directly without any further manipulation or purification.

MS (ESI) m/z : 490.1 (**M+H**⁺)

- 5 Step K: tert-butyl (4,4-diethyl-1-((2R,3S)-5-(((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)carbamoyl)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-3-yl)-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate **75-12A**

N-ethyl-N-isopropylpropan-2-amine (7.06 g, 54.6 mmol) was added to a solution of (2R,3S)-3-(2-(((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxylic acid **75-11A** (5.35 g, 10.93 mmol), N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (4.19 g, 21.86 mmol), (1R,2R)-1-amino-2,3-dihydro-1H-inden-2-ol (1.956 g, 13.11 mmol) and 1H-benzo[d][1,2,3]triazol-1-ol (2.95 g, 21.86 mmol) in THF (100 mL). The reaction was stirred at 27 °C for 3 h under N₂ atmosphere. The mixture was quenched with water (100 mL), and extracted with EtOAc (100 mL x 2). The organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, petroleum ether: EtOAc: DCM=100:10:10-20:10:10) to give tert-butyl (4,4-diethyl-1-((2R,3S)-5-(((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)carbamoyl)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-3-yl)-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate **75-12A**.

- 20 **MS (ESI)** m/z : 621.5 (**M+H**⁺)

¹H NMR (500 MHz, chloroform-d) δ 10.00 (s, 1H), 7.68 (s, 1H), 7.61 (dd, $J=1.5, 8.5$ Hz, 1H), 7.26-7.32 (m, 3H), 6.85 (d, $J=8.5$ Hz, 1H), 6.51 (s, 1H), 6.44 (d, $J=6.0$ Hz, 1H), 5.28-5.29 (m, 1H), 4.82 (s, 1H), 4.47 (q, $J=7.5$ Hz, 1H), 3.55 (d, $J=1.5$ Hz, 2H), 3.39 (s, 3H), 3.30-3.37 (m, 1H), 2.98 (dd, $J=8.0, 15.5$ Hz, 1H), 2.45 (d, $J=2.5$ Hz, 2H), 1.58-1.66 (m, 4H), 1.49-1.56 (m, 12H), 0.94 (q, $J=7.5$ Hz, 6H).

Step L: (2R,3S)-3-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxamide **Example 75A**

- 30 A solution of tert-butyl (4,4-diethyl-1-((2R,3S)-5-(((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)carbamoyl)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-3-yl)-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate **75-12A** (5.5 g, 8.86 mmol) in 4N HCl-dioxane (100 mL) was stirred at 27 °C for 1 h. The mixture was concentrated and purified by HPLC (Instrument ACSSH-prepL-K3 Method Column YMC-Triart Prep C18 250*50mm*10um Condition water (0.05% ammonia hydroxide v/v)-ACN Begin B 35 End B 55 Gradient Time (min) 15 100%B

Hold Time(min) 5 FlowRate (mL/min) 110) then freeze-drying to give free base of desired product. The free base product was dissolved in MeCN (50 mL) and conc HCl (2mL) in water (150 mL) and freeze-drying to afford product (2R,3S)-3-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-2-(methoxymethyl)-2-methyl-2,3-

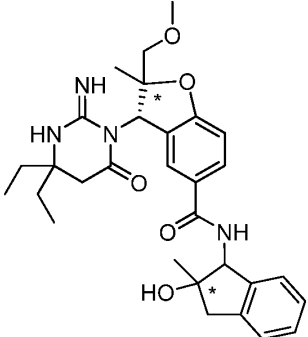
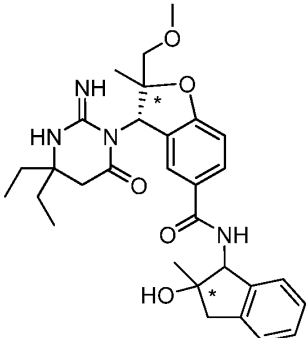
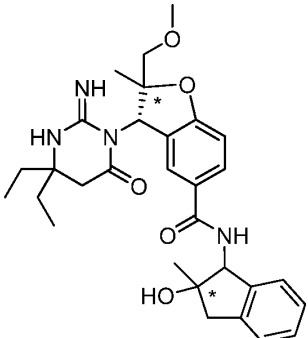
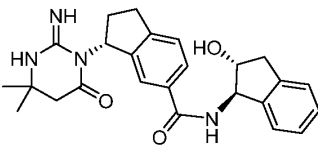
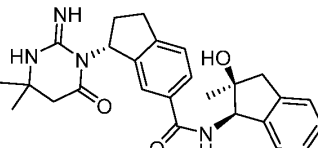
5 dihydrobenzofuran-5-carboxamide **Example 75A**.

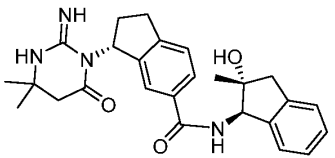
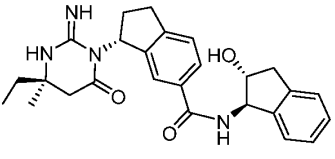
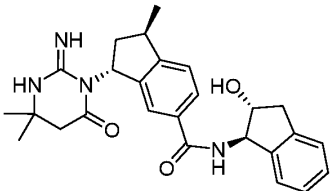
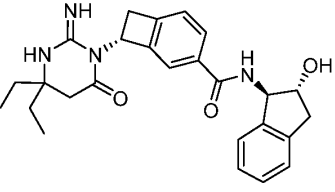
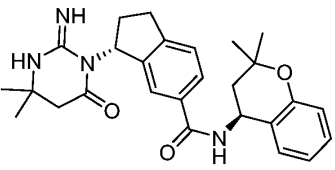
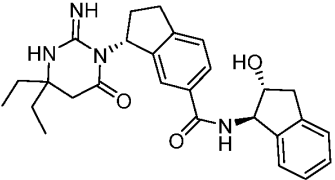
MS (ESI) m/z : 521.2 ($M+H^+$)

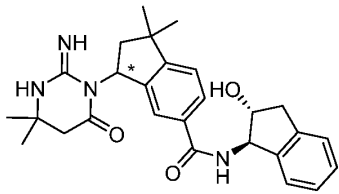
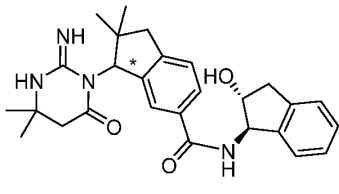
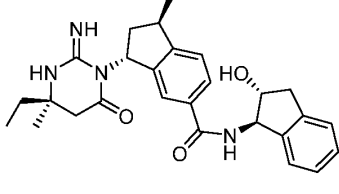
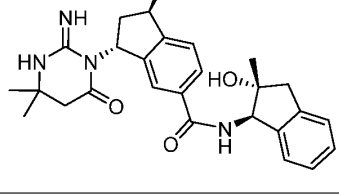
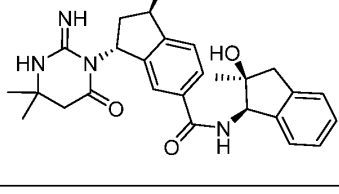
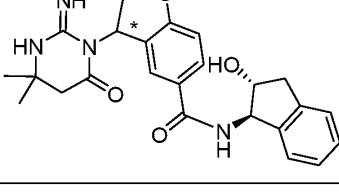
1H NMR (500 MHz, methanol- d_4) δ 7.81-8.05 (m, 2H), 7.15-7.30 (m, 4H), 7.06 (d, $J=8.5$ Hz, 0.38H), 6.89 (d, $J=9.0$ Hz, 0.6H), 6.38 (s, 0.4H), 5.40-5.47 (m, 1.6H), 4.47-4.53 (m, 1H), 3.66-3.79 (m, 1.4H), 3.53 (d, $J=9.5$ Hz, 0.6H), 3.40-3.46 (m, 3H), 3.27-3.31 (m, 1H), 2.84-3.09 (m, 2H), 2.56-2.81 (m, 1H), 1.64-1.94 (m, 4H), 1.55 (d, $J=14.5$ Hz, 3H), 0.93-1.04 (m, 6H).

TABLE 2

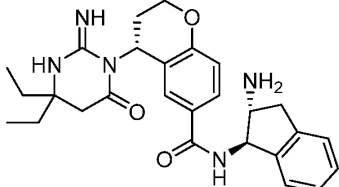
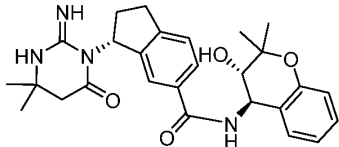
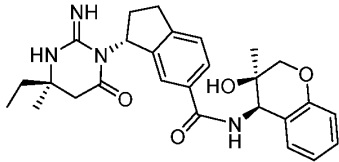
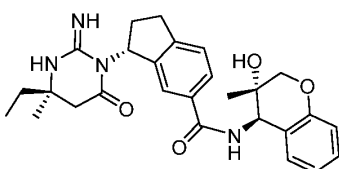
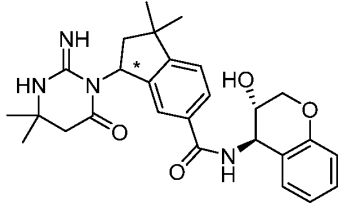
Example	Structure	LC/MS ($M+1$) ⁺	Name
75B		521.2	(2S,3S)-3-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxamide
76A		535.3	(2S,3S)-3-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-(2-hydroxy-2-methyl-2,3-dihydro-1H-inden-1-yl)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxamide

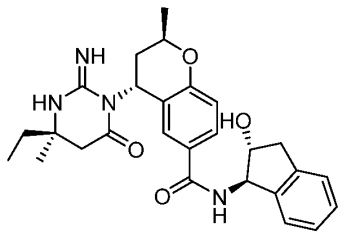
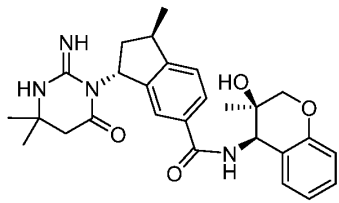
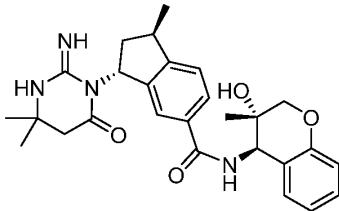
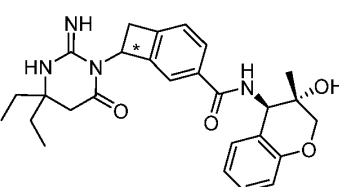
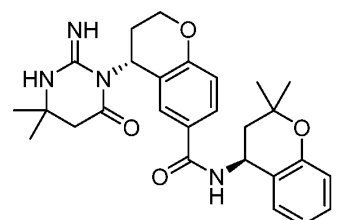
76B		535.4	(2S,3S)-3-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-(2-hydroxy-2-methyl-2,3-dihydro-1H-inden-1-yl)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxamide
77A		535.3	(2S,3S)-3-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-(2-hydroxy-2-methyl-2,3-dihydro-1H-inden-1-yl)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxamide
77B		535.3	(2S,3S)-3-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-(2-hydroxy-2-methyl-2,3-dihydro-1H-inden-1-yl)-2-(methoxymethyl)-2-methyl-2,3-dihydrobenzofuran-5-carboxamide
78		433.0	(3R)-N-[(1R,2R)-2-hydroxyindan-1-yl]-3-(2-imino-4,4-dimethyl-6-oxohexahydropyrimidin-1-yl)indane-5-carboxamide
79		447.3	(3R)-N-[(1R,2S)-2-hydroxy-2-methyl-indan-1-yl]-3-(2-imino-4,4-dimethyl-6-oxohexahydropyrimidin-1-yl)indane-5-carboxamide

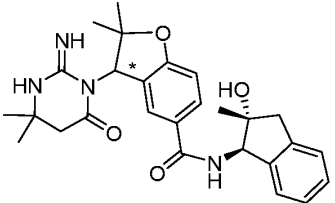
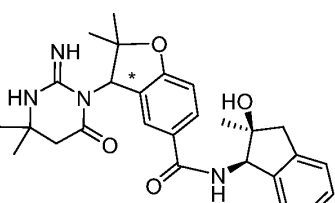
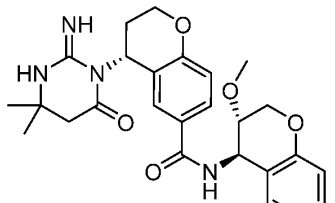
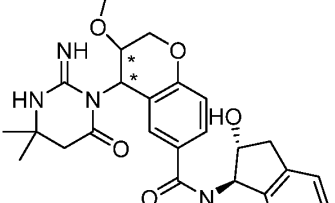
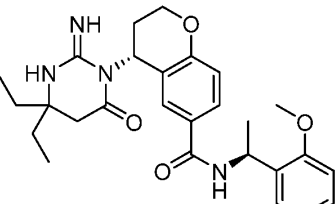
			yl)indane-5-carboxamide
80		447.0	(3R)-N-[(1R,2R)-2-hydroxy-2-methyl-indan-1-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)indane-5-carboxamide
81		447.3	(3R)-3-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(1R,2R)-2-hydroxyindan-1-yl]indane-5-carboxamide
82		447.3	(1R,3R)-N-[(1R,2R)-2-hydroxyindan-1-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-1-methyl-indane-5-carboxamide
83		447.1	(8R)-8-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxyindan-1-yl]bicyclo[4.2.0]octa-1(6),2,4-triene-3-carboxamide
84		461.1	(3R)-N-[(4S)-2,2-dimethylchroman-4-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)indane-5-carboxamide
85		461.3	(3R)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxyindan-1-yl]indane-5-carboxamide

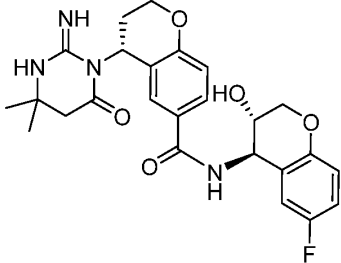
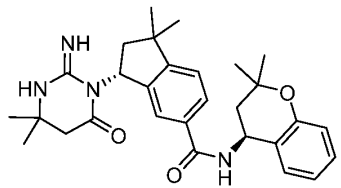
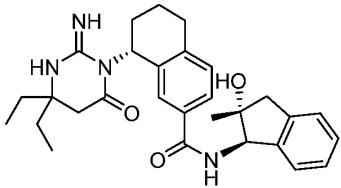
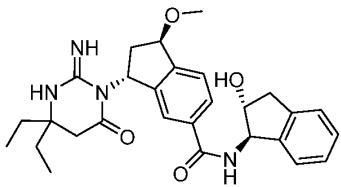
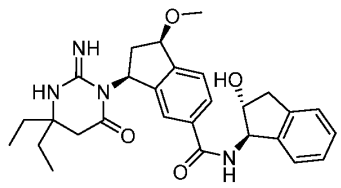
86		461.3	N-[(1R,2R)-2-hydroxyindan-1-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-1,1-dimethyl-indane-5-carboxamide
87		461.3	N-[(1R,2R)-2-hydroxyindan-1-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-2,2-dimethyl-indane-5-carboxamide
88		461.3	(1R,3R)-3-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(1R,2R)-2-hydroxyindan-1-yl]-1-methyl-indane-5-carboxamide
89		461.3	(1R,3R)-N-[(1R,2R)-2-hydroxy-2-methyl-indan-1-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-1-methyl-indane-5-carboxamide
90		461.3	(1R,3R)-N-[(1R,2S)-2-hydroxy-2-methyl-indan-1-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-1-methyl-indane-5-carboxamide
91		463.1	N-[(1R,2R)-2-hydroxyindan-1-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-2,2-dimethyl-3H-benzofuran-5-carboxamide

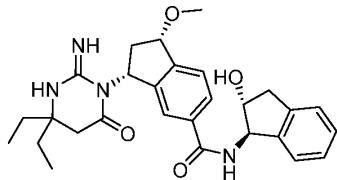
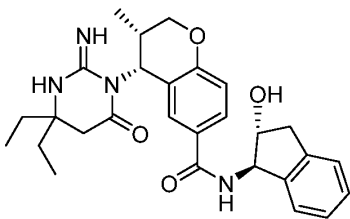
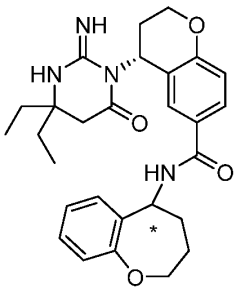
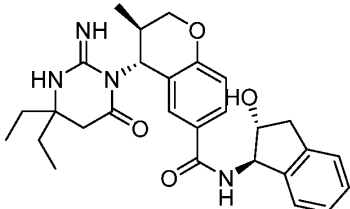
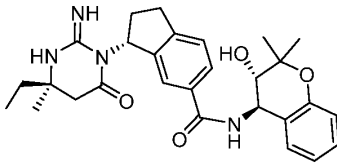
92		465.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R)-2-hydroxy-1-phenylethyl]chromane-6-carboxamide
93		475.3	N-[(1R,2R)-2-hydroxy-2-methyl-indan-1-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-1,1-dimethyl-indane-5-carboxamide
94		475.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxyindan-1-yl]tetralin-6-carboxamide
95		475.3	(1R,3R)-3-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(1R,2R)-2-hydroxy-2-methyl-indan-1-yl]-1-methyl-indane-5-carboxamide
96		475.3	(1R,3R)-3-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(1R,2S)-2-hydroxy-2-methyl-indan-1-yl]-1-methyl-indane-5-carboxamide

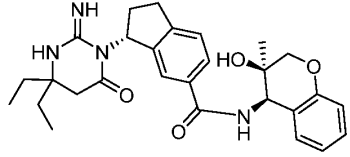
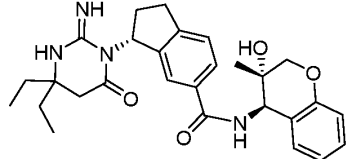
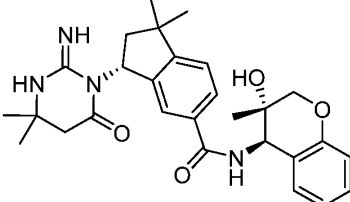
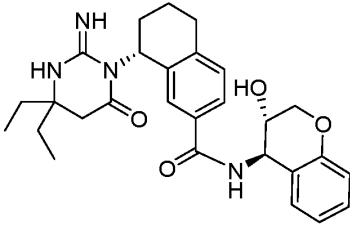
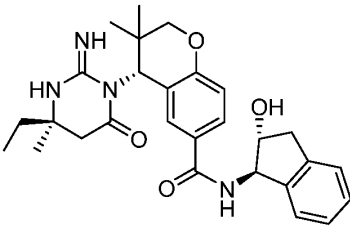
97		476.2	(4R)-N-[(1R,2R)-2-aminoindan-1-yl]-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)chromane-6-carboxamide
98		477.1	(3R)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)indane-5-carboxamide
99		477.4	(3R)-3-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(3R,4R)-3-hydroxy-3-methyl-chroman-4-yl]indane-5-carboxamide
100		477.3	(3R)-3-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]indane-5-carboxamide
101		477.3	N-[(3S,4R)-3-hydroxychroman-4-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-1,1-dimethyl-indane-5-carboxamide

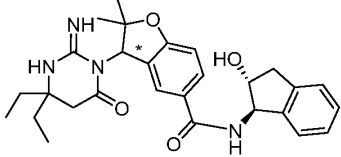
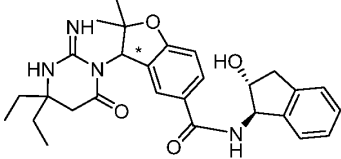
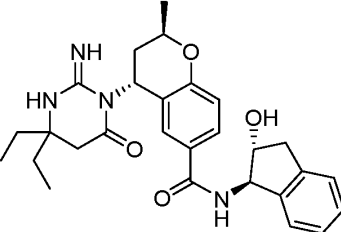
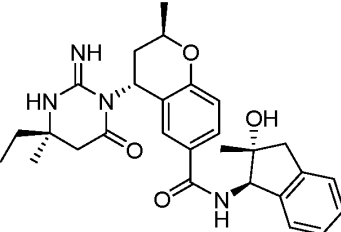
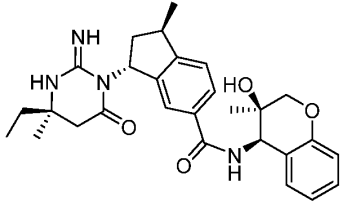
102		477.3	(2R,4R)-4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(1R,2R)-2-hydroxyindan-1-yl]-2-methyl-chromane-6-carboxamide
103		477.3	(1R,3R)-N-[(3R,4R)-3-hydroxy-3-methyl-chroman-4-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-1-methyl-indane-5-carboxamide
104		477.2	(1R,3R)-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-1-methyl-indane-5-carboxamide
105		477.1	8-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]bicyclo[4.2.0]octa-1(6),2,4-triene-3-carboxamide
106		477.3	(4R)-N-[(4S)-2,2-dimethylchroman-4-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)chromane-6-carboxamide

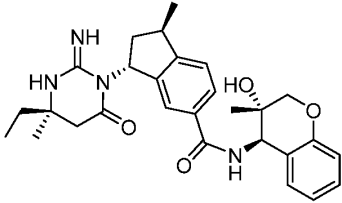
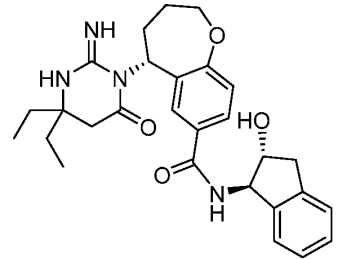
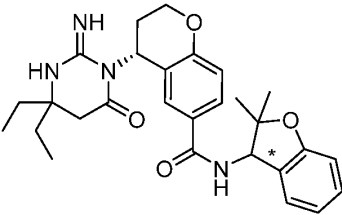
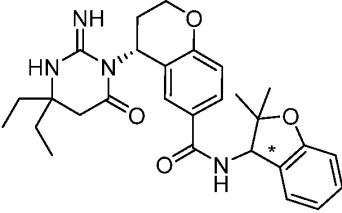
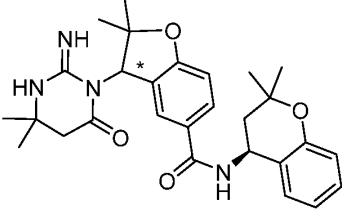
107		477.3	N-[(1R,2R)-2-hydroxy-2-methyl-indan-1-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-2,2-dimethyl-3H-benzofuran-5-carboxamide
108		477.3	N-[(1R,2S)-2-hydroxy-2-methyl-indan-1-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-2,2-dimethyl-3H-benzofuran-5-carboxamide
109		479.2	(4R)-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-methoxychroman-4-yl]chromane-6-carboxamide
110		479.2	N-[(1R,2R)-2-hydroxyindan-1-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-3-methoxy-chromane-6-carboxamide
111		479.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1S)-1-(2-methoxyphenyl)ethyl]chromane-6-carboxamide

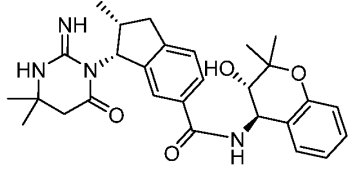
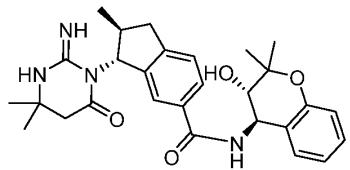
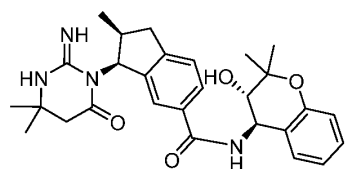
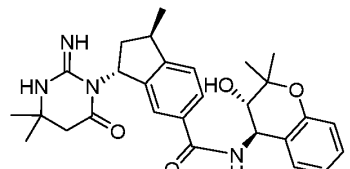
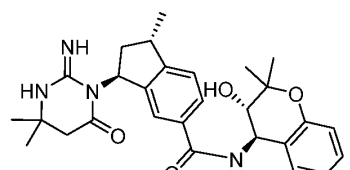
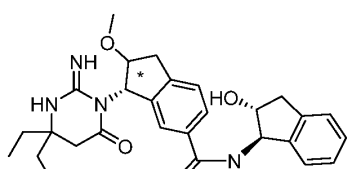
112		483.3	(4R)-N-[(3S,4R)-6-fluoro-3-hydroxy-chroman-4-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)chromane-6-carboxamide
113		489.3	(3R)-N-[(4S)-2,2-dimethylchroman-4-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-1,1-dimethyl-indane-5-carboxamide
114		489.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxy-2-methyl-indan-1-yl]tetralin-6-carboxamide
115		491.3	(1R,3R)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxyindan-1-yl]-1-methoxy-indane-5-carboxamide
116		491.3	(1R,3S)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxyindan-1-yl]-1-methoxy-indane-5-carboxamide

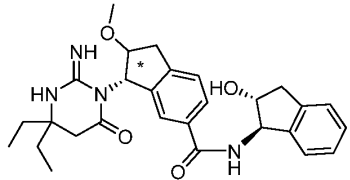
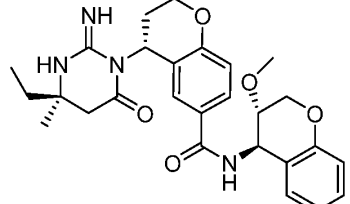
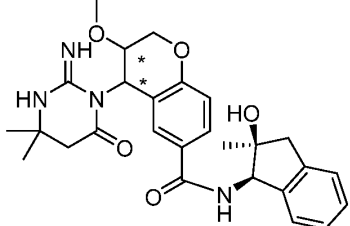
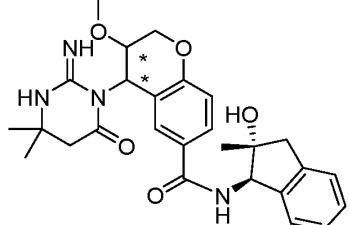
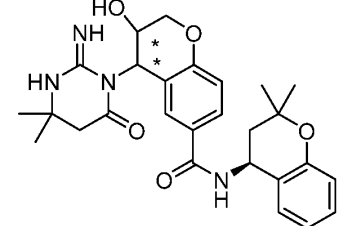
117		491.3	(1S,3R)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxyindan-1-yl]-1-methoxy-indane-5-carboxamide
118		491.3	(3S,4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxyindan-1-yl]-3-methyl-chromane-6-carboxamide
119		491.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-(2,3,4,5-tetrahydro-1-benzoxepin-5-yl)chromane-6-carboxamide
120		491.3	(3R,4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxyindan-1-yl]-3-methyl-chromane-6-carboxamide
121		491.3	(3R)-3-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]indane-5-carboxamide

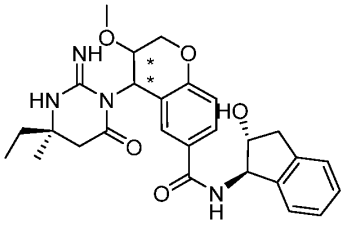
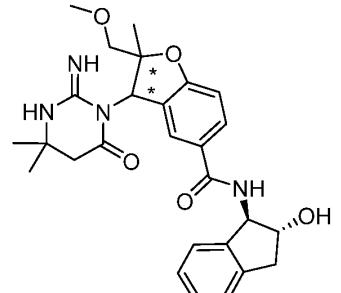
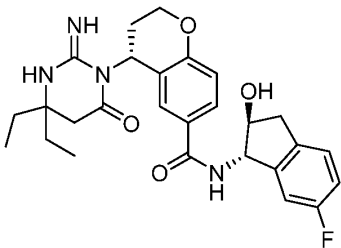
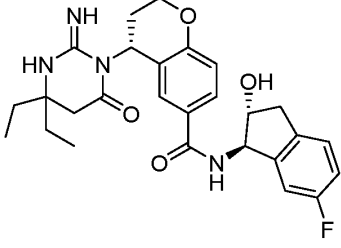
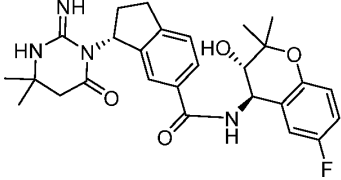
122		491.3	(3R)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3R,4R)-3-hydroxy-3-methyl-chroman-4-yl]indane-5-carboxamide
123		491.3	(3R)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]indane-5-carboxamide
124		491.3	(3R)-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-1,1-dimethyl-indane-5-carboxamide
125		491.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]tetralin-6-carboxamide
126		491.3	(4R)-4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(1R,2R)-2-hydroxyindan-1-yl]-3,3-dimethyl-chromane-6-carboxamide

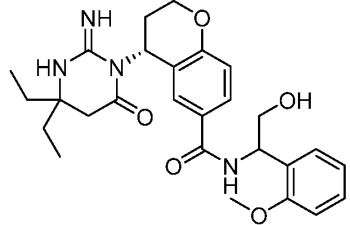
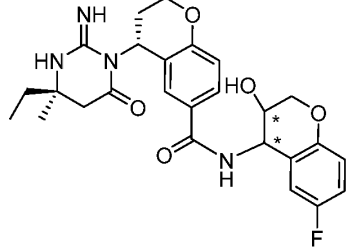
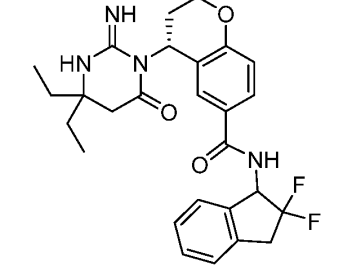
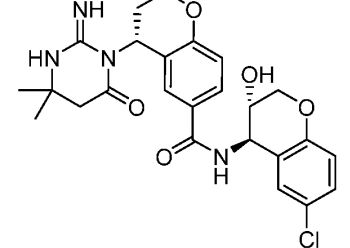
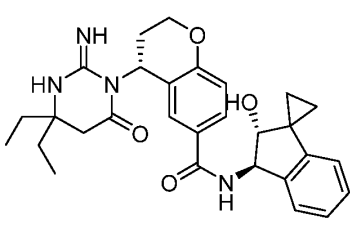
127A		491.3	3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxyindan-1-yl]-2,2-dimethyl-3H-benzofuran-5-carboxamide
127B		491.3	3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxyindan-1-yl]-2,2-dimethyl-3H-benzofuran-5-carboxamide
128		491.3	(2R,4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxyindan-1-yl]-2-methyl-chromane-6-carboxamide
129		491.3	(2R,4R)-4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(1R,2R)-2-hydroxy-2-methyl-indan-1-yl]-2-methyl-chromane-6-carboxamide
130		491.3	(1R,3R)-3-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(3R,4R)-3-hydroxy-3-methyl-chroman-4-yl]-1-methyl-indane-5-carboxamide

131		491.2	(1R,3R)-3-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]-1-methyl-indane-5-carboxamide
132		491.1	(5R)-5-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxyindan-1-yl]-2,3,4,5-tetrahydro-1-benzoxepine-7-carboxamide
133A		491.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-(2,2-dimethyl-3H-benzofuran-3-yl)chromane-6-carboxamide
133B		491.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-(2,2-dimethyl-3H-benzofuran-3-yl)chromane-6-carboxamide
134		491.3	N-[(4S)-2,2-dimethylchroman-4-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-2,2-dimethyl-3H-benzofuran-5-carboxamide

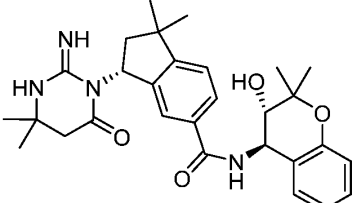
135		491.3	(2R,3R)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-2-methyl-indane-5-carboxamide
136		491.3	(2S,3R)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-2-methyl-indane-5-carboxamide
137		491.3	(2S,3S)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-2-methyl-indane-5-carboxamide
138		491.3	(1R,3R)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-1-methyl-indane-5-carboxamide
139		491.3	(1S,3S)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-1-methyl-indane-5-carboxamide
140A		491.3	(3S)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxyindan-1-yl]-2-methoxy-indane-5-carboxamide

140B		491.3	(3S)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxyindan-1-yl]-2-methoxy-indane-5-carboxamide
141		493.2	(4R)-4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(3S,4R)-3-methoxychroman-4-yl]chromane-6-carboxamide
142		493.2	N-[(1R,2S)-2-hydroxy-2-methyl-indan-1-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-3-methoxy-chromane-6-carboxamide
143		493.2	N-[(1R,2R)-2-hydroxy-2-methyl-indan-1-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-3-methoxy-chromane-6-carboxamide
144		493.3	N-[(4S)-2,2-dimethylchroman-4-yl]-3-hydroxy-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)chromane-6-carboxamide

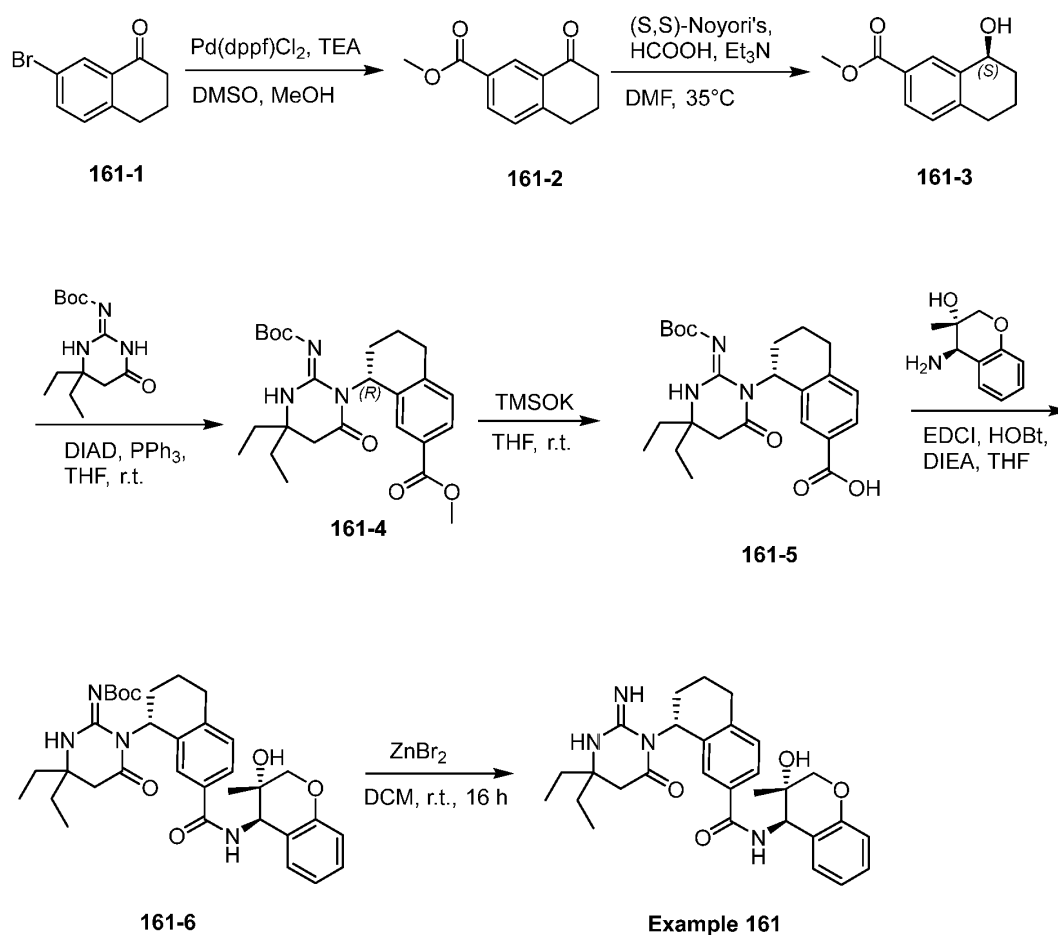
145		493.2	4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(1R,2R)-2-hydroxyindan-1-yl]-3-methoxy-chromane-6-carboxamide
146		493.1	N-[(1R,2R)-2-hydroxyindan-1-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-2-(methoxymethyl)-2-methyl-3H-benzofuran-5-carboxamide
147		495.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1S,2S)-6-fluoro-2-hydroxyindan-1-yl]chromane-6-carboxamide
148		495.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-6-fluoro-2-hydroxyindan-1-yl]chromane-6-carboxamide
149		495.1	(3R)-N-[(3S,4R)-6-fluoro-3-hydroxy-2,2-dimethyl-chroman-4-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)indane-5-carboxamide

150		495.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[2-hydroxy-1-(2-methoxyphenyl)ethyl]chromane-6-carboxamide
151		497.2	(4R)-4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-(6-fluoro-3-hydroxy-chroman-4-yl)chromane-6-carboxamide
152		497.2	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-(2,2-difluoroindan-1-yl)chromane-6-carboxamide
153		499.1	(4R)-N-[(3S,4R)-6-chloro-3-hydroxy-chroman-4-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)chromane-6-carboxamide
154		503.2	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1'R,2'R)-2'-hydroxyspiro[cyclopropane-1,3'-indane]-1'-yl]chromane-6-carboxamide

155		503.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1'S,2'S)-2'-hydroxyspiro[cyclopropane-1,3'-indane]-1'-yl]chromane-6-carboxamide
156		503.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(4S)-2,2-dimethylchroman-4-yl]tetralin-6-carboxamide
157		505.3	(1R,3R)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxy-2-methyl-indan-1-yl]-1-methoxy-indane-5-carboxamide
158		505.3	(1S,3R)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxy-2-methyl-indan-1-yl]-1-methoxy-indane-5-carboxamide
159		505.4	(3R)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]indane-5-carboxamide

160		505.2	(3R)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-1,1-dimethyl-indane-5-carboxamide
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EXAMPLE 161

5 Step A: methyl 8-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylate **161-2**

PdCl₂(dppf) (11 g, 15.03 mmol) and triethylamine (108 mL, 777 mmol) was added to a solution of 7-bromo-1-tetralone **161-1** (35 g, 155 mmol) in MeOH (200 mL) and DMSO (100 mL).

The mixture was stirred at 80 °C for 48 h under 50 psi CO atmosphere. After cooled, the mixture was concentrated in vacuo. The residue was diluted with water (200 mL), and extracted with EtOAc (200 mL*3). The combined organic layers were washed with water (400 mL) and brine (400 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude was purified by column

- 5 chromatography (SiO₂, petroleum ether: EtOAc = 3:1) to afford methyl 8-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylate **161-2**.

¹H NMR (400 MHz, chloroform-d) δ 8.63 (d, *J* = 1.2 Hz, 1H), 8.08 (dd, *J* = 2.0, 6.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 3.90 (s, 3H), 2.99 (t, *J* = 6.0 Hz, 2H), 2.66 (t, *J* = 6.4 Hz, 2H), 2.10-2.17 (m, 2H)

- 10 Step B: methyl (S)-8-hydroxy-5,6,7,8-tetrahydronaphthalene-2-carboxylate **161-3**

A solution of formic acid (27.7 mL, 734 mmol) and TEA (205 mL, 1469 mmol) in DMF (400 mL) was stirred for 15 min, then methyl 8-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylate **161-2** (50 g, 245 mmol) and (S,S)-N-(p-toluenesulfonyl)-1,2-diphenylethanediamine(chloro)(p-cymene)ruthenium(II) (6.23 g, 9.79 mmol) were added and the mixture was stirred at 35 °C for 16 h. The mixture was diluted with water (800 mL) and extracted with EtOAc (500 mL x 3). The combined organic layers were washed with water (500 mL) and brine (500 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue which was purified by flash silica gel chromatography (ISCO®; Agela® Flash Column Silica-CS(330 g), Eluent of 0~30% Ethyl acetate/petroleum ether gradient @85 mL/min) to afford methyl (S)-8-hydroxy-5,6,7,8-tetrahydronaphthalene-2-carboxylate **161-3**.

- 20 ¹H NMR (400 MHz, chloroform-d) δ 8.13 (s, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 4.82-4.83 (m, 1H), 3.90 (s, 3H), 2.85-2.92 (m, 1H), 2.73-2.80 (m, 1H), 2.00-2.05 (m, 2H), 1.89-1.91 (m, 1H), 1.76-1.84 (m, 1H)

- 25 Step C: give methyl (R,E)-8-(2-(((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl))-5,6,7,8-tetrahydronaphthalene-2-carboxylate **161-4**

DIAD (36.8 mL, 189 mmol) was added dropwise to a solution of tert-butyl (E)-(4,4-diethyl-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate (43.1 g, 160 mmol), methyl (S)-8-hydroxy-5,6,7,8-tetrahydronaphthalene-2-carboxylate **161-3** (30 g, 145 mmol) and triphenylphosphane (49.6 g, 189 mmol) in THF (500 mL) at 0 °C under N₂ atmosphere. The mixture was stirred at 27 °C for 2 h. The product was diluted with EtOAc (100 mL) and petroleum ether (500 mL) was slowly added while stirring. The mixture was filtered. The filtrate was concentrated in vacuo and purified by flash silica gel chromatography (ISCO®; Agela® Flash Column Silica-CS(330 g), Eluent of 10% Ethyl acetate/petroleum ether gradient @85 mL/min to

give methyl (R,E)-8-(2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-5,6,7,8-tetrahydronaphthalene-2-carboxylate **161-4**. **MS (ESI) m/z : 458.3 ($M+H^+$)**

¹H NMR (400 MHz, chloroform-d) δ 10.11 (br s, 1H), 7.72 (d, $J = 8.0$ Hz, 1H), 7.62 (s, 1H), 7.13 (d, $J = 8.4$ Hz, 1H), 6.17-6.33 (m, 1H), 3.85 (s, 3H), 2.90-3.08 (m, 1H), 2.75-2.78 (m, 1H), 2.47-2.59 (m, 2H), 2.23-2.35 (m, 1H), 2.01-2.10 (m, 2H), 1.77-1.88 (m, 1H), 1.62-1.76 (m, 4H), 1.51 (br s, 9H), 0.92-1.01 (m, 6H).

Step D: (E)-8-(2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid **161-5**

Potassium trimethylsilanolate (21.31 g, 166 mmol) was added to a solution of methyl (E)-8-(2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-5,6,7,8-tetrahydronaphthalene-2-carboxylate **161-4** (19 g, 41.5 mmol) in THF (450 mL). The reaction was stirred at 25°C for 0.5 h. The solution of (E)-8-(2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid **161-5** was used for next step directly without any further manipulation or purification.

MS (ESI) m/z 444.7 ($M+H^+$)

Step E: tert-butyl ((E)-4,4-diethyl-1-(7-(((3S,4R)-3-hydroxy-3-methylchroman-4-yl)carbamoyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate **161-6**

DIEA (36.4 mL, 209 mmol) was added to a solution of (E)-8-(2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid **161-5** (18.5 g, 41.7 mmol), EDCI (40.0 g, 209 mmol), HOBt (16.91 g, 125 mmol) and (3S,4R)-4-amino-3-methylchroman-3-ol (8.22 g, 45.9 mmol) in THF (450 mL). The reaction was stirred at 25 °C for 2.5 h. The mixture was quenched with water (400 mL), and extracted with EtOAc (500 mL*3). The combined organic layers were washed with brine (350 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude was purified by flash silica gel chromatography (ISCO®; Agela® Flash Column Silica-CS(120 g), Eluent of 0~30% Ethyl acetate/petroleum ether gradient @85 mL/min) to afford tert-butyl ((E)-4,4-diethyl-1-(7-(((3S,4R)-3-hydroxy-3-methylchroman-4-yl)carbamoyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate **161-6**. **MS (ESI) m/z 605.3 ($M+H^+$)**

¹H NMR (400 MHz, chloroform-d) δ 10.15 (br s, 1H), 7.56 (br s, 1H), 7.42 (d, $J = 8.0$ Hz, 1H), 7.27-7.31 (m, 1H), 7.23 (d, $J = 7.6$ Hz, 1H), 7.15 (d, $J = 8.0$ Hz, 1H), 6.99 (t, $J = 7.6$ Hz, 1H), 6.91 (d, $J = 8.0$ Hz, 1H), 6.36 (d, $J = 7.2$ Hz, 1H), 6.25-6.28 (m, 1H), 5.31 (d, $J = 7.2$ Hz, 1H), 4.96 (s, 1H), 3.96-4.04 (m, 2H), 2.91-3.09 (m, 1H), 2.76-2.80 (m, 1H), 2.53 (br s, 2H), 2.28-2.32 (m, 1H),

2.00-2.11 (m, 2H), 1.73-1.88 (m, 1H), 1.62-1.67 (m, 4H), 1.50 (s, 9H), 1.24 (s, 3H), 0.88-0.97 (m, 6H).

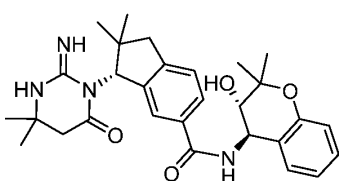
Step F: 8-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((3S,4R)-3-hydroxy-3-methylchroman-4-yl)-5,6,7,8-tetrahydronaphthalene-2-carboxamide **Example 161**

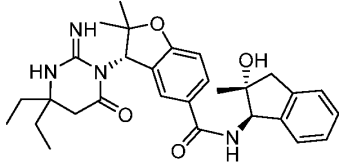
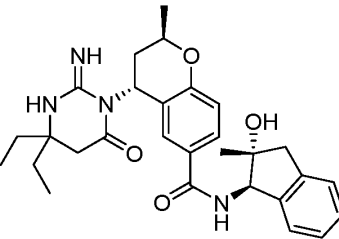
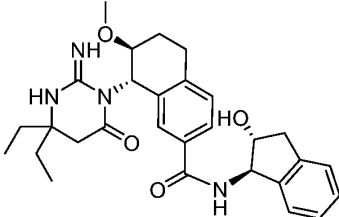
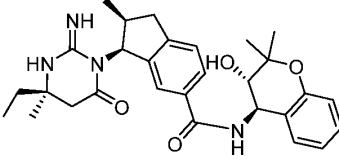
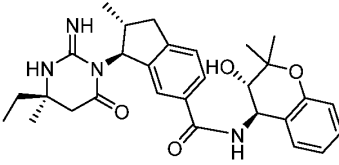
A solution of tert-butyl ((E)-4,4-diethyl-1-(7-(((3S,4R)-3-hydroxy-3-methylchroman-4-yl)carbamoyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate **161-6** (25 g, 41.3 mmol) and zinc(II) bromide (37.17 g, 165.2 mmol) in DCM (300 mL) at 25 °C under N₂ atmosphere was stirred at 25 °C for 16 h. The mixture was concentrated in vacuo at room temperature. MeCN (300 mL) was added and the mixture was stirred and then filtered. The filtrate was concentrated and purified by prep-HPLC (Instrument PREPL-X Method Column YMC-Triart Prep C18 250*50mm*10um Condition water(0.05%HCl)-ACN Begin B 10 End B 40 Gradient Time(min) 20 100%B Hold Time(min) 3 FlowRate(ml/min) 120 Injections 6) to afford 8-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((3S,4R)-3-hydroxy-3-methylchroman-4-yl)-5,6,7,8-tetrahydronaphthalene-2-carboxamide **Example 161**. MS (ESI) *m/z* 505.2 (**M+H**⁺)

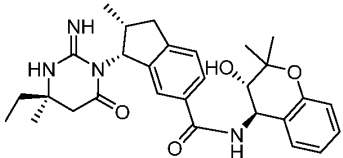
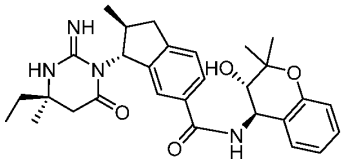
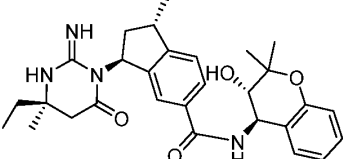
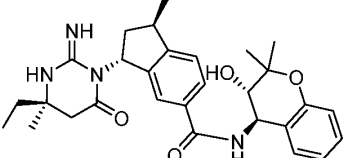
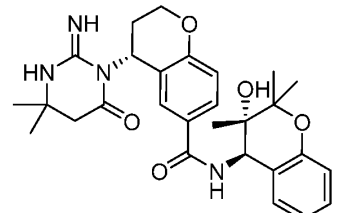
¹H NMR (400 MHz, methanol-d₄) δ 7.63 (br s, 1H), 7.59 (s, 1H), 7.20-7.24 (m, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.88-6.94 (m, 1H), 6.86 (d, *J* = 8.00 Hz, 1H), 5.19-5.64 (m, 2H), 3.94-4.05 (m, 2H), 2.67-2.97 (m, 4H), 2.08-2.45 (m, 3H), 1.64-1.89 (m, 5H), 1.28 (s, 3H), 0.98 (t, *J* = 7.2 Hz, 6H).

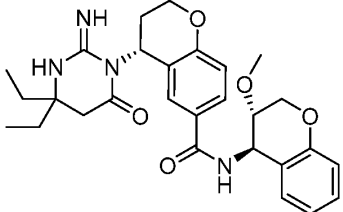
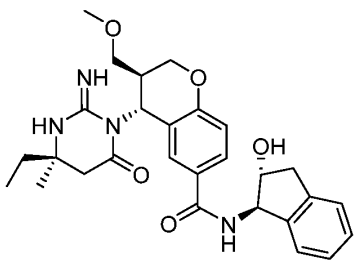
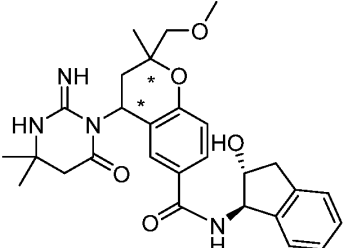
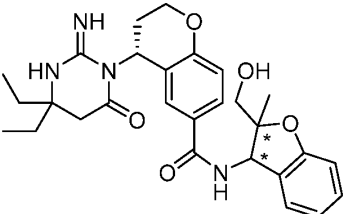
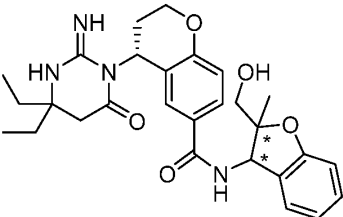
The compounds in Table 1-4 were prepared in an analogous fashion to that described in Scheme 1 and the experimentals described herein. The isomers were separated by preparative HPLC or/and preparative chiral SFC.

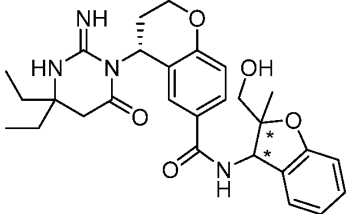
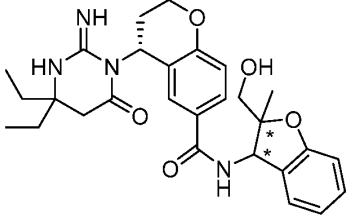
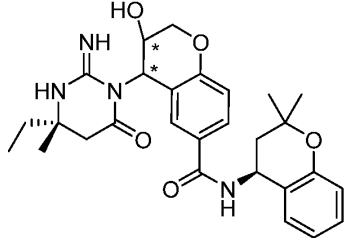
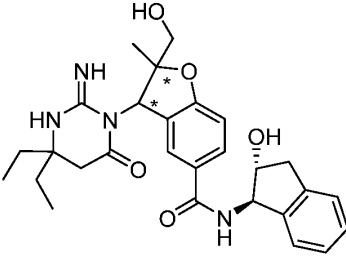
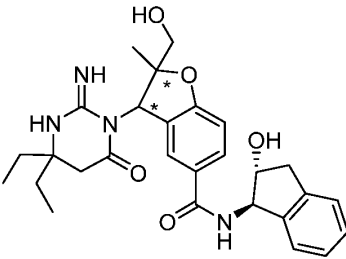
TABLE 3

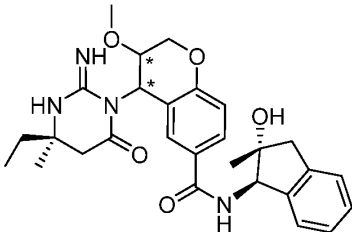
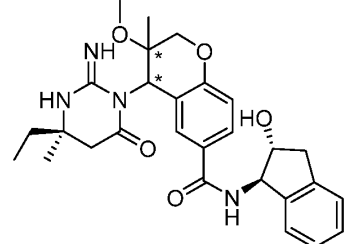
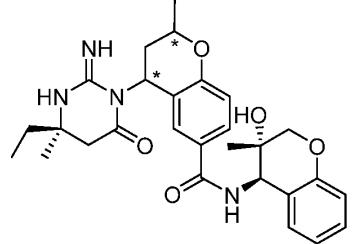
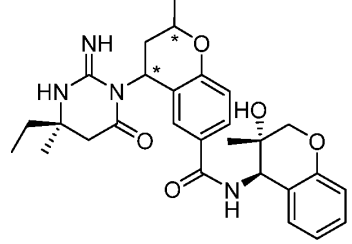
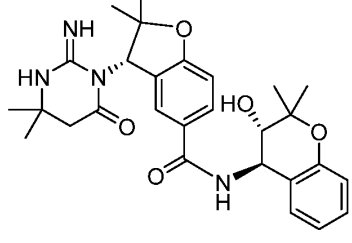
Example	Structure	LC/MS (M+1) ⁺	Name
162		505.3	(3R)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-2,2-dimethyl-indane-5-carboxamide

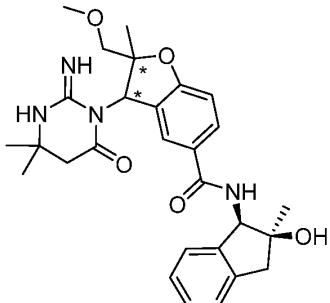
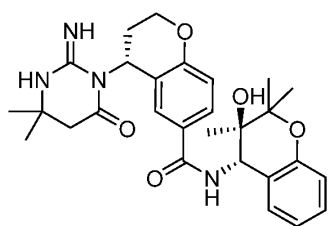
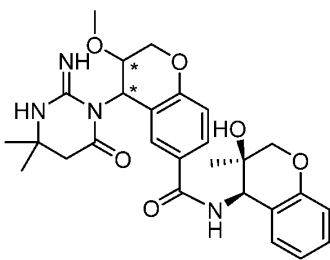
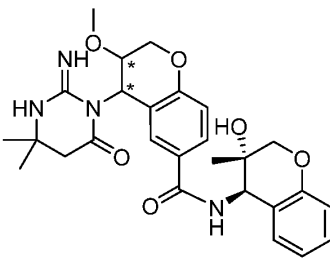
163		505.3	(3S)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxy-2-methyl-indan-1-yl]-2,2-dimethyl-3H-benzofuran-5-carboxamide
164		505.3	(2R,4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxy-2-methyl-indan-1-yl]-2-methyl-chromane-6-carboxamide
165		505.1	(3S,4S)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxyindan-1-yl]-3-methoxy-tetralin-6-carboxamide
166		505.3	(2S,3S)-3-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-2-methyl-indane-5-carboxamide
167		505.3	(2R,3S)-3-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-2-methyl-indane-5-carboxamide

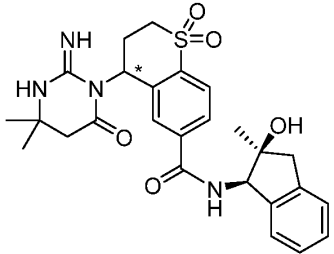
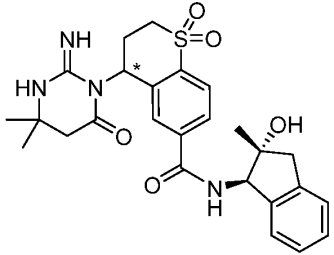
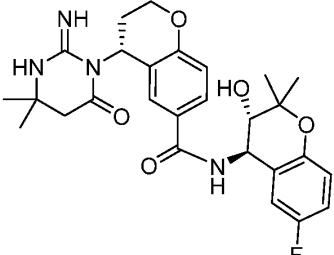
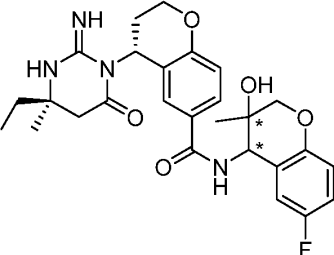
168		505.3	(2R,3R)-3-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-2-methyl-indane-5-carboxamide
169		505.3	(2S,3R)-3-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-2-methyl-indane-5-carboxamide
170		505.3	(1S,3S)-3-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-1-methyl-indane-5-carboxamide
171		505.3	(1R,3R)-3-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-1-methyl-indane-5-carboxamide
172		507.3	(4R)-N-[(3S,4R)-3-hydroxy-2,2,3-trimethyl-chroman-4-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)chromane-6-carboxamide

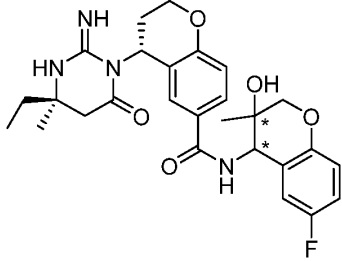
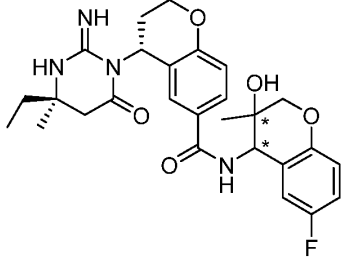
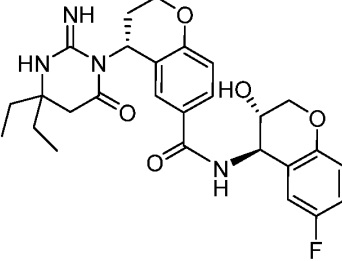
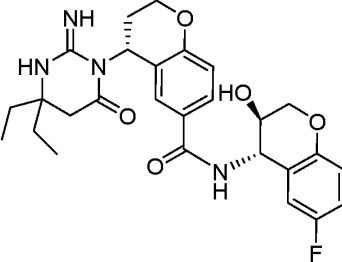
173		507.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-methoxychroman-4-yl]chromane-6-carboxamide
174		507.1	(3S,4R)-4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(1R,2R)-2-hydroxyindan-1-yl]-3-(methoxymethyl)chromane-6-carboxamide
175		507.3	N-[(1R,2R)-2-hydroxyindan-1-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-2-(methoxymethyl)-2-methyl-chromane-6-carboxamide
176A		507.2	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[2-(hydroxymethyl)-2-methyl-3H-benzofuran-3-yl]chromane-6-carboxamide
176B		507.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[2-(hydroxymethyl)-2-methyl-3H-benzofuran-3-yl]chromane-6-carboxamide

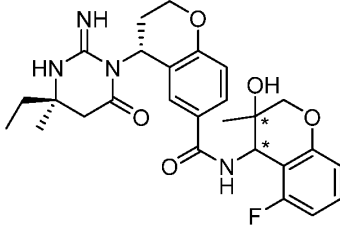
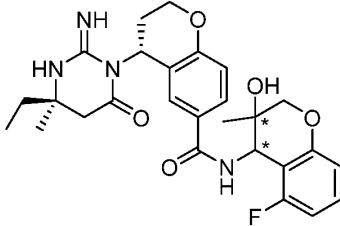
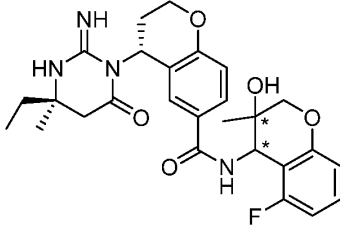
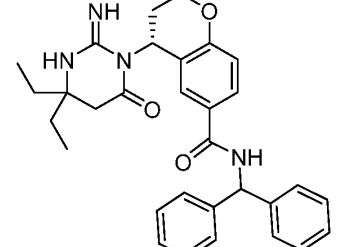
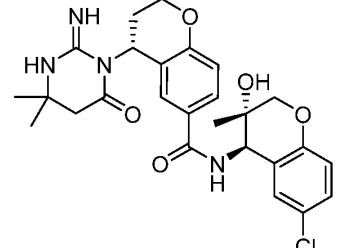
176C		507.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[2-(hydroxymethyl)-2-methyl-3H-benzofuran-3-yl]chromane-6-carboxamide
176D		507.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[2-(hydroxymethyl)-2-methyl-3H-benzofuran-3-yl]chromane-6-carboxamide
177		507.3	N-[(4S)-2,2-dimethylchroman-4-yl]-4-[(4S)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-3-hydroxy-chromane-6-carboxamide
178A		507.3	3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxyindan-1-yl]-2-(hydroxymethyl)-2-methyl-3H-benzofuran-5-carboxamide
178B		507.3	3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxyindan-1-yl]-2-(hydroxymethyl)-2-methyl-3H-benzofuran-5-carboxamide

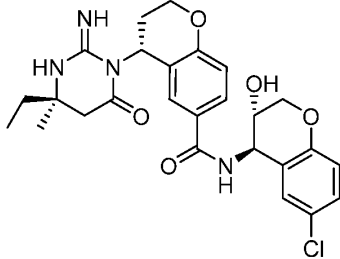
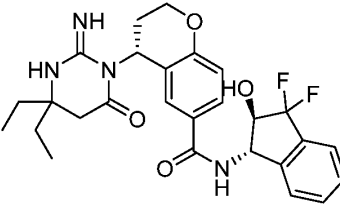
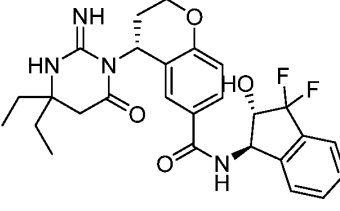
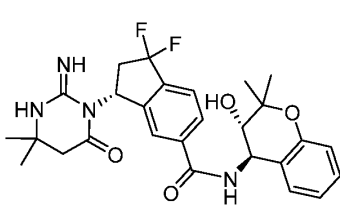
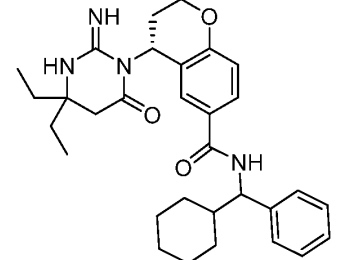
179		507.3	4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(1R,2R)-2-hydroxy-2-methylindan-1-yl]-3-methoxy-chromane-6-carboxamide
180		507.3	4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(1R,2R)-2-hydroxyindan-1-yl]-3-methoxy-3-methyl-chromane-6-carboxamide
181A		507.3	4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]-2-methyl-chromane-6-carboxamide
181B		507.3	4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]-2-methyl-chromane-6-carboxamide
182		507.3	(3S)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-2,2-dimethyl-3H-benzofuran-5-carboxamide

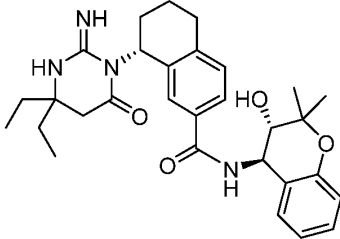
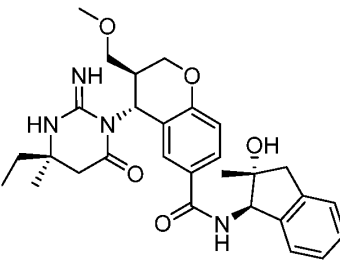
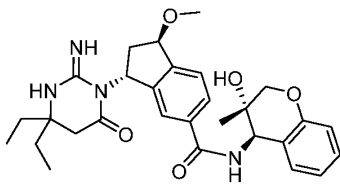
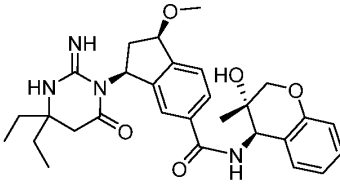
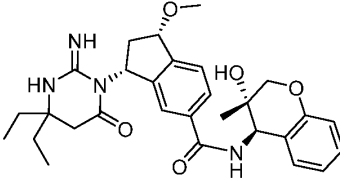
183		507.3	N-[(1R,2S)-2-hydroxy-2-methyl-indan-1-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-2-(methoxymethyl)-2-methyl-3H-benzofuran-5-carboxamide
184		507.3	(4R)-N-[(3R,4S)-3-hydroxy-2,2,3-trimethyl-chroman-4-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)chromane-6-carboxamide
185		509.2	N-[(3R,4R)-3-hydroxy-3-methyl-chroman-4-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-3-methoxy-chromane-6-carboxamide
186		509.2	N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-3-methoxy-chromane-6-carboxamide

187		511.3	N-[(1R,2S)-2-hydroxy-2-methyl-indan-1-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-1,1-dioxo-3,4-dihydro-2H-thiochromene-6-carboxamide
188		511.2	N-[(1R,2R)-2-hydroxy-2-methyl-indan-1-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-1,1-dioxo-3,4-dihydro-2H-thiochromene-6-carboxamide
189		511.3	(4R)-N-[(3S,4R)-6-fluoro-3-hydroxy-2,2-dimethyl-chroman-4-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)chromane-6-carboxamide
190A		511.2	(4R)-4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-(6-fluoro-3-hydroxy-3-methyl-chroman-4-yl)chromane-6-carboxamide

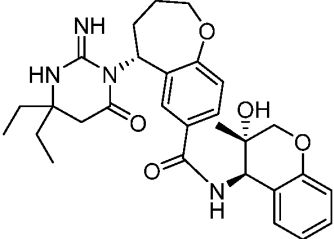
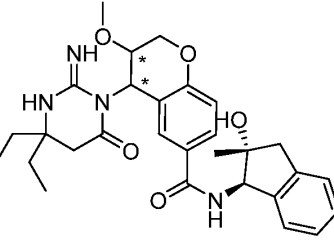
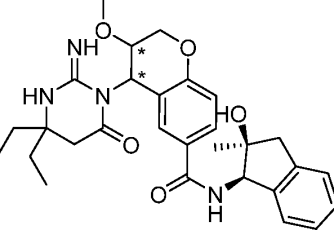
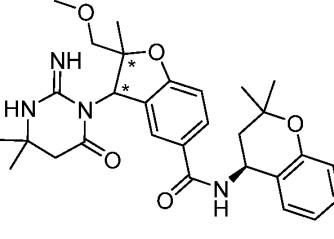
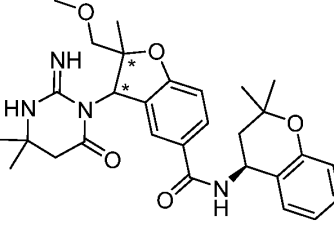
190B		511.2	(4R)-4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-(6-fluoro-3-hydroxy-3-methyl-chroman-4-yl)chromane-6-carboxamide
190C		511.2	(4R)-4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-(6-fluoro-3-hydroxy-3-methyl-chroman-4-yl)chromane-6-carboxamide
191		511.2	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-6-fluoro-3-hydroxy-chroman-4-yl]chromane-6-carboxamide
192		511.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3R,4S)-6-fluoro-3-hydroxy-chroman-4-yl]chromane-6-carboxamide

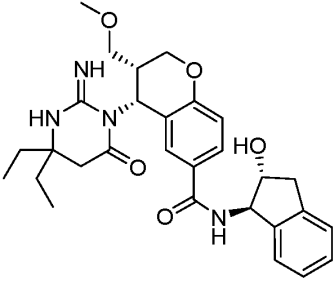
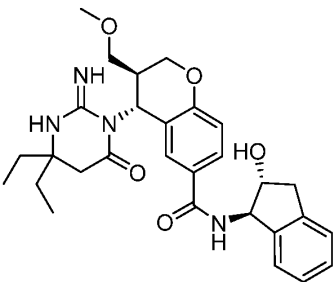
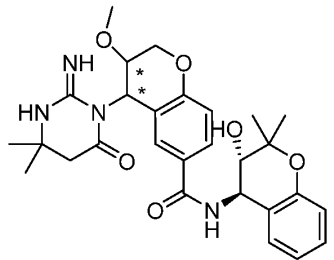
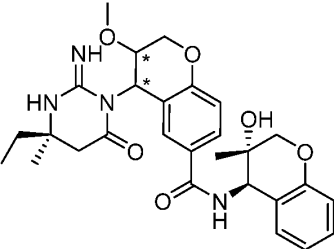
193A		511.3	(4R)-4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-(5-fluoro-3-hydroxy-3-methyl-chroman-4-yl)chromane-6-carboxamide
193B		511.3	(4R)-4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-(5-fluoro-3-hydroxy-3-methyl-chroman-4-yl)chromane-6-carboxamide
193C		511.3	(4R)-4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-(5-fluoro-3-hydroxy-3-methyl-chroman-4-yl)chromane-6-carboxamide
194		511.3	(4R)-N-benzhydryl-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)chromane-6-carboxamide
195		513.1	(4R)-N-[(3S,4R)-6-chloro-3-hydroxy-3-methyl-chroman-4-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)chromane-6-carboxamide

196		513.2	(4R)-N-[(3S,4R)-6-chloro-3-hydroxy-chroman-4-yl]-4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]chromane-6-carboxamide
197		513.2	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1S,2R)-3,3-difluoro-2-hydroxy-indan-1-yl]chromane-6-carboxamide
198		513.2	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2S)-3,3-difluoro-2-hydroxy-indan-1-yl]chromane-6-carboxamide
199		513.3	(3R)-1,1-difluoro-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)indane-5-carboxamide
200		517.3	(4R)-N-[cyclohexyl(phenyl)methyl]-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)chromane-6-carboxamide

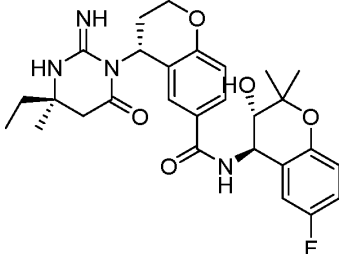
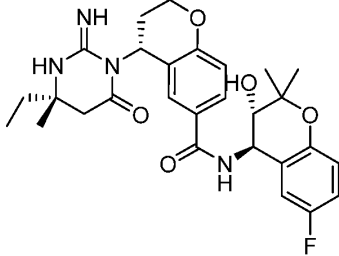
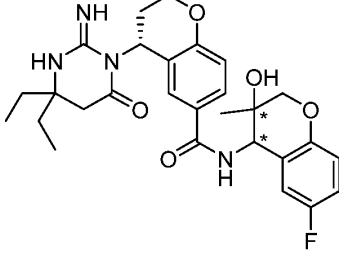
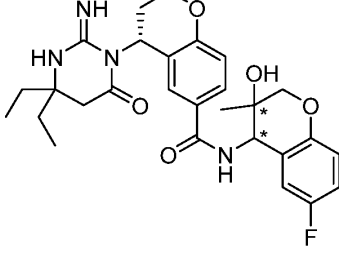
201		519.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]tetralin-6-carboxamide
202		521.2	(3S,4R)-4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(1R,2R)-2-hydroxy-2-methyl-indan-1-yl]-3-(methoxymethyl)chromane-6-carboxamide
203		521.3	(1R,3R)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]-1-methoxy-indane-5-carboxamide
204		521.3	(1R,3S)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]-1-methoxy-indane-5-carboxamide
205		521.3	(1S,3R)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]-1-methoxy-indane-5-carboxamide

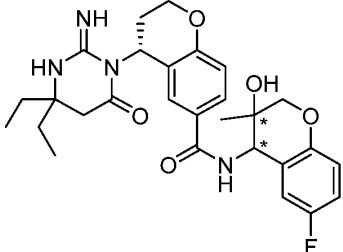
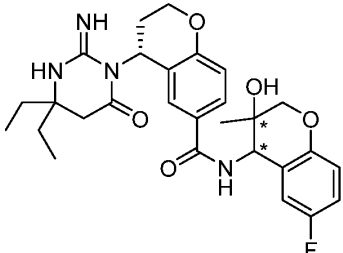
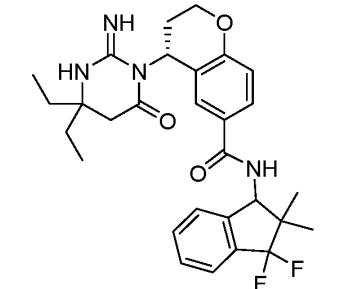
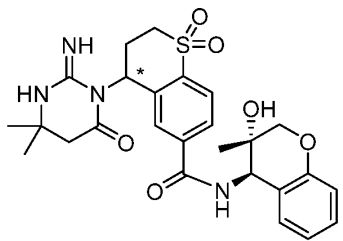
206		521.3	N-[(1R,2S)-2-hydroxy-2-methyl-indan-1-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-2-(methoxymethyl)-2-methyl-chromane-6-carboxamide
207		521.2	4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(4S)-2,2-dimethylchroman-4-yl]-3-hydroxy-chromane-6-carboxamide
208		521.3	4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxyindan-1-yl]-3-methoxy-3-methyl-chromane-6-carboxamide
209		521.3	4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]-2-methyl-chromane-6-carboxamide
210		521.3	4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-2-methyl-chromane-6-carboxamide

211		521.2	(5R)-5-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]-2,3,4,5-tetrahydro-1-benzoxepine-7-carboxamide
212		521.3	4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxy-2-methyl-indan-1-yl]-3-methoxy-chromane-6-carboxamide
213		521.3	4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2S)-2-hydroxy-2-methyl-indan-1-yl]-3-methoxy-chromane-6-carboxamide
214A		521.3	N-[(4S)-2,2-dimethylchroman-4-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-2-(methoxymethyl)-2-methyl-3H-benzofuran-5-carboxamide
214B		521.3	N-[(4S)-2,2-dimethylchroman-4-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-2-(methoxymethyl)-2-methyl-3H-benzofuran-5-carboxamide

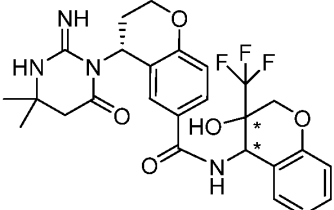
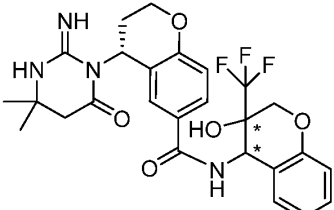
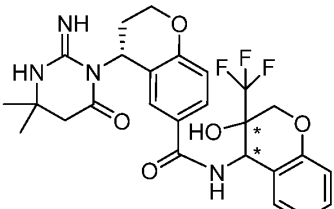
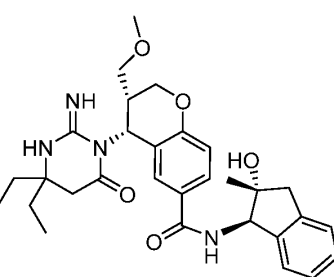
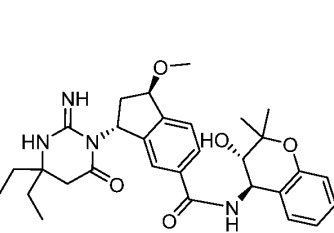
215		521.3	(3R,4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxyindan-1-yl]-3-(methoxymethyl)chromane-6-carboxamide
216		521.3	(3S,4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxyindan-1-yl]-3-(methoxymethyl)chromane-6-carboxamide
217		523.3	N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-3-methoxy-chromane-6-carboxamide
218		523.2	4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]-3-methoxy-chromane-6-carboxamide

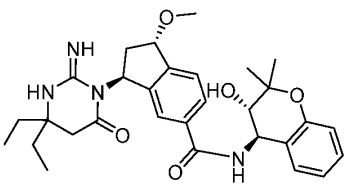
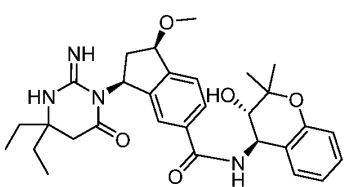
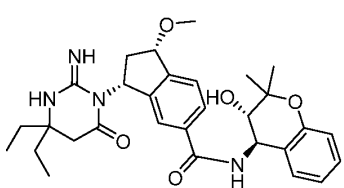
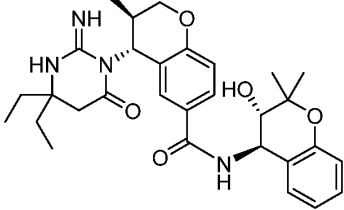
219		523.3	N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-2-(methoxymethyl)-2-methyl-3H-benzofuran-5-carboxamide
220		525.2	(4R)-N-[(4S)-2,2-dimethylchroman-4-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-1,1-dioxo-3,4-dihydro-2H-thiochromene-6-carboxamide
221		525.3	(4S)-N-[(4S)-2,2-dimethylchroman-4-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-1,1-dioxo-3,4-dihydro-2H-thiochromene-6-carboxamide
222		525.2	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxyindan-1-yl]-1,1-dioxo-3,4-dihydro-2H-thiochromene-6-carboxamide
223		525.3	(4S)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxyindan-1-yl]-1,1-dioxo-3,4-dihydro-2H-thiochromene-6-carboxamide

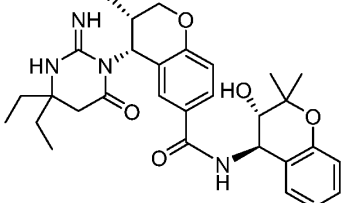
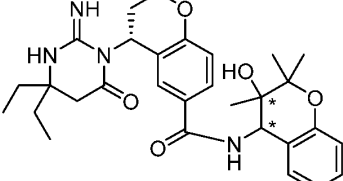
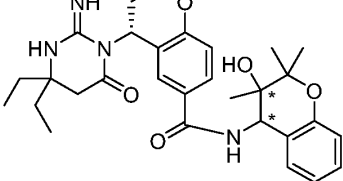
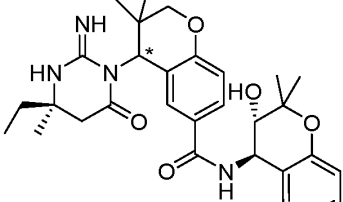
224		525.3	(4R)-4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(3S,4R)-6-fluoro-3-hydroxy-2,2-dimethyl-chroman-4-yl]chromane-6-carboxamide
225		525.2	(4R)-4-[(4S)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(3S,4R)-6-fluoro-3-hydroxy-2,2-dimethyl-chroman-4-yl]chromane-6-carboxamide
226A		525.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-(6-fluoro-3-hydroxy-3-methyl-chroman-4-yl)chromane-6-carboxamide
226B		525.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-(6-fluoro-3-hydroxy-3-methyl-chroman-4-yl)chromane-6-carboxamide

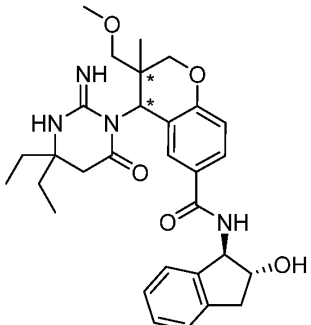
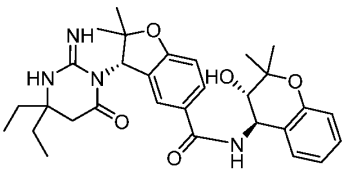
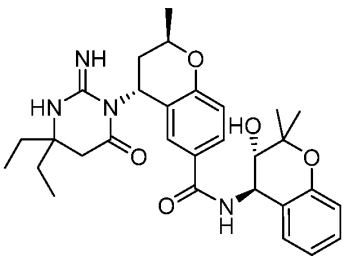
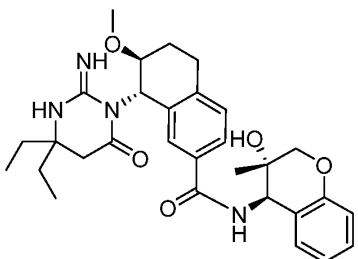
226C		525.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-(6-fluoro-3-hydroxy-3-methyl-chroman-4-yl)chromane-6-carboxamide
226D		525.1	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-(6-fluoro-3-hydroxy-3-methyl-chroman-4-yl)chromane-6-carboxamide
227		525.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-(3,3-difluoro-2,2-dimethyl-indan-1-yl)chromane-6-carboxamide
228		527.2	N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-1,1-dioxo-3,4-dihydro-2H-thiochromene-6-carboxamide

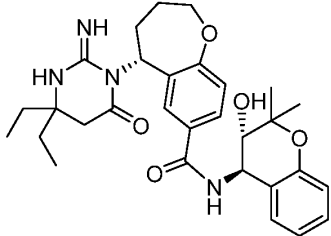
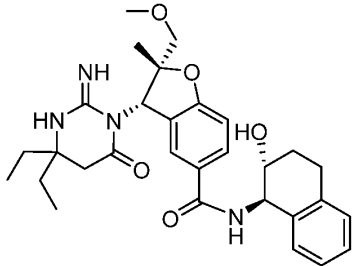
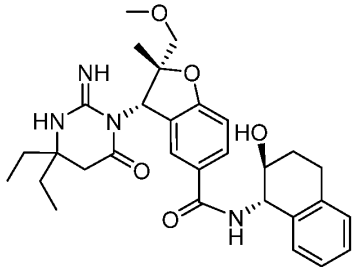
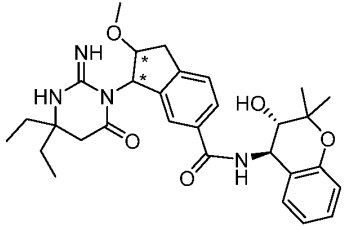
229		527.2	N-[(3R,4R)-3-hydroxy-3-methyl-chroman-4-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-1,1-dioxo-3,4-dihydro-2H-thiochromene-6-carboxamide
230		527.1	(4R)-N-[(3S,4R)-6-chloro-3-hydroxy-3-methyl-chroman-4-yl]-4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]chromane-6-carboxamide
231		527.3	(4R)-N-[(3S,4R)-6-chloro-3-hydroxy-chroman-4-yl]-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)chromane-6-carboxamide
232		529.3	(3R,4S)-N-[(1R,2S)-3,3-difluoro-2-hydroxy-indan-1-yl]-4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-3-methoxy-chromane-6-carboxamide
233		531.3	(4R)-N-(2-cyclohexyl-1-phenyl-ethyl)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)chromane-6-carboxamide

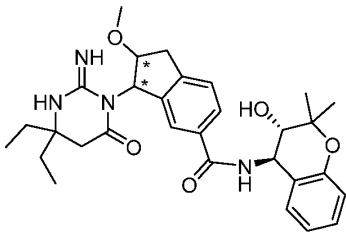
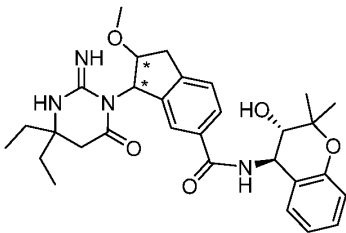
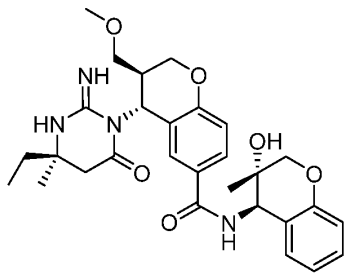
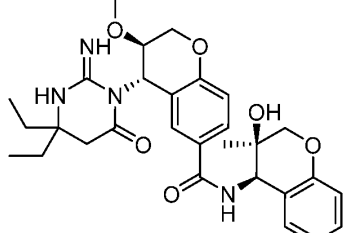
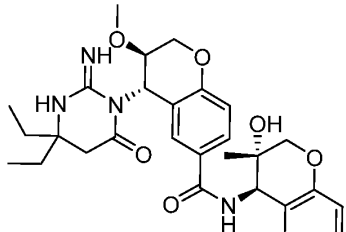
234A		533.3	(4R)-N-[3-hydroxy-3-(trifluoromethyl)chroman-4-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)chromane-6-carboxamide
234B		533.2	(4R)-N-[3-hydroxy-3-(trifluoromethyl)chroman-4-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)chromane-6-carboxamide
234C		533.2	(4R)-N-[3-hydroxy-3-(trifluoromethyl)chroman-4-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)chromane-6-carboxamide
235		535.1	(3R,4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxy-2-methyl-indan-1-yl]-3-(methoxymethyl)chromane-6-carboxamide
236		535.3	(1R,3R)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-1-methoxy-indane-5-carboxamide

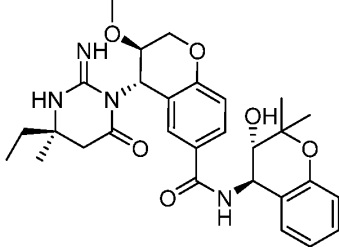
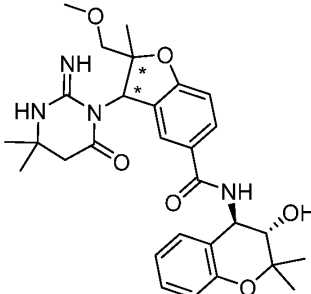
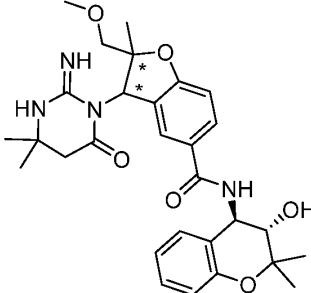
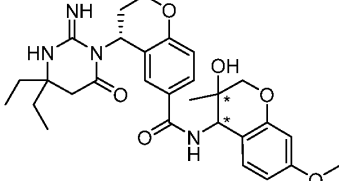
237		535.3	(1S,3S)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-1-methoxy-indane-5-carboxamide
238		535.4	(1R,3S)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-1-methoxy-indane-5-carboxamide
239		535.3	(1S,3R)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-1-methoxy-indane-5-carboxamide
240		535.4	(3R,4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-3-methyl-chromane-6-carboxamide

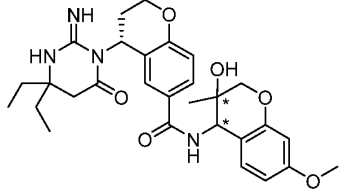
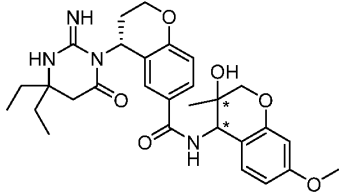
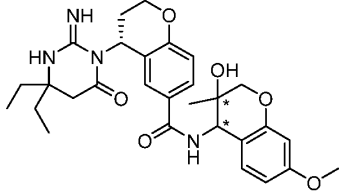
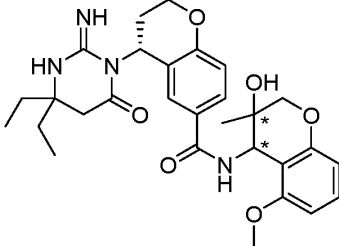
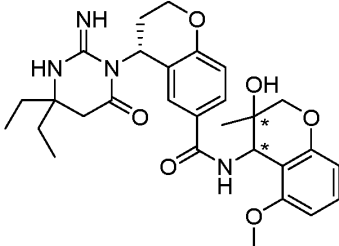
241		535.3	(3S,4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-3-methyl-chromane-6-carboxamide
242A		535.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-(3-hydroxy-2,2,3-trimethyl-chroman-4-yl)chromane-6-carboxamide
242B		535.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-(3-hydroxy-2,2,3-trimethyl-chroman-4-yl)chromane-6-carboxamide
243		535.3	4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-3,3-dimethyl-chromane-6-carboxamide

244		535.3	4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxyindan-1-yl]-3-(methoxymethyl)-3-methyl-chromane-6-carboxamide
245		535.4	(3S)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-2,2-dimethyl-3H-benzofuran-5-carboxamide
246		535.3	(2R,4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-2-methyl-chromane-6-carboxamide
247		535.1	(3S,4S)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]-3-methoxy-tetralin-6-carboxamide

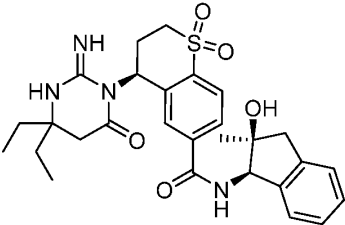
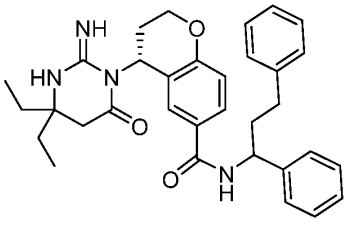
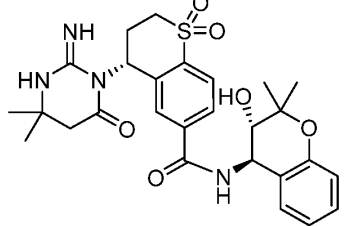
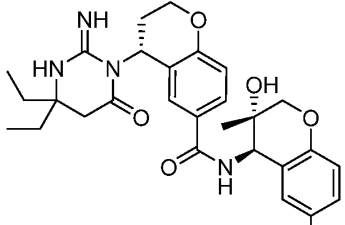
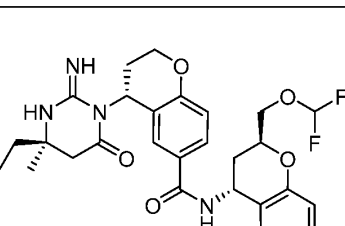
248		535.2	(5R)-5-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-2,3,4,5-tetrahydro-1-benzoxepine-7-carboxamide
249		535.3	(2R,3S)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxytetralin-1-yl]-2-(methoxymethyl)-2-methyl-3H-benzofuran-5-carboxamide
250		535.3	(2R,3S)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1S,2S)-2-hydroxytetralin-1-yl]-2-(methoxymethyl)-2-methyl-3H-benzofuran-5-carboxamide
251A		535.3	3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-2-methoxy-indane-5-carboxamide

251B		535.3	3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-2-methoxy-indane-5-carboxamide
251C		535.4	3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-2-methoxy-indane-5-carboxamide
252		537.2	(3S,4R)-4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]-3-(methoxymethyl)chromane-6-carboxamide
253		537.3	(3R,4S)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3R,4R)-3-hydroxy-3-methyl-chroman-4-yl]-3-methoxy-chromane-6-carboxamide
254		537.3	(3R,4S)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]-3-methoxy-chromane-6-carboxamide

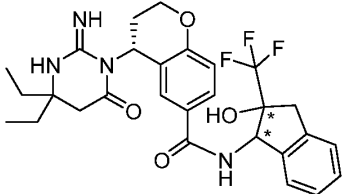
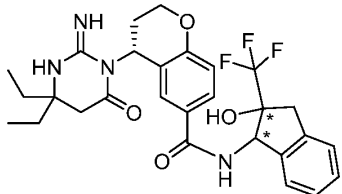
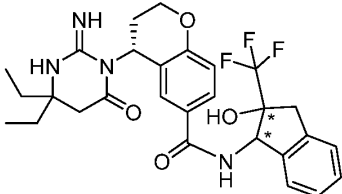
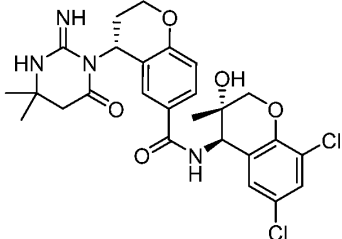
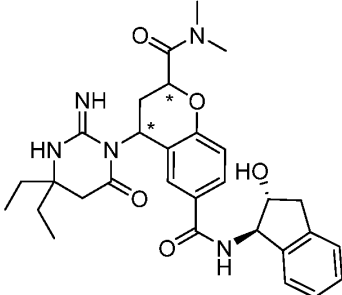
255		537.2	(3R,4S)-4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-3-methoxy-chromane-6-carboxamide
256		537.2	N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-2-(methoxymethyl)-2-methyl-3H-benzofuran-5-carboxamide
257		537.3	N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-3-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-2-(methoxymethyl)-2-methyl-3H-benzofuran-5-carboxamide
258A		537.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-(3-hydroxy-7-methoxy-3-methyl-chroman-4-yl)chromane-6-carboxamide

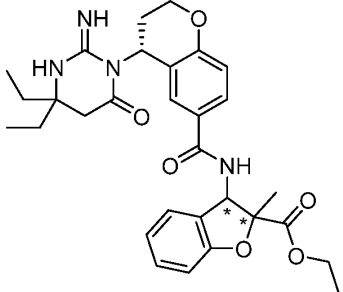
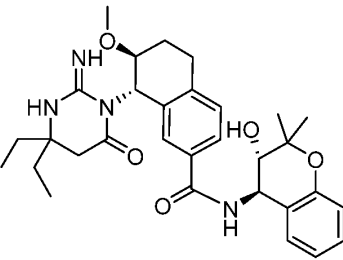
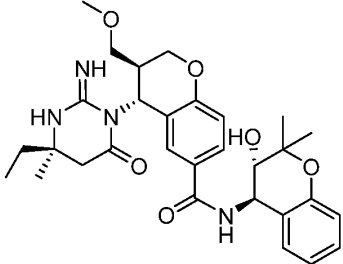
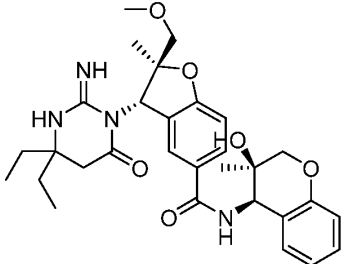
258B		537.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-(3-hydroxy-7-methoxy-3-methyl-chroman-4-yl)chromane-6-carboxamide
258C		537.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-(3-hydroxy-7-methoxy-3-methyl-chroman-4-yl)chromane-6-carboxamide
258D		537.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-(3-hydroxy-7-methoxy-3-methyl-chroman-4-yl)chromane-6-carboxamide
259A		537.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-(3-hydroxy-5-methoxy-3-methyl-chroman-4-yl)chromane-6-carboxamide
259B		537.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-(3-hydroxy-5-methoxy-3-methyl-chroman-4-yl)chromane-6-carboxamide

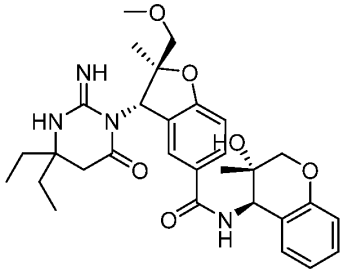
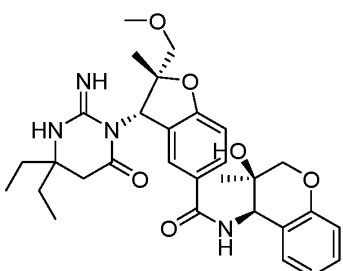
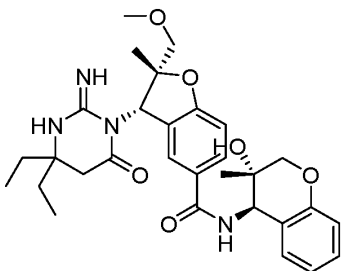
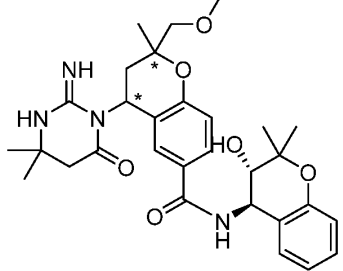
259C		537.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-(3-hydroxy-5-methoxy-3-methyl-chroman-4-yl)chromane-6-carboxamide
259D		537.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-(3-hydroxy-5-methoxy-3-methyl-chroman-4-yl)chromane-6-carboxamide
260		539.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxy-2-methyl-indan-1-yl]-1,1-dioxo-3,4-dihydro-2H-thiochromene-6-carboxamide
261		539.3	(4S)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxy-2-methyl-indan-1-yl]-1,1-dioxo-3,4-dihydro-2H-thiochromene-6-carboxamide
262		539.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2S)-2-hydroxy-2-methyl-indan-1-yl]-1,1-dioxo-3,4-dihydro-2H-thiochromene-6-carboxamide

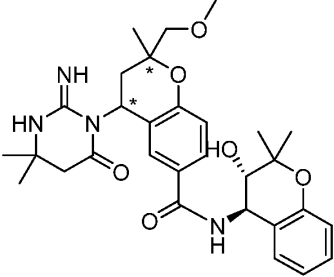
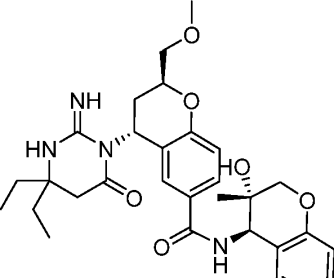
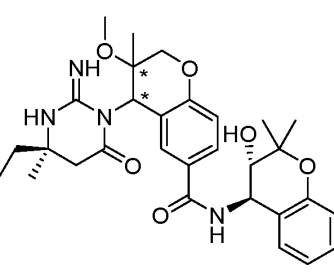
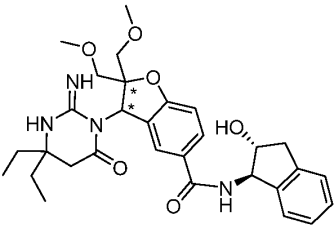
263		539.3	(4S)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2S)-2-hydroxy-2-methyl-indan-1-yl]-1,1-dioxo-3,4-dihydro-2H-thiochromene-6-carboxamide
264		539.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-(1,3-diphenylpropyl)chromane-6-carboxamide
265		541.3	(4R)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-1,1-dioxo-3,4-dihydro-2H-thiochromene-6-carboxamide
266		541.2	(4R)-N-[(3S,4R)-6-chloro-3-hydroxy-3-methyl-chroman-4-yl]-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)chromane-6-carboxamide
267		543.3	(4R)-N-[(2S,4R)-2-(difluoromethoxymethyl)chroman-4-yl]-4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]chromane-6-carboxamide

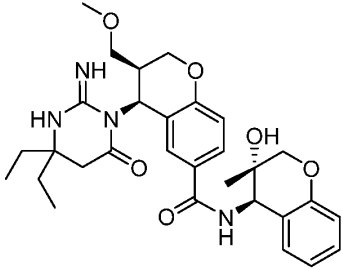
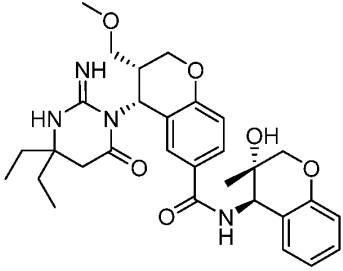
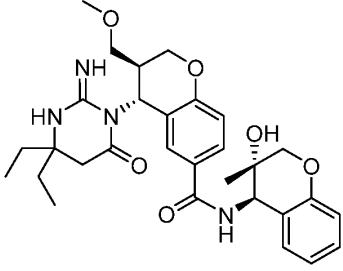
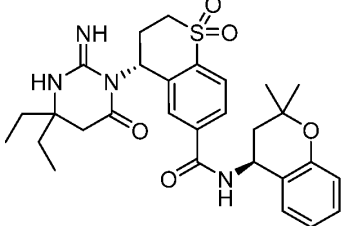
268		543.3	(4R)-N-[(2R,4R)-2-(difluoromethoxymethyl)chroman-4-yl]-4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]chromane-6-carboxamide
269		543.3	(4R)-N-[(2R,4S)-2-(difluoromethoxymethyl)chroman-4-yl]-4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]chromane-6-carboxamide
270		543.3	(4R)-N-[(2S,4S)-2-(difluoromethoxymethyl)chroman-4-yl]-4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]chromane-6-carboxamide
271		544.3	(4R)-N-[2-amino-5-(trifluoromethyl)indan-1-yl]-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)chromane-6-carboxamide
272A		545.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[2-hydroxy-2-(trifluoromethyl)indan-1-yl]chromane-6-carboxamide

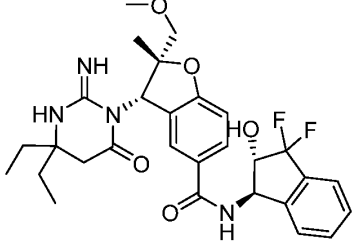
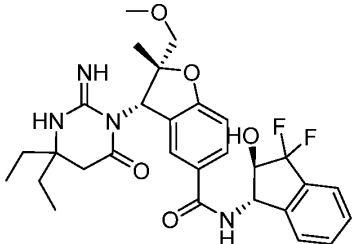
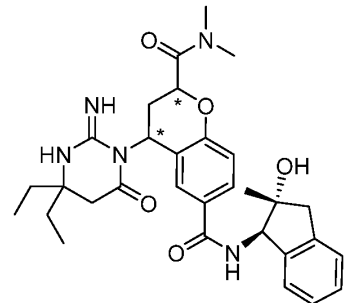
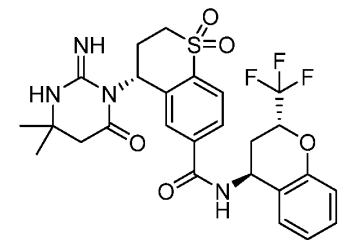
272B		545.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[2-hydroxy-2-(trifluoromethyl)indan-1-yl]chromane-6-carboxamide
272C		545.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[2-hydroxy-2-(trifluoromethyl)indan-1-yl]chromane-6-carboxamide
272D		545.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[2-hydroxy-2-(trifluoromethyl)indan-1-yl]chromane-6-carboxamide
273		547.1	(4R)-N-[(3S,4R)-6,8-dichloro-3-hydroxy-3-methyl-chroman-4-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)chromane-6-carboxamide
274		548.3	4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N6-[(1R,2R)-2-hydroxyindan-1-yl]-N2,N2-dimethyl-chromane-2,6-dicarboxamide

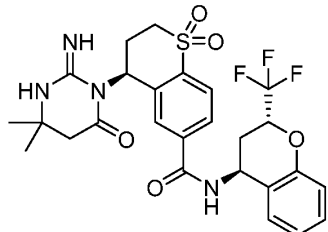
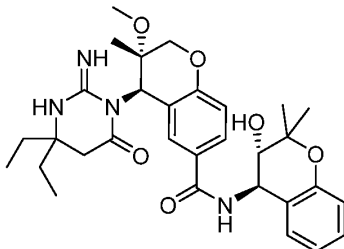
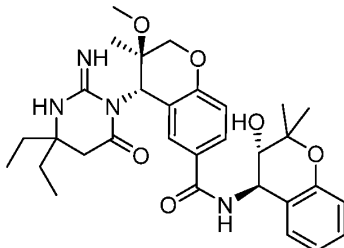
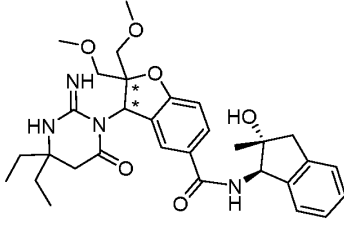
275		549.4	ethyl 3-[[[(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)chromane-6-carbonyl]amino]-2-methyl-3H-benzofuran-2-carboxylate
276		549.2	(3S,4S)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-3-methoxy-tetralin-6-carboxamide
277		551.1	(3S,4R)-4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-3-(methoxymethyl)chromane-6-carboxamide
278		551.3	(2S,3S)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3R,4R)-3-hydroxy-3-methyl-chroman-4-yl]-2-(methoxymethyl)-2-methyl-3H-benzofuran-5-carboxamide

279		551.3	(2S,3S)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]-2-(methoxymethyl)-2-methyl-3H-benzofuran-5-carboxamide
280		551.3	(2R,3S)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3R,4R)-3-hydroxy-3-methyl-chroman-4-yl]-2-(methoxymethyl)-2-methyl-3H-benzofuran-5-carboxamide
281		551.3	(2R,3S)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]-2-(methoxymethyl)-2-methyl-3H-benzofuran-5-carboxamide
282A		551.3	N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-2-(methoxymethyl)-2-methyl-chromane-6-carboxamide

282B		551.1	N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-2-(methoxymethyl)-2-methyl-chromane-6-carboxamide
283		551.2	(2S,4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]-2-(methoxymethyl)chromane-6-carboxamide
284		551.1	4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-3-methoxy-3-methyl-chromane-6-carboxamide
285		551.3	3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxyindan-1-yl]-2,2-bis(methoxymethyl)-3H-benzofuran-5-carboxamide

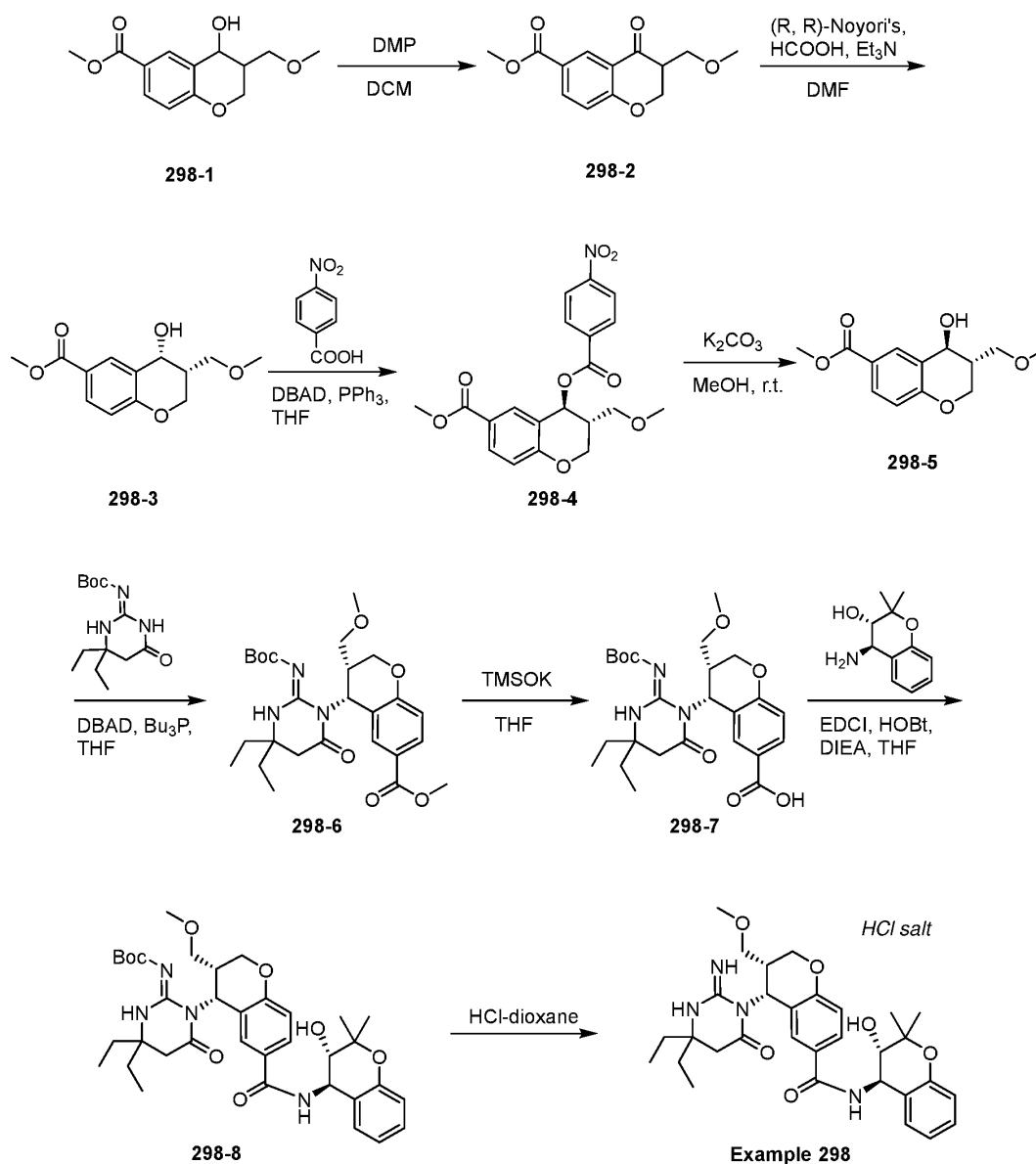
286		551.3	(3S,4S)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]-3-(methoxymethyl)chromane-6-carboxamide
287		551.3	(3R,4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]-3-(methoxymethyl)chromane-6-carboxamide
288		551.4	(3S,4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]-3-(methoxymethyl)chromane-6-carboxamide
289		553.3	(4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(4S)-2,2-dimethylchroman-4-yl]-1,1-dioxo-3,4-dihydro-2H-thiochromene-6-carboxamide

290		557.3	(2R,3S)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2S)-3,3-difluoro-2-hydroxy-indan-1-yl]-2-(methoxymethyl)-2-methyl-3H-benzofuran-5-carboxamide
291		557.2	(2R,3S)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1S,2R)-3,3-difluoro-2-hydroxy-indan-1-yl]-2-(methoxymethyl)-2-methyl-3H-benzofuran-5-carboxamide
292		562.4	4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N6-[(1R,2R)-2-hydroxy-2-methyl-indan-1-yl]-N2,N2-dimethyl-chromane-2,6-dicarboxamide
293		565.2	(4R)-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-1,1-dioxo-N-[(2R,4S)-2-(trifluoromethyl)chroman-4-yl]-3,4-dihydro-2H-thiochromene-6-carboxamide

294		565.2	(4S)-4-(2-imino-4,4-dimethyl-6-oxo-hexahydropyrimidin-1-yl)-1,1-dioxo-N-[(2R,4S)-2-(trifluoromethyl)chroman-4-yl]-3,4-dihydro-2H-thiochromene-6-carboxamide
295		565.3	(3S,4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-3-methoxy-3-methyl-chromane-6-carboxamide
296		565.3	(3R,4S)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-3-methoxy-3-methyl-chromane-6-carboxamide
297		565.3	3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(1R,2R)-2-hydroxy-2-methyl-indan-1-yl]-2,2-bis(methoxymethyl)-3H-benzofuran-5-carboxamide

EXAMPLE 298

(3R,4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((3S,4R)-3-hydroxy-2,2-dimethylchroman-4-yl)-3-(methoxymethyl)chromane-6-carboxamide



Step A: methyl 3-(methoxymethyl)-4-oxochromane-6-carboxylate **298-2**

5 DMP (121 g, 285 mmol) was added to a solution of methyl 4-hydroxy-3-(methoxymethyl)chromane-6-carboxylate **298-1** (60 g, 238 mmol) in CH₂Cl₂ (1500 mL) under nitrogen. The mixture was stirred at 25 °C for 2 h. The mixture was filtered, then concentrated and

purified by column chromatography (petroleum ether/EtOAc=100:0 to 10:1) to afford product methyl 3-(methoxymethyl)-4-oxochromane-6-carboxylate **298-2**.

MS (ESI) m/z 251.3 (**M+H**⁺)

¹H NMR (400 MHz, chloroform-d) δ 8.57 (d, J = 2.0 Hz, 1H), 8.13 (d, J = 2.4, 8.4 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 4.70 (dd, J = 5.2, 11.2 Hz, 1H), 4.47 (dd, J = 5.6, 11.6 Hz, 1H), 3.90 (s, 3H), 3.76-3.84 (m, 1H), 3.65-3.75 (m, 1H), 3.37 (s, 3H), 3.06-3.07 (m, 1H)

Step B: methyl (3R,4R)-4-hydroxy-3-(methoxymethyl)chromane-6-carboxylate **298-3**

A solution of formic acid (26.7 mL, 707 mmol) and triethylamine (197 mL, 1415 mmol) in DMF (200 mL) was stirred for 15 min, then methyl 3-(methoxymethyl)-4-oxochromane-6-carboxylate **298-2** (59 g, 236 mmol) in DMF (200 mL) and RuCl(p-cymene)[(R,R)-Ts-DPEN] (C₃₁H₃₅ClN₂O₂RuS) (4.50 g, 7.07 mmol) was added and stirred for 12 h at 25 °C under N₂ atmosphere. The mixture was diluted with water (600 mL), extracted with EtOAc (600 mL*3). The organic layers were washed with water (1200 mL) and brine (800 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue which was purified by flash silica gel chromatography (ISCO®; Agela® Flash Column Silica-CS(330 g), Eluent of 20% Ethyl acetate/petroleum ether gradient @100 mL/min) to afford methyl (3R,4R)-4-hydroxy-3-(methoxymethyl)chromane-6-carboxylate **298-3**.

MS (ESI) m/z 235.2 (**M-18+H**⁺)

¹H NMR (500 MHz, chloroform-d) δ 8.05 (d, J = 2.0 Hz, 1H), 7.89 (dd, J = 2.0, 8.5 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 4.86 (t, J = 3.5 Hz, 1H), 4.20-4.29 (m, 2H), 3.88 (s, 3H), 3.66-3.73 (m, 1H), 3.56-3.65 (m, 1H), 3.39 (s, 3H), 2.80 (d, J = 4.0 Hz, 1H), 2.32-2.47 (m, 1H)

Step C: (3R,4S)-3-(methoxymethyl)-4-((4-nitrobenzoyl)oxy)chromane-6-carboxylate **298-4**

4-nitrobenzoic acid (37.1 g, 222 mmol), triphenylphosphane (116 g, 444 mmol) and di-tert-butyl azodicarboxylate (102 g, 444 mmol) were added to a solution of methyl (3R,4R)-4-hydroxy-3-(methoxymethyl)chromane-6-carboxylate **298-3** (56 g, 222 mmol) in THF (600 mL) at 0 °C under N₂ atmosphere. The mixture was stirred at 25 °C for 1.5 h. The solvent was evaporated under reduced pressure to give the crude product. The crude product was purified by flash silica gel chromatography (ISCO®, 330 g SepaFlash® Silica Flash Column, Eluent of 24% EtOAc/petroleum ether gradient @ 100 mL/min) to give methyl (3R,4S)-3-(methoxymethyl)-4-((4-nitrobenzoyl)oxy)chromane-6-carboxylate **298-4**.

Step D: methyl (3R,4S)-4-hydroxy-3-(methoxymethyl)chromane-6-carboxylate **298-5**

K₂CO₃ (59.6 g, 431 mmol) was added to a solution of methyl (3R,4S)-3-(methoxymethyl)-4-((4-nitrobenzoyl)oxy)chromane-6-carboxylate **298-4** (86.5 g, 216 mmol) in MeOH (500 mL) and CH₂Cl₂ (300 mL) at 25 °C under N₂ atmosphere. The mixture was stirred at 25 °C for 12 h. The mixture was diluted with water (600 mL), extracted with DCM (800 mL x 3), dried over Na₂SO₄, and filtered. The solvent was evaporated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 330 g Sepa Flash® Silica Flash Column, Eluent of 30% EtOAc/petroleum ether gradient @ 100 mL/min) to give methyl (3R,4S)-4-hydroxy-3-(methoxymethyl)chromane-6-carboxylate **298-5**.

10 **MS (ESI) *m/z* 253.1 (M+H⁺)**

¹H NMR (500 MHz, chloroform-d) δ 8.12 (d, *J* = 2.0 Hz, 1H), 7.87 (dd, *J* = 2.5, 8.5 Hz, 1H), 6.83-6.89 (m, 1H), 4.69-4.75 (m, 1H), 4.33 (dd, *J* = 3.0, 11.0 Hz, 1H), 4.09-4.13 (m, 1H), 3.88 (s, 3H), 3.44-3.50 (m, 1H), 3.39-3.43 (m, 1H), 3.37 (s, 3H), 2.68 (d, *J* = 5.0 Hz, 1H), 2.31-2.33 (m, 1H).

15 Step E: methyl (3R,4R)-4-((E)-2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-3-(methoxymethyl)chromane-6-carboxylate **298-6**.

Di-tert-butyl azodicarboxylate (63.9 g, 277 mmol) was added to a solution of methyl (3R,4S)-4-hydroxy-3-(methoxymethyl)chromane-6-carboxylate **298-5** (35 g, 139 mmol), tert-butyl (E)-4,4-diethyl-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate (37.4 g, 139 mmol) and Bu₃P (56.1 g, 277 mmol) in THF (500 mL) at 0 °C under N₂ atmosphere. Then the mixture was stirred at 25 °C for 30 min. The mixture was concentrated in vacuo and purified by column chromatography (petroleum ether/EtOAc=50:1-5:1) to give a crude product, which was dissolved in pet. ether (800 mL), stirred and filtered. The filtrate was concentrated to afford product methyl (3R,4R)-4-((E)-2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-3-(methoxymethyl)chromane-6-carboxylate **298-6**.

25 **MS (ESI) *m/z* 504.5 (M+H⁺)**

¹H NMR (500 MHz, chloroform-d) δ 7.76-7.85 (m, 1H), 7.68 (d, *J* = 2.0 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 6.48 (d, *J* = 7.5 Hz, 1H), 4.44-4.57 (m, 1H), 4.31-4.32 (m, 1H), 3.83 (s, 3H), 3.57-3.58 (m, 1H), 3.47-3.48 (m, 1H), 3.27 (s, 3H), 2.66-2.78 (m, 1H), 2.41-2.53 (m, 2H), 1.63-1.71 (m, 4H), 1.47 (s, 9H), 0.93-0.96 (m, 6H)

Step F: (3R,4R)-4-((E)-2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-3-(methoxymethyl)chromane-6-carboxylic acid **298-7**

Potassium trimethylsilanolate (28.1 g, 219 mmol) was added to a solution of methyl (3R,4R)-4-((E)-2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-3-(methoxymethyl)chromane-6-carboxylate **298-6** (23 g, 36.5 mmol) in THF (400 mL) at 0 °C under N₂ atmosphere. The mixture was stirred at 25 °C for 1 h. (3R,4R)-4-((E)-2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-3-(methoxymethyl)chromane-6-carboxylic acid **298-7** in THF was used for the next step directly without further purification.

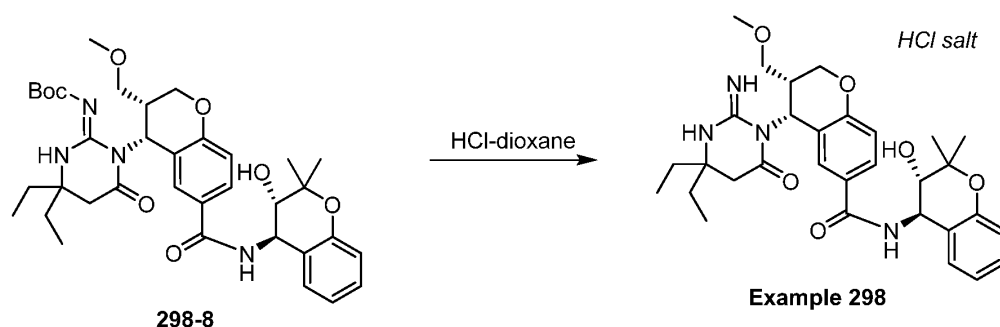
MS (ESI) *m/z*: 490.3 (**M+H**⁺)

- 10 Step G: tert-butyl ((E)-4,4-diethyl-1-((3R,4R)-6-(((3S,4R)-3-hydroxy-2,2-dimethylchroman-4-yl)carbamoyl)-3-(methoxymethyl)chroman-4-yl)-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate **298-8**

DIEA (31.2 mL, 179 mmol) was added to a solution of (3R,4R)-4-((E)-2-((tert-butoxycarbonyl)imino)-4,4-diethyl-6-oxotetrahydropyrimidin-1(2H)-yl)-3-(methoxymethyl)chromane-6-carboxylic acid **298-7** (17.5 g, 35.7 mmol), EDCI (20.56 g, 107 mmol), HOBt (7.25 g, 53.6 mmol) and (3S,4R)-4-amino-2,2-dimethylchroman-3-ol (7 g, 36.2 mmol) in THF (600 mL). The reaction was stirred at 25 °C for 2 h. The mixture was quenched with water (400 mL), and extracted with EtOAc (500 mL*3). The organic layers were washed with brine (600 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude was purified by flash silica gel chromatography (ISCO[®]; 330 g Sepa Flash[®] Silica Flash Column, Eluent of 40% EtOAc/petroleum ether gradient @ 100 mL/min) to give tert-butyl ((E)-4,4-diethyl-1-((3R,4R)-6-(((3S,4R)-3-hydroxy-2,2-dimethylchroman-4-yl)carbamoyl)-3-(methoxymethyl)chroman-4-yl)-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate **298-8**.

MS (ESI) *m/z* 665.4 (**M+H**⁺)

- 25 ¹H NMR (400 MHz, chloroform-d) δ 10.17 (s, 1H), 7.61 (d, *J* = 1.2 Hz, 1H), 7.45-7.47 (m, 1H), 7.27-7.30 (m, 1H), 7.15-7.25 (m, 1H), 6.96 (t, *J* = 7.34 Hz, 1H), 6.52 (br d, *J* = 6.8 Hz, 1H), 6.34 (br d, *J* = 7.2 Hz, 1H), 5.17 (br t, *J* = 8.0 Hz, 1H), 4.76 (br d, *J* = 1.6 Hz, 1H), 4.50 (t, *J* = 10.4 Hz, 1H), 4.32 (br dd, *J* = 4.0, 10.6 Hz, 1H), 3.69-3.78 (m, 1H), 3.58 (dd, *J* = 4.8, 9.6 Hz, 1H), 3.44-3.53 (m, 1H), 3.27 (s, 3H), 2.69-2.78 (m, 1H), 2.43-2.55 (m, 2H), 1.63-1.69 (m, 4H), 1.53 (s, 9H), 1.29 (d, *J* = 5.2 Hz, 6H), 0.89-1.00 (m, 6H)
- 30



Step H: product (3R,4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((3S,4R)-3-hydroxy-2,2-dimethylchroman-4-yl)-3-(methoxymethyl)chromane-6-carboxamide **Example 298**

A solution of tert-butyl ((E)-4,4-diethyl-1-(((3R,4R)-6-(((3S,4R)-3-hydroxy-2,2-dimethylchroman-4-yl)carbamoyl)-3-(methoxymethyl)chroman-4-yl)-6-oxotetrahydropyrimidin-2(1H)-ylidene)carbamate **298-8** (16.8 g, 25.3 mmol) in HCl-dioxane (4 N) (500 mL) was stirred at 25 °C for 12 hrs. The mixture was concentrated under reduced pressure, and the residue was purified by Prep-HPLC (Instrument L-Y Method Column YMC Exphere C18 250*50mm*10um Condition water(0.05%HCl)-ACN Begin B 10 End B 50 Gradient Time(min) 20 100%B Hold Time(min) 3 Flow Rate (mL/min) 120 Injections 9) to afford product (3R,4R)-4-(4,4-diethyl-2-imino-6-oxotetrahydropyrimidin-1(2H)-yl)-N-((3S,4R)-3-hydroxy-2,2-dimethylchroman-4-yl)-3-(methoxymethyl)chromane-6-carboxamide **Example 298**.

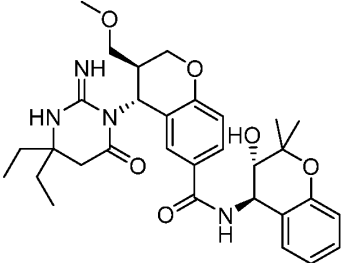
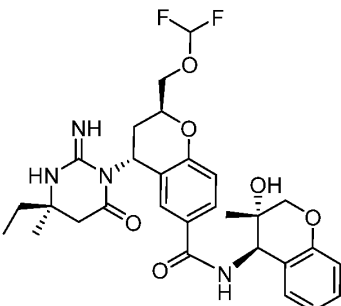
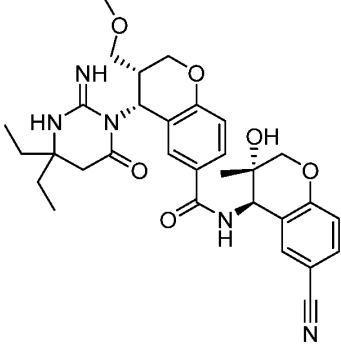
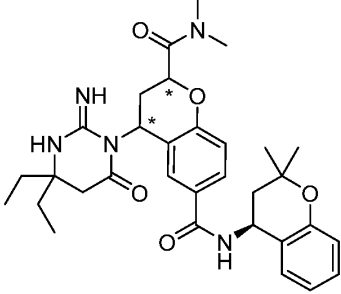
MS (ESI) m/z 565.2 ($M+H^+$)

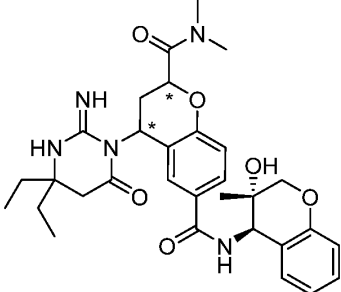
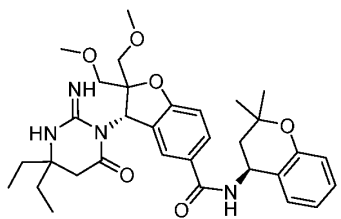
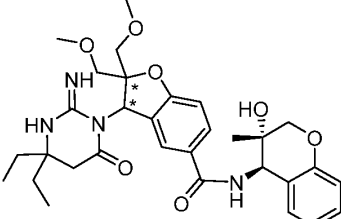
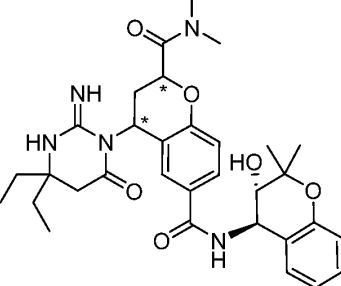
¹H NMR (500 MHz, methanol-d₄) δ 8.55 (d, $J = 8.5$ Hz, 1H), 7.77 (dd, $J = 2.0, 9.0$ Hz, 1H), 7.74 (d, $J = 2.0$ Hz, 1H), 7.10-7.16 (m, 2H), 6.91 (d, $J = 8.5$ Hz, 1H), 6.83-6.88 (m, 1H), 6.76 (d, $J = 8.5$ Hz, 1H), 5.39 (d, $J = 6.0$ Hz, 1H), 5.20-5.28 (m, 1H), 4.29-4.38 (m, 1H), 4.24-4.25 (m, 1H), 3.78 (d, $J = 10.0$ Hz, 1H), 3.58-3.60 (m, 1H), 3.47-3.53 (m, 1H), 3.40 (s, 3H), 2.88-2.96 (m, 1H), 2.83 (d, $J = 16.0$ Hz, 1H), 2.63 (d, $J = 16.0$ Hz, 1H), 1.56-1.77 (m, 4H), 1.48 (s, 3H), 1.27 (s, 3H), 0.97 (t, $J = 8.0$ Hz, 3H), 0.92 (t, $J = 7.5$ Hz, 3H)

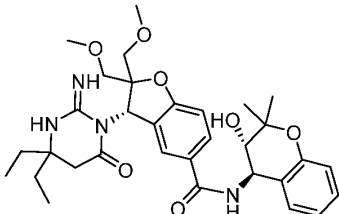
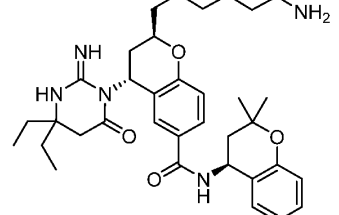
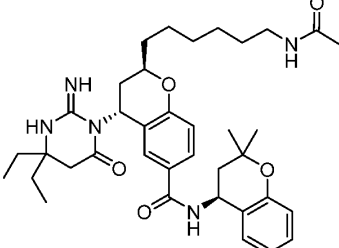
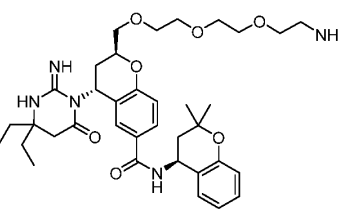
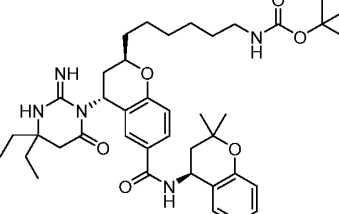
20

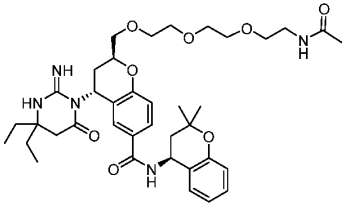
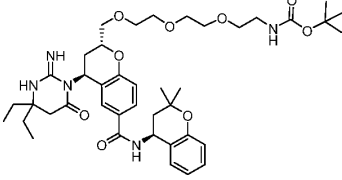
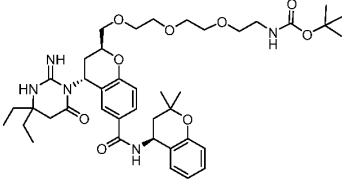
TABLE 4

Example	Structure	LC/MS ($M+1$) ⁺	Name
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299		565.3	(3S,4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-3-(methoxymethyl)chromane-6-carboxamide
300		573.3	(2S,4R)-2-(difluoromethoxymethyl)-4-[(4R)-4-ethyl-2-imino-4-methyl-6-oxo-hexahydropyrimidin-1-yl]-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]chromane-6-carboxamide
301		576.2	(3R,4R)-N-[(3S,4R)-6-cyano-3-hydroxy-3-methyl-chroman-4-yl]-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-3-(methoxymethyl)chromane-6-carboxamide
302		576.4	4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N6-[(4S)-2,2-dimethylchroman-4-yl]-N2,N2-dimethyl-chromane-2,6-dicarboxamide

303		578.3	4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N6-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]-N2,N2-dimethyl-chromane-2,6-dicarboxamide
304		579.3	(3S)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(4S)-2,2-dimethylchroman-4-yl]-2,2-bis(methoxymethyl)-3H-benzofuran-5-carboxamide
305		581.3	3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-3-methyl-chroman-4-yl]-2,2-bis(methoxymethyl)-3H-benzofuran-5-carboxamide
306		592.4	4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N6-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-N2,N2-dimethyl-chromane-2,6-dicarboxamide

307		595.3	(3S)-3-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(3S,4R)-3-hydroxy-2,2-dimethyl-chroman-4-yl]-2,2-bis(methoxymethyl)-3H-benzofuran-5-carboxamide
308		604.4	(2R,4R)-2-(6-aminohexyl)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(4S)-2,2-dimethylchroman-4-yl]chromane-6-carboxamide
309		646.3	(2R,4R)-2-(6-acetamidohexyl)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(4S)-2,2-dimethylchroman-4-yl]chromane-6-carboxamide
310		666.5	(2S,4R)-2-[2-[2-(2-aminoethoxy)ethoxy]ethoxymethyl]-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(4S)-2,2-dimethylchroman-4-yl]chromane-6-carboxamide
311		704.5	tert-butyl N-[6-[(2R,4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-6-[[[(4S)-2,2-dimethylchroman-4-yl]carbamoyl]chroman-2-yl]hexyl]carbamate

312		708.5	(2S,4R)-2-[2-[2-(2-acetamidoethoxy)ethoxy]ethoxymethyl]-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-N-[(4S)-2,2-dimethylchroman-4-yl]chromane-6-carboxamide
313		766.5	tert-butyl N-[2-[2-[2-[[[(2R,4S)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-6-[[[(4S)-2,2-dimethylchroman-4-yl]carbamoyl]chroman-2-yl]methoxy]ethoxy]ethoxy]ethyl]carbamate
314		766.5	tert-butyl N-[2-[2-[2-[[[(2S,4R)-4-(4,4-diethyl-2-imino-6-oxo-hexahydropyrimidin-1-yl)-6-[[[(4S)-2,2-dimethylchroman-4-yl]carbamoyl]chroman-2-yl]methoxy]ethoxy]ethoxy]ethyl]carbamate

EXAMPLE 315

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

5 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
10 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. 30ul of diluted parasites are then added into 10ul 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 are sealed with parafilm and frozen flat, in single file at -80°C overnight. On the following day, assay plates are allowed to thaw at room temperature for 4 hours to which an LDH assay is performed to measure parasite growth.

Assay EC₅₀ results are shown in Table 5.

10

TABLE 5

Example	EC₅₀ (nM)	Example	EC₅₀ (nM)
1A	0.5	153	11.5
1B	163	154	0.7
2A	0.5	155	82.5
2B	73	156	1.1
3A	2.2	157	19.9
4A	87	158	0.9
5A	5.9	159	0.5
6A	1.1	160	8.3
6B	8.8	161	0.8
7A	0.4	162	7.5
7B	19	163	8.4
8A	10	164	2.4
8B	22	165	3.4
8C	120	166	154
8D	86	167	250
9A	0.9	168	0.4
9B	170	169	0.3
10A	0.5	170	184
11A	0.9	171	0.7

11B	84	172	0.9
12A	1.1	173	2.8
13A	0.8	174	1.9
13B	54	175	31.0
14A	1	176A	29.2
15A	0.3	176B	7.8
16A	0.6	176C	2.4
16B	95	176D	114
17A	2.7	177	66.9
18A	0.8	178A	108
19A	0.3	178B	2.2
20A	0.8	179	65.4
21A	0.8	180	65.4
22A	0.7	181A	189
23A	5	181B	7.9
24A	9.3	182	6.1
25A	0.5	183	71.4
25B	59.8	184	105
26A	1.3	185	50.3
26B	180	186	70.0
27A	1.3	187	66.7
28A	1.8	188	203
29A	1	189	1.0
29B	39.7	190A	261
30A	0.8	190B	2.6
31A	22	190C	4.9
31B	1	191	2.6
32A	7.9	192	232
32B	290	193A	96.4

33A	28.3	193B	0.8
34A	1.2	193C	19.5
35A	2.4	194	0.9
36A	8.9	195	3.5
36B	2.2	196	8.6
37A	74.4	197	125
38A	2.8	198	11.3
39A	29.9	199	1.1
40A	69.5	200	2.9
41A	2.8	201	1.4
42A	1.0	202	0.8
42B	3.2	203	5.9
43A	8.1	204	247
43B	21	205	2.1
44A	1.5	206	66.0
44B	2.8	207	22.0
45A	2.6	208	3.7
46A	130	209	7.9
47A	4.7	210	195
48A	37.5	211	8.9
49A	49	212	6.5
50A	3.7	213	9.0
51A	22.5	214A	8.2
52A	14.4	214B	260
53A	0.3	215	4.2
54A	190	216	2.7
54B	160	217	4.9
55A	24.5	218	64
55B	83.1	219	208

56A	26.9	220	2.9
57A	18.3	221	190
58A	250	222	15.6
58B	3.8	223	300
59A	210	224	0.3
59B	1.6	225	0.8
60A	1.3	226A	2.6
60B	1.7	226B	69.0
61A	8.4	226C	273
62A	1.2	226D	1.0
63A	220	227	1.3
64A	12	228	282
64B	0.9	229	59.3
64C	64	230	2.7
64D	42	231	7.4
65A	68	232	21.8
65B	2.6	233	7.9
65C	26	234A	22.5
66A	76	234B	3.9
67A	170	234C	43.2
67B	0.8	235	0.7
68A	1.0	236	0.9
69A	2.6	237	240
70A	9.3	238	47.8
71A	3.5	239	0.9
72A	0.5	240	0.6
73A	0.3	241	0.4
73B	1.7	242A	0.6
74A	0.3	242B	10.5

74B	6.5	243	6.1
75A	0.4	244	7.8
75B	9.5	245	0.8
76A	8.5	246	2.0
76B	1.1	247	4.5
77A	57.1	248	0.8
77B	21.4	249	1.1
78	8.9	250	219
79	9.6	251A	0.4
80	18.0	251B	1.5
81	6.6	251C	84.4
82	15.5	252	2.1
83	20.0	253	4.3
84	0.9	254	3.4
85	10.7	255	3.3
86	87.8	256	8.9
87	105	257	189
88	3.4	258A	85.9
89	43.5	258B	2.4
90	26.8	258C	226
91	45.2	258D	6.7
92	97.2	259A	5.5
93	190	259B	24.2
94	1.9	259C	3.6
95	8.8	259D	10.6
96	6.5	260	8.2
97	19.0	261	133
98	1.5	262	7.4
99	4.2	263	74.8

100	5.3	264	3.3
101	46.7	265	31.1
102	14.0	266	2.6
103	6.1	267	24.0
104	5.0	268	25.0
105	8.8	269	2.9
106	6.6	270	1.8
107	222	271	182
108	74.3	272A	62.5
109	14.0	272B	14.3
110	60.0	272C	0.9
111	90.0	272D	2.3
112	11.4	273	7.8
113	16.4	274	98.5
114	1.8	275	25.7
115	3.6	276	0.6
116	210	277	0.4
117	2.5	278	12.2
118	0.9	279	31.4
119	2.8	28	0.4
120	0.8	281	1.1
121	0.6	282A	7.8
122	3.9	282B	40.5
123	2.8	283	2.6
124	57.5	284	8.5
125	2.1	285	35.5
126	14.3	286	240
127A	202	287	1.9
127B	222	288	1.8

128	2.8	289	0.6
129	3.5	290	0.3
130	2.1	291	240
131	2.0	292	49.7
132	1.6	293	2.8
133A	1.4	294	259
133B	17.0	295	100
134	8.8	296	0.3
135	0.9	297	241
136	1.3	298	0.5
137	239	299	0.8
138	0.9	300	3.8
139	180	301	1.8
140A	1.4	302	1.7
140B	1.7	303	50.8
141	8.4	304	5.6
142	98.5	305	75.8
143	178	306	27.4
144	194	307	3.2
145	40.8	308	40.5
146	35.5	309	3.2
147	160	310	211
148	2.7	311	2.4
149	1.1	312	53.9
150	49.0	313	260
151	5.4	314	7.3
152	7.7		

Example 1 as an inhibitor of PMX and PMIX function whilst C4 is specific for PMX

To confirm that Example 1 blocks PMX function in the *P. falciparum* parasite, the ability to inhibit cleavage of a known substrate for this protease was tested. SERA5 is a 120 kDa protein required for merozoite egress and is processed by subtilisin-like protease subtilisin 1 (SUB1) to release a soluble polypeptide of approximately 50 kDa (Pino, P., Caldelari, R., Mukherjee, B., Vahokoski, J., Klages, N., Maco, B., et al. (2017). A multistage antimalarial targets the plasmepsins IX and X essential for invasion and egress. *Science* 358, 522-528). The protease inhibitor E64, which prevents schizont rupture, but does not affect SERA5 processing was used as a negative control (Salmon, B.L., Oksman, A. and Goldberg, D.E. (2001). Malaria parasite exit from the host erythrocyte: A two- step process requiring extraerythrocytic proteolysis. *Proc Natl Acad Sci U S A* 98, 271-276). However, following incubation with Example 1, there was an accumulation of unprocessed SERA5 at 120 kDa confirming that SUB1 activation requires prior processing. SERA5 was included as a control in all subsequent experiments as a proxy for PMX-mediated activation of SUB1.

To confirm that Example 1 was a dual inhibitor of PMX and PMIX function, the ability of this compound to inhibit cleavage of the known PMIX substrate Rhoptry Associated Protein 1 (RAP1) in parasite extracts was tested (Pino *et al.*, 2017). RAP1 is a merozoite rhoptry protein that is localized to the parasitophorous vacuole after invasion and processed by both PMIX and SUB1 (Pino *et al.*, 2017). The processed forms of RAP1 (p82 and p69) are detected in untreated and E64-treated merozoites, showing that this protein was processed normally by PMIX and SUB1 under these conditions. RAP1 was not released into the parasite supernatant because it was deposited in the parasitophorous vacuole during the invasion process (Baldi, D., Andrews, K., Waller, R., Roos, D., Howard, R., Crabb, B. and Cowman, A. (2000)). RAP1 controls rhoptry targeting of RAP2 in the malaria parasite *Plasmodium falciparum*. *Embo Journal* 19, 2435-2443. In parasites treated with Example 1 only the unprocessed p87 form of RAP1 was present, indicating that both SUB1 and PMIX cleavage have been blocked. Similar results were obtained for Apical Sushi Protein (ASP) which has also been shown to be cleaved by PMIX (Pino *et al.*, 2017). ASP was processed into a 47 kDa polypeptide (p47) in untreated and E64-treated parasites. However, this cleavage event was inhibited by Example 1 and the full-length protein of 87 kDa (p87) was observed, indicating that PMIX processing of this protein was blocked by Example 1. These findings confirm that Example 1 acts as a dual inhibitor and blocks both PMX and PMIX protease activity in the *P. falciparum* parasite.

The development of Example 1 as a PMIX/PMX dual inhibitor of the *P. falciparum* parasite has allowed for the analysis of the function of these aspartic acid proteases. To do this, PMIX was processed to a 55 kDa (p55) protein and this was not inhibited by E64. Example 1 was used to inhibit this processing event, indicating that autocatalytic cleavage of PMIX was important for activation of this protease. The development of a PMX-specific inhibitor and a PMX/PIX dual

inhibitor confirms the PMIX specific processing of ASP and RAP1, and also shows that PMIX was autocatalytically processed and activated.