**CLAIMS**

1. A compound of formula (X):

MLKLi–L–E3L

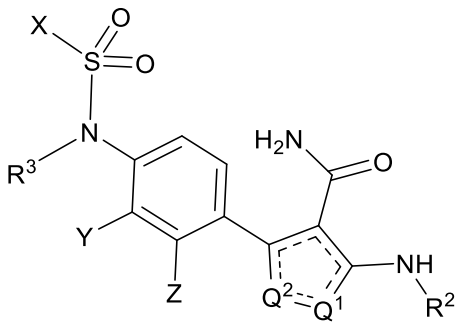
(X)

wherein

E3L is an E3 ligase binding moiety;

L is a linker covalently linking MLKLi to E3L; and

MLKLi is a radical of formula (I)



(I)

wherein

$Q^1$ and $Q^2$ are selected from N and $NR^1$, wherein when $Q^1$ is N, $Q^2$ is $NR^1$ and when $Q^2$ is N, $Q^1$ is $NR^1$;

$R^1$ and $R^3$ are independently selected from H and an optionally substituted $C_{1-6}$-alkyl;

$R^2$ is an optionally substituted $C_{1-6}$-alkyl, an optionally substituted aryl or an optionally substituted heterocyclyl;

X is selected from optionally substituted $C_{1-6}$alkyl, optionally substituted halo$C_{1-6}$alkyl, optionally substituted $C_{2-6}$alkynyl, optionally substituted cycloalkyl, optionally substituted halocycloalkyl, optionally substituted aryl, optionally substituted alkylaryl, optionally substituted $C_{1-6}$alkylcycloalkyl and optionally substituted amino;

Y and Z are independently selected from H, $R^4$, -$OR^4$, -$NR^4R^5$ and halo;

wherein at least one of Y and Z is H;

$R^4$ is selected from optionally substituted $C_{1-6}$alkyl, optionally substituted aryl, optionally substituted $C_{1-6}$alkylaryl, optionally substituted heterocyclyl, optionally substituted $C_{1-6}$alkylheterocyclyl, optionally substituted cycloalkyl, optionally substituted $C_{1-6}$alkyl$C_{3-10}$cycloalkyl, optionally substituted $C_{3-10}$cycloalkylaryl, optionally substituted $C_{3-10}$cycloalkylheterocyclyl, optionally substituted $C_{3-10}$cycloalkyl$C_{3-10}$cycloalkyl, optionally substituted 3-6 membered non-aromatic heterocyclyl-aryl, optionally substituted 3-6 membered non-aromatic heterocyclyl$C_{3-10}$cycloalkyl and optionally substituted 3-6 membered non-aromatic heterocyclyl-3-10 membered heterocyclyl; and

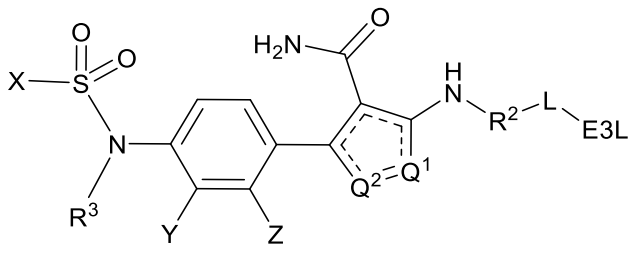
$R^5$ is H or optionally substituted $C_{1-6}$alkyl,

or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof.

2. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, tautomer, stereoisomer and/or prodrug thereof, wherein $R^2$ is an optionally substituted aryl or an optionally substituted heterocyclyl.

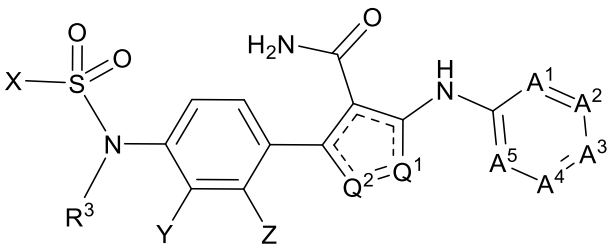
3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt, solvate, tautomer, stereoisomer and/or prodrug thereof, wherein $R^2$ is an optionally substituted 5- or 6-membered heterocyclyl.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, solvate, tautomer, stereoisomer and/or prodrug thereof, provided by the following formula (XI):




(XI).

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, solvate, tautomer, stereoisomer and/or prodrug thereof, provided by the following formula (XII):



(XII)

wherein $A^1$-$A^5$ are independently selected from N, $CR^{11}$ and C–L-E3L,

one of $A^1$-$A^5$ is C–L-E3L

wherein not more than 2 of $A^1$, $A^2$, $A^3$, $A^4$ and $A^5$ are N;

each $R^{11}$ is independently selected from H and $R^{10}$;

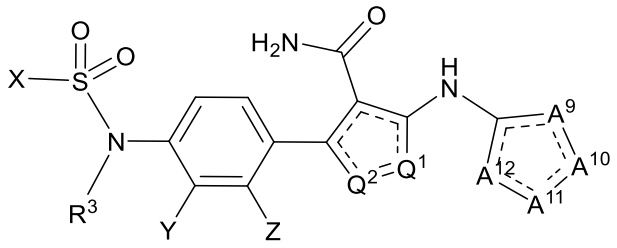
each $R^{10}$ is independently selected from halo, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, $C_{3\text{-}6}$cycloalkyl, -O$C_{1\text{-}6}$alkyl$C_{1\text{-}6}$alkoxy, halo$C_{1\text{-}6}$alkyl, halo$C_{1\text{-}6}$alkoxy, nitrile, amido, $C_{1\text{-}6}$alkylamido, ($C_{1\text{-}6}$alkyl)$_2$amido, halo$C_{1\text{-}6}$alkylamido, (halo$C_{1\text{-}6}$alkyl)$_2$amido, acyl, $C_{1\text{-}6}$alkylacyl, halo$C_{1\text{-}6}$alkylacyl, arylacyl, heterocyclylacyl, cycloalkylacyl, heterocyclyl, halo$C_{1\text{-}6}$alkoxy, $C_{3\text{-}10}$cycloalkyl, $C_{1\text{-}6}$alkyl$C_{3\text{-}10}$cycloalkyl, $C_{1\text{-}6}$alkoxy$C_{3\text{-}10}$cycloalkyl, halo$C_{1\text{-}6}$alkyl$C_{3\text{-}10}$cycloalkyl, halo$C_{1\text{-}6}$alkoxy$C_{3\text{-}10}$cycloalkyl, $C_{1\text{-}6}$alkylheterocyclyl, $C_{1\text{-}6}$alkoxyheterocyclyl, halo$C_{1\text{-}6}$alkylheterocyclyl, halo$C_{1\text{-}6}$alkoxyheterocyclyl, $C_{1\text{-}6}$alkyl$C_{1\text{-}6}$alkoxy, and -COOH;

or when two adjacent groups selected from $A^1$, $A^2$, $A^3$, $A^4$, $A^5$, are $CR^{11}$, two $R^{11}$ may together form an optionally substituted 5-10 membered ring selected from cycloalkyl, aryl and heterocyclyl.

6. The compound of claim 5, or a pharmaceutically acceptable salt, solvate, tautomer, stereoisomer and/or prodrug thereof, wherein $A^1$-$A^5$ are as defined for any one of embodiments 1-4:

| Embodiment No. | $A^1$ | $A^2$ | $A^3$ | $A^4$ | $A^5$ |
|---|---|---|---|---|---|
| 1 | $CR^{11}$ | C-L-E3L | N | $CR^{11}$ | $CR^{11}$ |
| 2 | N | $CR^{11}$ | C-L-E3L | $CR^{11}$ | $CR^{11}$ |
| 3 | N | $CR^{11}$ | C-L-E3L | N | $CR^{11}$ |
| 4 | N | C-L-E3L | N | $CR^{11}$ | $CR^{11}$ |

7. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, solvate, tautomer, stereoisomer and/or prodrug thereof, provided by the following formula (XIII):



(XIII)

wherein:

$A^9$, $A^{10}$, $A^{11}$ and $A^{12}$ are independently selected from $C(R^{11})_q$, O, S, N, $NR^{12}$, $C(R^{11})$–L-E3L, C–L-E3L and N-L-E3L;

one of $A^9$, $A^{10}$, $A^{11}$ and $A^{12}$ is selected from $C(R^{11})$–L-E3L, C–L-E3L and N-L-E3L;

at least one of $A^9$, $A^{10}$, $A^{11}$ and $A^{12}$ is selected from $C(R^{11})_2$, O, S, $NR^{12}$, $C(R^{11})$–L-E3L;

each $R^{11}$ is independently selected from H and $R^{10}$;

each $R^{10}$ is independently selected from halo, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, $C_{3\text{-}6}$cycloalkyl, -O$C_{1\text{-}6}$alkyl$C_{1\text{-}6}$alkoxy, halo$C_{1\text{-}6}$alkyl, halo$C_{1\text{-}6}$alkoxy, nitrile, amido, $C_{1\text{-}6}$alkylamido, ($C_{1\text{-}6}$alkyl)$_2$amido, halo$C_{1\text{-}6}$alkylamido, (halo$C_{1\text{-}6}$alkyl)$_2$amido, acyl, $C_{1\text{-}6}$alkylacyl, halo$C_{1\text{-}6}$alkylacyl, arylacyl, heterocyclylacyl, cycloalkylacyl, heterocyclyl, halo$C_{1\text{-}6}$alkoxy, $C_{3\text{-}10}$cycloalkyl, $C_{1\text{-}6}$alkyl$C_{3\text{-}10}$cycloalkyl, $C_{1\text{-}6}$alkoxy$C_{3\text{-}10}$cycloalkyl, halo$C_{1\text{-}6}$alkyl$C_{3\text{-}10}$cycloalkyl, halo$C_{1\text{-}6}$alkoxy$C_{3\text{-}10}$cycloalkyl, $C_{1\text{-}6}$alkylheterocyclyl, $C_{1\text{-}6}$alkoxyheterocyclyl, halo$C_{1\text{-}6}$alkylheterocyclyl, halo$C_{1\text{-}6}$alkoxyheterocyclyl, $C_{1\text{-}6}$alkyl$C_{1\text{-}6}$alkoxy, and -COOH;

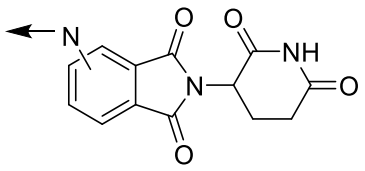
each $R^{12}$ is independently selected from H, $C_{1\text{-}6}$alkyl, halo$C_{1\text{-}4}$alkyl, $C_{1\text{-}6}$alkylacyl and halo$C_{1\text{-}6}$alkylacyl;

or when two adjacent groups selected from $A^9$, $A^{10}$, $A^{11}$ and $A^{12}$ are selected from $CR^{11}$, $C(R^{11})$–L-E3L and $NR^{12}$, two $R^{11}$, two $R^{12}$ or one $R^{11}$ and one $R^{12}$ may together form an optionally substituted 5-10 membered ring selected from cycloalkyl, aryl and heterocyclyl;

q is 1 or 2.

8. The compound of claim 7, or a pharmaceutically acceptable salt, solvate, tautomer, stereoisomer and/or prodrug thereof, wherein $A^{12}$ is N, $A^{11}$ is N-L-E3L, $A^{10}$ is $CR^{11}$ and $A^9$ is $CR^{11}$.

9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, wherein the E3 ligase binding moiety is selected from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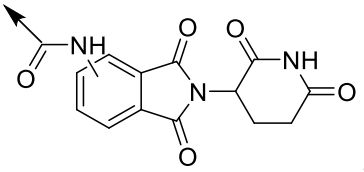
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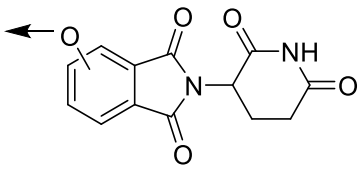
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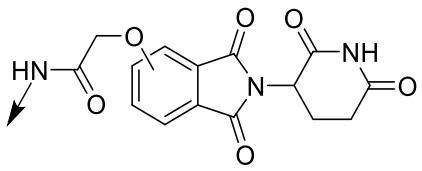
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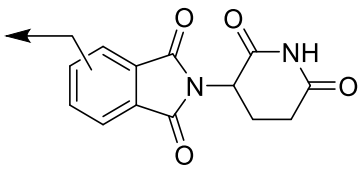
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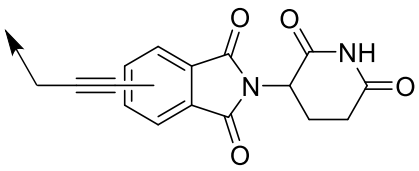
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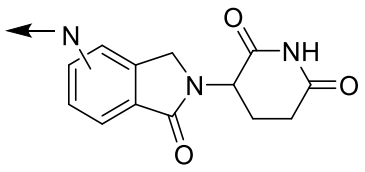
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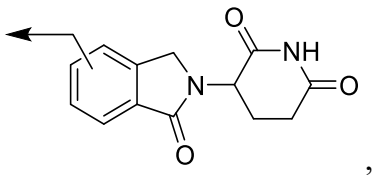
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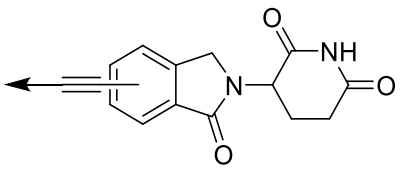
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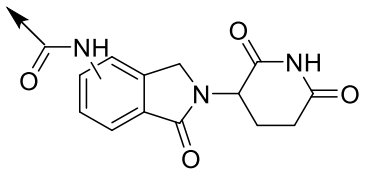
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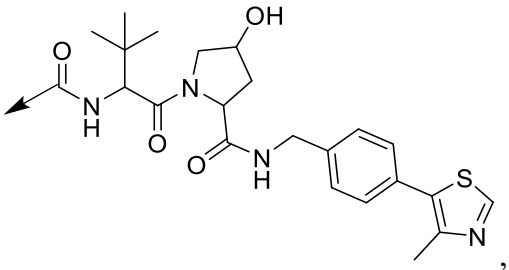
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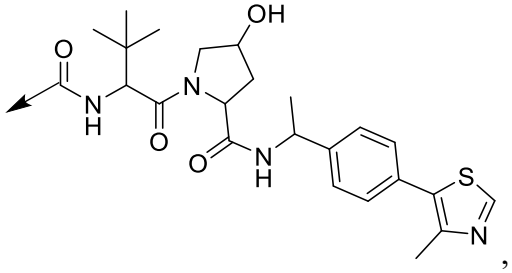
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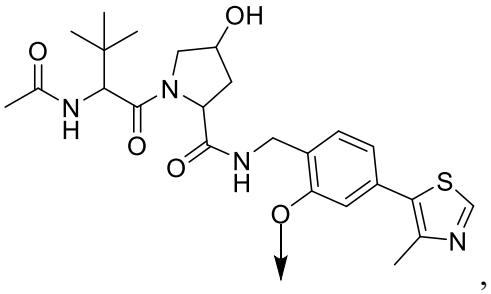
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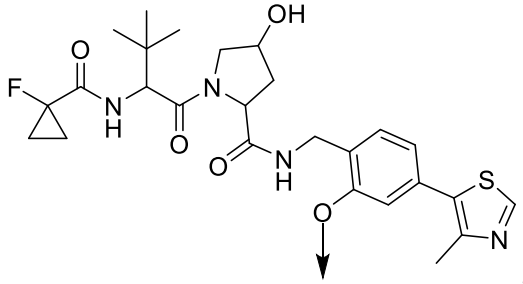
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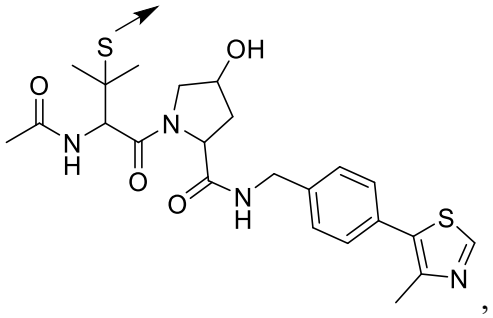
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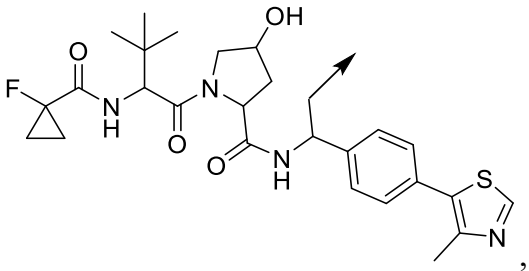
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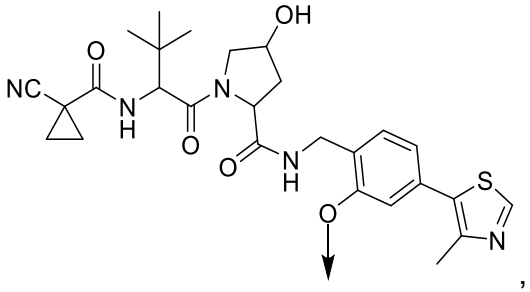
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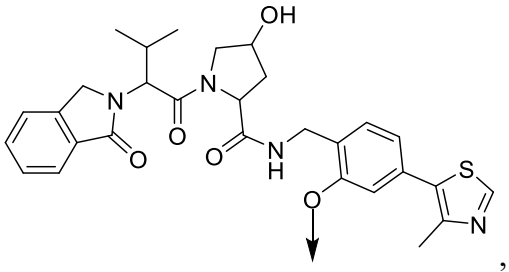
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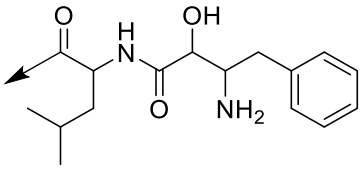
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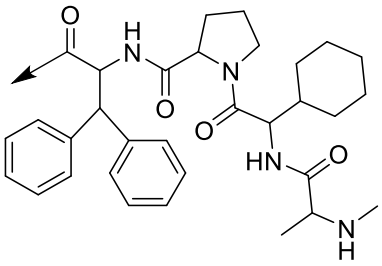
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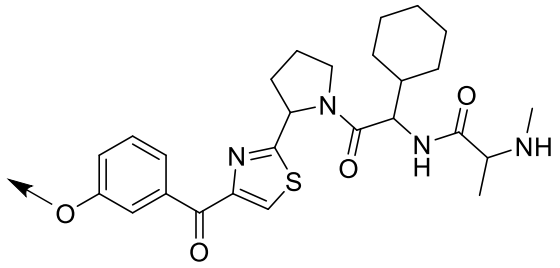
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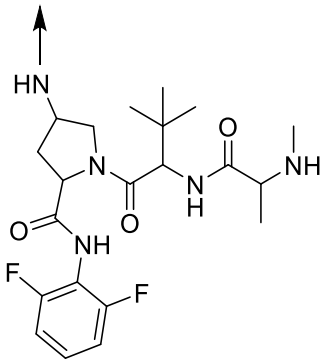
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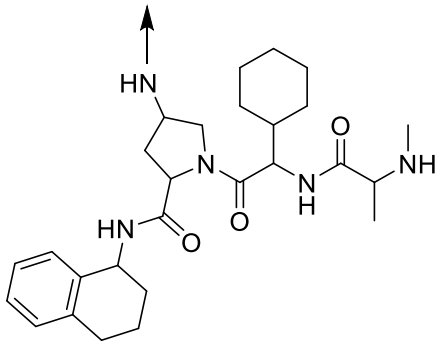
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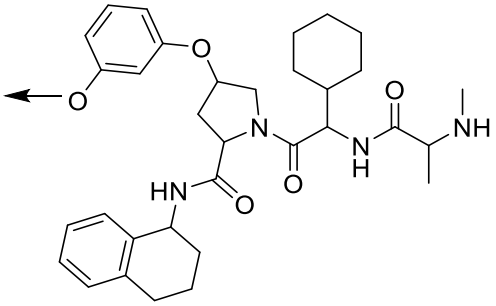
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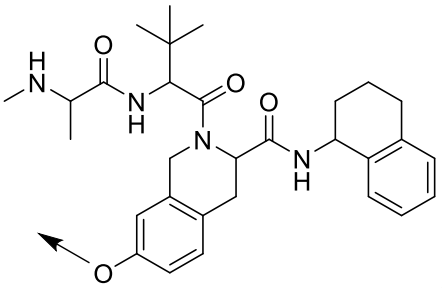
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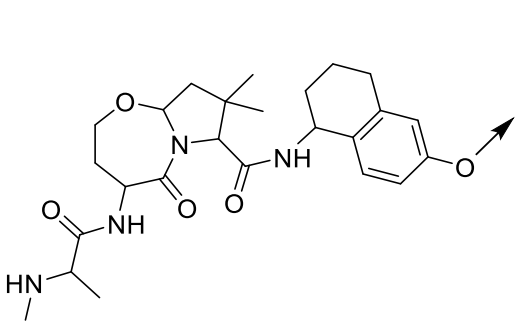
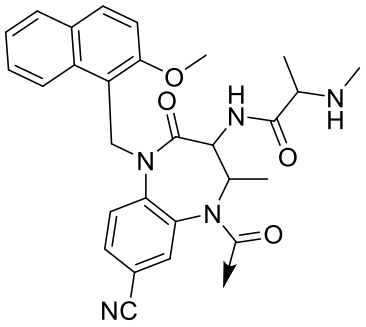
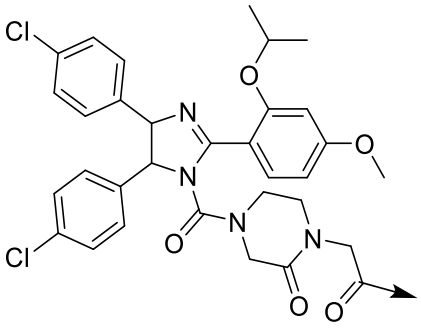
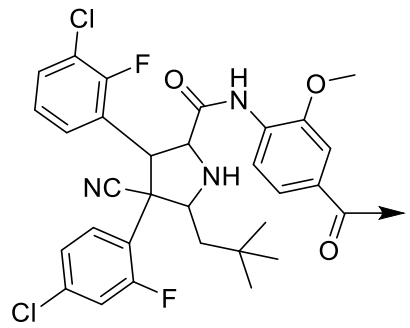
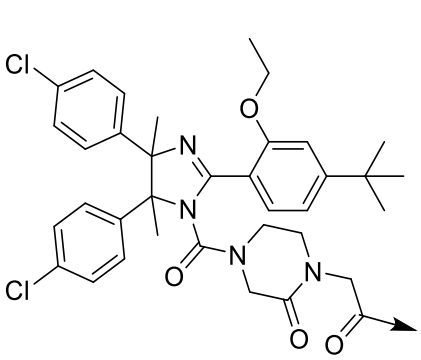
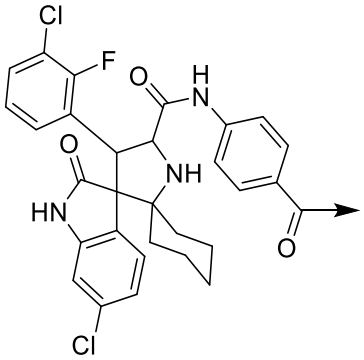
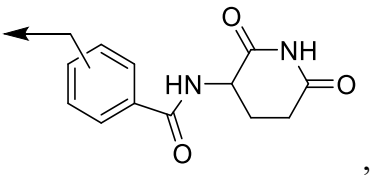
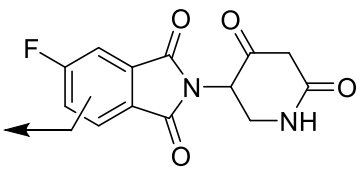
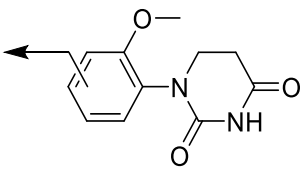
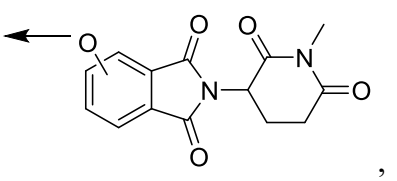
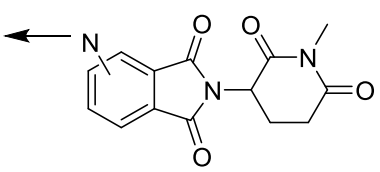
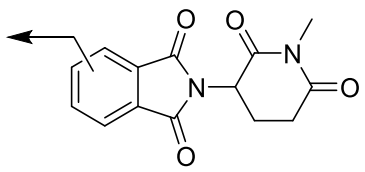
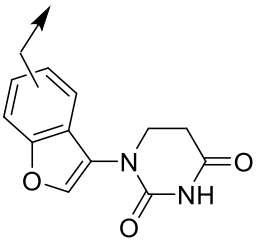
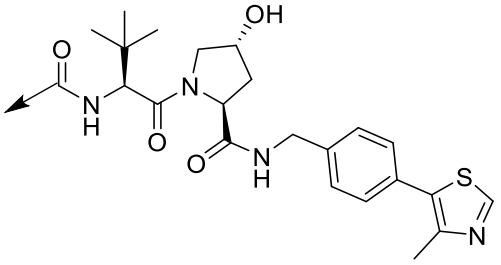













, and ;

wherein the arrow denotes the covalent bond to L,

the portion of L not depicted in the structure, or

an E3 ligase binding derivative thereof.

10. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, wherein the E3 ligase binding moiety is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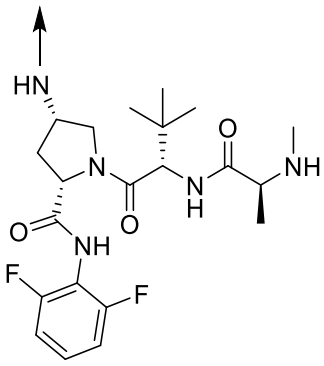
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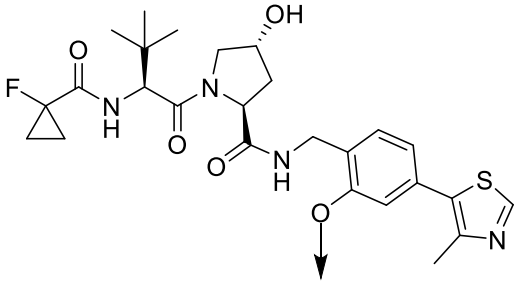
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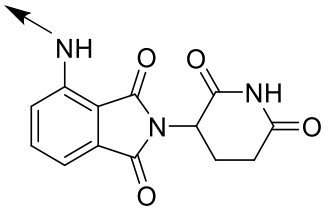
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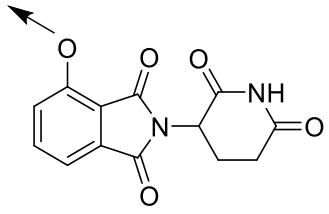
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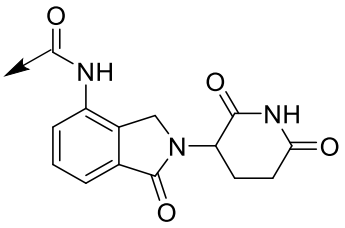
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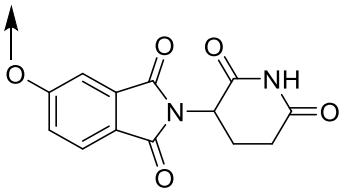
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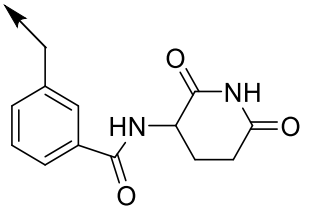
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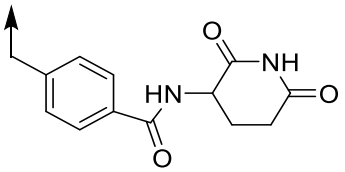
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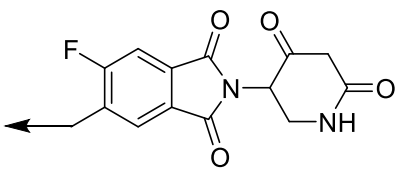
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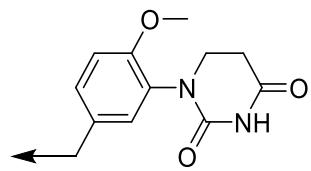
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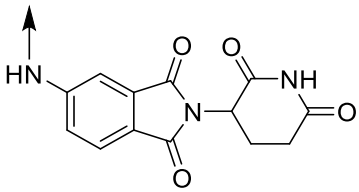
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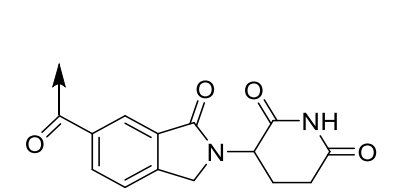
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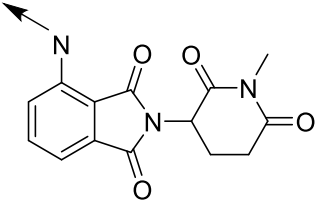
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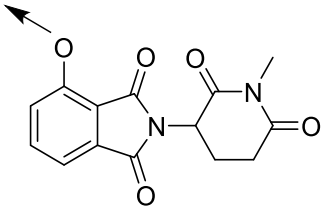
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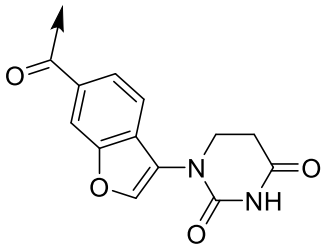
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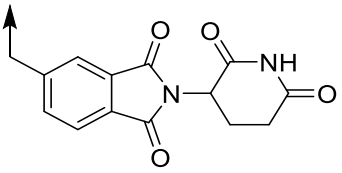
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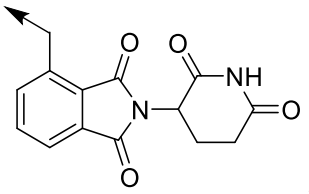
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wherein the arrow denotes the covalent bond to L,

the portion of L not depicted in the structure, or

an E3 ligase binding derivative thereof.

11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, wherein the linker has a shortest linear chain length of 1 to 50 atoms.

12. The compound of claim 11, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, wherein the linker has a shortest linear chain length of 1 to 10 atoms.

13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, wherein the linker is a $C_{1-50}$alkyl optionally interrupted by one or more groups selected from:

a. -O-,

b. -$NR^z$-,

c. $C_{3-8}$cycloalkyl,

d. aryl,

e. $C_{1-4}$alkaryl,

f. heteroaryl,

g. ($C_{1-4}$alkoxy)$_{1-4}$aryl,

h. haloaryl,

i. 4-8-membered non-aromatic heterocyclyl,

j. -C(O)$NR^z$-, wherein each $R^z$ is indepedently selected from H and $C_{1-4}$alkyl,

k. alkenyl,

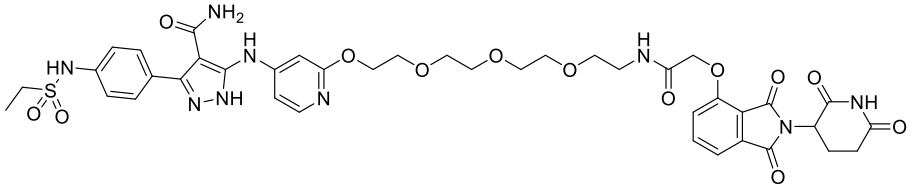
l. alkynyl,
and wherein each of the one or more groups a-l may be further optionally substituted with a group selected from: $C_{3-6}$cycloalkyl, halo, -OH, -CN, -$NR^z_2$, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, oxo, $C_{1-4}$alkylketone, -COOH, -$C(O)N(R^z)_2$, and -$NR^zC(O)R^z$.

14. The compound of claim 13, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, wherein the $C_{1-50}$alkyl is optionally interrupted by 1-20 of the one or more groups.

15. The compound of claim 13 or 14, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, wherein the linker comprises the moiety -$(OCH_2CH_2)_v$-, wherein v is an integer from 1 to 15.

16. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, wherein the linker comprises at least one coupling moiety selected from: -C(O)O-, -$C(O)NR^z$-, -OC(O)O-, -$NR^zC(O)NR^z$-, -$OC(O)NR^z$-, triazolyl, aryl, α,β-unsubstituted ketone, β-hydroxy-ketone, 4-8-membered heteroaryl, unsaturated $C_6$-cycloalkyl and optionally substituted $C_2$alkenyl, wherein each $R^z$ is indepedendently selected from H and $C_{1-4}$alkyl.

17. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, wherein the compound is selected from: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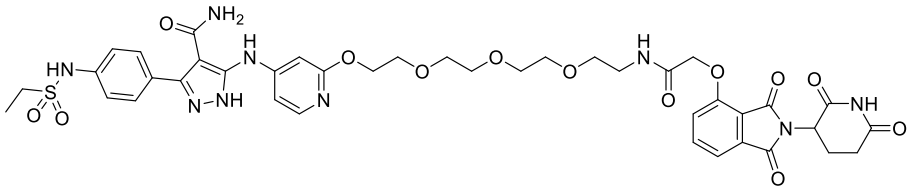
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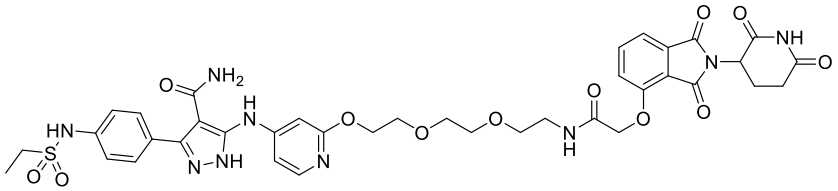
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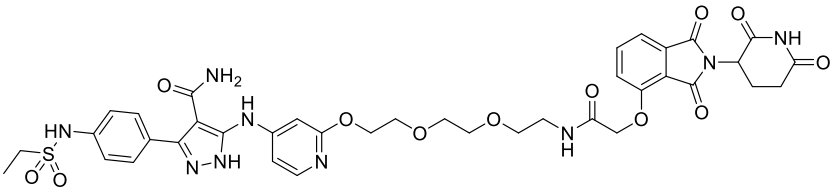
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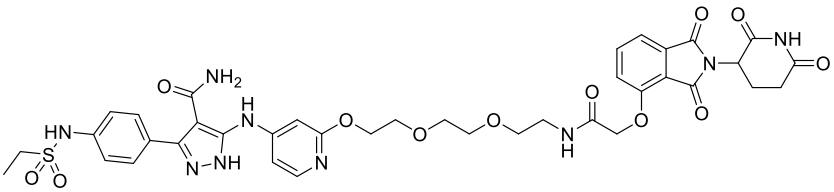
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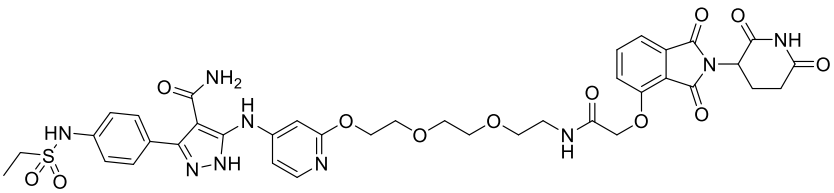
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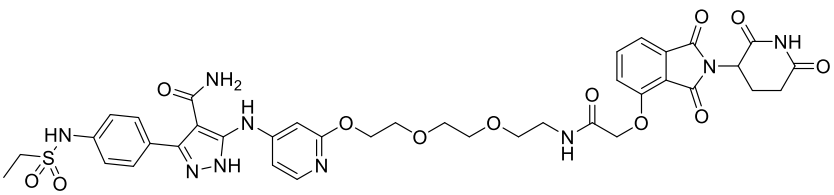
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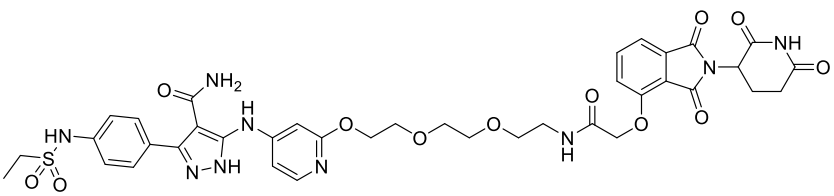
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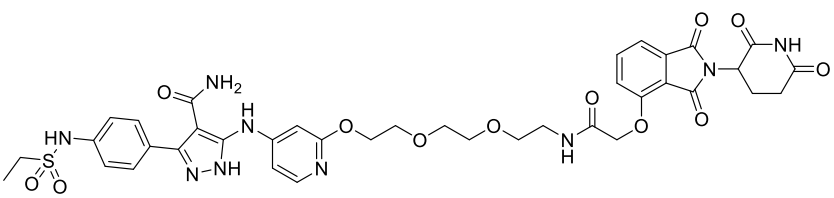
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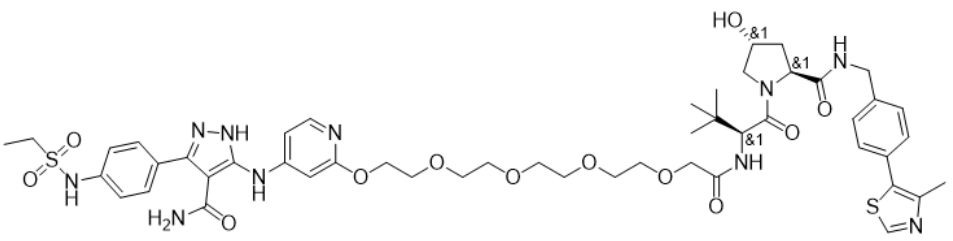
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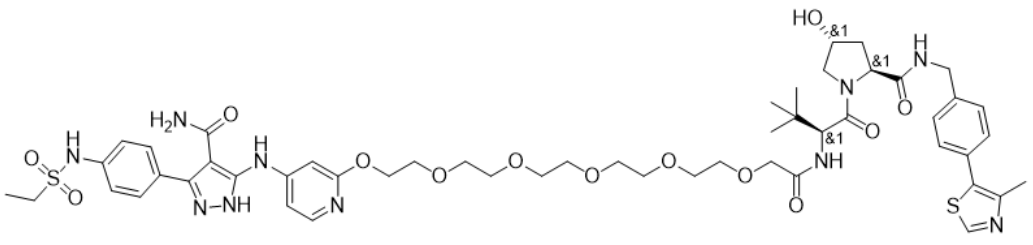
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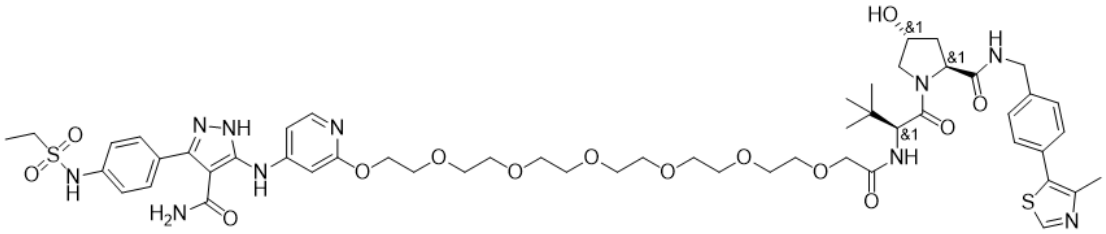
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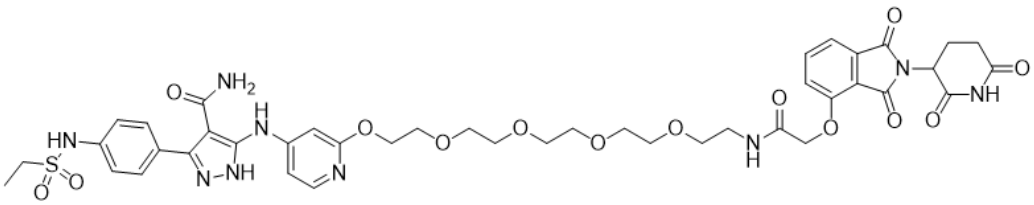
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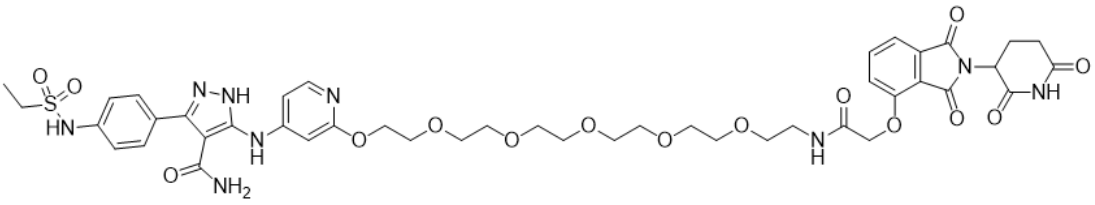
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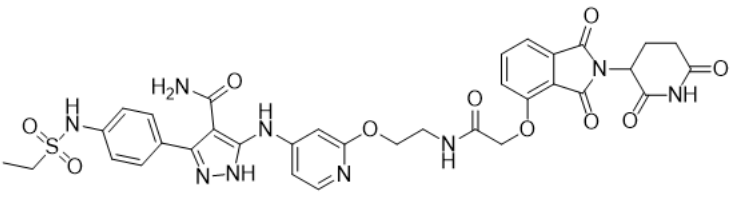
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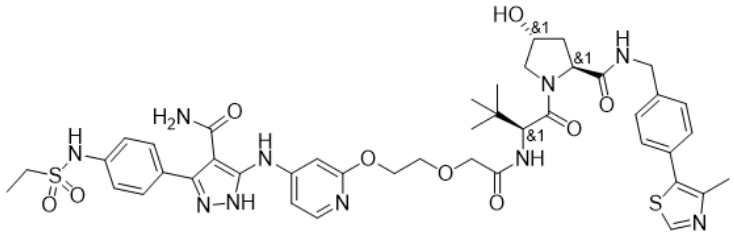
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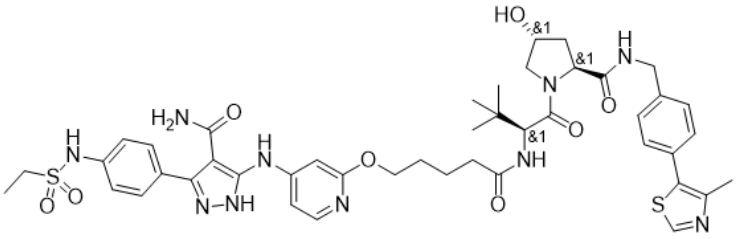
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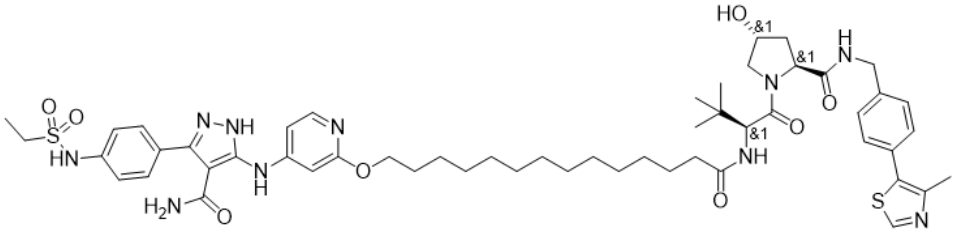
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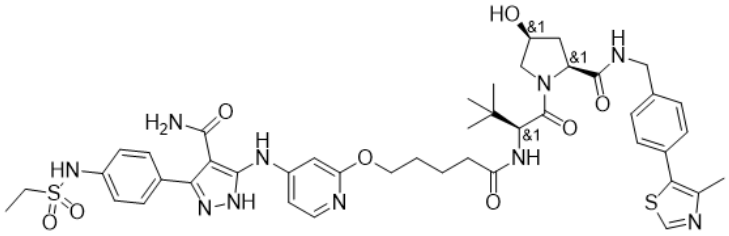

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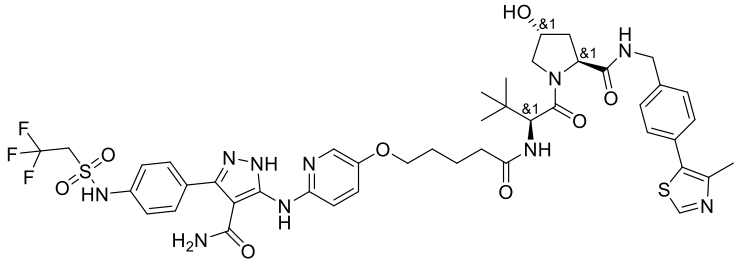

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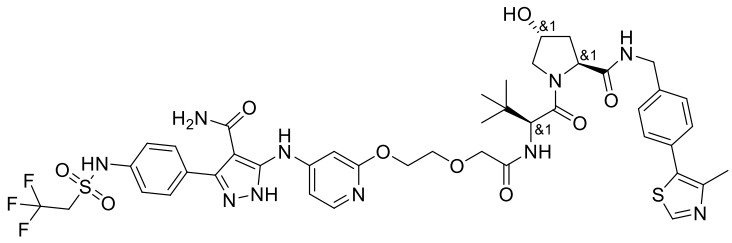

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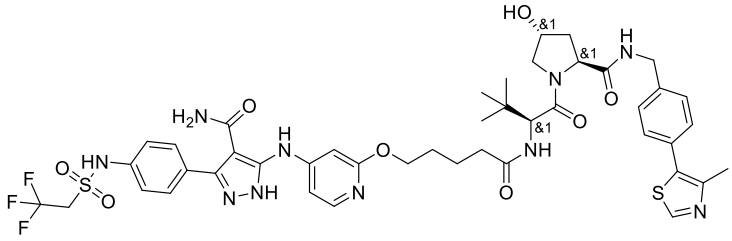

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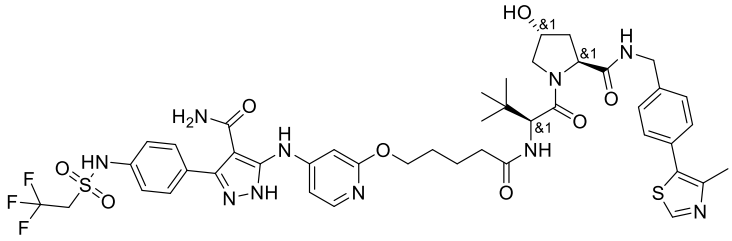

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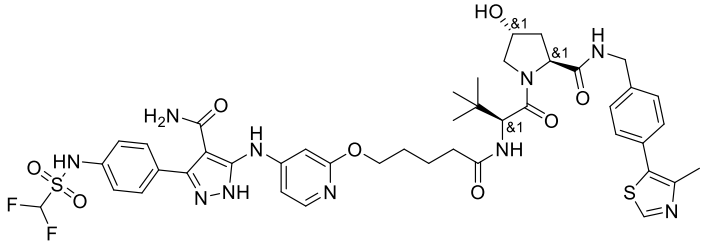

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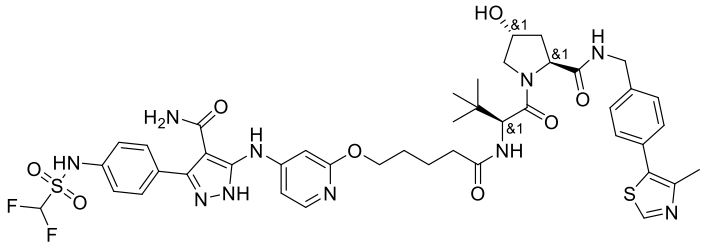

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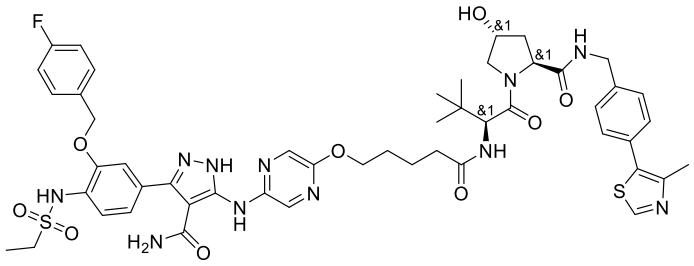

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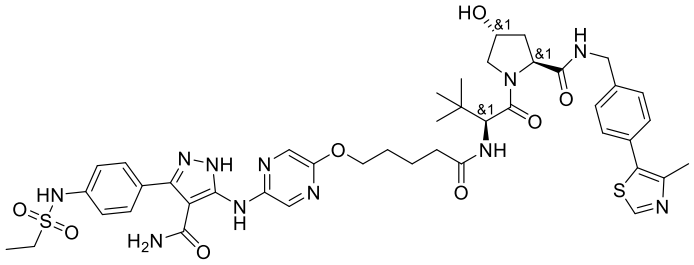

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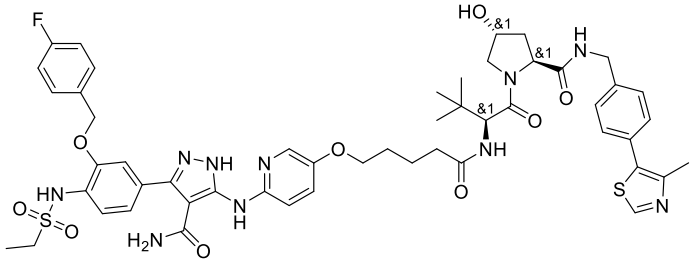

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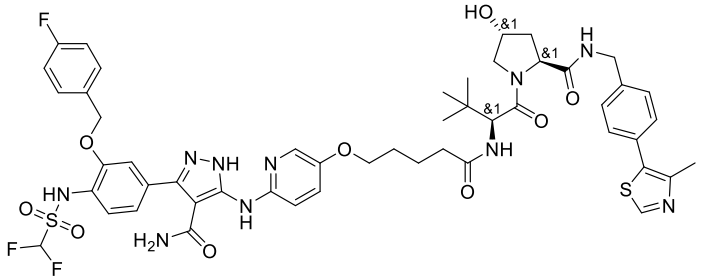

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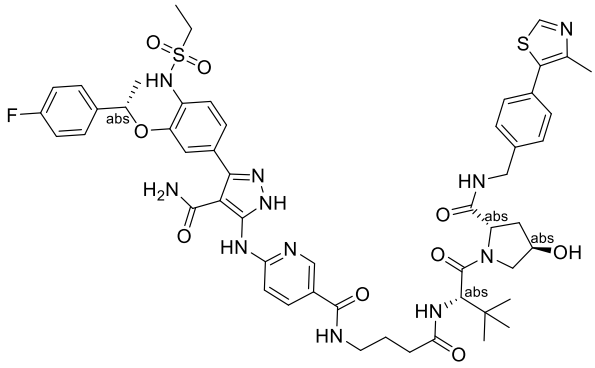

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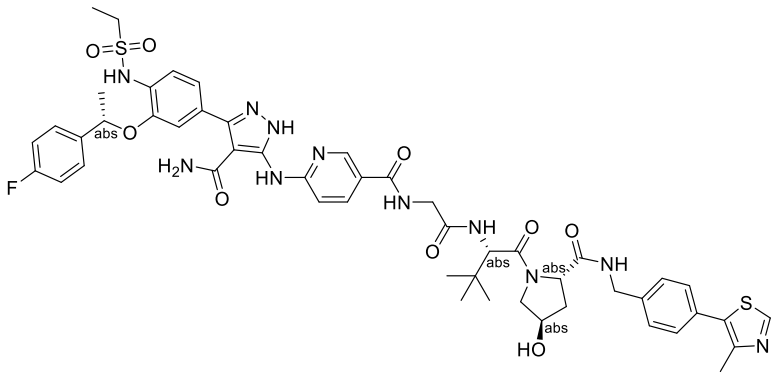

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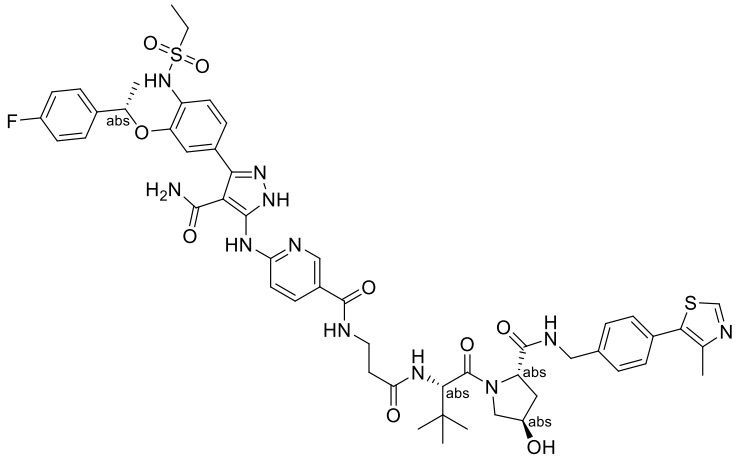

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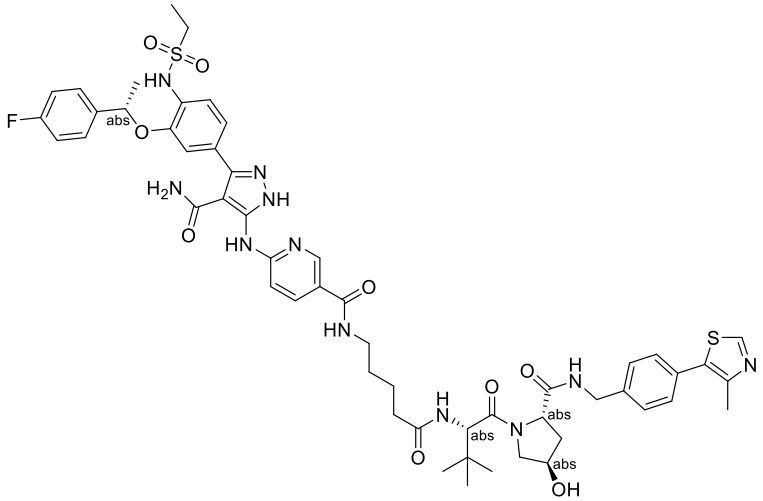

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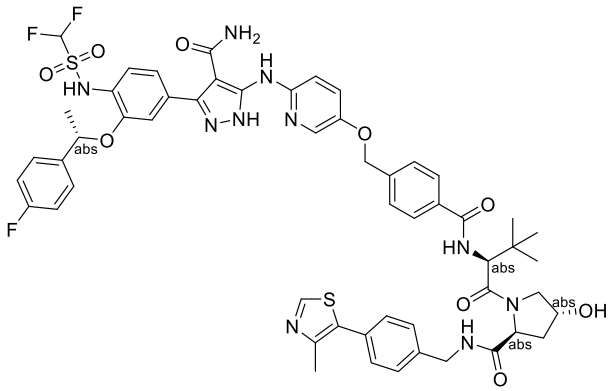

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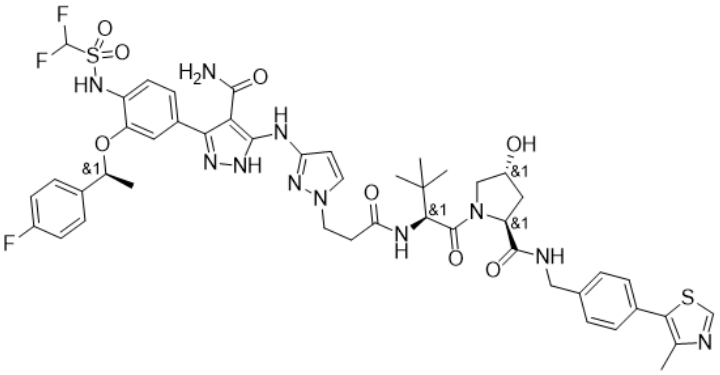

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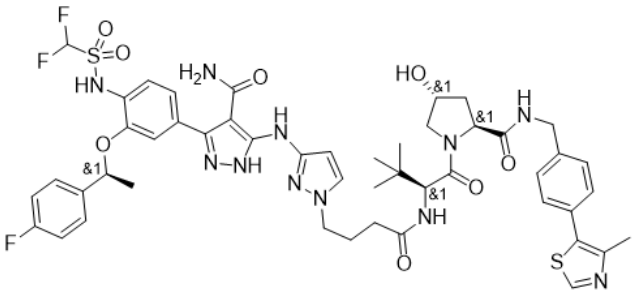

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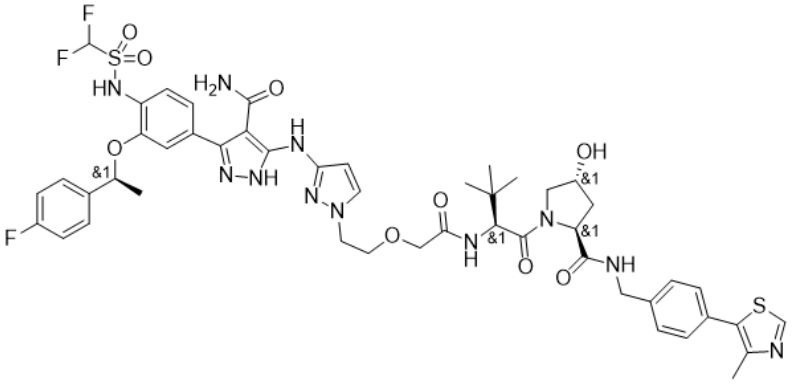

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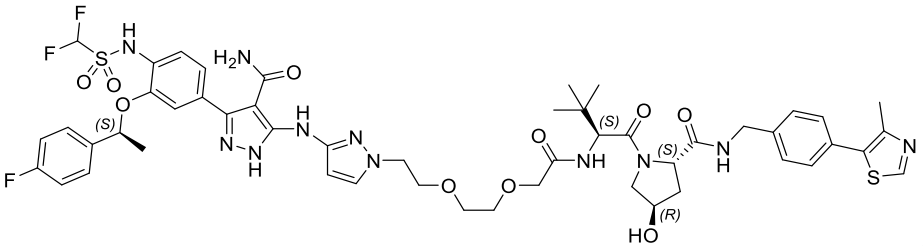

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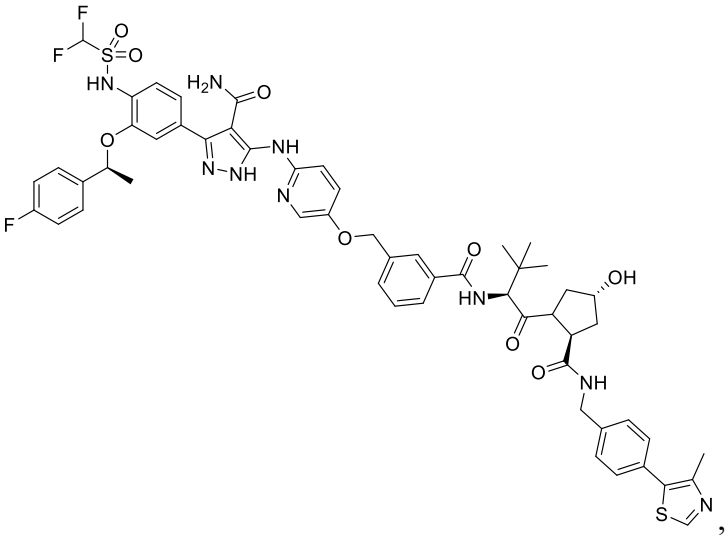

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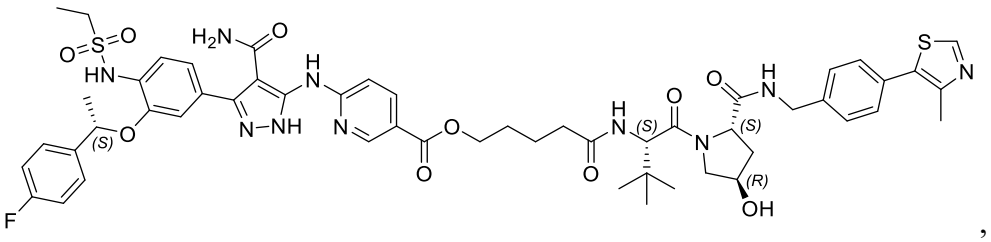

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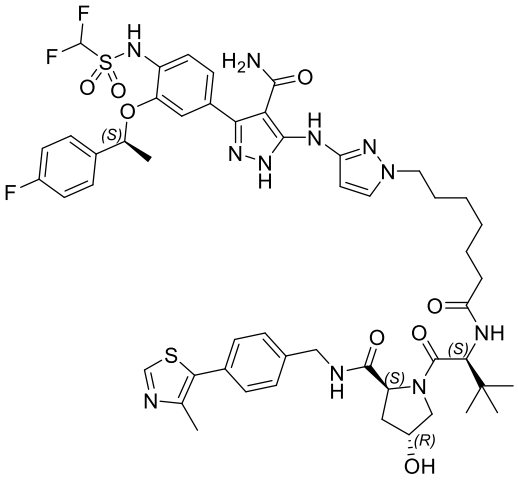

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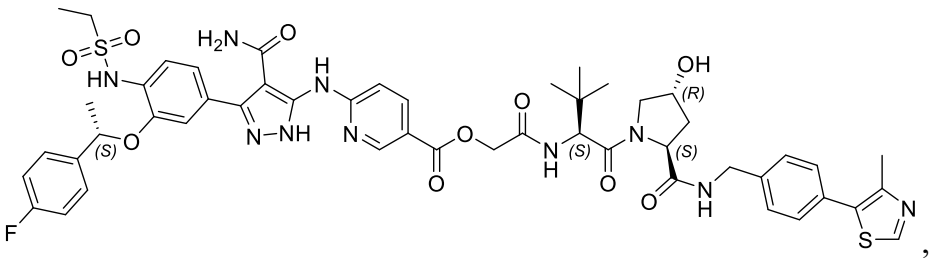

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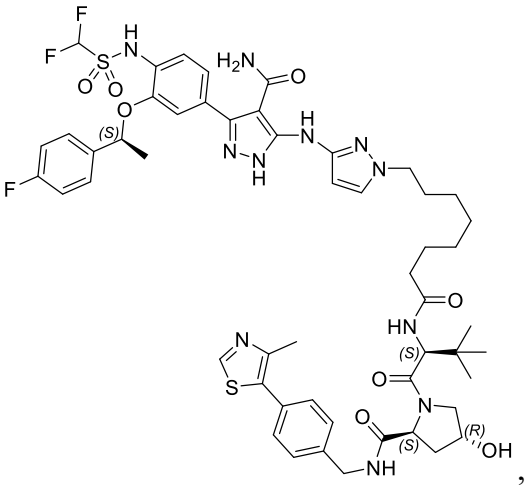

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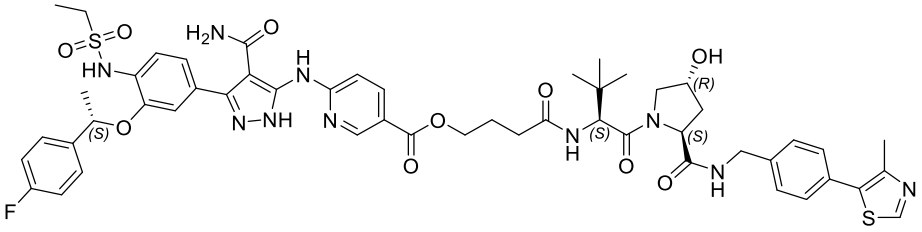

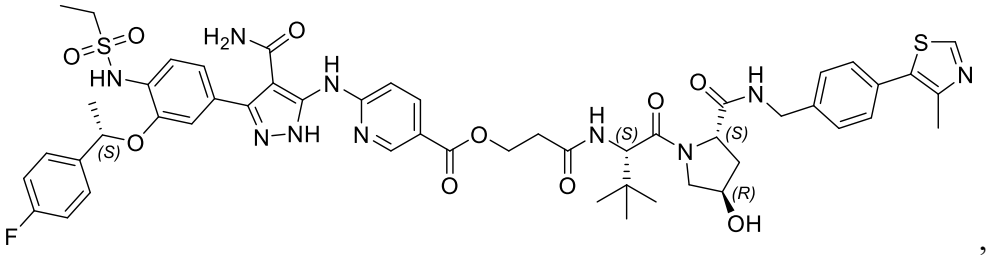

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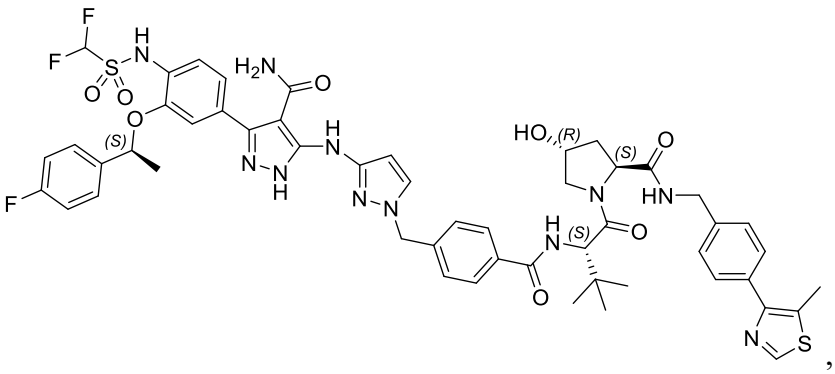

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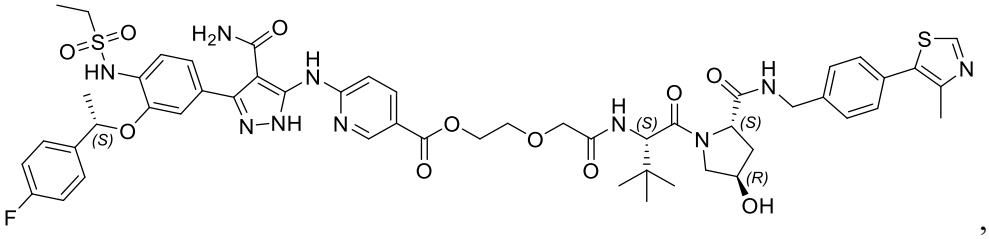

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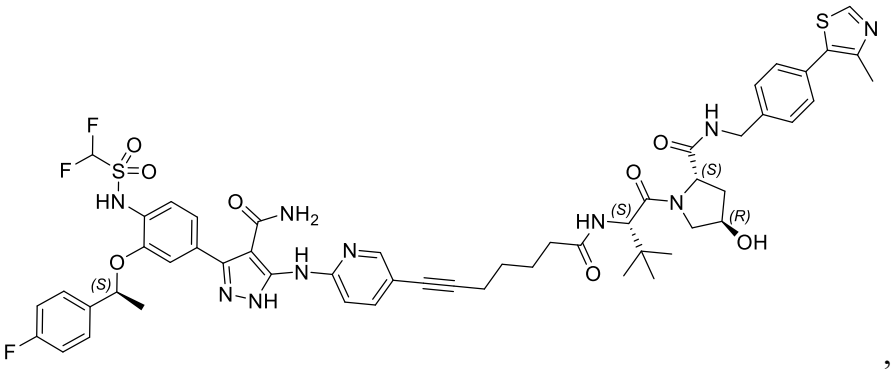

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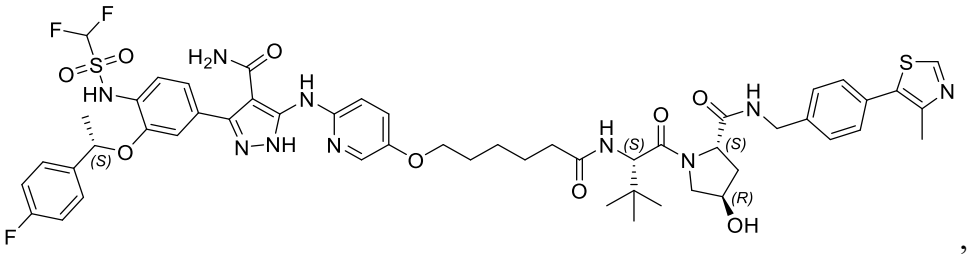

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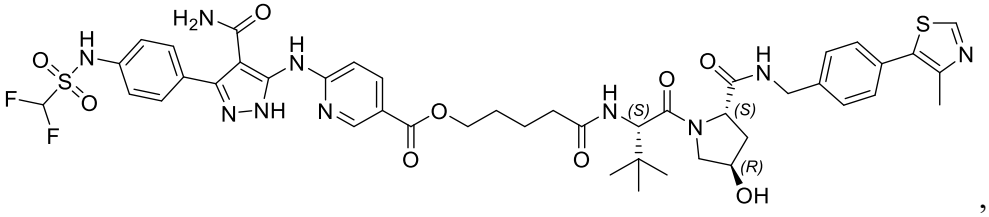

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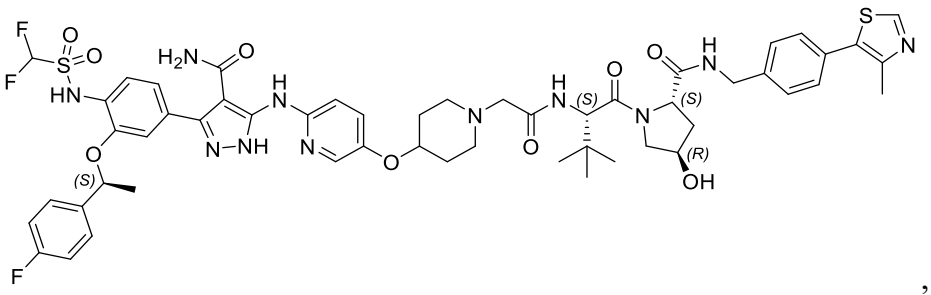

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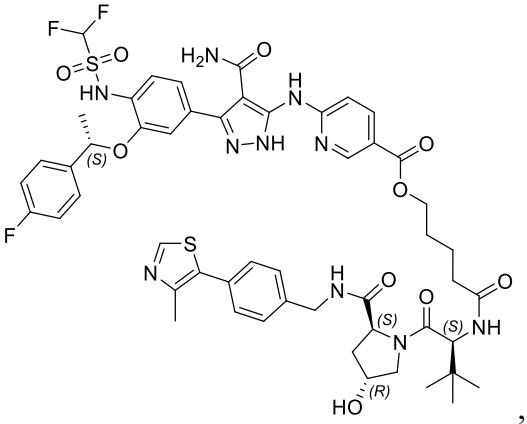

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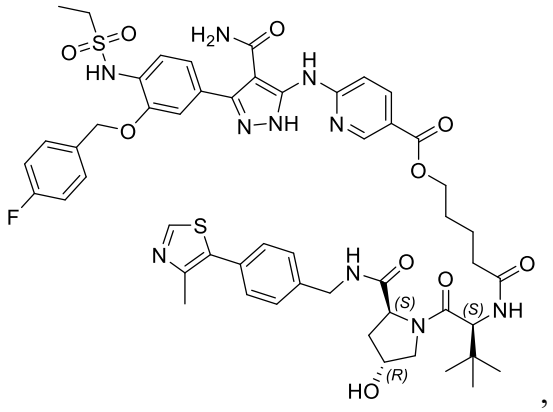

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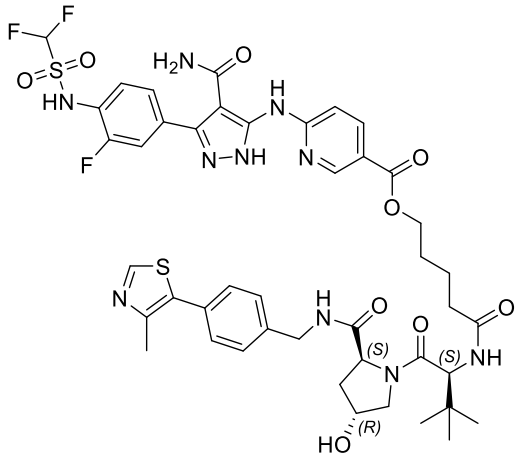

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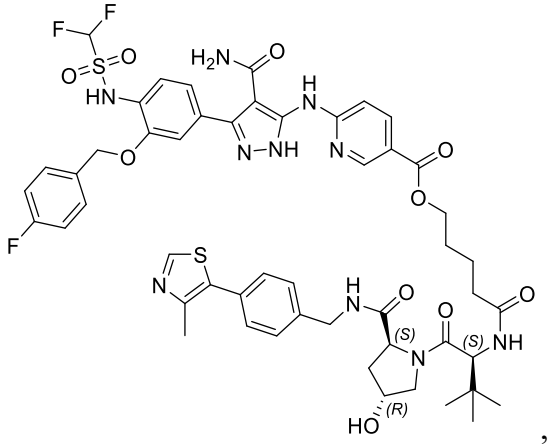

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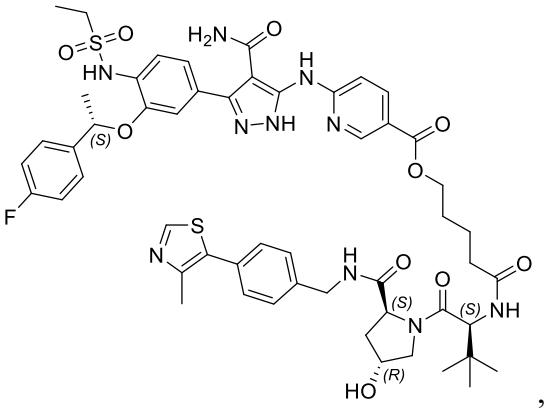

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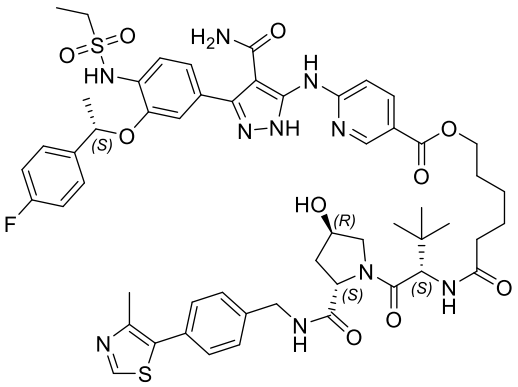

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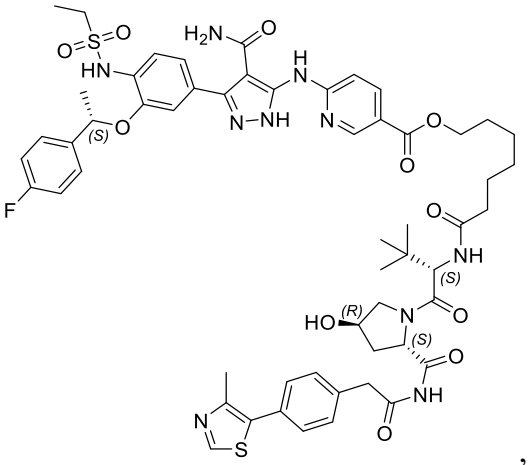

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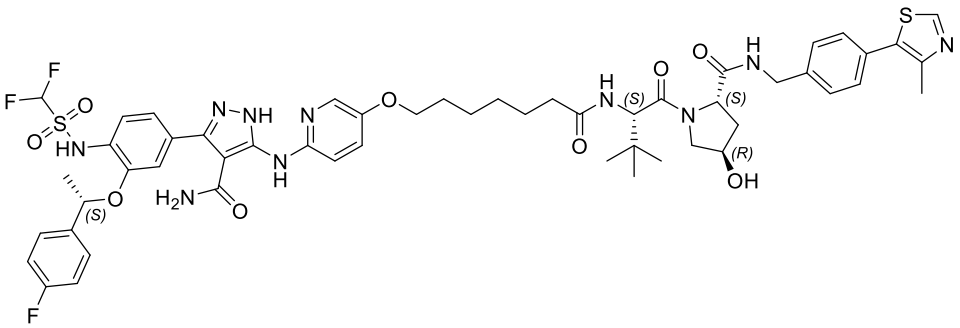

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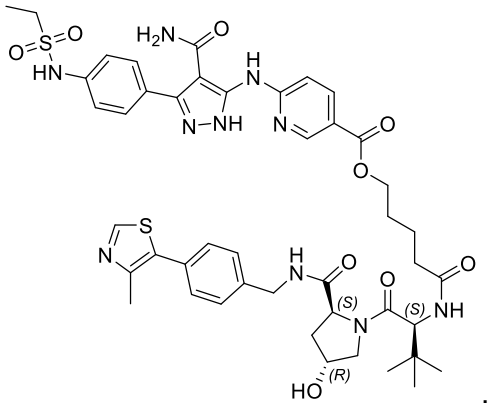

18. A medicament comprising a compound of any one of claims 1-17, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof.

19. A pharmaceutical composition comprising a compound of any one of claims 1-17, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, and a pharmaceutically acceptable excipient.

20. Use of a compound of any one of claims 1-17, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, in the manufacture of a medicament for treating necroptosis.

21. Use of a compound of any one of claims 1-17, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof, in the manufacture of a medicament for treating and/or preventing one or more disease(s), condition(s) and/or disorder(s) selected from:

- a disease, condition and/or disorder of the bones, joints, connective tissue and of cartilage;
- a muscular disease, condition and/or disorder;
- a disease, condition and/or disorder of the skin;
- a cardiovascular disease, condition and/or disorder;
- a circulatory disease, condition and/or disorder;
- a haematological and vascular disease, condition and/or disorder;
- a lung disease, condition and/or disorder;

- a disease, condition and/or disorder of the gastro-intestinal tract;
- a disease, condition and/or disorder of the liver;
- a disease, condition and/or disorder of the pancreas;
- a metabolic disease, condition and/or disorder;
- a disease, condition and/or disorder of the kidneys such as acute renal disorders (such as acute kidney injury (AKI), including ischaemic reperfusion injury (IRI)) or glomerulonephritis;
- a viral and/or bacterial infection;
- a severe intoxication by a chemical, toxin or drug;
- a degenerative disease associated with the Acquired Immune Deficiency Syndrome (AIDS);
- a disorder associated with aging;
- an inflammatory disease, condition and/or disorder;
- an auto-immune disease, condition and/or disorder;
- a dental disease, condition and/or disorder resulting in degradation of tissues;
- an ophthalmic disease, condition and/or disorder;
- a disease, condition and/or disorder of the audition tracts;
- an ischemic reperfusion injury;
- neuronal loss;
- a disease, condition and/or disorder associated with mitochondria;
- a cancer and/or metastasis; and
- a disease, condition and/or disorder of the central nervous system (CNS).

22. The use of claim 21, wherein:

- the disease, condition and/or disorder of the bones, joints, connective tissue and of cartilage is selected from the group consisting of osteoporosis, osteomyelitis including chronic recurrent multifocal osteomyelitis, arthritises including osteoarthritis, rheumatoid arthritis and psoriatic arthritis, avascular necrosis, progressive fibrodysplasia ossificans, rickets, and Cushing's syndrome;
- the muscular disease, condition and/or disorder is selected from the group consisting of muscular dystrophy, including Duchenne's muscular dystrophy, myotonic dystrophies, myopathies and myasthenias;
- the disease, condition and/or disorder of the skin is selected from the group consisting of dermatitis, eczema, psoriasis, aging and alterations of scarring;
- the cardiovascular disease, condition and/or disorder is selected from the group consisting of cardiac and/or vascular ischemia, myocardial infarction, ischemic cardiopathy, chronic or acute congestive heart failure, cardiac dysrythmia, atrial fibrillation, ventricular fibrillation, paroxystic tachycardia, congestive heart failure, hypertrophic cardiopathy, anoxia, hypoxia, and secondary effects due to therapies with anti-cancer agents;
- the circulatory disease, condition and/or disorder is selected from the group consisting of atherosclerosis, arterial scleroses and a peripheral vascular disease, a stroke including a cerebrovascular stroke, and an aneurism;
- the haematological and vascular disease, condition and/or disorder is selected from the group consisting of anemia, aplastic anemia, vascular amyloidosis, haemorrhages, drepanocytosis, red cell fragmentation syndrome, neutropenia, leukopenia, medullar aplasia, pantocytopenia, thrombocytopenia, haemophilia;
- the lung disease, condition and/or disorder is selected from the group consisting of pneumonia, asthma; and an obstructive chronic disease of the lungs including chronic obstructive pulmonary disease (COPD), chronic bronchitis and emphysema;
- the disease, condition and/or disorder of the gastro-intestinal tract is selected from an ulcer; and an inflammatory bowel disease (IBD), including Crohn’s disease, and ulcerative colitis;
- the disease, condition and/or disorder of the liver is selected from the group consisting of hepatitis particularly hepatitis of viral origin or having as causative agent other infectious agents, auto-immune hepatitis, fulminating hepatitis, inflammatory hepatitis, certain hereditary metabolic disorders, Wilson's disease, cirrhoses, non-alcoholic fatty liver disease (NAFLD) including non-alcoholic hepatic steatosis and/or non-alcoholic steatohepatitis (NASH), a disease of the liver due to toxins and to drugs such as drug-induced liver injury, and ethanol (or alcohol)-induced liver disease;

- the disease, condition and/or disorder of the pancreas is selected from the group consisting of acute or chronic pancreatitis;
- the metabolic disease, condition and/or disorder is selected from the group consisting of diabetes, including diabetes mellitus, pre-diabetes and insipid diabetes; and thyroiditis;
- the disease, condition and/or disorder of the kidneys is selected from the group consisting of an acute renal disorder, and an acute kidney injury (AKI), including ischaemic reperfusion injury (IRI)) and glomerulonephritis;
- the viral and/or bacterial infection is septicemia;
- the disorder associated with aging is the syndrome of accelerated aging;
- the inflammatory disease, condition and/or disorder is selected from the group consisting of Terminal ileitis including Crohn's disease, rheumatoid polyarthritis, and TNF-induced systemic inflammatory syndrome;
- the auto-immune disease, condition and/or disorder is selected from the group consisting of erythematous lupus, including systemic lupus erythematosus, and cleavage-resistant RIPK1-induced autoinflammatory (CRIA) syndrome;
- the dental disease, condition and/or disorder resulting in degradation of tissues is periodontitis;
- the ophthalmic disease, condition and/or disorder is selected from diabetic retinopathy, glaucoma, macular degeneration, retinal degeneration, retinitis pigmentosa, a retinal hole or tear, retinal detachment, retinal ischemia, acute retinopathies associated with trauma, inflammatory degeneration, post-surgical complication, medicinal retinopathy, a cataract, and cone cell degeneration;
- the disease, condition and/or disorder of the audition tracts is selected from the group consisting of otosclerosis and deafness induced by antibiotics;
- the ischemic reperfusion injury is retinal ischaemic reperfusion injury;
- the neuronal loss is selected from the group consisting of Alzheimer’s disease and a neurodegenerative disease including amyotrophic lateral sclerosis (ALS; also referred to as motor neuron disease (MND) and Charcot disease);
- the disease, condition and/or disorder associated with mitochondria is a mitochondrial pathology selected from the group consisting of Friedrich's ataxia, congenital muscular dystrophy with structural mitochondrial abnormality, MELAS syndrome, MERFF syndrome, Pearson's syndrome, MIDD (mitochondrial diabetes and deafness) syndrome, Wolfram's syndrome, and dystonia;
- the cancer and/or metastasis is selected from the group consisting of a cancer of the lung and bronchus, including non-small cell lung cancer (NSCLC), squamous lung cancer, brochioloalveolar carcinoma (BAC), adenocarcinoma of the lung, and small cell lung

cancer (SCLC); prostate cancer, including androgen-dependent and androgen-independent prostate cancer; breast cancer, including metastatic breast cancer; pancreatic cancer; cancers of the colon and rectum; thyroid cancer; a cancer of the liver and intrahepatic bile duct; hepatocellular cancer; gastric cancer; endometrial cancer; melanoma; a cancer of the kidney, renal pelvis, urinary bladder, uterine corpus and uterine cervix; ovarian cancer, including progressive epithelial or primary peritoneal cancer; multiple myeloma; oesophageal cancer, including squamous cell carcinoma and adenocarcinoma of the oesophagus; acute myelogenous leukemia (AML); chronic myelogenous leukemia (CML), including accelerated CML and CML blast phase (CML-BP); lymphocytic leukemia; myeloid leukemia; acute lymphoblastic leukemia (ALL); chronic lymphocytic leukemia (CLL); Hodgkin's disease (HD); non- Hodgkin's lymphoma (NHL), including follicular lymphoma and mantle cell lymphoma; B-cell lymphoma, including diffuse large B-cell lymphoma (DLBCL); T-cell lymphoma; multiple myeloma (MM); amyloidosis; Waldenstrom's macroglobulinemia; myelodysplastic syndromes (MDS), including refractory anemia (RA), refractory anemia with ringed siderblasts (RARS), (refractory anemia with excess blasts (RAEB), and RAEB in transformation (RAEB-T); and myeloproliferative syndromes; cancers of the brain, including glioma/glioblastoma, anaplastic oligodendroglioma, and adult anaplastic astrocytoma; neuroendocrine cancers, including metastatic neuroendocrine tumors; a cancer of the head and neck, including squamous cell carcinoma of the head and neck, and nasopharyngeal cancer; a cancer of the oral cavity, pharynx and small intestine; bone cancer; soft tissue sarcoma; and villous colon adenoma; and

- the disease, condition and/or disorder of the central nervous system (CNS) is multiple sclerosis (MS).

23. A method of inhibiting and/or degrading mixed lineage kinase domain-like protein (MLKL), comprising contacting a cell with a compound of any one of claims 1-17, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof.

24. A MLKL degrading agent comprising a compound of any one of claims 1-17, or a pharmaceutically acceptable salt, solvate, tautomer, N-oxide, stereoisomer and/or prodrug thereof.