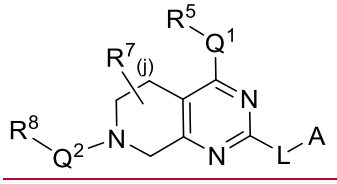
However, some disadvantages are associated with current TPD technologies. These include the promiscuous degradation of the target protein(s) in many tissues and organs, not just the tissue(s) and organ(s) where the target protein(s) is involved in a disease process, which is expected to result in unwanted side effects of treatment. Also, resistance to these technologies can develop through mutations or alterations in expression of components of the UPS such as E3 ligases (Ottis et al., ACS Chem Biol, 2019, 14:2215-2223; Zhang et al., Mol Cancer Ther, 2019, 18:1302-1311), resulting in loss of therapeutic efficacy. As such, a need exists for improved/alternative methods and compositions for TPD.

It is also desirable to develop improved/alternative TPD agents that mediate the degradation of proteins involved in cancer and other diseases. Activating mutations in KRAS are among the most frequent oncogenic changes found in human cancers (Simanshu et al., Cell, 2017, 170:17-33). In particular, mutated KRAS(G12C) is found in ~15% of lung adenocarcinomas, ~8% of colorectal carcinomas and ~4% of pancreatic adenocarcinomas, as well as in other cancers (Jiao and Yang, Innovation (N Y), 2020, 1:100035). Although mutated KRAS has historically been considered an undruggable cancer drug target, recent progress has led to the development of covalently binding pharmacological inhibitors of KRAS(G12C) (Ostrem et al., Nature, 2013, 503:548-551; Cannon et al., Nature, 2019, 575:217-223; O'Bryan, Pharmacol Res, 2019, 139:503-511; Hallin et al., Cancer Discov, 2020, 10:54-71). Although efficacy has been observed for such inhibitors in cancer patients in the clinic, innate resistance and tumor relapses have also been reported (Cannon et al., Nature, 2019, 575:217-223). The mechanisms underlying the innate and acquired resistance to covalent KRAS(G12C) inhibitors have also begun to be elucidated, mediated for example, through high EGFR signaling (Adachi et al., Clin Cancer Res, 2020, in press; Amodio et al., Cancer Discov, 2020; Hata and Shaw, Nat Med, 2020, 26:169-170; Jiao and Yang, Innovation (N Y), 2020, 1:100035; Koleilat and Kwong, Cancer Discov, 2020, 10:1094-1096; Ryan et al., Clin Cancer Res, 2020, 26:1633-1643; Xue et al., Nature, 2020, 577:421-425). As such, KRAS(G12C) represents an attractive drug target and it is desirable to develop agents that induce TPD of KRAS(G12C). It is also desirable to develop agents that induce degradation of both KRAS(G12C) and one or more other proteins, particularly those involved in mediating resistance to KRAS(G12C) inhibitors.

SUMMARY

In one aspect of the present disclosure, there is provided a compound of the Formula **I**:



(**I**);

or a pharmaceutically acceptable salt thereof, wherein,

A is a chemical moiety that binds HSP90 protein;

L is a linker;

Q^1 is a nitrogen containing heteroaryl or heterocyclyl ring, each of which are optionally substituted with 1 to 3 groups selected from R^6;

R^5 is –C(O)Y or $–S(O)_2Y$;

Y is a $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, halo$(C_2\text{-}C_6)$alkenyl, NH_2, -NH$(C_1\text{-}C_6)$alkyl, -N[$(C_1\text{-}C_6)$alkyl]$_2$, $NHNH_2$, or NHOH, wherein said $(C_2\text{-}C_6)$alkenyl, alone or as recited in halo$(C_2\text{-}C_6)$alkenyl, is optionally substituted with $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, heteroalkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $-C(O)NH_2$, -C(O)NH$(C_1\text{-}C_6)$alkyl, or -C(O)N[$(C_1\text{-}C_6)$alkyl]$_2$;

R^6 is $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkoxy, hydroxy$(C_1\text{-}C_6)$alkyl, cyano$(C_1\text{-}C_6)$alkyl, oxo, cyano, heteroalkyl, -C(O)OH, -C(O)O$(C_1\text{-}C_6)$alkyl, $-C(O)NH_2$, -C(O)NH$(C_1\text{-}C_6)$alkyl, or -C(O)N[$(C_1\text{-}C_6)$alkyl]$_2$, wherein said $(C_1\text{-}C_6)$alkyl is optionally substituted with heteroaryl;

R^7 is halo, hydroxyl, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkoxy, cylcoalkyl, heteroalkyl, hydroxy$(C_1\text{-}C_6)$alkyl, or S$(C_1\text{-}C_6)$alkyl;

j is 1 or 2;

Q^2 is a bond, -C(O)-, or $(C_1\text{-}C_3)$alkylene;

R^8 is cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which are optionally substituted with 1 to 3 groups selected from R^9;

R^9 is halo, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, halo$(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, oxo, cyano, -$(C_1\text{-}C_6)$alkylOR^c, -$(C_1\text{-}C_6)$alkylN$(R^d)_2$, -$(C_1\text{-}C_6)$alkylC(O)OR^d, OH, -$(C_1\text{-}C_6)$alkylC(O)N$(R^d)_2$, -$(C_1\text{-}C_6)$alkylO$(C_1\text{-}C_6)$alkylN$(R^d)_2$, -$(C_1\text{-}C_6)$alkylSOR^d, -$(C_1\text{-}C_6)$alkylS$(O)_2R^d$, -$(C_1\text{-}C_6)$alkylSON$(R^d)_2$, -$(C_1\text{-}C_6)$alkylSO$_2$N$(R^d)_2$, -$(C_1\text{-}C_6)$alkylcycloalkyl, -$(C_1\text{-}C_6)$alkylheterocyclyl, -$(C_1\text{-}C_6)$alkylheteroaryl, -$(C_1\text{-}C_6)$alkylaryl, -$(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkoxy, CN, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -C(O)R^d, -C(O)OR^d, -C(O)N$(R^d)_2$, N$(R^d)_2$, -C(O)NR^d$(C_1\text{-}C_6)$alkylN$(R^d)_2$, -NR^d$(C_1\text{-}C_6)$alkylN$(R^d)_2$, -NR^d$(C_1\text{-}C_6)$alkylOR^d, -SOR^d, -S$(O)_2R^d$, -SON$(R^d)_2$, -SO$_2$N$(R^d)_2$, or CN, wherein each aryl, cycloalkyl, heterocyclyl, and heteoaryl alone and in connection with -$(C_1$-

C_6)alkylcycloalkyl, -(C_1-C_6)alkylheterocyclyl, -(C_1-C_6)alkylheteroaryl, -(C_1-C_6)alkylaryl are optionally substituted with 1 to 3 groups selected from R^e;

R^c and R^d are each independently selected from hydrogen, (C_1-C_6)alkyl, and halo(C_1-C_6)alkyl; and

R^e is selected from halo, oxo, CN, NO_2, -$N(R^d)_2$, -OR^d, -$C(O)OR^d$, (C_1-C_6)alkyl, -(C_1-C_6)alkylOR^c, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -(C_1-C_6)alkyl$C(O)OR^d$, -(C_1-C_6)alkyl$C(O)N(R^d)_2$, (C_2-C_6)alkenyl, halo(C_2-C_6)alkenyl, (C_2-C_6)alkynyl, -(C_1-C_6)alkylSR^d, -(C_1-C_6)alkylOR^c, -(C_1-C_6)alkyl$N(R^d)_2$, -$C(O)N(R^d)_2$, -$C(O)NR^dC_{1-6}$alkyl$N(R^d)_2$, -NR^dC_{1-6}alkyl$N(R^d)_2$, -NR^dC_{1-6}alkylOR^d, -SOR^d, -$S(O)_2R^d$, -$SON(R^d)_2$, -$SO_2N(R^d)_2$, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl.

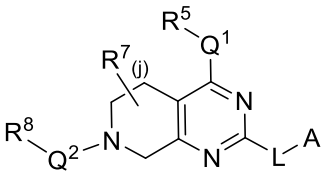
In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound disclosed herein, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or the composition disclosed herein, in the manufacture of a medicament for treating cancer.

In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or the composition of disclosed herein, for use in therapy.

The present disclosure provides tumor-targeted protein degradation chimeras,

termed chaperone-mediated protein degraders (CHAMPs) comprising a first moiety that is capable of binding to a target protein (e.g., KRAS(G12C)) or proteins and a second moiety that is capable of binding a chaperone protein or proteins or protein component of chaperone complexes (e.g., HSP90). Such CHAMP compounds include those having the Formula **I**:



(**I**);

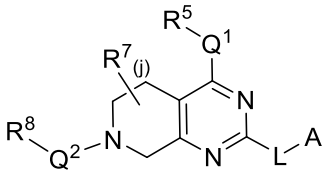
and pharmaceutically acceptable salts thereof, wherein L, A, Q^1, Q^2, R^5, R^7, R^8, and j are as defined herein.

Compositions comprising the disclosed compounds of Formula **I** as well as methods for their manufacture are also provided. In one ~~aspect~~example, the disclosed compounds induce targeted oncogenic protein degradation in a tumor-selective fashion and are useful in the treatment of cancer and related conditions.

DETAILED DESCRIPTION

1. General Description of Compounds

Provided herein are CHAMP compounds having the Formula **I**:



(**I**)

or a pharmaceutically acceptable salt thereof, wherein,

A is a chemical moiety that binds HSP90 protein;

L is a linker;

Q^1 is a nitrogen containing heteroaryl or heterocyclyl ring, each of which are optionally substituted with 1 to 3 groups selected from R^6;

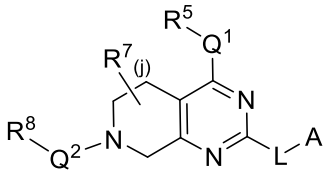
R^5 is –C(O)Y or $–S(O)_2Y$;

Y is a $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, halo$(C_2\text{-}C_6)$alkenyl, NH_2, -$NH(C_1\text{-}C_6)$alkyl, -$N[(C_1\text{-}C_6)\text{alkyl}]_2$, $NHNH_2$, or NHOH, wherein said $(C_2\text{-}C_6)$alkenyl, alone or as recited in halo$(C_2\text{-}C_6)$alkenyl, is optionally substituted with $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}$

WHAT IS CLAIMED IS:

Listing of Claims:

1. A compound of the Formula **I**:



(**I**);

or a pharmaceutically acceptable salt thereof, wherein,

A is a chemical moiety that binds HSP90 protein;

L is a linker;

Q^1 is a nitrogen containing heteroaryl or heterocyclyl ring, each of which are optionally substituted with 1 to 3 groups selected from R^6;

R^5 is $–C(O)Y$ or $–S(O)_2Y$;

Y is a $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, halo$(C_2\text{-}C_6)$alkenyl, NH_2, -$NH(C_1\text{-}C_6)$alkyl, -$N[(C_1\text{-}C_6)\text{alkyl}]_2$, $NHNH_2$, or NHOH, wherein said $(C_2\text{-}C_6)$alkenyl, alone or as recited in halo$(C_2\text{-}C_6)$alkenyl, is optionally substituted with $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, heteroalkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $-C(O)NH_2$, -$C(O)NH(C_1\text{-}C_6)$alkyl, or -$C(O)N[(C_1\text{-}C_6)\text{alkyl}]_2$;

R^6 is $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkoxy, hydroxy$(C_1\text{-}C_6)$alkyl, cyano$(C_1\text{-}C_6)$alkyl, oxo, cyano, heteroalkyl, -C(O)OH, -$C(O)O(C_1\text{-}C_6)$alkyl, $-C(O)NH_2$, -$C(O)NH(C_1\text{-}C_6)$alkyl, or -$C(O)N[(C_1\text{-}C_6)\text{alkyl}]_2$, wherein said $(C_1\text{-}C_6)$alkyl is optionally substituted with heteroaryl;

R^7 is halo, hydroxyl, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkoxy, cylcoalkyl, heteroalkyl, hydroxy$(C_1\text{-}C_6)$alkyl, or S$(C_1\text{-}C_6)$alkyl;

j is 1 or 2;

Q^2 is a bond, -C(O)-, or $(C_1\text{-}C_3)$alkylene;

R^8 is cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which are optionally substituted with 1 to 3 groups selected from R^9;

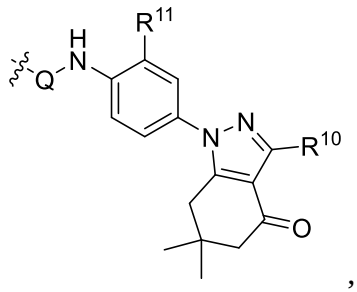
R^9 is halo, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, halo$(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, oxo, cyano, -$(C_1\text{-}C_6)\text{alkyl}OR^c$, -$(C_1\text{-}C_6)\text{alkyl}N(R^d)_2$, -$(C_1\text{-}C_6)\text{alkyl}C(O)OR^d$, OH, -$(C_1\text{-}C_6)\text{alkyl}C(O)N(R^d)_2$, -$(C_1\text{-}C_6)\text{alkyl}O(C_1\text{-}C_6)\text{alkyl}N(R^d)_2$, -$(C_1\text{-}C_6)\text{alkyl}SOR^d$, -$(C_1\text{-}C_6)\text{alkyl}S(O)_2R^d$, -$(C_1\text{-}C_6)\text{alkyl}SON(R^d)_2$, -$(C_1\text{-}C_6)\text{alkyl}SO_2N(R^d)_2$, -$(C_1\text{-}C_6)$alkylcycloalkyl, -$(C_1\text{-}C_6)$alkylheterocyclyl, -$(C_1\text{-}C_6)$alkylheteroaryl, -$(C_1\text{-}C_6)$alkylaryl, -$(C_1\text{-}C_6)$alkoxy,

halo(C_1-C_6)alkoxy, CN, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -C(O)R^d, -C(O)OR^d, -C(O)N(R^d)$_2$, N(R^d)$_2$, -C(O)NR^d(C_1-C_6)alkylN(R^d)$_2$, -NR^d(C_1-C_6)alkylN(R^d)$_2$, -NR^d(C_1-C_6)alkylOR^d, -SOR^d, -S(O)$_2$$R^d$, -SON($R^d$)$_2$, -SO$_2$N($R^d$)$_2$, or CN, wherein each aryl, cycloalkyl, heterocyclyl, and heteoaryl alone and in connection with -(C_1-C_6)alkylcycloalkyl, -(C_1-C_6)alkylheterocyclyl, -(C_1-C_6)alkylheteroaryl, -(C_1-C_6)alkylaryl are optionally substituted with 1 to 3 groups selected from R^e;

R^c and R^d are each independently selected from hydrogen, (C_1-C_6)alkyl, and halo(C_1-C_6)alkyl; and

R^e is selected from halo, oxo, CN, NO_2, -N(R^d)$_2$, -OR^d, -C(O)OR^d, (C_1-C_6)alkyl, -(C_1-C_6)alkylOR^c, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -(C_1-C_6)alkylC(O)OR^d, -(C_1-C_6)alkylC(O)N(R^d)$_2$, (C_2-C_6)alkenyl, halo(C_2-C_6)alkenyl, (C_2-C_6)alkynyl, -(C_1-C_6)alkylSR^d, -(C_1-C_6)alkylOR^c, -(C_1-C_6)alkylN(R^d)$_2$, -C(O)N(R^d)$_2$, -C(O)N$R^d$$C_{1-6}$alkylN($R^d$)$_2$, -N$R^d$$C_{1-6}$alkylN($R^d$)$_2$, -N$R^d$$C_{1-6}$alkylO$R^d$, -SO$R^d$, -S(O)$_2$$R^d$, -SON($R^d$)$_2$, -SO$_2$N($R^d$)$_2$, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl.

2. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein A is selected from



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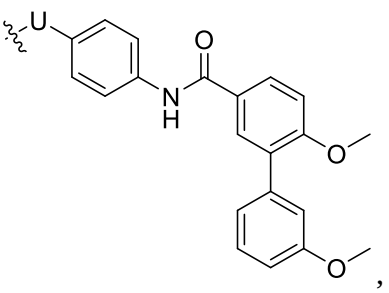

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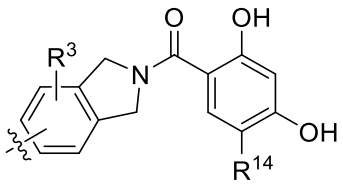

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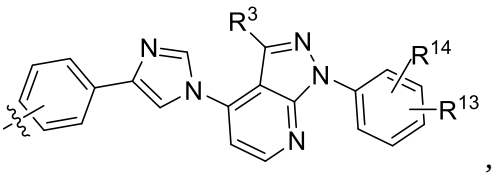

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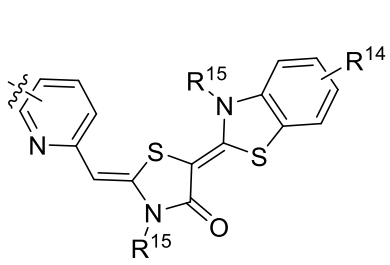
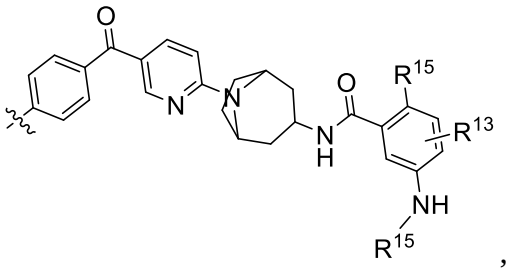
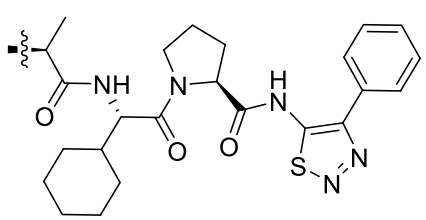
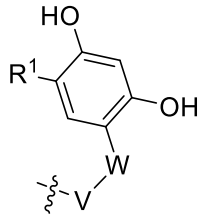





, , , and ; wherein

Q and U are each independently selected from phenyl, heteroaryl, heterocyclyl, and cycloalkyl, each of which being optionally substituted with 1 to 3 groups selected from R^2;

R^{13} and R^{14} are each independently selected from hydrogen, halo, -CN, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, and $-C(O)NR^aR^b$;

R^{15} is hydrogen, $(C_1\text{-}C_4)$alkyl, or halo$(C_1\text{-}C_4)$alkyl;

W is 5- or 6-membered heteroaryl optionally substituted with 1 to 3 groups selected from R^2;

V is phenyl or 5- to 9-membered heteroaryl optionally substituted with 1 to 3 groups selected from R^3;

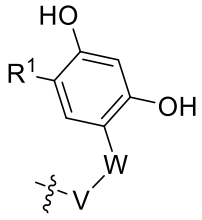
R^1 is halo, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, or halo$(C_1\text{-}C_4)$alkoxy;

R^2 is $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_6)$alkenyl, halo$(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, halo$(C_2\text{-}C_6)$alkynyl, CN, $-C_{1\text{-}4}$alkylOR^a, $-OR^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-C(O)NR^a(C_{1\text{-}4}$alkylene$)OR^a$, $-C(O)NR^a(C_{1\text{-}4}$alkylene$)NR^aR^b$, $-C(O)NR^a(C_{1\text{-}4}$alkylene$)OR$, $-NR^aR^b$, $-O(C_{1\text{-}4}$alkylene$)NR^aR^b$, -SH, $-S(C_{1\text{-}4}$alkyl$)$, $-C_{1\text{-}4}$alkylNR^aR^b, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^aR^b$, $-SO_2NR^aR^b$, $-NR^a(C_{1\text{-}4}$alkyl$)OR^a$, $-NR^a(C_{1\text{-}4}$alkyl$)NR^aR^b$, $-C_{1\text{-}6}$alkyl$C(O)NR^aR^b$, phenyl or 5- to 7-membered heteroaryl, wherein said phenyl and 5- to 7-membered heteroaryl are each optionally and independently substituted with 1 to 3 groups selected from R^4;

R^a and R^b are each independently selected from hydrogen and $(C_1\text{-}C_4)$alkyl, wherein said $(C_1\text{-}C_4)$alkyl is optionally substituted with one or more halo or a 3- to 7-membered heterocyclyl, or both; and

R^3 and R^4 are each independently halo, $-NR^aR^b$, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, or halo$(C_1\text{-}C_4)$alkoxy.

3. The compound of Claim 1 or 2, or a pharmaceutically acceptable salt thereof,

wherein A is 

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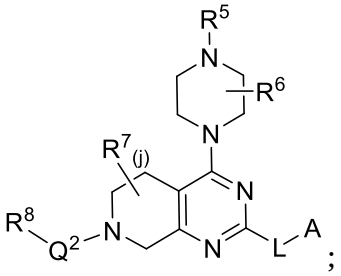
4. The compound of any one of Claims 1 to 3, wherein the compound is of the Formula:



;

or a pharmaceutically acceptable salt thereof.

5. The compound of any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein is R^5 is –C(O)Y.

6. The compound of any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein Y is (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_2-C_6)alkenyl, halo(C_2-C_6)alkenyl, or NH_2.

7. The compound of any one of Claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein Y is $C(O)CH_3$, $C(O)CHCH_2$, $C(O)CH_2CH_3$, $C(O)CF_3$, $C(O)CFCH_2$, $C(O)CCH_3$, or $C(O)NH_2$.

8. The compound of any one of Claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein Y is $C(O)CHCH_2$.

9. The compound of any one of Claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein R^6 is cyano(C_1-C_6)alkyl.

10. The compound of any one of Claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^6 is CH_2CN.

11. The compound of any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein j is 0.

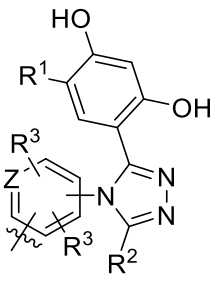
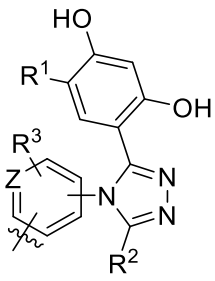
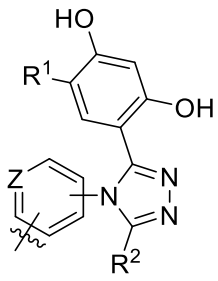
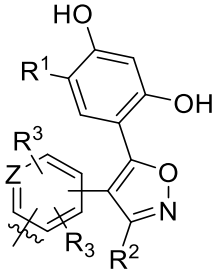
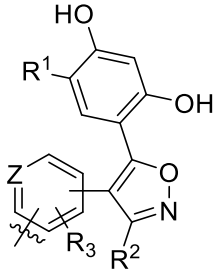
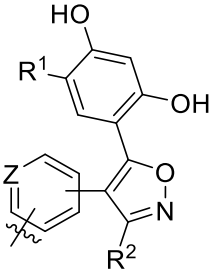
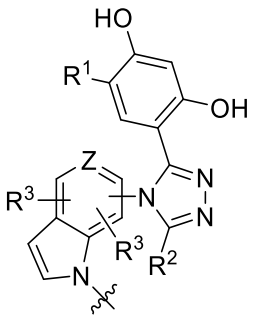
12. The compound of any one of Claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein Q^2 is a bond.

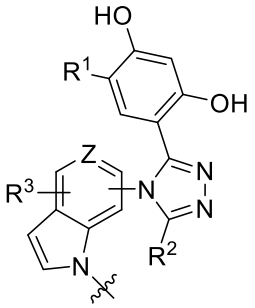
13. The compound of any one of Claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein R^8 is aryl optionally substituted with 1 to 3 groups selected from R^9.

14. The compound of any one of Claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein R^8 is naphthyl optionally substituted with 1 to 3 groups selected from R^9.

15. The compound of any one of Claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein R^9 is selected from halo, $(C_1$-$C_6)$alkyl, and OH.

16. The compound of any one of Claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein R^9 is selected from chloro and OH.

17. The compound of any one of Claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein A is selected from  ,  ,  ,  ,  ,  ,  ,



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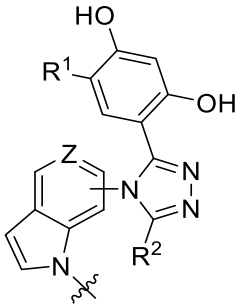

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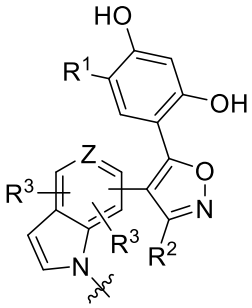

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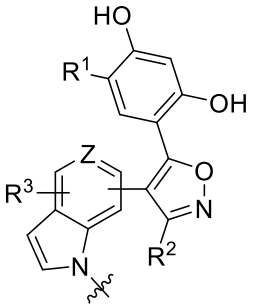

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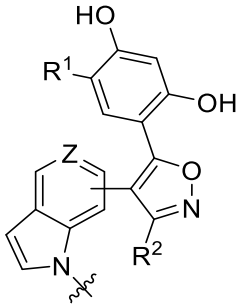


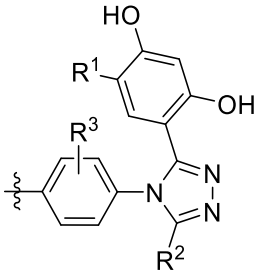
; and

Z is N or CH.

18. The compound of Claim 17, or a pharmaceutically acceptable salt thereof, wherein Z is CH.

19. The compound of any one of Claims 1 to 18, wherein each R^3 is independently (C_1-C_4)alkyl or halo.

20. The compound of any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, wherein A is



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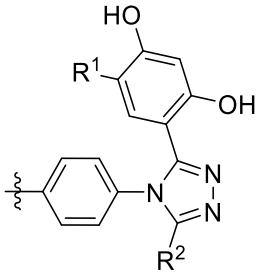

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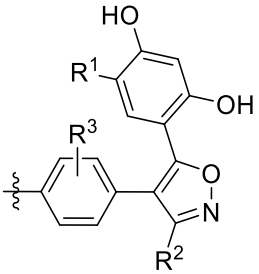

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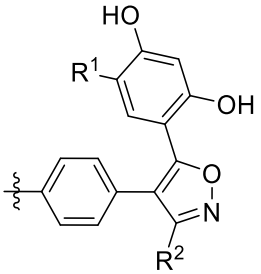

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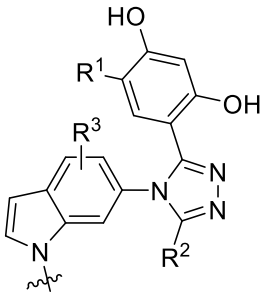

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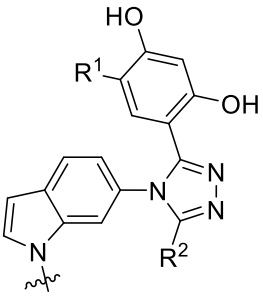

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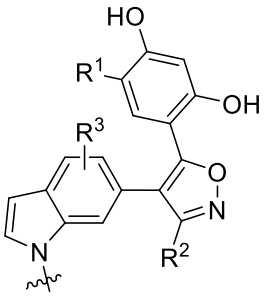

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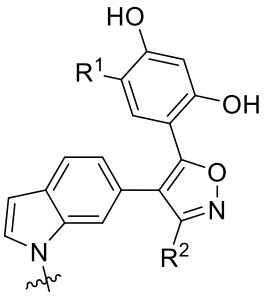

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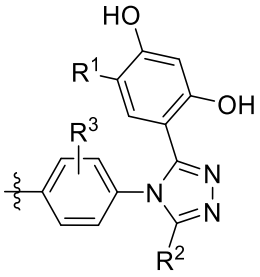
21. The compound of any one of Claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein A is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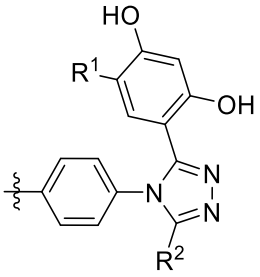
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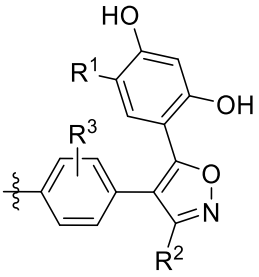
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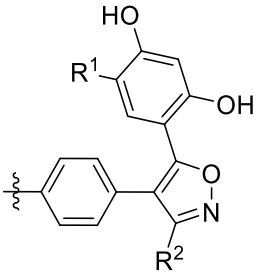
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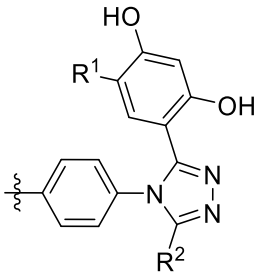
22. The compound of any one of Claims 1 to 21, or a pharmaceutically acceptable salt thereof, wherein A is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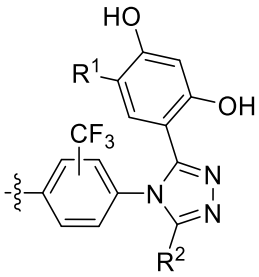
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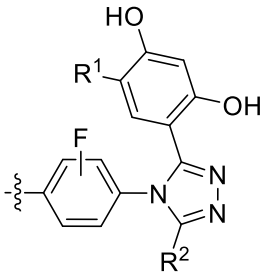
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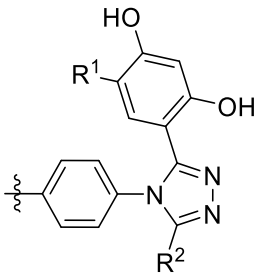
23. The compound of any one of Claims 1 to 22, or a pharmaceutically acceptable salt thereof, wherein A is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24. The compound of any one of Claims 1 to 23, or a pharmaceutically acceptable salt thereof, wherein R^1 is halo or $(C_1\text{-}C_4)$alkyl.

25. The compound of any one of Claims 1 to 24, or a pharmaceutically acceptable salt thereof, wherein R^1 is chloro, isopropyl, methyl, propyl, or ethyl.

26. The compound of any one of Claims 1 to 25, or a pharmaceutically acceptable salt thereof, wherein R^1 is isopropyl or ethyl.

27. The compound of any one of Claims 1 to 26, or a pharmaceutically acceptable salt thereof, wherein R^2 is $-OR^a$, $-SR^a$, $-C(O)NR^aR^b$, or $-C(O)NR^a(C_{1-4}alkylene)NR^aR^b$.

28. The compound of any one of Claims 1 to 27, or a pharmaceutically acceptable salt thereof, wherein R^a and R^b are each independently selected from hydrogen and (C_1-C_4)alkyl, wherein said (C_1-C_4)alkyl is optionally substituted with 1 to 3 halo or a 6-membered heterocyclyl.

29. The compound of any one of Claims 1 to 28, or a pharmaceutically acceptable salt thereof, wherein R^2 is OH, $-C(O)NHCH_2CF_3$, $-C(O)NHCH_2CH_3$, $-C(O)NHCH(CH_3)_2$, $-C(O)NH(CH_2CH_3)_2$, $-C(O)NHCH(CH_3)CF_3$, -C(O)NHcyclopropyl, -C(O)NHmethylcyclopropyl,$C(O)NH_2$, or $-C(O)NH(CH_2)_2$piperidinyl.

30. The compound of any one of Claims 1 to 29, or a pharmaceutically acceptable salt thereof, wherein R^2 is $-C(O)NHCH_2CF_3$ or OH.

31. The compound of any one of Claims 1 to 30, or a pharmaceutically acceptable salt thereof, wherein R^2 is OH.

32. The compound of any one of Claims 1 to 31, or a pharmaceutically acceptable salt thereof, wherein

L is $-Het^1-X^1-*$, $-Het^1-Het^2-X^1-*$, $*-X^1-Het^1-X^2-Het^2-(CH_2)_mO-$, $-NR^c-(CH_2)_m-X^1-Het^1-X^2-*$, $-NR^c-(CH_2)_m-X^1-NR^c-(CH_2CH_2O)_n-*$, $-NR^c-(CH_2)_m-X^1-NR^c-(CH_2)_p-*$, $-NR^c-(CH_2)_m-X^1-Het^1-X^2-Het^2-X^3-*$, $-O(CH_2)_m-X^1-Het^1-X^2-$ Het^2-X^3-*, $-O(CH_2)_m-X^1-NR^c-(CH_2)_p-Het^1-X^2-Het^2-X^3-*$, $*-X^1-NR^c-(CH_2)_m-Het^1-X^2-Het^2-X^3-(CH_2)_p-NR^d-(CH_2)_p-$, $-NR^c-(CH_2)_m-X^1-(CH)CH_3-Het^1-X^2-$ Het^3-X^3-*, $-NR^c-(CH_2)_m-X^1-(CH_2)_p-Het^1-X^2-$ Het^2-X^3-*, $-NR^c-(CH_2)_m-X^1-NR^d-(CH_2)_p-Het^1-X^2-$ Het^2-X^3-*, $-NR^c-(CH_2)_m-$ $NR^d-X^1-Het^1-X^2-*$, $*Het^1-X^1-Het^2-X^2-$, $*-Het^1-X^1-Het^2-X^2-O-$, $*-O(CH_2)_m-Het^1-(CH_2)_p-O(CH_2)_m-NR^c-X^2-$, $-O(CH_2)_m-Het^1-(CH_2)_p-O(CH_2)_m-NR^c-X^2-*$, $*-Het^1-O-(CH_2)_m-X^1-Het^2-X^2-$, $*-Het^1-O-(CH_2)_m-X^1-NR^c-(CH_2CH_2O)_n(CH_2)_m-Het^2-X^2-$, $*-Het^1-X^1-NR^c-(CH_2)_m-$, $*-Het^1-X^1-Het^2-Het^3-X^2-$, $*-Het^1-X^1-NR^c-(CH_2CH_2O)_n(CH_2)_m-$, $*-Het^1-X^1-NR^c-(CH_2CH_2O)_nHet^2-(CH_2)_m-X^2-$, $*-Het^1-X^1-$

NR^c-$(CH_2CH_2O)_n$-, *-Het^1-X^1-NR^c-$(CH_2)_m$-Het^2-X^2-Het^3-$(CH_2)_m$-, *-Het^1-X^1-Het^2-$(CH_2)_m$-Het^3-X^2-, *-Het^1-X^1-Het^2-, *-Het^1-X^1-NR^c-, *-Het^1-X^1-NR^c-$(CH_2)_m$-Phe-X^2-Het^2-$(CH_2)_m$-, *-Het^1-X^1-Het^2-Het^3-, *-Het^1-X^1-Het^2-$(CH_2)_m$-Het^3-X^2-$(CH_2)_p$-NR^c-$(CH_2)_m$-, *-Het^1-X^1-Het^2-$(CH_2)_m$-Het^3-$(CH_2)_m$-O-, *-Het^1-X^1-Het^2-$(CH_2)_m$-Het^3-$(CH_2)_p$-NR^c-$(CH_2)_m$-, *-Het^1-X^1-Het^2-$(CH_2CH_2O)_n$-,*-Het^1-X^1-$(CH_2)_m$ -Het^2-X^2-, *-$(CH_2CH_2O)_o$-$(CH_2)_p$-Het^1-X^1-Het^2-$(CH_2CH_2O)_n$, *-$(CH_2CH_2O)_n$-$(CH_2)_m$-Het^1-X^1-Het^2-X^2, *-Het^1-X^1-Phe-X^2-NR^c-X^3-, *-$(CH_2CH_2O)_o$-$(CH_2)_p$-Het^1-X^1-Phe-X^2-NR^c-$(CH_2CH_2O)_n$-, *-$(CH_2CH_2O)_n$-$(CH_2)_m$-NR^c-Phe-X^1-, *-$(CH_2CH_2O)_o$-$(CH_2)_p$-NR^c-Phe-$(CH_2CH_2O)_n$-, *-$(CH_2CH_2O)_o$-$(CH_2)_p$-NR^c-$(CH_2CH_2O)_n$-$(CH_2)_m$-, *- $(CH_2CH_2O)_n$-$(CH_2)_m$-NR^c-$(CH_2CH_2O)_n$-$(CH_2)_m$-C(O)-NR^d-$(CH_2CH_2O)_o$-$(CH_2)_p$-, *-$(CH_2CH_2O)_o$-$(CH_2)_p$-NR^c-$(CH_2CH_2O)_n$-$(CH_2)_m$-Het^1-X^1-Het^2-X^2-, *-$(CH_2CH_2O)_o$-$(CH_2)_p$-NR^c-$(CH_2CH_2O)_n$-$(CH_2)_m$-Het^1-X^1-Het^2-X^2-$(CH_2CH_2O)_o$, *-NR^c-$(CH_2CH_2O)_n$-$(CH_2)_m$-Phe-NH-X^1-Het^1-X^2, *-NR^c-$(CH_2CH_2O)_n$-$(CH_2)_m$-Phe-NH-X^1-Het^1-X^2-$(CH_2CH_2O)_o$, *-$(CH_2CH_2O)_o$-$(CH_2)_p$-NR^c-$(CH_2CH_2O)_n$-$(CH_2)_m$-Phe-X^1-NR^c-$(CH_2CH_2O)_o$-$(CH_2)_p$-, *-$(CH_2CH_2O)_o$-$(CH_2)_p$-NR^c-$(CH_2CH_2O)_n$-$(CH_2)_m$-Het^1-X^1-, *-$(CH_2CH_2O)_o$-$(CH_2)_p$-NR^c-$(CH_2CH_2O)_n$-$(CH_2)_m$-Het^1-X^1-$(CH_2CH_2O)_n$-, *-$(CH_2CH_2O)_n$-$(CH_2)_m$-NR^c-$(CH_2)_m$-C(O)-NR^d-Het^1-X^1-Het^2-$(CH_2CH_2O)_o$-$(CH_2)_p$, or *-NR^c-$(CH_2)_m$-C(O)-NR^d-$(CH_2)_m$-Het^1-X^1-Het^2-X^2-;

* indicates the point of attachment to A;

Het^1, Het^2, and Het^3 are each independently phenyl, a 4- to 6-membered heterocyclyl, 5- to 7-membered heteroaryl, or a 4- to 6-membered cycloalkyl, each of which are optionally substituted with $(C_1$-$C_4)$alkyl;

X^1, X^2, and X^3, are each independently C(O) or $(CH_2)_r$; and

m, n, o, p, q and r are each independently integers selected from 0, 1, 2, 3, 4, 5, and 6.

33. The compound of any one of Claims 1 to 32, or a pharmaceutically acceptable salt thereof, wherein L is -Het^1-X^1-*, -Het^1-Het^2-X^1-*, *-X^1-Het^1-X^2-Het^2-$(CH_2)_m$O-, -NR^c-$(CH_2)_m$-X^1-Het^1-X^2-*, -NR^c-$(CH_2)_m$-X^1-NR^c-$(CH_2CH_2O)_n$-*, -NR^c-$(CH_2)_m$-X^1-NR^c-$(CH_2)_p$-*, -NR^c-$(CH_2)_m$-X^1-Het^1-X^2- Het^2-X^3-*, -$O(CH_2)_m$-X^1-Het^1-X^2- Het^2-X^3-*, -$O(CH_2)_m$-X^1-NR^c-$(CH_2)_p$-Het^1-X^2-Het^2-X^3-*, *-X^1-NR^c-$(CH_2)_m$-Het^1-X^2-Het^2-X^3-$(CH_2)_p$-NR^d-, -NR^c-$(CH_2)_m$-X^1-(CH)CH_3-Het^1-X^2-Het^2-X^3-*, -NR^c-$(CH_2)_m$-X^1-$(CH_2)_p$-Het^1-X^2-Het^2-X^3-*, -NR^c-$(CH_2)_m$-X^1-NR^d-$(CH_2)_p$-Het^1-X^2- Het^2-X^3-*, -NR^c-$(CH_2)_m$- NR^d-X^1-Het^1-X^2-*, *Het^1-X^1-Het^2-X^2-, *-Het^1-X^1-Het^2-X^2-O-, *-O$(CH_2)_m$-Het^1-$(CH_2)_p$-O$(CH_2)_m$-NR^c-X^2-, or *-Het^1-X^1-Het^2-.

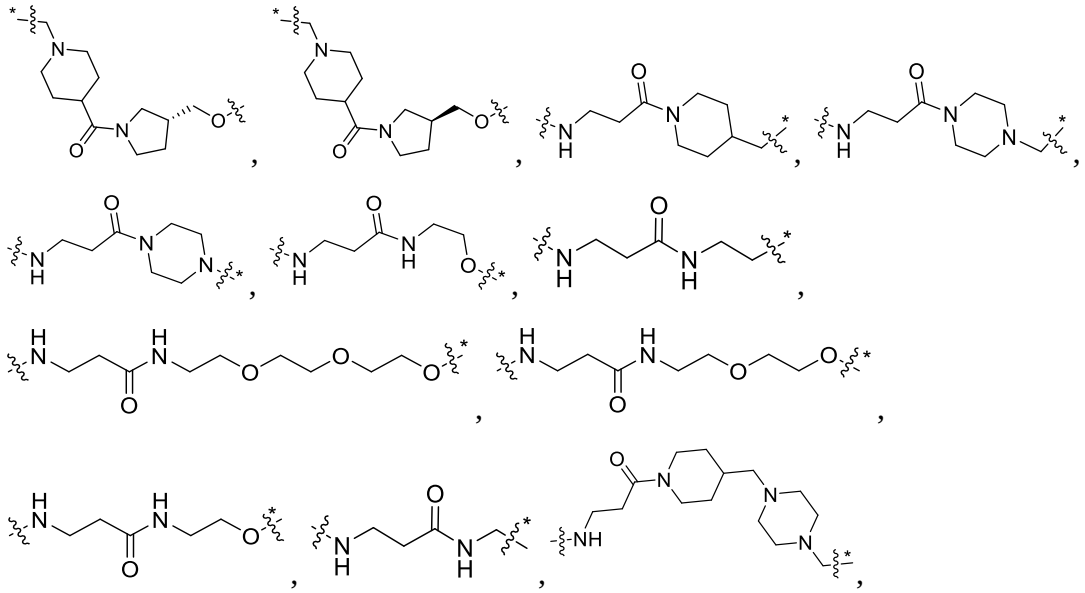
34. The compound of any one of Claims 1 to 33, or a pharmaceutically acceptable salt thereof, wherein L is -NR^c-$(CH_2)_m$-X^1-NR^c-$(CH_2)_p$-* or -NR^c-$(CH_2)_m$-X^1-Het^1-X^2- Het^2-X^3-*.

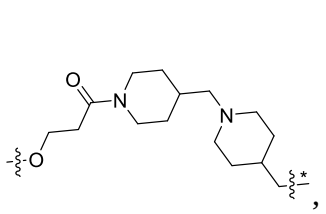
35. The compound of any one of Claims 32 to 34, or a pharmaceutically acceptable salt thereof, wherein Het^1 and Het^2 are each independently phenyl or a 4- to 6-membered heterocyclyl.

36. The compound of any one of Claims 32 to 35, or a pharmaceutically acceptable salt thereof, wherein Het^1 and Het^2 are each independently piperidinyl, phenyl, azetidinyl, piperazinyl, or pyrrolidinyl.

37. The compound of any one of Claims 32 to 36, or a pharmaceutically acceptable salt thereof, wherein m, n, o, p, q and r are each independently integers selected from 0, 1, 2, and 3.

38. The compound of any one of Claims 1 to 32, or a pharmaceutically acceptable salt thereof, wherein L is selected from

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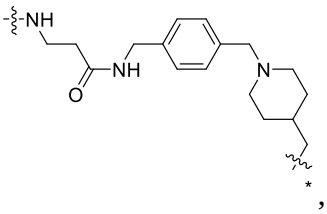
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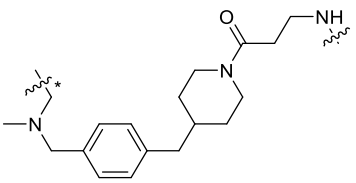
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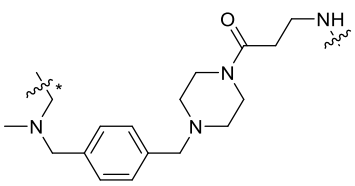
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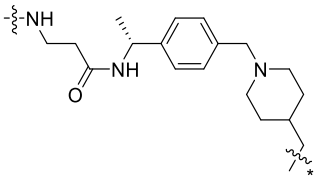
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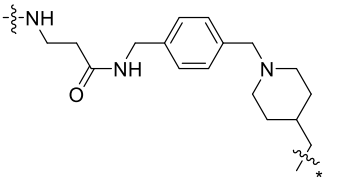
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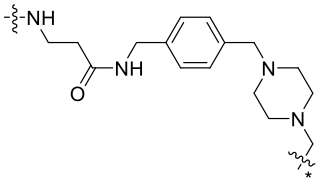
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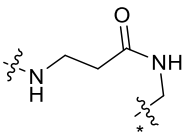
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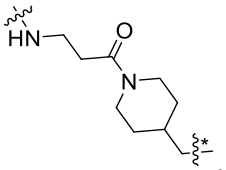
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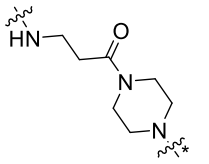
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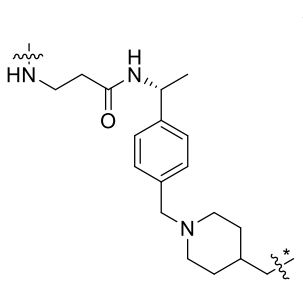
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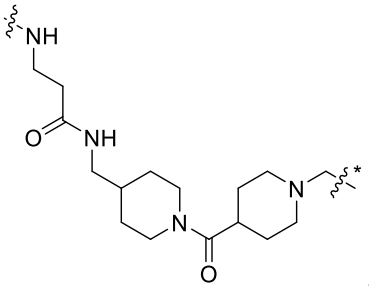
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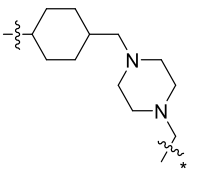
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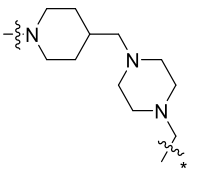
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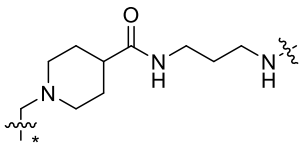
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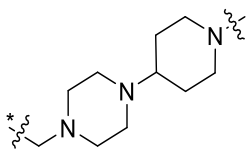
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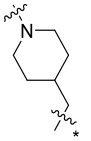
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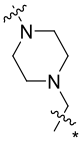
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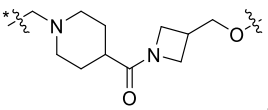
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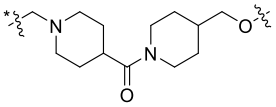
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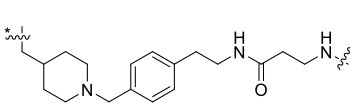
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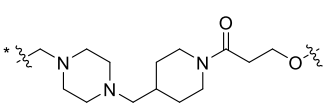
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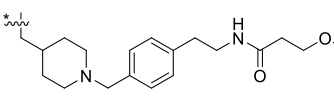
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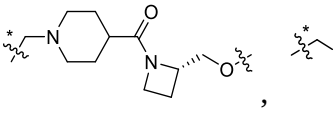
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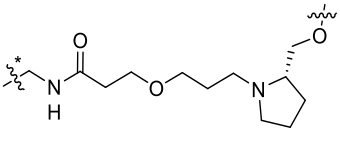
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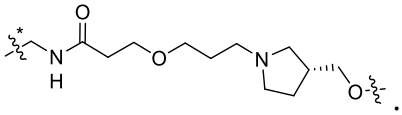
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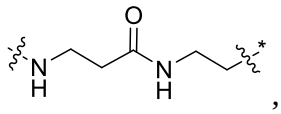
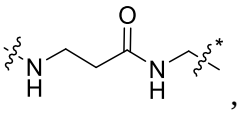
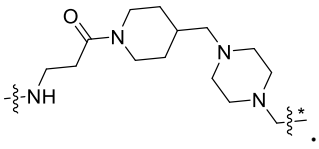
39. The compound of Claim 38, or a pharmaceutically acceptable salt thereof, wherein L is selected from  ,  , and  .

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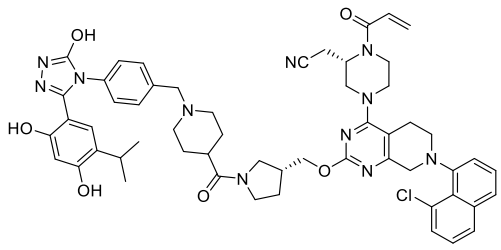
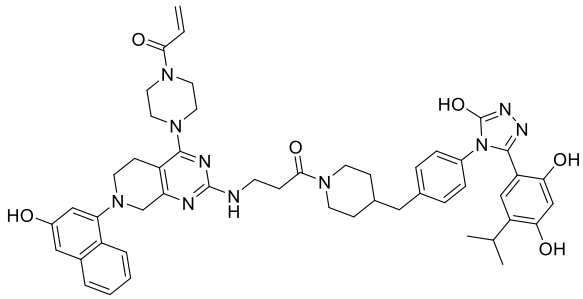
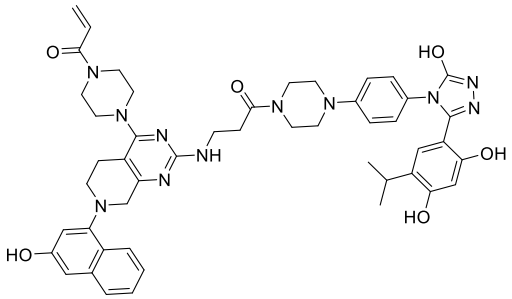
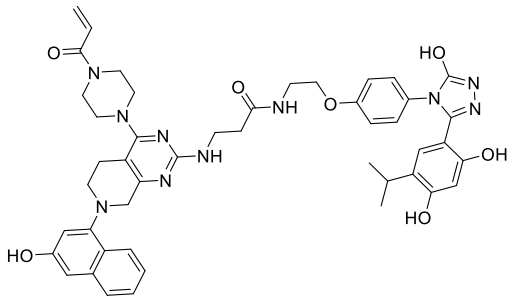
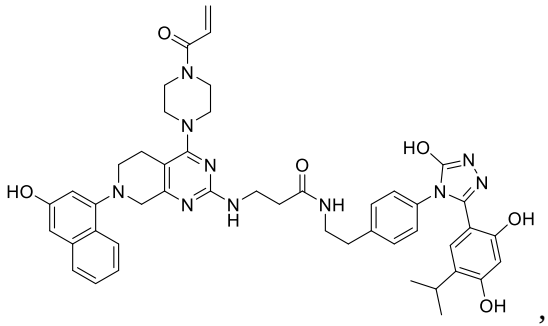
40. The compound of Claim 1, wherein the compound is selected from the following structural formula:

 ,

 ,

 ,

 ,



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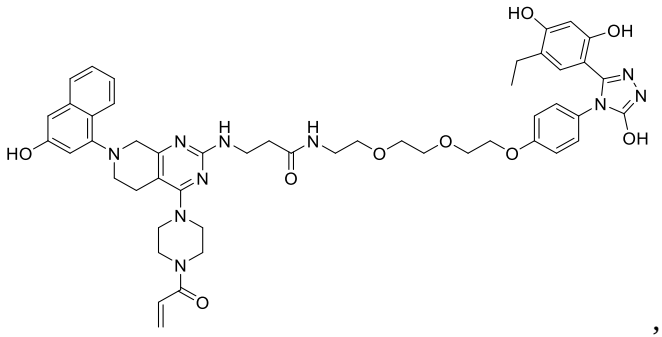

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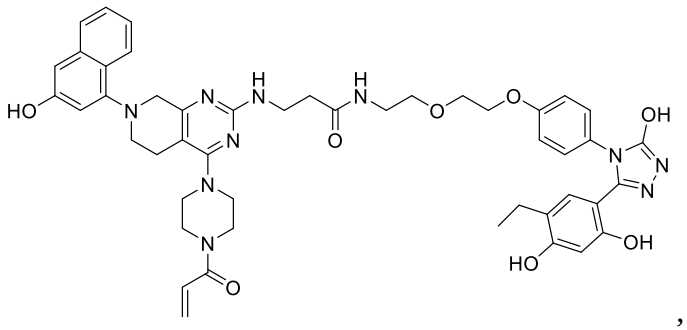

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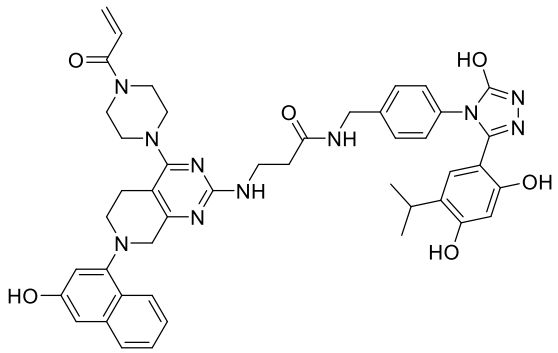

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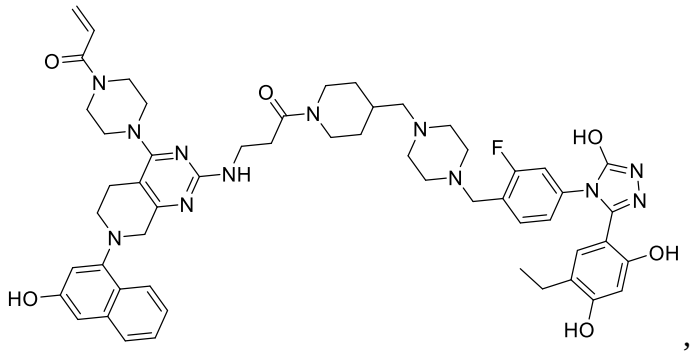

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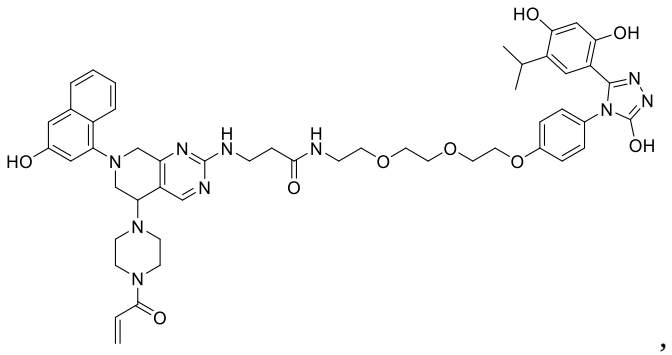

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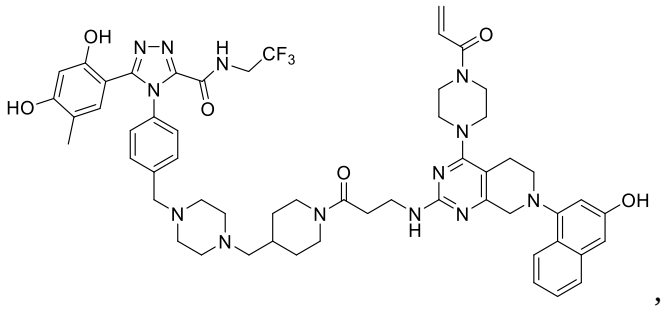

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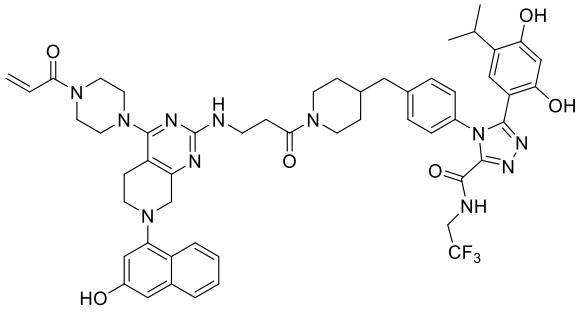

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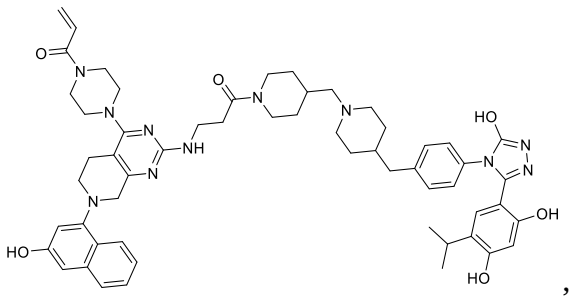

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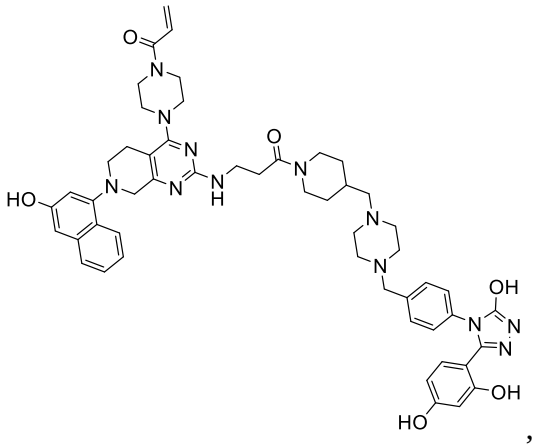
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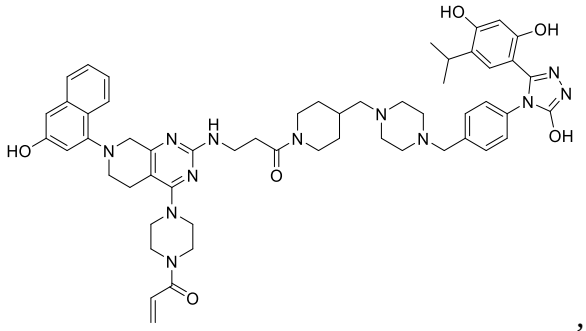
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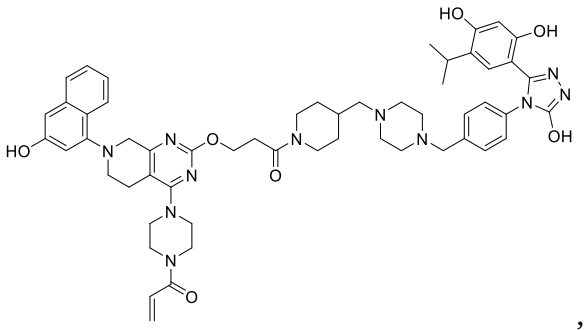
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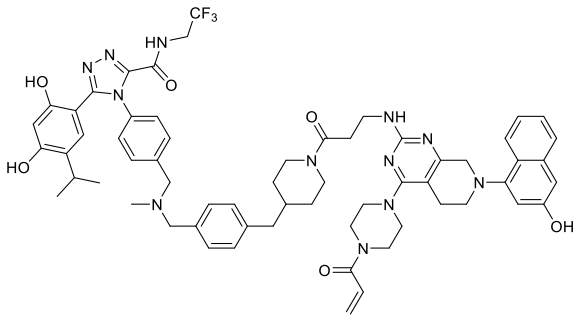
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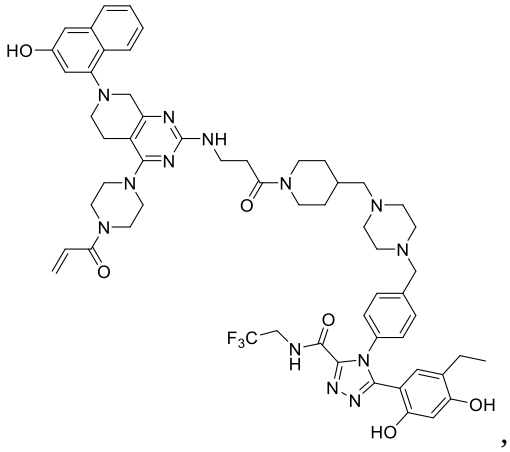
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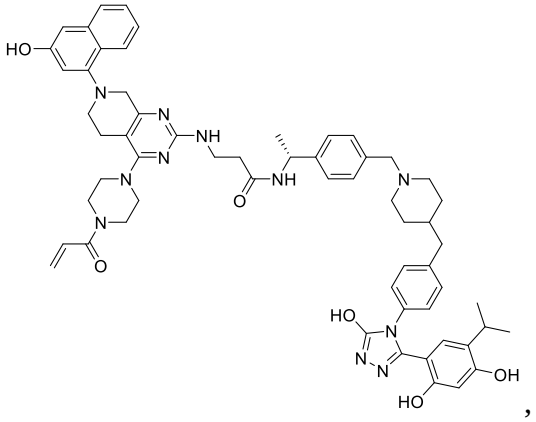
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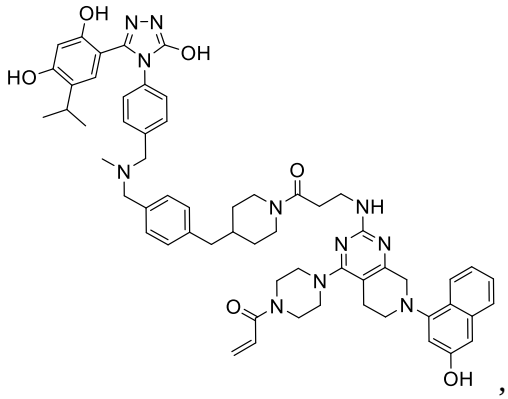
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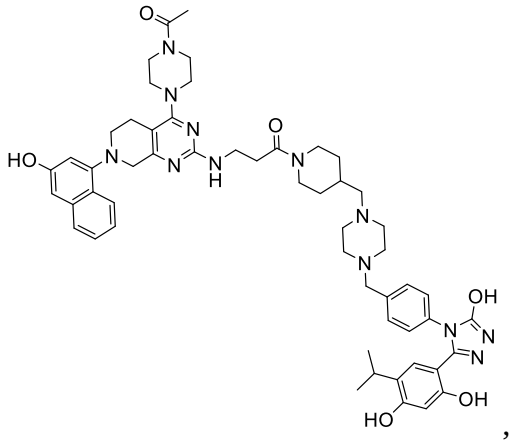
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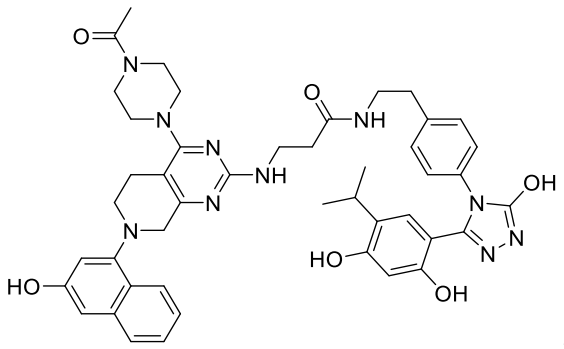

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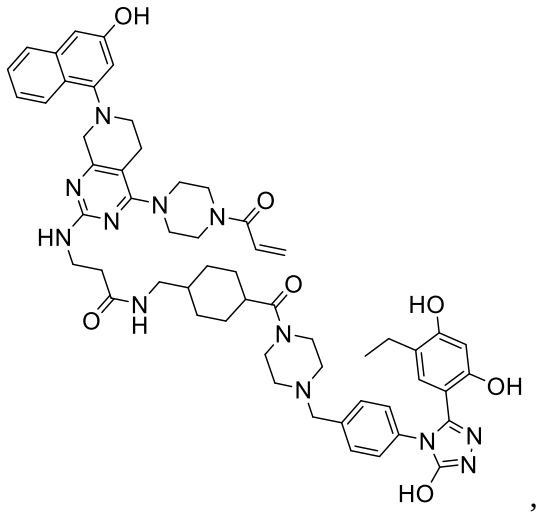

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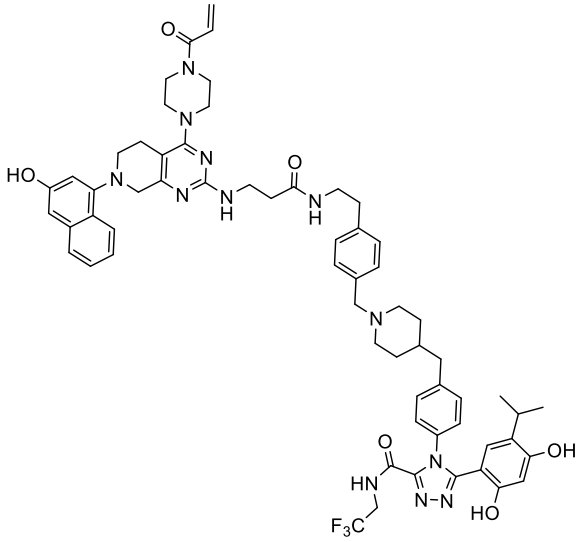

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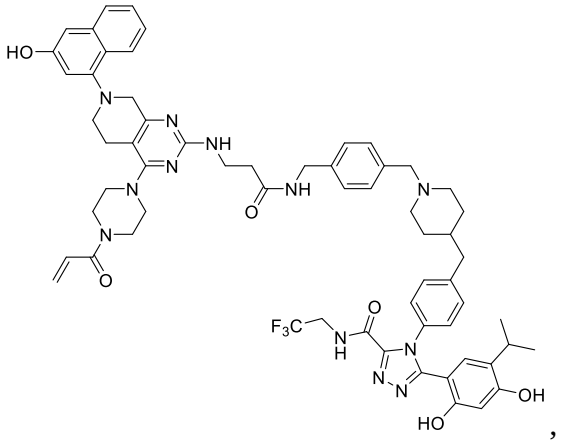
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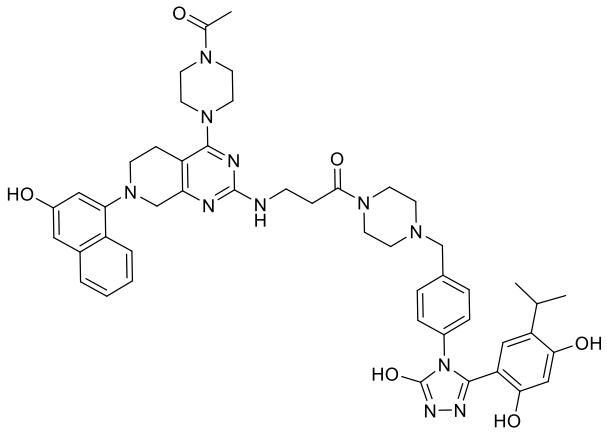
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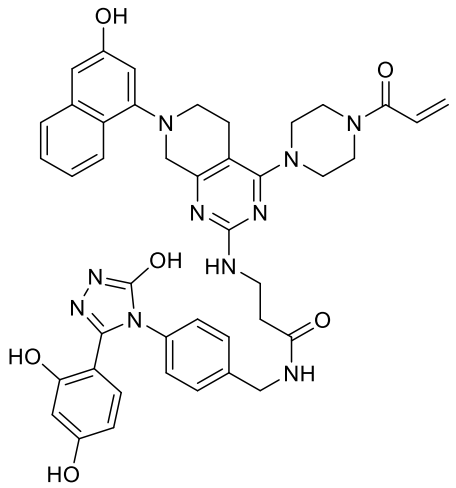
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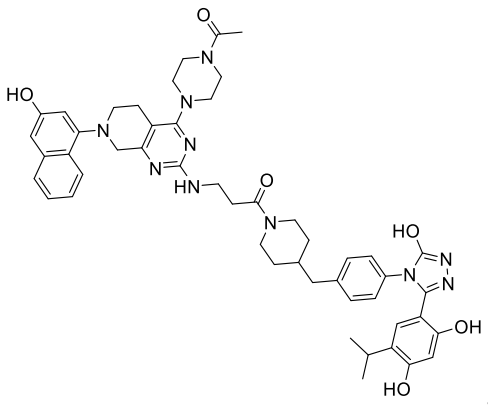
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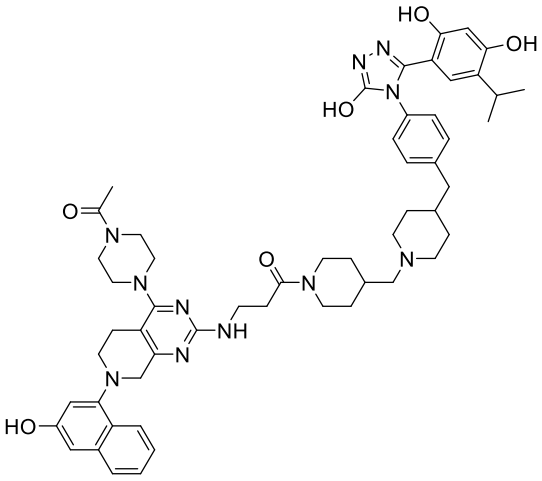

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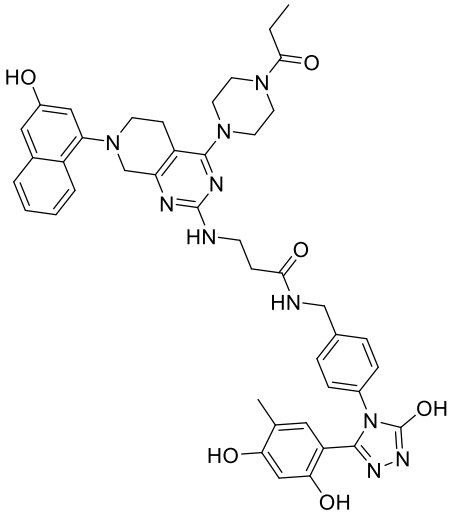

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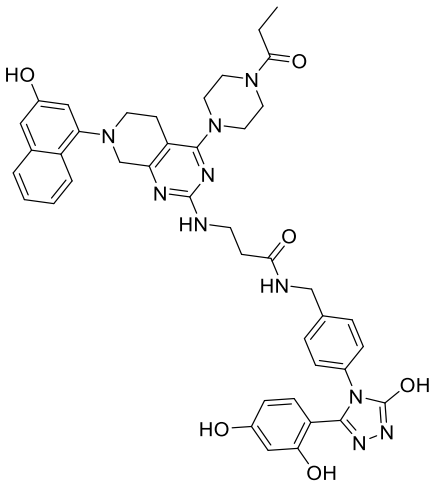

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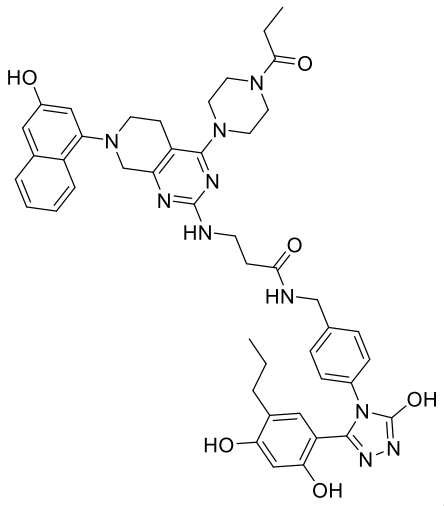
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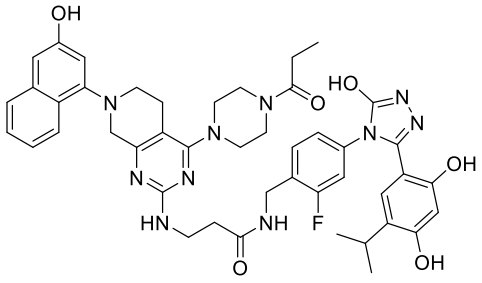
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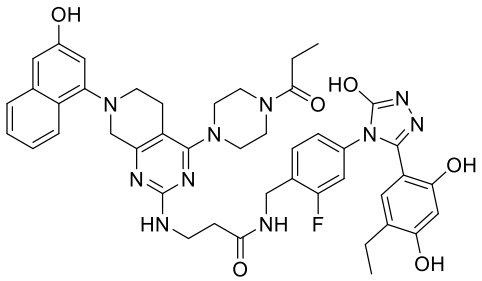
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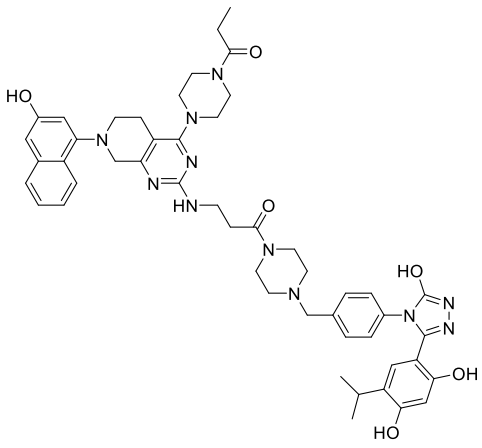
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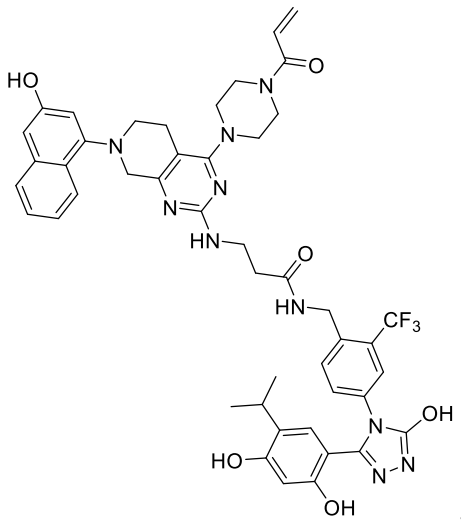
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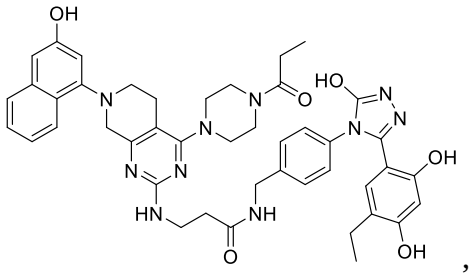
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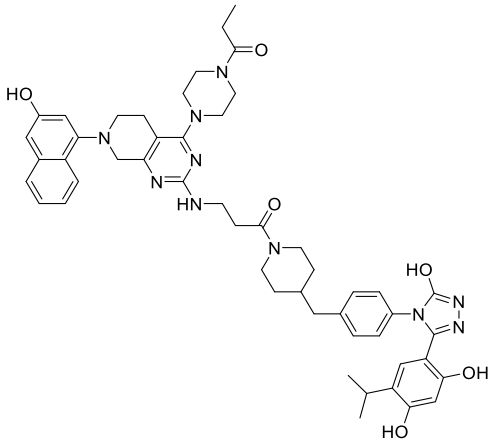
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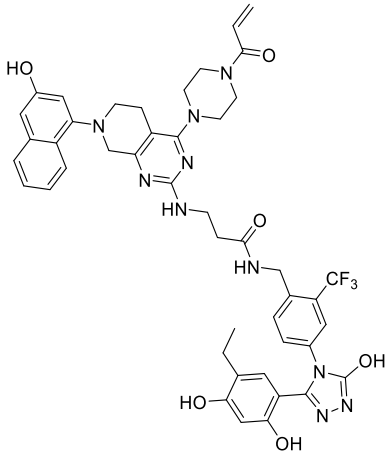
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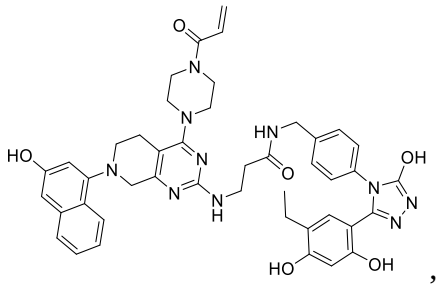
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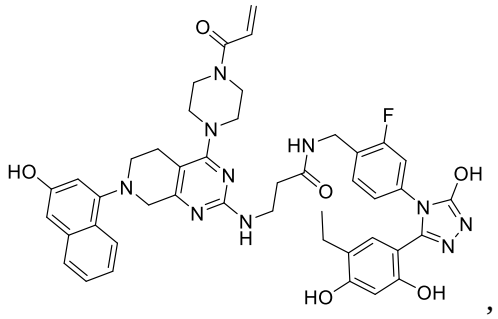
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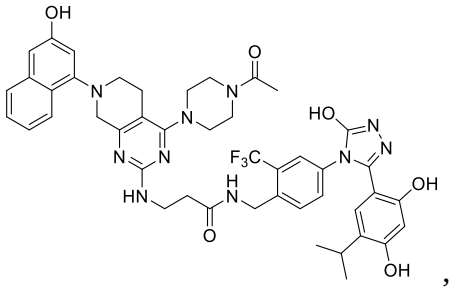
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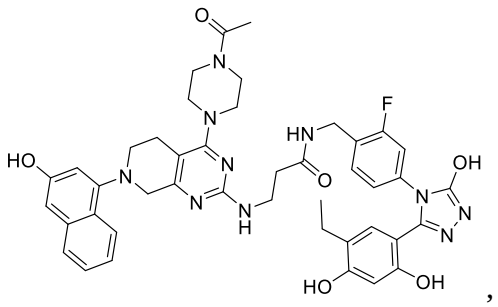
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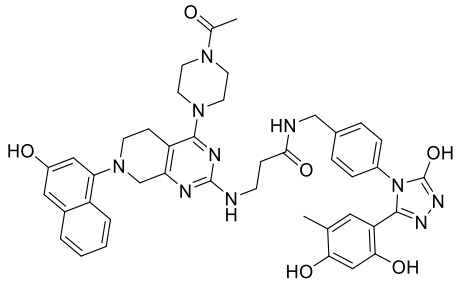
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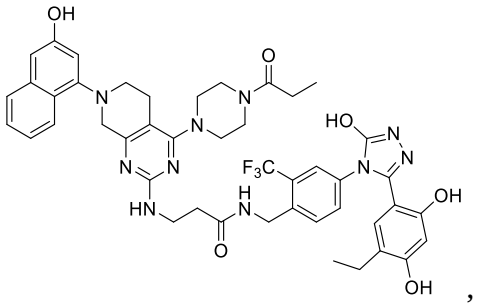
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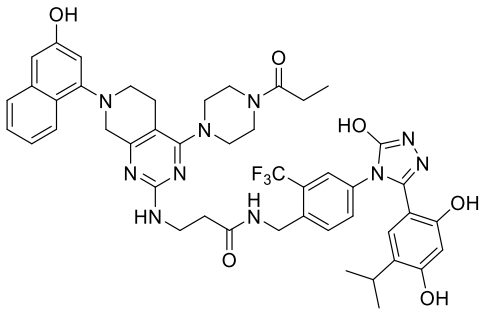
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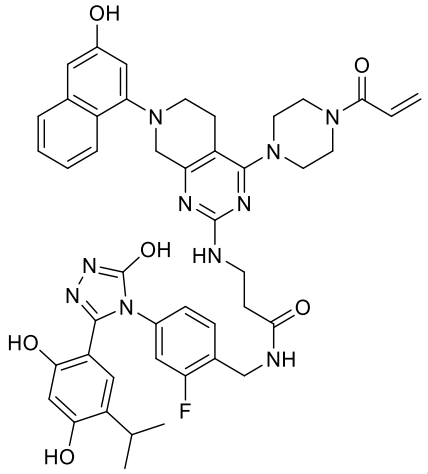
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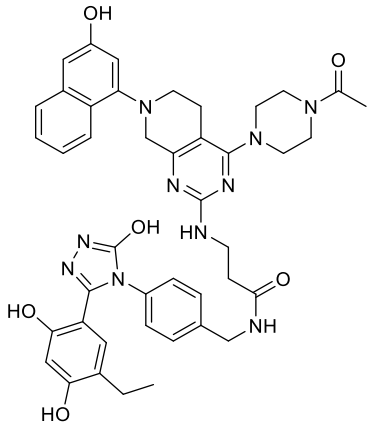
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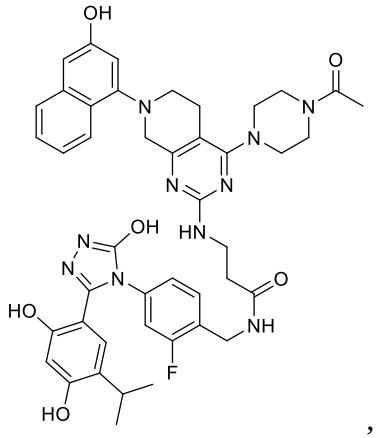
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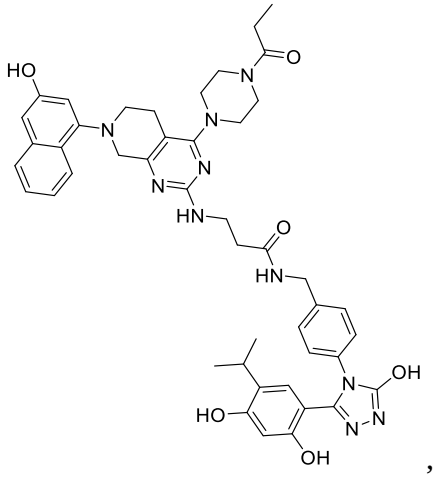
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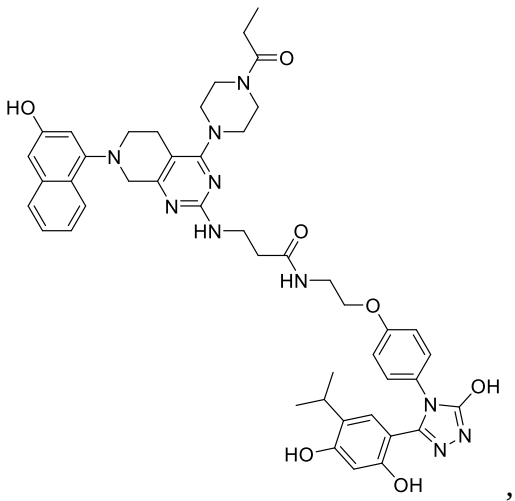
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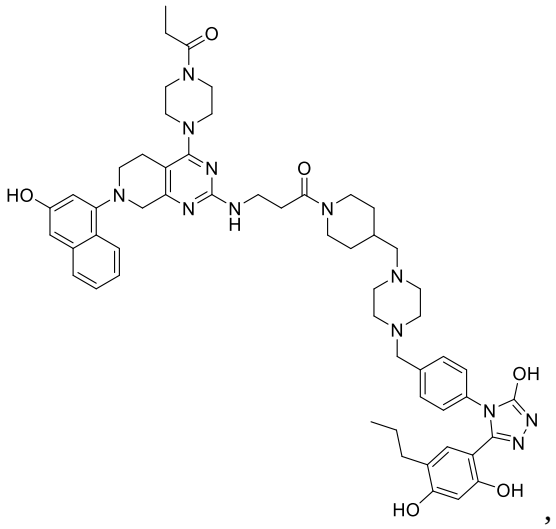

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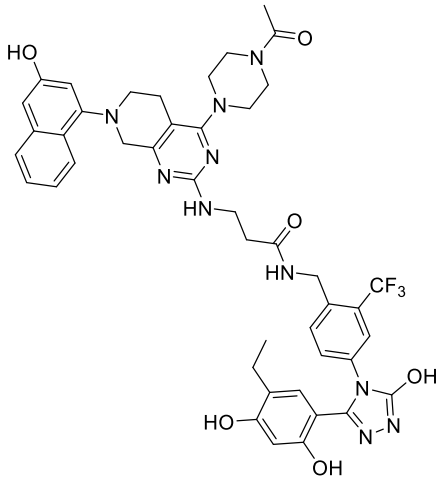

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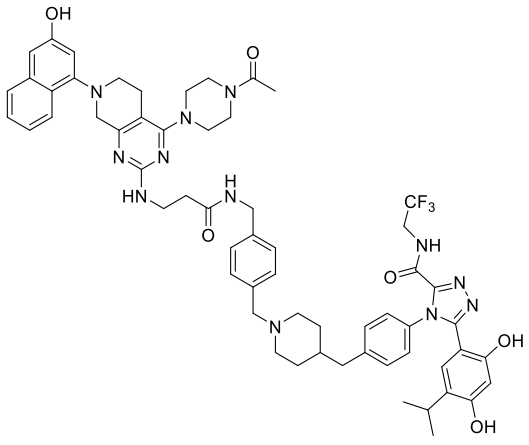

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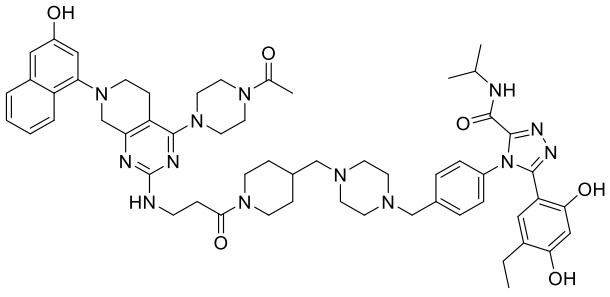

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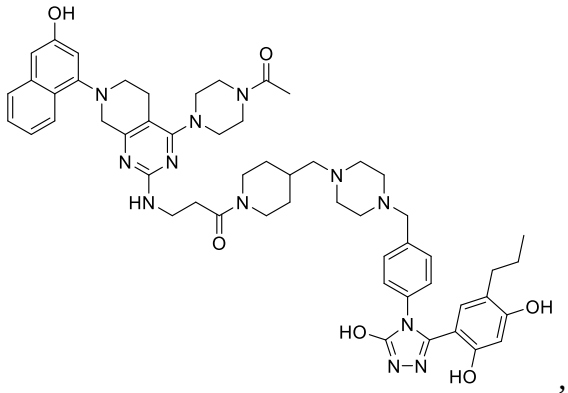

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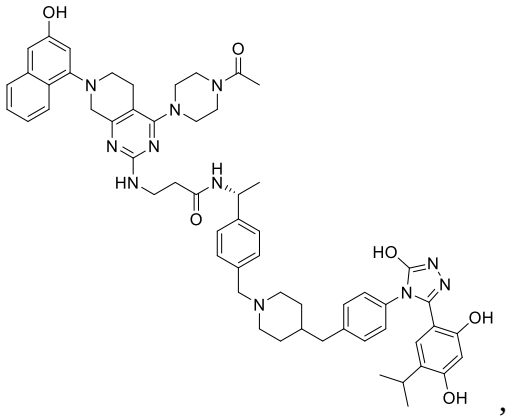

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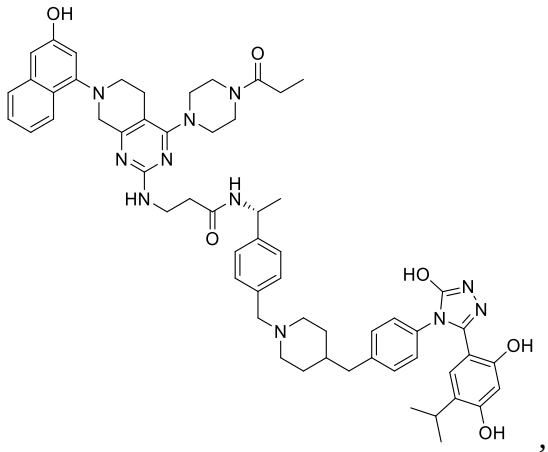

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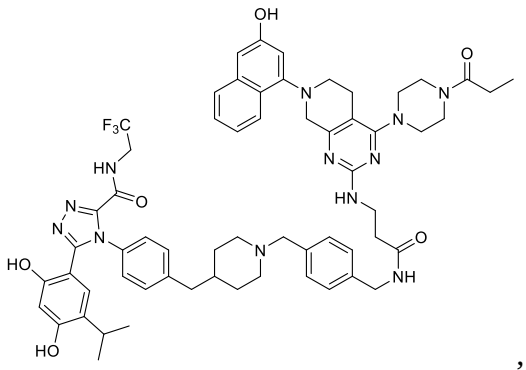

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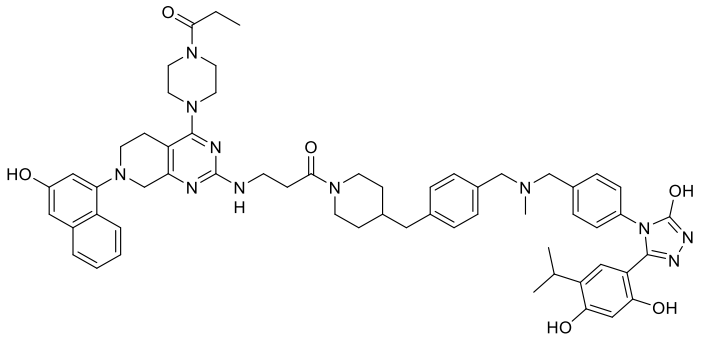
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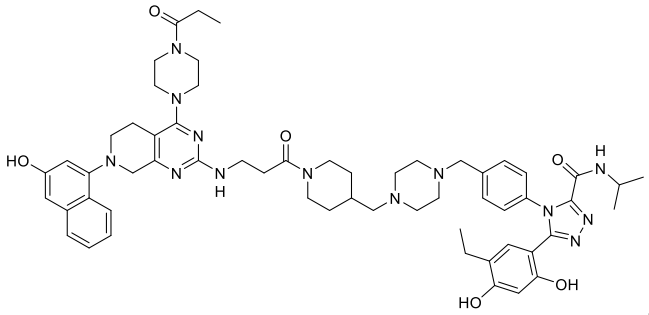
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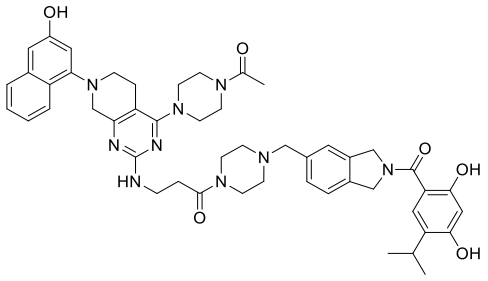
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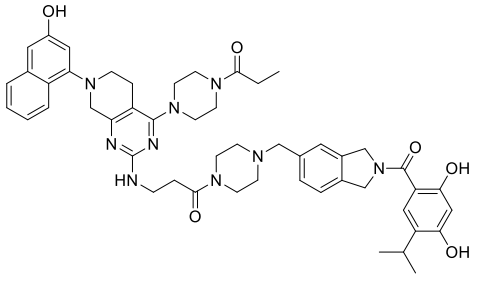
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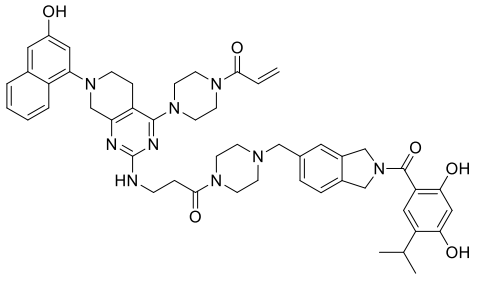
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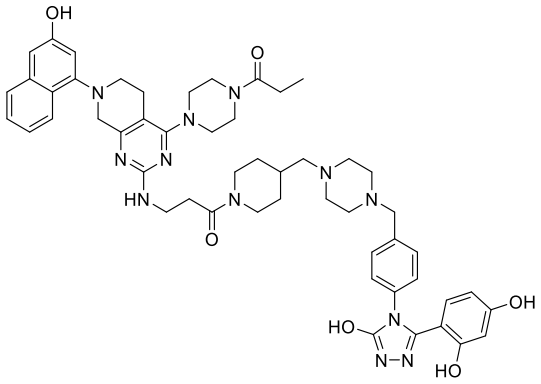
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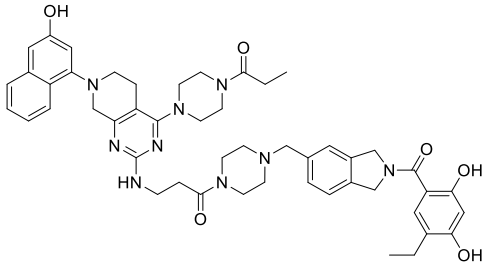
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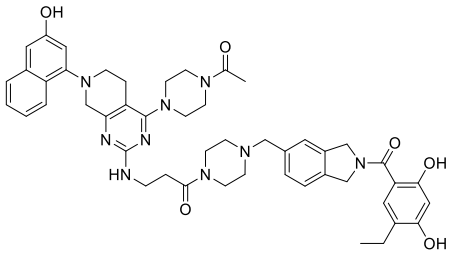
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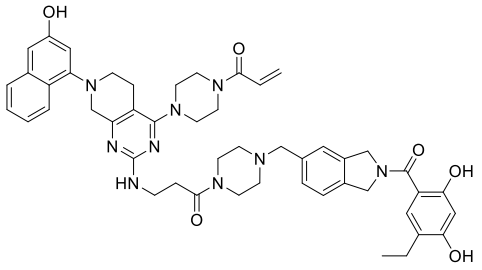
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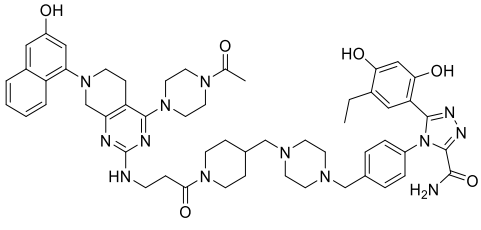
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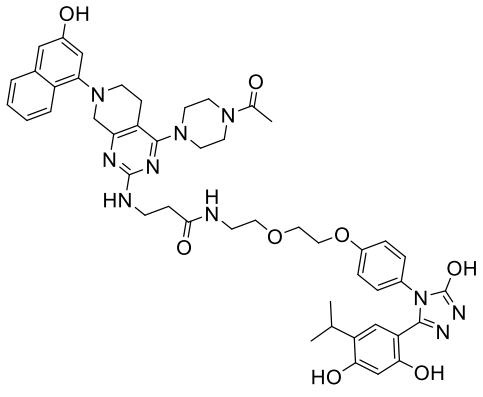
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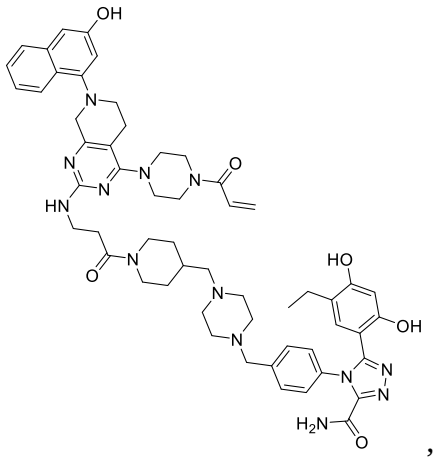
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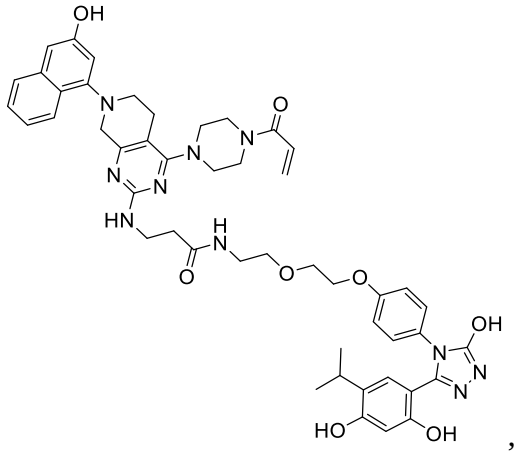
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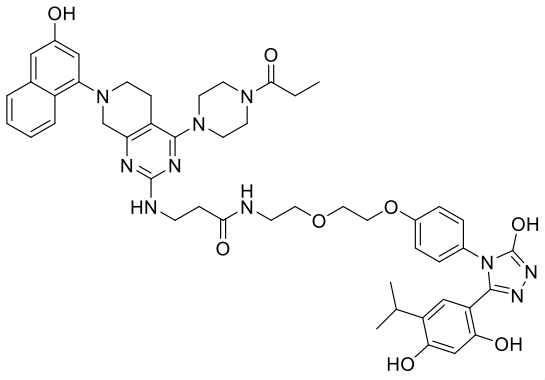
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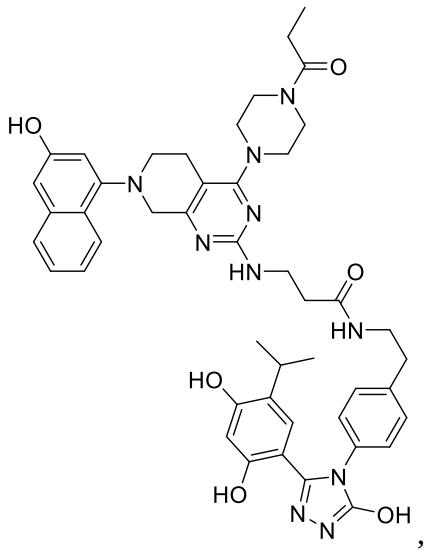

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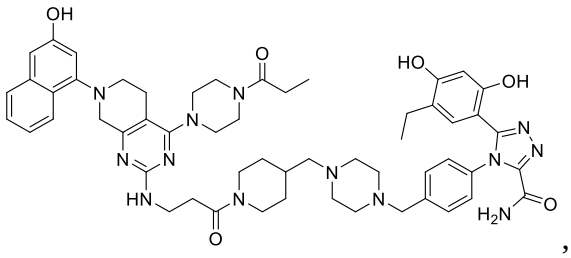

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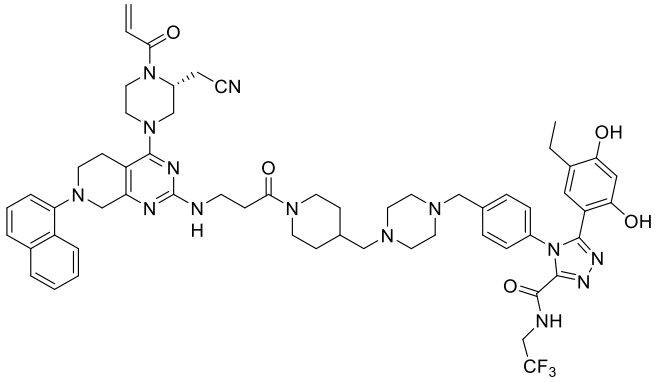

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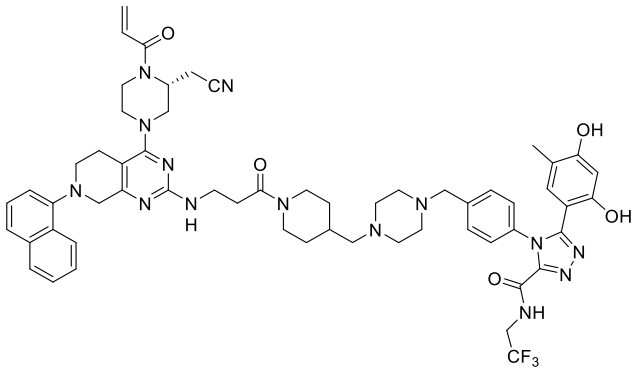

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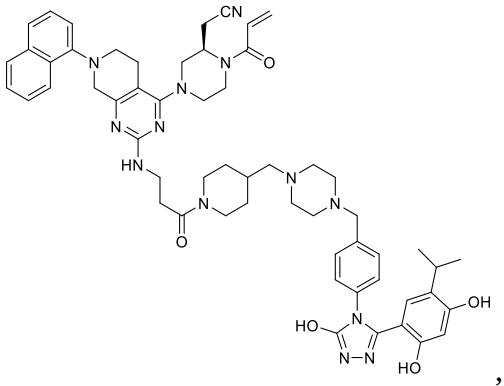

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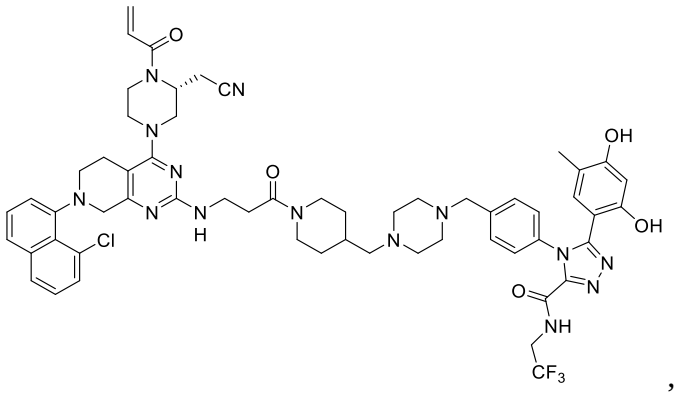

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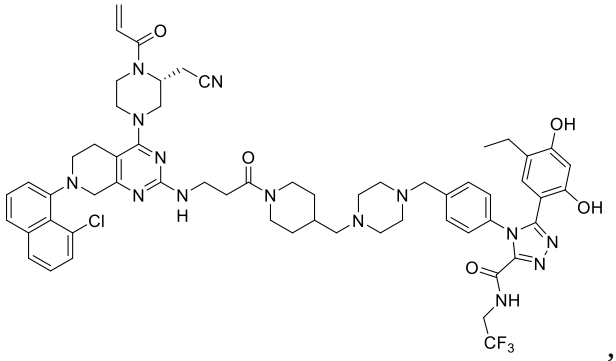

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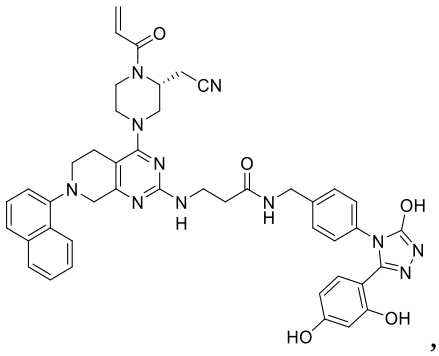

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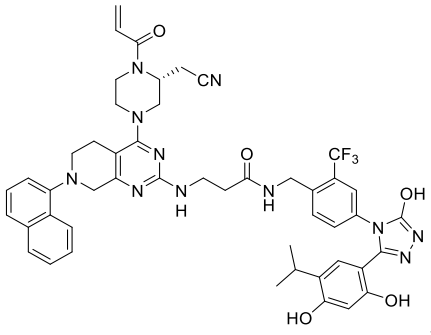
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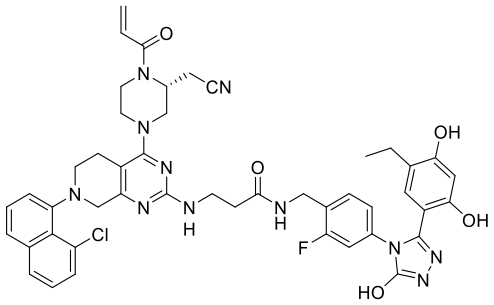
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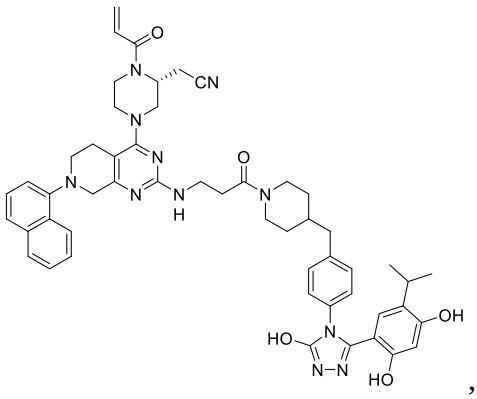
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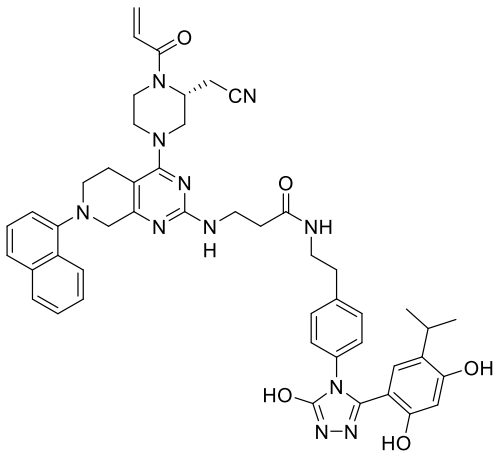
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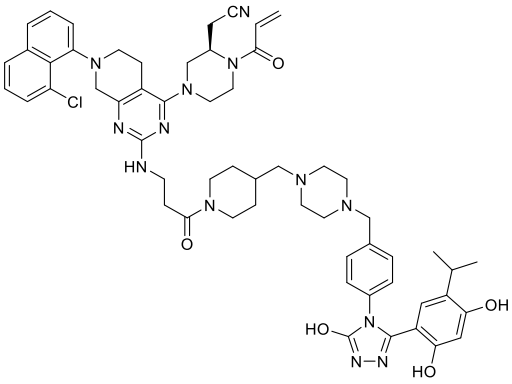
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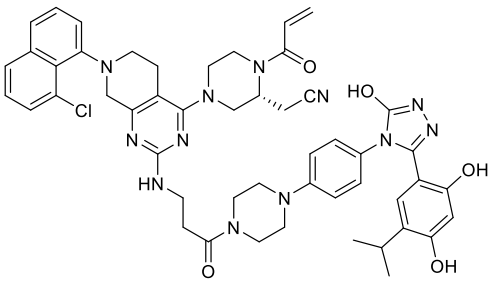
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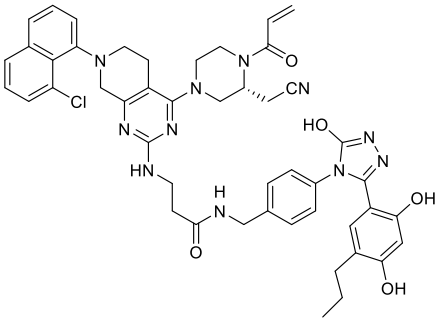
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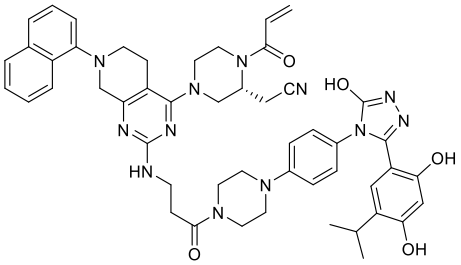
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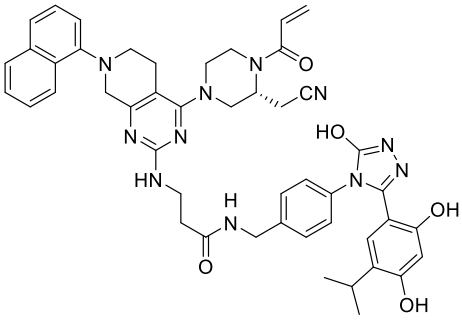
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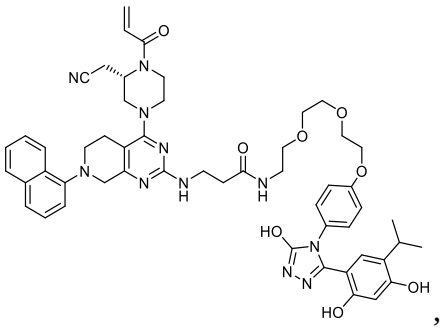
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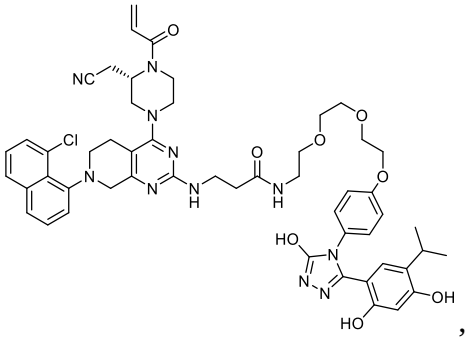
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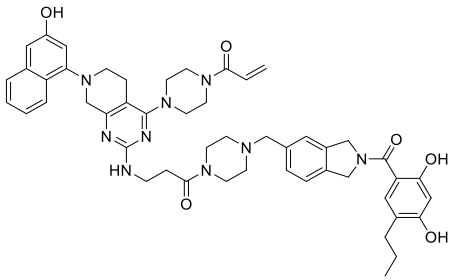
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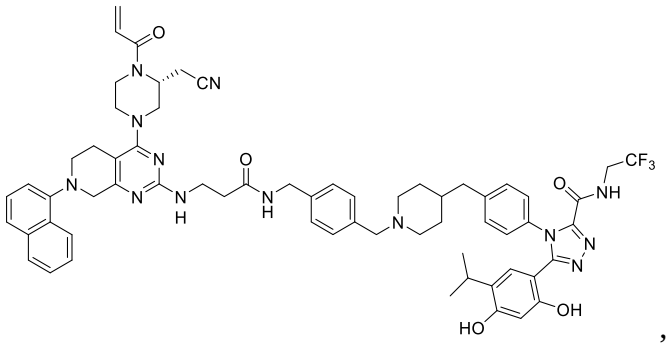
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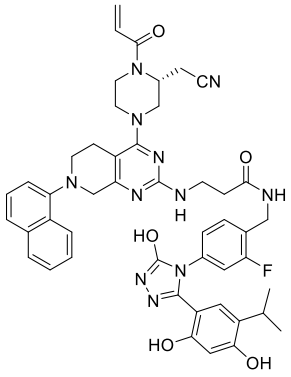
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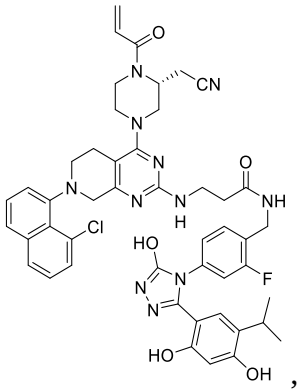
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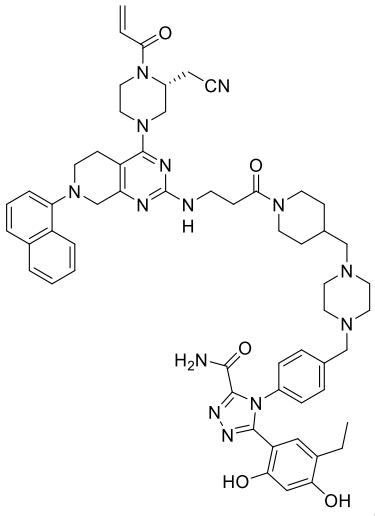
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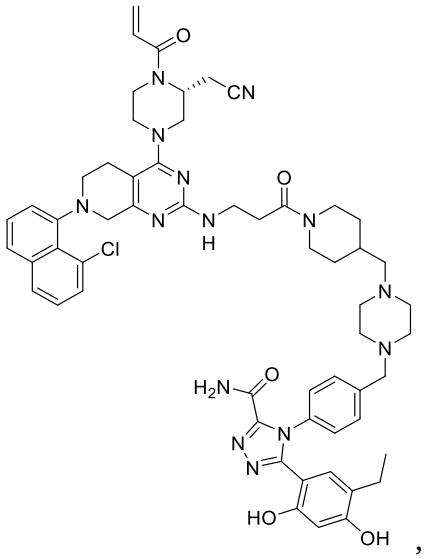
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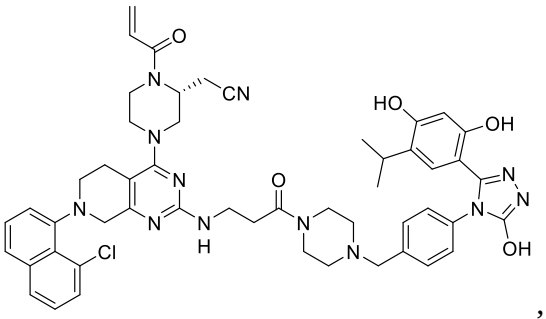

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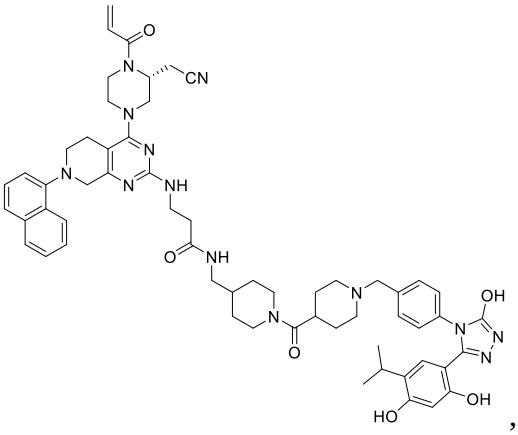

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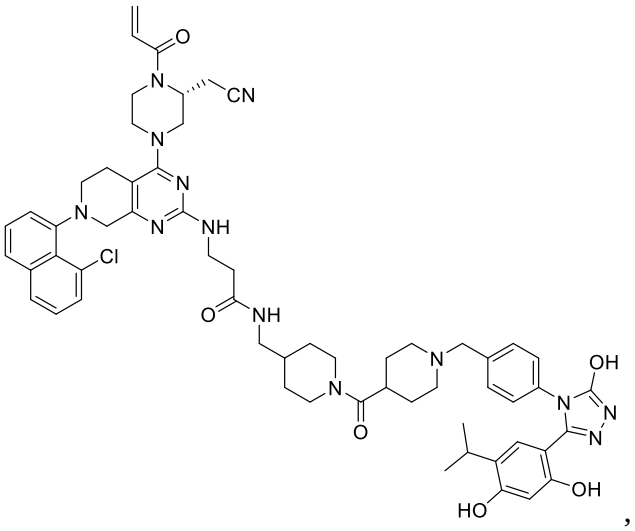

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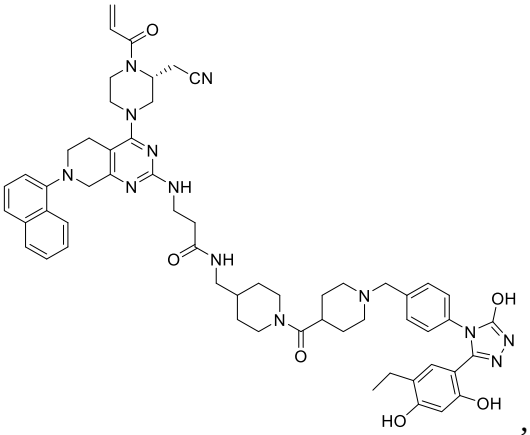

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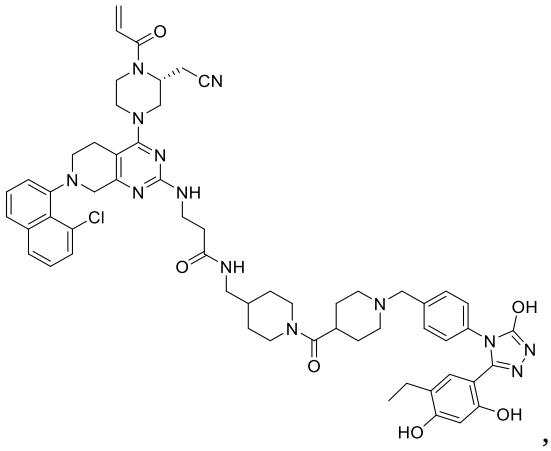
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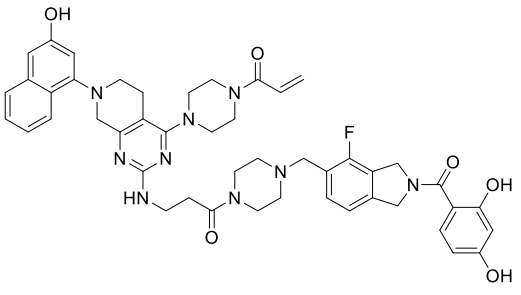
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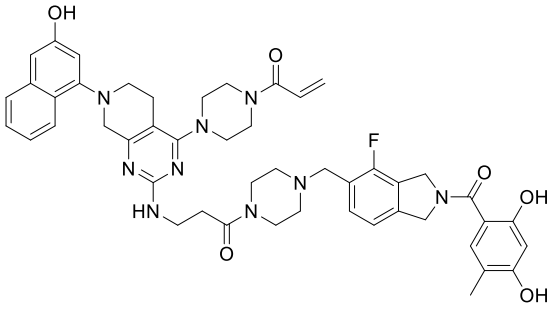
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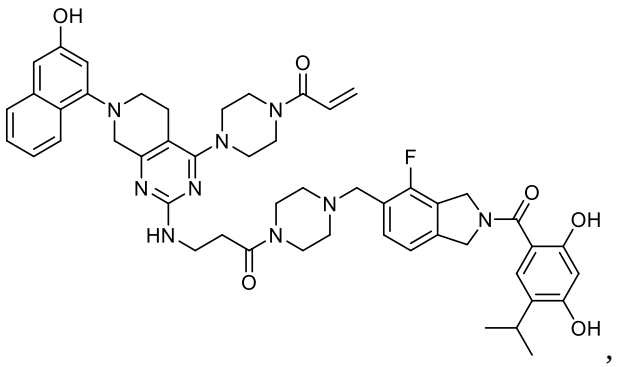
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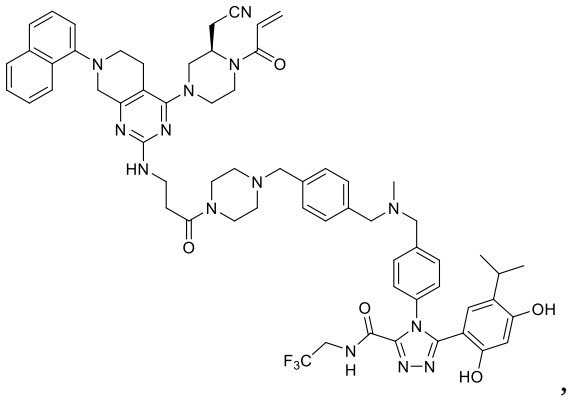

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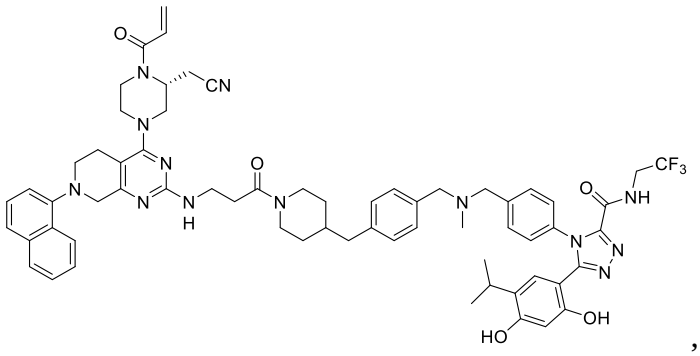

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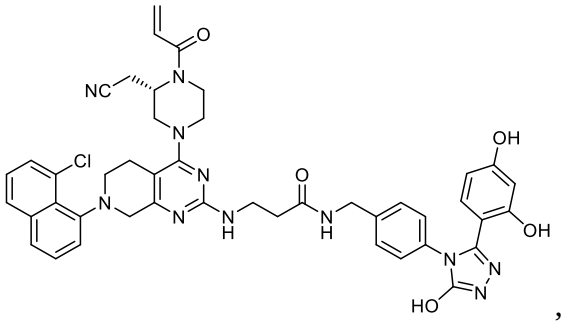

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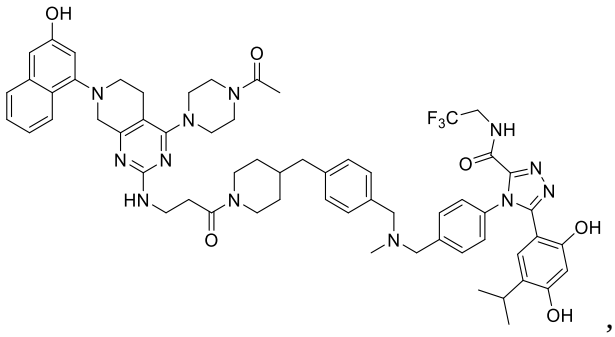

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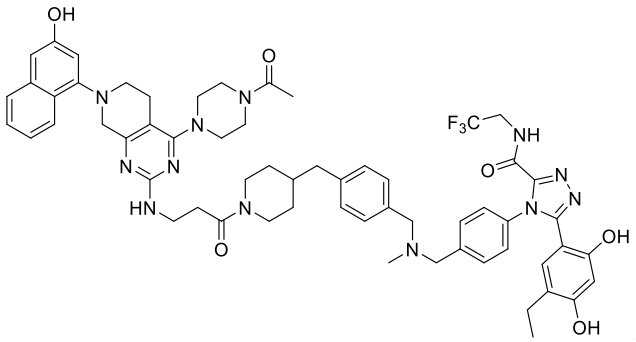

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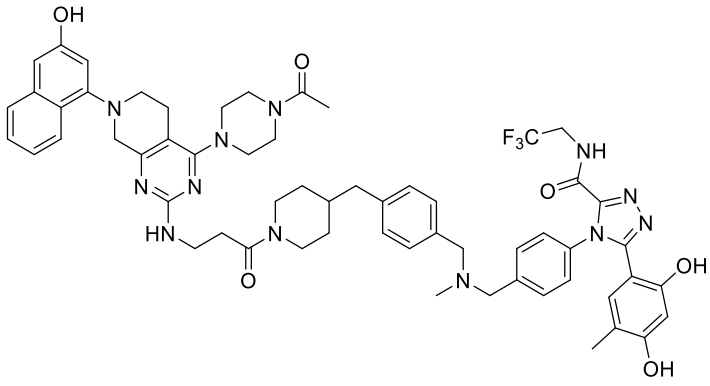
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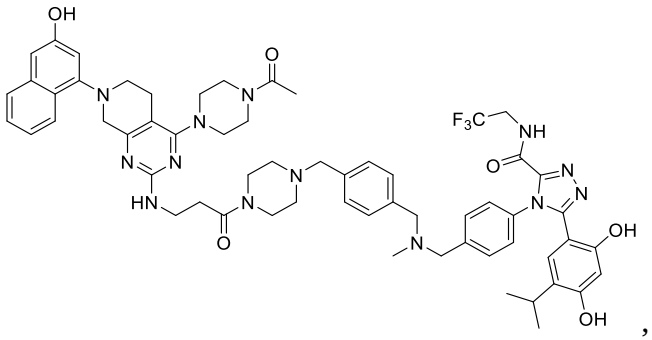
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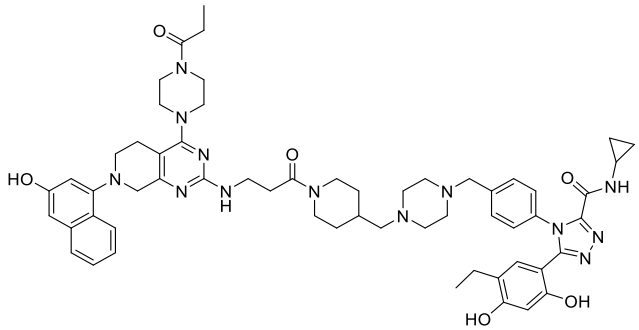
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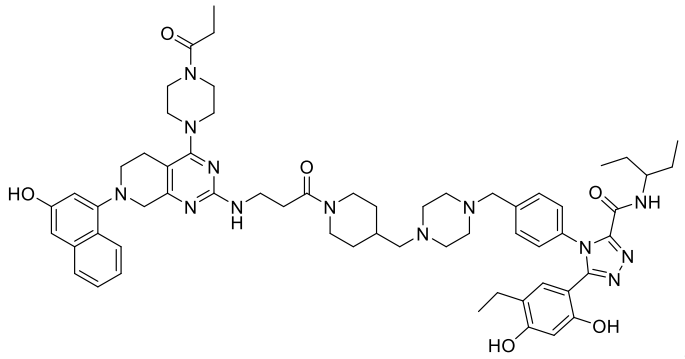
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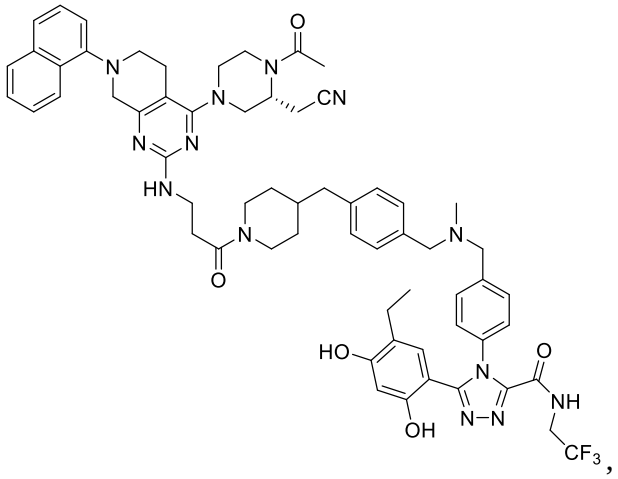

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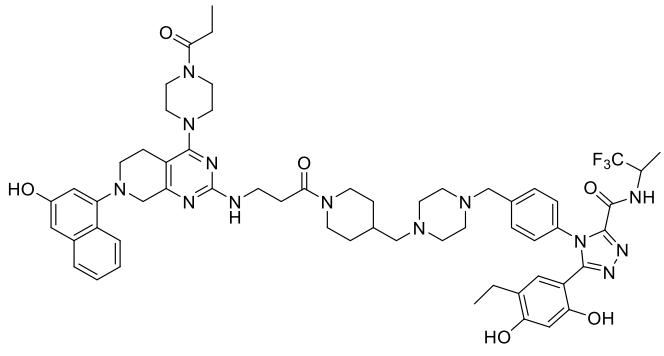

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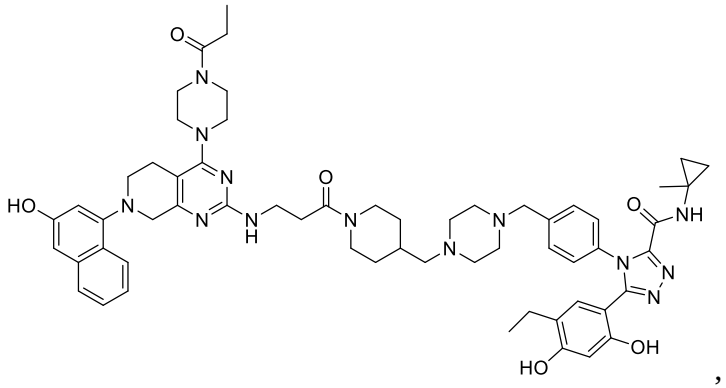

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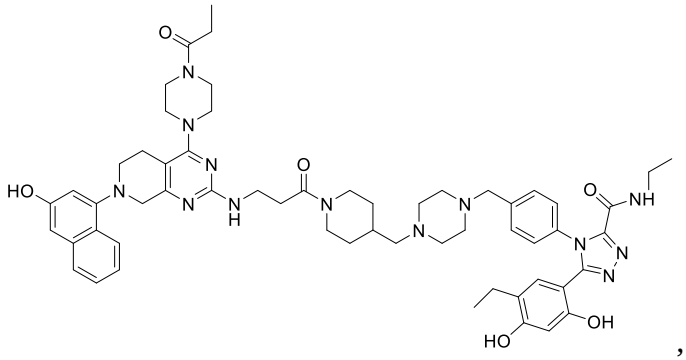

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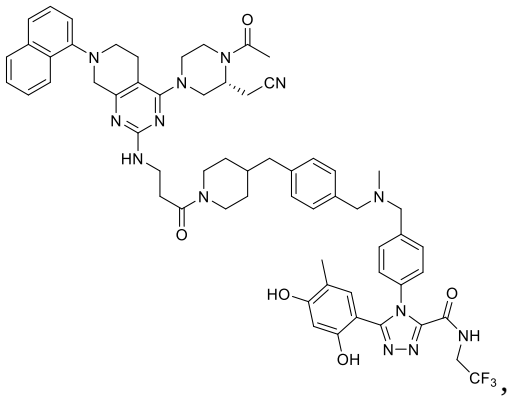

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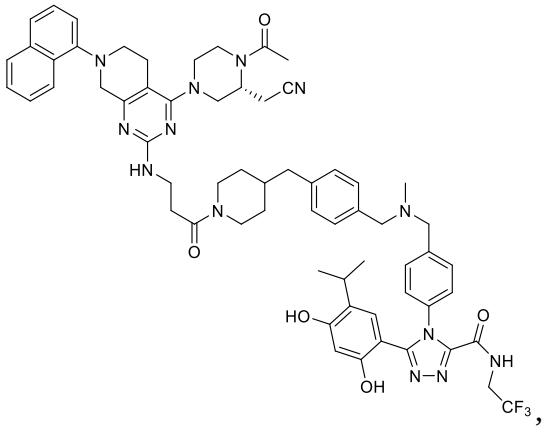

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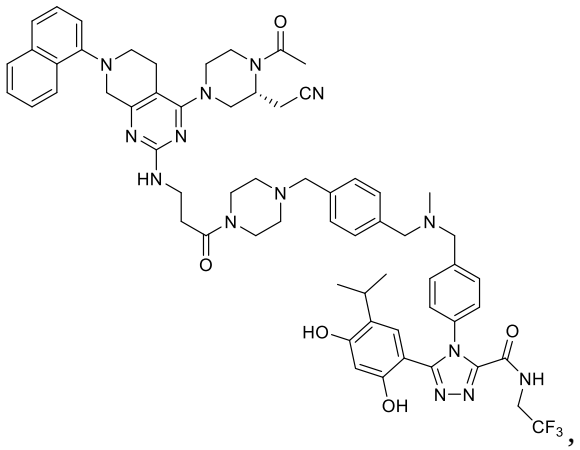

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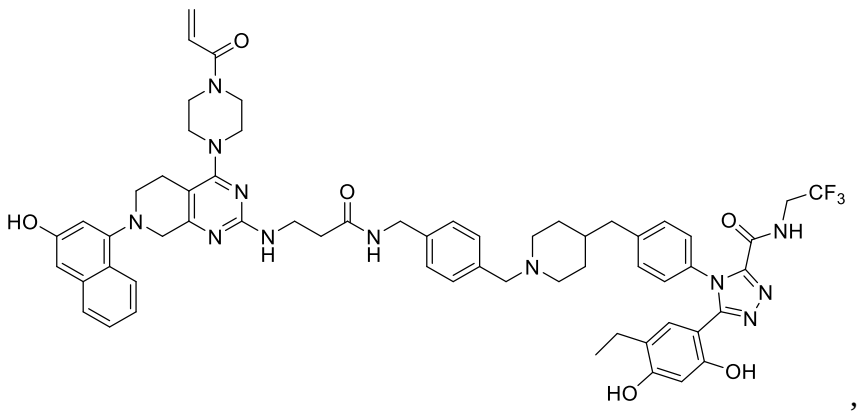

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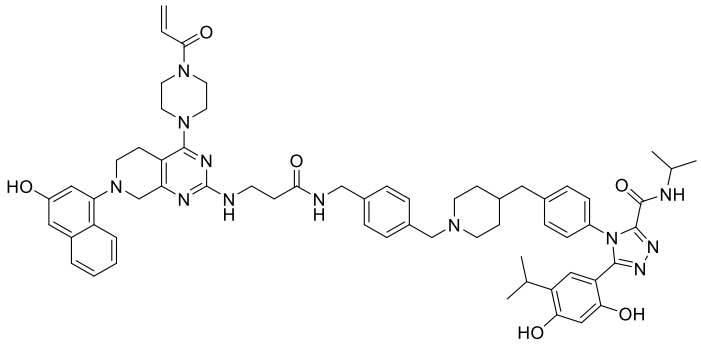

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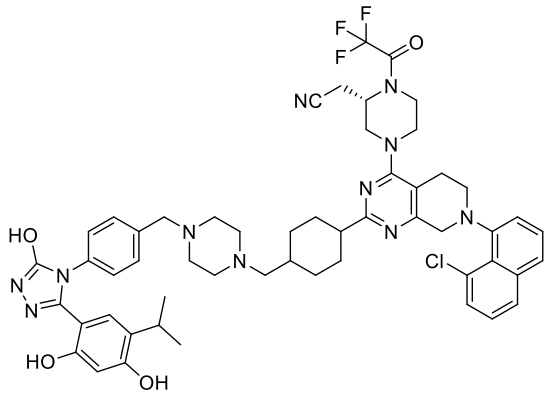

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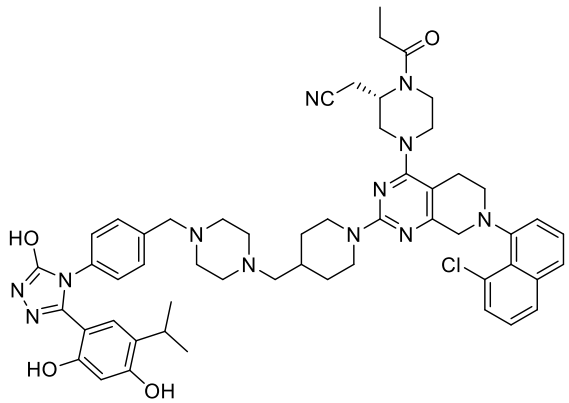

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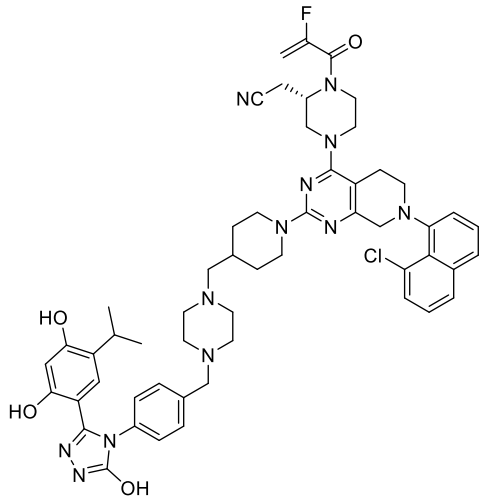

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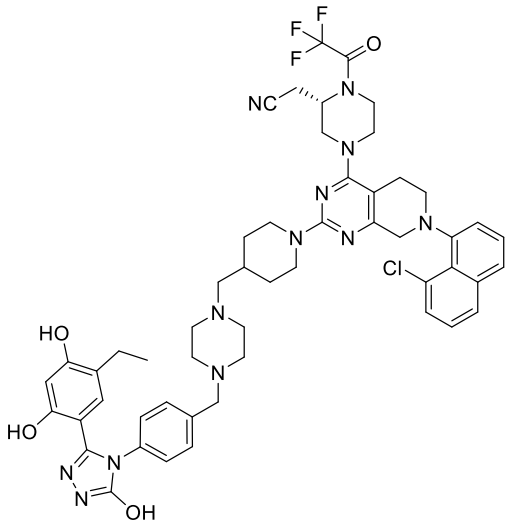

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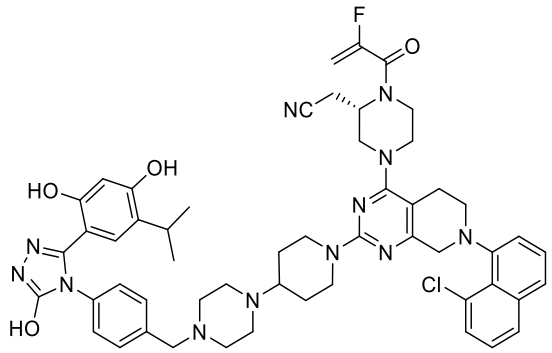

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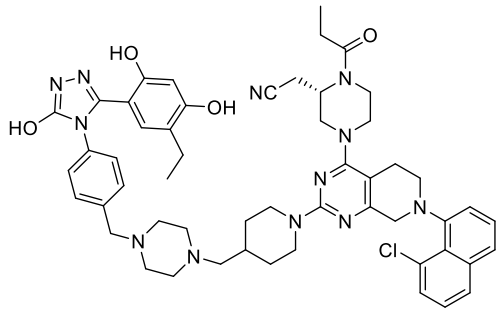

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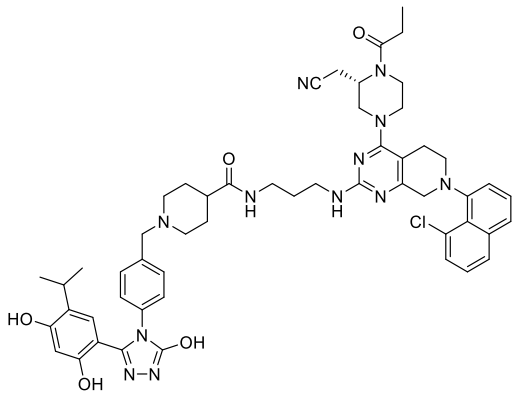

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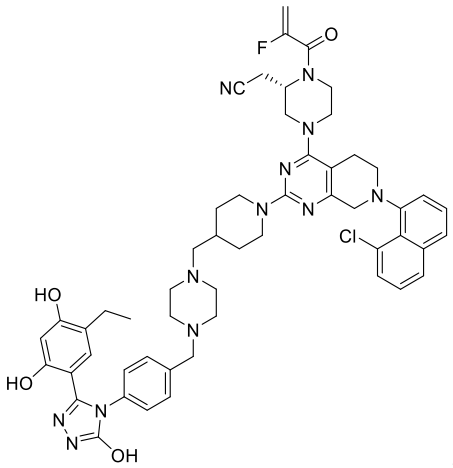

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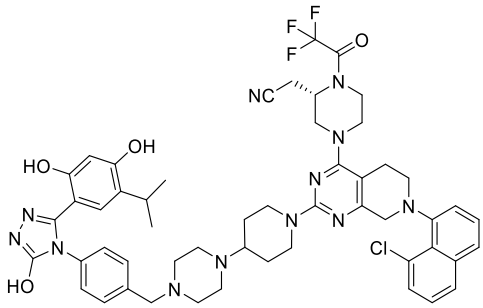

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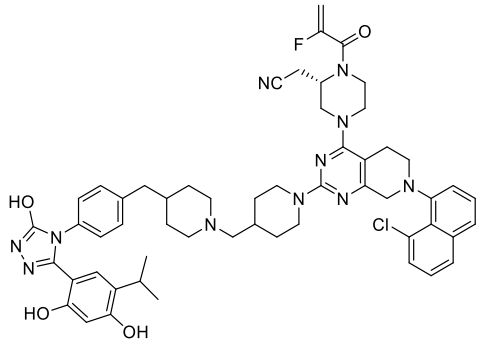

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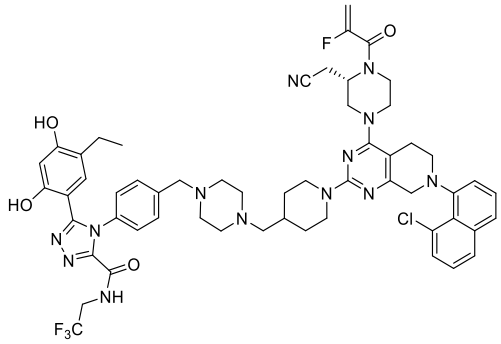

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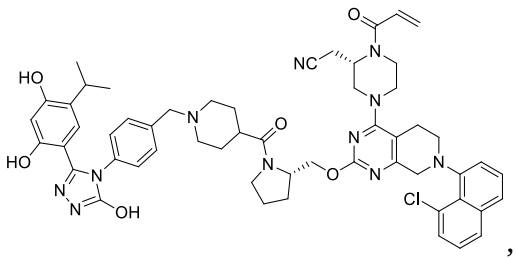
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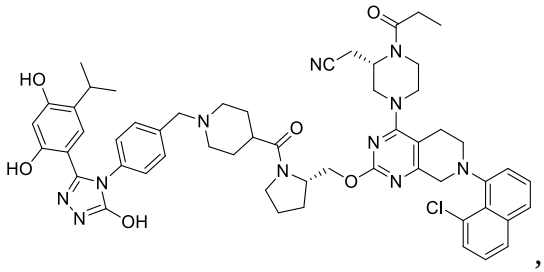
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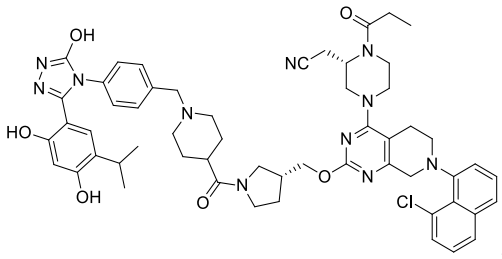
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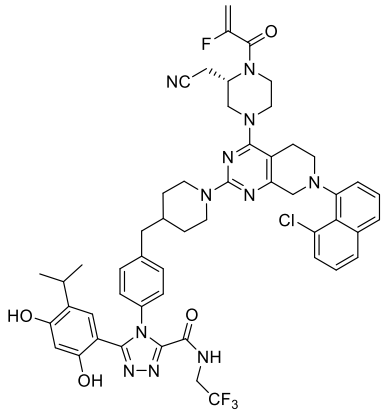
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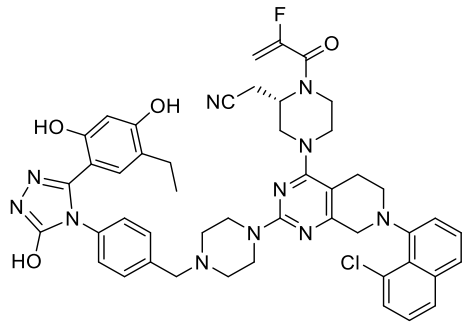
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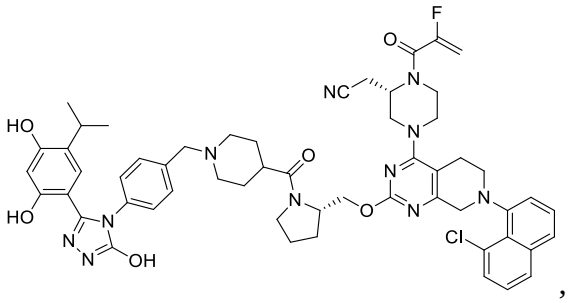

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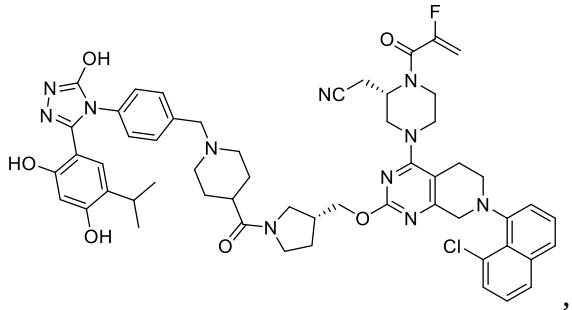

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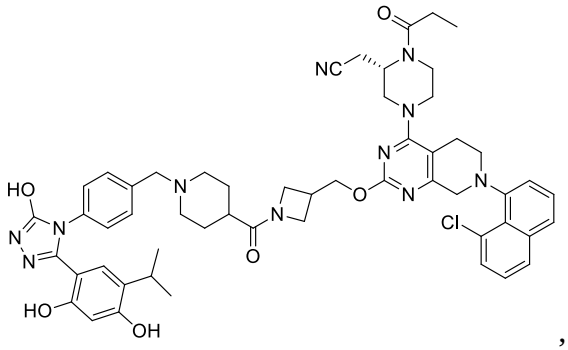

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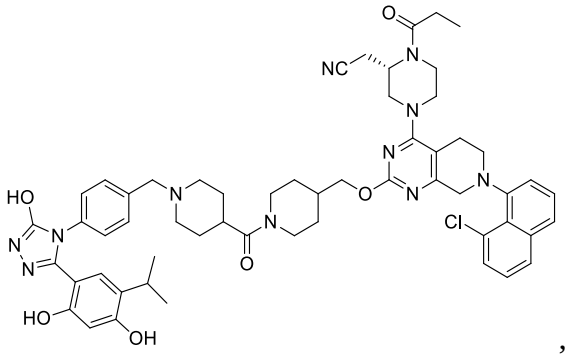

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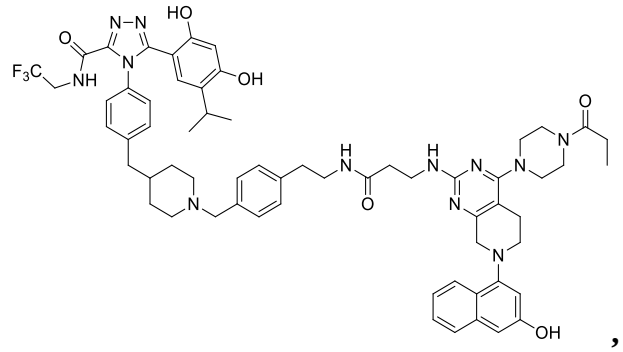
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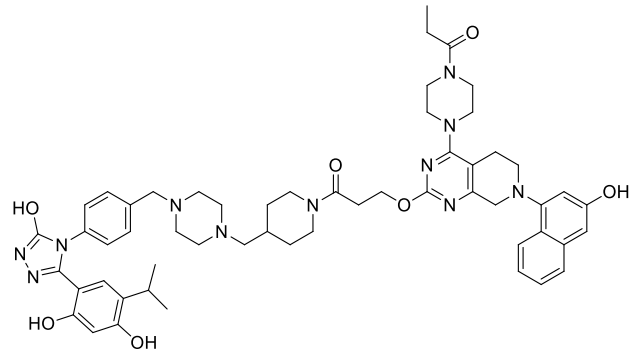
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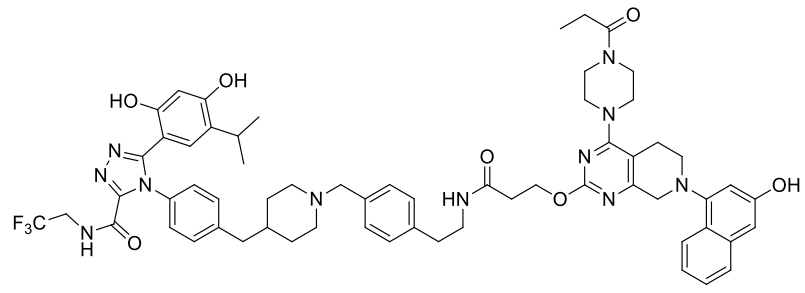
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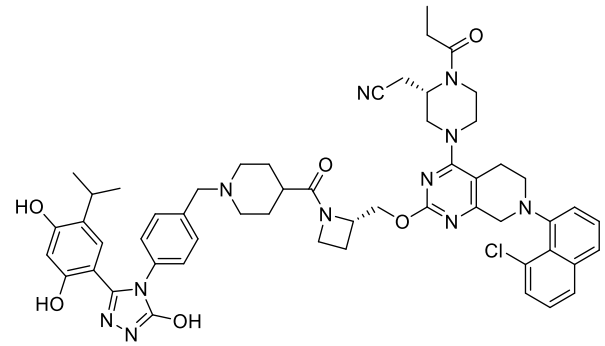
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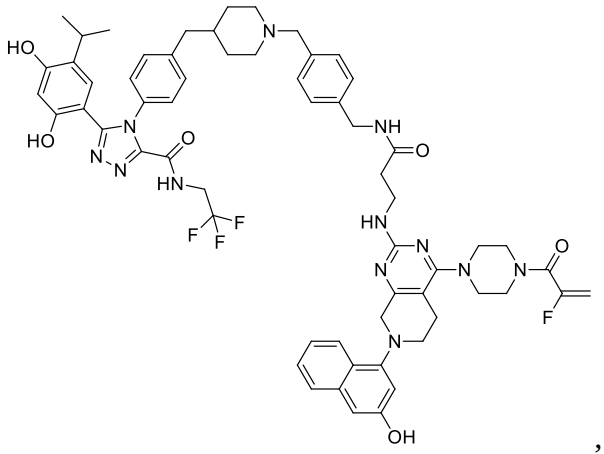
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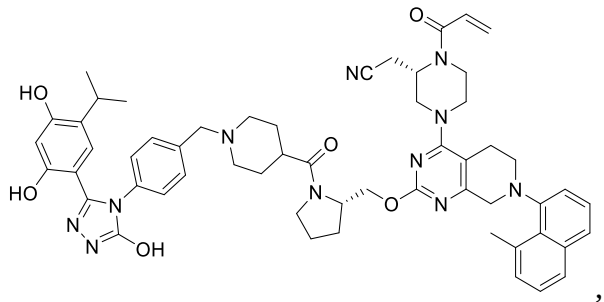
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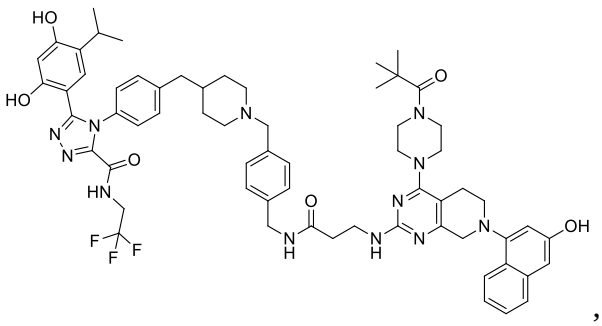
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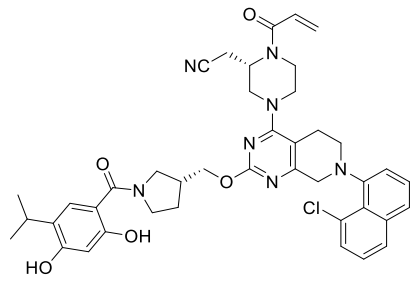
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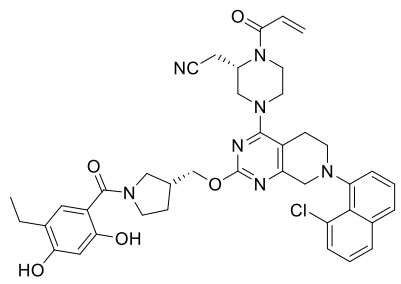
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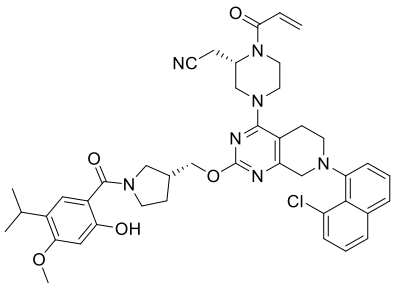

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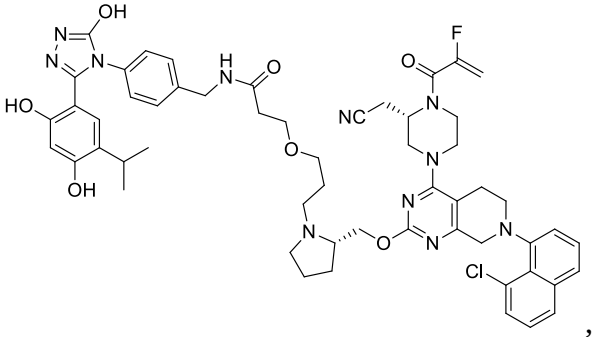

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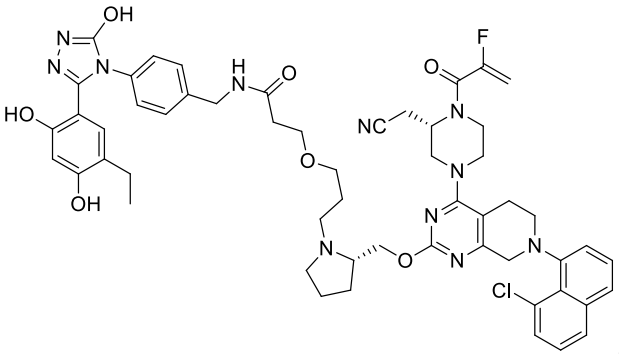

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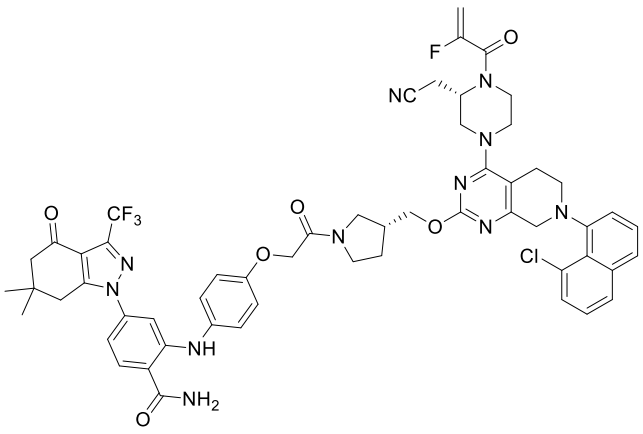

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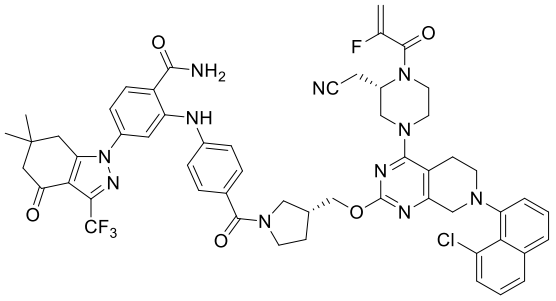

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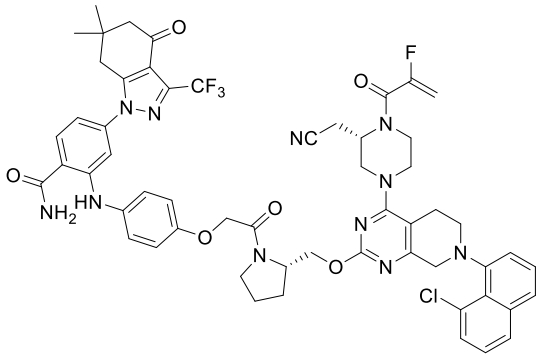

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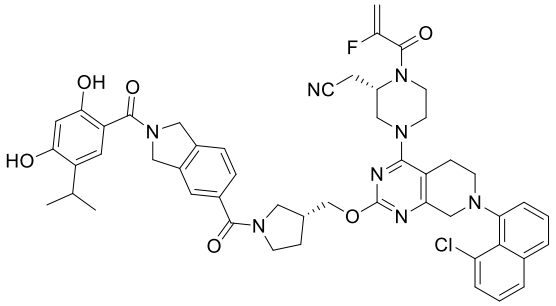

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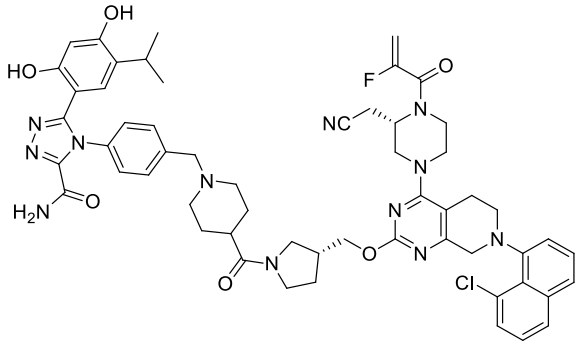

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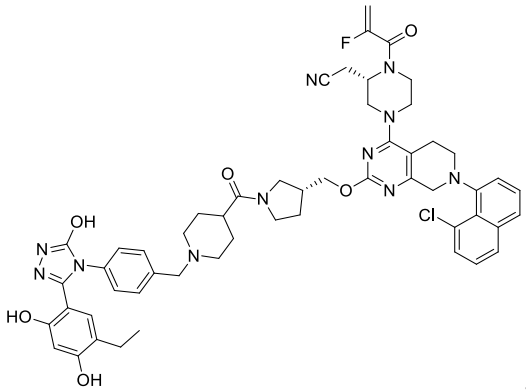

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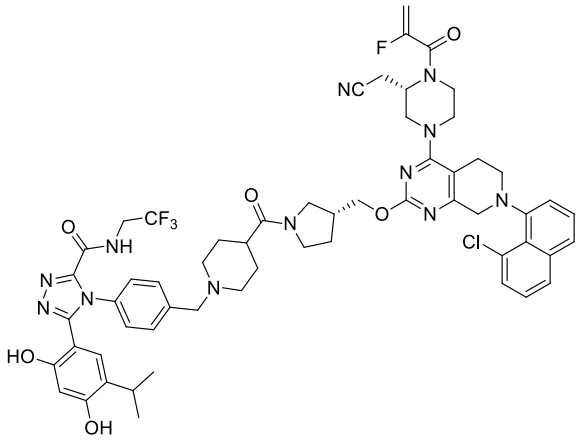

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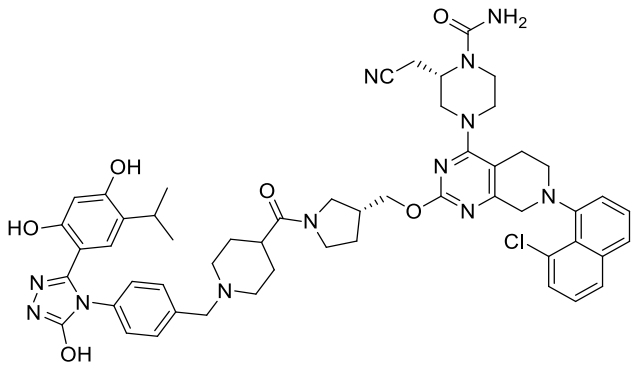

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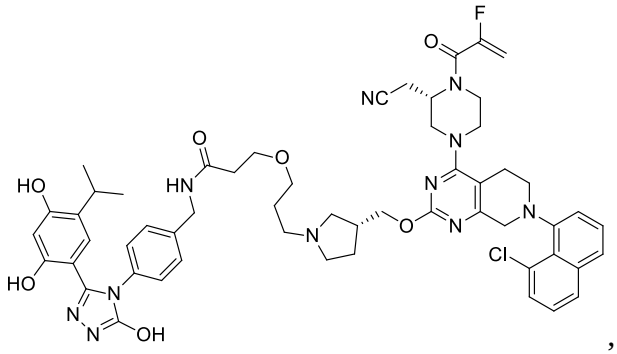

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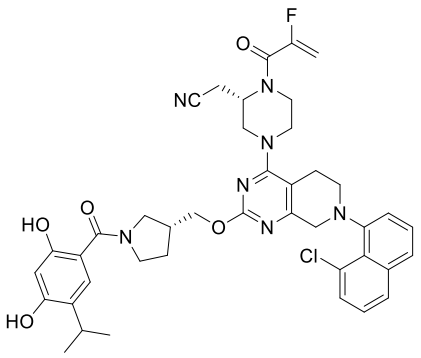

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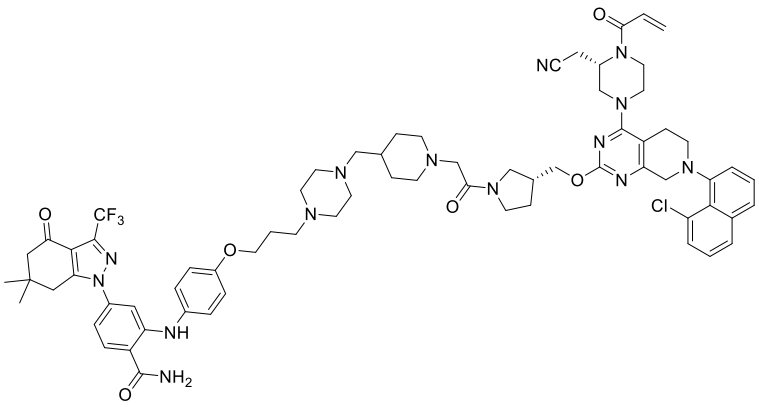

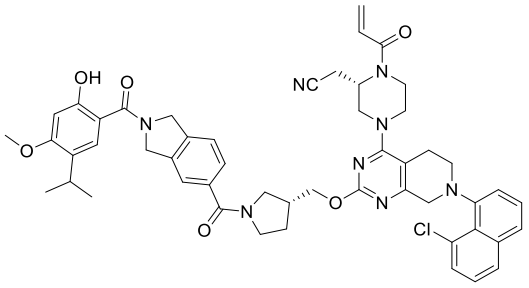

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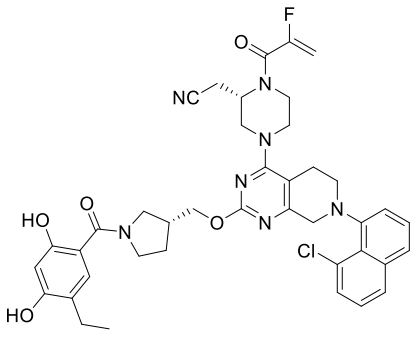

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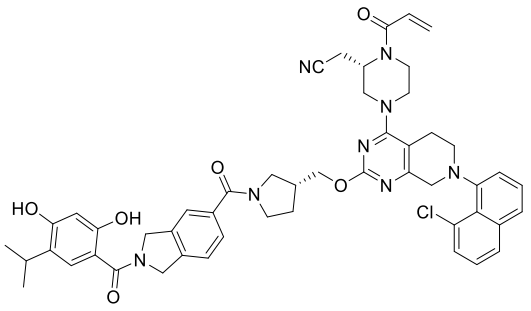

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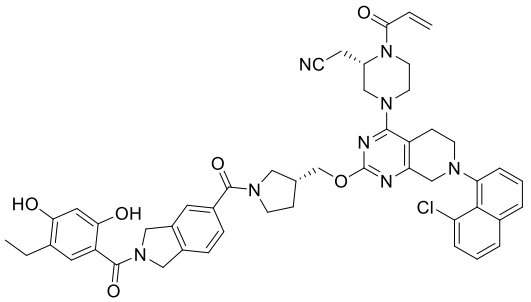

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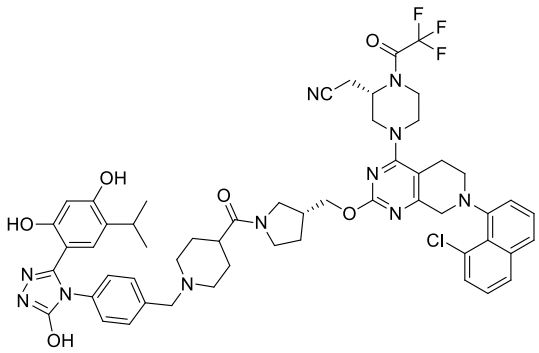

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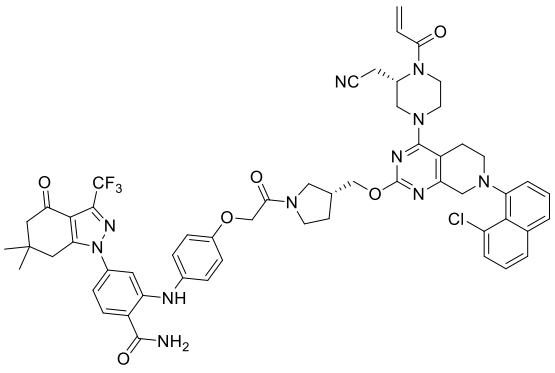

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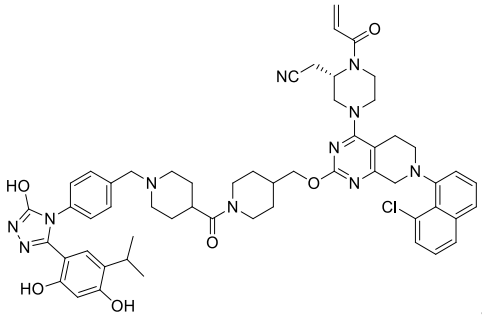

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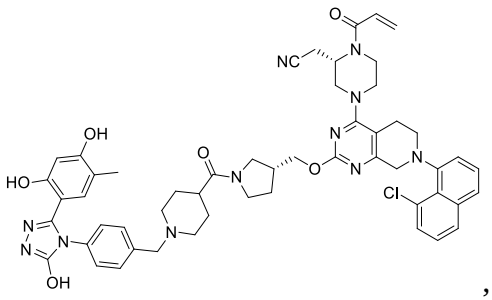

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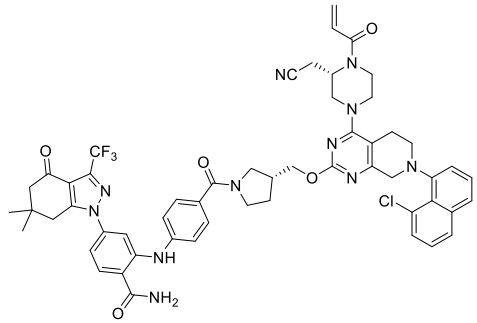

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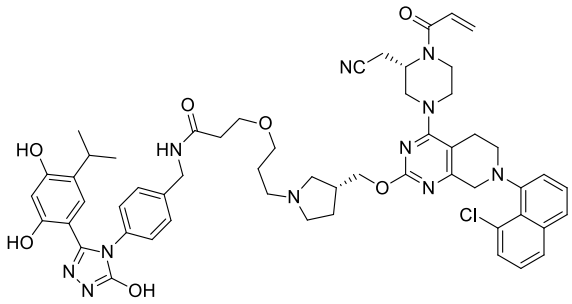

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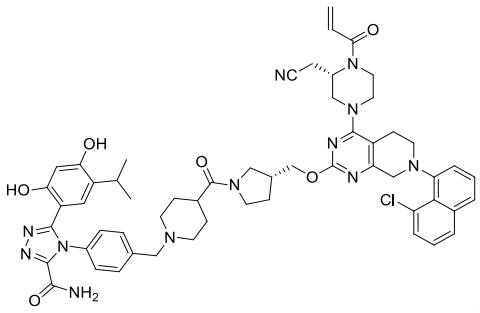

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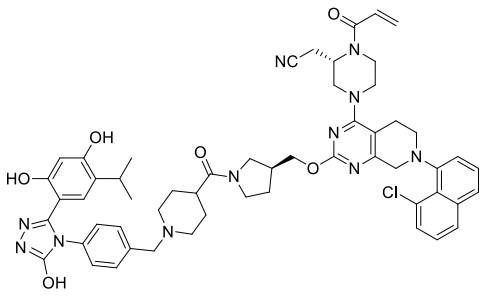

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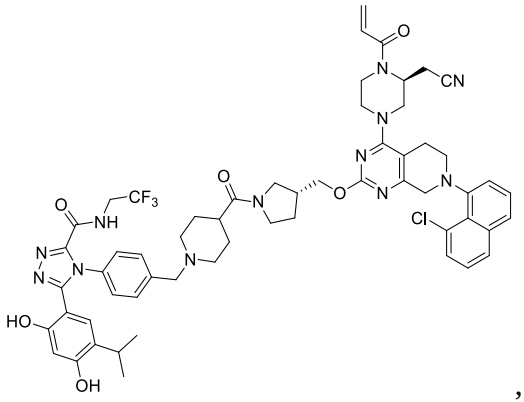

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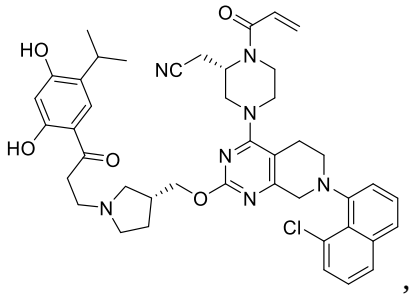

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, or a pharmaceutically acceptable salt of any of the foregoing.

41. The compound of Claim 1, wherein the compound is selected from compounds 187 to 351, or a pharmaceutically acceptable salt of any of compounds 187 to 351.

42. A pharmaceutical composition comprising the compound of any one of Claims 1 to 41, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

43. Use of ~~A method of treating cancer comprising administering to a subject a therapeutically effective amount of~~ a compound of any one of Claims 1 to 41, or a pharmaceutically acceptable salt thereof, or the composition of Claim 42, in the manufacture of a medicament for treating cancer.

44. A compound of any one of Claims 1 to 41, or a pharmaceutically acceptable salt thereof, or the composition of Claim 42, for use in therapy.