consequently are dose-limited by toxicity concerns related to EGFR inhibition (especially gastrointestinal and skin-related toxicities). These toxicities necessitate restrictive dosing regimens, leading to suboptimal target engagement and thus limited therapeutic benefit. Moreover, while current TKIs provide therapeutic benefit for cancers driven by ErbB2 overexpression, they may have limited efficacy in patients harboring specific genetic alterations, such as EGFR or ERBB2 exon 20 insertions, specific point mutations or genetic alterations associated with ErbB family ligands, such as NRG1 gene fusions.

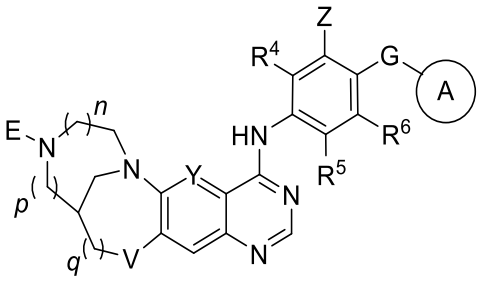
[0005] For example, in a small proportion of lung cancer patients, certain especially pernicious mutations in EGFR and ErbB2 known as EGFR exon 20 insertions/ErbB2 insertions are markedly less sensitive to first and second generation reversible TKIs. An added challenge to the development of viable therapies for these specific ErbB Exon 20 mutants (20ins or E20I) is the fact these alterations are heterogeneous, encompassing a diversity of amino acid insertions/deletions. In addition to E20I mutations, a number of other genetic alterations of the receptor, specifically point mutations leading to single amino acid substitutions, have been associated with the development of a variety of cancers, including lung cancer. Although the resistance mechanisms associated with each of these mutations are not fully understood, it is believed that the mutations may share a commonality in promoting ligand-independent activation of the kinases. Further investigation of the underlying mechanisms and development of TKIs tailored to these mutants are needed.

[0006] Other aggressive, refractory cancers exhibiting ErbB2 overexpression have been observed to harbor NRG1 gene re-arrangements resulting in novel fusion proteins. NRG1 gene fusions may induce overproduction of neuregulin-1, the cognate ligand for ErbB3. The simultaneous overexpression of ErbB2 and overproduction of neuregulin-1 may lead to excess activation of ErbB2-ErbB3 heterodimers and resultant hyperplasia.

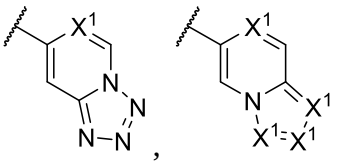
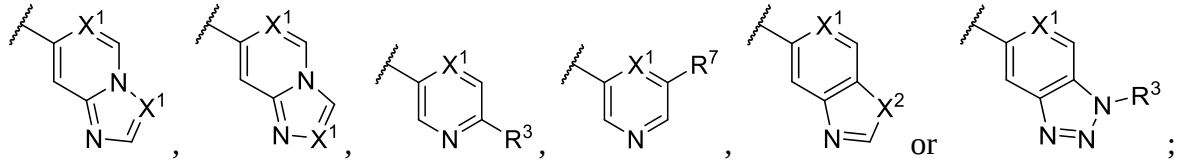
[0007] Accordingly, there remains a need for new therapeutics for the treatment of cancers driven by dysregulated ErbB2 receptor kinase activity, not only with improved safety and selectivity for ErbB2 over EGFR, but also for addressing mutation-associated sub-variants of ErbB2 (e.g., E20I mutations and NRG1 gene fusions) with enhanced potency.

SUMMARY

[0007a] In an aspect of the present disclosure, there is provided a compound of formula (I')



(I')

or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:Ring A is , ;

E is -C(=O)-R^1;

G is -O-, -C(=O)-, -S-, -S(O)-, -$S(O)_2$-, or -CH_2-;

V is O, S, or N-R^2;

each X^1 is independently N or CH;

X^2 is O, S, or N-R^3;

Y is N or C-R^y, wherein R^y is -H or -F;

Z is -H, halogen, -C≡CH, -OCH_3, or C_1-C_2 alkyl;

R^1 is C_2-C_4 alkenyl or C_2-C_4 alkynyl, each of which is independently optionally substituted by 1-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, a 3- to 7-membered carbon-linked N-heterocycloalkyl, or -$NR^{1a}R^{1b}$, wherein each R^{1a} and R^{1b} are independently -H, C_1-C_3 alkyl, or -CD_3, or wherein each pair of geminal R^{1a} and R^{1b} may be taken together with the nitrogen atom to which they are attached to form a 3- to 6-membered N-heterocyclyl, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl;

R^2 is C_1-C_6 alkyl or C_1-C_6 cycloalkyl, each of which is independently optionally substituted by 1-4 fluorines;

R^3 is -H, C_1-C_6 alkyl, -CD_3 or C_1-C_6 cycloalkyl;

R^4 is -H or halogen;

R^5 is -H or halogen;

R^6 is -H or halogen;

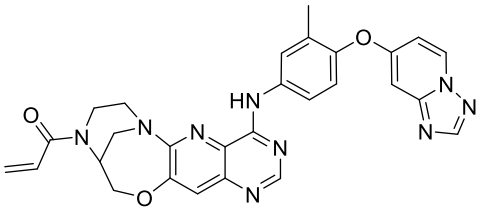
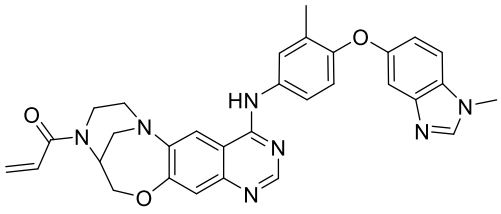
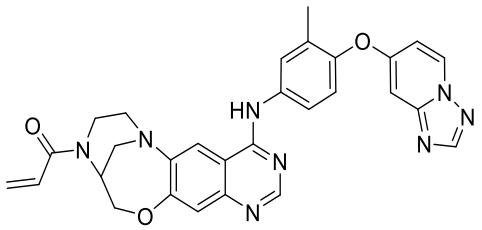
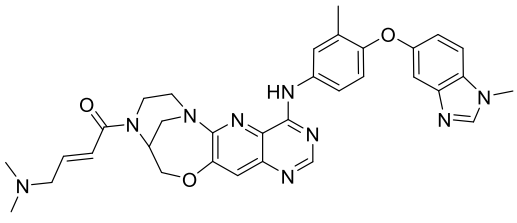
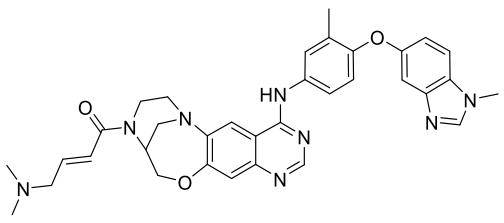
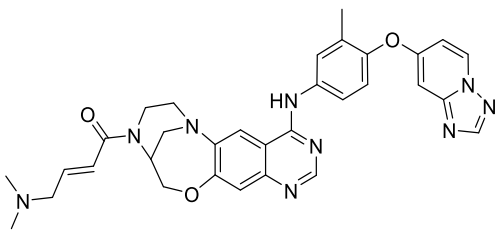
R^7 is -H, halogen, C_1-C_6 alkyl, -CD_3 or C_1-C_6 cycloalkyl;

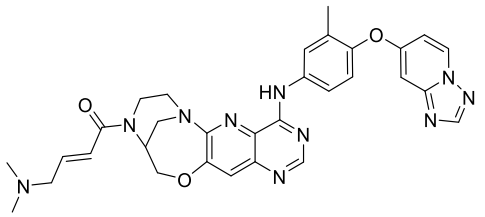
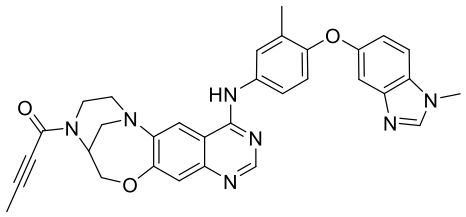
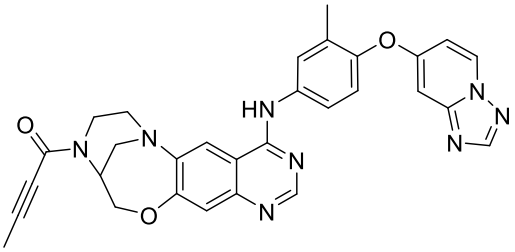
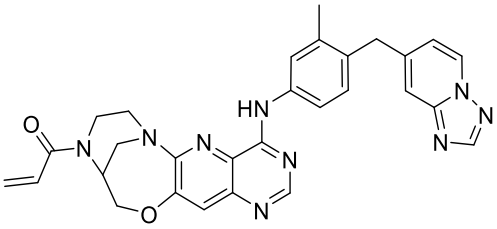
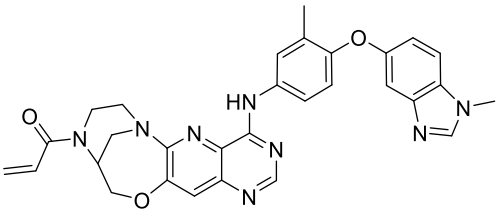
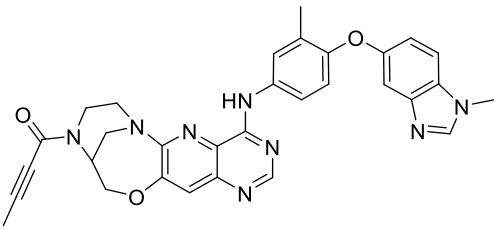
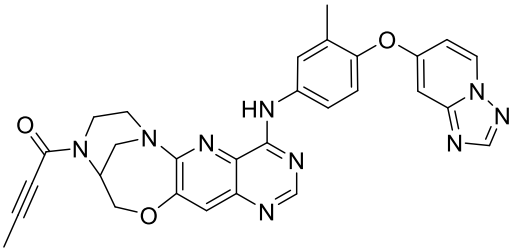
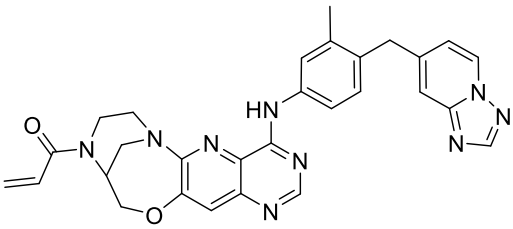
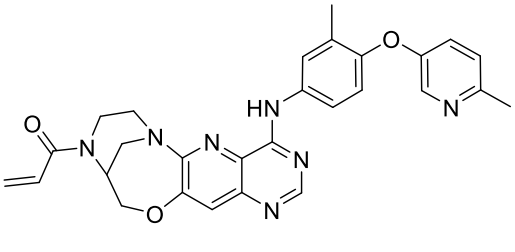
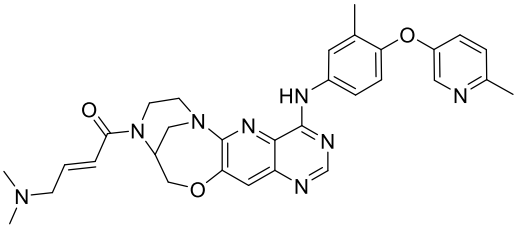
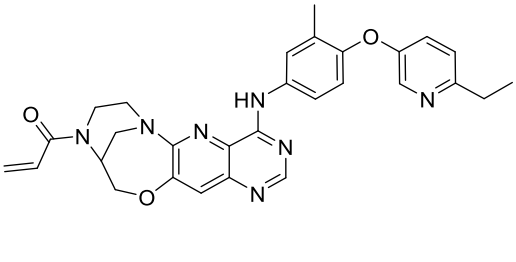
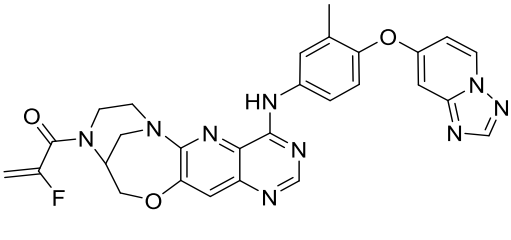
n is 1 or 2;

p is 0 or 1; and

q is 1 or 2.

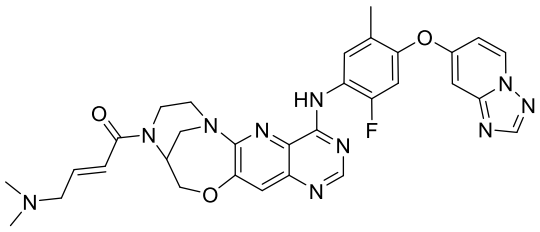
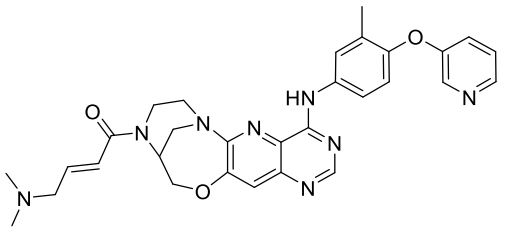
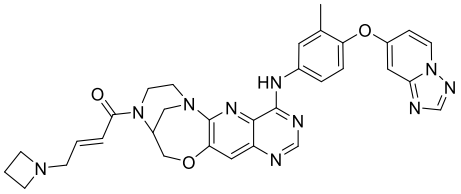
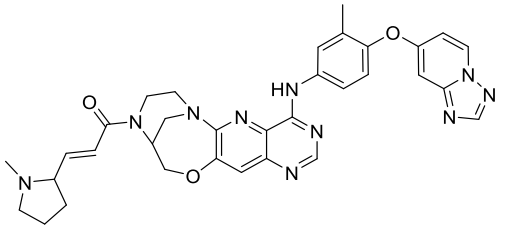
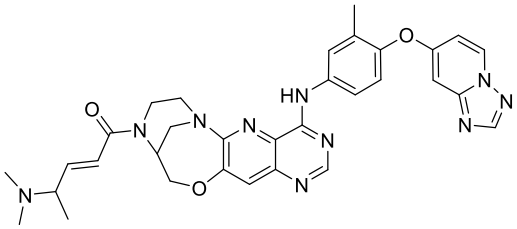
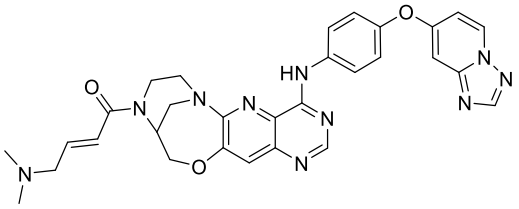
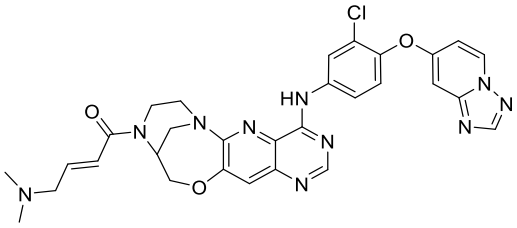
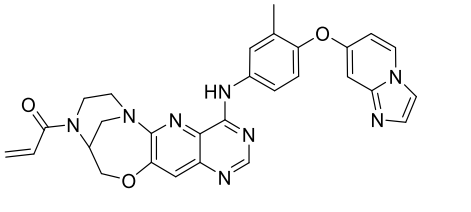
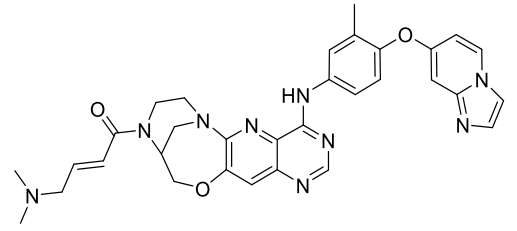
[0007b] In another aspect of the present disclosure, there is provided a compound selected from the group consisting of:


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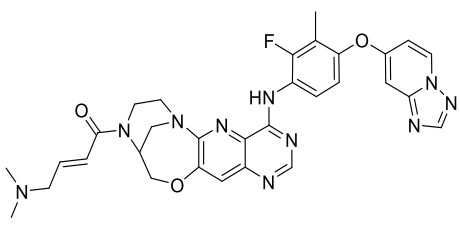
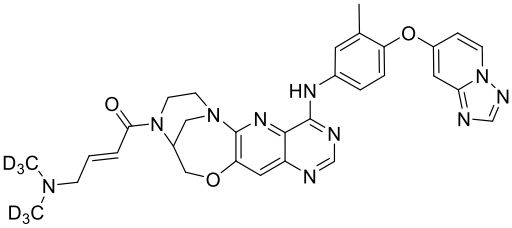
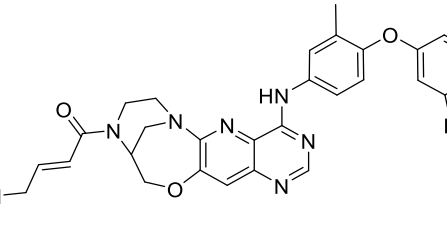

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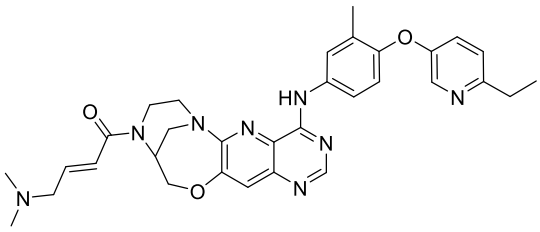
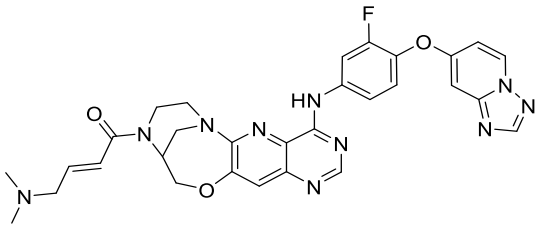
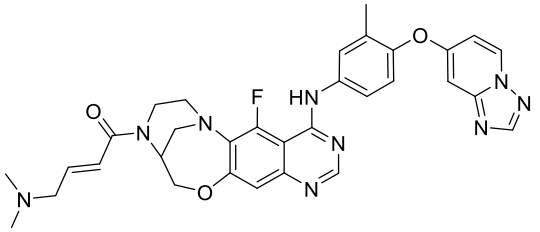
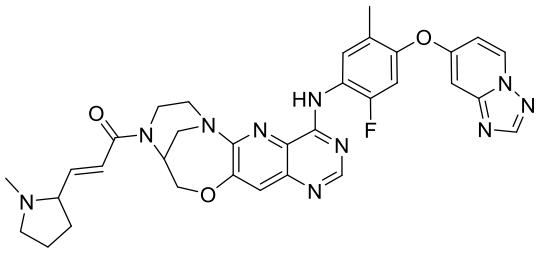
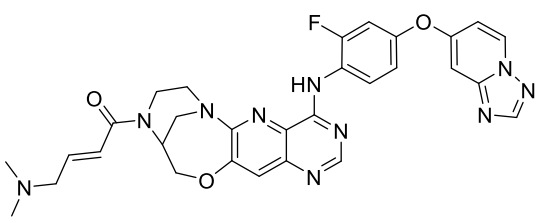
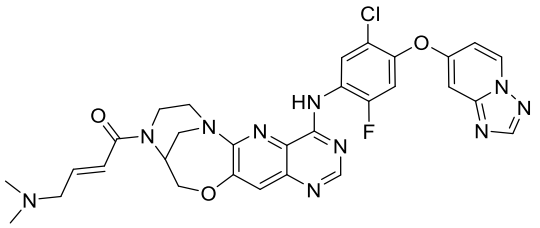
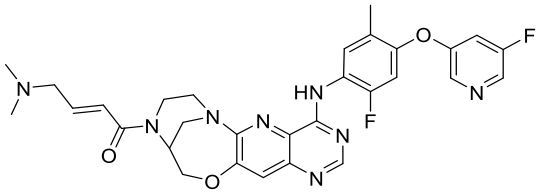
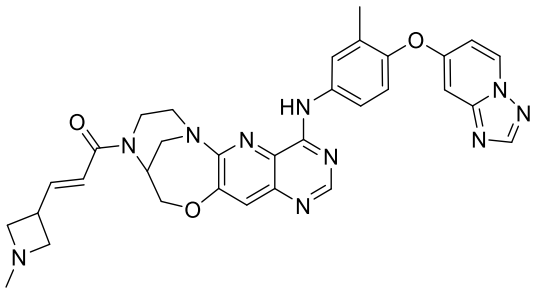
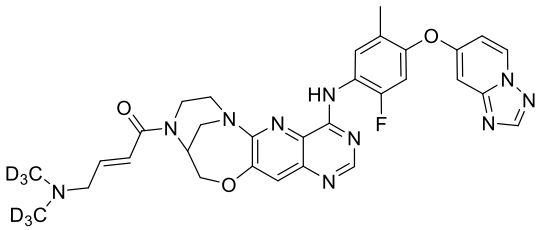
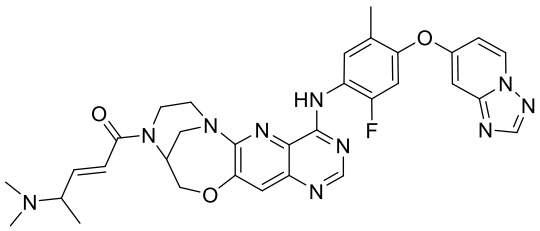
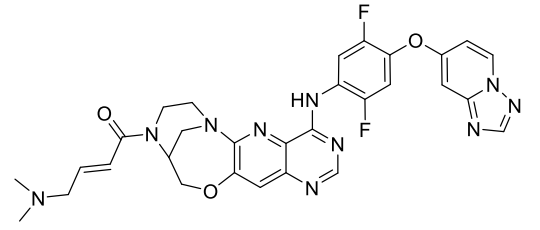
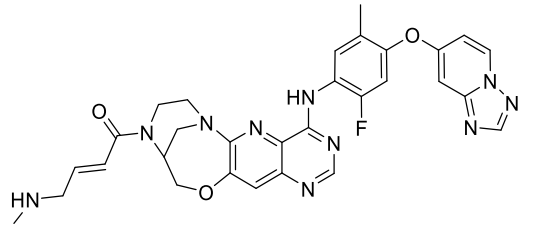

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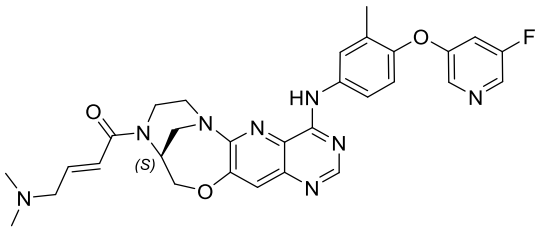
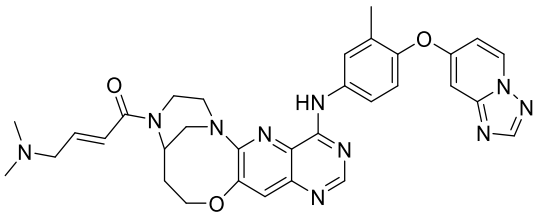
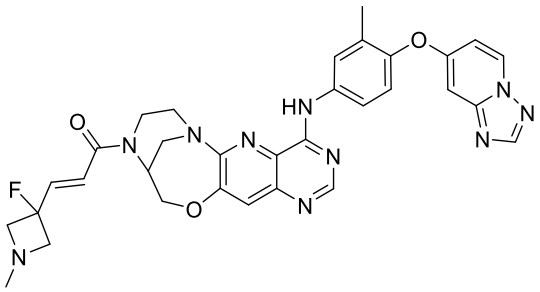
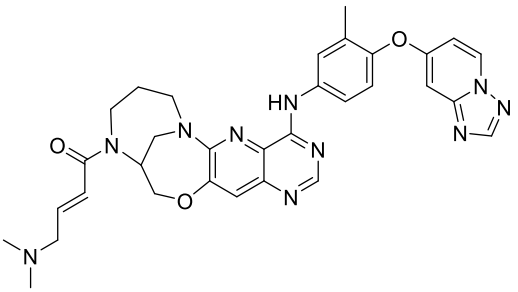
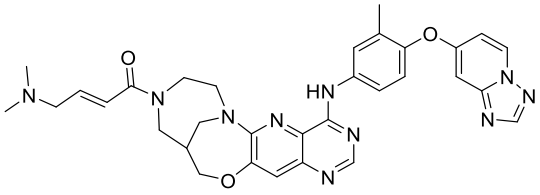
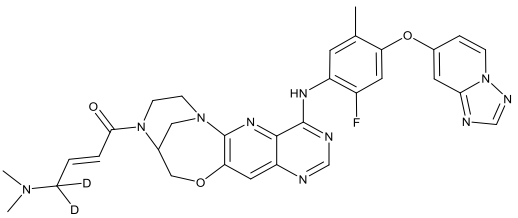
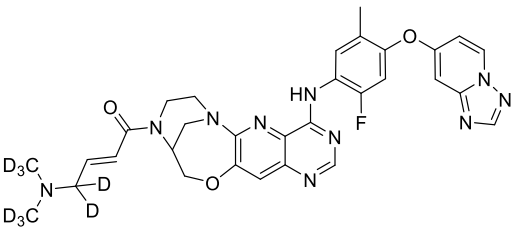
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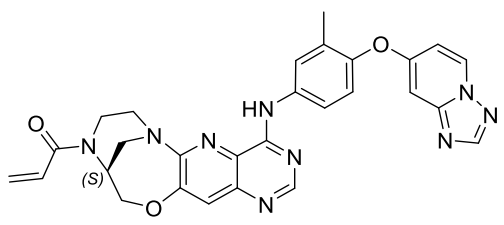
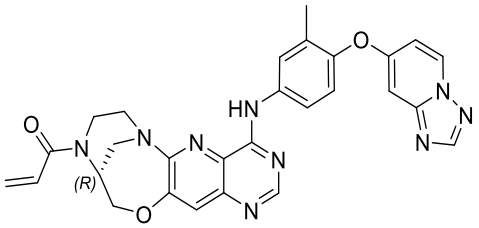
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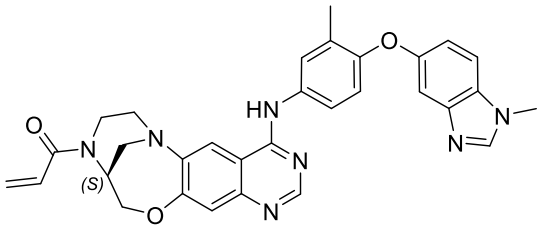
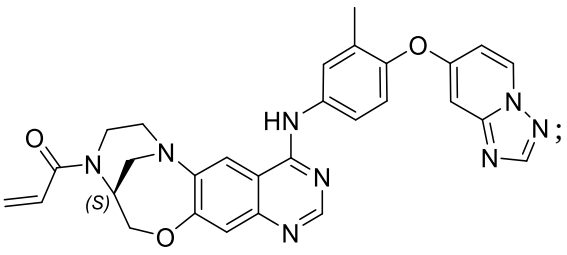
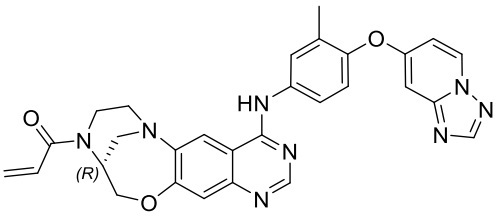
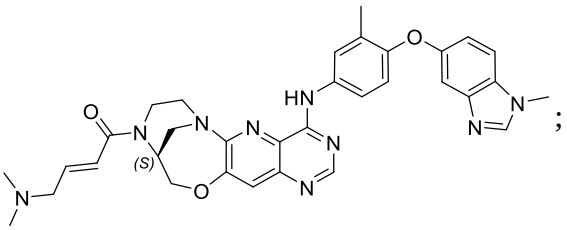
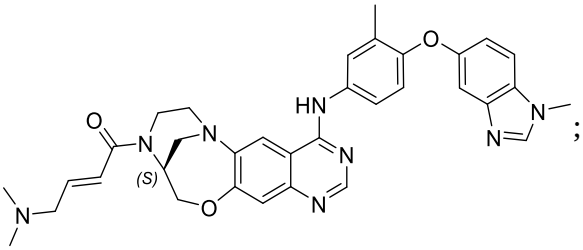
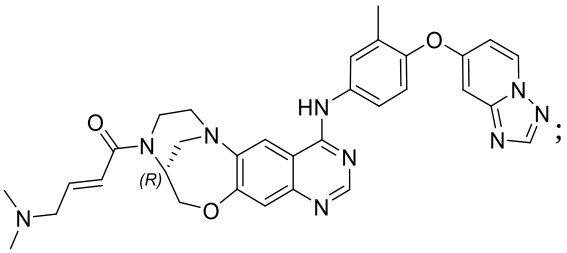
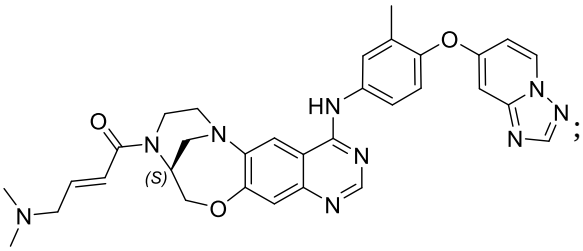
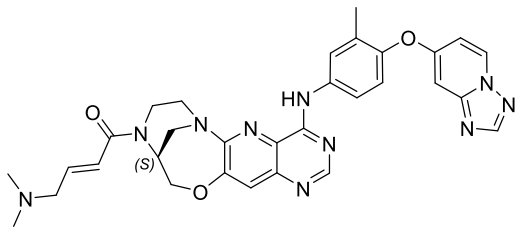
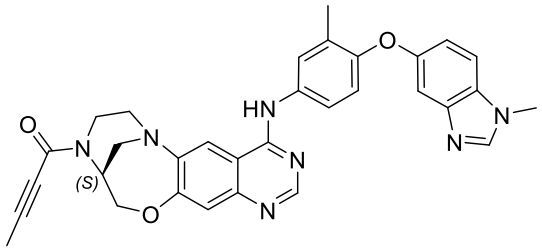
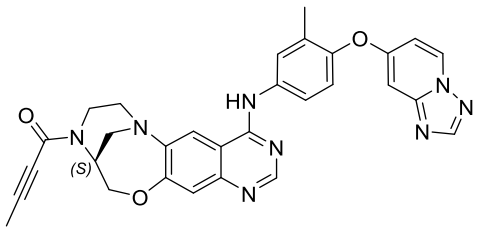
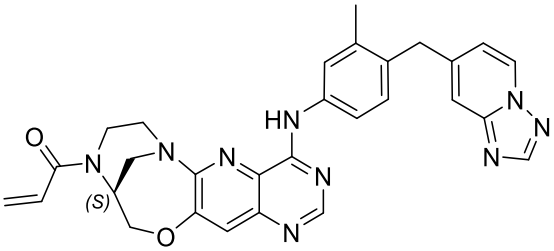
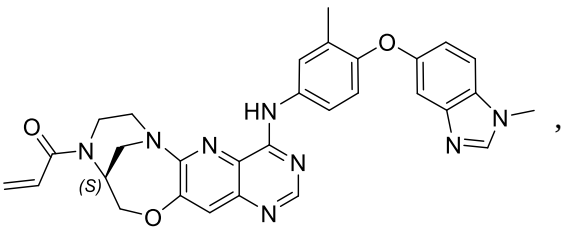

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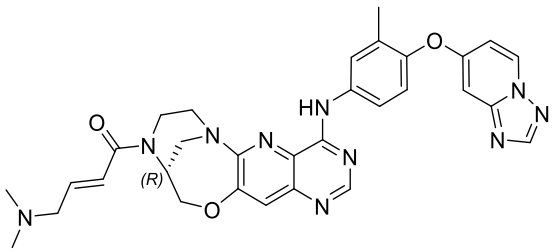
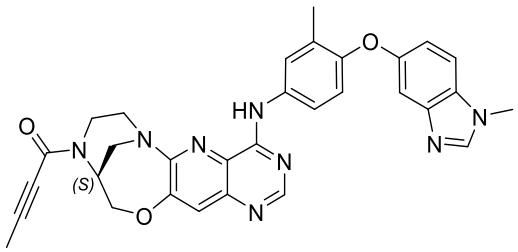
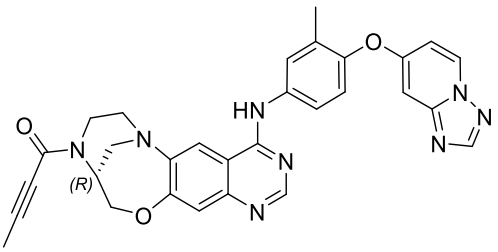
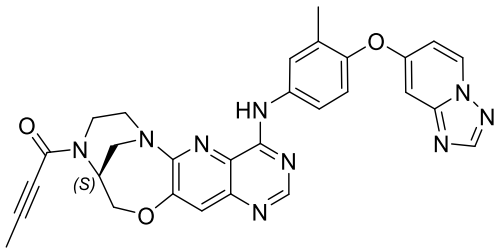
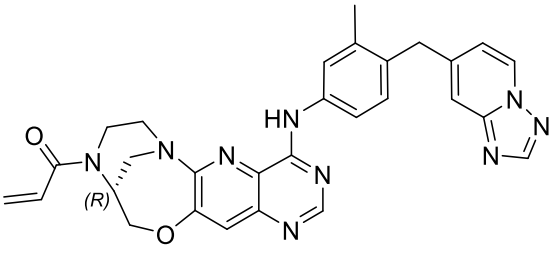
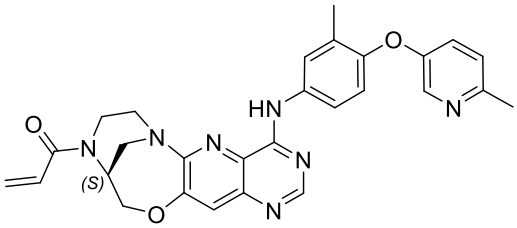
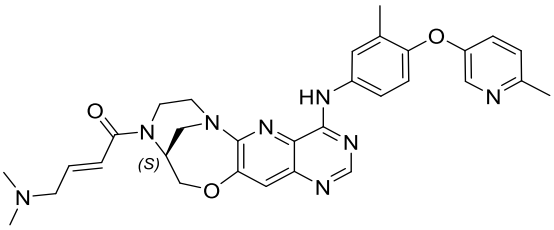
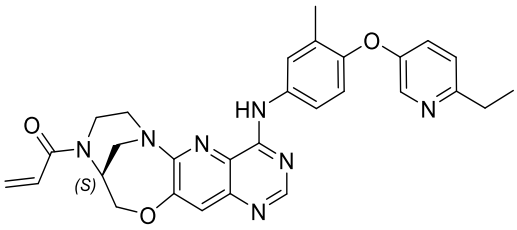
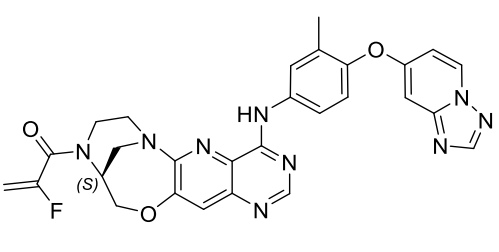
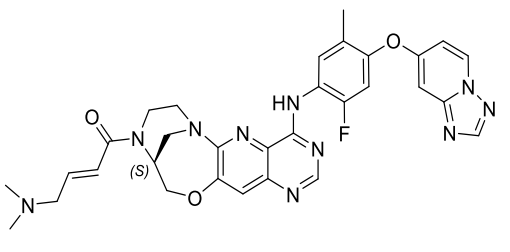
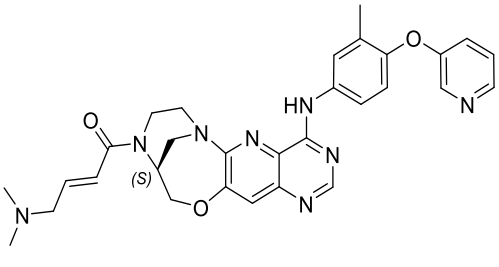
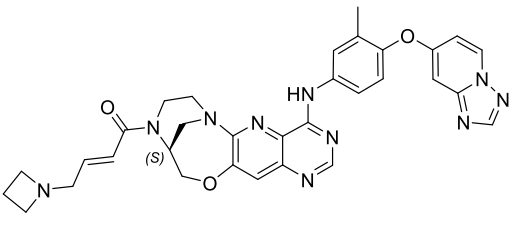

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or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing.

[0007c] In a further aspect of the present disclosure, there is provided a compound selected from the group consisting of:

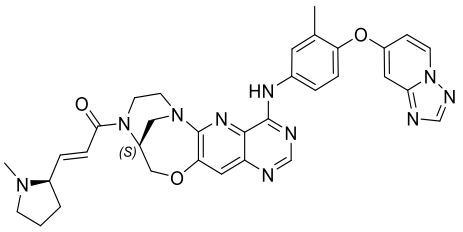
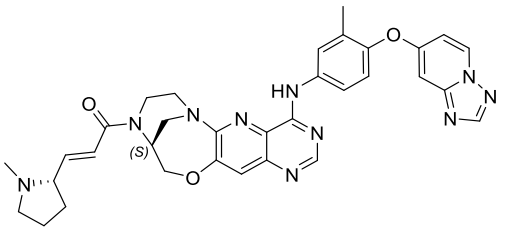
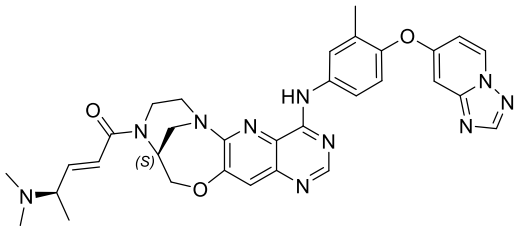
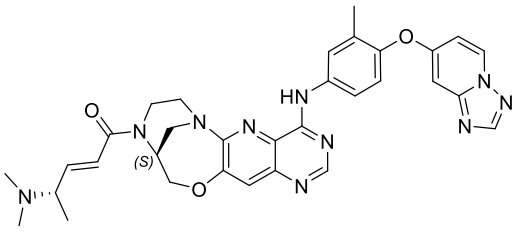
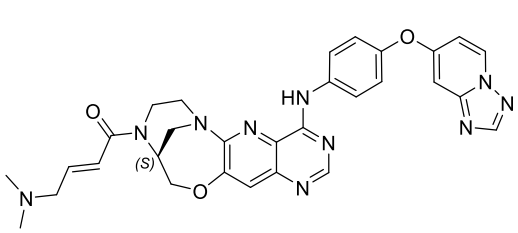
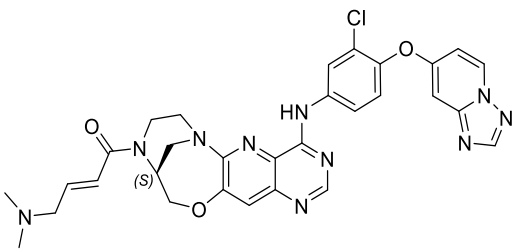
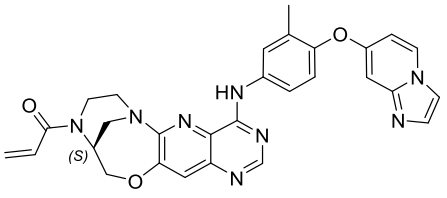
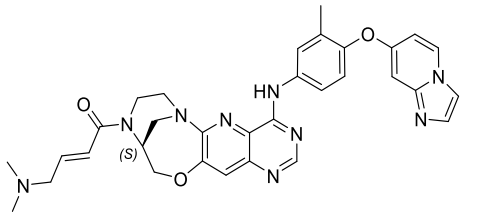
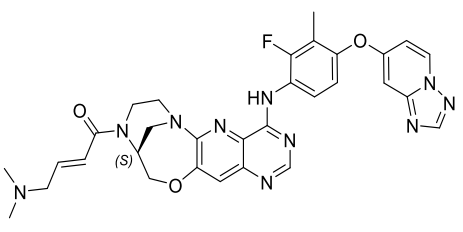
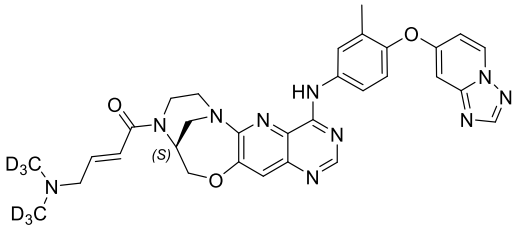
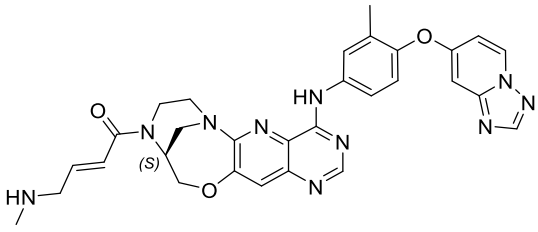
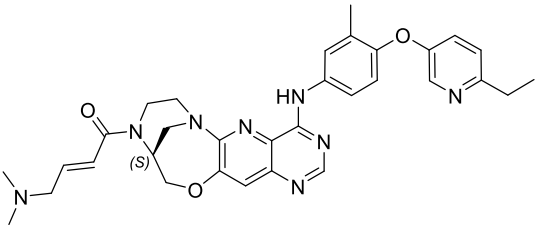

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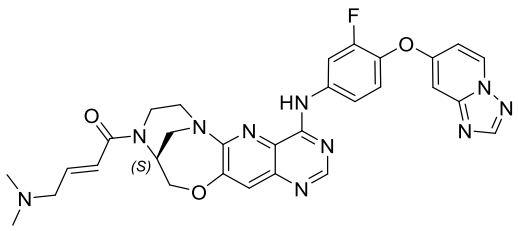
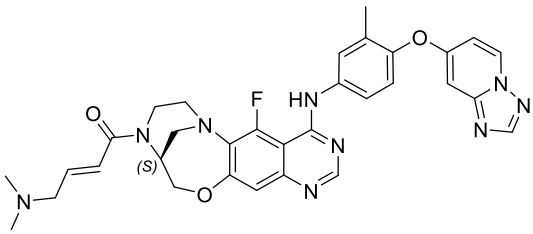
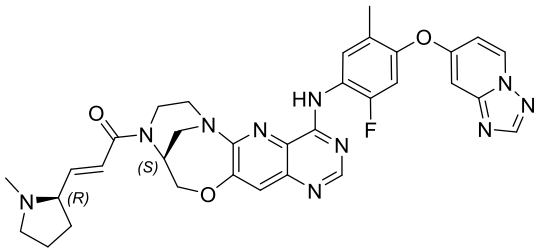
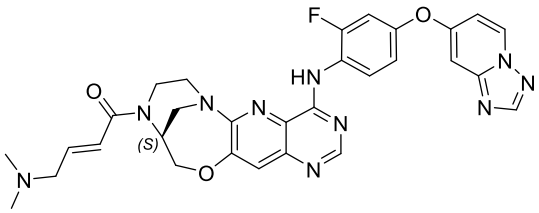
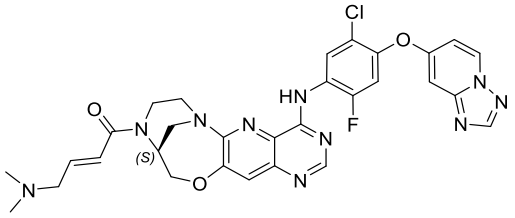
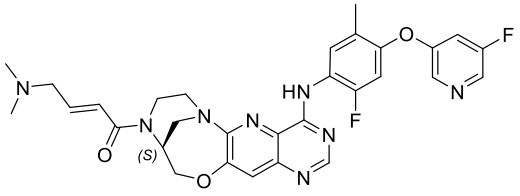
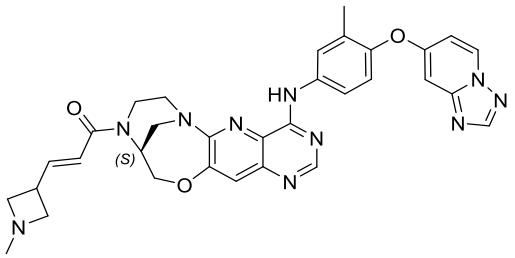
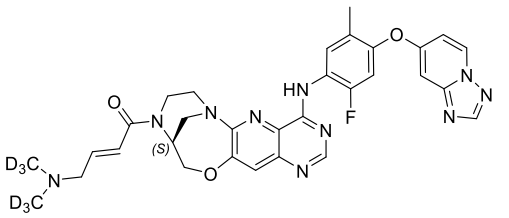
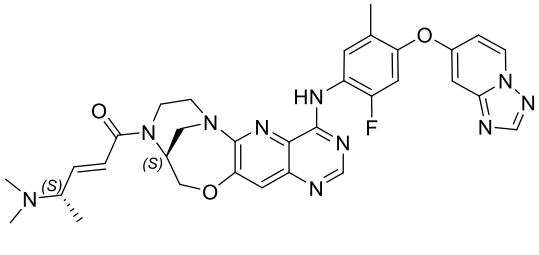
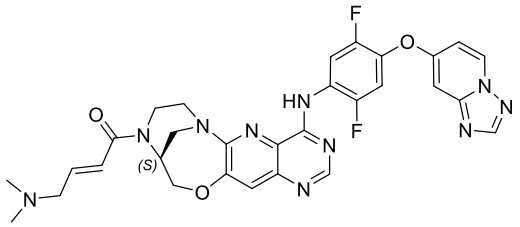
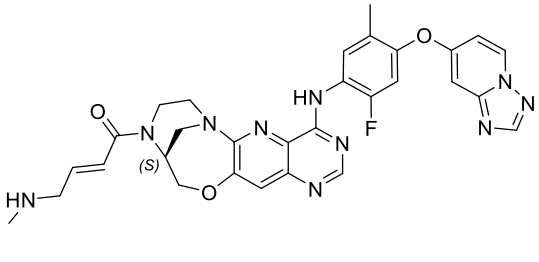
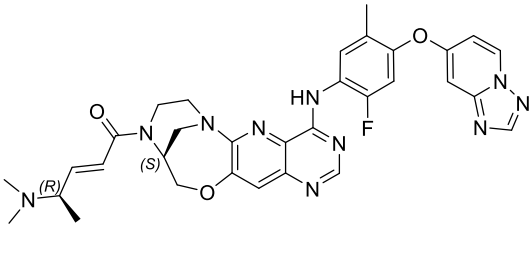
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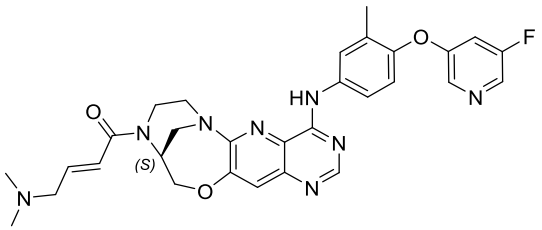
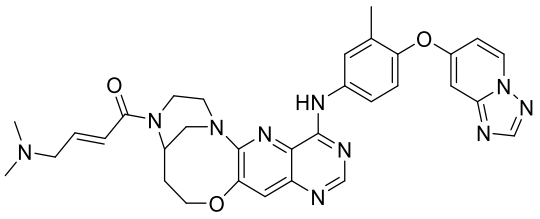
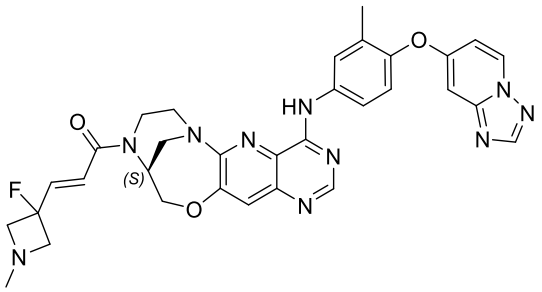
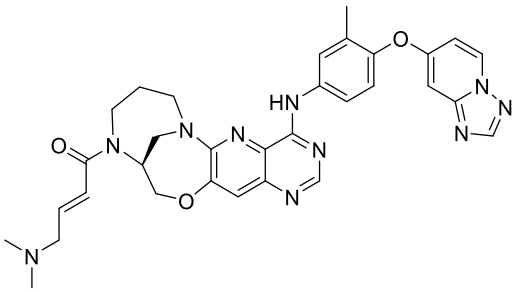
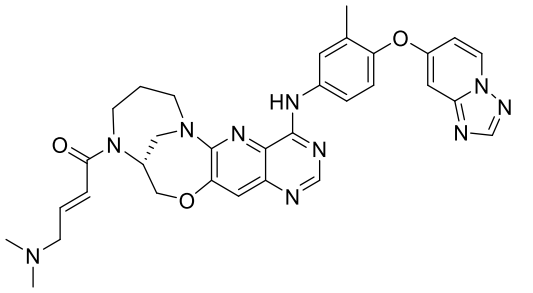
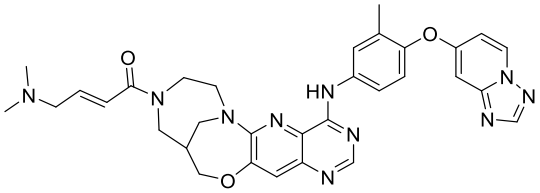
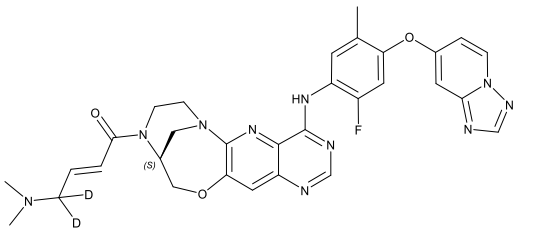
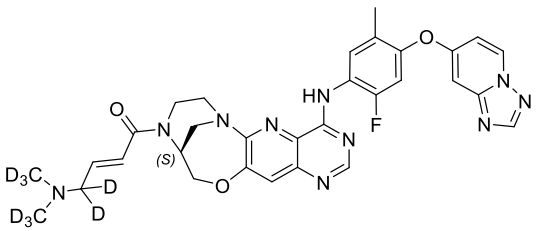
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or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing.

[0007d] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound disclosed herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, and at least one pharmaceutically acceptable excipient.

[0007e] In a further aspect of the present disclosure, there is provided a use of the compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a therapeutically

effective amount of the pharmaceutical composition disclosed herein, in the manufacture of a medicament for inhibiting kinase activity of a human receptor tyrosine kinase ErbB2 or a mutant form of human ErbB2.

[0007f] In another aspect of the present disclosure, there is provided a use of the compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a therapeutically effective amount of the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a patient having a cancer.

[0007g] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a therapeutically effective amount of the pharmaceutical composition disclosed herein, for use in therapy.

[0008] In one example provided is a compound of formula (I')

membered N-heterocyclyl, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl;

R^2 is C_1-C_6 alkyl or C_1-C_6 cycloalkyl, each of which is independently optionally substituted by 1-4 fluorines;

R^3 is -H, C_1-C_6 alkyl, -CD_3 or C_1-C_6 cycloalkyl;

R^4 is -H or halogen;

R^5 is -H or halogen;

R^6 is -H or halogen;

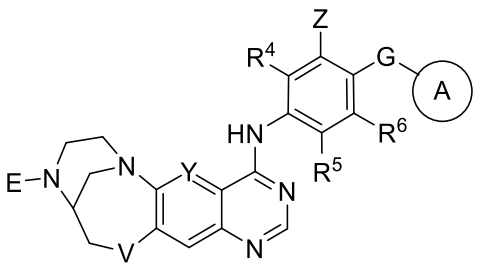
R^7 is -H, halogen, C_1-C_6 alkyl, -CD_3 or C_1-C_6 cycloalkyl;

n is 1 or 2;

p is 0 or 1; and

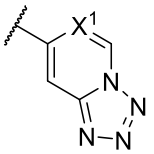
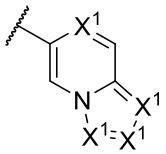
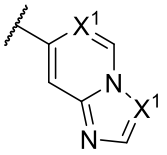
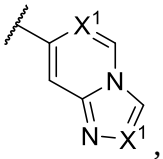
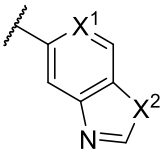
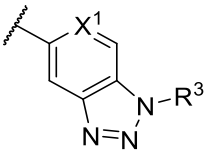
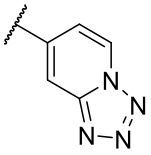
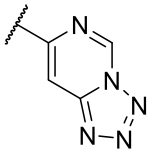
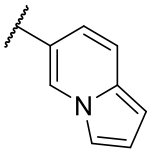
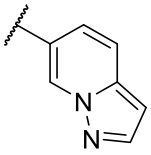
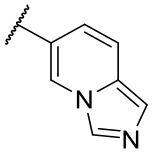
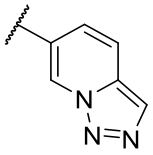
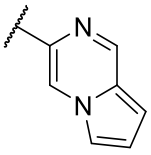
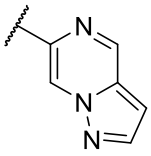
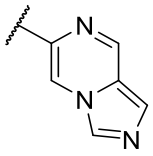
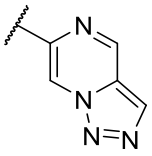
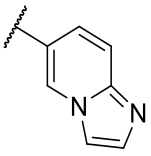
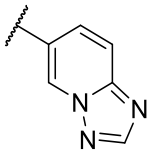
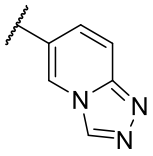
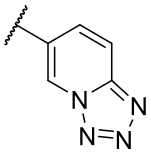
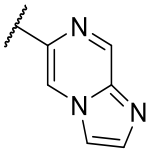
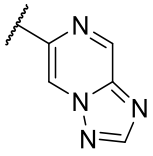
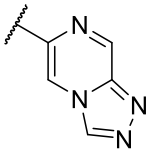
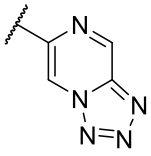
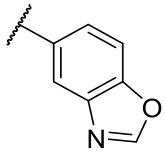
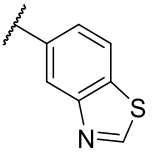
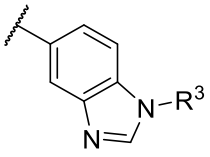
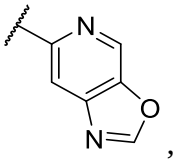
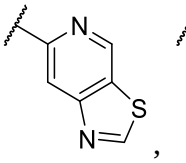
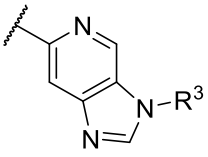
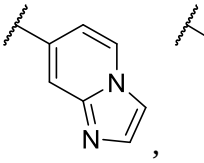
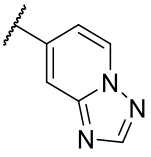
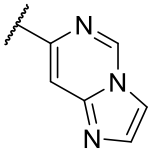
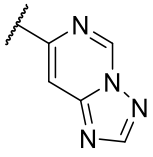
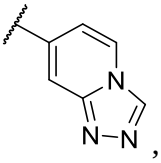
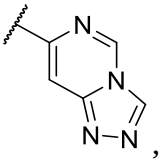
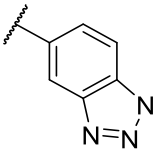
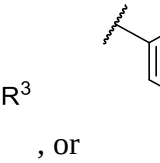
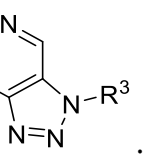
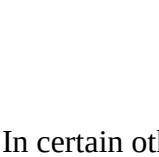
q is 1 or 2.

[0009] In one example, provided herein are compounds of formula (I)

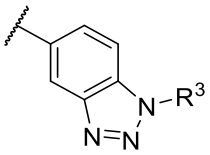
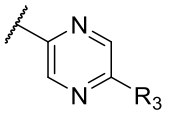
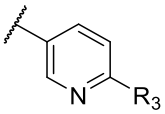
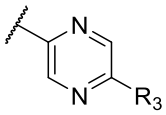
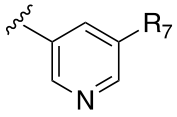
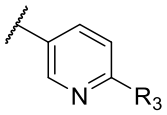


(I)

or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:

[0010] In some examples of the present example, ring A is , , , ,  or . In certain examples, ring A is , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , or .

In certain other examples of the present example, ring A is , or . In some examples, ring A is , , or


. In other examples, ring A is  or . In other examples ring A is ,  or .

[0011] In some examples, which may be combined with any of the preceding examples, R^3 is $-CH_3$. In some examples, which may be combined with any of the preceding examples, Z is -H, -F, -Cl, $-C\equiv CH$, $-OCH_3$, or $-CH_3$. In certain examples, Z is $-CH_3$. In some examples, which may be combined with any of the preceding examples, R^1 is C_2-C_4 alkenyl, optionally substituted by $-NR^{1a}R^{1b}$. In certain examples, R^1 is $-CH=CH_2$. In certain other examples, R^1 is $-CH=CH-CH_2-N(CH_3)_2$. In yet other examples, which may be combined with any of the preceding examples, R^1 is C_2-C_4 alkynyl, optionally substituted by $-NR^{1a}R^{1b}$. In certain examples, R^1 is $-C\equiv C-CH_3$.

[0012] In some examples, which may be combined with any of the preceding examples, R^3 is $-CH_3$. In some examples, which may be combined with any of the preceding examples, R^7 is $-CH_3$, $-CH_2CH_3$, or F. In some examples, which may be combined with any of the preceding examples, Z is -H, -F, -Cl, $-C\equiv CH$, $-OCH_3$, or $-CH_3$. In certain examples, Z is $-CH_3$. In some examples, which may be combined with any of the preceding examples, R^1 is C_2-C_4 alkenyl, optionally substituted by $-NR^{1a}R^{1b}$. In certain examples, R^1 is $-CH=CH_2$. In certain other examples, R^1 is $-CH=CH-CH_2-N(CH_3)_2$ or $-CH=CH-CH(CH_3)-N(CH_3)_2$. In yet other examples, which may be combined with any of the preceding examples, R^1 is C_2-C_4 alkynyl, optionally substituted by $-NR^{1a}R^{1b}$. In certain examples, R^1 is $-C\equiv C-CH_3$.

[0013] In some examples, Y is N. In other examples Y is C-R^y. In certain examples, Y is C-R^y, and R^y is -H. In certain other examples, Y is C-R^y, and R^y is -F. In some examples, V is O. In other examples, V is S. In yet other examples, V is N-R^2. In some examples, G is –O-. In other examples, G is –C(=O)-. In yet other examples, G is –S-, –S(O)-, or $-S(O)_2-$. In still other examples, G is $-CH_2-$. In some examples, R^4 is –H. In other examples, R^4 is halogen. In some examples, R^5 is –

H. In other examples, R^5 is halogen. In some examples, R^6 is –H. In other examples, R^6 is halogen.

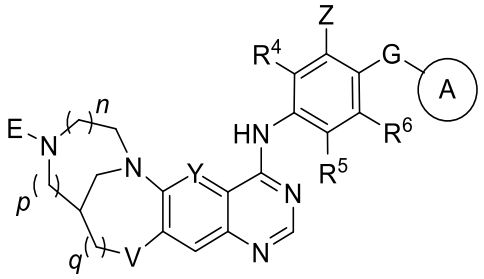
[0014] In another example, provided herein are compounds as described herein in Table 1. In yet another example, provided herein are pharmaceutical compositions comprising a compound of formula (I'), formula (I) or of Table 1 as described herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, and at least one pharmaceutically acceptable excipient.

[0015] In one example, provided herein is a method of inhibiting kinase activity of a human receptor tyrosine kinase ErbB2 or a mutant form of human ErbB2 comprising contacting the ErbB2 or the mutant form with a therapeutically effective amount of a compound of formula (I'), or a pharmaceutically acceptable salt thereof, as described herein, or a therapeutically effective amount of the pharmaceutical composition as described herein. In some examples of the present example, the mutant form of human ErbB2 comprises a mutation in Exon 20. In some examples of the present example, the mutant form of human ErbB2 comprises one or more mutations that introduce amino acid deletions and/or insertions selected from the group consisting of: A775_A776insYVMA, A775_A776insAYVM, A775_A776insYVMS, A775_A776insVVMA, A775_A776insMMAY, A775_A776insYVMA-R678Q, G778_P780insGSP, G776delinsVC, P780_Y781insGSP, M774delinsWLV, A775_G776insSVMA, A775_G776insI, G776delinsLC, G776delinsLV, G776delinsVV , G776insIC, G776delinsCVC, G776delinsAVGS, G776delinsAVGA, G776delinsAVGC G776_V777insLeu, G776_V777insVGS, G778_S779InsCPG; V777_G778insGSP, V777_G778insGC, V777_G778insCG, V777_G778insQ, V777_G778insG, G778_S779insLPS, and G778_S779insAVG. In further examples of the present example, the mutant form of human ErbB2 comprises one or more mutations that introduce amino acid deletions and/or insertions selected from the group consisting of: A775_A776insYVMA, G778_P780insGSP, G776delinsVC, P780_Y781insGSP, M774delinsWLV, A775_G776insSVMA, A775_G776insI, G776delinsLC, G778_S779InsCPG, and V777_G778insGSP. In other examples of the present example, the mutant form of human ErbB2 comprises a disease-associated point mutation in ErbB2. In other examples of the present example, the mutant form of human ErbB2 comprises one or more point mutations in ErbB2 that introduce (a) amino acid substitutions selected from the group consisting of P122L, R217C, I263T, A293T, S305C, S310F/Y/P, H470Q, I655V,

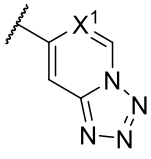
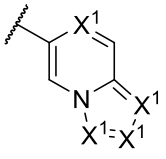
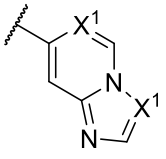
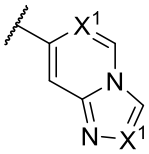
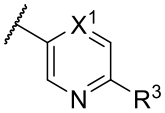
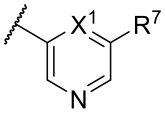
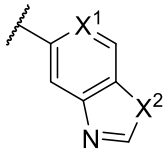
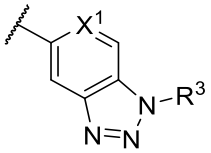
CLAIMS

What is claimed is:

Claim 1. A compound of formula (I’)



(I’)

or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:Ring A is , , , , , ,  or ;

E is -C(=O)-R^1;

G is -O-, -C(=O)-, -S-, -S(O)-, -$S(O)_2$-, or -CH_2-;

V is O, S, or N-R^2;

each X^1 is independently N or CH;

X^2 is O, S, or N-R^3;

Y is N or C-R^y, wherein R^y is -H or -F;

Z is -H, halogen, -C≡CH, -OCH_3, or C_1-C_2 alkyl;

R^1 is C_2-C_4 alkenyl or C_2-C_4 alkynyl, each of which is independently optionally substituted by 1-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, a 3- to 7-membered carbon-linked N-heterocycloalkyl, or -$NR^{1a}R^{1b}$, wherein each R^{1a} and R^{1b} are independently -H, C_1-C_3 alkyl, or -CD_3, or wherein each pair of geminal R^{1a} and R^{1b} may be taken together with the nitrogen atom to which they are attached to form a 3- to 6-membered N-heterocyclyl, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl;

R^2 is C_1-C_6 alkyl or C_1-C_6 cycloalkyl, each of which is independently optionally substituted by 1-4 fluorines;

R^3 is -H, C_1-C_6 alkyl, -CD_3 or C_1-C_6 cycloalkyl;

R^4 is -H or halogen;

R^5 is -H or halogen;

R^6 is -H or halogen;

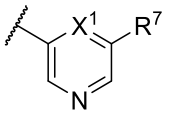
R^7 is -H, halogen, C_1-C_6 alkyl, -CD_3 or C_1-C_6 cycloalkyl;

n is 1 or 2;

p is 0 or 1; and

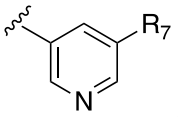
q is 1 or 2.

Claim 2. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein Ring A is



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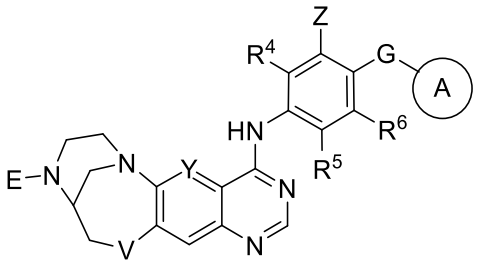
Claim 3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein Ring A is



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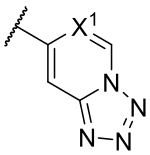
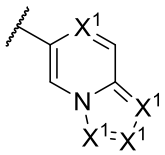
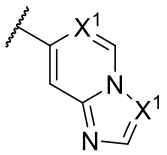
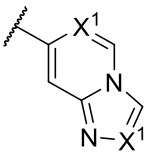
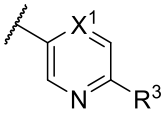
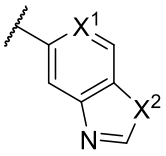
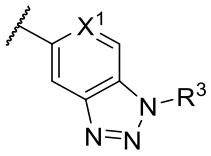
Claim 4. The compound of claim 2 or 3, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein R^7 is -F.

Claim 5. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein the compound is a compound of formula (I)



(I)

or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:

Ring A is , , , , ,  or ;

E is -C(=O)-R^1;

G is -O-, -C(=O)-, -S-, -S(O)-, -$S(O)_2$-, or -CH_2-;

V is O, S, or N-R^2;

each X^1 is independently N or CH;

X^2 is O, S, or N-R^3;

Y is N or C-R^y, wherein R^y is -H or -F;

Z is -H, halogen, -C≡CH, -OCH_3, or C_1-C_2 alkyl;

R^1 is C_2-C_4 alkenyl or C_2-C_4 alkynyl, each of which is independently optionally substituted by 1-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, a 3- to 7-membered carbon-linked N-heterocycloalkyl, or -$NR^{1a}R^{1b}$, wherein each R^{1a} and R^{1b} are independently -H, C_1-C_3 alkyl, or -CD_3, or wherein each pair of geminal R^{1a} and R^{1b} may be taken together with the nitrogen atom to which they are attached to form a 3- to 6-membered N-heterocyclyl, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl;

R^2 is C_1-C_6 alkyl or C_1-C_6 cycloalkyl, each of which is independently optionally substituted by 1-4 fluorines;

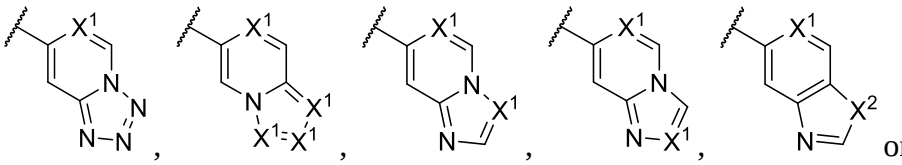
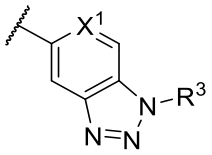
R^3 is -H, C_1-C_6 alkyl, -CD_3 or C_1-C_6 cycloalkyl;

R^4 is -H or halogen;

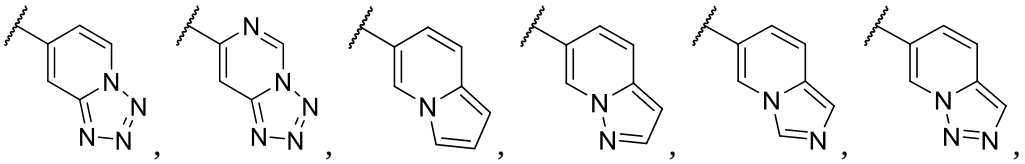
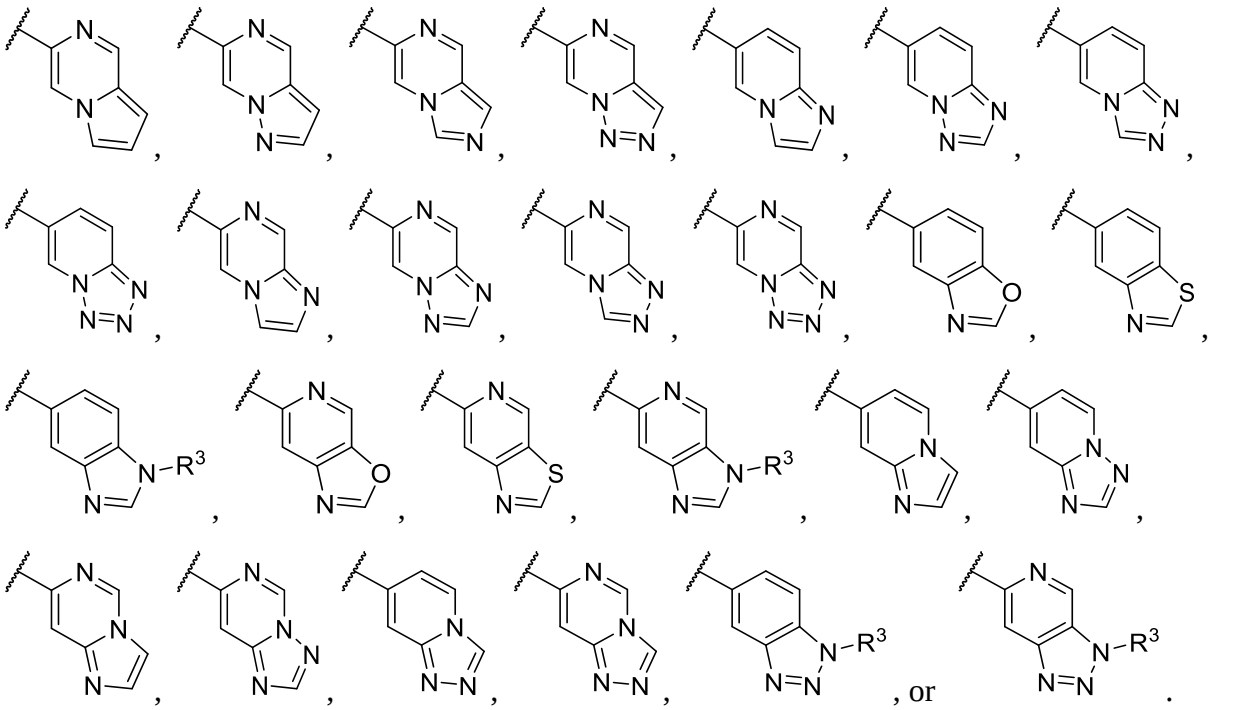
R^5 is -H or halogen; and

R^6 is -H or halogen.

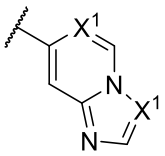
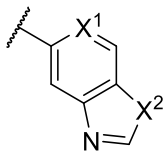
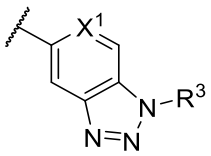
Claim 6. The compound of claim 1 or 5, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:

ring A is , .

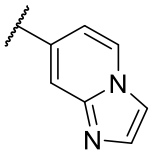
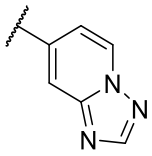
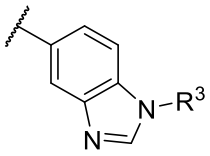
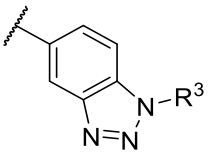
Claim 7. The compound of any one of claims 1, 5 and 6, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:

ring A is , .

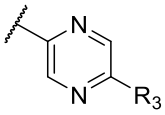
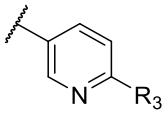
Claim 8. The compound of any one of claims 1, 5 and 6, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:

ring A is ,  or .

Claim 9. The compound of any one of claims 1 and 5 to 8, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:

ring A is , , , or .

Claim 10. The compound of claim 1 or 5, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:

ring A is  or .

Claim 11. The compound of any one of claims 1 and 5 to 10, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein R^3 is $-CH_3$.

Claim 12. The compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein Z is -H, -F, -Cl, $-C{\equiv}CH$, $-OCH_3$, or $-CH_3$.

Claim 13. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein Z is $-CH_3$.

Claim 14. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein R^1 is C_2-C_4 alkenyl, optionally substituted by $-NR^{1a}R^{1b}$.

Claim 15. The compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing,wherein R^1 is -$CH=CH_2$.

Claim 16. The compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing,wherein R^1 is -$CH=CH-CH_2-N(CH_3)_2$ or -$CH=CH-CH(CH_3)-N(CH_3)_2$.

Claim 17. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein R^1 is C_2-C_4 alkynyl, optionally substituted by -$NR^{1a}R^{1b}$.

Claim 18. The compound of any one of claims 1 to 13 and 17, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein R^1 is -$C\equiv C-CH_3$.

Claim 19. The compound of any one of claims 1 to 18, pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein Y is N.

Claim 20. The compound of any one of claims 1 to 18, pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein Y is C-R^y.

Claim 21. The compound of any one of claims 1 to 18 and 20, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein Y is C-R^y, and R^y is -H.

Claim 22. The compound of any one of claims 1 to 18 and 20, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein Y is C-R^y, and R^y is -F.

Claim 23. The compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein V is O.

Claim 24. The compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein V is S.

Claim 25. The compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein V is N-R^2.

Claim 26. The compound of any one of claims 1 to 25, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein G is -O-.

Claim 27. The compound of any one of claims 1 to 25, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein G is -C(=O)-.

Claim 28. The compound of any one of claims 1 to 25, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein G is -S-, –S(O)-, or –$S(O)_2$-.

Claim 29. The compound of any one of claims 1 to 25, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein G is –CH_2-.

Claim 30. The compound of any one of claims 1 to 29, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein R^4 is -H.

Claim 31. The compound of any one of claims 1 to 29, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein R^4 is halogen.

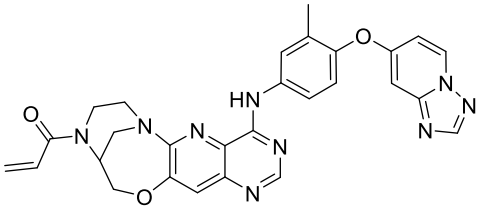
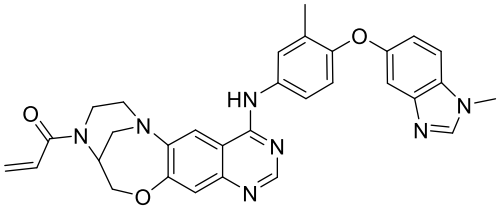
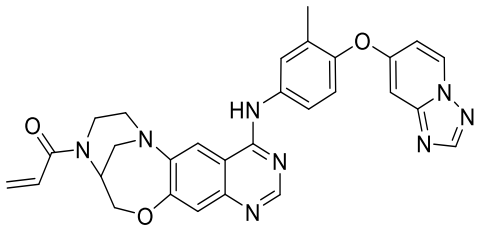
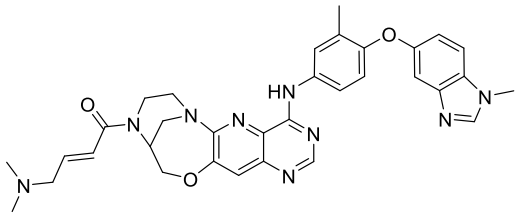
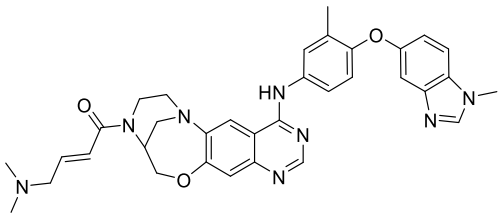
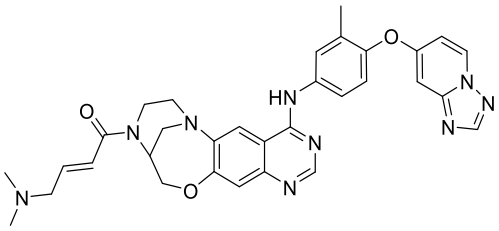
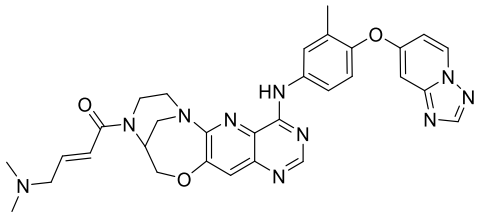
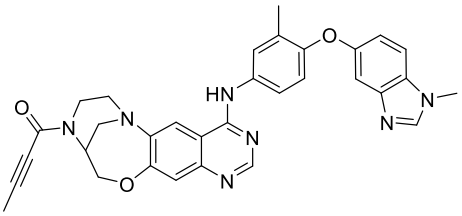
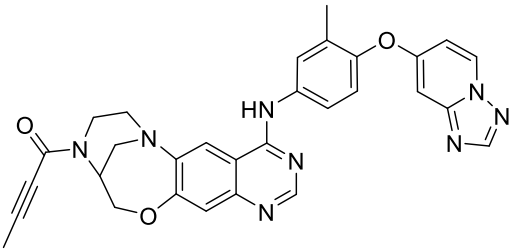
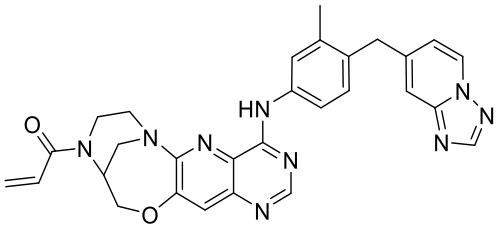
Claim 32. The compound of any one of claims 1 to 31, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein R^5 is -H.

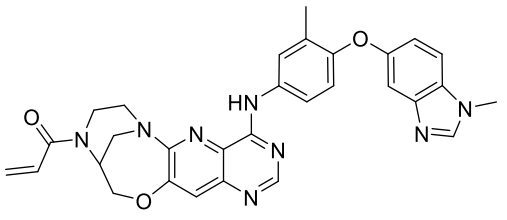
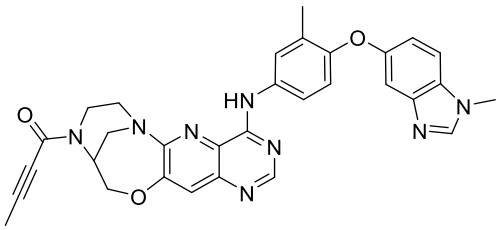
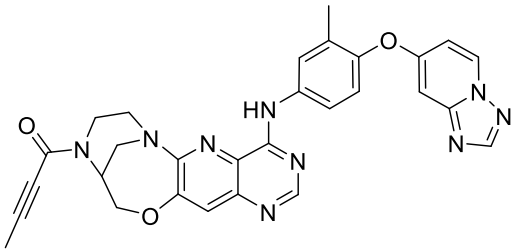
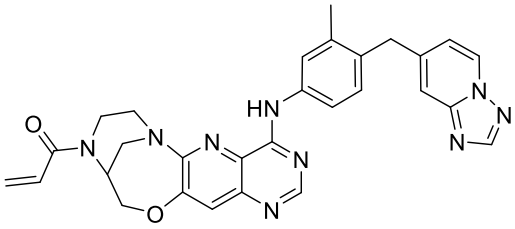
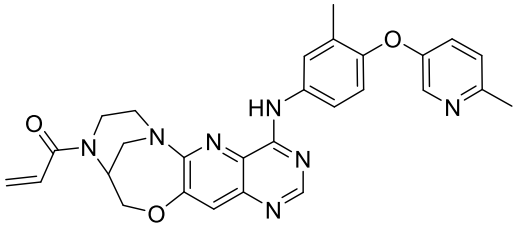
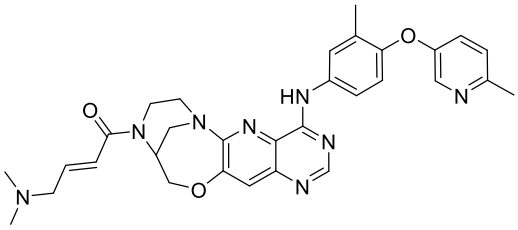
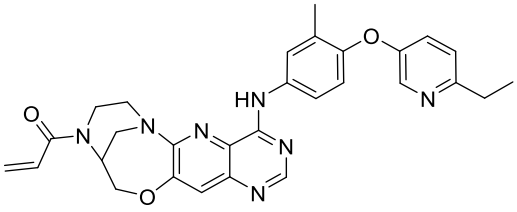
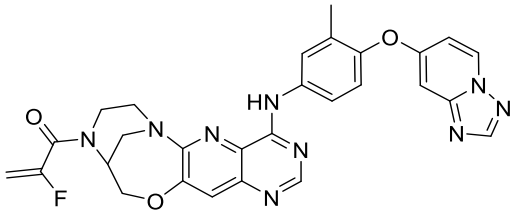
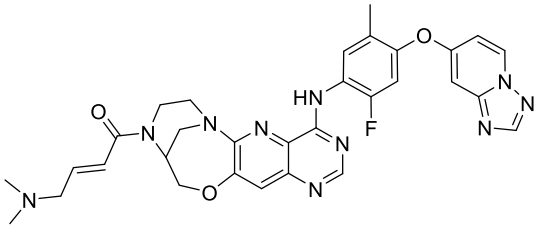
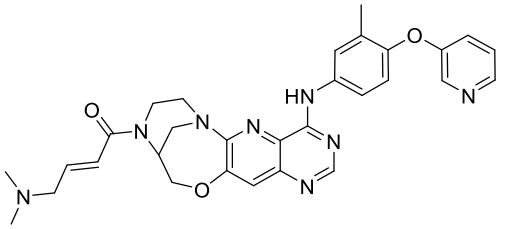
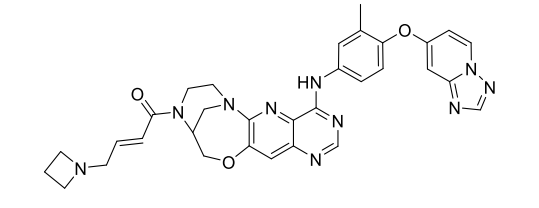
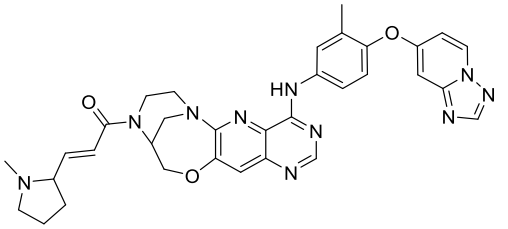
Claim 33. The compound of any one of claims 1 to 31, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein R^5 is halogen.

Claim 34. The compound of any one of claims 1 to 33, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein R^6 is -H.

Claim 35. The compound of any one of claims 1 to 33, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein R^6 is halogen.

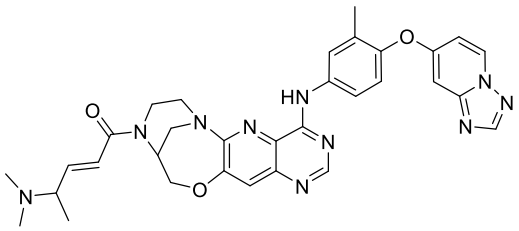
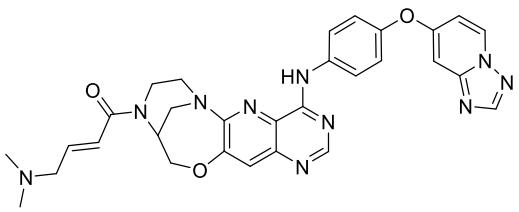
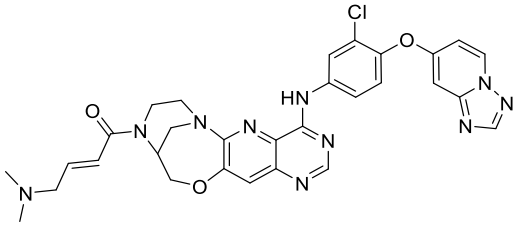
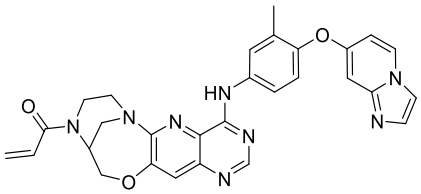
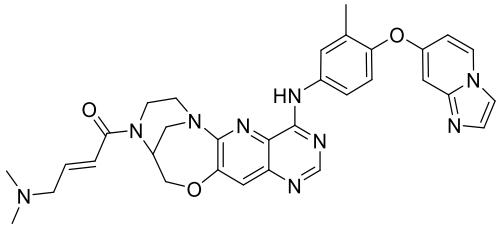
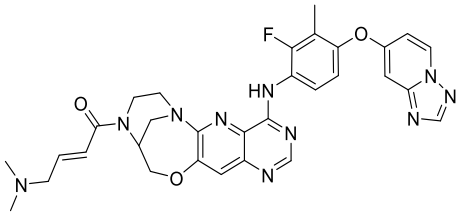
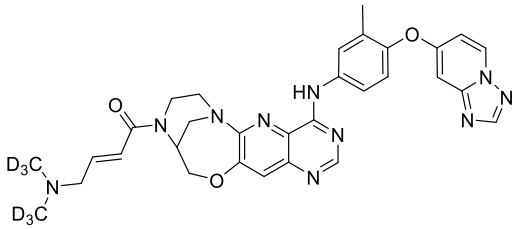
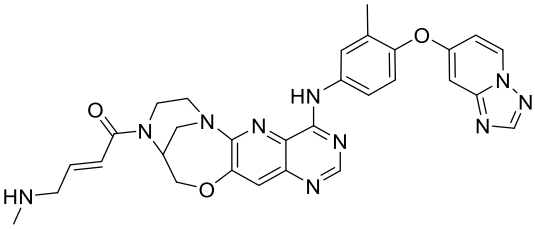
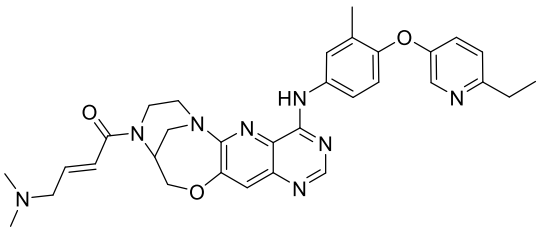
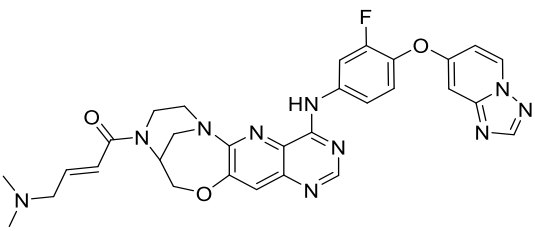
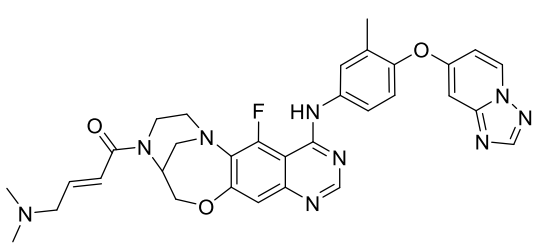
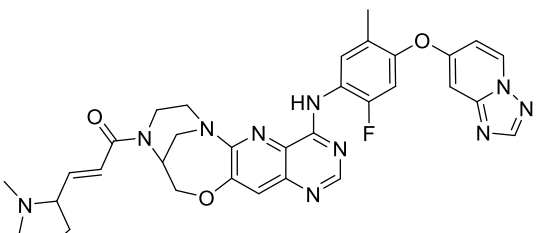
Claim 36. A compound selected from the group consisting of:


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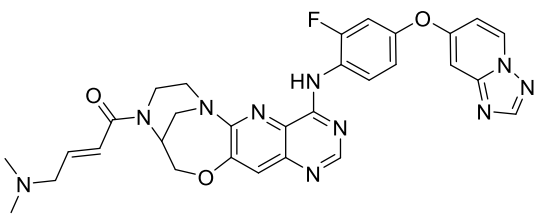
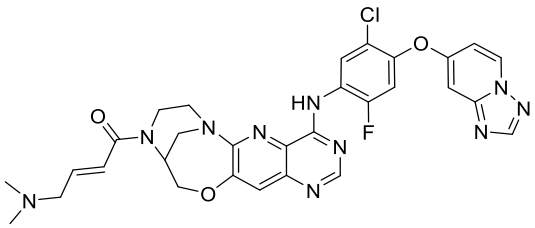
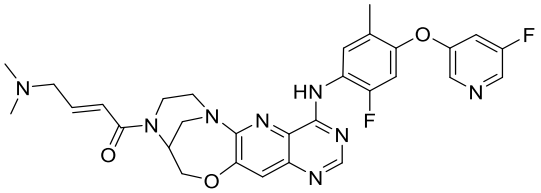
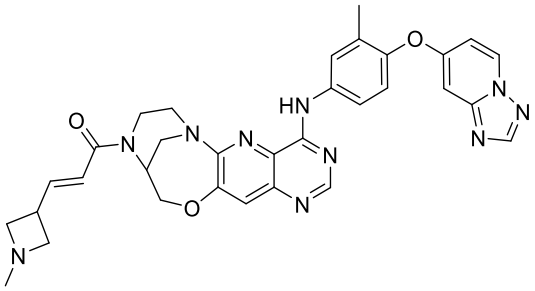
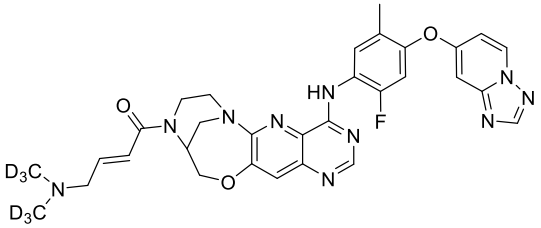
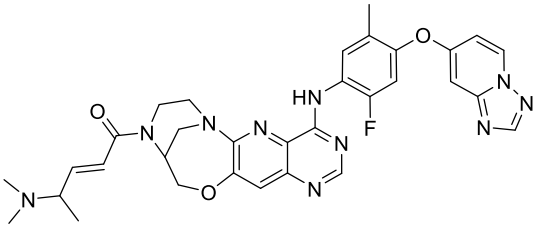
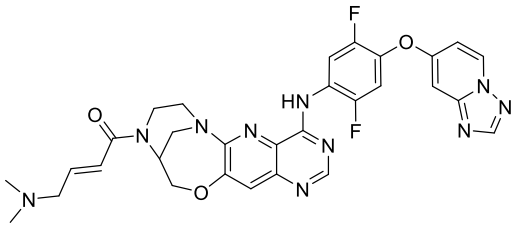
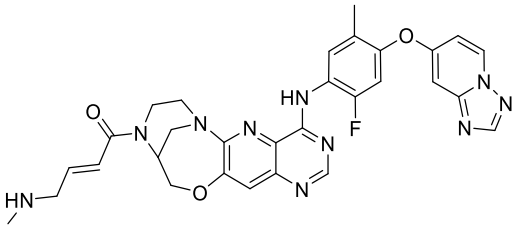
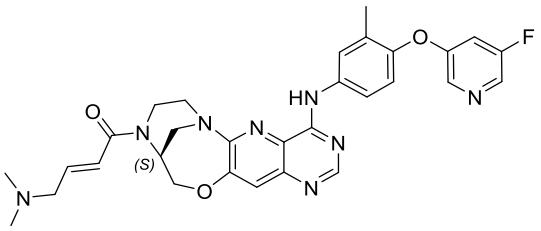
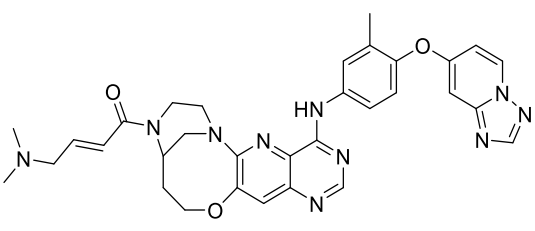
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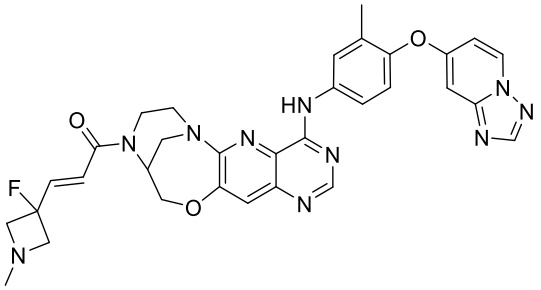
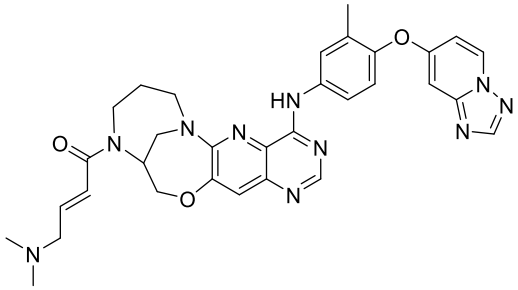

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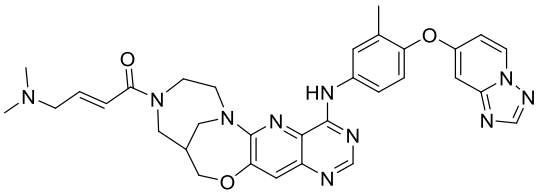
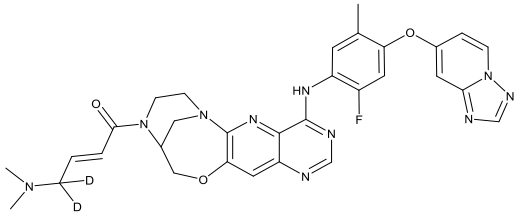
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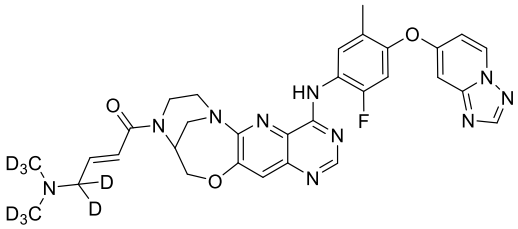
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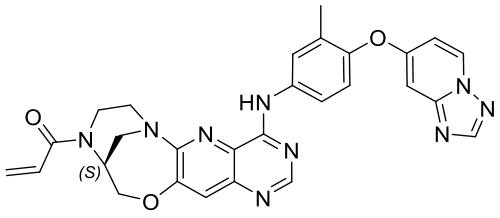
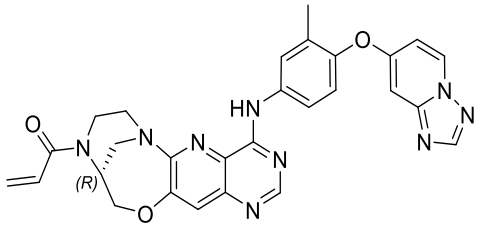

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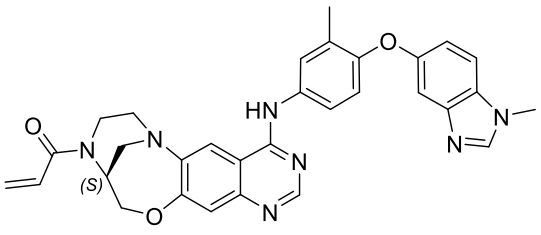
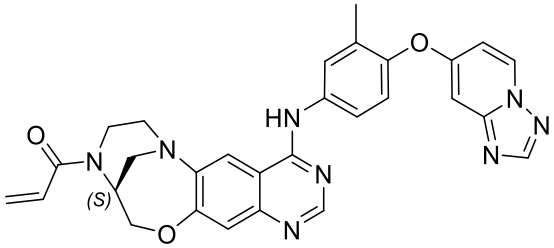

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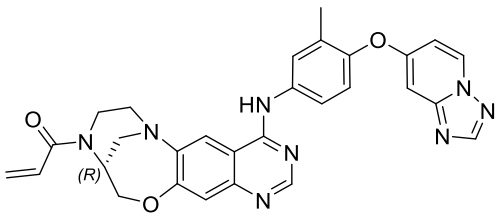
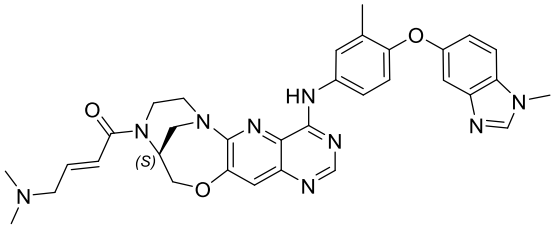
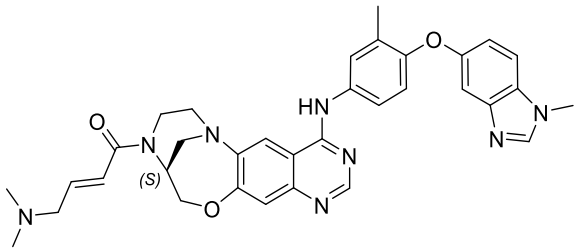
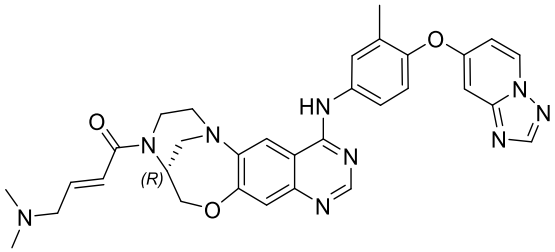
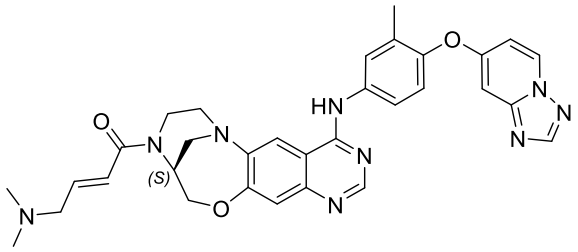
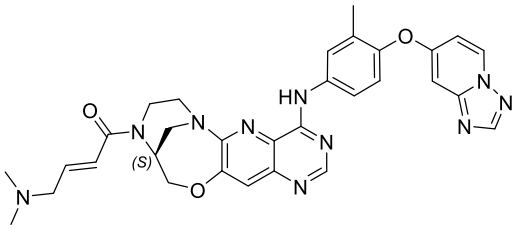
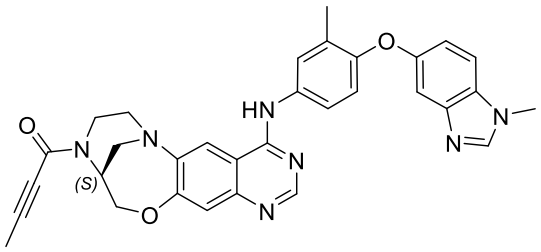
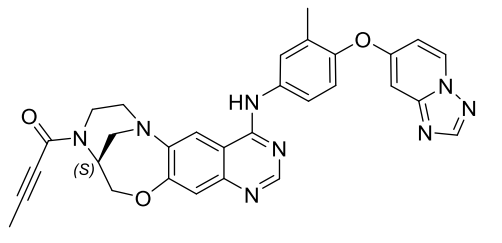
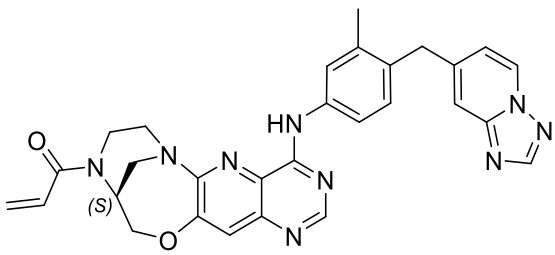
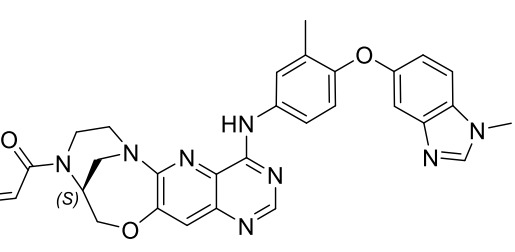
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or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing.

Claim 37. A compound selected from the group consisting of:

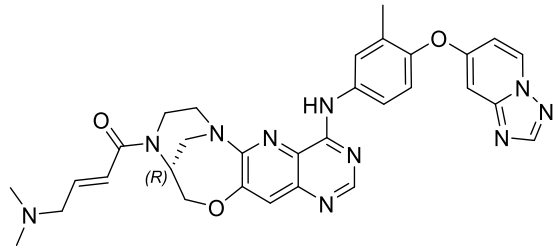
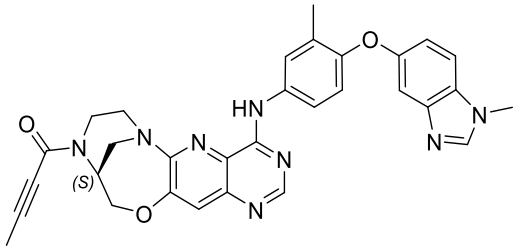
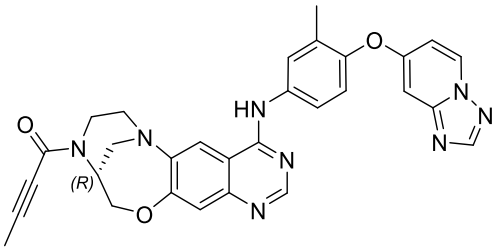
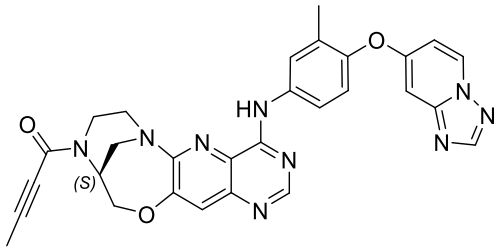
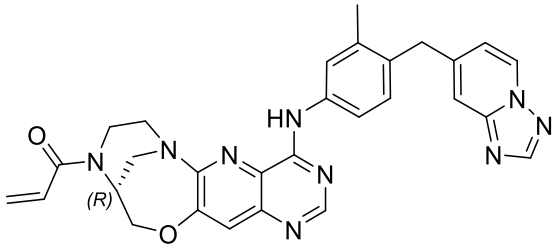
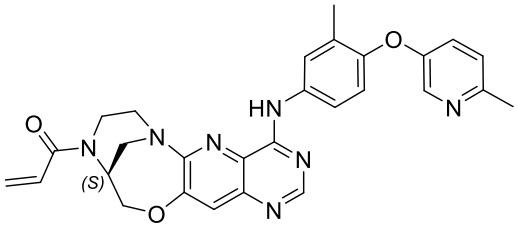
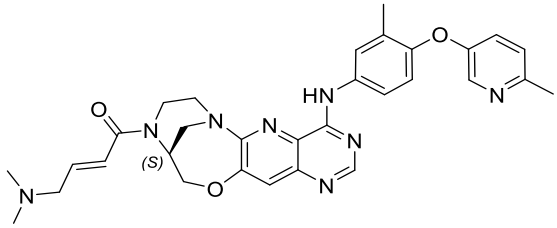
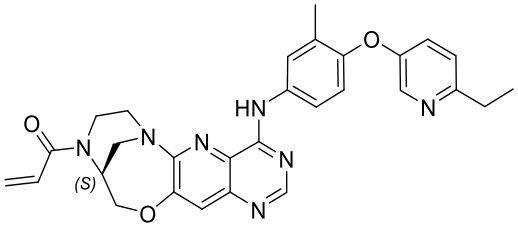
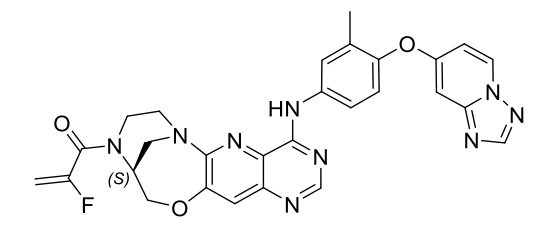
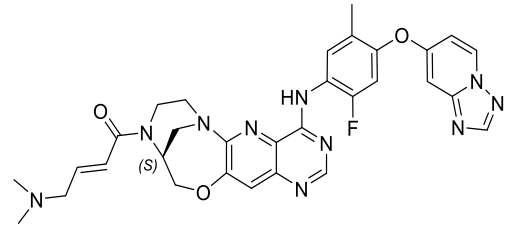

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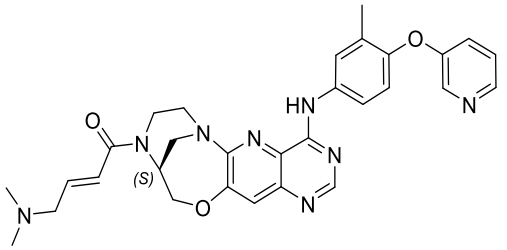
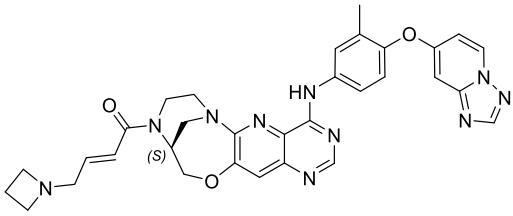
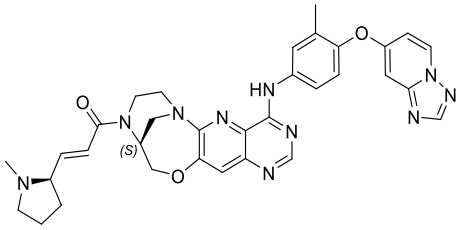
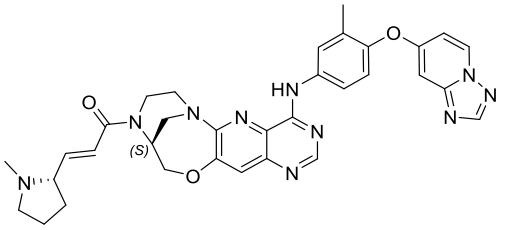
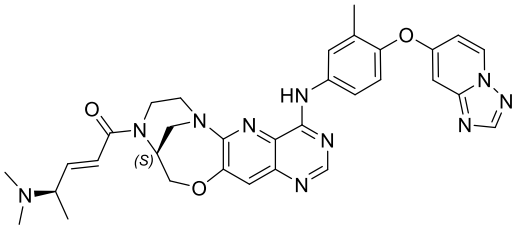
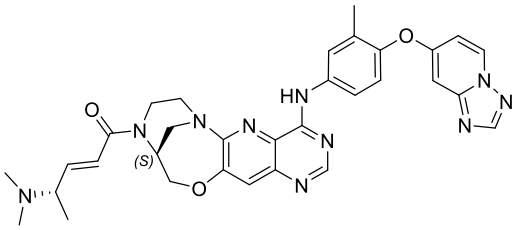
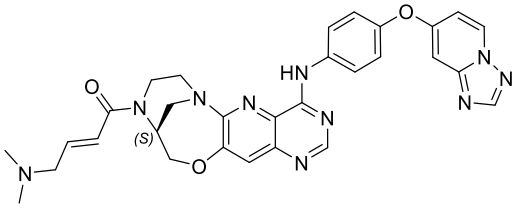
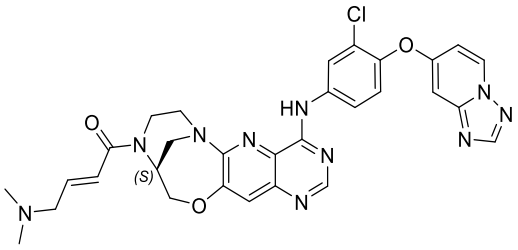
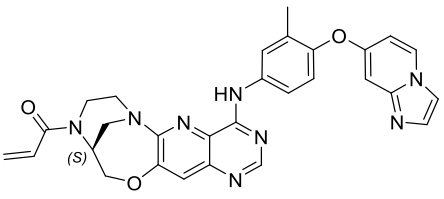
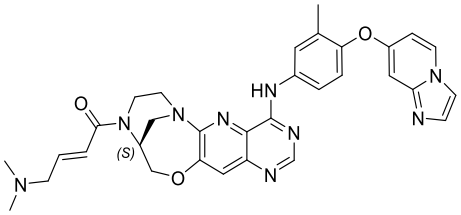
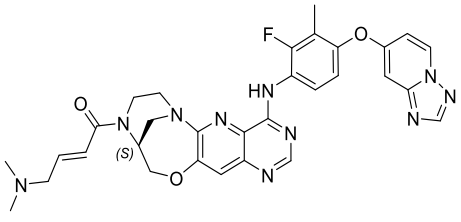
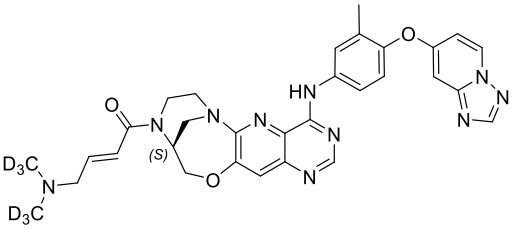
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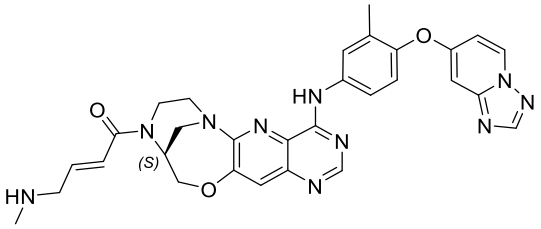
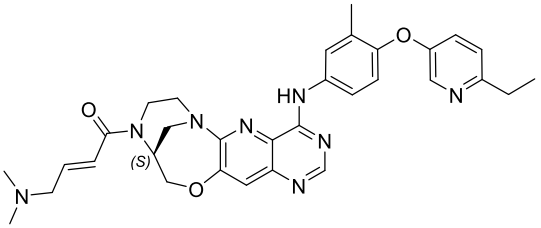
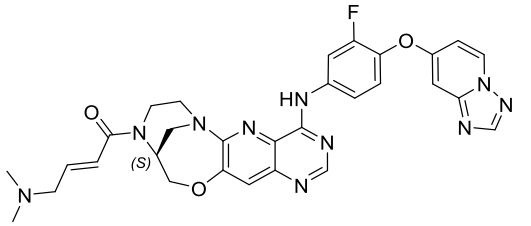
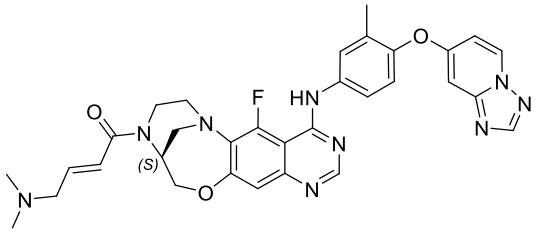
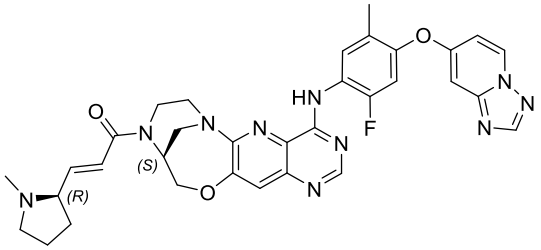
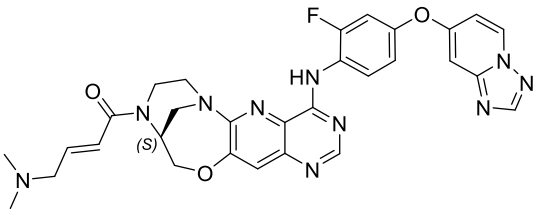
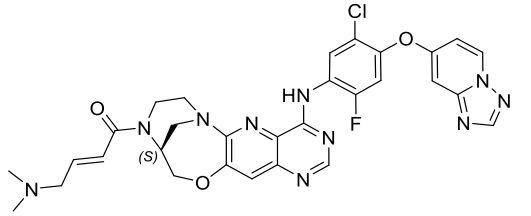
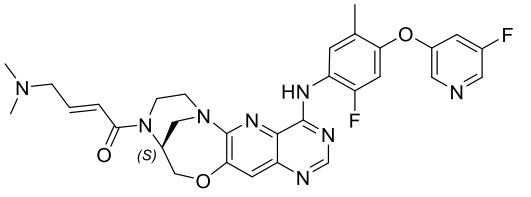
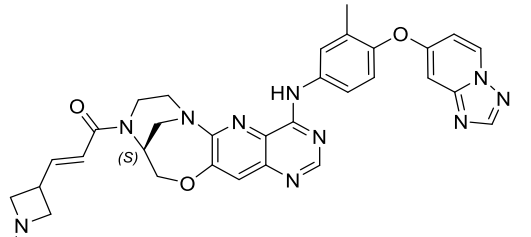
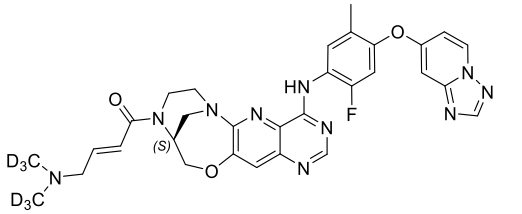
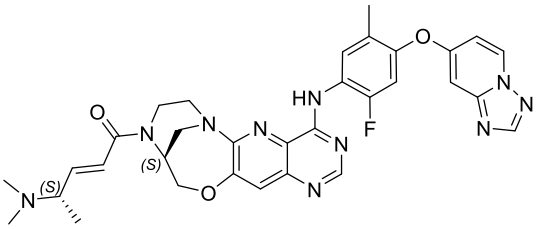
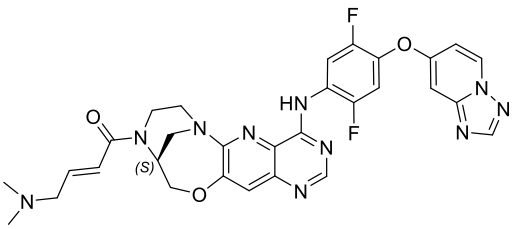
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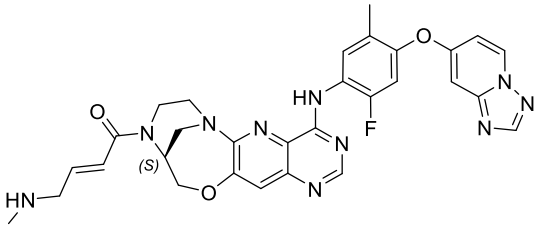
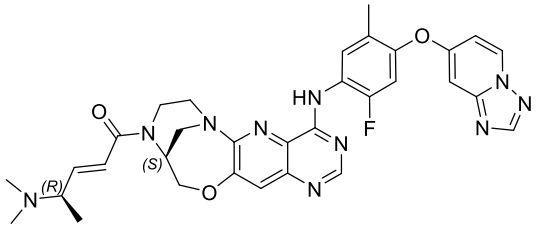
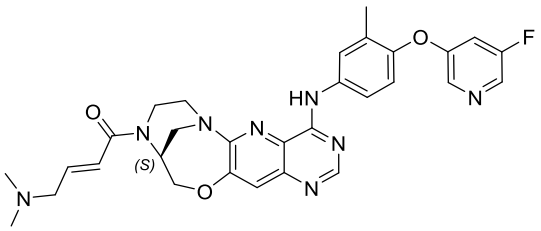
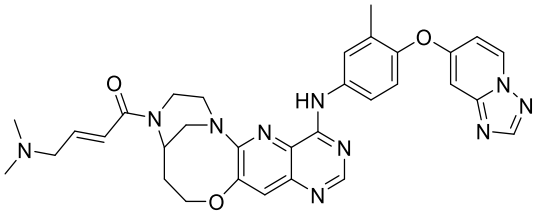
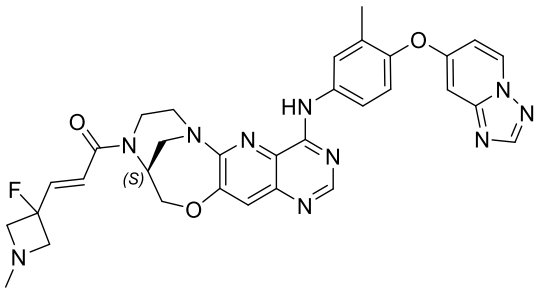
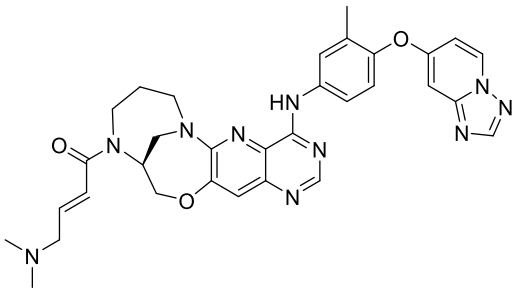
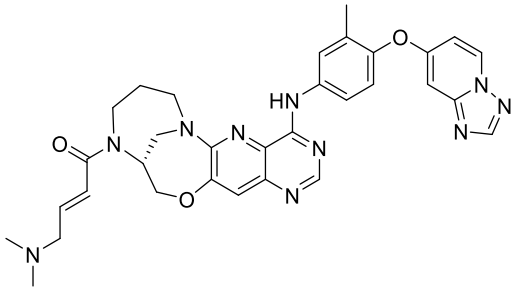
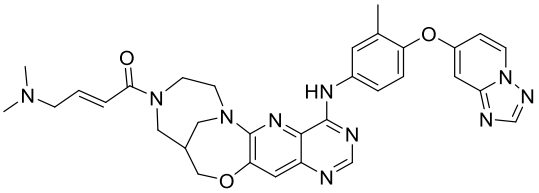
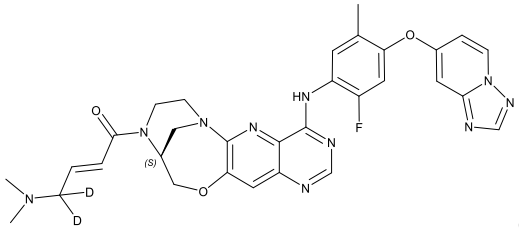
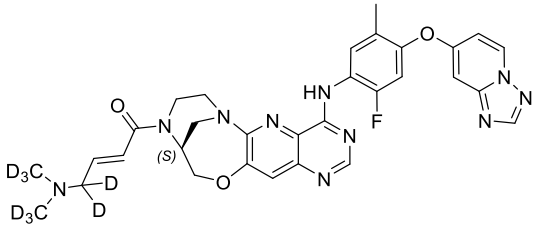
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or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing.

Claim 38. A pharmaceutical composition comprising the compound of any one of claims 1 to 37, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, and at least one pharmaceutically acceptable excipient.

Claim 39. Use of the compound of any one of claims 1 to 37, or a pharmaceutically acceptable salt thereof, or a therapeutically effective amount of the pharmaceutical composition of claim 38, in the manufacture of a medicament for inhibiting kinase activity of a human receptor tyrosine kinase ErbB2 or a mutant form of human ErbB2.

Claim 40. The use of claim 39, wherein the mutant form of human ErbB2 comprises a mutation in Exon 20.

Claim 41. The use of claim 39 or claim 40, wherein the mutant form of human ErbB2 comprises one or more mutations that introduce amino acid deletions and/or insertions selected from the group consisting of: A775_A776insYVMA, A775_A776insAYVM, A775_A776insYVMS, A775_A776insVVMA, A775_A776insMMAY, A775_A776insYVMA-R678Q, G778_P780insGSP, G776delinsVC, P780_Y781insGSP, M774delinsWLV, A775_G776insSVMA, A775_G776insI, G776delinsLC, G776delinsLV, G776delinsVV , G776insIC, G776delinsCVC, G776delinsAVGS, G776delinsAVGA, G776delinsAVGC G776_V777insLeu, G776_V777insVGS, G778_S779InsCPG; V777_G778insGSP, V777_G778insGC, V777_G778insCG, V777_G778insQ, V777_G778insG, G778_S779insLPS, and G778_S779insAVG.

Claim 42. The use of claim 39, wherein the mutant form of human ErbB2 comprises a disease-associated point mutation in ErbB2.

Claim 43. The use of claim 39 or 42, wherein the mutant form of human ErbB2 comprises one or more point mutations in ErbB2 that introduce:

(a) an amino acid substitution selected from the group consisting of P122L, R217C, I263T, A293T, S305C, S310F/Y/P, H470Q, I655V, V659E/D, L674F, G660D, R678Q/C, L755R/S/P/Y/M, I767M, D769H/N/Y, V777L/M, V842I, R868W, H878Y, E930K/D, E1021Q, F1030C, V1128I, N1219S, G222C, A1057V, V842I, G776S/C/V/A, V773M, L869R,Y803F, H878Y, R896G, and E1195G; or

(b) a frameshift at A1232.

Claim 44. The use of claim 40, wherein the mutant form of human ErbB2 comprises amino terminally truncated carboxyl-terminal fragments of HER2.

Claim 45. Use of the compound of any one of claims 1 to 37, or a pharmaceutically acceptable salt thereof, or a therapeutically effective amount of the pharmaceutical composition of claim 38, in the manufacture of a medicament for treating a patient having a cancer.

Claim 46. The use of claim 45, wherein the cancer comprises cells or cell tissue having increased ErbB2 kinase activity as compared to a control.

Claim 47. The use of claim 45 or claim 46, wherein the cancer comprises cells or cell tissue having one or more mutations in Exon 20 of the ErbB2.

Claim 48. The use of any one of claims 45 to 47, wherein the cancer comprises cells or cell tissue having one or more mutations in Exon 20 of the ErbB2 that introduce amino acid deletions and/or insertions selected from the group consisting of A775_A776insYVMA, A775_A776insAYVM, A775_A776insYVMS, A775_A776insVVMA, A775_A776insMMAY, A775_A776insYVMA-R678Q, G778_P780insGSP, G776delinsVC, P780_Y781insGSP, M774delinsWLV, A775_G776insSVMA, A775_G776insI, G776delinsLC, G776delinsLV, G776delinsVV , G776insIC, G776delinsCVC, G776delinsAVGS, G776delinsAVGA, G776delinsAVGC G776_V777insLeu, G776_V777insVGS, G778_S779InsCPG; V777_G778insGSP, V777_G778insGC, V777_G778insCG, V777_G778insQ, V777_G778insG, G778_S779insLPS, and G778_S779insAVG.

Claim 49. The use of claim 45 or claim 46, wherein the cancer comprises cells or cell tissue having one or more disease-associated point mutations in ErbB2.

Claim 50. The use of any one of claims 45, 46 and 49, wherein the cancer comprises cells or cell tissue having one or more point mutations that introduce:

(a) an amino acid substitution selected from the group consisting of P122L, R217C, I263T, A293T, S305C, S310F/Y/P, H470Q, I655V, V659E/D, L674F, G660D, R678Q/C, L755R/S/P/Y/M, I767M, D769H/N/Y, V777L/M, V842I, R868W, H878Y, E930K/D, E1021Q,

F1030C, V1128I, N1219S, G222C, A1057V, V842I, G776S/C/V/A, V773M, L869R,Y803F, H878Y, R896G, and E1195G; or

(b) a frameshift at A1232.

Claim 51. The use of claim 45 or 46, wherein the cancer comprises cells or cell tissue having, expressing or over-expressing amino terminally truncated carboxyl-terminal fragments of HER2.

Claim 52. The use of any one of claims 45 to 51, wherein the cancer is lung, glioma, skin, head and neck, salivary gland, breast, esophageal, liver, stomach (gastric), uterine, cervical, biliary tract, pancreatic, colorectal, renal, bladder or prostate cancer.

Claim 53. The use of any one of claims 45 to 52, wherein the cancer is non-small cell lung cancer.

Claim 54. The use of any one of claims 45 to 53, wherein the patient has received at least one, at least two, or at least three prior therapies for the cancer.

Claim 55. The use of claim 54, wherein one or more of the prior therapies selected from the group consisting of lapatinib, neratinib, afatinib, pyrotinib, poziotinib, TAK-788, and tucatinib.

Claim 56. The use of any one of claims 45 to 55, wherein one or more additional anti-cancer agents are to be further administered.

Claim 57. The use of claim 56, wherein an anti-HER2 antibody or an anti-HER2 drug conjugate is to be further administered.

Claim 58. The use of claim 56 or 57, wherein KADCYLA® (ado-trastuzumab emtansine), ENHERTU® (fam-trastuzumab deruxtecan-nxki), or any biosimilar thereof is to be further administered.

Claim 59. A compound of any one of claims 1 to 37, or a pharmaceutically acceptable salt thereof, or a therapeutically effective amount of the pharmaceutical composition of claim 38, for use in therapy.