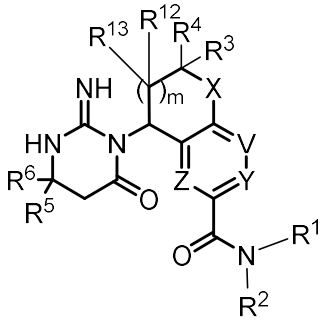
therapy (ACT) drug resistance, the development of new antimalarials with novel targets that inhibit multiple steps in the parasite life cycle is an urgent priority for the malaria control field. Such novel antimalarials, as monotherapies or ACT partner drugs, could make strides towards malaria elimination as there is a reduced likelihood of parasites with preexisting resistance mutations being present in the parasite population.

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

SUMMARY

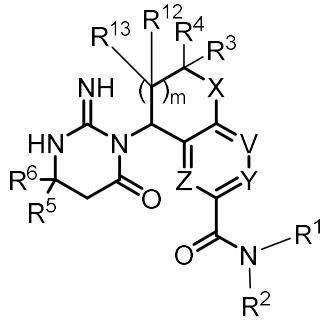
The present disclosure is directed to compounds of Formula (I'):



(I')

wherein X, V, Y, Z, R^1, R^2, R^3, R^4, R^5, R^6, R^{12} and R^{13} are described below.

In one aspect, there is provided a compound having the structural Formula (I'):



(I')

or a pharmaceutically acceptable salt thereof, wherein:

X is a bond, $C(R^{14})_2$, O, S, SO, SO_2 or NH;

Y is CR^9 or N, wherein when Y is N, Z is CR11 and V is CR^{10};

V is CR^{10} or N, wherein when V is N, Z is CR11 and Y is CR^9;

Z is CR^{11} or N, wherein when Z is N, V is CR10 and Y is CR^9;

R^1 is a heterocycloalkyl, C_3-C_{12}cycloalkyl, aryl, C_1-C_6alkylaryl 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_6alkylaryl 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_6alkoxy, C_1-C_6alkylOC_1-C_6alkyl, C_1-C_6alkylCOOH, COOH, oxo, $COOC_1$-C_6alkyl, C_1-C_6alkyl$COOC_1$-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, aryl, C_1-C_6alkyl, -C_1-C_6alkylOhaloC_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkylOH, $CON(R^7)(R^8)$, $N(R^7)(R^8)$ and C_1-C_6alkyl$N(R^7)(R^8)$;

R^2 is hydrogen, C_1-C_6alkylCOOH, COOH, C_3-C_6cycloalkyl, C_1-C_6alkyl, haloC_1-C_6alkyl or C_1-

C_6alkylOH or when taken with R^1, 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, C_1-C_6alkoxy, C_1-C_6alkylOC_1-C_6alkyl, C_1-C_6alkylCOOH, COOH, oxo, COOC_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkylOH, CON(R^7)(R^8), N(R^7)(R^8) and C_1-C_6alkylN(R^7)(R^8);

R^3 is hydrogen, halogen, CN, OH, C_1-C_6alkoxy, C_1-C_6alkylOC_1-C_6alkyl, C_1-C_6alkylCOOH, COOH, C_3-C_6cycloalkyl, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkylOH, CON(R^7)(R^8), N(R^7)(R^8), C_1-C_6alkylN(R^7)(R^8), C_1-C_6alkyl$(OCH_2CH_2)_n$N(R^7)(R^8) or C_1-C_6alkylOhaloC_1-C_6alkyl or when taken with R^4 forms a C_3-C_6cycloalkyl or C_3-C_6heterocycloalkyl;

R^4 is hydrogen, halogen, CN, OH, C_1-C_6alkoxy, C_1-C_6alkylOC_1-C_6alkyl, C_1-C_6alkylCOOH, COOH, C_3-C_6cycloalkyl, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkylOH, CON(R^7)(R^8), N(R^7)(R^8), C_1-C_6alkylN(R^7)(R^8), C_1-C_6alkyl$(OCH_2CH_2)_n$N(R^7)(R^8) or C_1-C_6alkylOhaloC_1-C_6alkyl or when taken with R^3 forms a C_3-C_6cycloalkyl or C_3-C_6heterocycloalkyl;

R^5 is hydrogen, halogen, CN, OH, C_1-C_6alkoxy, C_1-C_6alkylOC_1-C_6alkyl, C_1-C_6alkylCOOH, COOH, C_3-C_6cycloalkyl, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkylOH, CON(R^7)(R^8), N(R^7)(R^8) or C_1-C_6alkylN(R^7)(R^8) or when taken with R^6 forms a C_3-C_6cycloalkyl or C_3-C_6heterocycloalkyl;

R^6 is hydrogen, halogen, CN, OH, C_1-C_6alkoxy, C_1-C_6alkylOC_1-C_6alkyl, C_1-C_6alkylCOOH, COOH, C_3-C_6cycloalkyl, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkylOH, CON(R^7)(R^8), N(R^7)(R^8) or C_1-C_6alkylN(R^7)(R^8) or when taken with R^5 forms a C_3-C_6cycloalkyl or C_3-C_6heterocycloalkyl;

R^7 is hydrogen, C_1-C_6alkylCOOH, COOH, C_3-C_6cycloalkyl, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkylOH, COC_1-C_6alkyl or COOC_1-C_6alkyl;

R^8 is hydrogen, C_1-C_6alkylCOOH, COOH, C_3-C_6cycloalkyl, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkylOH, COC_1-C_6alkyl or COOC_1-C_6alkyl;

R^9 is hydrogen, halogen, CN, OH, C_1-C_6alkoxy, C_1-C_6alkylOC_1-C_6alkyl, C_1-C_6alkylCOOH, COOH, C_3-C_6cycloalkyl, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkylOH, CON(R^7)(R^8), N(R^7)(R^8) or C_1-C_6alkylN(R^7)(R^8);

R^{10} is hydrogen, halogen, CN, OH, C_1-C_6alkoxy, C_1-C_6alkylOC_1-C_6alkyl, C_1-C_6alkylCOOH, COOH, C_3-C_6cycloalkyl, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkylOH, CON(R^7)(R^8), N(R^7)(R^8) or

C_1-C_6alkylN(R^7)(R^8);

R^{11} is hydrogen, halogen, CN, OH, C_1-C_6alkoxy, C_1-C_6alkylOC_1-C_6alkyl, C_1-C_6alkylCOOH, COOH, C_3-C_6cycloalkyl, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkylOH, CON(R^7)(R^8), N(R^7)(R^8) or C_1-C_6alkylN(R^7)(R^8);

R^{12} is hydrogen, halogen, CN, OH, C_1-C_6alkoxy, C_1-C_6alkylOC_1-C_6alkyl, C_1-C_6alkylCOOH, COOH, C_3-C_6cycloalkyl, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkylOH, CON(R^7)(R^8), N(R^7)(R^8) or C_1-C_6alkylN(R^7)(R^8);

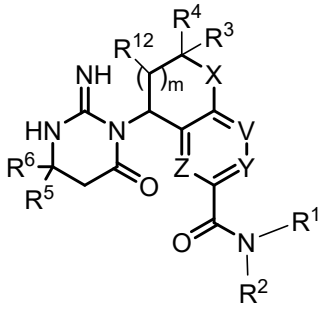
R^{13} is hydrogen, halogen, CN, OH, C_1-C_6alkoxy, C_1-C_6alkylOC_1-C_6alkyl, C_1-C_6alkylCOOH, COOH, C_3-C_6cycloalkyl, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkylOH, CON(R^7)(R^8), N(R^7)(R^8) or C_1-C_6alkylN(R^7)(R^8);

each occurrence of R^{14} is independently selected from the group consisting of hydrogen, halogen, CN, OH, C_1-C_6alkoxy, C_1-C_6alkylOC_1-C_6alkyl, C_1-C_6alkylCOOH, COOH, C_3-C_6cycloalkyl, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkylOH, CON(R^7)(R^8), N(R^7)(R^8) and C_1-C_6alkylN(R^7)(R^8);

n is 1, 2, 3 or 4; and

m is 0, 1 or 2.

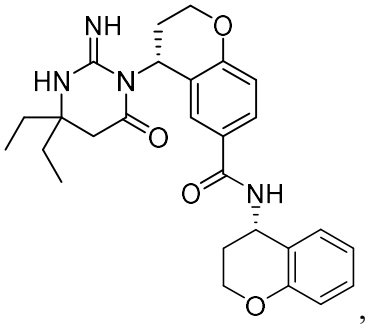
The present disclosure is directed to compounds of Formula (I):



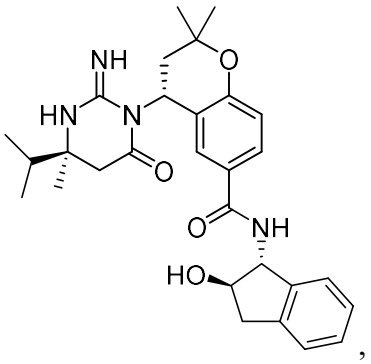
(I)

wherein X, V, Y, Z, R^1, R^2, R^3, R^4, R^5, R^6 and R^{12} are described below.

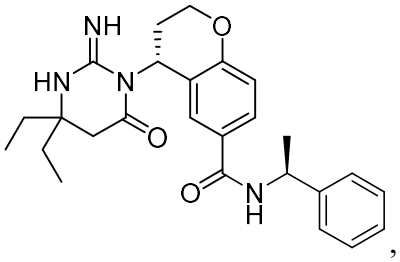
In another aspect, there is provided a compound selected from the group consisting of:



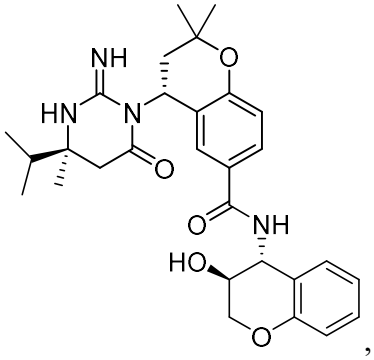
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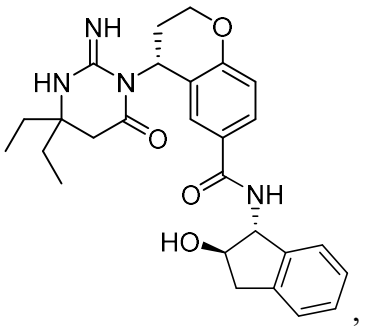
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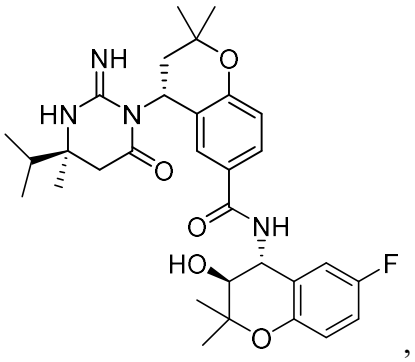
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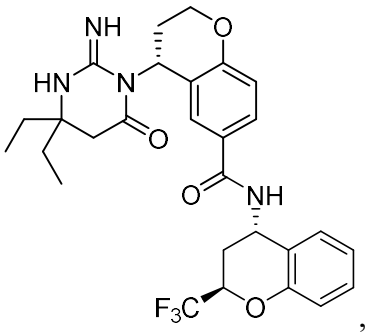
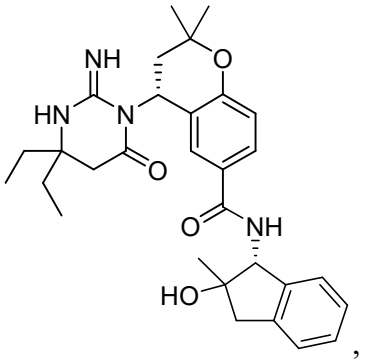
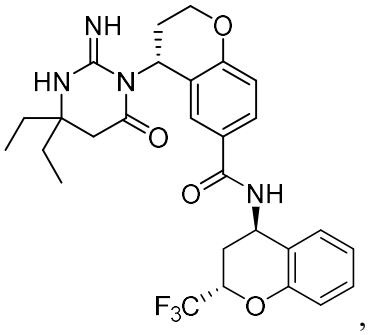
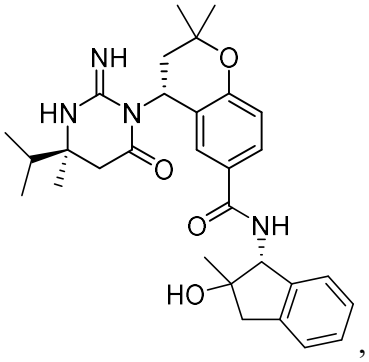
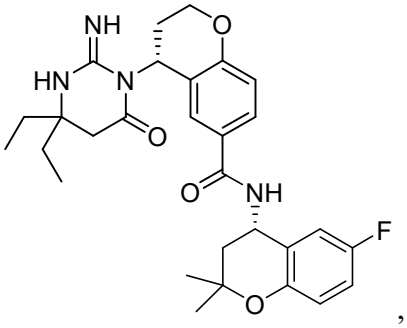
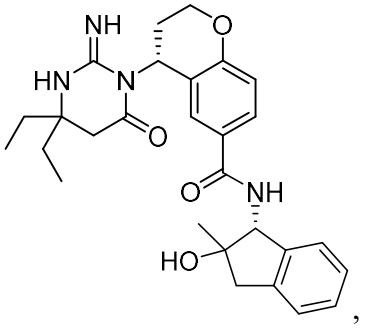
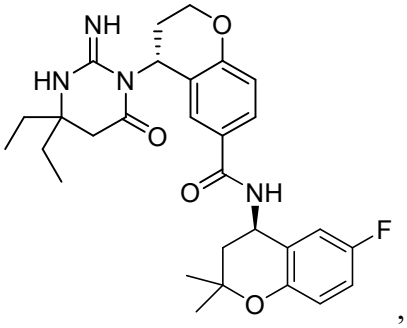
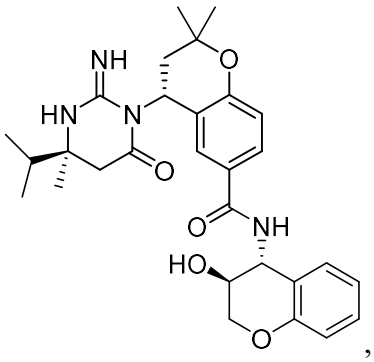
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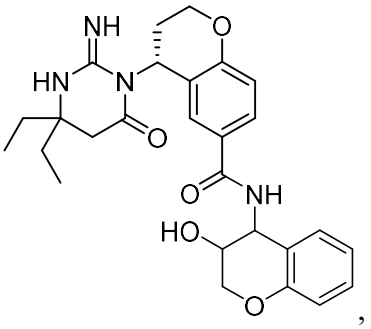
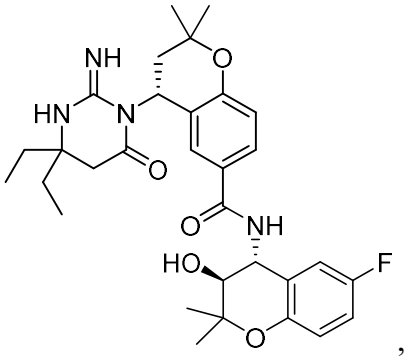
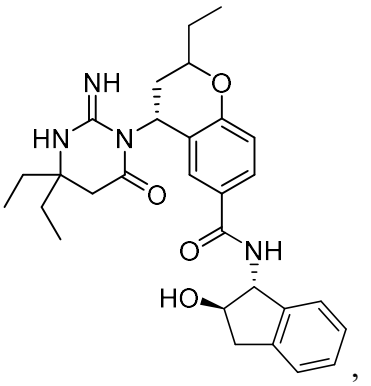
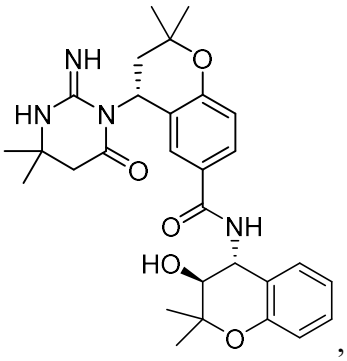
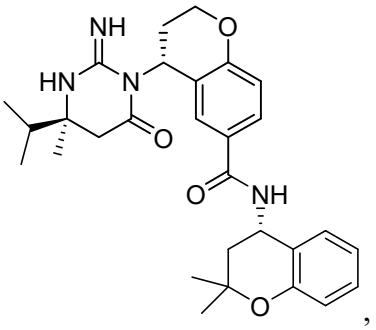
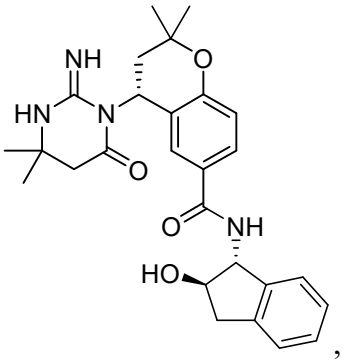
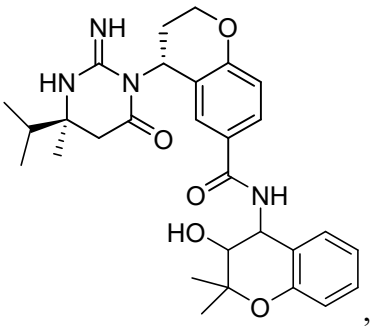
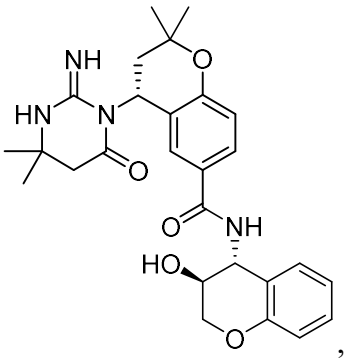


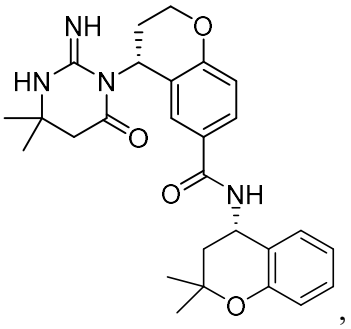
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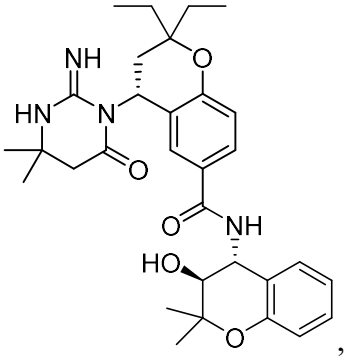


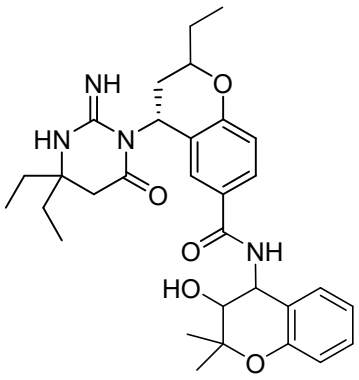
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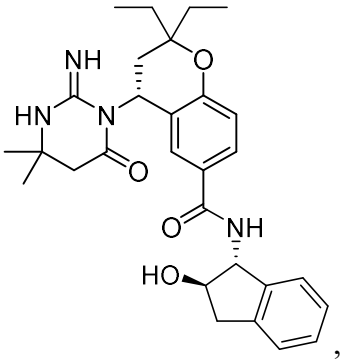

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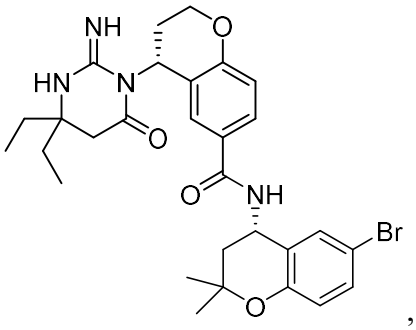

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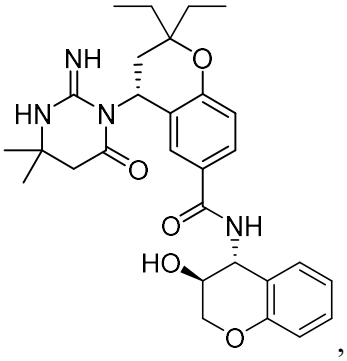

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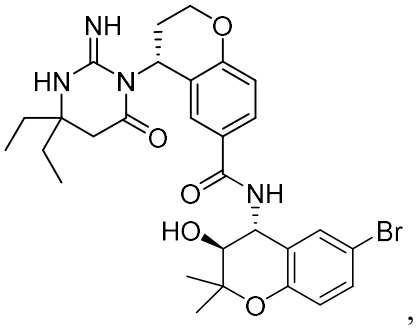

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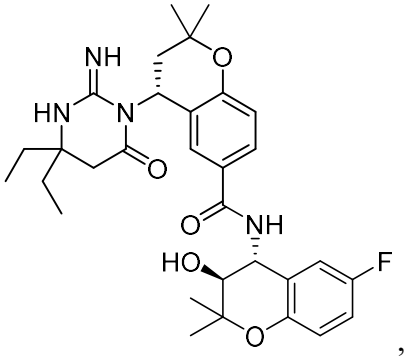

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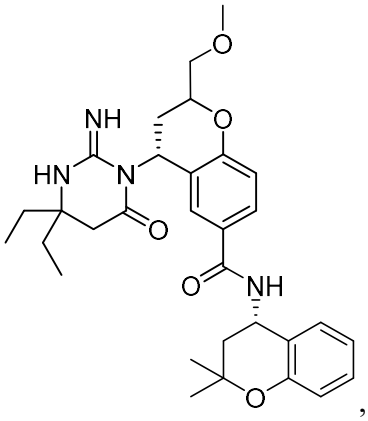

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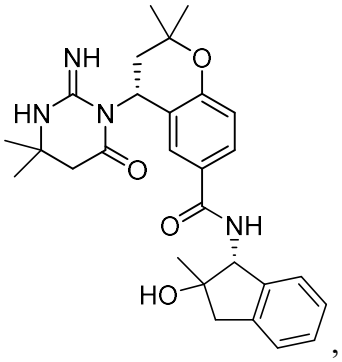

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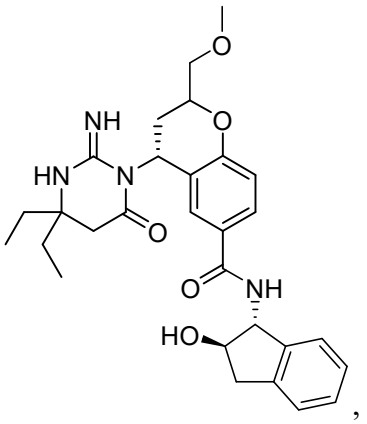

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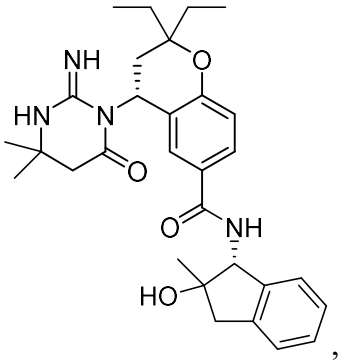

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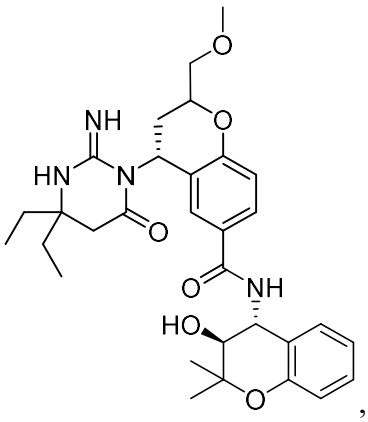

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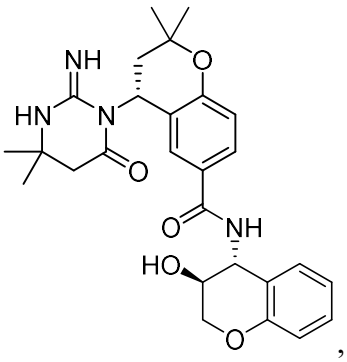

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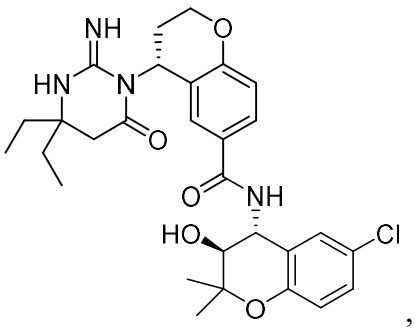

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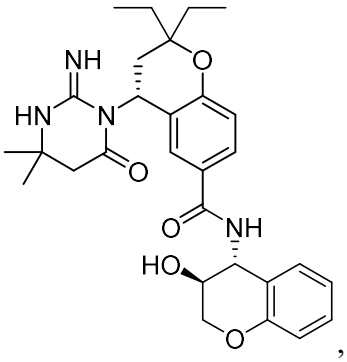

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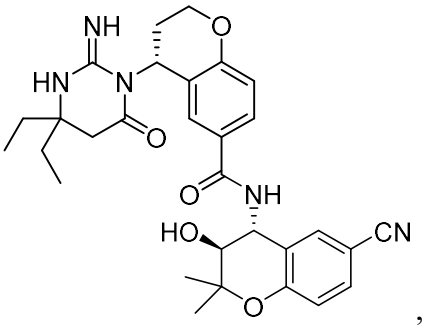
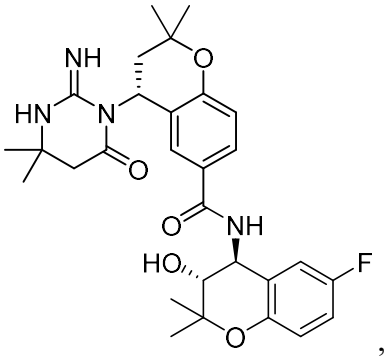
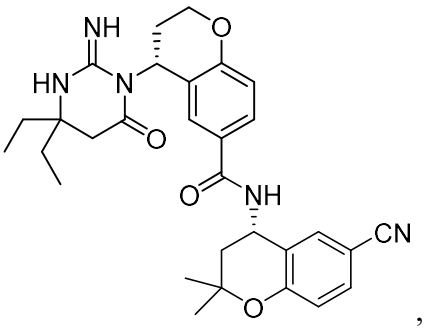
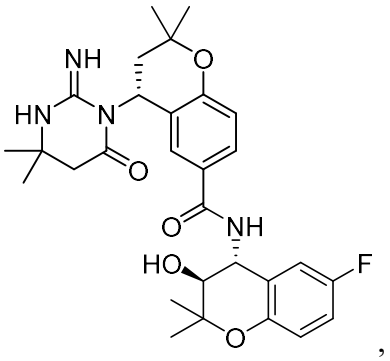
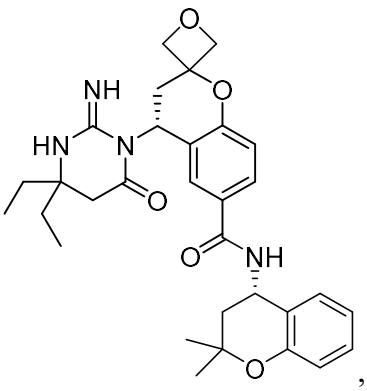
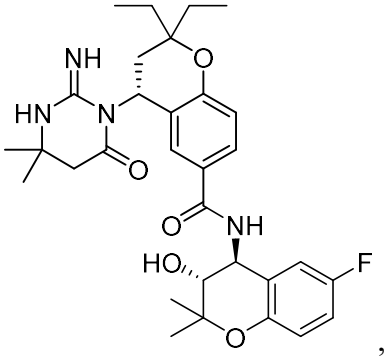
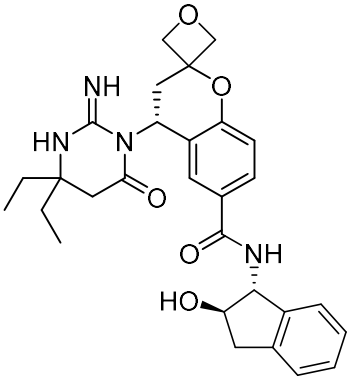
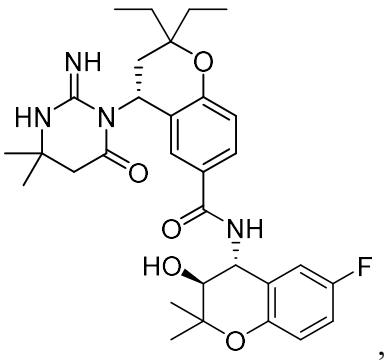

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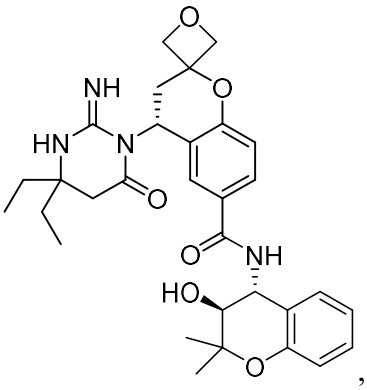

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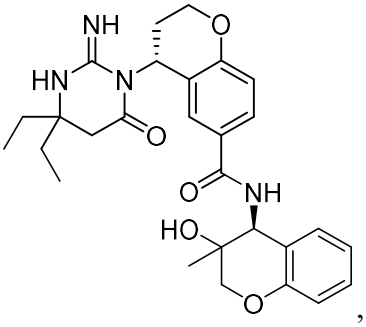

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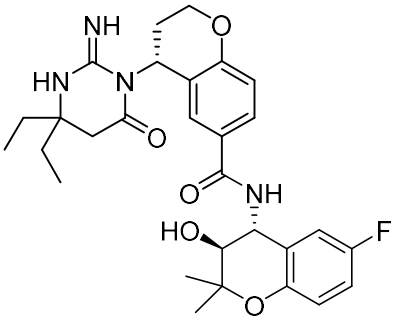

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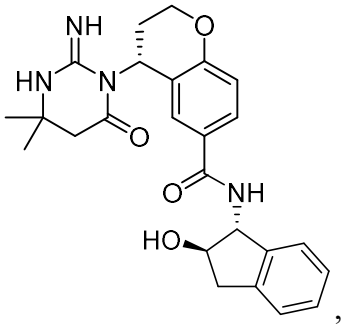

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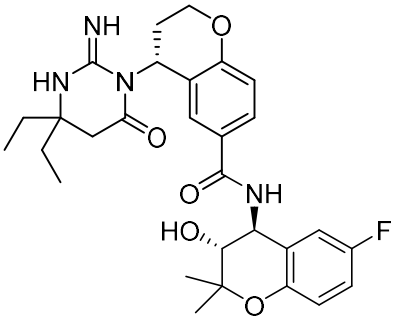

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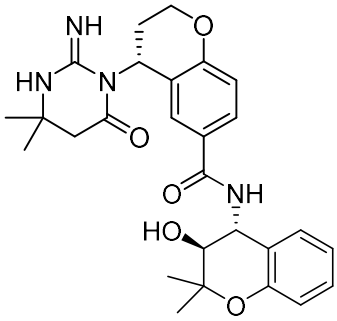

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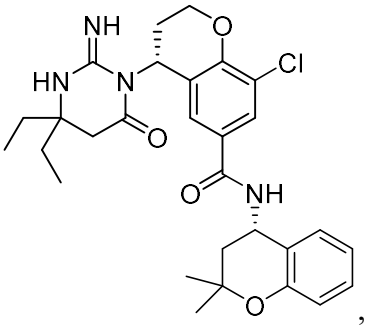

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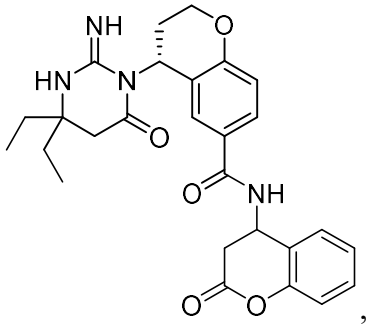

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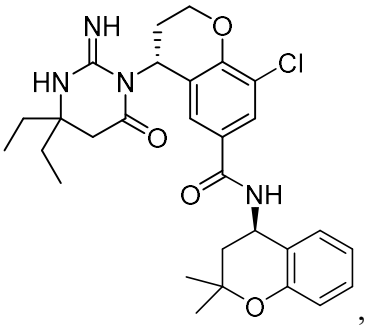
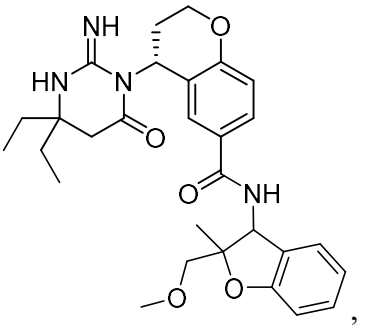
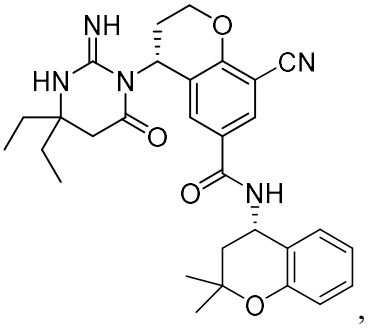
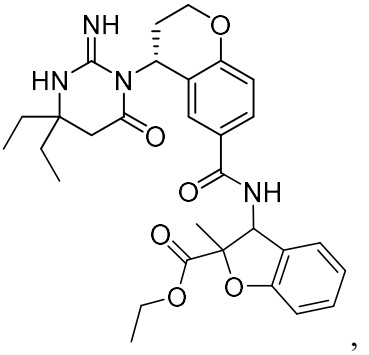
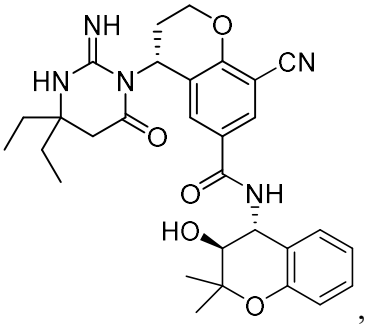
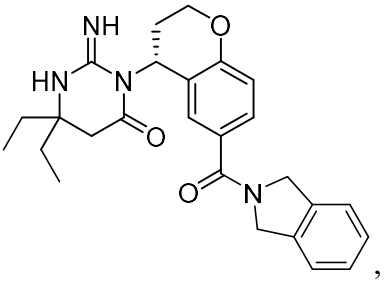
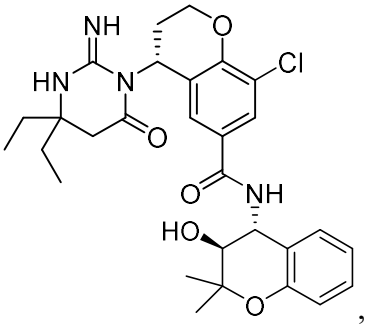
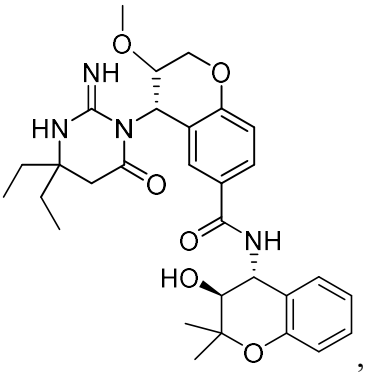

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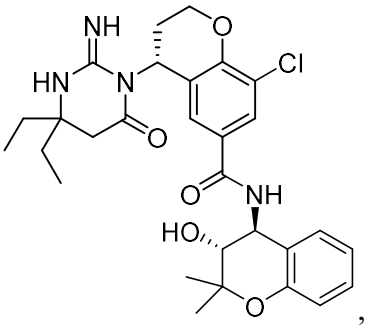
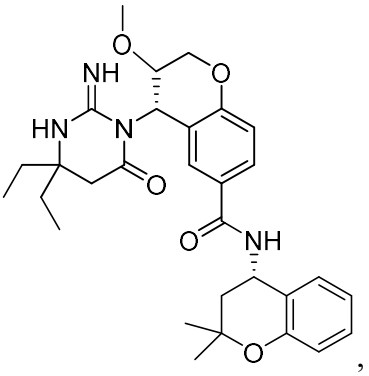
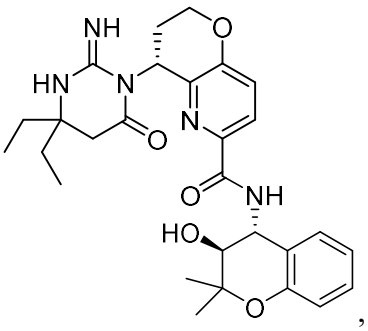
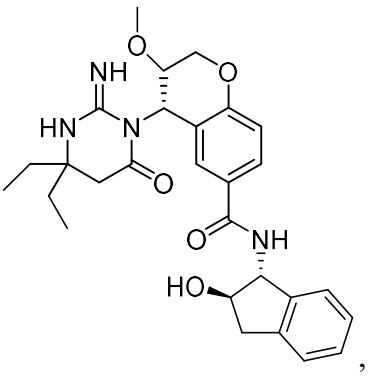
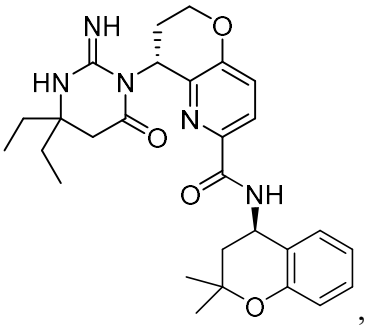
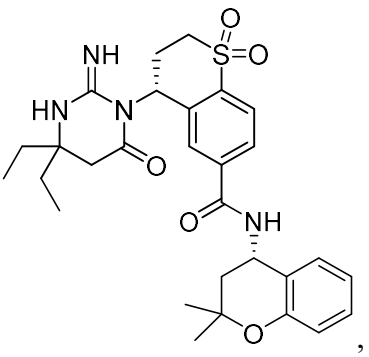
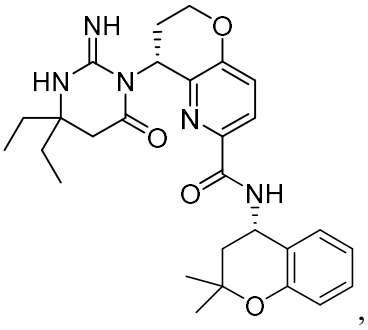
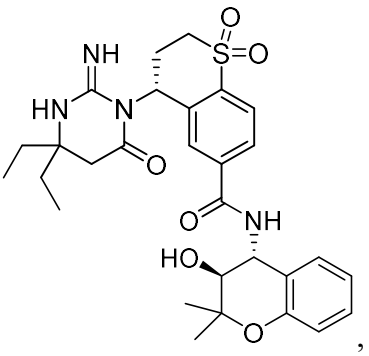

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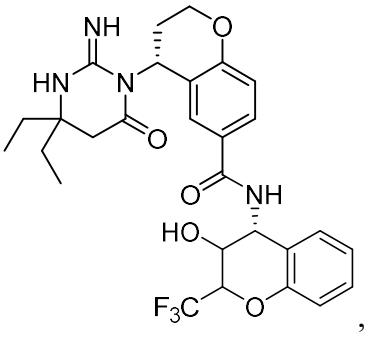

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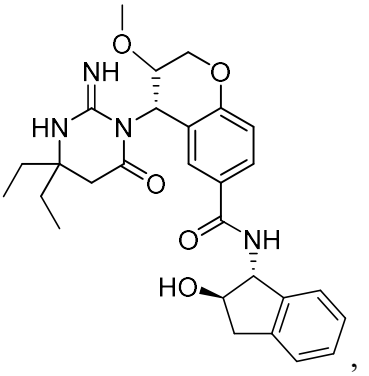

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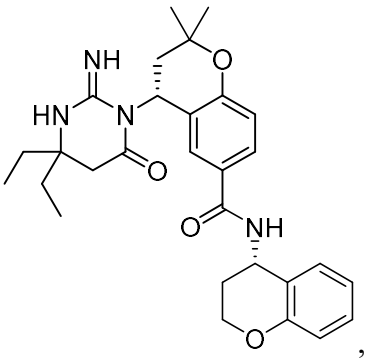

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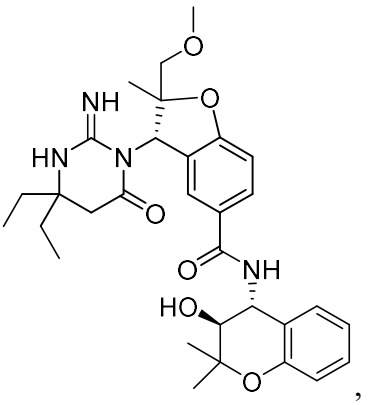

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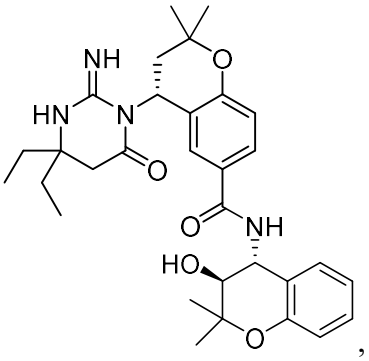

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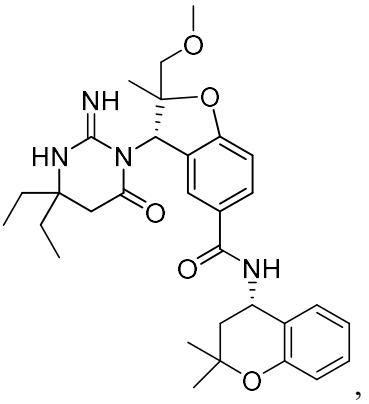

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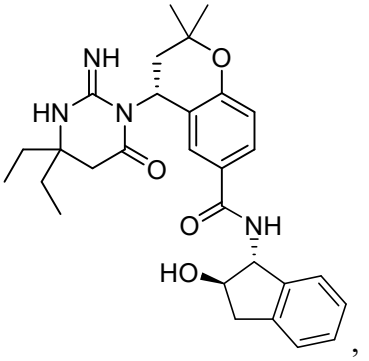

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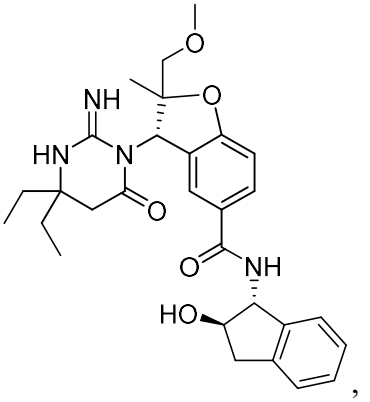

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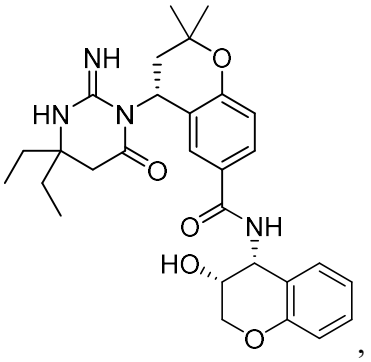

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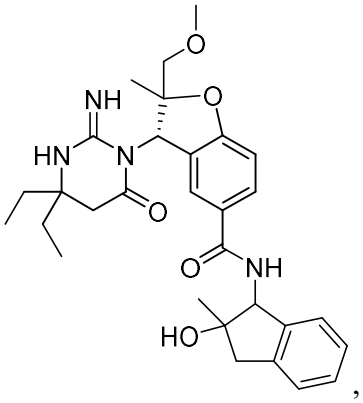

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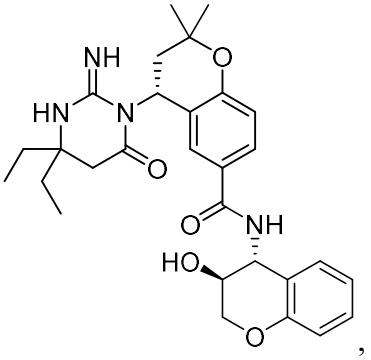

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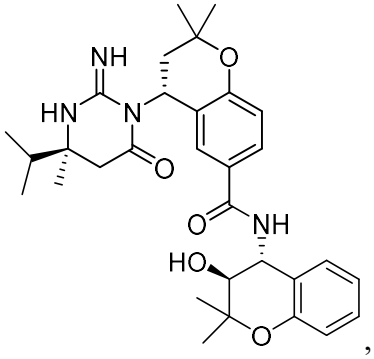

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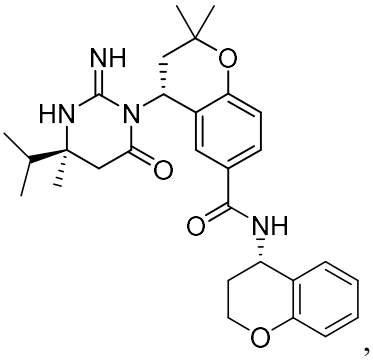

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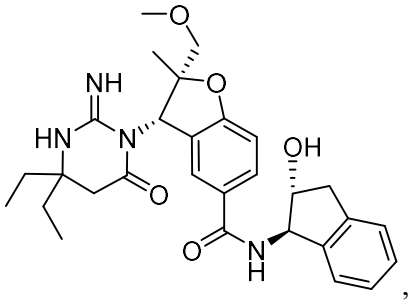

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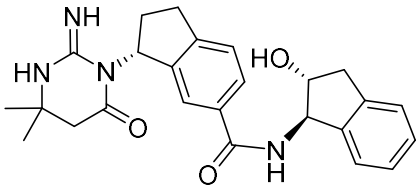
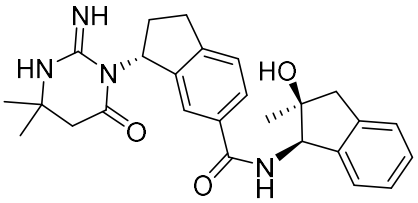
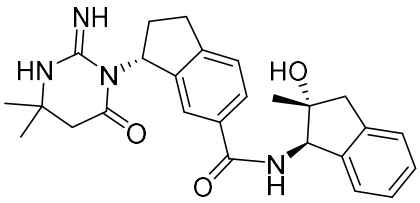
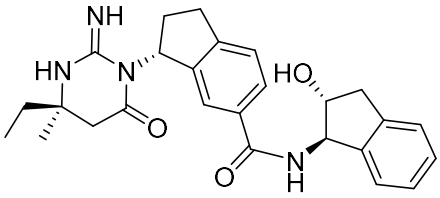
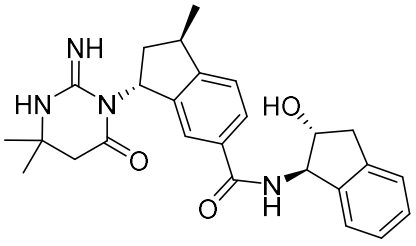
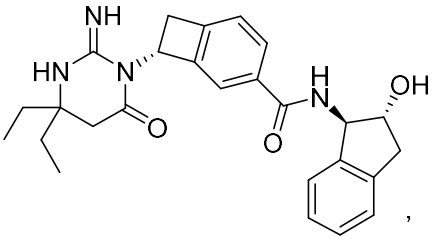
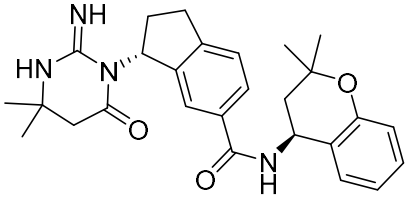
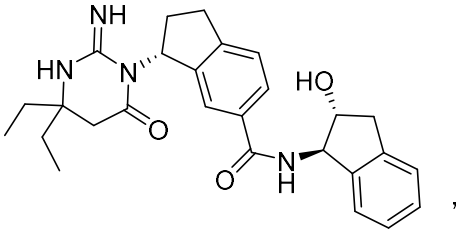
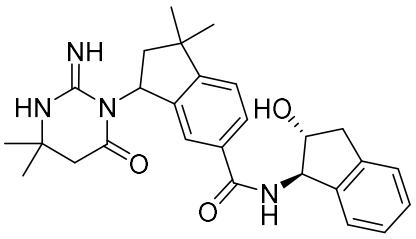
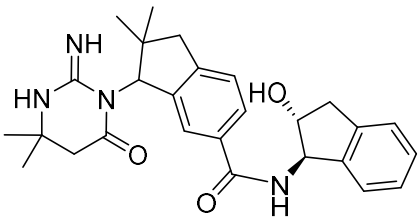

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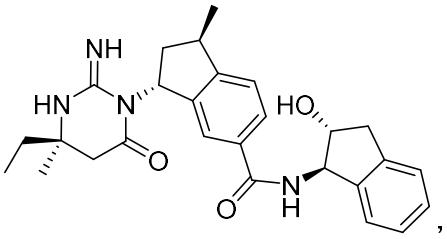

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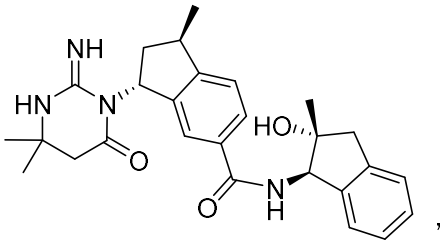

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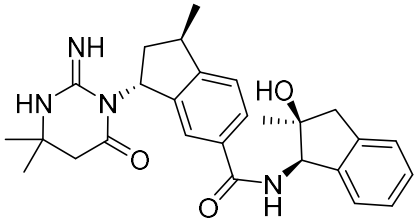

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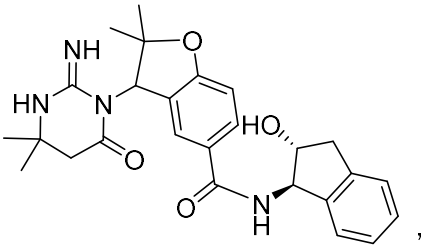

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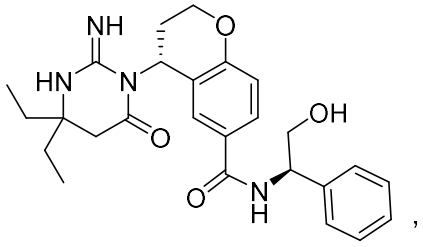

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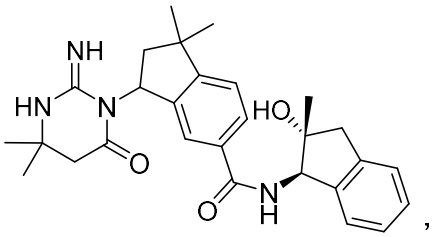


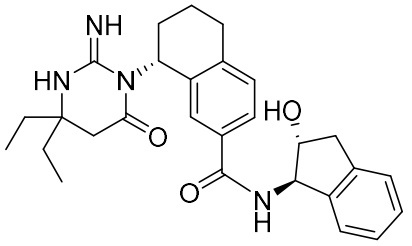


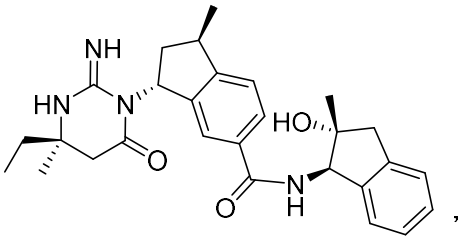


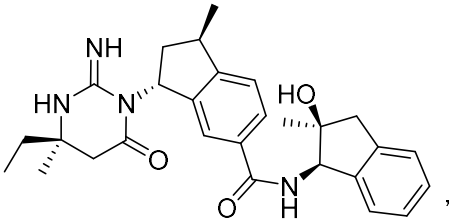


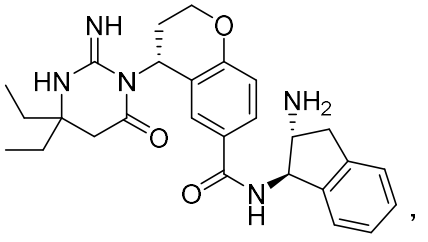


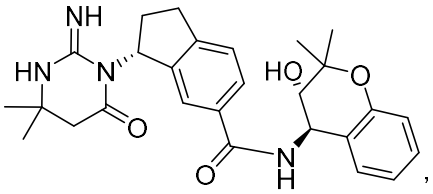


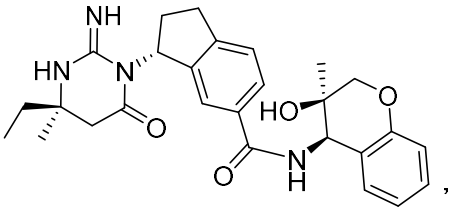


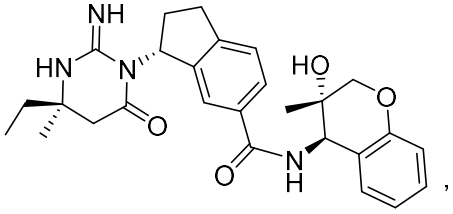


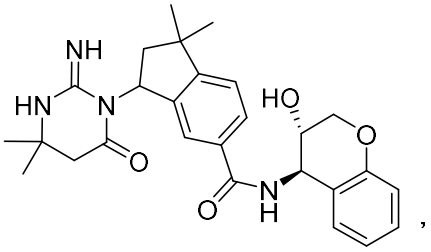


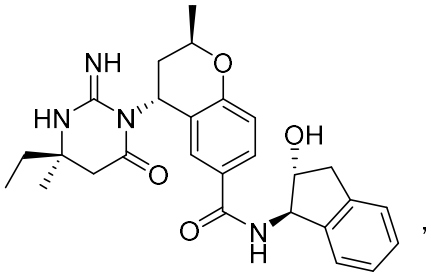


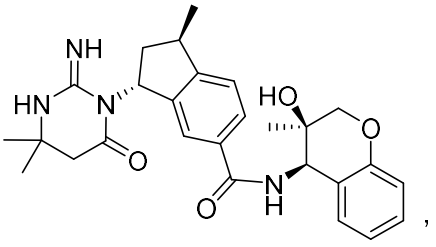


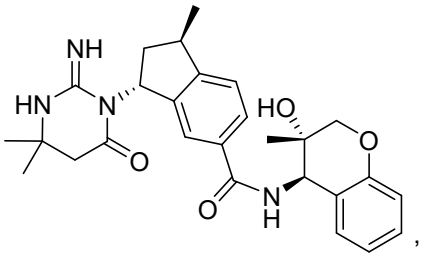


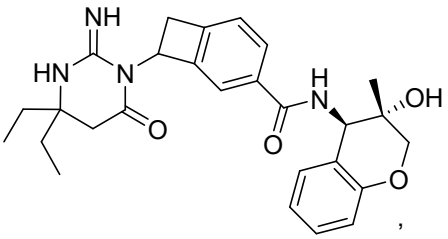


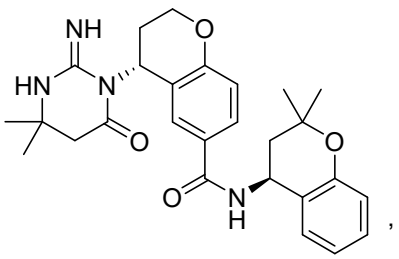


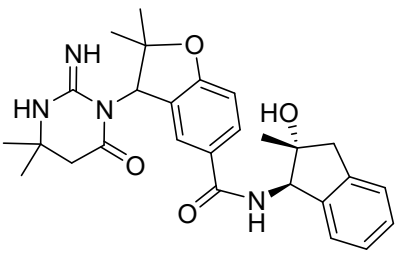


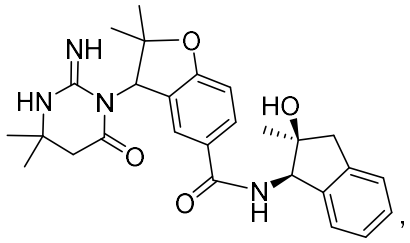


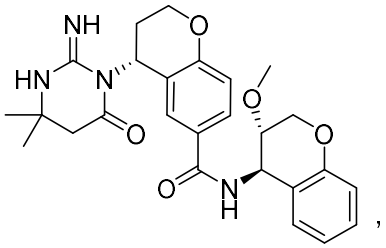


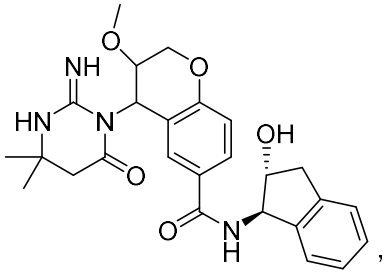


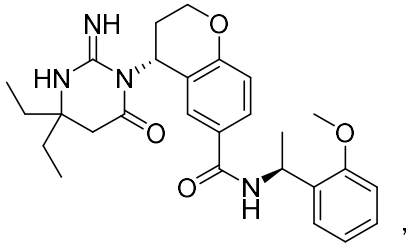


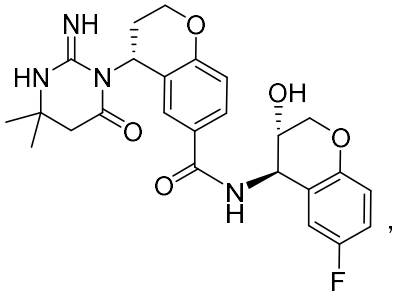


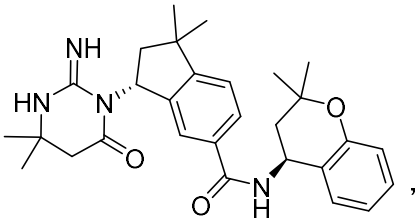


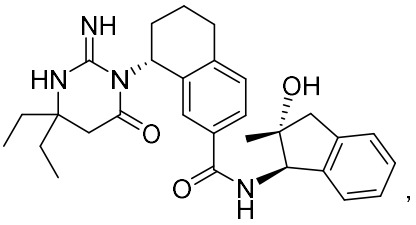


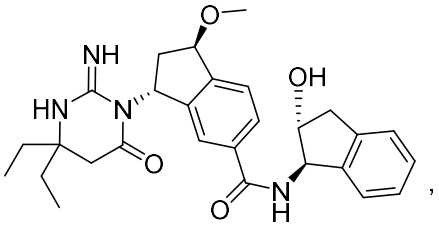


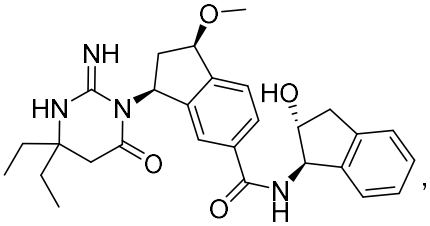


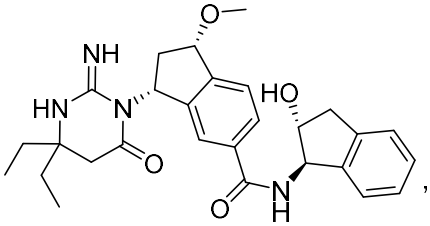


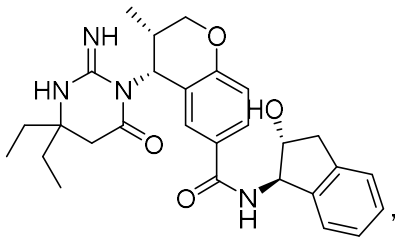


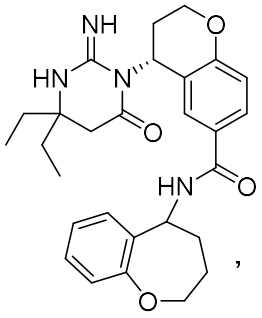


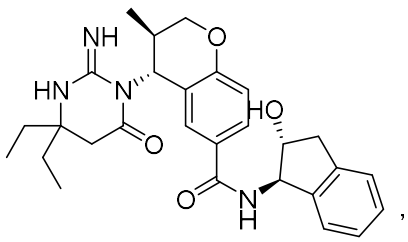


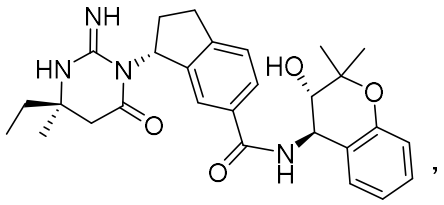


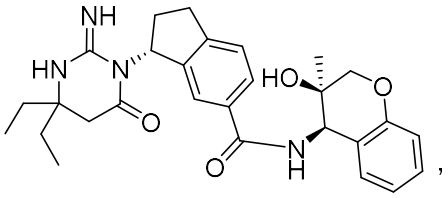


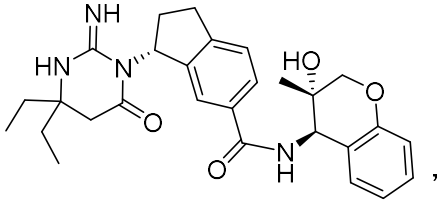


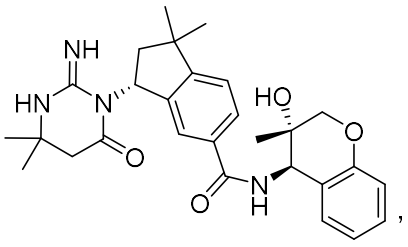


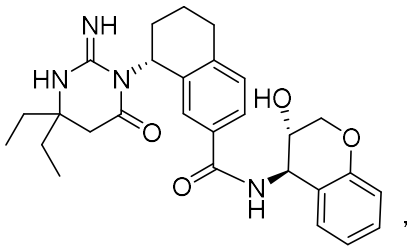


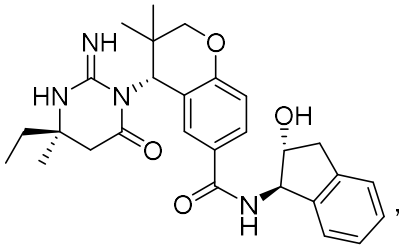


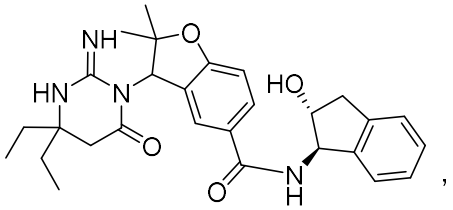


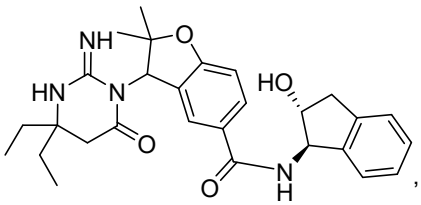


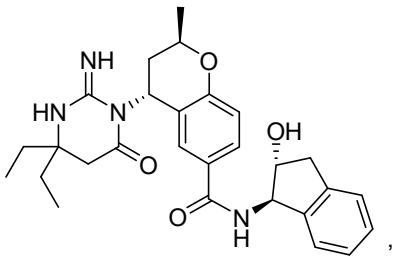


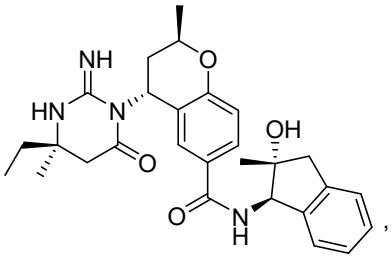


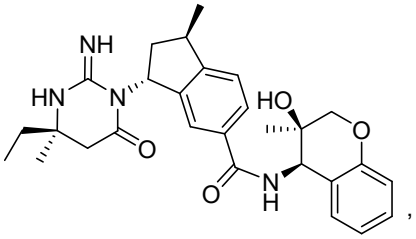


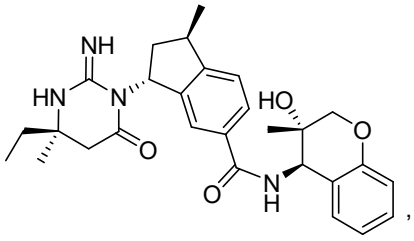


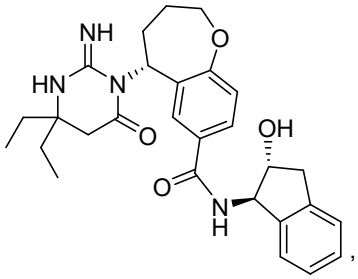


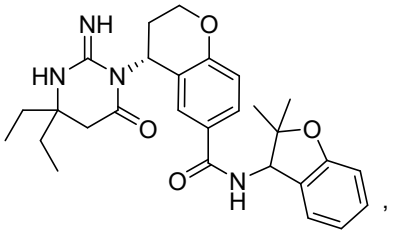


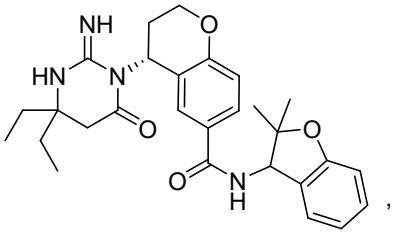


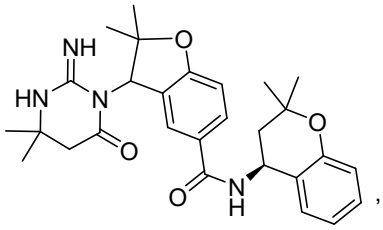


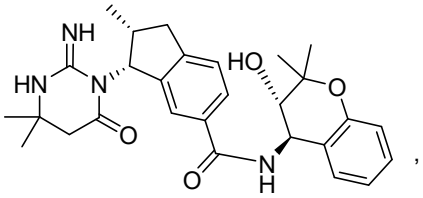


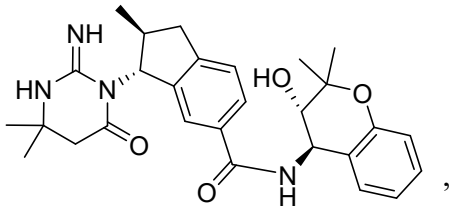
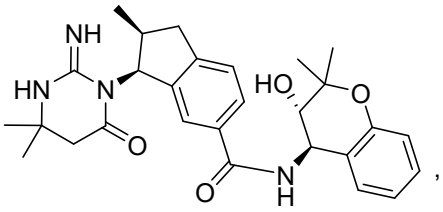
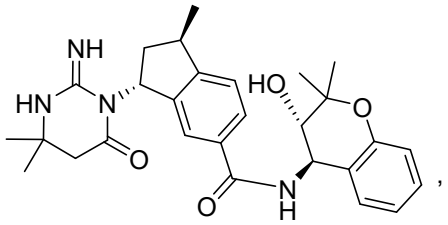
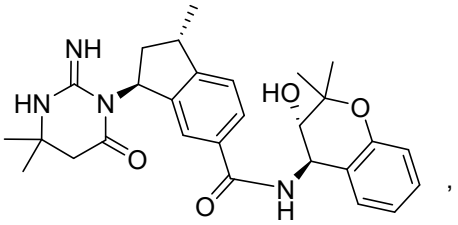
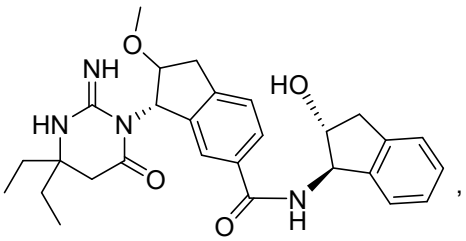
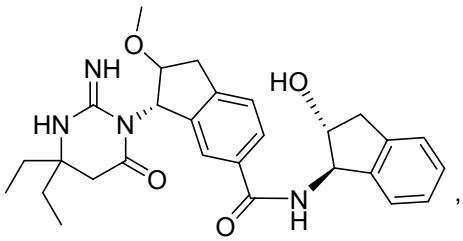
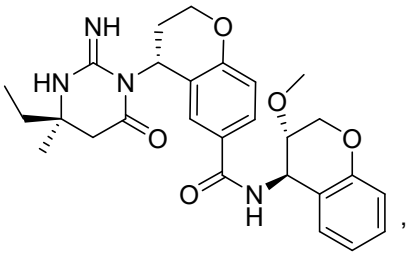
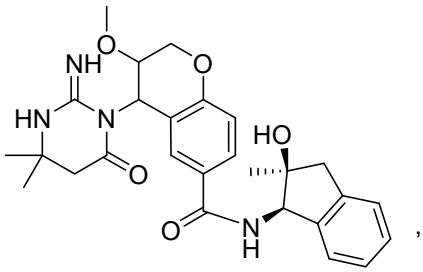
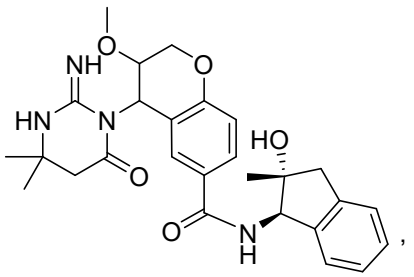
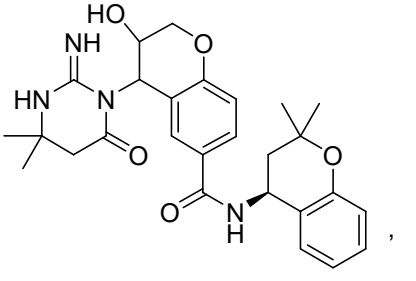


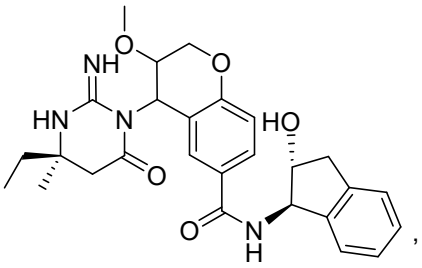


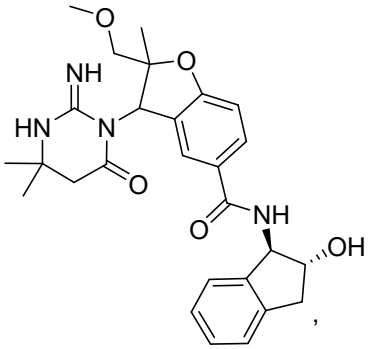


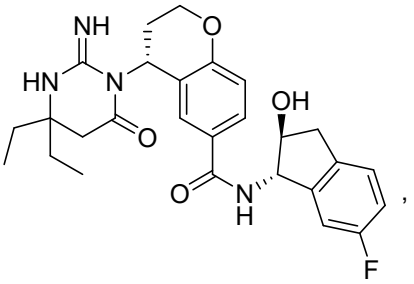


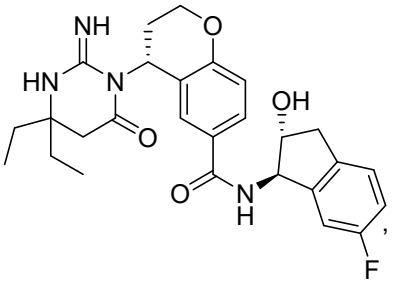


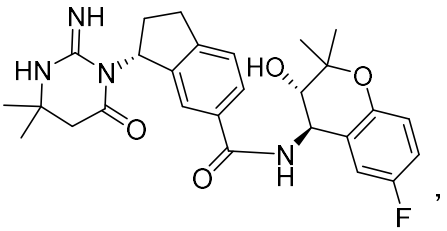

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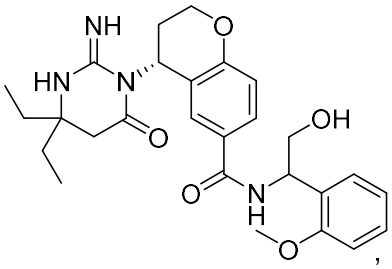


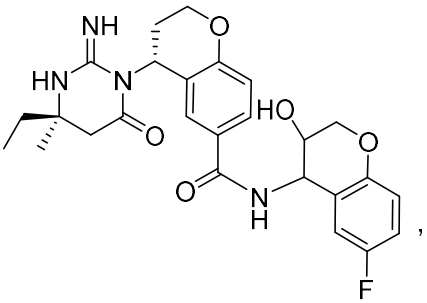


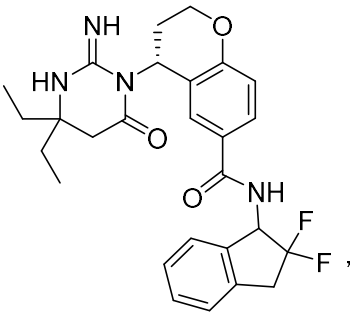


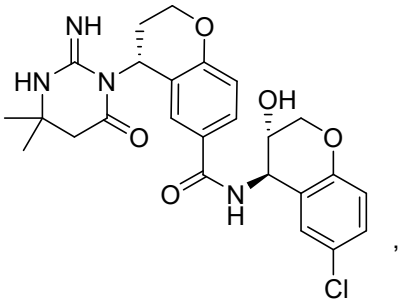


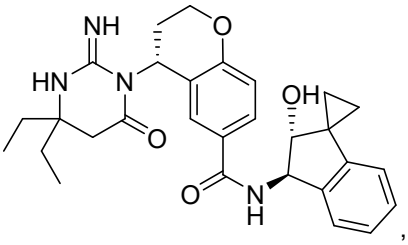


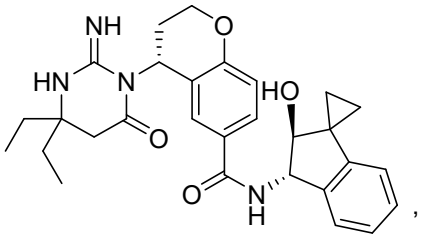


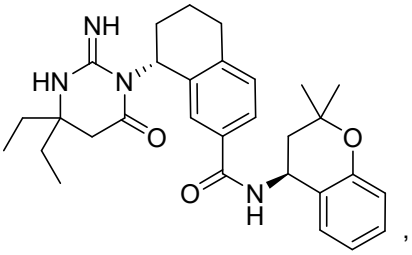


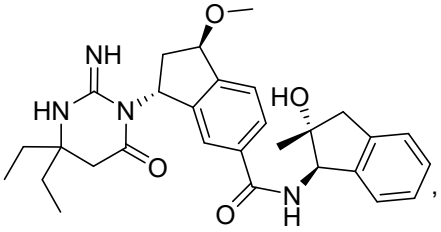


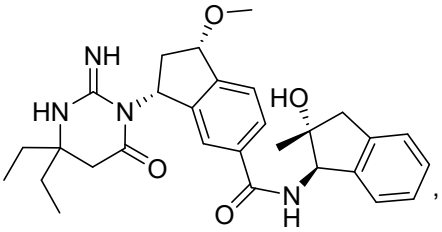

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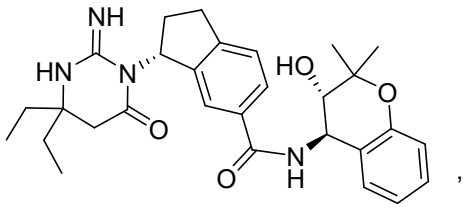

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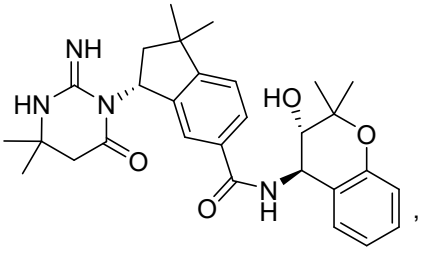

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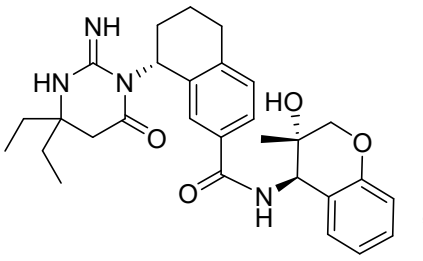

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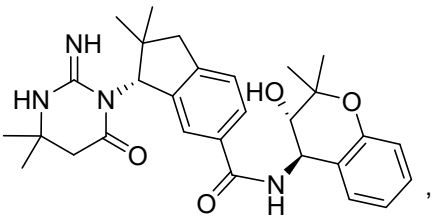

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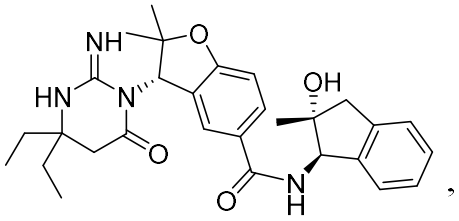

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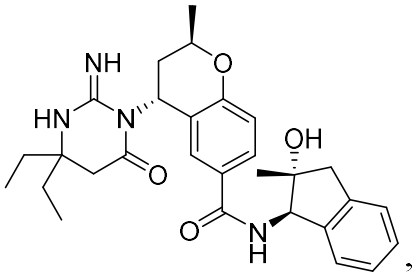

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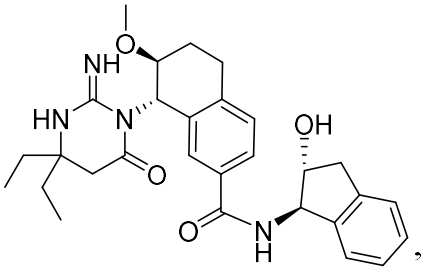

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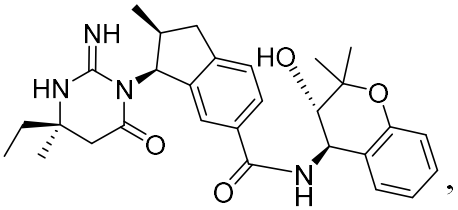

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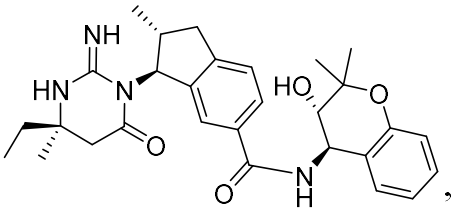
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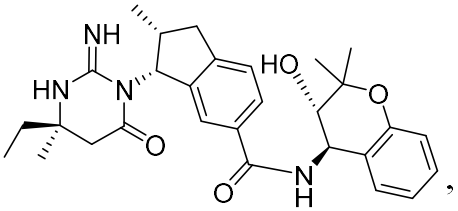


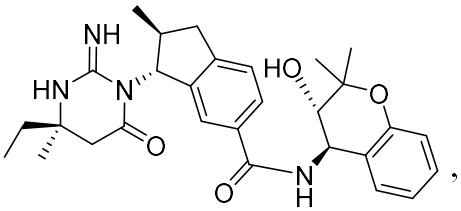


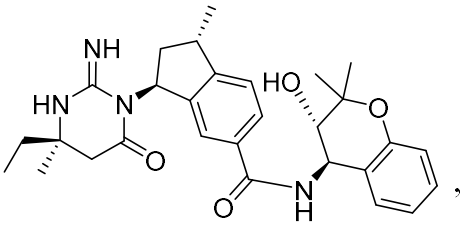


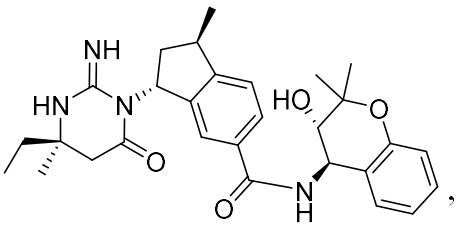


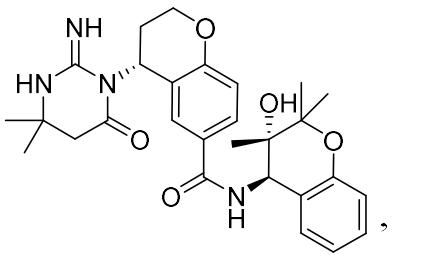




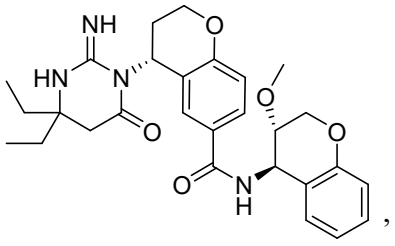


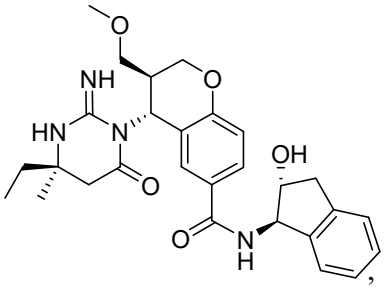


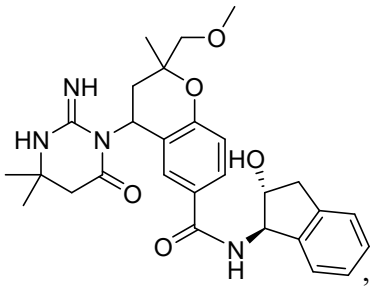


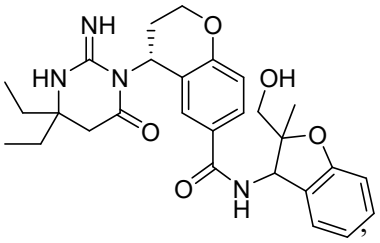


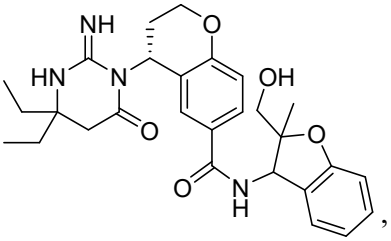
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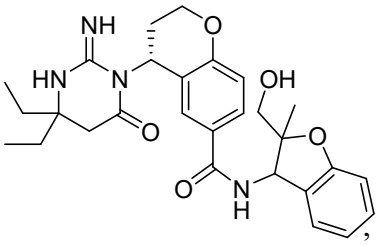


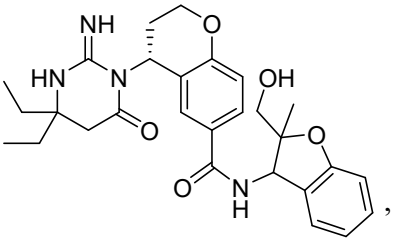


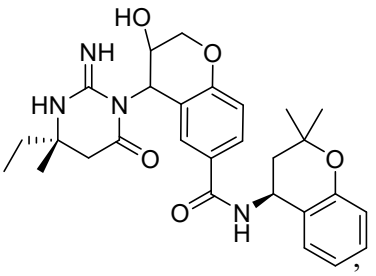


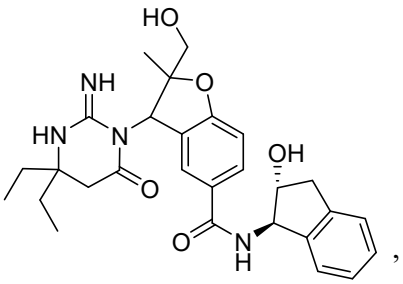


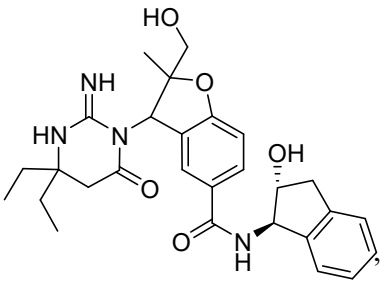


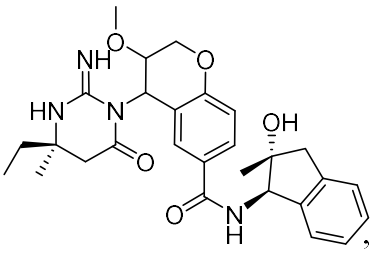


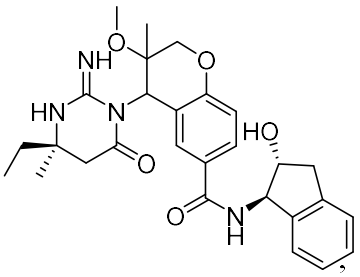


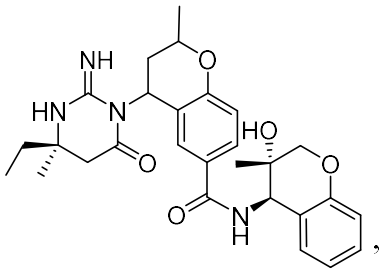


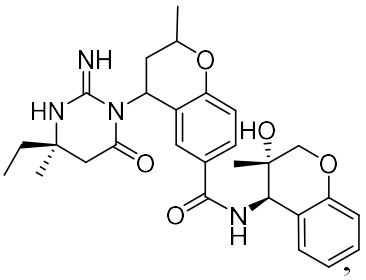


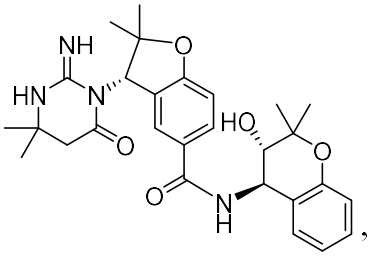


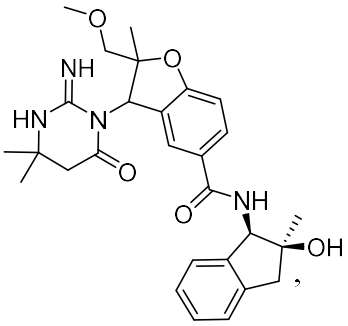


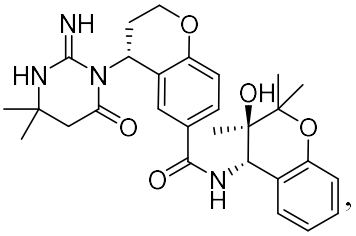


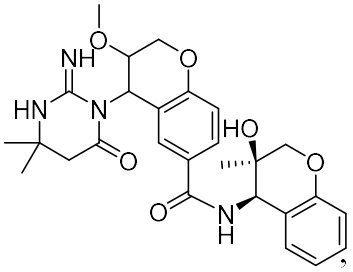


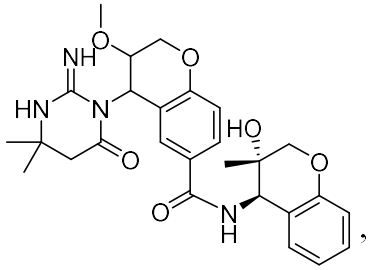


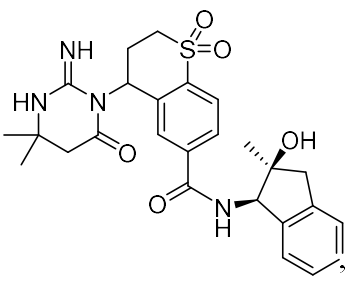


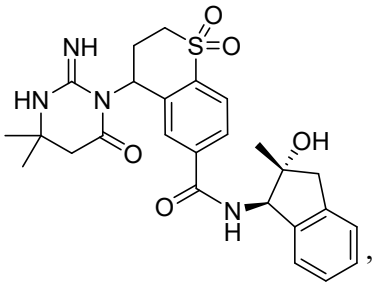


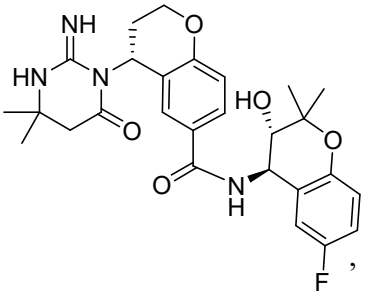


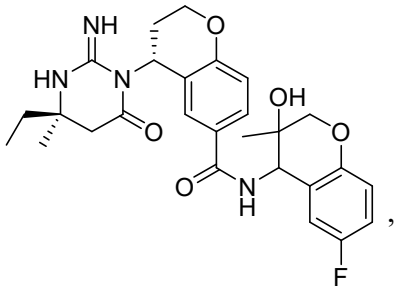


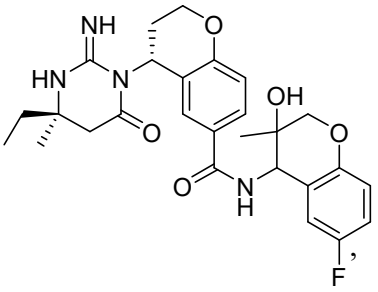


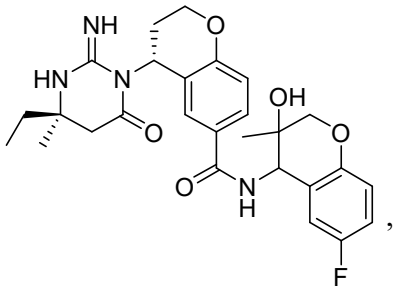


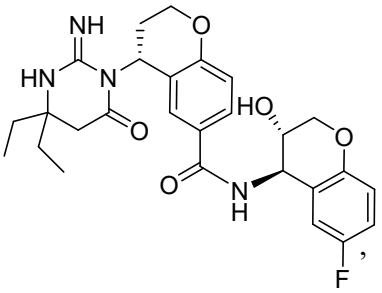


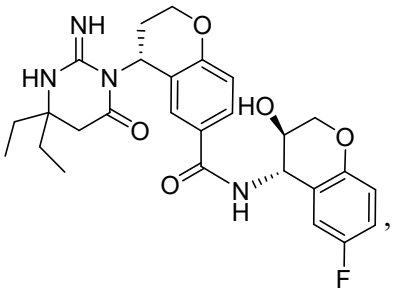


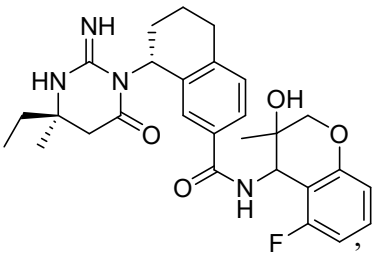


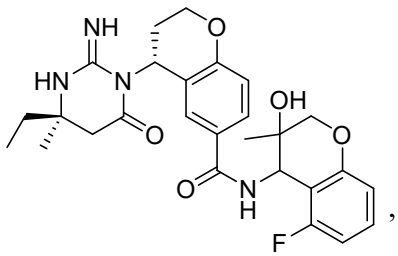


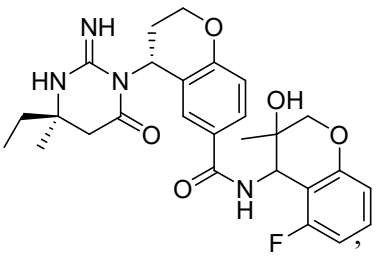


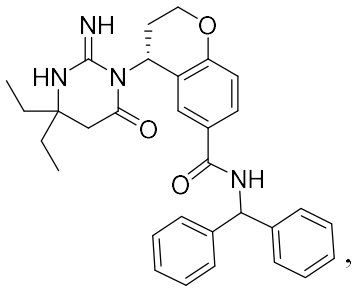


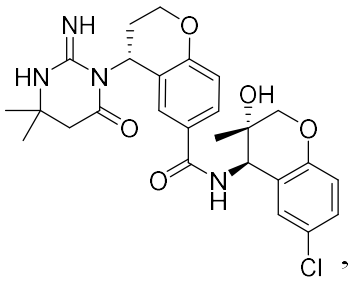


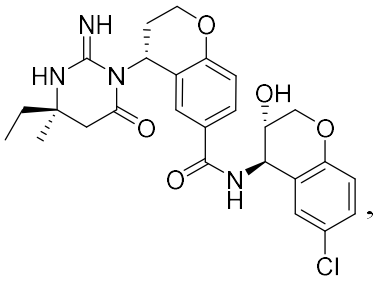


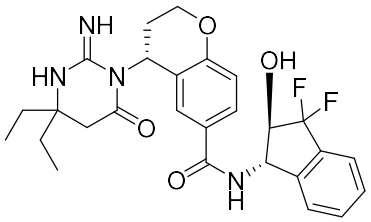


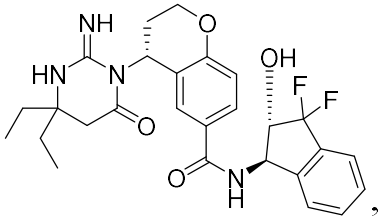


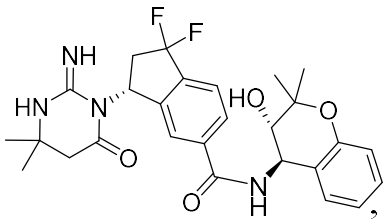


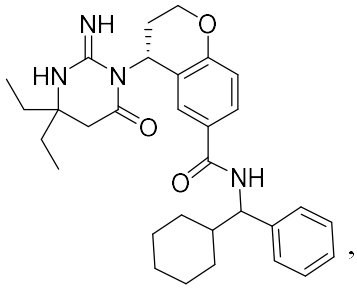


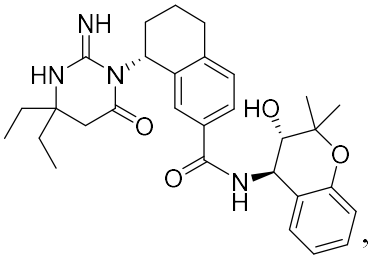


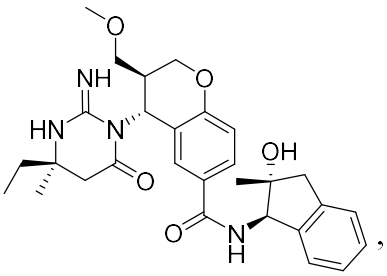


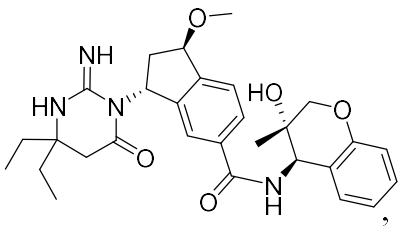


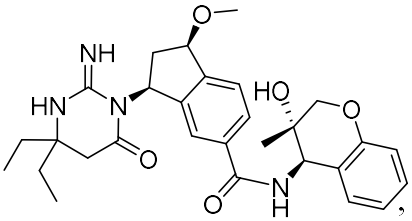


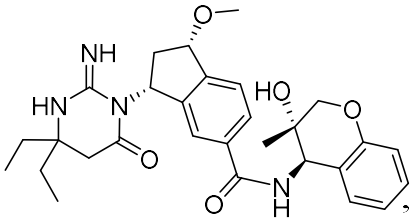


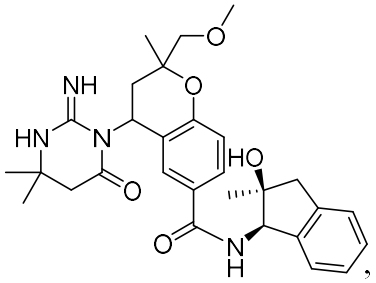


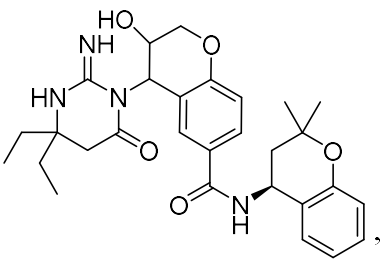


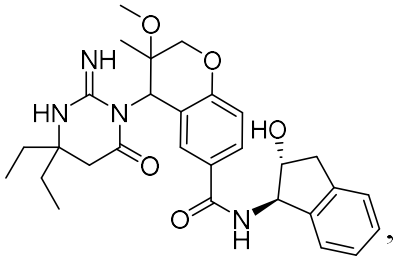


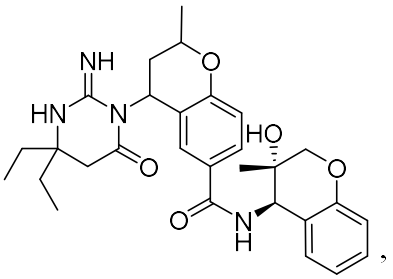


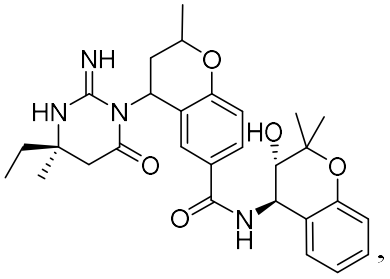


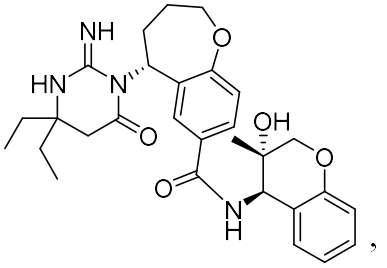


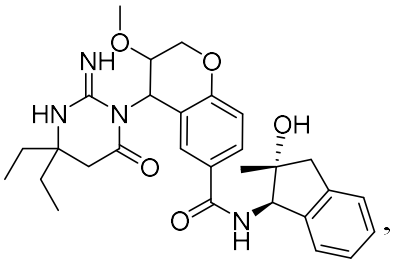


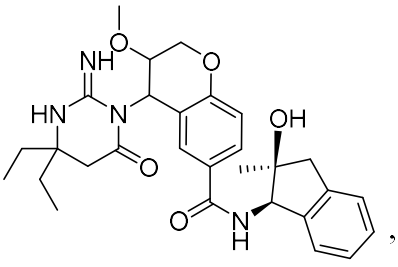




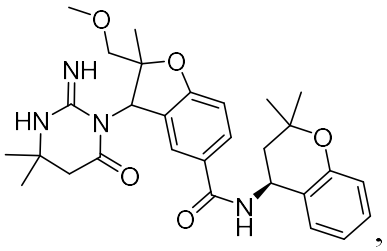


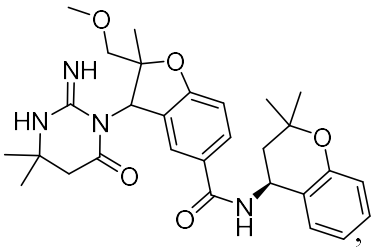


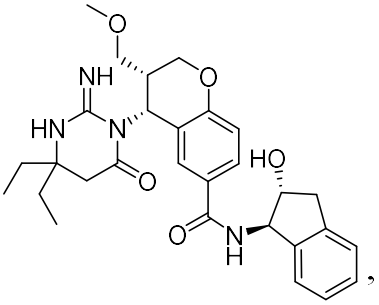


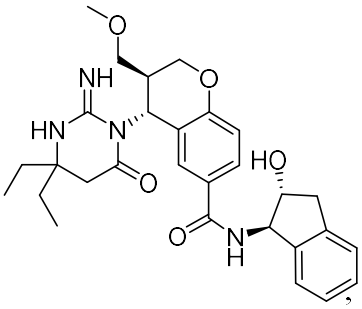


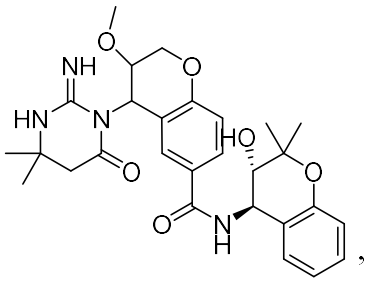
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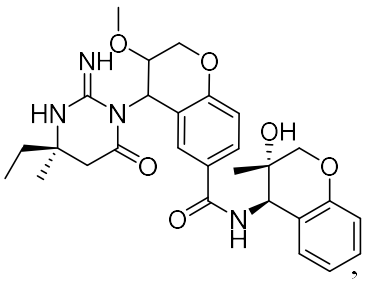


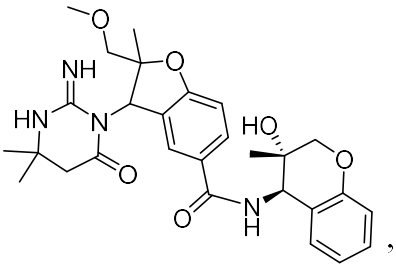


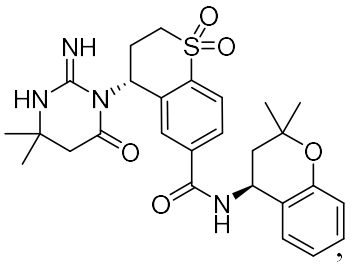


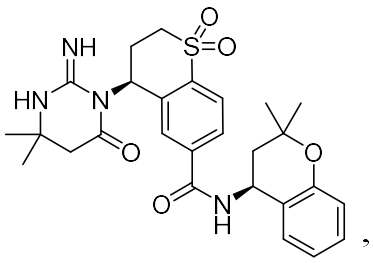


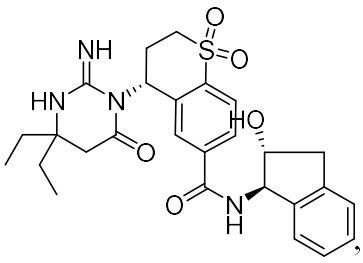


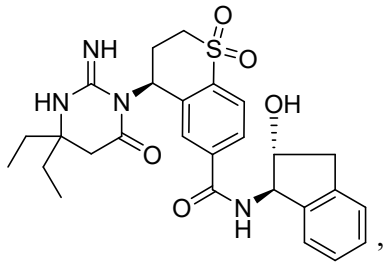


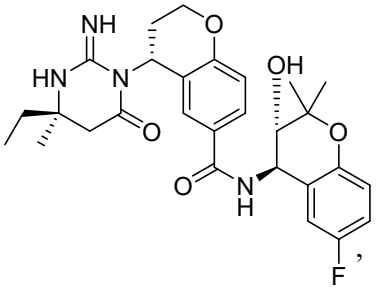


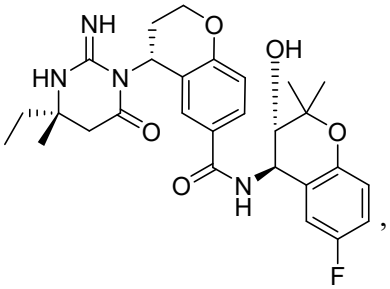


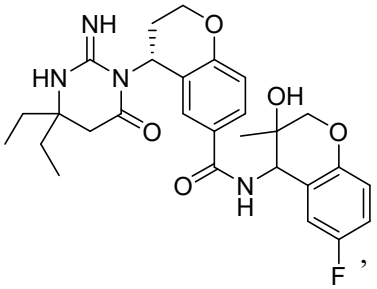


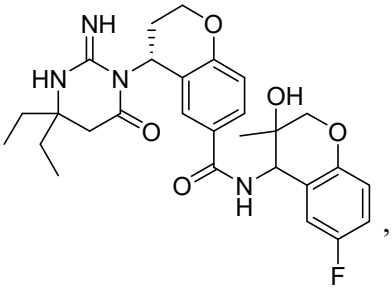


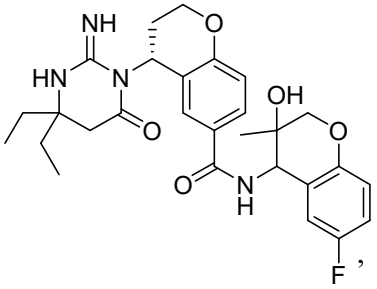


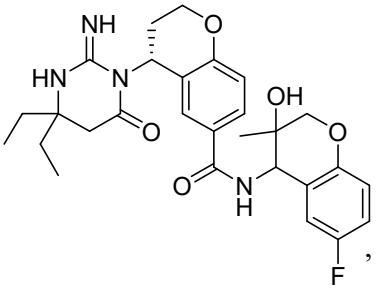


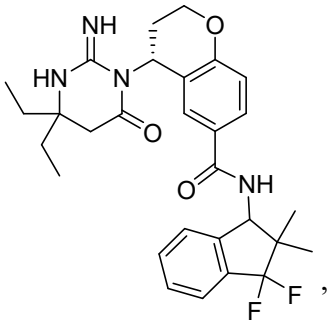


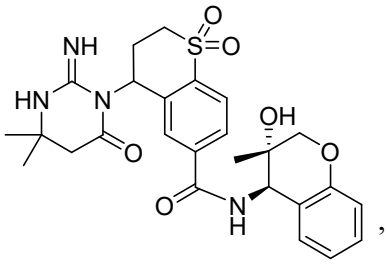


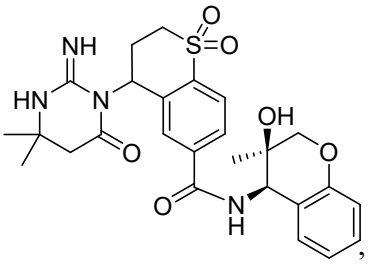


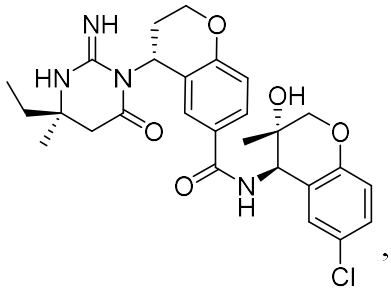


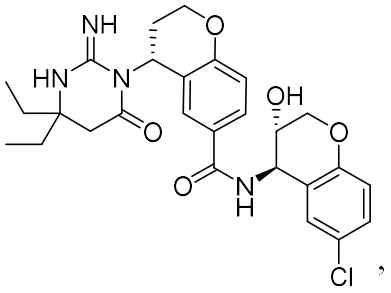


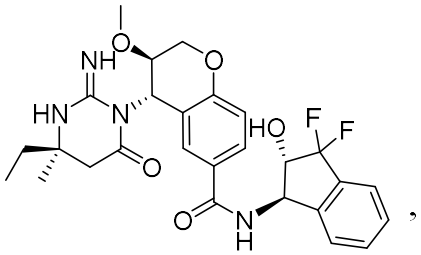


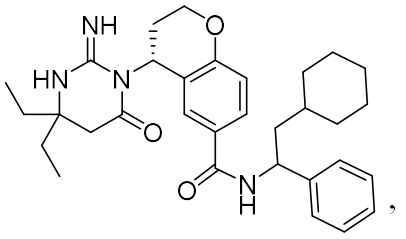


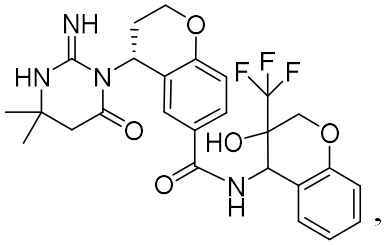


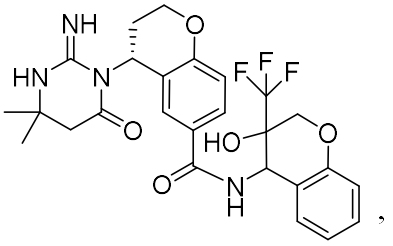


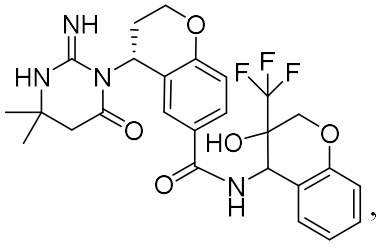


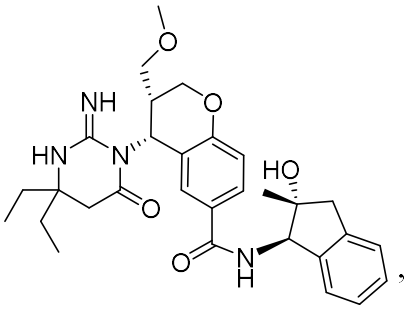


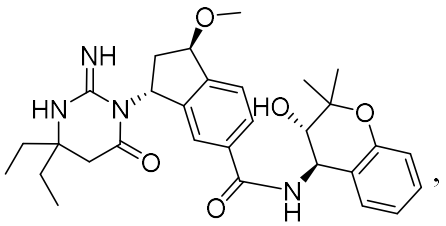


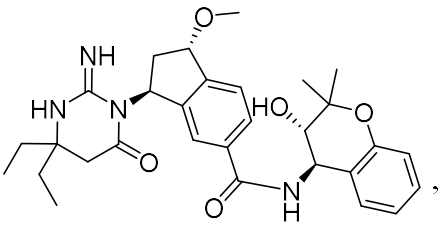


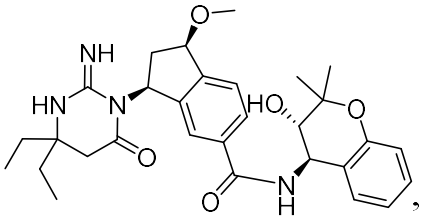


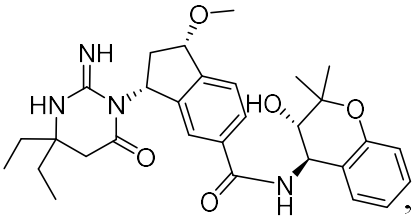


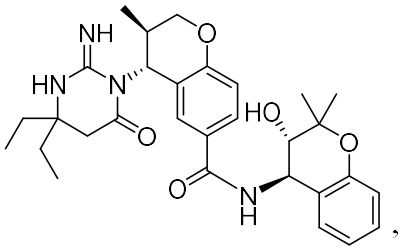


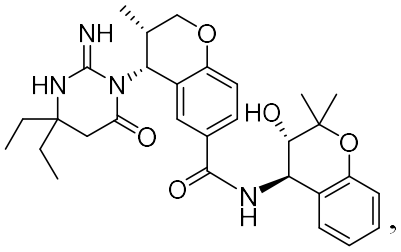


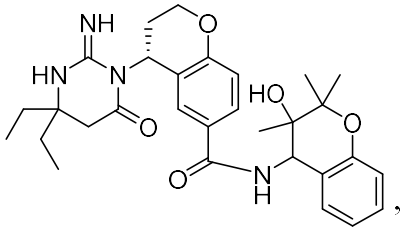


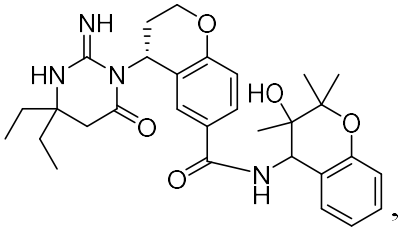


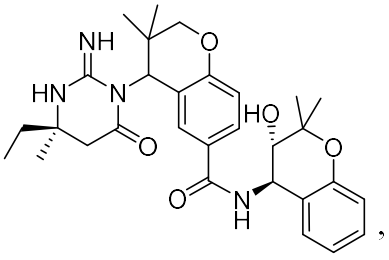


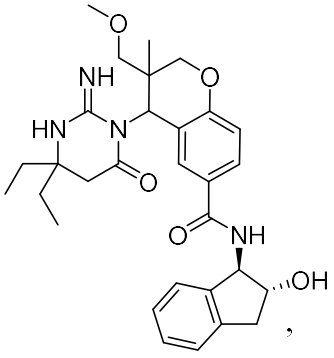


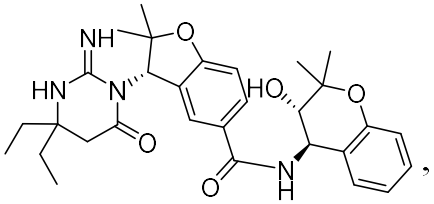


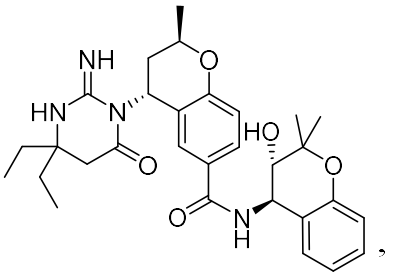


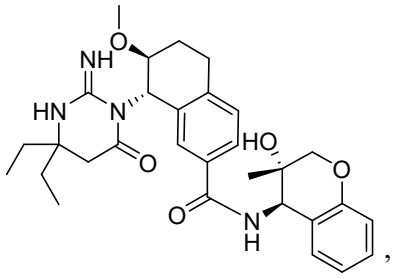


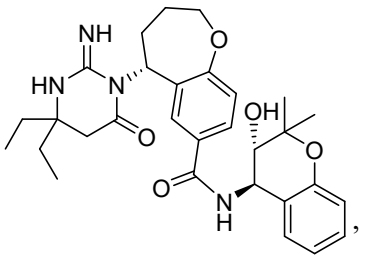


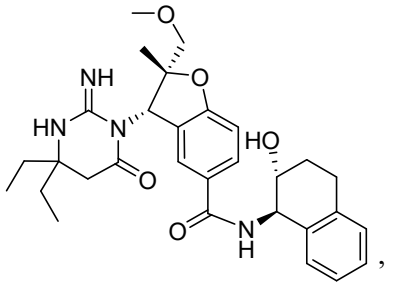


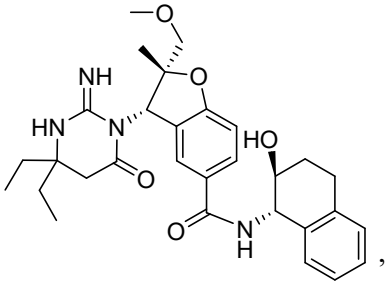


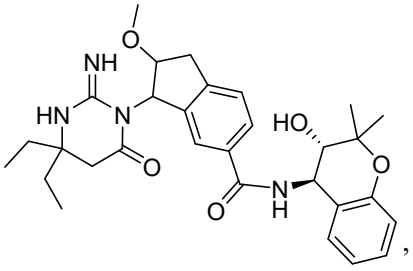


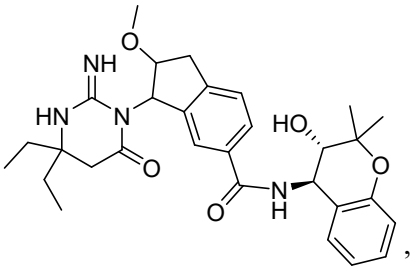


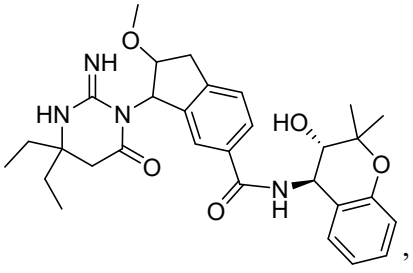


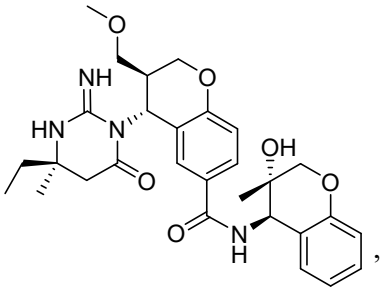


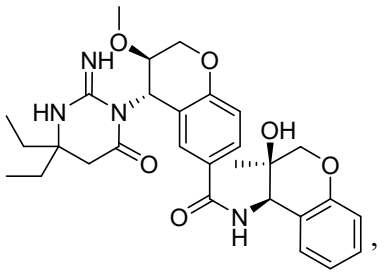


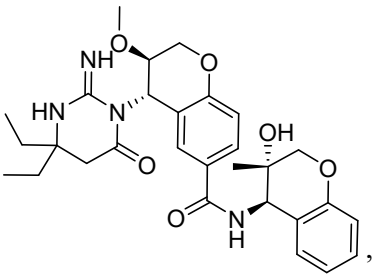




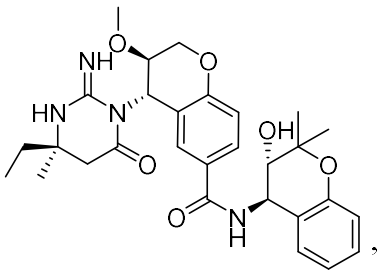


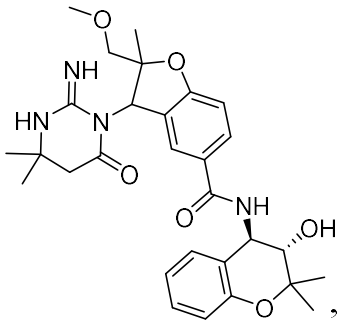


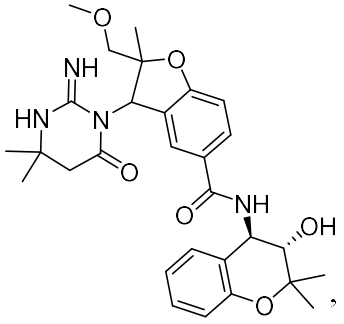


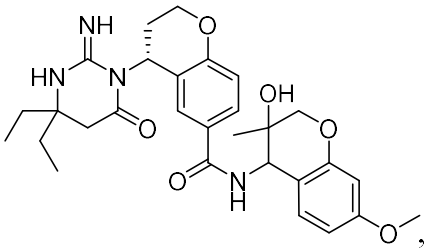


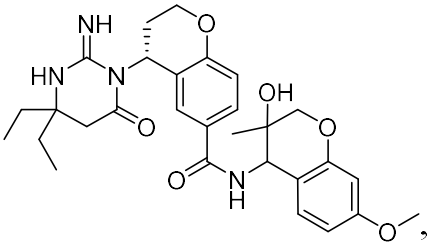
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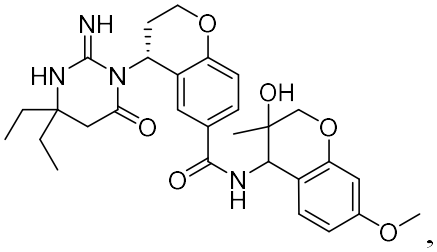


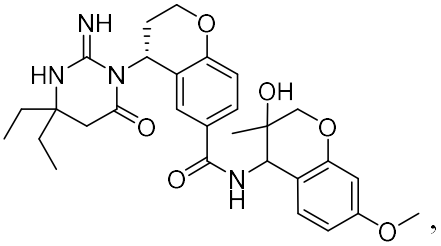


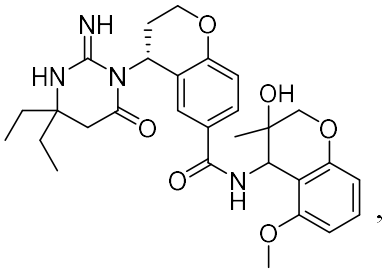


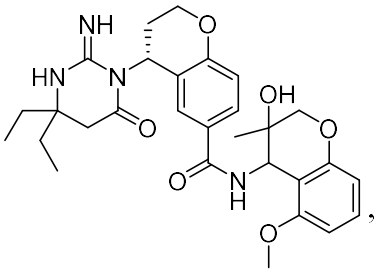


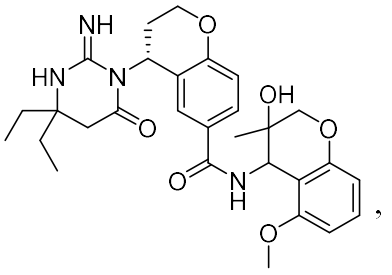


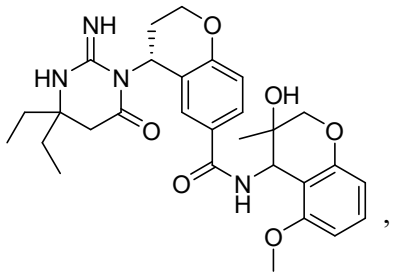


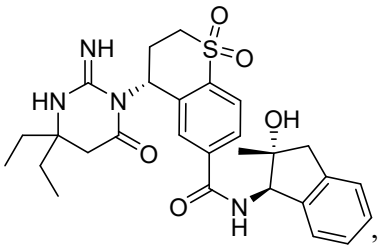


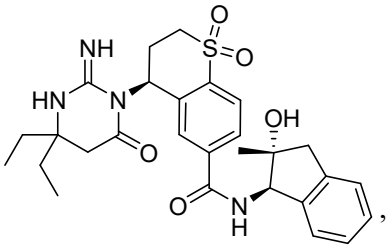


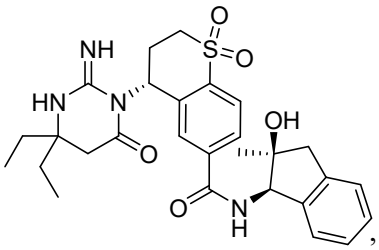


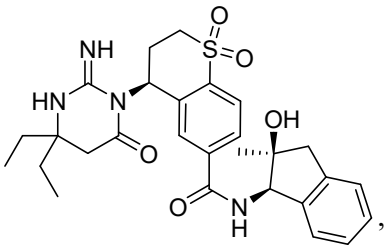


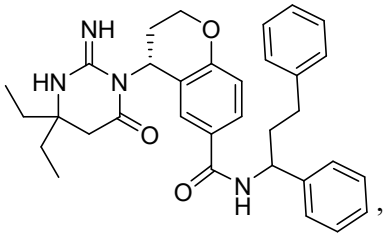


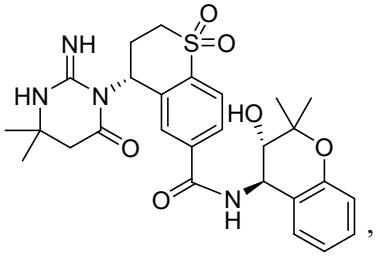


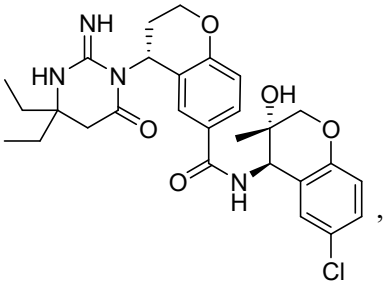


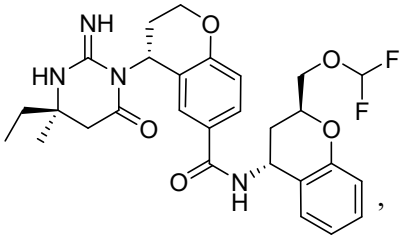


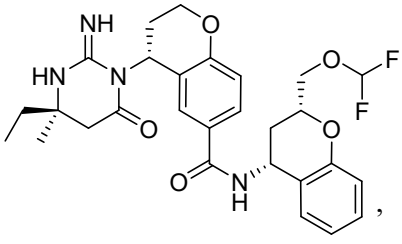


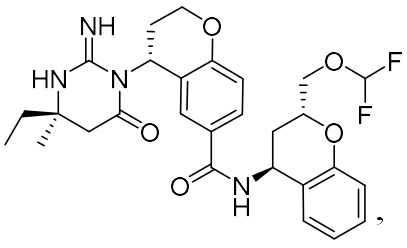


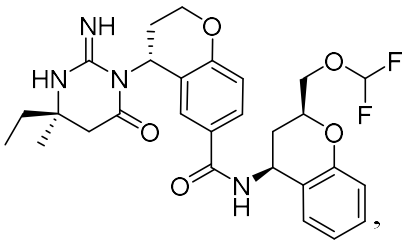


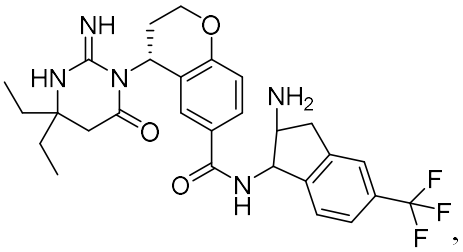


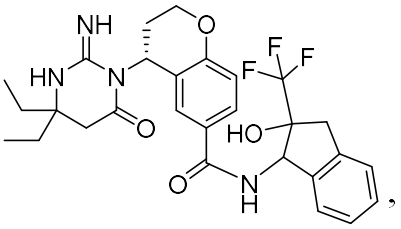


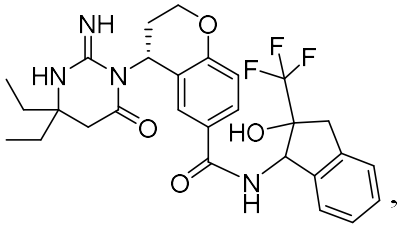


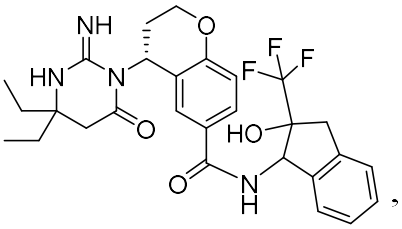


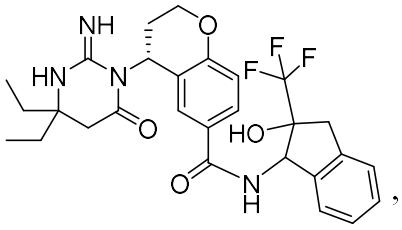


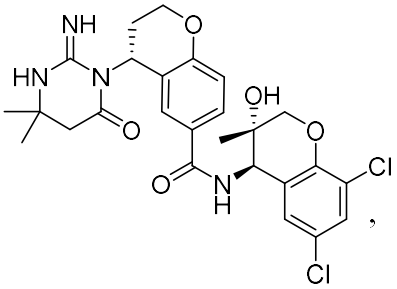


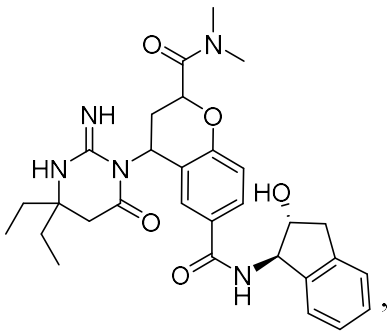


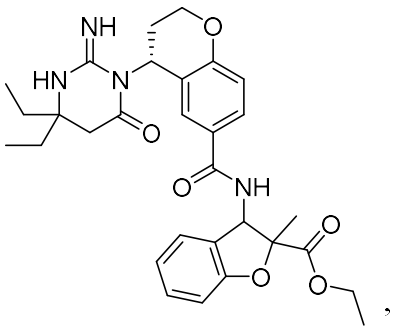


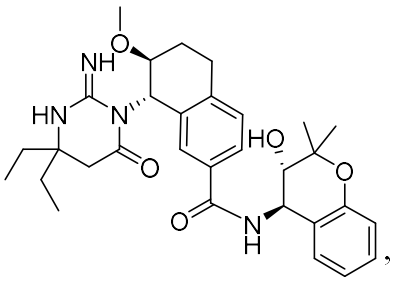


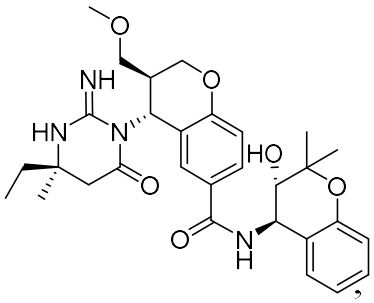


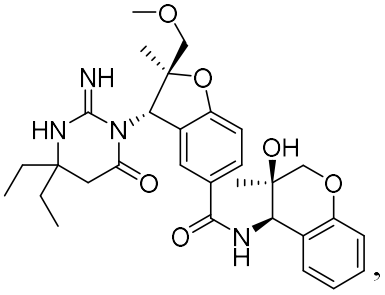


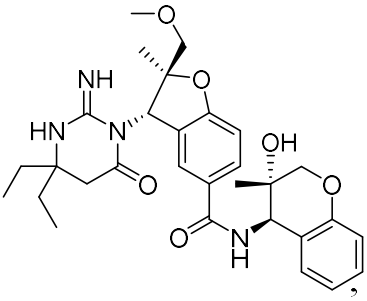


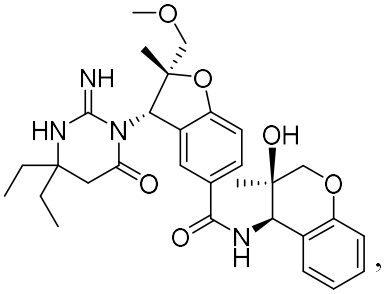


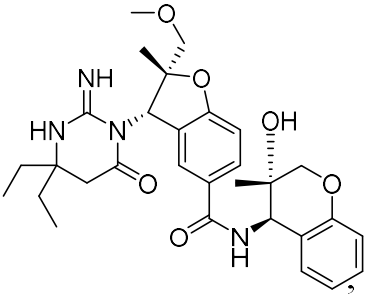


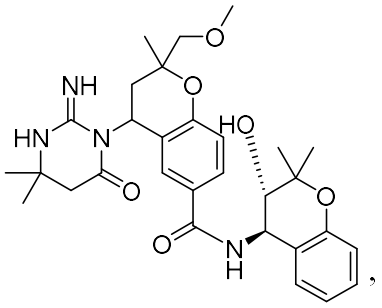


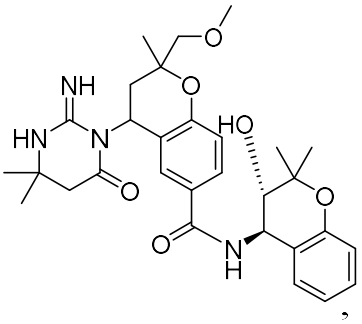


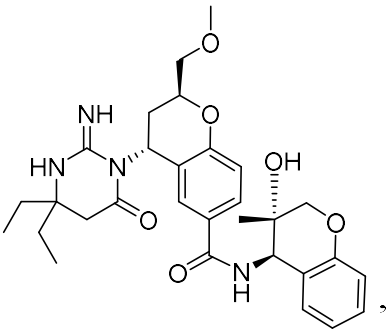


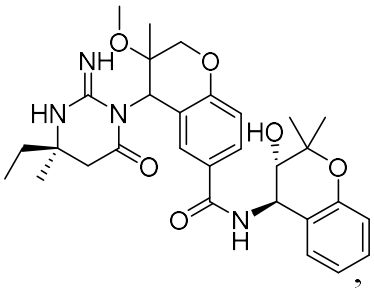


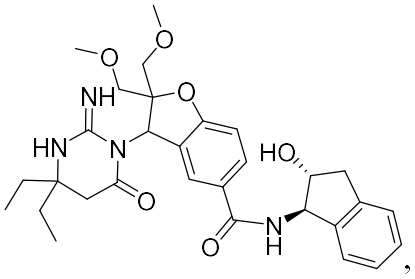


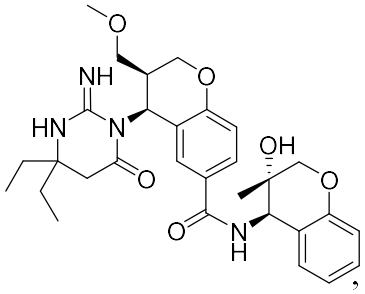


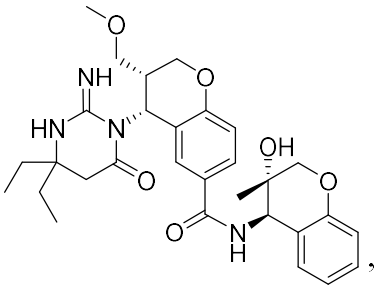


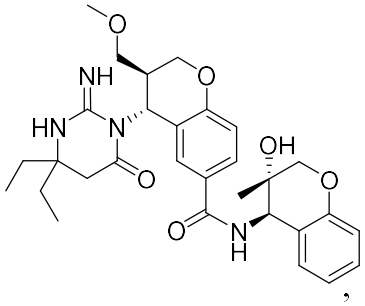


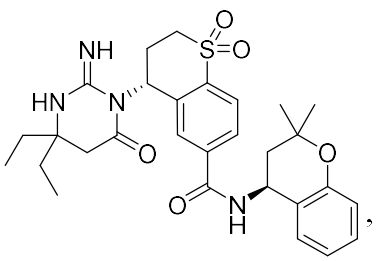


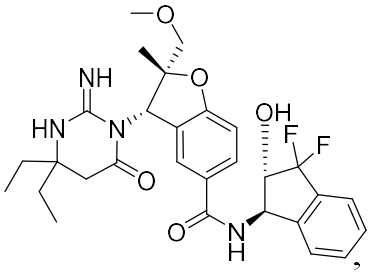


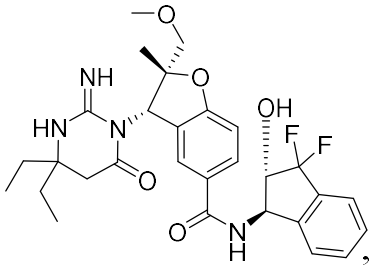


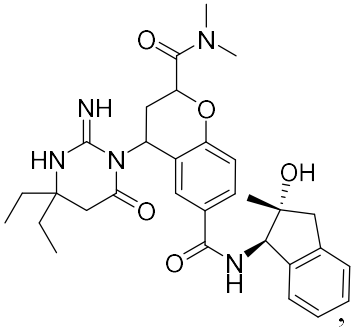


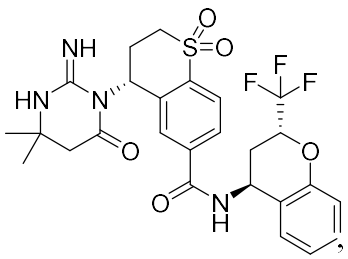


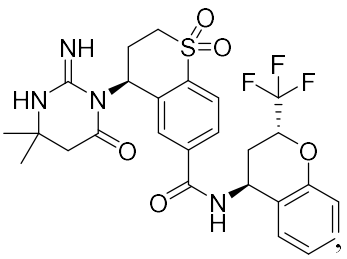


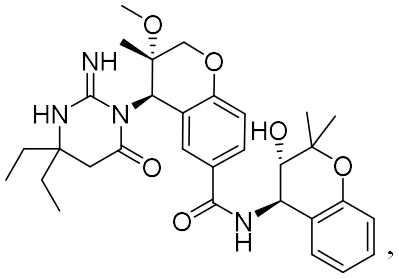


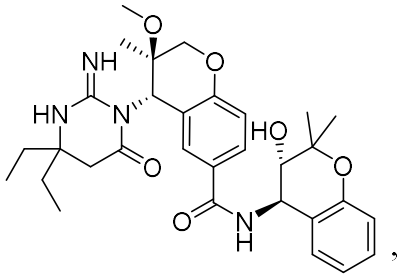


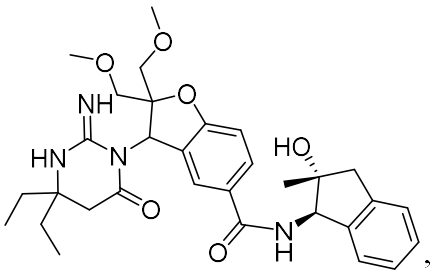


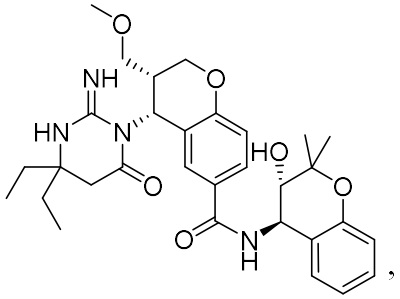


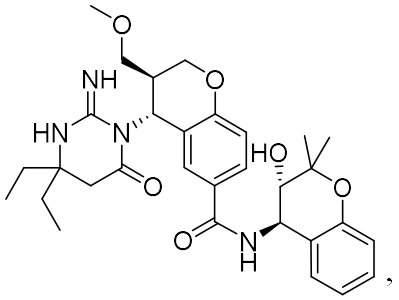


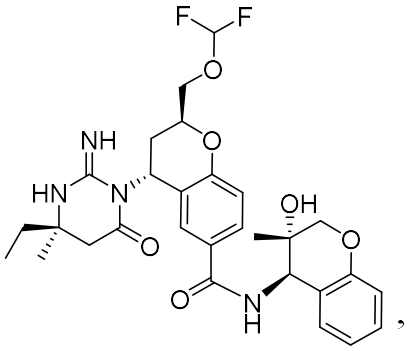


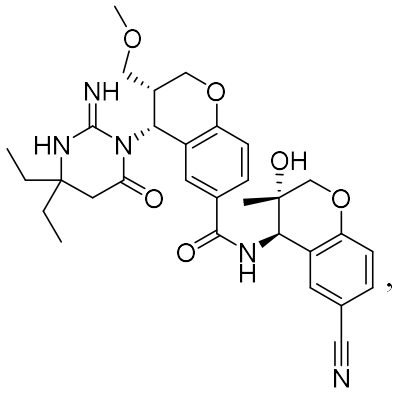


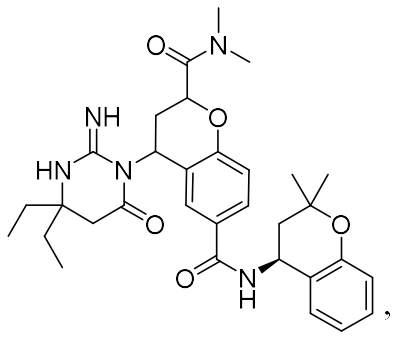


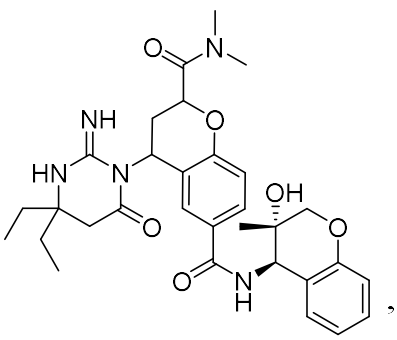


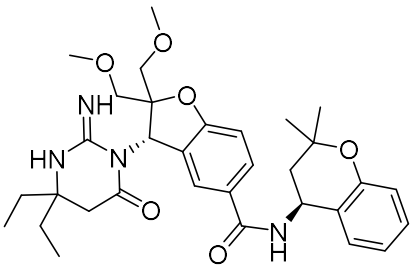


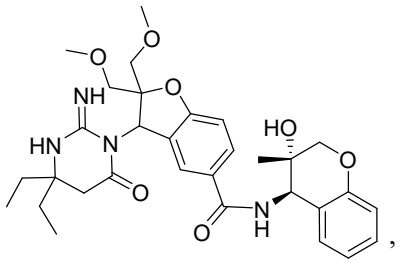


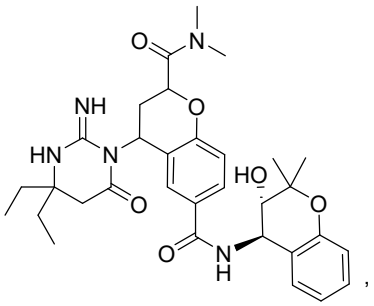


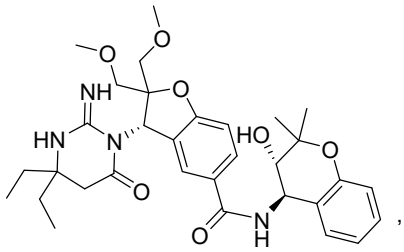


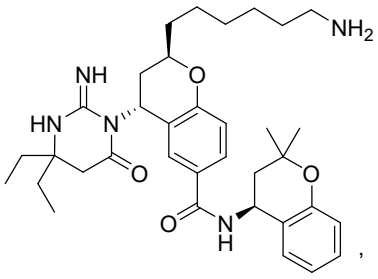


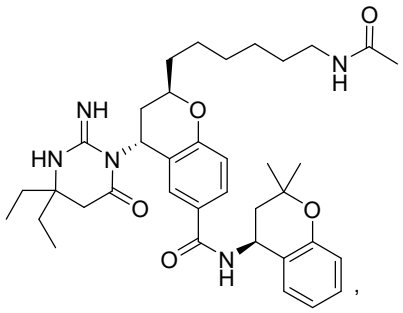


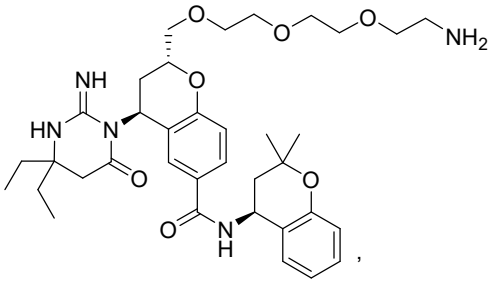

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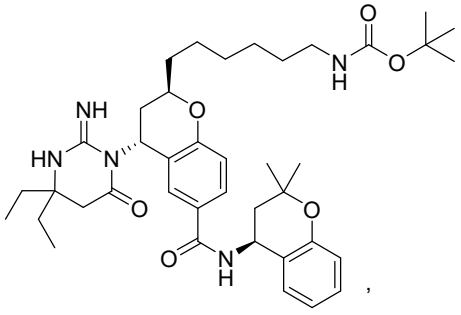

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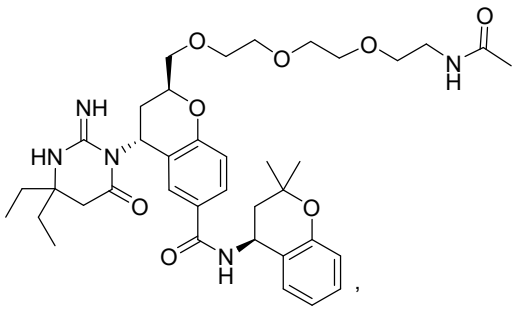

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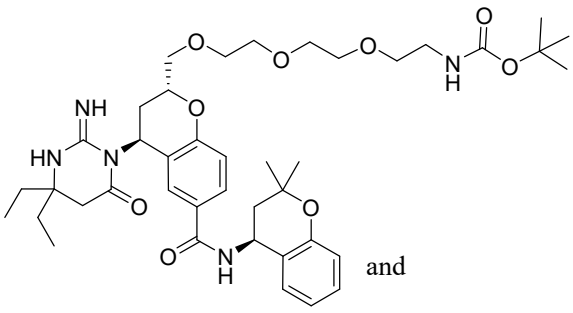

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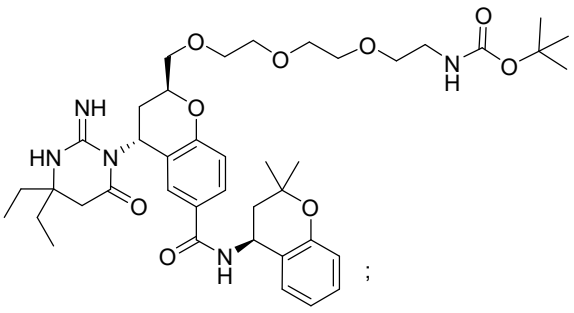

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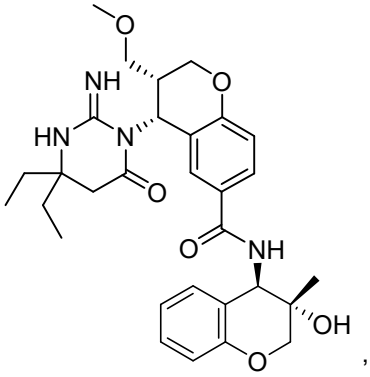

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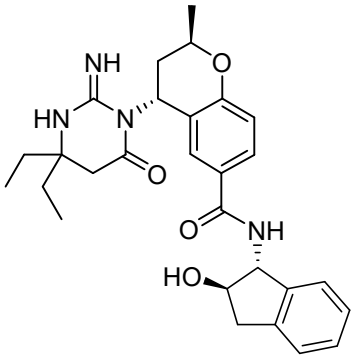

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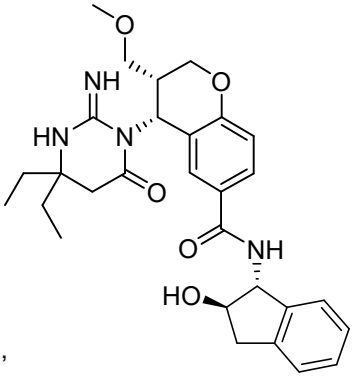

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or a pharmaceutically acceptable salt thereof.

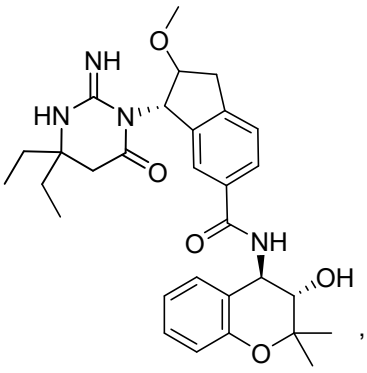
In another aspect, there is provided a compound selected from the group consisting of

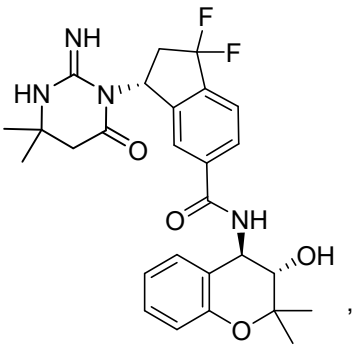


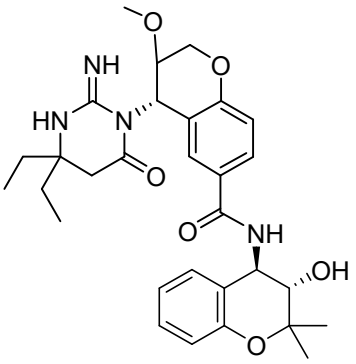
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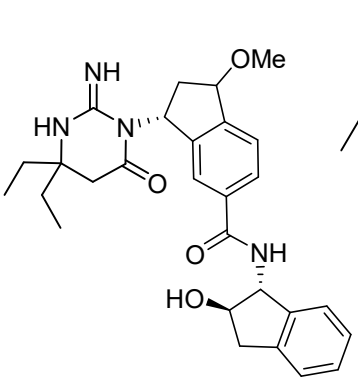
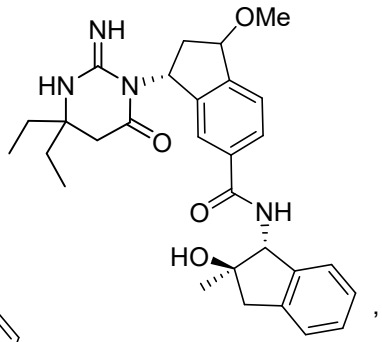
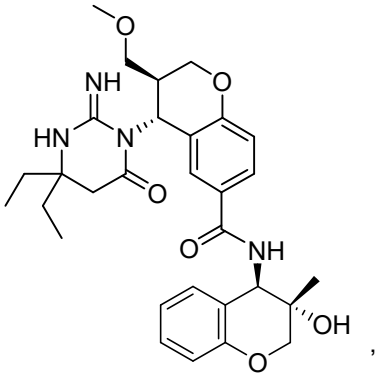
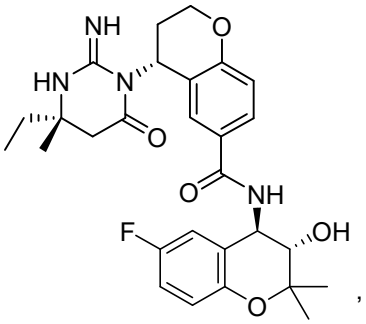
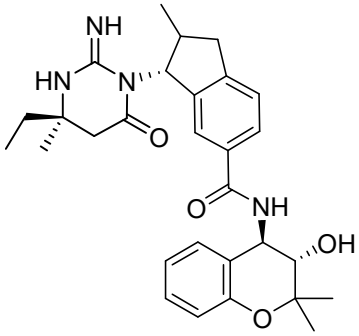
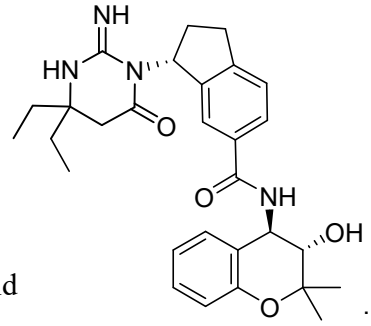
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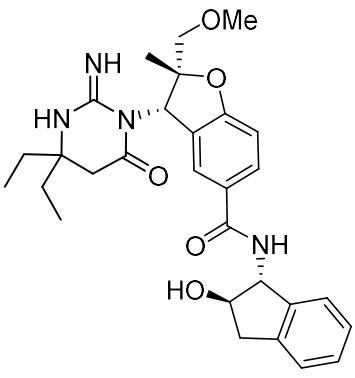
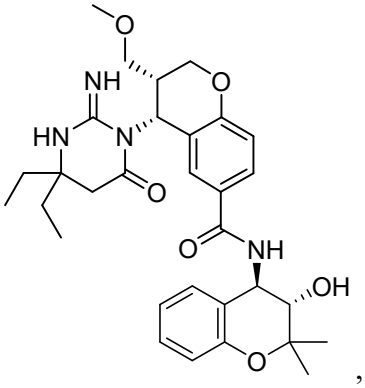
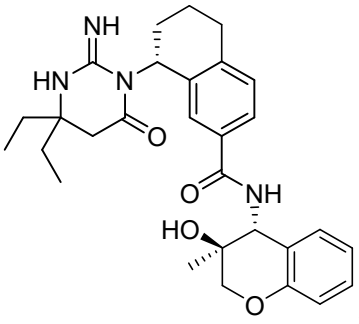


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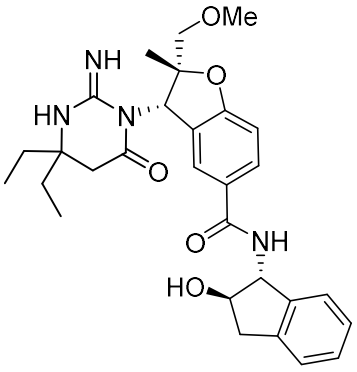





and

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In another aspect, there is provided a compound selected from the group consisting of




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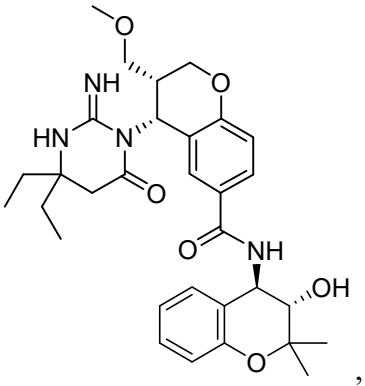
pharmaceutically acceptable salt thereof.

In another aspect, there is provided a compound having the formula



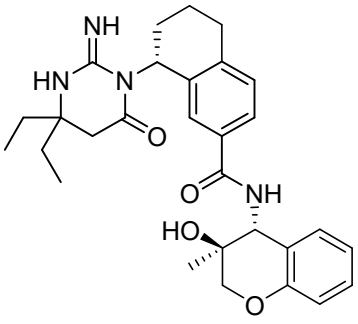
, or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a compound having the formula



, or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided compound having the formula



, 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. 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 disclosure further provides the use of compositions, including pharmaceutical compositions, comprising one or more compounds of the disclosure(e.g., one compound of the disclosure), or a tautomer thereof, or a pharmaceutically acceptable salt or solvate of said compound(s) and/or said tautomer(s), optionally together with one or more additional therapeutic agents, optionally in an acceptable (e.g., pharmaceutically acceptable) carrier or diluent, for the treatment of malaria. In another aspect, there is provided use of a compound, or pharmaceutically acceptable salt thereof, as described herein, in the manufacture of a medicament for the treatment of Plasmodium infection, or malaria.

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

The present disclosure further provides methods for the inhibition of plasmepsin X, or the dual inhibition of plasmepsin X and plasmepsin IX activity and of treatment, prevention,

amelioration and/or delaying onset of diseases or disorders in which the inhibition of plasmepsin X and/or plasmepsin IX has or may have a therapeutic effect, e.g. malaria.

In another aspect, there is provided use of a compound, or pharmaceutically acceptable salt thereof, as defined herein, in the manufacture of a medicament for inhibiting plasmepsin X. In another aspect, there is provided use of a compound, or pharmaceutically acceptable salt thereof, as defined herein, in the manufacture of a medicament for inhibiting plasmepsin IX. In another aspect, there is provided use of a compound, or pharmaceutically acceptable salt thereof, as defined herein, in the manufacture of a medicament for dual inhibition of plasmepsin IX and plasmepsin X.

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

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

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein, and a pharmaceutically acceptable carrier.

In another aspect, there is provided use of a compound as defined herein, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a *Plasmodium* infection, or for treating malaria, wherein the compound as defined herein, or a pharmaceutically acceptable salt thereof, is to be administered together with an effective amount of one or more additional anti-malarial agents. In another aspect, there is provided use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of malaria by inhibition of plasmepsin X, IX and at least one other mechanism, wherein the compound as defined herein, or pharmaceutically

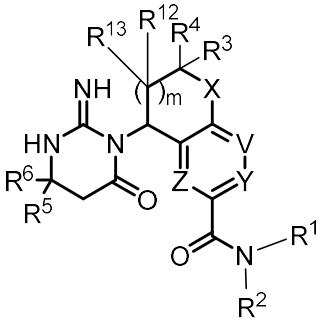
acceptable salt thereof, is to be administered together with an effective amount of one additional anti-malarial agent, wherein the additional anti-malarial agent acts through a different mechanism than inhibiting plasmepsin IX or plasmepsin X.

In another aspect, there is provided the compound as defined herein, or pharmaceutically acceptable salt thereof, for use as a medicament.

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

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, $C(R^{14})_2$, O, S, SO, SO_2 or NH;

Y is CR^9 or N, wherein when Y is N, Z is CR^{11} and V is CR^{10};

V is CR^{10} or N, wherein when V is N, Z is CR^{11} and Y is CR^9;

Z is CR^{11} or N, wherein when Z is N, V is CR^{10} and Y is CR^9;

R^1 is a heterocycloalkyl, C_3-C_{12}cycloalkyl, aryl, C_1-C_6alkylaryl 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_6alkylaryl 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_6alkoxy,