ANTI-VIRAL COMPOUNDS FOR TREATING CORONAVIRUS, PICORNAVIRUS, AND NOROVIRUS INFECTIONS

INCORPORATION BY REFERENCE TO ANY PRIORITY APPLICATIONS

[0001] Any and all applications for which a foreign or domestic priority claim is identified, for example, in the Application Data Sheet or Request as filed with the present application, are hereby incorporated by reference under 37 CFR 1.57, and Rules 4.18 and 20.6, including U.S. Provisional Applications Nos. 63/037,200, filed June 10, 2020, 63/055,679, filed July 23, 2020, 63/085,871, filed September 30, 2020, 63/086,787, filed October 2, 2020, 63/125,562, filed December 15, 2020 and 63/155,113, filed March 1, 2021.

BACKGROUND

Field

[0002] The present application relates to the fields of chemistry, biochemistry and medicine. Disclosed herein are compounds of Formula (I), or pharmaceutically acceptable salt thereof, pharmaceutical compositions that include a compound described herein (including pharmaceutically acceptable salts of a compound described herein) and methods of synthesizing the same. Also disclosed herein are methods of treating diseases and/or conditions with a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

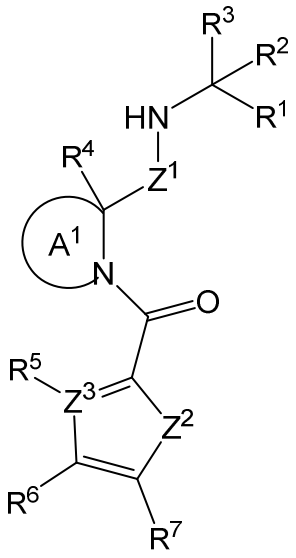
Description

[0003] A positive-sense single-stranded RNA virus ((+)ssRNA virus) is a virus that uses positive sense, single stranded, RNA as its genetic material. Positive-sense single-stranded RNA viruses can be enveloped or non-enveloped. Coronaviridae, Picornaviridae and Norviruses are each a (+)ssRNA virus. Each of the aforementioned viruses are known to infect mammals, including humans.

SUMMARY

[0004] Some examples disclosed herein relate to a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0004a] In one aspect, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:



(I)

wherein:

Z^1 is –C(=O)– or –CH(CF_3)–;

Z^2 is O, S or NR^8, wherein R^8 is H or an unsubstituted C_{1-4} alkyl;

Z^3 is N or C, and when Z^3 is N, then R^5 is absent;

Ring A^1 is selected from the group consisting of an unsubstituted or a substituted azetidine, an unsubstituted or a substituted pyrrolidine and an unsubstituted or a substituted piperidine, wherein the azetidine, the pyrrolidine and the piperidine can be optionally substituted with one or more R^x groups independently selected from the group consisting of deuterium, halogen, an unsubstituted or a substituted C_{1-4} alkyl, an unsubstituted or a substituted C_{2-4} alkenyl, an unsubstituted or a substituted C_{1-8} alkoxy, an unsubstituted or a substituted C_{3-6} cycloalkyl, an unsubstituted or a substituted aryl, an unsubstituted or a substituted heteroaryl, an unsubstituted or a substituted heterocyclyl and an unsubstituted C_{1-4} haloalkyl, and wherein the azetidine, the pyrrolidine and the piperidine can be connected to a cyclic moiety selected from the group consisting of a monocyclic C_{3-7} cycloalkyl, a bicyclic C_{5-9} cycloalkyl, a monocyclic C_{3-7} cycloalkenyl, a bicyclic C_{5-9} cycloalkenyl and phenyl, wherein the cyclic moiety is connected to the azetidine, the pyrrolidine and the piperidine in a fused-fashion or a spiro-fashion that can be optionally substituted with one or more moieties independently selected from the group consisting of halogen, an unsubstituted C_{1-4}

alkyl, an unsubstituted C_{2-4} alkenyl and an unsubstituted or a substituted C_{3-6} monocyclic cycloalkyl;

R^1 is selected from the group consisting of cyano, an unsubstituted or a substituted C_{2-5} alkynyl, an unsubstituted or a substituted acyl, an unsubstituted or a substituted ketoamide, an unsubstituted or a substituted –C(=O)-N-sulfonamido, –CH(OH)-($S(=O)_2$-O^-), –CH(OH)(($P=O)(OR^9)_2$), –C(=O)CH_2-O-(($P=O)(OR^{10})_2$), –C(=O)CH_2-O-C(R^{11A})$_2$-O-(($P=O)(OR^{11B})_2$), –C(=O)CH_2-O-C(R^{12A})$_2$-O-C(=O)-OR^{12B} and –C(=O)CH_2-O-C(R^{13A})$_2$-O-C(=O)-R^{13B}, wherein each R^9, each R^{10}, each R^{11B} and R^{12B} and R^{13B} are independently hydrogen, an unsubstituted C_{1-6} alkyl, an unsubstituted C_{2-6} alkenyl, an unsubstituted C_{1-6} haloalkyl, an unsubstituted or a substituted aryl or an unsubstituted or a substituted aryl(C_{1-4} alkyl);

each R^{11A}, each R^{12A} and each R^{13A} are independently hydrogen or an unsubstituted C_{1-4} alkyl;

R^2 is hydrogen, deuterium or halogen;

R^3 is an unsubstituted or a substituted C-amido(C_{1-4} alkyl), an unsubstituted or a substituted monocyclic nitrogen-containing heteroaryl(C_{1-4} alkyl), an unsubstituted or a substituted monocyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl), an unsubstituted or a substituted bicyclic nitrogen-containing heteroaryl(C_{1-4} alkyl) or an unsubstituted or a substituted bicyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl);

R^4 is hydrogen, deuterium or halogen;

R^5 is selected from the group consisting of hydrogen, deuterium, halogen, an unsubstituted C_{1-6} alkyl and an unsubstituted C_{1-4} haloalkyl; and

R^6 and R^7 are independently selected from the group consisting of hydrogen, deuterium, halogen, an unsubstituted or a substituted C_{1-6} alkyl, an unsubstituted or a substituted phenyl, an unsubstituted or a substituted acyl, an unsubstituted or a substituted C-carboxy and an unsubstituted or a substituted sulfonyl; or

R^6 and R^7 are taken together with the carbon to which R^6 and R^7 are each attached to form an optionally substituted 4-9 membered saturated or unsaturated ring or ring system that can optionally contain 1 or 2 ring heteroatoms selected from the group consisting of O, N and S.

[0005] In another aspect, there is provided a pharmaceutical composition comprising an effective amount of a compound as defined herein, or a pharmaceutically acceptable salt thereof, and excipient. Some examples disclosed herein relate to a pharmaceutical composition that can contain an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0006] Some examples described herein relate to a method of treating a coronavirus infection that can include administering to a subject identified as suffering from the coronavirus infection an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other examples described herein relate to a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the use of treating a coronavirus infection. In another aspect, there is provided use of the compound as defined herein, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of a coronavirus infection.

[0007] Some examples disclosed herein relate to a method of inhibiting replication of a coronavirus that can include contacting a cell infected with the coronavirus with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other examples described herein relate to a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the use of inhibiting the replication of a coronavirus.

[0008] Some examples described herein relate to a method of treating a picornavirus infection that can include administering to a subject identified as suffering from the picornavirus infection an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other examples described herein relate to a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the use of treating a picornavirus infection.

[0009] Some examples disclosed herein relate to a method of inhibiting replication of a picornavirus that can include contacting a cell infected with the picornavirus with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other examples described herein relate to a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the use of inhibiting the replication of a picornavirus.

[0010] Some examples described herein relate to a method of treating a norovirus infection that can include administering to a subject identified as suffering from the norovirus infection an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other examples described herein relate to a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the use of treating a norovirus infection.

[0011] Some examples disclosed herein relate to a method of inhibiting replication of a norovirus that can include contacting a cell infected with the norovirus with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other examples described herein relate to a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the use of inhibiting the replication of a norovirus.

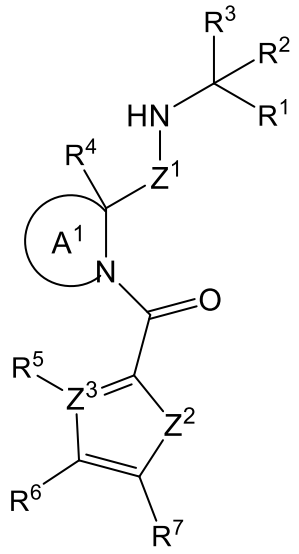
[0011a] In another aspect, there is provided use of the compound as defined herein, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of a viral infection, wherein the viral infection is selected from the group consisting of a picornavirus infection and a norovirus infection.

[0011b] In another aspect, there is provided use of an effective amount of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for inhibiting a coronavirus protease in a cell culture that is infected with a coronavirus

[0012] These are other examples are described in greater detail below.

WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:



(I)

wherein:

Z^1 is –C(=O)– or –CH(CF_3)–;

Z^2 is O, S or NR^8, wherein R^8 is H or an unsubstituted C_{1-4} alkyl;

Z^3 is N or C, and when Z^3 is N, then R^5 is absent;

Ring A^1 is selected from the group consisting of an unsubstituted or a substituted azetidine, an unsubstituted or a substituted pyrrolidine and an unsubstituted or a substituted piperidine, wherein the azetidine, the pyrrolidine and the piperidine can be optionally substituted with one or more R^x groups independently selected from the group consisting of deuterium, halogen, an unsubstituted or a substituted C_{1-4} alkyl, an unsubstituted or a substituted C_{2-4} alkenyl, an unsubstituted or a substituted C_{1-8} alkoxy, an unsubstituted or a substituted C_{3-6} cycloalkyl, an unsubstituted or a substituted aryl, an unsubstituted or a substituted heteroaryl, an unsubstituted or a substituted heterocyclyl and an unsubstituted C_{1-4} haloalkyl, and wherein the azetidine, the pyrrolidine and the piperidine can be connected to a cyclic moiety selected from the group consisting of a monocyclic C_{3-7} cycloalkyl, a bicyclic C_{5-9} cycloalkyl, a monocyclic C_{3-7} cycloalkenyl, a bicyclic C_{5-9} cycloalkenyl and phenyl, wherein the cyclic moiety is connected to the azetidine, the pyrrolidine and the piperidine in a fused-fashion or a spiro-fashion that can be optionally substituted with one or more moieties independently selected from the group consisting

of halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl and an unsubstituted or a substituted C_{3-6} monocyclic cycloalkyl;

R^1 is selected from the group consisting of cyano, an unsubstituted or a substituted C_{2-5} alkynyl, an unsubstituted or a substituted acyl, an unsubstituted or a substituted ketoamide, an unsubstituted or a substituted –C(=O)-N-sulfonamido, –CH(OH)-($S(=O)_2$-O^-), –CH(OH)(($P=O)(OR^9)_2$), –$C(=O)CH_2$-O-(($P=O)(OR^{10})_2$), –$C(=O)CH_2$-O-$C(R^{11A})_2$-O-(($P=O)(OR^{11B})_2$), –$C(=O)CH_2$-O-$C(R^{12A})_2$-O-C(=O)-OR^{12B} and –$C(=O)CH_2$-O-$C(R^{13A})_2$-O-C(=O)-R^{13B}, wherein each R^9, each R^{10}, each R^{11B} and R^{12B} and R^{13B} are independently hydrogen, an unsubstituted C_{1-6} alkyl, an unsubstituted C_{2-6} alkenyl, an unsubstituted C_{1-6} haloalkyl, an unsubstituted or a substituted aryl or an unsubstituted or a substituted aryl(C_{1-4} alkyl);

each R^{11A}, each R^{12A} and each R^{13A} are independently hydrogen or an unsubstituted C_{1-4} alkyl;

R^2 is hydrogen, deuterium or halogen;

R^3 is an unsubstituted or a substituted C-amido(C_{1-4} alkyl), an unsubstituted or a substituted monocyclic nitrogen-containing heteroaryl(C_{1-4} alkyl), an unsubstituted or a substituted monocyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl), an unsubstituted or a substituted bicyclic nitrogen-containing heteroaryl(C_{1-4} alkyl) or an unsubstituted or a substituted bicyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl);

R^4 is hydrogen, deuterium or halogen;

R^5 is selected from the group consisting of hydrogen, deuterium, halogen, an unsubstituted C_{1-6} alkyl and an unsubstituted C_{1-4} haloalkyl; and

R^6 and R^7 are independently selected from the group consisting of hydrogen, deuterium, halogen, an unsubstituted or a substituted C_{1-6} alkyl, an unsubstituted or a substituted phenyl, an unsubstituted or a substituted acyl, an unsubstituted or a substituted C-carboxy and an unsubstituted or a substituted sulfonyl; or

R^6 and R^7 are taken together with the carbon to which R^6 and R^7 are each attached to form an optionally substituted 4-9 membered saturated or unsaturated ring or ring system that can optionally contain 1 or 2 ring heteroatoms selected from the group consisting of O, N and S.

2. The compound of Claim 1, wherein R^1 is an unsubstituted or a substituted ketoamide.

3. The compound of Claim 1, wherein R^1 is an unsubstituted or a substituted acyl.

4. The compound of Claim 1, wherein R^1 is –CH(OH)-($S(=O)_2$-O^-), –CH(OH)((P=O)(OR^9)$_2$), wherein each R^9 are independently hydrogen, an unsubstituted C_{1-6} alkyl, an unsubstituted C_{2-6} alkenyl, an unsubstituted C_{1-6} haloalkyl, an unsubstituted or a substituted aryl or an unsubstituted or a substituted aryl(C_{1-4} alkyl), or –C(=O)CH_2-O-((P=O)(OR^{10})$_2$), wherein each R^{10} are independently hydrogen, an unsubstituted C_{1-6} alkyl, an unsubstituted C_{2-6} alkenyl, an unsubstituted C_{1-6} haloalkyl, an unsubstituted or a substituted aryl or an unsubstituted or a substituted aryl(C_{1-4} alkyl).

5. The compound of Claim 1, wherein R^1 is cyano.

6. The compound of Claim 1, wherein Z^1 is –C(=O)–.

7. The compound of Claim 1, wherein Ring A^1 is an unsubstituted or a substituted pyrrolidine.

8. The compound of Claim 1, wherein Ring A^1 is an unsubstituted or a substituted azetidine, wherein the azetidine is connected to a cyclic moiety selected from the group consisting of a monocyclic C_{3-7} cycloalkyl, a bicyclic C_{5-9} cycloalkyl, a monocyclic C_{3-7} cycloalkenyl, a bicyclic C_{5-9} cycloalkenyl and phenyl, wherein the cyclic moiety is connected to the azetidine in a fused-fashion or a spiro-fashion that can be optionally substituted with one or more moieties independently selected from the group consisting of halogen, an unsubstituted C_{1-4} alkyl and an unsubstituted C_{2-4} alkenyl, or an unsubstituted or a substituted pyrrolidine, wherein the pyrrolidine is connected to a cyclic moiety selected from the group consisting of a monocyclic C_{3-7} cycloalkyl, a bicyclic C_{5-9} cycloalkyl, a monocyclic C_{3-7} cycloalkenyl, a bicyclic C_{5-9} cycloalkenyl and phenyl, wherein the cyclic moiety is connected to the pyrrolidine in a fused-fashion or a spiro-fashion that can be optionally substituted with one or more moieties independently selected from the group consisting of halogen, an unsubstituted C_{1-4} alkyl and an unsubstituted C_{2-4} alkenyl, or an unsubstituted or a substituted piperidine, wherein the piperidine is connected to a cyclic moiety selected from the group consisting of a monocyclic C_{3-7} cycloalkyl, a bicyclic C_{5-9} cycloalkyl, a monocyclic C_{3-7} cycloalkenyl, a bicyclic C_{5-9} cycloalkenyl and phenyl, wherein the cyclic moiety is connected to the piperidine in a fused-fashion or a spiro-fashion that can be optionally substituted with one or more moieties independently selected from the group consisting of halogen, an unsubstituted C_{1-4} alkyl and an unsubstituted C_{2-4} alkenyl.

9. The compound of Claim 1, wherein Z^2 is NR^8; and Z^3 is CR^5.

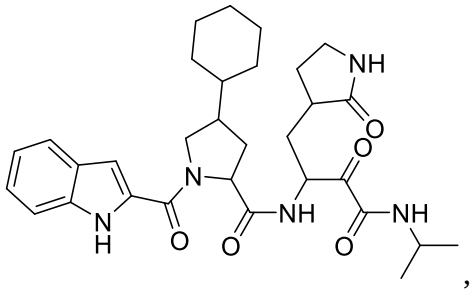
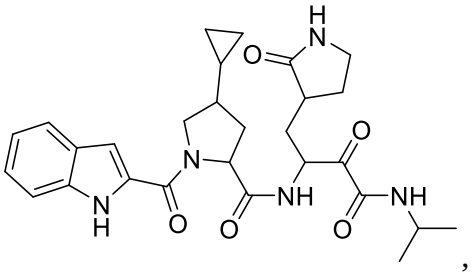
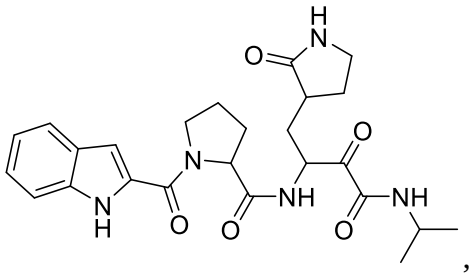
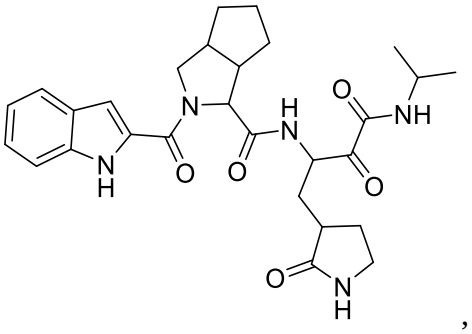
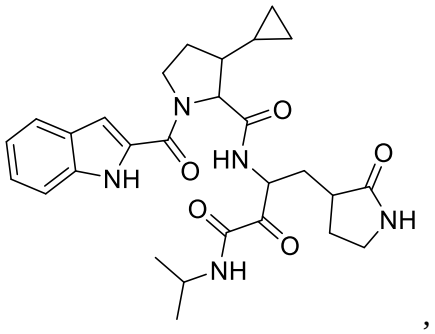
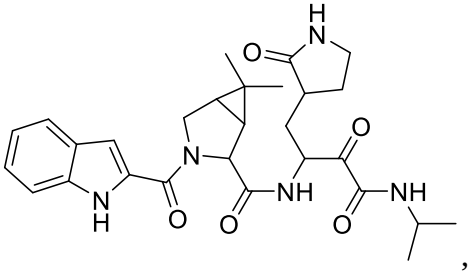
10. The compound of Claim 1, wherein R^6 and R^7 are taken together with the carbon to which R^6 and R^7 are each attached to form an optionally substituted 4-7 membered aryl ring or a 4-7 membered heteroaryl ring.

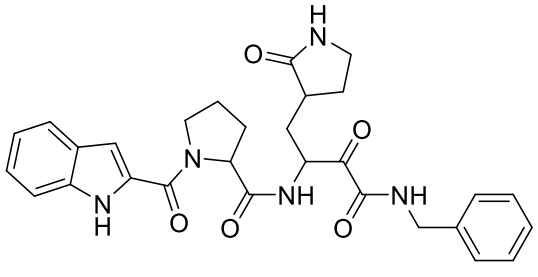
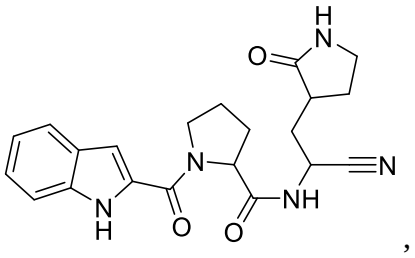
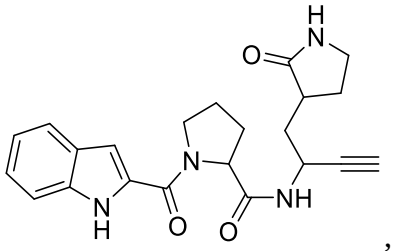
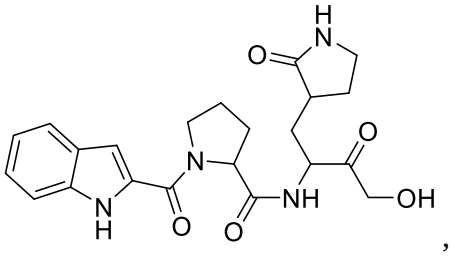
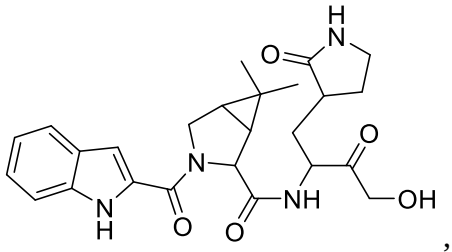
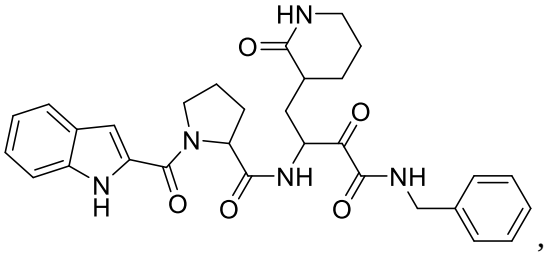
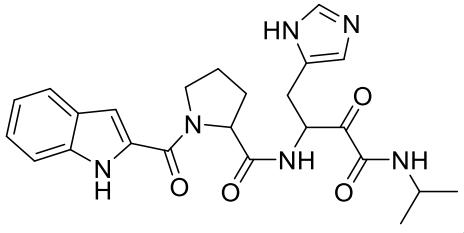
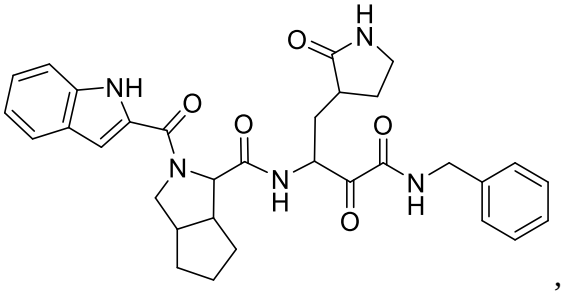
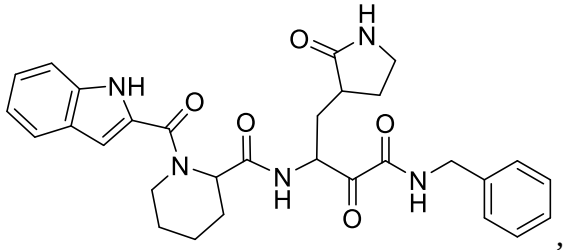
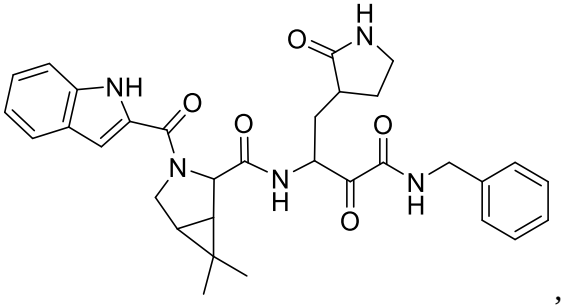
11. The compound of Claim 10, wherein R^6 and R^7 are taken together with the carbon to which R^6 and R^7 are each attached to form an optionally substituted phenyl ring.

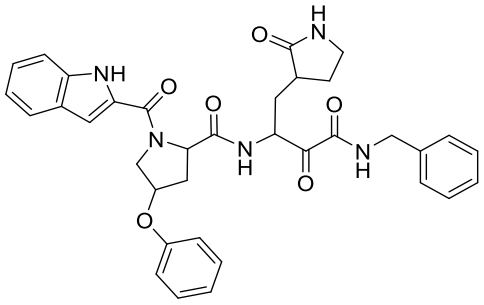
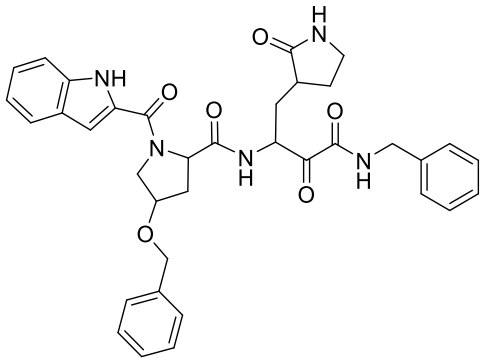
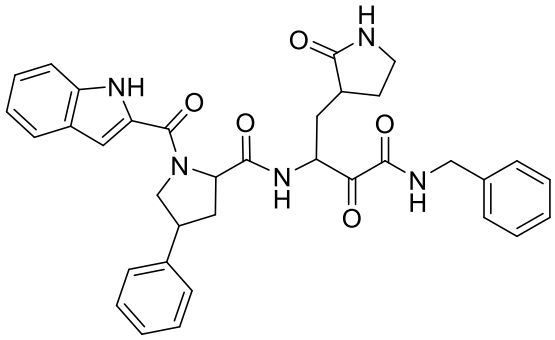
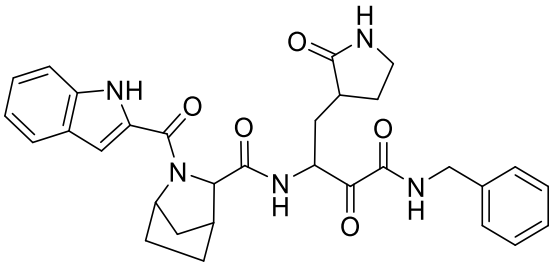
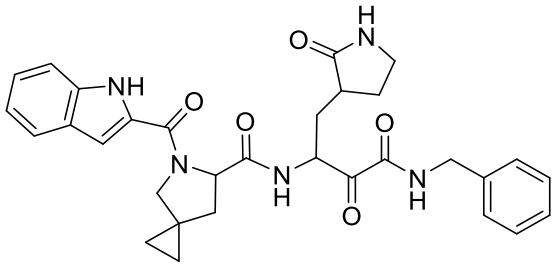
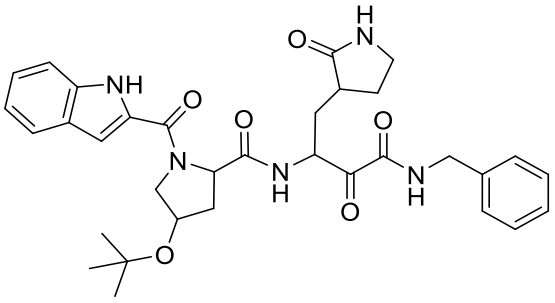
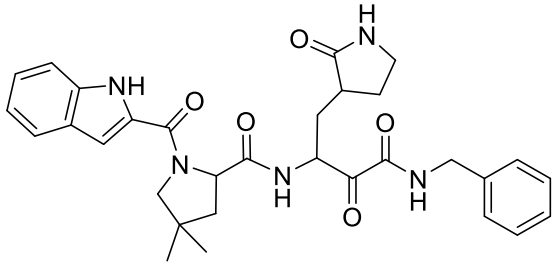
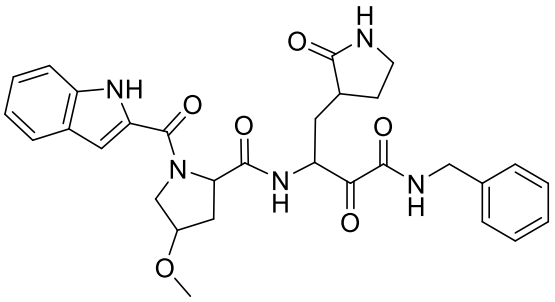
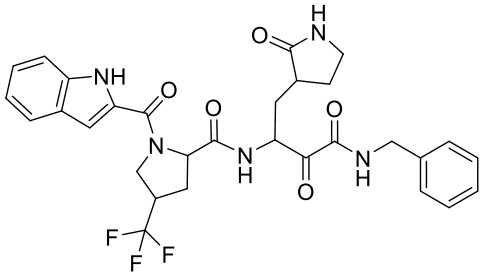
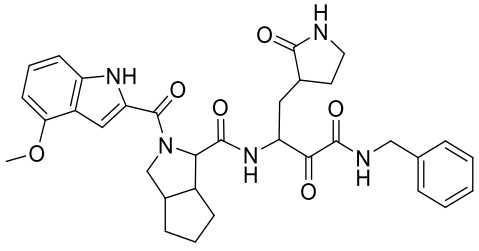
12. The compound of Claim 1, wherein R^3 is an unsubstituted monocyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl) or an unsubstituted or a substituted bicyclic nitrogen-containing heterocyclyl(C_{1-4} alkyl).

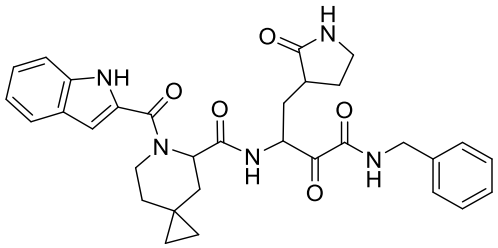
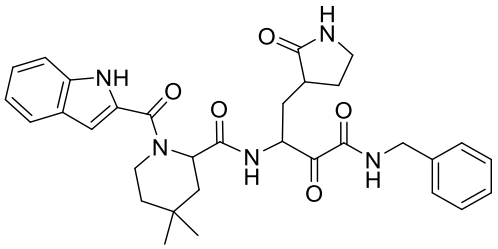
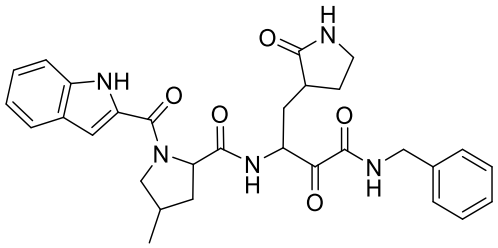
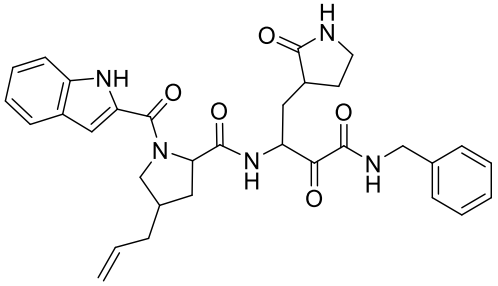
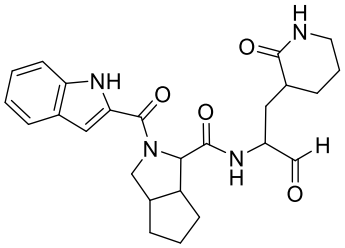
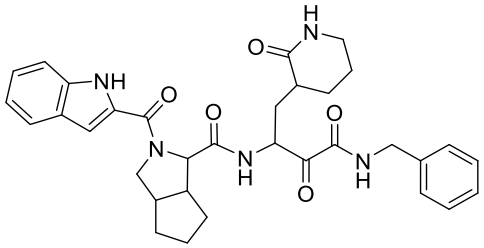
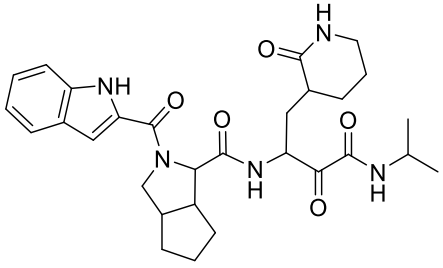
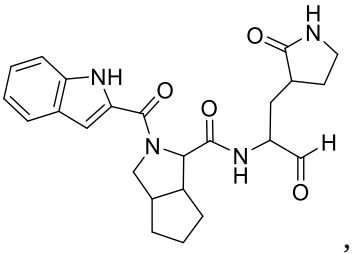
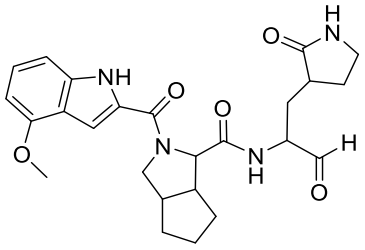
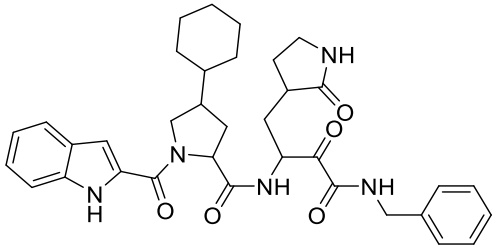
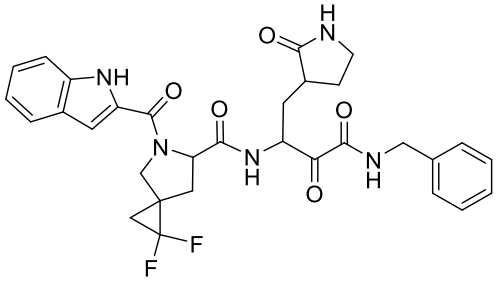
13. The compound of Claim 1, wherein R^2 is hydrogen; and R^4 is hydrogen.

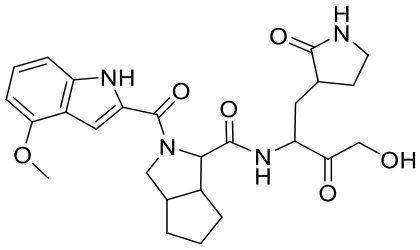
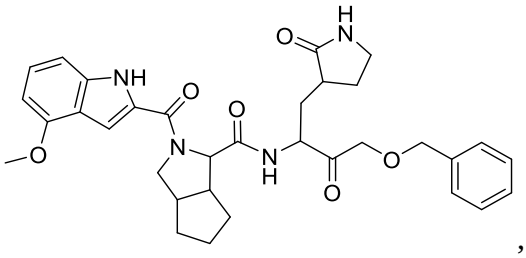
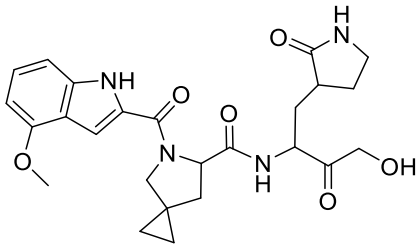
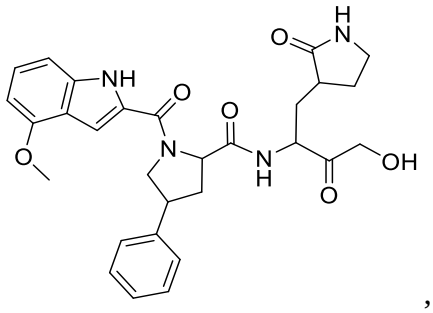
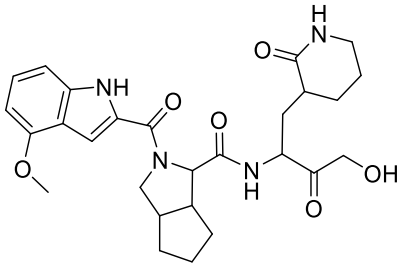
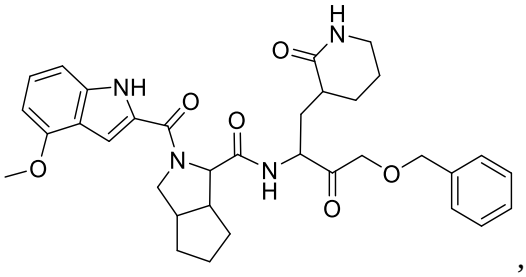
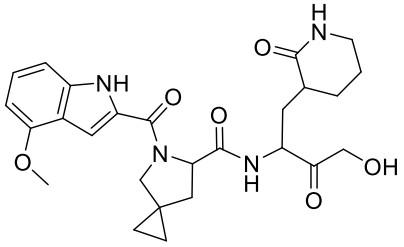
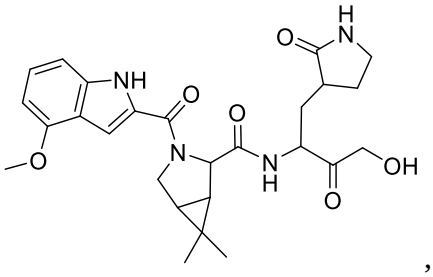
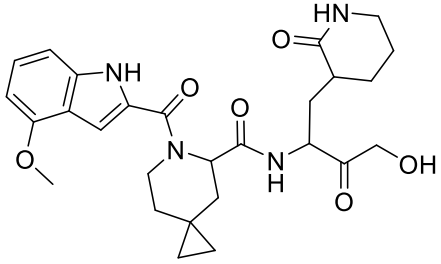
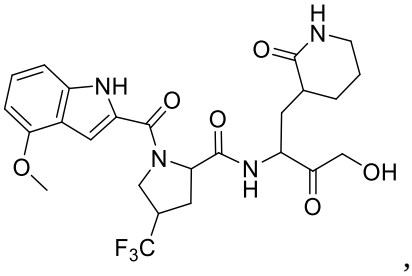
14. The compound of Claim 1, wherein the compound is selected from the group consisting of:

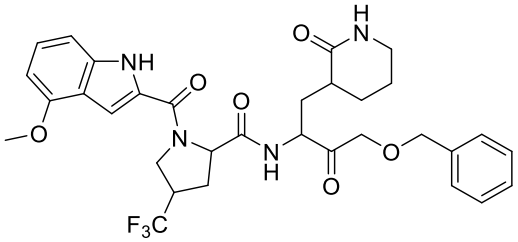
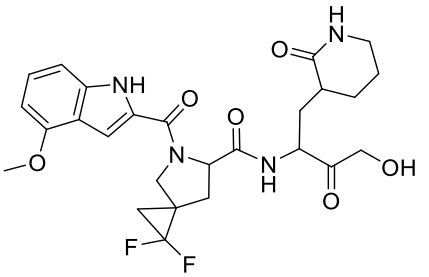
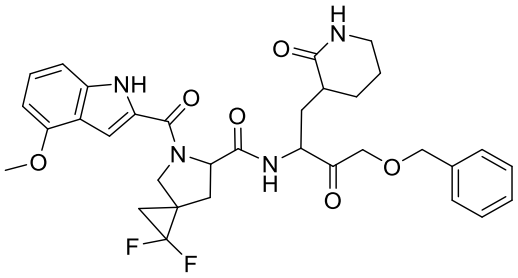
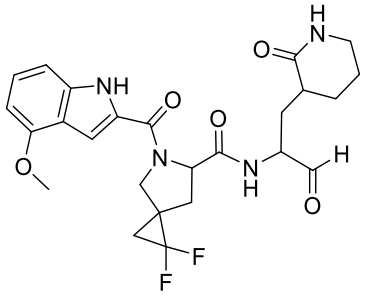
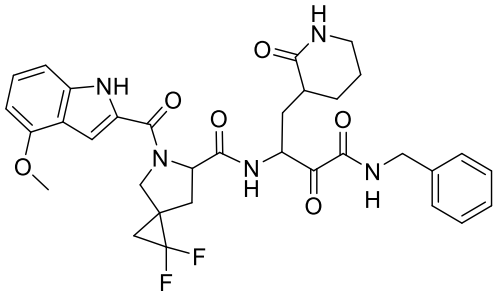
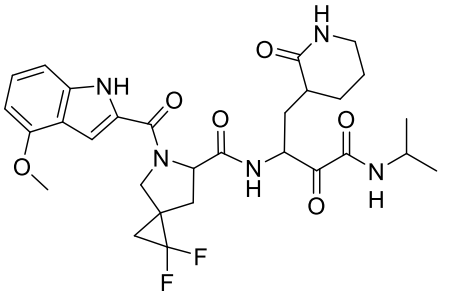
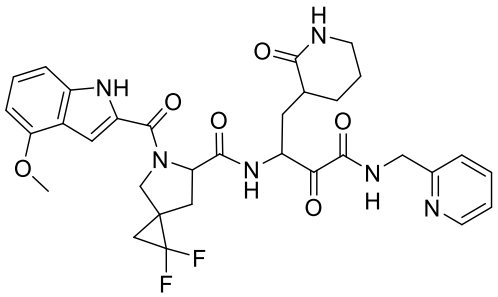
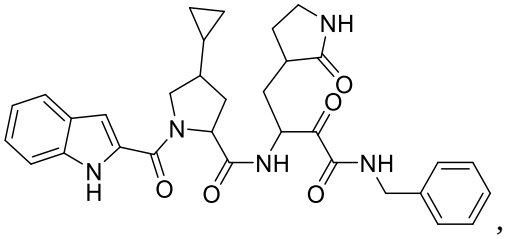
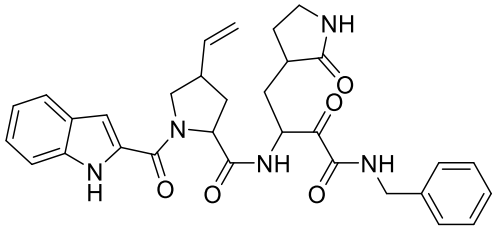
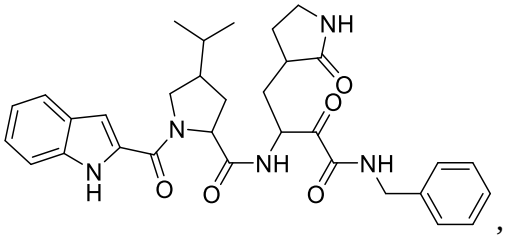

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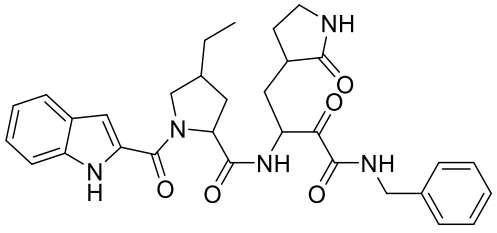
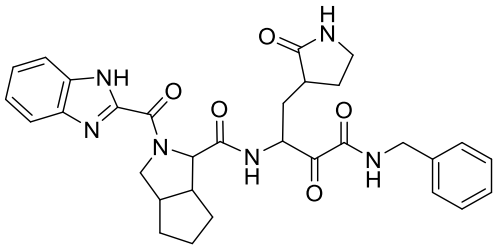
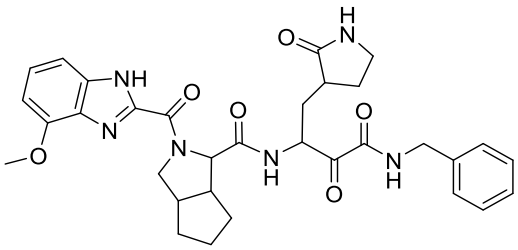
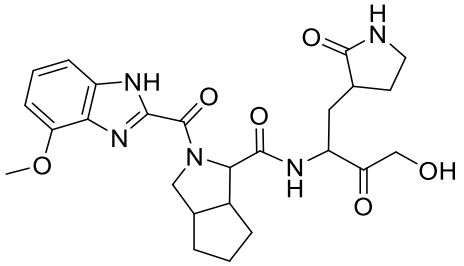
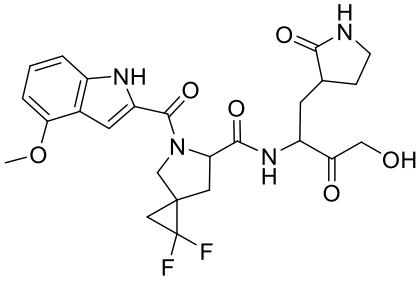
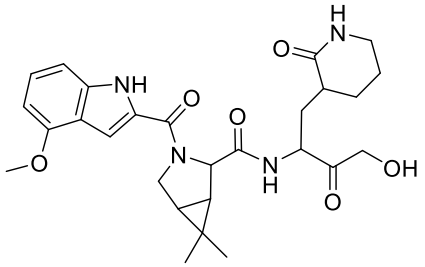
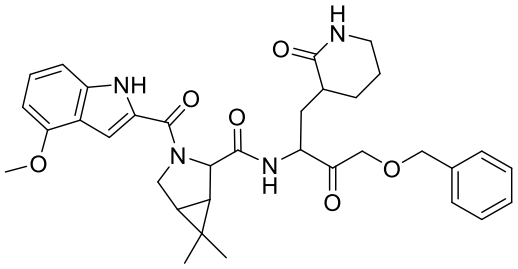
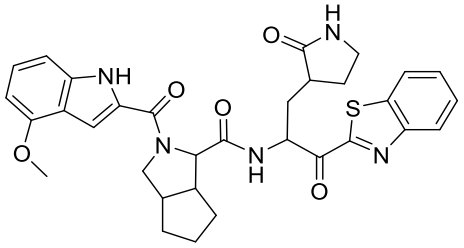
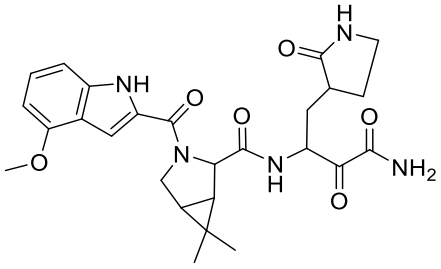
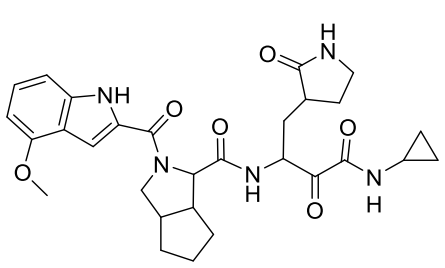

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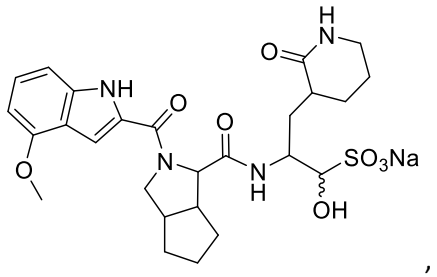
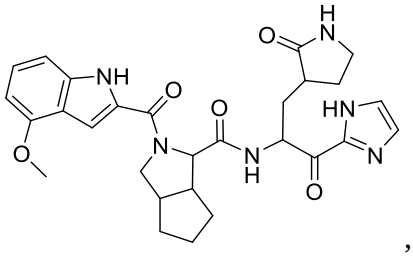
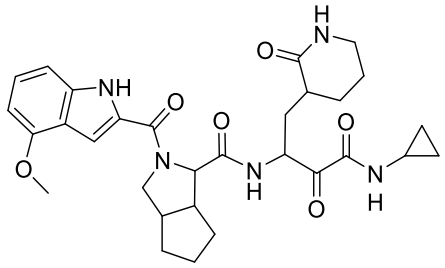
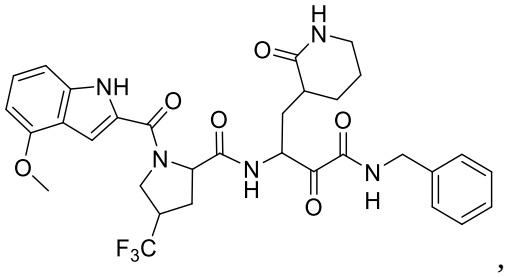
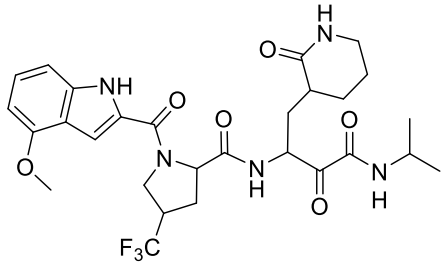
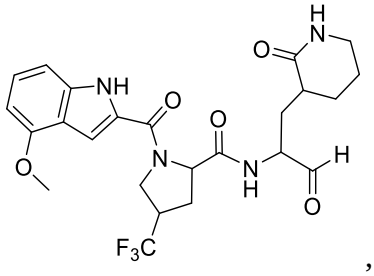
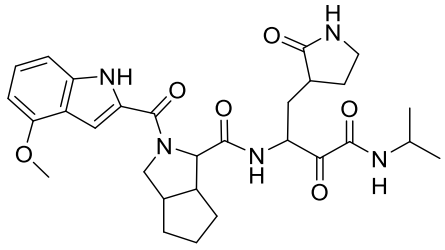
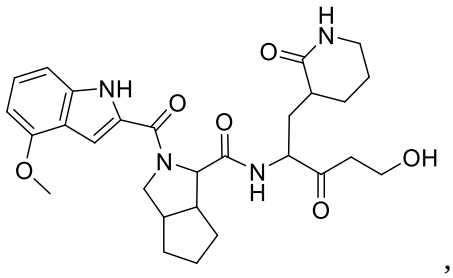
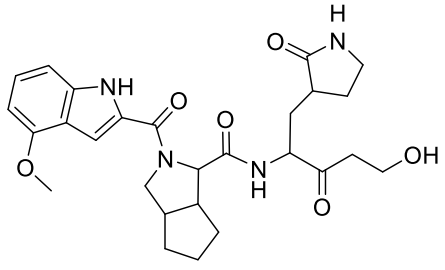
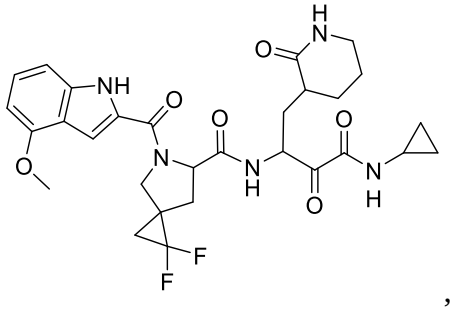

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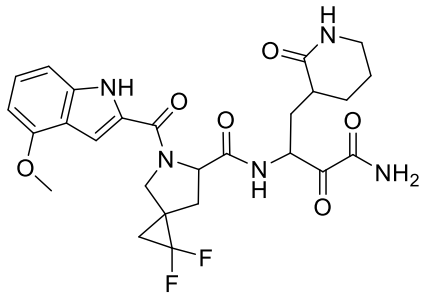
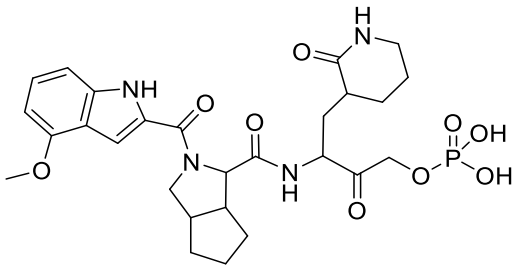
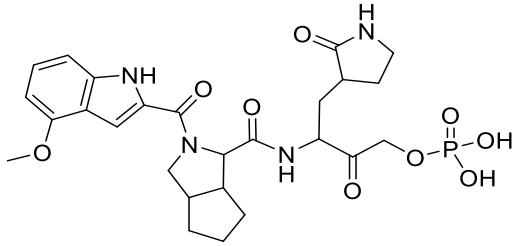
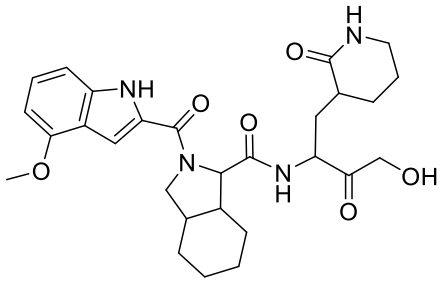
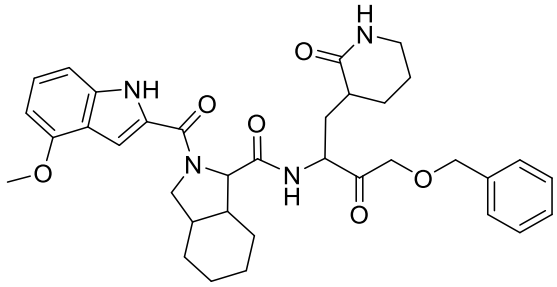
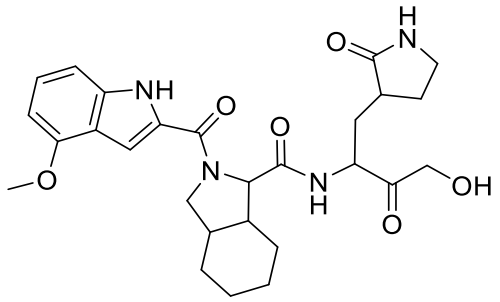
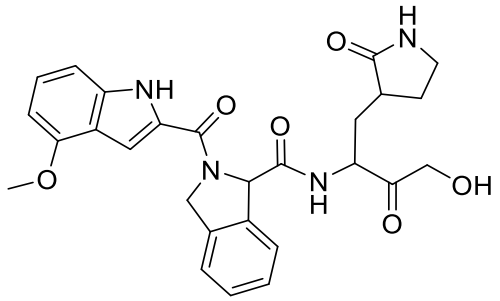
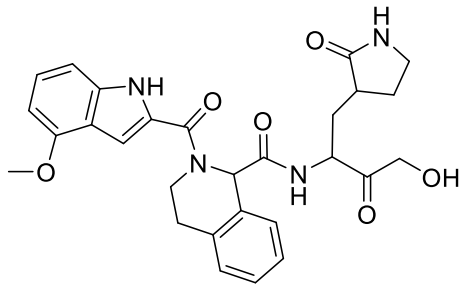
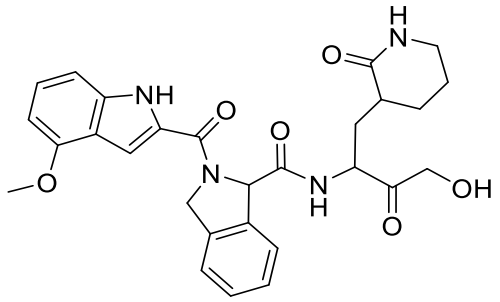
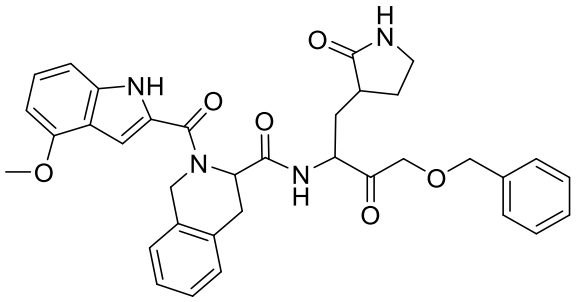

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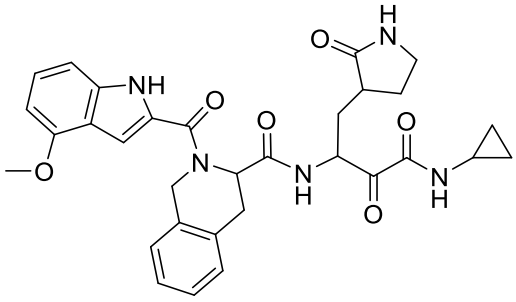
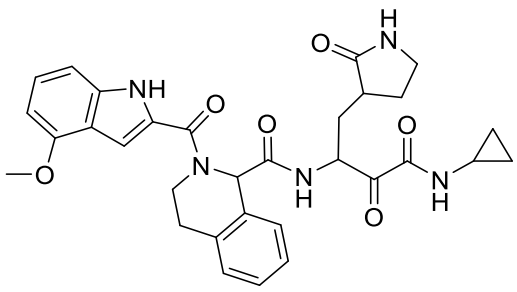
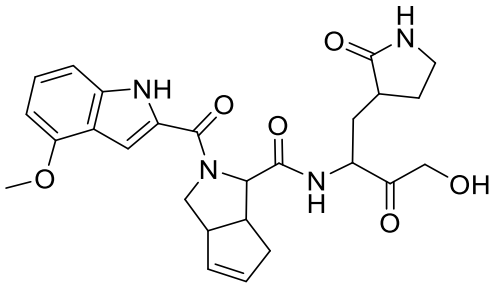
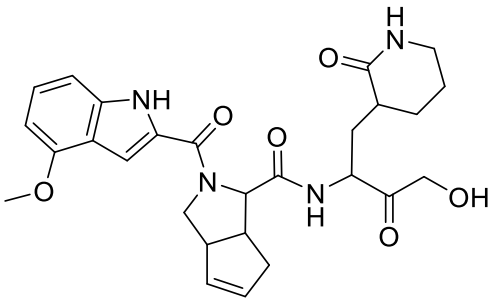
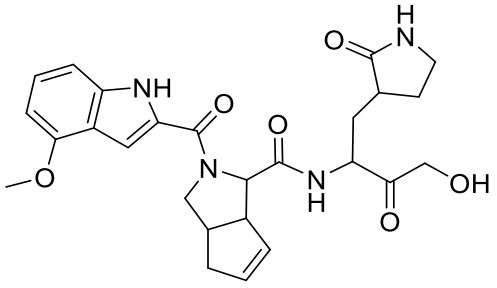
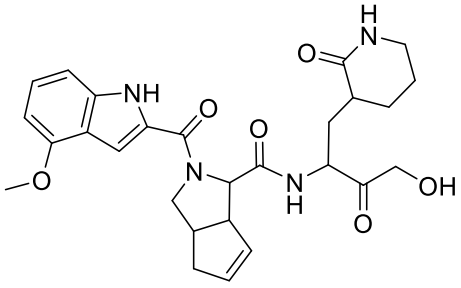
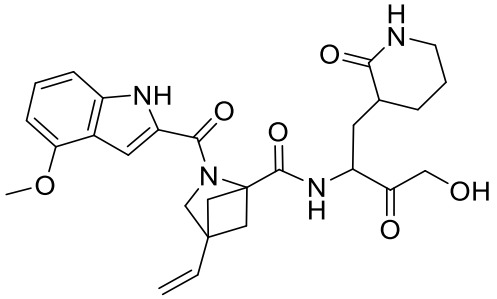
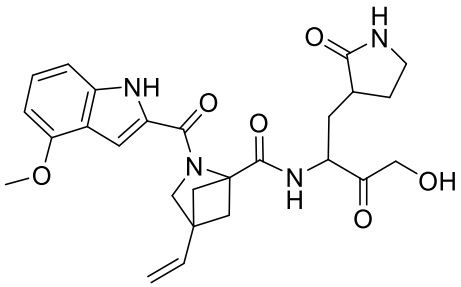
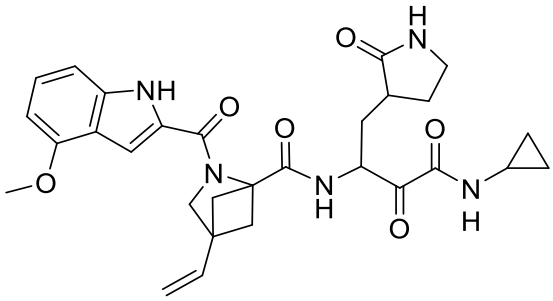
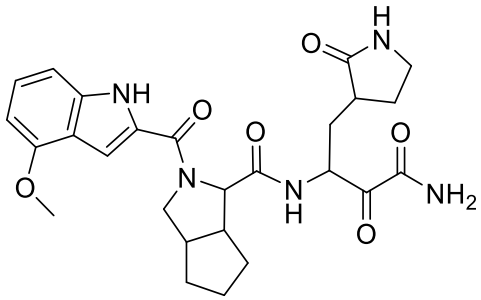

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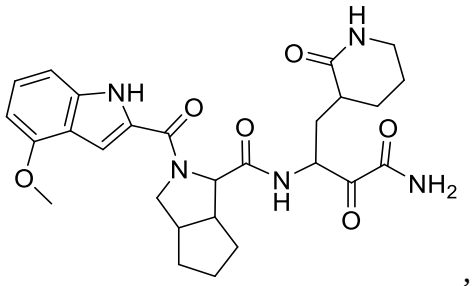
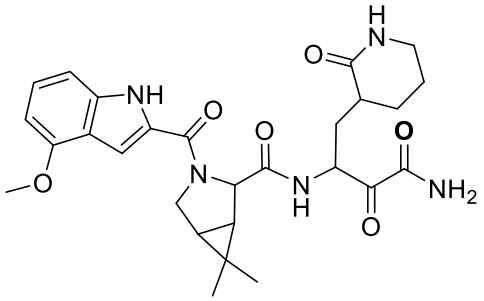
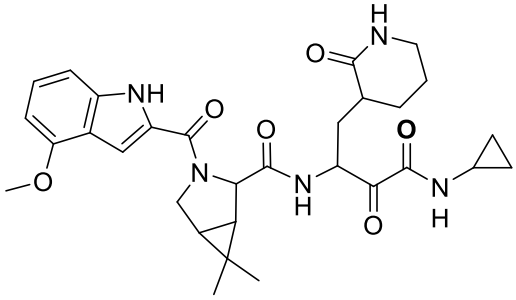
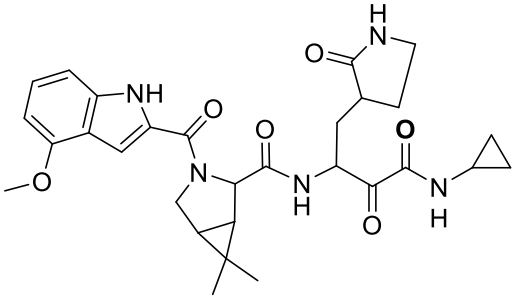
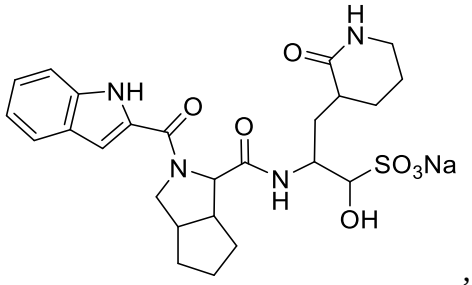
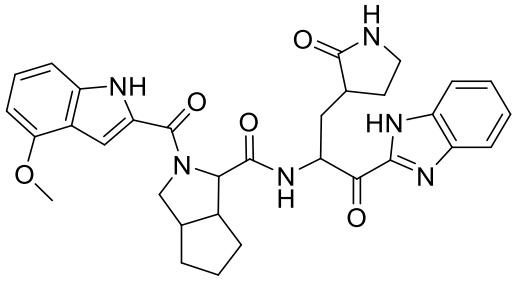
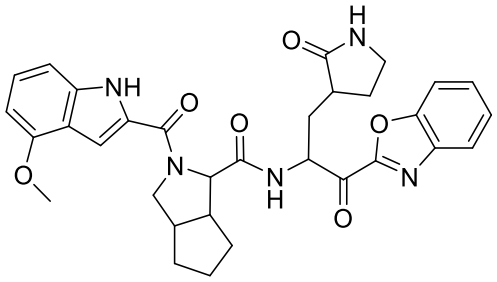
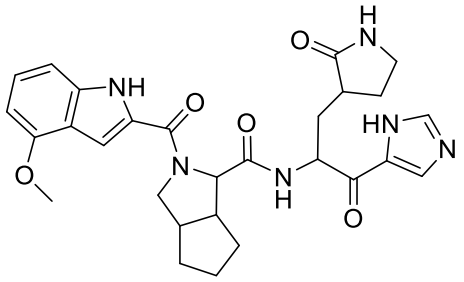
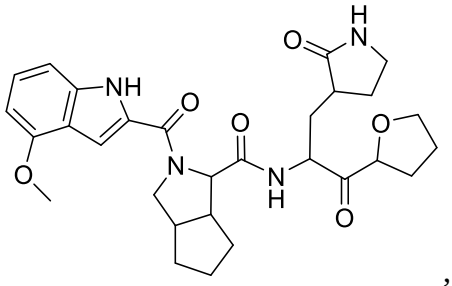
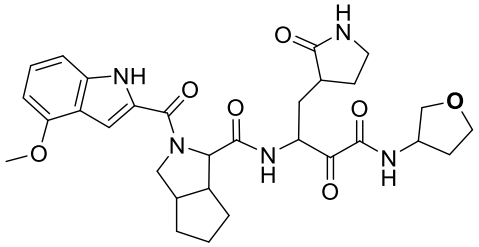

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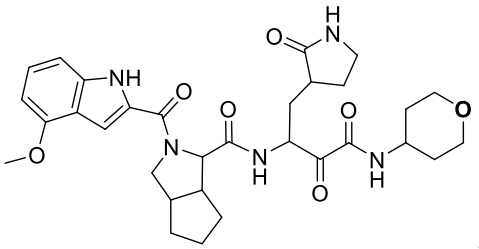
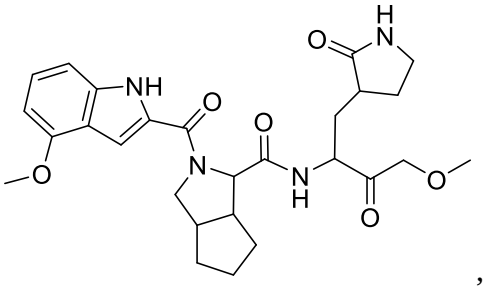
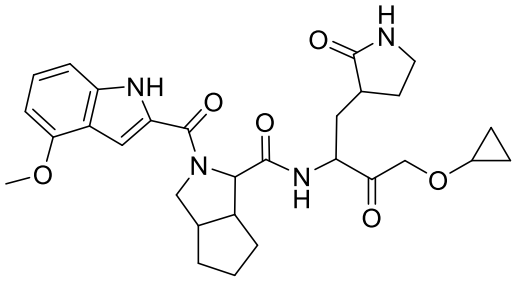
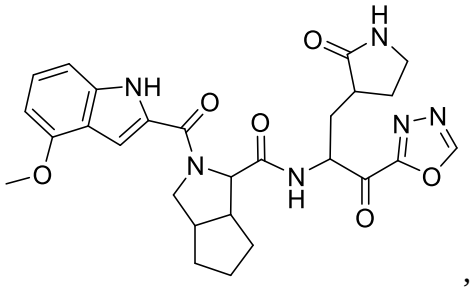
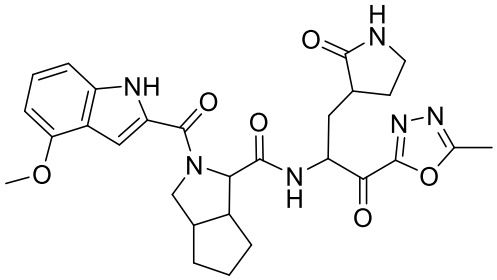
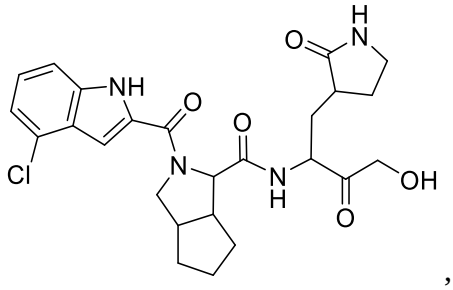
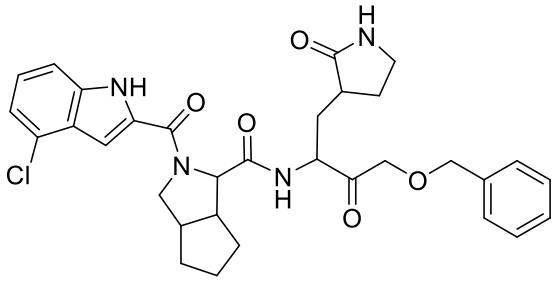
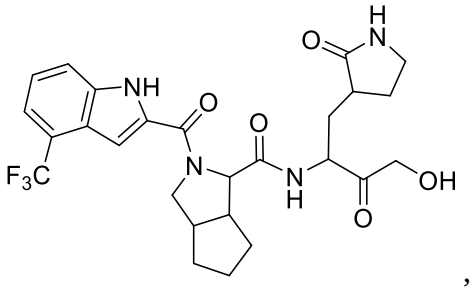
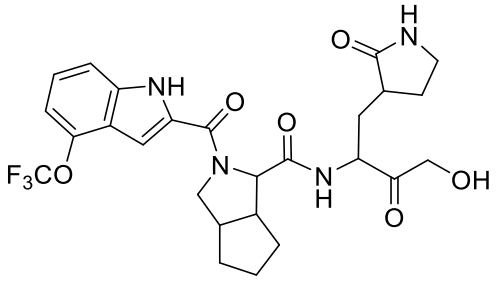
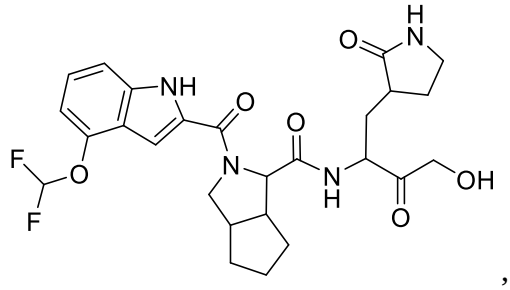

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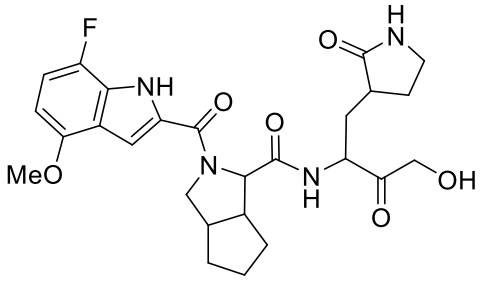
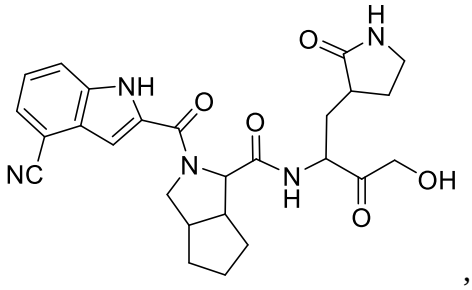
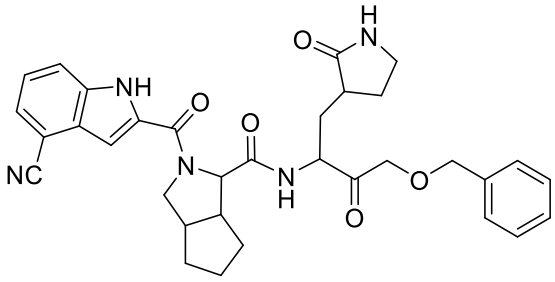
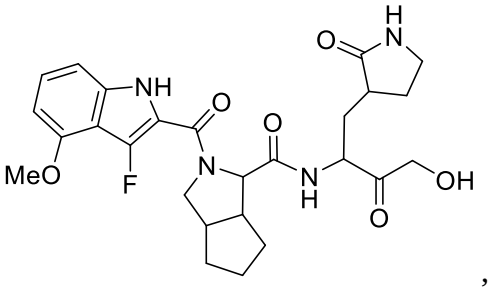
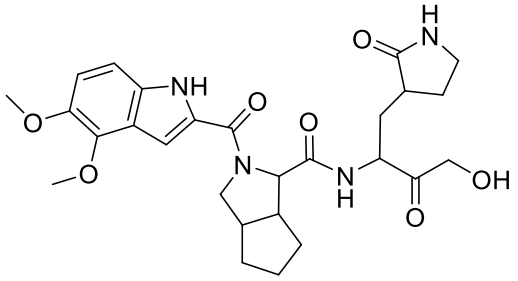
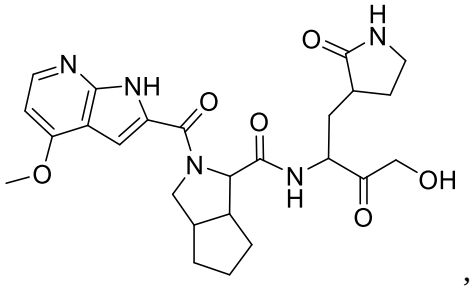
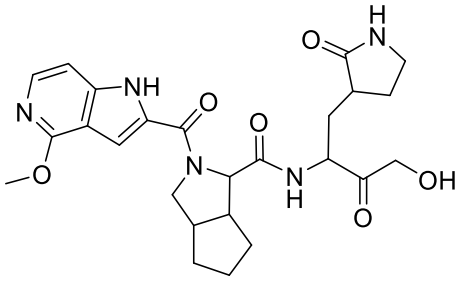
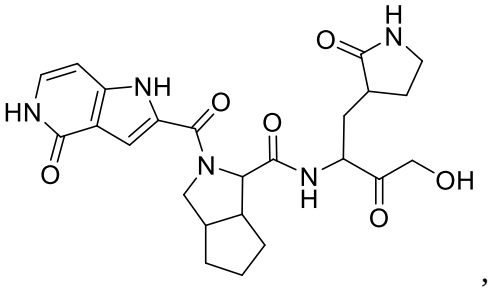
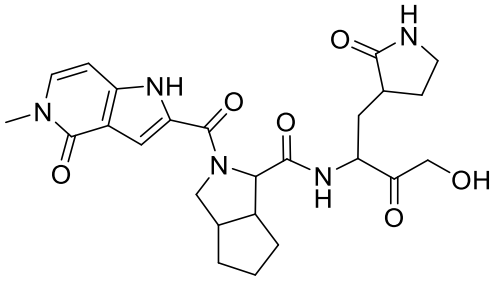
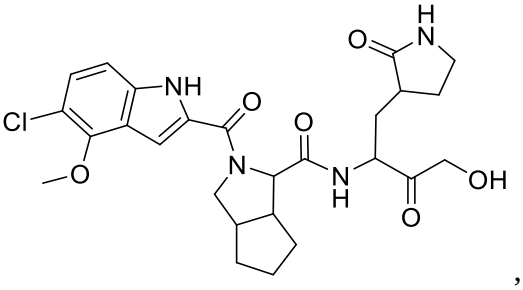

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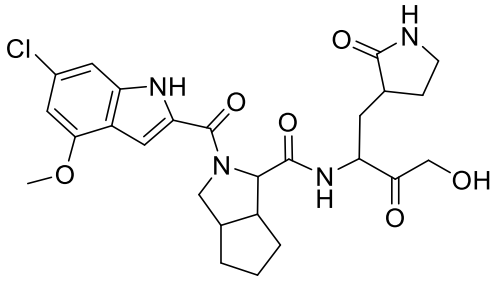
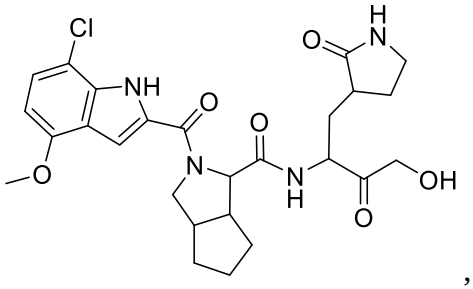
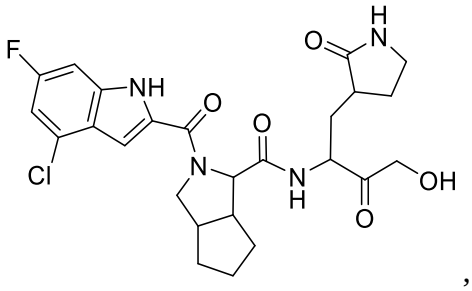
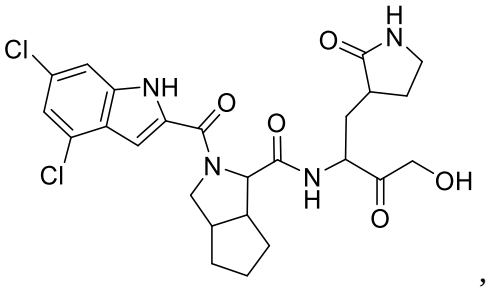
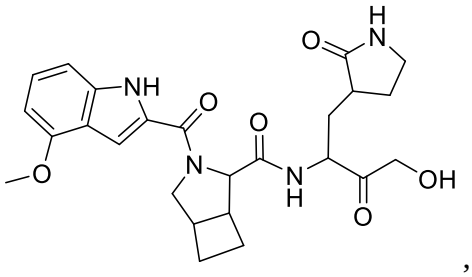
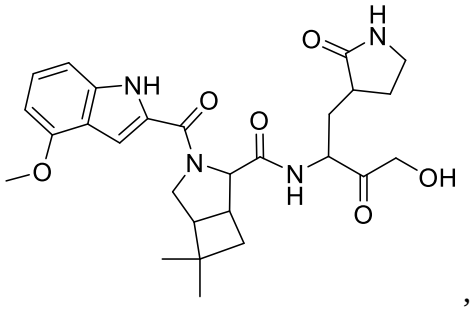
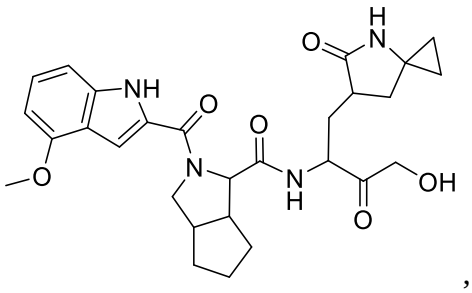
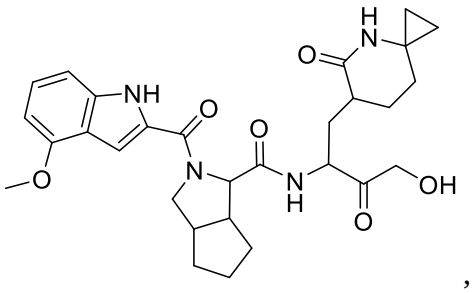
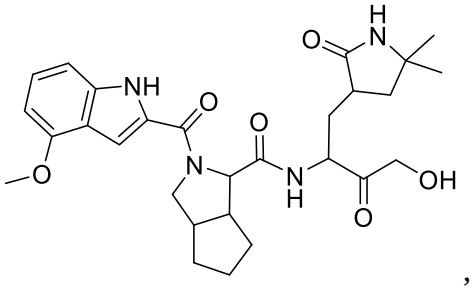
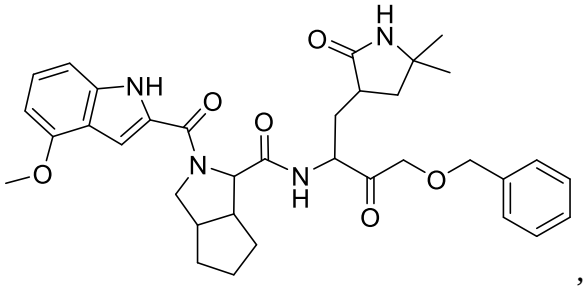

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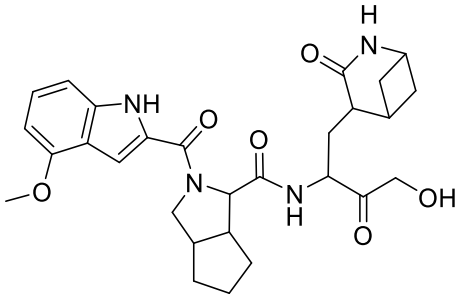
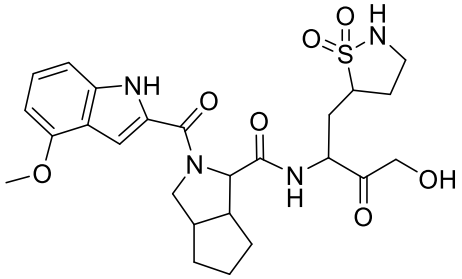
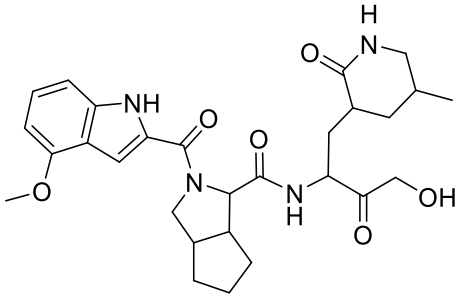
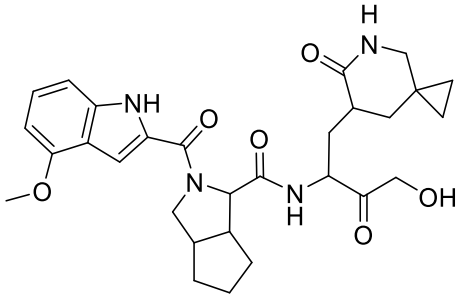
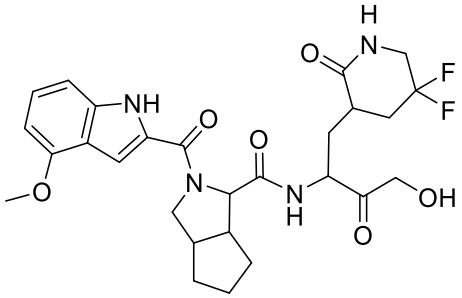
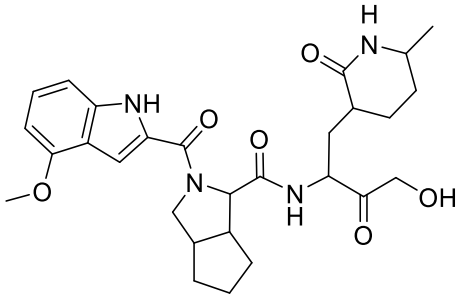
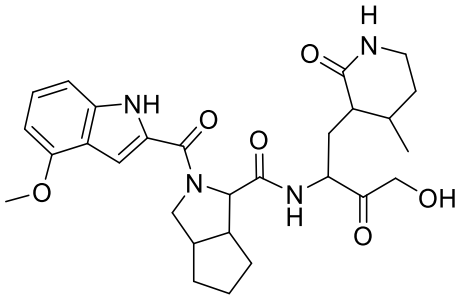
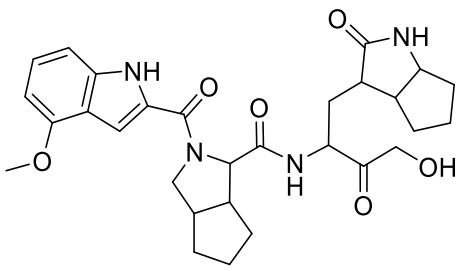
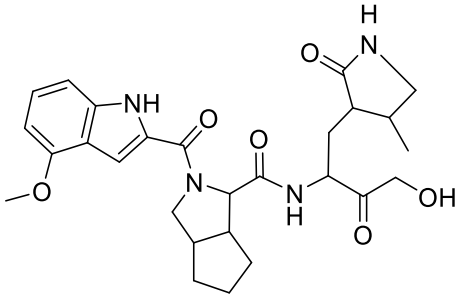
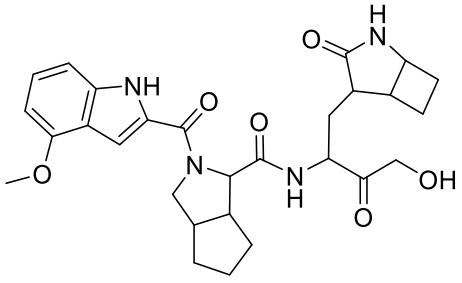

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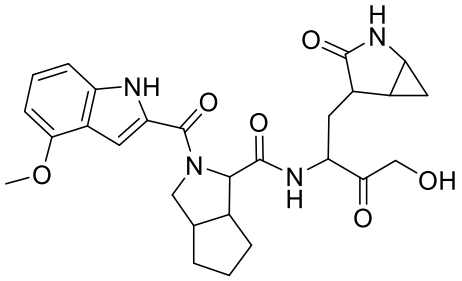
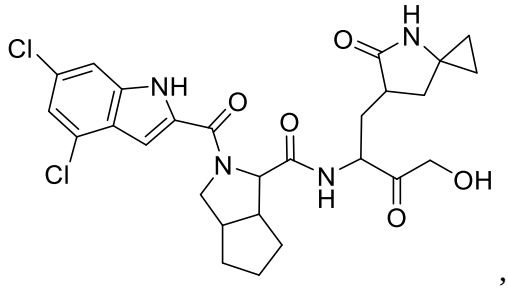
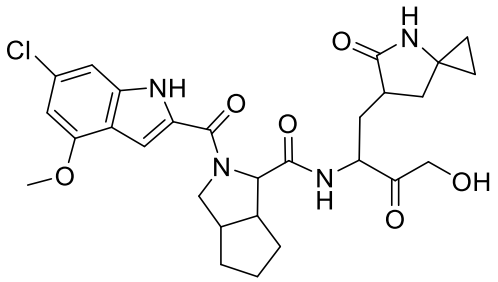
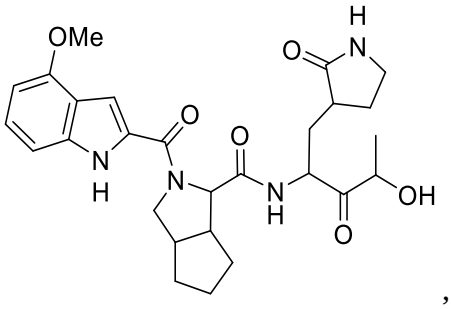
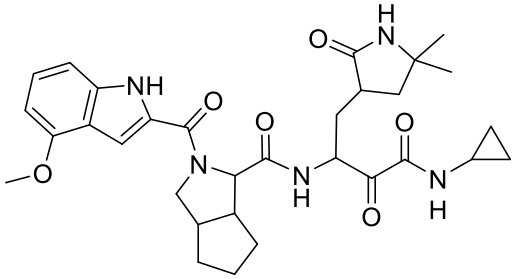
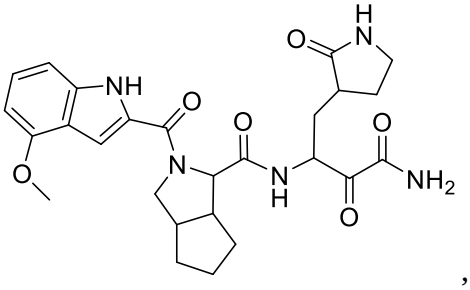
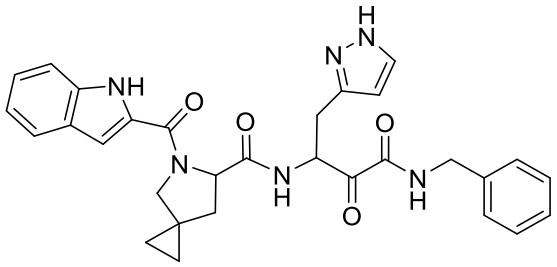
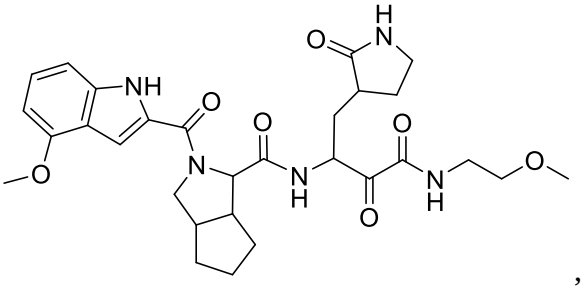
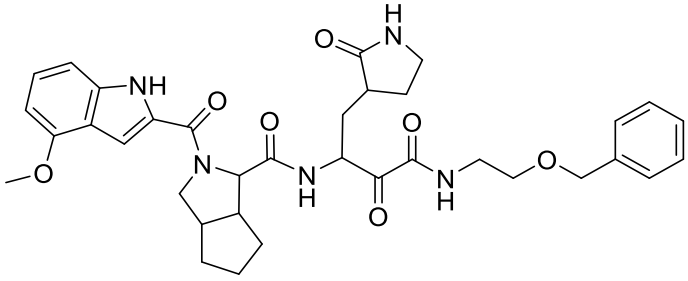

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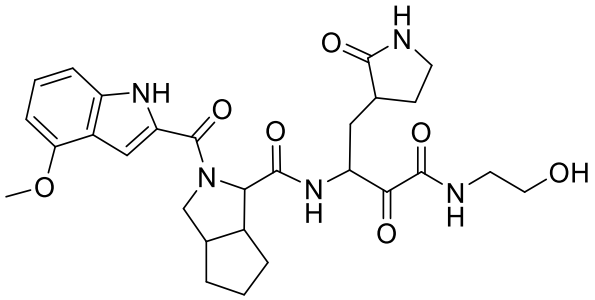
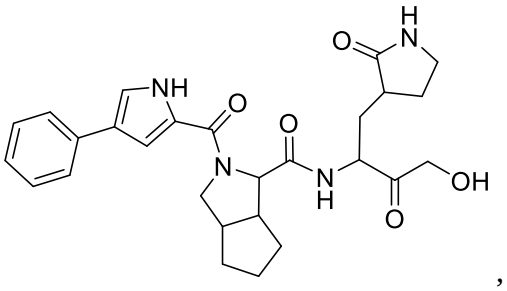
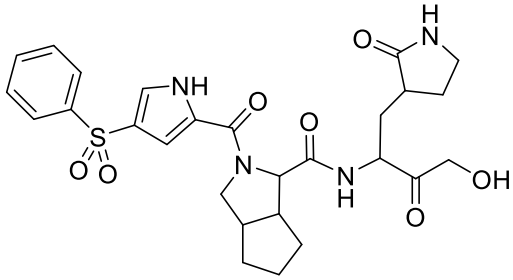
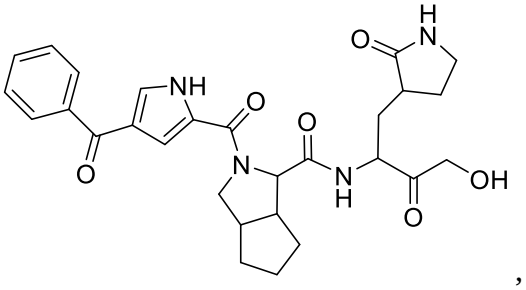
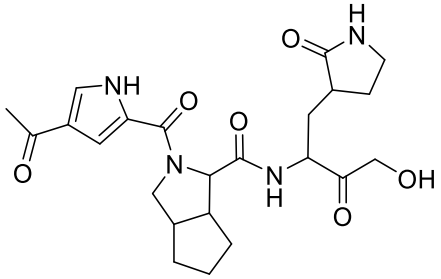
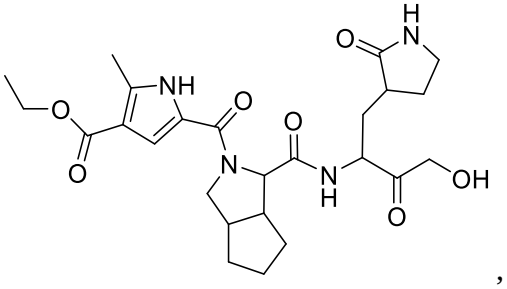
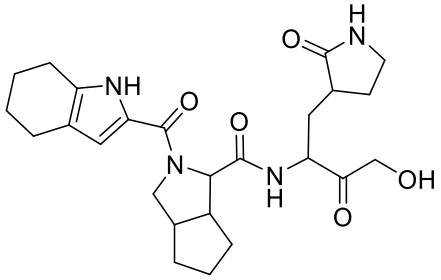
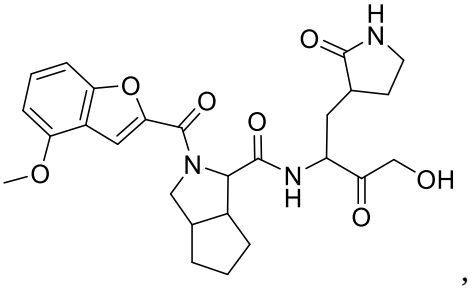
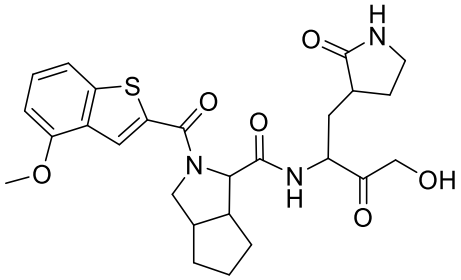
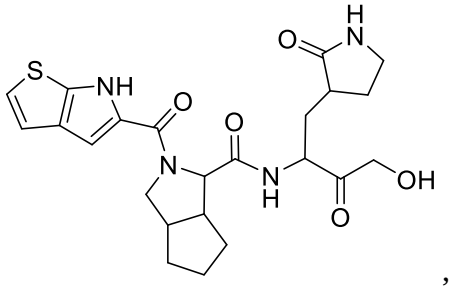

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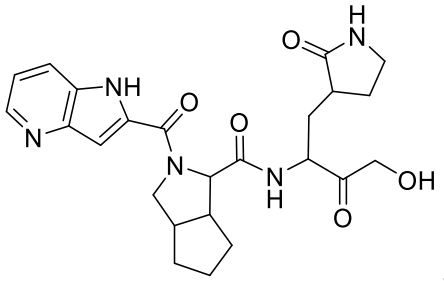
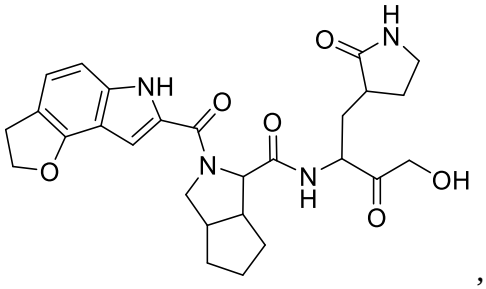
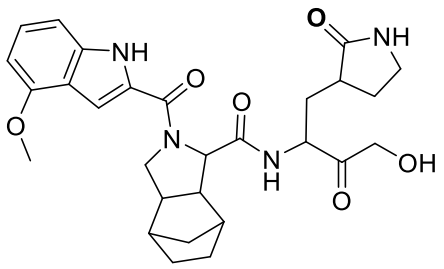
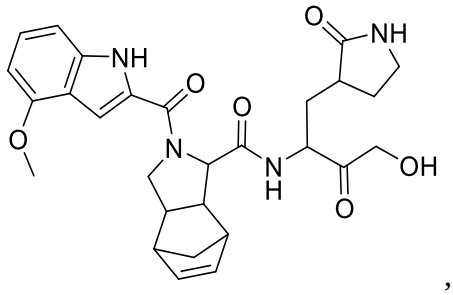
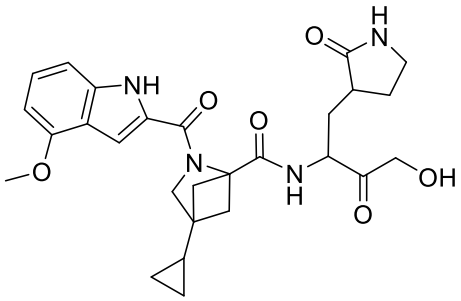
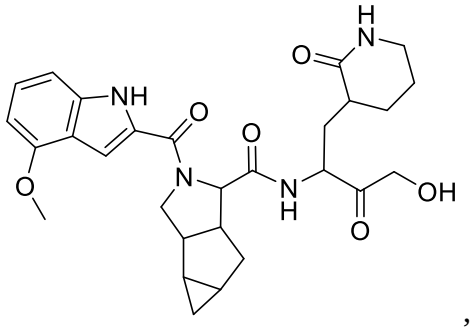
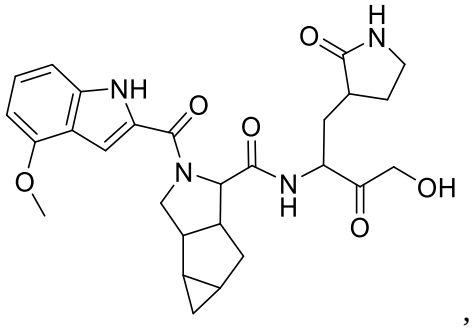
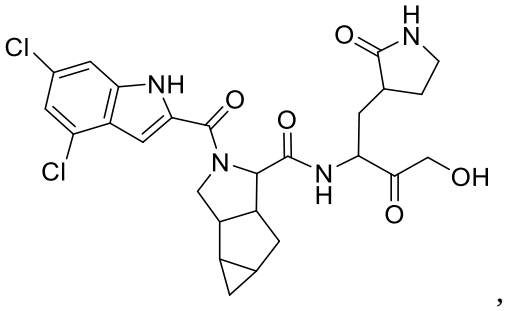
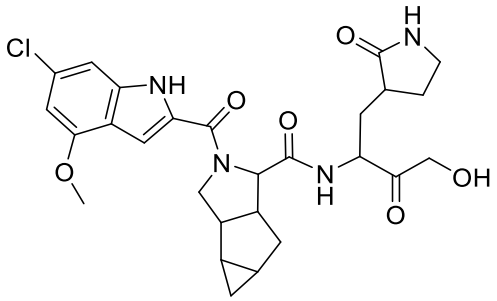
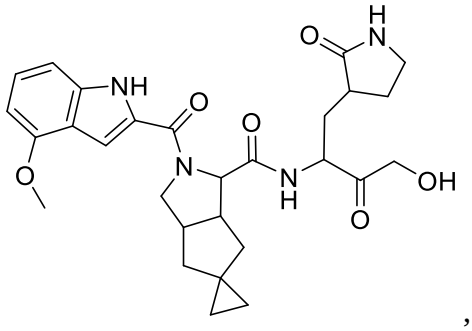

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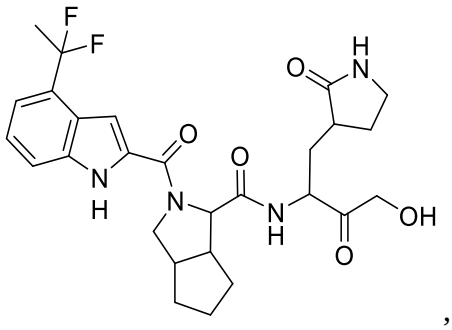
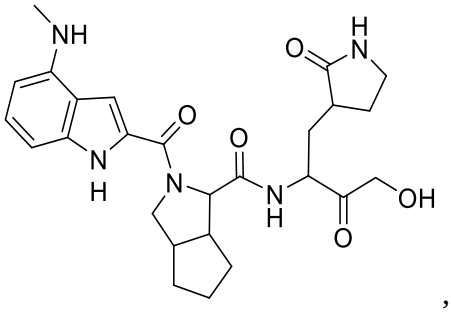
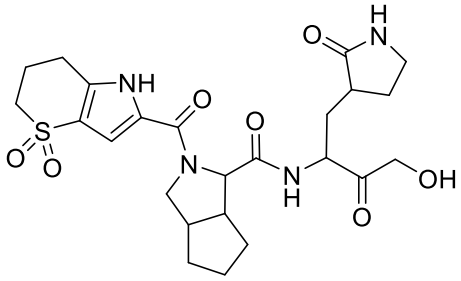
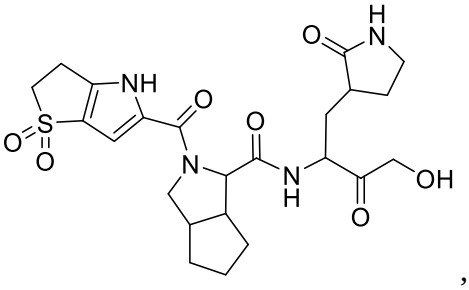
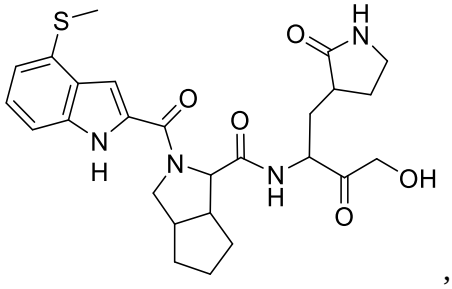
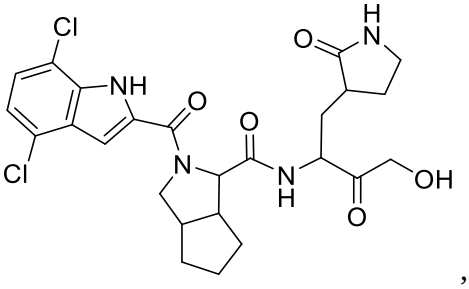
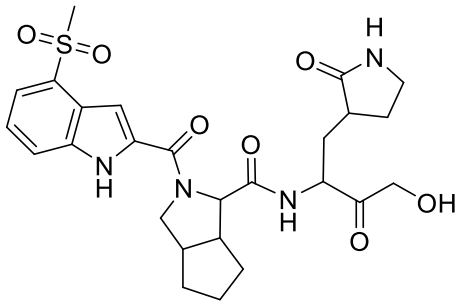
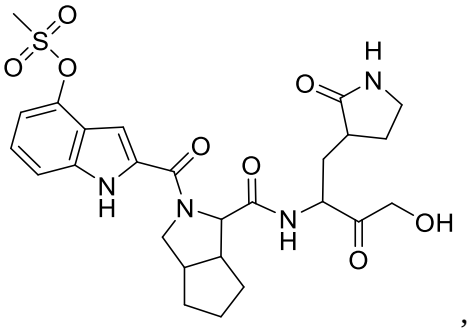
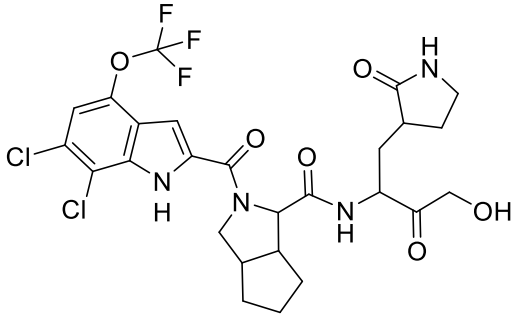
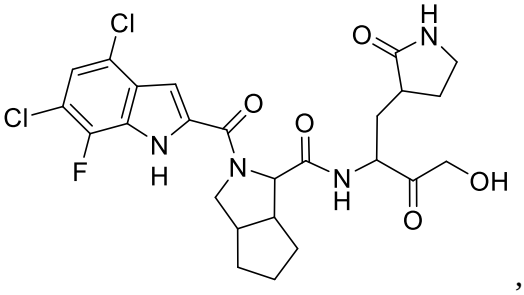

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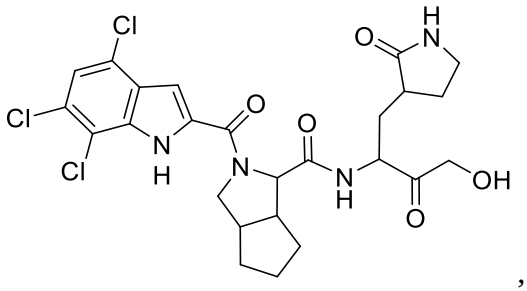
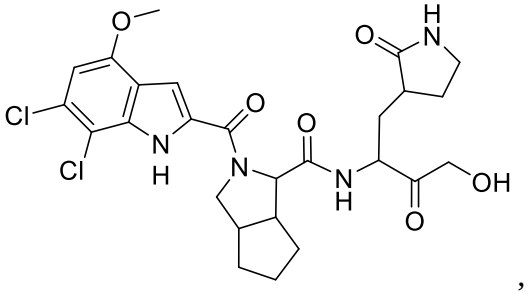
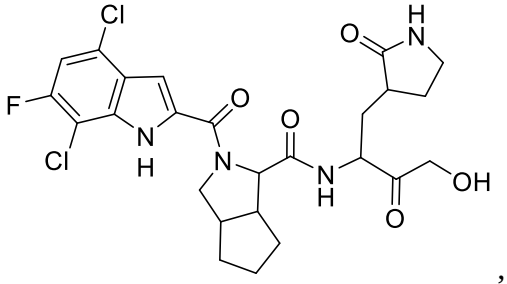
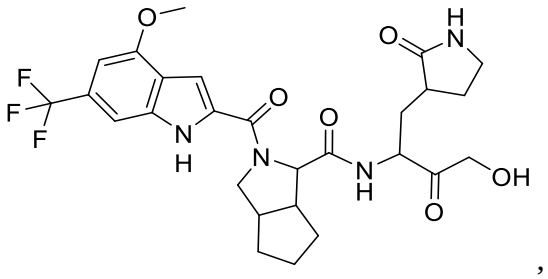
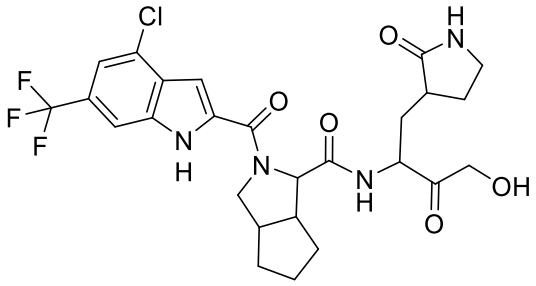
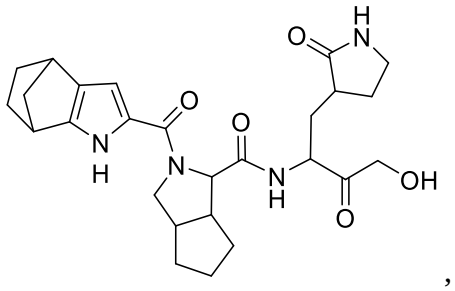
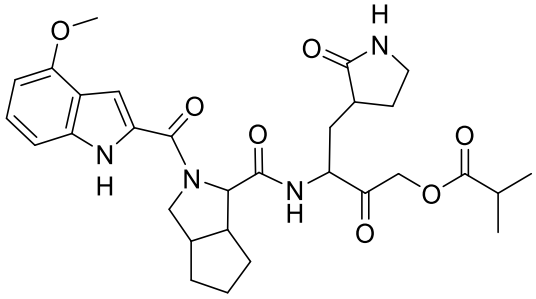
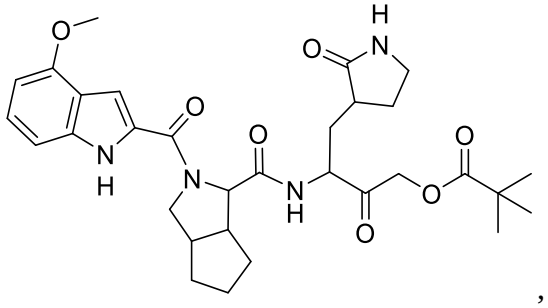
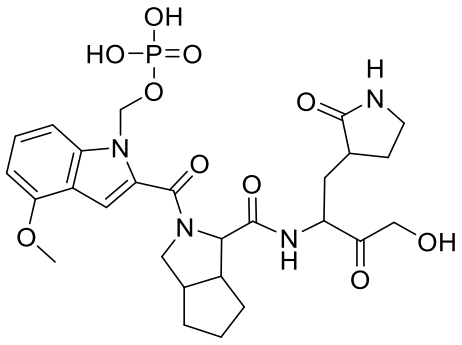
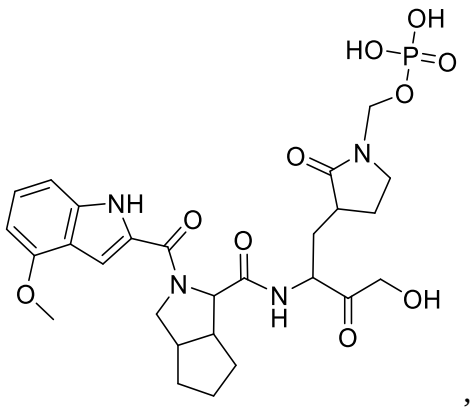

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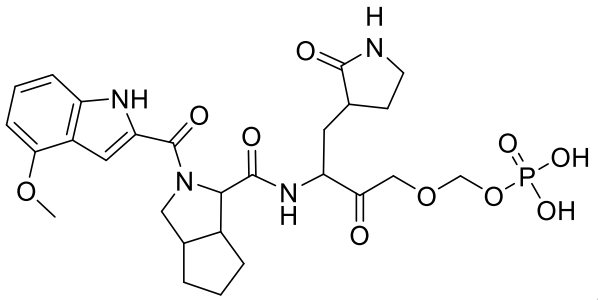
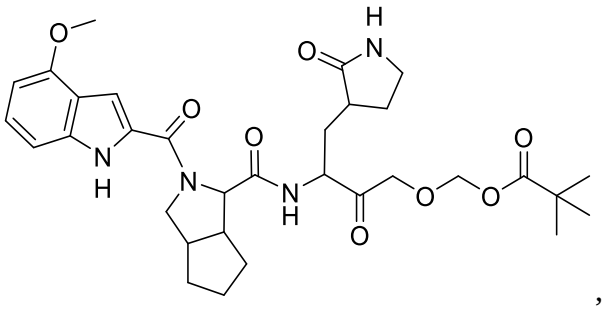
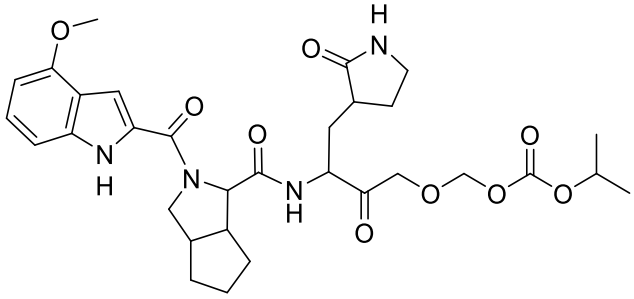
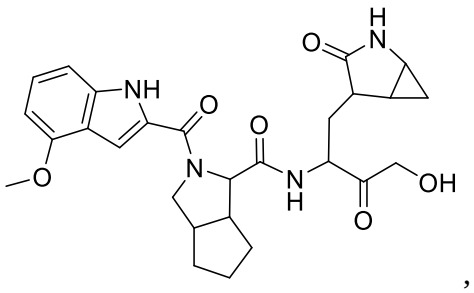
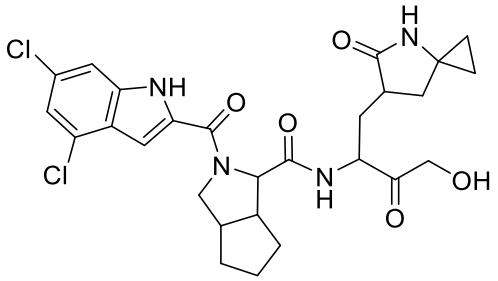
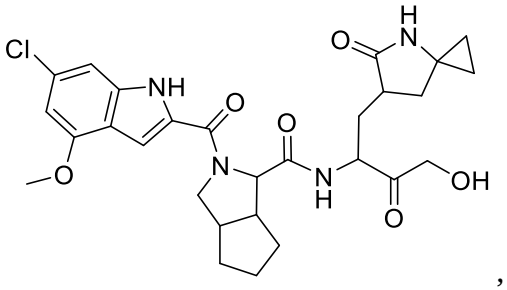
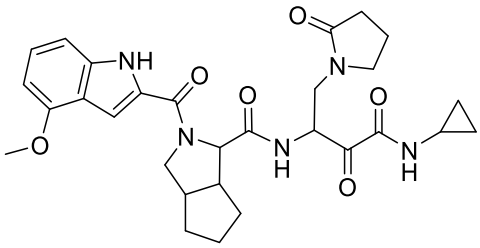
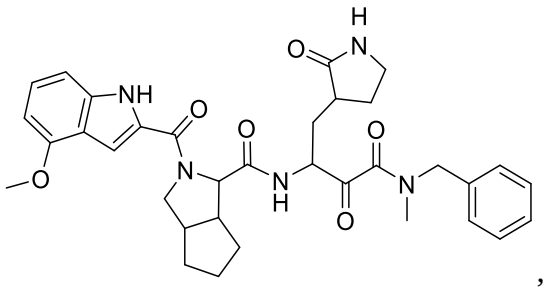
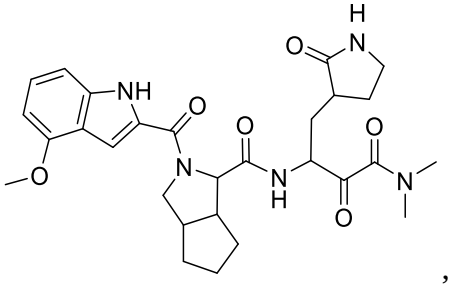
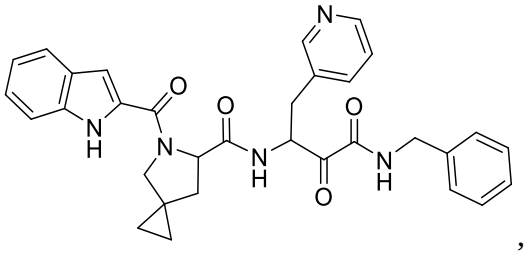

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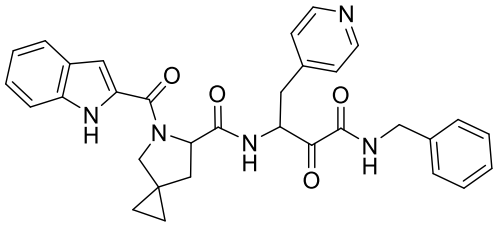
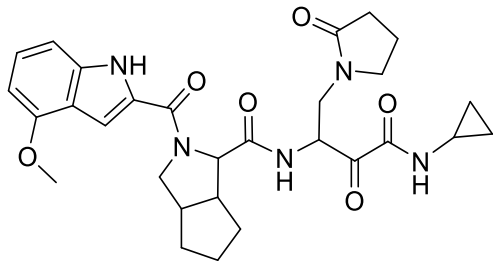
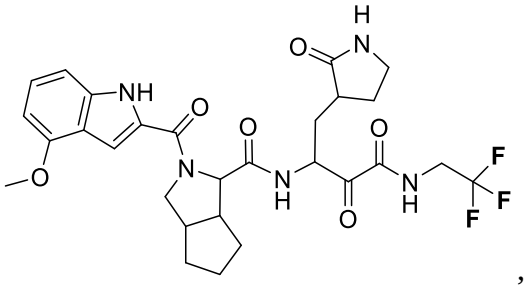
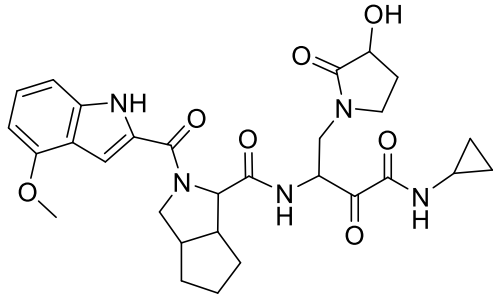
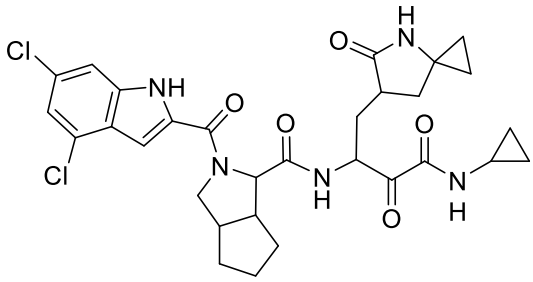
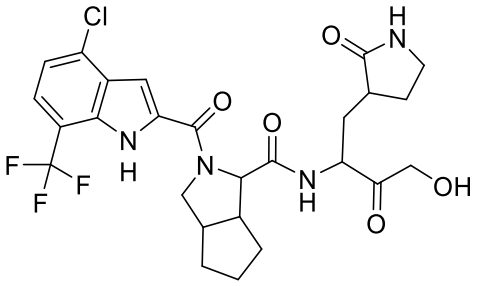
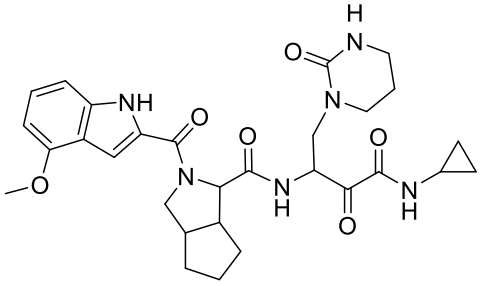
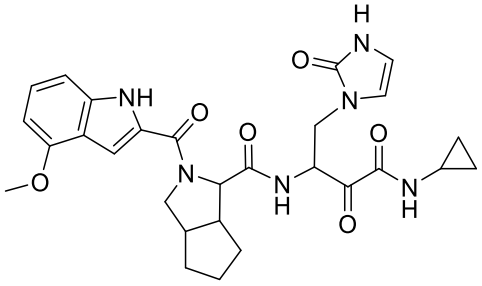
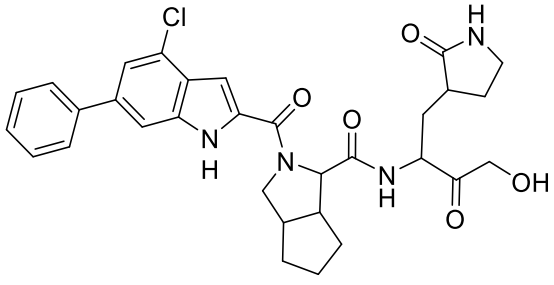
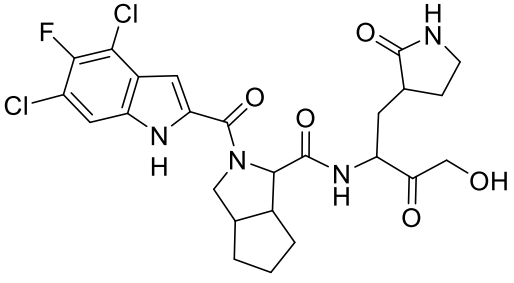

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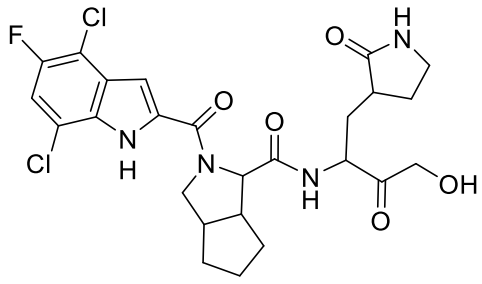
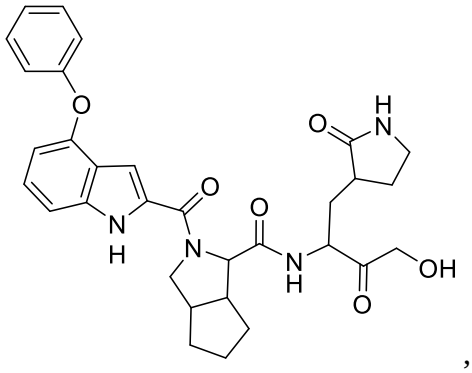
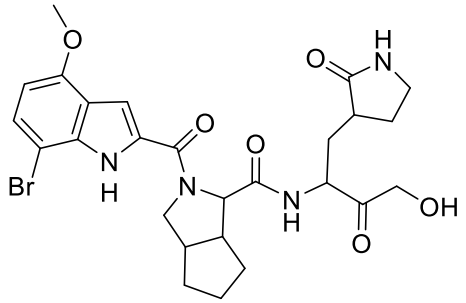
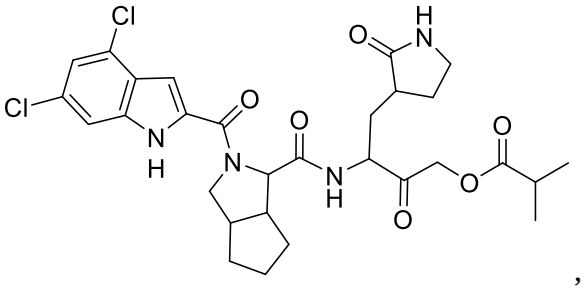
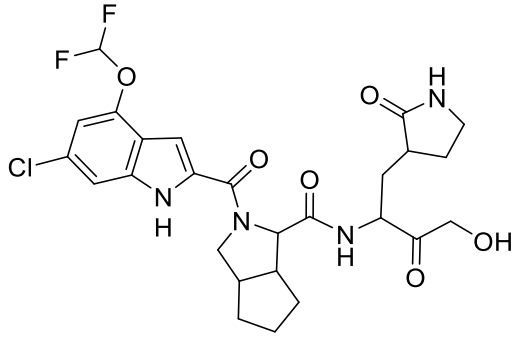
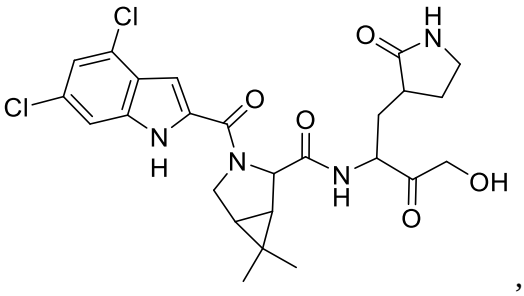
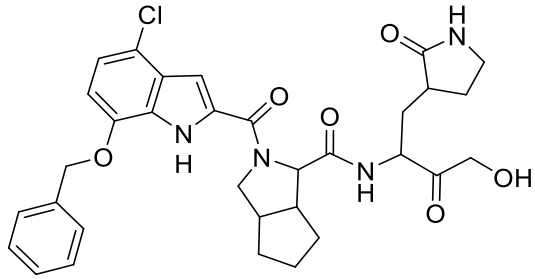
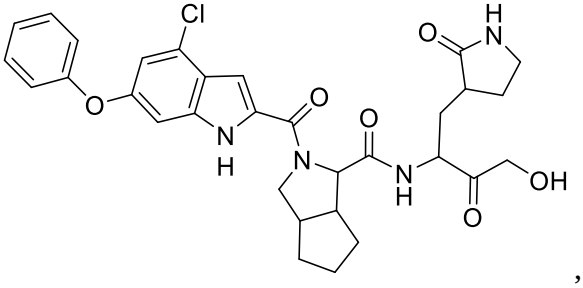

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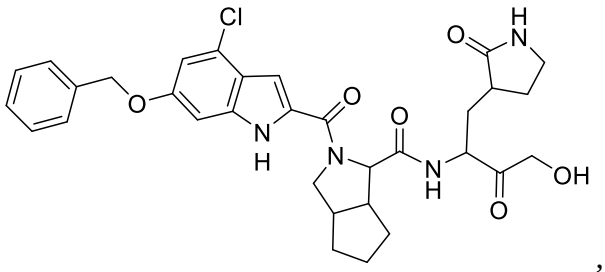
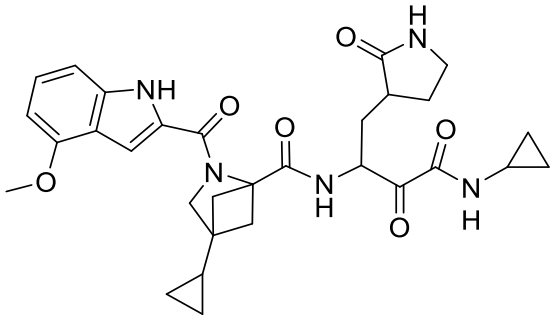
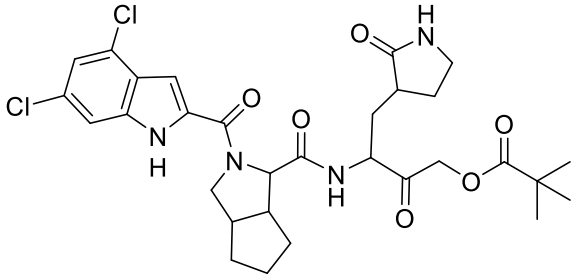
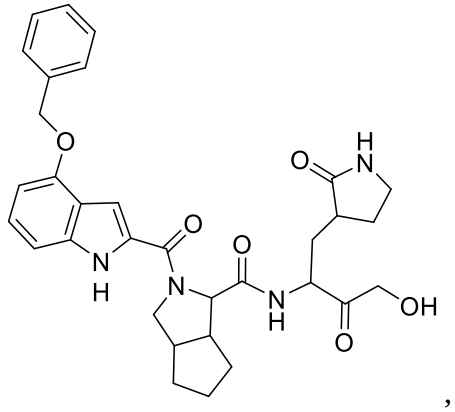
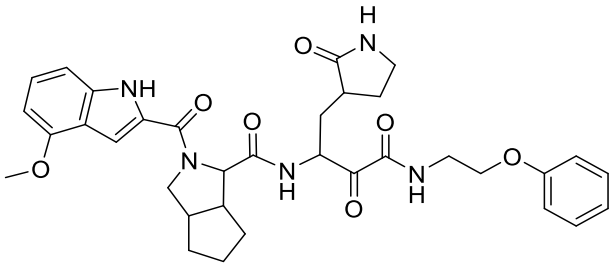
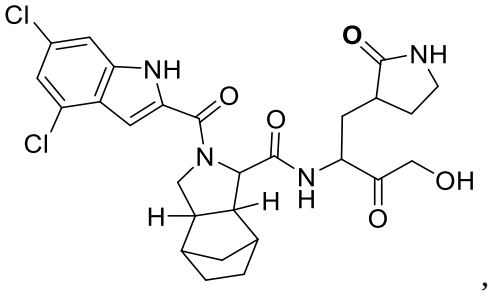
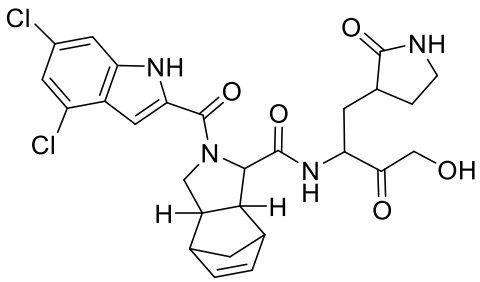
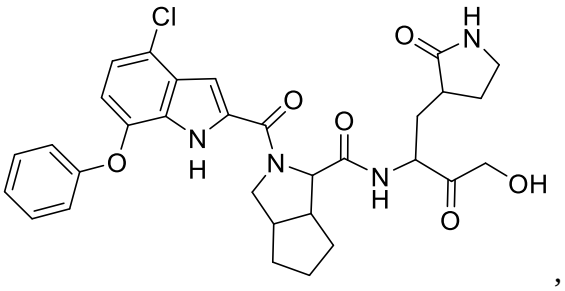

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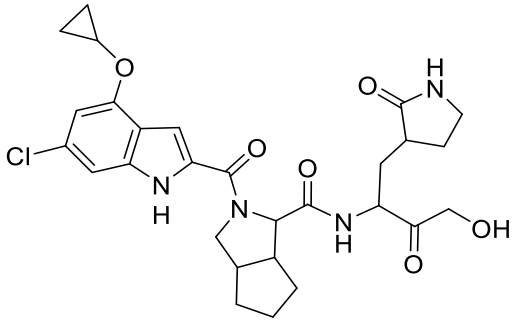
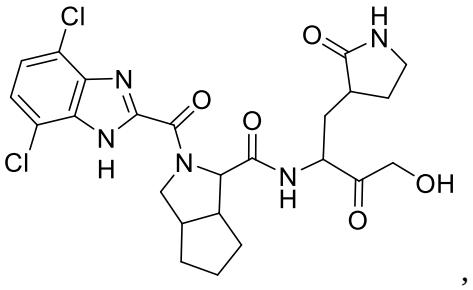
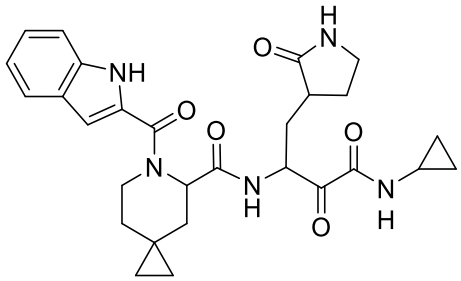
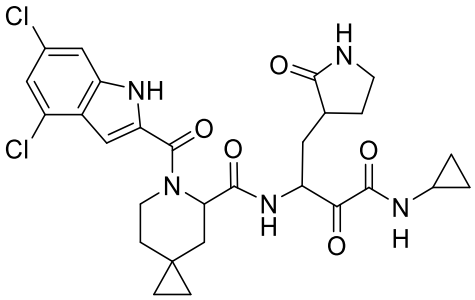
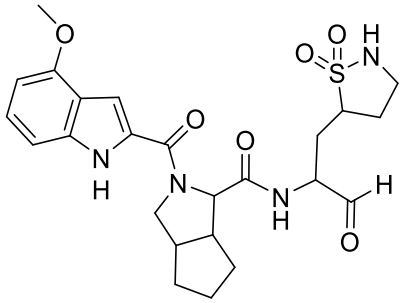
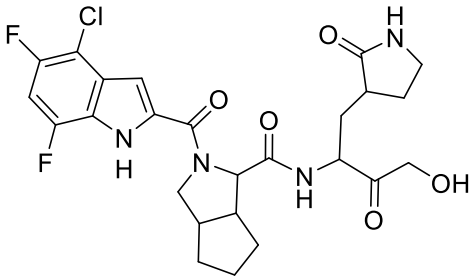
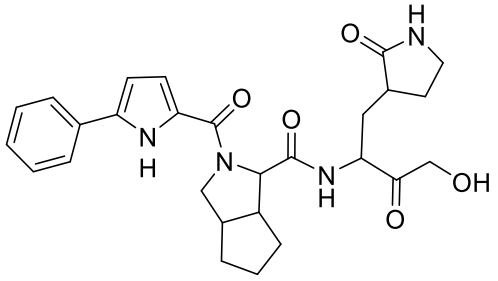
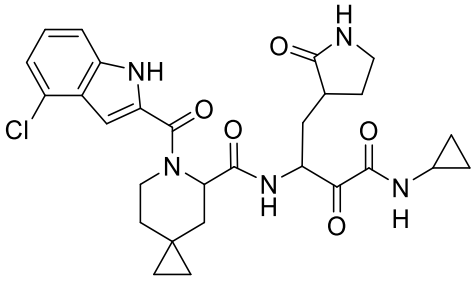
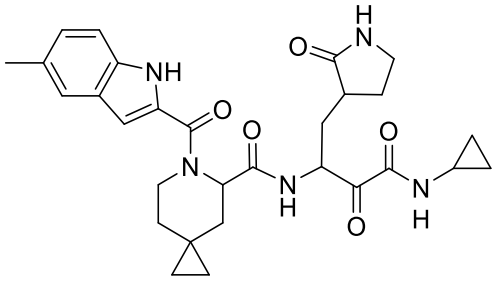
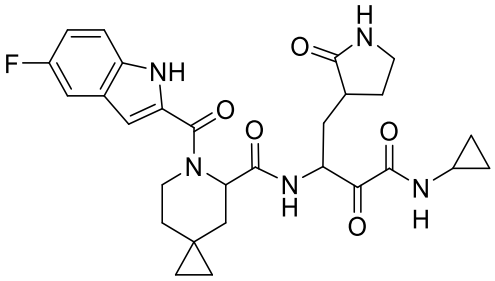
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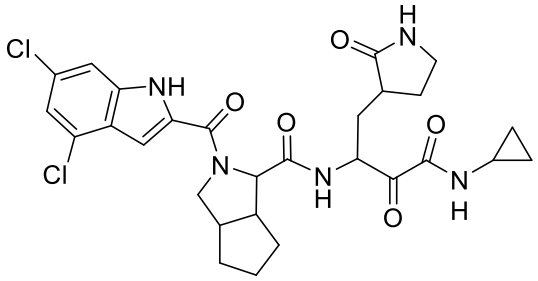
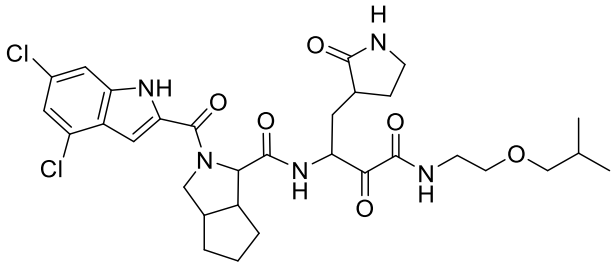
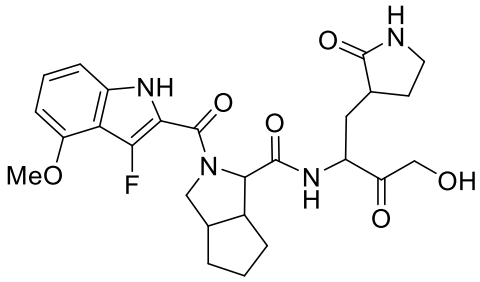
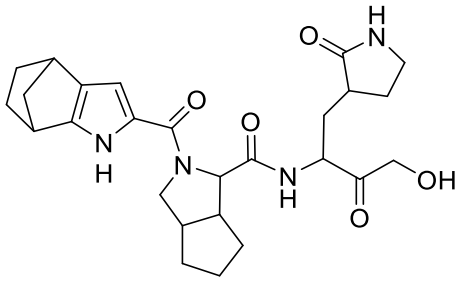
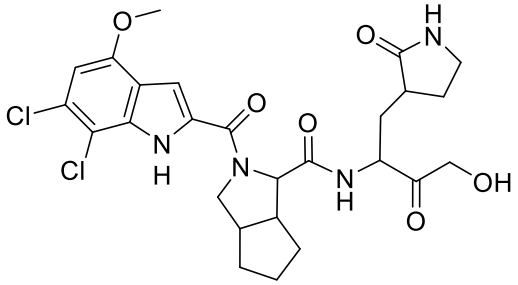
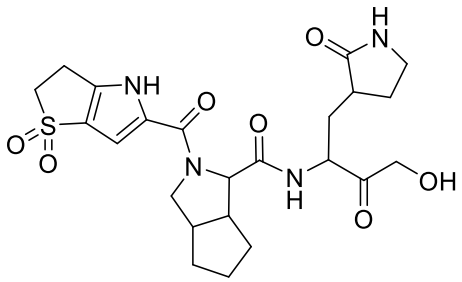
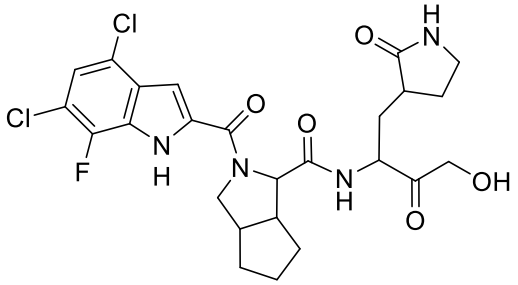
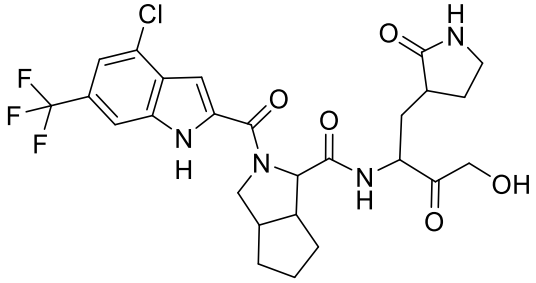
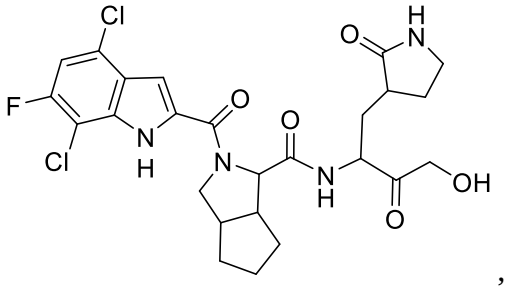
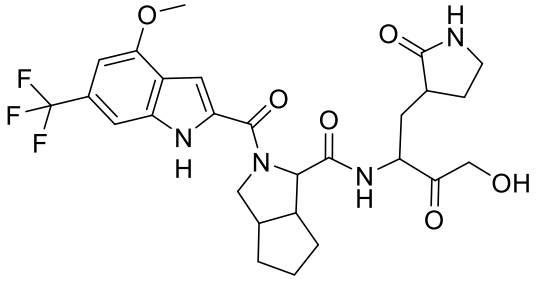
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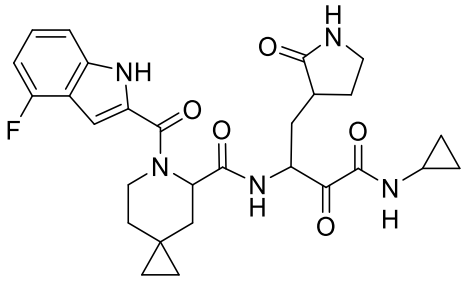
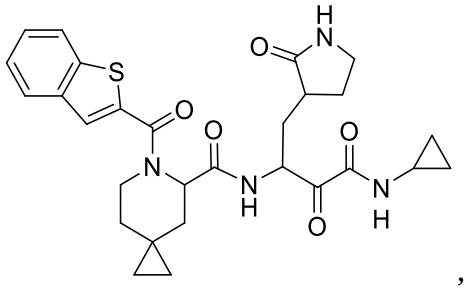
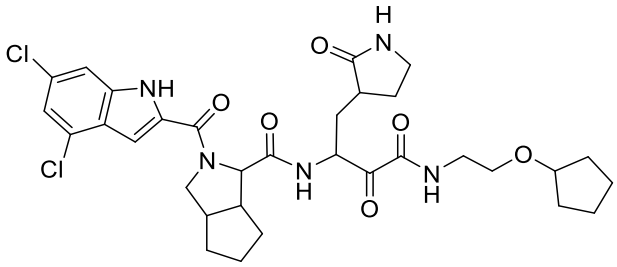
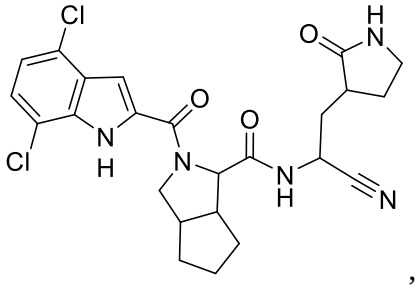
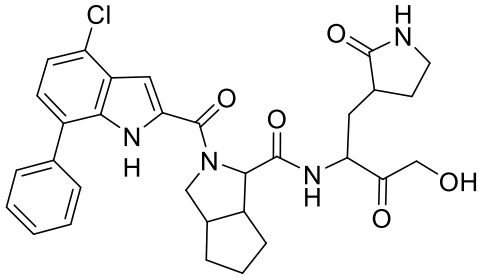
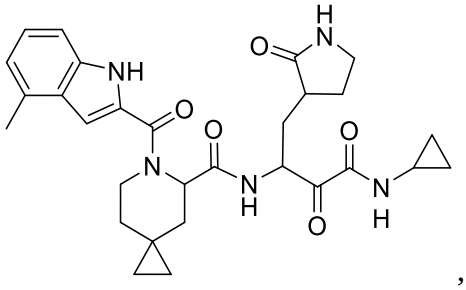
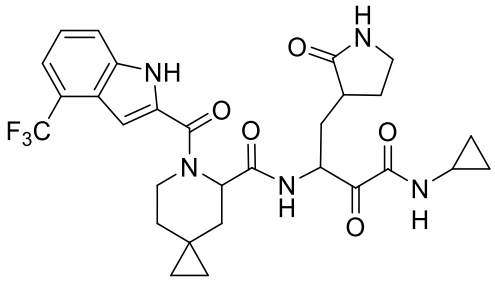
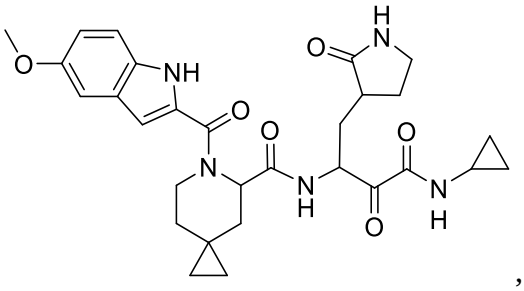
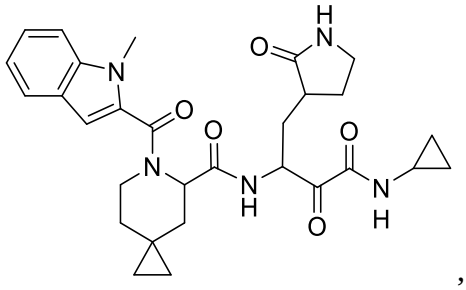
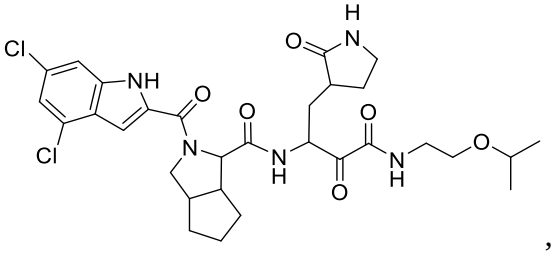

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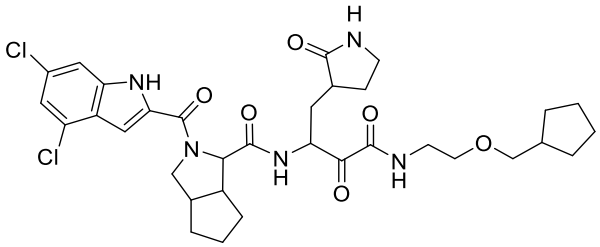
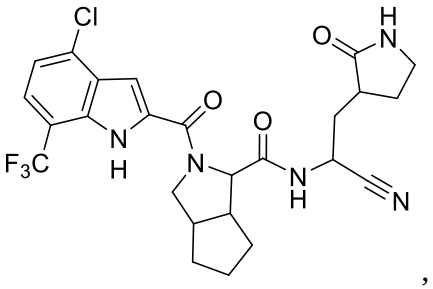
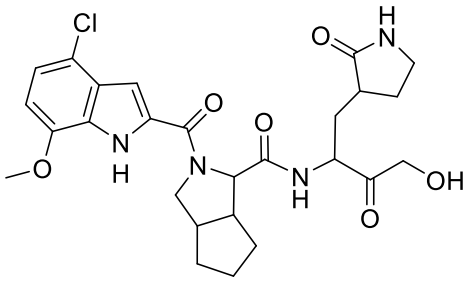
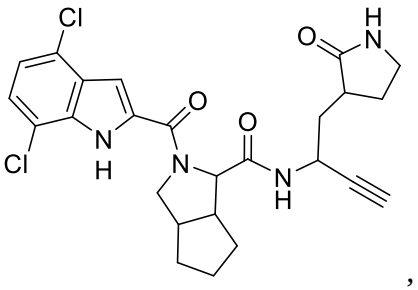
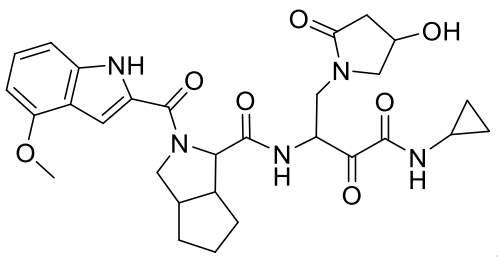
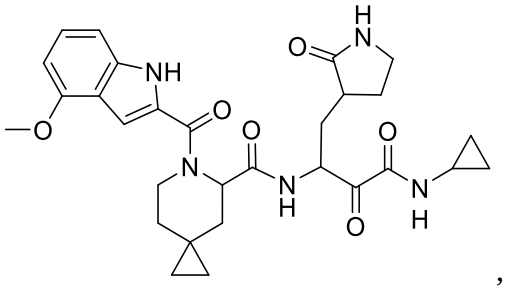
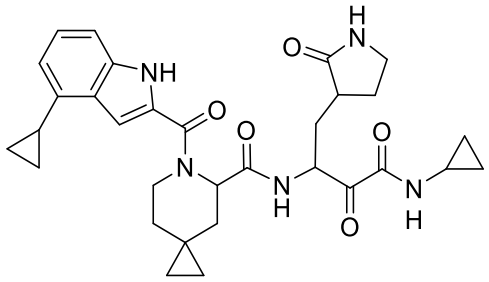
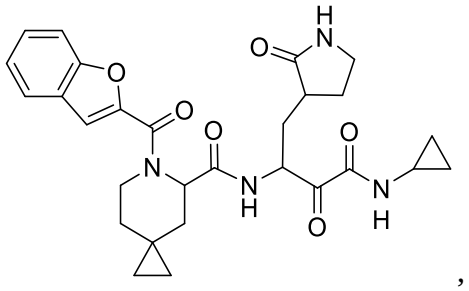
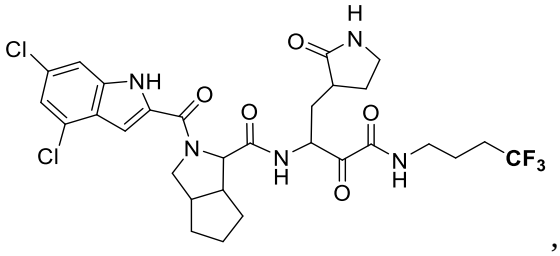
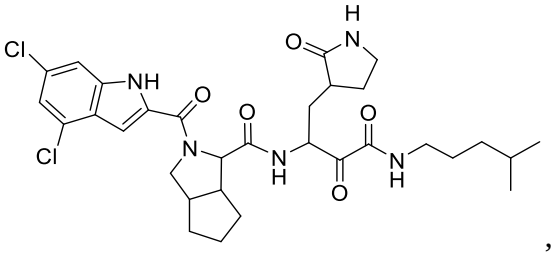

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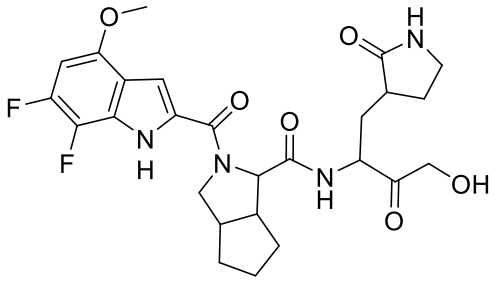
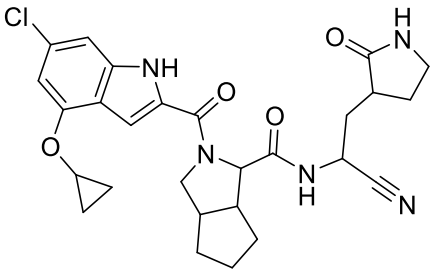
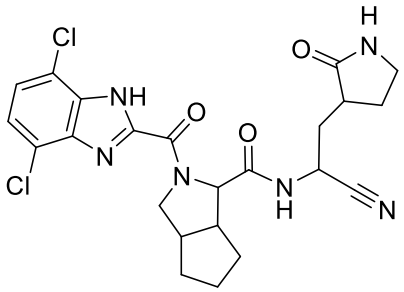
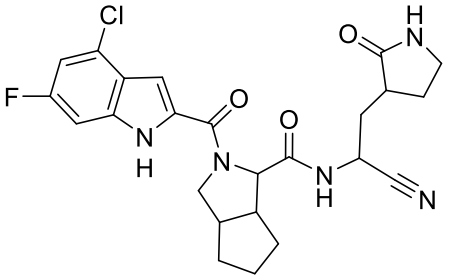
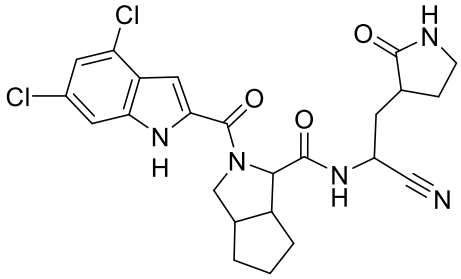
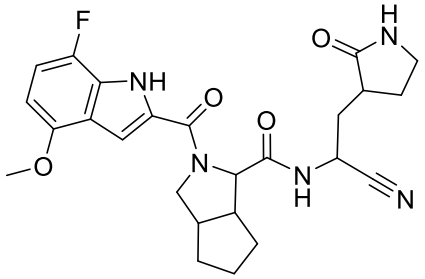
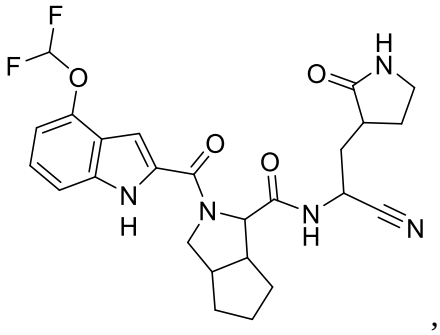
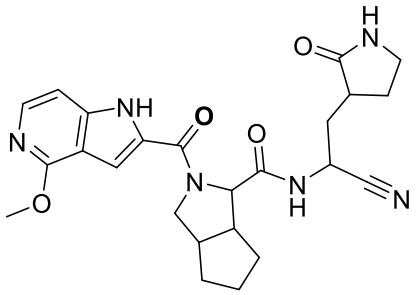
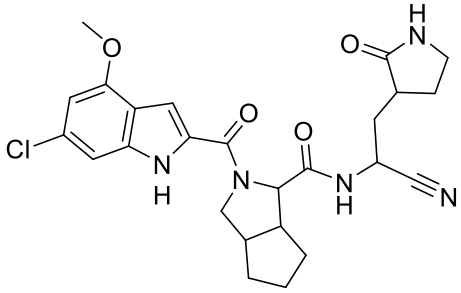
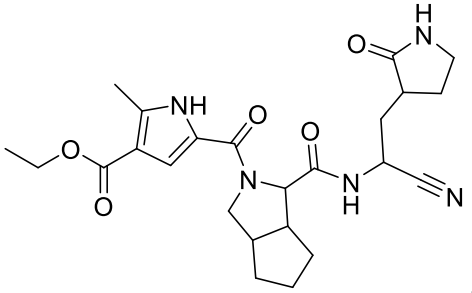

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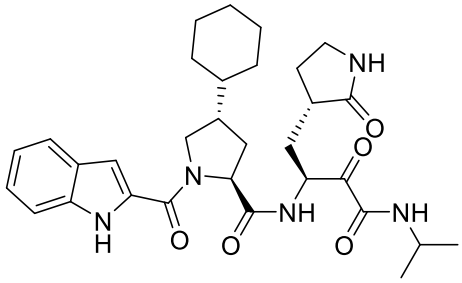
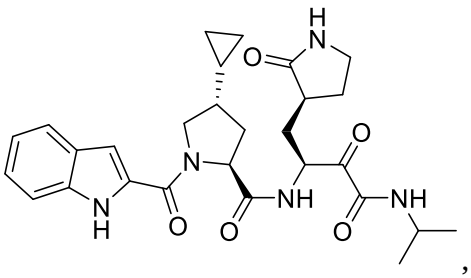
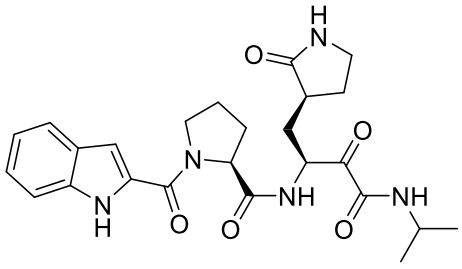
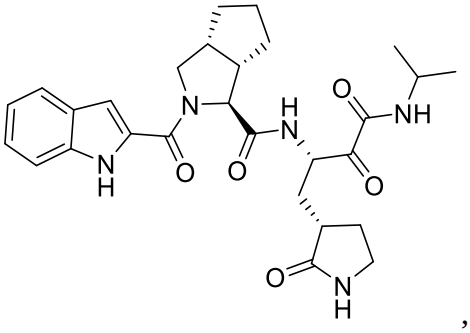
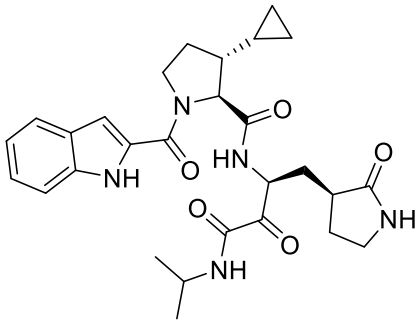
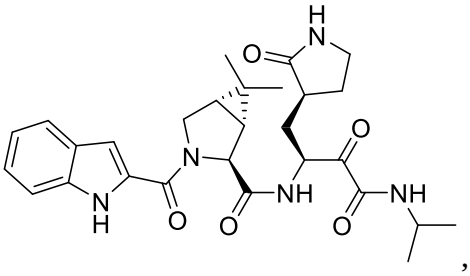
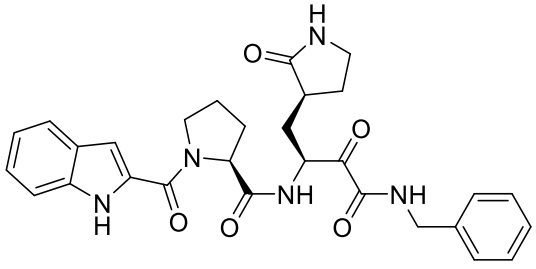
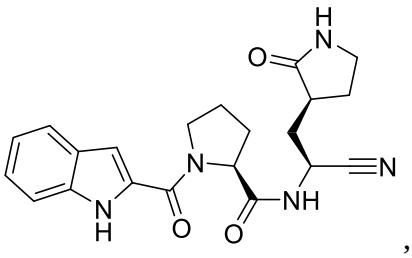
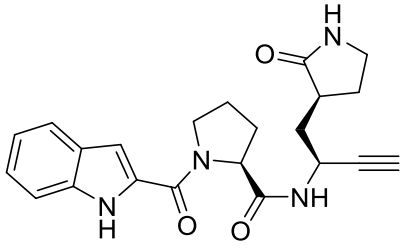
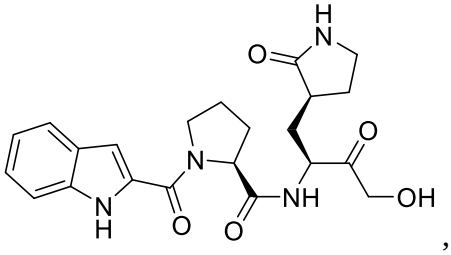

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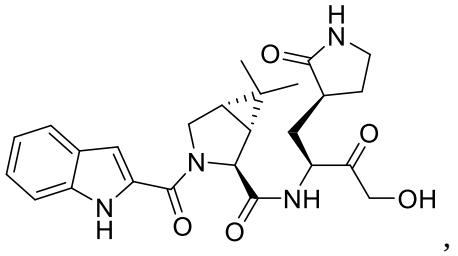
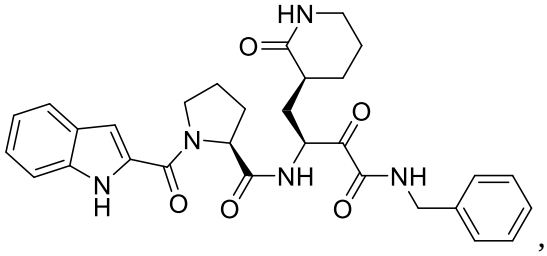
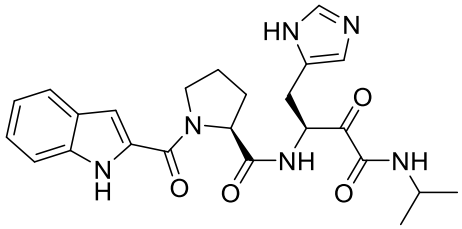
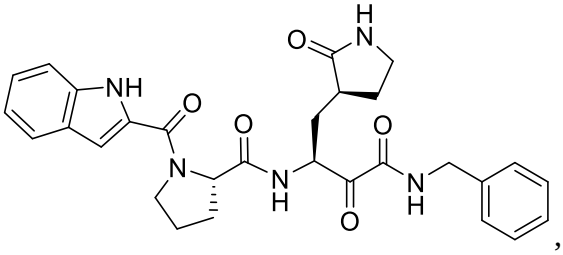
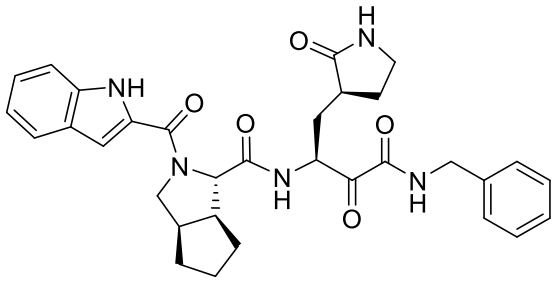
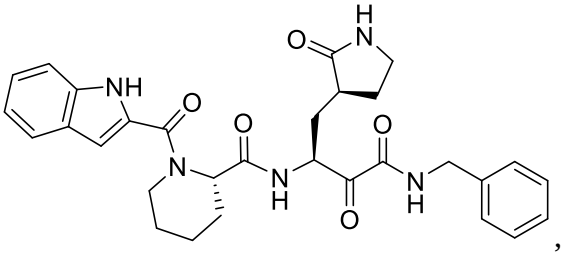
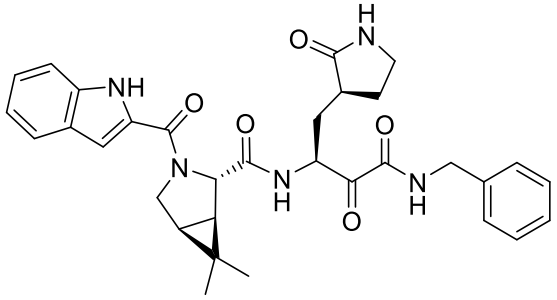
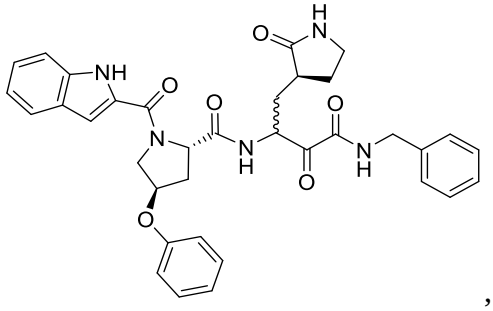
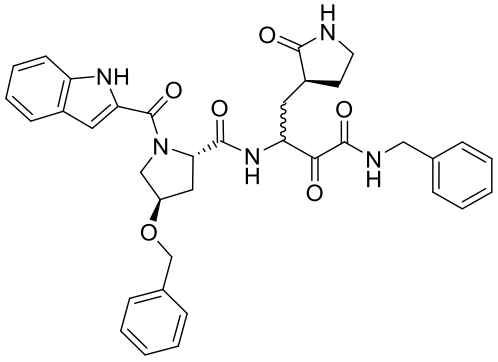
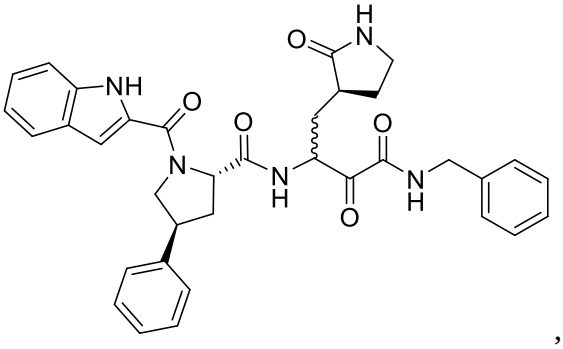

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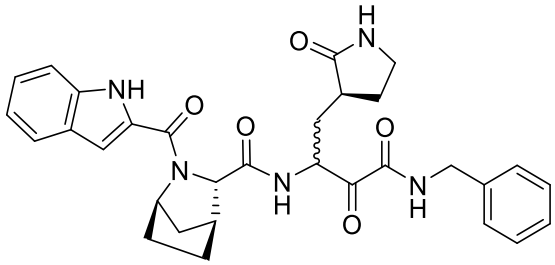
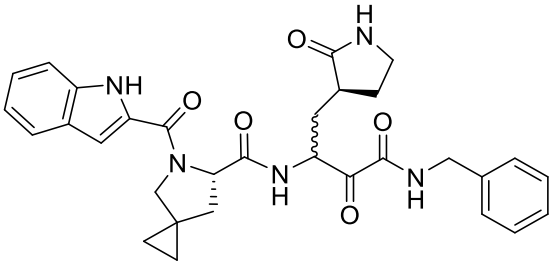
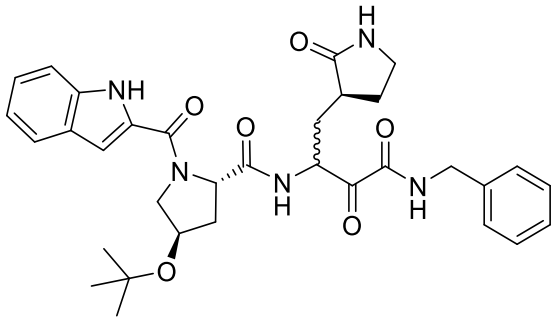
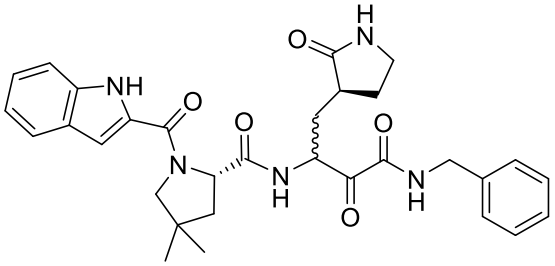
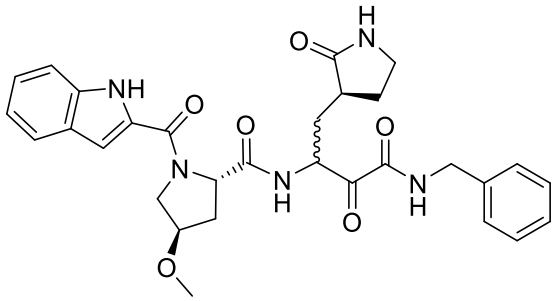
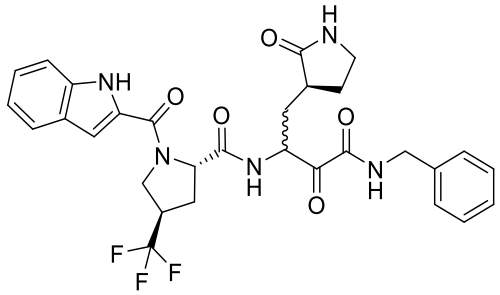
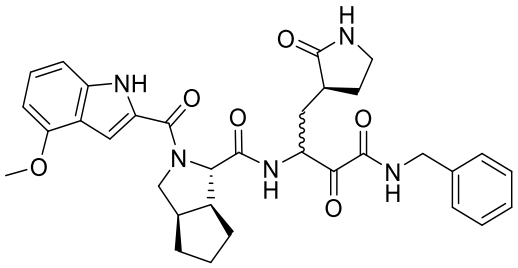
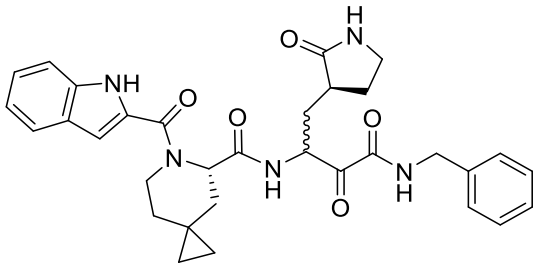
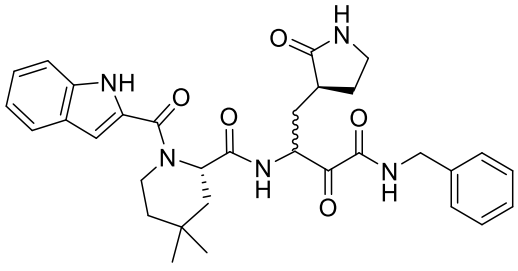
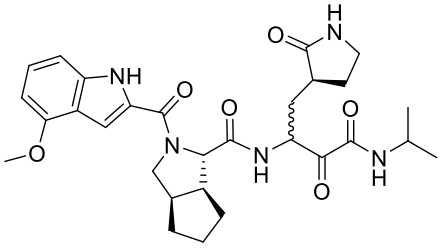

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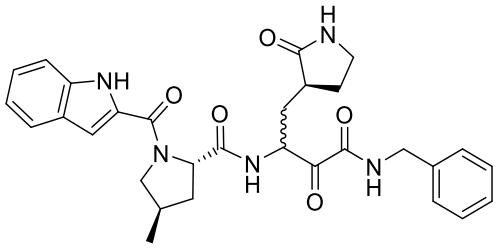
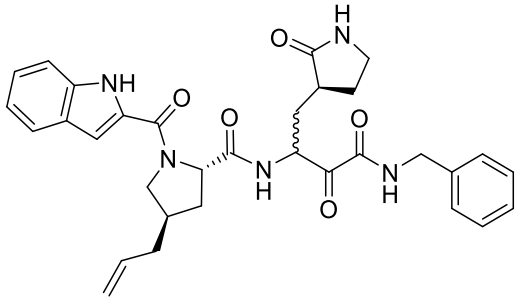
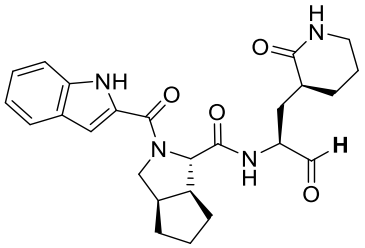
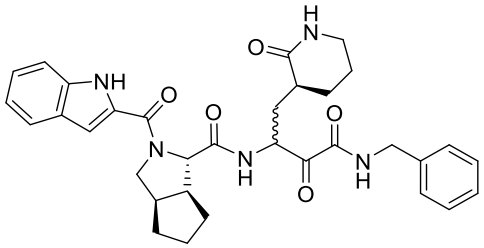
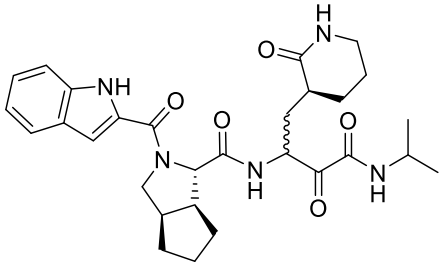
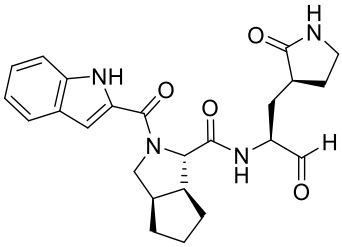
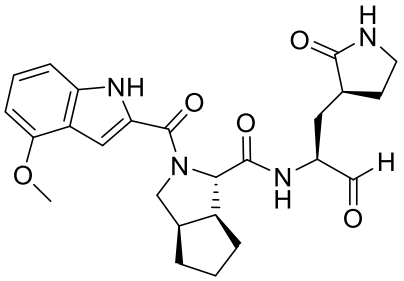
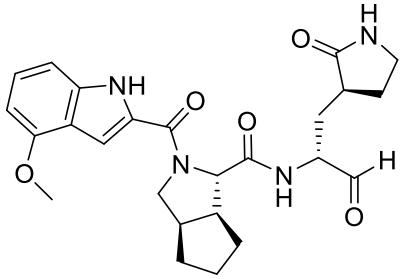
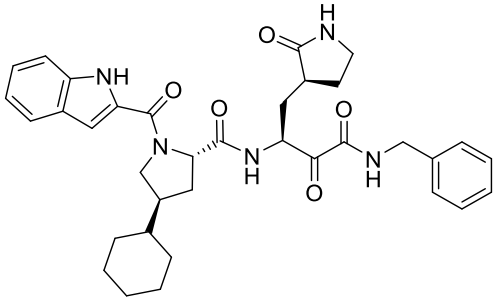
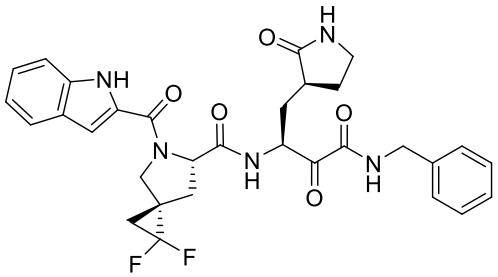
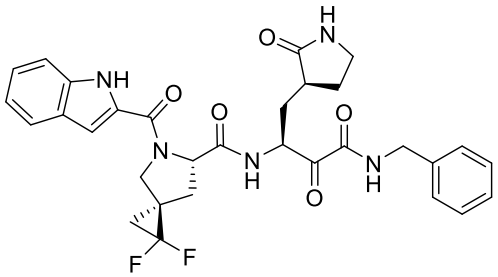
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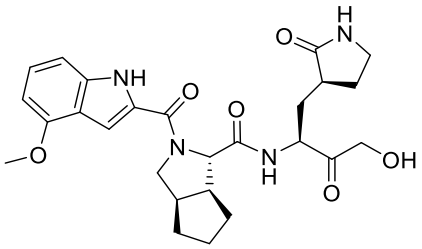
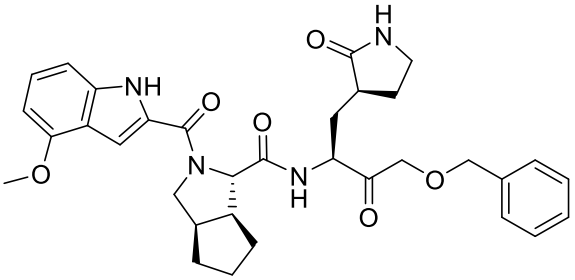
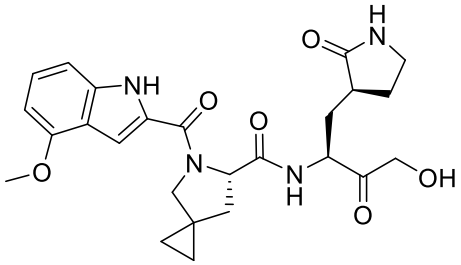
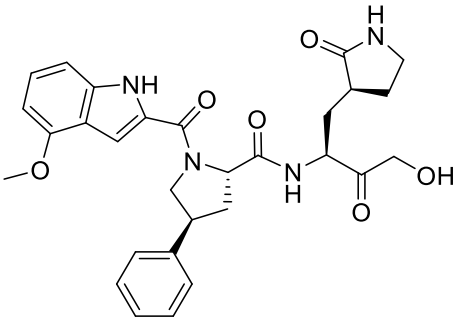
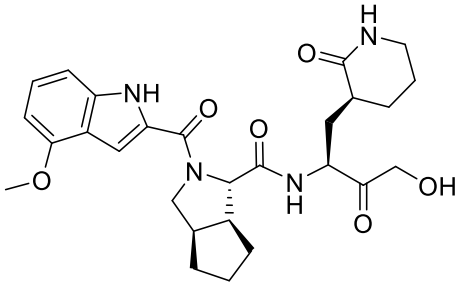
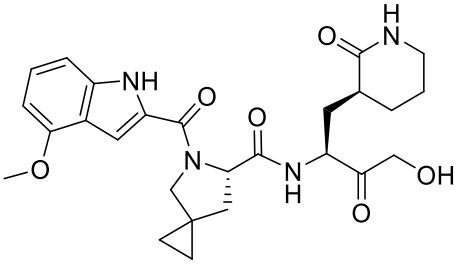
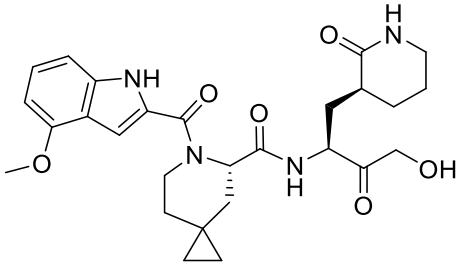
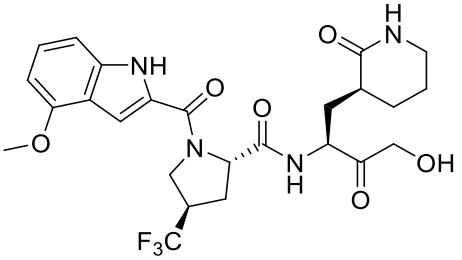
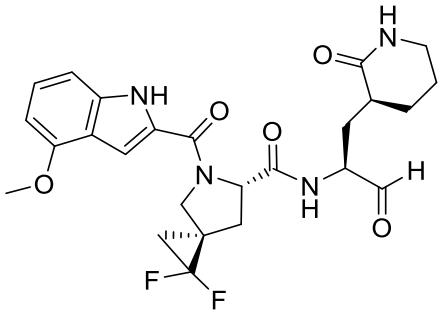
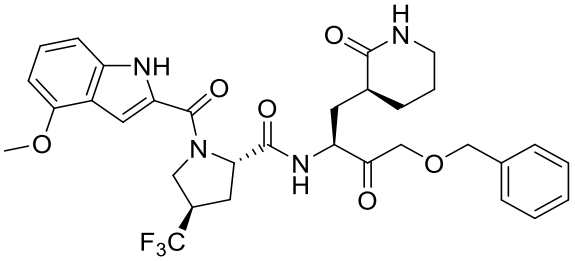
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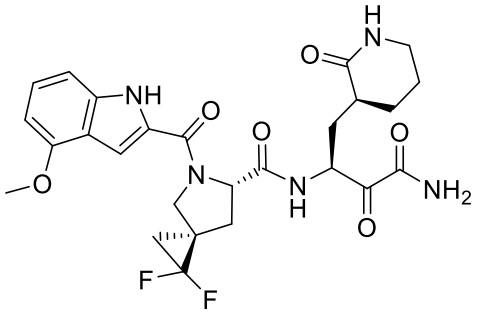
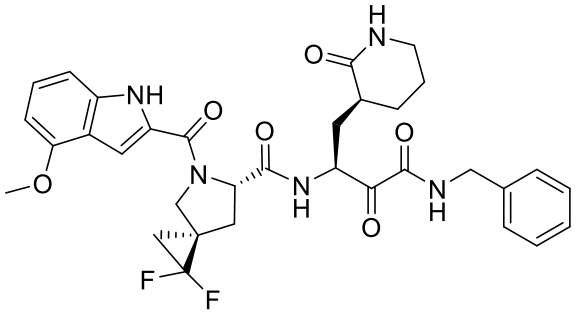
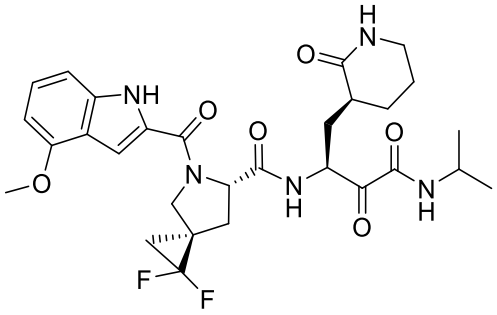
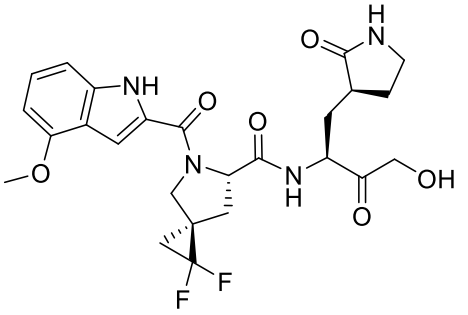
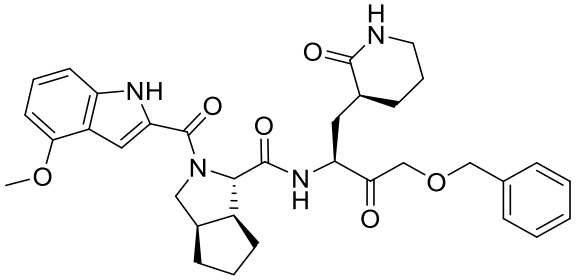
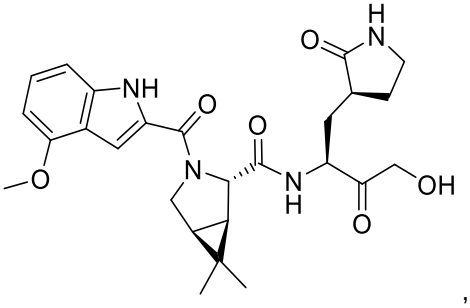
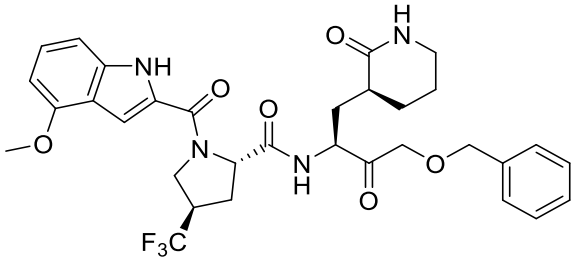
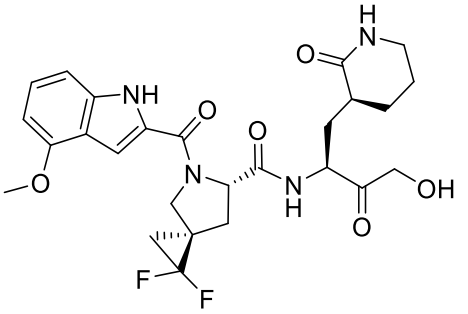
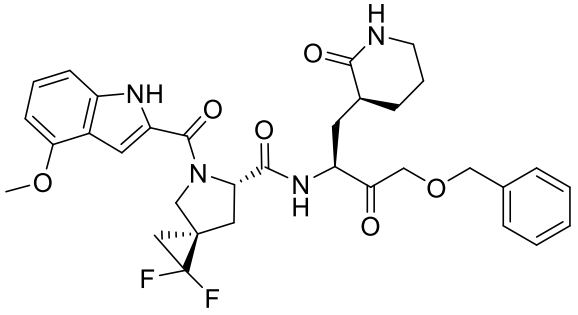
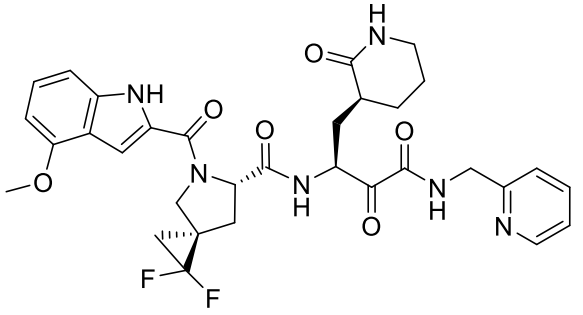

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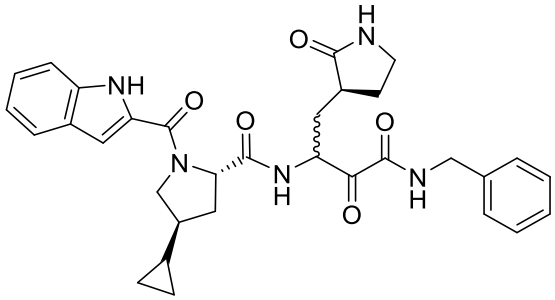
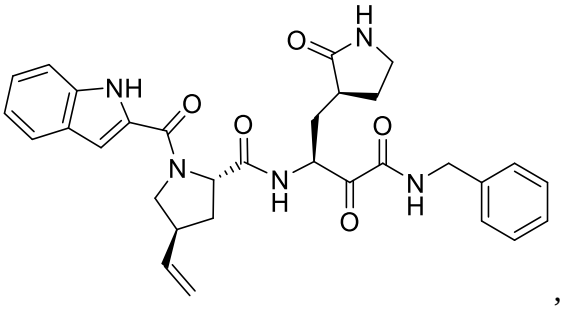
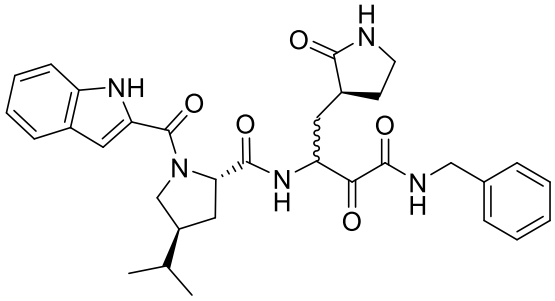
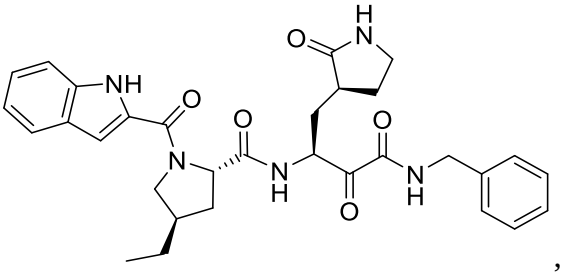
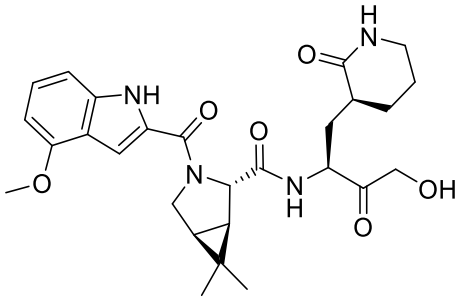
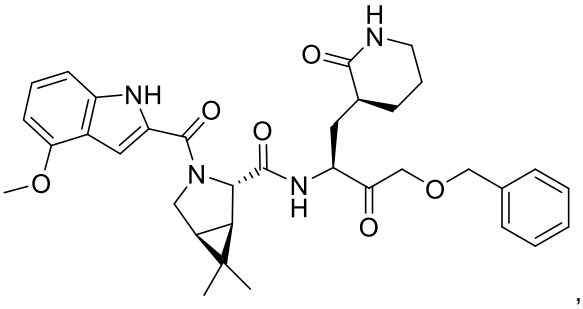
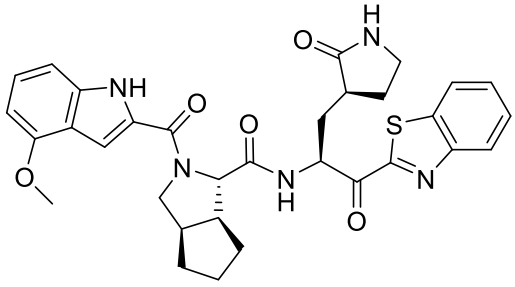
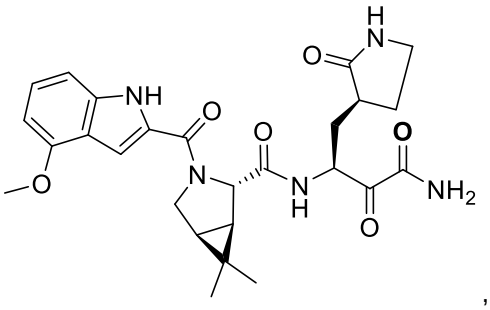
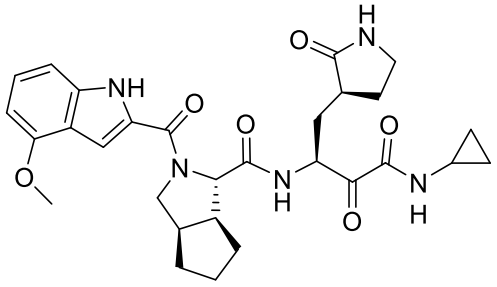
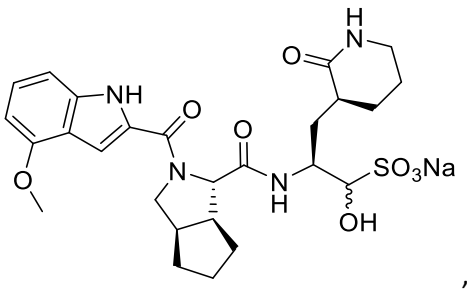

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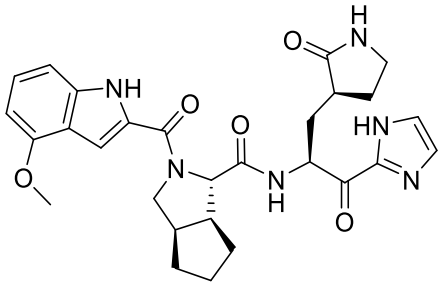
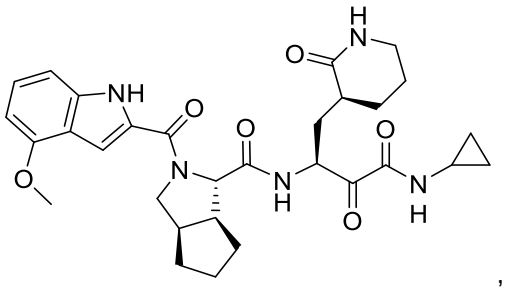
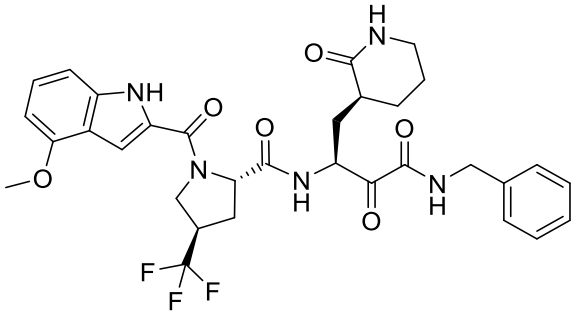
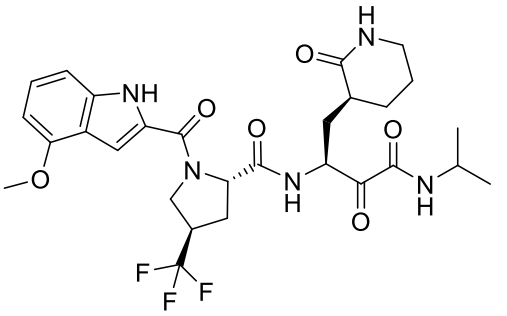
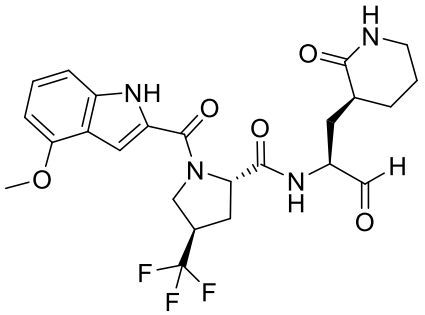
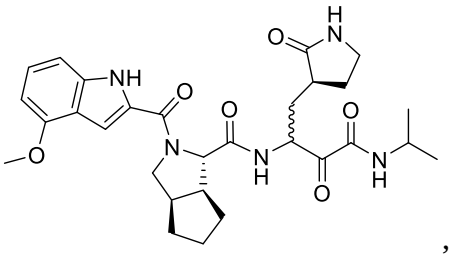
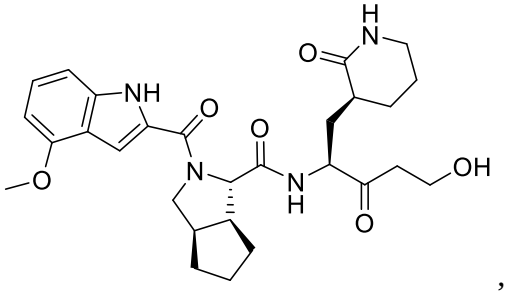
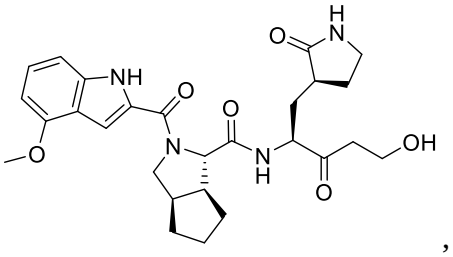
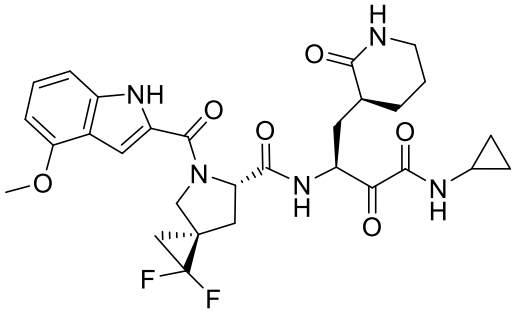
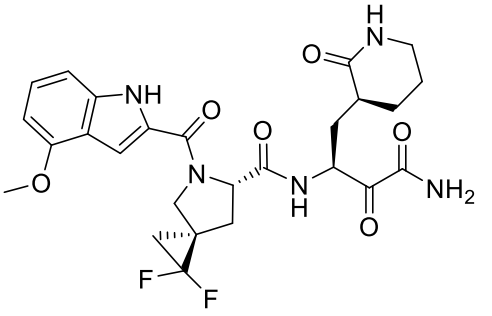

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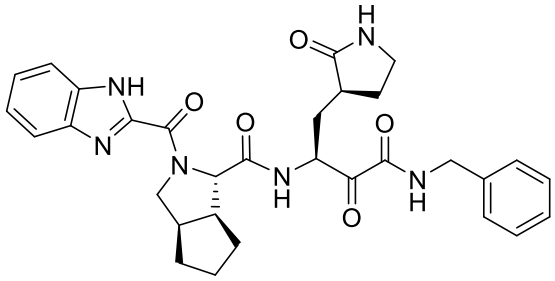
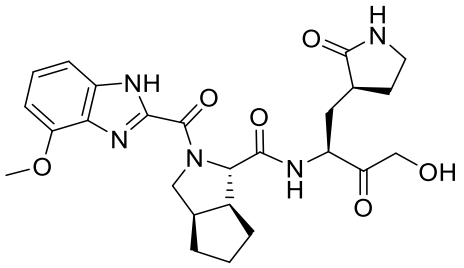
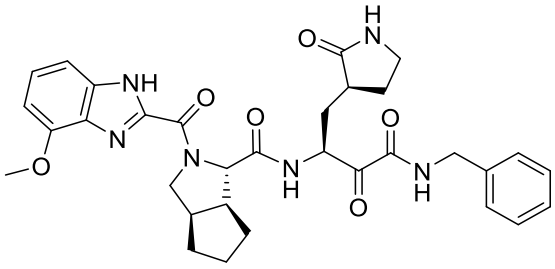
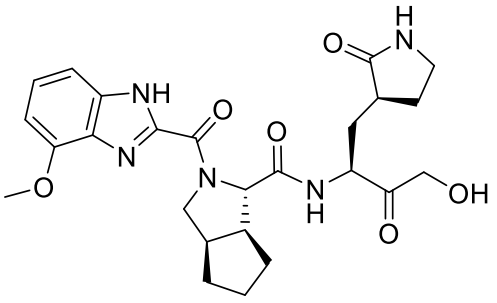
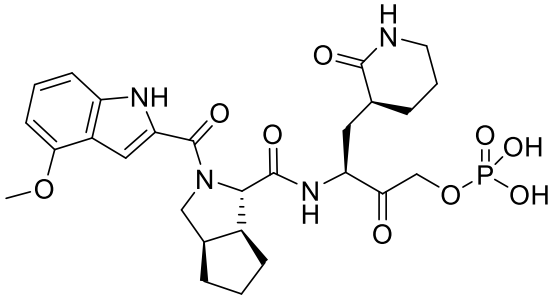
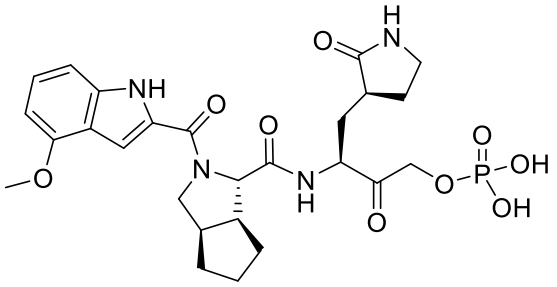
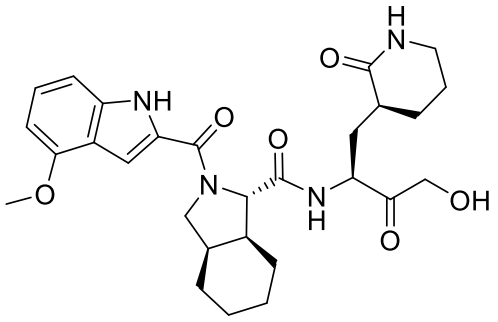
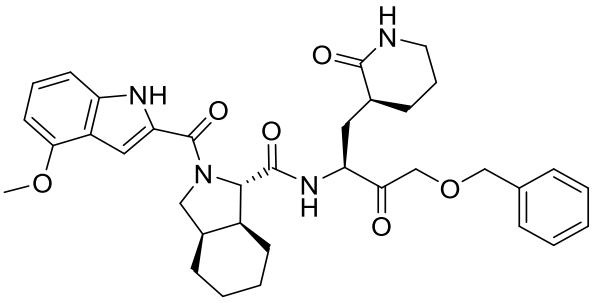
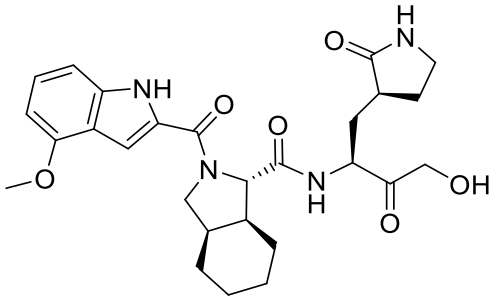
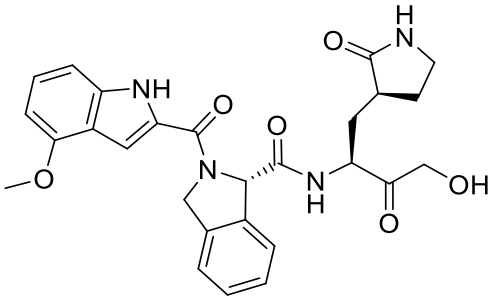

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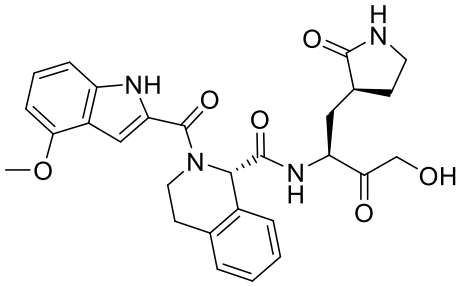
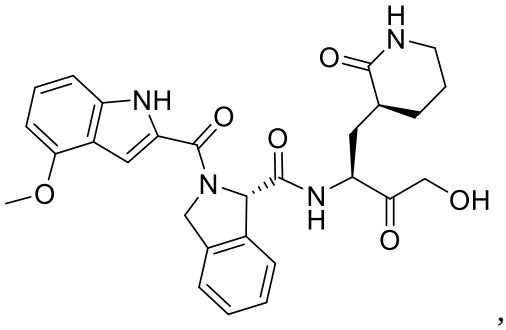
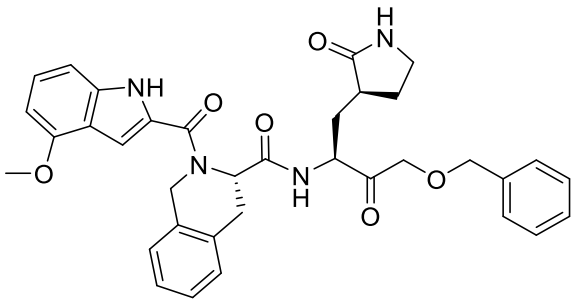
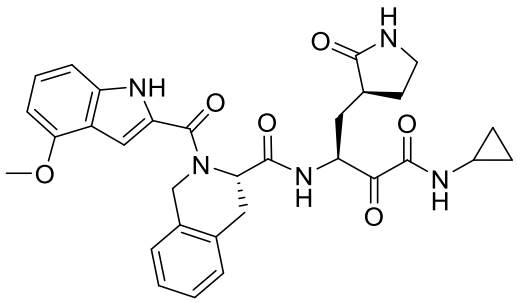
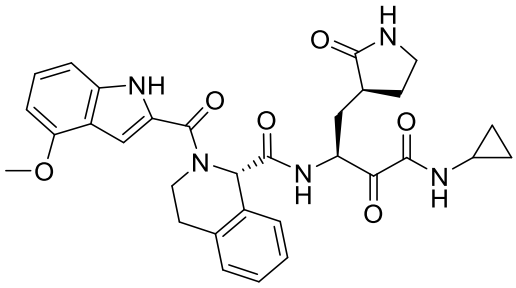
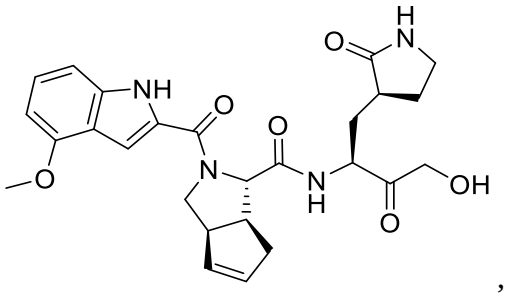
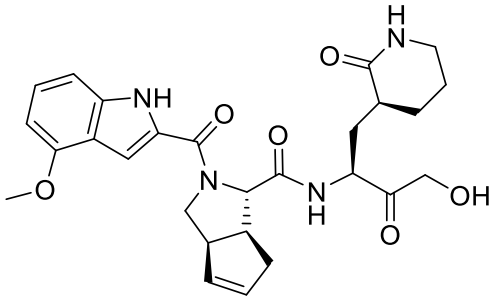
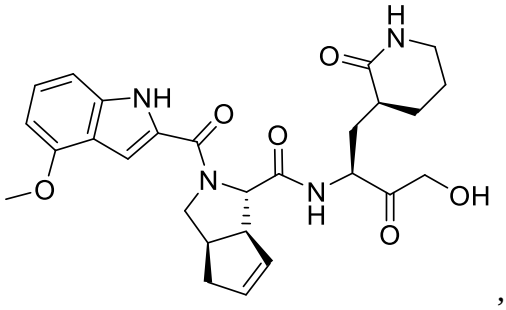
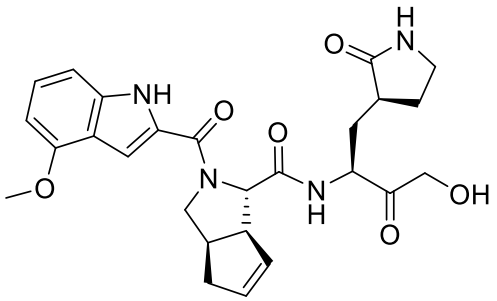
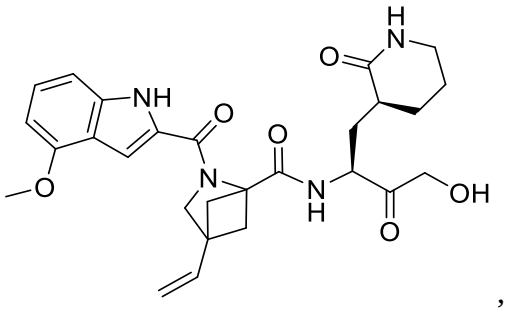

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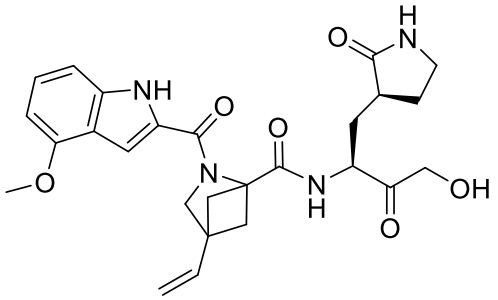
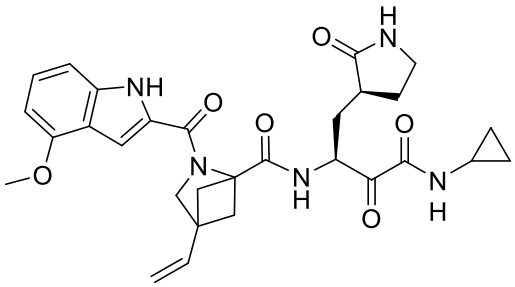
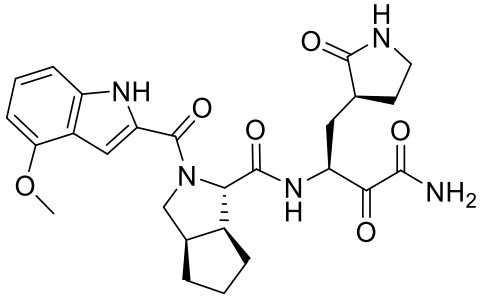
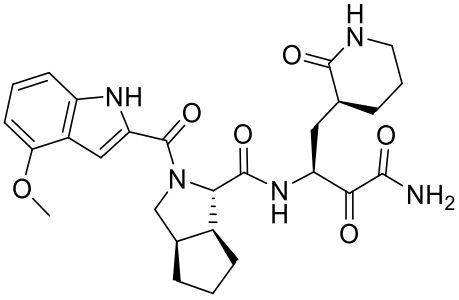
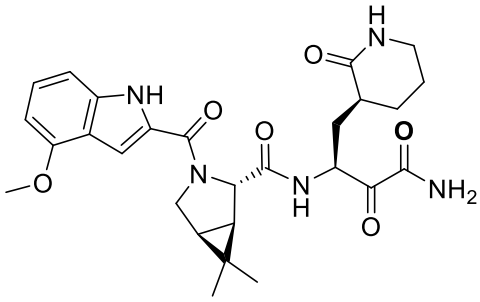
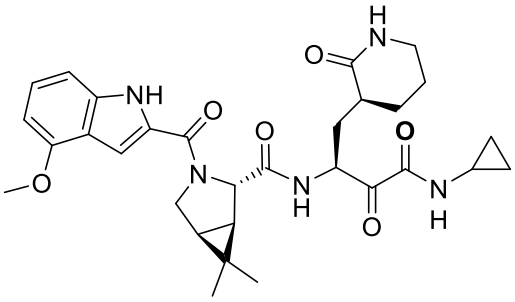
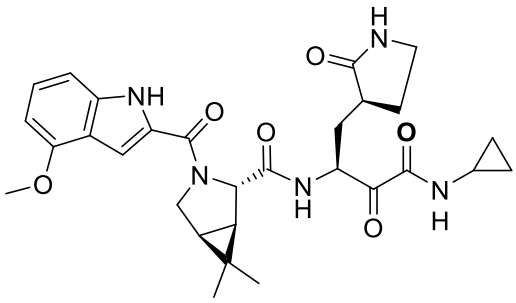
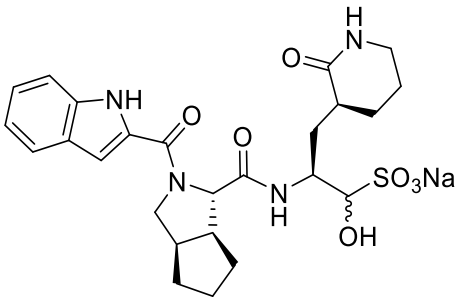
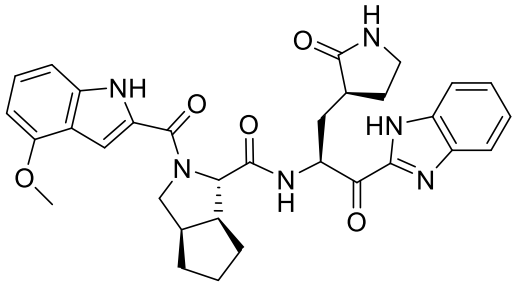
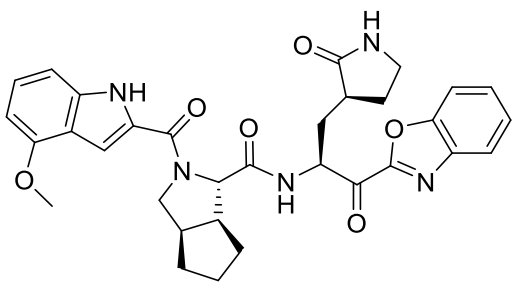

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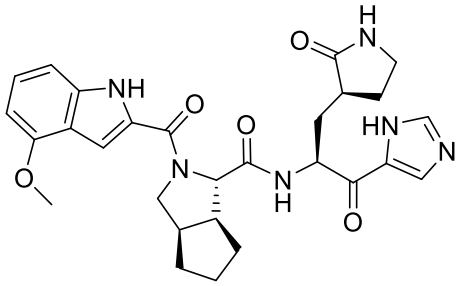
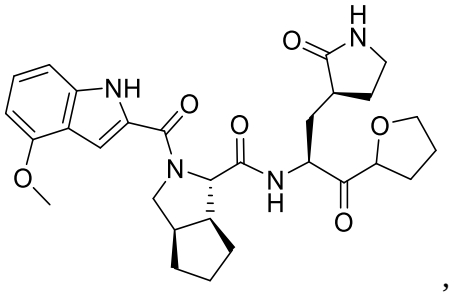
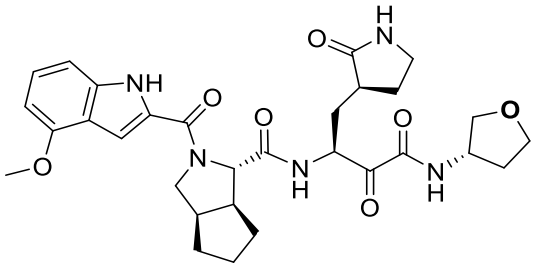
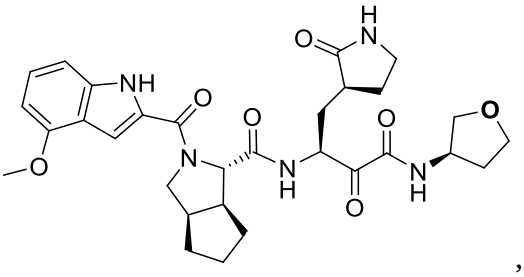
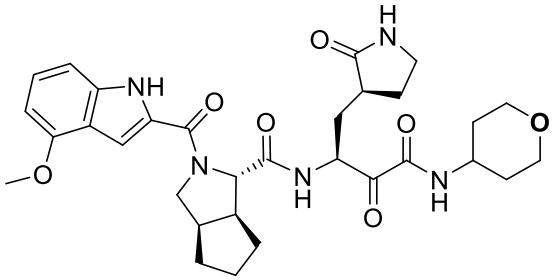
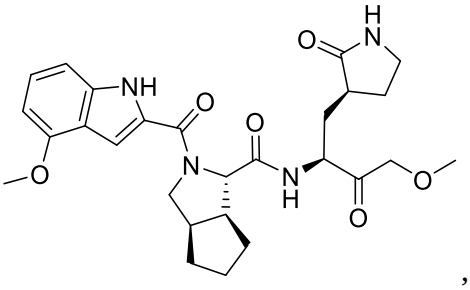
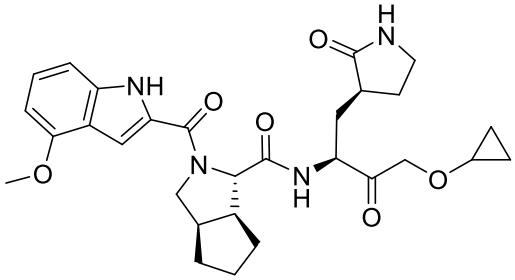
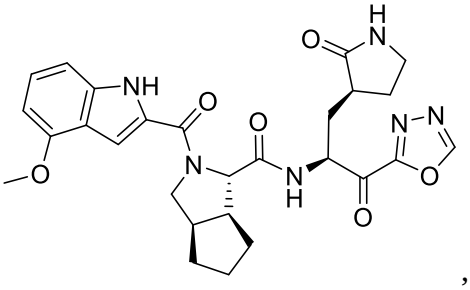
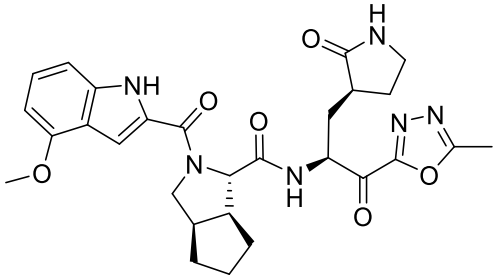
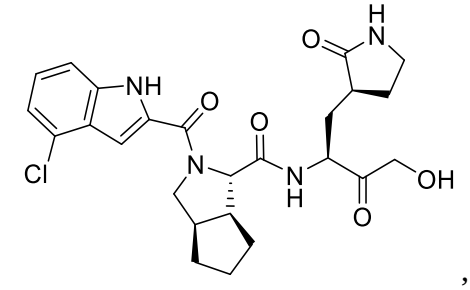

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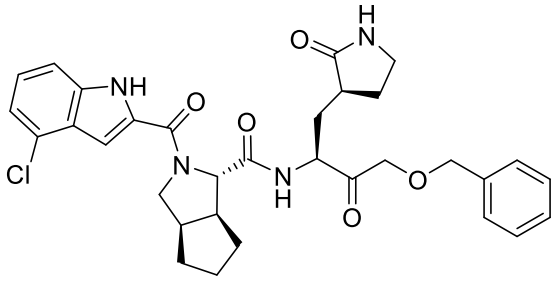
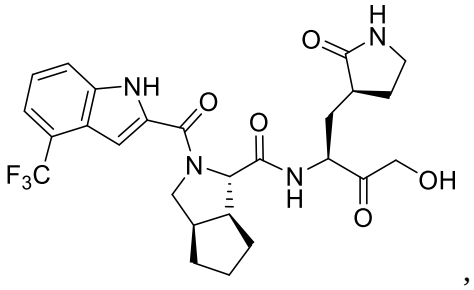
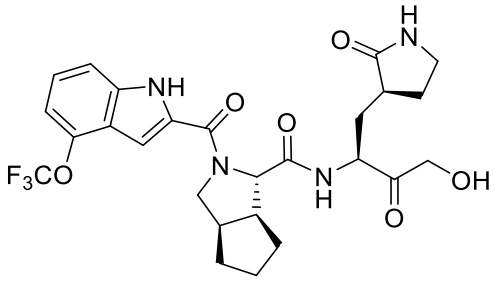
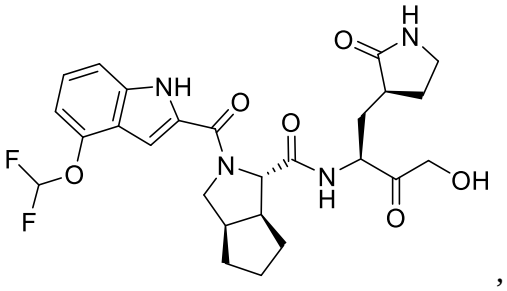
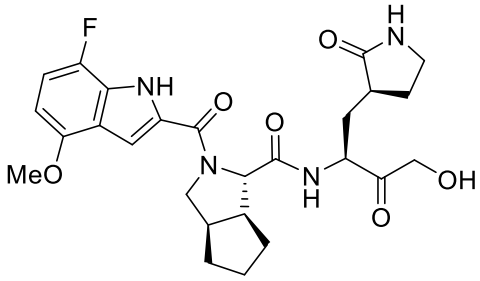
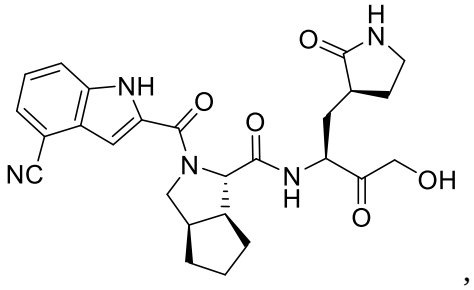
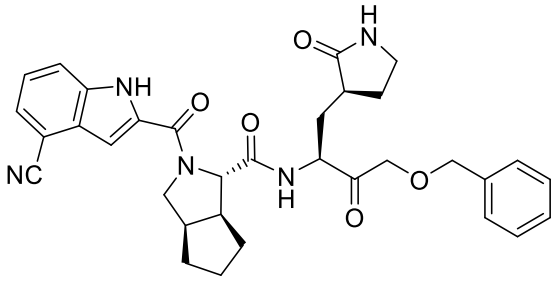
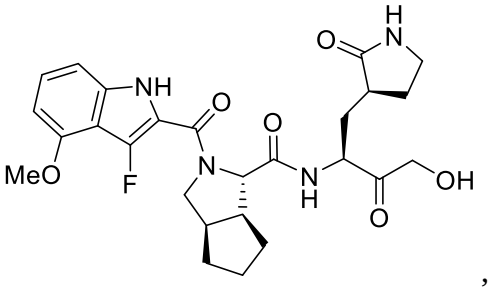
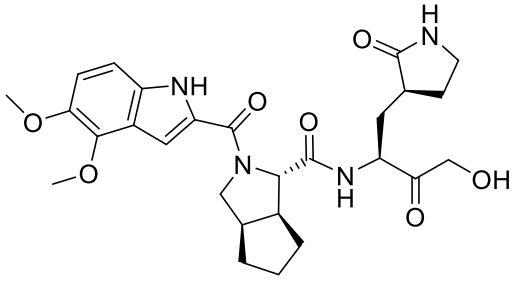
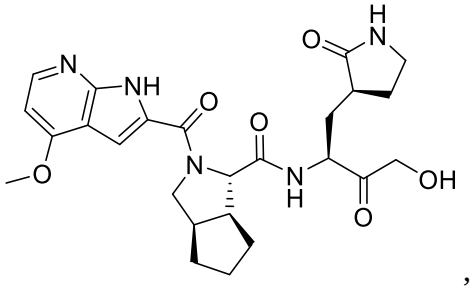

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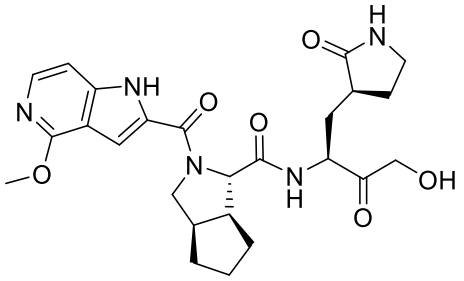
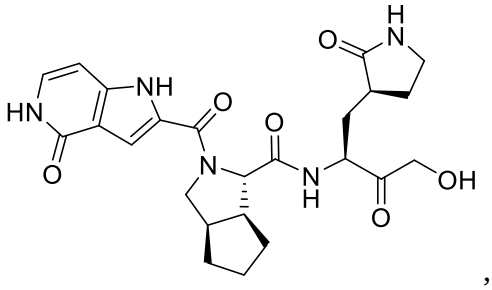
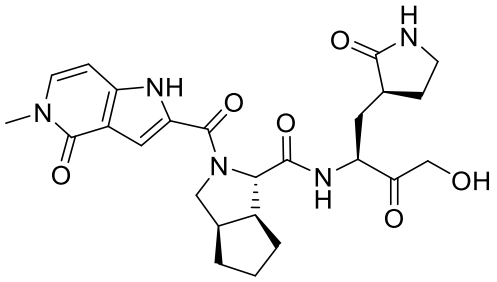
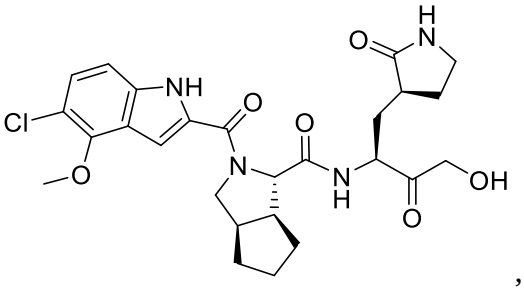
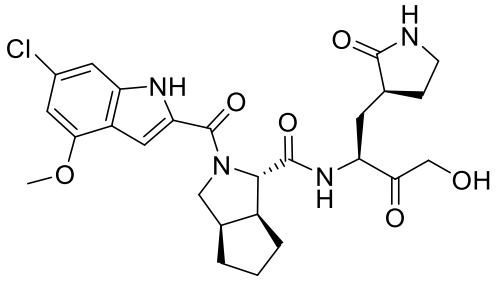
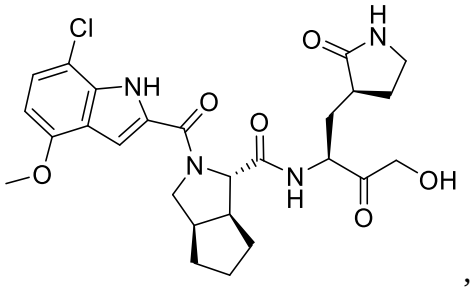
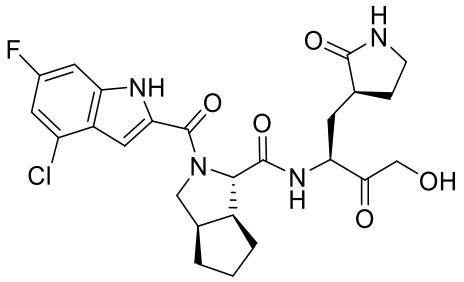
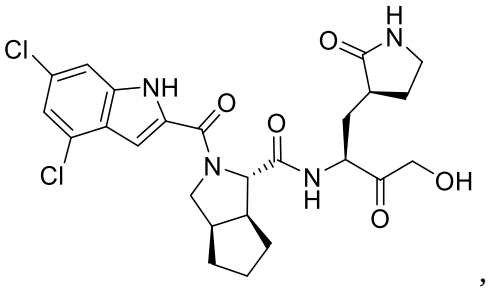
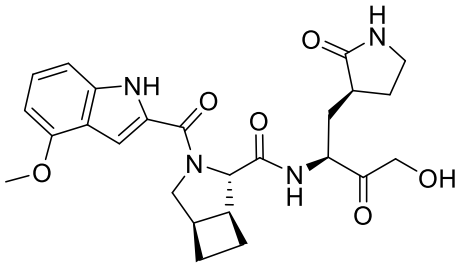
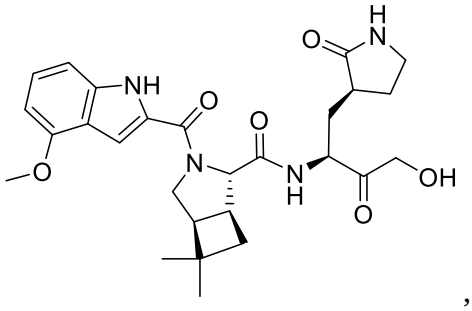

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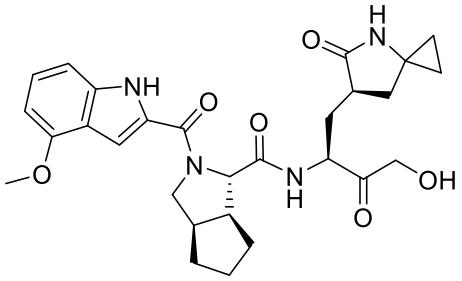
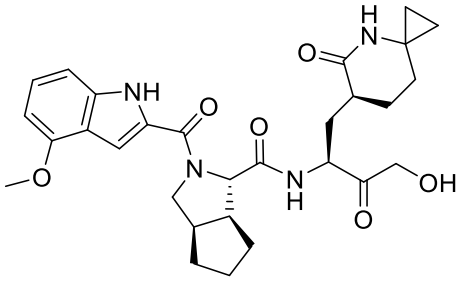
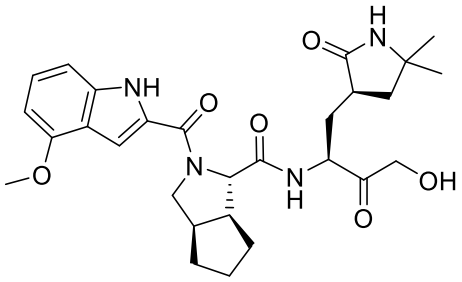
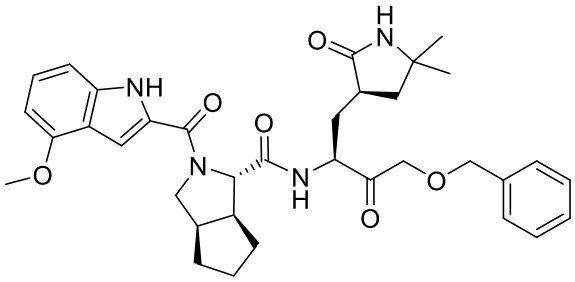
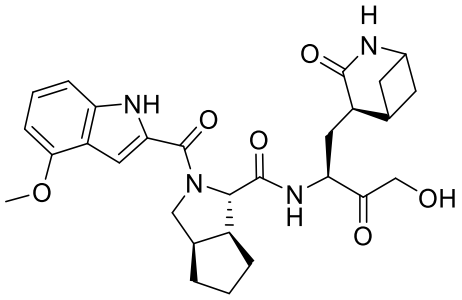
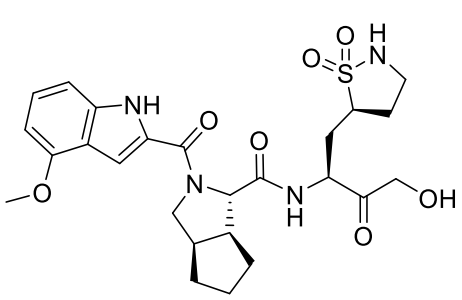
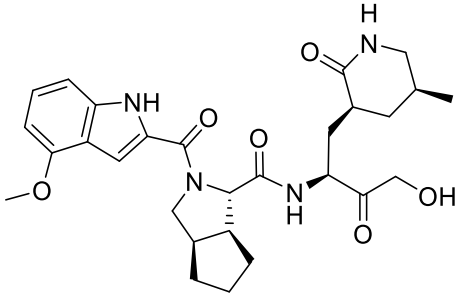
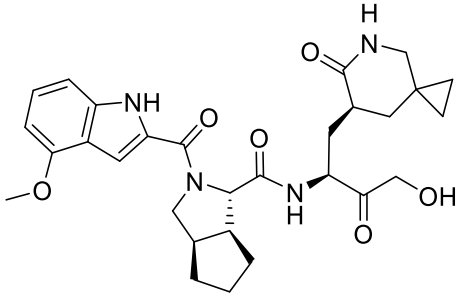
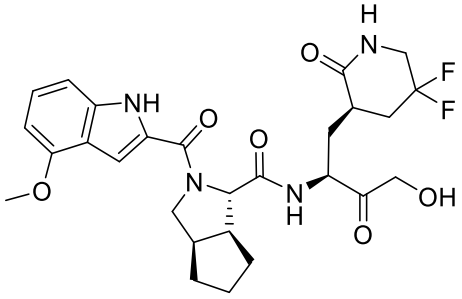
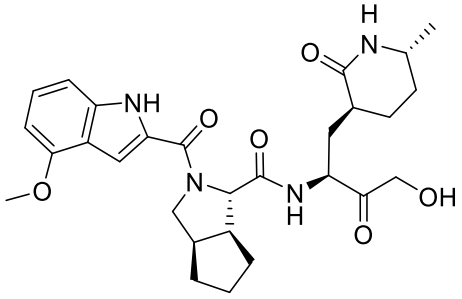

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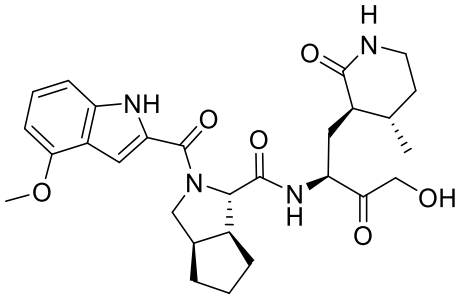
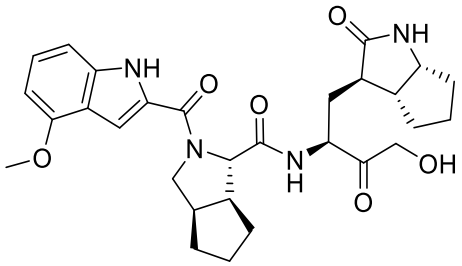
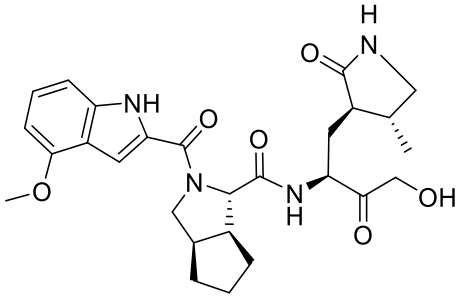
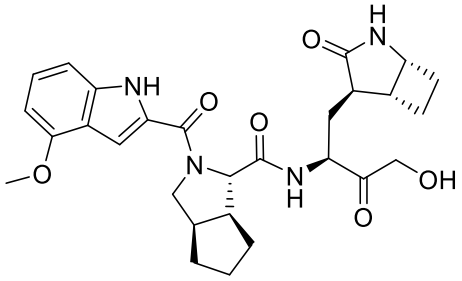
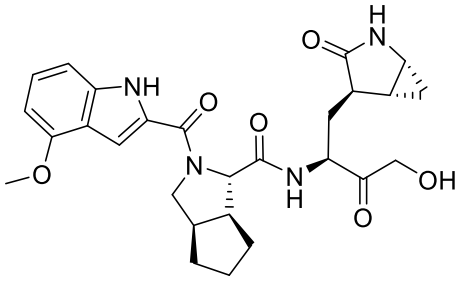
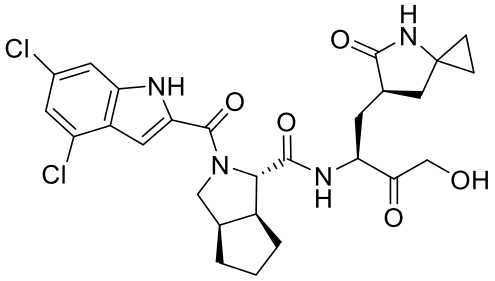
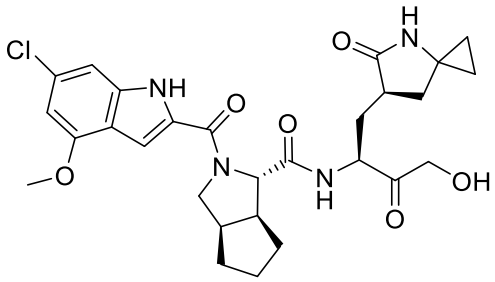
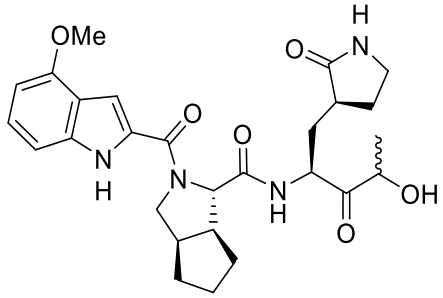
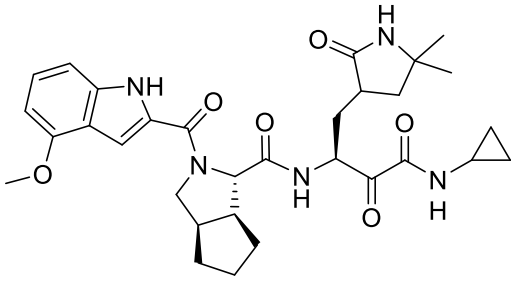
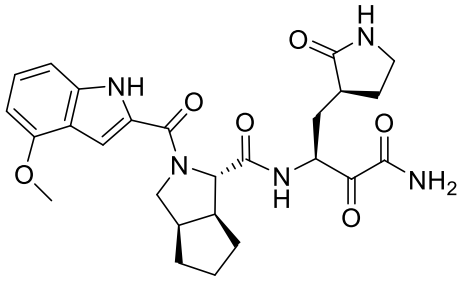

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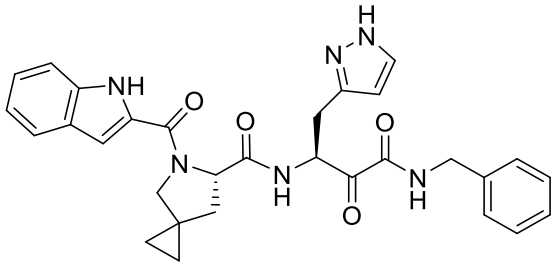
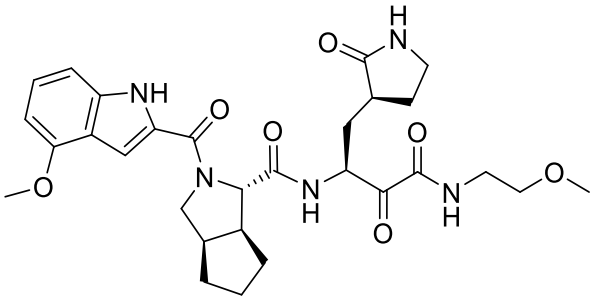
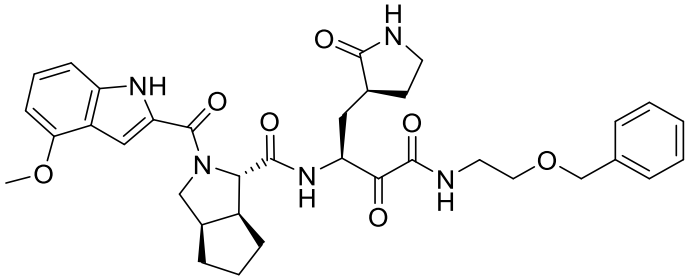
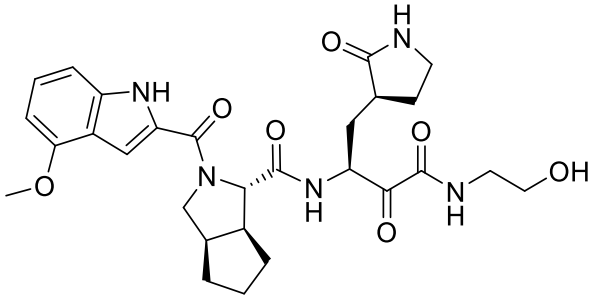
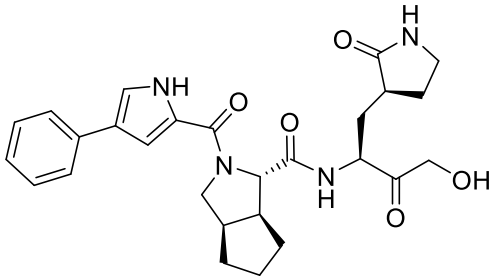
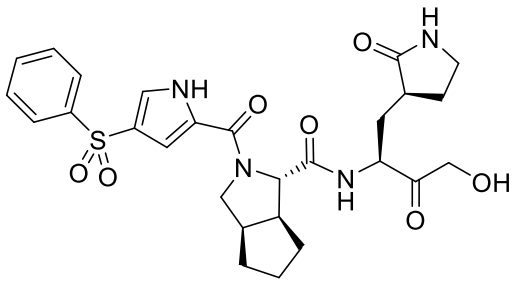
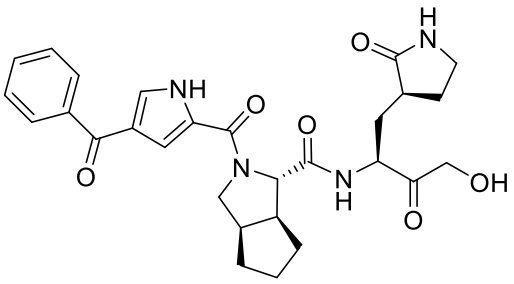
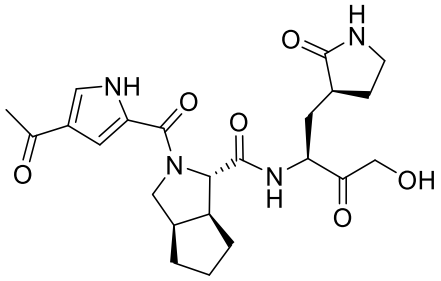
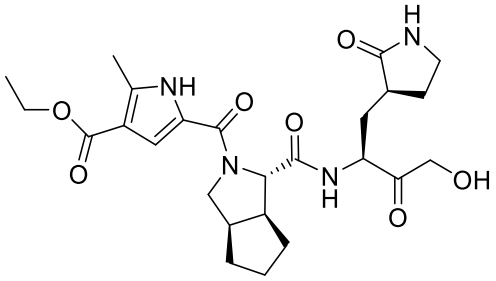

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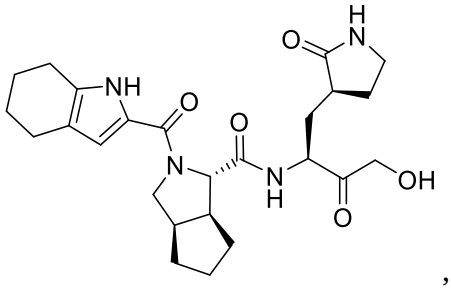
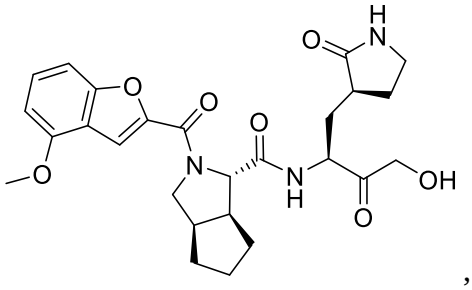
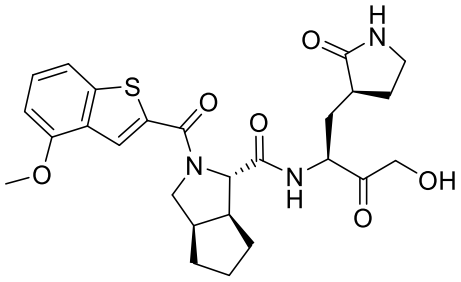
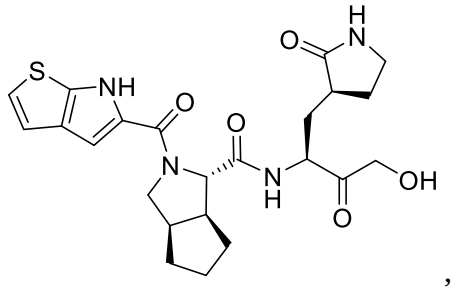
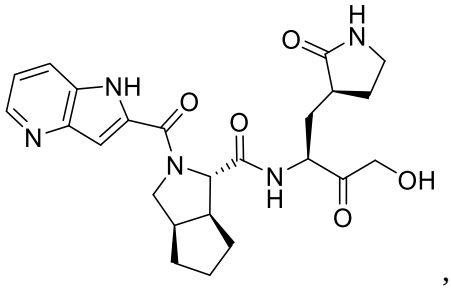
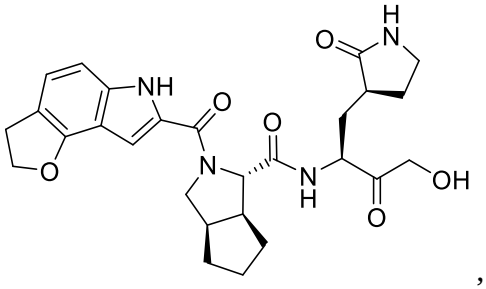
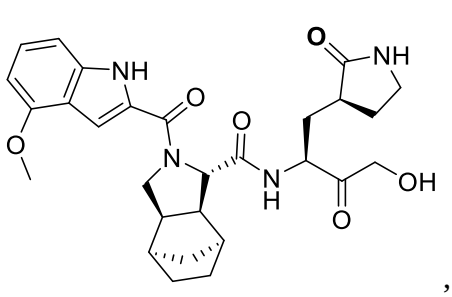
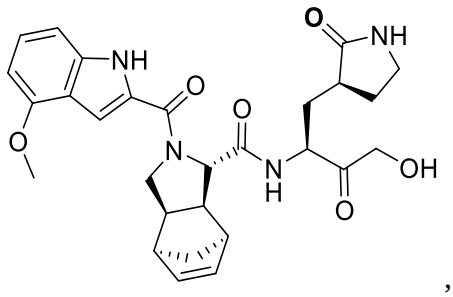
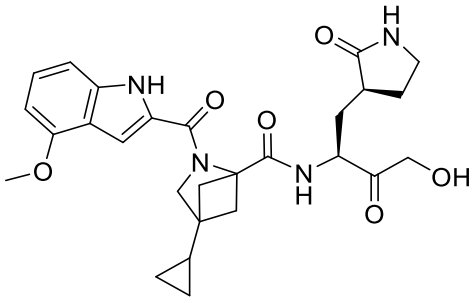
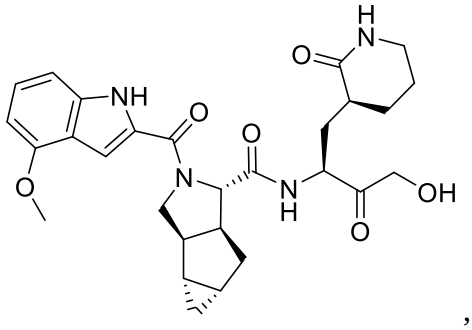

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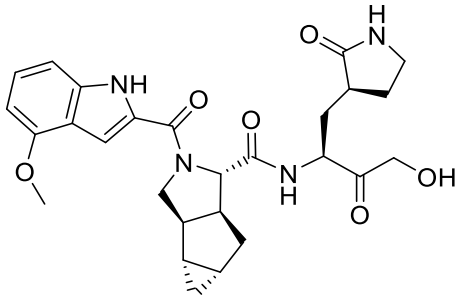
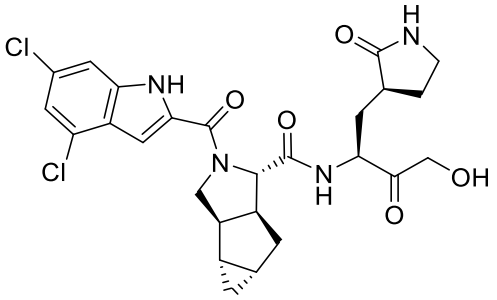
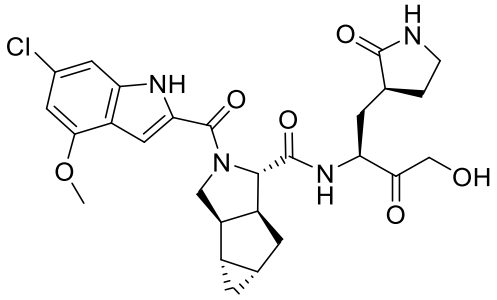
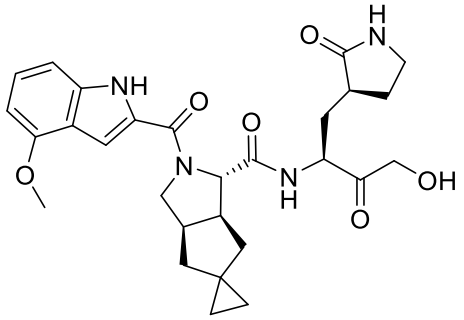
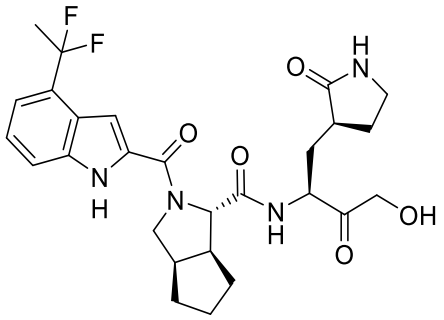
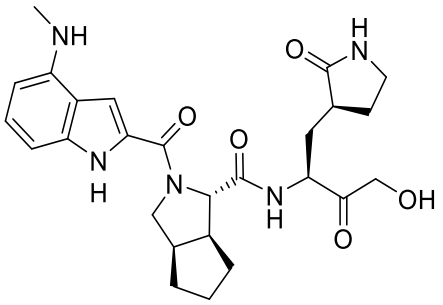
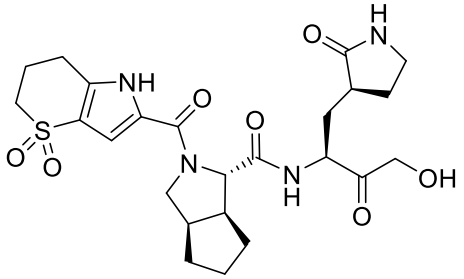
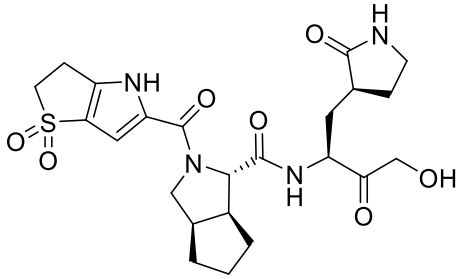
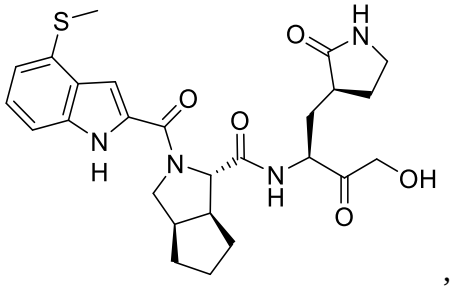
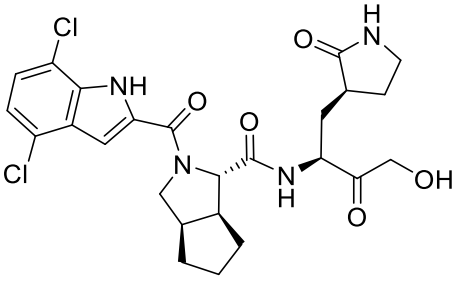

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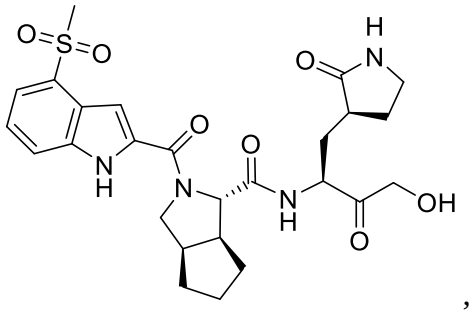
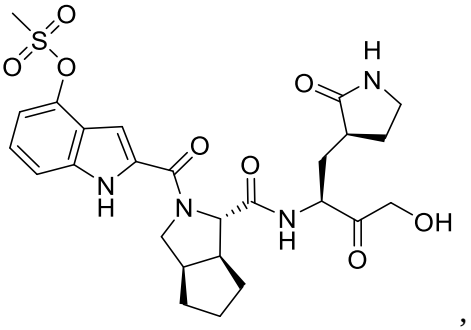
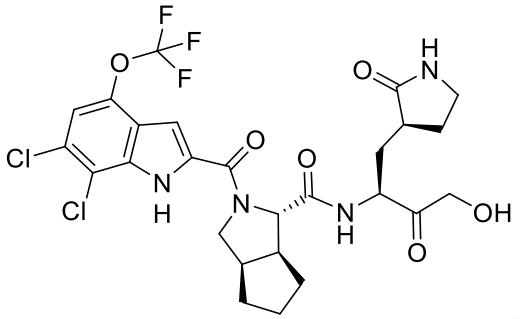
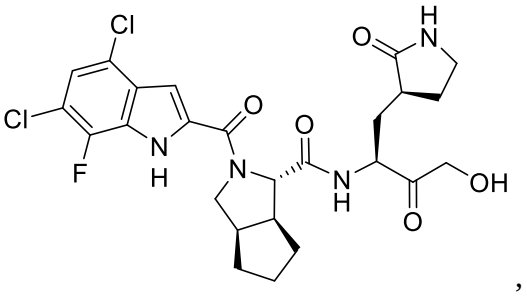
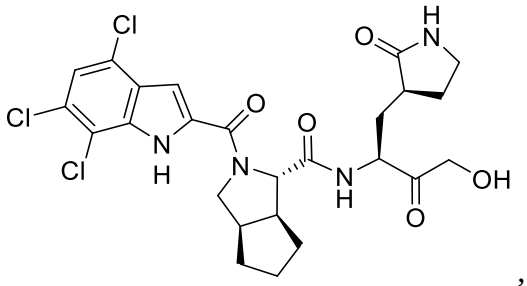
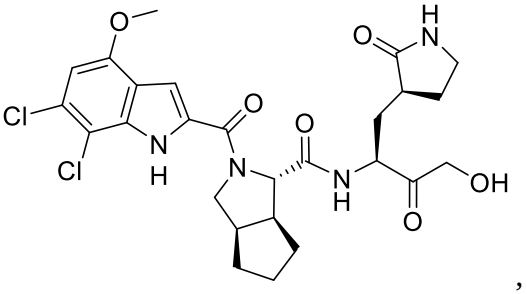
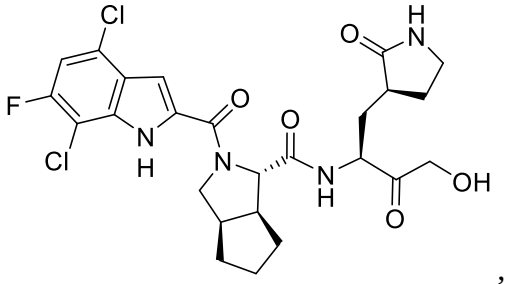
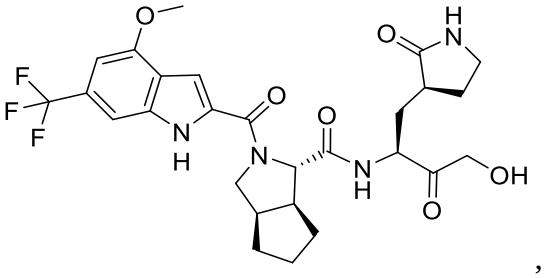
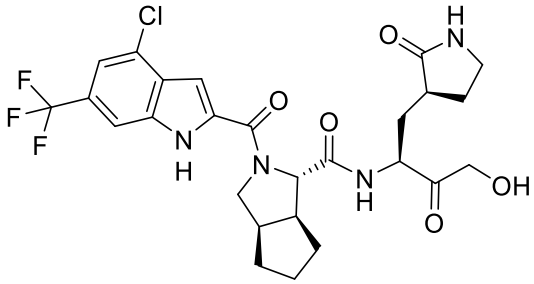
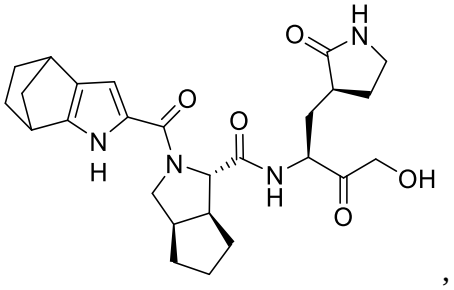

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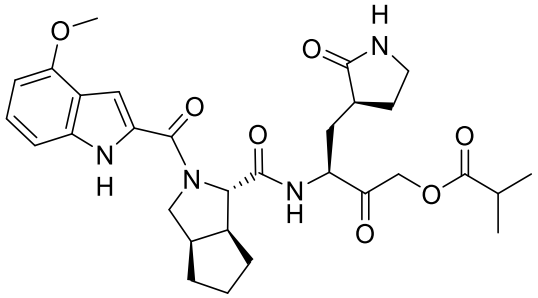
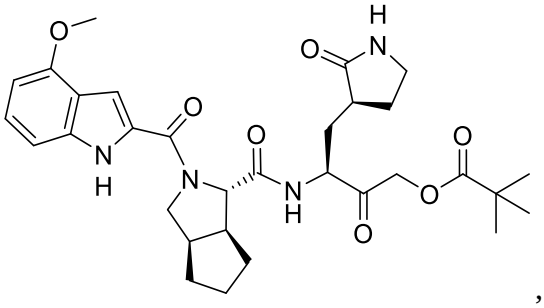
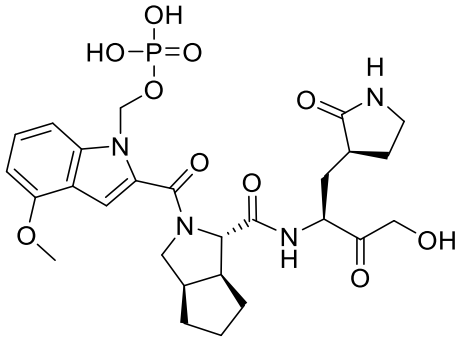
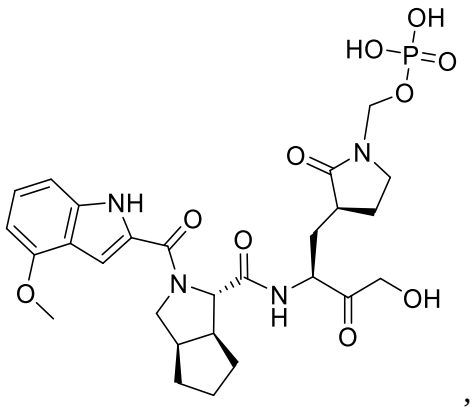
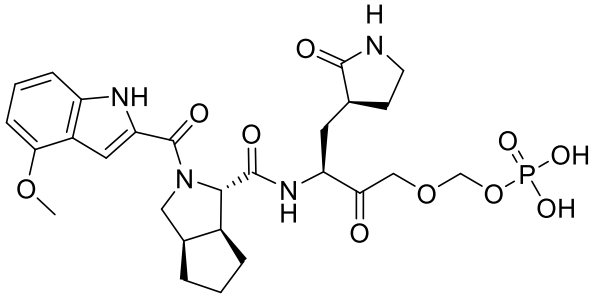
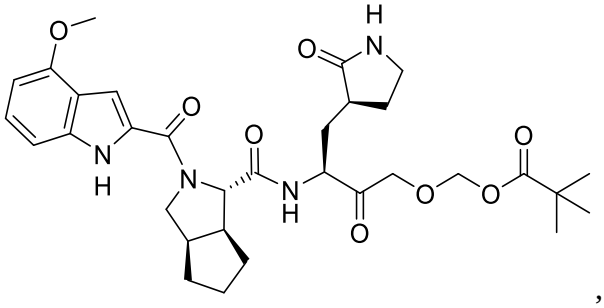
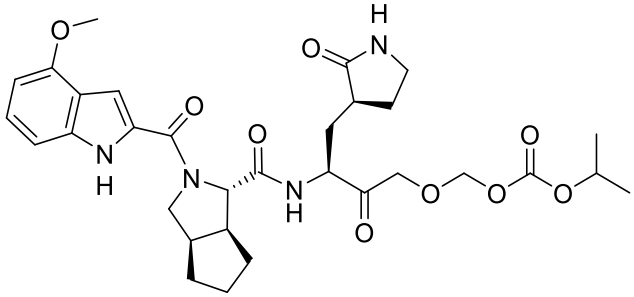
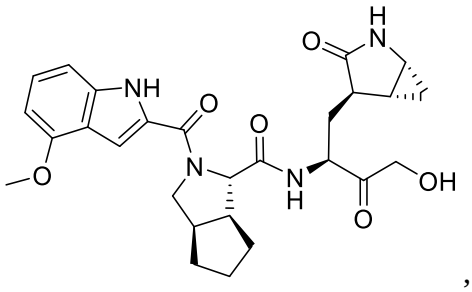
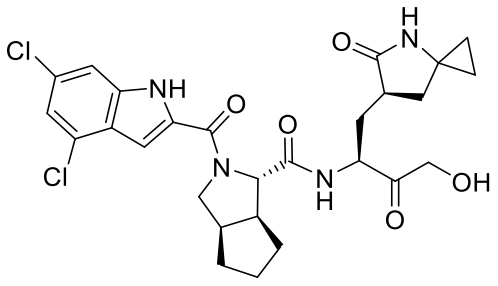
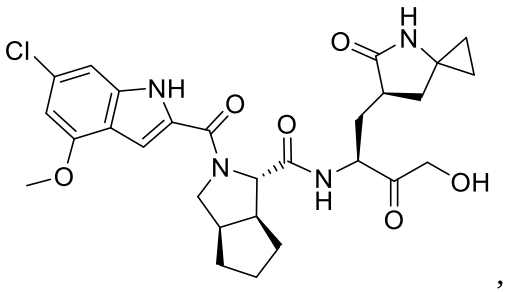

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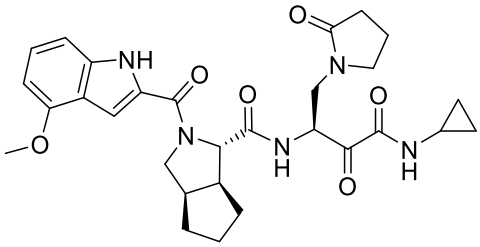
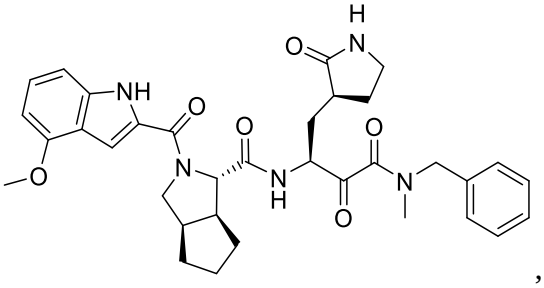
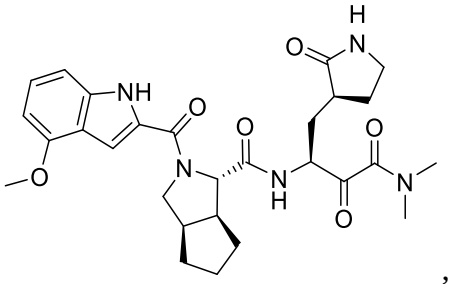
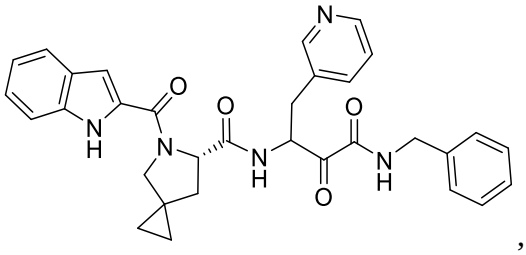
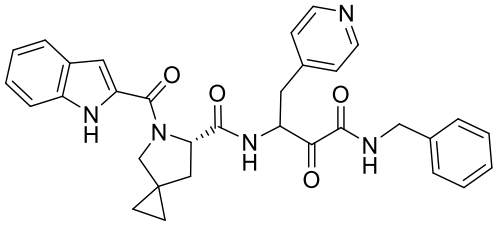
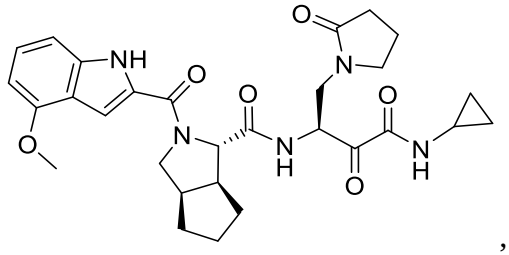
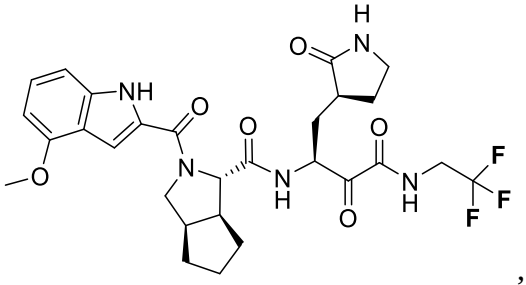
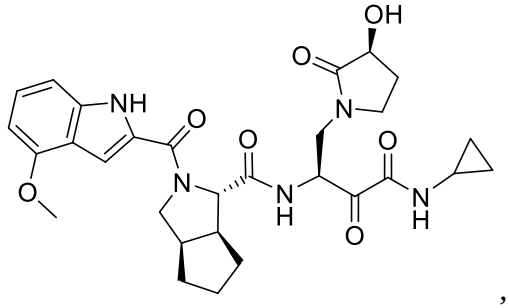
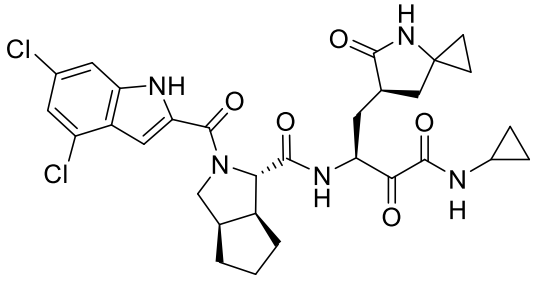
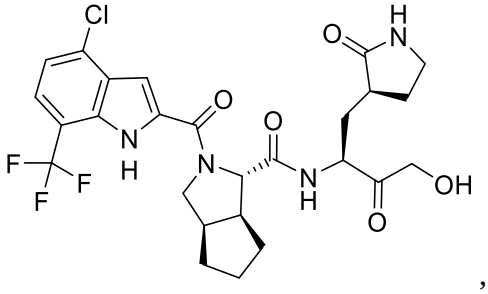

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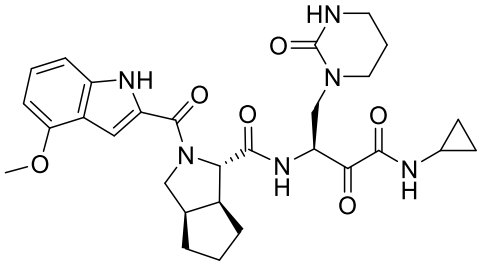
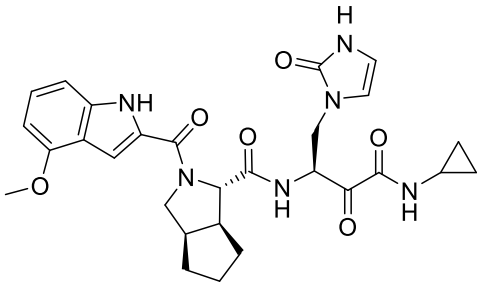
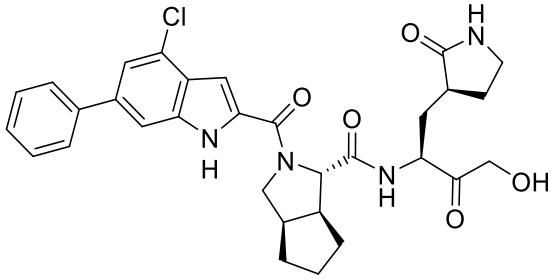
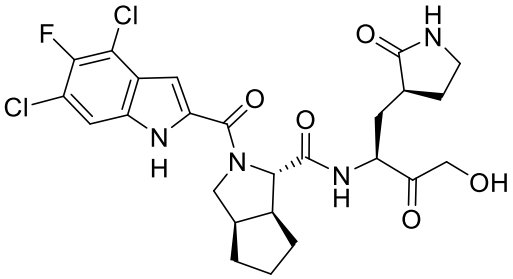
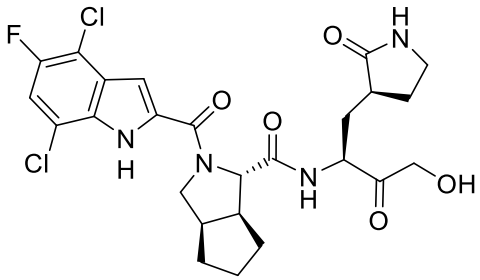
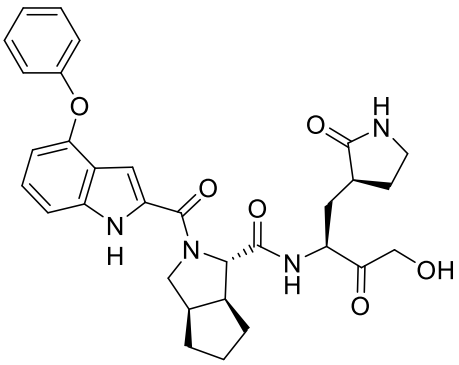
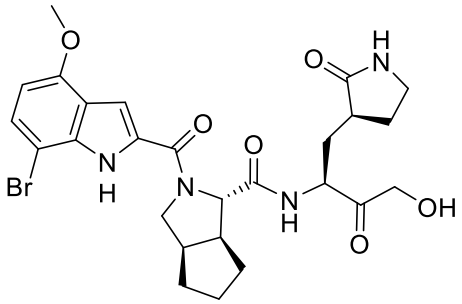
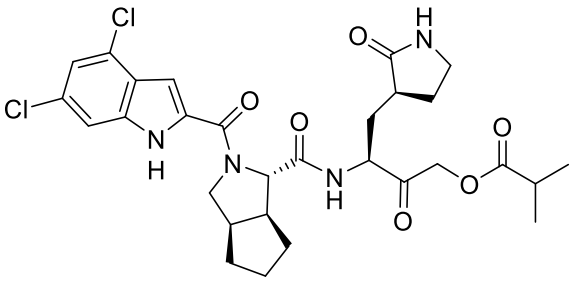
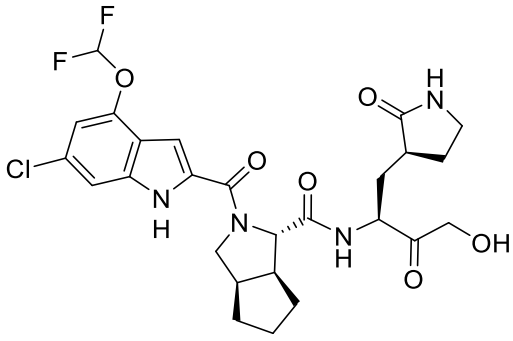
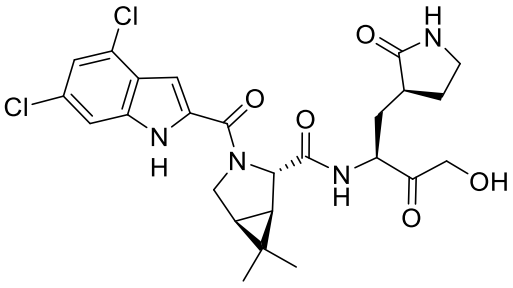

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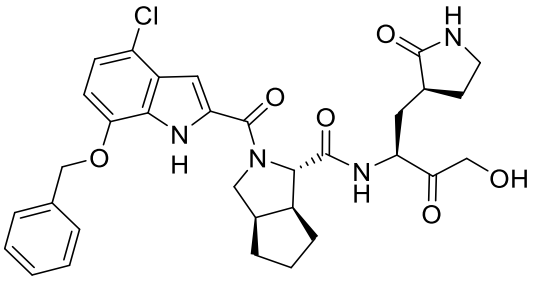
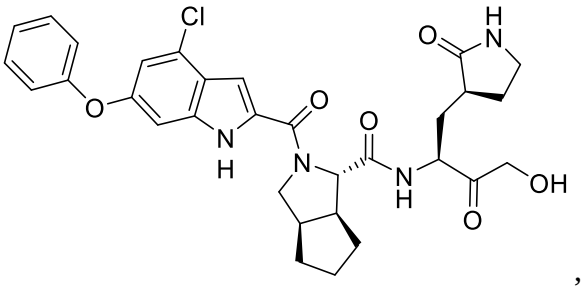
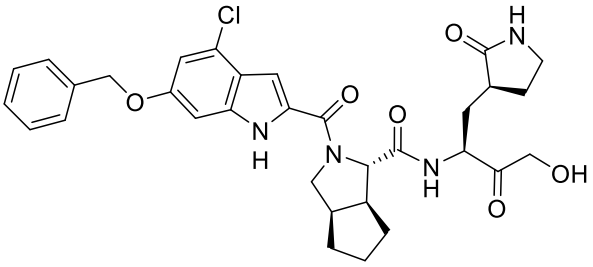
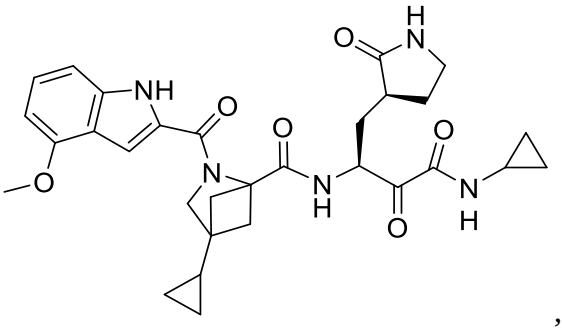
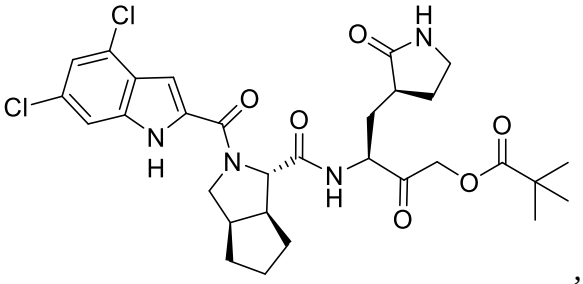
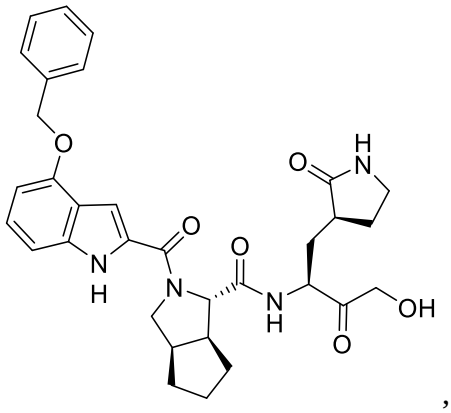
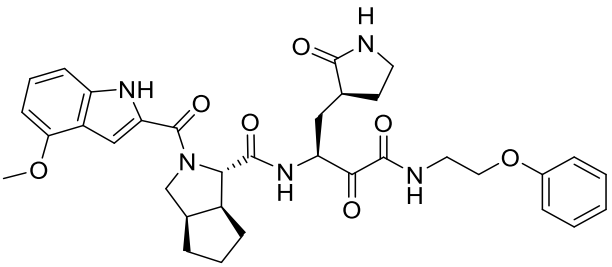
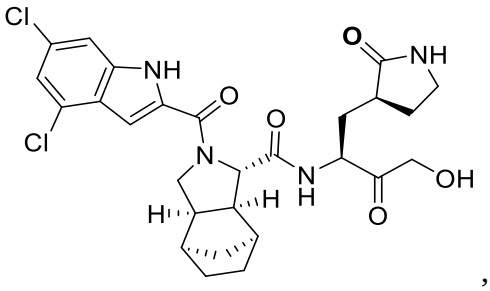
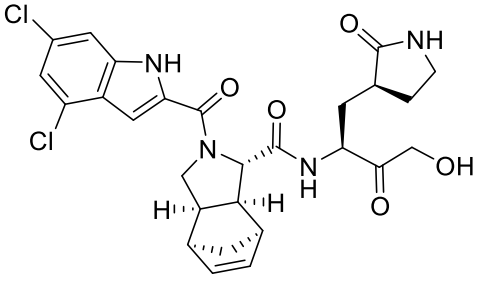
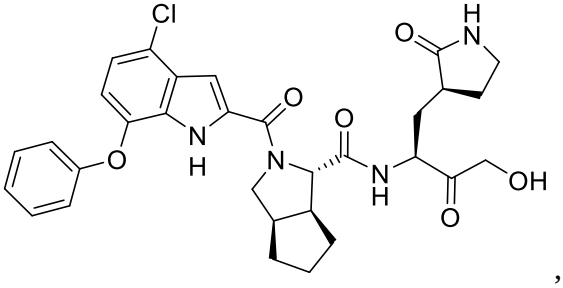

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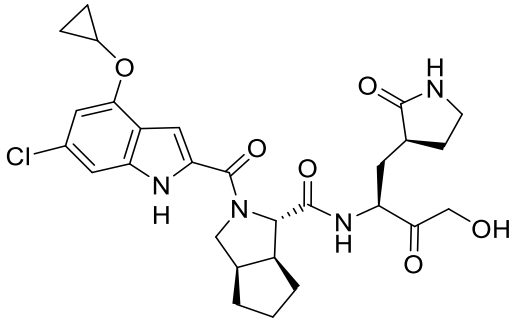
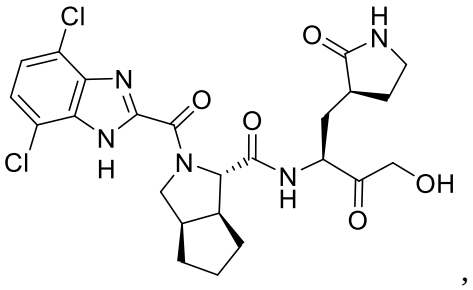
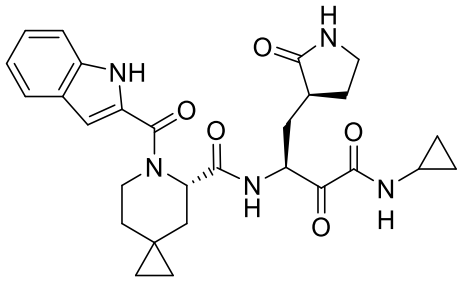
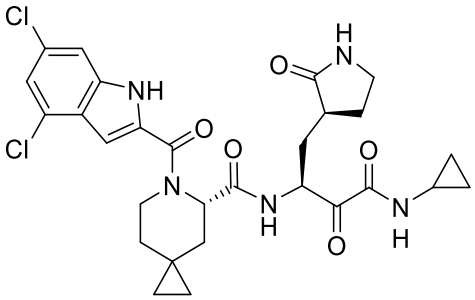
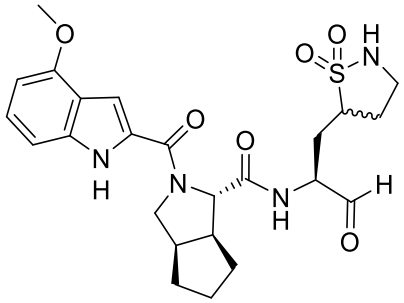
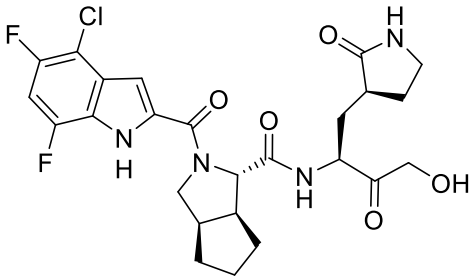
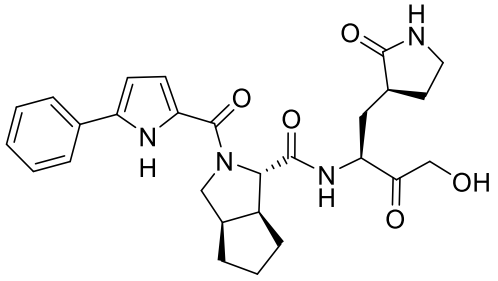
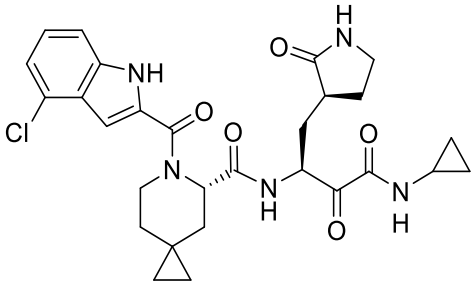
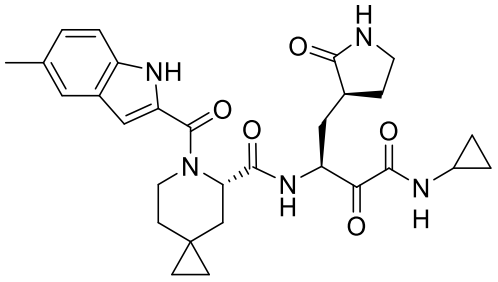
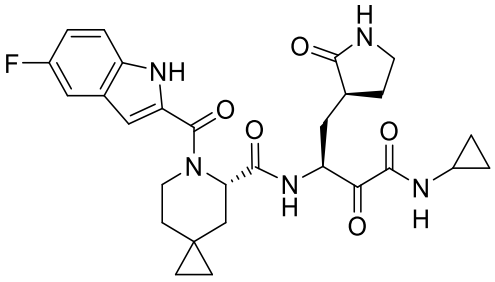

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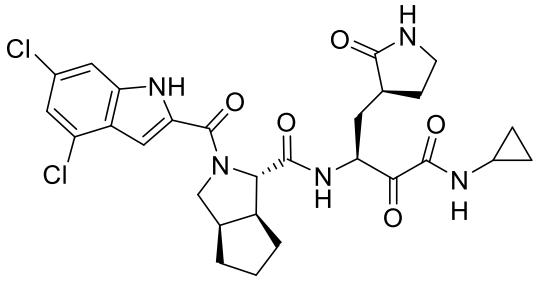
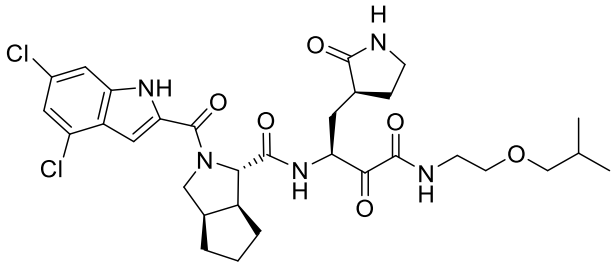
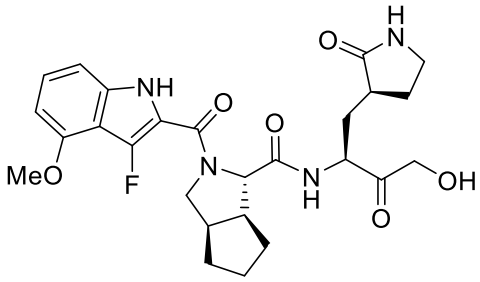
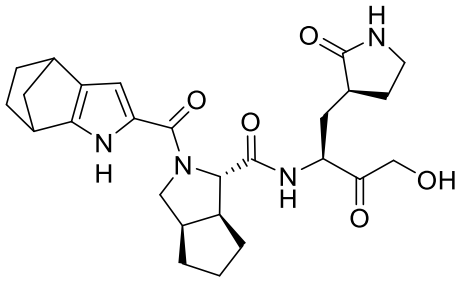
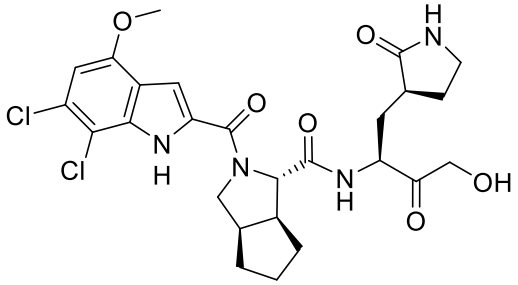
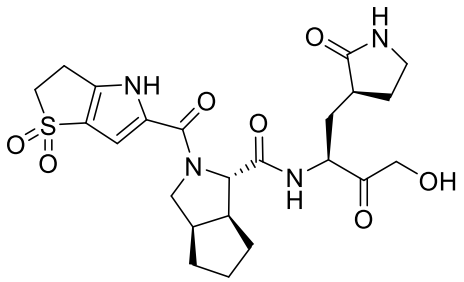
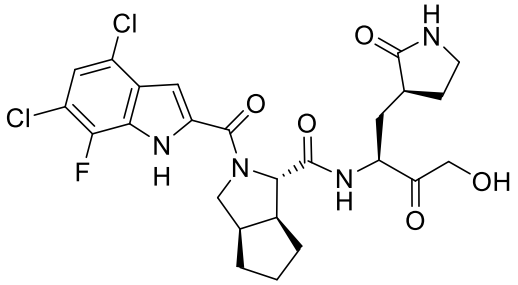
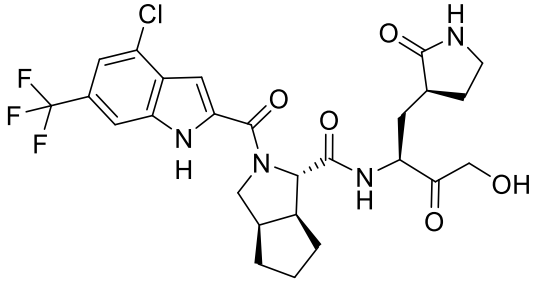
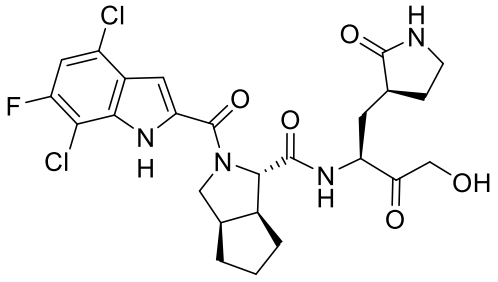
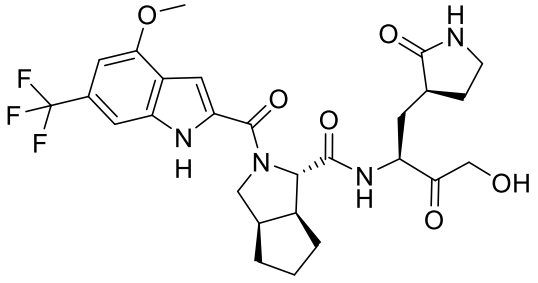

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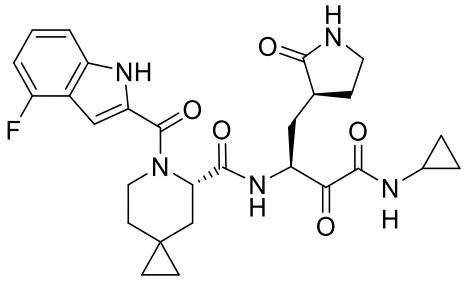
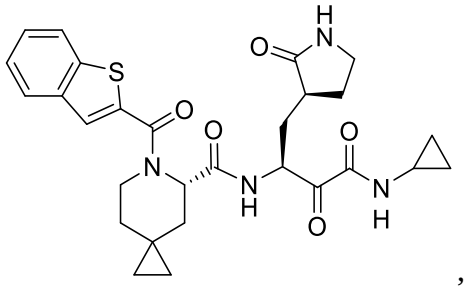
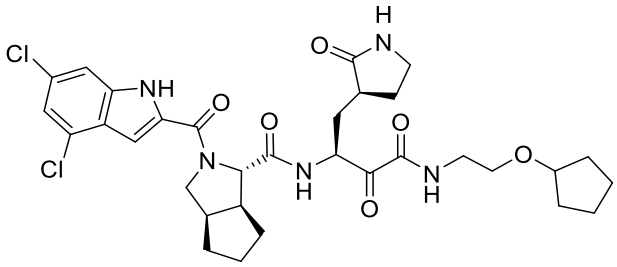
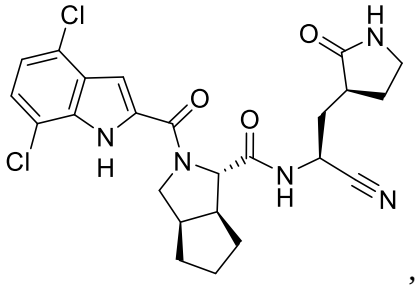
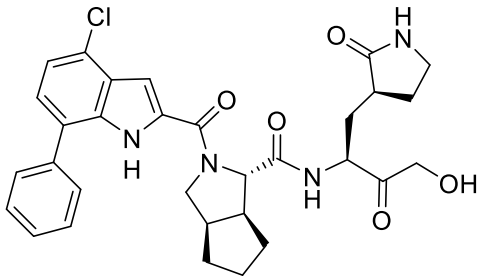
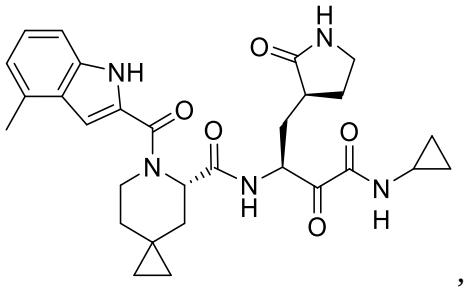
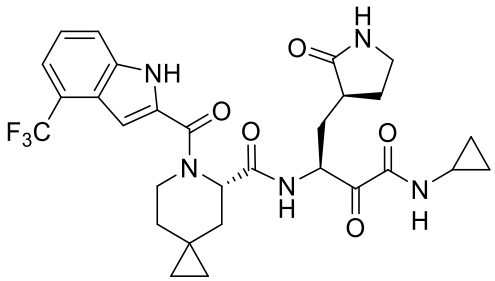
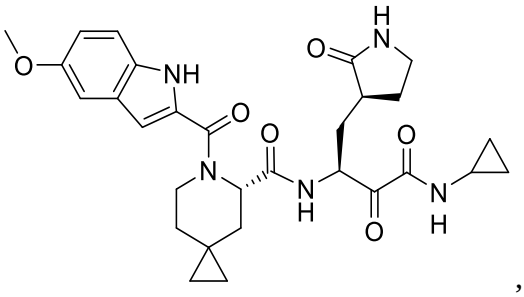
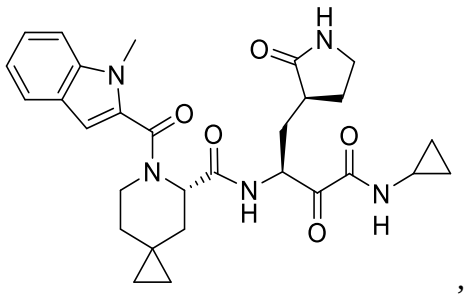
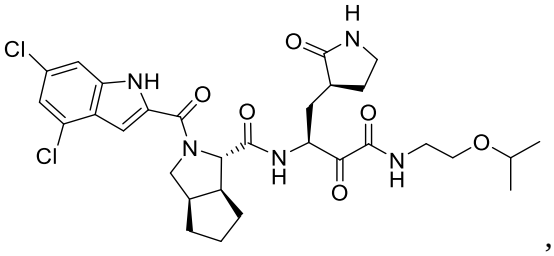

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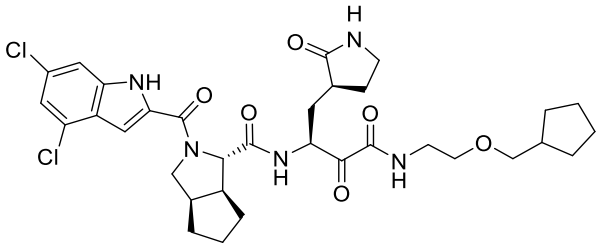
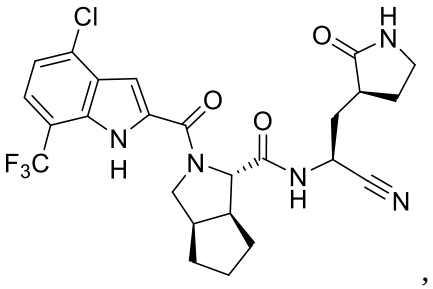
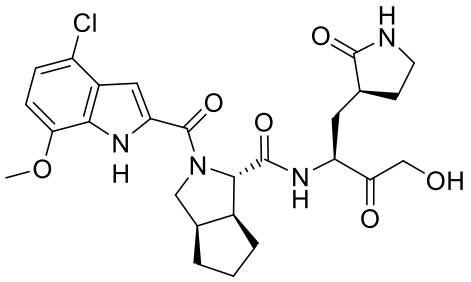
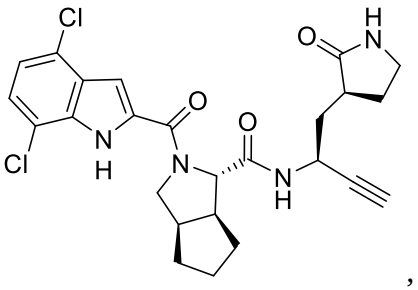
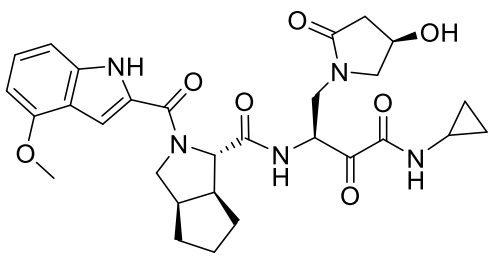
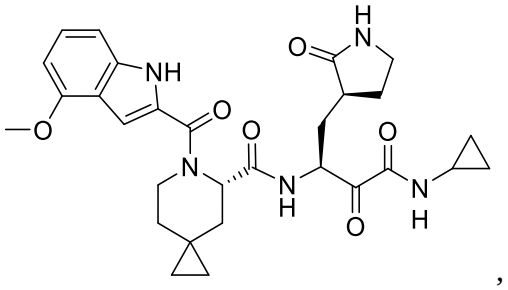
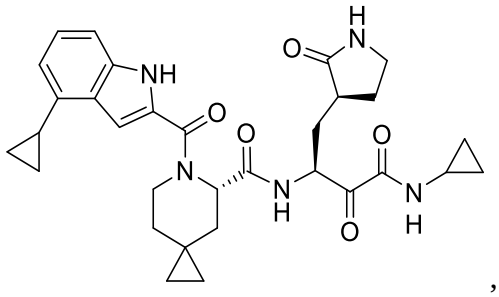
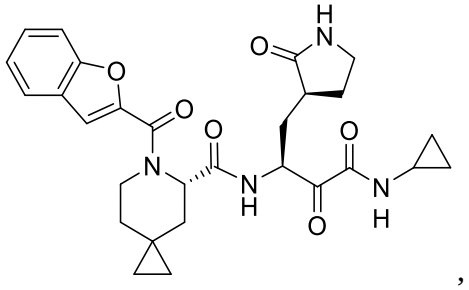
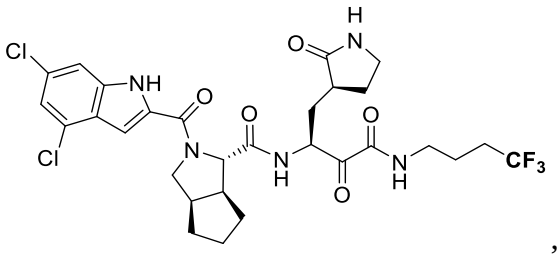
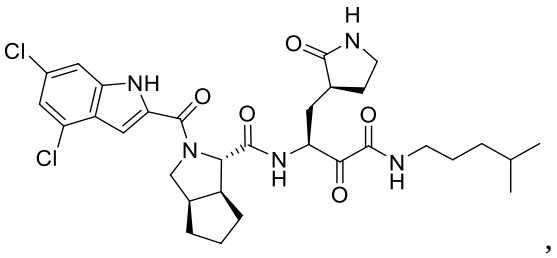

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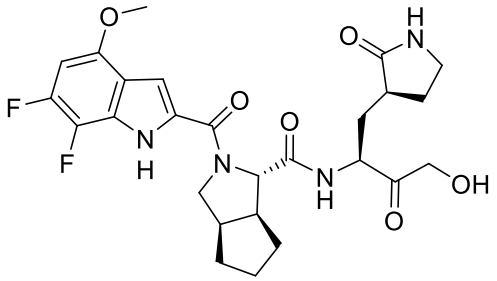
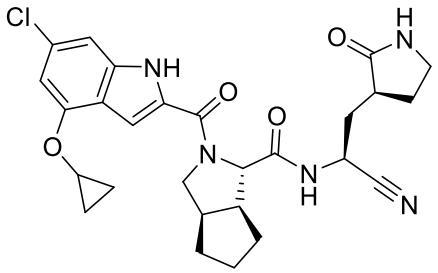
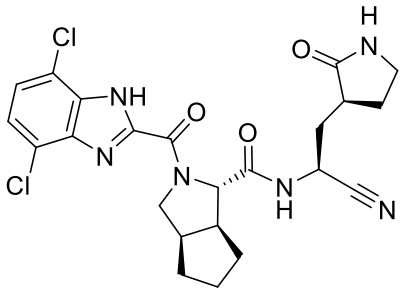
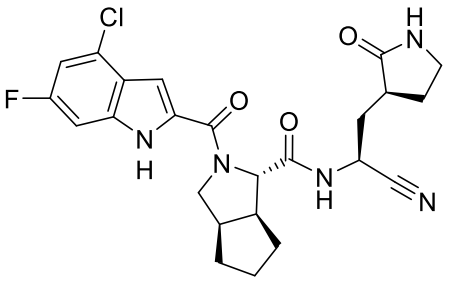
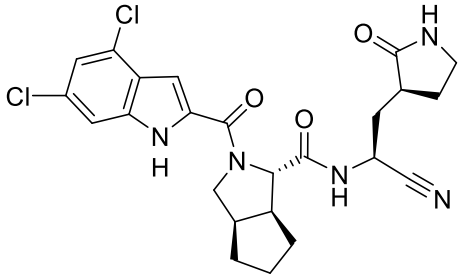
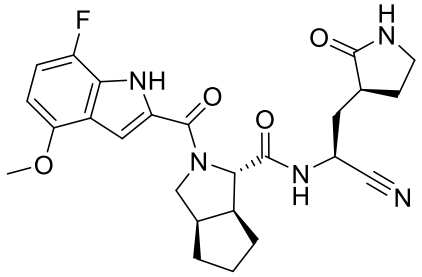
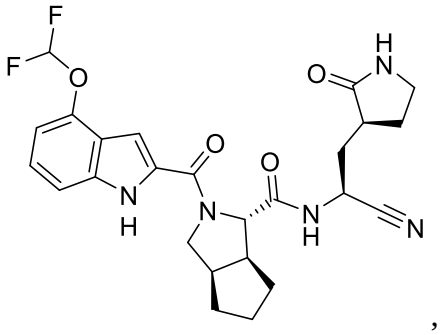
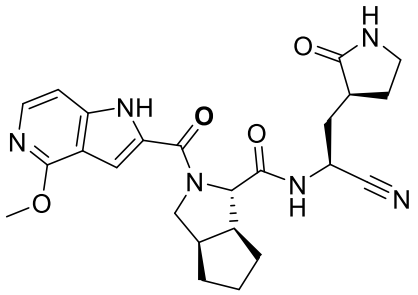
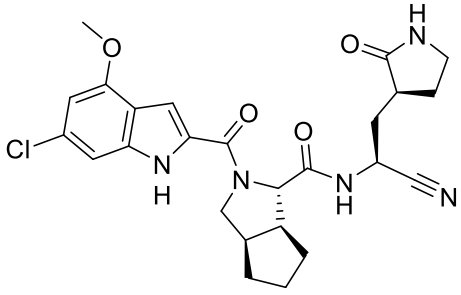
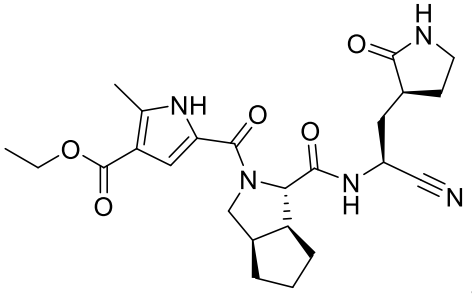

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and

, or

pharmaceutically acceptable salt of any of the foregoing.

16. A pharmaceutical composition comprising an effective amount of a compound of Claim 1, or a pharmaceutically acceptable salt thereof, and excipient.

17. Use of the compound of Claim 1, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of a coronavirus infection.

18. The use of Claim 17, wherein the use further comprises the use of an additional agent selected from the group consisting of an ACE inhibitor, an anticoagulant, an anti-inflammatory, an ARB, an ASO, a Covid-19 convalescent plasma, an entry inhibitor, an H_2 pump antagonist, an H-conducting channel, an HIV protease inhibitor, an HMG-CoA reductase inhibitor, an immune globulin, an immunosuppressant, an immunotherapeutic agent, a neuraminidase inhibitor, a nucleoside inhibitor, a nucleoside analog inhibitor, a polymerase inhibitor, a protease inhibitor, an siRNA, a statin, a tissue plasminogen activator, an antibiotic, an antimicrobial and a vaccine.

19. The use of Claim 17 or 18, wherein the coronavirus is β-coronavirus.

20. The use of Claim 17 or 18, wherein the coronavirus is coronavirus selected from the group consisting of CoV 229E, CoV NL63, CoV OC43, CoV HKU1, Middle East Respiratory Syndrome (MERS)-CoV, Severe Acute Respiratory Syndrome (SARS)-CoV, and SARS-CoV-2.

21. Use of the compound of Claim 1, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of a viral infection, wherein the viral infection is selected from the group consisting of a picornavirus infection and a norovirus infection.

22. Use of an effective amount of a compound of Claim 1, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for inhibiting a coronavirus protease in a cell culture that is infected with a coronavirus.

23. The use of Claim 22, wherein the compound of Formula (I) selectively inhibits the coronavirus protease over a protease is selected from the group consisting of Cathepsin L, Cathepsin B, Cathepsin D, Leukocyte Elastase, Chymotrypsin, Trypsin, Thrombin, Pepsin, Caspase 2, Elastase and Calpain.