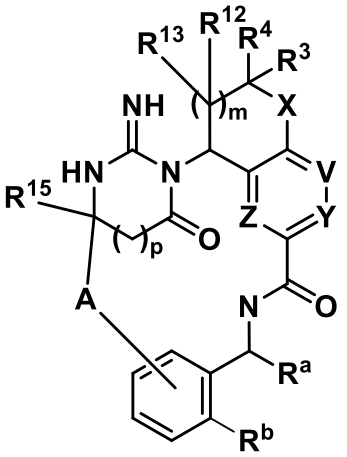
targets that inhibit multiple steps in the parasite life cycle is an urgent priority for the malaria control field. Such novel antimalarials, as monotherapies or ACT partner drugs, could make strides towards malaria elimination as there is a reduced likelihood of parasites with preexisting resistance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

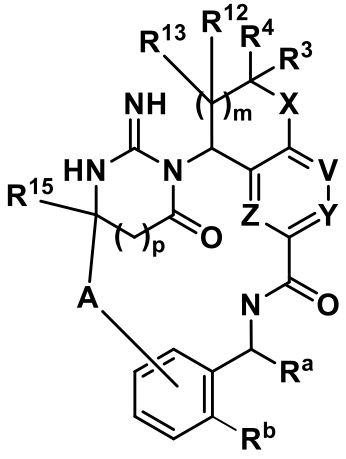
The present disclosure is directed to compounds of Formula (I):



(I)

wherein A, X, V, Y, Z, R^a, R^b, R^3, R^4, R^{12}, R^{13}, R^{15}, m and p are described below.

In one aspect, the present disclosure is directed to a compound having the structural Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

A is a straight or branched, saturated or unsaturated (C_3-C_{10})alkylene, phenyl(C_3-C_{10})alkylene or cycloalkyl(C_3-C_{10})alkylene comprising at least one $–CH_2$- group, wherein one or more additional $–CH_2$- groups in A are optionally and independently replaced with a moiety selected from the group consisting of O, S, NR, CONR, NRCO, SO_2, and SO_2NR and wherein one or more of the hydrogens along A can be replaced with a group independently selected from hydroxyl, halogen and C_{1-3} haloalkyl;

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 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^a is hydrogen, 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_6alkylCOOC_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, 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) or C_1-C_6alkylN(R^7)(R^8) or when taken with R^b forms a C_3-C_6cycloalkyl or heterocycloalkyl, wherein the C_3-C_6cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or two substituents 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_6alkylCOOC_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, 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_6alkylN(R^7)(R^8);

R^b is hydrogen, 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, C_1-C_6alkyl, -C_1-C_6alkylOhaloC_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkylOH, $CON(R^7)(R^8)$, $N(R^7)(R^8)$ or C_1-C_6alkyl$N(R^7)(R^8)$ or when taken with R^a forms a C_3-C_6cycloalkyl or heterocycloalkyl, wherein the C_3-C_6cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or three substituents 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, 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^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_6alkyl$N(R^7)(R^8)$, C_1-C_6alkyl$(OCH_2CH_2)_nN(R^7)(R^8)$ 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_6alkyl$N(R^7)(R^8)$, C_1-C_6alkyl$(OCH_2CH_2)_nN(R^7)(R^8)$ 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^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_6alkyl$N(R^7)(R^8)$;

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_6alkyl$N(R^7)(R^8)$;

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_6alkyl$N(R^7)(R^8)$;

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_6alkyl$N(R^7)(R^8)$;

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_6alkyl$N(R^7)(R^8)$;

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_6alkyl$N(R^7)(R^8)$;

R^{15} 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_6alkyl$N(R^7)(R^8)$;

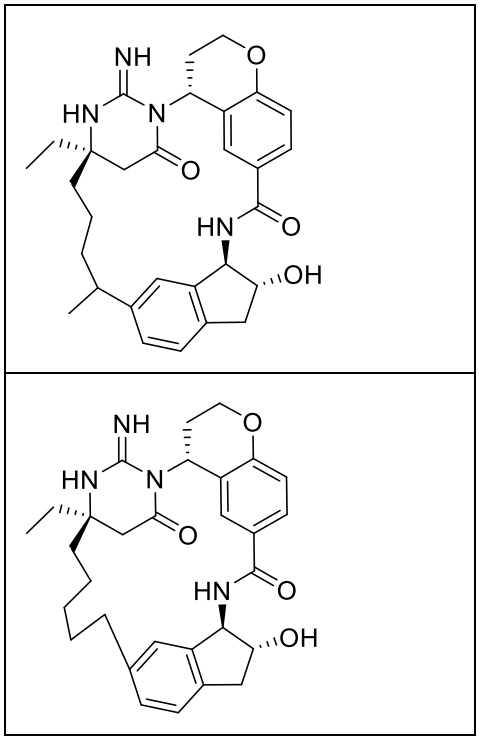
each occurrence of R^{16} is independently selected from the group consisting of hydrogen, halogen, CN, OH, C_1-C_6alkoxy, C_1-C_6alkylOC_1-C_6alkyl, C_1-C_6alkylCOOH, COOH, C_3-C_6cycloalkyl, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkylOH, $CON(R^7)(R^8)$, $N(R^7)(R^8)$ and C_1-C_6alkyl$N(R^7)(R^8)$;

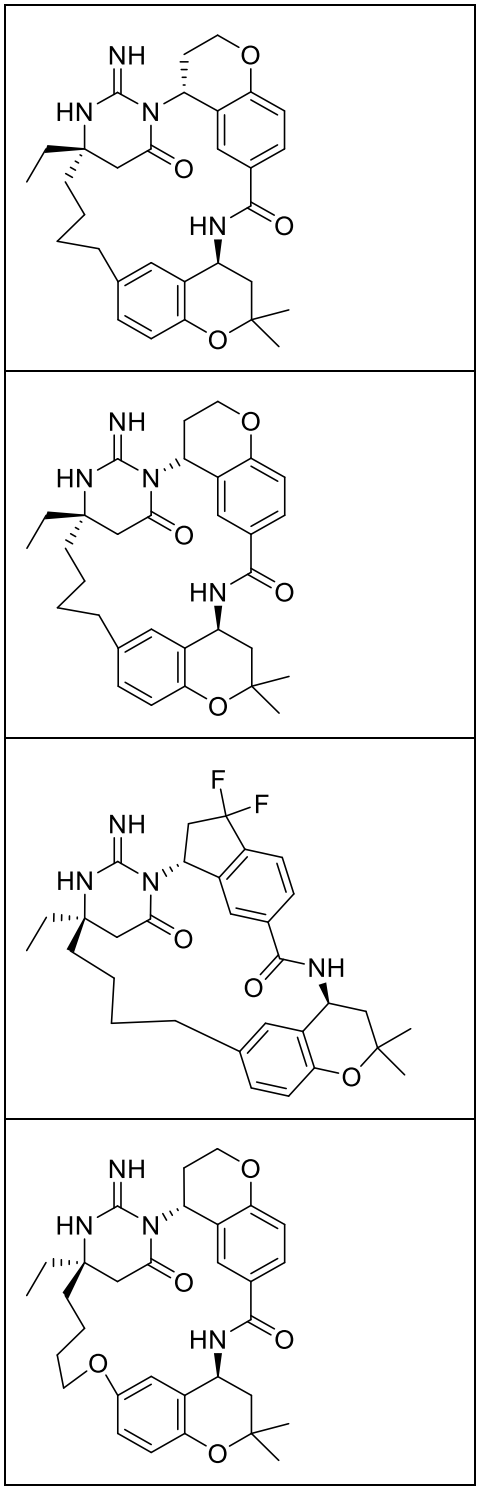
m is 0 or 1;

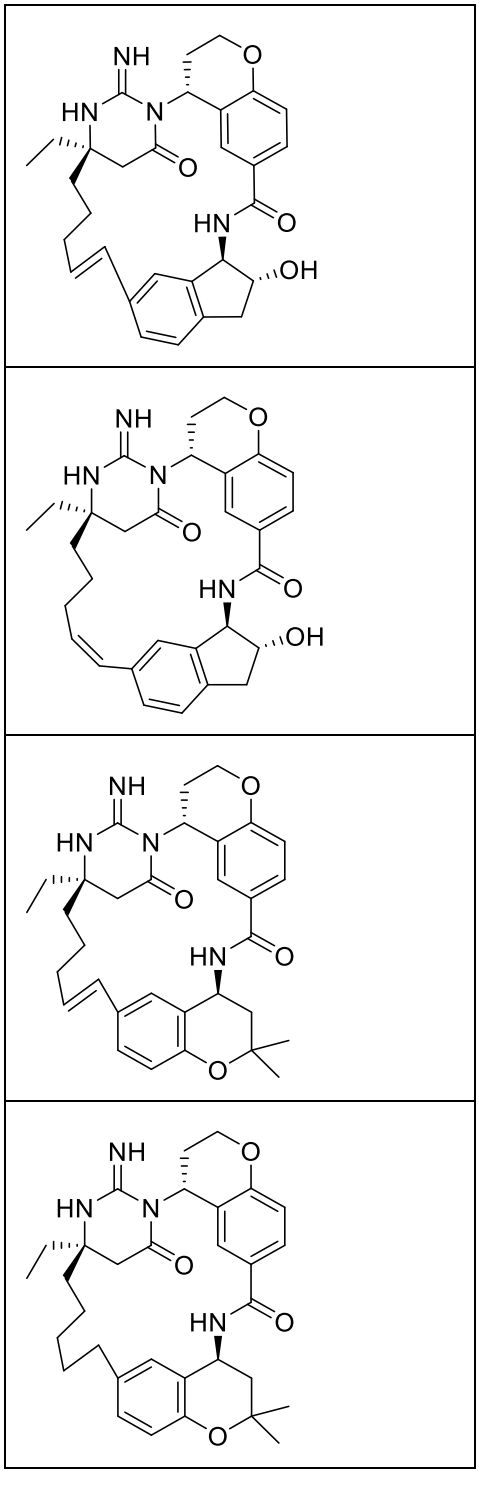
n is 1, 2, 3 or 4; and

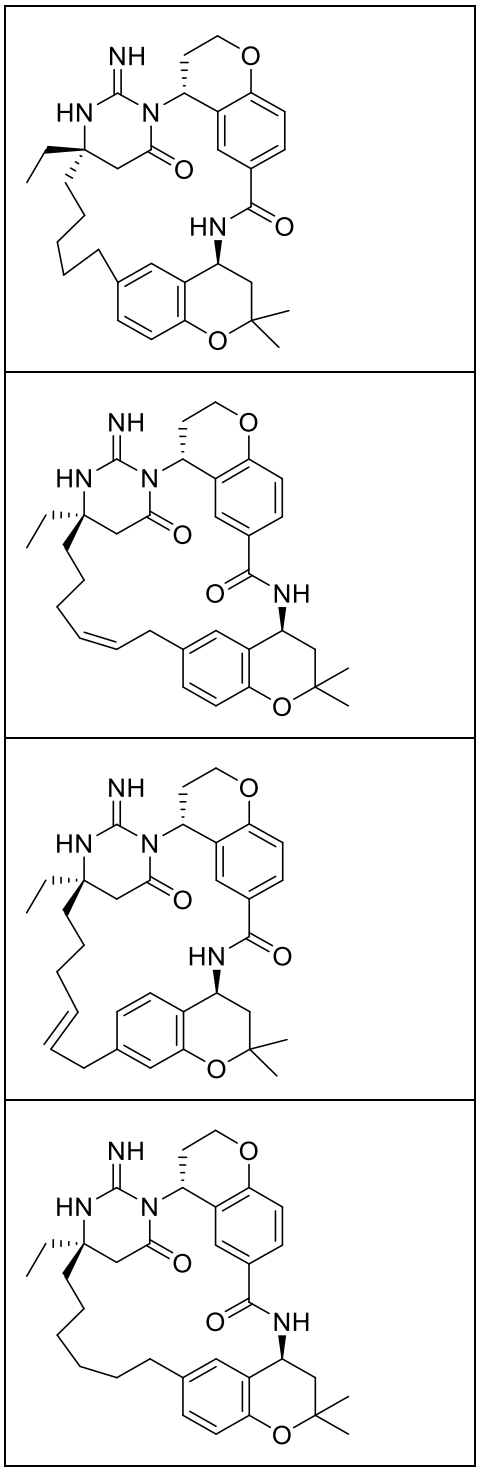
p is 0 or 1.

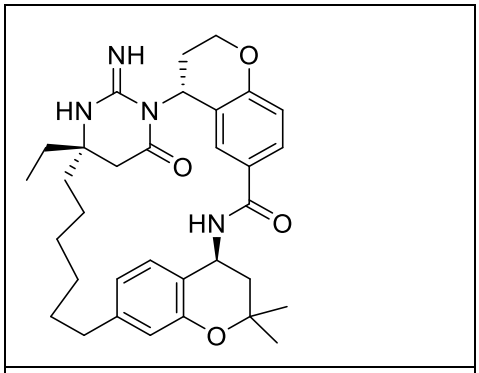
In another aspect, the present disclosure is directed to a compound selected from the group consisting of

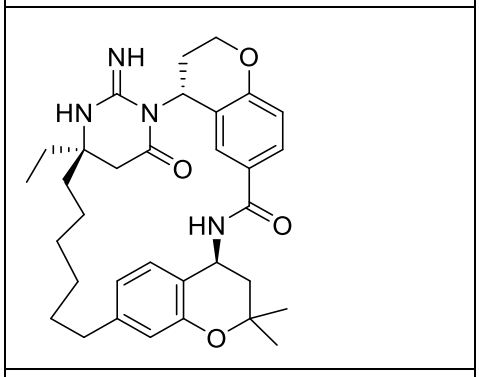


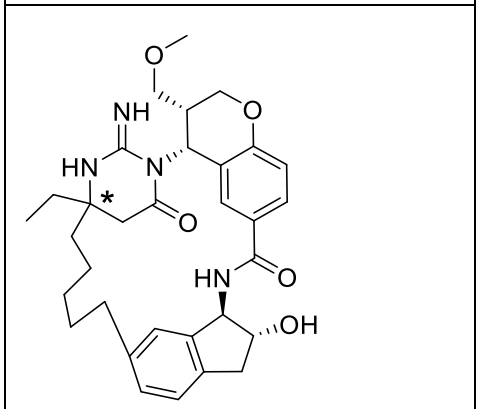


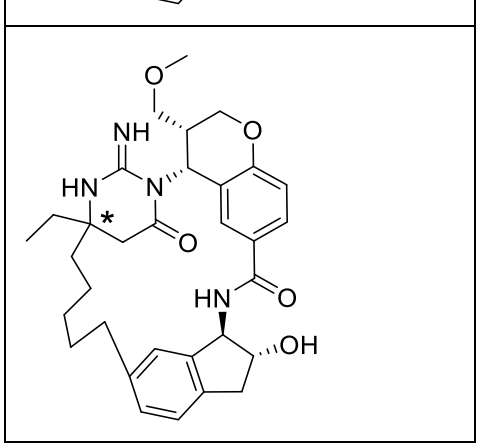


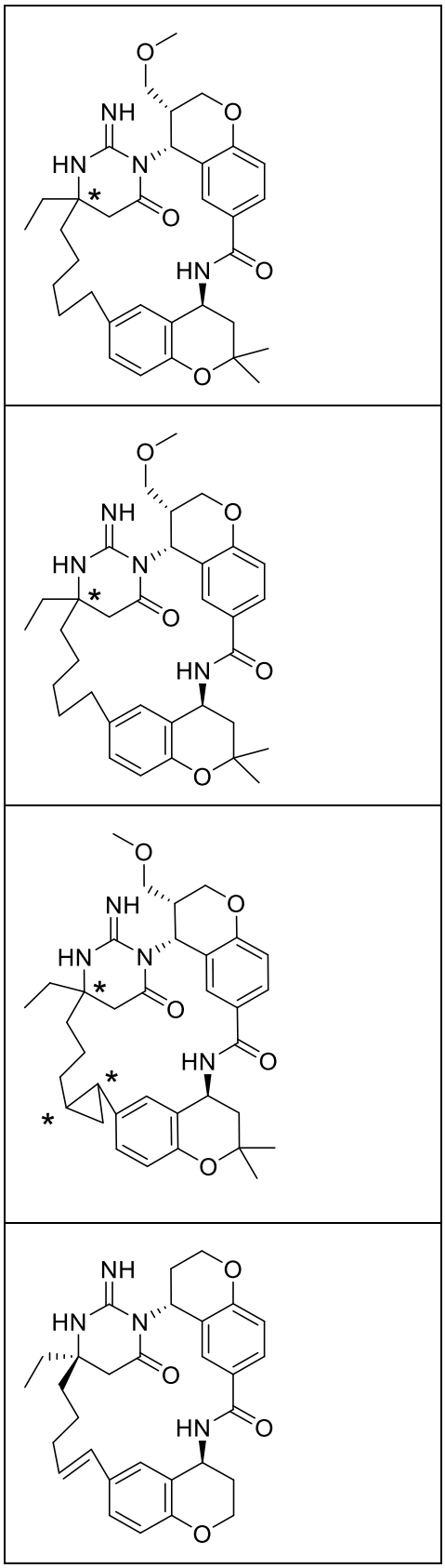


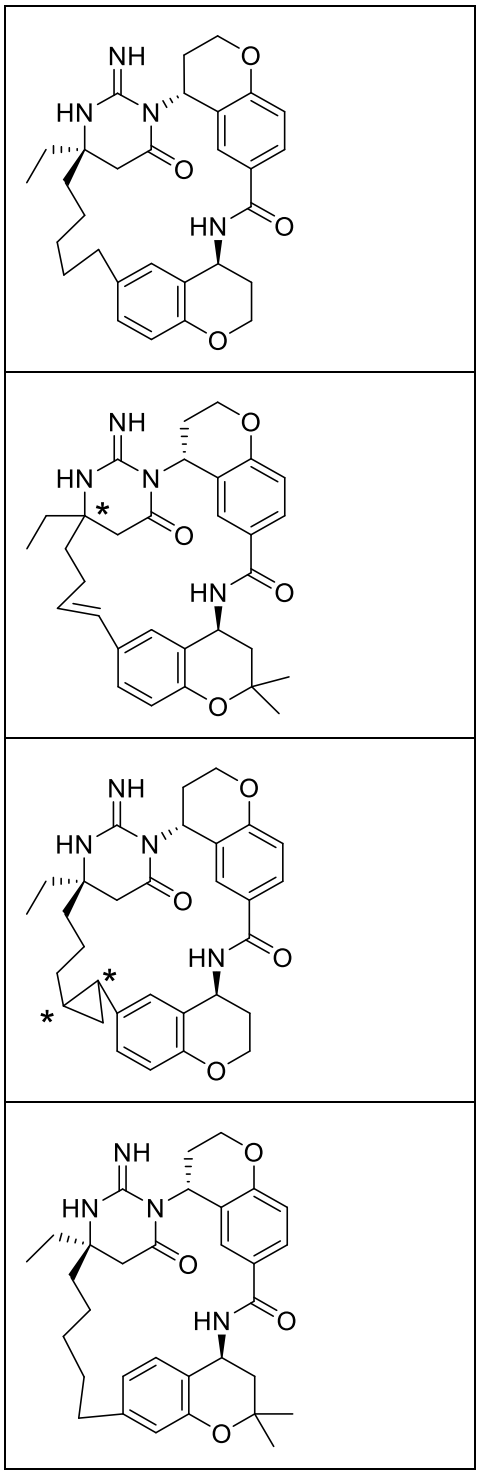

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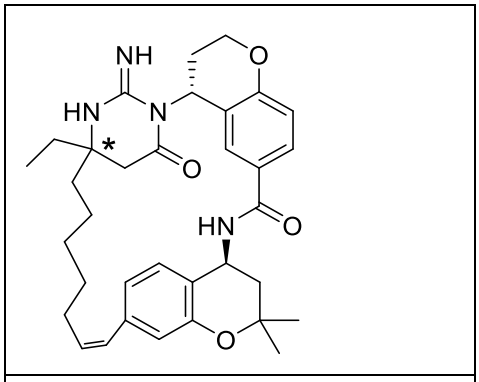

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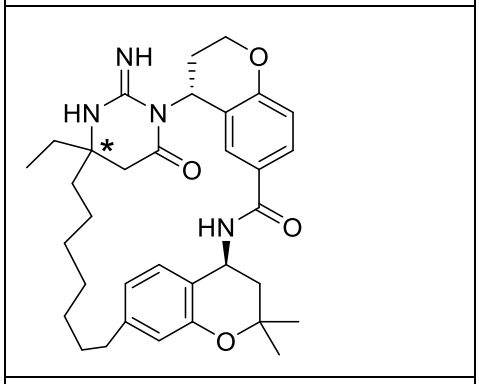

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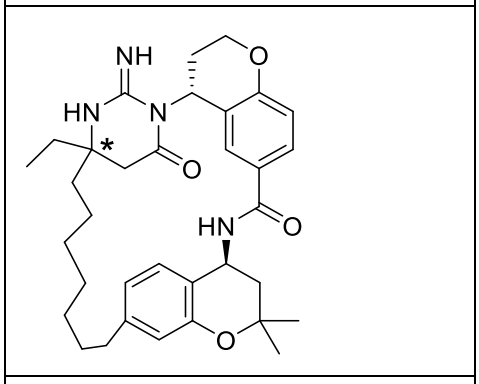

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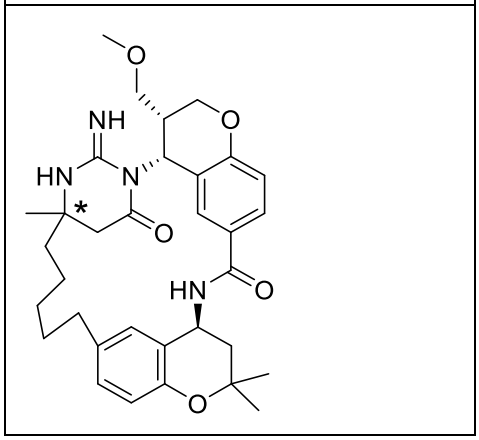


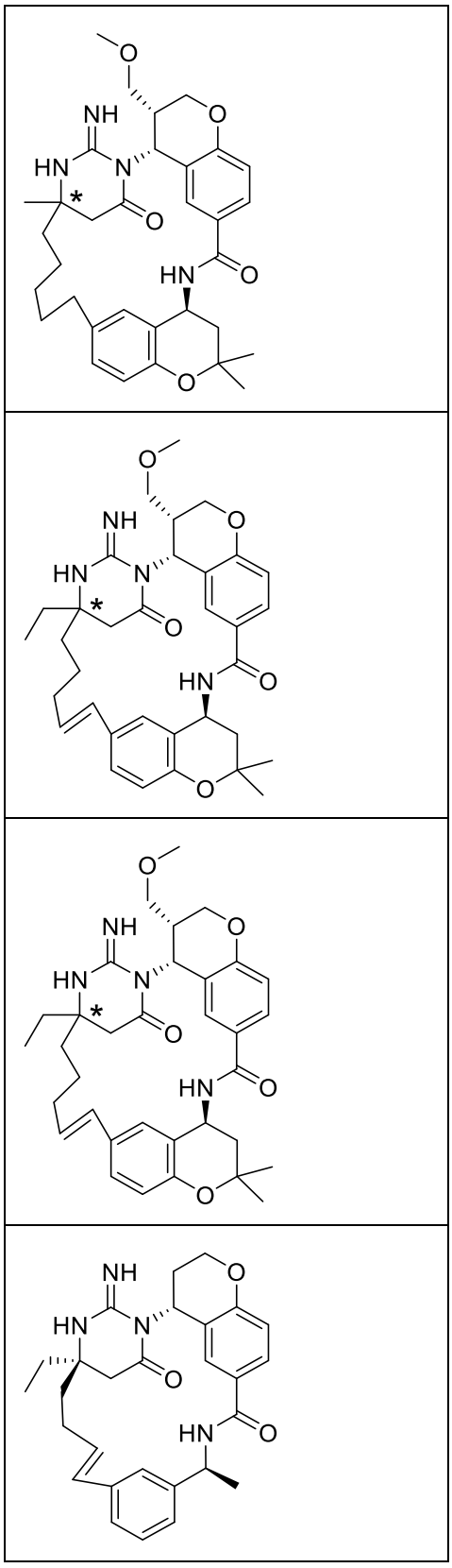


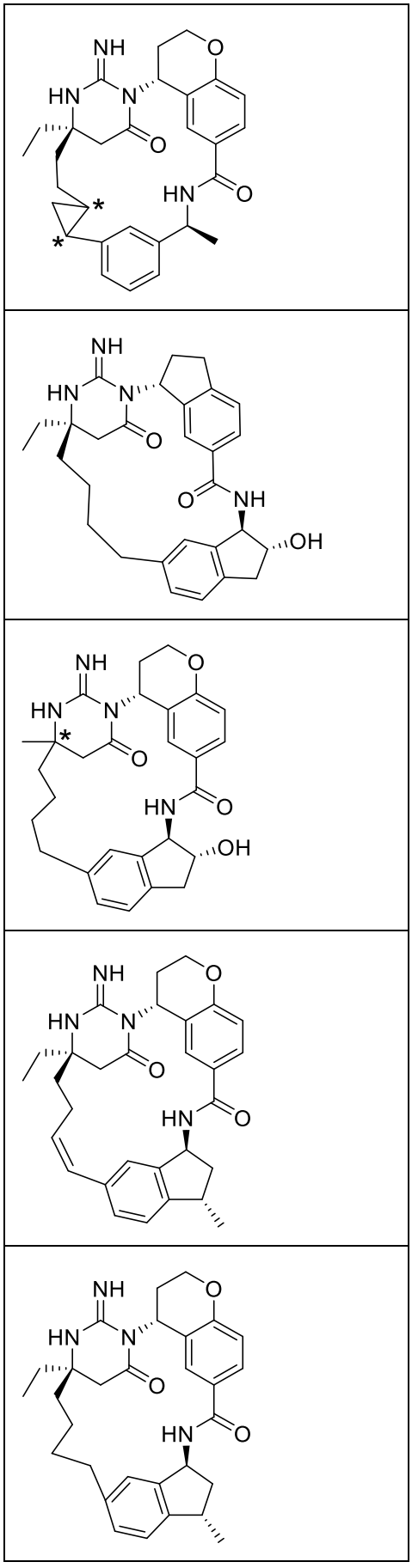

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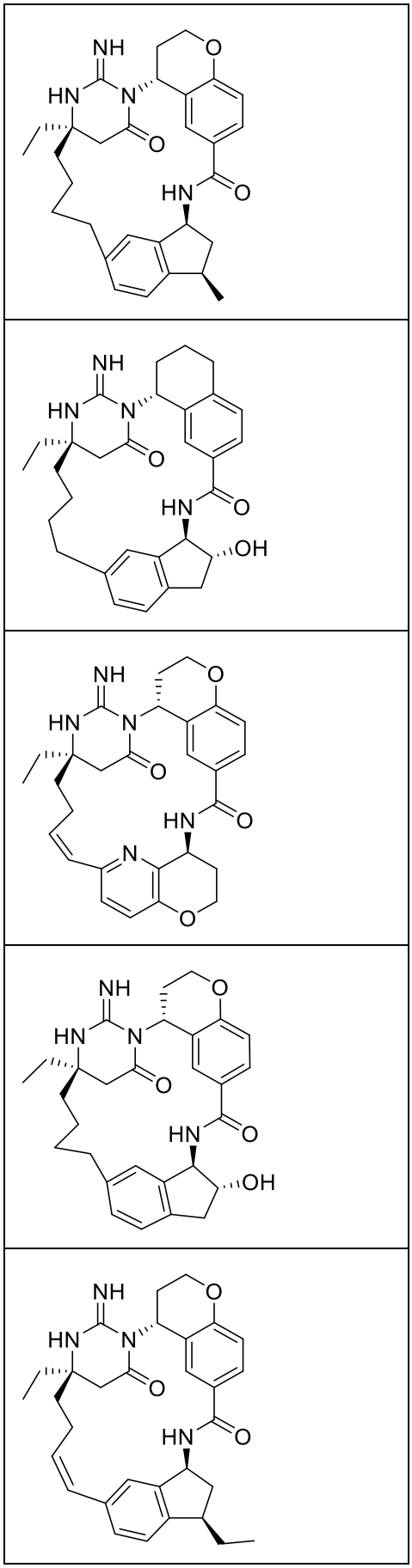

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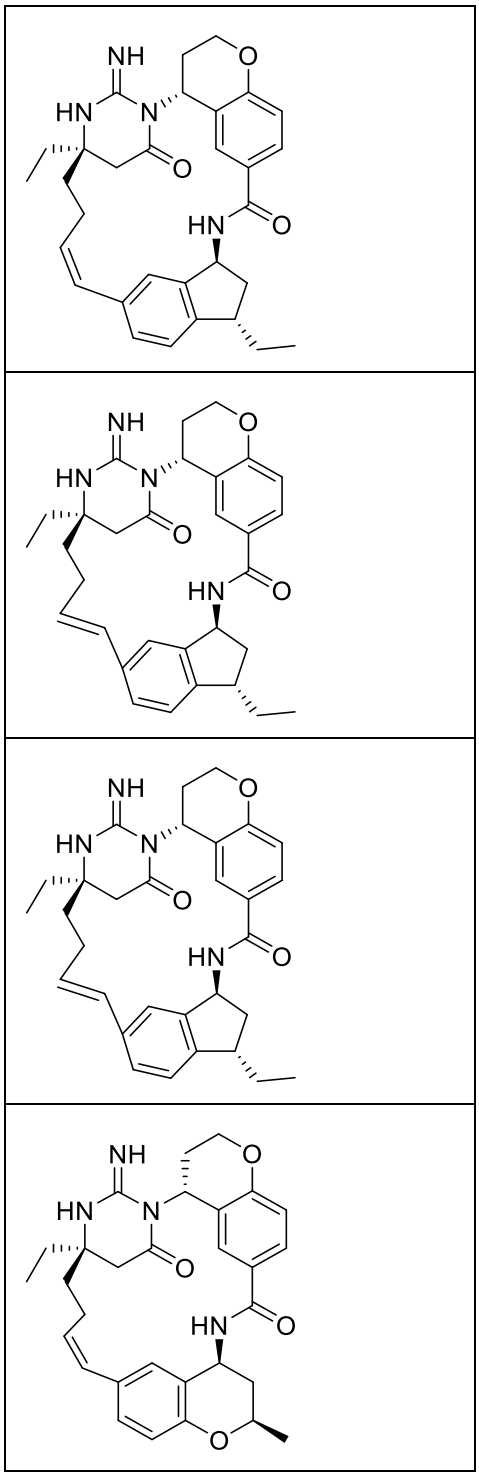

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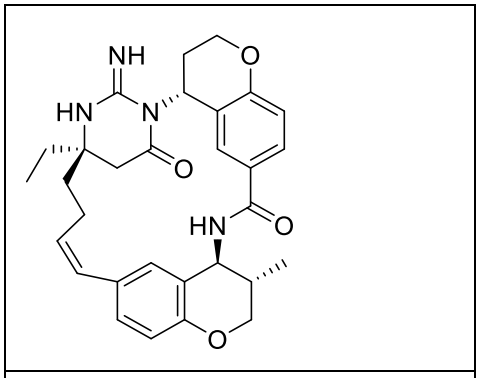

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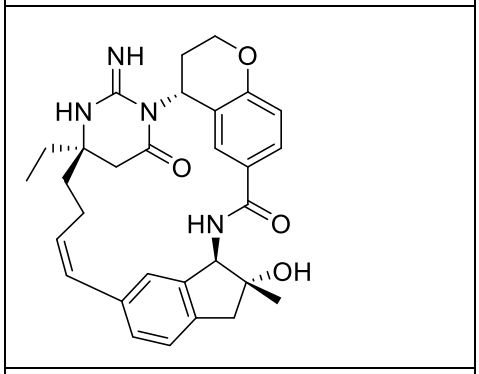


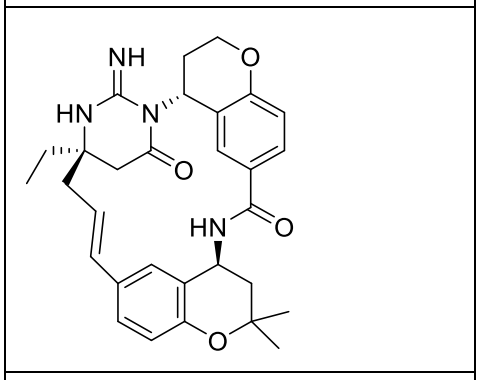


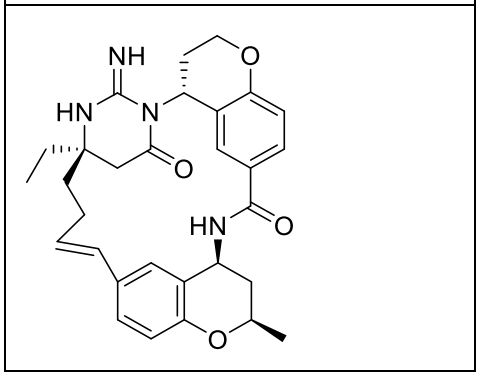


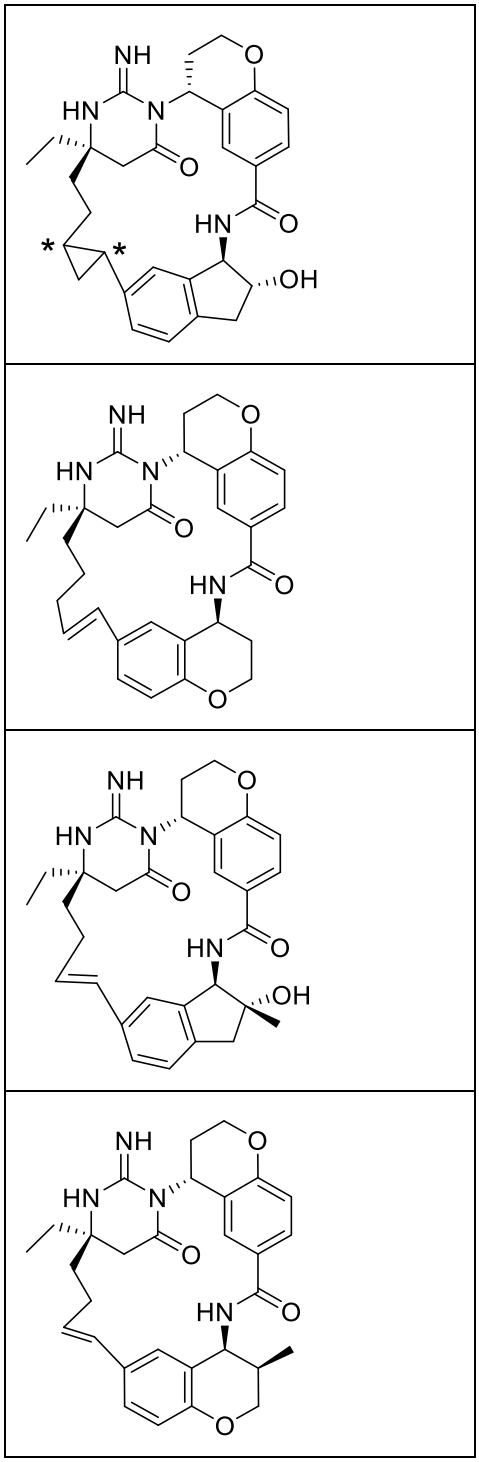


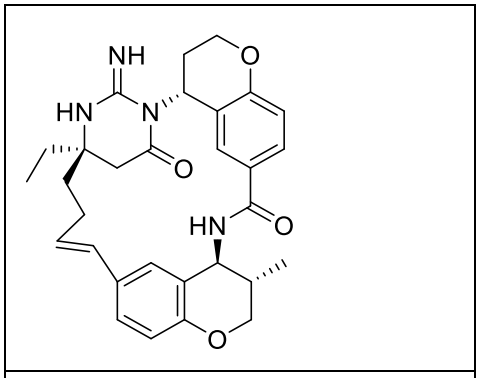
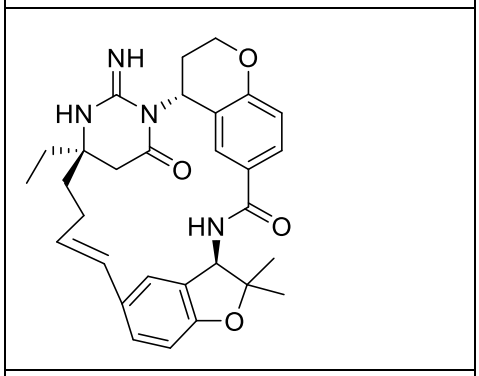
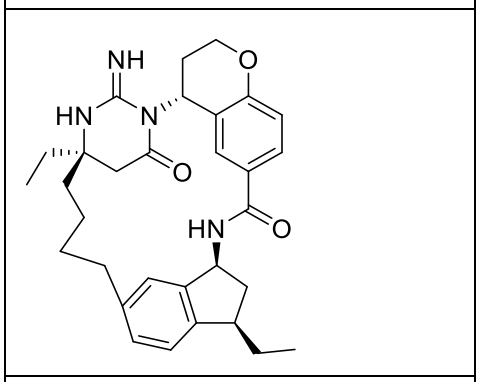
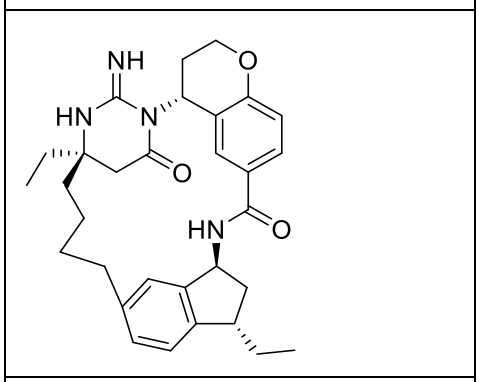
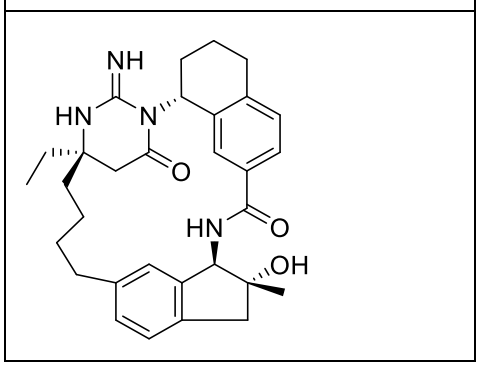

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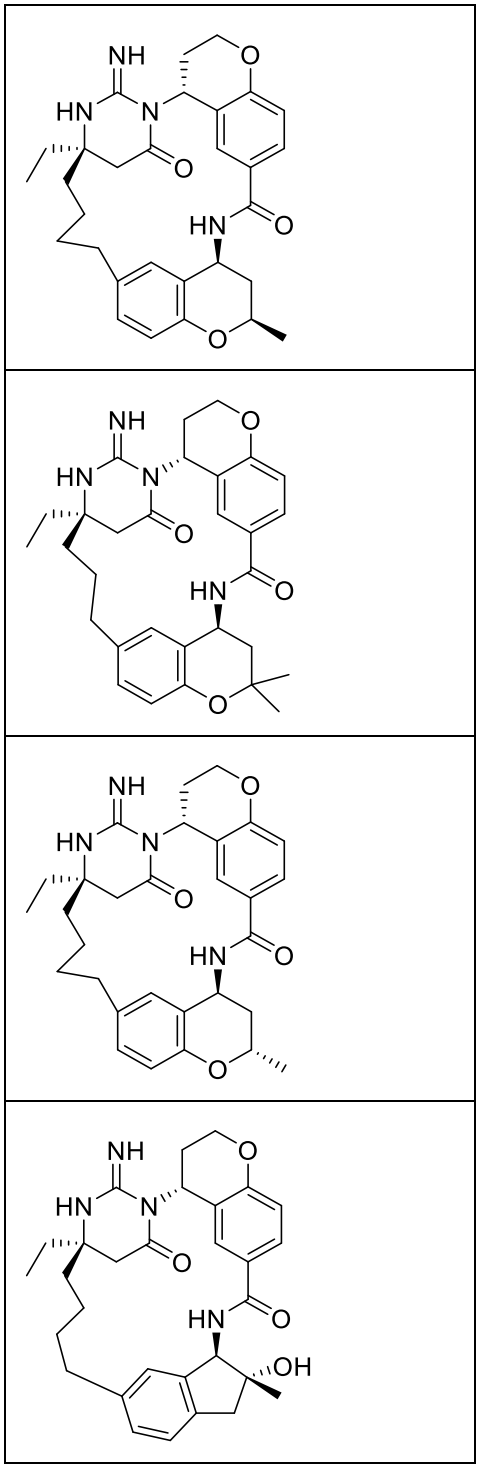

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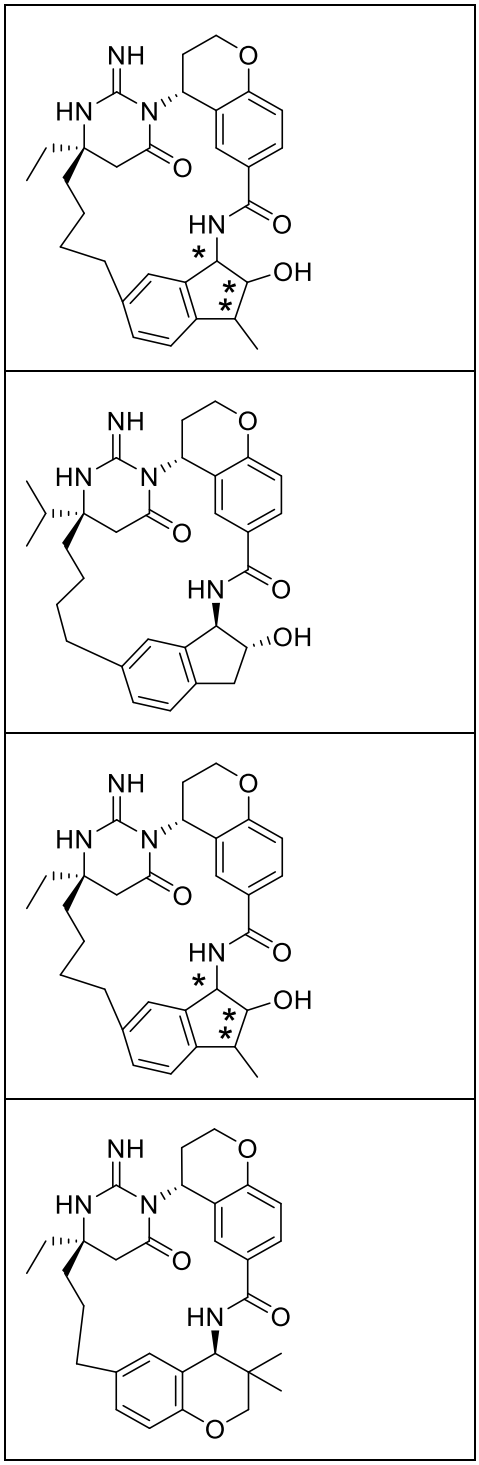

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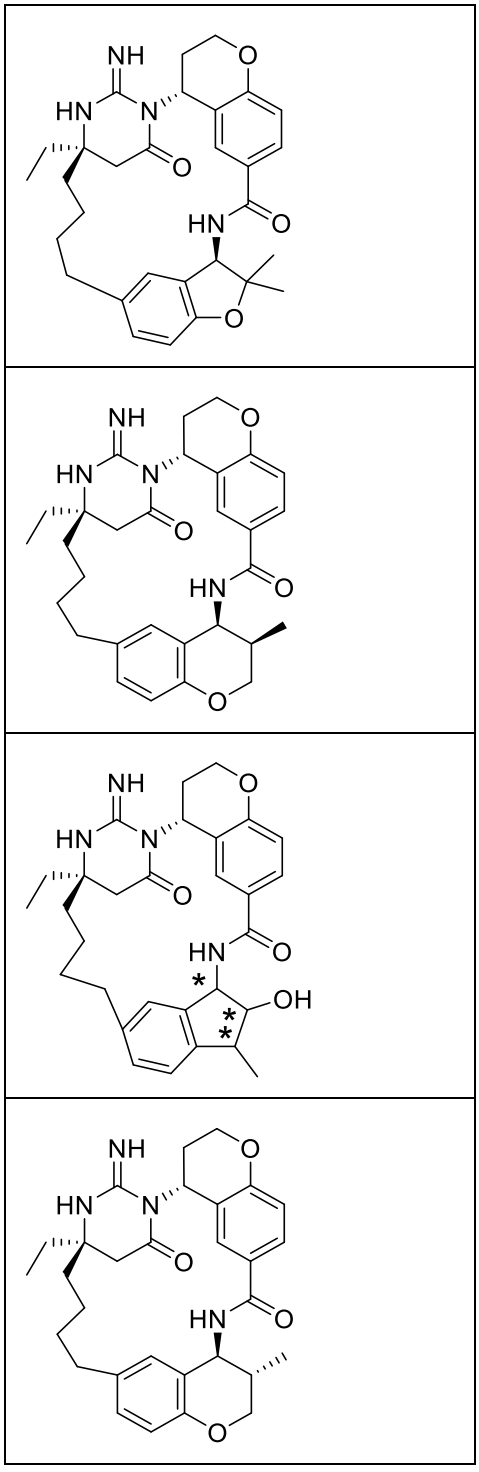

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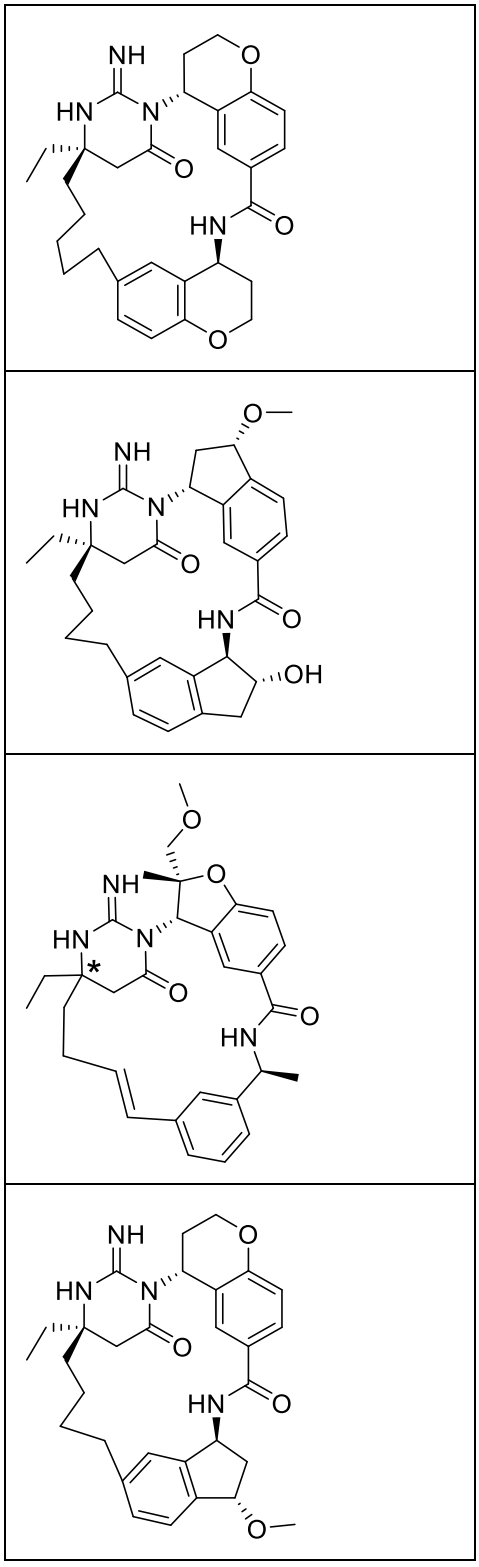


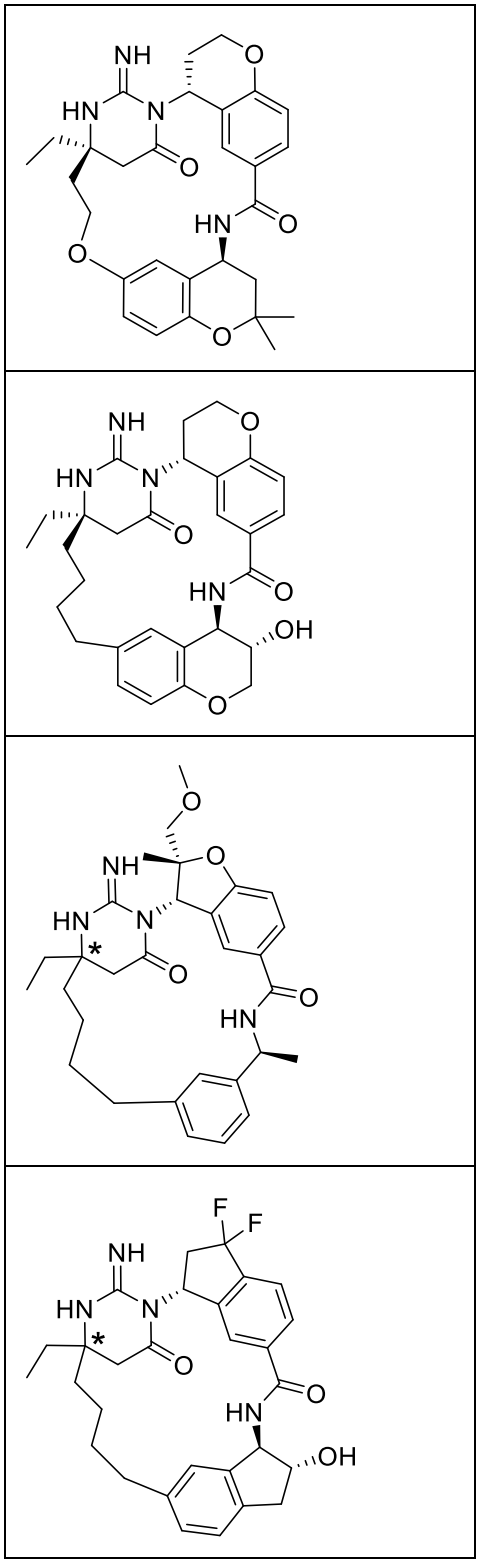






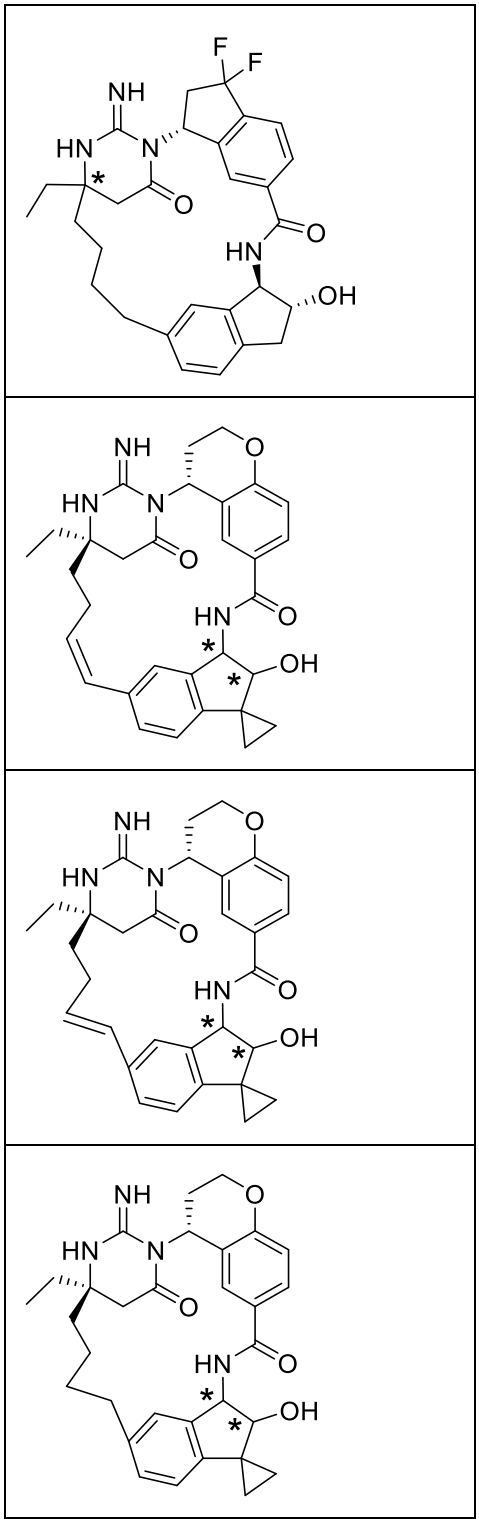


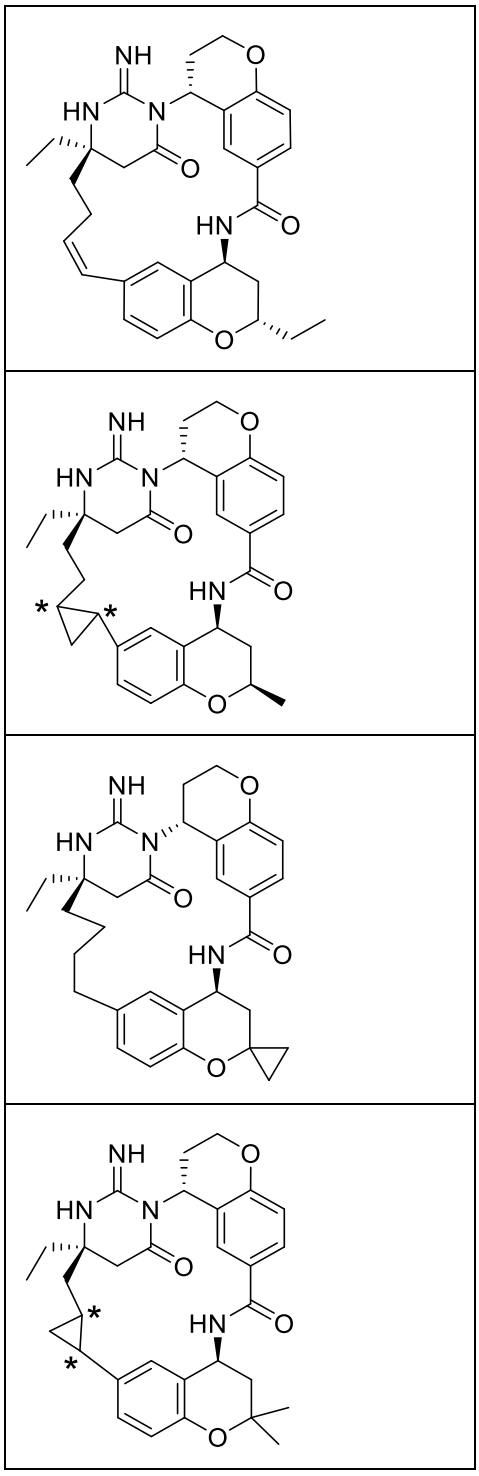

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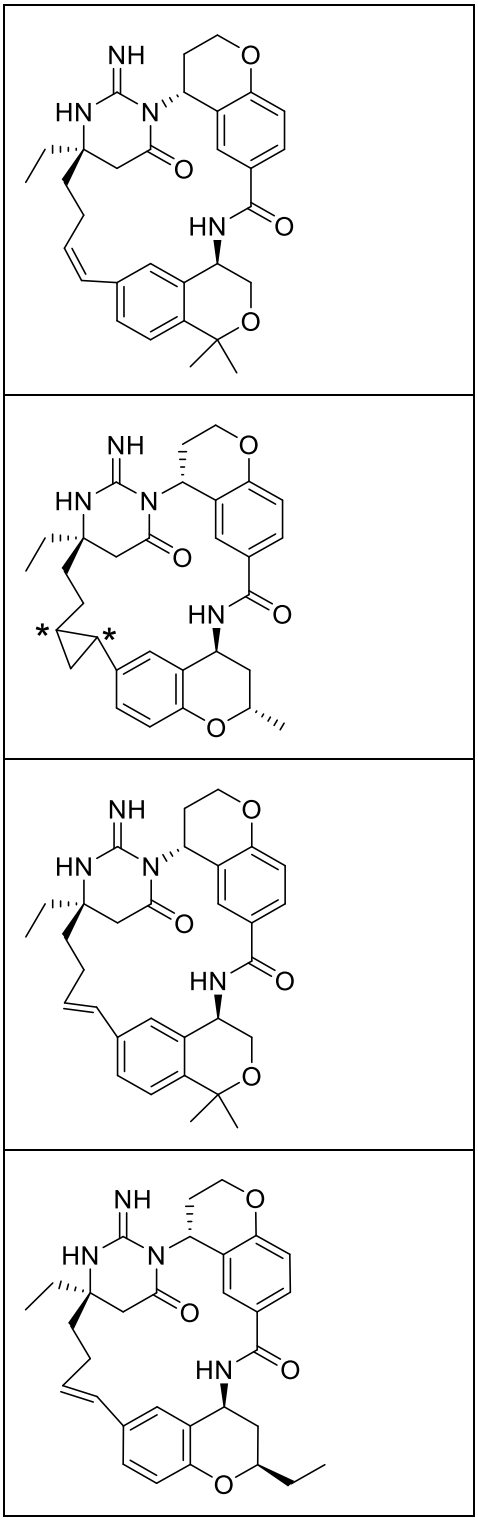


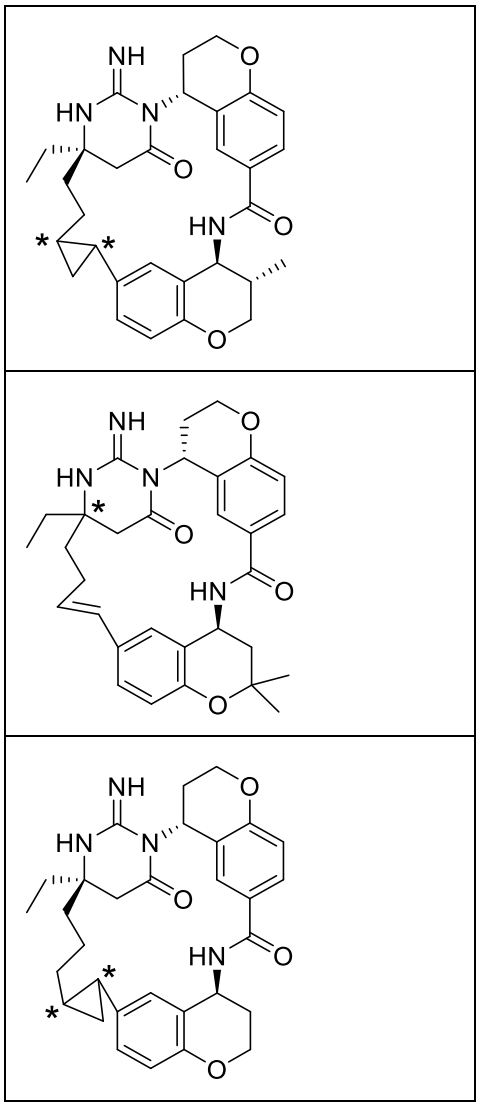


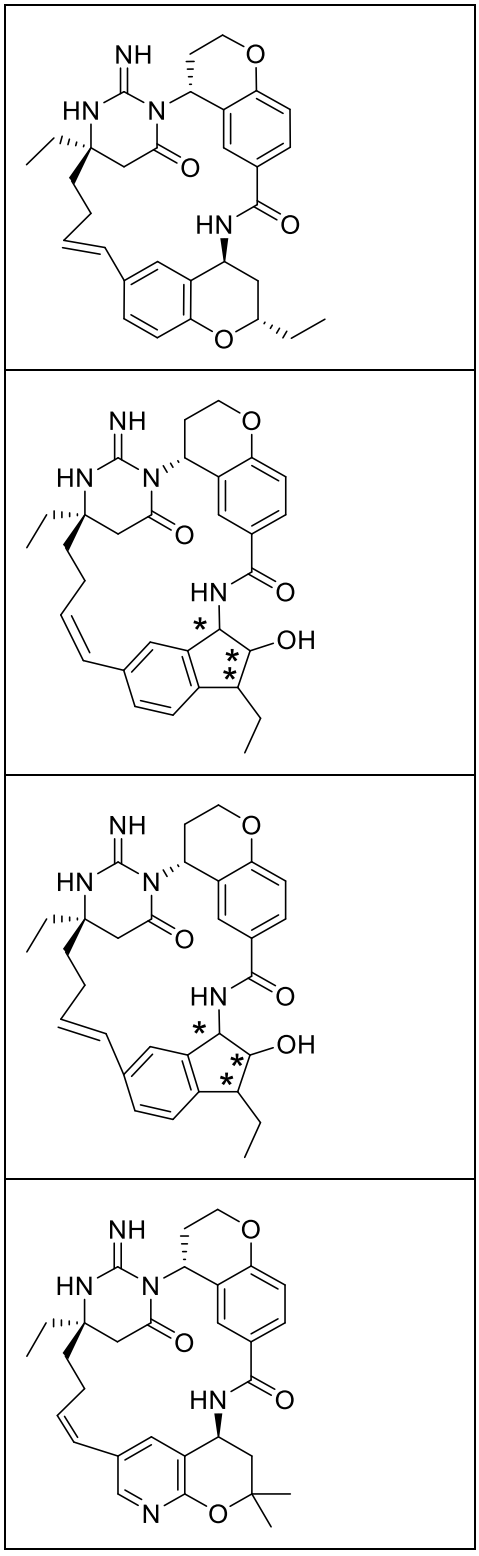


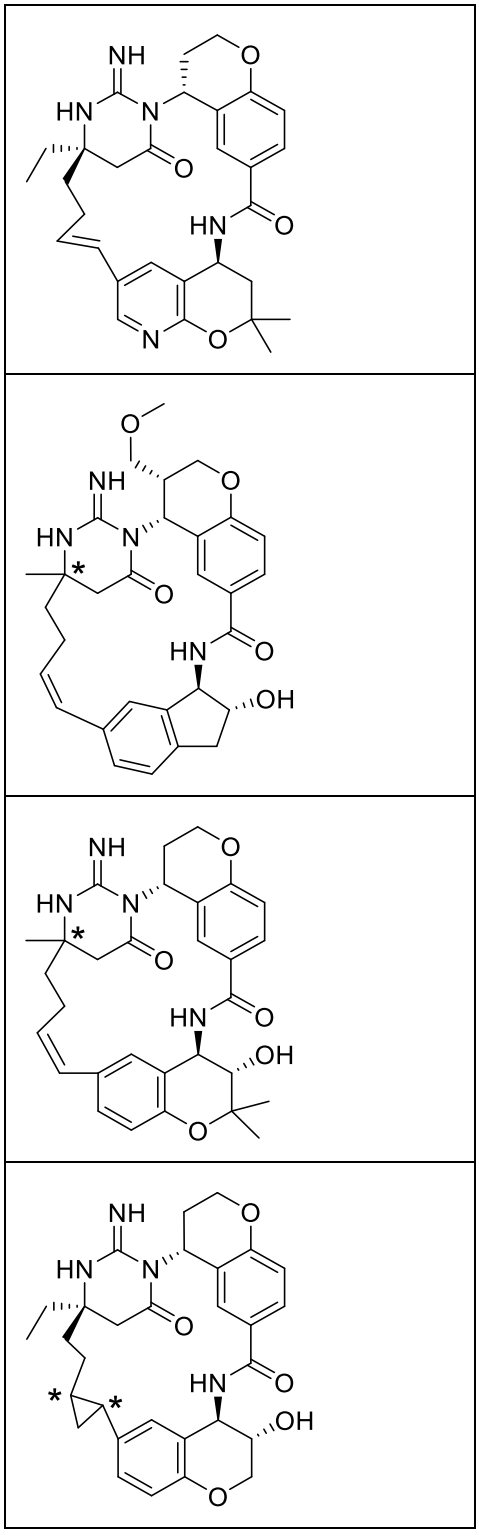


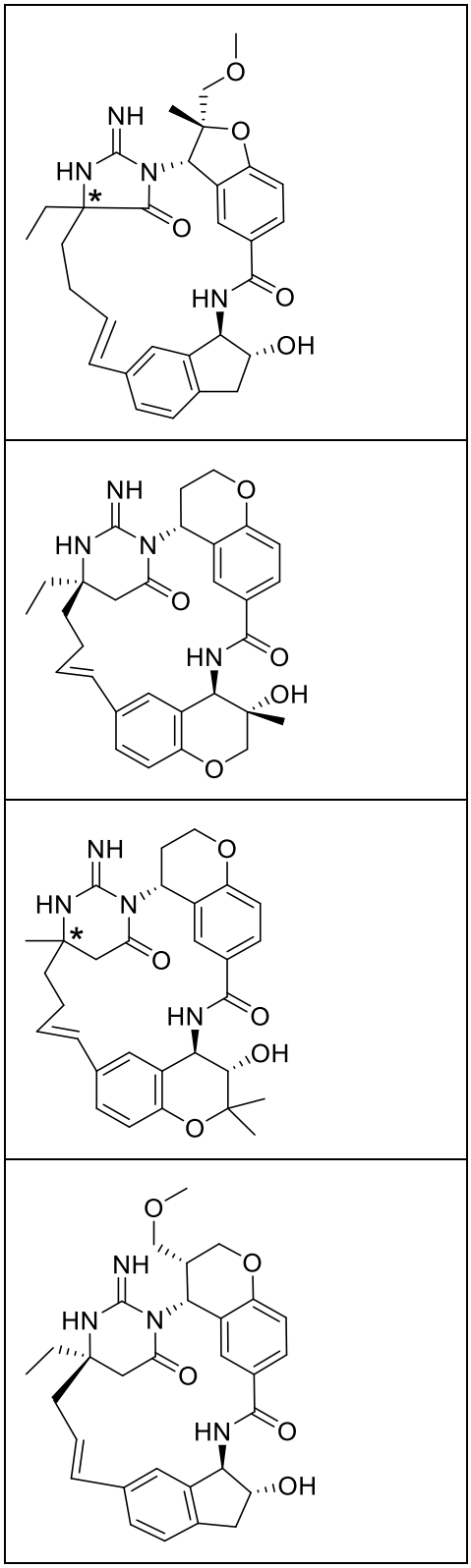


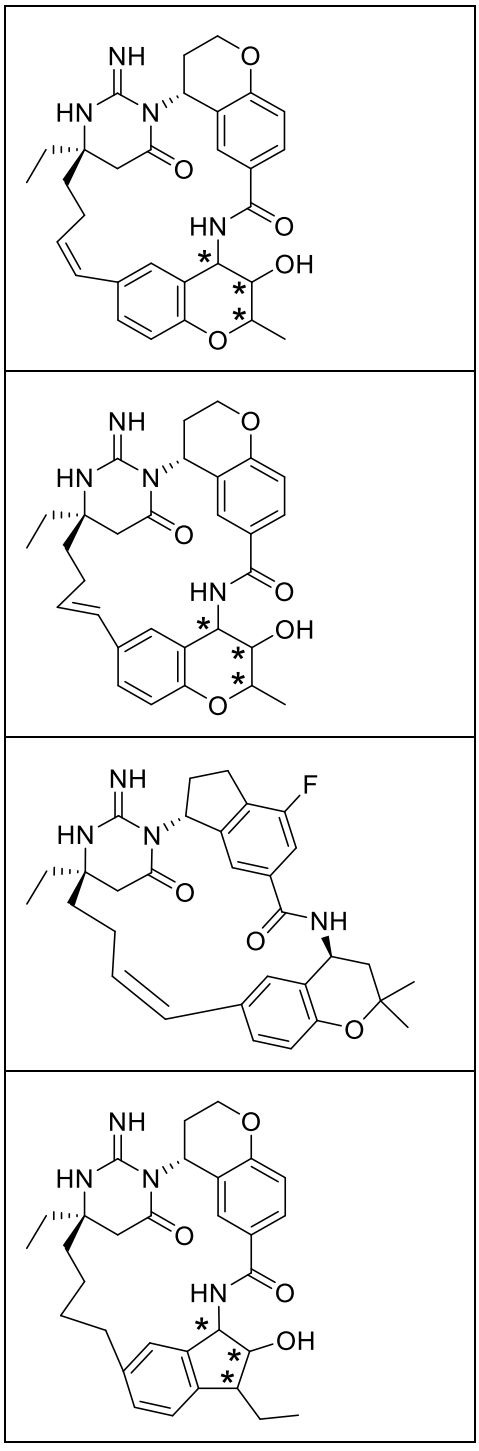


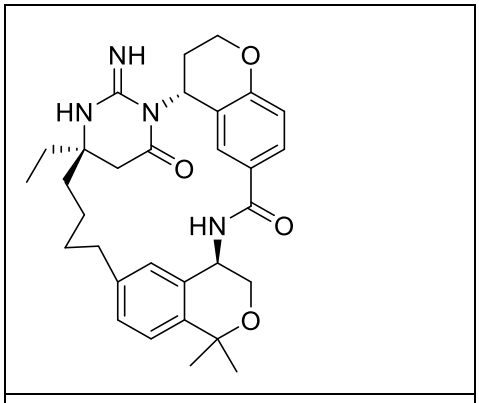


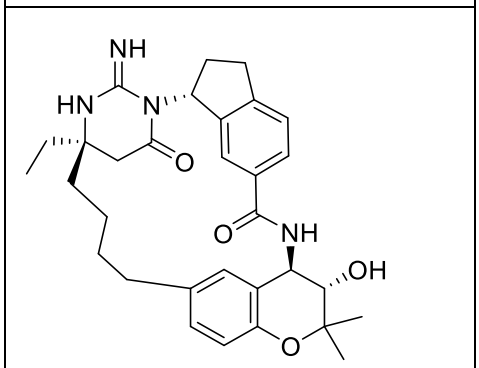


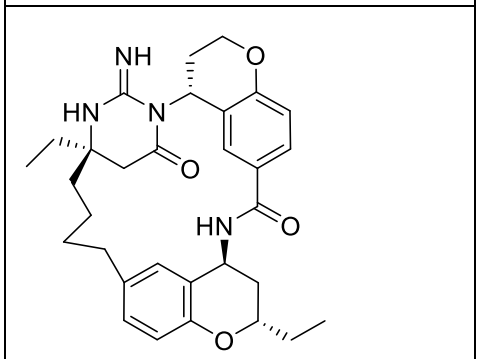


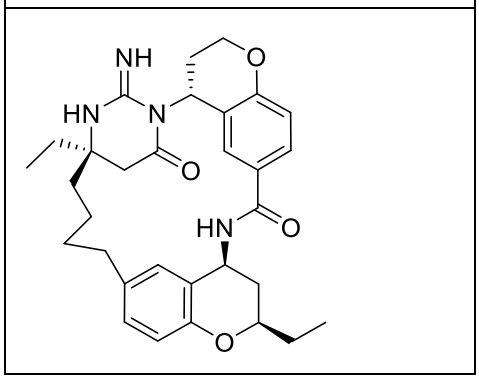


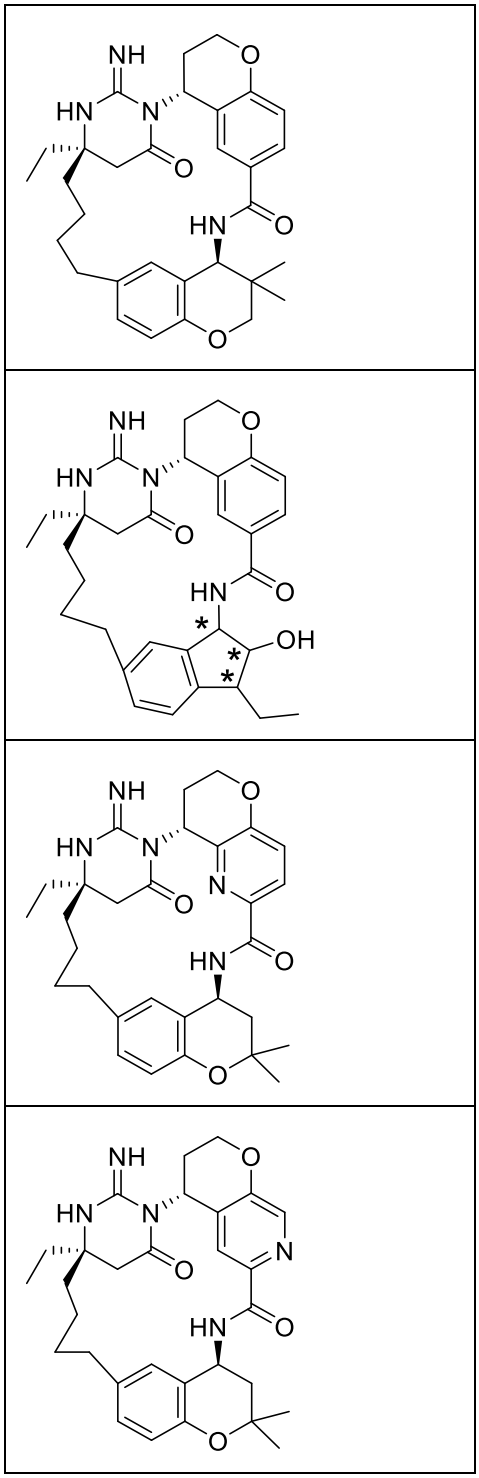


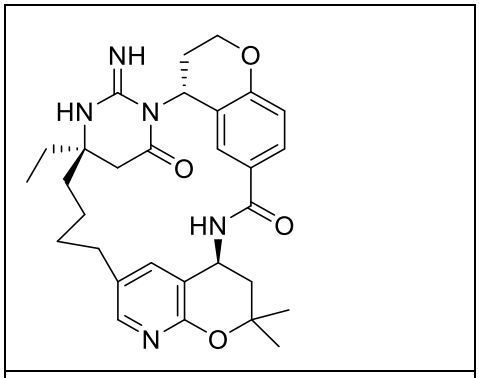

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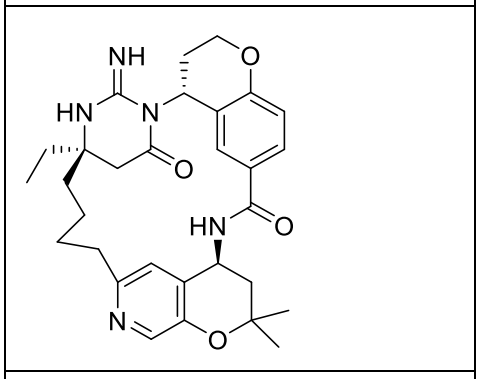

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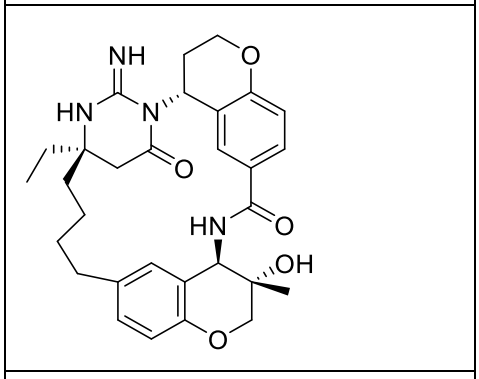

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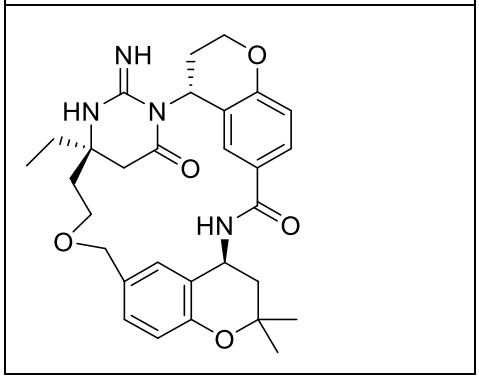

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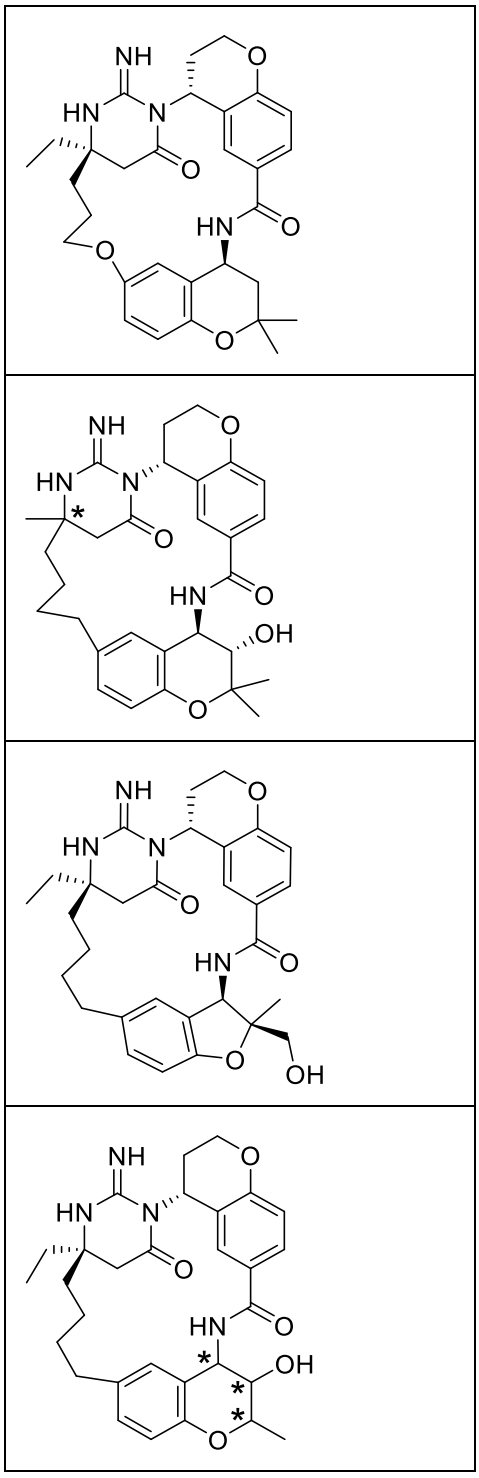


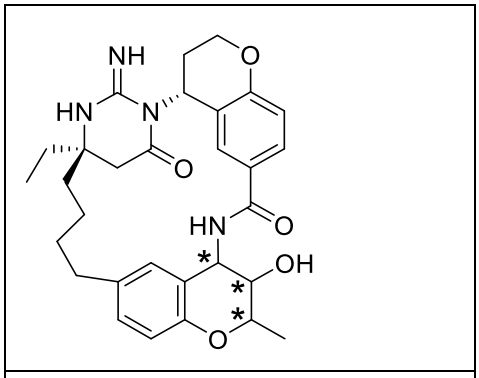

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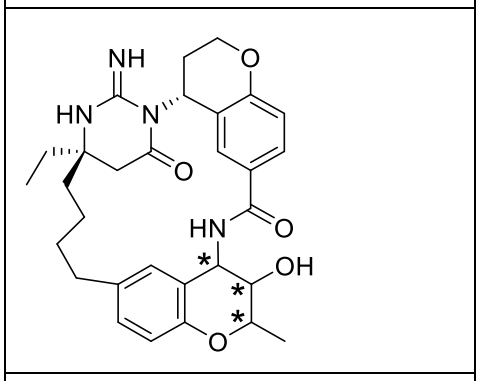

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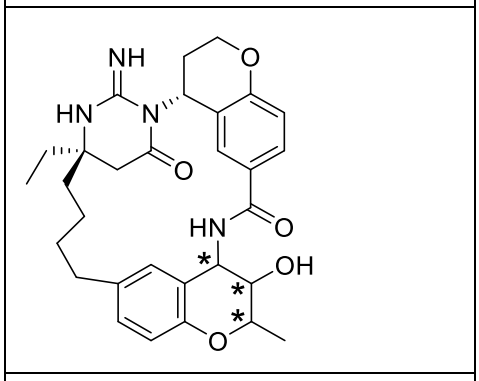

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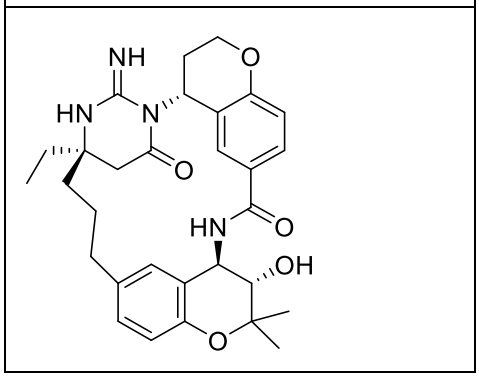

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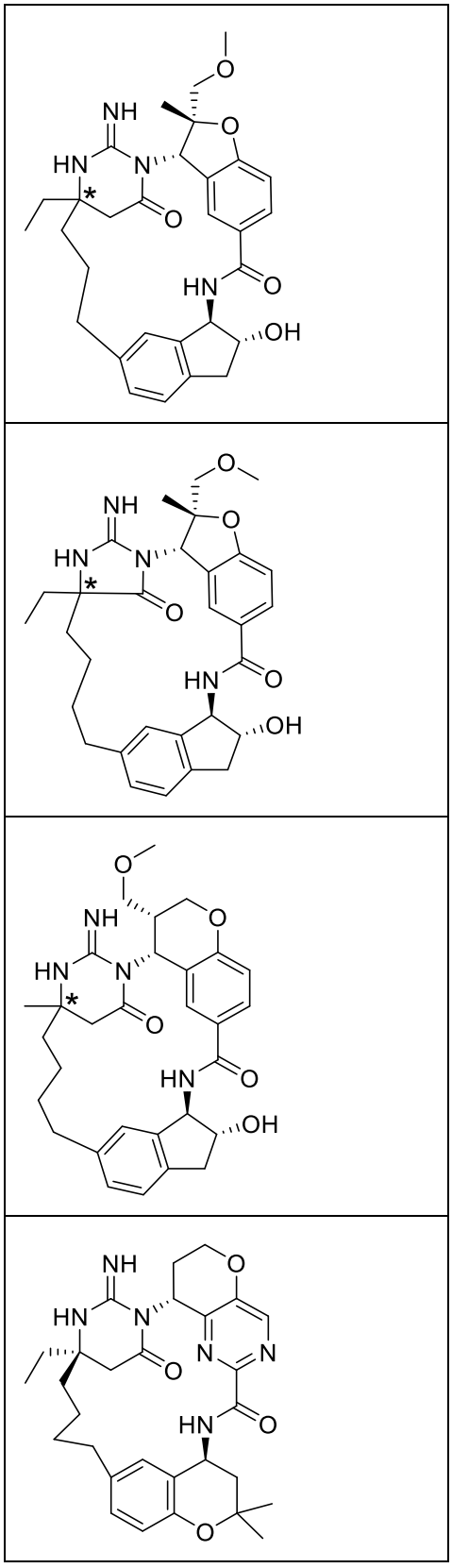


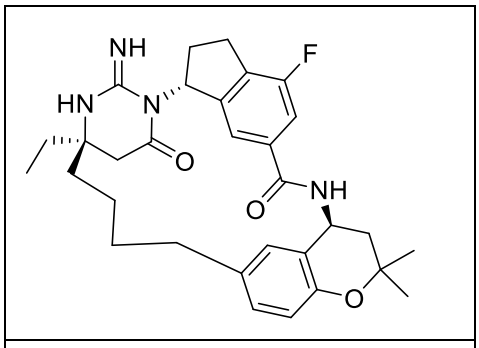
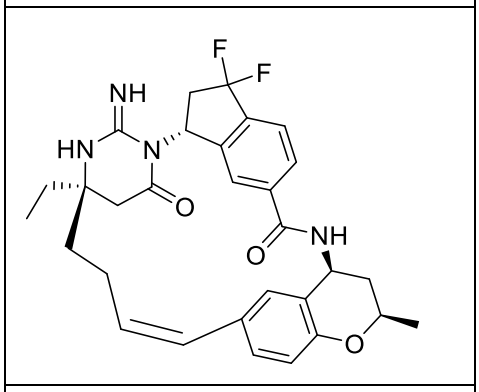
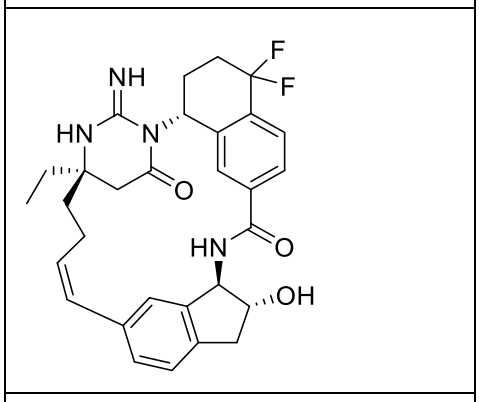
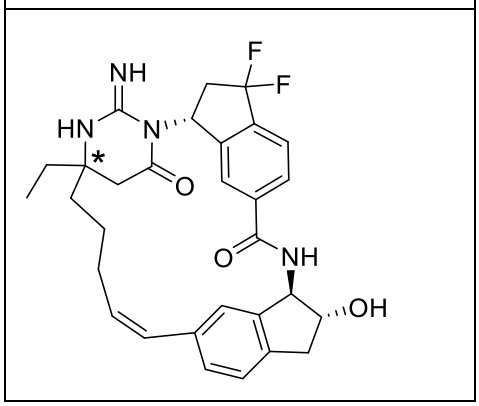

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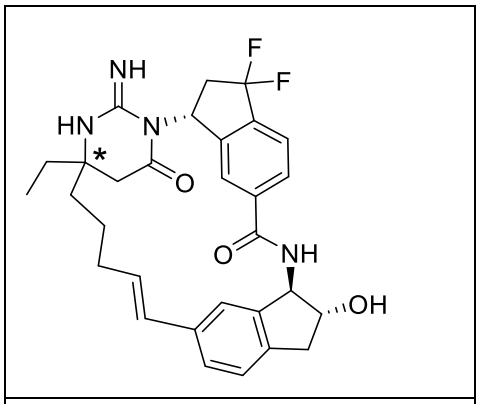
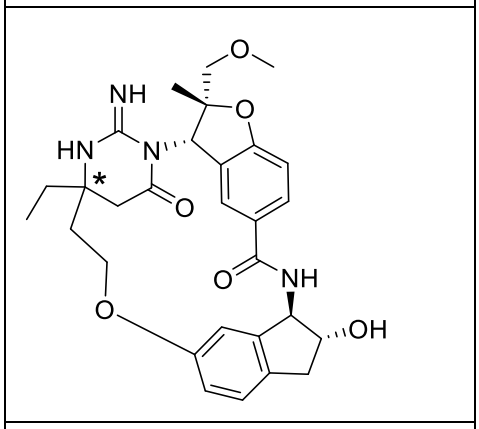
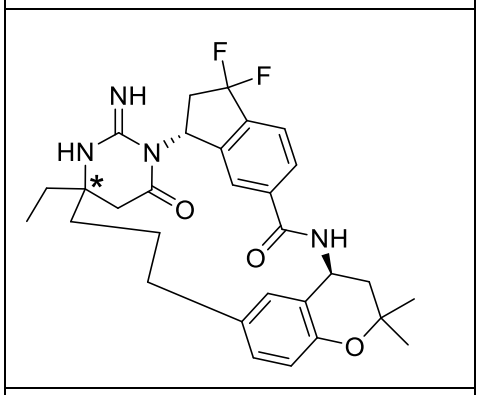
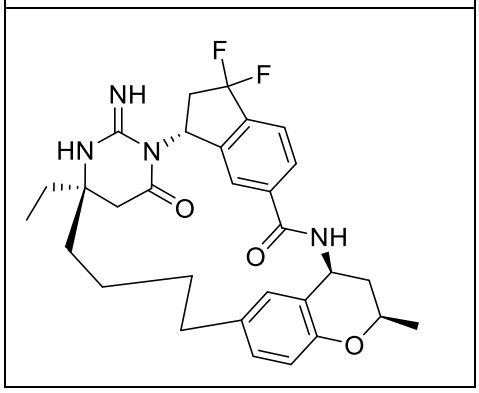

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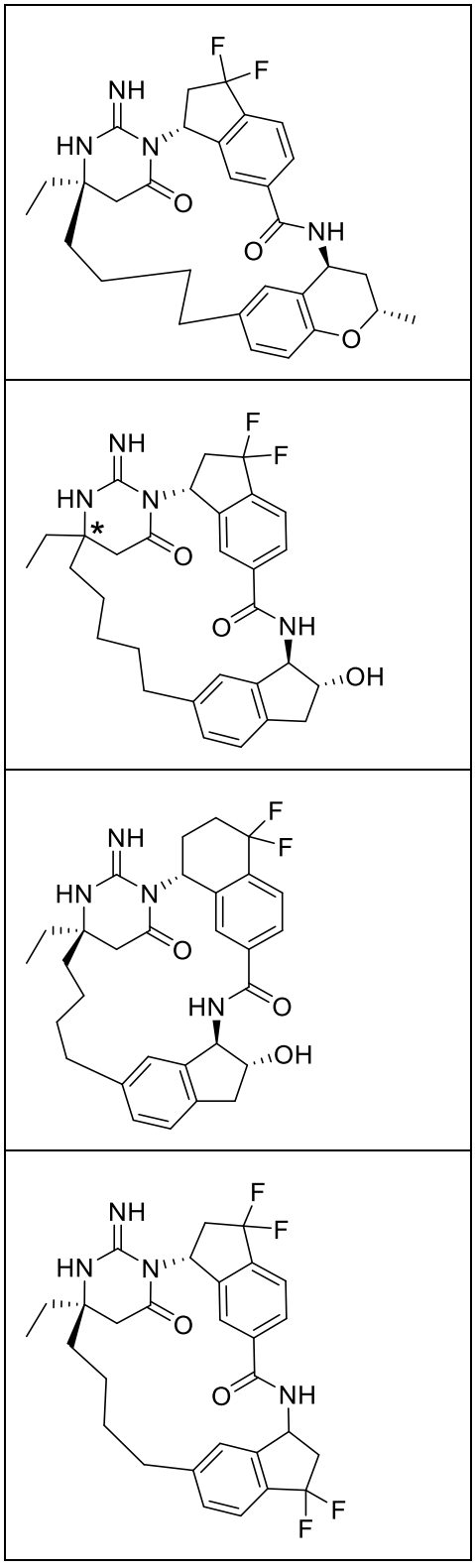

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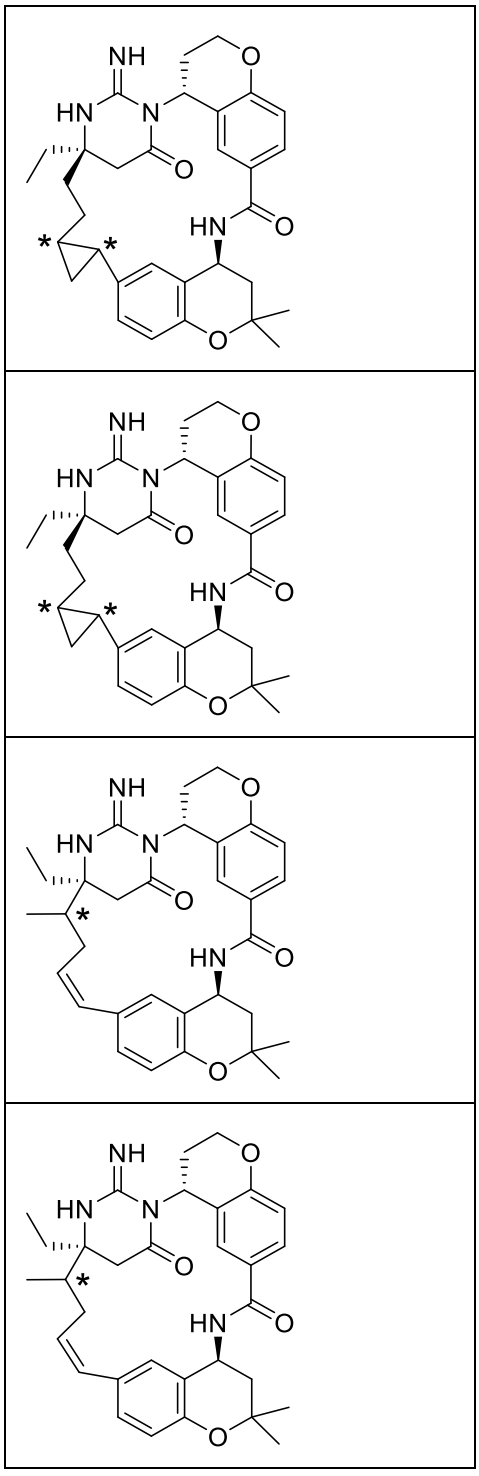

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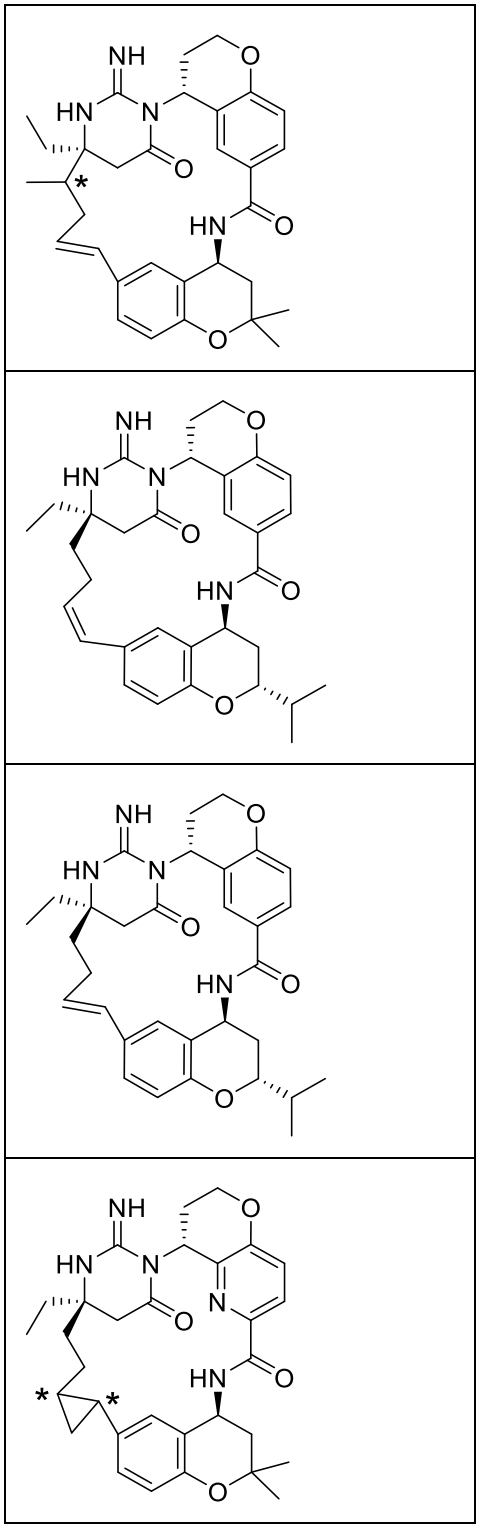


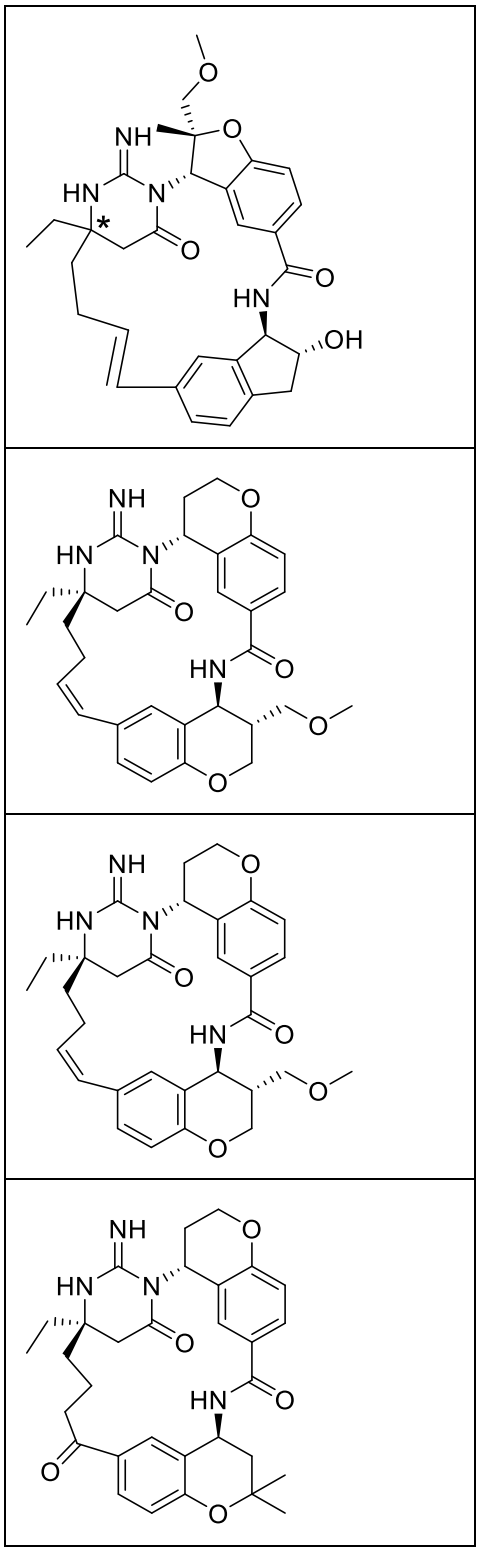





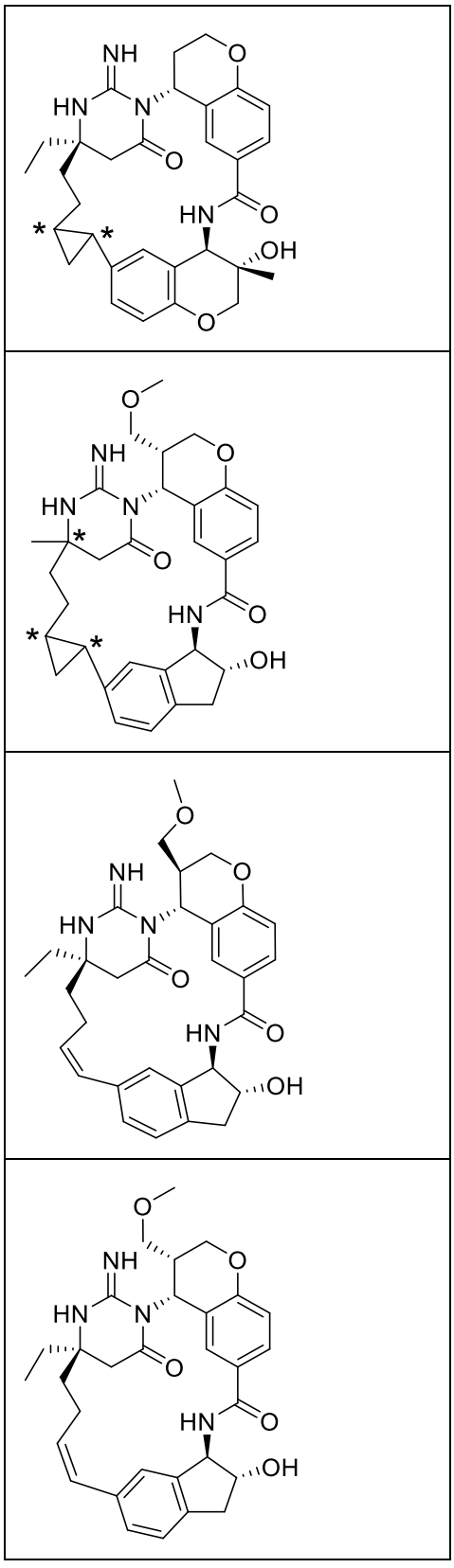





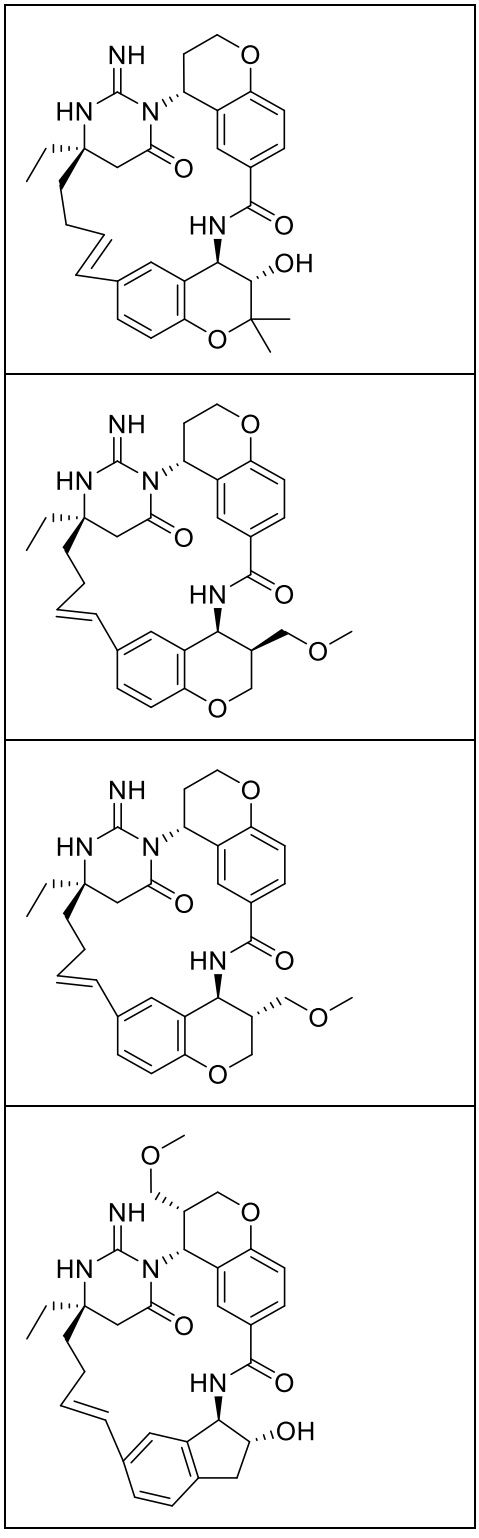


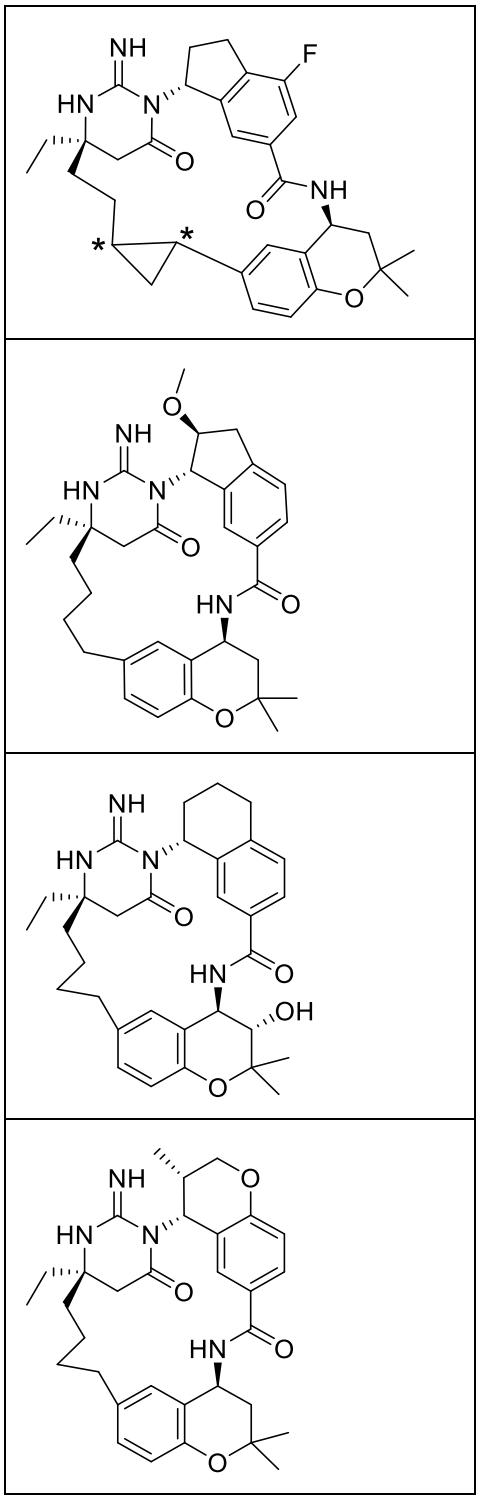


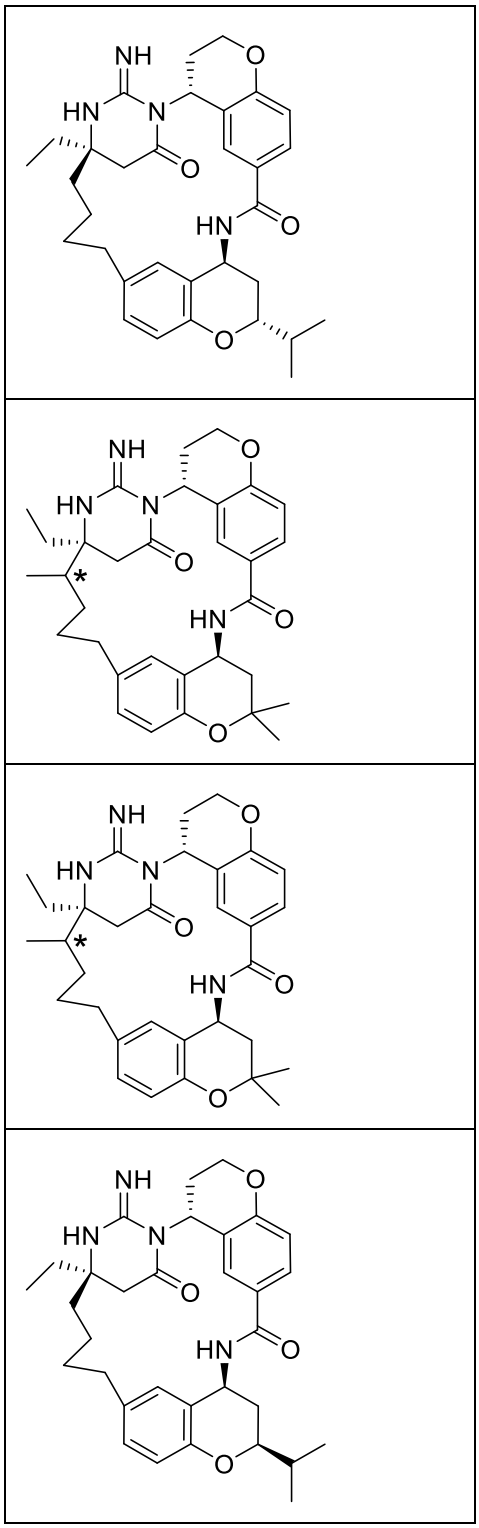


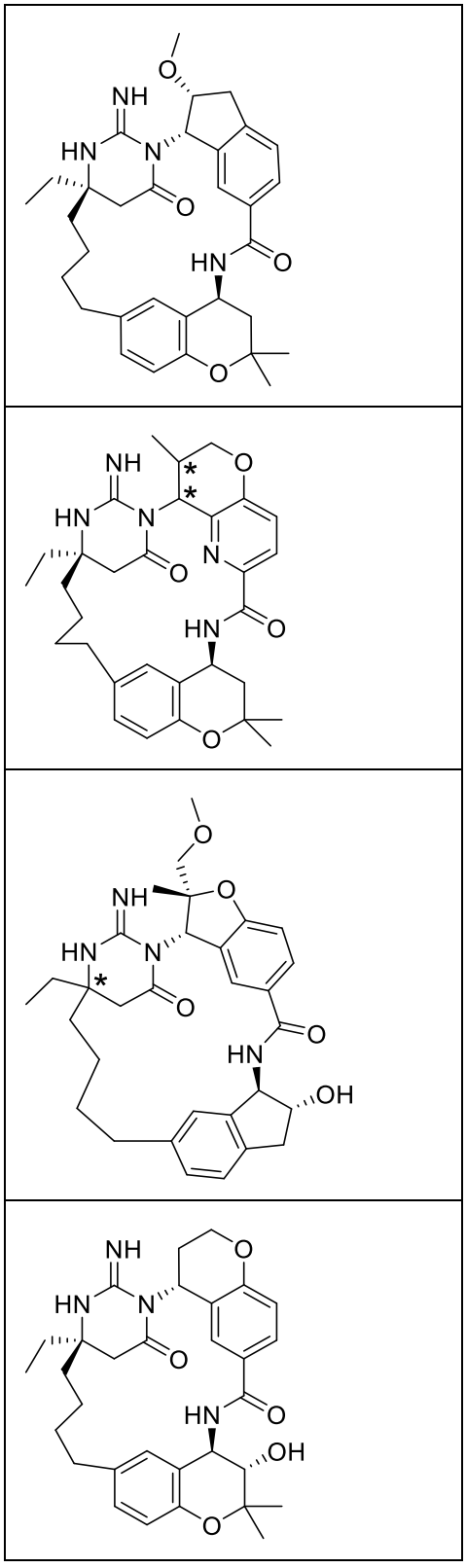


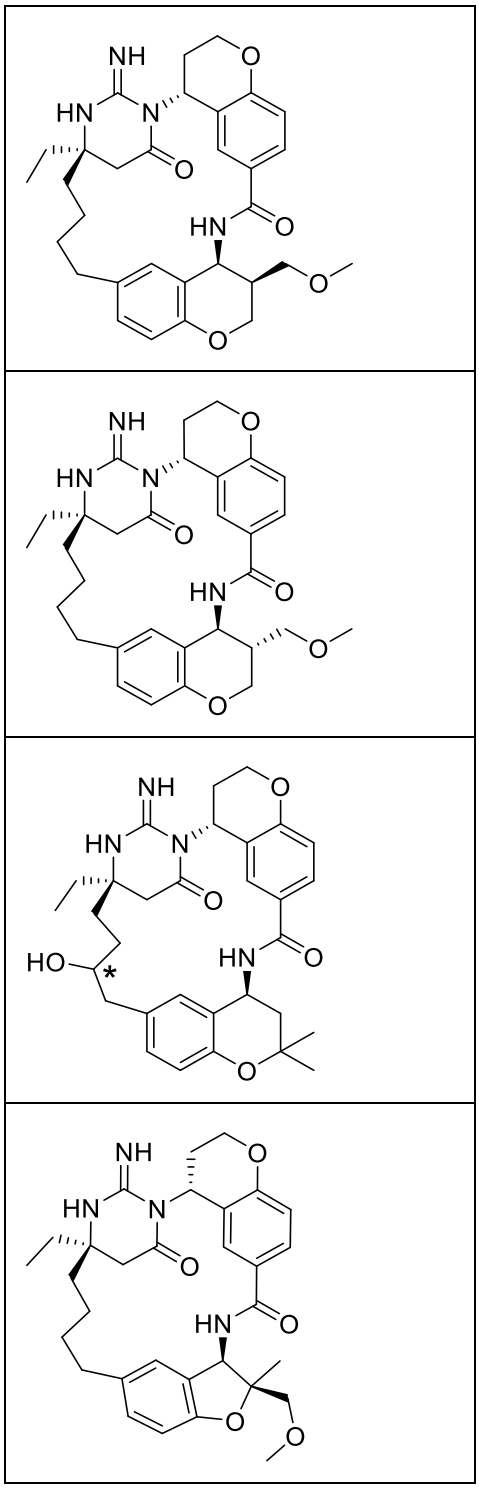


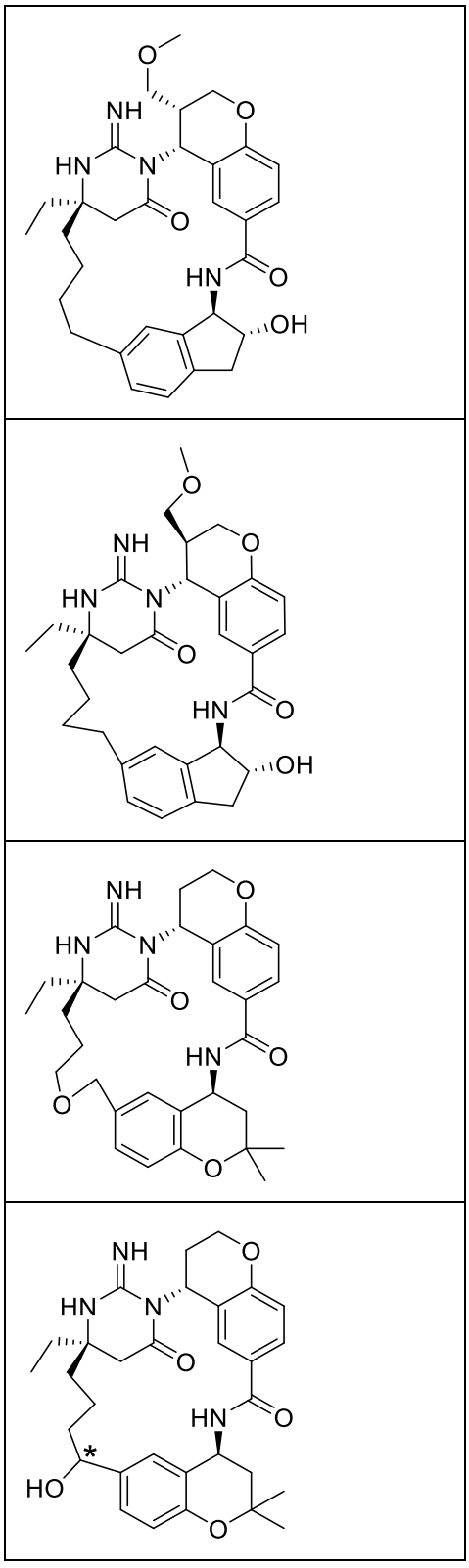

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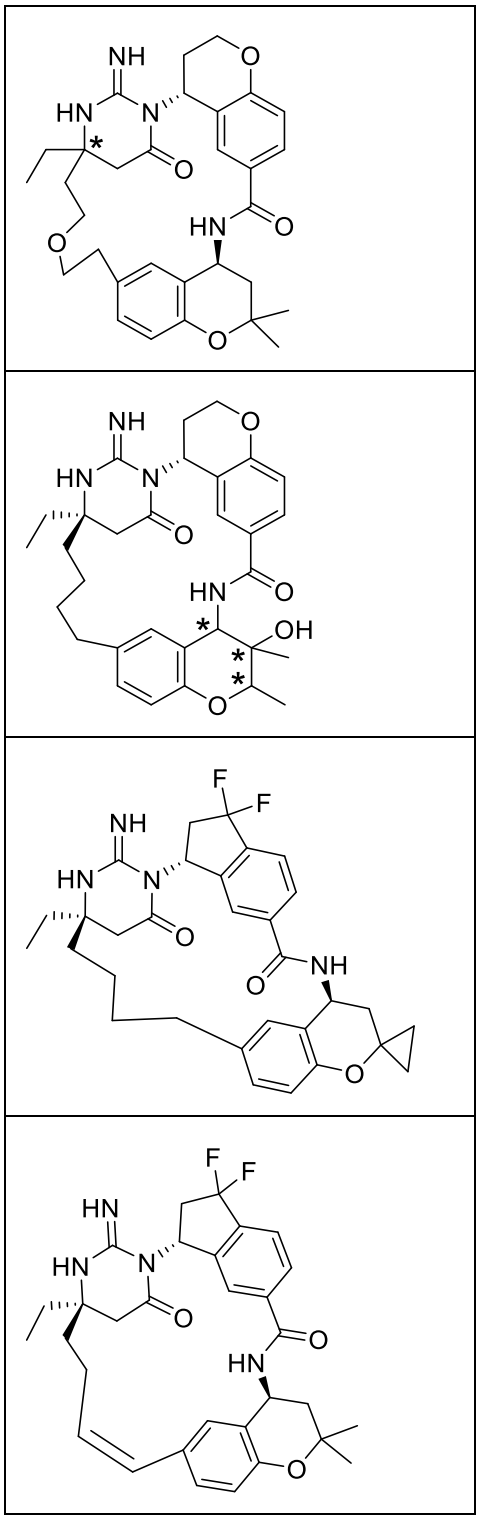


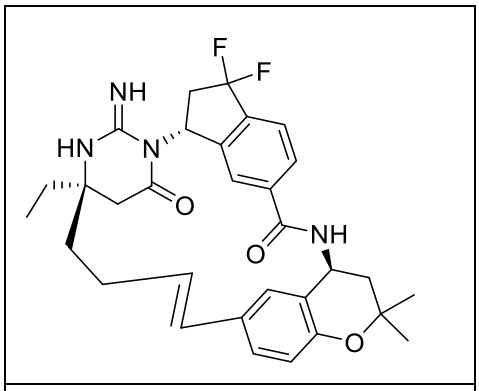
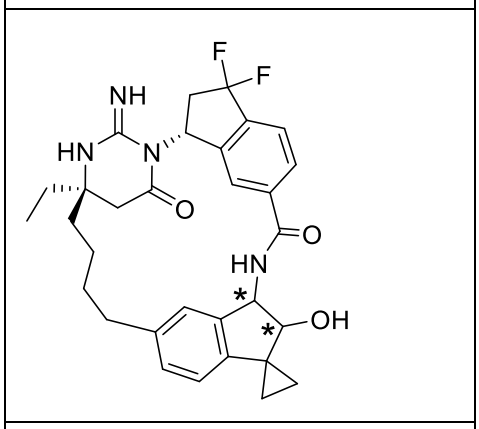
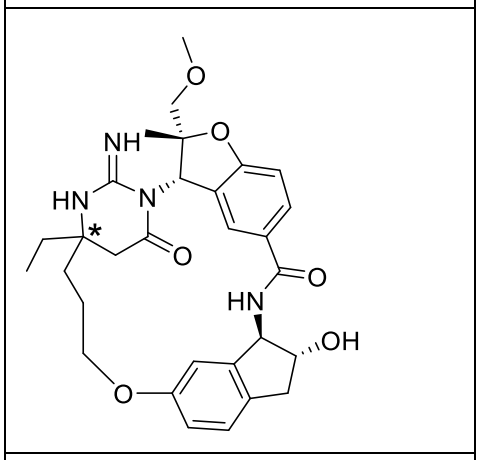
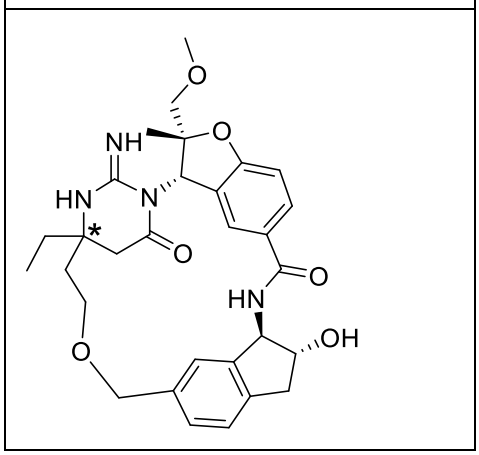


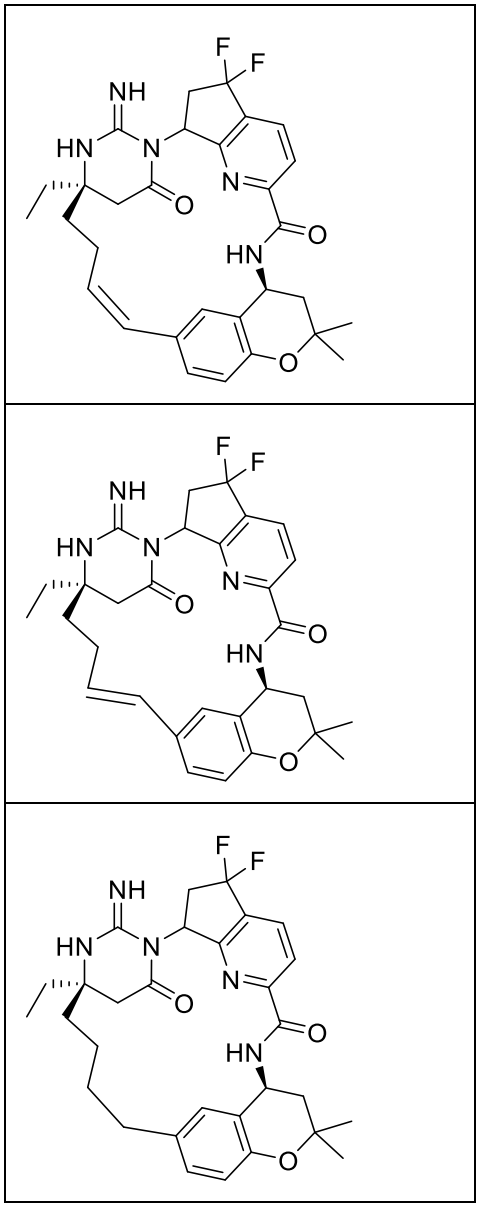


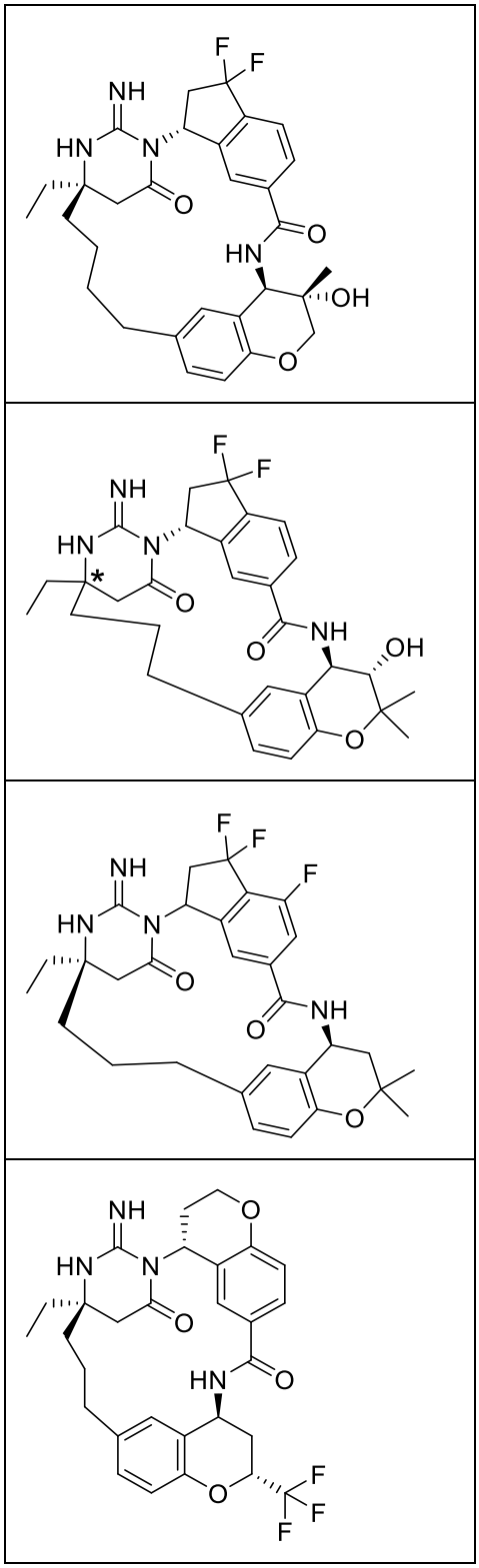


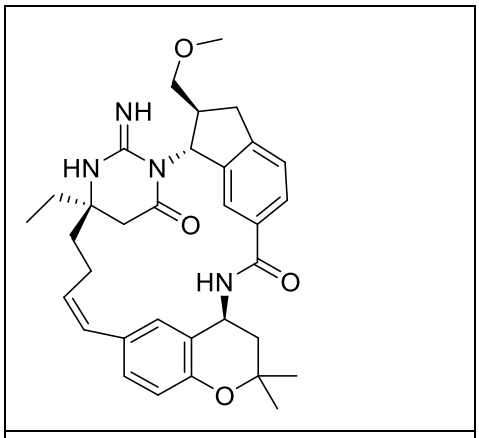
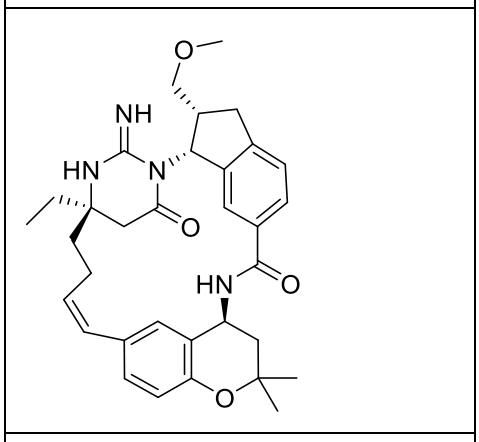
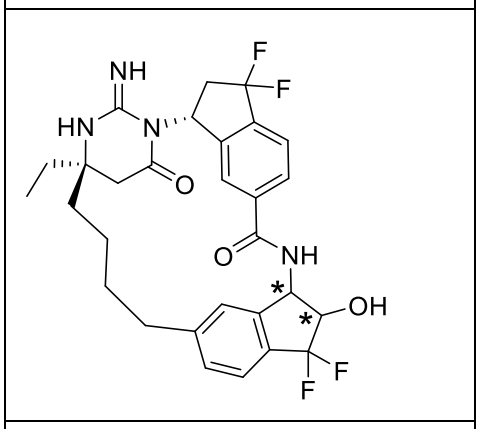
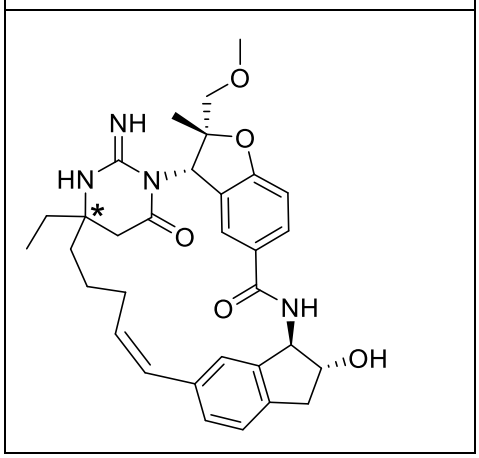

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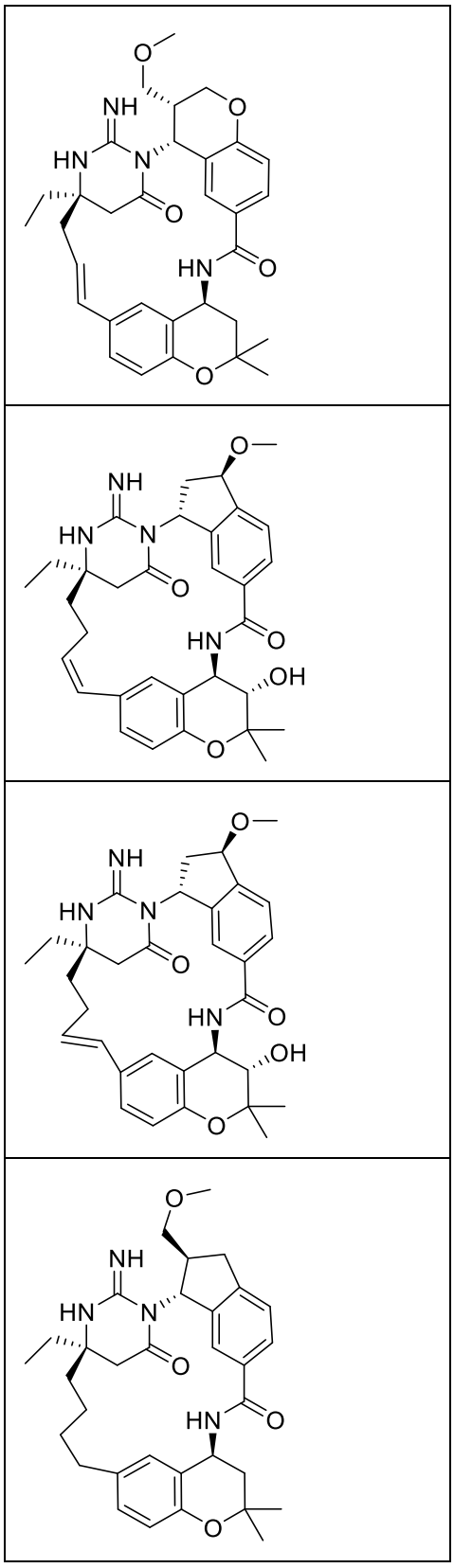


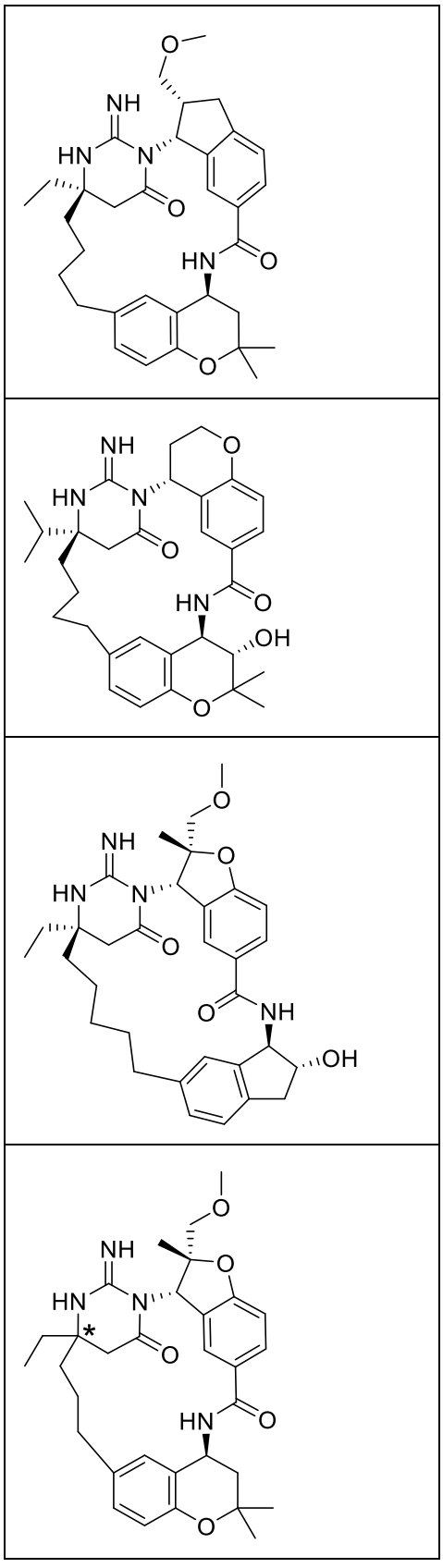





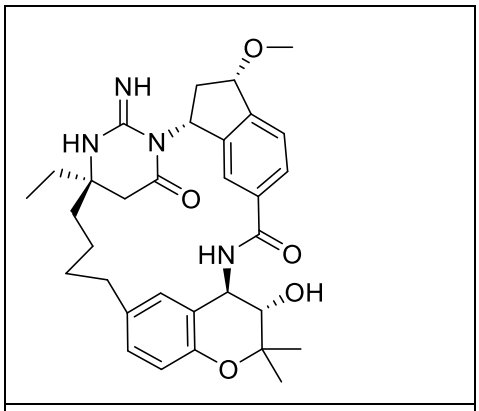
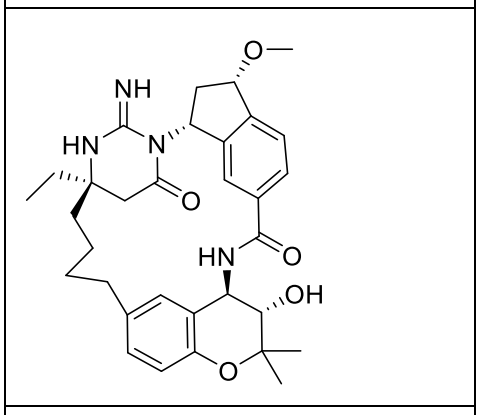
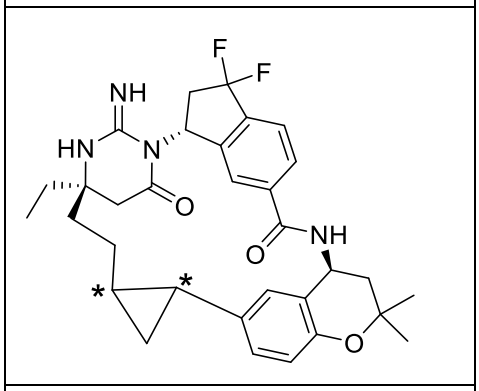
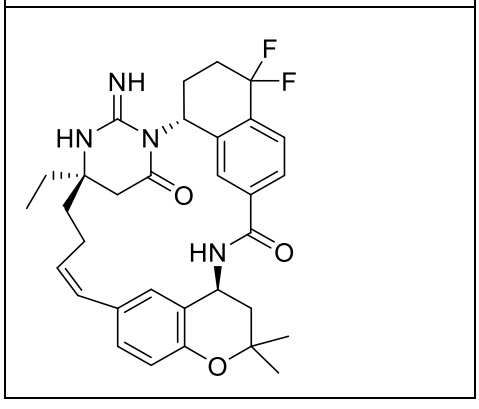


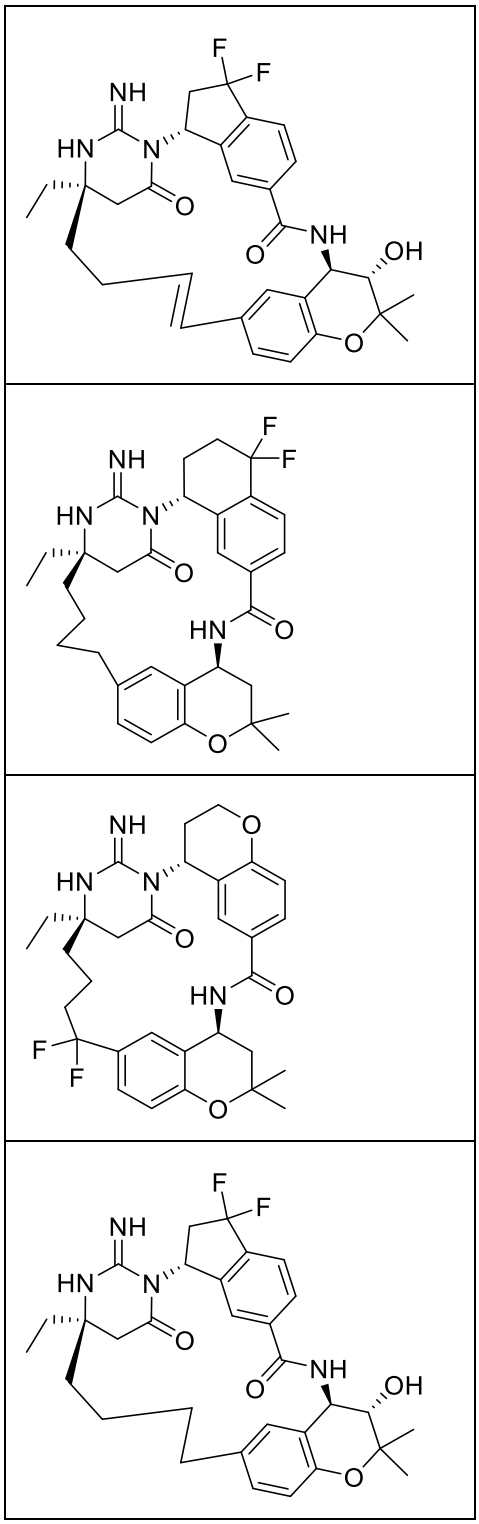


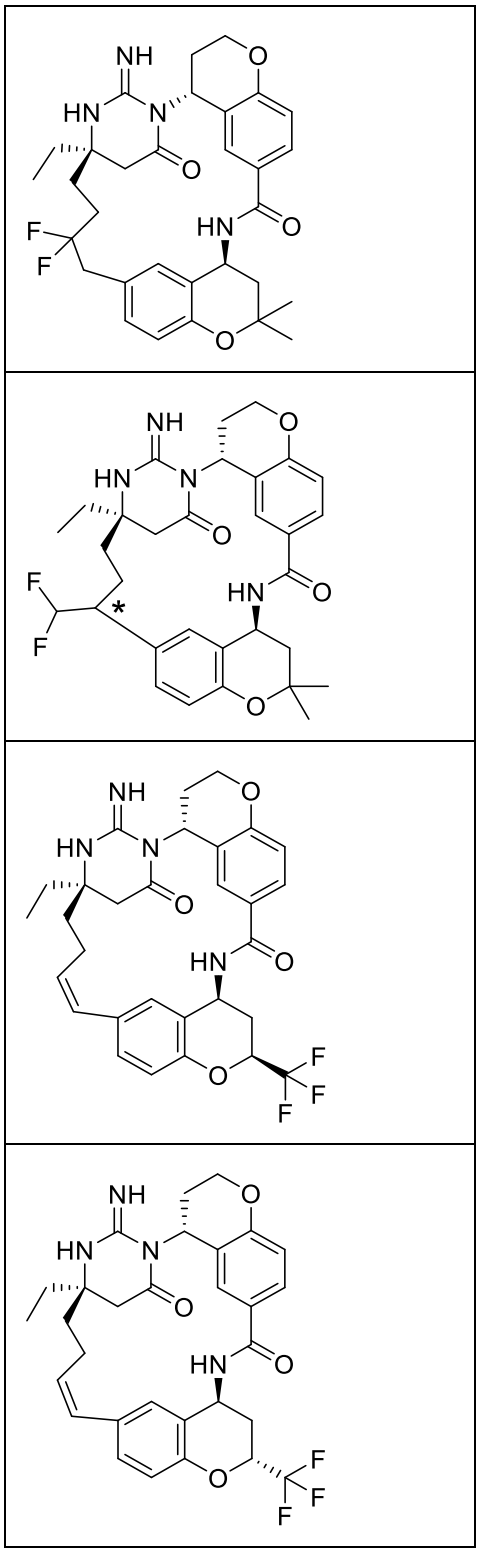





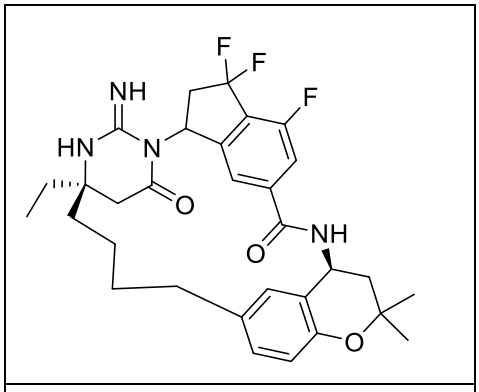


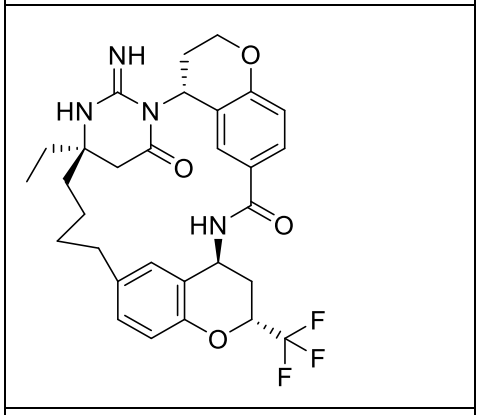


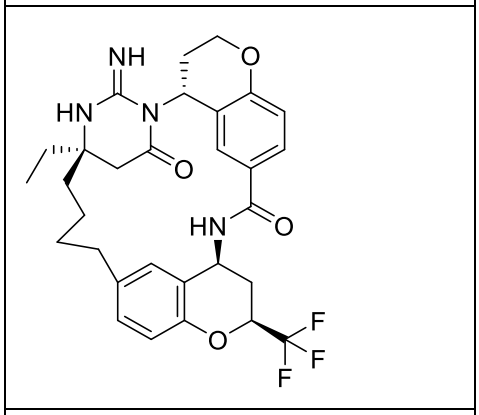





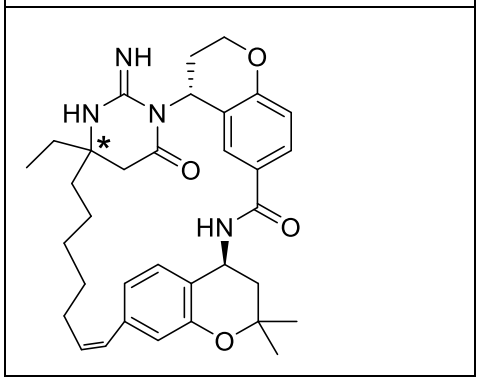


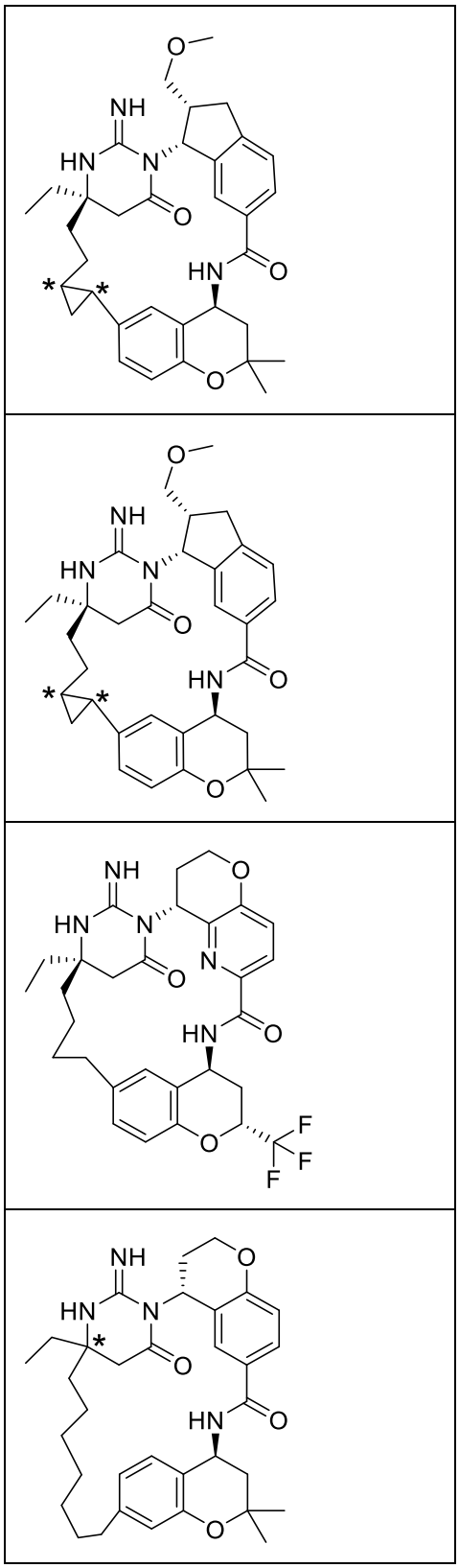


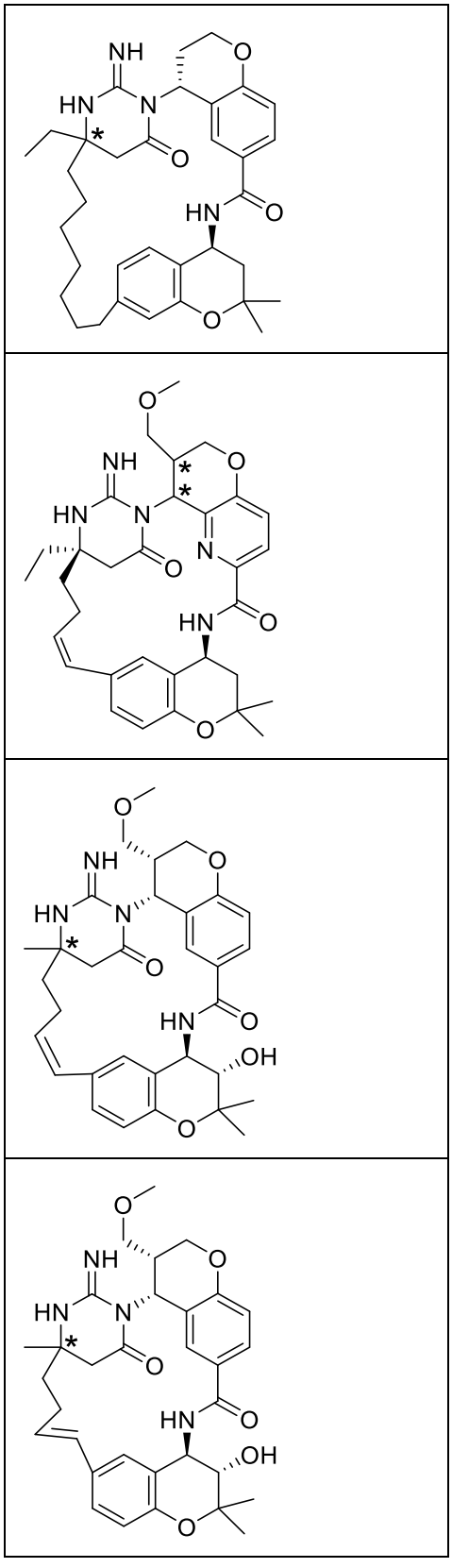


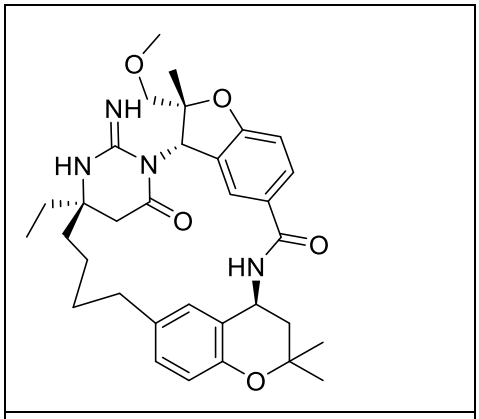
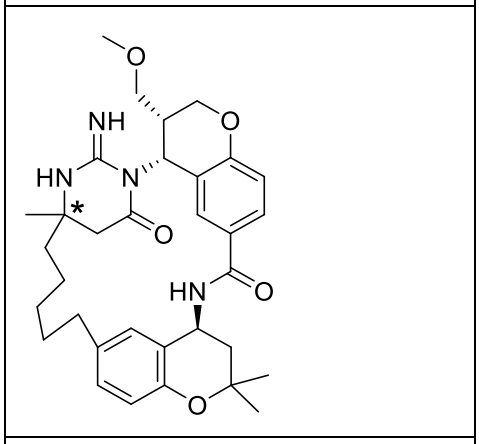
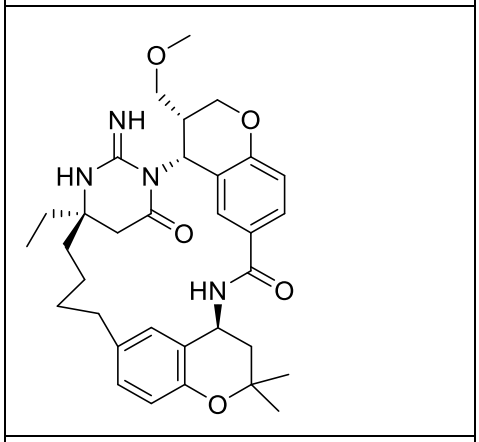
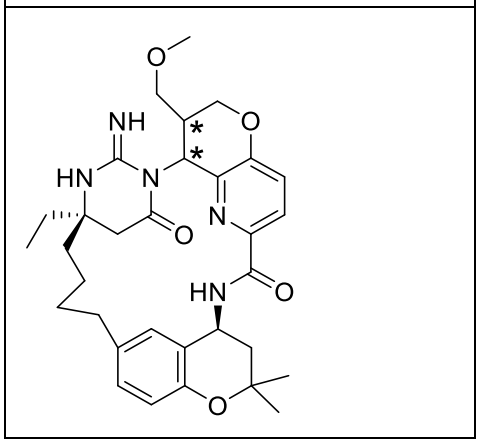


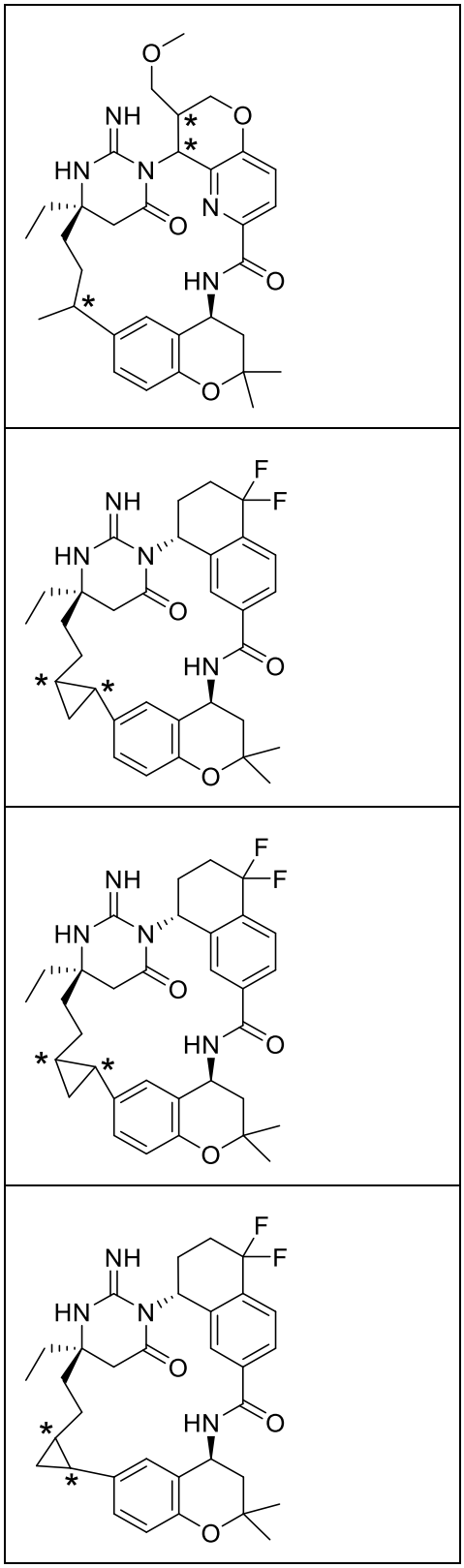


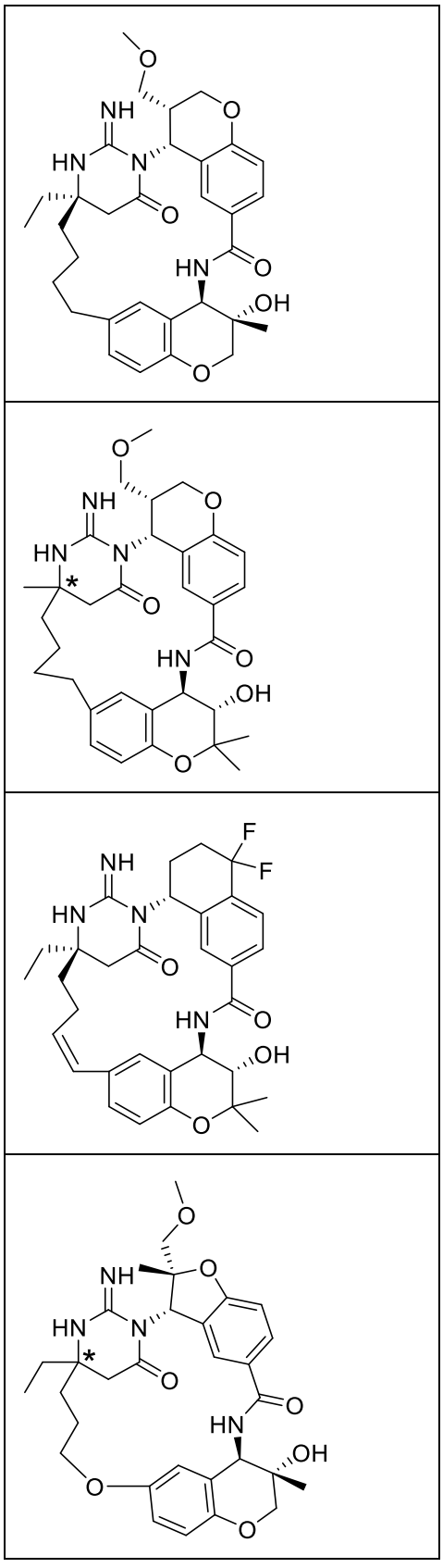


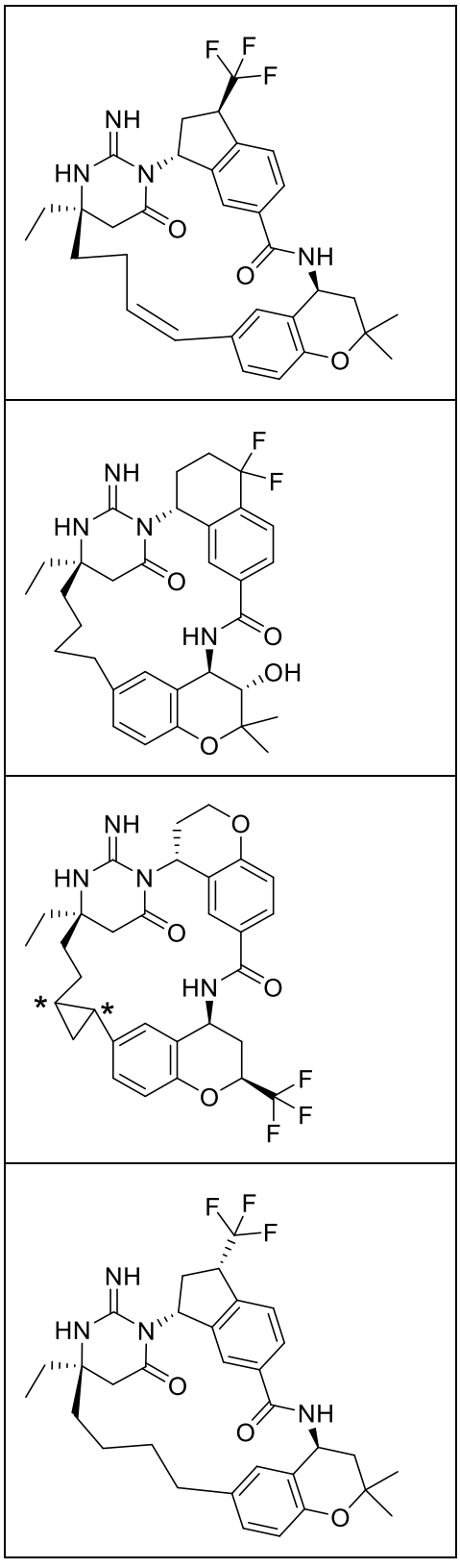


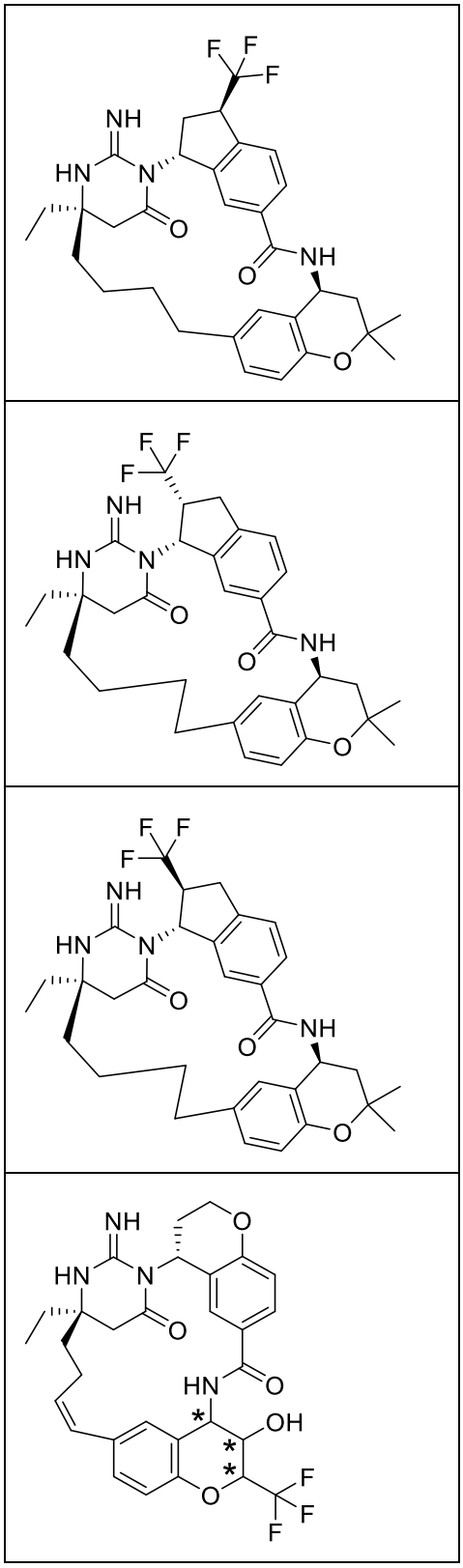


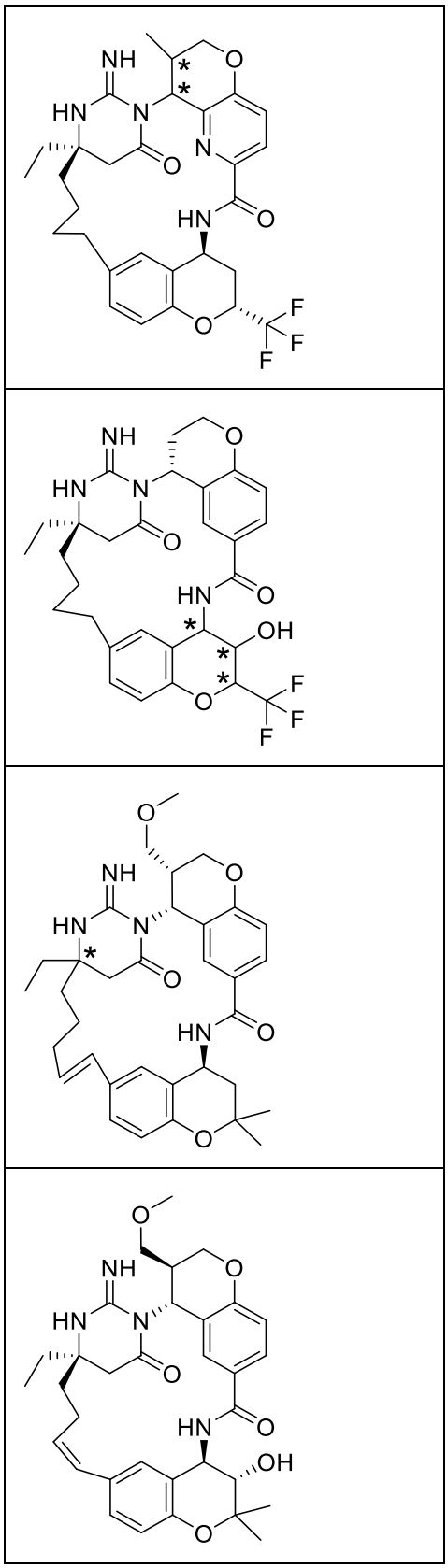





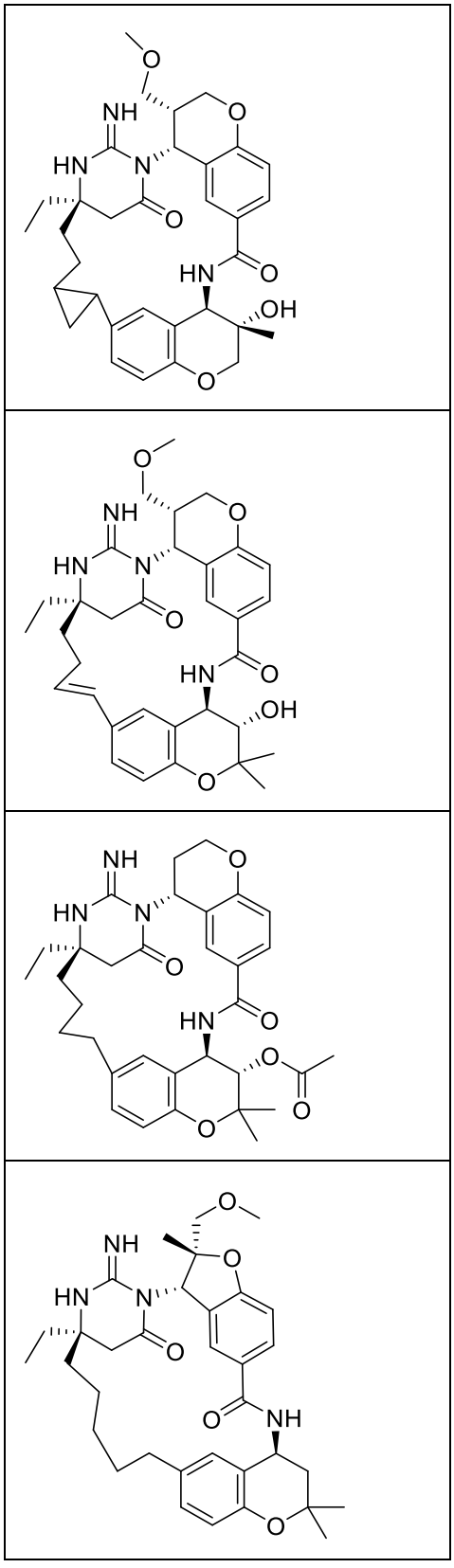


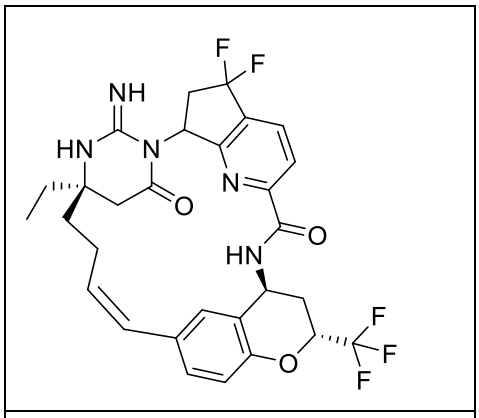
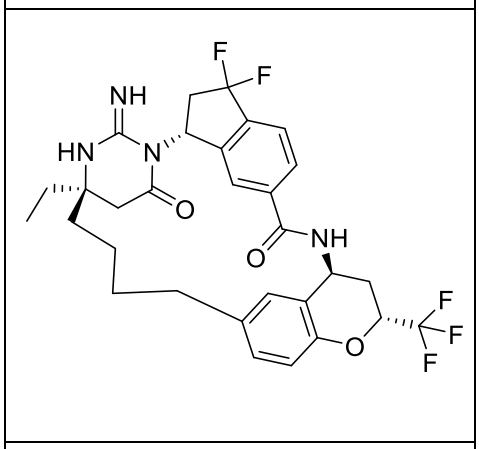
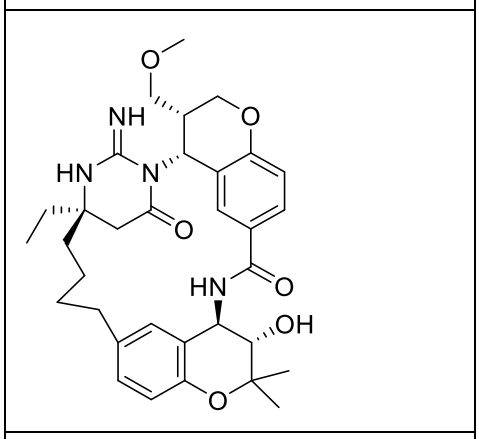
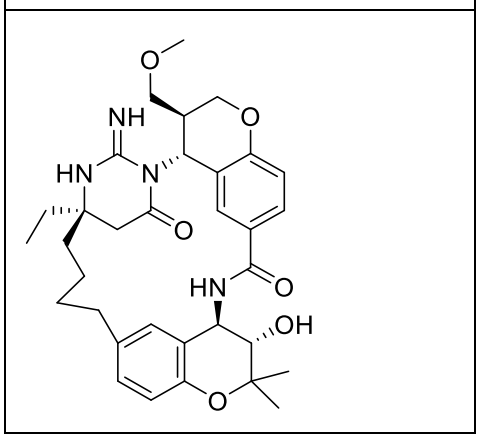


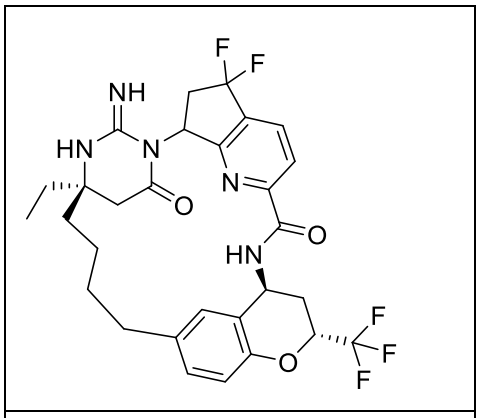


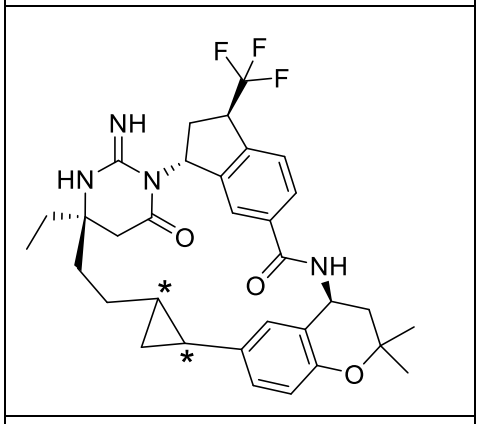


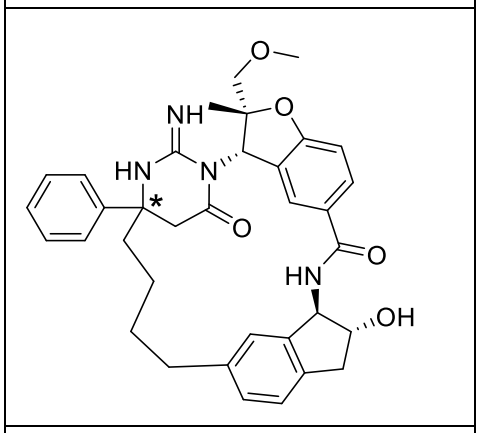


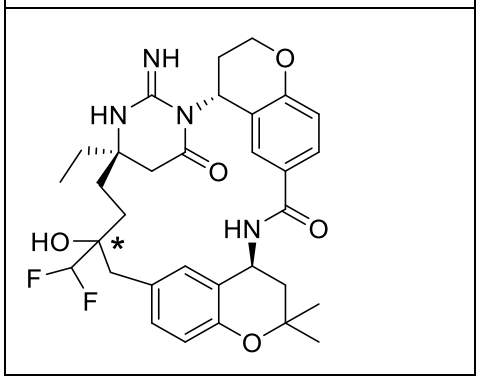


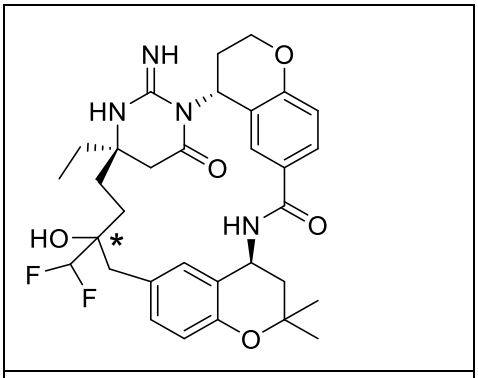





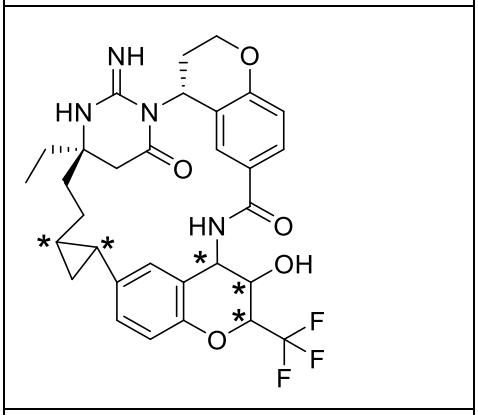


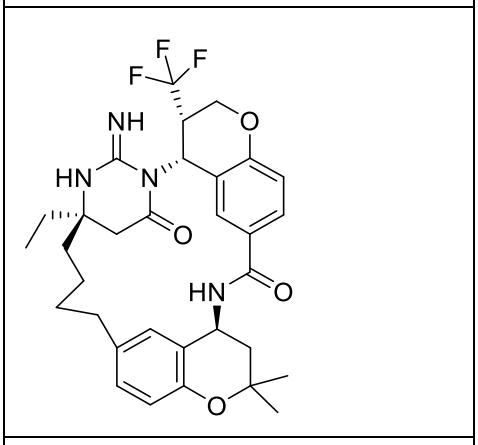


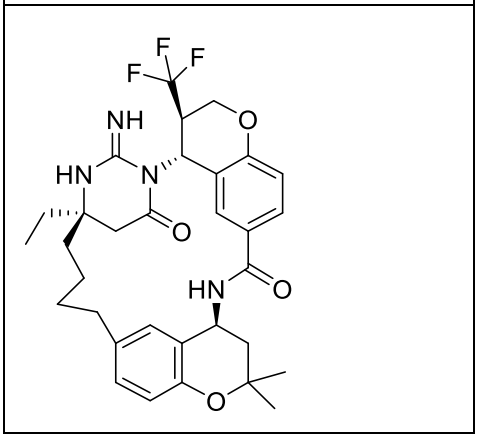


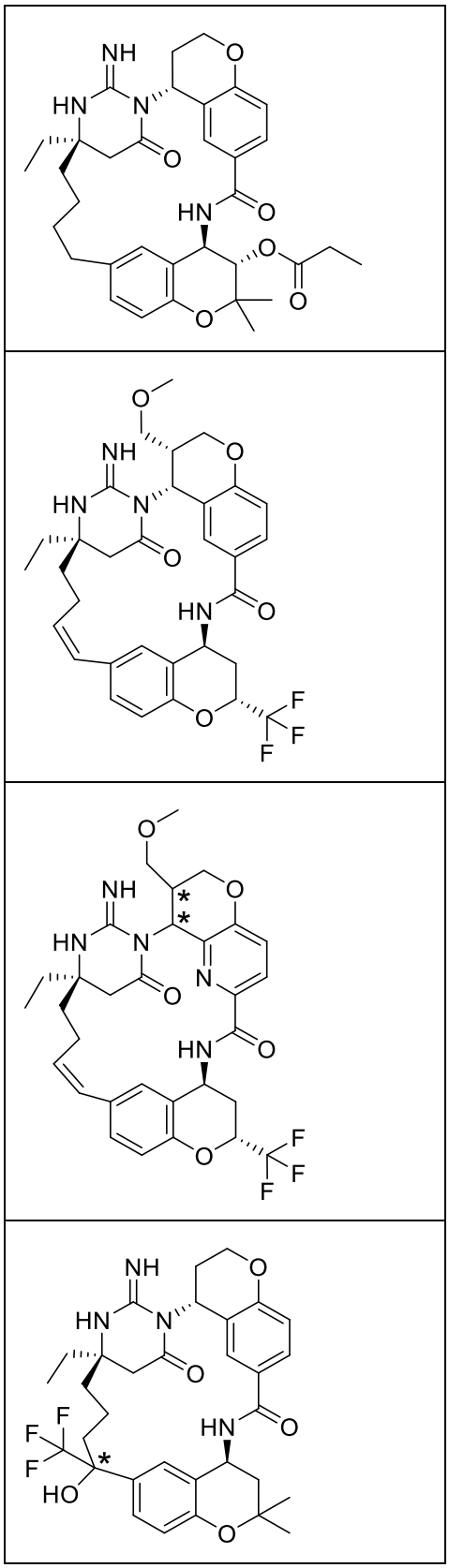


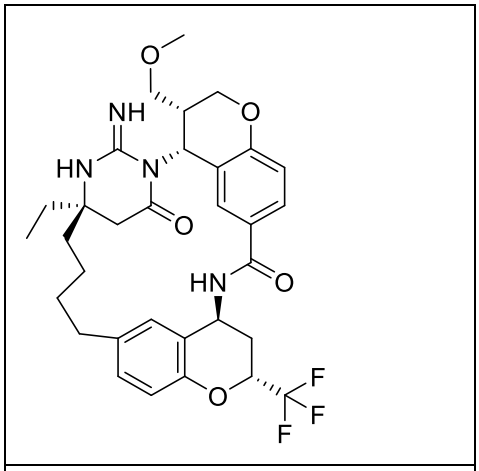
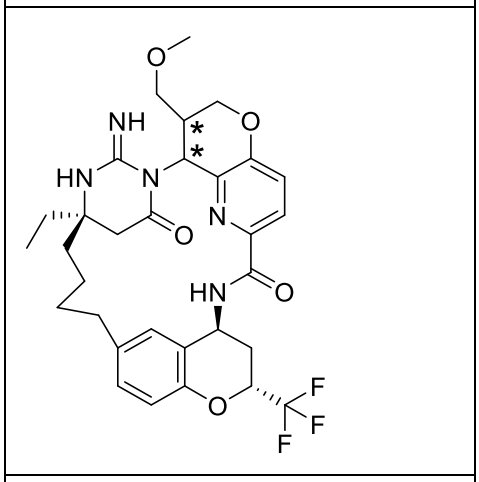
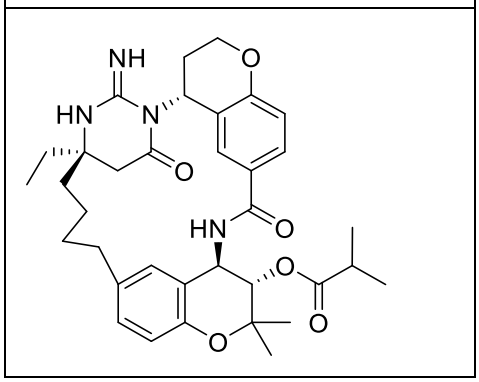






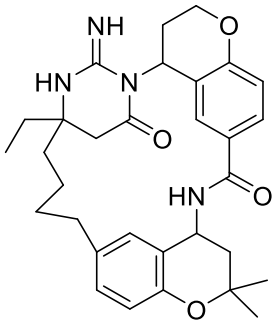




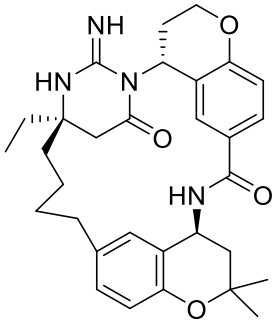
, or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure is directed to a compound having the formula



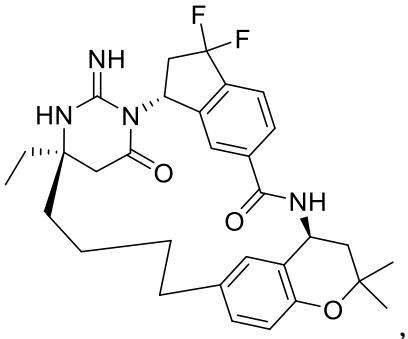
, or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure is directed to a compound having the formula



, or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure is directed to a compound having the formula:



, or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure is directed to a pharmaceutical composition comprising a compound as defined herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In another aspect, the present disclosure is directed to a pharmaceutical composition comprising a compound as defined herein and a pharmaceutically acceptable carrier.

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

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

In another aspect, the present disclosure is directed to use of a compound, or pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for treating a Plasmodium infection, or malaria.

In another aspect, the present disclosure is directed to 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, the present disclosure is directed to .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, the present disclosure is directed to use of a compound, or pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for inhibiting plasmepsin IX and plasmepsin X.

In another aspect, the present disclosure is directed to a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in therapy.

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.

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.

In another aspect, the present disclosure is directed to use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a *Plasmodium* infection, or for treating malaria, wherein the medicament is to be administered with one or more additional anti-malarial agents.

In another aspect, the present disclosure is directed to use of of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treatmenting malaria by inhibition of plasmepsin X, IX and at least one other mechanism, wherein the medicament is to be administered with 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, the present disclosure is directed to a compound as defined herein, or a pharmaceutically acceptable salt thereof, and one or more additional anti-malarial agents for use in therapy.

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.

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.

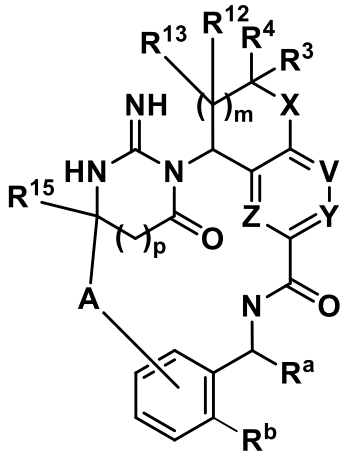
These and other examples of the disclosure, which are described in detail below or will become clear to those of ordinary skill in the art, are included within the scope of the disclosure.

DETAILED DESCRIPTION OF THE INVENTION

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

WHAT IS CLAIMED:

1. A compound having the structural Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

A is a straight or branched, saturated or unsaturated (C_3-C_{10})alkylene, phenyl(C_3-C_{10})alkylene or cycloalkyl(C_3-C_{10})alkylene comprising at least one –CH_2- group, wherein one or more additional –CH_2- groups in A are optionally and independently replaced with a moiety selected from the group consisting of O, S, NR, CONR, NRCO, SO_2, and SO_2NR and wherein one or more of the hydrogens along A can be replaced with a group independently selected from hydroxyl, halogen and C_{1-3} haloalkyl;

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 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^a is hydrogen, 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_6alkylCOOC_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, 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) or C_1-C_6alkylN(R^7)(R^8) or when taken with R^b forms a C_3-C_6cycloalkyl or heterocycloalkyl, wherein the C_3-C_6cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or two substituents 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_6alkylCOOC_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, C_1-C_6alkyl, -C_1-

C_6alkyl$O$haloC_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^b is hydrogen, halogen, CN, OH, C_1-C_6alkoxy, C_1-C_6alkylOC_1-C_6alkyl, C_1-C_6alkyl$COOH$, $COOH$, oxo, $COOC_1$-C_6alkyl, C_1-C_6alkyl$COOC_1$-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, C_1-C_6alkyl, -C_1-C_6alkyl$O$haloC_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_6alkyl$N(R^7)(R^8)$ or when taken with R^a forms a C_3-C_6cycloalkyl or heterocycloalkyl, wherein the C_3-C_6cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or three substituents selected from the group consisting of halogen, CN, OH, C_1-C_6alkoxy, C_1-C_6alkylOC_1-C_6alkyl, C_1-C_6alkyl$COOH$, $COOH$, oxo, $COOC_1$-C_6alkyl, C_1-C_6alkyl$COOC_1$-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_6alkylC_3-C_6cycloalkyl, C_1-C_6alkyl, -C_1-C_6alkyl$O$haloC_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^3 is hydrogen, halogen, CN, OH, C_1-C_6alkoxy, C_1-C_6alkylOC_1-C_6alkyl, C_1-C_6alkyl$COOH$, $COOH$, 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_6alkyl$N(R^7)(R^8)$, C_1-C_6alkyl$(OCH_2CH_2)_nN(R^7)(R^8)$ or C_1-C_6alkyl$O$haloC_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_6alkyl$COOH$, $COOH$, 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_6alkyl$N(R^7)(R^8)$, C_1-C_6alkyl$(OCH_2CH_2)_nN(R^7)(R^8)$ or C_1-C_6alkyl$O$haloC_1-C_6alkyl or when taken with R^3 forms a C_3-C_6cycloalkyl or C_3-C_6heterocycloalkyl;

R^7 is hydrogen, C_1-C_6alkyl$COOH$, $COOH$, 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_6alkyl$COOH$, $COOH$, 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_6alkyl$COOH$, $COOH$, 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_6alkyl$N(R^7)(R^8)$;

R^{10} is hydrogen, halogen, CN, OH, C_1-C_6alkoxy, C_1-C_6alkylOC_1-C_6alkyl, C_1-C_6alkyl$COOH$, $COOH$, 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_6alkyl$N(R^7)(R^8)$;

R^{11} is hydrogen, halogen, CN, OH, C_1-C_6alkoxy, C_1-C_6alkylOC_1-C_6alkyl, C_1-C_6alkyl$COOH$, $COOH$, 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_6alkyl$N(R^7)(R^8)$;

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_6alkyl$N(R^7)(R^8)$;

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_6alkyl$N(R^7)(R^8)$;

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_6alkyl$N(R^7)(R^8)$;

R^{15} 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_6alkyl$N(R^7)(R^8)$;

each occurrence of R^{16} 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_6alkyl$N(R^7)(R^8)$;

m is 0 or 1;

n is 1, 2, 3 or 4; and

p is 0 or 1.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein m is 1, p is 1 and X is O.

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein m is 1, p is 1 and X is a bond.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^a is taken with R^b and forms a heterocycloalkyl.

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R^a is taken with R^b and forms a heterocycloalkyl, wherein the heterocycloalkyl is


, and wherein the heterocycloalkyl is substituted with two C_1-C_6alkyl groups.

6. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^a is taken with R^b and forms a C_3-C_6cycloalkyl.

7. The compound of any one of claims 1-3 or 6, or a pharmaceutically acceptable salt thereof, wherein R^a is taken with R^b and forms a C_3-C_6cycloalkyl, wherein the heterocycloalkyl is


, and wherein the C_3-C_6cycloalkyl is unsubstituted or substituted with OH.

8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen, C_1-C_6alkylOC_1-C_6alkyl or C_1-C_6alkyl or when taken with R^4 forms a C_3-C_6heterocycloalkyl.

9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen or C_1-C_6alkyl or when taken with R^4 forms a C_3-C_6heterocycloalkyl.

10. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 are both halogen.

11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R^{15} is hydrogen or C_1-C_6alkyl.

12. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 are independently selected from the group consisting of hydrogen, halogen, OH, C_1-C_6alkylOH, C_1-C_6alkylalkoxy, C_1-C_6alkylOC_1-C_6alkyl, C_1-C_6alkyl, C_1-C_6alkylOhaloC_1-C_6alkyl, $CON(C_1$-C_6alkyl$)_2$, C_1-C_6alkyl$N(R^7)(R^8)$ and C_1-C_6alkyl$(OCH_2CH_2)_nN(R^7)(R^8)$;

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; and
n is 3.

13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein R^{12} and R^{13} are independently selected from the group consisting of hydrogen, halogen, OH, C_1-C_6alkylOH, C_1-C_6alkylalkoxy and C_1-C_6alkylOC_1-C_6alkyl, C_1-C_6alkyl.

14. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein X is $C(R^{14})_2$, R^{14} is independently selected from the group consisting of hydrogen, halogen, OH, C_1-C_6alkylOH, C_1-C_6alkylalkoxy, C_1-C_6alkylOC_1-C_6alkyl and C_1-C_6alkyl.

15. The compound of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein Y is CH.

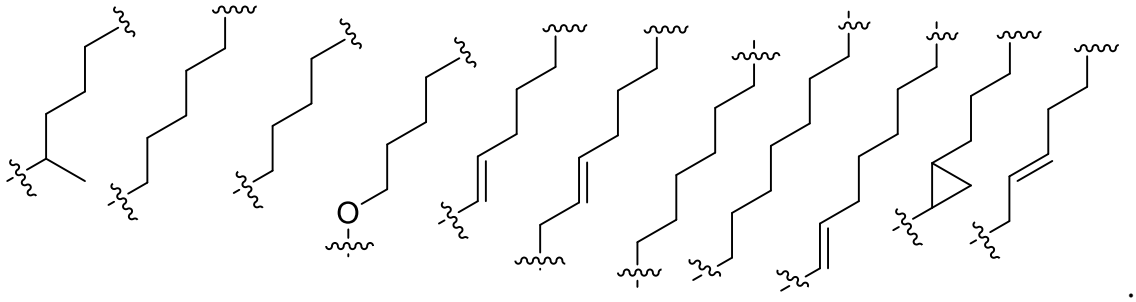
16. The compound of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein Z is CH.

17. The compound of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein V is CH.

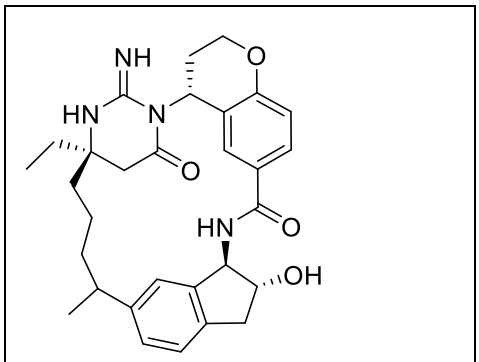
18. The compound of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein A is a straight, saturated or unsaturated (C_3-C_{10})alkylene.

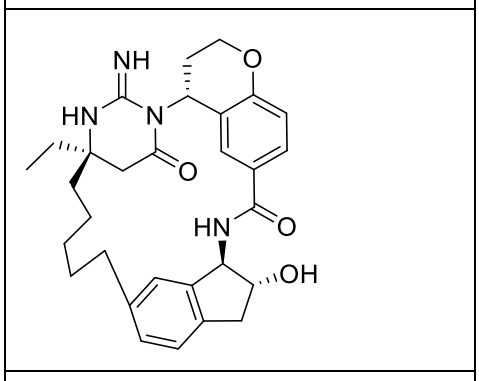
19. The compound of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein A is a branched, saturated or unsaturated (C_3-C_{10})alkylene.

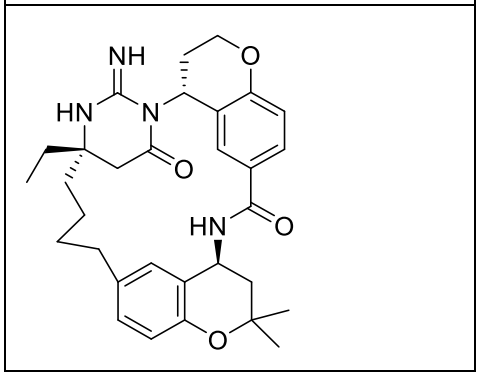
20. The compound of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein A is

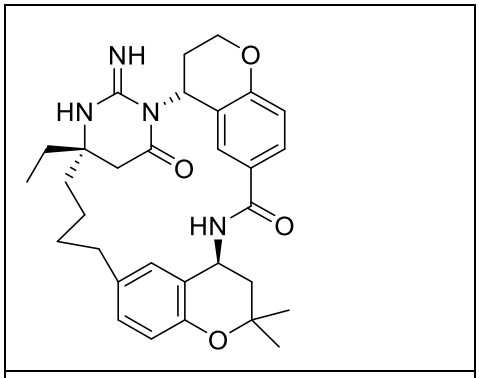
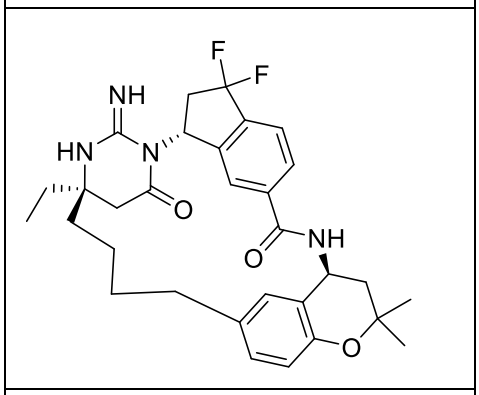
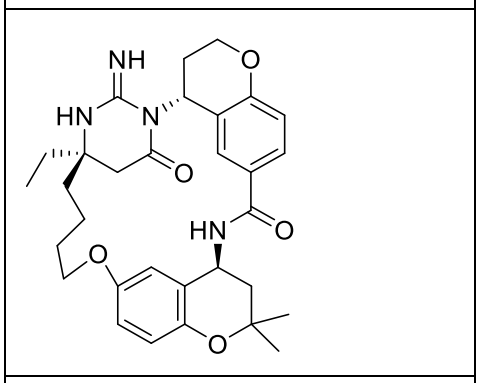
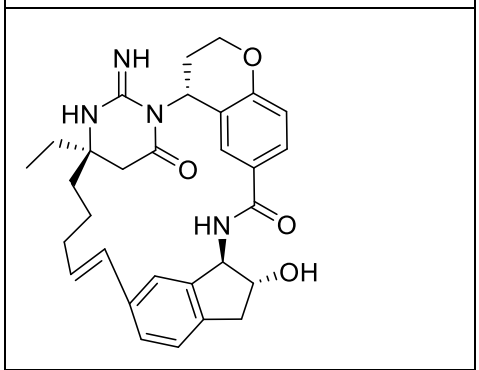
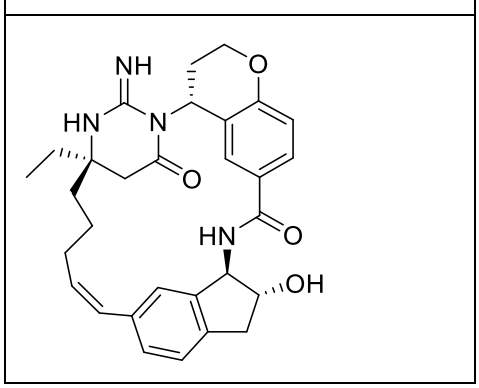


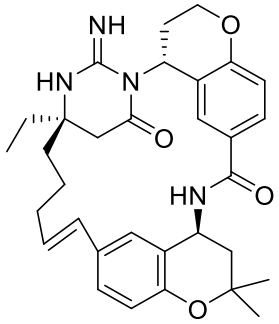
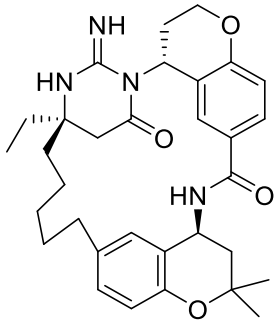
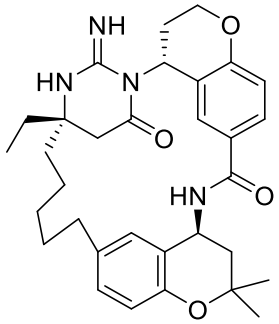
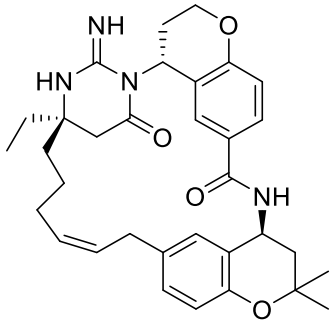
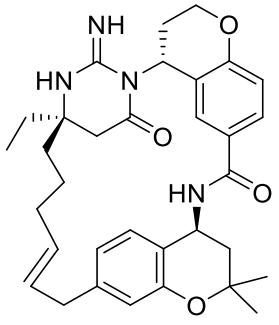
21. A compound selected from the group consisting of

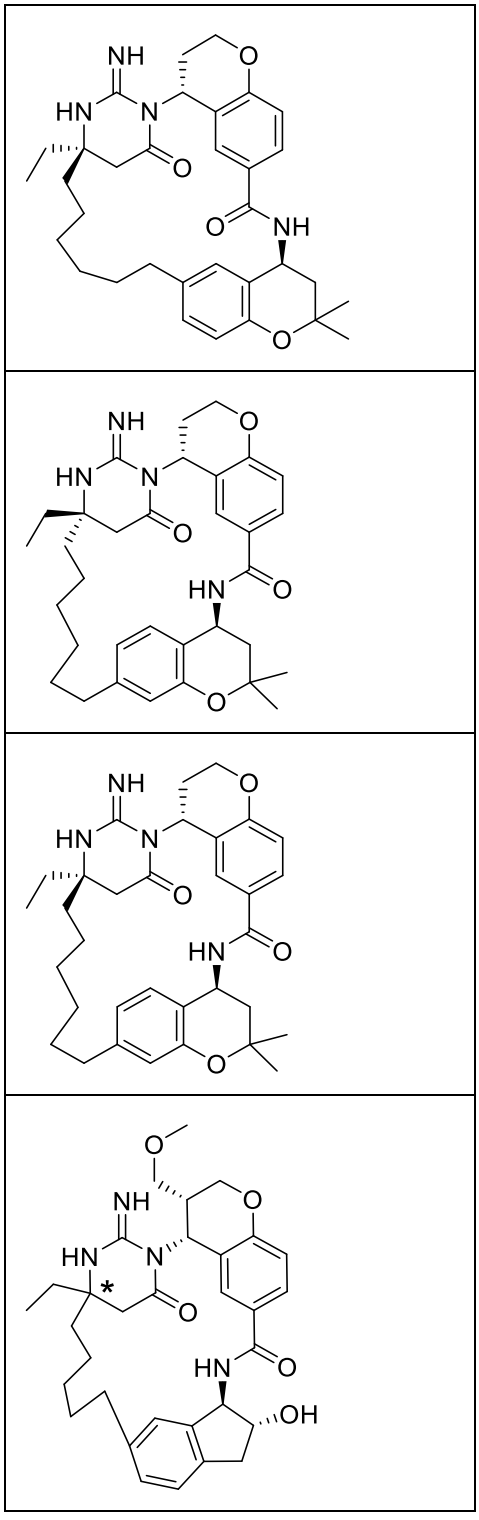


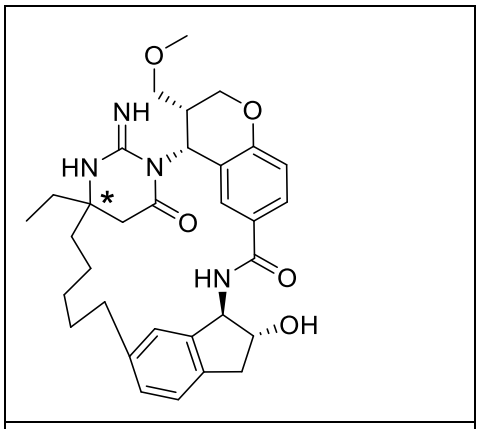
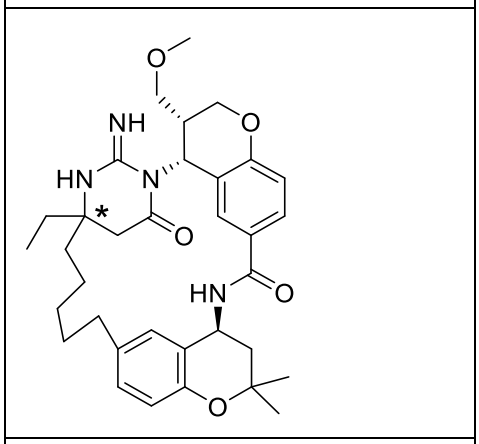
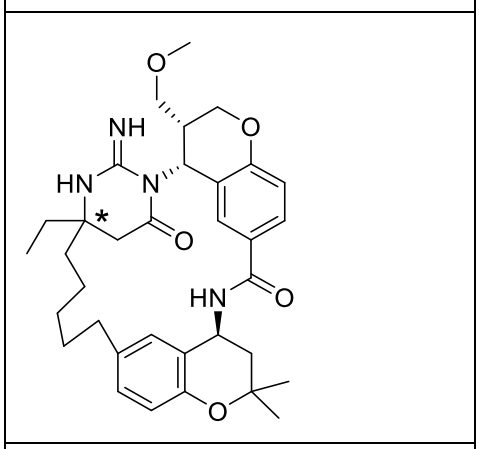
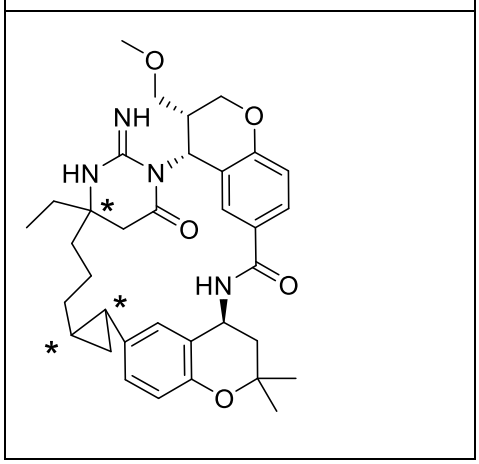


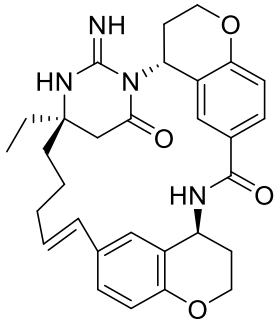
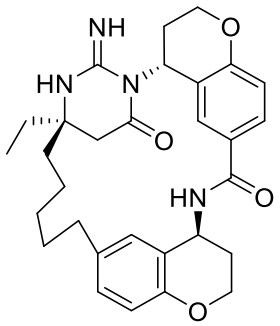
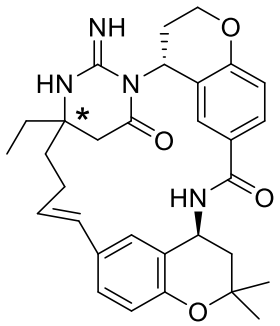
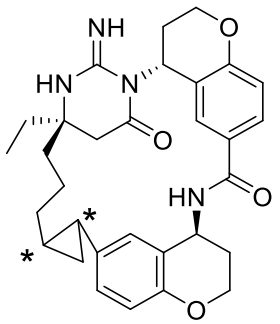
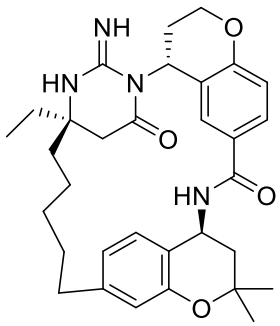


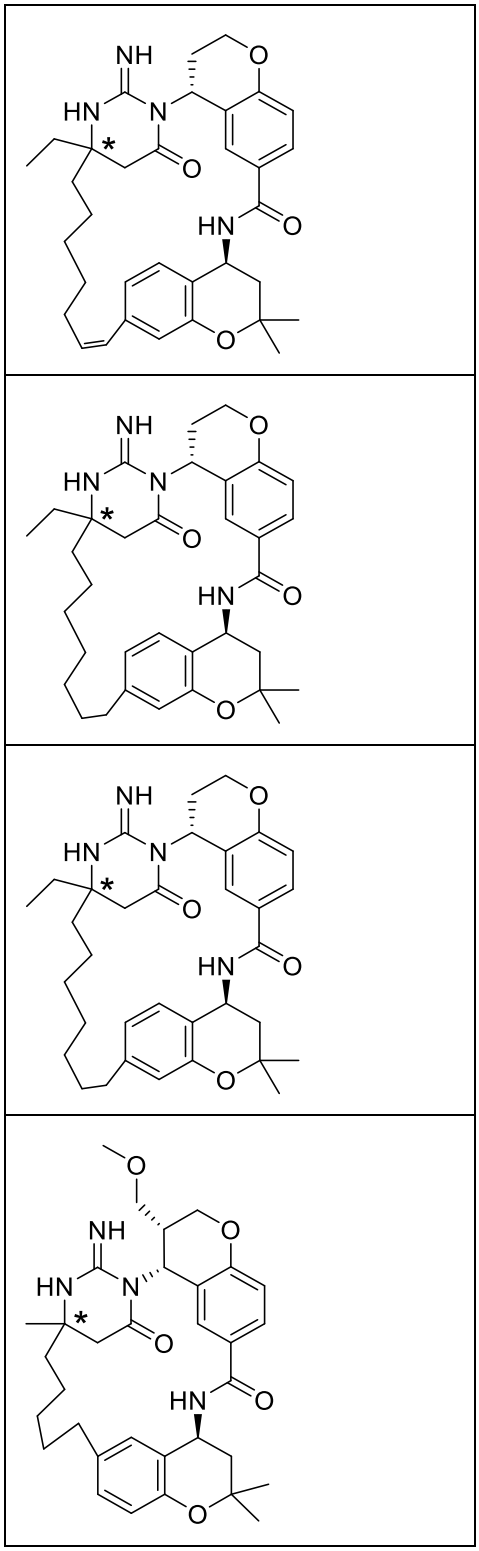






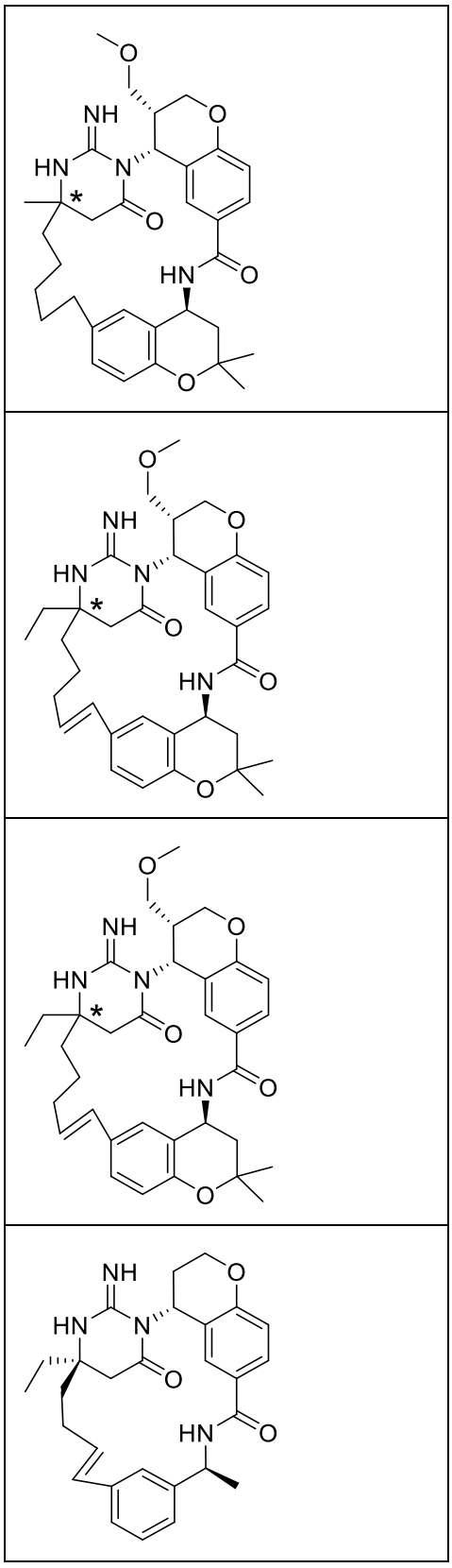






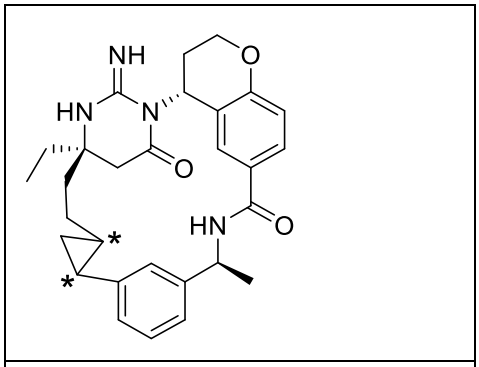
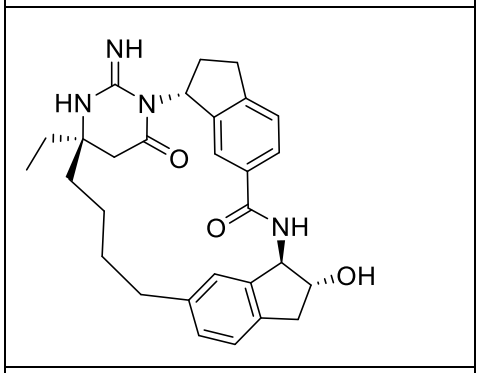
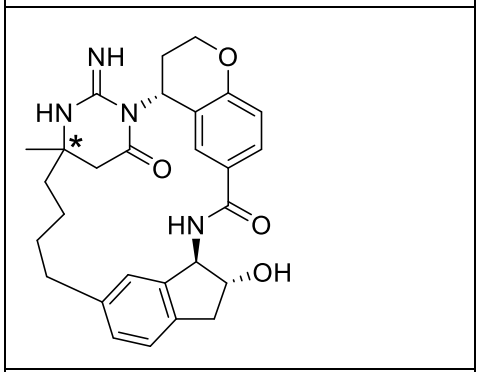
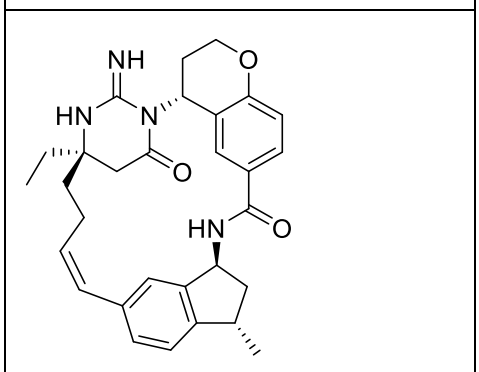
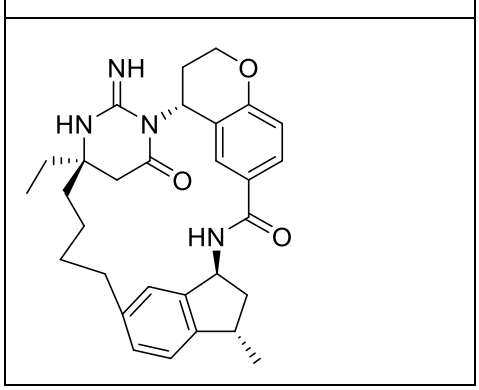


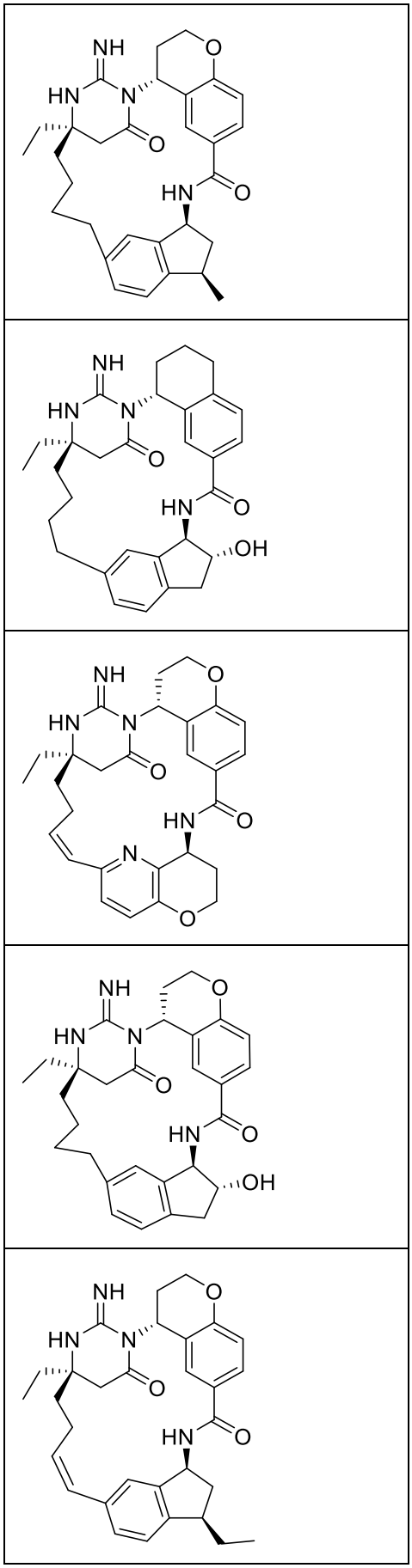





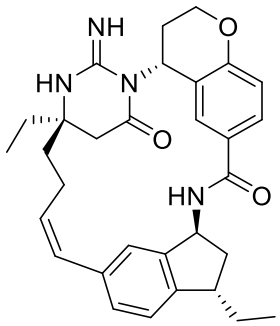
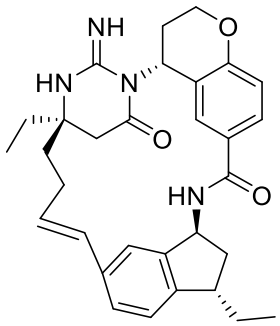
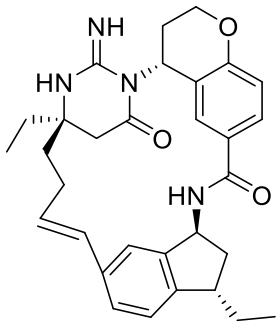
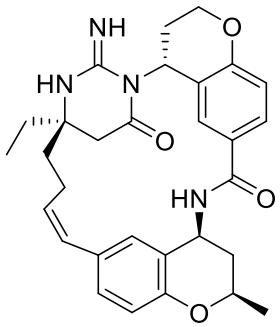
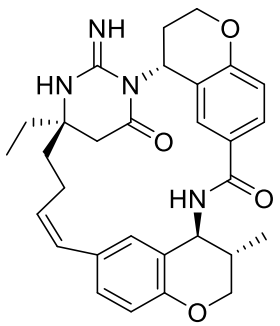






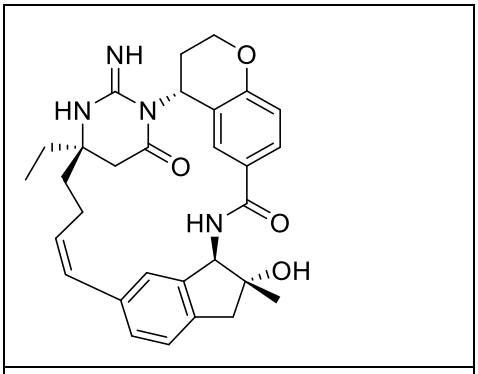
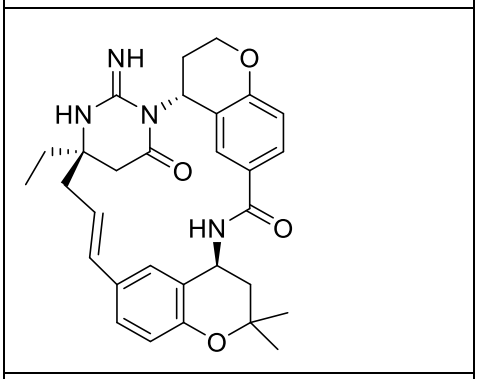
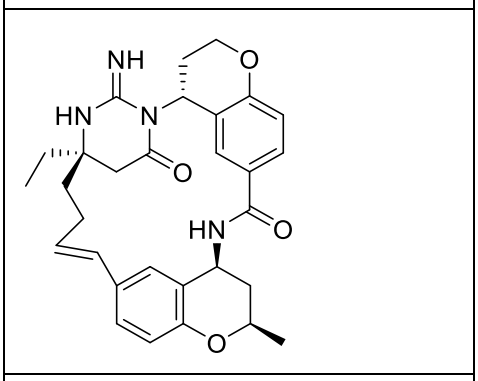
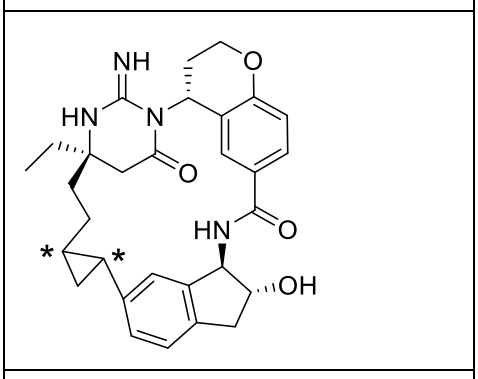
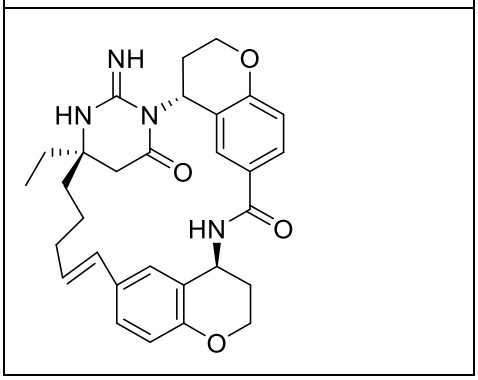


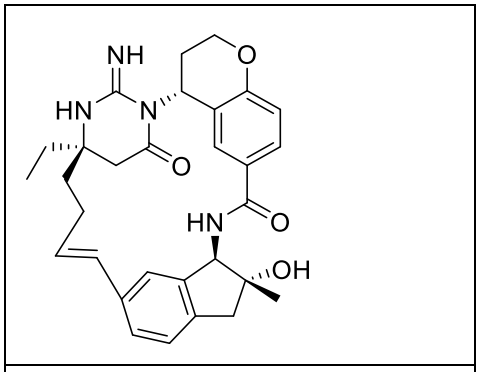
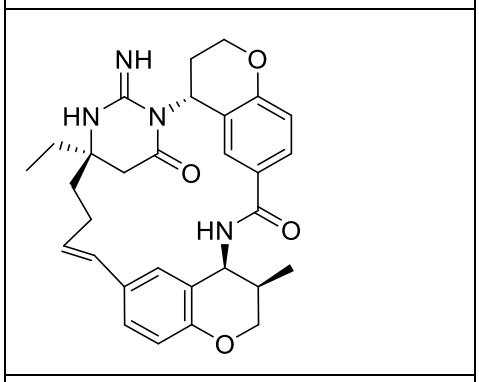
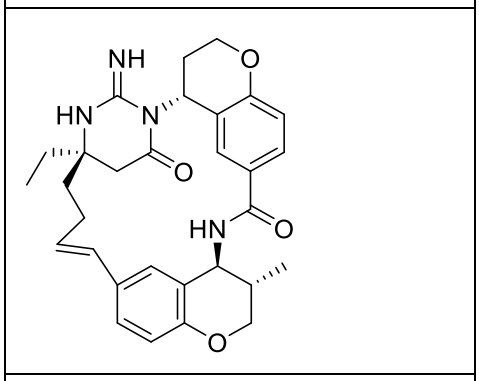
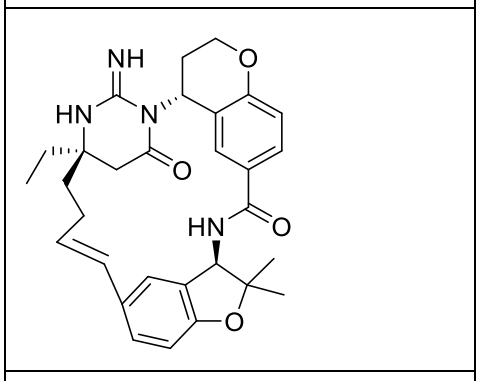
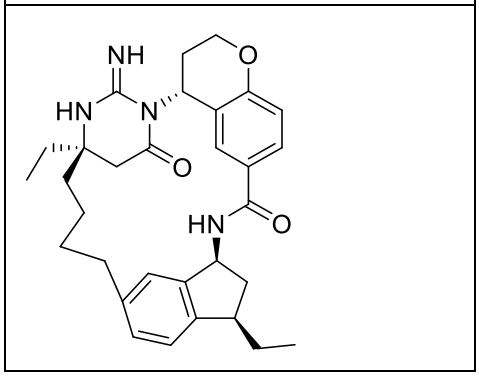


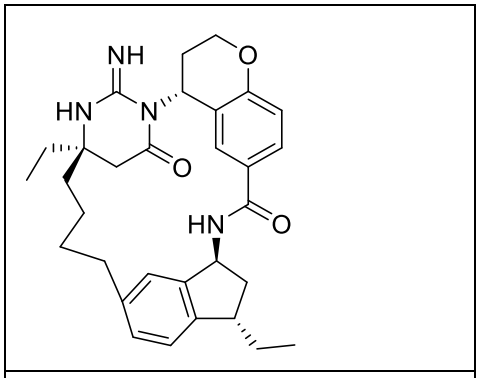
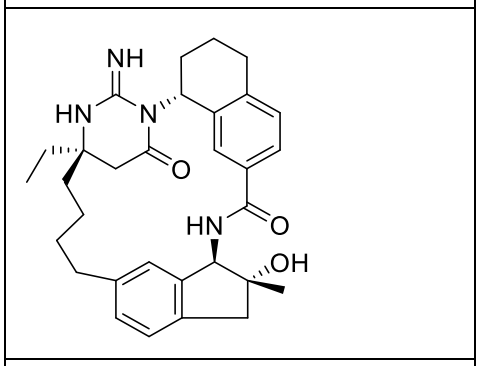
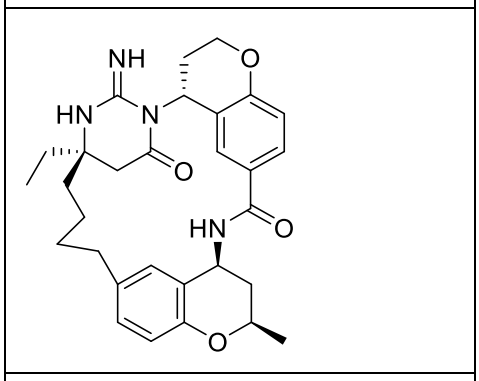
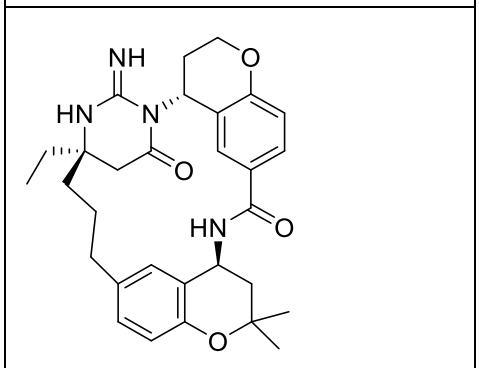
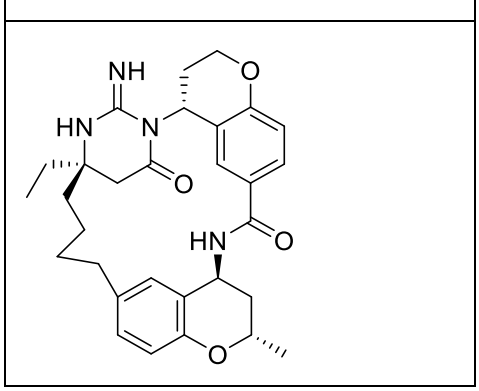






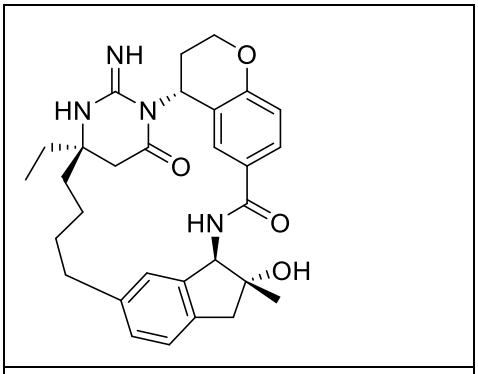
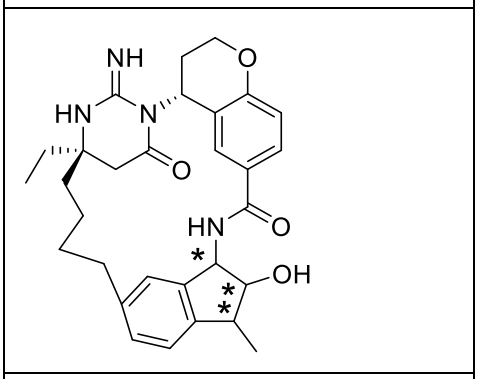
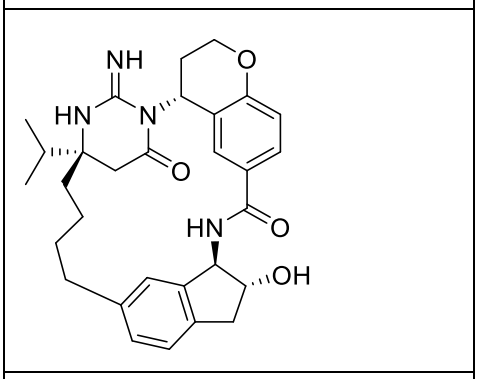
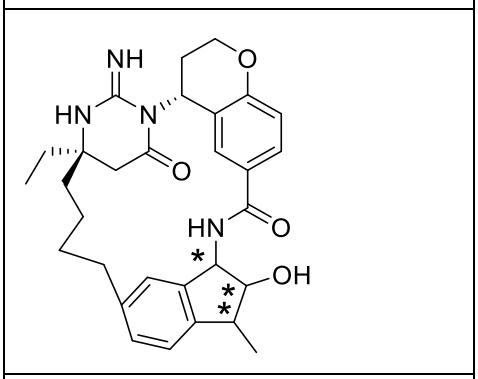
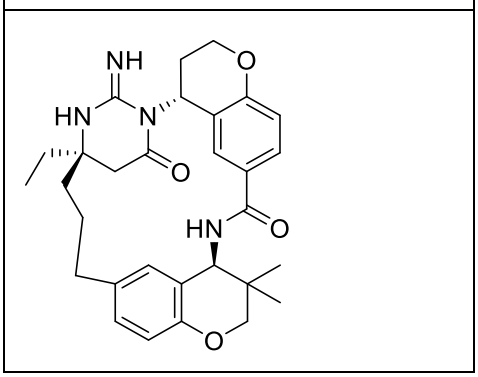


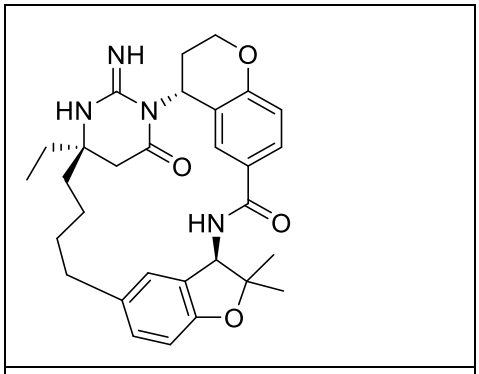
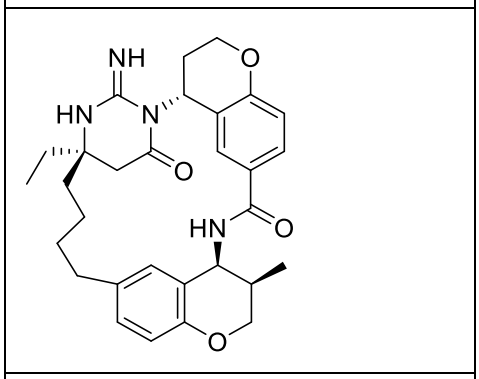
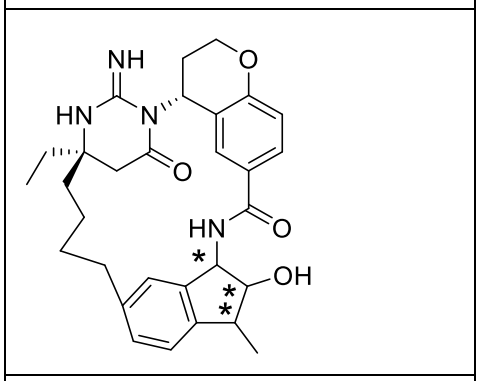
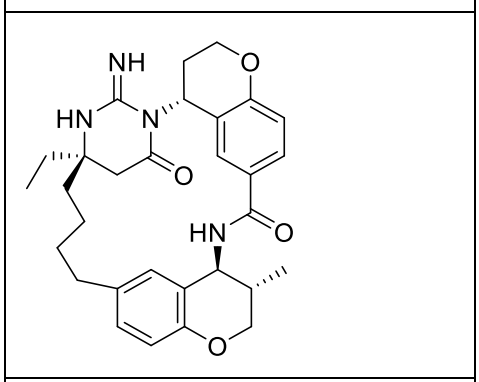
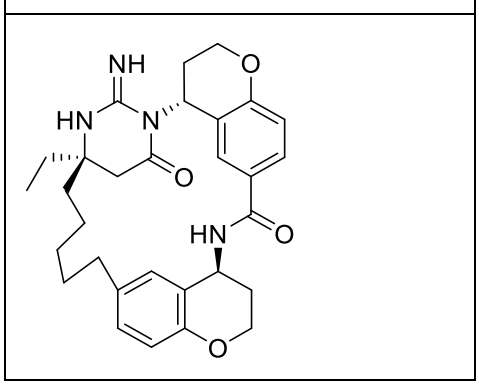






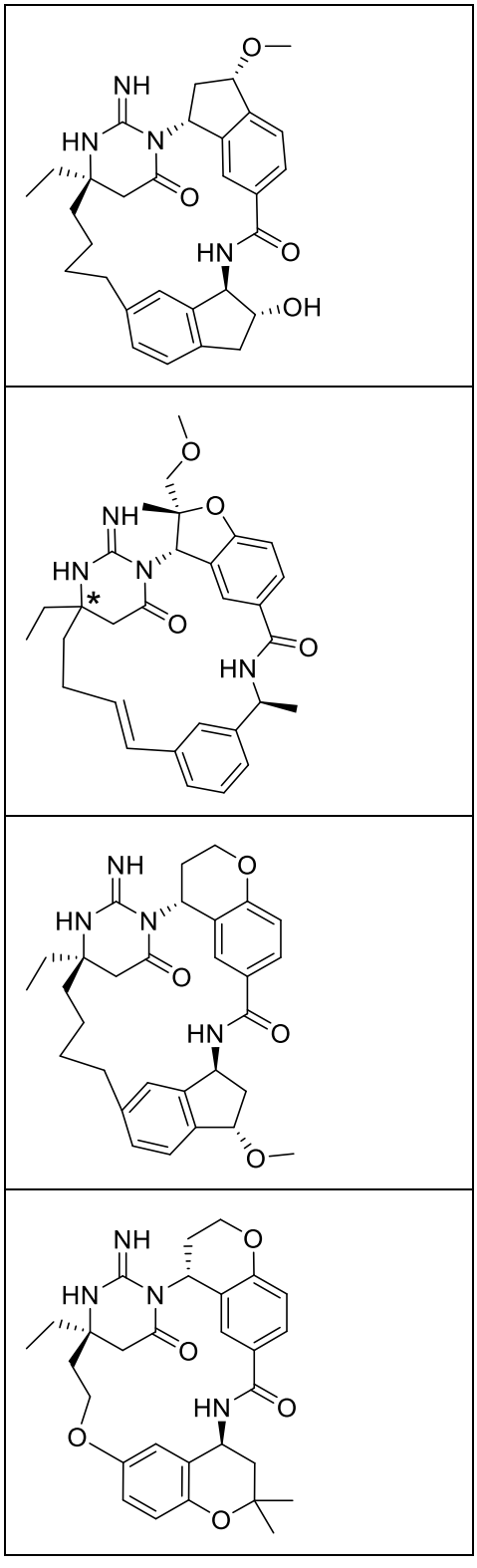






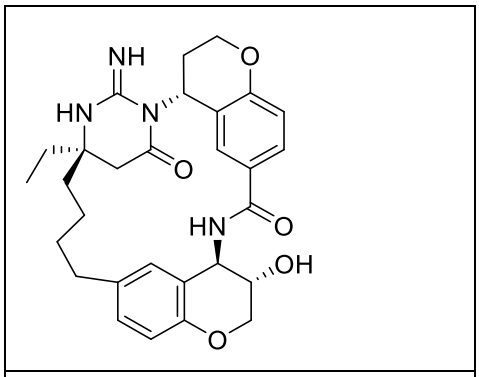
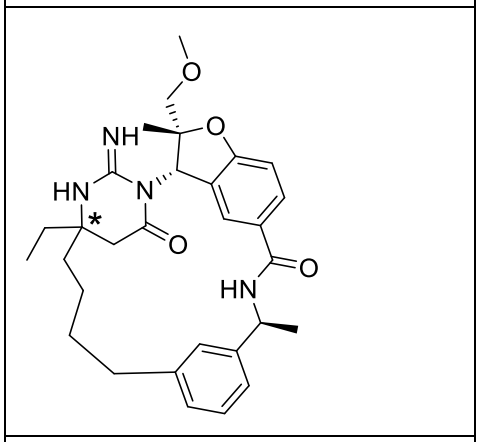
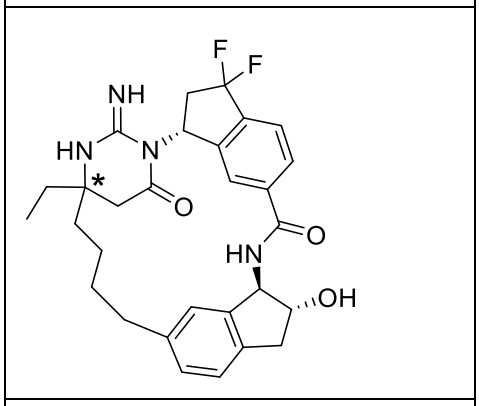
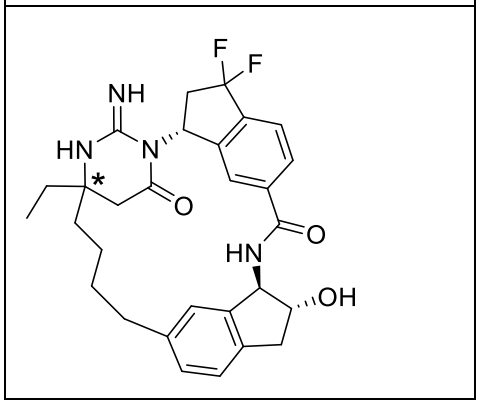






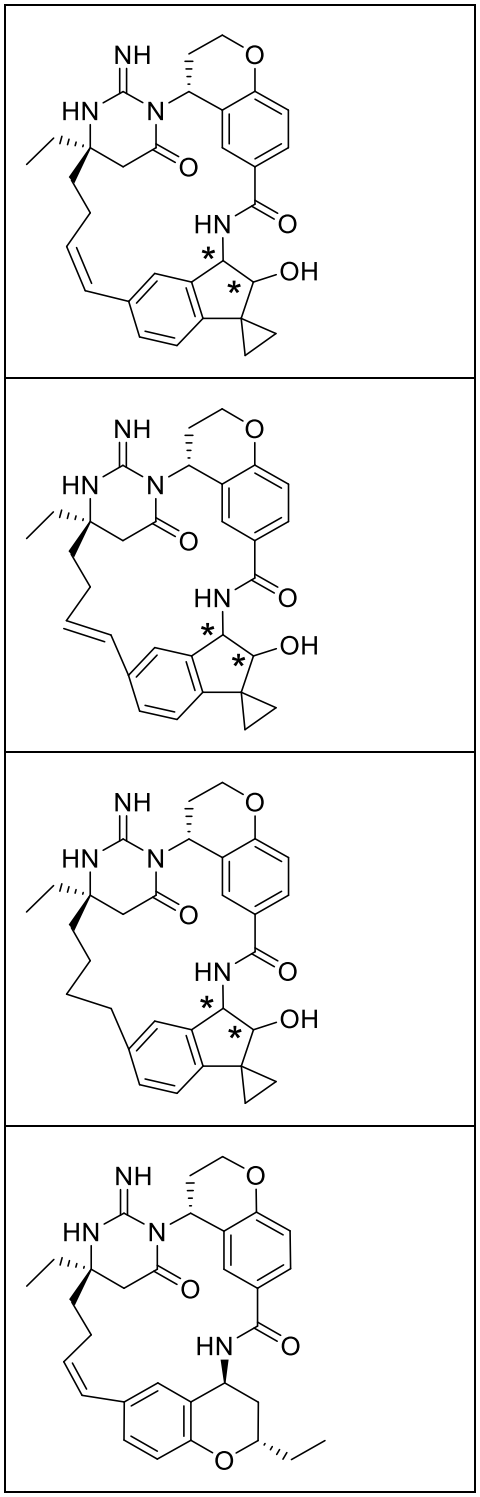






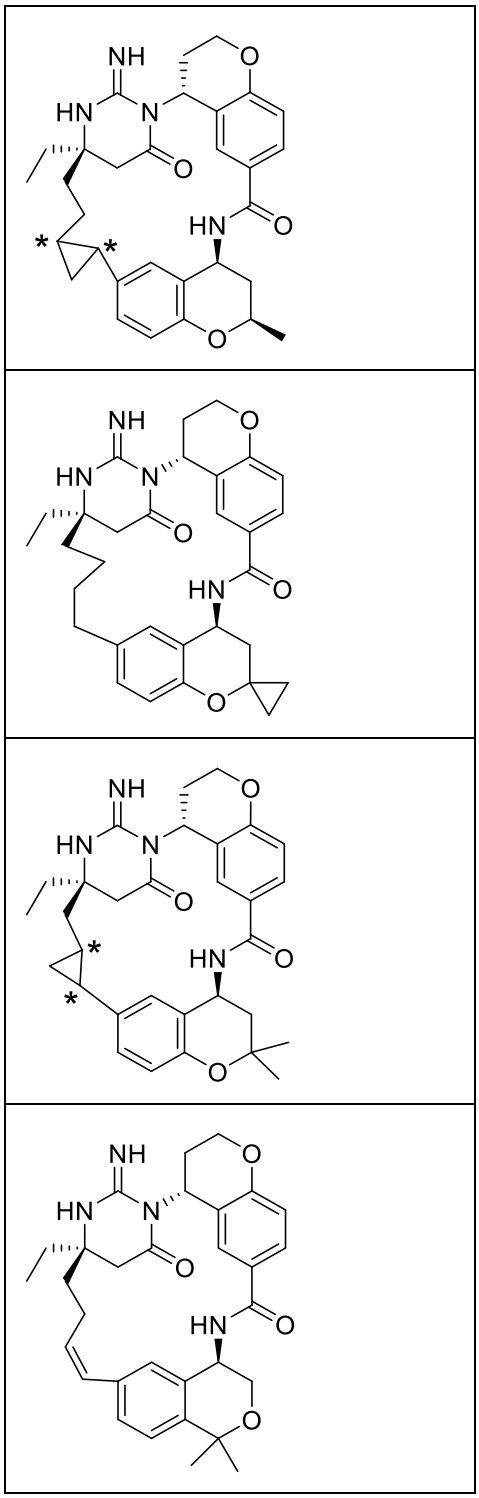






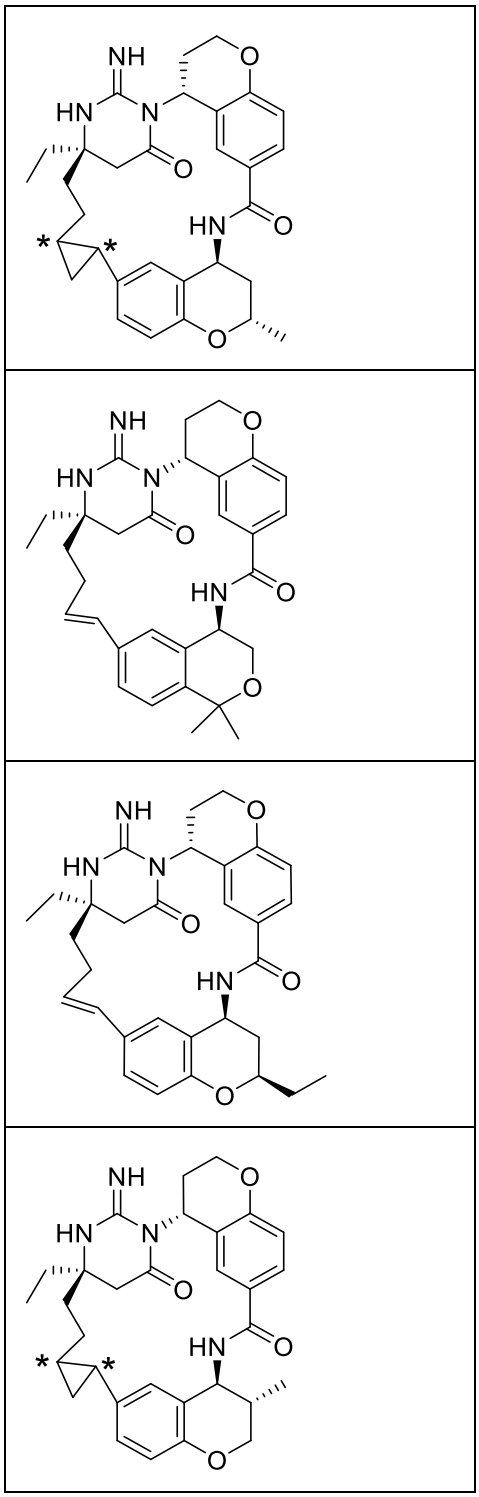






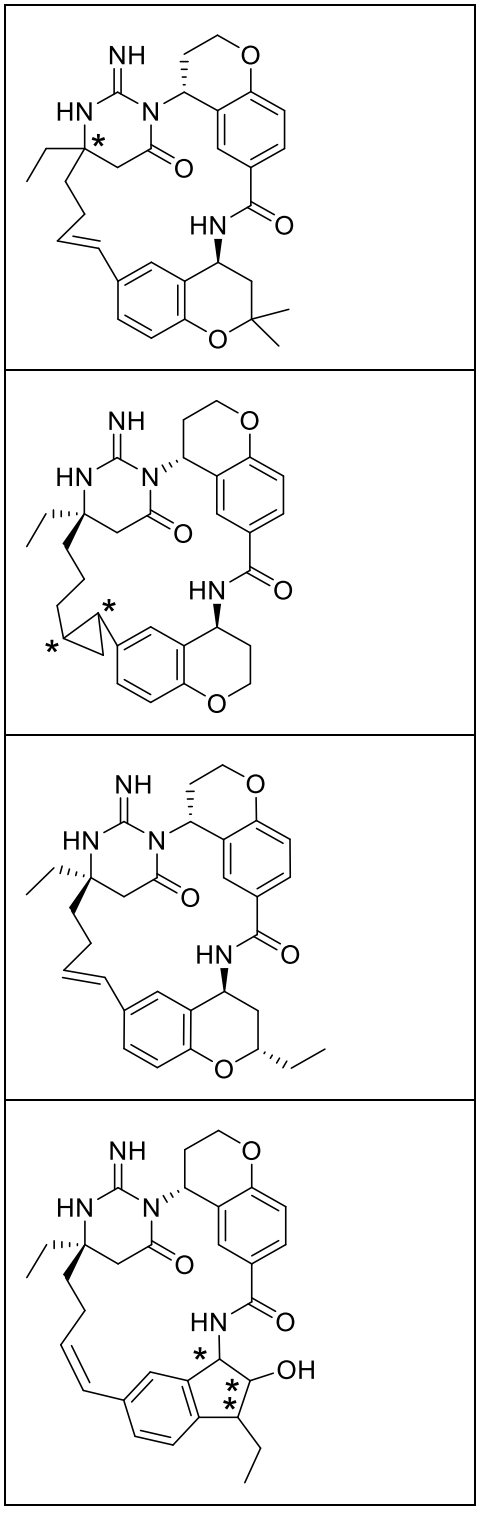


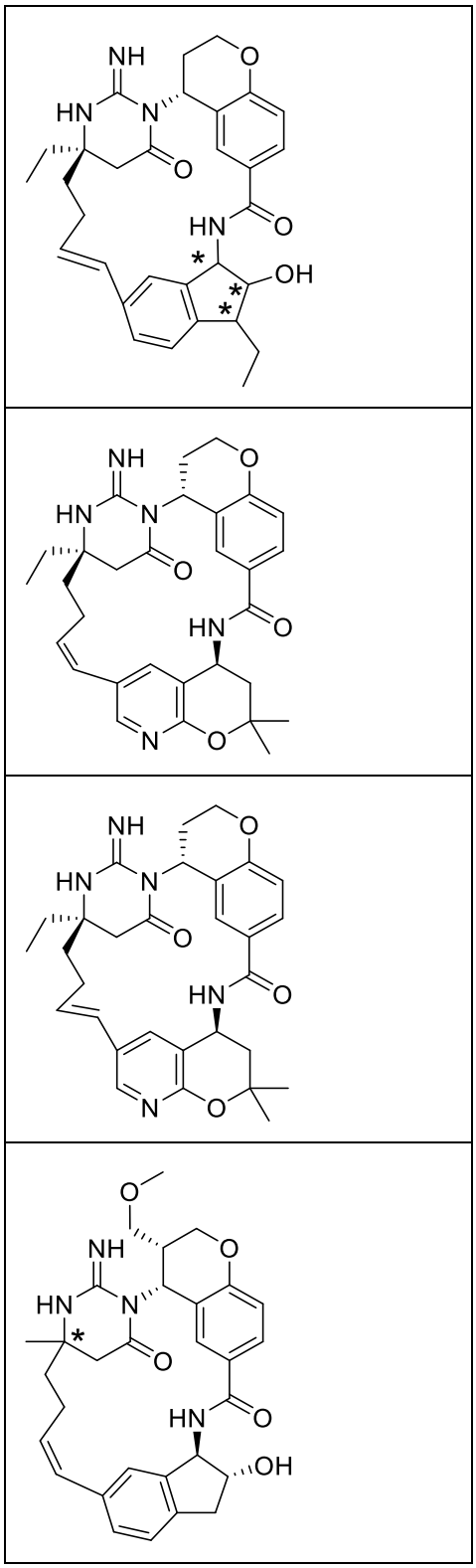





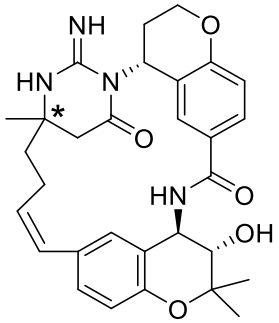
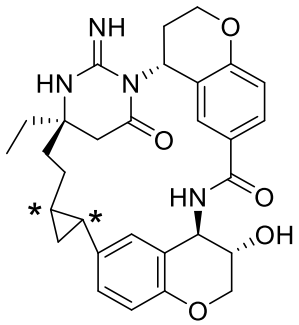
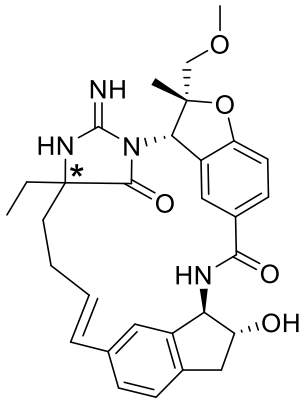
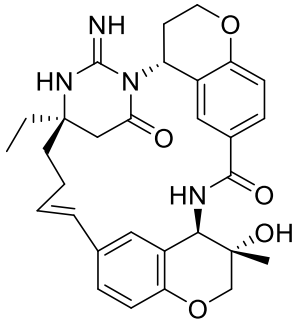


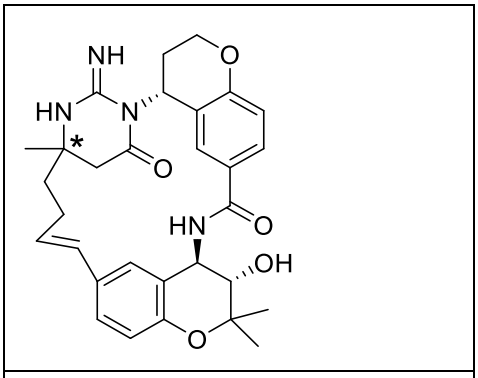
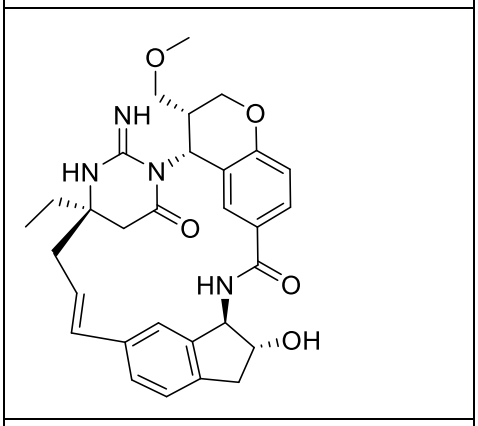
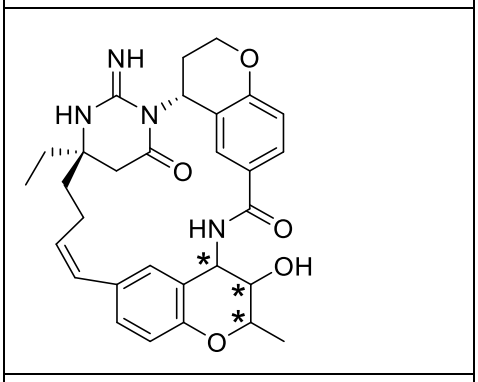
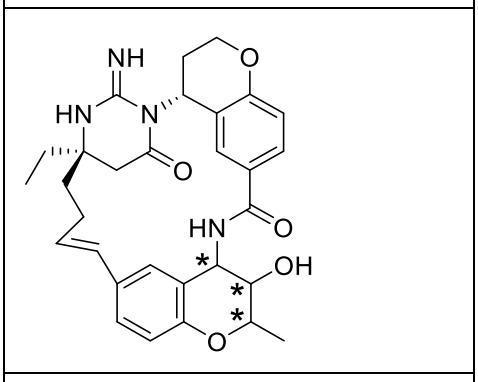
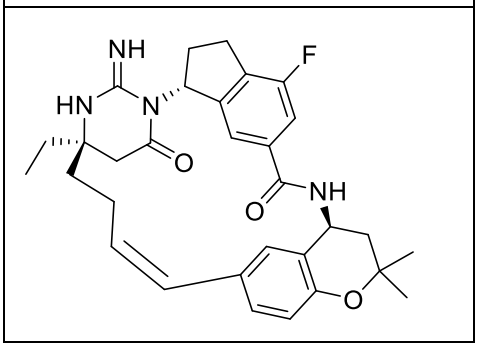


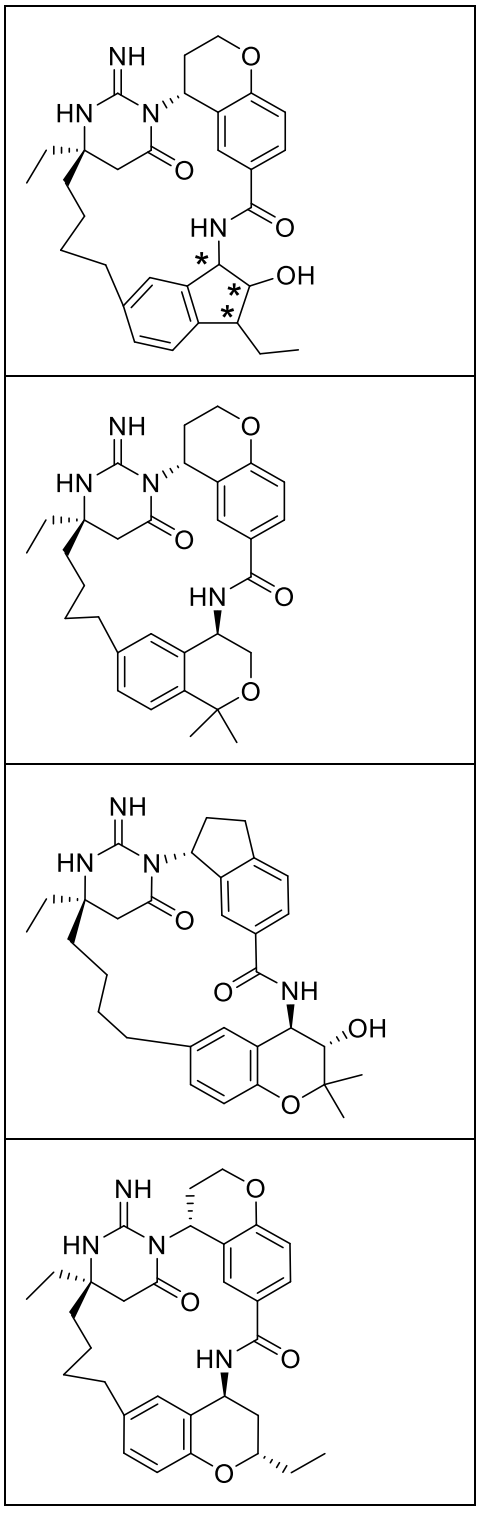


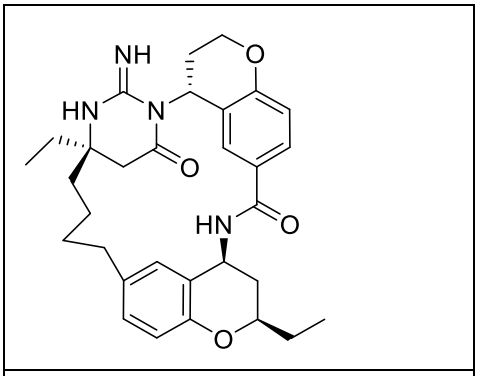


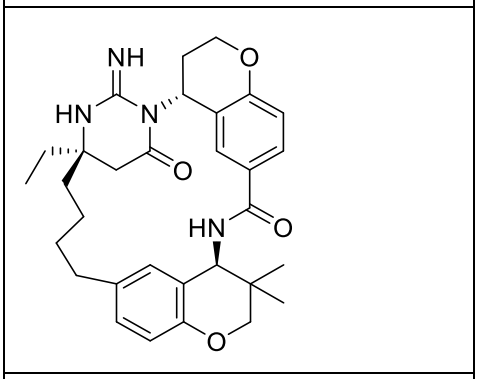


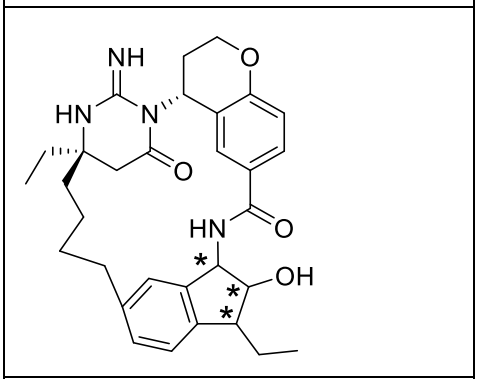





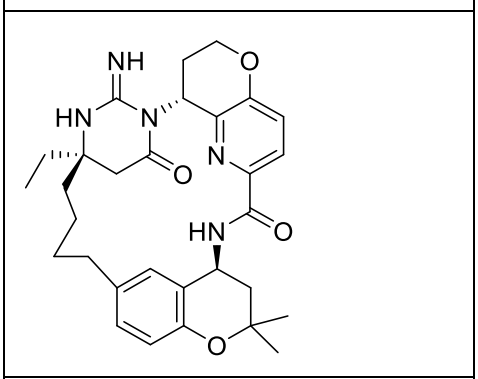






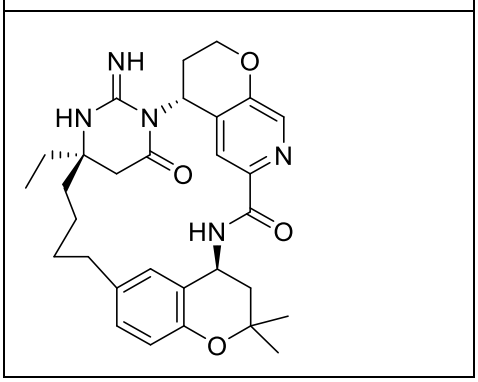


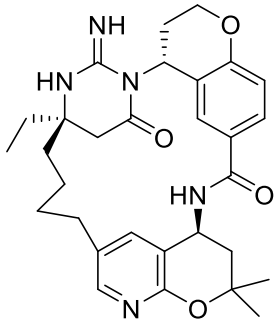
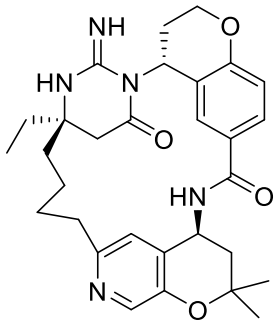
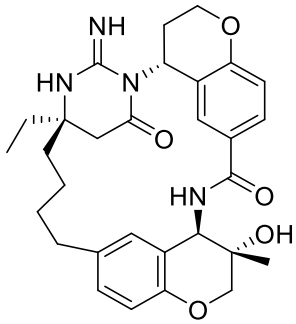
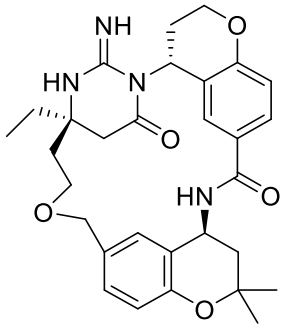
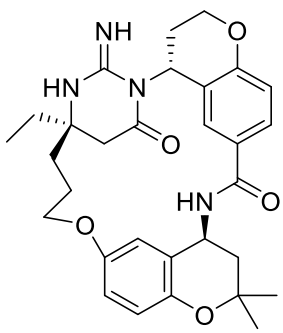

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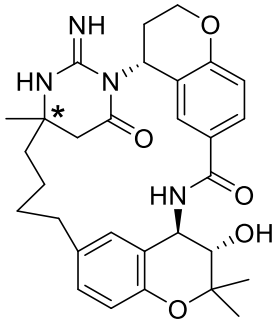
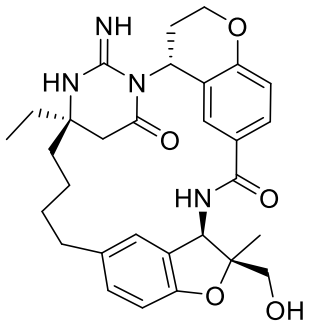
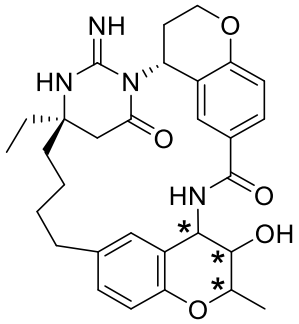
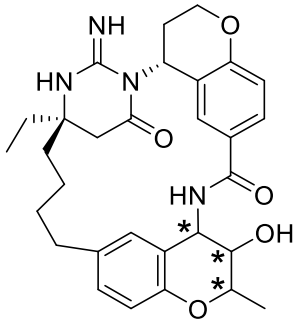
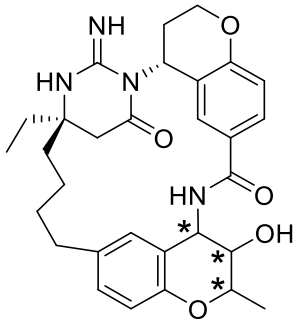

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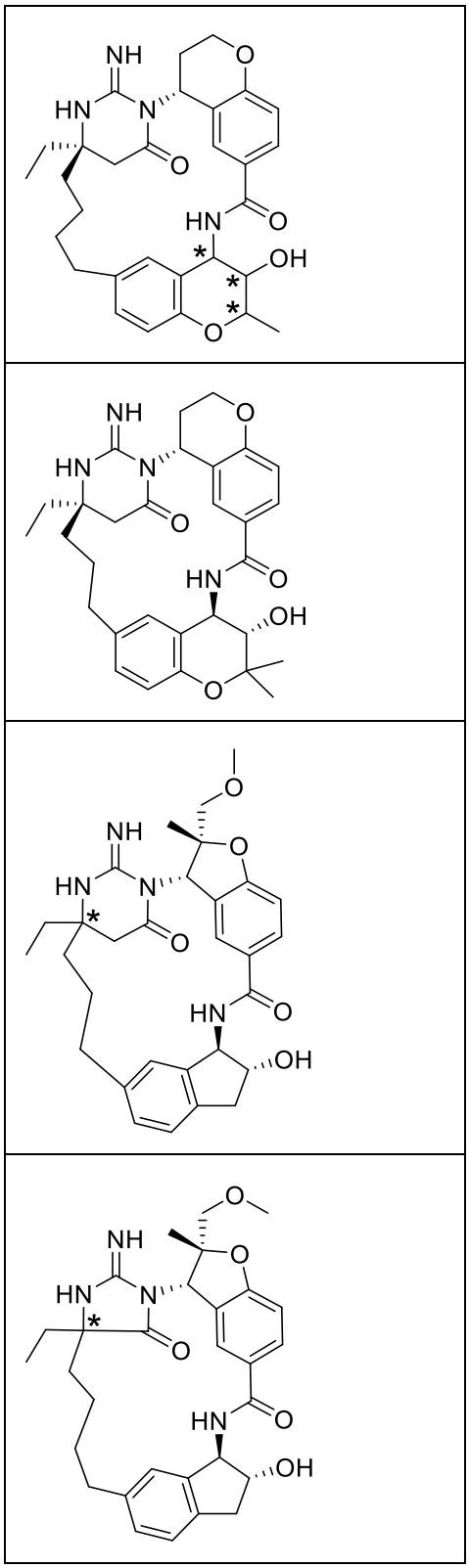

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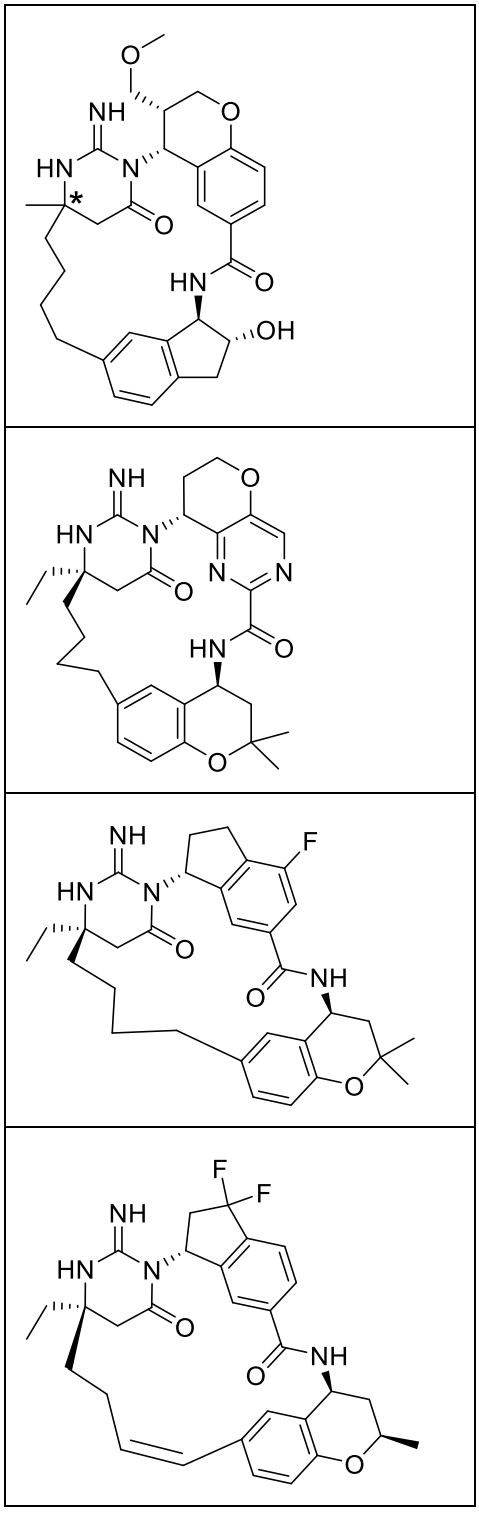

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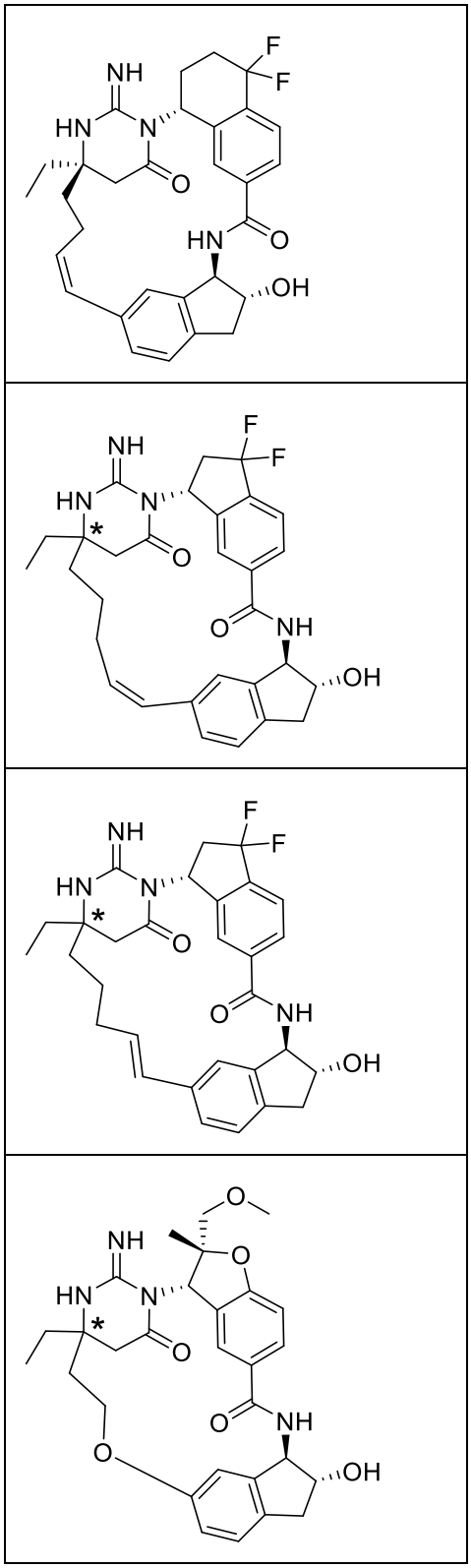

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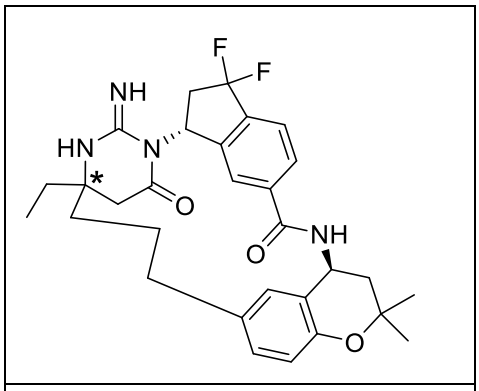
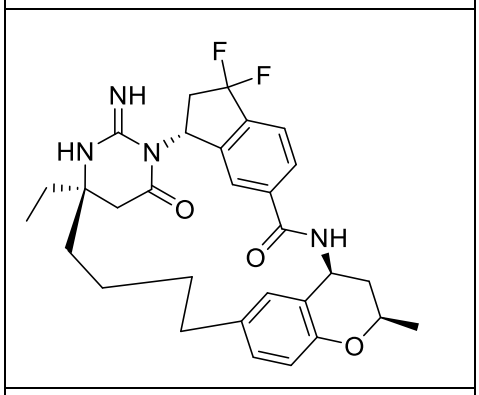
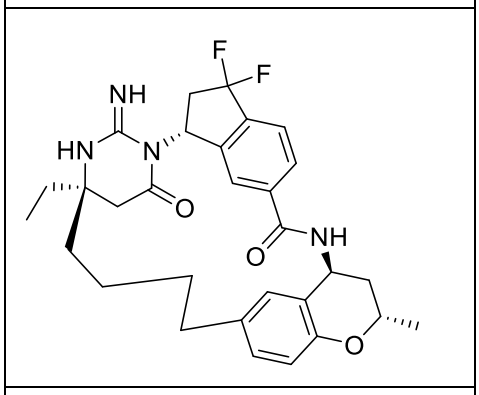
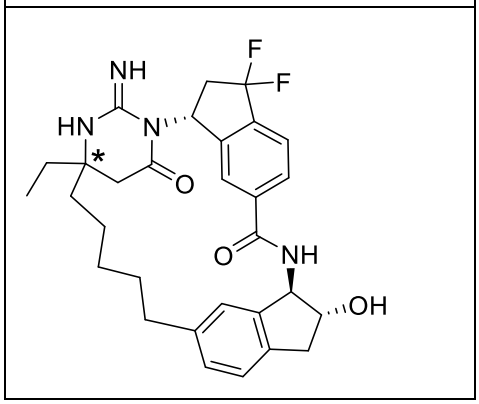






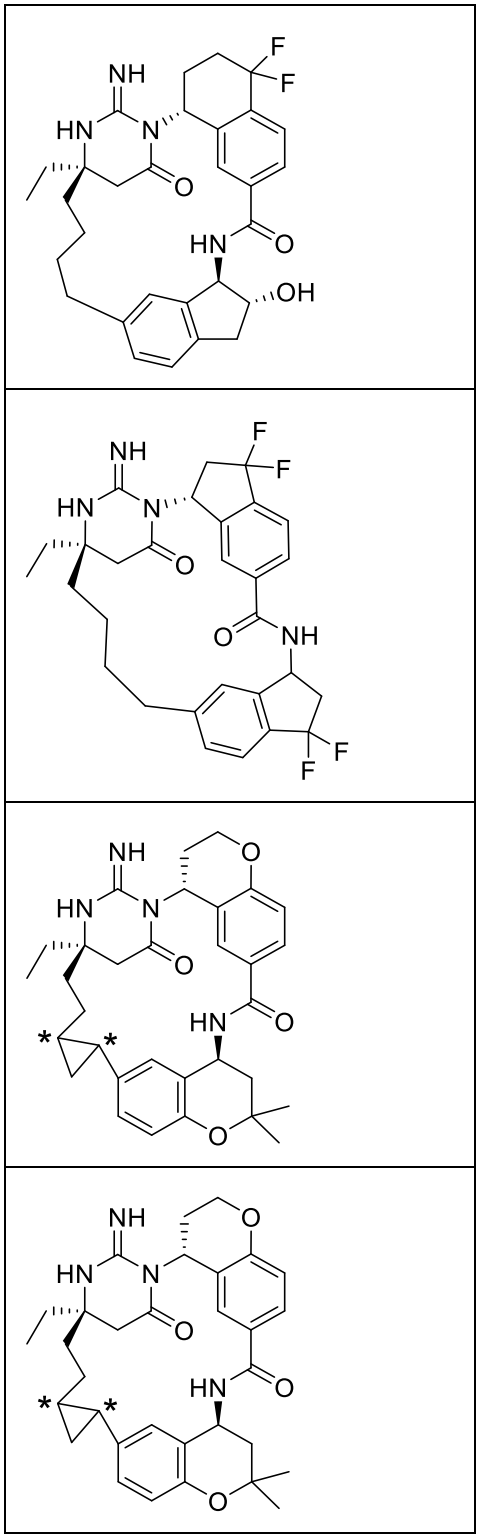






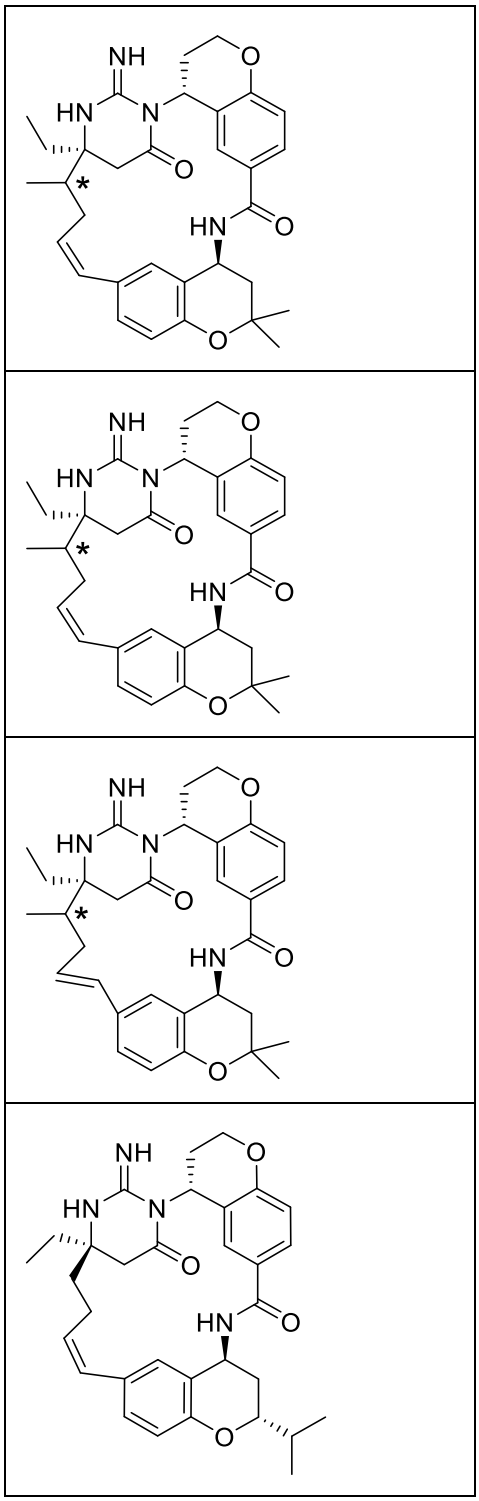


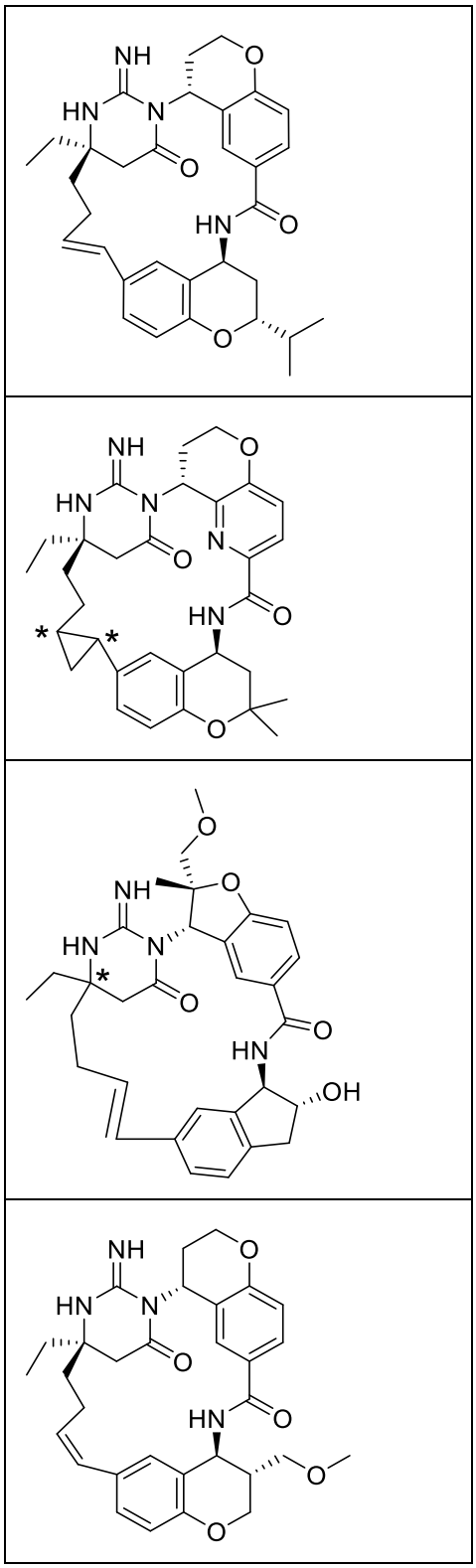


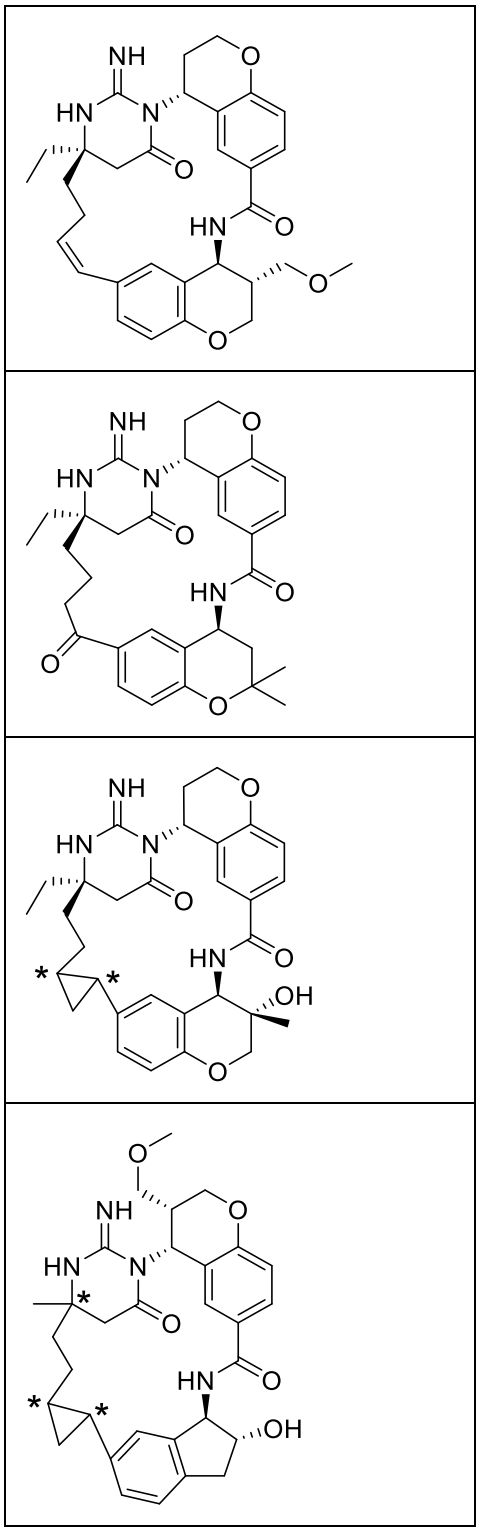


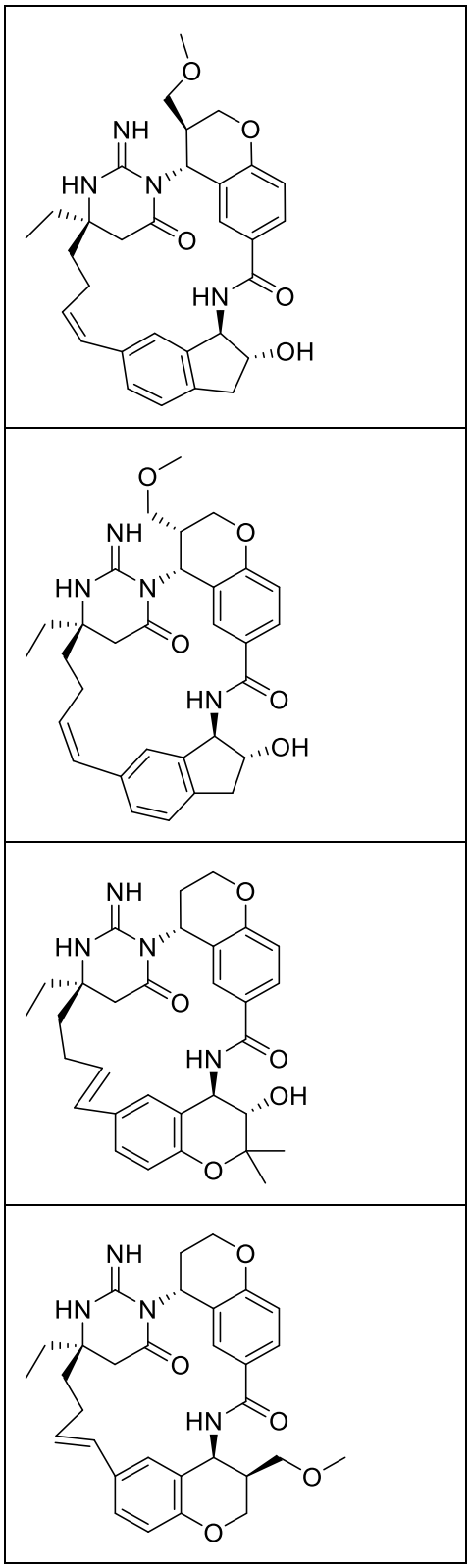





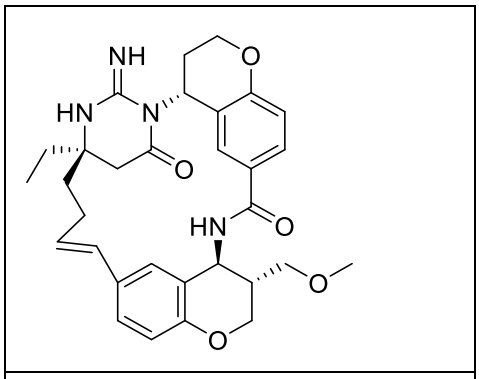
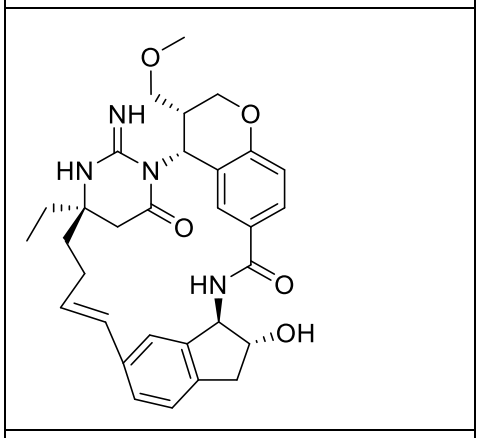
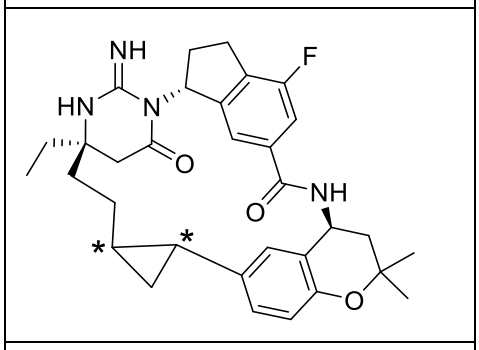
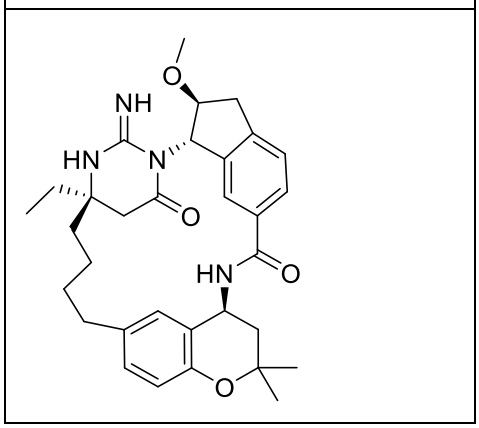

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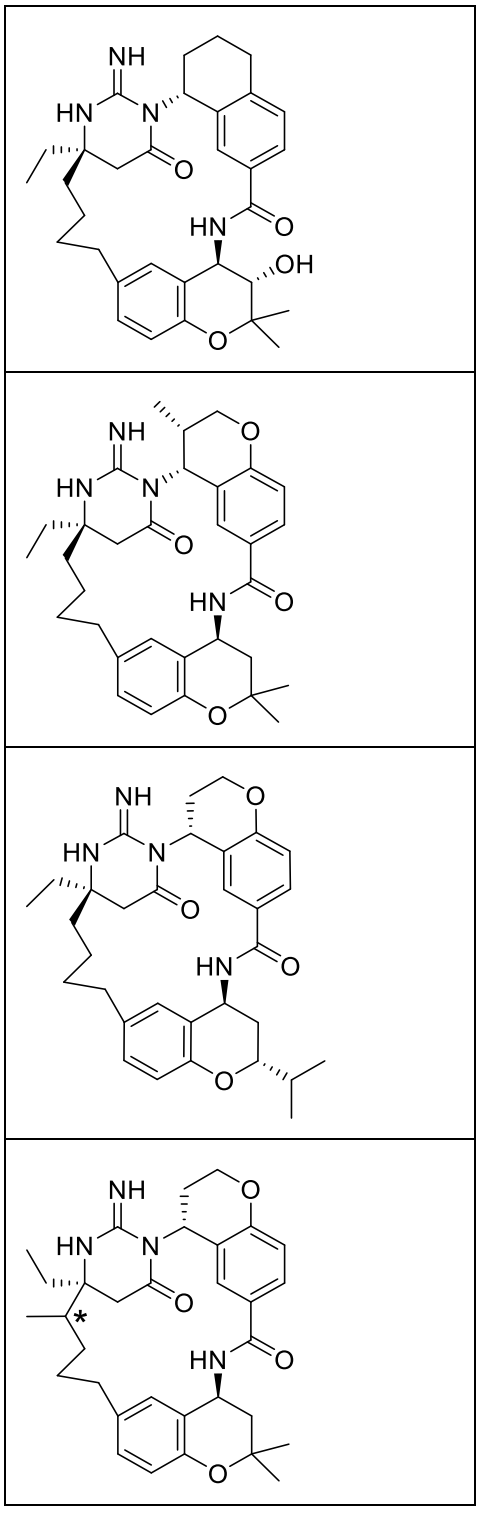


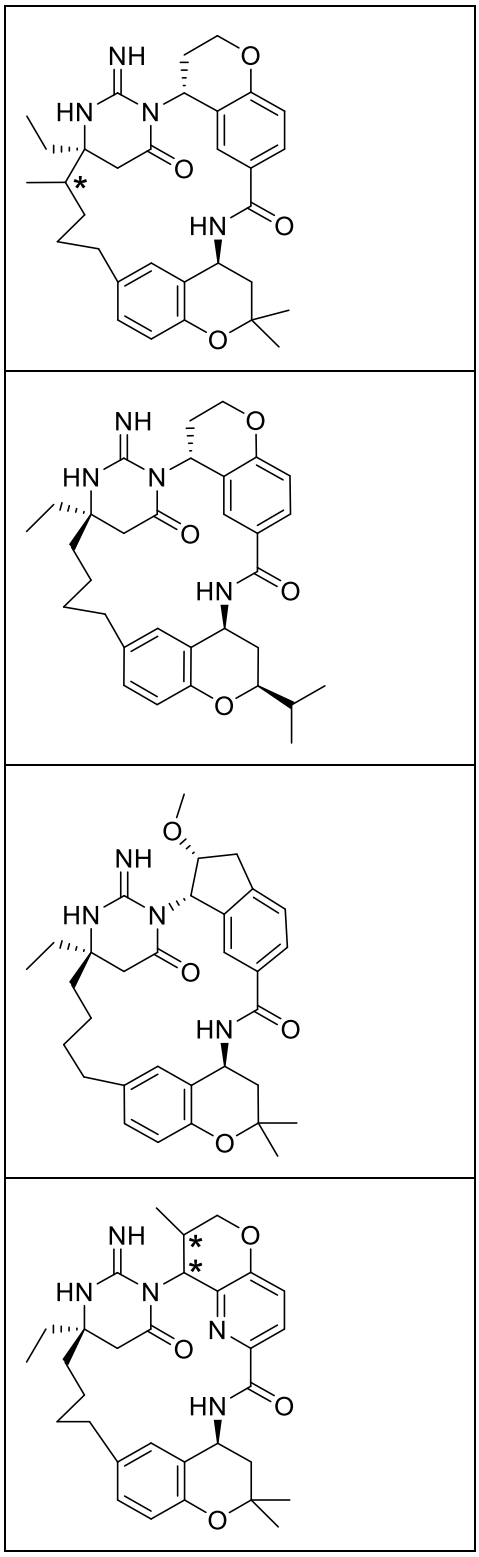


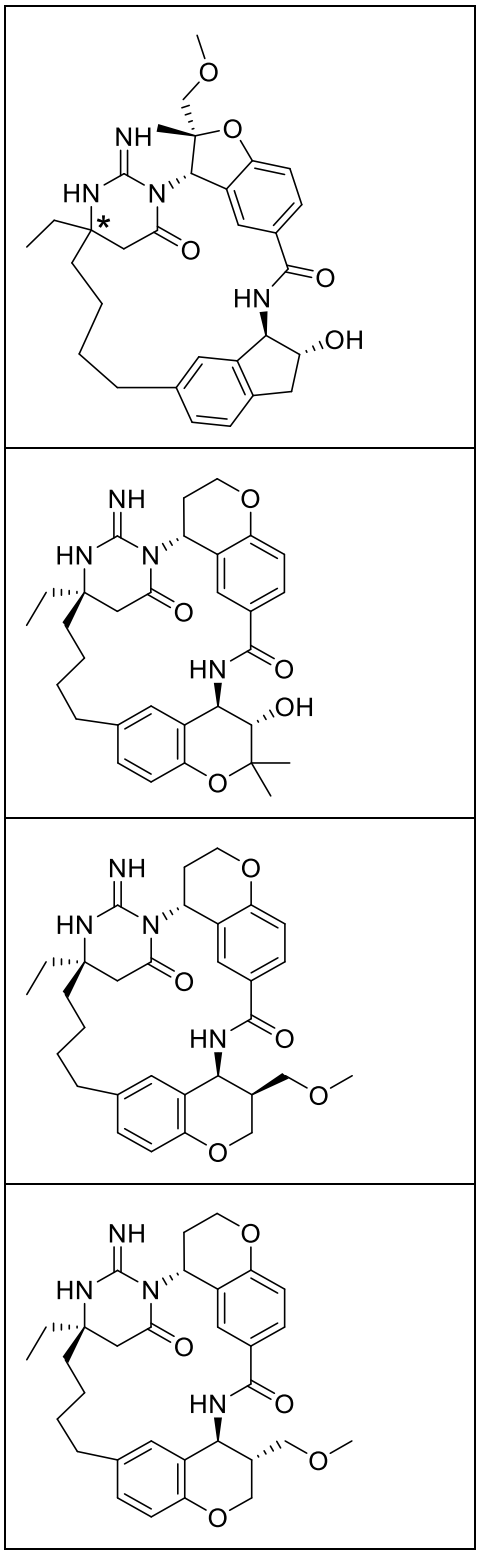


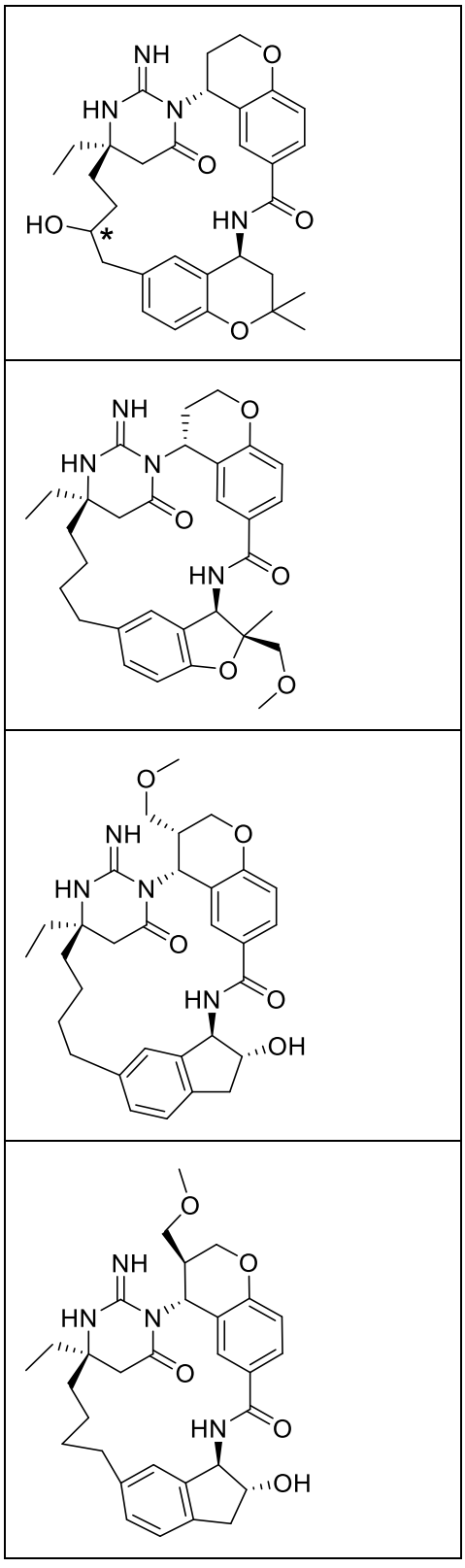


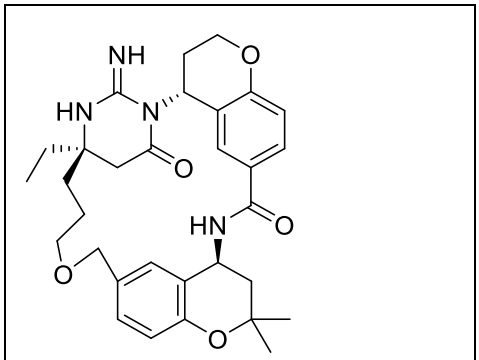
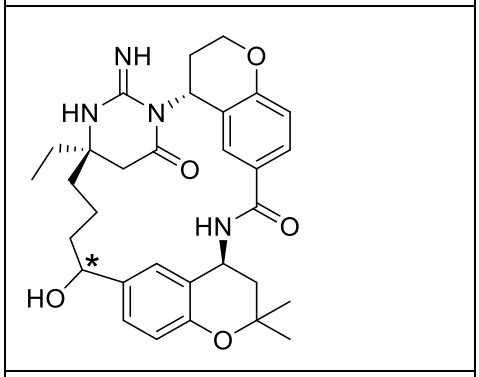
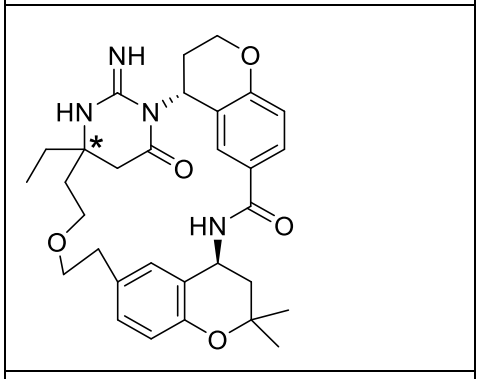
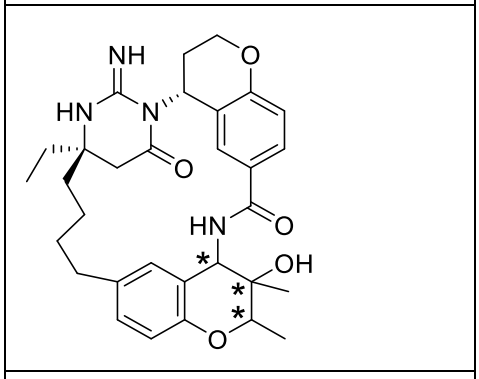
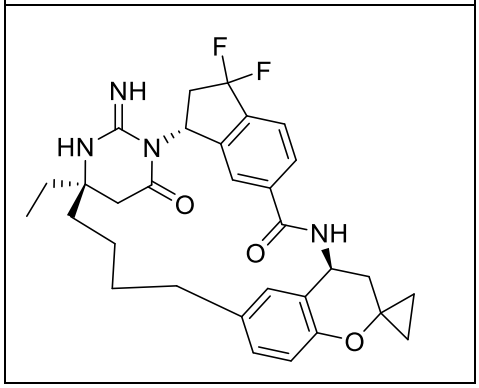





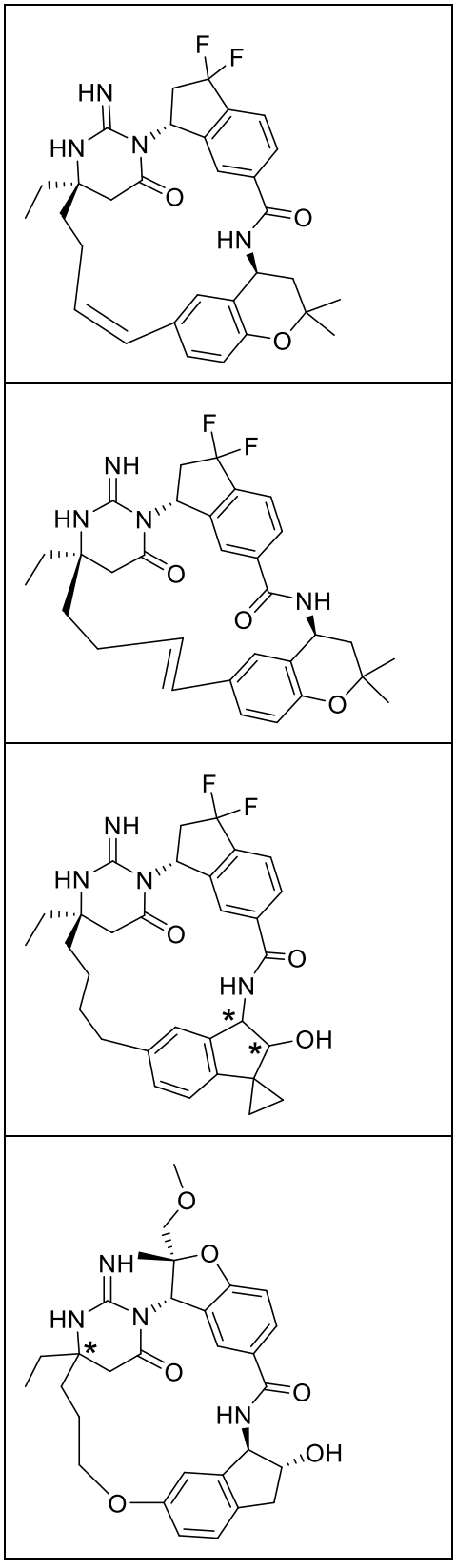

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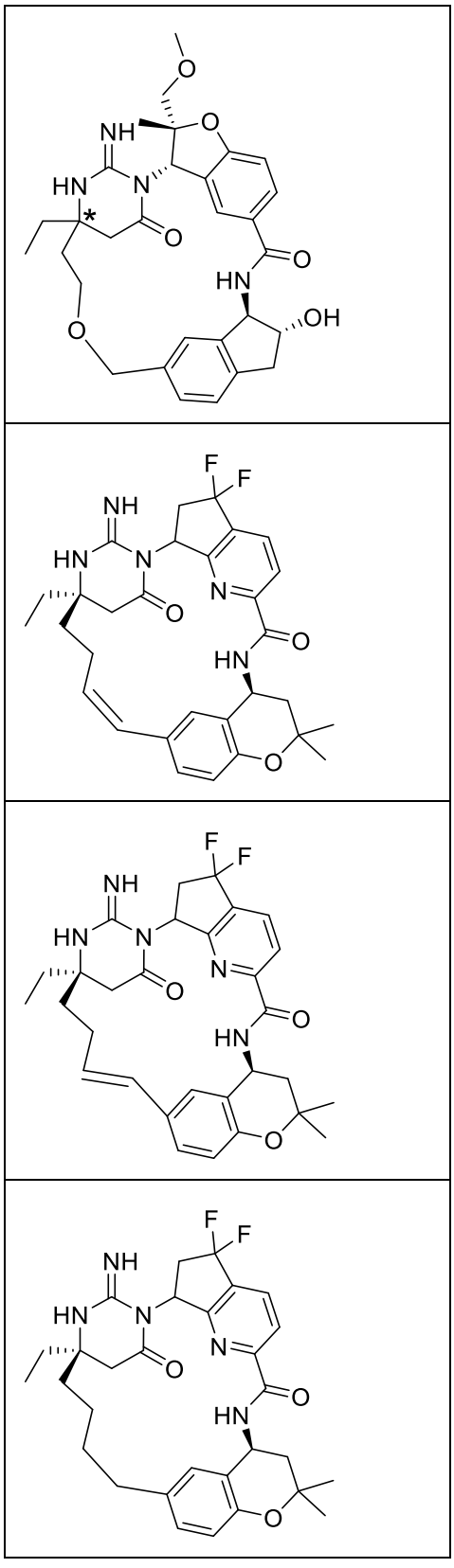


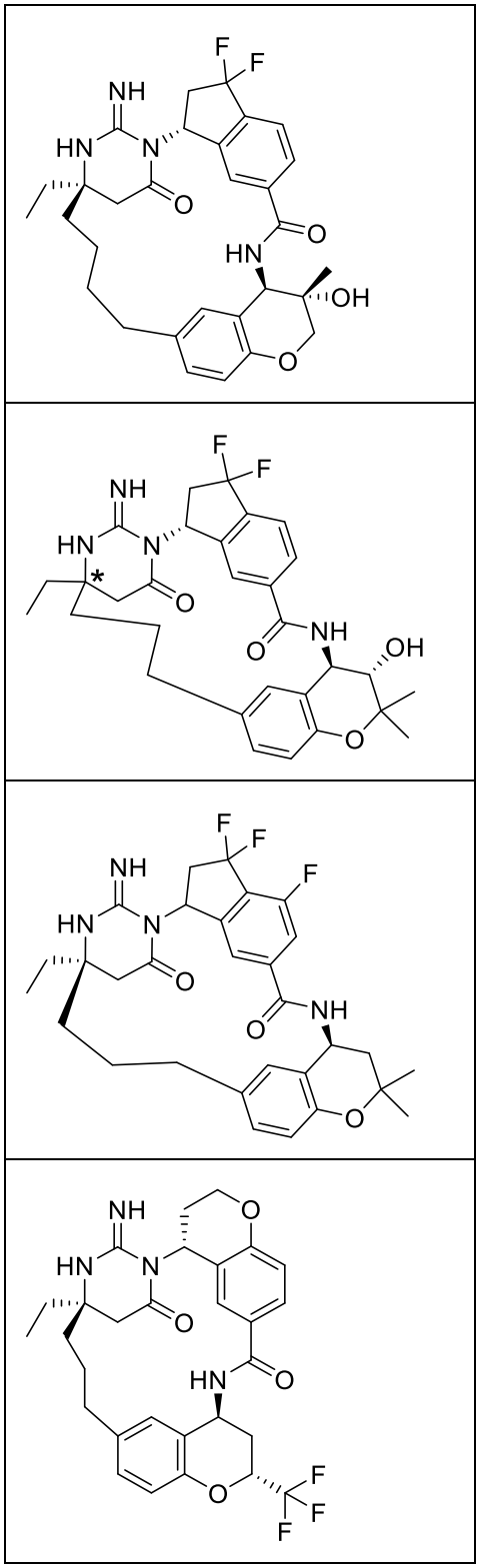


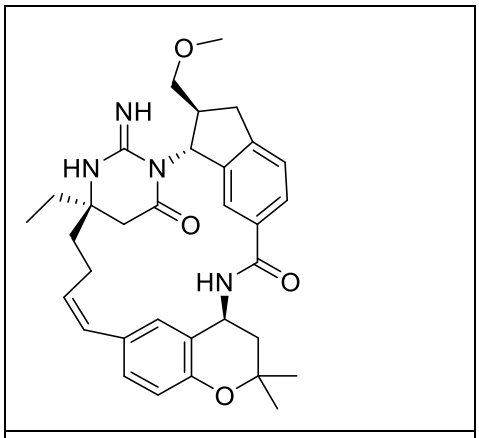
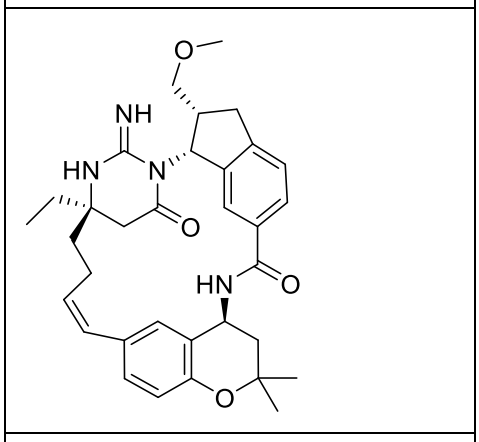
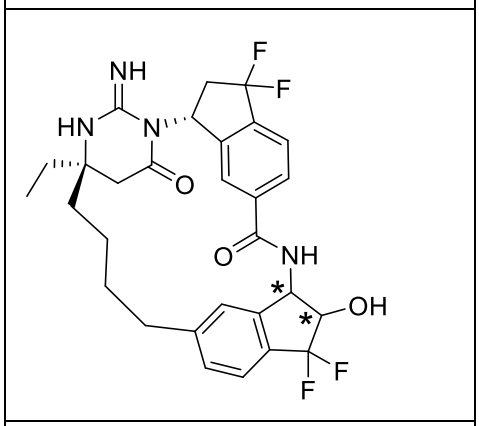
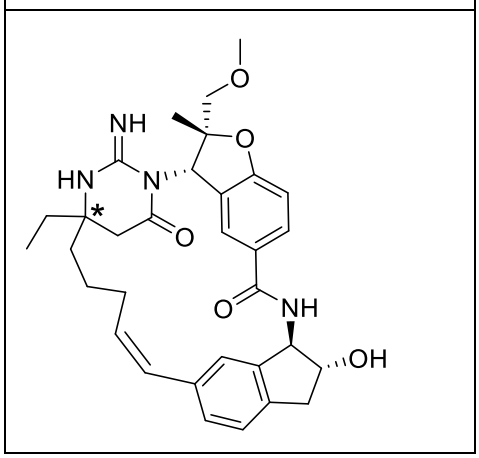


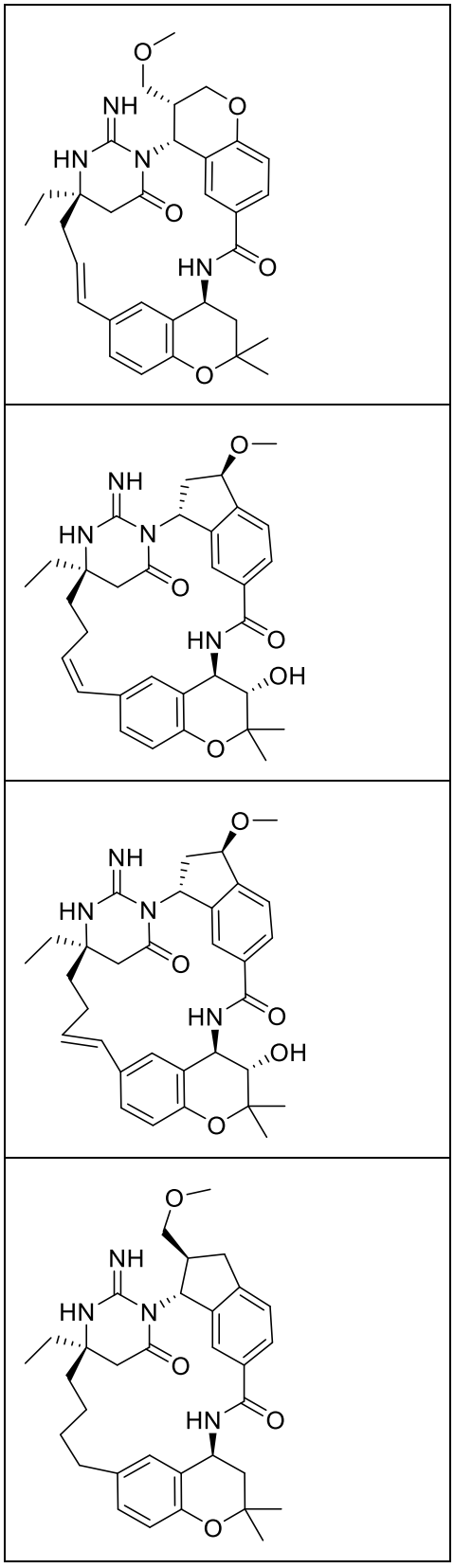






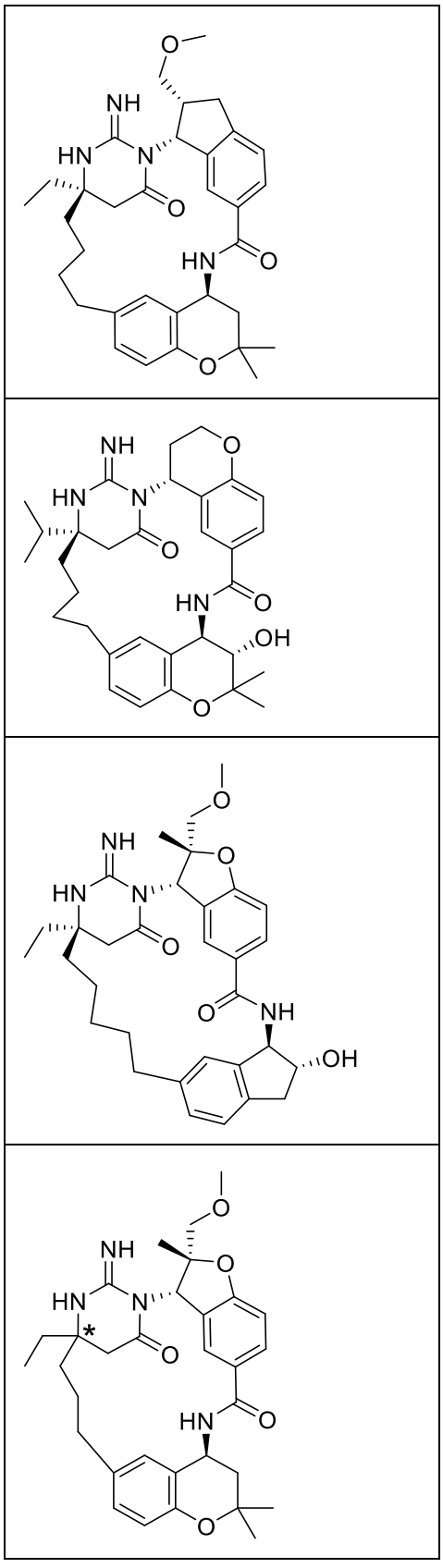

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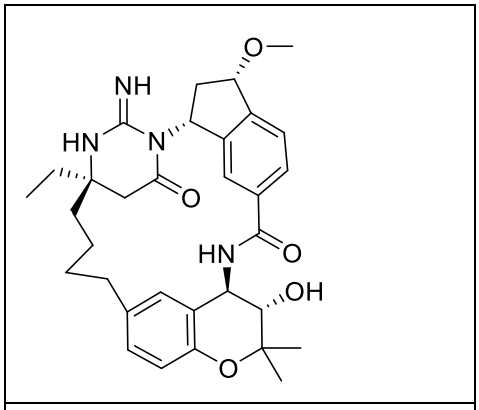

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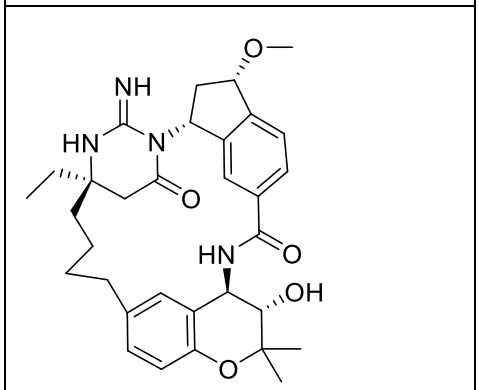


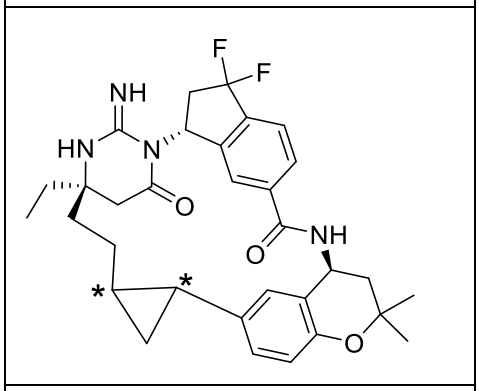





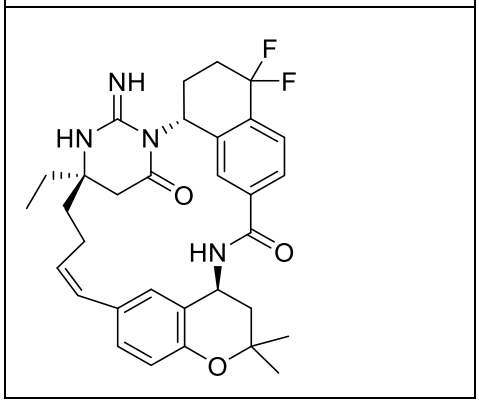


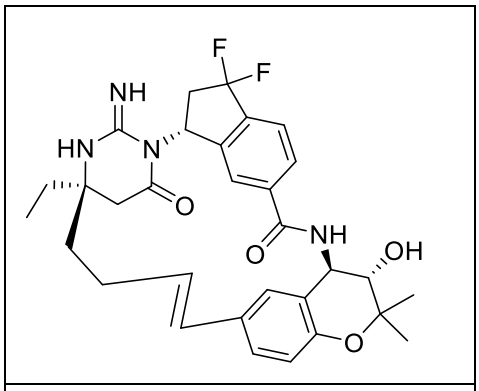
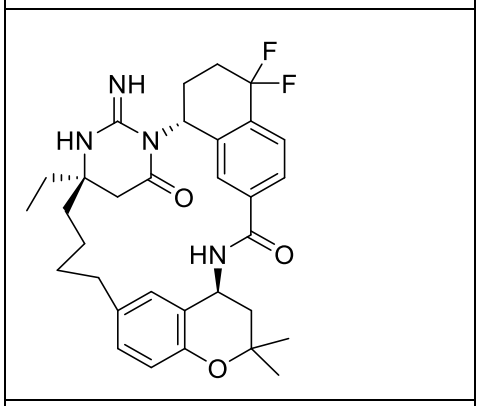
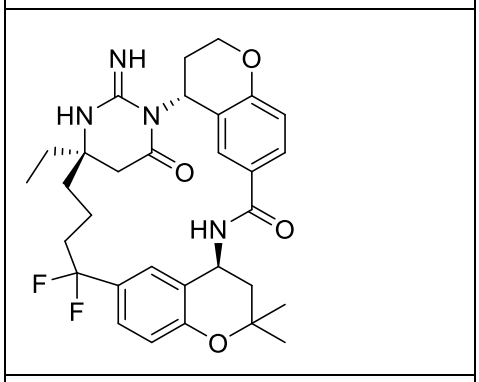
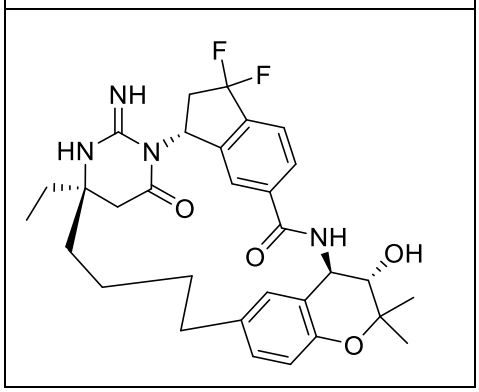


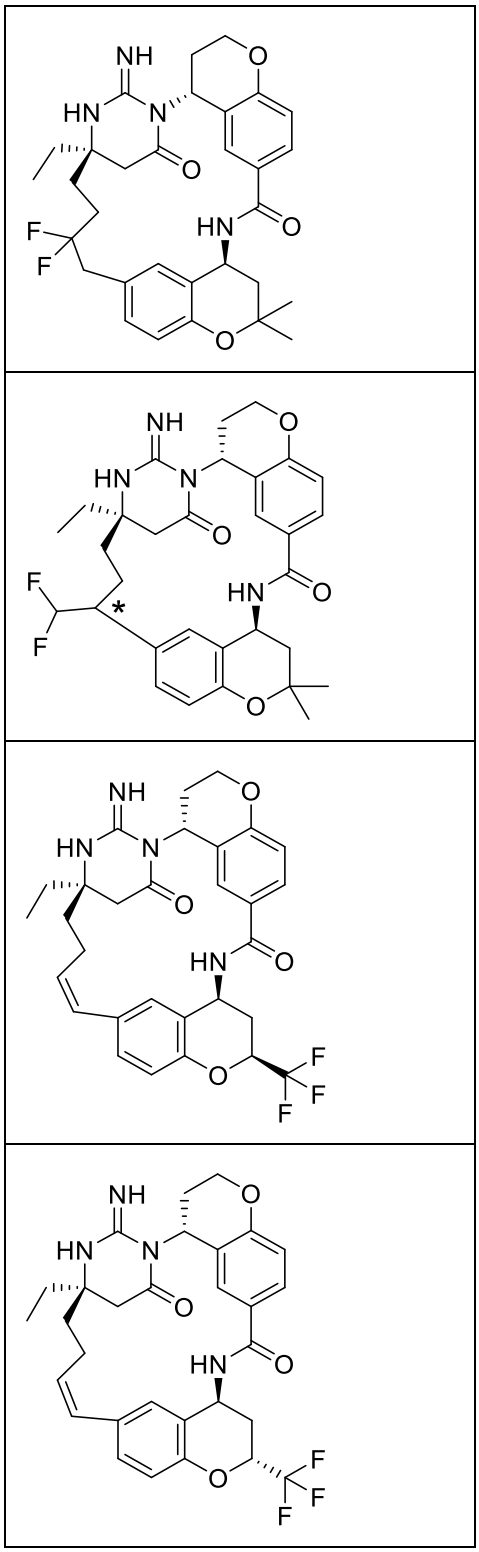

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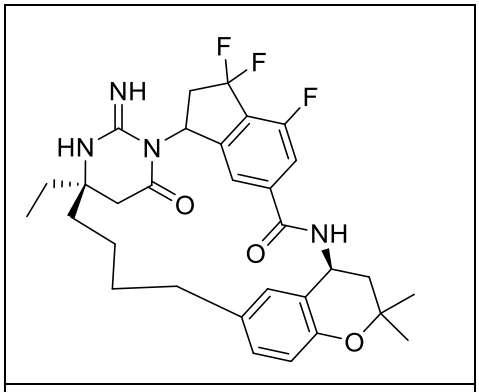
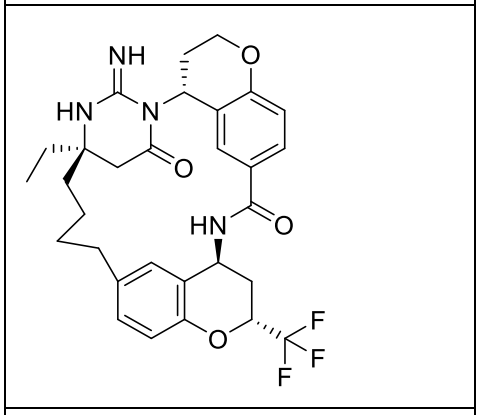
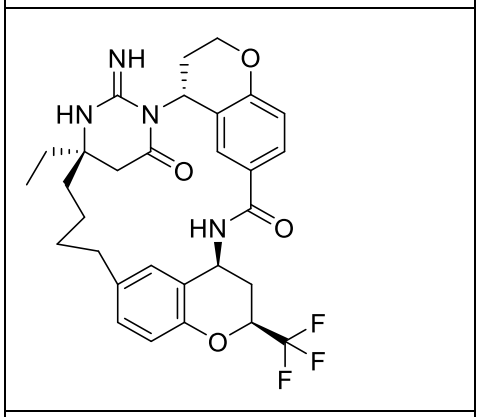
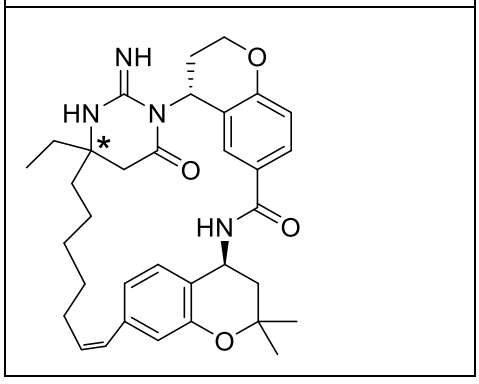

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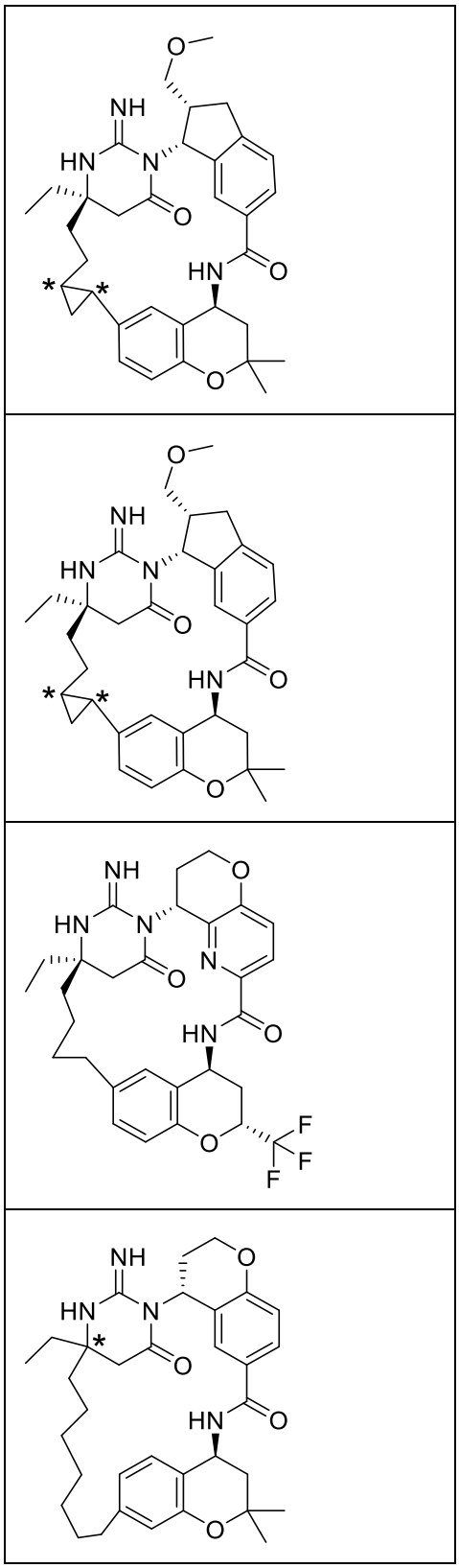

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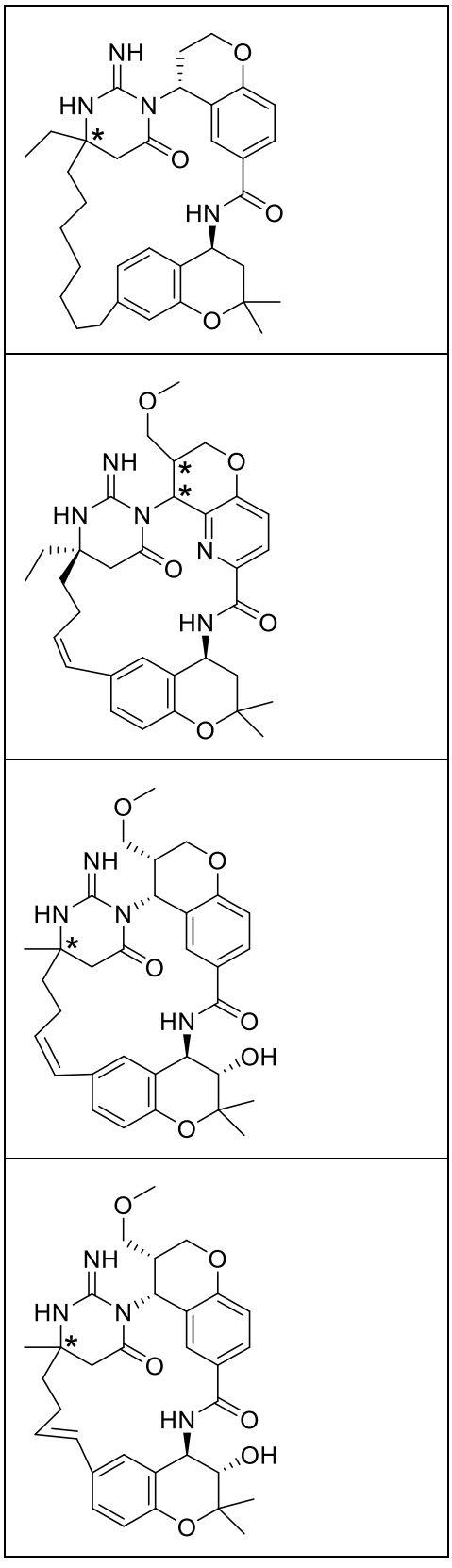

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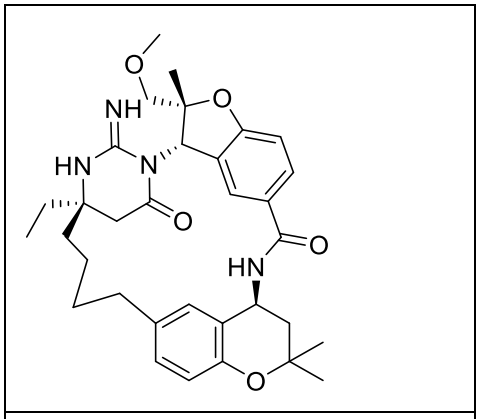
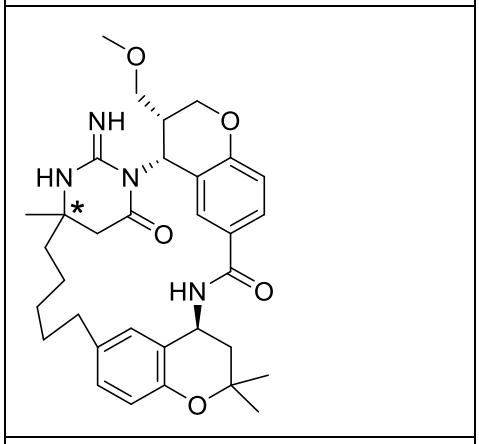
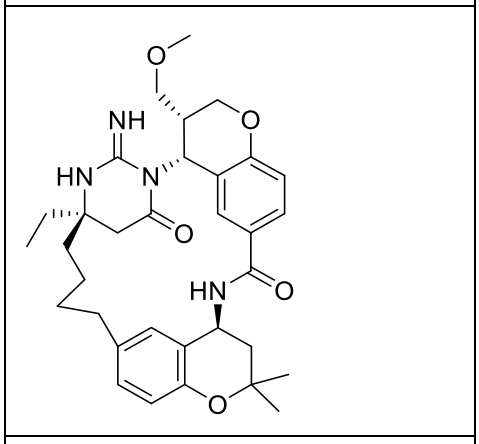
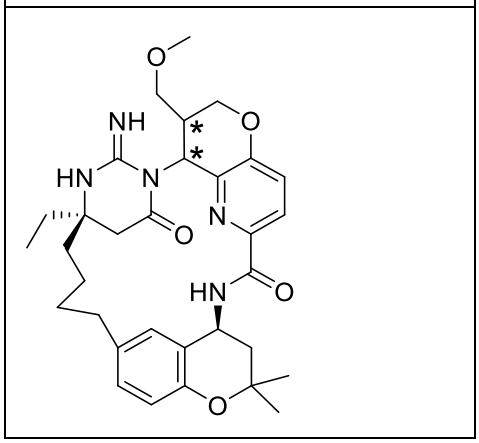





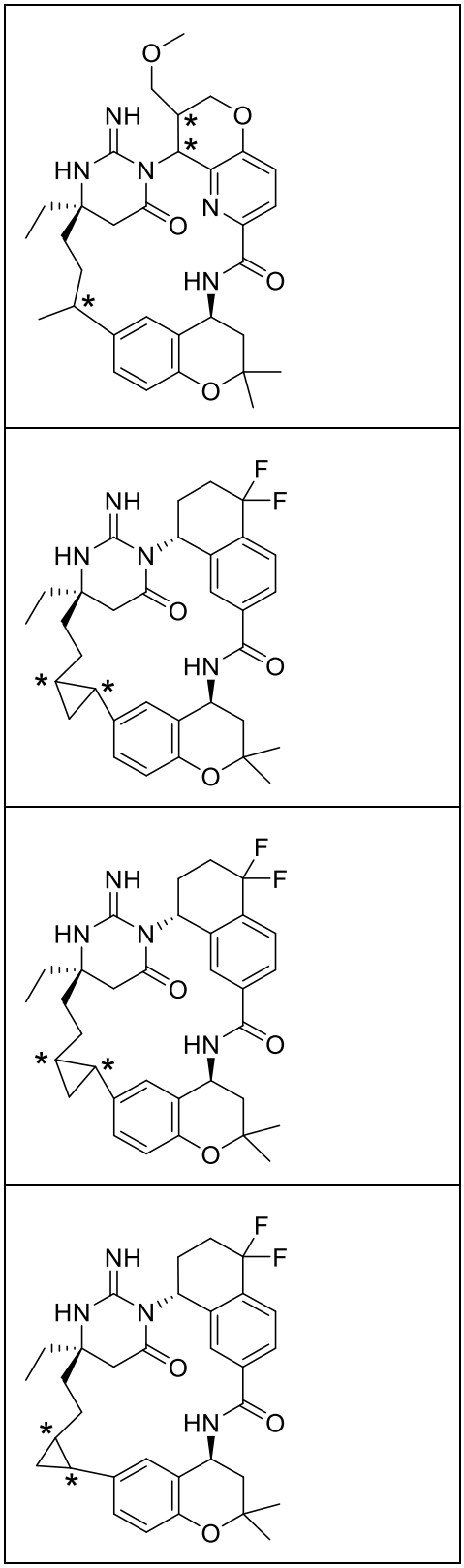


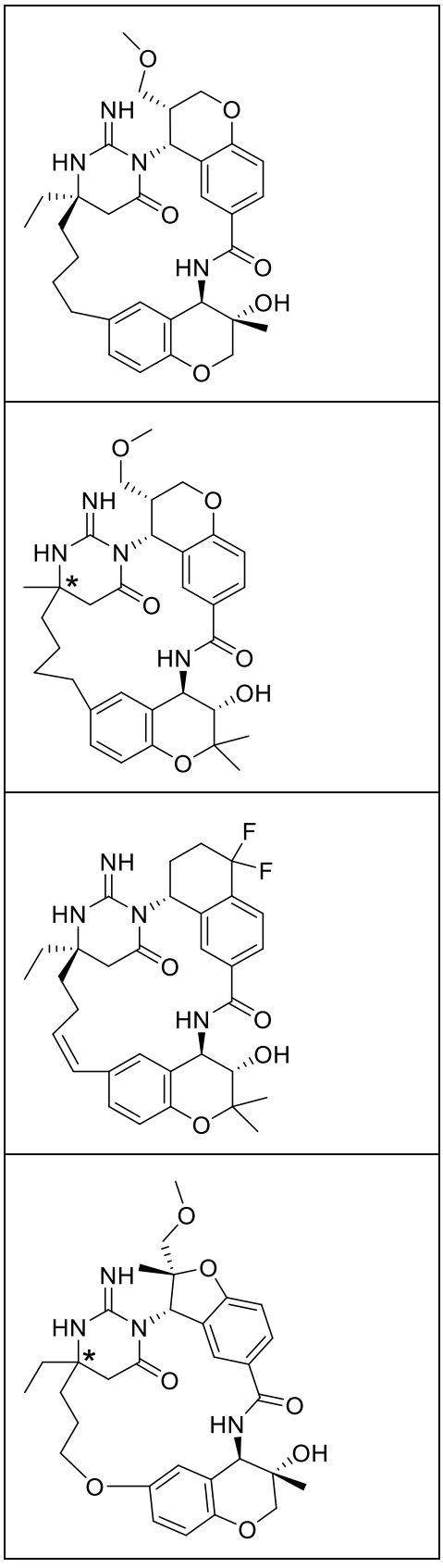





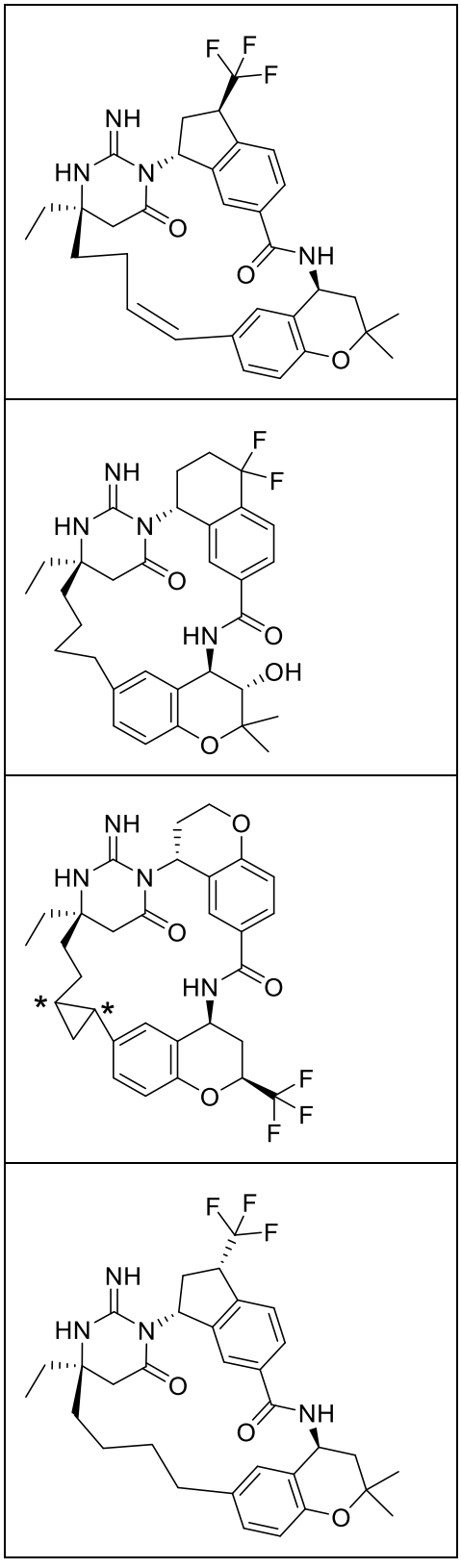


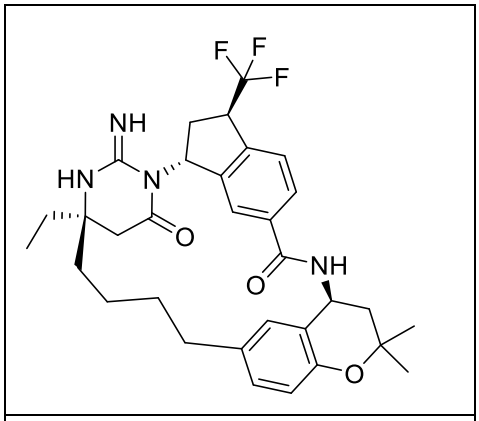
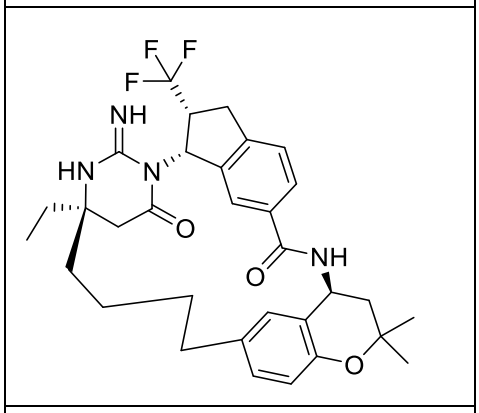
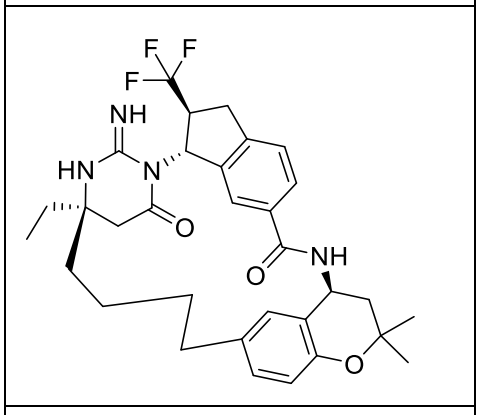
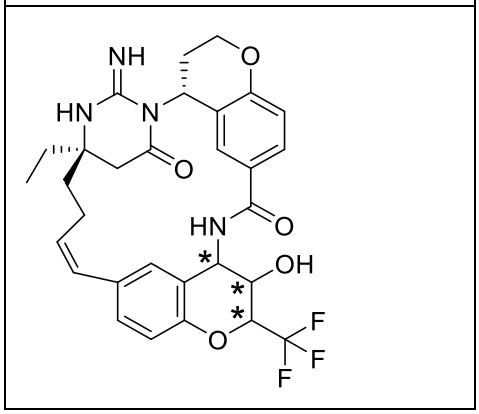


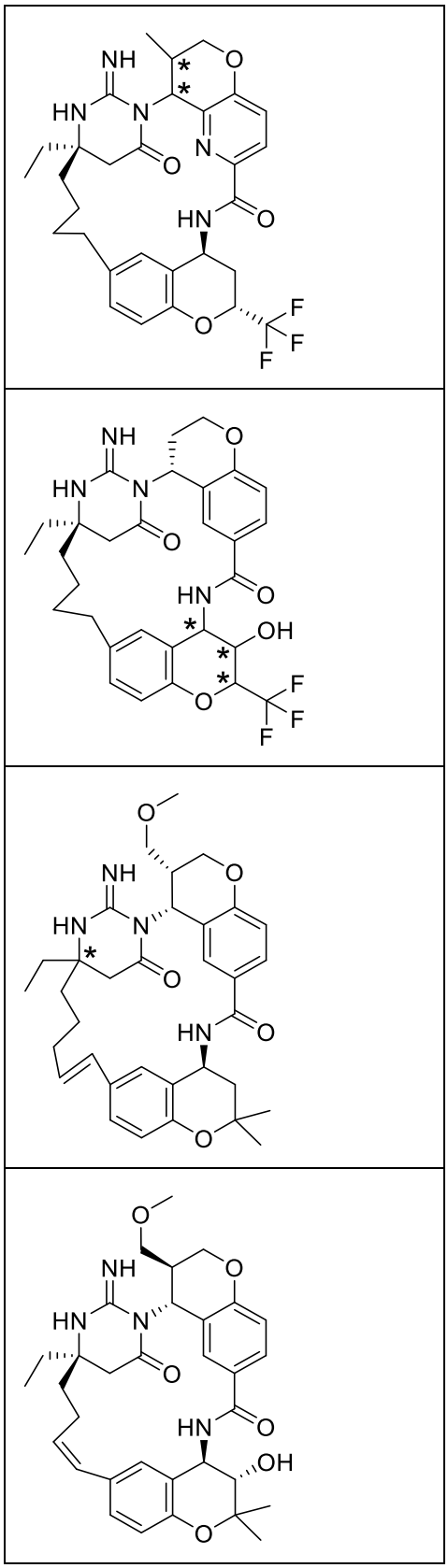





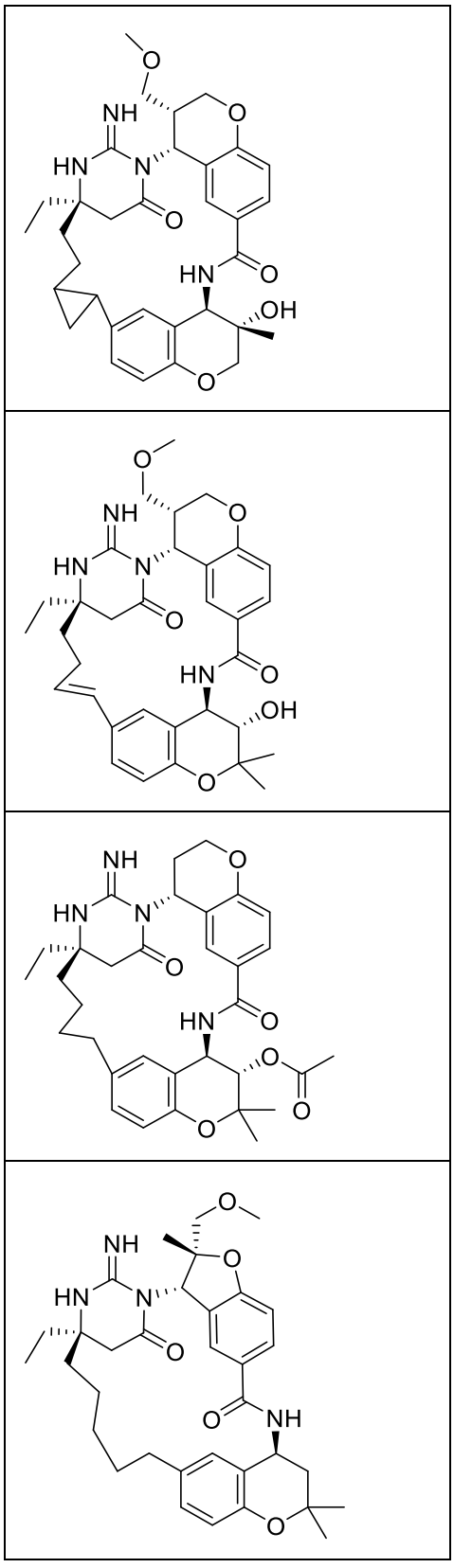


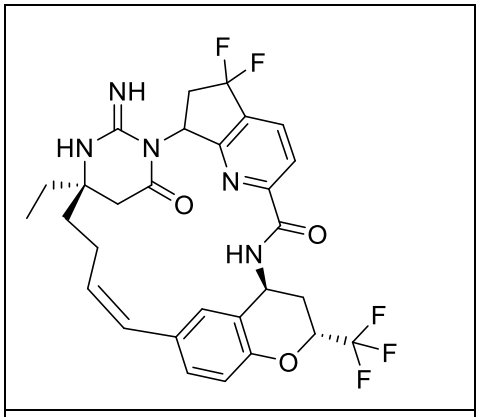
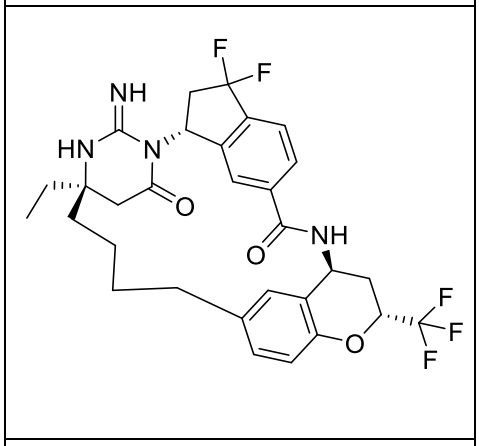
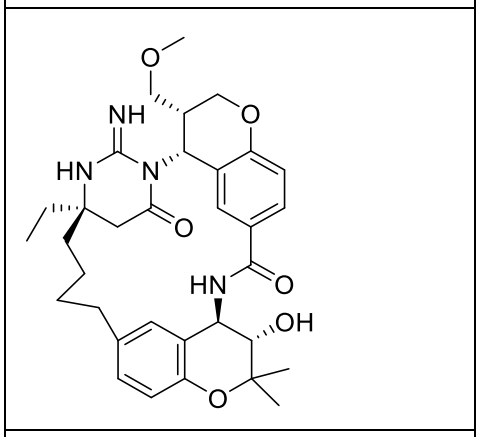
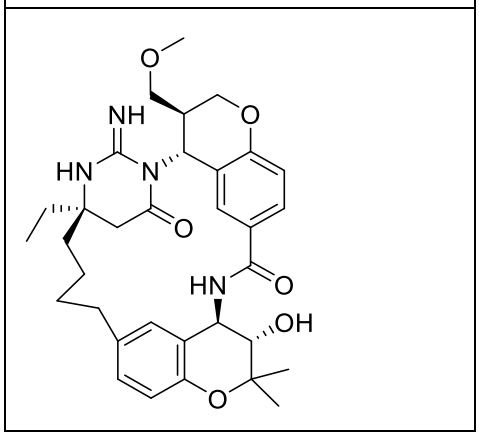


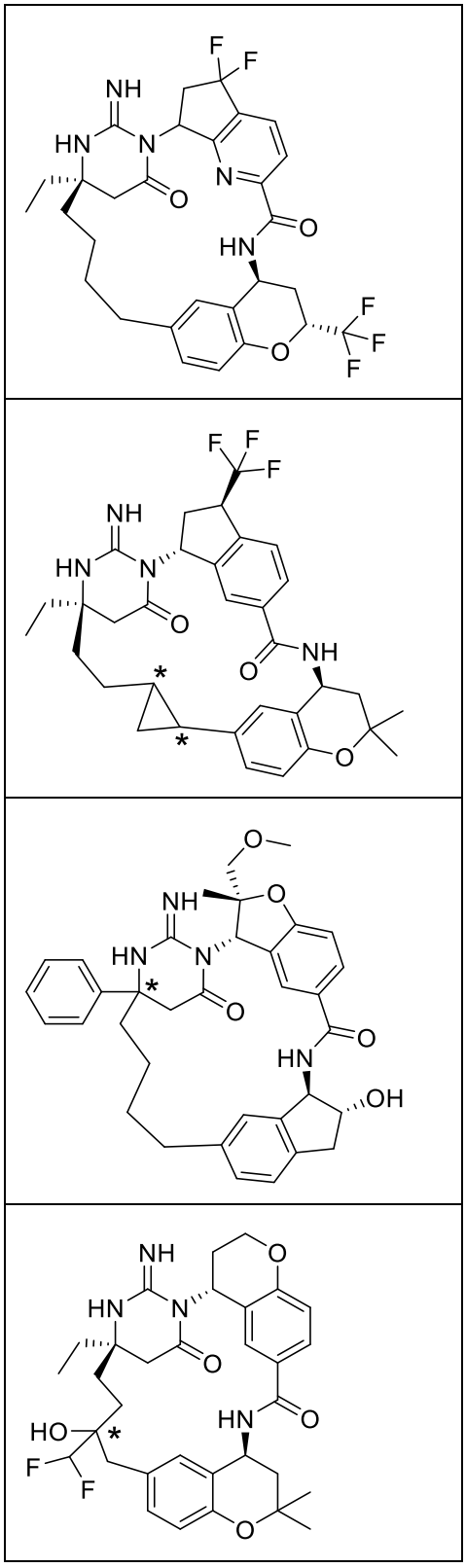


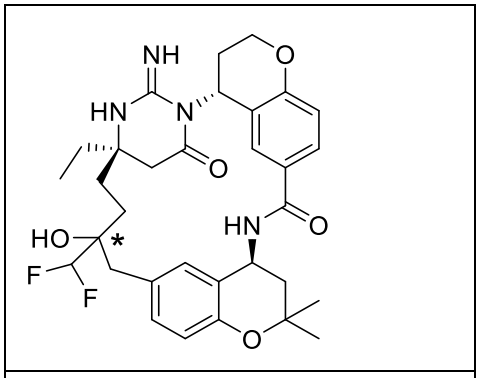
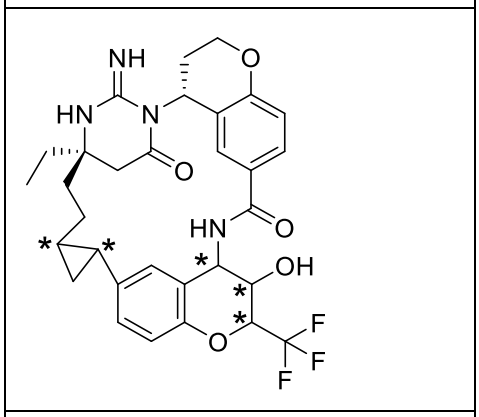
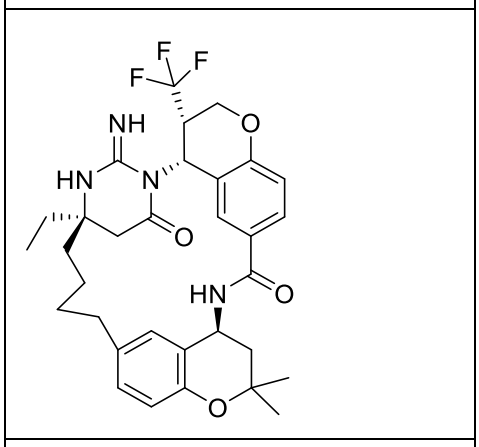
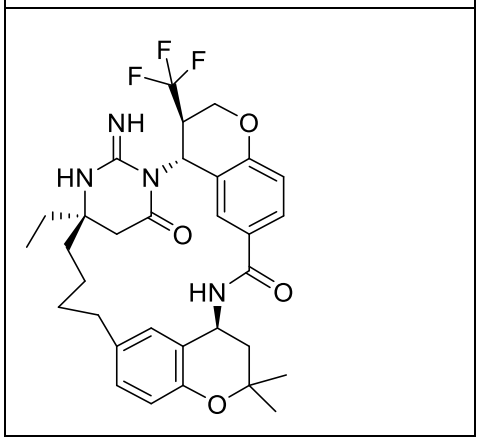





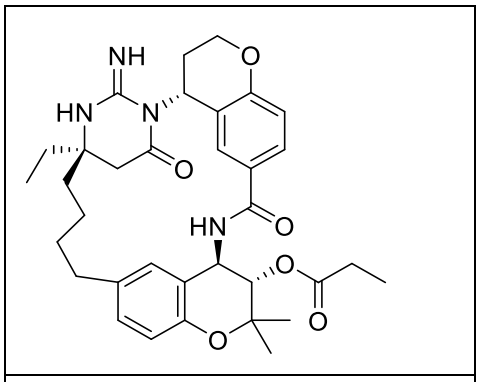
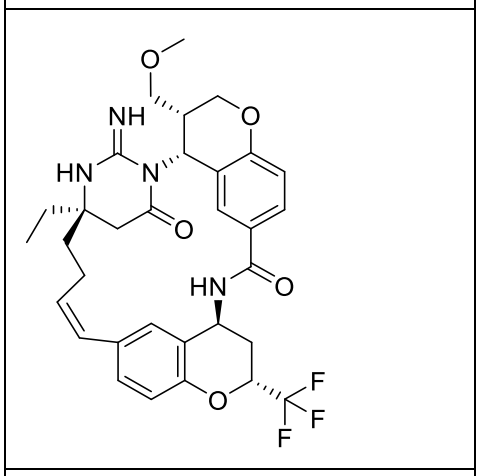
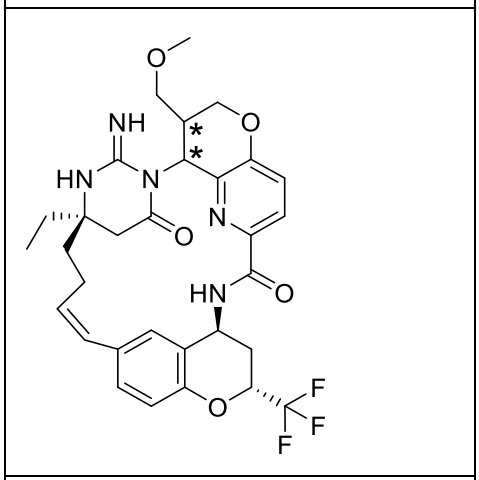
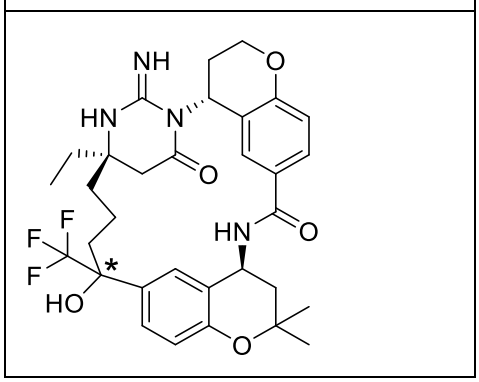


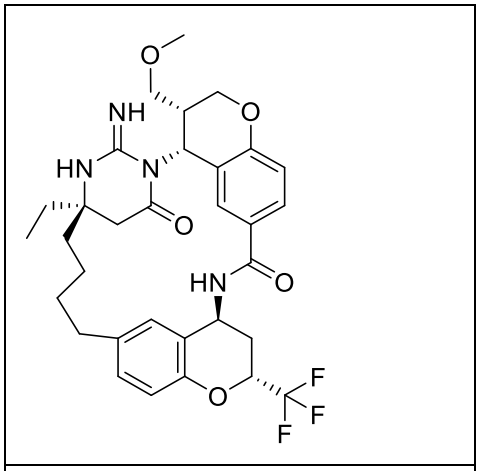
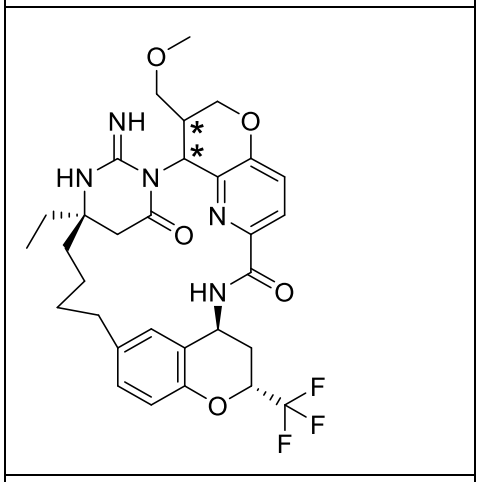
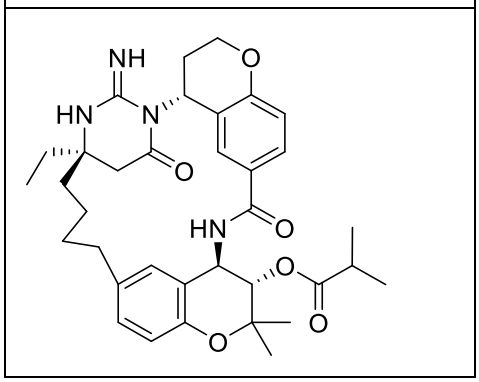




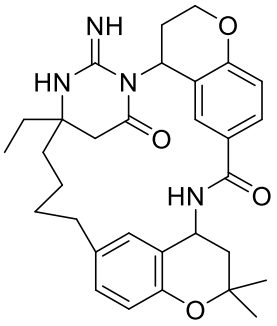





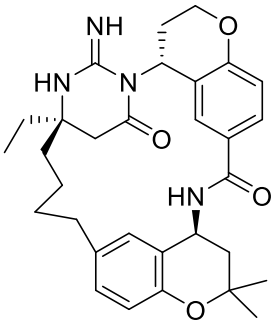
, or a pharmaceutically acceptable salt thereof.

22. A compound having the formula



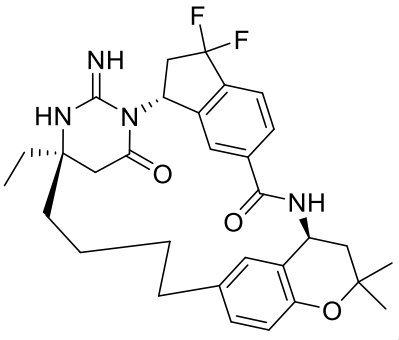
, or a pharmaceutically acceptable salt thereof.

23. A compound having the formula



, or a pharmaceutically acceptable salt thereof.

24. A compound having the formula:



, or a pharmaceutically acceptable salt thereof.

25. Use of a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-24 in the manufacture of a medicament for treating a Plasmodium infection, or malaria.

26. Use of a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-24 in the manufacture of a medicament for inhibiting plasmepsin X.

27. Use of a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-24 in the manufacture of a medicament for inhibiting plasmepsin IX.

28. Use of a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-24 in the manufacture of a medicament for inhibiting plasmepsin IX and plasmepsin X.

29. A pharmaceutical composition comprising a compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

30. A pharmaceutical composition comprising a compound of any one of claims 1-24 and a pharmaceutically acceptable carrier.

31. Use of a compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a *Plasmodium* infection, or for treating malaria, wherein the medicament is to be administered with one or more additional anti-malarial agents.

32. Use of a compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treatmenting malaria by inhibition of plasmepsin X, IX and at least one other mechanism, wherein the medicament is to be administered with one additional anti-malarial agent, wherein the additional anti-malarial agent acts through a different mechanism than inhibiting plasmepsin IX or plasmepsin X.

33. A compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof, for use in therapy.

34. A compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof, and one or more additional anti-malarial agents for use in therapy.