

COMPOUNDS AND COMPOSITIONS USEFUL FOR TREATING DISORDERS RELATED TO NTRK

CLAIM OF PRIORITY

This application claims priority from U.S.S.N. 62/210,264 filed August 26, 2015, which is incorporated herein by reference in its entirety.

BACKGROUND

Neurotrophic Tyrosine Receptor Kinase (NTRK) 1, 2 and 3 are receptor tyrosine kinases (RTKs) that activate multiple downstream pathways involved in cell proliferation and survival. Various genetic fusions, arising from aberrant chromosomal translocations of the genes coding for these RTKs, are implicated in the etiology of multiple cancers including high and low grade glioma, cholangiocarcinoma, papillary thyroid carcinoma, colon cancer and non-small cell lung cancer. A genomics analysis on the landscape of kinase fusions identified NTRK fusions in a wide array of additional cancer types including head and neck squamous cell carcinoma, pancreatic adenocarcinoma, sarcoma and melanoma, thereby providing further therapeutic rationale for deploying inhibitors of these kinases to treat multiple oncologic indications.

The identification of NTRK fusions as the underlying cause of certain cancers prompted the discovery and clinical development of several NTRK kinase inhibitors to treat tumors that harbor an NTRK fusion protein. Early clinical data support the viability of this approach in providing benefit to patients with specific human malignancies. Ultimately however, despite clear signs of clinical activity, most patients' cancers will become resistant to kinase inhibitor therapy leading to relapse and progression of the disease. Kinase reactivation via an intrinsic mutation is a frequent mechanism of resistance. When resistance occurs, the patient's treatment options are often very limited. There is thus a need for compounds that inhibit NTRK, as well as its resistant mutants.

SUMMARY

The present disclosure features compounds and pharmaceutical compositions comprising compounds of Formula (I) or pharmaceutically acceptable salts thereof, wherein:

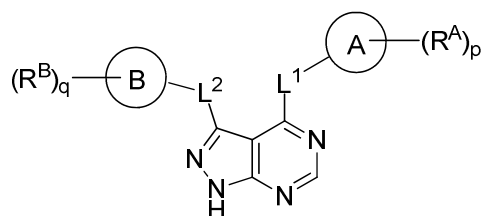
C₁-C₆ heteroalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, cycloalkyl, heterocyclyl, and cyano, wherein each of alkyl, haloalkyl, heteroalkyl, hydroxyalkyl, alkoxy, cycloalkyl and heterocyclyl is independently substituted with 0-5 occurrences of R';

each R' is independently selected from C₁-C₆ alkyl, C₁-C₆ heteroalkyl, halo, hydroxyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, cycloalkyl and cyano; or 2 R' together with the atom(s) to which they are attached form a cycloalkyl or heterocyclyl ring;

p is 0, 1, 2, 3, 4, or 5; and

q is 0, 1, 2, 3, or 4.

In one aspect, there is provided a compound of Formula (I):



(I), or a pharmaceutically acceptable salt thereof, wherein:

Ring A is selected from aryl, heteroaryl, cycloalkyl, cycloalkenyl and heterocyclyl;

Ring B is selected from aryl, heteroaryl, cycloalkyl, and heterocyclyl;

L¹ is selected from -C(O)-, -N(R¹)-, -N(R¹)-C(O)-†, -C(O)-N(R¹)-†, -(C₁-C₆ alkylene)-N(R¹)-†, -N(R¹)-(C₁-C₆ alkylene)-†, -N(R¹)-C(O)-(C₁-C₆ alkylene)-†, and -C(O)-N(R¹)-(C₁-C₆ alkylene)-†; wherein “†” represents a portion of L¹ bound to ring A and each alkylene portion of L¹ is independently substituted with 0-5 occurrences of R';

L² is selected from -C(O)-, -C(O)-N(R¹)-*, -N(R¹)-C(O)-(C₁-C₆ alkylene)-*, and -C(O)-N(R¹)-(C₁-C₆ alkylene)-*, wherein “*” represents a portion of L² bound to ring B and each alkylene portion of L² is independently substituted with 0-5 occurrences of R';

each R^A is independently selected from hydroxyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, halo, C₁-C₆ heteroalkyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, C₁-C₆ hydroxyalkyl, cycloalkyl, aryl, heteroaryl, aryloxy, aralkyl, heterocyclyl, heterocyclylalkyl, nitro, cyano, -C(O)R¹, -OC(O)R¹, -C(O)OR¹, -(C₁-C₆ alkylene)-C(O)R¹, -SR¹, -S(O)₂R¹, -S(O)₂-N(R¹)(R¹), -(C₁-C₆ alkylene)-S(O)₂R¹, -(C₁-C₆ alkylene)-S(O)₂-N(R¹)(R¹), -N(R¹)(R¹), -C(O)-N(R¹)(R¹), -N(R¹)-C(O)R¹, -N(R¹)-C(O)OR¹, -(C₁-C₆ alkylene)-N(R¹)-C(O)R¹, -N(R¹)S(O)₂R¹, and -P(O)(R¹)(R¹); wherein each alkyl, alkenyl, alkynyl, alkoxy, heteroalkyl, haloalkyl, haloalkoxy, hydroxyalkyl,

cycloalkyl, aryl, heteroaryl, aryloxy, aralkyl, heterocyclyl, and heterocyclylalkyl portion of each of R^A is independently substituted with 0-5 occurrences of R^a ; or 2 R^A together with the carbon atom(s) to which they are attached form a cycloalkyl or heterocyclyl ring independently substituted with 0-5 occurrences of R^a ;

each R^B is independently selected from oxo, hydroxyl, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, halo, C_1 - C_6 heteroalkyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, cycloalkyl, aryl, heteroaryl, aryloxy, aralkyl, heterocyclyl, heterocyclylalkyl, nitro, cyano, $-C(O)R^1$, $-OC(O)R^1$, $-C(O)OR^1$, $-(C_1-C_6 \text{ alkylene})-C(O)R^1$, $-SR^1$, $-S(O)_2R^1$, $-S(O)_2-N(R^1)(R^1)$, $-(C_1-C_6 \text{ alkylene})-S(O)_2R^1$, $-(C_1-C_6 \text{ alkylene})-S(O)_2-N(R^1)(R^1)$, $-N(R^1)(R^1)$, $-C(O)-N(R^1)(R^1)$, $-N(R^1)-C(O)R^1$, $-N(R^1)-C(O)OR^1$, $-(C_1-C_6 \text{ alkylene})-N(R^1)-C(O)R^1$, $-N(R^1)S(O)_2R^1$, and $-P(O)(R^1)(R^1)$, wherein each alkyl, alkenyl, alkynyl, alkoxy, heteroalkyl, haloalkyl, haloalkoxy, hydroxyalkyl, cycloalkyl, aryl, heteroaryl, aryloxy, aralkyl, heterocyclyl, and heterocyclylalkyl portion of each R^B is independently substituted with 0-5 occurrences of R^a , or 2 R^B together with the carbon atom(s) to which they are attached form a cycloalkyl or heterocyclyl ring independently substituted with 0-5 occurrences of R^a ;

each R^1 is independently selected from hydrogen, hydroxyl, halo, thiol, C_1 - C_6 alkyl, C_1 - C_6 thioalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each alkyl, thioalkyl, alkoxy, haloalkyl, hydroxyalkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl portion of R^1 is independently substituted with 0-5 occurrences of R^b , or 2 R^1 together with the atom(s) to which they are attached form a cycloalkyl or heterocyclyl ring independently substituted with 0-5 occurrences of R^b ;

each R^a and R^b is independently selected from C_1 - C_6 alkyl, halo, hydroxyl, C_1 - C_6 haloalkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 alkoxy, cycloalkyl, heterocyclyl, and cyano, wherein each alkyl, haloalkyl, heteroalkyl, hydroxyalkyl, alkoxy, cycloalkyl and heterocyclyl portion of R^a and R^b is independently substituted with 0-5 occurrences of R' ;

each R' is independently selected from C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, halo, hydroxyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, cycloalkyl and cyano; or 2 R' together with the atom(s) to which they are attached form a cycloalkyl or heterocyclyl ring; and

p is 0, 1, 2, 3, 4, or 5; and

q is 0, 1, 2, 3, or 4.

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

Any of the compounds disclosed herein may be used, alone or in combination with another therapeutic agent, to treat any of the diseases disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts the structure of various exemplary compounds of the invention, as well as their NMR peaks and mass as determined by LC-MS.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

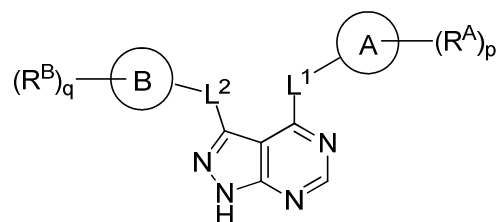
As used herein, the terms a “patient,” “subject,” “individual,” and “host” refer to either a human or a non-human animal suffering from or suspected of suffering from a disease or disorder associated with aberrant NTRK expression (*i.e.*, increased NTRK activity caused by signaling through NTRK) or biological activity.

“Treat” and “treating” such a disease or disorder refers to ameliorating at least one symptom of the disease or disorder. These terms, when used in connection with a condition such as a cancer, refer to one or more of: impeding growth of the cancer, causing the cancer to shrink by weight or volume, extending the expected survival time of the patient, inhibiting tumor growth, reducing tumor mass, reducing size or number of metastatic lesions, inhibiting the development of new metastatic lesions, prolonging survival, prolonging progression-free survival, prolonging time to progression, and/or enhancing quality of life.

The term “preventing” when used in relation to a condition or disease such as cancer, refers to a reduction in the frequency of, or delay in the onset of, symptoms of the condition or disease. Thus, prevention of cancer includes, for example, reducing the number of detectable cancerous

We claim:

1. A compound of Formula (I):



(I), or a pharmaceutically acceptable salt thereof,

wherein:

Ring A is selected from aryl, heteroaryl, cycloalkyl, cycloalkenyl and heterocyclyl;

Ring B is selected from aryl, heteroaryl, cycloalkyl, and heterocyclyl;

L^1 is selected from $-C(O)-$, $-N(R^1)-$, $-N(R^1)-C(O)-\dagger$, $-C(O)-N(R^1)-\dagger$, $-(C_1-C_6 \text{ alkylene})-N(R^1)-\dagger$, $-N(R^1)-(C_1-C_6 \text{ alkylene})-\dagger$, $-N(R^1)-C(O)-(C_1-C_6 \text{ alkylene})-\dagger$, and $-C(O)-N(R^1)-(C_1-C_6 \text{ alkylene})-\dagger$; wherein “ $\dagger$ ” represents a portion of L^1 bound to ring A and each alkylene portion of L^1 is independently substituted with 0-5 occurrences of R^1 ;

L^2 is selected from $-C(O)-$, $-C(O)-N(R^1)-*$, $-N(R^1)-C(O)-(C_1-C_6 \text{ alkylene})-*$, and $-C(O)-N(R^1)-(C_1-C_6 \text{ alkylene})-*$, wherein “ $*$ ” represents a portion of L^2 bound to ring B and each alkylene portion of L^2 is independently substituted with 0-5 occurrences of R^1 ;

each R^A is independently selected from hydroxyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, halo, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 hydroxyalkyl, cycloalkyl, aryl, heteroaryl, aryloxy, aralkyl, heterocyclyl, heterocyclylalkyl, nitro, cyano, $-C(O)R^1$, $-OC(O)R^1$, $-C(O)OR^1$, $-(C_1-C_6 \text{ alkylene})-C(O)R^1$, $-SR^1$, $-S(O)_2R^1$, $-S(O)_2-N(R^1)(R^1)$, $-(C_1-C_6 \text{ alkylene})-S(O)_2R^1$, $-(C_1-C_6 \text{ alkylene})-S(O)_2-N(R^1)(R^1)$, $-N(R^1)(R^1)$, $-C(O)-N(R^1)(R^1)$, $-N(R^1)-C(O)R^1$, $-N(R^1)-C(O)OR^1$, $-(C_1-C_6 \text{ alkylene})-N(R^1)-C(O)R^1$, $-N(R^1)S(O)_2R^1$, and $-P(O)(R^1)(R^1)$; wherein each alkyl, alkenyl, alkynyl, alkoxy, heteroalkyl, haloalkyl, haloalkoxy, hydroxyalkyl, cycloalkyl, aryl, heteroaryl, aryloxy, aralkyl, heterocyclyl, and heterocyclylalkyl portion of each of R^A is independently substituted with 0-5 occurrences of R^a ; or 2 R^A together with the carbon atom(s) to which they are attached form a cycloalkyl or heterocyclyl ring independently substituted with 0-5 occurrences of R^a ;

each R^B is independently selected from oxo, hydroxyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, halo, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 hydroxyalkyl, cycloalkyl, aryl, heteroaryl, aryloxy, aralkyl, heterocyclyl, heterocyclylalkyl, nitro, cyano, $-C(O)R^1$, $-OC(O)R^1$, $-C(O)OR^1$, $-(C_1-C_6 \text{ alkylene})-C(O)R^1$, $-SR^1$, $-S(O)_2R^1$, $-S(O)_2-N(R^1)(R^1)$, $-(C_1-C_6 \text{ alkylene})-S(O)_2R^1$, $-(C_1-C_6 \text{ alkylene})-S(O)_2-N(R^1)(R^1)$, $-N(R^1)(R^1)$, $-C(O)-N(R^1)(R^1)$, $-N(R^1)-C(O)R^1$, $-N(R^1)-C(O)OR^1$, $-(C_1-C_6 \text{ alkylene})-N(R^1)-C(O)R^1$, -

$N(R^1)S(O)_2R^1$, and $-P(O)(R^1)(R^1)$, wherein each alkyl, alkenyl, alkynyl, alkoxy, heteroalkyl, haloalkyl, haloalkoxy, hydroxyalkyl, cycloalkyl, aryl, heteroaryl, aryloxy, aralkyl, heterocyclyl, and heterocyclalkyl portion of each R^B is independently substituted with 0-5 occurrences of R^a , or 2 R^B together with the carbon atom(s) to which they are attached form a cycloalkyl or heterocycl ring independently substituted with 0-5 occurrences of R^a ;

each R^1 is independently selected from hydrogen, hydroxyl, halo, thiol, C_1 - C_6 alkyl, C_1 - C_6 thioalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heteroarylalkyl, heterocycl, and heterocyclalkyl, wherein each alkyl, thioalkyl, alkoxy, haloalkyl, hydroxyalkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, heteroarylalkyl, heterocycl, and heterocyclalkyl portion of R^1 is independently substituted with 0-5 occurrences of R^b , or 2 R^1 together with the atom(s) to which they are attached form a cycloalkyl or heterocycl ring independently substituted with 0-5 occurrences of R^b ;

each R^a and R^b is independently selected from C_1 - C_6 alkyl, halo, hydroxyl, C_1 - C_6 haloalkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 alkoxy, cycloalkyl, heterocycl, and cyano, wherein each alkyl, haloalkyl, heteroalkyl, hydroxyalkyl, alkoxy, cycloalkyl and heterocycl portion of R^a and R^b is independently substituted with 0-5 occurrences of R' ;

each R' is independently selected from C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, halo, hydroxyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, cycloalkyl and cyano; or 2 R' together with the atom(s) to which they are attached form a cycloalkyl or heterocycl ring; and

p is 0, 1, 2, 3, 4, or 5; and

q is 0, 1, 2, 3, or 4.

2. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein Ring A is selected from cycloalkyl, heterocycl, and cycloalkenyl.

3. The compound of claim 2 or a pharmaceutically acceptable salt thereof, wherein Ring A is selected from cyclopentyl, cyclohexyl, tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl, and cyclopentenyl.

4. The compound of any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof, wherein Ring B is selected from aryl, heteroaryl, or heterocycl.

5. The compound of claim 4 or a pharmaceutically acceptable salt thereof,

wherein Ring B is selected from phenyl, pyridyl, or pyrrolidinyl.

6. The compound of any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof, wherein

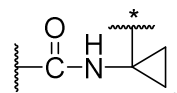
L^1 is $-C(O)-$, or $-N(R^1)-$; and

L^2 is $-N(R^1)-C(O)-(C_1-C_6 \text{ alkylene})-^*$ or $-C(O)-N(R^1)-(C_1-C_6 \text{ alkylene})-^*$, wherein each alkylene portion of L^2 is independently substituted with 0-5 occurrences of R^1 .

7. The compound of claim 6 or a pharmaceutically acceptable salt thereof, wherein:

L^1 is $-NH-$; and

L^2 is selected from $-C(O)-NH-CH(CH_2OH)-^*$, $-C(O)-N(CH_3)-CH_2-^*$, $-C(O)-N(CH_3)-CH(CH_3)-^*$, $-C(O)N(CH_2CH_3)CH_2-^*$, $-C(O)NHCH(CH_3)-^*$, $-C(O)NHCH(CF_3)-^*$, and



8. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein L^1 is $-NH-$, L^2 is $-C(O)-$ and Ring B is pyrrolidin-1-yl.

9. The compound of any one of claims 1 to 8 or a pharmaceutically acceptable salt thereof, wherein each R^1 is independently selected from hydrogen and C_1-C_6 alkyl substituted with 0-5 occurrences of R^b .

10. The compound of claim 9 or a pharmaceutically acceptable salt thereof, wherein each R^1 is independently selected from hydrogen and $-CH_3$.

11. The compound of any one of claims 1 to 10 or a pharmaceutically acceptable salt thereof, wherein each R^A and R^B is independently selected from hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 hydroxyalkyl, cycloalkyl, aryl, heteroaryl, nitro, cyano, $-C(O)R^1$, $-OC(O)R^1$, $-C(O)OR^1$, $-SR^1$, $-S(O)_2R^1$, $-S(O)_2-N(R^1)(R^1)$, $-N(R^1)(R^1)$, $-C(O)-N(R^1)(R^1)$, $-N(R^1)-C(O)R^1$, $-N(R^1)-C(O)OR^1$, and $-N(R^1)S(O)_2R^1$; wherein each alkyl, alkoxy, heteroalkyl, haloalkyl, haloalkoxy, hydroxyalkyl, cycloalkyl, aryl, and heteroaryl portion of each R^A and each R^B is

independently substituted with 0-5 occurrences of R^a; or 2 R^A or 2 R^B together with the carbon atom(s) to which they are attached form a cycloalkyl or heterocyclyl ring independently substituted with 0-5 occurrences of R^a.

12. The compound of any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof, wherein each R^A is independently selected from hydroxyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, halo, -C(O)-N(R¹)(R¹), -C(O)OR¹, -S(O)₂R¹, C₁-C₆ haloalkyl, cyano, oxetanyl, and C₁-C₆ hydroxyalkyl, or two R^A bound to adjacent ring carbon atoms on Ring A are taken together to form a C₃-C₆ cycloalkyl fused to Ring A.

13. The compound of claim 12 or a pharmaceutically acceptable salt thereof, wherein each R^A is independently selected from hydroxyl, fluoro, oxetan-3-yl, -CHF₂, -CH₂CH₃, -C(CH₃)₂OH, -OCH₃, -C(O)N(CH₃)₂, -C(O)OCH₃, -S(O)₂CH₃; or two R^A bound to adjacent ring carbon atoms on Ring A are taken together to form a cyclopropyl fused to Ring A.

14. The compound of any one of claims 1-10, 12, and 13 or a pharmaceutically acceptable salt thereof, wherein each R^B is independently selected from halo, C₁-C₆ alkyl, cyano, C₁-C₆ alkoxy, aryl, heteroaryl, oxo, and C₁-C₆ haloalkoxy.

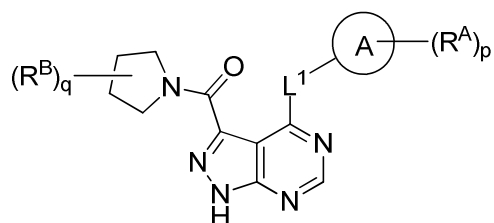
15. The compound of any one of claims 1-7 and 9-14, or a pharmaceutically acceptable salt thereof, wherein Ring B is pyrrolidinyl and at least one R^B is optionally substituted aryl or heteroaryl.

16. The compound of claim 15 or a pharmaceutically acceptable salt thereof, wherein Ring B is pyrrolidinyl, and at least one R^B is selected from 2,3,5-trifluorophenyl, 2,3-difluorophenyl, 2,5-difluorophenyl, 2-chloro-5-fluorophenyl, 2-chloro-5-fluoropyridin-3-yl, 2-cyano-5-fluorophenyl, 2-fluoro-5-chlorophenyl, 2-methoxy-3,5-difluorophenyl, 2-methoxy-5-fluoropyridin-3-yl, 2-trifluoromethoxy-5-fluorophenyl, 3,5-difluorophenyl, 3-chloro-5-fluorophenyl, 3-cyano-5-fluorophenyl, 3-difluoromethoxy-5-fluorophenyl, 3-fluorophenyl, 5-fluoropyridin-3-yl, and phenyl.

17. The compound of any one of claims 1-7, 9, 10, and 12-14 or a pharmaceutically acceptable salt thereof, wherein Ring B is not pyrrolidinyl, and each R^B is

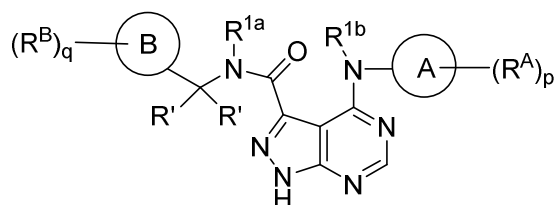
independently selected from chloro, fluoro, oxo, -CH₃, -CF₃, -CN, -OCH₃, -OCF₃, and -OCHF₂.

18. The compound of claim 1, wherein the compound is a compound of Formula (Ia):



(Ia), or a pharmaceutically acceptable salt thereof.

19. The compound of claim 1, wherein the compound is a compound of Formula (II):



(II) or a pharmaceutically acceptable salt thereof,

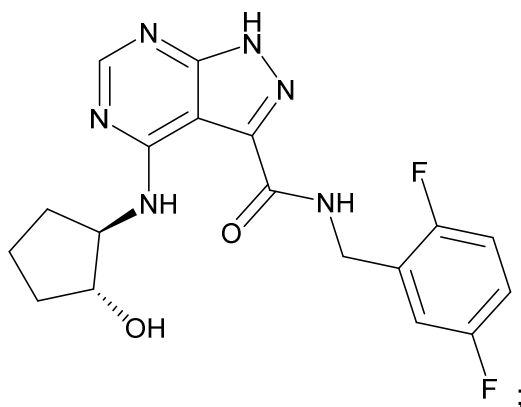
wherein:

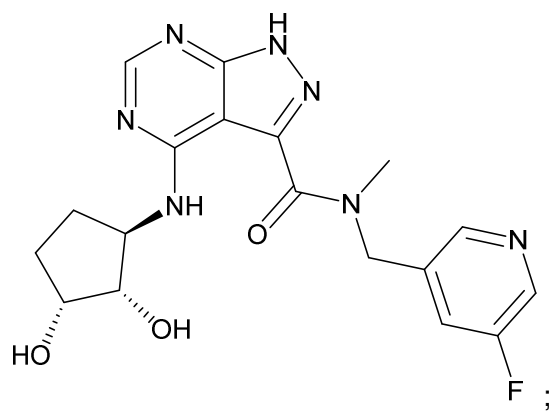
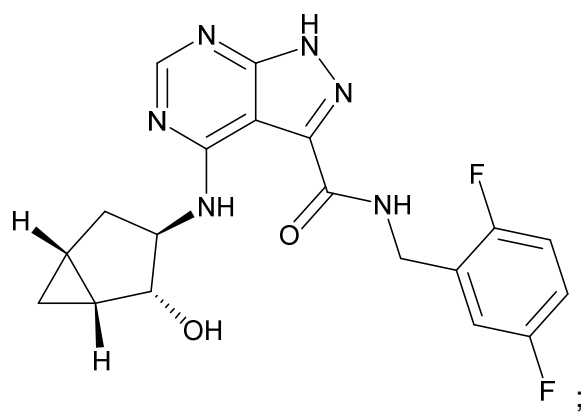
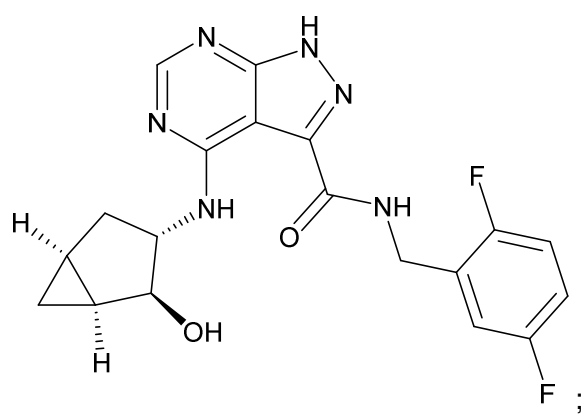
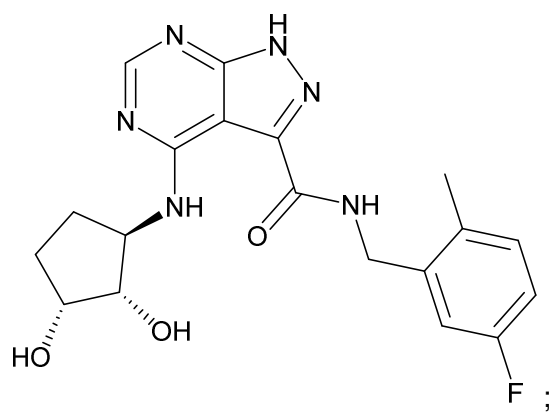
R^{1a} is selected from hydrogen and C₁-C₆ alkyl;

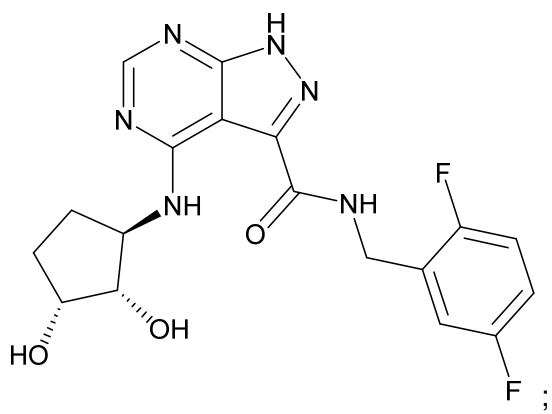
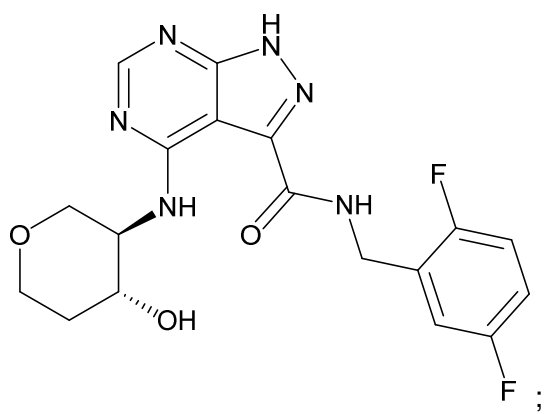
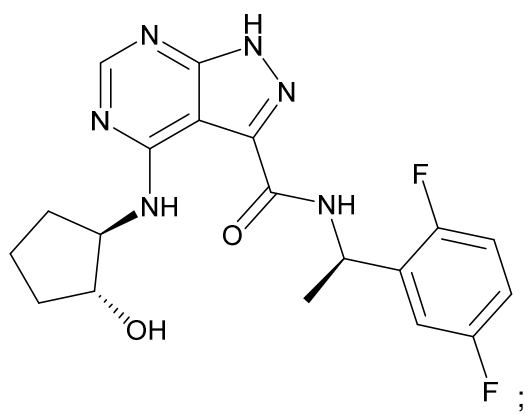
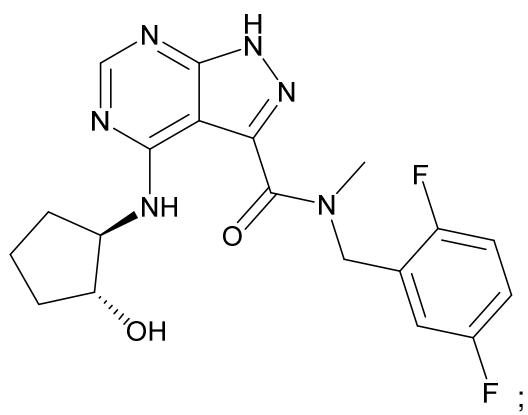
R^{1b} is selected from hydrogen and C₁-C₆ alkyl; and

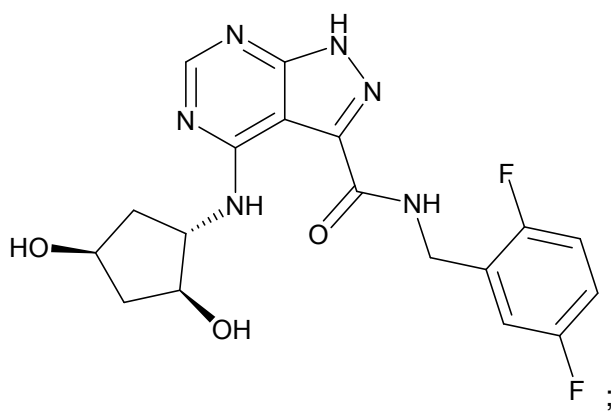
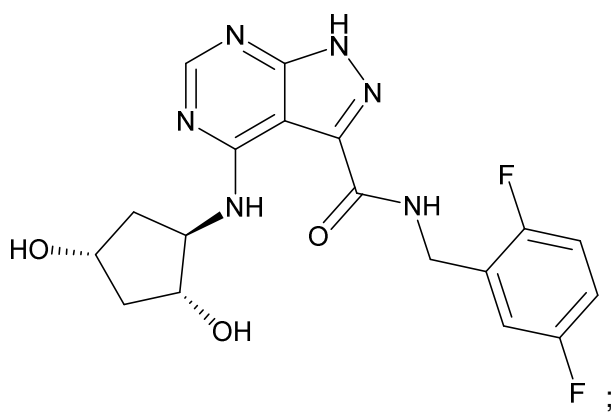
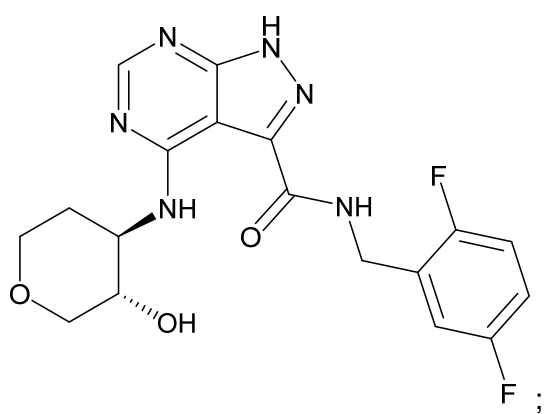
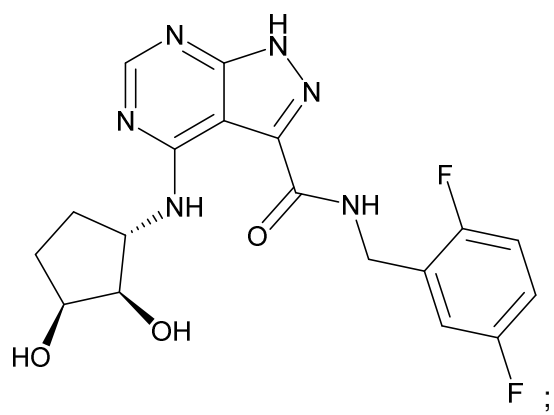
Ring A, Ring B, R', R^A, R^B, p and q are as defined in claim 1.

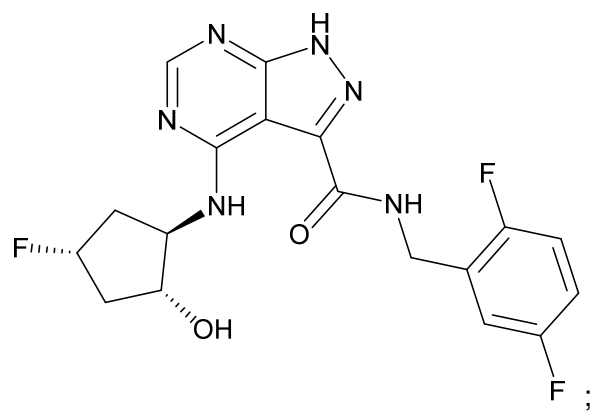
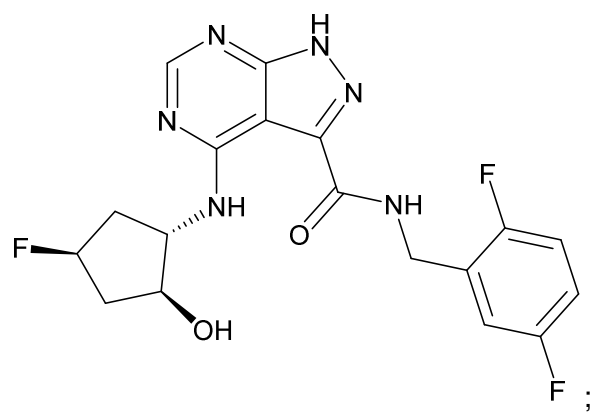
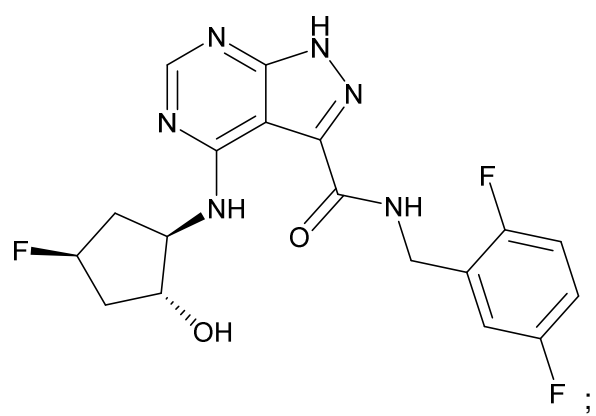
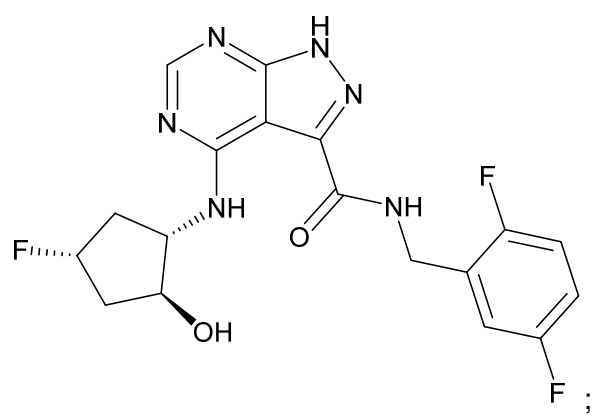
20. A compound selected from

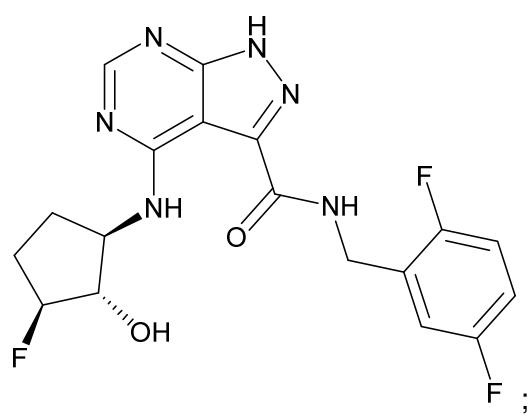
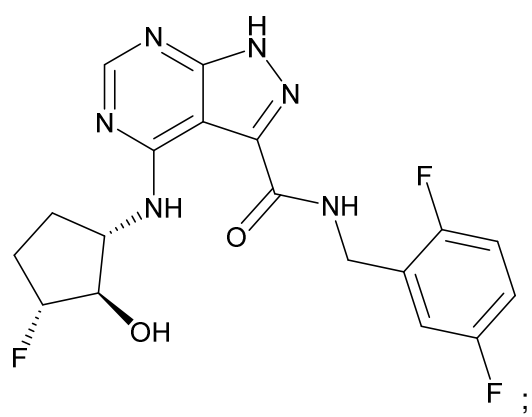
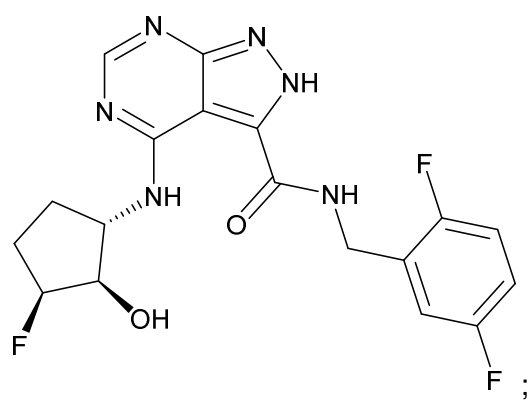
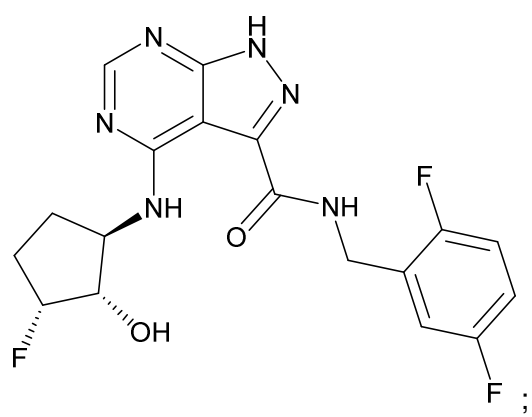


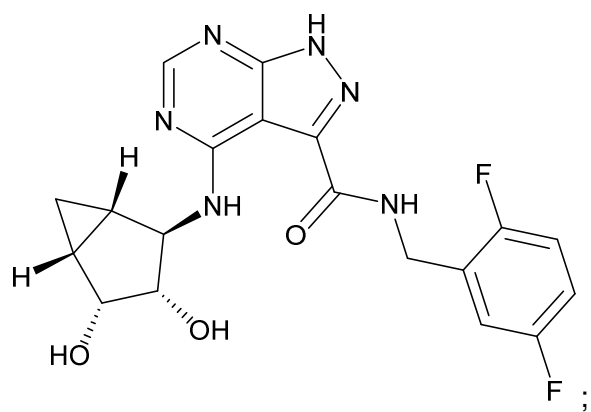
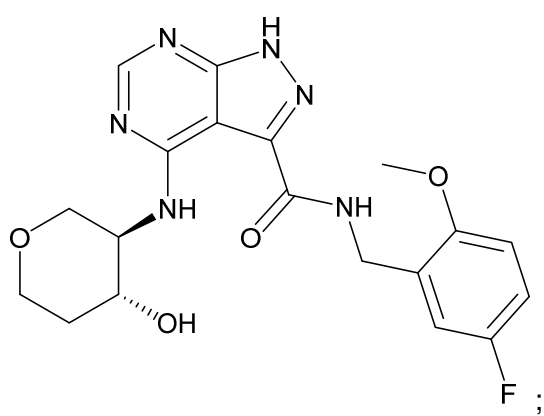
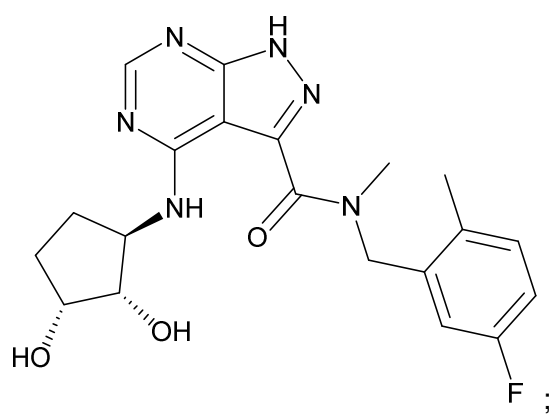
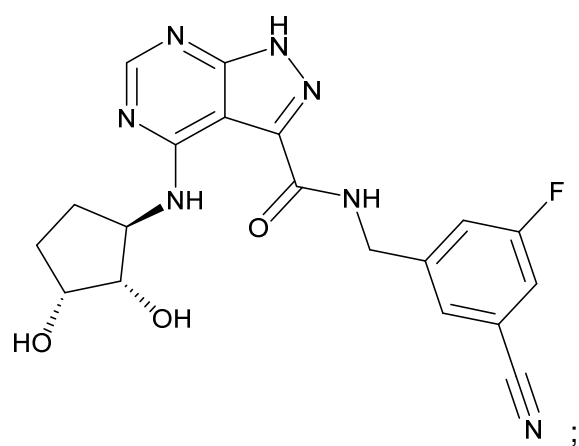


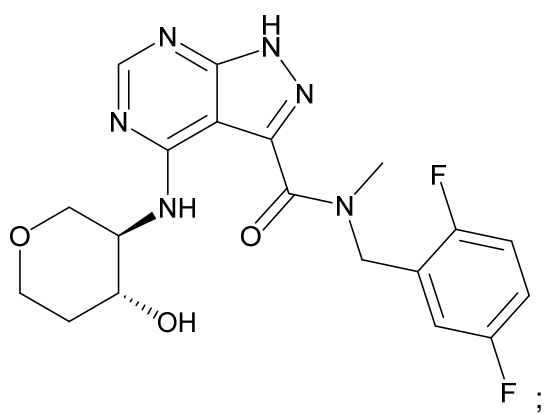
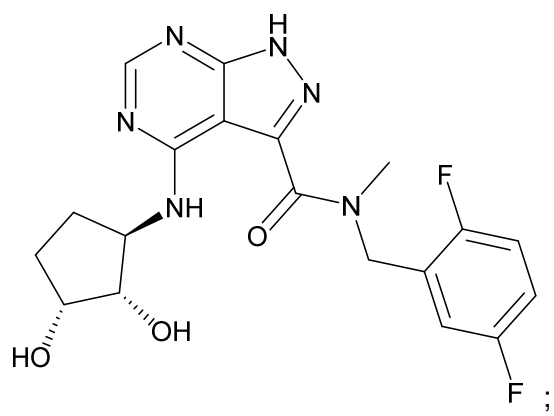
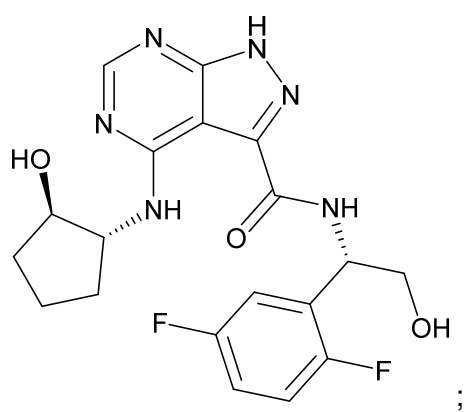
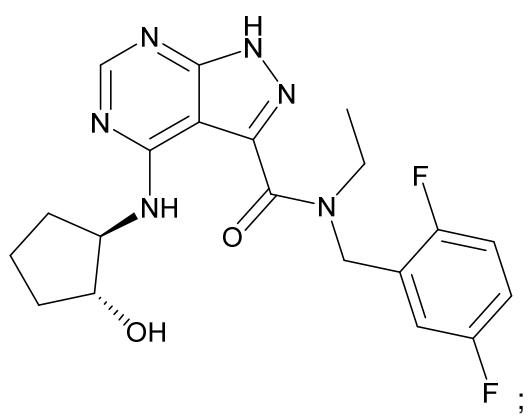


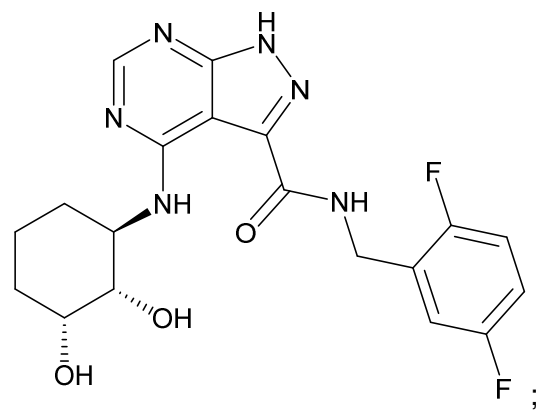
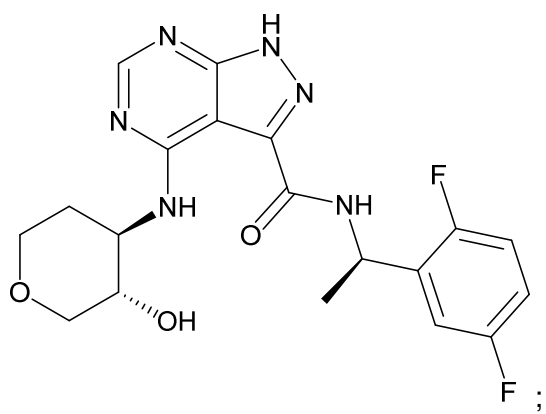
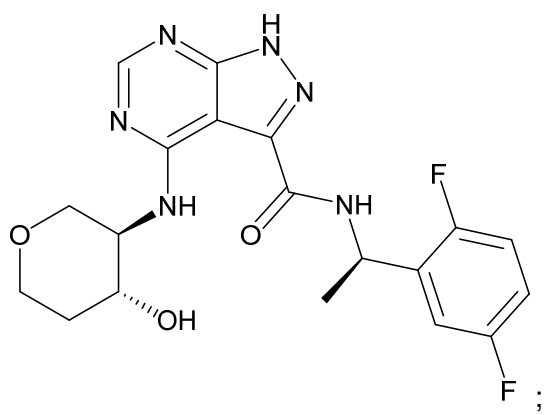


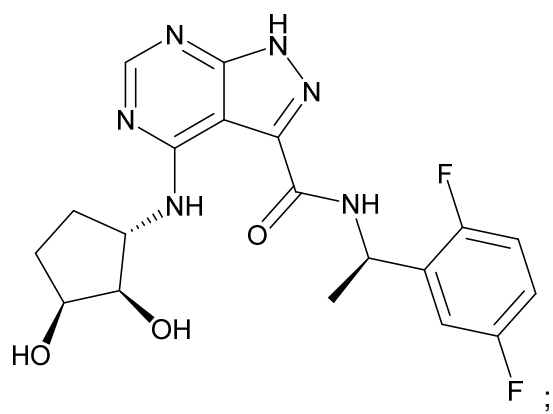
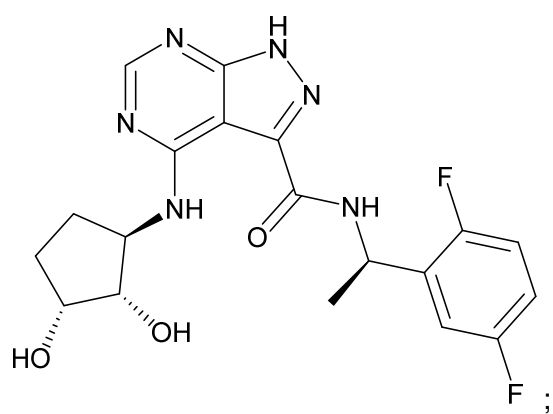
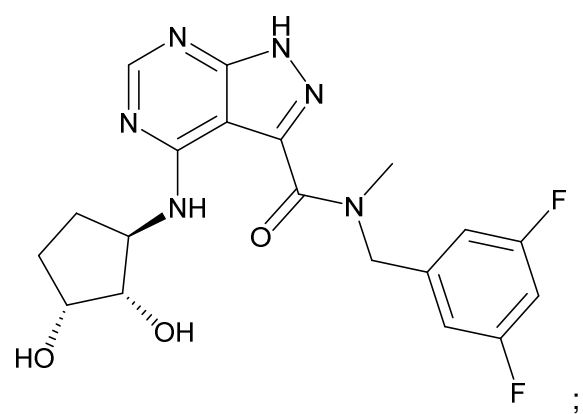


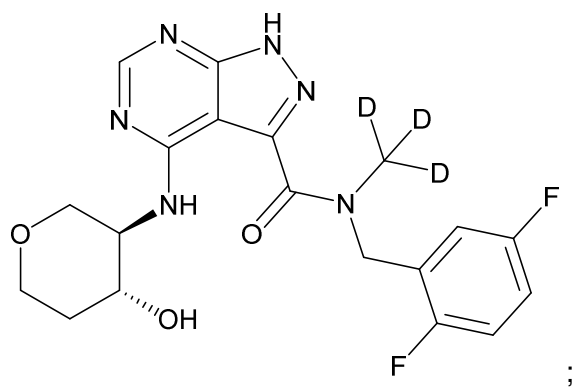
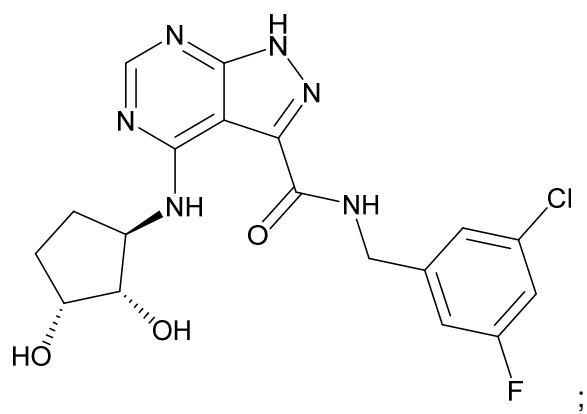
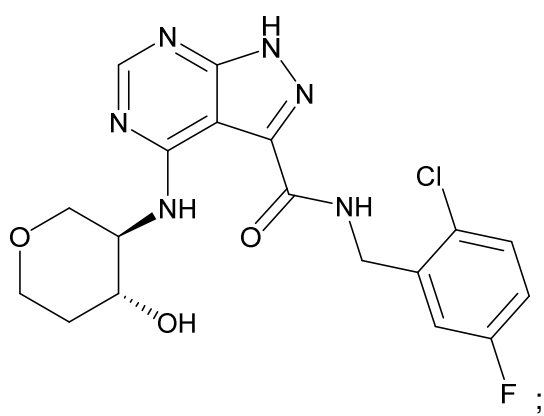
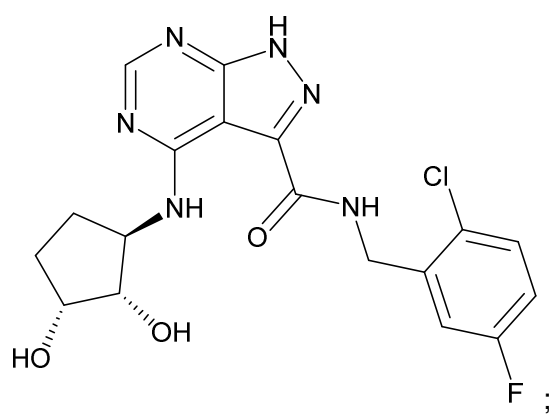


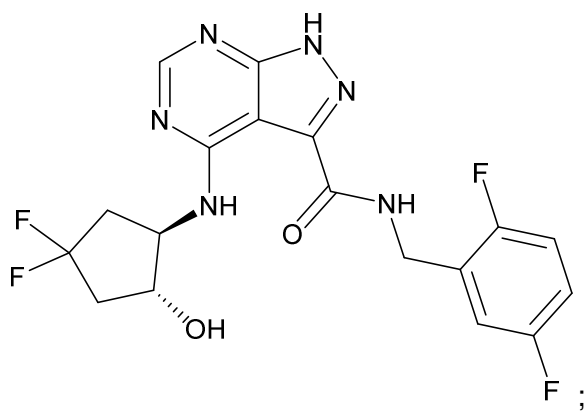
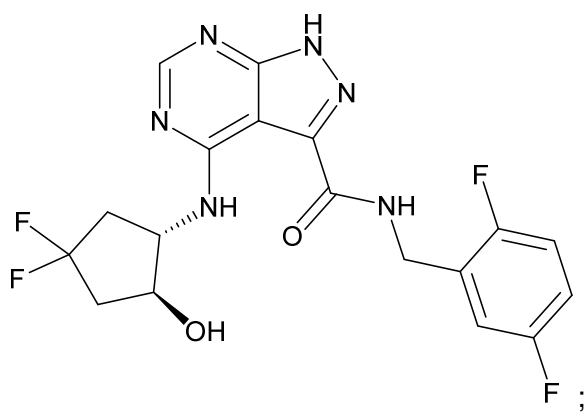
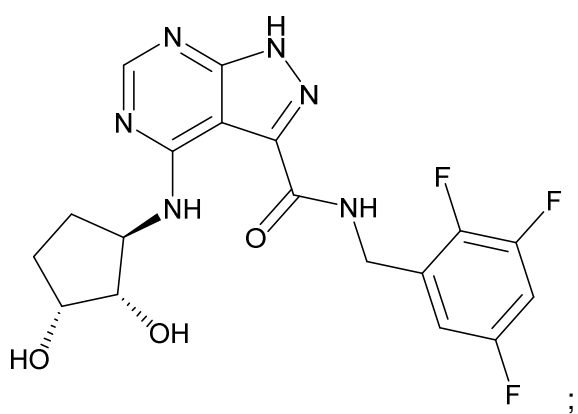
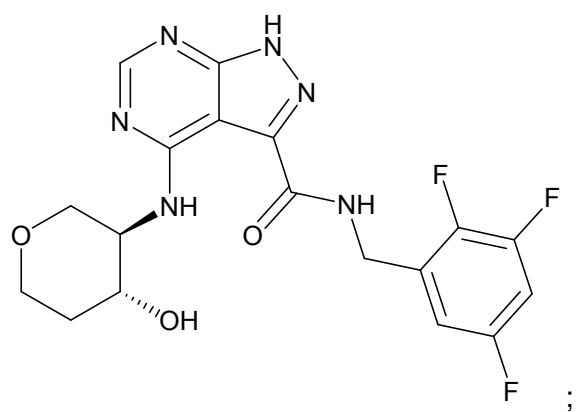


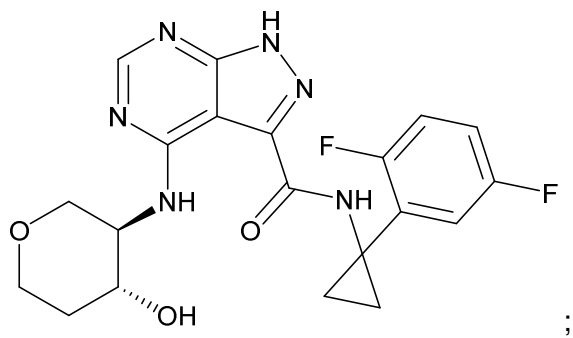
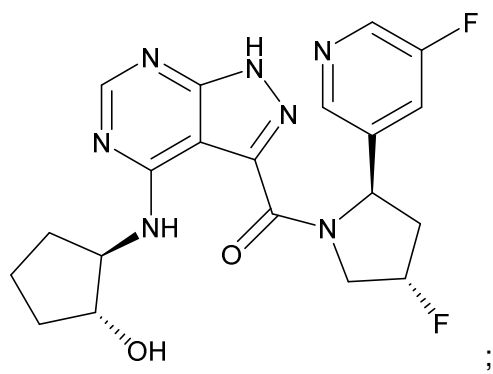
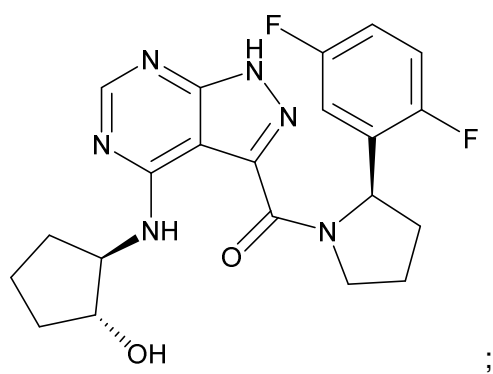
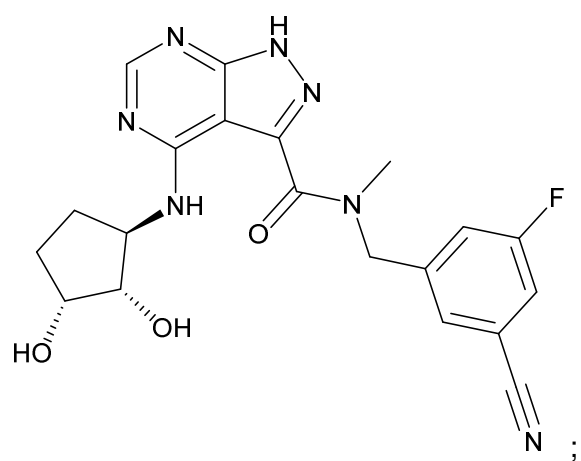


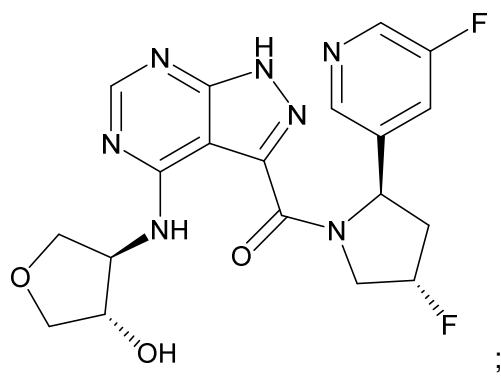
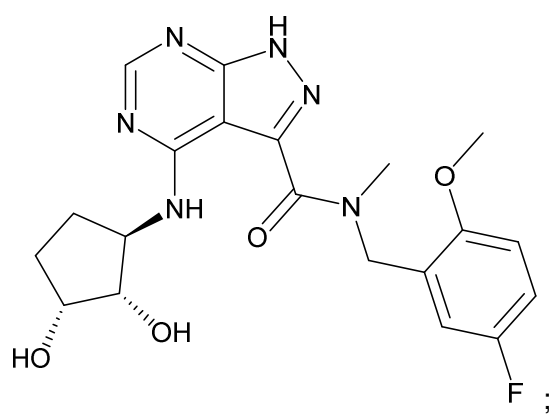
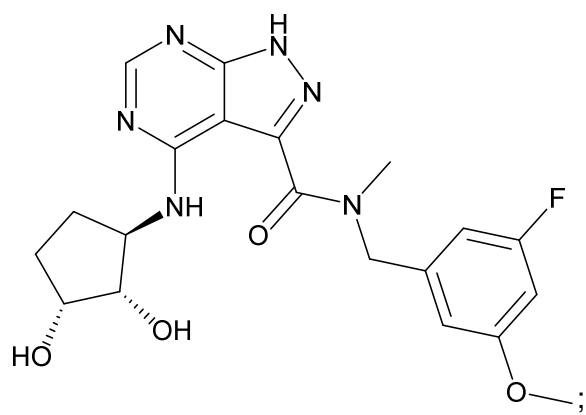


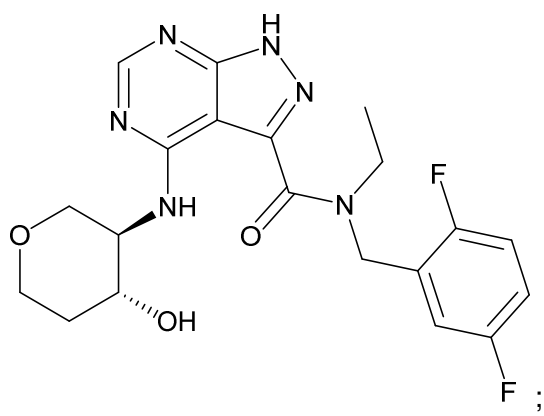
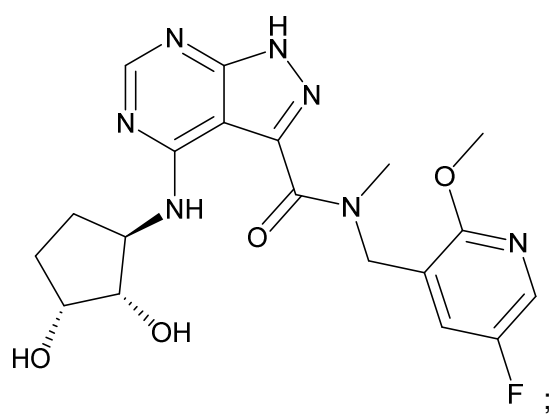
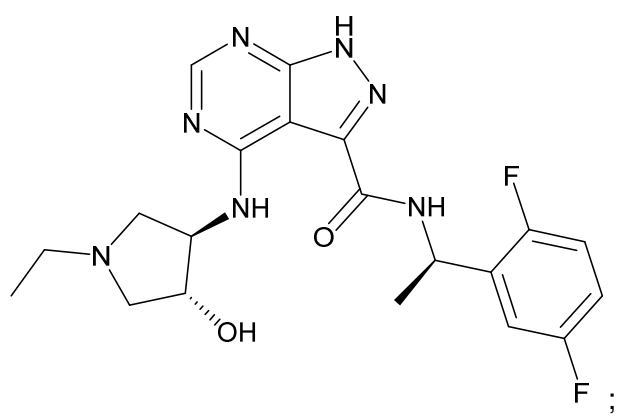


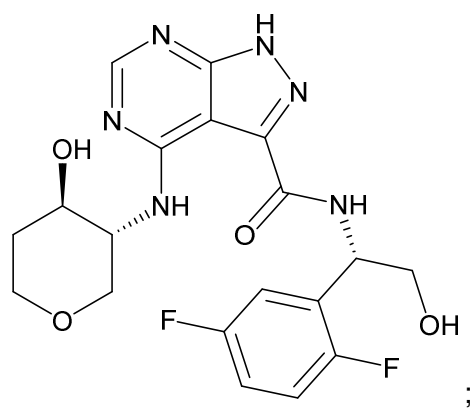
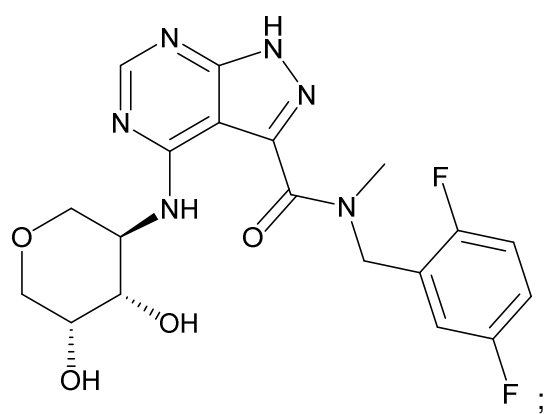
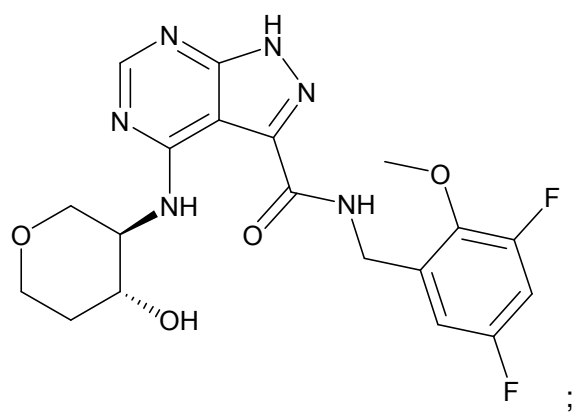


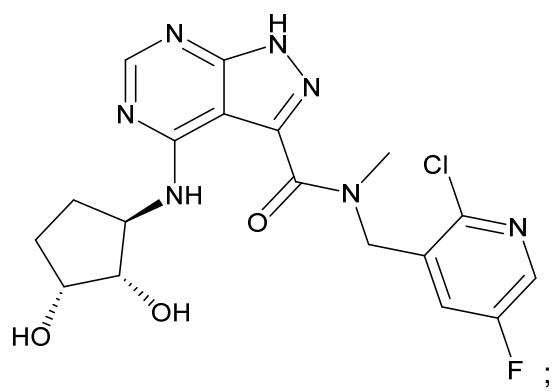
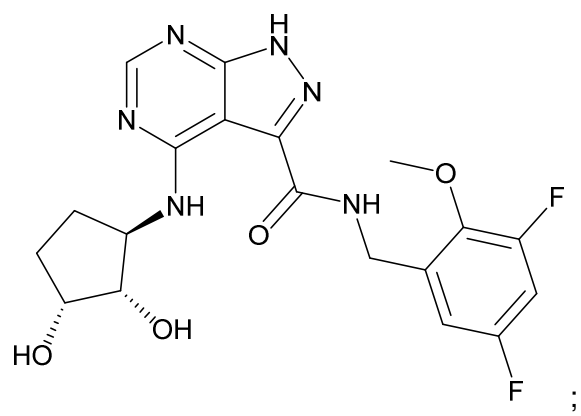
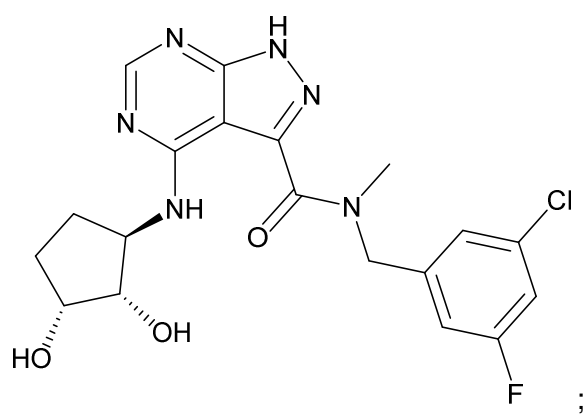
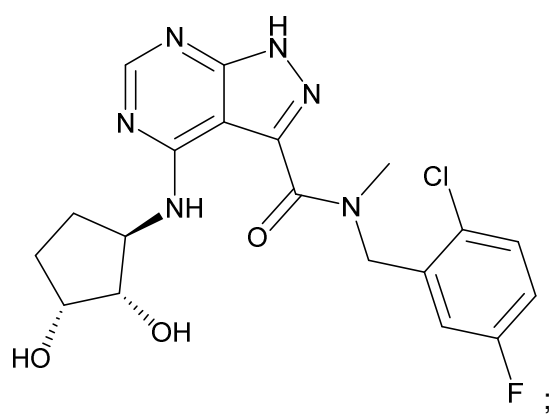


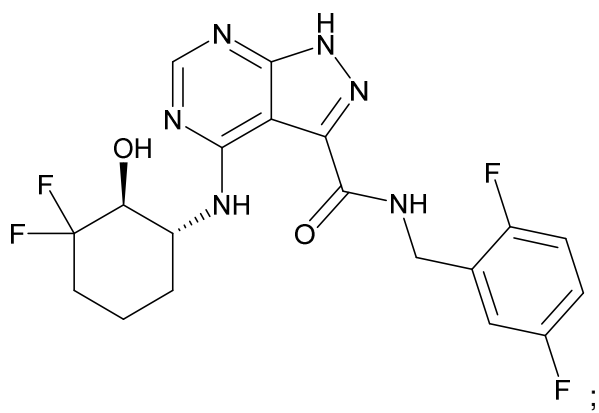
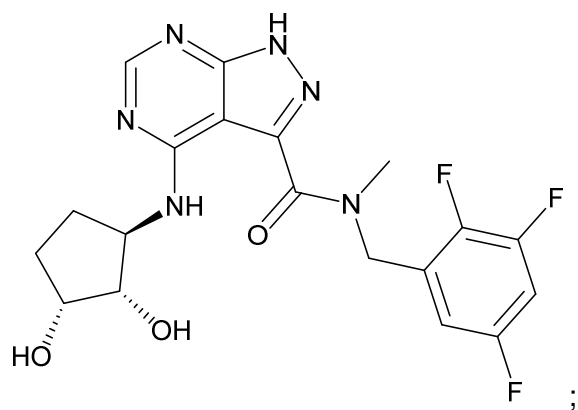
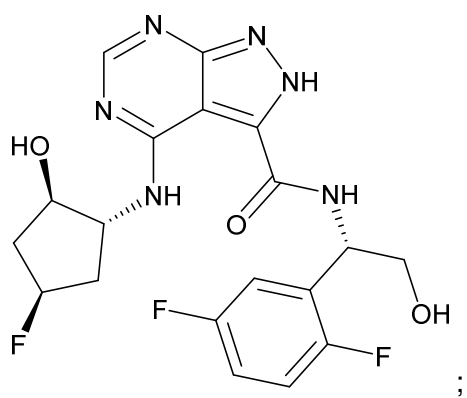
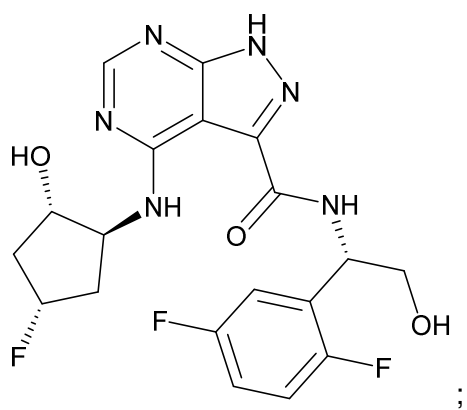


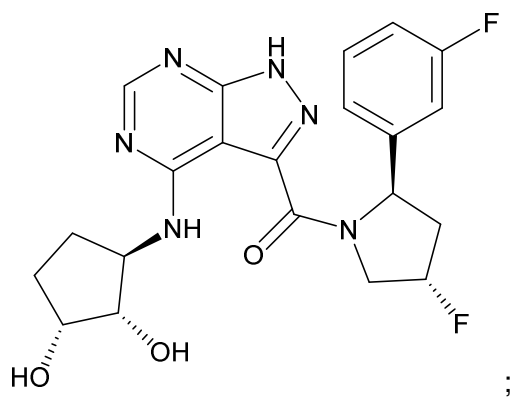
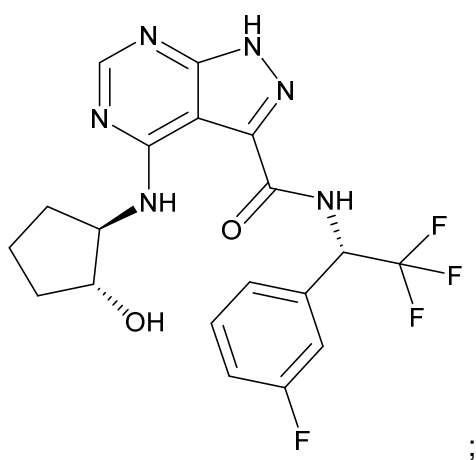
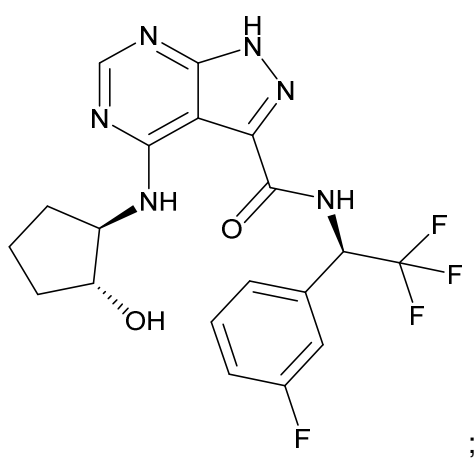
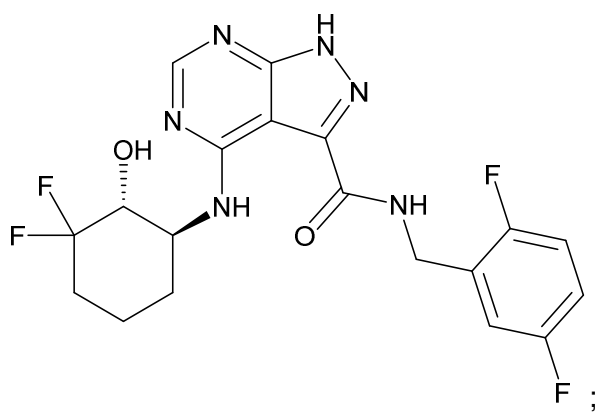


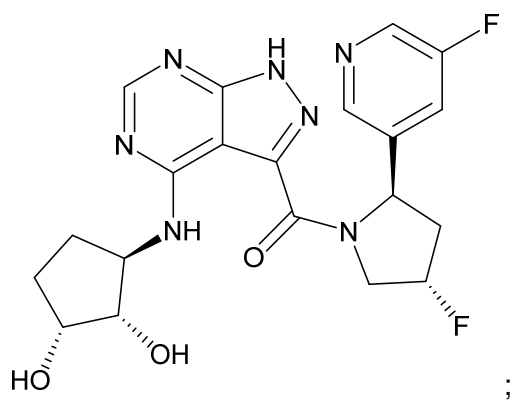
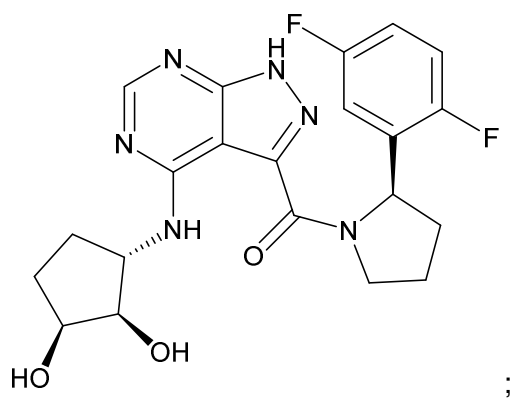
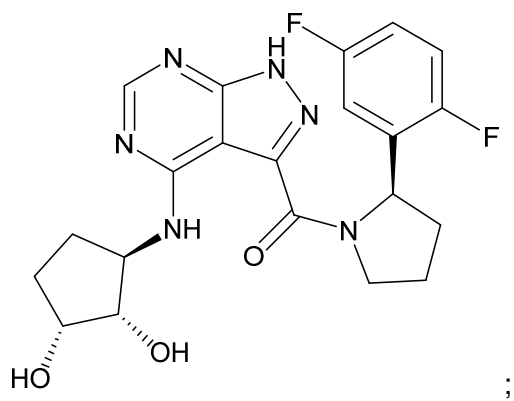
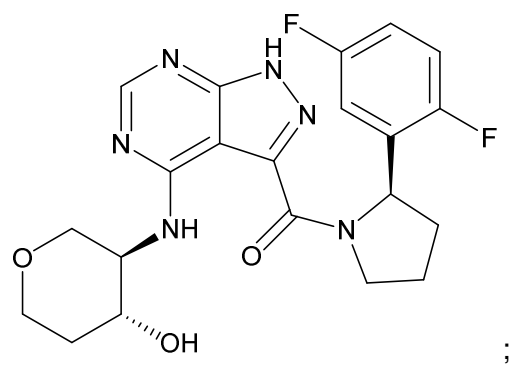


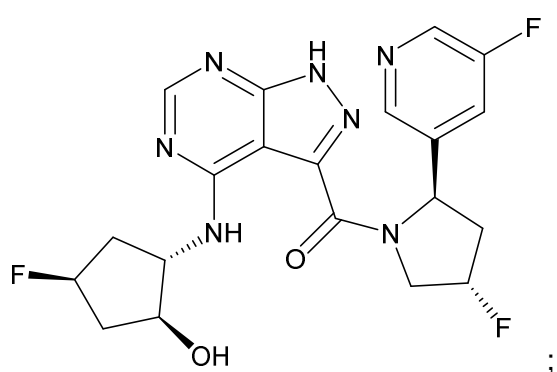
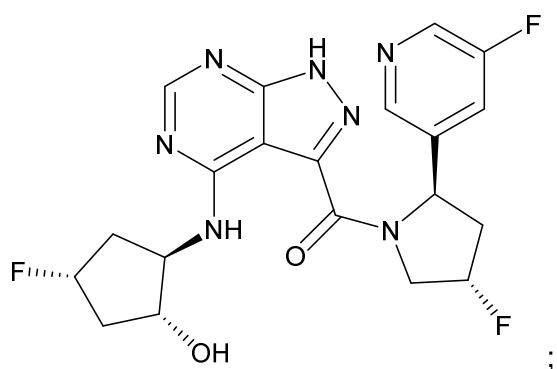
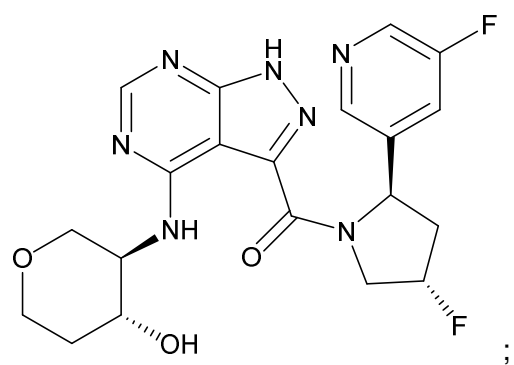
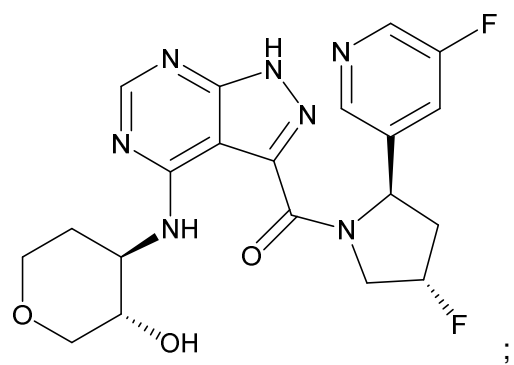


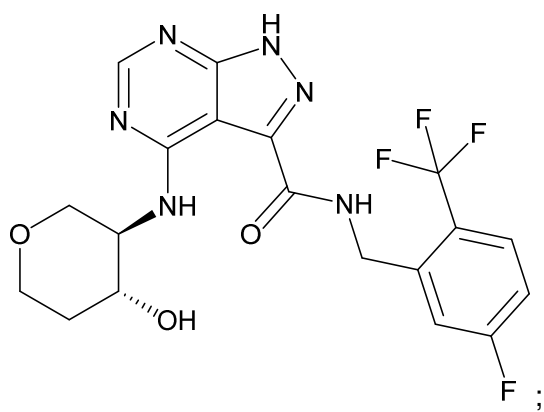
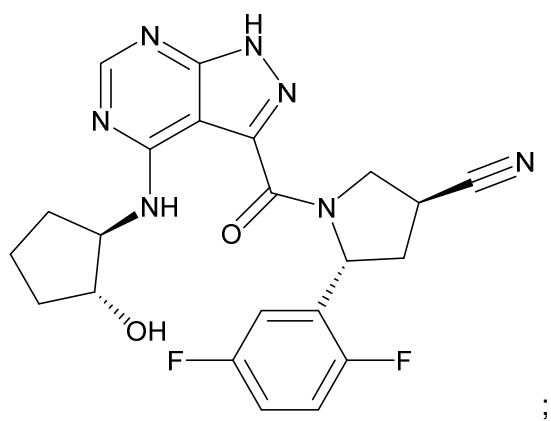
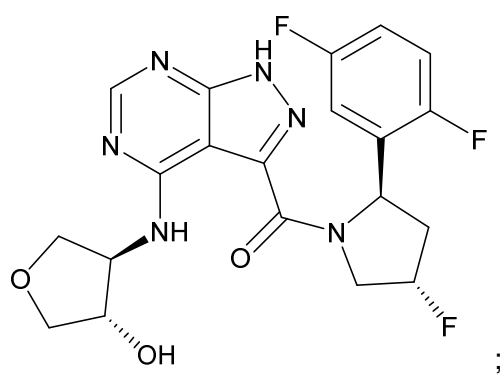
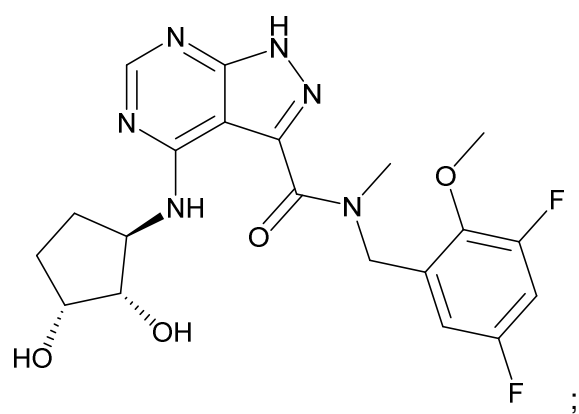


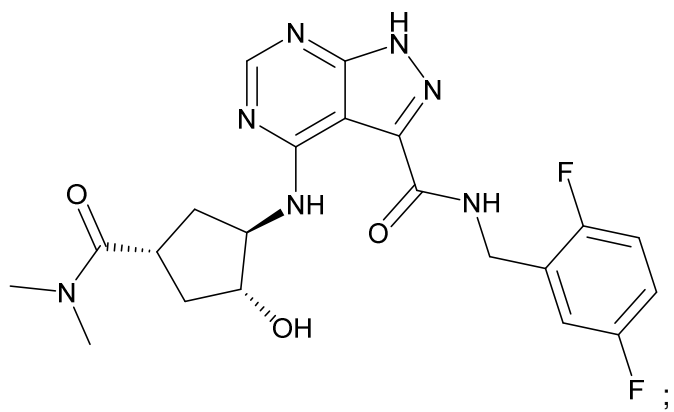
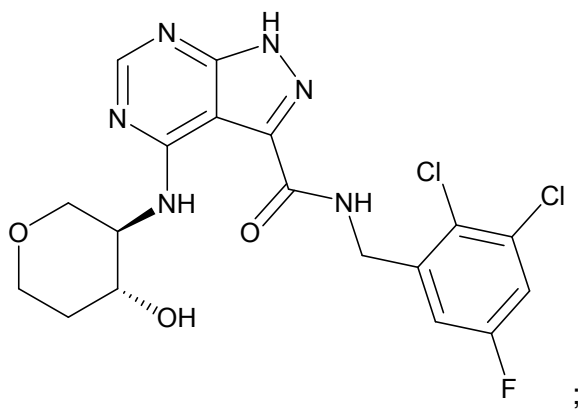
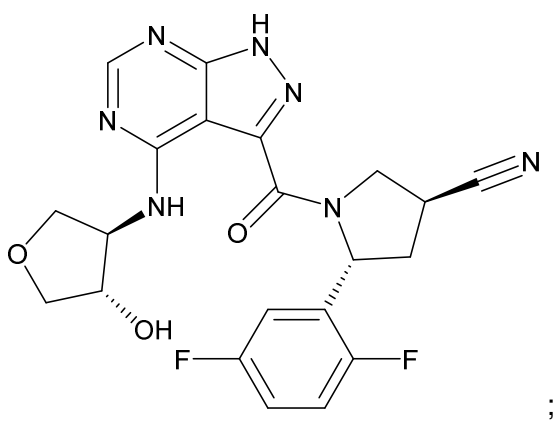
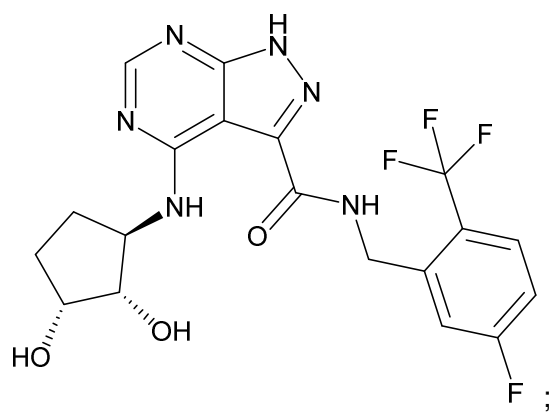


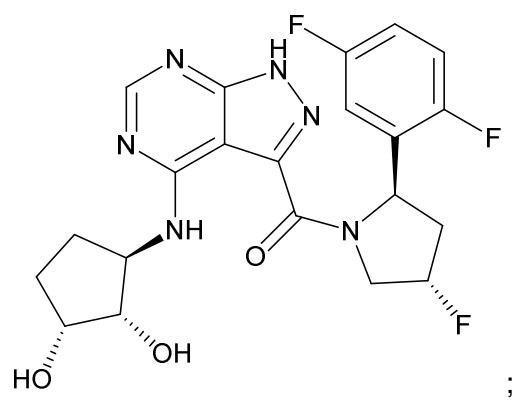
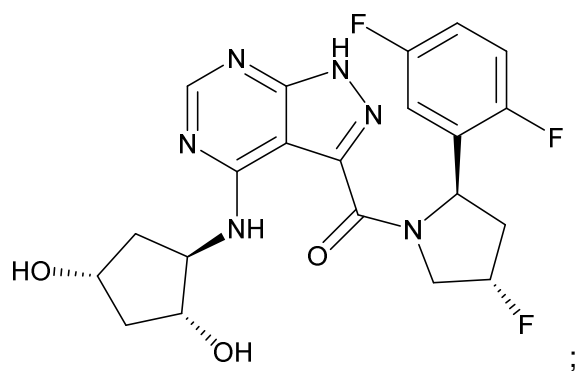
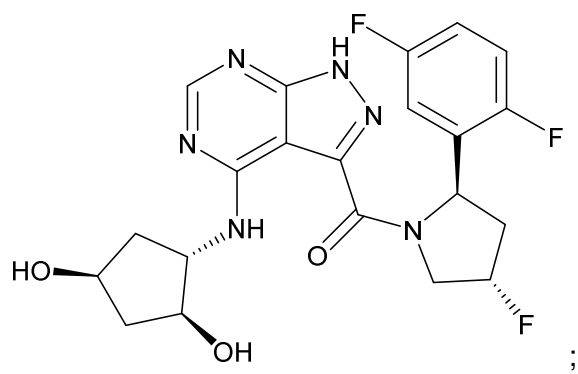
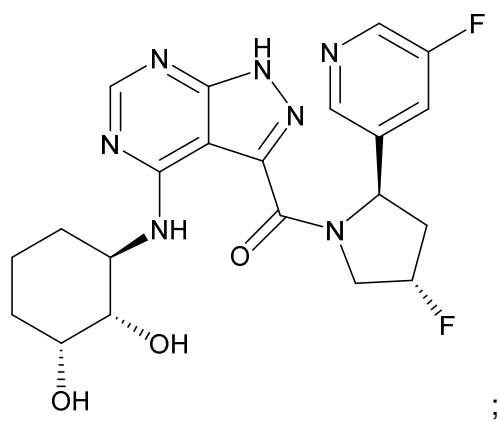


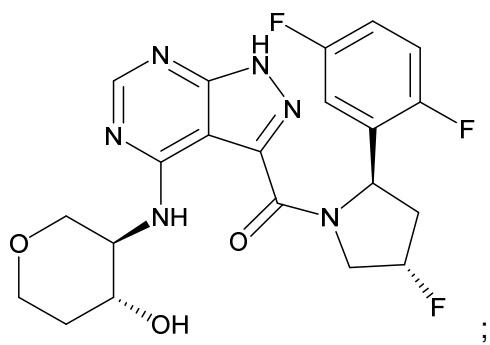
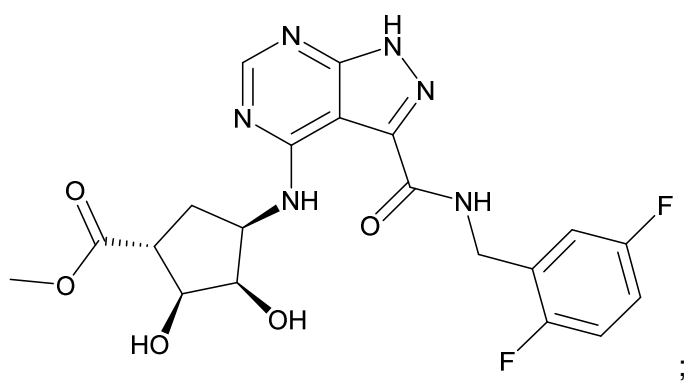
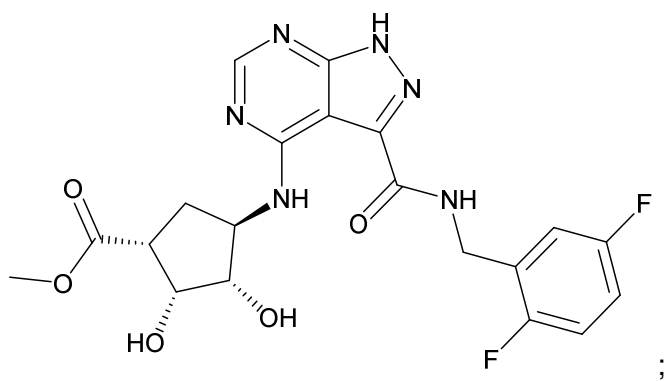
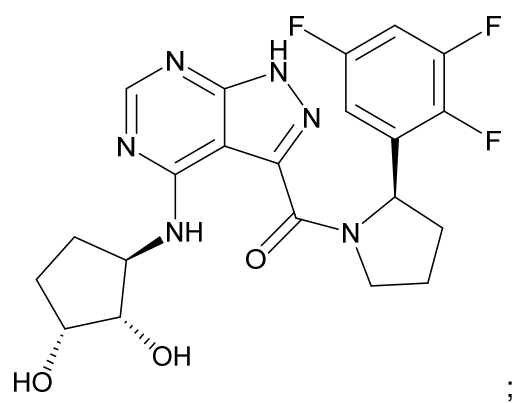


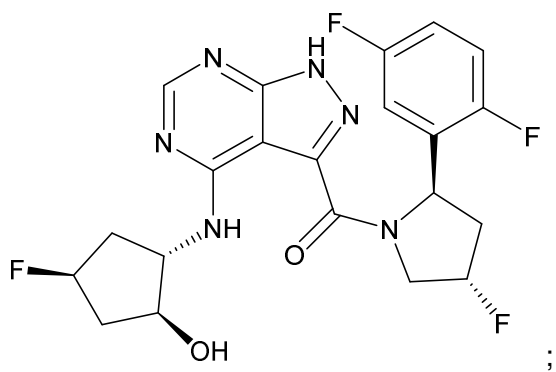
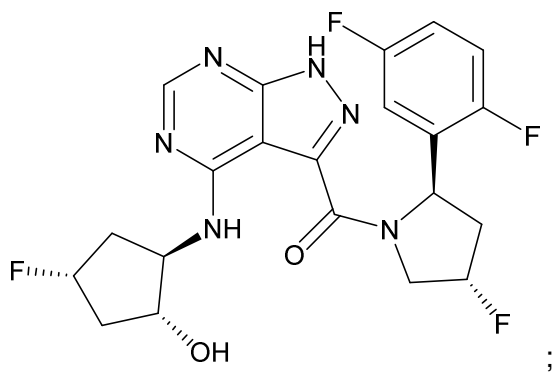
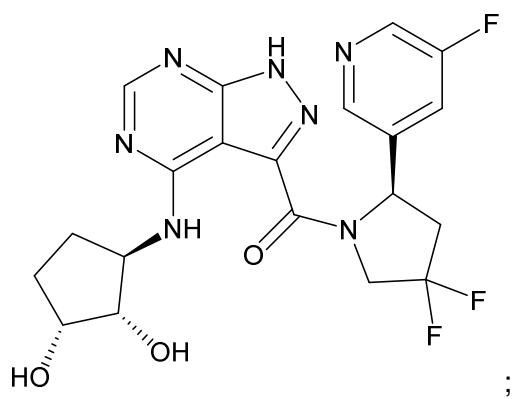
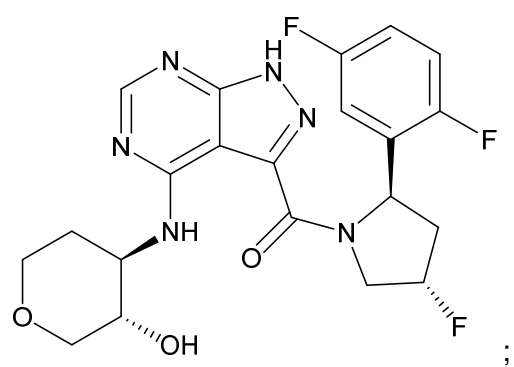


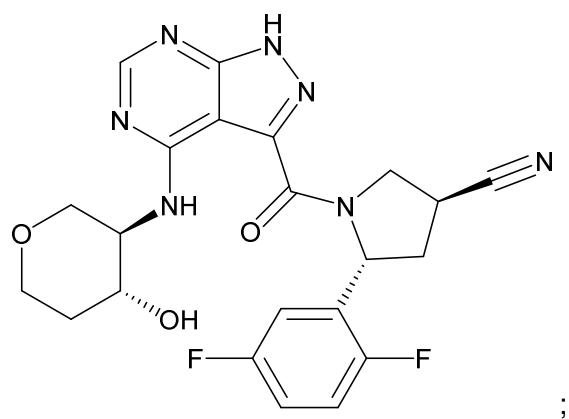
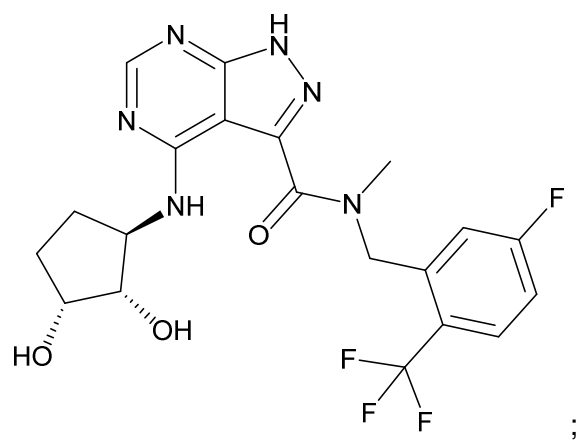
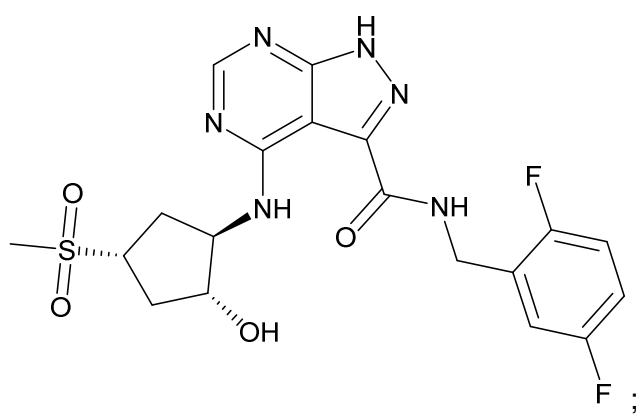
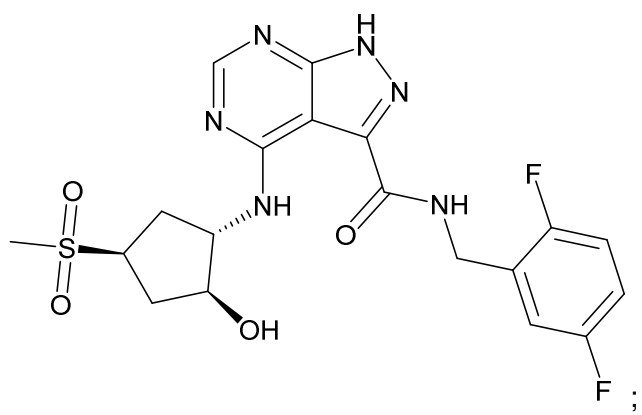


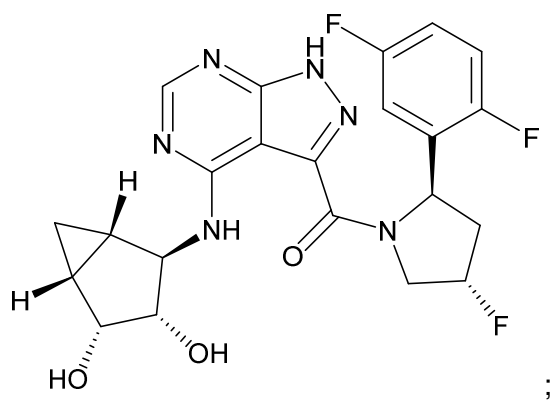
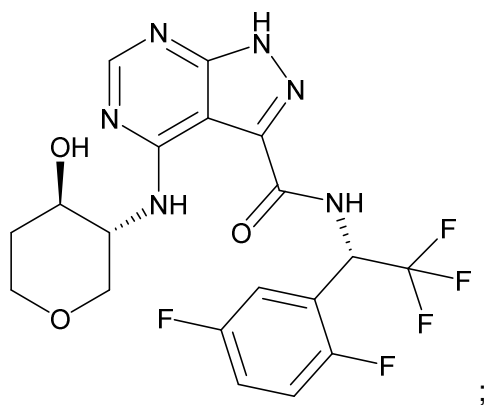
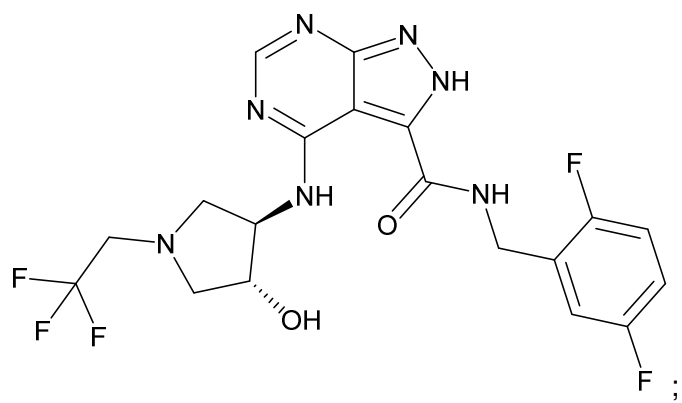
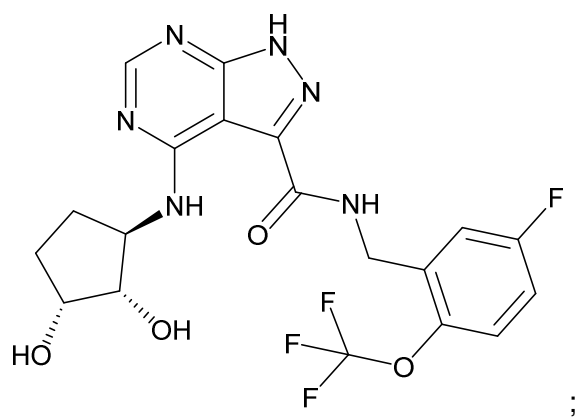


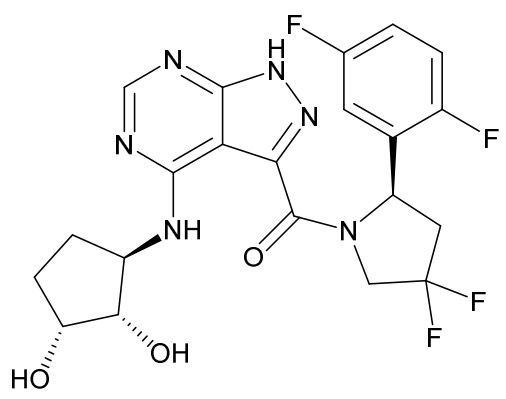
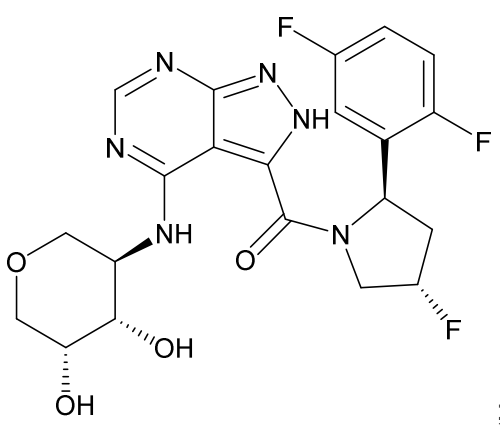
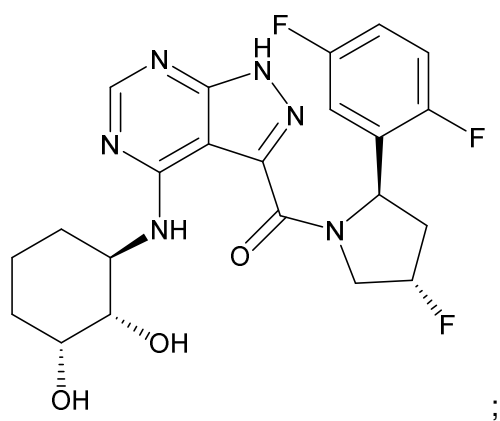
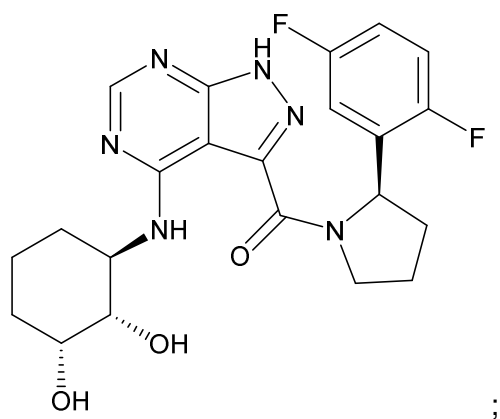


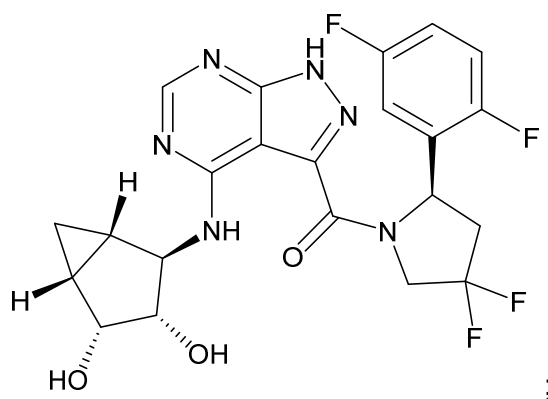
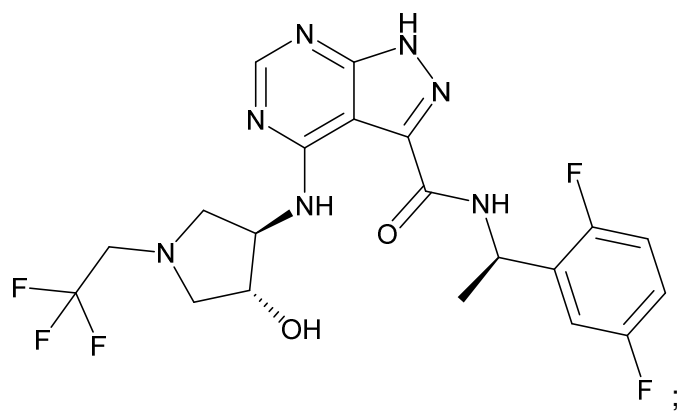
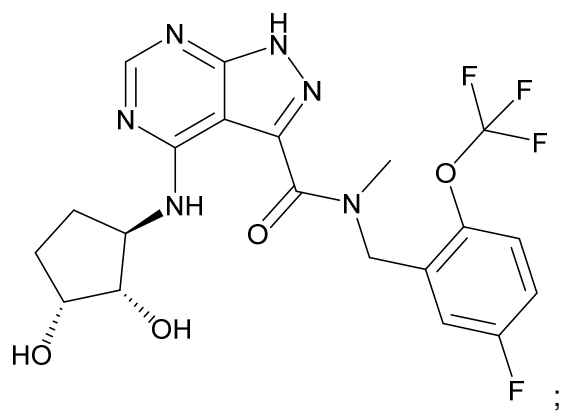
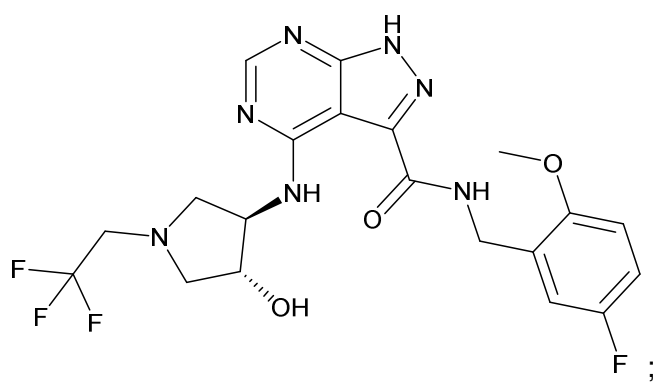


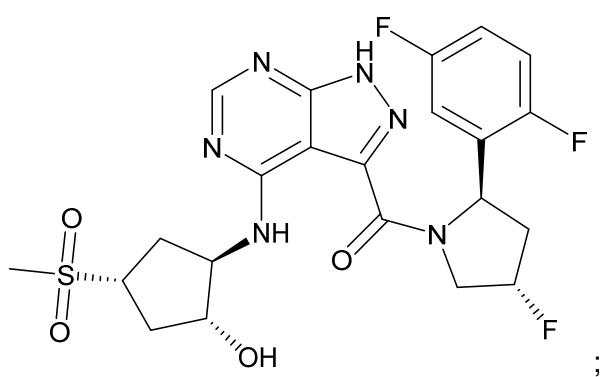
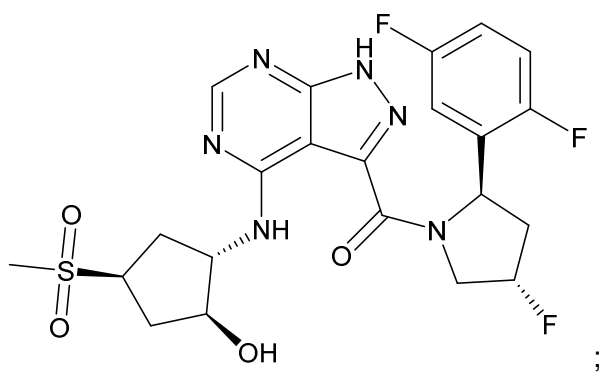
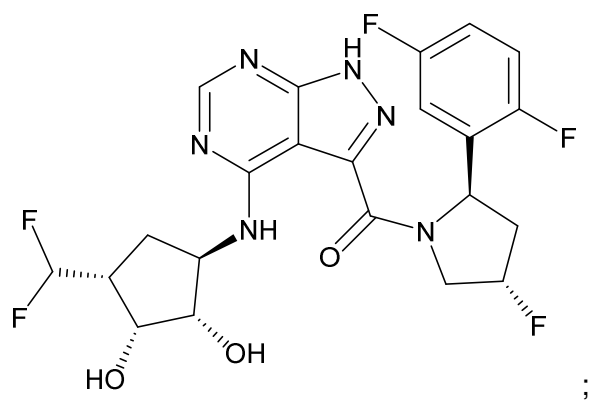
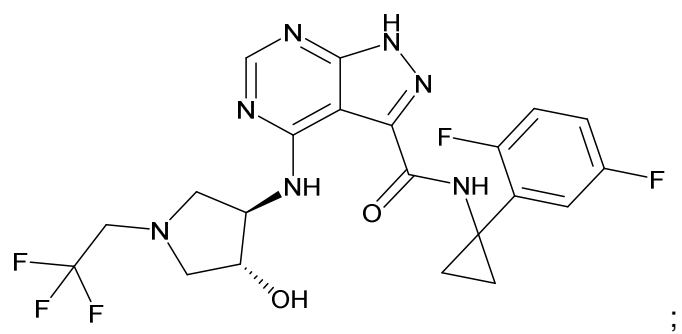


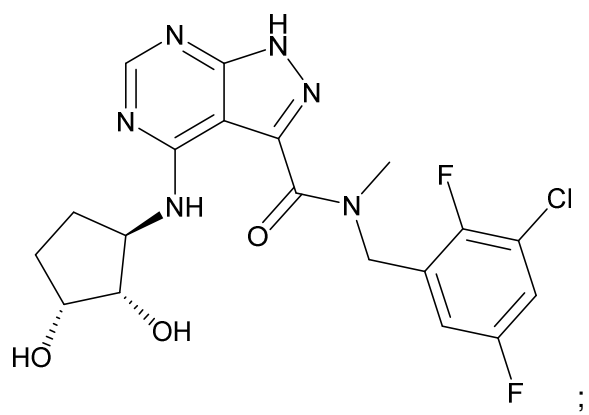
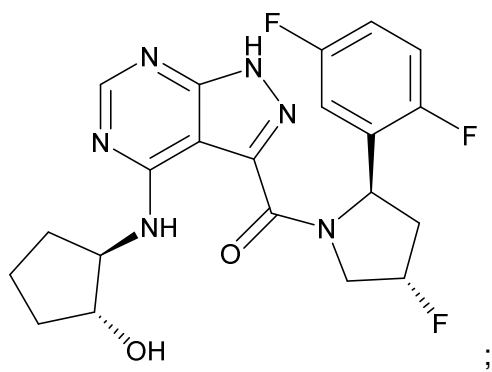
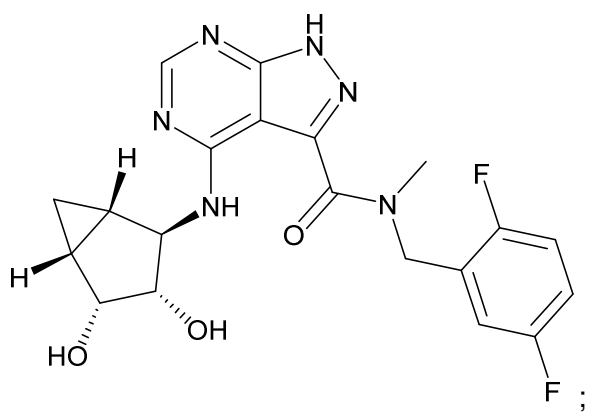
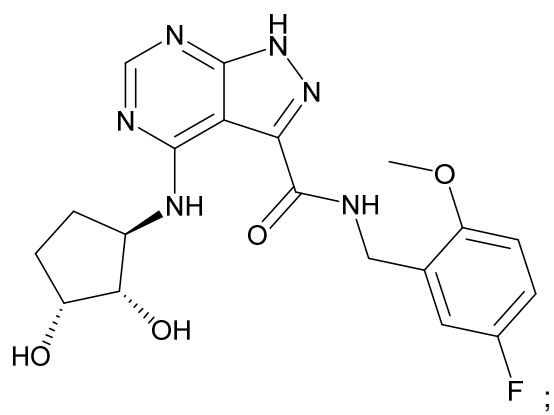


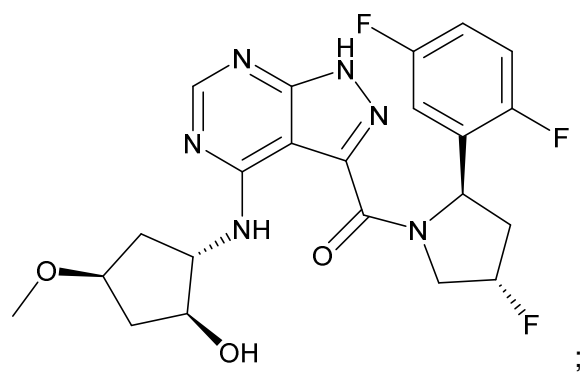
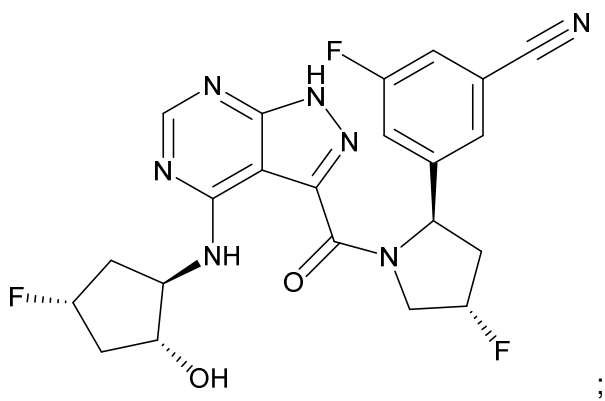
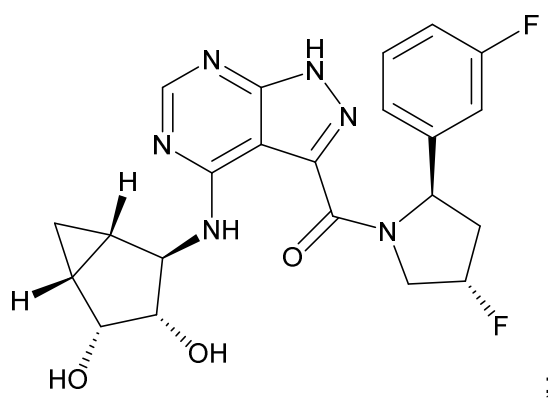
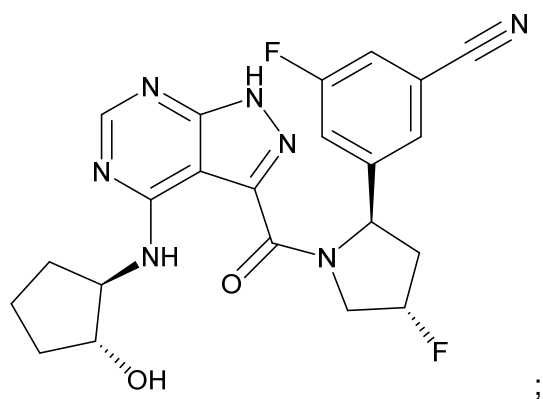


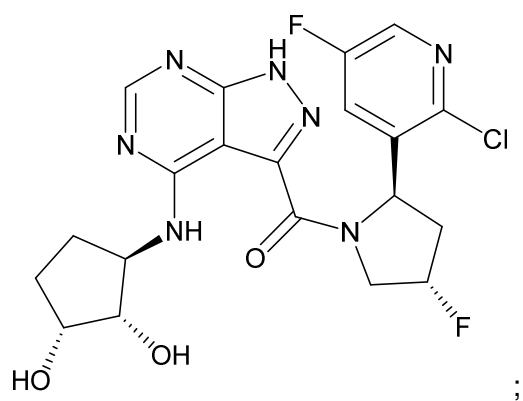
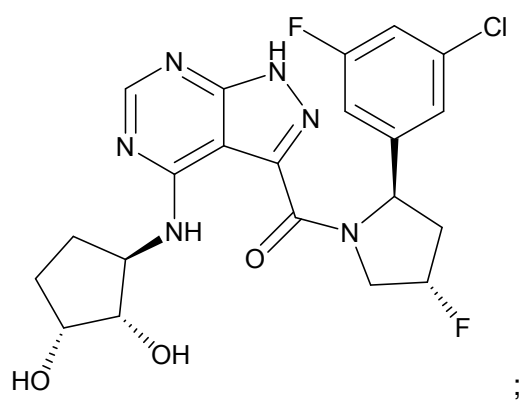
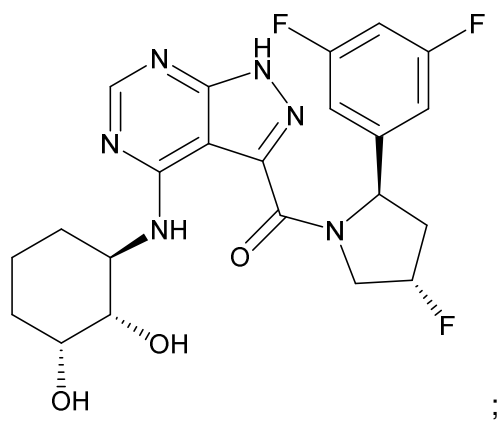
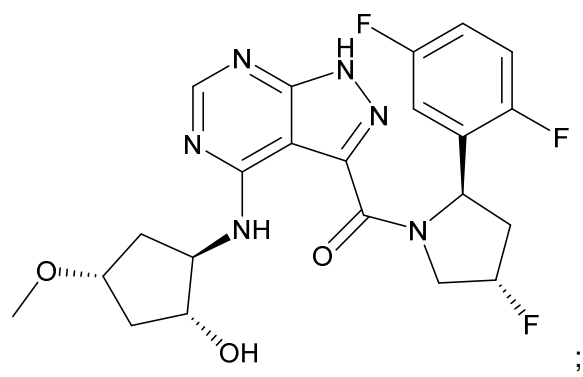


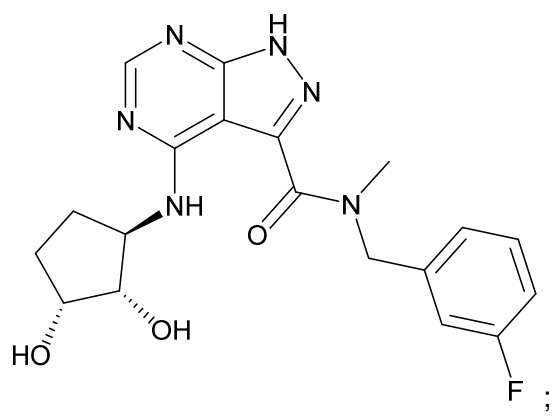
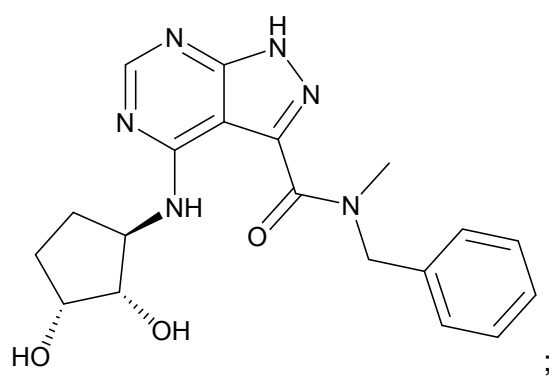
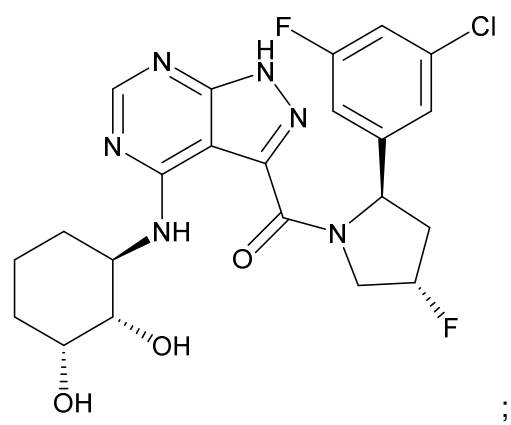
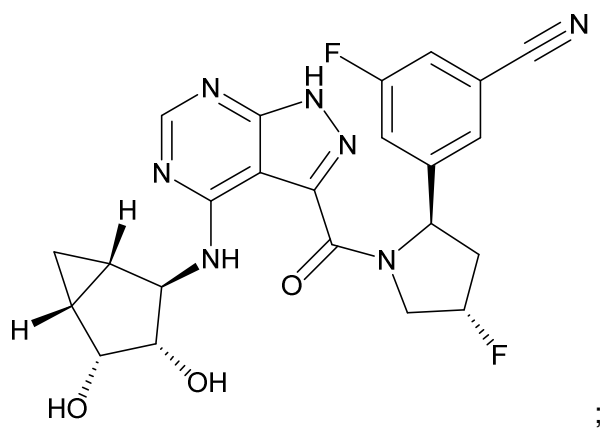


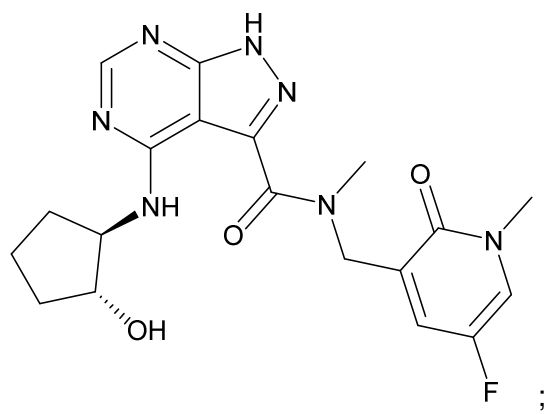
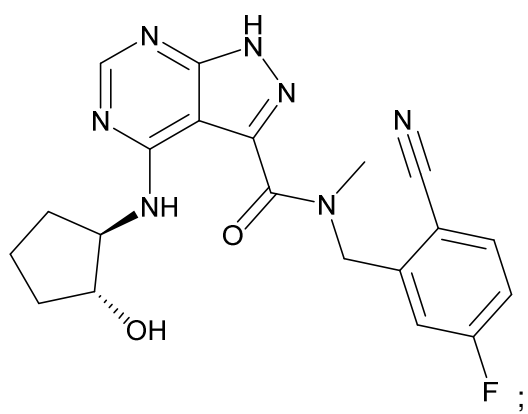
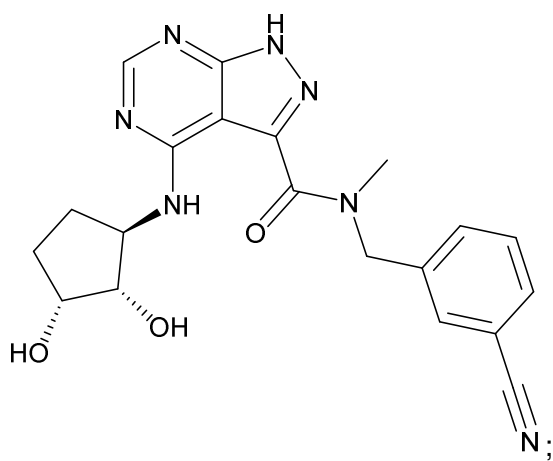
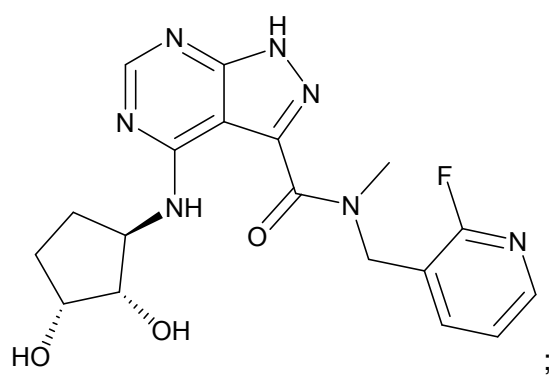


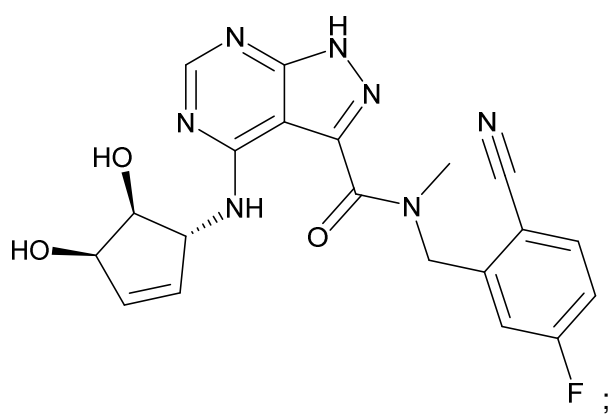
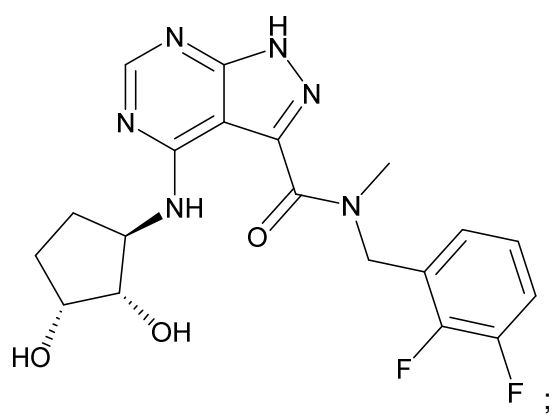
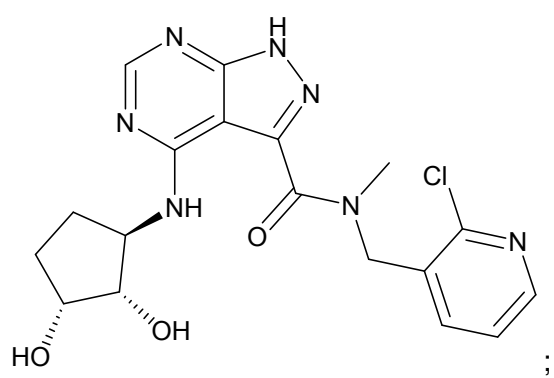
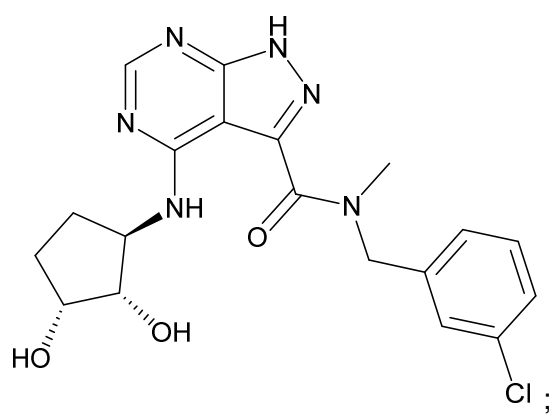


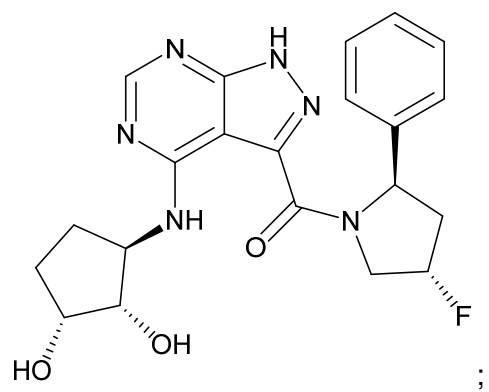
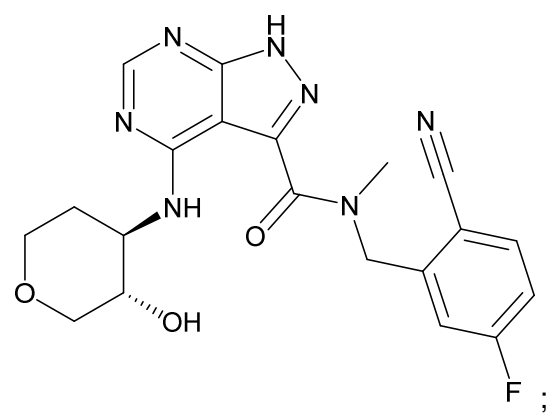
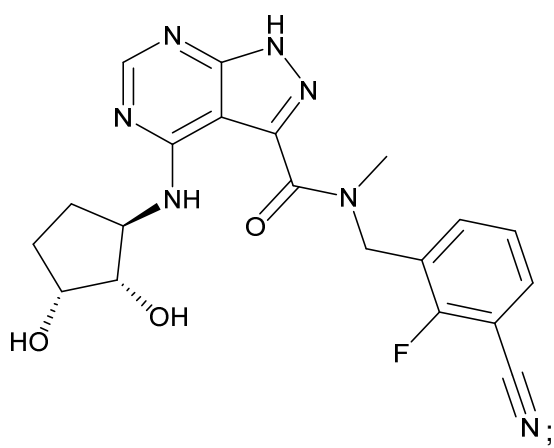
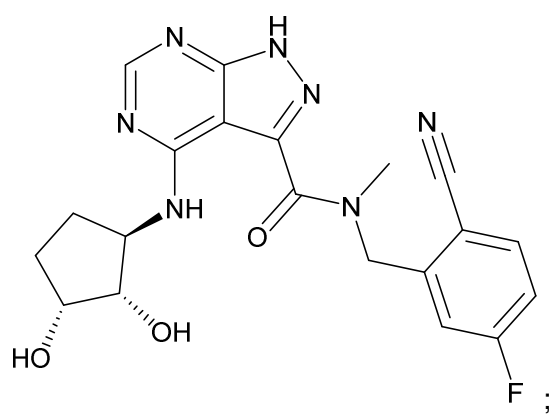


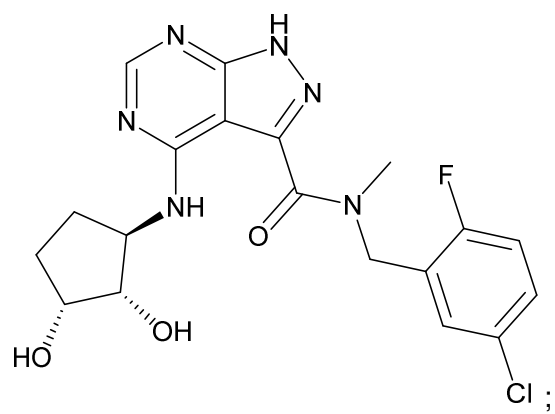
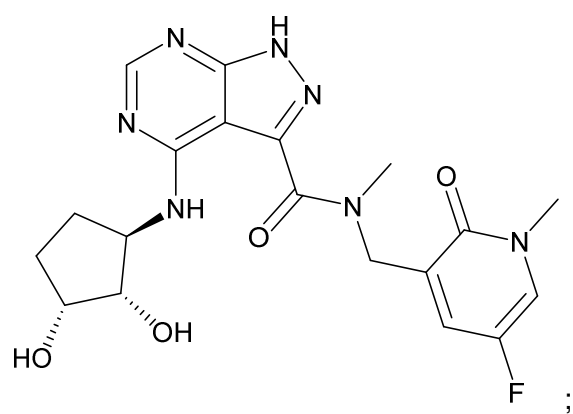
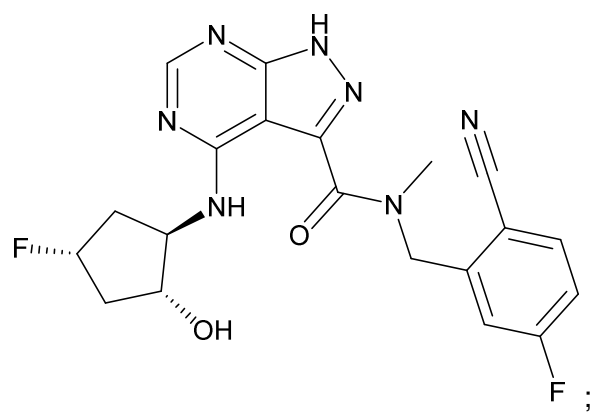
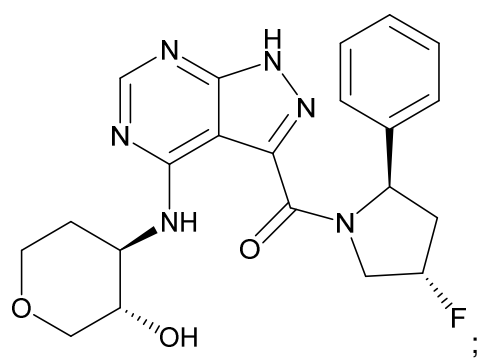


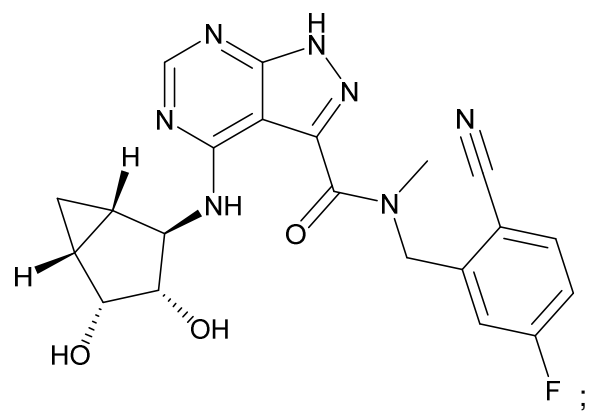
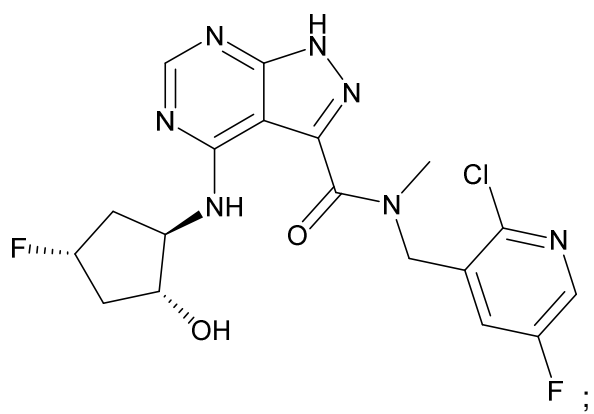
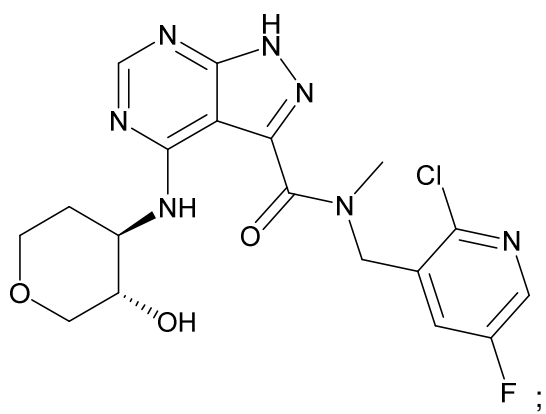
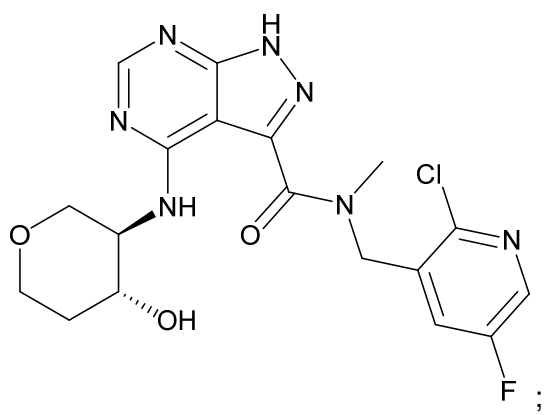


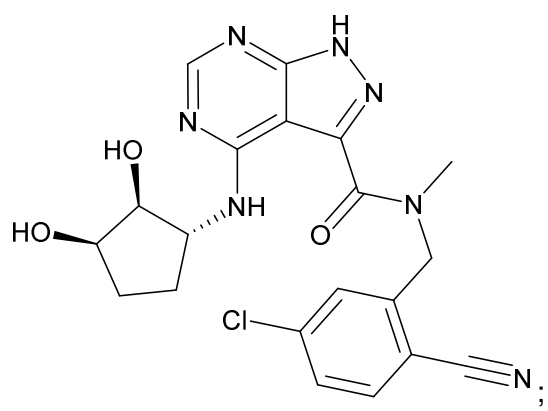
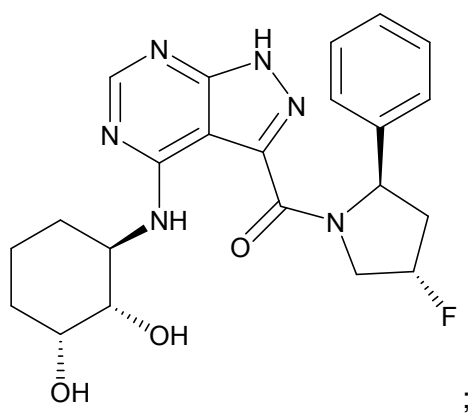
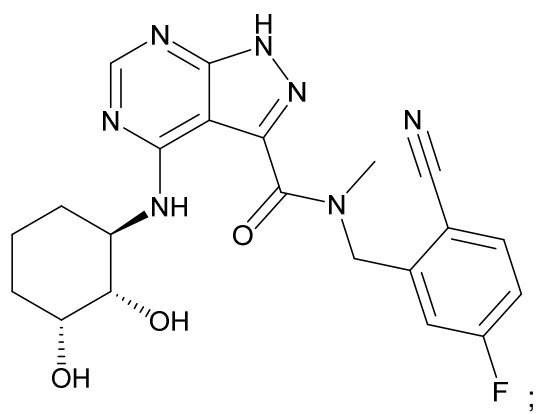
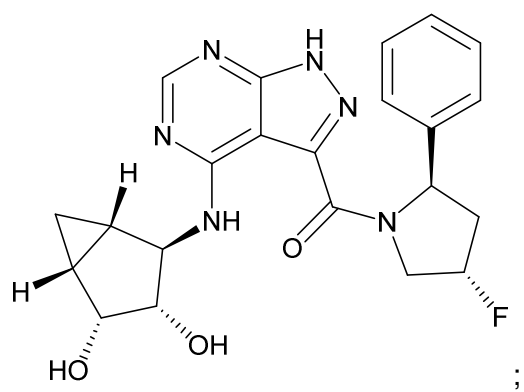


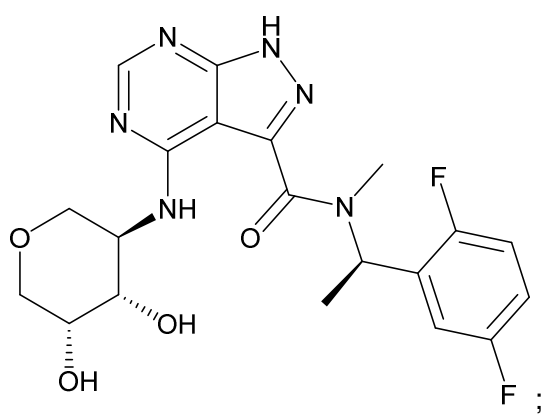
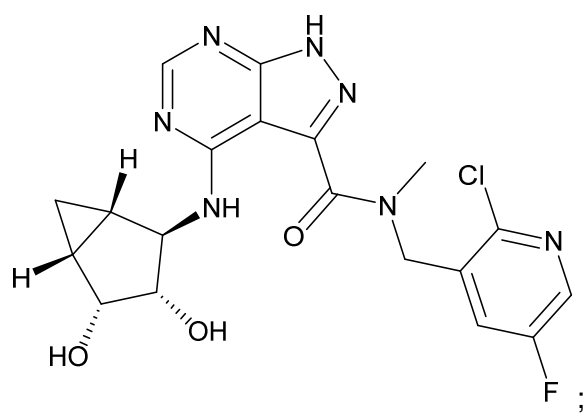
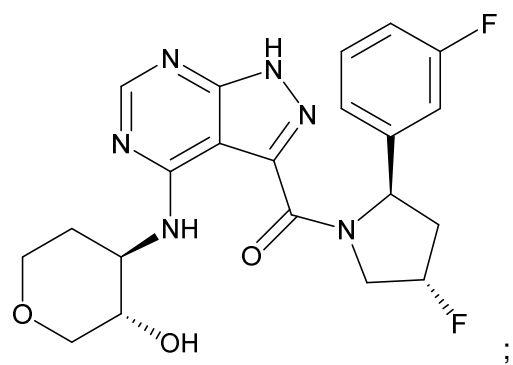
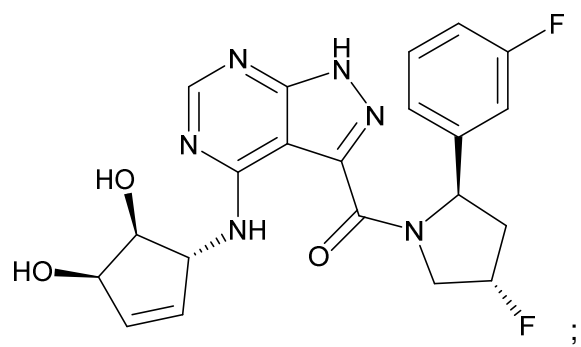


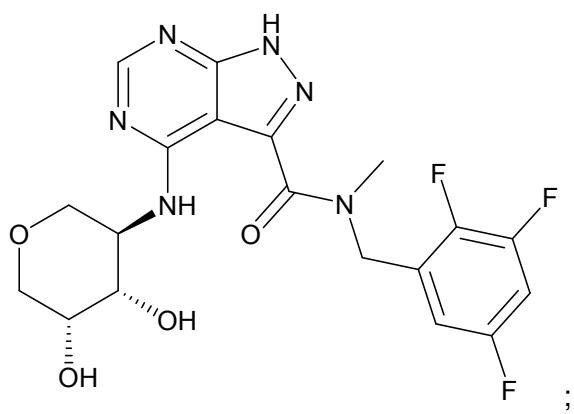
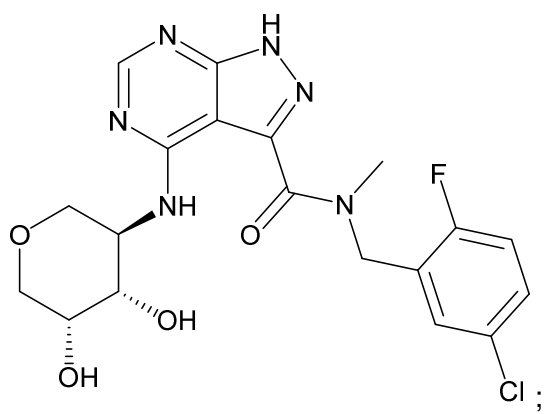
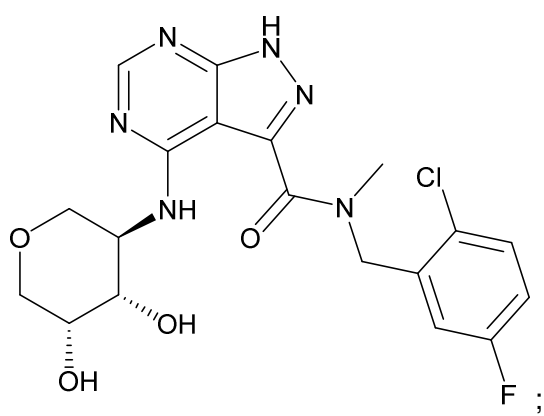
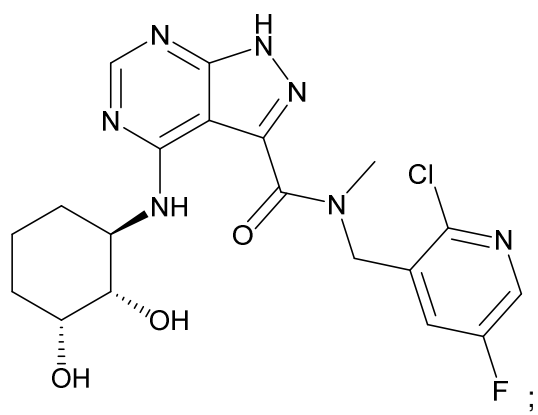


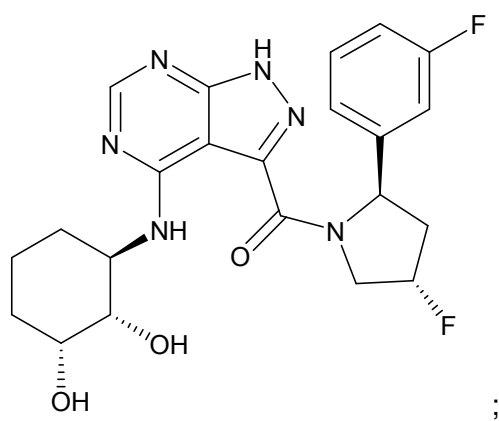
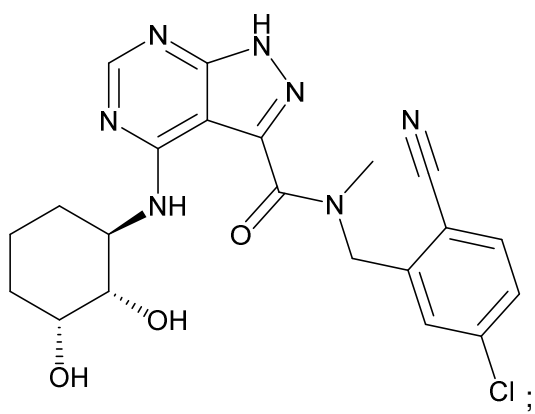
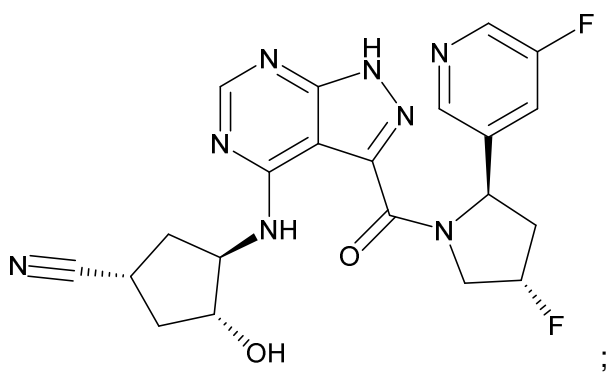
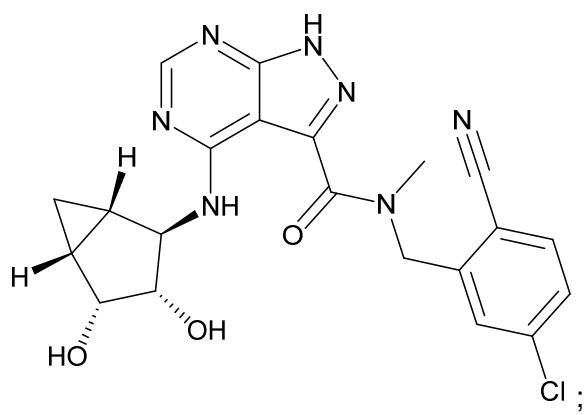


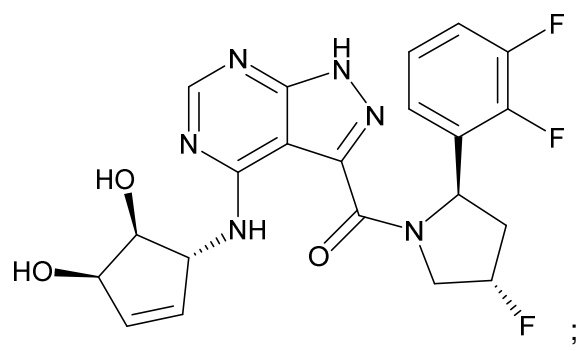
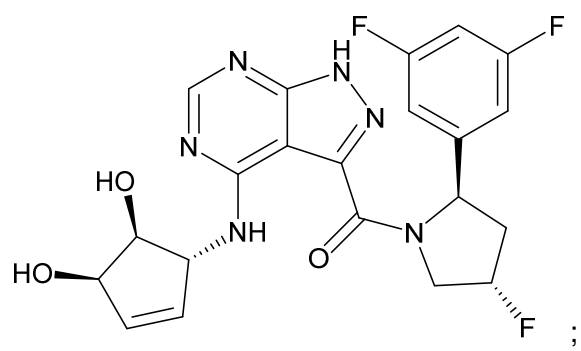
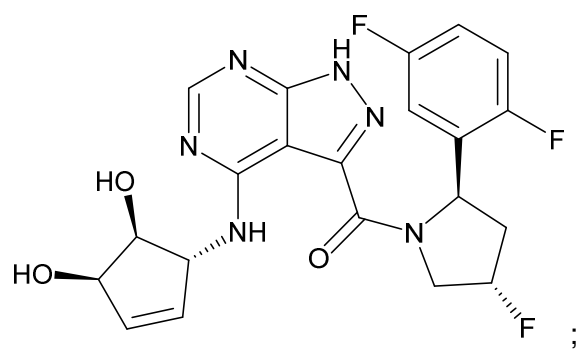
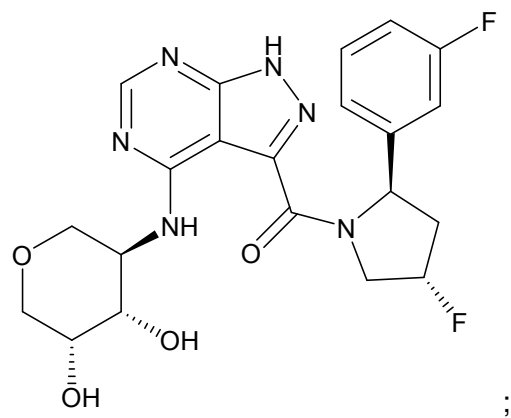


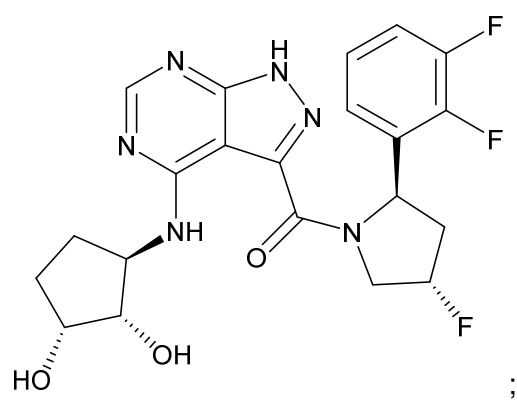
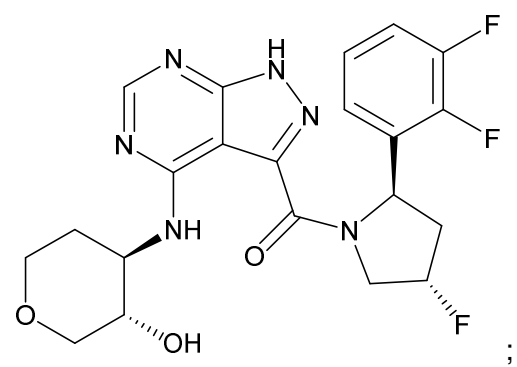
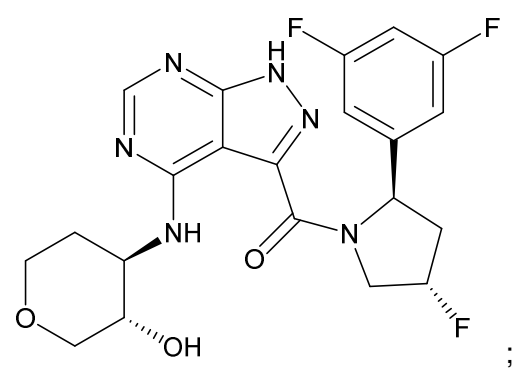
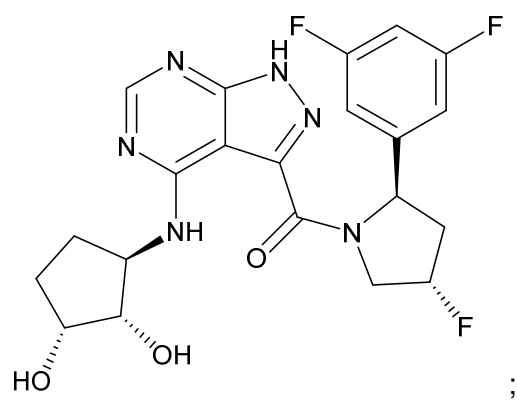


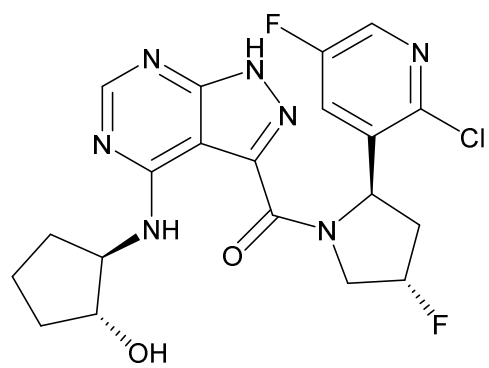




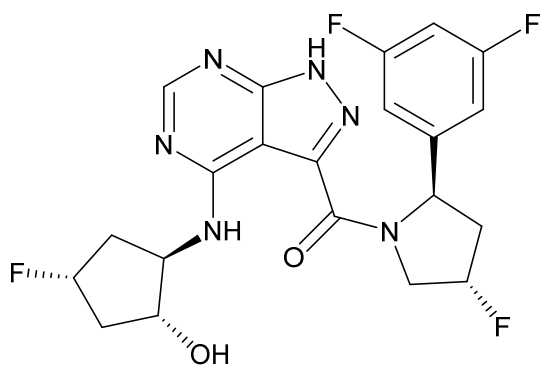




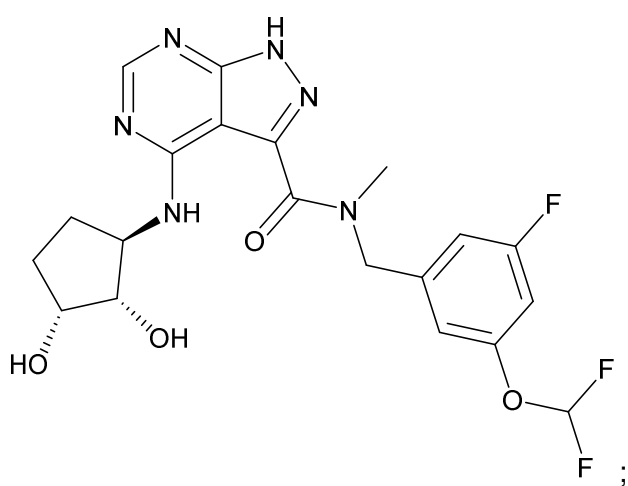




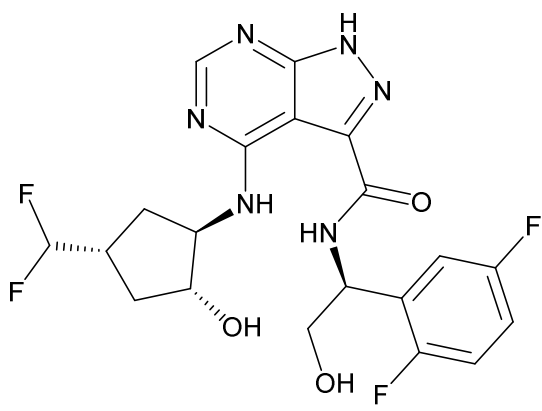
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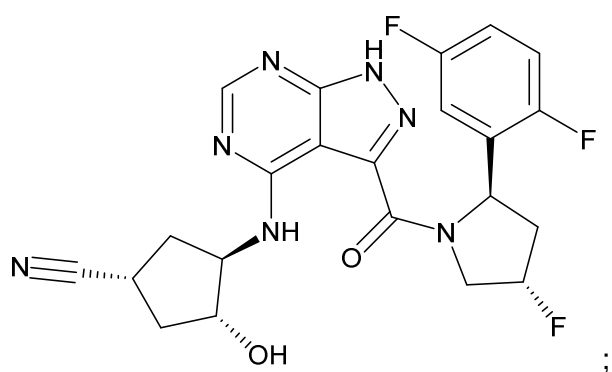
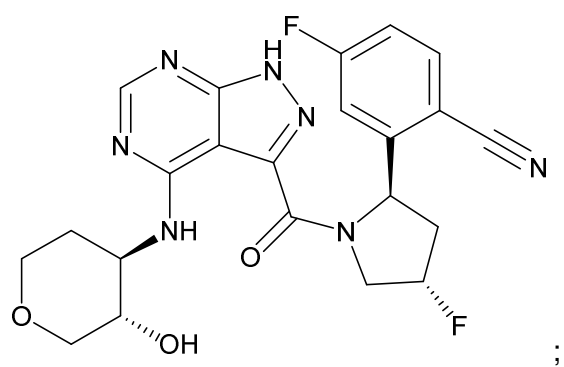
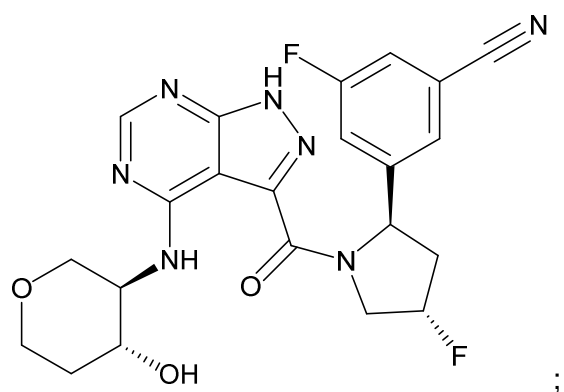
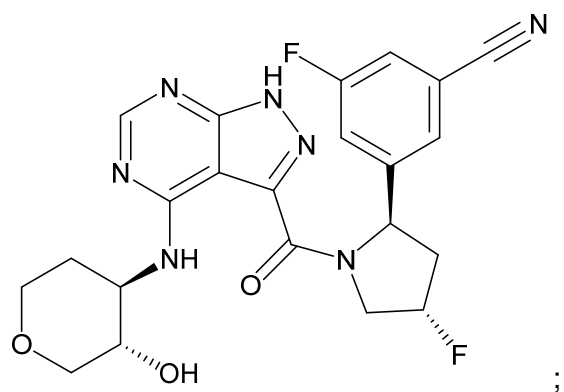
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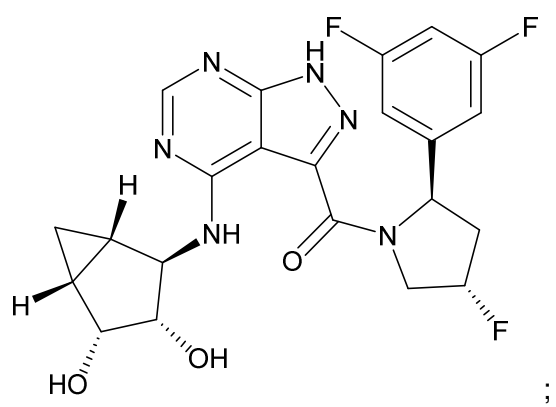
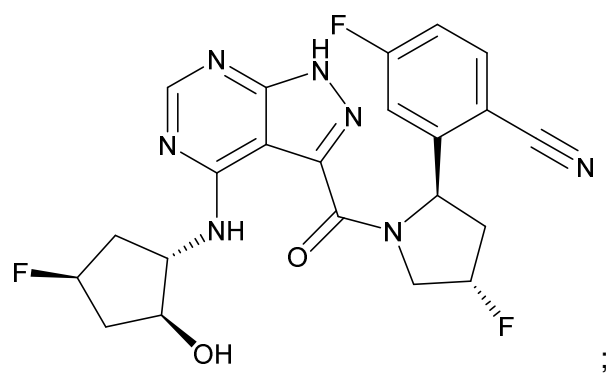
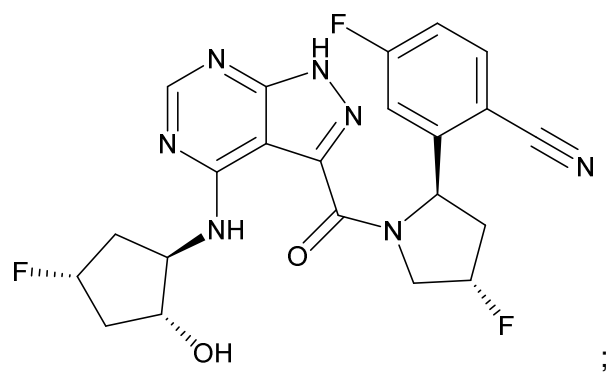
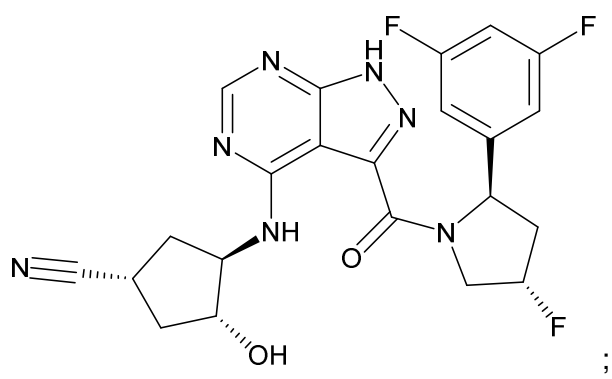


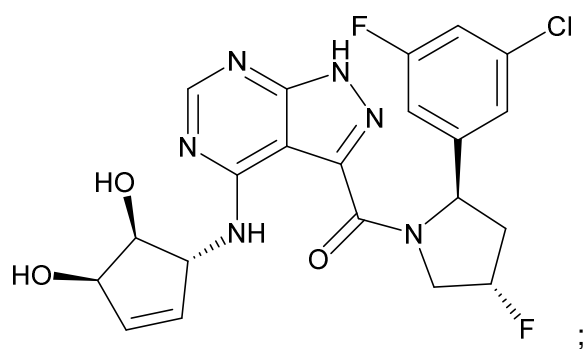
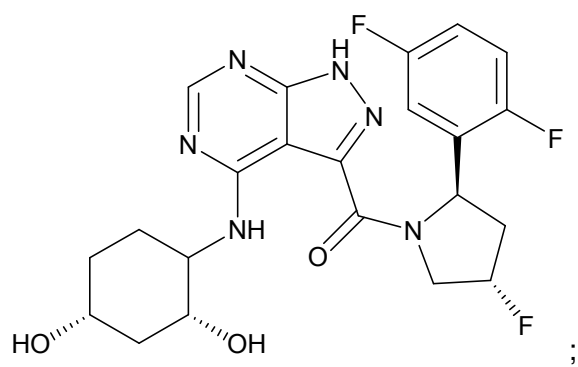
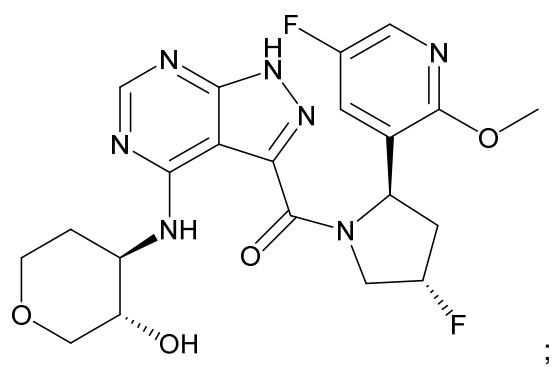
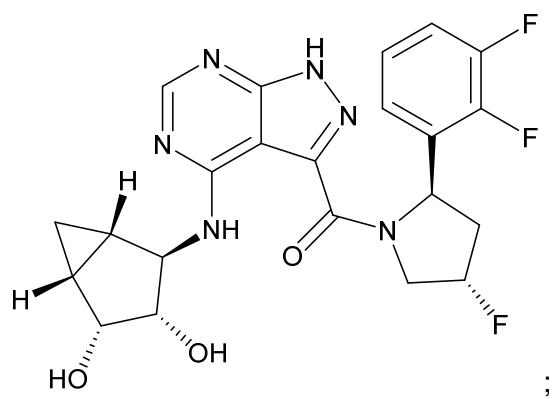
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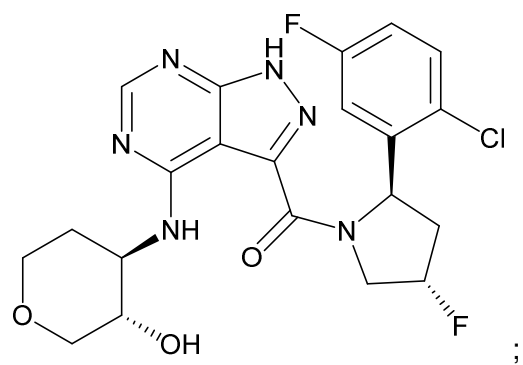
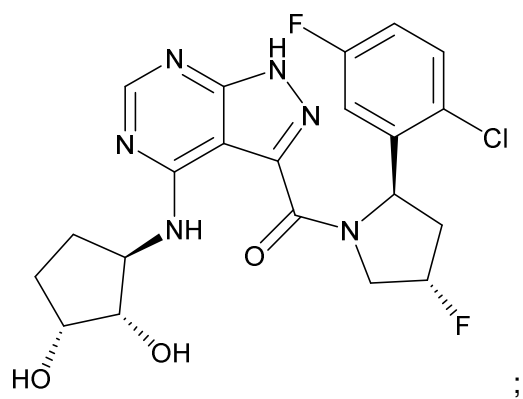
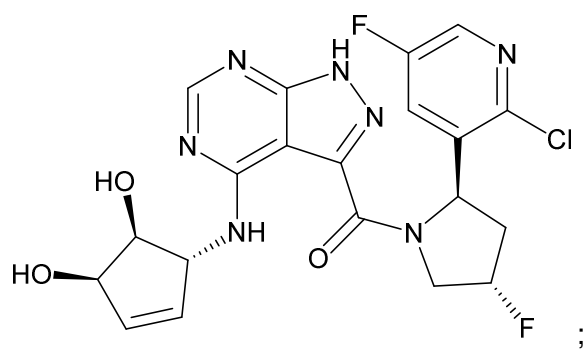
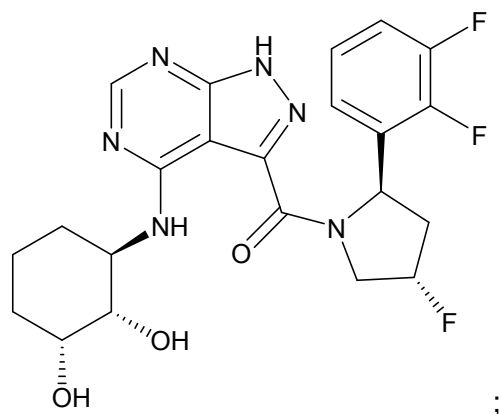


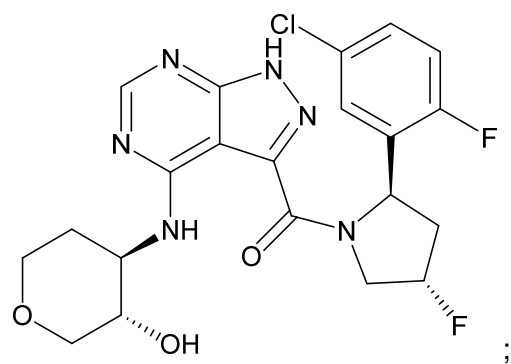
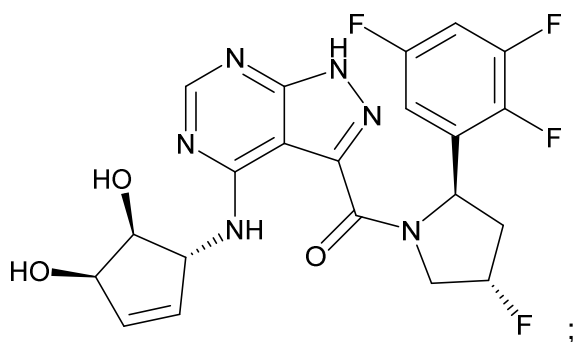
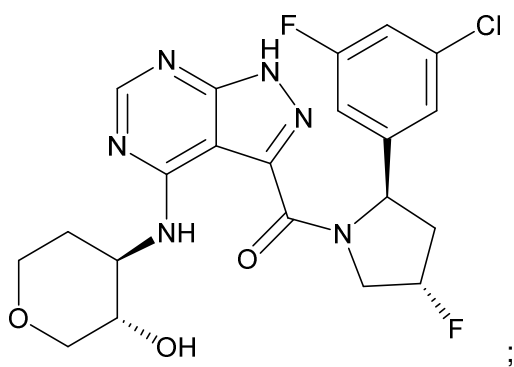
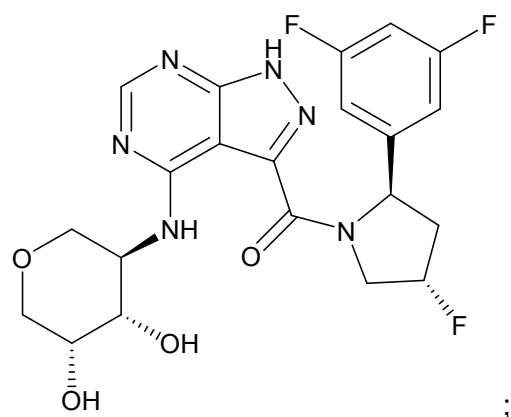
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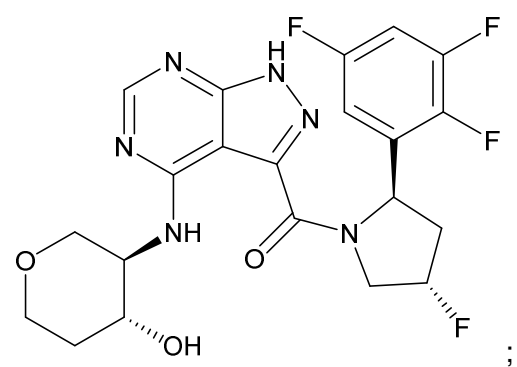
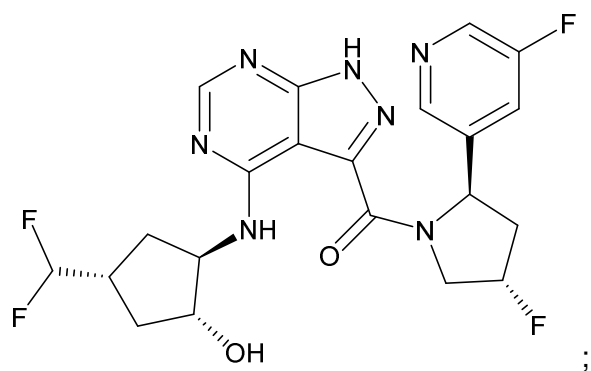
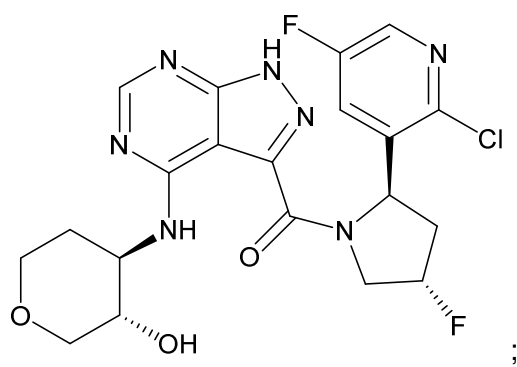
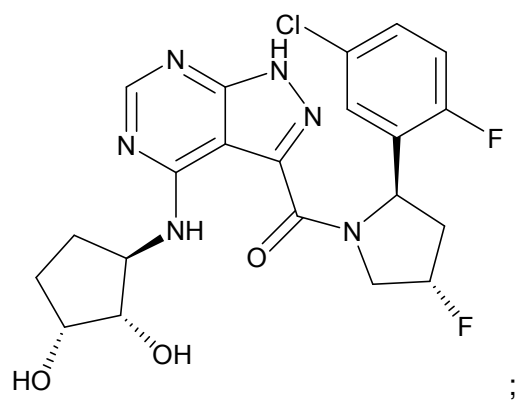


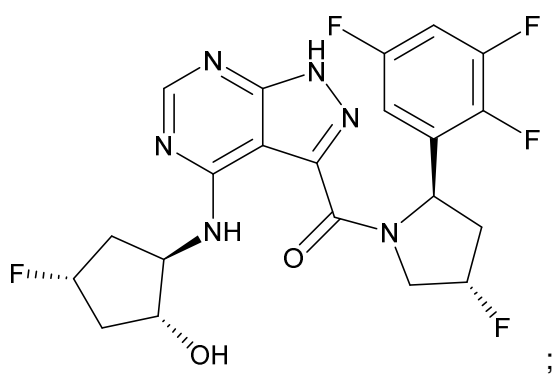
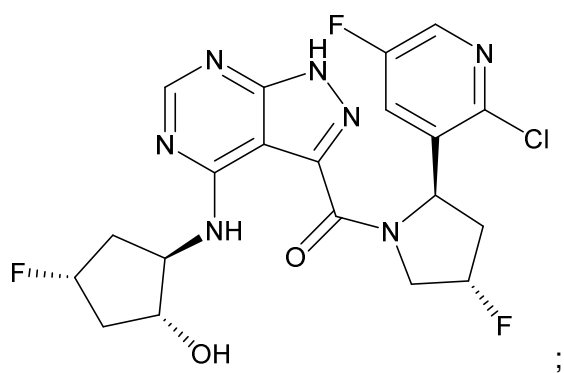
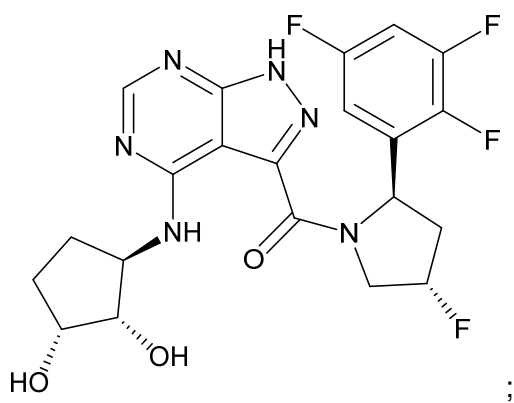
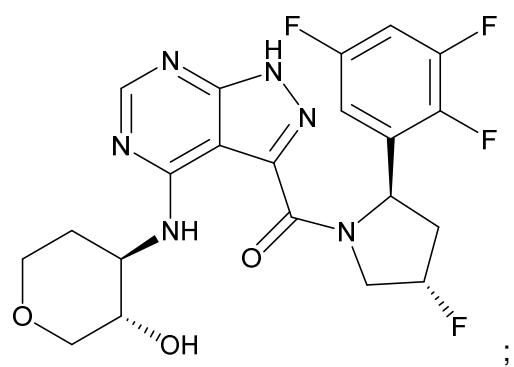


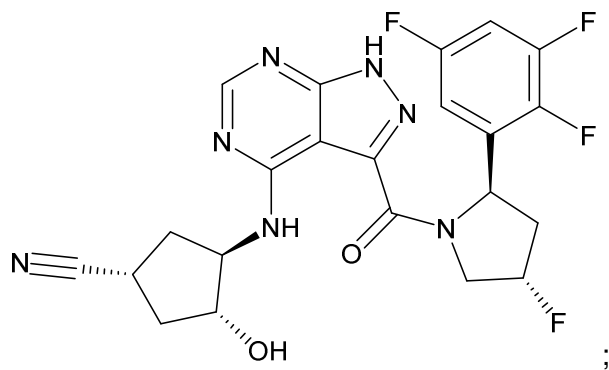
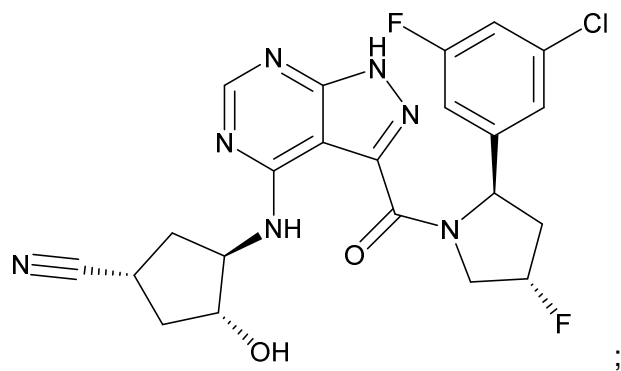
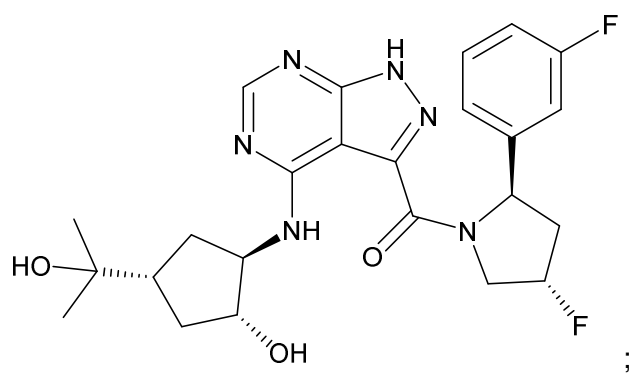
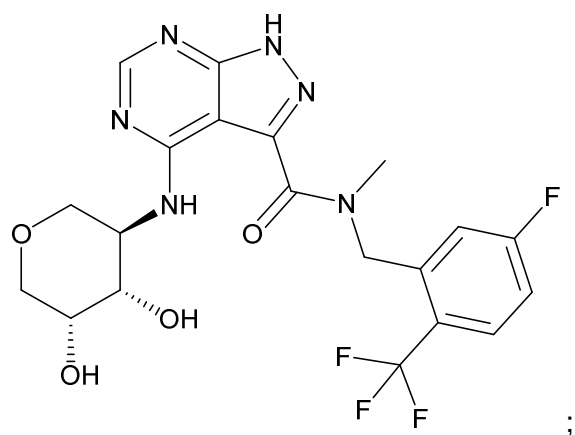


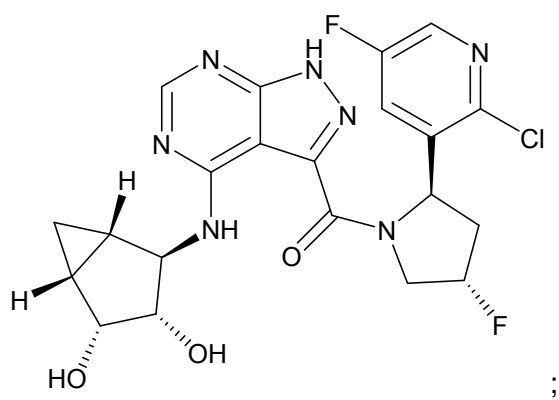
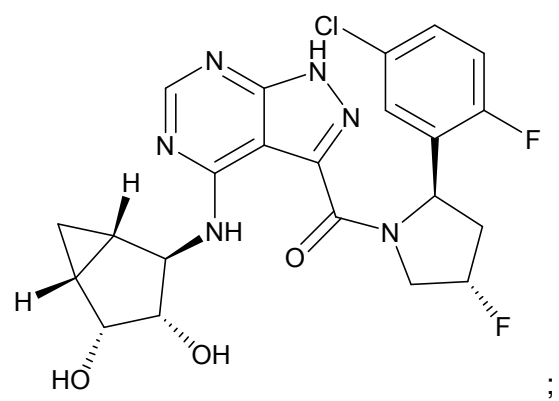
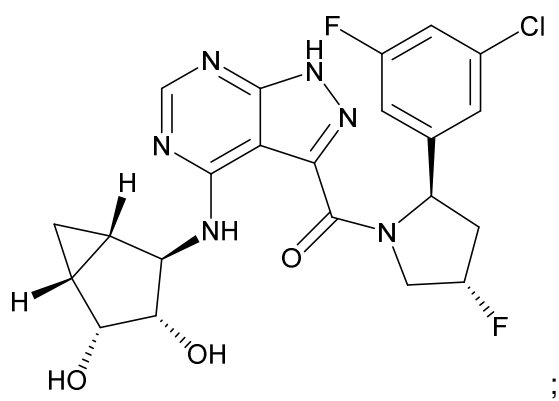
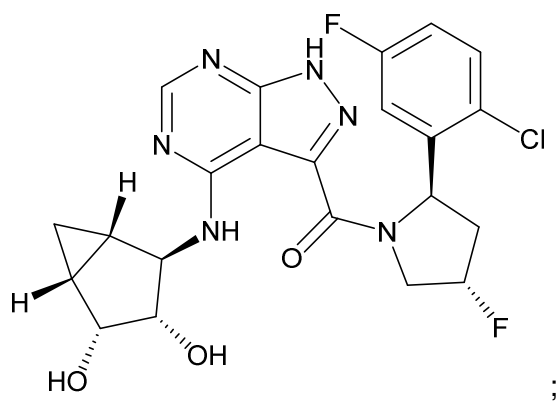


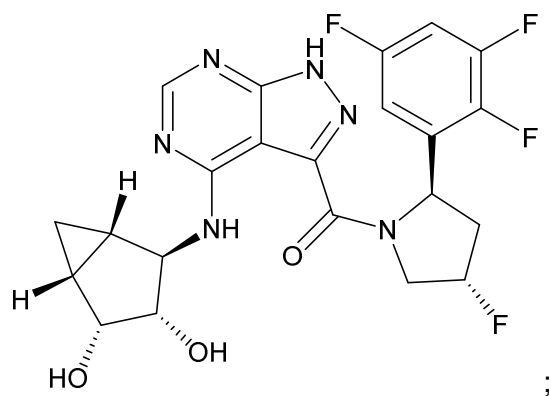
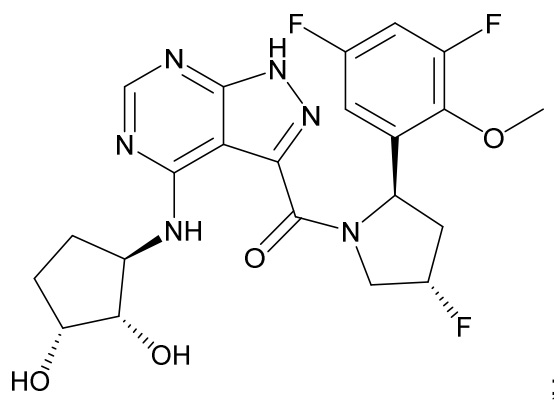
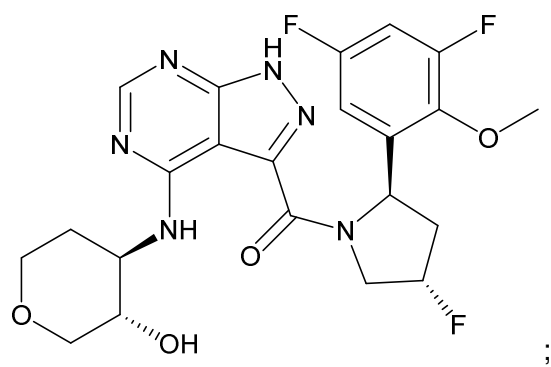
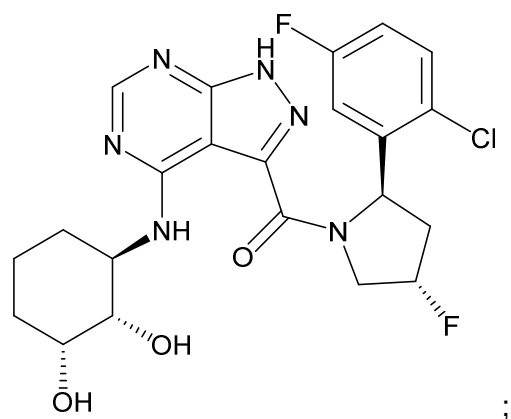


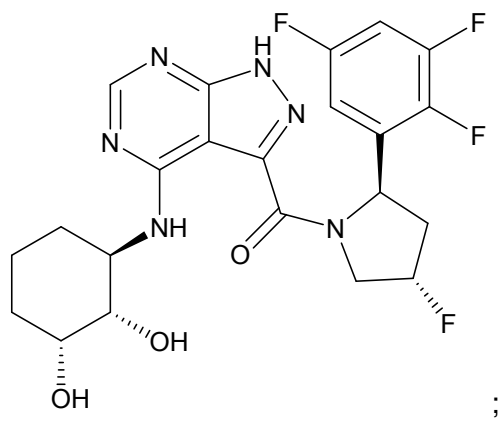
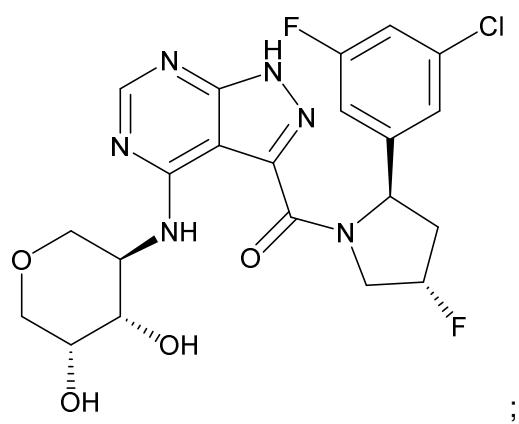
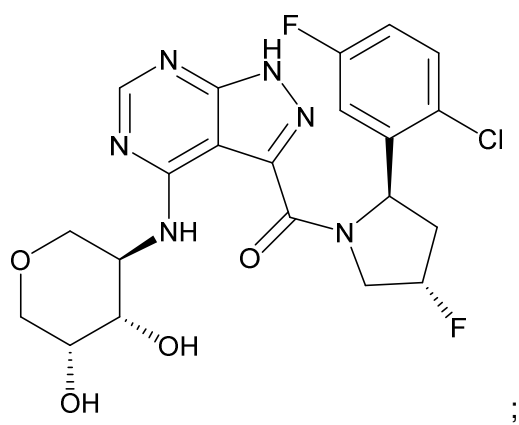
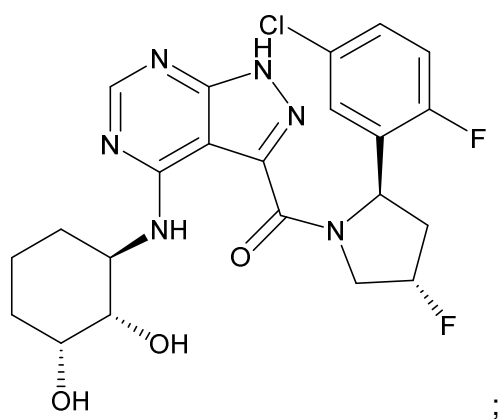


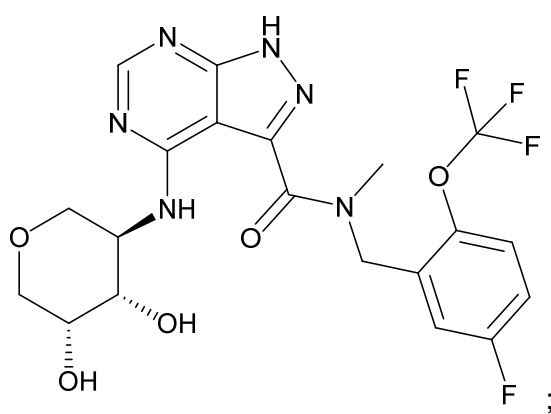
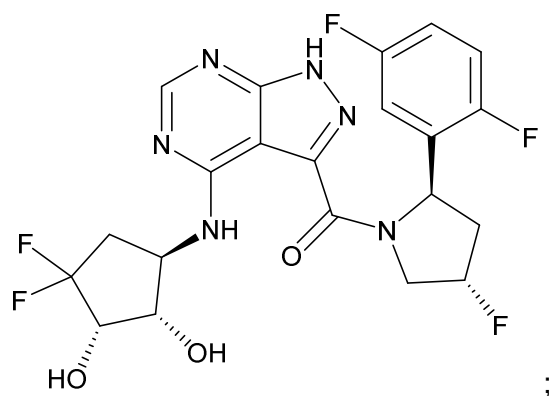
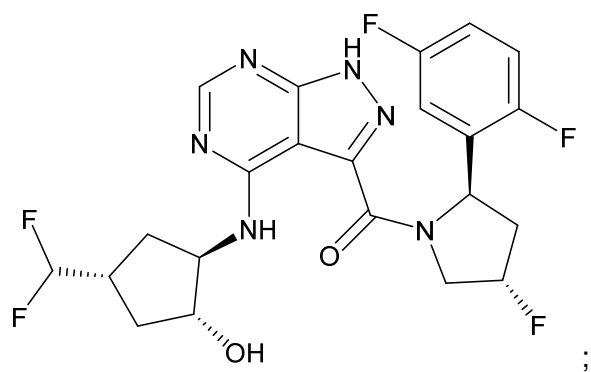
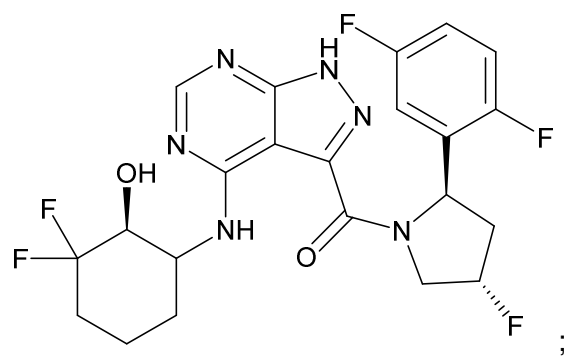


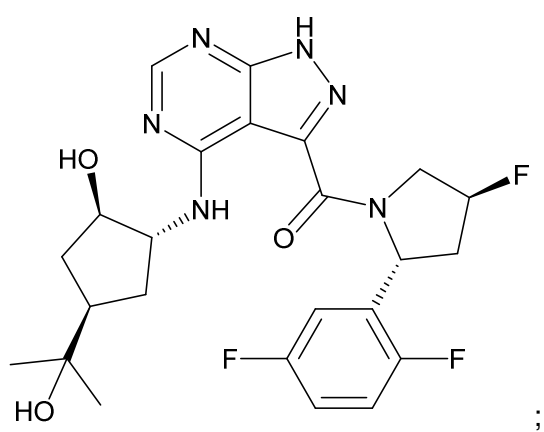
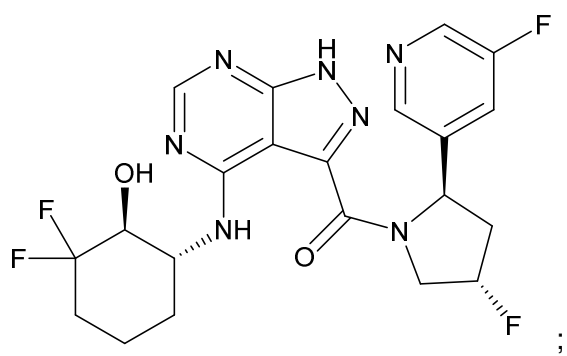
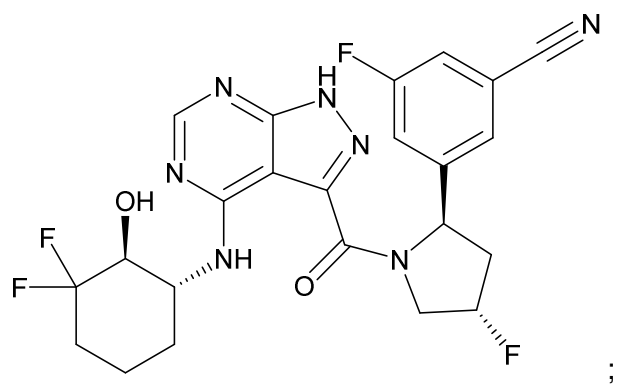
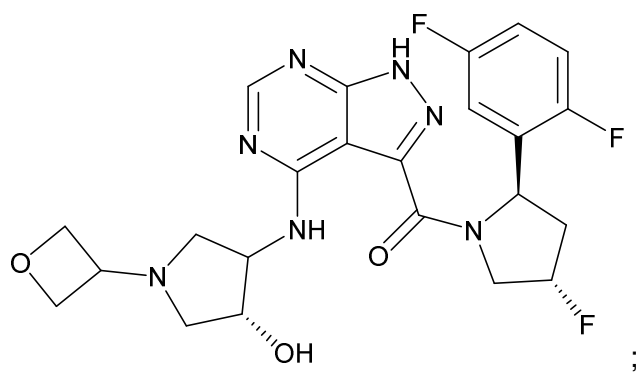


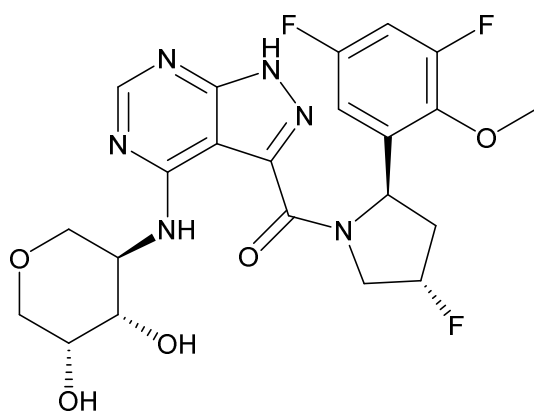
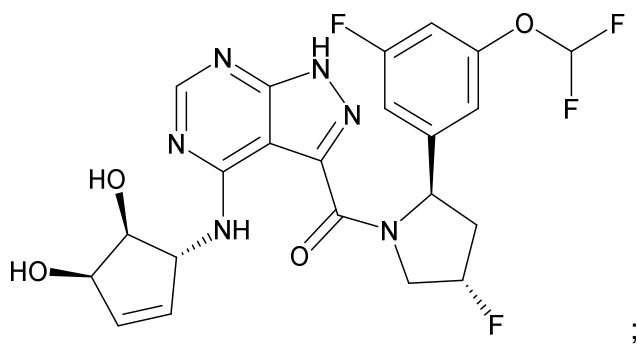
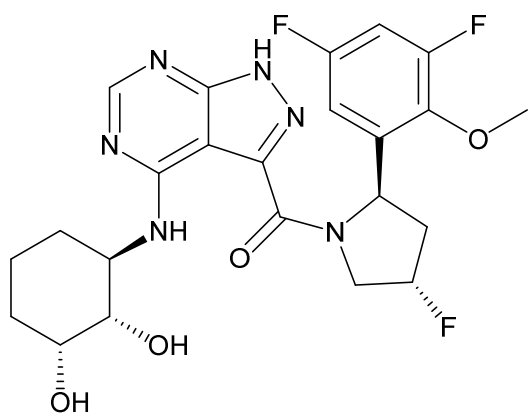
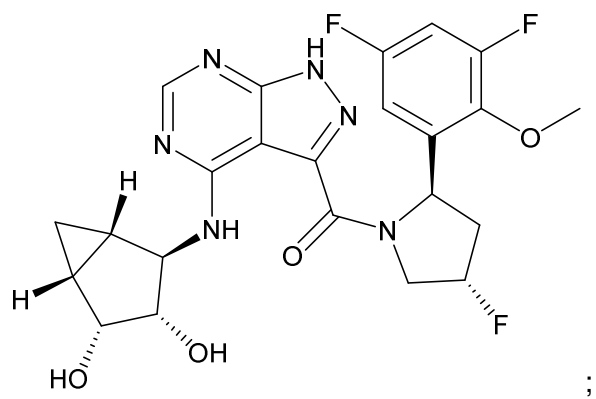


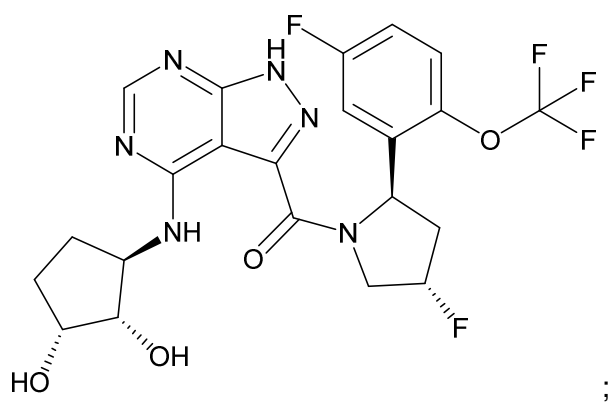
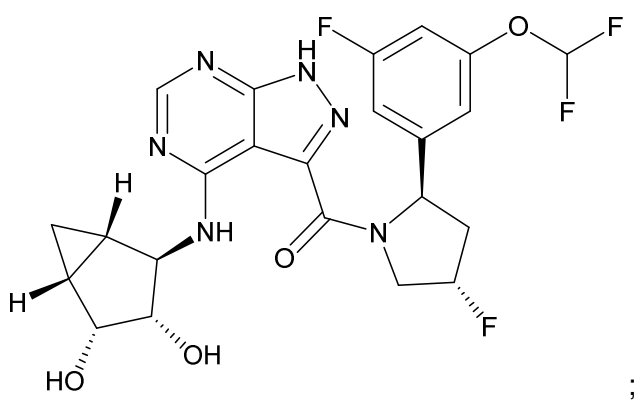
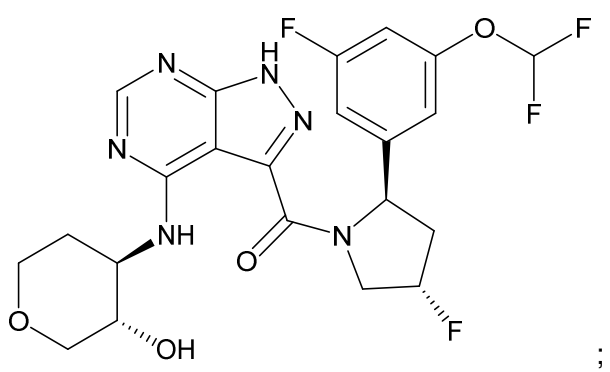
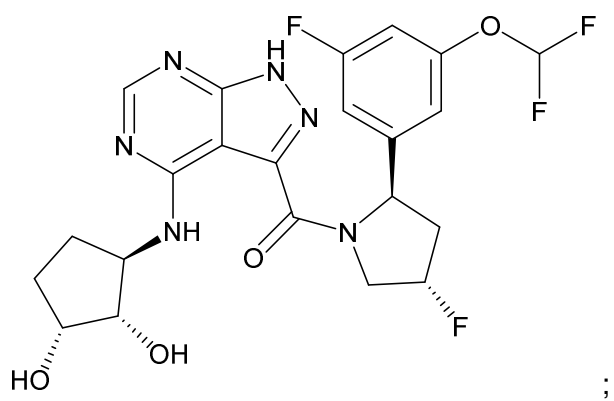


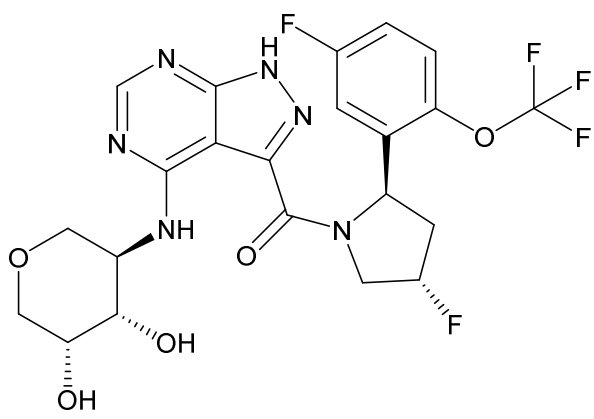
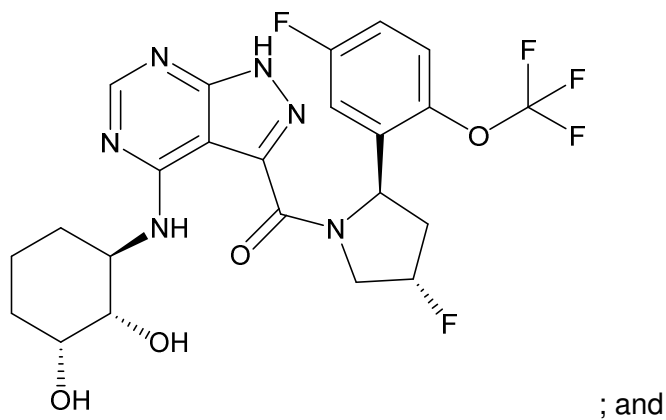
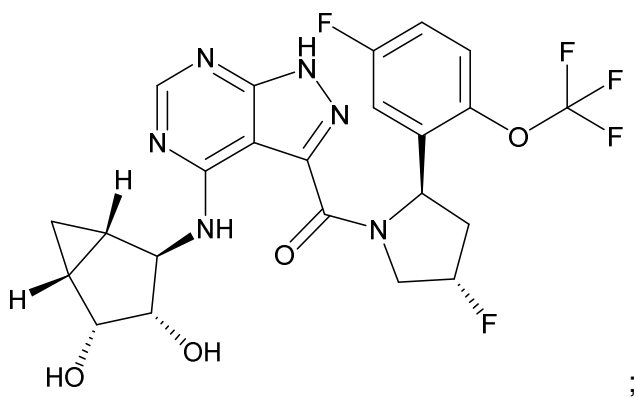
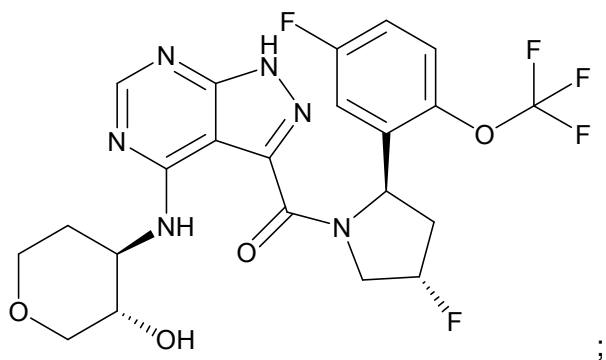










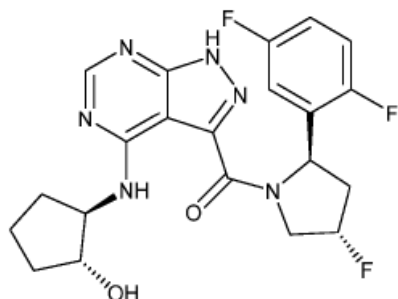


or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition comprising a pharmaceutically acceptable

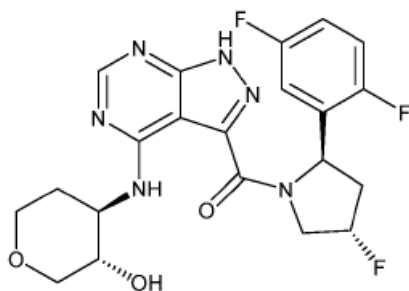
carrier and a compound of any one of claims 1 to 20 or a pharmaceutically acceptable salt thereof.

22. A compound which is



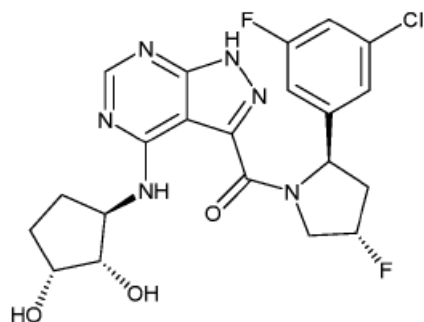
or a pharmaceutically acceptable salt thereof.

23. A compound which is



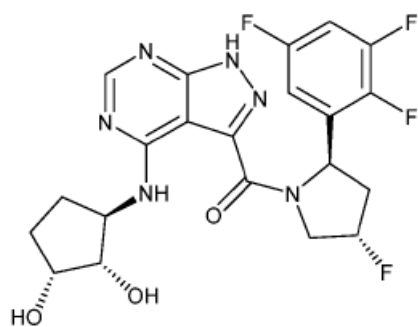
or a pharmaceutically acceptable salt thereof.

24. A compound which is



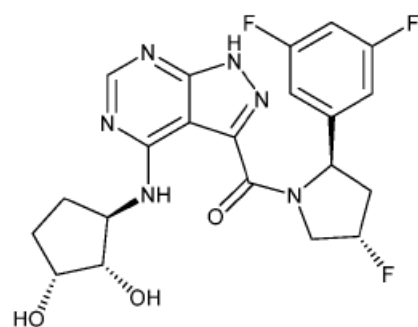
or a pharmaceutically acceptable salt thereof.

25. A compound which is



or a pharmaceutically acceptable salt thereof.

26. A compound which is



or a pharmaceutically acceptable salt thereof.