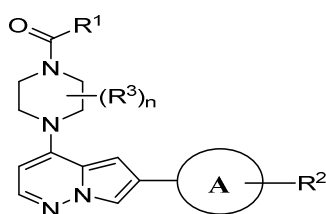


induce hepatic expression of hepcidin, which negatively regulates iron bioavailability by inactivating ferroportin. Hepcidin is transcriptionally regulated by amongst other things bone morphogenetic protein (BMP) signaling. Inhibition of BMP phosphorylation through inhibition of ALK2 can modulate BMP-mediated signaling, thus reducing hepcidin expression. Reduced hepcidin expression may be an effective strategy for the treatment of anemia of chronic disease, inflammation, or cancer.

SUMMARY

The present disclosure provides inhibitors of ALK2 and ALK2 mutants, *e.g.*, ALK2 mutants as defined herein, for example, inhibitors of structural formula (I) and formula (Ia) and pharmaceutically acceptable salts and compositions thereof. The present disclosure further provides methods of using the compounds of the disclosure, and pharmaceutically acceptable salts and compositions thereof, to inhibit the activity of ALK2 or ALK2 mutants in a cell or in a patient. The present disclosure further provides methods for using the compounds of the disclosure and pharmaceutically acceptable salts and compositions thereof, to treat a subject or patient suffering from a condition mediated by aberrant ALK2 activity, *e.g.*, at least one of fibrodysplasia ossificans progressiva (FOP) or heterotopic ossification or diffuse intrinsic pontine glioma (DIPG) or anemia of chronic disease or anemia of inflammation or anemia of cancer.

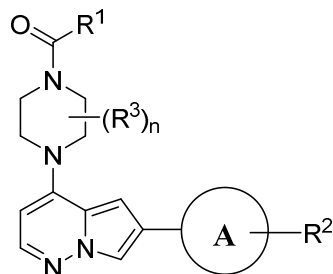
The disclosure features a compound of structural formula (I) or at least one of pharmaceutically acceptable salt thereof:



(I)

wherein each of ring A, R¹, R², R³, and n is defined as described herein.

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



(I),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is phenyl or heteroaryl, wherein ring A is optionally substituted with 1, 2, or 3

5 substituents independently selected from halo, =O,

cyano, -OR^c, -NR^dR^e, -S(O)_kR^c, -NR^cS(O)₂R^c, -S(O)₂NR^dR^e, -C(=O)OR^c, -OC(=O)OR^c, -OC(=O)
)R^c, -OC(=S)OR^c, -C(=S)OR^c, -O(C=S)R^c, -C(=O)NR^dR^e, -NR^cC(=O)R^c, -C(=S)NR^dR^e, -NR^cC(
 =S)R^c, -NR^c(C=O)OR^c, -O(C=O)NR^dR^e, -NR^c(C=S)OR^c, -O(C=S)NR^dR^e,

-NR^c(C=O)NR^dR^e, -NR^c(C=S)NR^dR^e, -C(=S)R^c, -C(=O)R^c, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆

10 heteroalkyl, carbocyclyl, (C₁-C₆-alkylene)-carbocyclyl, (C₁-C₆-heteroalkylene)-carbocyclyl,
 heterocyclyl, (C₁-C₆-alkylene)-heterocyclyl, (C₁-C₆-heteroalkylene)-heterocyclyl, aryl, (C₁-C₆-
 alkylene)-aryl, (C₁-C₆-heteroalkylene)-aryl, heteroaryl, (C₁-C₆-alkylene)-heteroaryl, and (C₁-C₆-
 heteroalkylene)-heteroaryl, wherein each of said alkyl, alkylene, heteroalkyl, heteroalkylene,
 carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more of

15 halo, OR^c, -NO₂,

cyano, -NR^cC(=O)R^c, -NR^dR^e, -S(O)_kR^c, -C(=O)OR^c, -C(=O)NR^dR^e, -C(=O)R^c, C₁-C₆ alkyl, C₁-
 C₆ haloalkyl, or C₁-C₆ heteroalkyl in addition to R²;

R¹ is selected from NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, C₁-C₆ alkyl, -O-C₁-C₆

alkyl, -C(O)-C₁-C₄ alkyl, carbocyclyl, heterocyclyl, -O-(C₀-C₄ alkylene)-carbocyclyl, -O-(C₀-C₄

20 alkylene)-heterocyclyl, -NH-(C₀-C₄ alkylene)-carbocyclyl, -NH-aryl, -NH-O-(C₁-C₄ alkyl), -S-
 heterocyclyl, -S-(C₀-C₃ alkylene)-(O-containing heterocyclyl), and -NH-(C₀-C₄

alkylene)-heterocyclyl, wherein each alkyl, alkylene, carbocyclyl, and heterocyclyl portion of R¹
 is optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, =O,

cyano, -OR^c, -NR^dR^e, -S(O)_kR^c, -NR^cS(O)₂R^c, -S(O)₂NR^dR^e, -C(=O)OR^c, -OC(=O)OR^c, -OC(=O)

R^c , $-\text{OC}(=\text{S})\text{OR}^c$, $-\text{C}(=\text{S})\text{OR}^c$, $-\text{O}(\text{C}=\text{S})\text{R}^c$, $-\text{C}(=\text{O})\text{NR}^d\text{R}^e$, $-\text{NR}^c\text{C}(=\text{O})\text{R}^c$, $-\text{C}(=\text{S})\text{NR}^d\text{R}^e$, $-\text{NR}^c\text{C}(=\text{S})\text{R}^c$, $-\text{NR}^c(\text{C}=\text{O})\text{OR}^c$, $-\text{O}(\text{C}=\text{O})\text{NR}^d\text{R}^e$, $-\text{NR}^c(\text{C}=\text{S})\text{OR}^c$, $-\text{O}(\text{C}=\text{S})\text{NR}^d\text{R}^e$, $-\text{NR}^c(\text{C}=\text{O})\text{NR}^d\text{R}^e$, $-\text{NR}^c(\text{C}=\text{S})\text{NR}^d\text{R}^e$, $-\text{C}(=\text{S})\text{R}^c$, $-\text{C}(=\text{O})\text{R}^c$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ heteroalkyl, carbocyclyl, $(\text{C}_1\text{-C}_6\text{-alkylene})\text{-carbocyclyl}$, $(\text{C}_1\text{-C}_6\text{-heteroalkylene})\text{-carbocyclyl}$, heterocyclyl,
 5 $(\text{C}_1\text{-C}_6\text{-alkylene})\text{-heterocyclyl}$, $(\text{C}_1\text{-C}_6\text{-heteroalkylene})\text{-heterocyclyl}$, aryl, $(\text{C}_1\text{-C}_6\text{-alkylene})\text{-aryl}$, $(\text{C}_1\text{-C}_6\text{-heteroalkylene})\text{-aryl}$, heteroaryl, $(\text{C}_1\text{-C}_6\text{-alkylene})\text{-heteroaryl}$, and $(\text{C}_1\text{-C}_6\text{-heteroalkylene})\text{-heteroaryl}$, wherein each of said alkyl, alkylene, heteroalkyl, heteroalkylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more of halo, OR^c , $-\text{NO}_2$,

10 cyano, $-\text{NR}^c\text{C}(=\text{O})\text{R}^c$, $-\text{NR}^d\text{R}^e$, $-\text{S}(\text{O})_k\text{R}^c$, $-\text{C}(=\text{O})\text{OR}^c$, $-\text{C}(=\text{O})\text{NR}^d\text{R}^e$, $-\text{C}(=\text{O})\text{R}^c$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, or $\text{C}_1\text{-C}_6$ heteroalkyl; or

R^1 is taken together with one R^3 to form a saturated ring fused to the piperazine ring in formula (I), and wherein the ring formed by R^1 and R^3 is optionally substituted with 1, 2, or 3 substituents independently selected from halo, $=\text{O}$,
 15 cyano, $-\text{OR}^c$, $-\text{NR}^d\text{R}^e$, $-\text{S}(\text{O})_k\text{R}^c$, $-\text{NR}^c\text{S}(\text{O})_2\text{R}^c$, $-\text{S}(\text{O})_2\text{NR}^d\text{R}^e$, $-\text{C}(=\text{O})\text{OR}^c$, $-\text{OC}(=\text{O})\text{OR}^c$, $-\text{OC}(=\text{O})\text{R}^c$, $-\text{OC}(=\text{S})\text{OR}^c$, $-\text{C}(=\text{S})\text{OR}^c$, $-\text{O}(\text{C}=\text{S})\text{R}^c$, $-\text{C}(=\text{O})\text{NR}^d\text{R}^e$, $-\text{NR}^c\text{C}(=\text{O})\text{R}^c$, $-\text{C}(=\text{S})\text{NR}^d\text{R}^e$, $-\text{NR}^c\text{C}(=\text{S})\text{R}^c$, $-\text{NR}^c(\text{C}=\text{O})\text{OR}^c$, $-\text{O}(\text{C}=\text{O})\text{NR}^d\text{R}^e$, $-\text{NR}^c(\text{C}=\text{S})\text{OR}^c$, $-\text{O}(\text{C}=\text{S})\text{NR}^d\text{R}^e$, $-\text{NR}^c(\text{C}=\text{O})\text{NR}^d\text{R}^e$, $-\text{NR}^c(\text{C}=\text{S})\text{NR}^d\text{R}^e$, $-\text{C}(=\text{S})\text{R}^c$, $-\text{C}(=\text{O})\text{R}^c$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ heteroalkyl, carbocyclyl, $(\text{C}_1\text{-C}_6\text{-alkylene})\text{-carbocyclyl}$, $(\text{C}_1\text{-C}_6\text{-heteroalkylene})\text{-carbocyclyl}$, heterocyclyl,
 20 $(\text{C}_1\text{-C}_6\text{-alkylene})\text{-heterocyclyl}$, $(\text{C}_1\text{-C}_6\text{-heteroalkylene})\text{-heterocyclyl}$, aryl, $(\text{C}_1\text{-C}_6\text{-alkylene})\text{-aryl}$, $(\text{C}_1\text{-C}_6\text{-heteroalkylene})\text{-aryl}$, heteroaryl, $(\text{C}_1\text{-C}_6\text{-alkylene})\text{-heteroaryl}$, and $(\text{C}_1\text{-C}_6\text{-heteroalkylene})\text{-heteroaryl}$, wherein each of said alkyl, alkylene, heteroalkyl, heteroalkylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more of halo, OR^c , $-\text{NO}_2$,

25 cyano, $-\text{NR}^c\text{C}(=\text{O})\text{R}^c$, $-\text{NR}^d\text{R}^e$, $-\text{S}(\text{O})_k\text{R}^c$, $-\text{C}(=\text{O})\text{OR}^c$, $-\text{C}(=\text{O})\text{NR}^d\text{R}^e$, $-\text{C}(=\text{O})\text{R}^c$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, or $\text{C}_1\text{-C}_6$ heteroalkyl;

if ring A is phenyl, then R^2 is selected from halo, $\text{C}_1\text{-C}_6$ alkyl, heterocyclyl, cycloalkyl, $-\text{NH}(\text{C}_0\text{-C}_4\text{ alkylene})\text{-heterocyclyl}$, $-(\text{C}_1\text{-C}_4\text{ alkylene})\text{-heterocyclyl}$, $-(\text{C}_1\text{-C}_4\text{ alkylene})\text{-NH-heterocyclyl}$, and $-\text{O}(\text{C}_0\text{-C}_4\text{ alkylene})\text{-heterocyclyl}$, wherein any heterocyclyl,
 30 cycloalkyl, alkyl, or alkylene portion of R^2 is optionally substituted with 1, 2, 3, or 4 substituents

independently selected from halo, =O,

cyano, -OR^c, -NR^dR^e, -S(O)_kR^c, -NR^cS(O)₂R^c, -S(O)₂NR^dR^e, -C(=O)OR^c, -OC(=O)OR^c, -OC(=O)R^c, -OC(=S)OR^c, -C(=S)OR^c, -O(C=S)R^c, -C(=O)NR^dR^e, -NR^cC(=O)R^c, -C(=S)NR^dR^e, -NR^cC(=S)R^c, -NR^c(C=O)OR^c, -O(C=O)NR^dR^e, -NR^c(C=S)OR^c, -O(C=S)NR^dR^e, -NR^c(C=O)NR^dR^e, -NR^c(C=S)NR^dR^e, -C(=S)R^c, -C(=O)R^c, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, carbocyclyl, (C₁-C₆-alkylene)-carbocyclyl, (C₁-C₆-heteroalkylene)-carbocyclyl, heterocyclyl, (C₁-C₆-alkylene)-heterocyclyl, (C₁-C₆-heteroalkylene)-heterocyclyl, aryl, (C₁-C₆-alkylene)-aryl, (C₁-C₆-heteroalkylene)-aryl, heteroaryl, (C₁-C₆-alkylene)-heteroaryl, and (C₁-C₆-

heteroalkylene)-heteroaryl, wherein each of said alkyl, alkylene, heteroalkyl, heteroalkylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more of halo, OR^c, -NO₂,

cyano, -NR^cC(=O)R^c, -NR^dR^e, -S(O)_kR^c, -C(=O)OR^c, -C(=O)NR^dR^e, -C(=O)R^c, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ heteroalkyl; or R² is taken together with any ring atom in ring A to form a cycloalkyl or saturated heterocyclyl ring that is fused to ring A, and wherein the ring formed by

R² and the ring atom in ring A is optionally substituted with 1, 2, or 3 substituents independently selected from halo, =O,

cyano, -OR^c, -NR^dR^e, -S(O)_kR^c, -NR^cS(O)₂R^c, -S(O)₂NR^dR^e, -C(=O)OR^c, -OC(=O)OR^c, -OC(=O)R^c, -OC(=S)OR^c, -C(=S)OR^c, -O(C=S)R^c, -C(=O)NR^dR^e, -NR^cC(=O)R^c, -C(=S)NR^dR^e, -NR^cC(=S)R^c, -NR^c(C=O)OR^c, -O(C=O)NR^dR^e, -NR^c(C=S)OR^c, -O(C=S)NR^dR^e,

-NR^c(C=O)NR^dR^e, -NR^c(C=S)NR^dR^e, -C(=S)R^c, -C(=O)R^c, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, carbocyclyl, (C₁-C₆-alkylene)-carbocyclyl, (C₁-C₆-heteroalkylene)-carbocyclyl, heterocyclyl, (C₁-C₆-alkylene)-heterocyclyl, (C₁-C₆-heteroalkylene)-heterocyclyl, aryl, (C₁-C₆-alkylene)-aryl, (C₁-C₆-heteroalkylene)-aryl, heteroaryl, (C₁-C₆-alkylene)-heteroaryl, and (C₁-C₆-heteroalkylene)-heteroaryl, wherein each of said alkyl, alkylene, heteroalkyl, heteroalkylene,

carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more of halo, OR^c, -NO₂,

cyano, -NR^cC(=O)R^c, -NR^dR^e, -S(O)_kR^c, -C(=O)OR^c, -C(=O)NR^dR^e, -C(=O)R^c, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ heteroalkyl;

if ring A is heteroaryl, then R² is selected from halo, C₁-C₆ alkyl, heterocyclyl,

cycloalkyl, -NH-(C₀-C₄ alkylene)-heterocyclyl, -(C₁-C₄ alkylene)-heterocyclyl, -(C₁-C₄

alkylene)-NH-heterocyclyl, and -O-(C₀-C₄ alkylene)-heterocyclyl, wherein any heterocyclyl, cycloalkyl, alkyl, or alkylene portion of R² is optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, =O,

cyano, -OR^c, -NR^dR^e, -S(O)_kR^c, -NR^cS(O)₂R^c, -S(O)₂NR^dR^e, -C(=O)OR^c, -OC(=O)OR^c, -OC(=O)R^c, -OC(=S)OR^c, -C(=S)OR^c, -O(C=S)R^c, -C(=O)NR^dR^e, -NR^cC(=O)R^c, -C(=S)NR^dR^e, -NR^cC(=S)R^c, -NR^c(C=O)OR^c, -O(C=O)NR^dR^e, -NR^c(C=S)OR^c, -O(C=S)NR^dR^e, -NR^c(C=O)NR^dR^e, -NR^c(C=S)NR^dR^e, -C(=S)R^c, -C(=O)R^c, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, carbocyclyl, (C₁-C₆-alkylene)-carbocyclyl, (C₁-C₆-heteroalkylene)-carbocyclyl, heterocyclyl, (C₁-C₆-alkylene)-heterocyclyl, (C₁-C₆-heteroalkylene)-heterocyclyl, aryl, (C₁-C₆-alkylene)-aryl, (C₁-C₆-heteroalkylene)-aryl, heteroaryl, (C₁-C₆-alkylene)-heteroaryl, and (C₁-C₆-heteroalkylene)-heteroaryl, wherein each of said alkyl, alkylene, heteroalkyl, heteroalkylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more of halo, OR^c, -NO₂,

cyano, -NR^cC(=O)R^c, -NR^dR^e, -S(O)_kR^c, -C(=O)OR^c, -C(=O)NR^dR^e, -C(=O)R^c, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ heteroalkyl; or

R² is taken together with any saturated ring atom in ring A to form a cycloalkyl or saturated heterocyclyl ring that is fused, spirofused, or bridged to ring A, and wherein the ring formed by R² and the ring atom in ring A is optionally substituted with 1, 2, or 3 substituents independently selected from halo, =O,

cyano, -OR^c, -NR^dR^e, -S(O)_kR^c, -NR^cS(O)₂R^c, -S(O)₂NR^dR^e, -C(=O)OR^c, -OC(=O)OR^c, -OC(=O)R^c, -OC(=S)OR^c, -C(=S)OR^c, -O(C=S)R^c, -C(=O)NR^dR^e, -NR^cC(=O)R^c, -C(=S)NR^dR^e, -NR^cC(=S)R^c, -NR^c(C=O)OR^c, -O(C=O)NR^dR^e, -NR^c(C=S)OR^c, -O(C=S)NR^dR^e, -NR^c(C=O)NR^dR^e, -NR^c(C=S)NR^dR^e, -C(=S)R^c, -C(=O)R^c, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, carbocyclyl, (C₁-C₆-alkylene)-carbocyclyl, (C₁-C₆-heteroalkylene)-carbocyclyl, heterocyclyl, (C₁-C₆-alkylene)-heterocyclyl, (C₁-C₆-heteroalkylene)-heterocyclyl, aryl, (C₁-C₆-alkylene)-aryl, (C₁-C₆-heteroalkylene)-aryl, heteroaryl, (C₁-C₆-alkylene)-heteroaryl, and (C₁-C₆-heteroalkylene)-heteroaryl, wherein each of said alkyl, alkylene, heteroalkyl, heteroalkylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more of halo, OR^c, -NO₂,

cyano, -NR^cC(=O)R^c, -NR^dR^e, -S(O)_kR^c, -C(=O)OR^c, -C(=O)NR^dR^e, -C(=O)R^c, C₁-C₆ alkyl, C₁-

C₆ haloalkyl, or C₁-C₆ heteroalkyl;

each R³ is independently selected from C₁-C₄ alkyl and C₁-C₄ haloalkyl;

each R^c is selected from hydrogen, hydroxy, C₁-C₆ alkyl, C₁-C₆ heteroalkyl, carbocyclyl, (C₁-C₆-alkylene)-carbocyclyl, (C₁-C₆-heteroalkylene)-carbocyclyl, heterocyclyl, (C₁-C₆-alkylene)-

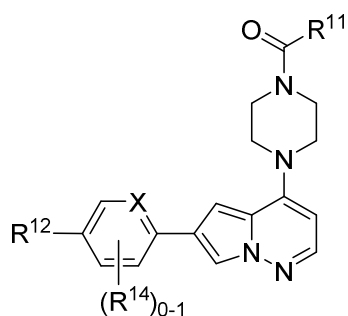
5 heterocyclyl, (C₁-C₆-heteroalkylene)-heterocyclyl, aryl, (C₁-C₆-alkylene)-aryl, (C₁-C₆-heteroalkylene)-aryl, heteroaryl, (C₁-C₆-alkylene)-heteroaryl, or (C₁-C₆-heteroalkylene)-heteroaryl, each of which is optionally substituted with one or more of halo, hydroxy, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl;

each R^d and R^e are independently selected from hydrogen, C₁-C₆ alkyl, or C₁-C₆ heteroalkyl;

10 each k is independently 0, 1, or 2; and

n is 0, 1, 2, or 3.

In another aspect, there is provided a compound of formula (II):



(II),

or a pharmaceutically acceptable salt thereof, wherein:

15 X is C(R¹³) or N;

R¹¹ is selected from -NH-(C₃-C₄ cycloalkyl); -NH-C₁-C₃ alkyl; -O-C₃-C₄ cycloalkyl; -O-C₁-C₃ alkyl optionally substituted with one or more substituents selected from fluoro, hydroxy, cyano, and deuterium; and -O-(O-containing heterocycle);

R¹² is selected from:

20 piperidin-3-yl optionally 3-substituted with C₁-C₃ alkoxy, fluoro, C₁-C₃ alkyl, or cyano; and piperidin-4-yl optionally 4-substituted with C₁-C₃ alkoxy, fluoro, C₁-C₃ alkyl, cyano,

wherein R¹² is additionally optionally 1-substituted with C₁-C₅ alkyl optionally substituted with one or more hydroxy and/or one or more -NH₂;

R¹³ is selected from hydrogen, cyano and fluoro; and

R¹⁴ is fluoro.

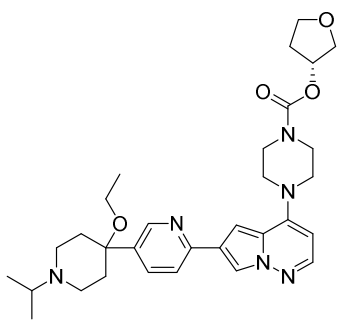
In yet another aspect, there is provided a compound selected from any one of the compounds as described in Table 1 and pharmaceutically acceptable salts thereof.

5 In another aspect, there is provided pharmaceutical compositions comprising a compound of structural formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

10 In another aspect, there is provided a use of a compound as described herein or a pharmaceutically acceptable salt thereof or a pharmaceutical composition as described herein in the manufacture of a medicament for treating or ameliorating fibrodysplasia ossificans progressive in a subject. In an embodiment, said use comprises administering to the subject a therapeutically effective amount of a compound of structural formula (I) or a pharmaceutically acceptable salt or composition thereof. In an embodiment, the subject has a mutation in an ALK2 gene that results in the expression of an ALK2 enzyme having an amino acid modification selected from one or more of L196P, PF197-8L, R202I, R206H, Q207E, R258S, R258G,
15 G328A, G328W, G328E, G328R, G356D, and R375P.

In another aspect, there is provided a use of a compound as described herein or a pharmaceutically acceptable salt thereof or a pharmaceutical composition as described herein in the manufacture of a medicament for treating or ameliorating diffuse intrinsic pontine glioma in a subject. In an embodiment, said use comprises administering to the subject a therapeutically
20 effective amount of a compound of structural formula (I) or a pharmaceutically acceptable salt or composition thereof. In an embodiment, the subject has a mutation in an ALK2 gene that results in the expression of an ALK2 enzyme having an amino acid modification selected from one or more of R206H, G328V, G328W, G328E, and G356D.

In yet another aspect, there is provided a compound of the following formula:



or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a pharmaceutical composition comprising the
 5 compound as described herein or a pharmaceutically acceptable salt thereof; and at least one pharmaceutically acceptable excipient.

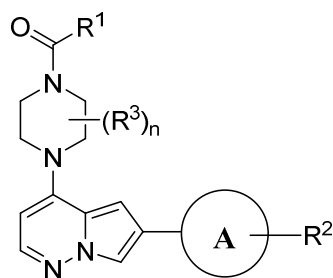
In yet another aspect, there is provided a use of compound as described herein or a pharmaceutically acceptable salt thereof or a pharmaceutical composition as described herein in the manufacture of a medicament for treating or ameliorating fibrodysplasia ossificans
 10 progressive in a subject.

In one embodiment, the present disclosure provides a method of inhibiting aberrant ALK2 activity in a subject. In an embodiment, said method comprises administering to the subject a therapeutically effective amount of a compound of structural formula (I) or a pharmaceutically acceptable salt or composition thereof. In an embodiment, the subject has a
 15 mutation in an ALK2 gene that results in the expression of an ALK2 enzyme having an amino acid modification selected from one or more of L196P, PF197-8L, R202I, R206H, Q207E, R258S, R258G, G328A, G328V, G328W, G328E, G328R, G356D, and R375P.

The methods described herein can additionally comprise various evaluation steps prior to, during, and/or following treatment with a compound of the disclosure. In an embodiment, prior
 20 to, during and/or following treatment with a compound of the disclosure, the method further comprises the step of evaluating, *e.g.*, visualizing, heterotopic ossification in the subject. This may be achieved by spectroscopic analysis, *e.g.*, magnetic resonance-based analysis, *e.g.*, MRI, positron emission tomography (PET), micro computed tomography (μ CT), or by histology.

Claims:

1. A compound of formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is phenyl or heteroaryl, wherein ring A is optionally substituted with 1, 2, or 3 substituents independently selected from halo, =O, cyano, $-\text{OR}^c$, $-\text{NR}^d\text{R}^e$, $-\text{S}(\text{O})_k\text{R}^c$, $-\text{NR}^c\text{S}(\text{O})_2\text{R}^c$, $-\text{S}(\text{O})_2\text{NR}^d\text{R}^e$, $-\text{C}(=\text{O})\text{OR}^c$, $-\text{OC}(=\text{O})\text{OR}^c$, $-\text{OC}(=\text{O})\text{R}^c$, $-\text{OC}(=\text{S})\text{OR}^c$, $-\text{C}(=\text{S})\text{OR}^c$, $-\text{O}(\text{C}=\text{S})\text{R}^c$, $-\text{C}(=\text{O})\text{NR}^d\text{R}^e$, $-\text{NR}^c\text{C}(=\text{O})\text{R}^c$, $-\text{C}(=\text{S})\text{NR}^d\text{R}^e$, $-\text{NR}^c\text{C}(=\text{S})\text{R}^c$, $-\text{NR}^c(\text{C}=\text{O})\text{OR}^c$, $-\text{O}(\text{C}=\text{O})\text{NR}^d\text{R}^e$, $-\text{NR}^c(\text{C}=\text{S})\text{OR}^c$, $-\text{O}(\text{C}=\text{S})\text{NR}^d\text{R}^e$, $-\text{NR}^c(\text{C}=\text{O})\text{NR}^d\text{R}^e$, $-\text{NR}^c(\text{C}=\text{S})\text{NR}^d\text{R}^e$, $-\text{C}(=\text{S})\text{R}^c$, $-\text{C}(=\text{O})\text{R}^c$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ heteroalkyl, carbocyclyl, $(\text{C}_1\text{-C}_6\text{-alkylene})\text{-carbocyclyl}$, $(\text{C}_1\text{-C}_6\text{-heteroalkylene})\text{-carbocyclyl}$, heterocyclyl, $(\text{C}_1\text{-C}_6\text{-alkylene})\text{-heterocyclyl}$, $(\text{C}_1\text{-C}_6\text{-heteroalkylene})\text{-heterocyclyl}$, aryl, $(\text{C}_1\text{-C}_6\text{-alkylene})\text{-aryl}$, $(\text{C}_1\text{-C}_6\text{-heteroalkylene})\text{-aryl}$, heteroaryl, $(\text{C}_1\text{-C}_6\text{-alkylene})\text{-heteroaryl}$, and $(\text{C}_1\text{-C}_6\text{-heteroalkylene})\text{-heteroaryl}$, wherein each of said alkyl, alkylene, heteroalkyl, heteroalkylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more of halo, OR^c , $-\text{NO}_2$,

cyano, $-\text{NR}^c\text{C}(=\text{O})\text{R}^c$, $-\text{NR}^d\text{R}^e$, $-\text{S}(\text{O})_k\text{R}^c$, $-\text{C}(=\text{O})\text{OR}^c$, $-\text{C}(=\text{O})\text{NR}^d\text{R}^e$, $-\text{C}(=\text{O})\text{R}^c$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, or $\text{C}_1\text{-C}_6$ heteroalkyl in addition to R^2 ;

R^1 is selected from $\text{NH}(\text{C}_1\text{-C}_6\text{ alkyl})$, $\text{N}(\text{C}_1\text{-C}_6\text{ alkyl})_2$, $\text{C}_1\text{-C}_6$ alkyl, $-\text{O}-\text{C}_1\text{-C}_6$ alkyl, $-\text{C}(\text{O})-\text{C}_1\text{-C}_4$ alkyl, carbocyclyl, heterocyclyl, $-\text{O}-(\text{C}_0\text{-C}_4\text{ alkylene})\text{-carbocyclyl}$, $-\text{O}-(\text{C}_0\text{-C}_4\text{ alkylene})\text{-heterocyclyl}$, $-\text{NH}-(\text{C}_0\text{-C}_4\text{ alkylene})\text{-carbocyclyl}$, $-\text{NH-aryl}$, $-\text{NH-O}-(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{S-heterocyclyl}$, $-\text{S}-(\text{C}_0\text{-C}_3\text{ alkylene})\text{-(O-containing heterocyclyl)}$, and $-\text{NH}-(\text{C}_0\text{-C}_4\text{ alkylene})\text{-heterocyclyl}$, wherein each alkyl, alkylene, carbocyclyl, and heterocyclyl portion of R^1

is optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, =O, cyano, -OR^c, -NR^dR^e, -S(O)_kR^c, -NR^cS(O)₂R^c, -S(O)₂NR^dR^e, -C(=O)OR^c, -OC(=O)OR^c, -OC(=O)R^c, -OC(=S)OR^c, -C(=S)OR^c, -O(C=S)R^c, -C(=O)NR^dR^e, -NR^cC(=O)R^c, -C(=S)NR^dR^e, -NR^cC(=S)R^c, -NR^c(C=O)OR^c, -O(C=O)NR^dR^e, -NR^c(C=S)OR^c, -O(C=S)NR^dR^e, -NR^c(C=O)NR^dR^e, -NR^c(C=S)NR^dR^e, -C(=S)R^c, -C(=O)R^c, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, carbocyclyl, (C₁-C₆-alkylene)-carbocyclyl, (C₁-C₆-heteroalkylene)-carbocyclyl, heterocyclyl, (C₁-C₆-alkylene)-heterocyclyl, (C₁-C₆-heteroalkylene)-heterocyclyl, aryl, (C₁-C₆-alkylene)-aryl, (C₁-C₆-heteroalkylene)-aryl, heteroaryl, (C₁-C₆-alkylene)-heteroaryl, and (C₁-C₆-heteroalkylene)-heteroaryl, wherein each of said alkyl, alkylene, heteroalkyl, heteroalkylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more of halo, OR^c, -NO₂, cyano, -NR^cC(=O)R^c, -NR^dR^e, -S(O)_kR^c, -C(=O)OR^c, -C(=O)NR^dR^e, -C(=O)R^c, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ heteroalkyl; or

R¹ is taken together with one R³ to form a saturated ring fused to the piperazine ring in formula (I), and wherein the ring formed by R¹ and R³ is optionally substituted with 1, 2, or 3 substituents independently selected from halo, =O, cyano, -OR^c, -NR^dR^e, -S(O)_kR^c, -NR^cS(O)₂R^c, -S(O)₂NR^dR^e, -C(=O)OR^c, -OC(=O)OR^c, -OC(=O)R^c, -OC(=S)OR^c, -C(=S)OR^c, -O(C=S)R^c, -C(=O)NR^dR^e, -NR^cC(=O)R^c, -C(=S)NR^dR^e, -NR^cC(=S)R^c, -NR^c(C=O)OR^c, -O(C=O)NR^dR^e, -NR^c(C=S)OR^c, -O(C=S)NR^dR^e, -NR^c(C=O)NR^dR^e, -NR^c(C=S)NR^dR^e, -C(=S)R^c, -C(=O)R^c, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, carbocyclyl, (C₁-C₆-alkylene)-carbocyclyl, (C₁-C₆-heteroalkylene)-carbocyclyl, heterocyclyl, (C₁-C₆-alkylene)-heterocyclyl, (C₁-C₆-heteroalkylene)-heterocyclyl, aryl, (C₁-C₆-alkylene)-aryl, (C₁-C₆-heteroalkylene)-aryl, heteroaryl, (C₁-C₆-alkylene)-heteroaryl, and (C₁-C₆-heteroalkylene)-heteroaryl, wherein each of said alkyl, alkylene, heteroalkyl, heteroalkylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more of halo, OR^c, -NO₂, cyano, -NR^cC(=O)R^c, -NR^dR^e, -S(O)_kR^c, -C(=O)OR^c, -C(=O)NR^dR^e, -C(=O)R^c, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ heteroalkyl;

if ring A is phenyl, then R² is selected from halo, C₁-C₆ alkyl, heterocyclyl, cycloalkyl, -NH-(C₀-C₄ alkylene)-heterocyclyl, -(C₁-C₄ alkylene)-heterocyclyl, -(C₁-C₄

alkylene)-NH-heterocyclyl, and -O-(C₀-C₄ alkylene)-heterocyclyl, wherein any heterocyclyl, cycloalkyl, alkyl, or alkylene portion of R² is optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, =O,

cyano, -OR^c, -NR^dR^e, -S(O)_kR^c, -NR^cS(O)₂R^c, -S(O)₂NR^dR^e, -C(=O)OR^c, -OC(=O)OR^c, -OC(=O)R^c, -OC(=S)OR^c, -C(=S)OR^c, -O(C=S)R^c, -C(=O)NR^dR^e, -NR^cC(=O)R^c, -C(=S)NR^dR^e, -NR^cC(=S)R^c, -NR^c(C=O)OR^c, -O(C=O)NR^dR^e, -NR^c(C=S)OR^c, -O(C=S)NR^dR^e, -NR^c(C=O)NR^dR^e, -NR^c(C=S)NR^dR^e, -C(=S)R^c, -C(=O)R^c, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, carbocyclyl, (C₁-C₆-alkylene)-carbocyclyl, (C₁-C₆-heteroalkylene)-carbocyclyl, heterocyclyl, (C₁-C₆-alkylene)-heterocyclyl, (C₁-C₆-heteroalkylene)-heterocyclyl, aryl, (C₁-C₆-alkylene)-aryl, (C₁-C₆-heteroalkylene)-aryl, heteroaryl, (C₁-C₆-alkylene)-heteroaryl, and (C₁-C₆-heteroalkylene)-heteroaryl, wherein each of said alkyl, alkylene, heteroalkyl, heteroalkylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more of halo, OR^c, -NO₂,

cyano, -NR^cC(=O)R^c, -NR^dR^e, -S(O)_kR^c, -C(=O)OR^c, -C(=O)NR^dR^e, -C(=O)R^c, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ heteroalkyl; or R² is taken together with any ring atom in ring A to form a cycloalkyl or saturated heterocyclyl ring that is fused to ring A, and wherein the ring formed by R² and the ring atom in ring A is optionally substituted with 1, 2, or 3 substituents independently selected from halo, =O,

cyano, -OR^c, -NR^dR^e, -S(O)_kR^c, -NR^cS(O)₂R^c, -S(O)₂NR^dR^e, -C(=O)OR^c, -OC(=O)OR^c, -OC(=O)R^c, -OC(=S)OR^c, -C(=S)OR^c, -O(C=S)R^c, -C(=O)NR^dR^e, -NR^cC(=O)R^c, -C(=S)NR^dR^e, -NR^cC(=S)R^c, -NR^c(C=O)OR^c, -O(C=O)NR^dR^e, -NR^c(C=S)OR^c, -O(C=S)NR^dR^e, -NR^c(C=O)NR^dR^e, -NR^c(C=S)NR^dR^e, -C(=S)R^c, -C(=O)R^c, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, carbocyclyl, (C₁-C₆-alkylene)-carbocyclyl, (C₁-C₆-heteroalkylene)-carbocyclyl, heterocyclyl, (C₁-C₆-alkylene)-heterocyclyl, (C₁-C₆-heteroalkylene)-heterocyclyl, aryl, (C₁-C₆-alkylene)-aryl, (C₁-C₆-heteroalkylene)-aryl, heteroaryl, (C₁-C₆-alkylene)-heteroaryl, and (C₁-C₆-heteroalkylene)-heteroaryl, wherein each of said alkyl, alkylene, heteroalkyl, heteroalkylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more of halo, OR^c, -NO₂,

cyano, -NR^cC(=O)R^c, -NR^dR^e, -S(O)_kR^c, -C(=O)OR^c, -C(=O)NR^dR^e, -C(=O)R^c, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ heteroalkyl;

if ring A is heteroaryl, then R^2 is selected from halo, C_1 - C_6 alkyl, heterocyclyl, cycloalkyl, -NH-(C_0 - C_4 alkylene)-heterocyclyl, -(C_1 - C_4 alkylene)-heterocyclyl, -(C_1 - C_4 alkylene)-NH-heterocyclyl, and -O-(C_0 - C_4 alkylene)-heterocyclyl, wherein any heterocyclyl, cycloalkyl, alkyl, or alkylene portion of R^2 is optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, =O,

cyano, $-OR^c$, $-NR^dR^e$, $-S(O)_kR^c$, $-NR^cS(O)_2R^c$, $-S(O)_2NR^dR^e$, $-C(=O)OR^c$, $-OC(=O)OR^c$, $-OC(=O)R^c$, $-OC(=S)OR^c$, $-C(=S)OR^c$, $-O(C=S)R^c$, $-C(=O)NR^dR^e$, $-NR^cC(=O)R^c$, $-C(=S)NR^dR^e$, $-NR^cC(=S)R^c$, $-NR^c(C=O)OR^c$, $-O(C=O)NR^dR^e$, $-NR^c(C=S)OR^c$, $-O(C=S)NR^dR^e$, $-NR^c(C=O)NR^dR^e$, $-NR^c(C=S)NR^dR^e$, $-C(=S)R^c$, $-C(=O)R^c$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 heteroalkyl, carbocyclyl, (C_1 - C_6 -alkylene)-carbocyclyl, (C_1 - C_6 -heteroalkylene)-carbocyclyl, heterocyclyl, (C_1 - C_6 -alkylene)-heterocyclyl, (C_1 - C_6 -heteroalkylene)-heterocyclyl, aryl, (C_1 - C_6 -alkylene)-aryl, (C_1 - C_6 -heteroalkylene)-aryl, heteroaryl, (C_1 - C_6 -alkylene)-heteroaryl, and (C_1 - C_6 -heteroalkylene)-heteroaryl, wherein each of said alkyl, alkylene, heteroalkyl, heteroalkylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more of halo, OR^c , $-NO_2$,

cyano, $-NR^cC(=O)R^c$, $-NR^dR^e$, $-S(O)_kR^c$, $-C(=O)OR^c$, $-C(=O)NR^dR^e$, $-C(=O)R^c$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, or C_1 - C_6 heteroalkyl; or

R^2 is taken together with any saturated ring atom in ring A to form a cycloalkyl or saturated heterocyclyl ring that is fused, spirofused, or bridged to ring A, and wherein the ring formed by R^2 and the ring atom in ring A is optionally substituted with 1, 2, or 3 substituents independently selected from halo, =O,

cyano, $-OR^c$, $-NR^dR^e$, $-S(O)_kR^c$, $-NR^cS(O)_2R^c$, $-S(O)_2NR^dR^e$, $-C(=O)OR^c$, $-OC(=O)OR^c$, $-OC(=O)R^c$, $-OC(=S)OR^c$, $-C(=S)OR^c$, $-O(C=S)R^c$, $-C(=O)NR^dR^e$, $-NR^cC(=O)R^c$, $-C(=S)NR^dR^e$, $-NR^cC(=S)R^c$, $-NR^c(C=O)OR^c$, $-O(C=O)NR^dR^e$, $-NR^c(C=S)OR^c$, $-O(C=S)NR^dR^e$, $-NR^c(C=O)NR^dR^e$, $-NR^c(C=S)NR^dR^e$, $-C(=S)R^c$, $-C(=O)R^c$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 heteroalkyl, carbocyclyl, (C_1 - C_6 -alkylene)-carbocyclyl, (C_1 - C_6 -heteroalkylene)-carbocyclyl, heterocyclyl, (C_1 - C_6 -alkylene)-heterocyclyl, (C_1 - C_6 -heteroalkylene)-heterocyclyl, aryl, (C_1 - C_6 -alkylene)-aryl, (C_1 - C_6 -heteroalkylene)-aryl, heteroaryl, (C_1 - C_6 -alkylene)-heteroaryl, and (C_1 - C_6 -heteroalkylene)-heteroaryl, wherein each of said alkyl, alkylene, heteroalkyl, heteroalkylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more of

halo, OR^c, -NO₂,

cyano, -NR^cC(=O)R^c, -NR^dR^e, -S(O)_kR^c, -C(=O)OR^c, -C(=O)NR^dR^e, -C(=O)R^c, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ heteroalkyl;

each R³ is independently selected from C₁-C₄ alkyl and C₁-C₄ haloalkyl;

each R^c is selected from hydrogen, hydroxy, C₁-C₆ alkyl, C₁-C₆ heteroalkyl, carbocyclyl, (C₁-C₆-alkylene)-carbocyclyl, (C₁-C₆-heteroalkylene)-carbocyclyl, heterocyclyl, (C₁-C₆-alkylene)-heterocyclyl, (C₁-C₆-heteroalkylene)-heterocyclyl, aryl, (C₁-C₆-alkylene)-aryl, (C₁-C₆-heteroalkylene)-aryl, heteroaryl, (C₁-C₆-alkylene)-heteroaryl, or (C₁-C₆-heteroalkylene)-heteroaryl, each of which is optionally substituted with one or more of halo, hydroxy, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl;

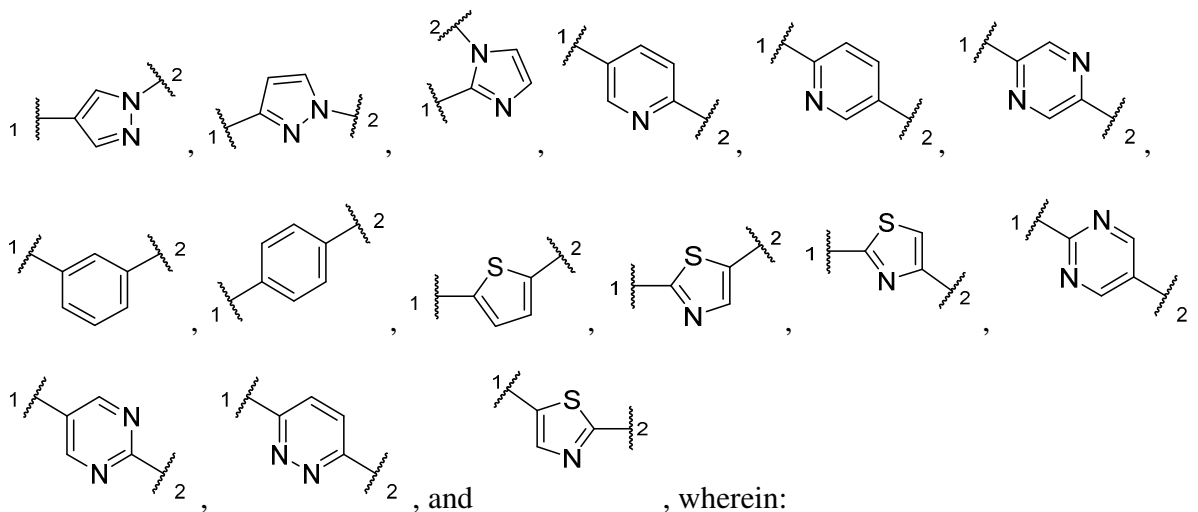
each R^d and R^e are independently selected from hydrogen, C₁-C₆ alkyl, or C₁-C₆ heteroalkyl;

each k is independently 0, 1, or 2; and

n is 0, 1, 2, or 3.

2. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein n is 0; or n is 1 and R³ is selected from methyl, ethyl, and CHF₂.

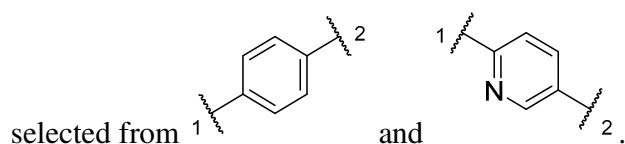
3. The compound of any one of claims 1-2 or a pharmaceutically acceptable salt thereof, wherein ring A is selected from:



“1” represents a portion of ring A bound to a pyrrolo[1,2-b]pyridazine moiety;

“2” represents a portion of ring A bound to R²; and
ring A is optionally substituted with 1, 2, or 3 substituents independently selected halo,
=O,
cyano, -OR^c, -NR^dR^e, -S(O)_kR^c, -NR^cS(O)₂R^c, -S(O)₂NR^dR^e, -C(=O)OR^c, -OC(=O)OR^c, -OC(=O)
R^c, -OC(=S)OR^c, -C(=S)OR^c, -O(C=S)R^c, -C(=O)NR^dR^e, -NR^cC(=O)R^c, -C(=S)NR^dR^e, -NR^cC(
=S)R^c, -NR^c(C=O)OR^c, -O(C=O)NR^dR^e, -NR^c(C=S)OR^c, -O(C=S)NR^dR^e, -NR^c(C=O)NR^dR^e, -N
R^c(C=S)NR^dR^e, -C(=S)R^c, -C(=O)R^c, C₁-C₆ alkyl, C₁-C₆ haloalkyl,
C₁-C₆ heteroalkyl, carbocyclyl, (C₁-C₆-alkylene)-carbocyclyl, (C₁-C₆-heteroalkylene)-
carbocyclyl, heterocyclyl, (C₁-C₆-alkylene)-heterocyclyl, (C₁-C₆-heteroalkylene)-heterocyclyl,
aryl, (C₁-C₆-alkylene)-aryl, (C₁-C₆-heteroalkylene)-aryl, heteroaryl,
(C₁-C₆-alkylene)-heteroaryl, and (C₁-C₆-heteroalkylene)-heteroaryl, wherein each of said alkyl,
alkylene, heteroalkyl, heteroalkylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are
optionally substituted with one or more of halo, OR^c, -NO₂,
cyano, -NR^cC(=O)R^c, -NR^dR^e, -S(O)_kR^c, -C(=O)OR^c, -C(=O)NR^dR^e, -C(=O)R^c, C₁-C₆ alkyl, C₁-
C₆ haloalkyl, or C₁-C₆ heteroalkyl in addition to R².

4. The compound of claim 3 or a pharmaceutically acceptable salt thereof, wherein ring A is



5. The compound of any one of claims 1-4 or a pharmaceutically acceptable salt thereof,
wherein ring A is optionally substituted with 1 or 2 substituents in addition to R², wherein each
optional substituent is independently selected from cyano, halo, methyl, and OCHF₂.

6. The compound of any one of claims 1-5 or a pharmaceutically acceptable salt thereof,
wherein R¹ is selected from -C(O)-(C₁-C₃ alkyl), C₁-C₃ alkyl, -O-(C₁-C₅ alkyl), -NH(C₁-C₅
alkyl), -N(C₁-C₄ alkyl)₂, -NH-(C₃-C₆ cycloalkyl), C₃-C₆ cycloalkyl, -O-(C₃-C₆
cycloalkyl), -O-(C₁-C₃ alkylene)-(C₃-C₆ cycloalkyl), -(C₁-C₃ alkylene)-(C₃-C₆ cycloalkyl), -O-
(C₀-C₃ alkylene)-(O-containing heterocyclyl), -NH-(C₀-C₃ alkylene)-(O-containing

heterocyclyl), an O-containing heterocyclyl, an N-containing heterocyclyl, -O-(C₀-C₃ alkylene)-(N-containing heterocyclyl), -S-(C₀-C₃ alkylene)-(O-containing heterocyclyl), -NH-O-(C₁-C₃ alkyl), and -NH-phenyl, wherein any alkyl, cycloalkyl, phenyl, or heterocyclyl portion of R¹ is optionally substituted with 1, 2, or 3 substituents independently selected from deuterium, halo, cyano, acetyl, C₁-C₄ alkyl, C₁-C₄ haloalkyl, -O-C₁-C₄ alkyl, -C₁-C₄ alkylene-O-C₁-C₄ alkyl, heteroaryl, phenyl, cycloalkyl, -COOH, and hydroxy, wherein each of said heteroaryl, phenyl, and cycloalkyl are optionally substituted with one or more of halo, OR^c, -NO₂, cyano, -NR^cC(=O)R^c, -NR^dR^e, -S(O)_kR^c, -C(=O)OR^c, -C(=O)NR^dR^e, -C(=O)R^c, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ heteroalkyl; or

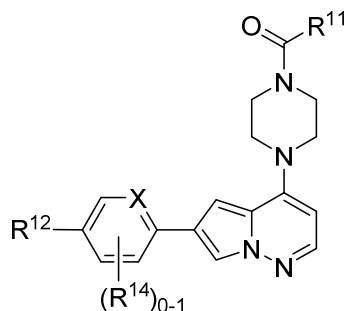
R¹ is taken together with any ring atom in the piperazine moiety of formula (I) to form a carbocyclyl or heterocyclyl ring fused to the piperazine moiety.

7. The compound of any one of claims 1-6 or a pharmaceutically acceptable salt thereof, wherein R² is selected from halo, cycloalkyl, heterocyclyl, -O-(C₀-C₄ alkylene)-heterocyclyl, -(C₁-C₃ alkylene)-heterocyclyl, -(C₁-C₃ alkylene)-NH-(C₁-C₃ alkyl), -(hydroxy-substituted C₁-C₃ alkylene)-NH-(C₁-C₃ alkyl), C₁-C₄ alkyl substituted with both hydroxy and one or more of amino, C₁-C₄ alkylamino or di-C₁-C₄ alkylamino cyano-substituted C₁-C₄ alkyl, hydroxy, -S(O)₂-C₁-C₄ alkyl, and -(amino substituted C₁-C₃ alkylene)-heterocyclyl; or

R² is taken together with a ring atom in ring A to form a heterocyclyl or a carbocyclyl that is fused to ring A, wherein any heterocyclyl or carbocyclyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, cyano, hydroxy, -NH₂, -NH(C₁-C₄ alkyl), -NH-C(O)-O-(C₁-C₄ alkyl), =O, -C(O)-C₁-C₄ alkyl, -C₁-C₄ alkyl, deuterated C₁-C₄ alkyl, -C₁-C₄ haloalkyl, hydroxy-substituted -C₁-C₄ alkyl, -O-C₁-C₄ alkyl, -O-C₁-C₄ haloalkyl, -(C₁-C₄ alkylene)-O-(C₁-C₄ alkyl), -(amino substituted C₁-C₄ alkylene)-O-(C₁-C₄ alkyl), -(C₁-C₄ alkylene)-O-(C₁-C₄ haloalkyl), -C(O)-O-C₁-C₄ alkyl, -COOH, C₃-C₆ cycloalkyl, heterocyclyl, and -NH-heterocyclyl, wherein each said heterocyclyl is optionally substituted with one or more of halo, OR^c, -NO₂, cyano, -NR^cC(=O)R^c, -NR^dR^e, -S(O)_kR^c, -C(=O)OR^c, -C(=O)NR^dR^e, -C(=O)R^c, C₁-C₆ alkyl, C₁-

C₆ haloalkyl, or C₁-C₆ heteroalkyl.

8. A compound of formula (II):



(II),

or a pharmaceutically acceptable salt thereof, wherein:

X is C(R¹³) or N;

R¹¹ is selected from -NH-(C₃-C₄ cycloalkyl); -NH-C₁-C₃ alkyl; -O-C₃-C₄ cycloalkyl; -O-C₁-C₃ alkyl optionally substituted with one or more substituents selected from fluoro, hydroxy, cyano, and deuterium; and -O-(O-containing heterocycle);

R¹² is selected from:

piperidin-3-yl optionally 3-substituted with C₁-C₃ alkoxy, fluoro, C₁-C₃ alkyl, or cyano; and

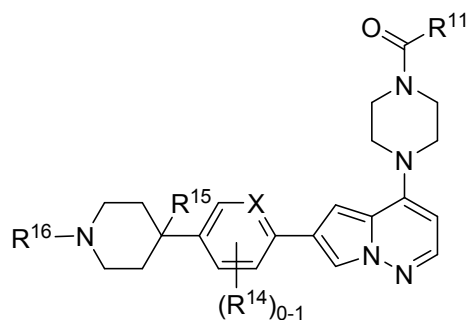
piperidin-4-yl optionally 4-substituted with C₁-C₃ alkoxy, fluoro, C₁-C₃ alkyl, cyano,

wherein R¹² is additionally optionally 1-substituted with C₁-C₅ alkyl optionally substituted with one or more hydroxy and/or one or more -NH₂;

R¹³ is selected from hydrogen, cyano and fluoro; and

R¹⁴ is fluoro.

9. The compound of claim 8, wherein the compound is a compound of formula (IIa):



(IIa),

or a pharmaceutically acceptable salt thereof, wherein:

X is C(R¹³) or N;

R¹¹ is selected from: -NH-(C₃-C₄ cycloalkyl); -NH-C₁-C₃ alkyl; -O-C₃-C₄ cycloalkyl; -O-(C₁-C₃ alkyl) optionally substituted with one or more substituents selected from fluoro, hydroxy, cyano, and deuterium; and -O-(O-containing heterocycle);

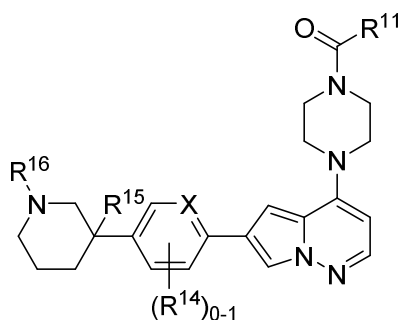
R¹³ is selected from hydrogen, cyano, and fluoro;

R¹⁴ is fluoro;

R¹⁵ is selected from hydrogen, C₁-C₃ alkoxy, fluoro, C₁-C₃ alkyl, and cyano; and

R¹⁶ is hydrogen or C₁-C₅ alkyl optionally substituted with one or more hydroxy and/or one or more -NH₂.

10. The compound of claim 8, wherein the compound is a compound of formula (IIb):



(IIb),

or a pharmaceutically acceptable salt thereof, wherein:

X is C(R¹³) or N;

R¹¹ is selected from: -NH-(C₃-C₄ cycloalkyl); -NH-C₁-C₃ alkyl; -O-C₃-C₄ cycloalkyl; -O-

(C₁-C₃ alkyl) optionally substituted with one or more substituents selected from fluoro, hydroxy, cyano, and deuterium; and -O-(O-containing heterocycle);

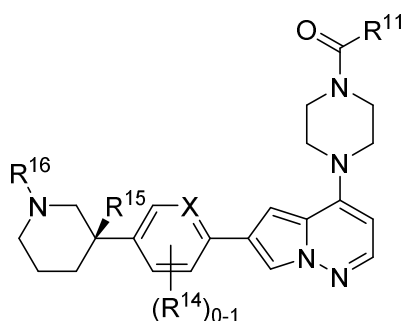
R¹³ is selected from hydrogen, cyano, and fluoro;

R¹⁴ is fluoro;

R¹⁵ is selected from hydrogen, C₁-C₃ alkoxy, fluoro, C₁-C₃ alkyl, and cyano; and

R¹⁶ is hydrogen or C₁-C₅ alkyl optionally substituted with one or more hydroxy and/or one or more -NH₂.

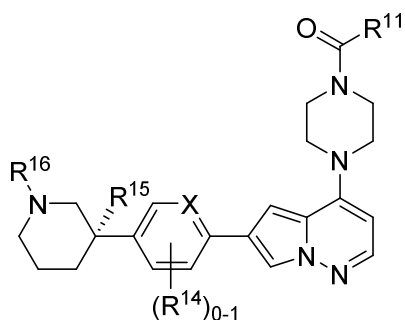
11. The compound of claim 10, wherein the compound is a compound of formula (IIb-1):



(IIb-1),

or a pharmaceutically acceptable salt thereof.

12. The compound of claim 10, wherein the compound is a compound of formula (IIb-2):



(IIb-2),

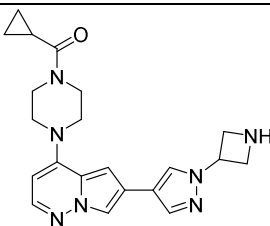
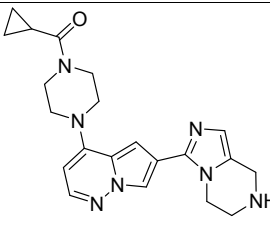
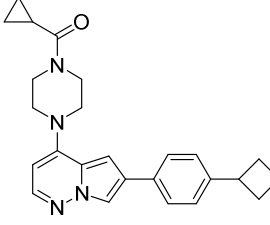
or a pharmaceutically acceptable salt thereof.

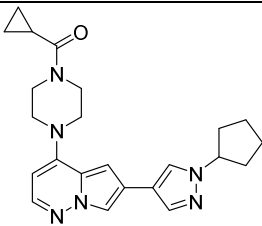
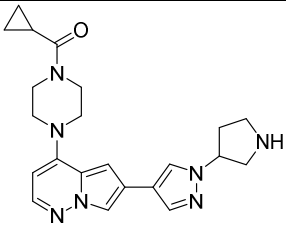
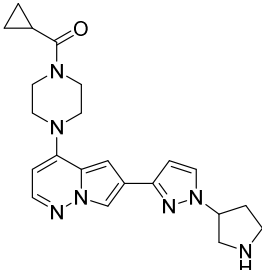
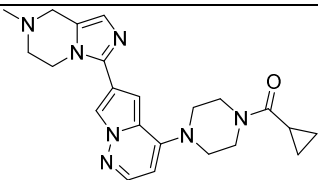
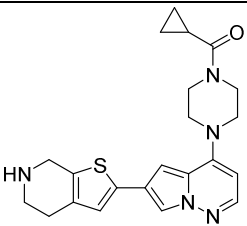
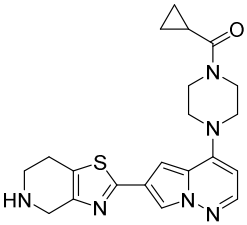
13. The compound of any one of claims 8-12 or a pharmaceutically acceptable salt thereof, wherein R¹⁴ is absent.

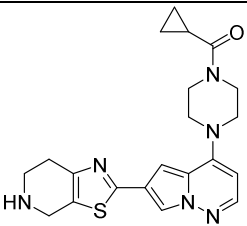
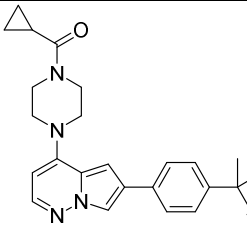
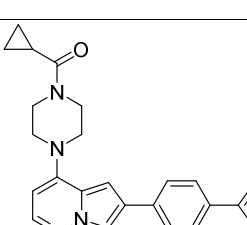
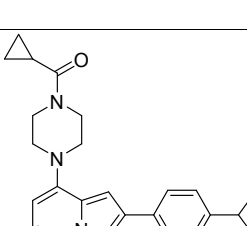
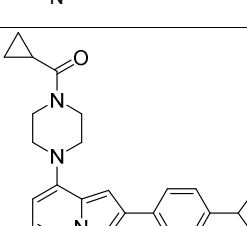
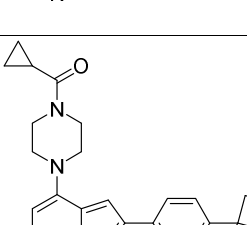
14. The compound of any one of claims 8-12 or a pharmaceutically acceptable salt thereof, wherein R¹³ is hydrogen.

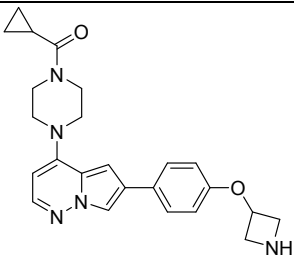
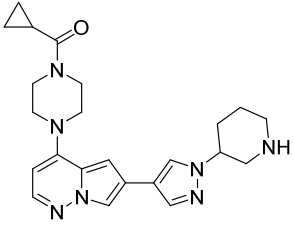
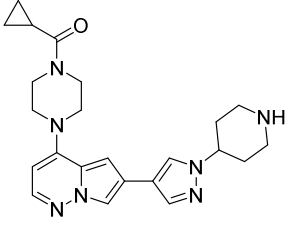
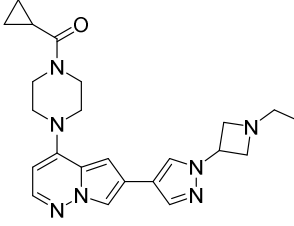
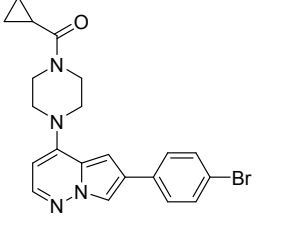
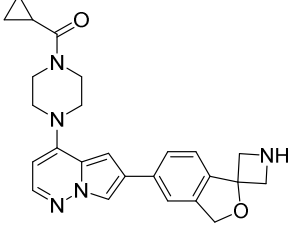
15. The compound of any one of claims 8-12 or a pharmaceutically acceptable salt thereof, wherein R¹¹ is selected from -NH-C₁-C₃ alkyl; -O-C₁-C₃ alkyl optionally substituted with one or more substituents selected from fluoro, hydroxy, cyano, and deuterium; oxetan-3-yloxy; and tetrahydrofuran-3-yloxy.

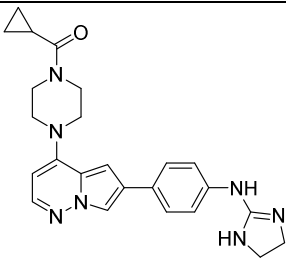
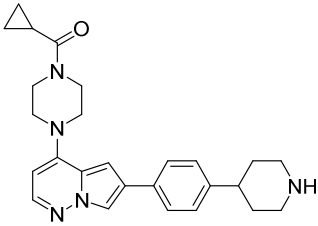
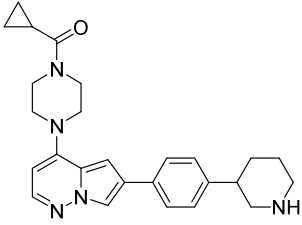
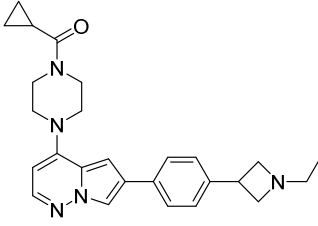
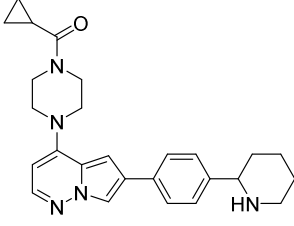
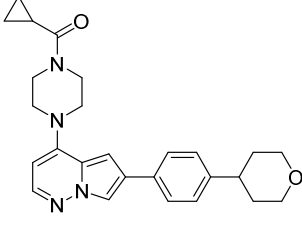
16. A compound selected from any one of the following compounds and pharmaceutically acceptable salts thereof:

#	Structure
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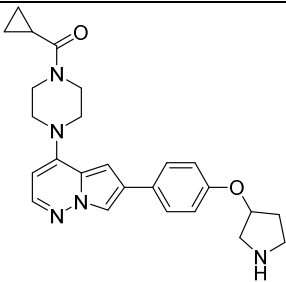
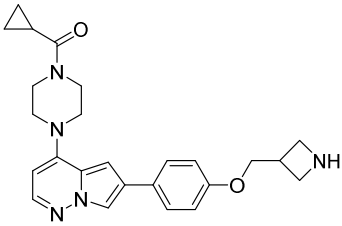
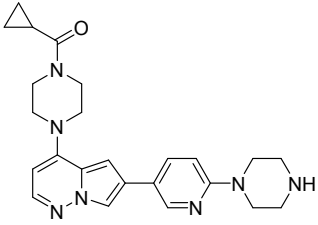
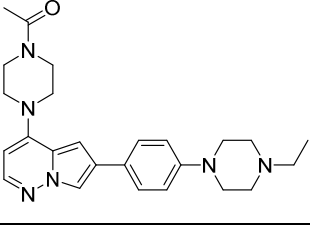
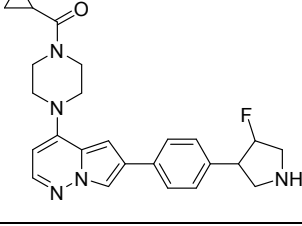
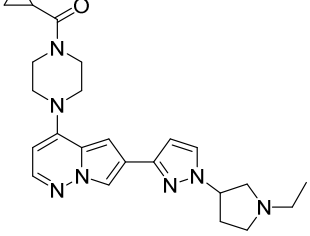
#	Structure
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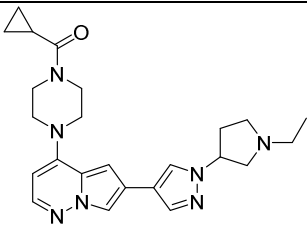
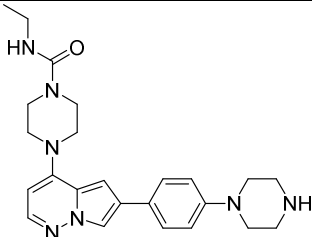
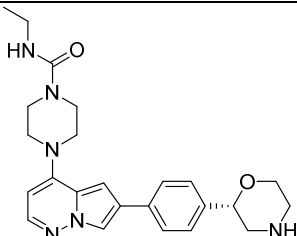
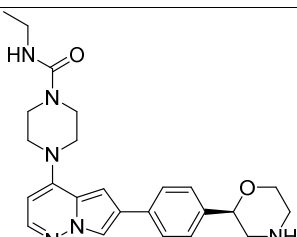
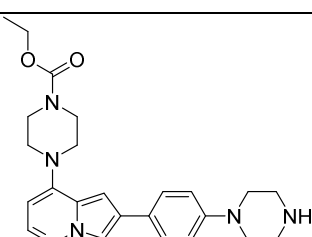
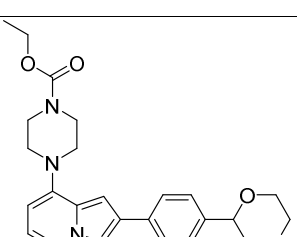
#	Structure
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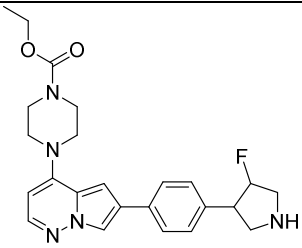
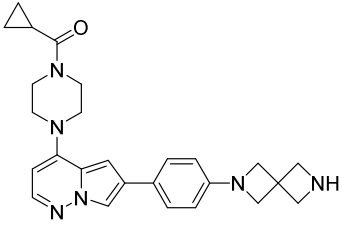
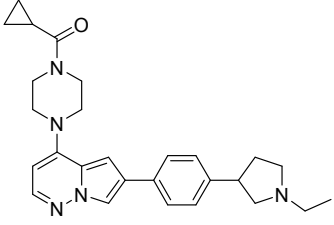
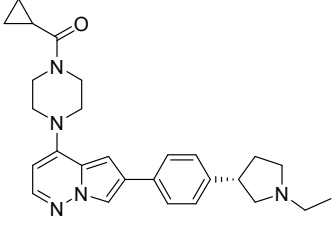
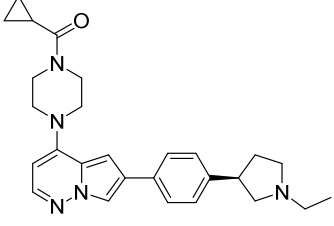
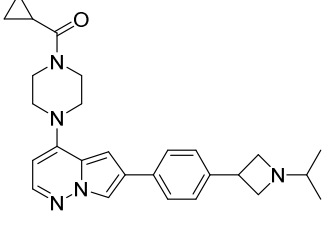
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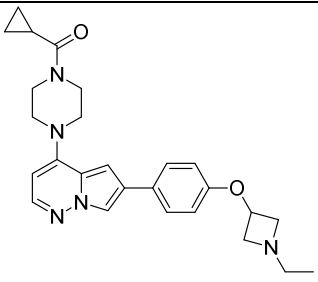
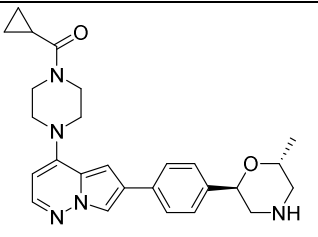
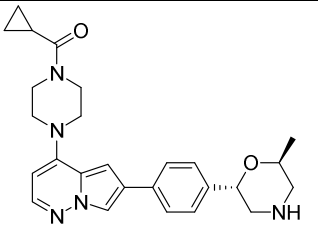
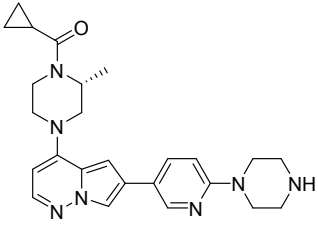
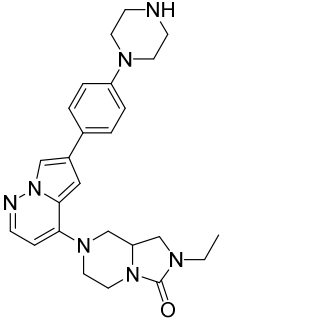
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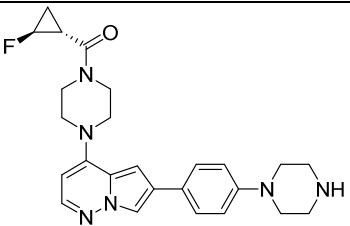
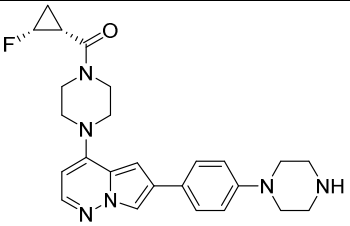
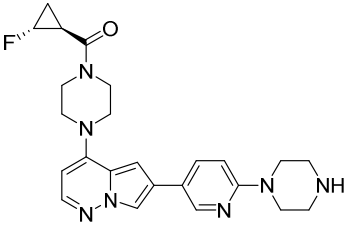
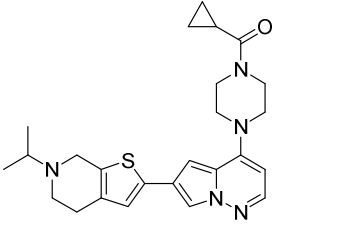
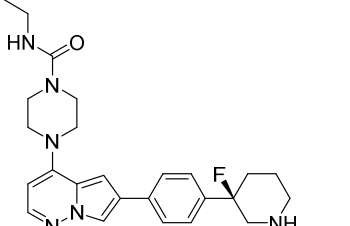
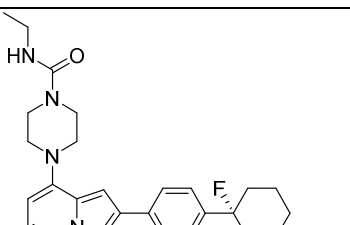
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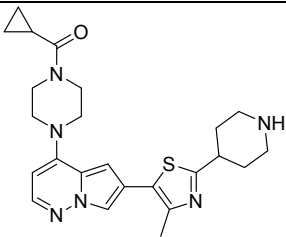
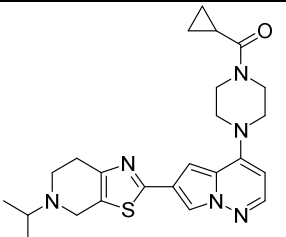
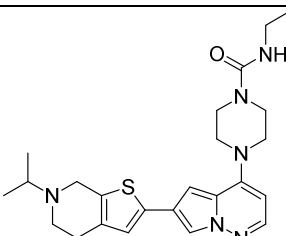
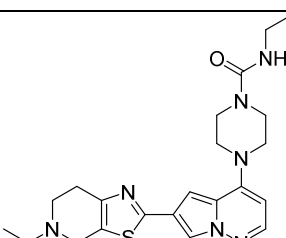
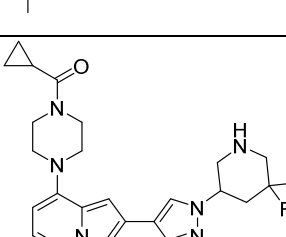
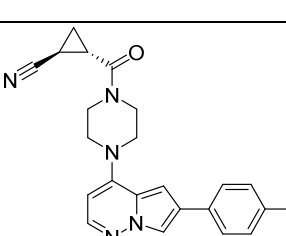
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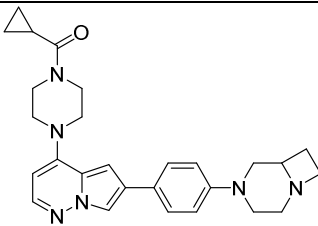
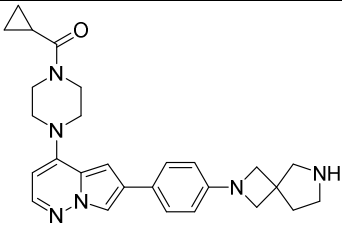
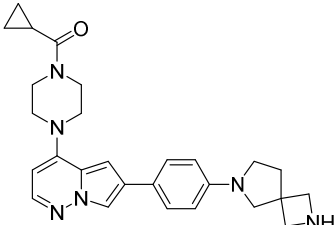
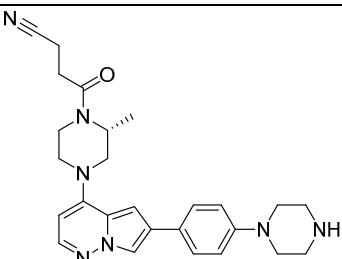
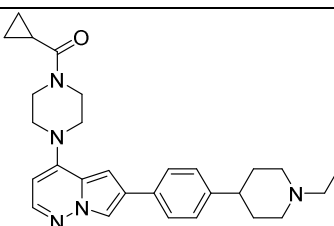
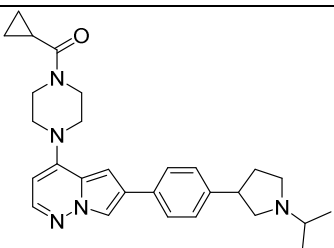
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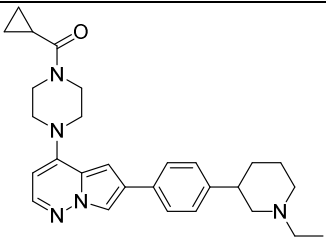
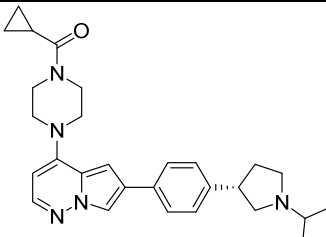
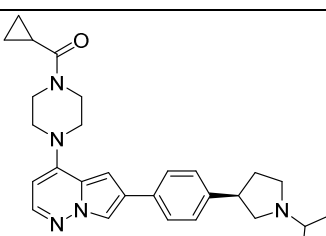
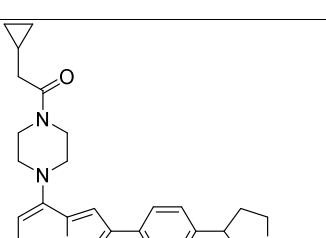
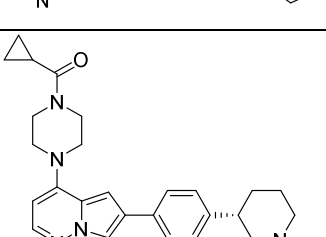
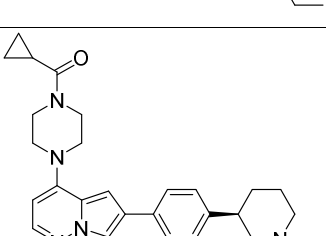
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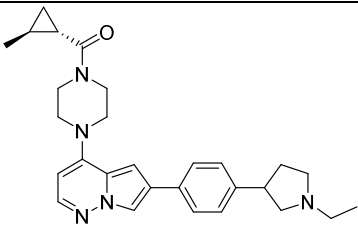
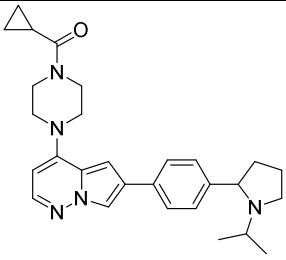
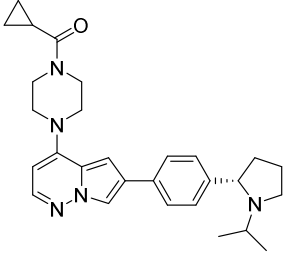
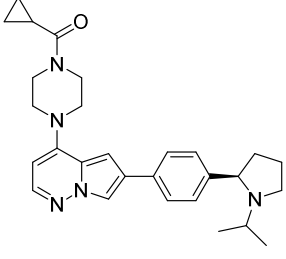
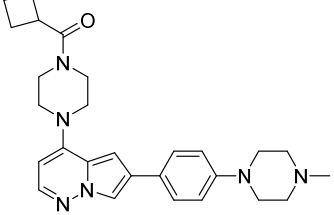
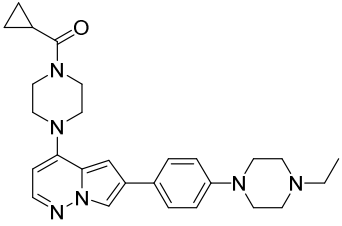
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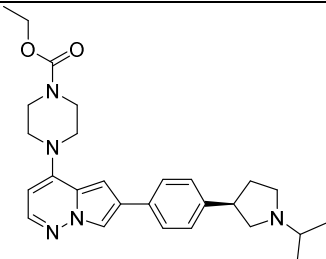
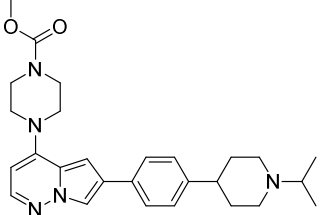
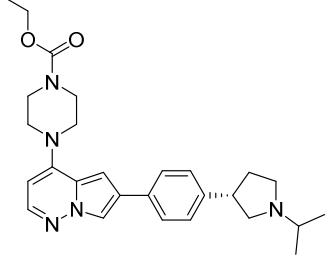
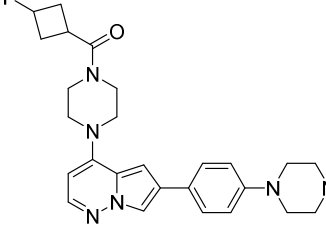
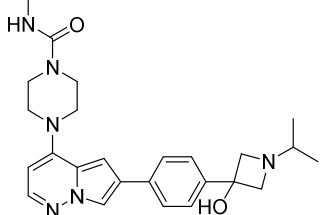
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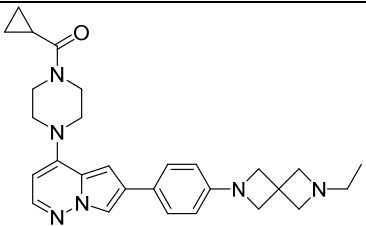
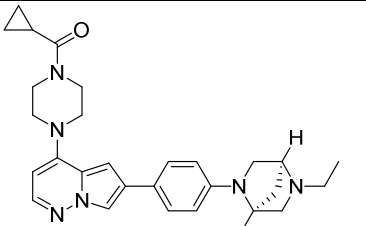
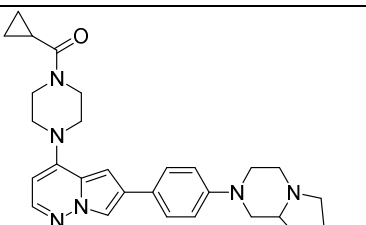
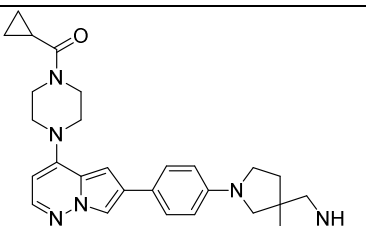
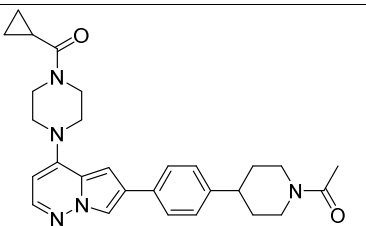
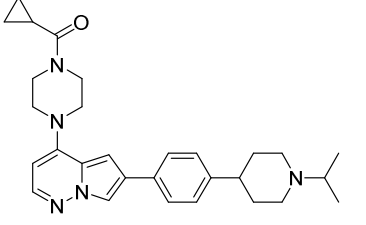
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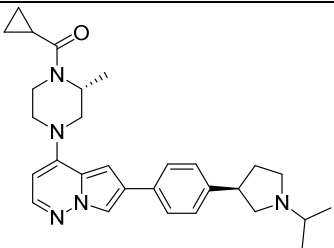
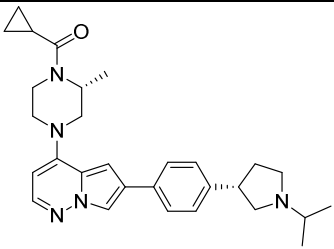
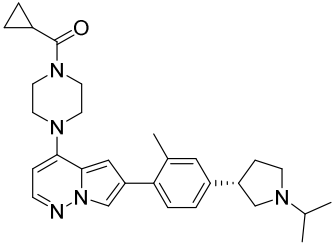
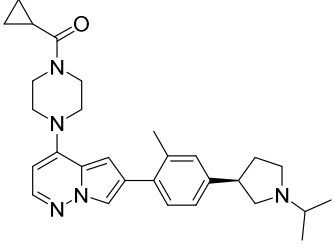
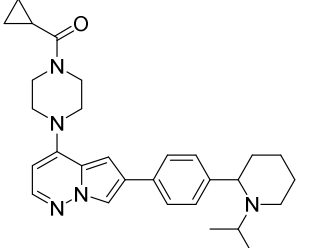
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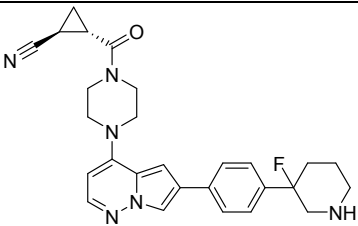
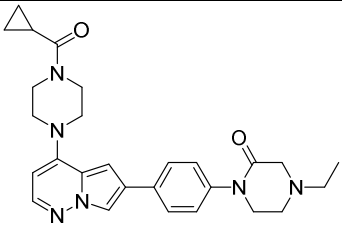
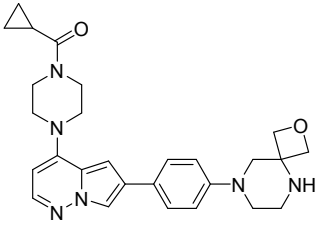
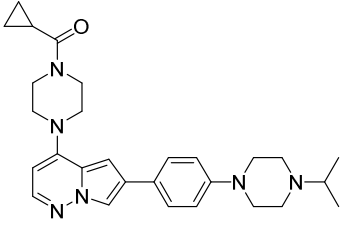
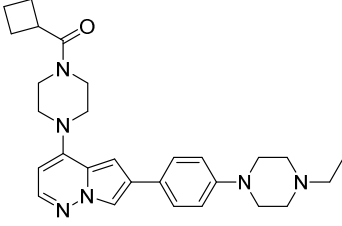
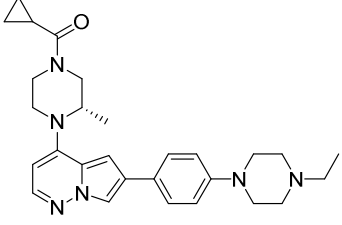
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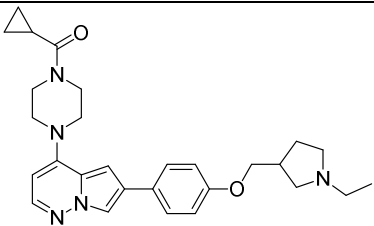
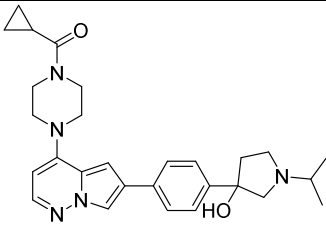
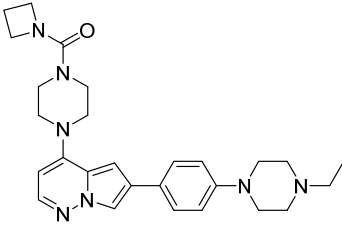
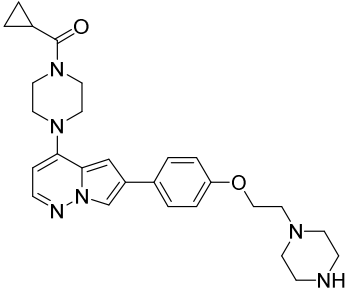
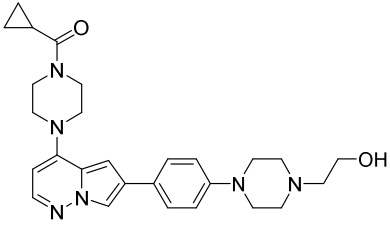
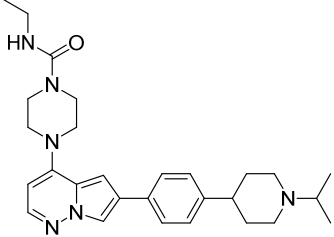
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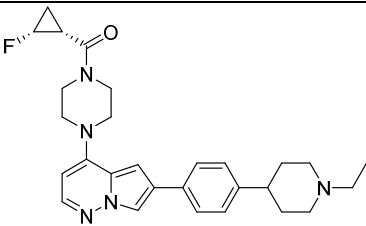
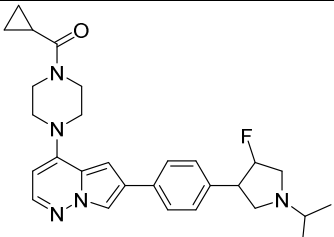
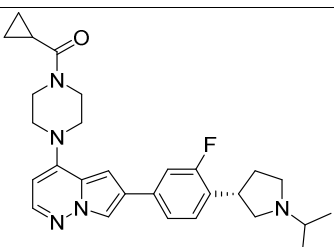
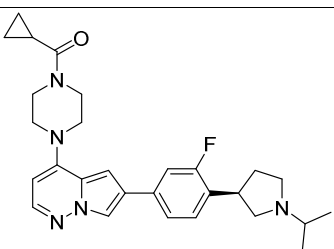
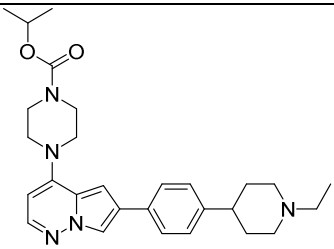
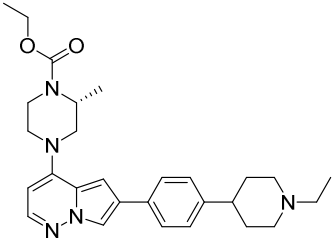
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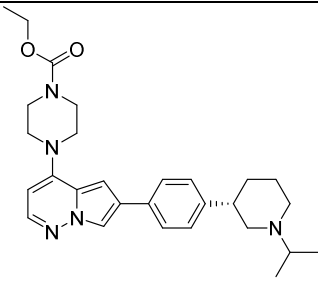
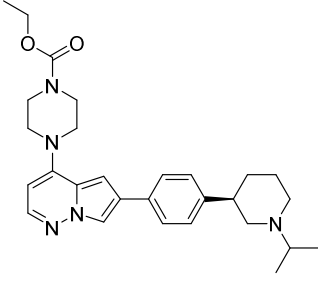
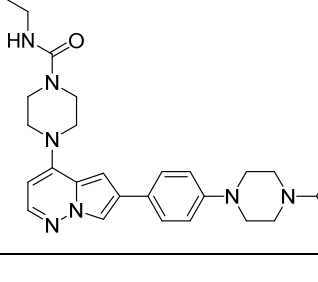
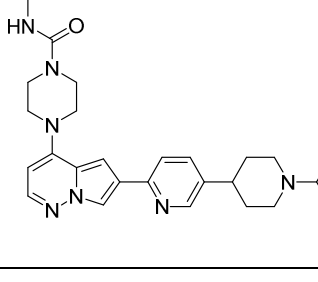
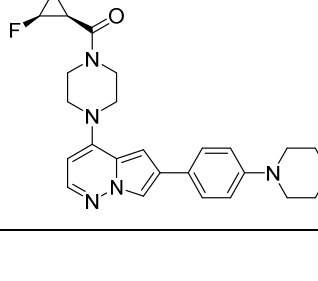
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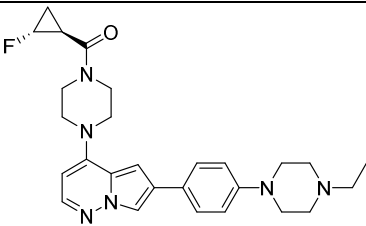
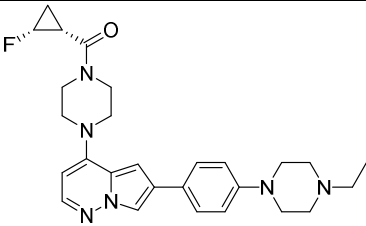
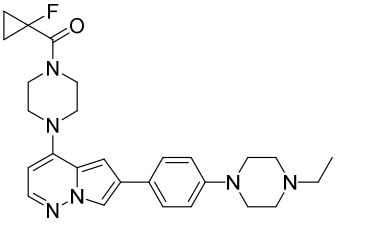
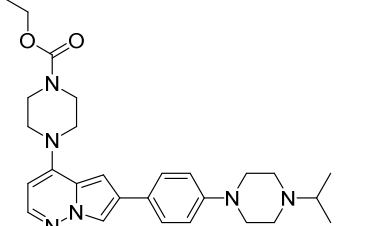
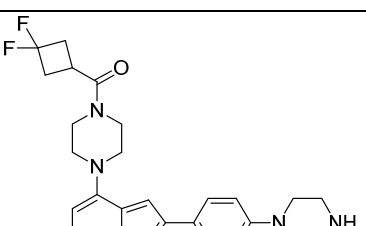
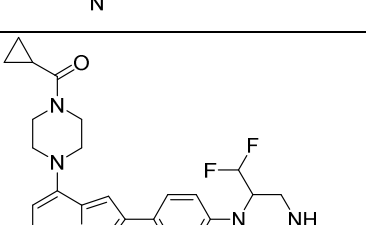
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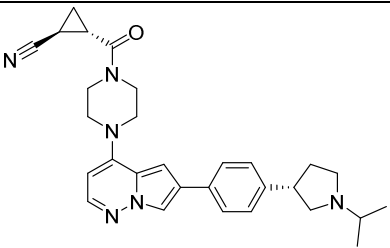
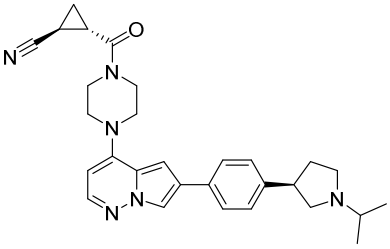
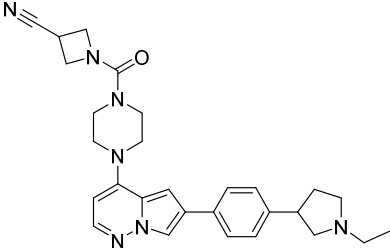
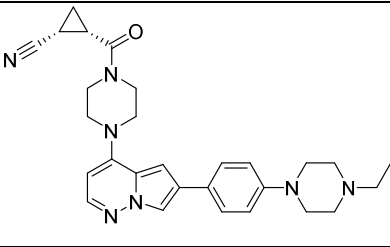
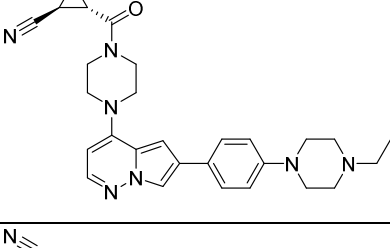
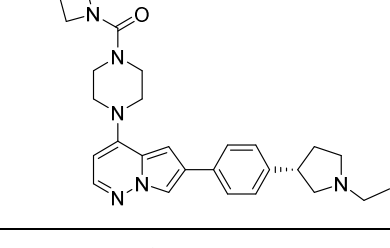
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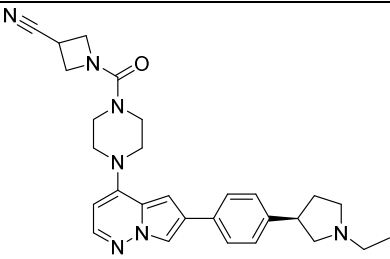
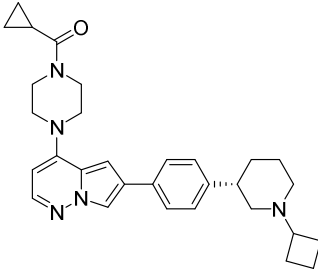
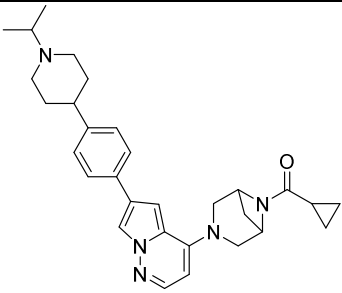
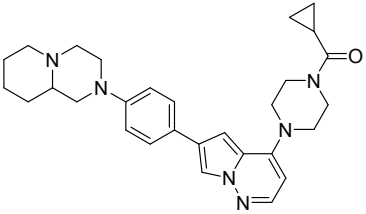
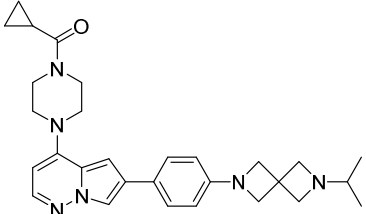
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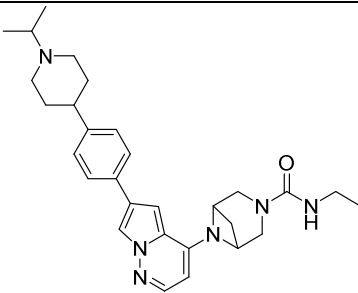
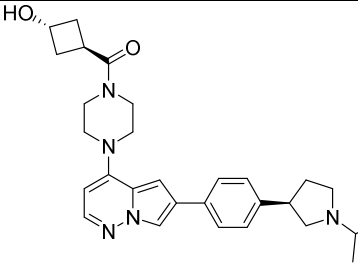
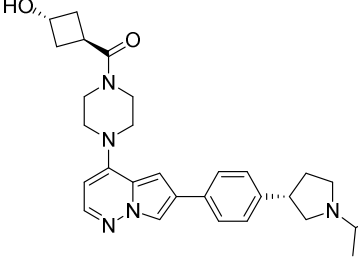
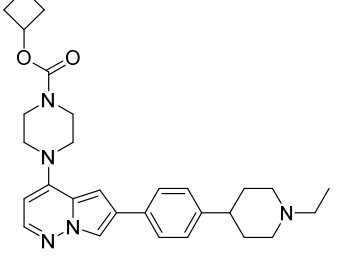
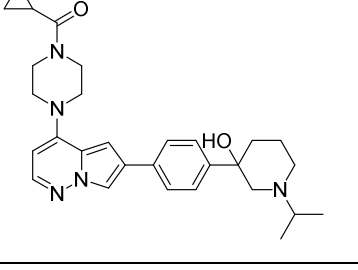
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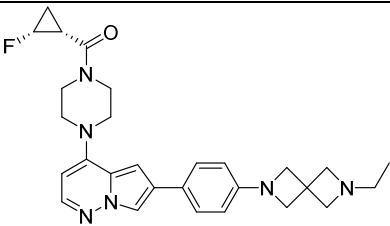
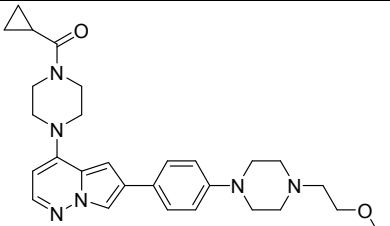
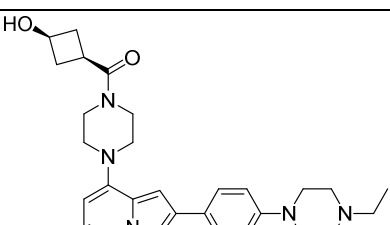
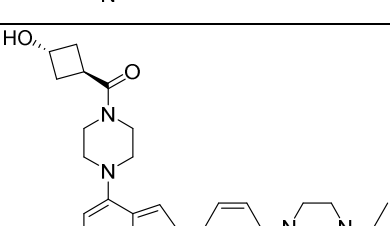
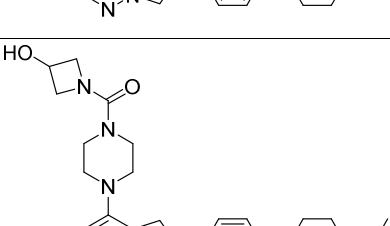
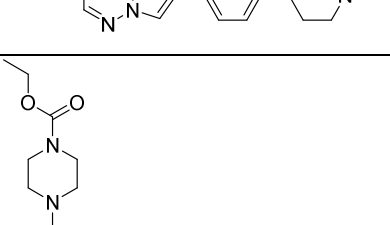
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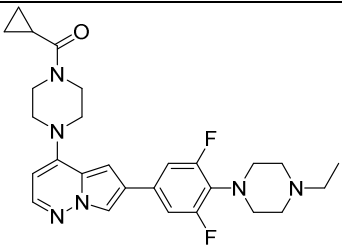
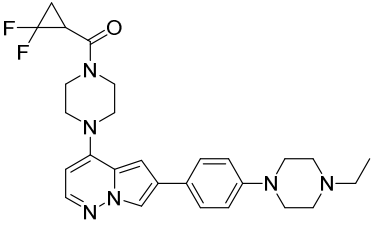
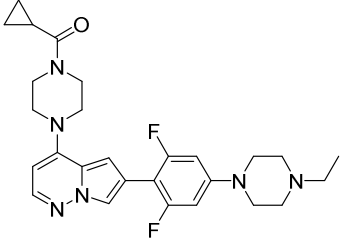
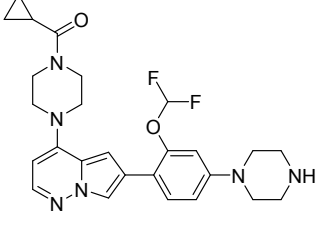
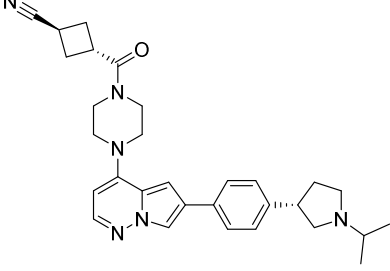
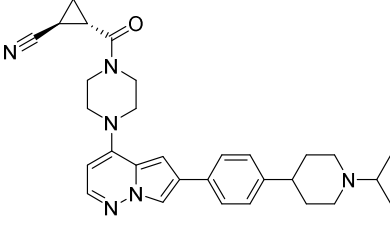
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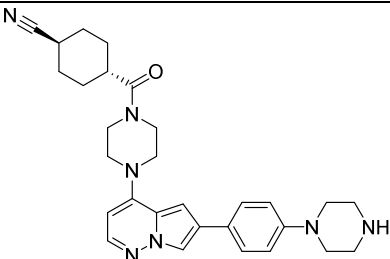
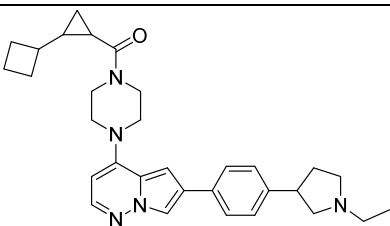
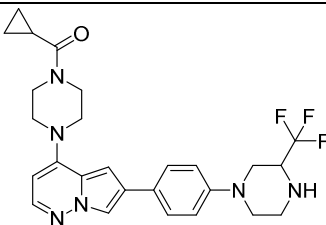
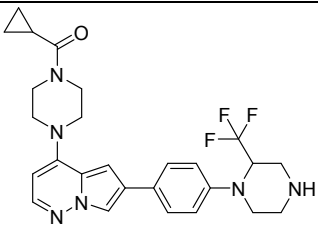
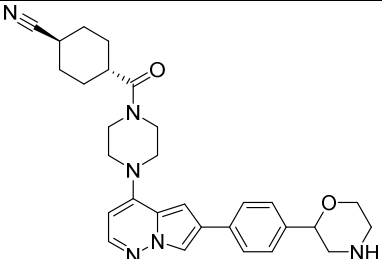
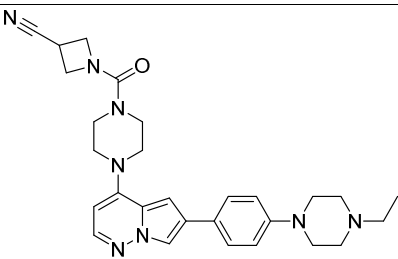
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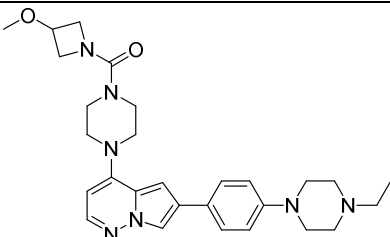
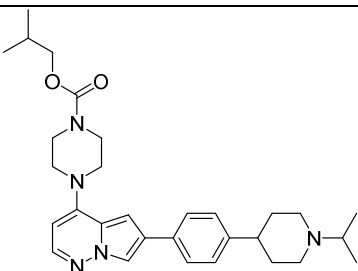
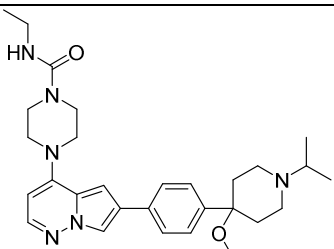
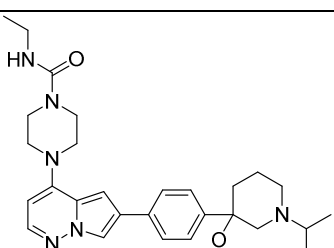
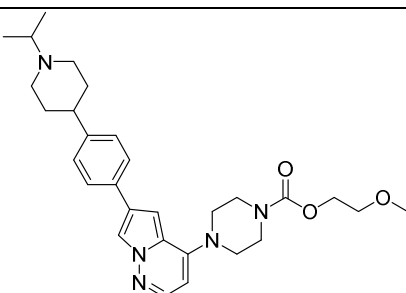
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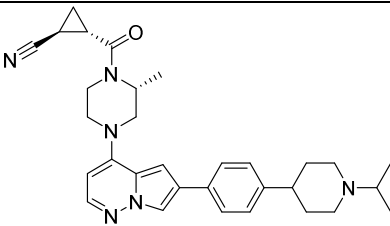
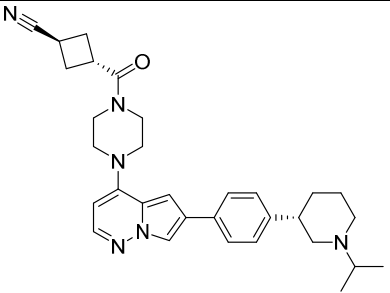
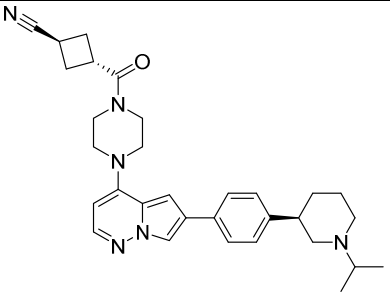
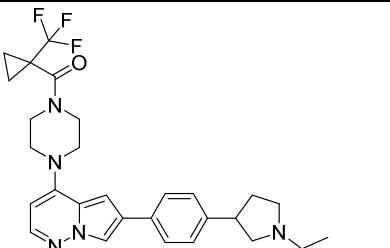
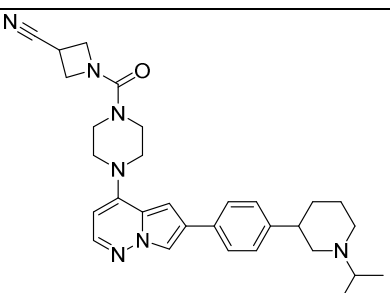
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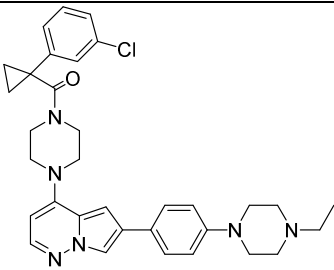
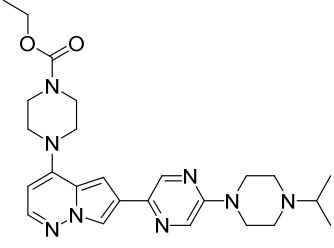
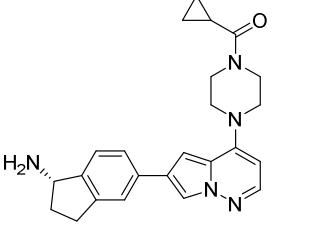
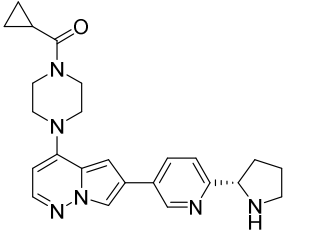
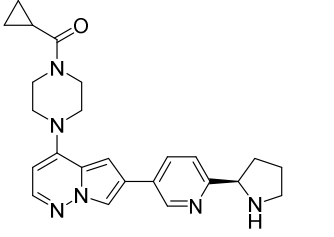
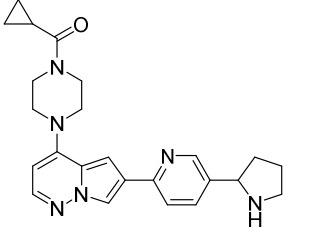
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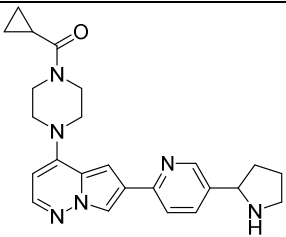
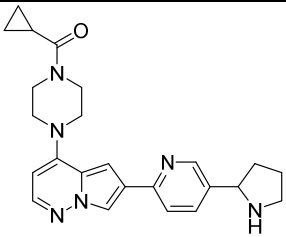
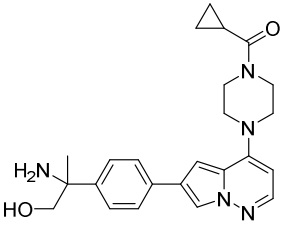
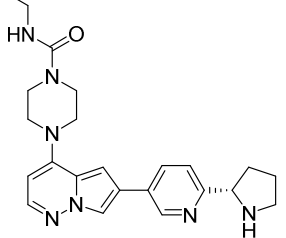
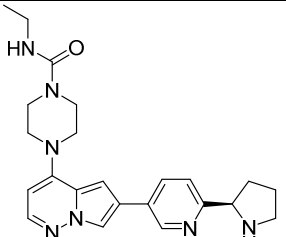
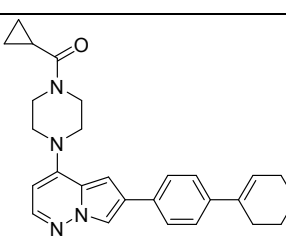
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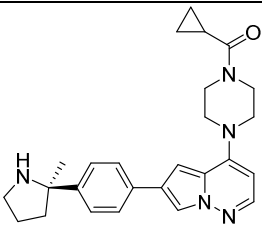
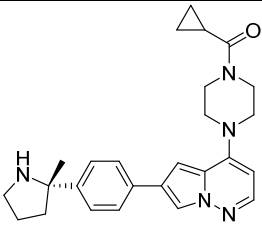
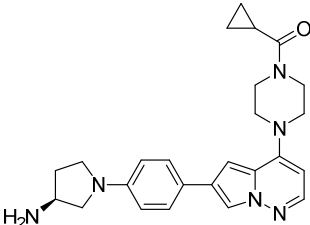
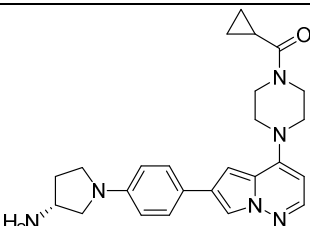
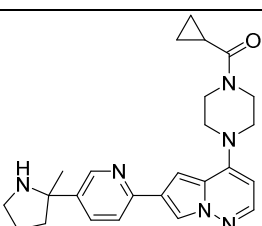
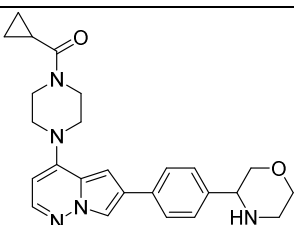
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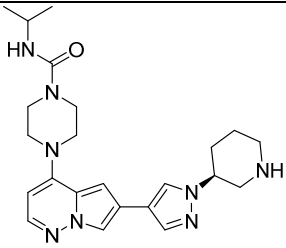
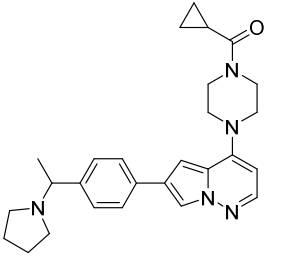
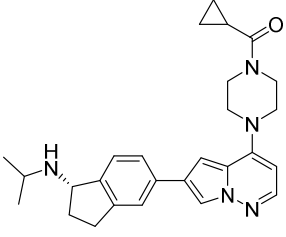
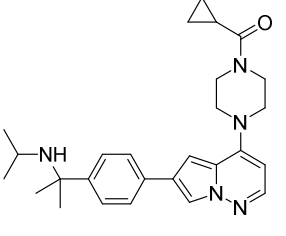
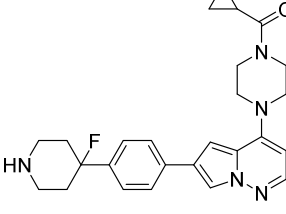
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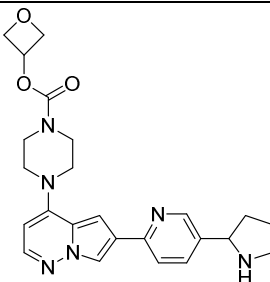
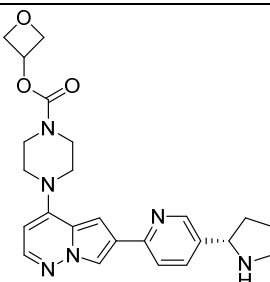
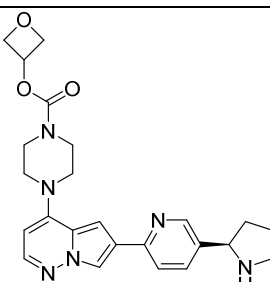
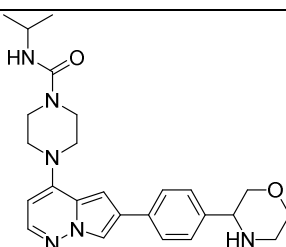
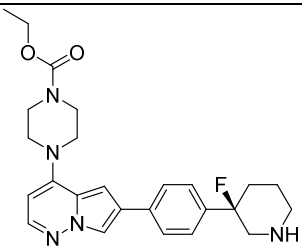
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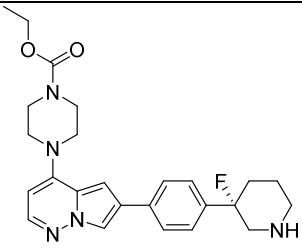
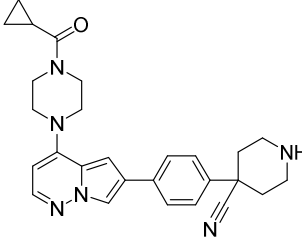
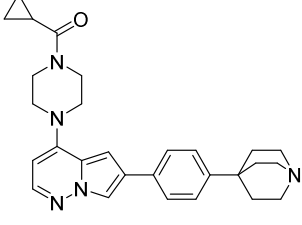
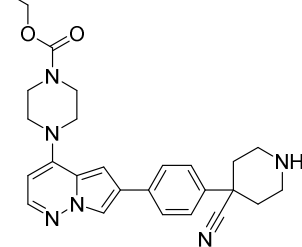
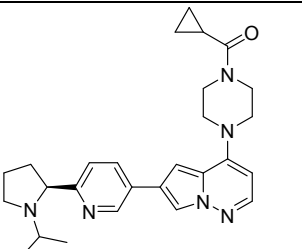
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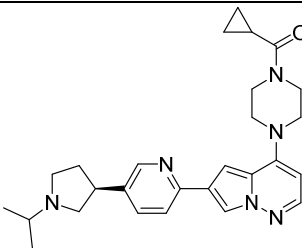
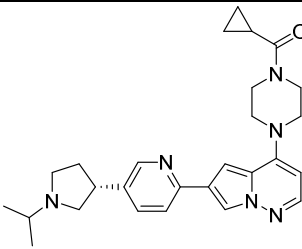
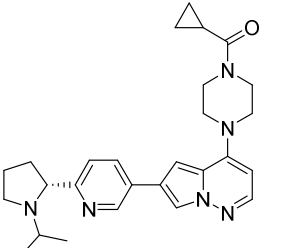
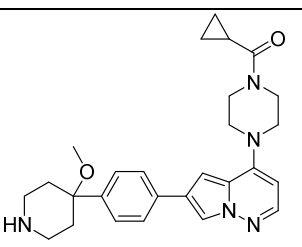
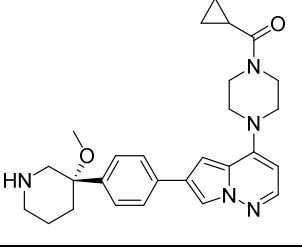
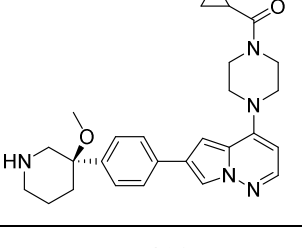
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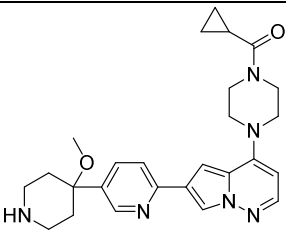
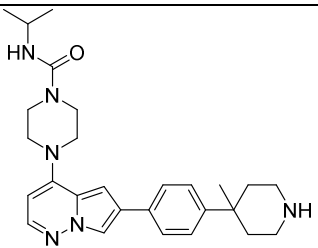
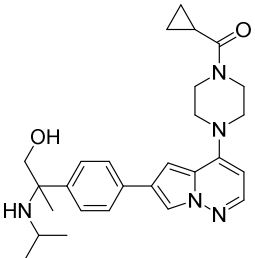
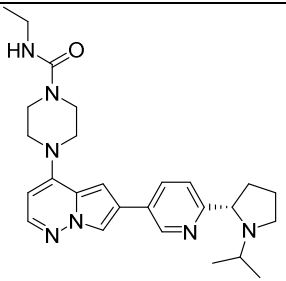
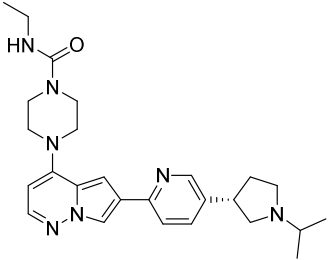
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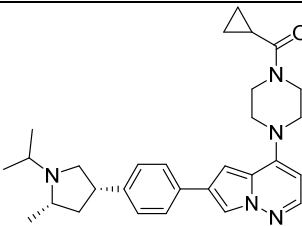
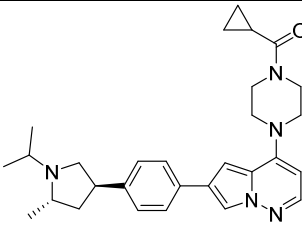
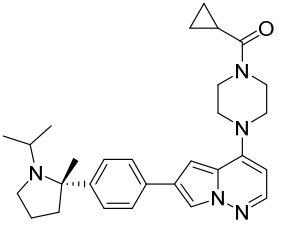
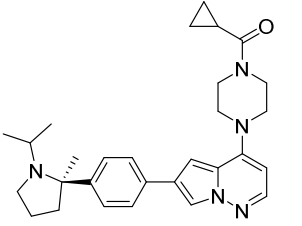
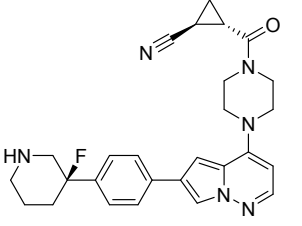
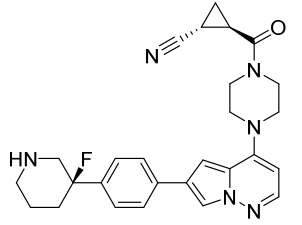
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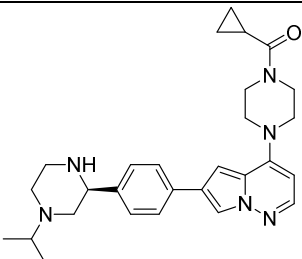
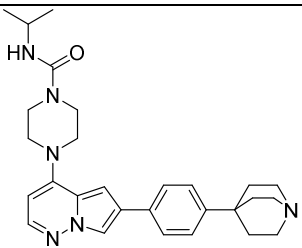
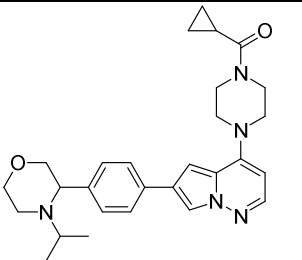
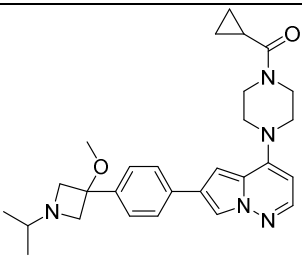
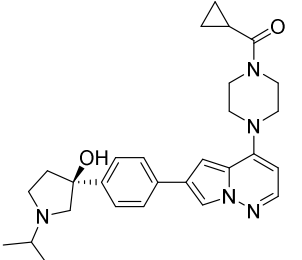
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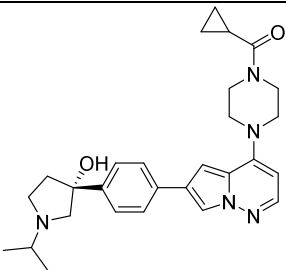
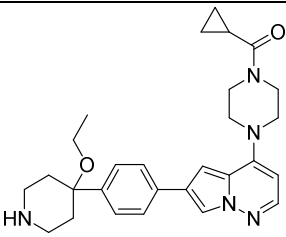
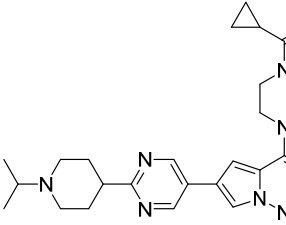
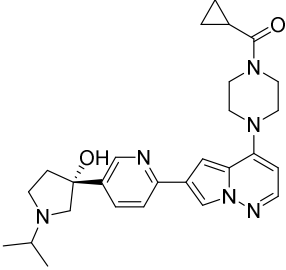
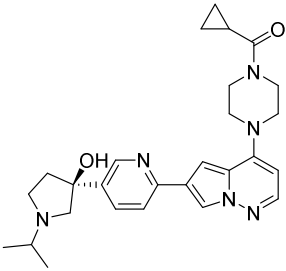
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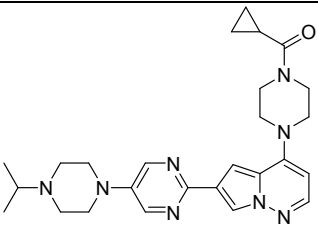
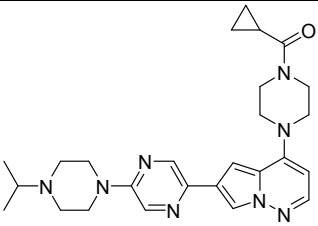
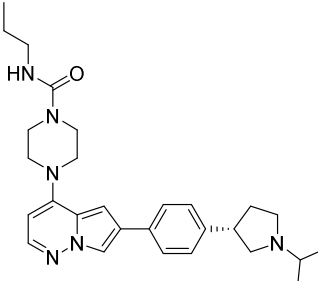
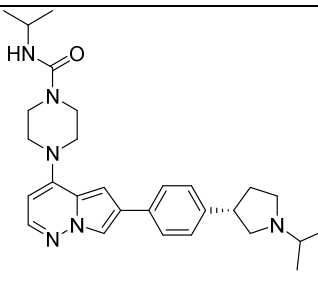
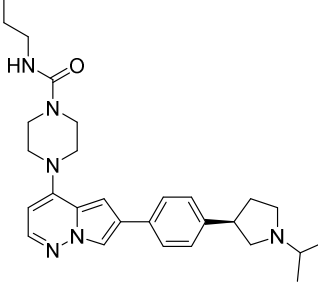
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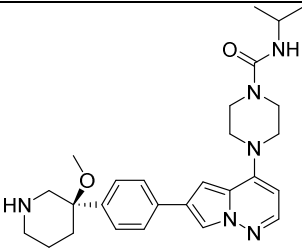
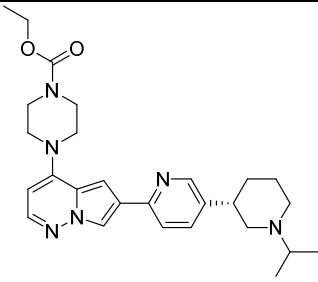
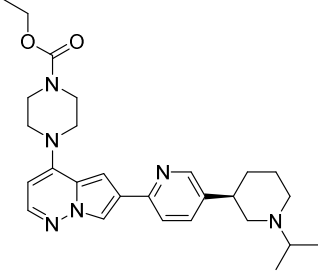
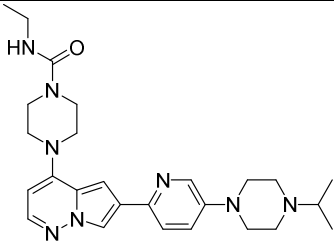
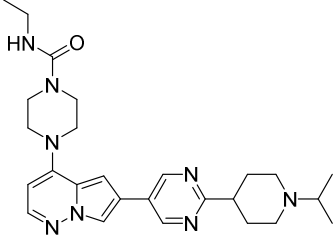
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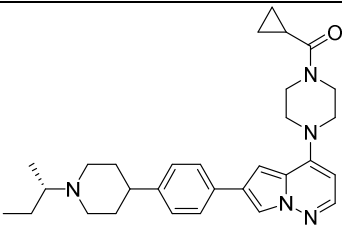
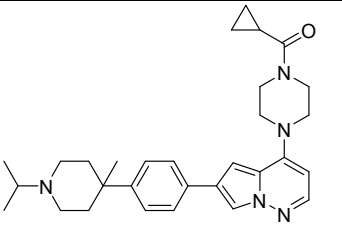
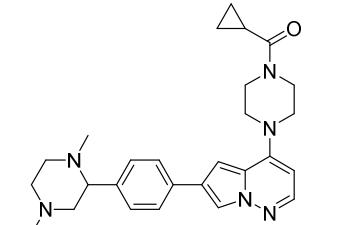
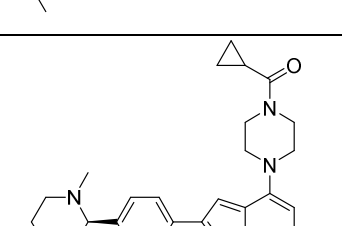
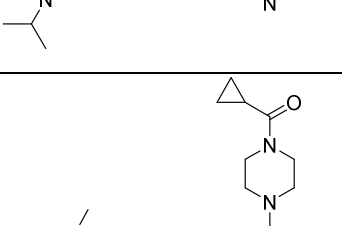
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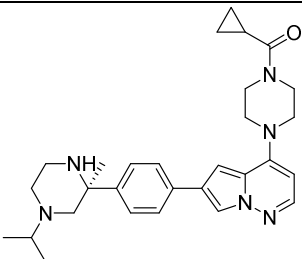
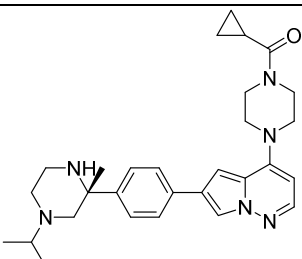
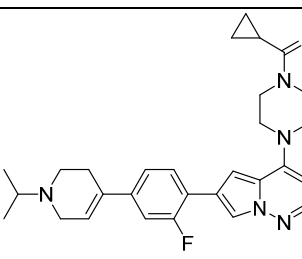
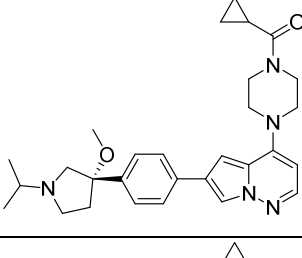
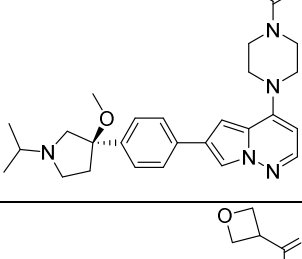
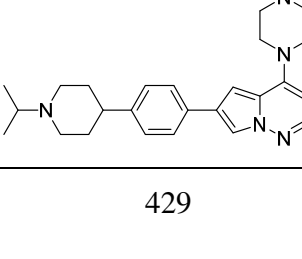
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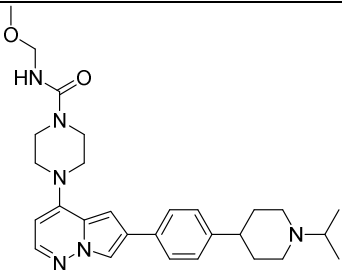
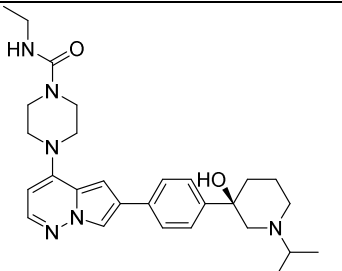
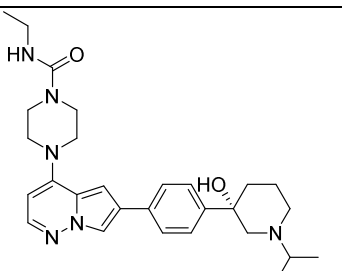
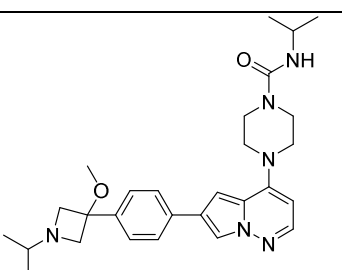
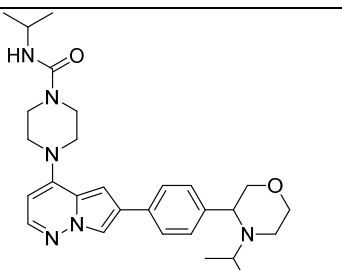
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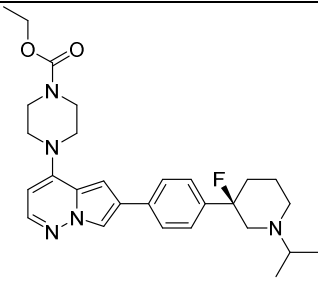
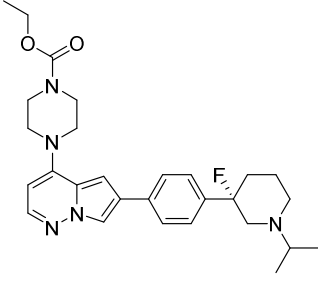
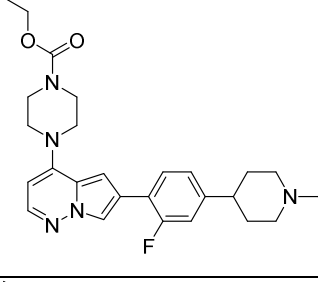
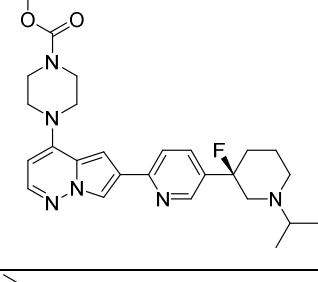
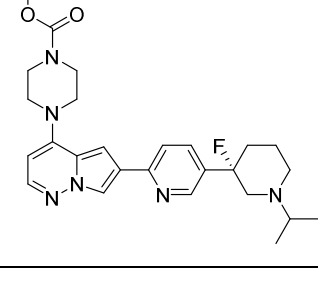
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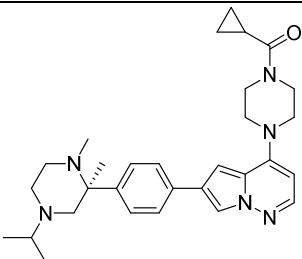
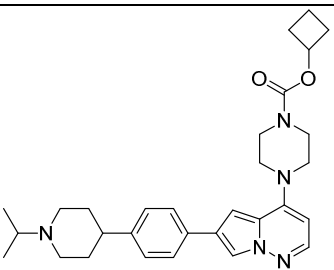
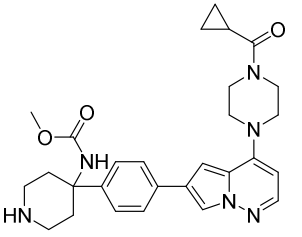
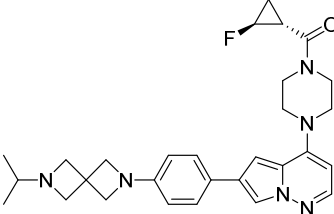
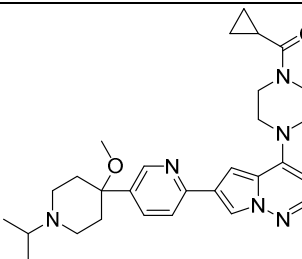
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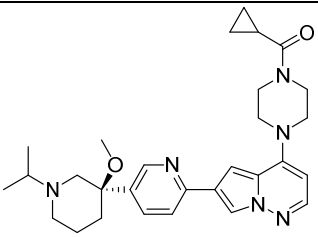
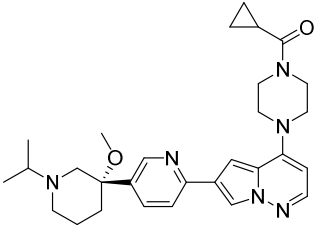
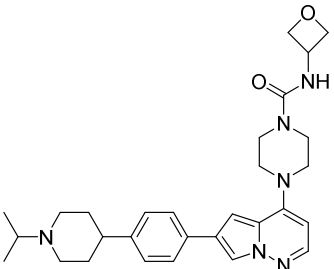
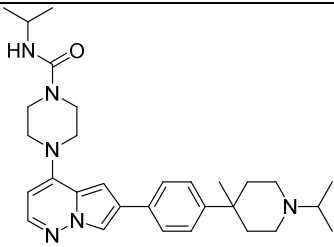
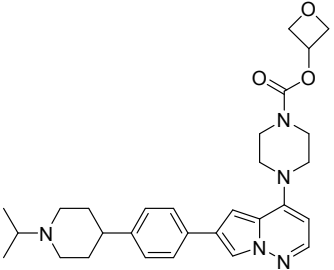
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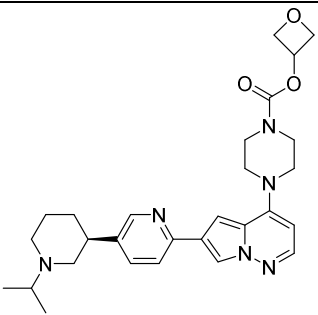
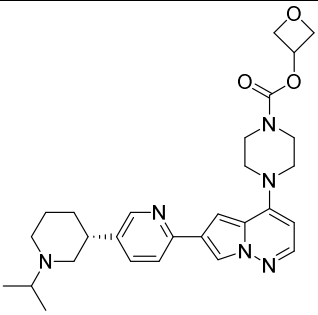
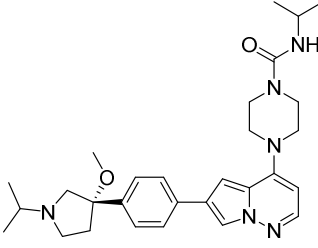
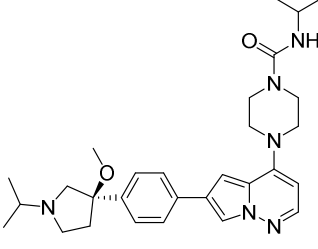
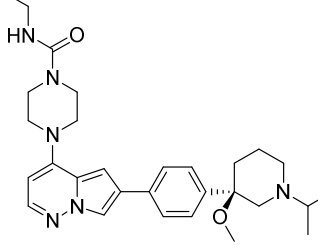
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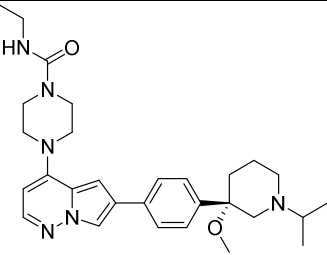
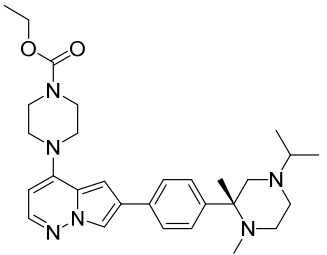
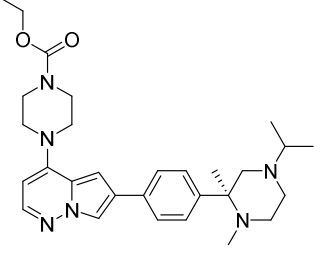
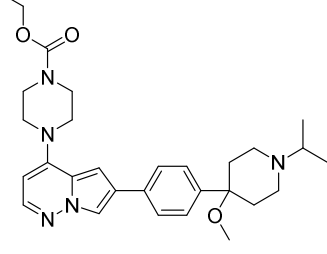
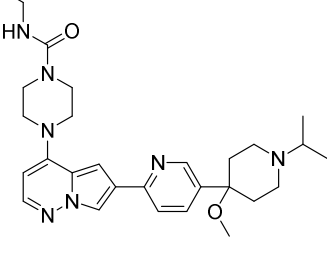
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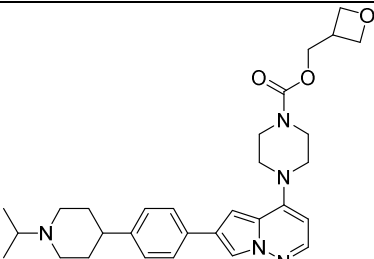
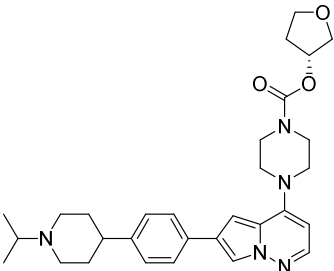
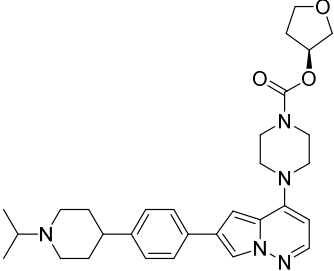
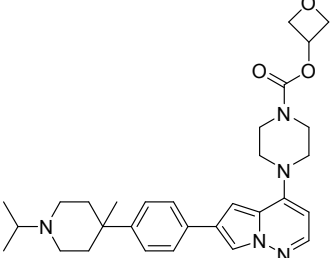
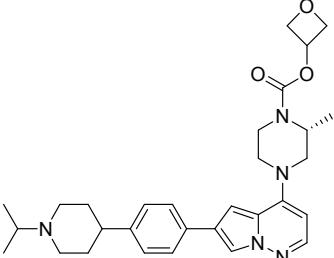
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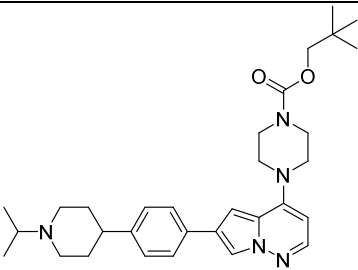
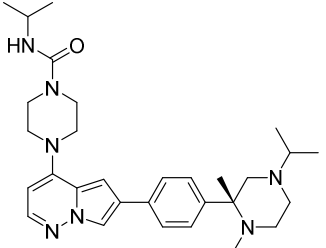
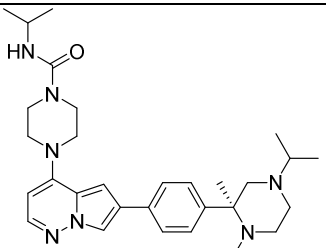
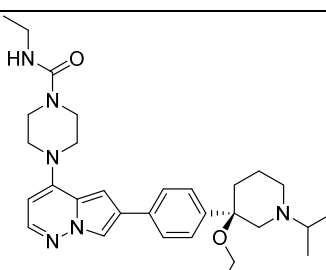
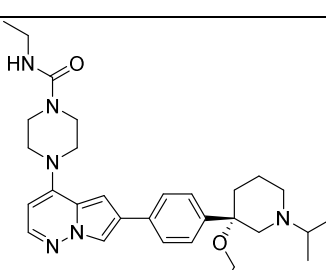
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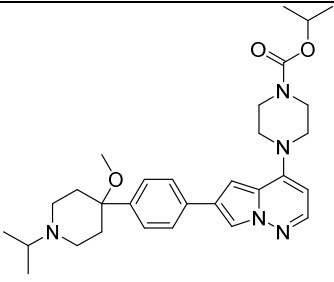
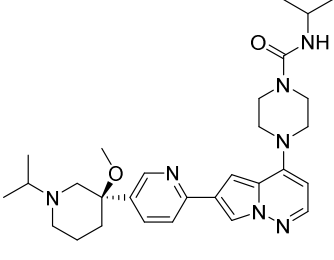
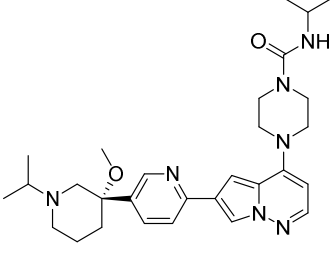
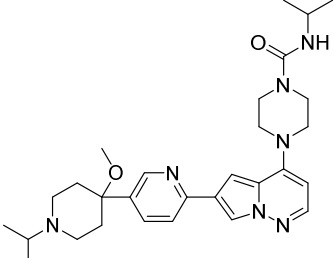
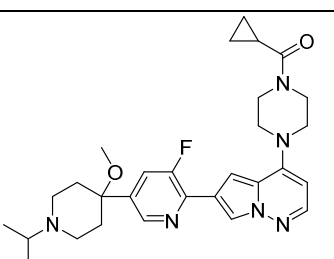
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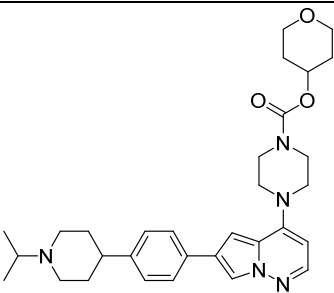
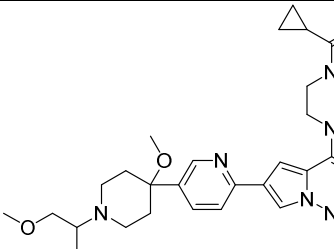
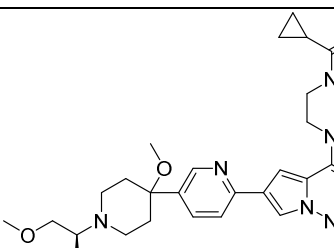
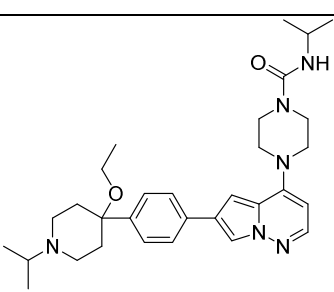
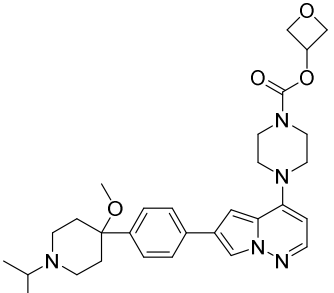
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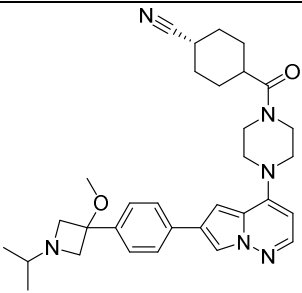
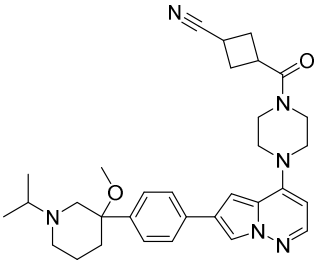
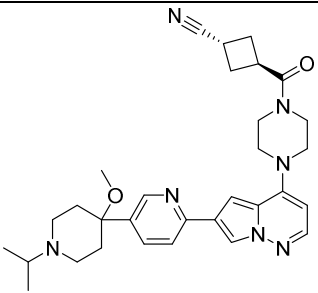
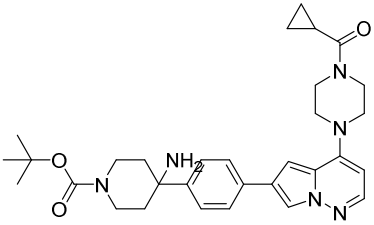
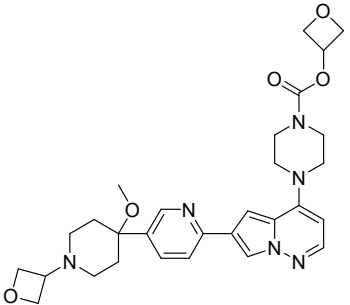
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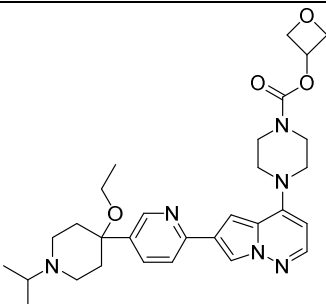
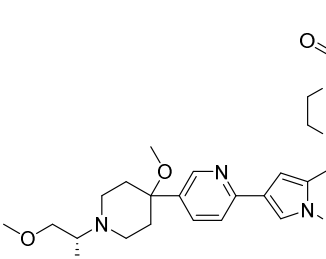
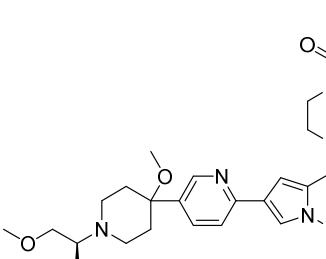
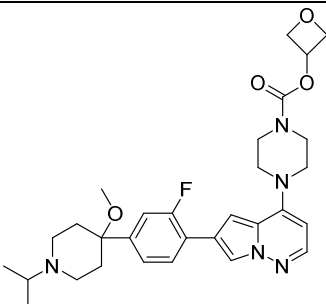
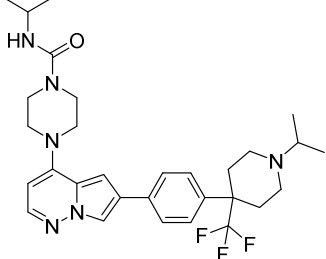
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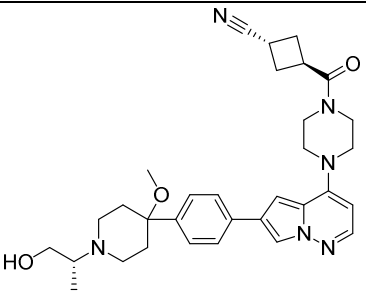
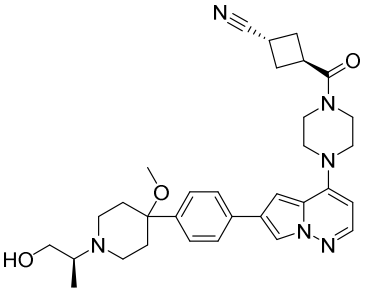
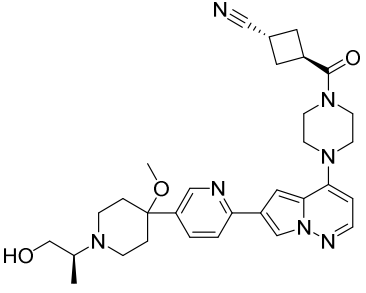
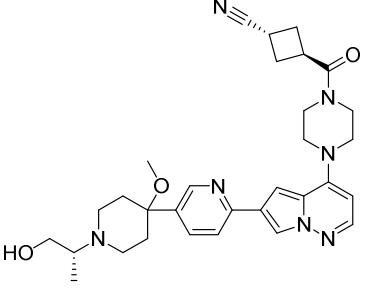
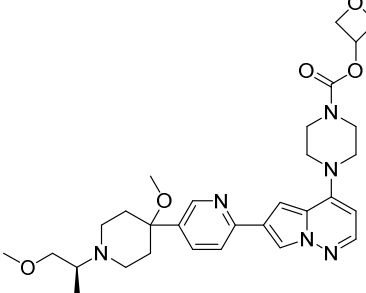
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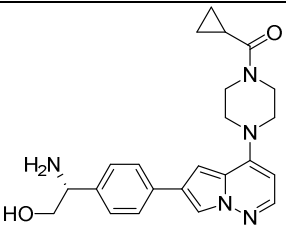
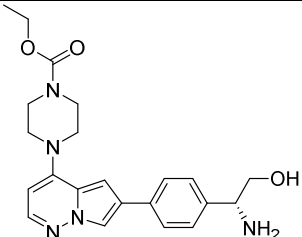
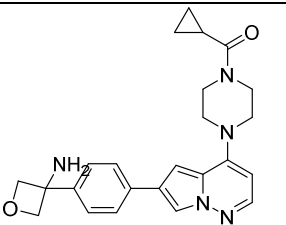
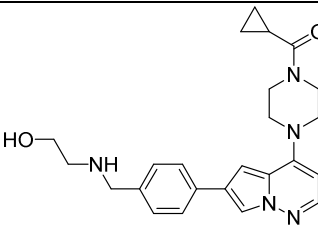
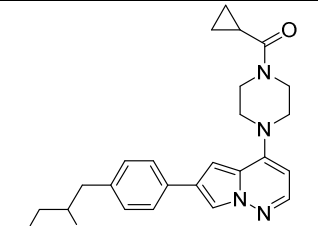
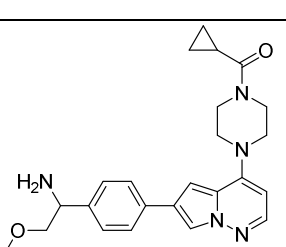
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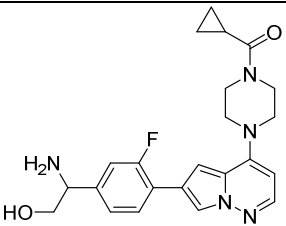
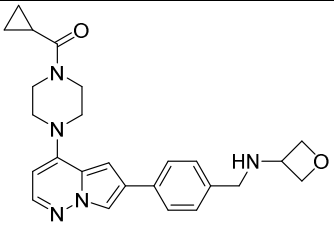
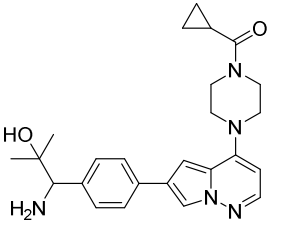
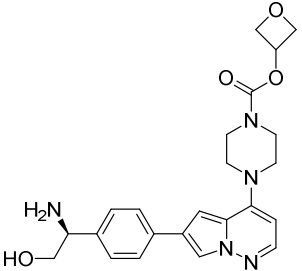
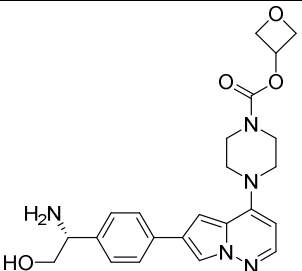
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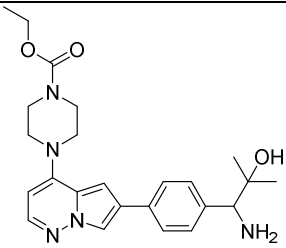
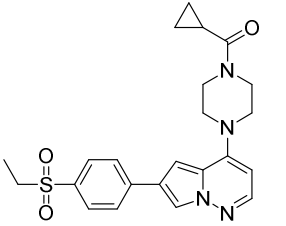
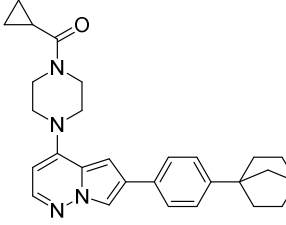
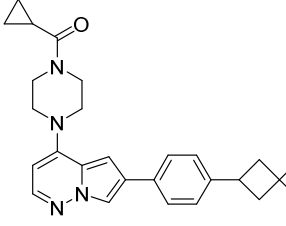
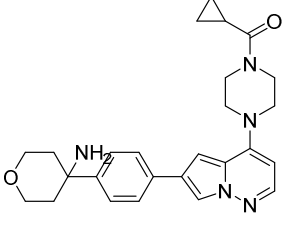
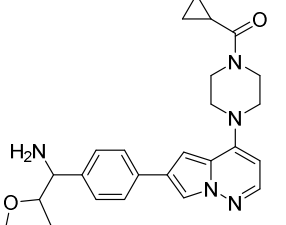
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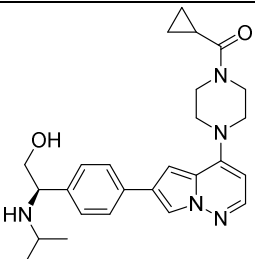
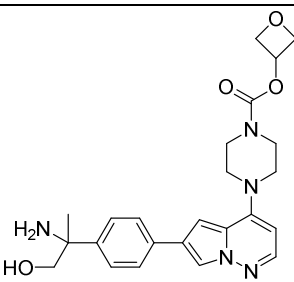
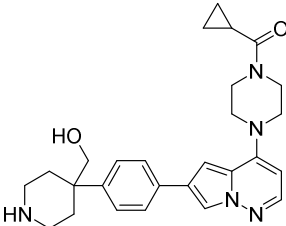
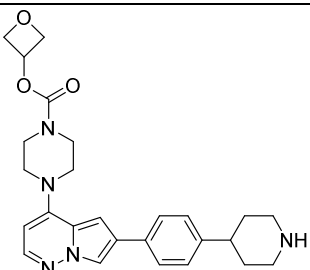
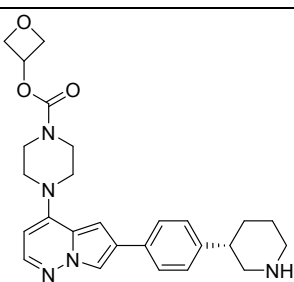
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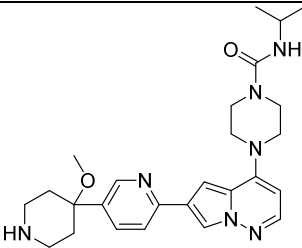
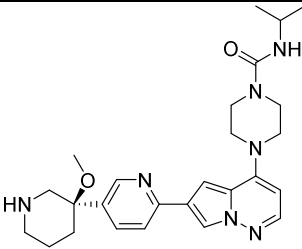
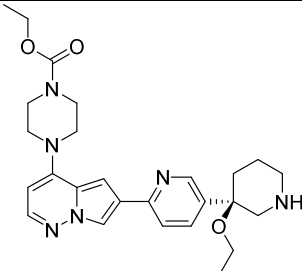
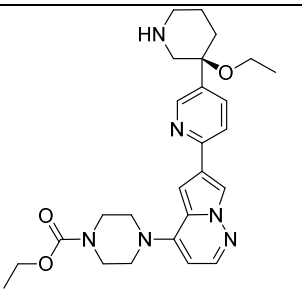
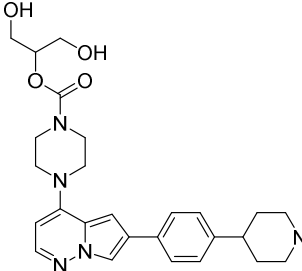
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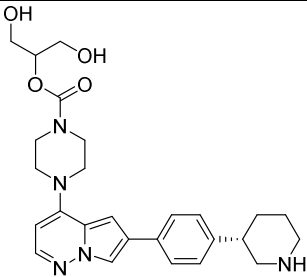
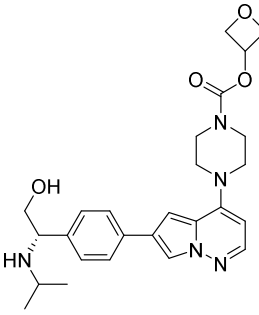
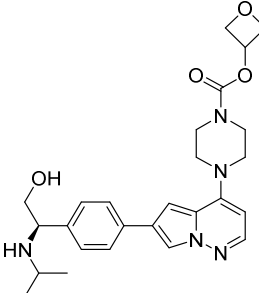
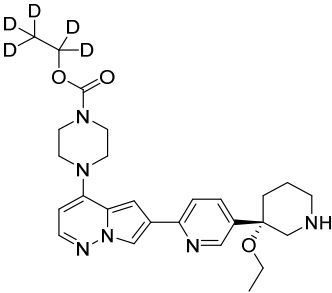
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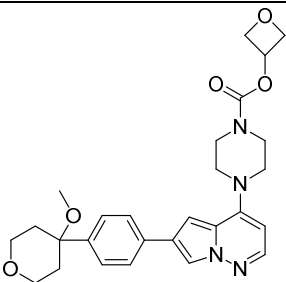
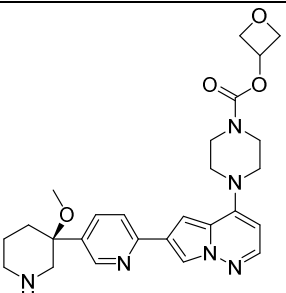
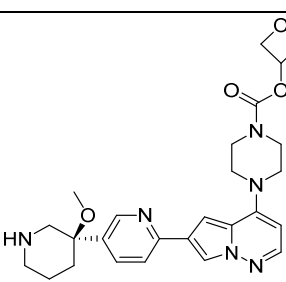
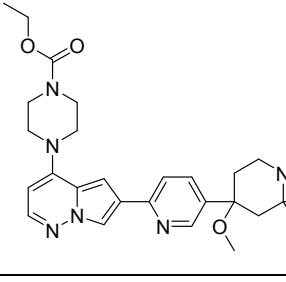
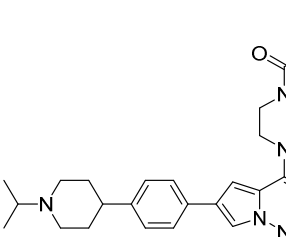
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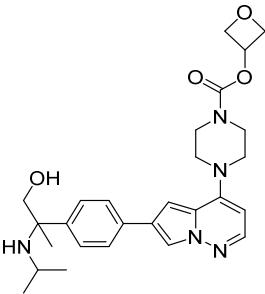
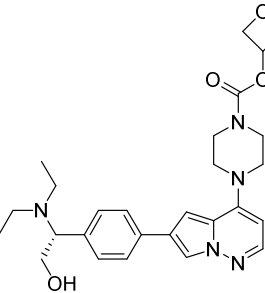
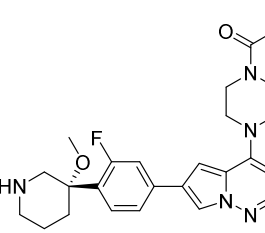
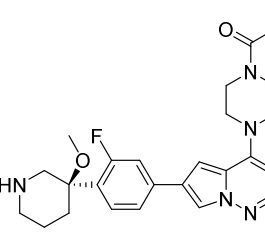
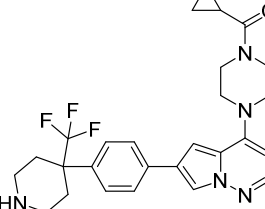
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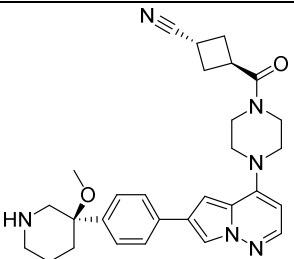
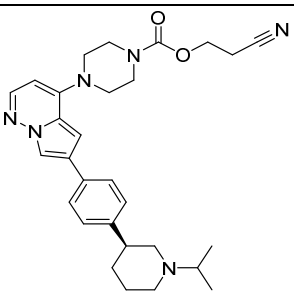
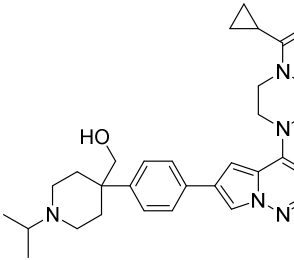
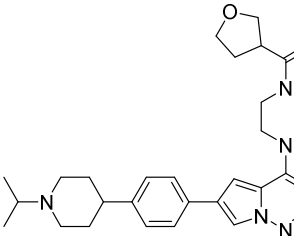
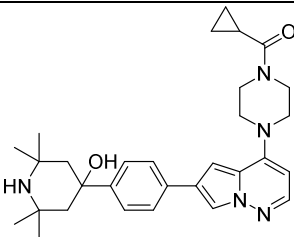
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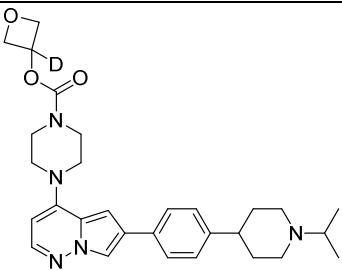
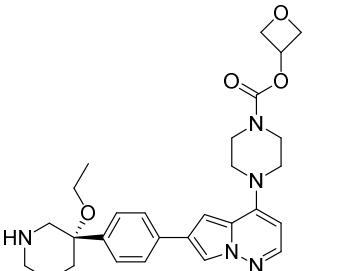
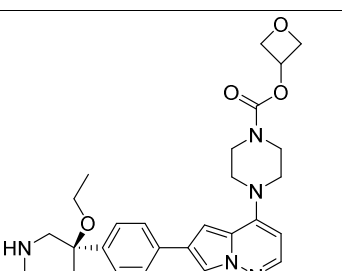
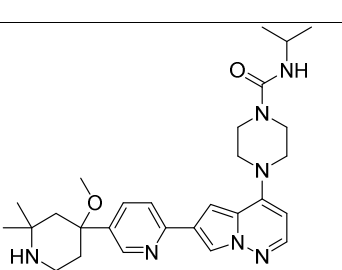
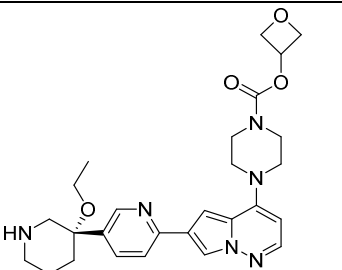
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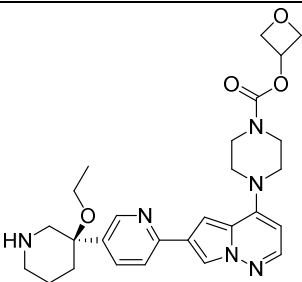
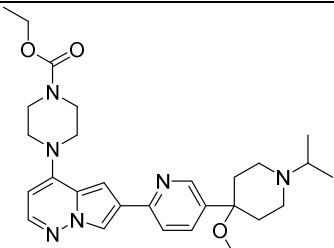
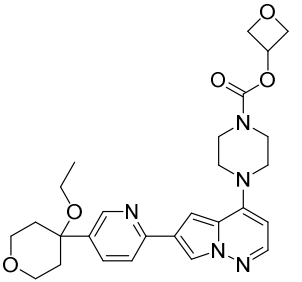
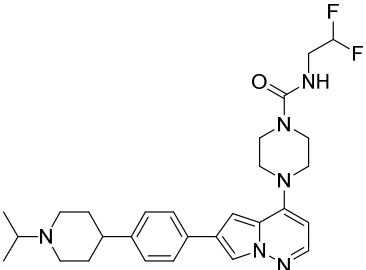
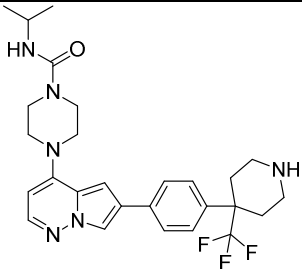
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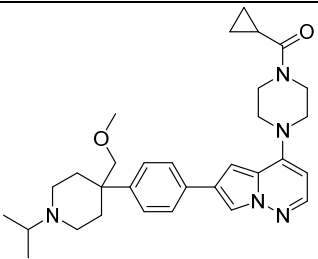
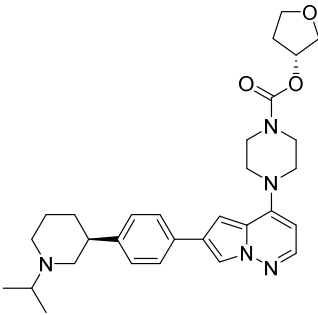
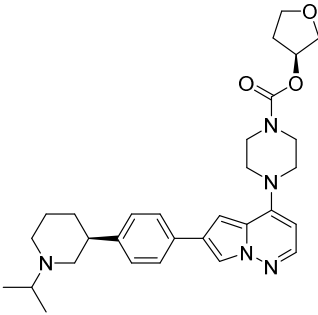
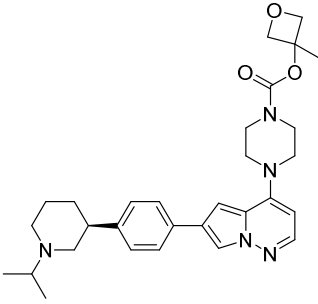
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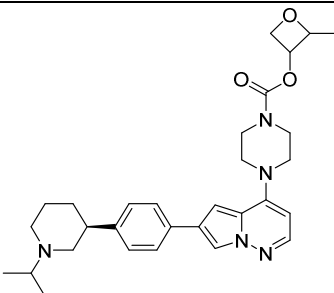
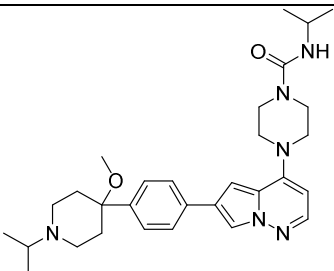
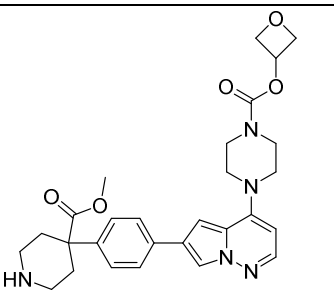
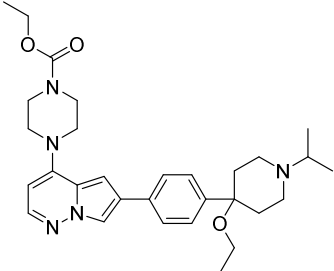
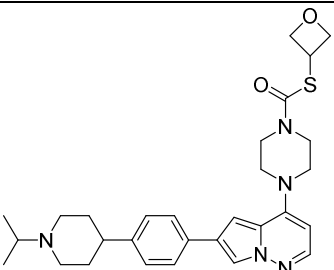
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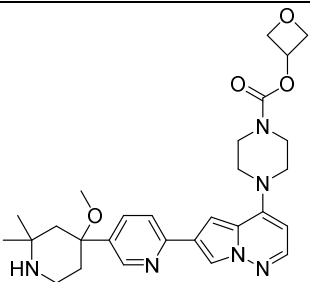
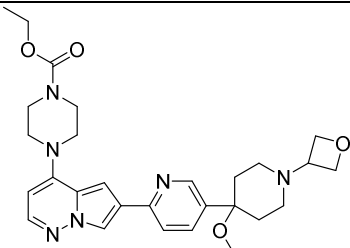
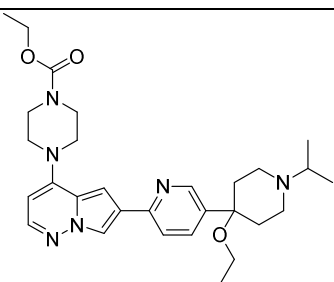
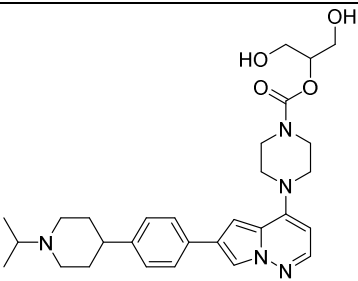
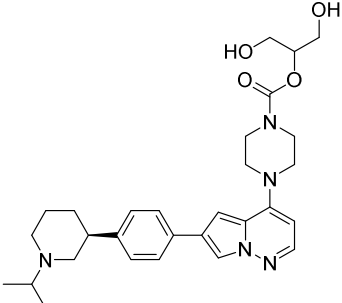
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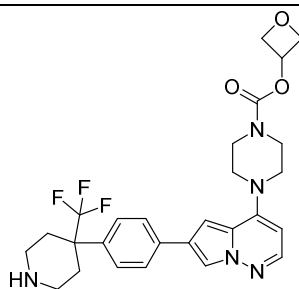
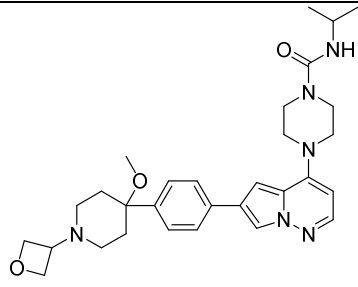
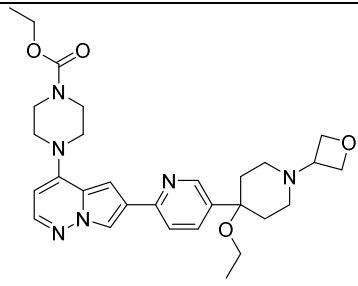
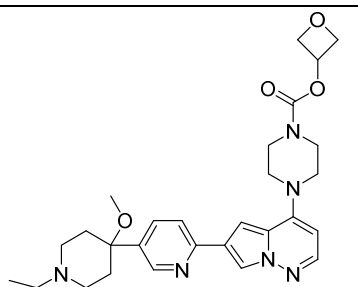
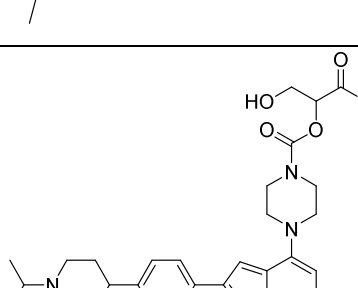
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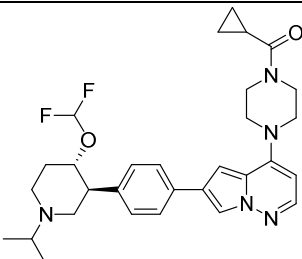
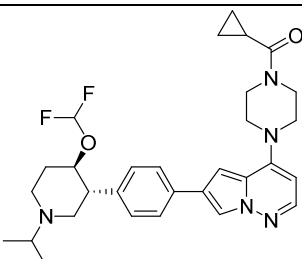
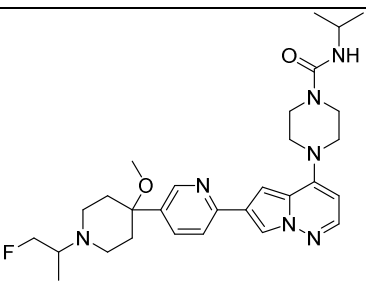
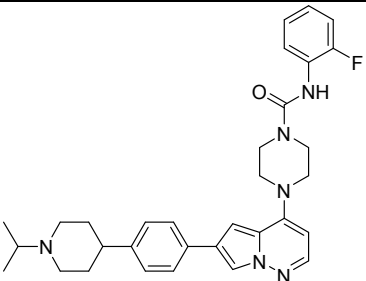
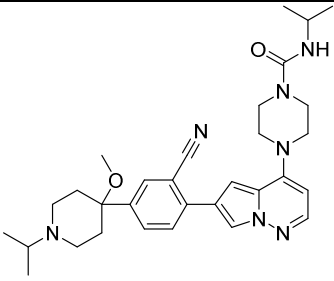
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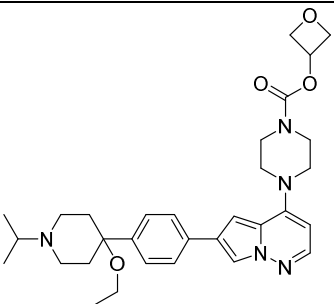
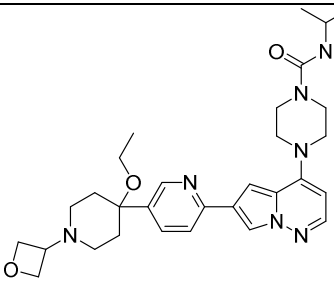
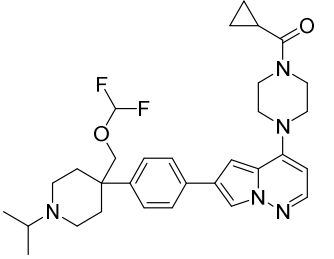
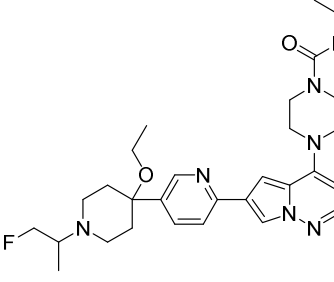
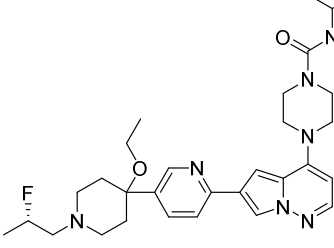
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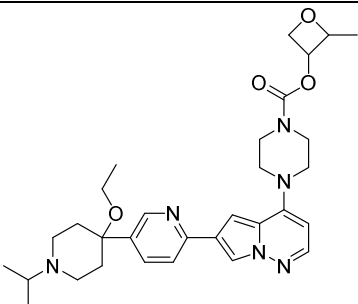
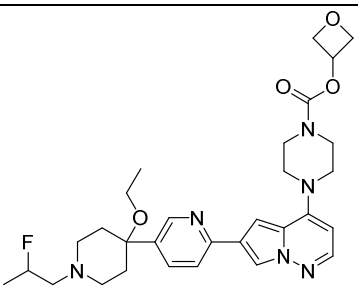
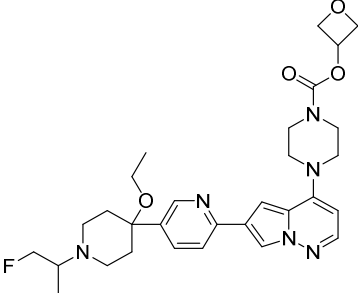
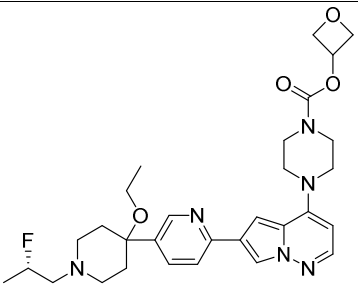
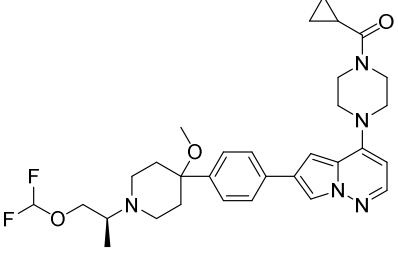
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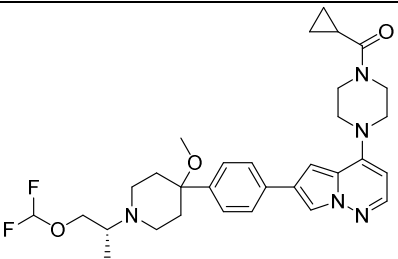
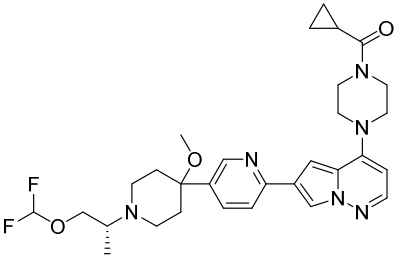
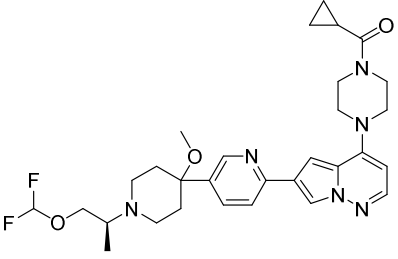
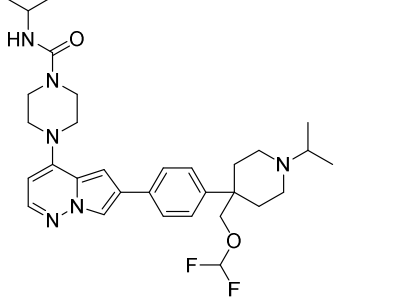
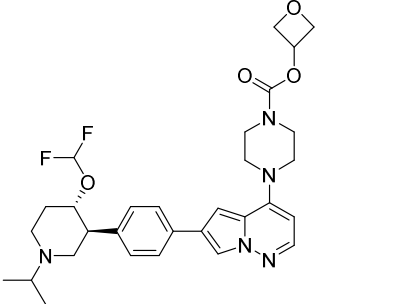
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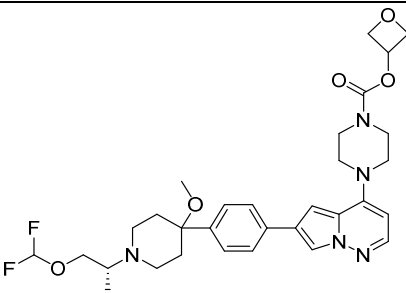
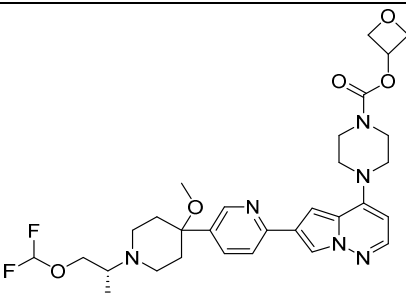
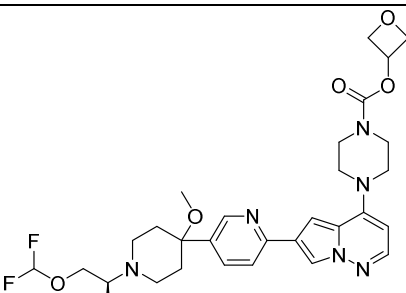
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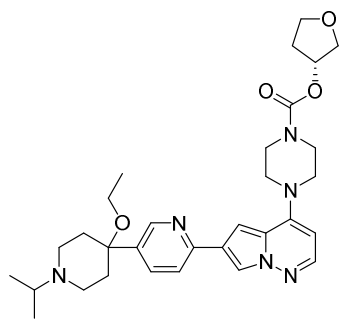
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17. A pharmaceutical composition, comprising at least one compound of any one of claims 1 to 16 or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

18. Use of a compound of any one of claims 1 to 16 or a pharmaceutically acceptable salt thereof or a pharmaceutical composition of claim 17 in the manufacture of a medicament for treating or ameliorating fibrodysplasia ossificans progressive in a subject.

19. The use of claim 18, wherein the subject has a mutation in an ALK2 gene that results in the expression of an ALK2 enzyme having an amino acid modification selected from one or more of L196P, PF197-8L, R202I, R206H, Q207E, R258S, R258G, G328A, G328W, G328E, G328R, G356D, and R375P.
20. The use of claim 18 or 19, wherein the ALK2 enzyme has the amino acid modification R206H.
21. Use of a compound of any one of claims 1 to 16 or a pharmaceutically acceptable salt thereof or a pharmaceutical composition of claim 17 in the manufacture of a medicament for treating or ameliorating diffuse intrinsic pontine glioma in a subject.
22. The use of claim 21, wherein the subject has a mutation in an ALK2 gene that results in the expression of an ALK2 enzyme having an amino acid modification selected from one or more of R206H, G328V, G328W, G328E, and G356D.
23. The use of claim 22, wherein the ALK2 enzyme has the amino acid modification R206H.
24. A compound of the following formula:



or a pharmaceutically acceptable salt thereof.

25. A pharmaceutical composition comprising:
the compound of claim 24 or a pharmaceutically acceptable salt thereof; and at least one pharmaceutically acceptable excipient.

26. Use of compound of claim 24 or a pharmaceutically acceptable salt thereof for a pharmaceutical composition of claim 25 in the manufacture of a medicament for treating or ameliorating fibrodysplasia ossificans progressive in a subject.