two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

r is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;and

LBM is a cereblon E3 ubiquitin ligase binding moiety.

[0008b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[0008c] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutical composition thereof, for use in treating a disorder, disease, or condition in a patient; wherein the disorder, disease or condition is selected from a cancer, a neurodegenerative disease, a viral disease, an autoimmune disease, an inflammatory disorder, a hereditary disorder, a hormone-related disease, a metabolic disorder, an immunodeficiency disorder, a destructive bone disorder, a proliferative disorder, an infectious disease, thrombin-induced platelet aggregation, liver disease, a pathologic immune condition involving T cell activation, a cardiovascular disorder, and a CNS disorder.

[0008d] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutical composition thereof, in the manufacture of a medicament for treating a disorder, disease, or condition in a patient; wherein the disorder, disease or condition is selected from a cancer, a neurodegenerative disease, a viral disease, an autoimmune disease, an inflammatory disorder, a hereditary disorder, a hormone-related disease, a metabolic disorder, an immunodeficiency disorder, a destructive bone disorder, a proliferative disorder, an infectious disease, thrombin-induced platelet aggregation, liver disease, a pathologic immune condition involving T cell activation, a cardiovascular disorder, and a CNS disorder.

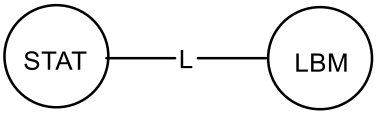
[0009] The present application relates novel bifunctional compounds, which function to recruit STAT proteins to E3 ubiquitin ligase for degradation, and methods of preparation and uses thereof. In particular, the present disclosure provides bifunctional compounds, which find utility as modulators of targeted ubiquitination of STAT proteins, which are then degraded and/or otherwise inhibited by the bifunctional compounds as described herein. Also provided are monovalent compounds, which find utility as inducers of targeted ubiquitination of STAT proteins, which are then degraded and/or otherwise inhibited by the monovalent compounds as described herein. An

advantage of the compounds provided herein is that a broad range of pharmacological activities is possible, consistent with the degradation/inhibition of STAT proteins. In addition, the description provides methods of using an effective amount of the compounds as described herein for the treatment or amelioration of a disease condition, such as cancer, e.g., breast cancer.

[00010] The present application further relates to targeted degradation of STAT proteins through the use of bifunctional molecules, including bifunctional molecules that link a cereblon-binding moiety to a ligand that binds STAT proteins.

[00011] It has now been found that compounds of this present disclosure, and pharmaceutically acceptable compositions thereof, are effective as degraders of STAT proteins.

Such compounds have the general formula **I**:



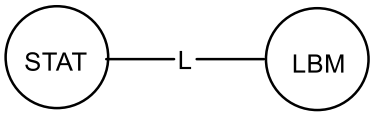
I

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

CLAIMS

We claim:

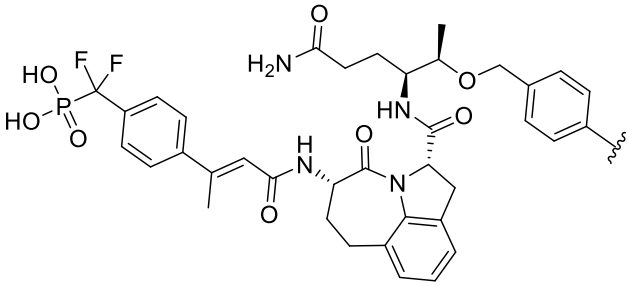
1. A compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

STAT is a STAT3 protein binding moiety selected from



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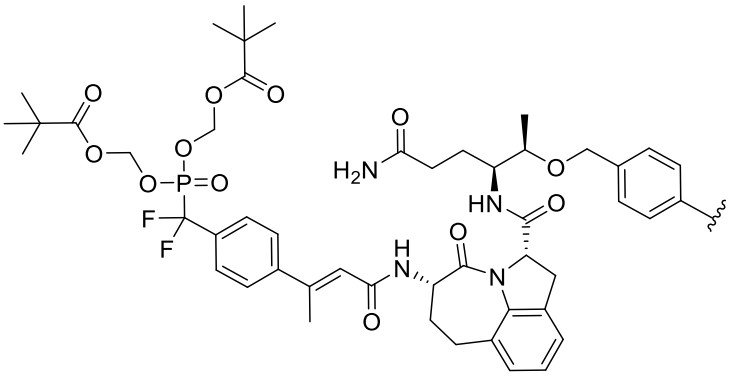

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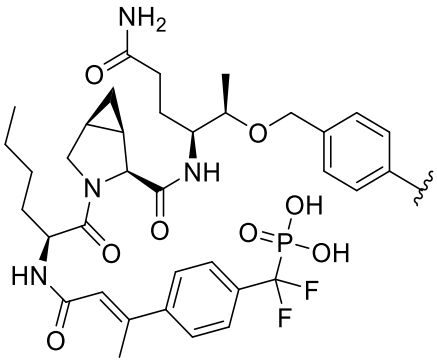

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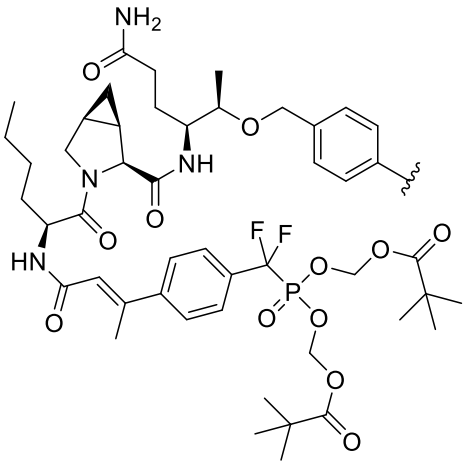

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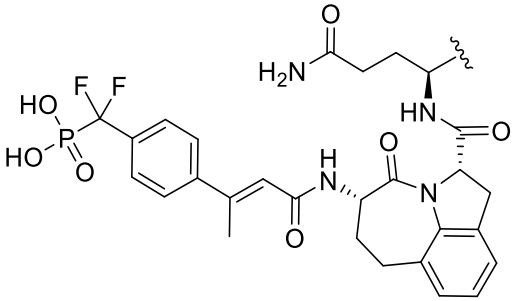

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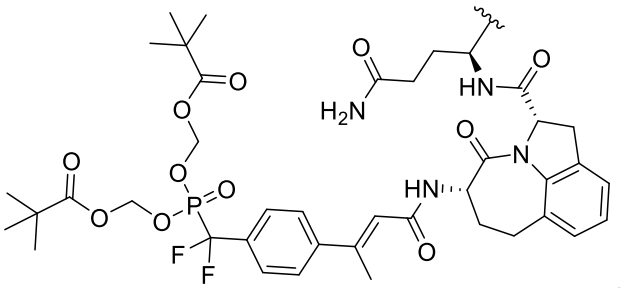

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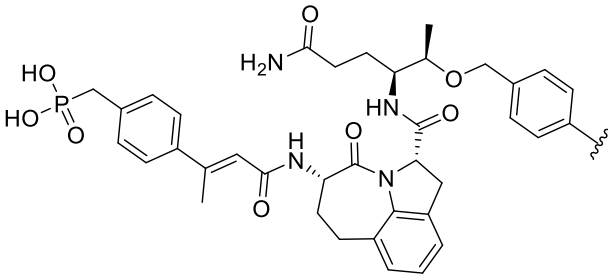

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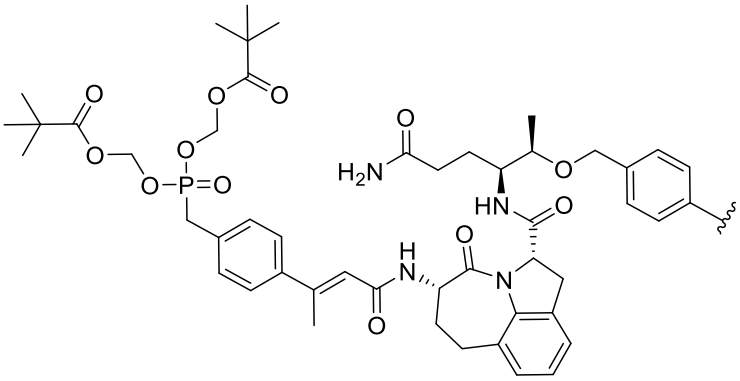

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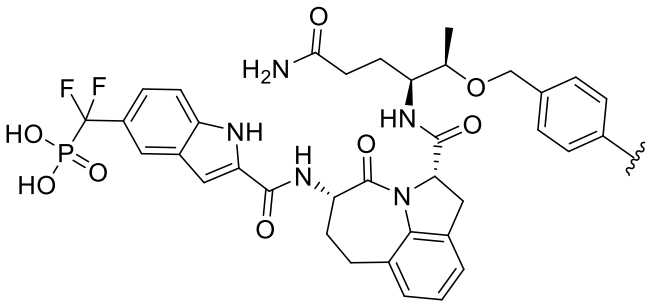

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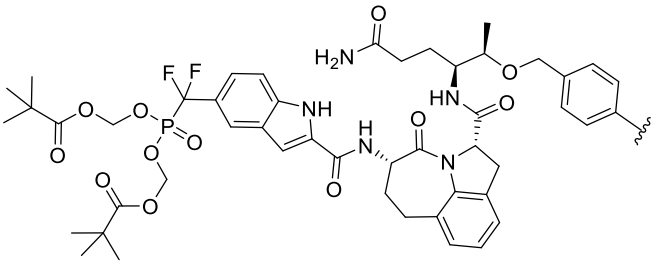

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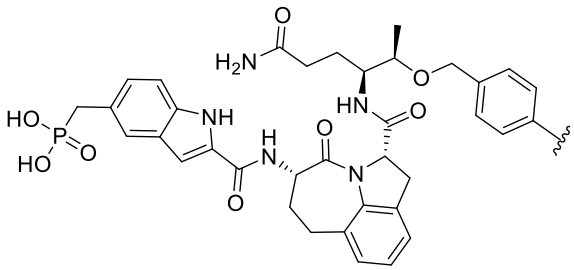
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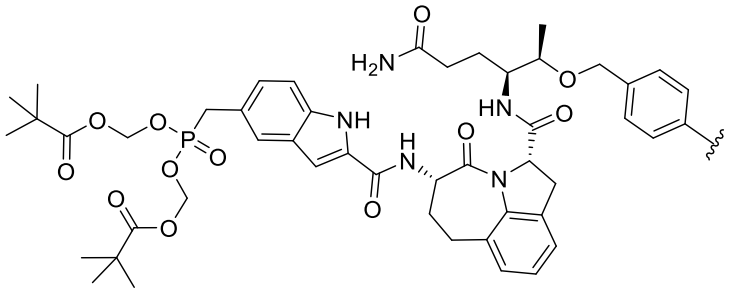
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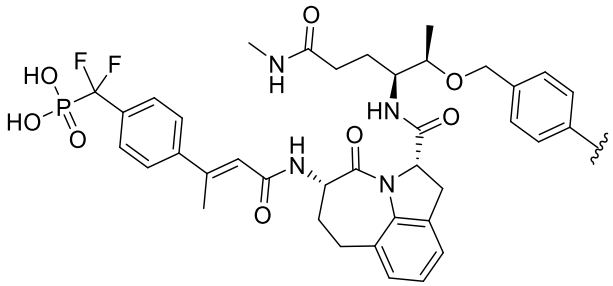
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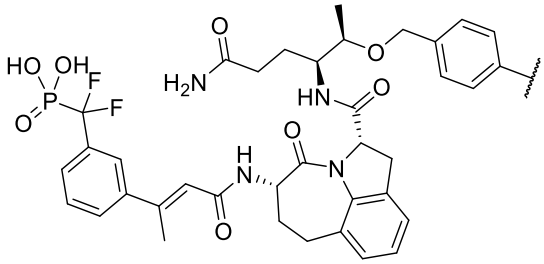
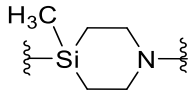
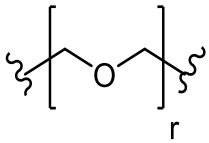
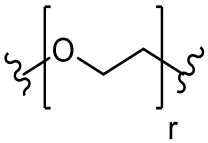
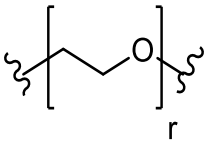
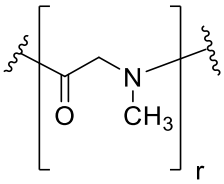

;

L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by –Cy-, -O-, -N(R)-, $–Si(R)_2–$, –Si(OH)(R)–, $–Si(OH)_2–$, –P(O)(OR)–, –P(O)(R)–, $–P(O)(NR_2)–$, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, $-S(O)_2-$, $-N(R)S(O)_2-$, $-S(O)_2N(R)-$, -N(R)C(O)-, -C(O)N(R)-, -OC(O)N(R)-, –N(R)C(O)O-,


, 
, 
, 
, 
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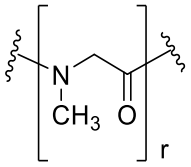

, wherein

each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

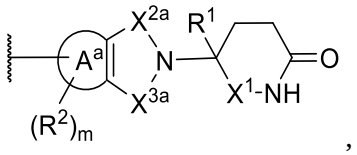
two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

r is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;and

LBM is a cereblon E3 ubiquitin ligase binding moiety.

2. The compound of claim 1, wherein L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-20} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by –Cy-, -O-, -NR-, -S-, -C(O)-, -S(O)-, or $-S(O)_2-$.

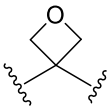
3. The compound of claim 1, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety of formula **I-aa-1**:



,

I-aa-1

or a pharmaceutically acceptable salt thereof, wherein:

each of X^1, X^{2a}, and X^{3a} is independently a bivalent moiety selected from covalent bond, $–CH_2–$, –C(O)–, –C(S)–, and  ;

R^1 is hydrogen, deuterium, halogen, –CN, –OR, –SR, –S(O)R, $–S(O)_2R$, $–NR_2$, or an optionally substituted C_{1-4} aliphatic;

each of R^2 is independently hydrogen, R^6, halogen, –CN, $–NO_2$, –OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $–C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, or $-N(R)S(O)_2R$;

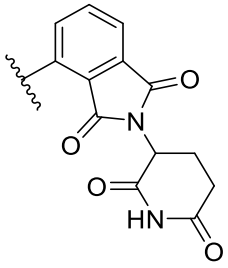
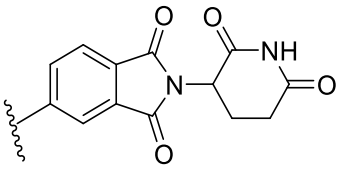
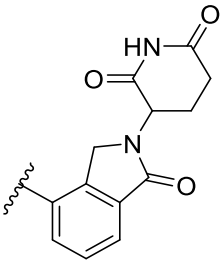
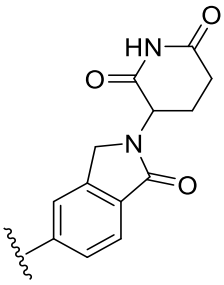
each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring A^a is a fused ring selected from 6-membered aryl containing 0-2 nitrogen atoms, 5 to 7-membered partially saturated carbocyclyl, 5 to 7-membered partially saturated heterocyclyl with 1-2 heteroatoms independently selected from nitrogen, oxygen and sulfur, and 5-membered heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur; and

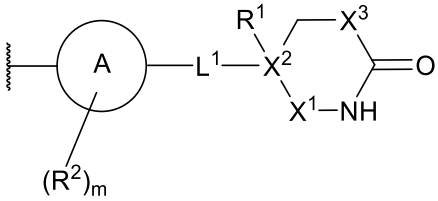
m is 0, 1, 2, 3 or 4.

4. The compound of claim 3, wherein Ring A^a is a fused ring selected from 6-membered aryl containing 0-2 nitrogen atoms and 5-membered heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur.

5. The compound of claim 3, wherein LBM is selected from

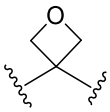
 ,  ,  , and  .

6. The compound of claim 1, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety and said compound is of formula **I-c**:



I-c

or a pharmaceutically acceptable salt thereof, wherein:

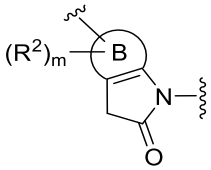
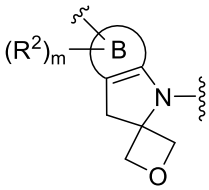
X^1 is a bivalent moiety selected from a covalent bond, $–CH_2–$, $–CHCF_3–$, $–SO_2–$, –S(O) –, –P(O)R–, –P(O)OR–, $–P(O)NR_2–$, –C(O)–, –C(S)–, or  ;

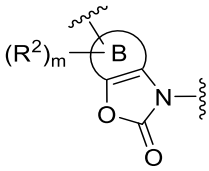
X^2 is a carbon atom or silicon atom;

X^3 is a bivalent moiety selected from $–CR_2–$, –NR–, –O–, –S–, or $–Si(R_2)–$;

R^1 is hydrogen, deuterium, halogen, –CN, –OR, –SR, –S(O)R, $–S(O)_2R$, $–N(R)_2$, $–P(O)(OR)_2$, $–P(O)(NR_2)OR$, $–P(O)(NR_2)_2$, $–Si(OH)_2R$, $–Si(OH)(R)_2$, $-Si(R)_3$, or an optionally substituted C_{1-4} aliphatic;

each R^2 is independently hydrogen, deuterium, $–R^6$, halogen, –CN, $–NO_2$, –OR, -SR, $-N(R)_2$, $-Si(R)_3$, $-S(O)_2R$, $-S(O)_2N(R)_2$, -S(O)R, -C(O)R, -C(O)OR, $–C(O)N(R)_2$, -C(O)N(R)OR, $-C(R)_2N(R)C(O)R$, $-C(R)_2N(R)C(O)N(R)_2$, -OC(O)R, $-OC(O)N(R)_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)(NR_2)$, $-OP(O)(NR_2)_2-$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)N(R)_2$, $–N(R)S(O)_2R$, $-NP(O)R_2$, $-N(R)P(O)(OR)_2$, $-N(R)P(O)(OR)(NR_2)$, $-N(R)P(O)(NR_2)_2$, or $–N(R)S(O)_2R$;

Ring A is a bicyclic or tricyclic ring selected from  ,  ,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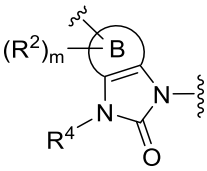
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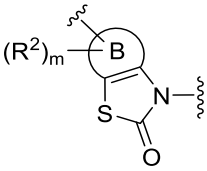
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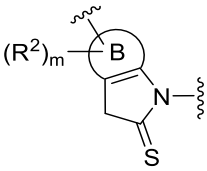
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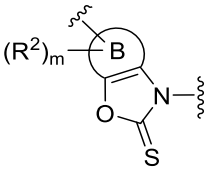
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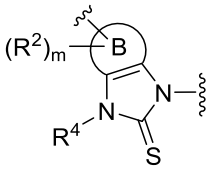
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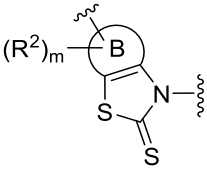
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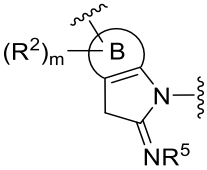
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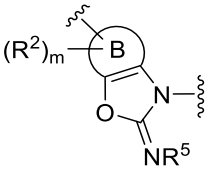
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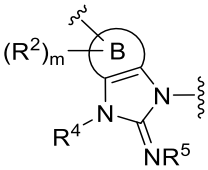
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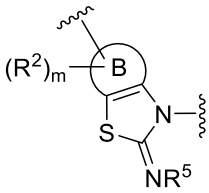
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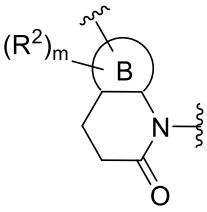
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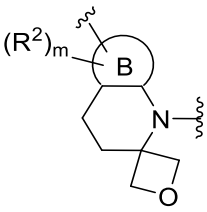
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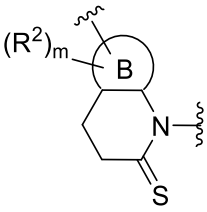
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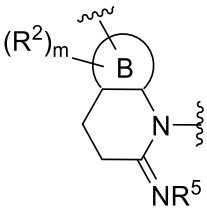
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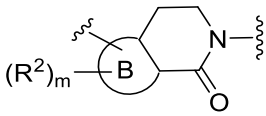
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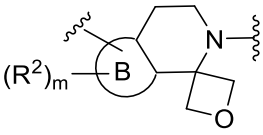
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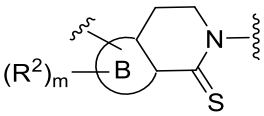
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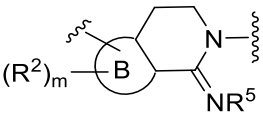
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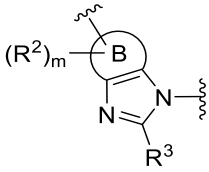
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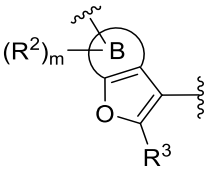
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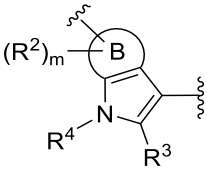
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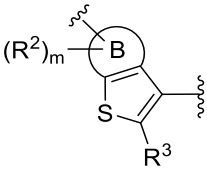
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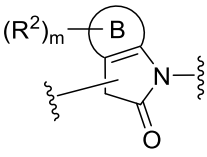
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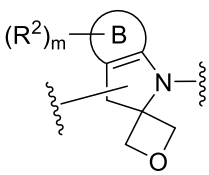
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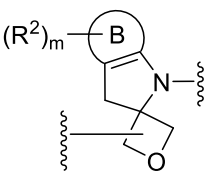
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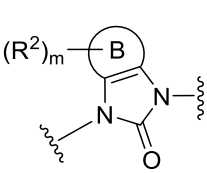
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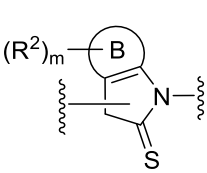
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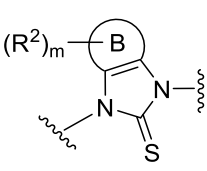
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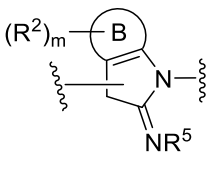
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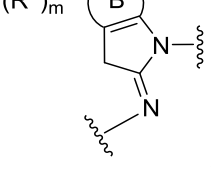
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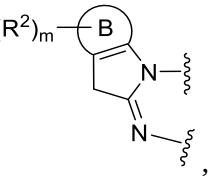
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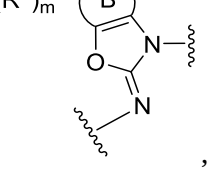
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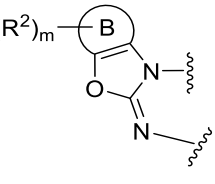
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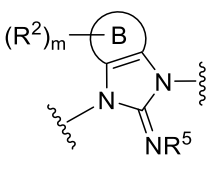
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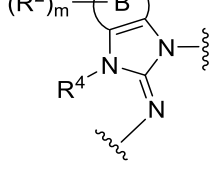
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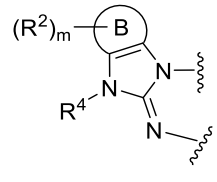
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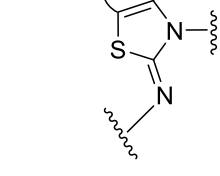
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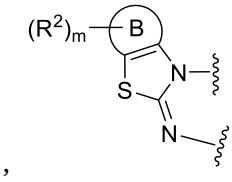
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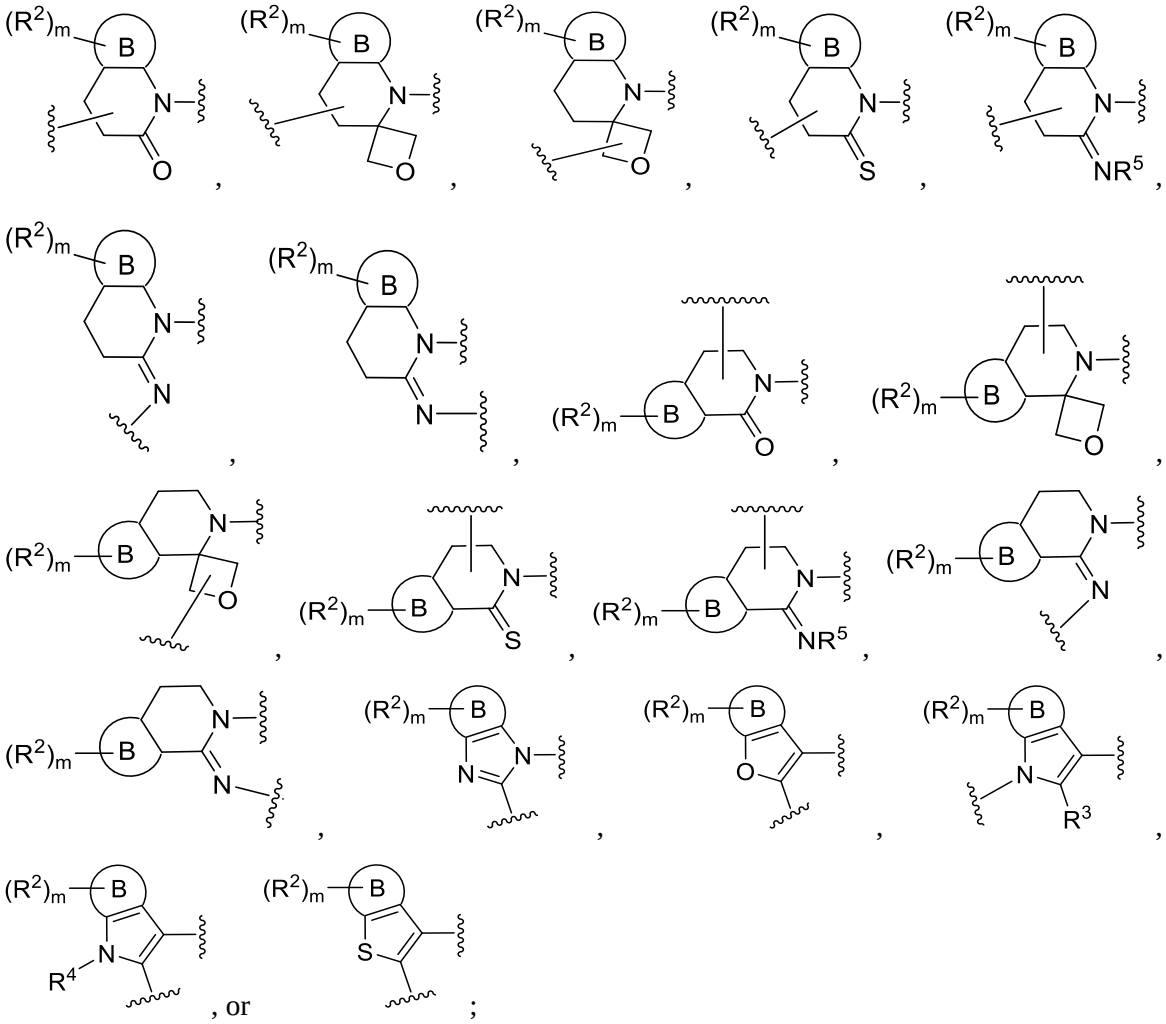


Ring B is a fused ring selected from 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, and sulfur, and 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

R^3 is selected from hydrogen, halogen, –OR, $–N(R)_2$, or –SR;

each R^4 is independently hydrogen, $–R^6$, halogen, –CN, $–NO_2$, –OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $–C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, or $–N(R)S(O)_2R$;

R^5 is hydrogen, C_{1-4} aliphatic, or –CN;

each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently

selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L^1 is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, $-C(R)_2-$, -CH(R)-, $-C(F)_2-$, -N(R)-, $-S(O)_2-$ or -(C)=CH-;

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

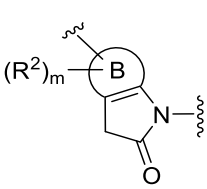
7. The compound of claim 6, wherein X^2 is a carbon atom.

8. The compound of claim 6, wherein X^3 is $–CR_2–$.

9. The compound of claim 6, wherein R^1 is hydrogen or an optionally substituted C_{1-4} aliphatic.

10. The compound of claim 6, wherein each R^2 is independently hydrogen, $–R^6$, halogen, –CN, $–NO_2$, –OR, -SR, $-N(R)_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $–C(O)NR_2$, -C(O)NROR, $-CR_2NRC(O)R$, $-CR_2NRC(O)NR_2$, -OC(O)R, $-OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)NR_2$, $–NRS(O)_2R$, or $–NRS(O)_2R$.

11. The compound of claim 6, wherein Ring A is a bicyclic or tricyclic ring selected from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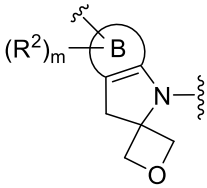
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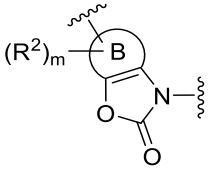
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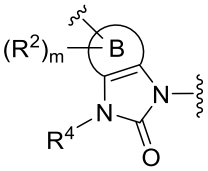
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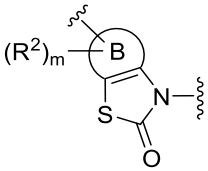
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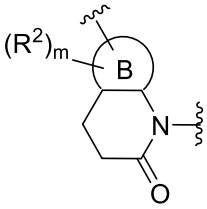
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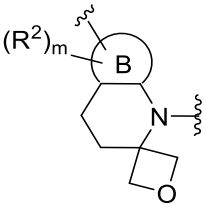
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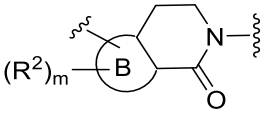
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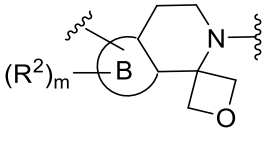
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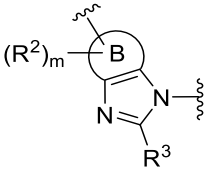
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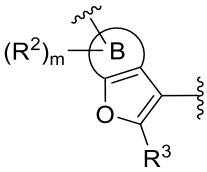
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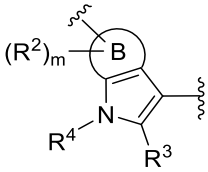
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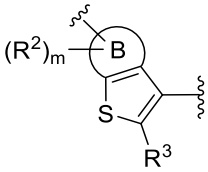
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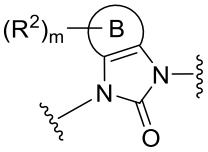
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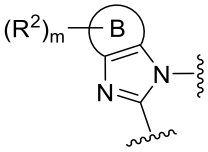
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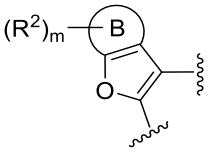
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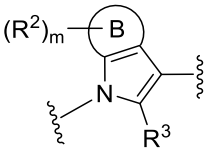
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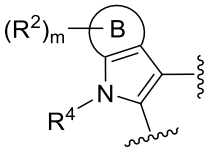
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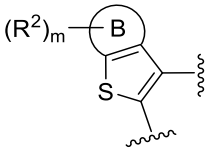
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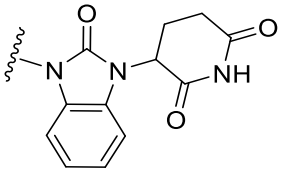
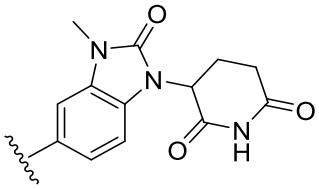
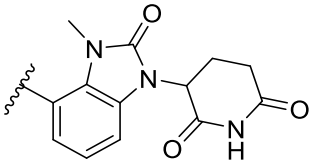
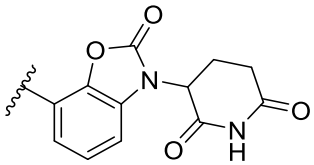
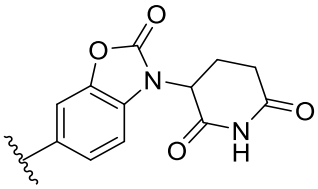
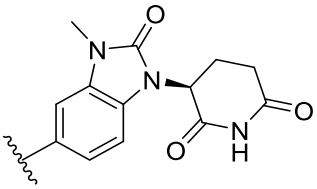
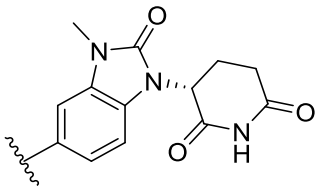
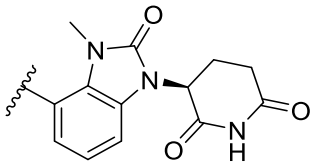
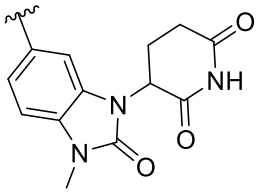
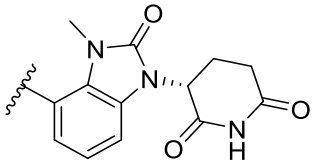
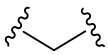
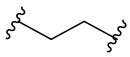
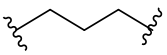
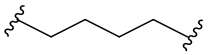
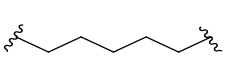
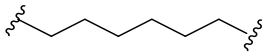
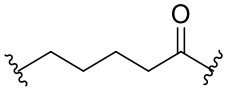
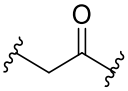
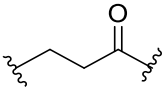
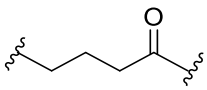
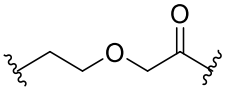
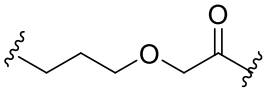
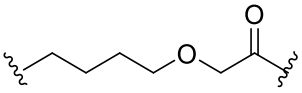
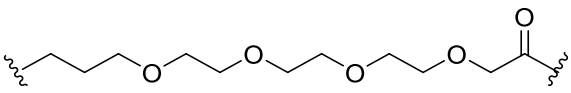
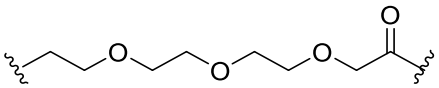
12. The compound of claim 6, wherein Ring B is a fused ring selected from 6-membered aryl or 5- to 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

13. The compound of claim 6, wherein L^1 is a covalent bond.

14. The compound of claim 6, wherein m is 0, 1, 2, or 3.

15. The compound according to claim 6, wherein the cereblon E3 ubiquitin ligase binding moiety is selected from:  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

16. The compound of any of any one of claims 1-15, wherein L is selected from a covalent bond,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,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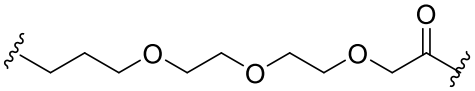
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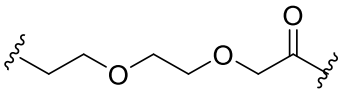
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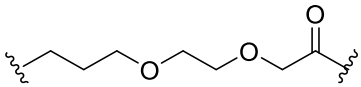
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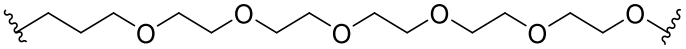
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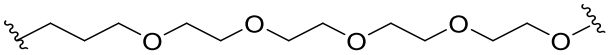
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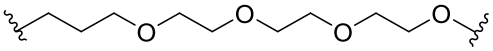
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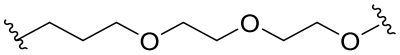
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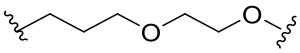
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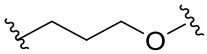
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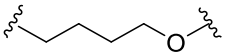
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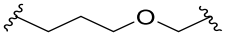
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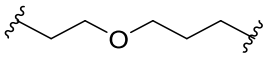
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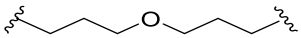
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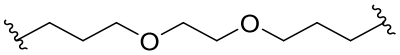
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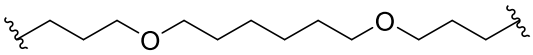
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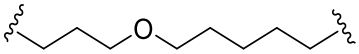
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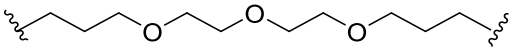
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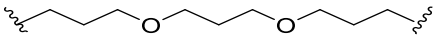
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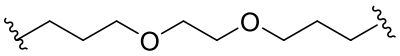
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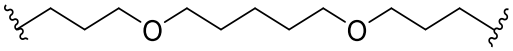
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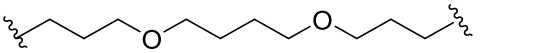
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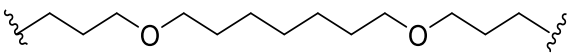
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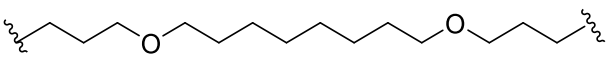
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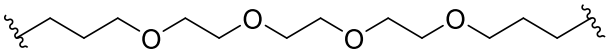
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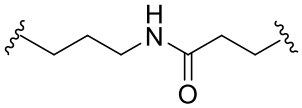
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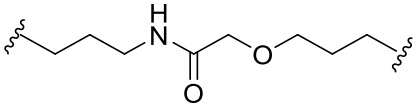
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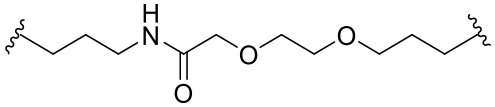
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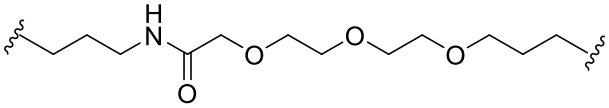
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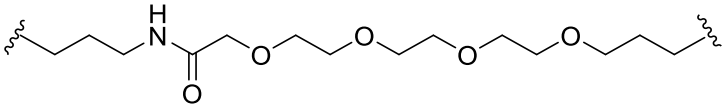
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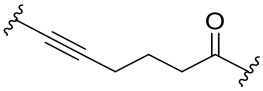
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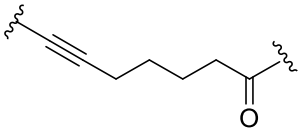
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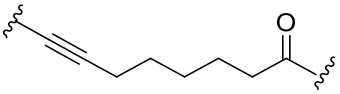
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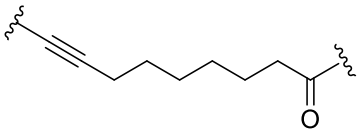
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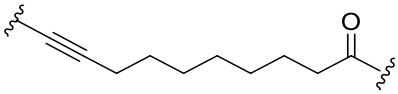
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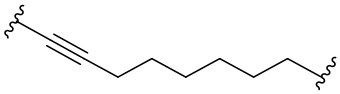
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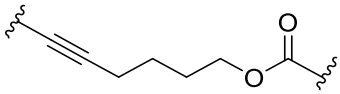
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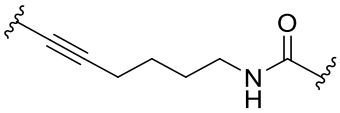
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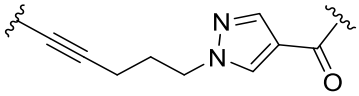
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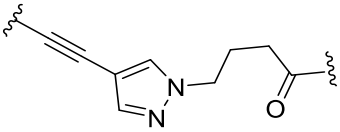
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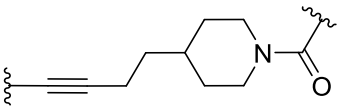
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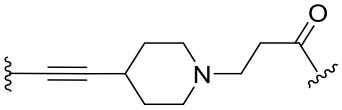
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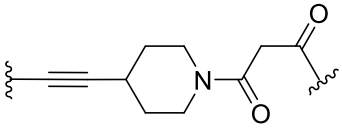
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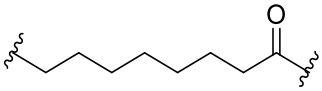
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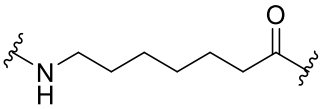
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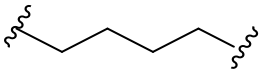
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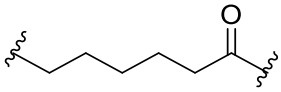
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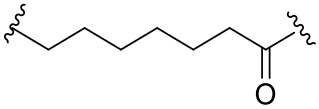
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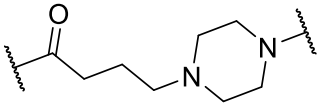
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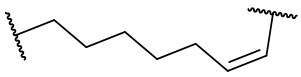
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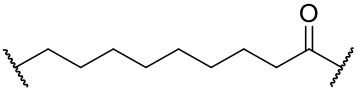
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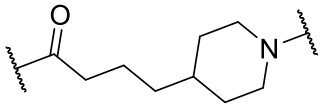
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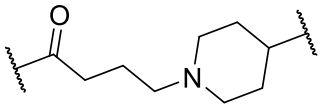
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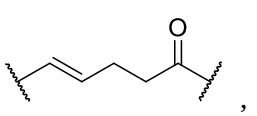
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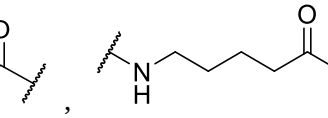
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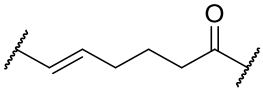
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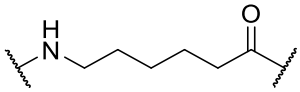
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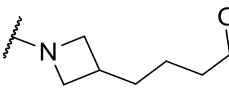
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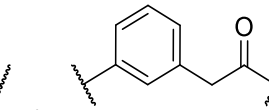
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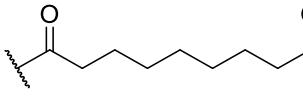
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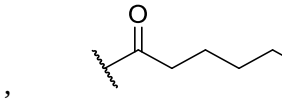
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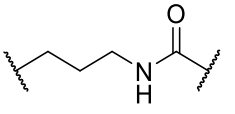
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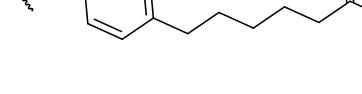
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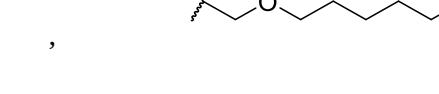
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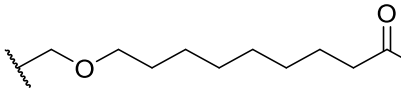
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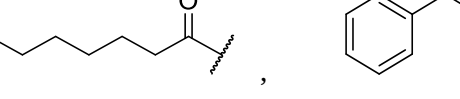
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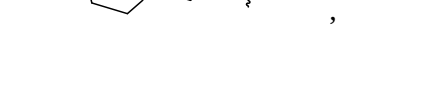
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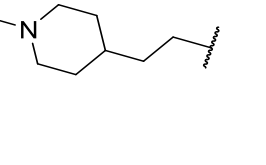
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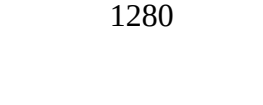
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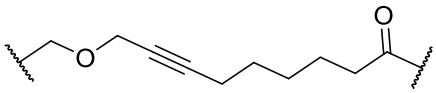
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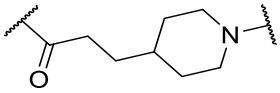
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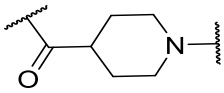
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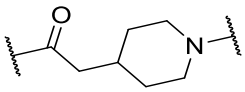
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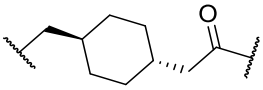
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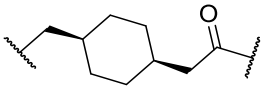
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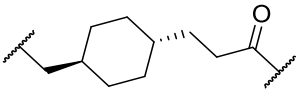
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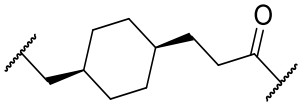
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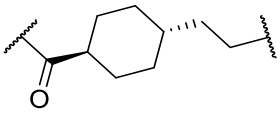
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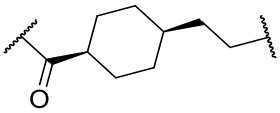
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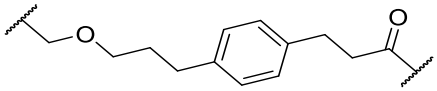
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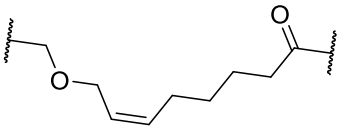
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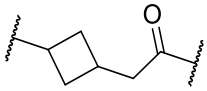
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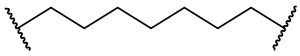
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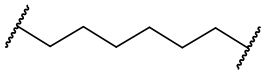
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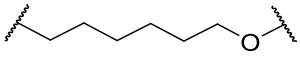
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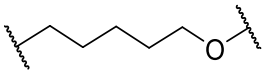
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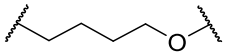
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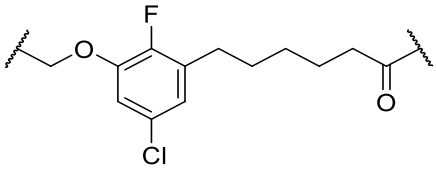
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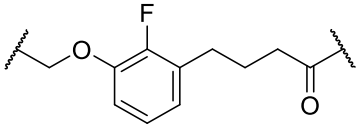
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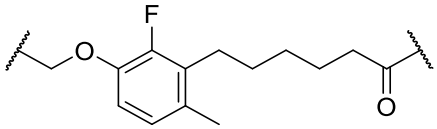
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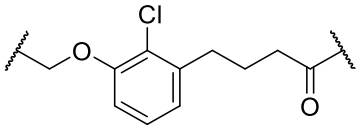
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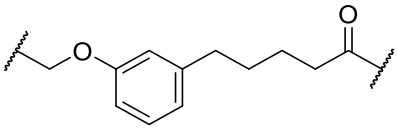
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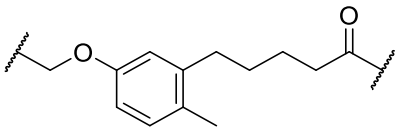
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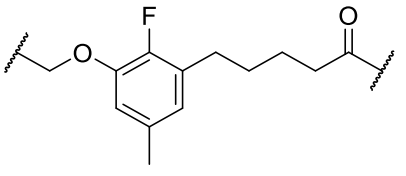
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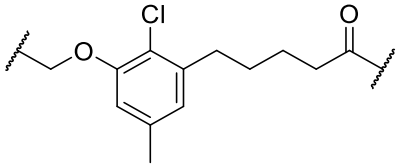
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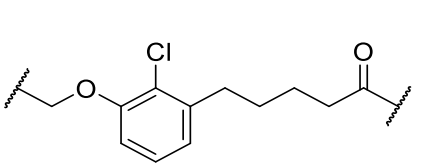
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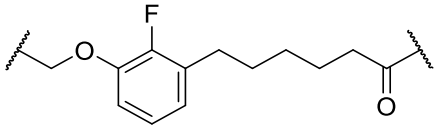
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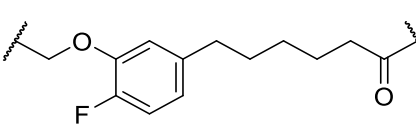
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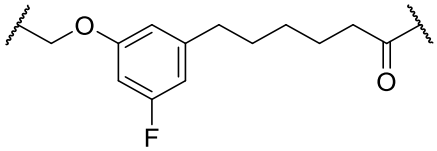
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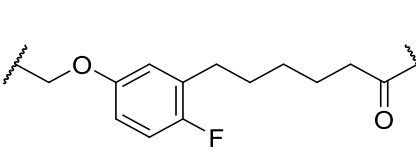
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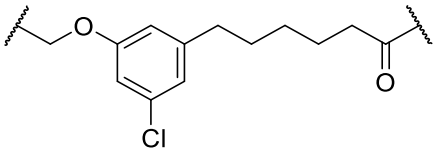
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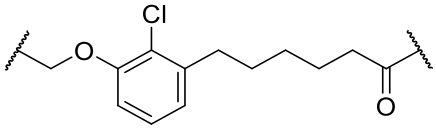
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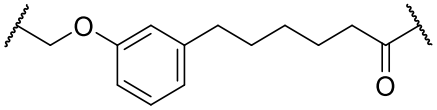
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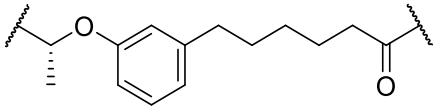
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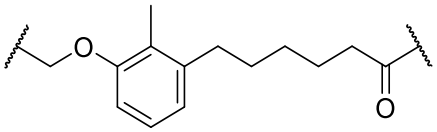
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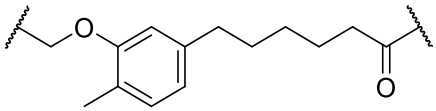
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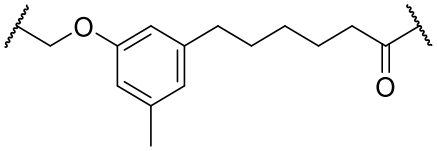
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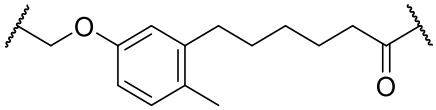
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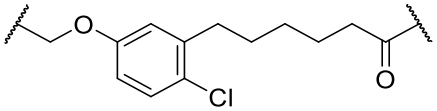
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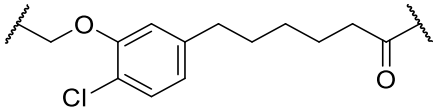
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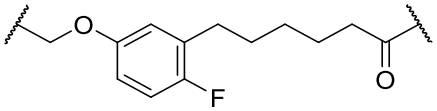
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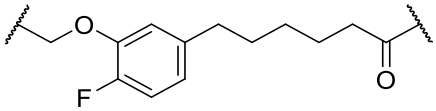
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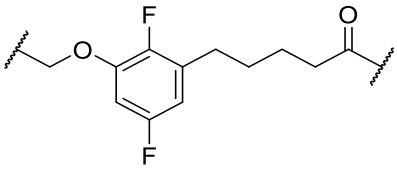
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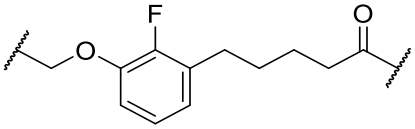
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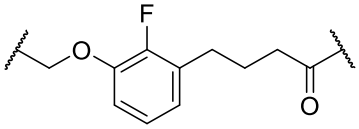
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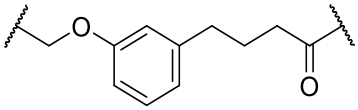
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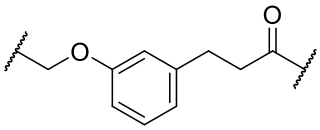
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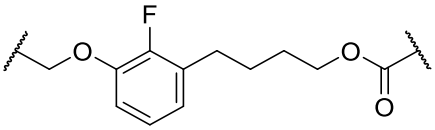
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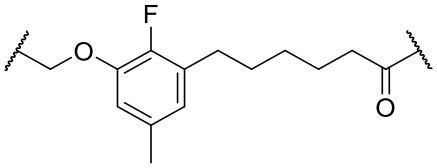
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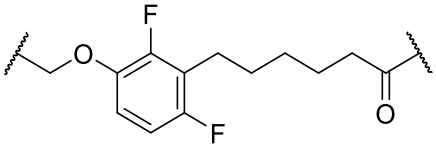
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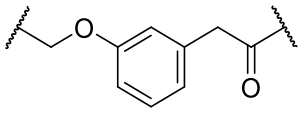
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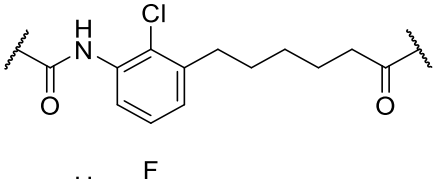
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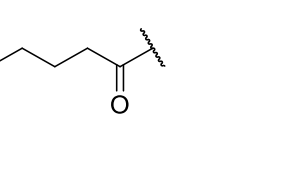
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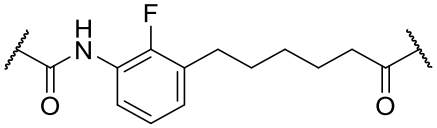
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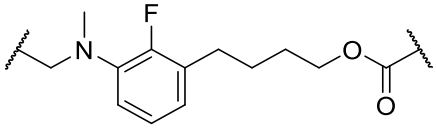
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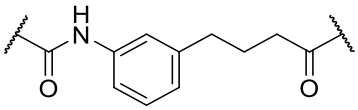
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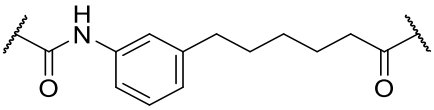
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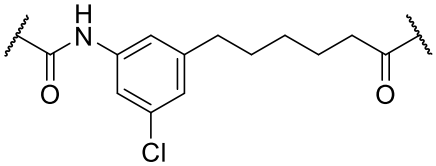
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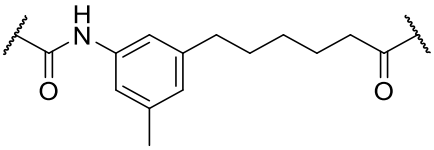
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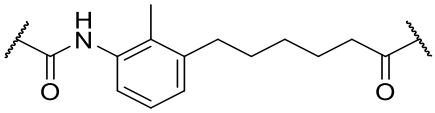
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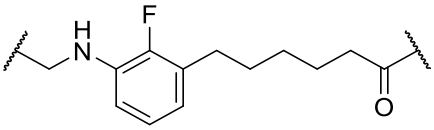
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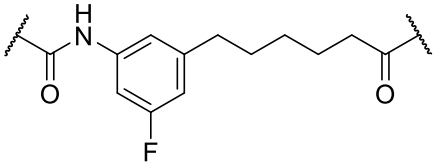
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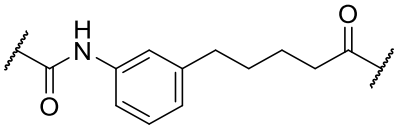
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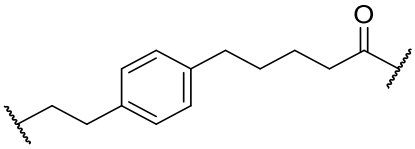
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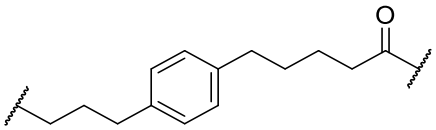
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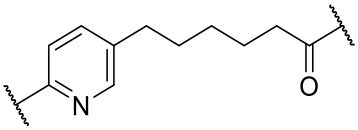
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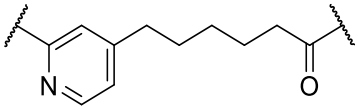
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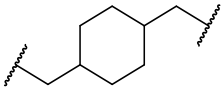
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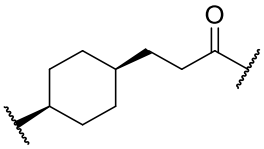
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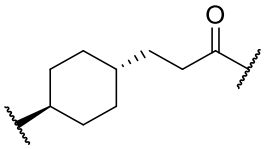
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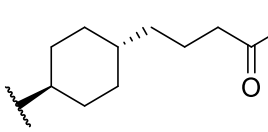
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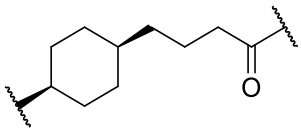
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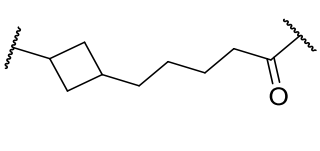
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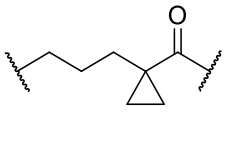
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17. The compound of any one of claims 1-2 and 6-16, wherein said compound is selected from:

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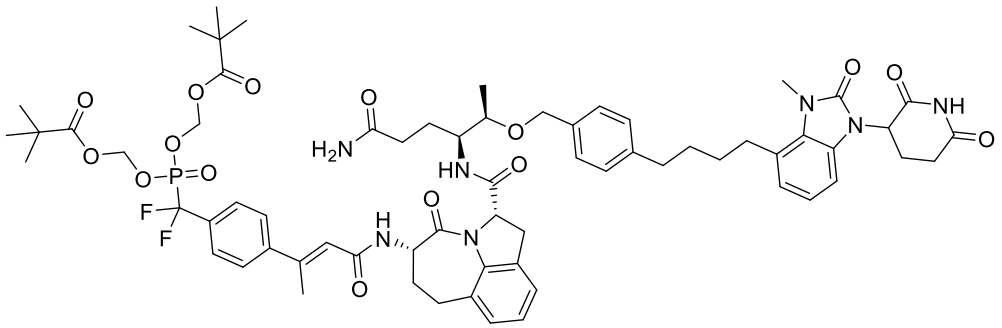

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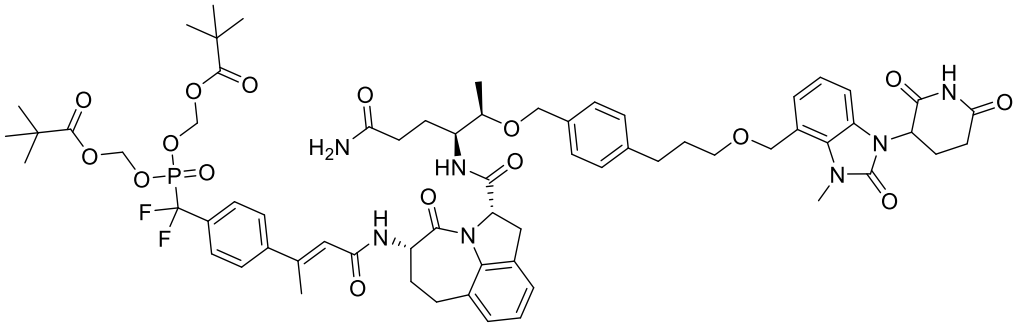

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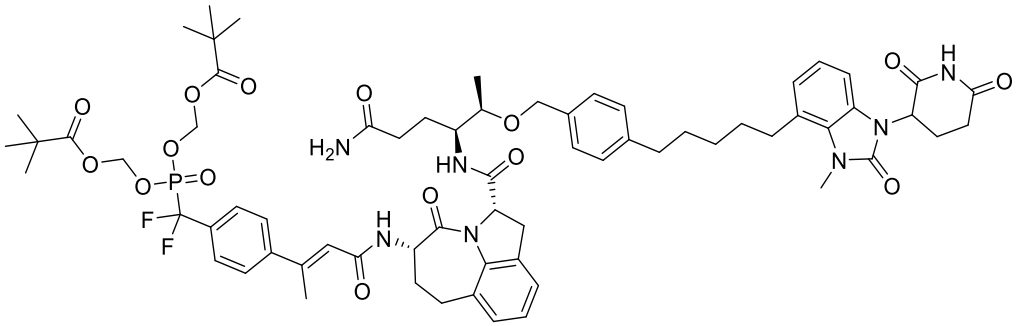

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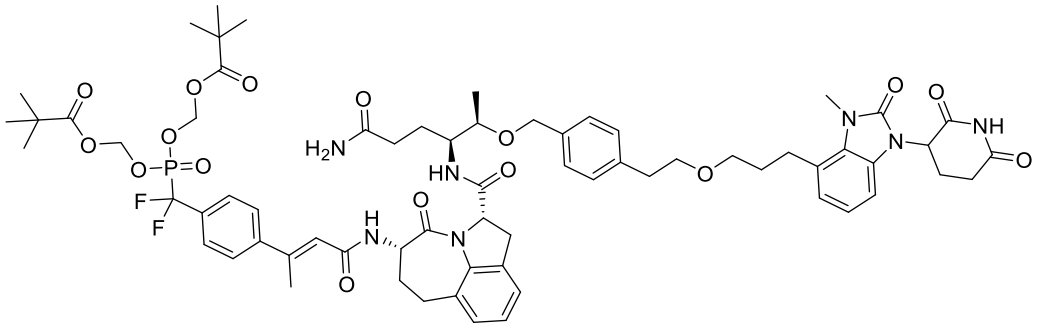

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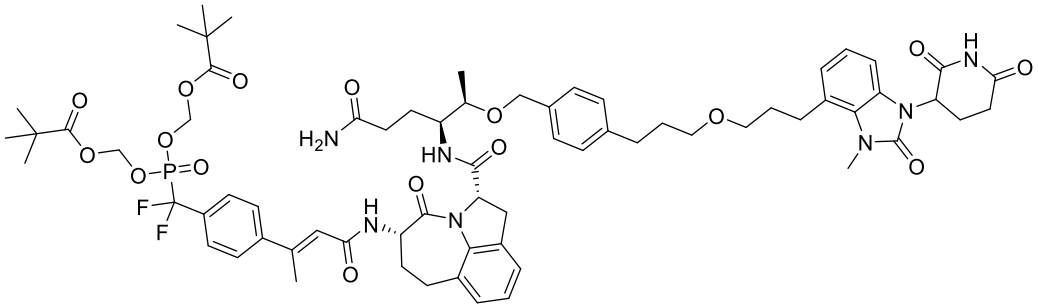

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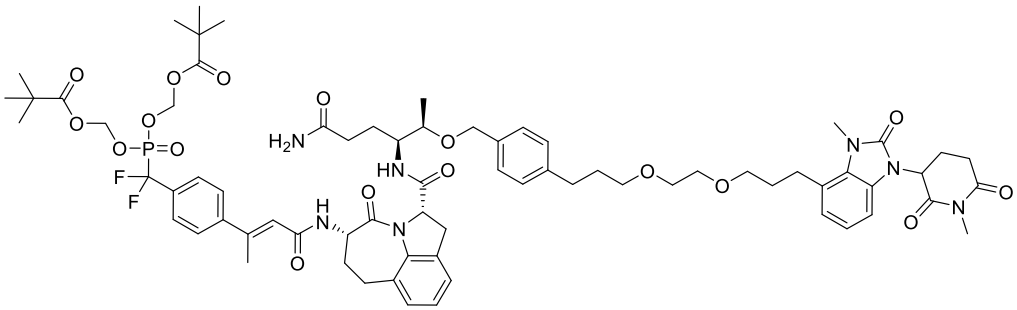

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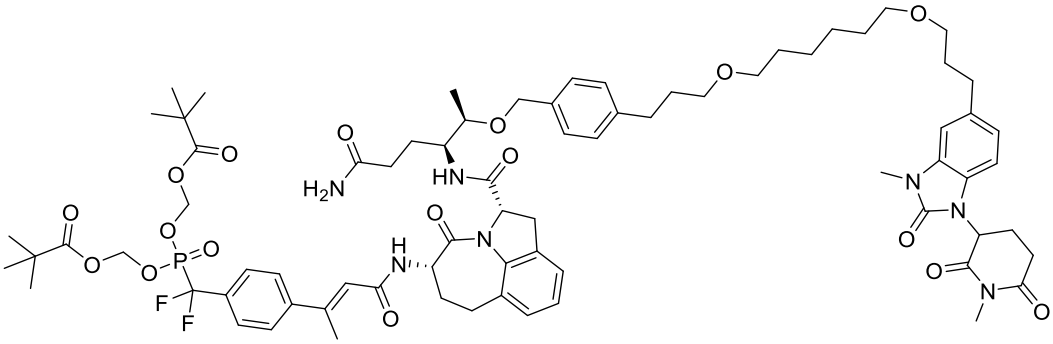

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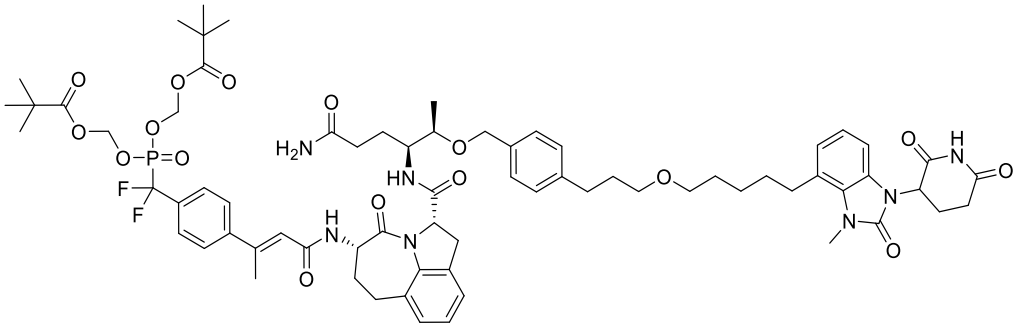

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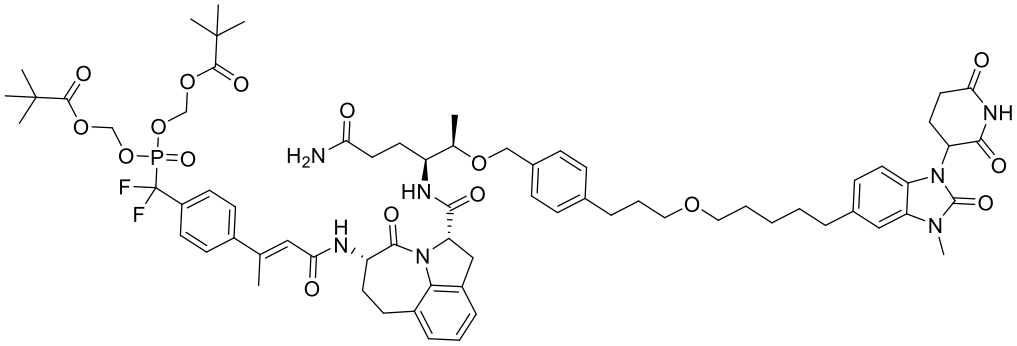

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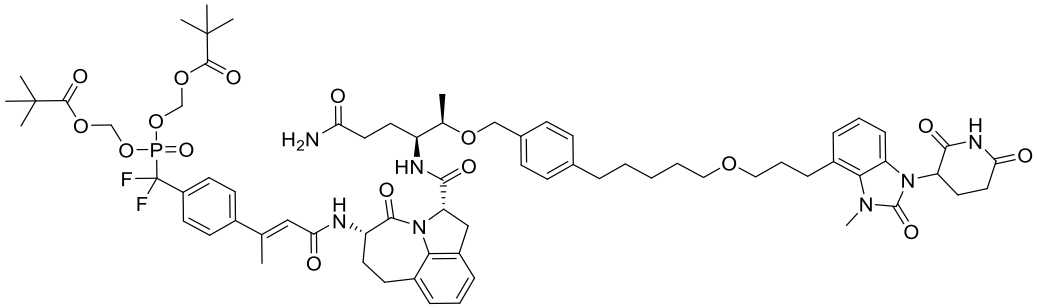

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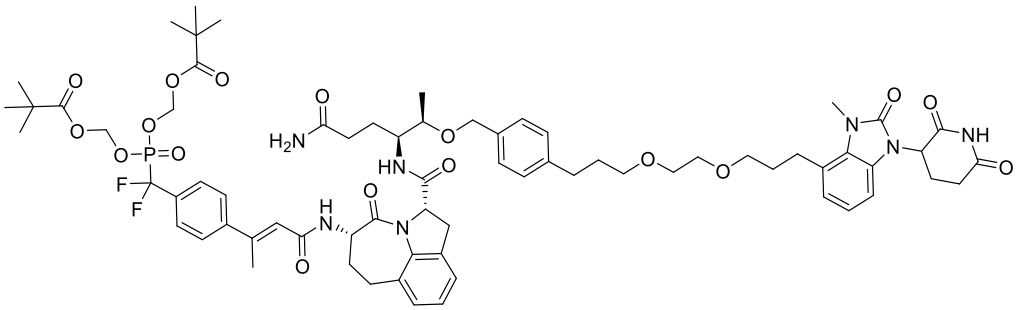

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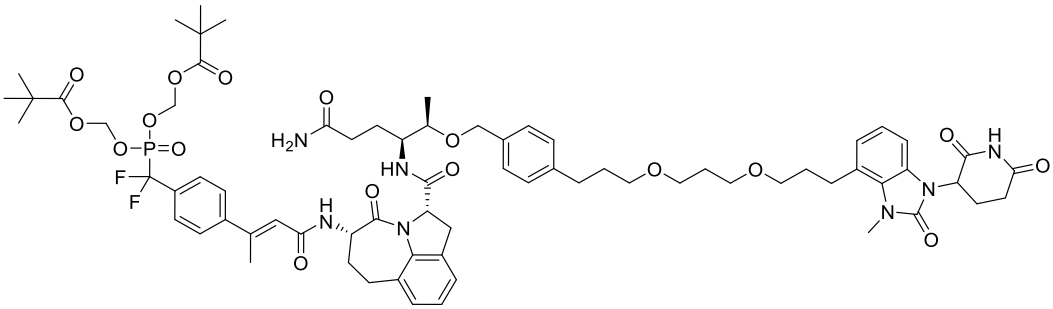

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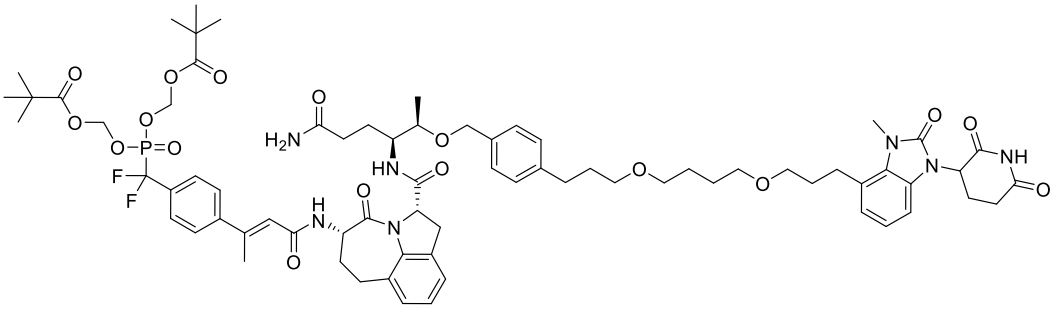

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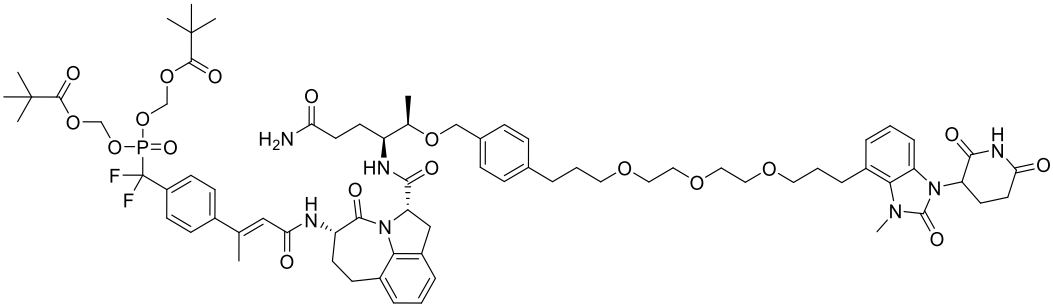

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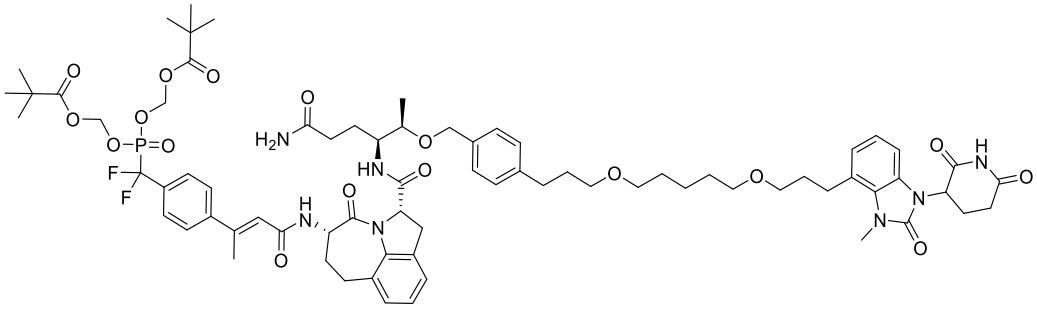

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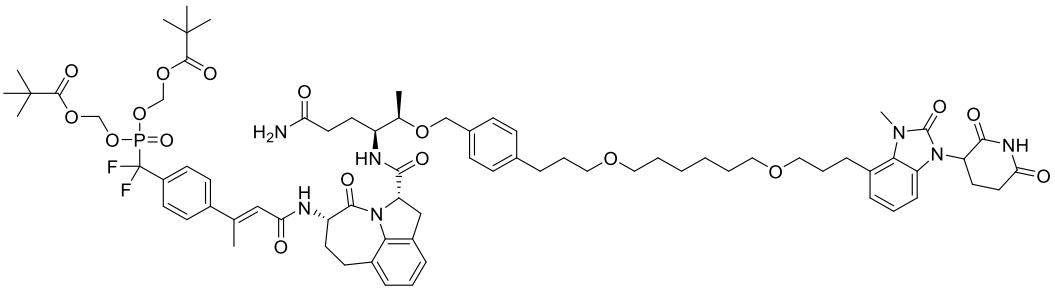

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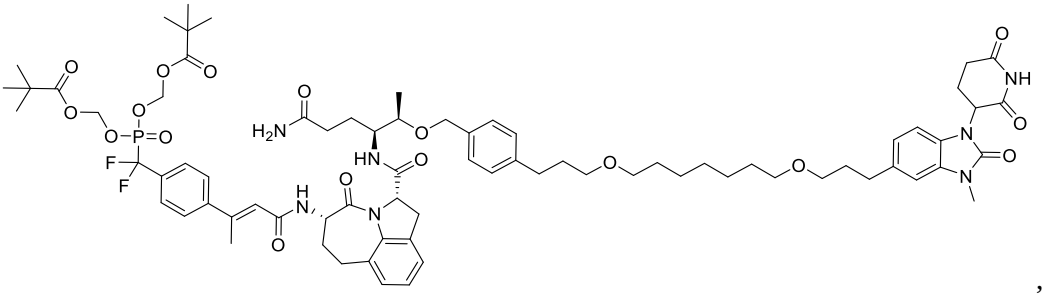

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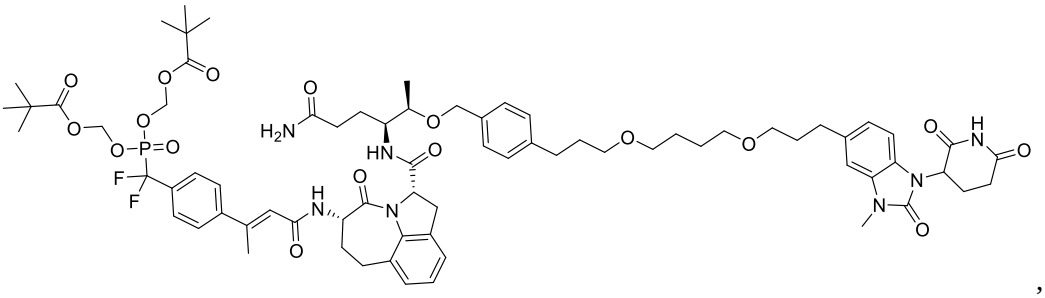

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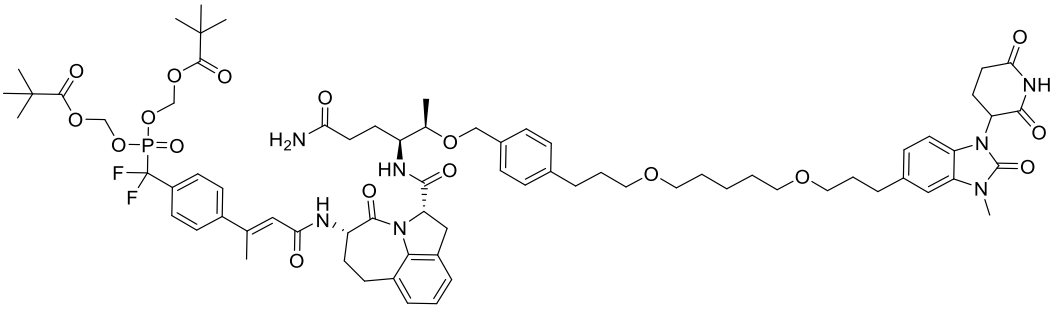

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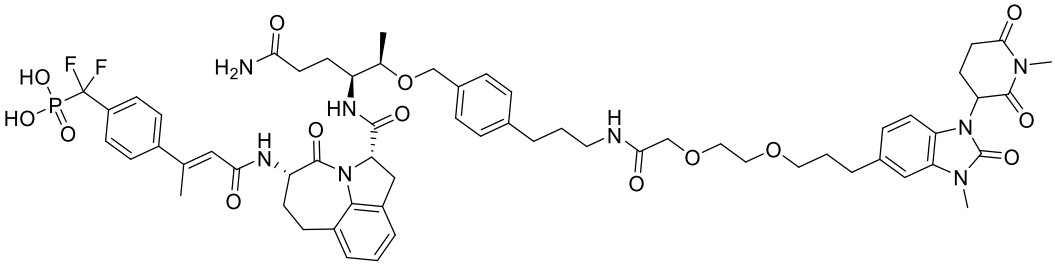

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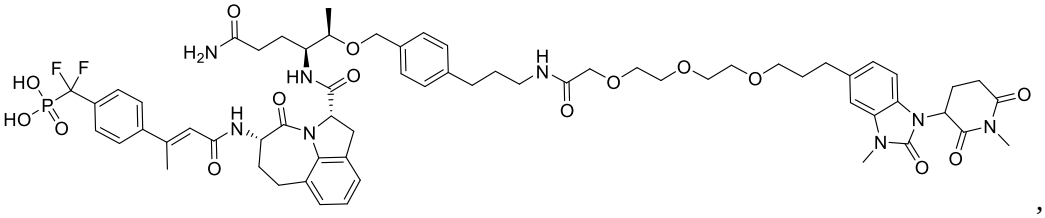

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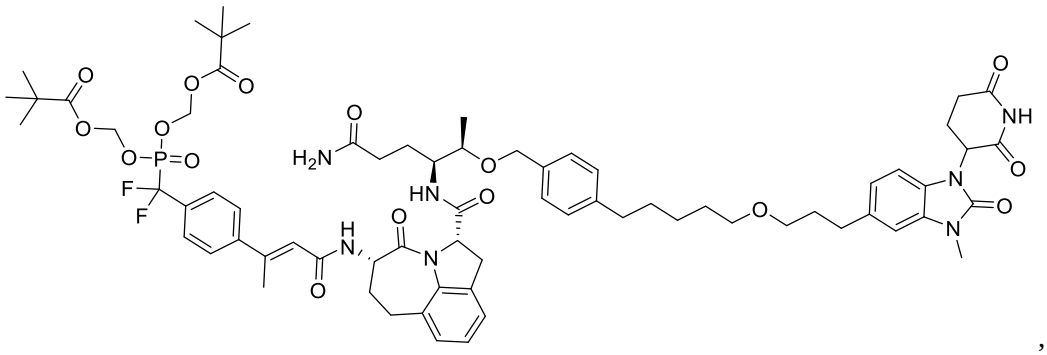

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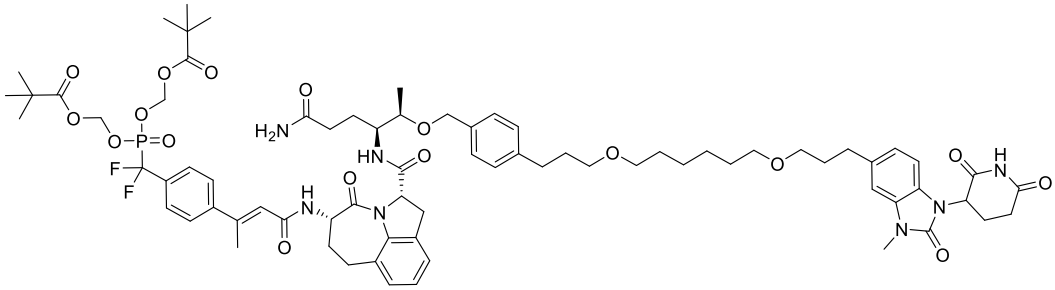

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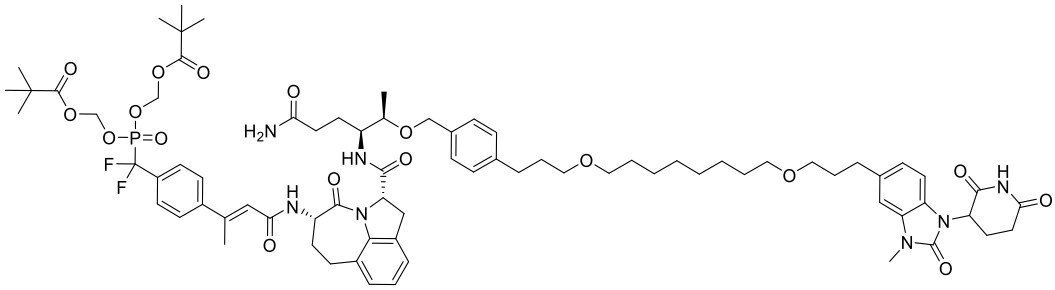

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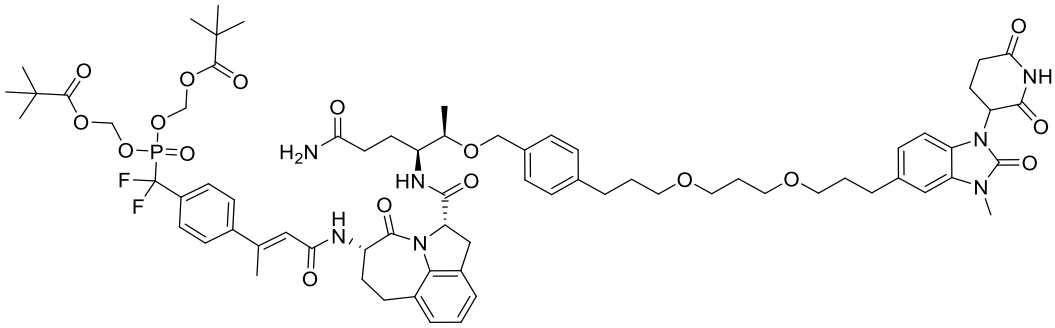

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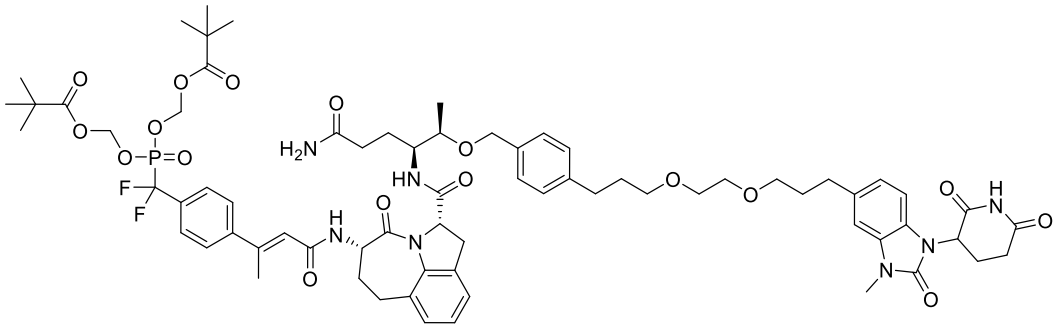

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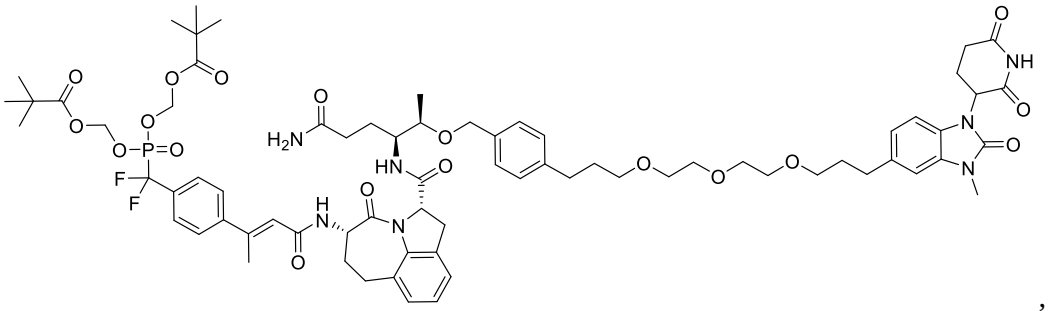

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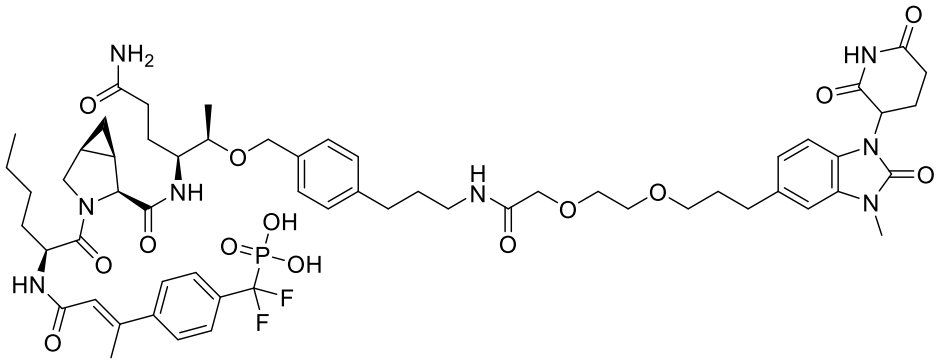

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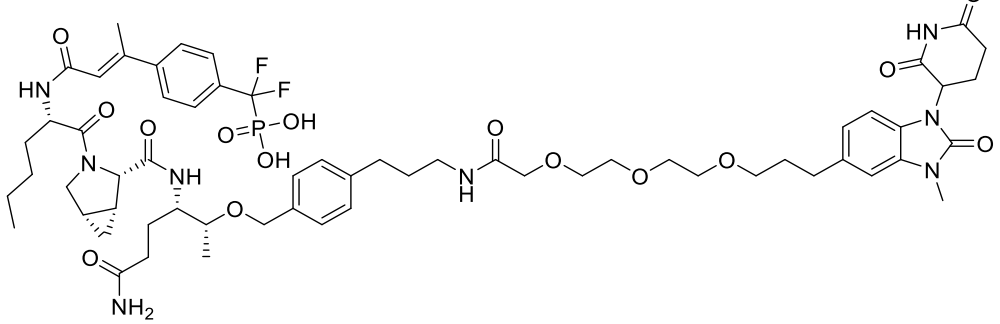

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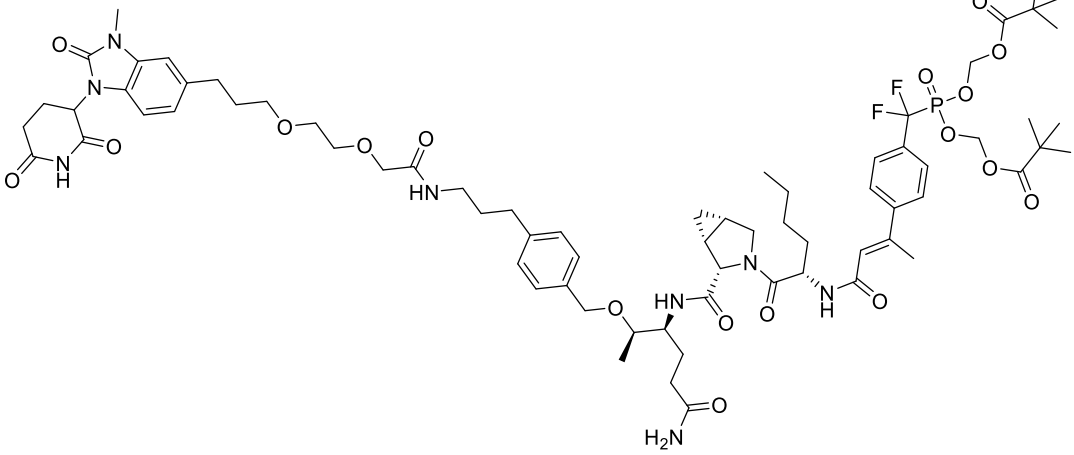

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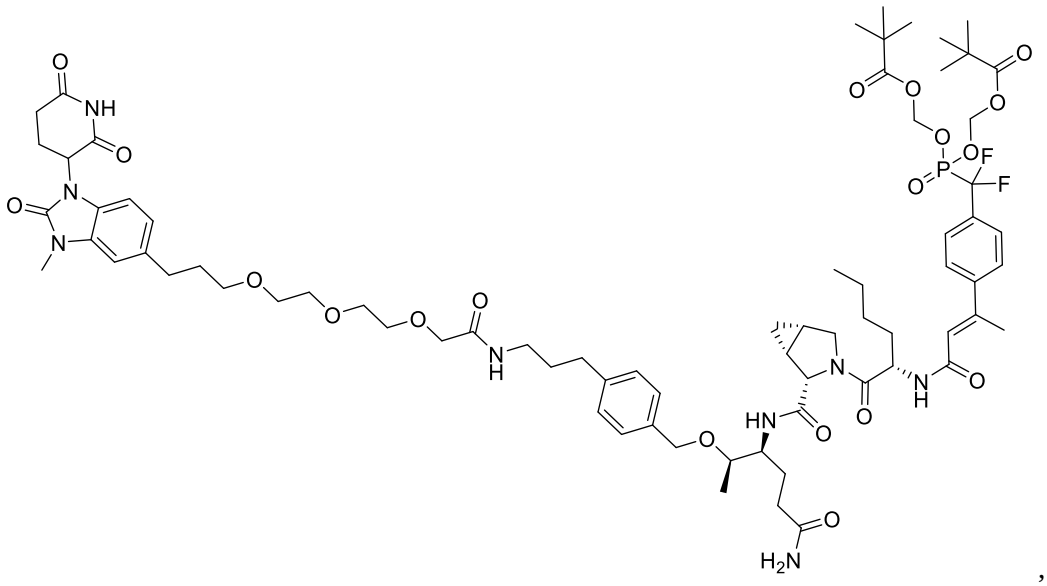

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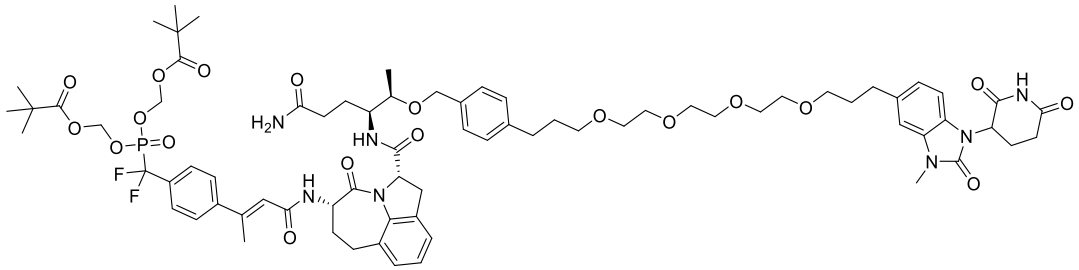

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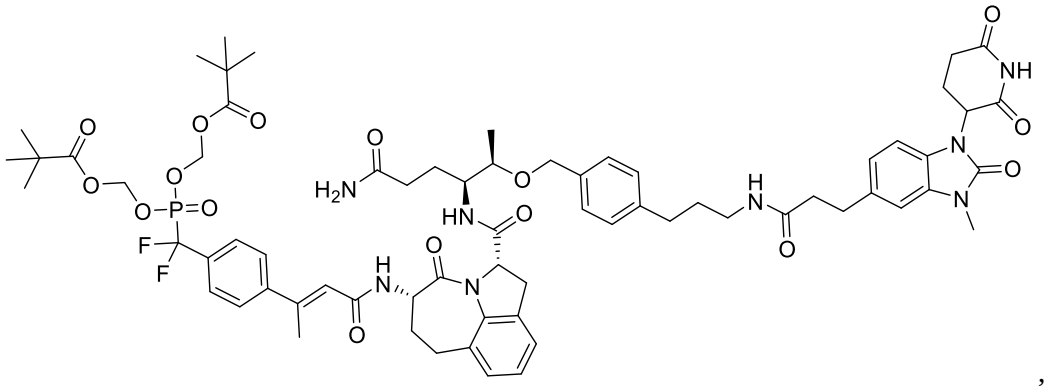

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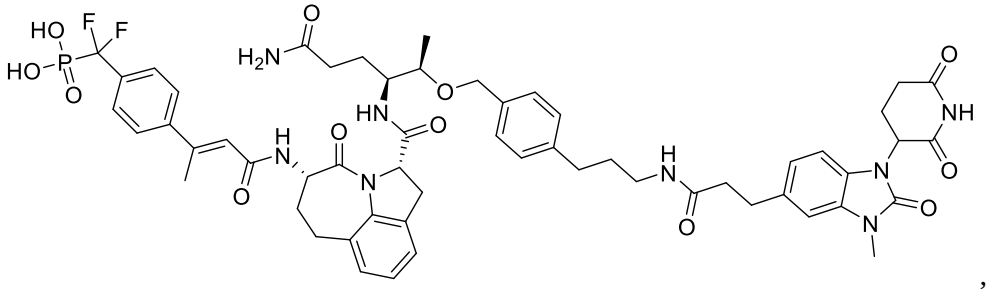

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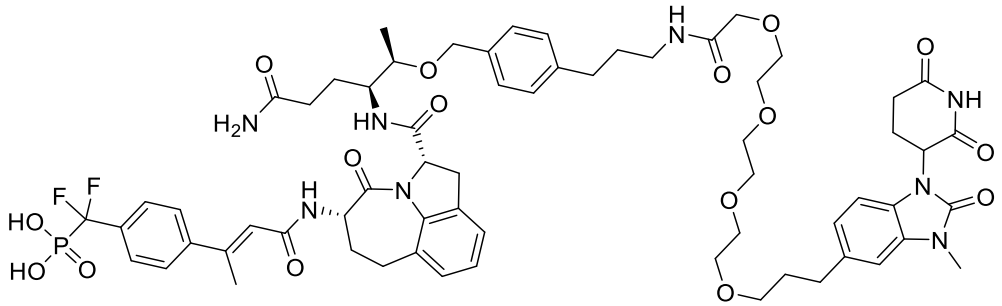

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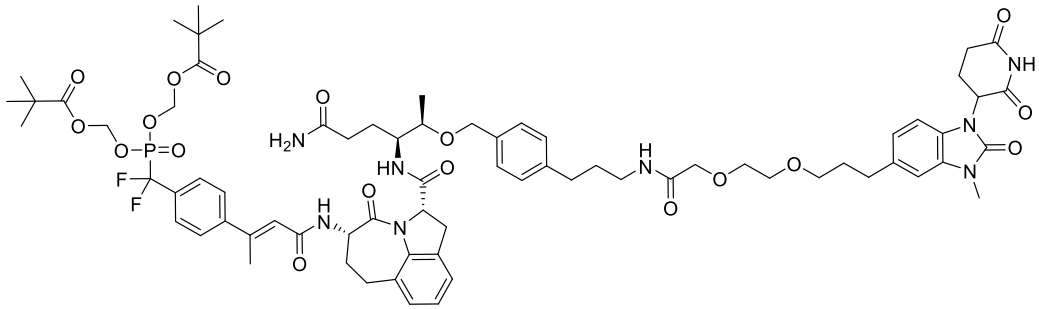

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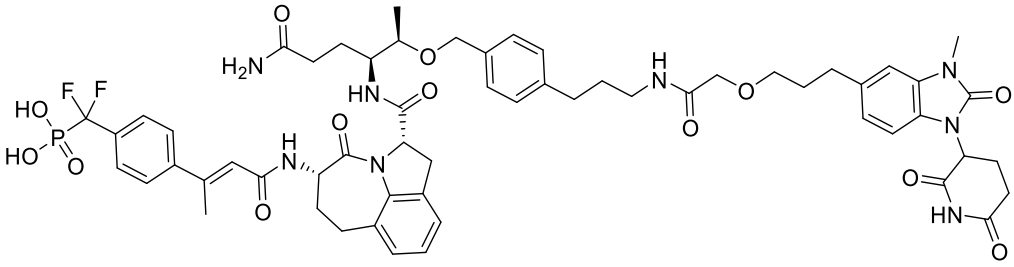

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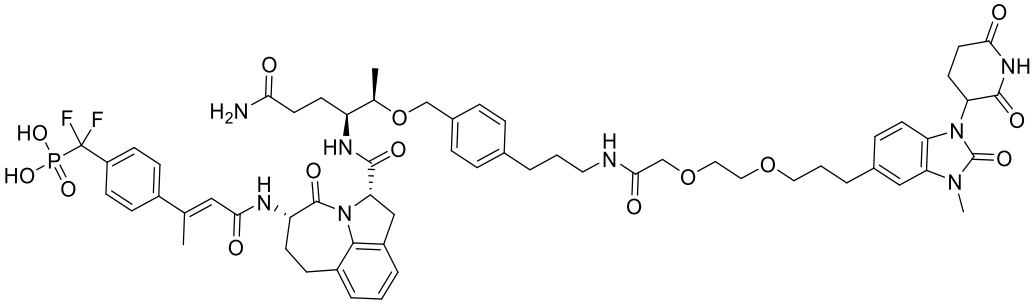

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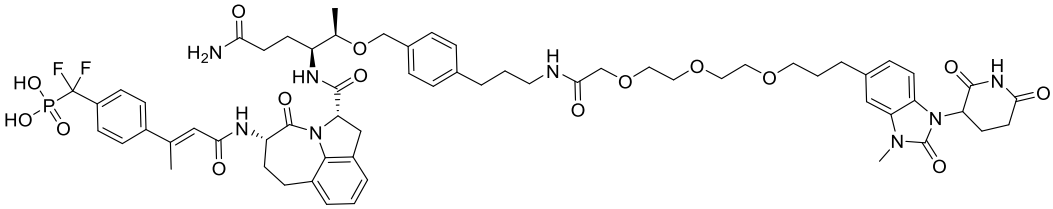

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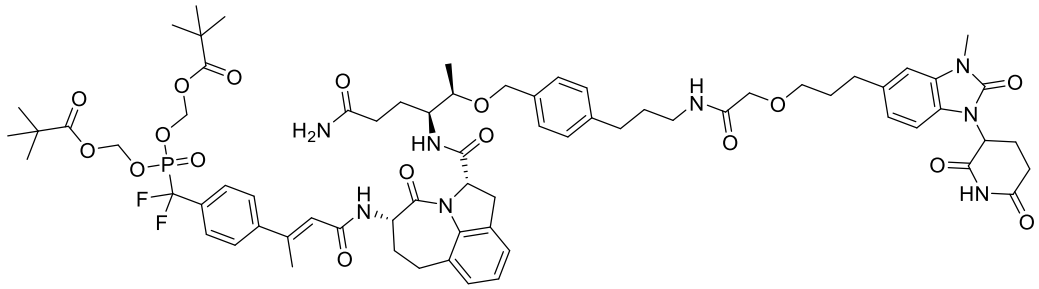

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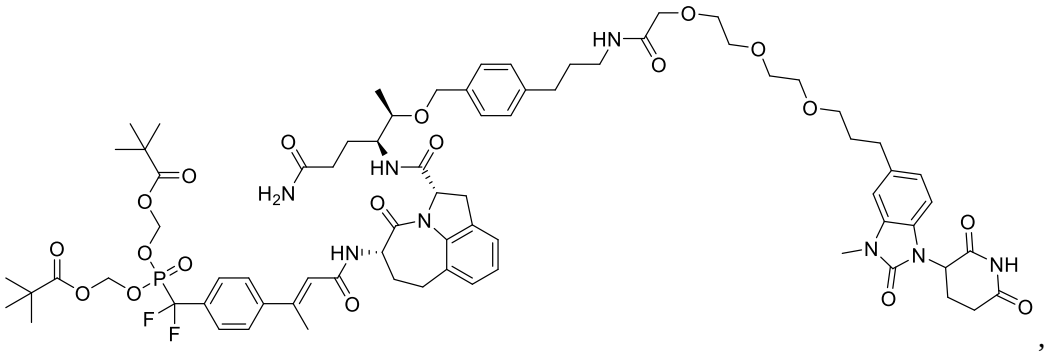

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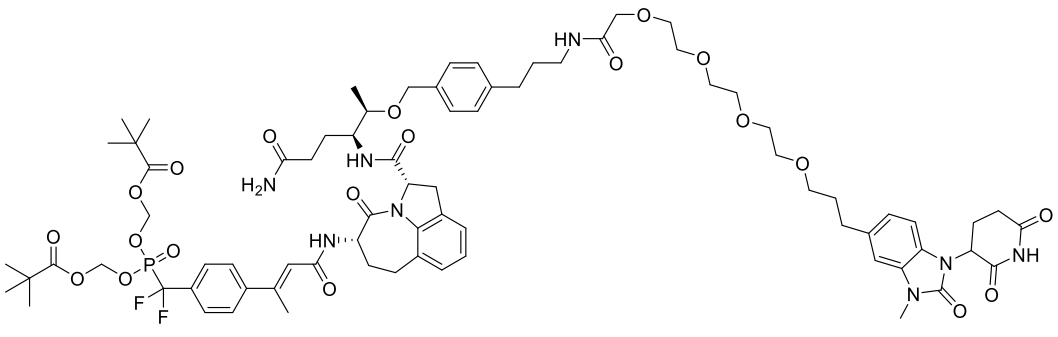

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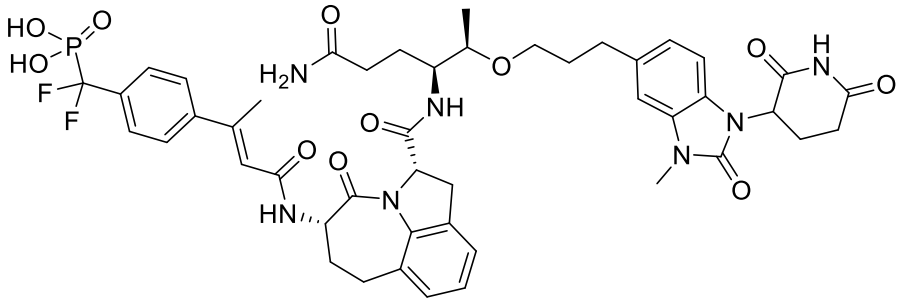

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or a pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition comprising a compound of any one of claims 1-17, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

19. The pharmaceutical composition according to claim 18, further comprising an additional therapeutic agent.

20. A compound according to any one of claims 1-17, or a pharmaceutical composition thereof, for use in treating a disorder, disease, or condition in a patient; wherein the disorder, disease or condition is selected from a cancer, a neurodegenerative disease, a viral disease, an autoimmune disease, an inflammatory disorder, a hereditary disorder, a hormone-related disease, a metabolic disorder, an immunodeficiency disorder, a destructive bone disorder, a proliferative disorder, an infectious disease, thrombin-induced platelet aggregation, liver disease, a pathologic immune condition involving T cell activation, a cardiovascular disorder, and a CNS disorder.

21. Use of a compound according to any one of claims 1-17, or a pharmaceutical composition thereof, in the manufacture of a medicament for treating a disorder, disease, or condition in a patient; wherein the disorder, disease or condition is selected from a cancer, a neurodegenerative disease, a viral disease, an autoimmune disease, an inflammatory disorder, a hereditary disorder, a hormone-related disease, a metabolic disorder, an immunodeficiency disorder, a destructive bone disorder, a proliferative disorder, an infectious disease, thrombin-induced platelet aggregation, liver disease, a pathologic immune condition involving T cell activation, a cardiovascular disorder, and a CNS disorder.

22. The compound for use of claim 20, or the use according to claim 21, wherein an additional therapeutic agent is to be futher administered.

23. The compound for use, or the use according to any one of claims 20-22, wherein the cancer is selected from glioma, breast cancer, prostate cancer, head and neck squamous cell carcinoma, skin melanomas, ovarian cancer, malignant peripheral nerve shealth tumors (MPNST), pancreatic cancer, non-small cell lung cancer, urothelial cancer, liver cancer, bile duct cancer, kidney cancer, colon cancer, esophageal cancer, gastric cancer, gastrointestinal stromal tumors, and hematological malignancies.

24. The compound for use, or the use according to any one of claims 20-22, wherein autoimmune disease is selected from systemic sclerosis, idiopathic pulmonary fibrosis, inflammatory bowel disease, atopic dermatitis, rheumatoid arthritis, acute graft versus host disease, chronic graft versus host disease, and tissue fibrosis diseases.

25. The compound for use, or the use according to any one of claims 20-22, wherein the hematologic malignancy is selected from large granular lymphocytic (LGL) leukemia (T and NK cell), cutaneous T cell lymphoma (CTCL), peripheral T cell lymphomas (PTCL), anaplastic large-cell lymphoma (ALCL), diffuse large B cell lymphoma (DLBCL), acute myelogenous leukemia, multiple myeloma, and myelofibrosis.