COMPOUNDS AND USES THEREOF

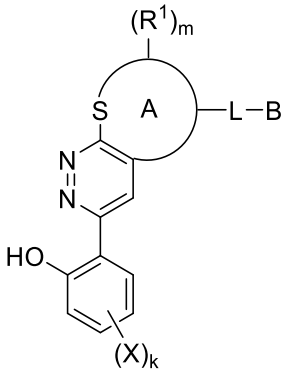
Background

The invention relates to compounds useful for modulating BRG1- or BRM-associated factors (BAF) complexes. In particular, the invention relates to compounds useful for treatment of disorders associated with BAF complex function.

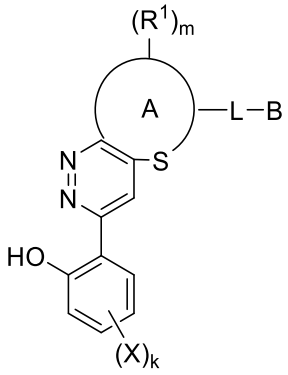
Chromatin regulation is essential for gene expression, and ATP-dependent chromatin remodeling is a mechanism by which such gene expression occurs. The human Switch/Sucrose Non-Fermentable (SWI/SNF) chromatin remodeling complex, also known as BAF complex, has two SWI2-like ATPases known as BRG1 (Brahma-related gene-1) and BRM (Brahma). The transcription activator BRG1, also known as ATP-dependent chromatin remodeler SMARCA4, is encoded by the SMARCA4 gene on chromosome 19. BRG1 is overexpressed in some cancer tumors and is needed for cancer cell proliferation. BRM, also known as probable global transcription activator SNF2L2 and/or ATP-dependent chromatin remodeler SMARCA2, is encoded by the SMARCA2 gene on chromosome 9 and has been shown to be essential for tumor cell growth in cells characterized by loss of BRG1 function mutations. Deactivation of BRG and/or BRM results in downstream effects in cells, including cell cycle arrest and tumor suppression.

Summary

In a first aspect of the present disclosure, there is provided a compound, or a pharmaceutically acceptable salt thereof, having the structure of **Formula I or II**:



Formula I



Formula II

wherein

ring system A is a 5 to 9-membered heterocyclyl or heteroaryl;

m is 0, 1, 2, or 3;

k is 0, 1, or 2;

each R^1 is, independently, halo, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_8 cycloalkyl, or optionally substituted C_2-C_9 heterocyclyl;

each X is, independently, halo;

L is a linker; and

B is a degradation moiety.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein, and a pharmaceutically acceptable excipient.

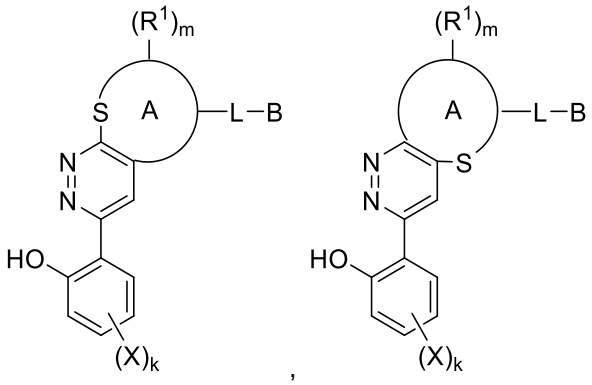
In yet another aspect of the present disclosure, there is provided a use of a compound as disclosed herein in the manufacture of a medicament for treating cancer in a subject in need thereof.

In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein in the manufacture of a medicament for treating a cancer selected from the group consisting of melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, and a hematologic cancer in a subject in need thereof.

In another aspect of the present disclosure, there is provided a compound as disclosed herein for use in therapy.

The present disclosure features compounds useful for modulating a BAF complex. In some examples, the compounds are useful for the treatment of disorders associated with an alteration in a BAF complex, e.g., a disorder associated with an alteration in one or both of the BRG1 and BRM proteins. The compounds of the disclosure, alone or in combination with other pharmaceutically active agents, can be used for treating such disorders.

In an example, the disclosure features a compound, or a pharmaceutically acceptable salt thereof, having the structure of **Formula I or II**:



Formula I **Formula II**

where

ring system A is a 5 to 9-membered heterocyclyl or heteroaryl;

m is 0, 1, 2, or 3;

k is 0, 1, or 2;

each R^1 is, independently, halo, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_8 cycloalkyl, or optionally substituted C_2-C_9 heterocyclyl;

each X is, independently, halo;

L is a linker; and

B is a degradation moiety.

In some examples,

ring system A is a 5 to 9-membered heterocyclyl or heteroaryl;

m is 0, 1, 2, or 3;

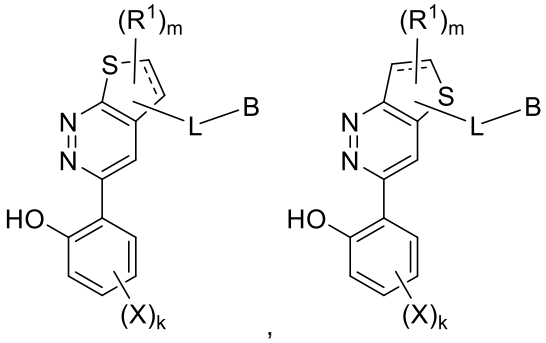
k is 0, 1, or 2;

each X is, independently, halo;

L is a linker; and

B is a degradation moiety.

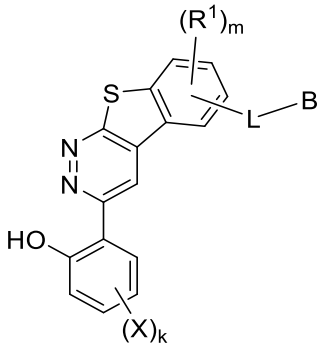
In some examples, the compound has the structure of **Formula I-A or II-A**:



Formula I-A **Formula II-A**

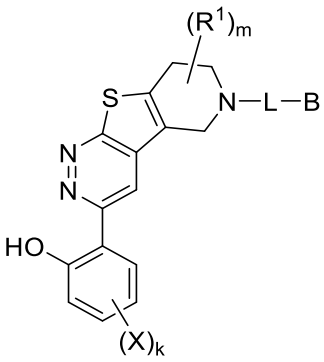
where the dashed bond represents a single or double bond.

In some examples, the compound has the structure of **Formula I-B**:



Formula I-B

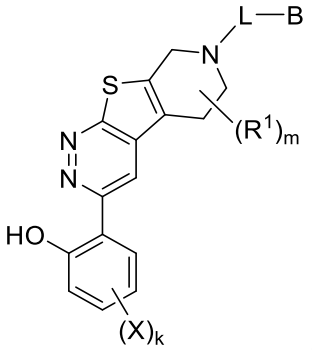
In some examples, the compound has the structure of **Formula I-C**:



Formula I-C

where each R^1 is, independently, optionally substituted C_1-C_6 alkyl.

In some examples, the compound has the structure of **Formula I-D**:

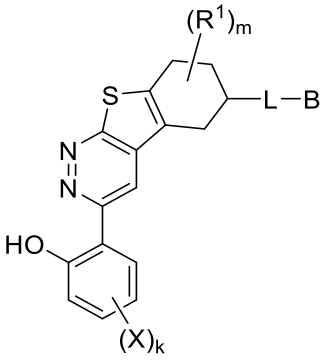


,

Formula I-D

where each R^1 is, independently, optionally substituted C_1-C_6 alkyl.

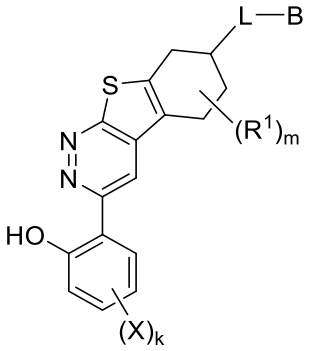
In some examples, the compound has the structure of **Formula I-E**:



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Formula I-E

In some examples, the compound has the structure of **Formula I-F**:

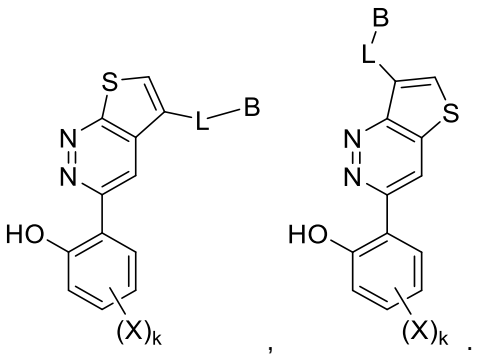


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Formula I-F

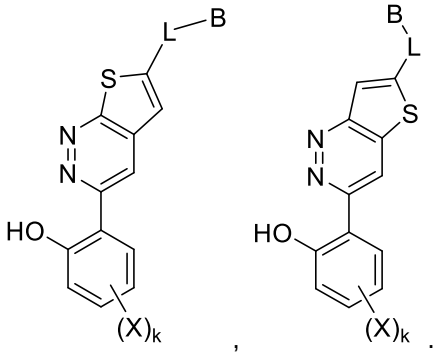
In some examples, m is 0.

In some examples, the compound has the structure of Formula I-G or II-G:



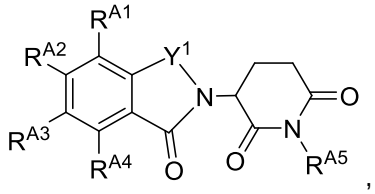
Formula I-G **Formula II-G**

In some examples, the compound has the structure of **Formula I-H or II-H**:



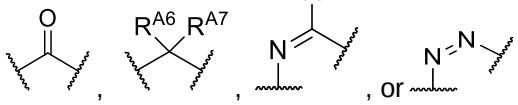
Formula I-H **Formula II-H**

In some examples, the degradation moiety, B, has the structure of **Formula A-1**:



Formula A-1

where

Y^1 is ;

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

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

each of R^{A1}, R^{A2}, R^{A3}, and R^{A4} is, independently, H, A^2, 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, optionally substituted -O-C_3-C_6

carbocyclyl, 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 

; and 

is 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, any of which is optionally substituted with A^2,

where one of R^{A1}, R^{A2}, R^{A3}, and R^{A4} is A^2, or 

is substituted with A^2; and

A^2 is a bond between the degradation moiety and the linker.

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

In some examples, each of R^{A1}, R^{A2}, R^{A3}, and R^{A4} is, independently, H or A^2.

In some examples, R^{A1} is A^2 and each of R^{A2}, R^{A3}, and R^{A4} is H.

In some examples, R^{A2} is A^2 and each of R^{A1}, R^{A3}, and R^{A4} is H.

In some examples, R^{A3} is A^2 and each of R^{A1}, R^{A2}, and R^{A4} is H.

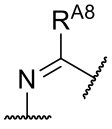
In some examples, R^{A4} is A^2 and each of R^{A1}, R^{A2}, and R^{A3} is H.

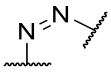
In some examples, Y^1 is 

or 

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In some examples, R^{A6} is H. In some examples, R^{A7} is H.

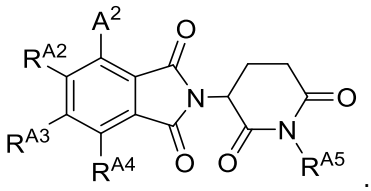
In some examples, Y^1 is 

or 

.

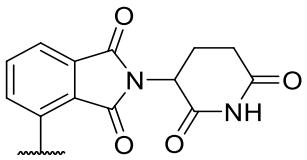
In some examples, R^{A8} is H or optionally substituted C_1-C_6 alkyl. In some examples, R^{A8} is H or methyl. In some examples, R^{A8} is methyl.

In some examples, the degradation moiety includes the structure of **Formula A2**:



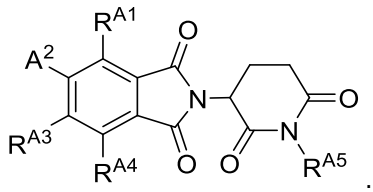
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Formula A2

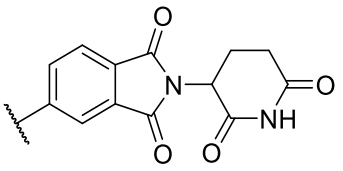
In some examples, where the degradation moiety is 

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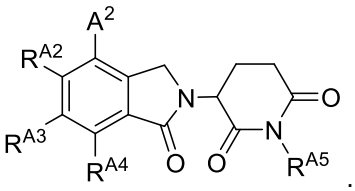
In some examples, the degradation moiety includes the structure of **Formula A4**:



Formula A4

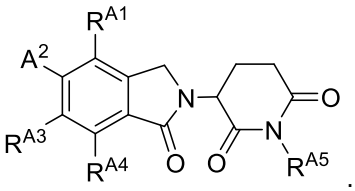
In some examples, the degradation moiety is .

In some examples, the degradation moiety includes the structure of **Formula A5**:



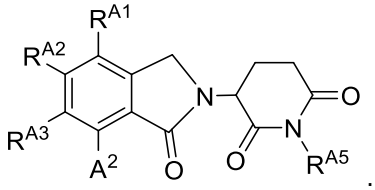
Formula A5

In some examples, the degradation moiety includes the structure of **Formula A6**:



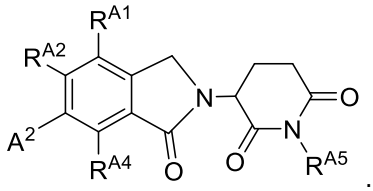
Formula A6

In some examples, the degradation moiety includes the structure of **Formula A8**:

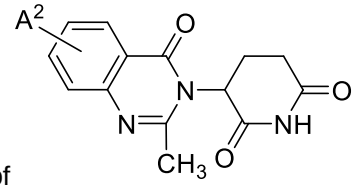


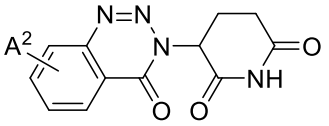
Formula A8

In some examples, the degradation moiety includes the structure of **Formula A10**:

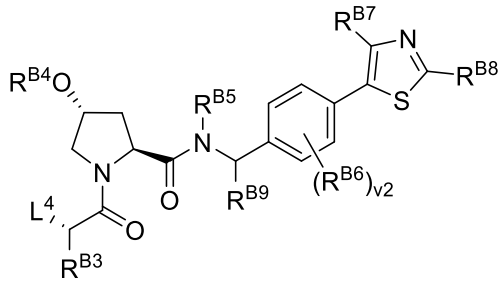


Formula A10

In some examples, the degradation moiety includes the structure of  .

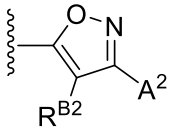
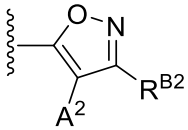
In some examples, the degradation moiety includes the structure of  .

In some examples, the degradation moiety has the structure of **Formula C**:



Formula C

where

L^4 is $-N(R^{B1})(R^{B2})$,  , or  ;

R^{B1} is H, A^2, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

R^{B2} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

R^{B3} is A^2, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_1-C_6 alkyl C_3-C_{10} carbocyclyl, or optionally substituted C_1-C_6 alkyl C_6-C_{10} aryl;

R^{B4} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_1-C_6 alkyl C_3-C_{10} carbocyclyl, or optionally substituted C_1-C_6 alkyl C_6-C_{10} aryl;

R^{B5} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

v2 is 0, 1, 2, 3, or 4;

each R^{B6} is, independently, A^2, 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 of R^{B7} and R^{B8} is, independently, H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

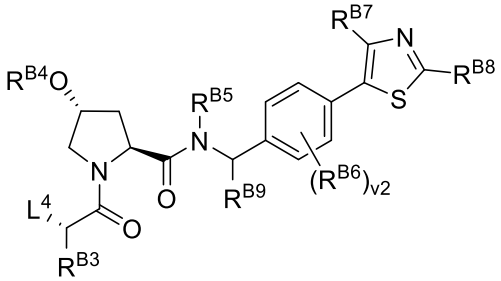
R^{B9} is H or optionally substituted C_1-C_6 alkyl; and

A^2 is a bond between the degradation moiety and the linker;

where one and only one of R^{B1}, R^{B3}, and R^{B6} is A^2,

or a pharmaceutically acceptable salt thereof.

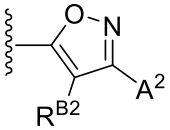
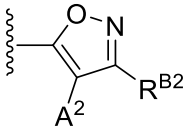
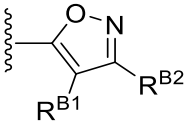
In some examples, the degradation moiety has the structure of **Formula C'**:



,

Formula C'

where

L^4 is $-N(R^{B1})(R^{B2})$, , , or ;

R^{B1} is H, A^2, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

R^{B2} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

R^{B3} is A^2, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_1-C_6 alkyl C_3-C_{10} carbocyclyl, or optionally substituted C_1-C_6 alkyl C_6-C_{10} aryl;

R^{B4} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_1-C_6 alkyl C_3-C_{10} carbocyclyl, or optionally substituted C_1-C_6 alkyl C_6-C_{10} aryl;

R^{B5} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

v2 is 0, 1, 2, 3, or 4;

each R^{B6} is, independently, A^2, 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 of R^{B7} and R^{B8} is, independently, H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

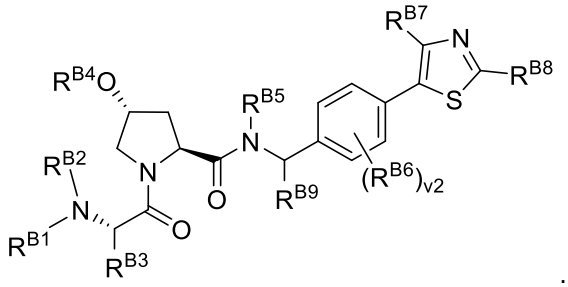
R^{B9} is H or optionally substituted C_1-C_6 alkyl; and

A^2 is a bond between the degradation moiety and the linker;

where one and only one of R^{B1}, R^{B3}, and R^{B6} is A^2,

or a pharmaceutically acceptable salt thereof.

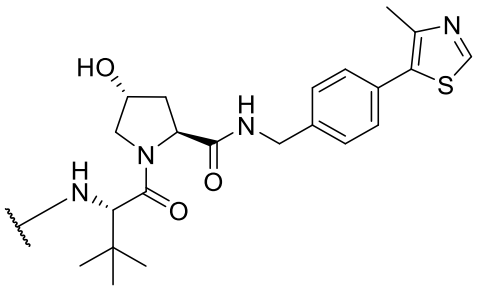
In some examples, the degradation moiety has the structure of **Formula C1**:



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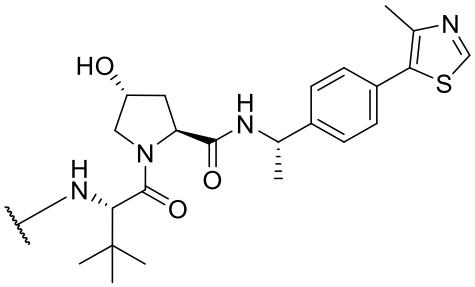
Formula C1

In some examples, the degradation moiety is



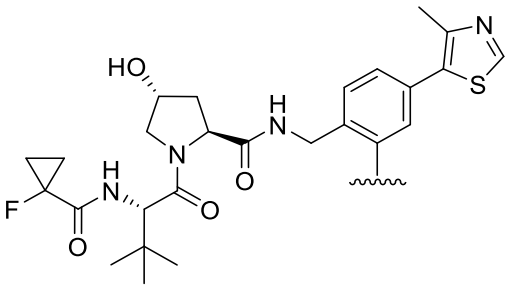
.

In some examples, the degradation moiety is



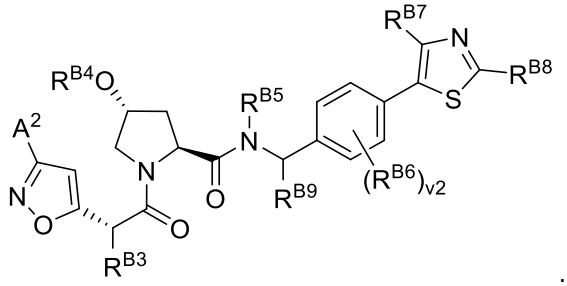
.

In some examples, the degradation moiety is



.

In some examples, the degradation moiety has the structure of **Formula C2**:



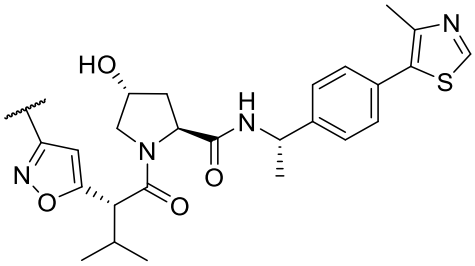
.

Formula C2

In some examples, R^{B9} is optionally substituted C_1-C_6 alkyl. In some examples, R^{B9} is methyl.

In some examples, R^{B9} is bonded to (*S*)-stereogenic center.

In some examples, the degradation moiety is



.

In some examples, the linker has the structure of **Formula III**:

$$A^1\text{-}(B^1)_f\text{-}(C^1)_g\text{-}(B^2)_h\text{-}(D)\text{-}(B^3)_i\text{-}(C^2)_j\text{-}(B^4)_k\text{–}A^2,$$

Formula III

or a pharmaceutically acceptable salt thereof,

where

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

A^2 is a bond between the degradation moiety and the linker;

each of B^1, B^2, B^3, and B^4 is, independently, optionally substituted C_1-C_4 alkyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_6-C_{10} aryl $C_{1\text{-}4}$ alkyl, optionally substituted C_1-C_4 heteroalkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_2-C_6 heterocyclyl, O, S, $S(O)_2$, or NR^N;

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

each of C^1 and C^2 is, independently, carbonyl, thiocarbonyl, sulphonyl, or phosphoryl;

each of f, g, h, i, j, and k is, independently, 0 or 1; and

D is optionally substituted $C_{1\text{–}10}$ alkyl, optionally substituted $C_{2\text{–}10}$ alkenyl, optionally substituted $C_{2\text{–}10}$ alkynyl, optionally substituted $C_{2\text{–}6}$ heterocyclyl, optionally substituted $C_{6\text{–}12}$ aryl, optionally substituted C_2-C_{10} polyethylene glycol, or optionally substituted $C_{1\text{–}10}$ heteroalkyl, or a chemical bond linking $A^1\text{-}(B^1)_f\text{-}(C^1)_g\text{-}(B^2)_h$- to -$(B^3)_i\text{-}(C^2)_j\text{-}(B^4)_k\text{–}A^2$.

In some examples, the linker has the structure of **Formula III**:

$$A^1\text{-}(B^1)_f\text{-}(C^1)_g\text{-}(B^2)_h\text{-}(D)\text{-}(B^3)_i\text{-}(C^2)_j\text{-}(B^4)_k\text{–}A^2,$$

Formula III

or a pharmaceutically acceptable salt thereof,

where

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

A^2 is a bond between the degradation moiety and the linker;

each of B^1, B^2, B^3, and B^4 is, independently, optionally substituted C_1-C_4 alkyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_6-C_{10} aryl $C_{1\text{-}4}$ alkyl, optionally substituted C_1-C_4 heteroalkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_2-C_6 heterocyclyl, optionally substituted C_2-C_9 heteroaryl, O, S, $S(O)_2$, 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;

each of C^1 and C^2 is, independently, carbonyl, thiocarbonyl, sulphonyl, or phosphoryl;

each of f, g, h, i, j, and k is, independently, 0 or 1; and

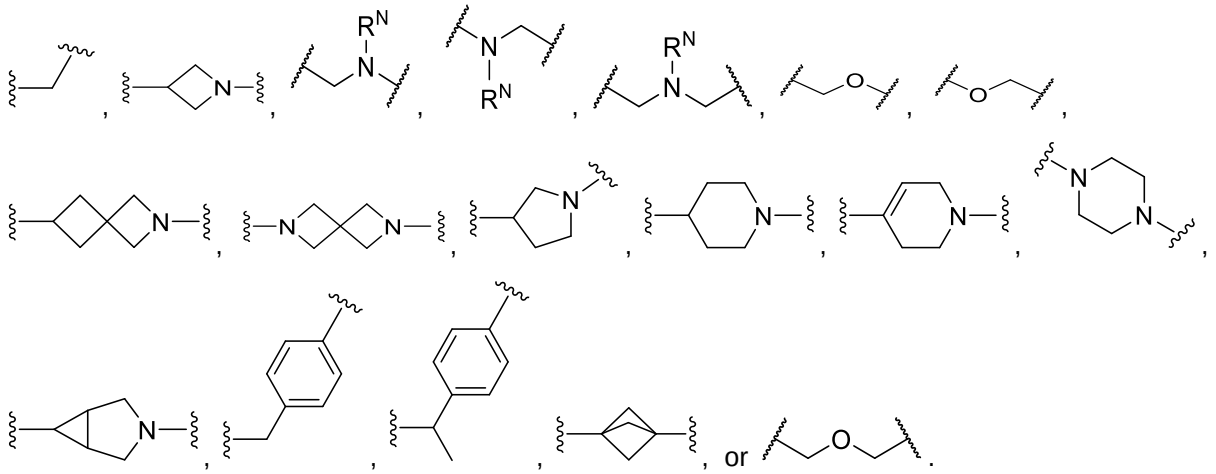
D is optionally substituted $C_{1–10}$ alkyl, optionally substituted $C_{2–10}$ alkenyl, optionally substituted $C_{2–10}$ alkynyl, optionally substituted $C_{2–6}$ heterocyclyl, optionally substituted $C_{6–12}$ aryl, optionally substituted C_2-C_{10} polyethylene glycol, or optionally substituted $C_{1–10}$ heteroalkyl, or a chemical bond linking A^1-$(B^1)_f$-$(C^1)_g$-$(B^2)_h$- to -$(B^3)_i$-$(C^2)_j$-$(B^4)_k$–A^2.

In some examples, each of B^1, B^2, B^3, and B^4 is, independently, optionally substituted C_1-C_2 alkyl, optionally substituted C_1-C_3 heteroalkyl, optionally substituted C_2-C_6 heterocyclyl, or NR^N.

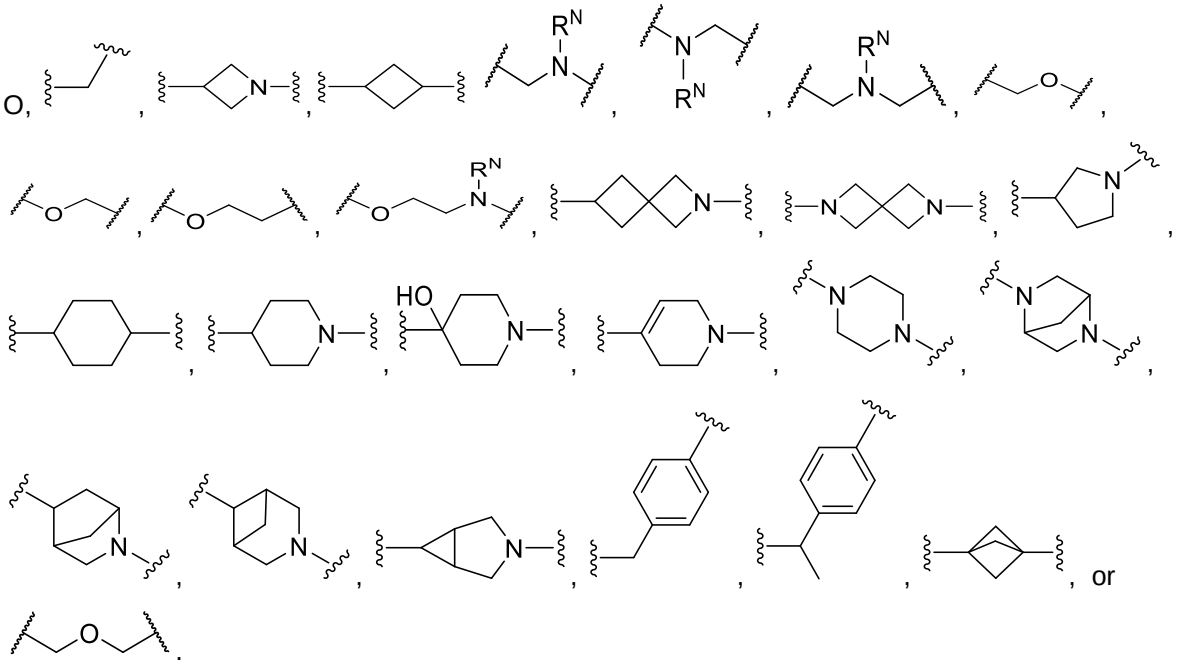
In some examples, each R^N is, independently, H or optionally substituted C_1–C_4 alkyl.

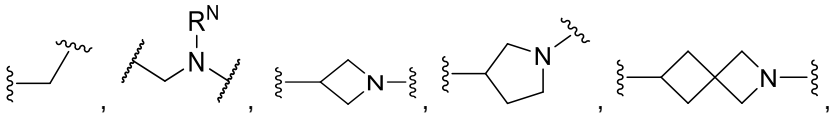
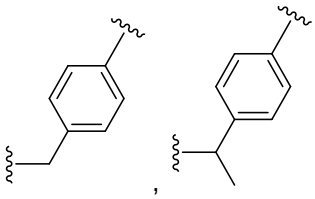
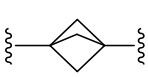
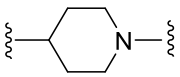
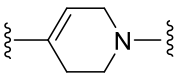
In some examples, each R^N is, independently, H or CH_3.

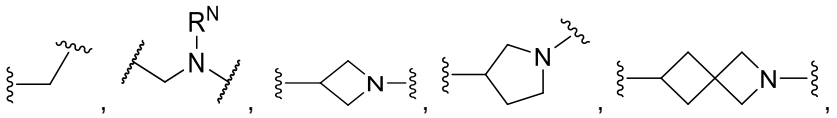
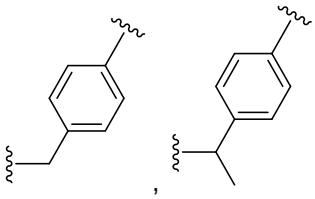
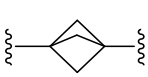
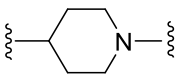
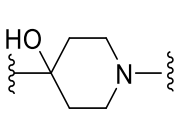
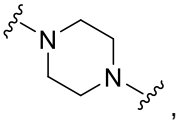
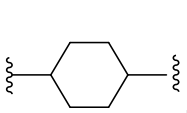
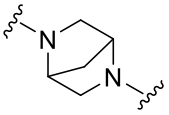
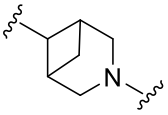
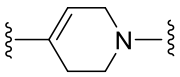
In some examples, each of B^1 and B^4 is, independently,

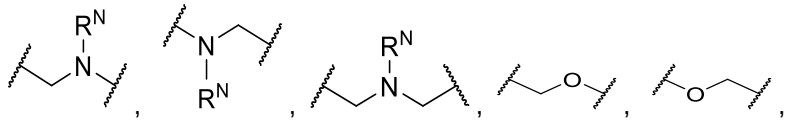
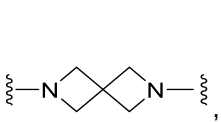
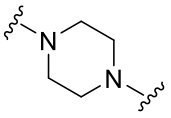
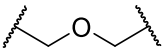


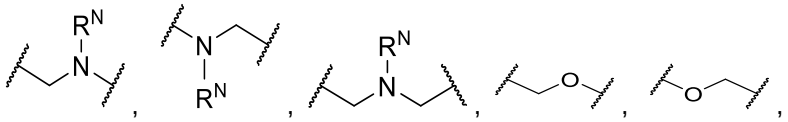
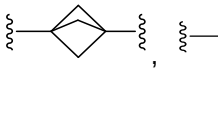
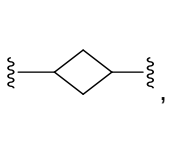
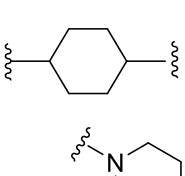
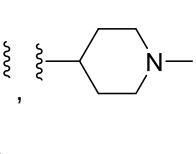
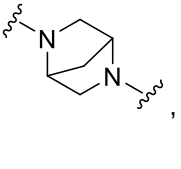
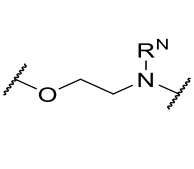
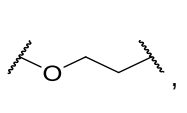
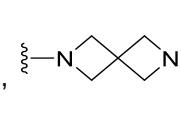
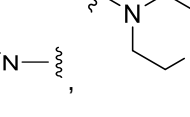
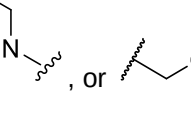
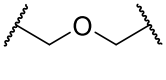
In some examples, each of B^1 and B^4 is, independently,

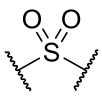


In some examples, B^1 is , , , , , or .

In some examples, B^1 is , , , , , , , , , , or .

In some examples, B^4 is , , , or .

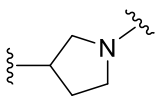
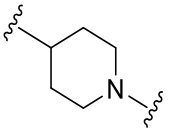
In some examples, B^4 is O, , , , , , , , , , , , , , , , , or .

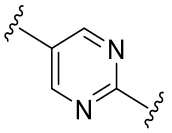
In some examples, each of C^1 and C^2 is  or .

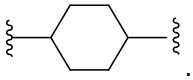
In some examples, C^1 is or .

In some examples, C^2 is .

In some examples, B^2 is optionally substituted C_1-C_4 alkyl. In some examples, B^2 is optionally substituted C_2-C_6 heterocyclyl.

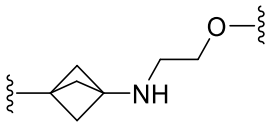
In some examples, B^2 is  or .

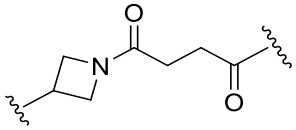
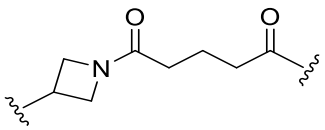
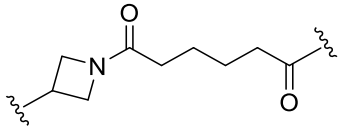
In some examples, B^2 is optionally substituted C_2-C_9 heteroaryl. In some examples, B^2 is .

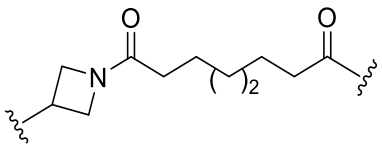
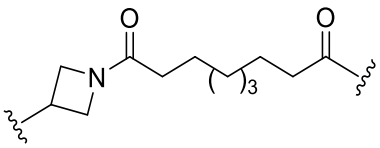
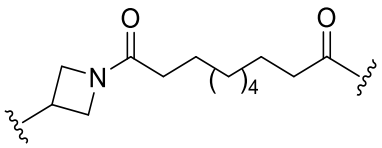
In some examples, B^3 is optionally substituted C_3-C_{10} cycloalkyl. In some examples, B^3 is .

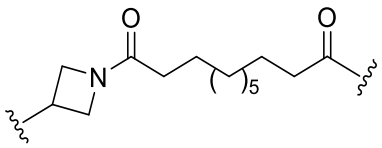
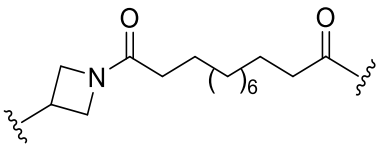
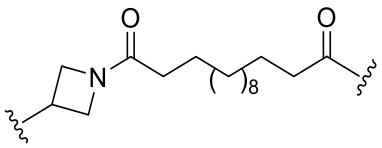
In some examples, D is optionally substituted C_1-C_{10} alkyl.

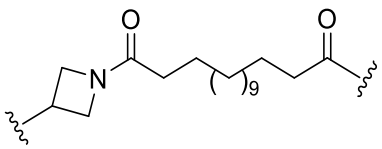
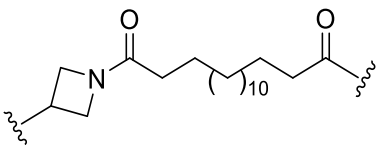
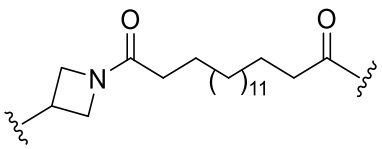
In some examples, f is 1. In some examples, g is 0. In some examples, g is 1. In some examples, h is 0. In some examples, h is 1. In some examples, i is 0. In some examples, i is 1. In some examples, j is 0. In some examples, j is 1. In some examples, k is 0. In some examples, k is 1.

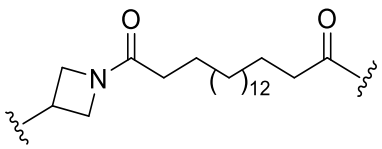
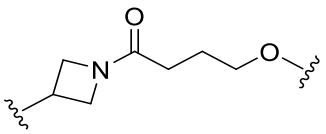
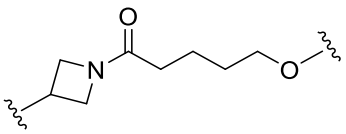
In some examples, the linker has the structure of ,

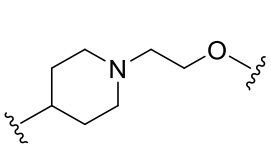
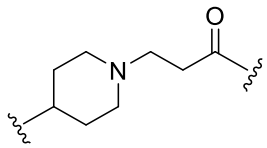
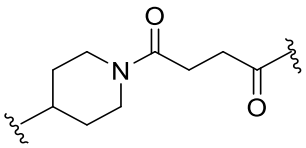
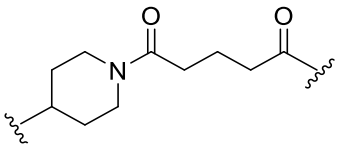
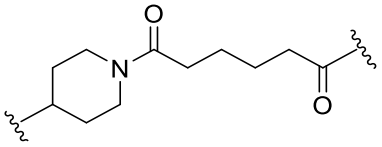
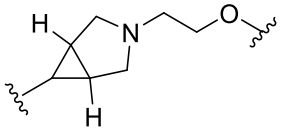
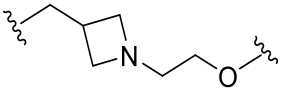
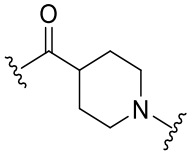
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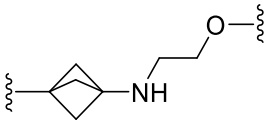
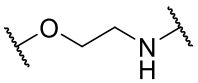
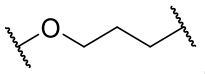
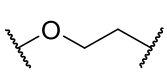
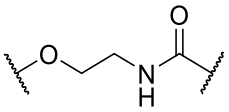
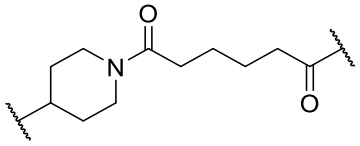
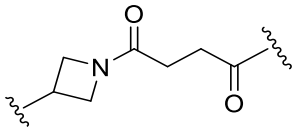
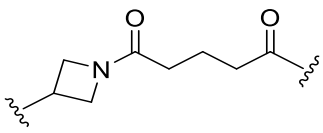
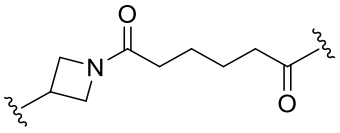
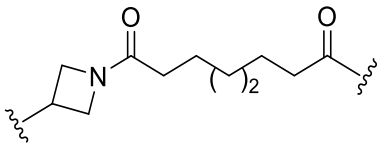
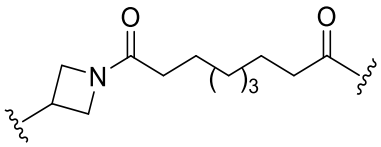
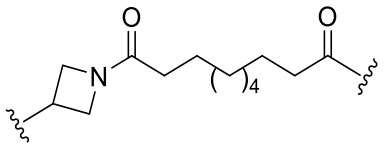
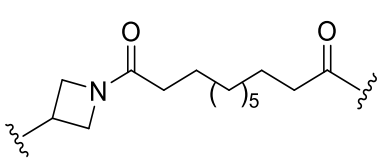
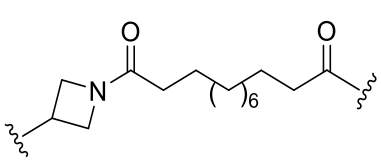
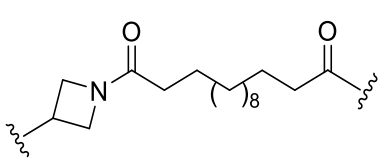
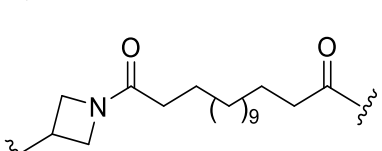
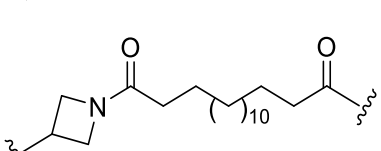
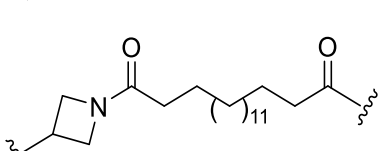
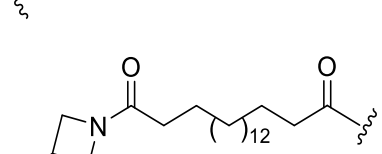
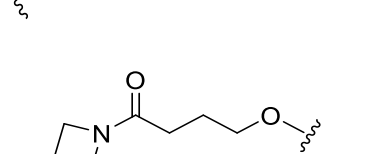
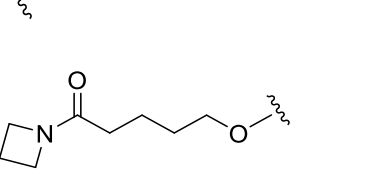
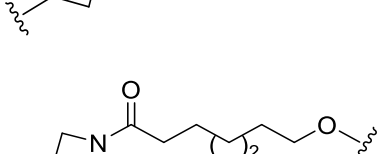
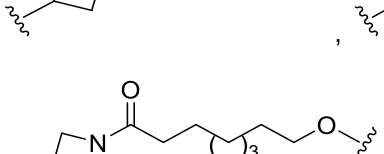
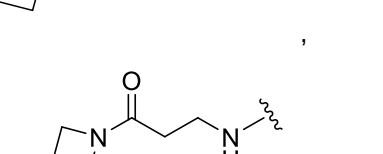
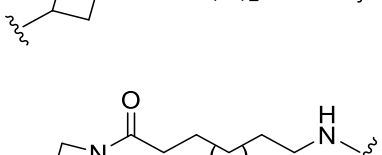
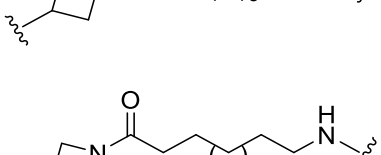
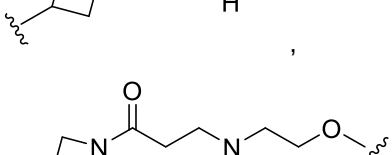
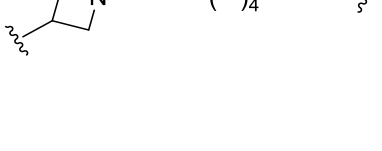
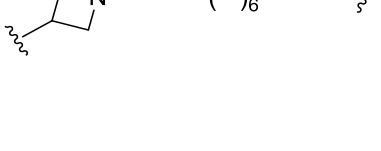
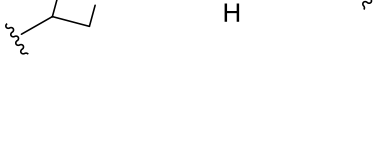
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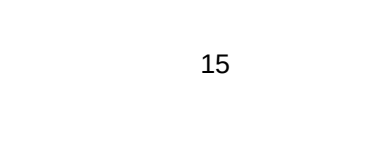
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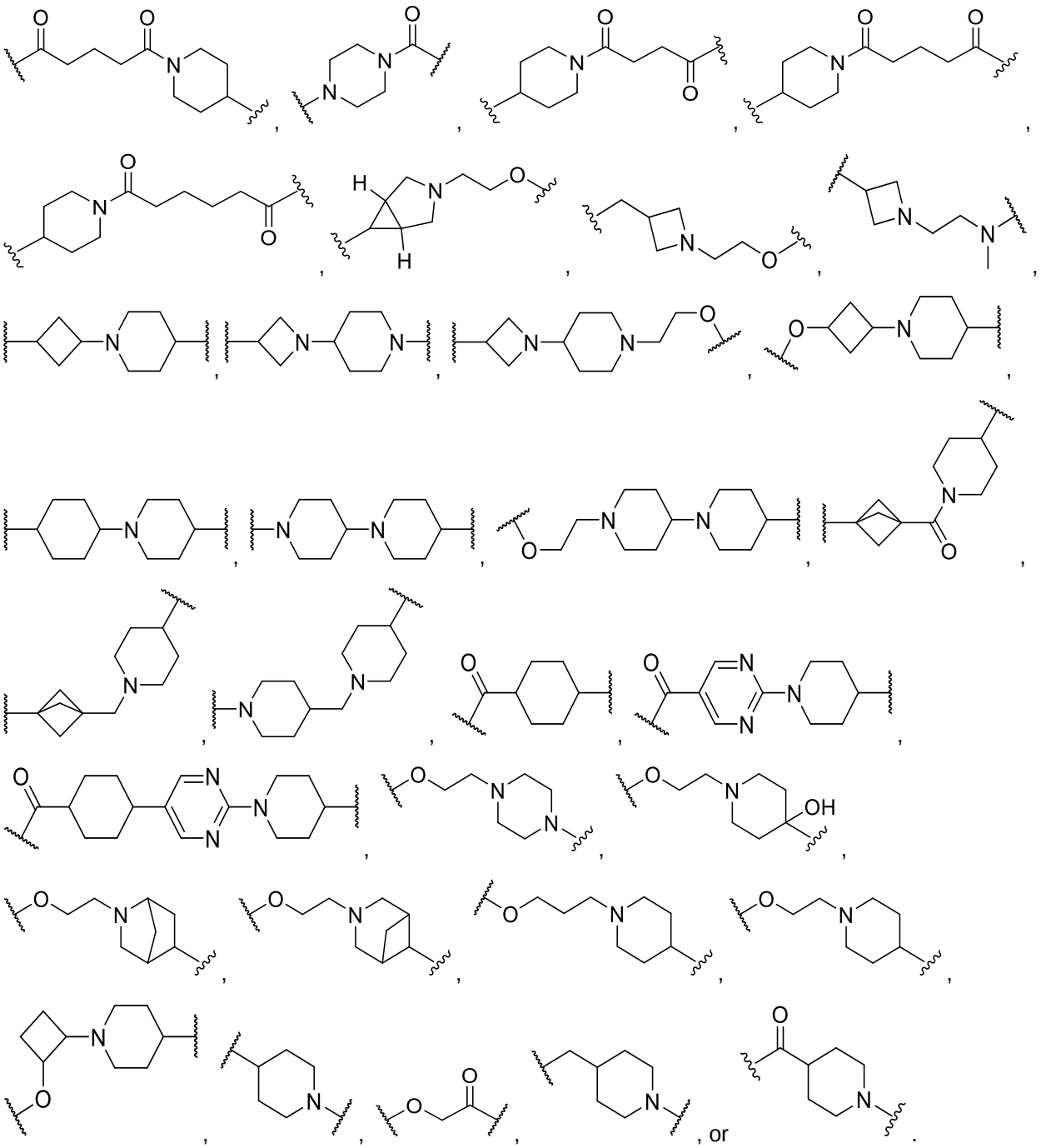
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In some examples, the linker has the structure of

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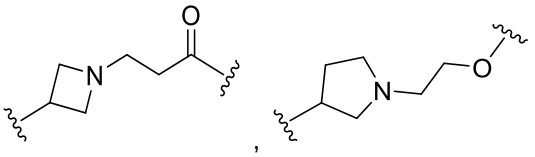
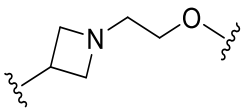
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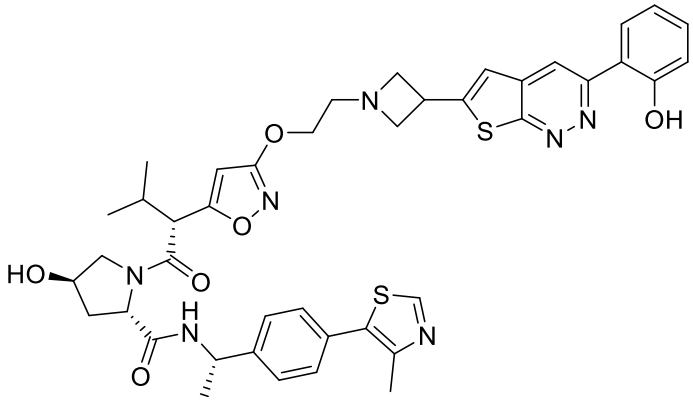
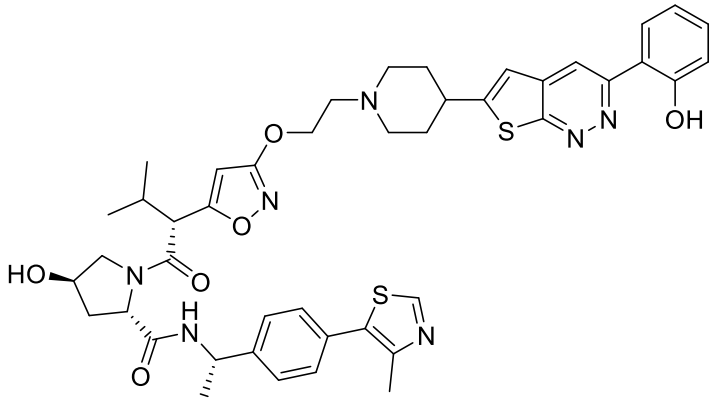
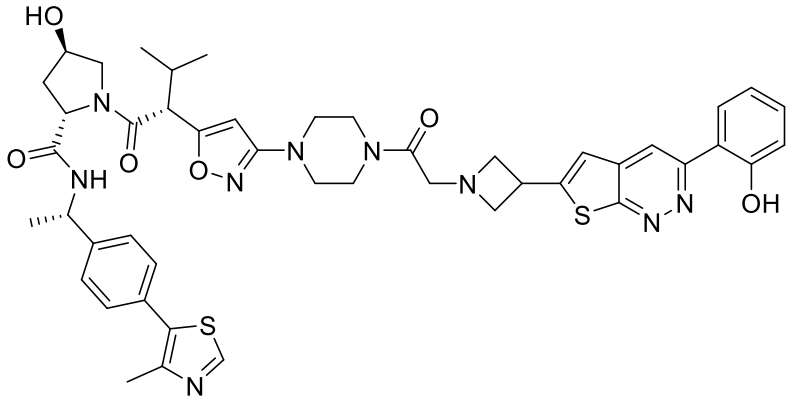
In some examples, the shortest chain of atoms connecting two valencies of the linker is 2 to 10 atoms long.

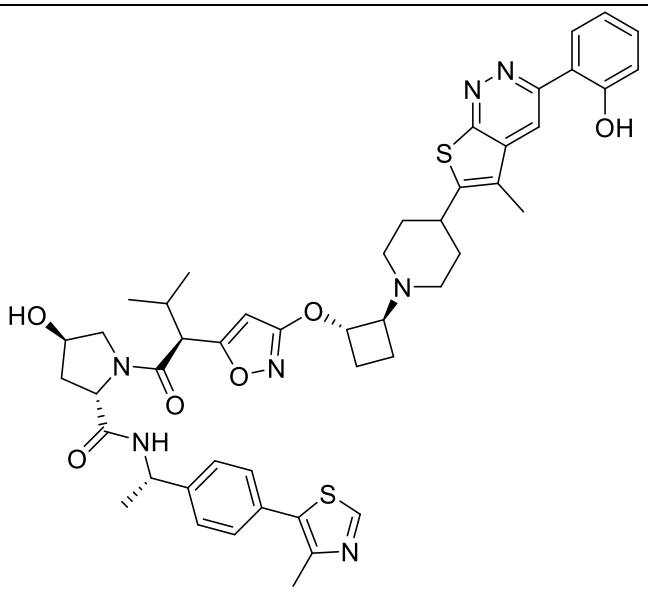
In some examples, the shortest chain of atoms connecting two valencies of the linker is 6 atoms long.

In some examples, the linker has the structure of  or .

In an example, the disclosure features a compound selected from the group consisting of 1-33 in Table 1 and pharmaceutically acceptable salts thereof. In an example, the disclosure features a compound selected from the group consisting of 1-115 in Table 1 and pharmaceutically acceptable salts thereof.

Table 1. Compounds of the Invention

#	**Compound**
1	
2	
3	

#	Compound
115	

In some examples, the compound has a ratio of BRG1 IC_{50} to BRM IC_{50} of at least 5. In some examples, the compound has a ratio of BRG1 IC_{50} to BRM IC_{50} of at least 7. In some examples, the compound has a ratio of BRG1 IC_{50} to BRM IC_{50} of at least 10. In some examples, the compound has a ratio of BRG1 IC_{50} to BRM IC_{50} of at least 15. In some examples, the compound has a ratio of BRG1 IC_{50} to BRM IC_{50} of at least 20. In some examples, the compound has a ratio of BRG1 IC_{50} to BRM IC_{50} of at least 25. In some examples, the compound has a ratio of BRG1 IC_{50} to BRM IC_{50} of at least 30.

In an example, the disclosure features a pharmaceutical composition comprising any of the foregoing compounds and a pharmaceutically acceptable excipient.

In another example, the disclosure features a method of decreasing the activity of a BAF complex in a cell, the method involving contacting the cell with an effective amount of any of the foregoing compounds or a pharmaceutical composition thereof.

In some examples, the cell is a cancer cell.

In another example, 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 (e.g., a BRM/BRG1 dual inhibitor compound or a BRM-selective compound) or a pharmaceutical composition thereof.

In some examples, the BAF complex-related disorder is cancer.

In a further example, the disclosure features a method of inhibiting BRM, the method involving contacting a cell with an effective amount of any of the foregoing compounds (e.g., a BRM/BRG1 dual inhibitor compound or a BRM-selective compound) or a pharmaceutical composition thereof.

In some examples, the cell is a cancer cell.

In another example, the disclosure features a method of inhibiting BRG1, the method involving contacting the cell with an effective amount of any of the foregoing compounds or a pharmaceutical composition thereof.

In some examples, the cell is a cancer cell.

In a further example, the disclosure features a method of inhibiting BRM and BRG1, the method involving contacting the cell with an effective amount of any of the foregoing compounds or a pharmaceutical composition thereof.

In some examples, the cell is a cancer cell.

In another example, the disclosure features a method of treating a disorder related to a BRG1 loss of function mutation in a subject in need thereof, the method involving administering to the subject an effective amount of any of the foregoing compounds (e.g., a BRM/BRG1 dual inhibitor compound or a BRM-selective compound) or a pharmaceutical composition thereof.

In some examples, the disorder related to a BRG1 loss of function mutation is cancer. In other examples, the subject is determined to have a BRG1 loss of function disorder, for example, is determined to have a BRG1 loss of function cancer (for example, the cancer has been determined to include cancer cells with loss of BRG1 function).

In another example, the disclosure features a method of inducing apoptosis in a cell, the method involving contacting the cell with an effective amount of any of the foregoing compounds (e.g., a BRM/BRG1 dual inhibitor compound or a BRM-selective compound) or a pharmaceutical composition thereof.

In some examples, the cell is a cancer cell.

In a further example, the disclosure features a method of treating cancer in a subject in need thereof, the method including administering to the subject an effective amount of any of the foregoing compounds (e.g., a BRM/BRG1 dual inhibitor compound or a BRM-selective compound) or a pharmaceutical composition thereof.

In some examples of any of the foregoing methods, the cancer is non-small cell lung cancer, colorectal cancer, bladder cancer, cancer of unknown primary, glioma, breast cancer, melanoma, non-melanoma skin cancer, endometrial cancer, esophagogastric cancer, pancreatic cancer, hepatobiliary cancer, soft tissue sarcoma, ovarian cancer, head and neck cancer, renal cell carcinoma, bone cancer, non-Hodgkin lymphoma, small-cell lung cancer, prostate cancer, embryonal tumor, germ cell tumor, cervical cancer, thyroid cancer, salivary gland cancer, gastrointestinal neuroendocrine tumor, uterine sarcoma, gastrointestinal stromal tumor, CNS cancer, thymic tumor, Adrenocortical carcinoma, appendiceal cancer, small bowel cancer, or penile cancer.

In some examples of any of the foregoing methods, the cancer is non-small cell lung cancer, colorectal cancer, bladder cancer, cancer of unknown primary, glioma, breast cancer, melanoma, non-melanoma skin cancer, endometrial cancer, or penile cancer.

In some examples of any of the foregoing methods, the cancer is a drug resistant cancer or has failed to respond to a prior therapy (e.g., vemurafenib, dacarbazine, a CTLA4 inhibitor, a PD1 inhibitor, interferon therapy, a BRAF inhibitor, a MEK inhibitor, radiotherapy, temozolomide, irinotecan, a CAR-T therapy, Herceptin®, Perjeta®, tamoxifen, Xeloda®, docetaxol, platinum agents such as carboplatin, taxanes such as paclitaxel and docetaxel, ALK inhibitors, MET inhibitors, Alimta®, Abraxane®, Adriamycin®, gemcitabine, Avastin®, Halaven®, neratinib, a PARP inhibitor, ARN810, an mTOR inhibitor, topotecan, Gemzar®, a VEGFR2 inhibitor, a folate receptor antagonist, demcizumab, fosbretabulin, or a PDL1 inhibitor).

In some examples of any of the foregoing methods, the cancer has or has been determined to have BRG1 mutations. In some examples of any of the foregoing methods, the BRG1 mutations

are homozygous. In some examples of any of the foregoing methods, the cancer does not have, or has been determined not to have, an epidermal growth factor receptor (EGFR) mutation. In some examples of any of the foregoing methods, the cancer does not have, or has been determined not to have, an anaplastic lymphoma kinase (ALK) driver mutation. In some examples of any of the foregoing methods, the cancer has, or has been determined to have, a KRAS mutation. In some examples of any of the foregoing methods, the BRG1 mutation is in the ATPase catalytic domain of the protein. In some examples of any of the foregoing methods, the BRG1 mutation is a deletion at the C-terminus of BRG1.

In another example, the disclosure provides a method treating a disorder related to BAF (e.g., cancer or viral infections) in a subject in need thereof. This method includes contacting a cell with an effective amount of any of the foregoing compounds (e.g., a BRM/BRG1 dual inhibitor compound or a BRM-selective compound), or pharmaceutically acceptable salts thereof, or any of the foregoing pharmaceutical compositions. In some examples, the disorder is a 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 some examples, the disorder is Coffin Siris, Neurofibromatosis (e.g., NF-1, NF-2, or Schwannomatosis), or Multiple Meningioma.

In another example, the disclosure provides 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 (e.g., a BRM/BRG1 dual inhibitor compound or a BRM-selective compound), or pharmaceutically acceptable salts thereof, or any of the foregoing pharmaceutical compositions. In some examples, 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), or Togaviridae family (e.g., Rubella virus).

In some examples of any of the foregoing examples, the compound is a BRM-selective compound. In some examples, the BRM-selective compound inhibits the level and/or activity of BRM at least 10-fold greater than the compound inhibits the level and/or activity of BRG1 and/or the compound binds to BRM at least 10-fold greater than the compound binds to BRG1. For example, in some examples, a BRM-selective compound has an IC_{50} or IP_{50} that is at least 10-fold lower than the IC_{50} or IP_{50} against BRG1. In some examples of any of the foregoing examples, the compound is a

BRM/BRG1 dual inhibitor compound. In some examples, the BRM/BRG1 dual inhibitor compound has similar activity against both BRM and BRG1 (e.g., the activity of the compound against BRM and BRG1 with within 10-fold (e.g., less than 5-fold, less than 2-fold). In some examples, the activity of the BRM/BRG1 dual inhibitor compound is greater against BRM. In some examples, the activity of the BRM/BRG1 dual inhibitor compound is greater against BRG1. For example, in some examples, a BRM/BRG1 dual inhibitor compound has an IC_{50} or IP_{50} against BRM that is within 10-fold of the IC_{50} or IP_{50} against BRG1.

In another example, the disclosure features a method of treating melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or a hematologic cancer in a subject in need thereof, the method including administering to the subject an effective amount of any of the foregoing compounds or pharmaceutical compositions thereof.

In another example, the disclosure features a method of reducing tumor growth of melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or a hematologic cancer in a subject in need thereof, the method including administering to the subject an effective amount of any of the foregoing compounds or pharmaceutical compositions thereof.

In another example, the disclosure features a method of suppressing metastatic progression of melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or a hematologic cancer in a subject, the method including administering an effective amount of any of the foregoing compounds or pharmaceutical compositions thereof.

In another example, the disclosure features a method of suppressing metastatic colonization of melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or a hematologic cancer in a subject, the method including administering an effective amount of any of the foregoing compounds or pharmaceutical compositions thereof.

In another example, the disclosure features a method of reducing the level and/or activity of BRG1 and/or BRM in a melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or hematologic cancer cell, the method including contacting the cell with an effective amount of any of the foregoing compounds or pharmaceutical compositions thereof.

In some examples of any of the above examples, the melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or hematologic cell is in a subject.

In some examples of any of the above examples, the effective amount of the compound reduces the level and/or activity of BRG1 by at least 5% (e.g., 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) as compared to a reference. In some examples, the effective amount of the compound that reduces the level and/or activity of BRG1 by at least 50% (e.g., 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) as compared to a reference. In some examples, the effective amount of the compound that reduces the level and/or activity of BRG1 by at least 90% (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%).

In some examples, the effective amount of the compound reduces the level and/or activity of BRG1 by at least 5% (e.g., 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) as compared to a reference for at least 12 hours (e.g., 14 hours, 16 hours, 18 hours, 20 hours, 22 hours, 24 hours, 30 hours, 36 hours, 48 hours, 72 hours, or more). In some examples, the effective amount of the compound that reduces the level and/or

activity of BRG1 by at least 5% (e.g., 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) as compared to a reference for at least 4 days (e.g., 5 days, 6 days, 7 days, 14 days, 28 days, or more).

In some examples of any of the above examples, the effective amount of the compound reduces the level and/or activity of BRM by at least 5% (e.g., 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) as compared to a reference. In some examples, the effective amount of the compound that reduces the level and/or activity of BRM by at least 50% (e.g., 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) as compared to a reference. In some examples, the effective amount of the compound that reduces the level and/or activity of BRM by at least 90% (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%).

In some examples, the effective amount of the compound reduces the level and/or activity of BRM by at least 5% (e.g., 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) as compared to a reference for at least 12 hours (e.g., 14 hours, 16 hours, 18 hours, 20 hours, 22 hours, 24 hours, 30 hours, 36 hours, 48 hours, 72 hours, or more). In some examples, the effective amount of the compound that reduces the level and/or activity of BRM by at least 5% (e.g., 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) as compared to a reference for at least 4 days (e.g., 5 days, 6 days, 7 days, 14 days, 28 days, or more).

In some examples, the subject has cancer. In some examples, the cancer expresses BRG1 and/or BRM protein and/or the cell or subject has been identified as expressing BRG1 and/or BRM. In some examples, the cancer expresses BRG1 protein and/or the cell or subject has been identified as expressing BRG1. In some examples, the cancer expresses BRM protein and/or the cell or subject has been identified as expressing BRM. In some examples, the cancer is melanoma (e.g., uveal melanoma, mucosal melanoma, or cutaneous melanoma). In some examples, the cancer is prostate cancer. In some examples, the cancer is a hematologic cancer, e.g., multiple myeloma, large cell lymphoma, acute T-cell leukemia, acute myeloid leukemia, myelodysplastic syndrome, immunoglobulin A lambda myeloma, diffuse mixed histiocytic and lymphocytic lymphoma, B-cell lymphoma, acute lymphoblastic leukemia (e.g., T-cell acute lymphoblastic leukemia or B-cell acute lymphoblastic leukemia), diffuse large cell lymphoma, or non-Hodgkin's lymphoma. In some examples, the cancer is breast cancer (e.g., an ER positive breast cancer, an ER negative breast cancer, triple positive breast cancer, or triple negative breast cancer). In some examples, the cancer is a bone cancer (e.g., Ewing's sarcoma). In some examples, the cancer is a renal cell carcinoma (e.g., a Microphthalmia Transcription Factor (MITF) family translocation renal cell carcinoma (tRCC)). In some examples, the cancer is metastatic (e.g., the cancer has spread to the liver). The metastatic cancer can include cells exhibiting migration and/or invasion of migrating cells and/or include cells exhibiting endothelial recruitment and/or angiogenesis. In other examples, the migrating cancer is a cell migration cancer. In still other examples, the cell migration cancer is a non-metastatic cell migration cancer. The metastatic cancer can be a cancer spread via seeding the surface of the peritoneal, pleural, pericardial, or subarachnoid spaces. Alternatively, the metastatic cancer can be a cancer spread via the lymphatic system, or a cancer spread hematogenously. In some examples, the effective amount of an agent that reduces the level and/or activity of BRG1 and/or BRM is an amount effective to inhibit metastatic colonization of the cancer to the liver.

In some examples the cancer harbors a mutation in GNAQ. In some examples the cancer harbors a mutation in GNA11. In some examples the cancer harbors a mutation in PLCB4. In some examples the cancer harbors a mutation in CYSLTR2. In some examples the cancer harbors a mutation in BAP1. In some examples the cancer harbors a mutation in SF3B1. In some examples the cancer harbors a mutation in EIF1AX. In some examples the cancer harbors a TFE3 translocation. In some examples the cancer harbors a TFEB translocation. In some examples the cancer harbors a MITF translocation. In some examples the cancer harbors an EZH2 mutation. In some examples the cancer harbors a SUZ12 mutation. In some examples the cancer harbors an EED mutation.

In some examples, the method further includes administering to the subject or contacting the cell with an anticancer therapy, e.g., a chemotherapeutic or cytotoxic agent, immunotherapy, surgery, radiotherapy, thermotherapy, or photocoagulation. In some examples, the anticancer therapy is a chemotherapeutic or cytotoxic agent, e.g., an antimetabolite, antimitotic, antitumor antibiotic, asparagine-specific enzyme, bisphosphonates, antineoplastic, alkylating agent, DNA-Repair enzyme inhibitor, histone deacetylase inhibitor, corticosteroid, demethylating agent, immunomodulatory, janus-associated kinase inhibitor, phosphinositide 3-kinase inhibitor, proteasome inhibitor, or tyrosine kinase inhibitor.

In some examples, the compound of the disclosure is used in combination with another anti-cancer therapy used for the treatment of uveal melanoma such as surgery, a MEK inhibitor, and/or a PKC inhibitor. For example, in some examples, the method further comprises performing surgery prior to, subsequent to, or at the same time as administration of the compound of the disclosure. In some examples, the method further comprises administration of a MEK inhibitor and/or a PKC inhibitor prior to, subsequent to, or at the same time as administration of the compound of the disclosure.

In some examples, the anticancer therapy and the compound of the disclosure are administered within 28 days of each other and each in an amount that together are effective to treat the subject.

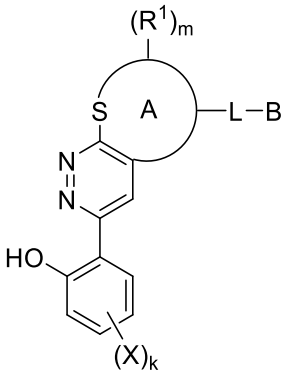
In some examples, the subject or cancer has and/or has been identified as having a BRG1 loss of function mutation.

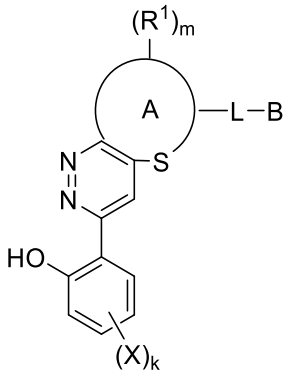
In some examples, the cancer is resistant to one or more chemotherapeutic or cytotoxic agents (e.g., the cancer has been determined to be resistant to chemotherapeutic or cytotoxic agents such as by genetic markers, or is likely to be resistant, to chemotherapeutic or cytotoxic agents such as a cancer that has failed to respond to a chemotherapeutic or cytotoxic agent). In some examples, the cancer has failed to respond to one or more chemotherapeutic or cytotoxic agents. In some examples, the cancer is resistant or has failed to respond to dacarbazine, temozolomide, cisplatin, treosulfan, fotemustine, IMCgp100, a CTLA-4 inhibitor (e.g., ipilimumab), a PD-1 inhibitor (e.g., Nivolumab or pembrolizumab), a PD-L1 inhibitor (e.g., atezolizumab, avelumab, or durvalumab), a mitogen-activated protein kinase (MEK) inhibitor (e.g., selumetinib, binimetinib, or tametinib), and/or a protein kinase C (PKC) inhibitor (e.g., sotrastaurin or IDE196).

In some examples, the cancer is resistant to or failed to respond to a previously administered therapeutic used for the treatment of uveal melanoma such as a MEK inhibitor or PKC inhibitor. For example, in some examples, the cancer is resistant to or failed to respond to a mitogen-activated protein kinase (MEK) inhibitor (e.g., selumetinib, binimetinib, or tametinib), and/or a protein kinase C (PKC) inhibitor (e.g., sotrastaurin or IDE196).

Claims

1. A compound, or a pharmaceutically acceptable salt thereof, having the structure of **Formula I or II**:



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Formula I **Formula II**

wherein

ring system A is a 5 to 9-membered heterocyclyl or heteroaryl;

m is 0, 1, 2, or 3;

k is 0, 1, or 2;

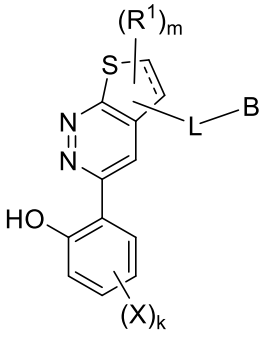
each R^1 is, independently, halo, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_8 cycloalkyl, or optionally substituted C_2-C_9 heterocyclyl;

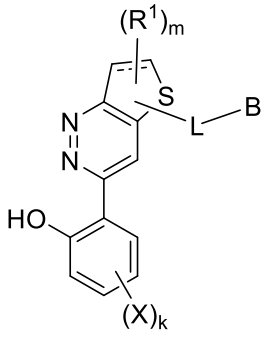
each X is, independently, halo;

L is a linker; and

B is a degradation moiety.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound has the structure of **Formula I-A or II-A**:

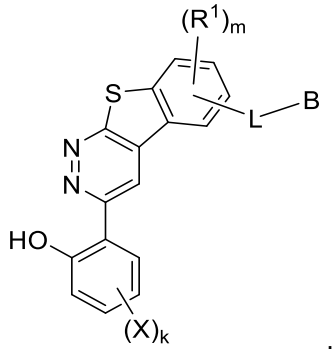


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Formula I-A **Formula II-A**

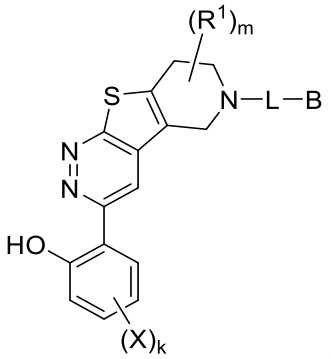
wherein the dashed bond represents a single or double bond.

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound has the structure of **Formula I-B**:



Formula I-B

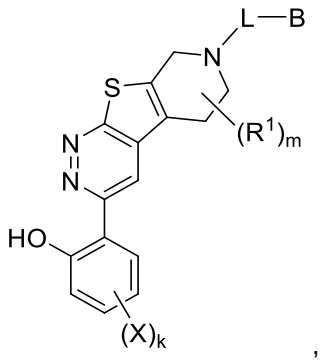
4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound has the structure of **Formula I-C**:



Formula I-C

wherein each R^1 is, independently, optionally substituted C_1-C_6 alkyl.

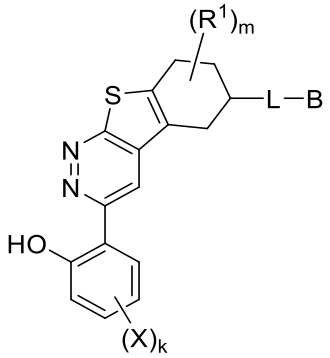
5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound has the structure of **Formula I-D**:



Formula I-D

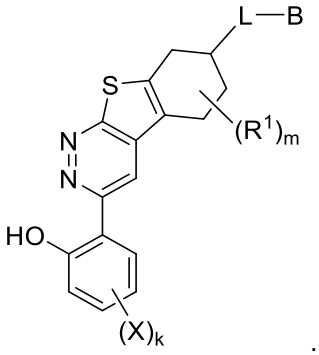
wherein each R^1 is, independently, optionally substituted C_1-C_6 alkyl.

6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound has the structure of **Formula I-E**:



Formula I-E

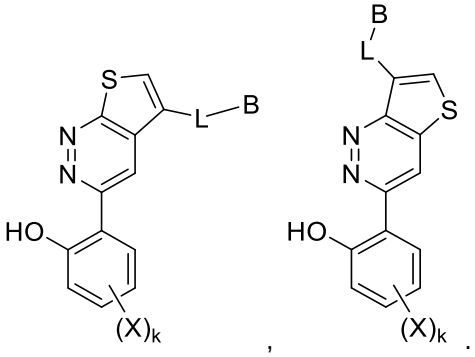
7. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound has the structure of **Formula I-F**:



Formula I-F

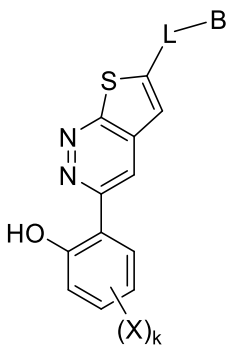
8. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein m is 0.

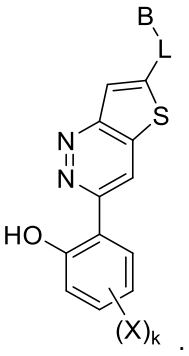
9. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound has the structure of **Formula I-G** or **II-G**:



Formula I-G **Formula II-G**

10. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound has the structure of **Formula I-H or II-H**:

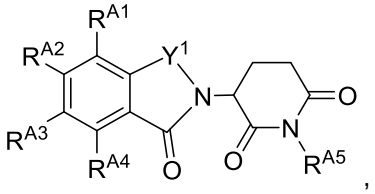


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Formula I-H **Formula II-H**

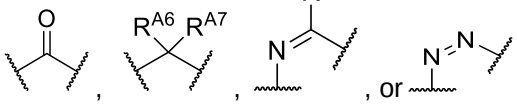
11. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the degradation moiety, B, has the structure of **Formula A-1**:



,

Formula A-1

wherein

Y^1 is 

, , , , or ;

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

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

each of R^{A1}, R^{A2}, R^{A3}, and R^{A4} is, independently, H, A^2, 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, optionally substituted -O-C_3-C_6 carbocyclyl, 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 

; and 

is 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, any of which is optionally substituted with A^2,

where one of R^{A1}, R^{A2}, R^{A3}, and R^{A4} is A^2, or 

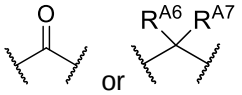
is substituted with A^2; and

A^2 is a bond between the degradation moiety and the linker.

12. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein R^{A5} is H or methyl.

13. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein each of R^{A1}, R^{A2}, R^{A3}, and R^{A4} is, independently, H or A^2.

14. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein Y^1 is

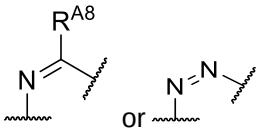


.

15. The compound of claim 14, or a pharmaceutically acceptable salt thereof, wherein R^{A6} is H.

16. The compound of claim 14, or a pharmaceutically acceptable salt thereof, wherein R^{A7} is H.

17. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein Y^1 is

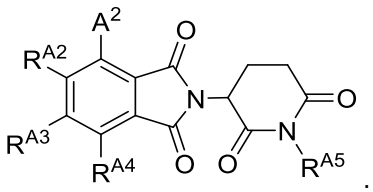


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18. The compound of claim 17, or a pharmaceutically acceptable salt thereof, wherein R^{A8} is H or optionally substituted C_1-C_6 alkyl.

19. The compound of claim 18, or a pharmaceutically acceptable salt thereof, wherein R^{A8} is H or methyl.

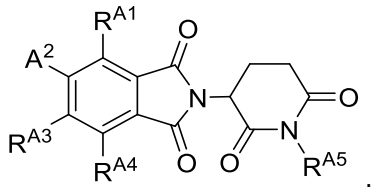
20. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein the degradation moiety comprises the structure of **Formula A2**:



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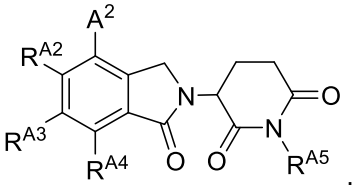
Formula A2

21. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein the degradation moiety comprises the structure of **Formula A4**:



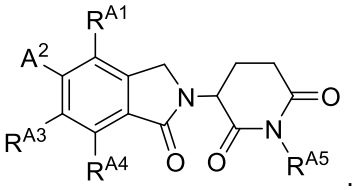
Formula A4

22. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein the degradation moiety comprises the structure of **Formula A5**:



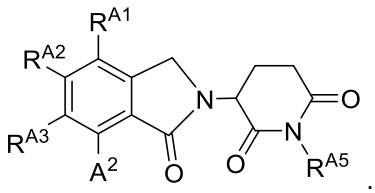
Formula A5

23. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein the degradation moiety comprises the structure of **Formula A6**:



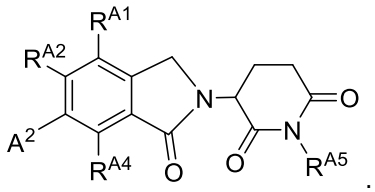
Formula A6

24. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein the degradation moiety comprises the structure of **Formula A8**:



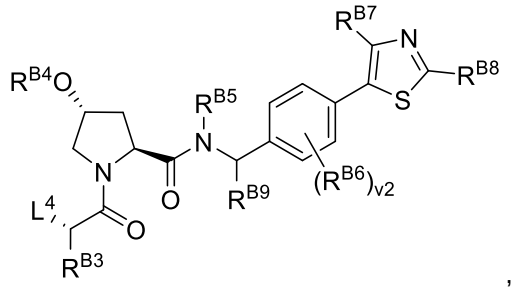
Formula A8

25. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein the degradation moiety comprises the structure of **Formula A10**:



Formula A10

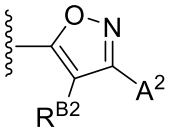
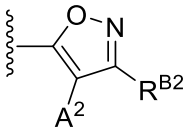
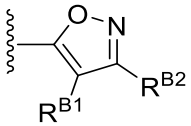
26. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the degradation moiety has the structure of **Formula C'**:



,

Formula C'

wherein

L^4 is $-N(R^{B1})(R^{B2})$, , , or ;

R^{B1} is H, A^2, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;R^{B2} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_9 heterocyclyl, or optionally substituted C_1-C_6 heteroalkyl;

R^{B3} is A^2, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_1-C_6 alkyl C_3-C_{10} carbocyclyl, or optionally substituted C_1-C_6 alkyl C_6-C_{10} aryl;

R^{B4} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_1-C_6 alkyl C_3-C_{10} carbocyclyl, or optionally substituted C_1-C_6 alkyl C_6-C_{10} aryl;

R^{B5} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

v2 is 0, 1, 2, 3, or 4;

each R^{B6} is, independently, A^2, 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 of R^{B7} and R^{B8} is, independently, H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

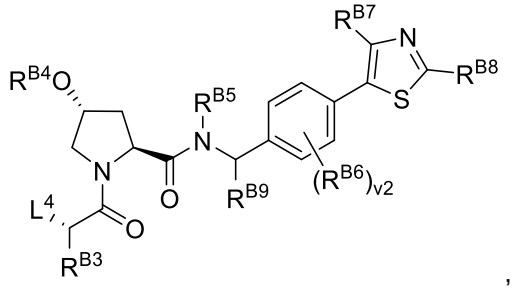
R^{B9} is H or optionally substituted C_1-C_6 alkyl; and

A^2 is a bond between the degradation moiety and the linker;

wherein one and only one of R^{B1}, R^{B3}, and R^{B6} is A^2,

or a pharmaceutically acceptable salt thereof.

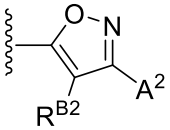
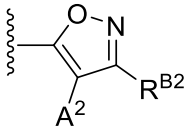
27. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the degradation moiety has the structure of **Formula C**:



,

Formula C

wherein

L^4 is $-N(R^{B1})(R^{B2})$,  or  ;

R^{B1} is H, A^2, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

R^{B2} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

R^{B3} is A^2, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_1-C_6 alkyl C_3-C_{10} carbocyclyl, or optionally substituted C_1-C_6 alkyl C_6-C_{10} aryl;

R^{B4} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_1-C_6 alkyl C_3-C_{10} carbocyclyl, or optionally substituted C_1-C_6 alkyl C_6-C_{10} aryl;

R^{B5} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

v2 is 0, 1, 2, 3, or 4;

each R^{B6} is, independently, A^2, 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 of R^{B7} and R^{B8} is, independently, H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

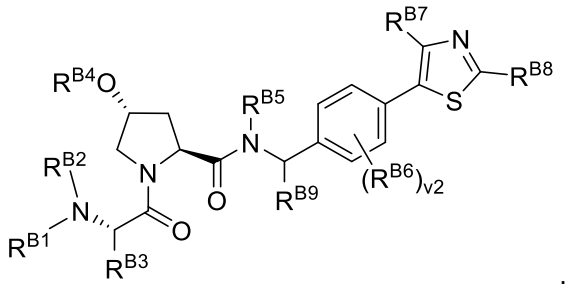
R^{B9} is H or optionally substituted C_1-C_6 alkyl; and

A^2 is a bond between the degradation moiety and the linker;

wherein one and only one of R^{B1}, R^{B3}, and R^{B6} is A^2,

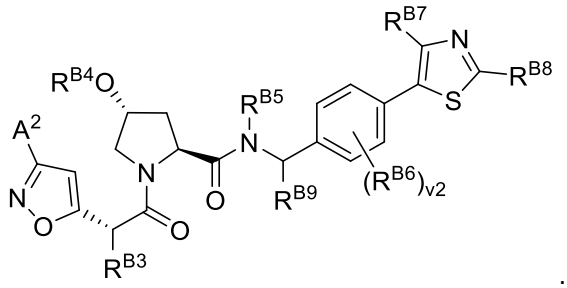
or a pharmaceutically acceptable salt thereof.

28. The compound of claim 26, or a pharmaceutically acceptable salt thereof, wherein the degradation moiety has the structure of **Formula C1**:



Formula C1

29. The compound of claim 26, or a pharmaceutically acceptable salt thereof, wherein the degradation moiety has the structure of **Formula C2**:



Formula C2

30. The compound of claim 26, or a pharmaceutically acceptable salt thereof, wherein R^{B9} is optionally substituted C_1-C_6 alkyl.

31. The compound of claim 30, or a pharmaceutically acceptable salt thereof, wherein R^{B9} is methyl.

32. The compound of claim 26, or a pharmaceutically acceptable salt thereof, wherein R^{B9} is bonded to (*S*)-stereogenic center.

33. The compound of claim 26, or a pharmaceutically acceptable salt thereof, wherein the linker has the structure of **Formula III**:

$$A^1\text{-}(B^1)_f\text{-}(C^1)_g\text{-}(B^2)_h\text{-}(D)\text{-}(B^3)_i\text{-}(C^2)_j\text{-}(B^4)_k\text{–}A^2,$$

Formula III

or a pharmaceutically acceptable salt thereof,

wherein

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

A^2 is a bond between the degradation moiety and the linker;

each of B^1, B^2, B^3, and B^4 is, independently, optionally substituted C_1-C_4 alkyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_6-C_{10} aryl $C_{1\text{-}4}$ alkyl, optionally substituted C_1-C_4 heteroalkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_2-C_6 heterocyclyl, optionally substituted C_2-C_9 heteroaryl, O, S, $S(O)_2$, 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;

each of C^1 and C^2 is, independently, carbonyl, thiocarbonyl, sulphonyl, or phosphoryl;

each of f, g, h, i, j, and k is, independently, 0 or 1; and

D is optionally substituted $C_{1–10}$ alkyl, optionally substituted $C_{2–10}$ alkenyl, optionally substituted $C_{2–10}$ alkynyl, optionally substituted $C_{2–6}$ heterocyclyl, optionally substituted $C_{6–12}$ aryl, optionally substituted C_2-C_{10} polyethylene glycol, or optionally substituted $C_{1–10}$ heteroalkyl, or a chemical bond linking A^1-$(B^1)_f$-$(C^1)_g$-$(B^2)_h$- to -$(B^3)_i$-$(C^2)_j$-$(B^4)_k$–A^2.

34. The compound of claim 20, or a pharmaceutically acceptable salt thereof, wherein the linker has the structure of **Formula III**:

$$A^1\text{-}(B^1)_f\text{-}(C^1)_g\text{-}(B^2)_h\text{-}(D)\text{-}(B^3)_i\text{-}(C^2)_j\text{-}(B^4)_k\text{–}A^2,$$

Formula III

or a pharmaceutically acceptable salt thereof,

wherein

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

A^2 is a bond between the degradation moiety and the linker;

each of B^1, B^2, B^3, and B^4 is, independently, optionally substituted C_1-C_4 alkyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_6-C_{10} aryl $C_{1\text{-}4}$ alkyl, optionally substituted C_1-C_4 heteroalkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_2-C_6 heterocyclyl, O, S, $S(O)_2$, 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;

each of C^1 and C^2 is, independently, carbonyl, thiocarbonyl, sulphonyl, or phosphoryl;

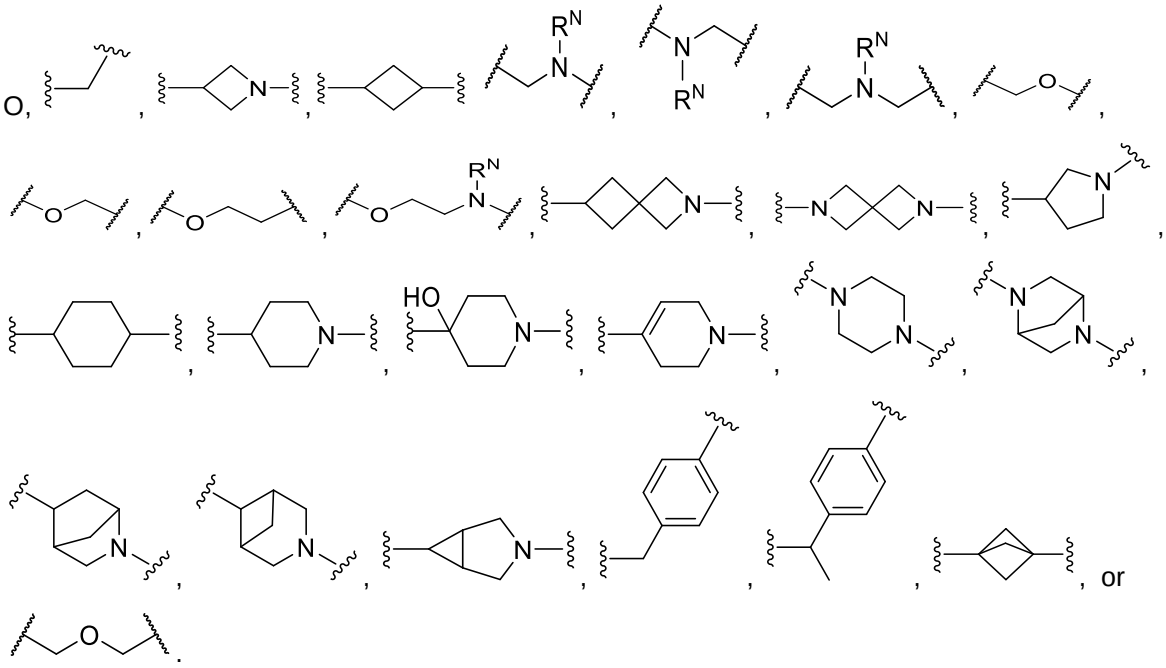
each of f, g, h, i, j, and k is, independently, 0 or 1; and

D is optionally substituted $C_{1–10}$ alkyl, optionally substituted $C_{2–10}$ alkenyl, optionally substituted $C_{2–10}$ alkynyl, optionally substituted $C_{2–6}$ heterocyclyl, optionally substituted $C_{6–12}$ aryl, optionally substituted C_2-C_{10} polyethylene glycol, or optionally substituted $C_{1–10}$ heteroalkyl, or a chemical bond linking A^1-$(B^1)_f$-$(C^1)_g$-$(B^2)_h$- to -$(B^3)_i$-$(C^2)_j$-$(B^4)_k$–A^2.

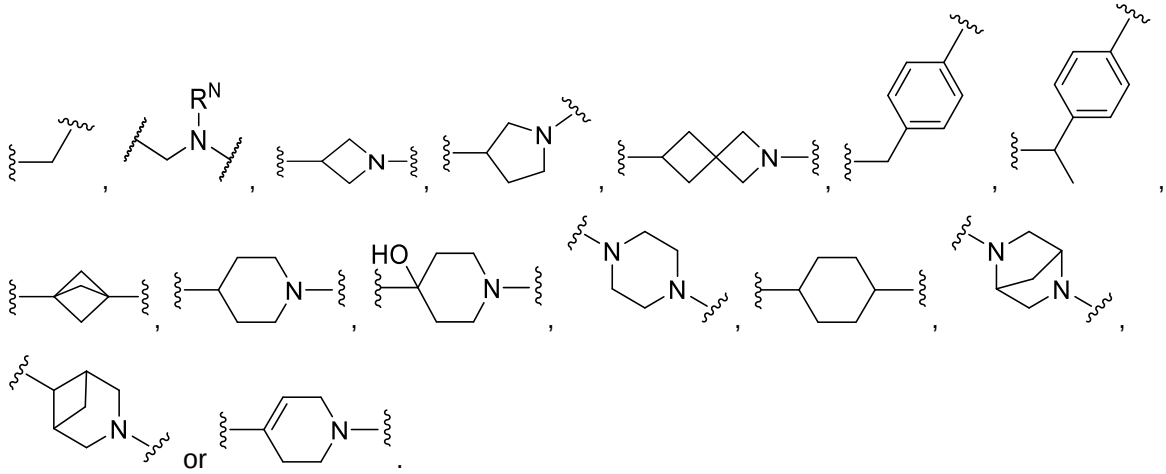
35. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein each of B^1, B^2, B^3, and B^4 is, independently, optionally substituted C_1-C_2 alkyl, optionally substituted C_1-C_3 heteroalkyl, optionally substituted C_2-C_6 heterocyclyl, or NR^N.

36. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein each R^N is, independently, H or optionally substituted C_1–C_4 alkyl.

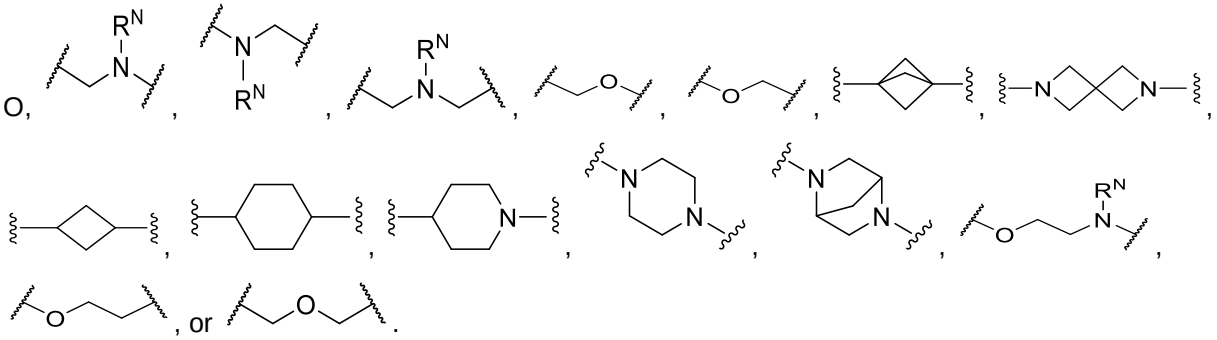
37. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein each of B^1 and B^4 is, independently,



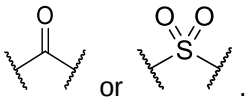
38. The compound of claim 37, or a pharmaceutically acceptable salt thereof, wherein B^1 is



39. The compound of claim 37, or a pharmaceutically acceptable salt thereof, wherein B^4 is

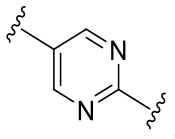
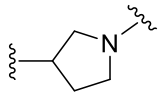
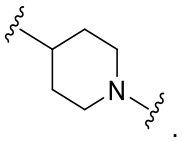


40. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein each of C^1 and C^2 is

 or .

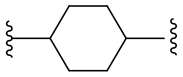
41. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein B^2 is optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_6 heterocyclyl or optionally substituted C_2-C_9 heteroaryl.

42. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein B^2 is

,  or .

43. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein B^3 is optionally substituted C_3-C_{10} cycloalkyl.

44. The compound of claim 43, or a pharmaceutically acceptable salt thereof, wherein B^3 is

.

45. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein D is optionally substituted C_1-C_{10} alkyl.

46. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein f is 1.

47. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein g is 0.

48. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein g is 1.

49. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein h is 0.

50. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein h is 1.

51. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein i is 0.

52. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein i is 1.

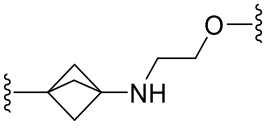
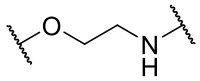
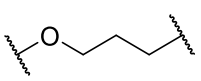
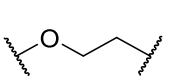
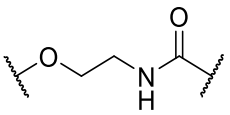
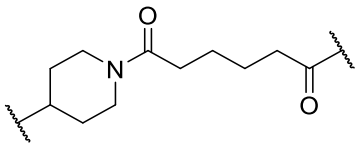
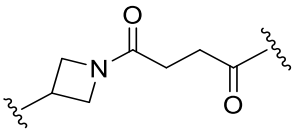
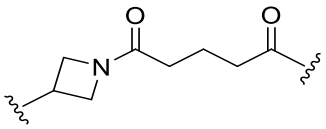
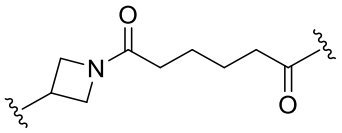
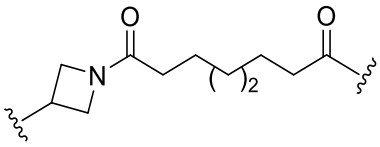
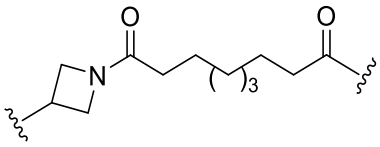
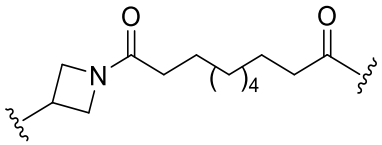
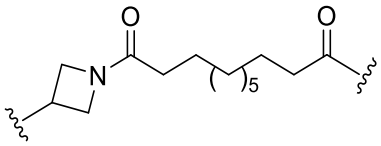
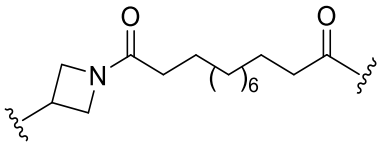
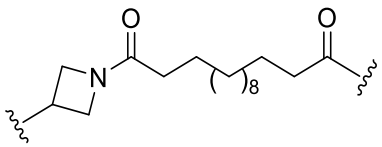
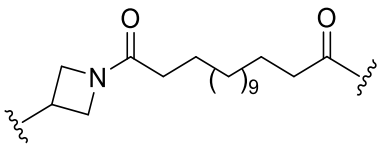
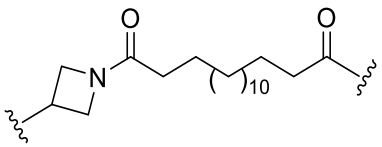
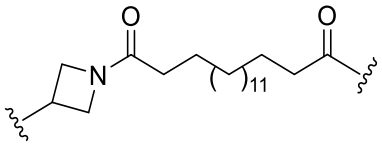
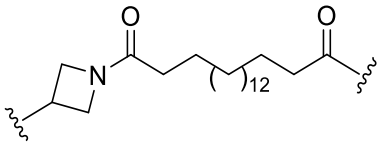
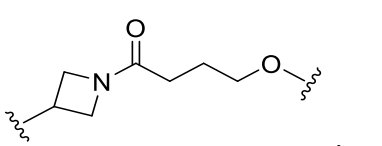
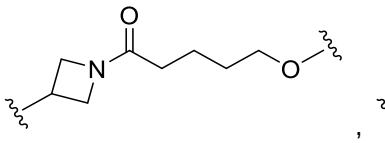
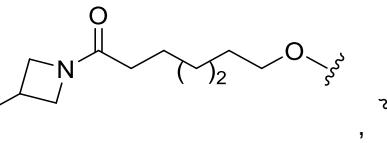
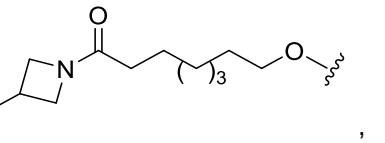
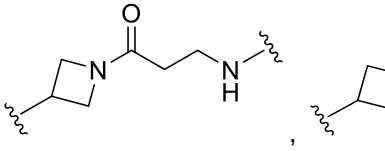
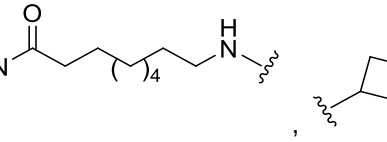
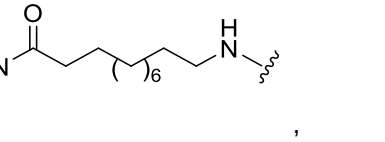
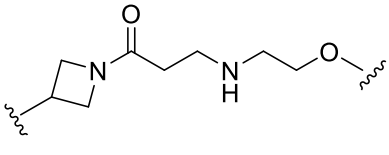
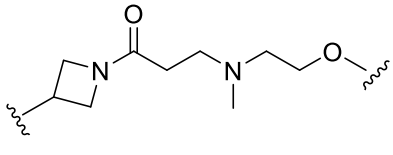
53. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein j is 0.

54. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein j is 1.

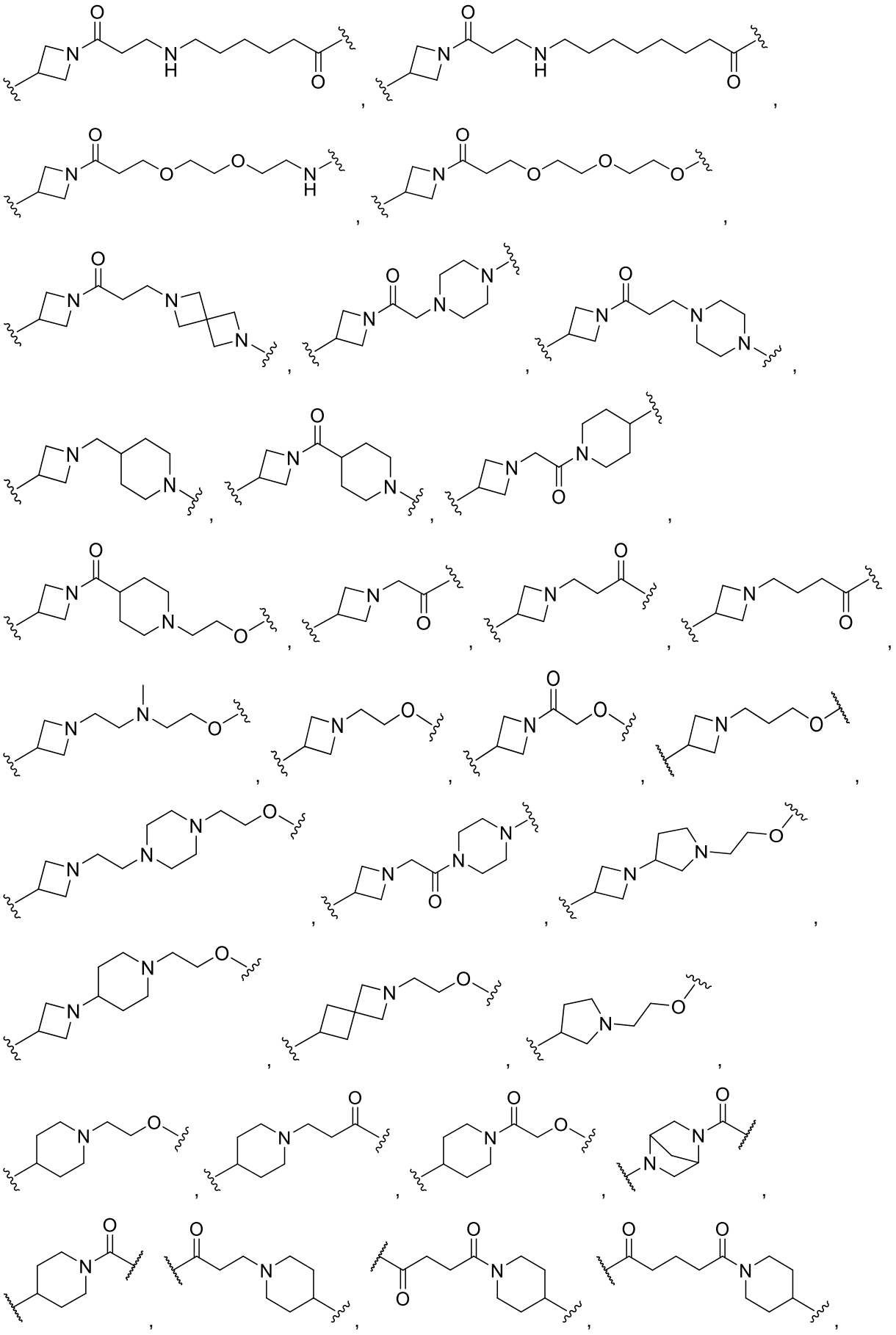
55. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein k is 0.

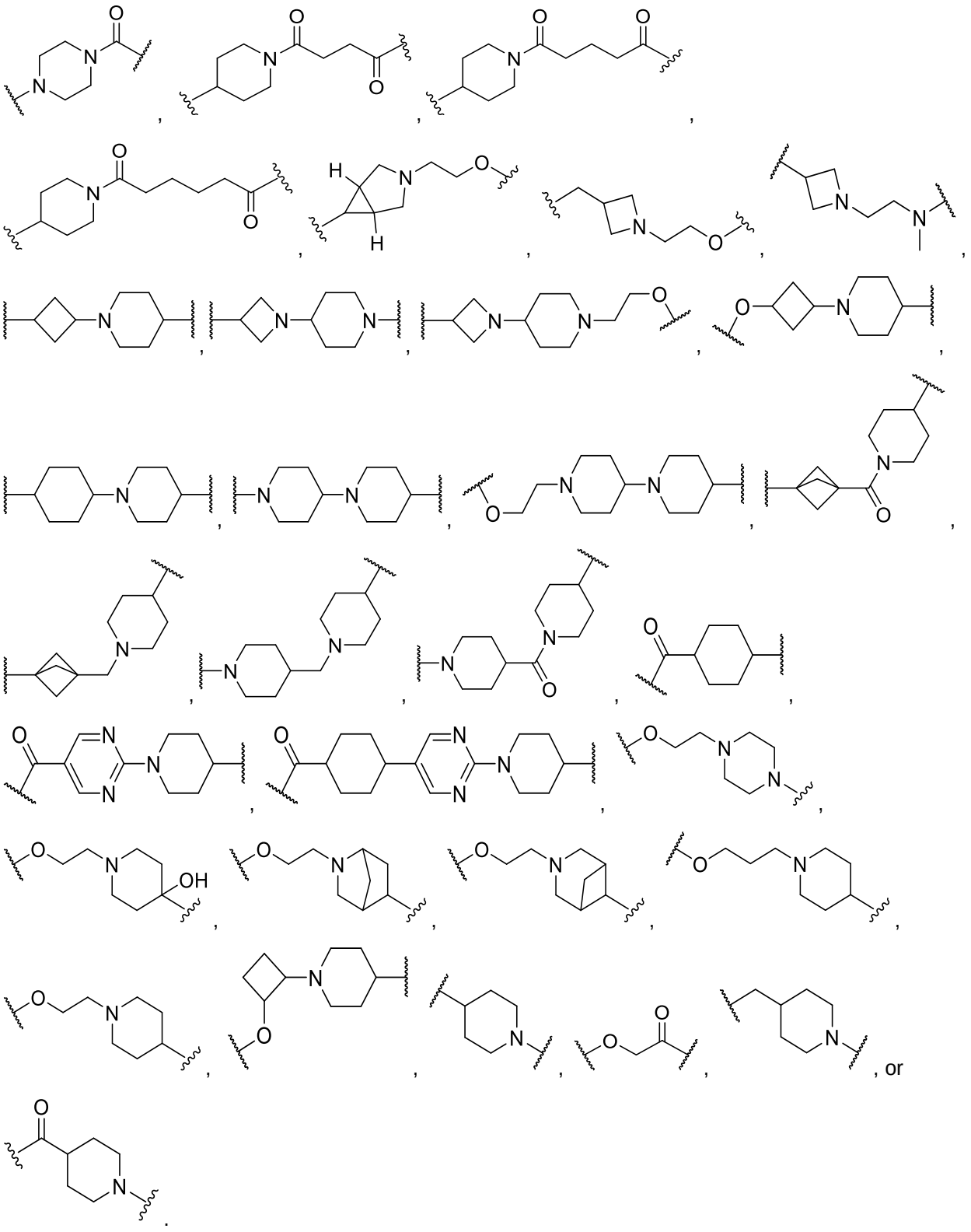
56. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein k is 1.

57. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein the linker has the structure of

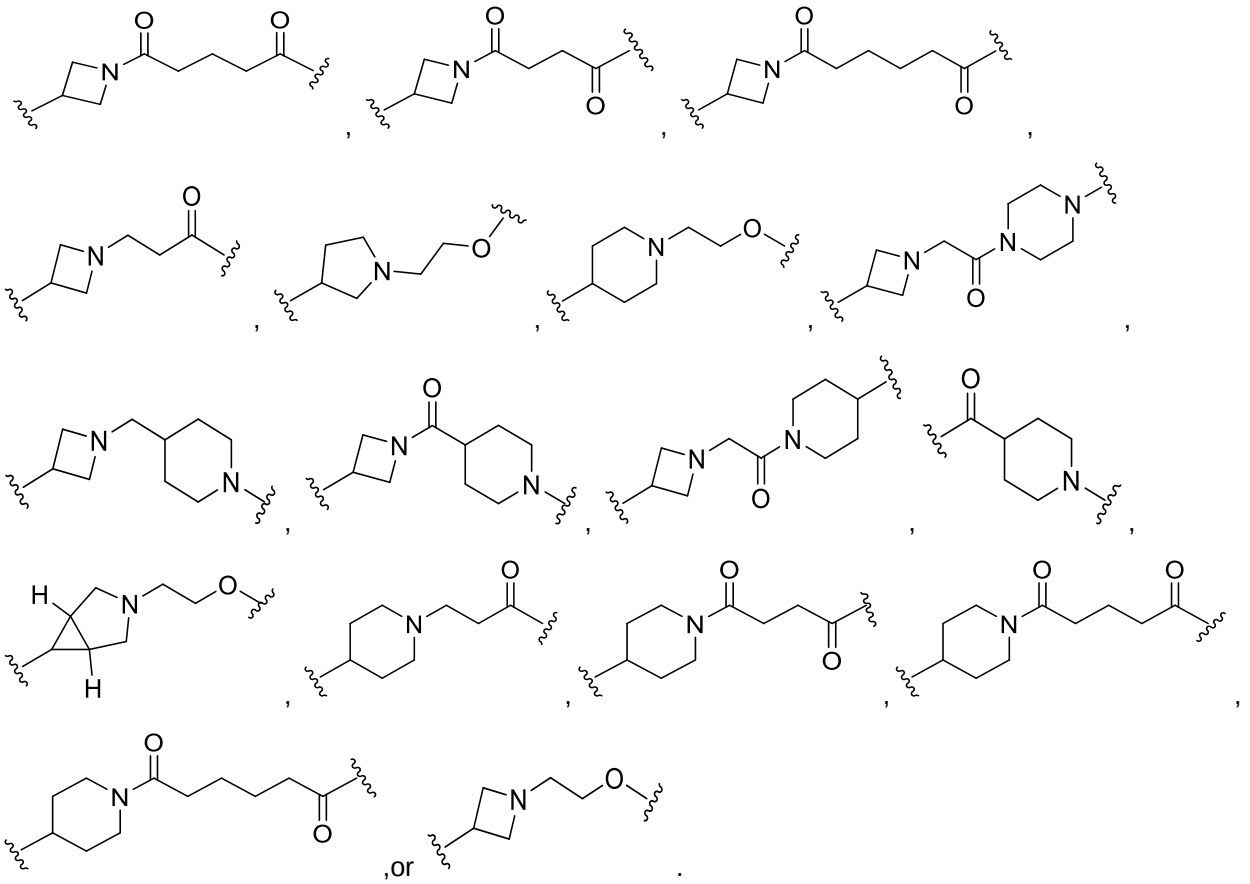



































58. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein the linker has the structure of



59. A pharmaceutical composition comprising a compound of claim 1, and a pharmaceutically acceptable excipient.

60. Use of a compound of claim 1 in the manufacture of a medicament for treating cancer in a subject in need thereof.

61. The use of claim 60, wherein the cancer is non-small cell lung cancer, colorectal cancer, bladder cancer, cancer of unknown primary, glioma, breast cancer, melanoma, non-melanoma skin cancer, endometrial cancer, esophagogastric cancer, pancreatic cancer, hepatobiliary cancer, soft tissue sarcoma, ovarian cancer, head and neck cancer, renal cell carcinoma, bone cancer, non-Hodgkin lymphoma, small-cell lung cancer, prostate cancer, embryonal tumor, germ cell tumor, cervical cancer, thyroid cancer, salivary gland cancer, gastrointestinal neuroendocrine tumor, uterine sarcoma, gastrointestinal stromal tumor, CNS cancer, thymic tumor, Adrenocortical carcinoma, appendiceal cancer, small bowel cancer, or penile cancer.

62. The use of claim 60, wherein the cancer is non-small cell lung cancer, colorectal cancer, bladder cancer, cancer of unknown primary, glioma, breast cancer, melanoma, non-melanoma skin cancer, endometrial cancer, or penile cancer.

63. The use of claim 60, wherein the cancer is non-small cell lung cancer.

64. The use of claim 60, wherein the cancer is soft tissue sarcoma.

65. Use of a compound of claim 1 in the manufacture of a medicament for treating a cancer selected from the group consisting of melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, and a hematologic cancer in a subject in need thereof.

66. The use of claim 65, wherein the medicament is to be administered to the subject, and wherein an anticancer therapy is to be further administered to the subject, or to be contacted with a cell.

67. A compound of claim 1 for use in therapy.