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THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS ***US62/798,374***

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COMPOUNDS AND USES THEREOF

Background

Disorders can be affected by the BAF complex. BRD9 is a component of the BAF complex. The present invention relates to useful compositions and methods for the treatment of BAF complex-related disorders, such as cancer and infection.

Summary

Bromodomain-containing protein 9 (BRD9) is a protein encoded by the BRD9 gene on chromosome 5. BRD9 is a component of the BAF (BRG1- or BRM-associated factors) complex, a SWI/SNF ATPase chromatin remodeling complex, and belongs to family IV of the bromodomain-containing proteins. BRD9 is present in several SWI/SNF ATPase chromatin remodeling complexes and is upregulated in multiple cancer cell lines. Accordingly, agents that reduce the levels and/or activity of BRD9 may provide new methods for the treatment of disease and disorders, such as cancer and infection. The inventors have found that depleting BRD9 in cells results in the depletion of the SS18-SSX fusion protein in those cells. The SS18-SSX fusion protein has been detected in more than 95% of synovial sarcoma tumors and is often the only cytogenetic abnormality in synovial sarcoma. Additionally, evidence suggests that the BAF complex is involved in cellular antiviral activities. Thus, agents that degrade BRD9 (e.g., compounds) are useful in the treatment of disorders (e.g., cancers or infections) related to BAF, BRD9, and/or SS18-SSX.

The present disclosure features compounds and methods useful for treating BAF-related disorders (e.g., cancer or infection).

In an aspect, the disclosure features a compound having the structure of **Formula I**:

A-L-B

Formula I,

where

A is a BRD9 binding moiety;

B is a degradation moiety; and

L has the structure of **Formula II**:

$$A^1–(E^1)–(F^1)–(C^3)_m–(E^3)_n–(F^2)_{o1}–(F^3)_{o2}–(E^2)_p–A^2,$$

Formula II

where

A^1 is a bond between the linker and A;

A^2 is a bond between B and the linker;

each of m, n, o1, o2, and p is, independently, 0 or 1;

each of E^1 and E^2 is, independently, O, S, NR^N, optionally substituted C_{1-10} alkyl, optionally substituted C_{2-10} alkenyl, optionally substituted C_{2-10} alkynyl, optionally substituted C_2-C_{10} polyethylene glycol, or optionally substituted C_{1-10} heteroalkyl;

E^3 is O, S, or NR^N;

each R^N is, independently, H, optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, optionally substituted C_{2-6} heterocyclyl, optionally substituted C_{6-12} aryl, or optionally substituted C_{1-7} heteroalkyl;

C^3 is carbonyl, thiocarbonyl, sulphonyl, or phosphoryl; and

each of F^1, F^2, and F^3 is, independently, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heteroaryl, or a pharmaceutically acceptable salt thereof.

In some embodiments, the linker has the structure of **Formula IIa**:

$$A^1–(E^1)–(F^1)–(C^3)_m–(E^2)_p–A^2.$$

Formula IIa

In some embodiments, the linker has the structure of **Formula IIb**:

$$A^1–(E^1)–(F^1)–(E^2)_p–A^2.$$

Formula IIb

In some embodiments, the linker has the structure of **Formula IIc**:

$$A^1–(E^1)–(F^1)–A^2.$$

Formula IIc

In some embodiments, the linker has the structure of **Formula IId**:

$$A^1–(E^1)–(F^1)–(C^3)_m–(F^2)_{o1}–A^2.$$

Formula IId

In some embodiments, the linker has the structure of **Formula IIe** :

$$A^1–(E^1)–(F^1)–(E^3)_n–(F^2)_{o1}–(E^2)_p–A^2.$$

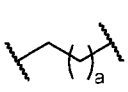
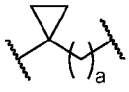
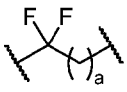
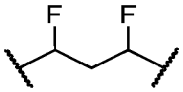
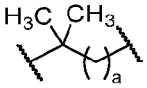
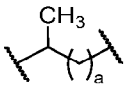
Formula IIe

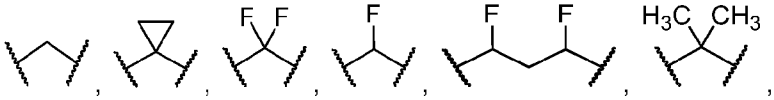
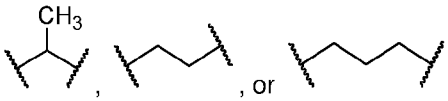
In some embodiments, each of E^1 and E^2 is, independently, NR^N, optionally substituted C_{1-10} alkyl, optionally substituted C_2-C_{10} polyethylene glycol, or optionally substituted C_{1-10} heteroalkyl.

In some embodiments, E^3 is O.

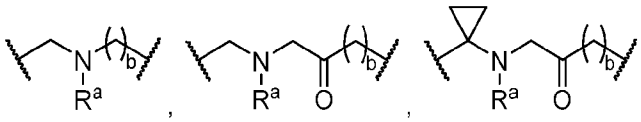
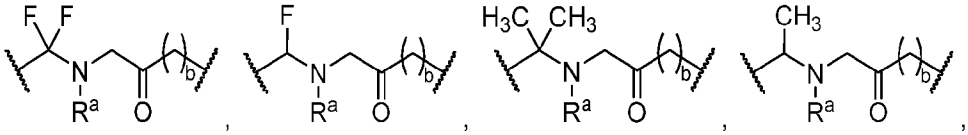
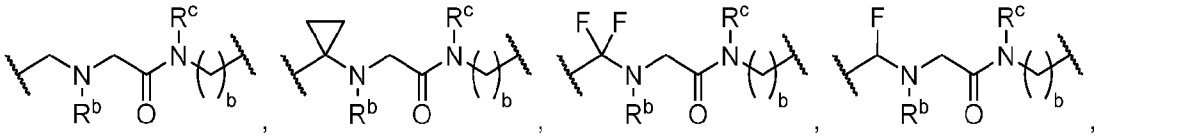
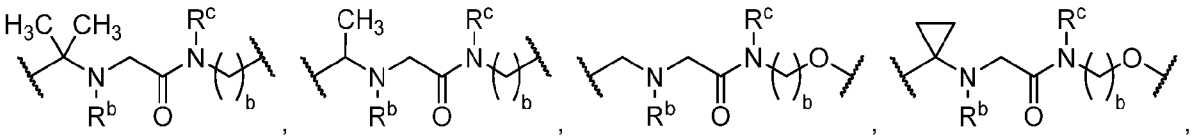
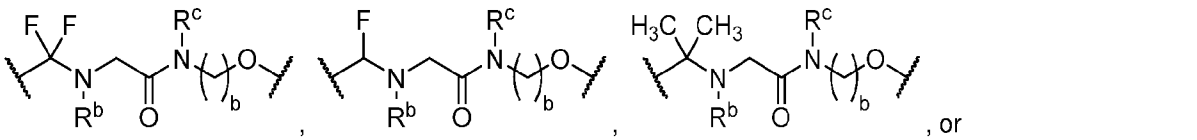
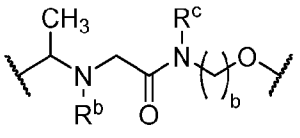
In some embodiments, each R^N is, independently, H or optionally substituted C_{1-4} alkyl.

In some embodiments, each R^N is, independently, H or methyl.

In some embodiments, E^1 is  ,  ,  , ,  ,  , or  , where a is 0, 1, 2, 3, 4, or 5.

In some embodiments, E^1 is  ,  , or .

In some embodiments, E^1 is .

In some embodiments, E^1 is  ,  ,  ,  , ,  , , , , , or  ,

where

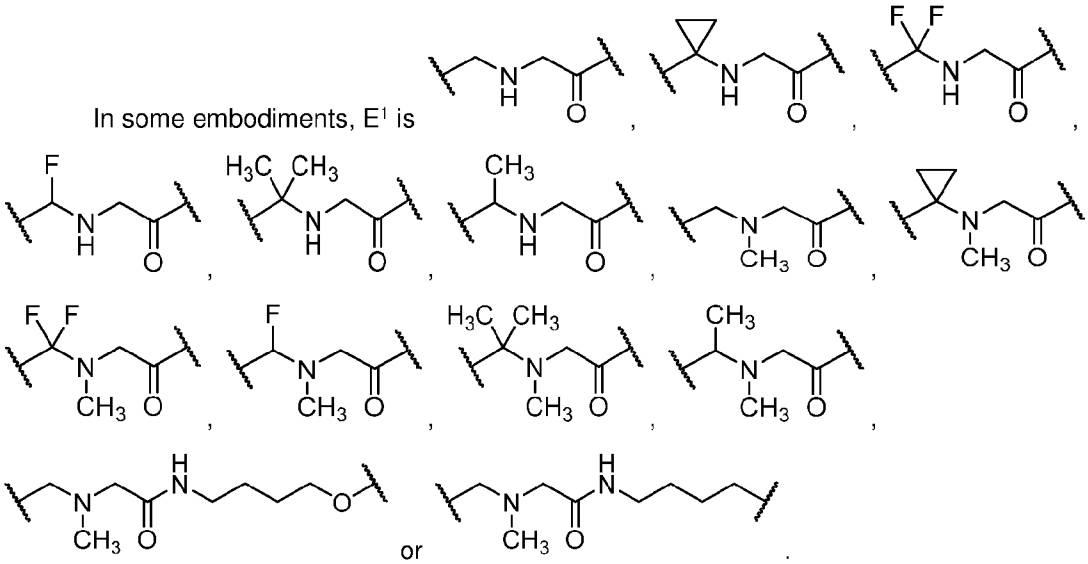
b is 0, 1, 2, 3, 4, 5, or 6;

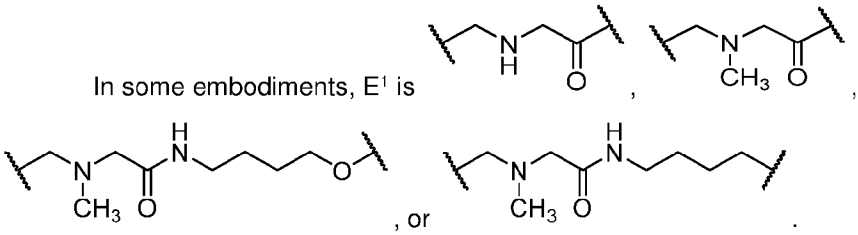
R^a is H or optionally substituted C_1-C_6 alkyl;

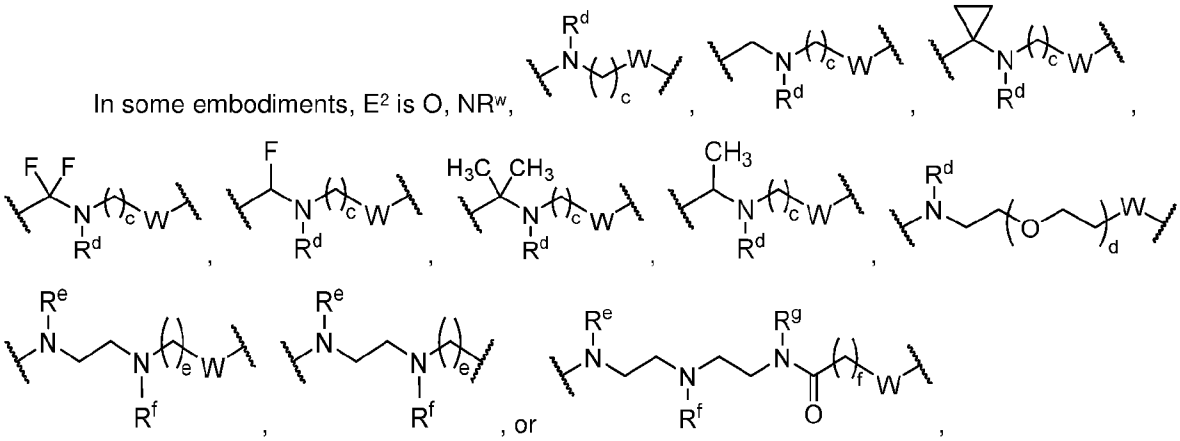
R^b is H or optionally substituted C_1-C_6 alkyl; and

R^c is H or optionally substituted C_1-C_6 alkyl.

In some embodiments, R^a is H or methyl. In some embodiments, R^b is H or methyl. In some embodiments, R^c is H or methyl.

In some embodiments, E^1 is 

In some embodiments, E^1 is 

In some embodiments, E^2 is O, NR^w, 

wherein

c is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

d is 0, 1, 2, or 3;

e is 0, 1, 2, 3, 4, 5, or 6;

f is 0, 1, 2, 3, or 4;

R^d is H or optionally substituted C_1-C_6 alkyl;

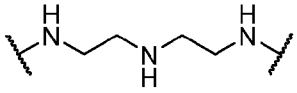
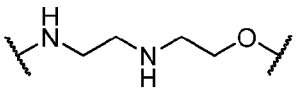
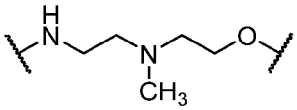
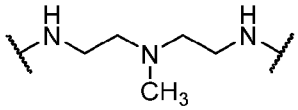
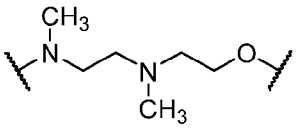
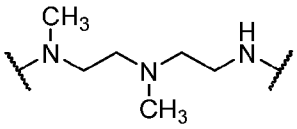
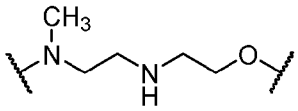
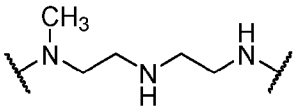
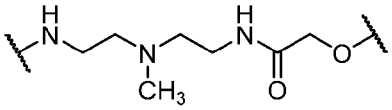
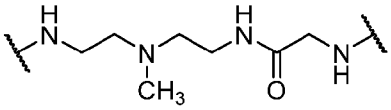
R^e is H or optionally substituted C_1-C_6 alkyl;

R^f is H or optionally substituted C_1-C_6 alkyl;

R^g is H or optionally substituted C_1-C_6 alkyl; and

W is O or NR^w, wherein R^w is H or optionally substituted C_1-C_6 alkyl.

In some embodiments, R^d is H or methyl. In some embodiments, R^e is H or methyl. In some embodiments, R^f is H or methyl. In some embodiments, R^g is H or methyl. In some embodiments, R^w is H or methyl.

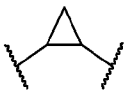
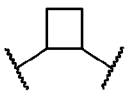
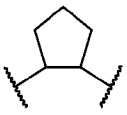
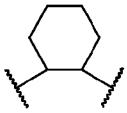
In some embodiments, E^2 is O,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

In some embodiments, each of F^1, F^2, or F^3 is, independently, optionally substituted C_3-C_{10} carbocyclyl.

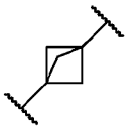
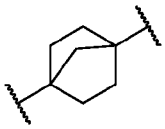
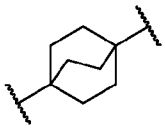
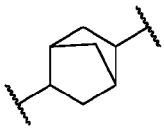
In some embodiments, the C_3-C_{10} carbocyclyl is monocyclic. In some embodiments, the C_3-C_{10} carbocyclyl is polycyclic.

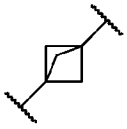
In some embodiments, the C_3-C_{10} carbocyclyl is bicyclic.

In some embodiments, the C_3-C_{10} carbocyclyl is bridged. In some embodiments, the C_3-C_{10} carbocyclyl is fused. In some embodiments, the C_3-C_{10} carbocyclyl is spirocyclic.

In some embodiments, the C_3-C_{10} carbocyclyl is  ,  ,  , or  .

In some embodiments, F^2 is .

In some embodiments, the C_3-C_{10} carbocyclyl is  ,  ,  , or  .

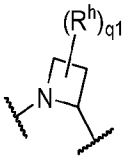
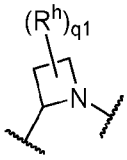
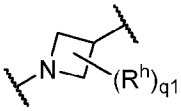
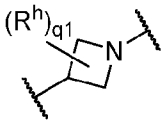
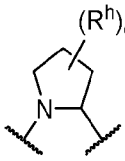
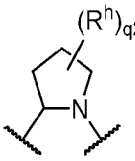
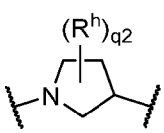
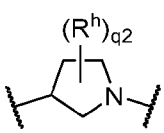
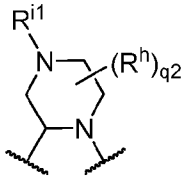
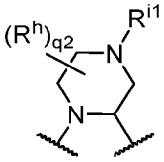
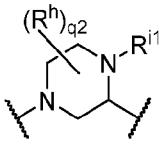
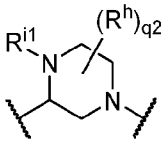
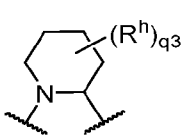
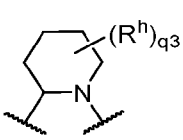
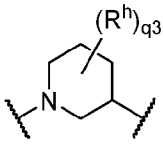
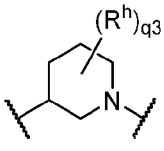
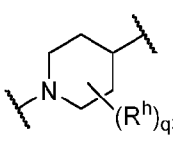
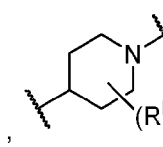
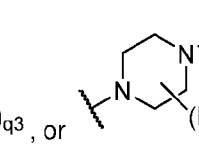
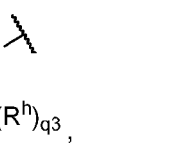
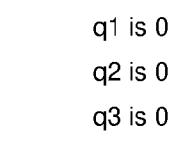
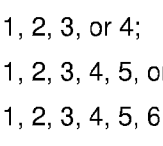
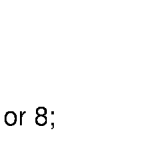
In some embodiments, F^1 is  .

In some embodiments, each of F^1, F^2, or F^3 is, independently, optionally substituted C_2-C_9 heterocyclyl.

In some embodiments, the C_2-C_9 heterocyclyl is monocyclic. In some embodiments, the C_2-C_9 heterocyclyl is polycyclic.

In some embodiments, the C_2-C_9 heterocyclyl is bicyclic.

In some embodiments, the C_2-C_9 heterocyclyl is bridged. In some embodiments, the C_2-C_9 heterocyclyl is fused. In some embodiments, the C_2-C_9 heterocyclyl is spirocyclic.

In some embodiments, the C_2-C_9 heterocyclyl is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , ,  ,  ,  , or ,

where

q1 is 0, 1, 2, 3, or 4;

q2 is 0, 1, 2, 3, 4, 5, or 6;

q3 is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

each R^h is, independently, halogen, optionally substituted C_1-C_6 alkyl, OR^{i2}, or $NR^{i3}R^{i4}$;

R^{i1} is H or optionally substituted C_1-C_6 alkyl;

R^{i2} is H or optionally substituted C_1-C_6 alkyl;

R^{i3} is H or optionally substituted C_1-C_6 alkyl; and

R^{i4} is H or optionally substituted C_1-C_6 alkyl.

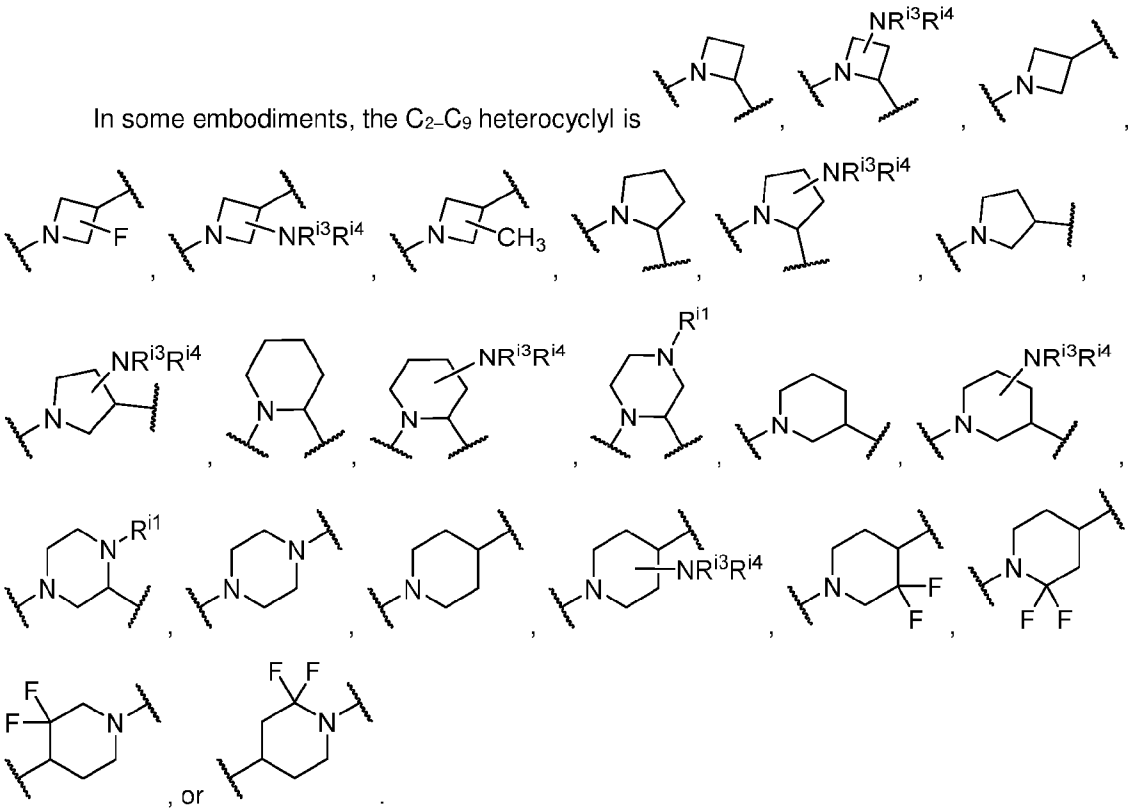
In some embodiments, each R^h is, independently, halogen, optionally substituted C_1-C_6 alkyl, or $NR^{i3}R^{i4}$.

In some embodiments, each R^h is, independently, F, methyl, or $NR^{i3}R^{i4}$.

In some embodiments, q1 is 0, 1, or 2. In some embodiments, q1 is 0. In some embodiments, q1 is 1. In some embodiments, q1 is 2.

In some embodiments, q2 is 0, 1, or 2. In some embodiments, q2 is 0. In some embodiments, q2 is 1. In some embodiments, q2 is 2.

In some embodiments, q3 is 0, 1, or 2. In some embodiments, q3 is 0. In some embodiments, q3 is 1. In some embodiments, q3 is 2.

In some embodiments, the C_2-C_9 heterocyclyl is 

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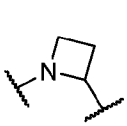
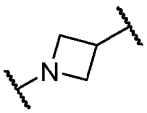
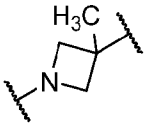
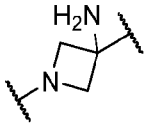
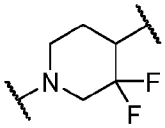
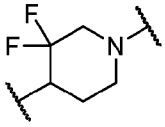
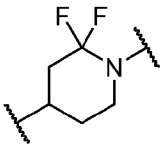
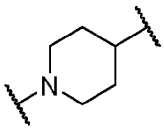
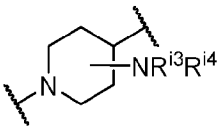
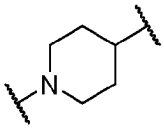
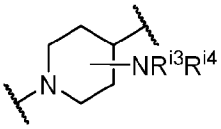
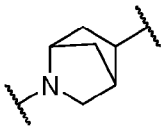
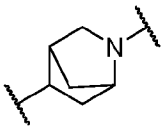
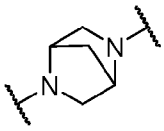
In some embodiments, F^1 is  ,  ,  ,  ,

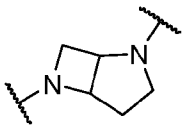
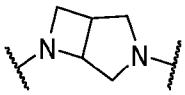
 , ,  , or  .

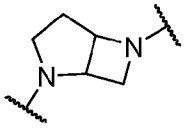
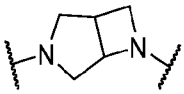
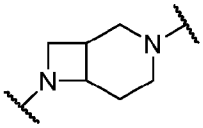
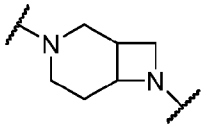
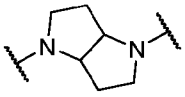
In some embodiments, F^2 is  or  .

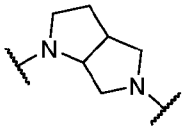
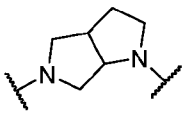
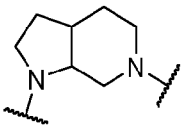
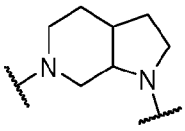
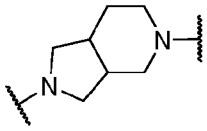
In some embodiments, F^3 is  or  .

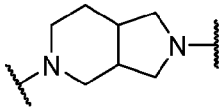
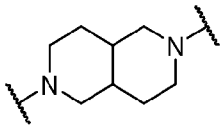
In some embodiments, R^{i1} is H or methyl. In some embodiments, R^{i2} is H or methyl. In some embodiments, R^{i3} is H or methyl. In some embodiments, R^{i4} is H or methyl.

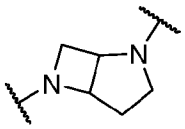
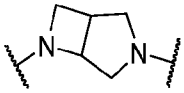
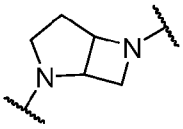
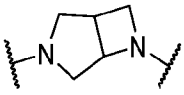
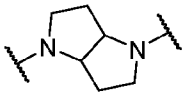
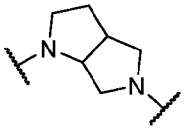
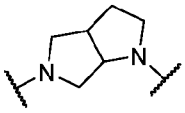
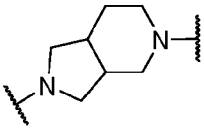
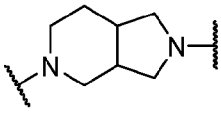
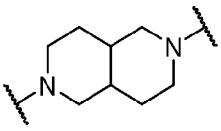
In some embodiments, the C_2–C_9 heterocyclyl is  ,  , or  .

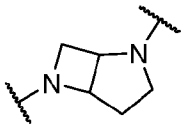
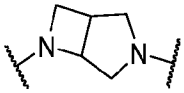
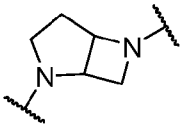
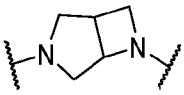
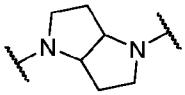
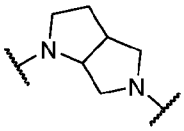
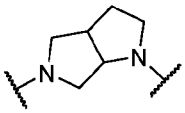
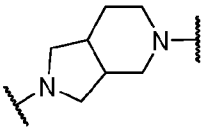
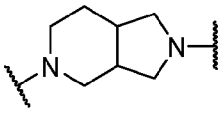
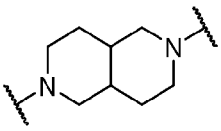
In some embodiments, the C_2–C_9 heterocyclyl is  ,  ,

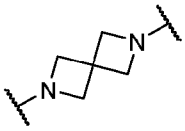
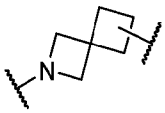
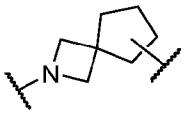
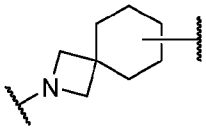
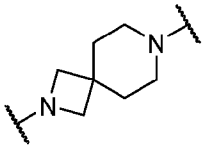
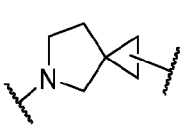
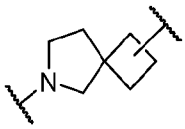
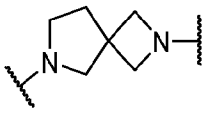
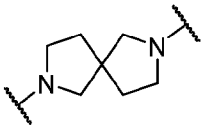
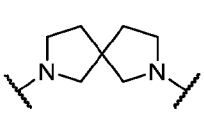
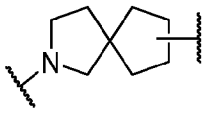
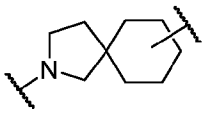
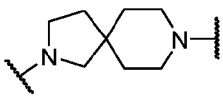
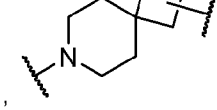
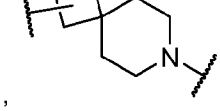
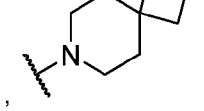
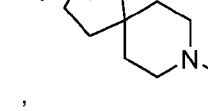
 ,  ,  ,  ,  ,

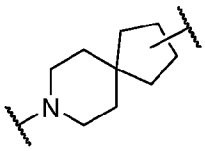
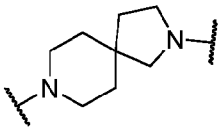
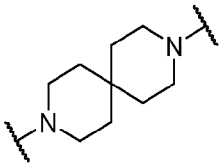
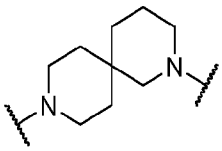
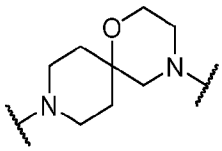
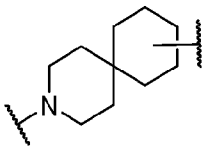
 ,  ,  ,  ,  ,

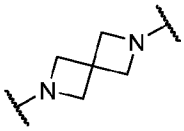
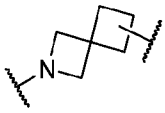
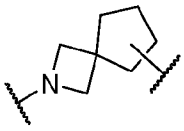
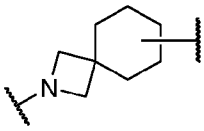
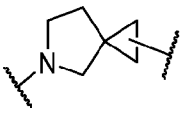
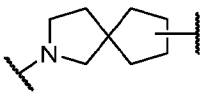
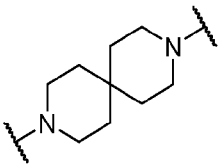
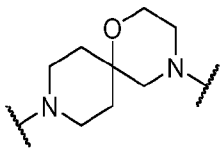
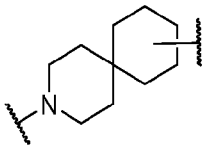
 , or  .

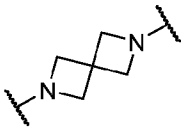
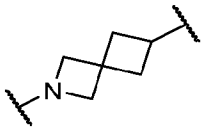
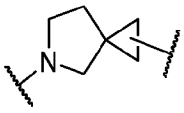
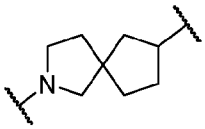
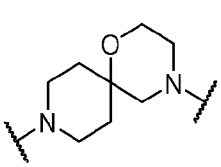
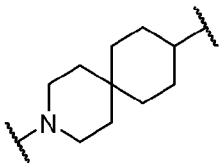
In some embodiments, F^1 is  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

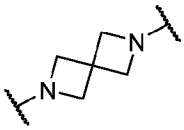
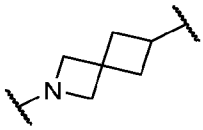
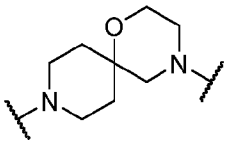
In some embodiments, F^2 is  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

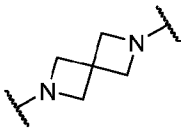
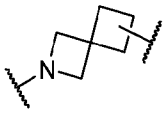
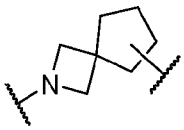
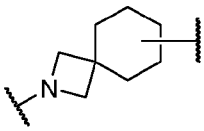
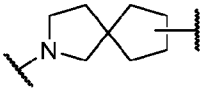
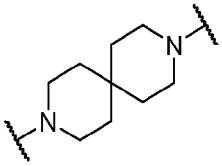
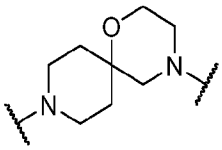
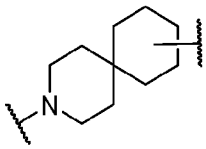
In some embodiments, the C_2–C_9 heterocyclyl is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , , , , .

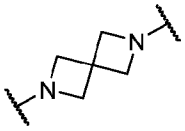
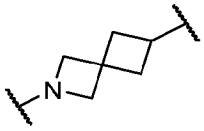
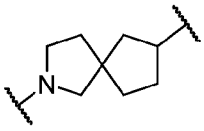
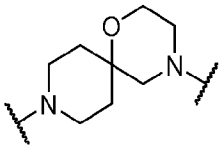
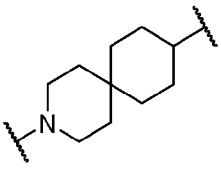
 ,  ,  ,  ,  , or  .

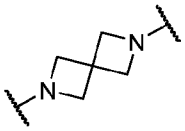
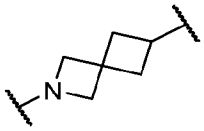
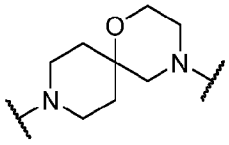
In some embodiments, F^1 is  ,  ,  ,  ,  ,  ,  ,  , or  .

In some embodiments, F^1 is  ,  ,  ,  ,  , or  .

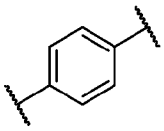
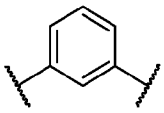
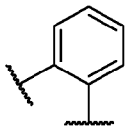
In some embodiments, F^1 is  ,  , or  .

In some embodiments, F^2 is  ,  ,  ,  ,  ,  ,  , or  .

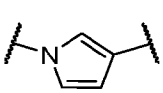
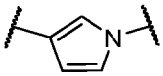
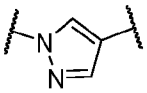
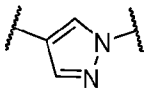
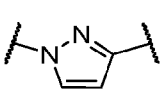
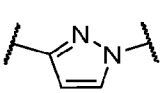
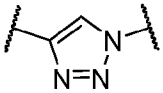
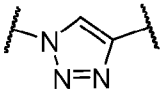
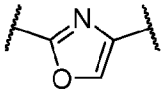
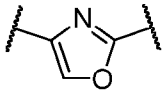
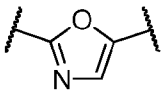
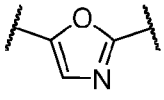
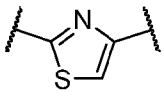
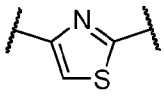
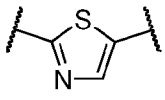
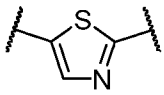
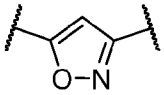
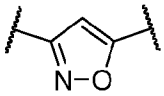
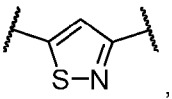
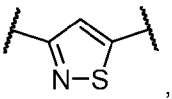
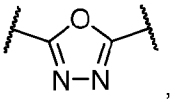
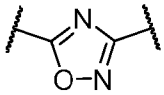
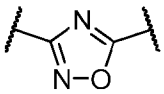
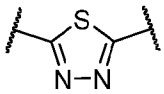
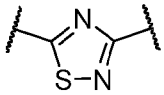
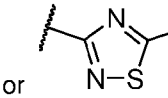
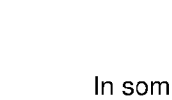
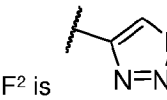
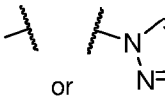
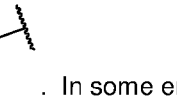
In some embodiments, F^2 is  ,  ,  ,  , or  .

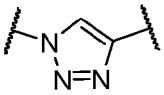
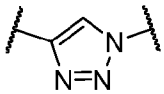
In some embodiments, F^2 is  ,  , or  .

In some embodiments, each of F^1, F^2, or F^3 is, independently, optionally substituted C_6-C_{10} aryl.

In some embodiments, the C_6-C_{10} aryl is  ,  , or  .

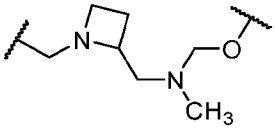
In some embodiments, each of F^1, F^2, or F^3 is, independently, optionally substituted C_2-C_9 heteroaryl.

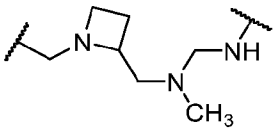
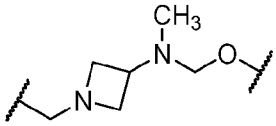
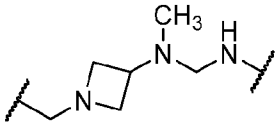
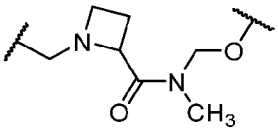
In some embodiments, the C_2-C_9 heteroaryl is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , ,  , ,  ,  , or  .

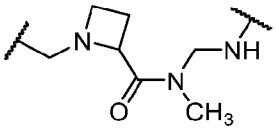
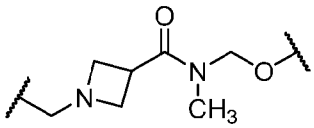
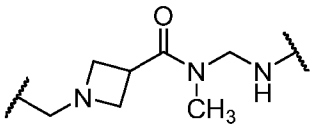
In some embodiments, F^2 is or  . In some embodiments, F^2 is  .

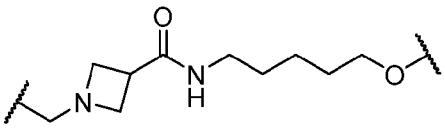
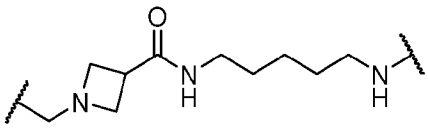
In some embodiments, C^3 is or . In some embodiments, C^3 is .

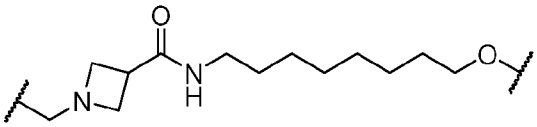
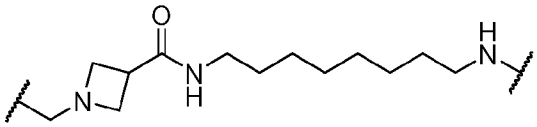
In some embodiments, m is 1. In some embodiments, p is 1.

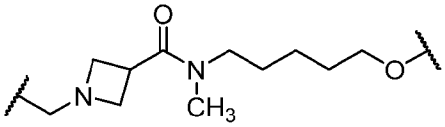
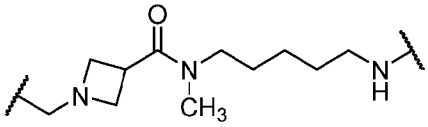
In some embodiments, the linker has the structure of  ,

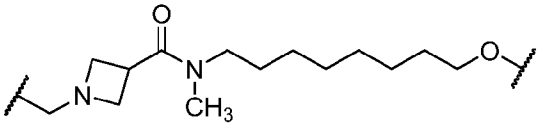
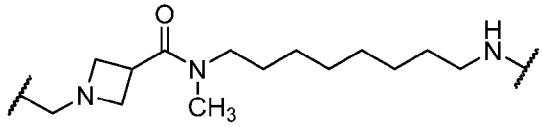
 ,  ,  ,  ,

 ,  ,  ,

 ,  ,

 ,  ,

 ,  ,

 ,  ,

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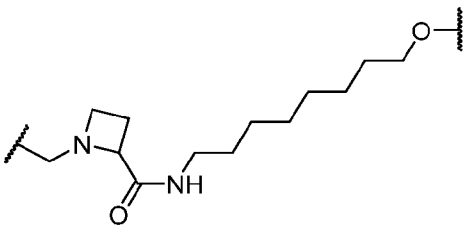
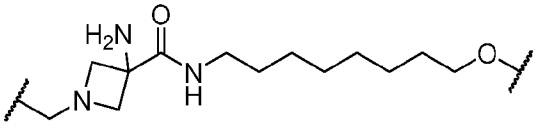
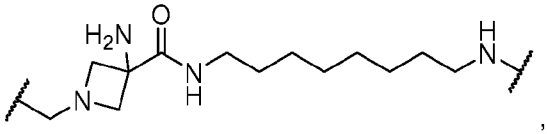
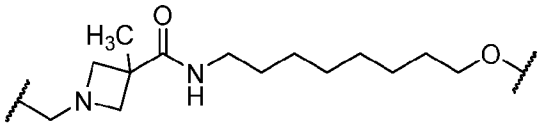
 , ,

 ,  ,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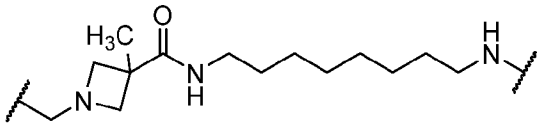
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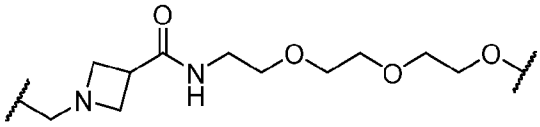
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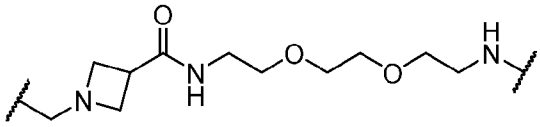
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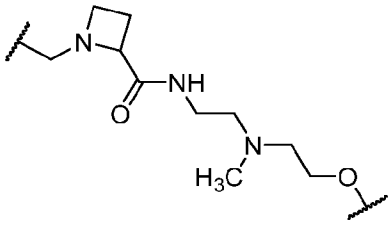
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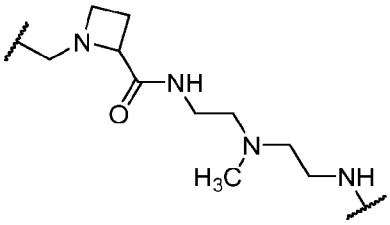
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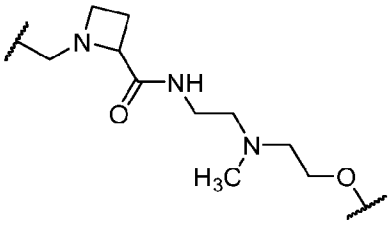
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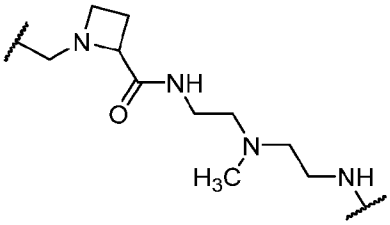
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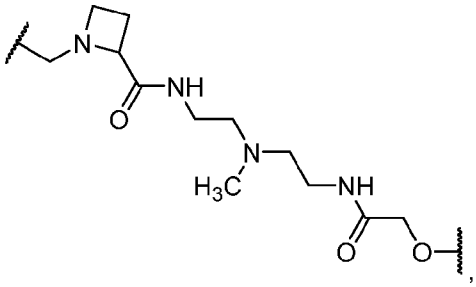
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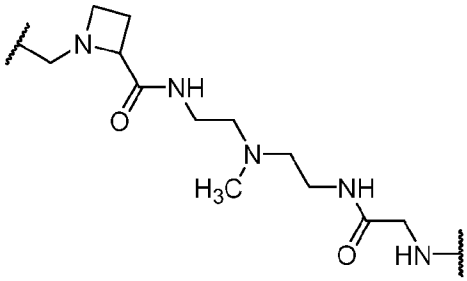
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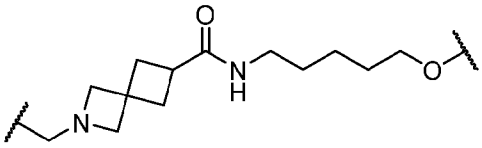
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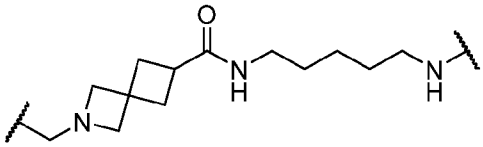
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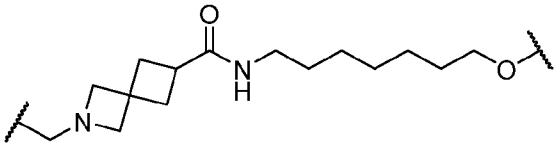
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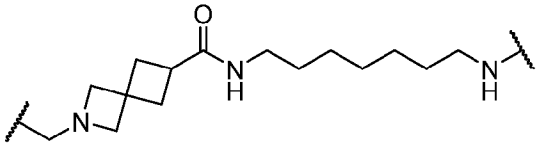
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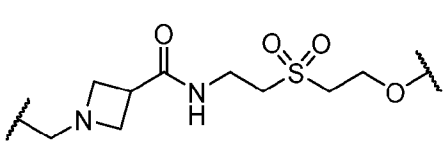
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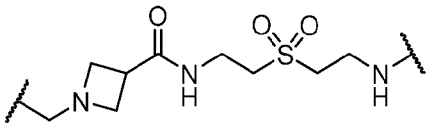
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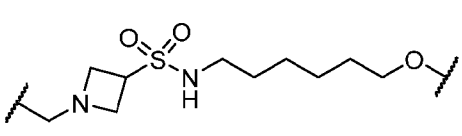
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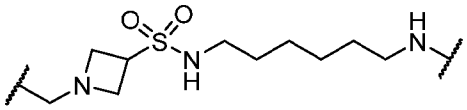
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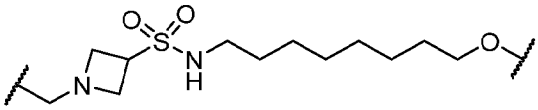
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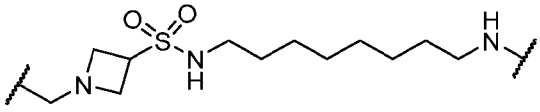
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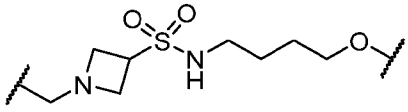
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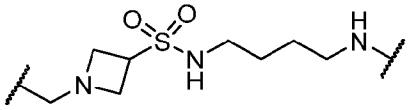
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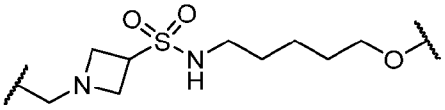
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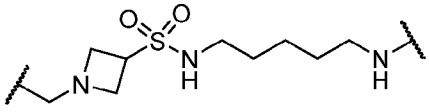
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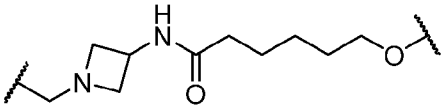
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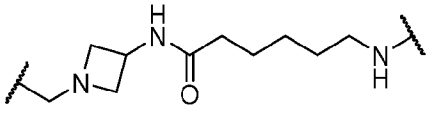
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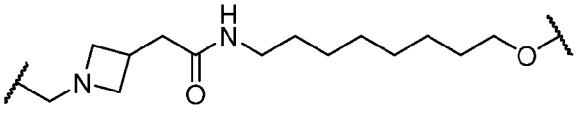
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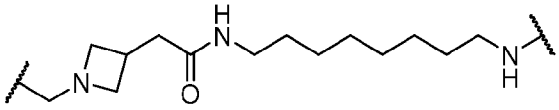
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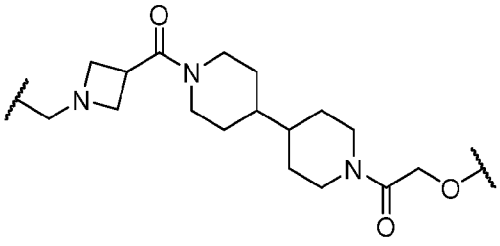
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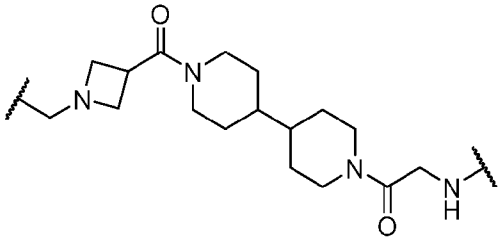
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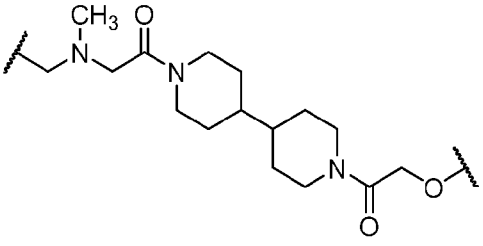
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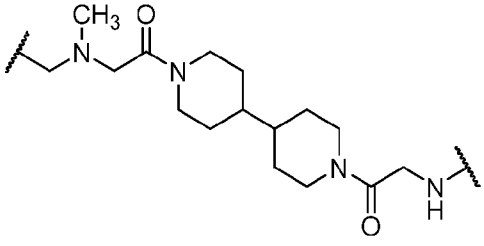
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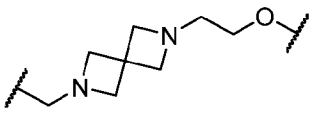
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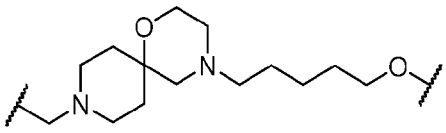
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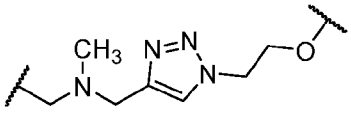
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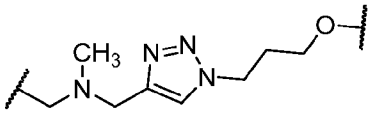
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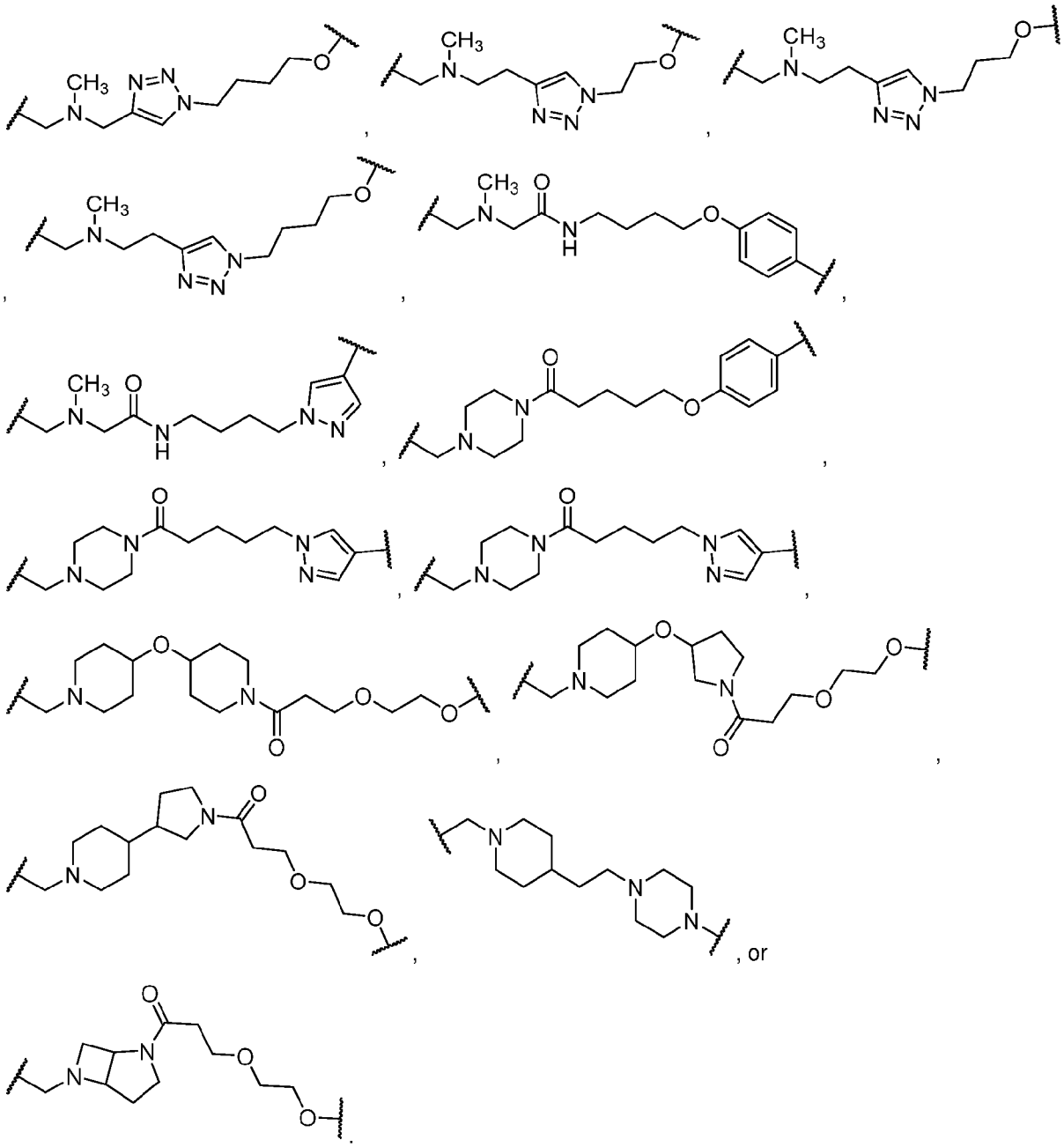
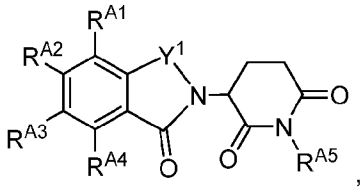


In some embodiments, the degradation moiety is a ubiquitin ligase binding moiety.

In some embodiments, the ubiquitin ligase binding moiety comprises Cereblon ligands, IAP (Inhibitors of Apoptosis) ligands, mouse double minute 2 homolog (MDM2), or von Hippel-Lindau (VHL) ligands, or derivatives or analogs thereof.

In some embodiments, the degradation moiety includes the structure of **Formula A**:

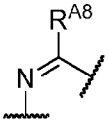


Formula A

where

each of R^{A1}, R^{A2}, R^{A3}, and R^{A4} is, independently, H, a bond to the linker, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; or R^{A1} and R^{A2}, R^{A2} and R^{A3}, and/or R^{A3} and R^{A4}, together with the carbon atoms to which each is attached, combine to form an optionally substituted C_6-C_{10} aryl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heteroaryl, or C_2-C_9 heterocyclyl;

R^{A5} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

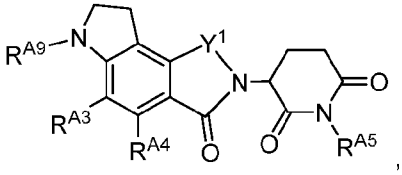
Y^1 is , , or  ;

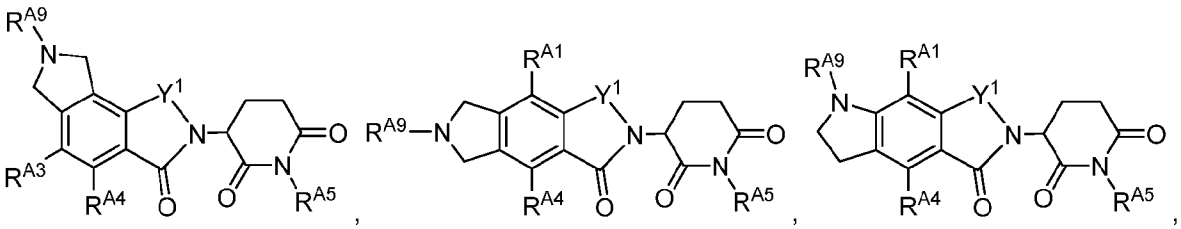
each of R^{A6} and R^{A7} is, independently, H, halogen, or optionally substituted C_1-C_6 alkyl; or R^{A6} and R^{A7}, together with the carbon atom to which each is bound, form an optionally substituted C_3-C_6 carbocyclyl or optionally substituted C_2-C_5 heterocyclyl;

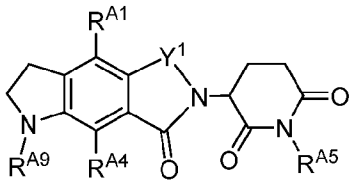
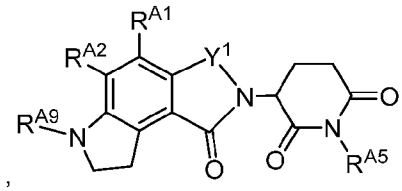
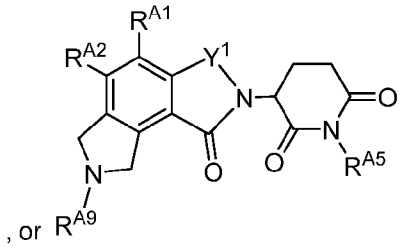
R^{A8} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

where one of R^{A1}, R^{A2}, R^{A3}, and R^{A4} is a bond to the linker, or a pharmaceutically acceptable salt thereof.

In some embodiments, each R^{A1}, R^{A2}, R^{A3}, and R^{A4} is, independently, a bond to the linker, H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, hydroxyl, optionally substituted amino; or R^{A1} and R^{A2}, R^{A2} and R^{A3}, or R^{A3} and R^{A4}, together with the carbon atoms to which each is attached, combine to form an optionally substituted C_2-C_9 heterocyclyl.

In some embodiments, the structure of **Formula A** is  ,



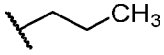
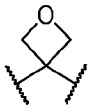
where R^{A9} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl.

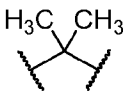
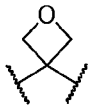
In some embodiments, R^{A1} is a bond to the linker. In some embodiments, R^{A2} is a bond to the linker. In some embodiments, R^{A3} is a bond to the linker. In some embodiments, R^{A4} is a bond to the linker. In some embodiments, R^{A5} is a bond to the linker.

In some embodiments, R^{A5} is H or optionally substituted C_1-C_6 alkyl.

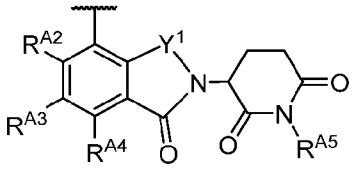
In some embodiments, R^{A5} is H or . In some embodiments, R^{A5} is H. In some embodiments, R^{A5} is .

In some embodiments, Y^1 is or . In some embodiments, Y^1 is . In some embodiments, Y^1 is .

In some embodiments, each of R^{A6} and R^{A7} is, independently, H, F, , , or  ; or R^{A6} and R^{A7}, together with the carbon atom to which each is bound, form , , , or  .

In some embodiments, Y^1 is  , , , ,  , or .

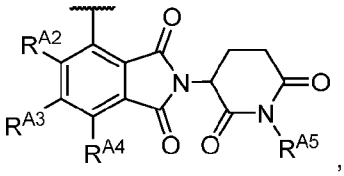
In some embodiments, the structure of **Formula A** has the structure of **Formula A1**:



Formula A1

or a pharmaceutically acceptable salt thereof.

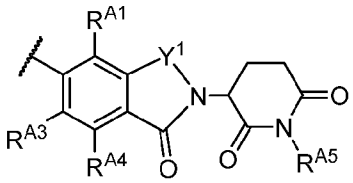
In some embodiments, the structure of **Formula A** has the structure of **Formula A2**:



Formula A2

or a pharmaceutically acceptable salt thereof.

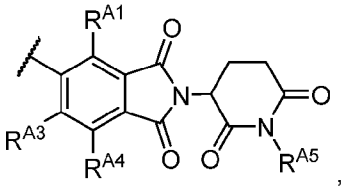
In some embodiments, the structure of **Formula A** has the structure of **Formula A3**:



Formula A3

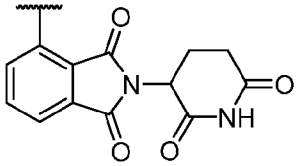
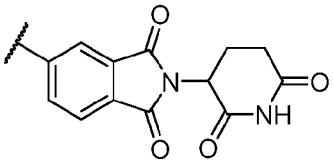
or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of **Formula A** has the structure of **Formula A4**:

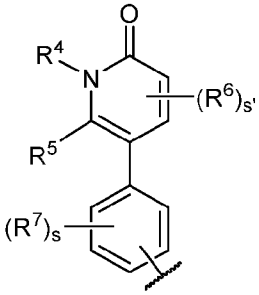


Formula A4

or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of **Formula A** is  or  , or is a derivative or an analog thereof.

In some embodiments, A includes the structure of **Formula III**:



Formula III,

where

R^4 is, independently, H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

R^5 is H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

s' is 0, 1, or 2;

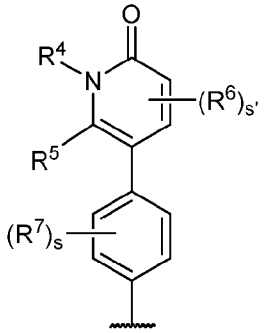
R^6 is halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino, or two R^{24} combine with the carbon atoms to which they are attached to form an optionally substituted C_6-C_{10} aryl or optionally substituted C_2-C_9 heteroaryl;

s is 0, 1, 2, 3, or 4; and

each R^7 is, independently, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino,

or a pharmaceutically acceptable salt thereof.

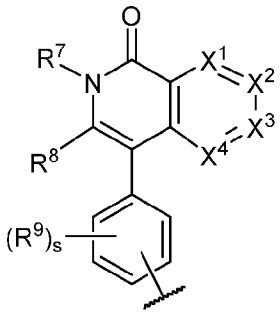
In some embodiments, A includes the structure of **Formula IIIa**:



Formula IIIa,

or a pharmaceutically acceptable salt thereof.

In some embodiments, A includes the structure of **Formula IV**:



Formula IV,

where

R^7 is, independently, H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

R^8 is H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

s is 0, 1, 2, 3, or 4;

each R^9 is, independently, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

X^1 is N or CR^{10a};

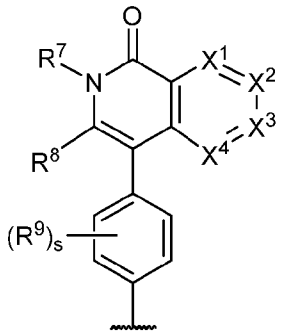
X^2 is N or CR^{10b};

X^3 is N or CR^{10c};

X^4 is N or CR^{10d}; and

each of R^{10a}, R^{10b}, R^{10c}, and R^{10d} is, independently, H, halogen, hydroxy, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino, or a pharmaceutically acceptable salt thereof.

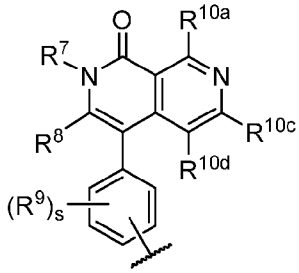
In some embodiments, A includes the structure of **Formula IVa**:



Formula IVa,

or a pharmaceutically acceptable salt thereof.

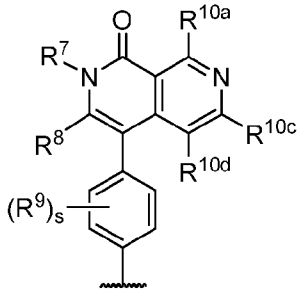
In some embodiments, A includes the structure of **Formula IVb**:



Formula IVb,

or a pharmaceutically acceptable salt thereof.

In some embodiments, A includes the structure of **Formula IVc**:



Formula IVc,

or a pharmaceutically acceptable salt thereof.

In some embodiments, R^7 is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 carbocyclyl.

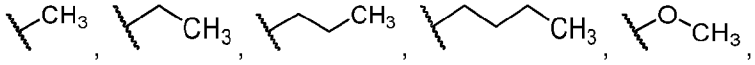
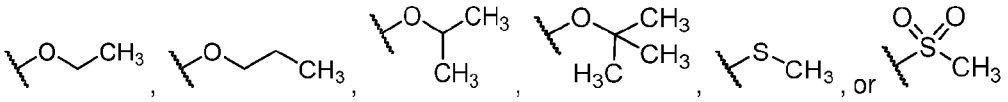
In some embodiments, R^7 is H or CH_3.

In some embodiments, R^8 is H or optionally substituted C_1-C_6 alkyl.

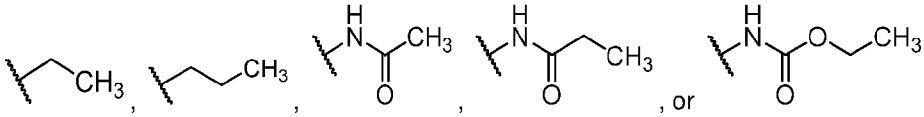
In some embodiments, R^8 is H.

In some embodiments, s is 0, 1, or 2. In some embodiments, s is 1 or 2. In some embodiments, s is 2.

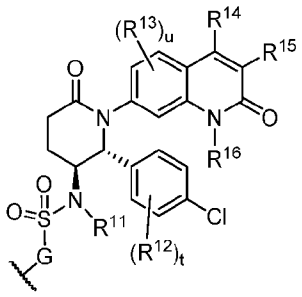
In some embodiments, each R^9 is, independently, optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_6 heteroalkyl.

In some embodiments, R^9 is  ,  , or .

In some embodiments, each of R^{10a}, R^{10b}, R^{10c}, and R^{10d} is, independently, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted amino.

In some embodiments, each of R^{10a}, R^{10b}, R^{10c}, and R^{10d} is, independently, $-NH_2$, ,  , or .

In some embodiments, A includes the structure of **Formula V**



Formula V,

where

each R^{11} and R^{16} is, independently, H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

t is 0, 1, 2, 3, or 4;

each R^{12} is, independently, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

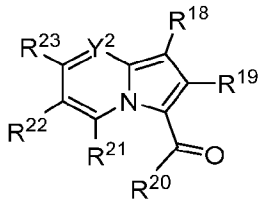
u is 0, 1, 2, 3, or 4;

each R^{13} is, independently, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

each R^{14} and R^{15} is, independently, selected form the group consisting of H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl; and

G is optionally substituted C_1-C_6 alkylene, optionally substituted C_6-C_{10} arylene, or optionally substituted C_3-C_6 carbocyclylene, or a pharmaceutically acceptable salt thereof.

In some embodiments, A includes the structure of **Formula VI**:



Formula VI,

where

Y^2 is CR^{17} or N;

R^{18} is optionally substituted C_6-C_{10} aryl or C_2-C_9 heteroaryl;

R^{19} is H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

R^{20} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

each R^{17}, R^{21}, and R^{22} is, independently, H, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

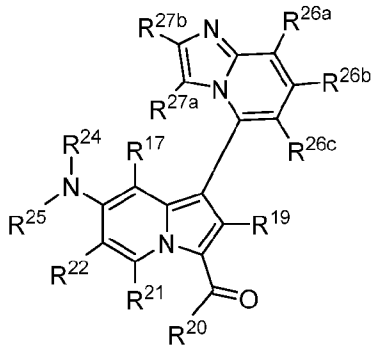
R^{23} is H or $-NR^{24}R^{25}$; and

each of R^{24} and R^{25} is, independently, H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl, or R^{24} and R^{25} combine to form an optionally substituted C_2-C_9 heterocyclyl,

where at least one of R^{18}, R^{24}, or R^{25} includes a bond to the linker,

or a pharmaceutically acceptable salt thereof.

In some embodiments, A includes the structure of **Formula VII**:



Formula VII,

where

each R^{26a}, R^{26b}, and R^{26c} is, independently, H, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

each R^{27a} and R^{27b} is, independently, H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

R^{19} is H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

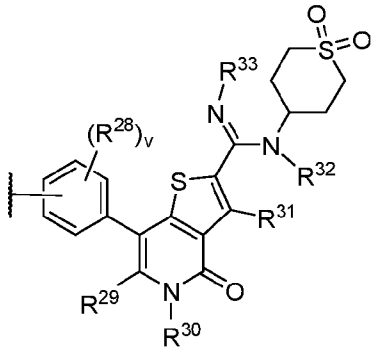
R^{20} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

each R^{17}, R^{21}, and R^{22} is, independently, H, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino; and

each of R^{24} and R^{25} is, independently, H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl, or R^{24} and R^{25} combine to form an optionally substituted C_2-C_9 heterocyclyl,

where at least one of R^{26a}, R^{26b}, R^{26c}, R^{24}, or R^{25} includes a bond to the linker, or a pharmaceutically acceptable salt thereof.

In some embodiments, A includes the structure of **Formula VIII**:



Formula VIII,

where

v is 0, 1, 2, 3, or 4;

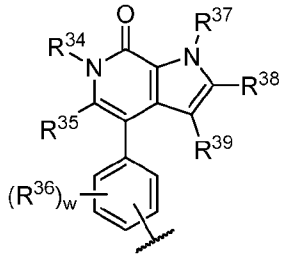
each R^{28} is, independently, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

R^{29} is H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

R^{31} is H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl; and

each R^{30}, R^{32}, and R^{33} is, independently, H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl, or a pharmaceutically acceptable salt thereof.

In some embodiments, A includes the structure of **Formula IX**:



Formula IX,

where

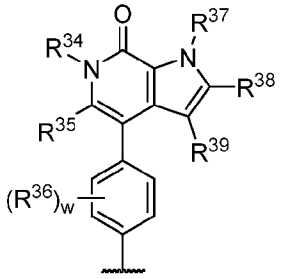
each R^{34} and R^{37} is, independently, H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

each R^{35}, R^{38}, and R^{39} is, independently, H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

w is 0, 1, 2, 3, or 4; and

each R^{36} is, independently, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino, or a pharmaceutically acceptable salt thereof.

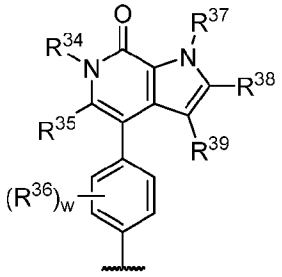
In some embodiments, A includes the structure of **Formula IXa**:



Formula IXa,

or a pharmaceutically acceptable salt thereof.

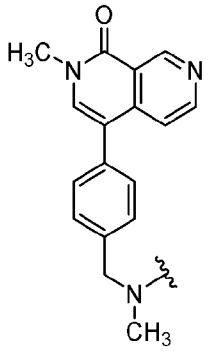
In some embodiments, A includes the structure of **Formula IXb**:



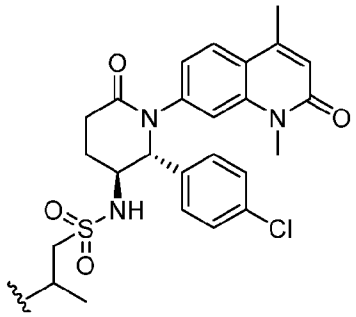
Formula IXb,

or a pharmaceutically acceptable salt thereof.

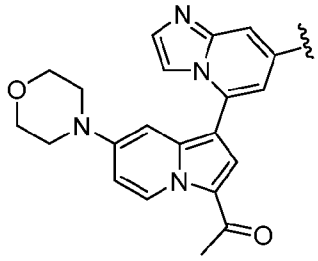
In some embodiments, A includes the structure of:



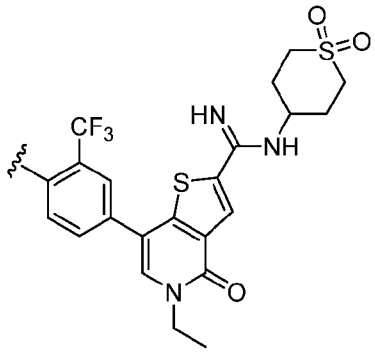
X2,



X3,

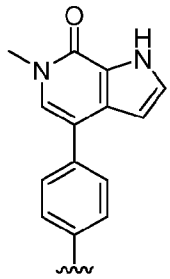


X4,



X5,

or



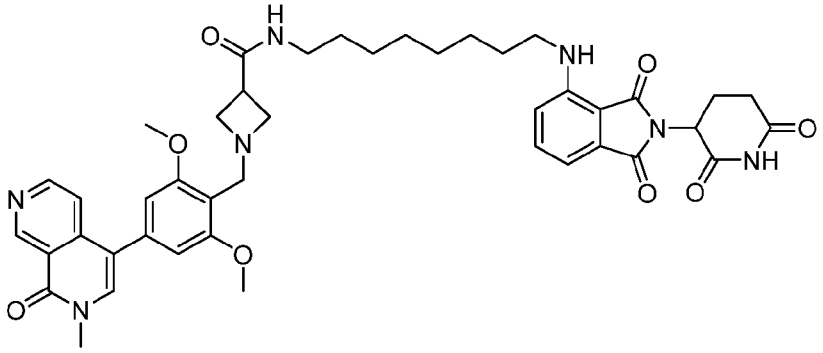
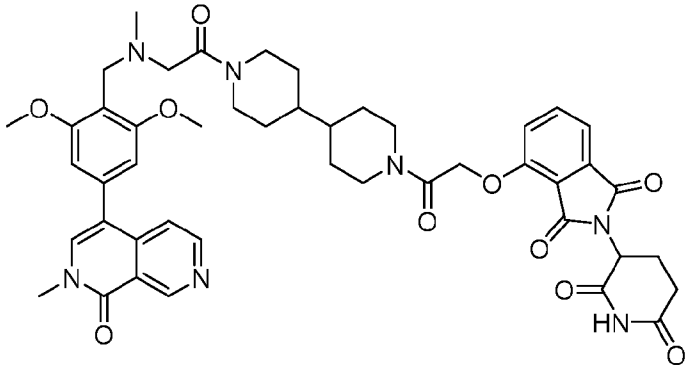
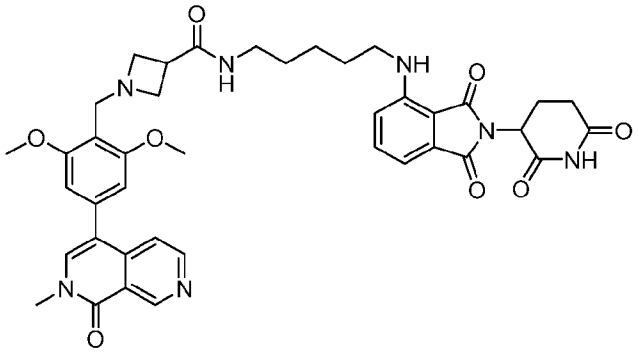
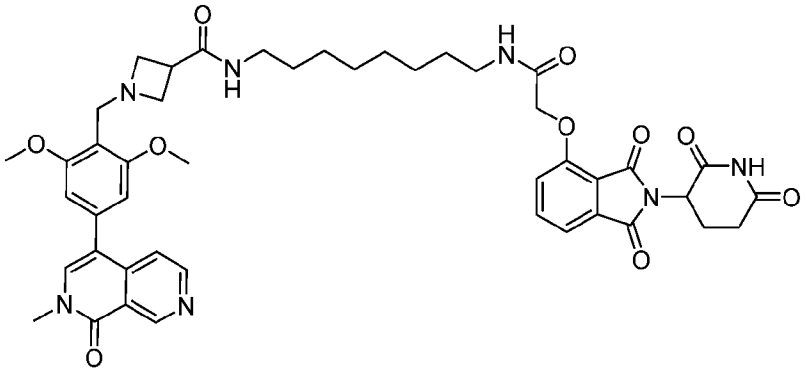
X6,

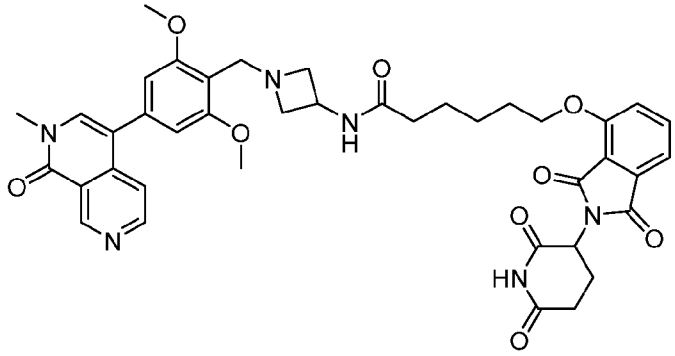
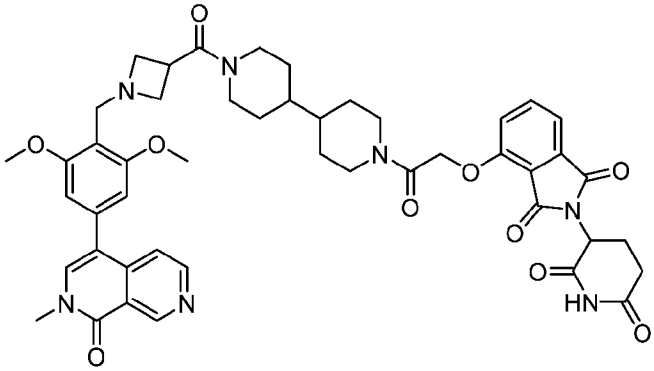
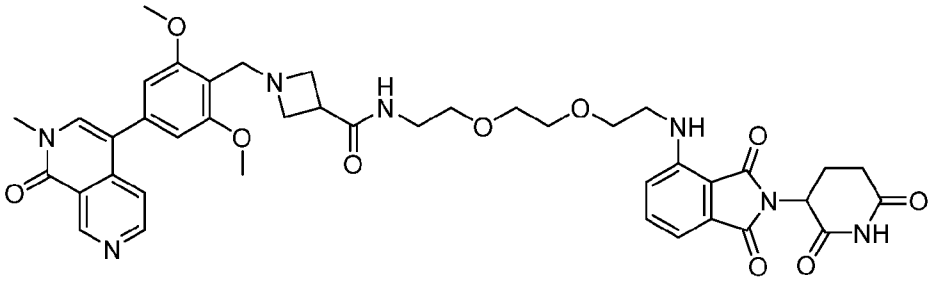
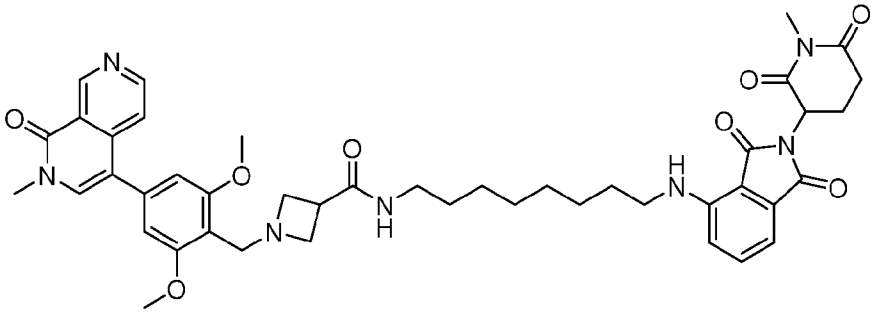
or is a derivative or an analog thereof.

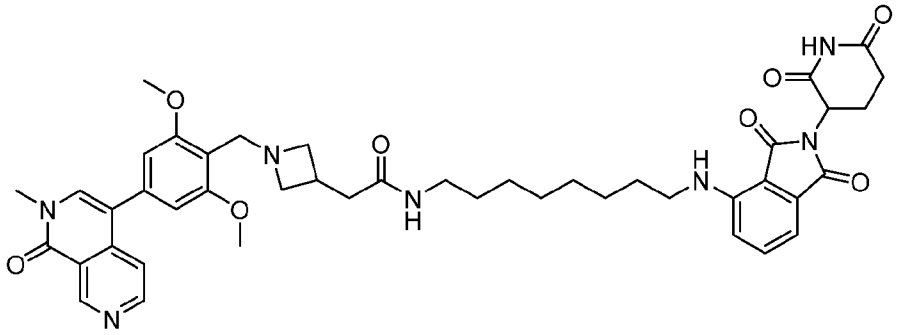
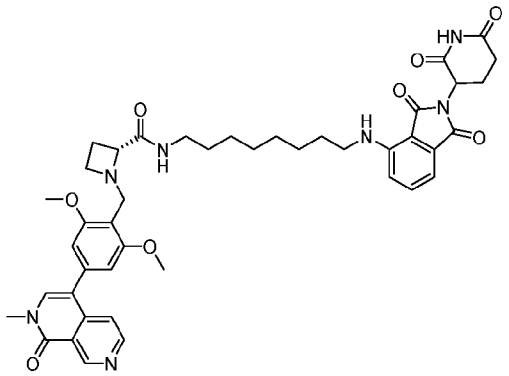
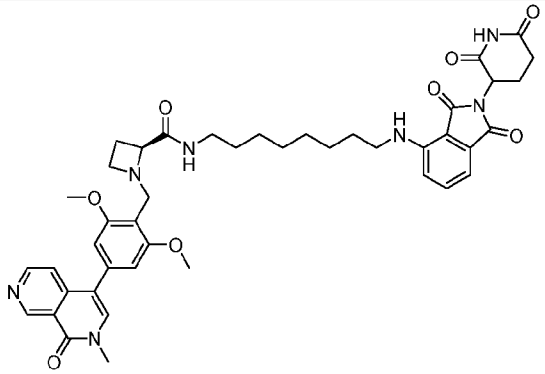
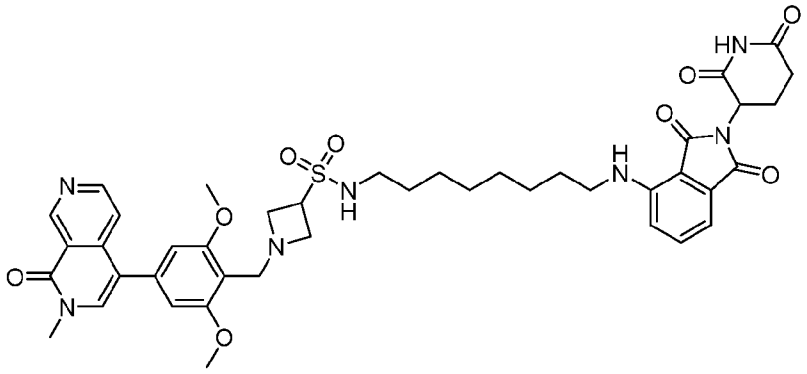
In some embodiments, the compound has the structure of compounds D1-D177 in Table 1.

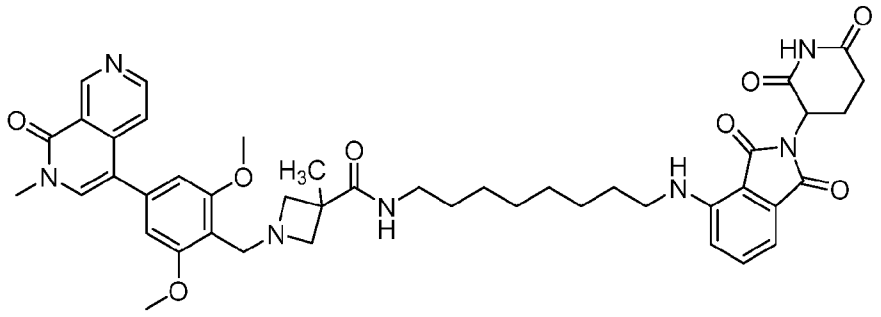
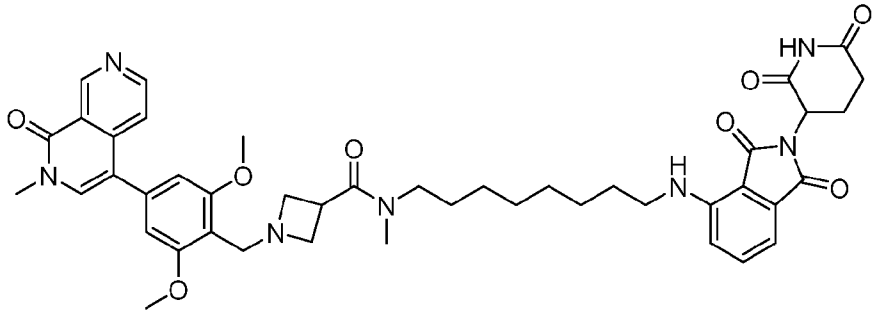
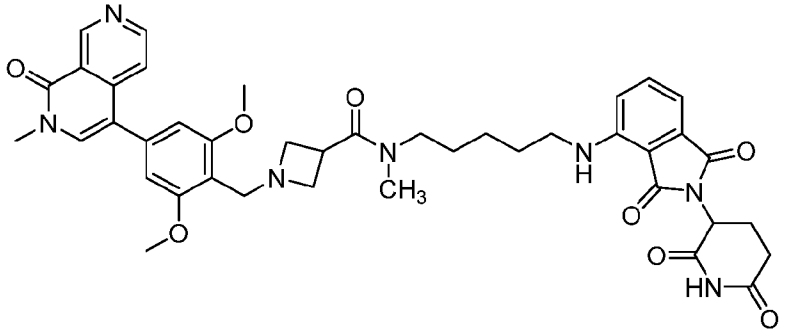
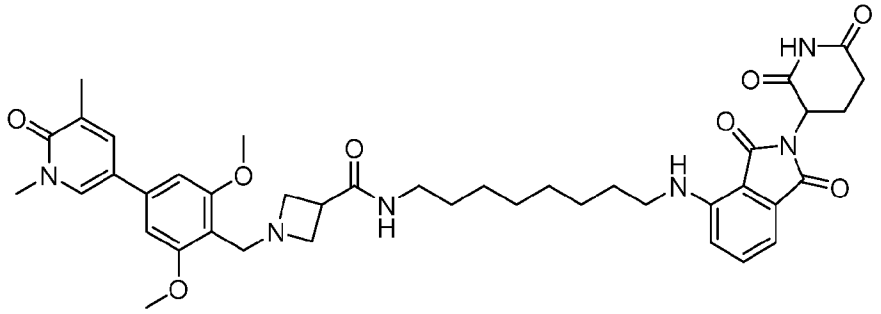
In an aspect, the disclosure features compounds D1-D177 in Table 1.

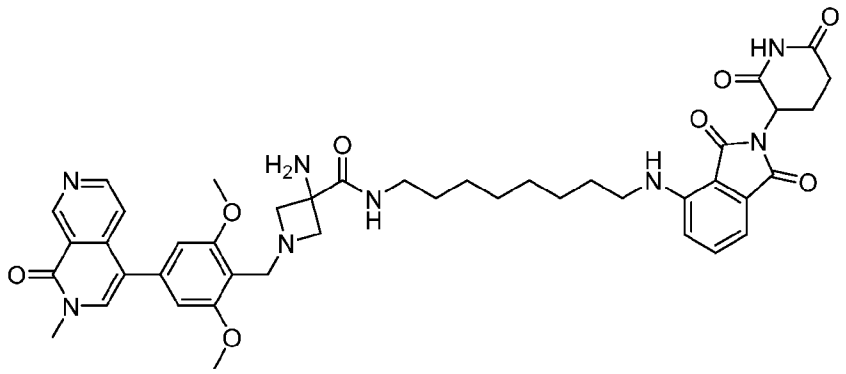
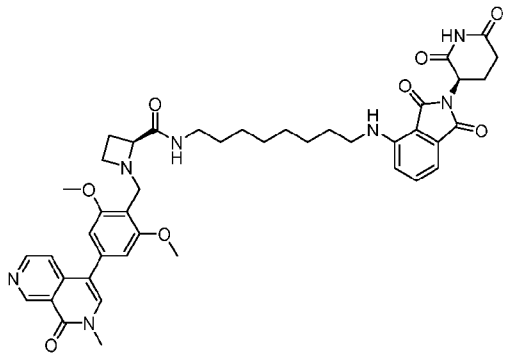
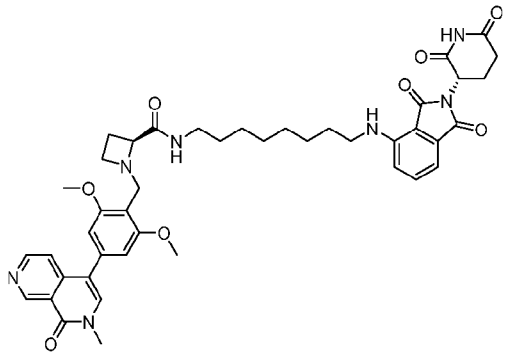
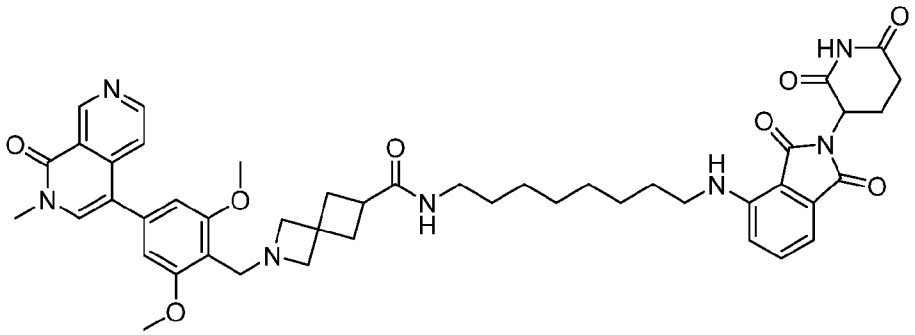
Table 1. Compounds D1-D177 of the Disclosure

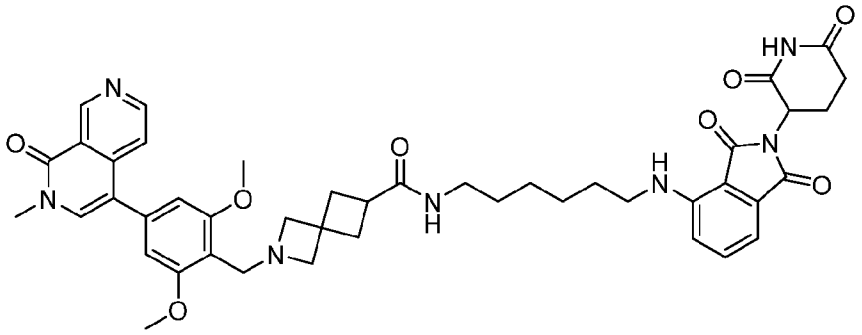
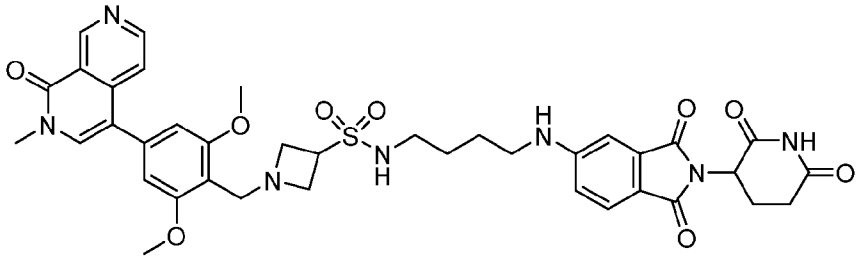
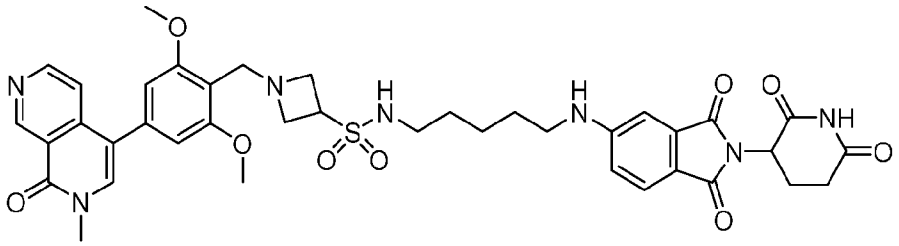
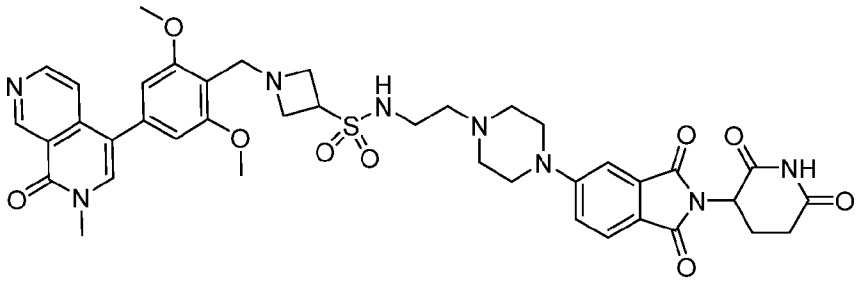
Compound No.	Structure
D1	
D2	
D3	
D4	

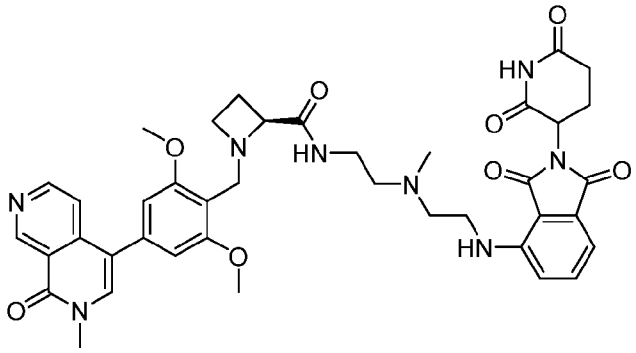
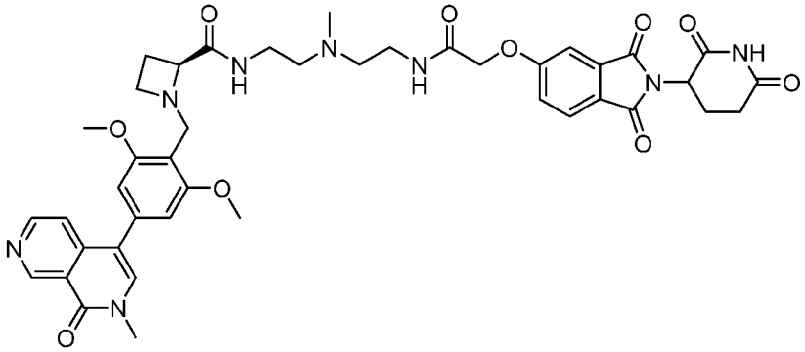
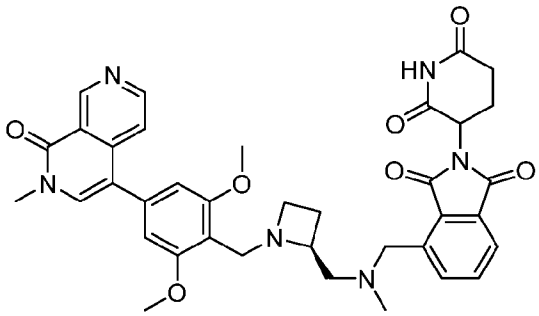
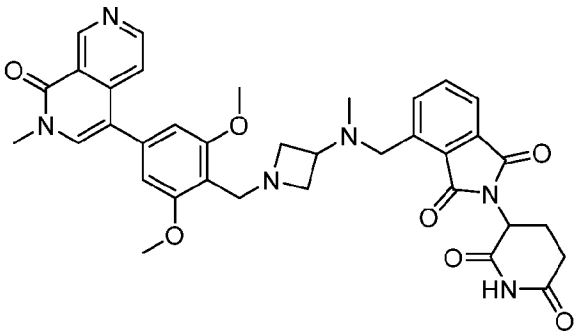
Compound No.	Structure
D5	
D6	
D7	
D8	

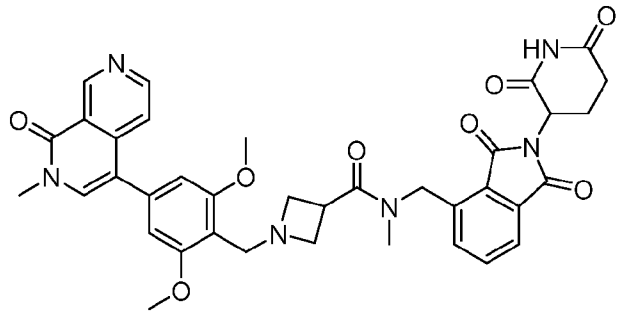
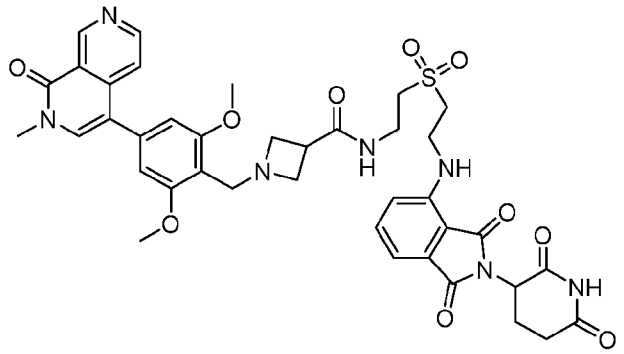
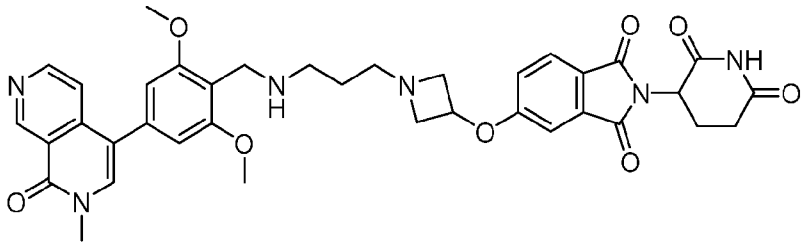
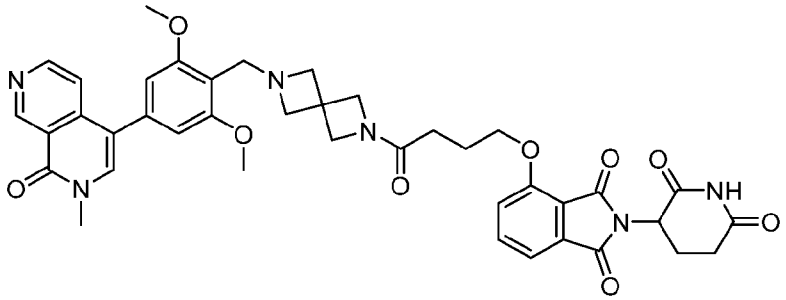
Compound No.	Structure
D9	
D10	
D11	
D12	

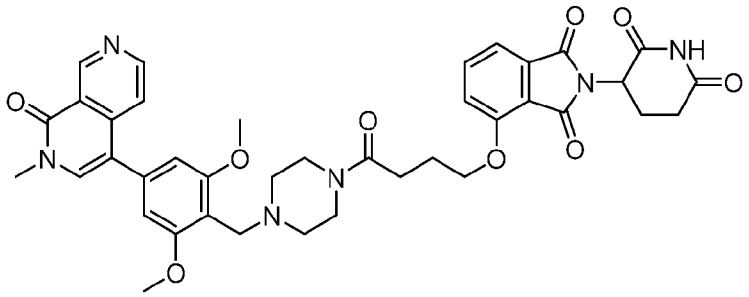
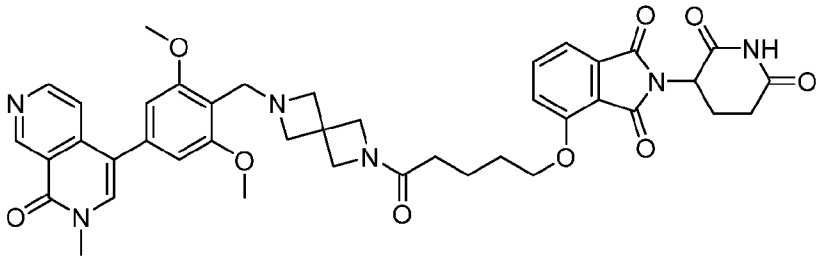
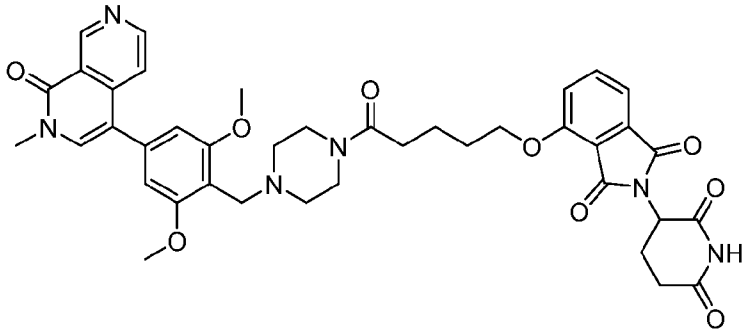
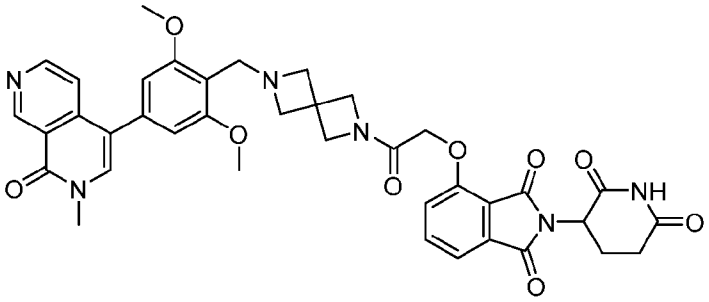
Compound No.	Structure
D13	
D14	
D15	
D16	

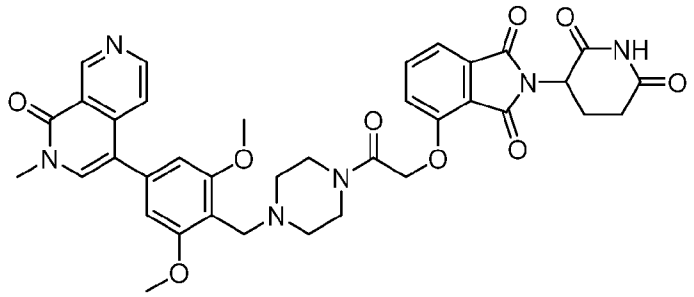
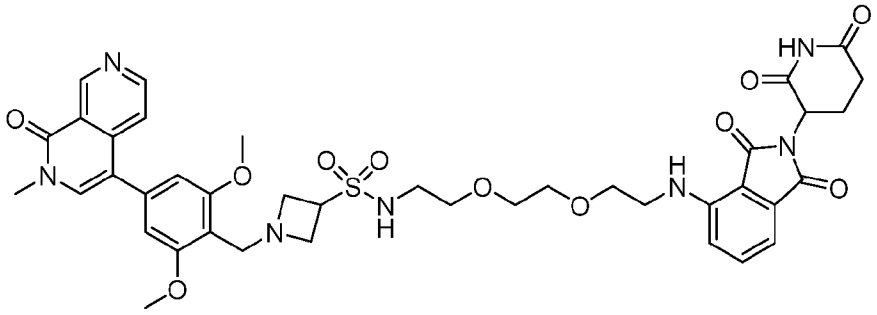
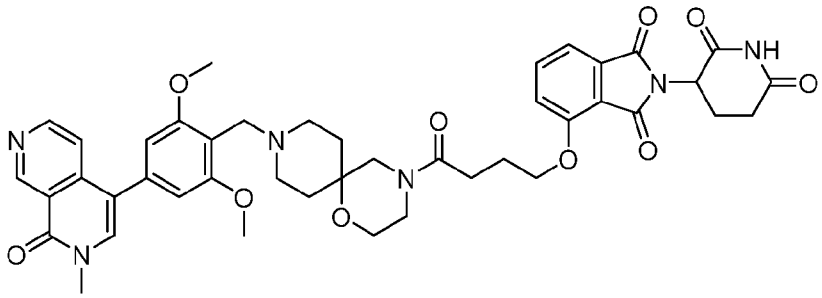
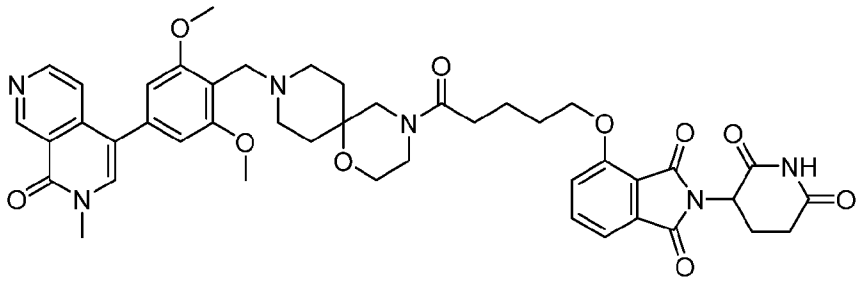
Compound No.	Structure
D17	
D18	
D19	
D20	

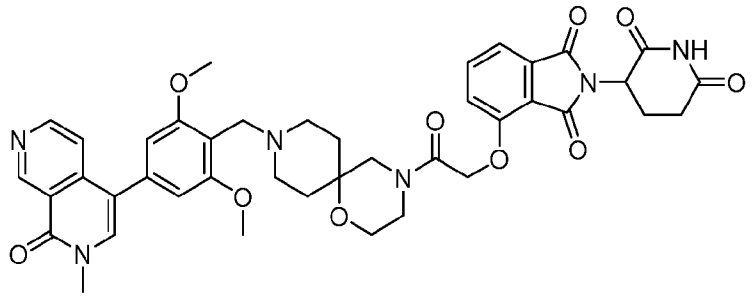
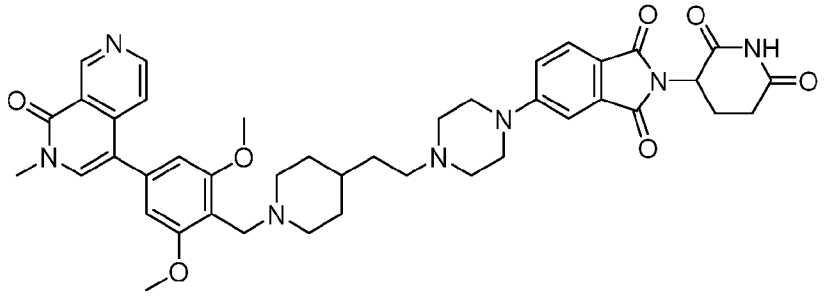
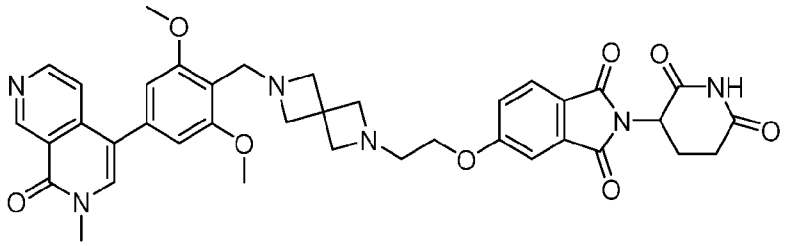
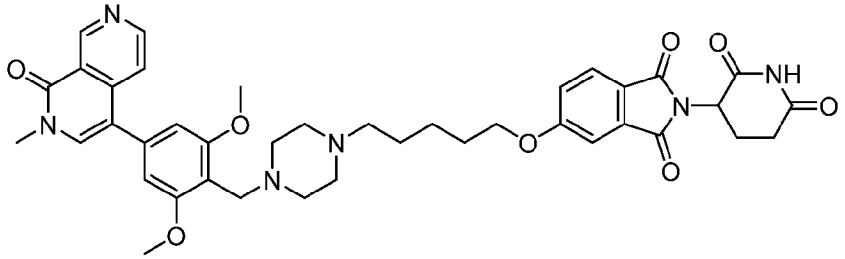
Compound No.	Structure
D21	
D22	
D23	
D24	

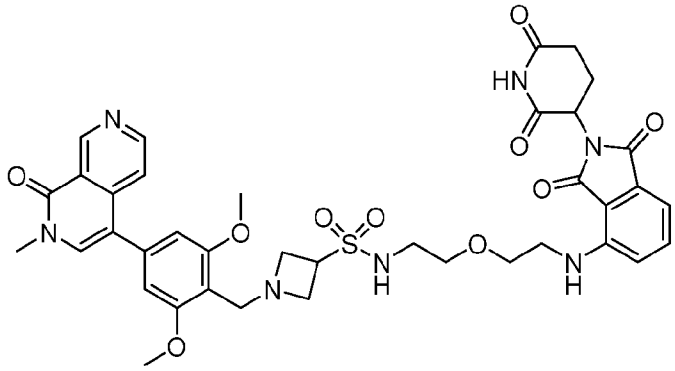
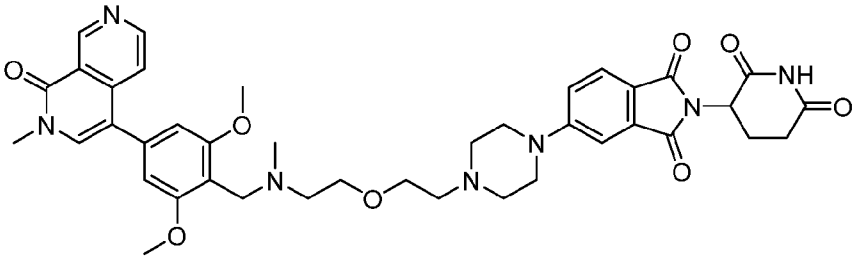
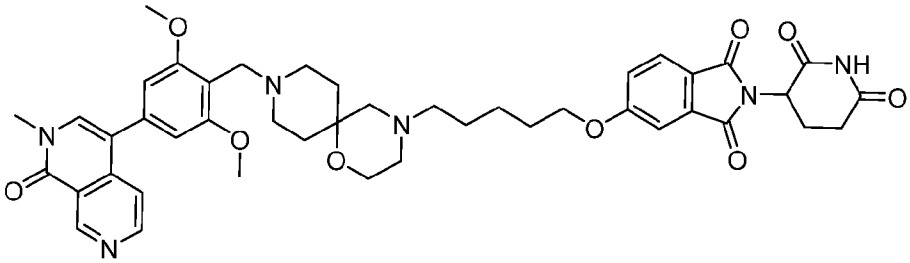
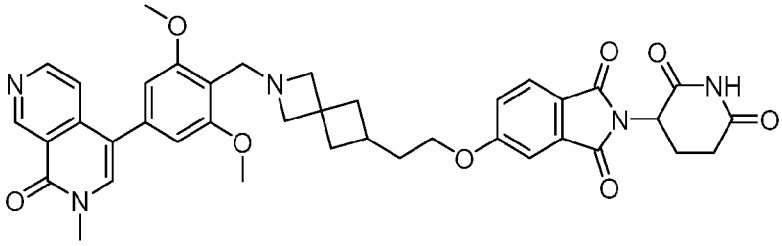
Compound No.	Structure
D25	
D26	
D27	
D28	

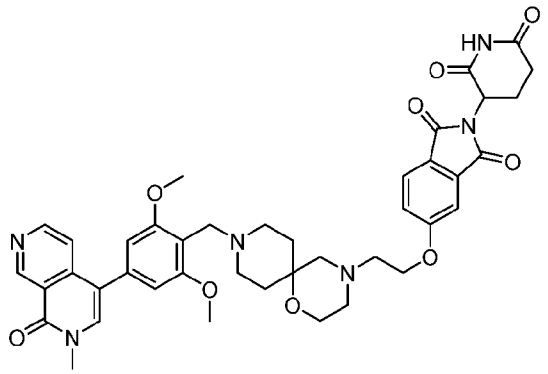
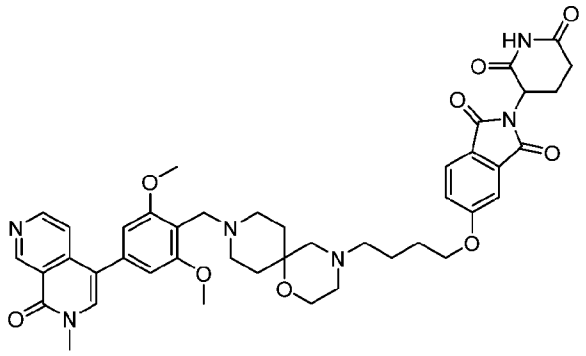
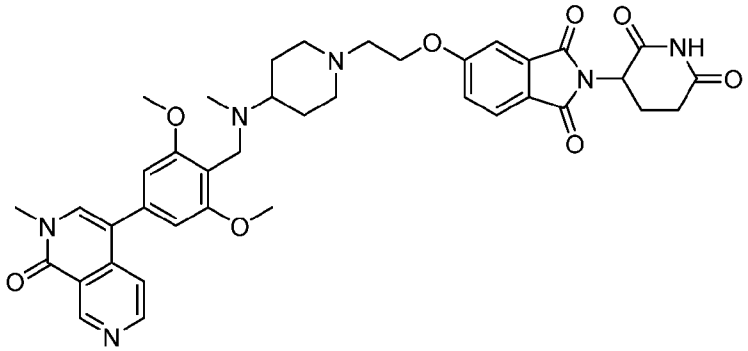
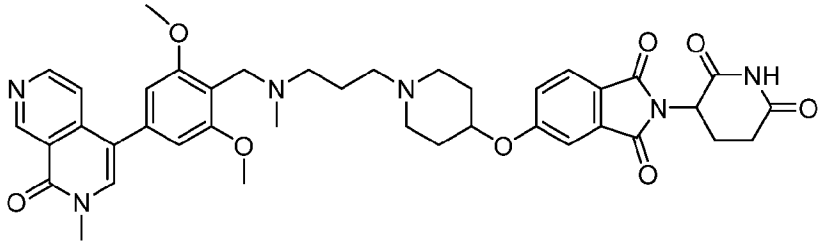
Compound No.	Structure
D29	
D30	
D31	
D32	

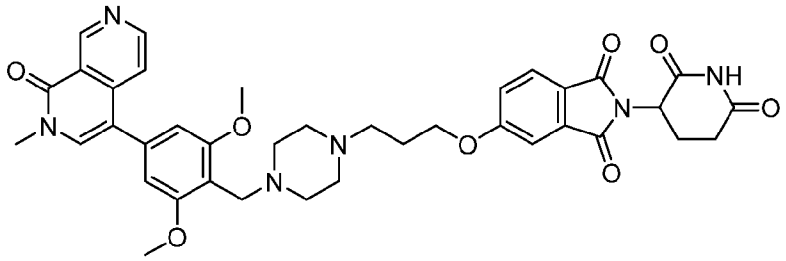
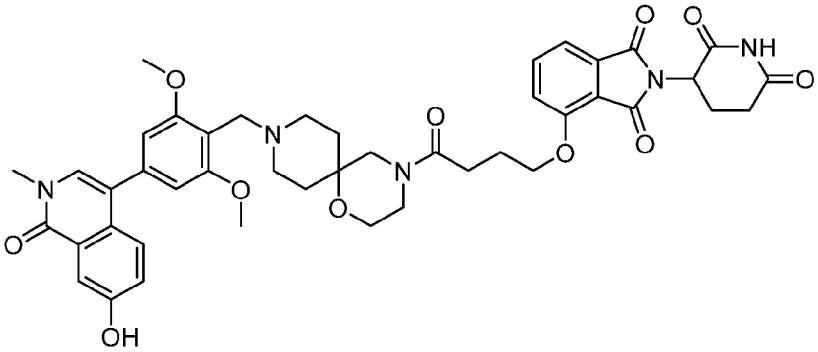
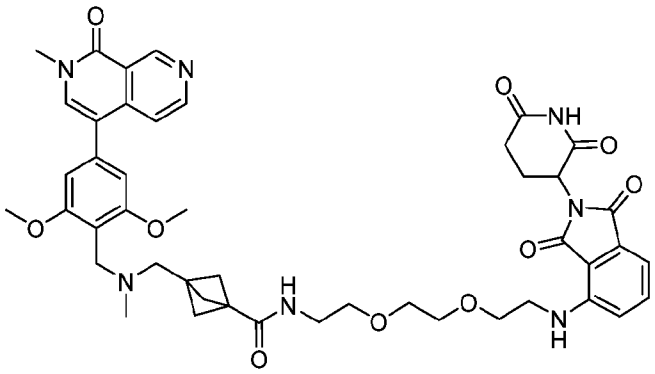
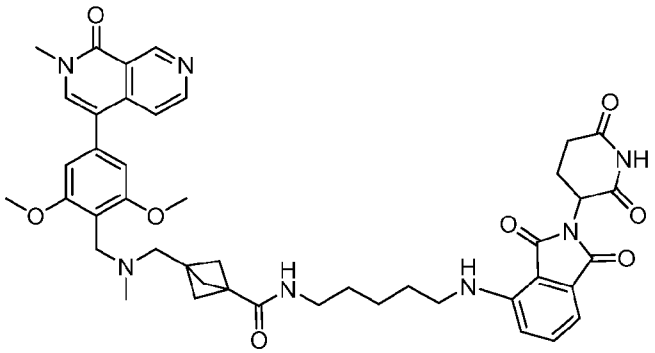
Compound No.	Structure
D33	
D34	
D35	
D36	

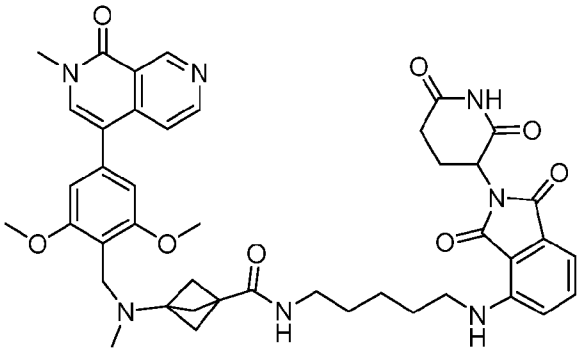
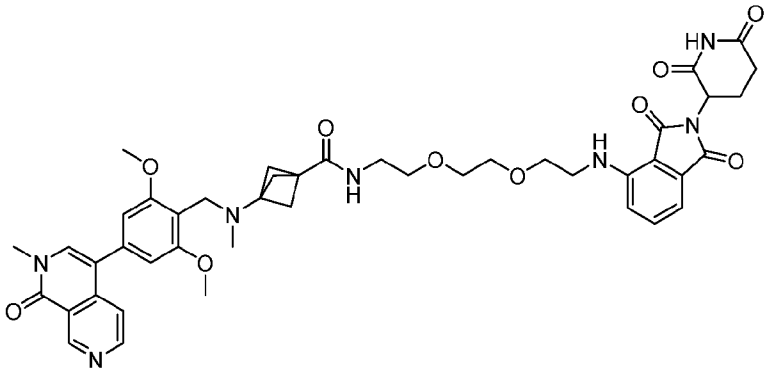
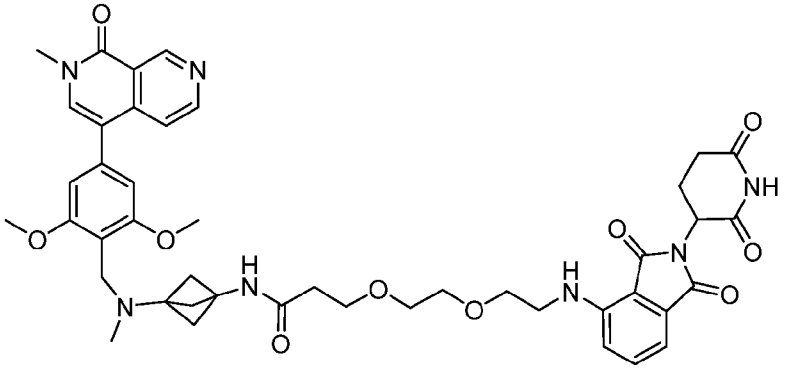
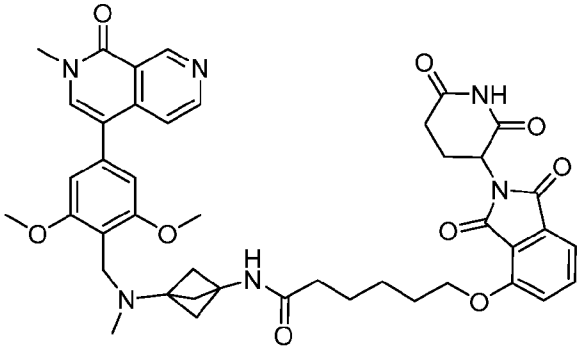
Compound No.	Structure
D37	
D38	
D39	
D40	

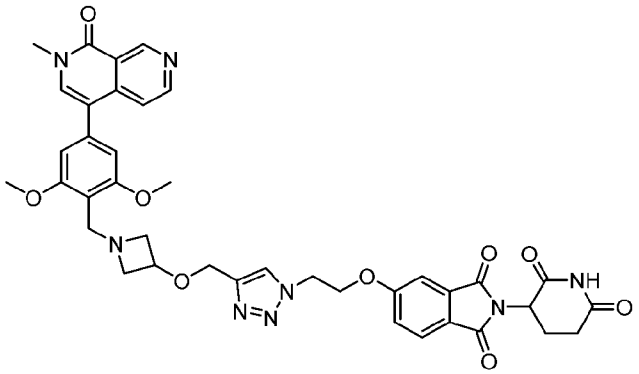
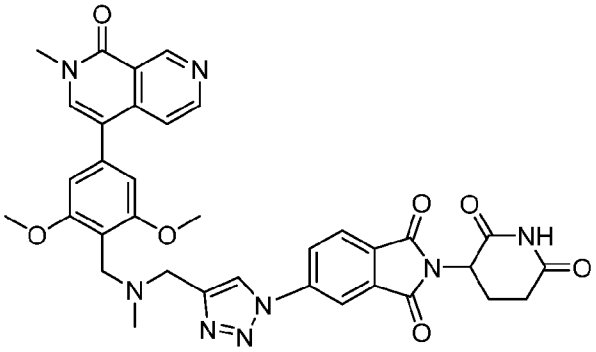
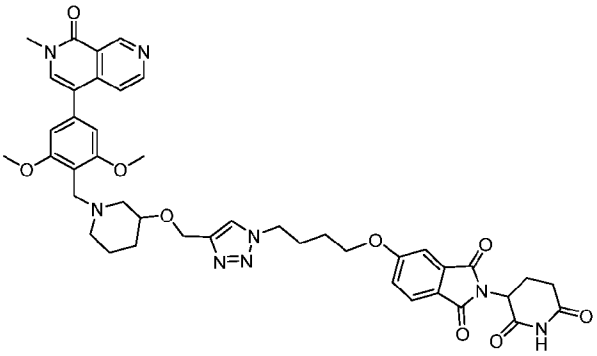
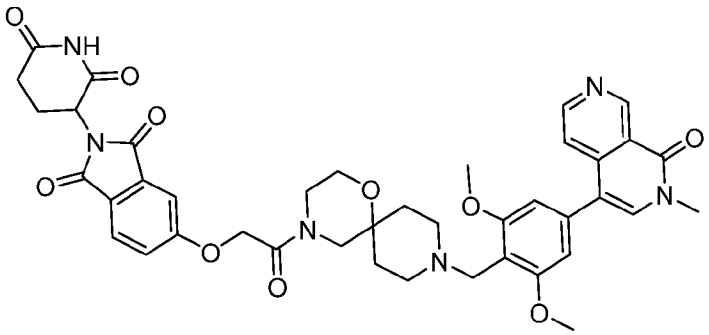
Compound No.	Structure
D41	
D42	
D43	
D44	

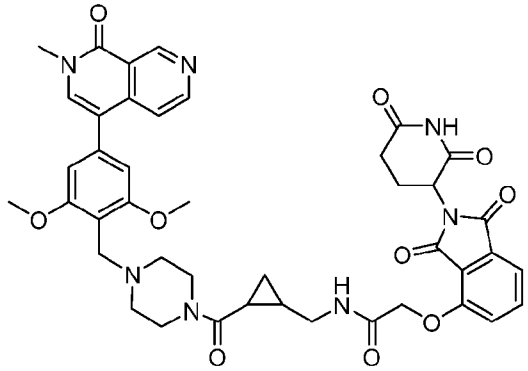
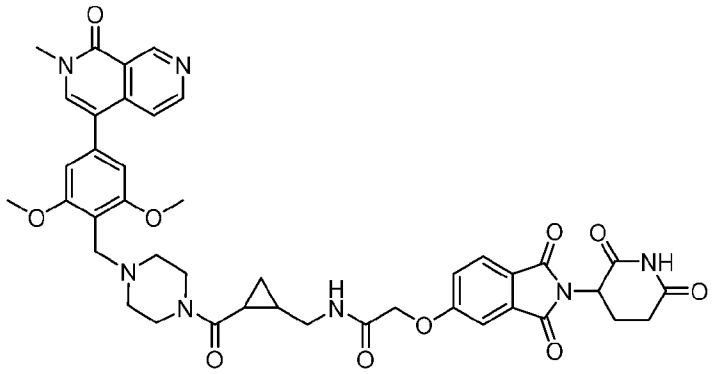
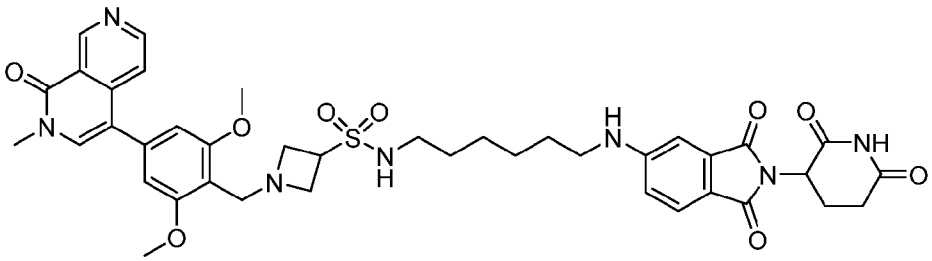
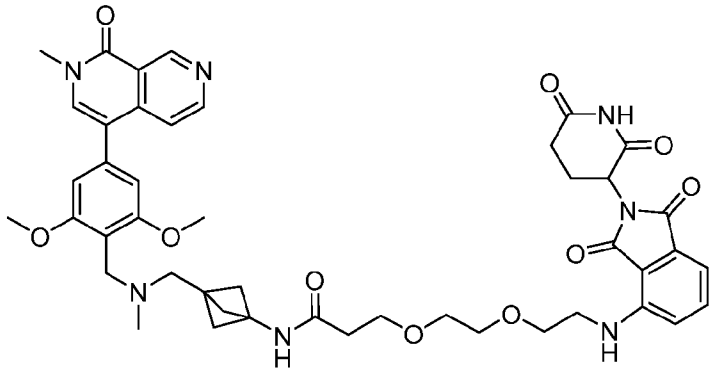
Compound No.	Structure
D45	
D46	
D47	
D48	

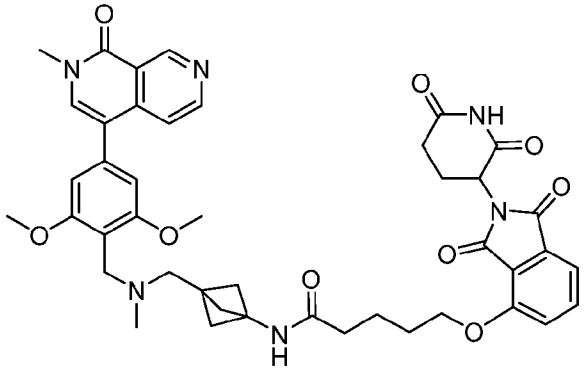
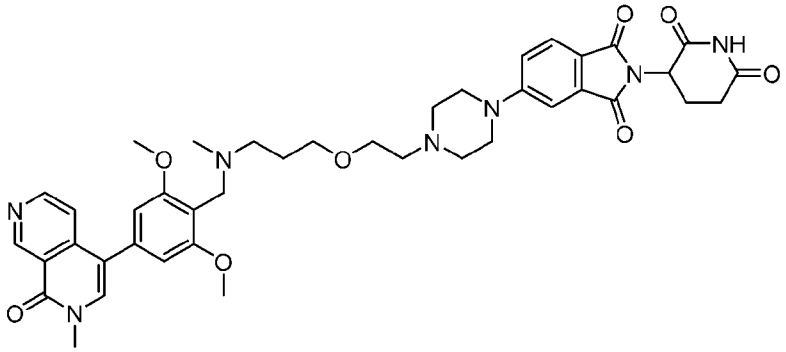
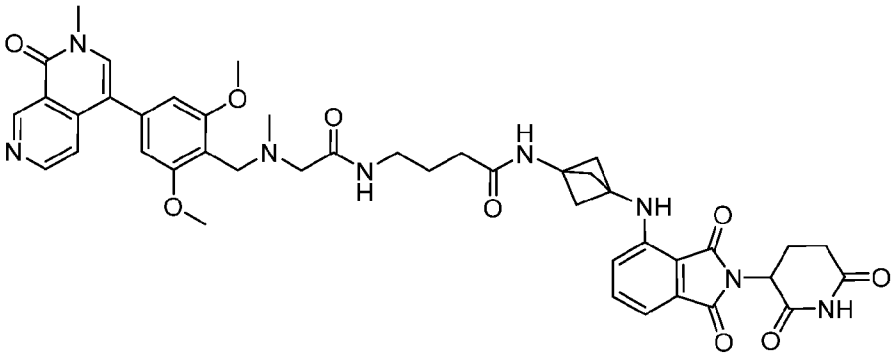
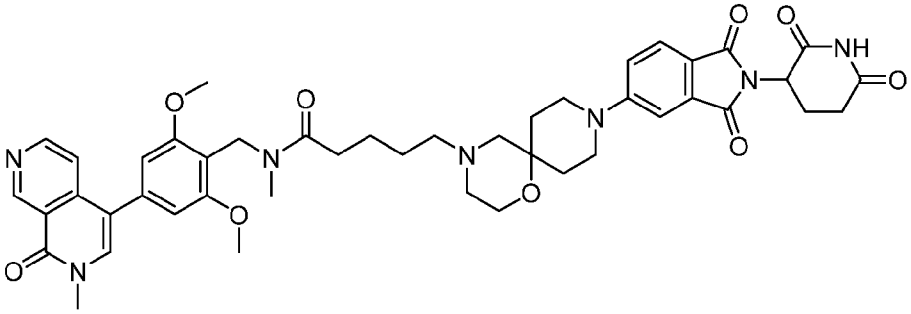
Compound No.	Structure
D49	
D50	
D51	
D52	

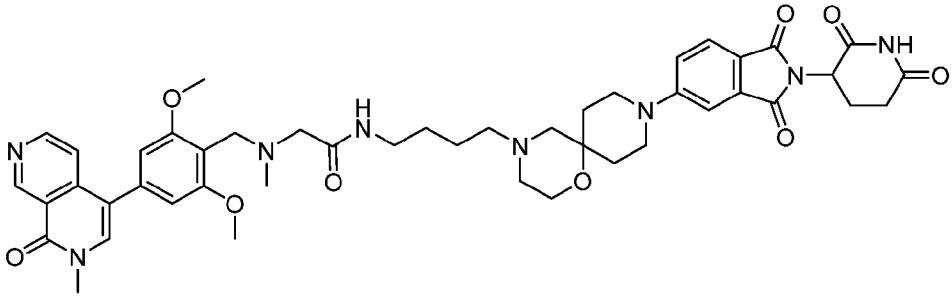
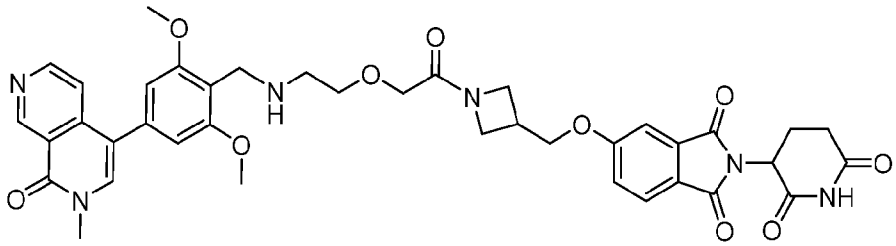
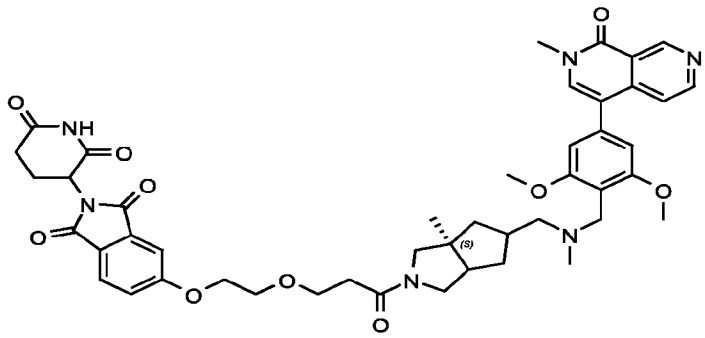
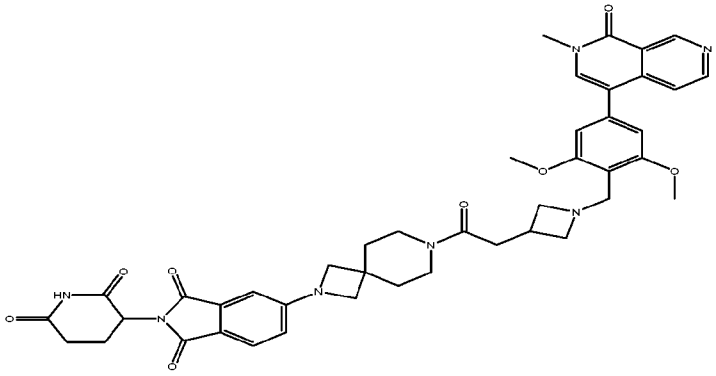
Compound No.	Structure
D53	
D54	
D55	
D56	

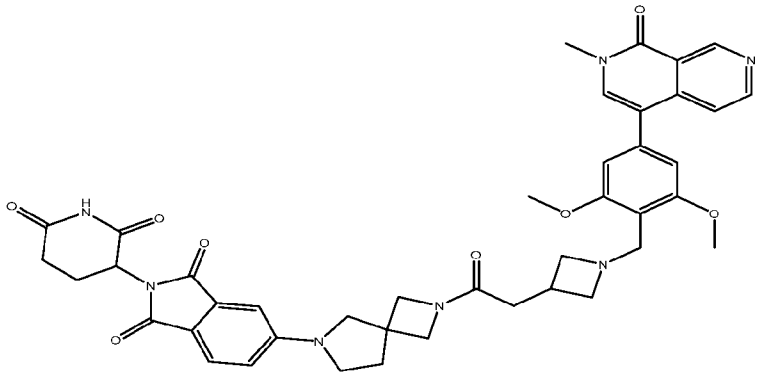
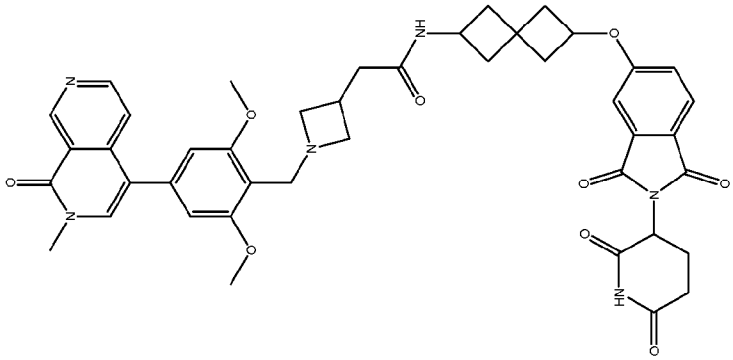
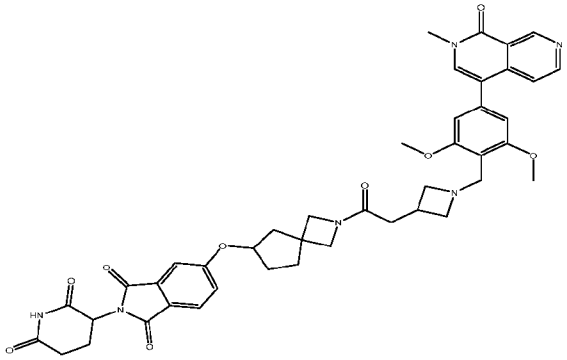
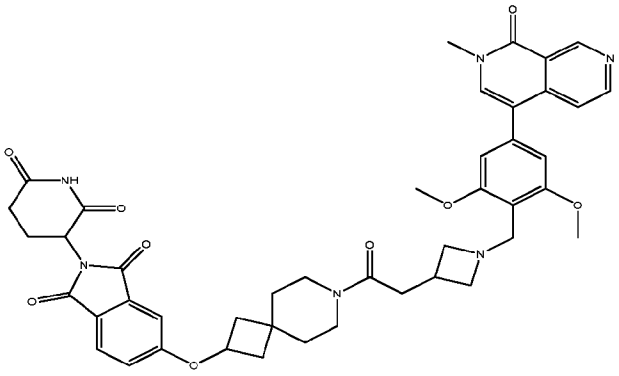
Compound No.	Structure
D57	
D58	
D59	
D60	

Compound No.	Structure
D61	
D62	
D63	
D64	

Compound No.	Structure
D65	
D66	
D67	
D68	

Compound No.	Structure
D69	
D70	
D71	
D72	

Compound No.	Structure
D73	
D74	
D75	
D76	

Compound No.	Structure
D77	
D78	
D79	
D80	

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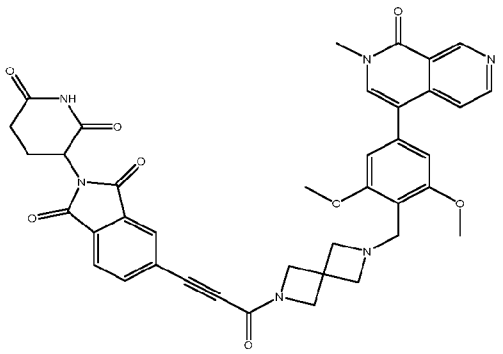
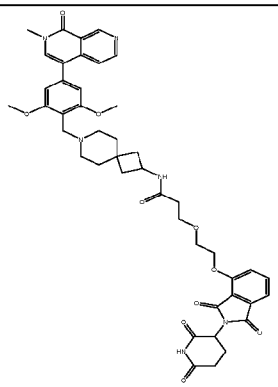
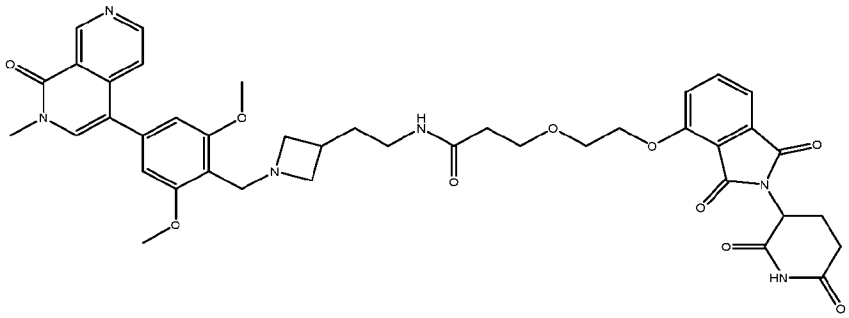
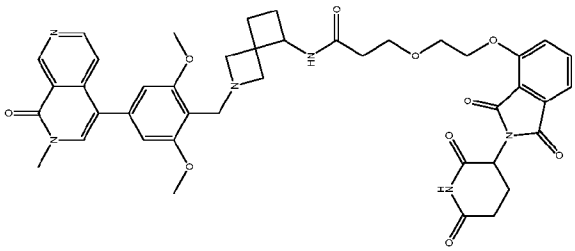
D81	
D82	
D83	
D84	

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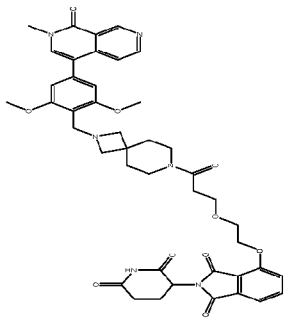
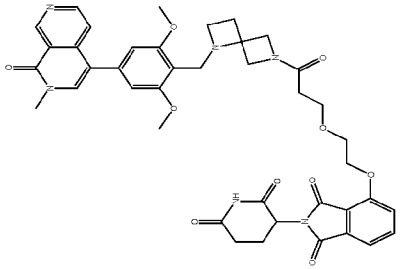
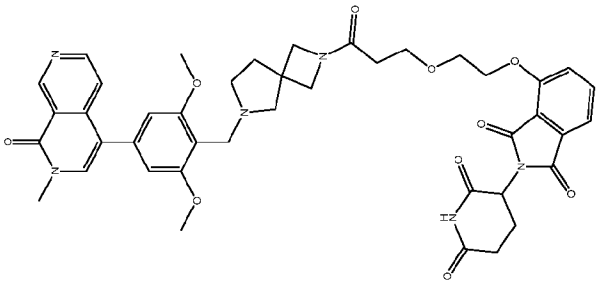
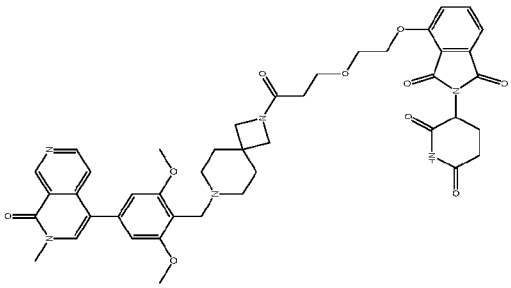
D85	
D86	
D87	
D88	

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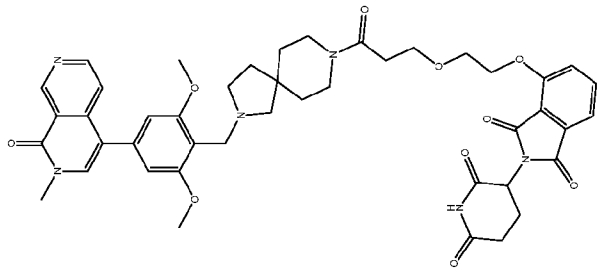
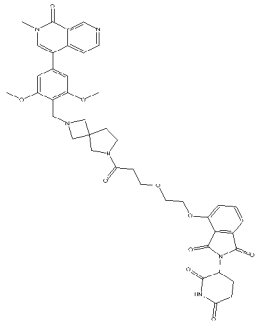
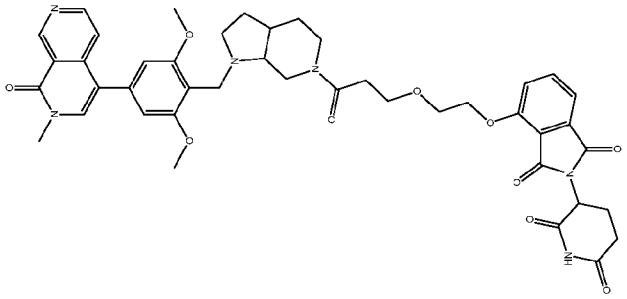
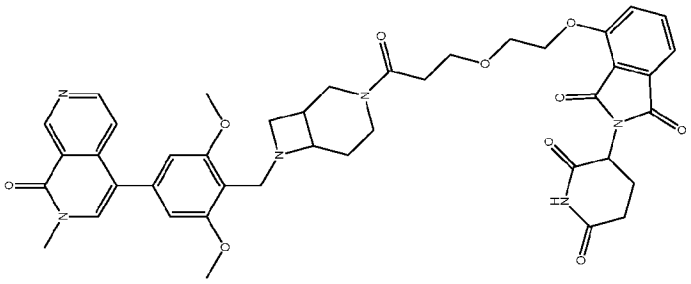
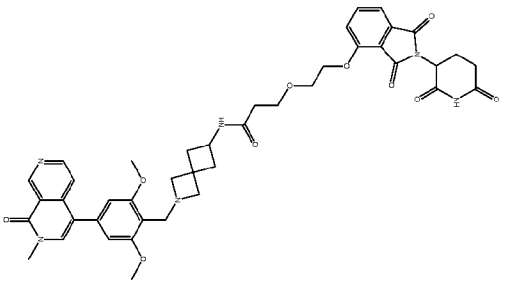
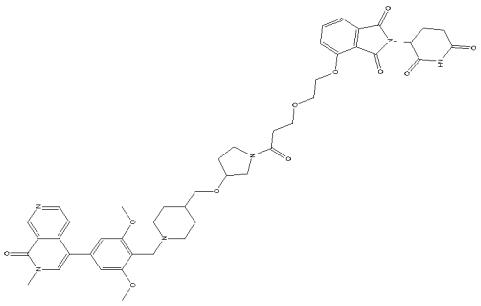
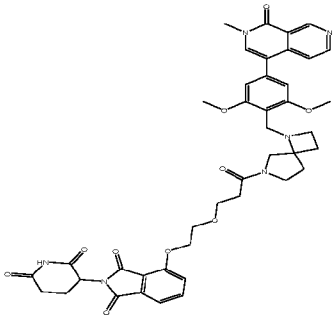
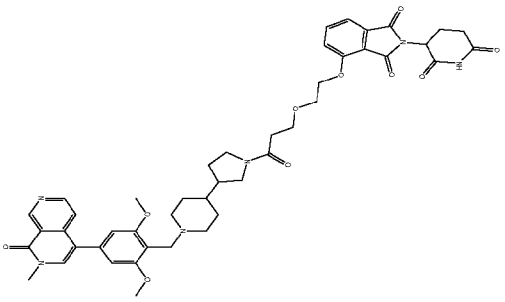
D89	
D90	
D91	
D92	

Compound No.	Structure
D93	
D94	
D95	
D96	

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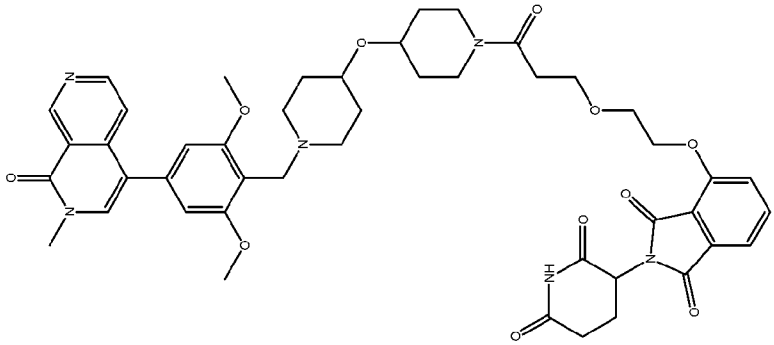
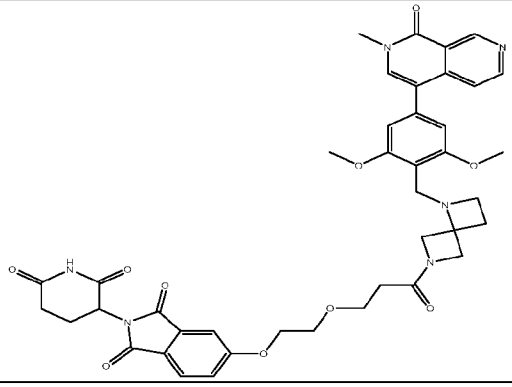
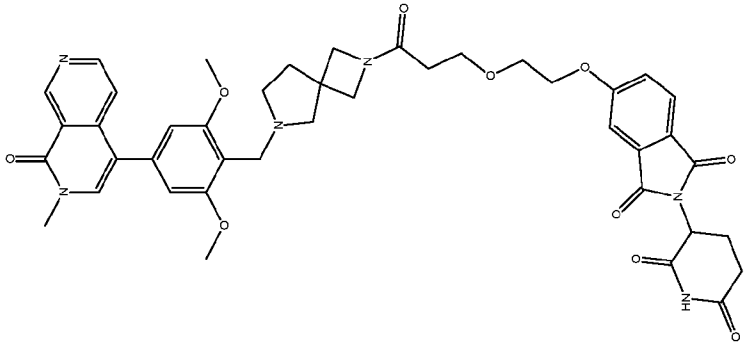
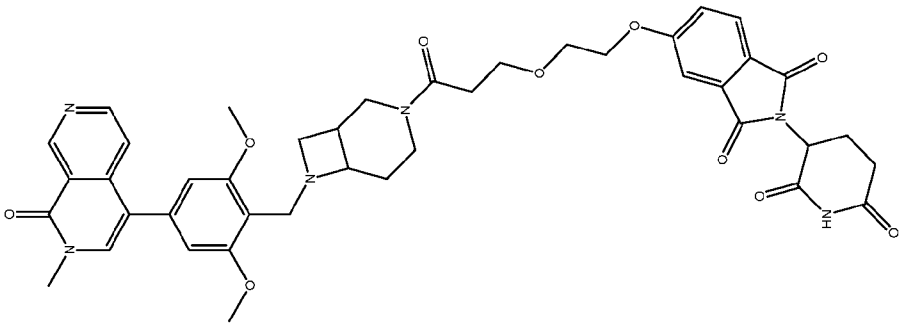
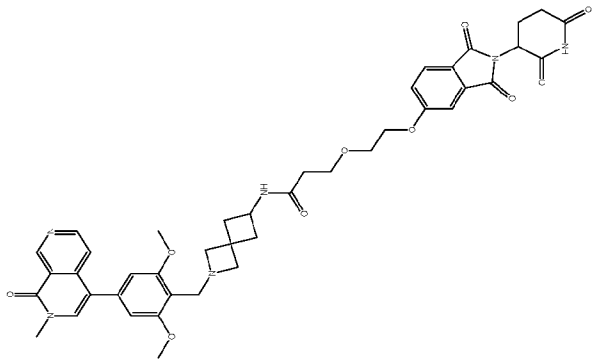
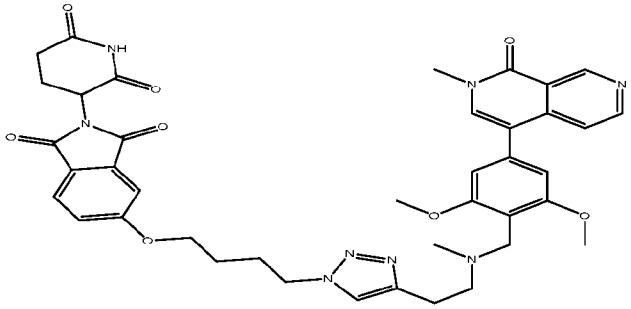
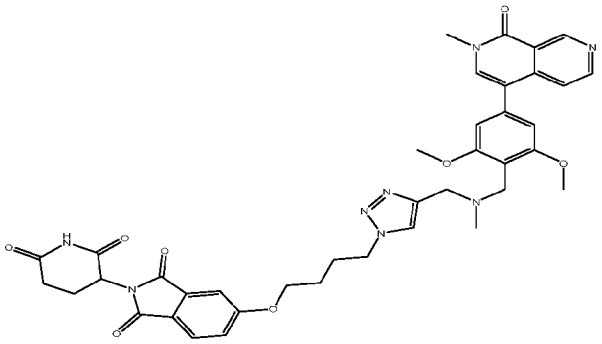
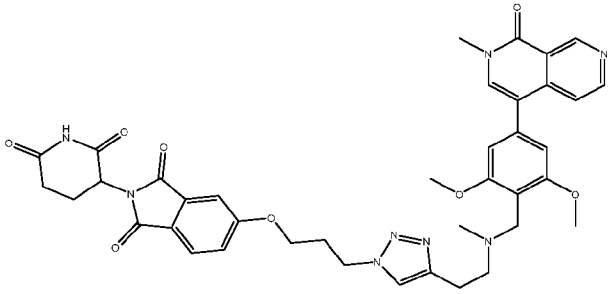
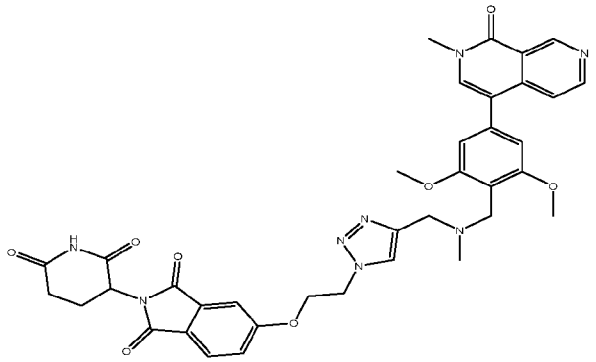
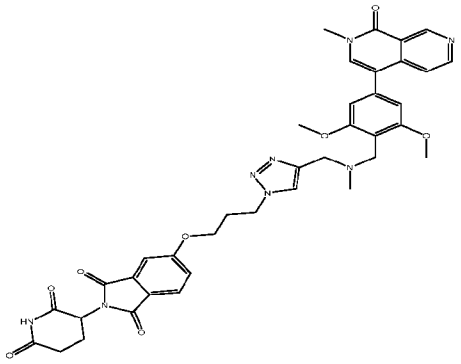
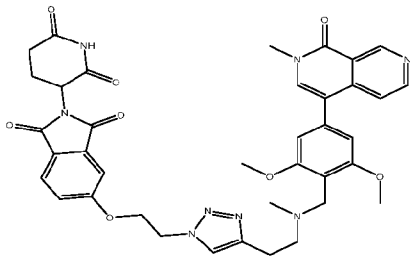
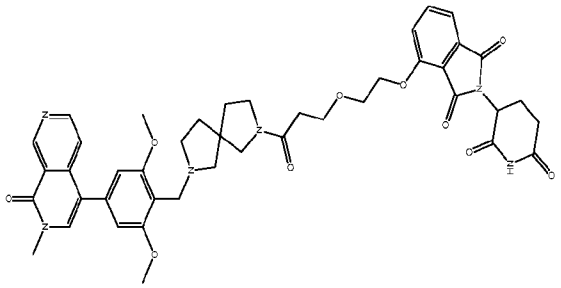
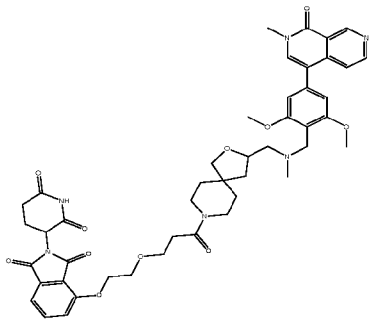
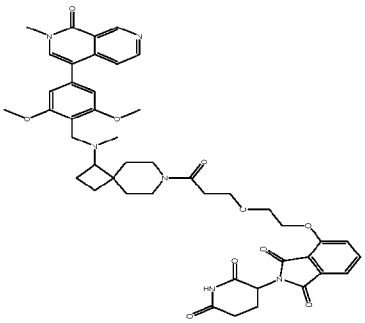
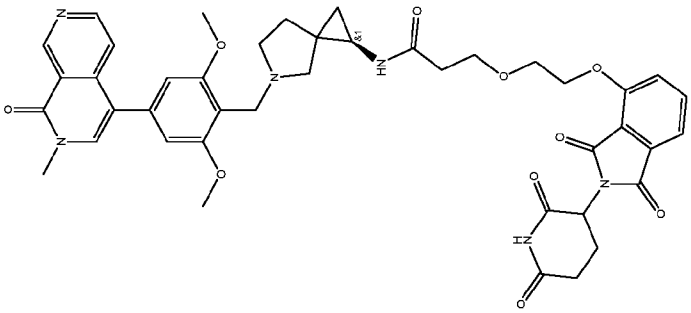
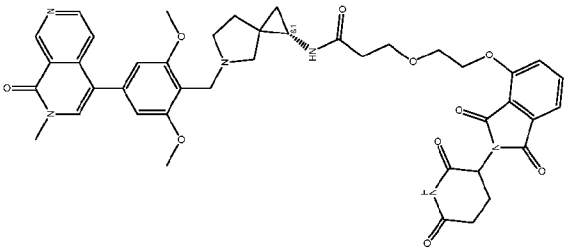
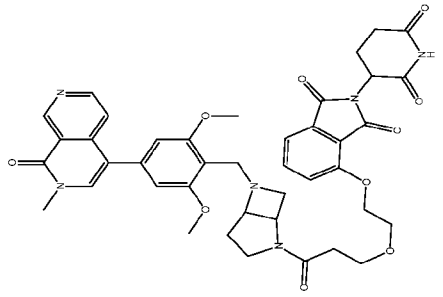
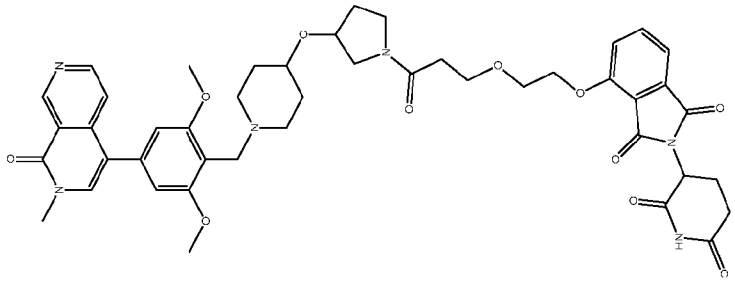
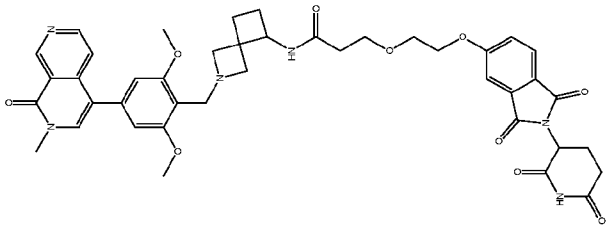
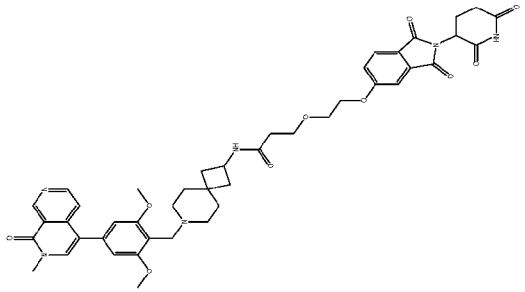
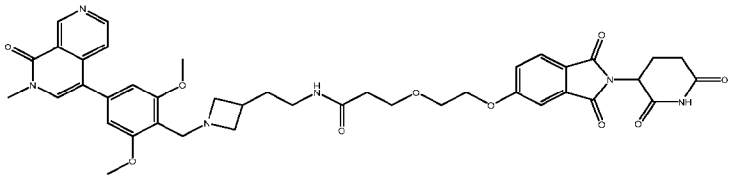
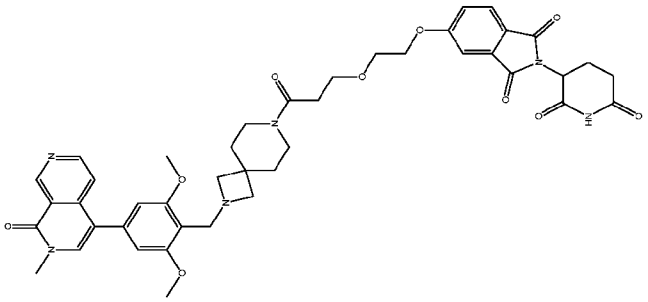
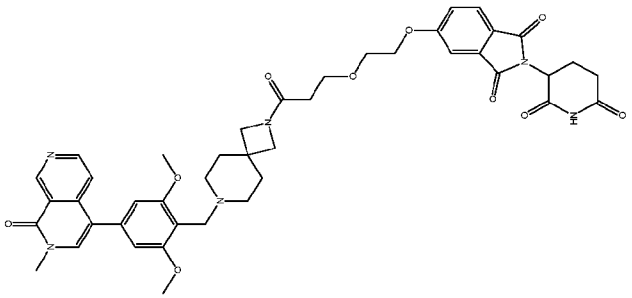
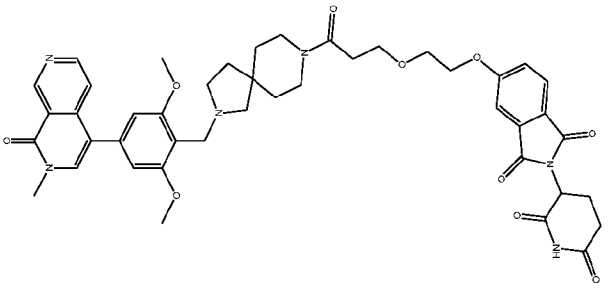
D97	
D98	
D99	
D100	

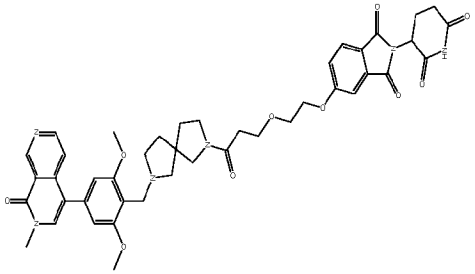
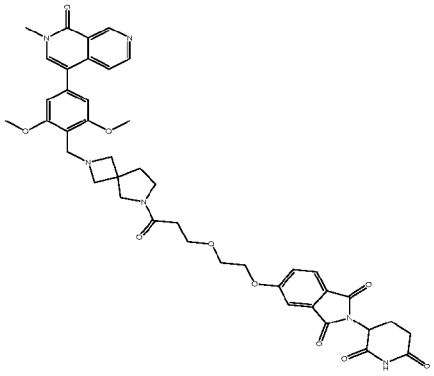
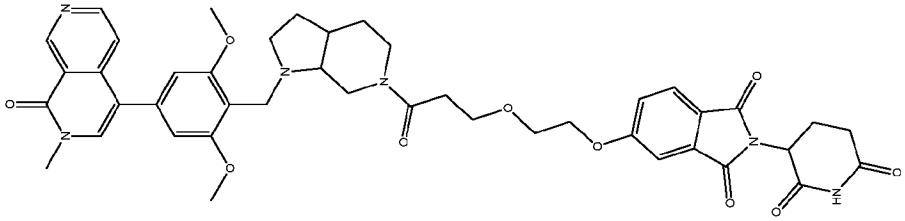
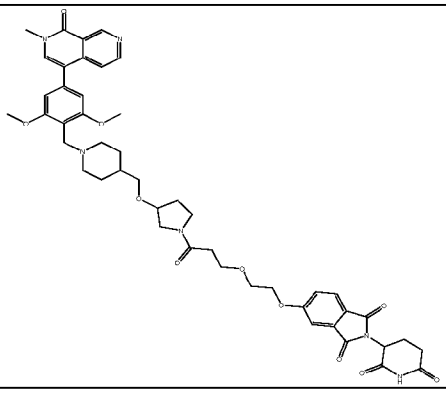
Compound No.	Structure
D101	
D102	
D103	
D104	

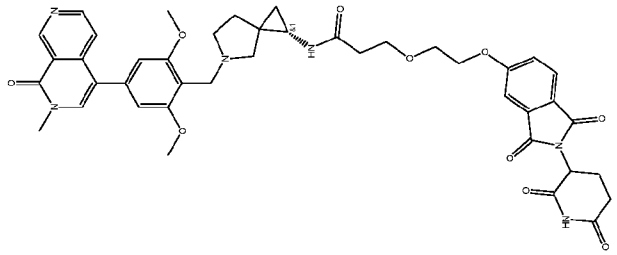
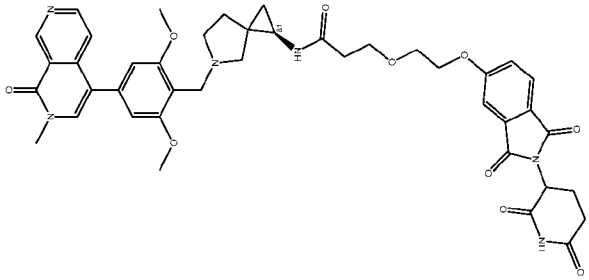
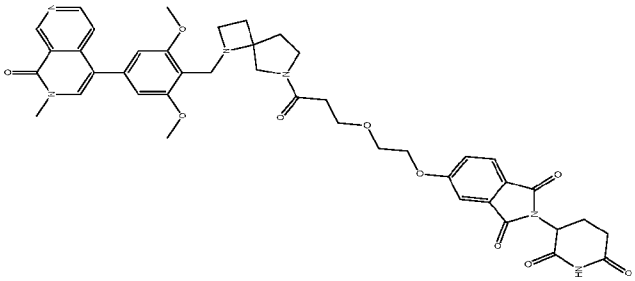
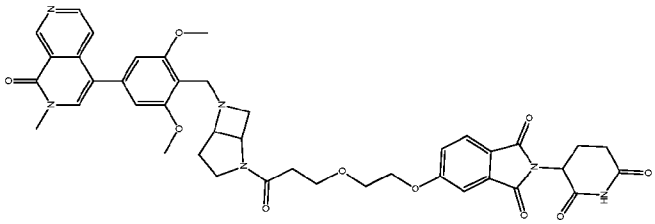
Compound No.	Structure
D105	
D106	
D107	
D108	

Compound No.	Structure
D109	
D110	
D111	
D112	

Compound No.	Structure
D113	
D114	
D115	
D116	

Compound No.	Structure
D117	
D118	
D119	
D120	

Compound No.	Structure
D121	
D122	
D123	
D124	

Compound No.	Structure
D125	
D126	
D127	
D128	

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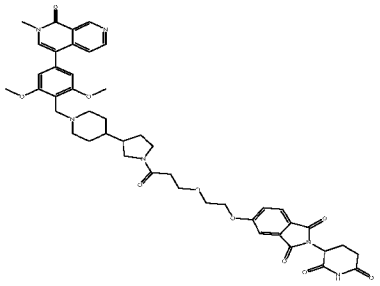
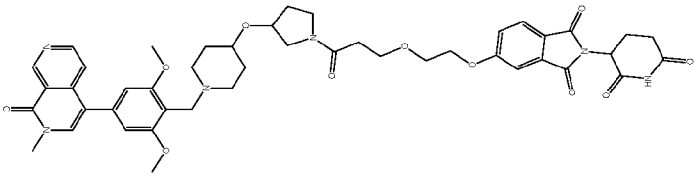
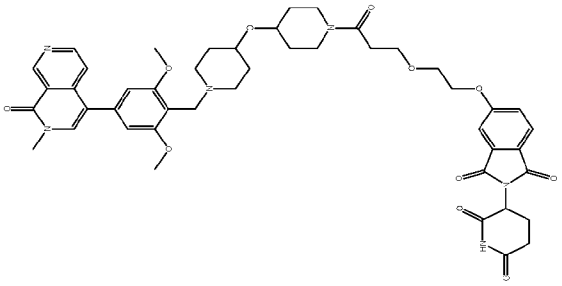
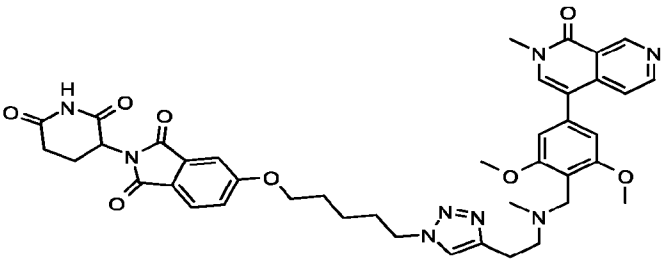
D129	
D130	
D131	
D132	

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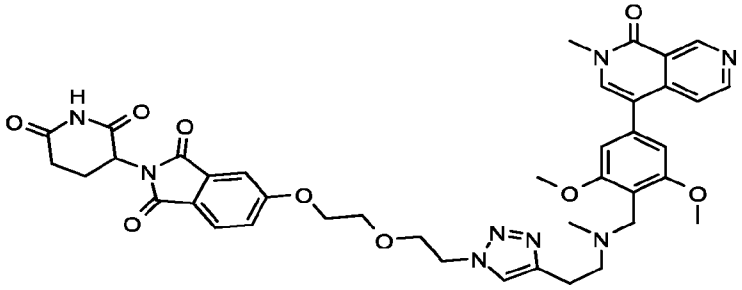
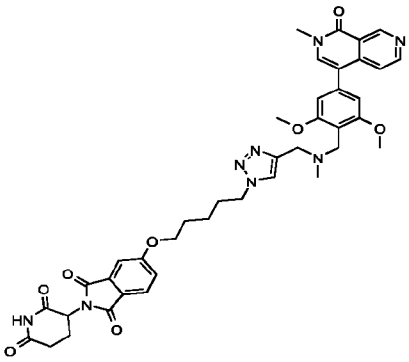
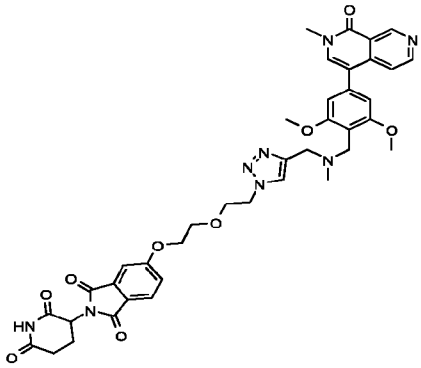
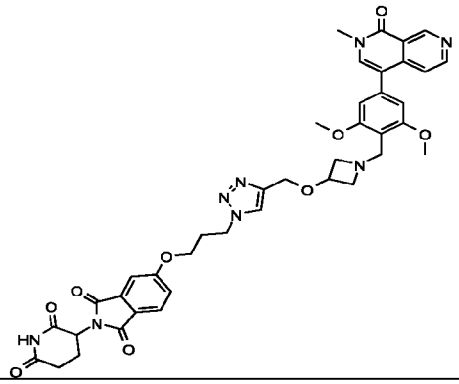
D133	
D134	
D135	
D136	

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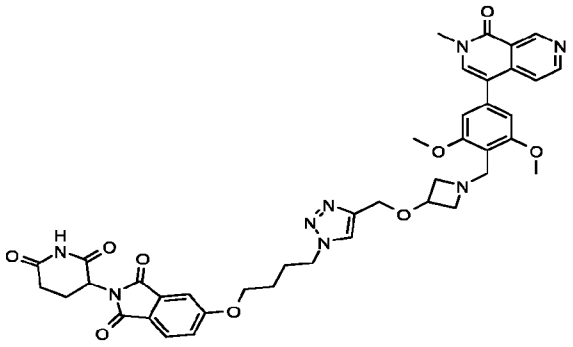
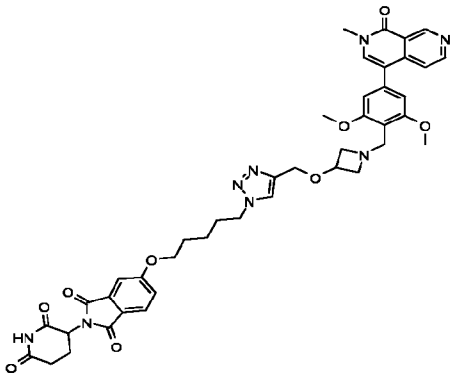
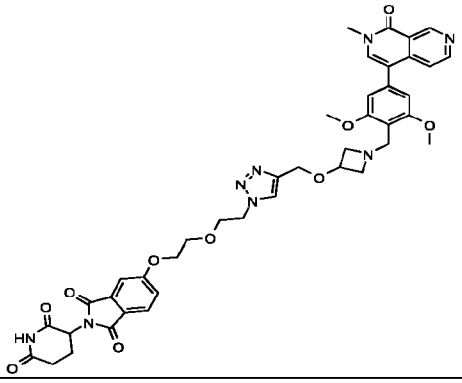
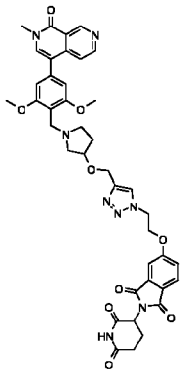
D137	
D138	
D139	
D140	

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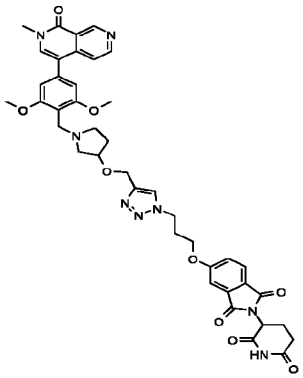
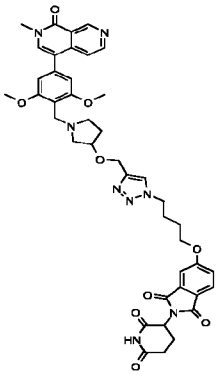
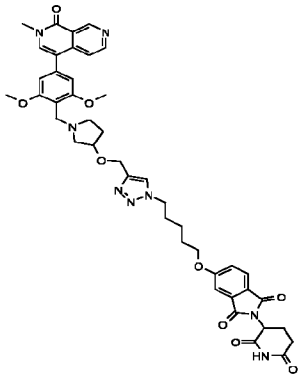
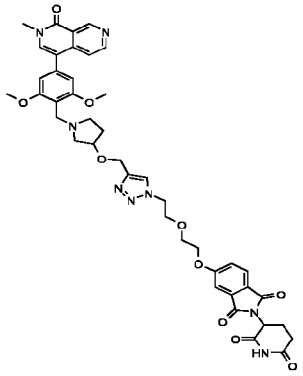
D141	
D142	
D143	
D144	

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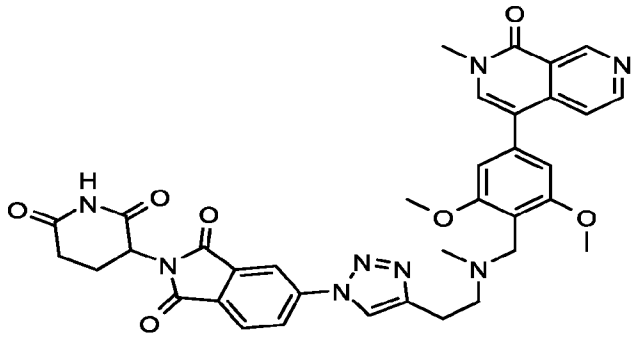
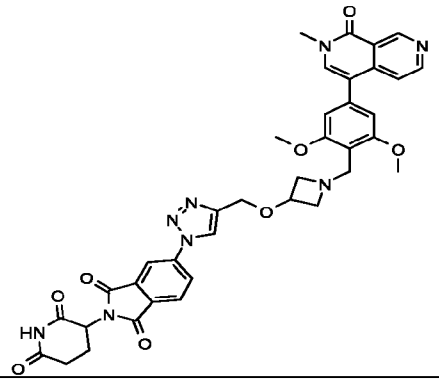
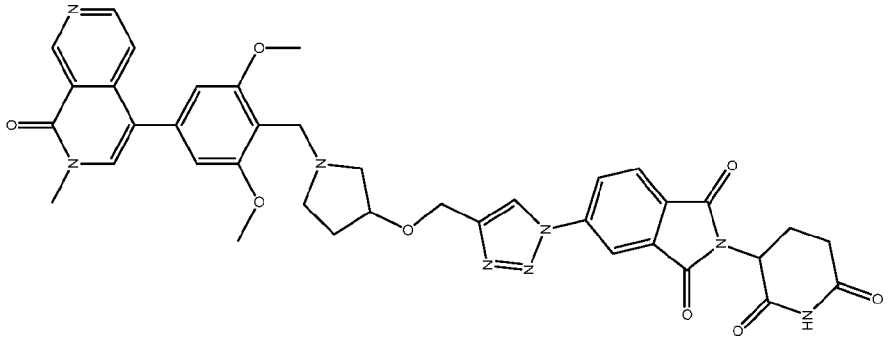
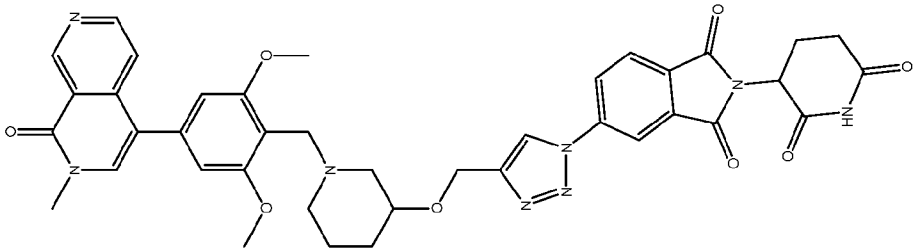
D145	
D146	
D147	
D148	

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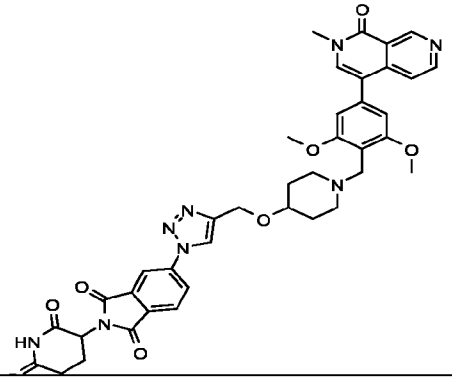
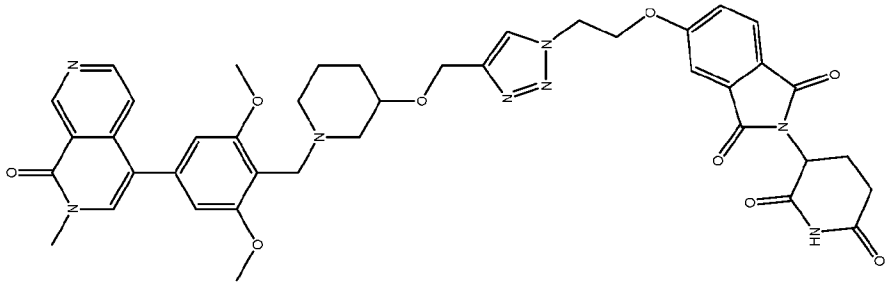
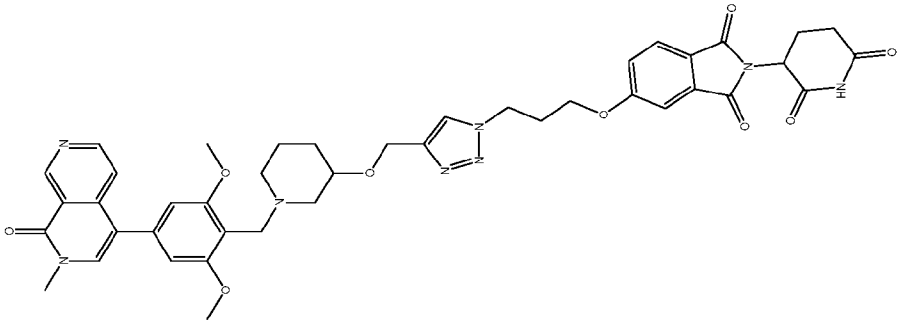
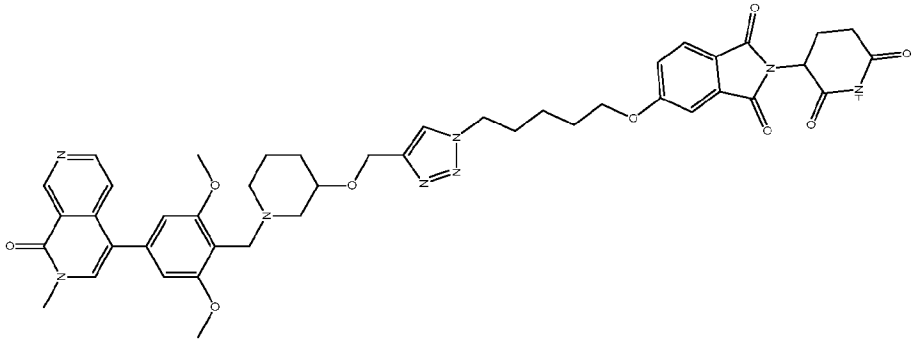
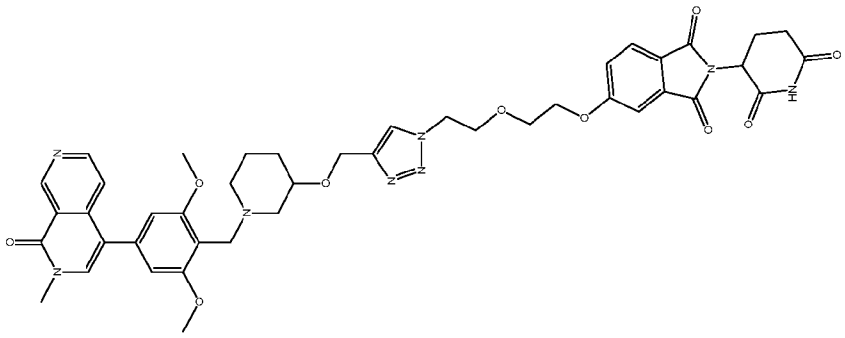
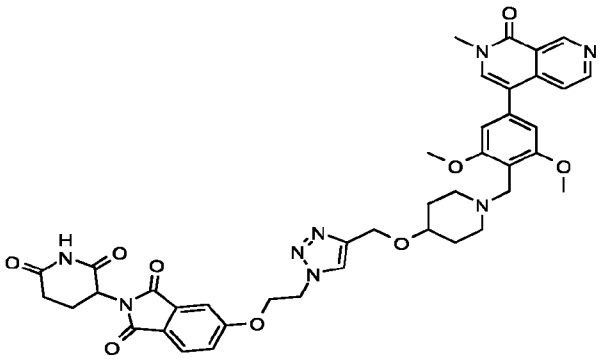
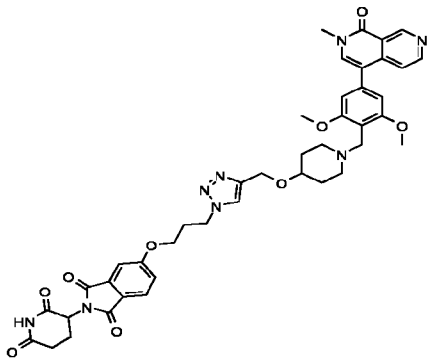
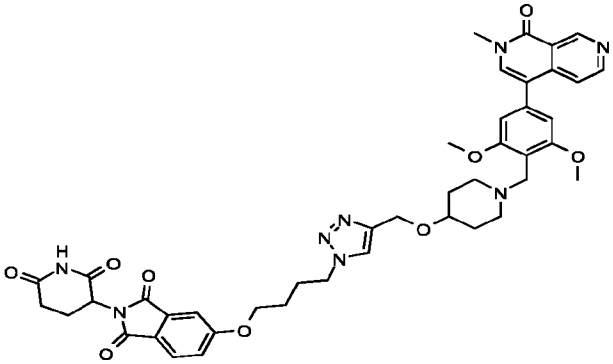
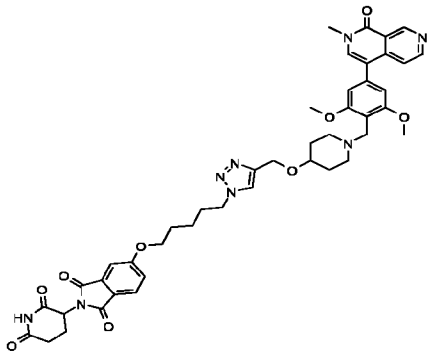
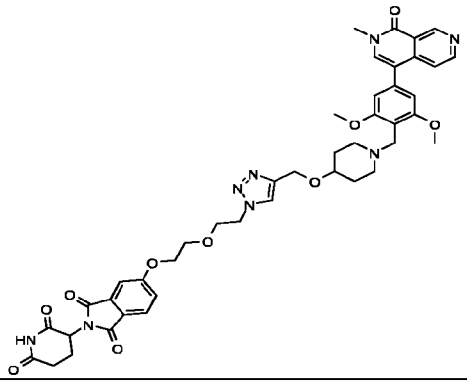
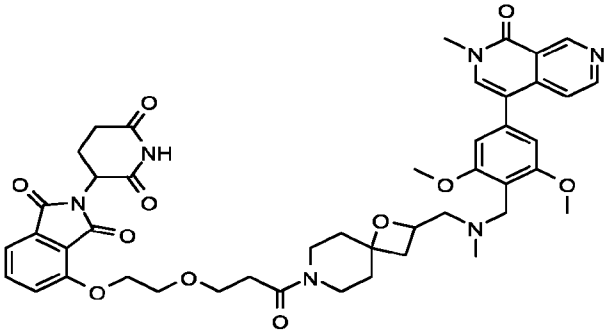
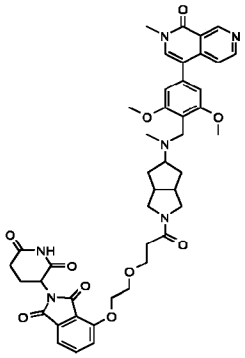
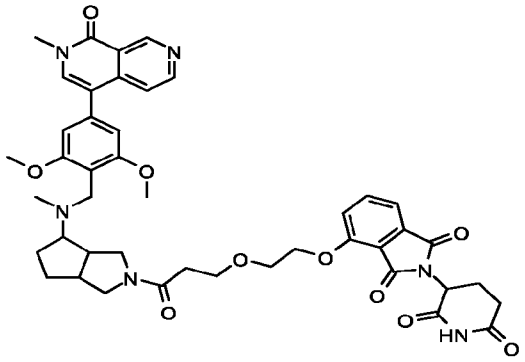
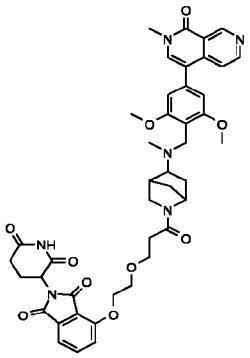
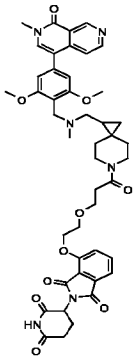
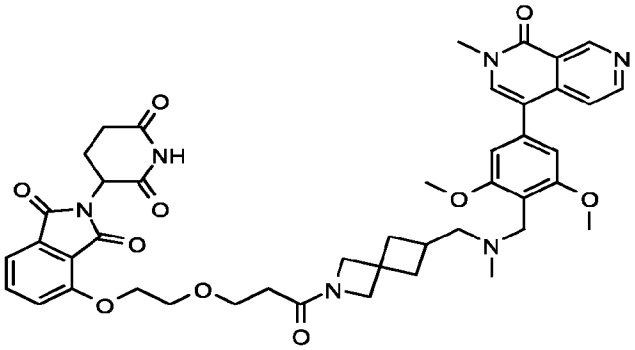
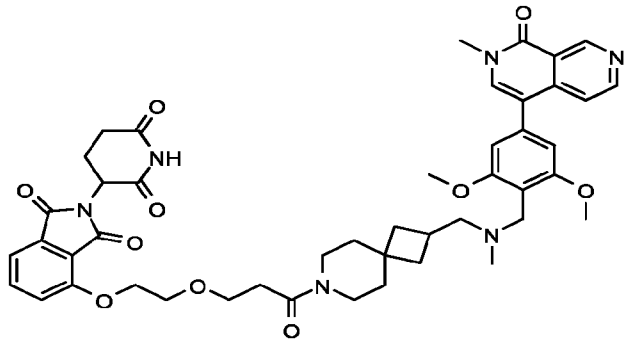
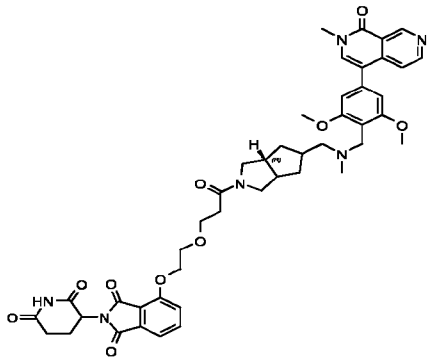
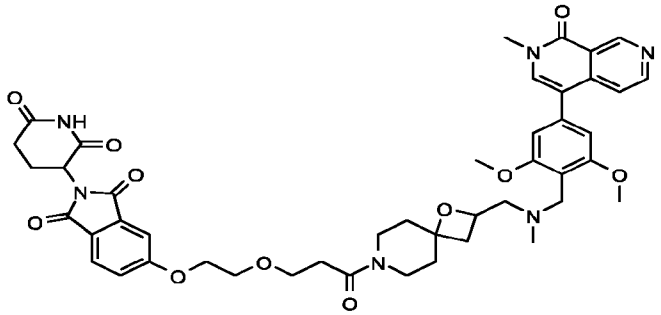
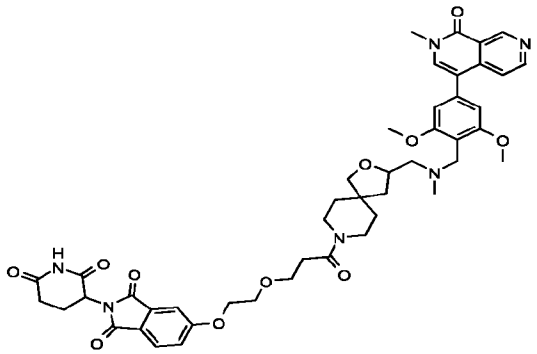
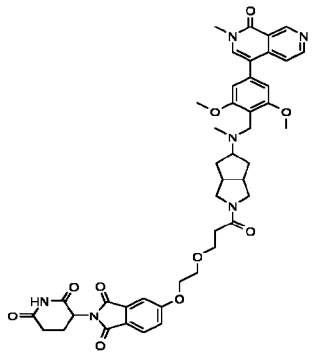
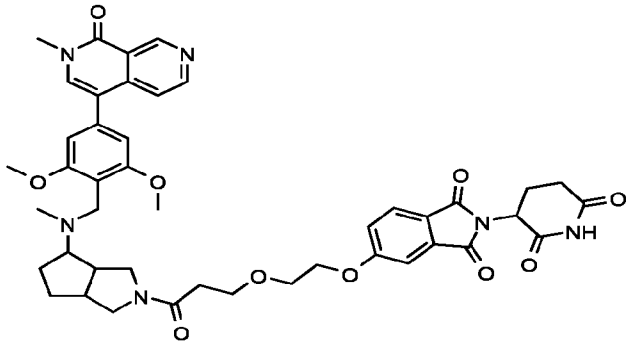
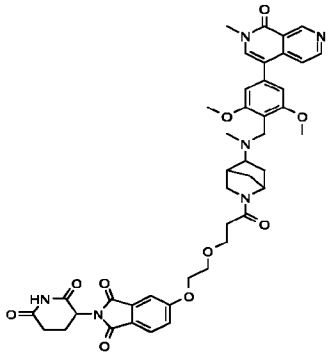
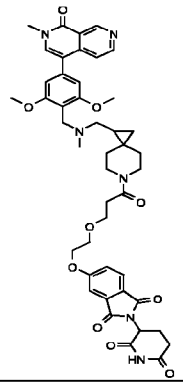
D149	
D150	
D151	
D152	

Compound No.	Structure
D153	
D154	
D155	
D156	

Compound No.	Structure
D157	
D158	
D159	
D160	

Compound No.	Structure
D161	
D162	
D163	
D164	

Compound No.	Structure
D165	
D166	
D167	
D168	

Compound No.	Structure
D169	
D170	
D171	
D172	

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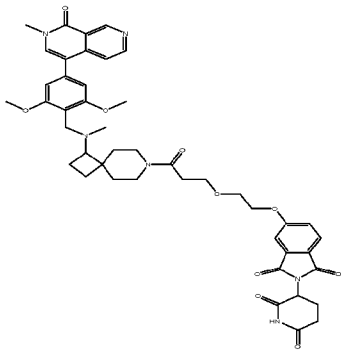
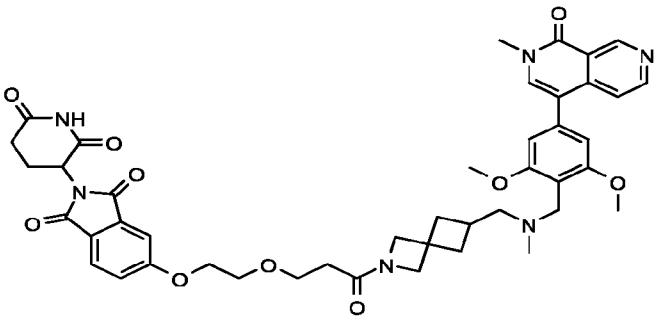
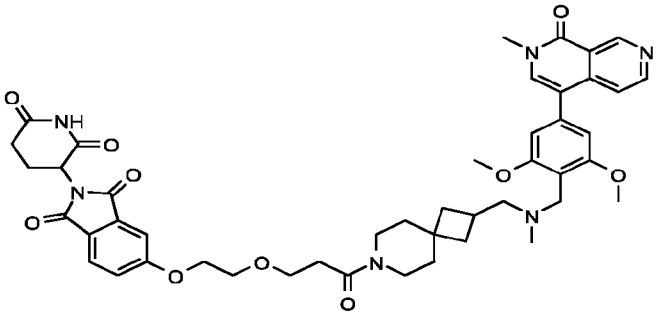
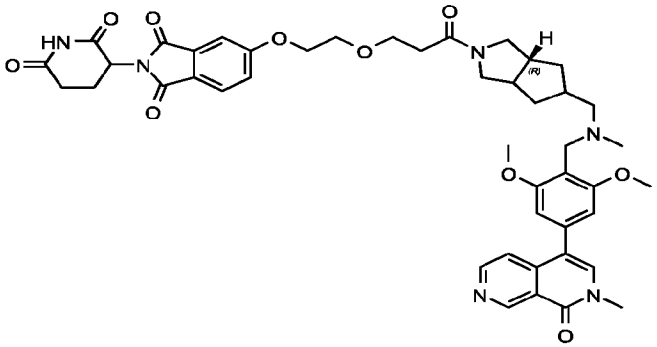
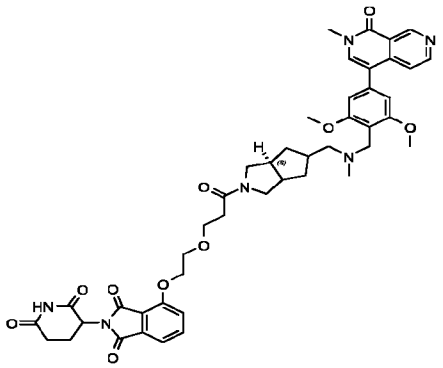
D173	
D174	
D175	
D176	

Compound No.	Structure
D177	

In another aspect, the disclosure features a pharmaceutical composition including any of the foregoing compounds, or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable excipient.

In an aspect, the disclosure features a method of inhibiting the level and/or activity of BRD9 in a cell, the method involving contacting the cell with an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof.

In another aspect, the disclosure features a method of reducing the level and/or activity of BRD9 in a cell, the method involving contacting the cell with an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof.

In some embodiments, the cell is a cancer cell.

In some embodiments, the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, colorectal cancer, a sarcoma (e.g., a soft tissue sarcoma, synovial sarcoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, adult fibrosarcoma, alveolar soft-part sarcoma, angiosarcoma, clear cell sarcoma, desmoplastic small round cell tumor, epithelioid sarcoma, fibromyxoid sarcoma, gastrointestinal stromal tumor, Kaposi sarcoma, liposarcoma, leiomyosarcoma, malignant mesenchymoma malignant peripheral nerve sheath tumors, myxofibrosarcoma, low-grade rhabdomyosarcoma), non-small cell lung cancer (e.g., squamous or adenocarcinoma), stomach cancer, or breast cancer. In some embodiments, the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, or colorectal cancer. In some embodiments, the cancer is a sarcoma (e.g., synovial sarcoma or Ewing's sarcoma), non-small cell lung cancer (e.g., squamous or adenocarcinoma), stomach cancer, or breast cancer. In some embodiments, the cancer is sarcoma (e.g., synovial sarcoma or Ewing's sarcoma). In some embodiments, the sarcoma is synovial sarcoma.

In an aspect, the disclosure features a method of treating a BAF complex-related disorder in a subject in need thereof, the method involving administering to the subject an effective amount of any of

the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof. In some embodiments, the BAF complex-related disorder is cancer. In some embodiments, the BAF complex-related disorder is infection.

In another aspect, the disclosure features a method of treating an SS18-SSX fusion protein-related disorder in a subject in need thereof, the method involving administering to the subject an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof. In some embodiments, the SS18-SSX fusion protein-related disorder is cancer. In some embodiments, the SS18-SSX fusion protein-related disorder is infection. In some embodiments of any of the foregoing methods, the SS18-SSX fusion protein is a SS18-SSX1 fusion protein, a SS18-SSX2 fusion protein, or a SS18-SSX4 fusion protein.

In yet another aspect, the disclosure features a method of treating a BRD9-related disorder in a subject in need thereof, the method involving administering to the subject an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof. In some embodiments, the BRD9-related disorder is cancer. In some embodiments, the BRD9-related disorder is infection.

In some embodiments, the cancer is squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, hepatocellular carcinomas, and renal cell carcinomas, cancer of the bladder, bowel, breast, cervix, colon, esophagus, head, kidney, liver, lung, neck, ovary, pancreas, prostate, and stomach; leukemias; benign and malignant lymphomas, particularly Burkitt's lymphoma and Non-Hodgkin's lymphoma; benign and malignant melanomas; myeloproliferative diseases; sarcomas, including Ewing's sarcoma, hemangiosarcoma, Kaposi's sarcoma, liposarcoma, myosarcomas, peripheral neuroepithelioma, synovial sarcoma, gliomas, astrocytomas, oligodendrogliomas, ependymomas, gliobastomas, neuroblastomas, ganglioneuromas, gangliogliomas, medulloblastomas, pineal cell tumors, meningiomas, meningeal sarcomas, neurofibromas, and Schwannomas; bowel cancer, breast cancer, prostate cancer, cervical cancer, uterine cancer, lung cancer, ovarian cancer, testicular cancer, thyroid cancer, astrocytoma, esophageal cancer, pancreatic cancer, stomach cancer, liver cancer, colon cancer, melanoma; carcinosarcoma, Hodgkin's disease, Wilms' tumor and teratocarcinomas. Additional cancers which may be treated using the disclosed compounds according to the present invention include, for example, acute granulocytic leukemia, acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), adenocarcinoma, adenosarcoma, adrenal cancer, adrenocortical carcinoma, anal cancer, anaplastic astrocytoma, angiosarcoma, appendix cancer, astrocytoma, Basal cell carcinoma, B-Cell lymphoma, bile duct cancer, bladder cancer, bone cancer, bone marrow cancer, bowel cancer, brain cancer, brain stem glioma, breast cancer, triple (estrogen, progesterone and HER-2) negative breast cancer, double negative breast cancer (two of estrogen, progesterone and HER-2 are negative), single negative (one of estrogen, progesterone and HER-2 is negative), estrogen-receptor positive, HER2-negative breast cancer, estrogen receptor-negative breast cancer, estrogen receptor positive breast cancer, metastatic breast cancer, luminal A breast cancer, luminal B breast cancer, Her2-negative breast

cancer, HER2-positive or negative breast cancer, progesterone receptor-negative breast cancer, progesterone receptor-positive breast cancer, recurrent breast cancer, carcinoid tumors, cervical cancer, cholangiocarcinoma, chondrosarcoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), colon cancer, colorectal cancer, craniopharyngioma, cutaneous lymphoma, cutaneous melanoma, diffuse astrocytoma, ductal carcinoma in situ (DCIS), endometrial cancer, ependymoma, epithelioid sarcoma, esophageal cancer, ewing sarcoma, extrahepatic bile duct cancer, eye cancer, fallopian tube cancer, fibrosarcoma, gallbladder cancer, gastric cancer, gastrointestinal cancer, gastrointestinal carcinoid cancer, gastrointestinal stromal tumors (GIST), germ cell tumor glioblastoma multiforme (GBM), glioma, hairy cell leukemia, head and neck cancer, hemangioendothelioma, Hodgkin lymphoma, hypopharyngeal cancer, infiltrating ductal carcinoma (IDC), infiltrating lobular carcinoma (ILC), inflammatory breast cancer (IBC), intestinal Cancer, intrahepatic bile duct cancer, invasive/infiltrating breast cancer, Islet cell cancer, jaw cancer, Kaposi sarcoma, kidney cancer, laryngeal cancer, leiomyosarcoma, leptomeningeal metastases, leukemia, lip cancer, liposarcoma, liver cancer, lobular carcinoma in situ, low-grade astrocytoma, lung cancer, lymph node cancer, lymphoma, male breast cancer, medullary carcinoma, medulloblastoma, melanoma, meningioma, Merkel cell carcinoma, mesenchymal chondrosarcoma, mesenchymous, mesothelioma metastatic breast cancer, metastatic melanoma metastatic squamous neck cancer, mixed gliomas, monodermal teratoma, mouth cancer mucinous carcinoma, mucosal melanoma, multiple myeloma, Mycosis Fungoides, myelodysplastic syndrome, nasal cavity cancer, nasopharyngeal cancer, neck cancer, neuroblastoma, neuroendocrine tumors (NETs), non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), oat cell cancer, ocular cancer, ocular melanoma, oligodendroglioma, oral cancer, oral cavity cancer, oropharyngeal cancer, osteogenic sarcoma, osteosarcoma, ovarian cancer, ovarian epithelial cancer ovarian germ cell tumor, ovarian primary peritoneal carcinoma, ovarian sex cord stromal tumor, Paget's disease, pancreatic cancer, papillary carcinoma, paranasal sinus cancer, parathyroid cancer, pelvic cancer, penile cancer, peripheral nerve cancer, peritoneal cancer, pharyngeal cancer, pheochromocytoma, pilocytic astrocytoma, pineal region tumor, pineoblastoma, pituitary gland cancer, primary central nervous system (CNS) lymphoma, prostate cancer, rectal cancer, renal cell carcinoma, renal pelvis cancer, rhabdomyosarcoma, salivary gland cancer, soft tissue sarcoma, bone sarcoma, sarcoma, sinus cancer, skin cancer, small cell lung cancer (SCLC), small intestine cancer, spinal cancer, spinal column cancer, spinal cord cancer, squamous cell carcinoma, stomach cancer, synovial sarcoma, T-cell lymphoma, testicular cancer, throat cancer, thymoma/thymic carcinoma, thyroid cancer, tongue cancer, tonsil cancer, transitional cell cancer, tubal cancer, tubular carcinoma, undiagnosed cancer, ureteral cancer, urethral cancer, uterine adenocarcinoma, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, T-cell lineage acute lymphoblastic leukemia (T-ALL), T-cell lineage lymphoblastic lymphoma (T-LL), peripheral T-cell lymphoma, Adult T-cell leukemia, Pre-B ALL, Pre-B lymphomas, large B-cell lymphoma, Burkitts lymphoma, B-cell ALL, Philadelphia chromosome positive ALL, Philadelphia chromosome positive CML, juvenile myelomonocytic leukemia (JMML), acute promyelocytic leukemia (a subtype of AML), large

granular lymphocytic leukemia, Adult T-cell chronic leukemia, diffuse large B cell lymphoma, follicular lymphoma; Mucosa-Associated Lymphatic Tissue lymphoma (MALT), small cell lymphocytic lymphoma, mediastinal large B cell lymphoma, nodal marginal zone B cell lymphoma (NMZL); splenic marginal zone lymphoma (SMZL); intravascular large B-cell lymphoma; primary effusion lymphoma; or lymphomatoid granulomatosis;; B-cell prolymphocytic leukemia; splenic lymphoma/leukemia, unclassifiable, splenic diffuse red pulp small B-cell lymphoma; lymphoplasmacytic lymphoma; heavy chain diseases, for example, Alpha heavy chain disease, Gamma heavy chain disease, Mu heavy chain disease, plasma cell myeloma, solitary plasmacytoma of bone; extraosseous plasmacytoma; primary cutaneous follicle center lymphoma, T cell/histocyte rich large B-cell lymphoma, DLBCL associated with chronic inflammation; Epstein-Barr virus (EBV)+ DLBCL of the elderly; primary mediastinal (thymic) large B-cell lymphoma, primary cutaneous DLBCL, leg type, ALK+ large B-cell lymphoma, plasmablastic lymphoma; large B-cell lymphoma arising in HHV8-associated multicentric, Castleman disease; B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma, or B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma.

In some embodiments, the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, colorectal cancer, a sarcoma (e.g., a soft tissue sarcoma, synovial sarcoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, adult fibrosarcoma, alveolar soft-part sarcoma, angiosarcoma, clear cell sarcoma, desmoplastic small round cell tumor, epithelioid sarcoma, fibromyxoid sarcoma, gastrointestinal stromal tumor, Kaposi sarcoma, liposarcoma, leiomyosarcoma, malignant mesenchymoma malignant peripheral nerve sheath tumors, myxofibrosarcoma, low-grade rhabdomyosarcoma), non-small cell lung cancer (e.g., squamous or adenocarcinoma), stomach cancer, or breast cancer. In some embodiments, the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, or colorectal cancer. In some embodiments, the cancer is a sarcoma (e.g., synovial sarcoma or Ewing's sarcoma), non-small cell lung cancer (e.g., squamous or adenocarcinoma), stomach cancer, or breast cancer. In some embodiments, the cancer is sarcoma (e.g., synovial sarcoma or Ewing's sarcoma). In some embodiments, the sarcoma is synovial sarcoma.

In some embodiments, the infection is viral infection (e.g., an infection with a virus of the Retroviridae family such as the lentiviruses (e.g. Human immunodeficiency virus (HIV) and deltaretroviruses (e.g., human T cell leukemia virus I (HTLV-I), human T cell leukemia virus II (HTLV-II)); Hepadnaviridae family (e.g. hepatitis B virus (HBV)); Flaviviridae family (e.g. hepatitis C virus (HCV)); Adenoviridae family (e.g. Human Adenovirus); Herpesviridae family (e.g. Human cytomegalovirus (HCMV), Epstein-Barr virus, herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), human herpesvirus 6 (HHV-6), Herpesvitus K*, CMV, varicella-zoster virus); Papillomaviridae family (e.g. Human Papillomavirus (HPV, HPV E1)); Parvoviridae family (e.g. Parvovirus B19); Polyomaviridae family (e.g. JC

virus and BK virus); Paramyxoviridae family (e.g. Measles virus); or Togaviridae family (e.g. Rubella virus)). In some embodiments, the disorder is Coffin Siris, Neurofibromatosis (e.g., NF-1, NF-2, or Schwannomatosis), or Multiple Meningioma.In an aspect, the disclosure features a method of treating a cancer in a subject in need thereof, the method including administering to the subject an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or any of the foregoing pharmaceutical compositions.

In some embodiments, the cancer is squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, hepatocellular carcinomas, and renal cell carcinomas, cancer of the bladder, bowel, breast, cervix, colon, esophagus, head, kidney, liver, lung, neck, ovary, pancreas, prostate, and stomach; leukemias; benign and malignant lymphomas, particularly Burkitt's lymphoma and Non-Hodgkin's lymphoma; benign and malignant melanomas; myeloproliferative diseases; sarcomas, including Ewing's sarcoma, hemangiosarcoma, Kaposi's sarcoma, liposarcoma, myosarcomas, peripheral neuroepithelioma, synovial sarcoma, gliomas, astrocytomas, oligodendrogliomas, ependymomas, gliobastomas, neuroblastomas, ganglioneuromas, gangliogliomas, medulloblastomas, pineal cell tumors, meningiomas, meningeal sarcomas, neurofibromas, and Schwannomas; bowel cancer, breast cancer, prostate cancer, cervical cancer, uterine cancer, lung cancer, ovarian cancer, testicular cancer, thyroid cancer, astrocytoma, esophageal cancer, pancreatic cancer, stomach cancer, liver cancer, colon cancer, melanoma; carcinosarcoma, Hodgkin's disease, Wilms' tumor and teratocarcinomas. Additional cancers which may be treated using the disclosed compounds according to the present invention include, for example, acute granulocytic leukemia, acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), adenocarcinoma, adenosarcoma, adrenal cancer, adrenocortical carcinoma, anal cancer, anaplastic astrocytoma, angiosarcoma, appendix cancer, astrocytoma, Basal cell carcinoma, B-Cell lymphoma, bile duct cancer, bladder cancer, bone cancer, bone marrow cancer, bowel cancer, brain cancer, brain stem glioma, breast cancer, triple (estrogen, progesterone and HER-2) negative breast cancer, double negative breast cancer (two of estrogen, progesterone and HER-2 are negative), single negative (one of estrogen, progesterone and HER-2 is negative), estrogen-receptor positive, HER2-negative breast cancer, estrogen receptor-negative breast cancer, estrogen receptor positive breast cancer, metastatic breast cancer, luminal A breast cancer, luminal B breast cancer, Her2-negative breast cancer, HER2-positive or negative breast cancer, progesterone receptor-negative breast cancer, progesterone receptor-positive breast cancer, recurrent breast cancer, carcinoid tumors, cervical cancer, cholangiocarcinoma, chondrosarcoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), colon cancer, colorectal cancer, craniopharyngioma, cutaneous lymphoma, cutaneous melanoma, diffuse astrocytoma, ductal carcinoma in situ (DCIS), endometrial cancer, ependymoma, epithelioid sarcoma, esophageal cancer, ewing sarcoma, extrahepatic bile duct cancer, eye cancer, fallopian tube cancer, fibrosarcoma, gallbladder cancer, gastric cancer, gastrointestinal cancer, gastrointestinal carcinoid cancer, gastrointestinal stromal tumors (GIST), germ cell tumor glioblastoma multiforme (GBM), glioma, hairy cell leukemia, head and neck cancer, hemangioendothelioma, Hodgkin

lymphoma, hypopharyngeal cancer, infiltrating ductal carcinoma (IDC), infiltrating lobular carcinoma (ILC), inflammatory breast cancer (IBC), intestinal Cancer, intrahepatic bile duct cancer, invasive/infiltrating breast cancer, Islet cell cancer, jaw cancer, Kaposi sarcoma, kidney cancer, laryngeal cancer, leiomyosarcoma, leptomeningeal metastases, leukemia, lip cancer, liposarcoma, liver cancer, lobular carcinoma in situ, low-grade astrocytoma, lung cancer, lymph node cancer, lymphoma, male breast cancer, medullary carcinoma, medulloblastoma, melanoma, meningioma, Merkel cell carcinoma, mesenchymal chondrosarcoma, mesenchymous, mesothelioma metastatic breast cancer, metastatic melanoma metastatic squamous neck cancer, mixed gliomas, monodermal teratoma, mouth cancer mucinous carcinoma, mucosal melanoma, multiple myeloma, Mycosis Fungoides, myelodysplastic syndrome, nasal cavity cancer, nasopharyngeal cancer, neck cancer, neuroblastoma, neuroendocrine tumors (NETs), non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), oat cell cancer, ocular cancer, ocular melanoma, oligodendroglioma, oral cancer, oral cavity cancer, oropharyngeal cancer, osteogenic sarcoma, osteosarcoma, ovarian cancer, ovarian epithelial cancer ovarian germ cell tumor, ovarian primary peritoneal carcinoma, ovarian sex cord stromal tumor, Paget's disease, pancreatic cancer, papillary carcinoma, paranasal sinus cancer, parathyroid cancer, pelvic cancer, penile cancer, peripheral nerve cancer, peritoneal cancer, pharyngeal cancer, pheochromocytoma, pilocytic astrocytoma, pineal region tumor, pineoblastoma, pituitary gland cancer, primary central nervous system (CNS) lymphoma, prostate cancer, rectal cancer, renal cell carcinoma, renal pelvis cancer, rhabdomyosarcoma, salivary gland cancer, soft tissue sarcoma, bone sarcoma, sarcoma, sinus cancer, skin cancer, small cell lung cancer (SCLC), small intestine cancer, spinal cancer, spinal column cancer, spinal cord cancer, squamous cell carcinoma, stomach cancer, synovial sarcoma, T-cell lymphoma, testicular cancer, throat cancer, thymoma/thymic carcinoma, thyroid cancer, tongue cancer, tonsil cancer, transitional cell cancer, tubal cancer, tubular carcinoma, undiagnosed cancer, ureteral cancer, urethral cancer, uterine adenocarcinoma, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, T-cell lineage acute lymphoblastic leukemia (T-ALL), T-cell lineage lymphoblastic lymphoma (T-LL), peripheral T-cell lymphoma, Adult T-cell leukemia, Pre-B ALL, Pre-B lymphomas, large B-cell lymphoma, Burkitts lymphoma, B-cell ALL, Philadelphia chromosome positive ALL, Philadelphia chromosome positive CML, juvenile myelomonocytic leukemia (JMML), acute promyelocytic leukemia (a subtype of AML), large granular lymphocytic leukemia, Adult T-cell chronic leukemia, diffuse large B cell lymphoma, follicular lymphoma; Mucosa-Associated Lymphatic Tissue lymphoma (MALT), small cell lymphocytic lymphoma, mediastinal large B cell lymphoma, nodal marginal zone B cell lymphoma (NMZL); splenic marginal zone lymphoma (SMZL); intravascular large B-cell lymphoma; primary effusion lymphoma; or lymphomatoid granulomatosis;; B-cell prolymphocytic leukemia; splenic lymphoma/leukemia, unclassifiable, splenic diffuse red pulp small B-cell lymphoma; lymphoplasmacytic lymphoma; heavy chain diseases, for example, Alpha heavy chain disease, Gamma heavy chain disease, Mu heavy chain disease, plasma cell myeloma, solitary plasmacytoma of bone; extraosseous plasmacytoma; primary cutaneous follicle center lymphoma, T cell/histocyte rich large B-cell lymphoma, DLBCL associated with chronic inflammation;

Epstein-Barr virus (EBV)+ DLBCL of the elderly; primary mediastinal (thymic) large B-cell lymphoma, primary cutaneous DLBCL, leg type, ALK+ large B-cell lymphoma, plasmablastic lymphoma; large B-cell lymphoma arising in HHV8-associated multicentric, Castleman disease; B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma, or B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma.

In some embodiments, the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, colorectal cancer, a sarcoma (e.g., a soft tissue sarcoma, synovial sarcoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, adult fibrosarcoma, alveolar soft-part sarcoma, angiosarcoma, clear cell sarcoma, desmoplastic small round cell tumor, epithelioid sarcoma, fibromyxoid sarcoma, gastrointestinal stromal tumor, Kaposi sarcoma, liposarcoma, leiomyosarcoma, malignant mesenchymoma malignant peripheral nerve sheath tumors, myxofibrosarcoma, low-grade rhabdomyosarcoma), non-small cell lung cancer (e.g., squamous or adenocarcinoma), stomach cancer, or breast cancer. In some embodiments, the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, or colorectal cancer. In some embodiments, the cancer is a sarcoma (e.g., synovial sarcoma or Ewing's sarcoma), non-small cell lung cancer (e.g., squamous or adenocarcinoma), stomach cancer, or breast cancer. In some embodiments, the cancer is sarcoma (e.g., synovial sarcoma or Ewing's sarcoma). In some embodiments, the sarcoma is synovial sarcoma.

In another aspect, the disclosure features a method for treating a viral infection in a subject in need thereof. This method includes administering to the subject an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or any of the foregoing pharmaceutical compositions. In some embodiments, the viral infection is an infection with a virus of the Retroviridae family such as the lentiviruses (e.g. Human immunodeficiency virus (HIV) and deltaretroviruses (e.g., human T cell leukemia virus I (HTLV-I), human T cell leukemia virus II (HTLV-II)); Hepadnaviridae family (e.g. hepatitis B virus (HBV)), Flaviviridae family (e.g. hepatitis C virus (HCV)), Adenoviridae family (e.g. Human Adenovirus), Herpesviridae family (e.g. Human cytomegalovirus (HCMV), , Epstein-Barr virus, herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), human herpesvirus 6 (HHV-6), Herpesvitus K*, CMV, varicella-zoster virus), Papillomaviridae family (e.g. Human Papillomavirus (HPV, HPV E1)), Parvoviridae family (e.g. Parvovirus B19), Polyomaviridae family (e.g. JC virus and BK virus), Paramyxoviridae family (e.g. Measles virus), Togaviridae family (e.g. Rubella virus).

In another embodiment of any of the foregoing methods, the method further includes administering to the subject an additional anticancer therapy (e.g., chemotherapeutic or cytotoxic agent or radiotherapy).

In particular embodiments, the additional anticancer therapy is: a chemotherapeutic or cytotoxic agent (e.g., doxorubicin or ifosfamide), a differentiation-inducing agent (e.g., retinoic acid, vitamin D,

cytokines), a hormonal agent, an immunological agent, or an anti-angiogenic agent. Chemotherapeutic and cytotoxic agents include, but are not limited to, alkylating agents, cytotoxic antibiotics, antimetabolites, vinca alkaloids, etoposides, and others (e.g., paclitaxel, taxol, docetaxel, taxotere, cis-platinum). A list of additional compounds having anticancer activity can be found in L. Brunton, B. Chabner and B. Knollman (eds). Goodman and Gilman's The Pharmacological Basis of Therapeutics, Twelfth Edition, 2011, McGraw Hill Companies, New York, NY.

In particular embodiments, the compound of the invention and the additional anticancer therapy and any of the foregoing compounds or pharmaceutical compositions are administered within 28 days of each other (e.g., within 21, 14, 10, 7, 5, 4, 3, 2, or 1 days) or within 24 hours (e.g., 12, 6, 3, 2, or 1 hours; or concomitantly) each in an amount that together are effective to treat the subject.

Chemical Terms

For any of the following chemical definitions, a number following an atomic symbol indicates that total number of atoms of that element that are present in a particular chemical moiety. As will be understood, other atoms, such as hydrogen atoms, or substituent groups, as described herein, may be present, as necessary, to satisfy the valences of the atoms. For example, an unsubstituted C_2 alkyl group has the formula $-CH_2CH_3$. When used with the groups defined herein, a reference to the number of carbon atoms includes the divalent carbon in acetal and ketal groups but does not include the carbonyl carbon in acyl, ester, carbonate, or carbamate groups. A reference to the number of oxygen, nitrogen, or sulfur atoms in a heteroaryl group only includes those atoms that form a part of a heterocyclic ring.

The term "acyl," as used herein, represents a hydrogen or an alkyl group that is attached to a parent molecular group through a carbonyl group, as defined herein, and is exemplified by formyl (i.e., a carboxyaldehyde group), acetyl, trifluoroacetyl, propionyl, and butanoyl. Exemplary unsubstituted acyl groups include from 1 to 6, from 1 to 11, or from 1 to 21 carbons.

The term "alkyl," as used herein, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of 1 to 20 carbon atoms (e.g., 1 to 16 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms).

An alkylene is a divalent alkyl group. The term "alkenyl," as used herein, alone or in combination with other groups, refers to a straight chain or branched hydrocarbon residue having a carbon-carbon double bond and having 2 to 20 carbon atoms (e.g., 2 to 16 carbon atoms, 2 to 10 carbon atoms, 2 to 6, or 2 carbon atoms).

The term "alkynyl," as used herein, alone or in combination with other groups, refers to a straight chain or branched hydrocarbon residue having a carbon-carbon triple bond and having 2 to 20 carbon atoms (e.g., 2 to 16 carbon atoms, 2 to 10 carbon atoms, 2 to 6, or 2 carbon atoms).

The term "amino," as used herein, represents $-N(R^{N1})_2$, wherein each R^{N1} is, independently, H, OH, NO_2, $N(R^{N2})_2$, SO_2OR^{N2}, SO_2R^{N2}, SOR^{N2}, an *N*-protecting group, alkyl, alkoxy, aryl, arylalkyl, cycloalkyl, acyl (e.g., acetyl, trifluoroacetyl, or others described herein), wherein each of these recited R^{N1}

groups can be optionally substituted; or two R^{N1} combine to form an alkylene or heteroalkylene, and wherein each R^{N2} is, independently, H, alkyl, or aryl. The amino groups of the compounds described herein can be an unsubstituted amino (i.e., $-NH_2$) or a substituted amino (i.e., $-N(R^{N1})_2$).

The term "aryl," as used herein, refers to an aromatic mono- or polycarbocyclic radical of 6 to 12 carbon atoms having at least one aromatic ring. Examples of such groups include, but are not limited to, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, 1,2-dihydronaphthyl, indanyl, and 1H-indenyl.

The term "arylalkyl," as used herein, represents an alkyl group substituted with an aryl group. Exemplary unsubstituted arylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C_1-C_6 alkyl C_6-C_{10} aryl, C_1-C_{10} alkyl C_6-C_{10} aryl, or C_1-C_{20} alkyl C_6-C_{10} aryl), such as, benzyl and phenethyl. In some embodiments, the alkyl and the aryl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.

The term "azido," as used herein, represents a $-N_3$ group.

The term "bridged polycycloalkyl," as used herein, refers to a bridged polycyclic group of 5 to 20 carbons, containing from 1 to 3 bridges.

The term "cyano," as used herein, represents a –CN group.

The term "carbocyclyl," as used herein, refers to a non-aromatic C_3-C_{12} monocyclic, bicyclic, or tricyclic structure in which the rings are formed by carbon atoms. Carbocyclyl structures include cycloalkyl groups and unsaturated carbocyclyl radicals.

The term "cycloalkyl," as used herein, refers to a saturated, non-aromatic, monovalent mono- or polycarbocyclic radical of 3 to 10, preferably 3 to 6 carbon atoms. This term is further exemplified by radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and adamantyl.

The term "halogen," as used herein, means a fluorine (fluoro), chlorine (chloro), bromine (bromo), or iodine (iodo) radical.

The term "heteroalkyl," as used herein, refers to an alkyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkyl groups. Examples of heteroalkyl groups are an "alkoxy" which, as used herein, refers alkyl–O– (e.g., methoxy and ethoxy). A heteroalkylene is a divalent heteroalkyl group. The term "heteroalkenyl," as used herein, refers to an alkenyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkenyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkenyl groups. Examples of heteroalkenyl groups are an "alkenoxy" which, as used herein, refers alkenyl–O–. A heteroalkenylene is a divalent heteroalkenyl group. The term "heteroalkynyl," as used herein, refers to an alkynyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkynyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkynyl groups.

Examples of heteroalkynyl groups are an "alkynoxy" which, as used herein, refers alkynyl–O–. A heteroalkynylene is a divalent heteroalkynyl group.

The term "heteroaryl," as used herein, refers to an aromatic mono- or polycyclic radical of 5 to 12 atoms having at least one aromatic ring containing 1, 2, or 3 ring atoms selected from nitrogen, oxygen, and sulfur, with the remaining ring atoms being carbon. One or two ring carbon atoms of the heteroaryl group may be replaced with a carbonyl group. Examples of heteroaryl groups are pyridyl, pyrazoyl, benzooxazolyl, benzoimidazolyl, benzothiazolyl, imidazolyl, oxaxolyl, and thiazolyl.

The term "heteroarylalkyl," as used herein, represents an alkyl group substituted with a heteroaryl group. Exemplary unsubstituted heteroarylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C_1-C_6 alkyl C_2-C_9 heteroaryl, C_1-C_{10} alkyl C_2-C_9 heteroaryl, or C_1-C_{20} alkyl C_2-C_9 heteroaryl). In some embodiments, the alkyl and the heteroaryl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.

The term "heterocyclyl," as used herein, refers a mono- or polycyclic radical having 3 to 12 atoms having at least one ring containing 1, 2, 3, or 4 ring atoms selected from N, O or S, wherein no ring is aromatic. Examples of heterocyclyl groups include, but are not limited to, morpholinyl, thiomorpholinyl, furyl, piperazinyl, piperidinyl, pyranyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrofuranyl, and 1,3-dioxanyl.

The term "heterocyclylalkyl," as used herein, represents an alkyl group substituted with a heterocyclyl group. Exemplary unsubstituted heterocyclylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C_1-C_6 alkyl C_2-C_9 heterocyclyl, C_1-C_{10} alkyl C_2-C_9 heterocyclyl, or C_1-C_{20} alkyl C_2-C_9 heterocyclyl). In some embodiments, the alkyl and the heterocyclyl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.

The term "hydroxyalkyl," as used herein, represents alkyl group substituted with an –OH group.

The term "hydroxyl," as used herein, represents an –OH group.

The term "*N*-protecting group," as used herein, represents those groups intended to protect an amino group against undesirable reactions during synthetic procedures. Commonly used *N*-protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis," 3rd Edition (John Wiley & Sons, New York, 1999). *N*-protecting groups include, but are not limited to, acyl, aryloyl, or carbamyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and chiral auxiliaries such as protected or unprotected D, L, or D, L-amino acids such as alanine, leucine, and phenylalanine; sulfonyl-containing groups such as benzenesulfonyl, and p-toluenesulfonyl; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4- 20 dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxy carbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl,

isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxy carbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, and phenylthiocarbonyl, arylalkyl groups such as benzyl, triphenylmethyl, and benzyloxymethyl, and silyl groups, such as trimethylsilyl. Preferred *N*-protecting groups are alloc, formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, alanyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc), and benzyloxycarbonyl (Cbz).

The term "nitro," as used herein, represents an $-NO_2$ group.

The term "thiol," as used herein, represents an –SH group.

The alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl (e.g., cycloalkyl), aryl, heteroaryl, and heterocyclyl groups may be substituted or unsubstituted. When substituted, there will generally be 1 to 4 substituents present, unless otherwise specified. Substituents include, for example: alkyl (e.g., unsubstituted and substituted, where the substituents include any group described herein, e.g., aryl, halo, hydroxy), aryl (e.g., substituted and unsubstituted phenyl), carbocyclyl (e.g., substituted and unsubstituted cycloalkyl), halogen (e.g., fluoro), hydroxyl, heteroalkyl (e.g., substituted and unsubstituted methoxy, ethoxy, or thioalkoxy), heteroaryl, heterocyclyl, amino (e.g., NH_2 or mono- or dialkyl amino), azido, cyano, nitro, or thiol. Aryl, carbocyclyl (e.g., cycloalkyl), heteroaryl, and heterocyclyl groups may also be substituted with alkyl (unsubstituted and substituted such as arylalkyl (e.g., substituted and unsubstituted benzyl)).

Compounds described herein can have one or more asymmetric carbon atoms and can exist in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, or mixtures of diastereoisomeric racemates. The optically active forms can be obtained for example by resolution of the racemates, by asymmetric synthesis or asymmetric chromatography (chromatography with a chiral adsorbent or eluant). That is, certain of the disclosed compounds may exist in various stereoisomeric forms. Stereoisomers are compounds that differ only in their spatial arrangement. Enantiomers are pairs of stereoisomers whose mirror images are not superimposable, most commonly because they contain an asymmetrically substituted carbon atom that acts as a chiral center. "Enantiomer" means one of a pair of molecules that are mirror images of each other and are not superimposable. Diastereomers are stereoisomers that are not related as mirror images, most commonly because they contain two or more asymmetrically substituted carbon atoms and represent the configuration of substituents around one or more chiral carbon atoms. Enantiomers of a compound can be prepared, for example, by separating an enantiomer from a racemate using one or more well-known techniques and methods, such as, for example, chiral chromatography and separation methods based thereon. The appropriate technique and/or method for separating an enantiomer of a compound described herein from a racemic mixture can be readily determined by those of skill in the art. "Racemate" or "racemic mixture" means a compound containing two enantiomers, wherein such mixtures exhibit no optical activity; i.e., they do not rotate the plane of polarized light. "Geometric isomer" means isomers that differ in the orientation of substituent

atoms in relationship to a carbon-carbon double bond, to a cycloalkyl ring, or to a bridged bicyclic system. Atoms (other than H) on each side of a carbon- carbon double bond may be in an E (substituents are on opposite sides of the carbon- carbon double bond) or Z (substituents are oriented on the same side) configuration. "R," "S," "S*," "R*," "E," "Z," "cis," and "trans," indicate configurations relative to the core molecule. Certain of the disclosed compounds may exist in atropisomeric forms. Atropisomers are stereoisomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers. The compounds described herein may be prepared as individual isomers by either isomer-specific synthesis or resolved from an isomeric mixture. Conventional resolution techniques include forming the salt of a free base of each isomer of an isomeric pair using an optically active acid (followed by fractional crystallization and regeneration of the free base), forming the salt of the acid form of each isomer of an isomeric pair using an optically active amine (followed by fractional crystallization and regeneration of the free acid), forming an ester or amide of each of the isomers of an isomeric pair using an optically pure acid, amine or alcohol (followed by chromatographic separation and removal of the chiral auxiliary), or resolving an isomeric mixture of either a starting material or a final product using various well known chromatographic methods. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by weight relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by weight optically pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by weight pure. Percent optical purity is the ratio of the weight of the enantiomer or over the weight of the enantiomer plus the weight of its optical isomer. Diastereomeric purity by weight is the ratio of the weight of one diastereomer or over the weight of all the diastereomers. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by mole fraction pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by mole fraction pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by mole fraction pure. Percent purity by mole fraction is the ratio of the moles of the enantiomer or over the moles of the enantiomer plus the moles of its optical isomer. Similarly, percent purity by moles fraction is the ratio of the moles of the diastereomer or over the moles of the diastereomer plus the moles of its isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry, and the compound has at least one chiral center, it is to be understood that the name or structure encompasses either enantiomer of the compound free from the corresponding optical isomer, a racemic mixture of the compound, or mixtures enriched in one enantiomer relative to its corresponding optical isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry and has two or more chiral centers, it is to be

understood that the name or structure encompasses a diastereomer free of other diastereomers, a number of diastereomers free from other diastereomeric pairs, mixtures of diastereomers, mixtures of diastereomeric pairs, mixtures of diastereomers in which one diastereomer is enriched relative to the other diastereomer(s), or mixtures of diastereomers in which one or more diastereomer is enriched relative to the other diastereomers. The invention embraces all of these forms.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials are described herein for use in the present disclosure; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Definitions

In this application, unless otherwise clear from context, (i) the term "a" may be understood to mean "at least one"; (ii) the term "or" may be understood to mean "and/or"; and (iii) the terms "including" and "including" may be understood to encompass itemized components or steps whether presented by themselves or together with one or more additional components or steps.

As used herein, the terms "about" and "approximately" refer to a value that is within 10% above or below the value being described. For example, the term "about 5 nM" indicates a range of from 4.5 to 5.5 nM.

As used herein, the term "administration" refers to the administration of a composition (e.g., a compound or a preparation that includes a compound as described herein) to a subject or system. Administration to an animal subject (e.g., to a human) may be by any appropriate route. For example, in some embodiments, administration may be bronchial (including by bronchial instillation), buccal, enteral, interdermal, intra-arterial, intradermal, intragastric, intramedullary, intramuscular, intranasal, intraperitoneal, intrathecal, intratumoral, intravenous, intraventricular, mucosal, nasal, oral, rectal, subcutaneous, sublingual, topical, tracheal (including by intratracheal instillation), transdermal, vaginal, and vitreal.

As used herein, the term "adult soft tissue sarcoma" refers to a sarcoma that develops in the soft tissues of the body, typically in adolescent and adult subjects (e.g., subjects who are at least 10 years old, 11 years old, 12 years old, 13 years old, 14 years old, 15 years old, 16 years old, 17 years old, 18 years old, or 19 years old). Non-limiting examples of adult soft tissue sarcoma include, but are not limited to, synovial sarcoma, fibrosarcoma, malignant fibrous histiocytoma, dermatofibrosarcoma, liposarcoma, leiomyosarcoma, hemangiosarcoma, Kaposi's sarcoma, lymphangiosarcoma, malignant peripheral nerve sheath tumor/neurofibrosarcoma, extraskeletal chondrosarcoma, extraskeletal osteosarcoma, extraskeletal myxoid chondrosarcoma, and extraskeletal mesenchymal.

The term "antisense," as used herein, refers to a nucleic acid comprising a polynucleotide that is sufficiently complementary to all or a portion of a gene, primary transcript, or processed mRNA, so as to interfere with expression of the endogenous gene (e.g., BRD9). "Complementary" polynucleotides are those that are capable of base pairing according to the standard Watson-Crick complementarity rules. Specifically, purines will base pair with pyrimidines to form a combination of guanine paired with cytosine (G:C) and adenine paired with either thymine (A:T) in the case of DNA, or adenine paired with uracil (A:U) in the case of RNA. It is understood that two polynucleotides may hybridize to each other even if they are not completely complementary to each other, provided that each has at least one region that is substantially complementary to the other.

The term "antisense nucleic acid" includes single-stranded RNA as well as double-stranded DNA expression cassettes that can be transcribed to produce an antisense RNA. "Active" antisense nucleic acids are antisense RNA molecules that are capable of selectively hybridizing with a primary transcript or mRNA encoding a polypeptide having at least 80% sequence identity (e.g., 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.9% identity, or more) with the targeted polypeptide sequence (e.g., a BRD9 polypeptide sequence). The antisense nucleic acid can be complementary to an entire coding strand, or to only a portion thereof. In some embodiments, an antisense nucleic acid molecule is antisense to a "coding region" of the coding strand of a nucleotide sequence. The term "coding region" refers to the region of the nucleotide sequence comprising codons that are translated into amino acid residues. In some embodiments, the antisense nucleic acid molecule is antisense to a "noncoding region" of the coding strand of a nucleotide sequence. The term "noncoding region" refers to 5′ and 3′ sequences that flank the coding region that are not translated into amino acids (i.e., also referred to as 5′ and 3′ untranslated regions). The antisense nucleic acid molecule can be complementary to the entire coding region of mRNA, or can be antisense to only a portion of the coding or noncoding region of an mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site. An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 nucleotides in length.

As used herein, the term "BAF complex" refers to the BRG1- or HRBM-associated factors complex in a human cell.

As used herein, the term "BAF complex-related disorder" refers to a disorder that is caused or affected by the level and/or activity of a BAF complex.

As used herein, the terms "GBAF complex" and "GBAF" refer to a SWI/SNF ATPase chromatin remodeling complex in a human cell. GBAF complex subunits may include, but are not limited to, ACTB, ACTL6A, ACTL6B, BICRA, BICRAL, BRD9, SMARCA2, SMARCA4, SMARCC1, SMARCD1, SMARCD2, SMARCD3, and SS18.The term "cancer" refers to a condition caused by the proliferation of malignant neoplastic cells, such as tumors, neoplasms, carcinomas, sarcomas, leukemias, and lymphomas.

As used herein, the term "BRD9" refers to bromodomain-containing protein 9, a component of the BAF (BRG1- or BRM-associated factors) complex, a SWI/SNF ATPase chromatin remodeling complex,

and belongs to family IV of the bromodomain-containing proteins. BRD9 is encoded by the *BRD9* gene, the nucleic acid sequence of which is set forth in SEQ ID NO: 1. The term "BRD9" also refers to natural variants of the wild-type BRD9 protein, such as proteins having at least 85% identity (e.g., 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.9% identity, or more) to the amino acid sequence of wild-type BRD9, which is set forth in SEQ ID NO: 2.

As used herein, the term "BRD9-related disorder" refers to a disorder that is caused or affected by the level and/or activity of BRD9.The term "cancer" refers to a condition caused by the proliferation of malignant neoplastic cells, such as tumors, neoplasms, carcinomas, sarcomas, leukemias, and lymphomas.

As used herein, a "combination therapy" or "administered in combination" means that two (or more) different agents or treatments are administered to a subject as part of a defined treatment regimen for a particular disease or condition. The treatment regimen defines the doses and periodicity of administration of each agent such that the effects of the separate agents on the subject overlap. In some embodiments, the delivery of the two or more agents is simultaneous or concurrent and the agents may be co-formulated. In some embodiments, the two or more agents are not co-formulated and are administered in a sequential manner as part of a prescribed regimen. In some embodiments, administration of two or more agents or treatments in combination is such that the reduction in a symptom, or other parameter related to the disorder is greater than what would be observed with one agent or treatment delivered alone or in the absence of the other. The effect of the two treatments can be partially additive, wholly additive, or greater than additive (e.g., synergistic). Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination may be administered by intravenous injection while a second therapeutic agent of the combination may be administered orally.

As used herein, the term "degrader" refers to a small molecule compound including a degradation moiety, wherein the compound interacts with a protein (e.g., BRD9) in a way which results in degradation of the protein, e.g., binding of the compound results in at least 5% reduction of the level of the protein, e.g., in a cell or subject.

As used herein, the term "degradation moiety" refers to a moiety whose binding results in degradation of a protein, e.g., BRD9. In one example, the moiety binds to a protease or a ubiquitin ligase that metabolizes the protein, e.g., BRD9.

By "determining the level of a protein" is meant the detection of a protein, or an mRNA encoding the protein, by methods known in the art either directly or indirectly. "Directly determining" means performing a process (e.g., performing an assay or test on a sample or "analyzing a sample" as that term is defined herein) to obtain the physical entity or value. "Indirectly determining" refers to receiving the physical entity or value from another party or source (e.g., a third-party laboratory that directly acquired

the physical entity or value). Methods to measure protein level generally include, but are not limited to, western blotting, immunoblotting, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), immunoprecipitation, immunofluorescence, surface plasmon resonance, chemiluminescence, fluorescent polarization, phosphorescence, immunohistochemical analysis, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, liquid chromatography (LC)-mass spectrometry, microcytometry, microscopy, fluorescence activated cell sorting (FACS), and flow cytometry, as well as assays based on a property of a protein including, but not limited to, enzymatic activity or interaction with other protein partners. Methods to measure mRNA levels are known in the art.

As used herein, the terms "effective amount," "therapeutically effective amount," and "a "sufficient amount" of an agent that reduces the level and/or activity of BRD9 (e.g., in a cell or a subject) described herein refer to a quantity sufficient to, when administered to the subject, including a human, effect beneficial or desired results, including clinical results, and, as such, an "effective amount" or synonym thereto depends on the context in which it is being applied. For example, in the context of treating cancer, it is an amount of the agent that reduces the level and/or activity of BRD9 sufficient to achieve a treatment response as compared to the response obtained without administration of the agent that reduces the level and/or activity of BRD9. The amount of a given agent that reduces the level and/or activity of BRD9 described herein that will correspond to such an amount will vary depending upon various factors, such as the given agent, the pharmaceutical formulation, the route of administration, the type of disease or disorder, the identity of the subject (e.g., age, sex, and/or weight) or host being treated, and the like, but can nevertheless be routinely determined by one of skill in the art. Also, as used herein, a "therapeutically effective amount" of an agent that reduces the level and/or activity of BRD9 of the present disclosure is an amount which results in a beneficial or desired result in a subject as compared to a control. As defined herein, a therapeutically effective amount of an agent that reduces the level and/or activity of BRD9 of the present disclosure may be readily determined by one of ordinary skill by routine methods known in the art. Dosage regimen may be adjusted to provide the optimum therapeutic response.

As used herein, the term "inhibitor" refers to any agent which reduces the level and/or activity of a protein (e.g., BRD9). Non-limiting examples of inhibitors include small molecule inhibitors, degraders, antibodies, enzymes, or polynucleotides (e.g., siRNA).

The term "inhibitory RNA agent" refers to an RNA, or analog thereof, having sufficient sequence complementarity to a target RNA to direct RNA interference. Examples also include a DNA that can be used to make the RNA. RNA interference (RNAi) refers to a sequence-specific or selective process by which a target molecule (e.g., a target gene, protein, or RNA) is down-regulated. Generally, an interfering RNA ("iRNA") is a double-stranded short-interfering RNA (siRNA), short hairpin RNA (shRNA), or single-stranded micro-RNA (miRNA) that results in catalytic degradation of specific mRNAs, and also can be used to lower or inhibit gene expression.

By "level" is meant a level of a protein, or mRNA encoding the protein, as compared to a reference. The reference can be any useful reference, as defined herein. By a "decreased level" or an "increased level" of a protein is meant a decrease or increase in protein level, as compared to a reference (e.g., a decrease or an increase by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 100%, about 150%, about 200%, about 300%, about 400%, about 500%, or more; a decrease or an increase of more than about 10%, about 15%, about 20%, about 50%, about 75%, about 100%, or about 200%, as compared to a reference; a decrease or an increase by less than about 0.01-fold, about 0.02-fold, about 0.1-fold, about 0.3-fold, about 0.5-fold, about 0.8-fold, or less; or an increase by more than about 1.2-fold, about 1.4-fold, about 1.5-fold, about 1.8-fold, about 2.0-fold, about 3.0-fold, about 3.5-fold, about 4.5-fold, about 5.0-fold, about 10-fold, about 15-fold, about 20-fold, about 30-fold, about 40-fold, about 50-fold, about 100-fold, about 1000-fold, or more). A level of a protein may be expressed in mass/vol (e.g., g/dL, mg/mL, µg/mL, ng/mL) or percentage relative to total protein or mRNA in a sample.

The terms "miRNA" and "microRNA" refer to an RNA agent, preferably a single-stranded agent, of about 10-50 nucleotides in length, preferably between about 15-25 nucleotides in length, which is capable of directing or mediating RNA interference. Naturally-occurring miRNAs are generated from stem-loop precursor RNAs (i.e., pre-miRNAs) by Dicer. The term "Dicer" as used herein, includes Dicer as well as any Dicer ortholog or homolog capable of processing dsRNA structures into siRNAs, miRNAs, siRNA-like or miRNA-like molecules. The term microRNA ("miRNA") is used interchangeably with the term "small temporal RNA" ("stRNA") based on the fact that naturally-occurring miRNAs have been found to be expressed in a temporal fashion (e.g., during development).

By "modulating the activity of a BAF complex," is meant altering the level of an activity related to a BAF complex (e.g., GBAF), or a related downstream effect. The activity level of a BAF complex may be measured using any method known in the art, e.g., the methods described in Kadoch et al, Cell 153:71-85 (2013), the methods of which are herein incorporated by reference.

"Percent (%) sequence identity" with respect to a reference polynucleotide or polypeptide sequence is defined as the percentage of nucleic acids or amino acids in a candidate sequence that are identical to the nucleic acids or amino acids in the reference polynucleotide or polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid or amino acid sequence identity can be achieved in various ways that are within the capabilities of one of skill in the art, for example, using publicly available computer software such as BLAST, BLAST-2, or Megalign software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For example, percent sequence identity values may be generated using the sequence comparison computer program BLAST. As an illustration, the percent sequence identity of a given nucleic acid or

amino acid sequence, A, to, with, or against a given nucleic acid or amino acid sequence, B, (which can alternatively be phrased as a given nucleic acid or amino acid sequence, A that has a certain percent sequence identity to, with, or against a given nucleic acid or amino acid sequence, B) is calculated as follows:

100 multiplied by (the fraction X/Y)

where X is the number of nucleotides or amino acids scored as identical matches by a sequence alignment program (e.g., BLAST) in that program's alignment of A and B, and where Y is the total number of nucleic acids in B. It will be appreciated that where the length of nucleic acid or amino acid sequence A is not equal to the length of nucleic acid or amino acid sequence B, the percent sequence identity of A to B will not equal the percent sequence identity of B to A.

A "pharmaceutically acceptable excipient," as used herein, refers any ingredient other than the compounds described herein (for example, a vehicle capable of suspending or dissolving the active compound) and having the properties of being substantially nontoxic and non-inflammatory in a patient. Excipients may include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspensing or dispersing agents, sweeteners, and waters of hydration. Exemplary excipients include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

As used herein, the term "pharmaceutically acceptable salt" means any pharmaceutically acceptable salt of the compound of any of the compounds described herein. For example, pharmaceutically acceptable salts of any of the compounds described herein include those that are within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, allergic response and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, pharmaceutically acceptable salts are described in: Berge et al., J. Pharmaceutical Sciences 66:1-19, 1977 and in Pharmaceutical Salts: Properties, Selection, and Use, (Eds. P.H. Stahl and C.G. Wermuth), Wiley-VCH, 2008. The salts can be prepared in situ during the final isolation and purification of the compounds described herein or separately by reacting a free base group with a suitable organic acid.

The compounds described herein may have ionizable groups so as to be capable of preparation as pharmaceutically acceptable salts. These salts may be acid addition salts involving inorganic or organic acids or the salts may, in the case of acidic forms of the compounds described herein, be

prepared from inorganic or organic bases. Frequently, the compounds are prepared or used as pharmaceutically acceptable salts prepared as addition products of pharmaceutically acceptable acids or bases. Suitable pharmaceutically acceptable acids and bases and methods for preparation of the appropriate salts are well-known in the art. Salts may be prepared from pharmaceutically acceptable non-toxic acids and bases including inorganic and organic acids and bases. Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, and valerate salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, and magnesium, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, and ethylamine.

The term "pharmaceutical composition," as used herein, represents a composition containing a compound described herein formulated with a pharmaceutically acceptable excipient, and manufactured or sold with the approval of a governmental regulatory agency as part of a therapeutic regimen for the treatment of disease in a mammal. Pharmaceutical compositions can be formulated, for example, for oral administration in unit dosage form (e.g., a tablet, capsule, caplet, gelcap, or syrup); for topical administration (e.g., as a cream, gel, lotion, or ointment); for intravenous administration (e.g., as a sterile solution free of particulate emboli and in a solvent system suitable for intravenous use); or in any other pharmaceutically acceptable formulation.

By "reducing the activity of BRD9," is meant decreasing the level of an activity related to an BRD9, or a related downstream effect. A non-limiting example of inhibition of an activity of BRD9 is decreasing the level of a BAF complex (e.g., GBAF) in a cell. The activity level of BRD9 may be measured using any method known in the art. In some embodiments, an agent which reduces the activity of BRD9 is a small molecule BRD9 inhibitor. In some embodiments, an agent which reduces the activity of BRD9 is a small molecule BRD9 degrader.

By "reducing the level of BRD9," is meant decreasing the level of BRD9 in a cell or subject. The level of BRD9 may be measured using any method known in the art.

By a "reference" is meant any useful reference used to compare protein or mRNA levels. The reference can be any sample, standard, standard curve, or level that is used for comparison purposes. The reference can be a normal reference sample or a reference standard or level. A "reference sample" can be, for example, a control, e.g., a predetermined negative control value such as a "normal control" or a prior sample taken from the same subject; a sample from a normal healthy subject, such as a normal

cell or normal tissue; a sample (e.g., a cell or tissue) from a subject not having a disease; a sample from a subject that is diagnosed with a disease, but not yet treated with a compound described herein; a sample from a subject that has been treated by a compound described herein; or a sample of a purified protein (e.g., any described herein) at a known normal concentration. By "reference standard or level" is meant a value or number derived from a reference sample. A "normal control value" is a pre-determined value indicative of non-disease state, e.g., a value expected in a healthy control subject. Typically, a normal control value is expressed as a range ("between X and Y"), a high threshold ("no higher than X"), or a low threshold ("no lower than X"). A subject having a measured value within the normal control value for a particular biomarker is typically referred to as "within normal limits" for that biomarker. A normal reference standard or level can be a value or number derived from a normal subject not having a disease or disorder (e.g., cancer); a subject that has been treated with a compound described herein. In preferred embodiments, the reference sample, standard, or level is matched to the sample subject sample by at least one of the following criteria: age, weight, sex, disease stage, and overall health. A standard curve of levels of a purified protein, e.g., any described herein, within the normal reference range can also be used as a reference.

The terms "short interfering RNA" and "siRNA" (also known as "small interfering RNAs") refer to an RNA agent, preferably a double-stranded agent, of about 10-50 nucleotides in length, the strands optionally having overhanging ends comprising, for example 1, 2 or 3 overhanging nucleotides (or nucleotide analogs), which is capable of directing or mediating RNA interference. Naturally-occurring siRNAs are generated from longer dsRNA molecules (e.g., >25 nucleotides in length) by a cell's RNAi machinery (e.g., Dicer or a homolog thereof).

The term "shRNA", as used herein, refers to an RNA agent having a stem-loop structure, comprising a first and second region of complementary sequence, the degree of complementarity and orientation of the regions being sufficient such that base pairing occurs between the regions, the first and second regions being joined by a loop region, the loop resulting from a lack of base pairing between nucleotides (or nucleotide analogs) within the loop region.

As used herein, the term "subject" refers to any organism to which a composition in accordance with the invention may be administered, e.g., for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Typical subjects include any animal (e.g., mammals such as mice, rats, rabbits, non-human primates, and humans). A subject may seek or be in need of treatment, require treatment, be receiving treatment, be receiving treatment in the future, or be a human or animal who is under care by a trained professional for a particular disease or condition.

As used herein, the term "SS18-SSX fusion protein-related disorder" refers to a disorder that is caused or affected by the level and/or activity of SS18-SSX fusion protein.

As used herein, the terms "treat," "treated," or "treating" mean both therapeutic treatment and prophylactic or preventative measures wherein the object is to prevent or slow down (lessen) an undesired physiological condition, disorder, or disease, or obtain beneficial or desired clinical results.

Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of a condition, disorder, or disease; stabilized (i.e., not worsening) state of condition, disorder, or disease; delay in onset or slowing of condition, disorder, or disease progression; amelioration of the condition, disorder, or disease state or remission (whether partial or total), whether detectable or undetectable; an amelioration of at least one measurable physical parameter, not necessarily discernible by the patient; or enhancement or improvement of condition, disorder, or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment.

As used herein, the terms "variant" and "derivative" are used interchangeably and refer to naturally-occurring, synthetic, and semi-synthetic analogues of a compound, peptide, protein, or other substance described herein. A variant or derivative of a compound, peptide, protein, or other substance described herein may retain or improve upon the biological activity of the original material.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and from the claims.

Brief Description of the Drawings

FIG. 1 is a series of graphs illustrating the effect of specific guide RNA (sgRNA) targeting of the BRD9 BAF complex subunit on synovial sarcoma cell growth. The Y-axis indicated the dropout ratio. The X-axis indicates the nucleotide position of the BRD9 gene. The grey box indicates the range of the negative control sgRNAs in the screen. The SYO1 cell line carries SS18-SSX2 fusion protein. The breakpoint joining the N-terminal region of SS18 to the C-terminal region of SSX2 are indicated by the black lines in their respective panel. The linear protein sequence is show with BRD9 PFAM domains annotated from the PFAM database.

FIG. 2 is an image illustrating dose dependent depletion of BRD9 levels in a synovial sarcoma cell line (SYO1) in the presence of a BRD9 degrader.

FIG. 3 is an image illustrating sustained suppression of BRD9 levels in a synovial sarcoma cell line (SYO1) in the presence of a BRD9 degrader over 72 hours.

FIG. 4 is an image illustrating sustained suppression of BRD9 levels in two cell lines (293T and SYO1) in the presence of a BRD9 degrader over 5 days.

FIG. 5 is an image illustrating sustained suppression of BRD9 levels in three synovial sarcoma cell lines (293T, SYO1, and Yamato) in the presence of a BRD9 degrader over 7 days compared to the levels in cells treated with CRISPR reagents.

FIG. 6 is an image illustrating the effect on cell growth of six cell lines (SYO1, Yamato, A549, HS-SY-II, ASKA, and 293T) in the presence of a BRD9 degrader and a BRD9 inhibitor.

FIG. 7 is an image illustrating the effect on cell growth of two cell lines (SYO1 and G401) in the presence of a BRD9 degrader.

FIG. 8 is an image illustrating the effect on cell growth of three synovial sarcoma cell lines (SYO1, HS-SY-II, and ASKA) in the presence of a BRD9 degrader, BRD9 binder and E3 ligase binder.

FIG. 9 is an image illustrating the effect on cell growth of three non-synovial sarcoma cell lines (RD, HCT116, and Calu6) in the presence of a BRD9 degrader, BRD9 binder and E3 ligase binder.

FIG. 10 is a graph illustrating the percentage of SYO1 in various cell cycle phases following treatment with DMSO, Compound 1 at 200 nM, or Compound 1 at 1 μM for 8 or 13 days.

FIG. 11 is a series of contour plots illustrating the percentage of SYO1 cells in various cell cycle phases following treatment with DMSO, Compound 1 at 200 nM, Compound 1 at 1 μM, or lenalidomide at 200nM for 8 days. Numerical values corresponding to each contour plot are found in the table below.

FIG. 12 is a series of contour plots illustrating the percentage of SYO1 cells in various cell cycle phases following treatment with DMSO, Compound 1 at 200 nM, Compound 1 at 1 μM, or lenalidomide at 200nM for 13 days. Numerical values corresponding to each contour plot are found in the table below.

FIG. 13 is a series of contour plots illustrating the percentage of early- and late-apoptotic SYO1 cells following treatment with DMSO, Compound 1 at 200 nM, Compound 1 at 1 μM, or lenalidomide at 200nM for 8 days. Numerical values corresponding to each contour plot are found in the table below.

FIG. 14 is a graph illustrating the proteins present in BAF complexes including the SS18-SSX fusion protein.

Detailed Description

The present disclosure features compositions and methods useful for the treatment of BAF-related disorders (e.g., cancer and infection). The disclosure further features compositions and methods useful for inhibition of the level and/or activity of BRD9, e.g., for the treatment of disorders such as cancer (e.g., sarcoma) and infection (e.g., viral infection), e.g., in a subject in need thereof.

Compounds

Compounds described herein reduce the level of an activity related to BRD9, or a related downstream effect, or reduce the level of BRD9 in a cell or subject. Exemplary compounds described herein have the structure according to **Formula I**.

Formula I is

A-L-B

Formula I,

where

A is a BRD9 binding moiety;

B is a degradation moiety; and

L has the structure of **Formula II**:

$$A^1–(E^1)–(F^1)–(C^3)_m–(E^3)_n–(F^2)_{o1}–(F^3)_{o2}–(E^2)_p–A^2,$$

Formula II

wherein

A^1 is a bond between the linker and A;

A^2 is a bond between B and the linker;

each of m, n, o1, o2, and p is, independently, 0 or 1;

each of E^1 and E^2 is, independently, O, S, NR^N, optionally substituted C_{1-10} alkyl, optionally substituted C_{2-10} alkenyl, optionally substituted C_{2-10} alkynyl, optionally substituted C_2-C_{10} polyethylene glycol, or optionally substituted C_{1-10} heteroalkyl;

E^3 is O, S, or NR^N;

each R^N is, independently, H, optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, optionally substituted C_{2-6} heterocyclyl, optionally substituted C_{6-12} aryl, or optionally substituted C_{1-7} heteroalkyl;

C^3 is carbonyl, thiocarbonyl, sulphonyl, or phosphoryl; and

each of F^1, F^2, and F^3 is, independently, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heteroaryl, or a pharmaceutically acceptable salt thereof.

Pharmaceutical Uses

The compounds described herein are useful in the methods of the invention and, while not bound by theory, are believed to exert their desirable effects through their ability to modulate the level, status, and/or activity of a BAF complex, e.g., by inhibiting the activity or level of the BRD9 protein in a cell within the BAF complex in a mammal.

An aspect of the present invention relates to methods of treating disorders related to BRD9 such as cancer in a subject in need thereof. In some embodiments, the compound is administered in an amount and for a time effective to result in one of (or more, e.g., two or more, three or more, four or more of): (a) reduced tumor size, (b) reduced rate of tumor growth, (c) increased tumor cell death (d) reduced tumor progression, (e) reduced number of metastases, (f) reduced rate of metastasis, (g) decreased tumor recurrence (h) increased survival of subject, and (i) increased progression free survival of a subject.

Treating cancer can result in a reduction in size or volume of a tumor. For example, after treatment, tumor size is reduced by 5% or greater (e.g., 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or greater) relative to its size prior to treatment. Size of a tumor may be measured by any reproducible means of measurement. For example, the size of a tumor may be measured as a diameter of the tumor.

Treating cancer may further result in a decrease in number of tumors. For example, after treatment, tumor number is reduced by 5% or greater (e.g., 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or greater) relative to number prior to treatment. Number of tumors may be measured by any reproducible means of measurement, e.g., the number of tumors may be measured by counting tumors visible to the naked eye or at a specified magnification (e.g., 2x, 3x, 4x, 5x, 10x, or 50x).

Treating cancer can result in a decrease in number of metastatic nodules in other tissues or organs distant from the primary tumor site. For example, after treatment, the number of metastatic nodules is reduced by 5% or greater (e.g., 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or greater) relative to number prior to treatment. The number of metastatic nodules may be measured by any reproducible means of measurement. For example, the number of metastatic nodules may be measured by counting metastatic nodules visible to the naked eye or at a specified magnification (e.g., 2x, 10x, or 50x).

Treating cancer can result in an increase in average survival time of a population of subjects treated according to the present invention in comparison to a population of untreated subjects. For example, the average survival time is increased by more than 30 days (more than 60 days, 90 days, or 120 days). An increase in average survival time of a population may be measured by any reproducible means. An increase in average survival time of a population may be measured, for example, by calculating for a population the average length of survival following initiation of treatment with the compound described herein. An increase in average survival time of a population may also be measured, for example, by calculating for a population the average length of survival following completion of a first round of treatment with a pharmaceutically acceptable salt of a compound described herein.

Treating cancer can also result in a decrease in the mortality rate of a population of treated subjects in comparison to an untreated population. For example, the mortality rate is decreased by more than 2% (e.g., more than 5%, 10%, or 25%). A decrease in the mortality rate of a population of treated subjects may be measured by any reproducible means, for example, by calculating for a population the average number of disease-related deaths per unit time following initiation of treatment with a pharmaceutically acceptable salt of a compound described herein. A decrease in the mortality rate of a population may also be measured, for example, by calculating for a population the average number of disease-related deaths per unit time following completion of a first round of treatment with a pharmaceutically acceptable salt of a compound described herein.

Combination Therapies

A method of the invention can be used alone or in combination with an additional therapeutic agent, e.g., other agents that treat cancer or symptoms associated therewith, or in combination with other types of therapies to treat cancer. In combination treatments, the dosages of one or more of the therapeutic compounds may be reduced from standard dosages when administered alone. For example, doses may be determined empirically from drug combinations and permutations or may be deduced by isobolographic analysis (e.g., Black et al., *Neurology* 65:S3-S6 (2005)). In this case, dosages of the compounds when combined should provide a therapeutic effect.

In some embodiments, the second therapeutic agent is a chemotherapeutic agent (e.g., a cytotoxic agent or other chemical compound useful in the treatment of cancer). These include alkylating agents, antimetabolites, folic acid analogs, pyrimidine analogs, purine analogs and related inhibitors,

vinca alkaloids, epipodopyyllotoxins, antibiotics, L-Asparaginase, topoisomerase inhibitors, interferons, platinum coordination complexes, anthracenedione substituted urea, methyl hydrazine derivatives, adrenocortical suppressant, adrenocorticosteroides, progestins, estrogens, antiestrogen, androgens, antiandrogen, and gonadotropin-releasing hormone analog. Also included is 5-fluorouracil (5-FU), leucovorin (LV), irenotecan, oxaliplatin, capecitabine, paclitaxel, and doxetaxel. Non-limiting examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethiylenethiophosphoramide and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin gammall and calicheamicin omegall (see, e.g., *Agnew, Chem. Intl. Ed Engl.* 33:183-186 (1994)); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antiobiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, ADRIAMYCIN® (doxorubicin, including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5- FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK®

polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, e.g., TAXOL® (paclitaxel; Bristol-Myers Squibb Oncology, Princeton, NJ), ABRAXANE®, cremophor-free, albumin-engineered nanoparticle formulation of paclitaxel (American Pharmaceutical Partners, Schaumberg, IL), and TAXOTERE® doxetaxel (Rhone-Poulenc Rorer, Antony, France); chloranbucil; GEMZAR® gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum coordination complexes such as cisplatin, oxaliplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; NAVELBINE® vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; irinotecan (e.g., CPT-11); topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Two or more chemotherapeutic agents can be used in a cocktail to be administered in combination with the first therapeutic agent described herein. Suitable dosing regimens of combination chemotherapies are known in the art and described in, for example, Saltz et al., *Proc. Am. Soc. Clin. Oncol.* 18:233a (1999), and Douillard et al., *Lancet* 355(9209):1041-1047 (2000).

In some embodiments, the second therapeutic agent is a therapeutic agent which is a biologic such a cytokine (e.g., interferon or an interleukin (e.g., IL-2)) used in cancer treatment. In some embodiments the biologic is an anti-angiogenic agent, such as an anti-VEGF agent, e.g., bevacizumab (AVASTIN®). In some embodiments the biologic is an immunoglobulin-based biologic, e.g., a monoclonal antibody (e.g., a humanized antibody, a fully human antibody, an Fc fusion protein or a functional fragment thereof) that agonizes a target to stimulate an anti-cancer response, or antagonizes an antigen important for cancer. Such agents include RITUXAN® (rituximab); ZENAPAX® (daclizumab); SIMULECT® (basiliximab); SYNAGIS® (palivizumab); REMICADE® (infliximab); HERCEPTIN® (trastuzumab); MYLOTARG® (gemtuzumab ozogamicin); CAMPATH® (alemtuzumab); ZEVALIN® (ibritumomab tiuxetan); HUMIRA® (adalimumab); XOLAIR® (omalizumab); BEXXAR® (tositumomab-I-131); RAPTIVA® (efalizumab); ERBITUX® (cetuximab); AVASTIN® (bevacizumab); TYSABRI® (natalizumab); ACTEMRA® (tocilizumab); VECTIBIX® (panitumumab); LUCENTIS® (ranibizumab); SOLIRIS® (eculizumab); CIMZIA® (certolizumab pegol); SIMPONI® (golimumab); ILARIS® (canakinumab); STELARA® (ustekinumab); ARZERRA® (ofatumumab); PROLIA® (denosumab); NUMAX® (motavizumab); ABTHRAX® (raxibacumab); BENLYSTA® (belimumab); YERVOY® (ipilimumab); ADCETRIS® (brentuximab vedotin); PERJETA® (pertuzumab); KADCYLA® (ado-trastuzumab emtansine); and GAZYVA® (obinutuzumab). Also included are antibody-drug conjugates.

The second agent may be a therapeutic agent which is a non-drug treatment. For example, the second therapeutic agent is radiation therapy, cryotherapy, hyperthermia, and/or surgical excision of tumor tissue.

The second agent may be a checkpoint inhibitor. In one embodiment, the inhibitor of checkpoint is an inhibitory antibody (e.g., a monospecific antibody such as a monoclonal antibody). The antibody may be, e.g., humanized or fully human. In some embodiments, the inhibitor of checkpoint is a fusion protein, e.g., an Fc-receptor fusion protein. In some embodiments, the inhibitor of checkpoint is an agent, such as an antibody, that interacts with a checkpoint protein. In some embodiments, the inhibitor of checkpoint is an agent, such as an antibody, that interacts with the ligand of a checkpoint protein. In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor) of CTLA-4 (e.g., an anti-CTLA4 antibody or fusion a protein such as ipilimumab/YERVOY® or tremelimumab). In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor) of PD-1 (e.g., nivolumab/OPDIVO®; pembrolizumab/KEYTRUDA®; pidilizumab/CT-011). In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor) of PDL1 (e.g., MPDL3280A/RG7446; MEDI4736; MSB0010718C; BMS 936559). In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or Fc fusion or small molecule inhibitor) of PDL2 (e.g., a PDL2/Ig fusion protein such as AMP 224). In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor) of B7-H3 (e.g., MGA271), B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, B-7 family ligands, or a combination thereof.

In some embodiments, the anti-cancer therapy is a T cell adoptive transfer (ACT) therapy. In some embodiments, the T cell is an activated T cell. The T cell may be modified to express a chimeric antigen receptor (CAR). CAR modified T (CAR-T) cells can be generated by any method known in the art. For example, the CAR-T cells can be generated by introducing a suitable expression vector encoding the CAR to a T cell. Prior to expansion and genetic modification of the T cells, a source of T cells is obtained from a subject. T cells can be obtained from a number of sources, including peripheral blood mononuclear cells, bone marrow, lymph node tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural effusion, spleen tissue, and tumors. In certain embodiments of the present invention, any number of T cell lines available in the art, may be used. In some embodiments, the T cell is an autologous T cell. Whether prior to or after genetic modification of the T cells to express a desirable protein (e.g., a CAR), the T cells can be activated and expanded generally using methods as described, for example, in U.S. Patents 6,352,694; 6,534,055; 6,905,680; 6,692,964; 5,858,358; 6,887,466; 6,905,681; 7,144,575; 7,067,318; 7,172,869; 7,232,566; 7,175,843; 5,883,223; 6,905,874; 6,797,514; 6,867,041; and U.S. Patent Application Publication No. 20060121005.

In any of the combination embodiments described herein, the first and second therapeutic agents are administered simultaneously or sequentially, in either order. The first therapeutic agent may be administered immediately, up to 1 hour, up to 2 hours, up to 3 hours, up to 4 hours, up to 5 hours, up to 6 hours, up to 7 hours, up to, 8 hours, up to 9 hours, up to 10 hours, up to 11 hours, up to 12 hours, up to 13 hours, 14 hours, up to hours 16, up to 17 hours, up 18 hours, up to 19 hours up to 20 hours, up to 21

hours, up to 22 hours, up to 23 hours up to 24 hours or up to 1-7, 1-14, 1-21 or 1-30 days before or after the second therapeutic agent.

Pharmaceutical Compositions

The pharmaceutical compositions described herein are preferably formulated into pharmaceutical compositions for administration to human subjects in a biologically compatible form suitable for administration in vivo.

The compounds described herein may be used in the form of the free base, in the form of salts, solvates, and as prodrugs. All forms are within the methods described herein. In accordance with the methods of the invention, the described compounds or salts, solvates, or prodrugs thereof may be administered to a patient in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. The compounds described herein may be administered, for example, by oral, parenteral, buccal, sublingual, nasal, rectal, patch, pump, intratumoral, or transdermal administration and the pharmaceutical compositions formulated accordingly. Parenteral administration includes intravenous, intraperitoneal, subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary, intrathecal, rectal, and topical modes of administration. Parenteral administration may be by continuous infusion over a selected period of time.

A compound described herein may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, a compound described herein may be incorporated with an excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, and wafers. A compound described herein may also be administered parenterally. Solutions of a compound described herein can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, DMSO, and mixtures thereof with or without alcohol, and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington's Pharmaceutical Sciences (2012, 22nd ed.) and in The United States Pharmacopeia: The National Formulary (USP 41 NF36), published in 2018. The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that may be easily administered via syringe. Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels, and powders. Aerosol formulations typically include a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomizing device. Alternatively,

the sealed container may be a unitary dispensing device, such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal after use. Where the dosage form includes an aerosol dispenser, it will contain a propellant, which can be a compressed gas, such as compressed air or an organic propellant, such as fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomizer. Compositions suitable for buccal or sublingual administration include tablets, lozenges, and pastilles, where the active ingredient is formulated with a carrier, such as sugar, acacia, tragacanth, gelatin, and glycerine. Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base, such as cocoa butter. A compound described herein may be administered intratumorally, for example, as an intratumoral injection. Intratumoral injection is injection directly into the tumor vasculature and is specifically contemplated for discrete, solid, accessible tumors. Local, regional, or systemic administration also may be appropriate. A compound described herein may advantageously be contacted by administering an injection or multiple injections to the tumor, spaced for example, at approximately, 1 cm intervals. In the case of surgical intervention, the present invention may be used preoperatively, such as to render an inoperable tumor subject to resection. Continuous administration also may be applied where appropriate, for example, by implanting a catheter into a tumor or into tumor vasculature.

The compounds described herein may be administered to an animal, e.g., a human, alone or in combination with pharmaceutically acceptable carriers, as noted herein, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration, and standard pharmaceutical practice.

Dosages

The dosage of the compounds described herein, and/or compositions including a compound described herein, can vary depending on many factors, such as the pharmacodynamic properties of the compound; the mode of administration; the age, health, and weight of the recipient; the nature and extent of the symptoms; the frequency of the treatment, and the type of concurrent treatment, if any; and the clearance rate of the compound in the animal to be treated. One of skill in the art can determine the appropriate dosage based on the above factors. The compounds described herein may be administered initially in a suitable dosage that may be adjusted as required, depending on the clinical response. In general, satisfactory results may be obtained when the compounds described herein are administered to a human at a daily dosage of, for example, between 0.05 mg and 3000 mg (measured as the solid form). Dose ranges include, for example, between 10-1000 mg (e.g., 50-800 mg). In some embodiments, 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, or 1000 mg of the compound is administered.

Alternatively, the dosage amount can be calculated using the body weight of the patient. For example, the dose of a compound, or pharmaceutical composition thereof, administered to a patient may range from 0.1-50 mg/kg (e.g., 0.25-25 mg/kg). In exemplary, non-limiting embodiments, the dose may

range from 0.5-5.0 mg/kg (e.g., 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, or 5.0 mg/kg) or from 5.0-20 mg/kg (e.g., 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mg/kg).

Kits

The invention also features kits including (a) a pharmaceutical composition including an agent that reduces the level and/or activity of BRD9 in a cell or subject described herein, and (b) a package insert with instructions to perform any of the methods described herein. In some embodiments, the kit includes (a) a pharmaceutical composition including an agent that reduces the level and/or activity of BRD9 in a cell or subject described herein, (b) an additional therapeutic agent (e.g., an anti-cancer agent), and (c) a package insert with instructions to perform any of the methods described herein.

Examples

Example 1 – High density tiling sgRNA screen against human BAF complex subunits in synovial sarcoma cell line SYO1

The following example shows that BRD9 sgRNA inhibits cell growth in synovial sarcoma cells.

Procedure: To perform high density sgRNA tiling screen, an sgRNA library against BAF complex subunits was custom synthesized at Cellecta (Mountain View, CA). Sequences of DNA encoding the BRD9-targeting sgRNAs used in this screen are listed in Table 2. Negative and positive control sgRNA were included in the library. Negative controls consisted of 200 sgRNAs that do not target human genome. The positive controls are sgRNAs targeting essential genes (CDC16, GTF2B, HSPA5, HSPA9, PAFAH1B1, PCNA, POLR2L, RPL9, and SF3A3). DNA sequences encoding all positive and negative control sgRNAs are listed in Table 3. Procedures for virus production, cell infection, and performing the sgRNA screen were previously described (Tsherniak et al, *Cell* 170:564-576 (2017); Munoz et al, *Cancer Discovery* 6:900-913 (2016)). For each sgRNA, 50 counts were added to the sequencing counts and for each time point the resulting counts were normalized to the total number of counts. The log2 of the ratio between the counts (defined as dropout ratio) at day 24 and day 1 post-infection was calculated. For negative control sgRNAs, the 2.5 and 97.5 percentile of the log2 dropout ratio of all non-targeting sgRNAs was calculated and considered as background (grey box in the graph). Protein domains were obtained from PFAM regions defined for the UNIPROT identifier: Q9H8M2.

Results: As shown in FIG. 1, targeted inhibition of the GBAF complex component BRD9 by sgRNA resulted in growth inhibition of the SYO1 synovial sarcoma cell line. sgRNAs against other components of the BAF complexes resulted in increased proliferation of cells, inhibition of cell growth, or had no effect on SYO1 cells. These data show that targeting various subunits of the GBAF complex represents a therapeutic strategy for the treatment of synovial sarcoma.

Table 2: BRD9 sgRNA Library

SEQ ID NO	Nucleic Acid Sequence		SEQ ID NO	Nucleic Acid Sequence
203	CAAGAAGCACAAGAAGCACA		319	GCTCTACAGCGTGGTCAACA
204	CTTGTGCTTCTTGCCCATGG		320	CGGGAGCCTGCTCTACAGCG
205	CTTCTTGTGCTTCTTGCCCA		321	CGTGGTCAACACGGCCGAGC
206	ACAAGAAGCACAAGGCCGAG		322	CCCACCATCAGCGTCCGGCT
207	CTCGTAGGACGAGCGCCACT		323	ACGGCCGAGCCGGACGCTGA
208	CGAGTGGCGCTCGTCCTACG		324	GGGCACCCACCATCAGCGTC
209	GAGTGGCGCTCGTCCTACGA		325	GCCGAGCCGGACGCTGATGG
210	AGGCTTCTCCAGGGGCTTGT		326	CCATGTCCGTGTTGCAGAGG
211	AGATTATGCCGACAAGCCCC		327	CCGAGCCGGACGCTGATGGT
212	ACCTTCAGGACTAGCTTTAG		328	CGAGCTCAAGTCCACCGGGT
213	AGCTTTAGAGGCTTCTCCAG		329	GCGAGCTCAAGTCCACCGGG
214	CTAGCTTTAGAGGCTTCTCC		330	AGAGCGAGCTCAAGTCCACC
215	TAGCTTTAGAGGCTTCTCCA		331	GAGAGCGAGCTCAAGTCCAC
216	CTAAAGCTAGTCCTGAAGGT		332	GAAGCCTGGGAGTAGCTTAC
217	GCCTCTAAAGCTAGTCCTGA		333	CTCTCCAGTAAGCTACTCCC
218	CTTCACTTCCTCCGACCTTC		334	AGCCCAGCGTGGTGAAGCCT
219	AAGCTAGTCCTGAAGGTCGG		335	AAGCCCAGCGTGGTGAAGCC
220	AGTGAAGTGACTGAACTCTC		336	ACTCCCAGGCTTCACCACGC
221	GTGACTGAACTCTCAGGATC		337	CTCCCAGGCTTCACCACGCT
222	ATAGTAACTGGAGTCGTGGC		338	CTCGTCTTTGAAGCCCAGCG
223	CATCATAGTAACTGGAGTCG		339	CACTGGAGAGAAAGGTGACT
224	TGACCTGTCATCATAGTAAC		340	GCACTGGAGAGAAAGGTGAC
225	ACTCCAGTTACTATGATGAC		341	AGTAGTGGCACTGGAGAGAA
226	CTTTGTGCCTCTCTCGCTCA		342	CGAAAGCGCAGTAGTGGCAC
227	GGTCAGACCATGAGCGAGAG		343	CTGCATCGAAAGCGCAGTAG
228	GAAGAAGAAGAAGTCCGAGA		344	ATGCAGAATAATTCAGTATT
229	GTCCAGATGCTTCTCCTTCT		345	AGTATTTGGCGACTTGAAGT
230	GTCCGAGAAGGAGAAGCATC		346	CGACTTGAAGTCGGACGAGA
231	GGAGAAGCATCTGGACGATG		347	GAGCTGCTCTACTCAGCCTA
232	TGAGGAAAGAAGGAAGCGAA		348	CACGCCTGTCTCATCTCCGT
233	ATCTGGACGATGAGGAAAGA		349	TCAGCCTACGGAGATGAGAC

SEQ ID NO	Nucleic Acid Sequence		SEQ ID NO	Nucleic Acid Sequence
234	AGAAGAAGCGGAAGCGAGAG		350	CAGGCGTGCAGTGTGCGCTG
235	GAAGAAGCGGAAGCGAGAGA		351	CCGCGGCCCCTCTAGCCTGC
236	CCGCCCAGGAAGAGAAGAAG		352	CATCCTTCACAAACTCCTGC
237	AGAGAGGGAGCACTGTGACA		353	TAGCCTGCAGGAGTTTGTGA
238	AGGGAGCACTGTGACACGGA		354	CAGGAGTTTGTGAAGGATGC
239	GAGGGAGCACTGTGACACGG		355	AGGAGTTTGTGAAGGATGCT
240	GCACTGTGACACGGAGGGAG		356	TGGGAGCTACAGCAAGAAAG
241	GAGGCTGACGACTTTGATCC		357	GAGCTACAGCAAGAAAGTGG
242	AGGCTGACGACTTTGATCCT		358	GAAAGTGGTGGACGACCTCC
243	TCCACCTCCACCTTCTTCCC		359	CGCCTGTGATCTGGTCCAGG
244	CGACTTTGATCCTGGGAAGA		360	CTCCGCCTGTGATCTGGTCC
245	CTTTGATCCTGGGAAGAAGG		361	GACCTCCTGGACCAGATCAC
246	TGATCCTGGGAAGAAGGTGG		362	CTCCTGGACCAGATCACAGG
247	TCCTGGGAAGAAGGTGGAGG		363	GCTGGAAGAGCGTCCTAGAG
248	CGGACTGGCCGATCTGGGGG		364	TGCAGCCCACCTGCTTCAGC
249	ACGCTCGGACTGGCCGATCT		365	GACGCTCTTCCAGCTGAAGC
250	AGGTGGAGCCGCCCCCAGAT		366	CTCTTCCAGCTGAAGCAGGT
251	CGCTCGGACTGGCCGATCTG		367	GCTCTTCCAGCTGAAGCAGG
252	GCTCGGACTGGCCGATCTGG		368	CCTCCAGATGAAGCCAAGGT
253	CACGCTCGGACTGGCCGATC		369	GCTTCATCTGGAGGCTTCAT
254	TGTGTCCGGCACGCTCGGAC		370	GGCTTCATCTGGAGGCTTCA
255	CTGGCTGTGTCCGGCACGCT		371	CTTACCTTGGCTTCATCTGG
256	ATCGGCCAGTCCGAGCGTGC		372	AAACTTACCTTGGCTTCATC
257	CACCCTTGCCTGGCTGTGTC		373	GAAGCCTCCAGATGAAGCCA
258	CGAGCGTGCCGGACACAGCC		374	TCCTAGGGTGTCCCCAACCT
259	TGTTCCAGGAGTTGCTGAAT		375	CCTAGGGTGTCCCCAACCTG
260	CACACCTATTCAGCAACTCC		376	GTGTCTGTCTCCACAGGTTG
261	GCTGGCGGAGGAAGTGTTCC		377	TGTGTCTGTCTCCACAGGTT
262	TTTACCTCTGAAGCTGGCGG		378	CCACAGGTTGGGGACACCCT
263	CCCCGGTTTACCTCTGAAGC		379	AGAGCTGCTGCTGTCTCCTA
264	ACTTCCTCCGCCAGCTTCAG		380	CAGAGCTGCTGCTGTCTCCT
265	CAGGAAAAGCAAAAAATCCA		381	AGACAGCAGCAGCTCTGTTC
266	GCTTTCAGAAAAGATCCCCA		382	ATCCACAGAAACGTCGGGAT

SEQ ID NO	Nucleic Acid Sequence		SEQ ID NO	Nucleic Acid Sequence
267	AGGAAAAGCAAAAAATCCAT		383	GAGATATCCACAGAAACGTC
268	GGAAAAGCAAAAAATCCATG		384	GGAGATATCCACAGAAACGT
269	GGAGCAATTGCATCCGTGAC		385	GTCCTATCCCGACGTTTCTG
270	GTCACGGATGCAATTGCTCC		386	TCTCCATGCTCAGCTCTCTG
271	TTTATTATCATTGAATATCC		387	CTCACCCAGAGAGCTGAGCA
272	AATGATAATAAAACATCCCA		388	ATCTCCATGCTCAGCTCTCT
273	ATAAAACATCCCATGGATTT		389	TATCTCCATGCTCAGCTCTC
274	TTCATGGTGCCAAAATCCAT		390	ATGTCCTGTTTACACAGGGA
275	TTTCATGGTGCCAAAATCCA		391	TTACACAGGGAAGGTGAAGA
276	TAATGAATACAAGTCAGTTA		392	AGTTCAAATGGCTGTCGTCA
277	CAAGTCAGTTACGGAATTTA		393	TGACGACAGCCATTTGAACT
278	ATAATGCAATGACATACAAT		394	AAGTTCAAATGGCTGTCGTC
279	AACTTGTAGTACACGGTATC		395	TCGTCTCATCCAAGTTCAAA
280	CTTCGCCAACTTGTAGTACA		396	TGAGACGACGAAGCTCCTGC
281	AGATACCGTGTACTACAAGT		397	GTGCTTCGTGCAGGTCCTGC
282	GCGAAGAAGATCCTTCACGC		398	GCAGGACCTGCACGAAGCAC
283	TCATCTTAAAGCCTGCGTGA		399	GCTCCGCCTGTGCTTCGTGC
284	TTCTCAGCAGGCAGCTCTTT		400	GGACCTGCACGAAGCACAGG
285	CAATGAAGATACAGCTGTTG		401	CACGAAGCACAGGCGGAGCG
286	ACTGGTACAACTTCAGGGAC		402	AGGCGGAGCGCGGCGGCTCT
287	CTTGTACTGGTACAACTTCA		403	AGGGAGCTGAGGTTGGACGA
288	ACTTGTACTGGTACAACTTC		404	GTTGGACAGGGAGCTGAGGT
289	TTGGCAGTTTCTACTTGTAC		405	AGGCGTTGGACAGGGAGCTG
290	TACCTGATAACTTCTCTACT		406	CCCTCTCGGAGGCGTTGGAC
291	AGCCGAGTAGAGAAGTTATC		407	CCTCTCGGAGGCGTTGGACA
292	AGCTGCATGTTTGAGCCTGA		408	CTGGTCCCTCTCGGAGGCGT
293	GCTGCATGTTTGAGCCTGAA		409	CCCTGTCCAACGCCTCCGAG
294	AAGCTGCAGGCATTCCCTTC		410	CCTGTCCAACGCCTCCGAGA
295	GGTACTGTCCGTCAAGCTGC		411	GTGGTGCTGGTCCCTCTCGG
296	AGGGAATGCCTGCAGCTTGA		412	CAGGTGGTGCTGGTCCCTCT
297	CTTGACGGACAGTACCGCAG		413	GCATCTCACCCAGGTGGTGC
298	CGCCAGCACGTGCTCCTCTG		414	CGAGAGGGACCAGCACCACC
299	TACCGCAGAGGAGCACGTGC		415	GAGAGGGACCAGCACCACCT

SEQ ID NO	Nucleic Acid Sequence		SEQ ID NO	Nucleic Acid Sequence
300	AGAGGAGCACGTGCTGGCGC		416	GTGGGGGCATCTCACCCAGG
301	GGAGCACGTGCTGGCGCTGG		417	CCCCGACACTCAGGCGAGAA
302	AGCACGCAGCTGACGAAGCT		418	TCCCCGACACTCAGGCGAGA
303	GCACGCAGCTGACGAAGCTC		419	AGCCCTTCTCGCCTGAGTGT
304	CAGCTGACGAAGCTCGGGAC		420	CTGGCTGCTCCCCGACACTC
305	AAGCTCGGGACAGGATCAAC		421	CCCTTCTCGCCTGAGTGTCG
306	CCTTGCCGCCTGGGAGGAAC		422	GCCCTTCTCGCCTGAGTGTC
307	AGGATCAACCGGTTCCTCCC		423	TAGGGGTCGTGGGTGACGTC
308	ATCAACCGGTTCCTCCCAGG		424	AAGAAACTCATAGGGGTCGT
309	GCACTACCTTGCCGCCTGGG		425	GAAGAAACTCATAGGGGTCG
310	AGAGCACTACCTTGCCGCCT		426	GAGACTGAAGAAACTCATAG
311	CCGGTTCCTCCCAGGCGGCA		427	GGAGACTGAAGAAACTCATA
312	TCCTCTTCAGATAGCCCATC		428	TGGAGACTGAAGAAACTCAT
313	ATGGGCTATCTGAAGAGGAA		429	TCTTCAGTCTCCAGAGCCTG
314	GGGCTATCTGAAGAGGAACG		430	TTGGCAGAGGCCGCAGGCTC
315	TGGGCTATCTGAAGAGGAAC		431	TAGGTCTTGGCAGAGGCCGC
316	TATCTGAAGAGGAACGGGGA		432	CTAGAGTTAGGTCTTGGCAG
317	ATCTGAAGAGGAACGGGGAC		433	GGTGGTCTAGAGTTAGGTCT
318	TGTTGACCACGCTGTAGAGC			

Table 3: Control sgRNA Library

SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
434	1|sg_Non_Targeting_Human_0001|Non_Targeting_Human	Non_Targeting_Human	GTAGCGAACGTGTCCGGCGT
435	1|sg_Non_Targeting_Human_0002|Non_Targeting_Human	Non_Targeting_Human	GACCGGAACGATCTCGCGTA
436	1|sg_Non_Targeting_Human_0003|Non_Targeting_Human	Non_Targeting_Human	GGCAGTCGTTCGGTTGATAT
437	1|sg_Non_Targeting_Human_0004|Non_Targeting_Human	Non_Targeting_Human	GCTTGAGCACATACGCGAAT
438	1|sg_Non_Targeting_Human_0005|Non_Targeting_Human	Non_Targeting_Human	GTGGTAGAATAACGTATTAC
439	1|sg_Non_Targeting_Human_0006|Non_Targeting_Human	Non_Targeting_Human	GTCATACATGGATAAGGCTA

SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
440	1|sg_Non_Targeting_Human_0007|Non_Targeting_Human	Non_Targeting_Human	GATACACGAAGCATCACTAG
441	1|sg_Non_Targeting_Human_0008|Non_Targeting_Human	Non_Targeting_Human	GAACGTTGGCACTACTTCAC
442	1|sg_Non_Targeting_Human_0009|Non_Targeting_Human	Non_Targeting_Human	GATCCATGTAATGCGTTCGA
443	1|sg_Non_Targeting_Human_0010|Non_Targeting_Human	Non_Targeting_Human	GTCGTGAAGTGCATTCGATC
444	1|sg_Non_Targeting_Human_0011|Non_Targeting_Human	Non_Targeting_Human	GTTCGACTCGCGTGACCGTA
445	1|sg_Non_Targeting_Human_0012|Non_Targeting_Human	Non_Targeting_Human	GAATCTACCGCAGCGGTTCG
446	1|sg_Non_Targeting_Human_0013|Non_Targeting_Human	Non_Targeting_Human	GAAGTGACGTCGATTCGATA
447	1|sg_Non_Targeting_Human_0014|Non_Targeting_Human	Non_Targeting_Human	GCGGTGTATGACAACCGCCG
448	1|sg_Non_Targeting_Human_0015|Non_Targeting_Human	Non_Targeting_Human	GTACCGCGCCTGAAGTTCGC
449	1|sg_Non_Targeting_Human_0016|Non_Targeting_Human	Non_Targeting_Human	GCAGCTCGTGTGTCGTACTC
450	1|sg_Non_Targeting_Human_0017|Non_Targeting_Human	Non_Targeting_Human	GCGCCTTAAGAGTACTCATC
451	1|sg_Non_Targeting_Human_0018|Non_Targeting_Human	Non_Targeting_Human	GAGTGTCGTCGTTGCTCCTA
452	1|sg_Non_Targeting_Human_0019|Non_Targeting_Human	Non_Targeting_Human	GCAGCTCGACCTCAAGCCGT
453	1|sg_Non_Targeting_Human_0020|Non_Targeting_Human	Non_Targeting_Human	GTATCCTGACCTACGCGCTG
454	1|sg_Non_Targeting_Human_0021|Non_Targeting_Human	Non_Targeting_Human	GTGTATCTCAGCACGCTAAC
455	1|sg_Non_Targeting_Human_0022|Non_Targeting_Human	Non_Targeting_Human	GTCGTCATACAACGGCAACG
456	1|sg_Non_Targeting_Human_0023|Non_Targeting_Human	Non_Targeting_Human	GTCGTGCGCTTCCGGCGGTA
457	1|sg_Non_Targeting_Human_0024|Non_Targeting_Human	Non_Targeting_Human	GCGGTCCTCAGTAAGCGCGT
458	1|sg_Non_Targeting_Human_0025|Non_Targeting_Human	Non_Targeting_Human	GCTCTGCTGCGGAAGGATTC
459	1|sg_Non_Targeting_Human_0026|Non_Targeting_Human	Non_Targeting_Human	GCATGGAGGAGCGTCGCAGA

SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
460	1|sg_Non_Targeting_Human_0027|Non_Targeting_Human	Non_Targeting_Human	GTAGCGCGCGTAGGAGTGGC
461	1|sg_Non_Targeting_Human_0028|Non_Targeting_Human	Non_Targeting_Human	GATCACCTGCATTCGTACAC
462	1|sg_Non_Targeting_Human_0029|Non_Targeting_Human	Non_Targeting_Human	GCACACCTAGATATCGAATG
463	1|sg_Non_Targeting_Human_0030|Non_Targeting_Human	Non_Targeting_Human	GTTGATCAACGCGCTTCGCG
464	1|sg_Non_Targeting_Human_0031|Non_Targeting_Human	Non_Targeting_Human	GCGTCTCACTCACTCCATCG
465	1|sg_Non_Targeting_Human_0032|Non_Targeting_Human	Non_Targeting_Human	GCCGACCAACGTCAGCGGTA
466	1|sg_Non_Targeting_Human_0033|Non_Targeting_Human	Non_Targeting_Human	GGATACGGTGCGTCAATCTA
467	1|sg_Non_Targeting_Human_0034|Non_Targeting_Human	Non_Targeting_Human	GAATCCAGTGGCGGCGACAA
468	1|sg_Non_Targeting_Human_0035|Non_Targeting_Human	Non_Targeting_Human	GCACTGTCAGTGCAACGATA
469	1|sg_Non_Targeting_Human_0036|Non_Targeting_Human	Non_Targeting_Human	GCGATCCTCAAGTATGCTCA
470	1|sg_Non_Targeting_Human_0037|Non_Targeting_Human	Non_Targeting_Human	GCTAATATCGACACGGCCGC
471	1|sg_Non_Targeting_Human_0038|Non_Targeting_Human	Non_Targeting_Human	GGAGATGCATCGAAGTCGAT
472	1|sg_Non_Targeting_Human_0039|Non_Targeting_Human	Non_Targeting_Human	GGATGCACTCCATCTCGTCT
473	1|sg_Non_Targeting_Human_0040|Non_Targeting_Human	Non_Targeting_Human	GTGCCGAGTAATAACGCGAG
474	1|sg_Non_Targeting_Human_0041|Non_Targeting_Human	Non_Targeting_Human	GAGATTCCGATGTAACGTAC
475	1|sg_Non_Targeting_Human_0042|Non_Targeting_Human	Non_Targeting_Human	GTCGTCACGAGCAGGATTGC
476	1|sg_Non_Targeting_Human_0043|Non_Targeting_Human	Non_Targeting_Human	GCGTTAGTCACTTAGCTCGA
477	1|sg_Non_Targeting_Human_0044|Non_Targeting_Human	Non_Targeting_Human	GTTCACACGGTGTCGGATAG
478	1|sg_Non_Targeting_Human_0045|Non_Targeting_Human	Non_Targeting_Human	GGATAGGTGACCTTAGTACG
479	1|sg_Non_Targeting_Human_0046|Non_Targeting_Human	Non_Targeting_Human	GTATGAGTCAAGCTAATGCG

SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
480	1|sg_Non_Targeting_Human_0047|Non_Targeting_Human	Non_Targeting_Human	GCAACTATTGGAATACGTGA
481	1|sg_Non_Targeting_Human_0048|Non_Targeting_Human	Non_Targeting_Human	GTTACCTTCGCTCGTCTATA
482	1|sg_Non_Targeting_Human_0049|Non_Targeting_Human	Non_Targeting_Human	GTACCGAGCACCACAGGCCG
483	1|sg_Non_Targeting_Human_0050|Non_Targeting_Human	Non_Targeting_Human	GTCAGCCATCGGATAGAGAT
484	1|sg_Non_Targeting_Human_0051|Non_Targeting_Human	Non_Targeting_Human	GTACGGCACTCCTAGCCGCT
485	1|sg_Non_Targeting_Human_0052|Non_Targeting_Human	Non_Targeting_Human	GGTCCTGTCGTATGCTTGCA
486	1|sg_Non_Targeting_Human_0053|Non_Targeting_Human	Non_Targeting_Human	GCCGCAATATATGCGGTAAG
487	1|sg_Non_Targeting_Human_0054|Non_Targeting_Human	Non_Targeting_Human	GCGCACGTATAATCCTGCGT
488	1|sg_Non_Targeting_Human_0055|Non_Targeting_Human	Non_Targeting_Human	GTGCACAACACGATCCACGA
489	1|sg_Non_Targeting_Human_0056|Non_Targeting_Human	Non_Targeting_Human	GCACAATGTTGACGTAAGTG
490	1|sg_Non_Targeting_Human_0057|Non_Targeting_Human	Non_Targeting_Human	GTAAGATGCTGCTCACCGTG
491	1|sg_Non_Targeting_Human_0058|Non_Targeting_Human	Non_Targeting_Human	GTCGGTGATCCAACGTATCG
492	1|sg_Non_Targeting_Human_0059|Non_Targeting_Human	Non_Targeting_Human	GAGCTAGTAGGACGCAAGAC
493	1|sg_Non_Targeting_Human_0060|Non_Targeting_Human	Non_Targeting_Human	GTACGTGGAAGCTTGTGGCC
494	1|sg_Non_Targeting_Human_0061|Non_Targeting_Human	Non_Targeting_Human	GAGAACTGCCAGTTCTCGAT
495	1|sg_Non_Targeting_Human_0062|Non_Targeting_Human	Non_Targeting_Human	GCCATTCGGCGCGGCACTTC
496	1|sg_Non_Targeting_Human_0063|Non_Targeting_Human	Non_Targeting_Human	GCACACGACCAATCCGCTTC
497	1|sg_Non_Targeting_Human_0064|Non_Targeting_Human	Non_Targeting_Human	GAGGTGATCGATTAAGTACA
498	1|sg_Non_Targeting_Human_0065|Non_Targeting_Human	Non_Targeting_Human	GTCACTCGCAGACGCCTAAC
499	1|sg_Non_Targeting_Human_0066|Non_Targeting_Human	Non_Targeting_Human	GCGCTACGGAATCATACGTT

SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
500	1|sg_Non_Targeting_Human_0067|Non_Targeting_Human	Non_Targeting_Human	GGTAGGACCTCACGGCGCGC
501	1|sg_Non_Targeting_Human_0068|Non_Targeting_Human	Non_Targeting_Human	GAACTGCATCTTGTTGTAGT
502	1|sg_Non_Targeting_Human_0069|Non_Targeting_Human	Non_Targeting_Human	GATCCTGATCCGGCGGCGCG
503	1|sg_Non_Targeting_Human_0070|Non_Targeting_Human	Non_Targeting_Human	GGTATGCGCGATCCTGAGTT
504	1|sg_Non_Targeting_Human_0071|Non_Targeting_Human	Non_Targeting_Human	GCGGAGCTAGAGAGCGGTCA
505	1|sg_Non_Targeting_Human_0072|Non_Targeting_Human	Non_Targeting_Human	GAATGGCAATTACGGCTGAT
506	1|sg_Non_Targeting_Human_0073|Non_Targeting_Human	Non_Targeting_Human	GTATGGTGAGTAGTCGCTTG
507	1|sg_Non_Targeting_Human_0074|Non_Targeting_Human	Non_Targeting_Human	GTGTAATTGCGTCTAGTCGG
508	1|sg_Non_Targeting_Human_0075|Non_Targeting_Human	Non_Targeting_Human	GGTCCTGGCGAGGAGCCTTG
509	1|sg_Non_Targeting_Human_0076|Non_Targeting_Human	Non_Targeting_Human	GAAGATAAGTCGCTGTCTCG
510	1|sg_Non_Targeting_Human_0077|Non_Targeting_Human	Non_Targeting_Human	GTCGGCGTTCTGTTGTGACT
511	1|sg_Non_Targeting_Human_0078|Non_Targeting_Human	Non_Targeting_Human	GAGGCAAGCCGTTAGGTGTA
512	1|sg_Non_Targeting_Human_0079|Non_Targeting_Human	Non_Targeting_Human	GCGGATCCAGATCTCATTCG
513	1|sg_Non_Targeting_Human_0080|Non_Targeting_Human	Non_Targeting_Human	GGAACATAGGAGCACGTAGT
514	1|sg_Non_Targeting_Human_0081|Non_Targeting_Human	Non_Targeting_Human	GTCATCATTATGGCGTAAGG
515	1|sg_Non_Targeting_Human_0082|Non_Targeting_Human	Non_Targeting_Human	GCGACTAGCGCCATGAGCGG
516	1|sg_Non_Targeting_Human_0083|Non_Targeting_Human	Non_Targeting_Human	GGCGAAGTTCGACATGACAC
517	1|sg_Non_Targeting_Human_0084|Non_Targeting_Human	Non_Targeting_Human	GCTGTCGTGTGGAGGCTATG
518	1|sg_Non_Targeting_Human_0085|Non_Targeting_Human	Non_Targeting_Human	GCGGAGAGCATTGACCTCAT
519	1|sg_Non_Targeting_Human_0086|Non_Targeting_Human	Non_Targeting_Human	GACTAATGGACCAAGTCAGT

SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
520	1|sg_Non_Targeting_Human_0087|Non_Targeting_Human	Non_Targeting_Human	GCGGATTAGAGGTAATGCGG
521	1|sg_Non_Targeting_Human_0088|Non_Targeting_Human	Non_Targeting_Human	GCCGACGGCAATCAGTACGC
522	1|sg_Non_Targeting_Human_0089|Non_Targeting_Human	Non_Targeting_Human	GTAACCTCTCGAGCGATAGA
523	1|sg_Non_Targeting_Human_0090|Non_Targeting_Human	Non_Targeting_Human	GACTTGTATGTGGCTTACGG
524	1|sg_Non_Targeting_Human_0091|Non_Targeting_Human	Non_Targeting_Human	GTCACTGTGGTCGAACATGT
525	1|sg_Non_Targeting_Human_0092|Non_Targeting_Human	Non_Targeting_Human	GTACTCCAATCCGCGATGAC
526	1|sg_Non_Targeting_Human_0093|Non_Targeting_Human	Non_Targeting_Human	GCGTTGGCACGATGTTACGG
527	1|sg_Non_Targeting_Human_0094|Non_Targeting_Human	Non_Targeting_Human	GAACCAGCCGGCTAGTATGA
528	1|sg_Non_Targeting_Human_0095|Non_Targeting_Human	Non_Targeting_Human	GTATACTAGCTAACCACACG
529	1|sg_Non_Targeting_Human_0096|Non_Targeting_Human	Non_Targeting_Human	GAATCGGAATAGTTGATTCG
530	1|sg_Non_Targeting_Human_0097|Non_Targeting_Human	Non_Targeting_Human	GAGCACTTGCATGAGGCGGT
531	1|sg_Non_Targeting_Human_0098|Non_Targeting_Human	Non_Targeting_Human	GAACGGCGATGAAGCCAGCC
532	1|sg_Non_Targeting_Human_0099|Non_Targeting_Human	Non_Targeting_Human	GCAACCGAGATGAGAGGTTC
533	1|sg_Non_Targeting_Human_0100|Non_Targeting_Human	Non_Targeting_Human	GCAAGATCAATATGCGTGAT
534	1|sg_Non_Targeting_Human_GA_0101|Non_Targeting_Human	Non_Targeting_Human	ACGGAGGCTAAGCGTCGCAA
535	1|sg_Non_Targeting_Human_GA_0102|Non_Targeting_Human	Non_Targeting_Human	CGCTTCCGCGGCCCGTTCAA
536	1|sg_Non_Targeting_Human_GA_0103|Non_Targeting_Human	Non_Targeting_Human	ATCGTTTCCGCTTAACGGCG
537	1|sg_Non_Targeting_Human_GA_0104|Non_Targeting_Human	Non_Targeting_Human	GTAGGCGCGCCGCTCTCTAC
538	1|sg_Non_Targeting_Human_GA_0105|Non_Targeting_Human	Non_Targeting_Human	CCATATCGGGGCGAGACATG
539	1|sg_Non_Targeting_Human_GA_0106|Non_Targeting_Human	Non_Targeting_Human	TACTAACGCCGCTCCTACAG

SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
540	1|sg_Non_Targeting_Human_GA_0107|Non_Targeting_Human	Non_Targeting_Human	TGAGGATCATGTCGAGCGCC
541	1|sg_Non_Targeting_Human_GA_0108|Non_Targeting_Human	Non_Targeting_Human	GGGCCCGCATAGGATATCGC
542	1|sg_Non_Targeting_Human_GA_0109|Non_Targeting_Human	Non_Targeting_Human	TAGACAACCGCGGAGAATGC
543	1|sg_Non_Targeting_Human_GA_0110|Non_Targeting_Human	Non_Targeting_Human	ACGGGCGGCTATCGCTGACT
544	1|sg_Non_Targeting_Human_GA_0111|Non_Targeting_Human	Non_Targeting_Human	CGCGGAAATTTTACCGACGA
545	1|sg_Non_Targeting_Human_GA_0112|Non_Targeting_Human	Non_Targeting_Human	CTTACAATCGTCGGTCCAAT
546	1|sg_Non_Targeting_Human_GA_0113|Non_Targeting_Human	Non_Targeting_Human	GCGTGCGTCCCGGGTTACCC
547	1|sg_Non_Targeting_Human_GA_0114|Non_Targeting_Human	Non_Targeting_Human	CGGAGTAACAAGCGGACGGA
548	1|sg_Non_Targeting_Human_GA_0115|Non_Targeting_Human	Non_Targeting_Human	CGAGTGTTATACGCACCGTT
549	1|sg_Non_Targeting_Human_GA_0116|Non_Targeting_Human	Non_Targeting_Human	CGACTAACCGGAAACTTTTT
550	1|sg_Non_Targeting_Human_GA_0117|Non_Targeting_Human	Non_Targeting_Human	CAACGGGTTCTCCCGGCTAC
551	1|sg_Non_Targeting_Human_GA_0118|Non_Targeting_Human	Non_Targeting_Human	CAGGAGTCGCCGATACGCGT
552	1|sg_Non_Targeting_Human_GA_0119|Non_Targeting_Human	Non_Targeting_Human	TTCACGTCGTCTCGCGACCA
553	1|sg_Non_Targeting_Human_GA_0120|Non_Targeting_Human	Non_Targeting_Human	GTGTCGGATTCCGCCGCTTA
554	1|sg_Non_Targeting_Human_GA_0121|Non_Targeting_Human	Non_Targeting_Human	CACGAACTCACACCGCGCGA
555	1|sg_Non_Targeting_Human_GA_0122|Non_Targeting_Human	Non_Targeting_Human	CGCTAGTACGCTCCTCTATA
556	1|sg_Non_Targeting_Human_GA_0123|Non_Targeting_Human	Non_Targeting_Human	TCGCGCTTGGGTTATACGCT
557	1|sg_Non_Targeting_Human_GA_0124|Non_Targeting_Human	Non_Targeting_Human	CTATCTCGAGTGGTAATGCG
558	1|sg_Non_Targeting_Human_GA_0125|Non_Targeting_Human	Non_Targeting_Human	AATCGACTCGAACTTCGTGT
559	1|sg_Non_Targeting_Human_GA_0126|Non_Targeting_Human	Non_Targeting_Human	CCCGATGGACTATACCGAAC

SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
560	1|sg_Non_Targeting_Human_GA_0127|Non_Targeting_Human	Non_Targeting_Human	ACGTTCGAGTACGACCAGCT
561	1|sg_Non_Targeting_Human_GA_0128|Non_Targeting_Human	Non_Targeting_Human	CGCGACGACTCAACCTAGTC
562	1|sg_Non_Targeting_Human_GA_0129|Non_Targeting_Human	Non_Targeting_Human	GGTCACCGATCGAGAGCTAG
563	1|sg_Non_Targeting_Human_GA_0130|Non_Targeting_Human	Non_Targeting_Human	CTCAACCGACCGTATGGTCA
564	1|sg_Non_Targeting_Human_GA_0131|Non_Targeting_Human	Non_Targeting_Human	CGTATTCGACTCTCAACGCG
565	1|sg_Non_Targeting_Human_GA_0132|Non_Targeting_Human	Non_Targeting_Human	CTAGCCGCCCAGATCGAGCC
566	1|sg_Non_Targeting_Human_GA_0133|Non_Targeting_Human	Non_Targeting_Human	GAATCGACCGACACTAATGT
567	1|sg_Non_Targeting_Human_GA_0134|Non_Targeting_Human	Non_Targeting_Human	ACTTCAGTTCGGCGTAGTCA
568	1|sg_Non_Targeting_Human_GA_0135|Non_Targeting_Human	Non_Targeting_Human	GTGCGATGTCGCTTCAACGT
569	1|sg_Non_Targeting_Human_GA_0136|Non_Targeting_Human	Non_Targeting_Human	CGCCTAATTTCCGGATCAAT
570	1|sg_Non_Targeting_Human_GA_0137|Non_Targeting_Human	Non_Targeting_Human	CGTGGCCGGAACCGTCATAG
571	1|sg_Non_Targeting_Human_GA_0138|Non_Targeting_Human	Non_Targeting_Human	ACCCTCCGAATCGTAACGGA
572	1|sg_Non_Targeting_Human_GA_0139|Non_Targeting_Human	Non_Targeting_Human	AAACGGTACGACAGCGTGTG
573	1|sg_Non_Targeting_Human_GA_0140|Non_Targeting_Human	Non_Targeting_Human	ACATAGTCGACGGCTCGATT
574	1|sg_Non_Targeting_Human_GA_0141|Non_Targeting_Human	Non_Targeting_Human	GATGGCGCTTCAGTCGTCGG
575	1|sg_Non_Targeting_Human_GA_0142|Non_Targeting_Human	Non_Targeting_Human	ATAATCCGGAAACGCTCGAC
576	1|sg_Non_Targeting_Human_GA_0143|Non_Targeting_Human	Non_Targeting_Human	CGCCGGGCTGACAATTAACG
577	1|sg_Non_Targeting_Human_GA_0144|Non_Targeting_Human	Non_Targeting_Human	CGTCGCCATATGCCGGTGGC
578	1|sg_Non_Targeting_Human_GA_0145|Non_Targeting_Human	Non_Targeting_Human	CGGGCCTATAACACCATCGA
579	1|sg_Non_Targeting_Human_GA_0146|Non_Targeting_Human	Non_Targeting_Human	CGCCGTTCCGAGATACTTGA

SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
580	1|sg_Non_Targeting_Human_GA_0147|Non_Targeting_Human	Non_Targeting_Human	CGGGACGTCGCGAAAATGTA
581	1|sg_Non_Targeting_Human_GA_0148|Non_Targeting_Human	Non_Targeting_Human	TCGGCATACGGGACACACGC
582	1|sg_Non_Targeting_Human_GA_0149|Non_Targeting_Human	Non_Targeting_Human	AGCTCCATCGCCGCGATAAT
583	1|sg_Non_Targeting_Human_GA_0150|Non_Targeting_Human	Non_Targeting_Human	ATCGTATCATCAGCTAGCGC
584	1|sg_Non_Targeting_Human_GA_0151|Non_Targeting_Human	Non_Targeting_Human	TCGATCGAGGTTGCATTCGG
585	1|sg_Non_Targeting_Human_GA_0152|Non_Targeting_Human	Non_Targeting_Human	CTCGACAGTTCGTCCCGAGC
586	1|sg_Non_Targeting_Human_GA_0153|Non_Targeting_Human	Non_Targeting_Human	CGGTAGTATTAATCGCTGAC
587	1|sg_Non_Targeting_Human_GA_0154|Non_Targeting_Human	Non_Targeting_Human	TGAACGCGTGTTTCCTTGCA
588	1|sg_Non_Targeting_Human_GA_0155|Non_Targeting_Human	Non_Targeting_Human	CGACGCTAGGTAACGTAGAG
589	1|sg_Non_Targeting_Human_GA_0156|Non_Targeting_Human	Non_Targeting_Human	CATTGTTGAGCGGGCGCGCT
590	1|sg_Non_Targeting_Human_GA_0157|Non_Targeting_Human	Non_Targeting_Human	CCGCTATTGAAACCGCCCAC
591	1|sg_Non_Targeting_Human_GA_0158|Non_Targeting_Human	Non_Targeting_Human	AGACACGTCACCGGTCAAAA
592	1|sg_Non_Targeting_Human_GA_0159|Non_Targeting_Human	Non_Targeting_Human	TTTACGATCTAGCGGCGTAG
593	1|sg_Non_Targeting_Human_GA_0160|Non_Targeting_Human	Non_Targeting_Human	TTCGCACGATTGCACCTTGG
594	1|sg_Non_Targeting_Human_GA_0161|Non_Targeting_Human	Non_Targeting_Human	GGTTAGAGACTAGGCGCGCG
595	1|sg_Non_Targeting_Human_GA_0162|Non_Targeting_Human	Non_Targeting_Human	CCTCCGTGCTAACGCGGACG
596	1|sg_Non_Targeting_Human_GA_0163|Non_Targeting_Human	Non_Targeting_Human	TTATCGCGTAGTGCTGACGT
597	1|sg_Non_Targeting_Human_GA_0164|Non_Targeting_Human	Non_Targeting_Human	TACGCTTGCGTTTAGCGTCC
598	1|sg_Non_Targeting_Human_GA_0165|Non_Targeting_Human	Non_Targeting_Human	CGCGGCCCACGCGTCATCGC
599	1|sg_Non_Targeting_Human_GA_0166|Non_Targeting_Human	Non_Targeting_Human	AGCTCGCCATGTCGGTTCTC

SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
600	1|sg_Non_Targeting_Human_GA_0167|Non_Targeting_Human	Non_Targeting_Human	AACTAGCCCGAGCAGCTTCG
601	1|sg_Non_Targeting_Human_GA_0168|Non_Targeting_Human	Non_Targeting_Human	CGCAAGGTGTCGGTAACCCT
602	1|sg_Non_Targeting_Human_GA_0169|Non_Targeting_Human	Non_Targeting_Human	CTTCGACGCCATCGTGCTCA
603	1|sg_Non_Targeting_Human_GA_0170|Non_Targeting_Human	Non_Targeting_Human	TCCTGGATACCGCGTGGTTA
604	1|sg_Non_Targeting_Human_GA_0171|Non_Targeting_Human	Non_Targeting_Human	ATAGCCGCCGCTCATTACTT
605	1|sg_Non_Targeting_Human_GA_0172|Non_Targeting_Human	Non_Targeting_Human	GTCGTCCGGGATTACAAAAT
606	1|sg_Non_Targeting_Human_GA_0173|Non_Targeting_Human	Non_Targeting_Human	TAATGCTGCACACGCCGAAT
607	1|sg_Non_Targeting_Human_GA_0174|Non_Targeting_Human	Non_Targeting_Human	TATCGCTTCCGATTAGTCCG
608	1|sg_Non_Targeting_Human_GA_0175|Non_Targeting_Human	Non_Targeting_Human	GTACCATACCGCGTACCCTT
609	1|sg_Non_Targeting_Human_GA_0176|Non_Targeting_Human	Non_Targeting_Human	TAAGATCCGCGGGTGGCAAC
610	1|sg_Non_Targeting_Human_GA_0177|Non_Targeting_Human	Non_Targeting_Human	GTAGACGTCGTGAGCTTCAC
611	1|sg_Non_Targeting_Human_GA_0178|Non_Targeting_Human	Non_Targeting_Human	TCGCGGACATAGGGCTCTAA
612	1|sg_Non_Targeting_Human_GA_0179|Non_Targeting_Human	Non_Targeting_Human	AGCGCAGATAGCGCGTATCA
613	1|sg_Non_Targeting_Human_GA_0180|Non_Targeting_Human	Non_Targeting_Human	GTTCGCTTCGTAACGAGGAA
614	1|sg_Non_Targeting_Human_GA_0181|Non_Targeting_Human	Non_Targeting_Human	GACCCCCGATAACTTTTGAC
615	1|sg_Non_Targeting_Human_GA_0182|Non_Targeting_Human	Non_Targeting_Human	ACGTCCATACTGTCGGCTAC
616	1|sg_Non_Targeting_Human_GA_0183|Non_Targeting_Human	Non_Targeting_Human	GTACCATTGCCGGCTCCCTA
617	1|sg_Non_Targeting_Human_GA_0184|Non_Targeting_Human	Non_Targeting_Human	TGGTTCCGTAGGTCGGTATA
618	1|sg_Non_Targeting_Human_GA_0185|Non_Targeting_Human	Non_Targeting_Human	TCTGGCTTGACACGACCGTT
619	1|sg_Non_Targeting_Human_GA_0186|Non_Targeting_Human	Non_Targeting_Human	CGCTAGGTCCGGTAAGTGCG

SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
620	1|sg_Non_Targeting_Human_GA_0187|Non_Targeting_Human	Non_Targeting_Human	AGCACGTAATGTCCGTGGAT
621	1|sg_Non_Targeting_Human_GA_0188|Non_Targeting_Human	Non_Targeting_Human	AAGGCGCGCGAATGTGGCAG
622	1|sg_Non_Targeting_Human_GA_0189|Non_Targeting_Human	Non_Targeting_Human	ACTGCGGAGCGCCCAATATC
623	1|sg_Non_Targeting_Human_GA_0190|Non_Targeting_Human	Non_Targeting_Human	CGTCGAGTGCTCGAACTCCA
624	1|sg_Non_Targeting_Human_GA_0191|Non_Targeting_Human	Non_Targeting_Human	TCGCAGCGGCGTGGGATCGG
625	1|sg_Non_Targeting_Human_GA_0192|Non_Targeting_Human	Non_Targeting_Human	ATCTGTCCTAATTCGGATCG
626	1|sg_Non_Targeting_Human_GA_0193|Non_Targeting_Human	Non_Targeting_Human	TGCGGCGTAATGCTTGAAAG
627	1|sg_Non_Targeting_Human_GA_0194|Non_Targeting_Human	Non_Targeting_Human	CGAACTTAATCCCGTGGCAA
628	1|sg_Non_Targeting_Human_GA_0195|Non_Targeting_Human	Non_Targeting_Human	GCCGTGTTGCTGGATACGCC
629	1|sg_Non_Targeting_Human_GA_0196|Non_Targeting_Human	Non_Targeting_Human	TACCCTCCGGATACGGACTG
630	1|sg_Non_Targeting_Human_GA_0197|Non_Targeting_Human	Non_Targeting_Human	CCGTTGGACTATGGCGGGTC
631	1|sg_Non_Targeting_Human_GA_0198|Non_Targeting_Human	Non_Targeting_Human	GTACGGGGCGATCATCCACA
632	1|sg_Non_Targeting_Human_GA_0199|Non_Targeting_Human	Non_Targeting_Human	AAGAGTAGTAGACGCCCGGG
633	1|sg_Non_Targeting_Human_GA_0200|Non_Targeting_Human	Non_Targeting_Human	AAGAGCGAATCGATTTCGTG
634	3|sg_hCDC16_CC_1|CDC16	CDC16	TCAACACCAGTGCCTGACGG
635	3|sg_hCDC16_CC_2|CDC16	CDC16	AAAGTAGCTTCACTCTCTCG
636	3|sg_hCDC16_CC_3|CDC16	CDC16	GAGCCAACCAATAGATGTCC
637	3|sg_hCDC16_CC_4|CDC16	CDC16	GCGCCGCCATGAACCTAGAG
638	3|sg_hGTF2B_CC_1|GTF2B	GTF2B	ACAAAGGTTGGAACAGAACC
639	3|sg_hGTF2B_CC_2|GTF2B	GTF2B	GGTGACCGGGTTATTGATGT

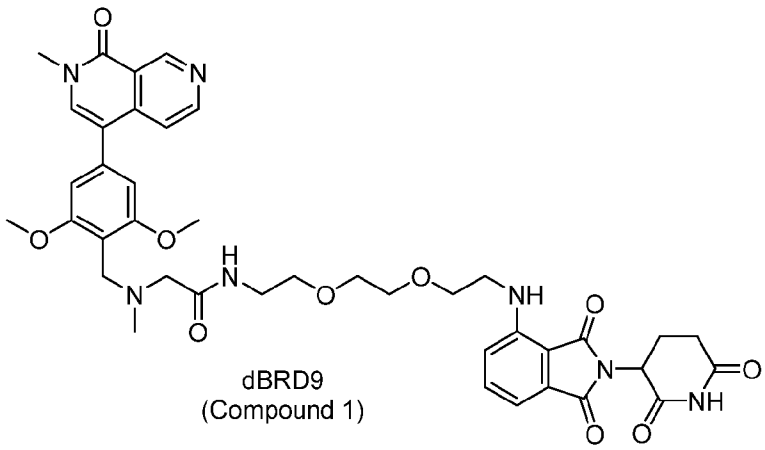
SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
640	3|sg_hGTF2B_CC_3|GTF2B	GTF2B	TTAGTGGAGGACTACAGAGC
641	3|sg_hGTF2B_CC_4|GTF2B	GTF2B	ACATATAGCCCGTAAAGCTG
642	3|sg_hHSPA5_CC_1|HSPA5	HSPA5	CGTTGGCGATGATCTCCACG
643	3|sg_hHSPA5_CC_2|HSPA5	HSPA5	TGGCCTTTTCTACCTCGCGC
644	3|sg_hHSPA5_CC_3|HSPA5	HSPA5	AATGGAGATACTCATCTGGG
645	3|sg_hHSPA5_CC_4|HSPA5	HSPA5	GAAGCCCGTCCAGAAAGTGT
646	3|sg_hHSPA9_CC_1|HSPA9	HSPA9	CAATCTGAGGAACTCCACGA
647	3|sg_hHSPA9_CC_2|HSPA9	HSPA9	AGGCTGCGGCGCCCACGAGA
648	3|sg_hHSPA9_CC_3|HSPA9	HSPA9	ACTTTGACCAGGCCTTGCTA
649	3|sg_hHSPA9_CC_4|HSPA9	HSPA9	ACCTTCCATAACTGCCACGC
650	3|sg_hPAFAH1B1_CC_1|PAFAH1B1	PAFAH1B1	CGAGGCGTACATACCCAAGG
651	3|sg_hPAFAH1B1_CC_2|PAFAH1B1	PAFAH1B1	ATGGTACGGCCAAATCAAGA
652	3|sg_hPAFAH1B1_CC_3|PAFAH1B1	PAFAH1B1	TCTTGTAATCCCATACGCGT
653	3|sg_hPAFAH1B1_CC_4|PAFAH1B1	PAFAH1B1	ATTCACAGGACACAGAGAAT
654	3|sg_hPCNA_CC_1|PCNA	PCNA	CCAGGGCTCCATCCTCAAGA
655	3|sg_hPCNA_CC_2|PCNA	PCNA	TGAGCTGCACCAAAGAGACG
656	3|sg_hPCNA_CC_3|PCNA	PCNA	ATGTCTGCAGATGTACCCCT
657	3|sg_hPCNA_CC_4|PCNA	PCNA	CGAAGATAACGCGGATACCT
658	3|sg_hPOLR2L_CC_1|POLR2L	POLR2L	GCTGCAGGCCGAGTACACCG
659	3|sg_hPOLR2L_CC_2|POLR2L	POLR2L	ACAAGTGGGAGGCTTACCTG

SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
660	3|sg_hPOLR2L_CC_3|POLR2L	POLR2L	GCAGCGTACAGGGATGATCA
661	3|sg_hPOLR2L_CC_4|POLR2L	POLR2L	GCAGTAGCGCTTCAGGCCCA
662	3|sg_hRPL9_CC_1|RPL9	RPL9	CAAATGGTGGGGTAACAGAA
663	3|sg_hRPL9_CC_2|RPL9	RPL9	GAAAGGAACTGGCTACCGTT
664	3|sg_hRPL9_CC_3|RPL9	RPL9	AGGGCTTCCGTTACAAGATG
665	3|sg_hRPL9_CC_4|RPL9	RPL9	GAACAAGCAACACCTAAAAG
666	3|sg_hSF3A3_CC_1|SF3A3	SF3A3	TGAGGAGAAGGAACGGCTCA
667	3|sg_hSF3A3_CC_2|SF3A3	SF3A3	GGAAGAATGCAGAGTATAAG
668	3|sg_hSF3A3_CC_3|SF3A3	SF3A3	GGAATTTGAGGAACTCCTGA
669	3|sg_hSF3A3_CC_4|SF3A3	SF3A3	GCTCACCGGCCATCCAGGAA
670	3|sg_hSF3B3_CC_1|SF3B3	SF3B3	ACTGGCCAGGAACGATGCGA
671	3|sg_hSF3B3_CC_2|SF3B3	SF3B3	GCAGCTCCAAGATCTTCCCA
672	3|sg_hSF3B3_CC_3|SF3B3	SF3B3	GAATGAGTACACAGAACGGA
673	3|sg_hSF3B3_CC_4|SF3B3	SF3B3	GGAGCAGGACAAGGTCGGGG

Example 2 – BRD9 degrader depletes BRD9 protein

The following example demonstrates the depletion of the BRD9 protein in synovial sarcoma cells treated with a BRD9 degrader.

Procedure: Cells were treated with DMSO or the BRD9 degrader, Compound 1 (also known as dBRD9, see Remillard et al, *Angew. Chem. Int. Ed. Engl.* 56(21):5738-5743 (2017); see structure of Compound 1 below), for indicated doses and timepoints.



dBRD9
(Compound 1)

Whole cell extracts were fractionated by SDS-PAGE and transferred to a polyvinylidene difluoride membrane using a transfer apparatus according to the manufacturer's protocols (Bio-Rad). After incubation with 5% nonfat milk in TBST (10 mM Tris, pH 8.0, 150 mM NaCl, 0.5% Tween 20) for 60 minutes, the membrane was incubated with antibodies against BRD9 (1:1,000, Bethyl laboratory A303-781A), GAPDH (1:5,000, Cell Signaling Technology), and/or MBP (1:1,000, BioRad) overnight at 4°C. Membranes were washed three times for 10 min and incubated with anti-mouse or anti-rabbit antibodies conjugated with either horseradish peroxidase (HRP, FIGS. 2-3) or IRDye (FIG. 4, 1:20,000, LI-COR) for at least 1h. Blots were washed with TBST three times and developed with either the ECL system according to the manufacturer's protocols (FIGS. 2-3) or scanned on an Odyssey CLx Imaging system (FIG. 4).

Results: Treatment of SYO1 synovial sarcoma cells with the BRD9 degrader Compound 1 results in dose dependent (FIG. 2) and time dependent (FIG. 3) depletion of BRD9 in the cells. Further, as shown in FIG. 4, the depletion of BRD9 by Compound 1 is replicated in a non-synovial sarcoma cell line (293T) and may be sustained for at least 5 days.

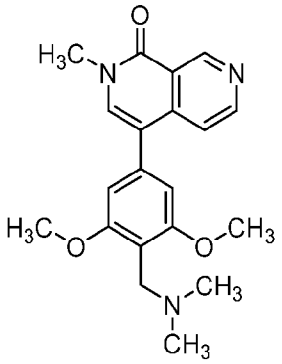
Example 3 – Inhibition of growth of synovial cell lines by BRD9 inhibitors and BRD9 degraders

The following example demonstrates that BRD9 degraders and inhibitors selectively inhibit growth of synovial sarcoma cells.

Procedures:

Cells were treated with DMSO or the BRD9 degrader, Compound 1, at indicated concentrations, and proliferation was monitored from day 7 to day 14 by measuring confluency over time using an IncuCyte live cell analysis system (FIG. 5). Growth medium and compounds were refreshed every 3-4 days.

Cells were seeded into 12-well plates and treated with DMSO, 1 μM BRD9 inhibitor, Compound 2 (also known as BI-7273, see Martin et al, *J Med Chem.* 59(10):4462-4475 (2016); see structure of Compound 2 below), or 1 μM BRD9 degrader, Compound 1.



BI-7273
(Compound 2)

The number of cells was optimized for each cell line. Growth medium and compounds were refreshed every 3-5 days. SYO1, Yamato, A549, 293T and HS-SY-II cells were fixed and stained at day 11. ASKA cells were fixed and stained at day 23. Staining was done by incubation with crystal violet solution (0.5 g Crystal Violet, 27 ml 37% Formaldehyde, 100 mL 10X PBS, 10 mL Methanol, 863 dH20 to 1L) for 30min followed by 3x washes with water and drying the plates for at least 24h at room temperature. Subsequently plates were scanned on an Odyssey CLx Imaging system (FIG. 6).

Cells were seeded into 96-well ultra low cluster plate (Costar, #7007) in 200 µL complete media and treated at day 2 with DMSO, Staurosporin, or BRD9 degarder, Compound 1, at indicated doses (FIG. 7). Media and compounds were changed every 5 d and cell colonies were imaged at day 14.

Results: As shown in FIGS. 5, 6, and 7, treatment of synovial sarcoma cell lines (SYO1, Yamato, HS-SY-II, and ASKA) with a BRD9 inhibitor, Compound 2, or a BRD9 degrader, Compound 1, results in inhibition of the growth of the cells, but does not result in inhibition of the growth of non-synovial control cancer cell lines (293T, A549, G401).

Example 4 – Selective inhibition of growth of synovial cell lines by BRD9 degraders and BRD9 binders

The following example demonstrates that BRD9 degraders and binders selectively inhibit growth of synovial sarcoma cells.

Procedure: Cells were seeded into 6-well or 12-well plates and were treated daily with a BRD9 degrader (Compound 1), a bromo-domain BRD9 binder (Compound 2), E3 ligase binder (lenalidomide), DMSO, or staurosporin (positive control for cell killing), at indicated concentrations. The number of cells was optimized for each cell line. Growth media was refreshed every 5 days. By day 14, medium was removed, cells were washed with PBS, and stained using 500 µL of 0.005% (w/v) crystal violet solution in 25% (v/v) methanol for at least 1 hour at room temperature. Subsequently plates were scanned on an Odyssey CLx Imaging system.

Results: As shown in FIGS. 8 and 9, treatment of synovial sarcoma cell lines (SYO1, HS-SY-II, and ASKA) with Compound 1 or Compound 2 resulted in inhibition of the growth of the cells, but did not

result in inhibition of the growth of non-synovial control cancer cell lines (RD, HCT116, and Calu6). Overall, Compound 1 showed most significant growth inhibition in all synovial cell lines.

Example 5- Inhibition of cell growth in synovial sarcoma cells

The following example shows that BRD9 degraders inhibit cell growth and induce apoptosis in synovial sarcoma cells.

Procedure: SYO1 cells were treated for 8 or 13 days with DMSO, a BRD9 degrader (Compound 1) at 200nM or 1μM, or an E3 ligase binder (lenalidomide) at 200nM. Compounds were refreshed every 5 days. Cell cycle analysis was performed using the Click-iT™ Plus EdU Flow Cytometry Assay (Invitrogen). The apoptosis assay was performed using the Annexin V-FITC Apoptosis Detection Kit (Sigma A9210). Assays were performed according to the manufacturer's protocol.

Results: As shown in FIGS. 10-13, treatment with Compound 1 for 8 or 13 days resulted in reduced numbers of cells in the S-phase of the cell cycle as compared to DMSO and lenalidomide. Treatment with Compound 1 for 8 days also resulted in increased numbers of early- and late-apoptotic cells as compared to DMSO controls.

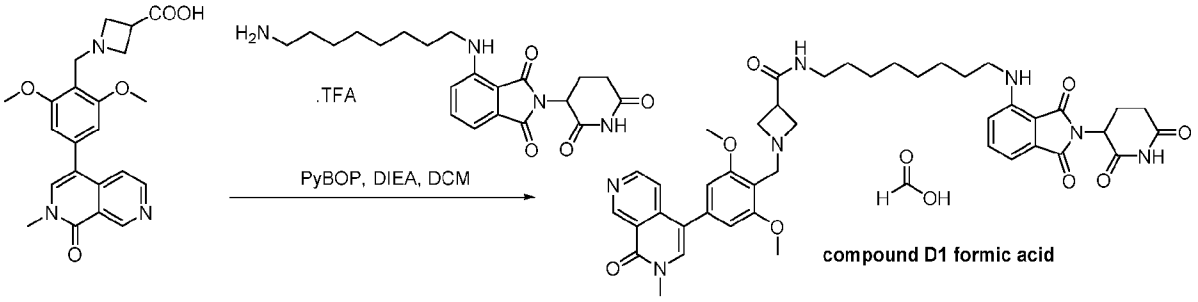
Example 6 – Composition for SS18-SSX1-BAF

The following example shows the identification of BRD9 as a component of SS18-SSX containing BAF complexes.

Procedure: A stable 293T cell line expressing HA-SS18SSX1 was generated using lentiviral integration. SS18-SSX1 containing BAF complexes were subject to affinity purification and subsequent mass spectrometry analysis revealed SS18-SSX1 interacting proteins.

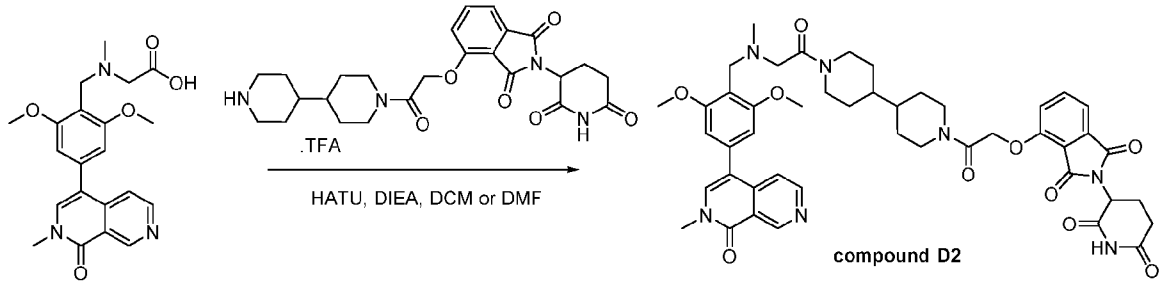
Results: As shown in FIG. 14, BAF complexes including the SS18-SSX fusion protein also included BRD9. More than 5 unique peptides were identified for ARID1A (95 peptides), ARID1B (77 peptides), SMARCC1 (69 peptides), SMARCD1 (41 peptides), SMARCD2 (37 peptides), DPF2 (32 peptides), SMARCD3 (26 peptides), ACTL6A (25 peptides), BRD9 (22 peptides), DPF1 Isoform 2 (18 peptides), DPF3 (13 peptides), and ACTL6B (6 peptides).

Example 7 – Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)azetidine-3-carboxamide formic acid (compound D1 formic acid)



To a stirred mixture of 4-[(8-aminooctyl)amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione trifluoroacetic acid salt (50 mg, 0.097 mmol, 1 equiv) and 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-3-carboxylic acid trifluoroacetic acid salt (50.87 mg, 0.097 mmol, 1 equiv) in DCM (2 mL, 31.460 mmol, 323.73 equiv) was added DIEA (37.68 mg, 0.292 mmol, 3 equiv) and PyBOP (75.86 mg, 0.146 mmol, 1.5 equiv). The mixture was stirred for 2 hours at room temperature, and then it was concentrated under vacuum. The residue was purified by Prep-HPLC (conditions: X Select CSH Prep C18 OBD Column, 5 μm, 19*150 mm; mobile phase, Water(0.1% FA) and ACN (25% Phase B up to 45% in 8 minutes); Detector, UV). This resulted in 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-*N*-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)azetidine-3-carboxamide formic acid (4 mg, 4.81%) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.54 (s, 1H), 8.69 (d, *J* = 5.7 Hz, 1H), 8.54 (s, 1H), 7.76 (s, 1H), 7.62 (d, *J* = 5.8 Hz, 1H), 7.60 – 7.51 (m, 1H), 7.04 (d, *J* = 7.8 Hz, 2H), 6.83 (s, 2H), 5.07 (dd, *J* = 12.5, 5.5 Hz, 1H), 4.31 (s, 2H), 4.05 (s, 4H), 3.94 (s, 6H), 3.71 (s, 3H), 3.52 - 3.45 (s, 2H), 3.22 (t, *J* = 7.0 Hz, 2H), 2.91 – 2.66 (m, 4H), 2.14 - 2.11 (m, 1H), 1.67 (q, *J* = 7.3 Hz, 2H), 1.54 (d, *J* = 7.3 Hz, 2H), 1.45 -1.38 (m, 8H). LCMS (ESI) m/z: $[M+H]^+$ = 792.36.

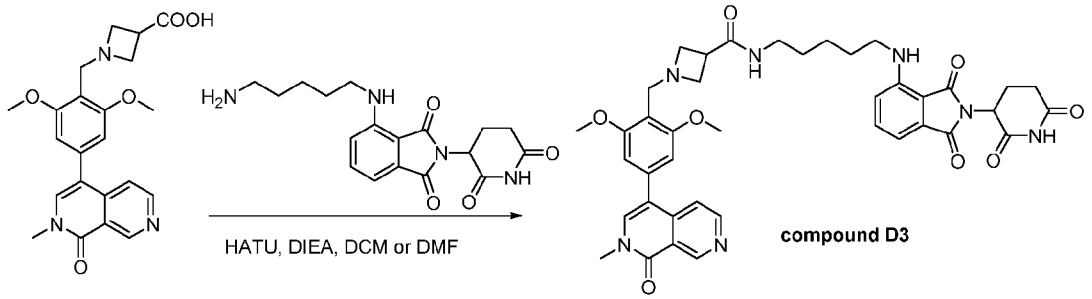
Example 8 – Preparation of 4-(2-[1-[2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)acetyl]-[4,4-bipiperidin]-1-yl]-2-oxoethoxy)-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (compound D2)



To a stirred solution of 2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)acetic acid (19.99 mg, 0.050 mmol, 1 equiv) and DIPEA (19.50 mg, 0.151 mmol, 3 equiv) in DMF (3 mL) was added PyBOP (28.68 mg, 0.075 mmol, 1.5 equiv) and 4-(2-[[4,4-bipiperidin]-1-yl]-2-oxoethoxy)-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione trifluoroacetic acid salt (30 mg, 0.050 mmol, 1 equiv). The solution was stirred for 2 hours at room

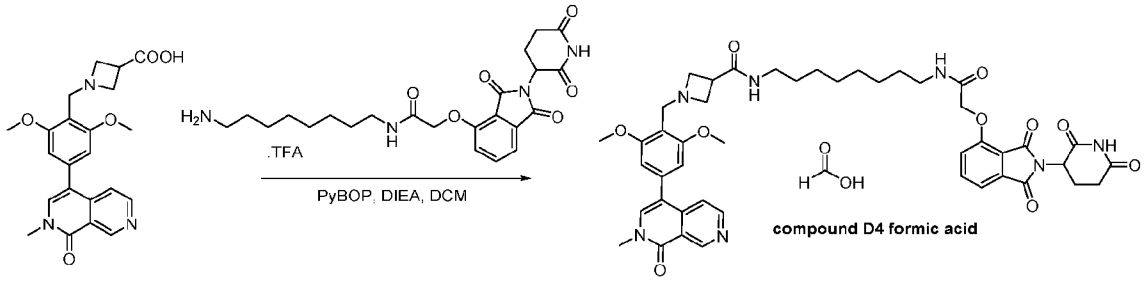
temperature. The resulting mixture was purified by Prep-HPLC (conditions: XSelect CSH Prep C18 OBD Column, 5 µm, 19*150 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 5% B to 30% B in 8 minutes; 254 nm; R_t: 7.56 minutes) to afford 4-(2-[1-[2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)acetyl]-[4,4-bipiperidin]-1-yl]-2-oxoethoxy)-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (19 mg, 43.83%) as a white solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.53 (d, *J* = 0.8 Hz, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.56 (s, 0.3H), 7.76 (s, 2H), 7.64 (d, *J* = 5.7 Hz, 1H), 7.49 (d, *J* = 7.3 Hz, 1H),7.36 (d, *J* = 8.2 Hz, 1H), 6.80 (s, 2H), 5.14 (t, *J* = 15.7 Hz, 3H), 4.60 – 4.43 (m, 3H), 4.02 (d, *J* = 13.6 Hz, 4H), 3.91 (s, 6H), 3.71 (s, 3H), 3.58 (s, 2H), 3.15 -2.59 (m,6H), 2.53 (s, 3H),2.15 (s, 1H), 1.85 - 1.67 (m, 4H), 1.41 - 1.16 (m, 6H). LCMS (ESI) m/z: [M+H]+ = 862.

Example 9 – Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl] methyl]-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]pentyl) azetidine-3-carboxamide (compound D3)



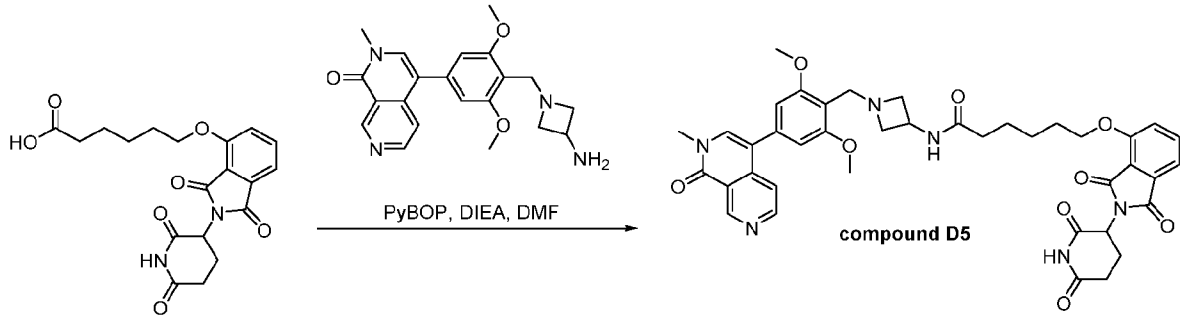
To a stirred mixture of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-3-carboxylic acid trifluoroacetic acid salt(55.40 mg, 0.106 mmol, 1 equiv) and 4-[(5-aminopentyl)amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione; trifluoroacetic acid salt (50 mg, 0.106 mmol, 1 equiv) in DCM (2 mL) was added DIEA (41.04 mg, 0.318 mmol, 3 equiv) and PyBOP (82.62 mg, 0.159 mmol, 1.5 equiv). The mixture was stirred for 2 hours at room temperature, and then it was concentrated under vacuum. The residue was purified by Prep-HPLC (conditions: X Select CSH Prep C18 OBD Column, 5 µm, 19*150 mm; mobile phase, Water(0.1% FA) and ACN (15% Phase B up to 35% in 8 minutes); Detector, UV). This resulted in 6 mg (6.98%) of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-*N*-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]pentyl) azetidine-3-carboxamide formate as a yellow solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.54 (s, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.53 (s, 1H), 7.76 (s, 1H), 7.65 – 7.51 (m, 2H), 7.05 (dd, *J* = 7.8, 6.0 Hz, 2H), 6.83 (s, 2H), 5.11 – 5.02 (m, 1H), 4.57 (s, 1H), 4.36 (s, 2H), 4.10 (s, 4H), 3.95 (s, 6H), 3.71 (s, 3H), 3.36 - 3.26 (m, 3H), 2.91 – 2.68 (m, 3H), 2.12 (d, *J* = 10.0 Hz, 1H), 1.76 – 1.67 (m, 2H), 1.60 (q, *J* = 7.3, 6.8 Hz, 2H), 1.49 (d, *J* = 7.1 Hz, 2H). LCMS (ESI) m/z: $[M+H]^+$ = 750.32.

Example 10 – Preparation of N-[8-[(1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidin-3-yl)formamido]octyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy]acetamide formic acid (compound D4 formic acid)



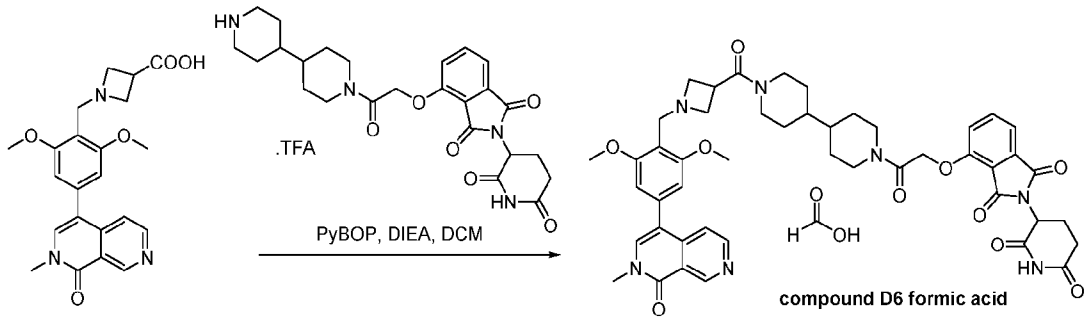
To a stirred mixture of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl] methyl]azetidine-3-carboxylic acid; trifluoroacetic acid salt (68.57 mg, 0.131 mmol, 1.50 equiv) and *N*-(8-aminooctyl)-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetamide trifluoroacetic acid salt (50.00 mg, 0.087 mmol, 1.00 equiv) in DCM (2.00 mL) was added DIEA (67.72 mg, 0.524 mmol, 6.00 equiv) and PyBOP (68.17 mg, 0.131 mmol, 1.50 equiv). The mixture was stirred for 2 hours at room temperature, and then it was concentrated under vacuum. The residue was purified by Prep-HPLC (conditions: X Bridge Shield RP18 OBD Column, 5 μm, 19*150 mm; mobile phase, Water(0.1% FA) and ACN (20% Phase B up to 32% in 7 minutes); Detector, UV). This resulted in *N*-[8-[(1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidin-3-yl)formamido]octyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3 -dihydro-1H-isoindol-4-yl]oxy]acetamide formic acid (12 mg, 14.77%) as a white solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.53 (s, 1H), 8.68 (d, *J* = 5.8 Hz, 1H), 7.87 – 7.78 (m, 1H), 7.75 (s, 1H), 7.63 (d, *J* = 5.8 Hz, 1H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 6.80 (s, 2H), 5.15 (dd, *J* = 12.6, 5.3 Hz, 1H), 4.76 (s, 2H), 4.14 (s, 2H), 3.92 (s, 6H), 3.80 (s, 4H), 3.71 (s, 3H), 3.20 (t, *J* = 7.0 Hz, 2H), 2.94 – 2.71 (m, 6H), 2.15 (s, 1H), 1.58 (d, *J* = 7.9 Hz, 2H), 1.51 (s, 2H), 1.35 (s, 8H). LCMS (ESI) m/z: $[M+H]^+$ = 850.37.

Example 11 – Preparation of N-(1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidi n-3-yl)-6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy]hexanamide (compound D5)



To a solution of 6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy]hexanoic acid (50.00 mg, 0.129 mmol, 1.00 eq.) and DIEA (49.92 mg, 0.386 mmol, 3 eq.) in DCM (2.00 mL, 31.460 mmol, 244.37 eq.) was added PyBOP (100.49 mg, 0.193 mmol, 1.5 eq.) and 4-[4-[(3-aminoazetidin-1-yl)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (48.98 mg, 0.129 mmol, 1 eq.). The resulting solution was stirred at room temperature for 1 hour. The crude product (50 mg) was purified by Prep-HPLC (conditions: XSelect CSH Prep C18 OBD Column, 5 µm, 19*150 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 10% B to 30% B in 8 minutes; 254 nm; Rt: 6.57 minutes) to afford *N*-(1-[[2,6-dimethoxy-4-(2–methyl-1-oxo-1,2-dihydro -2,7-naphthyridin-4-yl)phenyl]methyl]azetidin-3-yl)-6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy]hexanamide (14.8 mg, 15.31%) as a white solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.54 (s,1H), 8.69 (d, *J* = 5.7 Hz, 1H), 7.82- 7.73 (m, 2H), 7.65 -7.58 (m, 1H), 7.44 (dd, *J* = 7.9, 3.2 Hz, 2H), 6.83 (s, 2H), 5.10 (dd, *J* = 12.4, 5.4 Hz, 1H), 4.60- 4.47 (m, 1H), 4.34 (s, 2H), 4.25 (t, *J* = 6.1 Hz, 2H), 4.18 (s, 2H), 3.94 (s, 8H), 3.71 (s, 3H), 2.87 -2.64 (m, 3H), 2.30 (t, *J* = 7.3 Hz, 2H), 2.17- 2.09 (m, 1H), 1.90 (p, *J* = 6.4 Hz, 2H), 1.75 (p, *J* = 7.4 Hz, 2H), 1.61 (q, *J* = 8.0 Hz, 2H). LCMS (ESI) m/z: [M+H]+ = 751.25.

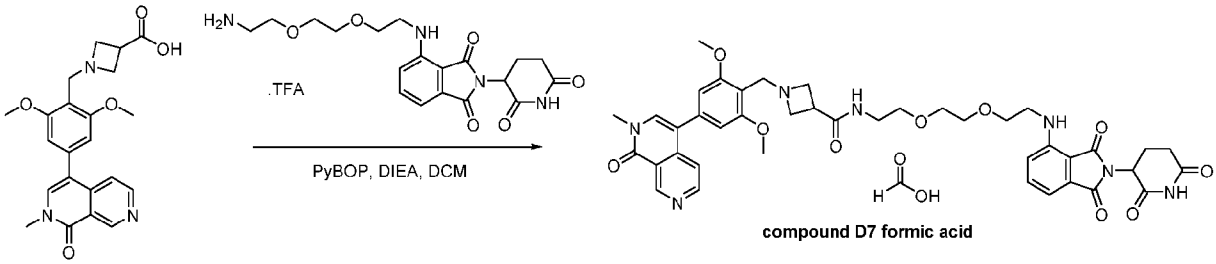
Example 12 – Preparation of 4-[2-[1-(1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-3-carbonyl)-[4,4-bipiperidin]-1-yl]-2-oxoethoxy]-2-(2,6-dioxo piperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione formic acid (compound D6 formic acid)



To a stirred mixture of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl] methyl]azetidine-3-carboxylic acid trifluoroacetic acid salt (26.32 mg, 0.050 mmol, 1.50 equiv) and 4-(2-[[4,4-bipiperidin]-1-yl]-2-oxoethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione trifluoroacetic acid salt (20.00 mg, 0.034 mmol, 1.00 equiv) in DCM (2 mL) was added DIEA (26.00 mg, 0.201 mmol, 6.00 equiv) and PyBOP (26.17 mg, 0.050 mmol, 1.50 equiv). The mixture was stirred for 2 hours at room temperature, and then it was concentrated under vacuum. The residue was purified was purified by Prep-HPLC (conditions: X Select CSH Prep C18 OBD Column, 5 µm, 19*150 mm; mobile phase, Water(0.1% FA) and ACN (8% Phase B up to 22% in 8 minutes); Detector, UV). This resulted in 4-[2-[1-(1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-3-carbonyl)-[4,4-bipiperidin]-1-yl]-2-oxoethoxy]-2-(2,6-dioxo piperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione formic acid (3.5 mg, 10.89%) as a white solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.54 (d, *J* = 0.8 Hz, 1H), 8.69 (d, *J*

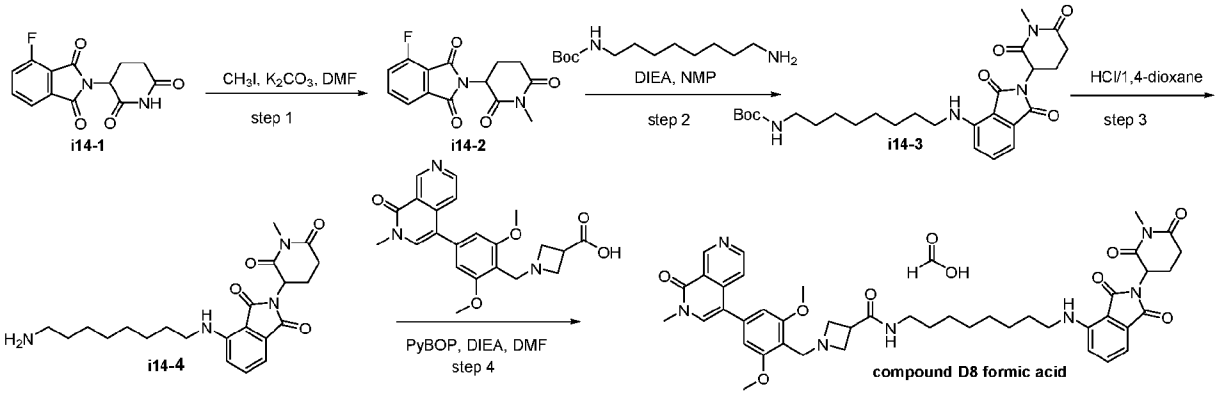
= 5.7 Hz, 1H), 8.56 (s, 1H), 7.84 – 7.72 (m, 2H), 7.63 (d, *J* = 5.8 Hz, 1H), 7.51 (d, *J* = 7.3 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 6.81 (s, 2H), 5.31 – 4.98 (m, 3H), 4.68 – 4.44 (m, 2H), 4.16 (s, 2H), 3.93 (s, 10H), 3.79 – 3.56 (m, 5H), 3.09 – 2.93 (m, 2H), 2.93 – 2.61 (m, 6H), 2.15 (d, *J* = 10.4 Hz, 1H), 1.86 – 1.67 (m, 4H), 1.50 – 1.25 (m, 3H), 1.23 – 1.04 (m, 2H). LCMS (ESI) m/z: $[M+H]^+$ = 874.37.

Example 13 – Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl] methyl]-N-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino] ethoxy)ethoxy]ethyl]azetidine-3-carboxamide formic acid (compound D7 formic acid)

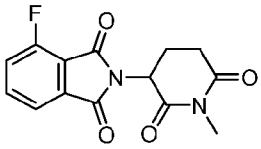


To a stirred mixture of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-3-carboxylic acid trifluoroacetic acid salt (75.73 mg, 0.145 mmol, 1.5 equiv) and 4-([2-[2-(2-aminoethoxy)ethoxy]ethyl]amino)-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione trifluoroacetic acid salt (50 mg, 0.096 mmol, 1 equiv) in DCM (2 mL) was added DIEA (74.79 mg, 0.579 mmol, 6 equiv) and PyBOP (75.28 mg, 0.145 mmol, 1.5 equiv). The mixture was stirred for 2 hours at room temperature, and then it was concentrated under vacuum. The residue was purified by Prep-HPLC (conditions: X Select CSH Prep C18 OBD Column, 5 μm, 19*150 mm; mobile phase, Water(0.1% FA) and ACN (10% Phase B up to 32% in 8 minutes); Detector, UV). This resulted in 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]ethoxy)ethoxy]ethyl]azetidine-3-carboxamide formic acid (13.2 mg, 15.77%) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.53 (s, 1H), 8.68 (d, *J* = 5.8 Hz, 1H), 8.56 (s, 1H), 7.75 (s, 1H), 7.62 (d, *J* = 5.9 Hz, 1H), 7.55 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.07(dd, *J* = 11.7, 7.8 Hz, 2H), 6.80 (s, 2H), 5.07 (dd, *J* = 12.4, 5.5 Hz, 1H), 4.20 (s, 2H), 3.92 (s, 10H), 3.78 – 3.57 (m, 9H), 3.61 – 3.43 (m, 4H), 3.41 (td, *J* = 5.2, 1.6Hz, 2H), 2.88 (ddd, *J* = 19.0, 14.0, 5.0 Hz, 1H), 2.80 – 2.64 (m, 3H). 2.17 – 2.08 (m, 1H). LCMS (ESI) m/z: $[M+H]^+$ = 796.25.

Example 14 – Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)azetidine-3-carboxamide formic acid (compound D8 formic acid)



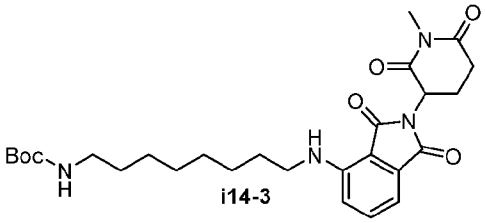
Step 1: Preparation of 4-fluoro-2-(1-methyl-2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (i14-2)



i14-2

To a solution of 2-(2,6-dioxopiperidin-3-yl)-4-fluoro-2,3-dihydro-1H-isoindole-1,3-dione (500 mg, 1.810 mmol, 1 equiv) in DMF (10 mL) was added CH_3I (385.39 mg, 2.715 mmol, 1.5 equiv) and K_2CO_3 (750.51 mg, 5.430 mmol, 3 equiv). The resulting solution was stirred for overnight at 25 °C. The solids were filtered out. The resulting mixture was concentrated. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:2). This resulted in 4-fluoro-2-(1-methyl-2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (480 mg, 91.36%) as a white solid. LCMS (ESI) m/z: [M-H]+ = 291.

Step 2: Preparation of tert-butyl N-(8-[[2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)carbamate (i14-3)

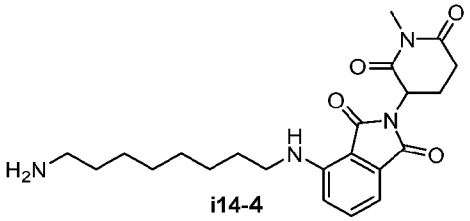


i14-3

To a solution of 4-fluoro-2-(1-methyl-2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (480 mg, 1.654 mmol, 1 equiv) and *tert*-butyl *N*-(8-aminooctyl)carbamate (404.14 mg, 1.654 mmol, 1

equiv) in NMP (10 mL) was added DIEA (641.21 mg, 4.961 mmol, 3 equiv). The resulting solution was stirred for 6 hours at 90 °C. The resulting solution was diluted with 20 mL of water and extracted with ethyl acetate (2 x 20 mL), and the organic layers were combined and dried over anhydrous sodium sulfate and concentrated. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in *tert*-butyl *N*-(8-[[2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)carbamate (480 mg, 56.40%) as a green solid. LCMS (ESI) m/z: [M-H]+ = 515.

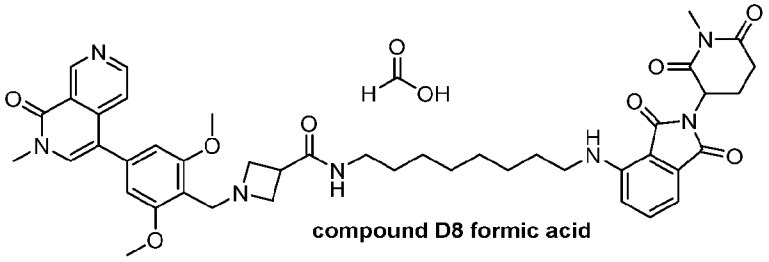
Step 3: Preparation of 4-[(8-aminooctyl)amino]-2-(1-methyl-2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (i14-4)



i14-4

A mixture of *tert*-butyl *N*-(8-[[2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)carbamate (150 mg, 0.291 mmol, 1 equiv) and 4 M HCl in 1,4-dioxane (5 mL) was stirred for 1 hour at 25 °C. The resulting mixture was concentrated. This resulted in 4-[(8-aminooctyl)amino]-2-(1-methyl-2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (100 mg, 82.77%) as a white solid, that was used directly without further purification. LCMS (ESI) m/z: [M-H]+ = 415.

Step 4: Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)azetidine-3-carboxamide formic acid (compound D8 formic acid)

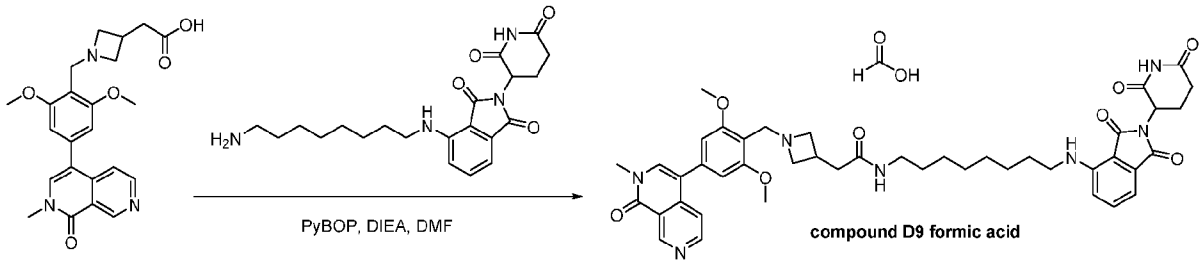


compound D8 formic acid

To a solution of 4-[(8-aminooctyl)amino]-2-(1-methyl-2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (80 mg, 0.193 mmol, 1 equiv) and 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-3-carboxylic acid (79.02 mg, 0.193 mmol, 1 equiv) in DMF (3 mL) was added HATU (110.08 mg, 0.290 mmol, 1.5 equiv) and DIEA (49.89 mg, 0.386 mmol, 2 equiv). The resulting solution was stirred for 2 hours at 25 °C. The crude product was purified by Prep-HPLC (conditions: XBridge Prep C18 OBD Column, 5 μm, 19*150 mm; mobile phase, Water(0.1% FA) and ACN; Detector, UV 254nm). This resulted in 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-

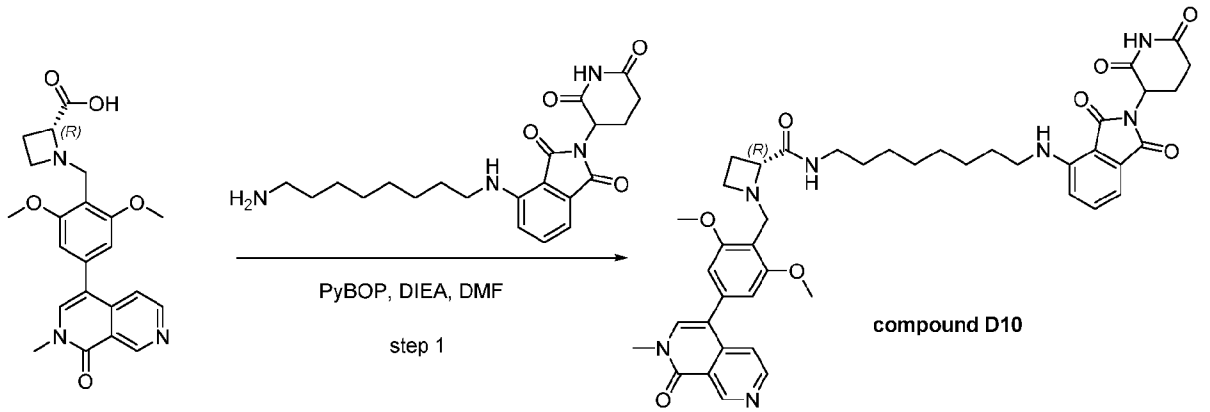
naphthyridin-4-yl)phenyl]methyl]-*N*-(8-[[2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)azetidine-3-carboxamide (15 mg, 9.64%) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.54 (d, *J* = 0.8 Hz, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.54 (s, 1.2H, FA), 7.77 (s, 1H), 7.65 – 7.52 (m, 2H), 7.10 – 7.01 (m, 2H), 6.84 (s, 2H), 5.10 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.39 (s, 2H), 4.14 (d, *J* = 8.2 Hz, 3H), 3.95 (s, 6H), 3.71 (s, 3H), 3.54 (d, *J* = 8.1 Hz, 1H), 3.22 (t, *J* = 7.0 Hz, 2H), 3.17 (d, *J* = 3.1 Hz, 1H), 3.15 (s, 3H), 2.99 (s, 1H), 2.96 – 2.86 (m, 2H), 2.69 (dt, *J* = 12.7, 6.3 Hz, 2H), 2.15 – 2.05 (m, 1H), 1.68 (p, *J* = 7.1 Hz, 2H), 1.52 (q, *J* = 7.1 Hz, 2H), 1.38 (s, 8H). LCMS (ESI) m/z: [M-H]+ = 806.40.

Example 15 – Preparation of 2-(1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidin-3-yl)-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)acetamide formic acid (compound D9 formic acid)



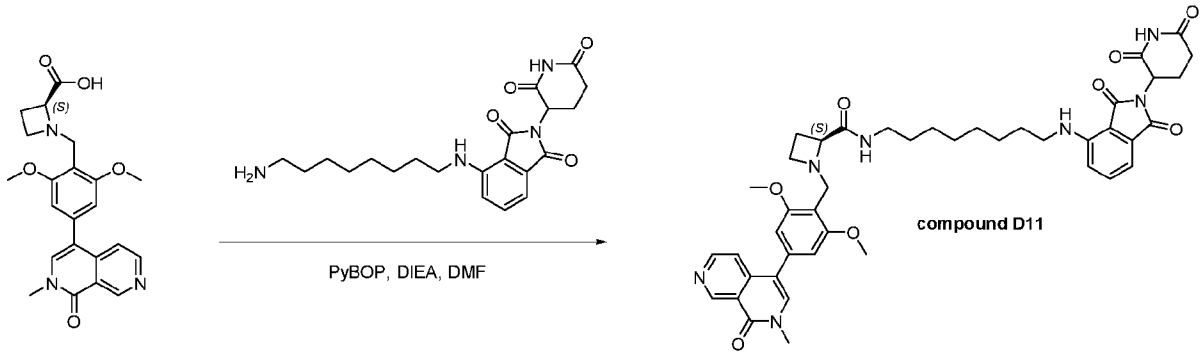
To a solution of 2-(1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidin-3-yl)acetic acid (110 mg, 0.260 mmol, 1 equiv) in DMF (3 mL) was added 4-[(8-aminooctyl)amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (104.03 mg, 0.260 mmol, 1.00 equiv), PyBOP (202.77 mg, 0.390 mmol, 1.50 equiv), and DIEA (167.86 mg, 1.299 mmol, 5.00 equiv). The resulting mixture was stirred at room temperature for 16 hours. Without workup, the crude product was purified by Prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100Å, 5 µm, 19 mm X 250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 27% B to 34% B in 8 minutes; 254 nm; Rt: 6.28 minutes) to afford 2-(1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidin-3-yl)-*N*-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)acetamide formic acid (26.7 mg) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.52 (s, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.56 (s, 0.8H, FA), 7.76 (s, 1H), 7.61 (d, *J* = 5.7 Hz, 1H), 7.54 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.03 (dd, *J* = 7.8, 3.5 Hz, 2H), 6.85 (s, 2H), 5.06 (dd, *J* = 12.4, 5.4 Hz, 1H), 4.43 (s, 2H), 4.18 (t, *J* = 9.5 Hz, 2H), 4.02–3.90 (m, 7H), 3.70 (s, 3H), 3.30 (d, *J* = 6.8 Hz, 2H), 3.17 (t, *J* = 7.1 Hz, 3H), 2.97 – 2.62 (m, 3H), 2.58 (d, *J* = 7.4 Hz, 2H), 2.19 – 2.05 (m, 1H), 1.65 (q, *J* = 7.0 Hz, 2H), 1.57–1.37 (m, 10H). LCMS (ESI) m/z: $[M+H]^+$ = 806.25.

Example 16 – Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl] methyl]-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl) azetidine-3-carboxamide (D10)



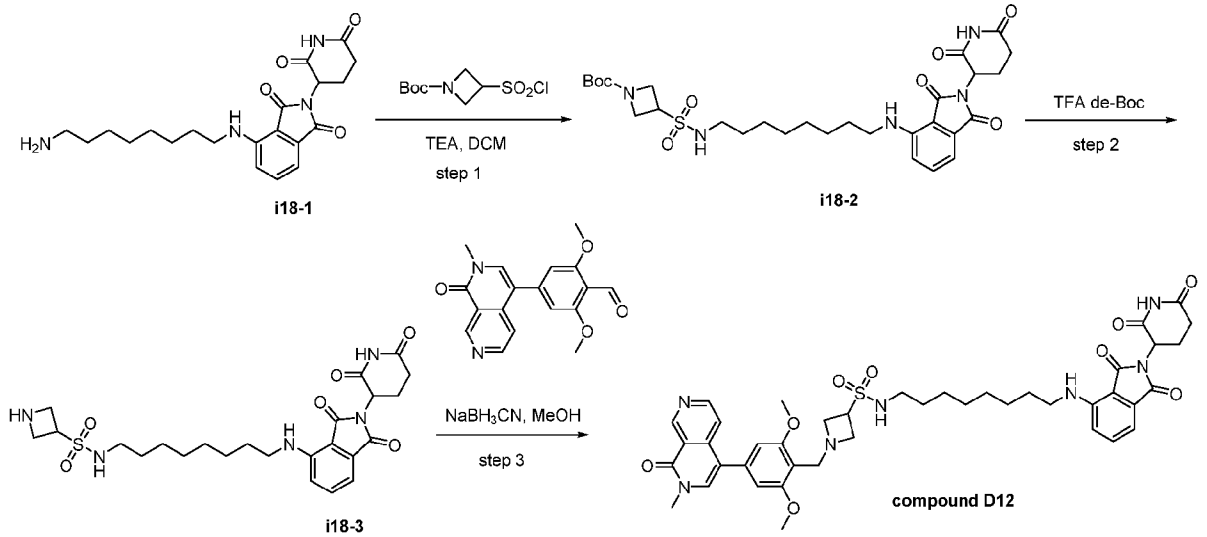
To a stirred solution of (*R*)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-3-carboxylic acid (40.9 mg, 0.100 mmol, 1 equiv), DIEA (64.55 mg, 0.499 mmol, 5 equiv), and PyBOP (155.95 mg, 0.300 mmol, 3 equiv) in DMF (1 mL) was added 4-[(8-aminooctyl)amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione hydrochloride (43.65 mg, 0.100 mmol, 1 equiv) at ambient atmosphere. The mixture was stirred for 1 hour at room (conditions: XBridge Shield RP18 OBD Column, 5 μm, 19*150 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minuteute; Gradient: 18% B to 35% B in 12 minutes; 254/220 nm; R_t: 11.74 minutes) to afford (*R*)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-*N*-(8-[[2-(2,6-dioxopiperidin -3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)azetidine-3-carboxamide (25 mg, 31.60%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.52 (s, 1H), 8.68 (d, *J* = 5.8 Hz, 1H), 7.74 (s, 1H), 7.62 (d, *J* = 5.8 Hz, 1H), 7.54 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.01 (t, *J* = 7.8 Hz, 2H), 6.78 (s, 2H), 5.06 (dd, *J* = 12.3, 5.5 Hz, 1H), 4.17 (s, 2H), 3.93 (s, 6H), 3.97 – 3.82 (m, 1H), 3.74 (s, 2H), 3.69 (s, 3H), 3.31 – 3.09 (m, 4H), 2.97–2.62 (m, 3H), 2.50 (d, *J* = 9.2 Hz, 1H), 2.32 – 2.20 (m, 1H), 2.19 – 2.09 (m, 1H), 1.57 (q, *J* = 6.9 Hz, 2H), 1.45–1.30 (m, 10H). LCMS (ESI) m/z: [M+H]+ = 792.20.

Example 17 – Preparation of (2S)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]octyl)azetidine-2-carboxamide (compound D11)

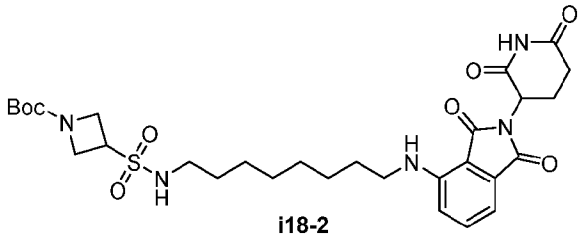


To a solution of (2*S*)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-2-carboxylic acid (50.00 mg, 0.122 mmol, 1.00 equiv) and 4-[(8-aminooctyl)amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (48.91 mg, 0.122 mmol, 1.00 equiv) in DMF (2.00 mL) was added PyBOP (127.10 mg, 0.244 mmol, 2.00 equiv) and DIEA (47.35 mg, 0.366 mmol, 3.00 equiv). The resulting solution was stirred at 25 ℃ for 2 hours. The crude product was purified by preparative HPLC (condition: XSelect CSH Prep C18 OBD Column, 5 μm,19*150 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minuteute; Gradient: 20% B to 55% B in 8 minutes; 254 nm; R_t: 7.12 minutes). Fractions containing the desired compound were evaporated to dryness to afford (2*S*)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]octyl)azetidine-2-carboxamide (35 mg, 35.47%) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.51 (s, 1H), 8.68 (d, *J* = 5.7 Hz, 1H), 7.72 (s, 1H), 7.62 (d, *J* = 5.8 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.00 (dd, *J* = 10.6, 7.8 Hz, 2H), 6.75 (s, 2H), 5.05 (dd, *J* = 12.4, 5.4 Hz, 1H), 3.89 (s, 9H), 3.69 (s, 3H), 3.30 (s, 2H), 3.25 (t, *J* = 6.9 Hz, 2H), 3.15 (t, *J* = 7.1 Hz, 2H), 2.94– 2.64 (m, 3H), 2.35 (d, *J* = 9.5 Hz, 1H), 2.16 – 2.00 (m, 1H), 1.58 (t, *J* = 7.1 Hz, 2H), 1.40 (d, *J* = 6.7 Hz, 2H), 1.30 (s, 8H). LCMS (ESI) m/z: [M+H]+ = 792.60.

Example 18 – Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)azetidine-3-sulfonamide (compound D12)

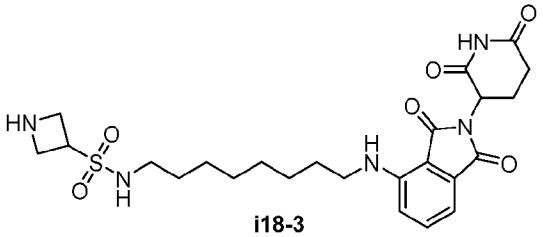


Step 1: Preparation of tert-butyl 3-[(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)sulfamoyl]azetidine-1-carboxylate (i18-2)



To a solution of 4-[(8-aminooctyl)amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-*1H*-isoindole-1,3-dione (100.00 mg, 0.250 mmol, 1.00 equiv) in DCM (2.00 mL) was added tert-butyl 3-(chlorosulfonyl)azetidine-1-carboxylate (95.78 mg, 0.375 mmol, 1.50 equiv) and TEA (50.53 mg, 0.499 mmol, 2.00 equiv) at 0 ℃. The resulting solution was stirred for 2 hours at 25 ℃. The reaction was then quenched by the addition of 5 mL of MeOH. The resulting mixture was concentrated. The residue was applied onto a silica gel column with ethyl DCM/MeOH (20:1). This resulted in 110 mg (71.08%) of *tert*-butyl 3-[(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-*1H*-isoindol-4-yl]amino]octyl) sulfamoyl]azetidine-1-carboxylate as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 620.

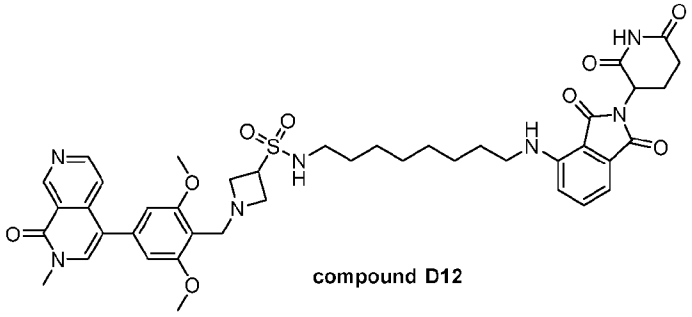
Step 2: Preparation of N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]octyl)azetidine-3-sulfonamide (i18-3)



i18-3

A solution of tert-butyl 3-[(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]octyl) sulfamoyl]azetidine-1-carboxylate (110.00 mg, 0.177 mmol, 1.00 equiv) in TFA (2.00 mL) and CH_2Cl_2 (2.00 mL) was stirred at 0 ℃ for 1 hour. The resulting mixture was concentrated under reduced pressure to afford *N*-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]octyl)azetidine-3-sulfonamide (85 mg, 92.16%) as a yellow solid, which was used directly without further purification. LCMS (ESI) m/z: [M+H]+ = 520.

Step 3: Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)azetidine-3-sulfonamide (compound D12)

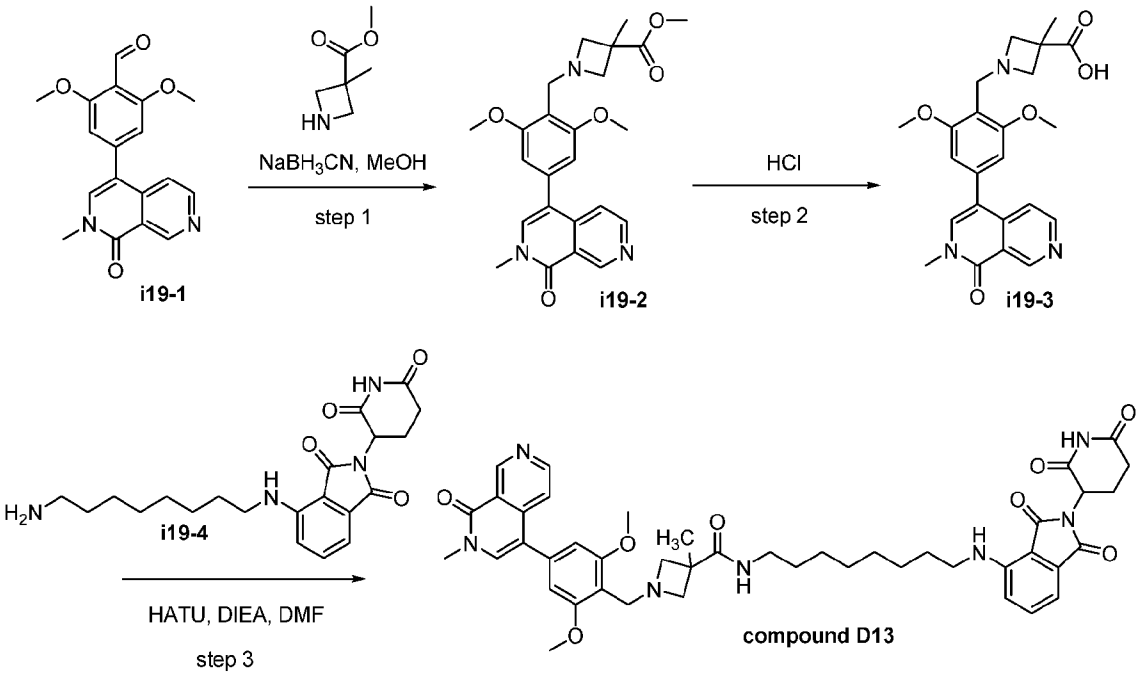


compound D12

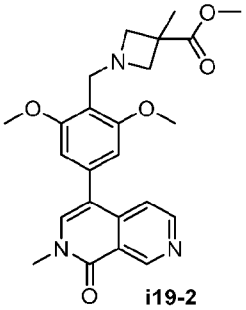
To a solution of *N*-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino]octyl)azetidine-3-sulfonamide (85.00 mg, 0.164 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (53.06 mg, 0.164 mmol, 1.00 equiv) in MeOH (2.00 mL) was added $NaBH_3CN$ (20.56 mg, 0.327 mmol, 2.00 equiv). The resulting solution was stirred at 25 ℃ for 2 hours. The crude product was purified by preparative HPLC Column (condition: XSelect CSH Prep C18 OBD Column, 5 μm,19*150 mm; Mobile Phase A: Water(0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minuteutes; Gradient: 20% B to 55% B in 8 minutes; 254 nm; R_t: 7.12 minutes). Fractions containing the desired compound were evaporated to dryness to afford 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-*N*-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino]octyl)azetidine-3-sulfonamide(50mg,36.92%) as a white solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.52 (d, *J* = 0.9 Hz, 1H), 8.68 (d, *J* = 5.7 Hz, 1H), 8.53 (s, 0.47H, FA), 7.74 (s, 1H), 7.63 (dd, *J* = 5.8, 0.9 Hz, 1H), 7.55 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.03 (dd, *J* = 7.8, 4.8 Hz, 2H),

6.77 (s, 2H), 5.06 (dd, J = 12.5, 5.5 Hz, 1H), 4.03 (p, J = 8.2, 7.8 Hz, 1H), 3.91 (d, J = 4.1 Hz, 2H), 3.89 (s, 6H), 3.78 – 3.68 (m, 8H), 3.30 (d, J = 6.8 Hz, 1H), 3.03 (t, J = 7.0 Hz, 2H), 2.94 – 2.80 (m, 1H), 2.80 – 2.66 (m, 2H), 2.17 – 2.08 (m, 1H), 1.70 – 1.62 (m, 2H), 1.51 (d, J = 6.9 Hz, 2H), 1.44 -1.37 (m, 8H). LCMS (ESI) m/z: [M+H]+ = 828.35.

Example 19 – Preparation of 1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-N-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octyl)-3-methylazetidine-3-carboxamide (compound D13)



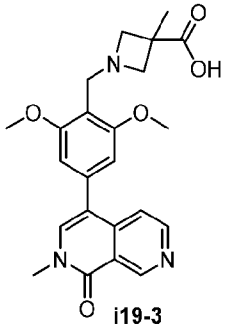
Step 1: Preparation of methyl 1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-3-methylazetidine-3-carboxylate (i19-2)



To a solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (200 mg, 0.617 mmol, 1 equiv) and methyl 3-methylazetidine-3-carboxylate (79.65 mg, 0.617 mmol, 1.00 equiv) in MeOH(2 mL) was added $NaBH_3CN$ (77.50 mg, 1.233 mmol, 2 equiv). The resulting solution was stirred at 25 ℃ for 1 hour. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (9:1) to afford methyl 1-[[2, 6-dimethoxy -4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-

yl) phenyl] methyl]-3- methylazetidine-3-carboxylate (247 mg, 91.56%) as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 438.

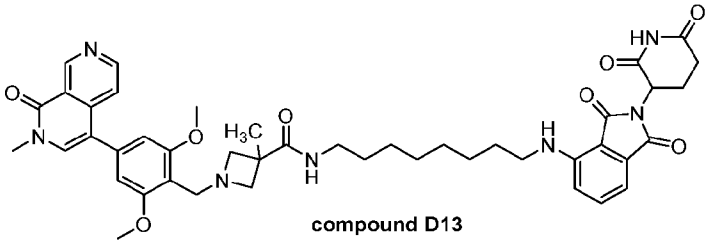
Step 2: Preparation of 1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-3-methylazetidine-3-carboxylic acid (i19-3)



i19-3

A solution of methyl 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-3-methylazetidine-3-carboxylate (235 mg, 0.537 mmol, 1 equiv) in HCl (12 M, 5 mL) was stirred at 25 ℃ for 40 minutes. The mixture was concentrated under reduced pressure afford 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-3-methylazeti- dine-3-carboxylic acid (185 mg, 81.33%) as a brown solid, that was used directly without further purification. LCMS (ESI) m/z: [M+H]+ = 424.

Step 3: Preparation of 1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-N-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octyl)-3-methylazetidine-3-carboxamide (compound D13)

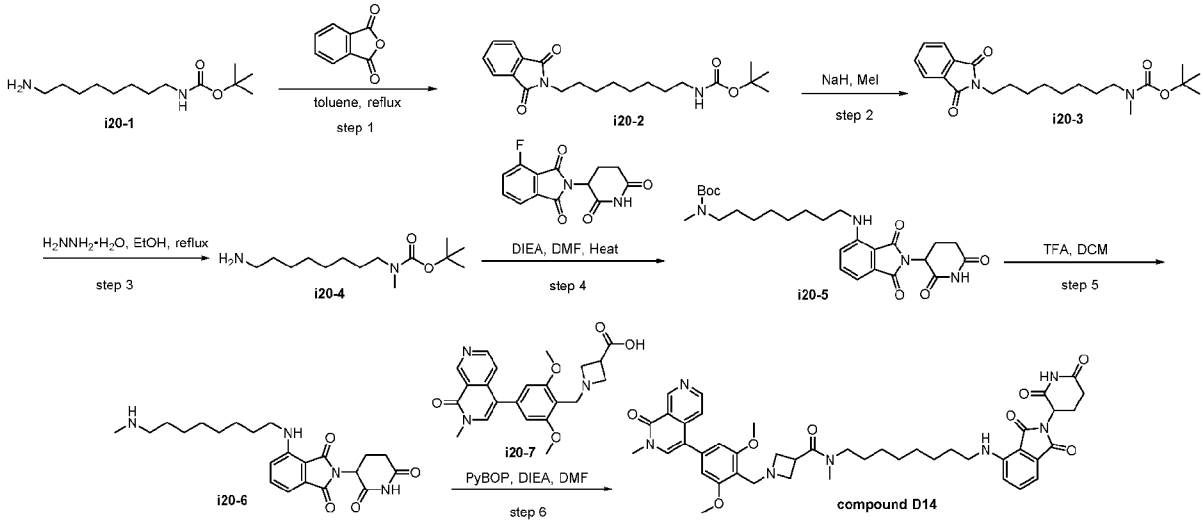


compound D13

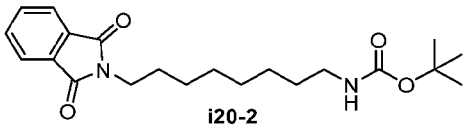
To a solution of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl] -3-methylazetidine-3-carboxylic acid (50 mg, 0.118 mmol, 1 equiv), 4-[(8-aminooctyl)amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (94.57 mg, 0.236 mmol, 2 equiv) and Et_3N (119.48 mg, 1.181 mmol, 10.00 equiv) in DMF (3 mL), was added EDCI (27.16 mg, 0.142 mmol, 1.2 equiv) and HOBT (19.15 mg, 0.142 mmol, 1.2 equiv), the resulting solution was stirred at 25 ℃ for 24 hours. The crude product was purified by Prep-HPLC with the following conditions (condition: XBridge Prep C18 OBD Column, 5 μm, 19*150 mm; mobile phase, Water (0.1% FA) and ACN; Detector, UV) to give 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-*N*-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)-3-

methylazetidine-3-carboxamide (21.7 mg, 22.80%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.53 (s, 1H), 8.69 (d, *J* = 5.7 Hz, 1H), 8.55 (s, 1H), 7.76 (s, 1H), 7.62 (d, *J* = 5.7 Hz, 1H), 7.59 – 7.49 (m, 1H), 7.07 – 6.98 (m, 2H), 6.81 (s, 2H), 5.06 (dd, *J* = 12.3, 5.4 Hz, 1H), 4.19 (s, 2H), 4.06 (s, 2H), 3.93 (s, 6H), 3.71 (s, 5H), 3.32 – 3.16 (m, 1H), 2.92 – 2.66 (m, 4H), 2.15 -2.06 (m, 1H), 1.64 (d, *J* = 7.4 Hz, 2H), 1.55 (s, 5H), 1.39 – 1.32 (m, 8H). LCMS (ESI) m/z: [M+H]+ = 806.50.

Example 20 – Preparation of 1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)-N-methylazetidine-3-carboxamide (compound D14)

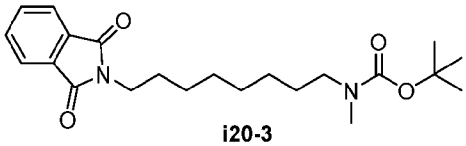


Step 1: preparation of tert-butyl N-[8-(1,3-dioxoisoindol-2-yl)octyl]carbamate (i20-2)



A mixture of tert-butyl *N*-(8-aminooctyl)carbamate (1.00 g, 4.092 mmol, 1.00 equiv) and phthalic anhydride (606.10 mg, 4.092 mmol, 1.00 equiv) in toluene (20.00 mL) was stirred for 2 hours at 130 ℃ under nitrogen atmosphere. The mixture was allowed to cool down to room temperature and the solvent was evaporated. The resulting residue was purified by silica gel column chromatography, eluted with PE/EtOAc (10:1) to afford *tert*-butyl N-[8-(1,3-dioxoisoindol-2-yl)octyl]carbamate (1.7 g, 95.41%) as a white solid. LCMS (ESI) m/z: [M+H]+ = 375.

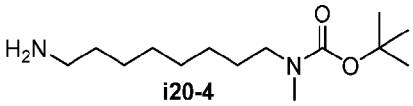
Step 2: Preparation of tert-butyl N-[8-(1,3-dioxoisoindol-2-yl)octyl]-N-methylcarbamate (i20-3)



i20-3

To a stirred solution of *tert*-butyl *N*-[8-(1,3-dioxoisoindol-2-yl)octyl]carbamate(1.24 g, 3.311 mmol, 1.00 equiv) in DMF (1.00 mL) was added NaH (0.16 g, 6.622 mmol, 2 equiv) in portions at 0 ℃ under nitrogen atmosphere. Then CH_3I (1.88 g, 13.245 mmol, 4 equiv) was added. The resulting mixture was stirred for 1 hour at room temperature under nitrogen atmosphere. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (12:1) to afford *tert*-butyl *N*-[8-(1,3-dioxoisoindol-2-yl)octyl]-*N*-methylcarbamate (800 mg, 62.19%) as a colorless liquid. LCMS (ESI) m/z: [M+H]+ = 389.

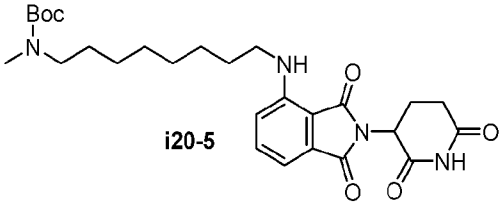
Step 3: Preparation of tert-butyl N-(8-aminooctyl)-N-methylcarbamate (i20-4)



i20-4

A solution of *tert*-butyl *N*-[8-(1,3-dioxoisoindol-2-yl)octyl]-*N*-methylcarbamate (700.00 mg, 1.802 mmol, 1.00 equiv) and NH_2NH_2 (259.84 mg, 3.604 mmol, 2 equiv) in EtOH (5.00 mL) was stirred for 1 hour at 90 ℃ under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. After filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography, eluted with PE/EtOAc (12:1) to afford *tert*-butyl *N*-(8-aminooctyl)-*N*-methylcarbamate (580 mg, 94.68%) as a colorless liquid. LCMS (ESI) m/z: [M+H]+ = 259.

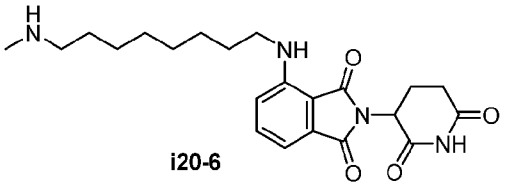
Step 4: Preparation of tert-butyl N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]octyl)-N-methylcarbamate (i20-5)



i20-5

To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindole-1,3-dione(520.00 mg, 1.883 mmol, 1.00 equiv) and *tert*-butyl *N*-(8-aminooctyl)-*N*-methylcarbamate (486.46 mg, 1.883 mmol, 1 equiv) in DMF (5.00 mL) was added DIPEA (1216.53 mg, 9.413 mmol, 5 equiv). The solution was stirred for 1 hour at 90 ℃ under nitrogen atmosphere, then it was cooled down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (12:1) to afford *tert*-butyl *N*-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]octyl)-*N*-methylcarbamate (260 mg, 26.84%) as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 515.

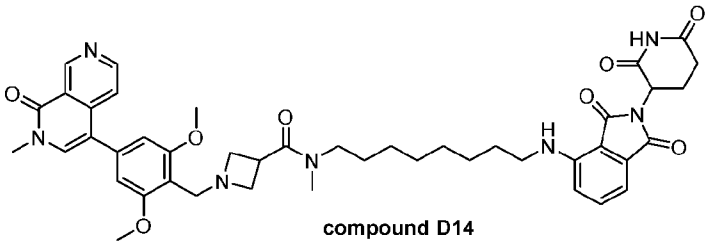
Step 5: Preparation of 2-(2,6-dioxopiperidin-3-yl)-4-[[8-(methylamino)octyl]amino]isoindole-1,3-dione (i20-6)



i20-6

A solution of *tert*-butyl *N*-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]octyl)-*N*-methylcarbamate (220.00 mg, 0.427 mmol, 1.00 equiv) in 4 M HCl in dioxane (6.00 mL) was stirred for 2 hours at room temperature. The solvent was evaporated and the residue was purified by reverse flash chromatography (condition: C18 silica gel column; mobile phase, MeOH in water, 10% to 50% gradient in 10 minutes; detector, UV 254 nm) to afford 2-(2,6-dioxopiperidin-3-yl)-4-[[8-(methylamino)octyl]amino]isoindole-1,3-dione(170 mg, 95.94%) as a dark yellow oil. LCMS (ESI) m/z: [M+H]+ = 415.

Step 6: Preparation of 1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)-N-methylazetidine-3-carboxamide (compound D14)

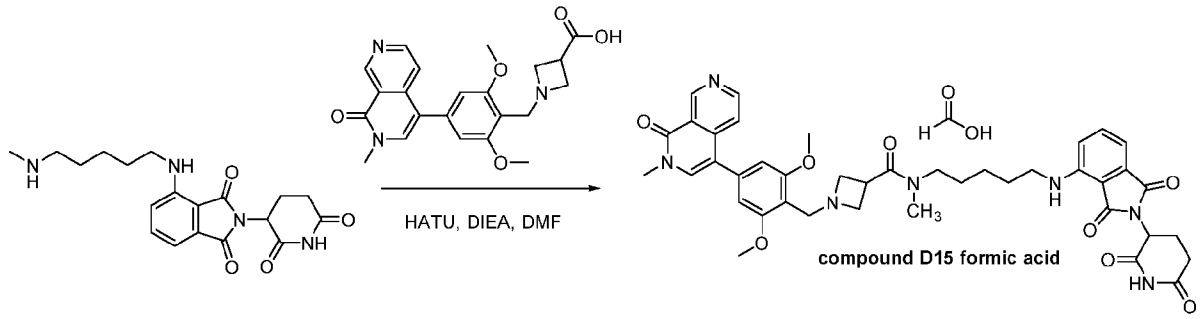


compound D14

To a stirred solution of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-3-carboxylic acid (30 mg, 0.073 mmol, 1 equiv) in DMF (0.5 mL), was added DIPEA (47.35 mg, 0.366 mmol, 5 equiv), HATU (55.72 mg, 0.147 mmol, 2 equiv), and 2-(2,6-dioxopiperidin-3-yl)-4-[[8-(methylamino)octyl]amino]-2,3-dihydro-1*H*-isoindole-1,3-dione (30.37 mg, 0.073 mmol, 1 equiv). The reaction was stirred at ambient atmosphere for 1 hour. The mixture was purified directly by Prep-HPLC (condition: SunFire C18 OBD Prep Column, 100 Å, 5 µm, 19 mm X 250 mm; Mobile Phase A: Water(0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minuteutes; Gradient: 24% B to 36% B in 8 minutes; 254 nm; R_t: 7.9 minutes) to afford 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-*N*-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino]octyl)-*N*-methylazetidine-3-carboxamide formate (25 mg, 40.05%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.52 (dd, *J* = 4.5, 0.9 Hz, 1H), 8.68 (dd, *J* = 5.8, 2.5 Hz, 1H), 8.56 (s, 0.5H, FA), 7.75 (d, *J* = 2.0 Hz, 1H), 7.67 – 7.58 (m, 1H), 7.53 (ddd, *J* = 8.5, 7.1, 4.7 Hz, 1H), 7.07 – 6.95 (m, 2H), 6.81 (d, *J* = 1.8 Hz, 2H), 5.06 (ddd, *J* = 12.1, 5.4, 2.5 Hz, 1H), 4.21 (d, *J* = 4.7 Hz, 2H), 4.00 (dd, *J* = 17.1, 8.8 Hz, 4H), 3.93 (s, 6H), 3.80 (t, *J* = 8.2 Hz, 1H), 3.70 (d, *J* = 3.3 Hz, 3H), 3.45 – 3.19 (m, 2H),

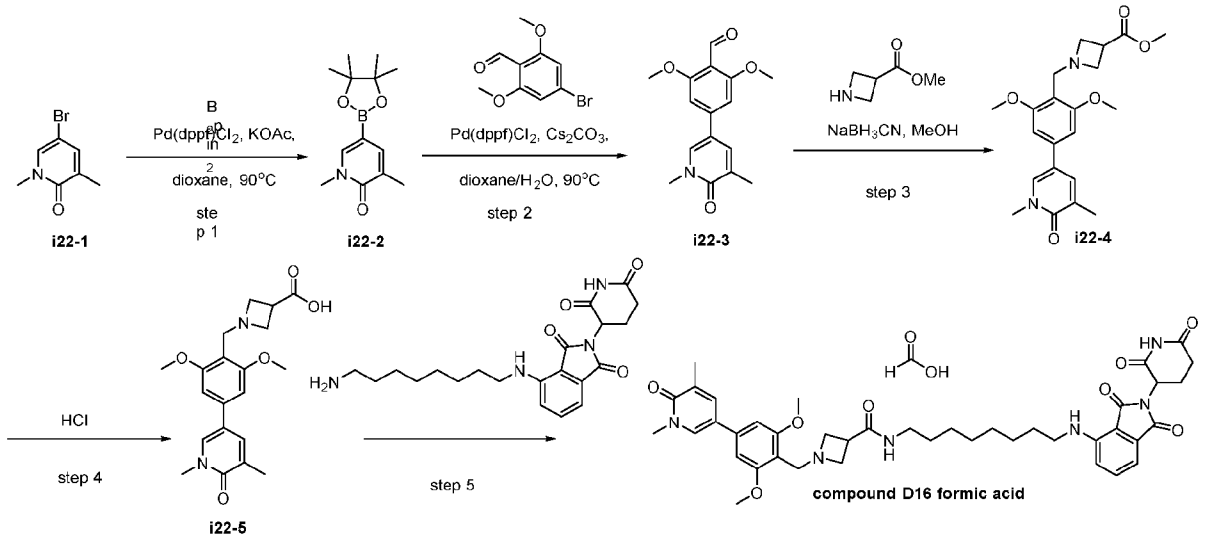
2.94 (d, J = 4.3 Hz, 3H), 2.91 – 2.68 (m, 3H), 2.12 (s, 1H), 1.67 (s, 2H), 1.57 (d, J = 6.9 Hz, 2H), 1.41 - 1.33 (m, 8H). LCMS (ESI) m/z: [M+H]+ = 806.35.

Example 21 – Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]pentyl)-N-methylazetidine-3-carboxamide formic acid (compound D15 formic acid)

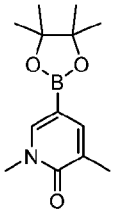


To a solution of 2-(2,6-dioxopiperidin-3-yl)-4-[[5-(methylamino)pentyl]amino]-2,3-dihydro-1*H*-isoindole-1,3-dione (60.00 mg, 0.161 mmol, 1.00 equiv), 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-3-carboxylic acid (65.96 mg, 0.161 mmol, 1.00 equiv), and DIEA (41.64 mg, 0.322 mmol, 2.00 equiv) in DMF (2.00 mL, 25.844 mmol, 160.41 equiv) was added HATU (91.89 mg, 0.242 mmol, 1.50 equiv). The resulting mixture was stirred at room temperature for 16 hours. Without workup, the crude product was purified by Prep-HPLC (condition: XBridge Shield RP18 OBD Column 30*150 mm, 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 40 mL/minuteute; Gradient: 18% B to 18% B in 2 minutes; 254/220 nm; R_t: 11.43 minutes) to afford 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino]pentyl)-N-methylazetidine-3-carboxamide; formic acid (25.1 mg) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.53 (dd, J = 5.4, 0.9 Hz, 1H), 8.68 (dd, J = 5.8, 1.2 Hz, 1H), 8.56 (s, 0.53H, FA), 7.79 – 7.73 (m, 1H), 7.67 – 7.50 (m, 2H), 7.09 – 6.99 (m, 2H), 6.80 (d, J = 3.2 Hz, 2H), 5.06 (ddd, J = 12.3, 5.4, 2.8 Hz, 1H), 4.17 (s, 2H), 3.92 - 3.90 (m, 10H), 3.78 (q, J = 9.0, 8.5 Hz, 1H), 3.71 (d, J = 2.2 Hz, 3H), 3.48 – 3.35 (m, 2H), 3.27 (t, J = 7.5 Hz, 1H), 2.98 – 2.85 (m, 3H), 2.89 – 2.64 (m, 4H), 2.22 – 2.08 (m, 1H), 1.75 -1.62 (m, 4H), 1.43 (s, 2H). LCMS (ESI) m/z: $[M+H]^+$ = 764.45.

Example 22 – Preparation of 2-(2,6-dihydroxypiperidin-3-yl)-4-[(8-[[hydroxy(1-[[4-(6-hydroxy-1,5-dimethyl-1,6-dihydropyridin-3-yl)-2,6-dimethoxyphenyl]methyl]azetidin-3-yl)methyl]amino]octyl)amino]-2,3-dihydro-1H-isoindole-1,3-diol formic acid (compound D16 formic acid)



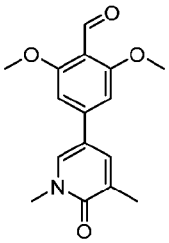
Step 1: Preparation of 1,3-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one (i22-2)



i22-2

To a solution of 5-bromo-1,3-dimethylpyridin-2-one(1.00 g, 4.949 mmol, 1.00 equiv) and bis(pinacolato)diboron (1508.17 mg, 5.939 mmol, 1.20 equiv) in dioxane (10.00 mL) was added KOAc (971.46 mg, 9.898 mmol, 2.00 equiv) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (404.18 mg, 0.495 mmol, 0.10 equiv). After stirring for 2 hours at 90 ℃ under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 250.

Step 2: Preparation of 4-(1,5-dimethyl-6-oxopyridin-3-yl)-2,6-dimethoxybenzaldehyde (i22-3)

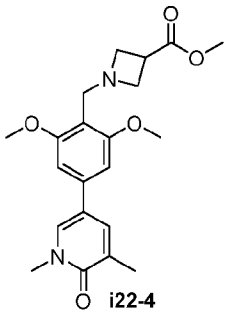


i22-3

To a solution of 1,3-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-one (1.20 g, 4.817 mmol, 1.00 equiv) and 4-bromo-2,6-dimethoxybenzaldehyde (1.18 g, 4.817 mmol, 1.00 equiv) in 1,4-dioxane (40.00 mL) and H_2O (4.00 mL) was added CS_2CO_3 (3.14 g, 9.634 mmol, 2.00 equiv) and

$Pd(dppf)Cl_2$ (0.35 g, 0.482 mmol, 0.10 equiv). After stirring for 2 hours at 80 ℃ under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH (18:1) to afford 4-(1,5-dimethyl-6-oxopyridin-3-yl)-2,6-dimethoxybenzaldehyde (1.43 g, 87.83%) as a brown syrup. LCMS (ESI) m/z: $[M+H]^+$ = 288.

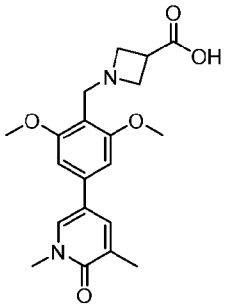
Step 3: Preparation of methyl 1-[[4-(1,5-dimethyl-6-oxopyridin-3-yl)-2,6-dimethoxyphenyl]methyl]azetidine-3-carboxylate (i22-4)



i22-4

To a solution of methyl azetidine-3-carboxylate hydrochloride(1.13 g, 7.466 mmol, 1.50 equiv) in MeOH (10.00 mL) was added Et_3N to pH 7-8. Then 4-(1,5-dimethyl-6-oxopyridin-3-yl)-2,6-dimethoxybenzaldehyde (1.43 g, 4.977 mmol, 1.00 equiv) was added. After stirring for 5-10 minutes, $NaBH_3CN$ (0.63 g, 9.954 mmol, 2.00 equiv) was added in portions at ambient atmosphere. The resulting mixture was concentrated after stirring for 1 hour at room temperature. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford methyl 1-[[4-(1,5-dimethyl-6-oxopyridin-3-yl)-2,6-dimethoxyphenyl]methyl]azetidine-3-carboxylate (1.06 g, 52.36%) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 387.

Step4: Preparation of 1-[[4-(1,5-dimethyl-6-oxopyridin-3-yl)-2,6-dimethoxyphenyl]methyl]azetidine-3-carboxylic acid (i22-5)

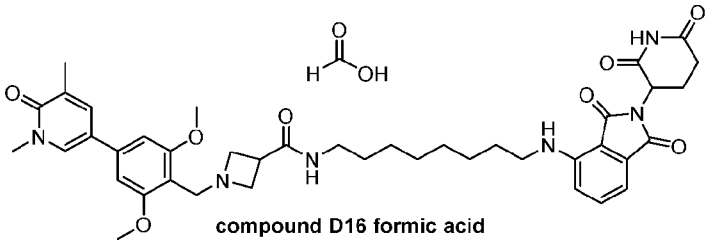


i22-5

A mixture of methyl 1-[[4-(1,5-dimethyl-6-oxopyridin-3-yl)-2,6-dimethoxyphenyl]methyl]azetidine-3-carboxylate (203.00 mg, 0.525 mmol, 1.00 equiv) in HCl (12 N, 2.00 mL) was stirred for 2 hours at 90 ℃. The resulting mixture was concentrated under reduced pressure to give 1-[[4-(1,5-dimethyl-6-

oxopyridin-3-yl)-2,6-dimethoxyphenyl]methyl]azetidine-3-carboxylic acid (150 mg, 71.31%) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 373.

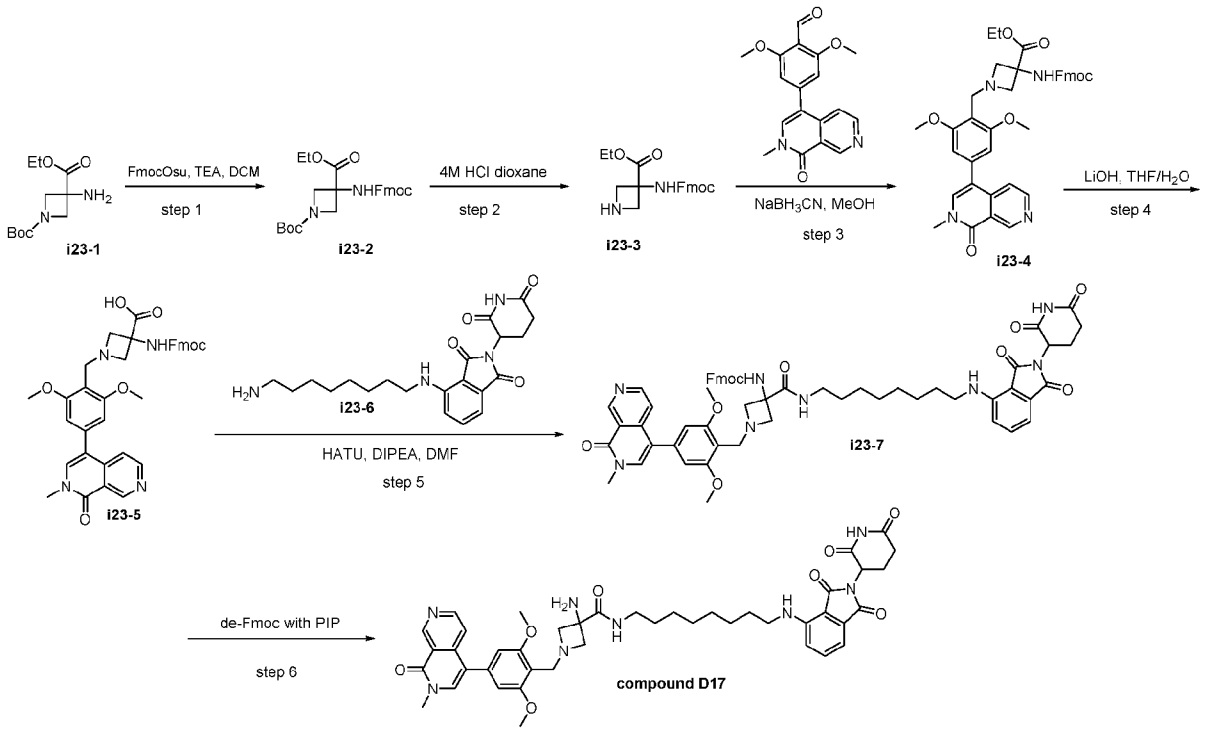
Step4: Preparation of 2-(2,6-dihydroxypiperidin-3-yl)-4-[(8-[[hydroxy(1-[[4-(6-hydroxy-1,5-dimethyl-1,6-dihydropyridin-3-yl)-2,6-dimethoxyphenyl]methyl]azetidin-3-yl)methyl]amino]octyl)amino]-2,3-dihydro-1H-isoindole-1,3-diol formic acid (compound D16 formic acid)



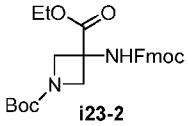
compound D16 formic acid

To a stirred mixture of 1-[[4-(1,5-dimethyl-6-oxo-1,6-dihydropyridin-3-yl)-2,6-dimethoxyphenyl] methyl]azetidine-3-carboxylic acid trifluoroacetic acid(50 mg, 0.103 mmol, 1 equiv) and 4-[(8-aminooctyl)amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione hydrochloride (44.91 mg, 0.103 mmol, 1 equiv) in DCM (2 mL) was added DIEA (53.57 mg, 0.415 mmol, 4 equiv). After stirring for 10 minutes, PyBOP (80.89 mg, 0.155 mmol, 1.5 equiv) was added. The resulting mixture was concentrated under reduced pressure, and then the residue was purified by Prep-HPLC (conditions: Sun Fire C18 OBD Prep Column, 19 mm X 250 mm; mobile phase, Water(0.1% FA) and ACN (23% Phase B up to 33% in 8 min, hold 33% in 1 minutes); Detector, UV). This resulted in 2-(2,6-dihydroxypiperidin-3-yl)-4-[(8-[[hydroxy(1-[[4-(6-hydroxy-1,5-dimethyl-1,6-dihydropyridin-3-yl)-2,6-dimethoxyphenyl]methyl]azetidin-3-yl)methyl]amino]octyl)amino]-2,3-dihydro-1H-isoindole-1,3-diol formic acid (2.4 mg, 2.73%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 8.56 (s, 2H, FA), 7.96 (s, 1H), 7.83 (s, 1H), 7.61 – 7.50 (m, 1H), 7.04 (d, *J* = 7.7 Hz, 2H), 6.88 (s, 2H), 4.62 (s, 1H), 4.32 (s, 2H), 4.09 (d, *J* = 7.9 Hz, 4H), 3.98 (s, 6H), 3.68 (s, 3H), 3.55 – 3.44 (m, 2H), 3.21 (t, *J* = 7.0 Hz, 2H), 2.91 – 2.68 (m, 4H), 2.22 (s, 3H), 2.12 (s, 1H), 1.68 (s, 2H), 1.64 -1.39 (m, 10H). LCMS (ESI) m/z: $[M+H]^+$ = 373.17.

Example 23 – Preparation of 3-amino-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)azetidine-3-carboxamide (compound D17)



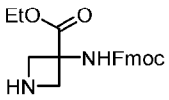
Step 1: Preparation of 1-tert-Butyl 3-ethyl 3-([[(9H-fluoren-9-yl)methoxy]carbonyl]amino)azetidine-1,3-dicarboxylate (i23-2)



i23-2

To a solution of 1-*tert*-butyl 3-ethyl 3-aminoazetidine-1,3-dicarboxylate (120 mg, 0.491 mmol, 1 equiv) and 2,5-dioxopyrrolidin-1-yl (9*H*-fluoren-9-yl)methyl carbonate (182.3 mg, 0.540 mmol, 1.1 equiv) in DCM (1 mL) was added TEA (149.1 mg, 1.474 mmol, 3 equiv). The resulting solution was stirred at room temperature for 1 hour. The residue was purified by Prep-TLC (PE/EtOAc 1:1) to afford 1-*tert*-butyl 3-ethyl 3-([[(9*H*-fluoren-9-yl)methoxy]carbonyl]amino)azetidine-1,3-dicarboxylate(120 mg, 48%) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 467.

Step 2: Preparation of Ethyl 3-([[(9H-fluoren-9-yl)methoxy]carbonyl]amino)azetidine-3-carboxylate (i23-3)

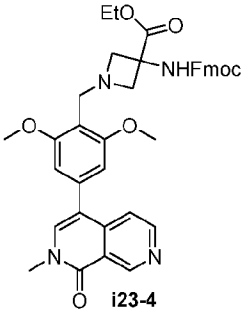


i23-3

A mixture of 1-tert-*butyl* 3-ethyl 3-([[(9*H*-fluoren-9-yl)methoxy]carbonyl]amino)azetidine-1,3-dicarboxylate (120.00 mg, 0.257 mmol, 1.00 equiv) and 4 M HCl in 1,4-dioxane (2 mL) was stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure to afford

ethyl 3-([[(9*H*-fluoren-9-yl)methoxy]carbonyl]amino)azetidine-3-carboxylate (120 mg, 89%) as a white solid that was used directly without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 367.

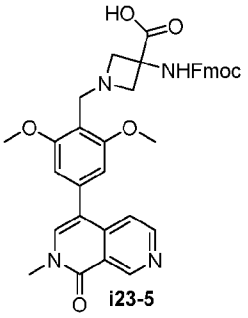
Step 3: Preparation of Ethyl 1-[[2,6-Dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-3-([[(9H-fluoren-9-yl)methoxy]carbonyl]amino)azetidine-3-carboxylate (i23-4)



i23-4

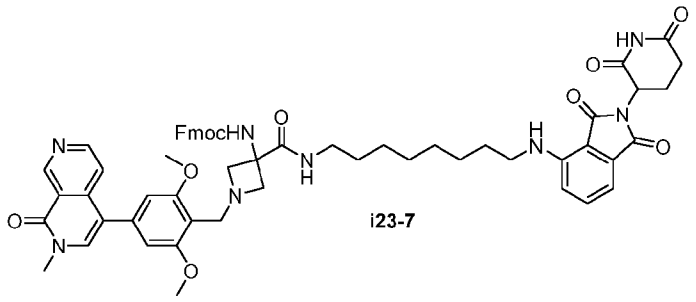
To a solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (127.5 mg, 0.393 mmol, 1.20 equiv) and ethyl 3-([[(9*H*-fluoren-9-yl)methoxy]carbonyl]amino)azetidine-3-carboxylate (120 mg, 0.327 mmol, 1 equiv) in MeOH (1 mL) was added $NaBH_3CN$ (41.2 mg, 0.655 mmol, 2 equiv). The resulting solution was stirred at room temperature for 1 hour. The mixture was then concentrated under reduced pressure and the residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 12:1) to afford ethyl 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-3-([[(9*H*-fluoren-9-yl)methoxy]carbonyl]amino)azetidine-3-carboxylate (100 mg, 45%) as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 675.

Step 4: Preparation of Ethyl 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-3-([[(9H-fluoren-9-yl)methoxy]carbonyl]amino)azetidine-3-carboxylic acid (i23-5)



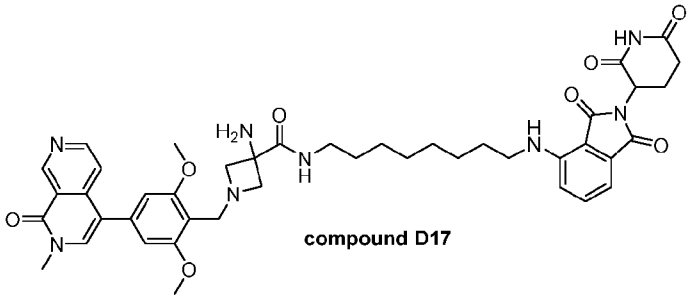
A solution of ethyl 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-3-([[(9*H*-fluoren-9-yl)methoxy]carbonyl]amino)azetidine-3-carboxylate (100 mg, 0.148 mmol, 1 equiv) in concentrated HCl (2 mL) was stirred at 90 °C for 1 hour. The resulting mixture was concentrated under reduced pressure to afford 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-3-([[(9*H*-fluoren-9-yl)methoxy]carbonyl]amino)azetidine-3-carboxylic acid (100 mg, 94%) as a yellow solid that was used directly without further purification. LCMS (ESI) m/z: [M+H]+ = 647.3

Step 5: Preparation of (9H-fluoren-9-yl)methyl N-(1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl] methyl]-3-[(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)carbamoyl] azetidin-3-yl)carbamate (i23-7)



To a solution of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-3-([[(9*H*-fluoren-9-yl)methoxy]carbonyl]amino)azetidine-3-carboxylic acid (100 mg, 0.155 mmol, 1 equiv) and 4-[(8-aminooctyl)amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1*H*-isoindole-1,3-dione (74.3 mg, 0.186 mmol, 1.2 equiv) in DMF (1 mL) was added DIEA (60.0 mg, 0.464 mmol, 3 equiv) and HATU (88.2 mg, 0.232 mmol, 1.5 equiv). The resulting solution was stirred at room temperature for 1 hour. The mixture was then concentrated under reduced pressure and the residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 12:1) to afford (9*H*-fluoren-9-yl)methyl N-(1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl] methyl]-3-[(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino]octyl)carbamoyl] azetidin-3-yl)carbamate (90 mg, 51%) as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 1029.

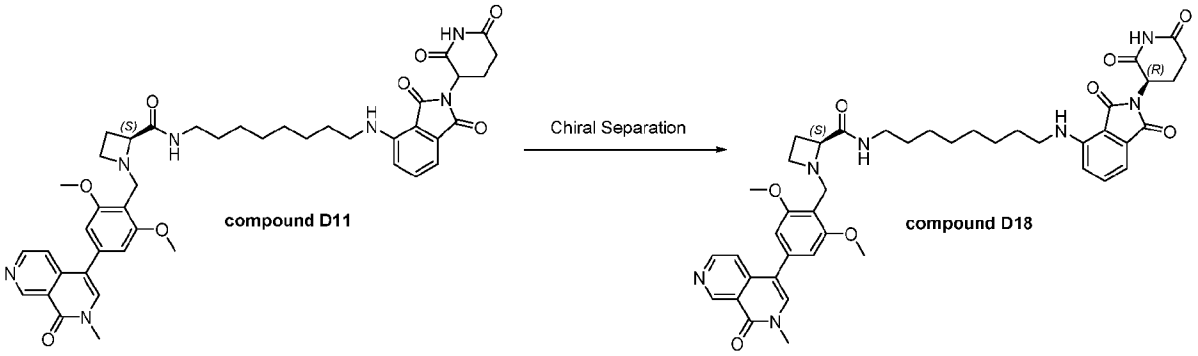
Step 6: Preparation of 3-Amino-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)azetidine-3-carboxamide (compound D17)



compound D17

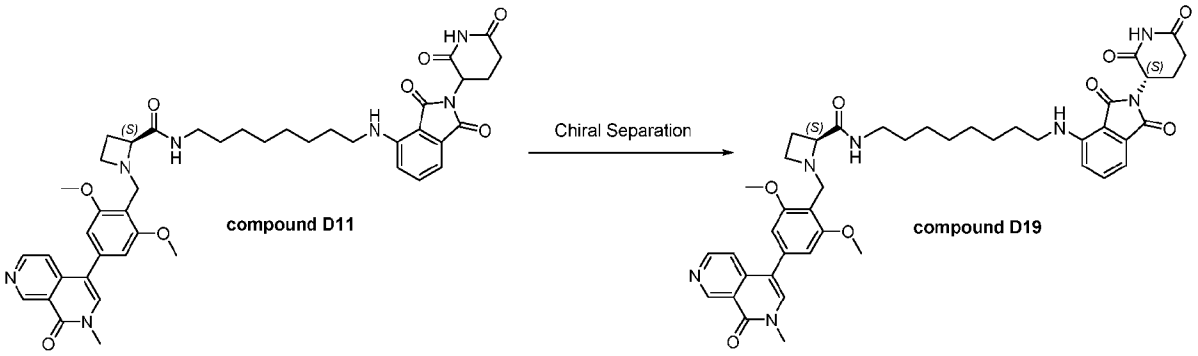
A solution of (9*H*-fluoren-9-yl)methyl N-(1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-3-[(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino]octyl)carbamoyl]azetidin-3-yl)carbamate (90 mg, 0.087 mmol, 1.00 equiv) in piperidine (1 mL) and DMF (4 mL) was stirred at room temperature for 1 hour. The crude solution was purified by Prep-HPLC (condition: SunFire C18 OBD Prep Column, 100 Å, 5 µm, 19 mm X 250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minuteute; Gradient: 28% B to 28% B in 2 minutes; 254 nm; R_t: 6.9 minutes) to afford 3-amino-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-*N*-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino]octyl)azetidine-3-carboxamide (3.8 mg, 5.2%) as a yellow solid. ^{1}H NMR (300 MHz, Acetonitrile-*d3*) δ 9.52 (s, 1H), 8.70 (d, *J* = 5.7 Hz, 1H), 8.26 (s, 0.53H, FA), 7.78-7.42 (m, 4H), 7.02 (dd, *J* = 7.8, 4.2 Hz, 2H), 6.75 (s, 2H), 6.30 (t, *J* = 5.9 Hz, 1H), 4.95 (dd, *J* = 12.4, 5.2 Hz, 1H), 4.10 (s, 2H), 3.95 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 6H), 3.50 (s, 3H), 3.24 (dq, *J* = 23.4, 6.6 Hz, 4H), 2.83-2.59 (m, 3H), 1.63 (s, 2H), 1.49 (s, 2H), 1.32 (d, *J* = 13.1 Hz, 10H). LCMS (ESI) m/z: [M+H]+ = 807.40.

Example 24 – Preparation of (2S)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]octyl)azetidine-2-carboxamide (compound D18)



Compound D11 was further separated by chiral HPLC to afford (2*S*)-1-((2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl)methyl)-*N*-(8-((2-((*R*)-2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl)amino)octyl) azetidine-2-carboxamide (10 mg, 10.34%) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.51 (s, 1H), 8.68 (d, *J* = 5.7 Hz, 1H), 7.72 (s, 1H), 7.62 (d, *J* = 5.8 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.00 (dd, *J* = 10.6, 7.8 Hz, 2H), 6.75 (s, 2H), 5.05 (dd, *J* = 12.4, 5.4 Hz, 1H), 3.89 (s, 9H), 3.69 (s, 3H), 3.30 (s, 2H), 3.25 (t, *J* = 6.9 Hz, 2H), 3.15 (t, *J* = 7.1 Hz, 2H), 2.94– 2.64 (m, 3H), 2.35 (d, *J* = 9.5 Hz, 1H), 2.16 – 2.00 (m, 1H), 1.58 (t, *J* = 7.1 Hz, 2H), 1.40 (d, *J* = 6.7 Hz, 2H), 1.30 (s, 8H). LCMS (ESI) m/z: [M+H]+ = 792.60.

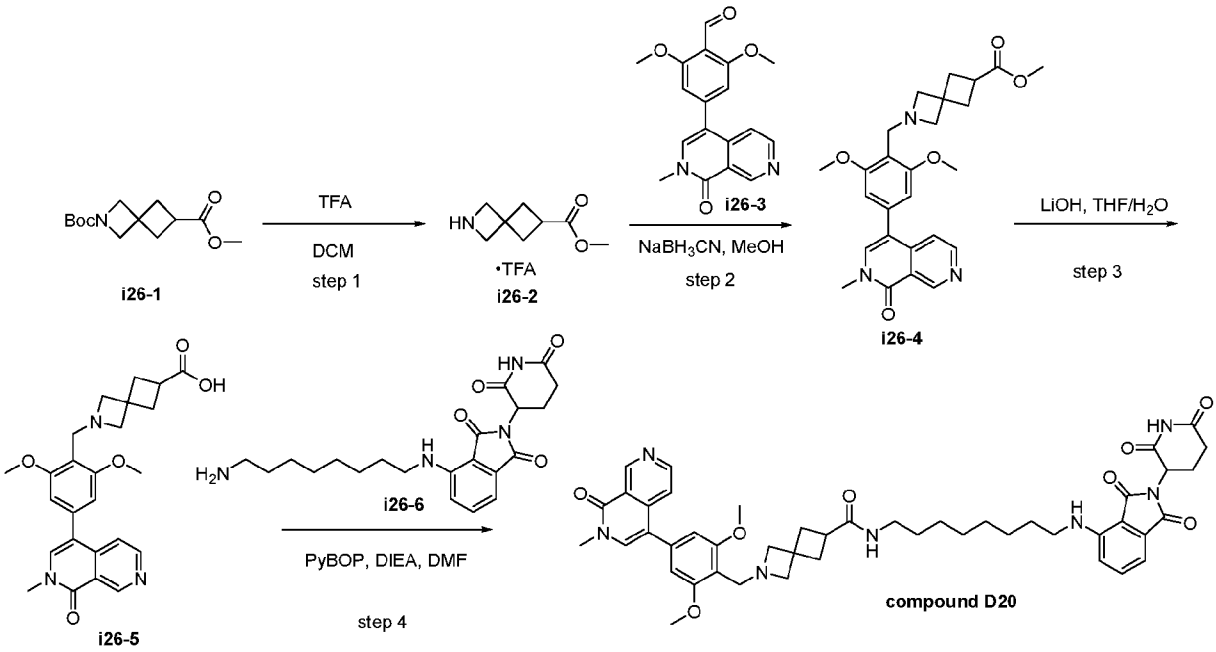
Example 25 – Preparation of (2S)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]octyl)azetidine-2-carboxamide (compound D19)



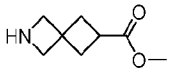
Compound D11 was further separated by chiral HPLC to afford (2*S*)-1-((2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl)methyl)-*N*-(8-((2-((*S*)-2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl)amino)octyl) azetidine-2-carboxamide (10 mg, 10.34%) as a yellow solid.^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.51 (s, 1H), 8.68 (d, *J* = 5.7 Hz, 1H), 7.72 (s, 1H), 7.62 (d, *J* = 5.8 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.00 (dd, *J* = 10.6, 7.8 Hz, 2H), 6.75 (s, 2H), 5.05 (dd, *J* = 12.4, 5.4 Hz, 1H), 3.89 (s, 9H), 3.69 (s, 3H), 3.30 (s, 2H), 3.25 (t, *J* = 6.9 Hz, 2H), 3.15 (t, *J* = 7.1 Hz, 2H), 2.94– 2.64 (m, 3H), 2.35 (d, *J*

= 9.5 Hz, 1H), 2.16 – 2.00 (m, 1H), 1.58 (t, *J* = 7.1 Hz, 2H), 1.40 (d, *J* = 6.7 Hz, 2H), 1.30 (s, 8H). LCMS (ESI) m/z: [M+H]+ = 792.60

Example 26 – Preparation of 6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2,4a,8a-tetrahydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)spiro[3.3]heptane-2-carboxamide (compound D20)



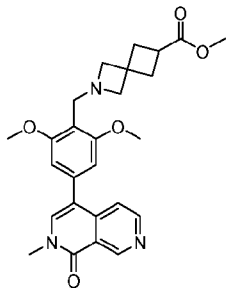
Step 1: Preparation of methyl 2-azaspiro[3.3]heptane-6-carboxylate trifluoroacetic acid (i26-2)



i26-2

A mixture of 2-*tert*-butyl 6-methyl 2-azaspiro[3.3]heptane-2,6-dicarboxylate (127.60 mg, 0.500 mmol, 1.00 equiv) and TFA (1 mL) in DCM (3.00 mL) was stirred for 2 hours at room temperature. Then, the solvent was evaporated, and the resulting residue was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]+ = 156.

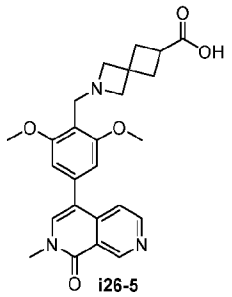
Step 2: Preparation of methyl 2-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-2-azaspiro[3.3]heptane-6-carboxylate (i26-4)



i26-4

To a stirred solution of methyl 2-azaspiro[3.3]heptane-6-carboxylate trifluoroacetic acid (77.60 mg, 0.288 mmol, 1.00 equiv), Et_3N (116.67 mg, 1.153 mmol, 4 equiv), and 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (93.49 mg, 0.288 mmol, 1 equiv) in MeOH (2.00 mL) was added $NaBH_3CN$ (36.23 mg, 0.576 mmol, 2 equiv) in portions at room temperature. After the solvent was evaporated, the residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (12:1) to afford methyl 2-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-2-azaspiro[3.3]heptane-6-carboxylate (156 mg, 96.91%) as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 464.

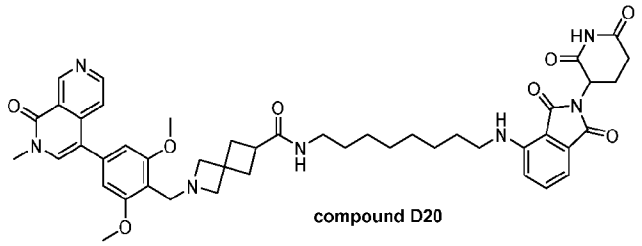
Step 3: Preparation of 2-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-2-azaspiro[3.3]heptane-6-carboxylic acid (i26-5)



i26-5

A solution of methyl 2-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-2-azaspiro[3.3]heptane-6-carboxylate (156.00 mg, 0.347 mmol, 1.00 equiv) and LiOH (83.28 mg, 3.47 mmol, 10.0 equiv) in mixed THF (2.00 mL) and H_2O (1.00 mL) was stirred for 1 hour at room temperature. Then solvent was evaporated, and the resulting solution was purified by Prep-HPLC (0-100% ACN/water, with 0.1% TFA) to afford 2-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-2-azaspiro[3.3] heptane-6-carboxylic acid(114.7 mg, 75.89%) as a dark yellow oil. LCMS (ESI) m/z: [M+H]+ = 450.

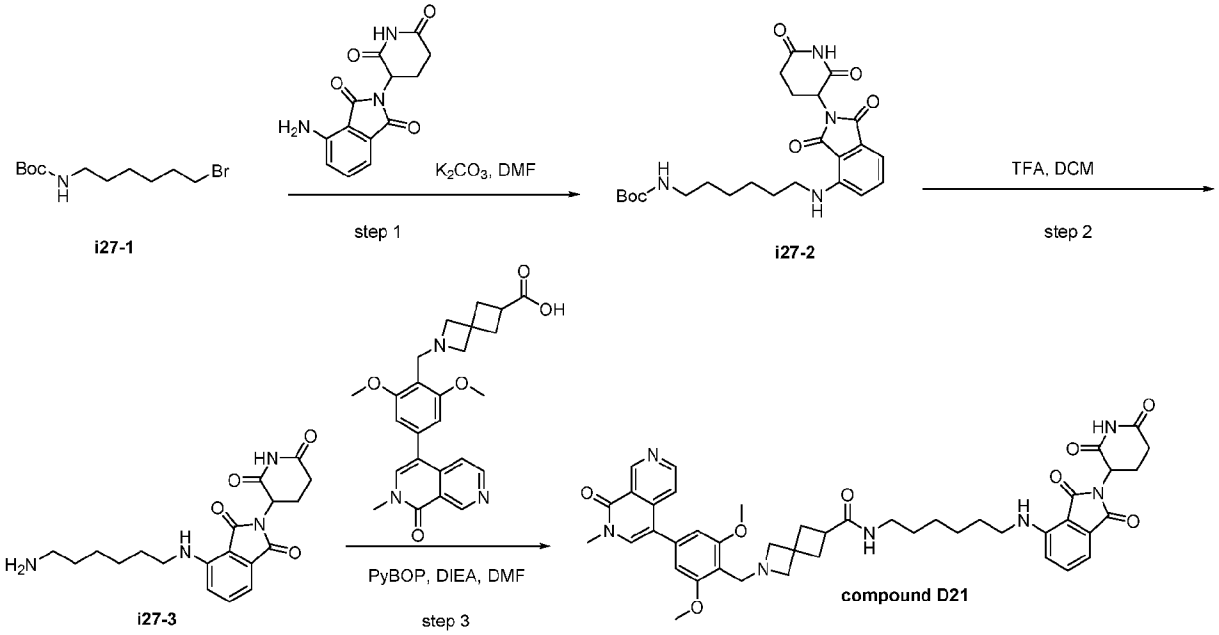
Step 4: Preparation of 6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2,4a,8a-tetrahydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)spiro[3.3]heptane-2-carboxamide (compound D20)



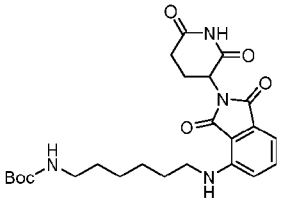
compound D20

To a stirred solution of 6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2,4a,8a-tetrahydro-2,7-naphthyridin-4-yl)phenyl]methyl]spiro[3.3]heptane-2-carboxylic acid (45 mg, 0.100 mmol, 1 equiv) and 4-[(8-aminooctyl)amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (40.00 mg, 0.100 mmol, 1 equiv) in DMF (0.5 mL), was added DIEA (64.54 mg, 0.499 mmol, 5 equiv) and PyBOP (103.95 mg, 0.200 mmol, 2 equiv) at room temperature. The mixture was stirred for 1 h and directly purified by Prep-HPLC with the following conditions (conditions: SunFire C18 OBD Prep Column, 19 mm X 250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minuteute; Gradient: 29% B to 32% B in 8 minutes; 254 nm; R_t: 6.55 minutes) to afford 6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2,4a,8a-tetrahydro-2,7-naphthyridin-4-yl)phenyl]methyl]-*N*-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)spiro[3.3]heptane-2-carboxamide (14.1 mg, 14.24%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.54 (d, *J* = 0.9 Hz, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 7.78 (s, 1H), 7.65 – 7.50 (m, 2H), 7.04 (d, *J* = 7.9 Hz, 2H), 6.86 (s, 2H), 5.05 (dd, *J* = 12.6, 5.7 Hz, 1H), 4.63 (s, 2H), 4.44 (s, 2H), 4.18 (s, 3H), 3.97 (s, 6H), 3.88 (s, 1H), 3.71 (s, 3H), 3.34 – 3.11 (m, 3H), 3.10 – 2.67 (m, 5H), 2.61 – 2.37 (m, 4H), 2.27 – 2.13 (m, 1H), 1.67 (q, *J* = 7.0 Hz, 2H), 1.59 – 1.26 (m, 10H). LCMS (ESI) m/z: [M+H]+ = 832.5.

Example 27 – Preparation of 6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2,4a,8a-tetrahydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]hexyl)spiro[3.3]heptane-2-carboxamide (compound D21)

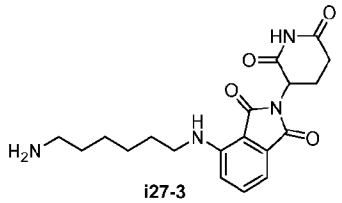


Step 1: preparation o tert-butyl N-(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]hexyl) carbamate (i27-2)



To a stirred solution of pomalidomide (150.30 mg, 0.550 mmol, 1.00 equiv) and *tert*-butyl *N*-(6-bromohexyl)carbamate (154.13 mg, 0.550 mmol, 1 equiv) in DMF (1.00 mL) was added K_2CO_3 (152.04 mg, 1.100 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature, and then it was concentrated and purified by silica gel column chromatography, elutinged with PE/EtOAc (10:1) to afford *tert*-butyl *N*-(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]hexyl) carbamate (293 mg, 95.82%) as a yellow oil. LCMS (ESI) m/z: [M+H]+ = 473.

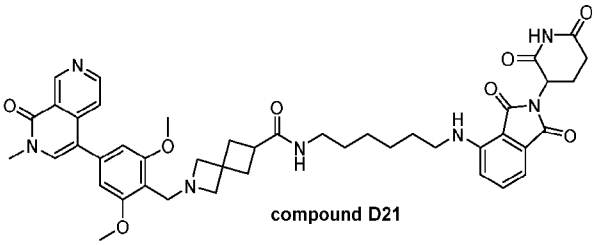
Step 2: Preparation of 4-[(6-aminohexyl)amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione trifluoroacetic acid (i27-3)



i27-3

A solution of *tert*-butyl *N*-(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]hexyl) carbamate (293.00 mg, 0.620 mmol, 1.00 equiv) and TFA (2.0 mL) in DCM (5.00 mL) was stirred for 1 h at room temperature. The mixture was then concentrated to afford 4-[(6-aminohexyl)amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (243 mg, 80.56%) as a yellow semi-solid, that was used directly without further purification. LCMS (ESI) m/z: [M+H]+ = 373.

Step 3: Preparation of 6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2,4a,8a-tetrahydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]hexyl) spiro[3.3]heptane-2-carboxamide (compound D21)

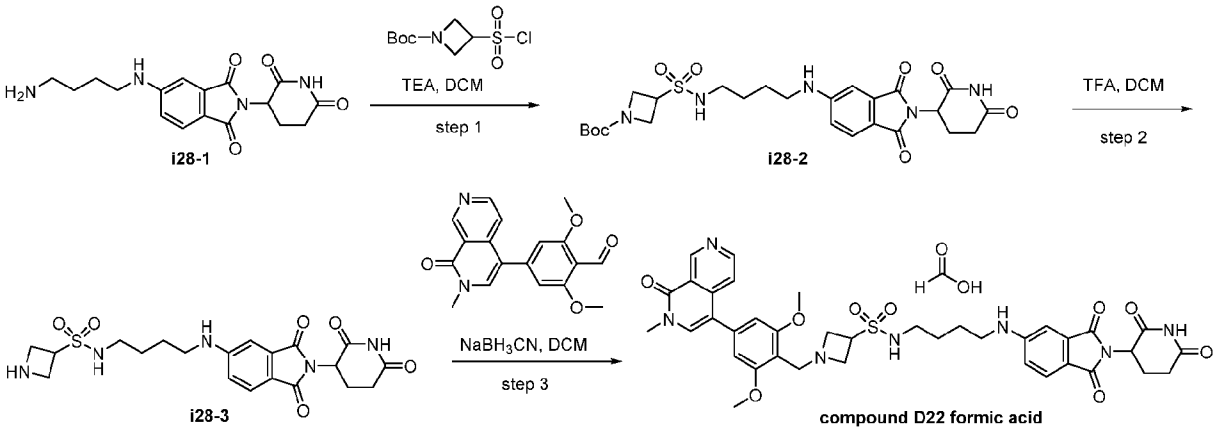


compound D21

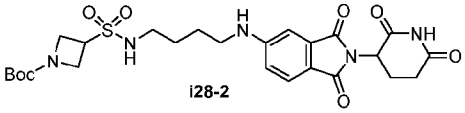
To a stirred solution of 6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2,4a,8a-tetrahydro-2,7-naphthyridin-4-yl)phenyl]methyl]spiro[3.3]heptane-2-carboxylic acid (30 mg, 0.067 mmol, 1 equiv) in DMF (0.5 mL) was added DIEA (43.03 mg, 0.333 mmol, 5 equiv), PyBOP (69.30 mg, 0.133 mmol, 2 equiv), and 4-[(6-aminohexyl)amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1*H*-isoindole-1,3-dione(24.80 mg, 0.067 mmol, 1 equiv). The reaction was stirred at ambient atmosphere for 1 hour. The mixture was purified directly by Prep-HPLC (condition: SunFire C18 OBD Prep Column, 100 Å, 5 µm, 19 mm X 250 mm; Mobile Phase A: Water(0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minuteute; Gradient: 12% B to 38% B in 8 minutes; 254 nm; R_t: 7.58 minutes), to afford 6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2,4a,8a-tetrahydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]hexyl)spiro[3.3]heptane-2-carboxamide(11.2mg,20.90%) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.52 (s, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 7.77 (s, 1H), 7.61 (d, *J* = 5.8 Hz, 1H), 7.50 – 7.39 (m, 1H), 7.01 (dd, *J* = 17.7, 7.7 Hz, 2H), 6.85 (s, 2H), 5.09 (dd, *J* = 12.9, 5.5 Hz, 1H), 4.42 (s, 2H), 4.16 (d, *J* = 3.1 Hz, 4H), 3.96 (s, 6H), 3.78 (t, *J* = 7.4 Hz, 2H), 3.71 (s, 3H), 3.50 (q, *J* = 7.3 Hz, 1H), 3.20 (qd, *J* = 7.3, 5.4 Hz, 9H), 2.99 – 2.87 (m, 2H), 2.91 – 2.83 (m, 1H), 2.75 – 2.61 (m, 1H), 2.53 (s, 2H), 2.53 – 2.47 (m, 1H), 2.47 – 2.37 (m, 2H), 2.22 - 2.09 (m, 2H), 1.94 (s, 2H), 1.93 (s, 6H), 1.61

(s, 1H), 1.51 (tt, J = 15.1, 8.0 Hz, 4H), 1.46 – 1.26 (m, 23H), 1.12 (t, J = 7.3 Hz, 10H), 0.91 (q, J = 9.7, 7.9 Hz, 3H). LCMS (ESI) m/z: [M+H]+ = 804.40.

Example 28 – Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl] methyl]-N-(4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]amino]butyl) azetidine-3-sulfonamide formic acid (compound D22 formic acid)

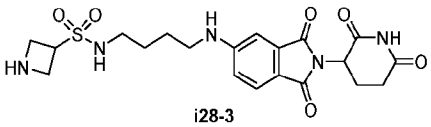


Step 1: Preparation of tert-butyl-3-[(4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]butyl)sulfamoyl]azetidine-1-carboxylate (i28-2)



To a stirred mixture of 5-[(4-aminobutyl)amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (60.00 mg, 0.174 mmol, 1.00 equiv) and *tert*-butyl 3-(chlorosulfonyl)azetidine-1-carboxylate (111.38 mg, 0.436 mmol, 2.50 equiv) in DCM (2.00 mL) was added TEA (52.89 mg, 0.523 mmol, 3.00 equiv). After stirring for 1.5 hours at room temperature, the resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / EtOAc (1:2)) to afford *tert*-butyl-3-[(4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]butyl)sulfamoyl]azetidine-1-carboxylate(78 mg, 73.87%) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 564.20.

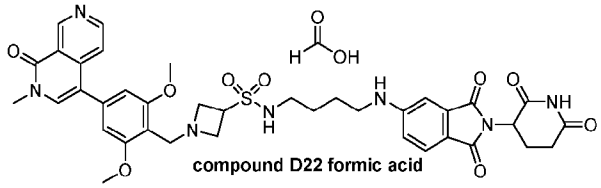
Step 2: Preparation of N-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)butyl)azetidine-3-sulfonamide (i28-3)



To a stirred mixture of *tert*-butyl-3-[(4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl] amino]butyl)sulfamoyl]azetidine-1-carboxylate (78.00 mg, 0.138 mmol, 1.00 equiv) in DCM (2.00 mL, 0.012 mmol, 0.10 equiv) was added TFA (0.40 mL, 5.385 mmol, 38.91 equiv). After stirring for 1 hour at

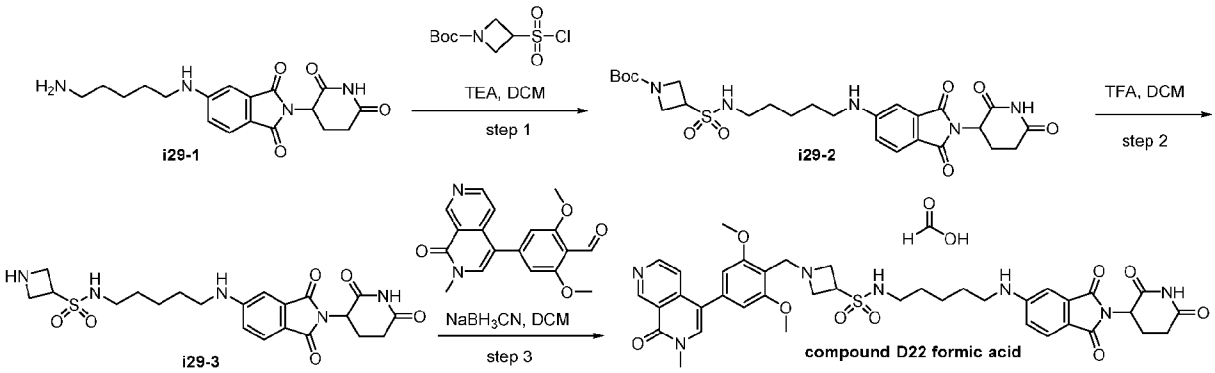
room temperature, the resulting mixture was concentrated under reduced pressure. The residue was used in the next step directly without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 464.15.

Step 3: Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl] methyl]-N-(4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]amino]butyl)azetidine-3-sulfonamide formic acid (compound D38 formic acid).

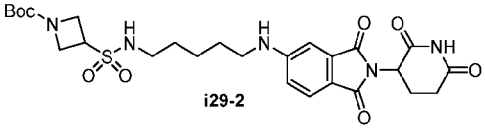


A mixture of *N*-(4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]amino]butyl) azetidine-3-sulfonamide (64.17 mg, 0.138 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (44.90 mg, 0.138 mmol, 1.00 equiv) in DMF (2 mL) was stirred at room temperature, then adjusted to pH 8~9 by addition of TEA. The above mixture was added $NaBH_3CN$ (26.10 mg, 0.415 mmol, 3.00 equiv) in portions, the resulting mixture was stirred for 2 hours at room temperature. The resulting mixture was concentrated under reduced pressure, the residue was purified by Prep-HPLC (condition: X Select CSH Prep C18 OBD Column, 5 μm, 19*150 mm; mobile phase, Water (0.1% FA) and ACN (15% Phase B up to 30% in 14 minutes); Detector, UV). This resulted in 15 mg (12.59%) of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]amino]butyl)azetidine-3-sulfonamide formic acid as a yellow solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.07 (s, 1H), 9.45 (s, 1H), 8.73 (d, *J* = 5.7 Hz, 1H), 8.14 (s, 0.5 H, FA), 7.87 (s, 1H), 7.59 – 7.52 (m, 2H), 7.13 (s, 1H), 6.94 (s, 1H), 6.84 (d, *J* = 8.6 Hz, 1H), 6.78 (s, 2H), 6.55 (s, 1H), 5.03 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.84 (s, 7H), 3.60 (s, 4H), 3.28 – 3.20 (m, 3H), 3.16 (d, *J* = 6.3 Hz, 3H), 2.97 (d, *J* = 6.5 Hz, 2H), 2.92 – 2.81 (m, 1H), 2.61 – 2.53 (m, 3H), 2.03 – 1.95 (m, 1H), 1.55 (s, 4H). LCMS (ESI) m/z: $[M+H]^+$ = 772.30.

Example 29 – Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl] methyl]-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]amino]pentyl) azetidine-3-sulfonamide formic acid (compound D23 formic acid)

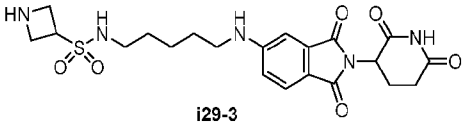


Step 1: Preparation of tert-butyl-3-[(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]pentyl) sulfamoyl]azetidine-1-carboxylate (i28-2)



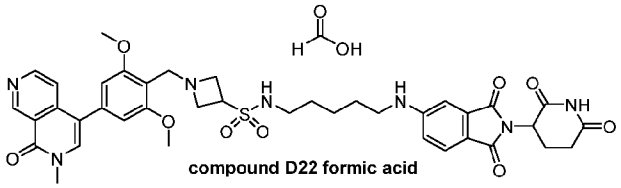
To a stirred mixture of 5-[(5-aminopentyl)amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (100.00 mg, 0.279 mmol, 1.00 equiv) and *tert*-butyl 3-(chlorosulfonyl)azetidine-1-carboxylate(178.37 mg, 0.698 mmol, 2.50 equiv) in DCM (2.00 mL) was added TEA (84.70 mg, 0.837 mmol, 3.00 equiv). After stirring for 1.5 hours at room temperature, the resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/EA (1:2)) to afford *tert*-butyl-3-[(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]pentyl)sulfamoyl]azetidine-1-carboxylate (58.7mg,33.87%) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 578.

Step 2: Preparation of N-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)pentyl)azetidine-3-sulfonamide (i28-3)



To a stirred mixture of tert-butyl 3-[(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]pentyl)sulfamoyl]azetidine-1-carboxylate (58.70 mg, 0.102 mmol, 1.00 equiv) in DCM (2.00 mL) was added TFA (0.40 mL, 5.385 mmol, 52.99 equiv). After stirring for 1 hour at room temperature, the resulting mixture was concentrated under reduced pressure. The residue was used in the next step directly without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 478.17.

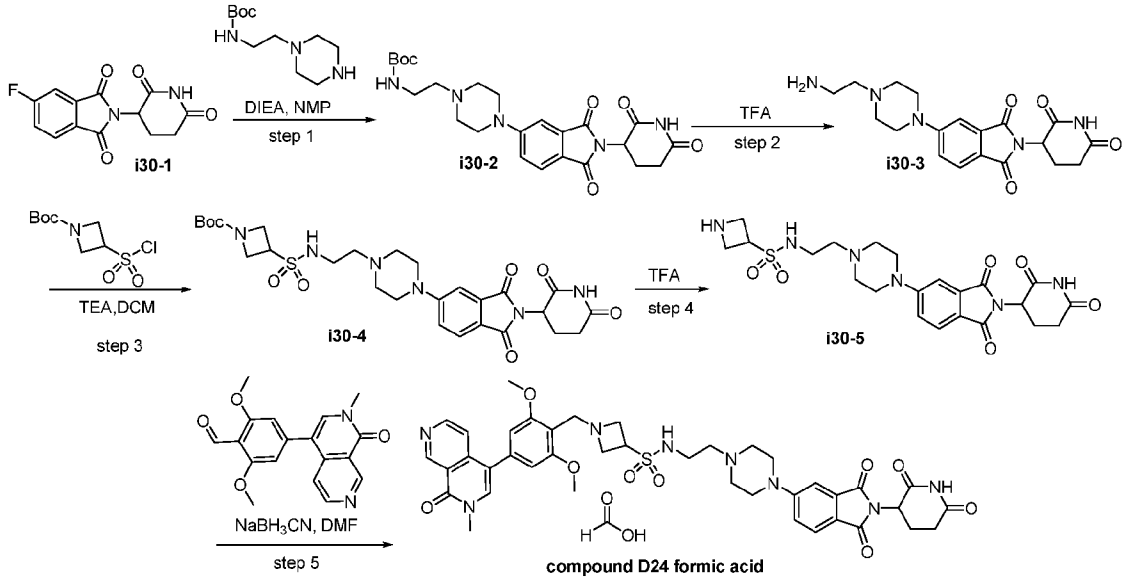
Step 3: Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl] methyl]-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]amino]pentyl)azetidine-3-sulfonamide formic acid (compound D22 formic acid)



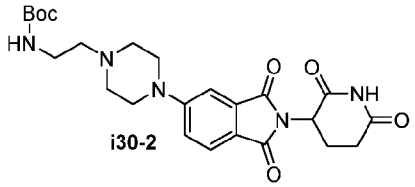
compound D22 formic acid

A mixture of *N*-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl]amino]pentyl) azetidine-3-sulfonamide (48.54 mg, 0.102 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (39.56 mg, 0.122 mmol, 1.20 equiv) in THF (2 mL) was stirred at room temperature, then adjusted to pH 8--~9 with TEA. To the above mixture was added $NaBH_3CN$ (12.78 mg, 0.203 mmol, 2.00 equiv) in portions, and the resulting mixture was stirred for 2 hours at room temperature. The resulting mixture was concentrated under reduced pressure, and the residue was purified by Prep-HPLC (conditions: Sun Fire C18 OBD Prep Column,19 mm X 250 mm; mobile phase, Water (0.1% FA) and ACN (hold 3% Phase B in 2 minutes, up to 15% in 8 minutes); Detector, UV). This resulted in 7.4 mg (8.31%) of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-*N*-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]amino]pentyl)azetidine-3-sulfonamide formic acid as a yellow solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.07 (s, 1H), 9.44 (s, 1H), 8.72 (d, *J* = 5.7 Hz, 1H), 7.86 (s, 1H), 7.59 – 7.52 (m, 2H), 7.21 (s, 1H), 7.11 (s, 1H), 6.93 (s, 1H), 6.83 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.76 (s, 2H), 6.55 (s, 1H), 5.03 (dd, *J* = 13.0, 5.4 Hz, 1H), 4.02 (s, 1H), 3.83 (s, 6H), 3.60 (s, 4H), 3.29 – 3.20 (m, 2H), 3.19 – 3.08 (m, 3H), 3.01 – 2.78 (m, 4H), 2.61 – 2.51 (m, 3H), 2.06 – 1.93 (t, *J* = 12.7 Hz, 1H), 1.60 – 1.51 (m, 2H), 1.50 – 1.42 (m, 2H), 1.42 – 1.32 (m, 2H). LCMS (ESI) m/z: $[M+H]^+$ = 786.28.

Example 30 – Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)azetidine-3-sulfonamide formic acid (compound D24 formic acid)

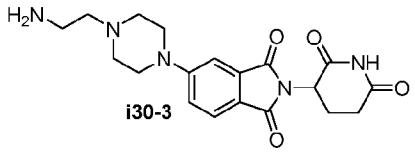


Step 1: Preparation of tert-butyl N-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)carbamate (i30-2)



To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisoindole-1,3-dione (1.50 g, 5.430 mmol, 1.00 equiv) and *tert*-butyl *N*-[2-(piperazin-1-yl)ethyl]carbamate (1.49 g, 6.516 mmol, 1.20 equiv) in NMP (10.00 mL) was added DIEA (1.40 g, 10.861 mmol, 2.00 equiv) dropwise at room temperature. The resulting mixture was stirred for 6 hours at 90 ℃ under nitrogen atmosphere. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 20 minutes; detector, UV 254 nm). This resulted in *tert*-butyl *N*-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)carbamate(2g,75.85%) as a green oil. LCMS (ESI) m/z: [M+H]+ = 486.

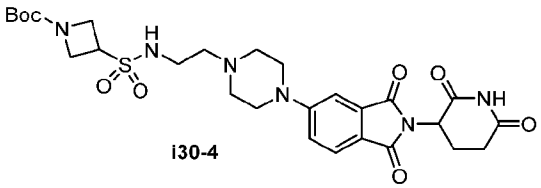
Step 2: Preparation of 5-*[4-(2-aminoethyl)piperazin-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (i30-3)*



i30-3

A solution of *tert*-butyl *N*-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl) carbamate (2.00 g, 4.119 mmol, 1.00 equiv) and TFA (2.00 mL, 26.926 mmol, 6.54 equiv) in DCM (5.00 mL, 78.650 mmol, 19.09 equiv) was stirred for 1 hours at room temperature. The resulting mixture was concentrated under vacuum. This resulted in 5-[4-(2-aminoethyl)piperazin-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (1.5 g, 94.48%) as a green solid. LCMS (ESI) m/z: [M+H]+ = 386.

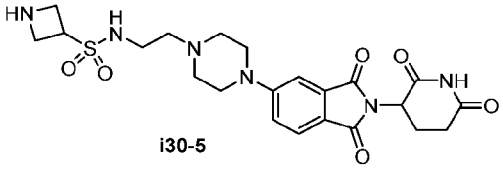
Step 3: Preparation of tert-butyl 3-[(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)sulfamoyl]azetidine-1-carboxylate (i30-4)



i30-4

To a stirred solution of 5-[4-(2-aminoethyl)piperazin-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (400.00 mg, 1.038 mmol, 1.00 equiv) and *tert*-butyl 3-(chlorosulfonyl)azetidine-1-carboxylate (318.46 mg, 1.245 mmol, 1.20 equiv) in DCM (10.00 mL) was added TEA (210.03 mg, 2.076 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred for 2 hours at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM/EtOAc (1:1) to afford *tert*-butyl 3-[(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)sulfamoyl]azetidine-1-carboxylate (500 mg, 79.68%) as a green solid. LCMS (ESI) m/z: $[M+H]^+$ = 605.

Step 4: Preparation of N-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)azetidine-3-sulfonamide (i30-5)

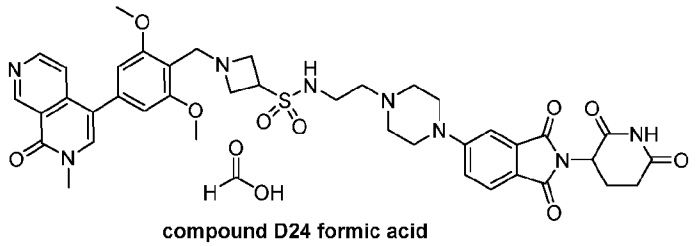


i30-5

A solution of *tert*-butyl 3-[(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl) sulfamoyl]azetidine-1-carboxylate (500.00 mg, 0.827 mmol, 1.00 equiv) and TFA (3.00 mL) in DCM (5.00 mL) was stirred for 1 hour at room temperature. The resulting mixture was concentrated

under vacuum. This resulted in *N*-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)azetidine-3-sulfonamide (400 mg, 95.87%) as a green solid. LCMS (ESI) m/z: $[M+H]^+$ = 505.

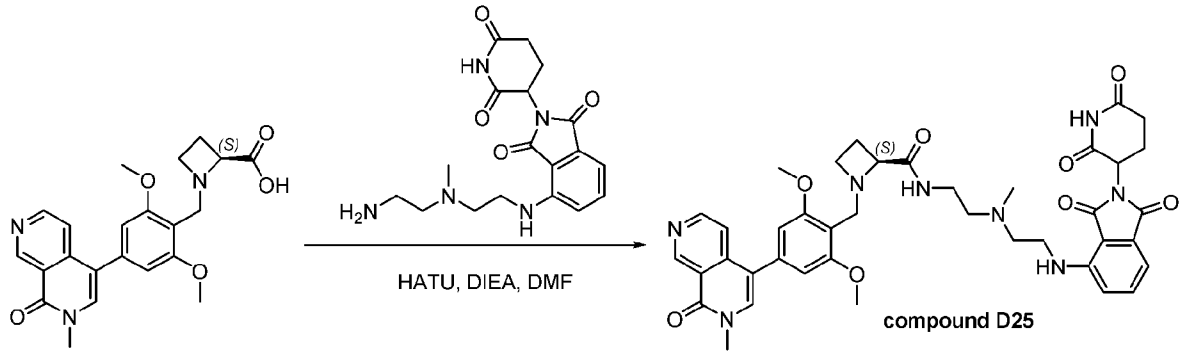
Step 5: Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)azetidine-3-sulfonamide formic acid (compound D24 formic acid)



compound D24 formic acid

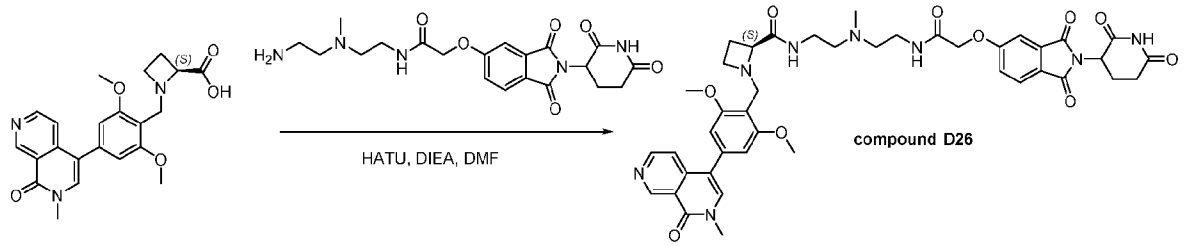
A solution of *N*-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)azetidine-3-sulfonamide (60.00 mg, 0.119 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (46.28 mg, 0.143 mmol, 1.20 equiv) in DMF (1.50 mL) was stirred for 20 minutes at room temperature. Then $NaBH_3CN$ (14.95 mg, 0.238 mmol, 2.00 equiv) was added to the reaction mixture. The resulting mixture was stirred for 1 hour at room temperature. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 20 minutes; detector, UV 254 nm). This resulted in 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-*N*-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)azetidine-3-sulfonamide (9.4 mg ,9.72%) as a green solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 12.79 (brs, 0.8H, FA(COOH)), 11.08 (s, 1H), 9.44 (s, 1H), 8.71 (d, *J* = 5.7 Hz, 1H), 8.14 (s, 0.8H, FA), 7.86 (s, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.56 (d, *J* = 5.8 Hz, 1H), 7.33 (d, *J* = 2.3 Hz, 1H), 7.24 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.11 (s, 1H), 6.73 (s, 2H), 5.07 (dd, *J* = 13.0, 5.4 Hz, 1H), 4.08 – 4.02 (m, 1H), 3.82 (s, 7H), 3.69 – 3.62 (m, 2H), 3.60 (s, 3H), 3.50 – 3.39 (m, 8H), 3.12 – 3.05 (m, 2H), 2.95 – 2.83 (m, 1H), 2.63 – 2.55 (m, 3H), 2.55 (s, 2H), 2.47 – 2.39 (m, 3H), 2.07 – 1.98 (m, 1H). LCMS (ESI) m/z: $[M+H]^+$ = 813.30.

Example 31 – Preparation of (2S)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-[2-[(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]ethyl)(methyl)amino]ethyl]azetidine-2-carboxamide (compound D25)



To a solution of (2*S*)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-2-carboxylic acid (80 mg, 0.195 mmol, 1.00 equiv) and DIEA (75.8 mg, 0.586 mmol, 3.00 equiv) in DMF (1.50 mL) was added HATU (111.4 mg, 0.293 mmol, 1.50 equiv), and the resulting solution was stirred at room temperature for 1 hour. The crude mixture was directly purified by Prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100 Å, 5 µm, 19 mm X 250 mm; Mobile Phase A: Water(0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minuteute; Gradient: 7% B to 22% B in 8 minutes; 254 nm; R_t: 7.75 minutes) to afford (2*S*)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-*N*-[2-[(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino]ethyl)(methyl)amino]ethyl]azetidine-2-carboxamide (5.5 mg, 3.5%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.45 (d, *J* = 1.1 Hz, 1H), 8.67 (d, *J* = 5.8 Hz, 1H), 7.72 (s, 1H), 7.63 (d, *J* = 5.9 Hz, 1H), 7.54-7.42 (m, 1H), 6.99 (d, *J* = 7.1 Hz, 1H), 6.91 (dd, *J* = 8.5, 3.1 Hz, 1H), 6.71 (d, *J* = 0.9 Hz, 2H), 5.13-5.02 (m, 1H), 3.86 (s, 8H), 3.66 (d, *J* = 1.0 Hz, 5H), 3.28 (s, 5H), 2.76-2.66 (m, 6H), 2.53-2.42 (m, 2H), 2.34 (s, 3H), 2.30-2.19 (m, 1H), 2.15 -1.94 (m, 2H). LCMS (ESI) m/z: [M+H]+ = 765.30.

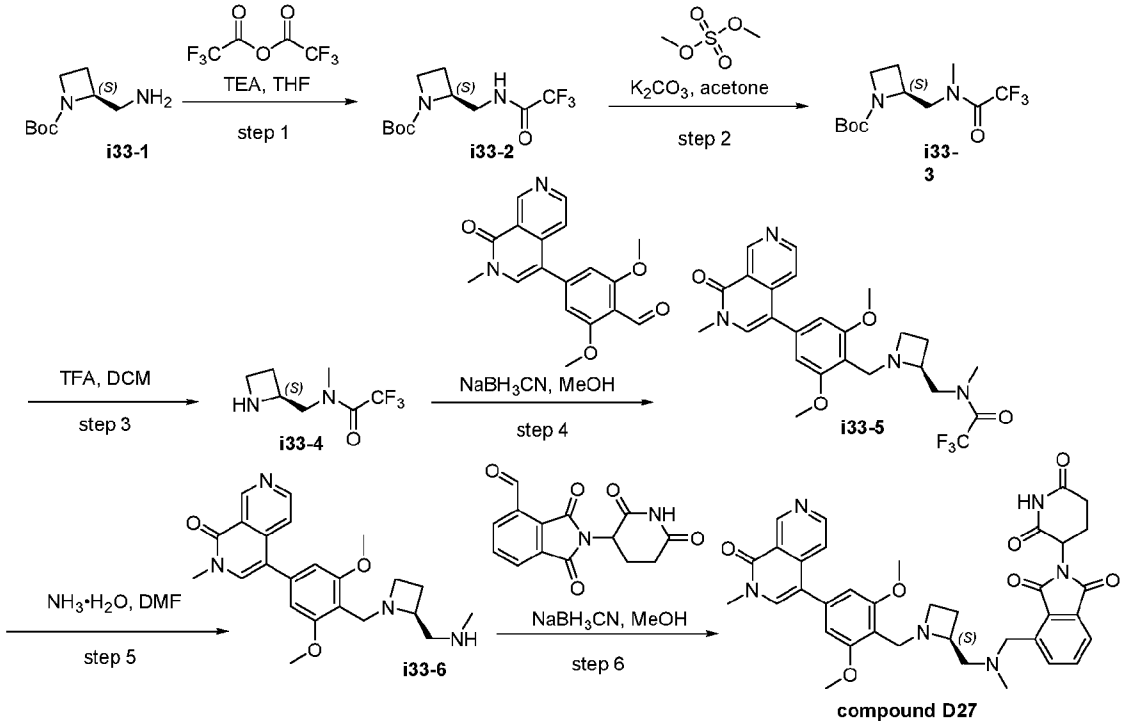
Example 32 – Preparation of *N*-[2-[(2-[[(2*S*)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidin-2-yl]formamido]ethyl)(methyl)amino]ethyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl]oxy]acetamide (compound D26)



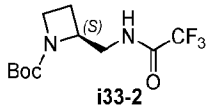
To a solution of (2*S*)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-2-carboxylic acid (30 mg, 0.073 mmol, 1.00 equiv) and DIEA (28.4 mg, 0.220

mmol, 3.00 equiv) in DMF (1.00 mL) was added HATU (41.8 mg, 0.110 mmol, 1.50 equiv) and *N*-[2-[(2-aminoethyl)(methyl)amino]ethyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl]oxy]acetamide (31.61 mg, 0.073 mmol, 1.00 equiv). The resulting solution was stirred at room temperature for 1 hour. The crude mixture was directly purified by Prep-HPLC (condition: SunFire C18 OBD Prep Column , 100 Å, 5 µm, 19 mm X 250 mm; Mobile Phase A: Water(0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minuteute; Gradient: 5% B to 5% B in 2 minutes; 254 nm; R_t: 9.88 minutes) to afford *N*-[2-[(2-[[(2*S*)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidin-2-yl]formamido]ethyl)(methyl)amino]ethyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]oxy]acetamide (4.8 mg, 7.5%) as a yellow solid. ^{1}H NMR (300 MHz, Acetonitrile-*d3*) δ 9.52 (s, 1H), 9.11 (s, 1H), 8.70 (d, *J* = 5.7 Hz, 1H), 8.20-8.02 (m, 1H), 7.79 (t, *J* = 6.5 Hz, 2H), 7.57 (d, *J* = 5.0 Hz, 2H), 7.45-7.23 (m, 2H), 6.73 (s, 2H), 4.99 (dd, *J* = 12.1, 5.3 Hz, 1H), 4.63 (s, 2H), 4.38 (s, 1H), 4.11 (s, 2H), 3.87 (s, 6H), 3.72-3.60 (m, 5H), 3.59-3.49 (m, 2H), 3.45 (d, *J* = 5.6 Hz, 2H), 3.01 (dt, *J* = 11.1, 5.7 Hz, 4H), 2.83-2.72 (m, 2H), 2.72-2.60 (m, 5H), 2.13 (ddd, *J* = 10.6, 5.5, 3.1 Hz, 2H). LCMS (ESI) m/z: [M+H]+ = 823.45.

Example 33 - Preparation of 4-(((((S)-1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)azetidin-2-yl)methyl)(methyl)amino)methyl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound D27)



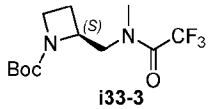
Step 1: Preparation of tert-butyl (2S)-2-((2,2,2-trifluoroacetamido)methyl)azetidine-1-carboxylate (i33-2)



i33-2

To a solution of tert-butyl (2*S*)-2-(aminomethyl)azetidine-1-carboxylate (900.00 mg, 4.832 mmol, 1.00 equiv) and trifluoroacetic anhydride (1522.33 mg, 7.248 mmol, 1.5 equiv) in THF (9.00 mL) was added TEA (977.92 mg, 9.664 mmol, 2 equiv). The mixture was stirred at 25 ℃ for 12 hours. The resulting solution was diluted with EA. Then washed with water (3 x 50 mL). The residue was applied onto a silica gel column with ethyl EA/PE(15/85). The resulting mixture were evaporated to dryness to afford *tert*-butyl (2*S*)-2-[(2,2,2-trifluoroacetamido) methyl]azetidine-1-carboxylate (1270 mg, 93.11%) as a yellow oil. LCMS (ESI) m/z: [M+H]+ = 283.

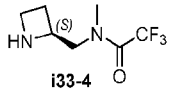
Step 2: Preparation of tert-butyl (2S)-2-[(2,2,2-trifluoro-N-methylacetamido)methyl]azetidine-1-carboxylate (i33-3)



i33-3

To a solution of *tert*-butyl (2*S*)-2-[(2,2,2-trifluoroacetamido)methyl]azetidine-1-carboxylate (1270.00 mg, 4.499 mmol, 1.00 equiv) and dimethyl sulfate (681.00 mg, 5.399 mmol, 1.2 equiv) in acetone (15.00 mL) was added K_2CO_3 (621.83 mg, 4.499 mmol, 1 equiv). The mixture was stirred at 25 ℃ for 12 hours. The resulting mixture were evaporated to dryness to afford *tert*-butyl (2*S*)-2-[(2,2,2-trifluoro-*N*-methylacetamido)methyl]azetidine-1-carboxylate (1640 mg,123.02%) as a yellow oil that was used directly without further purification. LCMS (ESI) m/z: [M+H]+ = 297.

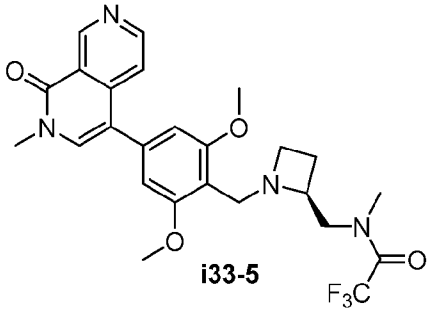
Step 3: Preparation of N-[(2S)-azetidin-2-ylmethyl]-2,2,2-trifluoro-N-methylacetamide (i33-4)



i33-4

A solution of *tert*-butyl (2*S*)-2-[(2,2,2-trifluoro-*N*-methylacetamido)methyl]azetidine-1-carboxylate (1.64 g, 5.535 mmol, 1.00 equiv) and TFA (3.50 mL, 47.121 mmol, 8.51 equiv) in DCM (16.00 mL) was stirred for 1 hour at 25 ℃. The mixture was concentrated to give *N*-[(2*S*)-azetidin-2-ylmethyl]-2,2,2-trifluoro-*N*-methylacetamide (2.08 g) as a brown oil that was used directly without further purification. LCMS (ESI) m/z: [M+H]+ = 197.

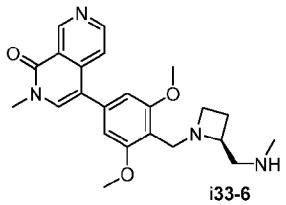
Step 4: Preparation of N-[[(2S)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] azetidin-2-yl]methyl]-2,2,2-trifluoro-N-methylacetamide (i33-5)



i33-5

To a solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde(552.00 mg, 1.702 mmol, 1.00 equiv) and *N*-[(2*S*)-azetidin-2-ylmethyl]-2,2,2-trifluoro-*N*-methylacetamide(500.81 mg, 2.553 mmol, 1.50 equiv) in DMF (6.00 mL) was added $NaBH(OAc)_3$ (721.42 mg, 3.404 mmol, 2.00 equiv). The resulting solution was stirred at 25 ℃ for 1 hour. The mixture was concentrated to give crude product that was purified by chromatography on silica gel eluted with MeOH /DCM (5:95) to give *N*-[[(2S)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]azetidin-2-yl]methyl]-2,2,2-trifluoro-*N*-methylacetamide (275 mg, 32.03%) as an off-white solid. LCMS (ESI) m/z: [M+H]+ = 505.

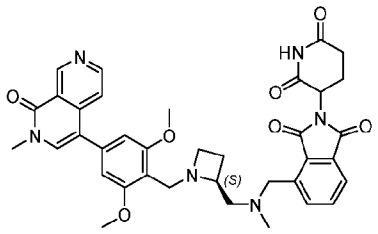
Step 5: Preparation of (S)-4-(3,5-dimethoxy-4-((2-((methylamino)methyl)azetidin-1-yl)methyl)phenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (i33-6)



i33-6

A solution of *N*-[[(2*R*)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] azetidin-2-yl]methyl]-2,2,2-trifluoro-*N*-methylacetamide (230 mg, 0.456 mmol, 1.00 equiv) and $NH_3{\cdot}H_2O$ (1 mL, 0.008 mmol, 0.05 equiv) in DMF(2.50 mL) was stirred at 25 ℃ for 1 hour. The resulting mixture were evaporated to dryness to afford 4-(3,5-dimethoxy-4-[[(2R)-2-[(methylamino) methyl]azetidin-1-yl]methyl]phenyl)-2-methyl-2,7-naphthyridin-1-one(219mg) as a brown oil that was used directly without further purification. LCMS (ESI) m/z: [M+H]+ = 409.

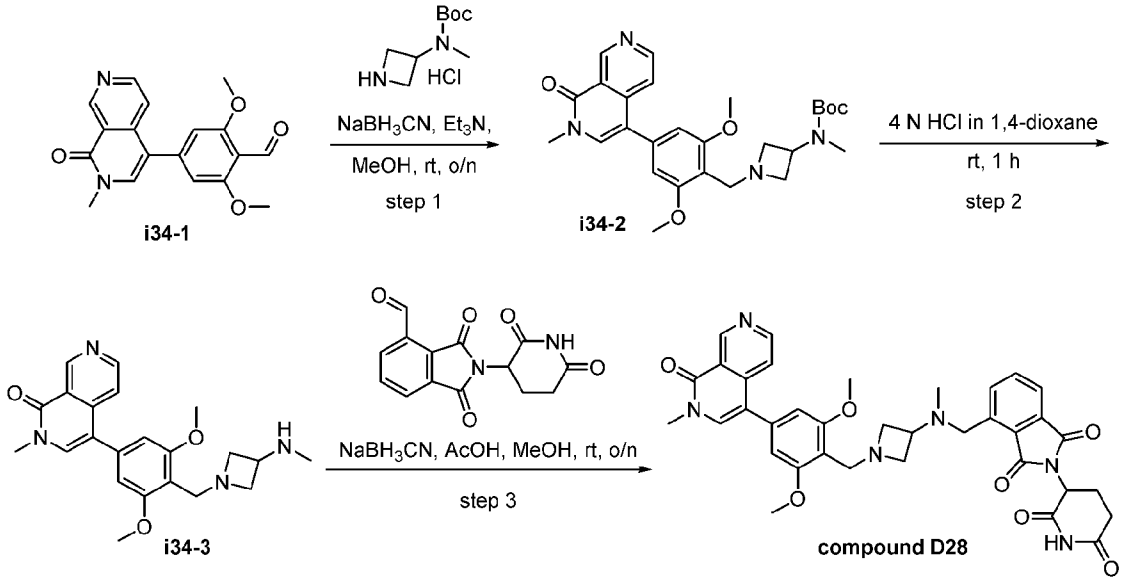
Step 6: Preparation of 4-(((((S)-1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)azetidin-2-yl)methyl)(methyl)amino)methyl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound D27)



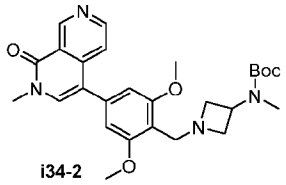
compound D27

To a stirred solution of 4-(3,5-dimethoxy-4-[[(2*R*)-2-[(methylamino)methyl]azetidin-1-yl]methyl]phenyl)-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (150.00 mg, 0.367 mmol, 1.00 equiv) and 2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindole-4-carbaldehyde (105.11 mg, 0.367 mmol, 1.00 equiv) in MeOH (2.00 mL) was added $NaBH_3CN$ (115.38 mg, 1.836 mmol, 5 equiv). The mixture was stirred at 25 ℃ for 1 hour. Without any additional work-up, the mixture was purified by prep-HPLC (conditions: SunFire C18 OBD Prep Column , 100Å, 5 µm, 19 mm X 250 mm; Mobile Phase A: Water (0.05%TFA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 3% B to 3% B in 2 minutes; 254 nm; Rt: 14.55 minutes) to give 4-(((((S)-1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)azetidin-2-yl)methyl)(methyl)amino)methyl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (8.0 mg, 3.01 %) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.54 (s, 1H), 8.67 (d, *J* = 5.7 Hz, 1H), 8.57 (s, 0.4H, FA), 7.91 – 7.86 (m, 1H), 7.84 (d, *J* = 6.0 Hz, 2H), 7.74 (d, *J* = 6.5 Hz, 1H), 7.57 (t, *J* = 6.3 Hz, 1H), 6.84 (d, *J* = 5.4 Hz, 2H), 5.20 – 5.08 (m, 1H), 4.72 – 4.31 (m, 3H), 4.15 – 3.98 (m, 3H), 3.92 (d, *J* = 11.5 Hz, 6H), 3.71 (d, *J* = 1.8 Hz, 3H), 2.99 – 2.80 (m, 3H), 2.80 – 2.49 (m, 4H), 2.38 – 1.98 (m, 5H). LCMS (ESI) m/z: [M+H]+ = 679.30.

Example 34 – Preparation of 4-(((1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)azetidin-3-yl)(methyl)amino)methyl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound D28)

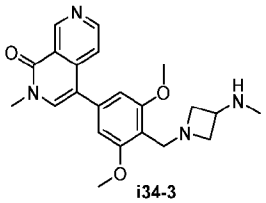


Step 1: Preparation of tert-butyl (1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)azetidin-3-yl)(methyl)carbamate (i34-2)



To a solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl) benzaldehyde (250.00 mg, 0.772mmol, 1.00 equiv) and *tert*-butyl azetidin-3-yl(methyl) carbamate hydrochloride (171.38 mg, 0.772 mmol, 1.00 equiv), was added Et_3N (77.97 mg, 0.772 mmol, 1.00 equiv) and $NaBH_3CN$ (97.27 mg, 1.544 mmol, 2.00 equiv). The resulting mixture was stirred overnight. The mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA in PE from 0% to 40% to afford *tert*-butyl (1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)azetidin-3-yl)(methyl) carbamate (170 mg, 0.344 mmol, 44.62%) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ =495.

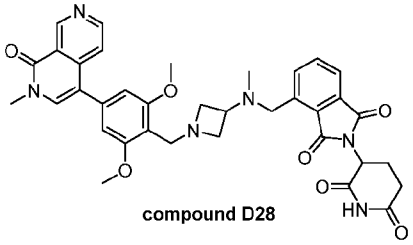
Step 2: Preparation of 4-(3,5-dimethoxy-4-((3-(methylamino)azetidin-1-yl)methyl)phenyl) -2-methyl-2,7-naphthyridin-1(2H)-one (i34-3)



i34-3

Tert-butyl(1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl) azetidin-3-yl) (methyl) carbamate (170 mg, 0.344 mmol, 1.00 equiv) was dissolved in 4 N HCl in 1,4-dioxane (5 mL, 20 mmol, 58.13 equiv). The resulting solution was stirred for one hour at room temperature. The resulting mixture was concentrated to afford 4-(3,5-dimethoxy-4-((3-(methylamino)azetidin-1-yl)methyl)phenyl)-2-methyl-2,7-naphthyridin-1(2*H*)-one (180 mg, crude) as a white solid, that was used directly without further purification. LCMS (ESI) m/z: $[M+H]^+$ =395.

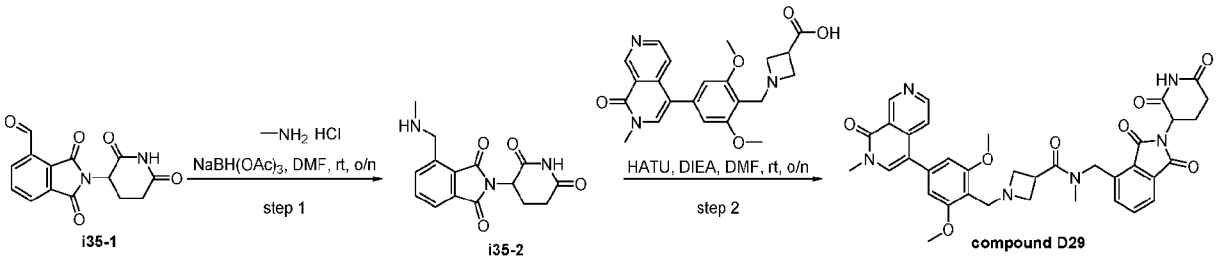
Step 3: Preparation of 4-(((1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)azetidin-3-yl)(methyl)amino)methyl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound D28)



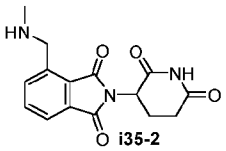
compound D28

To a mixture of 4-(3,5-dimethoxy-4-[[3-(methylamino)azetidin-1-yl]methyl]phenyl)-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (30.00 mg, 0.076 mmol, 1.00 equiv) and 2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo- 2,3-dihydro-1H-isoindole-4-carbaldehyde (21.77 mg, 0.076 mmol, 1.00 equiv) in MeOH (2.00 mL) was added AcOH (0.05 mg, 0.001 mmol, 0.01 equiv). The mixture was stirred for 1 hour. $NaBH_3CN$ (9.56 mg, 0.152 mmol, 2.00 equiv) was added. The resulting mixture was stirred for 1 hour. The crude product was purified by preparative HPLC (condition: SunFire C_{18} OBD Prep Column, 100 Å, 5 µm, 19 mm X 250 mm; Mobile Phase A: Water(0.05% TFA), Mobile Phase B: ACN; Flow rate: 25 mL/minuteute; Gradient: 5% B to 5% B in 2 minutes; 254 nm; R_t: 12.63 minutes. This afforded 4-[[(1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7- naphthyridin-4-yl)phenyl]methyl]azetidin-3-yl)(methyl)amino]methyl]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (18.90 mg, 0.028 mmol, 36.53%) as a light yellow solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.60 (s, 1H), 8.70 (d, *J* = 6.3 Hz, 1H), 8.00 (s, 1H), 7.96 – 7.82 (m, 4H), 6.88 (s, 2H), 5.17 (dd, *J* = 12.4, 5.4 Hz, 1H), 4.58 (s, 2H), 4.33 (t, *J* = 7.2 Hz, 4H), 4.10 (d, *J* = 13.2 Hz, 1H), 4.02 (d, *J* = 13.2 Hz, 1H), 3.97 (s, 6H), 3.75 (s, 4H), 2.95 – 2.83 (m, 1H), 2.81 – 2.67 (m, 2H), 2.29 (s, 3H), 2.21–2.11 (m, 1H). LCMS (ESI) m/z: $[M+H]^+$ =665.30.

Example 35 - Preparation of 1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-N-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)methyl)-N-methylazetidine-3-carboxamide (compound D29)

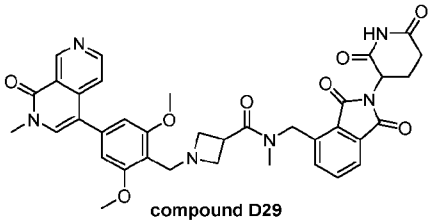


Step 1: Preparation of 2-(2,6-dioxopiperidin-3-yl)-4-((methylamino)methyl)isoindoline-1,3-dione (i35-2)



To a solution of 2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindoline-4-carbaldehyde (70.00 mg, 0.245 mmol, 1.00 equiv) in DMF (3.00 mL) was added methanamine hydrochloride (24.77 mg, 0.367 mmol, 1.50 equiv). The resulting mixture was stirred overnight at room temperature. Then $NaBH(OAc)_3$ (103.88 mg, 0.490 mmol, 2.00 equiv) was added. The resulting mixture was stirred for 1 hour at room temperature. The resulting mixture was purified by reverse phase column with ACN in water from (0% to 50%) to afford 2-(2,6-dioxopiperidin-3-yl)-4- ((methylamino)methyl)isoindoline-1,3-dione (30 mg, 41.10%) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ =302.

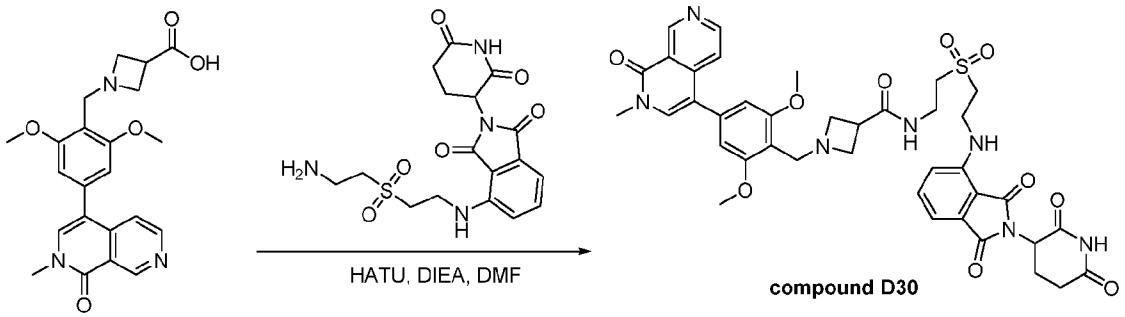
Step 2: Preparation of 1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-N-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)methyl)-N-methylazetidine-3-carboxamide (compound D29)



To a mixture of 1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)azetidine-3-carboxylic acid (40.77 mg, 0.100 mmol, 1.00 equiv) in DMF (3.00 mL) was added HATU (94.65 mg, 0.250 mmol, 2.50 equiv) and DIEA (38.61 mg, 0.300 mmol, 3.00 equiv). The resulting mixture was stirred for 2 hours at room temperature. Then 2-(2,6-dioxopiperidin-3-yl)-4-((methylamino)methyl)isoindoline-1,3-dione (30.00 mg, 0.100 mmol, 1.00 equiv) was added. The resulting mixture was stirred for 1 hour. The crude product was purified by preparative HPLC (conditions:

XSelect CSH Prep C_{18} OBD Column, 5 µm, 19*150 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minuteute; Gradient: 12% B to 12% B in 2 minutes; 254/220 nm; R_t: 13.57 min Fractions containing the desired compound were evaporated to dryness to afford 1-(2,6-dimethoxy-4-(2-methyl-1-oxo- 1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-*N*-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)methyl)-N-methylazetidine-3-carboxamide (17.10 mg, 24.25%) as a light yellow solid. ^{1}H-NMR (400 MHz, Methanol-*d4*) δ 9.58 (s, 1H), 8.69 (t, *J* = 7.8 Hz, 1H), 7.98–7.87 (m, 2H), 7.85 – 7.77 (m, 2H), 7.72 - 7.64 (m, 1H), 6.89 (d, *J* = 8.2 Hz, 2H), 5.22 – 5.01 (m, 3H), 4.65 – 4.36 (m, 5H), 4.34 - 4.21 (m, 1H), 4.20 - 4.07 (m, 1H), 4.01 – 3.92 (m, 6H), 3.74 (s, 3H), 3.02 (s, 3H), 2.96 – 2.84 (m, 1H), 2.80 – 2.71 (m, 2H), 2.24 – 2.12 (m, 1H). LCMS (ESI) m/z: $[M+H]^+$ =693.35.

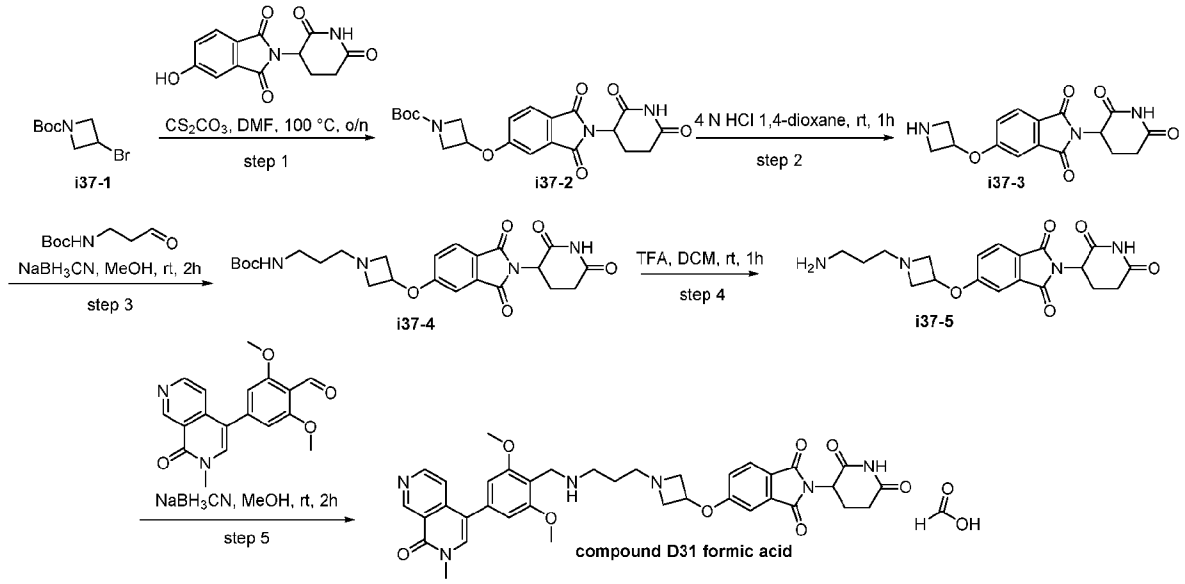
Example 36 – Preparation of 1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-N-(2-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)sulfonyl)ethyl)azetidine-3-carboxamide (compound D30)



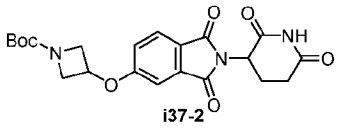
Into a stirred mixture of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] azetidine-3-carboxylic acid (53.00 mg, 0.129 mmol, 1.00 equiv) and DIEA (*N,N*-diisopropylamine) (50.19 mg, 0.388 mmol, 3.00 equiv) in DMF (dimethylformamide) (1.00 mL) was added 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate, N-[(Dimethylamino)-1H-1,2,3-triazolo-[4,5-b]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide (HATU) (73.83 mg, 0.194 mmol, 1.50 equiv) at 0 ℃. After 10 minutes, to the above mixture was added 4-[[2-(2-aminoethanesulfonyl) ethyl]amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (63.44 mg, 0.155 mmol, 1.20 equiv). Then the reaction was stirred at room temperature for 2 hours under N_2 atmosphere. The crude product was purified by Prep-HPLC (conditions: Sunfire C18 OBD Prep Column, 5 µm, 19mm*250 mm; Mobile Phase A: Water (0.05% TFA, trifluoroacetic acid), Mobile Phase B: acetonitrile (MeCN or ACN); Flow rate: 25 mL/minuteute; Gradient: 3% B to 3% B in 2 minutes; 254 nm; R_t: 13.98 minutes). This resulted in 1-*(2,6*-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-*N*-(2-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)sulfonyl)ethyl)azetidine-3-carboxamide 18.4 mg (16.47%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.52 (d, *J* = 0.8 Hz, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.56 (br s, 0.5 H, FA), 7.77 (s, 1H), 7.67-7.55 (m, 2H), 7.13 (t, *J* = 7 .6 Hz, 2H), 6.83 (s, 2H), 5.06 (dd, *J* = 12.3, 5.4 Hz, 1H), 4.37 (s, 2H), 4.23-4.06 (m, 4H), 3.95 (s, 6H), 3.89 (t, *J* = 6.3 Hz, 2H), 3.77-3.69 (m, 2H), 3.71 (s, 3H), 3.52 (q, *J* = 6.9,

6.3 Hz, 3H), 3.38 (t, J = 6.3 Hz, 2H), 2.62-2.93 (m, 3H), 2.07-2.17 (m, 1H). LCMS (ESI) m/z: $[M+H]^+$ = 800.35.

Example 37 – Preparation of 5-((1-(3-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4 -yl)benzyl)amino)propyl)azetidin-3-yl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (compound D31 formic acid)

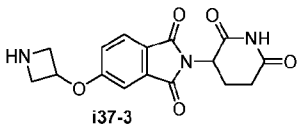


Step 1: Preparation of tert-butyl 3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)azetidine-1-carboxylate (i37-2)



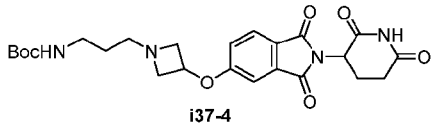
To a mixture of *tert*-butyl 3-bromoazetidine-1-carboxylate (2.00 g, 8.511 mmol, 1.00 equiv) and 2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindoline-1,3-dione (2.33 g, 8.511 mmol, 1.00 equiv) in DMF (30.00 mL) was added Cs_2CO_3 (5.53 g, 17.022 mmol, 2.00 equiv). The resulting mixture was stirred overnight at 90 °C. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA in PE from 0% to 50% to afford *tert*-butyl 3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)azetidine -1-carboxylate (400 mg, 10.96%) as a light yellow solid. LCMS (ESI) m/z: [M+H]+ = 430.

Step 2: Preparation of 5-(azetidin-3-yloxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (i37-3)



To a solution of *tert*-butyl 3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)azetidine -1-carboxylate (400.00 mg, 0.932 mmol, 1.00 equiv) in 1,4-dioxane (5 mL) was added HCl (4 N in 1,4-dioxane) (5 mL, 20.000 mmol, 21.46 equiv). The resulting solution was stirred for 1 hour at room temperature. The resulting mixture was concentrated under vacuum to afford 5-(azetidin-3-yloxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (440.00 mg, crude) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 330.

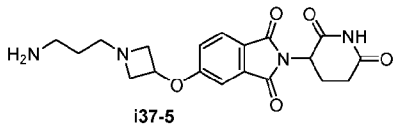
Step 3: Preparation of tert-butyl (3-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy) zetidin-1-yl)propyl)carbamate (i37-4)



i37-4

A mixture of 5-(azetidin-3-yloxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (200.00 mg, 0.608 mmol, 1.00 equiv) and *tert*-butyl (3-oxopropyl)carbamate (105.18 mg, 0.608 mmol, 1.00 equiv) in MeOH (5.00 mL) was stirred for 1.5 hours at room temperature. Then $NaBH_3CN$ (75.39 mg, 1.216 mmol, 2.00 equiv) was added. The resulting mixture was stirred for 1 hour at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatograpy, eluted with EA in PE from 0% to 50% to afford *tert*-butyl (3-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)zetidin -1-yl)propyl)carbamate (100.00 mg, 33.89%) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 487.

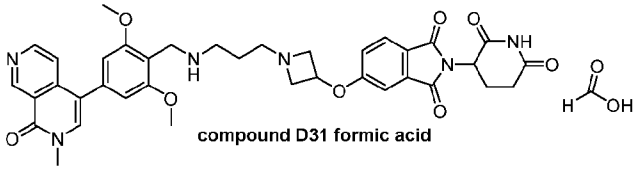
Step 4: Preparation of 5-((1-(3-aminopropyl)azetidin-3-yl)oxy)-2-(2,6-dioxopiperidin-3–yl) isoindoline-1,3-dione (i37-5)



i37-5

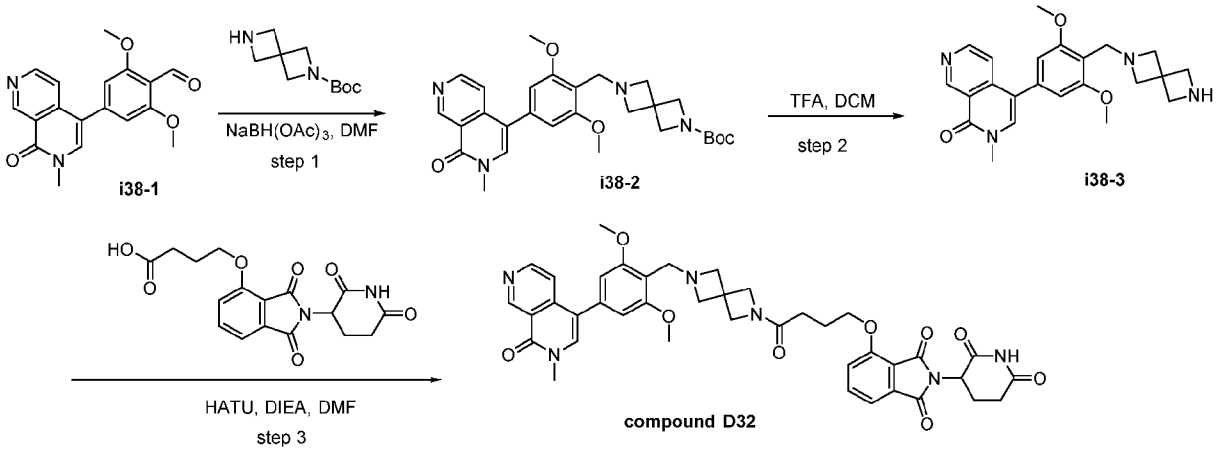
To a solution of *tert*-butyl (3-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy) azetidin-1-yl)propyl)carbamate (100.00 mg, 0.206 mmol, 1.00 equiv) in DCM (4.00 mL) was added TFA (4.00 mL, 53.860 mmol, 261.46 equiv). The resulting mixture was stirred for one hour at room temperature. The resulting mixture was concentrated under vacuum to afford 5-((1-(3-aminopropyl)azetidin-3-yl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione(120 mg , crude). LCMS (ESI) m/z: [M+H]+ = 387.

Step 5: Preparation of 5-((1-(3-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)amino)propyl)azetidin-3-yl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (compound D31 formic acid)

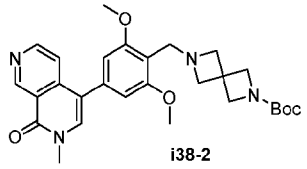


To a solution of 5-((1-(3-aminopropyl)azetidin-3-yl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline -1,3-dione (60.00 mg, 0.155 mmol, 1.00 equiv) in MeOH (5.00 mL, 123.495 mmol, 795.32 equiv) was added 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (50.36 mg, 0.155 mmol, 1 equiv). The resulting mixture was stirred for 1 hour. Then $NaBH_3CN$ (19.52 mg, 0.311 mmol, 2 equiv) was added. The resulting mixture was stirred for 1 hour. The resulting mixture was filtered, and the filtrate was purified by prep-HPLC (conditions: SunFire C_{18} OBD Prep Column , 100Å, 5 µm, 19 mm X 250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 5% B to 5% B in 2 minutes; 254 nm; Rt: 9.75 minutes) to afford 5-((1-(3-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)amino)propyl)azetidin-3-yl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione;formate (14.4 mg, 12.52%) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.52 (s, 1H), 8.67 (d, *J* = 5.7 Hz, 1H), 8.26 (br s, 0.65H, FA), 7.82 – 7.75 (m, 2H), 7.60 (dd, *J* = 5.8, 0.9 Hz, 1H), 7.21 (dq, *J* = 4.6, 2.3 Hz, 2H), 6.88 (s, 2H), 5.13 – 5.00 (m, 2H), 4.36 (s, 2H), 3.99 (s, 6H), 3.93 – 3.89 (m, 2H), 3.71 (s, 3H), 3.44 (d, *J* = 8.2 Hz, 2H), 3.22 (t, *J* = 6.7 Hz, 2H), 2.95 – 2.82 (m, 3H), 2.82 – 2.62 (m, 2H), 2.21 – 2.05 (m, 1H), 1.89 – 1.81 (m, 2H). LCMS (ESI) m/z: $[M+H]^+$ = 695.40.

Example 38 – Preparation of 4-(4-(6-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-2,6-diazaspiro[3.3]heptan-2-yl)-4-oxobutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound D32)



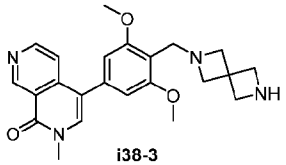
Step 1: Preparation of tert-butyl 6-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (i38-2)



i38-2

To a solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde(700.00 mg, 2.158 mmol, 1.00 equiv) and *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate (427.91 mg, 2.158 mmol, 1.00 equiv) in DMF (10.00 mL, 129.218 mmol, 59.87 equiv) was added $NaBH(OAc)_3$ (914.85 mg, 4.317 mmol, 2.00 equiv). The resulting solution was stirred at 25 °C for 1 hour. The mixture was concentrated to give crude product that was purified by chromatography on silica gel eluted with MeOH /DCM (6:94) to give *tert*-butyl6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-2,6-diazaspiro [3.3] heptane-2-carboxylate(808mg,73.90%) as an off-white solid. LCMS (ESI) m/z: [M+H]+ = 507.

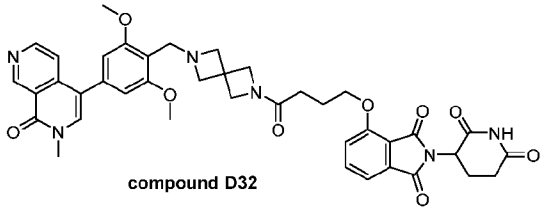
Step 2: Preparation of 4-(4-((2,6-diazaspiro[3.3]heptan-2-yl)methyl)-3,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (i38-3)



i38-3

A solution of *tert*-butyl 6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl] methyl]-2,6-diazaspiro[3.3]heptane-2-carboxylate (708.00 mg, 1.398 mmol, 1.00 equiv) and TFA (1.50 mL, 20.195 mmol, 14.45 equiv) in DCM (7.00 mL, 110.110 mmol, 78.79 equiv) was stirred at 25 °C for 1 hour. The mixture was concentrated to give crude product 4-(4-[2, 6-diazaspiro[3.3]heptan-2-ylmethyl]-3,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1-one(696mg) as a brown oil that was used directly without further purification. LCMS (ESI) m/z: [M+H]+ = 407.

Step 3: Preparation of 4-(4-(6-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-2,6-diazaspiro[3.3]heptan-2-yl)-4-oxobutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound D32)

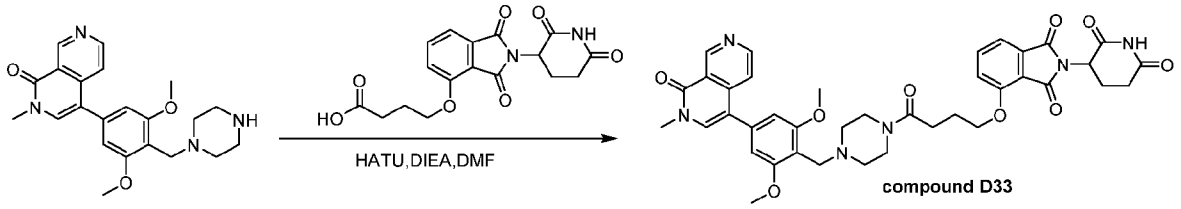


compound D32

To a solution of 4-(4-[2,6-diazaspiro[3.3]heptan-2-ylmethyl]-3,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1-one (40.00 mg, 0.098 mmol, 1.00 equiv) and 4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoi

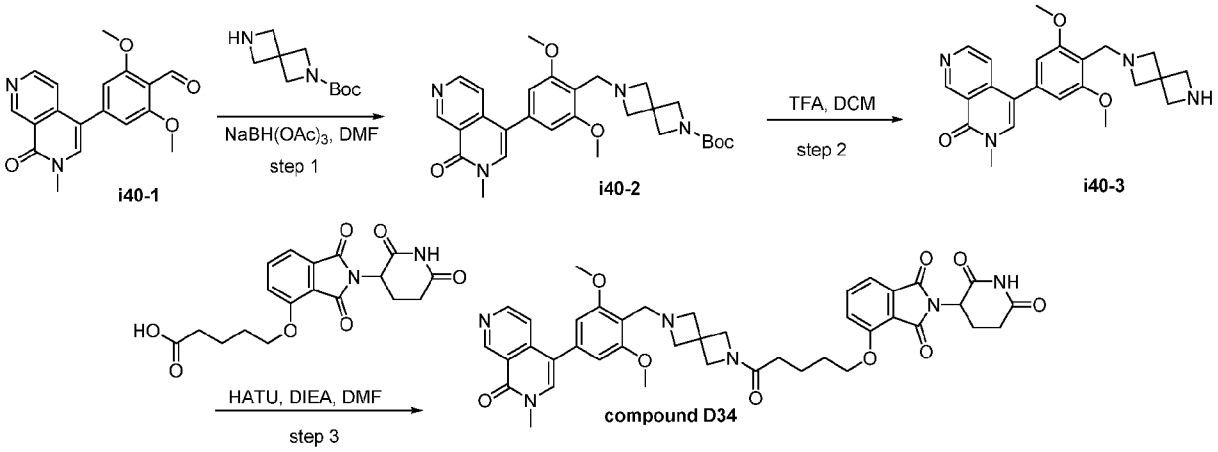
soindol-4-yl]oxy]butanoic acid (35.46 mg, 0.098 mmol, 1.00 equiv) in DMF (1.0 mL) was added HATU (56.12 mg, 0.148 mmol, 1.5 equiv) and DIEA (31.80 mg, 0.246 mmol, 10 equiv). The mixture was stirred at 25 ℃ for 1 hour. The mixture was purified by prep-HPLC (conditions: Kinetex EVO C18 Column 21.2*150, 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 16% B to 26% B in 8 minutes; 254/220 nm; Rt: 7.03 minutes) to afford 4-[4-(6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-2,6-diazaspiro[3.3]heptan-2-yl)-4-oxobutoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (12 mg, 16.29%) as a white solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.53 (s, 1H), 8.70 (d, *J* = 5.8 Hz, 1H), 7.79 (dd, *J* = 8.5, 7.4 Hz, 1H), 7.78 (s, 1H), 7.62 (d, *J* = 5.8 Hz, 1H), 7.46 (dd, *J* = 14.7, 7.9 Hz, 2H), 6.86 (s, 2H), 5.13 (dd, *J* = 12.5, 5.4 Hz, 1H), 4.60 (s, 1H), 4.40 (d, *J* = 13.7 Hz, 4H), 4.32 – 4.19 (m, 6H), 4.14 (s, 2H), 3.96 (s, 6H), 3.71 (s, 3H), 2.95 – 2.68 (m, 3H), 2.53 – 2.34 (m, 2H), 2.20 – 2.10 (m, 3H). LCMS (ESI) m/z: [M+H]+ = 749.40.

Example 39 – Preparation of 4-(4-(4-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl) piperazin-1-yl)-4-oxobutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound D33)

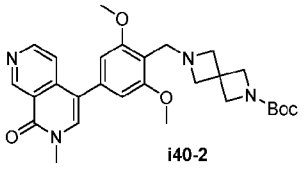


To a stirred mixture of 4-[3,5-dimethoxy-4-(piperazin-1-ylmethyl)phenyl]-2-methyl-2,7-naphthyridin-1-one (50.00 mg, 0.127 mmol, 1.00 equiv) and 4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]butanoic acid (45.67 mg, 0.127 mmol, 1.00 equiv) in DMF (2.00 mL) was added DIEA (163.82 mg, 1.268 mmol, 10.00 equiv) and HATU (96.39 mg, 0.254 mmol, 2.00 equiv) at 0 ℃. The above mixture was stirred for 3 hours at room temperature. Then the crude product was purified by preparative HPLC (conditions: XBridge Shield RP18 OBD Column, 5 μm, 19*250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 12% B to 26% B in 8 minutes; 254 nm; Rt: 7.91 minutes). This resulted in 4-(4-(4-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)piperazin-1-yl)-4-oxobutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (5.60 mg, 5.54%) as a white solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.54 (s, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 7.85 – 7.73 (m, 2H), 7.63 (d, *J* = 5.7 Hz, 1H), 7.52 – 7.43 (m, 2H), 6.79 (s, 2H), 5.11 (dd, *J* = 12.2, 5.4 Hz, 1H), 4.30 (t, *J* = 5.8 Hz, 2H), 4.01 (s, 2H), 3.90 (s, 6H), 3.81 – 3.65 (m, 7H), 2.98 – 2.81 (m, 6H), 2.79 – 2.67 (m, 3H), 2.24 – 2.07 (m, 3H). vLCMS (ESI) m/z: $[M+H]^+$ = 737.40.

Example 40 – Preparation of 4-((5-(6-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-2,6-diazaspiro[3.3]heptan-2-yl)-5-oxopentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound D34)

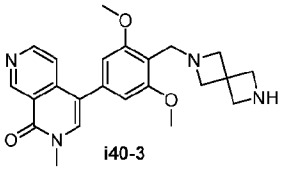


Step 1: Preparation of tert-butyl 6-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (i40-2)



To a solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (700.00 mg, 2.158 mmol, 1.00 equiv) and *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate (427.91 mg, 2.158 mmol, 1.00 equiv) in DMF (10.00 mL, 129.218 mmol, 59.87 equiv) was added $NaBH(OAc)_3$ (914.85 mg, 4.317 mmol, 2.00 equiv). The resulting solution was stirred at 25 ℃ for 1 hour. The mixture was concentrated to give crude product that was purified by chromatography on silica gel eluted with MeOH]/DCM (6:94) to give *tert*-butyl 6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl] methyl]-2,6-diazaspiro[3.3]heptane-2-carboxylate(808mg,73.90%) as an off-white solid. LCMS (ESI) m/z: [M+H]+ = 507.

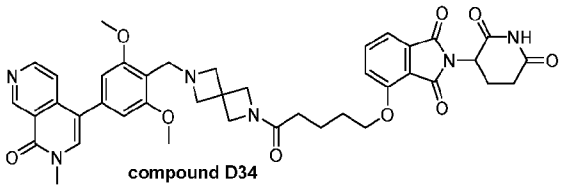
Step 2: Preparation of 4-(4-((2,6-diazaspiro[3.3]heptan-2-yl)methyl)-3,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (i40-3)



A solution of *tert*-butyl 6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] -2,6-diazaspiro[3.3]heptane-2-carboxylate (708.00 mg, 1.398 mmol, 1.00 equiv) and TFA (1.50 mL, 20.195 mmol, 14.45 equiv) in DCM (7 mL) was stirred at 25 ℃ for 1 hour. The mixture was concentrated to give crude product 4-(4-[2,6-diazaspiro[3.3]heptan-2-ylmethyl]-3,5-dimethoxyphenyl)-2-methyl-2,7-

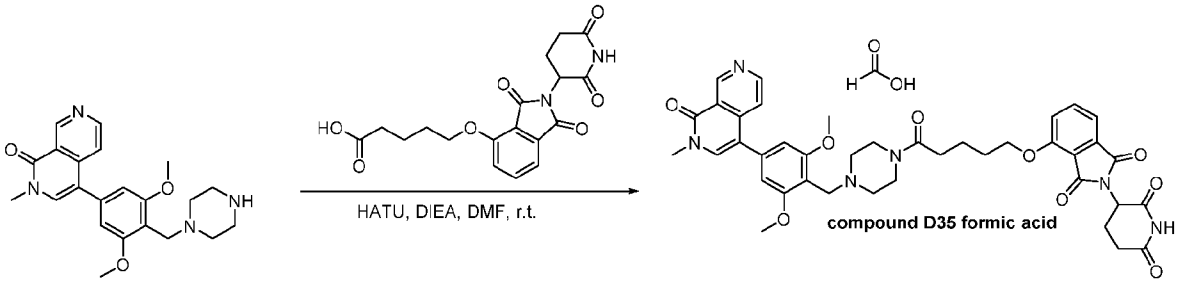
naphthyridin-1-one (696 mg) as a brown oil that was used directly without further purification. LCMS (ESI) m/z: [M+H]+ = 407.

Step 3: Preparation of 4-((5-(6-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl) -2,6-diazaspiro[3.3]heptan-2-yl)-5-oxopentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound D34)



To a solution of 4-(4-[2,6-diazaspiro[3.3]heptan-2-ylmethyl]-3,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1-one (40.00 mg, 0.098 mmol, 1.00 equiv) and 5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]pentanoic acid (36.84 mg, 0.098 mmol, 1 equiv) in DMF(1 mL) was added HATU (56.12 mg, 0.148 mmol, 1.5 equiv) and DIEA (31.80 mg, 0.246 mmol, 10 equiv). The mixture was stirred at 25 ℃ for 1 hour. The mixture was purified by prep-HPLC (conditions: XSelect CSH Prep C18 OBD Column, 5 μm, 19*150 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 12% B to 22% B in 12 minutes; 254/220 nm; Rt: 10.52 minutes) to afford 4-[[5-(6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-2,6-diazaspiro[3.3]heptan-2-yl)-5-oxop entyl]oxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (10.1 mg, 13.46%) as a light yellow solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.58 (s, 1H), 8.73 – 8.67 (m, 1H), 7.92 (d, *J* = 6.9 Hz, 1H), 7.84 – 7.76 (m, 1H), 7.47 (t, *J* = 8.1 Hz, 2H), 6.89 (d, *J* = 3.5 Hz, 2H), 5.17 – 5.07 (m, 1H), 4.51 (d, *J* = 3.0 Hz, 2H), 4.45 – 4.31 (m, 6H), 4.27 (t, *J* = 5.5 Hz, 2H), 4.19 (s, 1H), 4.12 (s, 1H), 3.98 (d, *J* = 3.4 Hz, 6H), 3.74 (d, *J* = 1.7 Hz, 3H), 2.96 – 2.65 (m, 3H), 2.34 – 2.30 (m, 2H), 2.19 – 2.12 (m, 1H), 1.96 – 1.89 (m, 2H), 1.88 – 1.80 (m, 2H). LCMS (ESI) m/z: [M+H]+ = 763.40.

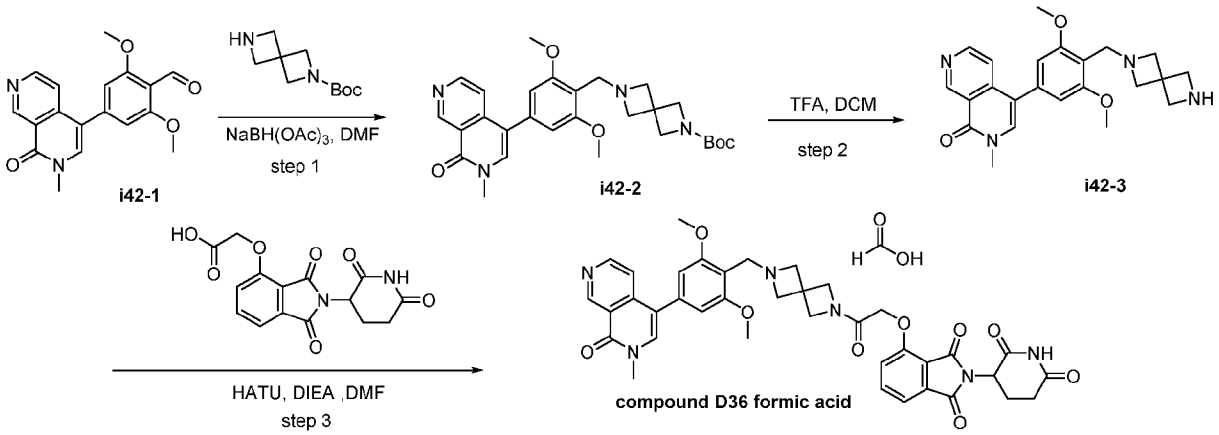
Example 41 – Preparation of 4-((5-(4-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)piperazin-1-yl)-5-oxopentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (compound D35 formic acid)



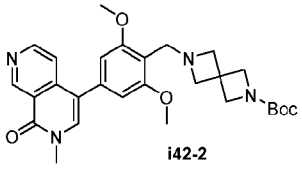
To a stirred solution of 4-[3,5-dimethoxy-4-(piperazin-1-ylmethyl)phenyl]-2-methyl-2,7-naphthyridin-1-one (50.0 mg, 0.127 mmol, 1.00 equiv) and 5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-

dioxoisoindol-4-yl]oxy]pentanoic acid (47.5 mg, 0.127 mmol, 1.00 equiv) in DMF (1 mL) was added DIEA (163.8 mg, 1.268 mmol, 10.00 equiv) dropwise at room temperature. The resulting mixture was stirred for 10 min at room temperature. To the above mixture was added HATU (96.4 mg, 0.254 mmol, 2.00 equiv). The resulting mixture was stirred for additional 2 hours at room temperature. The residue was purified by reverse flash chromatography (conditions: SunFire C18 OBD Prep Column, 100Å, 5 µm, 19 mm X 250 mm; Mobile Phase A: Water(0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 9 B to 27 B in 10 minutes; 254 nm; R_T: 10.12) to afford 4-[[5-(4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]piperazin-1-yl)-5-oxopentyl]oxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (6.6 mg, 6.7%) as a white solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.53 (d, *J* = 0.9 Hz, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.45 (br s, 0.13H, FA), 7.81 – 7.73 (m, 2H), 7.64 (dd, *J* = 5.8, 0.9 Hz, 1H), 7.45 (dd, *J* = 7.9, 6.2 Hz, 2H), 6.79 (s, 2H), 5.11 (dd, *J* = 12.5, 5.5 Hz, 1H), 4.28 (t, *J* = 5.7 Hz, 2H), 3.97 (s, 2H), 3.90 (s, 6H), 3.74 – 3.62 (m, 7H), 2.95 – 2.81 (m, 3H), 2.80 – 2.65 (m, 4H), 2.60 (t, *J* = 7.4 Hz, 2H), 2.17 – 2.07 (m, 1H), 1.99 – 1.83 (m, 4H). LCMS (ESI) m/z: [M+H]+ = 751.40

Example 42 – Preparation of 4-(2-(6-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-2,6-diazaspiro[3.3]heptan-2-yl)-2-oxoethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound D36 formic acid)



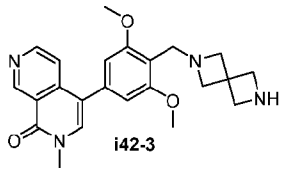
Step 1: Preparation of tert-butyl 6-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (i42-2)



To a solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (700.00 mg, 2.158 mmol, 1.00 equiv) and *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate (427.91 mg, 2.158 mmol, 1.00 equiv) in DMF(10 mL) was added $NaBH(OAc)_3$ (914.85 mg, 4.317 mmol, 2.00 equiv). The

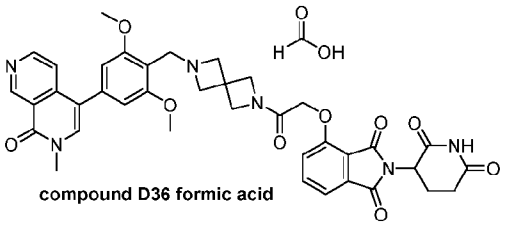
resulting solution was stirred at 25 °C for 1 hour. The mixture was concentrated to give crude product that was purified by chromatography on silica gel eluted with MeOH]/DCM (6:94) to give *tert*-butyl 6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-2,6-diazaspiro[3.3]heptane-2-carboxyl ate(808mg,73.90%) as an off-white solid. LCMS (ESI) m/z: [M+H]+ = 507.

Step 2: Preparation of 4-(4-((2,6-diazaspiro[3.3]heptan-2-yl)methyl)-3,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (i42-3)



To a solution of *tert*-butyl 6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl] methyl]-2,6-diazaspiro[3.3]heptane-2-carboxylate (708.00 mg, 1.398 mmol, 1.00 equiv) and TFA (1.50 mL, 20.195 mmol, 14.45 equiv) in DCM (7 mL) was stirred at 25 °C for 1 hour. The mixture was concentrated to give crude product 4-(4-[2,6-diazaspiro[3.3]heptan-2-ylmethyl]-3,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1-one(696mg) as a brown oil that was used directly without further purification. LCMS (ESI) m/z: [M+H]+ = 407.

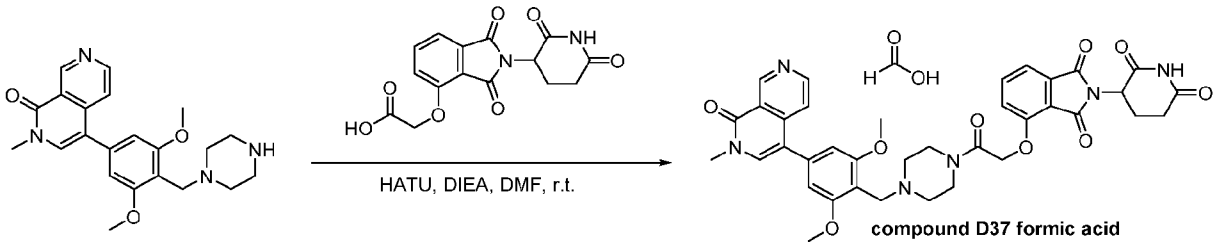
Step 3: Preparation of 4-(2-(6-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl) -2,6-diazaspiro[3.3]heptan-2-yl)-2-oxoethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (compound D35 formic acid)



To a solution of 4-(4-[2,6-diazaspiro[3.3]heptan-2-ylmethyl]-3,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1-one (40.00 mg, 0.098 mmol, 1.00 equiv) and [[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetic acid (32.70 mg, 0.098 mmol, 1.00 equiv) in DMF (1 mL) was added HATU (56.12 mg, 0.148 mmol, 1.50 equiv) and DIEA (31.80 mg, 0.246 mmol, 10 equiv). The mixture was stirred at 25 °C for 1 hour. The mixture was purified by prep-HPLC (conditions: SunFire Prep C18 OBD Column 19×150 mm 5 μm 10 nm;Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 8% B to 21% B in 10 minutes; 254/220 nm; Rt: 8.20 minutes) to afford 4-[2-(6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-2,6-diazaspiro[3.3]heptan-2-yl)-2-oxoethoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (6.2 mg, 8.74%) as a white solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.51 (s, 1H), 8.68 (d, *J* = 5.8 Hz, 1H), 8.55 (br s, 0.46H, FA), 7.80 (s, 1H), 7.69 (t, *J* = 8.1 Hz, 1H), 7.62 (d, *J* = 5.7 Hz, 1H), 7.44 (dd, *J* = 11.8, 7.2 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 6.87 (s, 2H),

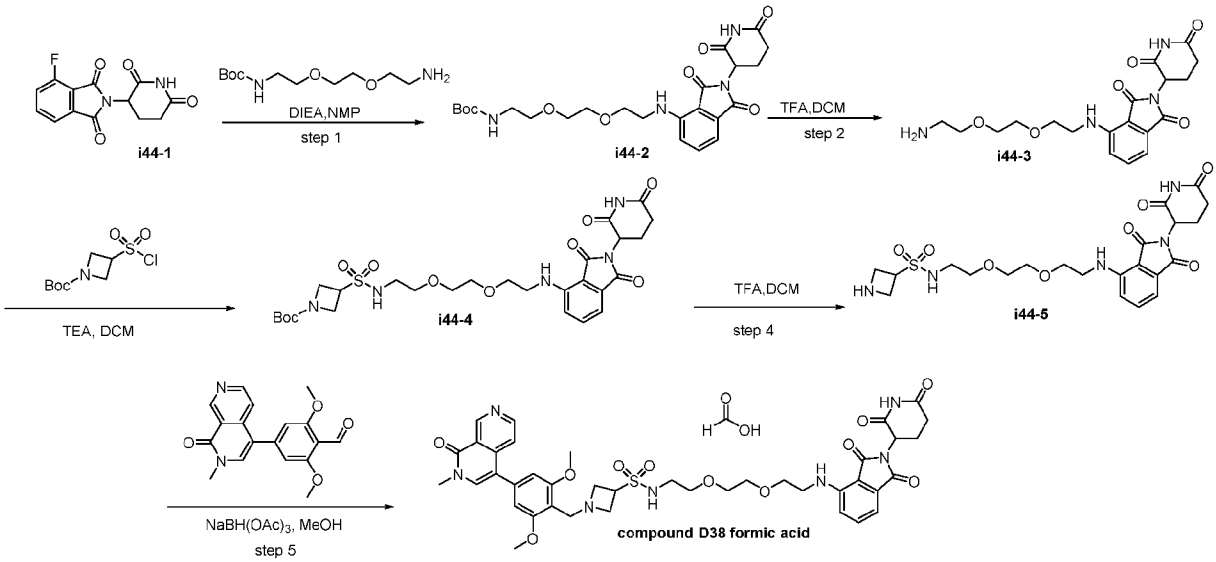
5.19 – 5.10 (m, 1H), 4.69 – 4.51 (m, 6H), 4.39 (s, 2H), 4.34 – 4.26 (m, 2H), 4.22 (s, 2H), 3.97 (s, 6H), 3.69 (s, 3H), 2.95 – 2.68 (m, 3H), 2.20 – 2.09 (m, 1H). LCMS (ESI) m/z: [M+H]+ = 721.35.

Example 43 – Preparation of 4-(2-(4-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)piperazin-1-yl)-2-oxoethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (compound D37 formic acid)

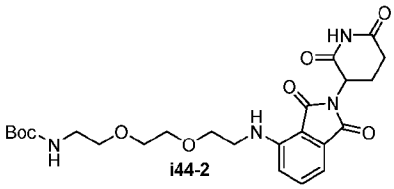


To a stirred solution of 4-[3,5-dimethoxy-4-(piperazin-1-ylmethyl)phenyl]-2-methyl-2,7-naphthyridin-1-one (50.0 mg, 0.127 mmol, 1.00 equiv) and [[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetic acid (42.1 mg, 0.127 mmol, 1.00 equiv) in DMF (1 mL) was added DIEA (163.8 mg, 1.268 mmol, 10.00 equiv) dropwise at room temperature. The resulting mixture was stirred for 10 minutes at room temperature. To the above mixture was added HATU (96.4 mg, 0.254 mmol, 2.00 equiv). The resulting mixture was stirred for additional 2 hours at room temperature. The residue was purified by reverse flash chromatography (conditions: SunFire C18 OBD Prep Column, 100Å, 5 µm, 19 mm X 250 mm; Mobile Phase A: Water(0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 9 B to 27 B in 10 minutes; 254 nm; R_T: 10.12 minutes) to afford 4-[2-(4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]piperazin-1-yl)-2-oxoethoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (12.2 mg,13.6%) as a white solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.54 (s, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.34 (br s, 0.28H, FA), 7.83 – 7.73 (m, 2H), 7.67 – 7.61 (m, 1H), 7.52 (d, *J* = 7.1 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 6.81 (s, 2H), 5.15 – 5.09 (m, 3H), 4.08 (s, 2H), 3.92 (s, 6H), 3.83 – 3.73 (m, 4H), 3.72 (s, 3H), 3.05 – 2.96 (m, 2H), 2.96 – 2.80 (m, 3H), 2.77 – 2.69 (m, 2H), 2.17 – 2.11 (m, 1H). LCMS (ESI) m/z: [M+H]+ = 709.35.

Example 44 – Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-N-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]ethyl]azetidine-3-sulfonamide formic acid (compound D38 formic acid)

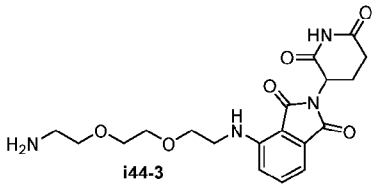


Step 1: Preparation of tert-butyl N-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]ethoxy)ethoxy]ethyl]carbamate (i44-2)



To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-4-fluoro-2,3-dihydro-1*H*-isoindole-1,3-dione (1.0 g, 3.620 mmol, 1.00 equiv) in NMP (15.00 mL) was added DIEA (940.47 mg, 7.277 mmol, 2.01 equiv) and *tert*-butyl *N*-[2-[2-(2-aminoethoxy)ethoxy]ethyl]carbamate (988.89 mg, 3.982 mmol, 1.10 equiv) in portions at room temperature. The resulting solution was stirred for 12 hours at 90 ℃. The resulting mixture was washed with water (3 x 100 mL). The resulting solution was extracted with ethyl acetate (3 x 200 mL). The organic layers combined and concentrated. This resulted in *tert*-butyl *N*-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]ethoxy)ethoxy]ethyl]carbamate (1.2 g, 65.70%) as light yellow oil. LCMS (ESI) m/z: [M+H]+ = 505.

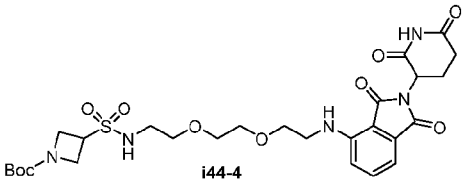
Step 2: Preparation of 4-([2-[2-(2-aminoethoxy)ethoxy]ethyl]amino)-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (i44-3)



i44-3

To a stirred solution of *tert*-butyl *N*-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4yl]amino]ethoxy)ethoxy]ethyl]carbamate (1.2 g, 2.378 mmol, 1.00 equiv) in DCM (40 mL) was added TFA (10 mL) in portions at room temperature. The resulting solution was stirred for 4 hours at room temperature. The resulting mixture was concentrated. This resulted in 4-([2-[2-(2-aminoethoxy)ethoxy]ethyl]amino)-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (0.8 g, 83.17%) as light yellow oil. LCMS (ESI) m/z: [M+H]+ = 405.

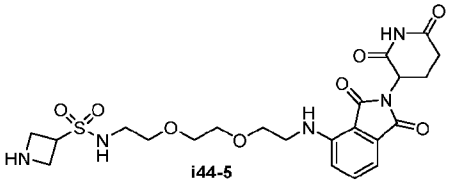
Step 3: Preparation of tert-butyl 3-([2-[2-(2-[[2-(2, 6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]ethyl]sulfamoyl)azetidine-1-carboxylate (i44-4)



i44-4

To a stirred solution of 4-([2-[2-(2-aminoethoxy)ethoxy]ethyl]amino)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (238.00 mg, 0.588 mmol, 1.00 equiv) in DCM was added TEA (120.00 mg, 1.186 mmol, 2.02 equiv) in portions at room temperature. To the above mixture was added *tert*-butyl 3-(chlorosulfonyl) azetidine-1-carboxylate (150.00 mg, 0.587 mmol, 1.00 equiv) in portions. The resulting mixture was stirred for additional 2 hours at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / EtOAc (1:1) to afford *tert*-butyl 3-([2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy] ethyl]sulfamoyl)azetidine-1-carboxylate (130 mg, 35.42%) as a light yellow oil. LCMS (ESI) m/z: [M+H] + = 624.

Step 4: Preparation of N-(2-(2-(2-((2-(2, 6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)azetidine-3-sulfonamide (i44-5)

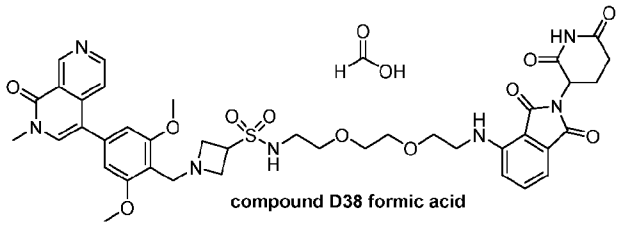


i44-5

To a stirred solution/mixture of *tert*-butyl 3-([2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]ethyl]sulfamoyl)azetidine-1-carboxylate (120.00 mg, 0.192 mmol, 1.00 equiv) in DCM (4 mL) was added TFA (1 mL) in portions at room temperature. The resulting mixture was stirred for 1 hour at room temperature. The resulting mixture was concentrated under reduced pressure. The

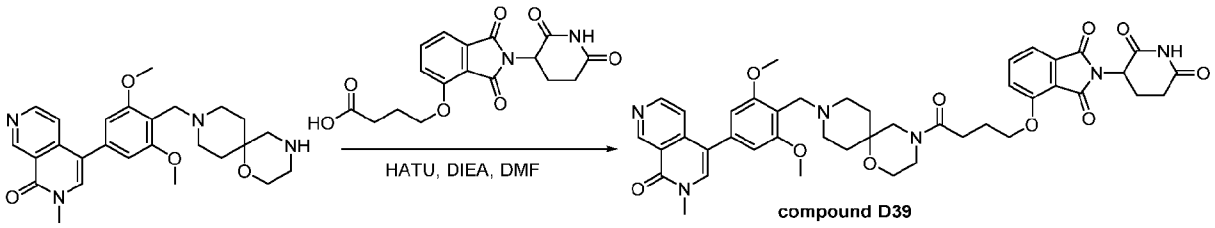
crude product 130 mg was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]+ = 524.

Step 5: Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-N-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]ethyl]azetidine-3-sulfonamide formic acid (compound D38 formic acid)



To a stirred solution of *N*-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy) ethoxy]ethyl]azetidine-3-sulfonamide (60.00 mg, 0.115 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (74.34 mg, 0.229 mmol, 2.00 equiv) in MeOH was added $NaBH(OAc)_3$ (97.15 mg, 0.458 mmol, 4.00 equiv) in portions at room temperature. The resulting mixture was stirred for 12 hours at room temperature. The crude product was purified by Prep-HPLC (conditions: SunFire Prep C18 OBD Column, 19*150 mm 5 µm 10 nm; mobile phase, Water (0.1% FA) and ACN (10% Phase B up to 27% in 8 minutes); Detector, UV). This resulted in 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-*N*-[2-[2-(2[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]ethyl]azetidine-3-sulfonamide formic acid (8.1 mg, 8.05%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.49 (d, *J* = 0.9 Hz, 1H), 8.66 (d, *J* = 5.8 Hz, 1H), 8.45 (br s, 1H, FA), 7.74 (s, 1H), 7.62 (dd, *J* = 5.8, 0.9 Hz, 1H), 7.50 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.02 (dd, *J* = 7.8, 5.3 Hz, 2H), 6.79 (s, 2H), 5.07 (dd, *J* = 12.4, 5.4 Hz, 1H), 4.61 (s, 1H), 4.36 – 4.23 (m, 1H), 4.20 (s, 2H), 4.13 – 3.99 (m, 4H), 3.92 (s, 6H), 3.73 – 3.64 (m, 9H), 3.55 (t, *J* = 5.1 Hz, 2H), 3.50 – 3.41 (m, 2H), 3.28 (t, *J* = 5.1 Hz, 2H), 2.96 – 2.61 (m, 3H), 2.18 – 2.04 (m, 1H). LCMS (ESI) m/z: [M+H]+ = 832.45.

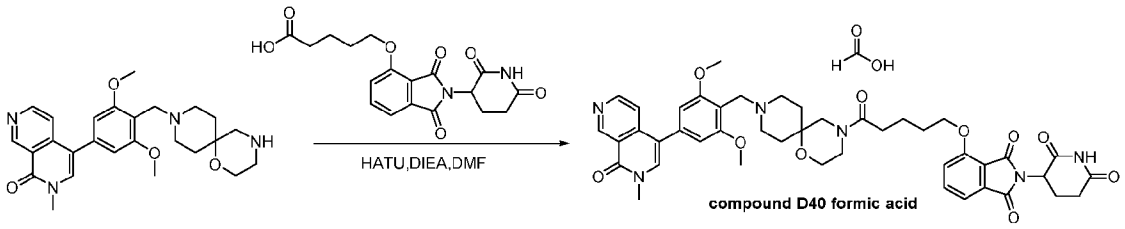
Example 45 – Preparation of 4-[4-(9-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-4-oxobutoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione. (compound D39)



To a stirred solution of 4-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-2-methyl -2,7naphthyridin-1-one (20.00 mg, 0.043 mmol, 1.00 equiv) and 4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]butanoic acid (15.00 mg, 0.042 mmol, 0.97 equiv) in DMF was added HATU

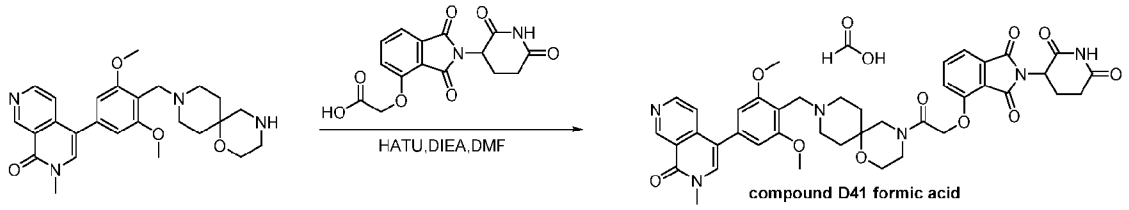
(25.00 mg, 0.066 mmol, 1.53 equiv) and DIEA (60.00 mg, 0.464 mmol, 10.78 equiv) in portions at room temperature. The resulting mixture was stirred for 2 hours at room temperature. The crude product was purified by Prep-HPLC (conditions: Gemini-NX C18 AXAI Packed, 21.2*150 mm 5 µm; mobile phase, Water (0.1% FA) and ACN (14% Phase B up to 19% in 10 minutes); Detector, UV). This resulted in 4-[4-(9-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-1-oxa-4,9diaza spiro[5.5]undecan-4-yl)-4-oxobutoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (5.1 mg, 14.68%) as a white solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.55 (s, 1H), 8.70 (d, *J* = 5.6 Hz, 1H), 7.85 – 7.75 (m, 2H), 7.63 (d, *J* = 5.8 Hz, 1H), 7.57 – 7.43 (m, 2H), 6.87 (d, *J* = 5.2 Hz, 2H), 5.12 (d, *J* = 11.8 Hz, 1H), 4.41 (s, 2H), 4.37 – 4.27 (m, 2H), 3.96 (d, *J* = 8.2 Hz, 6H), 3.84 – 3.60 (m, 9H), 3.58 – 3.45 (m, 3H), 2.92 – 2.69 (m, 5H), 2.26 – 2.04 (m, 6H), 1.85 – 1.60 (m, 2H). LCMS (ESI) m/z: [M+H]+ = 807.40.

Example 46 – Preparation of 4-[[5-(9-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-5-oxopentyl]oxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (compound D40 formic acid)



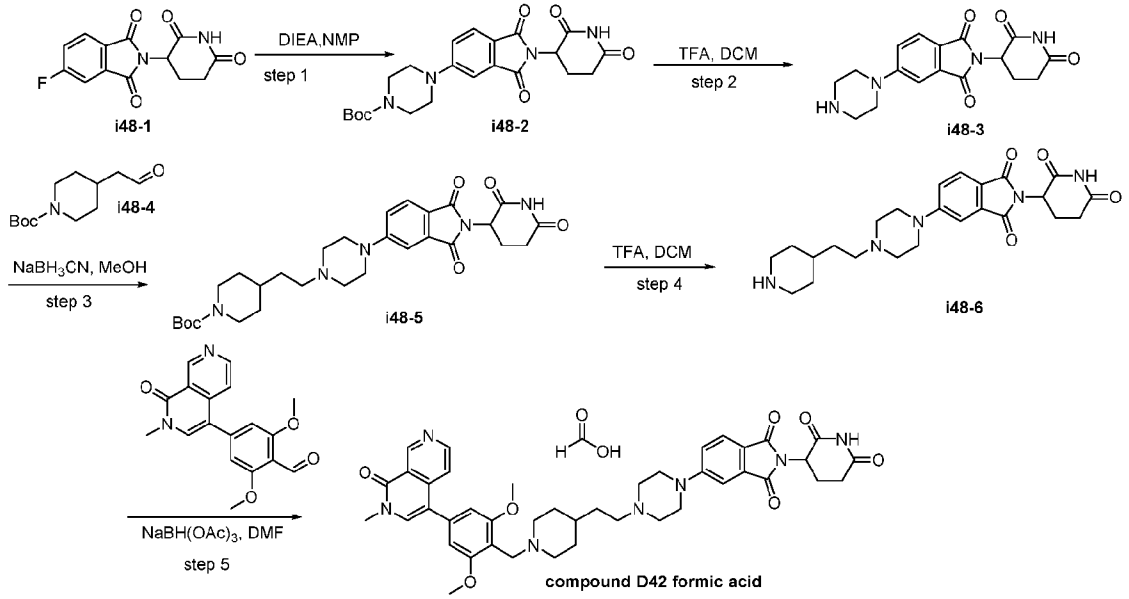
To a stirred solution of 4-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-2-methyl-2,7-naphthyridin-1-one (30.00 mg, 0.065 mmol, 1.00 equiv) and 5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]pentanoic acid (24.17 mg, 0.065 mmol, 1 equiv) in DMF (1.00 mL) was added DIEA (83.46 mg, 0.646 mmol, 10.00 equiv) and HATU (36.83 mg, 0.097 mmol, 1.50 equiv). The resulting solution was stirred at room temperature for 1 hour. Without any additional work-up, the mixture was purified by prep-HPLC (conditions: SunFire C18 OBD Prep Column , 100Å, 5 µm, 19 mm X 250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 9% B to 25% B in 10 minutes; 254 nm; Rt: 10.95 minutes) to give (4-[[5-(9-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-5-oxopentyl]oxy]-2-(2,6-dioxopip eridin-3-yl)isoindole-1,3-dione formic acid (8.6 mg, 15.25%) as a white solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.54 (s, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.53 (br s, 1H, FA), 7.85 – 7.74 (m, 2H), 7.62 (dd, *J* = 5.9, 0.9 Hz, 1H), 7.46 (dd, *J* = 7.8, 2.3 Hz, 2H), 6.86 (d, *J* = 5.7 Hz, 2H), 5.12 (dd, *J* = 12.3, 5.4 Hz, 1H), 4.39 (s, 2H), 4.35 – 4.25 (m, 3H), 3.96 (s, 6H), 3.83 – 3.74 (m, 2H), 3.72 (s, 3H), 3.67 – 3.61 (m, 2H), 3.55 – 3.50 (m, 3H), 3.00 – 2.51 (m, 6H), 2.20 – 1.71 (m, 10H). LCMS (ESI) m/z: [M+H]+ = 821.45.

Example 47 – Preparation of 4-[2-(9-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2-oxoethoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (compound D41 formic acid)

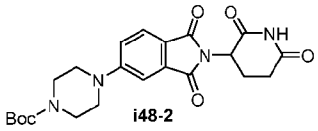


To a solution of 4-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-2-methyl-2,7-naphthyridin-1-one (30.00 mg, 0.065 mmol, 1.00 equiv) and [[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetic acid (21.46 mg, 0.065 mmol, 1.00 equiv) in DMF (1.00 mL) was added DIEA (83.46 mg, 0.646 mmol, 10.00 equiv) and HATU (36.83 mg, 0.097 mmol, 1.50 equiv). The resulting solution was stirred at room temperature for 1 hour. Without any additional work-up, the mixture was purified by prep-HPLC (conditions: Phenomenex Gemini C6-Phenyl, 21.2*250 mm, 5 μm; Mobile Phase A: Water (0.05% FA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient:7 B to 26 B in 15 minutes; 254 nm; R_T: 14.62 minutes) to give 4-[2-(9-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2-oxoethoxy]-2-(2,6-dioxopip eridin-3-yl)isoind ole-1,3-dione formic acid (3.7 mg, 6.80%) as a white solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.54 (d, *J* = 0.8 Hz, 1H), 8.70 (d, *J* = 5.8 Hz, 1H), 8.56 (br s, 1H, FA), 7.86 – 7.75 (m, 2H), 7.63 (dd, *J* = 5.8, 0.9 Hz, 1H), 7.54 (d, *J* = 7.2 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 6.86 (s, 2H), 5.17 – 5.07 (m, 3H), 4.30 (s, 2H), 3.95 (s, 6H), 3.87 – 3.75 (m, 2H), 3.72 (s, 3H), 3.68 – 3.62 (m, 2H), 3.54 (s, 2H), 3.23 – 3.17 (m, 4H), 2.91 – 2.65 (m, 3H), 2.22 – 2.02 (m, 3H), 1.80 (s, 2H). LCMS (ESI) m/z: [M+H]+ = 779.40.

Example 48 – Preparation of 5-(4-(2-(1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl) piperidin-4-yl)ethyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (compound D42 formic acid)



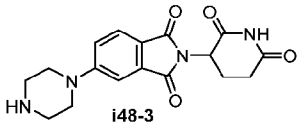
Step 1: Preparation of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)piperazine-1-carboxylate (i42-2)



i48-2

To a solution of 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisoindole-1,3-dione (1.38 g, 4.996 mmol, 1.00 equiv) and *tert*-butyl piperazine-1-carboxylate (930.52 mg, 4.996 mmol, 1.00 equiv) in NMP (20 mL) was added DIPEA (1937.08 mg, 14.988 mmol, 3 equiv). The mixture was stirred at 90 ℃ for 2 hours (under nitrogen atmosphere). The reaction was monitored by LC-MS. The resulting mixture was diluted with water (70 mL) and then extracted with EA (3 x 25 mL). The combined organic layers were washed with water (2 x 25 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; mobile phase, 0.5% FA in water, 10% to 90% gradient in 25 minutes; detector, UV 220 nm). The fractions were concentrated under reduced pressure afford *tert*-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)piperazine-1-carboxylate (700 mg, 31.67%) as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 443.

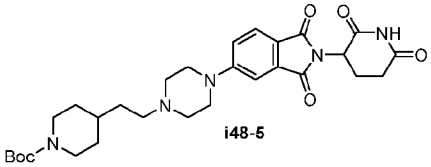
Step 2: Preparation of 2-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)isoindoline-1,3-dione (i42-3)



i48-3

A solution of *tert*-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazine-1-carbo xylate(500.00 mg, 1.130 mmol, 1.00 equiv) and TFA(1.50 mL, 20.195 mmol, 17.87 equiv) in DCM(5.00 mL) was stirred at 25 ℃ for 1 hour. The resulting mixture were evaporated to dryness to afford 2-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)isoindole-1,3-dione (350 mg, 90.47%) as a brown solid. LCMS (ESI) m/z: [M+H]+ = 343

Step 3: Preparation of tert-butyl 4-(2-(4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)piperazin-1-yl)ethyl)piperidine-1-carboxylate (i42-5)

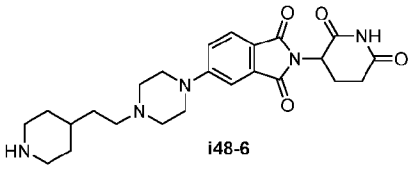


i48-5

To a solution of 2-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)isoindole-1,3-dione (200.00 mg, 0.584 mmol, 1.00 equiv) and *tert*-butyl 4-(2-oxoethyl)piperidine-1-carboxylate (132.79 mg, 0.584 mmol, 1 equiv) in DMF (3.00 mL) was added $NaBH(OAc)_3$ (247.63 mg, 1.168 mmol, 2 equiv). The resulting solution was stirred at 25 ℃ for 1 hour. The residue was purified by reverse flash chromatography

(conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 10 minutes; detector, UV 254 nm) to give *tert*-butyl 4-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)piperidine-1-carboxylate (197.5 mg, 61.06%) as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 554.

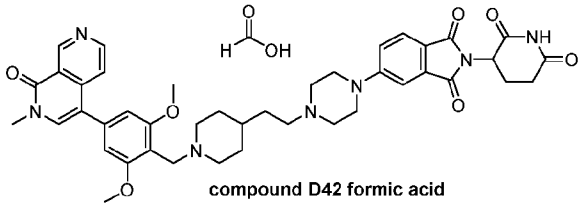
Step 4: Preparation of 2-(2,6-dioxopiperidin-3-yl)-5-(4-(2-(piperidin-4-yl)ethyl)piperazin-1-yl)isoindoline-1,3-dione (i42-6)



i48-6

To a solution of *tert*-butyl 4-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)piperidine-1-carboxylate (197.00 mg, 0.356 mmol, 1.00 equiv) and TFA (0.50 mL, 6.732 mmol, 18.92 equiv) in DCM (2.00 mL) was stirred at 25 °C for 1 hour. The mixture was concentrated to give crude product 2-(2,6-dioxopiperidin-3-yl)-5-[4-[2-(piperidin-4-yl)ethyl]piperazin-1-yl]isoindole-1,3-dione (320 mg) as a yellow oil, that was used directly without further purification. LCMS (ESI) m/z: [M+H]+ = 454.

Step 5: Preparation of 5-(4-(2-(1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)piperidin-4-yl)ethyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (compound D42 formic acid)

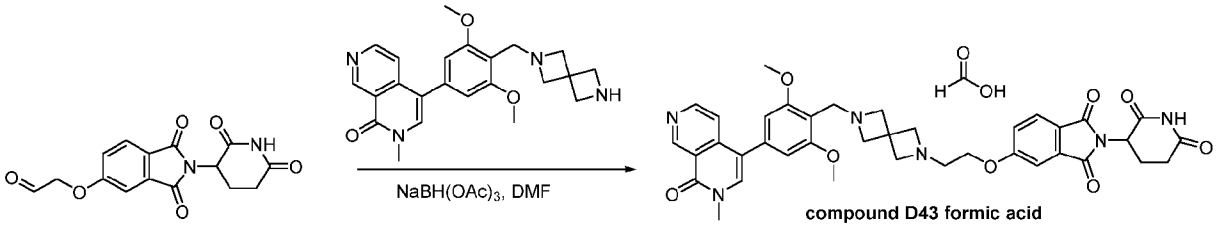


compound D42 formic acid

To a solution of 2-(2,6-dioxopiperidin-3-yl)-5-[4-[2-(piperidin-4-yl)ethyl]piperazin-1-yl]isoindole-1,3-dione(100.68 mg, 0.222 mmol, 1.20 equiv) and 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (60.00 mg, 0.185 mmol, 1.00 equiv) in DMF(1.5mL) was added $NaBH(OAc)_3$ (78.42 mg, 0.370 mmol, 2 equiv). The mixture was stirred at 25 °C for 1 hour. The mixture was purified by prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100Å, 5 µm, 19 mm X 250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient:10 B to 12 B in 10 minutes; 254 nm; R_T: 8.7 minutes) to afford 5-[4-[2-(1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]piperidin-4-yl)ethyl]piperazin-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoi ndole-1,3-dione (24 mg, 17.03%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.55 (d, *J* = 0.9 Hz, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.15 (br s, 0.2H, FA), 7.80 – 7.71 (m, 2H), 7.63 (d, *J* = 5.8 Hz, 1H), 7.43 (s, 1H), 7.31 (d, *J* = 9.2 Hz, 1H), 6.89 (s, 2H), 5.10 (dd, *J* = 12.3, 5.4 Hz, 1H), 4.41 (s, 2H), 3.98 (s, 6H), 3.72 (s, 3H), 3.67 – 3.55

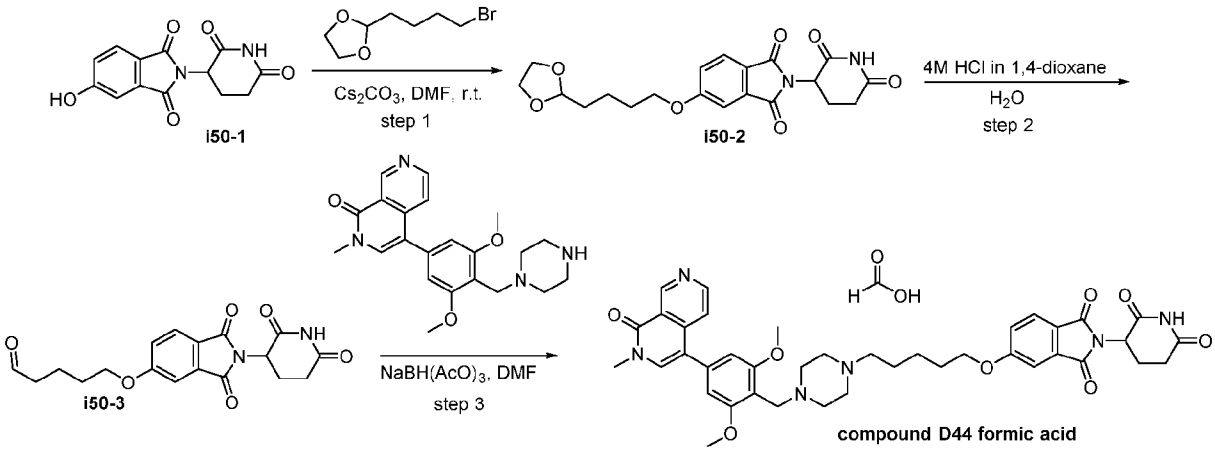
(m, 6H), 3.17 (d, *J* = 12.9 Hz, 2H), 3.05 – 2.92 (m, 4H), 2.90 – 2.70 (m, 5H), 2.17 – 2.00 (m, 3H), 1.81 – 1.51 (m, 5H). LCMS (ESI) m/z: [M+H]+ = 762.45.

Example 49 – Preparation of 5-[2-(6-[[2,6-Dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-2,6-diazaspiro[3.3]heptan-2-yl)ethoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (compound D43 formic acid)

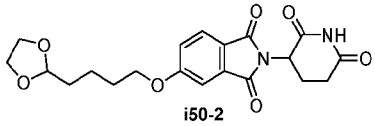


To a solution of 2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]acetaldehyde (60.00 mg, 0.190 mmol, 1.00 equiv) and 4-(4-[2,6-diazaspiro[3.3]heptan-2-ylmethyl]-3,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1-one (77.12 mg, 0.190 mmol, 1 equiv) in DMF(1.00 mL)was added $NaBH(OAc)_3$ (80.42 mg, 0.379 mmol, 2 equiv). The resulting solution was stirred at room temperature for 1 hour. The crude product (60 mg) was purified by Prep-HPLC (conditions: SunFire Prep C18 OBD Column 19×150 mm 5 μm 10nm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 7% B to 10% B in 12 minutes; 254/220 nm; Rt: 9.65 minutes) to afford 5-[2-(6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-2,6-diazaspiro[3.3]heptan-2-yl)ethoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (14.3 mg, 9.82%) as a light yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.54 (s, 1H), 8.68 (d, *J* = 5.8 Hz, 1H), 8.14 (br s, 0.2H, FA), 7.76 (s, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.62-7.54 (m, 1H), 7.19 (d, *J* = 2.2 Hz, 1H), 7.13 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.86 (s, 2H), 5.16 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.47 (s, 2H), 4.34 (s, 4H), 3.98 (s, 6H), 3.95-3.87 (m, 2H), 3.80 (s, 4H), 3.71 (s, 3H), 3.00-2.85 (m, 4H), 2.81-2.63 (m, 1H), 2.20-2.05 (m, 1H). LCMS (ESI) m/z: [M+H]+ = 707.5.

Example 50 – Preparation of 5-((5-(4-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)piperazin-1-yl)pentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (compound D44 formic acid)

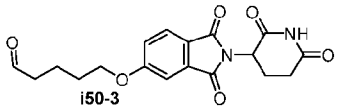


Step 1: 5-(4-(1,3-dioxolan-2-yl)butoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (i50-2)



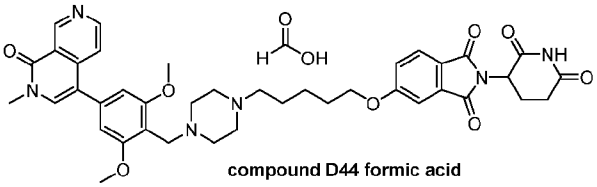
To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-hydroxy-2,3-dihydro-1H-isoindole-1,3-dione (400.0 mg, 1.459 mmol, 1.00 equiv) and 2-(4-bromobutyl)-1,3-dioxolane (305.0 mg, 1.459 mmol, 1.00 equiv) in DMF was added cesium carbonate (475.3 mg, 1.459 mmol, 1.00 equiv) at room temperature. The resulting mixture was filtered, and the filter cake was washed with DCM (3 x 5 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EtOAc 1:1) to afford 5-[4-(1,3-dioxolan-2-yl)butoxy]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (40 mg, 6.5%) as an off-white oil. LCMS (ESI) m/z: [M+H]+ = 403.

Step 2: Preparation of 5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)pentanal (i50-3)



To a stirred mixture of 5-[4-(1,3-dioxolan-2-yl)butoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (40.0 mg, 0.099 mmol, 1.00 equiv) in water (1.50 mL) was added HCl in 1,4-dioxane (4 M, 3.00 mL) at room temperature. The resulting mixture was stirred for 2 hours at room temperature. The resulting mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (8 mL), and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]+ = 359.

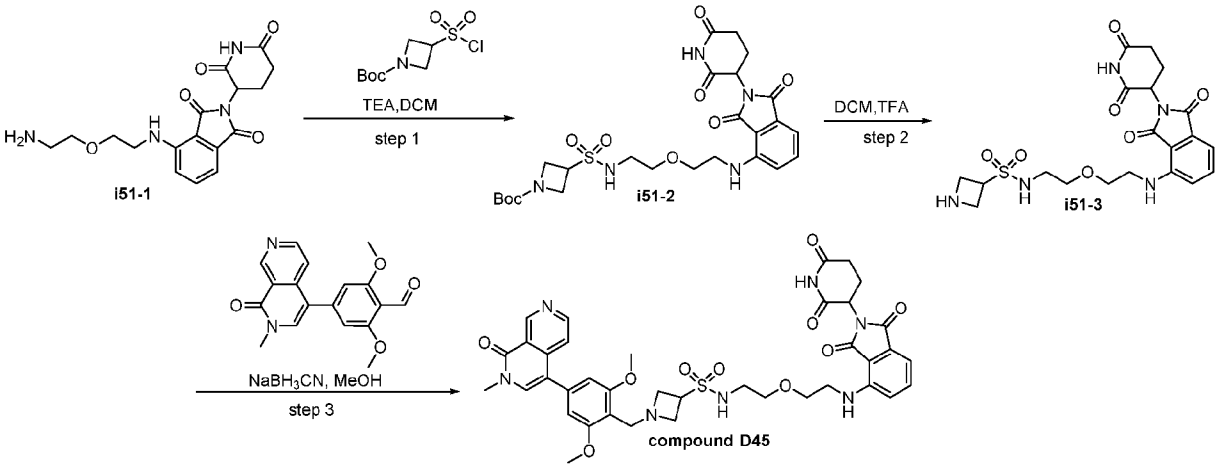
Step 3: Preparation of N-(6-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-3-methyl-[1,2,4]triazolo[4,3-a]pyridin-8-yl)acetamide formic acid (compound D44 formic acid)



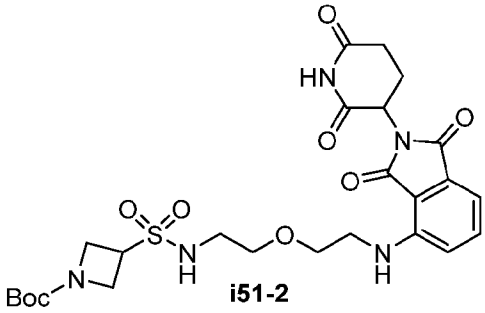
compound D44 formic acid

To a stirred solution/mixture of 5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]pentanal (20 mg, 0.056 mmol, 1.00 equiv) in DMF (1 mL) was added 4-[3,5-dimethoxy-4-(piperazin-1-ylmethyl)phenyl]-2-methyl-2,7-naphthyridin-1-one (22.0 mg, 0.056 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for 30 minutes at room temperature. To the above mixture was added $NaBH(OAc)_3$ (23.7 mg, 0.112 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred for additional 2 hours at room temperature. The crude product was purified by Prep-HPLC (conditions: SunFire Prep C18 OBD Column, 19×150 mm 5 μm 10 nm; Mobile Phase A: Water(0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 10 B to 25 B in 8 minutes; 254/220 nm; R_T: 6.53 minutes) to afford 5-[[5-(4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]piperazin-1-yl)pentyl]oxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione; formic acid (5 mg, 10.9%) as a white solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.54 (d, *J* = 0.9 Hz, 1H), 8.69 (d, *J* = 5.7 Hz, 1H), 8.52 (br s, 0.3H, FA),7.82 (d, *J* = 8.3 Hz, 1H), 7.75 (s, 1H), 7.62 (dd, *J* = 5.8, 0.9 Hz, 1H), 7.41 (d, *J* = 2.2 Hz, 1H), 7.33 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.82 (s, 2H), 5.12 (dd, *J* = 12.5, 5.4 Hz, 1H), 4.20 (t, *J* = 6.2 Hz, 2H), 4.10 (s, 2H), 3.93 (s, 6H), 3.72 (s, 3H), 3.12 – 2.59 (m, 13H), 2.19 – 2.10 (m, 1H), 1.97 – 1.86 (m, 2H), 1.72 – 1.54 (m, 4H). LCMS (ESI) m/z: [M+H]+ = 737.40.

Example 51 – Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-N-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethyl]azetidine-3-sulfonamide (compound D45)

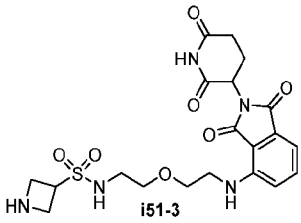


Step 1: Preparation of tert-butyl 3-[[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy) ethyl]sulfamoyl]azetidine-1-carboxylate (i51-2)



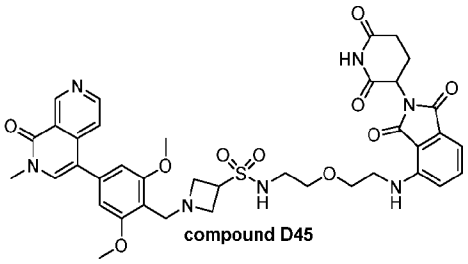
To a stirred solution of 4-[[2-(2-aminoethoxy)ethyl]amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (200.00 mg, 0.555 mmol, 1.00 equiv) and TEA (168.48 mg, 1.665 mmol, 3.00 equiv) in DCM (2mL) was added *tert*-butyl 3-(chlorosulfonyl)azetidine-1-carboxylate (170.30 mg, 0.666 mmol, 1.20 equiv) at room temperature. The resulting mixture was stirred for 2 hours at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (7:1) to afford *tert*-butyl 3-[[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethyl]sulfamoyl]azetidine-1-carboxylate (150 mg, 46.63%) as a yellow solid. LCMS (ESI) m/z: [M-H]+ = 580.20.

Step 2: Preparation of N-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethyl]azeti dine-3-sulfonamide (i51-3)



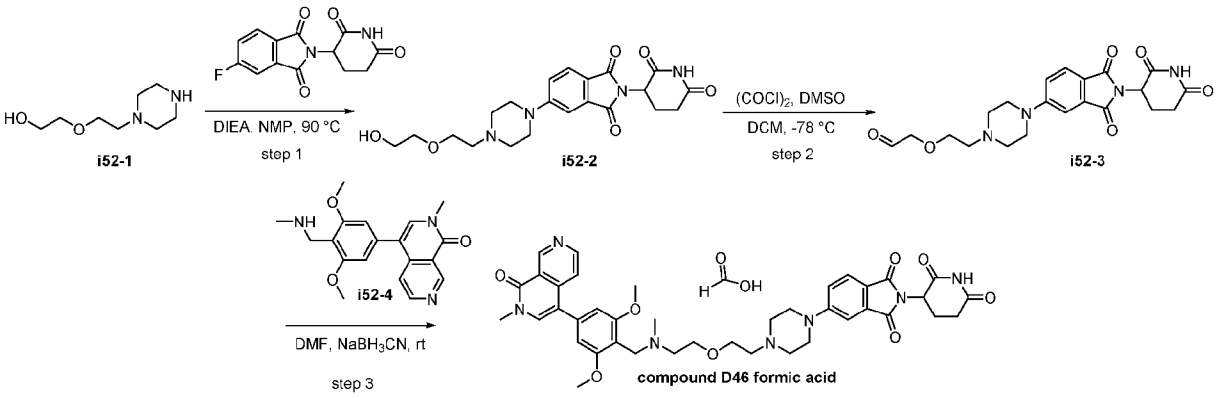
A solution of *tert*-butyl 3-[[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethyl] sulfamoyl]azetidine-1-carboxylate (100.00 mg, 0.173 mmol, 1.00 equiv) and TFA (1.00 mL) in DCM was stirred for 1 hour at room temperature. The resulting mixture was concentrated under vacuum. This resulted in *N*-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl] amino]ethoxy)ethyl]azetidine-3-sulfonamide (75 mg, 90.66%) as a red oil. LCMS (ESI) m/z: [M-H]+ = 480.15.

Step 3: Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-N-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethyl]azetidine-3-sulfonamide (compound D45)

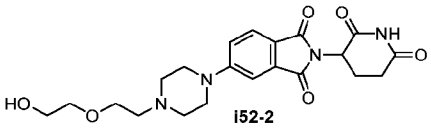


A solution of *N*-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethyl] azetidine-3-sulfonamide (30.00 mg, 0.063 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (26.38 mg, 0.081 mmol, 1.30 equiv) in DMF (2.00 mL) was stirred for 20 minutes at room temperature. Then $NaBH(OAc)_3$ (39.78 mg, 0.188 mmol, 3.00 equiv) was added to the reaction mixture. The resulting mixture was stirred for 1 hour at room temperature. The crude product was purified by Prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100Å, 5 µm, 19 mm X 250 mm; mobile phase, Water(0.1% FA) and ACN (11% PhaseB up to 18% in 20 min, hold 18% in 3 minutes); Detector, UV). This resulted in 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-*N*-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethyl]azetidine-3-sulfonamide (7.9 mg, 16.03%) as a green solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.52 (s, 1H), 8.67 (d, *J* = 5.8 Hz, 1H), 8.35 (br s, 0.3H, FA), 7.75 (s, 1H), 7.61 (dd, *J* = 5.7, 0.9 Hz, 1H), 7.55 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.07 (dd, *J* = 16.6, 7.8 Hz, 2H), 6.81 (s, 2H), 5.07 (d, *J* = 12.3 Hz, 1H), 4.60 (s, 2H), 4.36 (s, 3H), 4.23 (d, *J* = 7.7 Hz, 4H), 3.93 (s, 6H), 3.75 (t, *J* = 5.2 Hz, 2H), 3.71 (s, 3H), 3.59 (t, *J* = 5.2 Hz, 2H), 3.53 (t, *J* = 5.2 Hz, 2H), 2.92 – 2.66 (m, 3H), 2.12 (ddd, *J* = 12.7, 6.9, 3.9 Hz, 1H). LCMS (ESI) m/z: [M-H]+ = 788.26.

Example 52 – Preparation of 5-(4-(2-(2-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)(methyl)amino)ethoxy)ethyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (compound D46 formic acid)

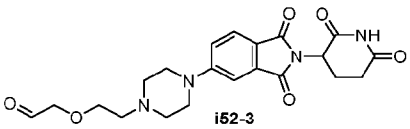


Step 1: Preparation of 2-(2,6-dioxopiperidin-3-yl)-5-(4-(2-(2-hydroxyethoxy)ethyl)piperazin-1-yl)isoindoline-1,3-dione (i52-2)



To a solution of 2-[2-(piperazin-1-yl)ethoxy]ethan-1-ol (315.4 mg, 1.810 mmol, 1.00 equiv) and 2-(2,6-dioxopiperidin-3-yl)-5-fluoro-2,3-dihydro-1*H*-isoindole-1,3-dione (500.0 mg, 1.810 mmol, 1.00 equiv) in NMP (5 mL) was added DIEA (467.9 mg, 3.620 mmol, 2.00 equiv). The resulting mixture was stirred for 3 hours at 90 °C. Without any additional work-up, the mixture was purified by reverse phase column, elution gradient 0% to 50% ACN in water to afford 2-(2,6-dioxopiperidin-3-yl)-5-[4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl]-2,3-dihydro-1H-isoindole-1,3-dione (700.0 mg, 89.8%) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 431.

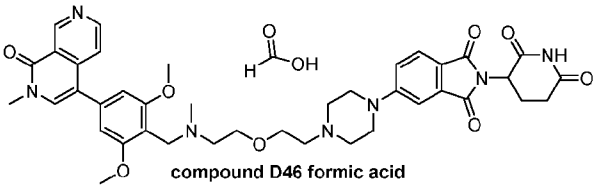
Step 2: Preparation of 2-(2-(4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)piperazin-1-yl)ethoxy)acetaldehyde (i52-3)



A solution of DMSO (54.5 mg, 0.697 mmol, 1.00 equiv) in DCM (6.00 mL) was added slowly to a stirred solution of oxalyl chloride (176.9 mg, 1.394 mmol, 2.00 equiv) in DCM (6.00 mL) at -78 °C under nitrogen atmosphere. After 30 minutes 2-(2,6-dioxopiperidin-3-yl)-5-[4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl]isoindole-1,3-dione (300.0 mg, 0.697 mmol, 1.00 equiv) in DCM (6.00 mL) was added slowly. The resulting mixture was stirred for 2 hours at -78 °C and 1.5 hours at -55 °C. Et_3N (0.48 mL, 4.787 mmol, 5.00 equiv) was added slowly at -60 °C. After stirring for an additional 10 minutes, the reaction was allowed to warm to room temperature. The resulting mixture was quenched with saturated ammonium chloride aqueous solution (50 mL) and extracted with DCM (100 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered,

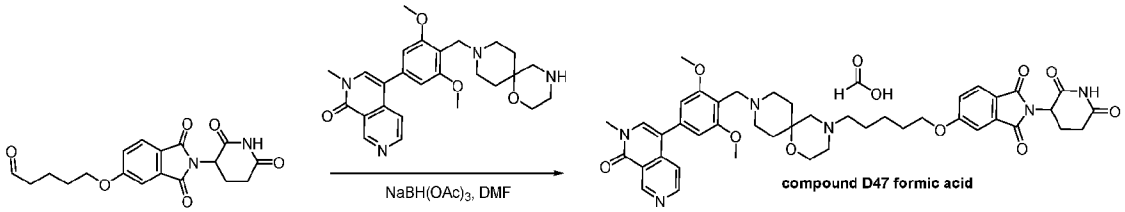
and concentrated in vacuo. The residue was purified by prep-TLC (EtOAc/PE = 1:1) to afford 2-(2-(4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)piperazin-1-yl)ethoxy)acetaldehyde (30.0 mg, 5.7%) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 429.

Step 3: Preparation of 5-(4-(2-(2-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)(methyl)amino)ethoxy)ethyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (compound D46 formic acid)



To a mixture of 2-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethoxy)acetaldehyde (30.0 mg, 0.070 mmol, 1.00 equiv) in DMF (2.00 mL) was added 4-[3,5-dimethoxy-4-[(methylamino)methyl]phenyl]-2-methyl-2,7-naphthyridin-1-one (23.7 mg, 0.070 mmol, 1.00 equiv). The resulting mixture was stirred for 1 hour at room temperature, STAB (29.6 mg, 0.140 mmol, 2.00 equiv) was added. The resulting mixture was stirred for 1 hour at room temperature. The resulting mixture, without any additional wok-up, was purified by prep-HPLC (conditions: SunFire C_{18} OBD Prep Column, 100Å, 5 µm, 19 mm x 250 mm; Mobile Phase A:Water (0.1% FA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient: 5% B to 30% B in 10 minutes; 254 nm; R_T: 8.82 minutes) to afford 5-(4-(2-(2-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)(methyl)amino)ethoxy)ethyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione;formate (6.2 mg, 15.6%) as a light yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 752.15. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.47 (s, 1H), 8.64 (d, *J* = 5.8 Hz, 1H), 8.57 (br s, 0.7H), 7.75 (s, 1H), 7.62 (dd, *J* = 12.9, 7.1 Hz, 2H), 7.28 (d, *J* = 2.3 Hz, 1H), 7.19 (d, *J* = 9.0 Hz, 1H), 6.89 (s, 2H), 5.07 (dd, *J* = 12.3, 5.4 Hz, 1H), 4.53 (s, 2H), 3.99 (s, 6H), 3.91 (t, *J* = 4.7 Hz, 2H), 3.76 (t, *J* = 5.1 Hz, 2H), 3.67 (s, 3H), 3.53 – 3.40 (m, 6H), 2.91 (s, 4H), 2.81 – 2.67 (m, 8H), 2.18 – 2.05 (m, 1H).

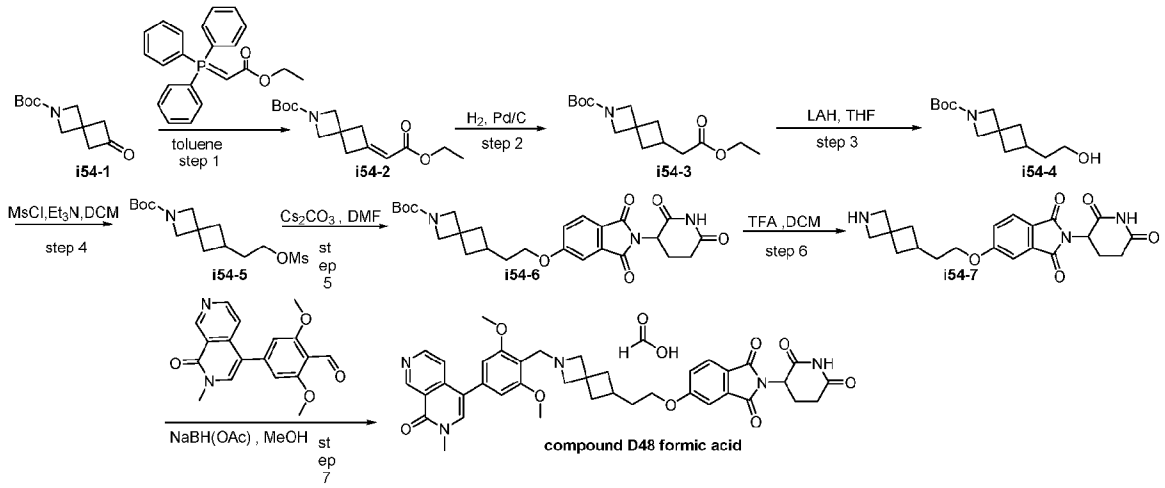
Example 53 – Preparation of 5-[[5-(9-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)pentyl]oxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (compound D47 formic acid)



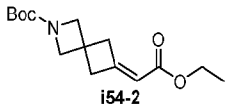
A solution of 5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]pentanal (25 mg, 0.070 mmol, 1.00 equiv) and 4-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-2-

methyl-2,7-naph thyridin-1-one (32.4 mg, 0.070 mmol, 1.00 equiv) in DMF (0.8 mL) was stirred for 30 minutes at room temperature. $NaBH(OAc)_3$ (29.57 mg, 0.140 mmol, 2.00 equiv) was then added and the resulting mixture was stirred for 1 hour at room temperature. Without any additional work-up, the mixture was purified by Prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100Å, 5 µm, 19 mm X 250 mm;Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 7% B to 20% B in 12 minutes; 254 nm; Rt: 11.57 minutes) to afford 5-[[5-(9-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)pentyl]oxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (7.9 mg,13%) as a white solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.55 (s, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.50 (br s, 1H, FA), 7.86 – 7.75 (m, 2H), 7.63 (d, *J* = 5.8 Hz, 1H), 7.40 (d, *J* = 2.2 Hz, 1H), 7.32 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.88 (s, 2H), 5.11 (dd, *J* = 12.3, 5.4 Hz, 1H), 4.42 (s, 2H), 4.19 (t, *J* = 6.2 Hz, 2H), 3.98 (s, 6H), 3.76 (t, *J* = 4.9 Hz, 2H), 3.72 (s, 3H), 3.44–3.35 (3H), 2.93 – 2.67 (m, 3H), 2.53 – 2.10 (m, 10H), 1.98– 1.51 (m, 8H). LCMS (ESI) m/z: [M+H]+ = 807.50.

Example 54 – Preparation of N-(6-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-3-methyl-[1,2,4]triazolo[4,3-a]pyridin-8-yl) acetamide formic acid (compound D48 formic acid)



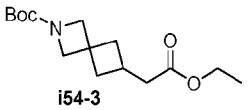
Step 1: Preparation of tert-butyl 6-(2-ethoxy-2-oxoethylidene)-2-azaspiro[3.3]heptane-2-carboxylate (i54-2)



A solution of *tert*-butyl 6-oxo-2-azaspiro[3.3]heptane-2-carboxylate (2.0 g, 9.467 mmol, 1.00 equiv) and ethyl2-(triphenyl-lambda5-phosphanylidene)acetate (3.63 g, 10.414 mmol, 1.10 equiv) in toluene was stirred for 4 hours at 80 ℃ under nitrogen atmosphere. The resulting mixture was washed with water (3 x 30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford *tert*-butyl 6-(2-ethoxy-2-

oxoethylidene)-2-azaspiro[3.3]heptane-2-carboxylate (2.51 g, 94.09%) as a light yellow oil. LCMS (ESI) m/z: [M+H]+ = 282.

Step 2: Preparation of tert-butyl 6-(2-ethoxy-2-oxoethyl)-2-azaspiro[3.3]heptane-2-carboxylate (i54-3)



i54-3

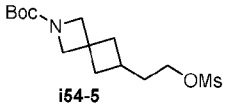
To a solution of *tert*-butyl 6-(2-ethoxy-2-oxoethylidene)-2-azaspiro[3.3]heptane-2-carboxylate (2506.00 mg, 8.907 mmol, 1.00 equiv) in MeOH (25 mL) was added Pd/C (10%, 1g) under nitrogen atmosphere. The mixture was hydrogenated at room temperature for 1 day under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad, and concentrated under reduced pressure afford *tert*-butyl 6-(2-ethoxy-2-oxoethyl)-2-azaspiro[3.3]heptane-2-carboxylate (2100.00 mg,81.4%) as a light yellow oil. LCMS (ESI) m/z: [M+H]+ = 284.

Step 3: Preparation of tert-butyl 6-(2-hydroxyethyl)-2-azaspiro[3.3]heptane-2-carboxylate (i54-4)

i54-4

To a stirred solution of *tert*-butyl 6-(2-ethoxy-2-oxoethyl)-2-azaspiro[3.3]heptane-2-carboxylate (1.0 g, 3.529 mmol, 1.00 equiv) in THF(20 ml) was added LAH (267.88 mg, 7.058 mmol, 2 equiv) in portions at 0 ℃ under nitrogen atmosphere. The reaction was quenched with Na_2SO_4•$10H_2O$ at room temperature. The resulting mixture was filtered. The filter cake was washed with MeOH (3 x 20 mL). The filtrate was concentrated under reduced pressure. The crude product (537.00 mg, 63.0%) was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]+ = 242.

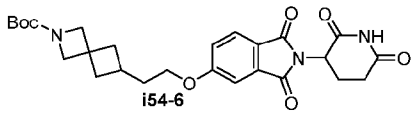
Step 4: Preparation of tert-butyl 6-(2-((methylsulfonyl)oxy)ethyl)-2-azaspiro[3.3]heptane-2-carboxylate (i54-5)



i54-5

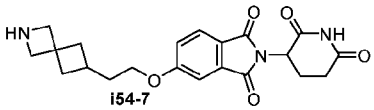
A solution of *tert*-butyl 6-(2-hydroxyethyl)-2-azaspiro[3.3]heptane-2-carboxylate (537.00 mg, 2.225 mmol, 1.00 equiv), Et_3N (450.33 mg, 4.450 mmol, 2.00 equiv), and MsCl (280.38 mg, 2.448 mmol, 1.10 equiv) in DCM (5 mL) was stirred for 3 hours at room temperature under nitrogen atmosphere. The resulting mixture was extracted with EtOAc (1 x 20mL). The combined organic layers were washed with water (3 x 10 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH (0% to 18%) to afford *tert*-butyl 6-[2-(methanesulfonyloxy)ethyl]-2-azaspiro[3.3]heptane-2-carboxylate (593 mg, 83.43%) as a white solid. LCMS (ESI) m/z: [M+H]+ = 320

Step 5: Preparation of tert-butyl 6-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)ethyl)-2-azaspiro[3.3] heptane-2-carboxylate (i54-6)



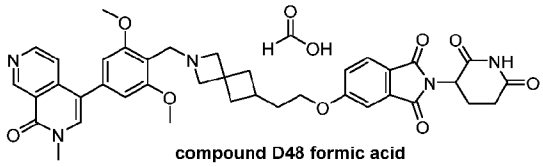
A solution of *tert*-butyl 6-[2-(methanesulfonyloxy)ethyl]-2-azaspiro[3.3]heptane-2-carboxylate (320.00 mg, 1.002 mmol, 1.00 equiv) ,Cs_2CO_3 (652.82 mg, 2.004 mmol, 2.00 equiv), and 2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindole-1,3-dione (274.73 mg, 1.002 mmol, 1.00 equiv) in DMF (3 mL) was stirred for 15 hours at room temperature under nitrogen atmosphere. The resulting mixture was extracted with EtOAc (1 x100 mL). The combined organic layers was washed with water (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford tert-butyl6-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]ethyl)-2-azaspiro[3.3]heptane-2-carboxylate (265.0 0mg, 53.2 %) as a yellow oil. LCMS (ESI) m/z: [M+H]+ = 498.

Step 6: Preparation of 5-(2-(2-azaspiro[3.3]heptan-6-yl)ethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (i54-7)



A solution of *tert*-butyl 6-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]ethyl)-2-azaspiro[3.3] heptane-2-carboxylate (265.00 mg, 0.533 mmol, 1.00 equiv) and TFA (2.5 mL) in DCM (5.0 mL) was stirred for 1.5 hours at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / EtOAc 1:1) to afford 5-(2-[2-azaspiro[3.3]heptan-6-yl]ethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindole -1,3-dione (200 mg, 94.48%) as a yellow oil. LCMS (ESI) m/z: [M+H]+ = 398.

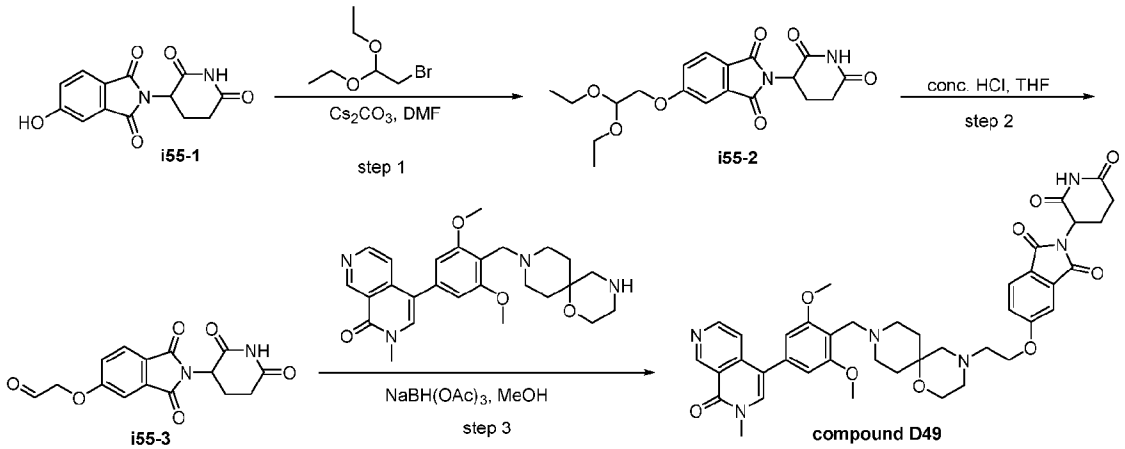
Step 7: Preparation of 5-(2-(2-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl) benzyl) -2-azaspiro[3.3] heptan-6-yl)ethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (compound D48 formic acid)



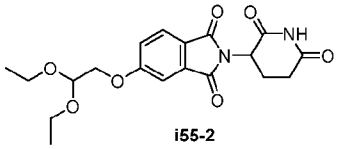
A solution of 5-(2-[2-azaspiro[3.3]heptan-6-yl]ethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (51.00 mg, 0.128 mmol, 1.00 equiv) in MeOH (1 mL) was treated with 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (41.62 mg, 0.128 mmol, 1.00 equiv) for 20 minutes at room temperature under nitrogen atmosphere followed by the addition of $NaBH_3CN$ (16.13 mg, 0.257 mmol,

2.00 equiv) in portions at room temperature. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; mobile phase, MeOH in water, 10% to 50% gradient in 10 minutes; detector, UV 254 nm). This resulted in 5-(2-(2-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-2-azaspiro[3.3]heptan-6-yl)ethoxy)-2-(2,6-dioxopiperidin-3-yl)iso indoline-1,3-dione formic acid (2.4 mg, 2.2%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.54 (s, 1H), 8.68 (d, *J* = 5.7 Hz, 1H), 8.56 (brs, 1.1H, FA), 7.77 (s, 1H), 7.68 – 7.56 (m, 2H), 7.13 (d, *J* = 2.2 Hz, 1H), 7.05 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.85 (s, 2H), 5.10 (dd, *J* = 12.9, 5.5 Hz, 1H), 4.40 (s, 2H), 4.21 – 4.12 (m, 2H), 4.05 (s, 2H), 3.96 (s, 6H), 3.79 – 3.70 (m, 5H), 2.95 – 2.84 (m, 2H), 2.75 – 2.59 (m, 1H), 2.49 – 2.36 (m, 2H), 2.27 – 2.06 (m, 2H), 2.05 – 1.92 (m, 2H), 1.72 – 1.54 (m, 2H). LCMS (ESI) m/z: [M+H]+ =706.50 .

Example 55 – Preparation of 5-[2-(9-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)ethoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (compound D49)

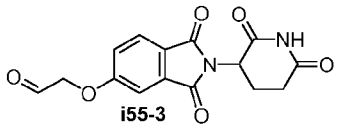


Step 1: Preparation of 5-(2,2-Diethoxyethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (i55-2)



To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindole-1,3-dione (500.00 mg, 1.823 mmol, 1.00 equiv) and Cs_2CO_3 (980.20 mg, 3.008 mmol, 3 equiv) in DMF(10.00 mL) was added 2-bromo-1,1-diethoxyethane (538.97 mg, 2.735 mmol, 1.5 equiv). The mixture was stirred at 80 ℃ for 16 hours. The mixture was acidified to pH 6 with HCl (aq.). The mixture was diluted with water (40 mL) and extracted with EtOAc/DCM (60 mL x 3). The organic layers were combined and dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product. The residue was purified by Prep-TLC (PE/EtOAc 1:1) to afford 5-(2,2-diethoxyethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione(110mg, 15.45%) as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 391.

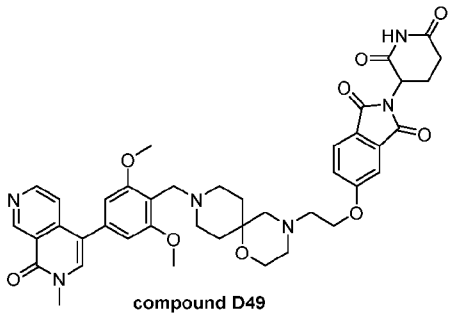
Step 2: Preparation of 2-[[2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]acetaldehyde (i55-3)



i55-3

To a stirred solution of 5-(2,2-diethoxyethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (100.00 mg, 0.256 mmol, 1.00 equiv) in THF (2.00 mL) was added HCl (4 M) (2.00 mL). The mixture was stirred at room temperature for 4 hours. The mixture was diluted with water (20 mL) and extracted with EtOAc/DCM (30 mL x 3). The organic layers were combined and dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product. This resulted in 2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]aceta ldehyde(95mg,crude) as a white solid. LCMS (ESI) m/z: [M+H]+ = 317.

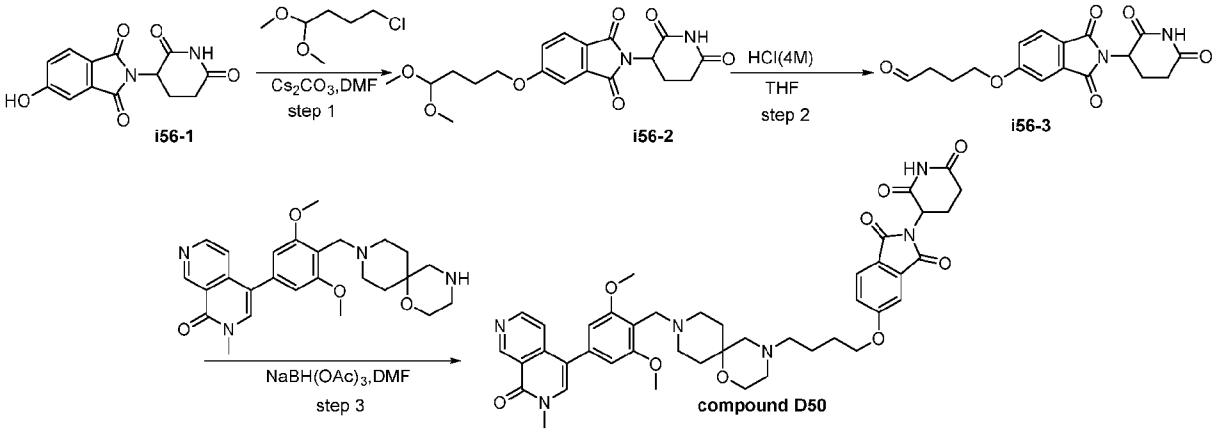
Step 3: Preparation of 5-[2-(9-[[2,6-Dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)ethoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (compound D49)



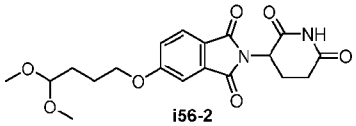
compound D49

To a stirred solution of 2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]acetaldehyde (60.00 mg, 0.190 mmol, 1.00 equiv) and 4-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-2-methyl-2,7-naphthyridin-1-one (88.13 mg, 0.190 mmol, 1.00 equiv) in DMF (1.50 mL) was added $NaBH(OAc)_3$ (80.42 mg, 0.379 mmol, 2.00 equiv). The mixture was stirred at room temperature for 2 hours. Without any additional work-up, the mixture was purified by prep-HPLC (conditions: Xcelect CSH F-pheny OBD Column, 19*250 mm, 5 μm; Mobile Phase A: Water (0.05%TFA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient:11 B to 19 B in 12 minutes; 254/220 nm; R_T:10.70 minutes) to give 5-[2-(9-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)ethoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione(8.2mg,5.52%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.59 (s, 1H), 8.71 (s, 1H), 7.96 (d, *J* = 7.2 Hz, 1H), 7.82 (d, *J* = 11.3 Hz, 1H), 7.71 (t, *J* = 8.8 Hz, 1H), 7.24-7.05 (m, 2H), 6.85 (d, *J* = 18.8 Hz, 2H), 5.32-5.16 (m, 1H), 4.43 (s, 2H), 4.20 (s, 2H), 3.97 (s, 7H), 3.90 (s, 1H), 3.75 (s, 3H), 3.59-3.38 (m, 4H), 3.31-3.12 (m, 5H), 3.05-2.86 (m, 2H), 2.82-2.63 (m, 1H), 2.47 -1.84 (m, 5H). LCMS (ESI) m/z: [M+H]+ = 765.45.

Example 56 – Preparation of 5-(4-(9-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-1 -oxa-4,9-diazaspiro[5.5]undecan-4-yl)butoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound D50)

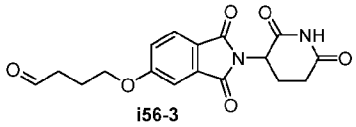


Step 1: Preparation of 5-(4,4-dimethoxybutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (i56-2)



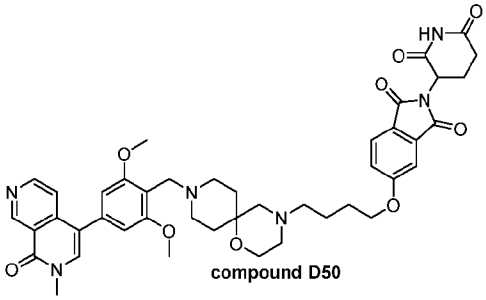
To a solution of 2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindole-1,3-dione (500.00 mg, 1.823 mmol, 1.00 equiv) and 4-chloro-1,1-dimethoxybutane (278.27 mg, 1.823 mmol, 1 equiv) in DMF (7.00 mL) was added K_2CO_3 (755.96 mg, 5.470 mmol, 3 equiv). The resulting solution was stirred at 80 ℃ for 12 hours. The resulting mixture was extracted with EA (50 mL x 2). The combined organic layers were washed with saturated NaCl (50 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA/PE (100:0) to afford 5-(4,4-dimethoxybutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (43.6 mg, 6.13%) as an off-white solid. LCMS (ESI) m/z: [M+H]+ = 391.

Step 2: Preparation of 4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)butanal (i56-3)



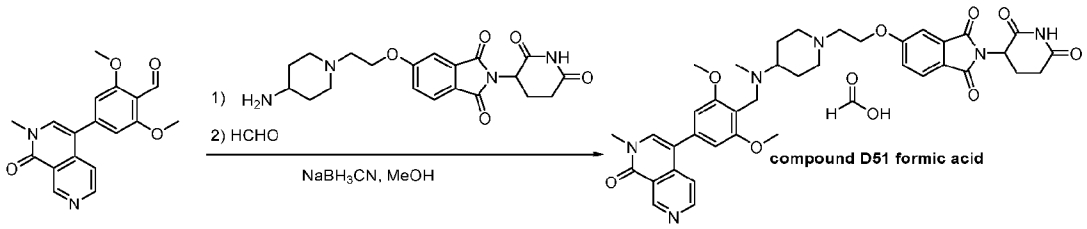
A solution of 5-(4,4-dimethoxybutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (43.60 mg, 0.112 mmol, 1.00 equiv) and HCl (1.00 mL, 4M) in THF (1.00 mL) was stirred at 25 ℃ for 1 hour. The resulting mixture was extracted with EA (50 mL x 2). The combined organic layers were washed with saturated NaCl (50 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]butanal (34.6mg, 89.98%) as an off-white solid. LCMS (ESI) m/z: [M+H]+ = 345.

Step 3: Preparation of 5-(4-(9-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)butoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound D50)



To a solution of 4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]butanal (34.00 mg, 0.099 mmol, 1.00 equiv) and 4-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-2-methyl-2,7-naphthyridin-1-one (45.87 mg, 0.099 mmol, 1 equiv) in DMF(1.00 mL) was added $NaBH(OAc)_3$ (41.86 mg, 0.197 mmol, 2 equiv). The resulting solution was stirred at 25 ℃ for 1 hour. The mixture was purified by prep-HPLC (conditions: Xselect CSH F-Phenyl OBD Column 19*150 mm 5 μm; Mobile Phase A: Water (0.05%TFA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient:10 B to 19 B in 15 minutes; 254/220 nm; R_T: 14.53 minutes) to afford 5-[4-(9-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)butoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (14 mg,17.88%) as an off-white solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.57 (s, 1H), 8.70 (d, *J* = 6.0 Hz, 1H), 7.87 (s, 1H), 7.74 (d, *J* = 7.7 Hz, 2H), 7.27 – 7.14 (m, 2H), 6.89 (s, 2H), 5.16 (dd, *J* = 12.8, 5.5 Hz, 1H), 4.45 (s, 2H), 4.09 – 4.01 (m, 2H), 3.98 (s, 6H), 3.89 (t, *J* = 6.4 Hz, 2H), 3.73 (s, 3H), 3.57 – 3.48 (m, 2H), 3.28 – 3.17 (m, 4H), 2.98 – 2.87 (m, 2H), 2.85 – 2.59 (m, 2H), 2.41 – 2.25 (m, 1H), 2.23 – 2.07 (m, 2H), 2.05 – 1.90 (m, 2H), 1.89 – 1.59 (m, 5H). LCMS (ESI) m/z: [M+H]+ = 793.3.

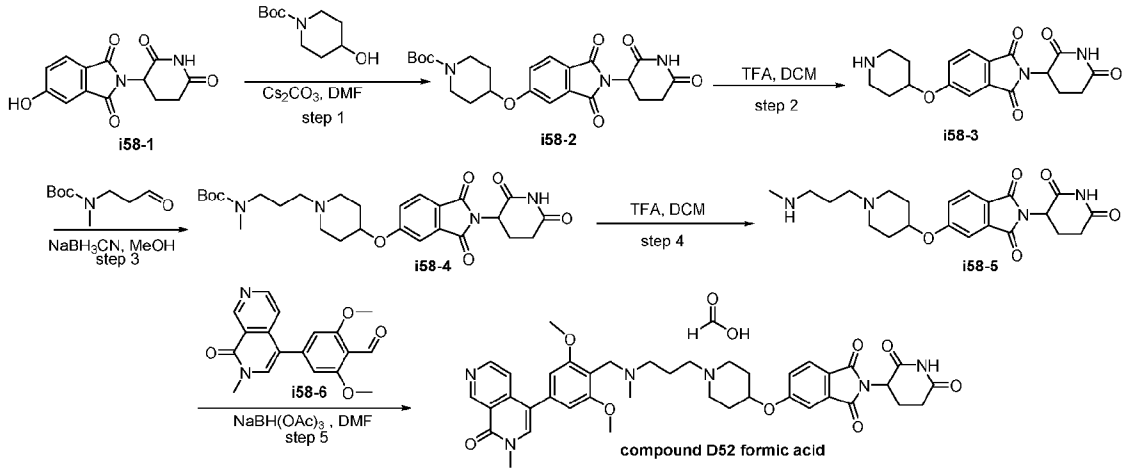
Example 57 – Preparation of 5-[2-[4-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] (methyl)amino)piperidin-1-yl]ethoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione; formic acid (compound D51 formic acid)



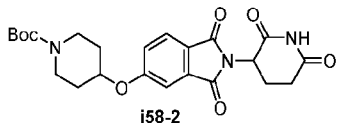
To a solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (30.00 mg, 0.092 mmol, 1.00 equiv) and 5-[2-(4-aminopiperidin-1-yl)ethoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (37.04 mg, 0.092 mmol, 1.00 equiv) in MeOH (1 mL) was stirred for 3 hours at room temperature under nitrogen atmosphere. To the above mixture was added $NaBH_3CN$ (11.63 mg, 0.185 mmol, 2.00

equiv), and the reaction was stirred for additional 1 hour at room temperature. To the above mixture was added HCHO (27.77 mg, 0.925 mmol, 10.00 equiv), and the reaction was stirred for 1 hour at room temperature under nitrogen atmosphere. Then $NaBH_3CN$ (11.63 mg, 0.185 mmol, 2.00 equiv) was added. The mixture was stirred for overnight at room temperature under nitrogen atmosphere. The crude product (40 mg) was purified by Prep-HPLC (conditions: Gemini-NX C18 AXAI Packed column, 21.2*150 mm 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient:5 B to 17 B in 9 minutes; 254-220 nm; R_T: 8.30 minutes) to afford 5-[2-[4-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)piperidin-1-yl]ethoxy]-2-(2,6-dioxopiperidin-3-yl)iso indole-1,3-dione formic acid (7.8 mg) as a white solid. ^{1}H NMR (300 MHz, DMSO-d6) δ 1.55 (2H, d), 1.77 (2H, d), 2.03 (3H, d), 2.16 (3H, s), 2.44 (3H, d), 2.73 (2H, s), 2.88 – 3.08 (3H, m), 3.61 (5H, s), 3.80 (6H, s), 4.30 (2H, s), 5.12 (1H, m), 6.72 (2H, s), 7.38 (1H, m), 7.48 (1H, d), 7.57 (1H, d), 7.80 – 7.90 (2H, m), 8.23 (1H, s), 8.72 (1H, d), 9.45 (1H, s), 11.12 (1H, s). LCMS (ESI) m/z: [M+H]+ = 723.40.

Example 58 – Preparation of 5-((1-(3-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl) (methyl)amino) propyl)piperidin-4-yl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (compound D52 formic acid)



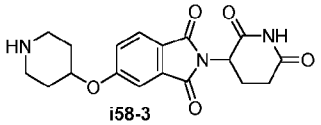
Step 1: Preparation of tert-butyl 4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)piperidine-1-carboxylate (i58-2)



A mixture of 2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindole-1,3-dione (1.00 g, 3.647 mmol, 1.00 equiv), *tert*-butyl 4- bromopiperidine-1-carboxylate (0.96 g, 3.634 mmol, 1.00 equiv) and Cs_2CO_3 (2.38 g, 7.293 mmol, 2.00 equiv) in DMF (20.00 mL) was stirred for overnight at 90 ℃ under air atmosphere. The resulting mixture was filtered, and the filter cake was washed with EtOAc (3 x 10 mL). The filtrate was

concentrated under reduced pressure. The residue was purified by Prep-TLC (hexane/ EtOAc 1:1) to afford *tert*-butyl4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]piperidine-1-carboxylate (280 mg, 11.19%) as a yellow oil. LCMS (ESI) m/z: [M+H]+ = 458.19.

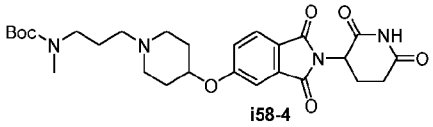
Step 2: Preparation of 2-(2,6-dioxopiperidin-3-yl)-5-(piperidin-4-yloxy)isoindoline-1,3-dione (i58-3)



i58-3

A solution of TFA (1.00 mL) and *tert*-butyl 4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]piperi dine-1-carboxylate(200.00 mg, 0.437 mmol, 1.00 equiv) in DCM (4.00 mL) was stirred for 2 hours at room temperature under air atmosphere. The resulting mixture was concentrated under reduced pressure to afford 2-(2,6-dioxopiperidin-3-yl)-5-(piperidin-4-yloxy) isoindole-1,3-dione (120 mg, 76.81%) as a brown solid. LCMS (ESI) m/z: [M+H]+ = 358.14 .

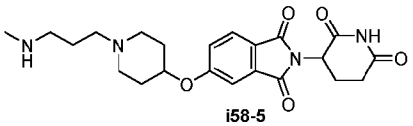
Step 3: Preparation of tert-butyl(3-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)piperidin-1-yl)propyl)(methyl) carbamate (i58-4)



i58-4

To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-(piperidin-4-yloxy)isoindole-1,3-dione (120.00 mg, 0.336 mmol, 1.00 equiv) and *tert*-butyl *N*-methyl-*N*-(3-oxopropyl)carbamate (62.87 mg, 0.336 mmol, 1.00 equiv) in MeOH (1.50 mL) was added $NaBH_3CN$ (42.20 mg, 0.672 mmol, 2.00 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 hours at room temperature under nitrogen atmosphere. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford tert-*butyl N*-[3-(4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]piperidin-1-yl)propyl]-*N*-methylcarbamate (88.00 mg, 49.57%) as a yellow oil. LCMS (ESI) m/z: [M+H]+ = 529.26 .

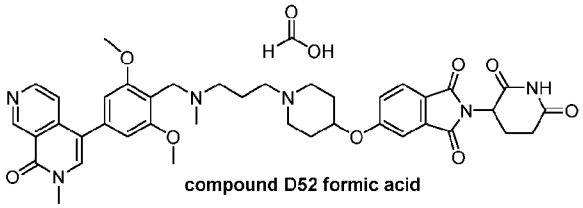
Step 4: Preparation of 2-(2,6-dioxopiperidin-3-yl)-5-((1-(3-(methylamino)propyl)piperidin-4-yl)oxy)isoindoline-1,3-dione (i58-5)



i58-5

A solution of *tert*-butyl *N*-[3-(4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]piperidin-1-yl)propyl]-*N*-methyl carbamate (88.00 mg, 0.166 mmol, 1.00 equiv) and TFA (1.00 mL) in DCM (4.00 mL) was stirred for 1 hour at room temperature. The resulting mixture was concentrated under reduced pressure to afford 2-(2,6-dioxopiperidin-3-yl)-5-((1-(3-(methylamino) propyl)piperidin-4-yl)oxy)isoindoline-1,3-dione (70 mg,98.50 %) as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 429.21 .

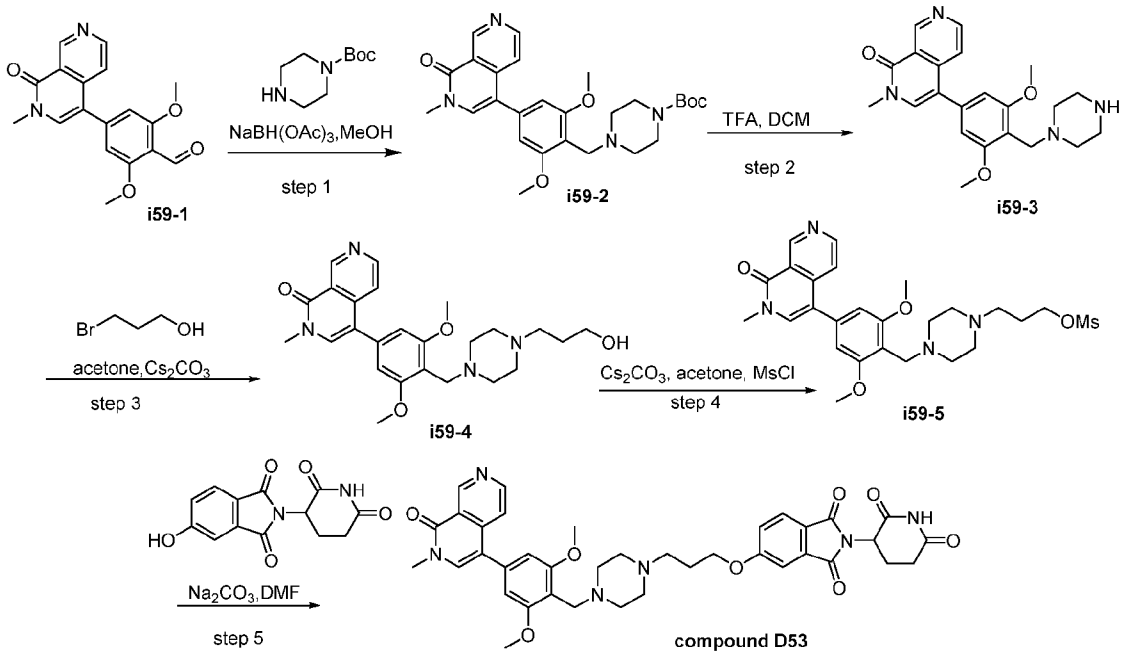
Step 5: Preparation of 5-((1-(3-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)(methyl)amino)propyl)piperidin-4-yl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (compound D52 formic acid)



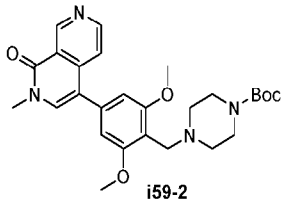
compound D52 formic acid

A solution of 2-(2,6-dioxopiperidin-3-yl)-5-([1-[3-(methylamino)propyl]piperidin-4-yl]oxy)isoindole-1,3-dione (70.00 mg, 0.163 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (52.99 mg, 0.163 mmol, 1.00 equiv) in DMF (3.00 mL) was stirred for 30 minutes at room temperature. To the above mixture was added $NaBH(AcO)_3$ (69.25 mg, 0.327 mmol, 2.00 equiv) in portions at room temperature. The resulting mixture was stirred for additional 2 days at 50 °C. The mixture was allowed to cool down to room temperature. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; mobile phase, MeOH in water, 10% to 50% gradient in 10 minutes; detector, UV 254 nm). The crude product (75 mg) was purified by Prep-HPLC (conditions: SunFire C18 OBD Prep Column, 19 mm X 250 mm; mobile phase, Water(0.1% FA) and ACN (hold 7% Phase B in 0 min, up to 12% in 10 minutes); Detector, UV 254/220 nm) to afford 5-([1-[3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)propyl]piperidin-4-yl]oxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (7.8 mg, 6.48%) as a white solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.52 (s, 1H), 8.68 (d, *J* = 5.7 Hz, 1H), 8.42 (brs, 1.4H, FA), 7.83 – 7.74 (m, 2H), 7.63 (d, *J* = 5.6 Hz, 1H), 7.41 (d, *J* = 2.1 Hz, 1H), 7.36 – 7.28 (m, 1H), 6.91 (s, 2H), 5.12 (dd, *J* = 12.5, 5.4 Hz, 1H), 4.76 (s, 1H), 4.45 (s, 2H), 4.01 (s, 6H), 3.70 (s, 3H), 3.37 (s, 2H), 3.00 (s, 2H), 2.95 – 2.84 (m, 4H), 2.82 – 2.63 (m, 6H), 2.22 – 2.07 (m, 5H), 1.88 (s, 2H). LCMS (ESI) m/z: [M+H]+ =737.40.

Example 59 – Preparation of 5-[3-(4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]piperazin-1-yl) propoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (compound D53)

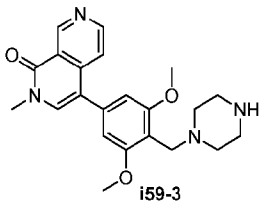


Step 1: Preparation of tert-butyl 4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] piperazine-1-carboxylate (i59-2)



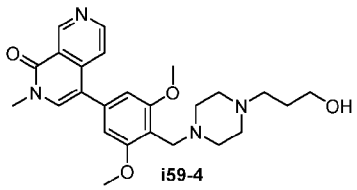
To a stirred solution of 2, 6-dimethoxy-4-(2-methyl-1-oxo-2, 7-naphthyridin-4-yl) benzaldehyde (200.00 mg, 0.617 mmol, 1.00 equiv) and *tert*-butyl piperazine-1-carboxylate (173.00 mg, 0.929 mmol, 1.51 equiv) in MeOH was added $NaBH(OAc)_3$ (527.00 mg, 2.487 mmol, 4.03 equiv) in portions at room temperature. The resulting mixture was stirred for 3 hours at room temperature. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford *tert*-butyl 4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]piperazine-1-carboxylate (204 mg, 66.89%) as a light yellow oil. LCMS (ESI) m/z: [M+H]+ = 495.

Step 2: Preparation of 4-(3, 5-dimethoxy-4-(piperazin-1-ylmethyl) phenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (i59-3)



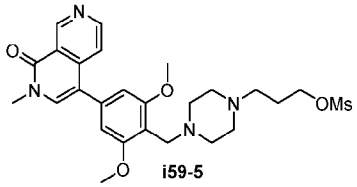
To a stirred solution of *tert*-butyl 4-[[2, 6-dimethoxy-4-(2-methyl-1-oxo-2, 7-naphthyridin-4-yl) phenyl] methyl] piperazine-1-carboxylate (204.00 mg, 0.412 mmol, 1.00 equiv) in DCM was added TFA (1.00 mL) dropwise at room temperature. The resulting mixture was stirred for 1 hour at room temperature. The resulting mixture was concentrated under vacuum. The 4-(3,5-dimethoxy-4-(piperazin-1-ylmethyl) phenyl) -2-methyl-2,7-naphthyridin-1(2H)-one (210 mg crude) was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]+ = 395.

Step 3: Preparation of 4-(4-((4-(3-hydroxypropyl) piperazin-1-yl) methyl)-3, 5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (i59-4)



To a stirred solution of 4-[3,5-dimethoxy-4-(piperazin-1-ylmethyl)phenyl]-2-methyl-2,7-naphthyridin-1-one (200.00 mg, 0.507 mmol, 1.00 equiv) and 3-bromopropanol (140.94 mg, 1.014 mmol, 2.00 equiv) in acetone was added Cs_2CO_3 (330.38 mg, 1.014 mmol, 2.00 equiv) in portions at room temperature. The resulting mixture was stirred for overnight at room temperature. Desired product could be detected by LCMS. The resulting mixture was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]+ = 453.

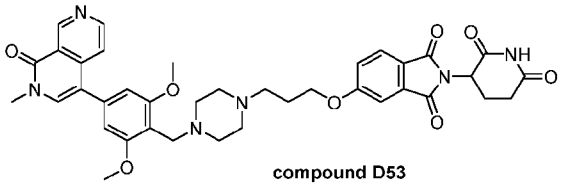
Step 4: Preparation of 3-(4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl) phenyl]methyl]pipera-zin-1-yl)propyl methanesulfonate (i59-5)



To a stirred solution of 4-(4-[[4-(3-hydroxypropyl) piperazin-1-yl] methyl]-3, 5-dimethoxyphenyl)-2-methyl-2, 7-naphthyridin-1-one (200.00 mg, 0.442 mmol, 1.00 equiv) and Cs_2CO_3 (287.98 mg, 0.884 mmol, 2.00 equiv) in acetone was added MsCl (101.25 mg, 0.884 mmol, 2.00 equiv) in portions at room

temperature. The resulting mixture was stirred for overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 3-(4-[[2, 6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl] methyl]piperazin-1-yl)propyl methanesulfonate (92 mg, 39.23%) as a light yellow oil. LCMS (ESI) m/z: [M+H]+ = 531.

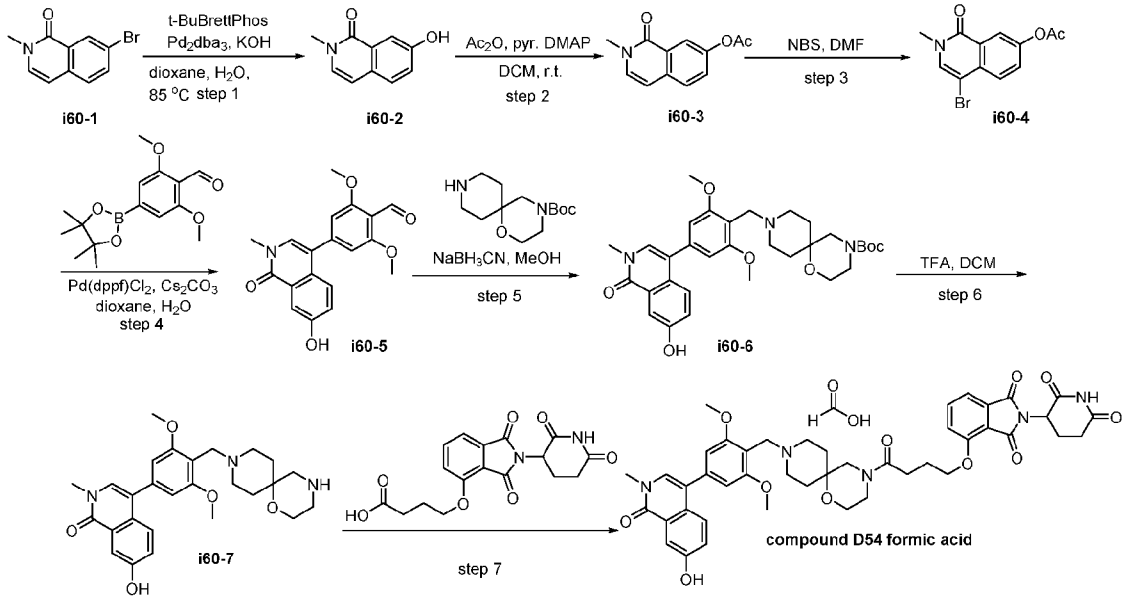
Step 5: Preparation of 5-[3-(4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]piper -azin-1-yl) propoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (compound D53)



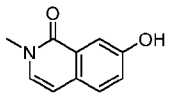
compound D53

To a stirred solution of 3-(4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl] methyl]piperazin-1-yl)propyl methanesulfonate (90.00 mg, 0.170 mmol, 1.00 equiv) and 2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindole-1,3-dione (47.00 mg, 0.171 mmol, 1.01 equiv) in DMF was added Na_2CO_3 (36.00 mg, 0.340 mmol, 2.00 equiv) in portions at room temperature. The resulting mixture was stirred for 2 hours at 80 ℃. The crude product was purified by Prep-HPLC (conditions: Xselect CSH F-Phenyl OBD column, 19*250, 5 μm; mobile phase, Water (0.05%TFA) and ACN (hold 5% Phase B in 2 min, up to 22% in 13 minutes); Detector, UV). This resulted in 5-[3-(4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]piperazin-1-yl)propoxy]-2-(2,6-dioxopipe ridin-3-yl)isoindole-1,3-dione (28.1 mg, 23.38%) as an off-white solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.59 (s, 1H), 8.70 (d, *J* = 6.0 Hz, 1H), 7.97 (s, 1H), 7.84 (t, *J* = 7.6 Hz, 2H), 7.45 (d, *J* = 2.1 Hz, 1H), 7.35 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.89 (s, 2H), 5.12 (dd, *J* = 12.4, 5.4 Hz, 1H), 4.49 (s, 2H), 4.30 (t, *J* = 5.7 Hz, 2H), 3.97 (s, 6H), 3.75 (s, 3H), 3.57 (s, 4H), 3.16 (s, 2H), 3.45 – 3.34 (m, 4H), 2.99 – 2.65 (m, 3H), 2.25 (s, 2H), 2.19 – 2.09 (m, 1H). LCMS (ESI) m/z: [M+H]+ =709.35.

Example 60 – Preparation of 2-(2,6-dioxopiperidin-3-yl)-4-[4-(9-[[4-(7-hydroxy-2-methyl-1-oxoisoquinolin-4-yl)-2,6-dimethoxyphenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-4-oxobutoxy]isoindole-1,3-dione formic acid (compound D54 formic acid)



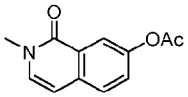
Step 1: Preparation of 7-hydroxy-2-methylisoquinolin-1-one (i60-2)



i60-2

To a mixture of 7-bromo-2-methylisoquinolin-1-one (500 mg, 2.100 mmol, 1.00 equiv), $Pd_2(dba)_3$ (96.2 mg, 0.105 mmol, 0.05 equiv), *tert*-BuBrettPhos (101.8 mg, 0.210 mmol, 0.10 equiv), and KOH (353.5 mg, 6.300 mmol, 3.00 equiv) was added dioxane (15 mL) and water(5 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 85 ℃. The mixture was acidified pH 4 with 1 M HCl (aq.) and extracted with EtOAc (3 x 30 mL). T he combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1 to 3:1) to afford 7-hydroxy-2-methylisoquinolin-1-one (312 mg, 85%) as a grey solid. LCMS (ESI) m/z: [M+H]+ = 176.

Step 2: Preparation of 2-methyl-1-oxoisoquinolin-7-yl acetate (i60-3)



i60-3

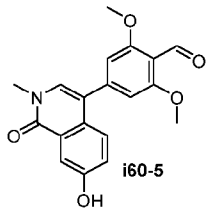
To a stirred solution/mixture of 7-hydroxy-2-methylisoquinolin-1-one (272 mg, 1.553 mmol, 1.00 equiv) and pyridine (614 mg, 7.763 mmol, 5.00 equiv) in DCM (6 mL) was added DMAP (10 mg, 0.082

mmol, 0.05 equiv) and Ac_2O (46.6 mg, 0.457 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred for 1 hour at room temperature. The resulting mixture was diluted with water (10 mL) and extracted with DCM (2 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 2-methyl-1-oxoisoquinolin-7-yl acetate (335 mg, 99%) as a light brown solid. LCMS (ESI) m/z: [M+H]+ = 218.

Step 3: Preparation of 4-bromo-2-methyl-1-oxoisoquinolin-7-yl acetate (i60-4)

To a stirred solution/mixture of 2-methyl-1-oxoisoquinolin-7-yl acetate (325 mg, 1.496 mmol, 1.00 equiv) in ACN (10 mL) was added NBS (292.9 mg, 1.646 mmol, 1.10 equiv) at room temperature. The resulting mixture was stirred for 0.5 h at room temperature. The resulting mixture was diluted with DCM (30 mL) and washed with 10 mL of water and 10 mL of brine. The organic layer was dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was suspended in EtOAc (3 mL), then filtered and the light grey solid was collected as 4-bromo-2-methyl-1-oxoisoquinolin-7-yl acetate (297mg, 67%). LCMS (ESI) m/z: [M+H]+ = 296.

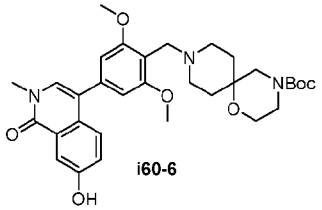
Step 4: Preparation of 4-(7-hydroxy-2-methyl-1-oxoisoquinolin-4-yl)-2,6-dimethoxybenzaldehyde (i60-5)



i60-5

To a mixture of 4-bromo-2-methyl-1-oxoisoquinolin-7-yl acetate (217 mg, 0.733 mmol, 1.00 equiv), 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (321.1 mg, 1.099 mmol, 1.50 equiv), $Pd(dppf)Cl_2.CH_2Cl_2$ (59.8 mg, 0.073 mmol, 0.10 equiv), and Cs_2CO_3 (716.3 mg, 2.198 mmol, 3.00 equiv) was added dioxane (4 mL) and water (1 mL) at room temperature under N_2 atmosphere. The resulting mixture was stirred overnight at 80 °C. The resulting mixture was diluted with sat. NH_4Cl solution (10 mL) and extracted with DCM/i-PrOH (3/1) (5 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (100:1 to 20:1) to afford 4-(7-hydroxy-2-methyl-1-oxoisoquinolin-4-yl)-2,6-dimethoxybenzaldehyde (248 mg, quant.) as a light brown solid. LCMS (ESI) m/z: [M+H]+ = 340.

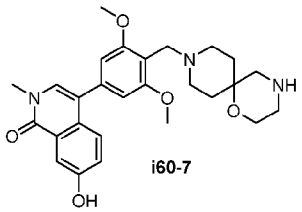
Step 5: Preparation of tert-butyl 9-[[4-(7-hydroxy-2-methyl-1-oxoisoquinolin-4-yl)-2,6-dimethoxyphenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (i60-6)



i60-6

A solution of 4-(7-hydroxy-2-methyl-1-oxoisoquinolin-4-yl)-2,6-dimethoxybenzaldehyde(100 mg, 0.295 mmol, 1.00 equiv) and *tert*-butyl 1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (83.1 mg, 0.324 mmol, 1.1 equiv) in MeOH (1.5 mL) was stirred for 30 minutes at room temperature. Then $NaBH_3CN$ (125 mg, 1.989 mmol, 6.75 equiv) was added. The resulting mixture was stirred for 2 hours at room temperature. The reaction solution was purified by Prep-TLC (DCM/ MeOH 20:1) to afford *tert*-butyl 9-[[4-(7-hydroxy-2-methyl-1-oxoisoquinolin-4-yl)-2,6-dimethoxyphenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (134 mg, 78%) as a light brown foam. LCMS (ESI) m/z: [M+H]+ = 580.

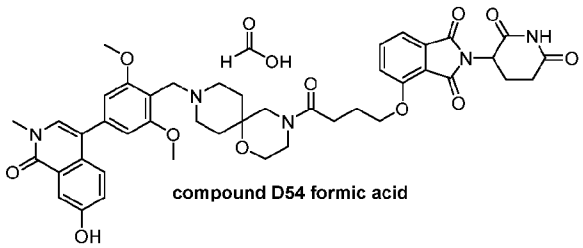
Step 6: Preparation of 4-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-7-hydroxy-2-methylisoquinolin-1-one (i60-7)



i60-7

To a stirred solution/mixture of tert-butyl 9-[[4-(7-hydroxy-2-methyl-1-oxoisoquinolin-4-yl)-2,6-dimethoxy phenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate(134 mg, 0.231 mmol, 1.00 equiv) in DCM (3 mL) was added TFA (1 mL) at room temperature. The resulting mixture was stirred for 30 minutes at room temperature. The mixture was concentrated to dryness to give 4-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-7-hydroxy-2-methylisoquinolin-1-one (135 mg, TFA salt, quant.) as a light brown solid. LCMS (ESI) m/z: [M+H]+ = 480.

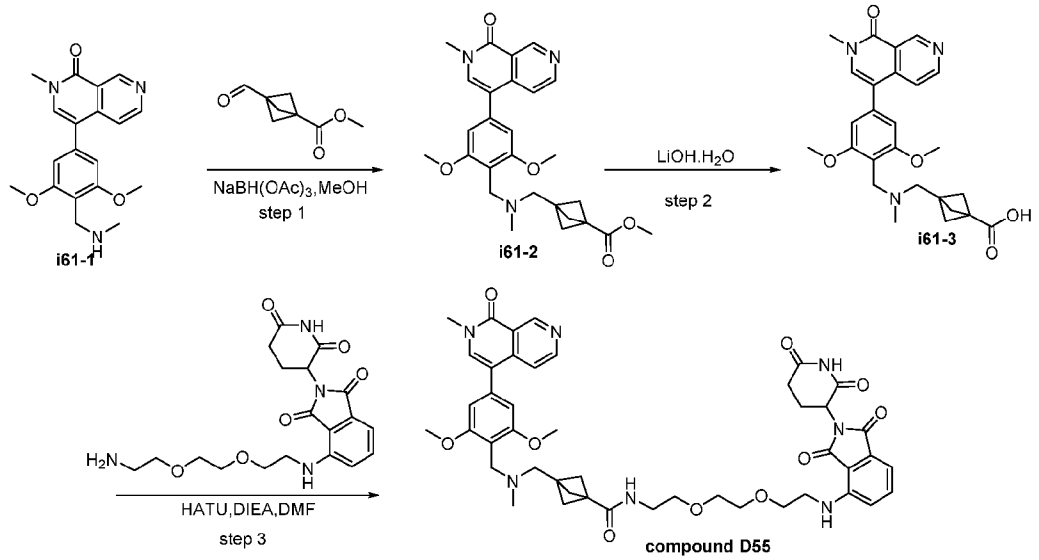
Step 7: Preparation of 2-(2,6-dioxopiperidin-3-yl)-4-[4-(9-[[4-(7-hydroxy-2-methyl-1-oxoisoquinolin-4-yl)-2,6-dimethoxyphenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-4-oxobutoxy]isoindole-1,3-dione formic acid (compound D54 formic acid)



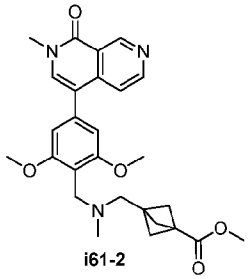
compound D54 formic acid

To a stirred solution of 4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]butanoic acid (33.8 mg, 0.094 mmol, 0.90 equiv) in DMF (1 mL) was added EDCI (40.0 mg, 0.209 mmol, 2.00 equiv) and HOBt (28.2 mg, 0.209 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred at room temperature for 20 minutes followed by addition of 4-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro [5.5]undecan-9-ylmethyl]phenyl)-7-hydroxy-2-methylisoquinolin-1-one (50.0 mg, 0.104 mmol, 1.00 equiv) and DIEA (67.4 mg, 0.521 mmol, 5.00 equiv). After stirring for 3 hours at room temperature, the reaction mixture was purified by Prep-HPLC (conditions: SunFire Prep C18 OBD Column, 19×150 mm 5 μm 10 nm; Mobile Phase A: Water (0.1% FA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient:15 B to 24 B in 12 minutes; 254/220 nm; R_T:11.28 minutes) to afford 2-(2,6-dioxopiperidin-3-yl)-4-[4-(9-[[4-(7-hydroxy-2-methyl-1-oxoisoquinolin-4-yl)-2,6-dimethoxyphenyl]methyl]-1-oxa-4,9-diazaspiro[5.5] undecan-4-yl)-4-oxobutoxy]isoindole-1,3-dione formic acid (11.5 mg, 13%) as an off-white solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 8.55 (s, 0.5H, FA), 7.84 – 7.75 (m, 2H), 7.56 (dd, *J* = 8.8, 3.3 Hz, 1H), 7.47 (dd, *J* = 7.6, 2.7 Hz, 2H), 7.31 – 7.19 (m, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 5.12 (dd, *J* = 12.5, 5.6 Hz, 1H), 4.40 – 4.20 (m, 4H), 3.93 (d, *J* = 12.4 Hz, 6H), 3.78 – 3.62 (m, 7H), 3.58 – 3.48 (m, 2H), 3.30– 3.17 (m, 4H), 2.97 – 2.53 (m, 5H), 2.24 – 1.99 (m, 5H), 1.95 – 1.71 (s, 2H). LCMS (ESI) m/z: [M+H]+ = 822.40.

Example 61 – Preparation of 3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)methyl]-N-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]ethyl]bicyclo[1.1.1]pentane-1-carboxamide (compound D55)

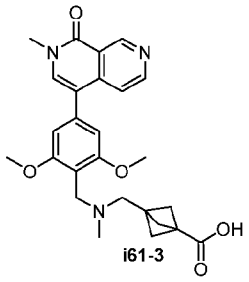


Step 1: Preparation of methyl 3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)methyl]bicyclo[1.1.1]pentane-1-carboxylate (i61-2)



To a stirred solution of 4-[3,5-dimethoxy-4-[(methylamino)methyl]phenyl]-2-methyl-2,7-naphthyridin-1-one (264.00 mg, 0.778 mmol, 1.20 equiv) and methyl 3-formylbicyclo[1.1.1]pentane-1-carboxylate (100.00 mg, 0.649 mmol, 1.00 equiv) in MeOH was added $NaBH(OAc)_3$ (549.91 mg, 2.595 mmol, 4.00 equiv) in portions at room temperature. The resulting solution was stirred for 4 hours at room temperature. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (8:1) to afford methyl3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)-methyl] bicyclo[1.1.1]pentane-1-carboxylate (220 mg, 71.02%) as a light yellow oil. LCMS (ESI) m/z: [M+H]+ = 478.

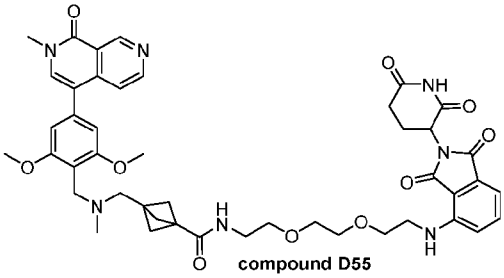
Step 2: Preparation of 3-(((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)(methyl)amino)methyl)bicyclo[1.1.1]pentane-1-carboxylic acid (i61-3)



i61-3

To a stirred solution of methyl 3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)methyl]bicyclo[1.1.1]pentane-1-carboxylate (200.00 mg, 0.419 mmol, 1.00 equiv) and LiOH•H_2O (35.15 mg, 0.838 mmol, 2.00 equiv) in THF(6 mL) was added H_2O (2.00 mL) dropwise at room temperature. The resulting mixture was stirred for overnight at room temperature. The mixture was acidified to pH <7 with conc. HCl. The resulting mixture was concentrated under vacuum. The 3-(((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)(methyl)amino)methyl)-bicyclo[1.1.1]pentane-1-carboxylic acid (215 mg crude) was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]+ = 464.

Step 3: Preparation of 3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)-amino)methyl]-N-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]ethyl]bic-yclo[1.1.1]pentane-1-carboxamide (compound D55)

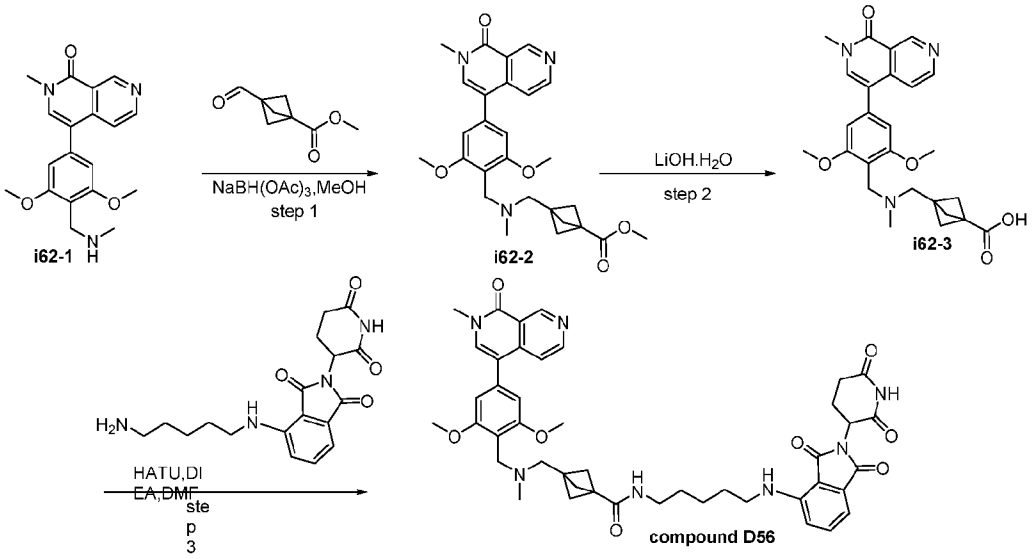


compound D55

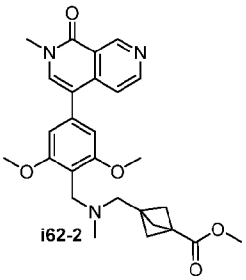
To a stirred solution of 3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] (methyl)amino)methyl]bicyclo[1.1.1]pentane-1-carboxylic acid (50.00 mg, 0.108 mmol, 1.00 equiv) and 4-([2-[2-(2-aminoethoxy)ethoxy]ethyl]amino)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (65.44 mg, 0.162 mmol, 1.50 equiv) in DMF were added DIEA (55.76 mg, 0.431 mmol, 4.00 equiv) and HATU (61.52 mg, 0.162 mmol, 1.50 equiv) in portions at room temperature. The resulting mixture was stirred for 3 h at room temperature. The crude product was purified by Prep-HPLC with the following conditions (NB-Prep-HPLC-01): Column, XSelect CSH Prep C18 OBD Column,, 5 μm,19*150 mm ; mobile phase, Water(0.05%TFA) and ACN (16% PhaseB up to 17% in 20 min ,hold 17% in 8 minutes); Detector, uv. This resulted in 3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)ami-no) methyl]-N-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]ethyl]bicyc-lo [1.1.1]pentane-1-carboxamide; formic acid (4.1 mg, 4.24%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.55 (s, 1H), 8.70 (d, *J* = 5.7 Hz, 1H), 8.55 (s, 1H), 7.78

(s, 1H), 7.65 (d, J = 5.9 Hz, 1H), 7.52 (dd, J = 8.6, 7.1 Hz, 1H), 7.09 (d, J = 8.5 Hz, 1H), 6.99 (d, J = 7.1 Hz, 1H), 6.84 (s, 2H), 5.07 (dd, J = 12.4, 5.4 Hz, 1H), 4.22 (s, 2H), 3.95 (s, 6H), 3.77 (t, J = 5.2 Hz, 2H), 3.73 (s, 3H), 3.71 – 3.65 (m, 4H), 3.59 (t, J = 5.4 Hz, 2H), 3.52 (t, J = 5.2 Hz, 2H), 3.44 – 3.38 (m, 2H), 3.28 – 3.24 (m, 1H), 2.91 – 2.81 (m, 1H), 2.80 – 2.77 (m, 1H), 2.75 – 2.69 (m, 1H), 2.66 (s, 3H), 2.20 (s, 6H), 2.17 – 2.05 (m, 2H). LCMS (ESI) m/z: [M+H]+ = 850.45.

Example 62 – Preparation of 3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)methyl]-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]pentyl)bicyclo[1.1.1]pentane-1-carboxamide (compound D56)



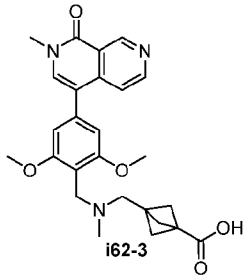
Step 1: Preparation of methyl 3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)methyl]bicyclo[1.1.1]pentane-1-carboxylate (i62-2)



To a stirred solution of 4-[3,5-dimethoxy-4-[(methylamino)methyl]phenyl]-2-methyl-2,7-naphthyridin-1-one (264.18 mg, 0.778 mmol, 1.20 equiv) and methyl 3-formylbicyclo[1.1.1]pentane-1-carboxylate (100.00 mg, 0.649 mmol, 1.00 equiv) in MeOH was added $NaBH(OAc)_3$ (549.91 mg, 2.595 mmol, 4.00 equiv) in portions at room temperature. The resulting solution was stirred for 4 hours at room temperature. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (8:1) to afford methyl3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-

yl)phenyl]methyl](methyl)amino)-methyl] bicyclo[1.1.1]pentane-1-carboxylate (220 mg, 71.02%) as a light yellow oil. LCMS (ESI) m/z: [M+H]+ = 478.

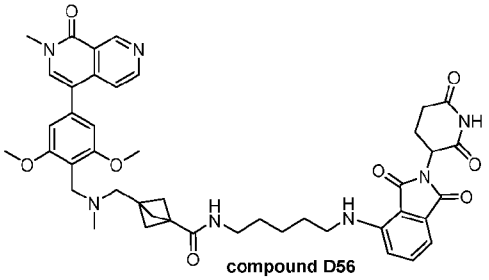
Step 2: Preparation of 3-(((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl) (methyl)amino)methyl)bicyclo[1.1.1]pentane-1-carboxylic acid (i62-3)



i62-3

To a stirred solution of methyl 3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl] methyl](methyl)amino)methyl]bicyclo[1.1.1]pentane-1-carboxylate (200.00 mg, 0.419 mmol, 1.00 equiv) and LiOH•H_2O (35.15 mg, 0.838 mmol, 2.00 equiv) in THF(6 mL) was added H_2O (2.00 mL) dropwise at room temperature. The resulting mixture was stirred for overnight at room temperature. The mixture was acidified to pH <7 with conc. HCl. The resulting mixture was concentrated under vacuum. The 3-(((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)(methyl)amino)methyl)-bicyclo[1.1.1] pentane-1-carboxylic acid (215 mg crude) was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]+ = 464.

Step 3: Preparation of 3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] (methyl) amino)methyl]-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]pentyl)bicyclo[1.1.1] pentane -1-carboxamide (compound D56)

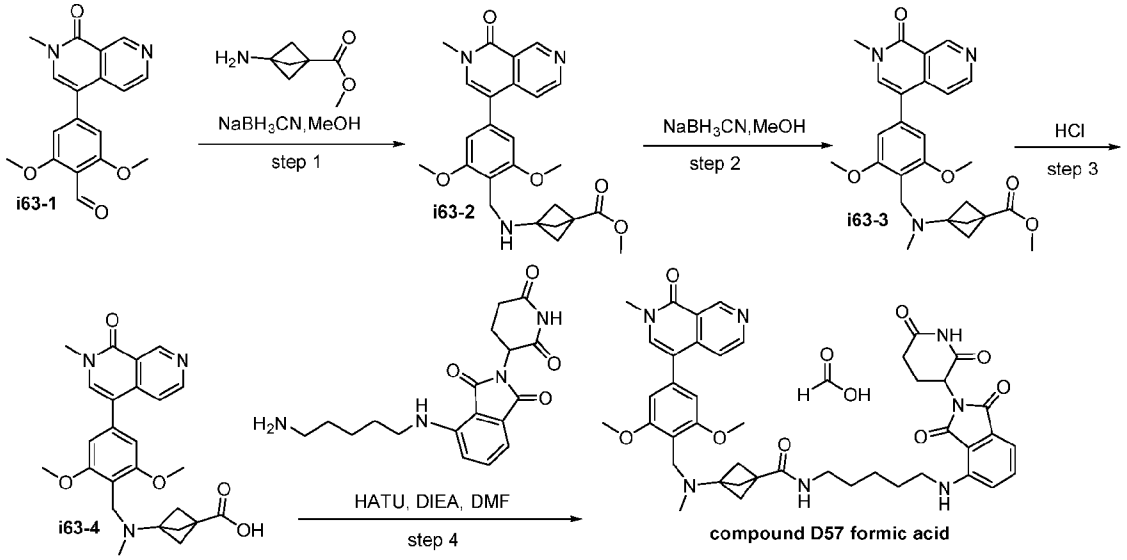


compound D56

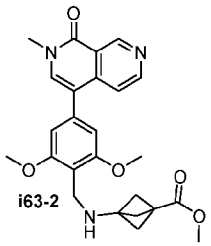
To a stirred solution of 3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] (methyl)amino)methyl]bicyclo[1.1.1]pentane-1-carboxylic acid (50.00 mg, 0.108 mmol, 1.00 equiv) and 4-((5-aminopentyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (65.44 mg, 0.162 mmol, 1.50 equiv) in DMF was added DIEA (55.76 mg, 0.431 mmol, 4.00 equiv) and HATU (61.52 mg, 0.162 mmol, 1.50 equiv) in portions at room temperature. The resulting mixture was stirred for 3 hours at room temperature. The crude product was purified by Prep-HPLC (conditions: XSelect CSH Prep C18 OBD Column, 5 μm, 19*150 mm; mobile phase, Water(0.05%TFA) and ACN (16% Phase B

up to 17% in 20 min ,hold 17% in 8 minutes); Detector, UV). This resulted in 3-(((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)(methyl)amino)-methyl)-*N*-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)pentyl)bicyclo[1.1.1]pentane-1-carboxamide (12.3 mg, 13.42%) as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 804.45.

Example 63 – Preparation of 3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] (methyl) amino)-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]pentyl)bicyclo[1.1.1]pentane -1-carboxamide; formic acid (compound D57 formic acid)

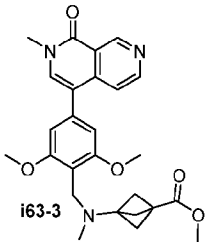


Step 1: Preparation of methyl-3-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)amino)bicyclo[1.1.1]pentane-1-carboxylate (i63-2)



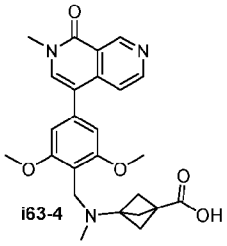
To a solution of methyl 3-aminobicyclo[1.1.1]pentane-1-carboxylate hydrochloride (195.2 mg, 1.099 mmol, 1.10 equiv) in MeOH (5.00 mL) was added Et_3N (111.0 mg, 1.099 mmol, 1.10 equiv), and then 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (324.0 mg, 0.999 mmol, 1.00 equiv) was added. After 10 minutes stirring, $NaBH_3CN$ (125.6 mg, 1.998 mmol, 2.00 equiv) was added in portions at ambient atmosphere. The resulting mixture was concentrated after stirring for 1 hour at room temperature. The mixture was used in the next step directly without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 450.

Step 2: Preparation of methyl-3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl] methyl](methyl)amino)bicyclo[1.1.1]pentane-1-carboxylate (i63-3)



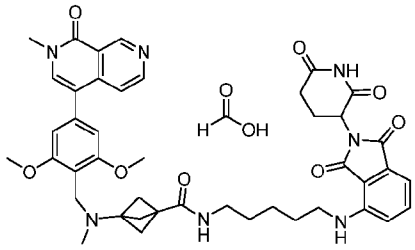
To a solution of crude methyl-3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] amino)bicyclo[1.1.1]pentane-1-carboxylate obtained last step in MeOH (5.00 mL, 12.349 mmol) was added formaldehyde in water (226.0 μL). After 10 min stirring, $NaBH_3CN$ (125.8 mg, 2.002 mmol, 2.00 equiv) was added in portions at ambient atmosphere. The resulting mixture was concentrated after stirring for 1 hour at room temperature. The mixture was purified by Prep-TLC (EtOAc) to afford methyl-3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)bicyclo[1.1.1]pentane-1-carboxylate (120 mg, 24.8%) as a light yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 464.

Step 3: Preparation of 3-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl) (methyl)amino)bicyclo[1.1.1]pentane-1-carboxylic acid (i63-4)



A mixture of methyl 3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] (methyl)amino)bicyclo[1.1.1]pentane-1-carboxylate (120.0 mg, 0.259 mmol, 1.00 equiv) in conc. HCl (2.00 mL) was stirred for 1 hour at 90 °C. The resulting mixture was concentrated under vacuum. The crude product was used in the next step directly without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 450.

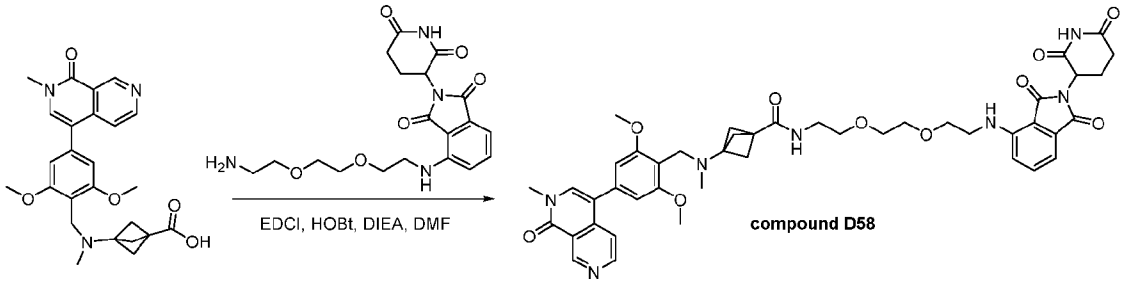
Step 4: Preparation of 3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]pentyl)bicyclo[1.1.1]pentane-1-carboxamide formic acid (compound D57 formic acid)



compound D57 formic acid

To a stirred mixture of 3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)bicyclo[1.1.1]pentane-1-carboxylic acid hydrochloride (50 mg, 0.103 mmol, 1.00 equiv) and 4-[(5-aminopentyl)amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione; trifluoroacetic acid (53.5 mg, 0.113 mmol, 1.10 equiv) in DMF (2.00 mL) was added DIEA (39.9 mg, 0.309 mmol, 3.00 equiv). The mixture was stirred at room temperature for 5 minutes, and then HATU (78.2 mg, 0.206 mmol, 2.00 equiv) was added. After stirring at room temperature for 2 hours, the mixture was purified by Prep-HPLC (conditions: X-select CSH F-Phenyl OBD Column 19*150 mm 5 μm, mobile phase, Water(0.05%TFA) and ACN (10% Phase B up to 26% in 15 minutes)). This resulted in of 3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)-*N*-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]pentyl)bicyclo[1.1.1]pentane-1-carboxamide formic acid (15.2 mg, 17.2%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.57 (s, 1H), 8.71 (d, *J* = 5.9 Hz, 1H), 8.18 (brs, 0.4H, FA), 7.86 (s, 1H), 7.72 (s, 1H), 7.58 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.07 (dd, *J* = 7.8, 5.2 Hz, 2H), 6.90 (s, 2H), 5.06 (dd, *J* = 12.0, 5.4 Hz, 1H), 4.51 (s, 2H), 3.99 (s, 6H), 3.73 (s, 3H), 3.41 – 3.35 (m, 2H), 3.31 – 3.23 (m, 2H), 2.89 – 2.64 (m, 6H), 2.42 (s, 6H), 2.17 – 2.08 (m, 1H), 1.78 – 1.67 (m, 2H), 1.66 – 1.56 (m, 2H), 1.54 – 1.43 (m, 2H). LCMS (ESI) m/z: $[M+H]^+$ = 790.40.

Example 64 – Preparation of 3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] (methyl)amino)-N-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy] ethyl]bicyclo[1.1.1]pentane-1-carboxamide (compound D58)

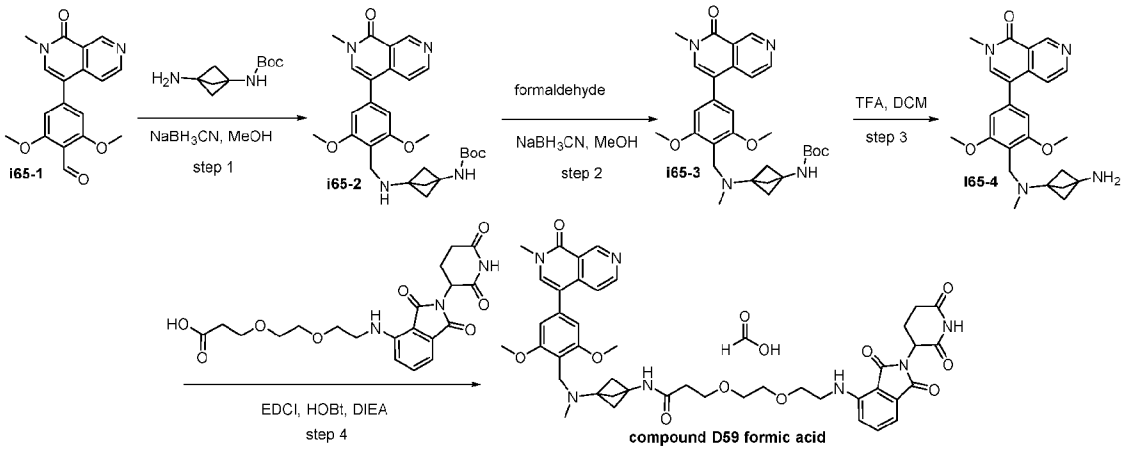


compound D58

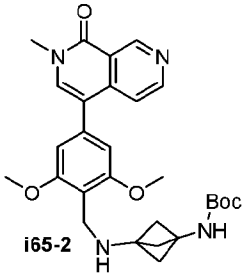
To a stirred mixture of 3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)bicyclo[1.1.1]pentane-1-carboxylic acid (50.0 mg, 0.111 mmol, 1.00 equiv) in DMF (2.00

mL) was added EDCI (42.7 mg, 0.222 mmol, 2.00 equiv) and 4-([2-[2-(2-aminoethoxy)ethoxy]ethyl]amino) -2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (49.5 mg, 0.122 mmol, 1.10 equiv). The mixture was stirred at room temperature for 30 minutes, and then DIEA (71.9 mg, 0.556 mmol, 5.00 equiv) and 4-([2-[2-(2-aminoethoxy)ethoxy]ethyl]amino)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (9.9 mg, 0.024 mmol, 1.10 equiv) were added. After stirring at room temperature for 2 hours, without any additional work-up, the mixture was purified by Prep-HPLC (conditions: column, Phenomenex Gemini C6-Phenyl, 21.2*250 mm, 5 μm; mobile phase, Water(0.05% FA) and ACN (11% Phase B up to 21% in 28 minutes). This resulted in 3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)-N-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino] ethoxy)ethoxy]ethyl]bicyclo[1.1.1]pentane-1-carboxamide (10.5 mg, 10.6%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.53 (s, 1H), 8.69 (d, *J* = 5.7 Hz, 1H), 7.75 (s, 1H), 7.64 (d, *J* = 5.7 Hz, 1H), 7.55 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.07 (dd, *J* = 19.4, 7.8 Hz, 2H), 6.74 (s, 2H), 5.07 (dd, *J* = 12.3, 5.4 Hz, 1H), 3.88 (s, 6H), 3.77 (t, *J* = 5.2 Hz, 2H), 3.73 – 3.63 (m, 9H), 3.59 (t, *J* = 5.5 Hz, 2H), 3.53 (t, *J* = 5.2 Hz, 2H), 3.41 (t, *J* = 5.5 Hz, 2H), 2.90 – 2.68 (m, 3H), 2.27 (s, 3H), 2.20 – 2.06 (m, 7H). LCMS (ESI) m/z: $[M+H]^+$ = 836.40.

Example 65 – Preparation of N-[3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)bicyclo[1.1.1]pentan-1-yl]-3-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]ami no]ethoxy)ethoxy]propanamide formic acid (compound D59 formic acid)

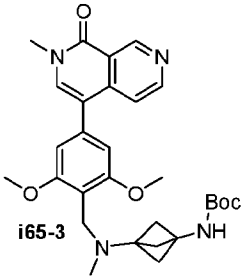


Step 1: Preparation of tert-butyl (3-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)amino)bicyclo[1.1.1]pentan-1-yl)carbamate (i65-2)



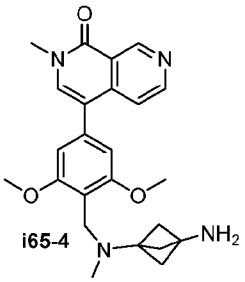
To a stirred solution of *tert*-butyl *N*-[3-aminobicyclo[1.1.1]pentan-1-yl]carbamate (134.49 mg, 0.678 mmol, 1.10 equiv) and *tert*-butyl *N*-[3-aminobicyclo[1.1.1]pentan-1-yl]carbamate (134.49 mg, 0.678 mmol, 1.00 equiv) in MeOH (3 mL) was added $NaBH_3CN$ (77.50 mg, 1.233 mmol, 2.00 equiv) in portions at room temperature. The resulting mixture was stirred for 2 hours at room temperature. The crude resulting mixture was used in the next step directly without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 507.

Step 2: Preparation of tert-butyl N-[3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl] methyl](methyl)amino)bicyclo[1.1.1]pentan-1-yl]carbamate (i65-3)



To a stirred solution of the product from step 1 was added $NaBH_3CN$ (49.62 mg, 0.790 mmol, 2.00 equiv) and formaldehyde (59.27 mg, 1.974 mmol, 5.00 equiv) in portions at room temperature. The resulting mixture was stirred for 2 hours at room temperature. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (8:1) to afford *tert*-butyl *N*-[3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)bicyclo[1.1.1]pentan-1-yl]carbamate (146 mg, 71.03%) as a light yellow oil. LCMS (ESI) m/z: $[M+H]^+$ = 521.

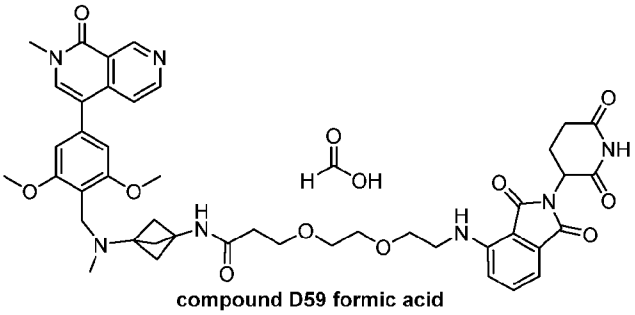
Step 3: Preparation of 4-(4-(((3-aminobicyclo[1.1.1]pentan-1-yl)(methyl)amino)methyl)-3,5-dimethoxy phenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (i65-4)



i65-4

To a stirred solution of *tert*-butyl *N*-[3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl] methyl](methyl)amino)bicyclo[1.1.1]pentan-1-yl]carbamate (146.00 mg, 0.300 mmol, 1.00 equiv) in DCM was added TFA (1.00 mL) at room temperature. The resulting mixture was stirred for 2 hours at room temperature. The resulting mixture was concentrated under reduced pressure to afford 4-(4-(((3-aminobicyclo[1.1.1]pentan-1-yl)(methyl)amino)methyl)-3,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1(2*H*)-one (210 mg crude), which was used in the next step directly without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 421.

Step 4: Preparation of N-[3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] (methyl)amino)bicyclo[1.1.1]pentan-1-yl]-3-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino] ethoxy)ethoxy]propanamide formic acid (compound D59 formic acid).

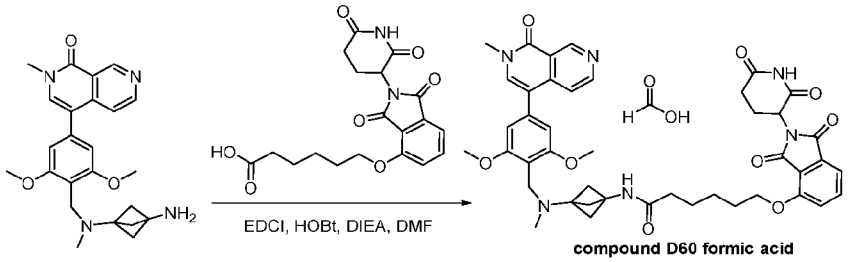


compound D59 formic acid

To a stirred solution of 4-[4-[([3-aminobicyclo[1.1.1]pentan-1-yl](methyl)amino)methyl]-3,5-dimethoxyphenyl]-2-methyl-2,7-naphthyridin-1-one (80.00 mg, 0.190 mmol, 1.00 equiv) and EDCI (72.94 mg, 0.380 mmol, 2.00 equiv) in DMF (1 mL) was added HOBT (51.41 mg, 0.380 mmol, 2.00 equiv) and DIEA (98.35 mg, 0.761 mmol, 4.00 equiv) in portions at room temperature. To the above mixture was added 3-[2-(2-[[2-(2, 6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]propanoic acid (82.45 mg, 0.190 mmol, 1.00 equiv) at room temperature. The resulting mixture was stirred for additional overnight at room temperature. Desired product could be detected by LCMS. The crude product (78.2mg) was purified by prep-HPLC (conditions: Xselect CSH F-Phenyl OBD column, 19*250, 5 μm; Mobile Phase A: Water (0.05% FA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient:15 B to 22 B in 17 minutes; 254/220 nm; R_T:15.32 minutes) to afford *N*-[3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-

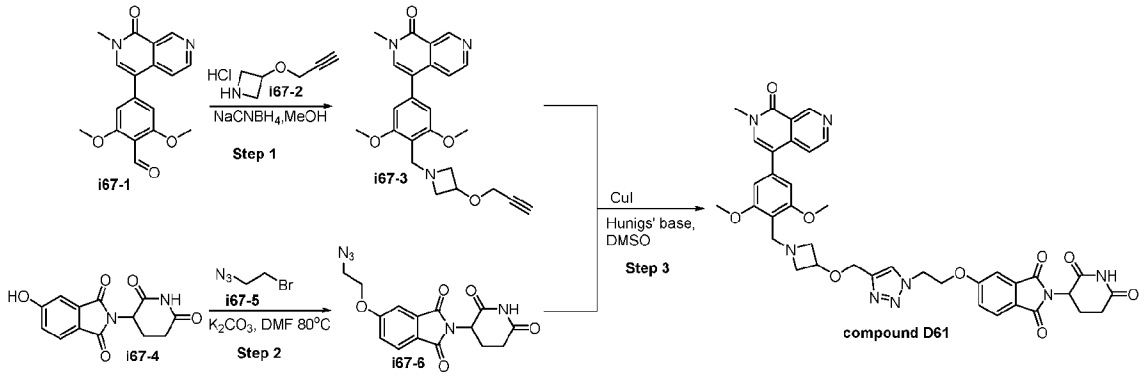
naphthyridin-4-yl)phenyl]methyl](methyl)amino)bicyclo[1.1.1]pentan-1-yl]-3-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]propanamide formic acid (23.7 mg, 14.13%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.53 (s, 1H), 8.70 (d, *J* = 5.8 Hz, 1H), 8.20 (brs, 0.3H, FA), 7.78 (s, 1H), 7.63 (d, *J* = 5.7 Hz, 1H), 7.55 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 1H), 7.03 (d, *J* = 7.1 Hz, 1H), 6.85 (s, 2H), 5.08 (dd, *J* = 12.3, 5.4 Hz, 1H), 4.20 (s, 2H), 3.95 (s, 6H), 3.78 – 3.63 (m, 11H), 3.52 (t, *J* = 5.3 Hz, 2H), 2.99 – 2.66 (m, 6H), 2.52 – 2.34 (m, 8H), 2.18 – 2.08 (m, 1H). LCMS (ESI) m/z: $[M+H]^+$ = 836.65.

Example 66 – Preparation of N-[3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](me thyl)amino)bicyclo[1.1.1]pentan-1-yl]-6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]hex anamide formic acid (compound D60 formic acid)

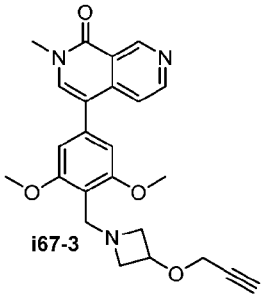


To a stirred solution of 4-[4-[([3-aminobicyclo[1.1.1]pentan-1-yl](methyl)amino)methyl]-3,5-dimethoxy phenyl]-2-methyl-2,7-naphthyridin-1-one (80.00 mg, 0.190 mmol, 1.00 equiv) and EDCI (72.94 mg, 0.380 mmol, 2.00 equiv) in DMF (1 mL) was added HOBt (51.41 mg, 0.380 mmol, 2.00 equiv) at room temperature. To the above mixture was added DIEA (98.35 mg, 0.761 mmol, 4.00 equiv). The resulting mixture was stirred for overnight at room temperature. Without any additional work-up, the mixture was purified by prep-HPLC (conditions: Xselect CSH F-Phenyl OBD column, 19*250, 5 μm; Mobile Phase A: Water (0.05% FA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient:5 B to 35 B in 13 minutes; 254/220 nm; R_T:12.05 minutes) to afford *N*-[3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl) amino)bicycle [1.1.1]pentan-1-yl]-6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]hexanamide formic acid (14.9 mg, 9.36%) as a white solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.53 (s, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.44 (brs, 0.3H, FA), 7.84 – 7.74 (m, 2H), 7.64 (d, *J* = 5.8 Hz, 1H), 7.46 (d, *J* = 7.9 Hz, 2H), 6.78 (s, 2H), 5.10 (dd, *J* = 12.0, 5.4 Hz, 1H), 4.25 (t, *J* = 6.2 Hz, 2H), 3.91 (s, 8H), 3.72 (s, 3H), 2.91 – 2.67 (m, 3H), 2.39 (s, 3H), 2.29 – 2.20 (m, 8H), 2.18 – 2.08 (m, 1H), 1.91 (p, *J* = 6.5 Hz, 2H), 1.73 (p, *J* = 7.2 Hz, 2H), 1.60 (q, *J* = 8.1 Hz, 2H). LCMS (ESI) m/z: $[M+H]^+$ = 791.40.

Example 67 – Preparation of 5-(2-(4-(((1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)azetidin-3-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound D61)

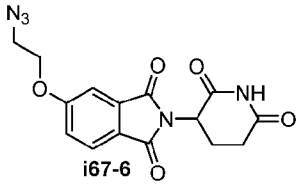


Step 1: Preparation of 4-(3,5-dimethoxy-4-((3-(prop-2-yn-1-yloxy)azetidin-1-yl)methyl)phenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (i67-3)



To a stirred solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (500 mg, 1.54 mmol, 1.00 equiv) in MeOH (15 mL) was added $NaBH_3CN$ (290 mg, 4.62 mmol, 3.00 equiv) and 3-(prop-2-yn-1-yloxy)azetidine hydrochloride (269 mg, 1.84 mmol, 1.20 equiv). The resulting mixture was stirred for 2 hours at room temperature. Solvent was removed and the residue was purified by Flash column chromatography with EtOAc/PE (0-100%) to afford 4-(3,5-dimethoxy-4-((3-(prop-2-yn-1-yloxy)azetidin-1-yl)methyl)phenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (451 mg, 70 %) as a solid. LCMS (ESI) m/z: $[M+H]^+$ = 420.4.

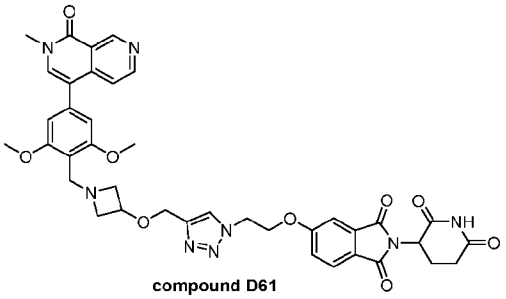
Step 2: Preparation of 5-(2-azidoethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (i67-6)



2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindoline-1,3-dione (500 mg, 1.82 mmol, 1.0 equiv) was dissolved in DMF (15 mL). Potassium carbonate was then added (753 mg, 545 mmol, 3 equiv) followed by potassium iodide (451 mg, 2.72 mmol, 1.5 equiv) and 1-azido-2-bromoethane (286 mg, 1.91 mmol,

1.05 equiv). The mixture was then heated to 80 °C and stirred for 2 hours. The solvent was then removed and Flash column chromatography with EtOAc/PE (0-100%), to afford 5-(2-azidoethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (385 mg, 62%) as a solid. LCMS (ESI) m/z: $[M+H]^+$ = 344.4.

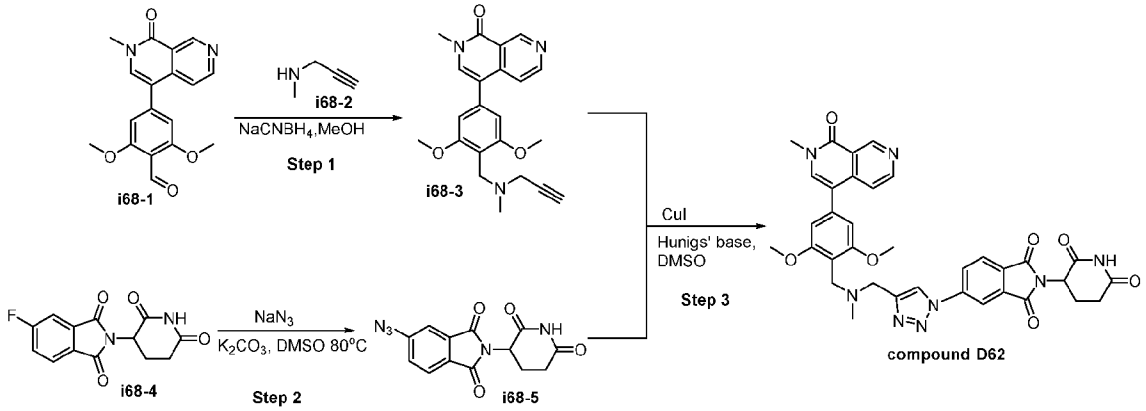
Step 3: Preparation of 5-(2-(4-(((1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)azetidin-3-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound D61)



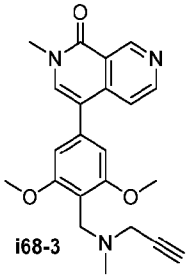
compound D61

5-(2-azidoethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (20 mg, 0.0595 mmol, 1.0 equiv) and 4-(3,5-dimethoxy-4-((3-(prop-2-yn-1-yloxy)azetidin-1-yl)methyl)phenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (25 mg, 0.0595 mmol, 1.0 equiv) were dissolved in DMSO (1 mL). Hünig;s base (0.020 mL, 0.119 mmol, 2 equiv) was then added followed by CuI (5.69 mg, 0.0297 mmol, 0.5 equiv). The mixture was stirred for 1 hour at room temperature. The solution was submitted directly for HPLC purification to give 5-(2-(4-(((1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)azetidin-3-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (14.8 mg, 33%) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.08 (s, 1H), 9.42 (s, 1H), 8.70 (s, 1H), 8.18 (s, 1H), 7.85 (s, 1H), 7.80 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 5.8 Hz, 1H), 7.46 (d, J = 2.3 Hz, 1H), 7.31 (dd, J = 8.3, 2.3 Hz, 1H), 6.69 (s, 2H), 5.09 (dd, J = 12.8, 5.4 Hz, 1H), 4.79 (t, J = 4.9 Hz, 2H), 4.60 (t, J = 5.0 Hz, 2H), 4.39 (s, 2H), 4.00 (t, J = 6.1 Hz, 1H), 3.83 – 3.76 (m, 1H), 3.76 (s, 6H), 3.57 (d, J = 4.2 Hz, 5H), 2.93 – 2.84 (m, 1H), 2.83 (s, 3H), 2.68 – 2.63 (m, 2H), 2.59 (s, 1H), 2.54 (s, 1H), 2.08 – 1.95 (m, 2H). LCMS (ESI) m/z: [M+H]+ = 761.4.

Example 68 – Preparation of 5-(4-(((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)(methyl)amino)methyl)-1H-1,2,3-triazol-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound D62)

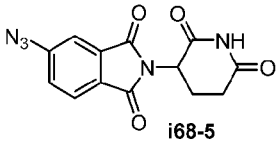


Step 1: Preparation of 4-(3,5-dimethoxy-4-((methyl(prop-2-yn-1-yl)amino)methyl)phenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (i68-3)



To a stirred solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (500 mg, 1.54 mmol, 1.00 equiv) in MeOH (15 mL) was added $NaBH_3CN$ (290 mg, 4.62 mmol, 3.00 equiv) and *N*-methylprop-2-yn-1-amine (127 mg, 1.84 mmol, 1.20 equiv). The resulting mixture was stirred for 2 hours at room temperature. Solvent was removed and the residue was purified by Flash column chromatography with EtOAc/PE (0-100%), to afford 4-(3,5-dimethoxy-4-((methyl(prop-2-yn-1-yl)amino)methyl)phenyl)-2-methyl-2,7-naphthyridin-1(2*H*)-one (390 mg, 67 %) as a solid. LCMS (ESI) m/z: $[M+H]^+$ = 378.7.

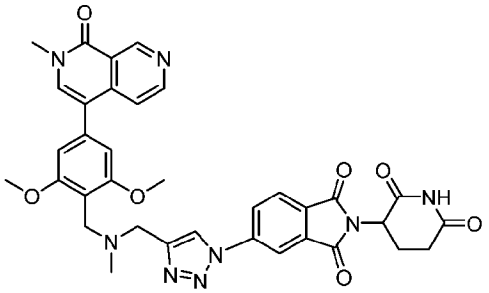
Step 2: Preparation of 5-azido-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (i68-5)



2-(2,6-dioxopiperidin-3-yl)-5-fluoroisoindoline-1,3-dione (500 mg, 1.81 mmol, 1.0 equiv) was dissolved in DMSO (5 mL). Hünig's base was then added (0.944 mL, 5.43 mmol, 3 equiv) followed by sodium azide (176 mg, 2.71 mmol, 1.5 equiv) and 1-azido-2-bromoethane (286 mg, 1.91 mmol, 1.05 equiv). The mixture was then heated to 50 ℃ and stirred for 2 hours. The solution was then loaded

directly onto silica gel and purified over silica gel with EtOAc/PE (0-100%) to afford 5-azido-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (480 mg, 89%) as a solid. LCMS (ESI) m/z: $[M+H]^+$ = 300.1.

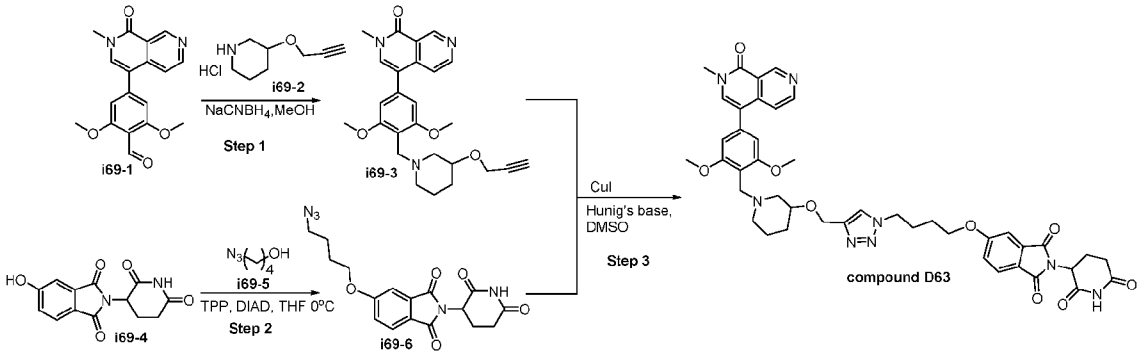
Step 3: 5-(4-(((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)(methyl)amino)methyl)-1H-1,2,3-triazol-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound D62)



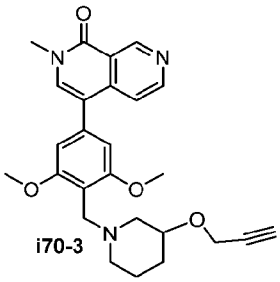
compound D62

5-(2-azidoethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (19.8 mg, 0.0662 mmol, 1.0 equiv) and 4-(3,5-dimethoxy-4-((3-(prop-2-yn-1-yloxy)azetidin-1-yl)methyl)phenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (25 mg, 0.0662 mmol, 1.0 equiv) were dissolved in DMSO (1 mL). Hünig's base (0.023 mL, 0.132 mmol, 2 equiv) was then added followed by CuI (6.3 mg, 0.0279 mmol, 0.5 equiv). The mixture was stirred for 1 hour at room temperature. The solution was submitted directly for HPLC purification to 5-(4-(((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)(methyl)amino)methyl)-1H-1,2,3-triazol-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (12.3 mg, 28%) as a solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.14 (s, 1H), 9.43 (s, 1H), 9.03 (s, 1H), 8.70 (d, J = 5.7 Hz, 1H), 8.52 – 8.45 (m, 2H), 8.13 (d, J = 14.2 Hz, 1H), 7.85 (s, 1H), 7.54 (d, J = 5.7 Hz, 1H), 6.73 (s, 2H), 5.20 (dd, J = 12.9, 5.3 Hz, 1H), 3.78 (s, 6H), 3.58 (s, 3H), 2.96 – 2.83 (m, 1H), 2.65 – 2.58 (m, 1H), 2.58 – 2.50 (m, 1H), 2.22 (s, 5H), 2.13 – 2.03 (m, 1H). LCMS (ESI) m/z: [M+H]+ = 675.4.

Example 69 – Preparation of 5-(4-(4-(((1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)piperidin-3-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)butoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound D63)

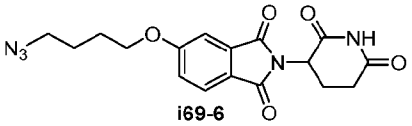


Step 1: Preparation of 4-(3,5-dimethoxy-4-((3-(prop-2-yn-1-yloxy)piperidin-1-yl)methyl)phenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (i69-3)



To a stirred solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (500 mg, 1.54 mmol, 1.00 equiv) in MeOH (15 mL) was added $NaBH_3CN$ (290 mg, 4.62 mmol, 3.00 equiv) and 3-(prop-2-yn-1-yloxy)piperidine hydrochloride (321 mg, 1.84 mmol, 1.20 equiv). The resulting mixture was stirred for 2 hours at room temperature. Solvent was removed and the residue was purified by Flash column chromatography with EtOAc/PE (0-100%) to afford 4-(3,5-dimethoxy-4-((3-(prop-2-yn-1-yloxy)piperidin-1-yl)methyl)phenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (323 mg, 47 %) as a solid. LCMS (ESI) m/z: $[M+H]^+$ = 448.5.

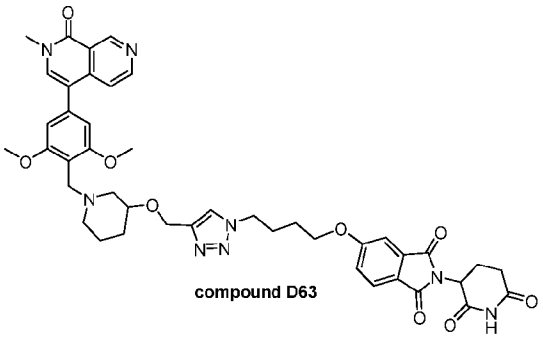
Step 2: Preparation of 5-(4-azidobutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (i69-6)



2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindoline-1,3-dione (500 mg, 1.82 mmol, 1.0 equiv) was dissolved in THF (18 mL). Triphenylphosphine was then added (571 mg, 2.18 mmol, 1.2 equiv) followed by 4-azidobutan-1-ol (246 mg, 2.91 mmol, 1.05 equiv). The solution was cooled to 0 °C and 1-diisopropyl azodicarboxylate (358 mL, 1.82 mmol, 1.0 equiv) was added. The mixture was then warmed to room

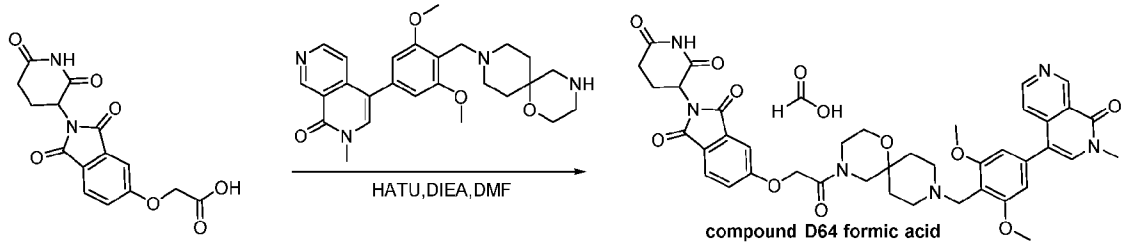
temperature and stirred for 2 hours. Water was added and the reaction extracted 3 times with ethyl acetate. The organics were dried over MgSO4, filtered, and evaporated. The resulting oil was columned over silica gel with EtOAc/PE (0-100%), to afford 5-(4-azidobutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (391 mg, 56%) as a solid. LCMS (ESI) m/z: $[M+H]^+$ = 372.4.

Step 3: 5-(4-(4-(((1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)piperidin-3-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)butoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound D63)



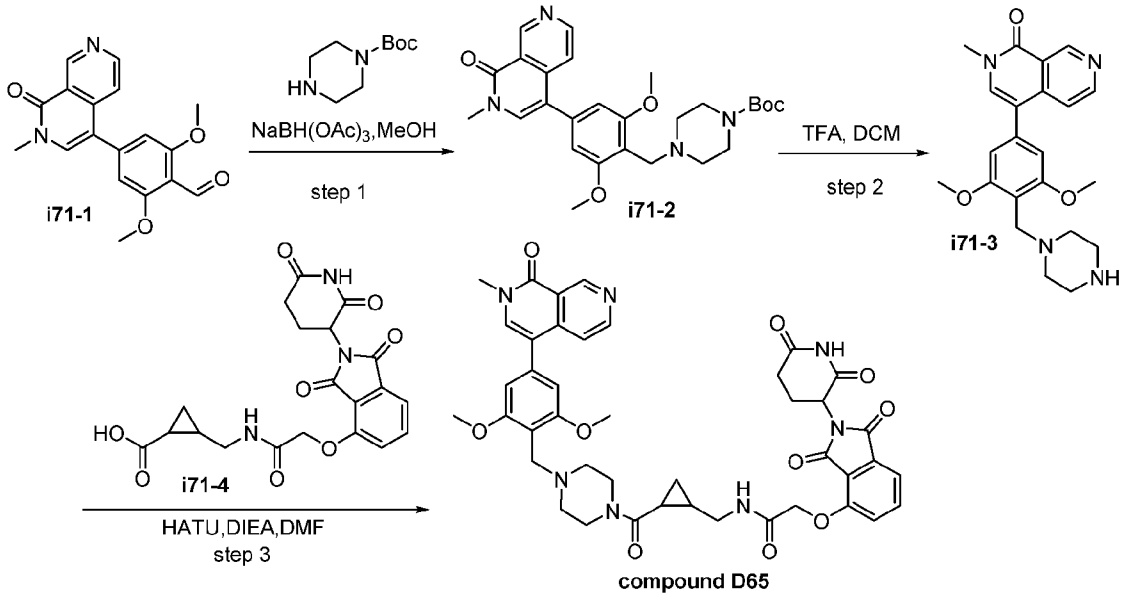
5-(4-azidobutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (21.5 mg, 0.0558 mmol, 1.0 equiv) and 4-(3,5-dimethoxy-4-((3-(prop-2-yn-1-yloxy)azetidin-1-yl)methyl)phenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (25 mg, 0.0558 mmol, 1.0 equiv) were dissolved in DMSO (1 mL). Hünig's base (0.0192 mL, 0.111 mmol, 2 equiv) was then added followed by CuI (5.31 mg, 0.0279 mmol, 0.5 equiv). The mixture was stirred for 1 hour at room temperature. The solution was submitted directly for HPLC purification to give 5-(4-(4-(((1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)piperidin-3-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)butoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (6.2 mg, 12%) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.08 (s, 1H), 8.09 (s, 1H), 7.87 (s, 1H), 7.80 (d, J = 8.3 Hz, 1H), 7.77 – 7.56 (m, 1H), 7.39 (d, J = 2.3 Hz, 1H), 7.31 (dd, J = 8.3, 2.3 Hz, 1H), 6.73 (s, 2H), 6.58 – 6.39 (m, 1H), 5.09 (dd, J = 12.9, 5.4 Hz, 1H), 4.59 – 4.47 (m, 2H), 4.42 (t, J = 7.0 Hz, 2H), 4.17 (t, J = 6.4 Hz, 2H), 3.80 (s, 6H), 3.70 (s, 2H), 3.58 (s, 2H), 3.00 (s, 1H), 2.87 (ddd, J = 17.4, 14.1, 5.4 Hz, 1H), 2.74 (s, 1H), 2.68 – 2.63 (m, 0H), 2.62 – 2.50 (m, 2H), 2.33 – 2.27 (m, 1H), 2.05 (s, 3H), 2.03 – 1.93 (m, 1H), 1.97 – 1.78 (m, 0H), 1.71 (q, J = 6.7 Hz, 3H), 1.40 (s, 1H). LCMS (ESI) m/z: $[M+H]^+$ = 817.2.

Example 70 – Preparation of 5-[2-(9-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-1-ox a-4,9-diazaspiro[5.5]undecan-4-yl)-2-oxoethoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (compound D64 formic acid)

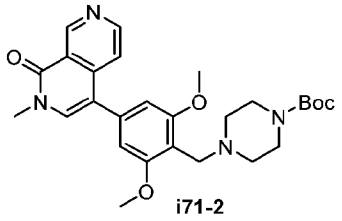


To a stirred solution of [[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]acetic acid (21.46 mg, 0.065 mmol,1.00 equiv) and 4-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-2-methyl-2,7-naphthyridin-1-one(30.00 mg,0.065 mmol,1.00 equiv) in DMF (1 mL) was added HATU (49.11 mg, 0.129 mmol,2.00 equiv) and DIEA (33.38 mg,0.258 mmol,4.00 equiv) at room temperature. The mixture was stirred at room temperature for 16 hours. Without any additional work-up, the mixture was purified by prep-HPLC (conditions: SunFire Prep C18 OBD Column, 19×150 mm 5 μm 10nm; Mobile Phase A: Water (0.1% FA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient:8 B to 33 B in 10 minutes; 254/220 nm; R_T: 8.05 minutes) to afford 5-[2-(9-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2-oxoethoxy]-2-(2,6-diox opiperidin-3-yl)isoindole-1,3-dione formic acid as a white gum (6.8 mg,12.77%). ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.54 (s, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.56 (brs, 0.3H, FA), 7.84 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.76 (d, *J* = 2.5 Hz, 1H), 7.67 – 7.62 (m, 1H), 7.45 (t, *J* = 2.8 Hz, 1H), 7.40 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.81 (d, *J* = 4.5 Hz, 2H), 5.16 – 5.00 (m, 3H), 4.18 – 3.98 (m, 2H), 3.92 (d, *J* = 1.6 Hz, 6H), 3.85 – 3.75 (m, 2H), 3.72 (s, 3H), 3.67 – 3.59 (m, 2H), 3.56 – 3.45 (m, 2H), 3.11 – 2.91 (m, 3H), 2.90 – 2.64 (m, 4H), 2.18 – 2.09 (m, 1H), 2.08 – 1.91 (m, 2H), 1.85 – 1.69 (m, 2H). LCMS (ESI) m/z: $[M+H]^+$ = 779.55.

Example 71 – Preparation of N-[[2-(4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] piperazine-1-carbonyl)cyclopropyl]methyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetamide (compound D65)

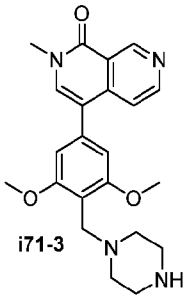


Step 1: Preparation of tert-butyl 4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl] methyl] piperazine-1-carboxylate (i71-2)



To a stirred solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde(100.00 mg, 0.308 mmol, 1.00 equiv) and *tert*-butyl piperazine-1-carboxylate(86.14 mg, 0.462 mmol, 1.50 equiv) in MeOH (1mL) was added $NaBH(OAc)_3$(261.38 mg, 1.233 mmol, 4.00 equiv) at room temperature. The resulting mixture was stirred for 2 hours at room temperature. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash silica chromatography, elution gradient 0 to 60% EtOAc in petroleum ether. Pure fractions were evaporated to dryness to afford product *tert*-butyl 4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl] methyl]piperazine-1-carboxylate (115 mg, 75.4%) as a yellow gum. LCMS (ESI) m/z: $[M+H]^+$ = 495.

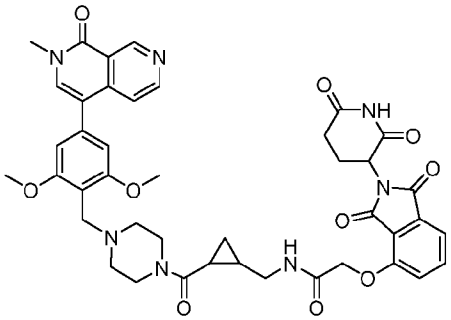
Step 2: Preparation of 4-[3,5-dimethoxy-4-(piperazin-1-ylmethyl)phenyl]-2-methyl-2,7-naphthyridin-1-one (i71-3)



i71-3

A solution of *tert*-butyl 4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]piperaz ine-1-carboxylate (115.00 mg) and TFA (1.00 mL) in DCM (1.00 mL) was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure to afford 4-[3,5-dimethoxy-4-(pipera zin-1-ylmethyl)phenyl]-2-methyl-2,7-naphthyridin-1-one (305 mg, crude), which was used directly without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 395.

Step 3: Preparation of N-[[2-(4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] piperazine-1-carbonyl)cyclopropyl]methyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acet amide (compound D65)

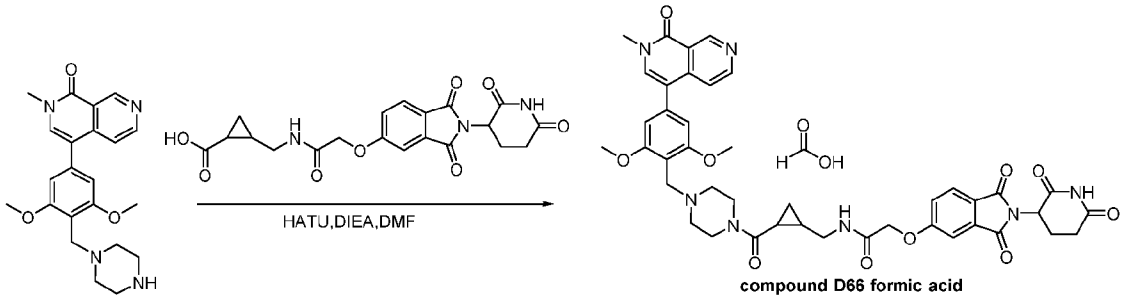


compound D65

To a stirred mixture of 4-[3,5-dimethoxy-4-(piperazin-1-ylmethyl)phenyl]-2-methyl-2,7-naphthyridin-1-one (22.05 mg, 0.056 mmol, 1.20 equiv) and 2-[(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetamido)methyl]cyclopropane-1-carboxylic acid (20.00 mg, 0.047 mmol, 1.00 equiv) in DMF (1 mL) was added HATU (35.42 mg, 0.093 mmol, 2.00 equiv) and DIEA (12.04 mg, 0.093 mmol, 2.00 equiv) at room temperature. Without any additional work-up, the mixture was purified by prep-HPLC (conditions: XBridge Shield RP18 OBD Column, 30*150 mm, 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient:13 B to 22 B in 12 minutes; 254/220 nm; R_T: 9.45 minutes). Pure fractions were evaporated to dryness to afford *N*-[[2-(4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]piperazine-1-carbonyl)cyclopropyl]meth-yl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetamide (12.4 mg, 33.04%) as a white solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.52 (s, 1H), 8.68 (dd, *J* = 5.8, 1.8 Hz, 1H), 8.43 (brs, 0.5H, FA), 7.81 (ddd, *J* =

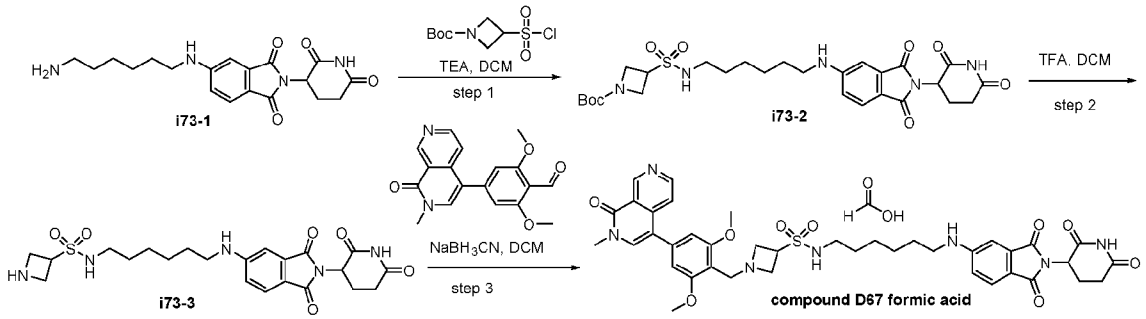
8.4, 7.3, 3.5 Hz, 1H), 7.75 (d, *J* = 3.7 Hz, 1H), 7.65 – 7.61 (m, 1H), 7.54 (dd, *J* = 6.9, 1.6 Hz, 1H), 7.45 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.76 (d, *J* = 2.5 Hz, 2H), 5.19 – 5.11 (m, 1H), 4.80 – 4.68 (m, 2H), 3.93 – 3.81 (m, 9H), 3.78 – 3.68 (m, 5H), 3.51 – 3.35 (m, 2H), 3.29 – 3.16 (m, 1H), 2.93 – 2.67 (m, 7H), 2.21 – 2.06 (m, 2H), 1.72 – 1.60 (m, 1H), 1.21 – 1.12 (m, 1H), 1.09 – 0.99 (m, 1H). LCMS (ESI) m/z: $[M+H]^+$ = 806.70.

Example 72 – Preparation of N-[[2-(4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] piperazine-1-carbonyl)cyclopropyl]methyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]acetamide formic acid (compound D66 formic acid)

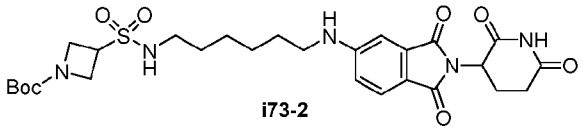


To a stirred mixture of 4-[3,5-dimethoxy-4-(piperazin-1-ylmethyl)phenyl]-2-methyl-2,7-naphthyridin-1-one (22.05 mg, 0.056 mmol, 1.20 equiv) and 2-[(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]ace tamido)methyl]cyclopropane-1-carboxylic acid (20.00 mg, 0.047 mmol, 1.00 equiv) in DMF(1 mL) was added HATU (35.42 mg, 0.093 mmol, 2.00 equiv) and DIEA (12.04 mg, 0.093 mmol, 2.00 equiv) at room temperature. Without any additional work-up, the mixture was purified by prep-HPLC (conditions: XBridge Shield RP18 OBD Column, 19*250 mm,10 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient:13 B to 22 B in 12 minutes; 254/220 nm; R_T: 10.22 minutes). Pure fractions were evaporated to dryness to afford *N*-[[2-(4-[[2,6-dimeth oxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]piperazine-1-carbonyl)cyclopropyl]methyl]-2-[[2-(2,6-dio xopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]acetamide (7.4 mg, 19.18%) as a white solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.52 (s, 1H), 8.68 (d, *J* = 5.8 Hz, 1H), 8.46 (brs, 1.0H, FA), 7.82 (d, *J* = 8.3 Hz, 1H), 7.73 (s, 1H), 7.63 (d, *J* = 5.8 Hz, 1H), 7.45 (d, *J* = 2.3 Hz, 1H), 7.40 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.78 (s, 2H), 5.11 (dd, *J* = 12.4, 5.4 Hz, 1H), 4.68 (s, 2H), 3.95 (s, 2H), 3.89 (s, 6H), 3.81 (s, 2H), 3.70 (s, 3H), 3.63 (s, 1H), 3.42 – 3.34 (m, 2H), 3.29 – 3.20 (m, 1H), 2.94 – 2.67 (m, 7H), 2.18 – 2.09 (m, 1H), 2.09 – 2.00 (m, 1H), 1.62 (q, *J* = 7.5 Hz, 1H), 1.11 (q, *J* = 5.5 Hz, 1H), 1.01 (td, *J* = 8.1, 4.5 Hz, 1H). LCMS (ESI) m/z: $[M+H]^+$ = 806.40.

Example 73 – Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl] methyl]-N-(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]amino]hexyl) azetidine-3-sulfonamide formic acid (compound D67 formic acid)

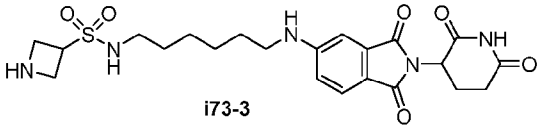


Step 1: Preparation of tert-butyl-3-[(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]hexyl) sulfamoyl]azetidine-1-carboxylate (i73-2)



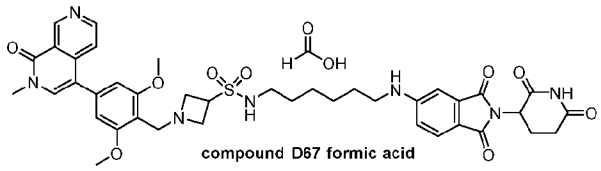
To a stirred mixture of 5-[(6-aminohexyl)amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione(60.00 mg, 0.161 mmol, 1.00 equiv) and *tert*-butyl 3-(chlorosulfonyl)azetidine-1-carboxylate(102.99 mg, 0.403 mmol, 2.50 equiv) in DCM(2.00 mL) was added TEA(48.91 mg, 0.483 mmol, 3.00 equiv). After stirring for 1.5 hours at room temperature, the resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/EA = 1:2) to afford *tert*-butyl-3-[(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]hexyl)sulfamoyl]azetidine-1-carboxylate (61.8 mg, 60.29%) as a light yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 592.

Step 2: Preparation of N-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)hexyl)azetidine-3-sulfonamide (i73-3)



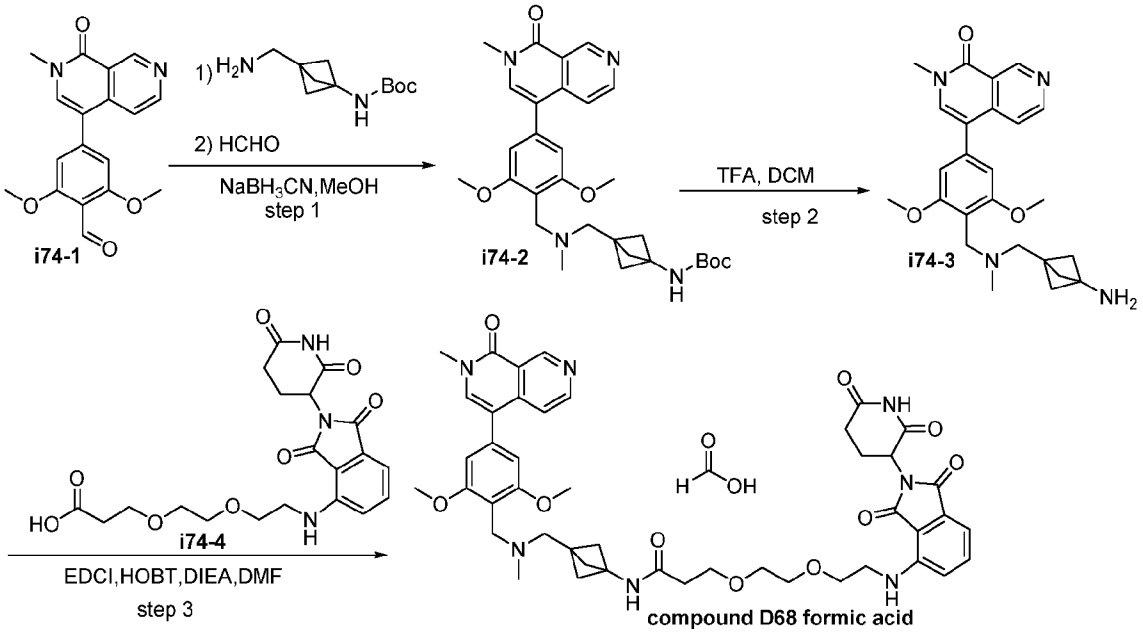
To a stirred mixture of *tert*-butyl 3-[(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino] hexyl)sulfamoyl]azetidine-1-carboxylate (61.8 mg, 0.104 mmol, 1.00 equiv) in DCM (2.00 mL) was added TFA (0.40 mL, 5.385 mmol, 51.56 equiv). After stirring for 1 hour at room temperature, the resulting mixture was concentrated under reduced pressure. The residue was used in the next step directly without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 492.

Step 3: Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl] methyl]-N-(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]amino]hexyl)azetidine-3-sulfonamide formic acid (compound D67 formic acid)

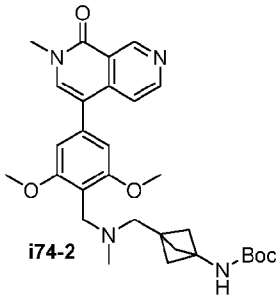


A mixture of *N*-(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]amino] hexyl)azetidine-3-sulfonamide(51.36 mg, 0.104 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (33.89 mg, 0.104 mmol, 1.00 equiv) in DMF(2 mL) was stirred at room temperature. The reaction mixture was then adjusted to pH 8-9 with TEA. To the above mixture was added $NaBH_3CN$ (19.70 mg, 0.313 mmol, 3.00 equiv) in portions, and the resulting mixture was stirred for 2 hours at room temperature. The resulting mixture was concentrated under reduced pressure, the residue was purified by Prep-HPLC (conditions: X Select CSH Prep C18 OBD Column, 5 μm, 19*150 mm; mobile phase, Water(0.1% FA) and ACN (15% Phase B up to 30% in 14 minutes); Detector, UV). This gave 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]amino]hexyl)azetidine-3-sulfonamide formic acid (13 mg, 14.12%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.45 (s, 1H), 8.73 (d, *J* = 5.7 Hz, 1H), 8.14 (s, 0.2H, FA), 7.87 (s, 1H), 7.56 (d, *J* = 5.7 Hz, 1H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.27 (br s, 1H), 6.94 (d, *J* = 2.0 Hz, 1H), 6.82 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.78 (s, 2H), 6.56 (d, *J* = 8.2 Hz, 2H), 5.10 (dd, *J* = 13.0, 5.4 Hz, 1H), 4.01 (br s, 2H), 3.84 (s, 7H), 3.60 (s, 6H), 3.47 – 3.35 (m, 2H), 3.05 – 2.83 (m, 3H), 2.77 – 2.65 (m, 1H), 2.49 – 2.41 (m, 2H), 2.03 – 1.96 (m, 1H), 1.39 (t, *J* = 7.0 Hz, 4H), 1.24 (s, 4H). LCMS (ESI) m/z: $[M+H]^+$ = 800.25.

Example 74 – Preparation of N-[3-[(([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](meth- yl)amino)methyl]bicyclo[1.1.1]pentan-1-yl]-3-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]propanamide formic acid (compound D68 formic acid)



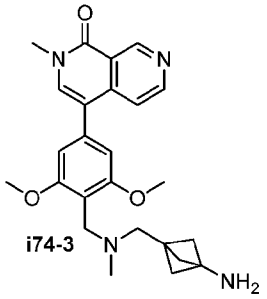
Step 1: Preparation of tert-butyl N-[3-[(([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]amino)methyl]bicyclo[1.1.1]pentan-1-yl]carbamate (i74-2)



To a stirred mixture of 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (200.00 mg, 0.617 mmol, 1.00 equiv) and *tert*-butyl *N*-[3-(aminomethyl)bicyclo[1.1.1]pentan-1-yl]carbamate (144.00 mg, 0.678 mmol, 1.10 equiv) in MeOH (1 mL) was added $NaBH_3CN$ (77.50 mg, 1.233 mmol, 2.00 equiv) in portions at room temperature. The resulting mixture was stirred for 2 hours at room temperature. To the above mixture was added formaldehyde (0.50 mL). The resulting mixture was stirred for 1 hour at room temperature. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash silica chromatography, elution gradient 0 to 30% EtOAc in petroleum ether. Pure fractions was concentrated under vacuum to afford tert-butyl N-[3-[(([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-

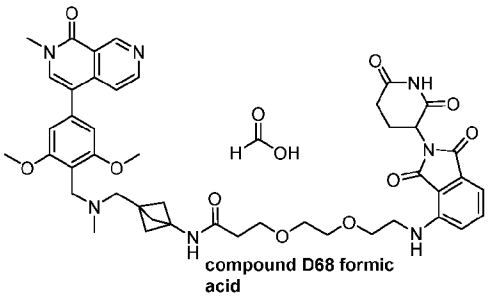
yl)phenyl]methyl]amino)methyl]bicyclo[1.1.1]pentan-1-yl] carbamate (284.8 mg) as a yellow gum. LCMS (ESI) m/z: $[M+H]^+$ = 535.

Step 2: Preparation of 4-(4-[[([3-aminobicyclo[1.1.1]pentan-1-yl]methyl)(methyl)amino]methyl]-3,5-dimeth oxyphenyl)-2-methyl-2,7-naphthyridin-1-one (i74-3)



A mixture of *tert*-butyl *N*-[3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](me- thyl)amino)methyl]bicyclo[1.1.1]pentan-1-yl]carbamate (284.80 mg) and TFA (1.00 mL) in DCM (1 mL) was stirred for overnight at room temperature. The reaction mixture was concentrated under vacuum to afford 4-(4-[[([3-aminobicyclo[1.1.1]pentan-1-yl]methyl)(methyl)amino]methyl]-3,5-dimethoxyphenyl)-2-me thyl-2,7-naphthyridin-1-one (639.4 mg, crude) as a yellow gum. LCMS (ESI) m/z: $[M+H]^+$ = 435.

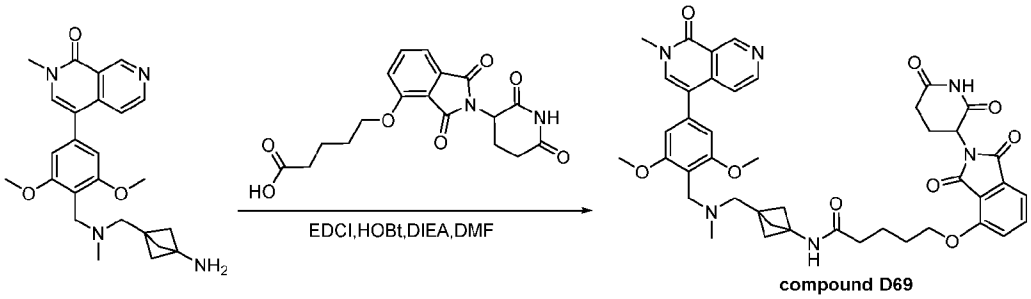
Step 3: Preparation of N-[3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)methyl]bicyclo[1.1.1]pentan-1-yl]-3-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]propanamide formic acid (compound D68 formic acid)



To a stirred solution of 4-(4-[[([3-aminobicyclo[1.1.1]pentan-1-yl]methyl)(methyl)amino]methyl]-3,5-dimet- hoxyphenyl)-2-methyl-2,7-naphthyridin-1-one (20.05 mg, 0.046 mmol, 1 equiv) and 3-[2-(2-[[2-(2,6-diox- opiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]propanoic acid (20.00 mg, 0.046 mmol, 1.00 equiv) in DMF (1 mL) was added EDCI (17.69 mg, 0.092 mmol, 2.00 equiv), HOBT (12.47 mg, 0.092 mmol, 2.00 equiv), and DIEA (23.86 mg, 0.185 mmol, 4.00 equiv). The resulting mixture was stirred overnight at room temperature. Without any additional work-up, the mixture was purified by prep-HPLC (conditions: Column: Gemini-NX C18 AXAI Packed, 21.2*150 mm 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient:8 B to 25 B in 12 minutes; 254/220

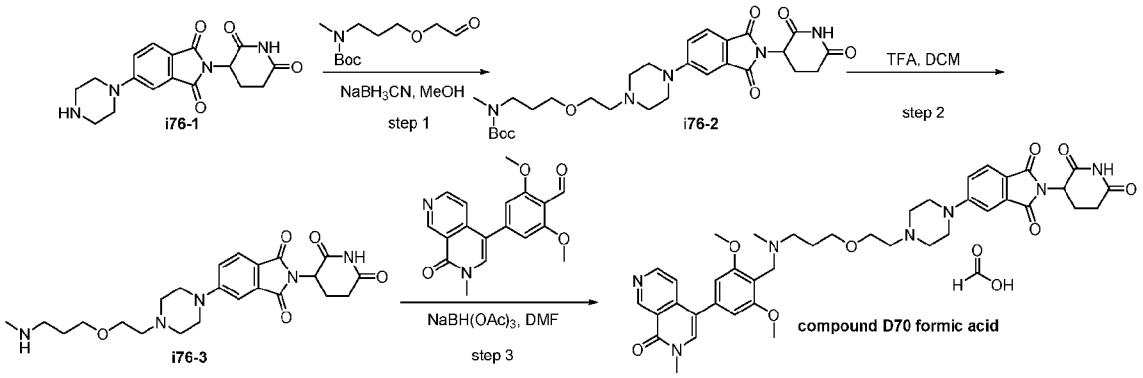
nm; R_T: 11.04 minutes) to afford *N*-[3-[(([2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methy-l)amino)methyl]bicycle[1.1.1]pentan-1-yl]-3-[2-(2-[[2-(2,6-dioxopi peridin-3-yl)-1,3-dioxoisoindol-4-yl]amin-o]ethoxy)ethoxy]propanamide (3.4 mg, 8.67%) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 9.45 (s, 1H), 8.72 (d, *J* = 5.6 Hz, 1H), 8.29 (s, 1H), 8.23 (brs, 1.0H, FA), 7.87 (s, 1H), 7.58 (t, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 8.6 Hz, 1H), 7.03 (d, *J* = 7.1 Hz, 1H), 6.72 (s, 2H), 6.61 (t, *J* = 5.8 Hz, 1H), 5.06 (dd, *J* = 12.7, 5.4 Hz, 1H), 3.81 (s, 6H), 3.58 – 3.54 (m, 5H), 3.54 – 3.49 (m, 6H), 3.48 – 3.42 (m, 4H), 2.96 – 2.81 (m, 1H), 2.64 – 2.58 (m, 1H), 2.55 (s, 3H), 2.26 (t, *J* = 6.4 Hz, 2H), 2.12 (s, 3H), 2.08 – 1.98 (m, 1H), 1.92 (s, 6H). LCMS (ESI) m/z: $[M+H]^+$ = 850.50.

Example 75 – Preparation of N-[3-[(([2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](meth- yl)amino)methyl]bicyclo[1.1.1]pentan-1-yl]-5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]ox- y]pentanamide (compound D69)

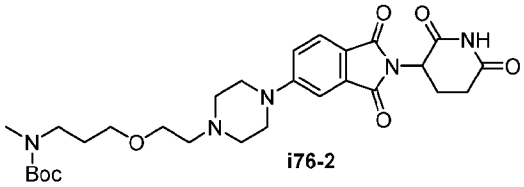


To a stirred solution of 4-(4-[[([3-aminobicyclo[1.1.1]pentan-1-yl]methyl)(methyl)amino]methyl]-3,5-dime thoxyphenyl)-2-methyl-2,7-naphthyridin-1-one (23.22 mg, 0.053 mmol, 1.00 equiv) and 5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]pentanoic acid (20.00 mg, 0.053 mmol, 1.00 equiv) in DMF (1 mL) was added EDCI (20.48 mg, 0.107 mmol, 2.00 equiv) and HOBT (14.44 mg, 0.107 mmol, 2.00 equiv) at room temperature. To the above mixture was added DIEA (27.62 mg, 0.214 mmol, 4.00 equiv). The resulting mixture was stirred for overnight at room temperature. Without any additional work-up, the mixture was purified by prep-HPLC (conditions: SunFire Prep C18 OBD Column, 19×150 mm 5 μm 10 nm; Mobile Phase A: Water (0.1% FA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient:13 B to 22 B in 13 minutes; 254/220 nm; R_T: 12.5 minutes) to afford *N*-[3-[(([2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)methy-l]bicyclo[1.1.1] pentan-1-yl]-5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]pentanamide (6.9 mg, 17.75%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d6) δ 11.10 (s, 1H), 9.46 (d, *J* = 0.8 Hz, 1H), 8.74 (d, *J* = 5.7 Hz, 1H), 8.36 (s, 1H), 7.88 (s, 1H), 7.82 (dd, *J* = 8.5, 7.2 Hz, 1H), 7.60 – 7.42 (m, 3H), 6.79 (s, 2H), 5.08 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.21 (t, *J* = 6.0 Hz, 2H), 3.86 (s, 6H), 3.61 (s, 3H), 3.40 (s, 2H), 2.98 – 2.80 (m, 2H), 2.62 (s, 2H), 2.46 – 2.30 (m, 4H), 2.15 – 2.00 (m, 9H), 1.78 – 1.64 (m, 4H). LCMS (ESI) m/z: $[M+H]^+$ = 791.40.

Example 76 – Preparation of 5-(4-[2-[3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]meth yl](methyl)amino)propoxy]ethyl]piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (compound D70 formic acid)

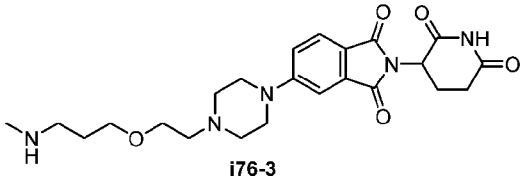


Step 1: Preparation of tert-butyl N-[3-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethoxy)propyl]-N-methylcarbamate (i76-2)



To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)isoindole-1,3-dione (250.00 mg, 0.730 mmol, 1.00 equiv) and *tert*-butyl *N*-methyl-*N*-[3-(2-oxoethoxy)propyl]carbamate (168.90 mg, 0.730 mmol, 1 equiv) in MeOH (3.00 mL) was added $NaBH_3CN$ (91.78 mg, 1.460 mmol, 2 equiv). The mixture was stirred at room temperature for 2 hours. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (Petroleum ether/EtOAc 1:3) to afford *tert*-butyl *N*-[3-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethoxy)propyl]-*N*-methylcarbamate (400 mg, crude) as a dark grey solid. LCMS (ESI) m/z: [M+H]+ = 558.

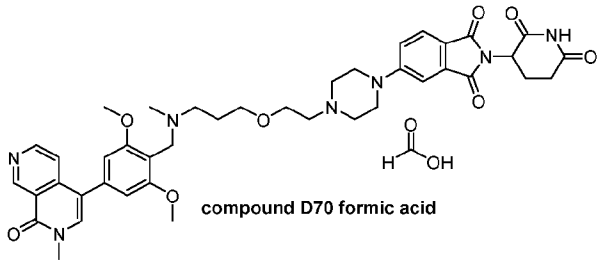
Step 2: Preparation of 2-(2,6-dioxopiperidin-3-yl)-5-(4-[2-[3-(methylamino)propoxy]ethyl]piperazin-1-yl)isoindole-1,3-dione *(i76-3)*



To a stirred solution of *tert*-butyl *N*-[3-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethoxy)propyl]-*N*-methylcarbamate (200.00 mg, 0.359 mmol, 1.00 equiv) in DCM (4.00 mL, 62.920 mmol) was added TFA (1.00 mg, 0.009 mmol). The mixture was stirred at room temperature for 2 hours. The resulting mixture was concentrated under reduced pressure to afford 2-(2,6-

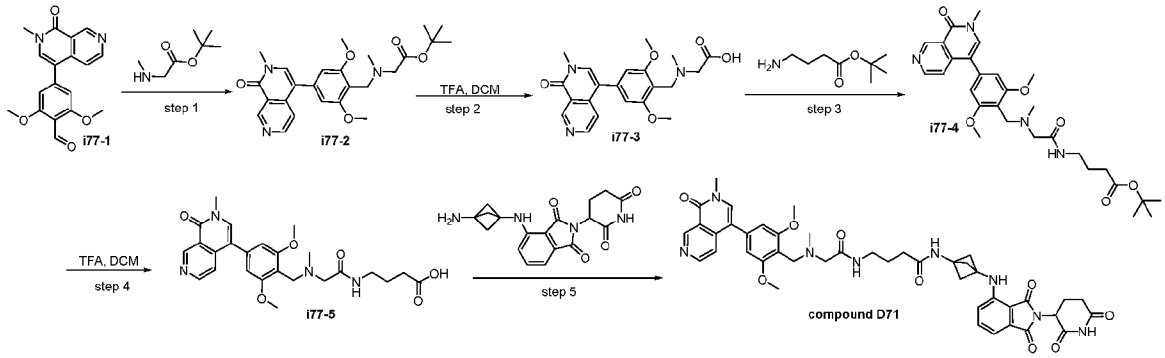
dioxopiperidin-3-yl)-5-(4-[2-[3-(methylamino)propoxy]ethyl]piperazin-1-yl)isoindole-1,3-dione (280 mg, crude) as a dark grey solid. LCMS (ESI) m/z: [M+H]+ = 458.

Step 3: Preparation of 5-(4-[2-[3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)propoxy]ethyl]piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (compound D70 formic acid)

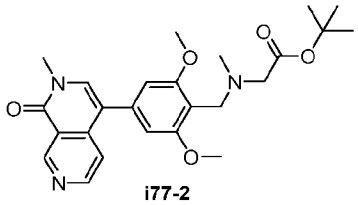


To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-(4-[2-[3-(methylamino)propoxy]ethyl]piperazin-1-yl)isoindole-1,3-dione (100.00 mg, 0.219 mmol, 1.00 equiv) and2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (70.89 mg, 0.219 mmol, 1 equiv) in DMF (1.50 mL) was added $NaBH(OAc)_3$ (92.65 mg, 0.437 mmol, 2 equiv). The mixture was stirred at room temperature for 2 hours. The crude product (100 mg) was purified by Prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100Å, 5 µm, 19 mm X 250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient:5 B to 13 B in 15 minutes; 254 nm; R_T: 12.23 minutes) to afford 5-(4-[2-[3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)propoxy]ethyl]piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione; formic acid(10mg,5.38%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.51 (d, *J* = 18.3 Hz, 1H), 8.68 (d, *J* = 5.7 Hz, 1H), 8.53 (brs, 4.1H, FA), 7.76 (s, 1H), 7.64 (d, *J* = 7.4 Hz, 2H), 7.25 (s, 1H), 7.17 (d, *J* = 8.6 Hz, 1H), 6.90 (s, 2H), 5.11 – 5.04 (m, 2H), 4.69 – 4.53 (m, 2H), 4.47 (s, 2H), 4.00 (s, 6H), 3.74 – 3.62 (m, 7H), 3.40 (d, *J* = 5.5 Hz, 4H), 2.91 (s, 3H), 2.87 – 2.73 (m, 3H), 2.69 (s, 6H), 2.23 – 2.08 (m, 3H). LCMS (ESI) m/z: $[M+H]^+$ = 766.45.

Example 77 – Preparation of 4-[2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](meth yl)amino)acetamido]-N-(3-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]bicycle[1.1.1] pentan-1-yl)butanamide (compound D71)

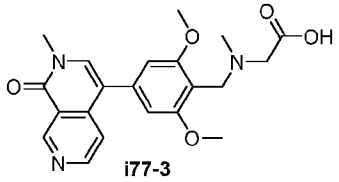


Step 1: Preparation of tert-butyl N-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl) benzyl)-N-methylglycinate (i77-2)



To a stirred solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (250.00 mg, 0.771 mmol, 1.00 equiv) and *tert*-butyl 2-(methylamino)acetate (111.92 mg, 0.771 mmol, 1.00 equiv) in MeOH (10.00 mL) was added $NaBH_3CN$ (96.88 mg, 1.542 mmol, 2.00 equiv) in portions at 50 ℃ under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched with Water at room temperature. The aqueous layer was extracted with EtOAc (3 x 30 mL). The resulting solid was dried under vacuum. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; mobile phase, MeOH in water, 10% to 50% gradient in 10 minutes; detector, UV 254 nm). This resulted in *tert*-butyl *N*-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-N-methylglycinate (101mg,28.92%) as a yellow oil. LCMS (ESI) m/z: [M+H]+ = 454.

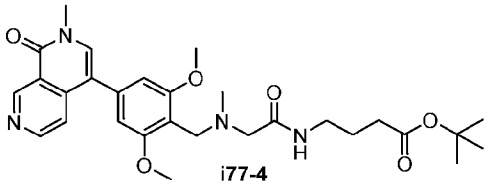
Step 2: Preparation of N-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-N-methylglycine *(i77-3)*



A solution of *tert*-butyl 2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] (methyl) amino) acetate (101.00 mg, 0.223 mmol, 1.00 equiv) and TFA (7.21 mL, 63.270 mmol, 436.14

equiv) in DCM (29.00 mL) was stirred for 15 hours at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The residue (108 mg, crude) was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]+ = 398.

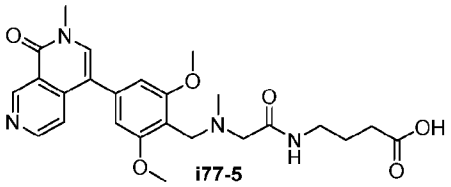
Step 3: Preparation of tert-butyl 4-(2-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)(methyl)amino)acetamido)butanoate (i77-4)



i77-4

A solution of ([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)acetic acid (108 mg (crude), 0.272 mmol, 1.00 equiv), DIEA (105.36 mg, 0.815 mmol, 3.00 equiv), and HATU (206.53 mg, 0.543 mmol, 2.00 equiv) in DMF (2.00 mL) was stirred for 30 minutes at room temperature under nitrogen atmosphere. To the above mixture was added *tert*-butyl 4-aminobutanoate (43.27 mg, 0.272 mmol, 1.00 equiv) at room temperature. The resulting mixture was stirred for additional 12 hours at room temperature. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; mobile phase, MeOH in water, 10% to 50% gradient in 10 minutes; detector, UV 254 nm). This resulted in *tert*-butyl 4-(2-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)(methyl)amino)acetamido) butanoate (75 mg, 62.33%) as a yellow oil. LCMS (ESI) m/z: [M+H]+ = 539.

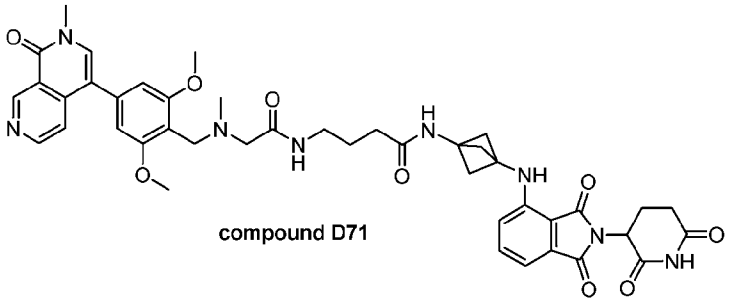
Step 4: Preparation of 4-(2-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)(methyl)amino)acetamido)butanoicacid (i77-5)



i77-5

A solution of *tert*-butyl 4-[2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](meth yl)amino) acetamido]butanoate (75.00 mg, 0.139 mmol, 1.00 equiv) and TFA (1 mL) in DCM (4.00 mL) was stirred for 2 hours at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The residue (73 mg, crude) was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]+ = 483.

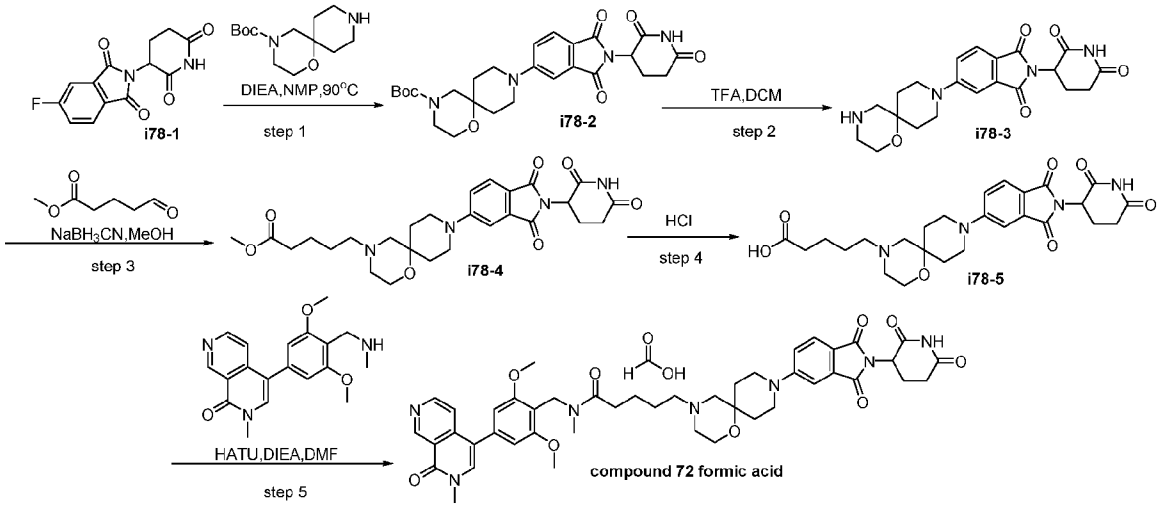
Step 5: Preparation of 4-(2-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)(methyl)amino)acetamido)-N-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)bicycle[1.1.1]pentan-1-yl)butanamide (compound D71)



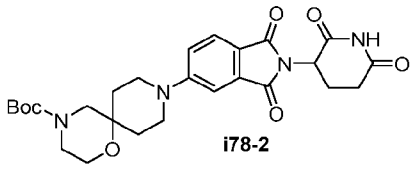
compound D71

To a stirred solution of 4-[2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] (methyl)amino) acetamido]butanoic acid (73.00 mg(crude), 0.151 mmol, 1.00 equiv) , DIEA (58.66 mg, 0.454 mmol, 3.00 equiv), and EDCI (58.00 mg, 0.303 mmol, 2.00 equiv) in DMF (2.00 mL) was added HOBT (40.88 mg, 0.303 mmol, 2.00 equiv) in portions at room temperature under nitrogen atmosphere. The reaction mixture was irradiated with microwave radiation for 1 hour at room temperature. To the above mixture was added 4-([3-aminobicyclo[1.1.1]pentan-1-yl]amino)-2-(2,6-dioxopiperidin-3-yl) isoindole-1,3-dione (53.61 mg, 0.151 mmol, 1.00 equiv) at room temperature. The resulting mixture was stirred for additional 2 days at room temperature. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; mobile phase, MeOH in water, 10% to 50% gradient in 10 minutes; detector, UV 254 nm). The crude product (70 mg) was purified by Prep-HPLC (conditions: Atlantis HILIC OBD Column 19*150 mm,5 μm ;Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 40 mL/minute; Gradient: 24% B to 24% B in 12 minutes; 254/220 nm; Rt: 11.43 minutes) to afford 4-[2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino) acetamido]-*N*-(3-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]bicyclo[1.1.1]pentan-1-yl)butane mide (10 mg, 8.07%) as a light yellow solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.56 (s, 1H), 8.70 (d, *J* = 6.0 Hz, 1H), 7.88 (d, *J* = 1.4 Hz, 1H), 7.75 (d, *J* = 5.9 Hz, 1H), 7.58 (dd, *J* = 9.5, 5.0 Hz, 1H), 7.27 (dd, *J* = 8.6, 3.5 Hz, 1H), 7.14 (d, *J* = 7.2 Hz, 1H), 6.89 (s, 2H), 5.08 (dd, *J* = 12.4, 5.4 Hz, 1H), 4.56 (d, *J* = 5.7 Hz, 2H), 4.01 – 3.97 (m, 7H), 3.93 – 3.87 (m, 1H), 3.73 (s, 3H), 3.29 – 3.23 (m, 2H), 2.97 (s, 3H), 2.90 – 2.83 (m, 1H), 2.80 – 2.68 (m, 2H), 2.43 (s, 6H), 2.22 (t, *J* = 7.3 Hz, 2H), 2.16 – 2.10 (m, 1H), 1.80 (p, *J* = 7.2 Hz, 2H). LCMS (ESI) m/z: $[M+H]^+$ = 819.35.

Example 78 – Preparation of N-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-5-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]-N-methyl pentanamide formic acid (compound D72 formic acid)

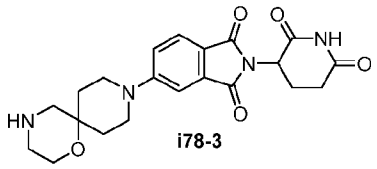


Step 1: Preparation of 2-(2,6-dioxopiperidin-3-yl)-5-[1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]isoindole-1,3-dione (i78-2)



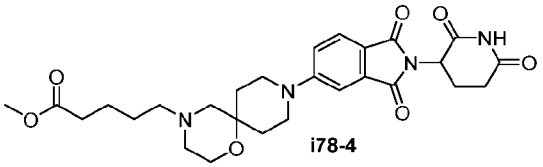
To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisoindole-1,3-dione (1.50 g, 5.430 mmol, 1.00 equiv) and *tert*-butyl 1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (1.67 g, 6.516 mmol, 1.20 equiv) in NMP (10.00 mL) was added DIEA (1.40 g, 10.861 mmol, 2.00 equiv) dropwise at room temperature. The resulting mixture was stirred for 6 hours at 90 ℃ under nitrogen atmosphere. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 20 minutes; detector, UV 254 nm). This resulted in *tert*-butyl 9-(2-(2,6- dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (2 g, 72%) as a green oil. LCMS (ESI) m/z: [M+H]+ = 513.

Step 2: Preparation of 2-(2,6-dioxopiperidin-3-yl)-5-[1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]isoindole-1,3-dione (*i78-3)*



To a stirred solution of *tert*-butyl 9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (430.00 mg, 0.839 mmol, 1.00 equiv) in DCM (3.50 mL) was added TFA (1.00 mL). The mixture was stirred at room temperature for 1 hour. The resulting mixture was concentrated under reduced pressure to afford 2-(2,6-dioxopiperidin-3-yl)-5-[1-oxa-4,9-diazaspiro [5.5]undecan-9-yl]isoindole-1,3-dione (670 mg, crude) as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 413

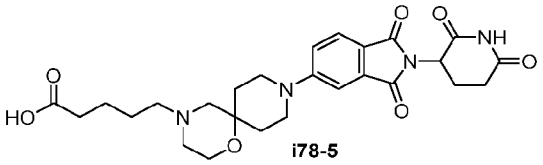
Step 3: Preparation of methyl 5-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]pentanoate (i78-4)



i78-4

To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-[1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]isoindole-1,3-dione (200.00 mg, 0.485 mmol, 1.00 equiv) and methyl 5-oxopentanoate (75.73 mg, 0.582 mmol, 1.2 equiv) in MeOH (2.00 mL) was added $NaBH_3CN$ (60.95 mg, 0.970 mmol, 2 equiv). The mixture was stirred at room temperature for 2 hours. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (Petroleum ether/EtOAc 1:3) to afford methyl 5-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]pentanoate (80 mg, 31.33%) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 527.

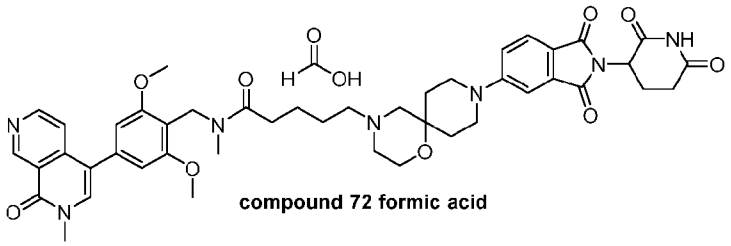
Step 4: Preparation of5-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro [5.5]undecan-4-yl]pentanoic acid (i78-5)



i78-5

Methyl 5-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]pentanoate (70.00 mg, 0.133 mmol, 1.00 equiv) was stirred at room temperature with HCl (aq.) for 2 hours. The resulting mixture was concentrated under reduced pressure. This resulted in 5-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]pentanoic acid (70 mg, crude) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 513.

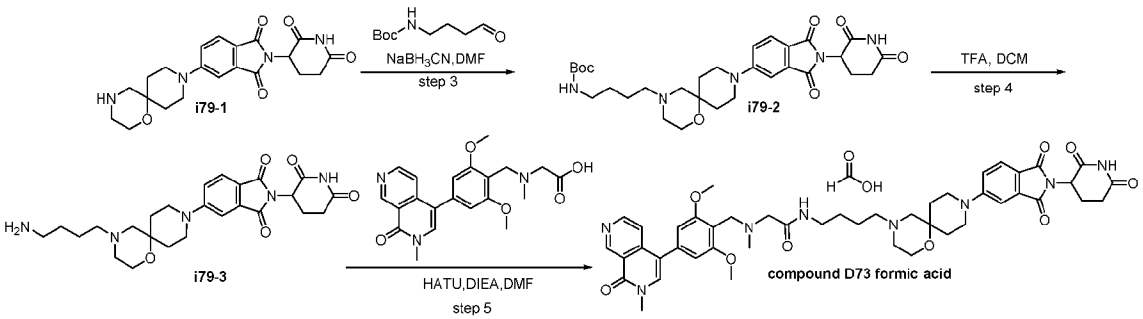
Step 5: Preparation of N-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-5-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]-N-methylpentanamide formic acid (compound D72 formic acid)



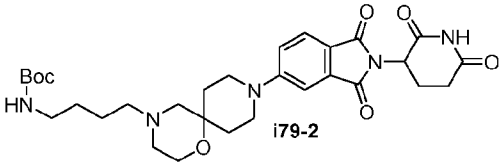
compound 72 formic acid

To a stirred solution of 5-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5] undecan-4-yl]pentanoic acid (55.00 mg, 0.107 mmol, 1.00 equiv) and 4-[3,5-dimethoxy-4-[(methylamino)methyl]phenyl]-2-methyl-2,7-naphthyridin-1-one (36.42 mg, 0.107 mmol, 1.00 equiv) in DMF (1.00 mL) was added DIEA (69.34 mg, 0.537 mmol, 5.00 equiv) and HATU (61.20 mg, 0.161 mmol, 1.50 equiv). The mixture was stirred at room temperature for 1 hours. The crude product (55 mg) was purified by Prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100Å, 5 µm, 19 mm X 250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient:9 B to 28 B in 13 minutes; 254 nm; R_T: 14.08 minutes) to afford *N*-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-5-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]-*N*-methylpentanamide formic acid (8.2 mg, 8.68%) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.50 (d, *J* = 3.4 Hz, 1H), 8.65 (dd, *J* = 12.4, 5.8 Hz, 1H), 8.39 (brs, 0.6H, FA), 7.74 (d, *J* = 4.5 Hz, 1H), 7.66 – 7.57 (m, 2H), 7.28 (dd, *J* = 12.7, 2.3 Hz, 1H), 7.22 – 7.14 (m, 1H), 6.80 (d, *J* = 20.6 Hz, 2H), 5.04 (dt, *J* = 12.8, 5.8 Hz, 1H), 4.75 (d, *J* = 16.1 Hz, 2H), 3.90 (d, *J* = 16.5 Hz, 6H), 3.87 – 3.82 (m, 2H), 3.74 – 3.63 (m, 5H), 3.32 – 3.26 (m, 2H), 2.92 – 2.82 (m, 2H), 2.78 (d, *J* = 6.8 Hz, 4H), 2.73 – 2.53 (m, 7H), 2.47 (t, *J* = 6.7 Hz, 1H), 2.17 – 2.01 (m, 3H), 1.82 – 1.62 (m, 6H). LCMS (ESI) m/z: $[M+H]^+$ = 834.40.

Example 79 – Preparation of 2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] (methyl)amino)-N-(4-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diaza spiro[5.5]undecan-4-yl]butyl)acetamide formic acid (compound D73 formic acid)



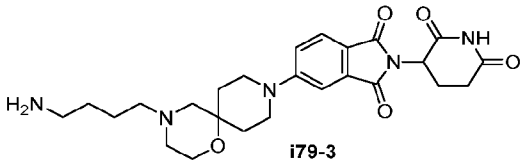
Step 1: Preparation of tert-butyl N-(4-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]butyl)carbamate (i79-2)



To a stirred solution of2-(2,6-dioxopiperidin-3-yl)-5-[1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]isoindole-1,3-dione (200.00 mg, 0.485 mmol, 1.00 equiv) and *tert*-butyl *N*-(4-oxobutyl)carbamate (907.94 mg, 4.849 mmol, 10.00 equiv) in DMF(1.50 mL) was added $NaBH_3CN$ (60.95 mg, 0.970 mmol, 2.00 equiv). The mixture was stirred at room temperature for 5 hours. The resulting mixture was

concentrated under vacuum. The residue was purified by Prep-TLC (Petroleum ether/EtOAc 1:3) to afford *tert*-butyl *N*-(4-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]butyl)carbamate(200 mg,crude) as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 584.

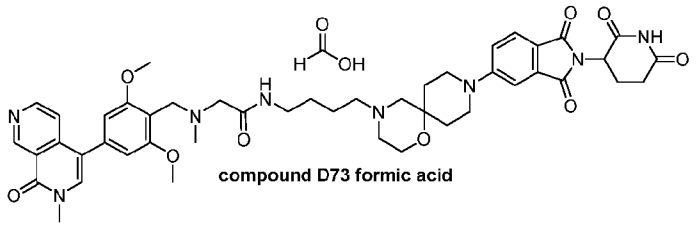
Step 2: Preparation of 5-[4-(4-aminobutyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione *(i79-3)*



i79-3

To a stirred solution of *tert*-butyl *N*-(4-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]butyl)carbamate (200.00 mg, 0.343 mmol, 1.00 equiv) in DCM (3.00 mL) was added TFA (1.00 mL). The mixture was stirred at room temperature for 2 hours. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 5-[4-(4-aminobutyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (60 mg, 36.21%) as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 484.

Step 3: Preparation of 2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)-N-(4-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]butyl)acetamide formic acid (compound D73 formic acid)

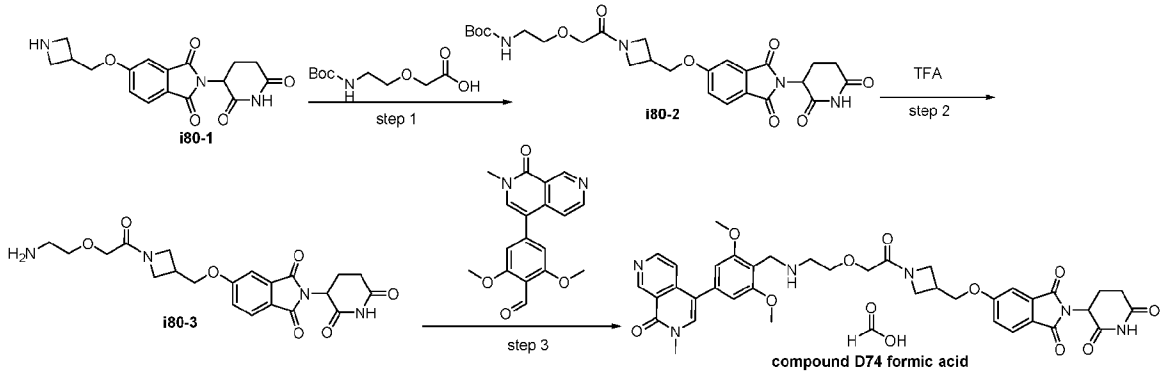


compound D73 formic acid

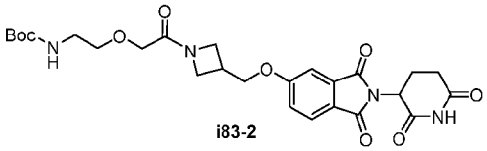
To a stirred solution of 5-[4-(4-aminobutyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (60.00 mg, 0.124 mmol, 1.00 equiv) and ([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)acetic acid (49.31 mg, 0.124 mmol, 1.00 equiv)in DMF (1.00 mg) was added DIEA (80.18 mg, 0.620 mmol, 5.00 equiv) and HATU (70.77 mg, 0.186 mmol, 1.50 equiv). The mixture was stirred at room temperature for 1 hour. The crude product (60mg) was purified by Prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100Å, 5 µm, 19 mm X 250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient:8 B to 17 B in 12 minutes; 254 nm; R_T: 11.87 minutes) to afford 2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)-*N*-(4-[9-[2-(2,6-dioxopip eridin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]butyl)acetamide formic acid (12. 6mg,10.72%) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.51 (s, 1H), 8.68 (d, *J* = 5.8 Hz, 1H), 8.53 (brs, 0.9H, FA), 7.74 (s,

1H), 7.62 (dd, J = 7.3, 6.3 Hz, 2H), 7.27 (d, J = 2.3 Hz, 1H), 7.16 (dd, J = 8.6, 2.4 Hz, 1H), 6.82 (s, 2H), 5.05 (dd, J = 12.7, 5.5 Hz, 1H), 4.15 (s, 2H), 3.94 (s, 6H), 3.75 (t, J = 4.8 Hz, 2H), 3.69 (s, 3H), 3.64 (d, J = 13.0 Hz, 2H), 3.54 (s, 2H), 3.31 – 3.25 (m, 4H), 2.94 – 2.81 (m, 1H), 2.80 – 2.68 (m, 2H), 2.63 (s, 3H), 2.46 (s, 2H), 2.37 (t, J = 6.6 Hz, 2H), 2.32 (s, 2H), 2.17 – 2.00 (m, 3H), 1.68 – 1.51 (m, 6H). LCMS (ESI) m/z: $[M+H]^+$ = 863.50.

Example 80 – Preparation of 5-[(1-[2-[2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] amino)ethoxy]acetyl]azetidin-3-yl)methoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (compound D74 formic acid)

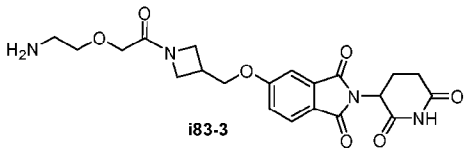


Step 1: Preparation of tert-butyl N-(2-[2-[3-([[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]methyl) azetidin-1-yl]-2-oxoethoxy]ethyl)carbamate (i80-2)



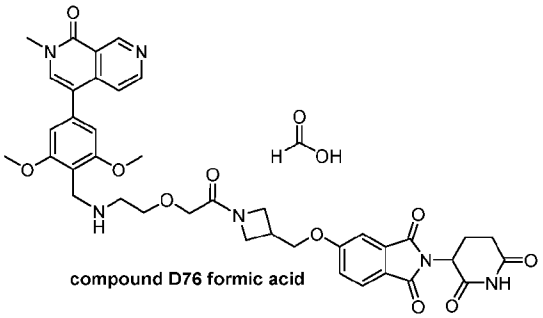
To a solution of [2-[(*tert*-butoxycarbonyl)amino]ethoxy]acetic acid (30.65 mg, 0.140 mmol, 1.20 equiv) and HATU (88.60 mg, 0.233 mmol, 2.00 equiv) in DMF (1.00 mL) was added 5-(azetidin-3-ylmethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (40.00 mg, 0.117 mmol, 1.00 equiv) and DIEA (45.17 mg, 0.350 mmol, 3.00 equiv), and the resulting solution was stirred at 25 ℃ for 2 hours. The resulting mixture was concentrated. The residue was applied onto a silica gel column with CH_2Cl_2/MeOH (20:1). This resulted in (50 mg, 78.81%) of *tert*-butyl *N*-(2-[2-[3-([[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]methyl)azetidin-1-yl]-2-oxoethoxy]ethyl)carbamate as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 545.30.

Step 2: Preparation of 5-([1-[2-(2-aminoethoxy)acetyl]azetidin-3-yl]methoxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (i80-3)



To a solution of *tert*-butyl N-(2-[2-[3-([[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]methyl) azetidin-1-yl]-2-oxoethoxy]ethyl)carbamate (50.00 mg, 0.092 mmol, 1.00 equiv) in TFA (2.00 mL) and DCM (2.00 mL), and the resulting solution was stirred at 25 ℃ for 2 hours. The resulting mixture was concentrated and used directly without further purification. This resulted in (60 mg, crude) of 5-([1-[2-(2-aminoethoxy)acetyl]azetidin-3-yl]methoxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 445.50.

Step 3: Preparation of 5-[(1-[2-[2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] amino)ethoxy]acetyl]azetidin-3-yl)methoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (compound D74 formic acid)



To a solution of 5-([1-[2-(2-aminoethoxy)acetyl]azetidin-3-yl]methoxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (20 mg, 0.045 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (17.51 mg, 0.054 mmol, 1.20 equiv) in DMF (2.00 mL) was added $NaBH_3CN$ (5.66 mg, 0.090 mmol, 2.00 equiv). The resulting solution was stirred at 25 ℃ for 2 hours. The resulting mixture was concentrated. The crude product was purified by preparative HPLC Column: XSelect CSH Prep C18 OBD Column, 5 μm, 19*150 mm;Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 20% B to 55% B in 8 minutes; 254 nm; Rt: 7.12 minutes). This resulted in (10 mg, 27.82%) of 5-[(1-[2-[2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] amino)ethoxy]acetyl]azetidin-3-yl)methoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione as an off-white solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.53 (s, 1H), 8.68 (d, *J* = 5.8 Hz, 1H), 8.57 (brs, 3.2H, FA), 7.82 (d, *J* = 8.3 Hz, 1H), 7.76 (s, 1H), 7.61 (d, *J* = 5.7 Hz, 1H), 7.43 (d, *J* = 2.3 Hz, 1H), 7.35 (dd, *J* = 8.1, 2.3 Hz, 1H), 6.84 (s, 2H), 5.12 (dd, *J* = 12.6, 5.4 Hz, 1H), 4.40 (t, *J* = 8.8 Hz, 1H), 4.35 (d, *J* = 3.8 Hz, 4H), 4.27 – 4.13 (m, 4H), 4.02 – 3.93 (m, 7H), 3.83 (t, *J* = 4.9 Hz, 2H), 3.71

(s, 3H), 3.27 – 3.21 (m, 3H), 2.94 – 2.83 (m, 1H), 2.82 – 2.67 (m, 2H), 2.20 – 2.10 (m, 1H). LCMS (ESI) m/z: [M+H]+ = 753.40.

Example 81 – Preparation of Compounds D75-D177

In analogy to the procedures described in the examples above, compounds D75-D177 were prepared using the appropriate starting materials.

Compound No.	Analytical Data
D75	LCMS: (ESI) m/z: $[M+H]^+$ = 835.70
D76	LCMS: (ESI) m/z: $[M+H]^+$ = 788.20
D77	LCMS: (ESI) m/z: $[M+H]^+$ = 774.10
D78	
D79	LCMS: (ESI) m/z: $[M+H]^+$ = 789.20; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.11 (s, 1H), 9.45 (s, 1H), 8.73 (d, *J* = 5.7 Hz, 1H), 8.21 (s, 0.7H, FA), 8.05 (d, *J* = 7.5 Hz, 1H), 7.87 (s, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.59 – 7.54 (m, 1H), 7.31 – 7.24 (m, 2H), 6.73 (s, 2H), 5.12 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.87 (t, *J* = 6.8 Hz, 1H), 4.14 – 3.99 (m, 1H), 3.81 (s, 6H), 3.66 (s, 2H), 3.61 (s, 3H), 3.44 – 3.35 (m, 3H), 2.98 (s, 2H), 2.92 – 2.83 (m, 1H), 2.73 – 2.55 (m, 4H), 2.44 – 2.32 (m, 1H), 2.25 (dd, *J* = 18.0, 6.8 Hz, 3H), 2.15 – 2.00 (m, 3H), 1.95 (td, *J* = 11.2, 8.4 Hz, 2H).
D80	LCMS: (ESI) m/z: $[M+H]^+$ = 803.15; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.12 (s, 1H), 9.45 (s, 1H), 8.73 (d, *J* = 5.6 Hz, 1H), 8.21 (s, 0.6H, FA), 7.97 – 7.77 (m, 2H), 7.56 (d, *J* = 5.7 Hz, 1H), 7.37 – 7.20 (m, 2H), 6.74 (s, 2H), 5.12 (dd, *J* = 12.8, 5.4 Hz, 1H), 5.10 – 4.97 (m, 1H), 3.82 (d, *J* = 2.0 Hz, 6H), 3.70 (s, 2H), 3.61 (s, 3H), 3.36 (s, 5H), 3.09 – 2.95 (m, 2H), 2.88 (d, *J* = 13.9 Hz, 1H), 2.58 (d, *J* = 10.3 Hz, 8H), 2.16 – 1.99 (m, 1H), 1.87 (d, *J* = 9.8 Hz, 2H), 1.63 (s, 1H), 1.55 (s, 2H), 1.47 (s, 1H).
D81	LCMS: (ESI) m/z: $[M+H]^+$ = 715.20
D82	LCMS: (ESI) m/z: $[M+H]^+$ = 821.25; ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.54 (d, *J* = 0.9 Hz, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.54 (s, 0.4H, FA), 7.86 – 7.75 (m, 2H), 7.63 (dd, *J* = 5.8, 0.9 Hz, 1H), 7.50 (dd, *J* = 7.8, 5.7 Hz, 2H), 6.87 (s, 2H), 5.14 (dd, *J* = 12.3, 5.4 Hz, 1H), 4.44 – 4.32 (m, 4H), 4.24 (p, *J* = 8.3 Hz, 1H), 3.97 (s, 6H), 3.93 – 3.83 (m, 4H), 3.72 (s, 3H), 3.22 – 3.02 (m, 2H), 2.99 – 2.65 (m, 4H), 2.46 (t, *J* = 5.9 Hz, 2H), 2.27 (s, 2H), 2.22 – 2.09 (m, 2H), 1.91 (s, 2H), 1.76 (s, 4H).
D83	LCMS: (ESI) m/z: $[M+H]^+$ = 781.55; ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.53 (s, 1H), 8.69 (d, *J* = 6.0 Hz, 1H), 7.85 (s, 1H), 7.82 – 7.66 (m, 2H), 7.50 – 7.36 (m, 2H), 6.85 (d, *J* = 1.2 Hz, 2H), 5.12 (dd, *J* = 12.5, 5.4 Hz, 1H), 4.50 (s, 1H), 4.42 (s, 1H), 4.35 – 4.11 (m, 4H), 4.02 (dd, *J* = 11.0, 6.7 Hz, 1H), 3.94 (d, *J* = 2.7 Hz, 6H), 3.91 – 3.76 (m, 5H), 3.71 (d, *J* = 1.5 Hz, 3H), 3.22 (t, *J* = 6.5 Hz, 2H), 3.08 – 2.59 (m, 4H), 2.46 (t, *J* = 5.8 Hz, 2H), 2.21 – 2.07 (m, 1H), 1.84 (p, *J* = 7.2, 6.7 Hz, 2H).
D84	LCMS: (ESI) m/z: $[M+H]^+$ = 793.55
D85	LCMS: (ESI) m/z: $[M+H]^+$ = 807.25
D86	LCMS: (ESI) m/z: $[M+H]^+$ = 779.20

Compound No.	Analytical Data
D87	LCMS: (ESI) m/z: $[M+H]^+$ = 793.45
D88	LCMS: (ESI) m/z: $[M+H]^+$ = 807.90; ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.55 (d, *J* = 0.8 Hz, 1H), 8.69 (d, *J* = 5.7 Hz, 1H), 8.56 (s, 0.5H, FA), 7.86 – 7.73 (m, 2H), 7.63 (d, *J* = 5.8 Hz, 1H), 7.48 (dd, *J* = 7.9, 6.2 Hz, 2H), 6.85 (s, 2H), 5.24 – 5.02 (m, 1H), 4.38 (t, *J* = 4.3 Hz, 2H), 4.33 (s, 2H), 3.95 (s, 6H), 3.93 – 3.81 (m, 4H), 3.72 (s, 4H), 3.71 – 3.40 (m, 4H), 3.25 – 3.01 (m, 3H), 2.98 – 2.82 (m, 2H), 2.82 – 2.61 (m, 3H), 2.21 – 2.07 (m, 1H), 1.91 (s, 2H), 1.63 (d, *J* = 17.7 Hz, 4H).
D89	LCMS: (ESI) m/z: $[M+H]^+$ = 821.30
D90	LCMS: (ESI) m/z: $[M+H]^+$ = 793.45
D91	LCMS: (ESI) m/z: $[M+H]^+$ = 807.50
D92	LCMS: (ESI) m/z: $[M+H]^+$ = 793.60; ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.53 (s, 1H), 8.68 (dd, *J* = 5.8, 2.4 Hz, 1H), 8.52 (s, 0.5H, FA), 7.90 – 7.73 (m, 2H), 7.62 (s, 1H), 7.47 (dd, *J* = 9.3, 3.5 Hz, 2H), 6.89 – 6.74 (m, 2H), 5.24 – 5.04 (m, 1H), 4.31 (d, *J* = 33.1 Hz, 5H), 3.90 (dd, *J* = 6.6, 4.5 Hz, 12H), 3.78 – 3.58 (m, 7H), 3.00 – 2.48 (m, 6H), 2.26 – 1.78 (m, 3H).
D93	LCMS: (ESI) m/z: $[M+H]^+$ = 793.50
D94	LCMS: (ESI) m/z: $[M+H]^+$ = 865.55
D95	LCMS: (ESI) m/z: $[M+H]^+$ = 793.65
D96	LCMS: (ESI) m/z: $[M+H]^+$ = 835.45
D97	LCMS: (ESI) m/z: $[M+H]^+$ = 865.50; ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.54 (d, *J* = 0.8 Hz, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.55 (s, 0.6H, FA), 7.90 – 7.71 (m, 2H), 7.64 (d, *J* = 5.8 Hz, 1H), 7.48 (dd, *J* = 7.9, 3.5 Hz, 2H), 6.87 (s, 2H), 5.12 (dd, *J* = 12.3, 5.4 Hz, 1H), 4.50 – 4.23 (m, 4H), 3.97 (s, 6H), 3.95 – 3.79 (m, 5H), 3.72 (s, 5H), 3.66 (dd, *J* = 5.8, 1.9 Hz, 1H), 3.59 – 3.32 (m, 3H), 3.30 – 2.98 (m, 2H), 2.98 – 2.59 (m, 6H), 2.25 – 1.70 (m, 7H), 1.49 (s, 2H).
D98	LCMS: (ESI) m/z: $[M+H]^+$ = 779.40; ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.51 (d, *J* = 1.5 Hz, 1H), 8.67 (d, *J* = 5.7 Hz, 1H), 7.69 (d, *J* = 1.8 Hz, 1H), 7.63 – 7.49 (m, 2H), 7.27 (dd, *J* = 5.8, 2.3 Hz, 1H), 7.16 (ddd, *J* = 11.0, 8.4, 2.3 Hz, 1H), 6.65 (d, *J* = 2.1 Hz, 2H), 5.04 (td, *J* = 12.4, 5.5 Hz, 1H), 4.80 (d, *J* = 10.2 Hz, 1H), 4.33 (d, *J* = 10.5 Hz, 2H), 4.25 (d, *J* = 16.3 Hz, 2H), 4.03 (d, *J* = 11.4 Hz, 1H), 3.95 – 3.74 (m, 12H), 3.74 (d, *J* = 1.3 Hz, 4H), 3.39– 3.30 (m, 1H), 2.80 (dt, *J* = 13.9, 4.7 Hz, 1H), 2.76 – 2.54 (m, 3H), 2.46 – 2.22 (m, 3H), 2.03 (td, *J* = 7.3, 6.8, 3.3 Hz, 1H).
D99	LCMS: (ESI) m/z: $[M+H]^+$ = 793.45
D100	LCMS: (ESI) m/z: $[M+H]^+$ = 793.35
D101	LCMS: (ESI) m/z: $[M+H]^+$ = 793.45; ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.53 (d, *J* = 0.8 Hz, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.56 (s, 0.7H, FA), 7.86 – 7.73 (m, 2H), 7.64 – 7.56 (m, 1H), 7.43 (d, *J* = 2.3 Hz, 1H), 7.34 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.84 (s, 2H), 5.12 (dd, *J* = 12.4, 5.4 Hz, 1H), 4.36 – 4.20 (m, 4H), 4.20 – 4.05 (m, 3H), 3.96 (d, *J* = 8.5 Hz, 8H), 3.90 – 3.75 (m, 4H), 3.71 (s, 3H), 2.97 – 2.55 (m, 5H), 2.43 (t, *J* = 5.9 Hz, 2H), 2.25 – 2.08 (m, 3H).

Compound No.	Analytical Data
D102	LCMS: (ESI) m/z: $[M+H]^+$ = 761.2
D103	LCMS: (ESI) m/z: $[M+H]^+$ = 747.3
D104	LCMS: (ESI) m/z: $[M+H]^+$ = 747.3
D105	LCMS: (ESI) m/z: $[M+H]^+$ = 719.3
D106	LCMS: (ESI) m/z: $[M+H]^+$ = 733.4
D107	LCMS: (ESI) m/z: $[M+H]^+$ = 733.3
D108	LCMS: (ESI) m/z: $[M+H]^+$ = 807.45
D109	LCMS: (ESI) m/z: $[M+H]^+$ = 865.35
D110	LCMS: (ESI) m/z: $[M+H]^+$ = 835.75
D111	LCMS: (ESI) m/z: $[M+H]^+$ = 793.50
D112	LCMS: (ESI) m/z: $[M+H]^+$ = 793.50
D113	LCMS: (ESI) m/z: $[M+H]^+$ = 779.35
D114	LCMS: (ESI) m/z: $[M+H]^+$ = 851.25
D115	LCMS: (ESI) m/z: $[M+H]^+$ = 793.45
D116	LCMS: (ESI) m/z: $[M+H]^+$ = 821.30
D117	LCMS: (ESI) m/z: $[M+H]^+$ = 781.60; ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.51 (s, 1H), 8.68 (d, *J* = 5.8 Hz, 1H), 8.56 (s, 0.7H, FA), 7.76 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 5.8 Hz, 1H), 7.39 (d, *J* = 2.2 Hz, 1H), 7.30 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.84 (s, 2H), 5.10 (dd, *J* = 12.5, 5.4 Hz, 1H), 4.37 (s, 2H), 4.33 – 4.24 (m, 2H), 4.22 – 4.08 (m, 2H), 3.95 (s, 6H), 3.85 (dq, *J* = 7.2, 5.7 Hz, 6H), 3.70 (s, 3H), 3.20 (t, *J* = 6.5 Hz, 2H), 3.02 – 2.62 (m, 4H), 2.47 (t, *J* = 5.8 Hz, 2H), 2.23 – 2.05 (m, 1H), 1.84 (q, *J* = 6.9 Hz, 2H).
D118	LCMS: (ESI) m/z: $[M+H]^+$ = 807.60; ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.53 (d, *J* = 0.8 Hz, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.55 (s, 0.7H, FA), 7.89 – 7.75 (m, 2H), 7.61 (dd, *J* = 5.8, 0.8 Hz, 1H), 7.44 (d, *J* = 2.2 Hz, 1H), 7.37 – 7.30 (m, 1H), 6.85 (s, 2H), 5.10 (dd, *J* = 12.4, 5.4 Hz, 1H), 4.41 (s, 2H), 4.35 – 4.25 (m, 2H), 3.95 (s, 6H), 3.91 – 3.77 (m, 8H), 3.72 (s, 3H), 3.54 (q, *J* = 5.6 Hz, 4H), 2.96 – 2.63 (m, 5H), 2.12 (dtd, *J* = 12.8, 4.8, 2.1 Hz, 1H), 1.83 (dt, *J* = 16.1, 5.8 Hz, 4H).
D119	LCMS: (ESI) m/z: $[M+H]^+$ = 807.45
D120	LCMS: (ESI) m/z: $[M+H]^+$ = 821.45
D121	LCMS: (ESI) m/z: $[M+H]^+$ = 807.40; ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.53 (d, *J* = 1.0 Hz, 1H), 8.69 (d, *J* = 5.7 Hz, 1H), 8.54 (s, 0.5H, FA), 7.88 – 7.73 (m, 2H), 7.66 – 7.59 (m, 1H), 7.41 (dd, *J* = 4.4, 2.3 Hz, 1H), 7.32 (ddd, *J* = 8.1, 6.0, 2.1 Hz, 1H), 6.84 (d, *J* = 7.6 Hz, 2H), 5.10 (dd, *J* = 6.9, 5.4 Hz, 1H), 4.38 (s, 1H), 4.30 (d, *J* = 4.9 Hz, 3H), 3.95 (d, *J* = 8.8 Hz, 6H), 3.87 (t, *J* = 4.6 Hz, 4H), 3.71 (d, *J* = 1.2 Hz, 3H), 3.71 – 3.56 (m, 2H), 3.55 – 3.37 (m, 3H), 3.33 – 3.26 (m, 3H), 2.97 – 2.52 (m, 5H), 2.21 – 1.92 (m, 5H).

Compound No.	Analytical Data
D122	LCMS: (ESI) m/z: $[M+H]^+$ = 793.35; ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.53 (d, *J* = 2.5 Hz, 1H), 8.68 (dd, *J* = 5.7, 1.6 Hz, 1H), 8.54 (s, 0.6H, FA), 7.85 – 7.70 (m, 2H), 7.60 (dd, *J* = 6.0, 3.1 Hz, 1H), 7.42 (dd, *J* = 3.5, 2.2 Hz, 1H), 7.37 – 7.29 (m, 1H), 6.84 (d, *J* = 9.2 Hz, 2H), 5.11 (dd, *J* = 12.5, 5.4 Hz, 1H), 4.40 (s, 1H), 4.31 (dt, *J* = 6.1, 3.1 Hz, 3H), 4.08 – 4.00 (m, 2H), 3.99 – 3.91 (m, 8H), 3.90 – 3.82 (m, 4H), 3.81 (s, 1H), 3.71 (d, *J* = 1.2 Hz, 3H), 3.68 – 3.58 (m, 2H), 3.47 (t, *J* = 7.1 Hz, 1H), 2.96 – 2.81 (m, 1H), 2.74 (dtt, *J* = 12.1, 6.1, 3.4 Hz, 2H), 2.62 (dt, *J* = 11.5, 5.9 Hz, 2H), 2.25 (t, *J* = 7.0 Hz, 1H), 2.22 – 2.05 (m, 2H).
D123	LCMS: (ESI) m/z: $[M+H]^+$ = 807.30
D124	LCMS: (ESI) m/z: $[M+H]^+$ = 865.90
D125	LCMS: (ESI) m/z: $[M+H]^+$ = 793.20
D126	LCMS: (ESI) m/z: $[M+H]^+$ = 793.20
D127	LCMS: (ESI) m/z: $[M+H]^+$ = 793.55
D128	LCMS: (ESI) m/z: $[M+H]^+$ = 779.40
D129	LCMS: (ESI) m/z: $[M+H]^+$ = 835.70
D130	LCMS: (ESI) m/z: $[M+H]^+$ = 851.40
D131	LCMS: (ESI) m/z: $[M+H]^+$ = 865.35
D132	LCMS: (ESI) m/z: $[M+H]^+$ = 775.3
D133	LCMS: (ESI) m/z: $[M+H]^+$ = 777.5
D134	LCMS: (ESI) m/z: $[M+H]^+$ = 761.4
D135	LCMS: (ESI) m/z: $[M+H]^+$ = 763.4
D136	LCMS: (ESI) m/z: $[M+H]^+$ = 775.2
D137	LCMS: (ESI) m/z: $[M+H]^+$ = 789.3
D138	LCMS: (ESI) m/z: $[M+H]^+$ = 803.5
D139	LCMS: (ESI) m/z: $[M+H]^+$ = 805.4
D140	LCMS: (ESI) m/z: $[M+H]^+$ = 775.2
D141	LCMS: (ESI) m/z: $[M+H]^+$ = 789.3
D142	LCMS: (ESI) m/z: $[M+H]^+$ = 803.5
D143	LCMS: (ESI) m/z: $[M+H]^+$ = 817.5
D144	LCMS: (ESI) m/z: $[M+H]^+$ = 819.3
D145	LCMS: (ESI) m/z: $[M+H]^+$ = 689.3

Compound No.	Analytical Data
D146	LCMS: (ESI) m/z: $[M+H]^+$ = 717.3
D147	LCMS: (ESI) m/z: $[M+H]^+$ = 731.4
D148	LCMS: (ESI) m/z: $[M+H]^+$ = 745.2
D149	LCMS: (ESI) m/z: $[M+H]^+$ = 745.3
D150	LCMS: (ESI) m/z: $[M+H]^+$ = 789.5
D151	LCMS: (ESI) m/z: $[M+H]^+$ = 805.9
D152	LCMS: (ESI) m/z: $[M+H]^+$ = 831.4
D153	LCMS: (ESI) m/z: $[M+H]^+$ = 833.3
D154	LCMS: (ESI) m/z: $[M+H]^+$ = 789.3
D155	LCMS: (ESI) m/z: $[M+H]^+$ = 803.2
D156	LCMS: (ESI) m/z: $[M+H]^+$ = 817.6
D157	LCMS: (ESI) m/z: $[M+H]^+$ = 831.6
D158	LCMS: (ESI) m/z: $[M+H]^+$ = 833.5
D159	LCMS: (ESI) m/z: $[M+H]^+$ = 851.25
D160	LCMS: (ESI) m/z: $[M+H]^+$ = 821.45
D161	LCMS: (ESI) m/z: $[M+H]^+$ = 821.35
D162	LCMS: (ESI) m/z: $[M+H]^+$ = 807.35
D163	LCMS: (ESI) m/z: $[M+H]^+$ = 835.50
D164	LCMS: (ESI) m/z: $[M+H]^+$ = 821.60
D165	LCMS: (ESI) m/z: $[M+H]^+$ = 849.60; ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.60 – 9.41 (m, 1H), 8.69 (dd, *J* = 5.6, 3.0 Hz, 1H), 8.53 (s, 0.6H, FA), 7.79 – 7.50 (m, 3H), 7.44 – 7.15 (m, 2H), 6.81 – 6.47 (m, 2H), 5.11 (dt, *J* = 11.6, 4.5 Hz, 1H), 4.57 – 4.07 (m, 5H), 4.05 – 3.76 (m, 13H), 3.74 – 3.66 (m, 3H), 3.64 – 3.44 (m, 1H), 3.05 – 2.65 (m, 5H), 2.64 – 2.02 (m, 6H).
D166	LCMS: (ESI) m/z: $[M+H]^+$ = 835.65
D167	LCMS: (ESI) m/z: $[M+H]^+$ = 851.25
D168	LCMS: (ESI) m/z: $[M+H]^+$ = 851.25
D169	LCMS: (ESI) m/z: $[M+H]^+$ = 821.35
D170	LCMS: (ESI) m/z: $[M+H]^+$ = 821.35
D171	LCMS: (ESI) m/z: $[M+H]^+$ = 807.35

Compound No.	Analytical Data
D172	LCMS: (ESI) m/z: $[M+H]^+$ = 835.35
D173	LCMS: (ESI) m/z: $[M+H]^+$ = 835.60
D174	LCMS: (ESI) m/z: $[M+H]^+$ = 821.65
D175	LCMS: (ESI) m/z: $[M+H]^+$ = 849.80
D176	LCMS: (ESI) m/z: $[M+H]^+$ = 835.70
D177	LCMS: (ESI) m/z: $[M+H]^+$ = 835.65

Example 82 – BRD9 bromodomain TR-FRET Competition Binding Assay

This example demonstrates the ability of the compounds of the disclosure to biochemically inhibit BRD9 bromodomain in a competition binding assay.

Procedure: His-Flag-BRD9 (P133-K239; Swiss Prot Q9H8M2; SEQ ID NO:1 mgsshhhhhhenlyfq/gdykddddkgslevlfqg/PAENESTPIQQLLEHFLRQLQRKDPHGFFAFPVTDAIAPGYSMII KHPMDFGTMKDKIVANEYKSVTEFKADFKLMCDNAMTYNRPDTVYYKLAKKILHAGFKMMSK) was cloned, expressed, purified, and then treated with TEV protease. Cleaved His tag was removed by purification. The binding of a biotinylated small molecule ligand of BRD9 was assessed via the LANCE® TR-FRET platform (PerkinElmer), and the compounds were assayed for inhibitory activity against this interaction.

A mixture of biotinylated-ligand and SureLight™ Allophycocyanin-Streptavidin (APC-SA, PerkinElmer AD0201) in 50 mM HEPES (pH 7.4), 50 mM NaCl, 1 mM TCEP (pH 7), 0.01% (v/v) Tween-20, 0.01% (w/v) bovine serum albumin was added to a white 384-well PerkinElmer Proxiplate Plus plate. DMSO or 3-fold serially diluted compounds were then added to the Proxiplate followed by addition of Flag-BRD9. After a 10 minute incubation at room temperature, Eu-W1024 anti-FLAG (PerkinElmer, AD0273) was added. The final reaction mixture that contained 3.75 nM biotinylated ligand, 3 nM Flag-BRD9, 7.5 nM SureLight™ Allophycocyanin-Streptavidin, and 0.2 nM Eu-W1024 anti-FLAG was incubated at room temperature for 90 minutes.

Results: The plates were then read on a PerkinElmer Envision plate reader to determine the ratio of emission at 665 nm over 615 nm. Data was normalized to a DMSO control (100%) and a no protein control (0%) and then fit to a four parameter, non-linear curve fit to calculate IC_{50} (μM) values as shown in Table 4. As shown by the results in Table 4, a number of compounds of the present disclosure exhibit an IC_{50} value of < 1 μM for BRD9 binding, indicating their affinity for targeting BRD9.

Table 4. Bromodomain 9 (BRD9) TR-FRET Binding of Compounds of the Disclosure

Compound No.	Bromodomain TR-FRET BRD9 IC_{50} (nM)
D1	+++
D2	++++
D3	++++
D4	++++
D5	++++
D6	++++
D7	++++
D8	++++
D9	++++
D10	+++
D11	+++
D12	++++
D13	++++
D14	++++
D15	++++
D16	NT
D17	NT
D18	NT
D19	NT
D20	NT
D21	NT
D22	++++
D23	++++
D24	NT
D25	++++
D26	+++
D27	++++

Compound No.	Bromodomain TR-FRET BRD9 IC_{50} (nM)
D28	NT
D29	NT
D30	++++
D31	++++
D32	++++
D33	++++
D34	++++
D35	++++
D36	++++
D37	++++
D38	++++
D39	++++
D40	++++
D41	++++
D42	NT
D43	NT
D44	NT
D45	NT
D46	NT
D47	NT
D48	NT
D49	NT
D50	NT
D51	NT
D52	++++
D53	++++
D54	+++
D55	+++

Compound No.	Bromodomain TR-FRET BRD9 IC_{50} (nM)
D56	++++
D57	+++
D58	++++
D59	++++
D60	++++
D61	++++
D62	+++
D63	+++
D64	+++
D65	+++
D66	+++
D67	++++
D68	++++
D69	++++
D70	+++
D71	++++
D72	++++
D73	+++
D74	++++
D75	NT
D76	NT
D77	NT
D78	NT
D79	NT
D80	NT
D81	NT
D82	NT
D83	NT

Compound No.	Bromodomain TR-FRET BRD9 IC_{50} (nM)
D84	+++
D85	+++
D86	+++
D87	++++
D88	++++
D89	++++
D90	++++
D91	+++
D92	++++
D93	++++
D94	+++
D95	+++
D96	++++
D97	++++
D98	++
D99	+++
D100	++++
D101	++++
D102	++++
D103	+++
D104	+++
D105	+++
D106	+++
D107	+++
D108	++++
D109	++++
D110	+++
D111	++++

Compound No.	Bromodomain TR-FRET BRD9 IC_{50} (nM)
D112	++++
D113	++++
D114	++++
D115	+++
D116	++++
D117	++++
D118	++++
D119	++++
D120	+++
D121	+++
D122	++++
D123	++++
D124	++++
D125	++++
D126	+++
D127	++++
D128	+++
D129	++++
D130	++++
D131	++++
D132	++++
D133	++++
D134	+++
D135	+++
D136	++++
D137	++++
D138	++++
D139	++++

Compound No.	Bromodomain TR-FRET BRD9 IC_{50} (nM)
D140	++++
D141	+++
D142	+++
D143	++++
D144	+++
D145	+++
D146	++++
D147	+++
D148	+++
D149	++++
D150	++++
D151	++++
D152	++++
D153	+++
D154	++++
D155	++++
D156	++++
D157	+++
D158	++++
D159	++++
D160	++++
D161	++++
D162	+++
D163	++++
D164	++++
D165	+++
D166	++++
D167	++++

Compound No.	Bromodomain TR-FRET BRD9 IC_{50} (nM)
D168	++++
D169	++++
D170	+++
D171	+++
D172	++++
D173	+++
D174	+++
D175	+++
D176	++++
D177	++++

"+" indicates inhibitory effect of > 1000 nM;
"++" indicates inhibitory effect of 100-1000 nM;
"+++" indicates inhibitory effect of 10-100 nM;
"++++" indicates inhibitory effect of < 10 nM;
"NT" indicates not tested

Example 83 – SYO1 BRD9 NanoLuc Degradation Assay

This example demonstrates the ability of the compounds of the disclosure to degrade a Nanoluciferase-BRD9 fusion protein in a cell-based degradation assay.

Procedure: A stable SYO-1 cell line expressing 3xFLAG-NLuc-BRD9 was generated. On day 0 cells were seeded in 30 µL media into each well of 384-well cell culture plates. The seeding density was 8000 cells/well. On day 1, cells were treated with 30 nL DMSO or 30 nL of 3-fold serially DMSO-diluted compounds (10 points in duplicates with 1 µM as final top dose). Subsequently plates were incubated for 6 hours in a standard tissue culture incubator and equilibrated at room temperature for 15 minutes. Nanoluciferase activity was measured by adding 15 µL of freshly prepared Nano-Glo Luciferase Assay Reagent (Promega N1130), shaking the plates for 10 minutes and reading the bioluminescence using an EnVision reader.

Results: The Inhibition% was calculated using the following formula: %Inhibition = 100 x (Lum_{HC} – Lum_{Sample}) / (Lum_{HC} –Lum_{LC}). DMSO treated cells are employed as High Control (HC) and 1 µM of a known BRD9 degrader standard treated cells are employed as Low Control (LC). The data was fit to a four parameter, non-linear curve fit to calculate IC_{50} (µM) values as shown in Table 5. As shown by the results in Table 5, a number of compounds of the present disclosure exhibit an IC_{50} value of < 1 µM for the degradation of BRD9, indicating their use as compounds for reducing the levels and/or activity of BRD9 and their potential for treating BRD9-related disorders.

Table 5. SYO1 Bromodomain 9-NanoLuc Degradation by Compounds of the Disclosure

Compound No.	**SYO1 BRD9-NanoLuc degradation IC_{50} (nM)**
D1	++++
D2	+++
D3	++++
D4	+++
D5	+++
D6	++++
D7	+++
D8	+
D9	++++
D10	++++
D11	++++
D12	++++
D13	++++
D14	++++
D15	++++
D16	++++
D17	++++
D18	++++
D19	++++
D20	++++
D21	+
D22	+++
D23	++++
D24	NT
D25	++
D26	+

Compound No.	SYO1 BRD9-NanoLuc degradation IC_{50} (nM)
D27	+++
D28	++
D29	+++
D30	+++
D31	+++
D32	+++
D33	++++
D34	++++
D35	++++
D36	++
D37	++++
D38	++++
D39	++++
D40	++++
D41	+++
D42	++++
D43	++
D44	++++
D45	++++
D46	++++
D47	++++
D48	+++
D49	+
D50	++++
D51	NT
D52	++++
D53	++++
D54	+++

Compound No.	SYO1 BRD9-NanoLuc degradation IC_{50} (nM)
D55	++
D56	++++
D57	++++
D58	++++
D59	++++
D60	++++
D61	NT
D62	NT
D63	NT
D64	++
D65	++
D66	++
D67	++++
D68	NT
D69	NT
D70	+++
D71	++++
D72	++++
D73	++++
D74	++
D75	++++
D76	NT
D77	NT
D78	NT
D79	NT
D80	NT
D81	NT
D82	+++

Compound No.	SYO1 BRD9-NanoLuc degradation IC_{50} (nM)
D83	++
D84	+
D85	++
D86	++
D87	+++
D88	+++
D89	++++
D90	+++
D91	+++
D92	++++
D93	+++
D94	+++
D95	++
D96	+++
D97	+++
D98	++
D99	+++
D100	++++
D101	++
D102	NT
D103	NT
D104	NT
D105	NT
D106	NT
D107	NT
D108	++++
D109	+++
D110	+++

Compound No.	SYO1 BRD9-NanoLuc degradation IC_{50} (nM)
D111	+++
D112	++
D113	++++
D114	+++
D115	++
D116	+++
D117	++
D118	+++
D119	+++
D120	+++
D121	+++
D122	++++
D123	++++
D124	++++
D125	+++
D126	++
D127	++
D128	++++
D129	++++
D130	++++
D131	++++
D132	NT
D133	NT
D134	NT
D135	NT
D136	NT
D137	NT
D138	NT

Compound No.	SYO1 BRD9-NanoLuc degradation IC_{50} (nM)
D139	NT
D140	NT
D141	NT
D142	NT
D143	NT
D144	NT
D145	NT
D146	NT
D147	NT
D148	NT
D149	NT
D150	NT
D151	NT
D152	NT
D153	NT
D154	NT
D155	NT
D156	NT
D157	NT
D158	NT
D159	+++
D160	+++
D161	+++
D162	+++
D163	+++
D164	+++
D165	+++
D166	+++

Compound No.	SYO1 BRD9-NanoLuc degradation IC_{50} (nM)
D167	++++
D168	++++
D169	+++
D170	++++
D171	++++
D172	+++
D173	++++
D174	++
D175	+++
D176	++++
D177	+++

"+" indicates inhibitory effect of > 1 μM;
"++" indicates inhibitory effect of 100-1000 nM;
"+++" indicates inhibitory effect of 10-100 nM;
"++++" indicates inhibitory effect of < 10 nM;
"NT" indicates not tested

Other Embodiments

All publications, patents, and patent applications mentioned in this specification are incorporated herein by reference in their entirety to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference in its entirety. Where a term in the present application is found to be defined differently in a document incorporated herein by reference, the definition provided herein is to serve as the definition for the term.

While the invention has been described in connection with specific embodiments thereof, it will be understood that invention is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure that come within known or customary practice within the art to which the invention pertains and may be applied to the essential features hereinbefore set forth, and follows in the scope of the claims.

Other embodiments are in the claims.

What is claimed is:

Claims

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

A-L-B

Formula I,

wherein

A is a BRD9 binding moiety;

B is a degradation moiety; and

L has the structure of **Formula II**:

$$A^1–(E^1)–(F^1)–(C^3)_m–(E^3)_n–(F^2)_{o1}–(F^3)_{o2}–(E^2)_p–A^2,$$

Formula II

wherein

A^1 is a bond between the linker and A;

A^2 is a bond between B and the linker;

each of m, n, o1, o2, and p is, independently, 0 or 1;

each of E^1 and E^2 is, independently, O, S, NR^N, optionally substituted C_{1-10} alkyl, optionally substituted C_{2-10} alkenyl, optionally substituted C_{2-10} alkynyl, optionally substituted C_2-C_{10} polyethylene glycol, or optionally substituted C_{1-10} heteroalkyl;

E^3 is O, S, or NR^N;

each R^N is, independently, H, optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, optionally substituted C_{2-6} heterocyclyl, optionally substituted C_{6-12} aryl, or optionally substituted C_{1-7} heteroalkyl;

C^3 is carbonyl, thiocarbonyl, sulphonyl, or phosphoryl; and

each of F^1, F^2, and F^3 is, independently, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heteroaryl,

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein the linker has the structure of **Formula IIa** :

$$A^1–(E^1)–(F^1)–(C^3)_m–(E^2)_p–A^2.$$

Formula IIa

3. The compound of claim 1, wherein the linker has the structure of **Formula IIb**:

$$A^1–(E^1)–(F^1)–(E^2)_p–A^2.$$

Formula IIb

4. The compound of claim 1, wherein the linker has the structure of **Formula IIc**:

$A^1–(E^1)–(F^1)–A^2$.

Formula IIc

5. The compound of claim 1, wherein the linker has the structure of **Formula IId**:

$A^1–(E^1)–(F^1)–(C^3)_m–(F^2)_{o1}–A^2$.

Formula IId

6. The compound of claim 1, wherein the linker has the structure of **Formula IIe** :

$A^1–(E^1)–(F^1)–(E^3)_n–(F^2)_{o1}–(E^2)_p–A^2$.

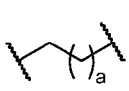
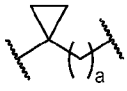
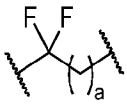
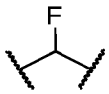
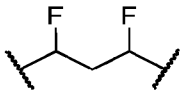
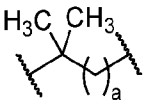
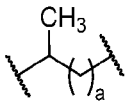
Formula IIe

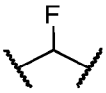
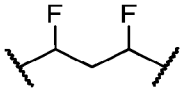
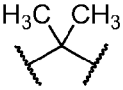
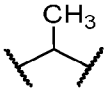
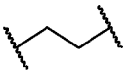
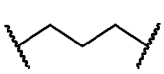
7. The compound of any one of claims 1 to 6, wherein each of E^1 and E^2 is, independently, NR^N, optionally substituted $C_{1–10}$ alkyl, optionally substituted C_2-C_{10} polyethylene glycol, or optionally substituted $C_{1–10}$ heteroalkyl.

8. The compound of any one of claims 1 to 7, wherein E^3 is O.

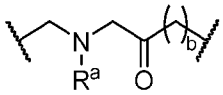
9. The compound of any one of claims 1 to 8, wherein each R^N is, independently, H or optionally substituted $C_{1–4}$ alkyl.

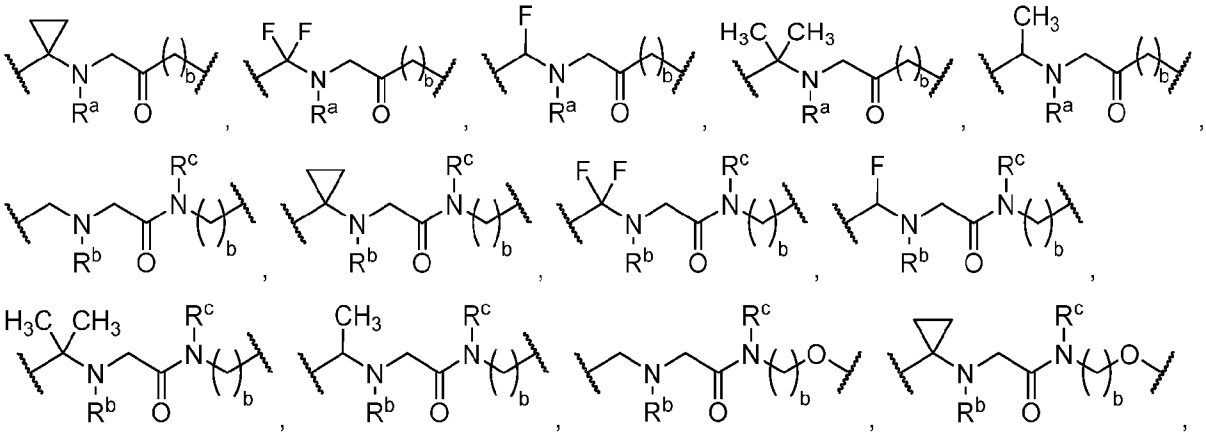
10. The compound of claim 9, wherein each R^N is, independently, H or CH_3.

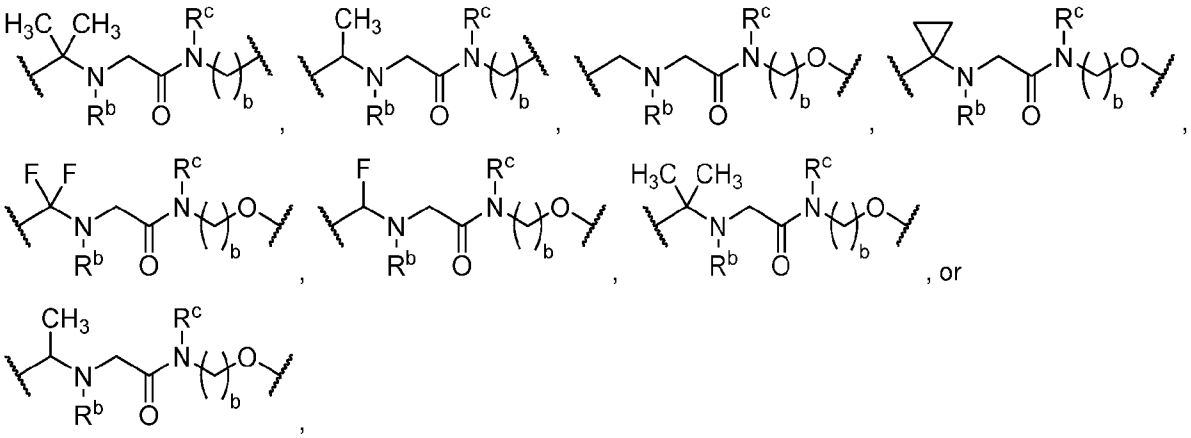
11. The compound of any one of claims 1 to 10, wherein E^1 is  ,  ,  ,  ,  ,  , or  , wherein a is 0, 1, 2, 3, 4, or 5.

12. The compound of claim 11, wherein E^1 is , , ,  ,  ,  ,  ,  , or  .

13. The compound of claim 12, wherein E^1 is .

14. The compound of any one of claims 1 to 13, wherein E^1 is  ,



 , or

,

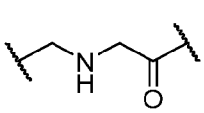
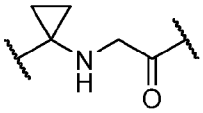
wherein

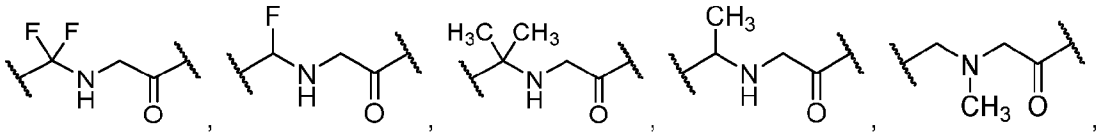
b is 0, 1, 2, 3, 4, 5, or 6;

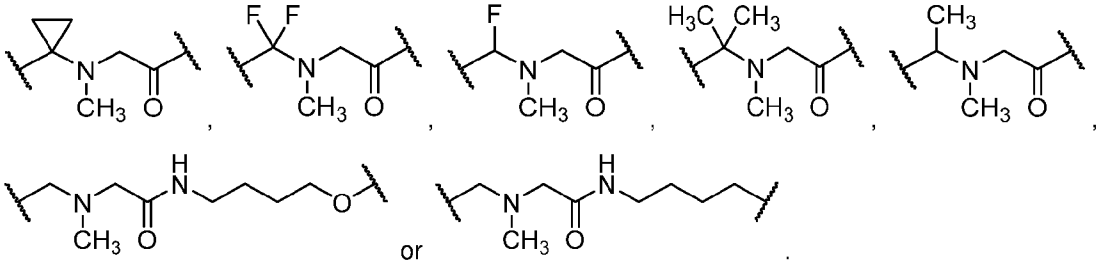
R^a is H or optionally substituted C_1-C_6 alkyl;

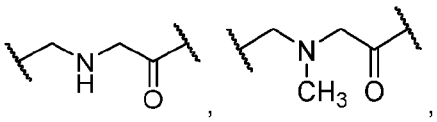
R^b is H or optionally substituted C_1-C_6 alkyl; and

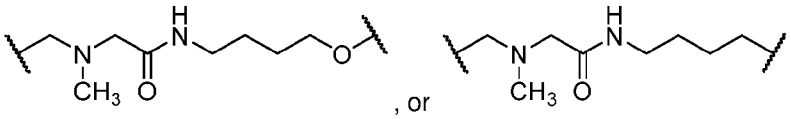
R^c is H or optionally substituted C_1-C_6 alkyl.

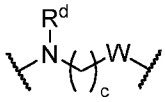
15. The compound of claim 14, wherein E^1 is  ,  ,

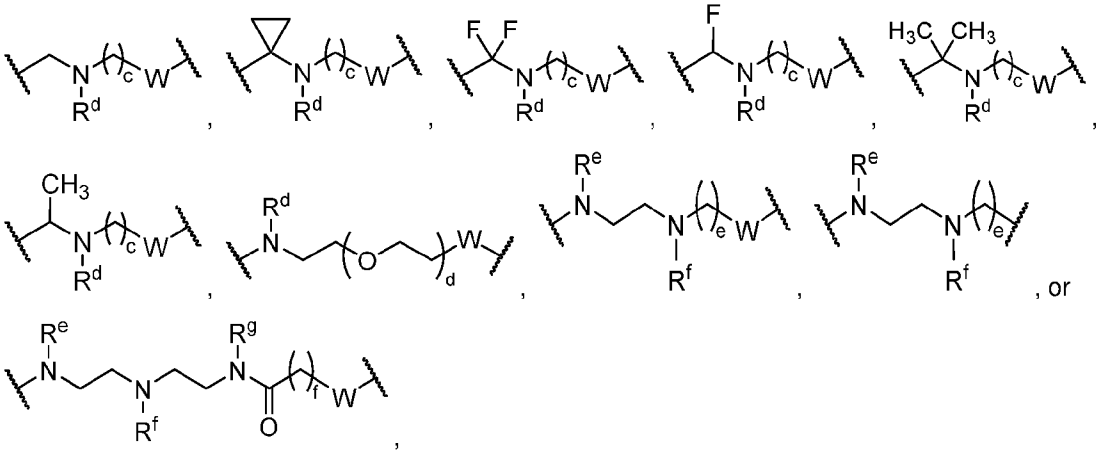




16. The compound of claim 15, wherein E^1 is 



17. The compound of any one of claims 1 to 16, wherein E^2 is O, NR^w, 



wherein

c is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

d is 0, 1, 2, or 3;

e is 0, 1, 2, 3, 4, 5, or 6;

f is 0, 1, 2, 3, or 4;

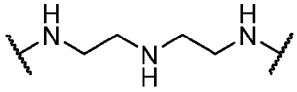
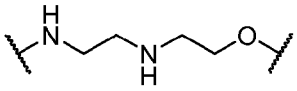
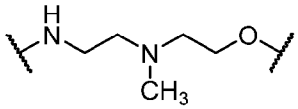
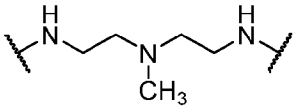
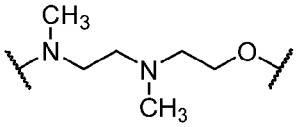
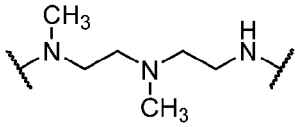
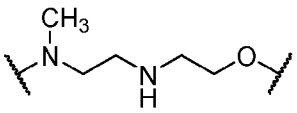
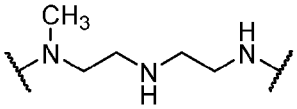
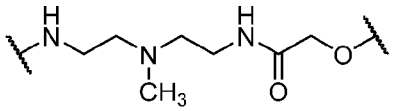
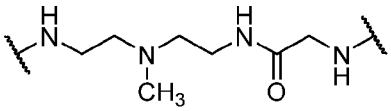
R^d is H or optionally substituted C_1-C_6 alkyl;

R^e is H or optionally substituted C_1-C_6 alkyl;

R^f is H or optionally substituted C_1-C_6 alkyl;

R^g is H or optionally substituted C_1-C_6 alkyl; and

W is O or NR^w, wherein R^w is H or optionally substituted C_1-C_6 alkyl.

18. The compound of any one of claims 1 to 17, wherein E^2 is O,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

19. The compound of any one of claims 1 to 18, wherein each of F^1, F^2, and F^3 is, independently, optionally substituted C_3-C_{10} carbocyclyl.

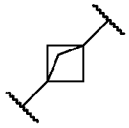
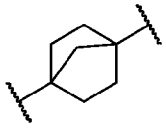
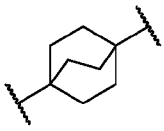
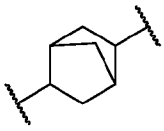
20. The compound of claim 19, wherein the C_3-C_{10} carbocyclyl is monocyclic.

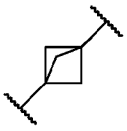
21. The compound of claim 19, wherein the C_3-C_{10} carbocyclyl is polycyclic.

22. The compound of claim 21, wherein the C_3-C_{10} carbocyclyl is fused.

23. The compound of claim 21, wherein the C_3-C_{10} carbocyclyl is spirocyclic.

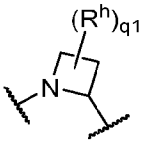
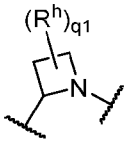
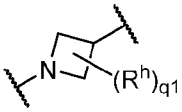
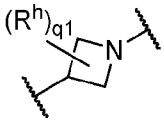
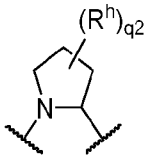
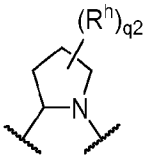
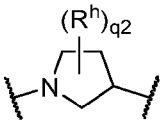
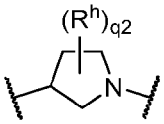
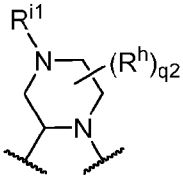
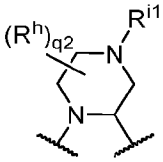
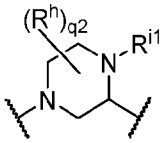
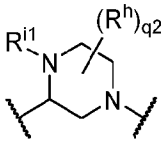
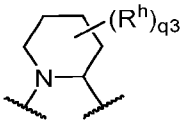
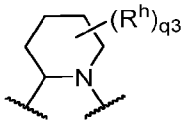
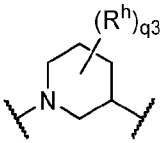
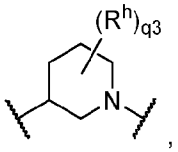
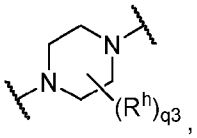
24. The compound of claim 21, wherein the C_3-C_{10} carbocyclyl is bridged.

25. The compound of claim 24, wherein the C_3-C_{10} carbocyclyl is  ,  ,  , or  .

26. The compound of claim 25, wherein the C_3-C_{10} carbocyclyl is  .

27. The compound of any one of claims 1 to 18, wherein each of F^1, F^2, and F^3 is, independently, optionally substituted C_2-C_9 heterocyclyl.

28. The compound of claim 27, wherein the C_2-C_9 heterocyclyl is monocyclic.

29. The compound of claim 28, wherein the C_2-C_6 heterocyclyl is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , or  ,

where

q1 is 0, 1, 2, 3, or 4;

q2 is 0, 1, 2, 3, 4, 5, or 6;

q3 is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

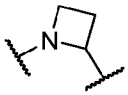
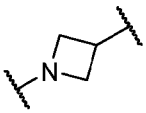
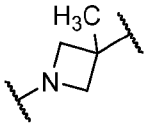
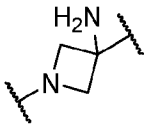
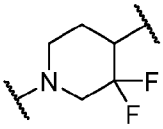
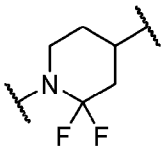
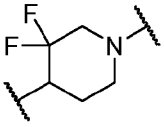
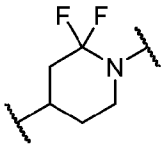
each R^h is, independently, halogen, optionally substituted C_1-C_6 alkyl, OR^{i2}, or $NR^{i3}R^{i4}$;

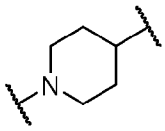
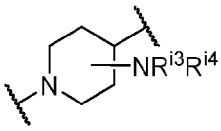
R^{i1} is H or optionally substituted C_1-C_6 alkyl;

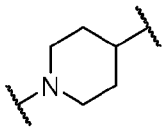
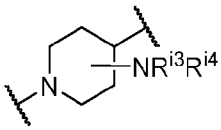
R^{i2} is H or optionally substituted C_1-C_6 alkyl;

R^{i3} is H or optionally substituted C_1-C_6 alkyl; and

R^{i4} is H or optionally substituted C_1-C_6 alkyl.

30. The compound of claim 29, wherein F^1 is  ,  ,  ,  ,  ,  ,  , or  .

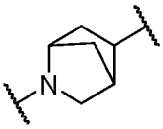
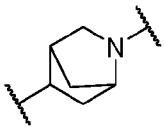
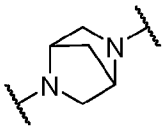
31. The compound of claim 29, wherein F^2 is  or  .

32. The compound of claim 29, wherein F^3 is  or  .

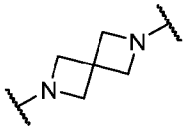
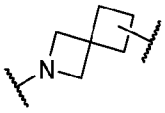
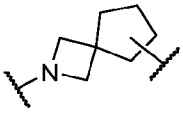
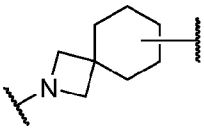
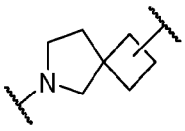
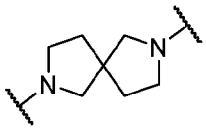
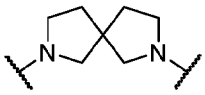
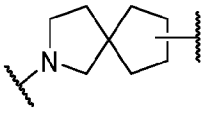
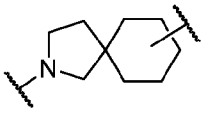
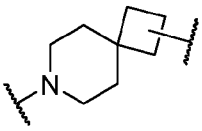
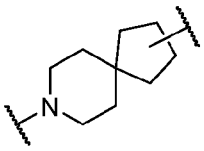
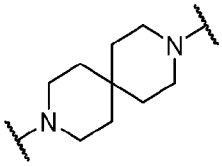
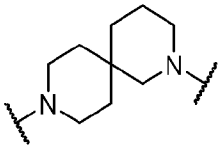
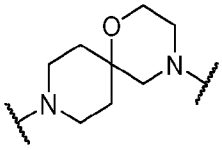
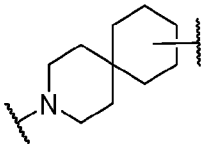
33. The compound of claim 27, wherein the C_2-C_9 heterocyclyl is polycyclic.

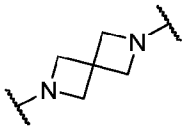
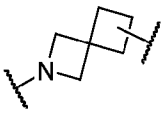
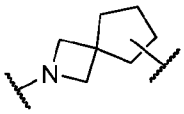
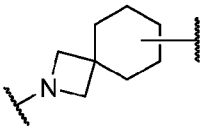
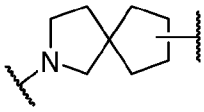
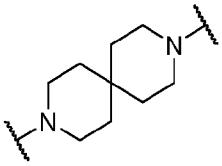
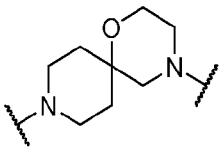
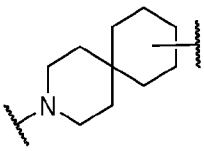
34. The compound of claim 33, wherein the C_2-C_9 heterocyclyl is bicyclic.

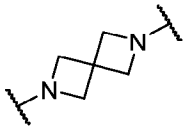
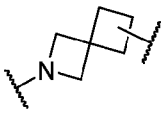
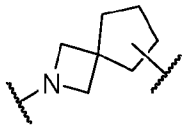
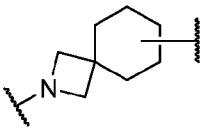
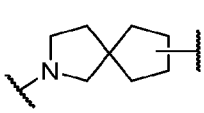
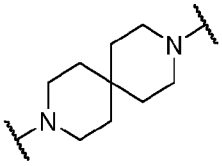
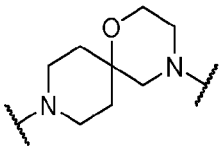
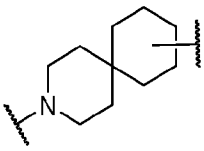
35. The compound of claim 33 or 34, wherein the C_2-C_9 heterocyclyl is bridged.

36. The compound of claim 35, wherein the C_2-C_6 heterocyclyl is  ,  , or  .

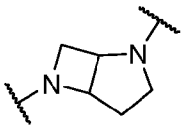
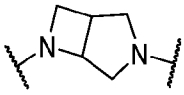
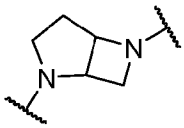
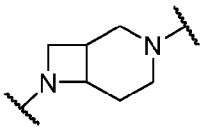
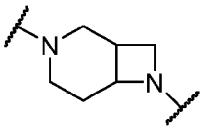
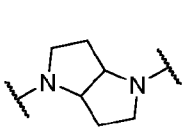
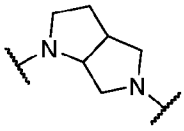
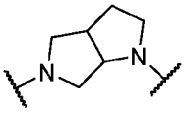
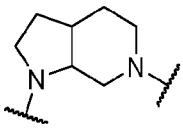
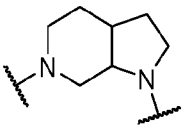
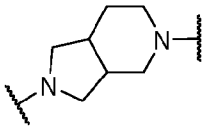
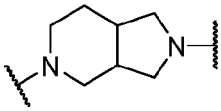
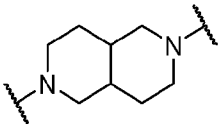
37. The compound of claim 33 or 34, wherein the C_2-C_9 heterocyclyl is spirocyclic.

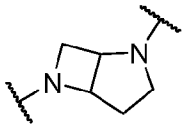
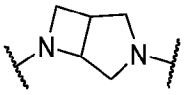
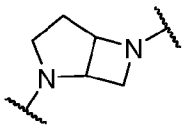
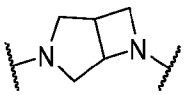
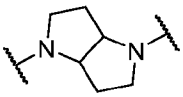
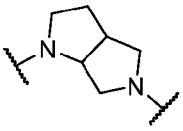
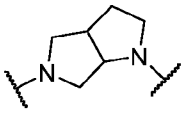
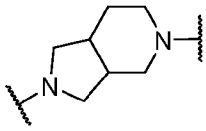
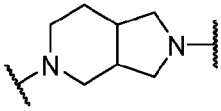
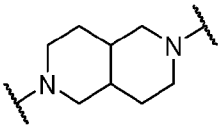
38. The compound of claim 37, wherein the C_2-C_6 heterocyclyl is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

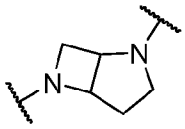
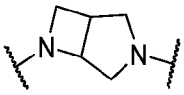
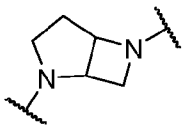
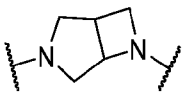
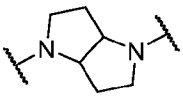
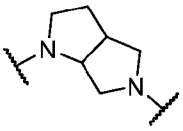
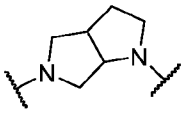
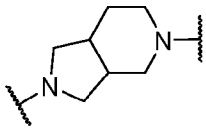
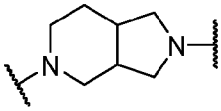
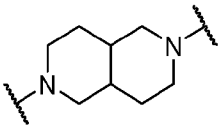
39. The compound of claim 38, wherein F^1 is  ,  ,  ,  ,  ,  ,  , or  .

40. The compound of claim 38, wherein F^2 is  ,  ,  ,  ,  ,  ,  , or  .

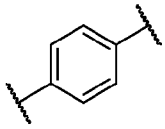
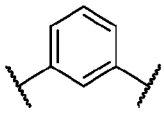
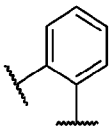
41. The compound of claim 33 or 34, wherein the C_2-C_9 heterocyclyl is fused.

42. The compound of claim 41, wherein the C_2–C_9 heterocyclyl is  ,  ,  , ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

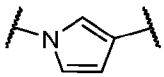
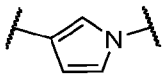
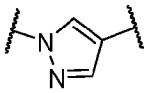
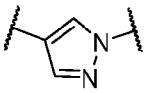
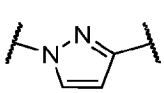
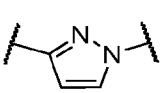
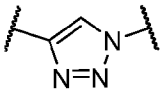
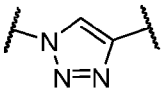
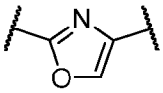
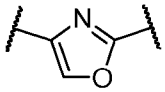
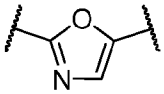
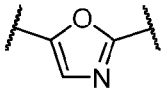
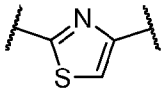
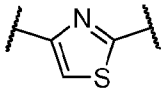
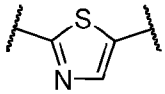
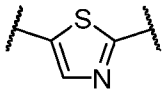
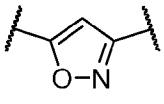
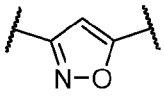
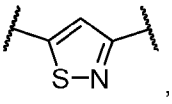
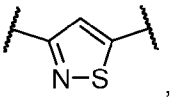
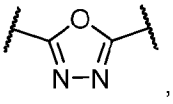
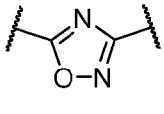
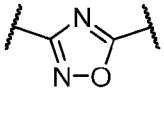
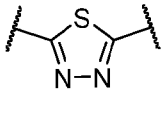
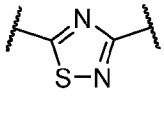
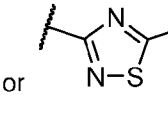
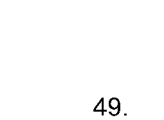
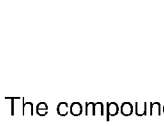
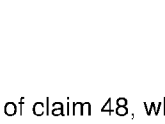
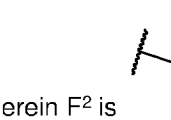
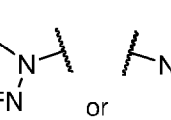
43. The compound of claim 42, wherein F^1 is  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

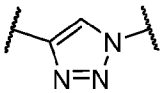
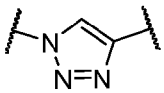
44. The compound of claim 42, wherein F^2 is  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

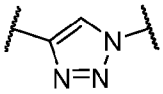
45. The compound of any one of claims 1 to 18, wherein each of F^1, F^2, and F^3 is, independently, optionally substituted C_6-C_{10} aryl.

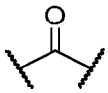
46. The compound of claim 45, wherein the C_6-C_{10} aryl is  ,  , or  .

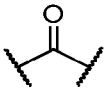
47. The compound of any one of claims 1 to 18, wherein each of F^1, F^2, and F^3 is, independently, optionally substituted C_2-C_9 heteroaryl.

48. The compound of claim 47, wherein the C_2-C_9 heteroaryl is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , ,  ,  ,  ,  , or  .

49. The compound of claim 48, wherein F^2 is  or  .

50. The compound of claim 49, wherein F^2 is  .

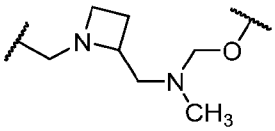
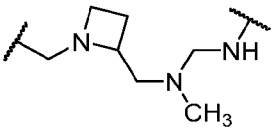
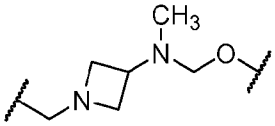
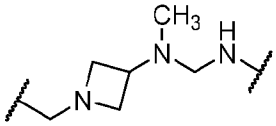
51. The compound of any one of claims 1 to 50, C^3 is  or .

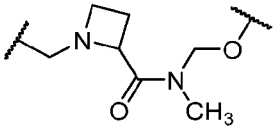
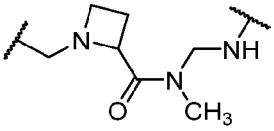
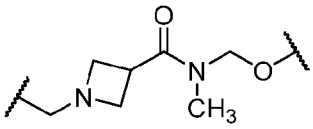
52. The compound of claim 51, wherein C^3 is  .

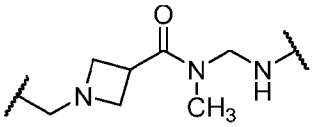
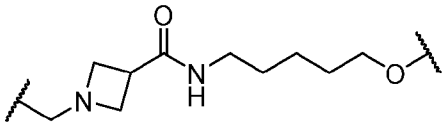
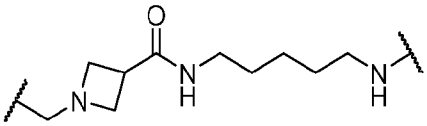
53. The compound of any one of claims 1 to 52, wherein m is 1.

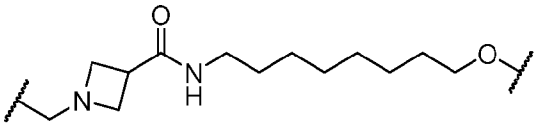
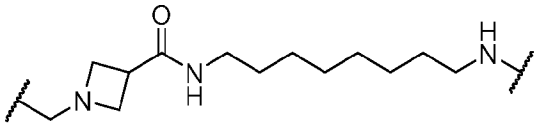
54. The compound of any one of claims 1 to 53, wherein p is 1.

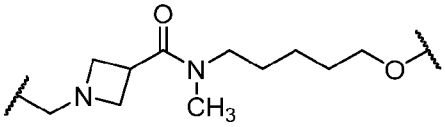
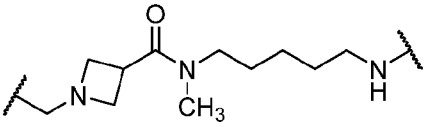
55. The compound of any one of claims 1 to 54 wherein the linker has the structure of

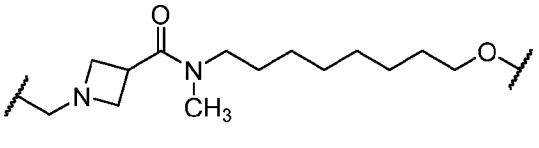
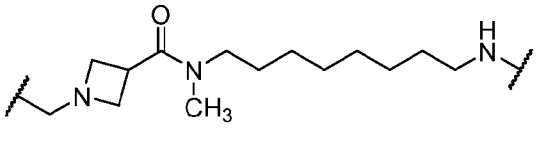
 ,  ,  ,  ,

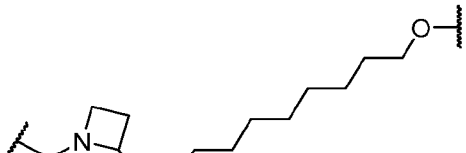
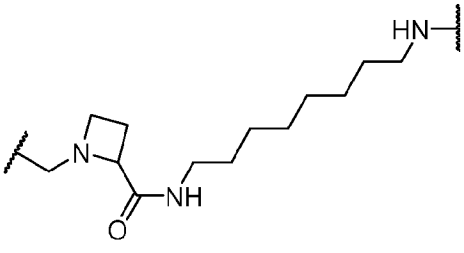
 ,  ,  ,

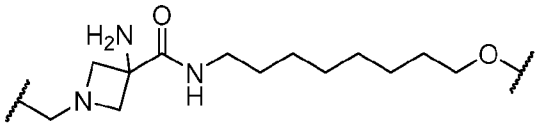
 ,  ,  ,

 ,  ,

 ,  ,

 ,  ,

 ,  ,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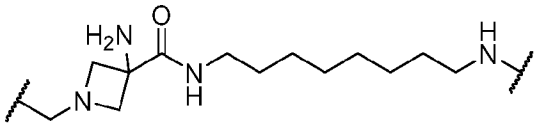
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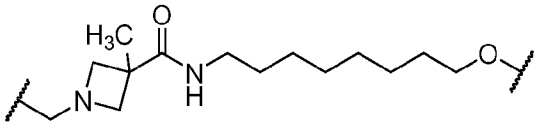
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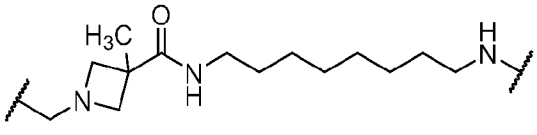
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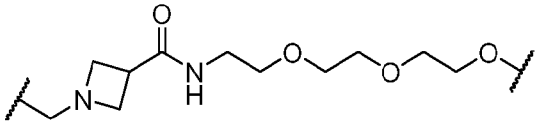
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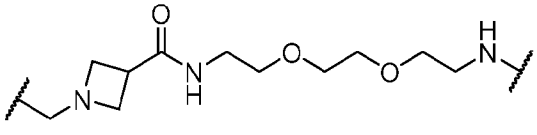
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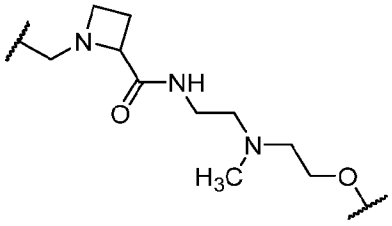
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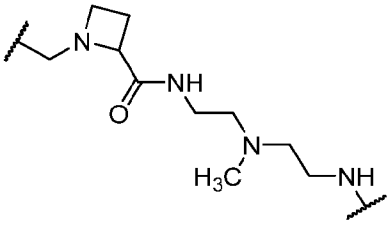
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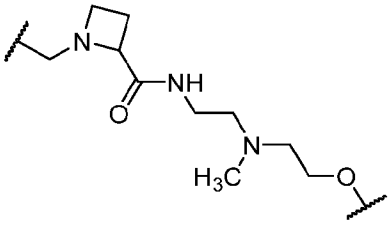
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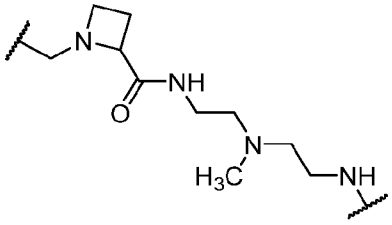
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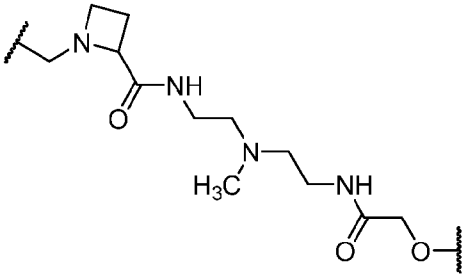
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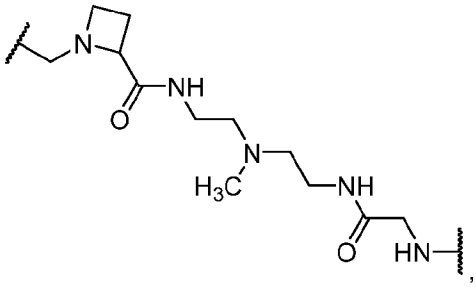
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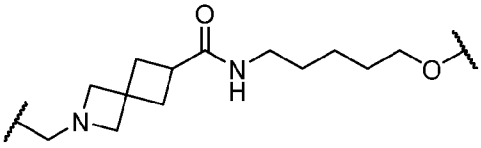
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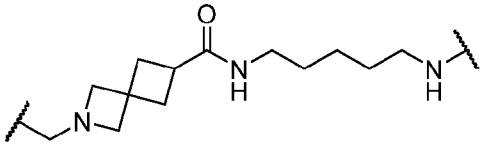
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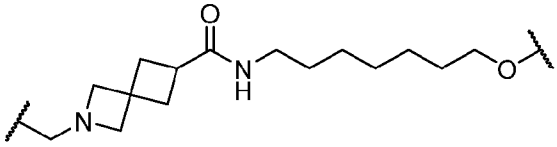
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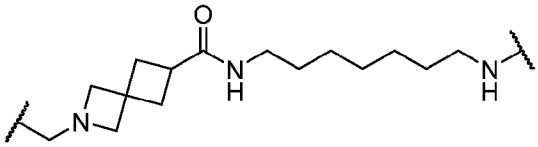
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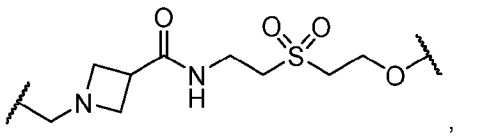
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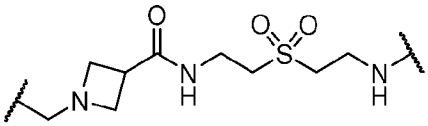
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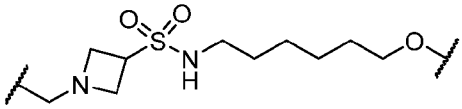
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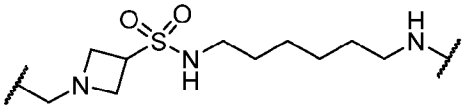
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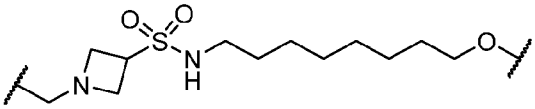
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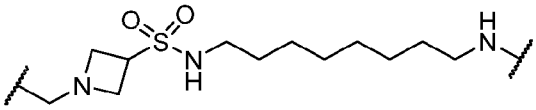
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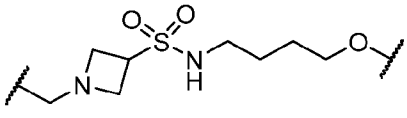
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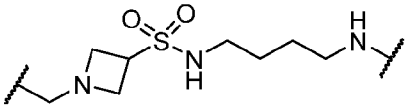
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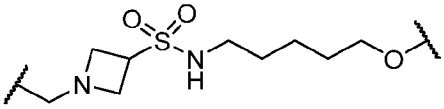
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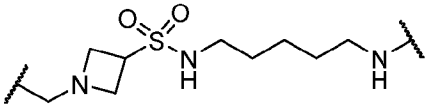
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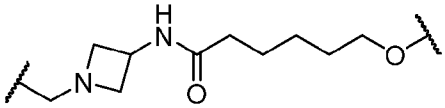
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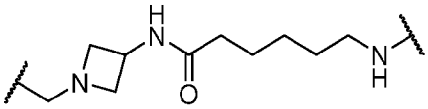
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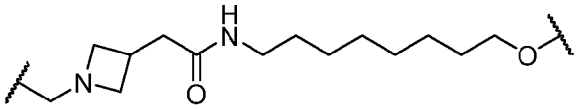
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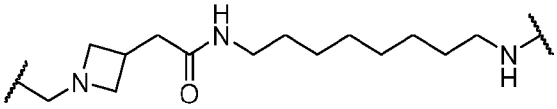
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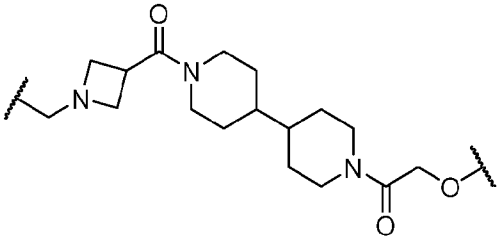
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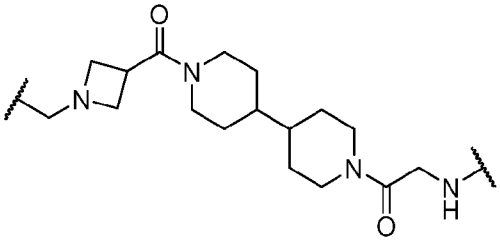
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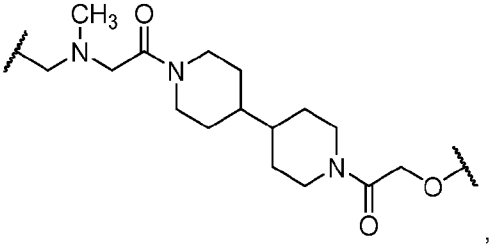
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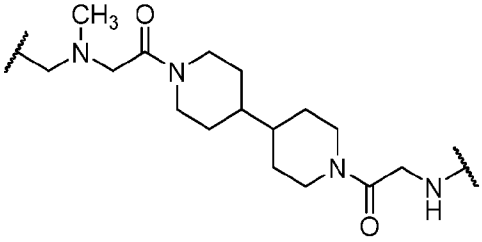
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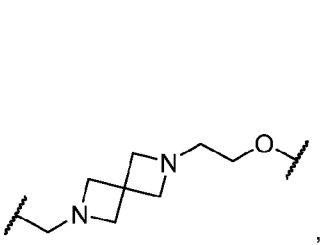
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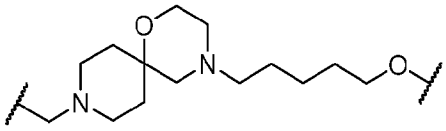
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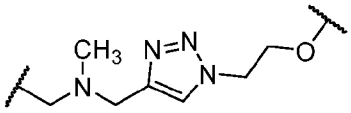
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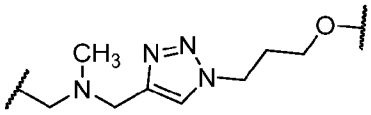
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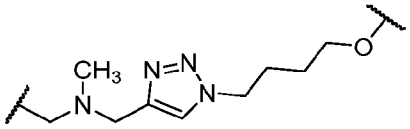
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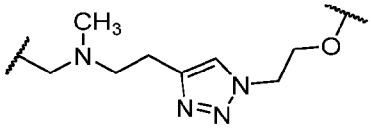
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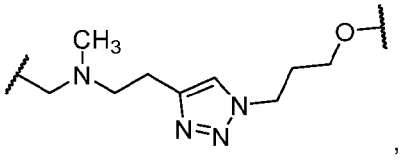
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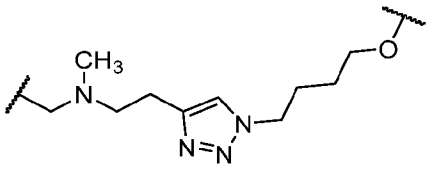
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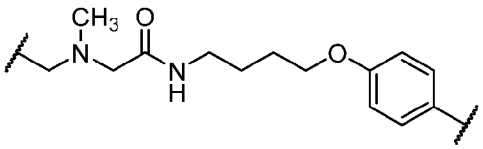
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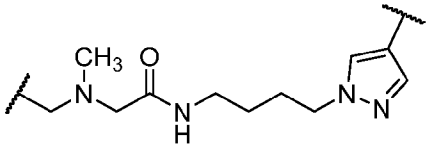
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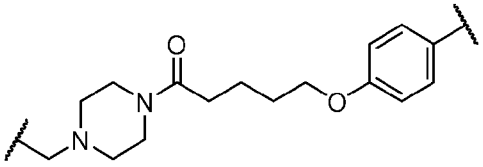
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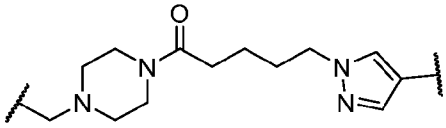
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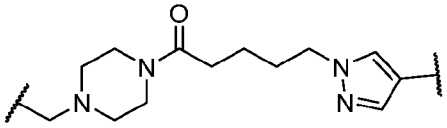
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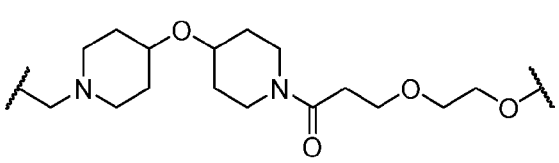
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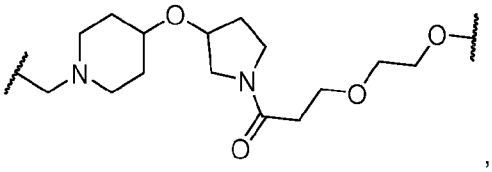
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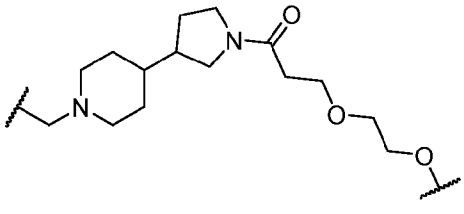
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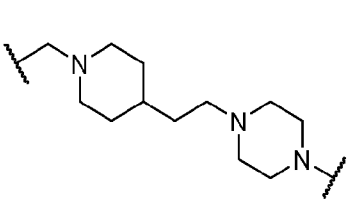
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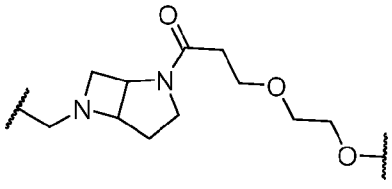
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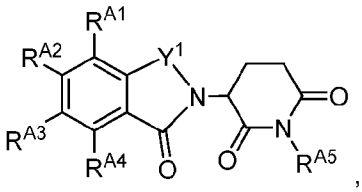
56. The compound of any one of claims 1 to 55, wherein the degradation moiety is a ubiquitin ligase binding moiety.

57. The compound of claim 56, wherein the ubiquitin ligase binding moiety comprises Cereblon ligands, IAP (Inhibitors of Apoptosis) ligands, mouse double minute 2 homolog (MDM2), or von Hippel-Lindau (VHL) ligands, or derivatives or analogs thereof.

58. The compound of claim 56 or 57, wherein the degradation moiety comprises the structure of **Formula A**:



Formula A

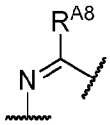
wherein

each of R^{A1}, R^{A2}, R^{A3}, and R^{A4} is, independently, H, a bond to the linker, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; or R^{A1} and R^{A2}, R^{A2} and R^{A3}, and/or R^{A3} and R^{A4}, together with the carbon atoms to which each is attached, combine to form optionally substituted C_6-C_{10} aryl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heteroaryl, or C_2-C_9 heterocyclyl;

R^{A5} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

Y^1 is

,

, or 

;

each of R^{A6} and R^{A7} is, independently, H or optionally substituted C_1-C_6 alkyl; or R^{A6} and R^{A7}, together with the carbon atom to which each is bound, form optionally substituted C_3-C_6 carbocyclyl or optionally substituted C_2-C_5 heterocyclyl;

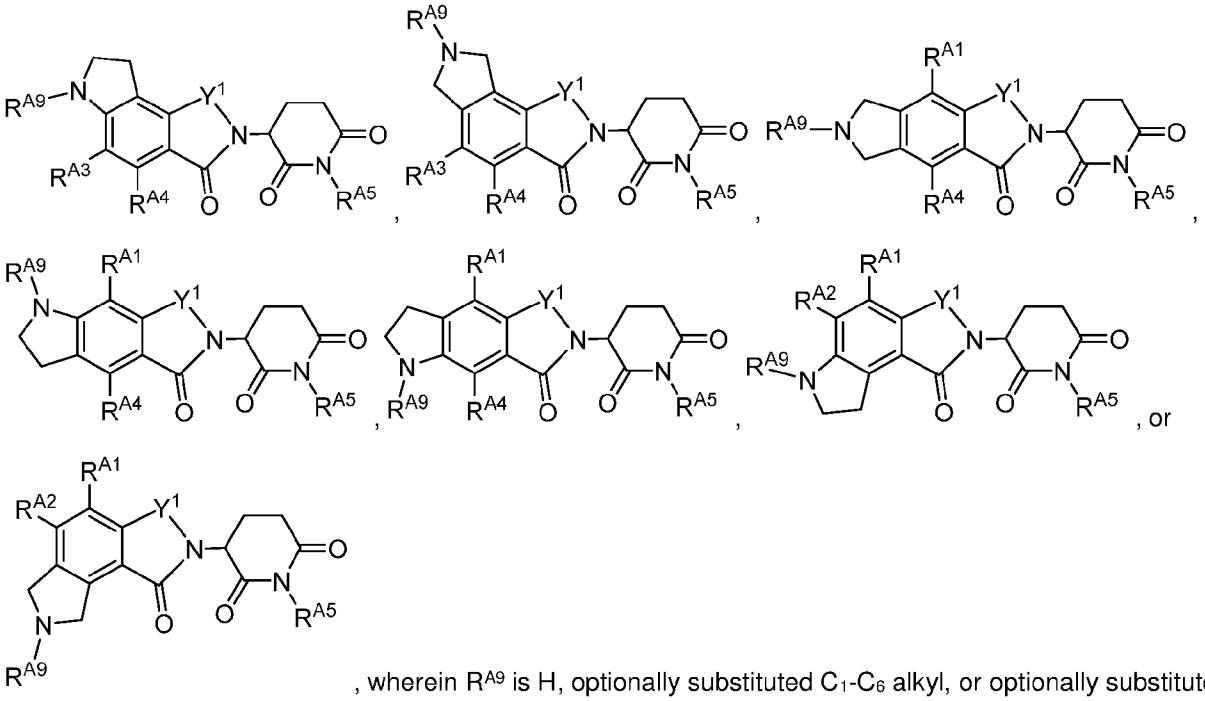
R^{A8} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

where one of R^{A1}, R^{A2}, R^{A3}, and R^{A4} is a bond to the linker,

or a pharmaceutically acceptable salt thereof.

59. The compound of claim 58, wherein each R^{A1}, R^{A2}, R^{A3}, and R^{A4} is, independently, a bond to the linker, H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, hydroxyl, optionally substituted amino; or R^{A1} and R^{A2}, R^{A2} and R^{A3}, or R^{A3} and R^{A4}, together with the carbon atoms to which each is attached, combine to form optionally substituted C_2-C_9 heterocyclyl.

60. The compound of claim 59, wherein the structure of **Formula A** is



, wherein R^{A9} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl.

61. The compound of any one of claims 58 to 60, wherein R^{A5} is H or optionally substituted C_1-C_6 alkyl.

62. The compound of claim 61, wherein R^{A5} is H or methyl.

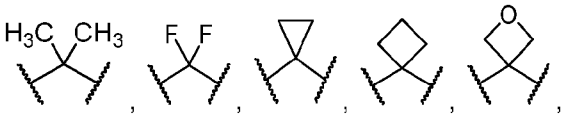
63. The compound of claim 62, wherein $R^{A5}$is H.

64. The compound of claim 63, wherein $R^{A5}$is methyl.

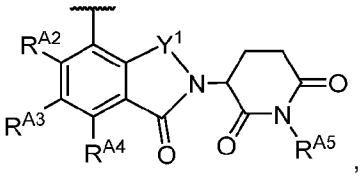
65. The compound of any one of claims 58 to 64, wherein Y^1 is or .

66. The compound of claim 65, wherein Y^1 is .

67. The compound of claim 66, wherein Y^1 is .

68. The compound of claim 67, wherein Y^1 is  , , , , , or .

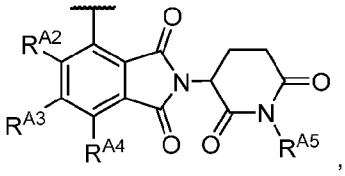
69. The compound of any one of claims 58 to 68, wherein the structure of **Formula A** has the structure of **Formula A1**:



Formula A1

or a pharmaceutically acceptable salt thereof.

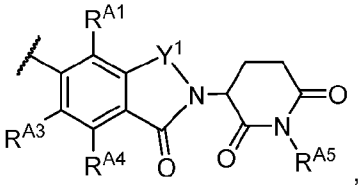
70. The compound of any one of claims 58 to 68, wherein the structure of **Formula A** has the structure of **Formula A2**:



Formula A2

or a pharmaceutically acceptable salt thereof.

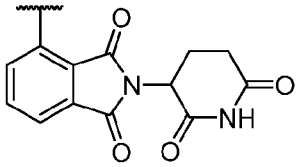
71. The compound of any one of claims 58 to 68, wherein the structure of **Formula A** has the structure of **Formula A3**:



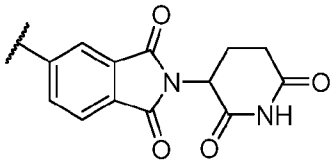
Formula A3

or a pharmaceutically acceptable salt thereof.

72. The compound of any one of claims 58 to 71, wherein the structure of **Formula A** is

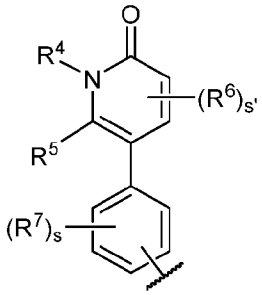


or



, or is a derivative or an analog thereof.

73. The compound of any one of claims 1 to 72, wherein the BRD9 binding moiety comprises the structure of **Formula III** :



Formula III,

wherein

R^4 is, independently, H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

R^5 is H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

s' is 0, 1, or 2;

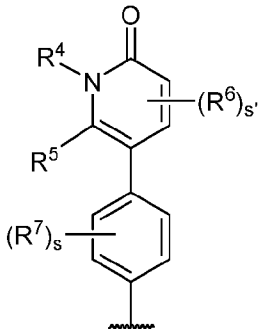
R^6 is halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino, or two R^{24} combine with the carbon atoms to which they are attached to form an optionally substituted C_6-C_{10} aryl or optionally substituted C_2-C_9 heteroaryl;

s is 0, 1, 2, 3, or 4; and

each R^7 is, independently, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino,

or a pharmaceutically acceptable salt thereof.

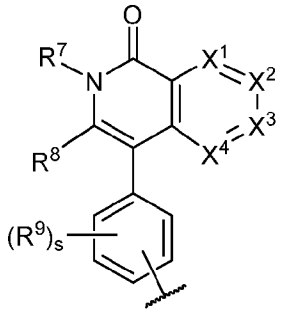
74. The compound of claim 73, wherein the structure of **Formula III** has the structure of **Formula IIIa**:



Formula IIIa,

or a pharmaceutically acceptable salt thereof.

75. The compound of any one of claims 1 to 72, wherein the BRD9 binding moiety comprises the structure **Formula IV**:



Formula IV,

wherein

R^7 is, independently, H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

R^8 is H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

s is 0, 1, 2, 3, or 4;

each R^9 is, independently, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

X^1 is N or CR^{10a};

X^2 is N or CR^{10b};

X^3 is N or CR^{10c};

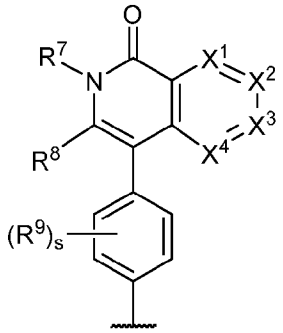
X^4 is N or CR^{10d}; and

each of R^{10a}, R^{10b}, R^{10c}, and R^{10d} is, independently, H, halogen, hydroxy, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl,

optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino,

or a pharmaceutically acceptable salt thereof.

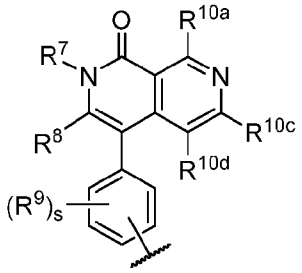
76. The compound of claim 75, wherein the structure of **Formula IV** has the structure of **Formula IVa**:



Formula IVa,

or a pharmaceutically acceptable salt thereof.

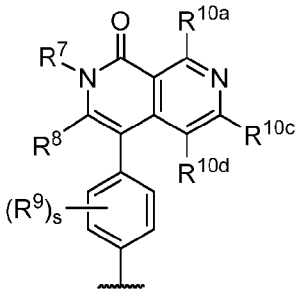
77. The compound of claim 75, wherein the structure of **Formula IV** has the structure of **Formula IVb**:



Formula IVb,

or a pharmaceutically acceptable salt thereof.

78. The compound of claim 75, wherein the structure of **Formula IV** has the structure of **Formula IVc**:



Formula IVc,

or a pharmaceutically acceptable salt thereof.

79. The compound of any one of claims 73 to 78, wherein R^7 is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 carbocyclyl.

80. The compound of claim 79, wherein R^7 is H or CH_3.

81. The compound of any one of claims 73 to 80, wherein R^8 is H or optionally substituted C_1-C_6 alkyl.

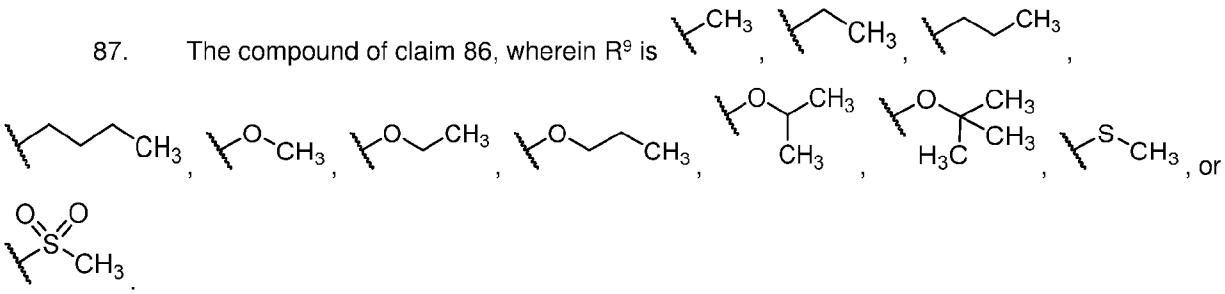
82. The compound of claim 81, wherein R^8 is H.

83. The compound of any one of claims 61 to 82, wherein s is 0, 1, or 2.

84. The compound of claim 83, wherein s is 1 or 2.

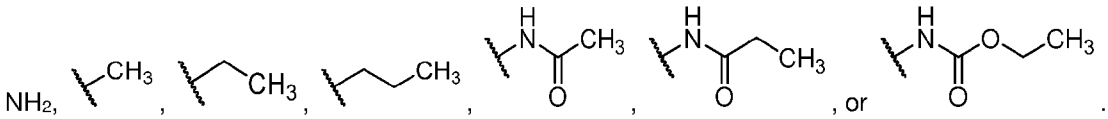
85. The compound of claim 84, wherein s is 2.

86. The compound of any one of claims 73 to 85, wherein each R^9 is, independently, optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_6 heteroalkyl.

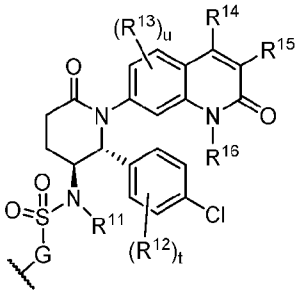
87. The compound of claim 86, wherein R^9 is  .

88. The compound of any one of claims 73 to 87, wherein each of R^{10a}, R^{10b}, R^{10c}, and R^{10d} is, independently, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted amino.

89. The compound of claim 88, wherein each of R^{10a}, R^{10b}, R^{10c}, and R^{10d} is, independently, -



90. The compound of any one of claims 1 to 72, wherein the BRD9 binding moiety comprises the structure of **Formula V**



Formula V,

wherein

each R^{11} and R^{16} is, independently, H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

t is 0, 1, 2, 3, or 4;

each R^{12} is, independently, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

u is 0, 1, 2, 3, or 4;

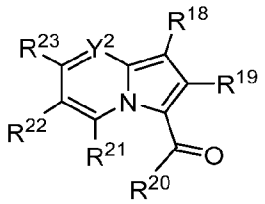
each R^{13} is, independently, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

each R^{14} and R^{15} is, independently, selected form the group consisting of H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl; and

G is optionally substituted C_1-C_6 alkylene, optionally substituted C_6-C_{10} arylene, or optionally substituted C_3-C_6 carbocyclylene,

or a pharmaceutically acceptable salt thereof.

91. The compound of any one of claims 1 to 72, wherein the BRD9 binding moiety comprises the structure of **Formula VI**:



Formula VI,

wherein

Y^2 is CR^{17} or N;

R^{18} is optionally substituted C_6-C_{10} aryl or C_2-C_9 heteroaryl;

R^{19} is H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

R^{20} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

each R^{17}, R^{21}, and R^{22} is, independently, H, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

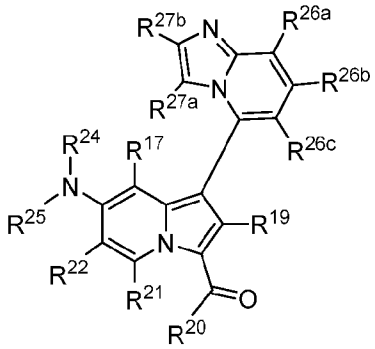
R^{23} is H or $-NR^{24}R^{25}$; and

each of R^{24} and R^{25} is, independently, H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl, or R^{24} and R^{25} combine to form an optionally substituted C_2-C_9 heterocyclyl,

wherein at least one of R^{18}, R^{24}, or R^{25} includes a bond to the linker,

or a pharmaceutically acceptable salt thereof.

92. The compound of any one of claims 1 to 72, wherein the BRD9 binding moiety comprises the structure of **Formula VII**:



Formula VII,

wherein

each R^{26a}, R^{26b}, and R^{26c} is, independently, H, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

each R^{27a} and R^{27b} is, independently, H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

R^{19} is H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

R^{20} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

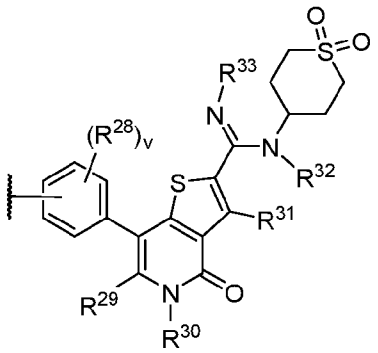
each R^{17}, R^{21}, and R^{22} is, independently, H, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino; and

each of R^{24} and R^{25} is, independently, H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl, or R^{24} and R^{25} combine to form an optionally substituted C_2-C_9 heterocyclyl,

wherein at least one of R^{26a}, R^{26b}, R^{26c}, R^{24}, or R^{25} includes a bond to the linker,

or a pharmaceutically acceptable salt thereof.

93. The compound of any one of claims 1 to 72, wherein the BRD9 binding moiety comprises the structure of **Formula VIII**:



Formula VIII,

wherein

v is 0, 1, 2, 3, or 4;

each R^{28} is, independently, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

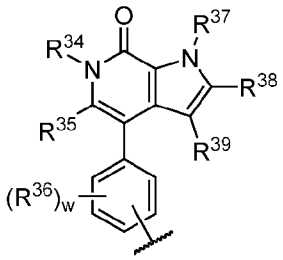
R^{29} is H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

R^{31} is H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl; and

each R^{30}, R^{32}, and R^{33} is, independently, H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl,

or a pharmaceutically acceptable salt thereof.

94. The compound of any one of claims 1 to 72, wherein the BRD9 binding moiety comprises the structure of **Formula IX**:



Formula IX,

wherein

each R^{34} and R^{37} is, independently, H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

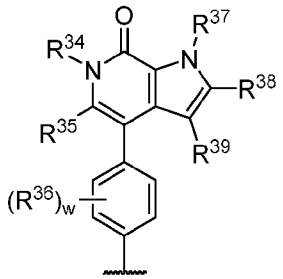
each R^{35}, R^{38}, and R^{39} is, independently, H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

w is 0, 1, 2, 3, or 4; and

each R^{36} is, independently, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino,

or a pharmaceutically acceptable salt thereof.

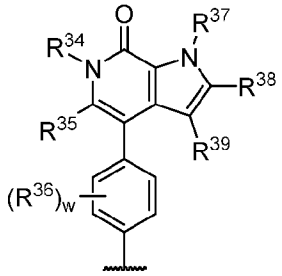
95. The compound of claim 94, wherein the structure of **Formula IX** has the structure of **Formula IXa**:



Formula IXa,

or a pharmaceutically acceptable salt thereof.

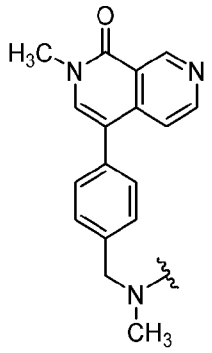
96. The compound of claim 94, wherein the structure of **Formula IX** has the structure of **Formula IXb**:



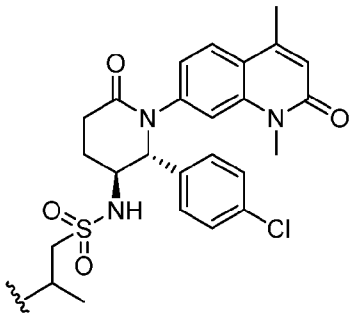
Formula IXb,

or a pharmaceutically acceptable salt thereof.

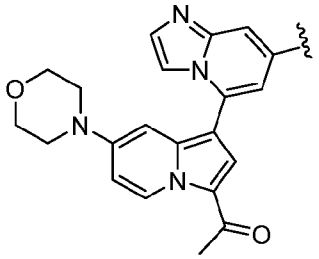
97. The compound of any one of claims 1 to 72, wherein the BRD9 binding moiety has the structure:



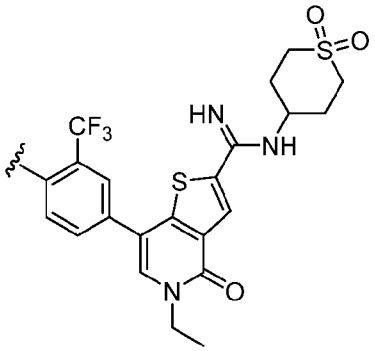
X2,



X3,

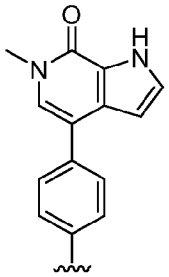


X4,



X5,

or



X6,

or is a derivative or an analog thereof.

98. The compound of any one of claims 1 to 97, wherein the compound has the structure of any one of compounds D1-D177 in Table 1.

99. A pharmaceutical composition comprising the compound of any one of claims 1 to 98 and a pharmaceutically acceptable excipient.

100. A method of inhibiting the level of BRD9 in a cell, the method involving contacting the cell with an effective amount of a compound of any one of claims 1 to 97, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 98.

101. A method of inhibiting the activity of BRD9 in a cell, the method involving contacting the cell with an effective amount of a compound of any one of claims 1 to 97, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 98.

102. The method of claim 100 or 101, wherein the cell is a cancer cell.

103. The method of claim 102, wherein the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, colorectal cancer, a sarcoma, non-small cell lung cancer, stomach cancer, or breast cancer.

104. The method of claim 103, wherein the cancer is a sarcoma.

105. The method of claim 104, wherein the sarcoma is a soft tissue sarcoma, synovial sarcoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, adult fibrosarcoma, alveolar soft-part sarcoma, angiosarcoma, clear cell sarcoma, desmoplastic small round cell tumor, epithelioid sarcoma, fibromyxoid sarcoma, gastrointestinal stromal tumor, Kaposi sarcoma, liposarcoma, leiomyosarcoma, malignant mesenchymoma malignant peripheral nerve sheath tumors, myxofibrosarcoma, or low-grade rhabdomyosarcoma.

106. The method of claim 105, wherein the sarcoma is synovial sarcoma.

107. A method of treating a BAF complex-related disorder in a subject in need thereof, the method involving administering to the subject an effective amount of a compound of any one of claims 1 to 97, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 98.

108. A method of treating an SS18-SSX fusion protein-related disorder in a subject in need thereof, the method involving administering to the subject an effective amount of a compound of any one of claims 1 to 97, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 98.

109. A method of treating a BRD9-related disorder in a subject in need thereof, the method involving administering to the subject an effective amount of a compound of any one of claims 1 to 97, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 98.

110. The method of any one of claims 107 to 109, wherein the disorder is cancer.

111. A method of treating a cancer in a subject in need thereof, the method including administering to the subject an effective amount of a compound of any one of claims 1 to 97, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 98.

112. The method of claim 110 or 111, wherein the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, colorectal cancer, a sarcoma, non-small cell lung cancer, stomach cancer, or breast cancer.

113. The method of claim 112, wherein the cancer is a sarcoma.

114. The method of claim 113, wherein the sarcoma is a soft tissue sarcoma, synovial sarcoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, adult fibrosarcoma, alveolar soft-part sarcoma, angiosarcoma, clear cell sarcoma, desmoplastic small round cell tumor, epithelioid sarcoma, fibromyxoid sarcoma, gastrointestinal stromal tumor, Kaposi sarcoma, liposarcoma, leiomyosarcoma, malignant mesenchymoma malignant peripheral nerve sheath tumors, myxofibrosarcoma, or low-grade rhabdomyosarcoma.

115. The method of claim 114, wherein the sarcoma is synovial sarcoma.

116. The method of any one of claims 107 to 109, wherein the disorder is infection.

117. A method of treating infection in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of any one of claims 1 to 97, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 98.

118. The method of claim 116 or 117, wherein the infection is viral infection.

119. The method of claim 118, wherein the viral infection is an infection with a virus of the Retroviridae family, Hepadnaviridae family, Flaviviridae family, Adenoviridae family, Herpesviridae family, Papillomaviridae family, Parvoviridae family, Polyomaviridae family, Paramyxoviridae family, or Togaviridae family.

120. The method of claim 118 or 119, wherein the viral infection is Coffin Siris, Neurofibromatosis, or Multiple Meningioma.

COMPOUNDS AND USES THEREOF

Abstract

The present invention relates to compositions and methods for the treatment of BAF-related disorders, such as cancers and viral infections.

FIG. 1

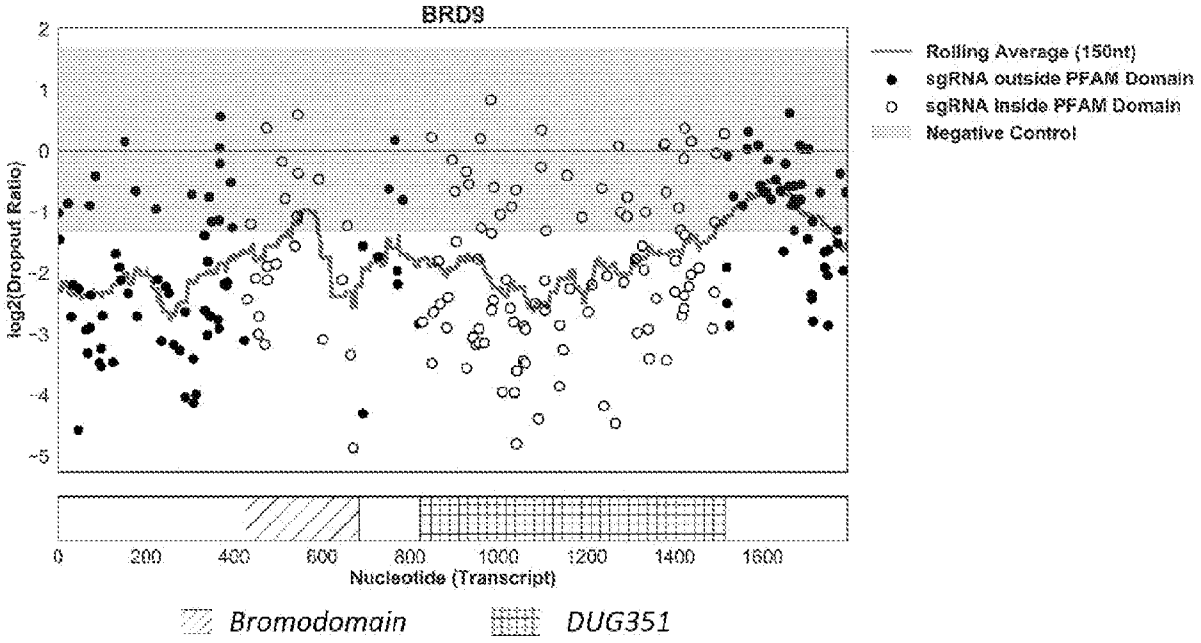

BRD9
Rolling Average (150nt)
sgRNA outside PFAM Domain
sgRNA inside PFAM Domain
Negative Control
log2(Dropout Ratio)
2
1
0
-1
-2
-3
-4
-5
0
200
400
600
800
1000
1200
1400
1600
Nucleotide (Transcript)
Bromodomain
DUG351

FIG. 2

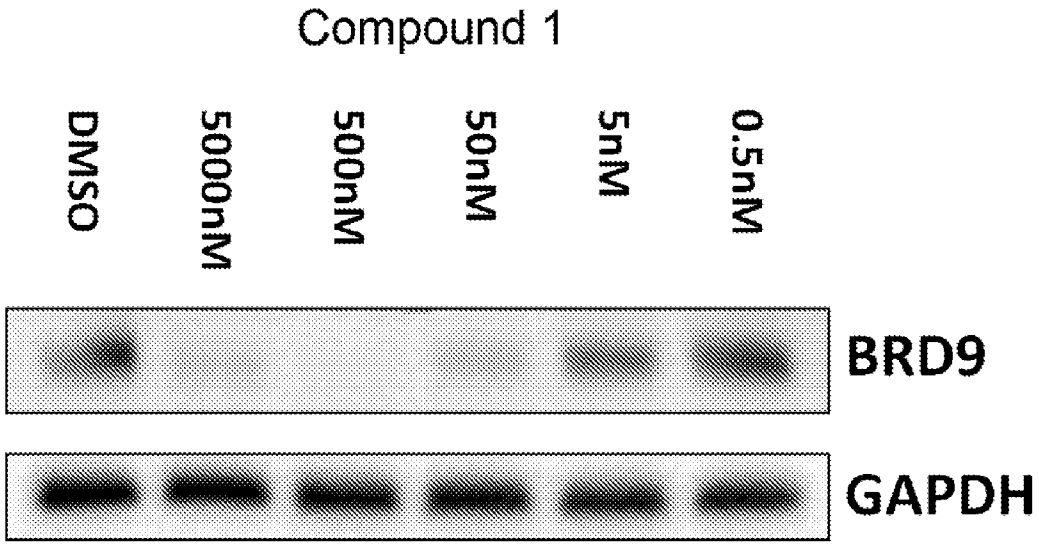


FIG. 3

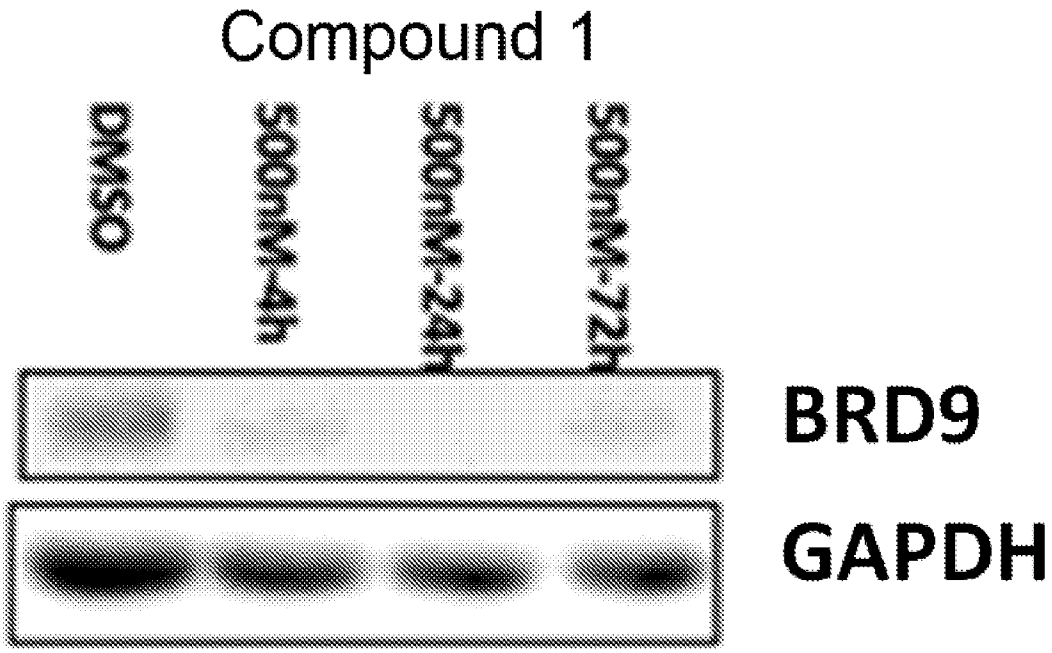


FIG. 4

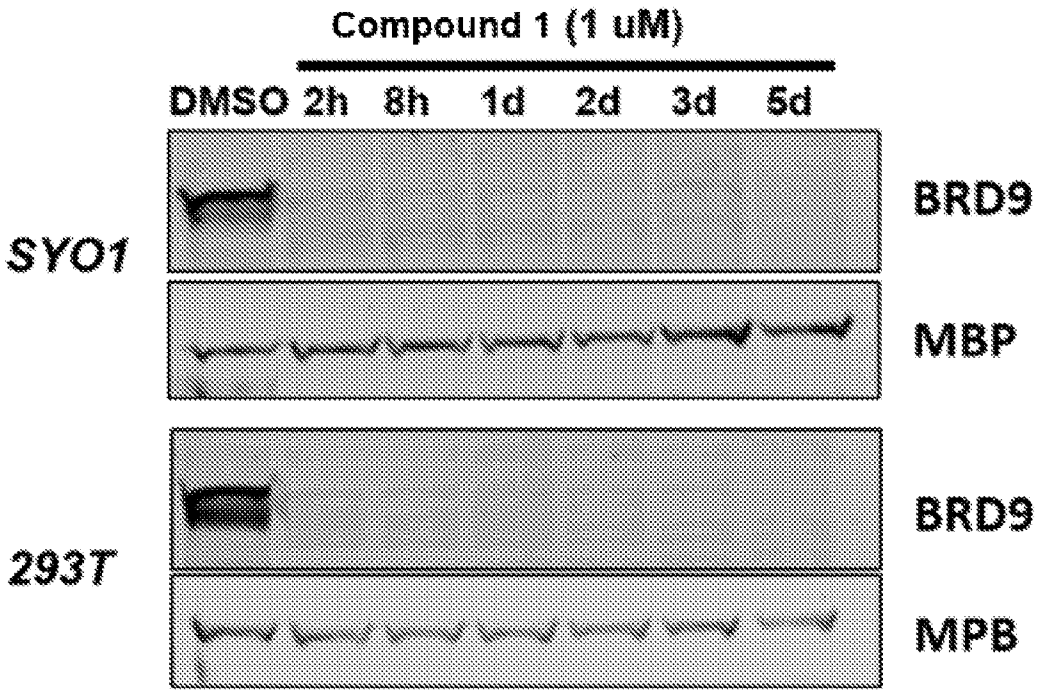

Compound 1 (1 uM)
DMSO 2h 8h 1d 2d 3d 5d
SYO1
BRD9
MBP
293T
BRD9
MPB

FIG. 5

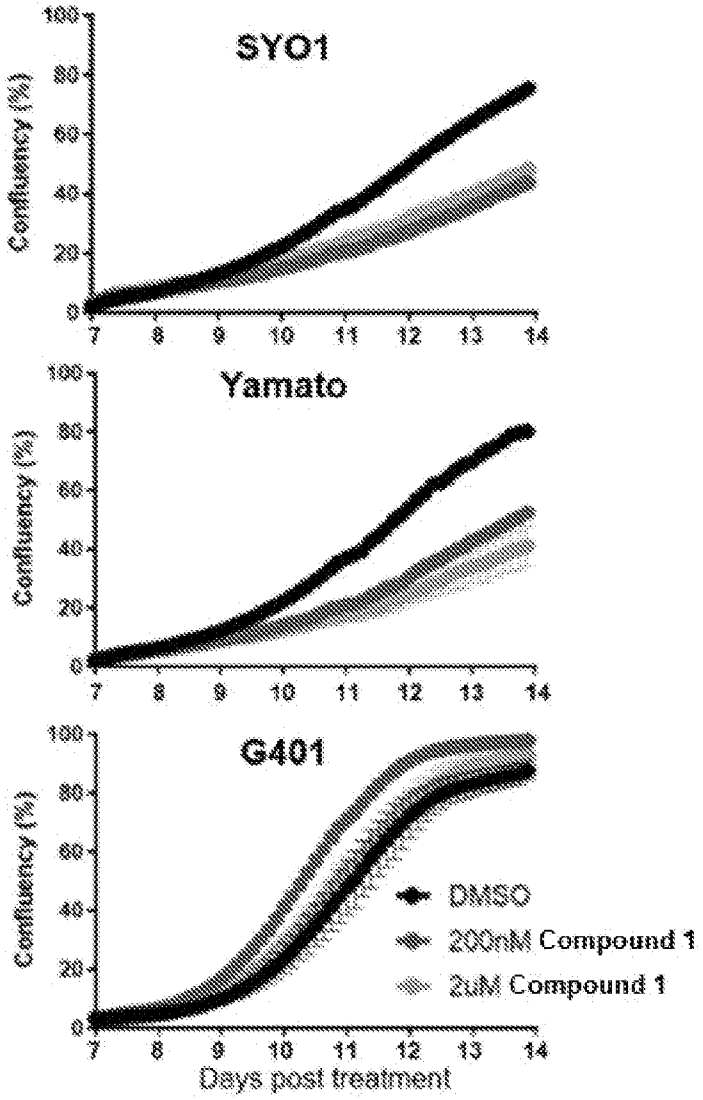

SYO1
Yamato
G401
Confluency (%)
0
20
40
60
80
100
7
8
9
10
11
12
13
14
Days post treatment
DMSO
200nM Compound 1
2uM Compound 1

FIG. 6

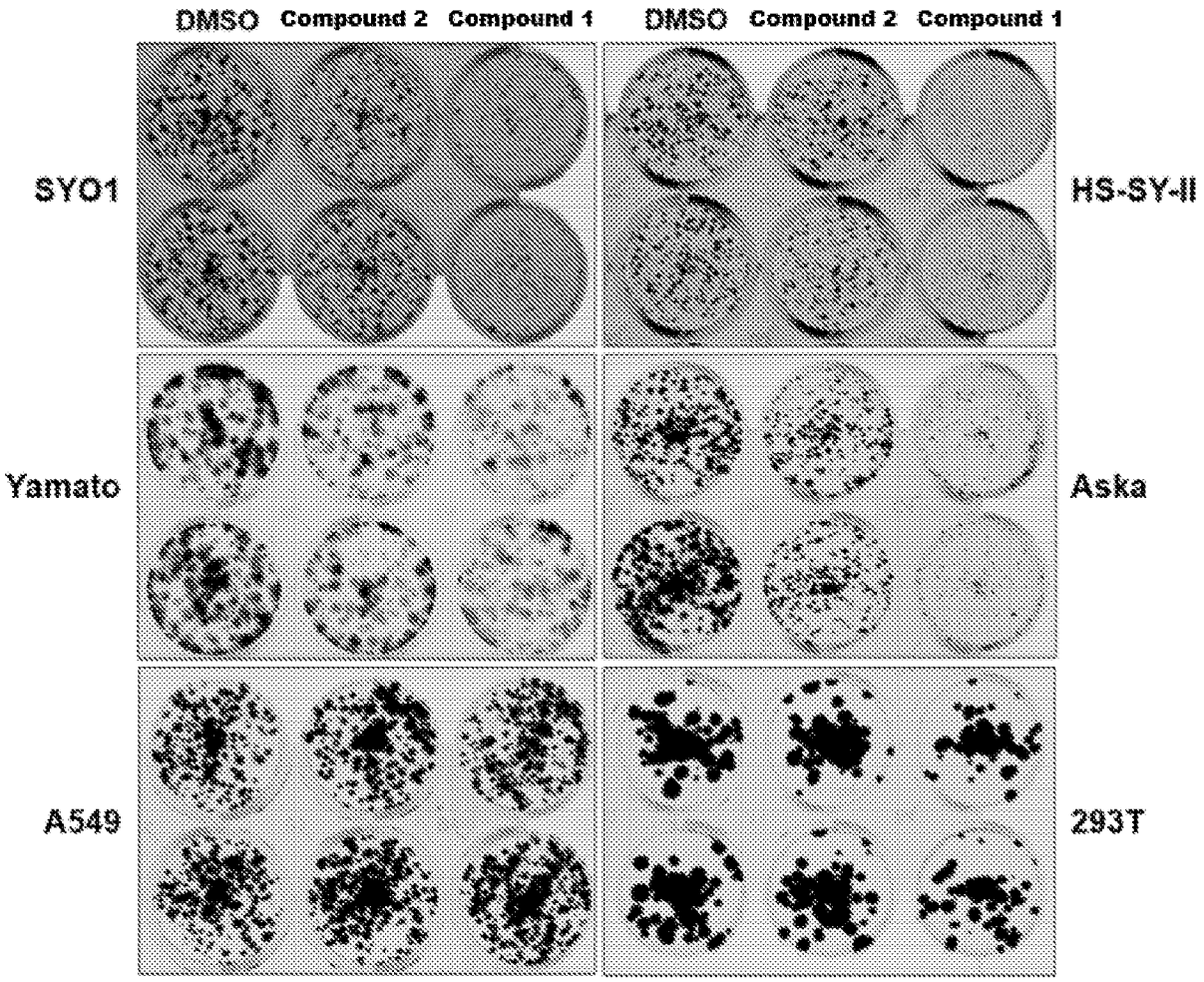

DMSO
Compound 2
Compound 1
DMSO
Compound 2
Compound 1
SYO1
HS-SY-II
Yamato
Aska
A549
293T

FIG. 7

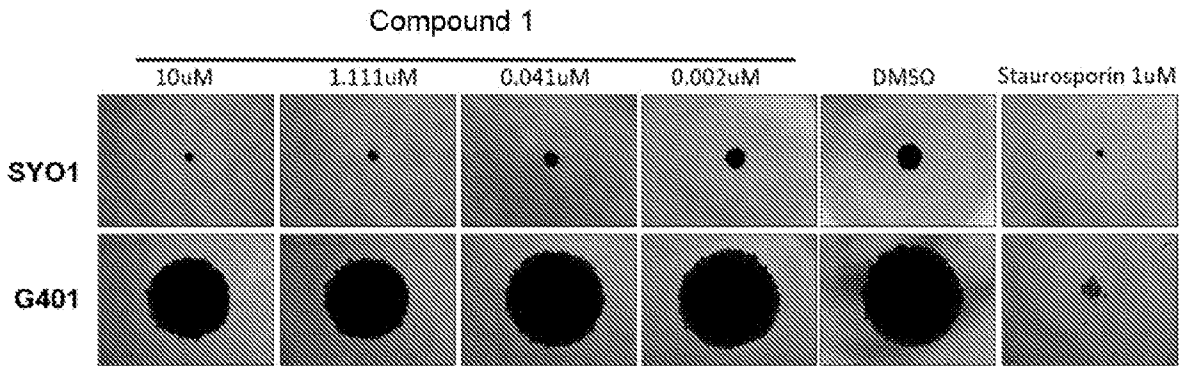
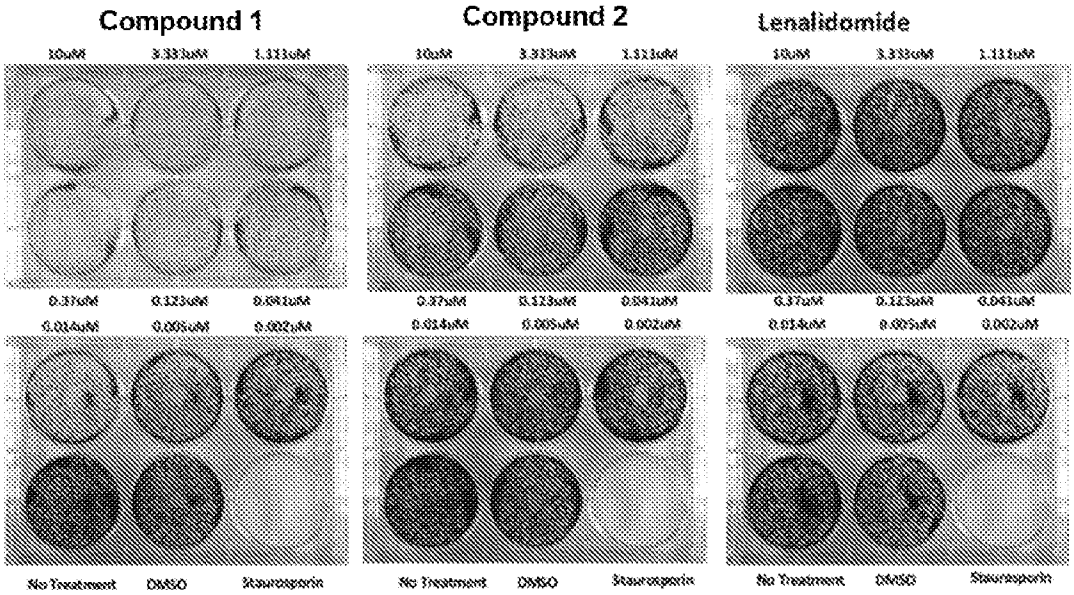
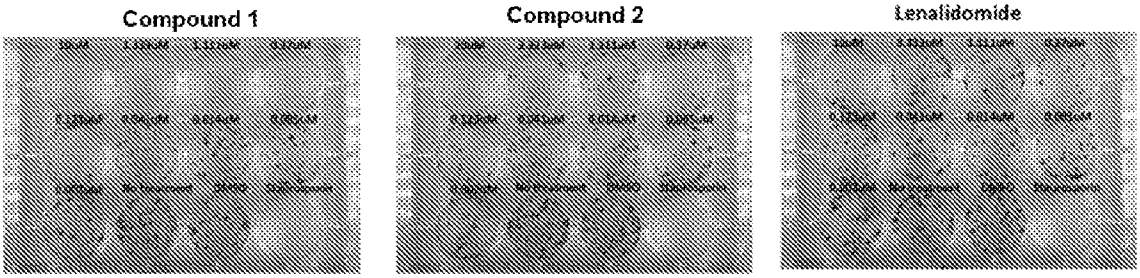

Compound 1
10uM
1.111uM
0.041uM
0.002uM
DMSO
Staurosporin 1uM
SYO1
G401

FIG. 8

SYO1



HS-SY-II



ASKA

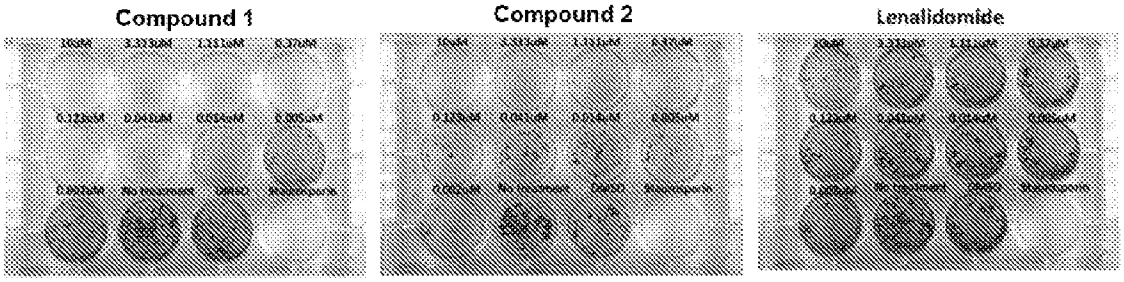
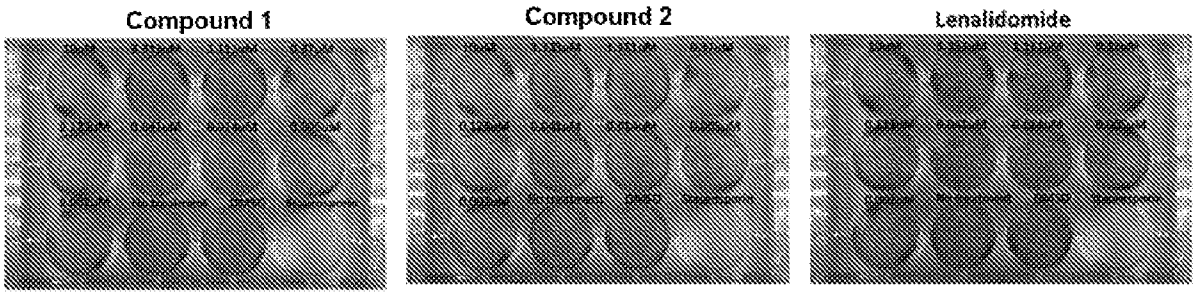
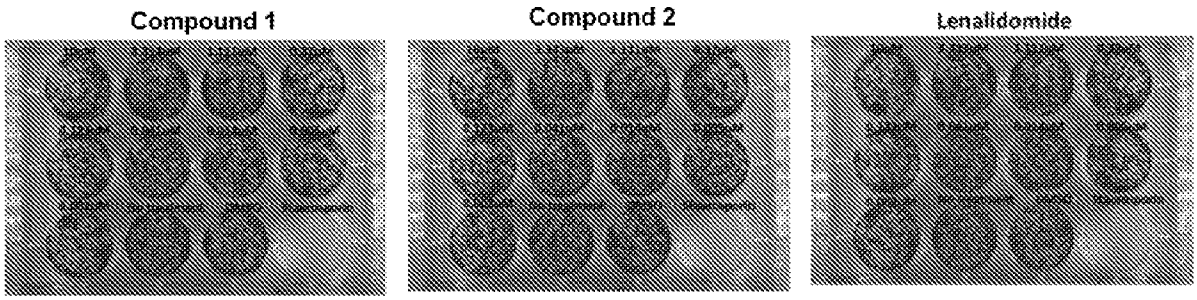


FIG. 9

RD



HCT116



Calu6

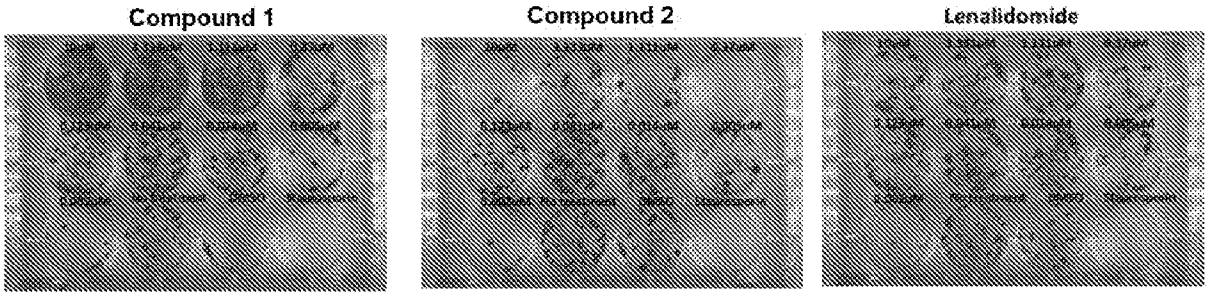
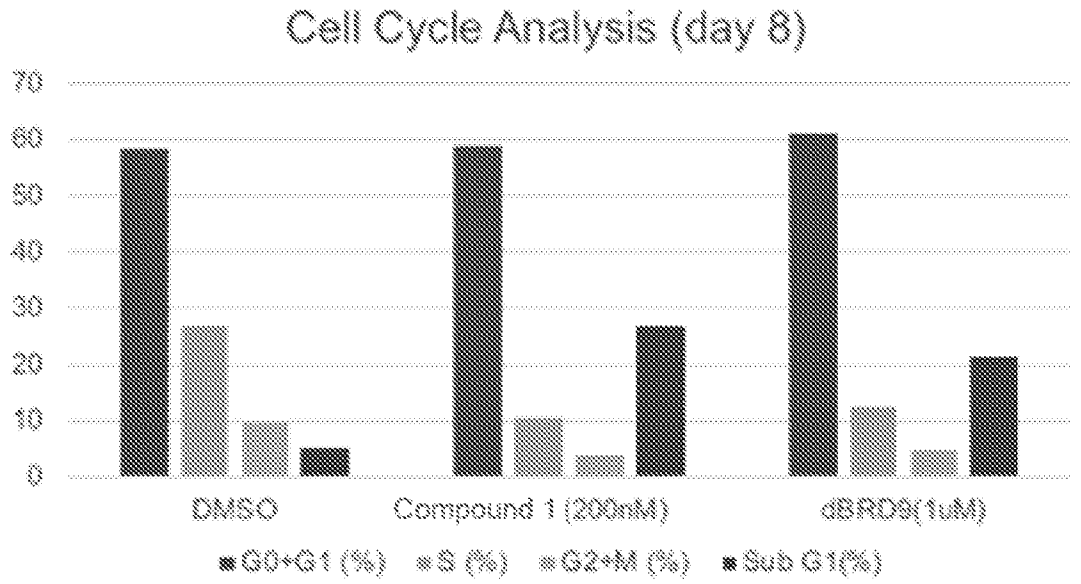


FIG. 10


Cell Cycle Analysis (day 8)
70
60
50
40
30
20
10
0
DMSO
Compound 1 (200nM)
dBRD9(1uM)
G0+G1 (%)
S (%)
G2+M (%)
Sub G1(%)

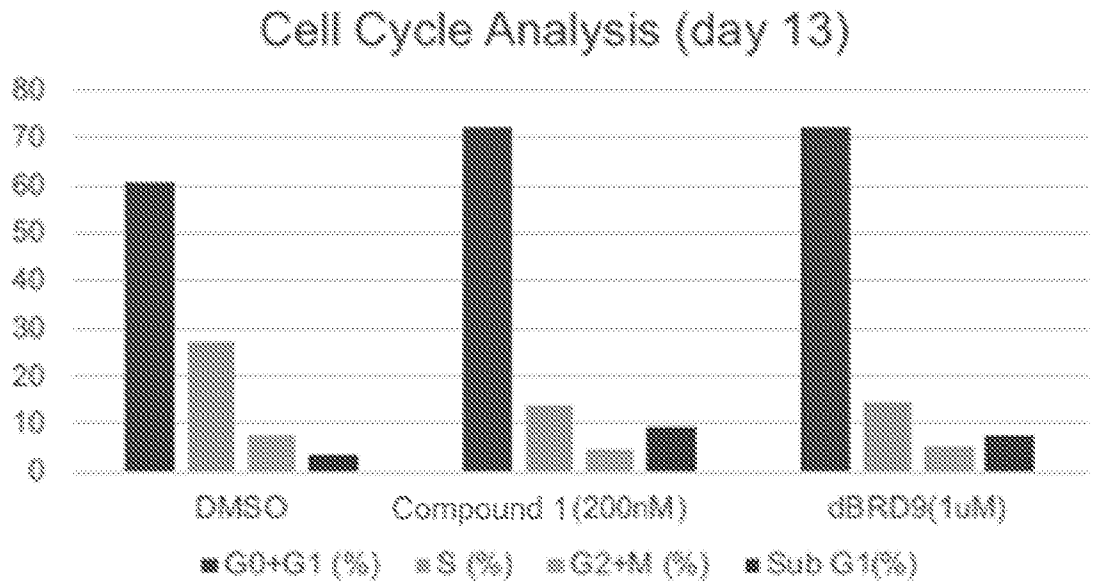
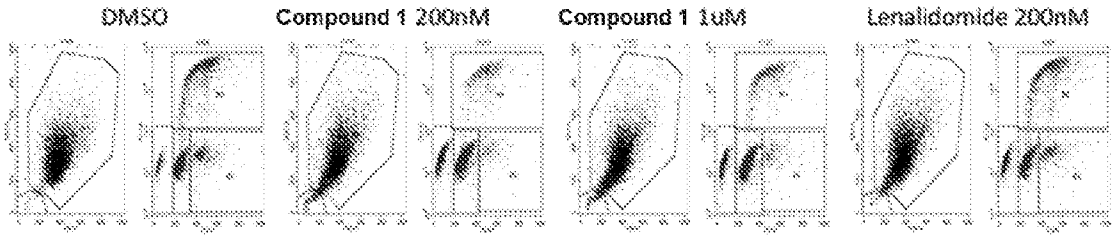
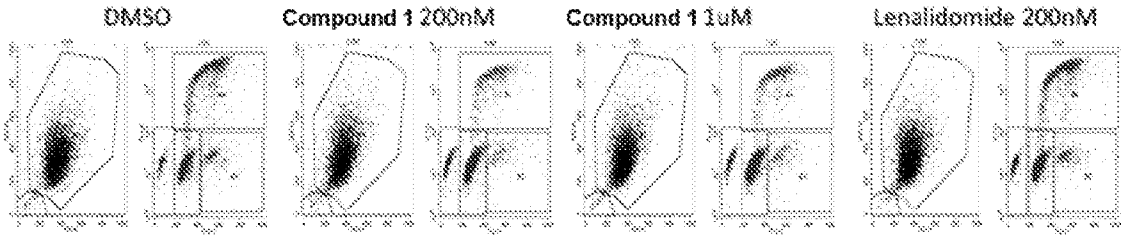

Cell Cycle Analysis (day 13)
80
70
60
50
40
30
20
10
0
DMSO
Compound 1 (200nM)
dBRD9(1uM)
G0+G1 (%)
S (%)
G2+M (%)
Sub G1(%)

FIG. 11



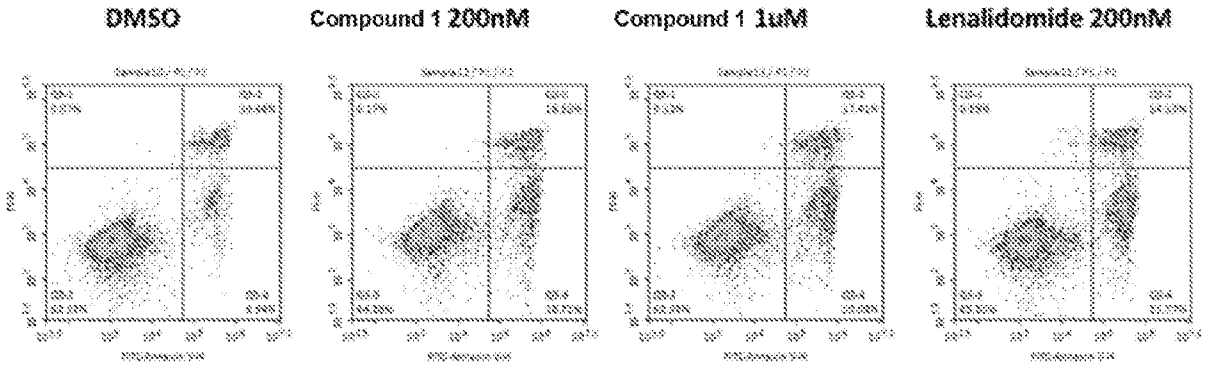
	G0+G1 (%)	S (%)	G2+M (%)	Sub G1(%)
DMSO	58.22	27.01	9.43	5.17
Compound 1 (200nM)	58.9	10.3	3.85	26.61
Compound 1 (1μM)	61.08	12.36	4.8	21.46
Lenalidomide (200nM)	50.45	22.27	8.61	18.43

FIG. 12



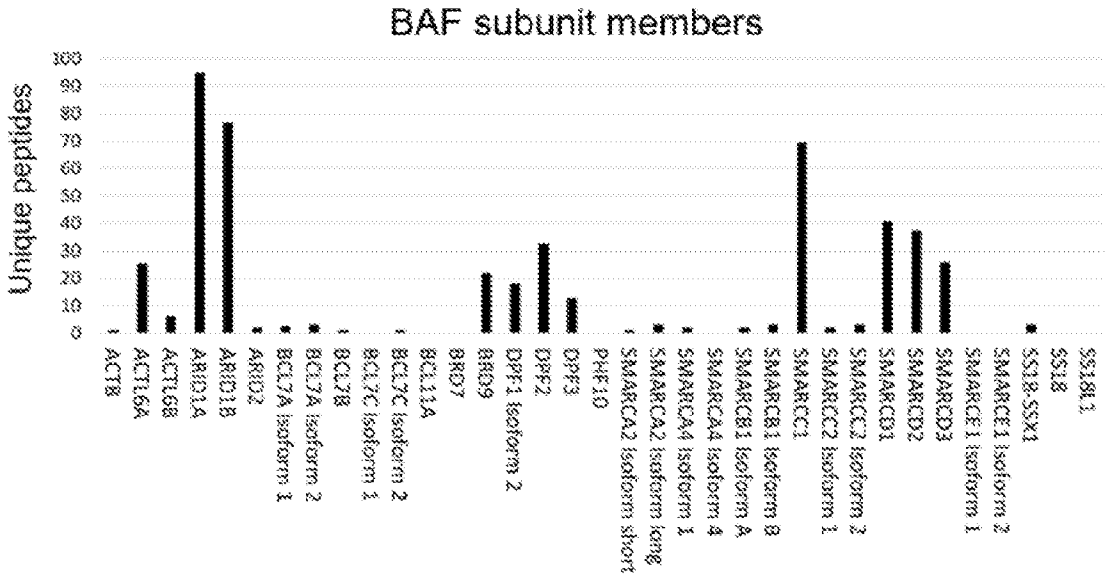
	G0+G1 (%)	S (%)	G2+M (%)	Sub G1(%)
DMSO	60.83	27.29	7.53	3.88
Compound 1 (200nM)	71.9	14.06	4.76	9.1
Compound 1 (1μM)	72.21	14.53	5.08	7.91
Lenalidomide(200nM)	58.67	27.28	6.71	7.11

FIG. 13



	DMSO	Compound 1 (200nM)	Compound 1 (1μM)	Lenalidomide(200nM)
Early Apoptosis Cell	6.94	18.72	20.08	21.77
Late Apoptosis Cell	10.66	16.52	17.41	14.13

FIG. 14


BAF subunit members
Unique peptides
0
10
20
30
40
50
60
70
80
90
100
ACTB
ACTL6A
ACTL6B
ARID1A
ARID1B
ARID2
BCL7A isoform 1
BCL7A isoform 2
BCL7B
BCL7C isoform 1
BCL7C isoform 2
BCL11A
BRD7
BRD9
DPF1 isoform 2
DPF2
DPF3
PHF10
SMARCA2 isoform short
SMARCA2 isoform long
SMARCA4 isoform 1
SMARCA4 isoform 4
SMARCB1 isoform A
SMARCB1 isoform B
SMARCC1
SMARCC2 isoform 1
SMARCC2 isoform 2
SMARCD1
SMARCD2
SMARCD3
SMARCE1 isoform 1
SMARCE1 isoform 2
SS18-SSX1
SS18
SS18L1

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	51121-027001
	Application Number	
Title of Invention	COMPOUNDS AND USES THEREOF	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Sabine	K.	RUPPEL	

Residence Information (Select One) ◉ US Residency ◯ Non US Residency ◯ Active US Military Service

City	Cambridge	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	c/o Foghorn Therapeutics Inc.		
Address 2	100 Binney Street, Suite 610		
City	Cambridge	State/Province	MA
Postal Code	02142	Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Zhaoxia		YANG	

Residence Information (Select One) ◉ US Residency ◯ Non US Residency ◯ Active US Military Service

City	Belmont	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	c/o Foghorn Therapeutics Inc.		
Address 2	100 Binney Street, Suite 610		
City	Cambridge	State/Province	MA
Postal Code	02142	Country	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Jason	T.	LOWE	

Residence Information (Select One) ◉ US Residency ◯ Non US Residency ◯ Active US Military Service

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	51121-027001
	Application Number	
Title of Invention	COMPOUNDS AND USES THEREOF	

City	East Bridgewater	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	c/o Foghorn Therapeutics Inc.		
Address 2	100 Binney Street, Suite 610		
City	Cambridge	State/Province	MA
Postal Code	02142	Country	US

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Johannes	H.	VOIGT	

Residence Information (Select One) (●) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Cambridge	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	c/o Foghorn Therapeutics Inc.		
Address 2	100 Binney Street, Suite 610		
City	Cambridge	State/Province	MA
Postal Code	02142	Country	US

Inventor 5 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Matthew	Russell	NETHERTON	

Residence Information (Select One) (●) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Cambridge	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	c/o Foghorn Therapeutics Inc.		
Address 2	100 Binney Street, Suite 610		
City	Cambridge	State/Province	MA
Postal Code	02142	Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	51121-027001
	Application Number	
Title of Invention	COMPOUNDS AND USES THEREOF	

Customer Number	21559		
Email Address		Add Email	Remove Email

Application Information:

Title of the Invention	COMPOUNDS AND USES THEREOF		
Attorney Docket Number	51121-027001	**Small Entity Status Claimed**	☒
Application Type	Provisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	14	**Suggested Figure for Publication (if any)**	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	21559		

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	51121-027001
	Application Number	
Title of Invention	COMPOUNDS AND USES THEREOF	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

			Remove
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	51121-027001
	Application Number	
Title of Invention	COMPOUNDS AND USES THEREOF	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	51121-027001
	Application Number	
Title of Invention	COMPOUNDS AND USES THEREOF	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Foghorn Therapeutics Inc.		
Mailing Address Information For Applicant:			
Address 1	100 Binney Street		
Address 2	Suite 610		
City	Cambridge	**State/Province**	MA
Country	US	Postal Code	02142
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button.

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	51121-027001
	Application Number	
Title of Invention	COMPOUNDS AND USES THEREOF	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Karen L. Elbing, Ph.D./			Date (YYYY-MM-DD)	2019-01-29
First Name	Karen	Last Name	Elbing	Registration Number	35,238

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	51121-027001
	Application Number	
Title of Invention	COMPOUNDS AND USES THEREOF	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc Code: **TR.PROV**
Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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Provisional Application for Patent Cover Sheet

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c)

Inventor(s)

Inventor 1 — Remove

Given Name	Middle Name	Family Name	City	State	Country
Sabine	K.	RUPPEL	Cambridge	MA	US

Inventor 2 — Remove

Given Name	Middle Name	Family Name	City	State	Country
Zhaoxia		YANG	Belmont	MA	US

Inventor 3 — Remove

Given Name	Middle Name	Family Name	City	State	Country
Jason	T.	LOWE	East Bridgewater	MA	US

Inventor 4 — Remove

Given Name	Middle Name	Family Name	City	State	Country
Johannes	H.	VOIGT	Cambridge	MA	US

Inventor 5 — Remove

Given Name	Middle Name	Family Name	City	State	Country
Matthew	Russell	NETHERTON	Cambridge	MA	US

All Inventors Must Be Listed – Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. — Add

Title of Invention	COMPOUNDS AND USES THEREOF
Attorney Docket Number (if applicable)	51121-027001

Correspondence Address

Direct all correspondence to (select one):

◉ The address corresponding to Customer Number	◯ Firm or Individual Name
Customer Number	21559

PTO/SB/16 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.
◉ No.
○ Yes, the invention was made by an agency of the United States Government. The U.S. Government agency name is:
○ Yes, the invention was under a contract with an agency of the United States Government. The name of the U.S. Government agency and Government contract number are:

PTO/SB/16 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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Entity Status
Applicant asserts small entity status under 37 CFR 1.27 or applicant certifies micro entity status under 37 CFR 1.29

- (●) Applicant asserts small entity status under 37 CFR 1.27
- ( ) Applicant certifies micro entity status under 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
- ( ) No

Warning

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

Signature

Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Karen L. Elbing, Ph.D./			Date (YYYY-MM-DD)	2019-01-29
First Name	Karen	Last Name	Elbing	Registration Number (If appropriate)	35238

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **This form can only be used when in conjunction with EFS-Web. If this form is mailed to the USPTO, it may cause delays in handling the provisional application.**

Privacy Act Statement

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
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6. A record in this system of records may be disclosed, as a routine use, t o a n other federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	34998132
Application Number:	62798374
International Application Number:	
Confirmation Number:	2346
Title of Invention:	COMPOUNDS AND USES THEREOF
First Named Inventor/Applicant Name:	Sabine K. RUPPEL
Customer Number:	21559
Filer:	Karen L. Elbing/Sabrina Chishti
Filer Authorized By:	Karen L. Elbing
Attorney Docket Number:	51121-027001
Receipt Date:	29-JAN-2019
Filing Date:	
Time Stamp:	19:27:35
Application Type:	Provisional

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$740
RAM confirmation Number	013019INTEFSW00005820032095
Deposit Account	032095
Authorized User	Sabrina Chishti

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.16 (National application filing, search, and examination fees)

37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Application_To_Be_Filed_New_Linkers.pdf	2970920 d968a081bf7795d08fabd4f00d77c3cc5ef78c89	yes	294

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	264
Claims	265	293
Abstract	294	294

Warnings:

Information:

2	Drawings-only black and white line drawings	Figures_To_Be_Filed_New_Linkers.pdf	2475755 d6836a5408e74059bf2e235fa293cc6c753aa8f4	no	14

Warnings:

Information:

3	Application Data Sheet	51121-027001_-_ADS.pdf	120770 729fdd56e86812f85522b75cc99a84c4c8643a2f	no	9

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Information:

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4	Provisional Cover Sheet (SB16)	51121-027001_-_Cover_Sheet.pdf	80729 c73ef0906c50a6725de3fa5f61e6250c70610e9a	no	4

Warnings:

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Information:

5	Fee Worksheet (SB06)	fee-info.pdf	31311 3599ff1b7862eb7b5e8b42a7cc65c60ba7f292c3	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	5679485		

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.