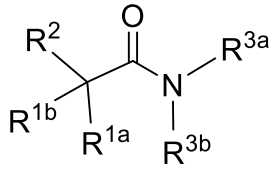
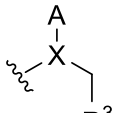
SUMMARY

[0005a] In one aspect of the present disclosure, there is provided a protease inhibitor compound represented by:



Formula II,

or a pharmaceutically acceptable salt, stereoisomer, ester, or prodrug thereof, wherein:

R^{3a} is selected from  and 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each independently selected from the group consisting of hydroxyl, C_1-C_8alkoxy, oxo and a warhead A;

R^{3b} is selected from hydrogen and C_1-C_8alkyl; wherein R^{3a} and R^{3b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each independently selected from C_6-C_{14}aryl and a warhead A;

R^{1a} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8heteroalkyl, –(C_1-C_8alkyl)-R^1, –(C_1-C_8alkyl)-CN, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle and 5-10 membered heteroaryl;

R^{1b} is selected from hydrogen and C_1-C_8alkyl;

or R^{1a} and R^{1b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle having a ring nitrogen NR^G, or a C_3-C_{10}cycloalkyl;

R^1 is selected from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^1 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^A is independently selected for each occurrence from the group consisting of halogen, cyano, hydroxyl, oxo, SF_5, $–CH_2CF_3$, $–CF_3$, $–O-CF_3$, $–O-CHF_2$, $–S-CH_3$, $–S(O)_2-CH_3$, $–NH_2$, –O-phenyl, $–O-(C_1-C_8alkyl)$-phenyl, $–NHC(O)R^B$, $–NHC(O)OR^B$, $–NHC(O)O-(C_1-C_8alkyl)-R^B$, $–N(R^y)_2$, $–N(R^y)(C_1-C_8alkyl)C(O)O$-phenyl, $–N(R^y)(C_1-C_8alkyl)C(O)N(R^y)_2$, $–C(O)-OC(CH_3)_3$, C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_1-C_8heteroalkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, $–(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl)$, $–(C_1-C_8alkyl)-(C_6-C_{14}aryl)$, $–(C_1-C_8alkyl)$-(5-10 membered heteroaryl), C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocyclyl, wherein the R^B, alkyl, heterocyclyl, heteroaryl, or aryl may optionally be substituted by one, two or three substituents each independently selected from the group consisting of halogen, C_1-C_8alkyl, C_1-C_8alkoxy, SF_5, $–NH_2$, hydroxyl and oxo;

R^2 is selected from the group consisting of $–NHC(O)R^B$, $–NHC(O)OR^B$, $–NHC(O)N(R^B)_2$, $–NHC(O)C(R^C)_2R^B$, $–NHS(O)_2R^B$, $–O-(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl)$, 4-10 membered heterocycle, C_6-C_{14}aryl and 5-10 membered heteroaryl bound through the carbon or nitrogen atom, wherein R^B or R^2 may optionally be substituted by one, two, or three substituents each selected from R^x;

or R^{1a} and R^2 may be joined together to form, together with the carbon to which they are attached, a 4-10 membered monocyclic or bicyclic heterocycle having a ring nitrogen NR^G, or a C_3-C_{10}cycloalkyl, wherein the cycloalkyl or heterocycle may optionally be substituted by one, two or three substituents on a free carbon each selected from R^A;

R^3 is selected from 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^3 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^B is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_6cycloalkyl, fluorenylmethyloxy, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle;

R^C is independently selected, for each occurrence, from hydrogen, halogen and C_1-C_8alkyl;

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, CF_3, SF_5, cyano, -O-(R^{xx})-OCH_3, –$OCHF_2$, –OCF_3, –O-(C_1-C_8alkyl), –C(O)O(CH_3), –N(R^y)$_2$, –N(R^y)C(O)R^y, –N(R^y)(C_1-C_8alkyl)C(O)N(R^y)$_2$, –N(R^y)(C_1-C_8alkyl)C(O)OH, -(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl), C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, -O-C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle;

wherein two geminal C_1-C_8alkyl groups, together with the carbon to which they are attached, may be joined together to form a C_3-C_6cycloalkyl optionally substituted by one, two or three substituents each independently selected from halogen, hydroxyl and oxo; and

wherein the alkyl, aryl, heterocycle or heteroaryl may optionally be substituted by one or more substituents each independently selected from oxo, halogen and C_1-C_8alkyl;

R^G is selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl optionally substituted by one, two or three R^{gg}, –C(=O)-$C_{1\text{-}6}$alkyl optionally substituted by one, two or three R^{hh}, -C(=O)-$C_{3\text{-}6}$cycloalkyl, –C(O)-(C_2-C_{10}alkenyl)-(C_6-C_{14}aryl), –C(O)-(C_1-C_6alkyl)-O-(C_6-C_{14}aryl), –C(O)-(5-10 membered heteroaryl), –C(O)-(4-10 membered heterocyclyl), and –C(O)-(4-10 membered heterocyclyloxy); wherein the aryl, heterocyclyl, or heteroaryl may optionally be substituted by one, two or three R^{jj};

R^{gg} is independently selected for each occurrence from the group consisting of -C(=O), halo, cyano, -N$R^m$$R^m$, and -NH(C=O)$R^m$;

R^{hh} is independently selected for each occurrence from the group consisting of halo, cyano, -NR^mR^m, -$NR^m(C=O)R^m$, phenyl, cycloalkyl, heterocyclyl and C_1-C_6alkoxy;

R^{jj} is independently selected for each occurrence from the group consisting of halo, oxo, hydroxyl, cyano, C_1-C_6alkyl, C_{1-6}haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_{3-6}cycloalkyl, SF_5, and NH_2;

R^m is independently selected for each occurrence from the group consisting of hydrogen, C_{1-3}alkyl, phenyl, -$S(O)_2$-CH_3, C_{3-6}cycloalkyl, and 5-6 membered heteroaryl; wherein C_{1-3}alkyl, phenyl, and C_{3-6}cycloalkyl may optionally be substituted by one, two or three halo;

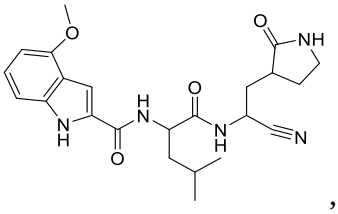
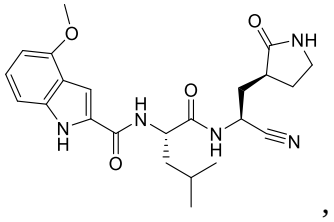
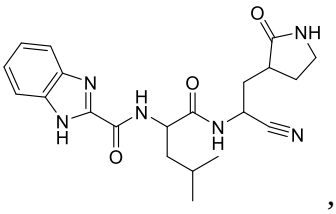
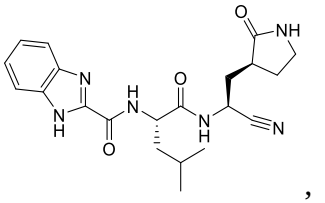
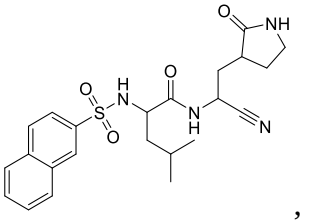
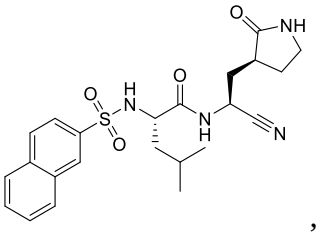
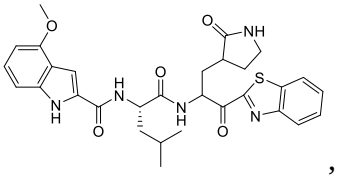
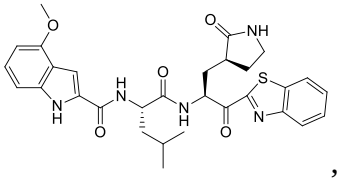
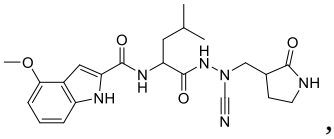
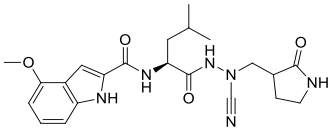
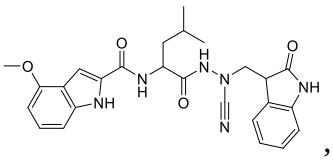
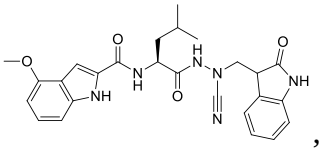
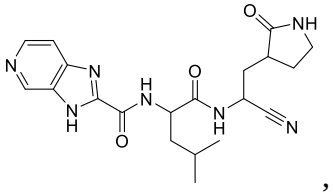
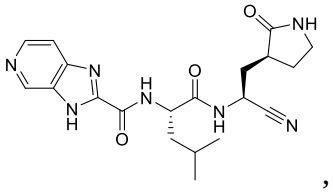
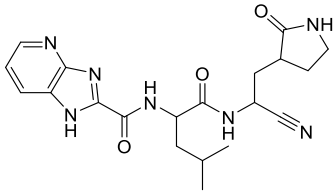
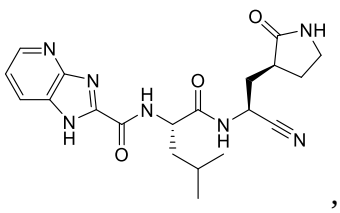
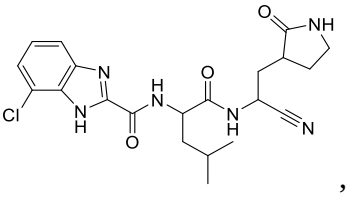
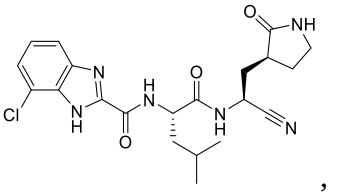
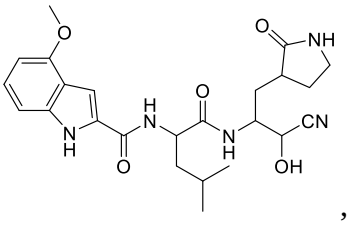
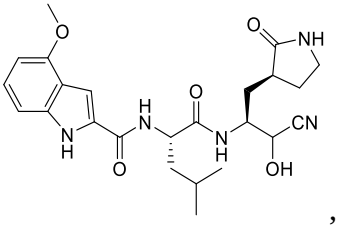
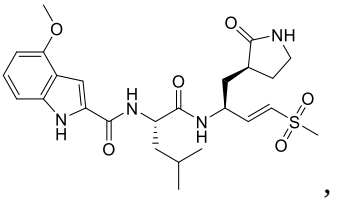
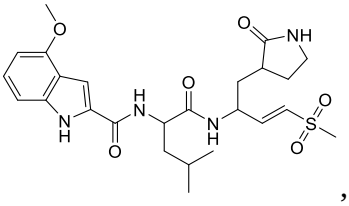
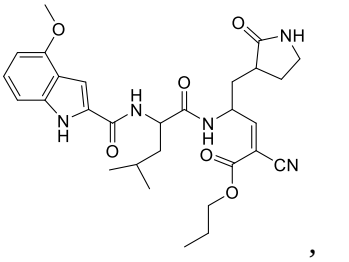
R^{xx} is –$(OCH_2CH_2)_{nn}$–, wherein nn is selected from 1, 2, 3, 4, 5 and 6;

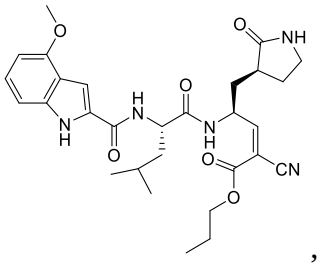
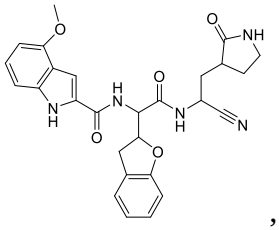
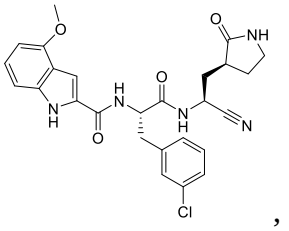
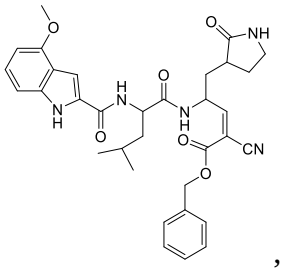
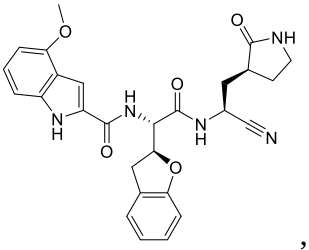
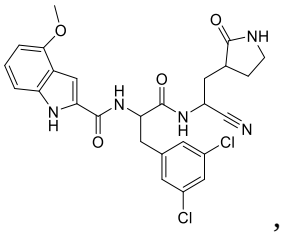
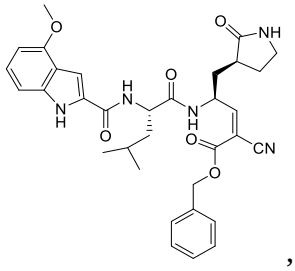
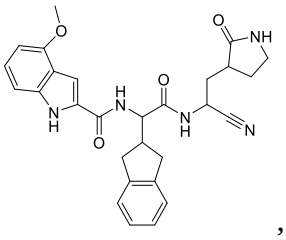
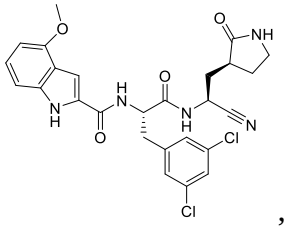
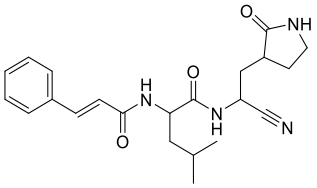
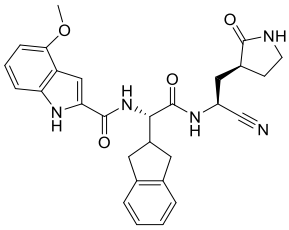
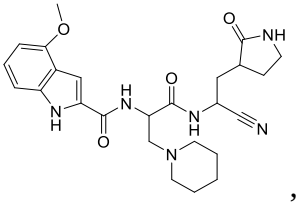
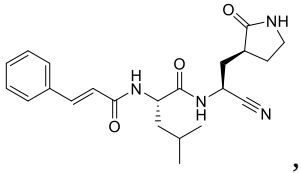
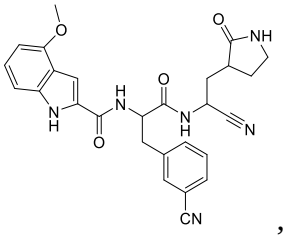
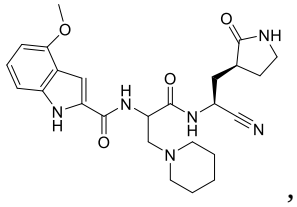
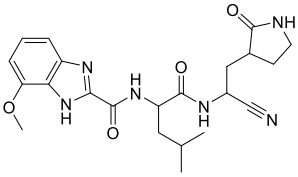
R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8heteroalkyl, –CF_3, –CH_2CF_3, C_1-C_8alkoxy,–(C_1-C_8alkoxy)-(5-10 membered aryl), C_3-C_6cycloalkyl and –(C_1-C_8alkyl)COOH;

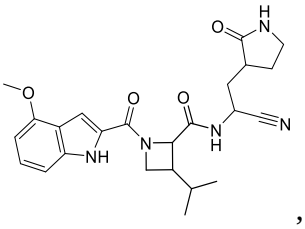
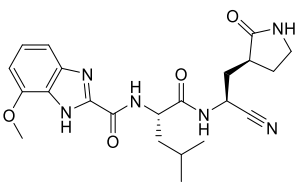
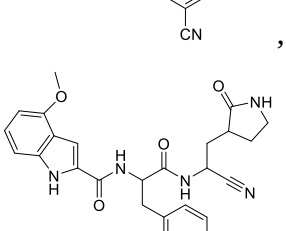
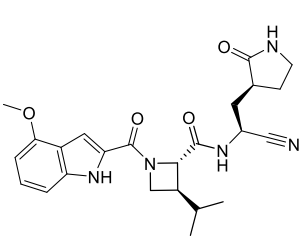
A is a warhead; and

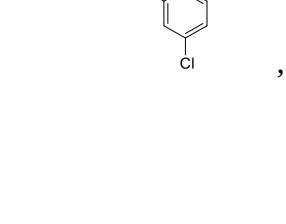
X is selected from the group consisting of C(R^{xy}) and N, wherein R^{xy} is selected from the group consisting of H, D, -OH, -NH_2, halogen, C_1-C_8alkyl, C_1-C_8 haloalkyl, and C_1-C_8alkoxy.

[0005b] In another aspect of the present disclosure, there is provided a compound selected from the group consisting of:

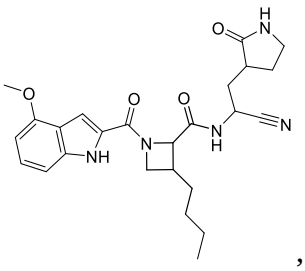
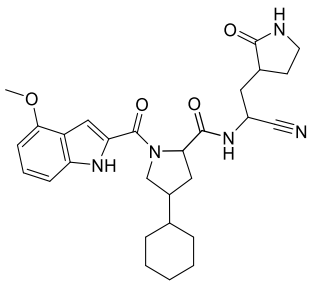
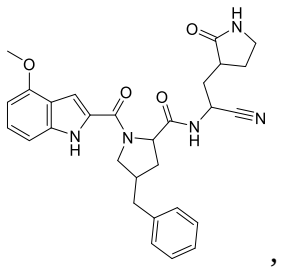
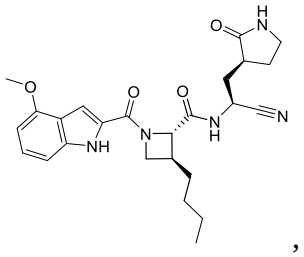
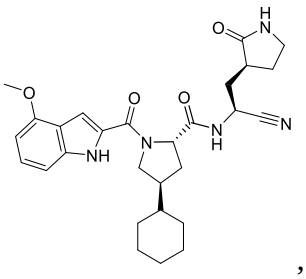
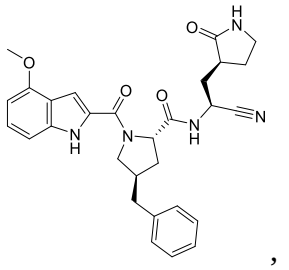
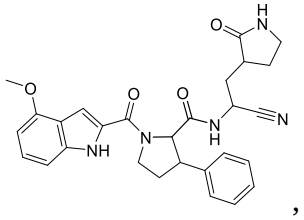
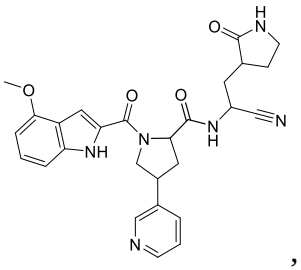
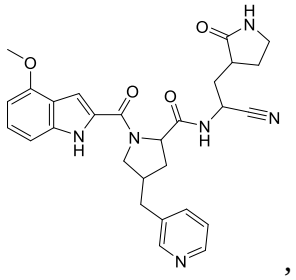
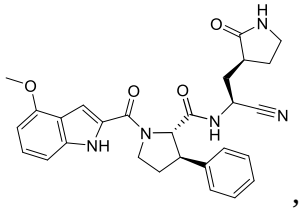
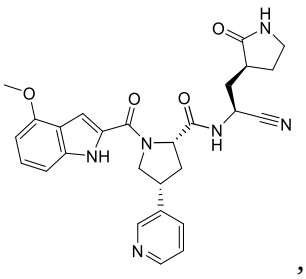
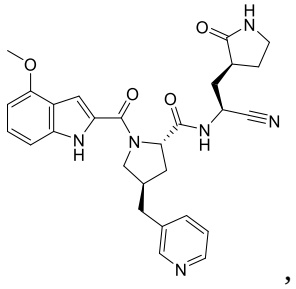
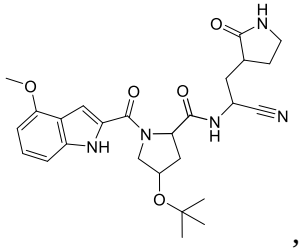

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

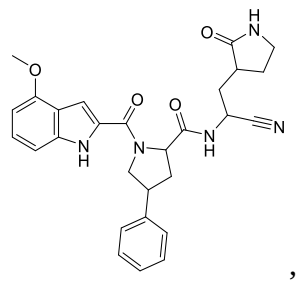
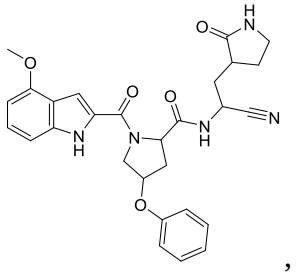
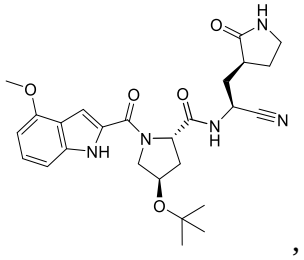
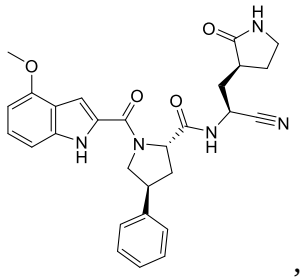
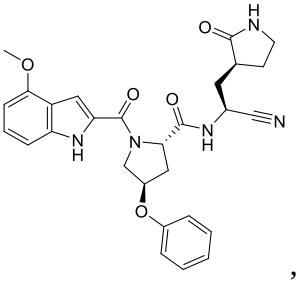
,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

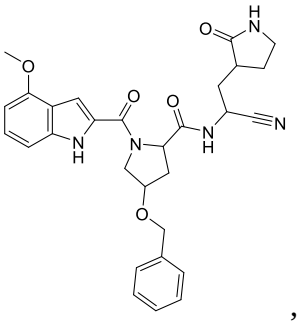
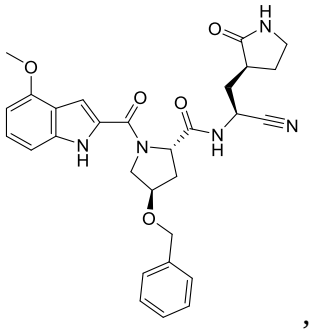
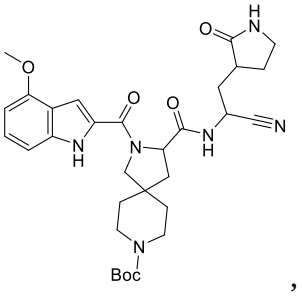
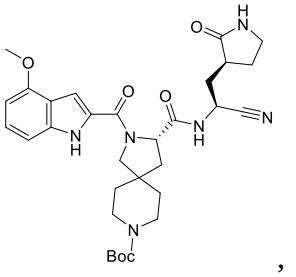
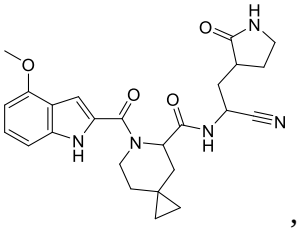
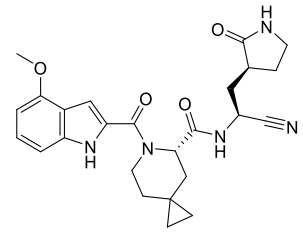
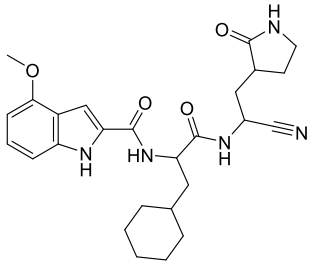
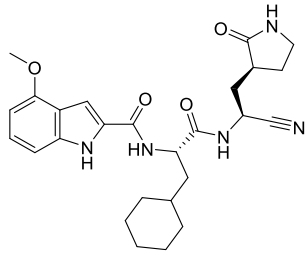
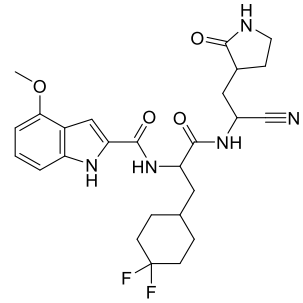
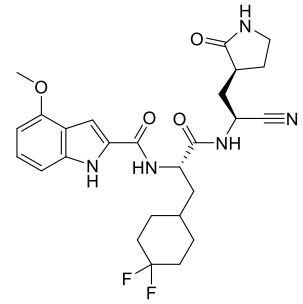
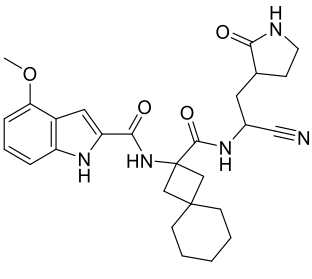
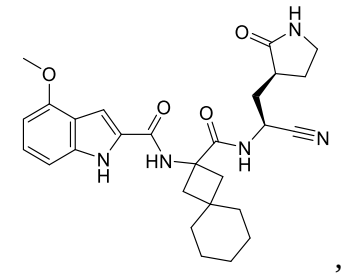
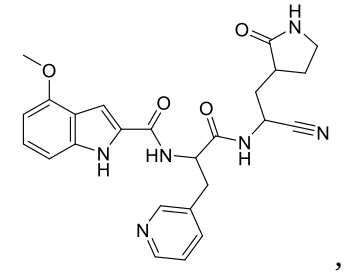
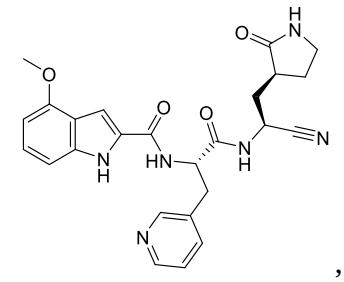
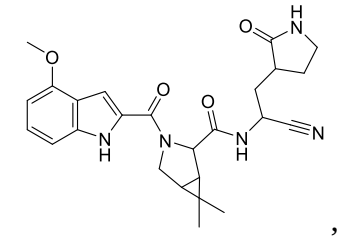
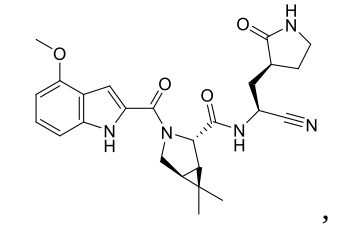
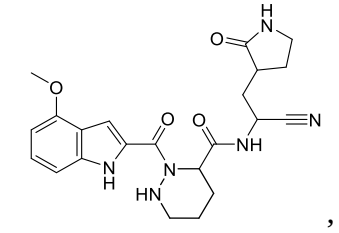
,

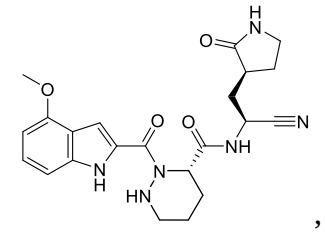
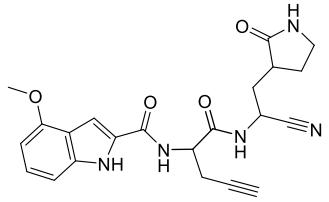
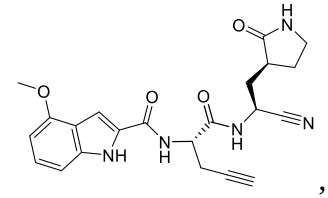
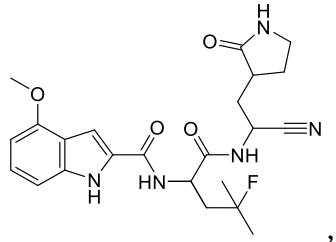
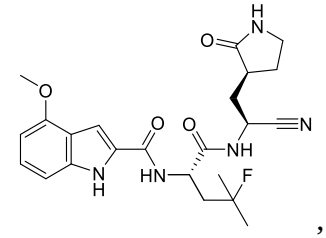
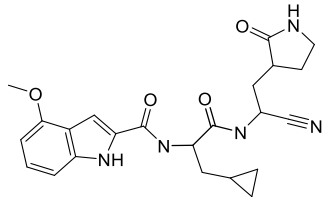
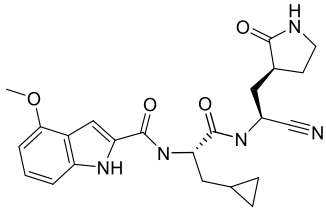
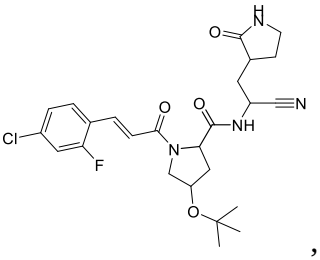
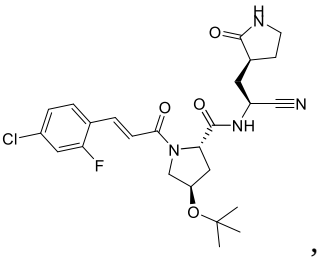
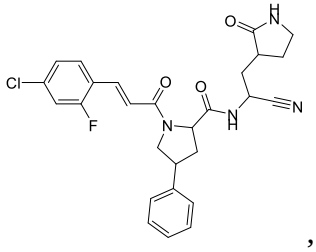
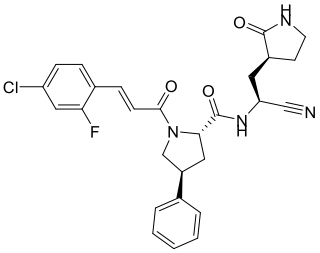
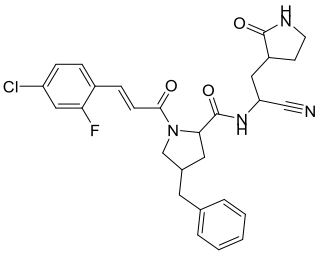
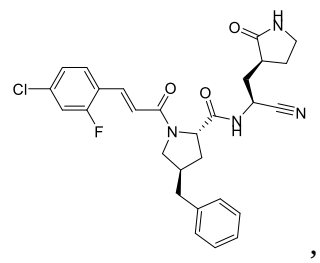
,

,

,

,

,

,

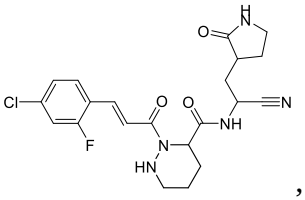
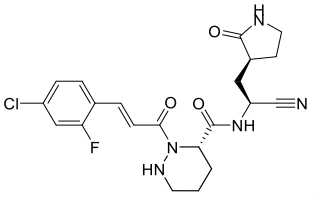
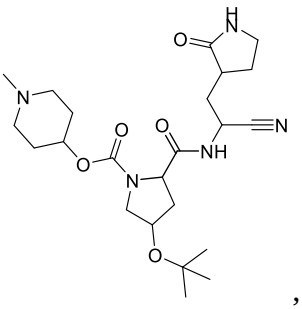
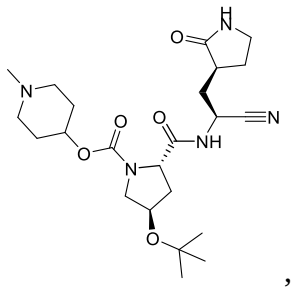
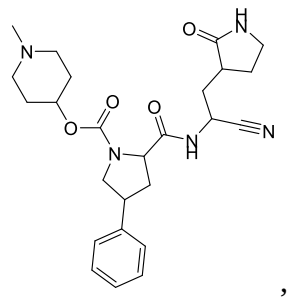
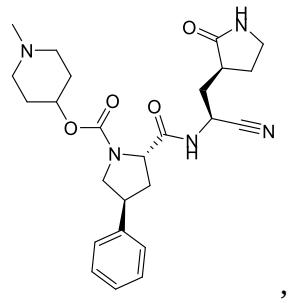
,

,

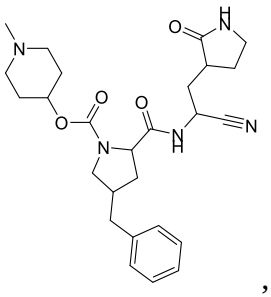
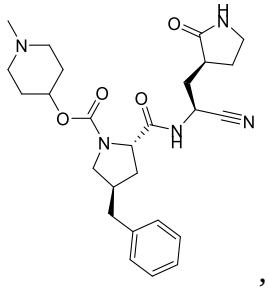
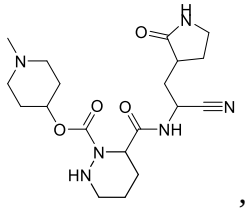
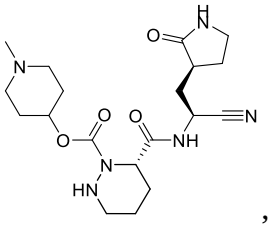
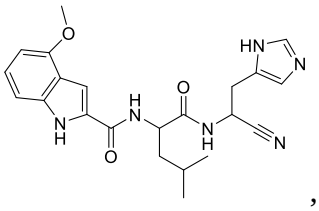
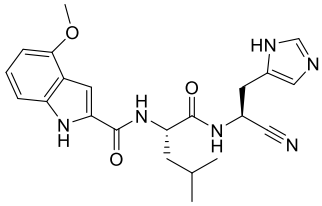
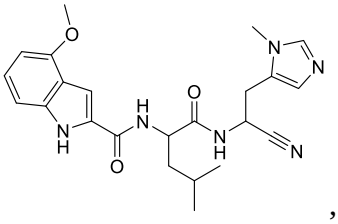
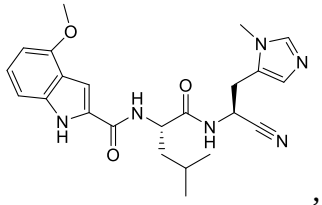
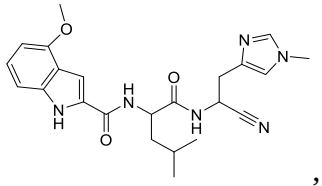
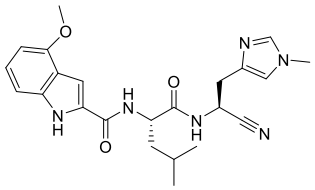
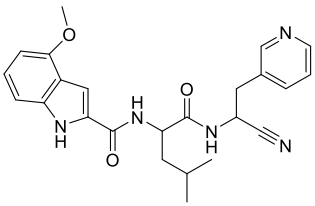
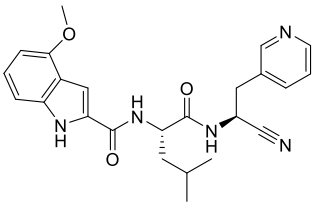
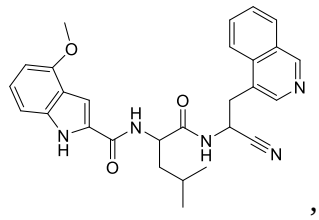
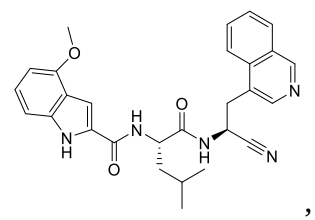
,

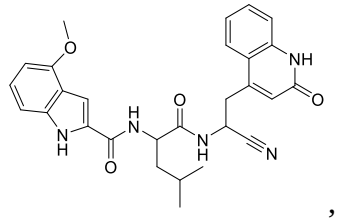
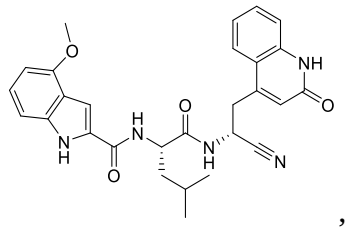
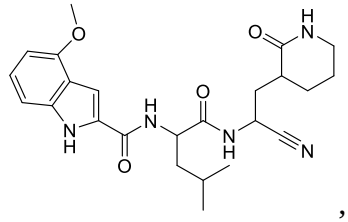
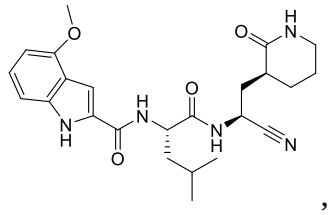

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

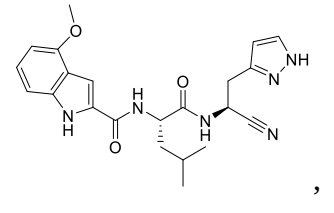
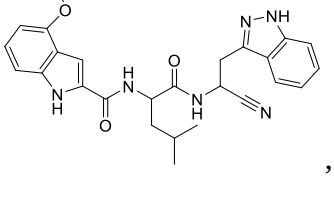

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

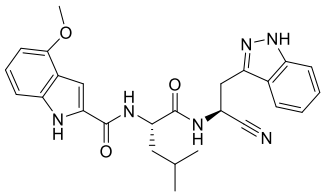
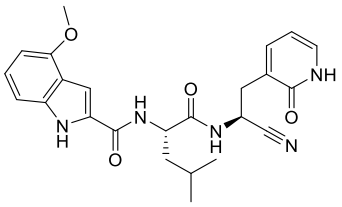
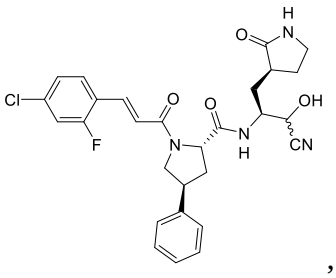
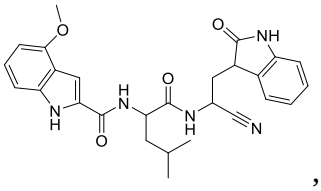
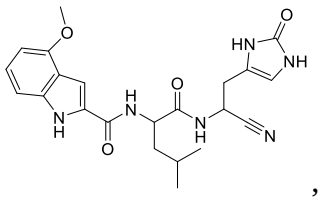
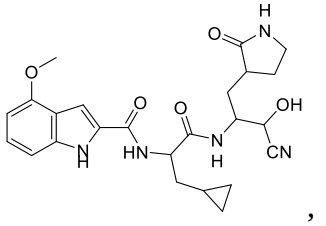
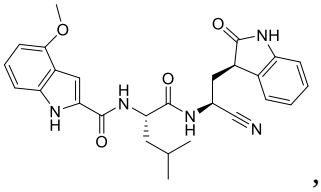
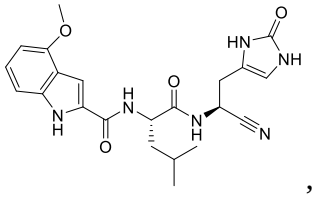
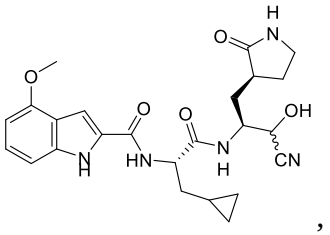
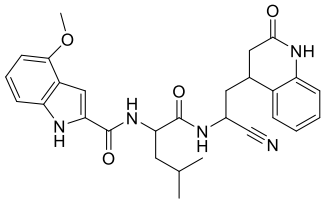
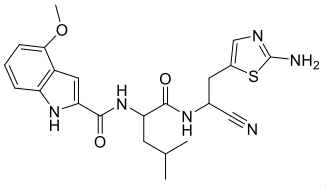
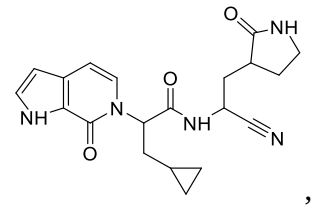
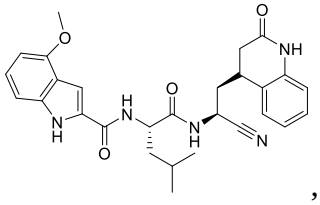
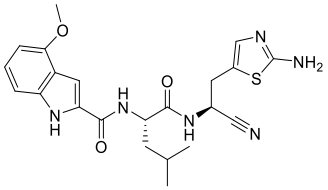
,

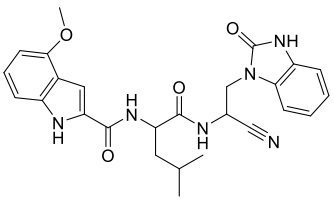
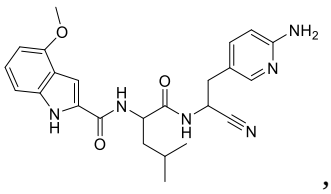
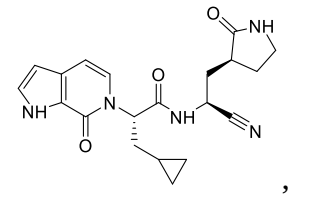

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

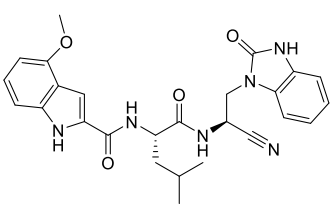
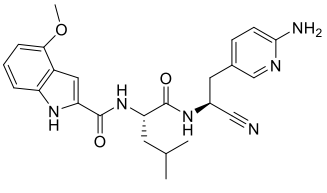
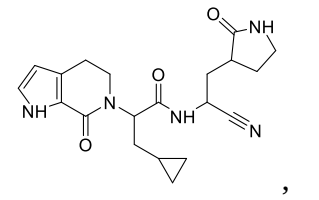
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

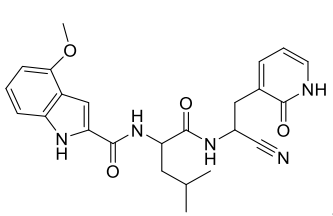
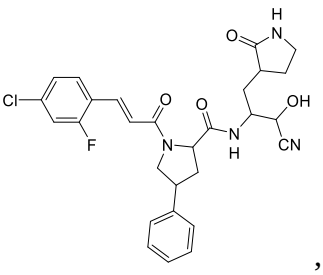
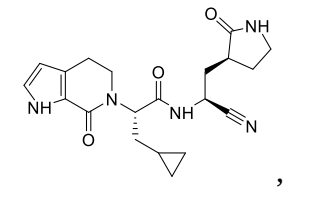
,

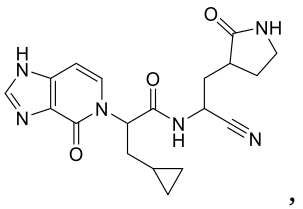
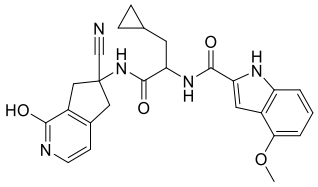
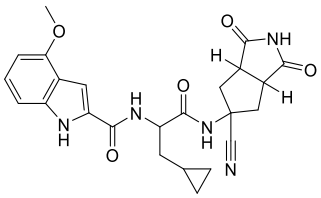
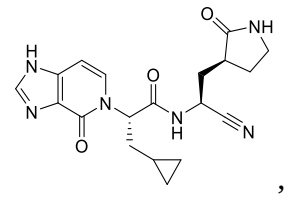
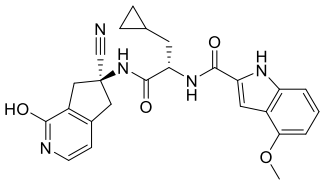
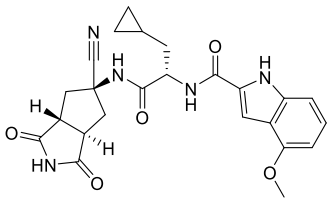
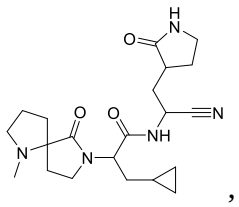
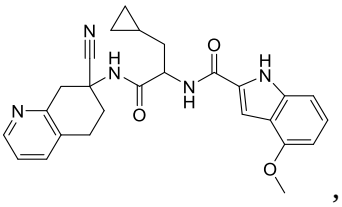
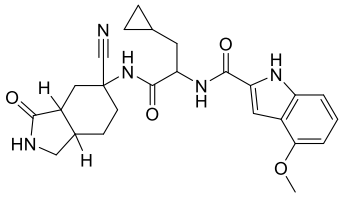
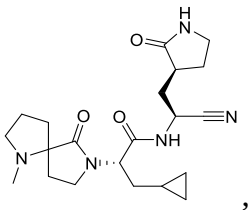
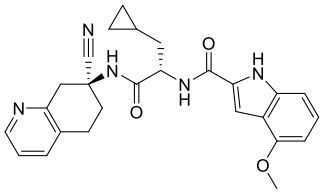
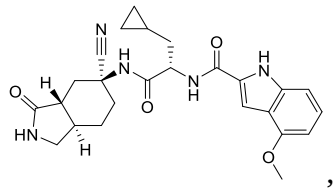
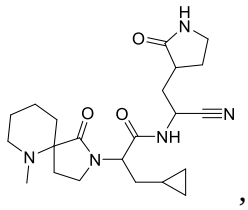
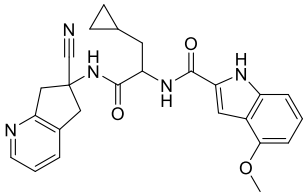
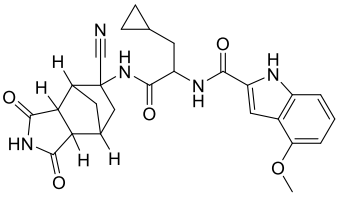
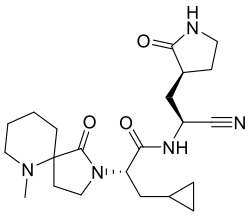
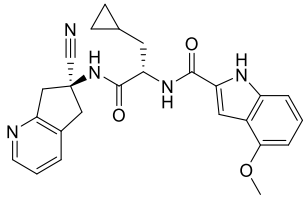
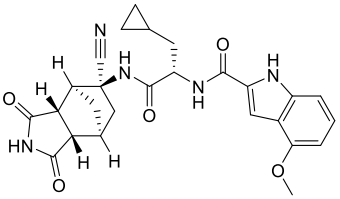
,

,

,

,

,

,

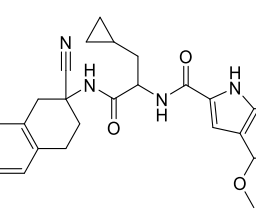
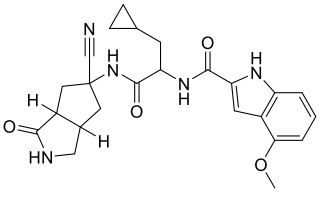
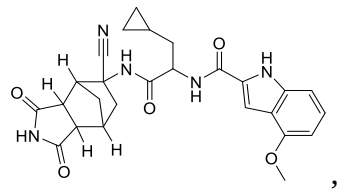
,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

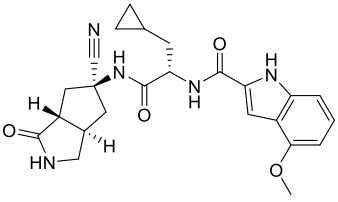
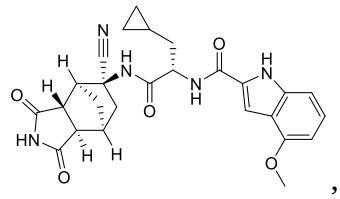
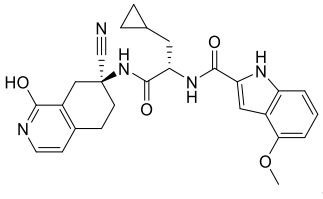
,

,

,

,

,

,

,

,

,

,

,

,

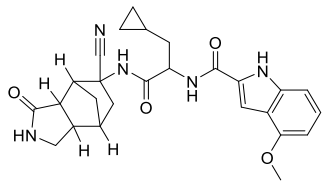
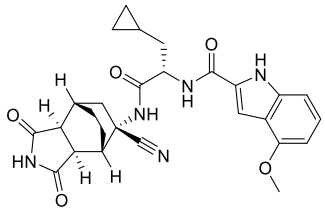
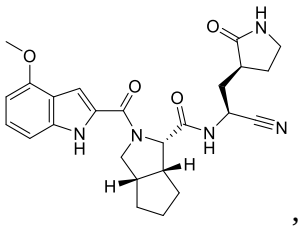
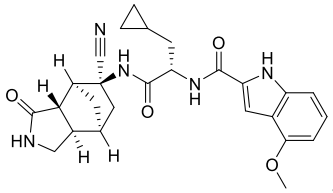
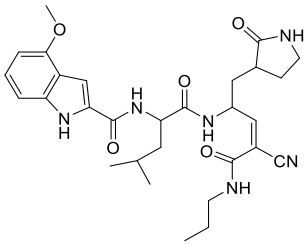
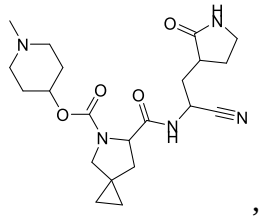
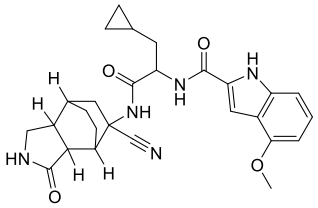
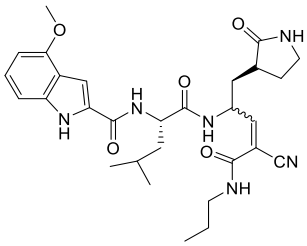
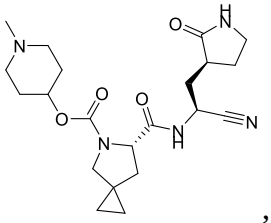
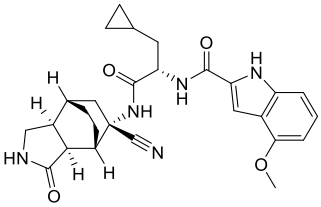
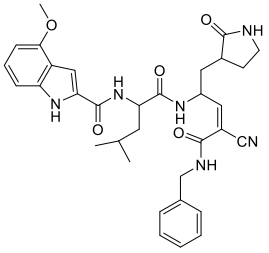
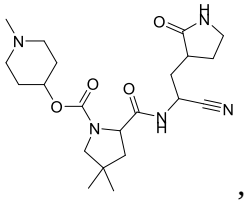
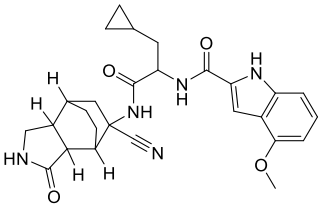
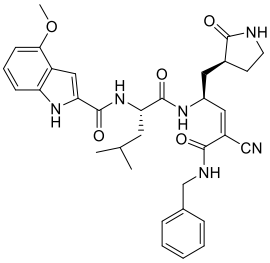
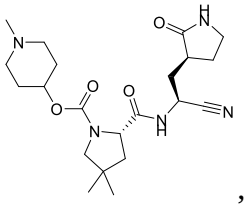
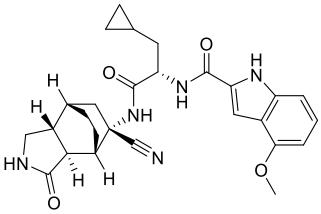
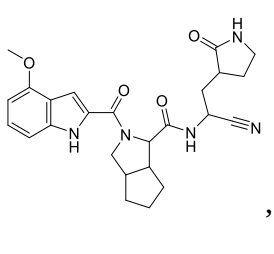
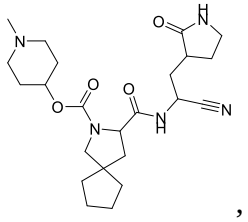
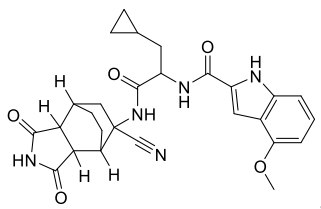
,

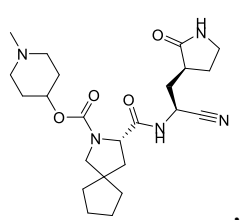
,

,

,

,

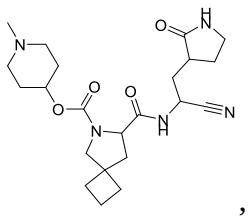
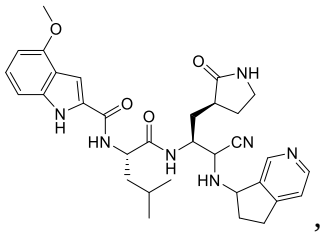
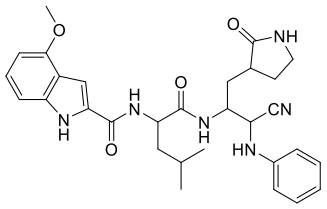
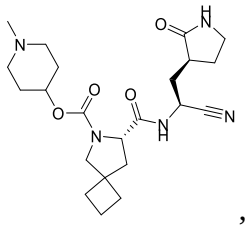
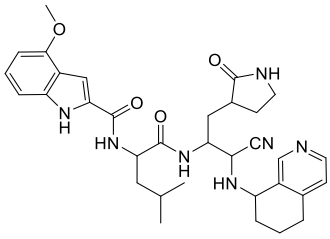
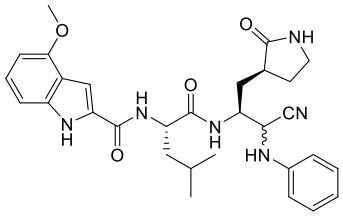
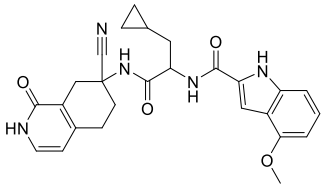
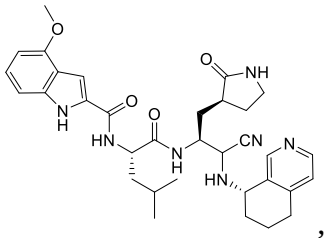
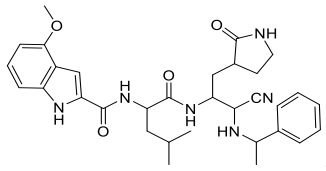
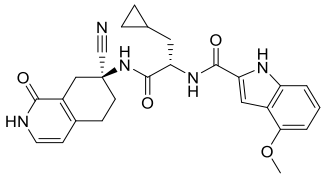
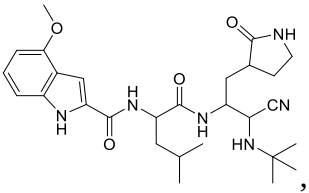
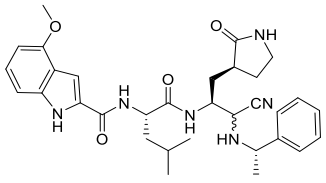
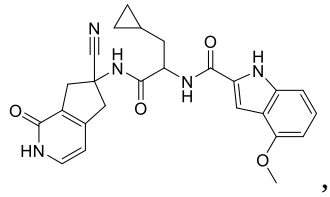
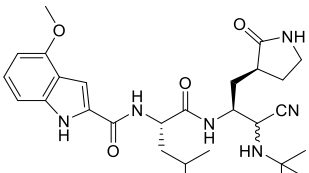
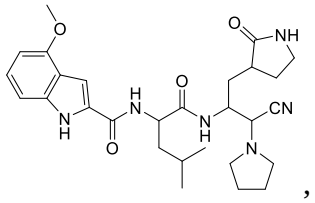
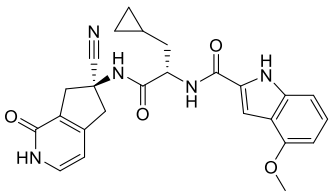

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

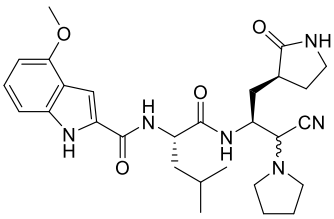
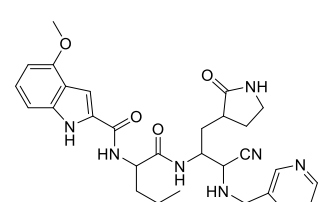
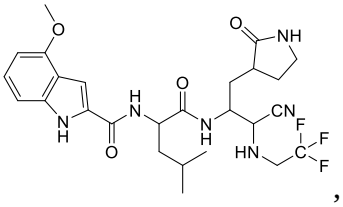
,

,

,

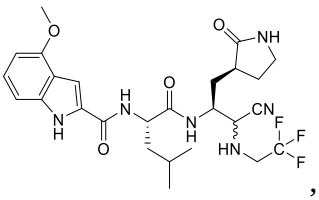
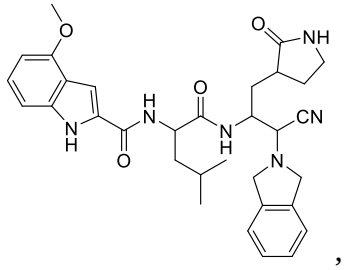
,

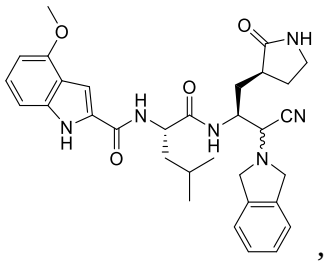
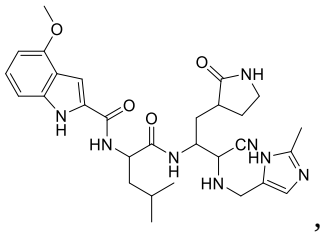
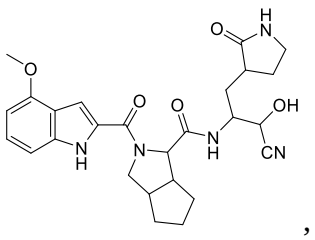
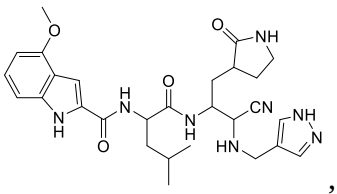
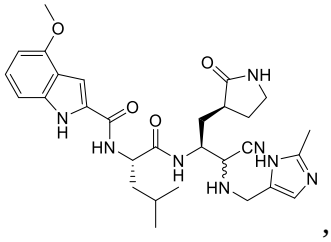
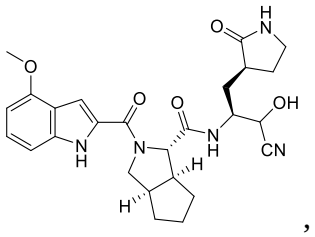
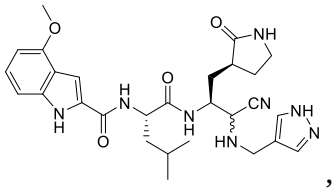
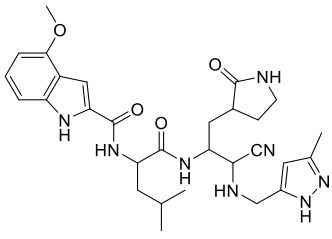
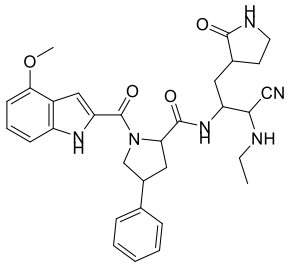
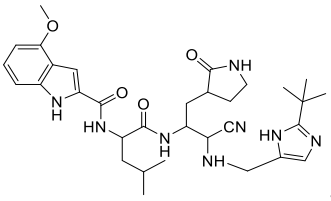
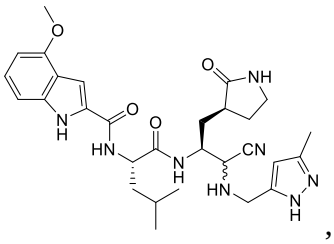
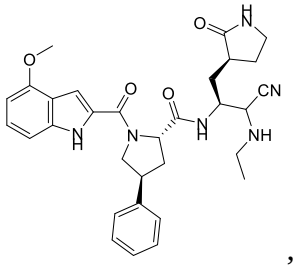
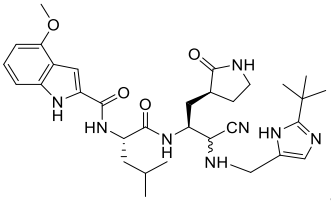
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

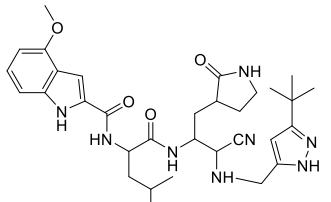
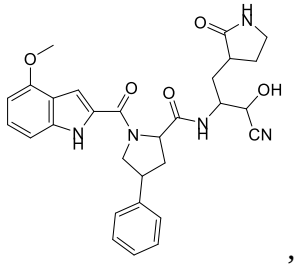
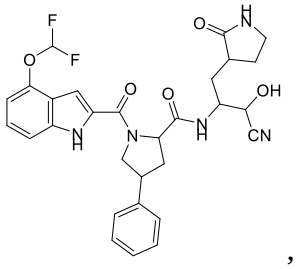
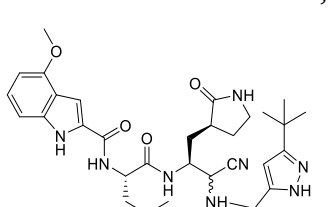
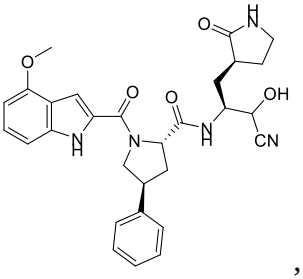
,

,

,

,

,

,

,

,

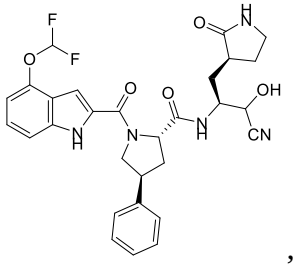

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

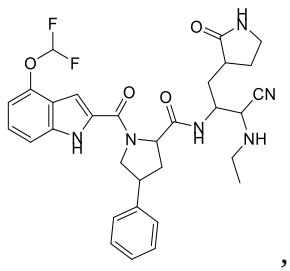
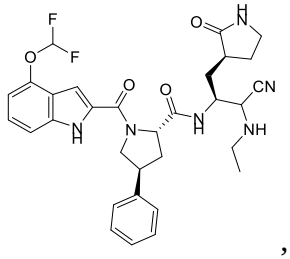
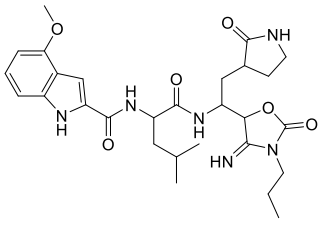
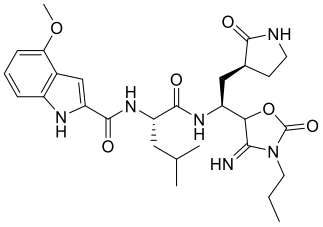
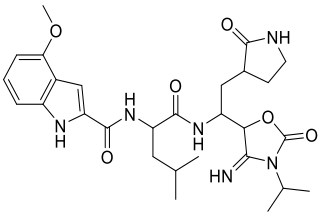
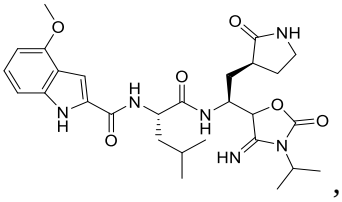
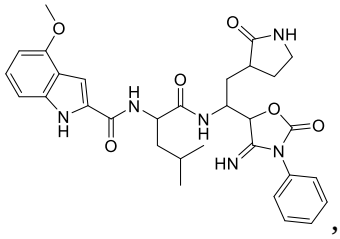
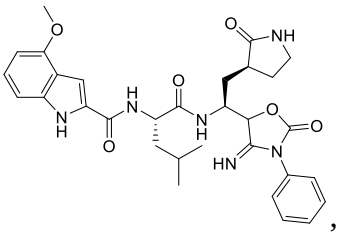
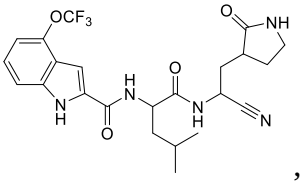
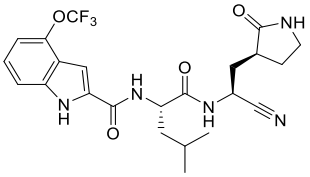
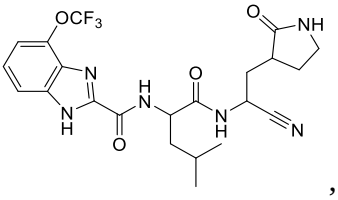
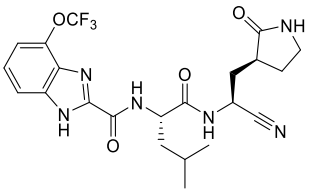
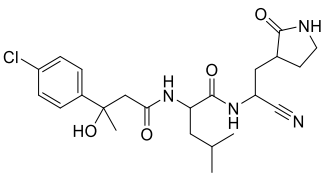
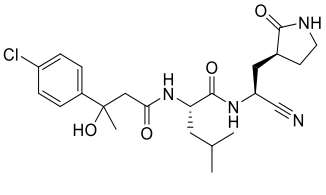
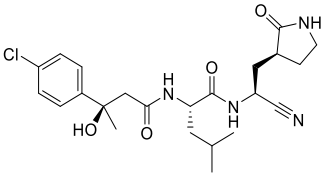
,

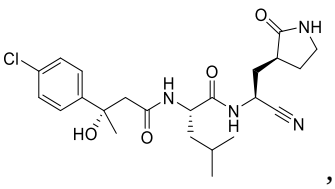
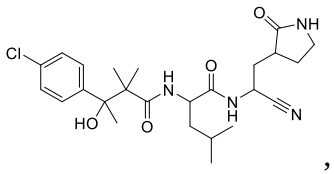
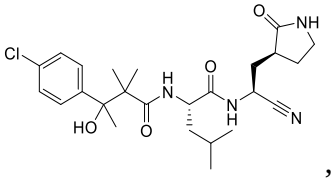
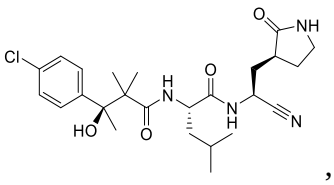
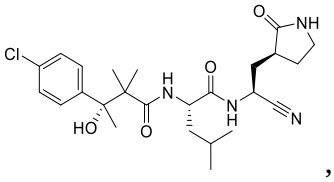
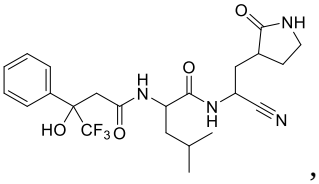
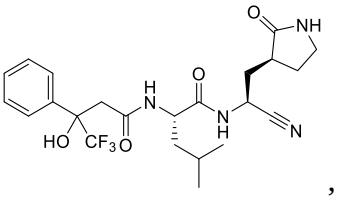
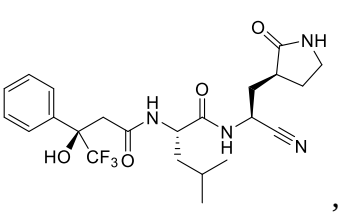
,

,

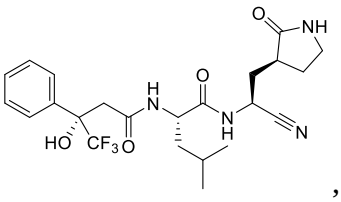
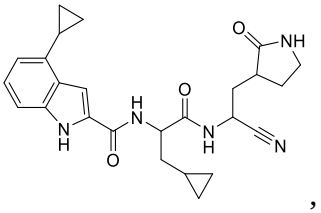
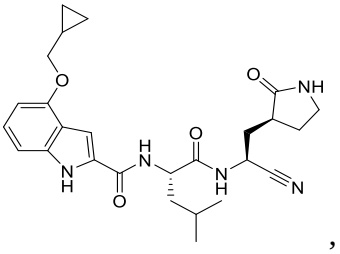
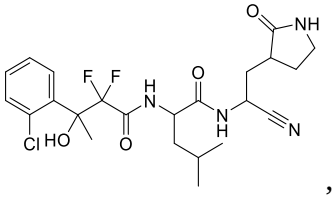
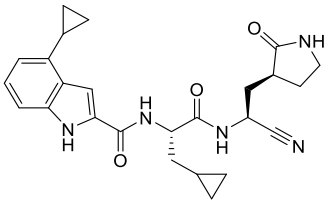
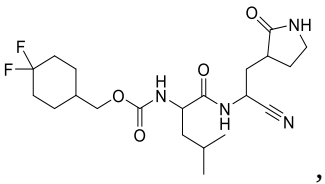
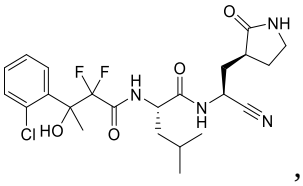
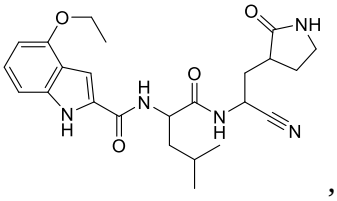
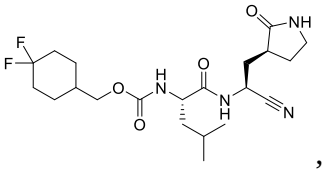
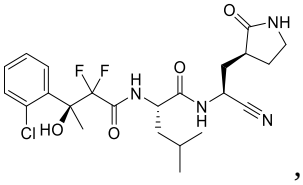
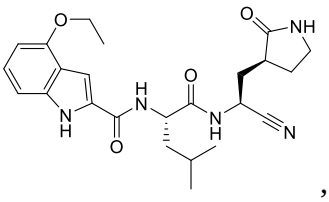
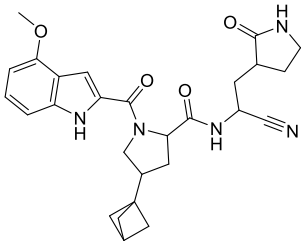
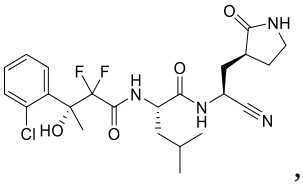
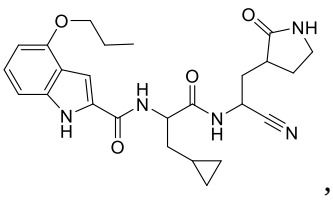
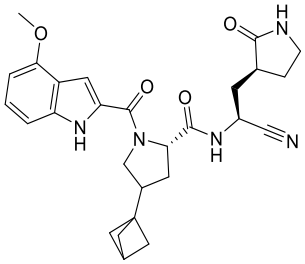
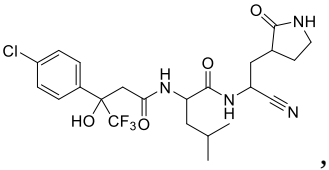
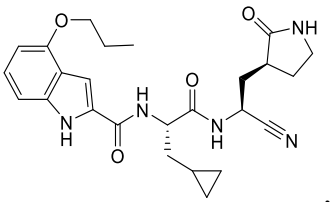
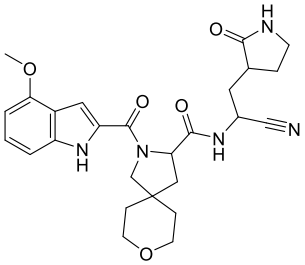
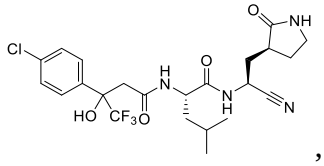
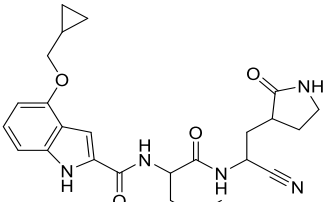
,

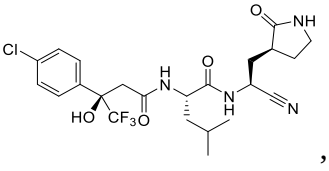
,

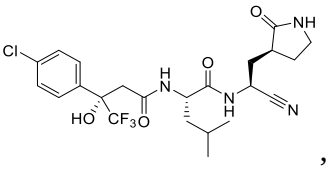
,

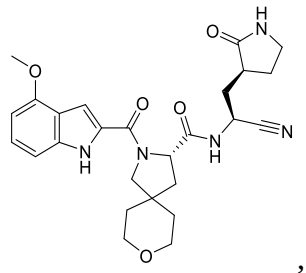
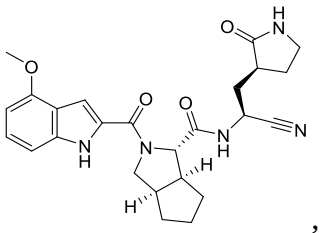
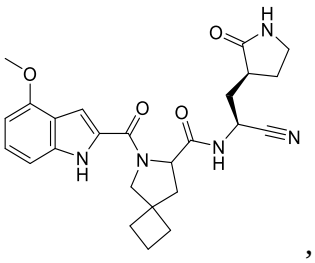
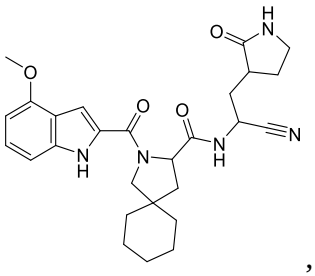
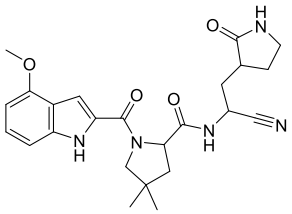
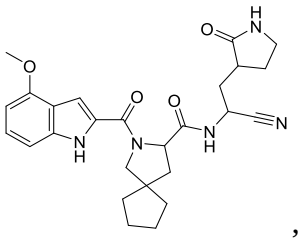
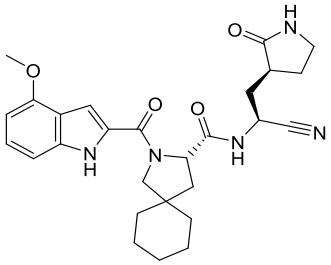
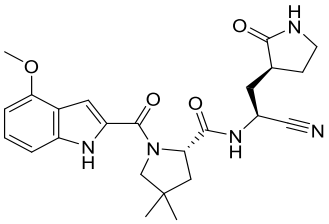
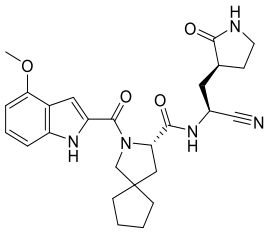
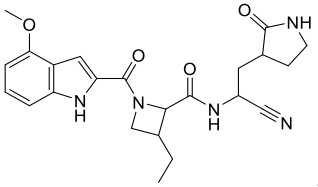
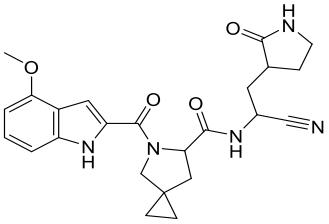
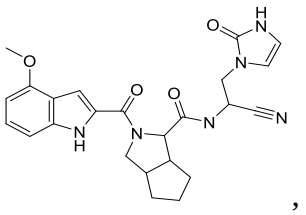
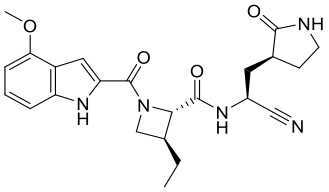
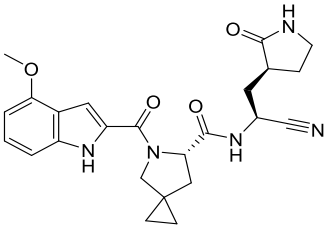
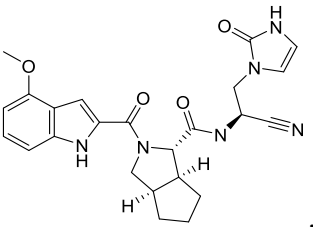
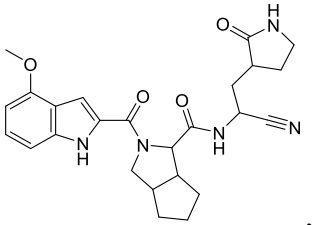
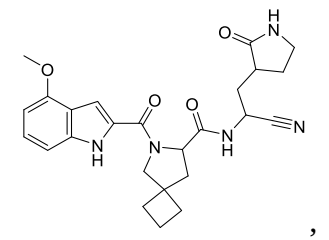
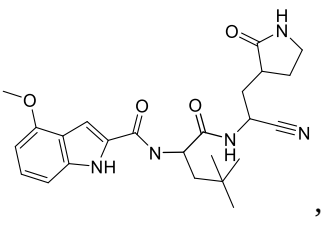
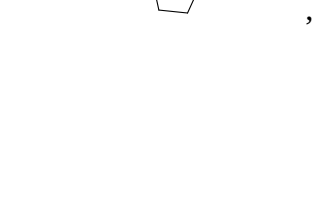

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

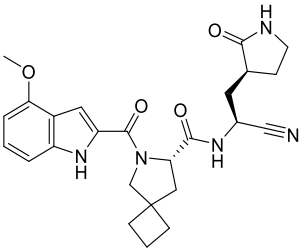
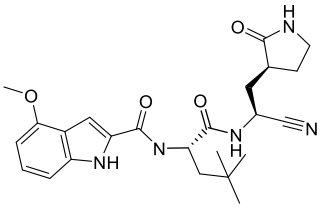
,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

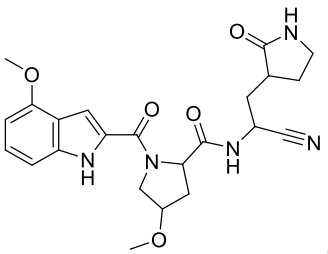
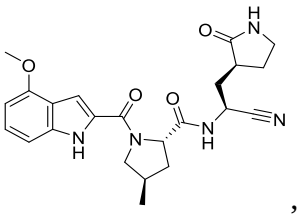
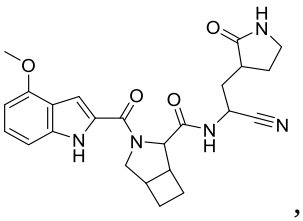
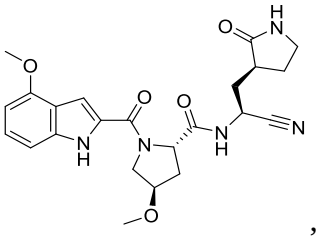
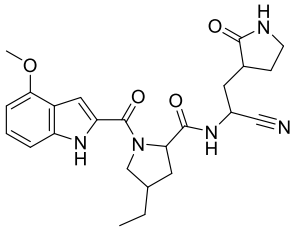
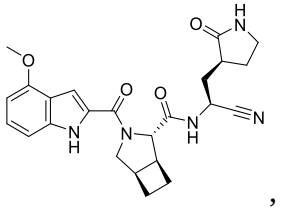
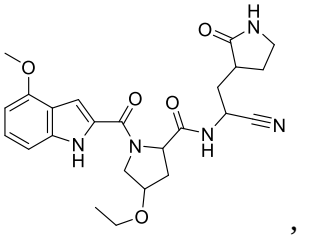
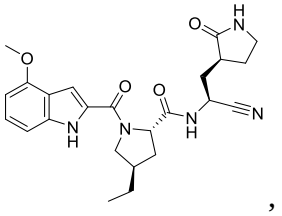
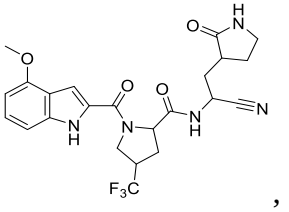
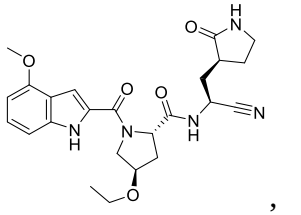
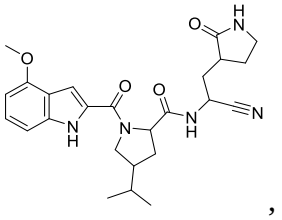
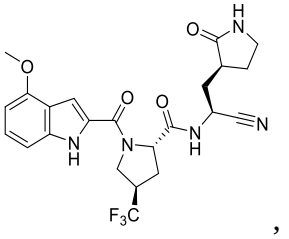
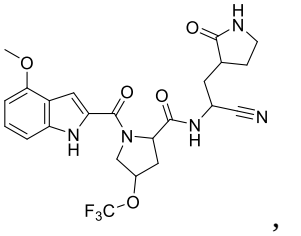
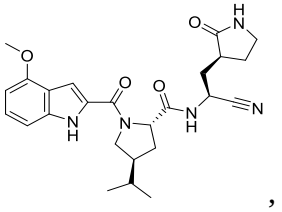
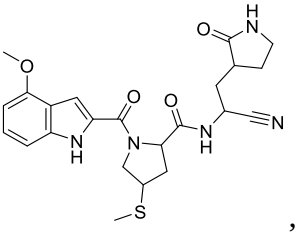
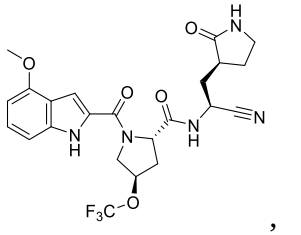
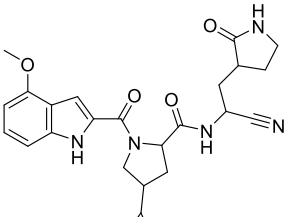
,

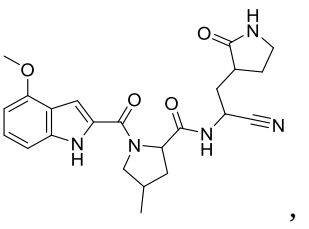
,

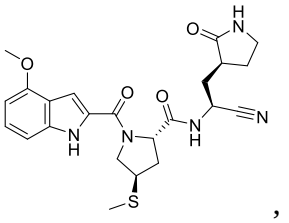
,

,

,

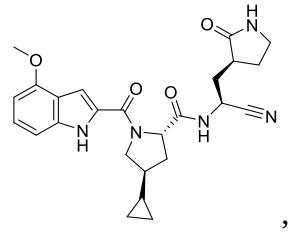
,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

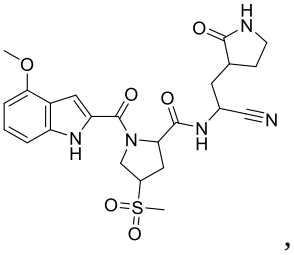
,

,

,

,

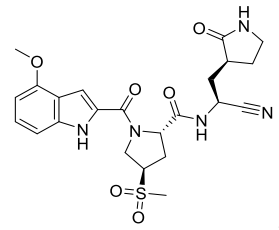
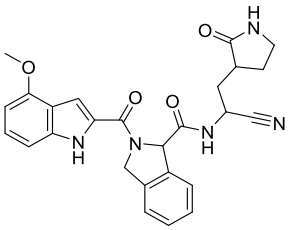
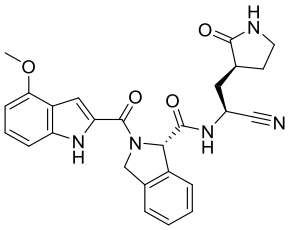
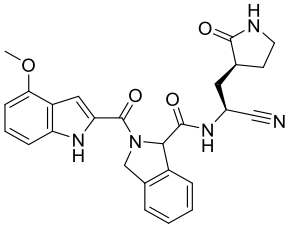
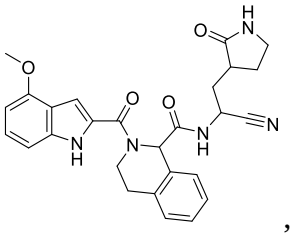
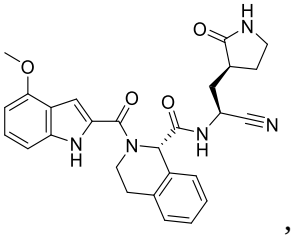
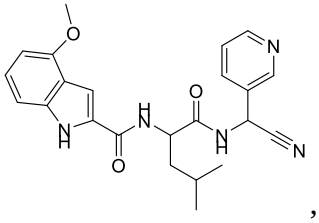
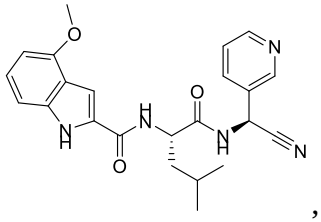
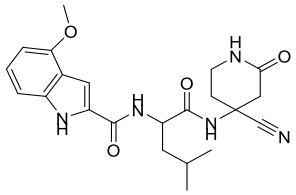
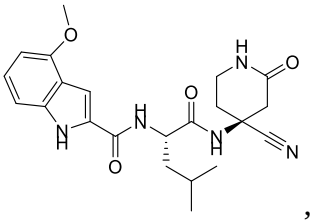
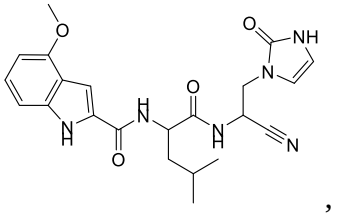
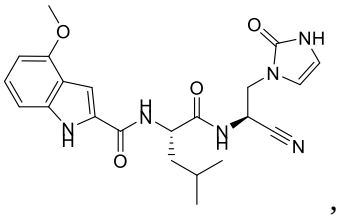
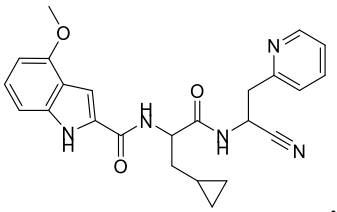
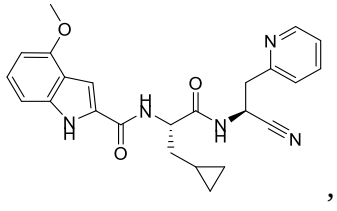
,

,

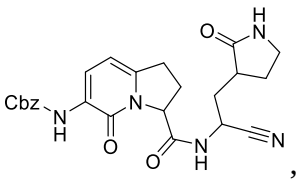
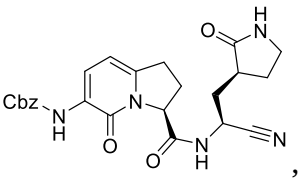
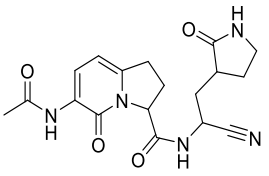
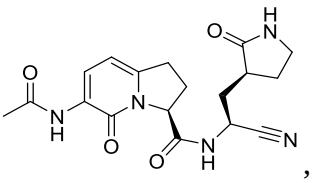
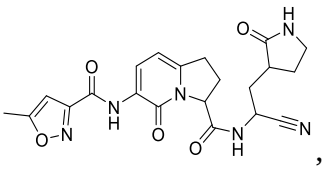
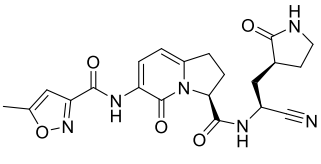
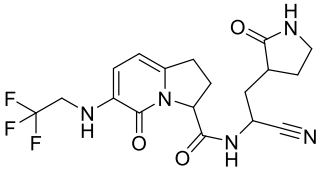
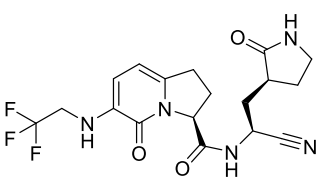
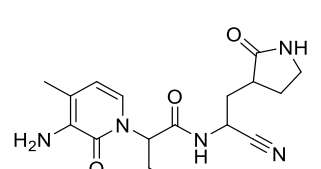
,

,

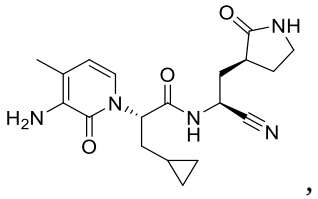
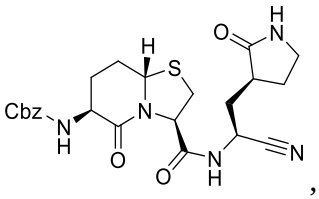
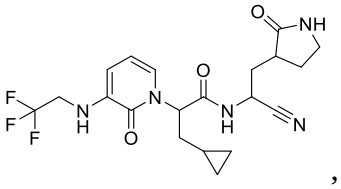
,

,

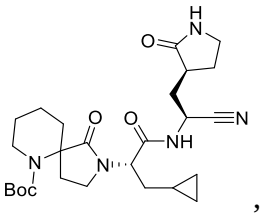
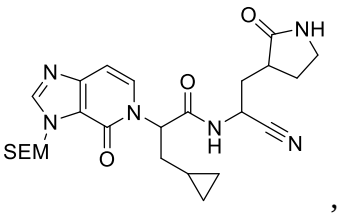
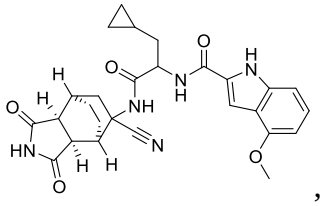
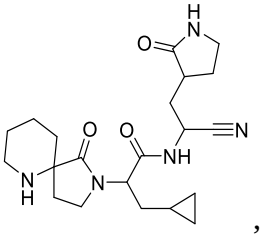
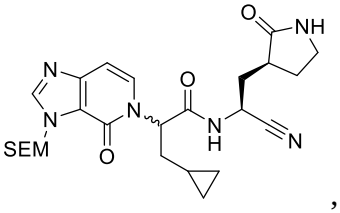
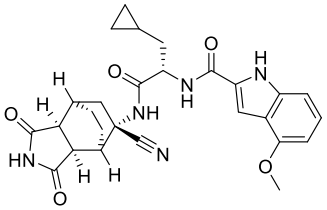
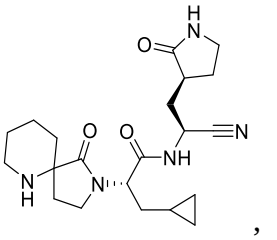
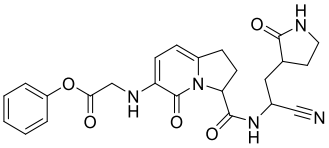
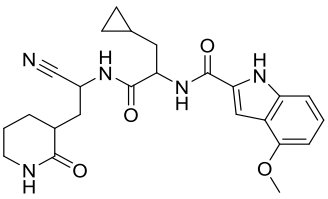
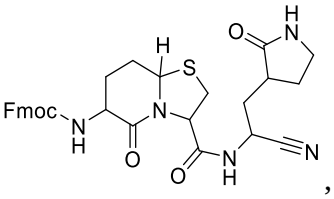
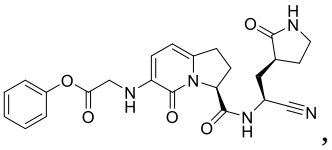
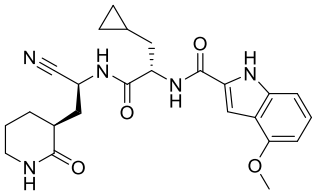
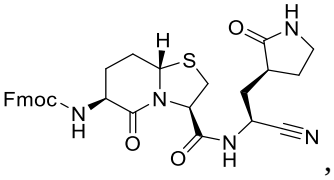
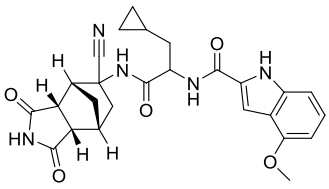
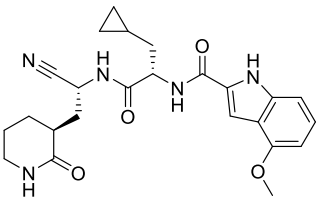
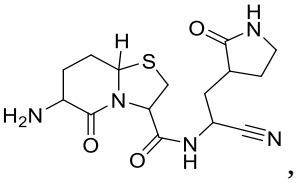
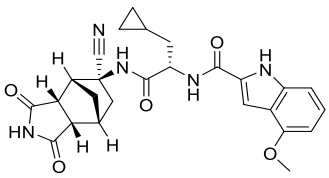
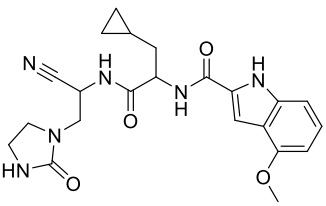
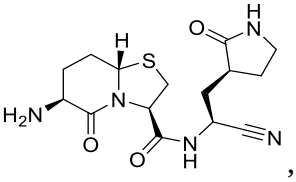
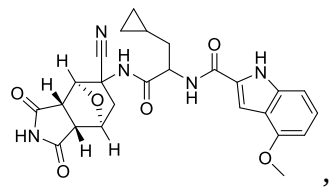
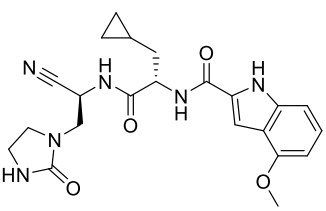
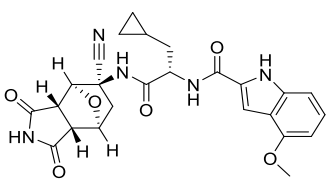
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

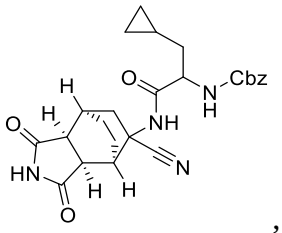
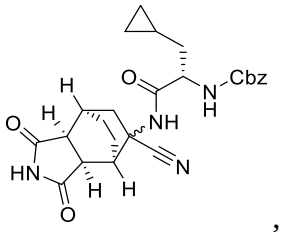
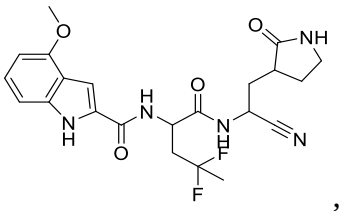
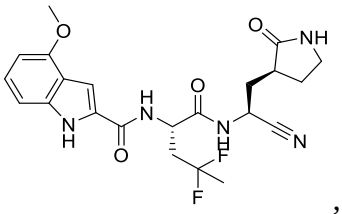
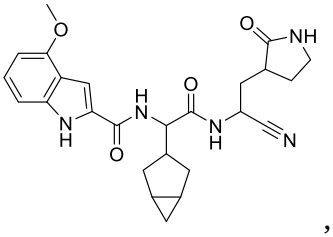
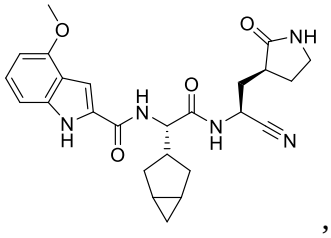
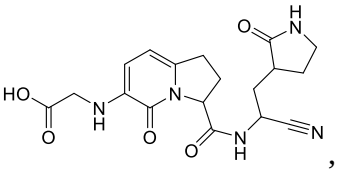
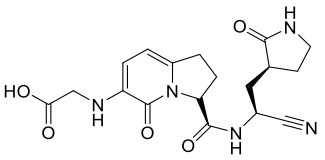
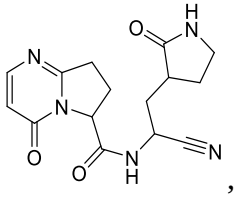
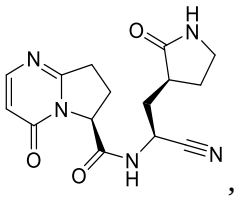
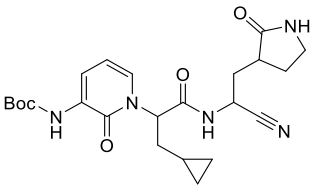
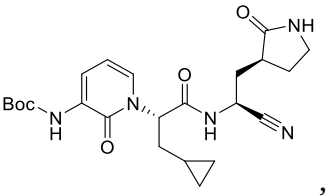
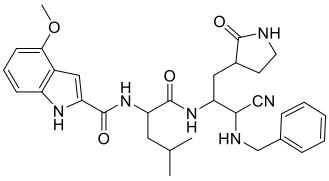
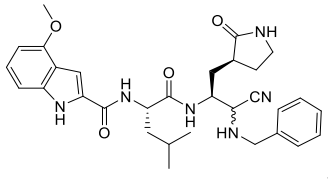
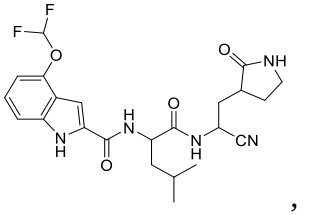
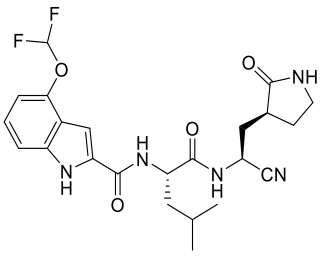
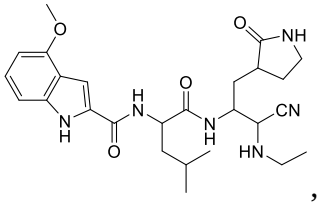
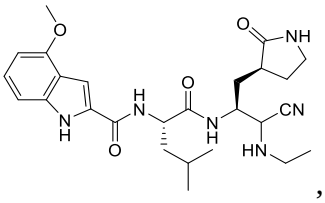
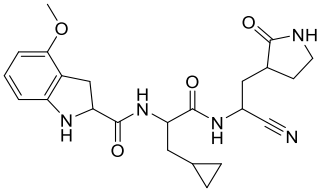
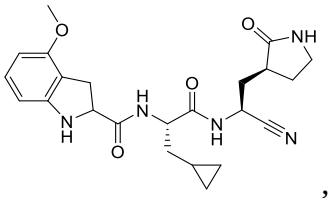
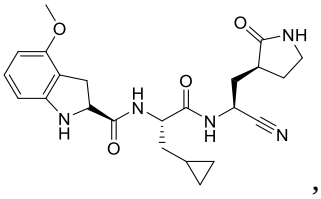
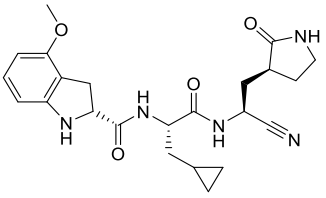
,

,

,

,

,

,

,

,

,

,

,

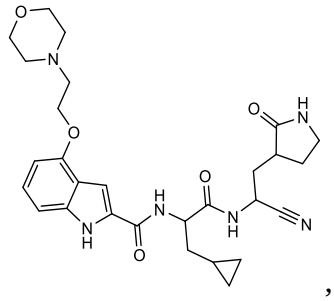
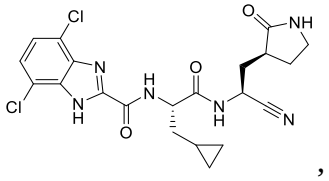
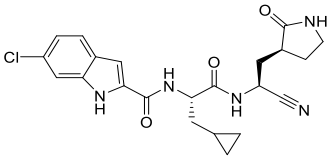
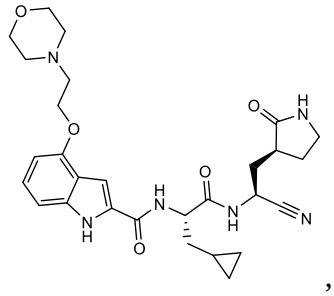
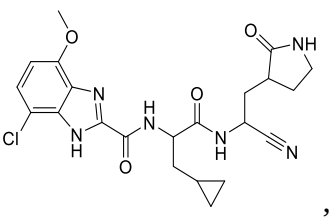
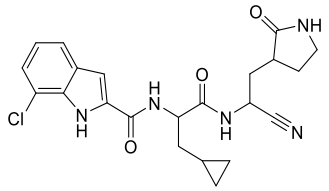

,

,

,

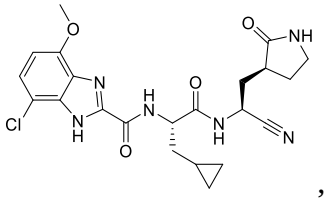
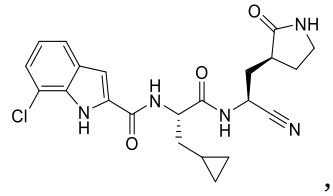
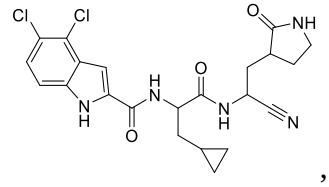
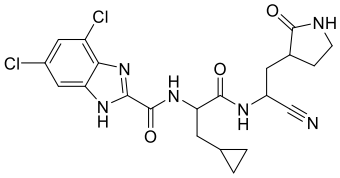
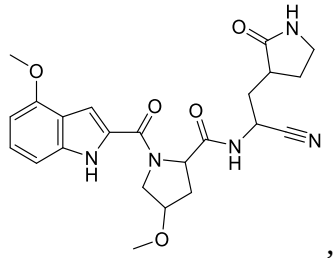
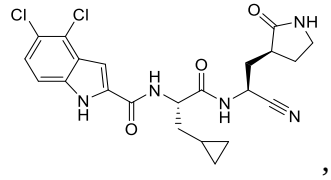
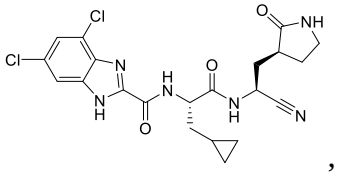
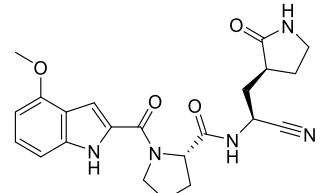
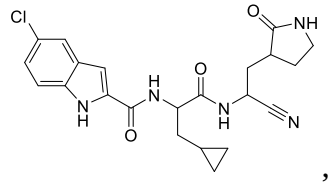
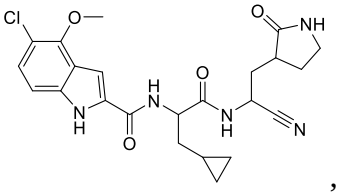

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

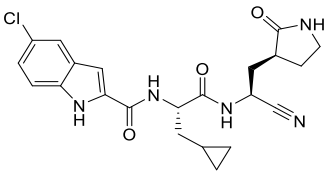
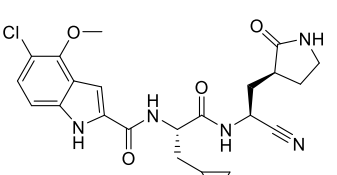
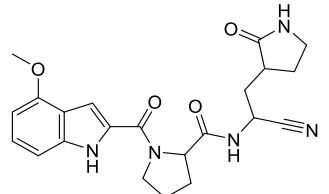
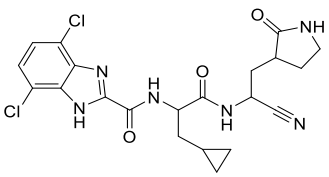
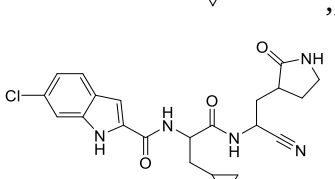
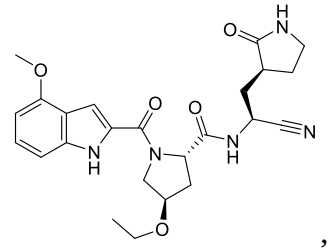

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

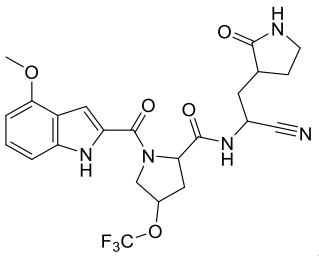
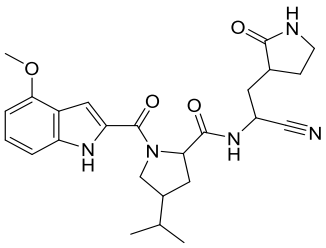
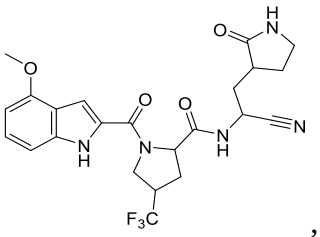
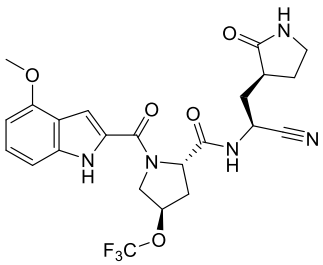
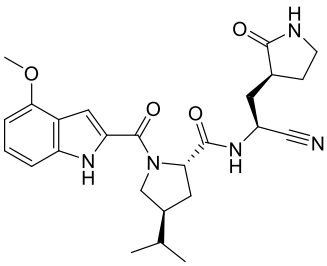
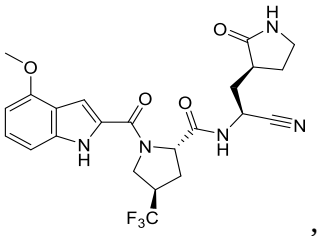
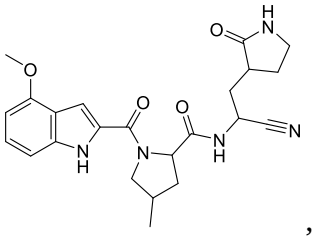
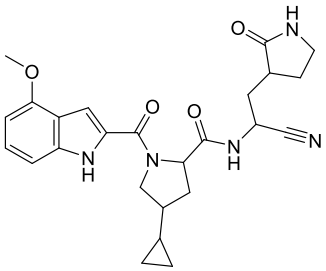
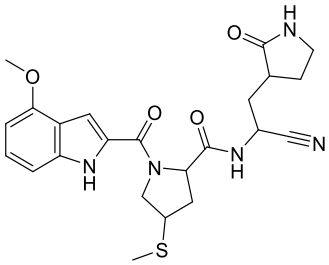
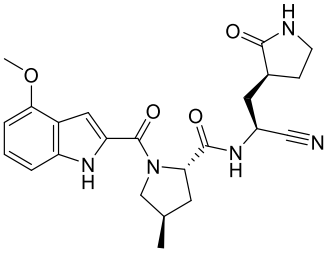
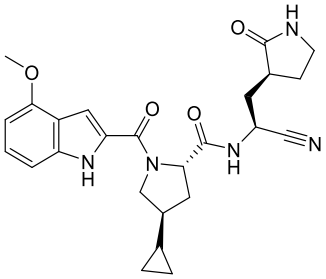
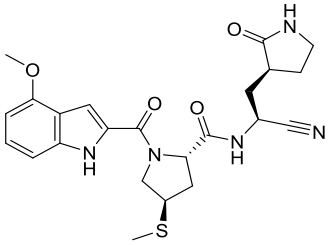
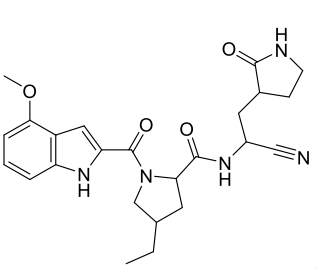
,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

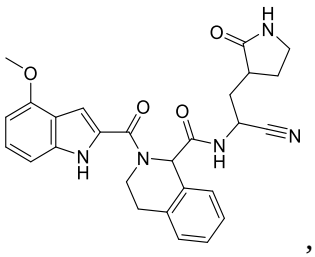
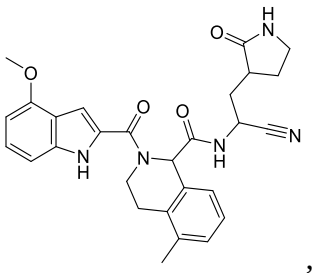
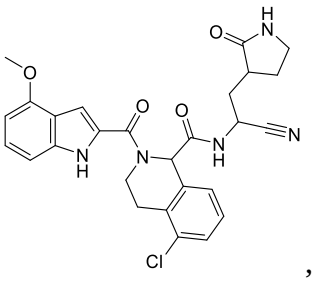
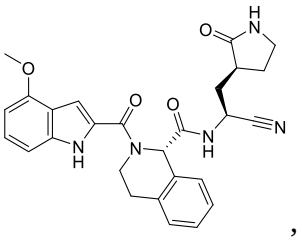
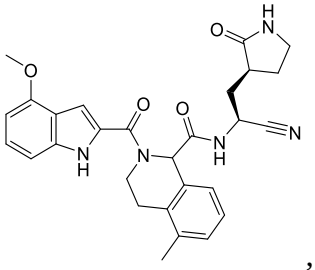
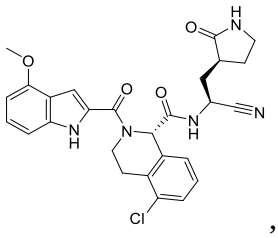
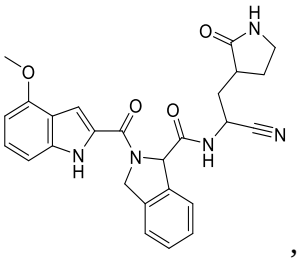
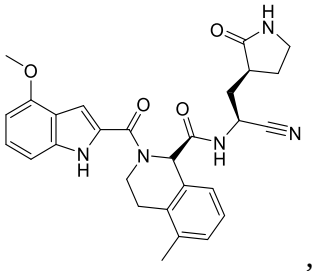
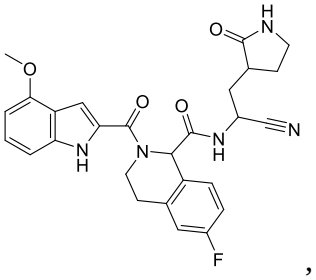
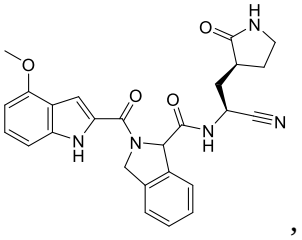
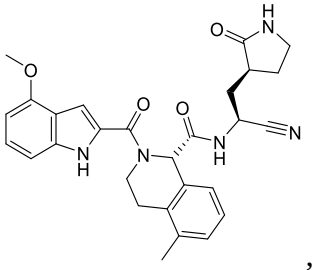
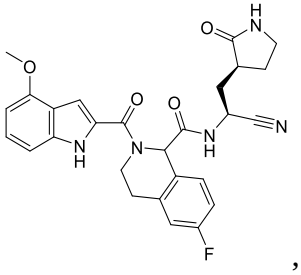
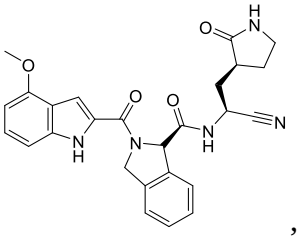
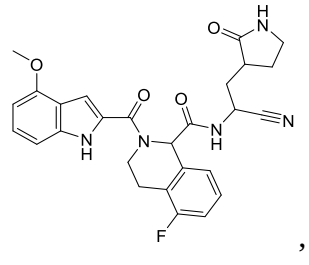
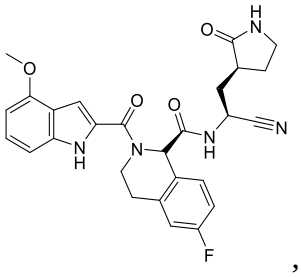
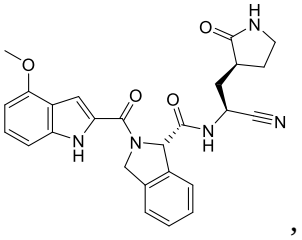
,

,

,

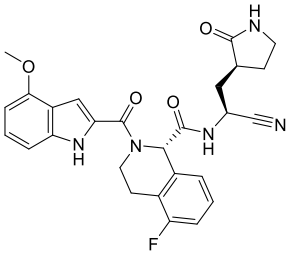
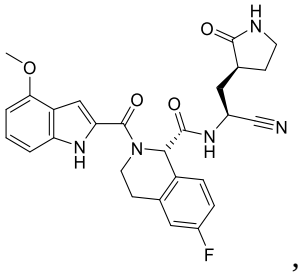
,

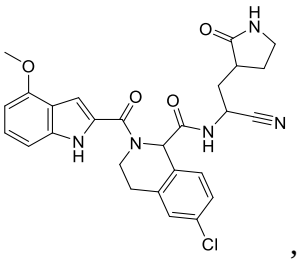
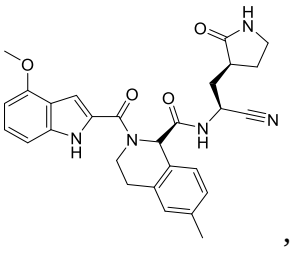
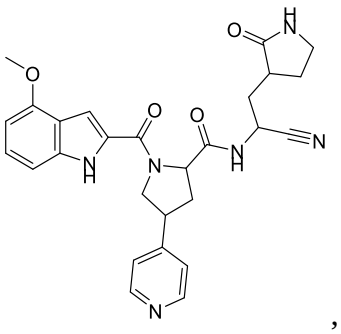
,

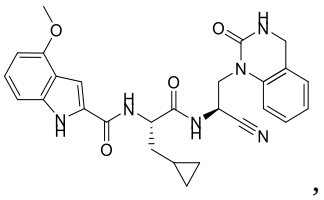
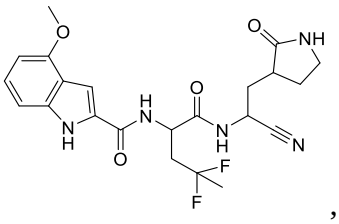
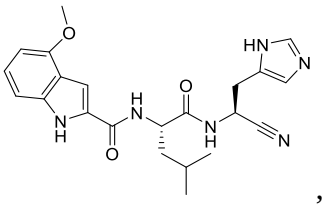
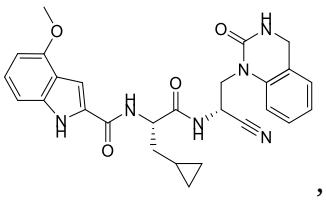
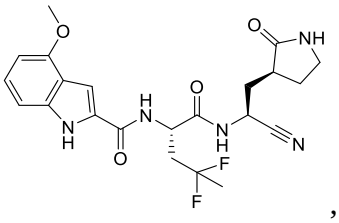
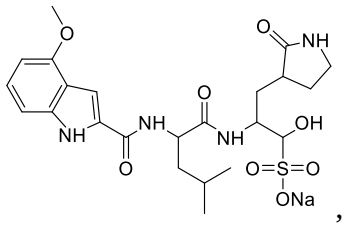
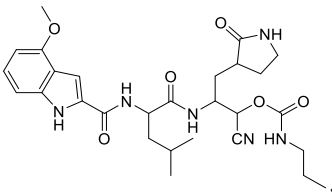
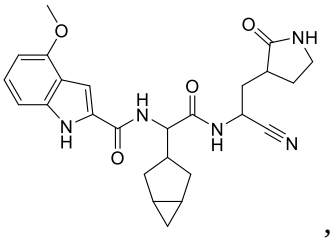
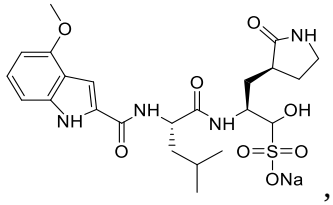
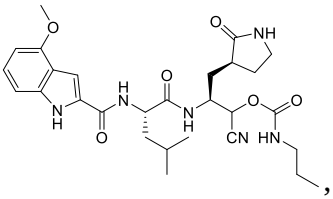
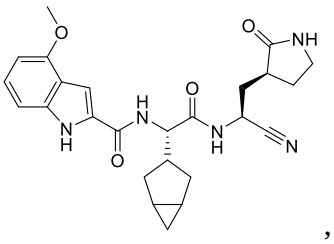
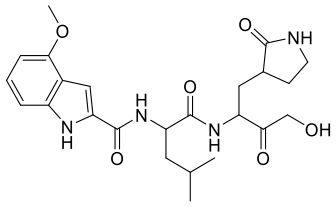
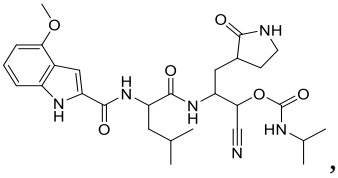

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

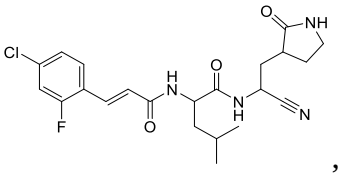
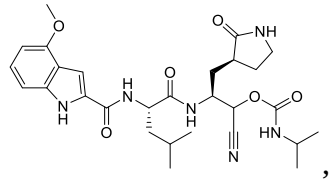
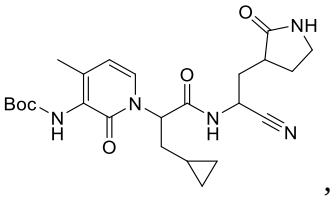
,

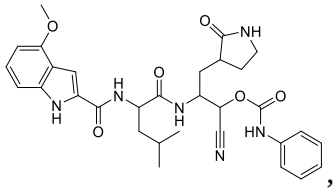
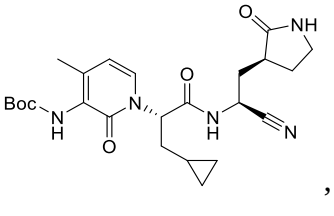
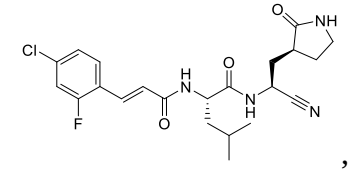
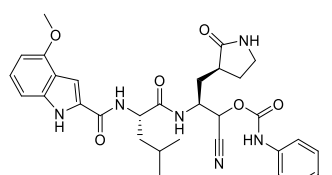
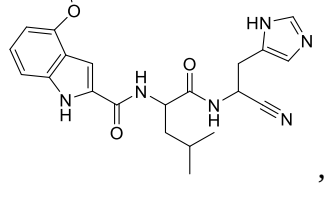
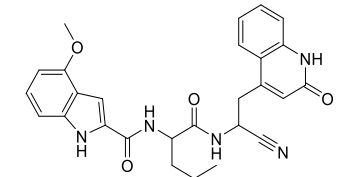
,

,

,

,

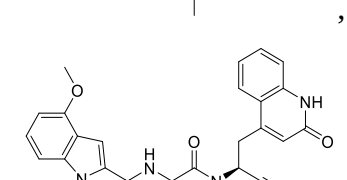

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

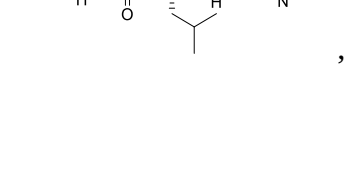
,

,

,

,

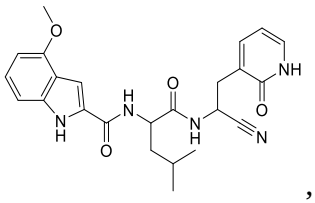
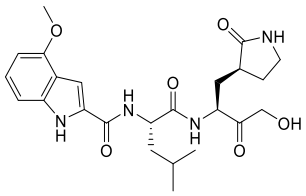
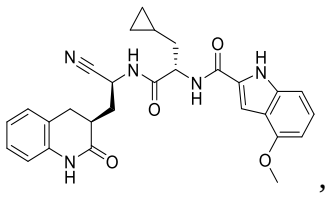
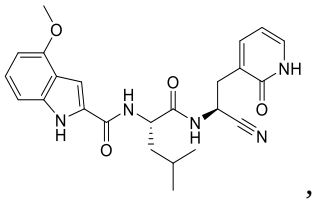
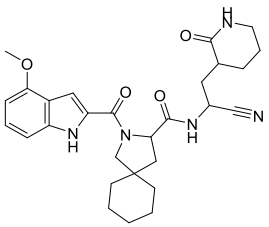
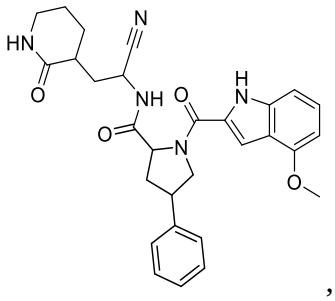
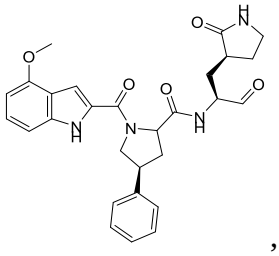
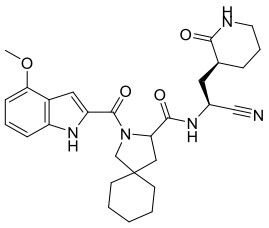
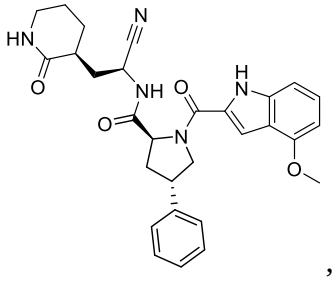
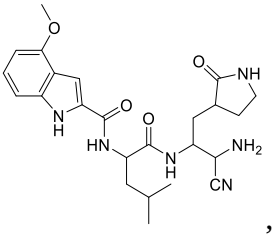
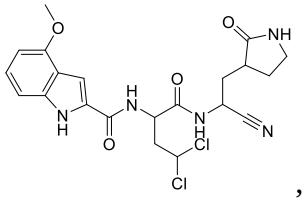
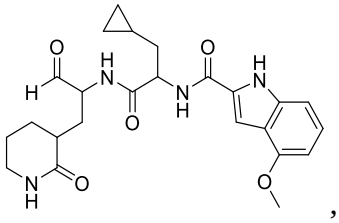
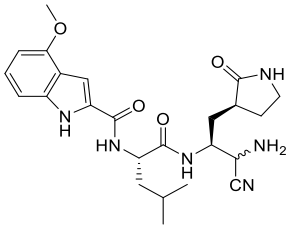
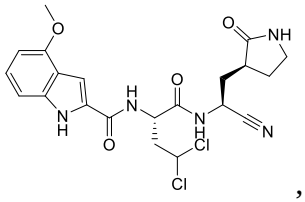
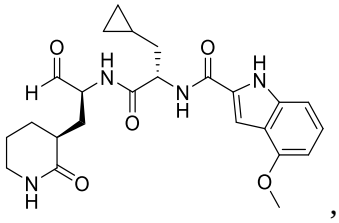
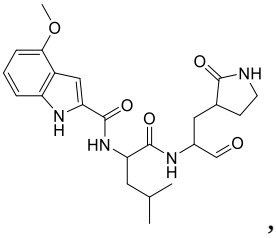
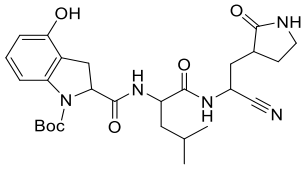
,

,

,

,

,

,

,

,

,

,

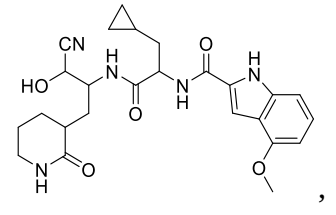
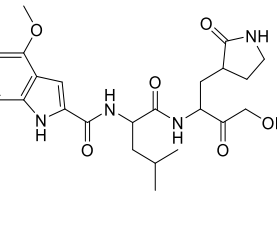
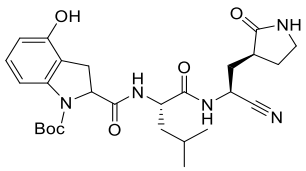
,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

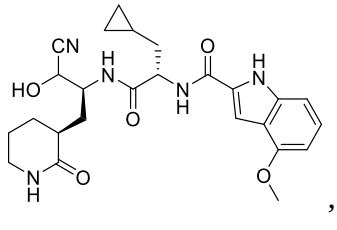
,

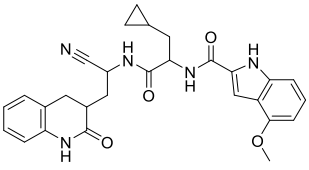
,

,

,

,

,

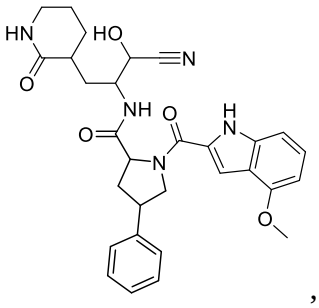
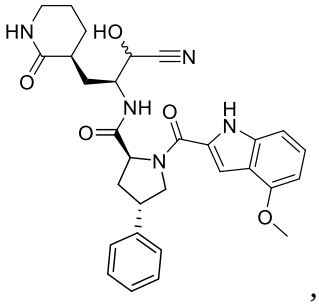
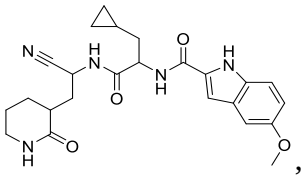
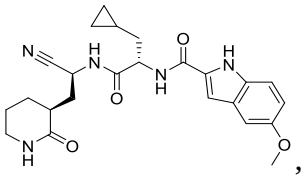
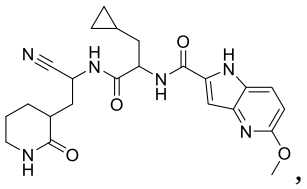
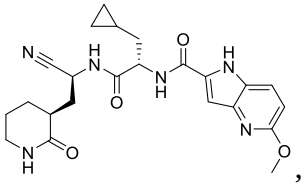
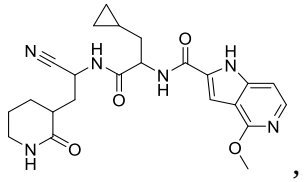
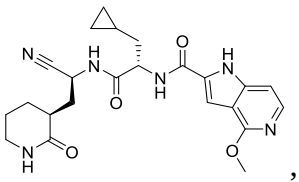
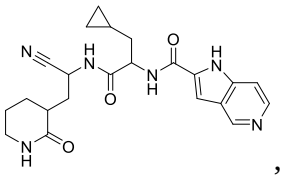
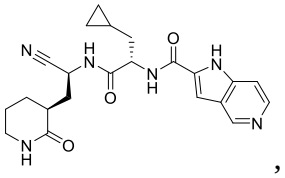
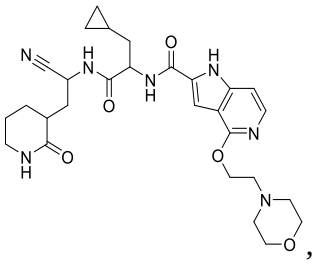
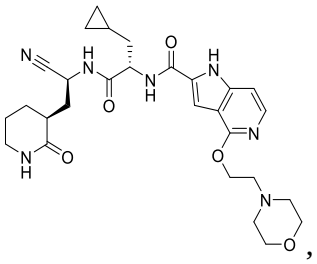
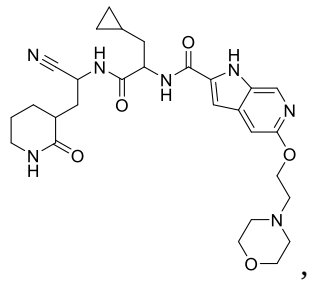
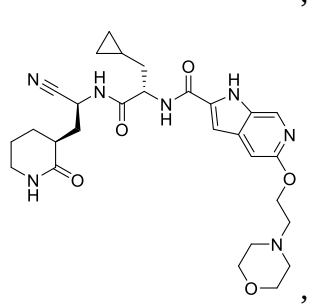
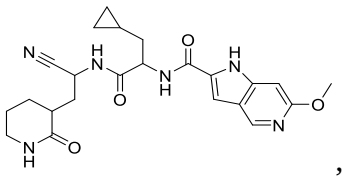
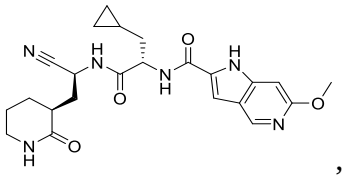
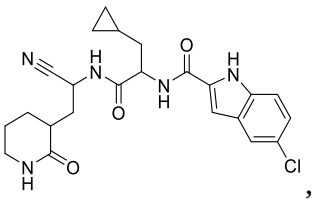
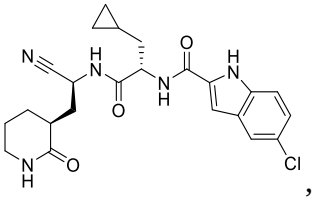
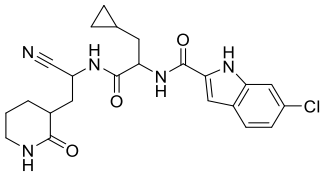
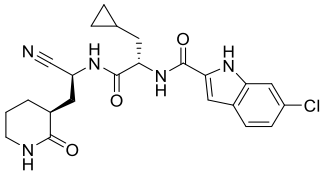
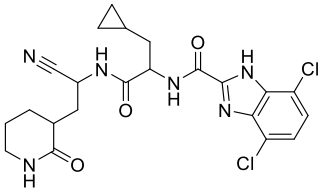
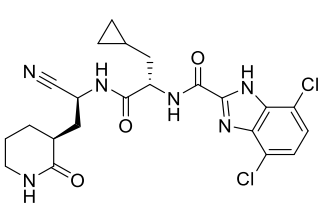
,

,

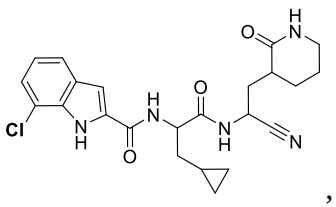
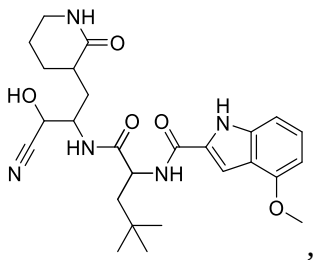
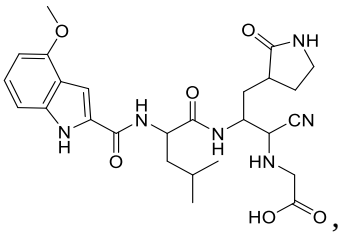
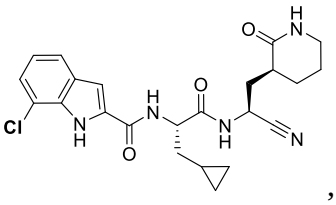
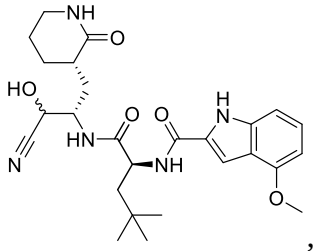
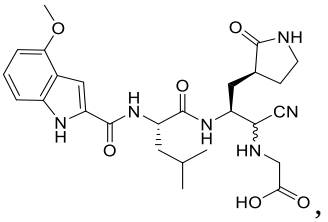
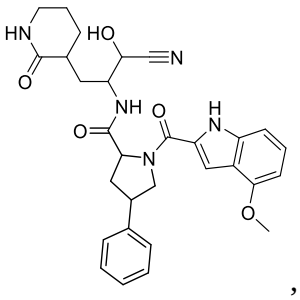
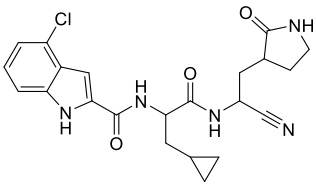
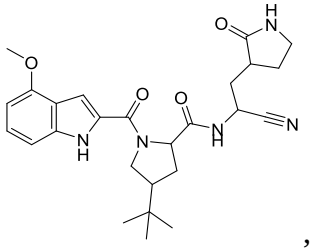
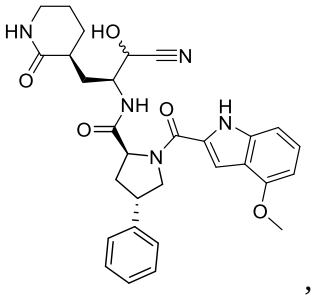
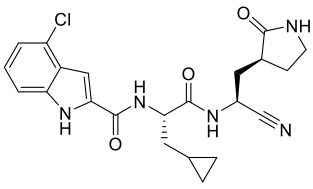
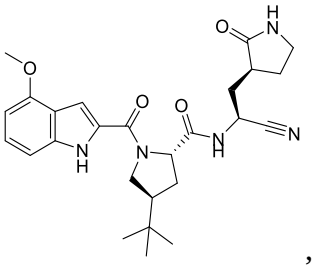
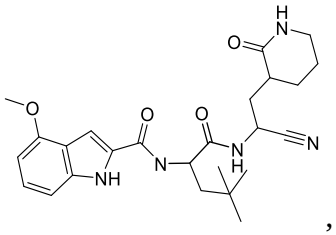
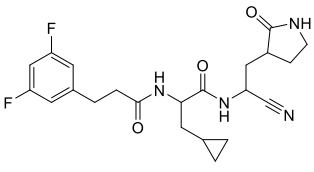
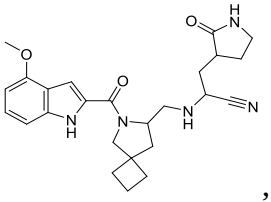
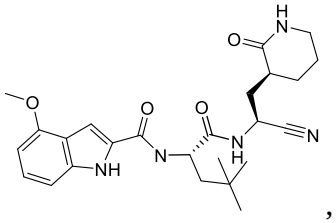
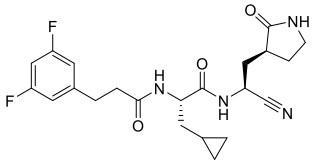
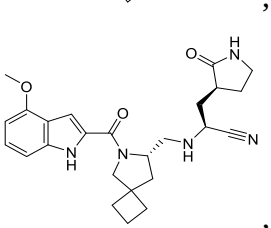
,

,

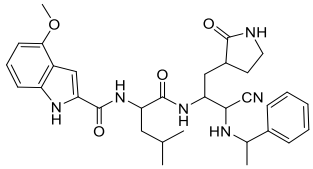
,

,

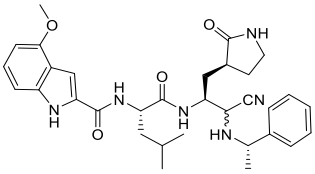
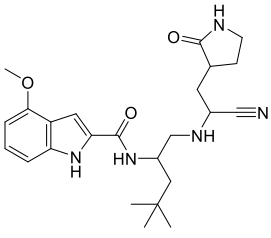
,

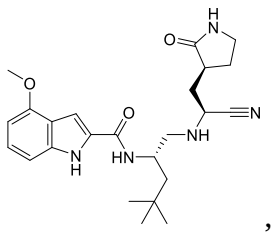
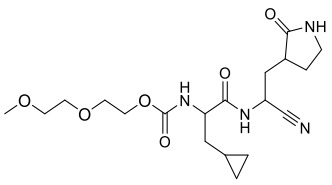
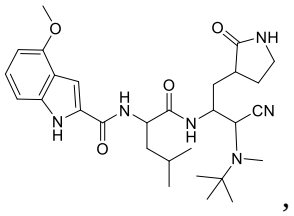
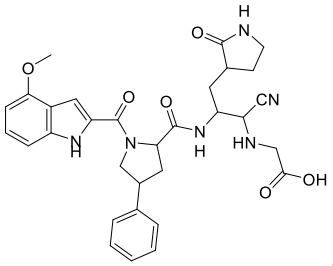
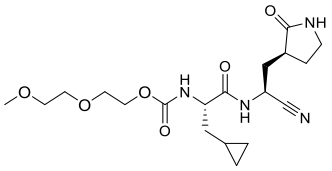
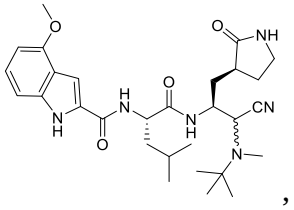
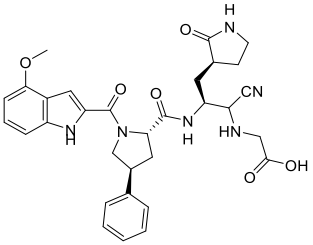
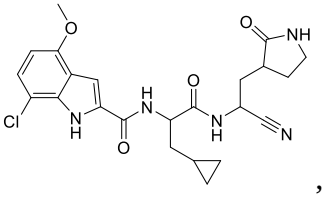
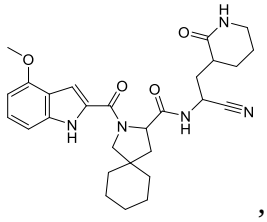
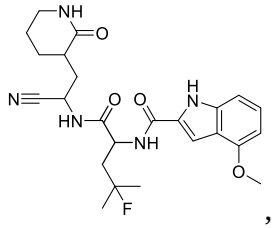
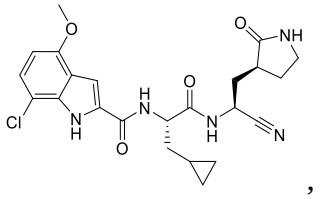
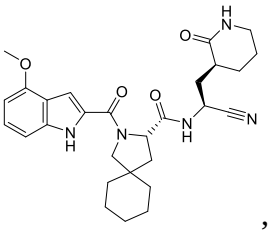
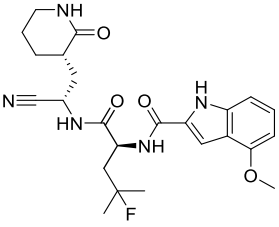
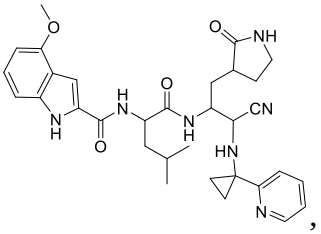
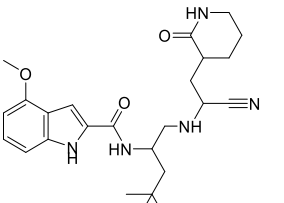

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

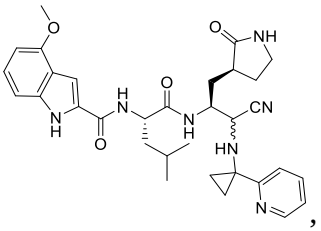
,

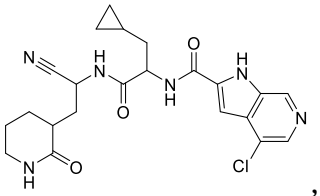
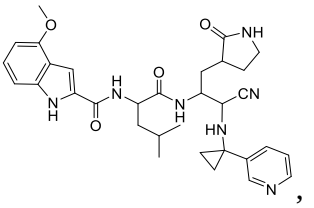
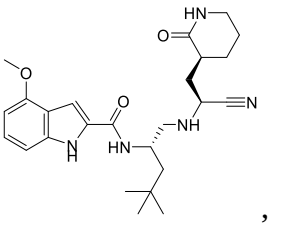

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

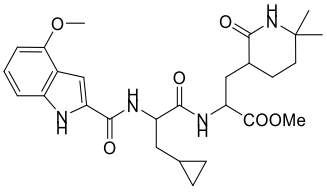
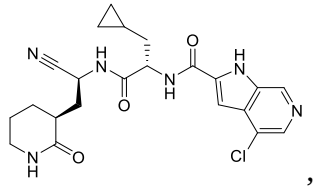
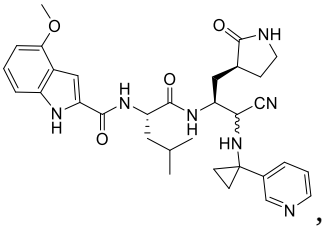

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

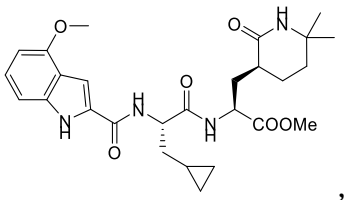
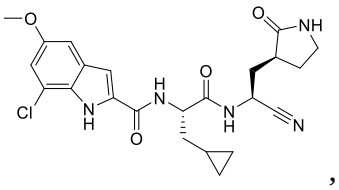
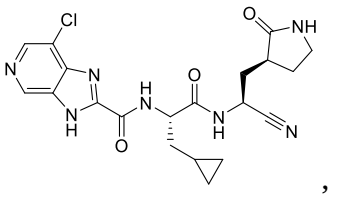
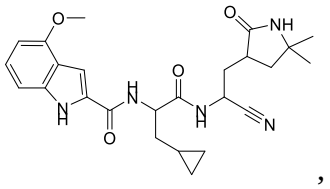
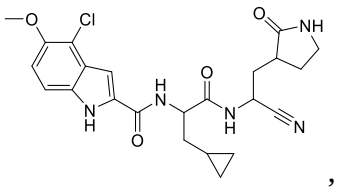
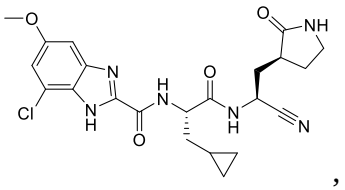
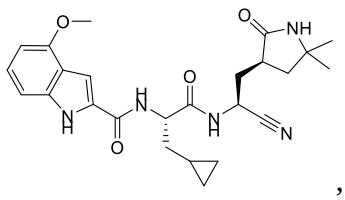
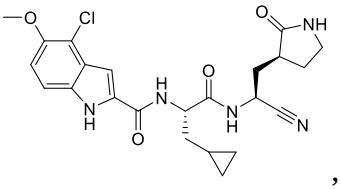
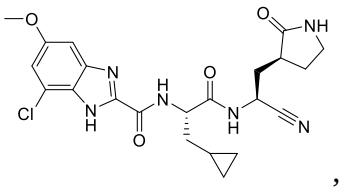
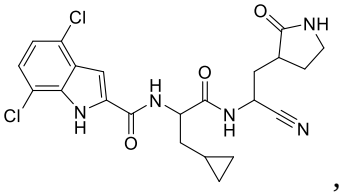
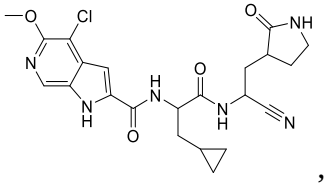
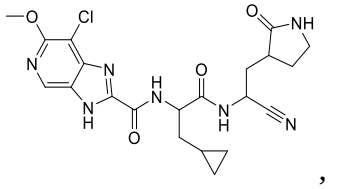
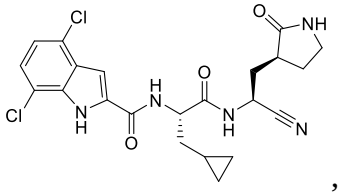
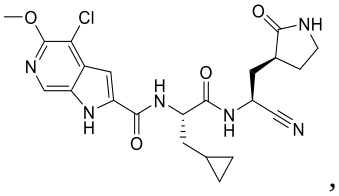
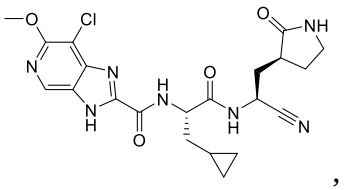
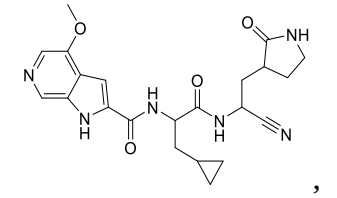
,

,

,

,

,

,

,

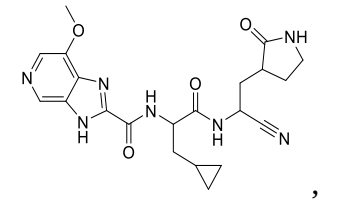
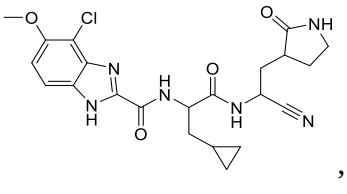
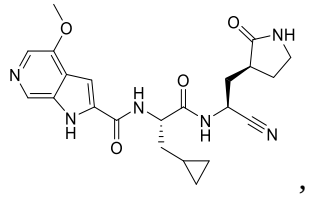
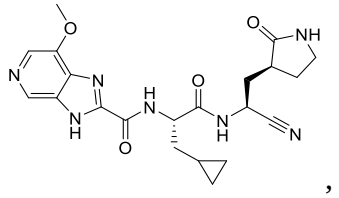
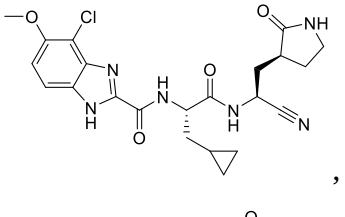
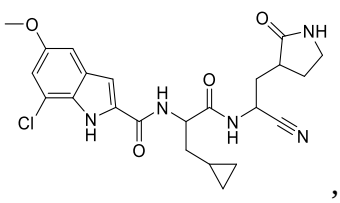
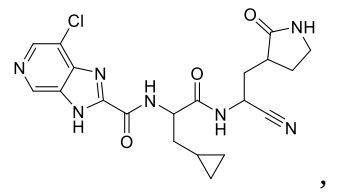
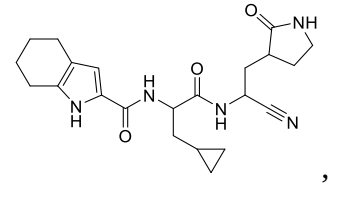
,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

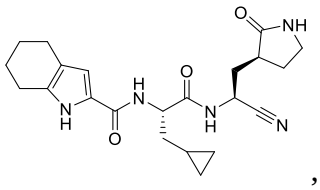
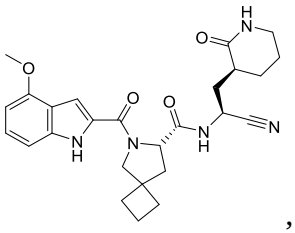
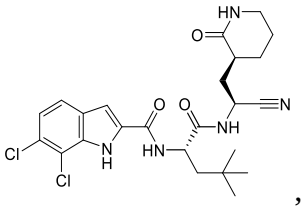
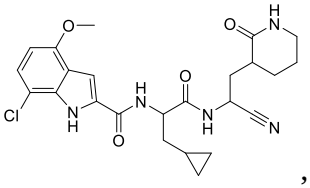
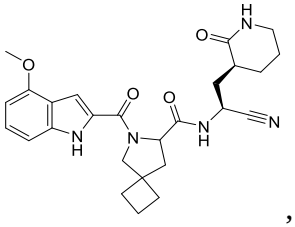
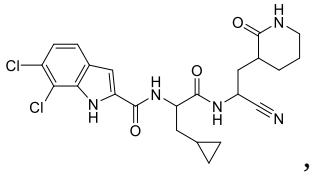
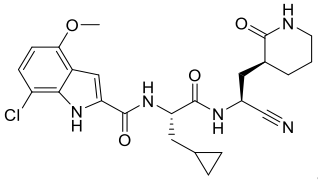
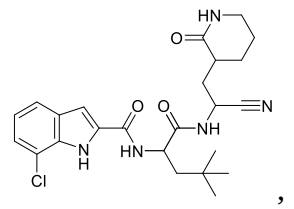
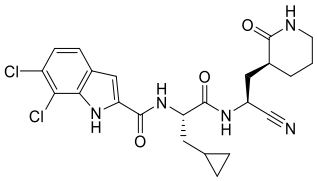
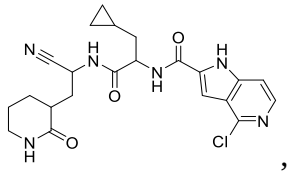
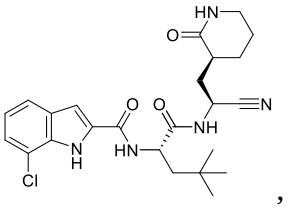
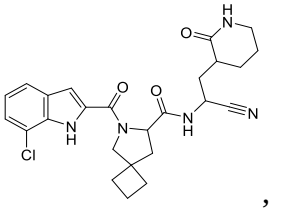
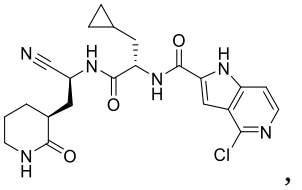
,

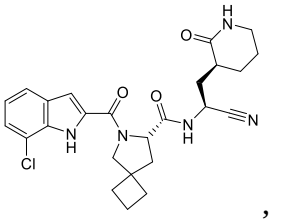
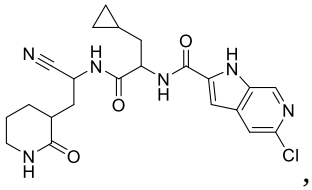
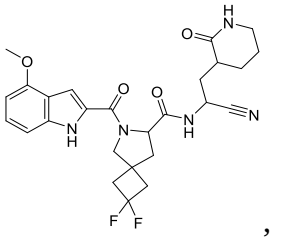
,

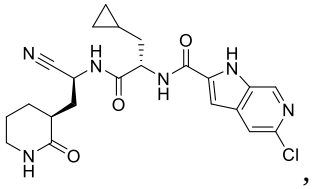
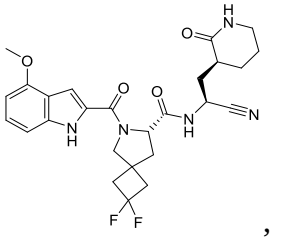
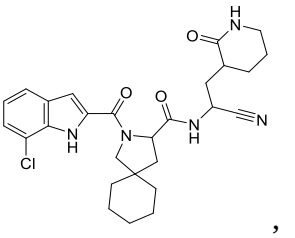
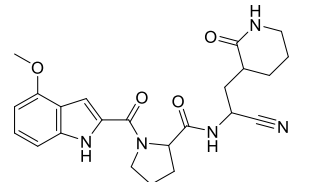
,

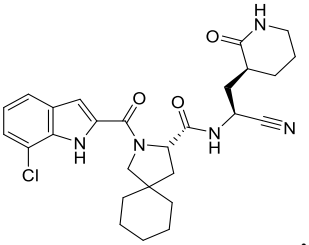
,

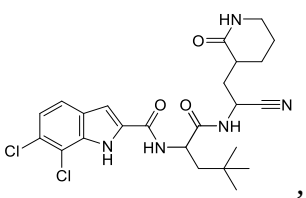
,


,

,

,

,

,

,

,

,

,

,

,

,

,

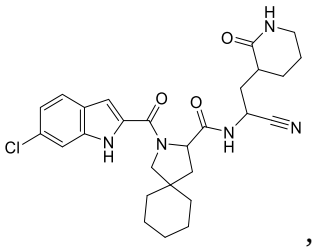
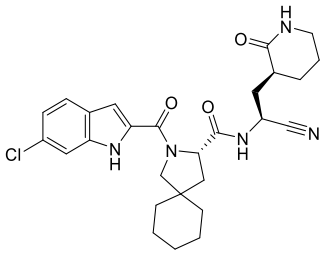
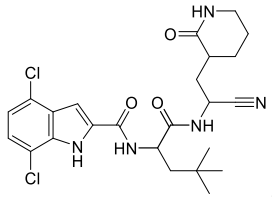
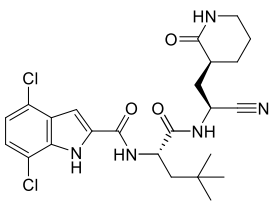
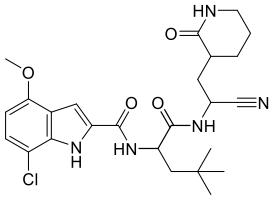
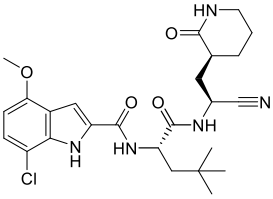
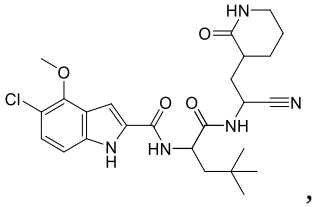
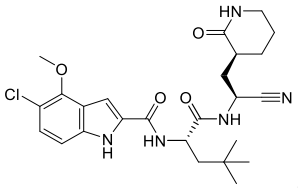
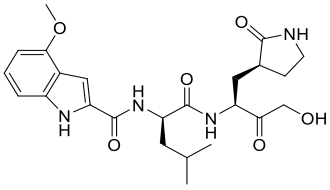
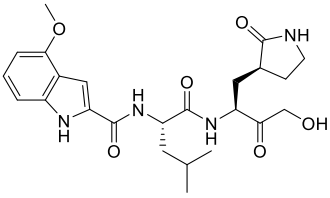
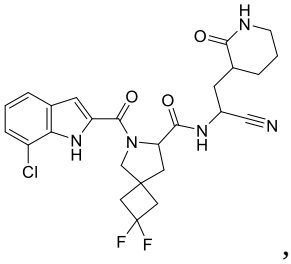
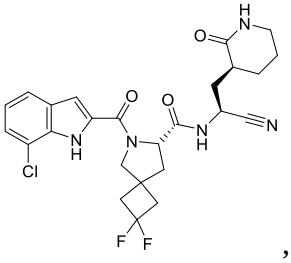
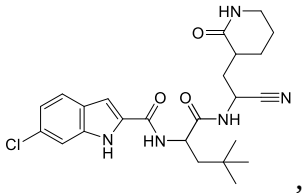
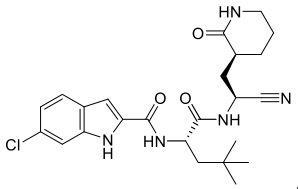
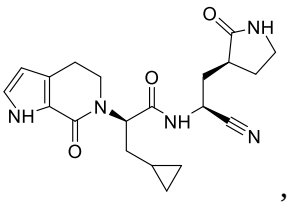
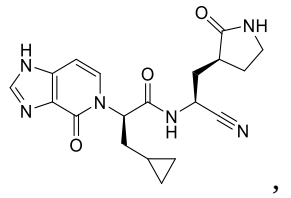
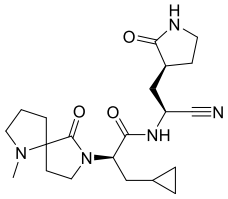
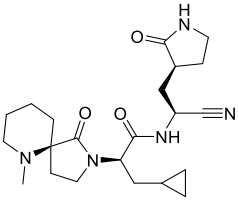
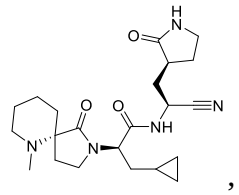
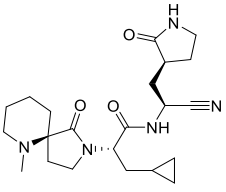
,

,

,

,

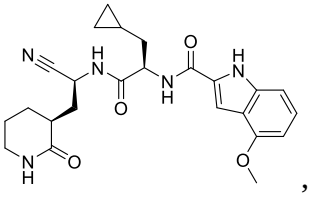
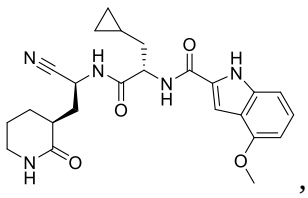
,

,

,

,

,

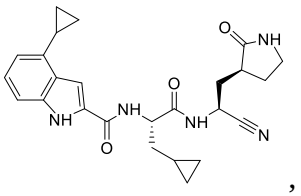
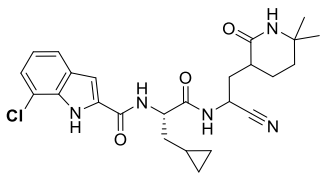
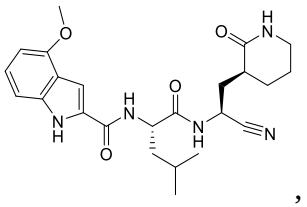
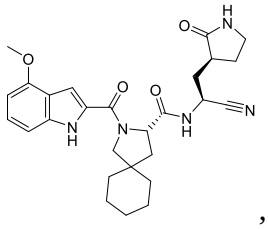
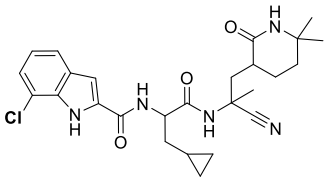
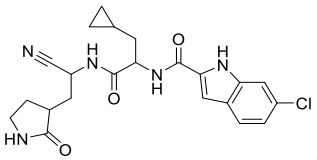
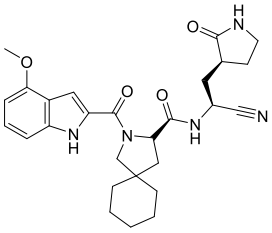
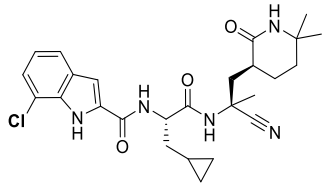
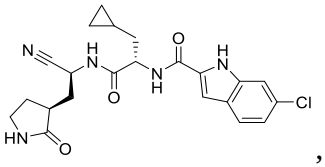
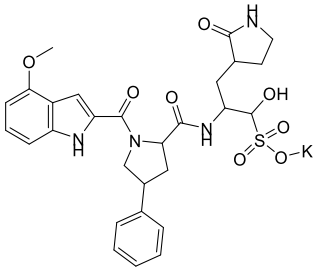
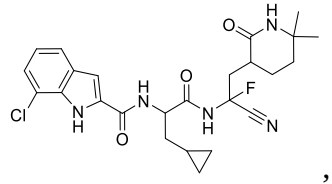
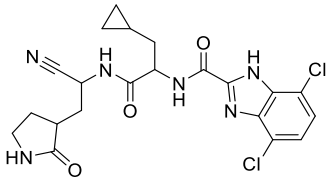
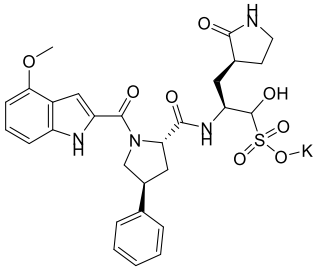
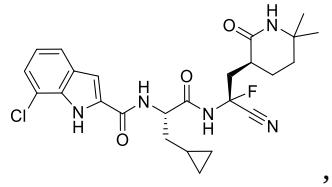
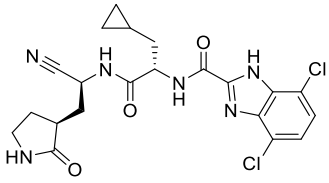
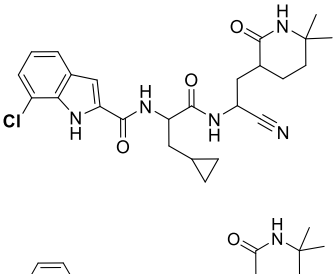
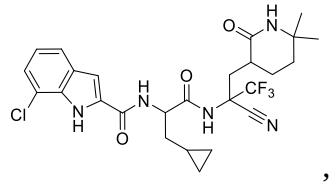
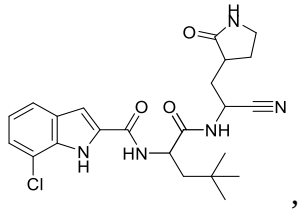
,

,

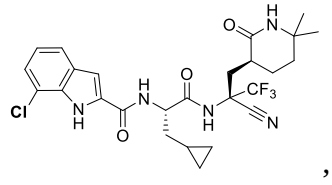
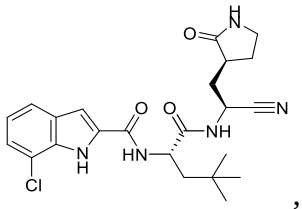
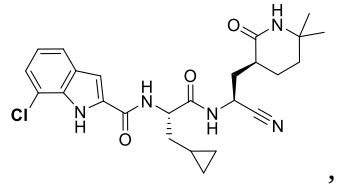
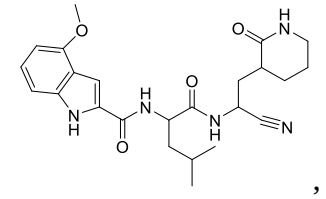
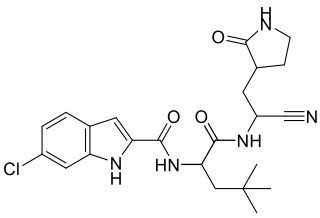
,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

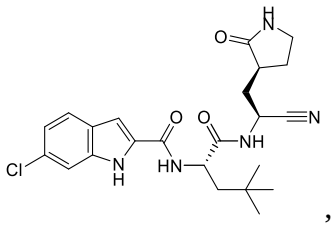
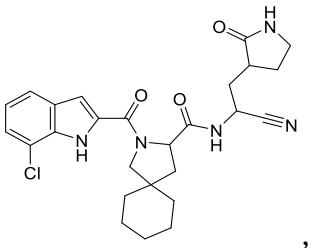
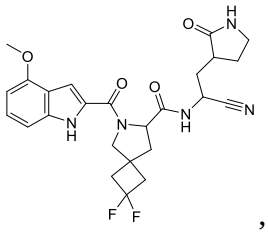
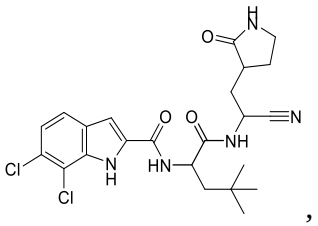
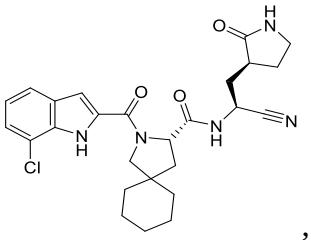
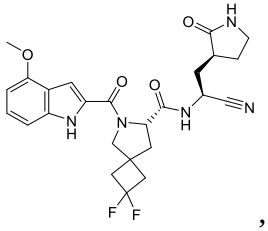
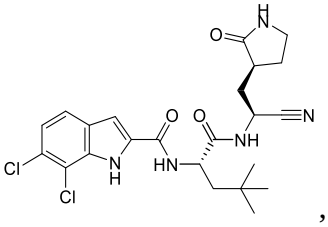
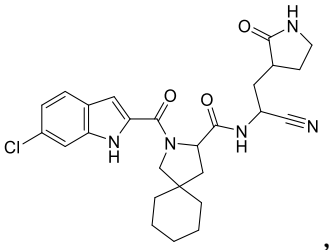
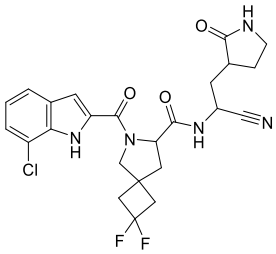
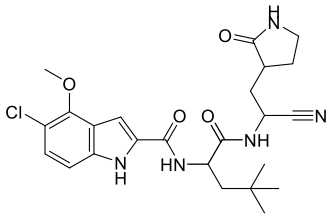
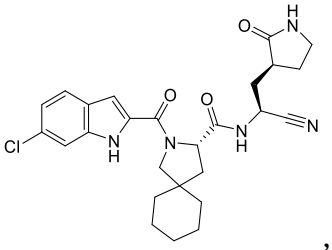
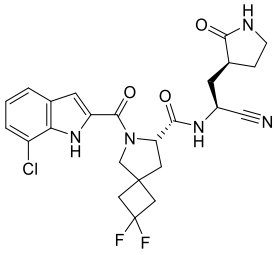
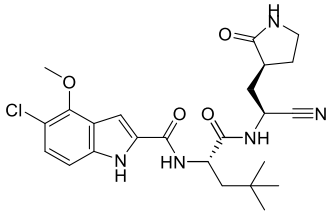
,

,

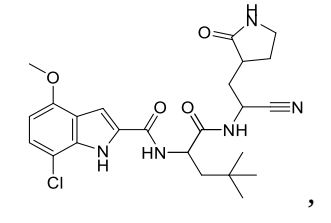
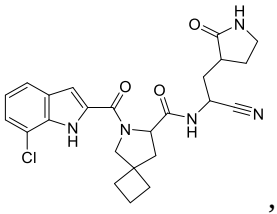
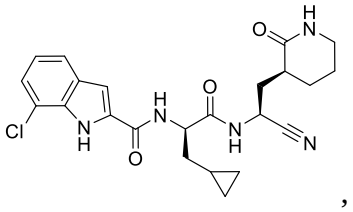
,

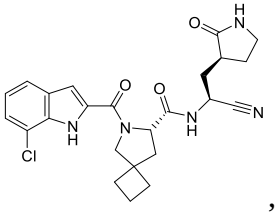
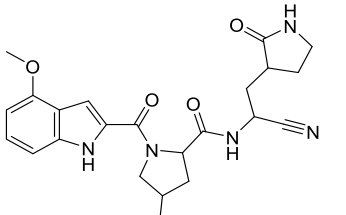
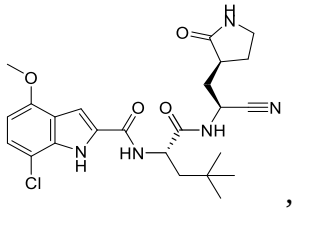
,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

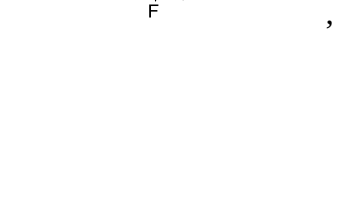
,

,

,

,

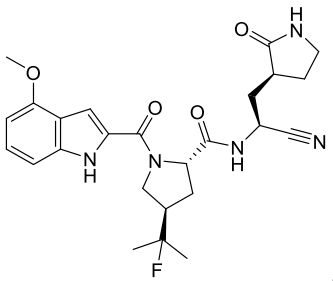
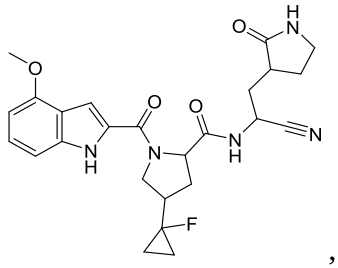
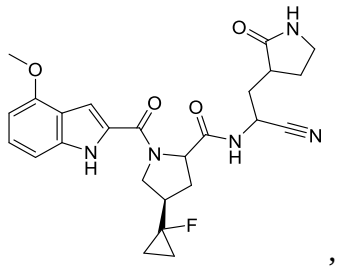
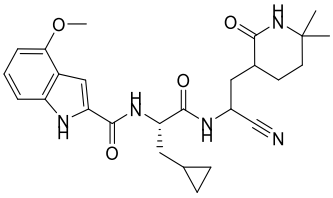
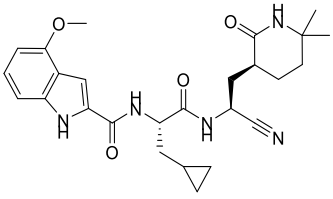
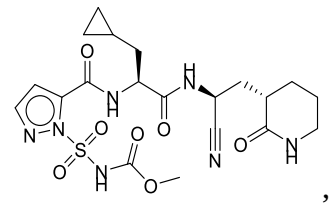
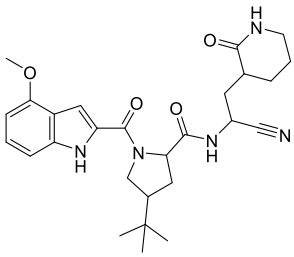
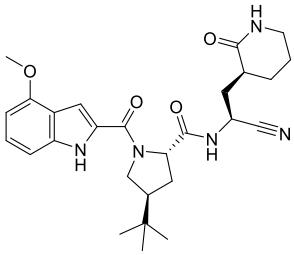
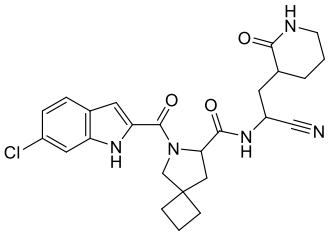
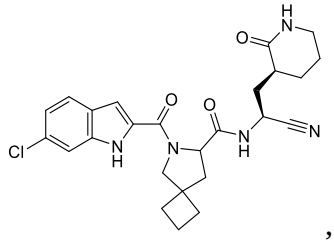
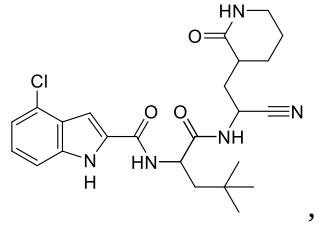
,

,

,

,

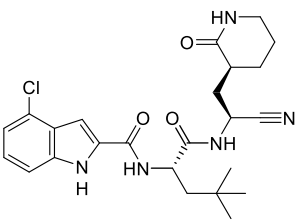
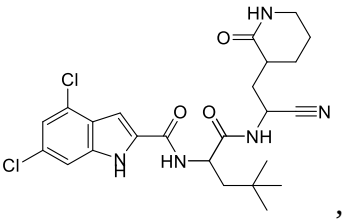
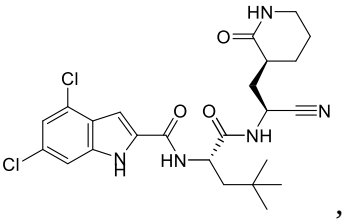
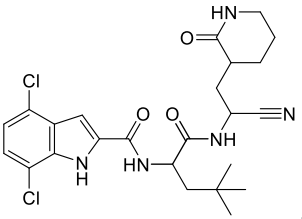
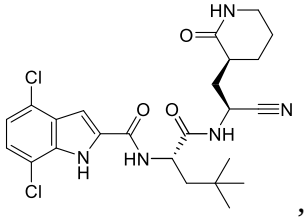
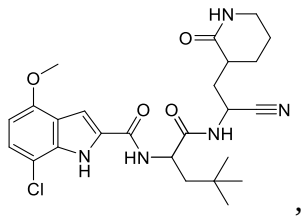
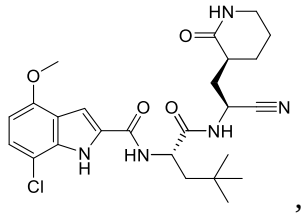
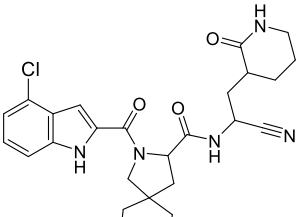
,

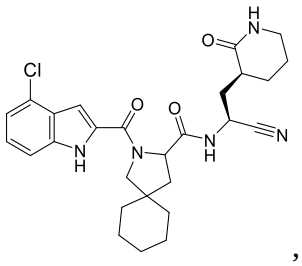
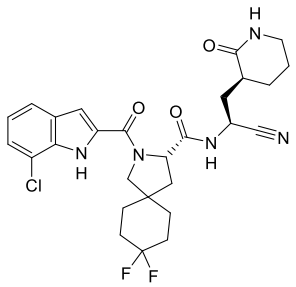
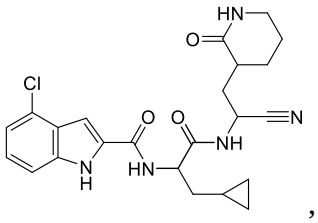
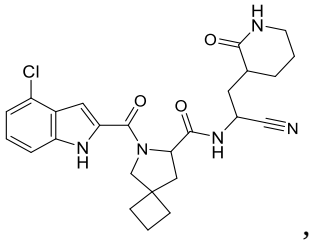
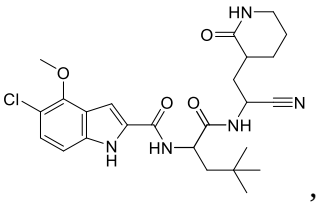
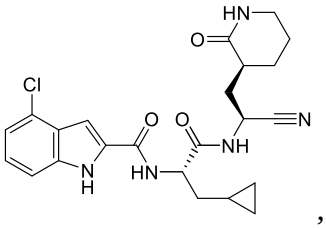
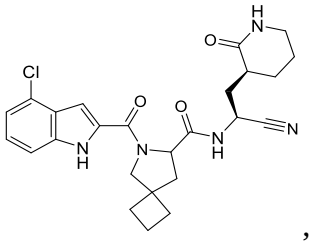
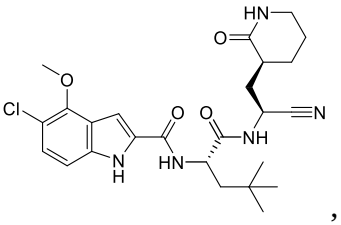
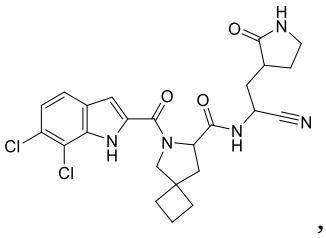
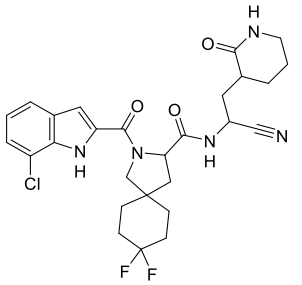
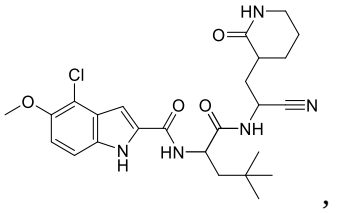
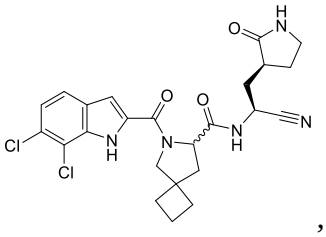
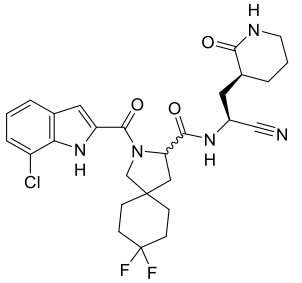
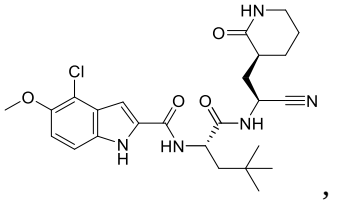
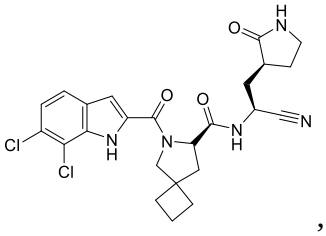
,

,

,

,

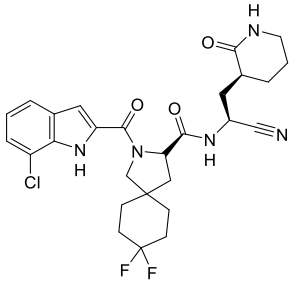
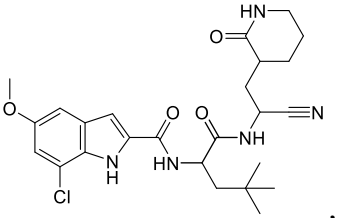
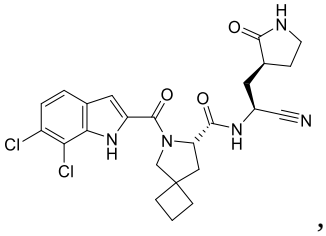

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

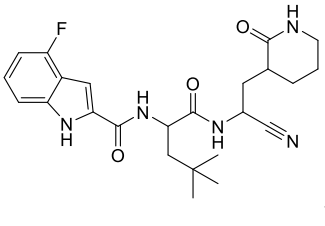
,

,

,

,

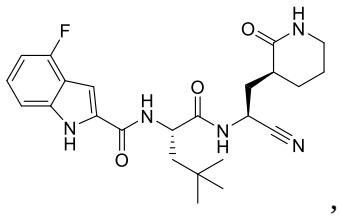
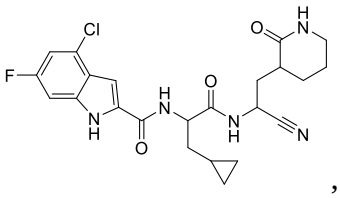
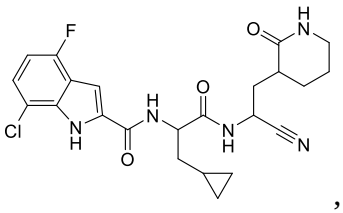
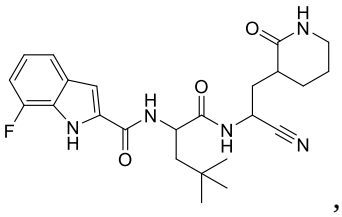
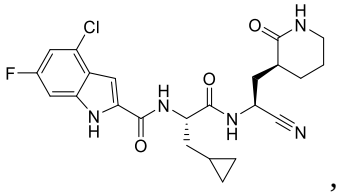
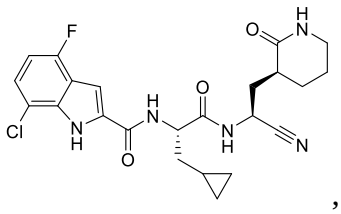
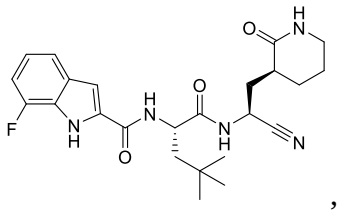
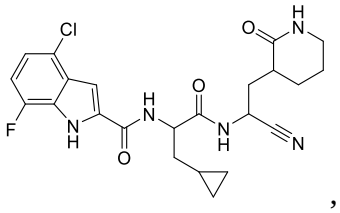
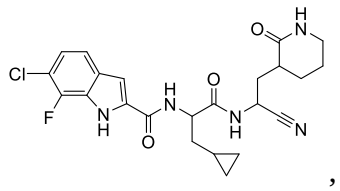
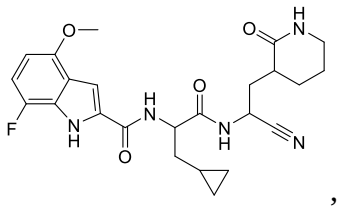
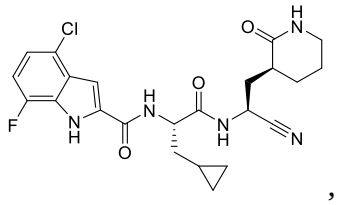
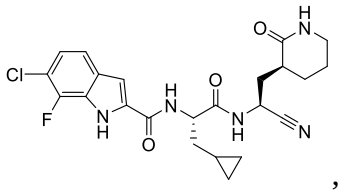
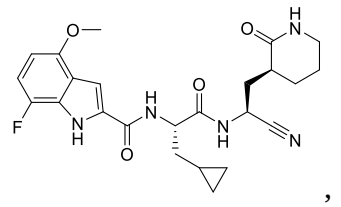
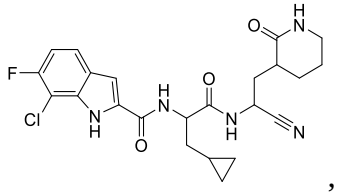
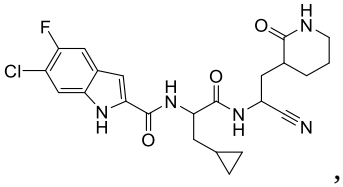
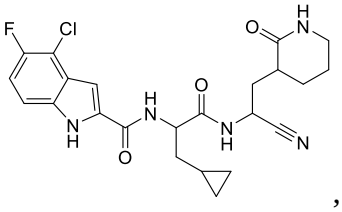
,

,

,

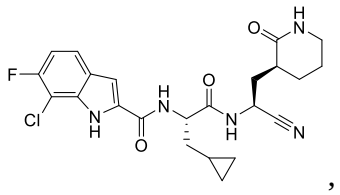
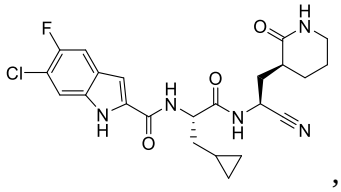
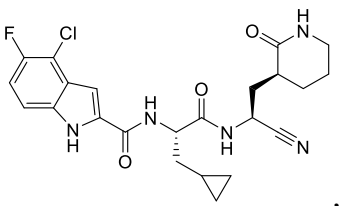
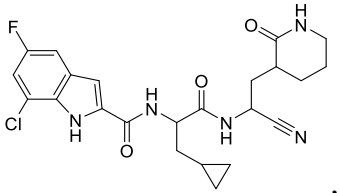
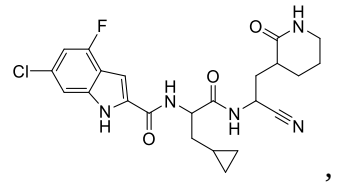
,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

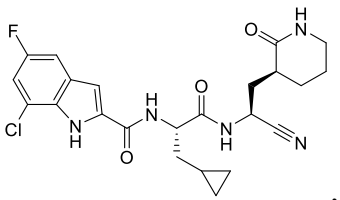
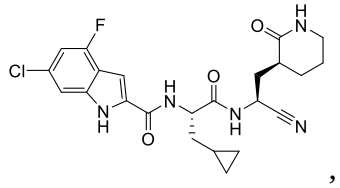
,

,

,

,

,

,

,

,

,

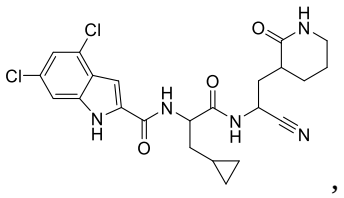
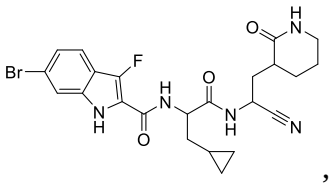
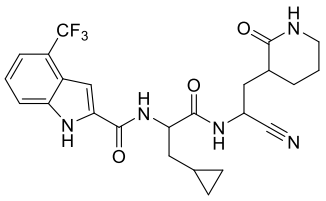
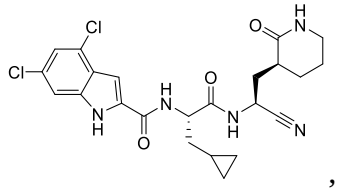
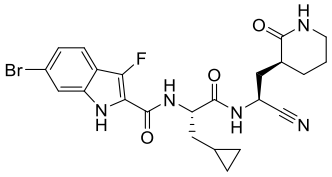
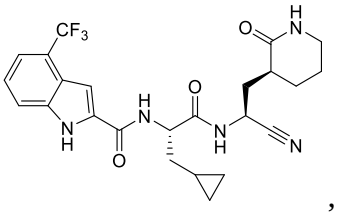
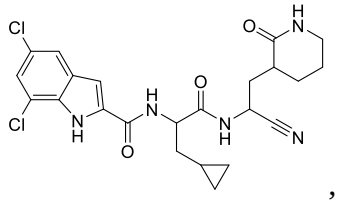
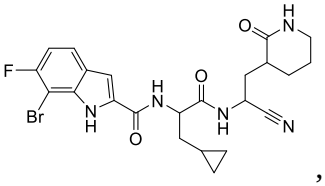
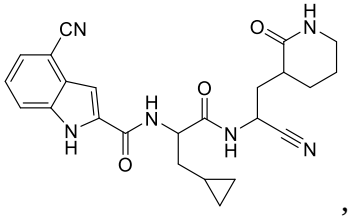
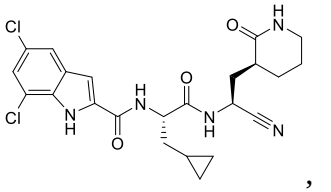
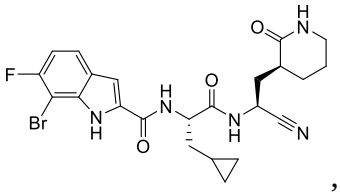
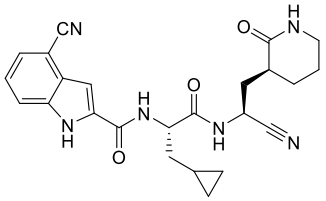
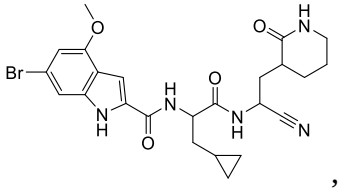
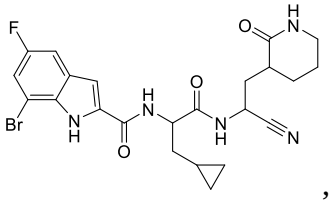
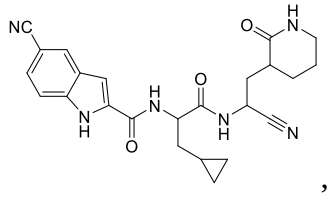
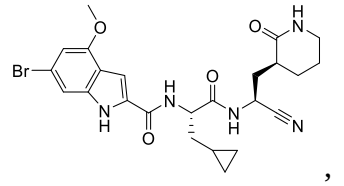
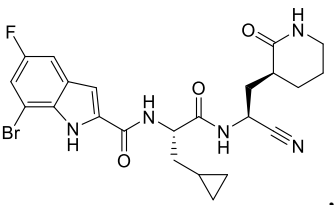
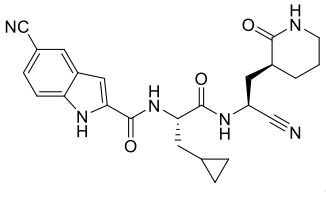
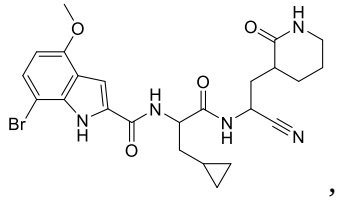
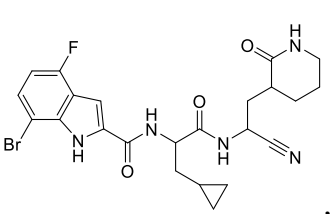
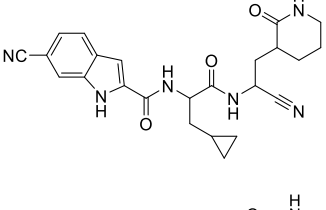
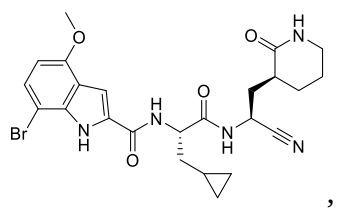
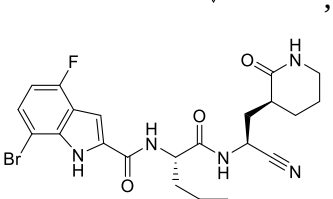
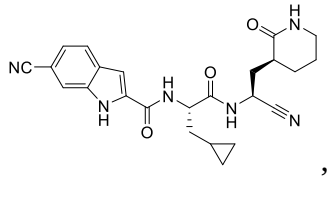
,

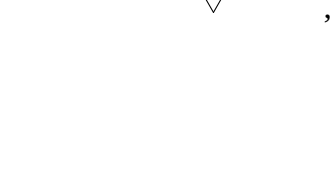
,

,

,

,

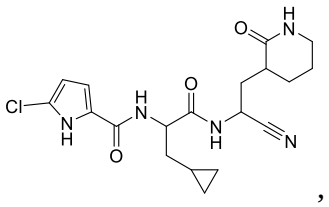
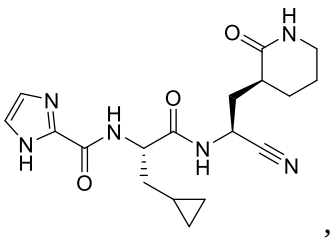
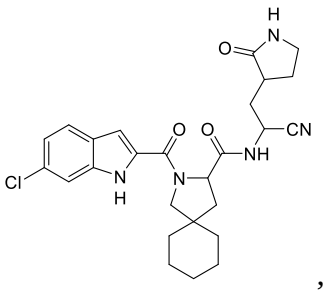
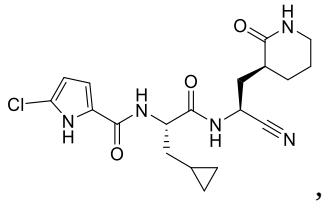
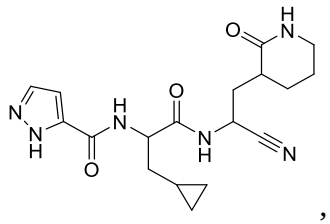
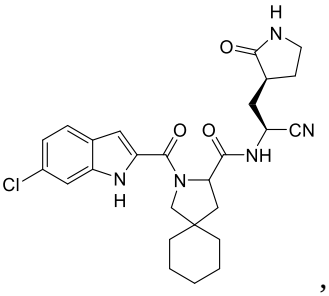
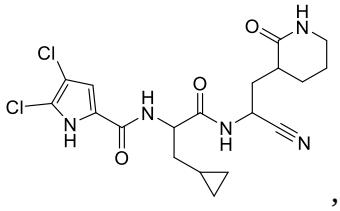
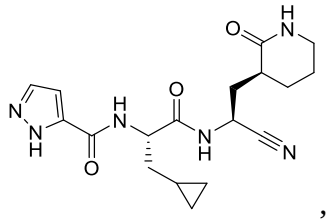
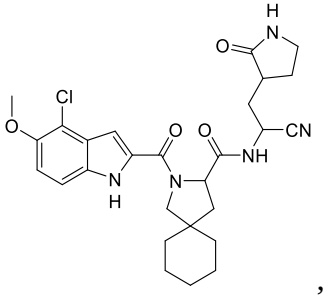
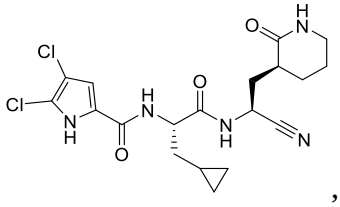
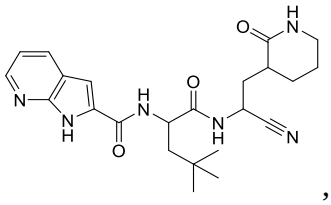
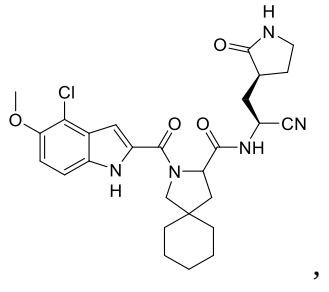
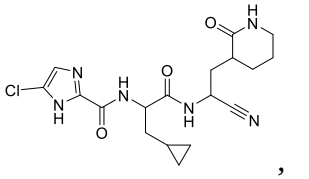
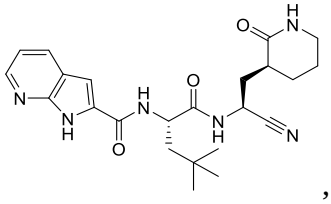
,

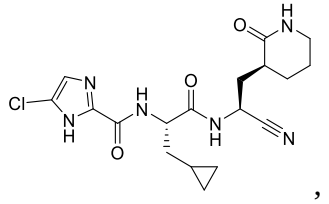
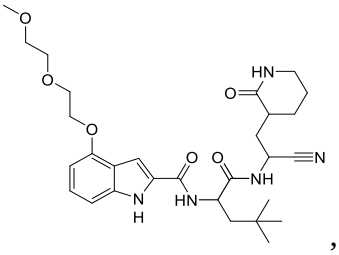
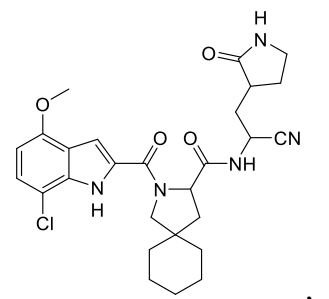
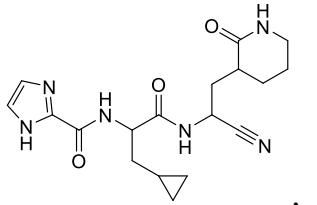
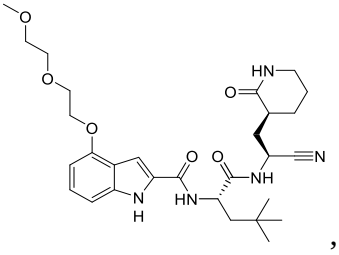
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

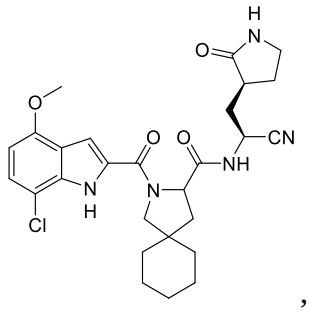
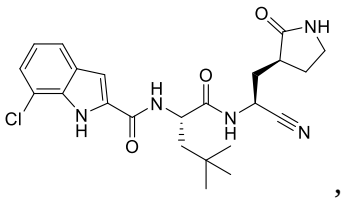
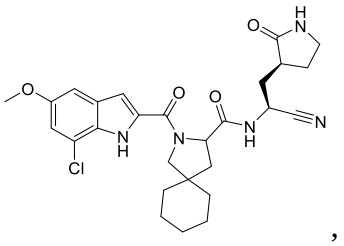
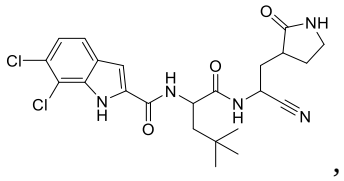
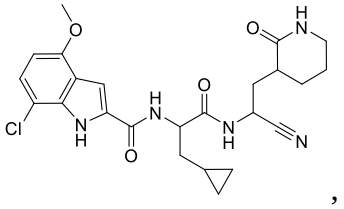
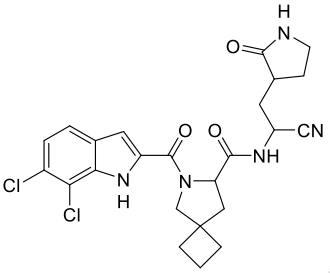
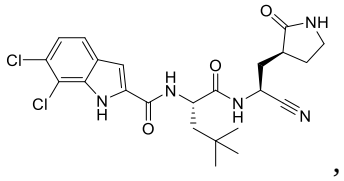
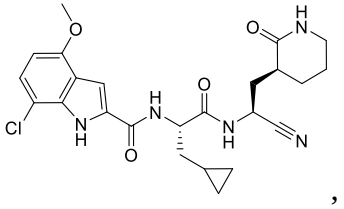
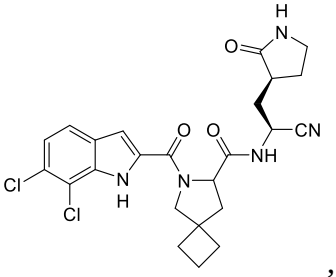
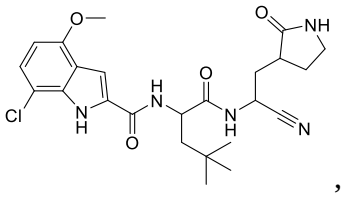
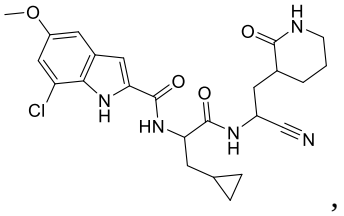
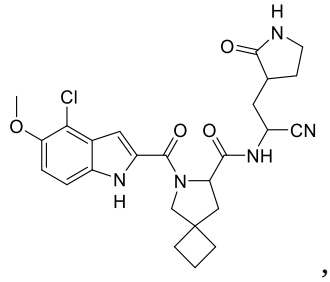
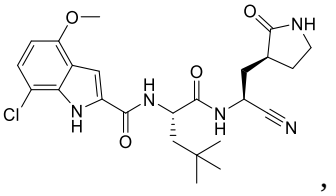
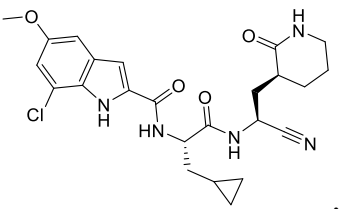
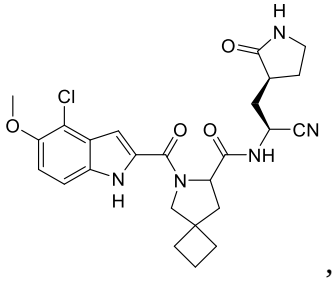
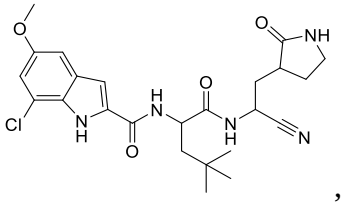
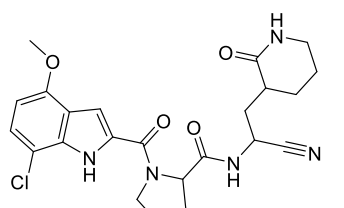
,

,

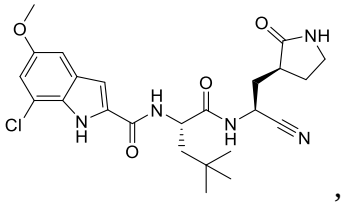
,

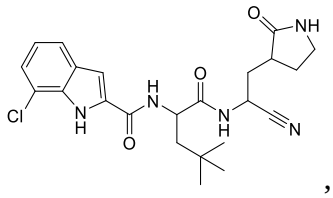

,

,

,

,

,

,

,

,

,

,

,

,

,

,

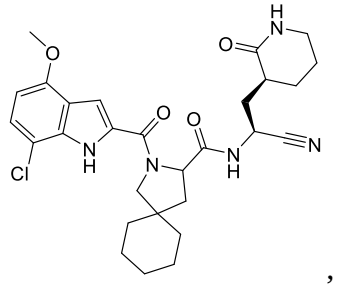
,

,

,

,

,

,

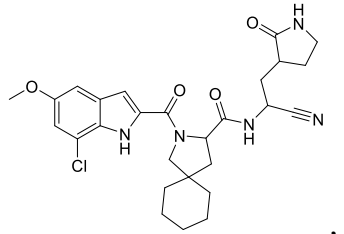
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

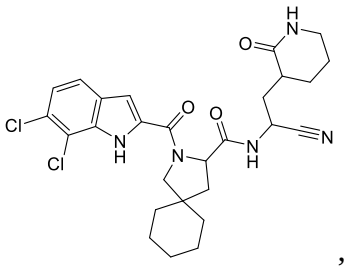
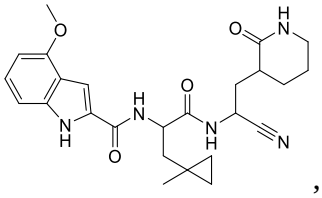
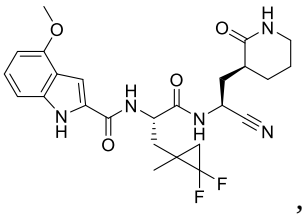
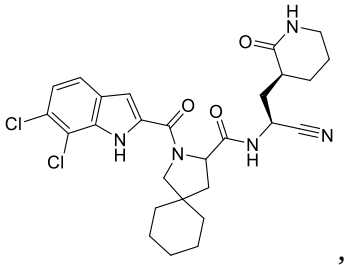
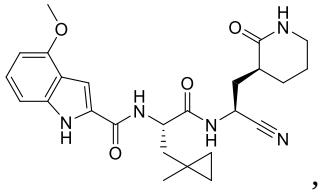
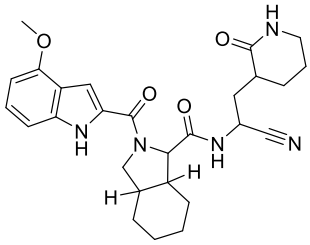
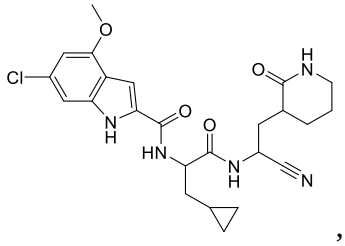
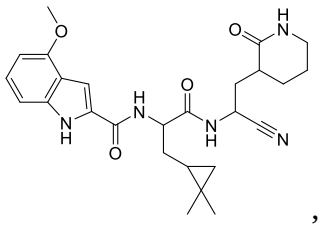
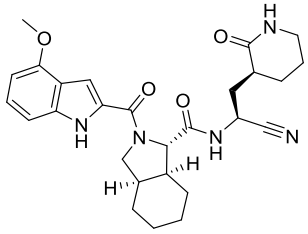
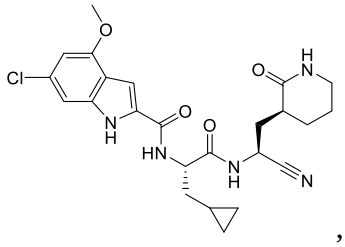
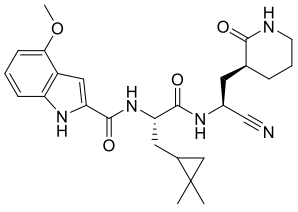
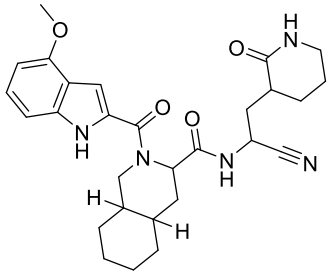
,

,

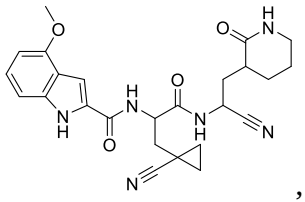
,

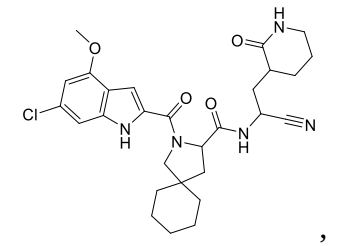
,

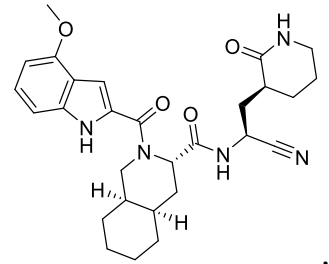
,

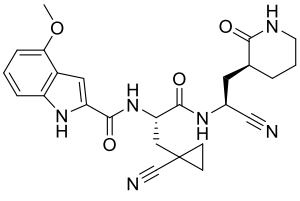
,

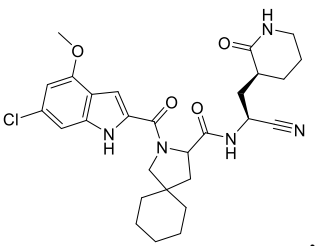
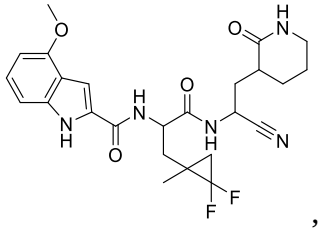
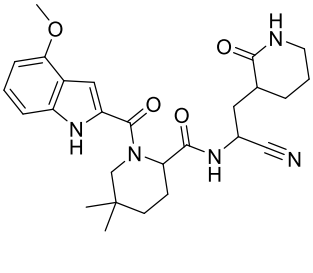

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

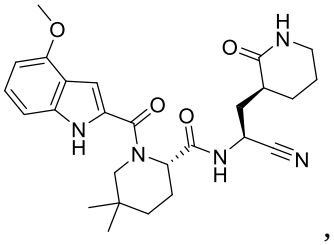
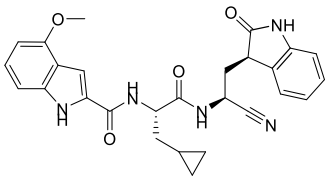
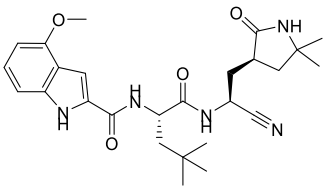
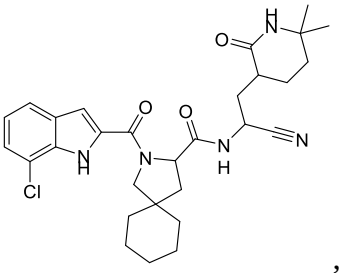
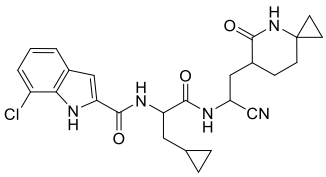
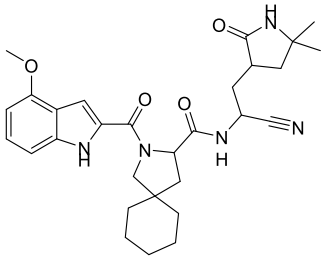
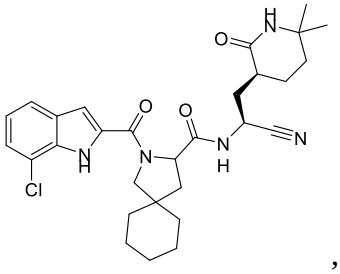
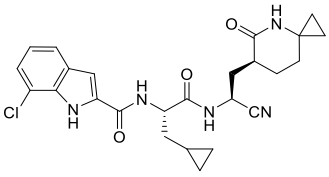
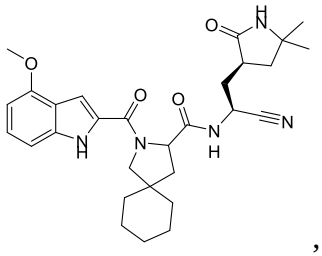
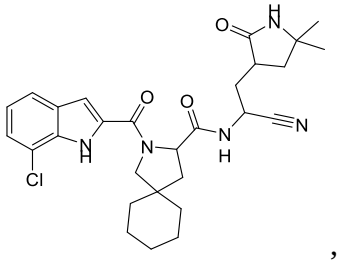
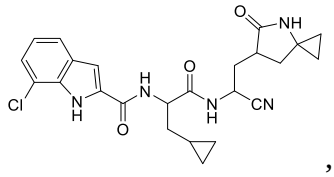
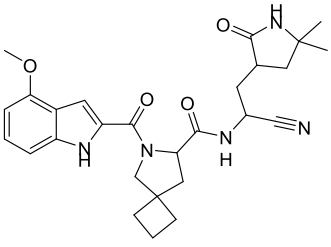
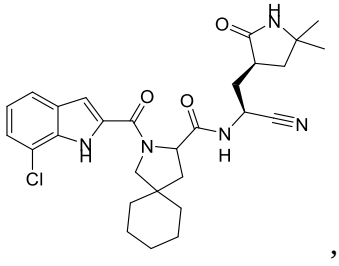
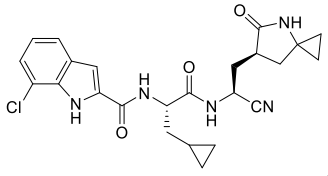
,

,

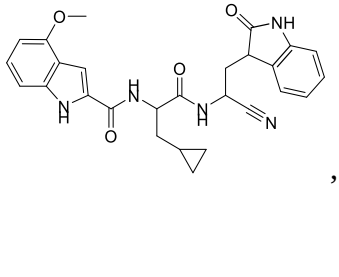
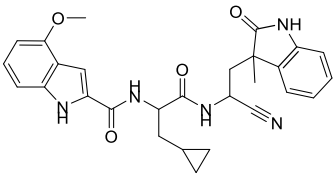
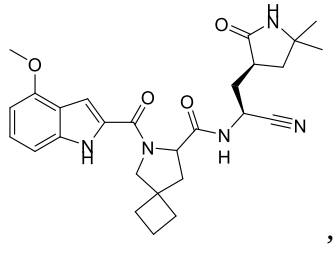
,

,

,

,

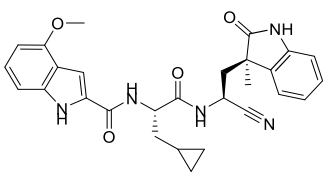
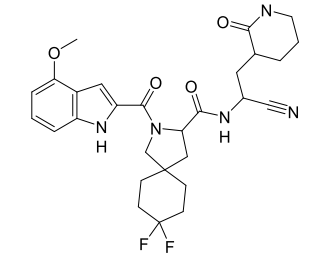
,

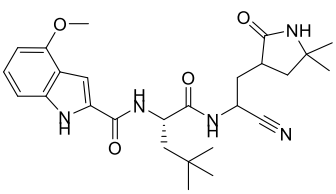
,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

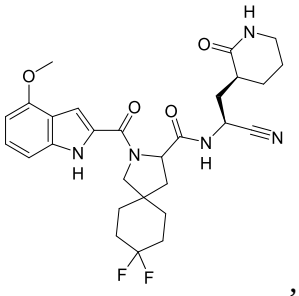
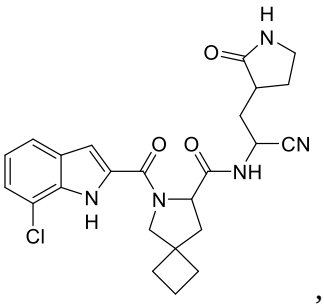
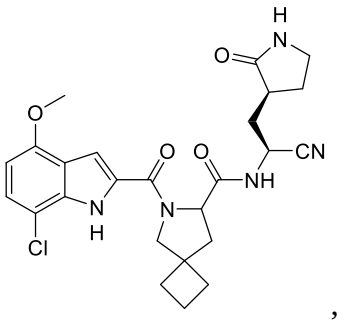
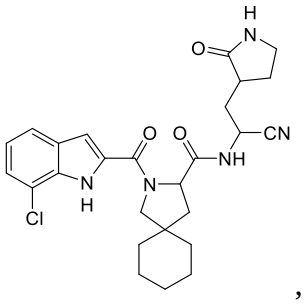
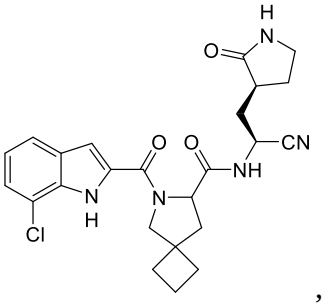
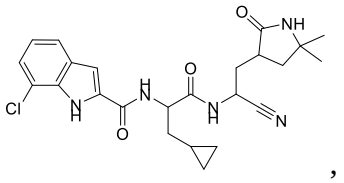
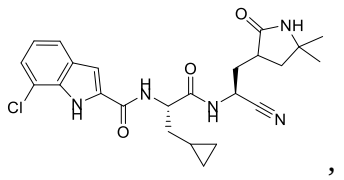
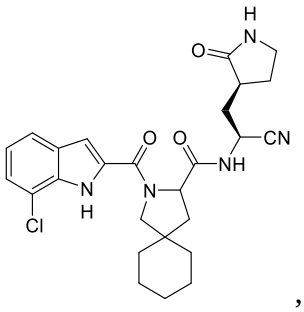
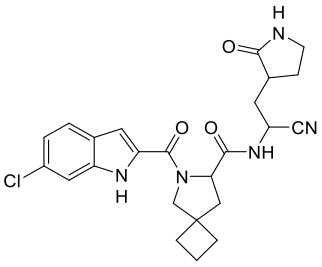
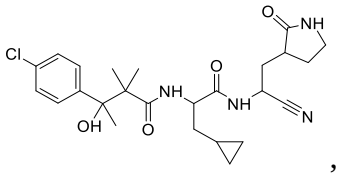
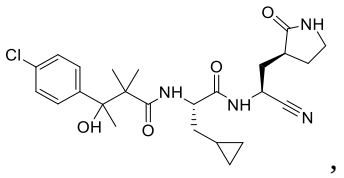
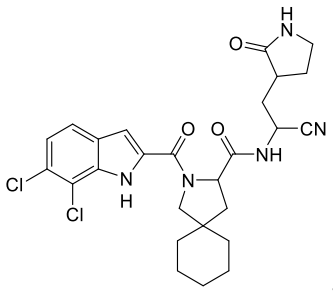
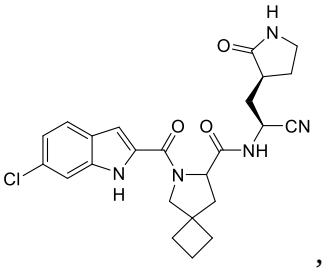
,

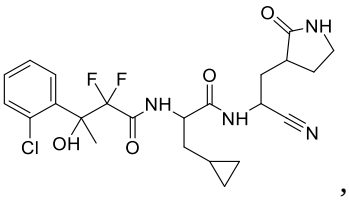
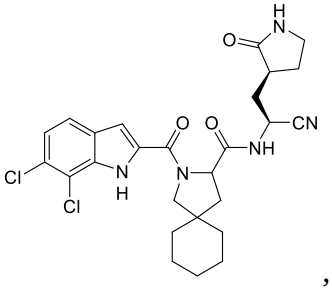
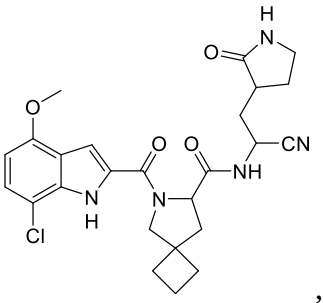
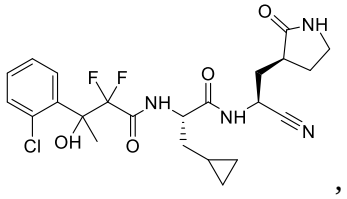
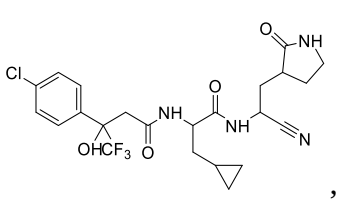
,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

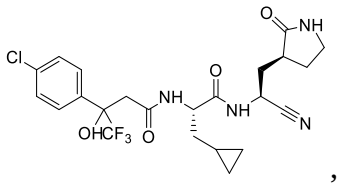
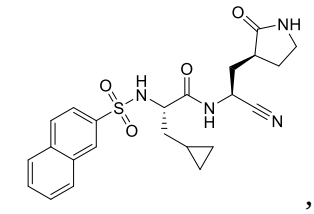
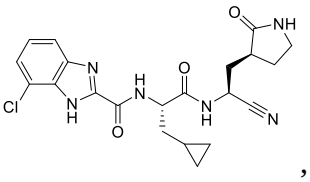
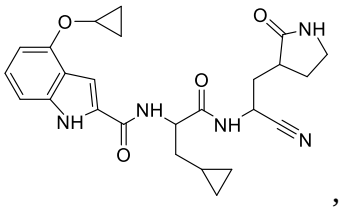
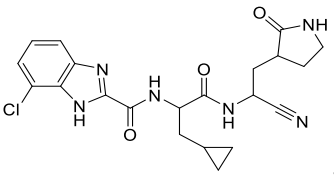
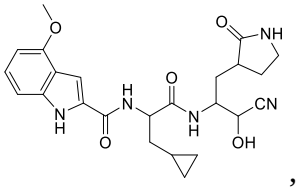
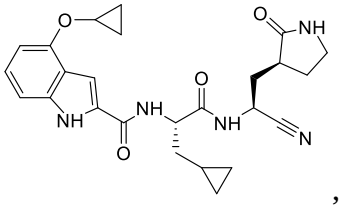
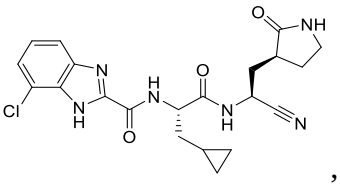
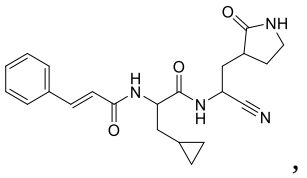
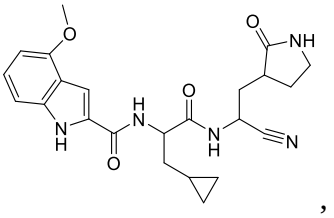
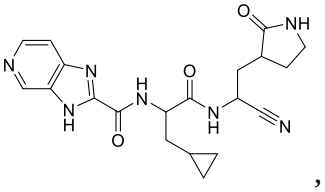
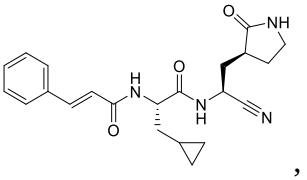
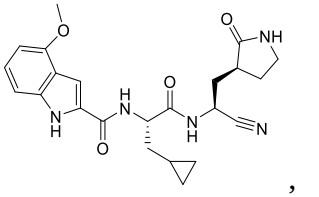
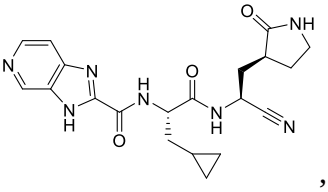
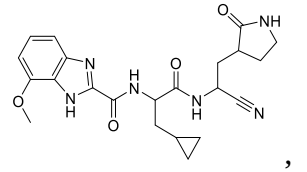
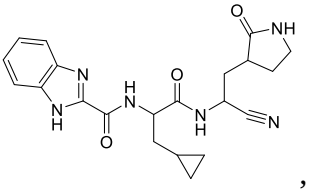
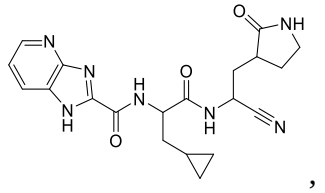
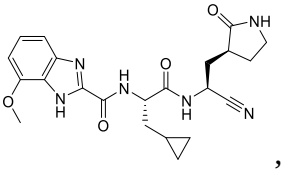
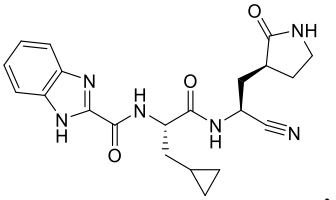
,

,

,

,

,

,

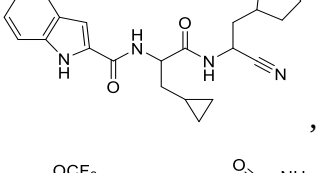
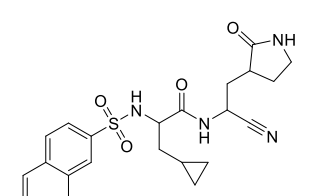
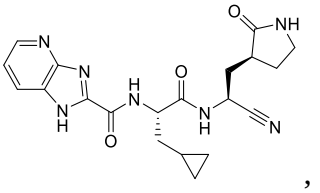
,

,

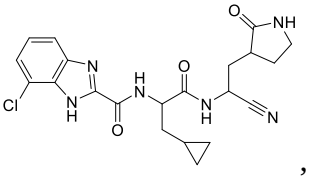
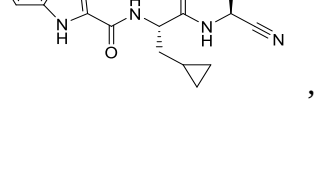
,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

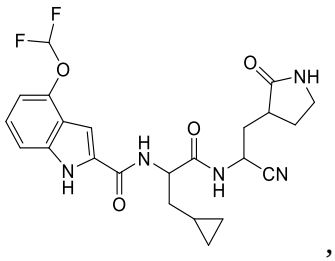
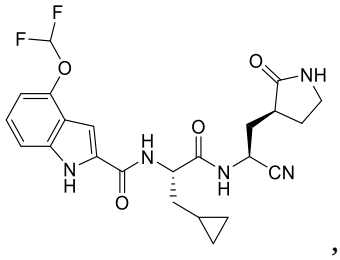
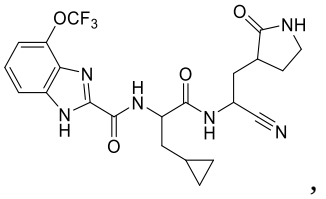
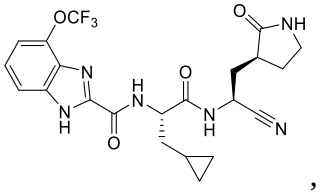
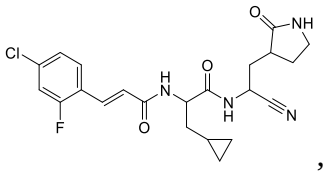
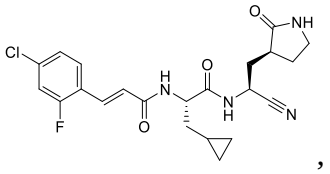
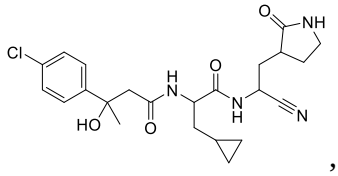
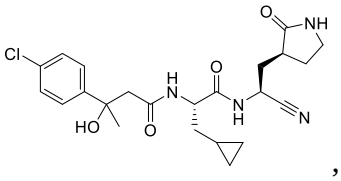
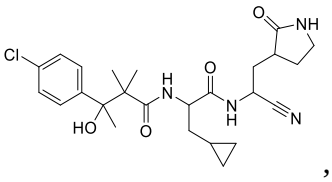
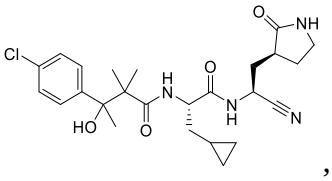
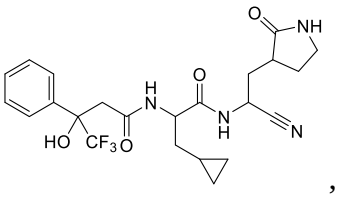
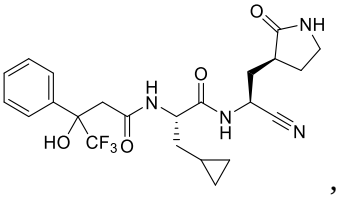
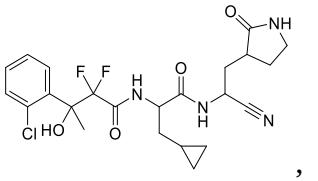
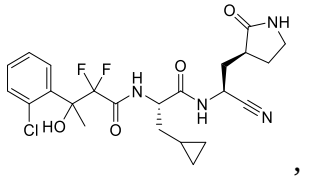
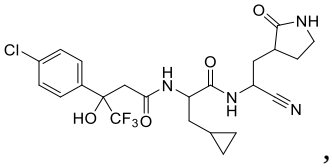
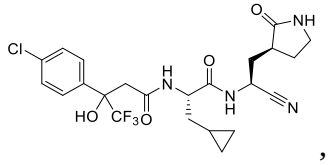
,

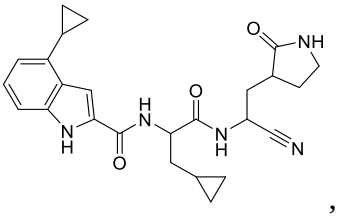
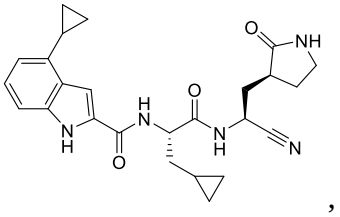
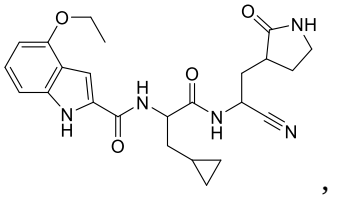
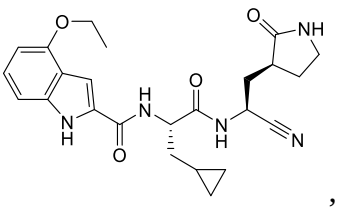
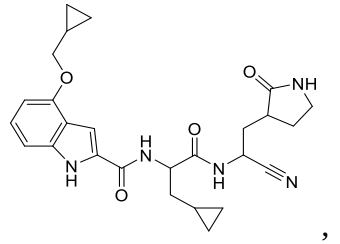
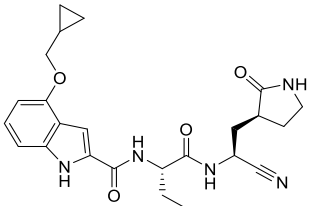
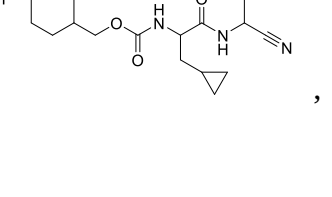
,

,

,

,

,

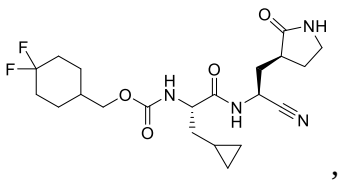
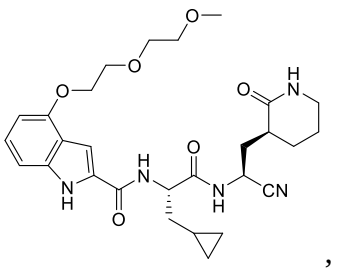
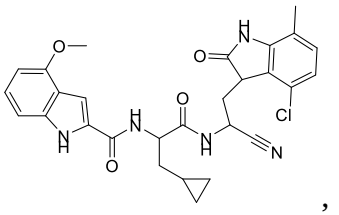
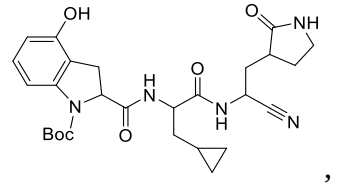
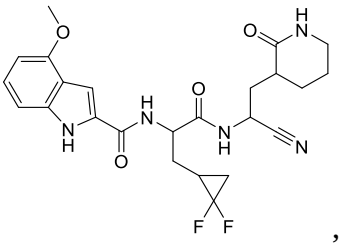
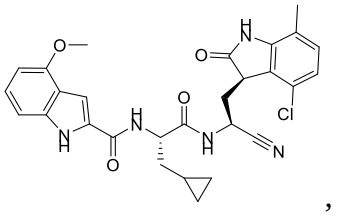
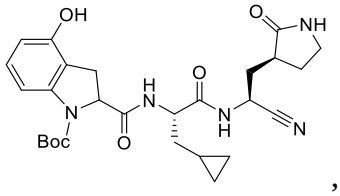
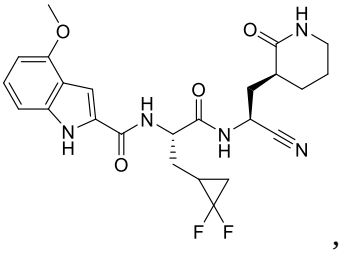
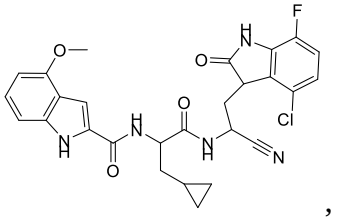
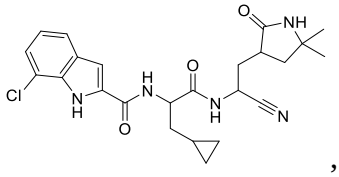
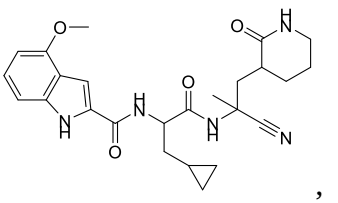
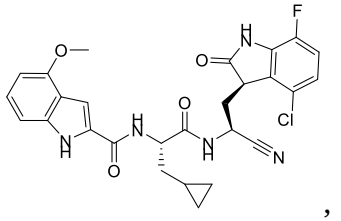
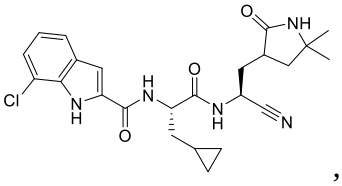
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

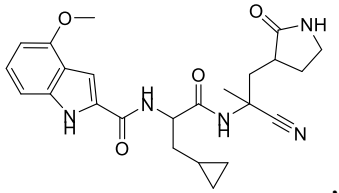
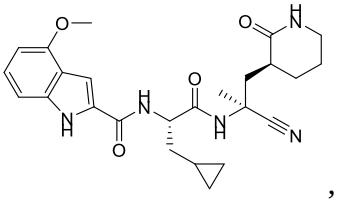
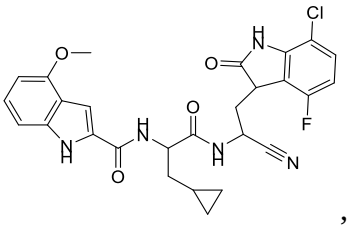
,

,

,

,

,

,

,

,

,

,

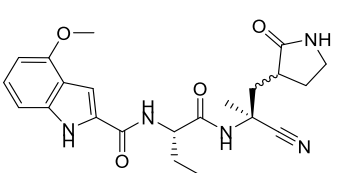

,

,

,

,

,

,

,

,

,

,

,

,

,

,

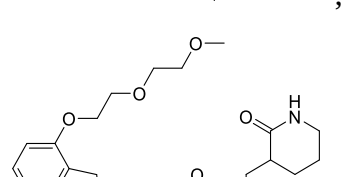
,

,

,

,

,

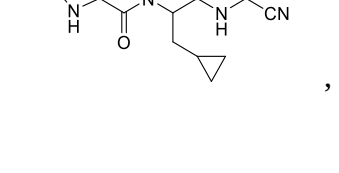
,

,

,

,

,

,

,

,

,

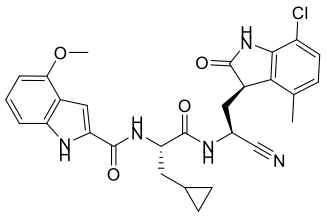
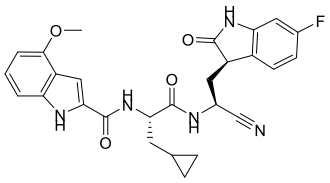
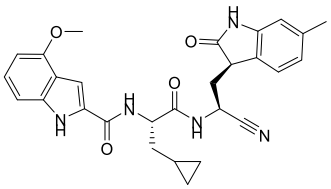
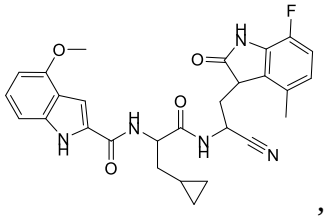
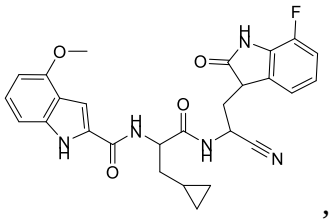
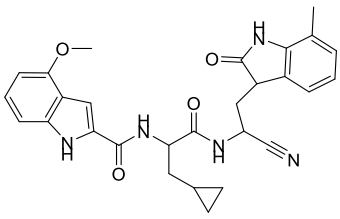
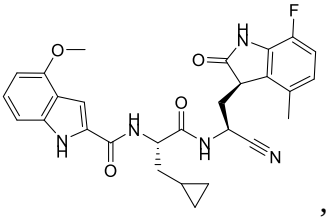
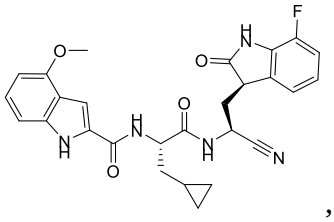
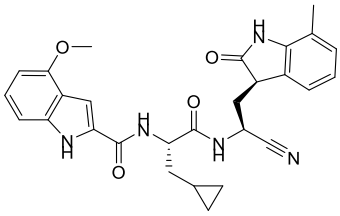
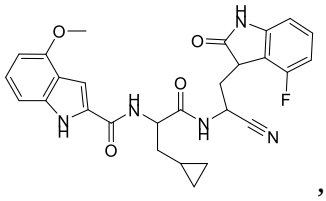
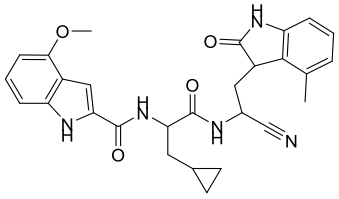
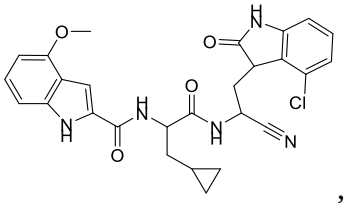
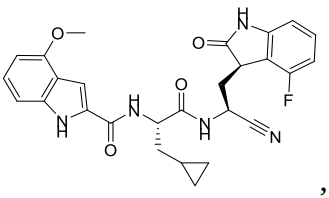
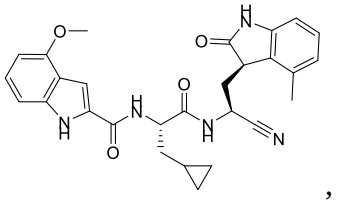
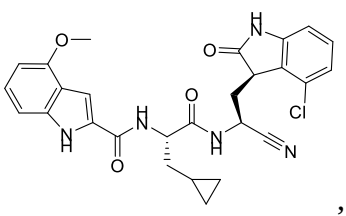
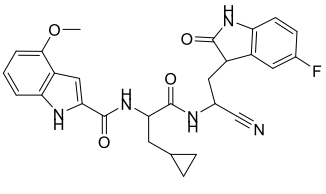
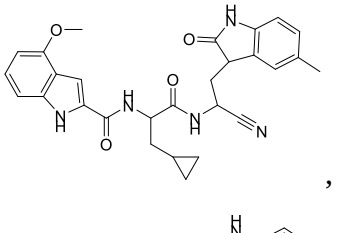
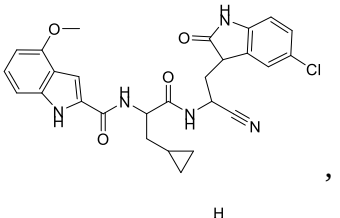
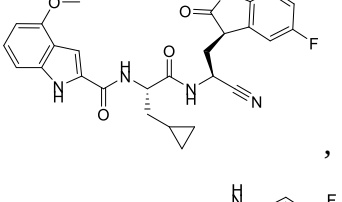
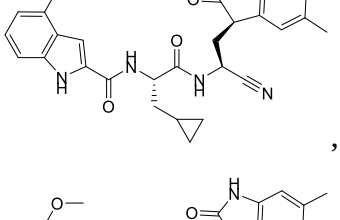
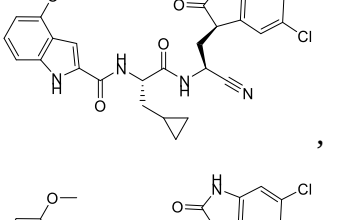
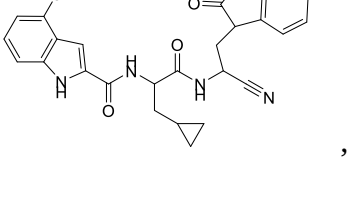
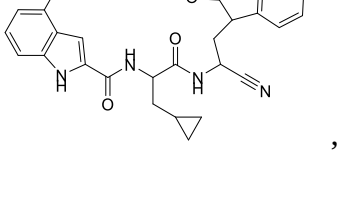
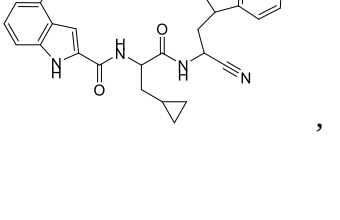
,

,

,

,

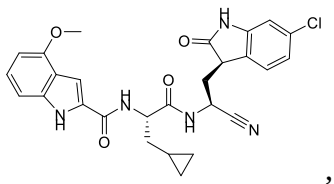
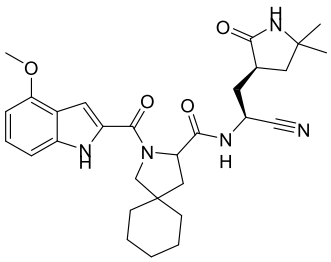
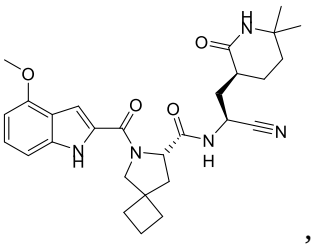
,

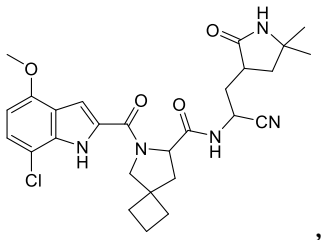
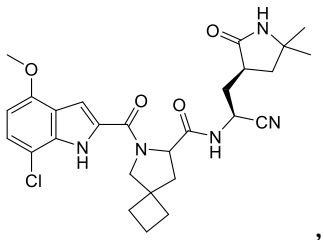
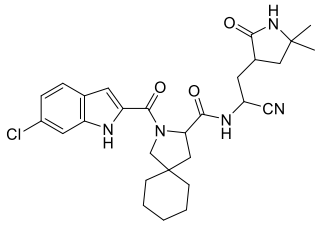
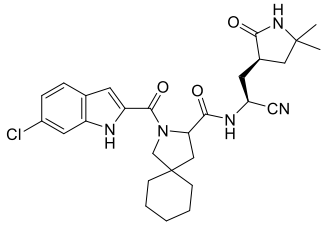
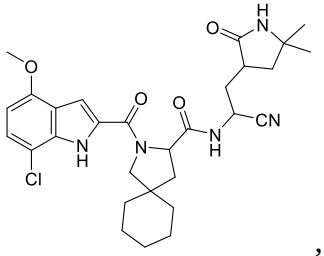
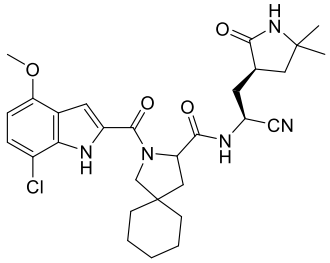
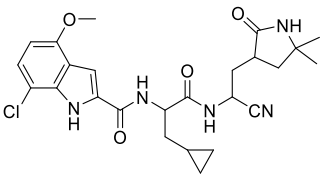
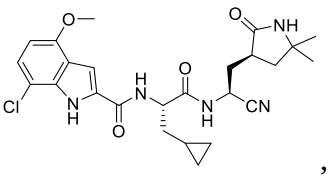
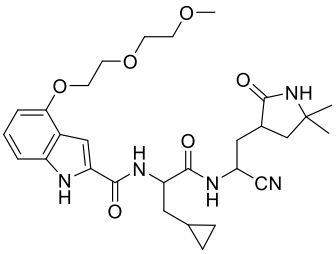
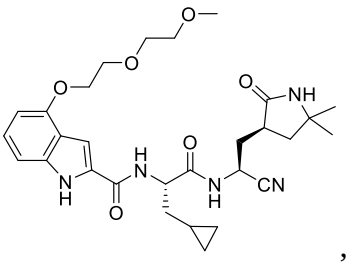
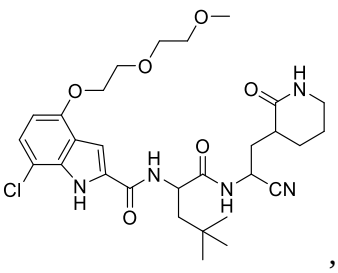
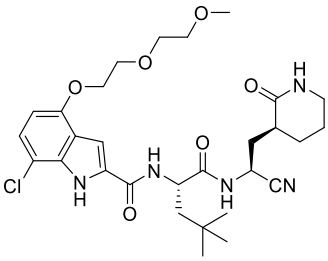
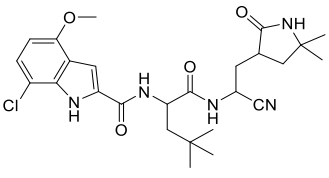
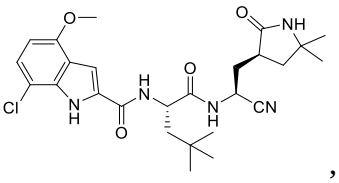
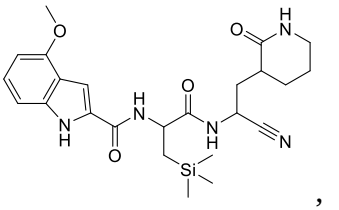
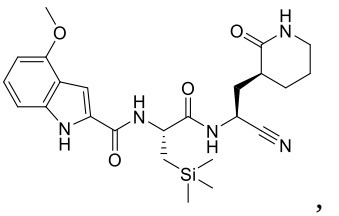
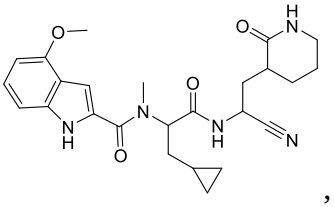
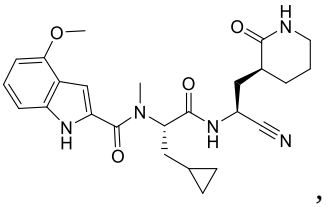
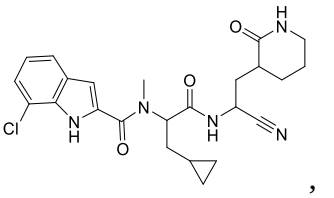
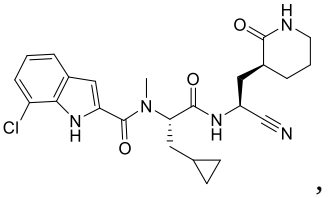
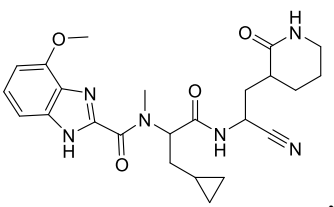

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

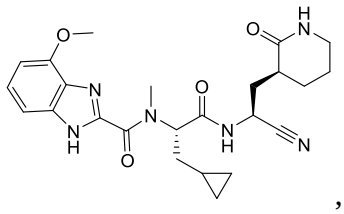
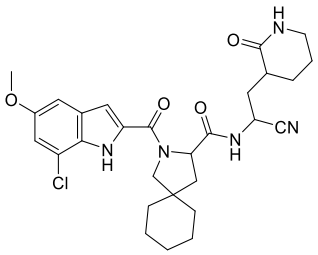
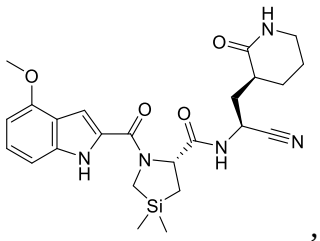
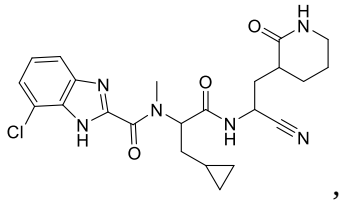
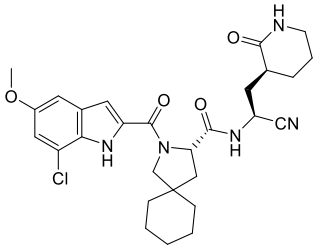
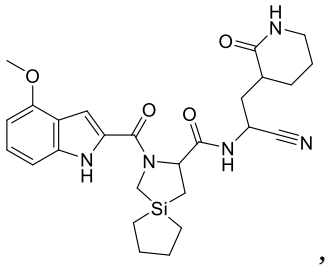
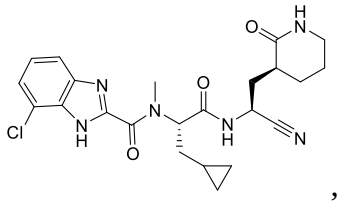
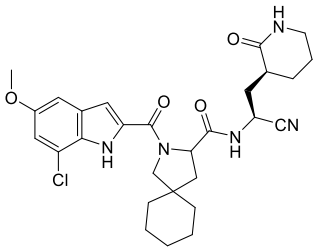
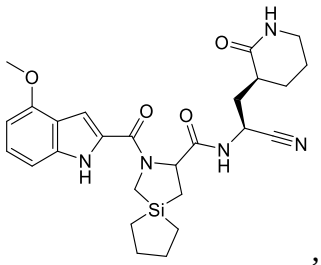
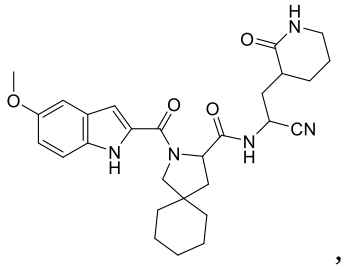
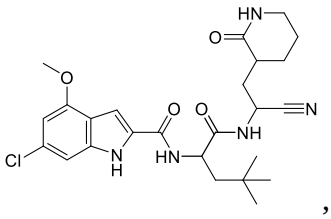
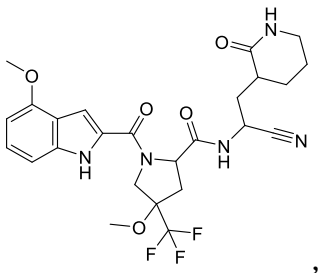
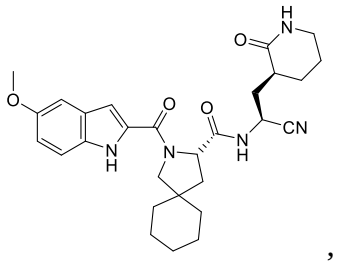
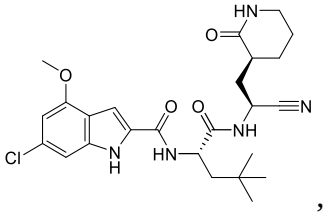
,

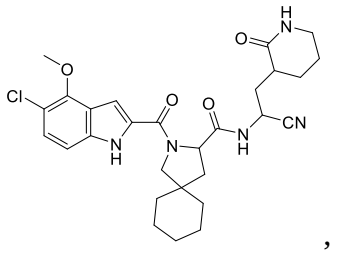
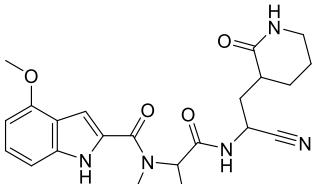
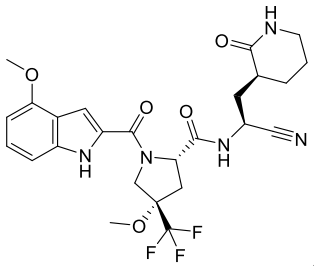
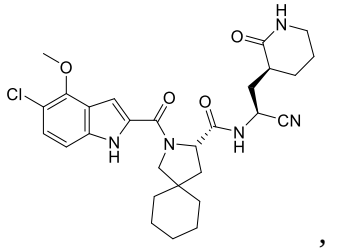
,

,


,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

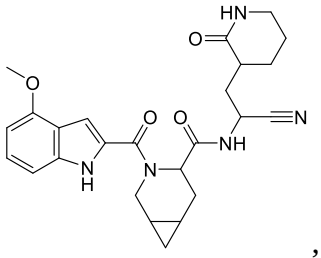

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

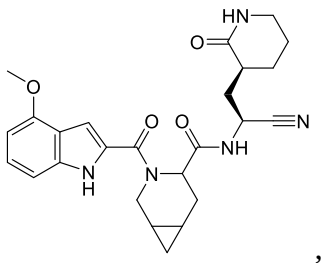
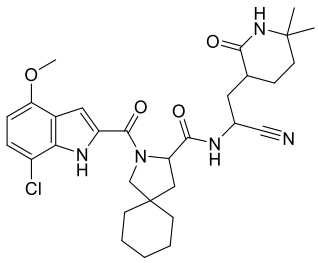
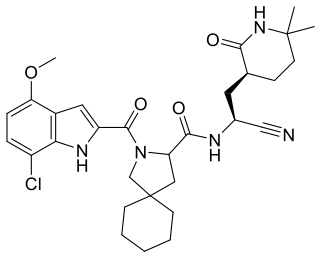
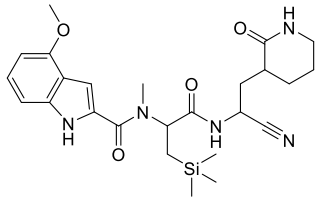
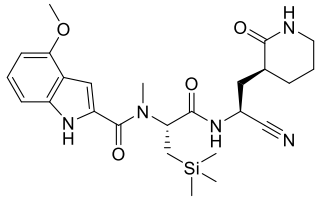
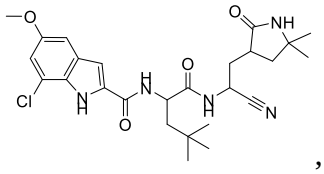
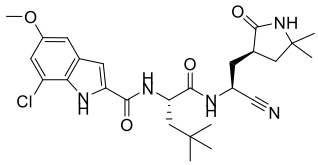
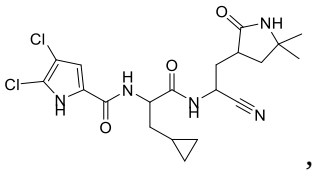
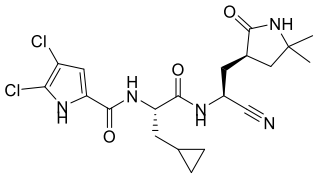
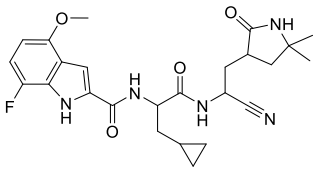
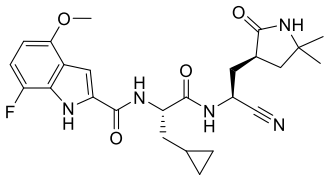
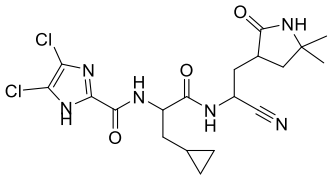
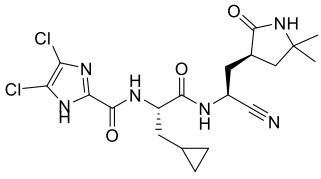
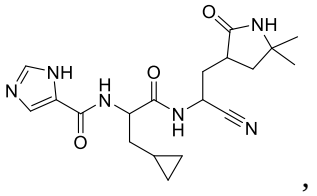
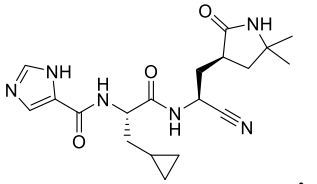
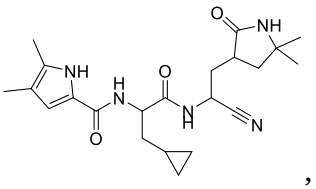
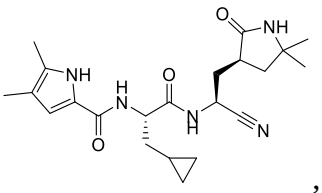
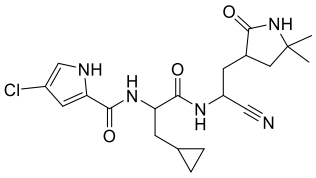
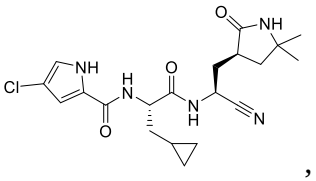
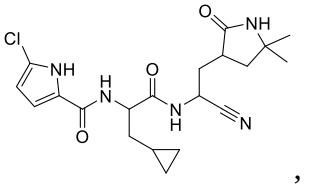
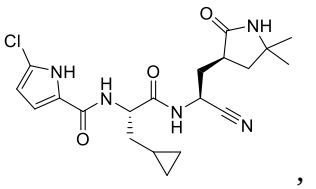
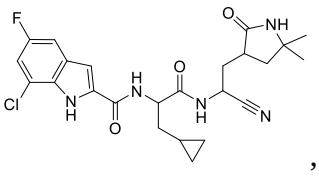
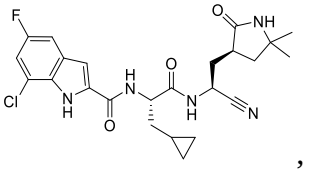
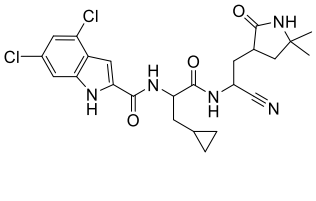
,

,

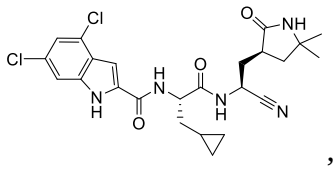
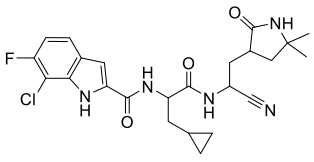
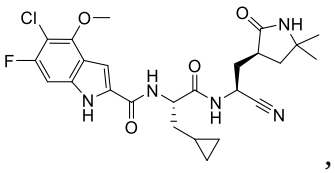
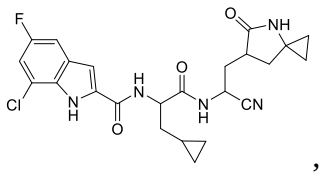
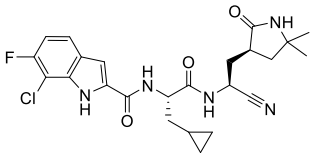
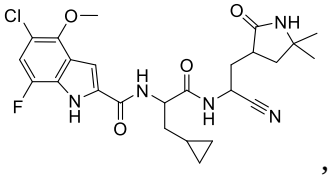
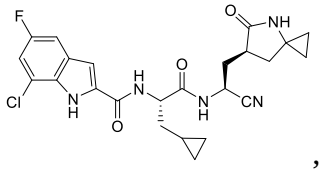
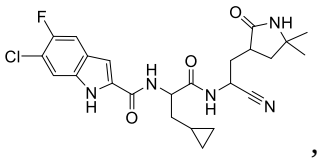
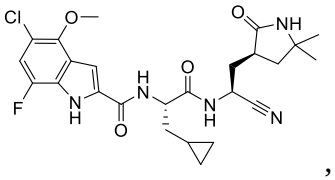
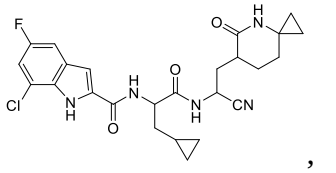
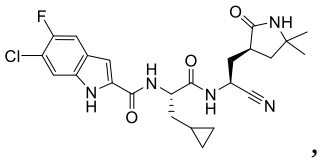
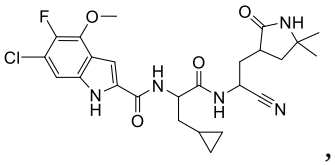
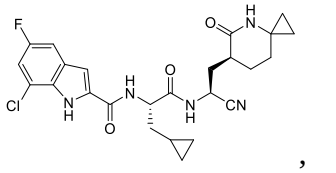
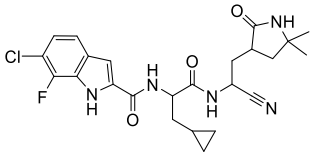
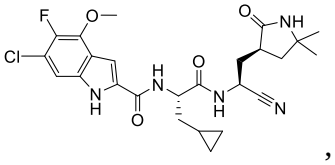
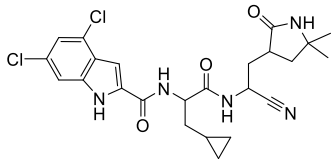
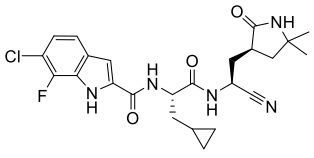
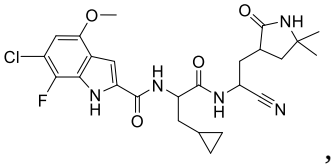
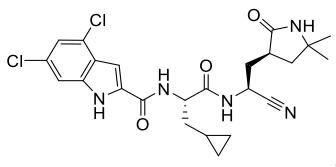
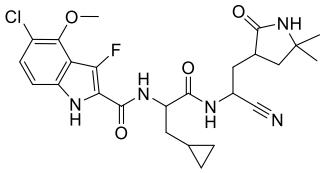
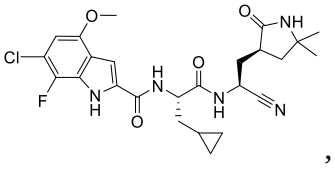
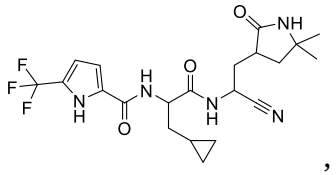
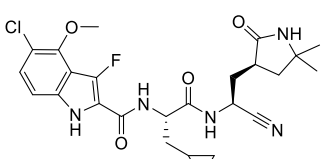
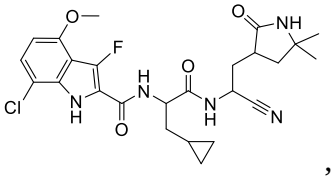
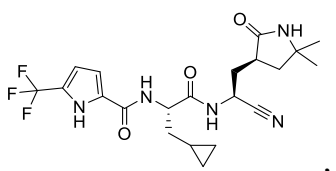
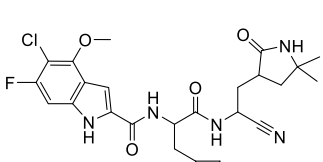
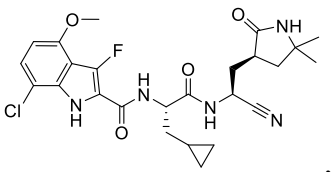
,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

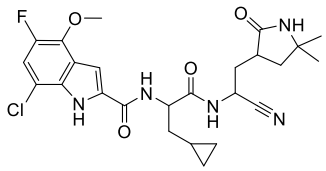
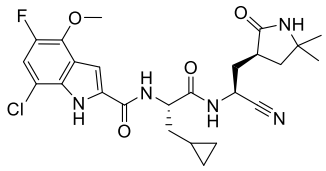
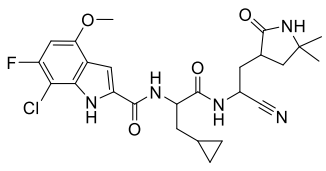
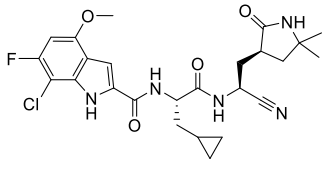
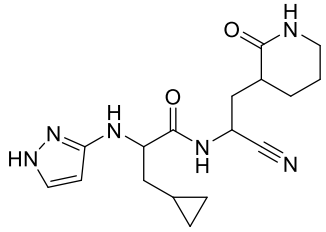
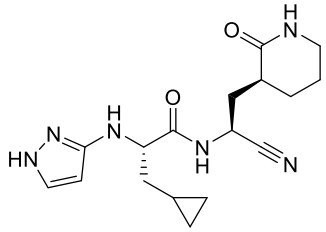
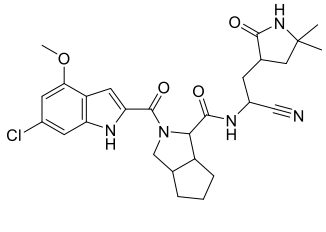
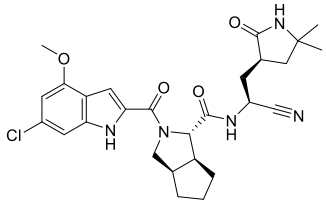
,

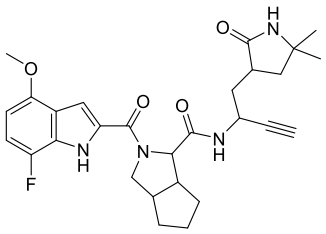
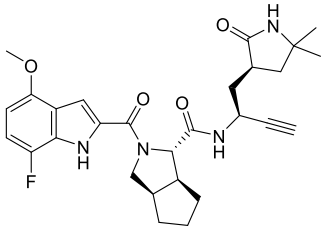
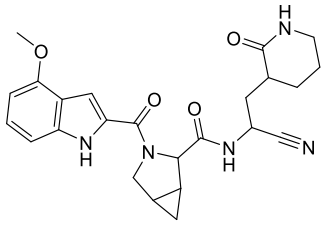
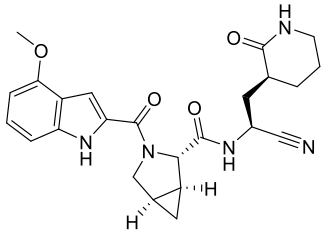
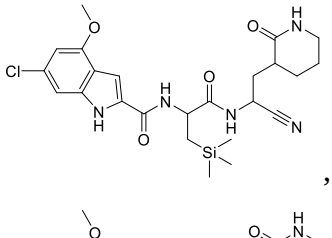
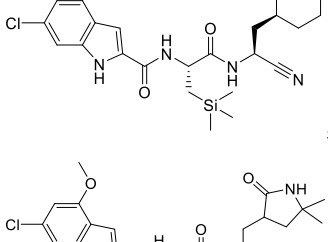
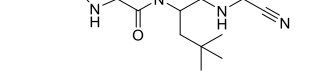

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

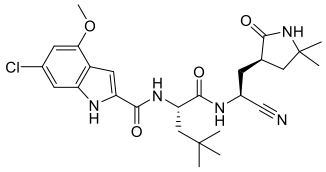
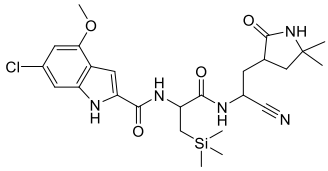
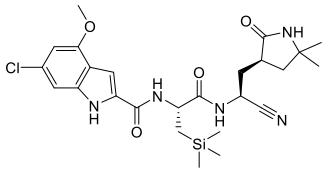
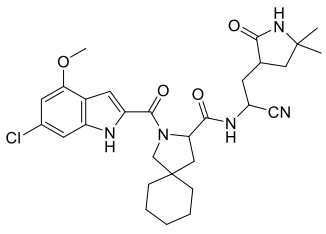
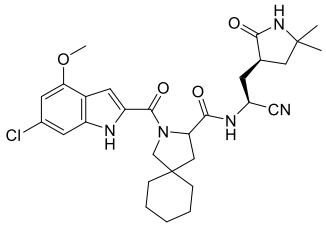
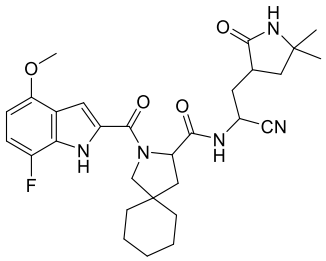
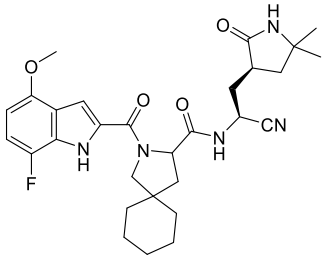
,

,

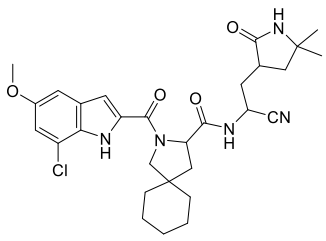
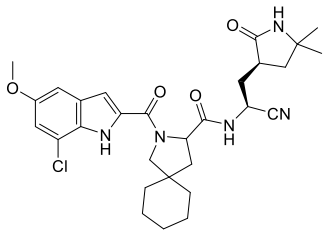
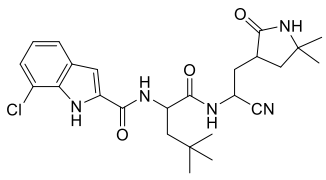
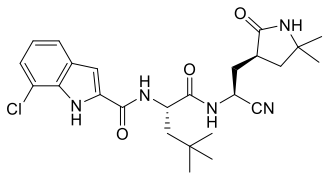
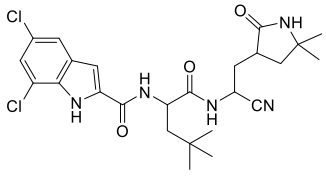
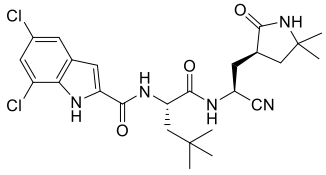
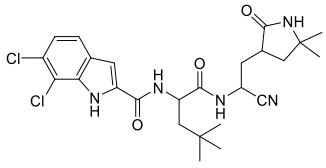
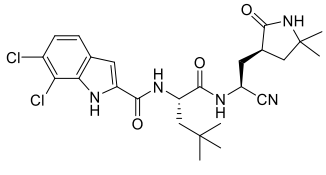
,

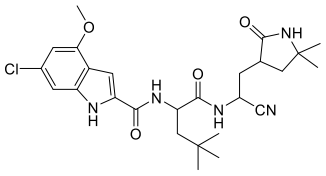
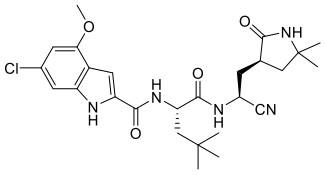
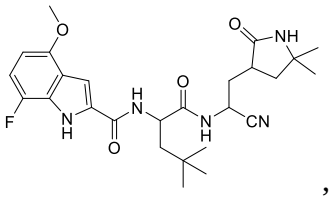
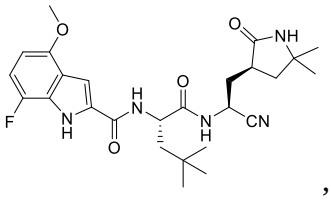
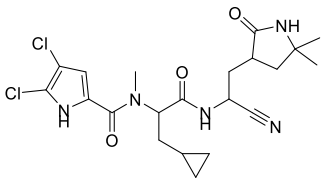
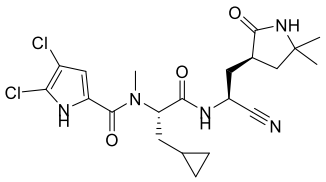
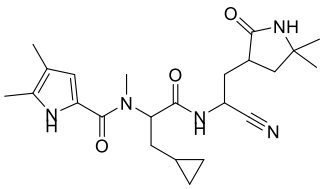
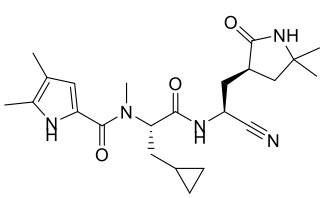

,

,

,

,

,

,

,

,

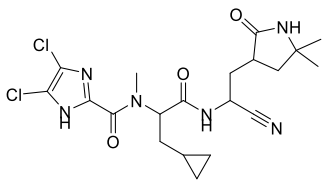
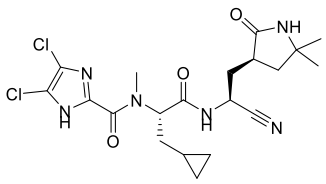
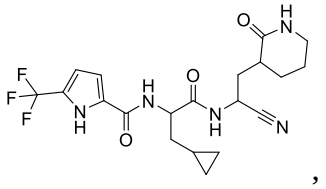
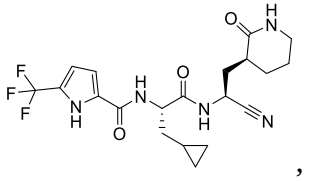
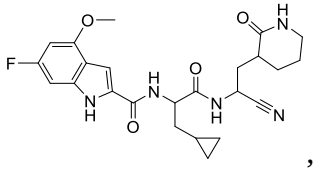
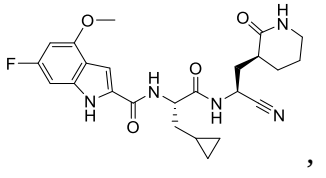
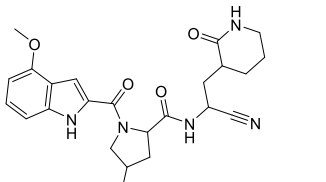
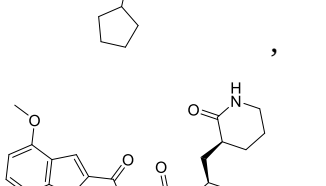
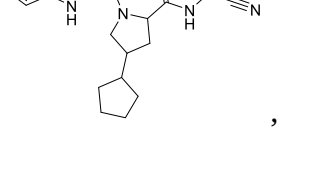

,

,

,

,

,

,

,

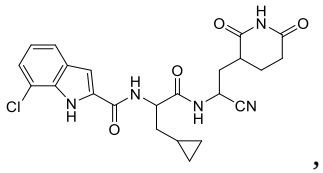
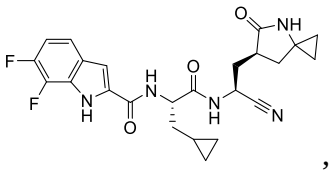
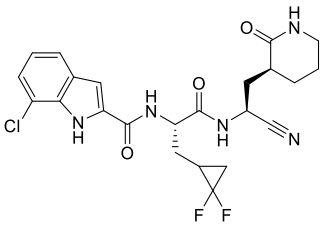
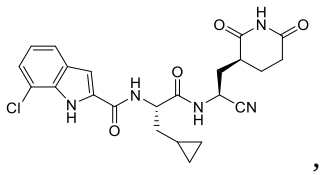
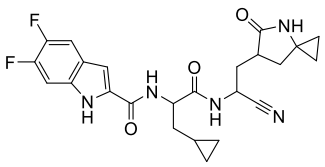
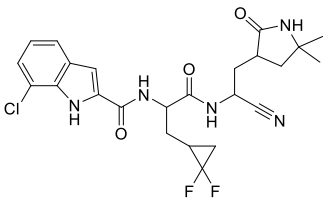
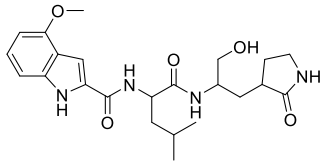
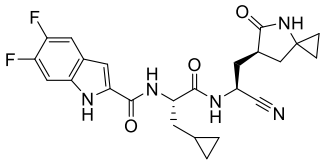
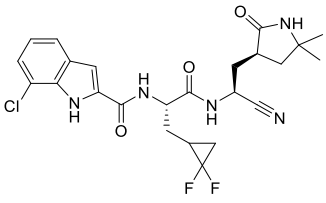
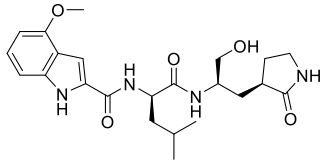
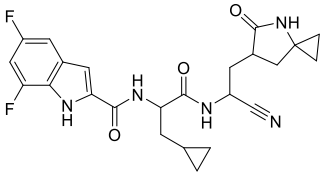
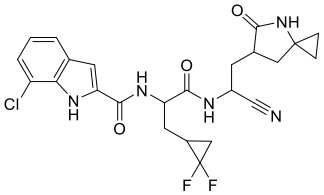
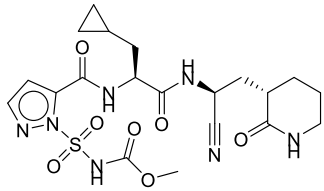
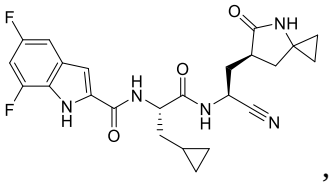
,

,

,

,

,

,

,

,

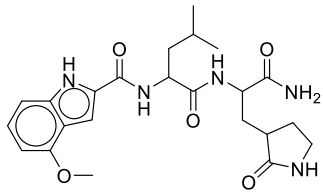
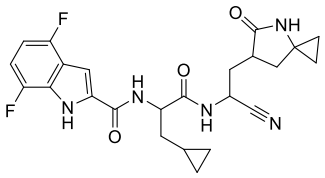
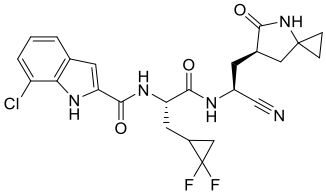
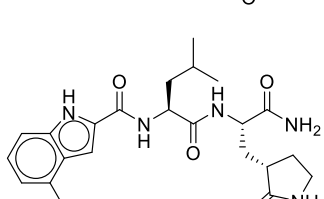
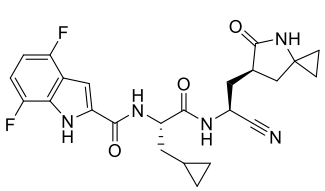
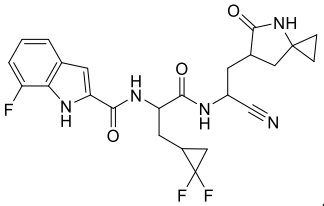
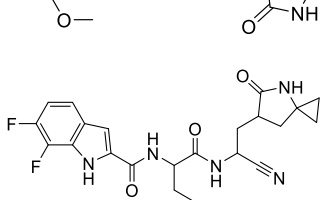
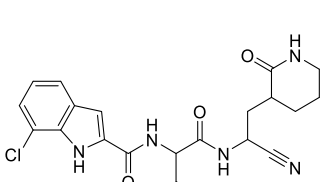
,

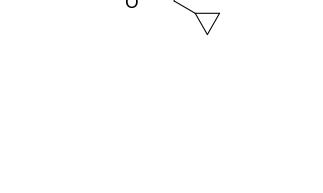
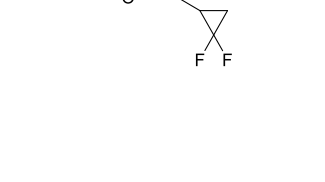
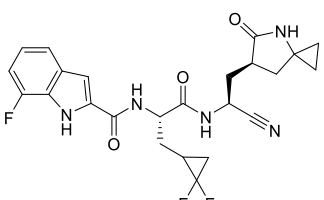

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

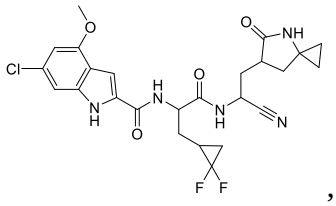
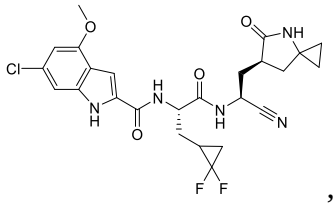
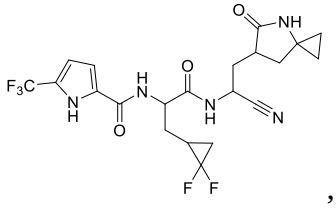
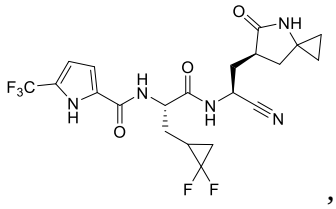
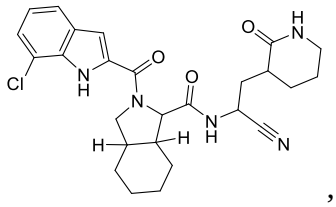
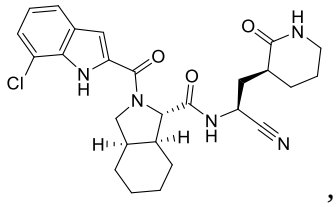
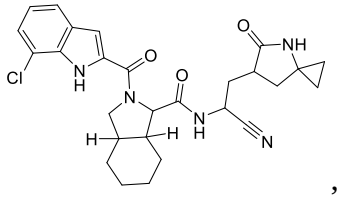
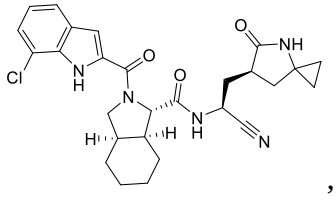
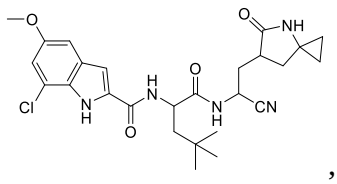
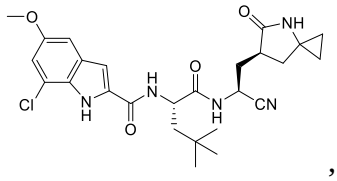
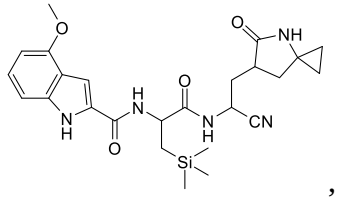
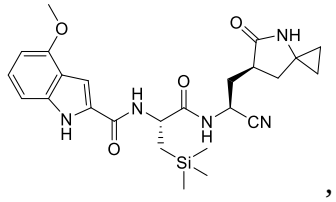
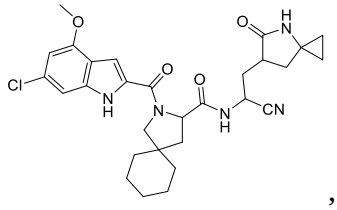
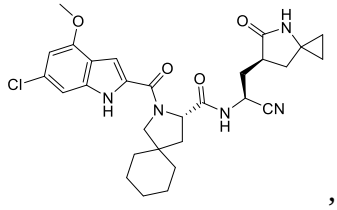
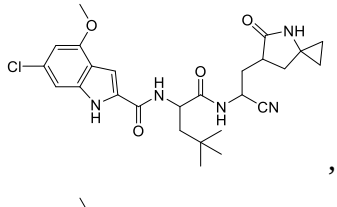
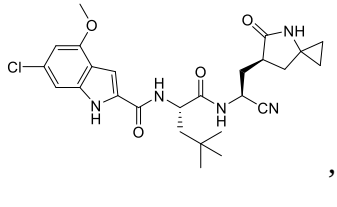
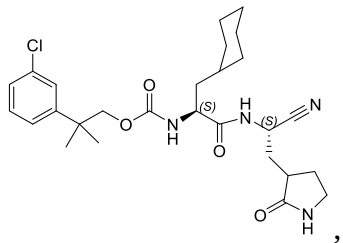
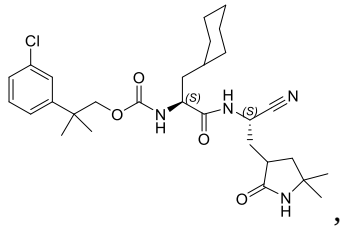
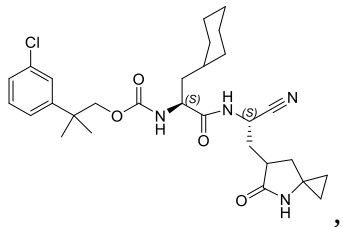
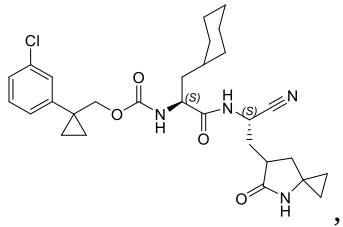
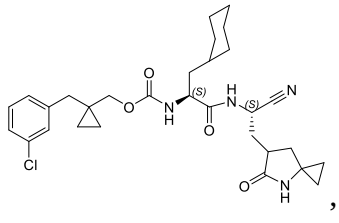
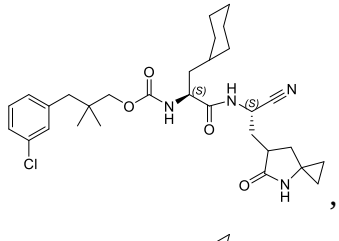
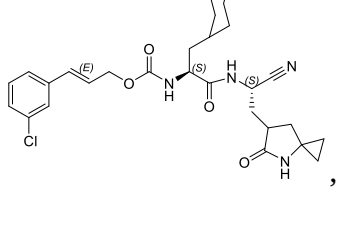
,

,

,

,

,

,

,

,

,

,

,

,

,

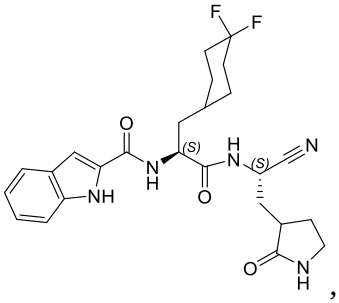
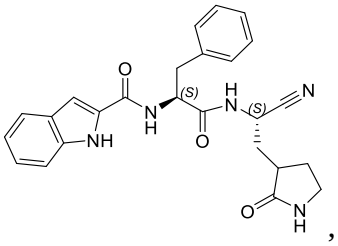
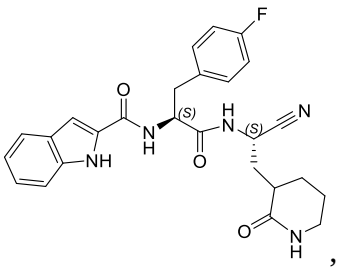
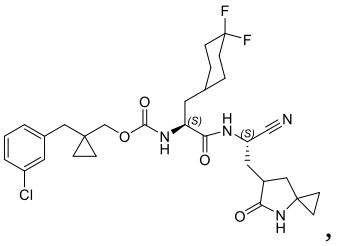
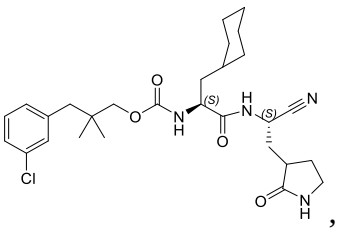
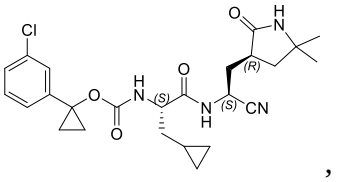
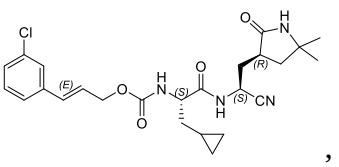
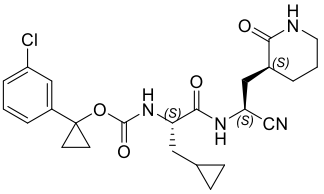
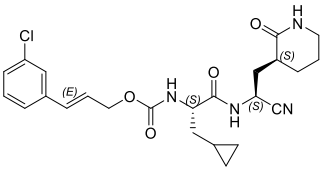
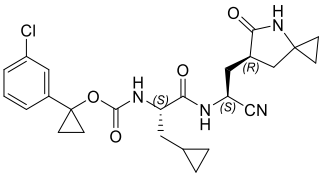
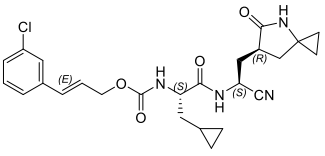
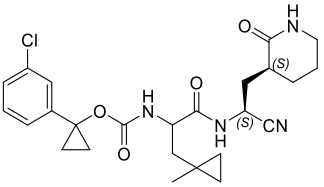
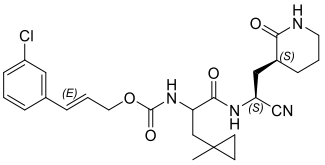
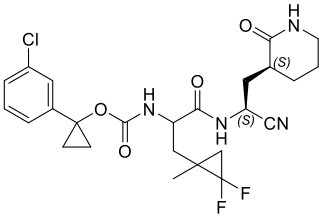
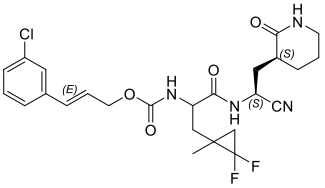
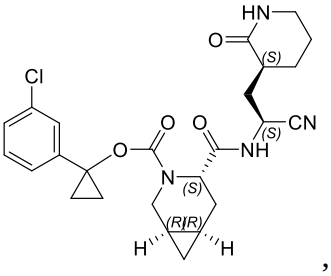
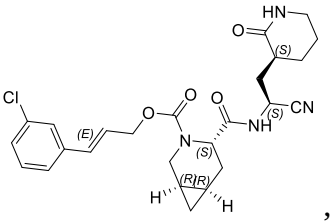
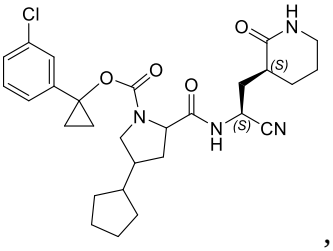
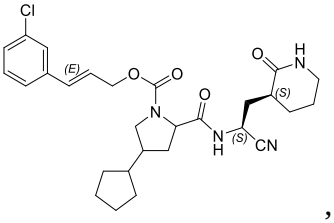
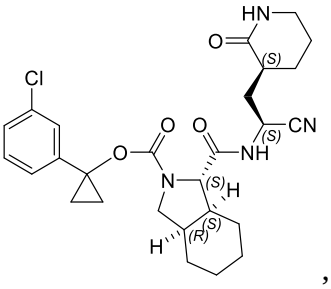
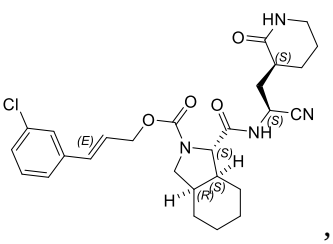
,

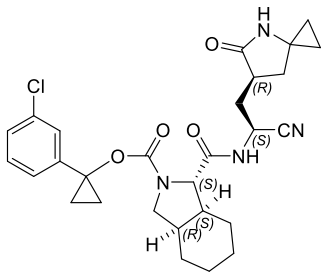
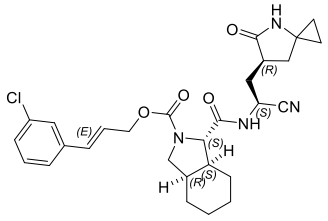
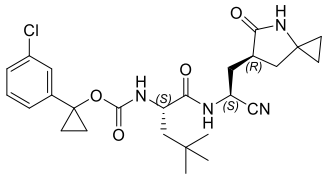
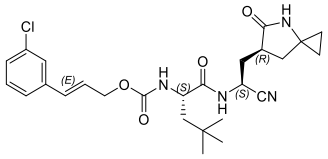
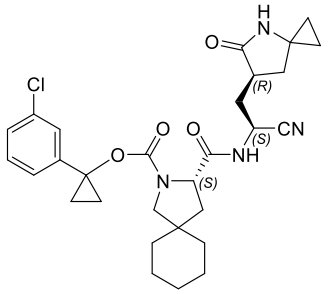
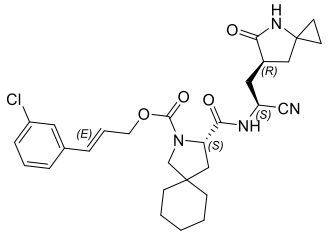
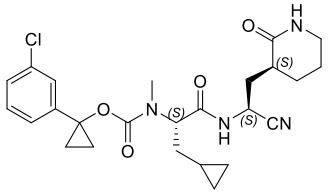
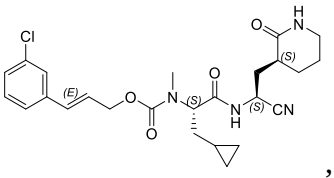
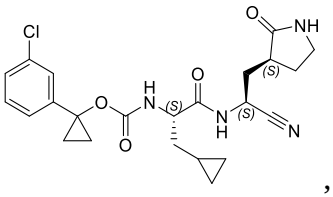
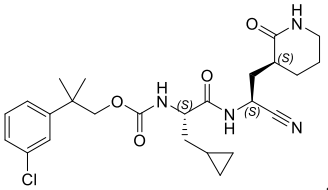
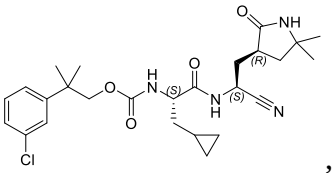
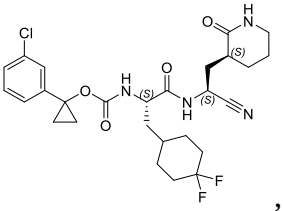
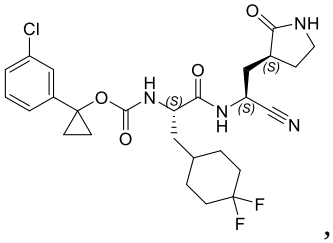
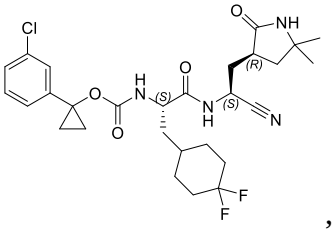
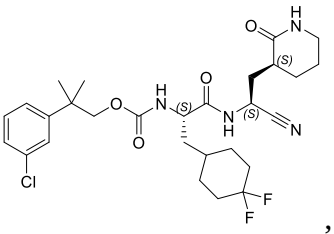
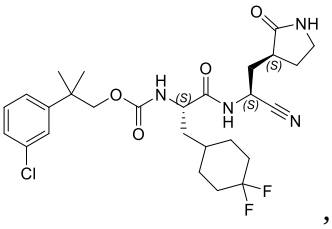
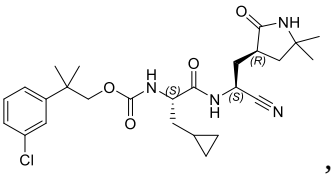
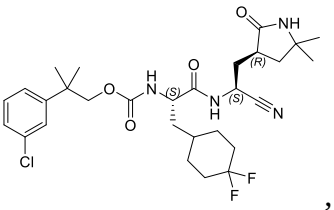
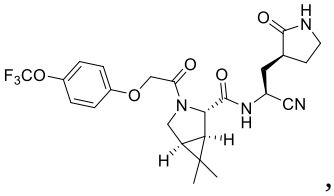
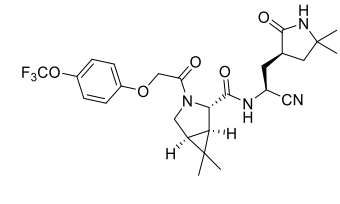
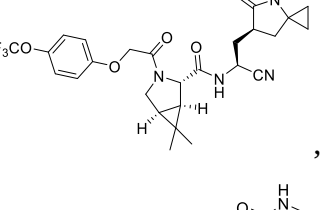
,

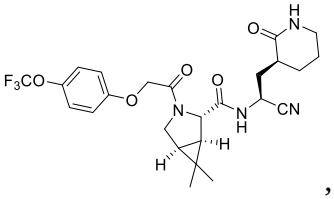
,

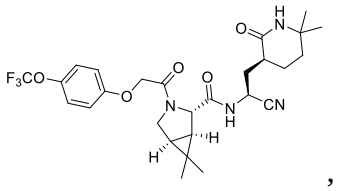
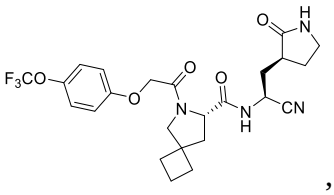
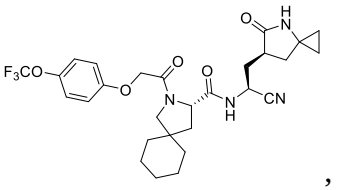
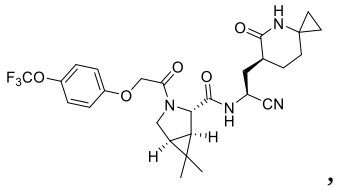
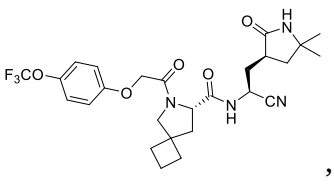
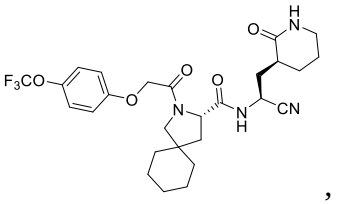
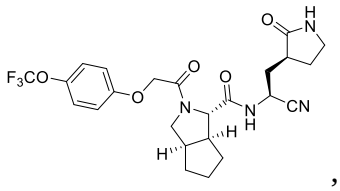
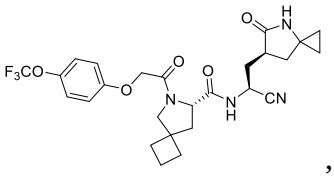
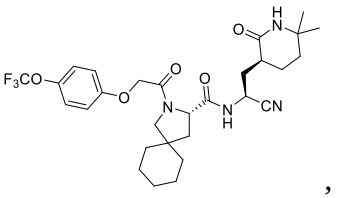
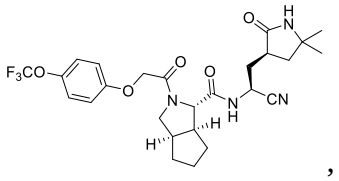
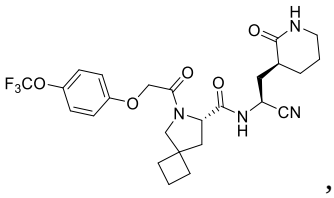
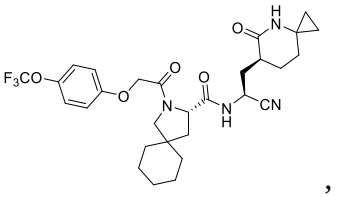
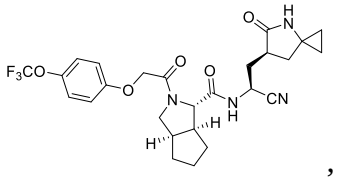
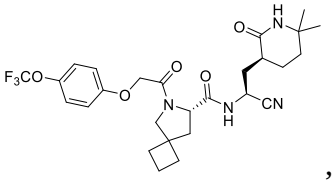
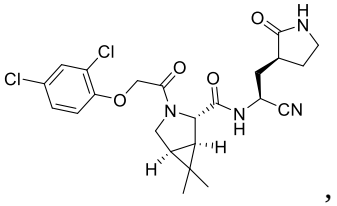
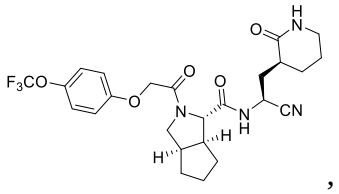
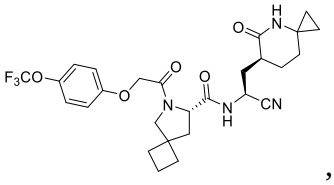
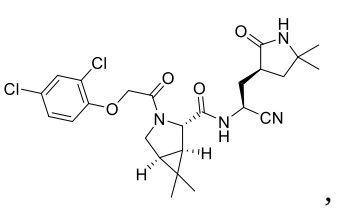
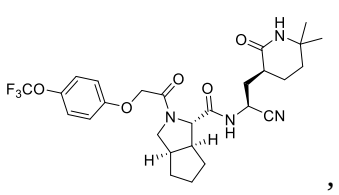
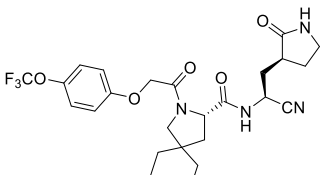

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

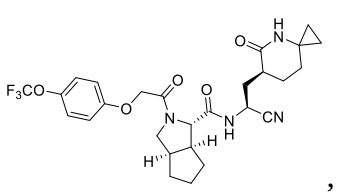
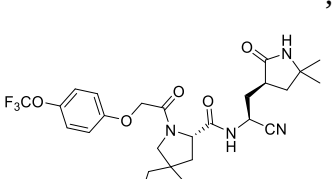
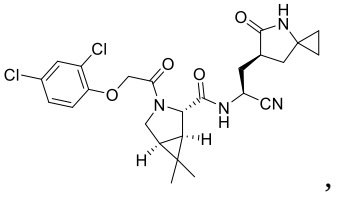
,

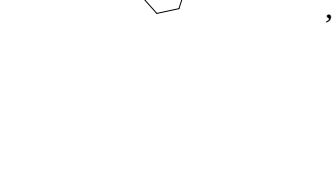
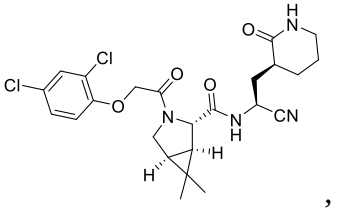
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,



,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

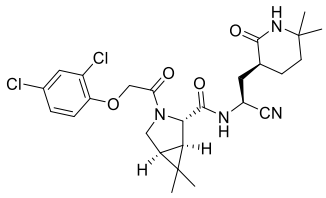
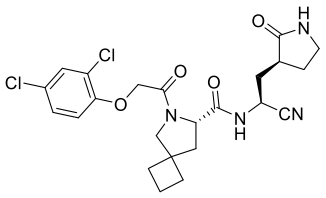
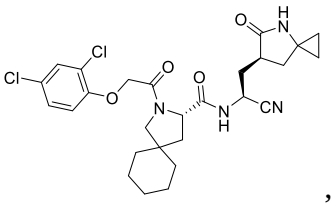
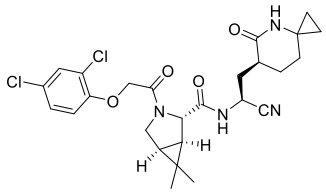
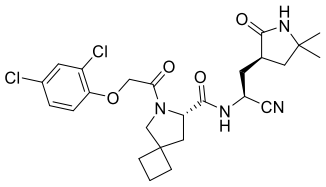
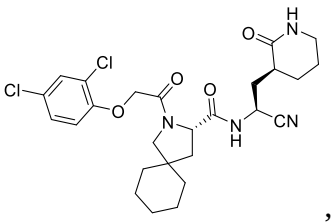
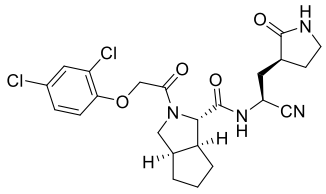
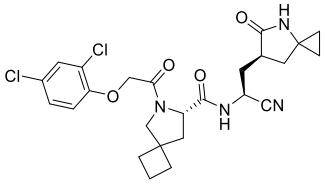
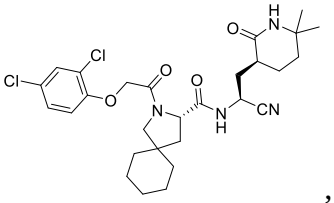
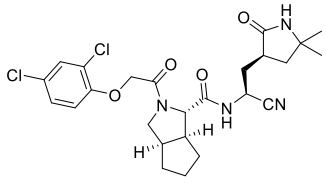
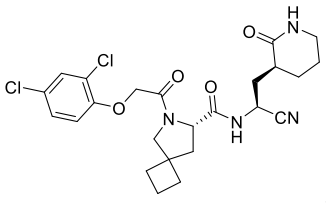
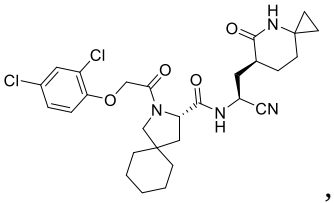
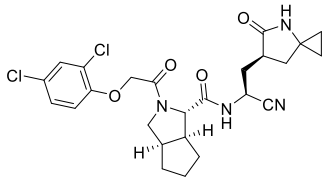
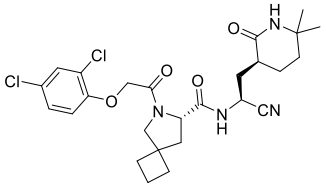
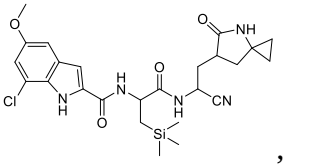
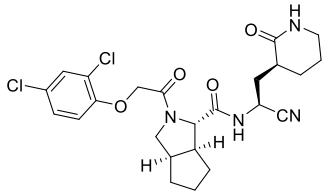
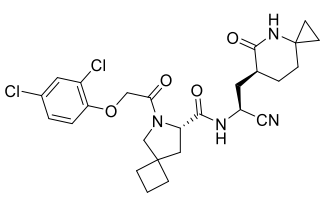
,

,

,

,

,

,

,

,

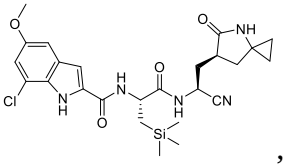
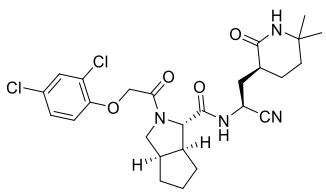
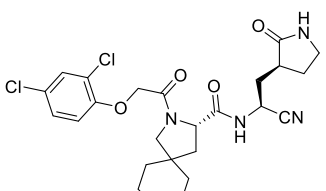
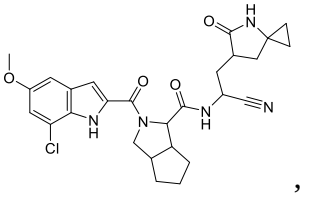
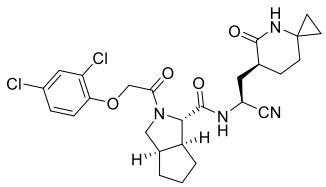
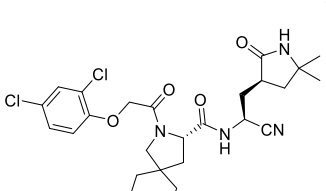
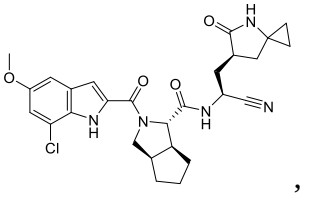
,

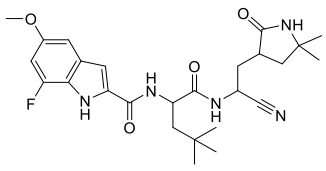
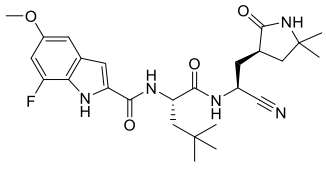
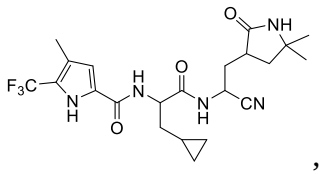
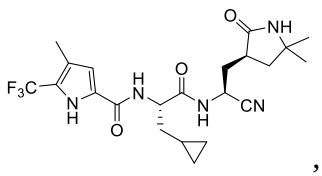
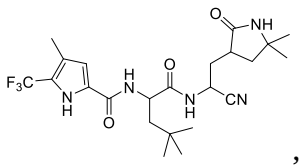
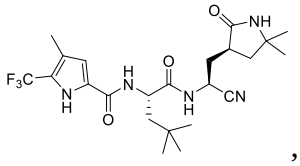
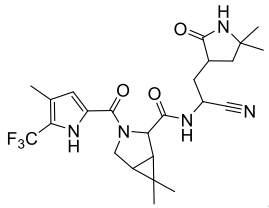
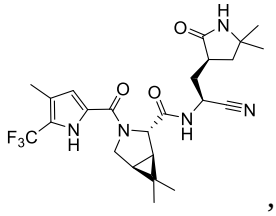
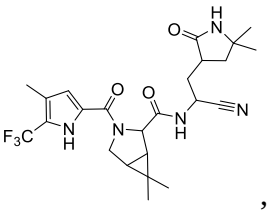
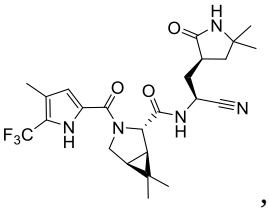
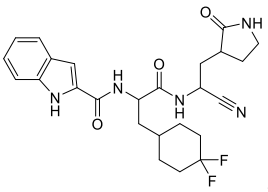
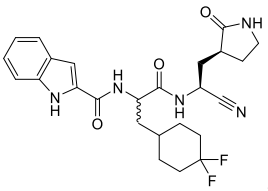
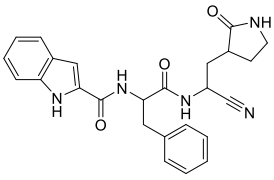
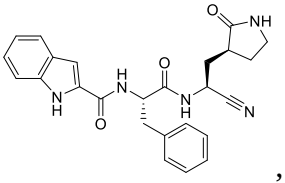
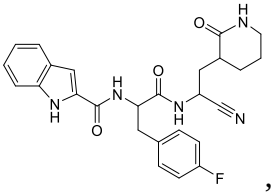
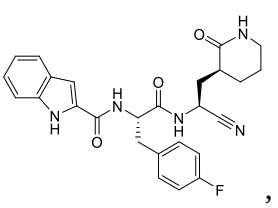
,

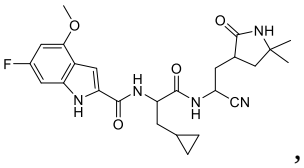
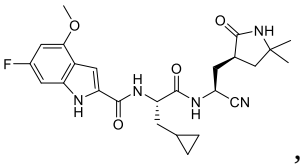
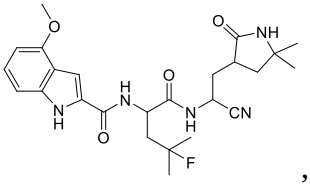
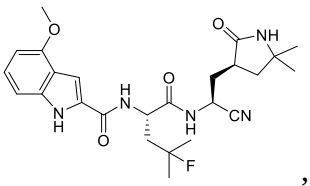
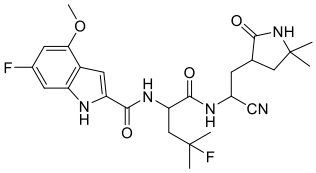
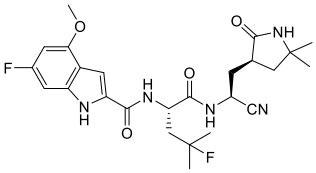
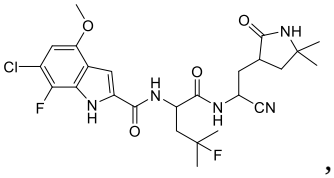
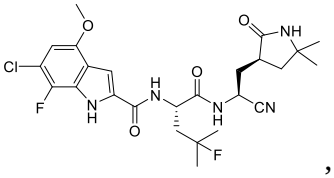
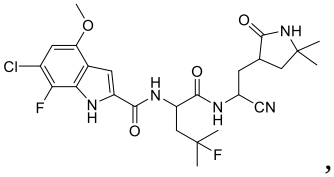

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

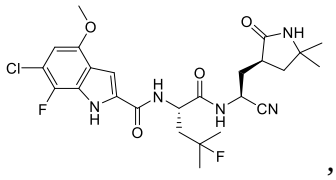
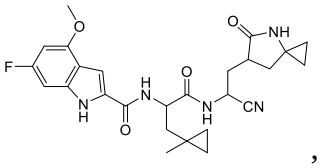
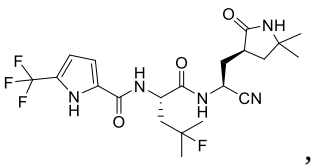
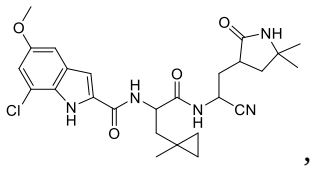
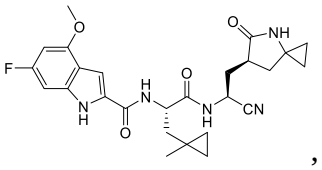
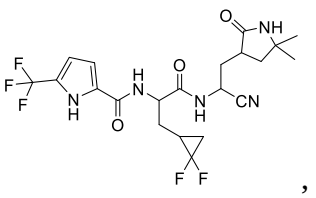
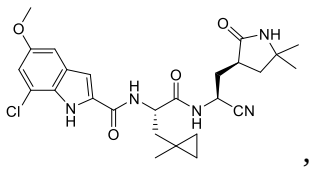
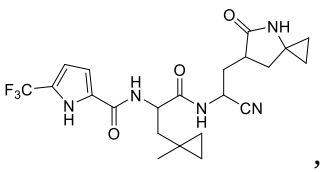
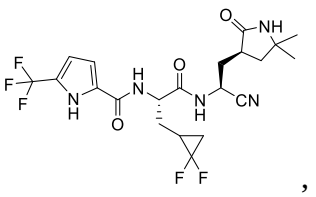
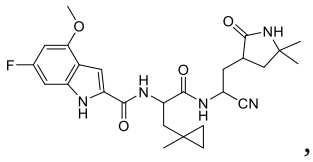
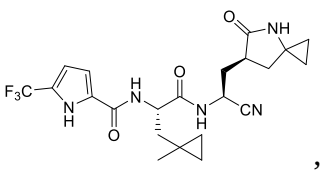
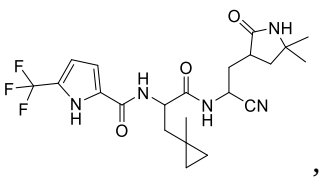
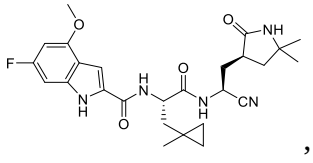
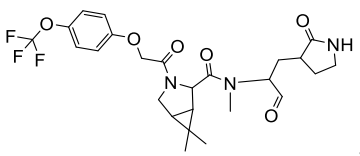
,

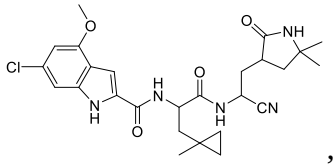
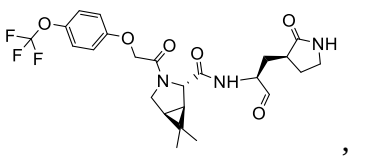
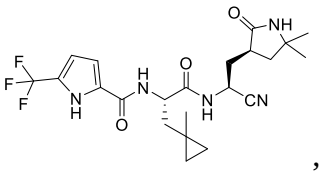
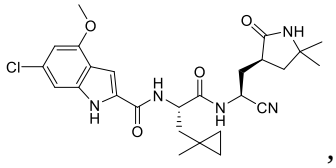
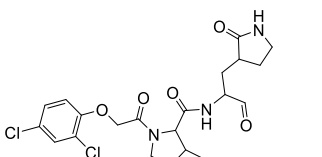
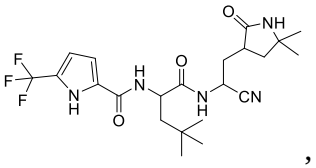
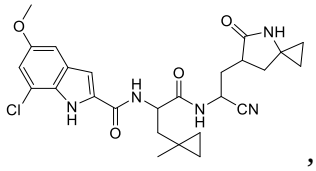
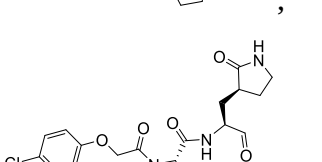
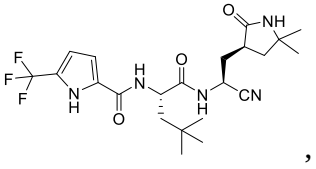
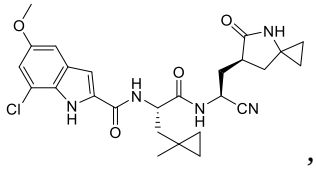
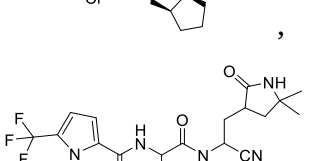
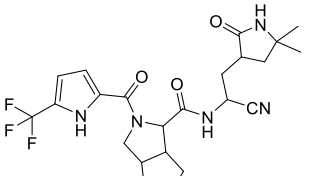
,

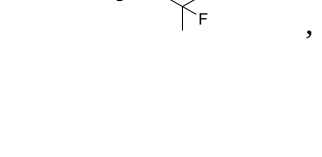
,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

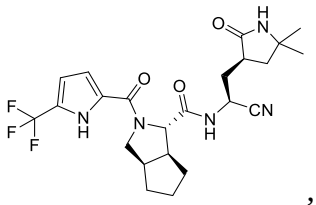
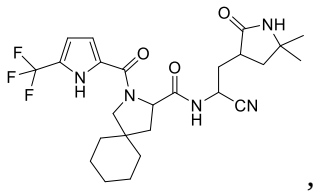
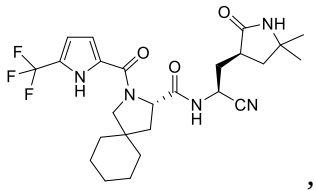
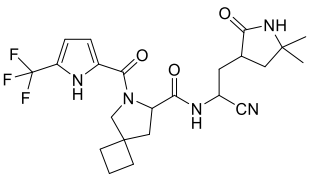
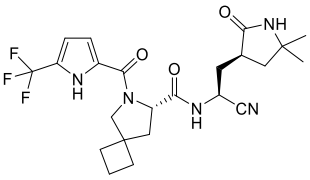
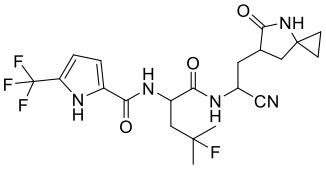
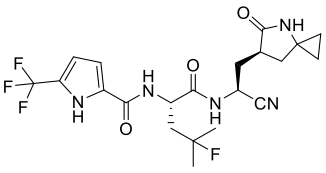
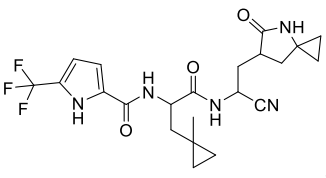
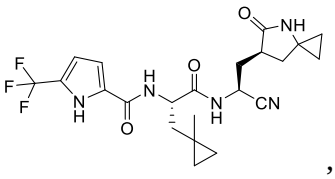
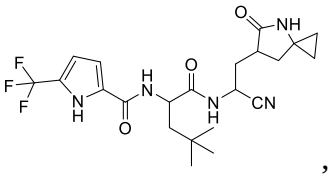
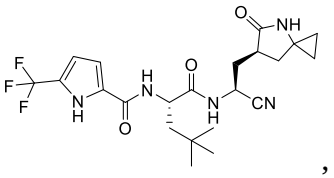
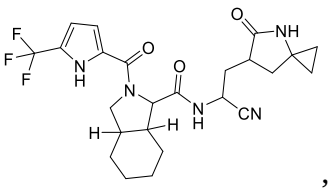
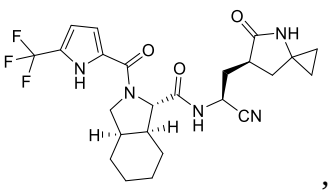
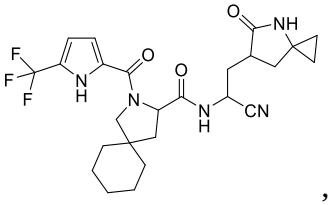
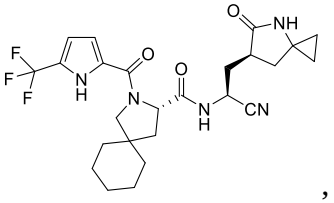
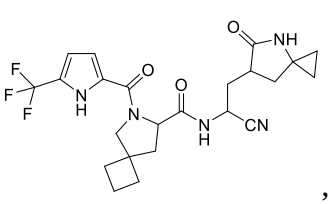
,

,

,

,

,

,

,

,

,


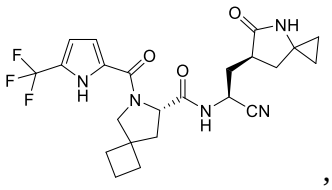
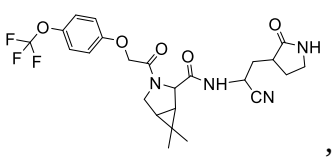
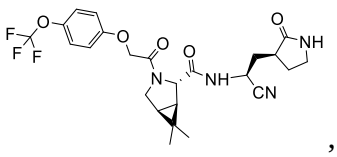
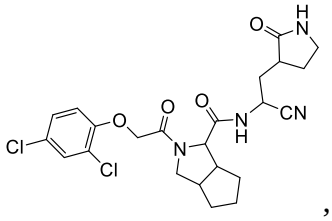
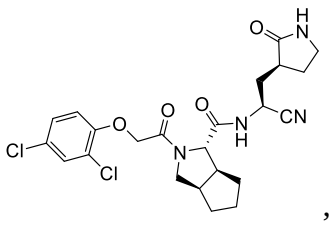
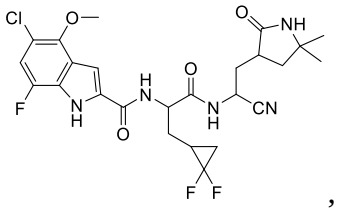

,

,

,

,

,

,

,

,

,

,

,

,

,

,

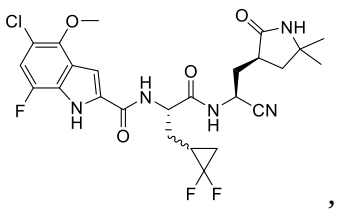
,

,

,

,

,

,

,

,

,

,

,

,

,

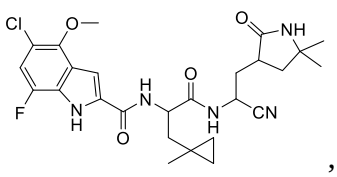
,

,

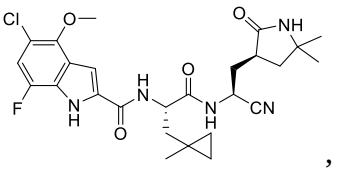
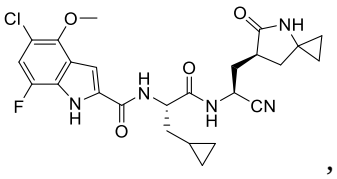
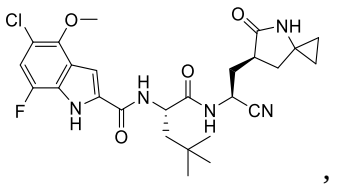
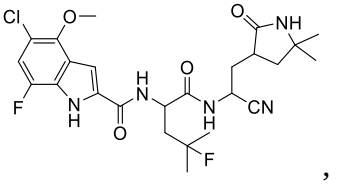
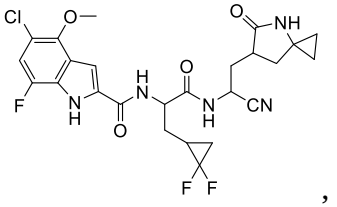
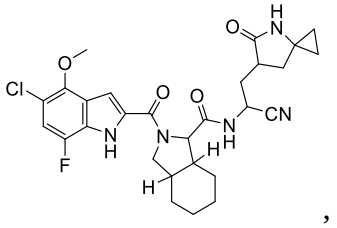
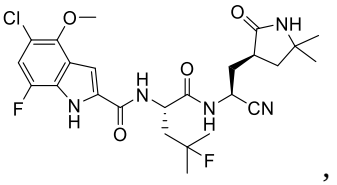
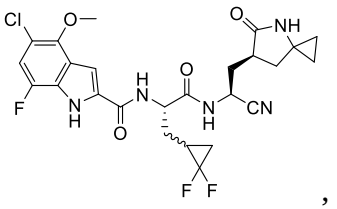
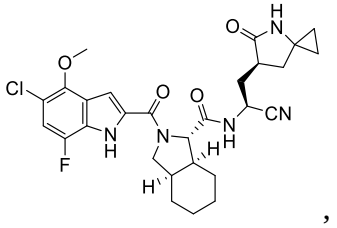
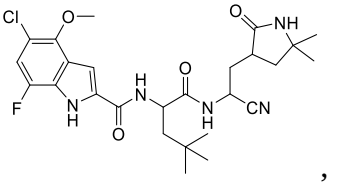
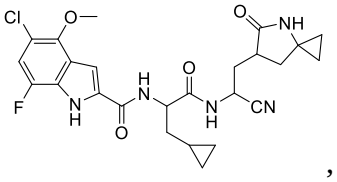
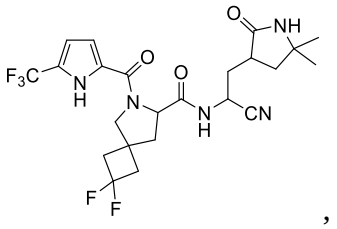
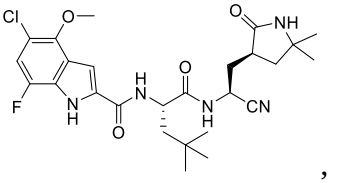
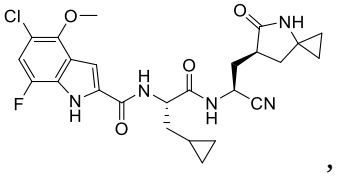
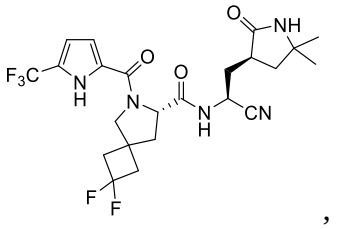
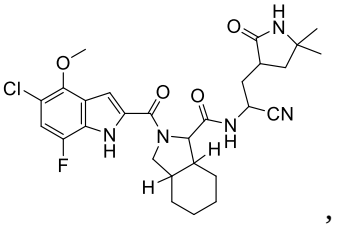
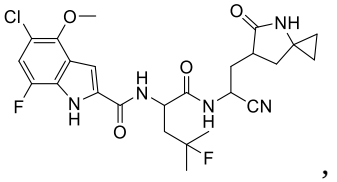
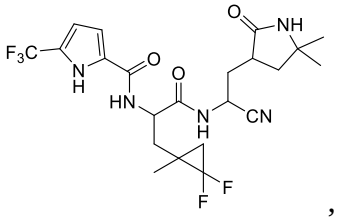
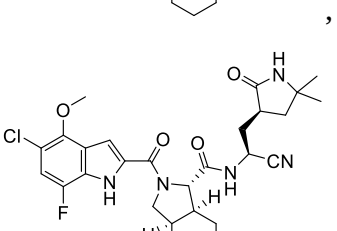
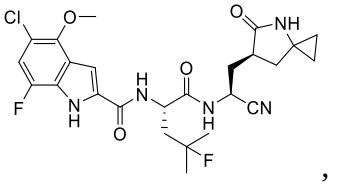
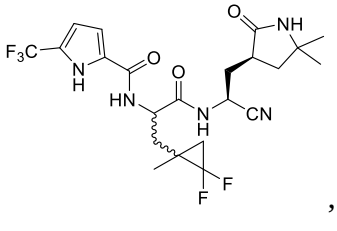
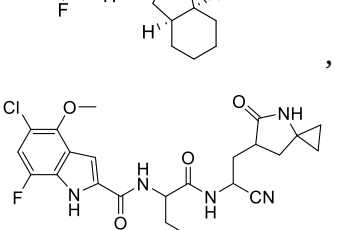
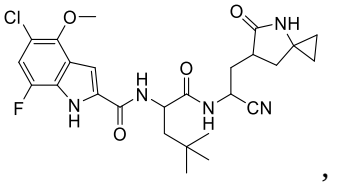
,

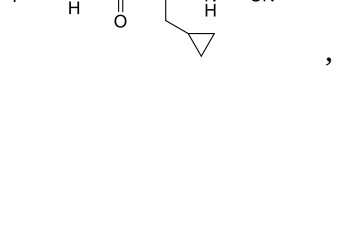

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

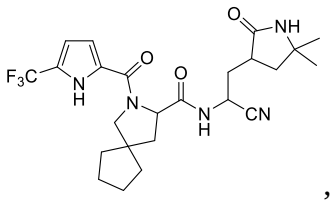
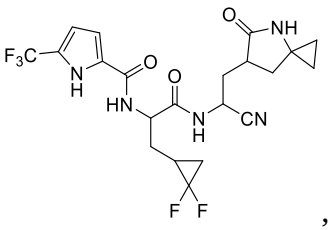
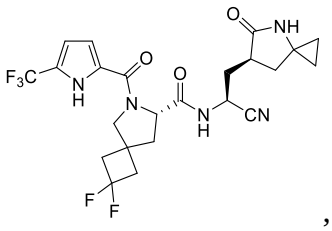
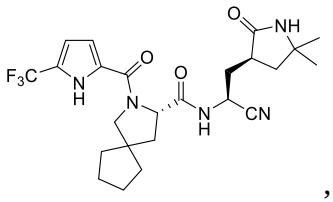
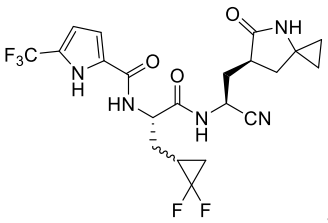
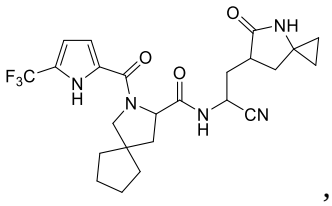
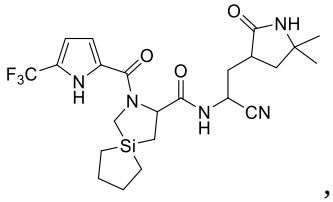
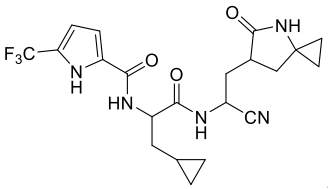
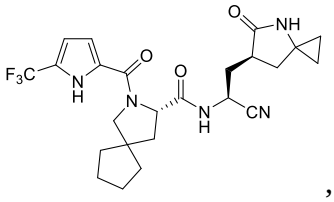
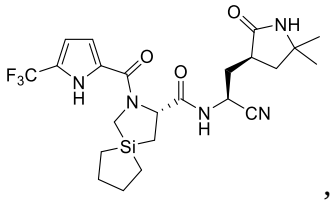
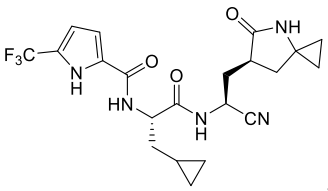
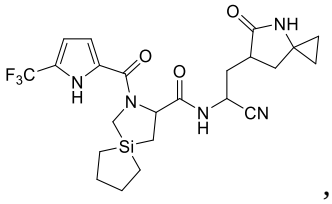
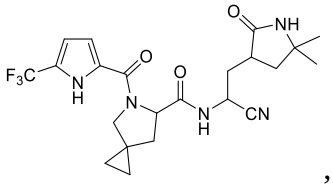
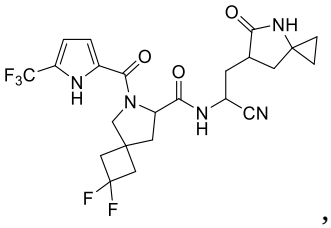
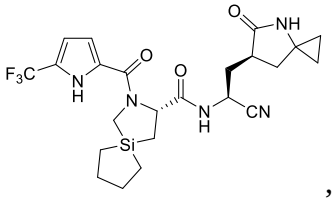
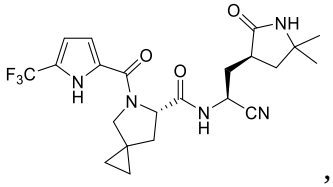
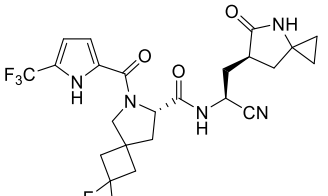
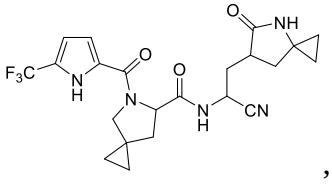
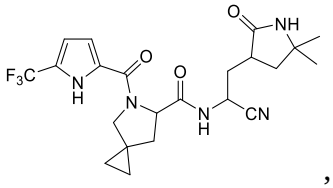
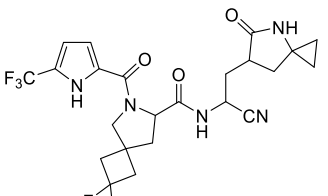
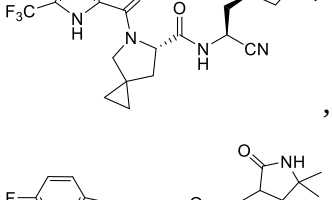
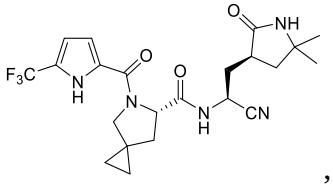
,

,

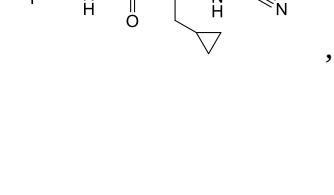
,

,

,

,

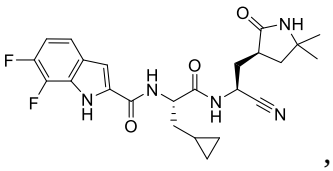
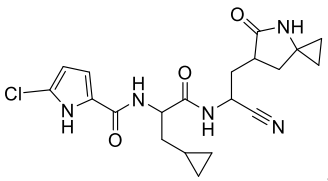
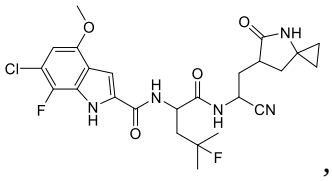
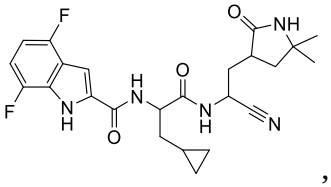
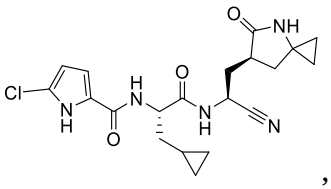
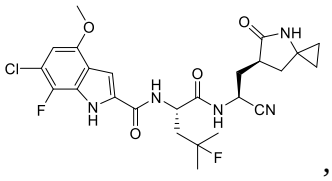
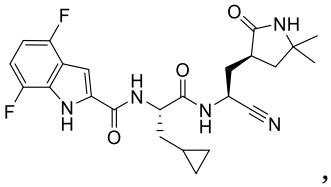
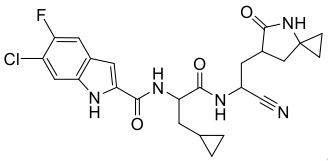
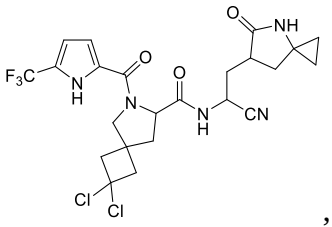
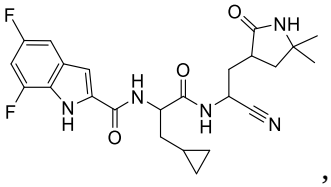
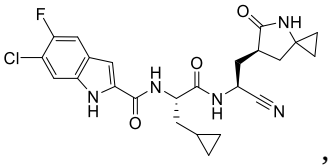
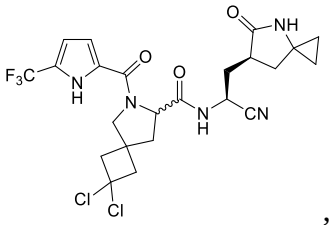
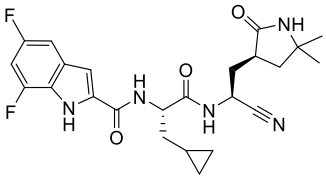
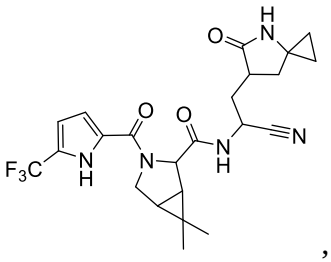

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

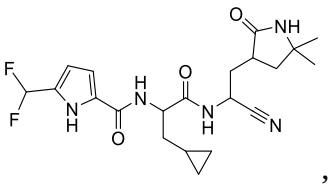
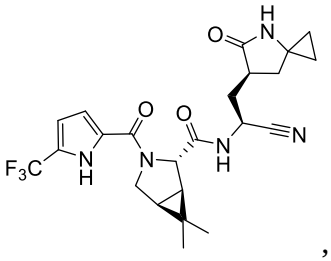
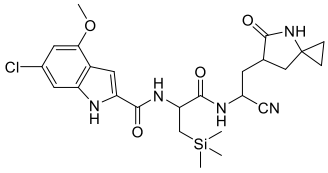
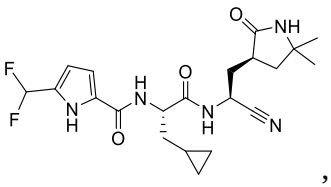
,

,

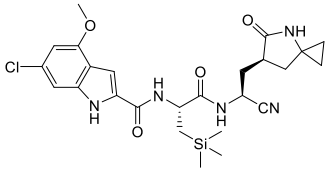
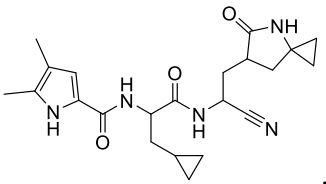
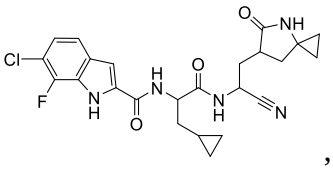
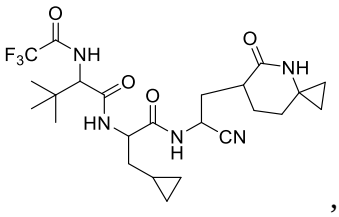
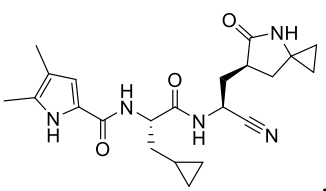
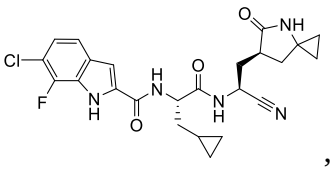
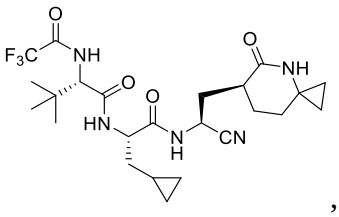
,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

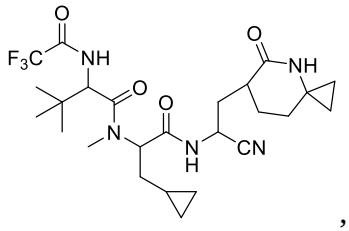
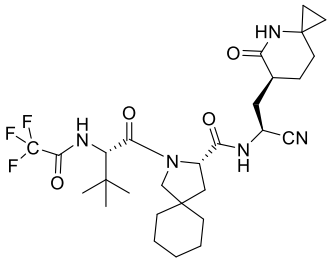
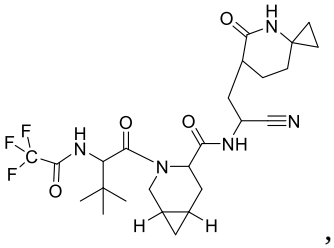
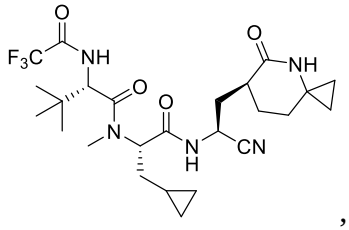
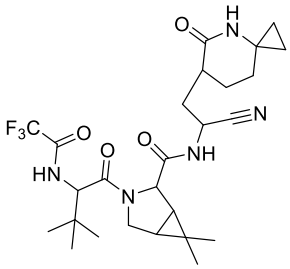
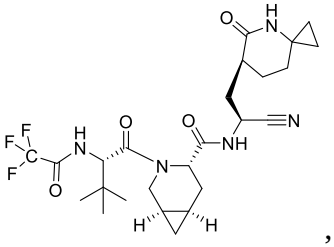
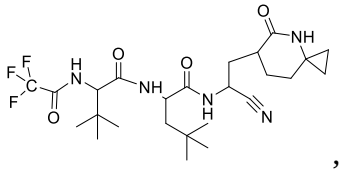
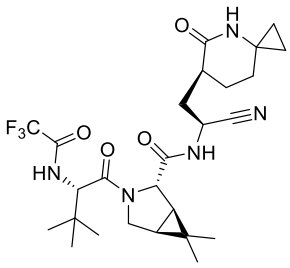
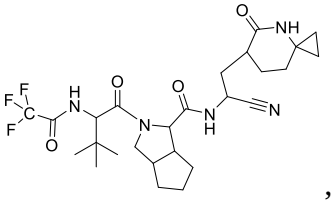
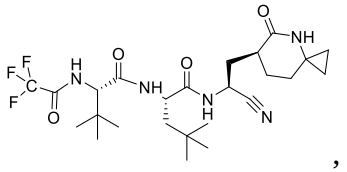
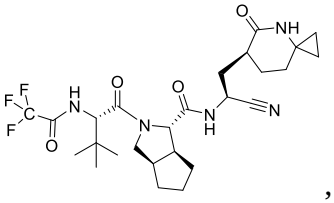
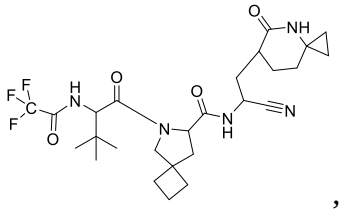
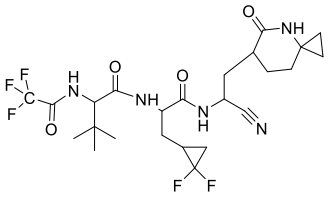
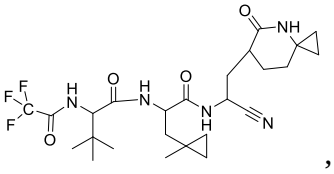
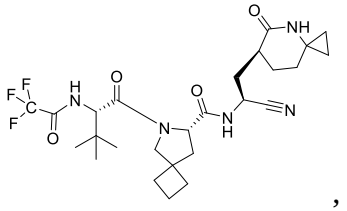
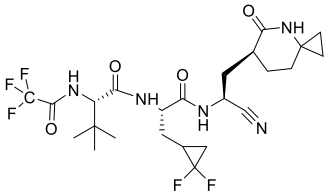
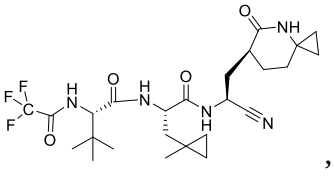
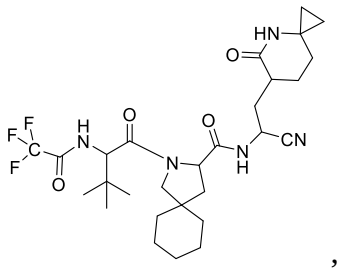
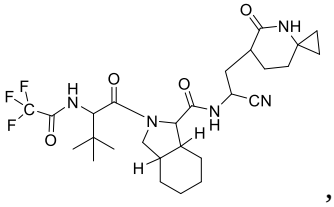
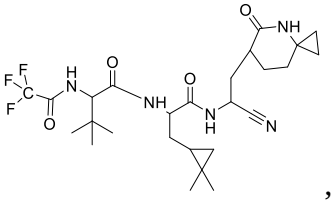
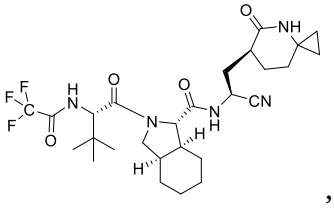
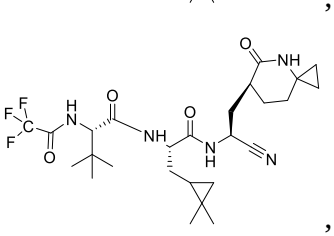
,

,

,

,

,

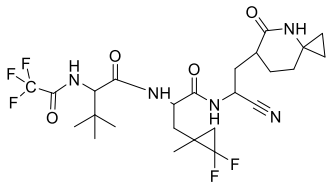
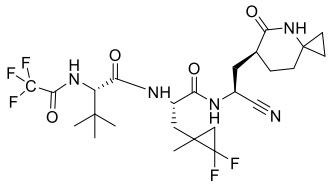
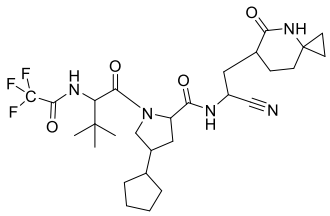
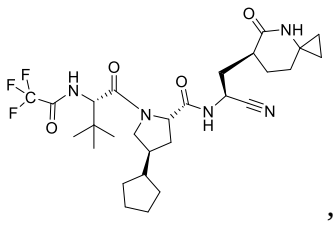
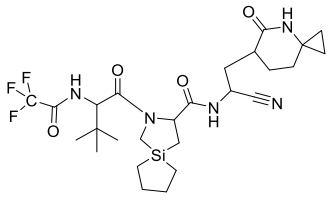
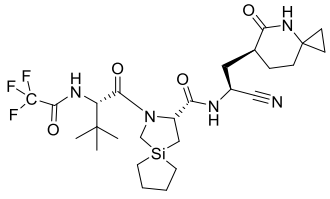
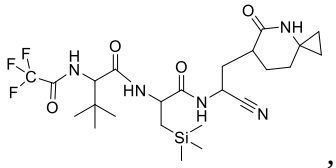
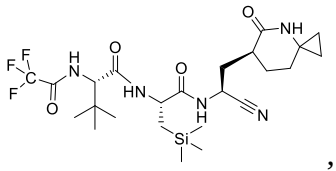
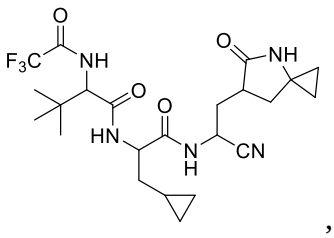
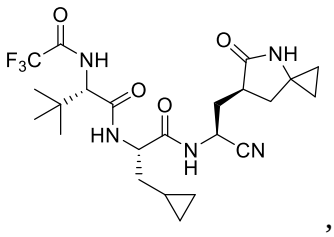
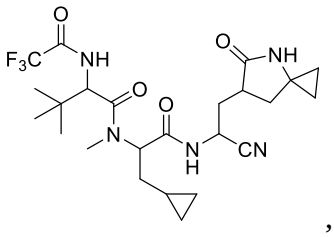
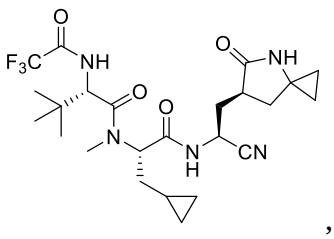
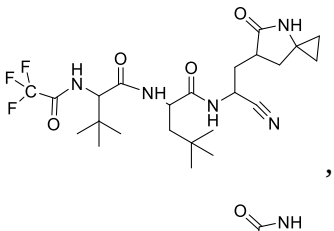
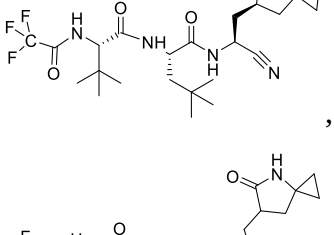
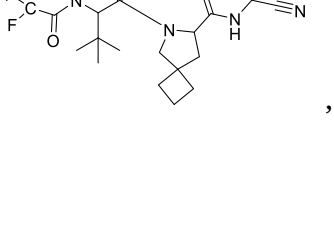
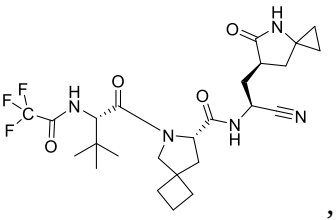
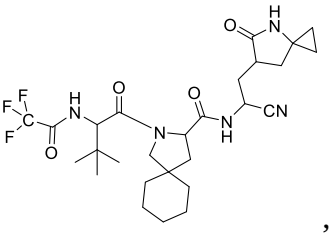
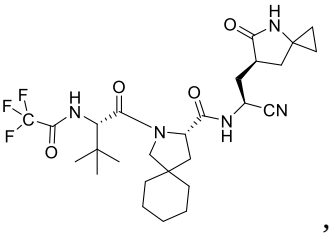
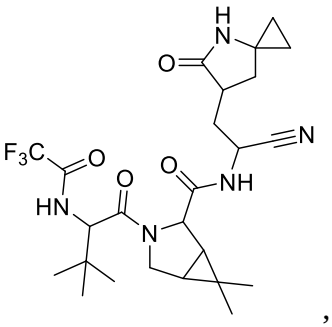
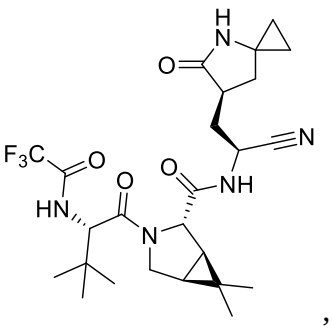
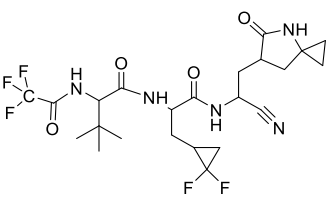
,

,

,

,

,

,

,

,

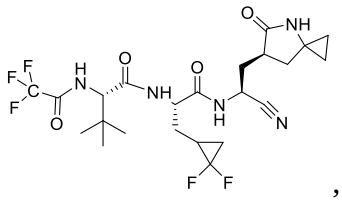
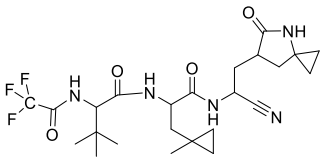
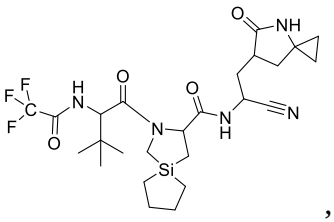
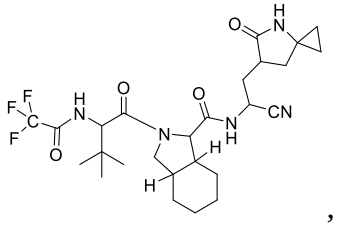
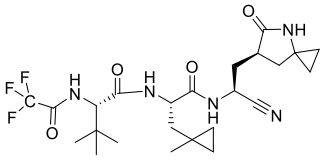
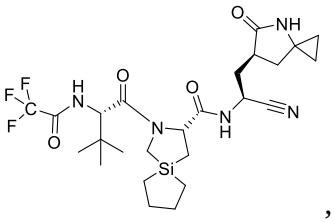
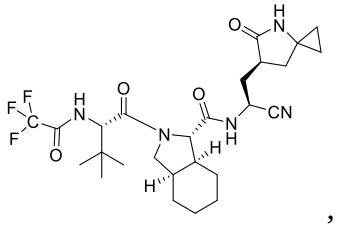
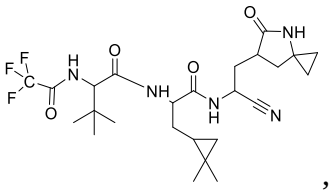
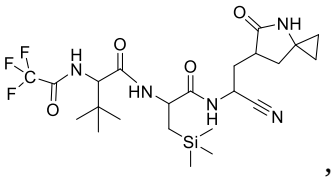
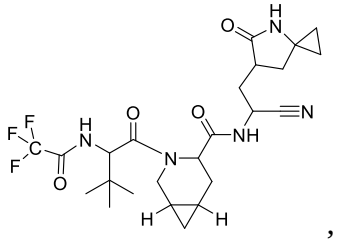
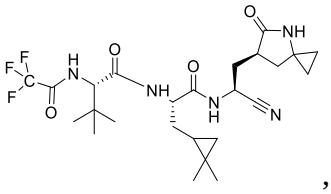
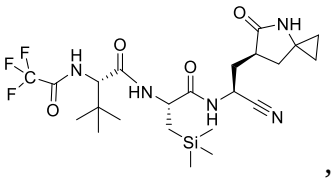
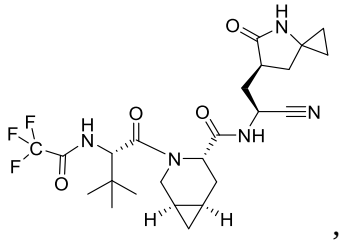
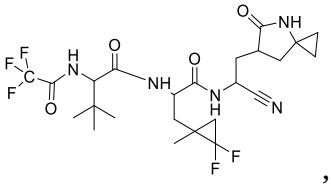
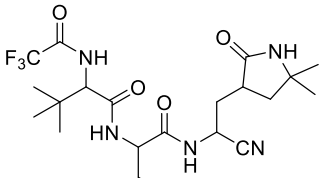
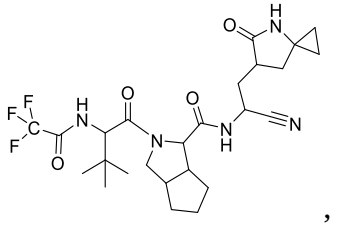
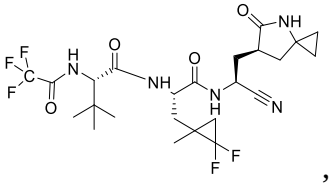
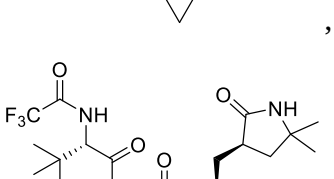
,

,

,

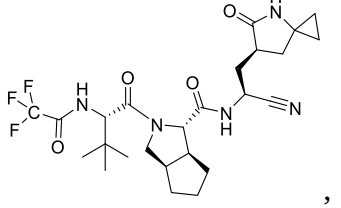
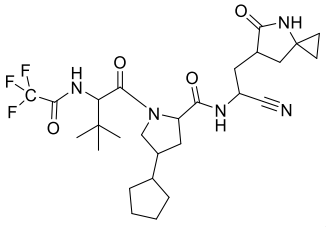
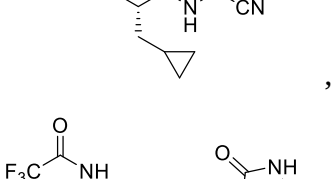

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

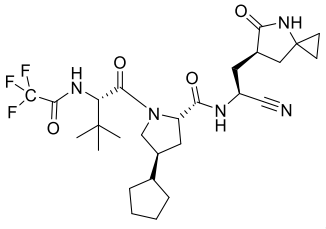
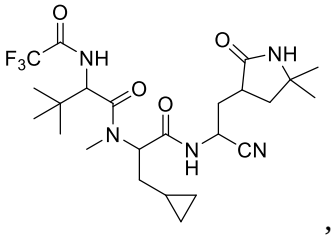

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

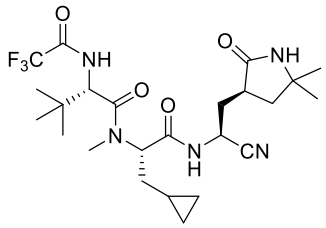
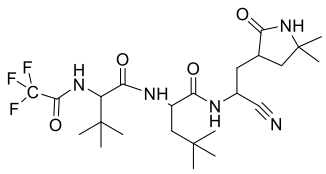
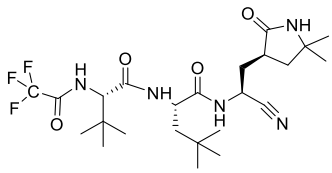
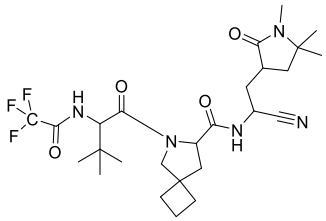
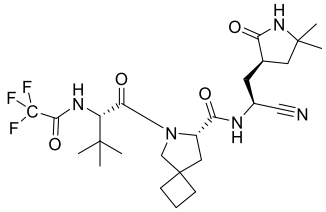
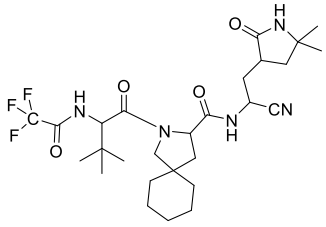
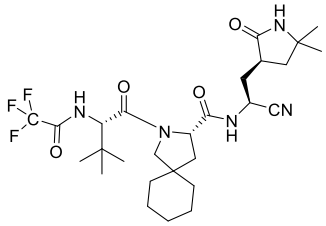
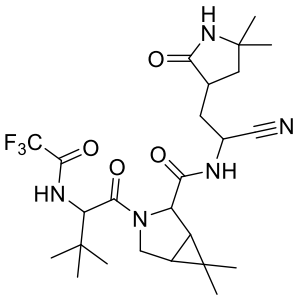
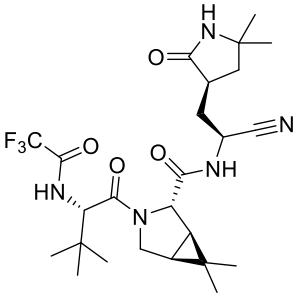
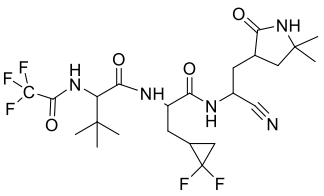
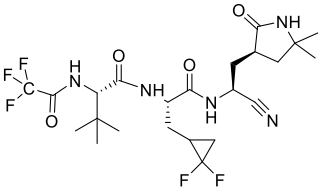
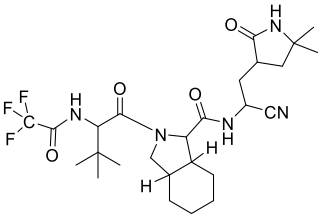
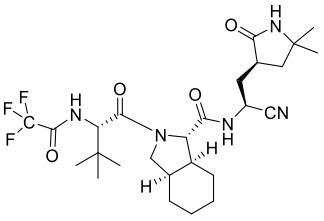
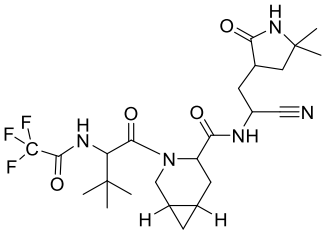
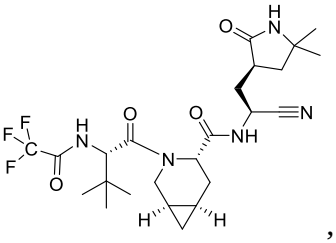
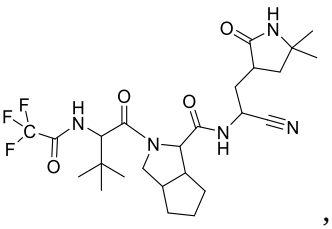
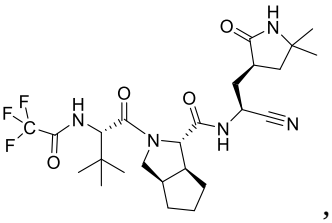
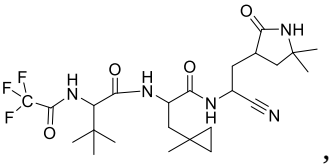
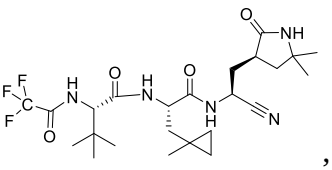
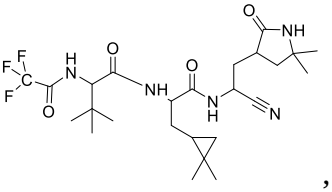
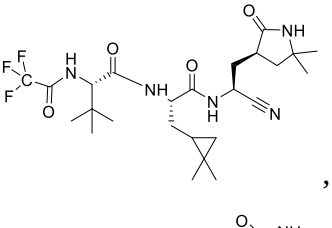
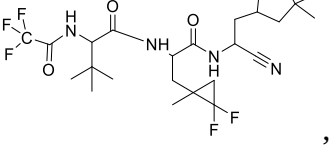

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

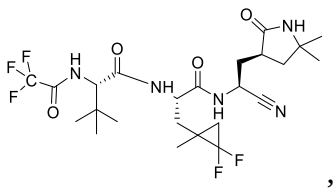
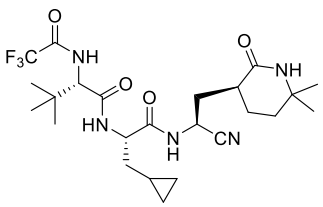
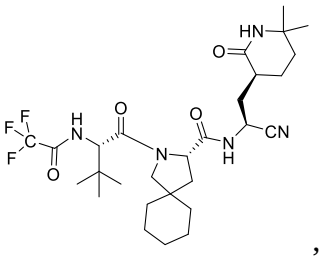
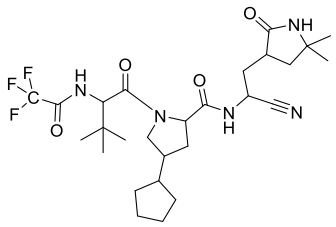
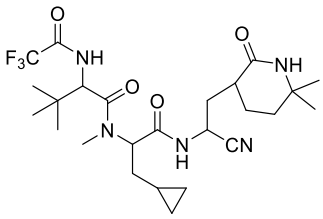
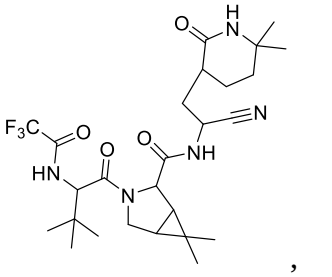
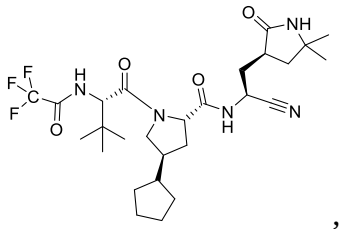
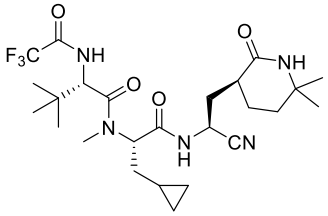
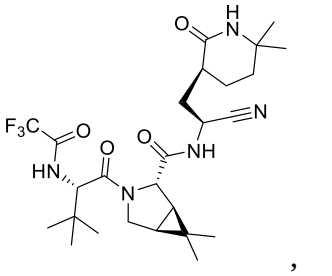
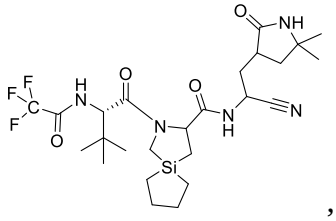
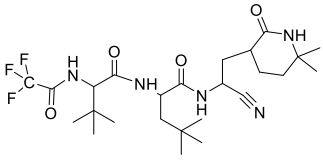
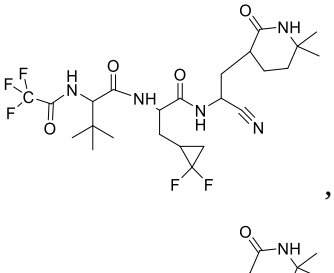
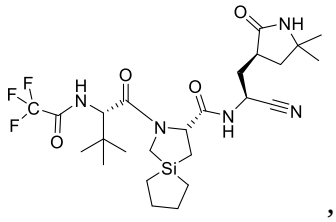
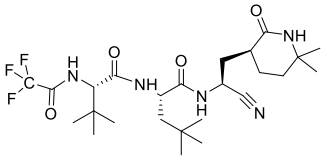
,

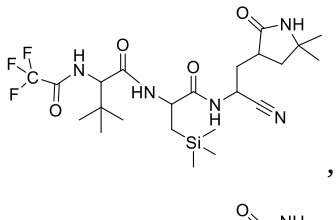
,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

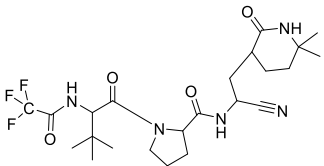
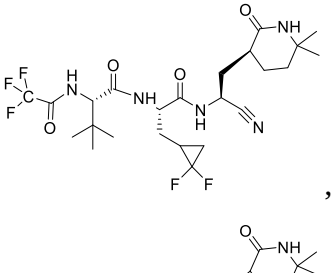
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

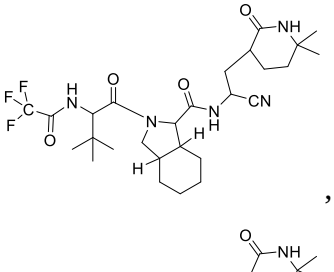
,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

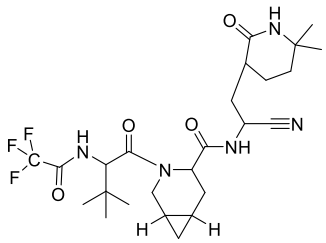
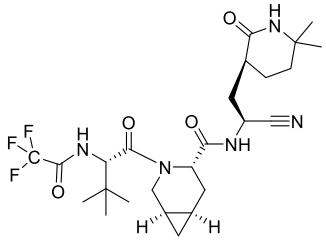
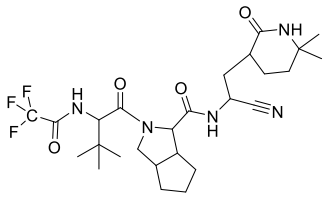
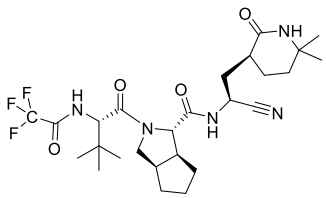
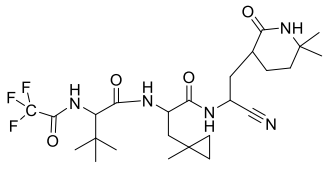
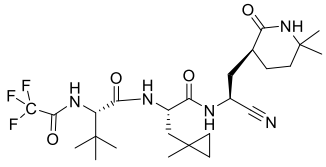
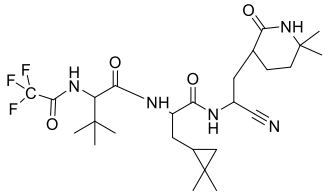
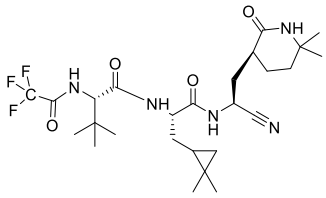
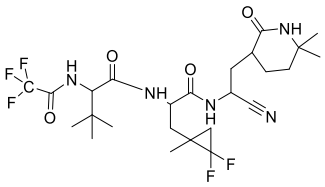
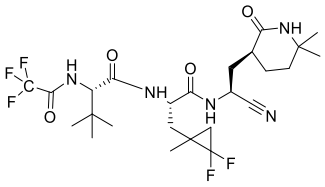
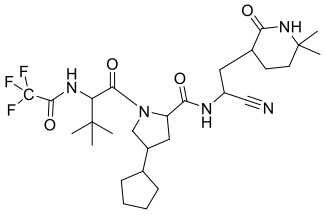
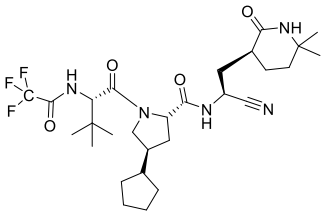
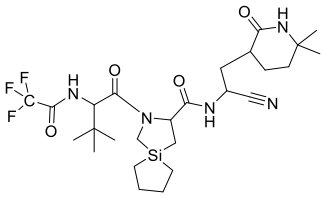
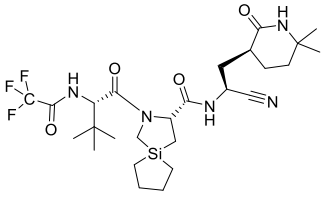
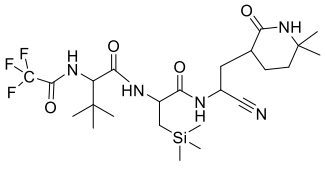
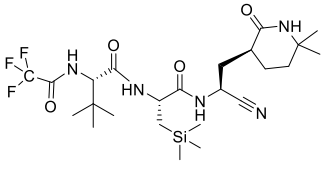
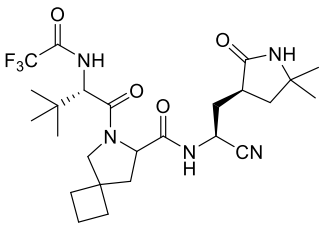
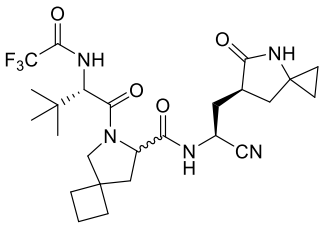
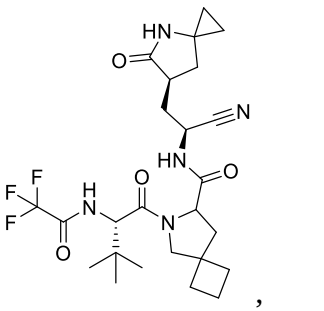
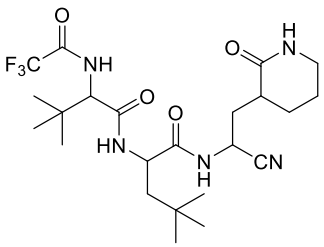
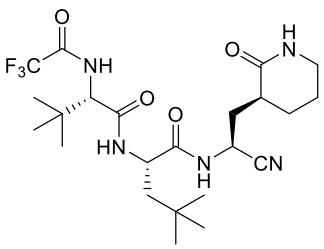
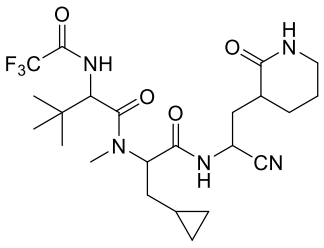
,

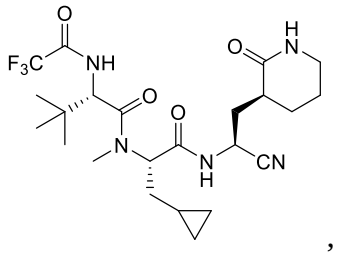
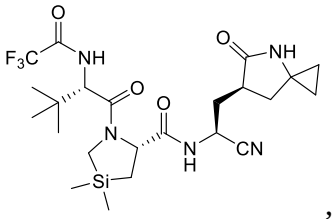
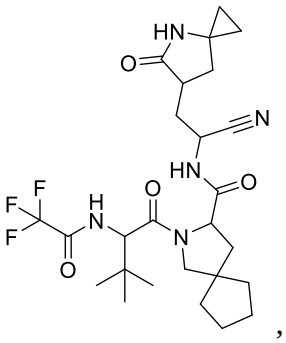
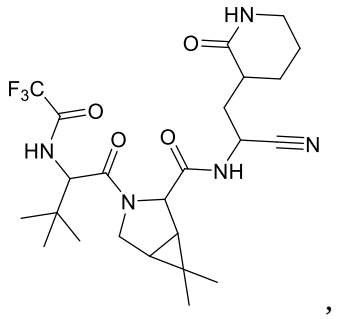
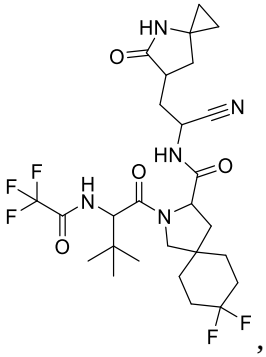
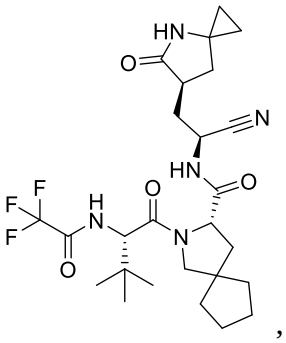
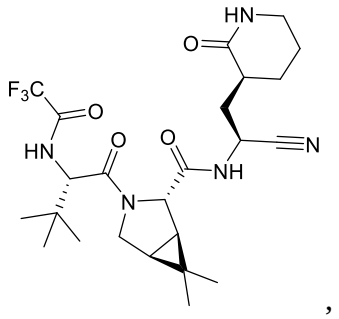
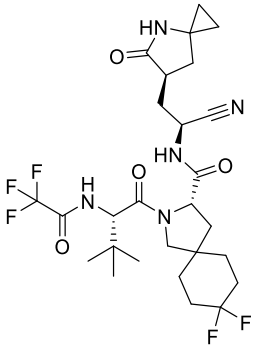
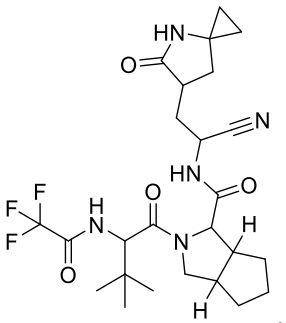
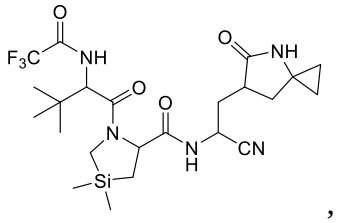
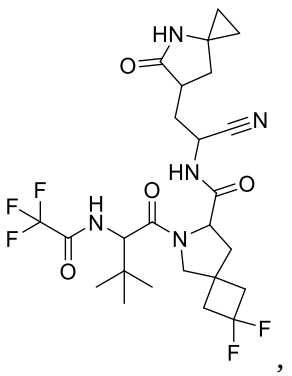
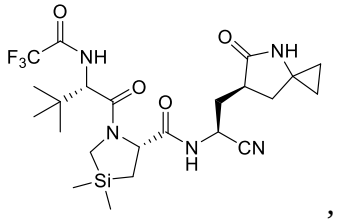
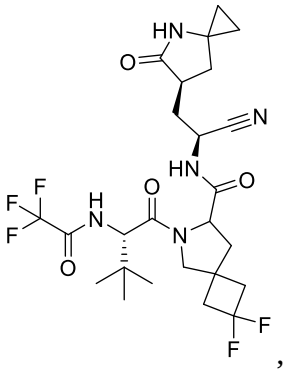
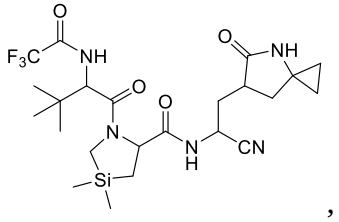
,

,

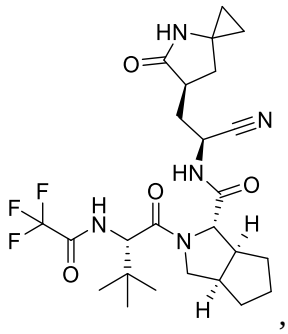
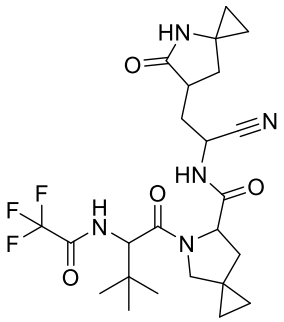
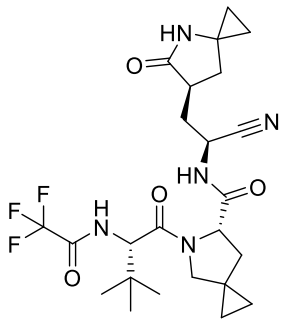
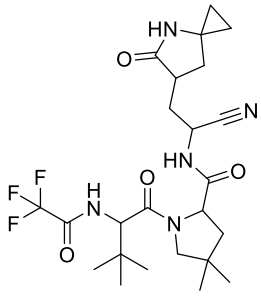
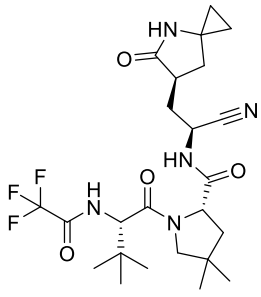
,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

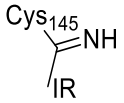
,


,

,

,

,

,

and a pharmaceutically acceptable salt or stereoisomer thereof.

[0005c] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable excipient.

[0005d] In another aspect of the present disclosure, there is provided a substantially reversible conjugate represented by:



Formula III,

wherein Cys_{145} is cysteine at position 145 or equivalent active site cysteine on a CL or 3CL protease; IR is a viral protease inhibitor; and wherein the compound that forms the conjugate comprises a -CN warhead.

[0005e] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for ameliorating or treating a viral infection in a patient in need thereof.

[0005f] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for inhibiting transmission of a virus, inhibiting viral replication, minimizing expression of viral proteins, or inhibiting virus release in a patient suffering from the virus, wherein the compound is to be administered to the patient, and/or wherein the compound is to be contacted with a virally infected cell.

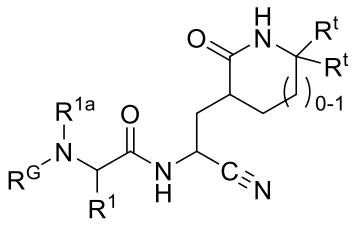
[0005g] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for prophylactically treating a patient at risk of viral infection.

[0005h] In another aspect of the present disclosure, there is provided an engineered CL or 3CL viral protease, wherein:

the cysteine at position 145 of the CL or 3CL protease has a non-naturally occurring covalent modification resulting from a reaction between an exogenous nitrile modifier having a nitrile function and the cysteine at position 145 of the CL or 3CL protease, and

wherein the sulfur atom at the cysteine residue and the nitrile of the exogenous nitrile modifier undergoes a reaction to form a thioimidate adduct, and wherein the engineered SARS- protease does not retain the protease activity of an unmodified CL or 2CL protease.

[0005i] In a further aspect of the present disclosure, there is provided an engineered SARS-COV2-3CL viral protease represented by SEQ ID NO: 1, wherein the cysteine at position 145 of SEQ ID NO: 1 has a non-naturally occurring covalent modification resulting from a reaction between an exogenous nitrile modifier, and the cysteine at position 145 of SEQ ID NO: 1, wherein the exogenous nitrile modifier is represented by:

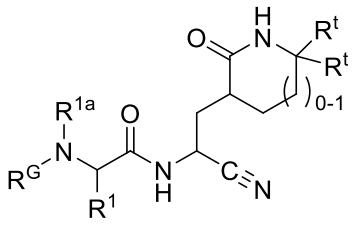


wherein the sulfur atom at the cysteine residue and the -C≡N of the exogenous nitrile modifier undergoes a reaction to form a thioimidate adduct, and wherein

R^1 is C_1-C_6alkyl or -CH_2-C_{3-10}cycloalkyl;
R^G is –C(O)R^B;
R^B is C_1-C_6alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, -NR^mR^m, and -NR^m(C=O)R^m, wherein R^m is selected for each occurrence from H or C_{1-3}alkyl (optionally substituted by one, two or three halo)); or a 8-10 membered bicyclic heteroaryl (optionally substituted by one, two, or three substituents each independently selected from halo or methoxy);
R^t is independently, for each occurrence, H or methyl; or each R^t may be taken, together with the carbon to which they are attached, to form a cyclopropyl;
R^{1a} is H; or

R^1 and R^{1a}, taken together with the nitrogen and the carbon to which they are attached, form a 4-10 membered monocyclic, bicyclic or spirocyclic heterocycle optionally substituted by one or two substituents on a free carbon each selected from methyl, halo or CF_3.

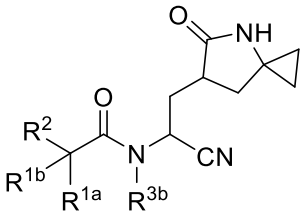
[0005j] In another aspect of the present disclosure, there is provided a compound represented by:



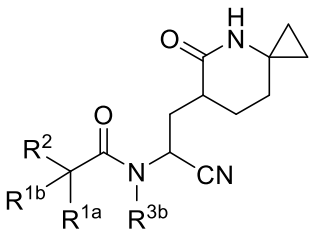
or a pharmaceutically acceptable salt or stereoisomer thereof, wherein

R^1 is C_1-C_6alkyl or -CH_2-C_{3-10}cycloalkyl;
R^G is –C(O)R^B;
R^B is C_1-C_6alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, -NR^mR^m, and -NR^m(C=O)R^m, wherein R^m is selected for each occurrence from H or C_{1-3}alkyl (optionally substituted by one, two or three halo)); or a 8-10 membered bicyclic heteroaryl (optionally substituted by one, two, or three substituents each independently selected from halo or methoxy);
R^t is independently, for each occurrence, H or methyl; or each R^t may be taken, together with the carbon to which they are attached, to form a cyclopropyl;
R^{1a} is H; or
R^1 and R^{1a}, taken together with the nitrogen and the carbon to which they are attached, form a 4-10 membered monocyclic, bicyclic or spirocyclic heterocycle optionally substituted by one or two substituents on a free carbon each selected from methyl, halo or CF_3.

[0005k] In a further aspect of the present disclosure, there is provided a compound represented by Formula IV-A or Formula IV-B:



(IV-A) or



(IV-B)

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

R^{1a} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8heteroalkyl, –(C_1-C_8alkyl)-R^1, –(C_1-C_8alkyl)-CN, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle and 5-10 membered heteroaryl;

R^{1b} is selected from hydrogen and C_1-C_8alkyl;

or R^{1a} and R^{1b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle having a ring nitrogen NR^G, or a C_3-C_{10}cycloalkyl;

R^1 is selected from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^1 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^A is independently selected for each occurrence from the group consisting of halogen, cyano, hydroxyl, oxo, SF_5, –CH_2CF_3, –CF_3, –O-CF_3, –O-CHF_2, –S-CH_3, –$S(O)_2$-CH_3, –NH_2, –O-phenyl, –O-(C_1-C_8alkyl)-phenyl, –$NHC(O)R^B$, –$NHC(O)OR^B$, –NHC(O)O-(C_1-C_8alkyl)-R^B, –$N(R^y)_2$, –$N(R^y)$(C_1-C_8alkyl)C(O)O-phenyl, –$N(R^y)$(C_1-C_8alkyl)$C(O)N(R^y)_2$, –C(O)-$OC(CH_3)_3$, C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_1-C_8heteroalkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, –(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl), –(C_1-C_8alkyl)-(C_6-C_{14}aryl), –(C_1-C_8alkyl)-(5-10 membered heteroaryl), C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocyclyl, wherein the R^B, alkyl, heterocyclyl, heteroaryl, or aryl may optionally be substituted by one, two or three substituents each independently selected from the group consisting of halogen, C_1-C_8alkyl, C_1-C_8alkoxy, SF_5, –NH_2, hydroxyl and oxo;

R^2 is selected from the group consisting of –NHC(O)R^B, –NHC(O)OR^B, –NHC(O)N(R^B)$_2$, –NHC(O)C(R^C)$_2$$R^B$, –NHS(O)$_2$$R^B$, –O-($C_1$-$C_8$alkyl)-($C_3$-$C_{10}$cycloalkyl), 4-10 membered heterocycle, C_6-C_{14}aryl and 5-10 membered heteroaryl bound through the carbon or nitrogen atom, wherein R^B or R^2 may optionally be substituted by one, two, or three substituents each selected from R^x;

or R^{1a} and R^2 may be joined together to form, together with the carbon to which they are attached, a 4-10 membered mono or bicyclic heterocycle having a ring nitrogen NR^G, or a C_3-C_{10}cycloalkyl, wherein the cycloalkyl or heterocycle may optionally be substituted by one, two or three substituents on a free carbon each selected from R^A;

R^{3b} is selected from hydrogen and C_1-C_8alkyl;

R^B is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_6cycloalkyl, fluorenylmethyloxy, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle;

R^C is independently selected, for each occurrence, from hydrogen, halogen and C_1-C_8alkyl;

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, CF_3, SF_5, cyano, -O-(R^{xx})-OCH_3, –$OCHF_2$, –OCF_3, –O-(C_1-C_8alkyl), –C(O)O(CH_3), –N(R^y)$_2$, –N(R^y)C(O)R^y, –N(R^y)(C_1-C_8alkyl)C(O)N(R^y)$_2$, –N(R^y)(C_1-C_8alkyl)C(O)OH, -(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl), C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, -O-C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle;

wherein two geminal C_1-C_8alkyl groups, together with the carbon to which they are attached, may be joined together to form a C_3-C_6cycloalkyl optionally substituted by one, two or three substituents each independently selected from halogen, hydroxyl and oxo; and

wherein the alkyl, aryl, heterocycle or heteroaryl may optionally be substituted by one or more substituents each independently selected from oxo, halogen and C_1-C_8alkyl;

R^G is selected from the group consisting of hydrogen, C_{1-6}alkyl optionally substituted by one, two or three R^{gg}, –C(=O)-C_{1-6}alkyl optionally substituted by one, two or three R^{hh}, -C(=O)-C_{3-6}cycloalkyl, –C(O)-(C_2-C_{10}alkenyl)-(C_6-C_{14}aryl), –C(O)-(5-10 membered heteroaryl), –C(O)-(C_1-C_6alkyl)-O-(C_6-C_{14}aryl), –C(O)-(4-10 membered heterocyclyl), and –C(O)-(4-10 membered heterocyclyloxy); wherein the aryl, heterocyclyl, or heteroaryl may optionally be substituted by one, two or three R^{jj};

R^{gg} is independently selected for each occurrence from the group consisting of -C(=O), halo, cyano, -NR^mR^m, and -NH(C=O)R^m;

R^{hh} is independently selected for each occurrence from the group consisting of halo, cyano, -NR^mR^m, -NR^m(C=O)R^m, phenyl, cycloalkyl, heterocyclyl and C_1-C_6alkoxy;

R^{jj} is independently selected for each occurrence from the group consisting of halo, oxo, hydroxyl, cyano, C_1-C_6alkyl, C_{1-6}haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_{3-6}cycloalkyl, SF_5, and NH_2;

R^m is independently selected for each occurrence from the group consisting of hydrogen, C_{1-3}alkyl, phenyl, -$S(O)_2$-CH_3, C_{3-6}cycloalkyl, and 5-6 membered heteroaryl; wherein C_{1-3}alkyl, phenyl, and C_{3-6}cycloalkyl may optionally be substituted by one, two or three halo;

R^{xx} is –$(OCH_2CH_2)_{nn}$–, wherein nn is selected from 1, 2, 3, 4, 5 and 6; and

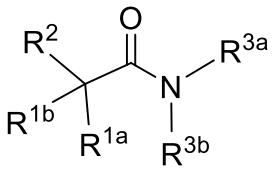
R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8heteroalkyl, –CF_3, –CH_2CF_3, C_1-C_8alkoxy, –(C_1-C_8alkoxy)-(5-10 membered aryl), C_3-C_6cycloalkyl and –(C_1-C_8alkyl)COOH.

[0005l] In another aspect of the present disclosure, there is provided a compound disclosed herein for use in therapy.

[0006] The disclosure is directed to, in part, viral protease inhibitors. Also disclosed herein are pharmaceutical compositions comprising at least one disclosed compound and a pharmaceutically acceptable carrier.

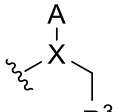
[0007] In an example, disclosed herein is an antiviral compound, comprising a warhead covalently bound to a 3C or 3CL protease inhibitor, wherein the antiviral compound covalently binds to a Cys residue of the protease, and wherein the antiviral compound is active against one or more viruses.

[0008] Also disclosed herein are compounds represented by Formula II:



Formula II,

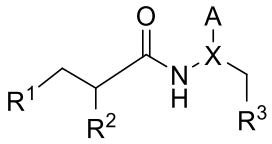
or a pharmaceutically acceptable salt, stereoisomer, ester, or prodrug thereof, wherein:

R^{3a} is selected from 

and 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each independently selected from the group consisting of hydroxyl, C_1-C_8alkoxy, oxo and a warhead A; R^{3b} is selected from hydrogen and C_1-C_8alkyl; wherein R^{3a} and R^{3b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each independently selected from C_6-C_{14}aryl and a warhead A; R^{1a} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8heteroalkyl, –(C_1-C_8alkyl)-R^1, –(C_1-C_8alkyl)-CN, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle and 5-10 membered heteroaryl; R^{1b} is selected from hydrogen and C_1-C_8alkyl; or R^{1a} and R^{1b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle having a ring nitrogen, NR^G, or a C_3-C_{10}cycloalkyl; R^1 is selected from the group

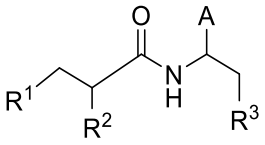
are attached, may be joined together to form a C_3-C_6cycloalkyl optionally substituted by one, two or three substituents each independently selected from halogen, hydroxyl and oxo; and wherein the alkyl, aryl, heterocycle or heteroaryl may optionally be substituted by one or more substituents each independently selected from oxo, halogen and C_1-C_8alkyl; R^G is selected from the group consisting of hydrogen, C_{1-6}alkyl optionally substituted by one, two or three R^{gg}, –C(=O)-C_{1-6}alkyl optionally substituted by one, two or three R^{hh}, -C(=O)-C_{3-6}cycloalkyl, –C(O)-(C_2-C_{10}alkenyl)-(C_6-C_{14}aryl), –C(O)-(C_1-C_6alkyl)-O-(C_6-C_{14}aryl), –C(O)-(5-10 membered heteroaryl), –C(O)-(4-10 membered heterocyclyl), and –C(O)-(4-10 membered heterocyclyloxy); wherein the aryl, heterocyclyl, or heteroaryl may optionally be substituted by one, two or three R^{jj}; R^{gg} is independently selected for each occurrence from the group consisting of -C(=O), halo, cyano, -NR^mR^m, and -NH(C=O)R^m; R^{hh} is independently selected for each occurrence from the group consisting of halo, cyano, -NR^mR^m, -NR^m(C=O)R^m, phenyl, cycloalkyl, heterocyclyl and C_1-C_6alkoxy; R^{jj} is independently selected for each occurrence from the group consisting of halo, oxo, hydroxyl, cyano, C_1-C_6alkyl, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_1-C_6alkoxy, C_{3-6}cycloalkyl, SF_5, and NH_2; R^m is independently selected for each occurrence from the group consisting of hydrogen, C_{1-3}alkyl, phenyl, -$S(O)_2$-CH_3, C_{3-6}cycloalkyl, and 5-6 membered heteroaryl; wherein C_{1-3}alkyl, phenyl, and C_{3-6}cycloalkyl may optionally be substituted by one, two or three halo; R^{xx} is –$(OCH_2CH_2)_{nn}$–, wherein nn is selected from 1, 2, 3, 4, 5 and 6; R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8heteroalkyl, –CF_3, –CH_2CF_3, C_1-C_8alkoxy, –(C_1-C_8alkoxy)-(5-10 membered aryl), C_3-C_6cycloalkyl and –(C_1-C_8alkyl)COOH; A is a warhead; and X is selected from the group consisting of C(R^{xy}) and N, wherein R^{xy} is selected from the group consisting of H, D, -OH, -NH_2, halogen, C_1-C_8alkyl, C_1-C_8 haloalkyl, and C_1-C_8alkoxy.

[0009] In some examples, disclosed herein are compounds represented by Formula II-A:



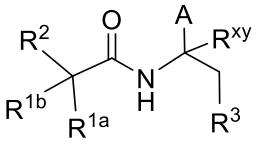
Formula II-A.

[00010] In some examples, disclosed herein are compounds represented by Formula II-B:



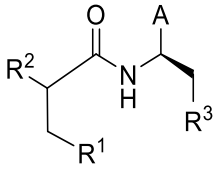
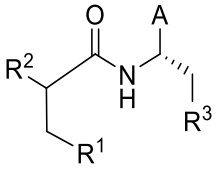
Formula II-B.

[00011] In some examples, disclosed herein are compounds represented by Formula II-C:

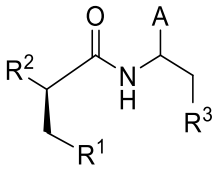
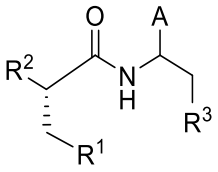


Formula II-C.

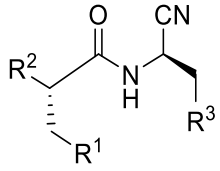
[00012] In some examples, disclosed herein are compounds represented by Formula II-D-A or Formula II-D-B:

 (Formula II-D-A) or  (Formula II-D-B).

[00013] In some examples, disclosed herein are compounds represented by Formula II-E-A or Formula II-E-B:

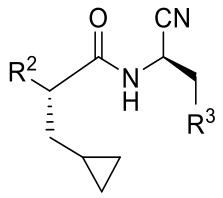
 (Formula II-E-A) or  (Formula II-E-B).

[00014] In some examples, disclosed herein are compounds represented by Formula II-F:



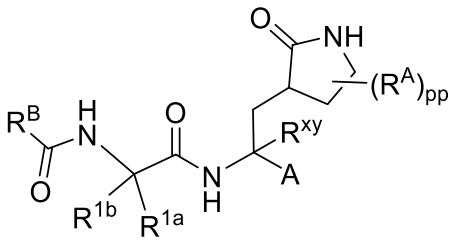
Formula II-F.

[00015] In some examples, disclosed herein are compounds represented by Formula II-G:

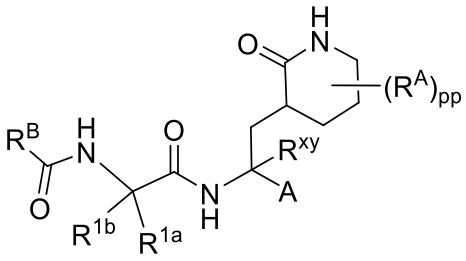


Formula II-G.

[00016] In some examples, disclosed herein are compounds represented by Formula II-H-A or Formula II-H-B:



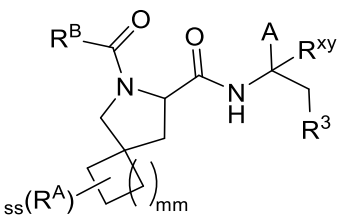
(Formula II-D-I), or



(Formula II-D-II),

wherein pp is selected from 0, 1, 2, and 3.

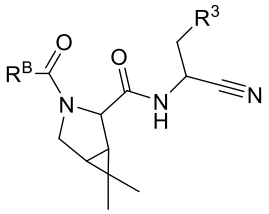
[00017] In some examples, disclosed herein are compounds represented by Formula II-E:



(Formula II-E),

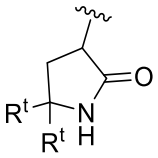
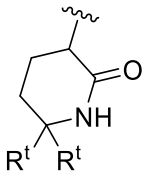
wherein ss is selected from 0, 1, 2, and 3, and mm is selected from 1, 2, and 3.

[00018] In some examples, disclosed herein are compounds represented by Formula II-I:

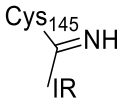


Formula II-I,

or a pharmaceutically acceptable salt thereof, wherein:

R^3 is  or  ; R^t is independently, for each occurrence, H or methyl; or each R^t may be taken, together with the carbon to which they are attached, to form a cyclopropyl; R^B is selected from the group consisting of: a 9-10 membered bicyclic heteroaryl having one ring nitrogen, C_1-C_6alkyl, and C_2-C_3alkenyl; wherein R^B is optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, C_1-C_3alkoxy, NHR^m, and phenyl (optionally substituted by one or two halogens); and R^m is C_1-C_3alkyl or -C(O)-C_{1-3}alkyl, wherein each C_1-C_3alkyl is independently optionally substituted by one, two or three halogens.

[00019] In certain examples, disclosed herein are conjugates represented by Formula III:



Formula III,

wherein Cys_{145} is cysteine at position 145 or equivalent active site cysteine on a CL or 3CL protease; IR is a viral protease inhibitor; and wherein the compound that forms the conjugate comprises a -CN warhead.

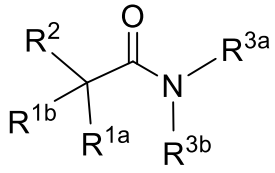
DETAILED DESCRIPTION

[00020] The features and other details of the disclosure will now be more particularly described. Before further description of the present disclosure, certain terms employed in the specification, examples and appended claims are collected here. These definitions

CLAIMS

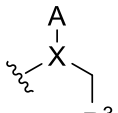
What is claimed is:

1. A protease inhibitor compound represented by:



Formula II,

or a pharmaceutically acceptable salt, stereoisomer, ester, or prodrug thereof, wherein:

R^{3a} is selected from 

and 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each independently selected from the group consisting of hydroxyl, C_1-C_8alkoxy, oxo and a warhead A;

R^{3b} is selected from hydrogen and C_1-C_8alkyl; wherein R^{3a} and R^{3b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each independently selected from C_6-C_{14}aryl and a warhead A;

R^{1a} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8heteroalkyl, –(C_1-C_8alkyl)-R^1, –(C_1-C_8alkyl)-CN, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle and 5-10 membered heteroaryl;

R^{1b} is selected from hydrogen and C_1-C_8alkyl;

or R^{1a} and R^{1b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle having a ring nitrogen NR^G, or a C_3-C_{10}cycloalkyl;

R^1 is selected from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^1 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^A is independently selected for each occurrence from the group consisting of halogen, cyano, hydroxyl, oxo, SF_5, $–CH_2CF_3$, $–CF_3$, $–O-CF_3$, $–O-CHF_2$, $–S-CH_3$, $–S(O)_2-CH_3$, $–NH_2$, –O-phenyl, $–O-(C_1-C_8alkyl)$-phenyl, $–NHC(O)R^B$, $–NHC(O)OR^B$, $–NHC(O)O-(C_1-C_8alkyl)-R^B$, $–N(R^y)_2$, $–N(R^y)(C_1-C_8alkyl)C(O)O$-phenyl, $–N(R^y)(C_1-C_8alkyl)C(O)N(R^y)_2$, $–C(O)-OC(CH_3)_3$, C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_1-C_8heteroalkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, $–(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl)$, $–(C_1-C_8alkyl)-(C_6-C_{14}aryl)$, $–(C_1-C_8alkyl)-$(5-10 membered heteroaryl), C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocyclyl, wherein the R^B, alkyl, heterocyclyl, heteroaryl, or aryl may optionally be substituted by one, two or three substituents each independently selected from the group consisting of halogen, C_1-C_8alkyl, C_1-C_8alkoxy, SF_5, $–NH_2$, hydroxyl and oxo;

R^2 is selected from the group consisting of $–NHC(O)R^B$, $–NHC(O)OR^B$, $–NHC(O)N(R^B)_2$, $–NHC(O)C(R^C)_2R^B$, $–NHS(O)_2R^B$, $–O-(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl)$, 4-10 membered heterocycle, C_6-C_{14}aryl and 5-10 membered heteroaryl bound through the carbon or nitrogen atom, wherein R^B or R^2 may optionally be substituted by one, two, or three substituents each selected from R^x;

or R^{1a} and R^2 may be joined together to form, together with the carbon to which they are attached, a 4-10 membered monocyclic or bicyclic heterocycle having a ring nitrogen NR^G, or a C_3-C_{10}cycloalkyl, wherein the cycloalkyl or heterocycle may optionally be substituted by one, two or three substituents on a free carbon each selected from R^A;

R^3 is selected from 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^3 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^B is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_6cycloalkyl, fluorenylmethyloxy, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle;

R^C is independently selected, for each occurrence, from hydrogen, halogen and C_1-C_8alkyl;

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, CF_3, SF_5, cyano, -O-(R^{xx})-OCH_3, –$OCHF_2$, –OCF_3, –O-(C_1-C_8alkyl), –C(O)O(CH_3), –N(R^y)$_2$, –N(R^y)C(O)R^y, –N(R^y)(C_1-C_8alkyl)C(O)N(R^y)$_2$, –N(R^y)(C_1-C_8alkyl)C(O)OH, -(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl), C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, -O-C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle;

wherein two geminal C_1-C_8alkyl groups, together with the carbon to which they are attached, may be joined together to form a C_3-C_6cycloalkyl optionally substituted by one, two or three substituents each independently selected from halogen, hydroxyl and oxo; and

wherein the alkyl, aryl, heterocycle or heteroaryl may optionally be substituted by one or more substituents each independently selected from oxo, halogen and C_1-C_8alkyl;

R^G is selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl optionally substituted by one, two or three R^{gg}, –C(=O)-$C_{1\text{-}6}$alkyl optionally substituted by one, two or three R^{hh}, -C(=O)-$C_{3\text{-}6}$cycloalkyl, –C(O)-(C_2-C_{10}alkenyl)-(C_6-C_{14}aryl), –C(O)-(C_1-C_6alkyl)-O-(C_6-C_{14}aryl), –C(O)-(5-10 membered heteroaryl), –C(O)-(4-10 membered heterocyclyl), and –C(O)-(4-10 membered heterocyclyloxy); wherein the aryl, heterocyclyl, or heteroaryl may optionally be substituted by one, two or three R^{jj};

R^{gg} is independently selected for each occurrence from the group consisting of -C(=O), halo, cyano, -N$R^m R^m$, and -NH(C=O)R^m;

R^{hh} is independently selected for each occurrence from the group consisting of halo, cyano, -NR^mR^m, -$NR^m(C=O)R^m$, phenyl, cycloalkyl, heterocyclyl and C_1-C_6alkoxy;

R^{jj} is independently selected for each occurrence from the group consisting of halo, oxo, hydroxyl, cyano, C_1-C_6alkyl, C_{1-6}haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_{3-6}cycloalkyl, SF_5, and NH_2;

R^m is independently selected for each occurrence from the group consisting of hydrogen, C_{1-3}alkyl, phenyl, -$S(O)_2$-CH_3, C_{3-6}cycloalkyl, and 5-6 membered heteroaryl; wherein C_{1-3}alkyl, phenyl, and C_{3-6}cycloalkyl may optionally be substituted by one, two or three halo;

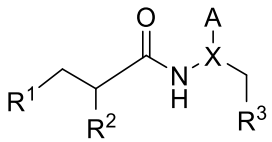
R^{xx} is –$(OCH_2CH_2)_{nn}$–, wherein nn is selected from 1, 2, 3, 4, 5 and 6;

R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8heteroalkyl, –CF_3, –CH_2CF_3, C_1-C_8alkoxy,–(C_1-C_8alkoxy)-(5-10 membered aryl), C_3-C_6cycloalkyl and –(C_1-C_8alkyl)COOH;

A is a warhead; and

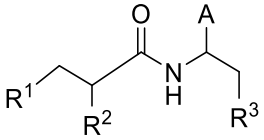
X is selected from the group consisting of C(R^{xy}) and N, wherein R^{xy} is selected from the group consisting of H, D, -OH, -NH_2, halogen, C_1-C_8alkyl, C_1-C_8 haloalkyl, and C_1-C_8alkoxy.

2. The compound of claim 1, wherein the compound is represented by:



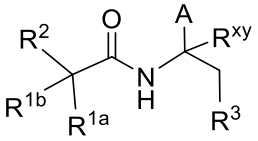
Formula II-A.

3. The compound of claim 1, wherein the compound is represented by:



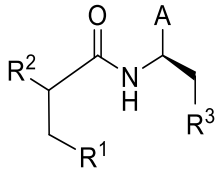
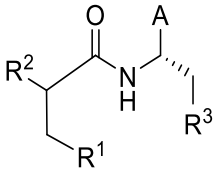
Formula II-B.

4. The compound of claim 1, wherein the compound is represented by:

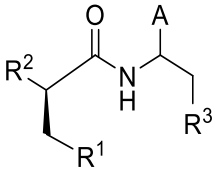
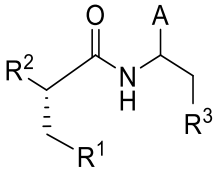


Formula II-C.

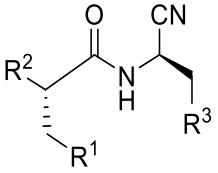
5. The compound of claim 1, wherein the compound is represented by:

 (Formula II-D-A) or  (Formula II-D-B).

6. The compound of claim 1, wherein the compound is represented by:

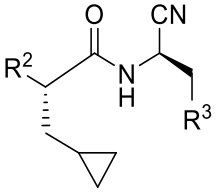
 (Formula II-E-A) or  (Formula II-E-B).

7. The compound of claim 1, wherein the compound is represented by:



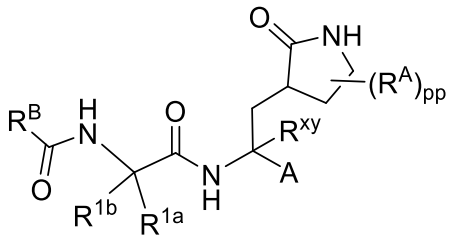
Formula II-F.

8. The compound of claim 1, wherein the compound is represented by:

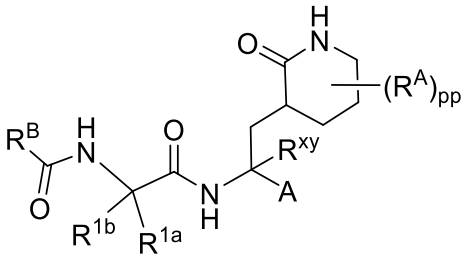


Formula II-G.

9. The compound of claim 1, wherein the compound is represented by:



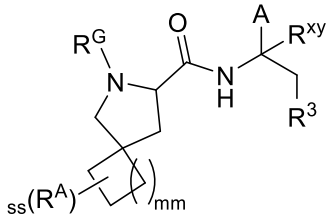
(Formula II-D-I), or



(Formula II-D-II),

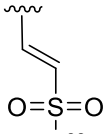
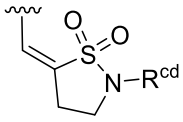
wherein pp is selected from 0, 1, 2, and 3.

10. The compound of claim 1, wherein the compound is represented by:



(Formula II-E-II),

wherein ss is selected from 0, 1, 2, and 3, and mm is selected from 1, 2, and 3.

11. The compound of any one of claims 1-6, 9 and 10, wherein A is selected from the group consisting of cyano, –C(O)R^D, –C(O)$CH_2N(R^bR^c)$, –C(O)$CH_2OC(O)R^D$, –C(O)C(O)R^D, –(CH=CH)C(O)OR^D, –(CH=CCN)C(O)OR^D, –(CH=CCN)C(O)(NH)R^D, –CH(CN)(OH), -CH(CN)(NR^bR^c),  , and  , wherein

R^D is selected from the group consisting of hydrogen, hydroxyl, -OR^{bb} –$N(R^bR^c)$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle; wherein R^D may optionally be substituted

by one, two, or three substituents each independently selected from the group consisting of halogen, hydroxyl, and R^E;

R^E is independently selected for each occurrence from the group consisting of C_1-C_8alkyl, C_1-C_8alkoxy, C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl, wherein R^E may optionally be substituted by one, two, or three substituents each independently selected from the group consisting of halogen, cyano, C_1-C_8alkyl and C_1-C_8alkoxy;

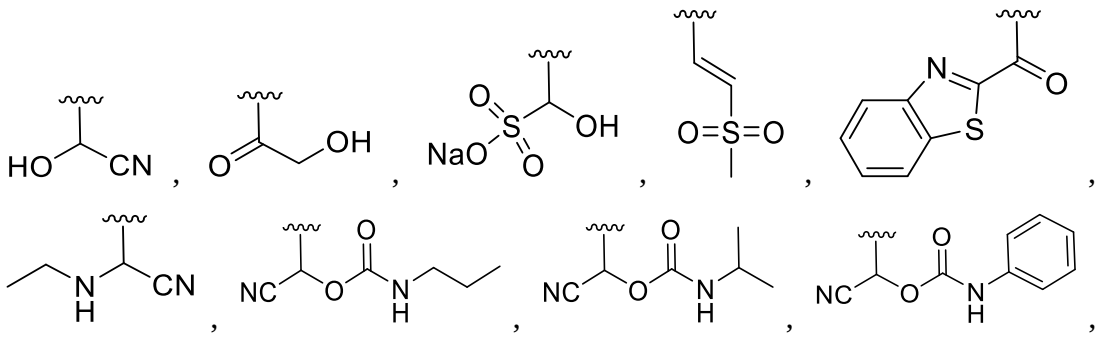
R^{bb} is selected from the group consisting of C_3-C_6cycloalkyl, C_6-C_{14}aryl, -(C_1-C_8alkyl)-C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle;

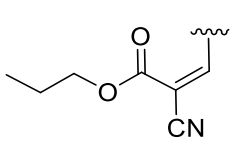
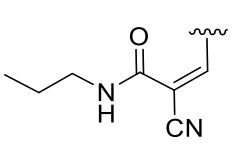
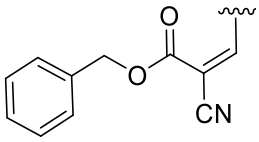
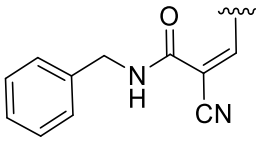
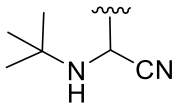
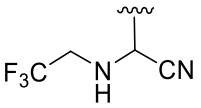
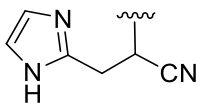
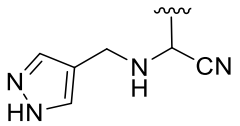
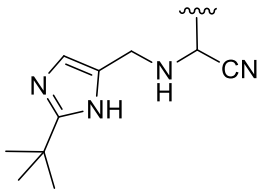
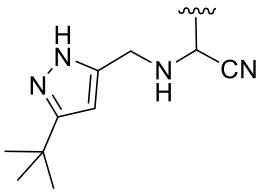
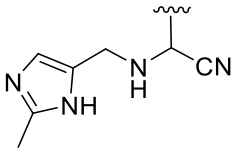
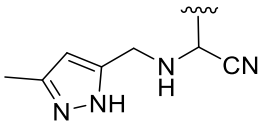
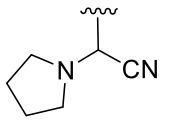
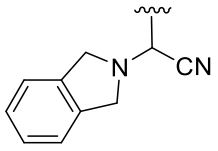
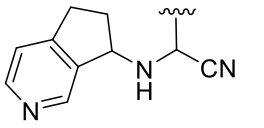
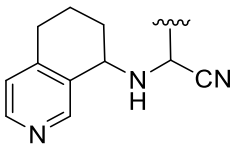
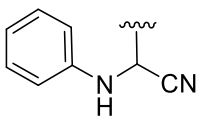
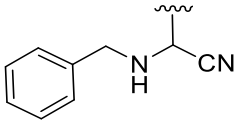
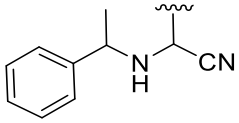
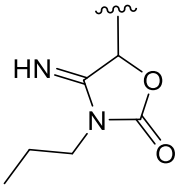
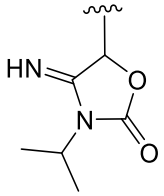
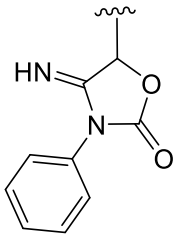
R^{cc} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_3-C_6cycloalkyl, -(C_1-C_8alkyl)-(C_6-C_{14}aryl), C_6-C_{14}aryl, 5-10 membered heteroaryl, -(C_1-C_8alkyl)-(5-10 membered heteroaryl), 5-10 membered heterocycle and -N(R^bR^c), wherein R^b and R^c are each independently selected from the group consisting of hydrogen, C1-C_8alkyl, and C_3-C_6cycloalkyl, or R^b and R^c may be joined together to form, together with the nitrogen to which they are attached, a 5-10 membered heterocycle;

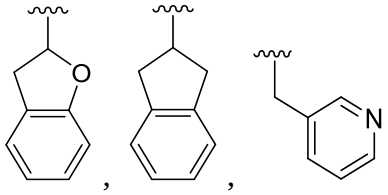
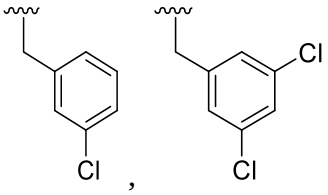
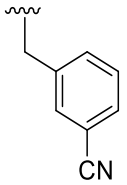
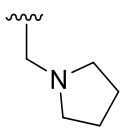
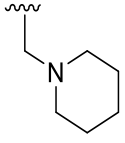
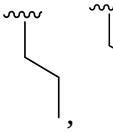
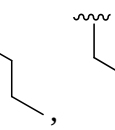
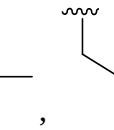
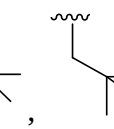
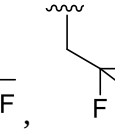
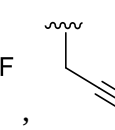
R^{cd} is selected from the group consisting of hydrogen, C_1-C_8alkyl, and C_3-C_6cycloalkyl; and

R^b and R^c are each selected from the group consisting of hydrogen, –$CH_2C(O)O(C_1$-C_8alkyl), –C(O)-(C_1-C_8alkyl), –$S(O)_2$-(C_1-C_8alkyl), C_1-C_8alkyl, C_3-C_6cycloalkyl and -(C_1-C_8alkyl)-C_6-C_{14}aryl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each independently selected from the group consisting of halogen, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl.

12. The compound of claim 11, wherein A is selected from the group consisting of -CN,




,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

, and

.

13. The compound of any one of claims 1, 4 and 9, wherein R^{1a} is selected from the group consisting of

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

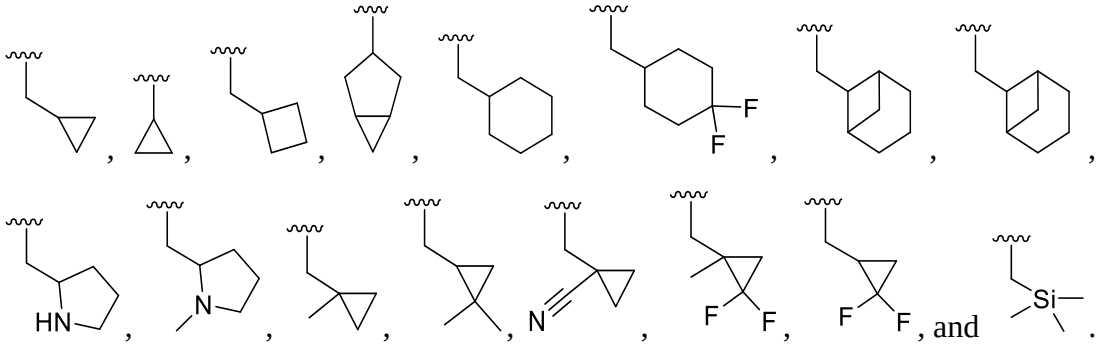
,

,

,

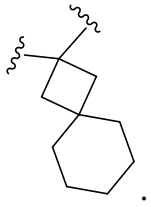
,

,



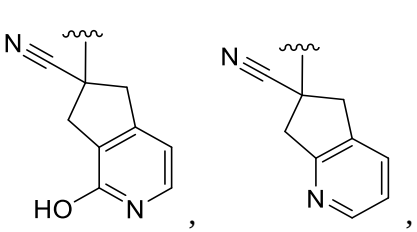
14. The compound of any one of claims 1, 4, and 9, wherein R^{1a} is $-(C_1\text{-}C_8\text{alkyl})\text{-}R^1$.

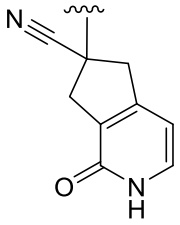
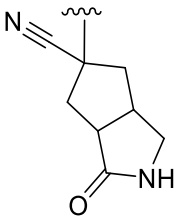
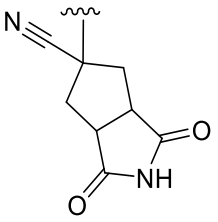
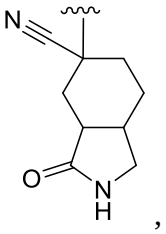
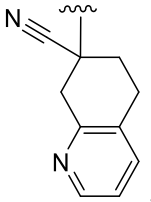
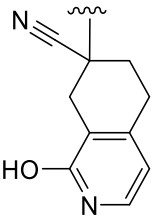
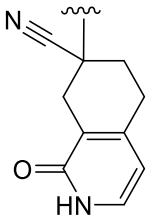
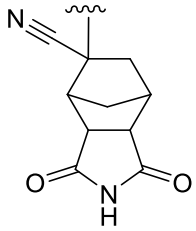
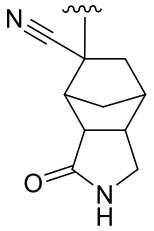
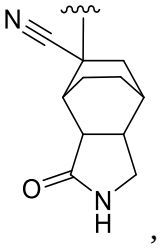
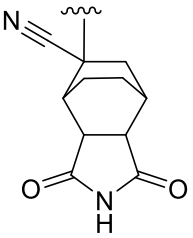
15. The compound of any one of claims 1, 4 and 9, wherein R^{1b} is hydrogen.

16. The compound of claim 1, wherein R^{1a} and R^{1b} are joined to together to form .

17. The compound of claim 1, wherein R^{3a} is a 4-10 membered heterocycle substituted by A.

18. The compound of claim 1, wherein R^{3a} is selected from the group consisting of

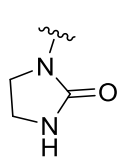
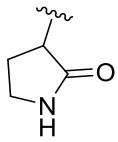
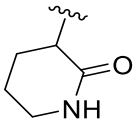
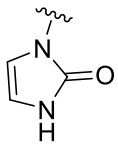
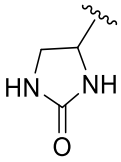
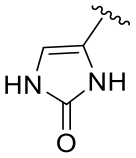
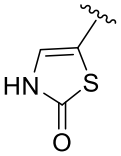
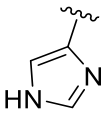
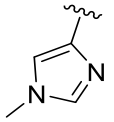
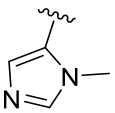
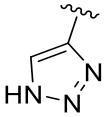
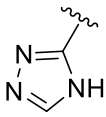
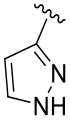
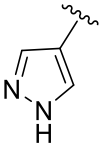
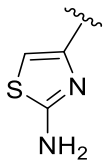
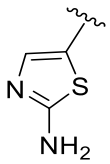
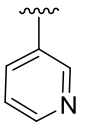
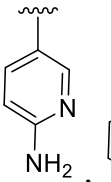
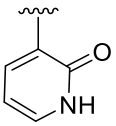
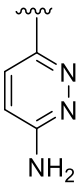
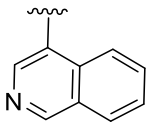
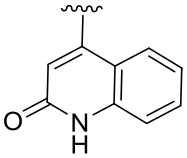
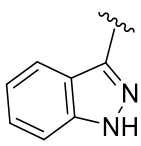
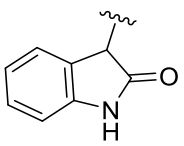
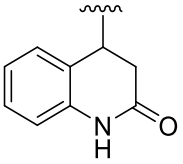
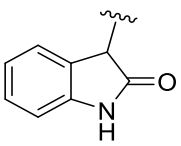
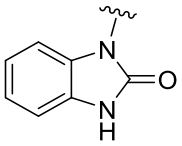


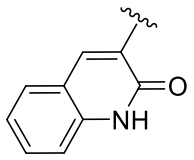
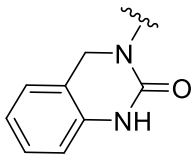
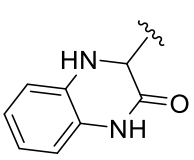
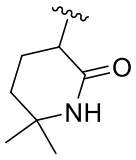
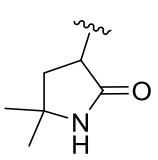
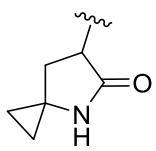
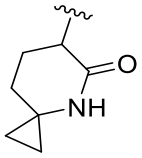
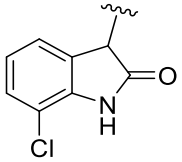
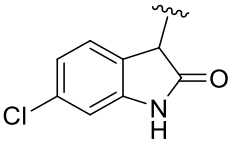
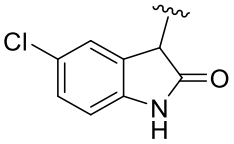
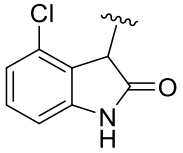
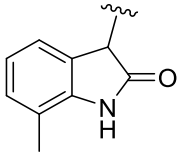
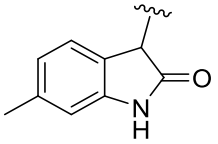
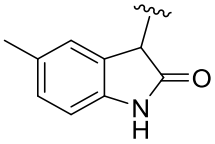
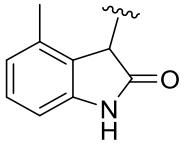
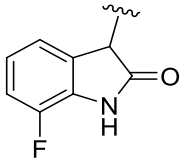
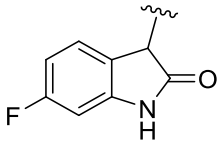
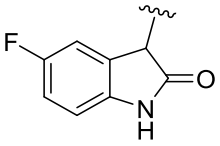
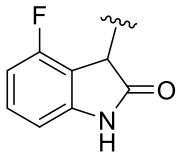
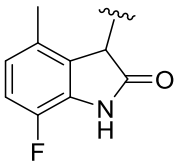
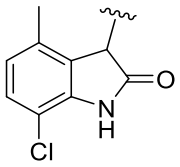
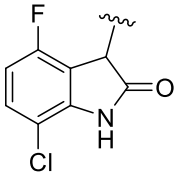
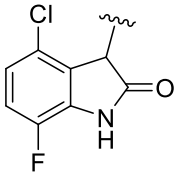
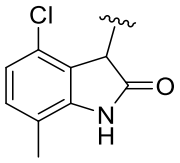
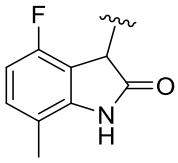
, and .

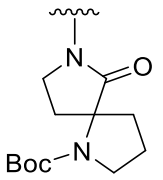
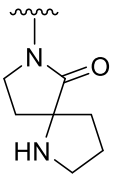
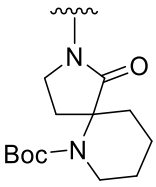
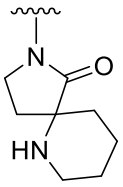
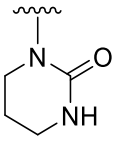
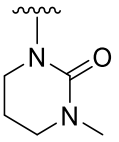
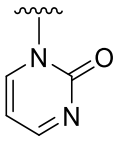
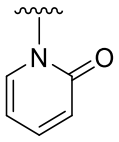
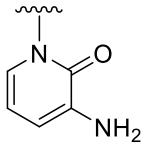
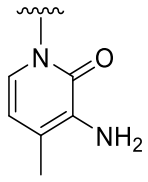
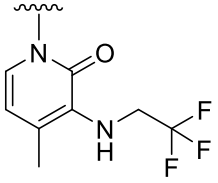
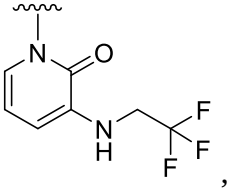
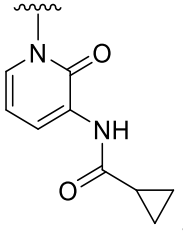
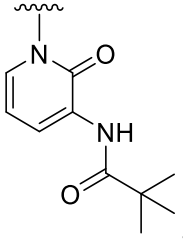
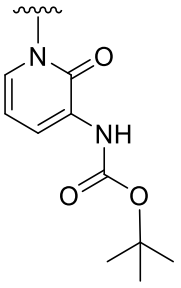
19. The compound of any one of claims 1-8, wherein R^3 is a 4-10 membered heterocycle.

20. The compound of any one of claims 1-8 and 10, wherein R^3 is selected from the group consisting of

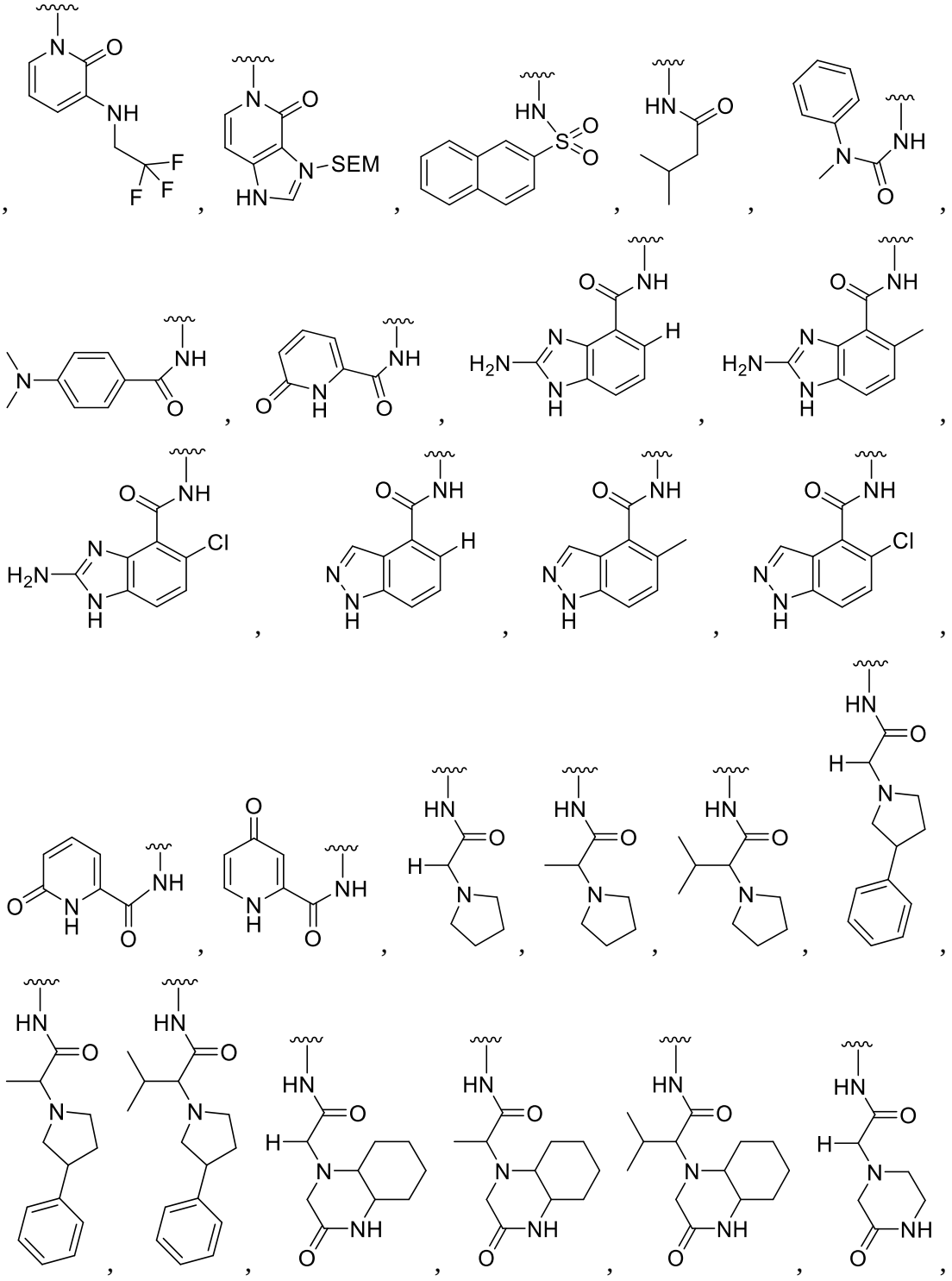
,

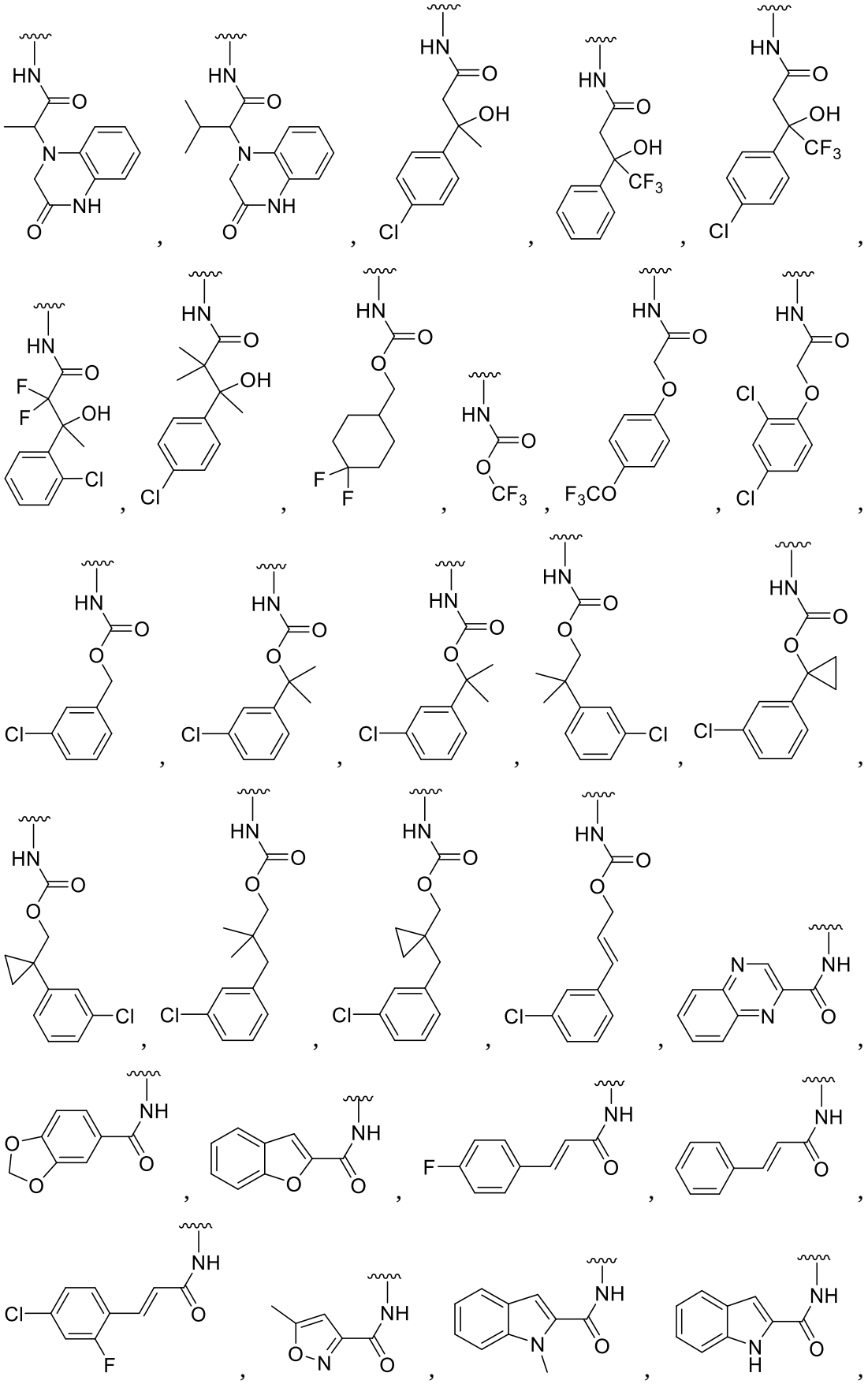

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

, and

.

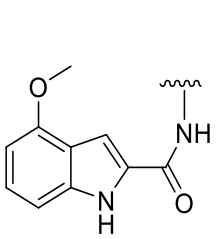
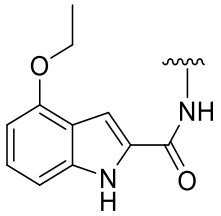
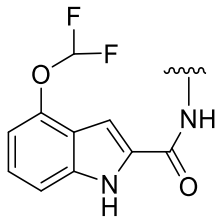
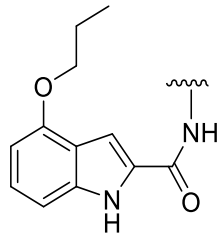
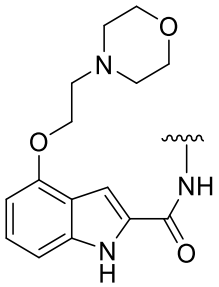
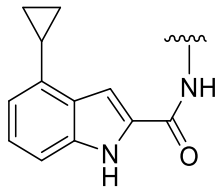
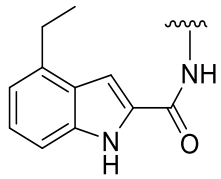
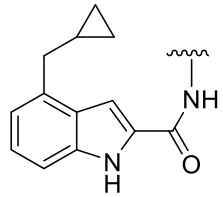
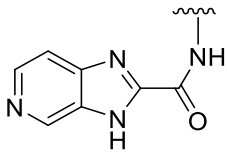
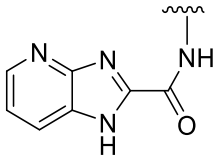
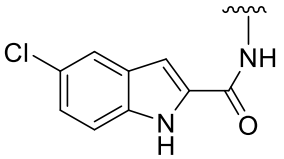
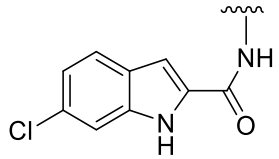
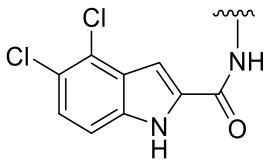
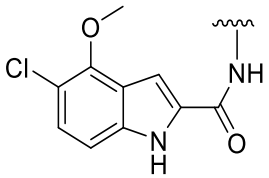
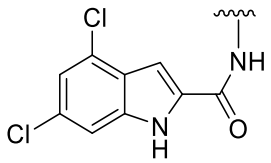
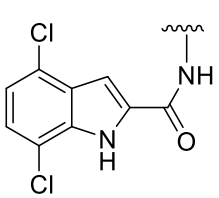
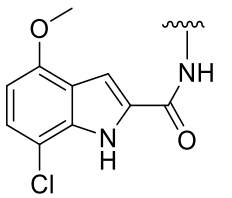
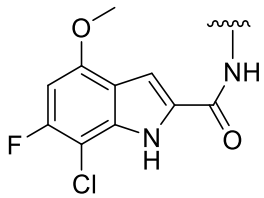
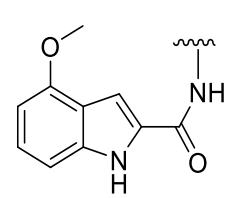
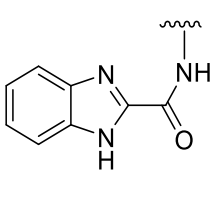
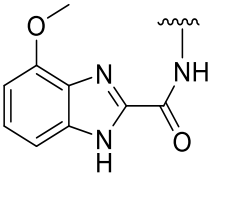
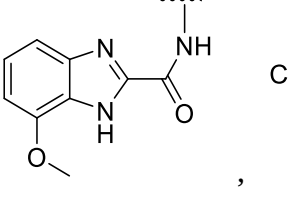
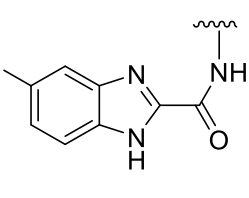
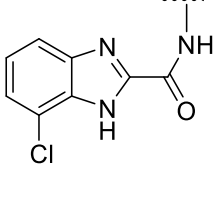
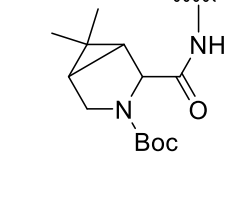
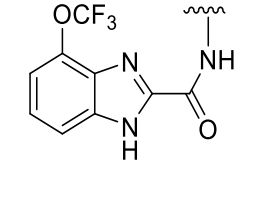
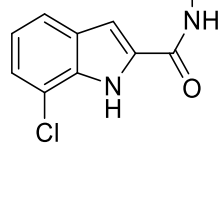
21. The compound of any one of claims 1-8, wherein R^2 is selected from the group consisting of

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,





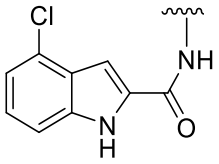
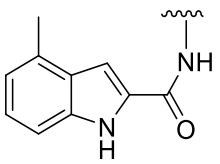
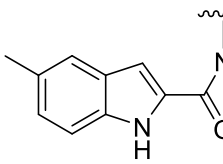
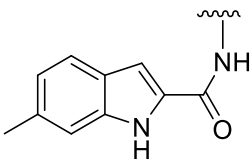
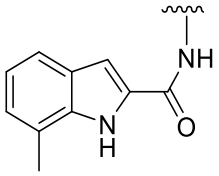
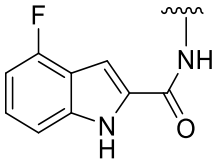
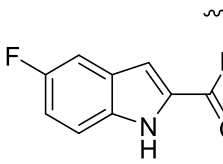
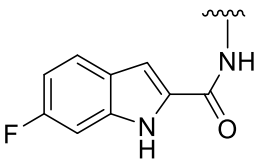
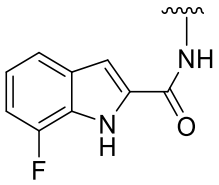
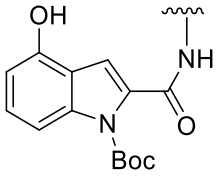
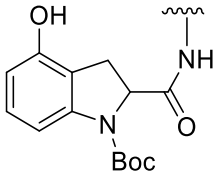
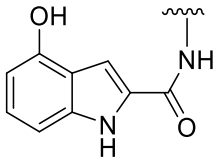
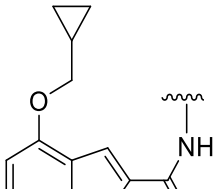
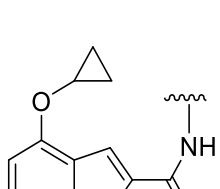
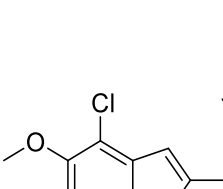
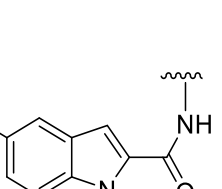
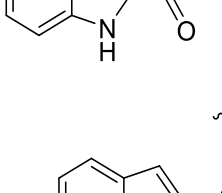
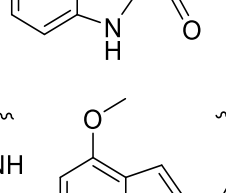
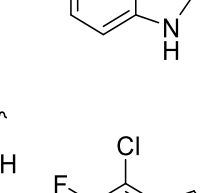
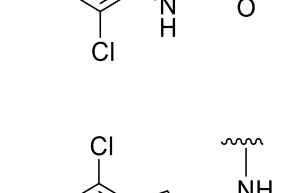
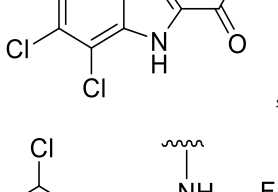
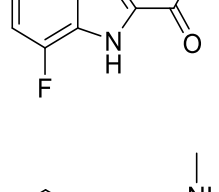
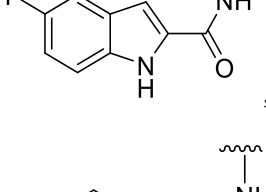
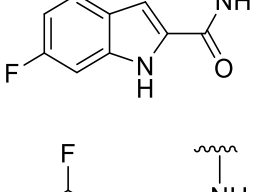
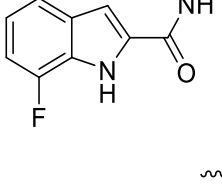
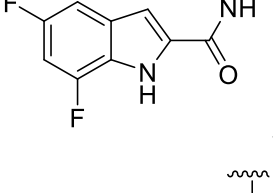
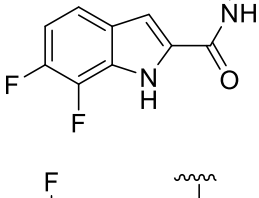
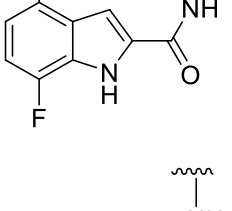
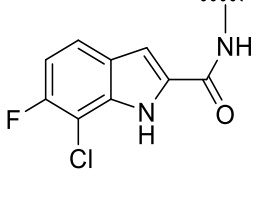
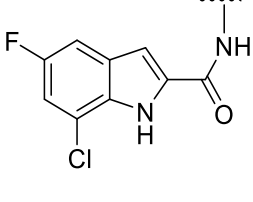
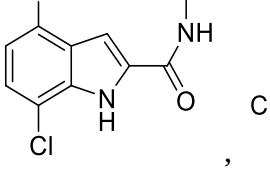
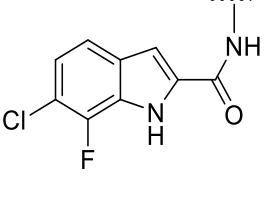
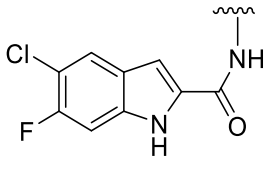
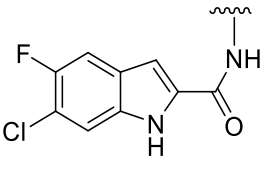
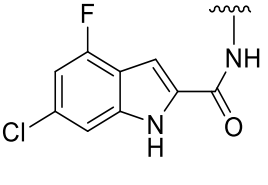

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

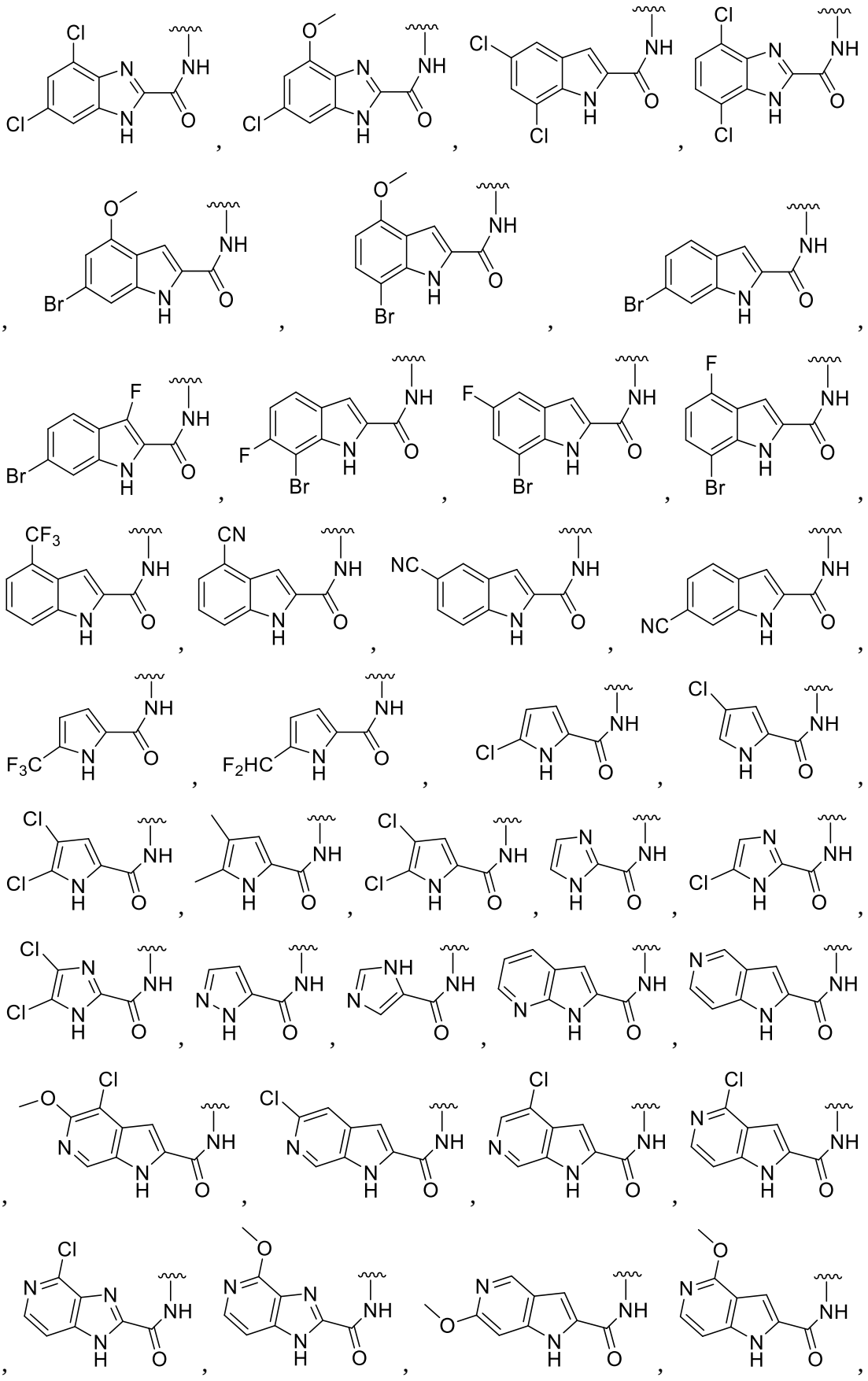
,

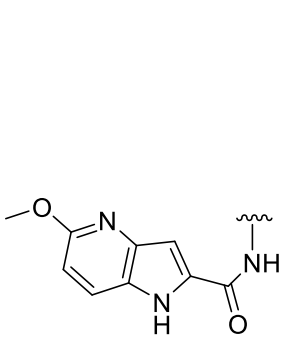
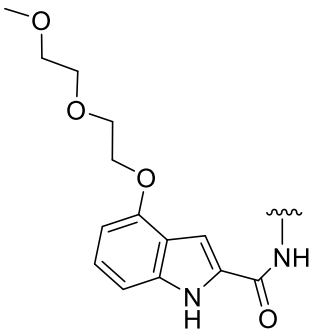
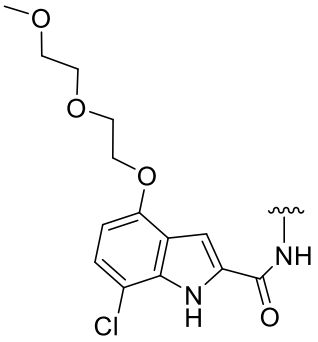
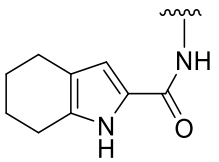
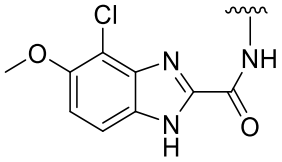
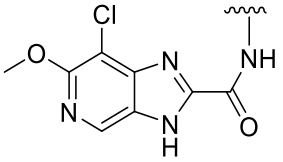
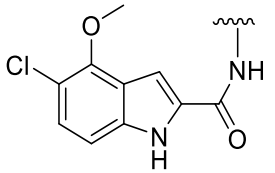
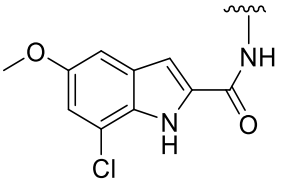
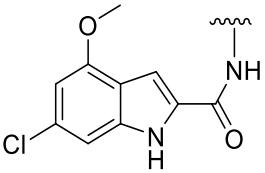
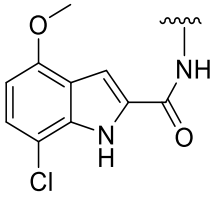
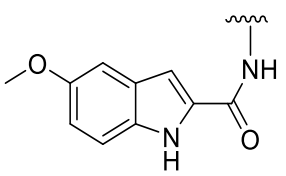
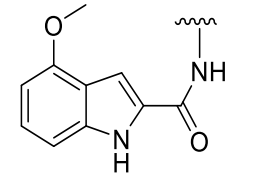
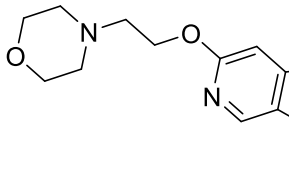
,

,

,

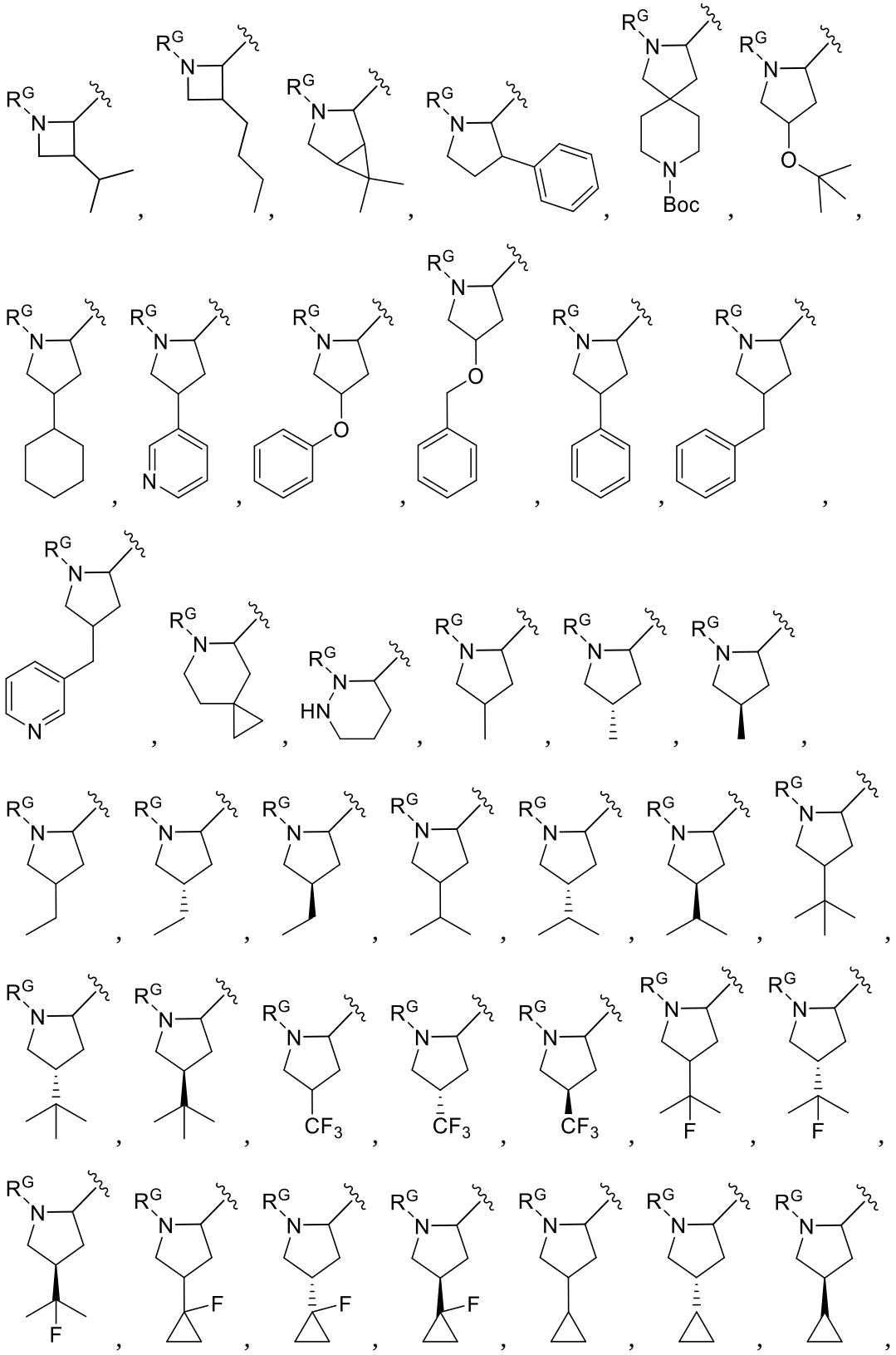


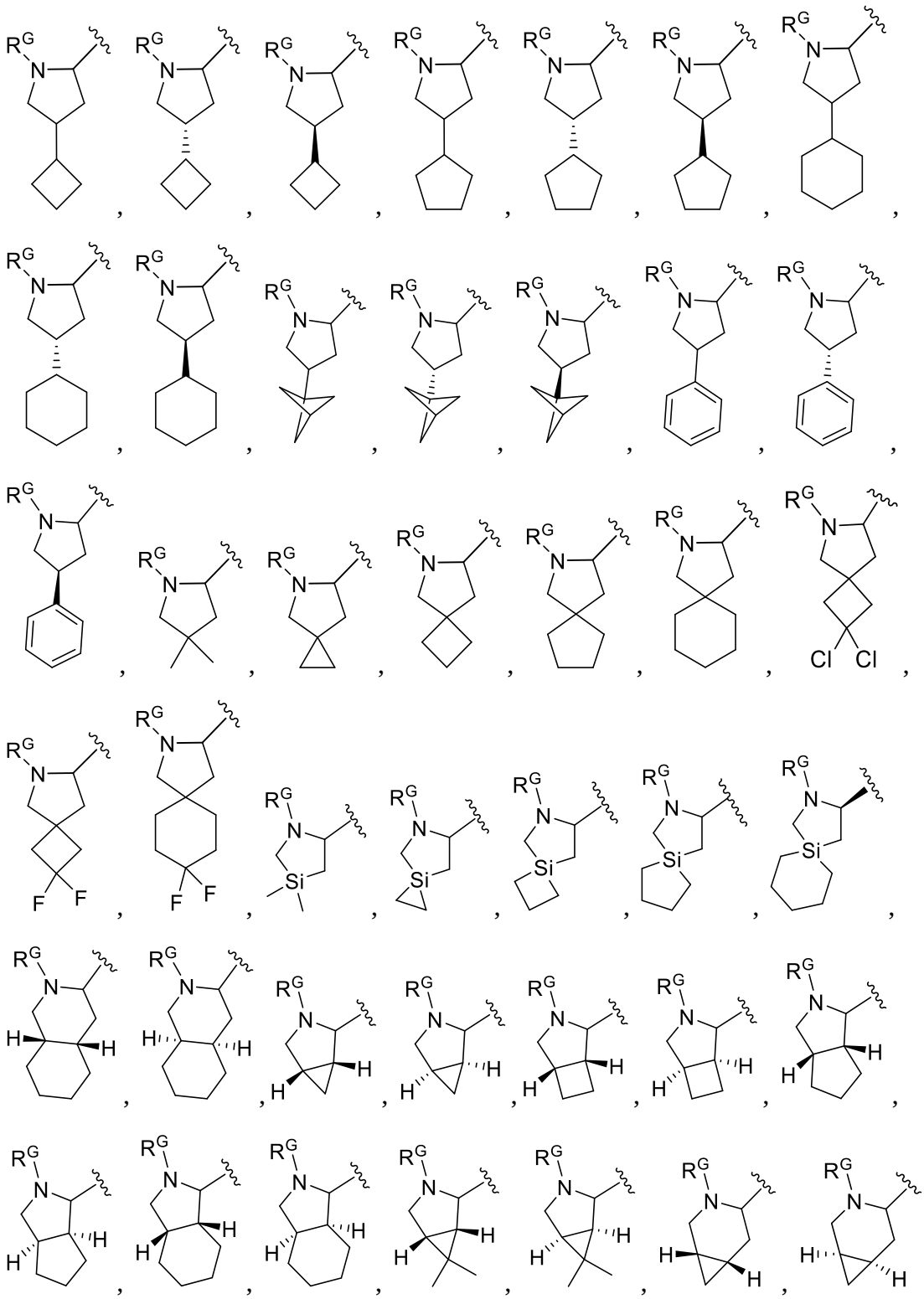

,

,

,

,

,

,

,

,

,

,

,

,

,

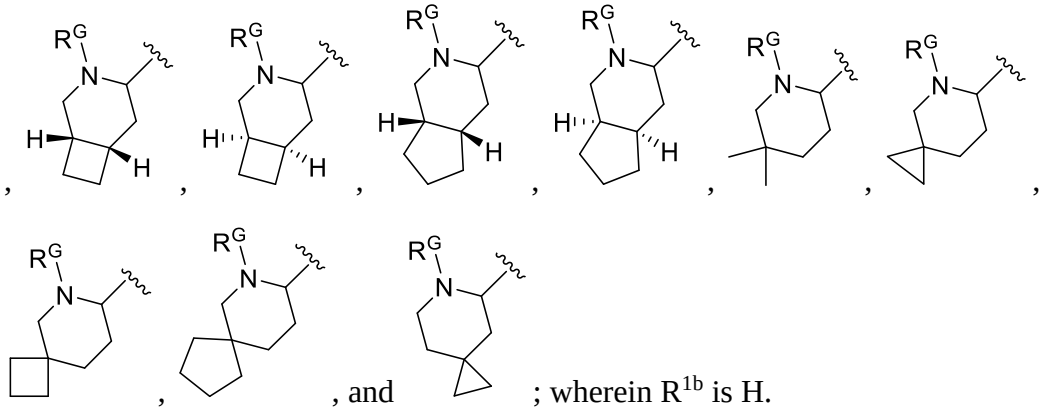
, and

.

22. The compound of claim 1, wherein R^{1a} and R^2 are joined to together to form the heterocycle selected from the group consisting of:


RG
N
Boc
O
HN
CF3
F

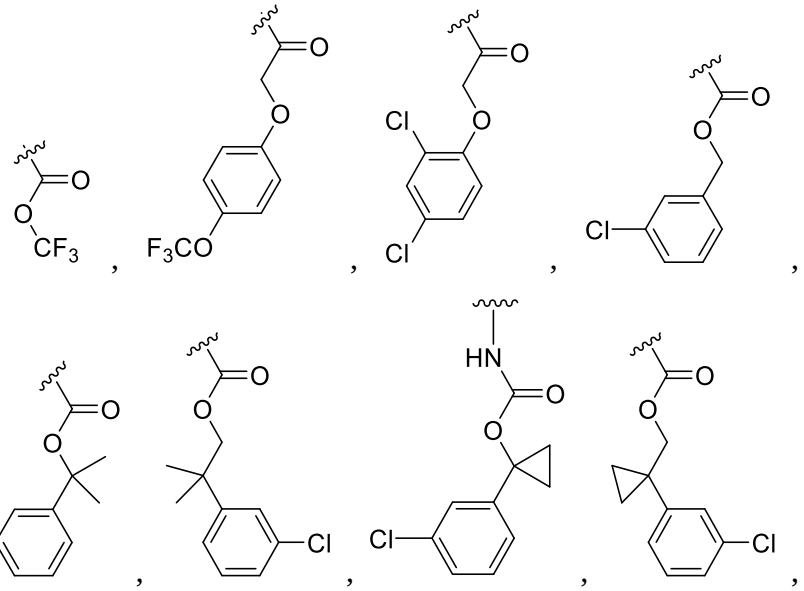


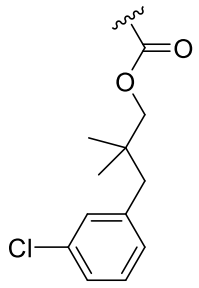
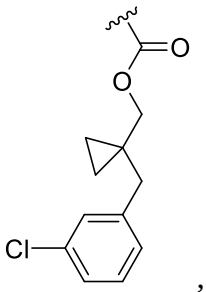
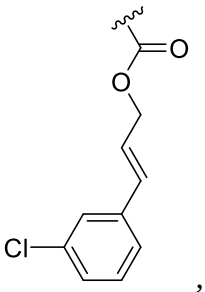
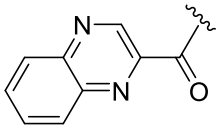
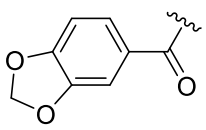
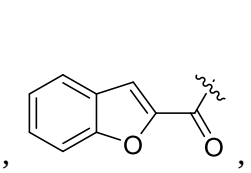
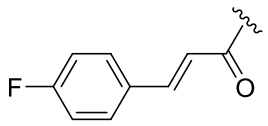
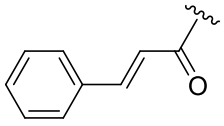
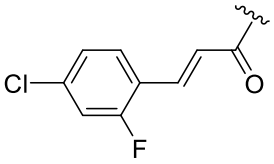
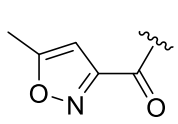
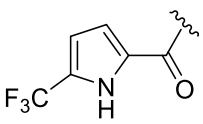
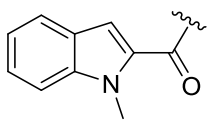
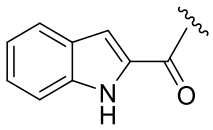
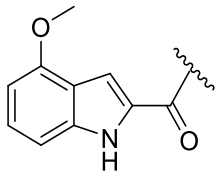
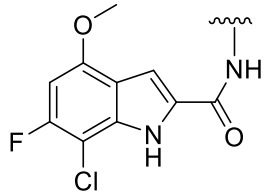
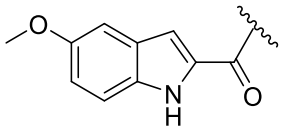
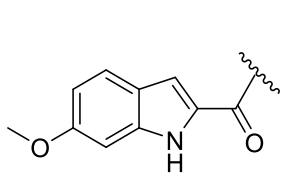
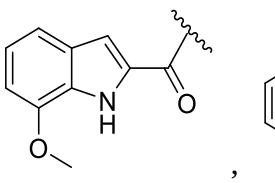
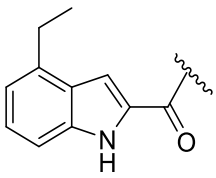
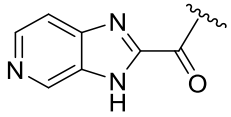
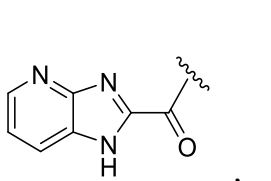
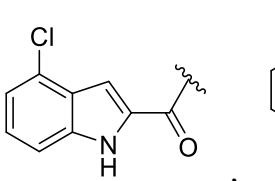
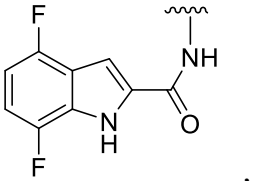
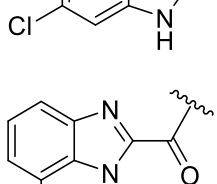
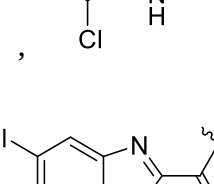
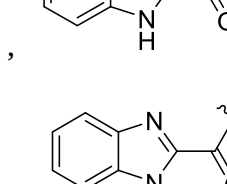
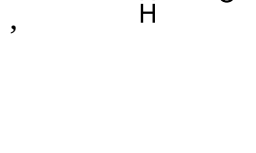
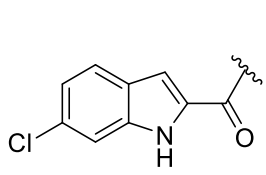
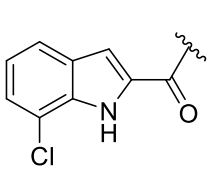
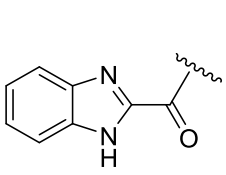
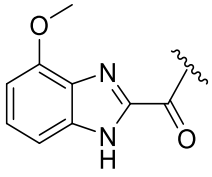
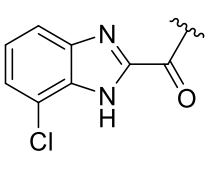


; wherein R^{1b} is H.

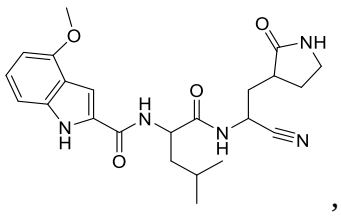
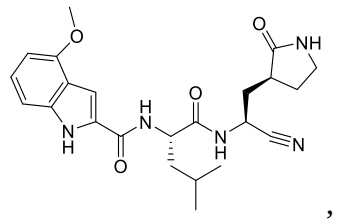
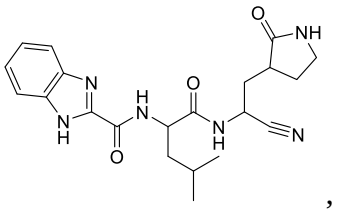
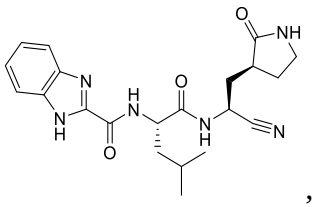
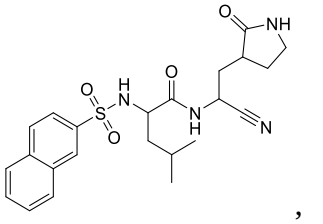
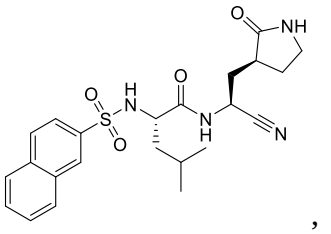
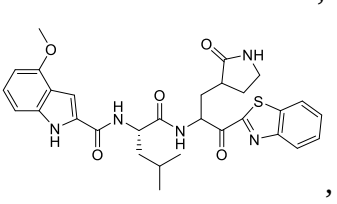
23. The compound of any one of claims 1, 10 and 22, wherein R^G is selected from the group consisting of hydrogen, C_{1-6}alkyl optionally substituted by one, two or three R^{gg}, –C(=O)-C_{1-6}alkyl optionally substituted by one, two or three R^{hh}, and -C(=O)-C_{3-6}cycloalkyl.

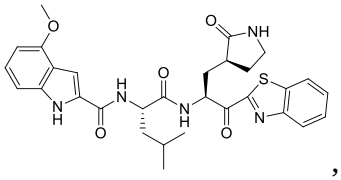
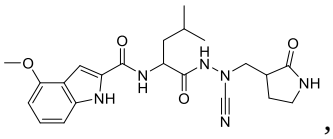
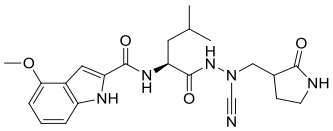
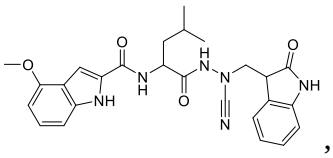
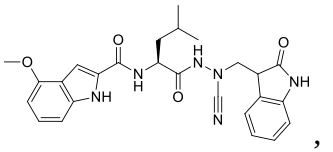
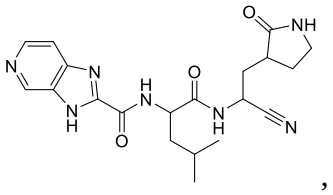
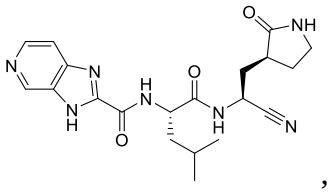
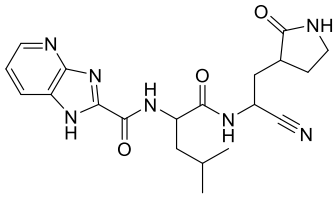
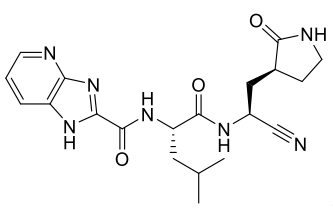
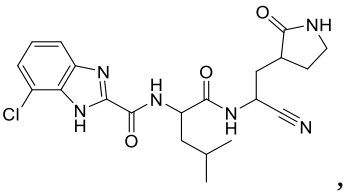
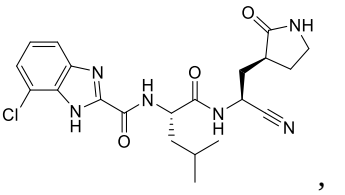
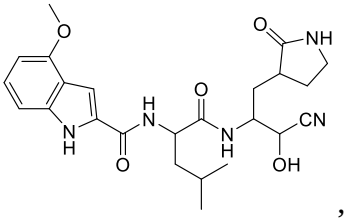
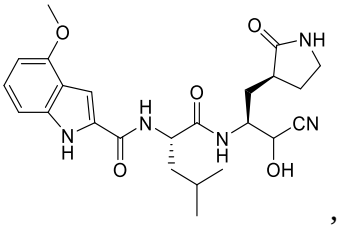
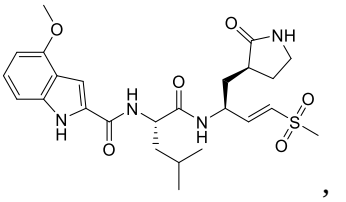
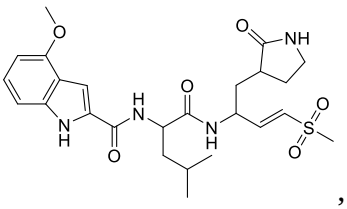
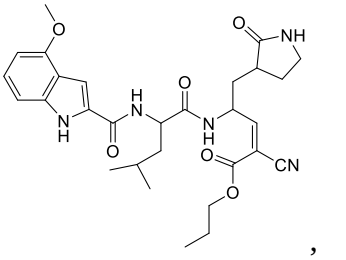
24. The compound of any one of claims 1, 10 and 22, wherein R^G is selected from the group consisting of –C(O)-(C_2-C_{10}alkenyl)-(C_6-C_{14}aryl), –C(O)-(C_1-C_6alkyl)-O-(C_6-C_{14}aryl), –C(O)-(5-10 membered heteroaryl), –C(O)-(4-10 membered heterocyclyl), and –C(O)-(4-10 membered heterocyclyloxy); wherein the aryl, heterocyclyl, or heteroaryl may optionally be substituted by one, two or three R^{jj}.

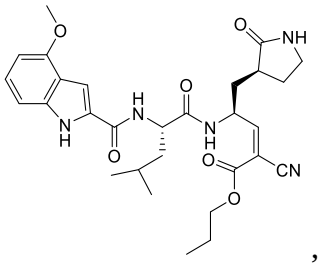
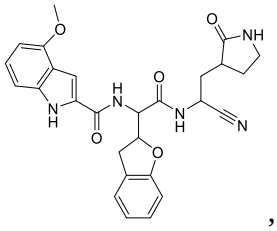
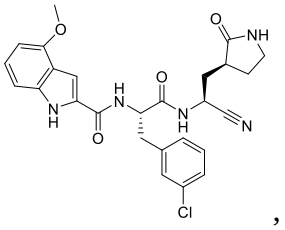
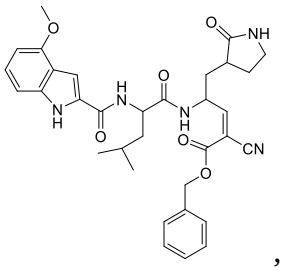
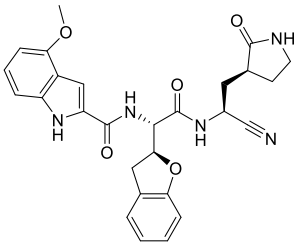
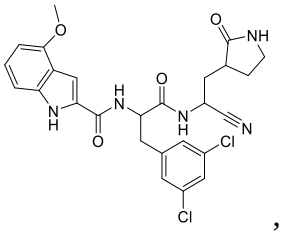
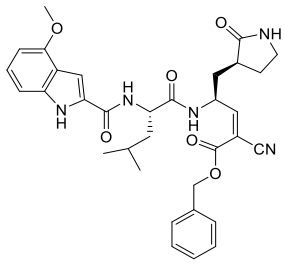
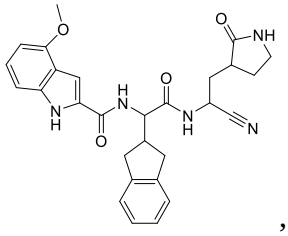
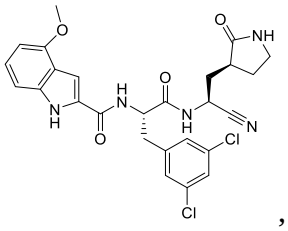
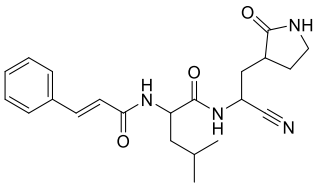
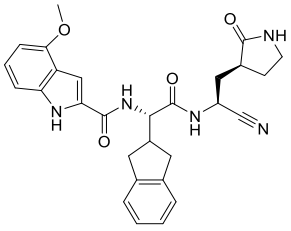
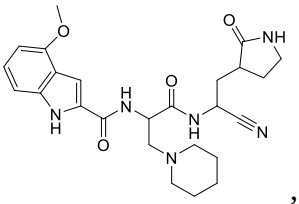
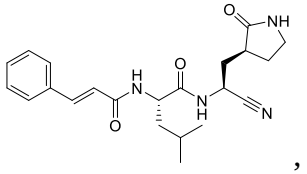
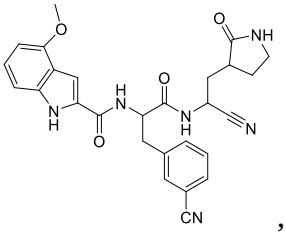
25. The compound of any one of claims 1, 10 and 22, wherein R^G is selected from the group consisting of 

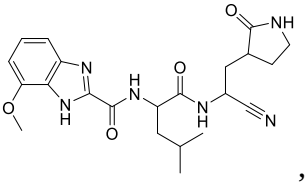
, , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , and .

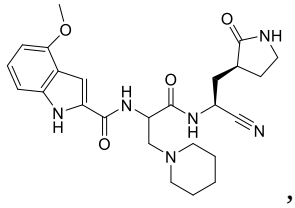
26. A compound selected from the group consisting of:

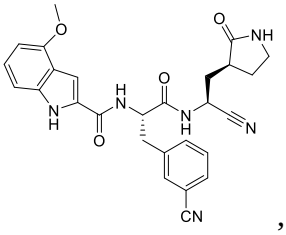
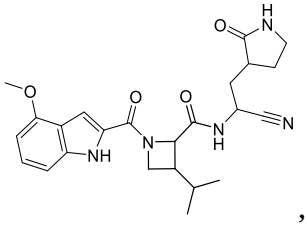
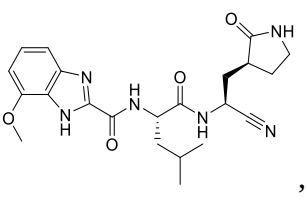

,

,

,

,

,

,

,

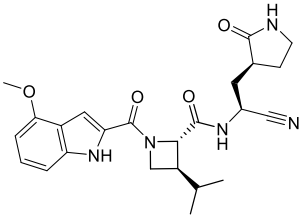
,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

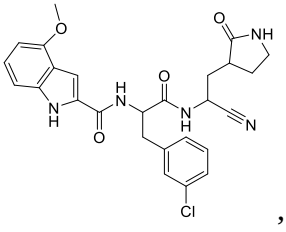

,

,

,

,

,

,

,

,

,

,

,

,

,

,

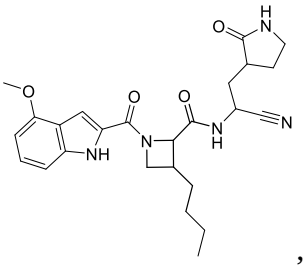
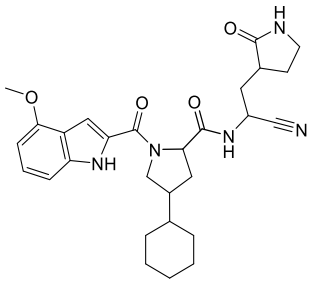
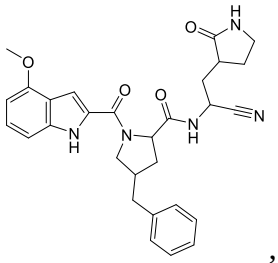
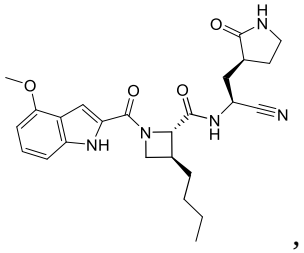
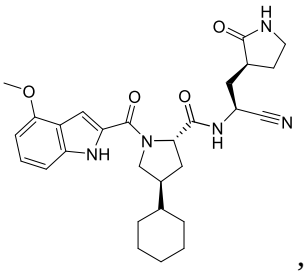
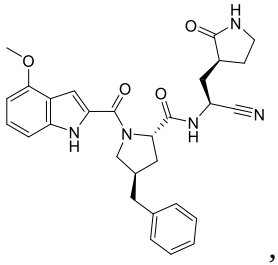
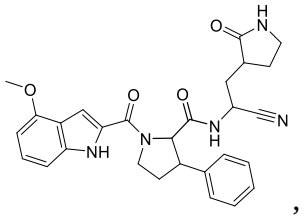
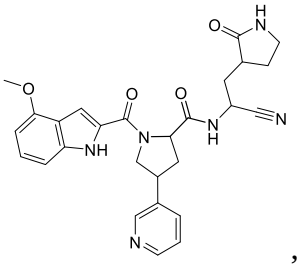
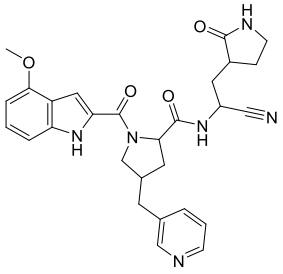
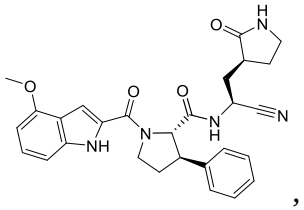
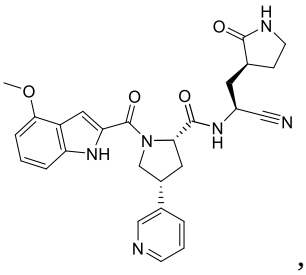
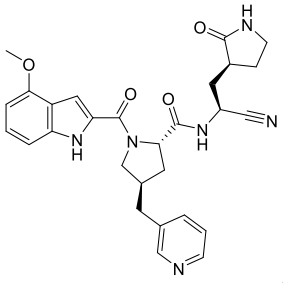
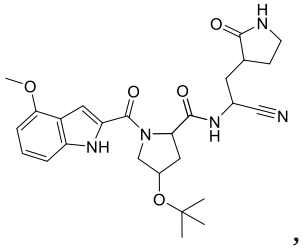
,

,

,

,

,

,

,

,

,

,

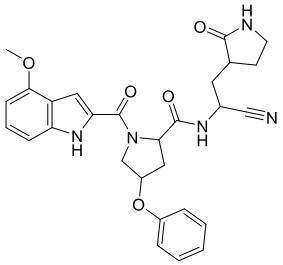
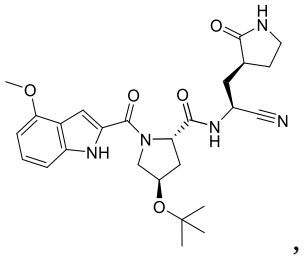
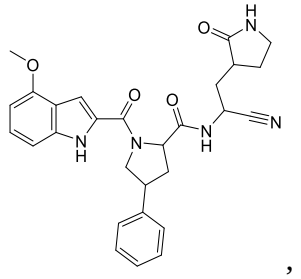
,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

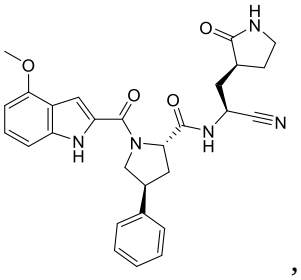
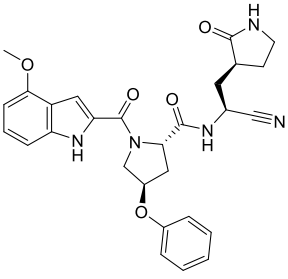
,

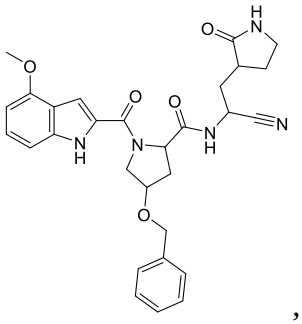
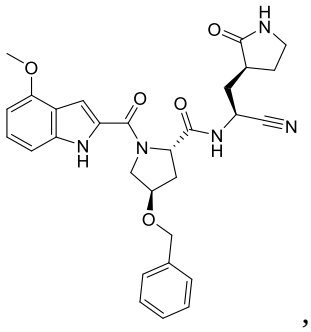
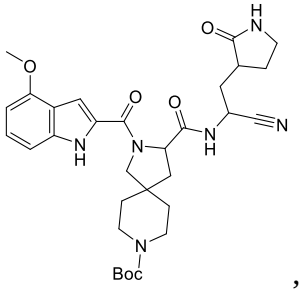
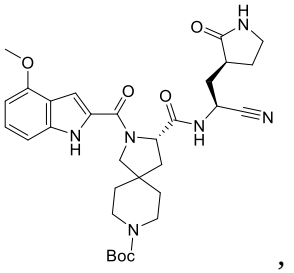
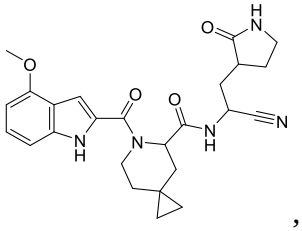
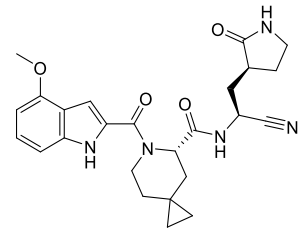
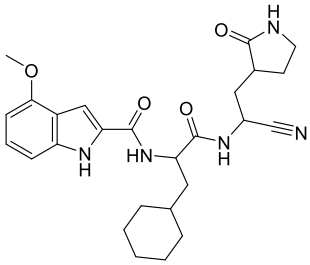
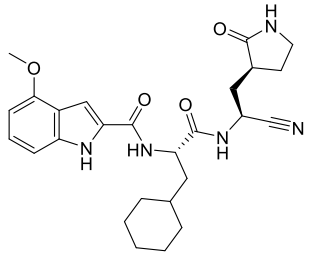
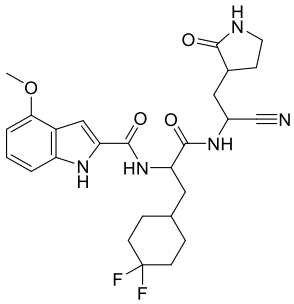
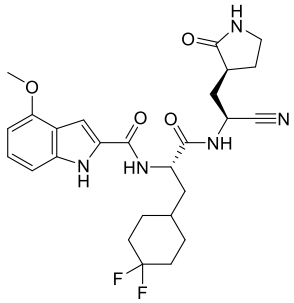
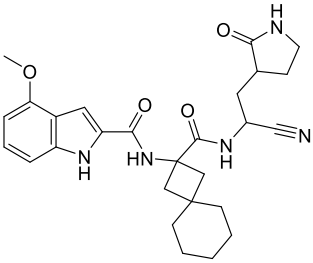
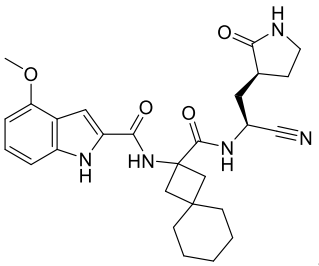
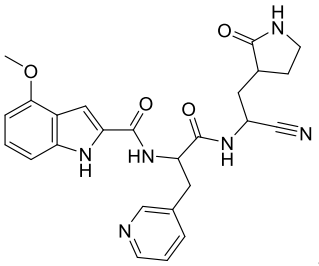
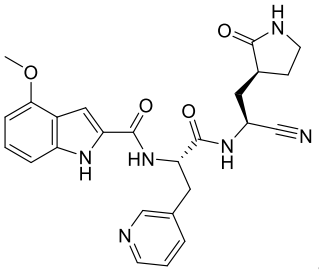
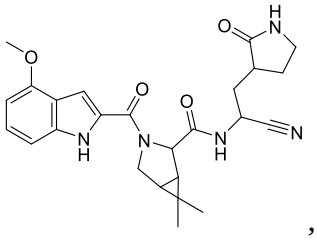
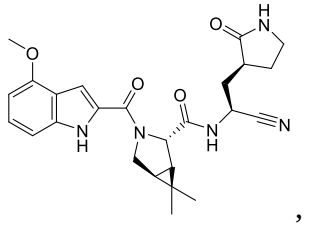
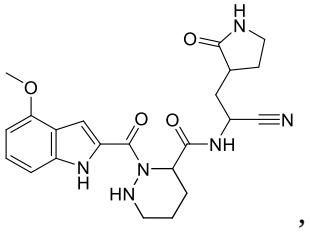
,

,

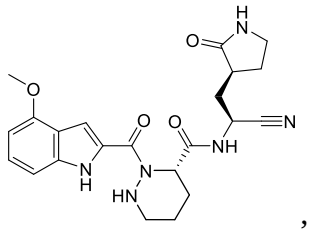
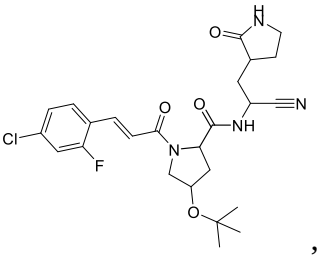
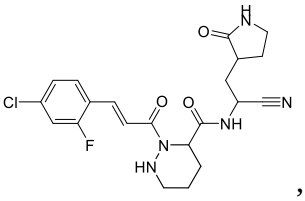
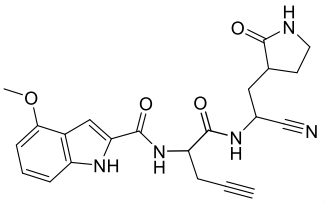
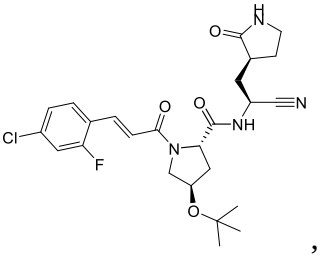
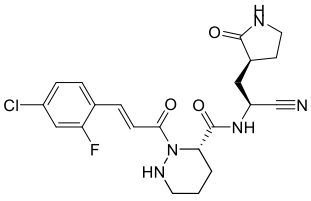
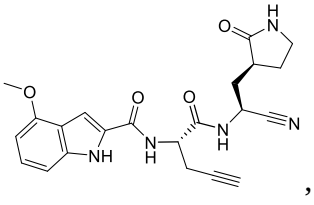
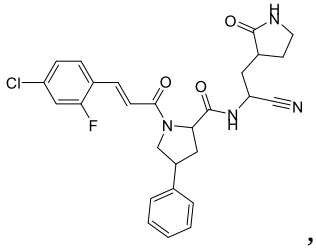
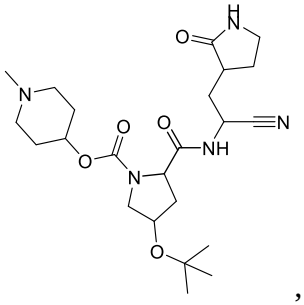
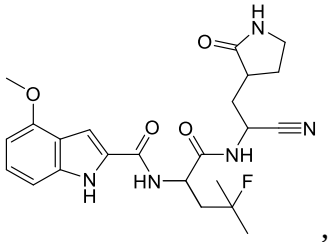
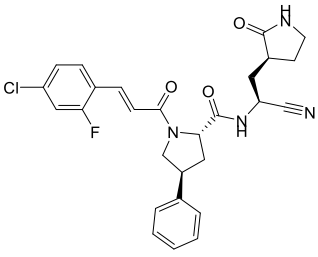
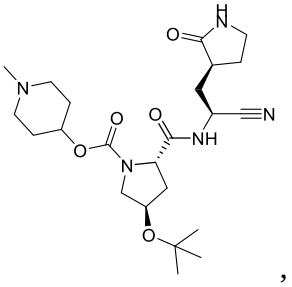
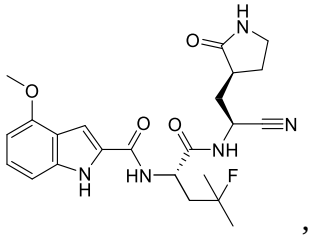
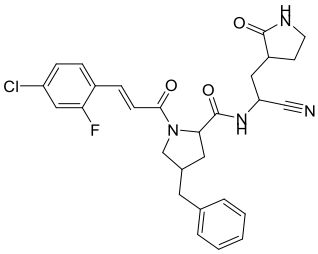
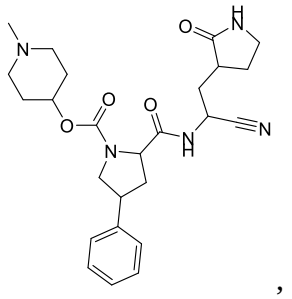
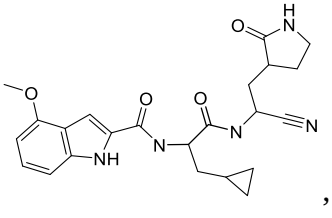
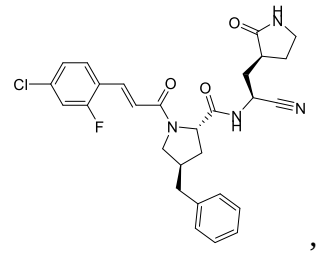
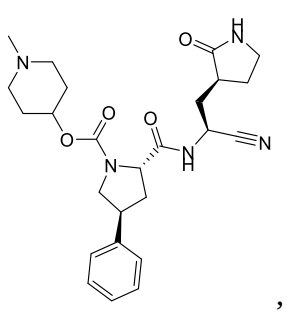
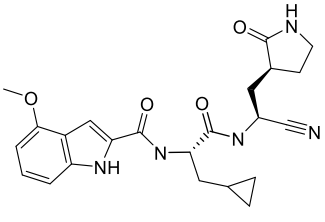
,

,

,

,

,

,

,

,

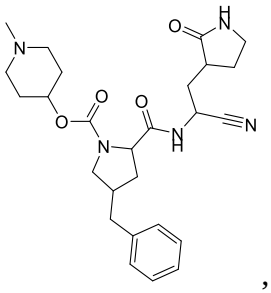
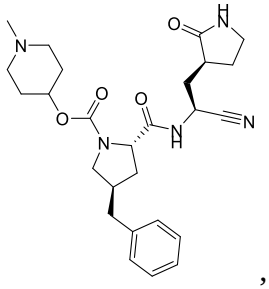
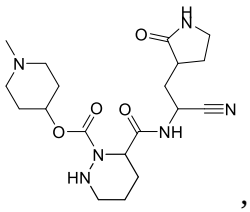
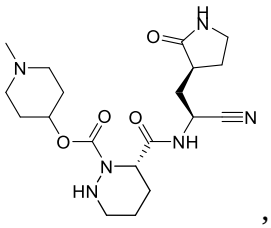
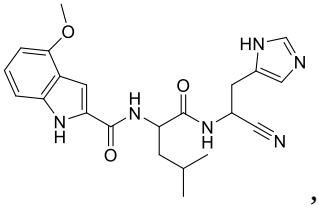
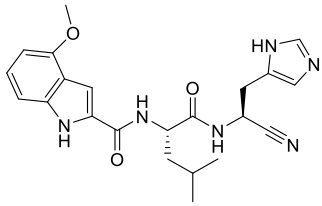
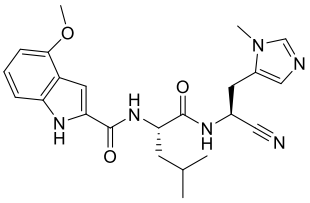
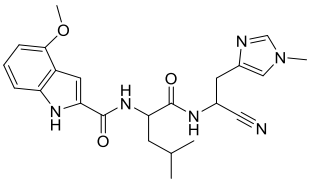
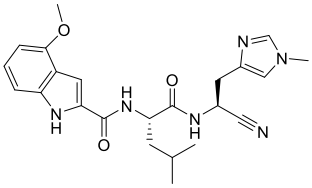
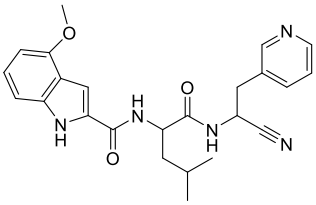
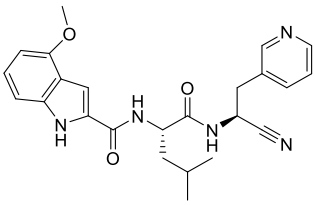
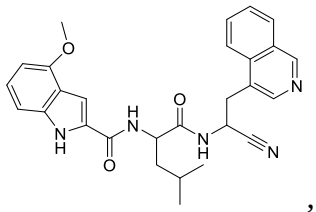
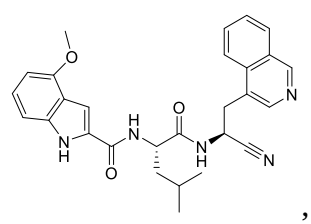

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

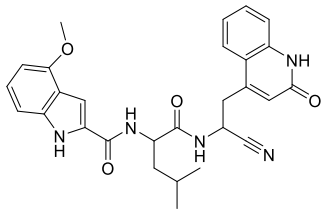
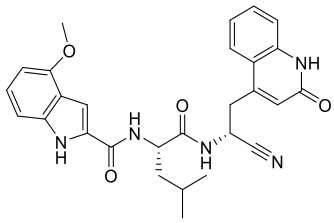
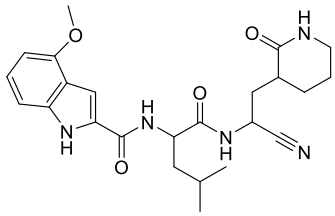
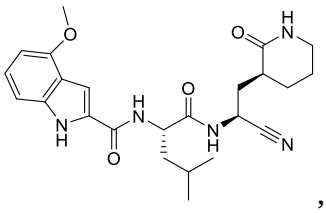
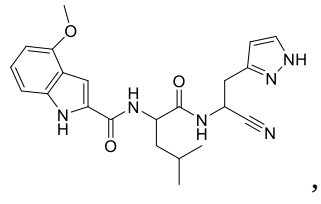
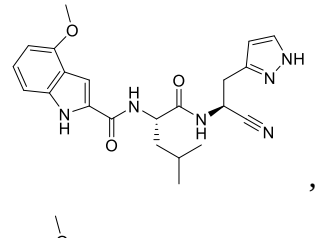
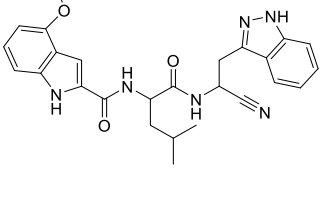
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

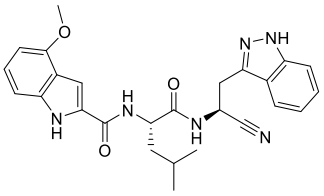
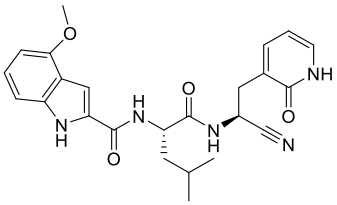
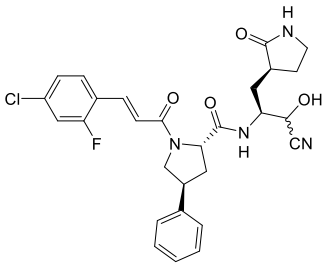
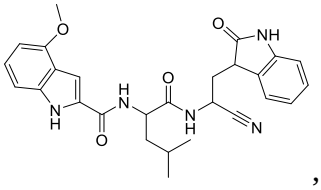
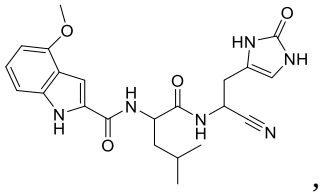
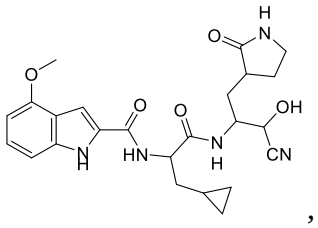
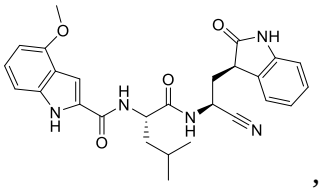
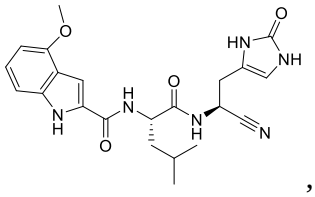
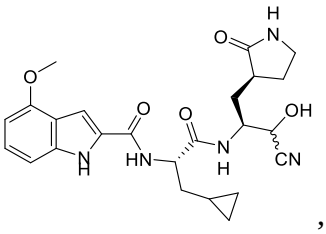
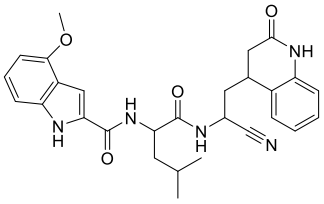
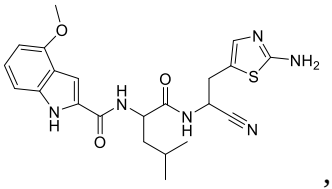
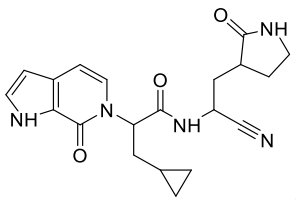
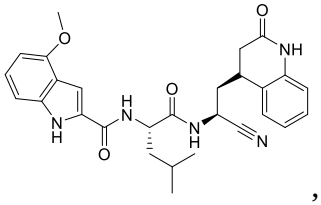
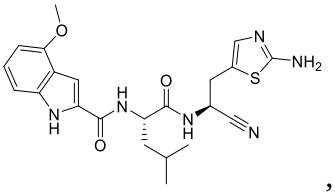
,

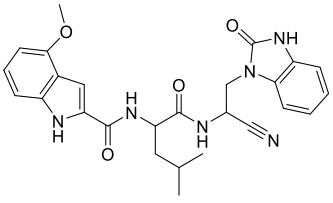
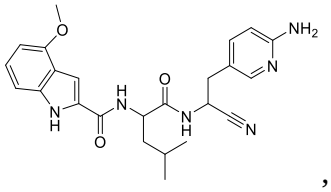
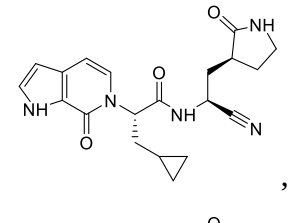
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

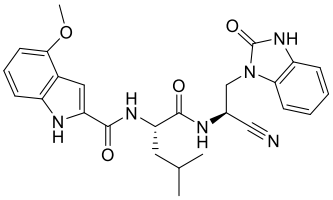
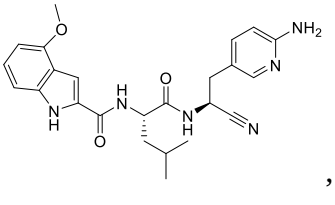
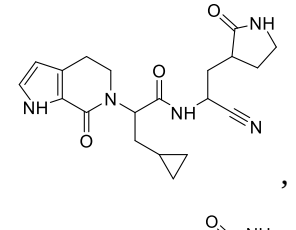
,

,

,

,

,

,

,

,

,

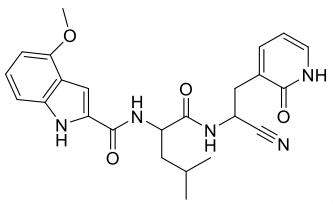
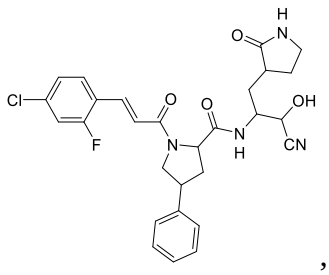
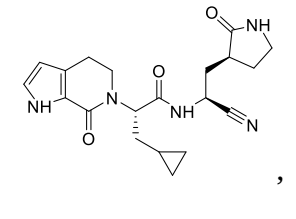
,

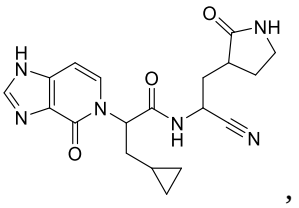
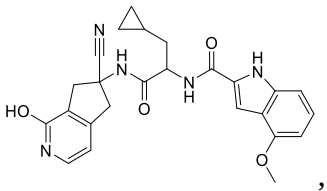
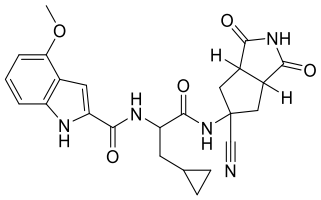
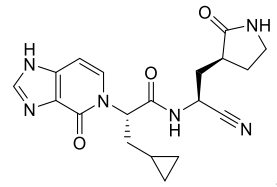
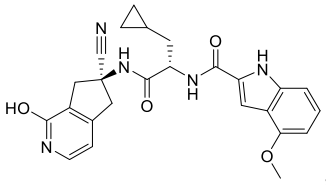
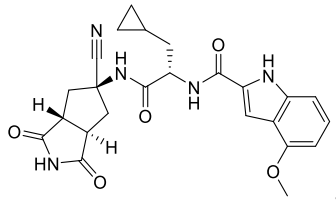
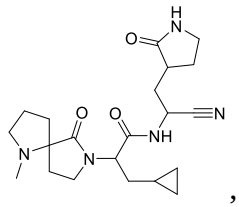
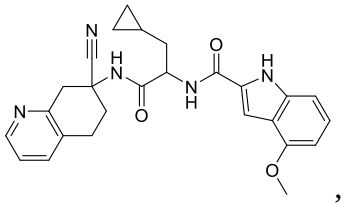
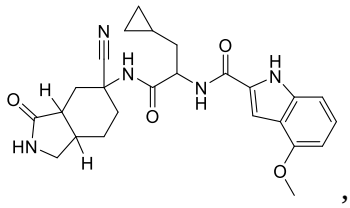
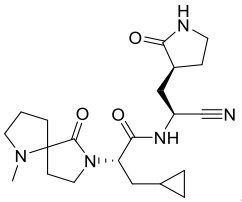
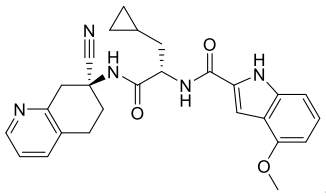
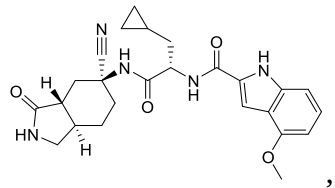
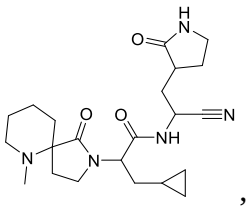
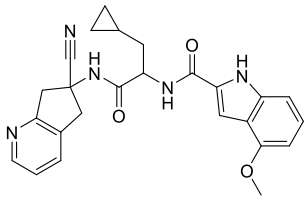
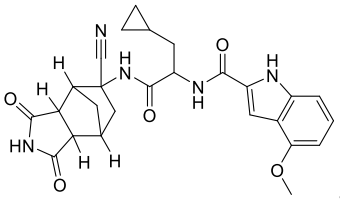
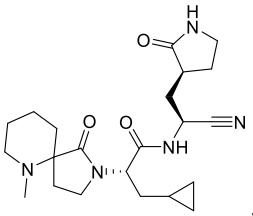
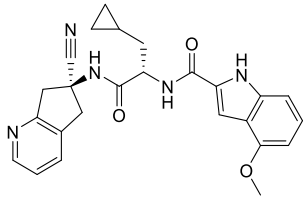
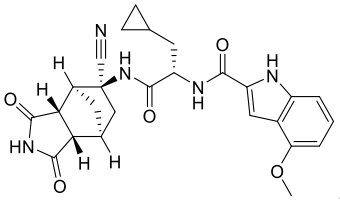
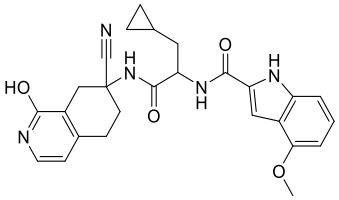
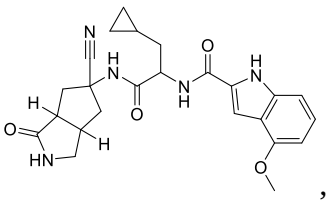
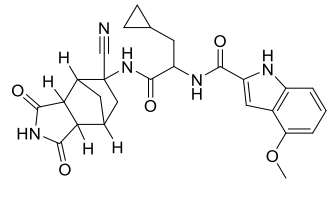
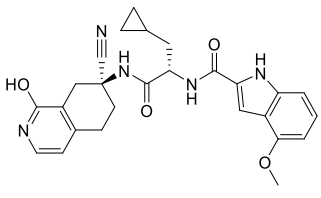
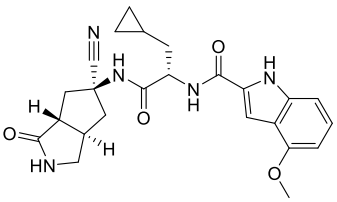
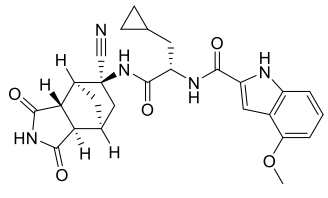
,

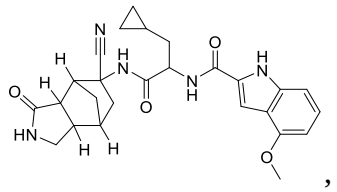
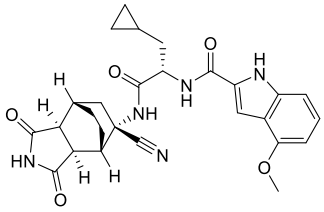
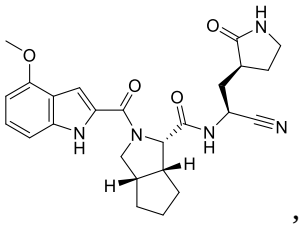
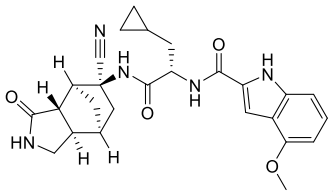
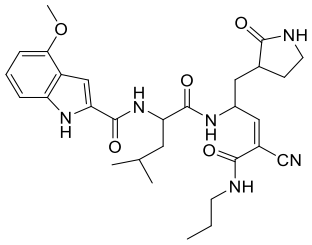
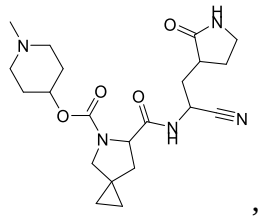
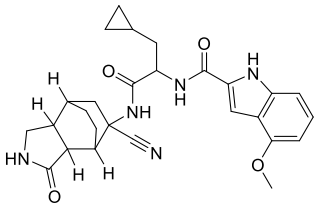
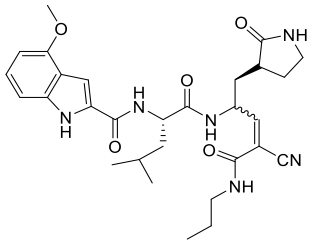
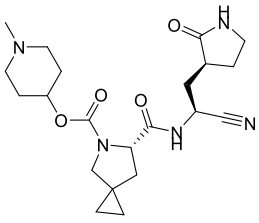
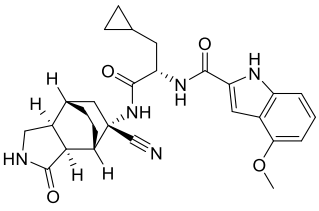
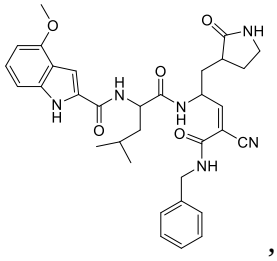
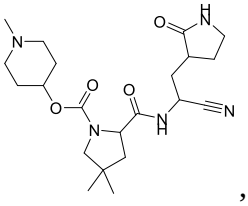
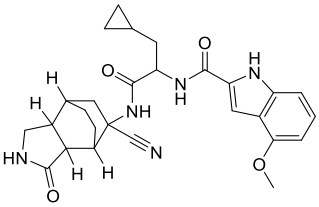
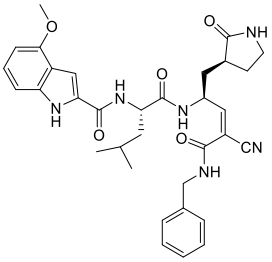
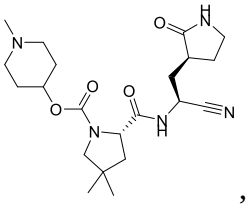
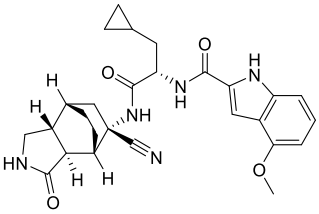
,

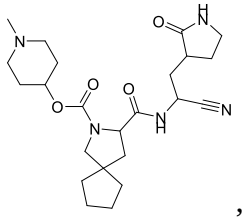
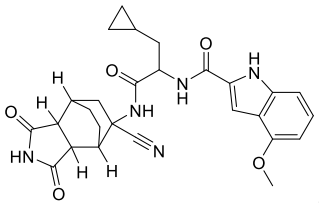
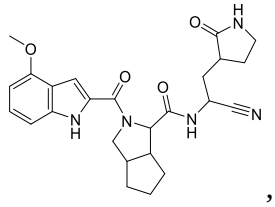
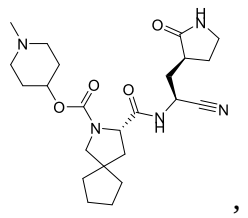
,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

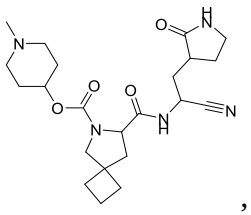
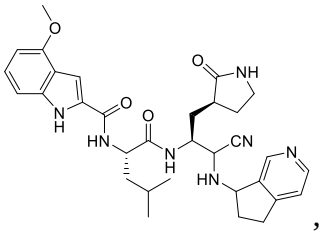
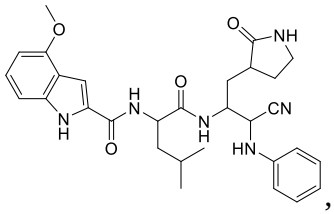
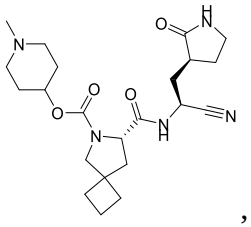
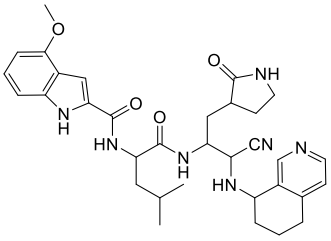
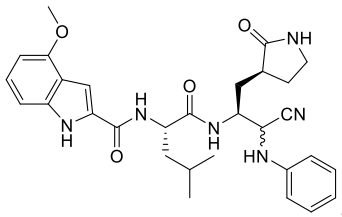
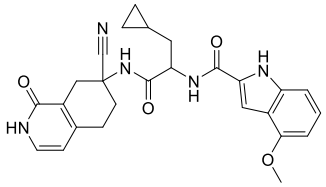
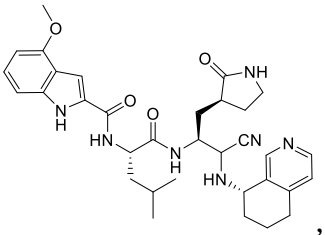
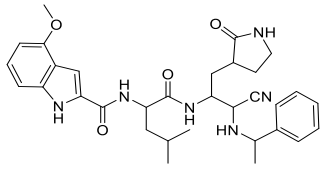
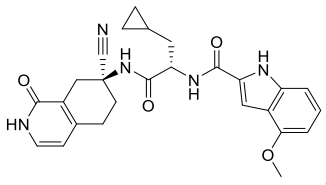
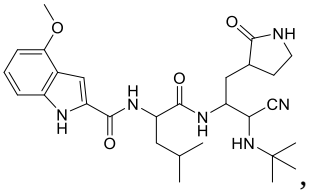
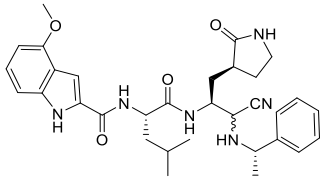
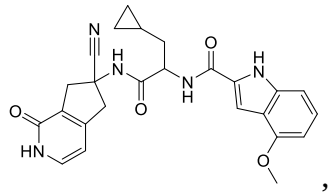
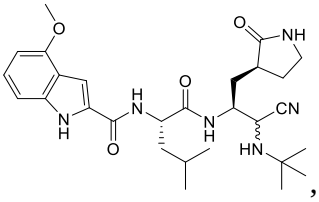
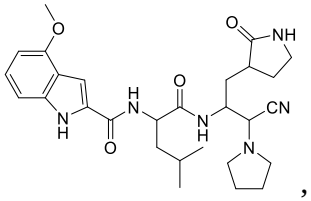
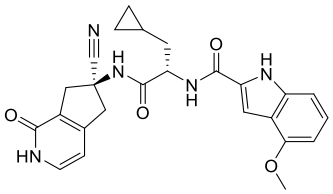

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

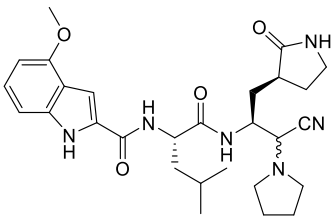
,

,

,

,

,

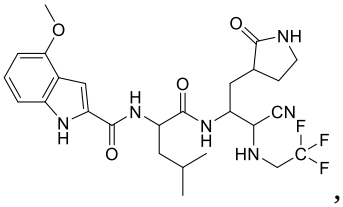
,

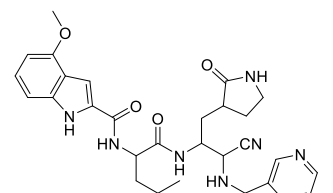
,

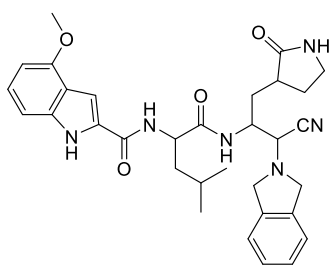
,

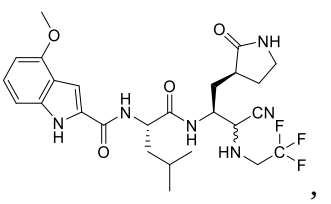

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

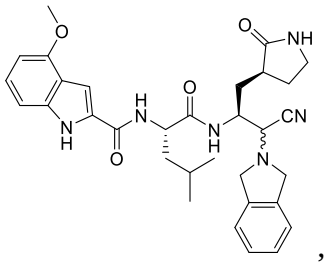
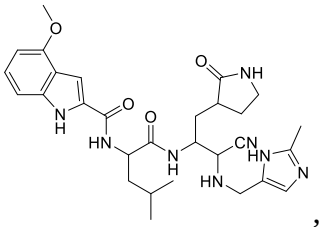
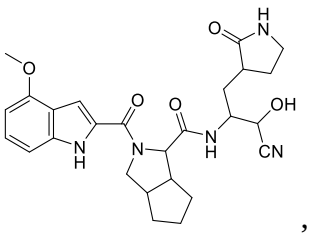
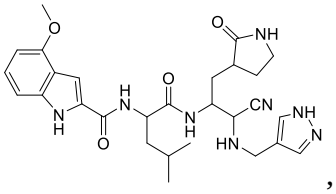
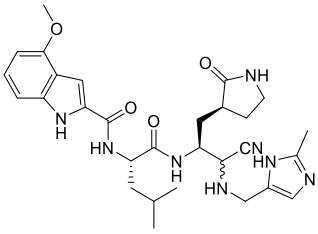
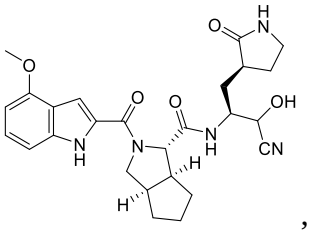
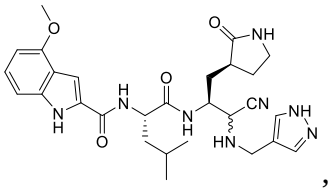
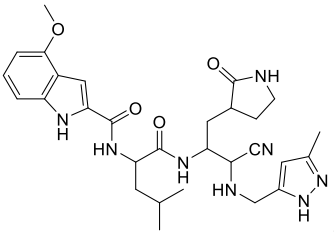
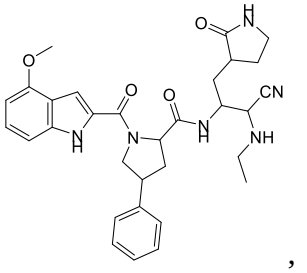
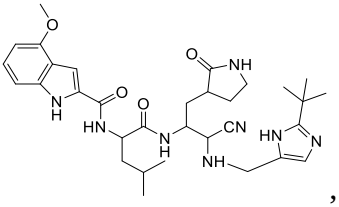
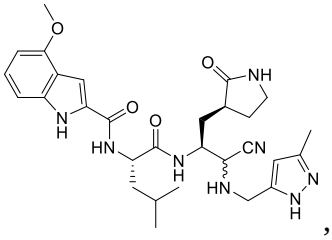
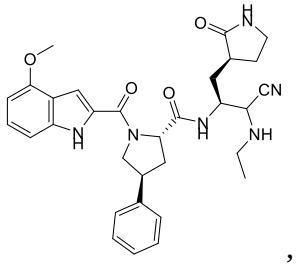
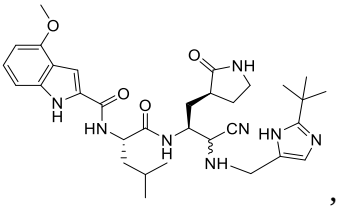
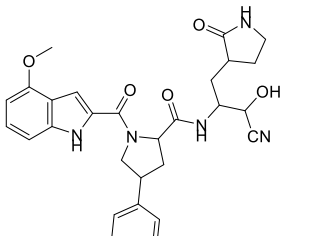
,

,

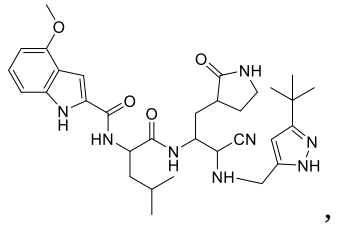
,

,

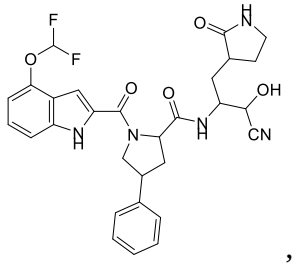
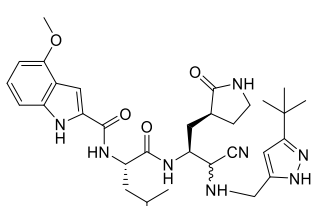
,

,

,

,

,

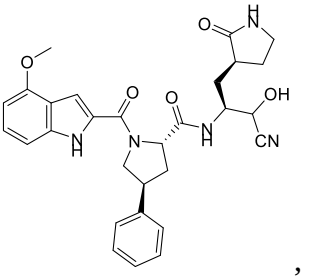
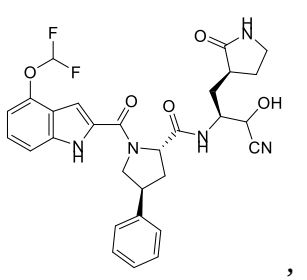

,

,

,

,

,

,

,

,

,

,

,

,

,

,

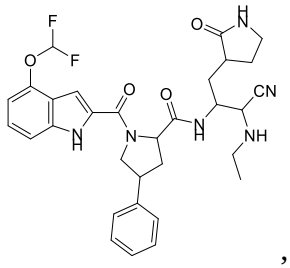
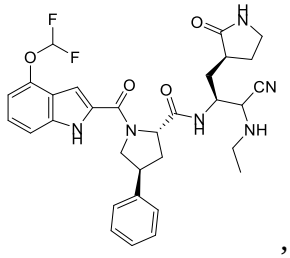
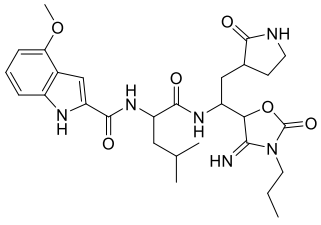
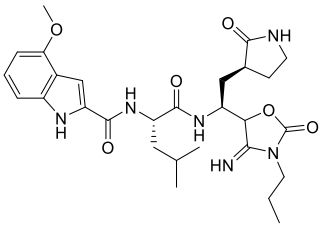
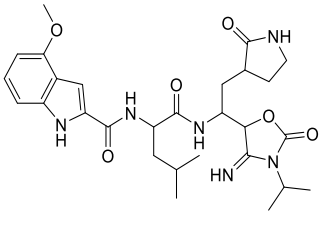
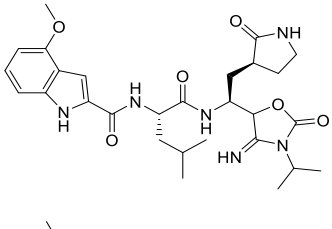
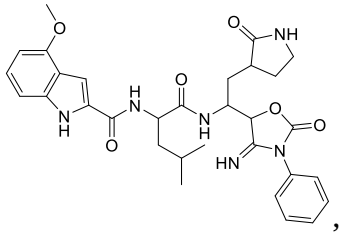
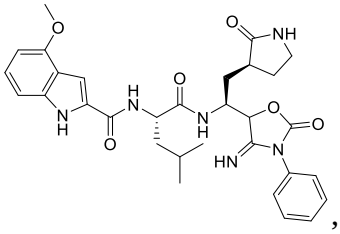
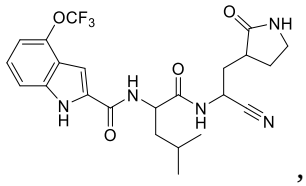
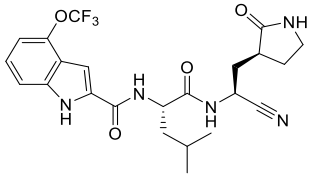
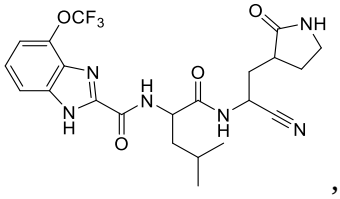
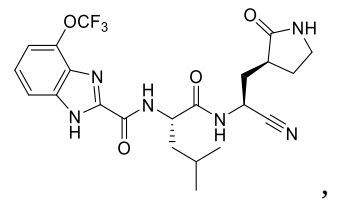
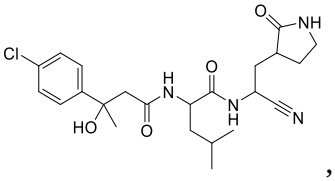
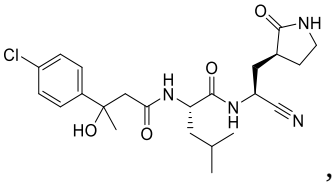
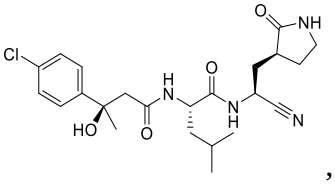
,

,

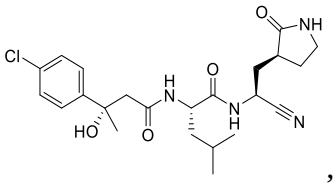
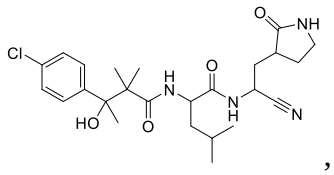
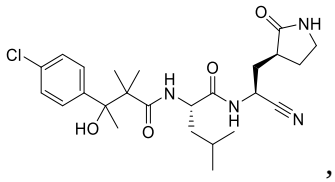
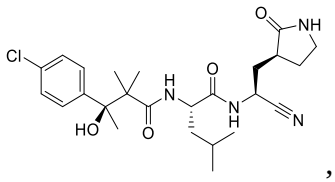
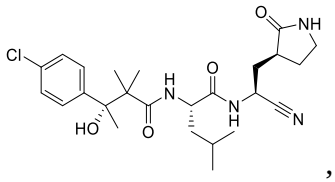
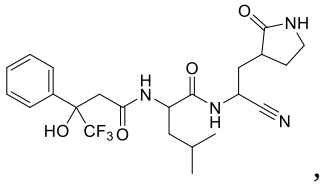
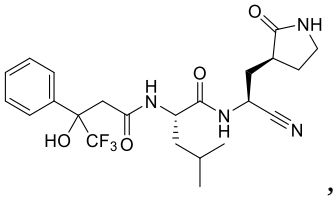
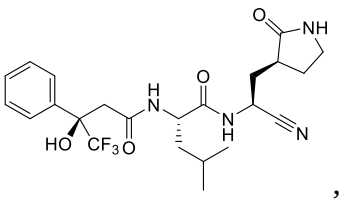
,

,

,

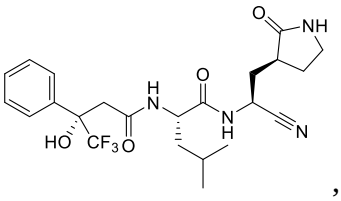
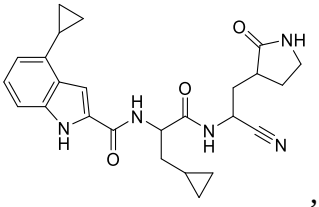
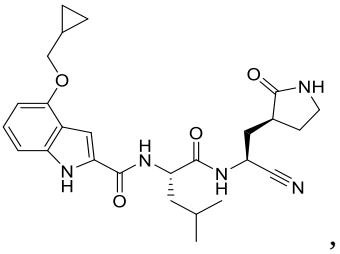
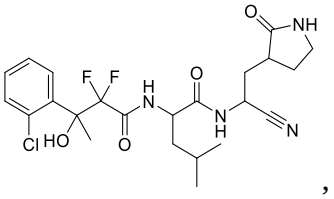
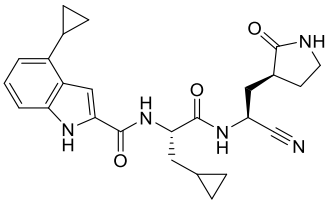
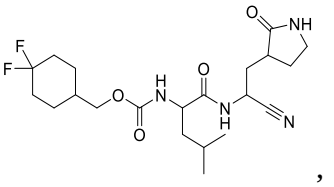
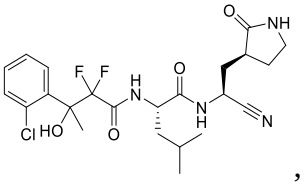
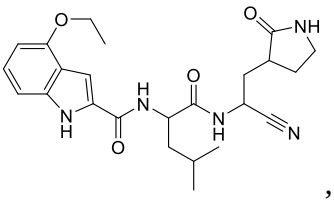
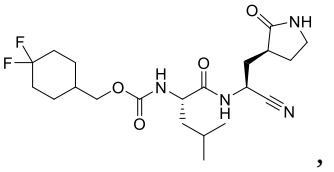
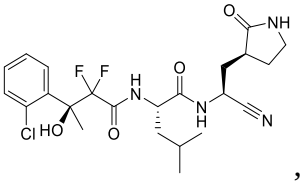
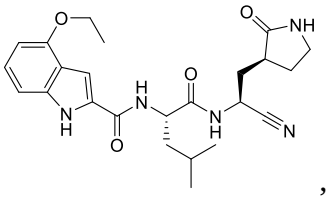
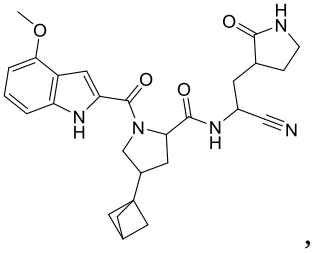
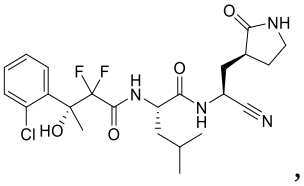
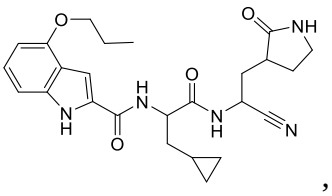
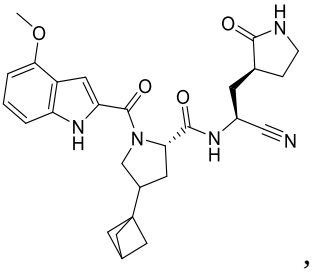
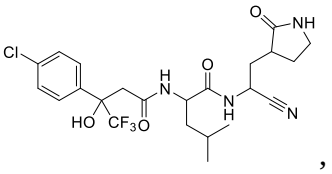
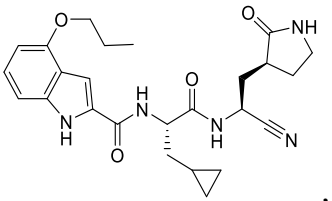
,

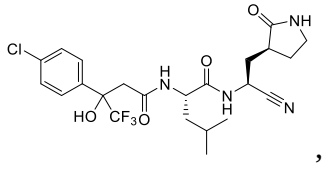
,

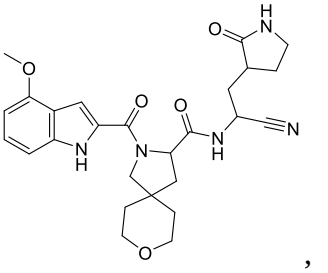
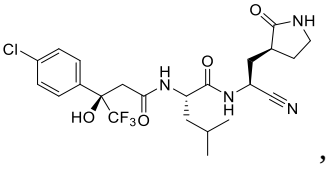
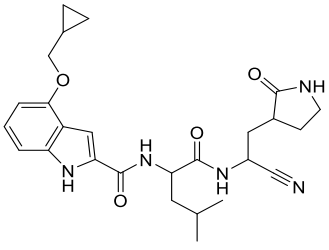
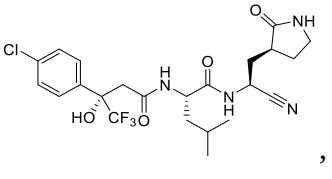
,

,

,

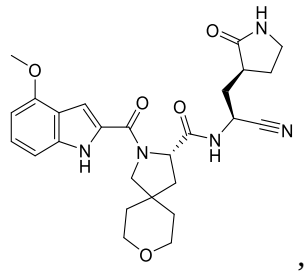
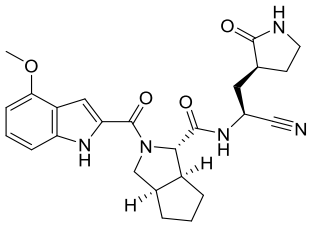
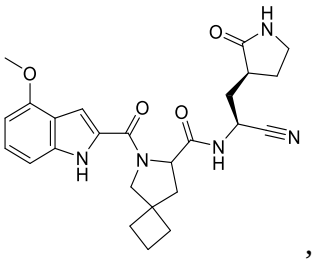
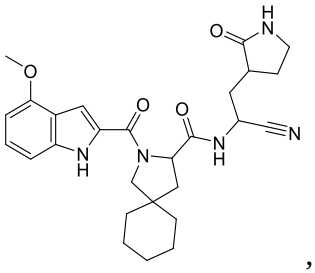
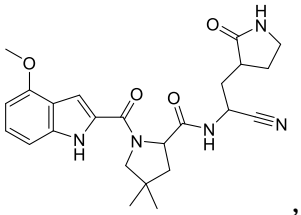
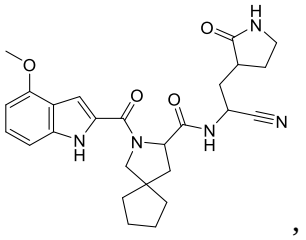
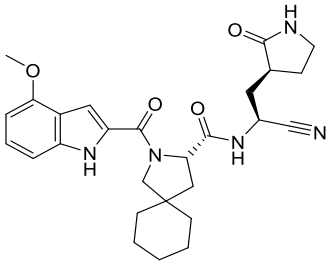
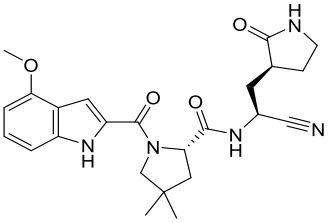
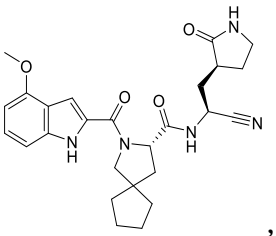
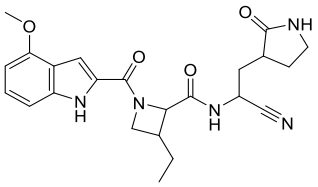
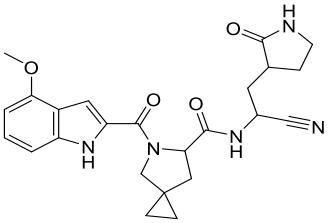
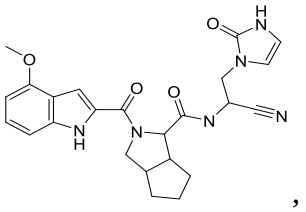
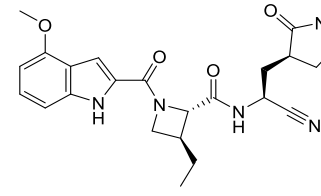
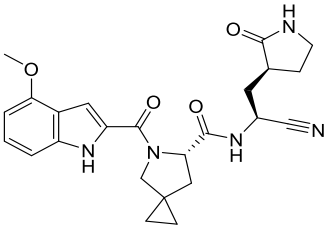
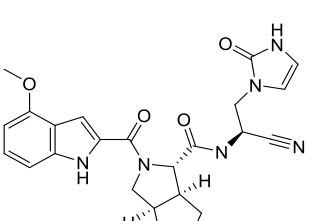

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

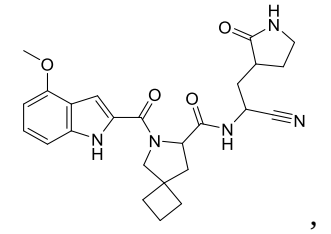
,

,

,

,

,

,

,

,

,

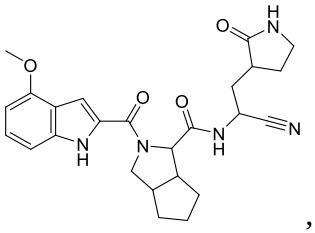

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

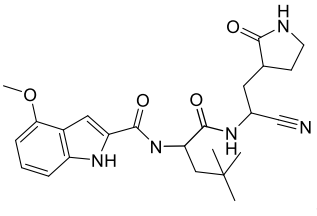
,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

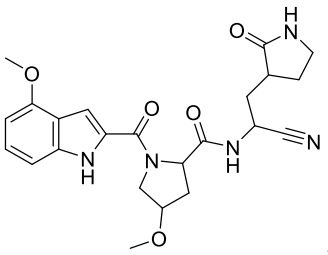
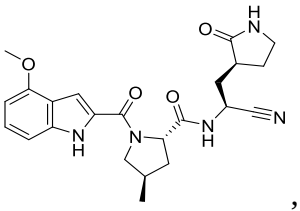
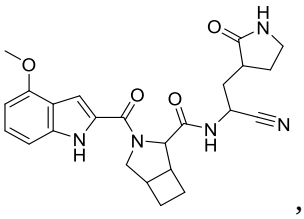
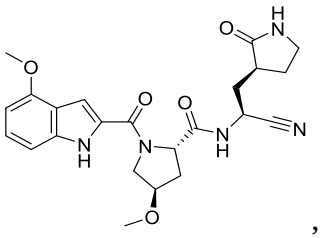
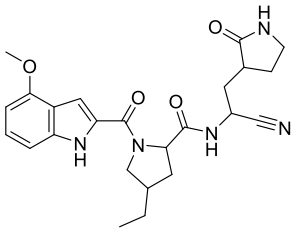
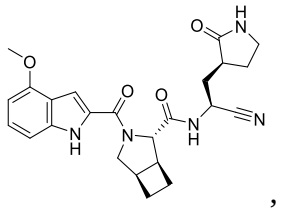
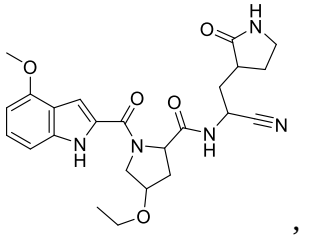
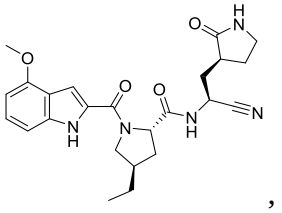
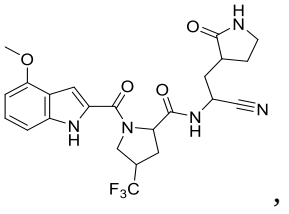
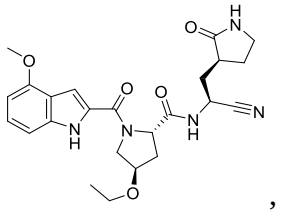
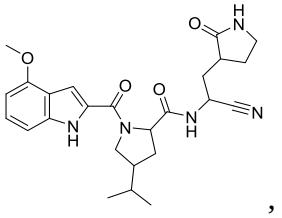
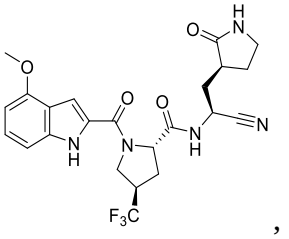
,

,

,

,

,

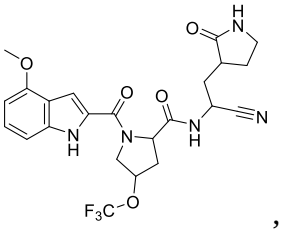
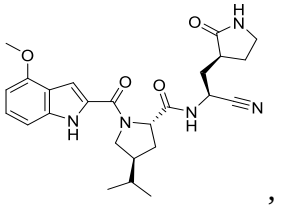
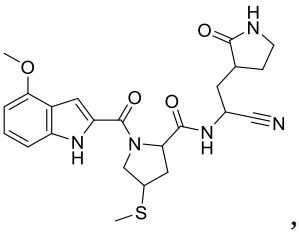
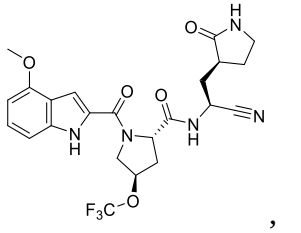
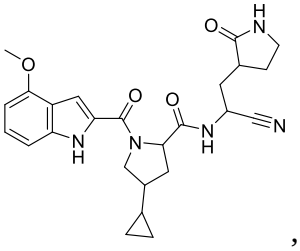
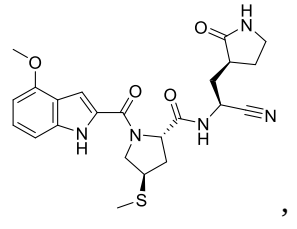
,

,


,

,

,

,

,

,

,

,

,

,

,

,

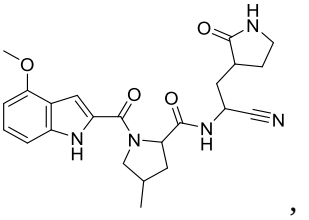
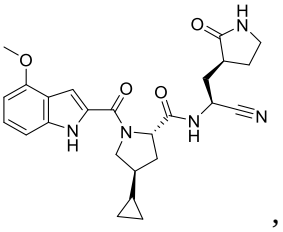
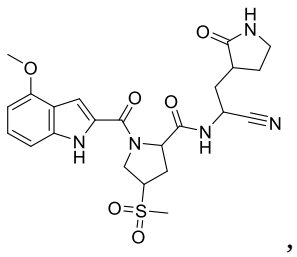
,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

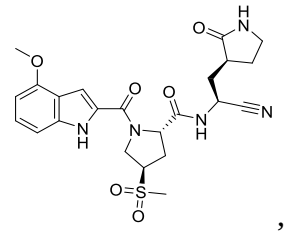
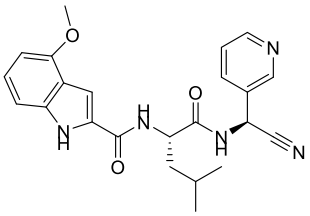
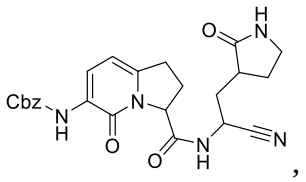
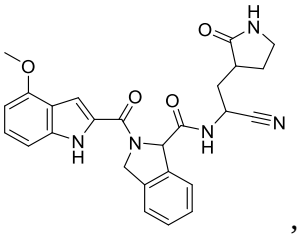
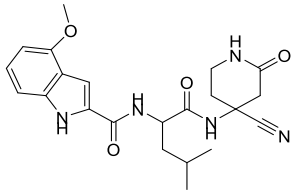
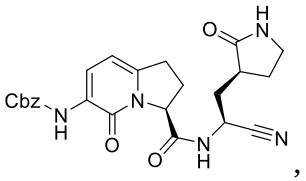
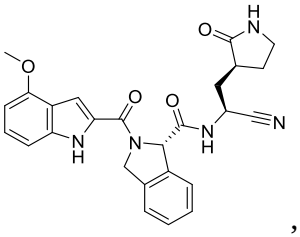
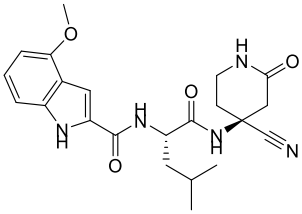
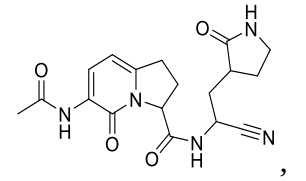
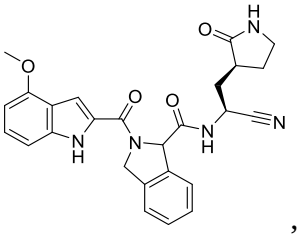
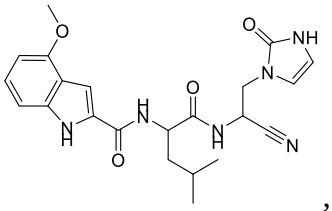
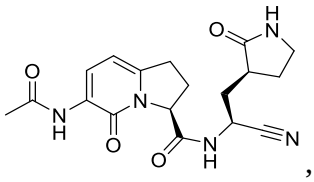
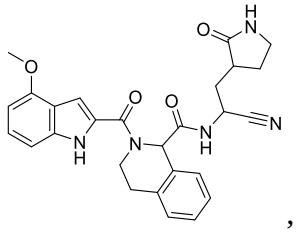
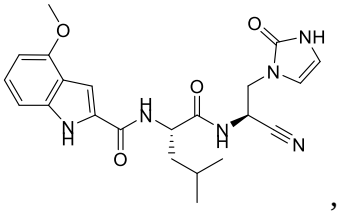
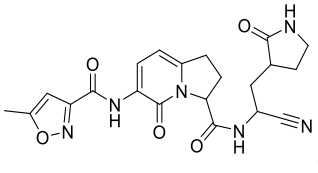
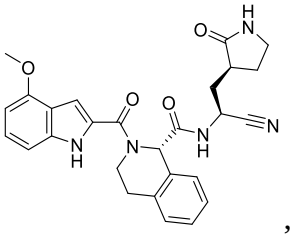
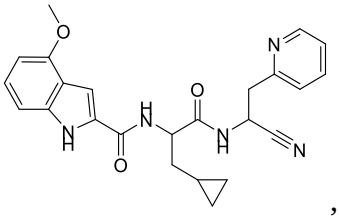
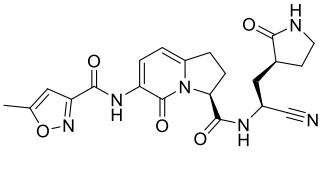
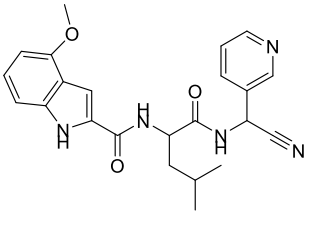
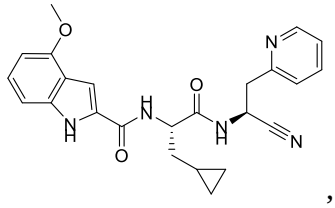
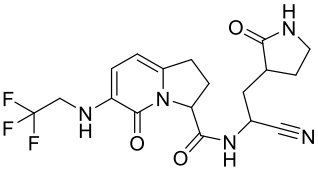
,

,

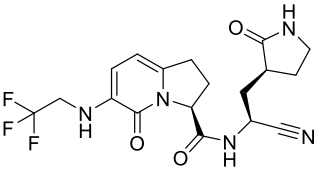
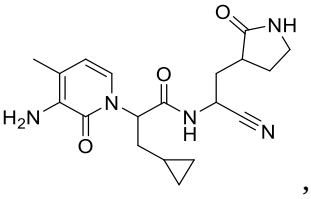
,

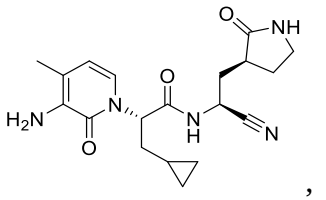
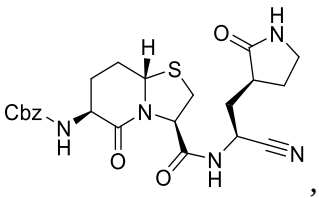
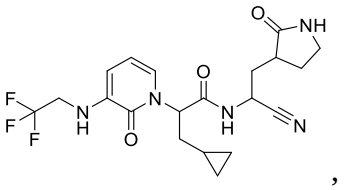
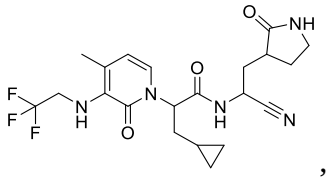
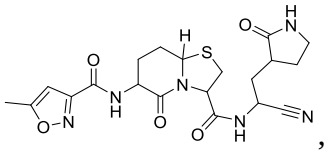
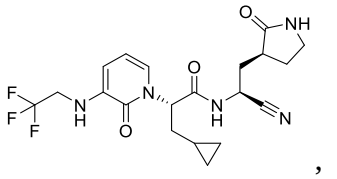
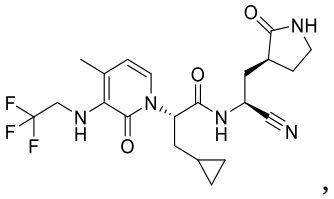
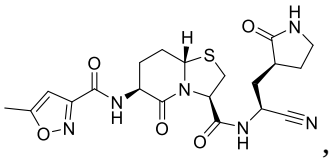
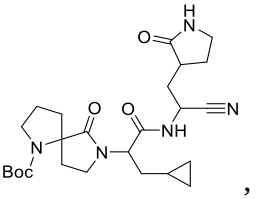
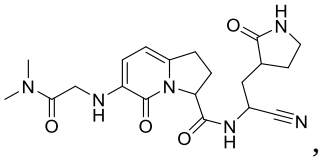
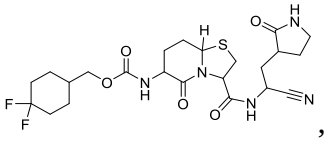
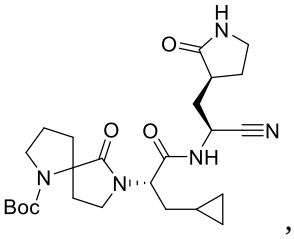
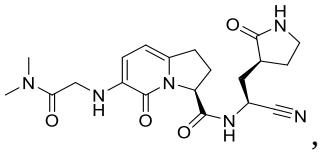
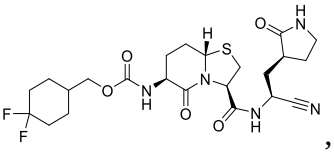
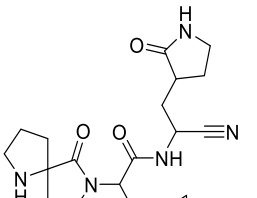
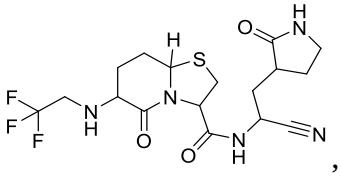
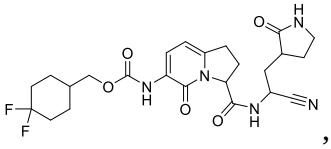
,

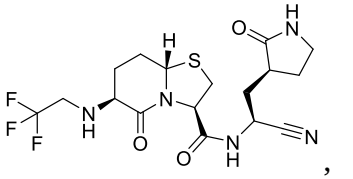
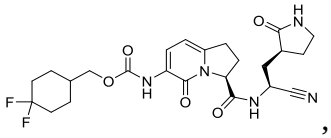
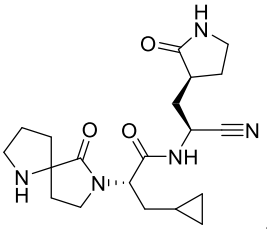
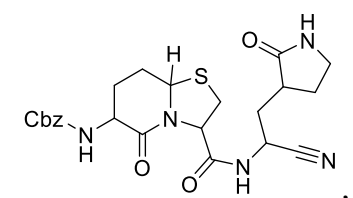
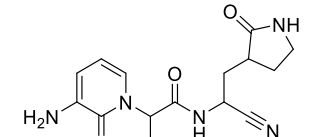
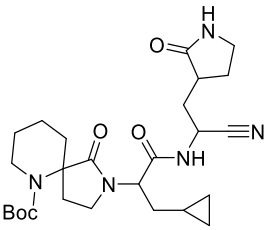
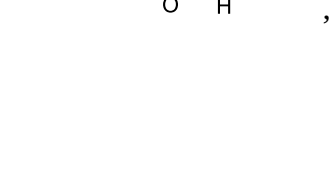
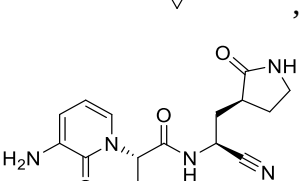
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

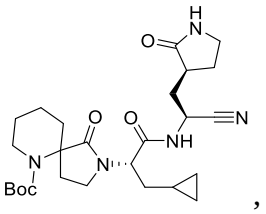
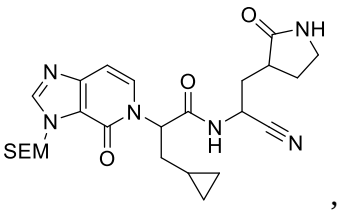
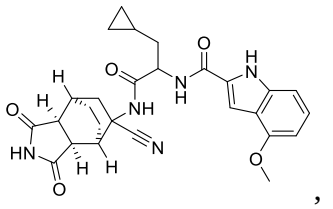
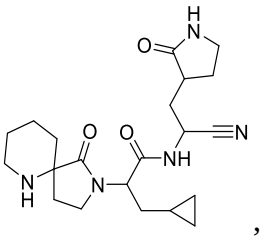
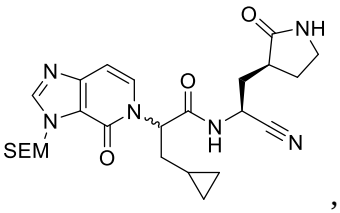
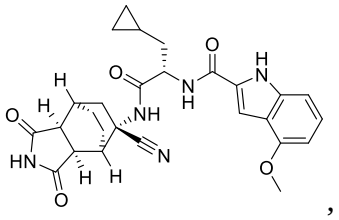
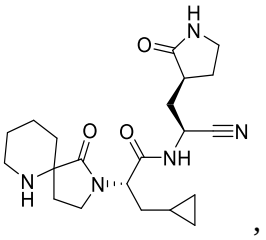
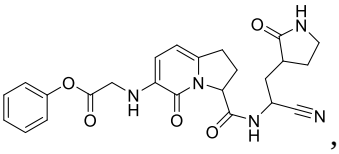
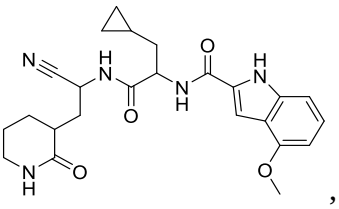
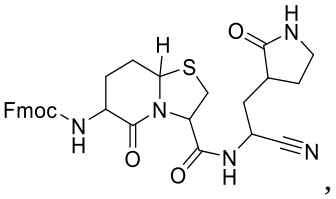
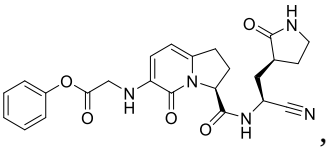
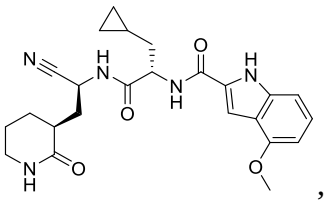
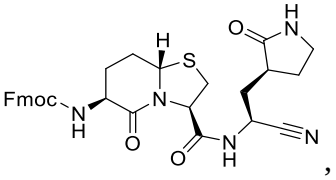
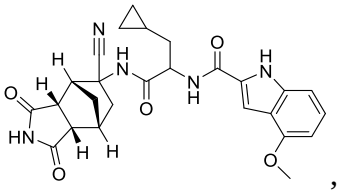
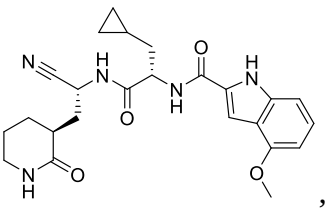
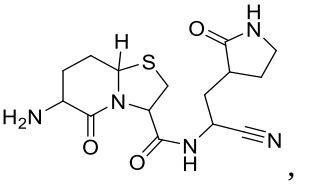
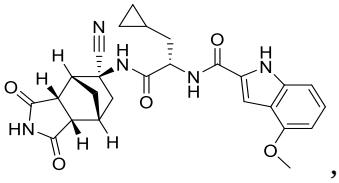
,

,

,

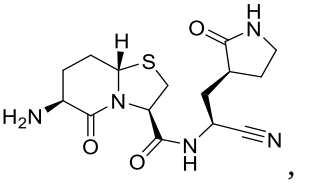
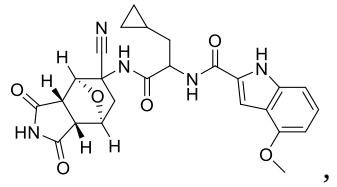
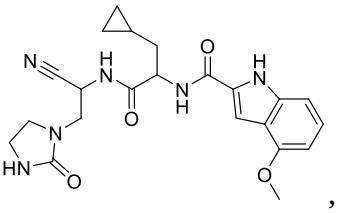
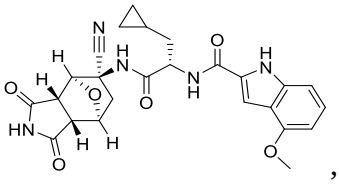
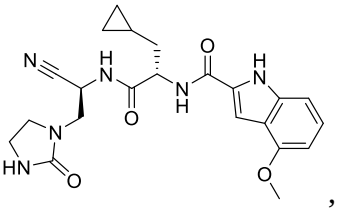

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

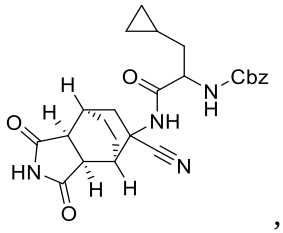
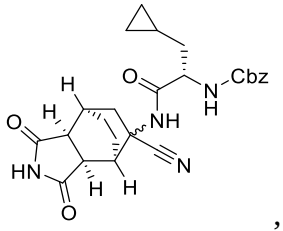
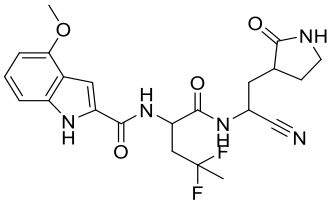
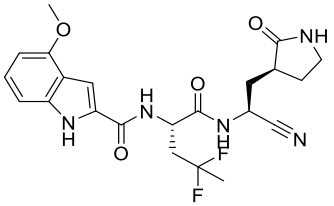
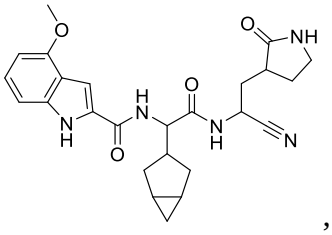
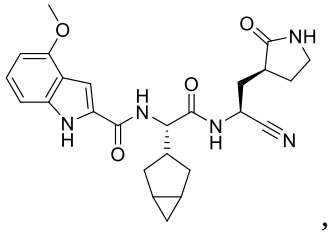
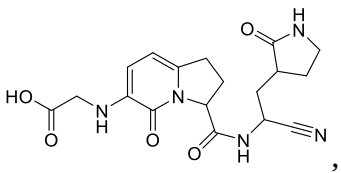
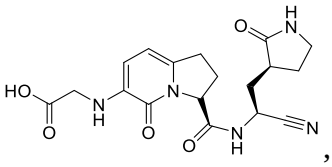
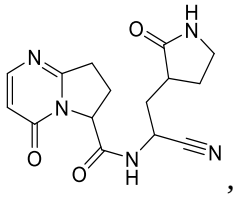
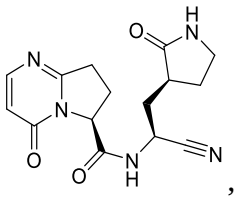
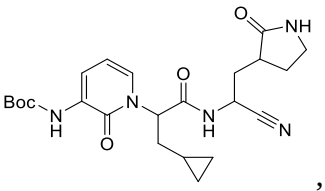
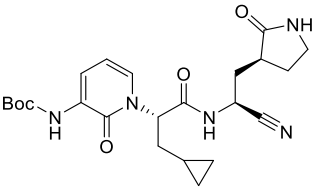
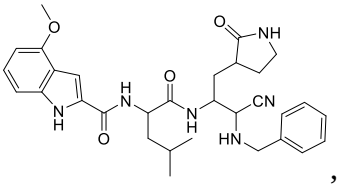
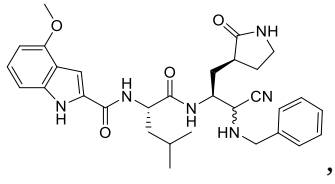
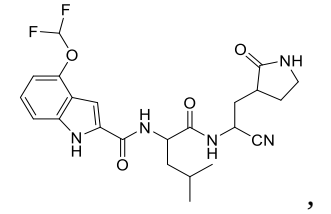
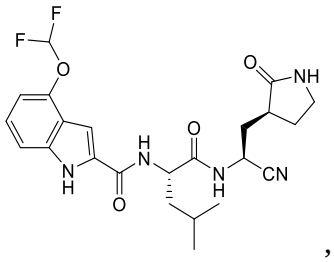
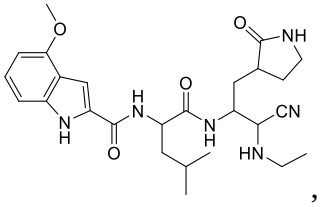
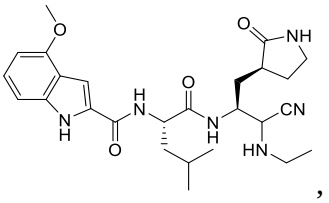
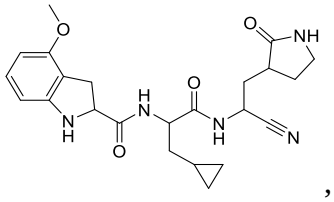
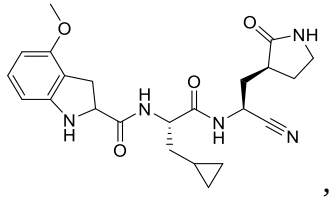
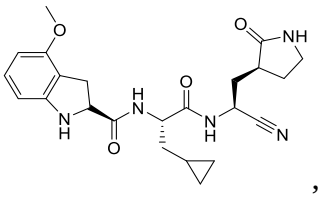
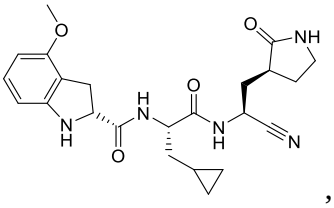
,

,

,

,

,

,

,

,

,

,

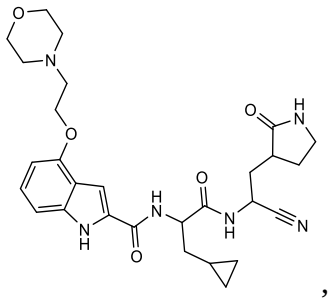
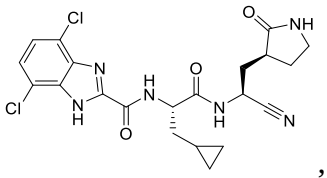
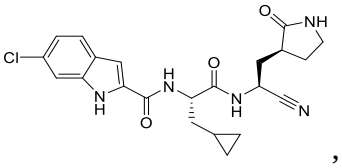
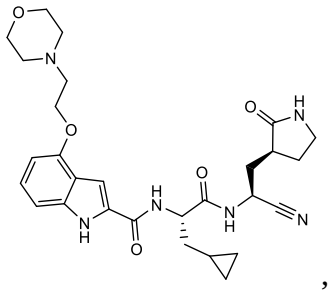
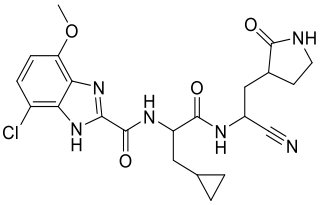
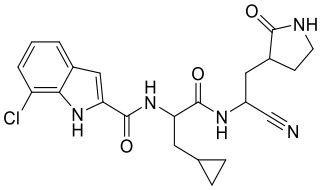
,

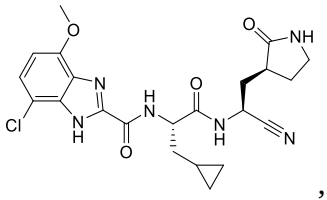
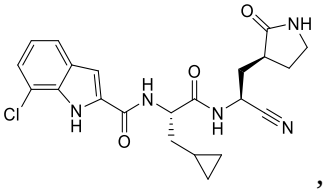
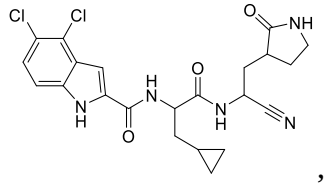
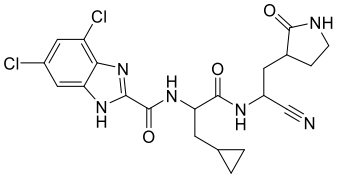
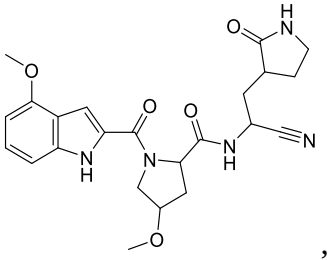
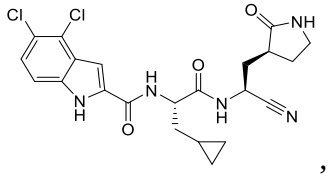
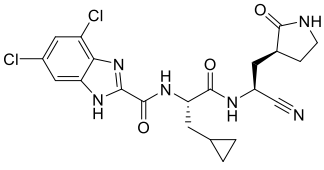
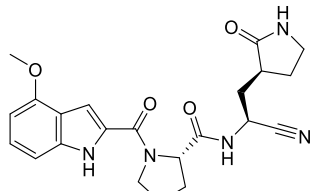
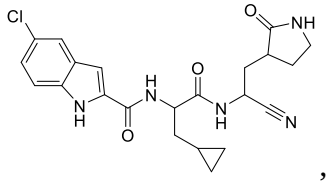
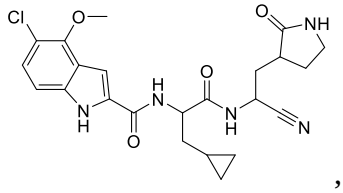

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

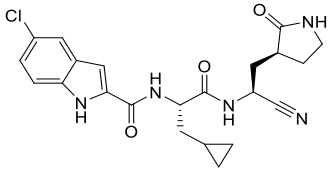
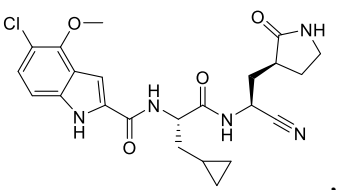
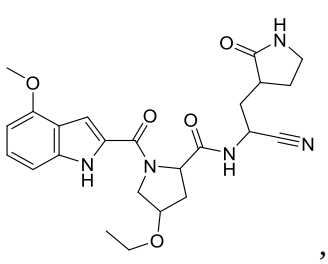
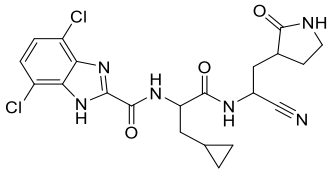
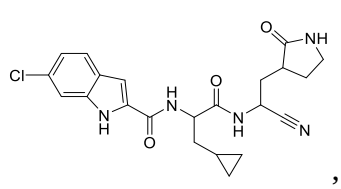
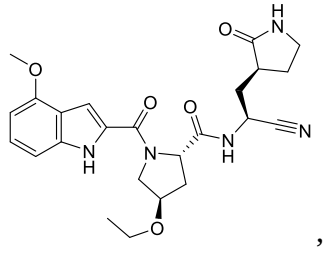
,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

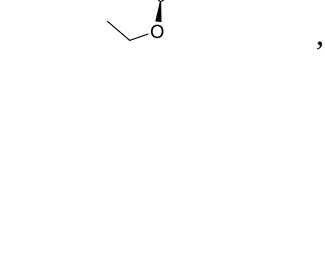
,

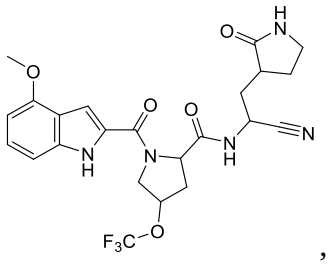
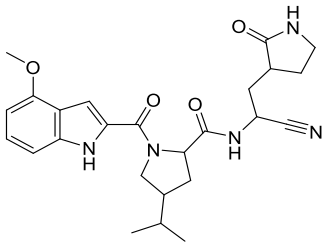
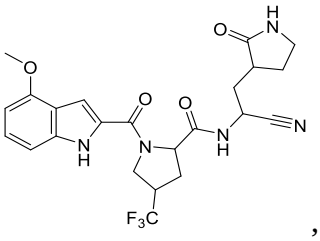
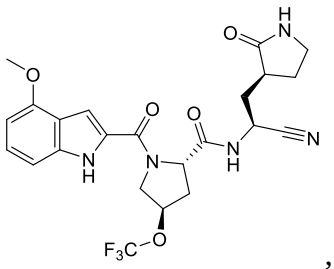
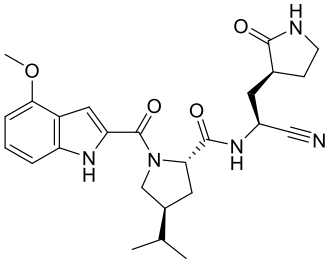
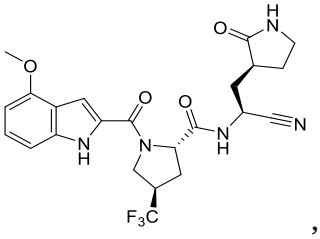
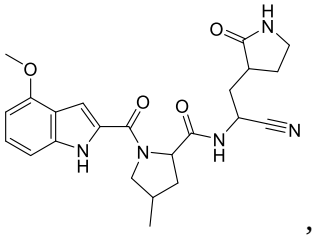
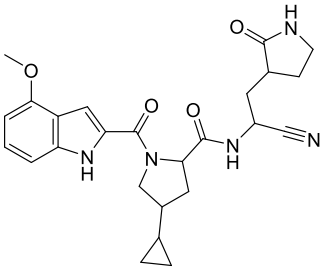
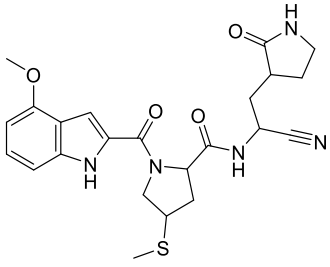
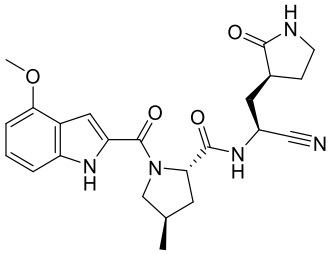
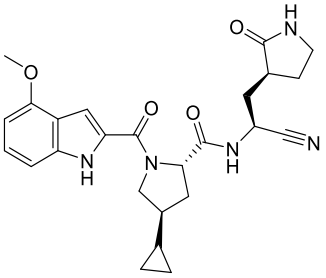
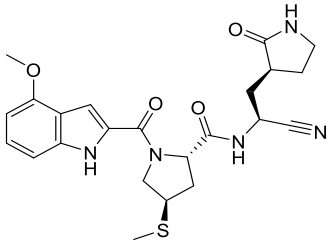
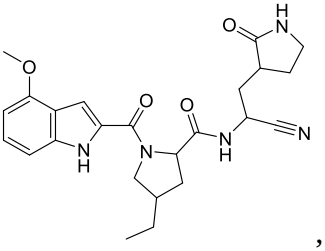

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

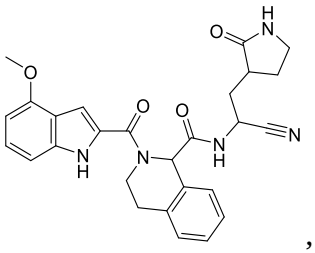
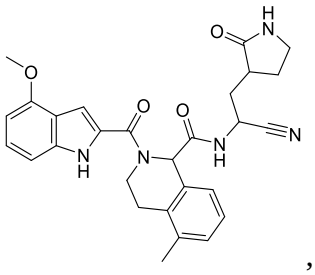
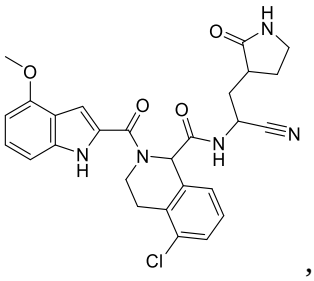
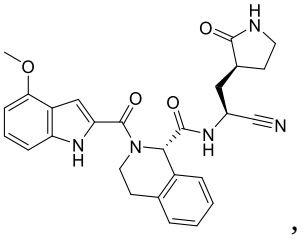
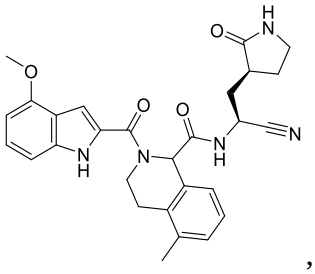
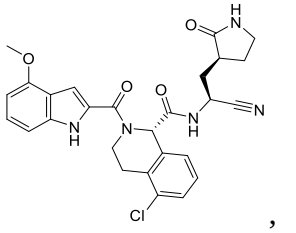
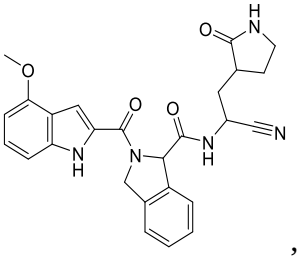
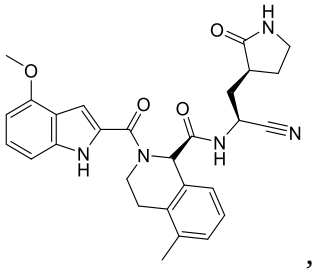
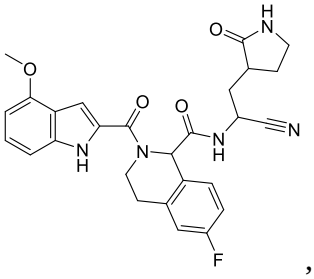
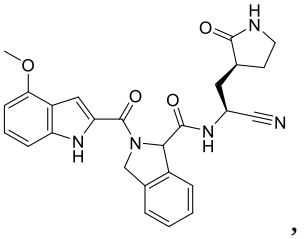
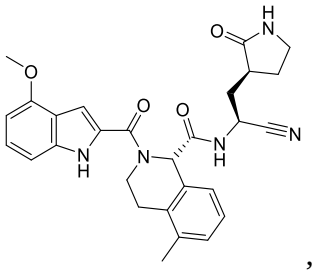
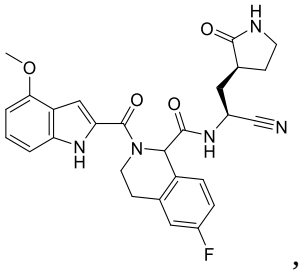
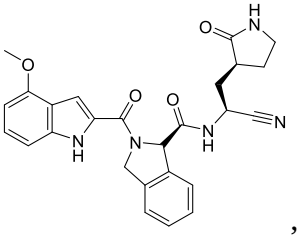
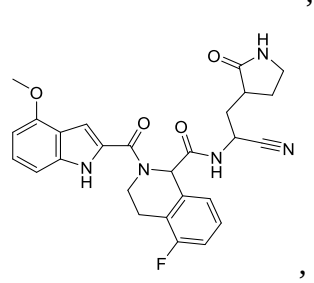
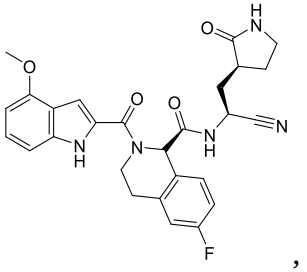
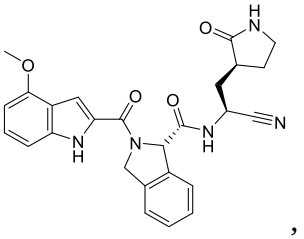
,

,

,

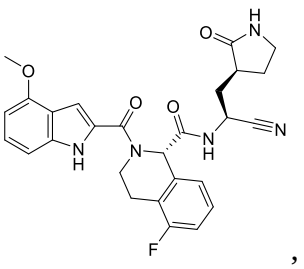
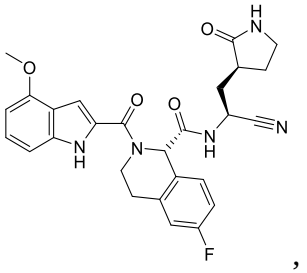
,

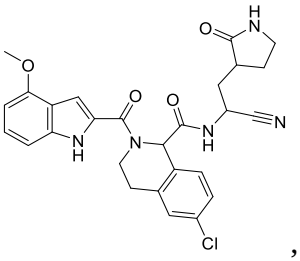
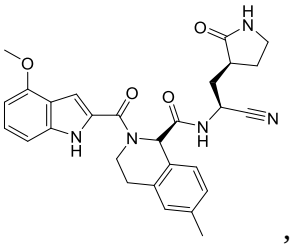
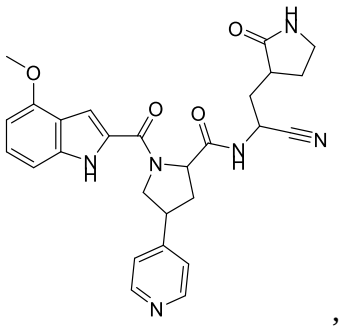
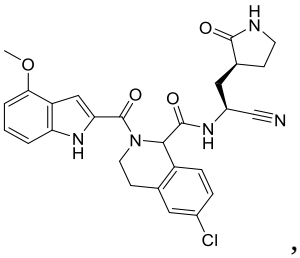
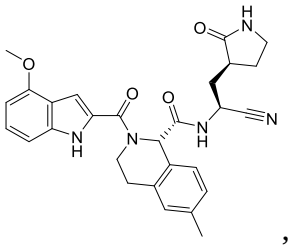
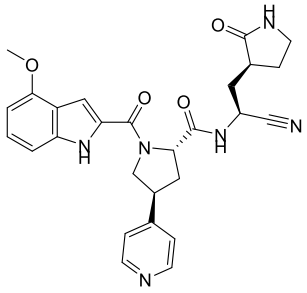
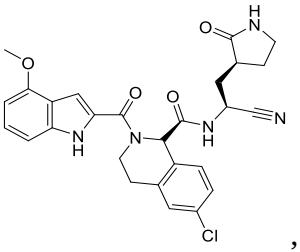
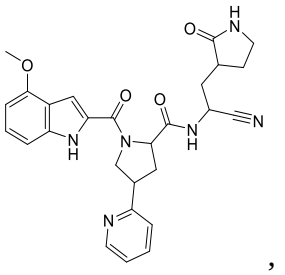
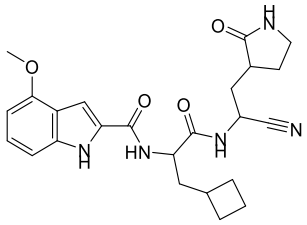
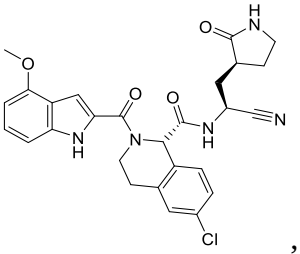
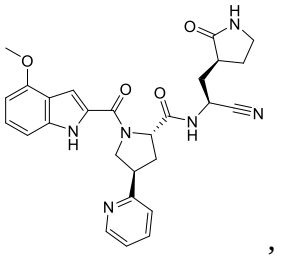
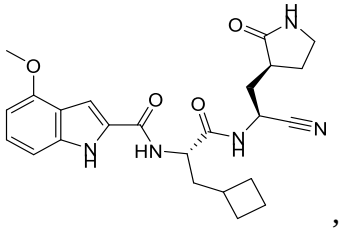
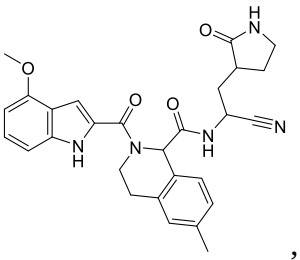
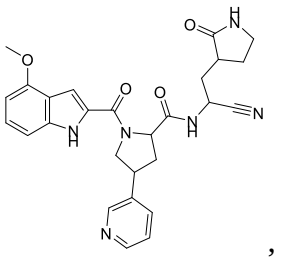
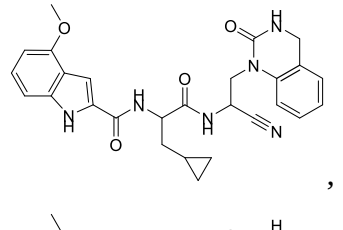
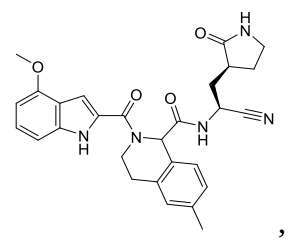
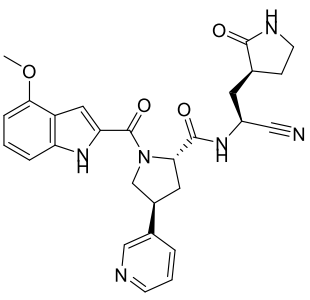
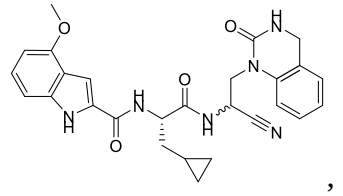
,

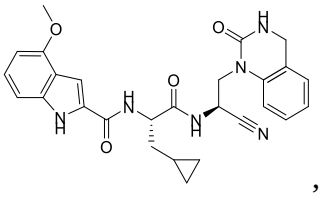
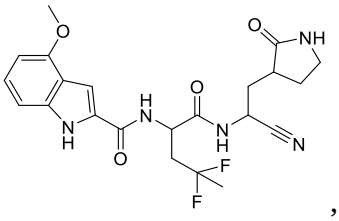
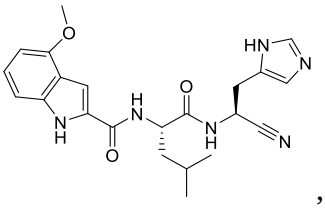
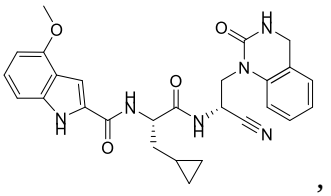
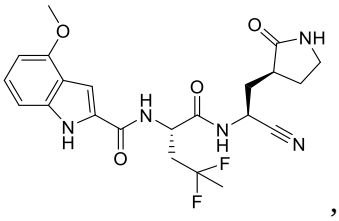
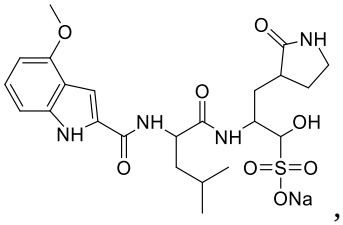
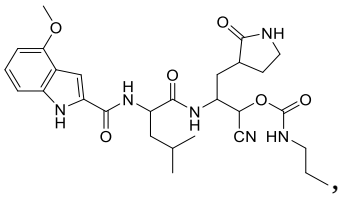
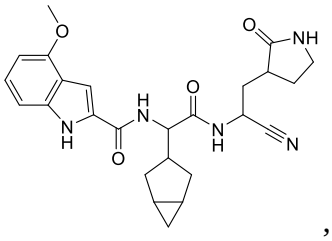
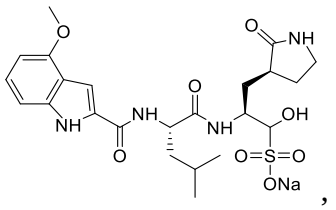
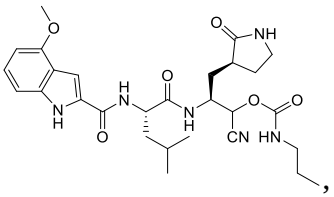
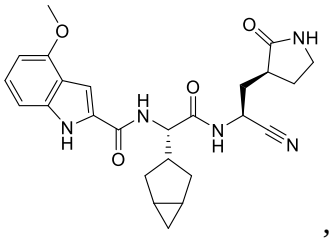
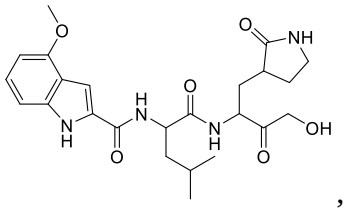
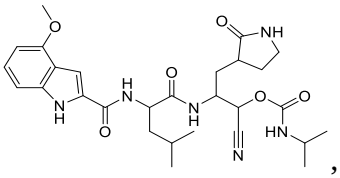

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

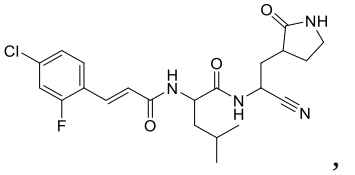
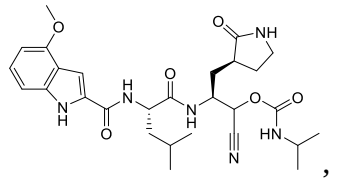
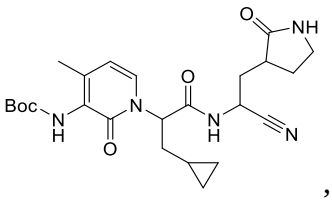
,

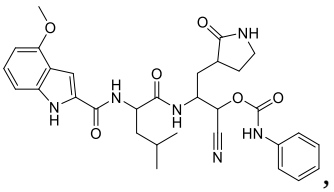
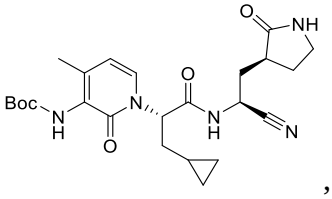
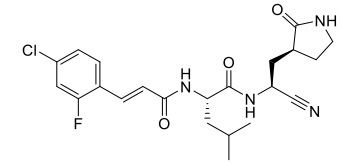
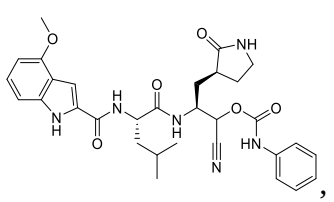
,

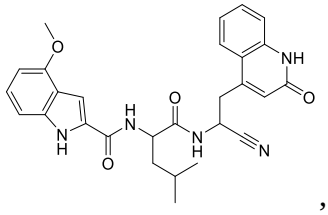
,

,

,

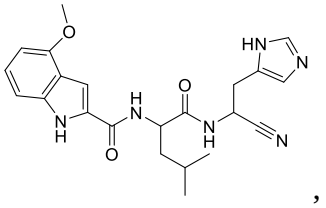

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

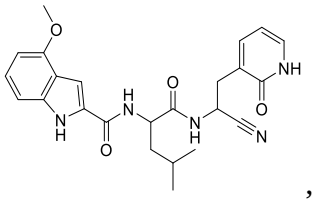
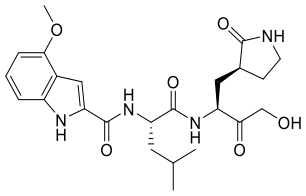
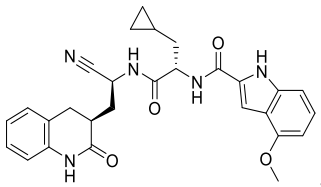
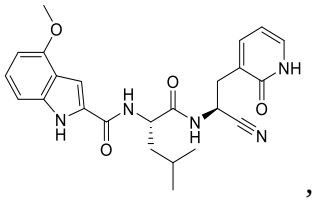
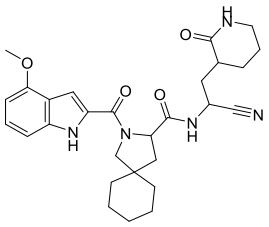
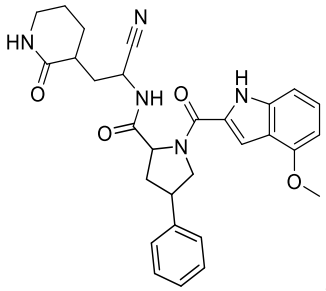
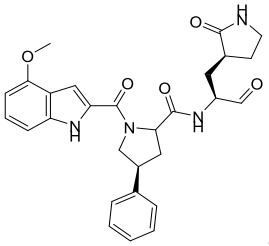
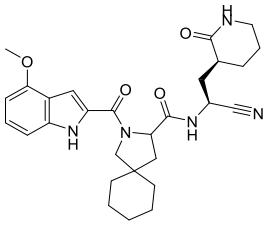
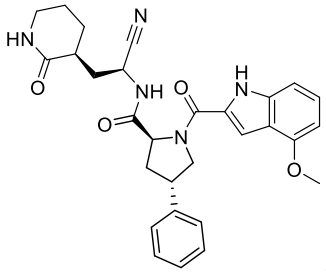
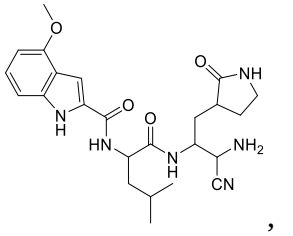
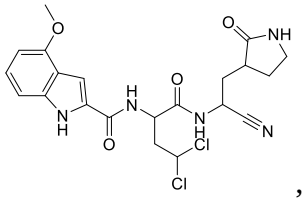
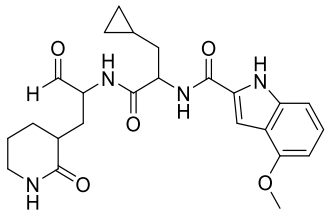
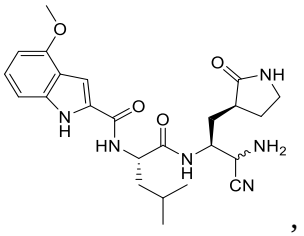
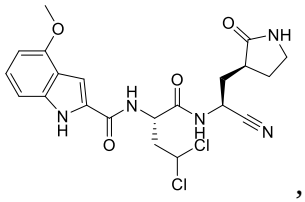
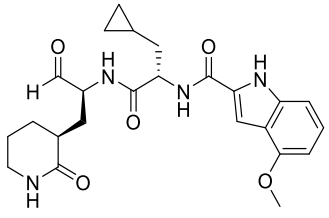
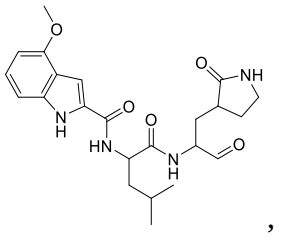
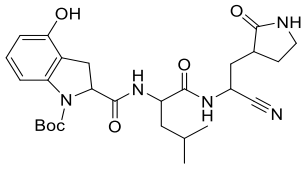
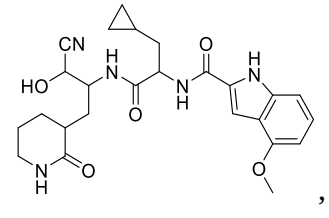
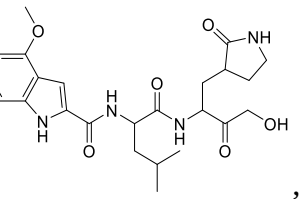
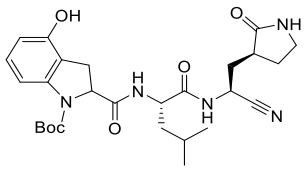
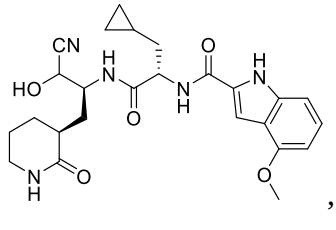
,

,

,

,

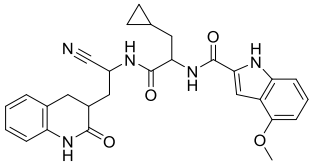
,

,

,

,

,

,

,

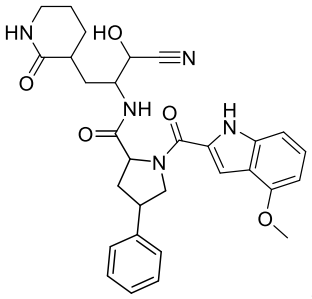
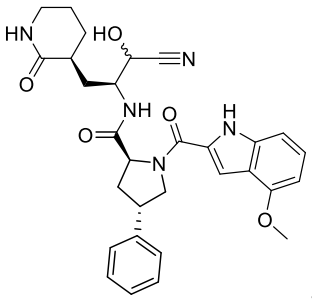
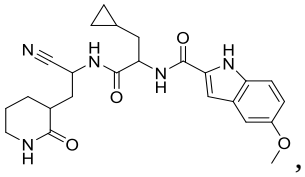
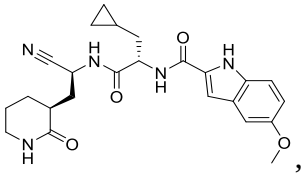
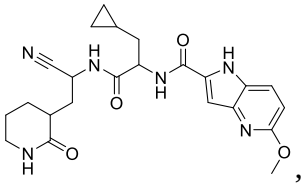
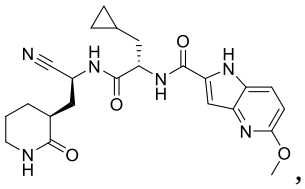
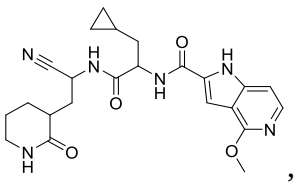
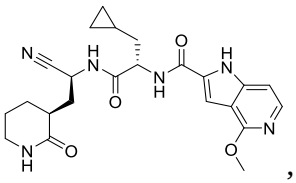
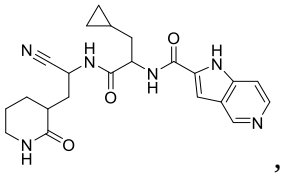
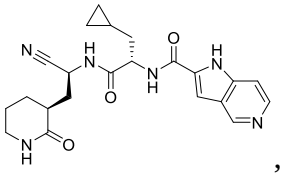
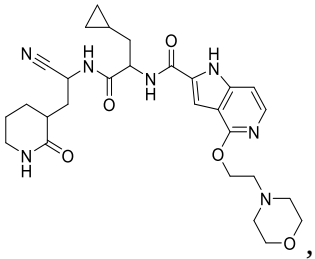
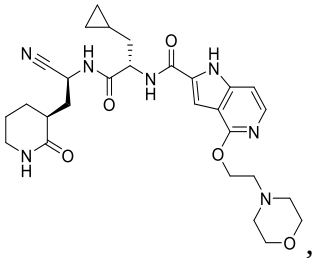
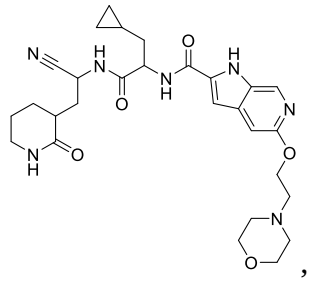
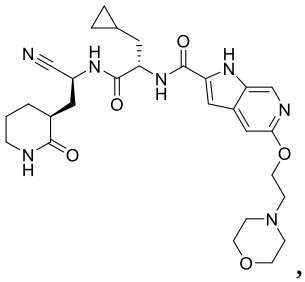
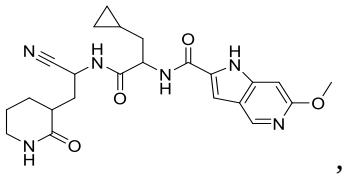
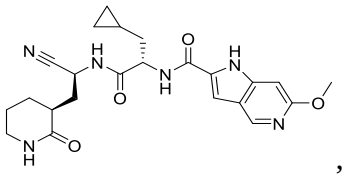
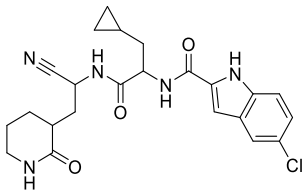
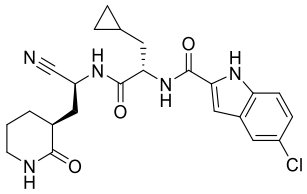
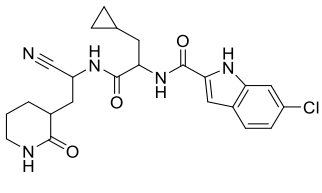
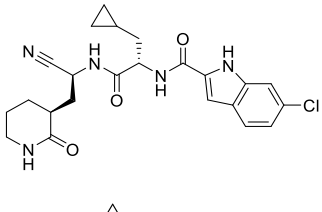
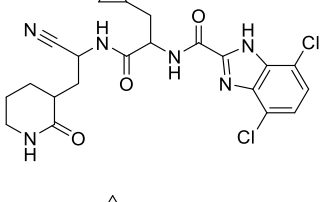
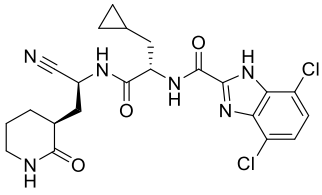
,

,

,

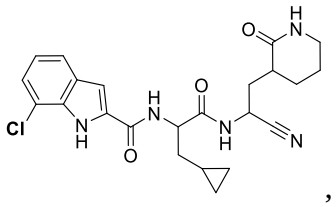
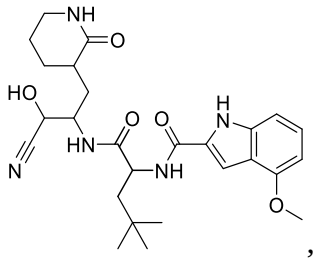
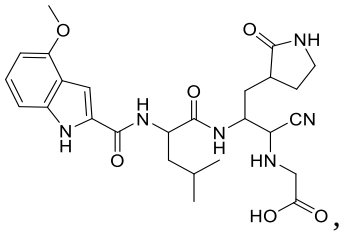
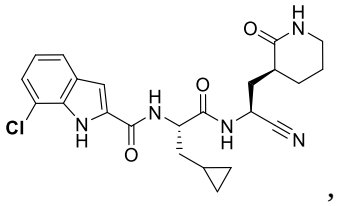
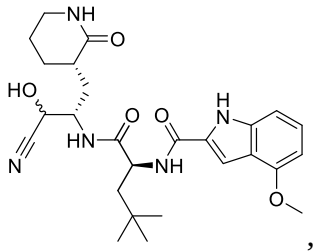
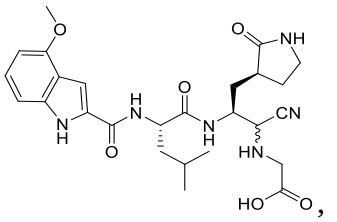
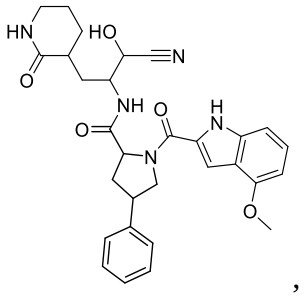
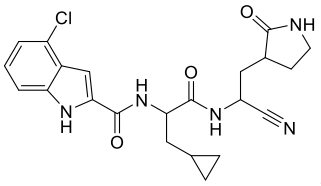
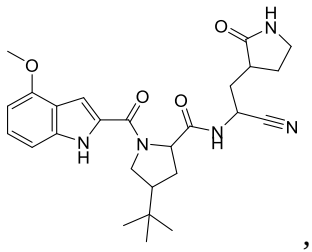
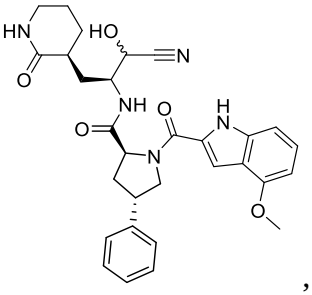
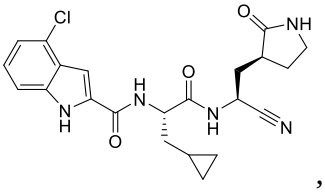
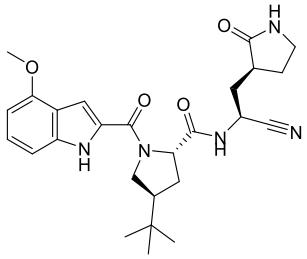
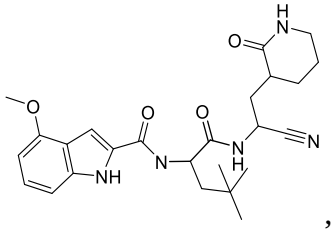
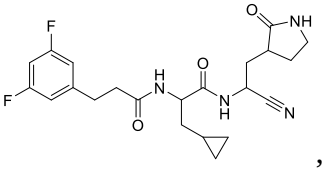
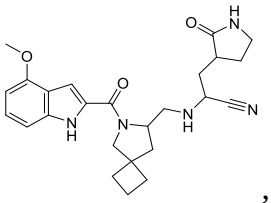
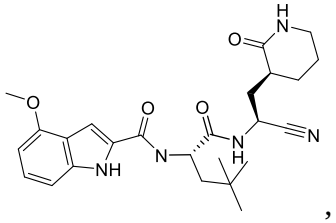
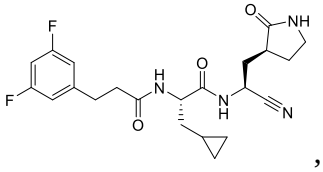
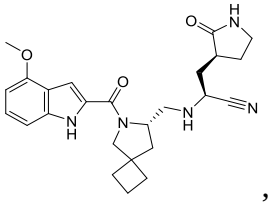

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

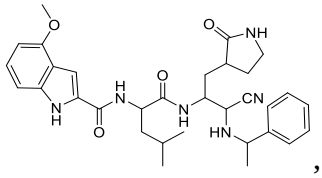
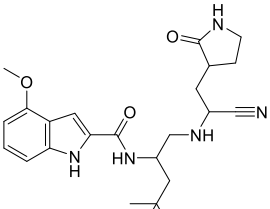
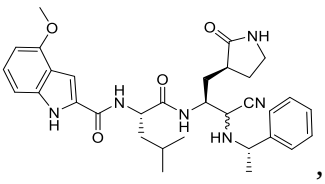
,

,

,

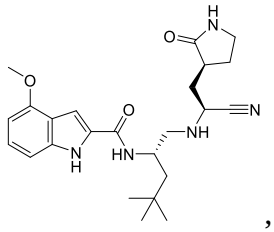
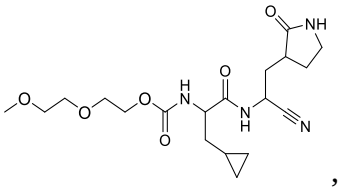
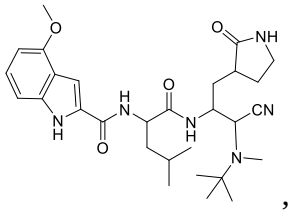
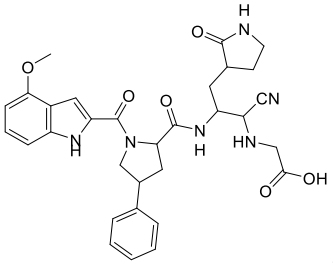
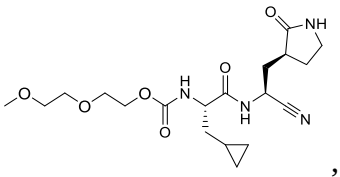
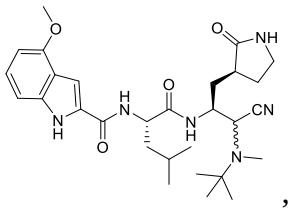
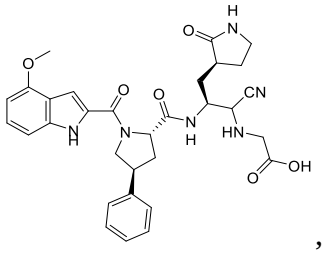
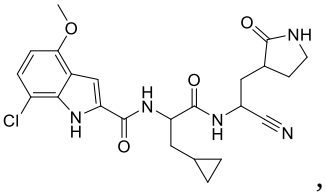
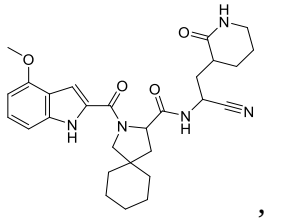
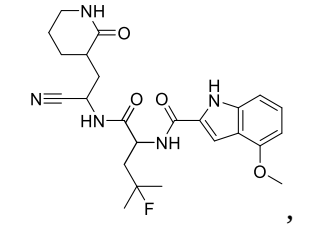
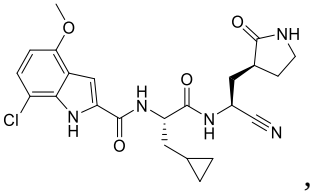
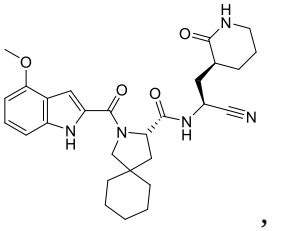
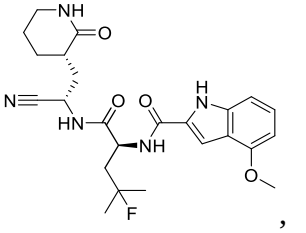
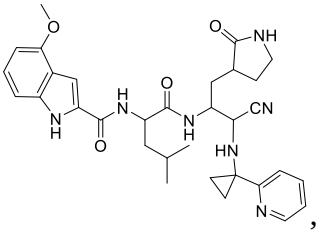
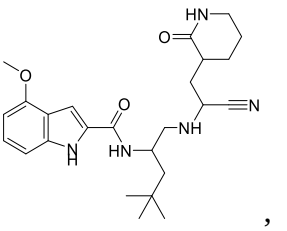

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

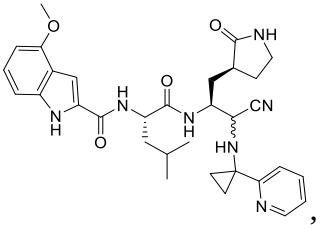
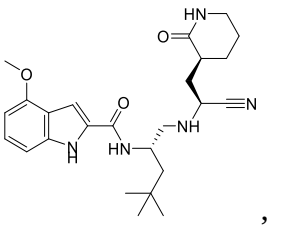
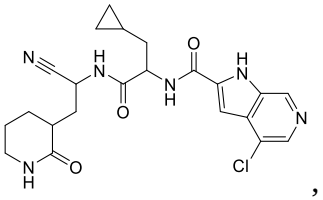
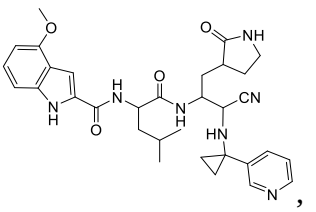
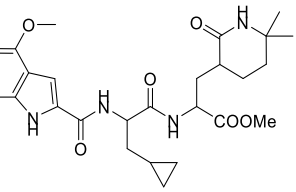
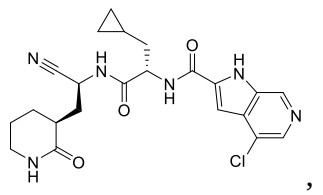
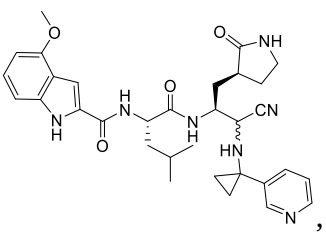
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

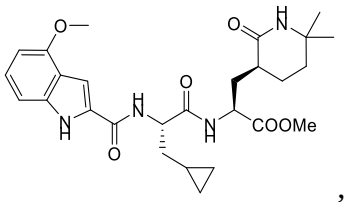
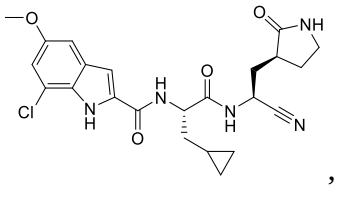
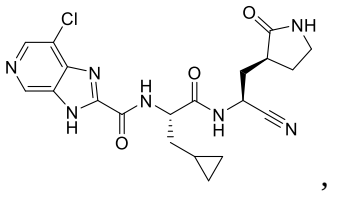
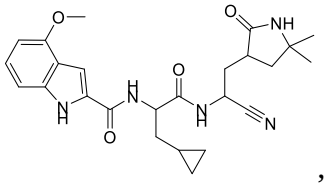
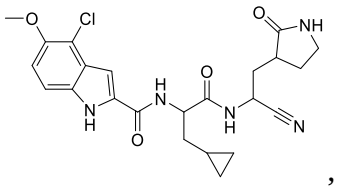
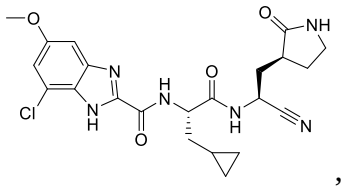
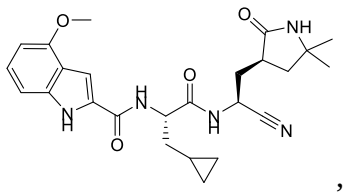
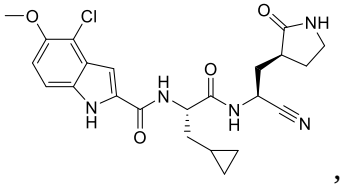
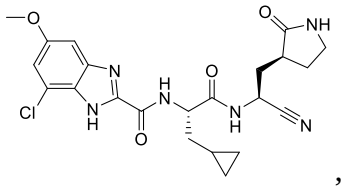
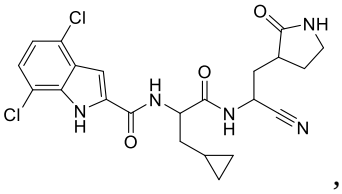
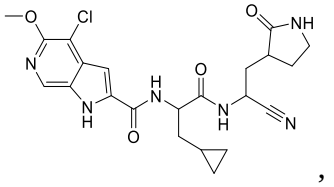
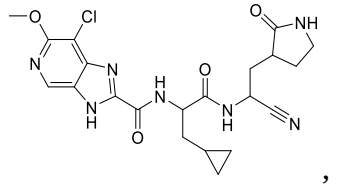
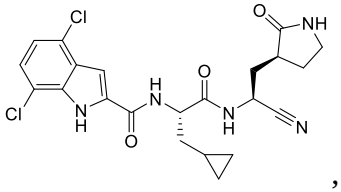
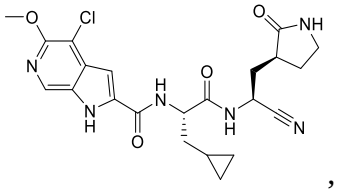
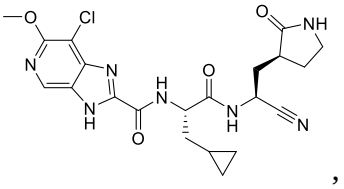
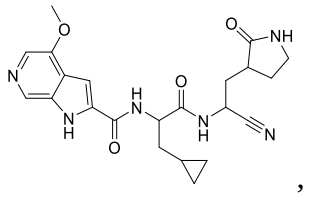
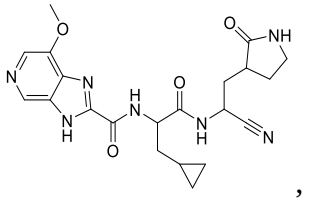
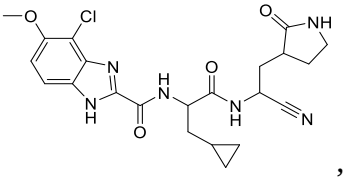
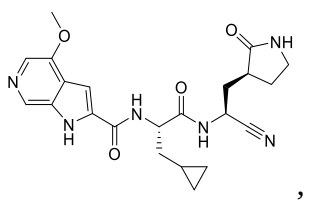
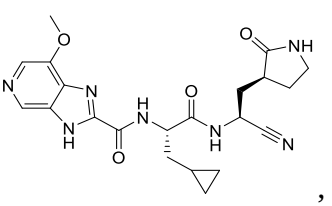
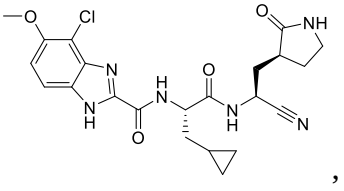
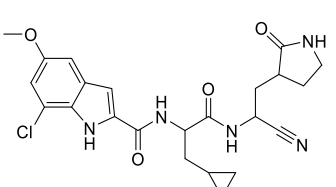
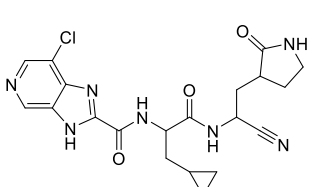
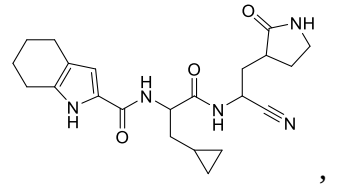
,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

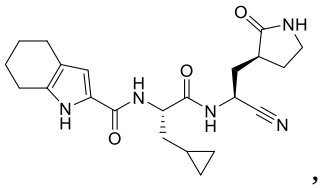
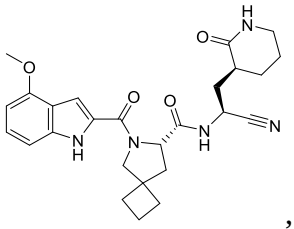
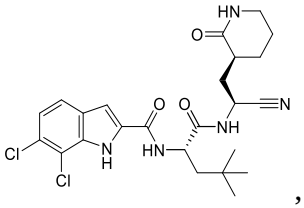
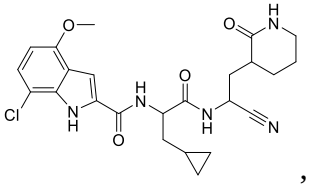
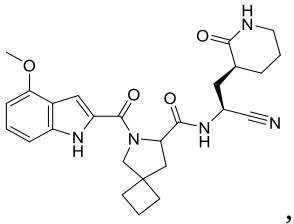
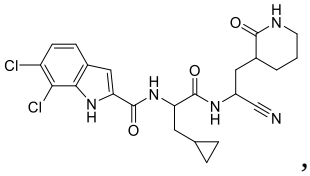
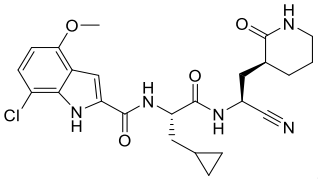
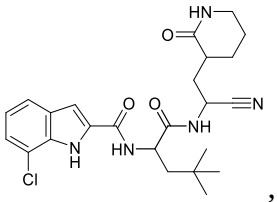
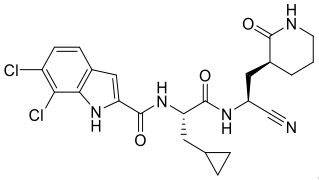
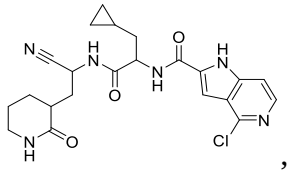
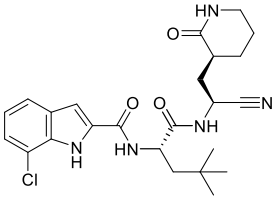
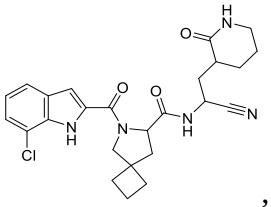
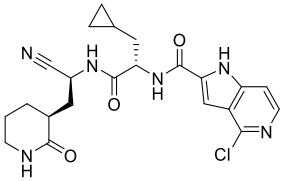
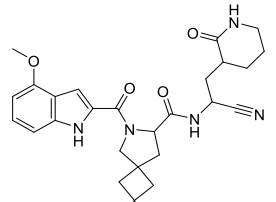
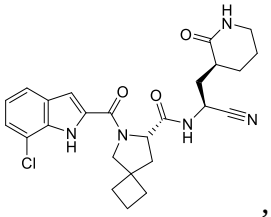
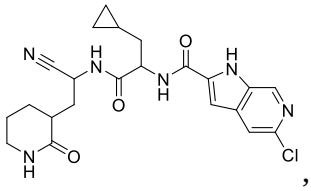
,

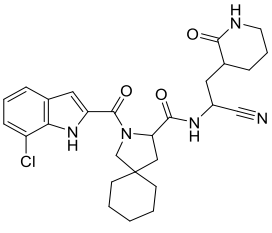
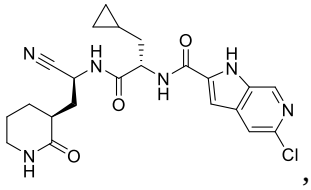
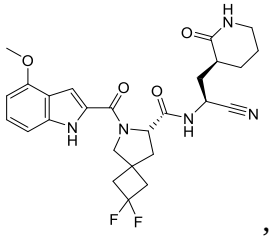

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

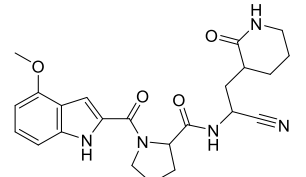
,

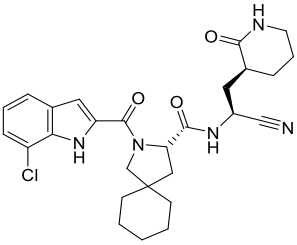
,

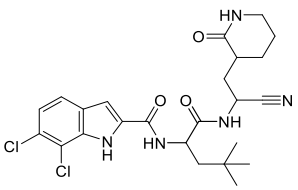
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

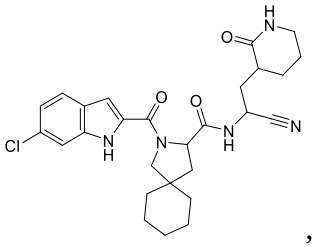
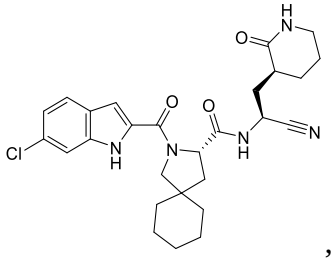
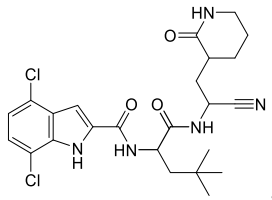
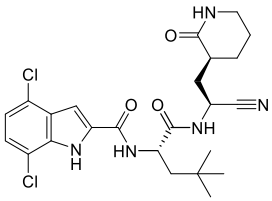
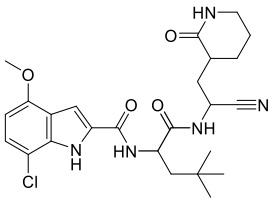
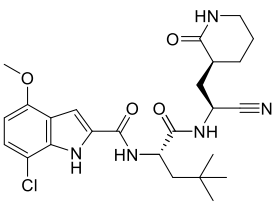
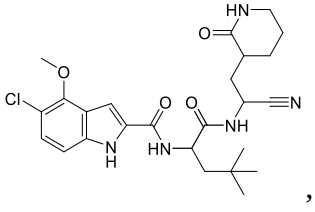
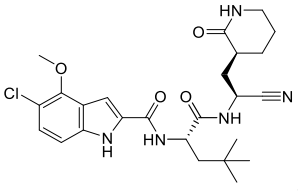
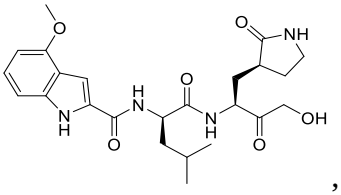
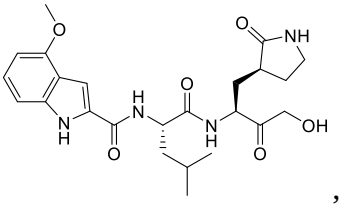
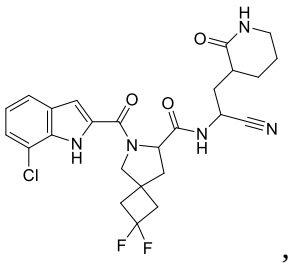
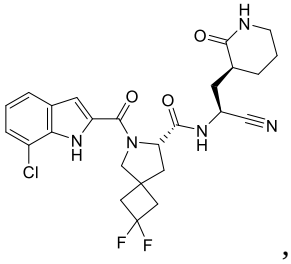
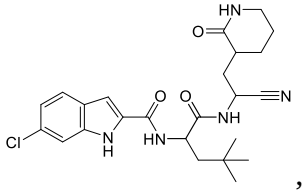
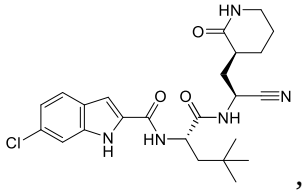
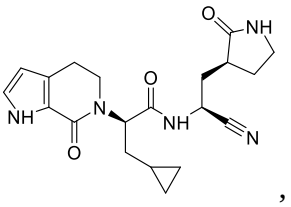
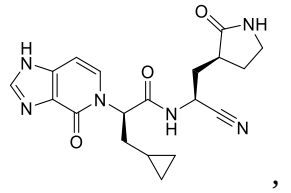
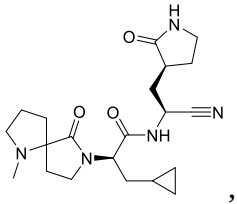
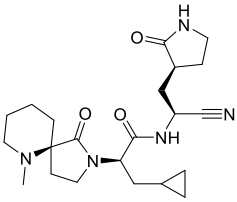
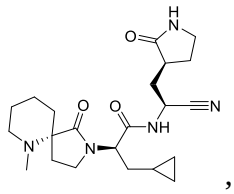
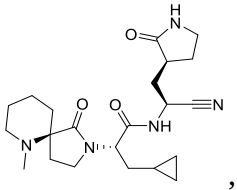
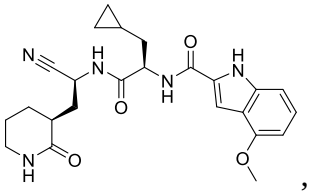
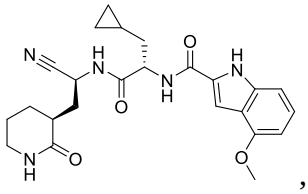
,

,

,

,

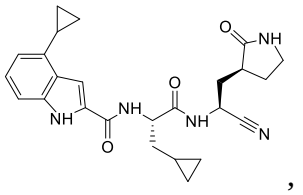
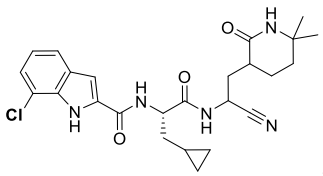
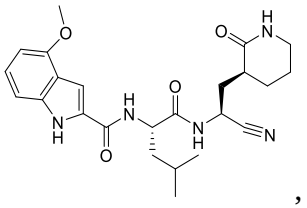
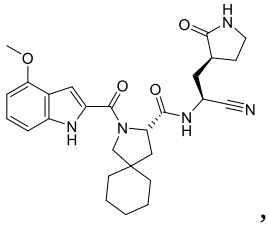
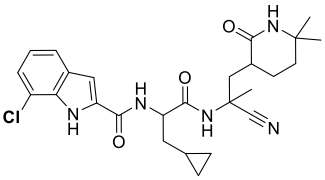
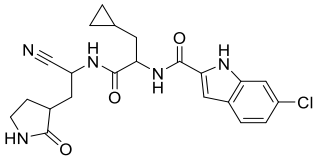
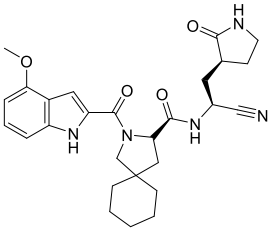
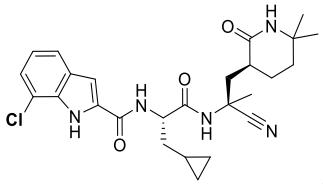
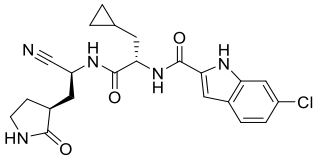
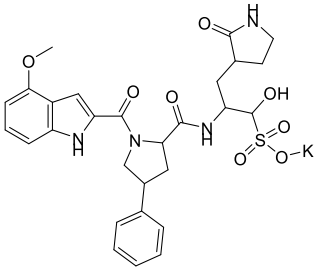
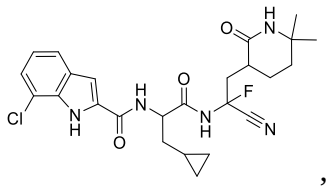
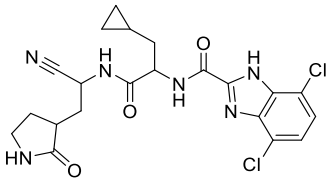
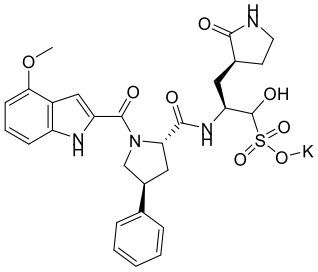
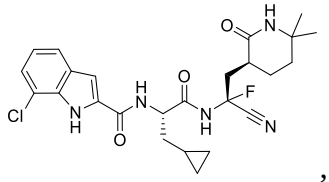
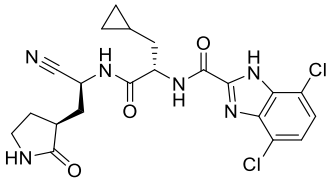
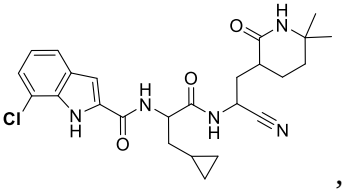
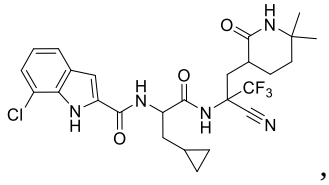
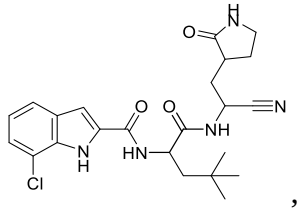
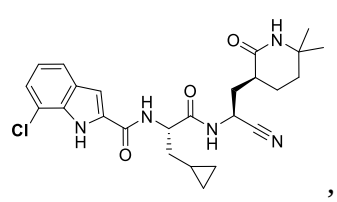
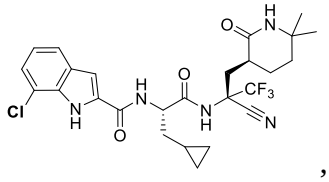
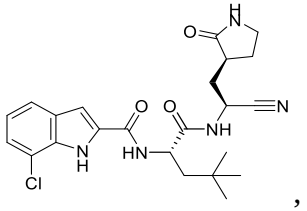
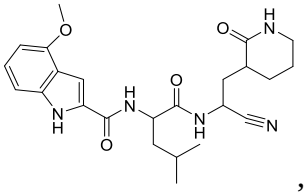
,

,

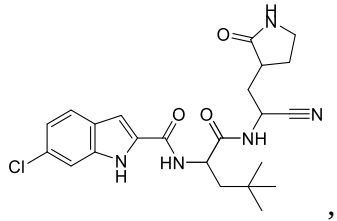
,

,

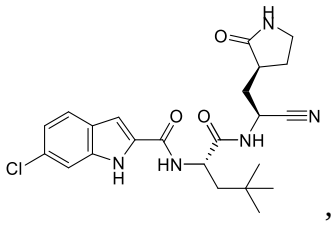
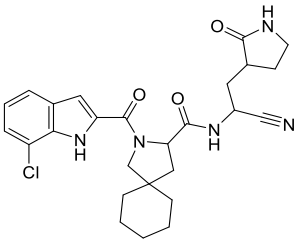
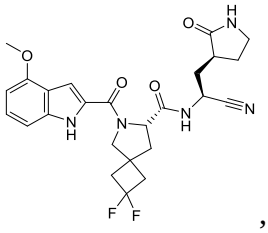
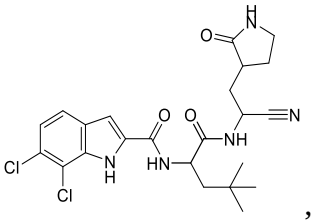
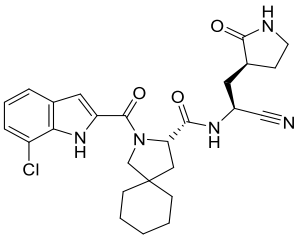
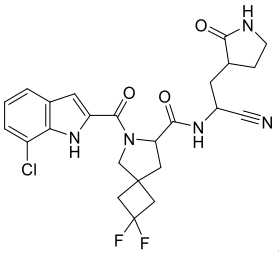
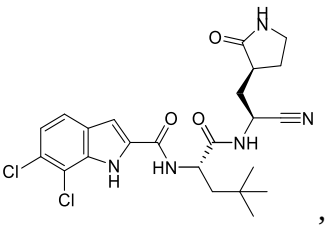
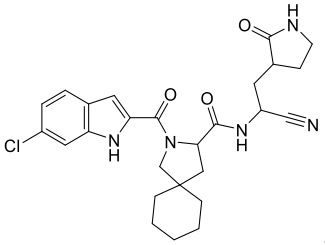
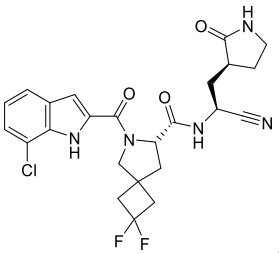
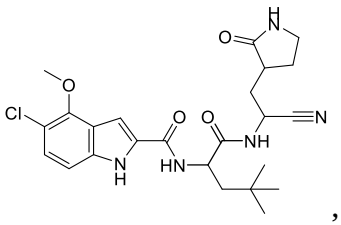
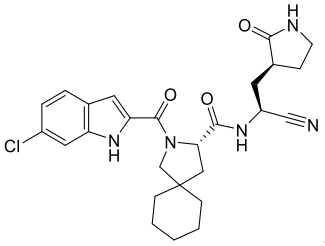
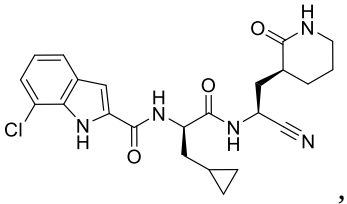
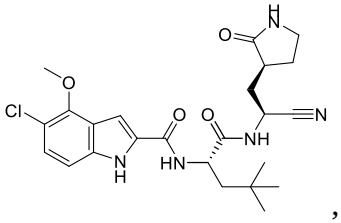
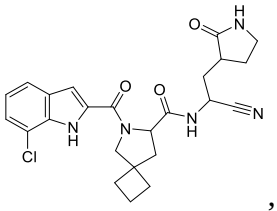
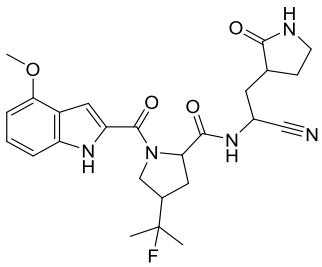
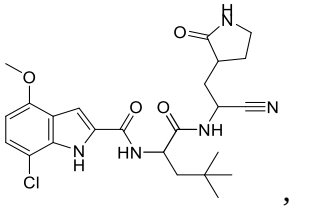
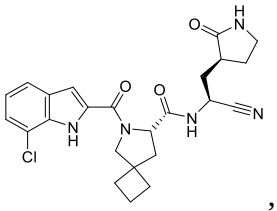
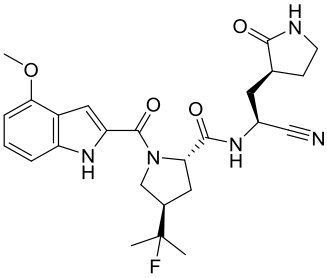
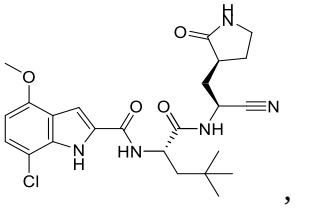
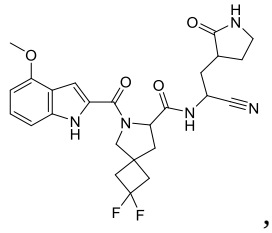
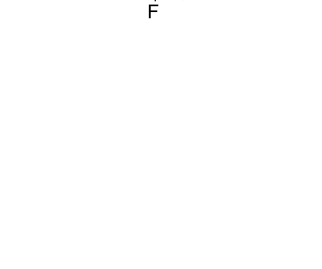
,

,

,

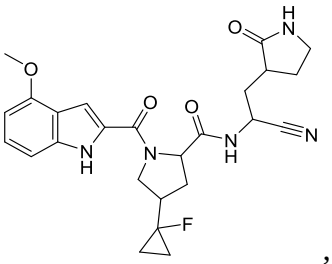
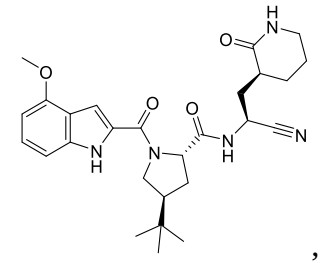
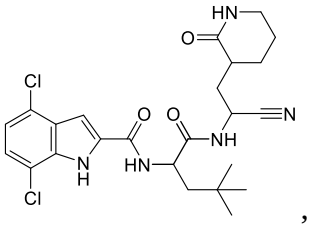
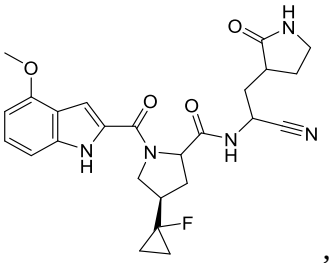
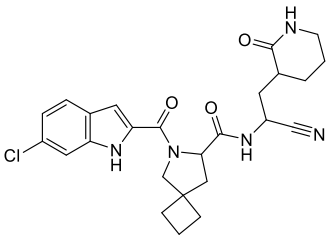
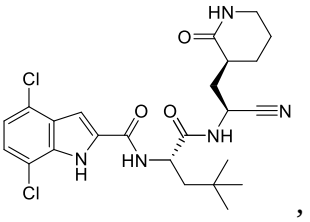
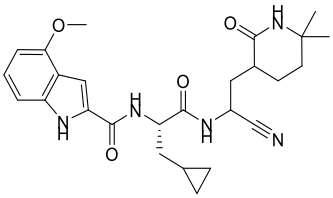
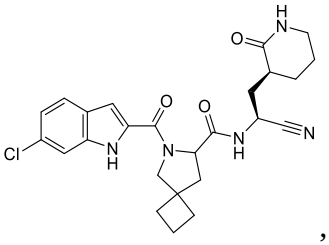
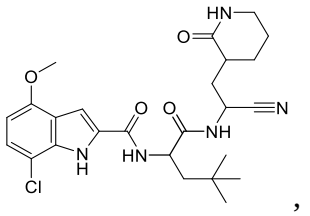
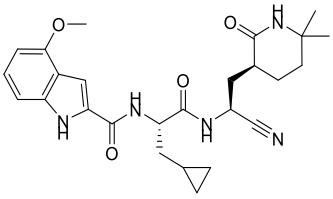
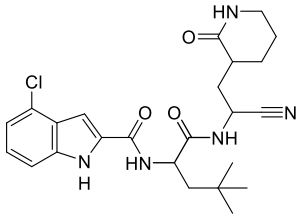
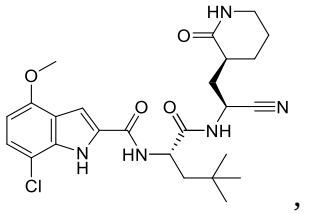
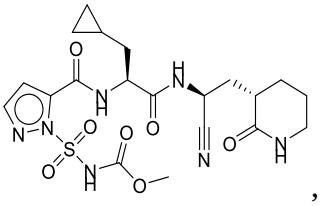
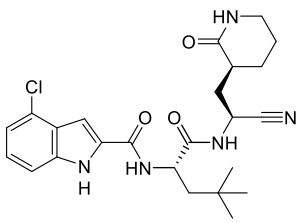
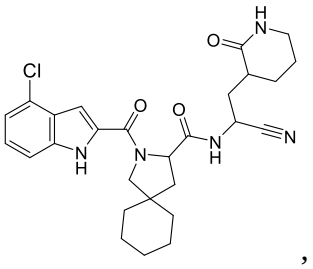
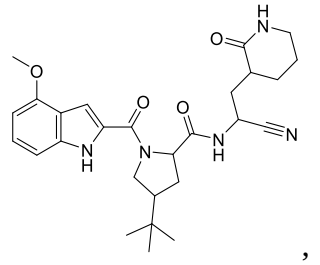
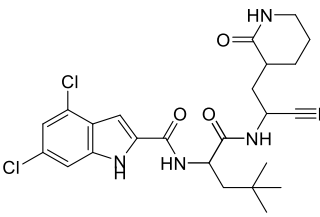
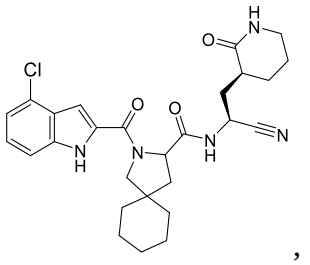

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

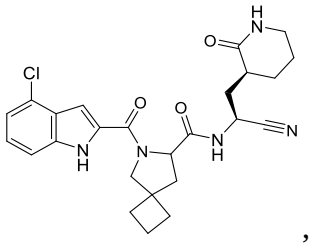
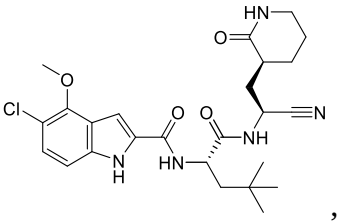
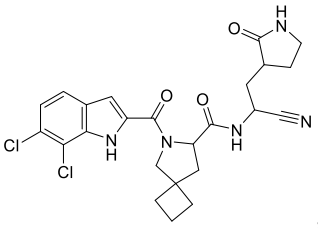
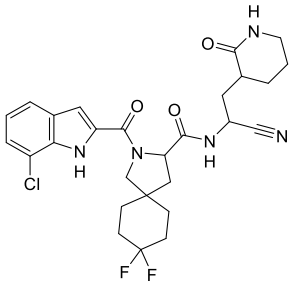
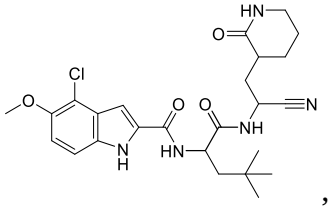
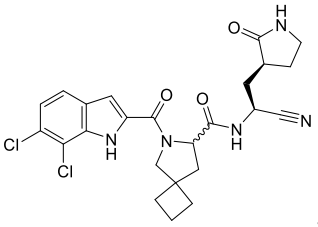
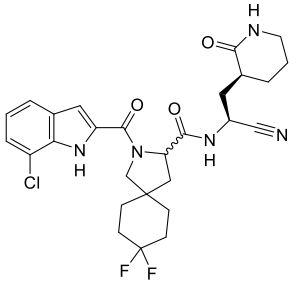
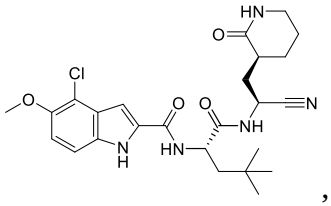
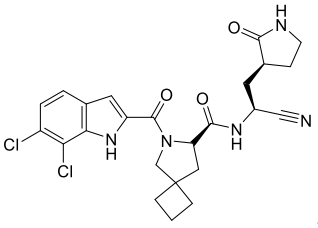
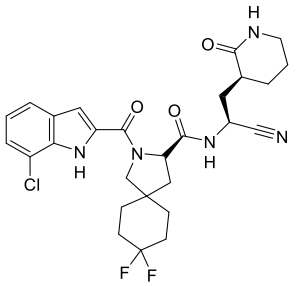
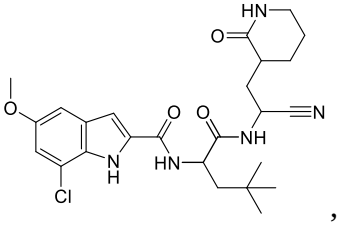
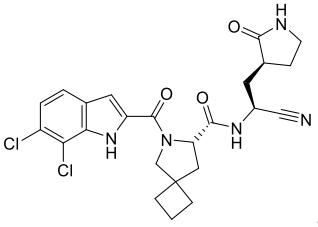
,

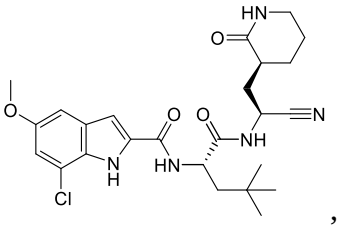
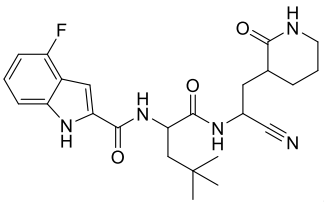
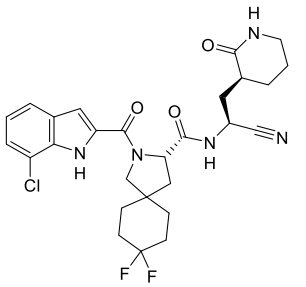
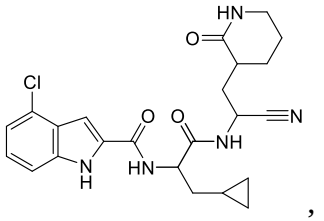
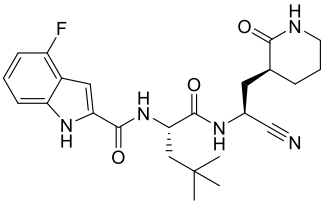
,

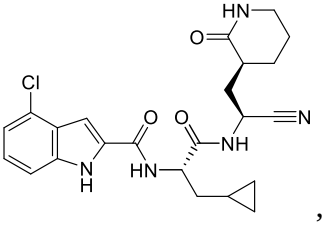
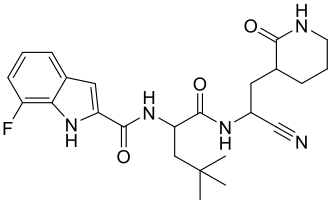
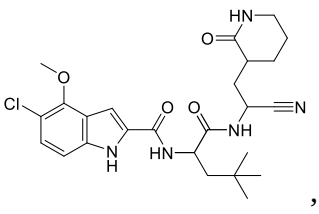
,

,

,

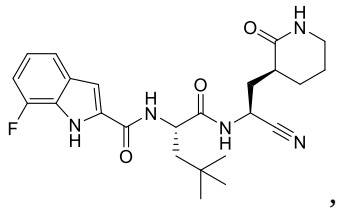
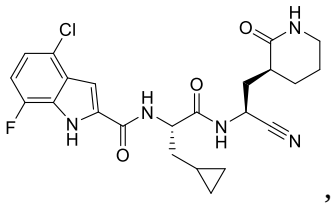
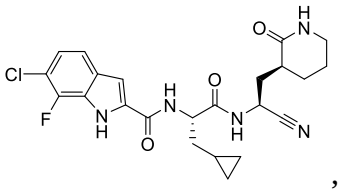
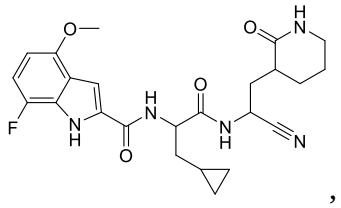
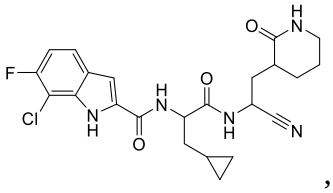
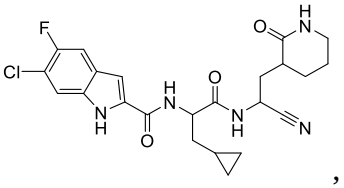
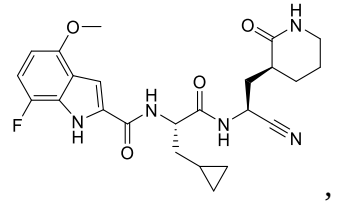
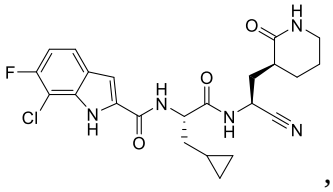
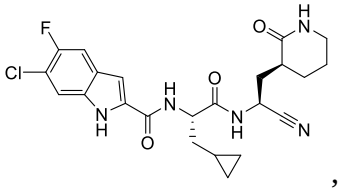
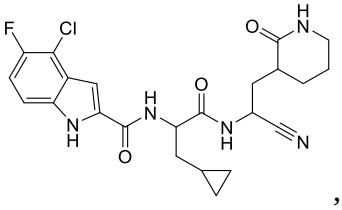
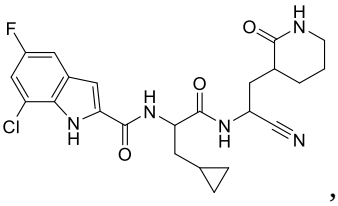
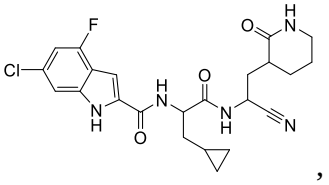
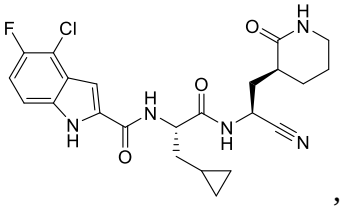
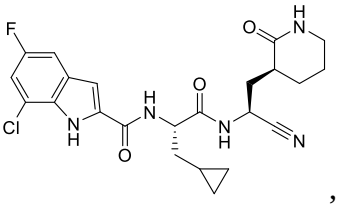
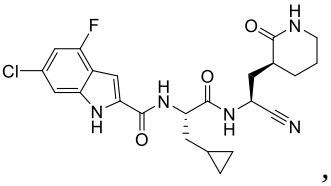
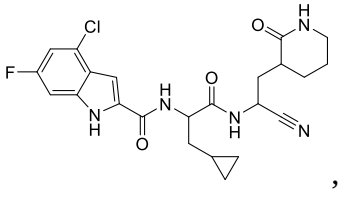
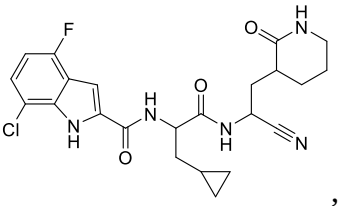
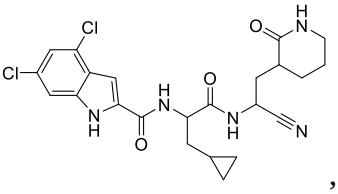
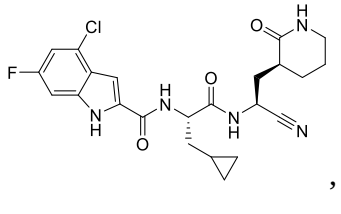
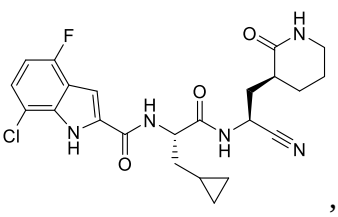
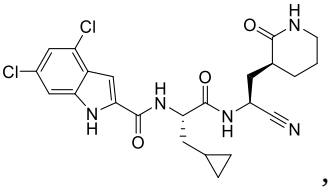
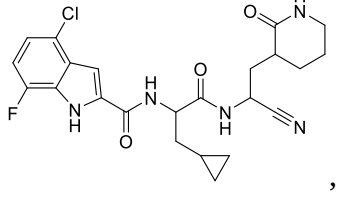
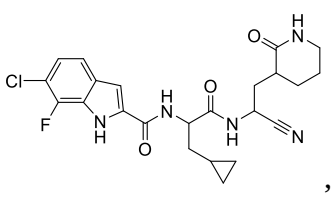
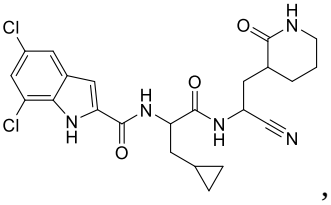

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

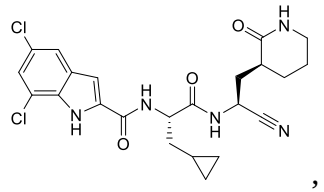
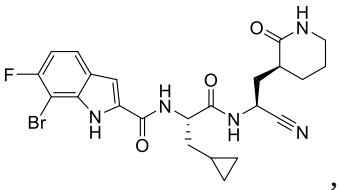
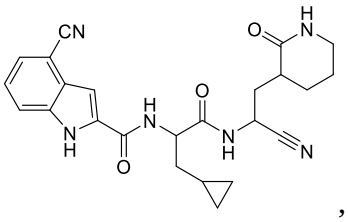
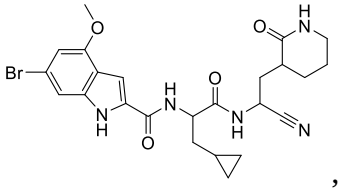
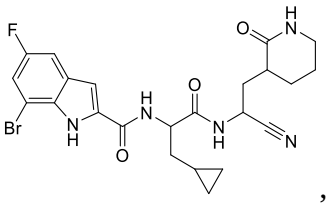
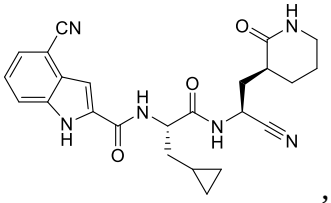
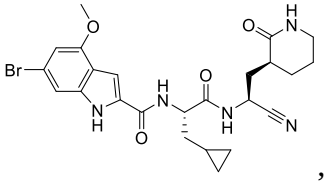
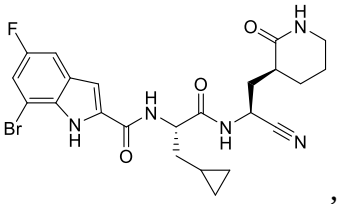
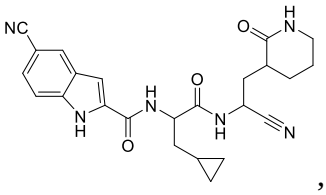
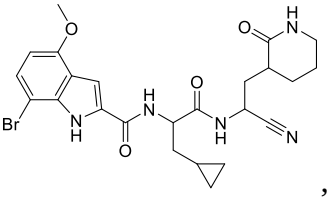
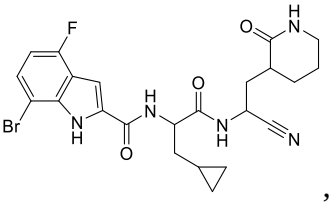
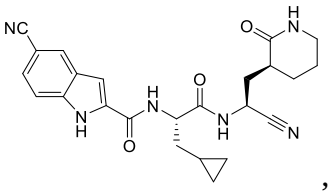
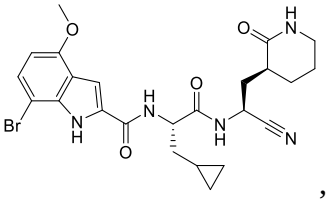
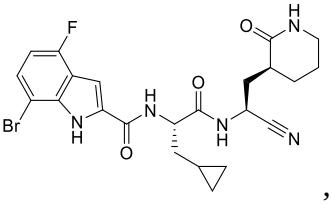
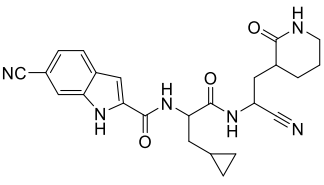
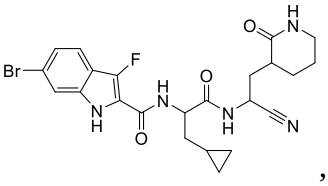
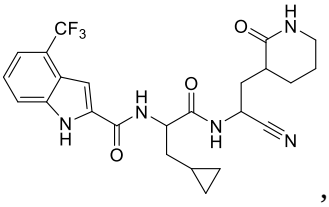
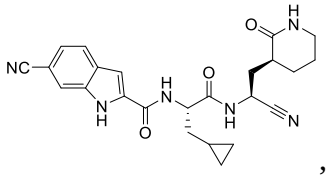
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

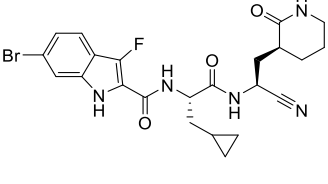
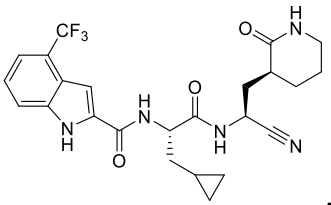
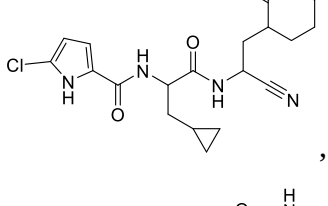
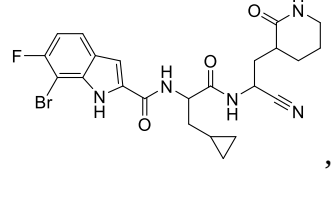
,

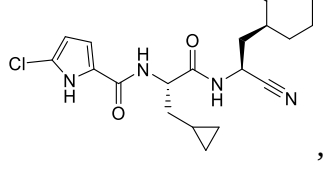
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

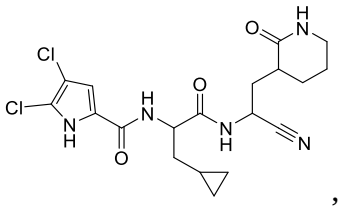
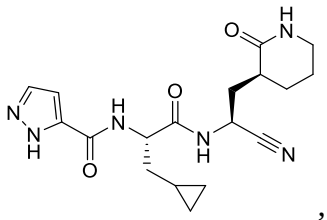
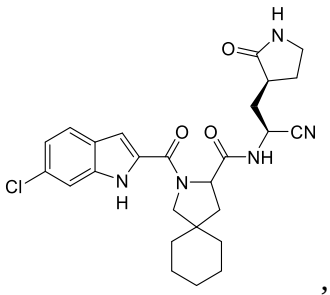
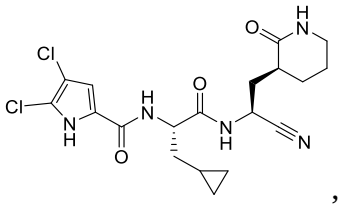
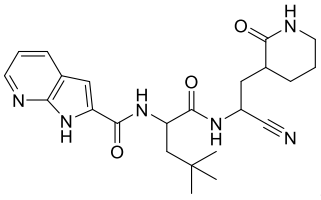
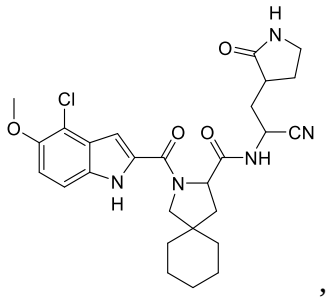
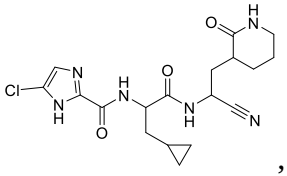
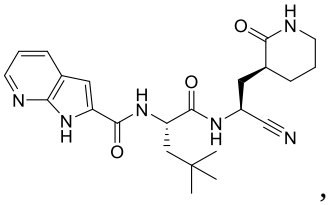
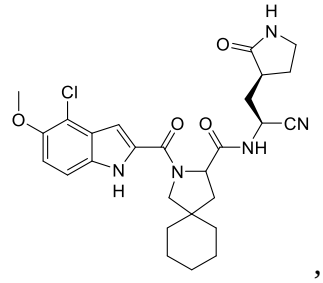
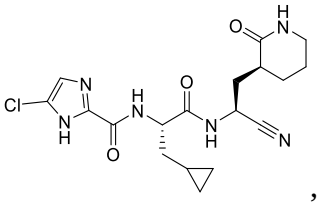
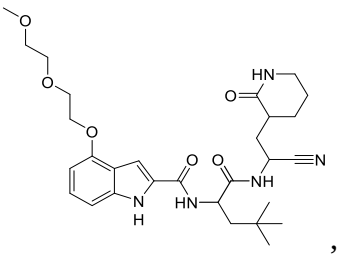
,

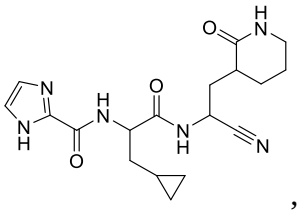
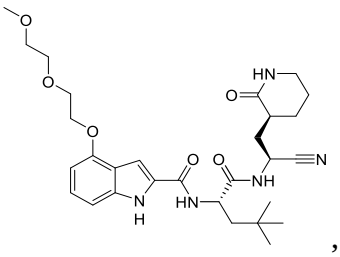
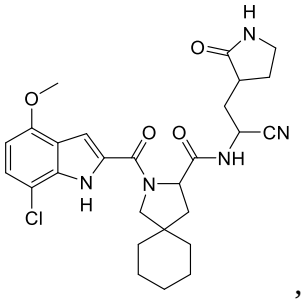
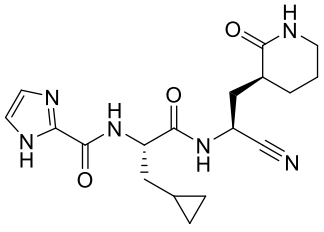
,

,

,

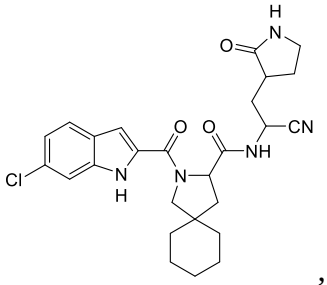
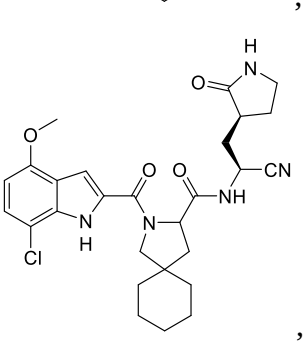
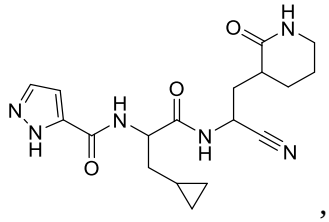
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

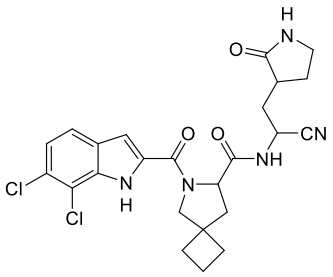
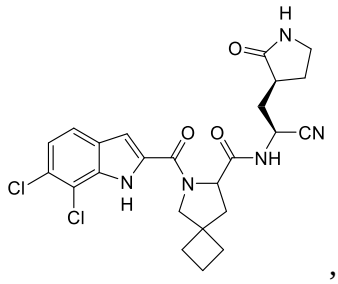
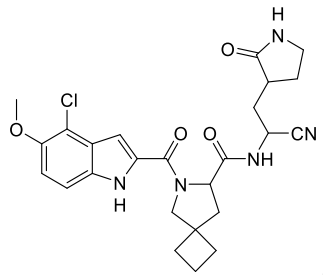
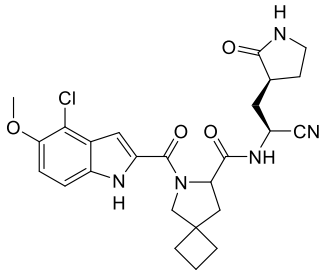
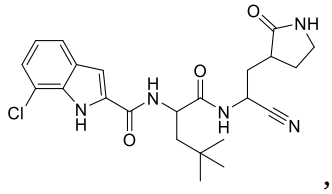
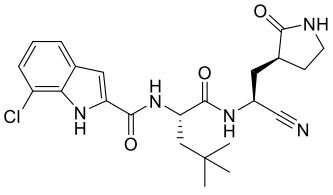
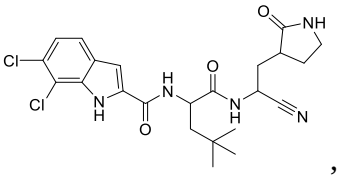
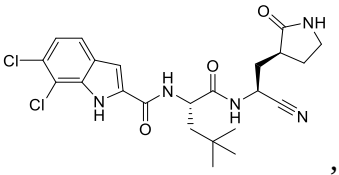
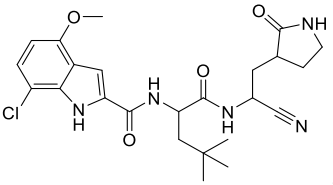
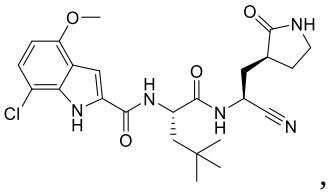
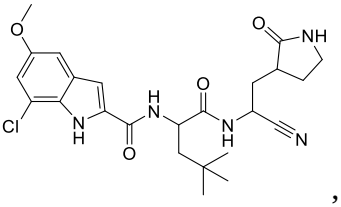
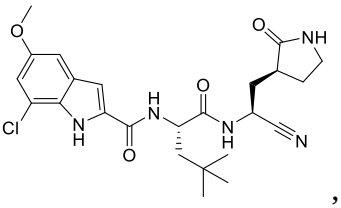
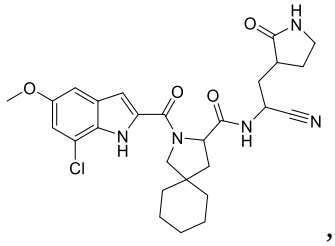
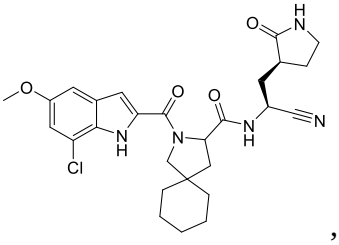
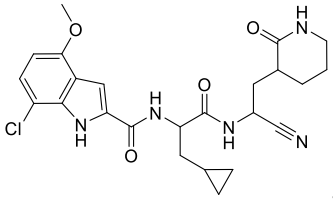
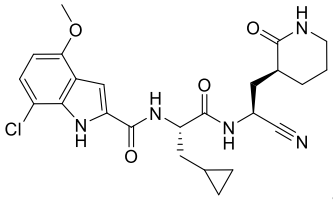
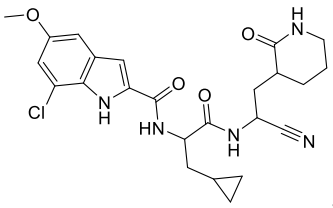
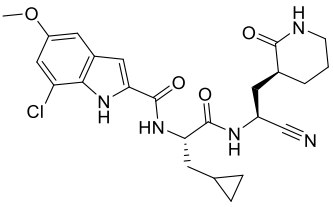
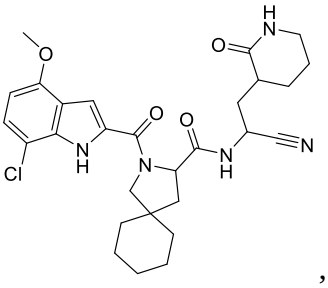
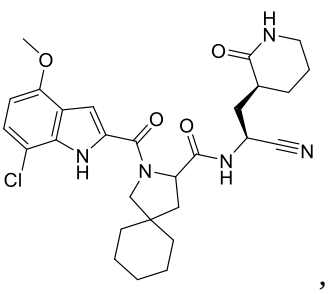
,

,

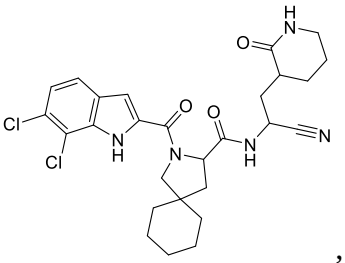
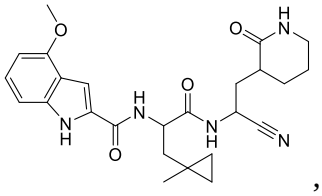
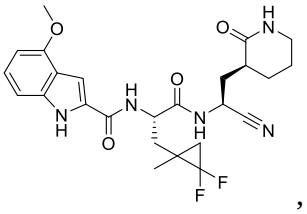
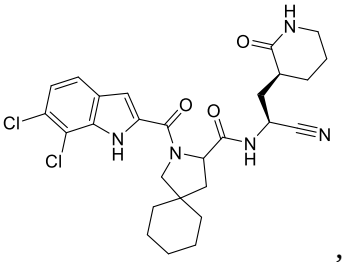
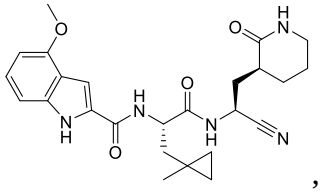
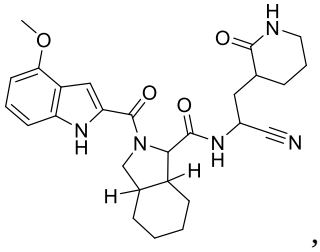
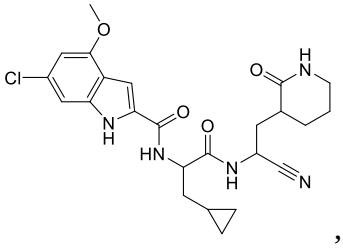
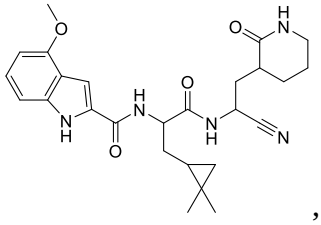
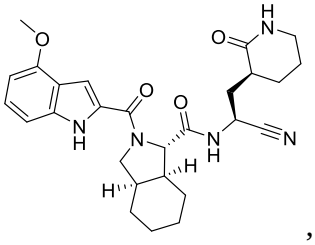
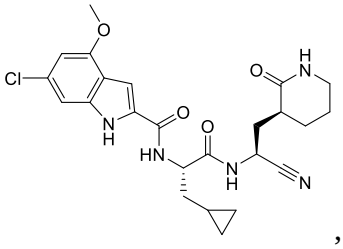
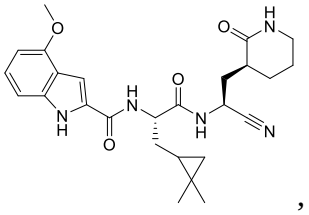
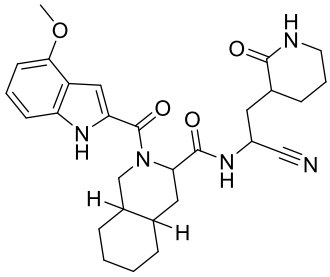
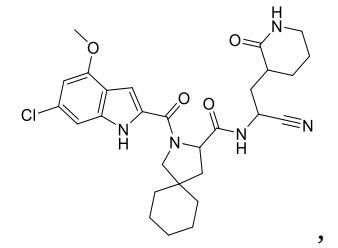
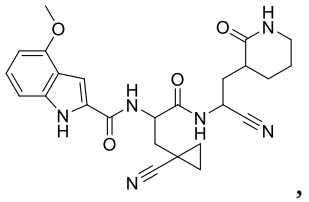
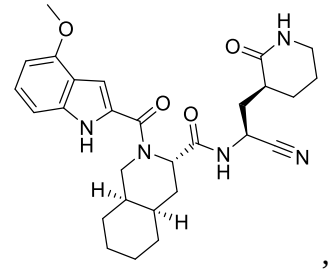
,

,

,

,

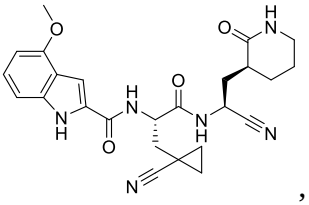
,

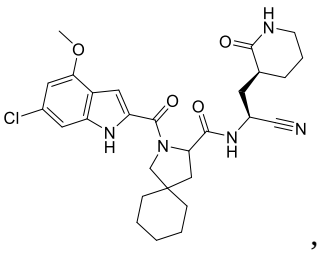
,

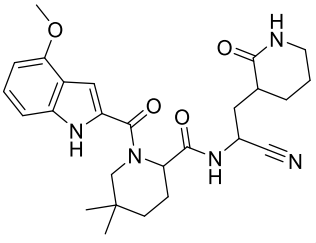

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

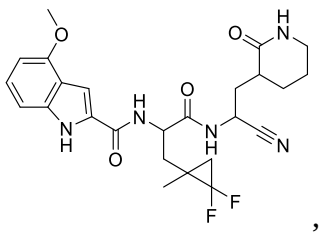
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

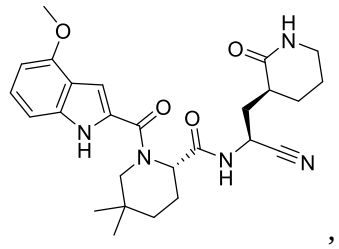
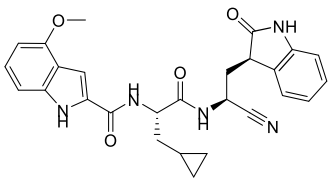
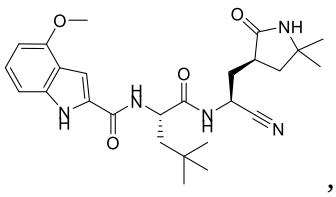
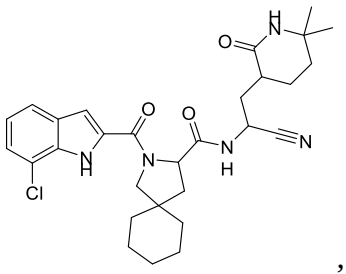
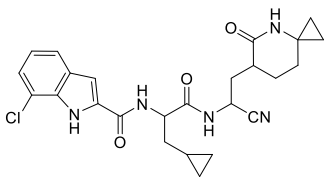
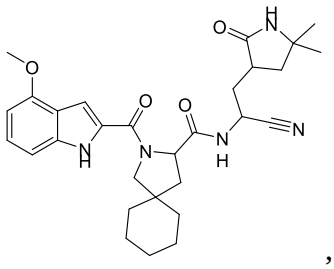
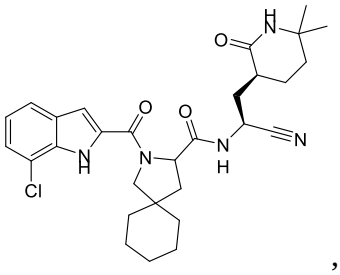
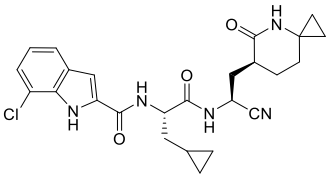
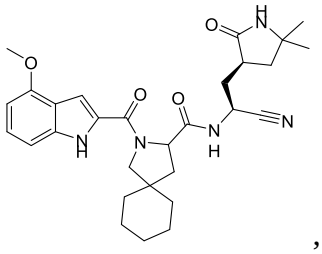
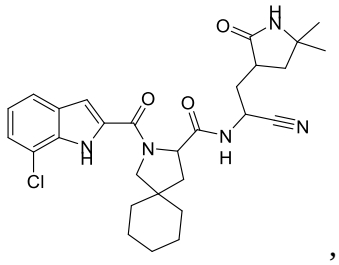
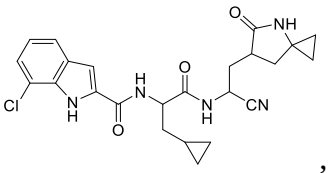
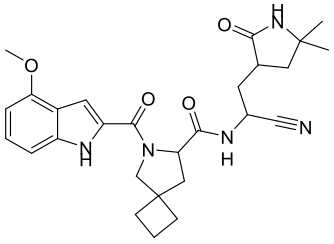
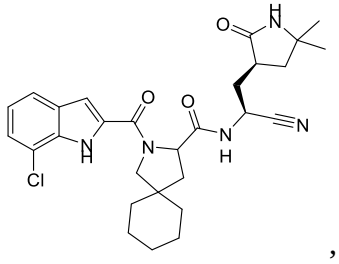
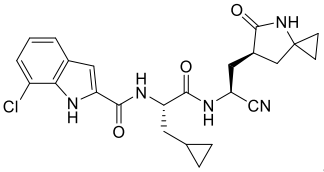
,

,

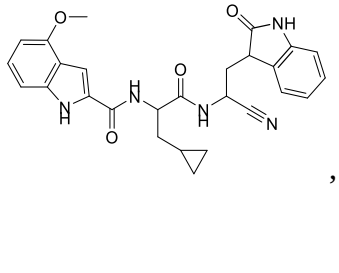
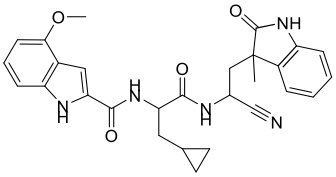
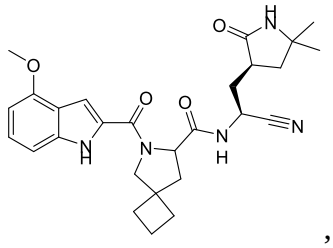
,

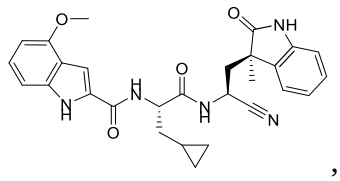
,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

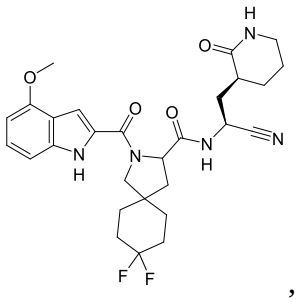
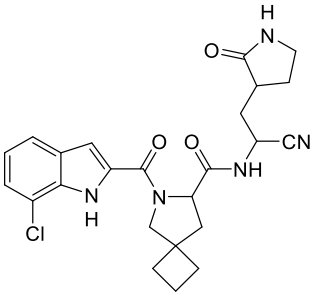
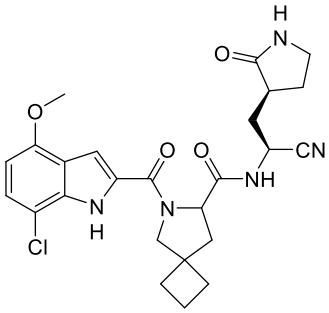
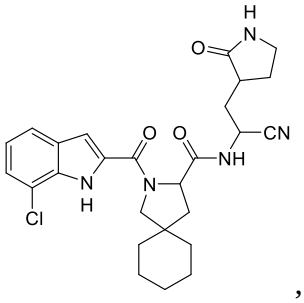
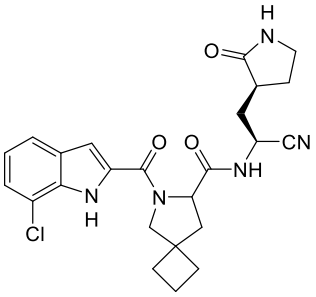
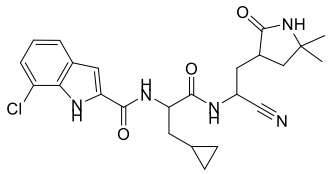
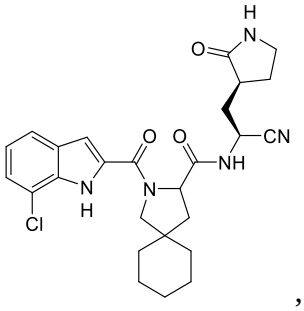
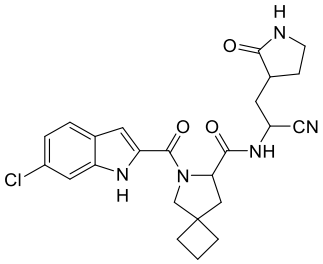
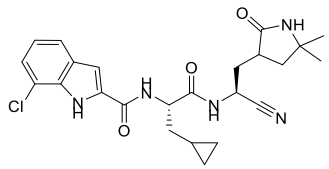
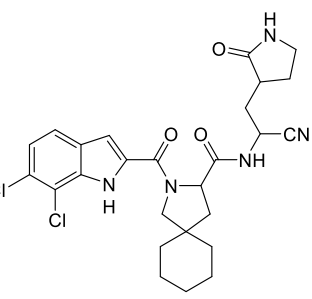
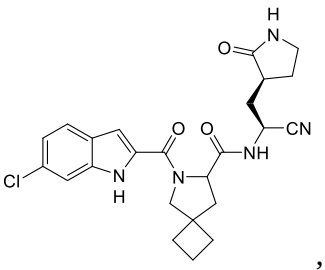
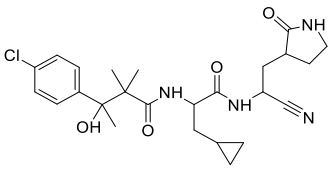
,

,

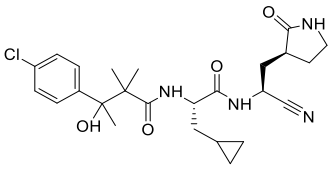
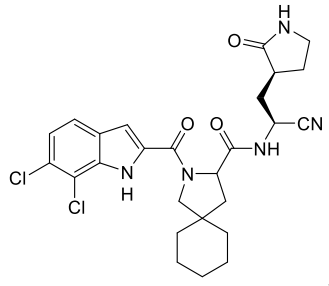
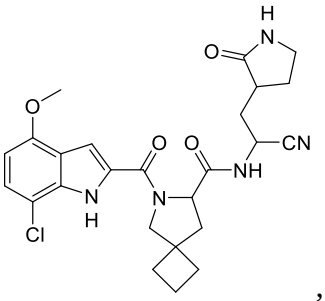
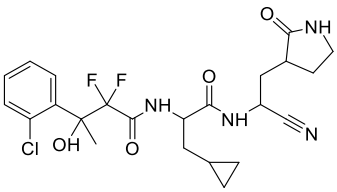
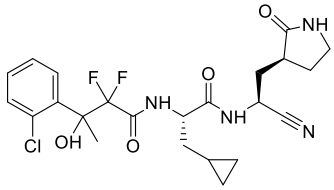
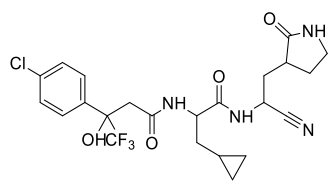
,

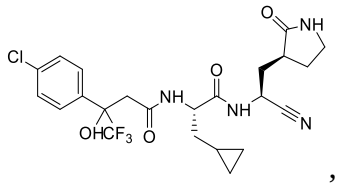
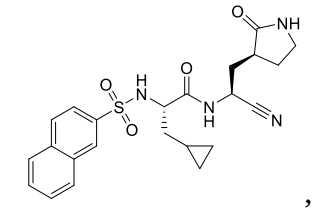
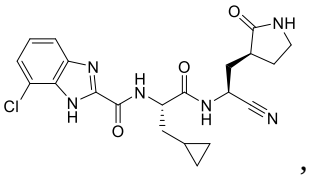
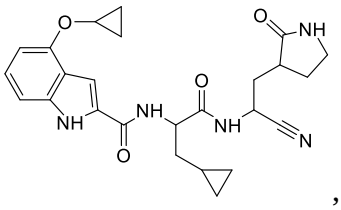
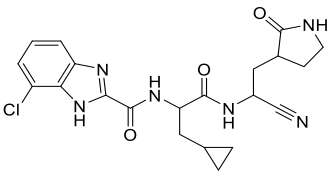
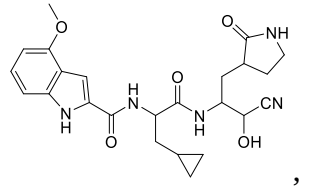
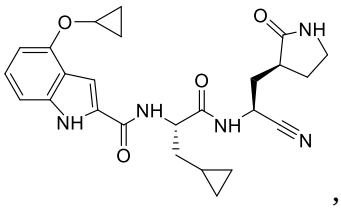
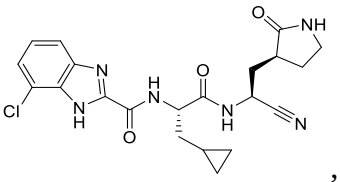
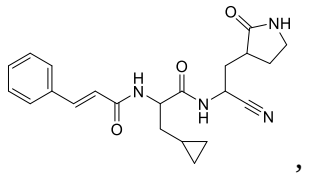
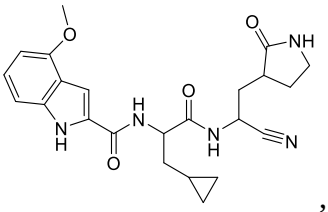
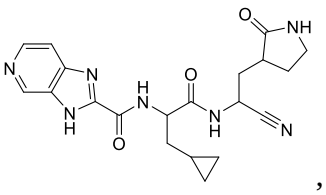
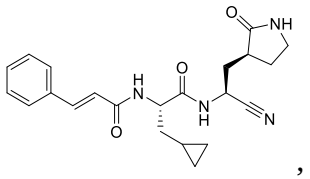
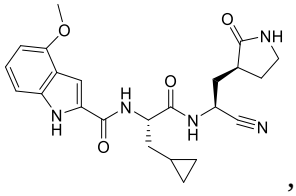
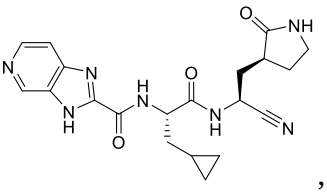
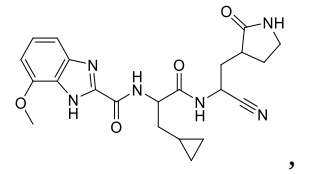
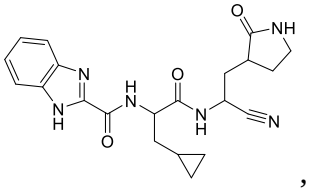
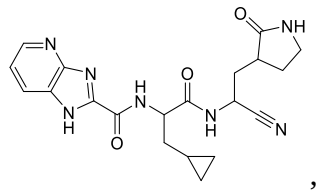
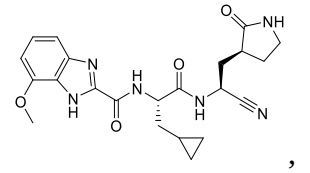
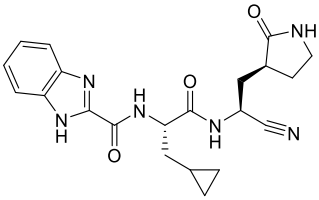
,

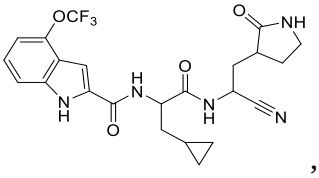
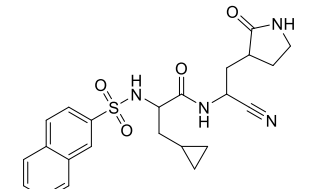
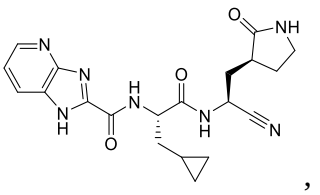
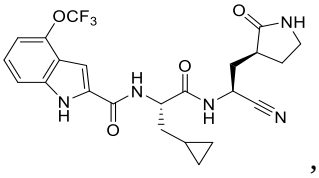
,

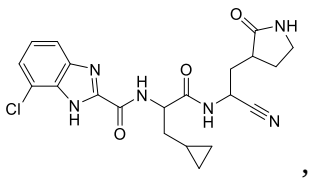

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

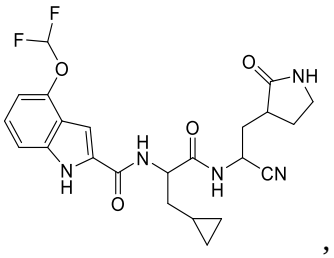
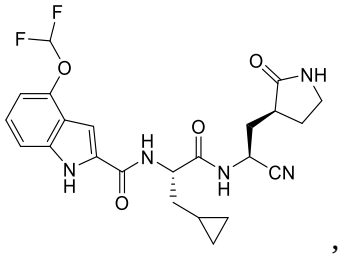
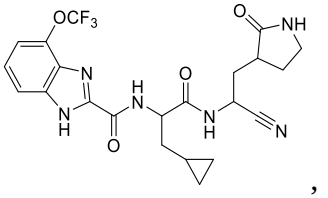
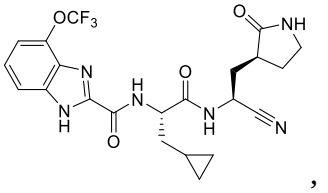
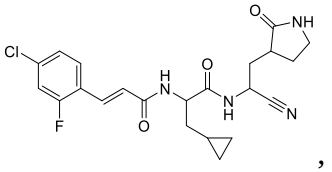
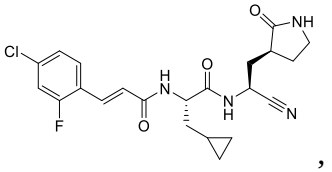
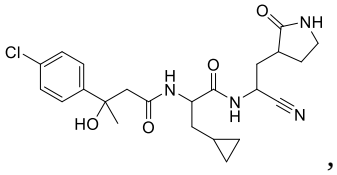
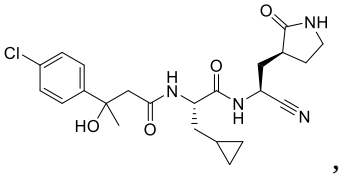
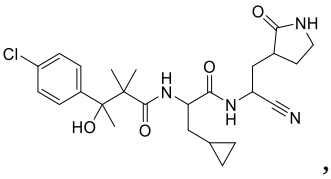
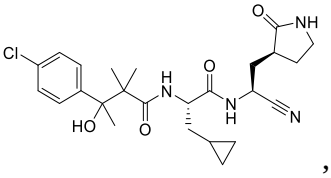
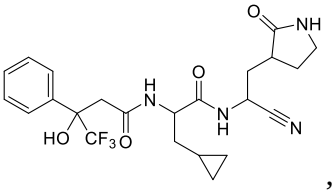
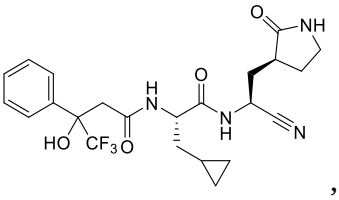
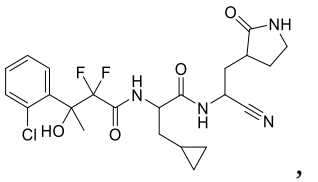
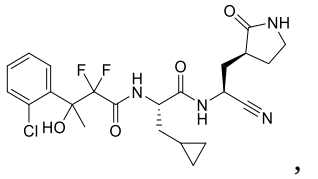
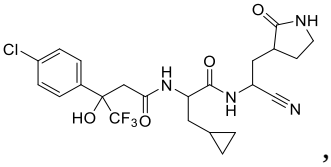
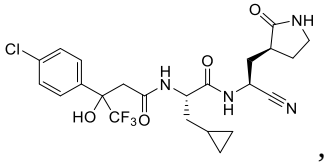
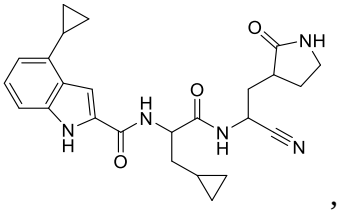
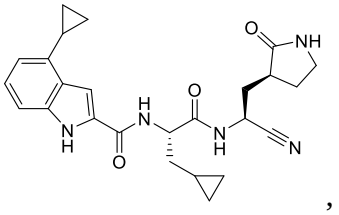
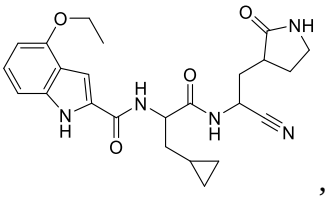
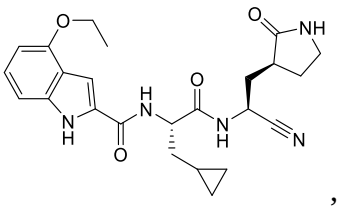
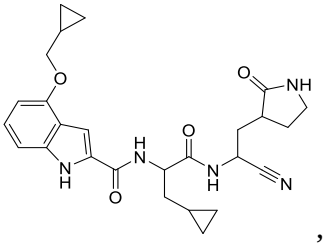
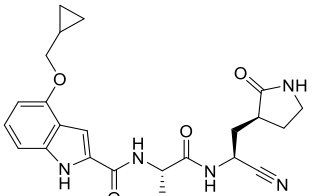
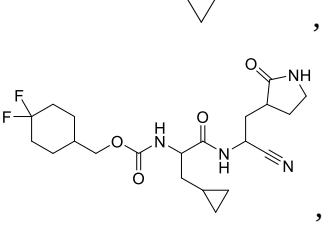
,

,

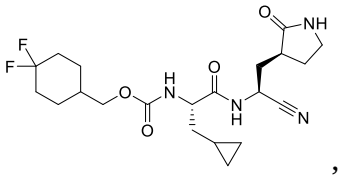
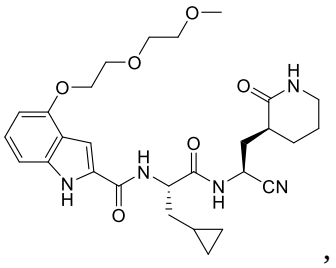
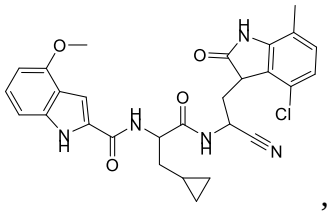
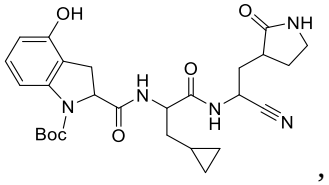
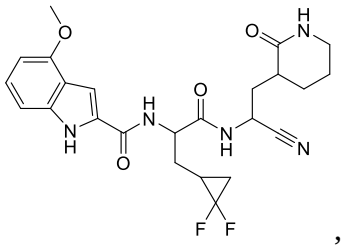
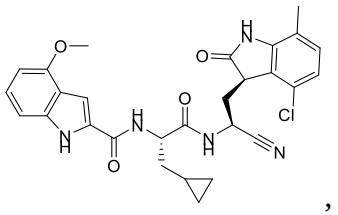
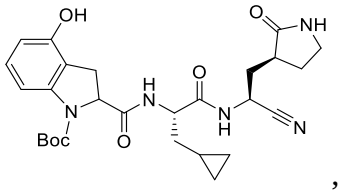
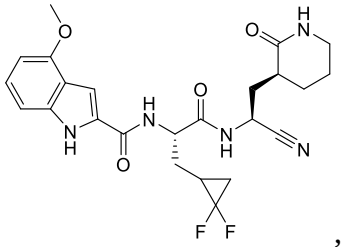
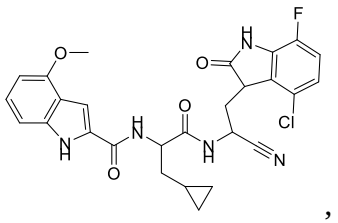
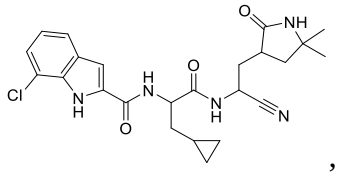
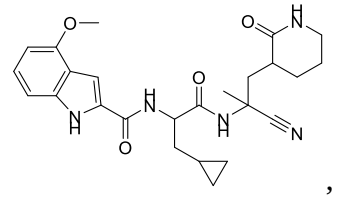
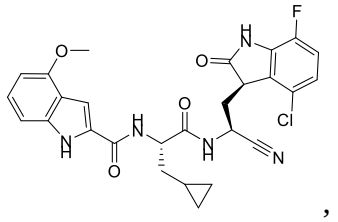
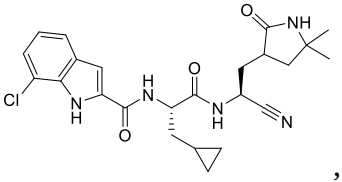
,

,

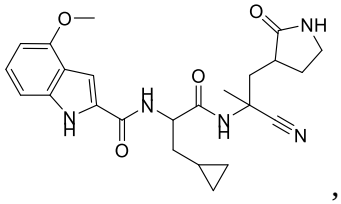
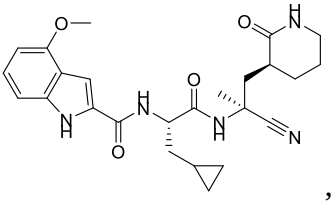
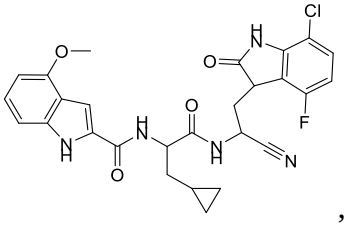
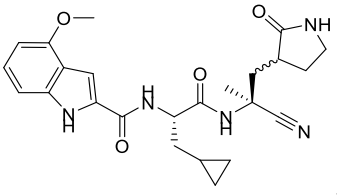
,

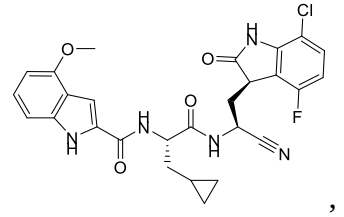

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

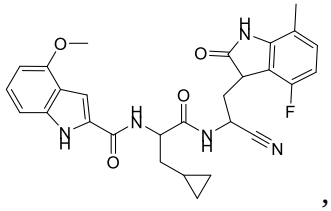
,

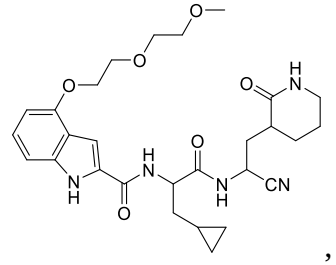
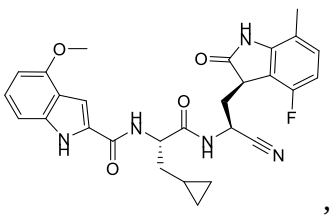
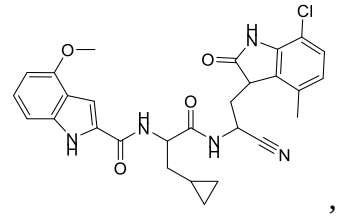

,

,

,

,

,

,

,

,

,

,

,

,

,

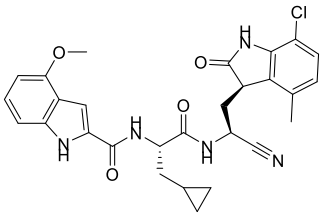
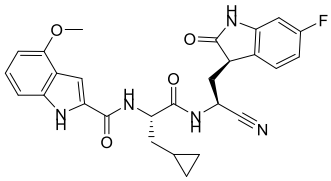
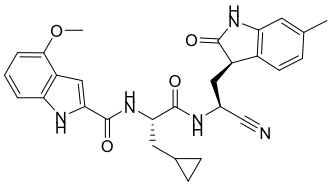
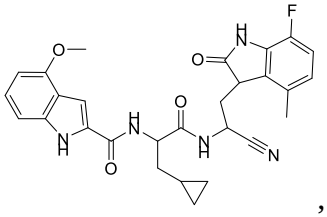
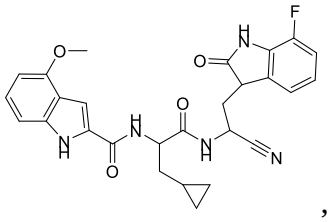
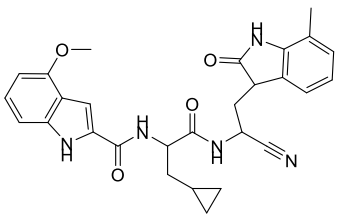
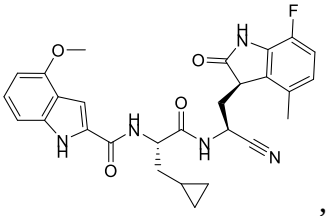
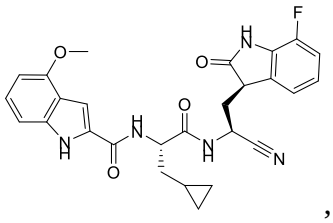
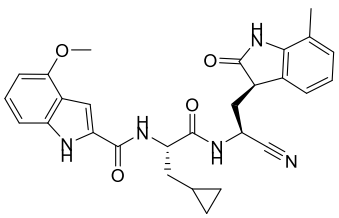
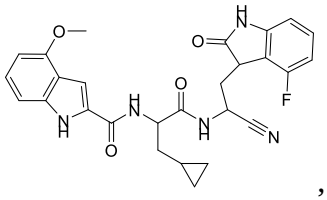
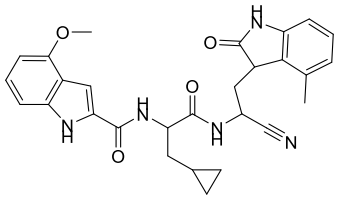
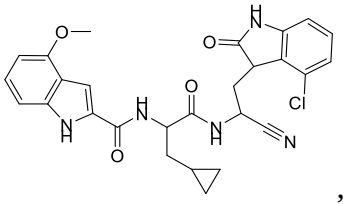
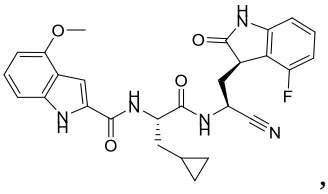
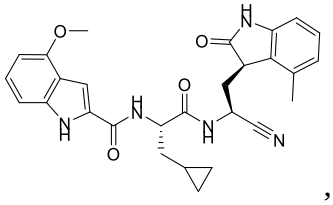
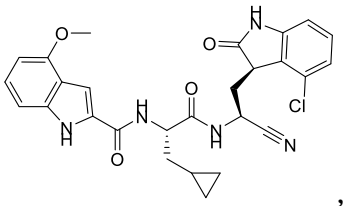
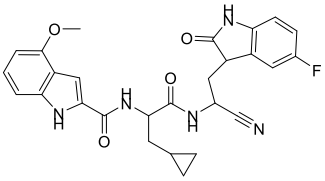
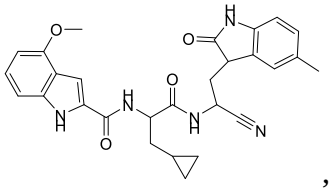
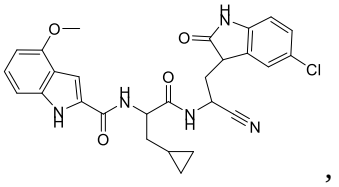
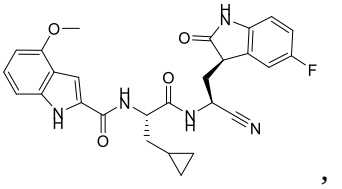
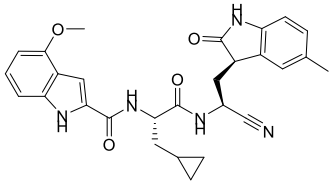
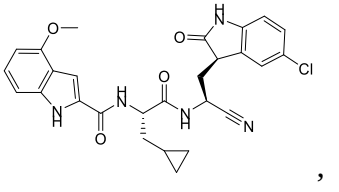
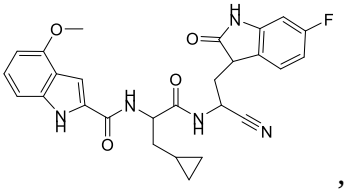
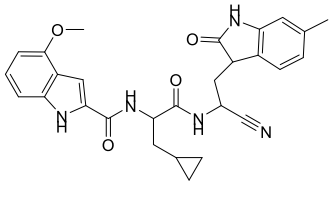
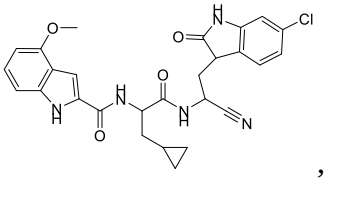
,

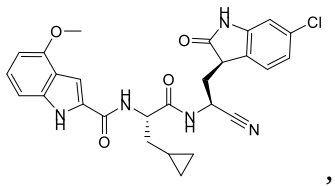
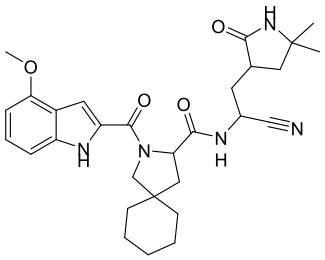
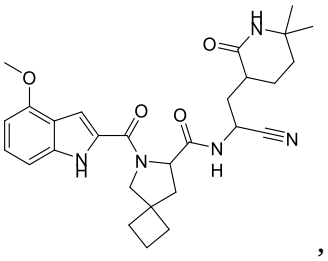
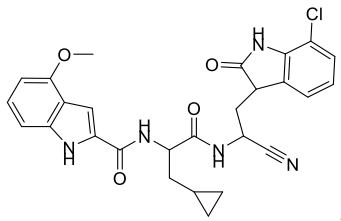
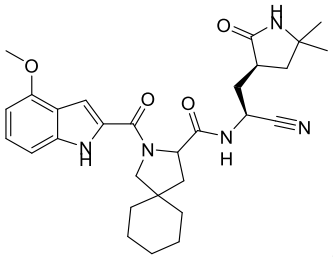
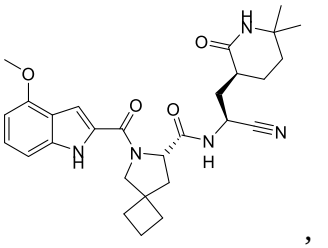
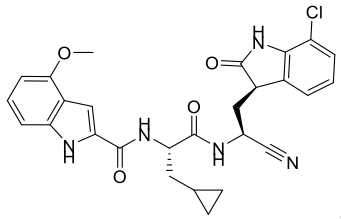
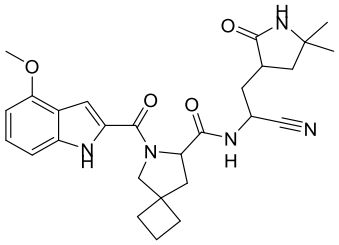
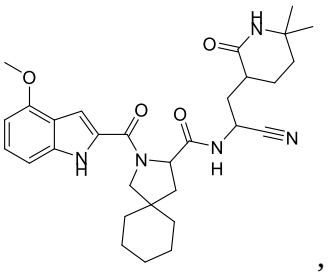
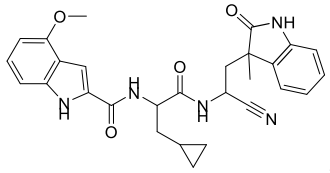
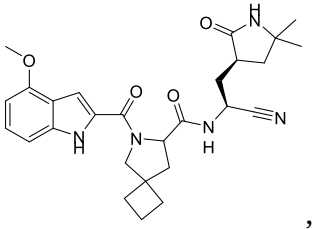
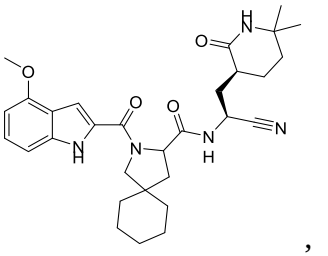
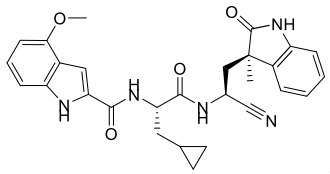
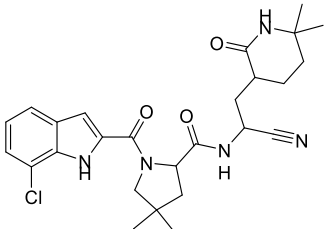
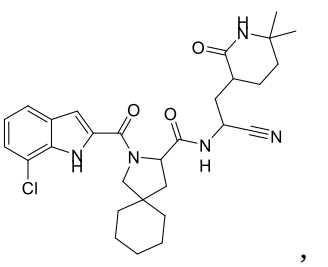
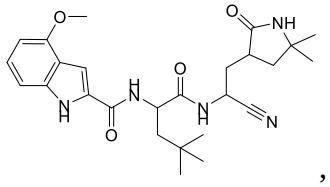
,

,

,

,

,

,

,

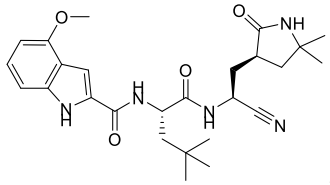
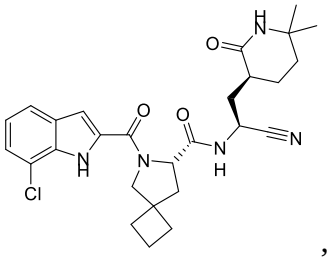
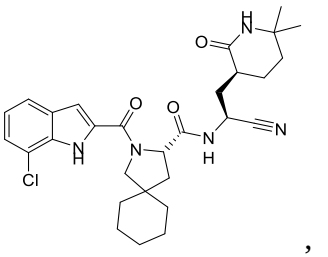
,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

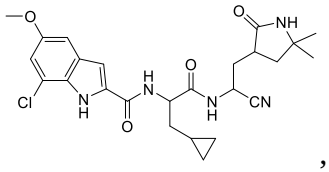
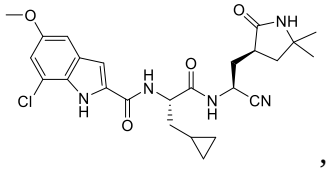
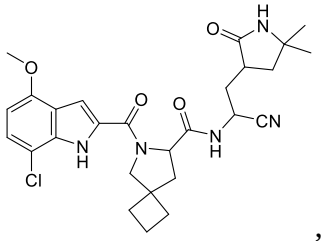
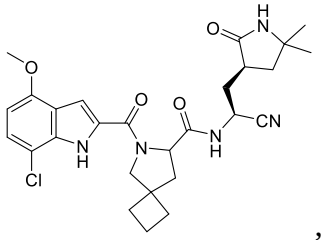
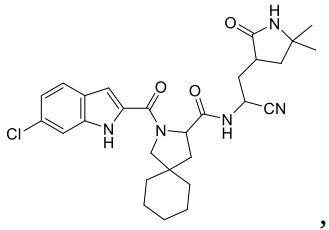
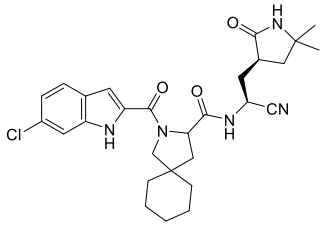
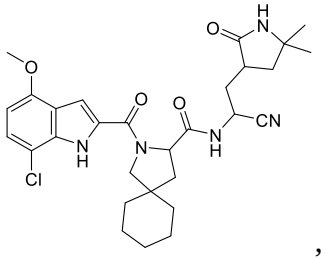
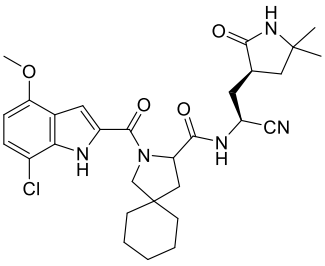
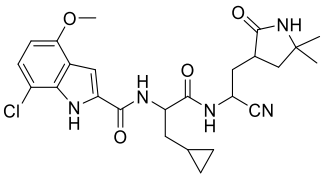
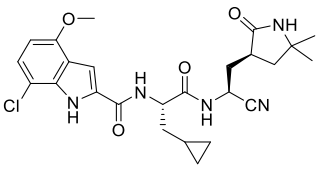
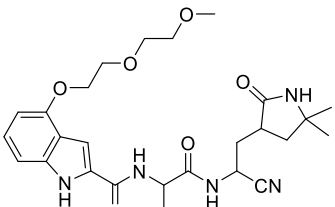
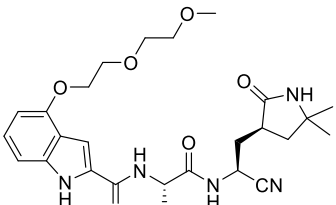
,

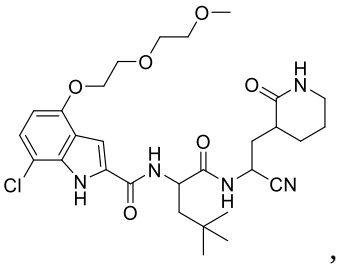
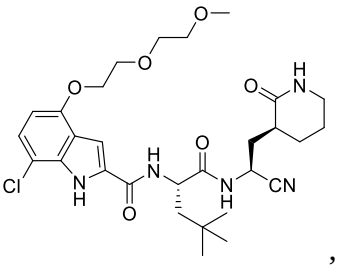
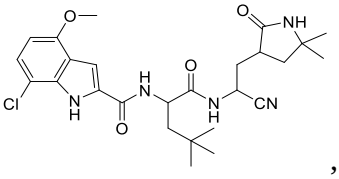
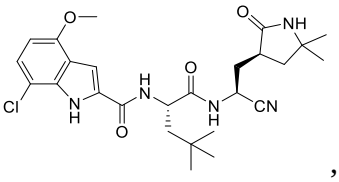
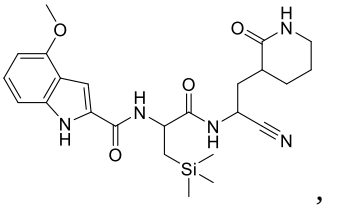
,

,

,

,

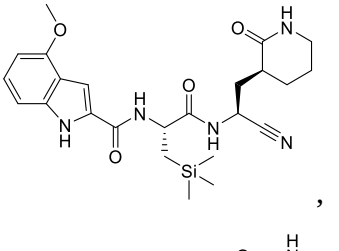
,

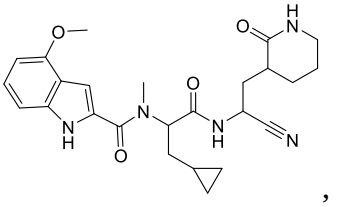
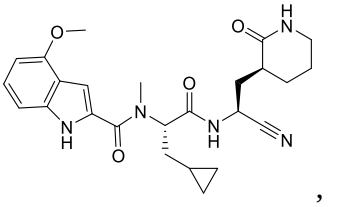
,

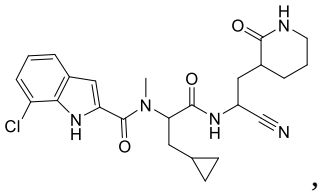
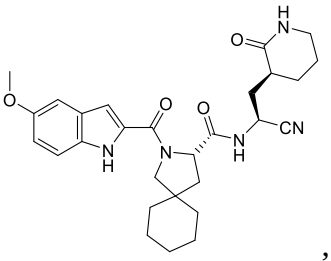
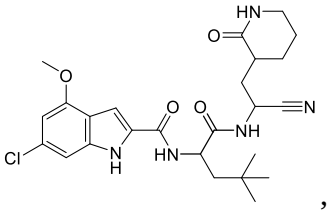
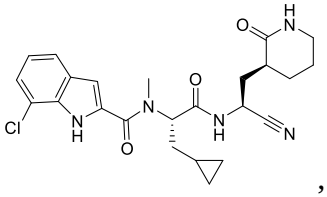
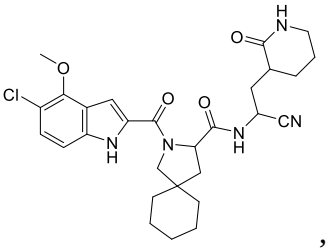
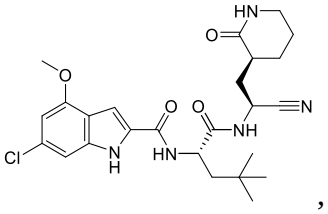
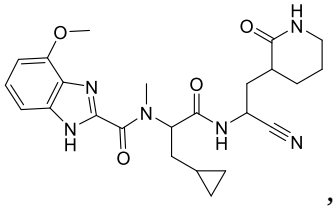
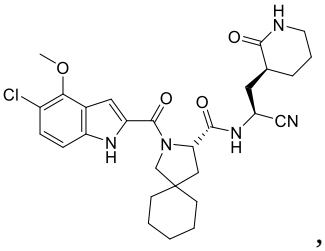
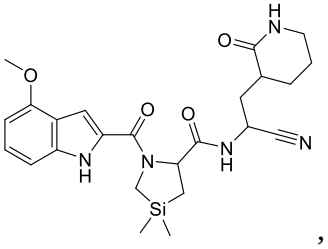
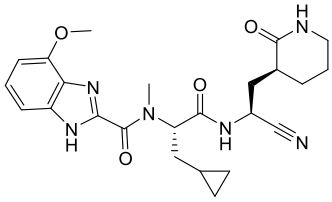
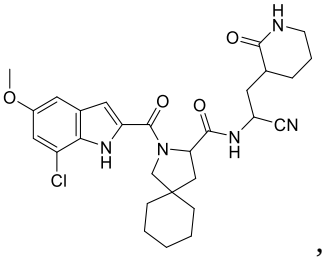
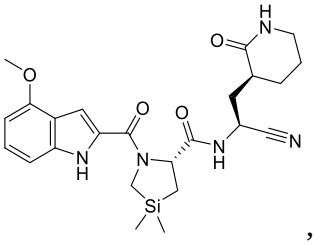
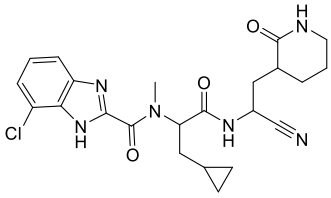
,

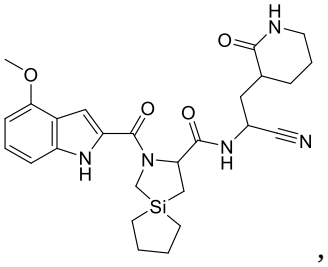
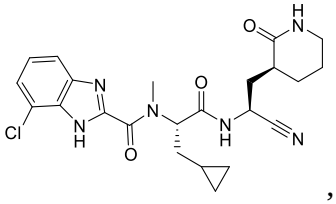
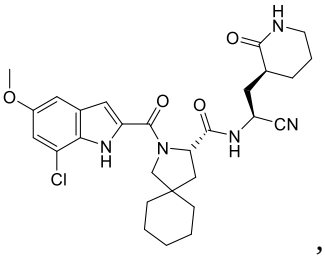

,

,

,

,

,

,

,

,

,

,

,

,

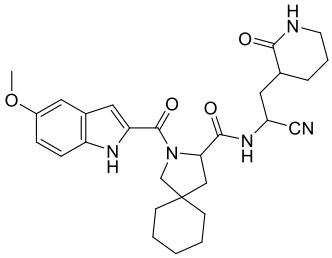
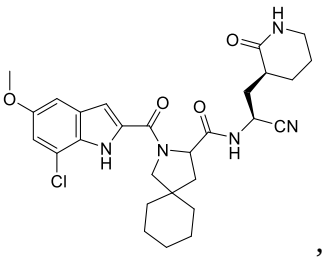
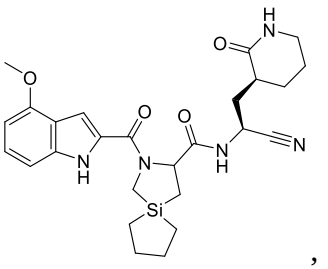
,

,

,

,

,

,

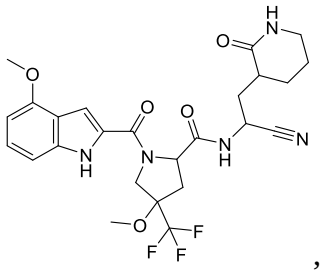
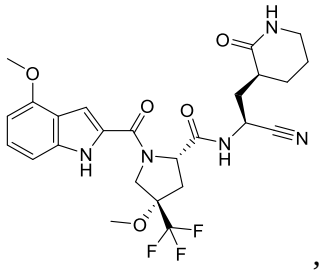
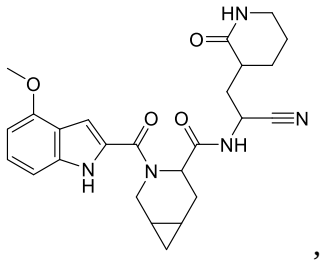
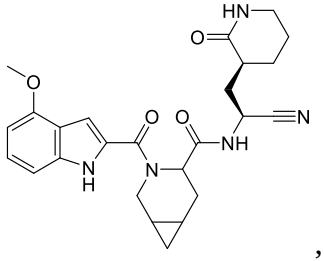
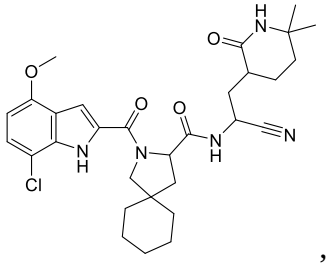
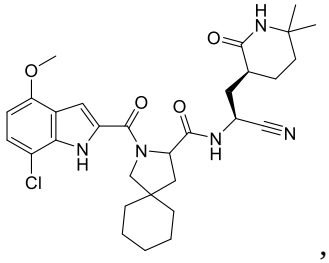
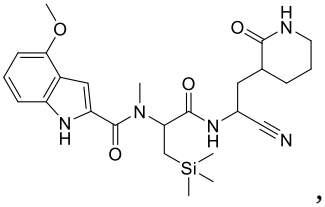
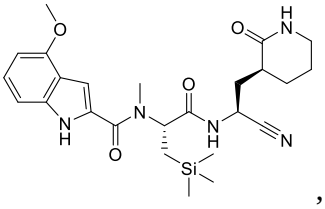
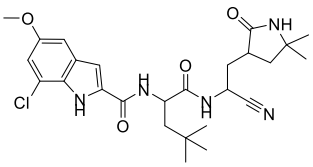
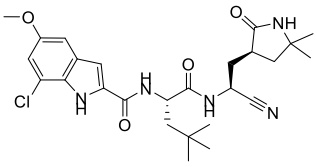
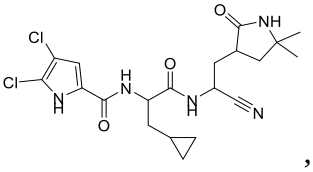
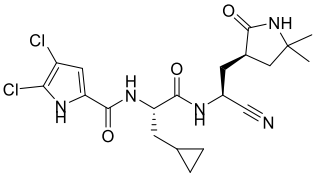
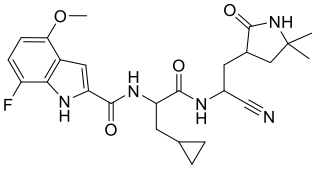
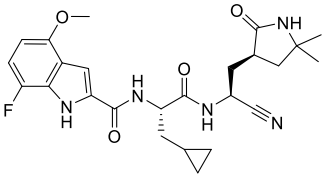
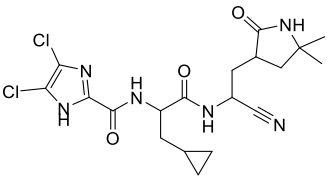
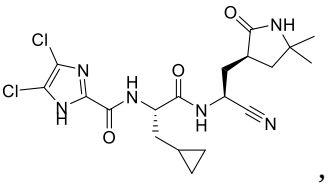
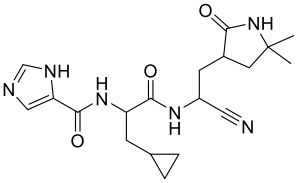
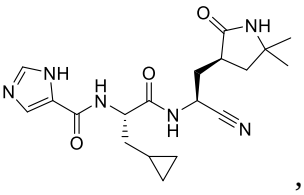
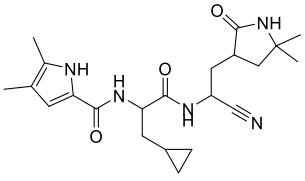
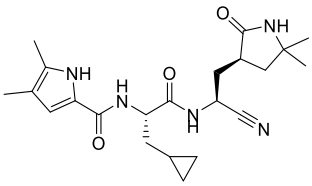
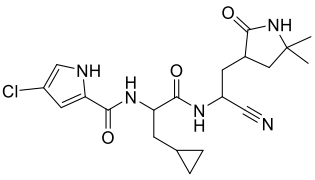
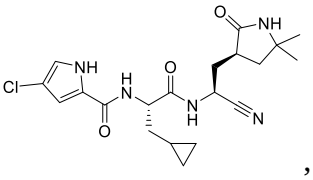
,

,

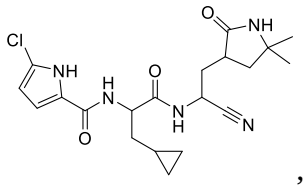
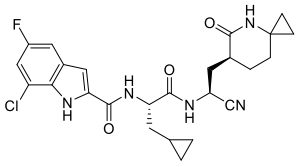
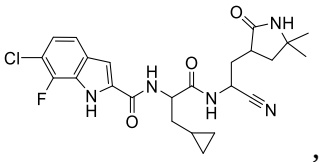
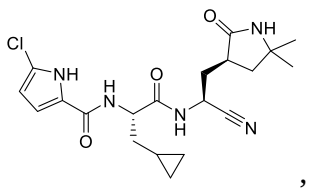
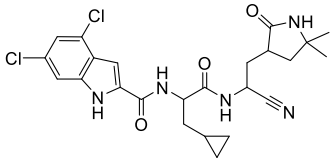
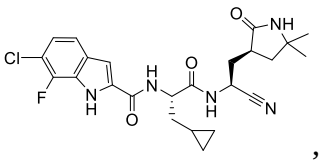
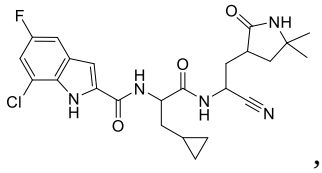
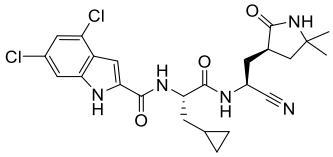
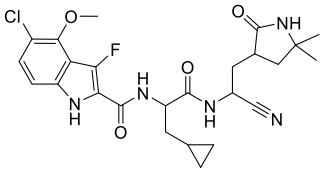
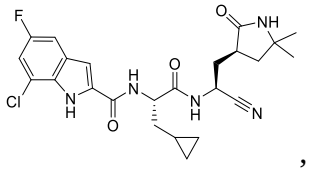
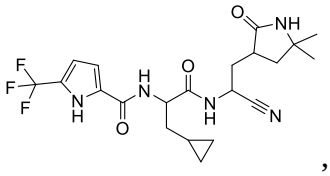
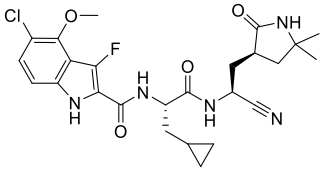
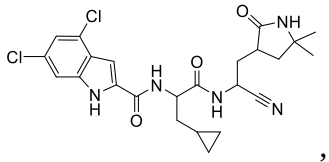
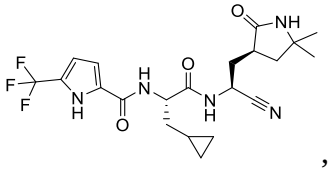
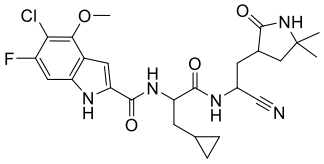
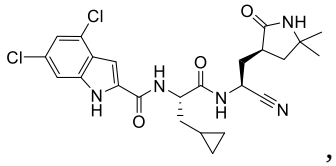
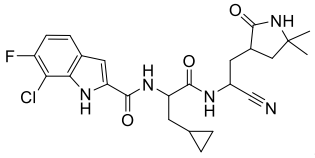
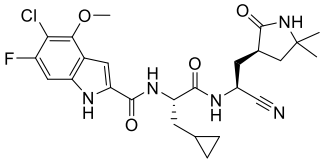
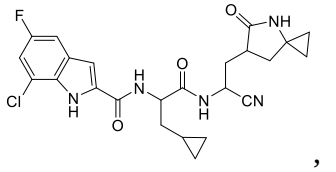
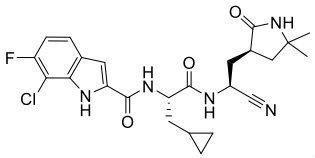
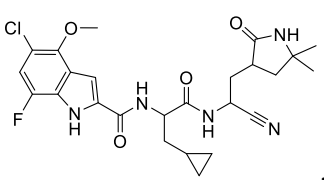
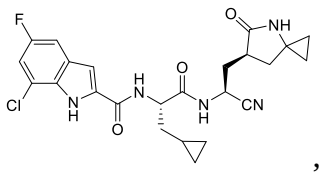
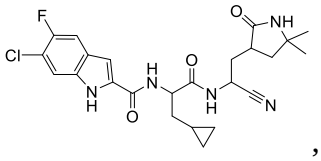
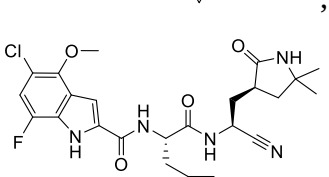
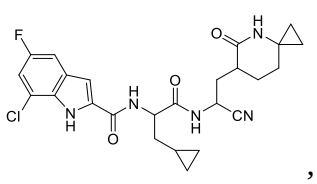
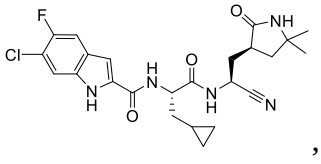
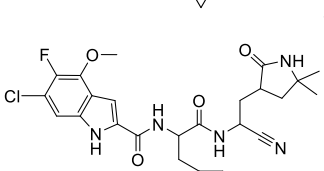
,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

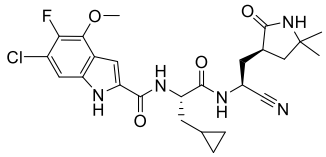
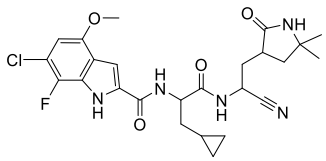
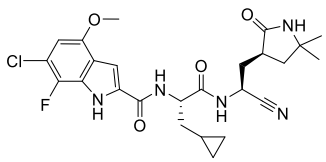
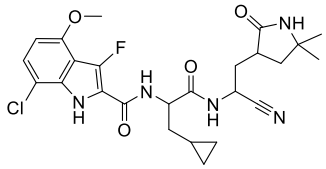
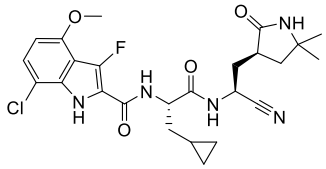
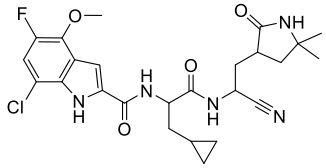
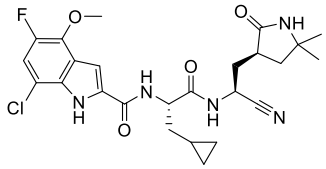
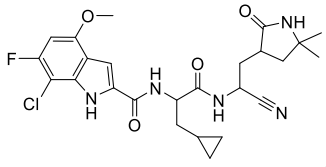
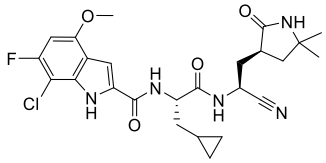
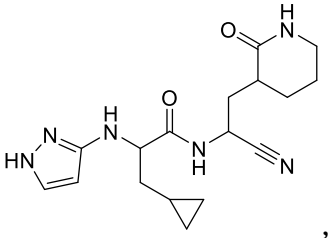
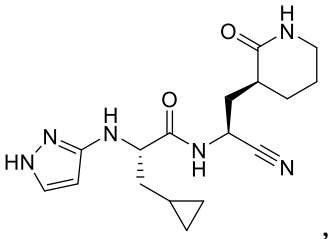
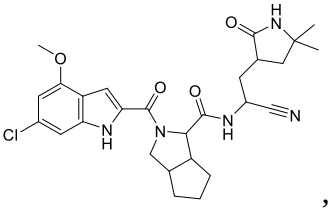
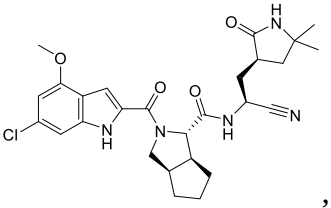
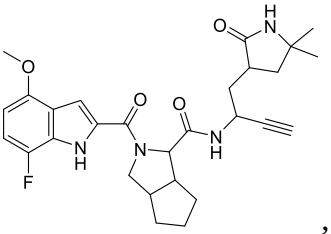
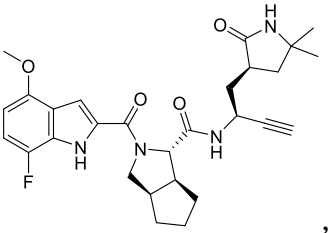
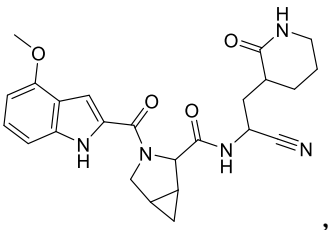

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

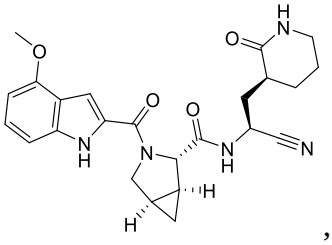
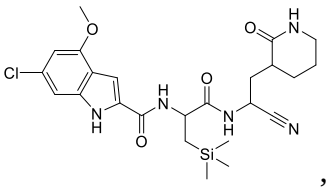
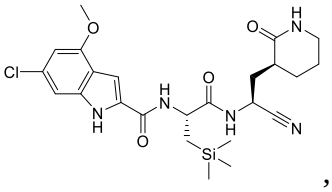
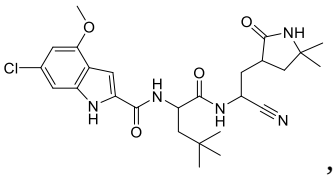
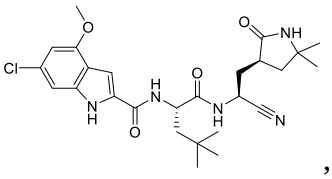
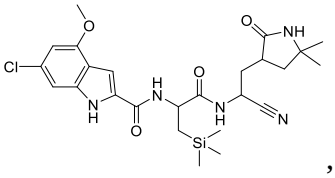
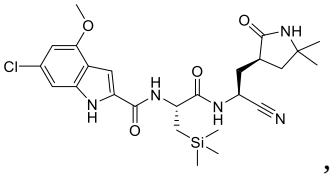
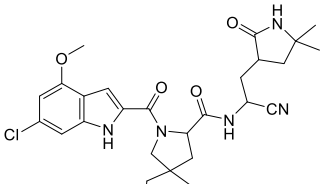

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

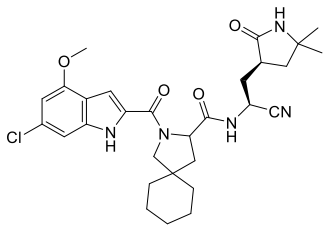
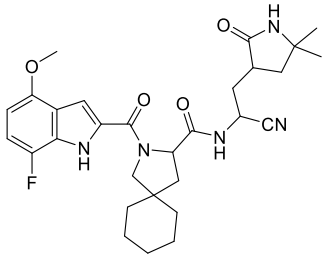
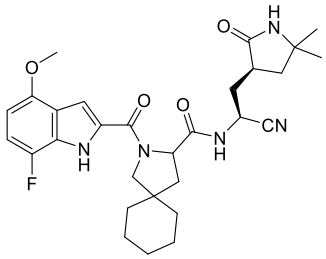
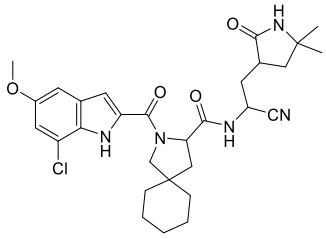
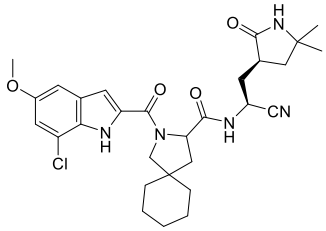
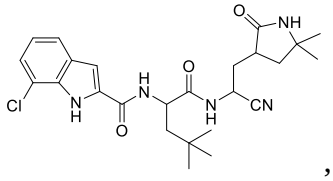
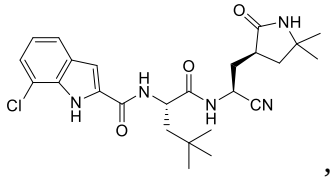
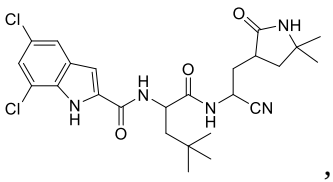
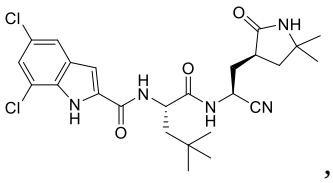
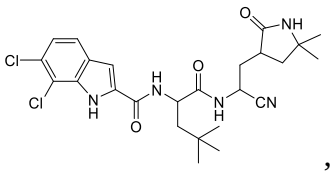
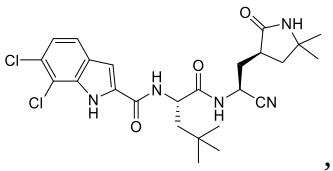
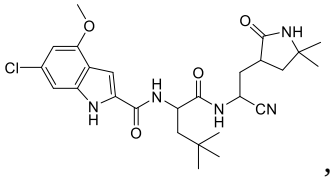
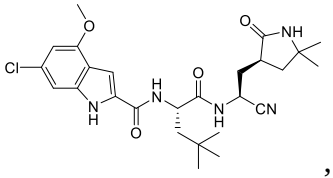
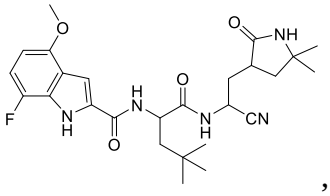
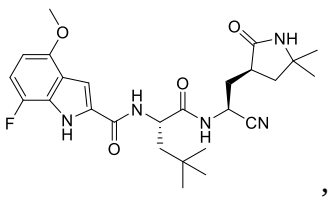
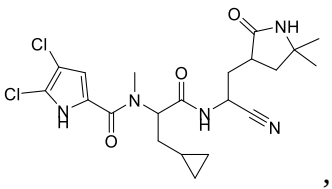
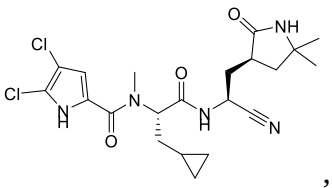
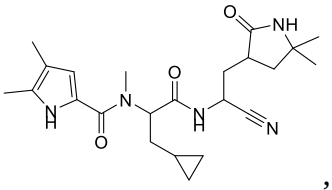
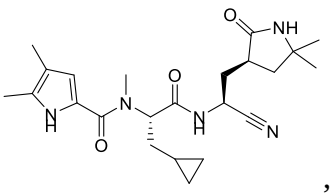
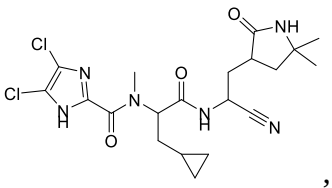
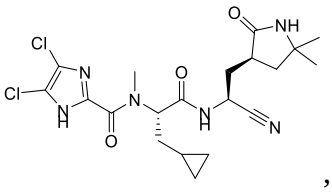
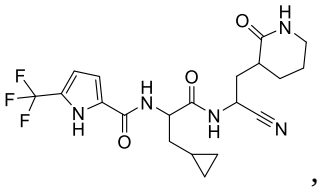
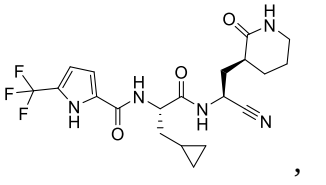
,

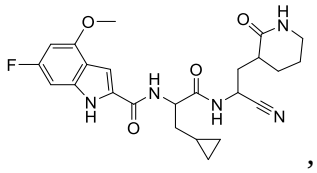
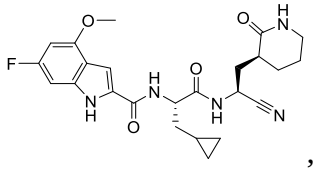
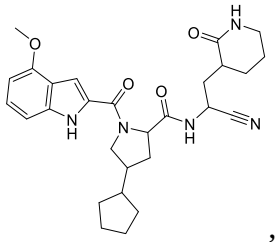
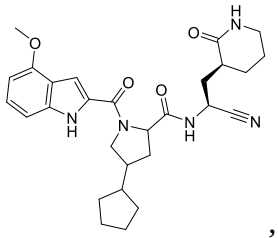
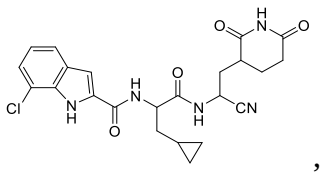
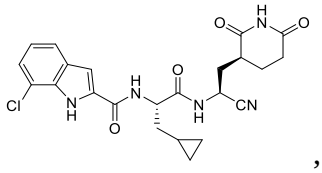
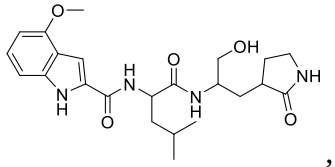
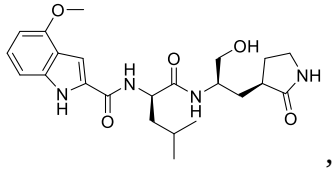
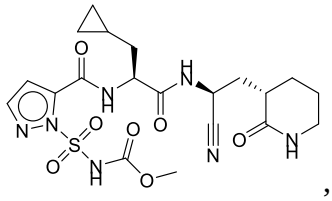
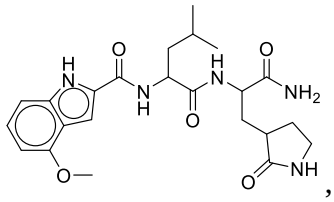
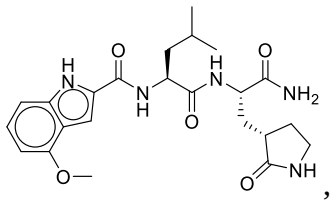
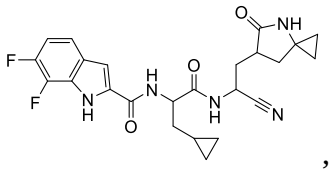
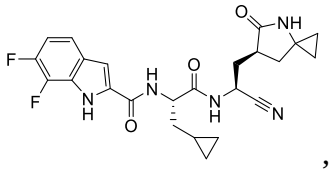
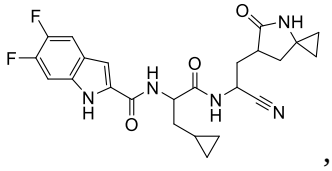
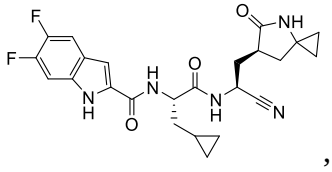
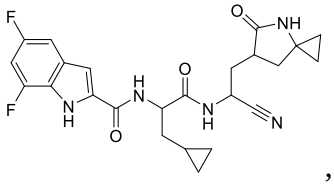
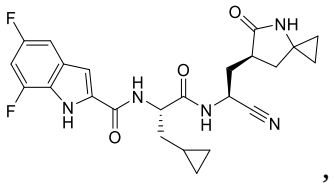
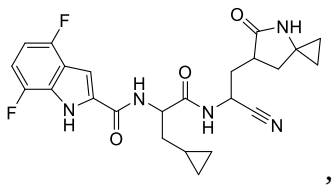
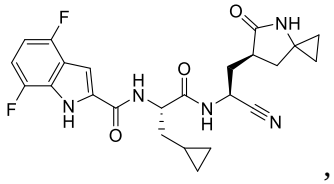
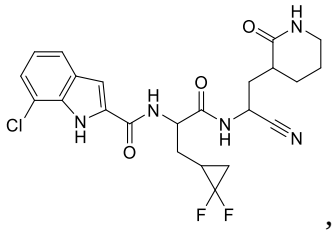
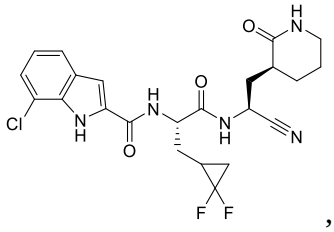
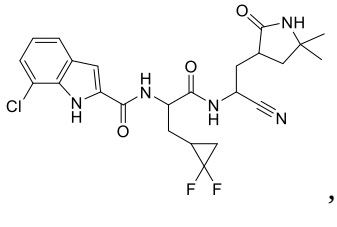
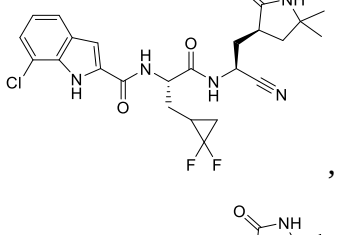
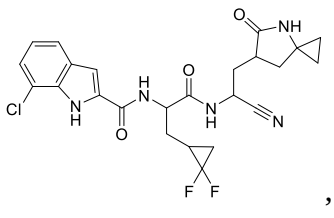
,

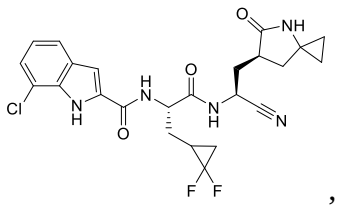
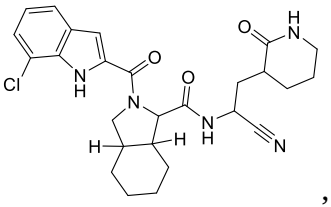
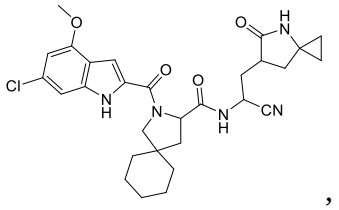
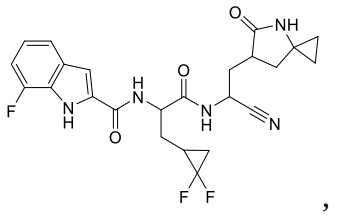
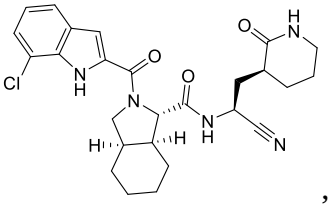
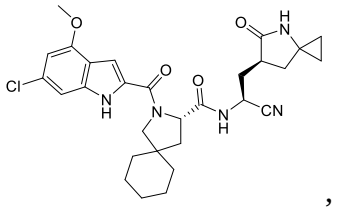
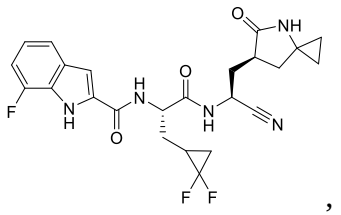
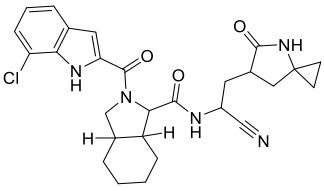
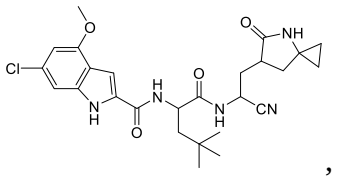
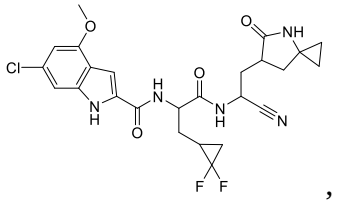
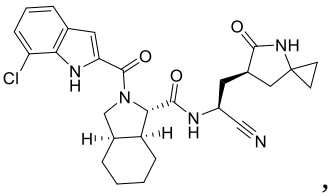
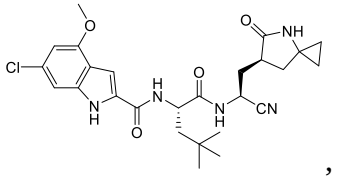
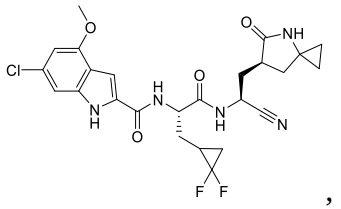
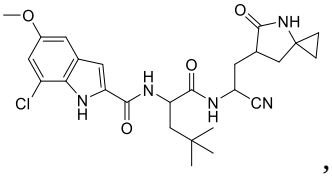
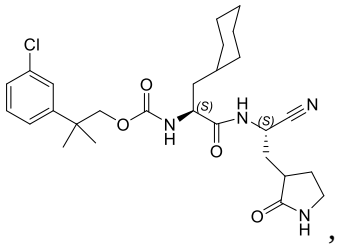
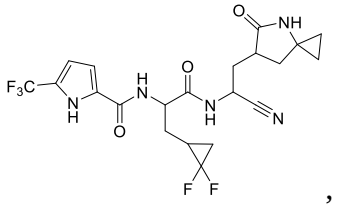
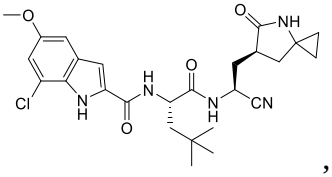
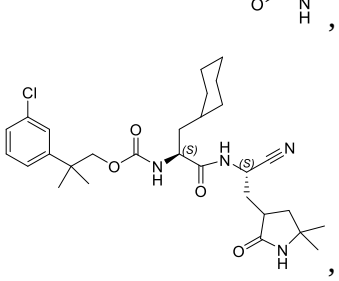
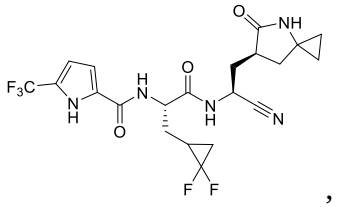
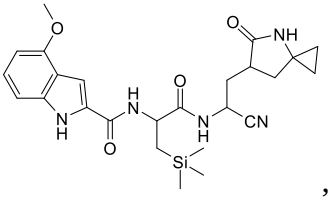
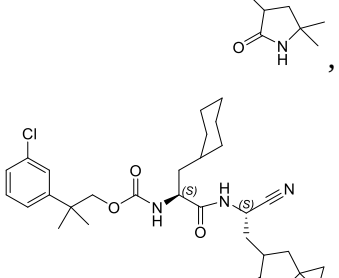

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

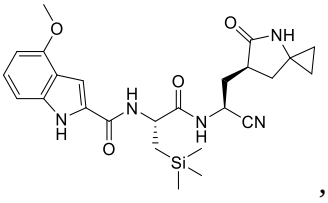
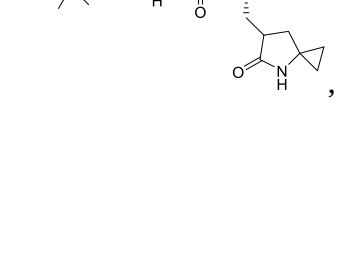
,

,

,

,

,

,

,

,

,

,

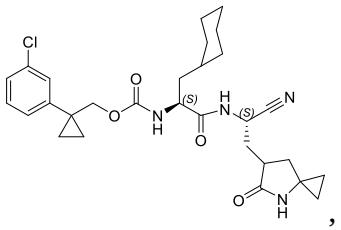
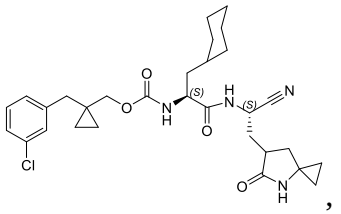
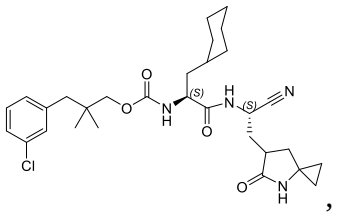
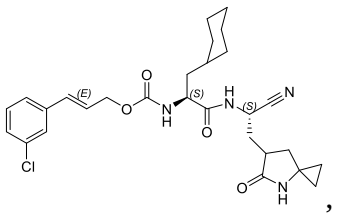
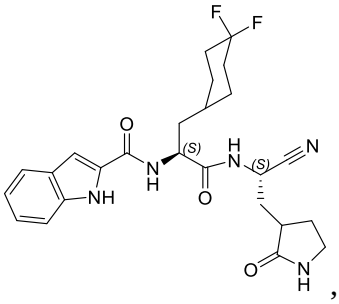
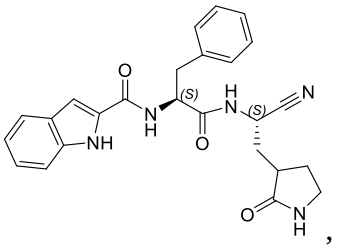
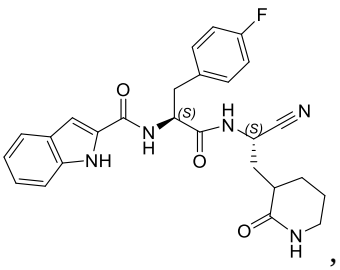
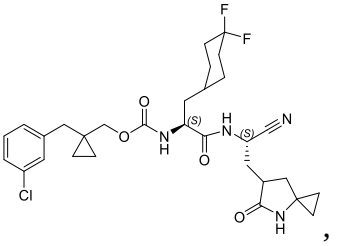
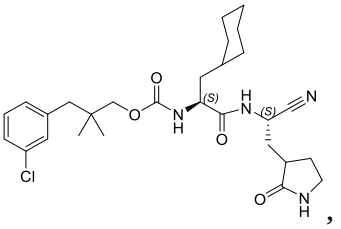
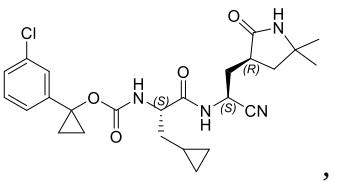
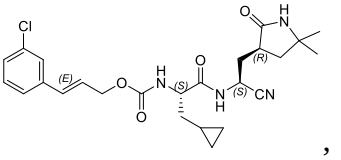
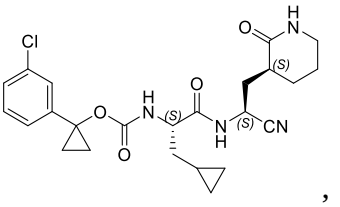
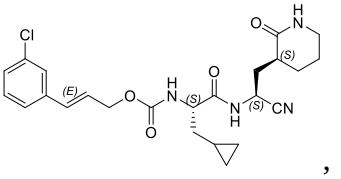
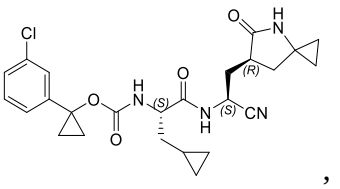
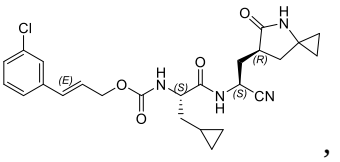
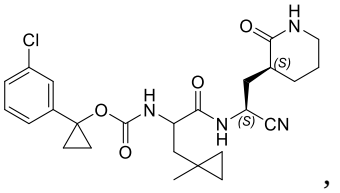
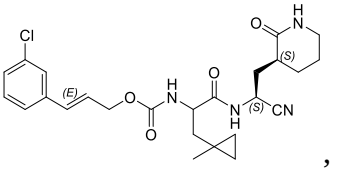
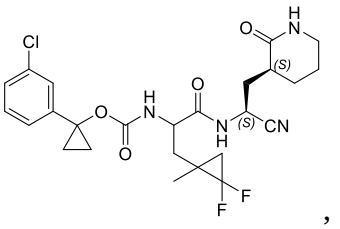
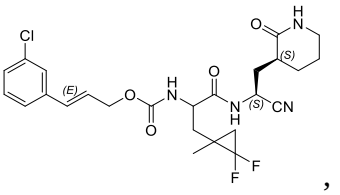
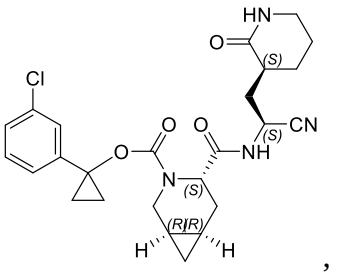
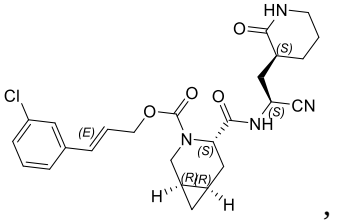

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

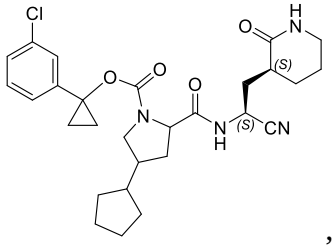
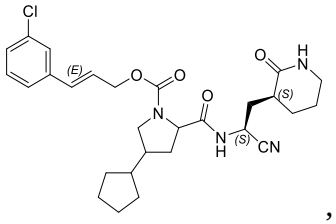
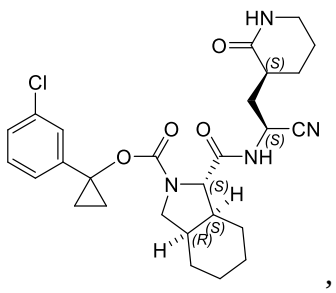
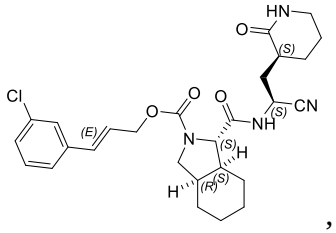
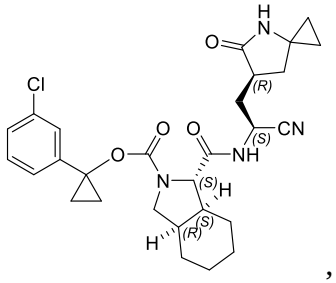
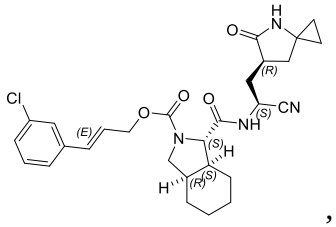
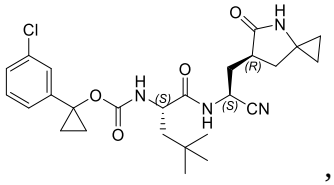
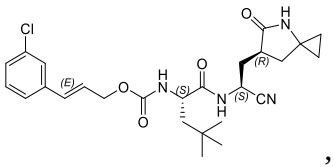
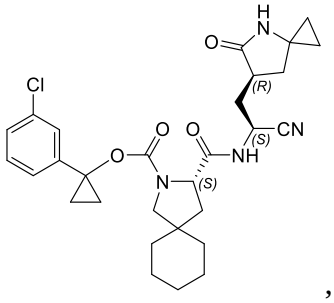
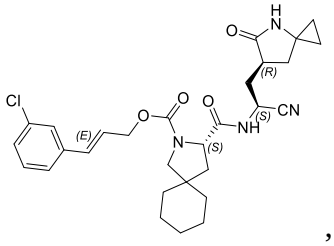
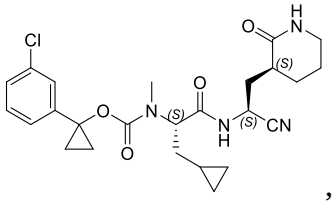
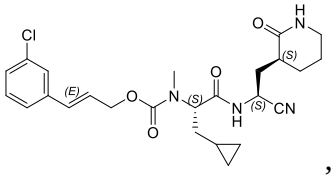
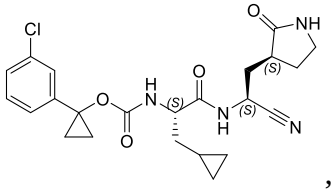
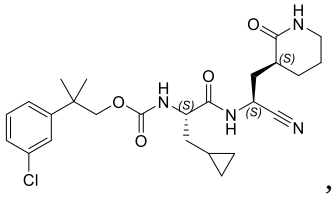
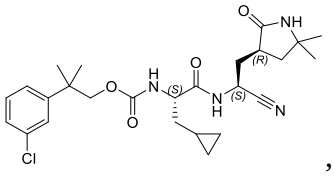
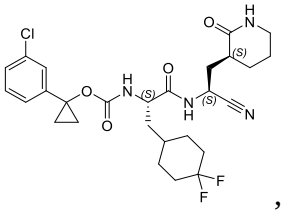
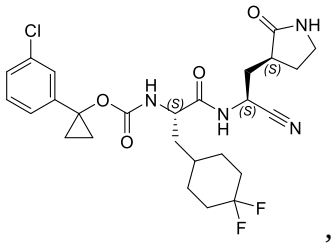
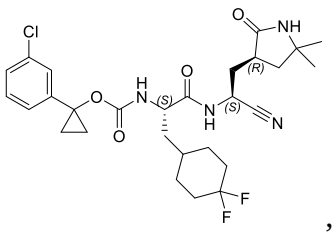
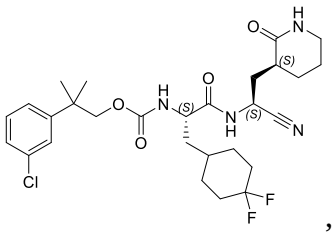
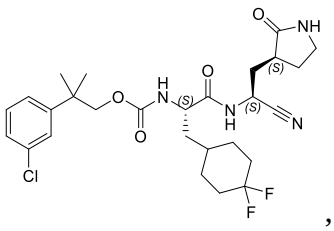

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

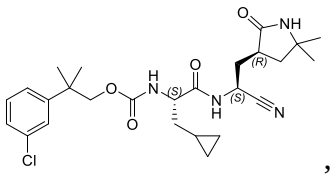
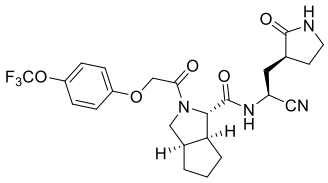
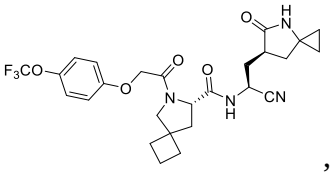
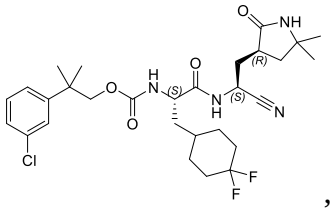
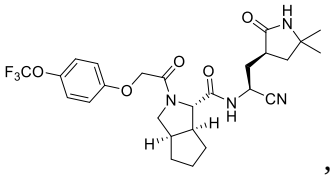
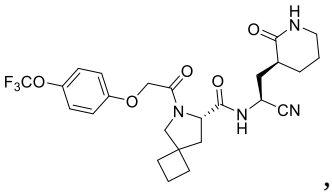
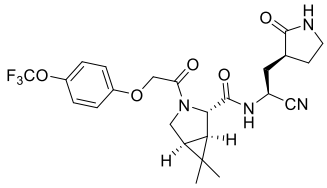
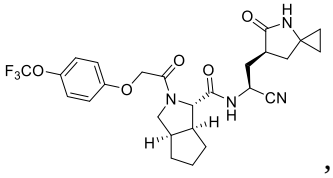
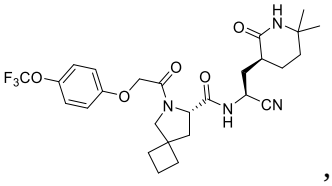
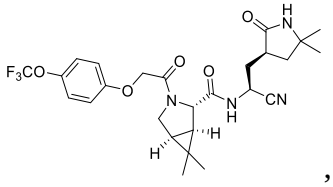
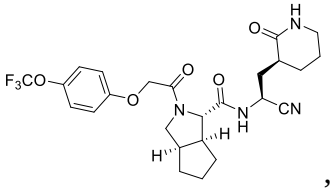
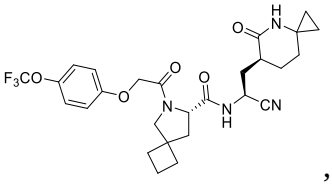
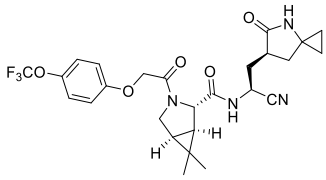
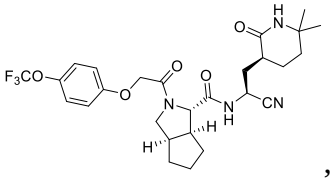
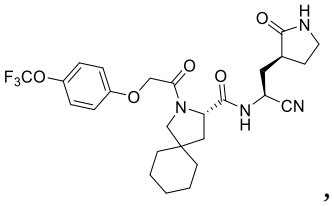
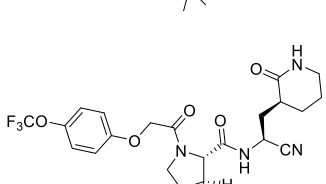
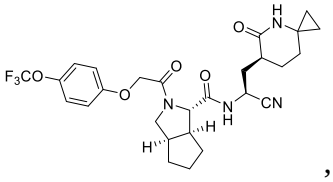
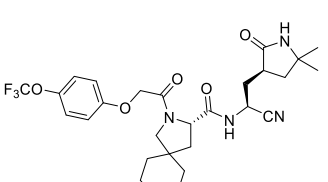
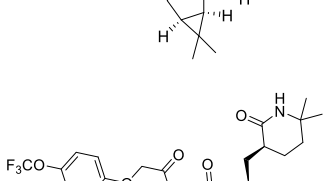
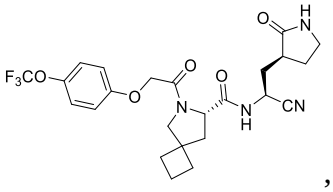
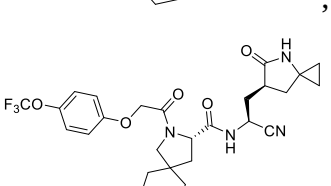
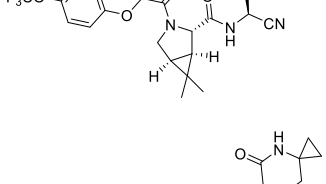
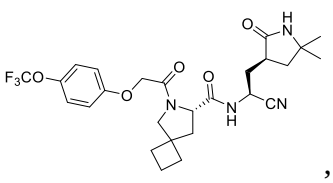
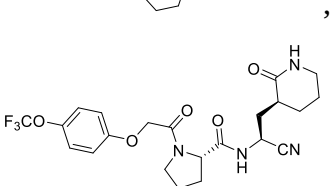
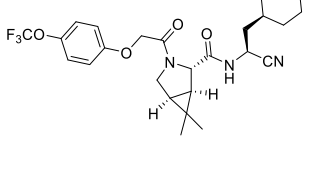

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

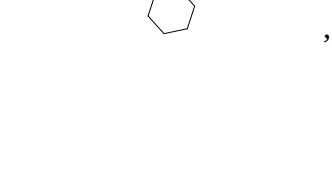
,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

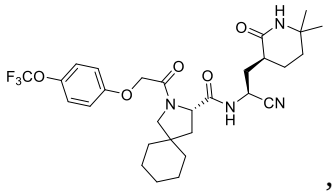
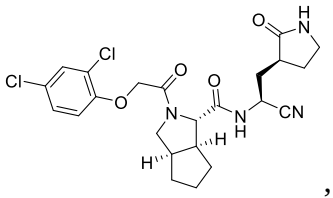
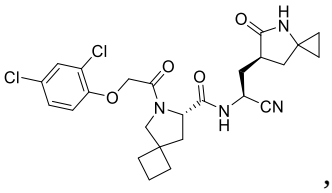
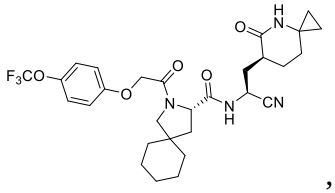
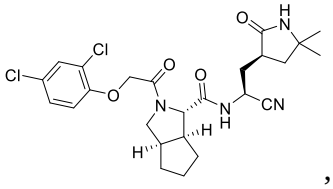
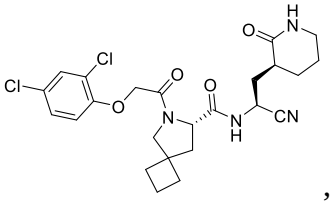
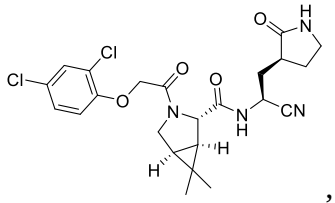
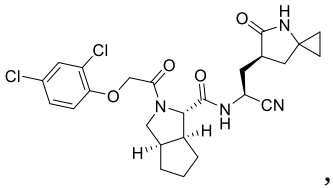
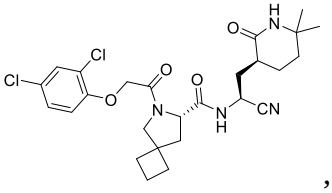
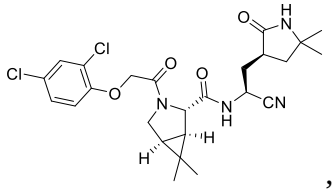
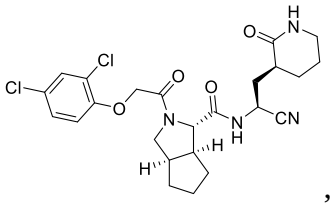
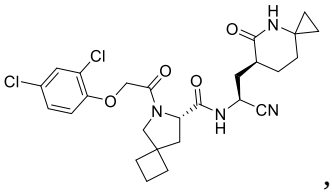
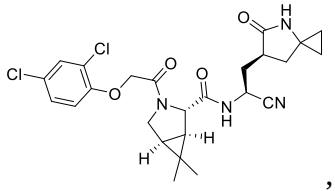
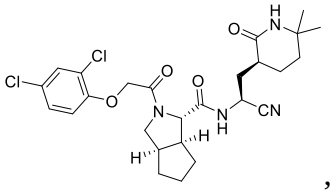
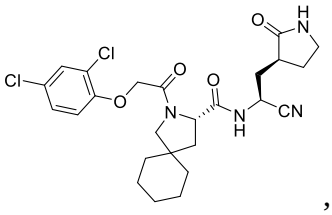
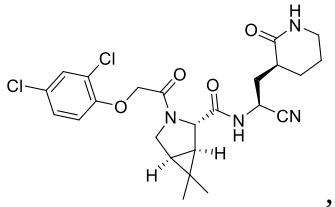
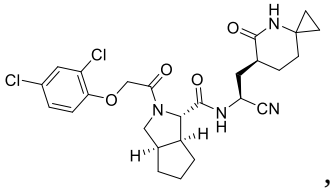
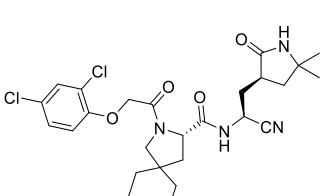
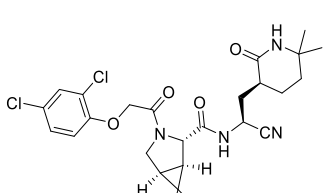
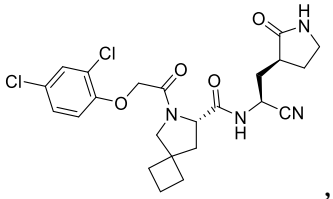
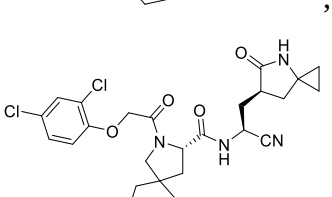
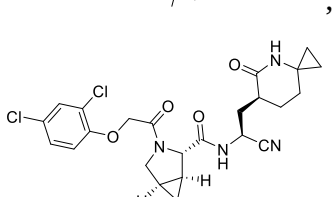
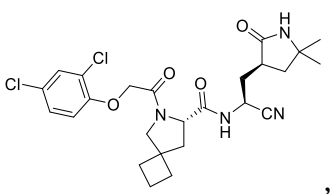
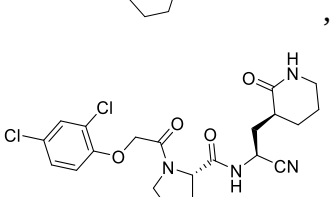
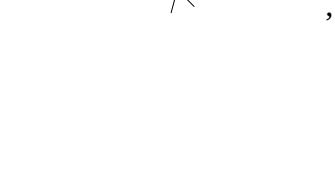

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

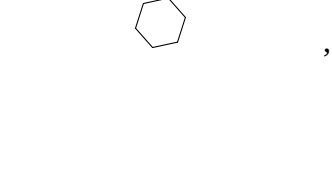
,

,

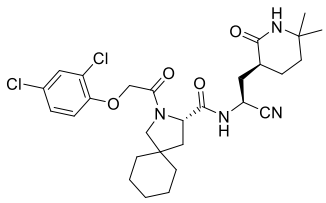
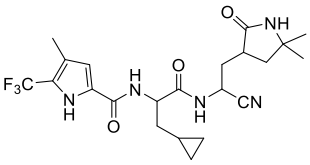
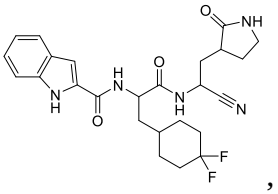
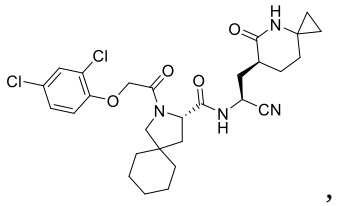
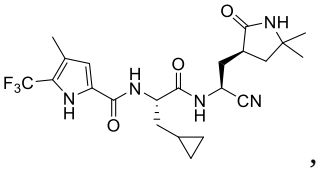
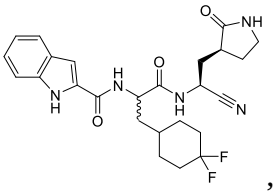
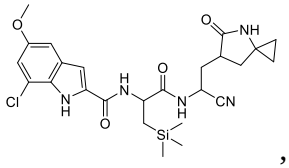
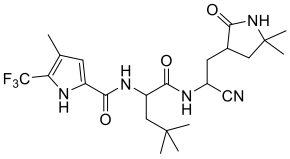
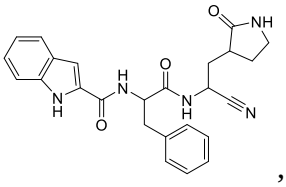
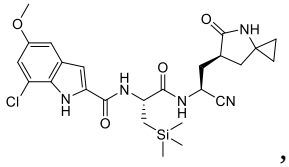
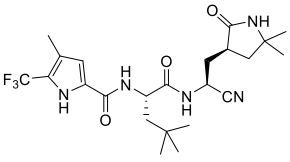
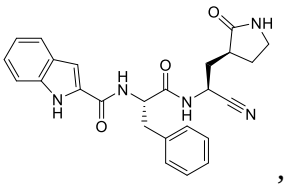
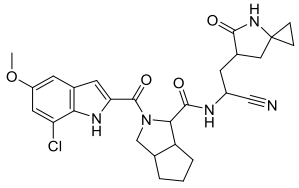
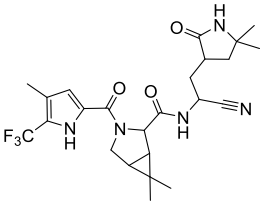
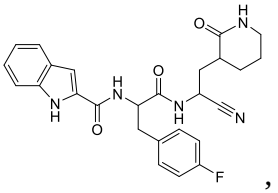
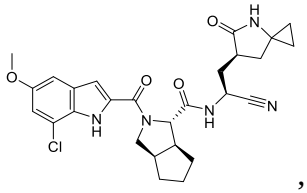
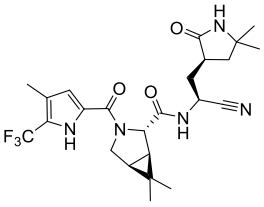
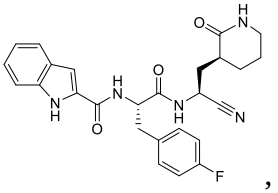
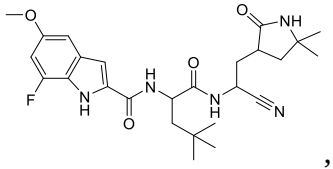
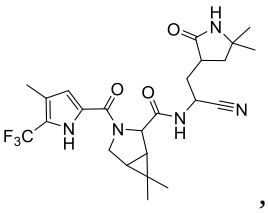
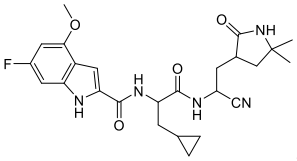
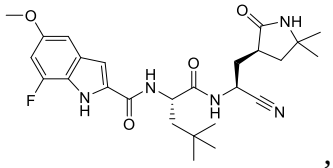
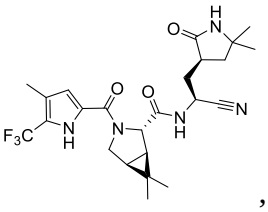
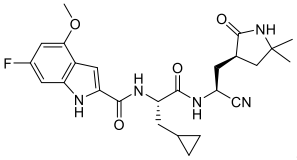
,

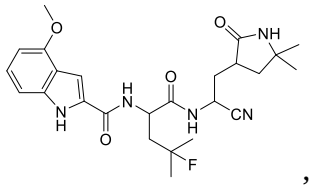
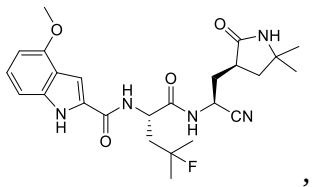
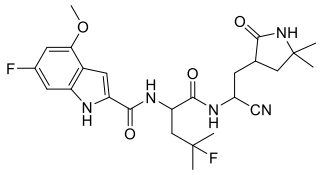
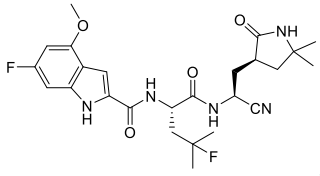
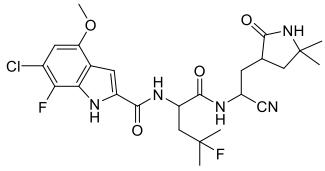
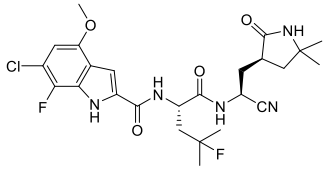
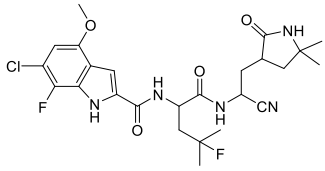
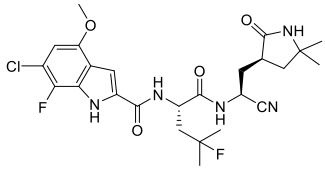
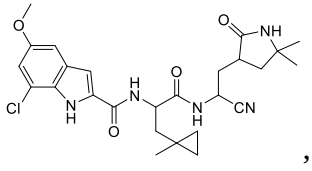
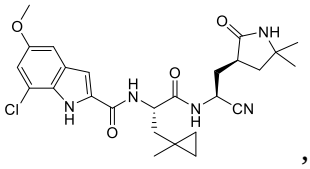
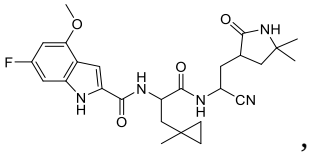
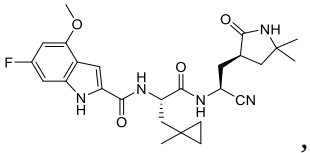
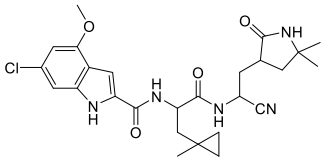
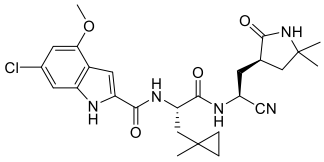
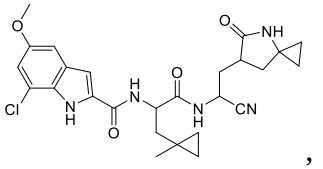
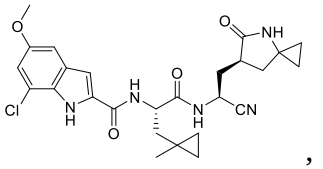
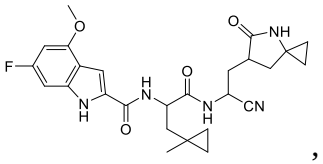
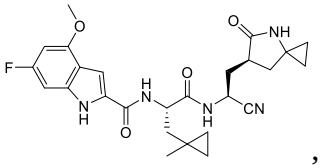
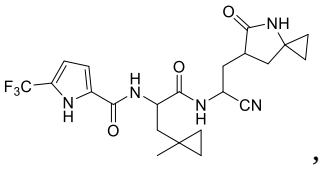
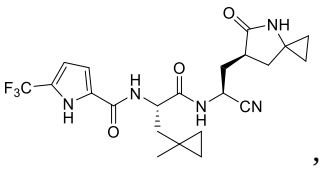
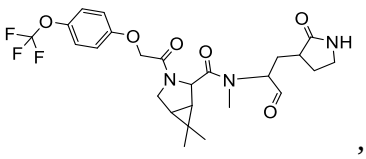
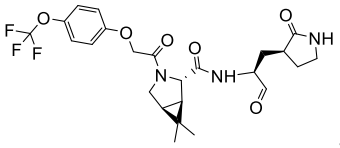
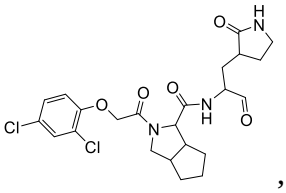
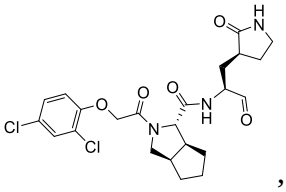
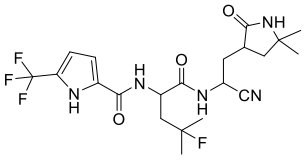
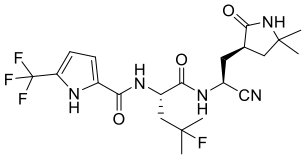
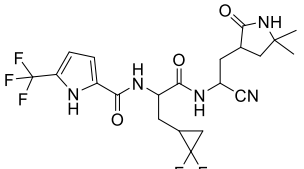
,

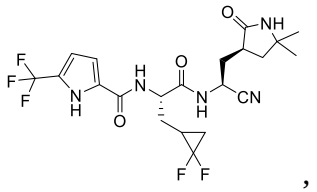
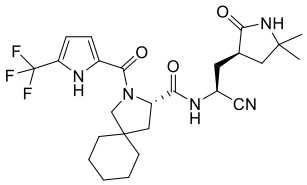
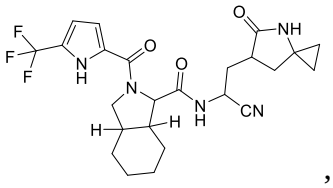
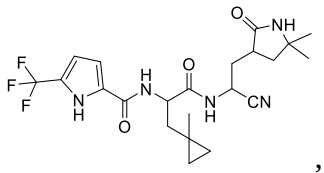
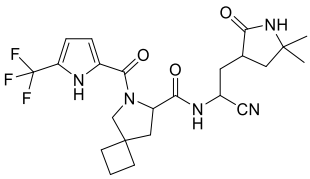
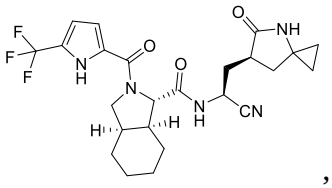
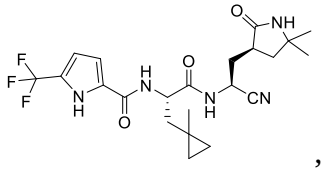
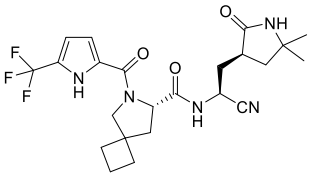
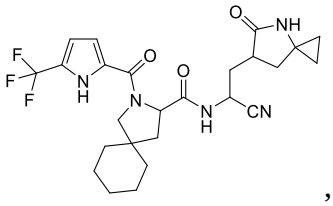
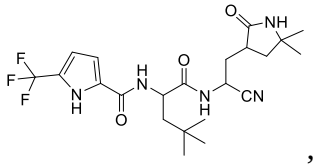
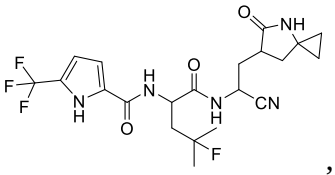
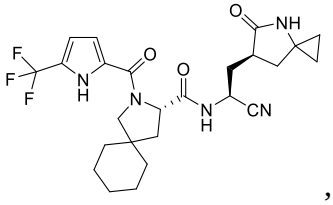
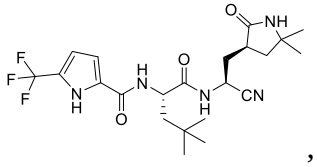
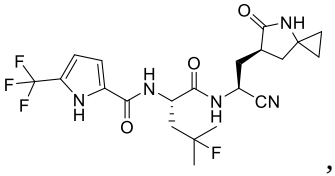
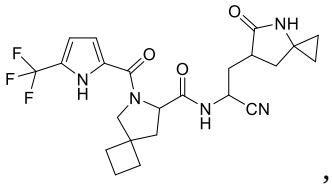
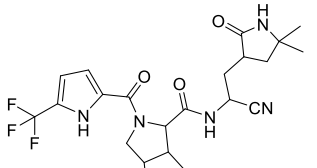
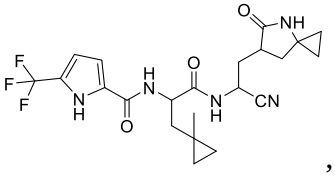
,

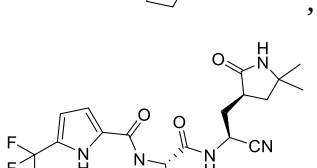
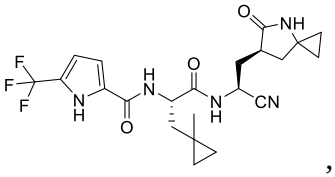
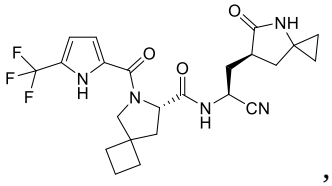
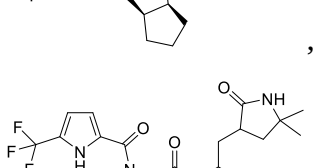
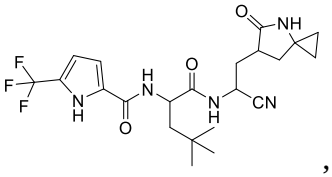
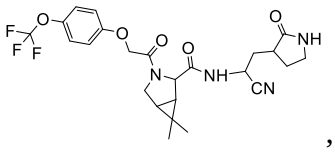
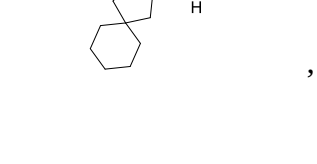
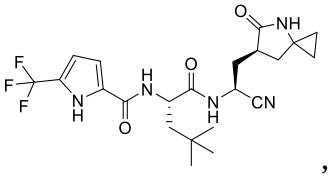
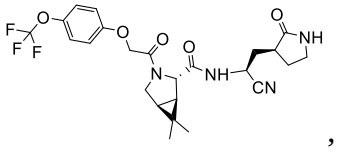

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

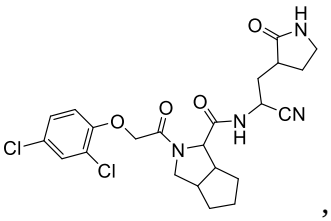
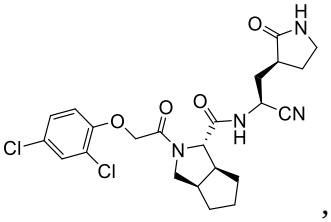
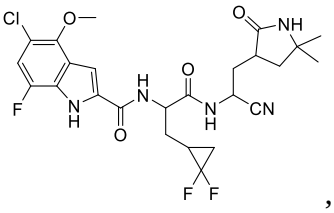
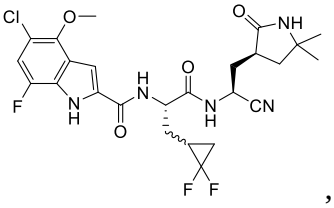
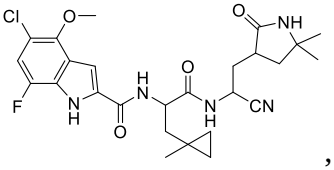
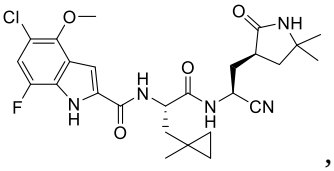
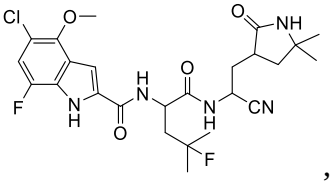
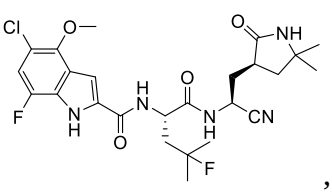

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

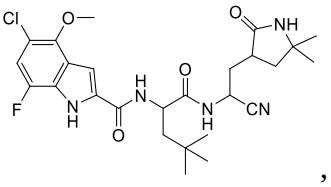
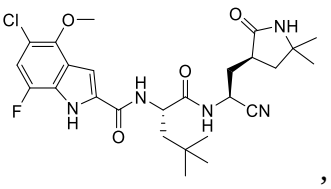
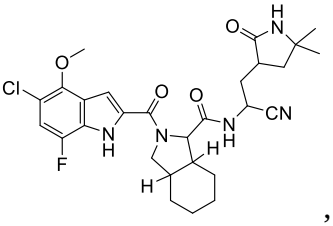
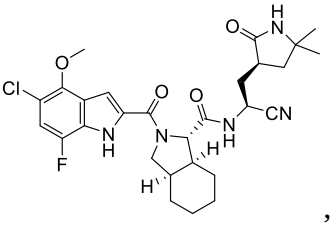
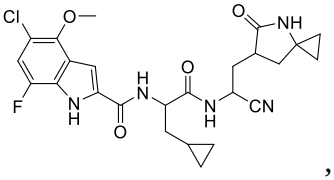
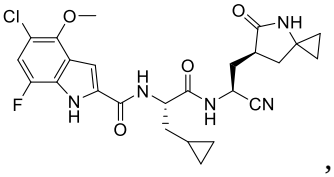
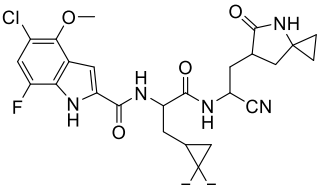
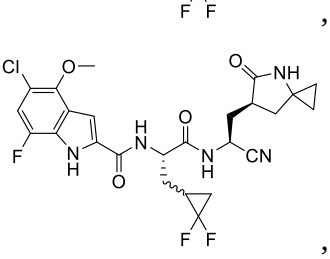

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

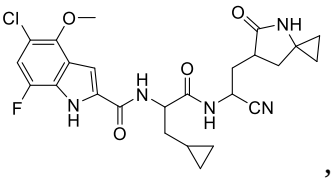
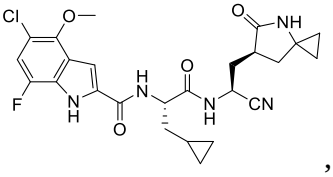
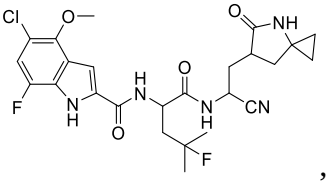
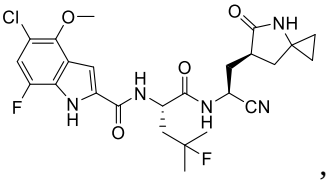
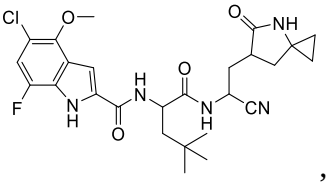
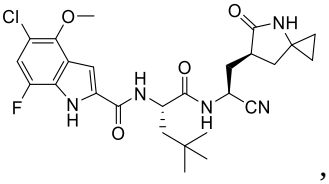
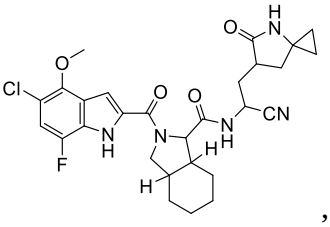
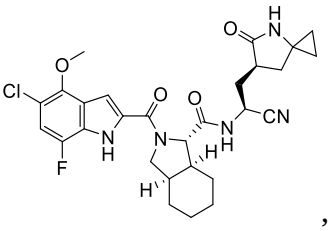
,

,

,

,

,

,

,

,

,

,

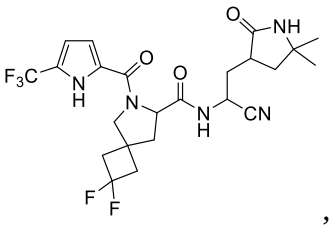
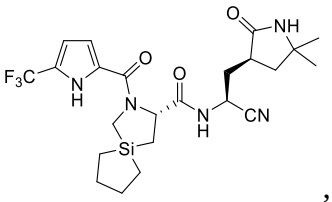
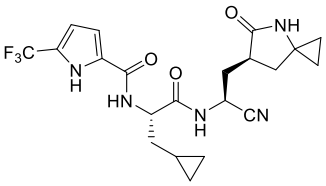
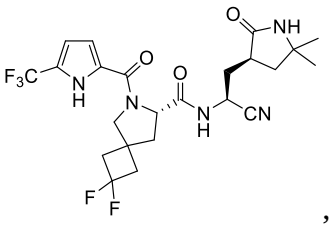
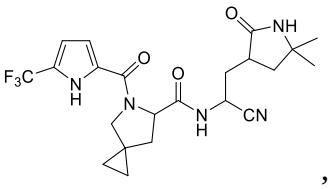
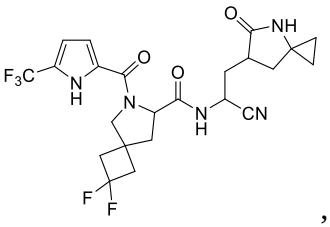
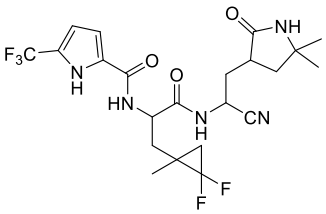
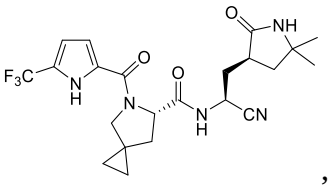
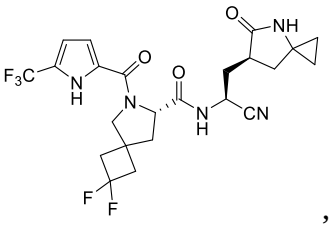
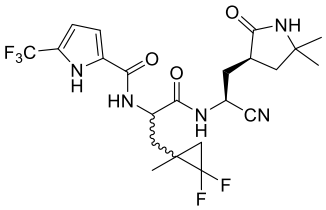
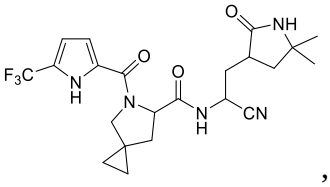
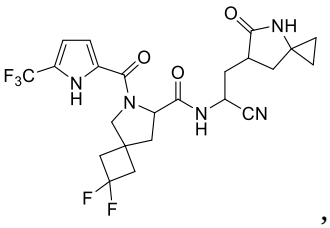
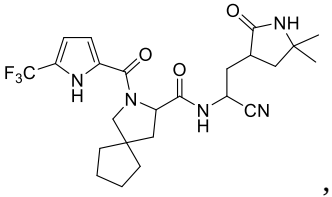
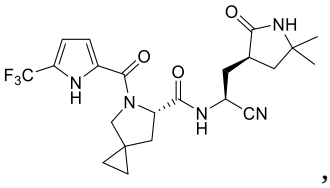
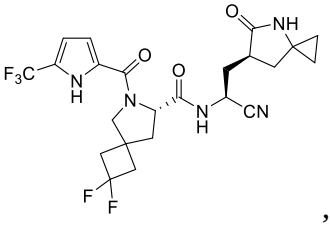
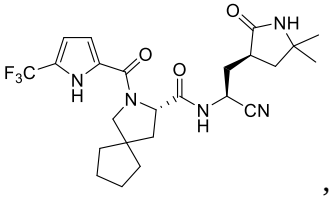
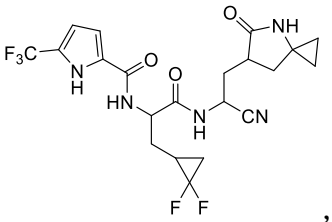
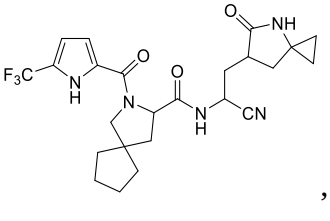
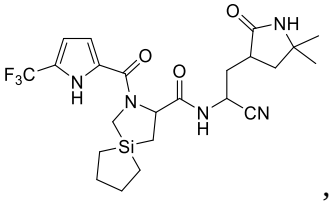
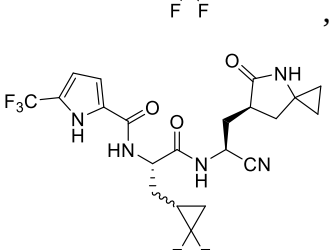
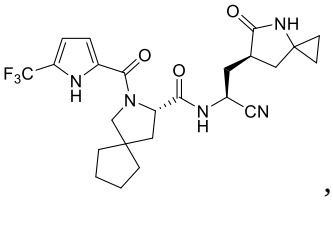
,

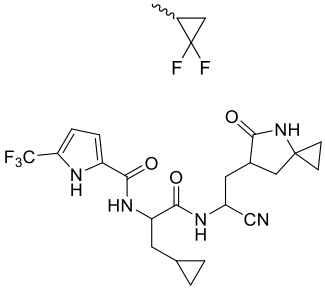
,


,

,

,

,

,

,

,

,

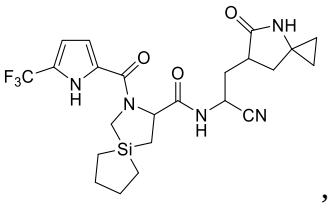
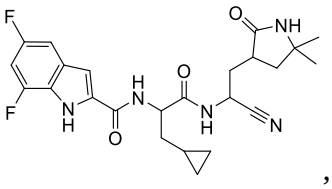
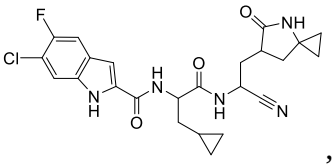
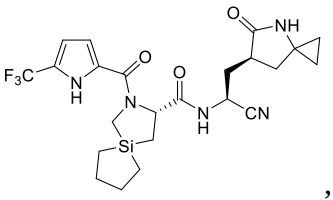
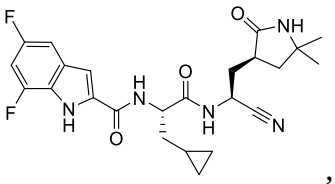
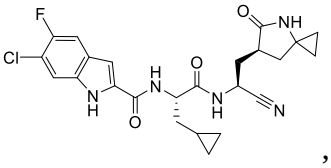
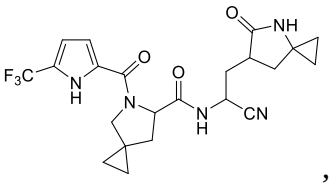
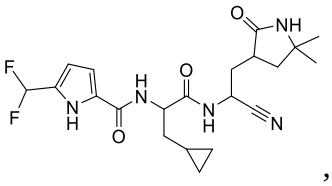
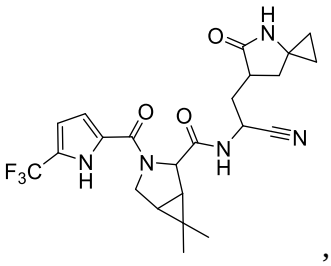
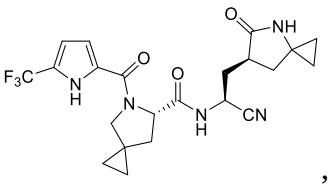
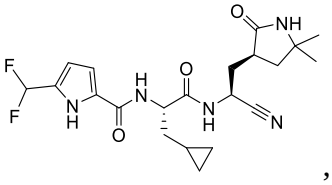
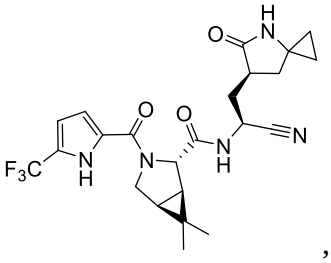
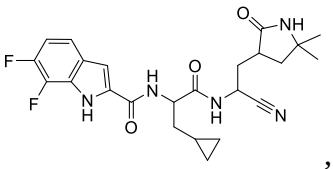
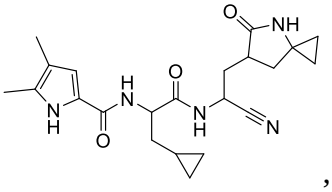
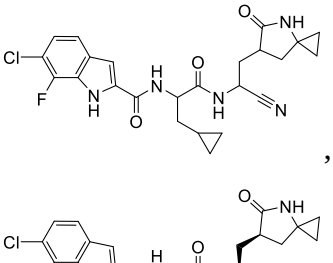
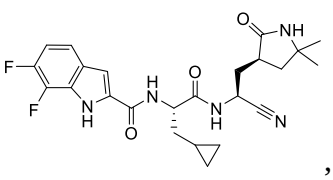
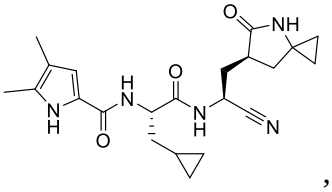
,

,

,

,

,

,

,

,

,

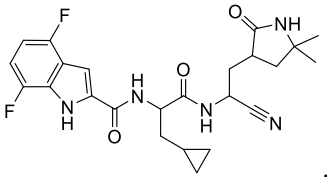
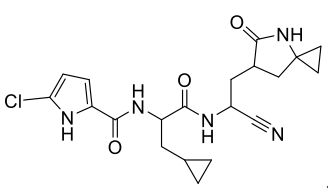
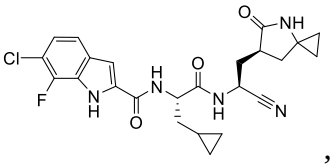
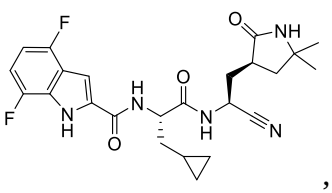
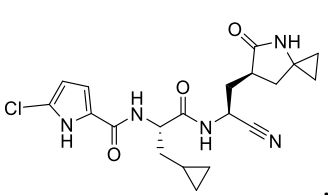
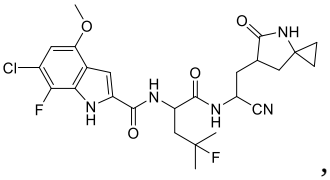
,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

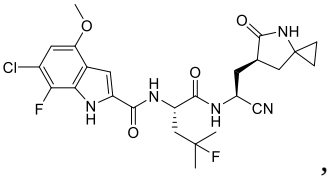
,

,

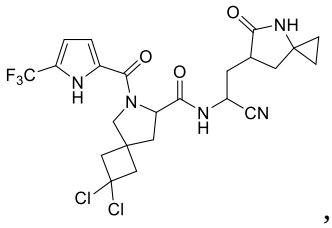
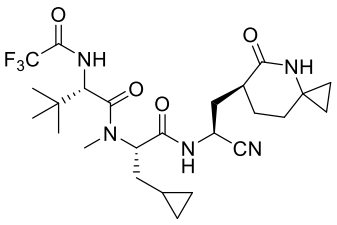
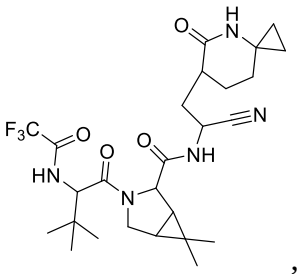
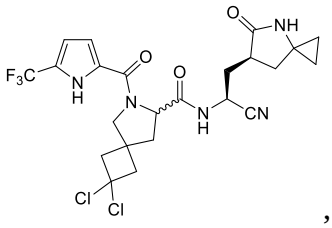
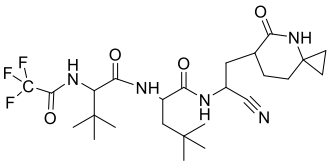
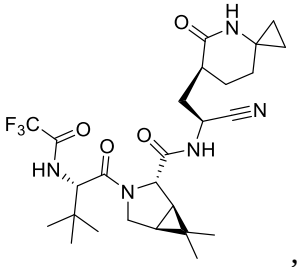
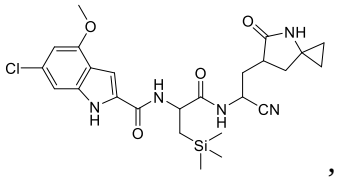
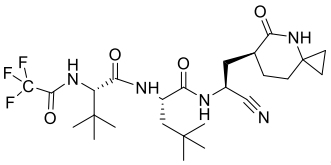
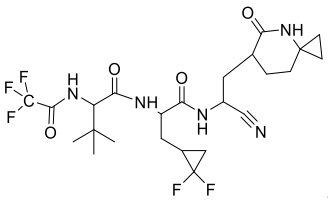
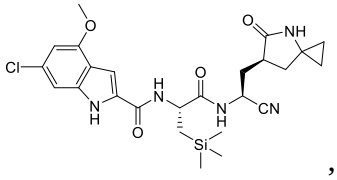
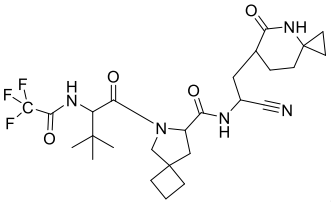
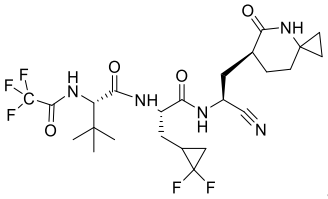
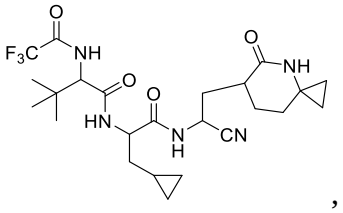
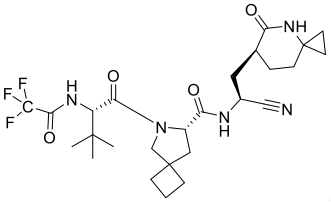
,

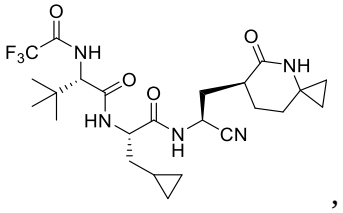
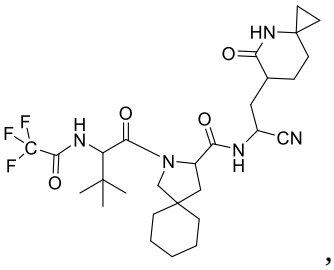
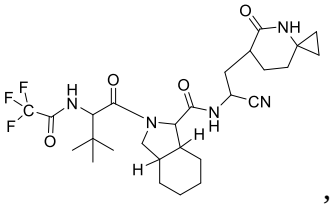
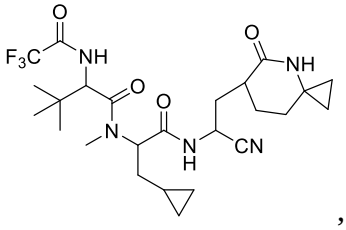
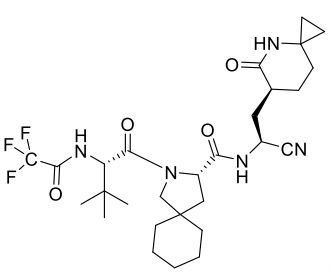
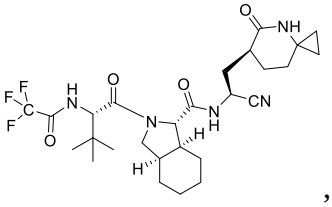

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

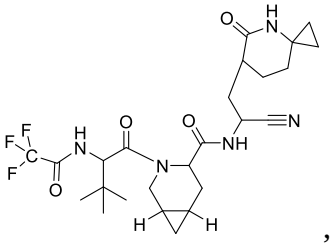
,

,

,

,

,

,

,

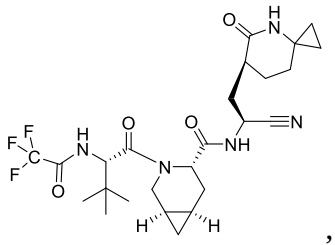
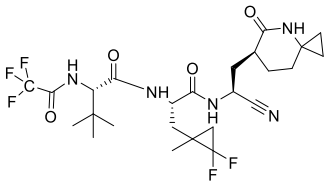
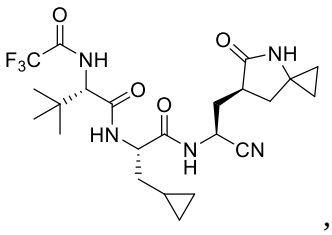
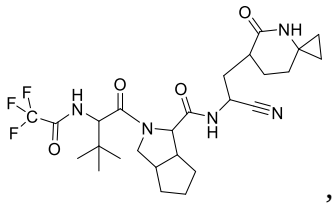
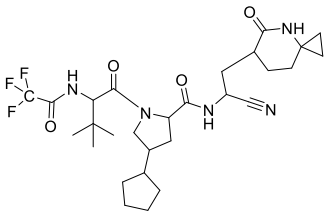
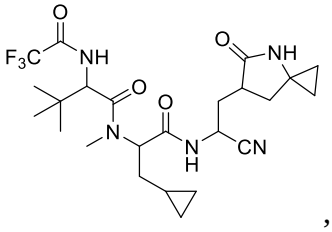
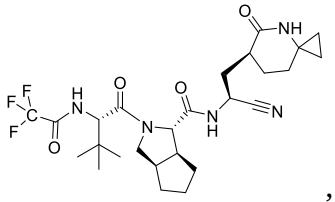
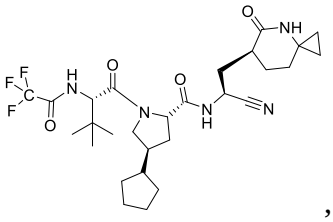
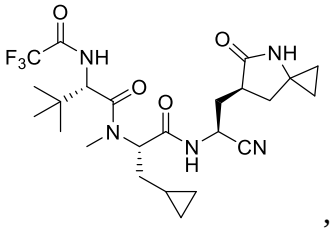
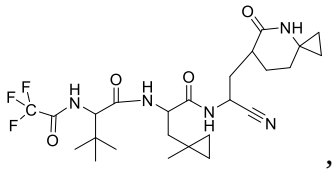
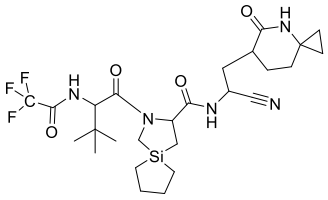
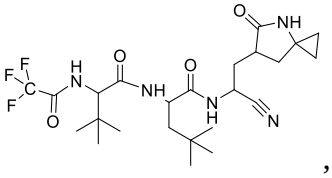
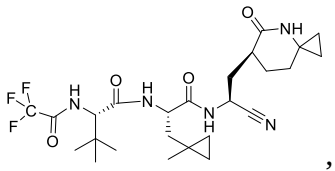
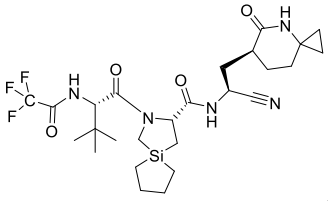
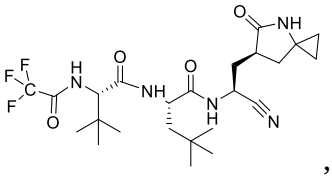
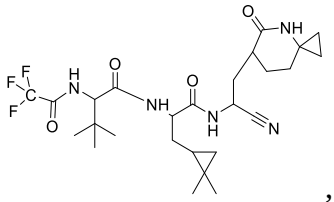
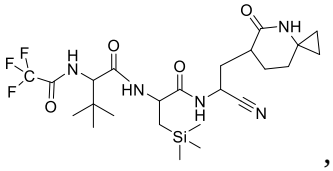
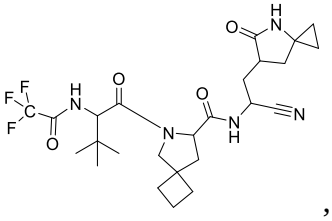
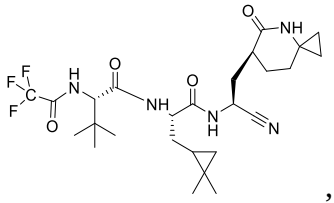
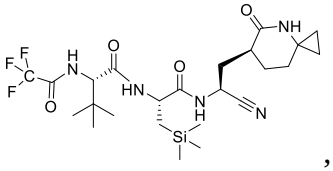
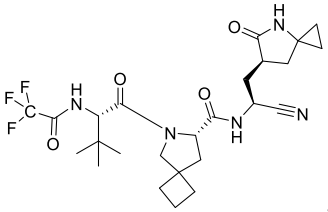
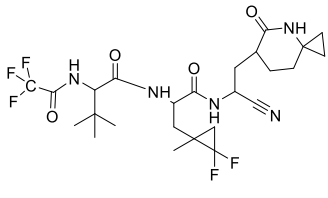
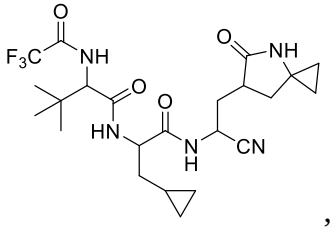
,

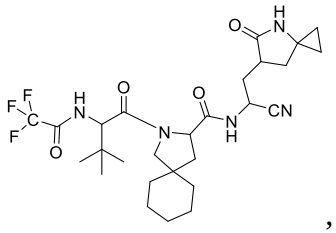
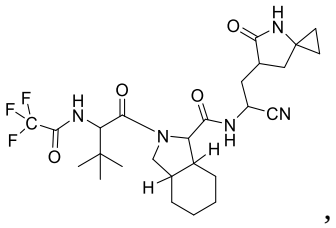
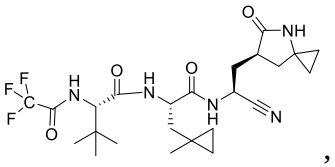
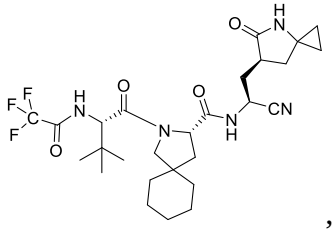
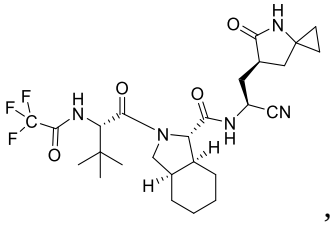
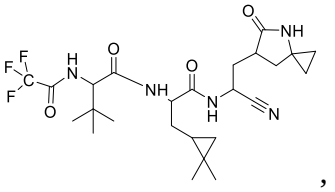
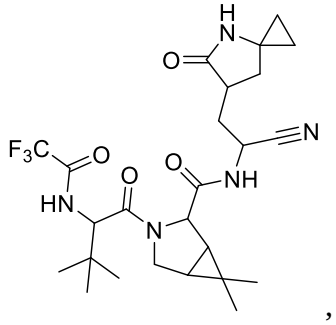
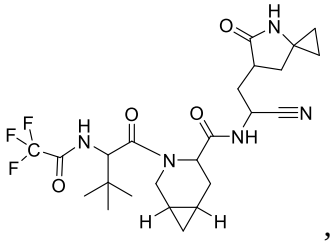
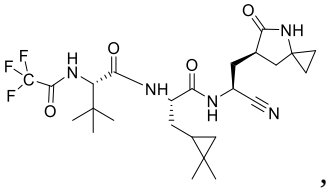
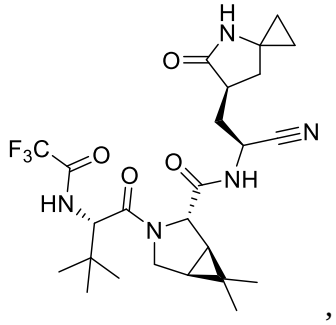
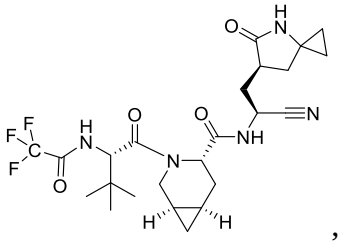
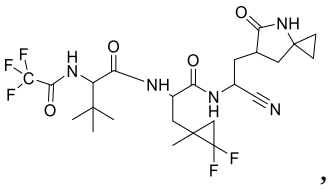
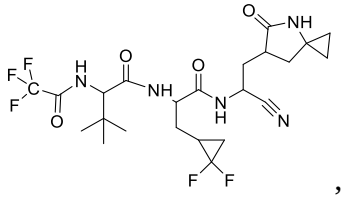
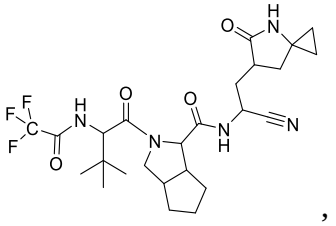
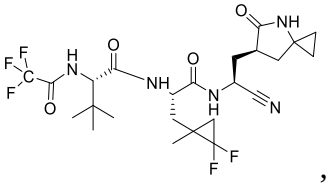
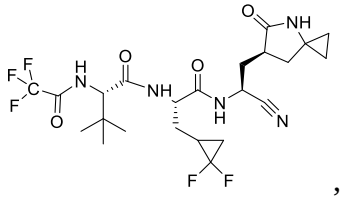
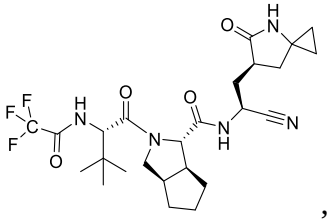
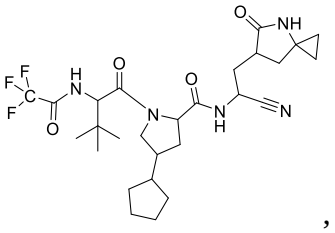
,

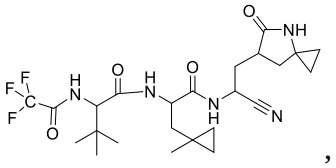
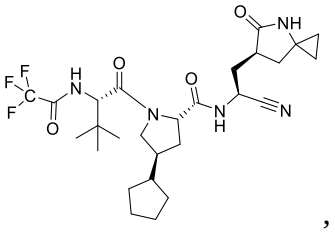
,

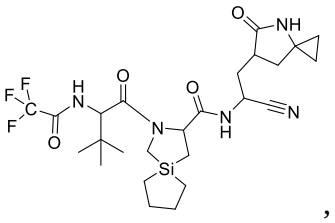
,

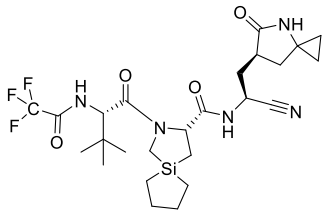
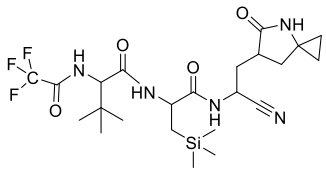
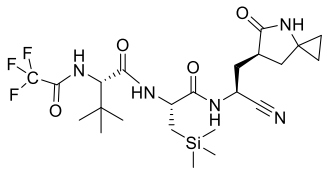
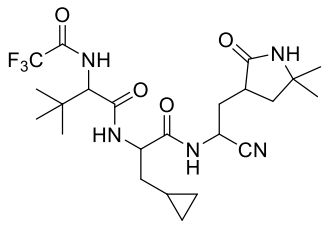
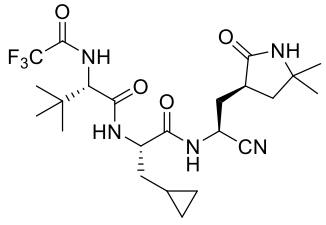
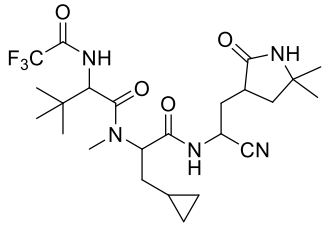
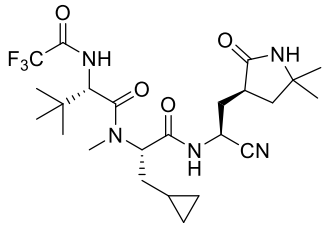
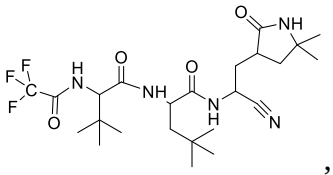
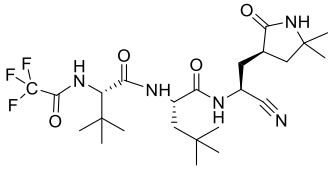
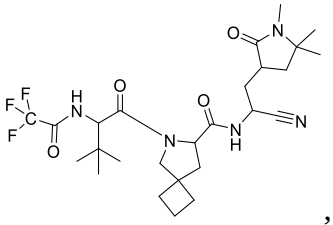
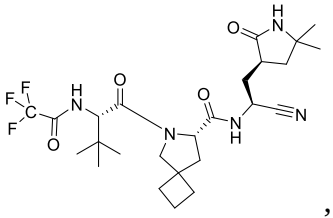
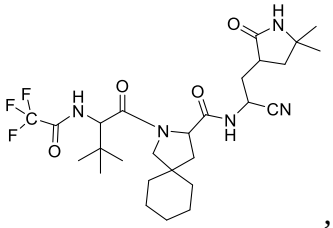
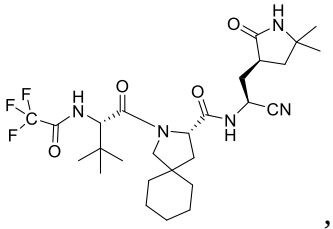
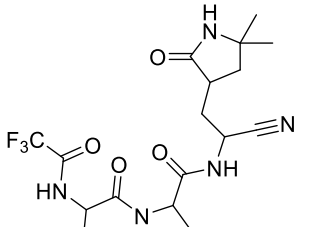
,

,

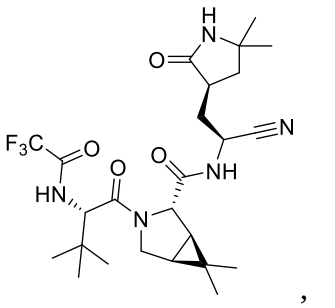
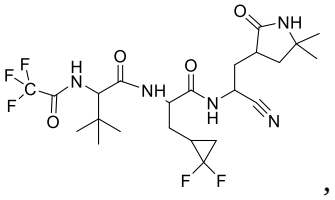
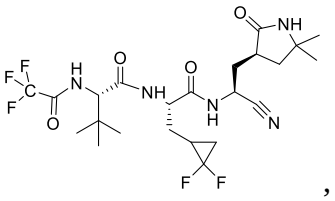
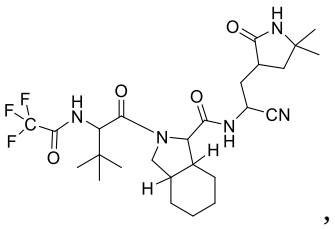
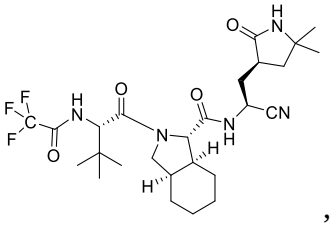
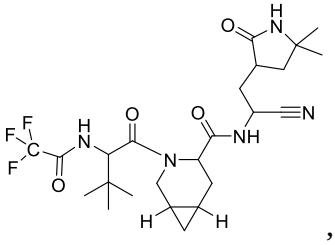
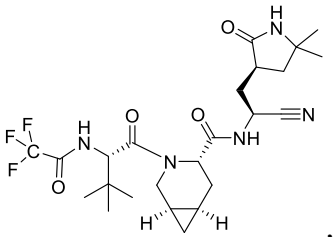

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

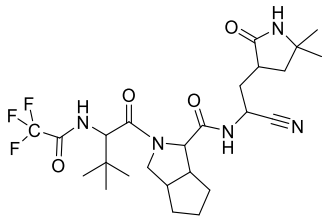
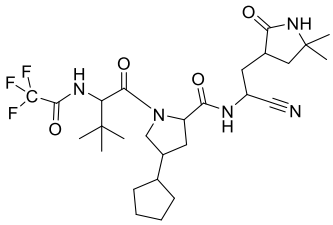
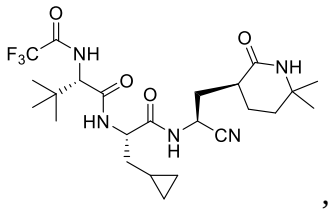
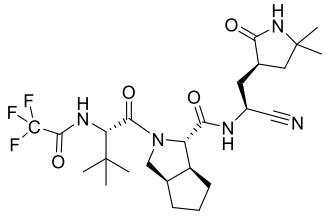
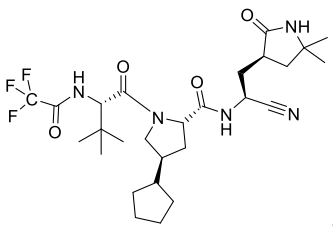
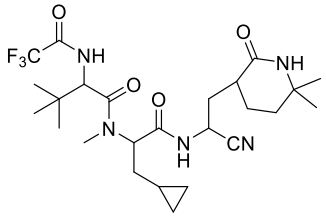
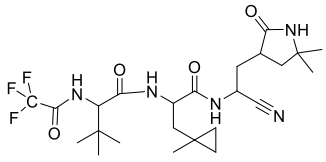
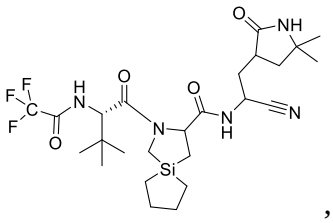
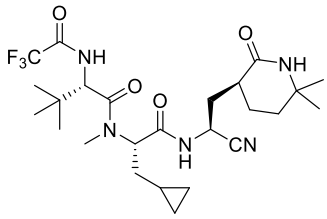
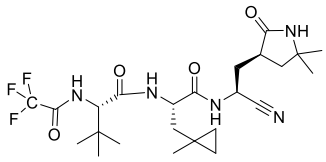
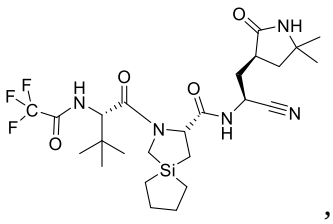
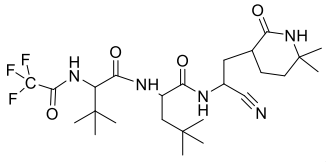
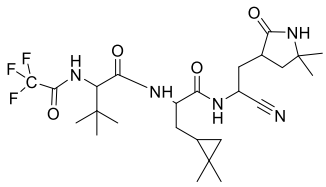
,

,

,

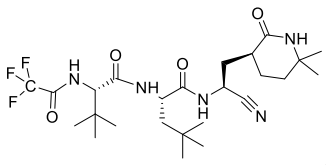
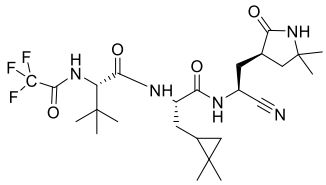
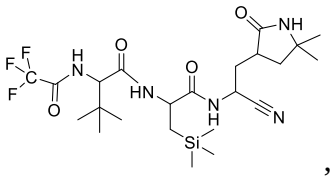
,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

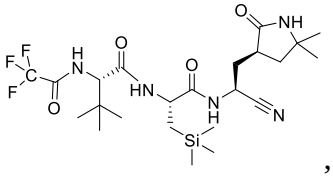
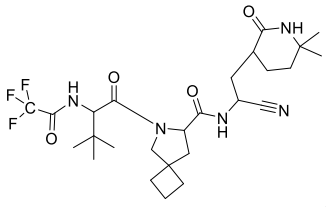
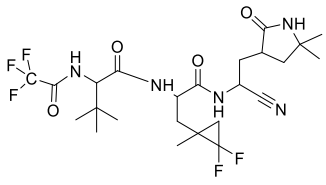
,

,

,

,

,

,

,

,

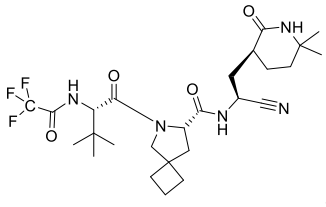
,

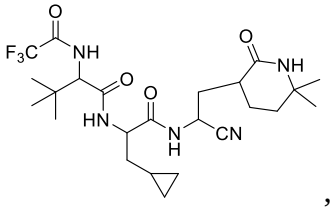

,

,

,

,

,

,

,

,

,

,

,

,

,

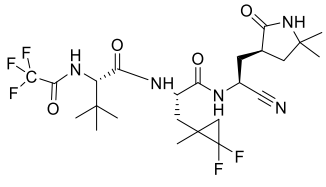
,

,

,

,

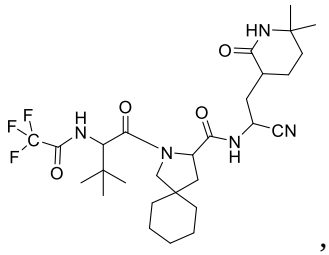
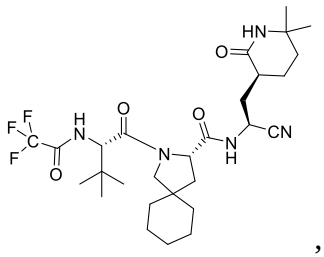
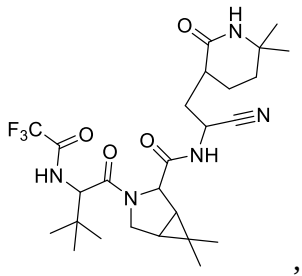
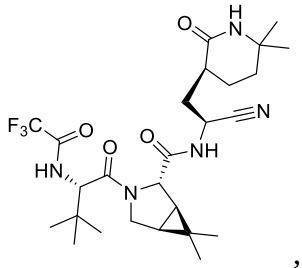
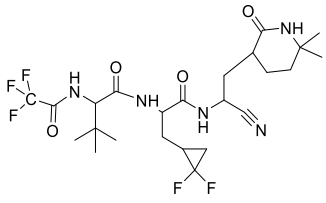
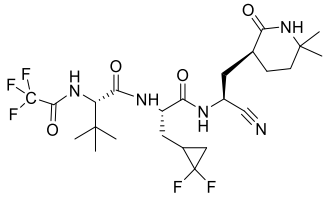
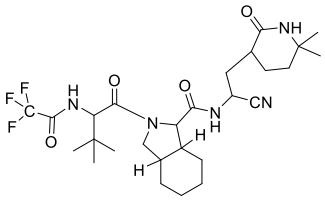
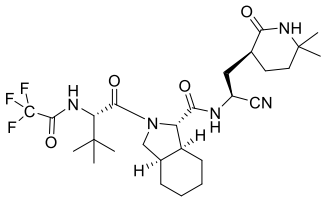
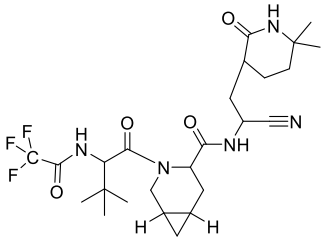
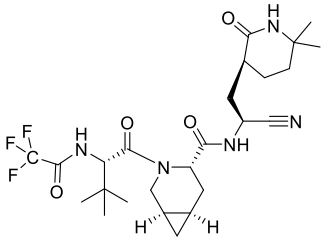
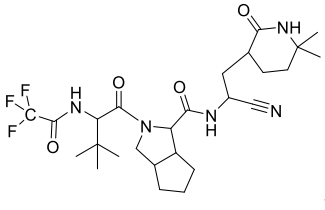
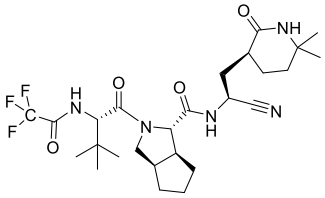
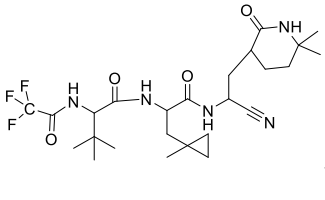
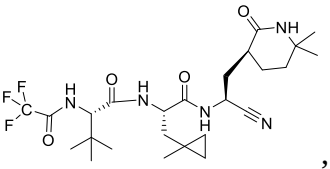
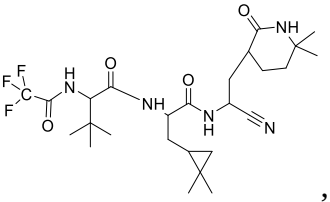
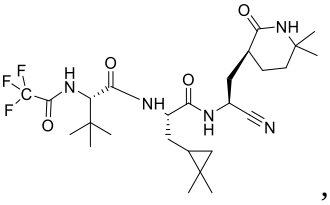
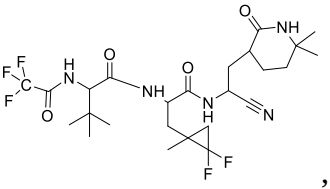
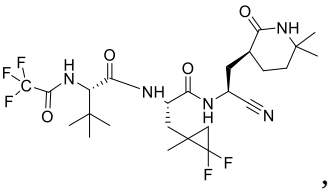
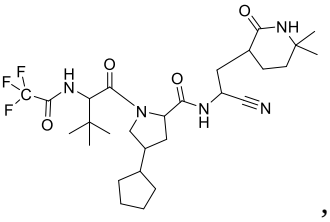
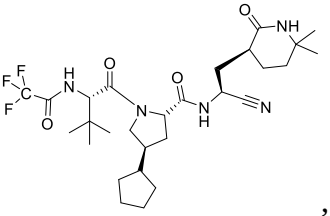
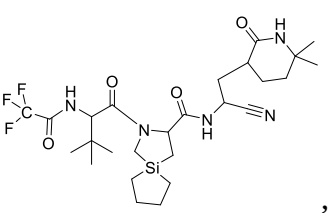
,

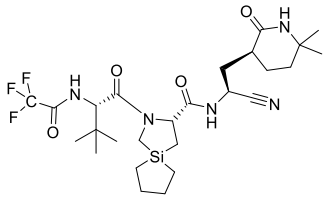
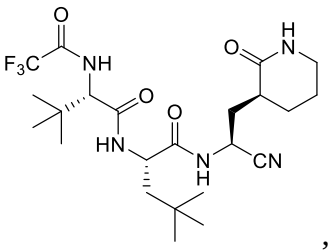
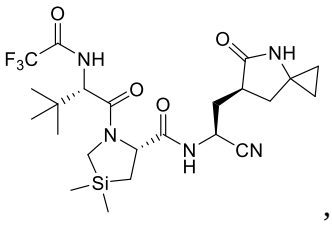
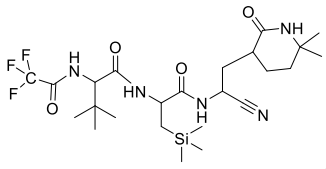
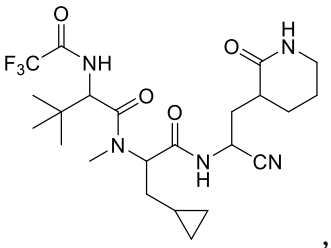
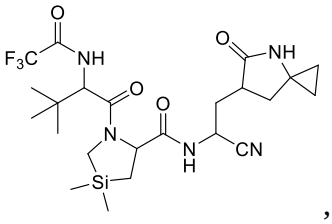
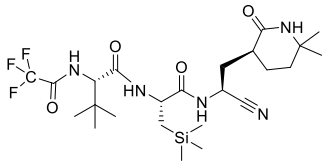
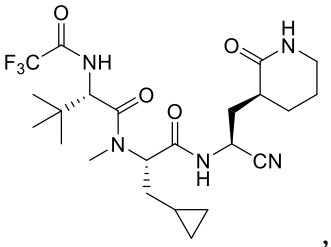
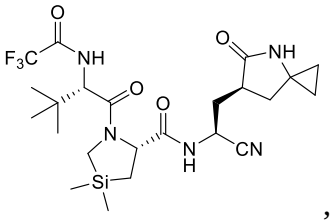
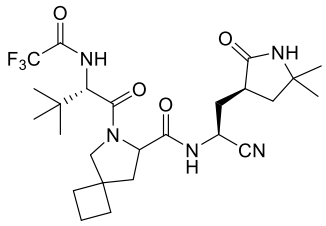
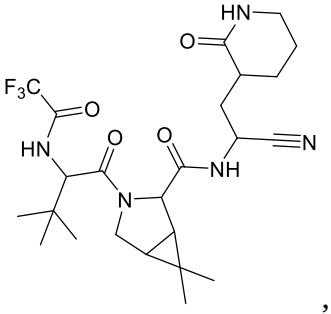
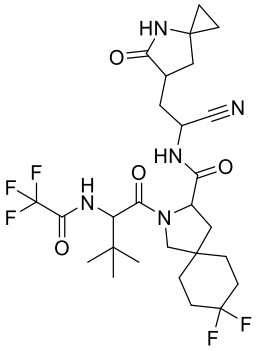
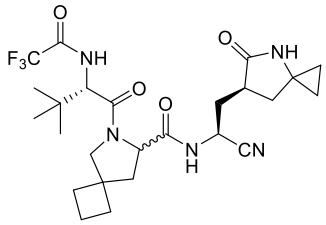
,

,

,

,

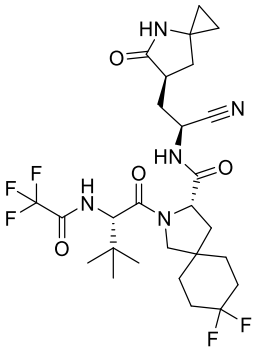
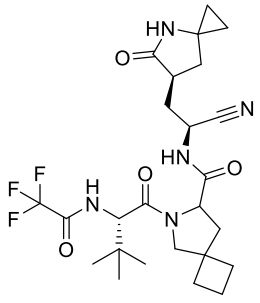
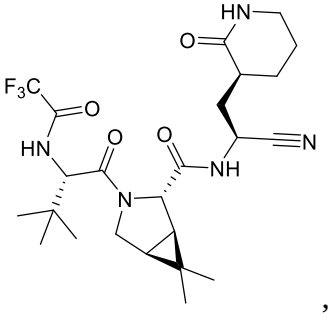
,

,

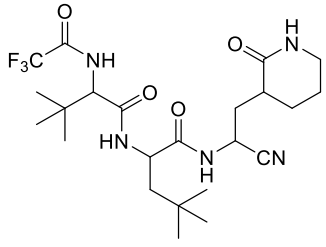
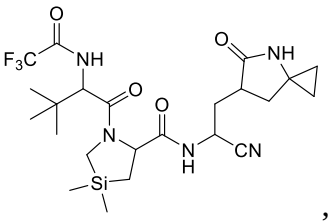
,

,

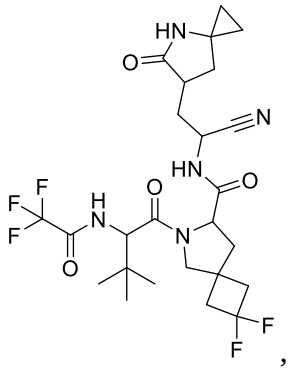
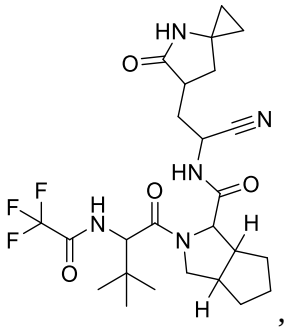
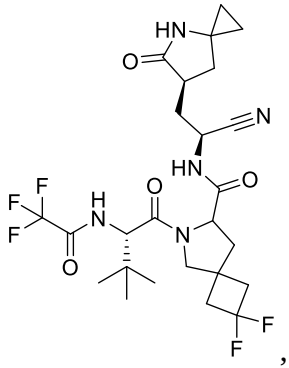
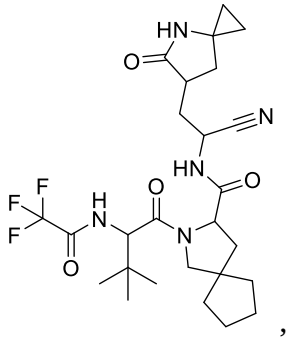
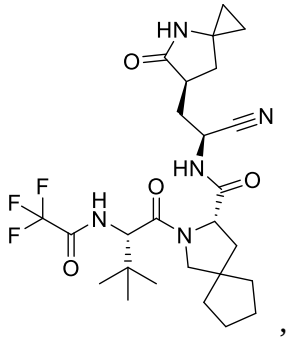
,

,

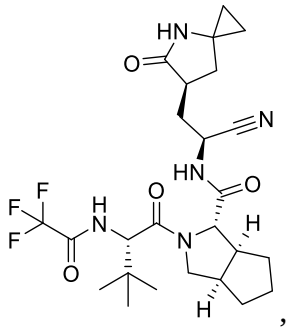
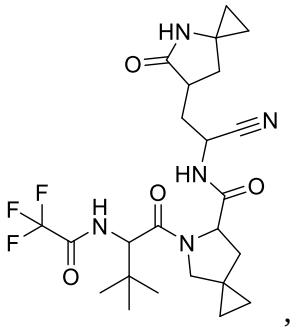
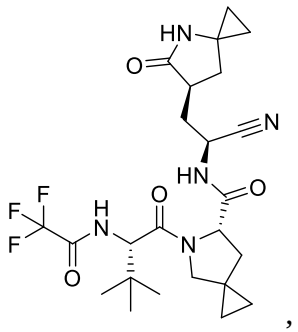
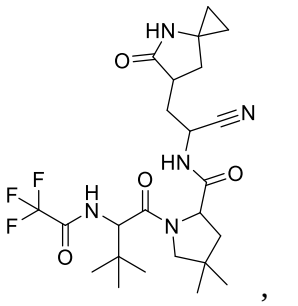
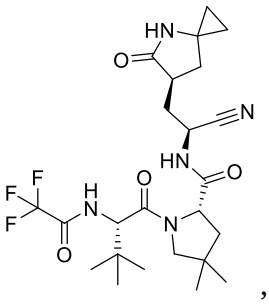

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

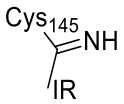

,

,

,

,

,


,

,

,

,

,

and a pharmaceutically acceptable salt or stereoisomer thereof.

27. A pharmaceutical composition comprising a compound of any one of claims 1-26 and a pharmaceutically acceptable excipient.

28. A substantially reversible conjugate represented by:



Formula III,

wherein Cys_{145} is cysteine at position 145 or equivalent active site cysteine on a CL or 3CL protease; IR is a viral protease inhibitor; and wherein the compound that forms the conjugate comprises a -CN warhead.

29. Use of a compound of any one of claims 1-26 in the manufacture of a medicament for ameliorating or treating a viral infection in a patient in need thereof.

30. The use of claim 29, wherein the viral infection is from a virus selected from the group consisting of an RNA virus, a DNA virus, a coronavirus, a papillomavirus, a pneumovirus, a picornavirus, an influenza virus, an adenovirus, a cytomegalovirus, a polyomavirus, a poxvirus, a flavivirus, an alphavirus, an ebola virus, a morbillivirus, an enterovirus, an orthopneumovirus, a lentivirus, arenavirus, a herpes virus, and a hepatovirus.
31. The use of claim 29, wherein the viral infection is from a virus selected from the group consisting of Norwalk virus, feline calicivirus, MD145, murine norovirus, vesicular exanthema of swine virus, rabbit hemorrhagic disease virus, enterovirus (EV)-68 virus, EV-71 virus, poliovirus, coxsackievirus, foot-and-mouth disease virus, hepatitis A, porcine teschovirus, rhinovirus, human coronavirus, transmissible gastroenteritis virus, murine hepatitis virus, bovine coronavirus, feline infectious peritonitis virus, and severe acute respiratory syndrome coronavirus.
32. The use of any one of claims 29-31, wherein the viral infection is a coronavirus infection.
33. The use of any one of claims 29-32, wherein the viral infection is a coronavirus selected from the group consisting of: 229E alpha coronavirus, NL63 alpha coronavirus, OC43 beta coronavirus, HKU1 beta coronavirus, Middle East Respiratory Syndrome (MERS) coronavirus (MERS-CoV), severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), and SARS-CoV-2 (COVID-19).
34. The use of any one of claims 29-33, wherein the viral infection is SARS-CoV-2.
35. The use of claim 29 or 30, wherein the viral infection is an arenavirus infection.
36. The use of claim 35, wherein the arenavirus is selected from the group consisting of: Junin virus, Lassa virus, Lujo virus, Machupo virus, and Sabia virus.
37. The use of claim 29 or 30, wherein the viral infection is an influenza infection.
38. The use of claim 37, wherein the influenza is influenza H1N1, H3N2 or H5N1.
39. Use of a compound of any one of claims 1-26 in the manufacture of a medicament for inhibiting transmission of a virus, inhibiting viral replication, minimizing expression of viral proteins, or inhibiting virus release in a patient suffering from the virus, wherein the compound is to be administered to the patient, and/or wherein the compound is to be contacted with a virally infected cell.

40. The use of any one of claims 29-39, wherein the compound is to be administered to the patient, and wherein another therapeutic is to be administered to the patient.
41. The use of any one of claims 29-39, wherein the compound is to be administered to the patient, and wherein an additional anti-viral therapeutic is to be administered to the patient.
42. The use of claim 41, wherein the anti-viral therapeutic is selected from the group consisting of ribavirin, favipiravir, ST-193, oseltamivir, zanamivir, peramivir, danoprevir, ritonavir, remdesivir, cobicistat, elvitegravir, emtricitabine, tenofovir, tenofovir disoproxil, tenofovir alafenamide hemifumarate, abacavir, dolutegravir, efavirenz, elbasvir, ledipasvir, glecaprevir, sofosbuvir, bictegravir, dasabuvir, lamivudine, atazanavir, ombitasvir, lamivudine, stavudine, nevirapine, rilpivirine, paritaprevir, simeprevir, daclatasvir, grazoprevir, pibrentasvir, adefovir, amprenavir, ampligen, aplaviroc, anti-caprine antibody, balavir, cabotegravir, cytarabine, ecoliever, epigallocatechin gallate, etravirine, fostemsavir, gemcitabine, griffithsin, imunovir, indinavir, maraviroc, methisazone, MK-2048, nelfmavir, nevirapine, nitazoxanide, norvir, plerixafor, PRO 140, raltegravir, pyramidine, saquinavir, telbivudine, TNX-355, valacyclovir, VIR- 576, and zalcitabine.
43. The use of claim 40, wherein the another therapeutic is selected from the group consisting of protease inhibitors, fusion inhibitors, M2 proton channel blockers, polymerase inhibitors, 6- endonuclease inhibitors, neuraminidase inhibitors, reverse transcriptase inhibitor, aciclovir, acyclovir, protease inhibitors, arbidol, atazanavir, atripla, boceprevir, cidofovir, combivir, darunavir, docosanol, edoxudine, entry inhibitors, entecavir, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, ibacitabine, immunovir, idoxuridine, imiquimod, inosine, integrase inhibitor, interferons, lopinavir, loviride, moroxydine, nexavir, nucleoside analogues, penciclovir, pleconaril, podophyllotoxin, ribavirin, tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, and zodovudine.

44. The use of claim 41, wherein the additional anti-viral therapeutic is selected from the group consisting of lamivudine, an interferon alpha, a VAP anti-idiotypic antibody, enfuvirtide, amantadine, rimantadine, pleconaril, aciclovir, zidovudine, fomivirsen, a morpholino, a protease inhibitor, double-stranded RNA activated caspase oligomerizer

(DRACO), rifampicin, zanamivir, oseltamivir, danoprevir, ritonavir, remdesivir, cobicistat, elvitegravir, emtricitabine, tenofovir, tenofovir disoproxil, tenofovir alafenamide hemifumarate, abacavir, dolutegravir, efavirenz, elbasvir, ledipasvir, glecaprevir, sofosbuvir, bictegravir, dasabuvir, lamivudine, atazanavir, ombitasvir, lamivudine, stavudine, nevirapine, rilpivirine, paritaprevir, simeprevir, daclatasvir, grazoprevir, pibrentasvir, adefovir, amprenavir, ampligen, aplaviroc, anti-caprine antibody, balavir, cabotegravir, cytarabine, ecoliever, epigallocatechin gallate, etravirine, fostemsavir, gemcitabine, griffithsin, imunovir, indinavir, maraviroc, methisazone, MK-2048, nelfmavir, nevirapine, nitazoxanide, norvir, plerixafor, PRO 140, raltegravir, pyramidine, saquinavir, telbivudine, TNX-355, valacyclovir, VIR-576, and zalcitabine.

45. Use of a compound of any one of claims 1-26 in the manufacture of a medicament for prophylactically treating a patient at risk of viral infection.
46. The use of claim 45, wherein the compound is to be administered to the patient before viral exposure.
47. The use of claim 45, wherein the compound is to be administered to the patient after viral exposure.

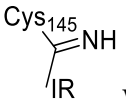
48. An engineered CL or 3CL viral protease, wherein:

the cysteine at position 145 of the CL or 3CL protease has a non-naturally occurring covalent modification resulting from a reaction between an exogenous nitrile modifier having a nitrile function and the cysteine at position 145 of the CL or 3CL protease, and

wherein the sulfur atom at the cysteine residue and the nitrile of the exogenous nitrile modifier undergoes a reaction to form a thioimidate adduct, and wherein the engineered SARS- protease does not retain the protease activity of an unmodified CL or 2CL protease.

49. The engineered viral protease of claim 48, wherein the engineered viral protease substantially prevents viral replication of SARS-COV2.
50. The engineered viral protease of claim 48, wherein the CL or 3CL protease is represented by SEQ ID NO: 1.

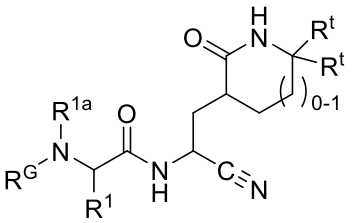
51. The engineered viral protease of claim 48, wherein the enzymatic inhibition IC_{50} of the exogenous nitrile modifier for SEQ ID NO: 1 is less than 20 micromolar.
52. The engineered viral protease of claim 48, wherein the thioimidate adduct resulting from the in vivo reaction between the exogenous nitrile modifier and the cysteine at position 145 of SEQ ID NO: 1 is represented by:



wherein

IR is the exogenous nitrile modifier after undergoing the reaction.

53. An engineered SARS-COV2-3CL viral protease represented by SEQ ID NO: 1, wherein the cysteine at position 145 of SEQ ID NO: 1 has a non-naturally occurring covalent modification resulting from a reaction between an exogenous nitrile modifier, and the cysteine at position 145 of SEQ ID NO: 1, wherein the exogenous nitrile modifier is represented by:



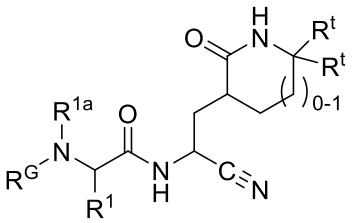
wherein the sulfur atom at the cysteine residue and the -C≡N of the exogenous nitrile modifier undergoes a reaction to form a thioimidate adduct, and wherein

R^1 is C_1-C_6alkyl or -CH_2-C_{3-10}cycloalkyl;
R^G is –C(O)R^B;
R^B is C_1-C_6alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, -NR^mR^m, and -NR^m(C=O)R^m, wherein R^m is selected for each occurrence from H or C_{1-3}alkyl (optionally substituted by one, two or three halo)); or a 8-10 membered bicyclic heteroaryl (optionally substituted by one, two, or three substituents each independently selected from halo or methoxy);
R^t is independently, for each occurrence, H or methyl; or each R^t may be taken, together with the carbon to which they are attached, to form a cyclopropyl;

R^{1a} is H; or

R^1 and R^{1a}, taken together with the nitrogen and the carbon to which they are attached, form a 4-10 membered monocyclic, bicyclic or spirocyclic heterocycle optionally substituted by one or two substituents on a free carbon each selected from methyl, halo or CF_3.

54. A compound represented by:



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein

R^1 is C_1-C_6alkyl or -CH_2-C_{3-10}cycloalkyl;

R^G is –C(O)R^B;

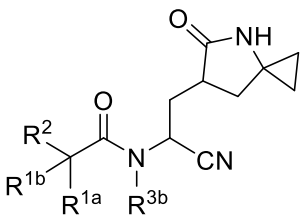
R^B is C_1-C_6alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, -NR^mR^m, and -NR^m(C=O)R^m, wherein R^m is selected for each occurrence from H or C_{1-3}alkyl (optionally substituted by one, two or three halo)); or a 8-10 membered bicyclic heteroaryl (optionally substituted by one, two, or three substituents each independently selected from halo or methoxy);

R^t is independently, for each occurrence, H or methyl; or each R^t may be taken, together with the carbon to which they are attached, to form a cyclopropyl;

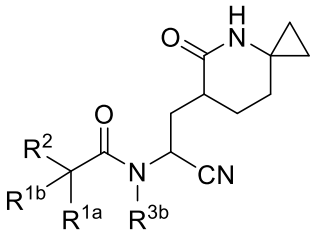
R^{1a} is H; or

R^1 and R^{1a}, taken together with the nitrogen and the carbon to which they are attached, form a 4-10 membered monocyclic, bicyclic or spirocyclic heterocycle optionally substituted by one or two substituents on a free carbon each selected from methyl, halo or CF_3.

55. A compound represented by Formula IV-A or Formula IV-B:



(IV-A) or



(IV-B)

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

R^{1a} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8heteroalkyl, –(C_1-C_8alkyl)-R^1, –(C_1-C_8alkyl)-CN, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle and 5-10 membered heteroaryl;

R^{1b} is selected from hydrogen and C_1-C_8alkyl;

or R^{1a} and R^{1b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle having a ring nitrogen NR^G, or a C_3-C_{10}cycloalkyl;

R^1 is selected from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^1 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^A is independently selected for each occurrence from the group consisting of halogen, cyano, hydroxyl, oxo, SF_5, –CH_2CF_3, –CF_3, –O-CF_3, –O-CHF_2, –S-CH_3, –$S(O)_2$-CH_3, –NH_2, –O-phenyl, –O-(C_1-C_8alkyl)-phenyl, –$NHC(O)R^B$, –$NHC(O)OR^B$, –$NHC(O)O$-(C_1-C_8alkyl)-R^B, –$N(R^y)_2$, –$N(R^y)$(C_1-C_8alkyl)$C(O)O$-phenyl, –$N(R^y)$(C_1-C_8alkyl)$C(O)N(R^y)_2$, –$C(O)$-$OC(CH_3)_3$, C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_1-C_8heteroalkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, –(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl), –(C_1-C_8alkyl)-(C_6-C_{14}aryl), –(C_1-C_8alkyl)-(5-10 membered heteroaryl), C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocyclyl, wherein the R^B, alkyl, heterocyclyl, heteroaryl, or aryl may optionally be substituted by one, two or three substituents each independently selected from the group consisting of halogen, C_1-C_8alkyl, C_1-C_8alkoxy, SF_5, –NH_2, hydroxyl and oxo;

R^2 is selected from the group consisting of –$NHC(O)R^B$, –$NHC(O)OR^B$, –$NHC(O)N(R^B)_2$, –$NHC(O)C(R^C)_2R^B$, –$NHS(O)_2R^B$, –O-(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl), 4-10 membered heterocycle, C_6-C_{14}aryl and 5-10 membered heteroaryl bound through the carbon or nitrogen atom, wherein R^B or R^2 may optionally be substituted by one, two, or three substituents each selected from R^x;

or R^{1a} and R^2 may be joined together to form, together with the carbon to which they are attached, a 4-10 membered mono or bicyclic heterocycle having a ring nitrogen NR^G, or a C_3-C_{10}cycloalkyl, wherein the cycloalkyl or heterocycle may optionally be substituted by one, two or three substituents on a free carbon each selected from R^A;

R^{3b} is selected from hydrogen and C_1-C_8alkyl;

R^B is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_6cycloalkyl, fluorenylmethyloxy, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle;

R^C is independently selected, for each occurrence, from hydrogen, halogen and C_1-C_8alkyl;

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, CF_3, SF_5, cyano, -O-(R^{xx})-OCH_3, –$OCHF_2$, –OCF_3, –O-(C_1-C_8alkyl), –C(O)O(CH_3), –N(R^y)$_2$, –N(R^y)C(O)R^y, –N(R^y)(C_1-C_8alkyl)C(O)N(R^y)$_2$, –N(R^y)(C_1-C_8alkyl)C(O)OH, -(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl), C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, -O-C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle;

wherein two geminal C_1-C_8alkyl groups, together with the carbon to which they are attached, may be joined together to form a C_3-C_6cycloalkyl optionally substituted by one, two or three substituents each independently selected from halogen, hydroxyl and oxo; and

wherein the alkyl, aryl, heterocycle or heteroaryl may optionally be substituted by one or more substituents each independently selected from oxo, halogen and C_1-C_8alkyl;

R^G is selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl optionally substituted by one, two or three R^{gg}, –C(=O)-$C_{1\text{-}6}$alkyl optionally substituted by one, two or three R^{hh}, -C(=O)-$C_{3\text{-}6}$cycloalkyl, –C(O)-(C_2-C_{10}alkenyl)-(C_6-C_{14}aryl), –C(O)-(5-10 membered heteroaryl), –C(O)-(C_1-C_6alkyl)-O-(C_6-C_{14}aryl), –C(O)-(4-10

membered heterocyclyl), and –C(O)-(4-10 membered heterocyclyloxy); wherein the aryl, heterocyclyl, or heteroaryl may optionally be substituted by one, two or three R^{jj};

R^{gg} is independently selected for each occurrence from the group consisting of -C(=O), halo, cyano, -NR^mR^m, and -$NH(C=O)R^m$;

R^{hh} is independently selected for each occurrence from the group consisting of halo, cyano, -NR^mR^m, -$NR^m(C=O)R^m$, phenyl, cycloalkyl, heterocyclyl and C_1-C_6alkoxy;

R^{jj} is independently selected for each occurrence from the group consisting of halo, oxo, hydroxyl, cyano, C_1-C_6alkyl, C_{1-6}haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_{3-6}cycloalkyl, SF_5, and NH_2;

R^m is independently selected for each occurrence from the group consisting of hydrogen, C_{1-3}alkyl, phenyl, -$S(O)_2$-CH_3, C_{3-6}cycloalkyl, and 5-6 membered heteroaryl; wherein C_{1-3}alkyl, phenyl, and C_{3-6}cycloalkyl may optionally be substituted by one, two or three halo;

R^{xx} is –$(OCH_2CH_2)_{nn}$–, wherein nn is selected from 1, 2, 3, 4, 5 and 6; and

R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8heteroalkyl, –CF_3, –CH_2CF_3, C_1-C_8alkoxy, –(C_1-C_8alkoxy)-(5-10 membered aryl), C_3-C_6cycloalkyl and –(C_1-C_8alkyl)COOH.

56. A compound of any one of claims 1-26 for use in therapy.