PATENT COOPERATION TREATY

From the RECEIVING OFFICE

PCT

To:

MICHAEL J. BELLIVEAU
CLARK & ELBING LLP
101 FEDERAL STREET
15TH FLOOR
BOSTON, MASSACHUSETTS 02110

Confirmation No: 1031

NOTIFICATION OF THE INTERNATIONAL APPLICATION NUMBER AND OF THE INTERNATIONAL FILING DATE

(PCT Rule 20.2(c))

Date of mailing *(day/month/year)*	26 Feb 2020
Applicant's or agent's file reference: 51121-027WO3	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2020/015746	29 Jan 2020	29 Jan 2019

Applicant: FOGHORN THERAPEUTICS INC.

Title of the invention: COMPOUNDS AND USES THEREOF

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.

2. The applicant is further notified that the record copy of the international application:

☒ was transmitted to the International Bureau on 26 Feb 2020 .

☐ has not yet been transmitted to the International Bureau for the reason indicated below and a copy of this notification has been sent to the International Bureau*:

☐ because the necessary national security clearance has not yet been obtained.

☐ because *(reason to be specified)*:

* The International Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(c)).

3. FOREIGN TRANSMITTAL LICENSE INFORMATION Completed by: MF

☐ Additional license for foreign transmittal not required. This subject matter is covered by a license already granted or the equivalent U.S. national application. Refer to that license for information concerning its scope.

☐ License for foreign transmittal not required. 37 CFR. 5.11(e)(1) or 37 CFR 5.11(e)(2). However, a license may be required for additional subject matter. See 37 CFR 5.15(b).

☒ Foreign transmittal license granted. 35 U.S.C. 184; 37 CFR 5.11 on 25 Feb 2020 (date) :

☐ 37 CFR 5.15(a) ☒ 37 CFR 5.15(b)

Name and mailing address of the receiving Office	Authorized officer
Mail Stop PCT, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450	Michael Fletcher
Facsimile No. 571-273-8300	Telephone No. 571-272-9069

Form PCT/RO/105 (July 2008)

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/US20/15746
International Application No.

29 January 2020 (29.01.2020)
International Filing Date

PCT INTERNATIONAL APPLICATION
RO/US
Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (25 characters maximum)*
51121-027WO3

Box No. I TITLE OF INVENTION

COMPOUNDS AND USES THEREOF

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

FOGHORN THERAPEUTICS INC.
100 Binney Street
Suite 610
Cambridge, MA 02142
United States of America

Telephone No.

Facsimile No.

Applicant's registration No. with the Office

E-mail authorization: Marking one of the check-boxes below authorizes the receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority to use the e-mail address indicated in this Box to send, notifications issued in respect of this international application to that e-mail address if those offices are willing to do so.

☐ as advance copies followed by paper notifications; or ☐ exclusively in electronic form (no paper notifications will be sent).

E-mail address:

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

This person is applicant for the purposes of: ☒ all designated States ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BELLIVEAU, Michael J.
Clark & Elbing LLP
101 Federal Street
15th Floor
Boston, MA 02110
United States of America

Telephone No.
(617) 428-0200

Facsimile No.
(617) 428-7045

Agent's registration No. with the Office
52,608

E-mail authorization: Marking one of the check-boxes below authorizes the receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority to use the e-mail address indicated in this Box to send, notifications issued in respect of this international application to that e-mail address if those offices are willing to do so.

☐ as advance copies followed by paper notifications; or ☒ exclusively in electronic form (no paper notifications will be sent).

E-mail address: patentadmin@clarkelbing.com

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

RUPPEL, Sabine K.
c/o Foghorn Therapeutics Inc.
100 Binney Street, Suite 610
Cambridge, MA 02142
United States of America

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [X] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

YANG, Zhaoxia
c/o Foghorn Therapeutics Inc.
100 Binney Street, Suite 610
Cambridge, MA 02142
United States of America

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [X] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

LOWE, Jason T.
c/o Foghorn Therapeutics Inc.
100 Binney Street, Suite 610
Cambridge, MA 02142
United States of America

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [X] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

VOIGT, Johannes H.
c/o Foghorn Therapeutics Inc.
100 Binney Street, Suite 610
Cambridge, MA 02142
United States of America

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [X] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] the States indicated in the Supplemental Box

[X] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

NETHERTON, Matthew
c/o Foghorn Therapeutics Inc.
100 Binney Street, Suite 610
Cambridge, MA 02142
United States of America

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [x] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] the States indicated in the Supplemental Box

- [ ] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATIONS

The filing of this request **constitutes under Rule 4.9(a) the designation** of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.

However,

☐ DE Germany **is not designated** for any kind of national protection

☐ JP Japan **is not designated** for any kind of national protection

☐ KR Republic of Korea **is not designated** for any kind of national protection

(The check-boxes above may only be used to exclude (irrevocably) the designations concerned if, at the time of filing or subsequently under Rule 26bis.1, the international application contains in Box No. VI a priority claim to an earlier national application filed in the particular State concerned, in order to avoid the ceasing of the effect, under the national law, of this earlier national application.)

Box No. VI PRIORITY CLAIM AND DOCUMENT

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application: regional Office	international application: receiving Office
item (1) 29 January 2019 (29.01.2019)	62/798,374	US		
item (2) 31 July 2019 (31.07.2019)	62/881,195	US		
item (3)				

☐ Further priority claims are indicated in the Supplemental Box.

Furnishing the priority document(s):

☒ The **receiving Office** is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application(s) was filed with the receiving Office which, for the purposes of this international application, is the receiving Office)* identified above as:

☒ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ other, see Supplemental Box

☐ The **International Bureau** is requested to obtain from a digital library a certified copy of the earlier application(s) identified above, using, where applicable, the access code(s) indicated below *(if the earlier application(s) is available to it from a digital library)*:

☐ item (1) access code _____ ☐ item (2) access code _____ ☐ item (3) access code _____ ☐ other, see Supplemental Box

Restore the right of priority: the receiving Office is requested to restore the right of priority for the earlier application(s) identified above or in the Supplemental Box as item(s) (_____). *(See also the Notes to Box No. VI; information **must** be provided to support a request to restore the right of priority.)*

Incorporation by reference: where an element of the international application referred to in Article 11(1)(iii)(d) or (e) or a part of the description, claims or drawings referred to in Rule 20.5(a) is not otherwise contained in this international application but is completely contained in an earlier application whose priority is claimed on the date on which one or more elements referred to in Article 11(1)(iii) were first received by the receiving Office, that element or part is, subject to confirmation under Rule 20.6, incorporated by reference in this international application for the purposes of Rule 20.6.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if more than one International Searching Authority is competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*:

ISA / US

Box No. IX CHECK LIST for EFS-Web filings - this sheet is only to be used when filing an international application with RO/US via **EFS-Web**

This international application **contains** the following:	Number of sheets
(a) request form PCT/RO/101 (including any declarations and supplemental sheets)	5
(b) description (excluding any sequence listing part of the description, see (f), below)	419
(c) claims	74
(d) abstract	1
(e) drawings (if any)	14
(f) sequence listing part of the description in the form of an **image file** (e.g. PDF)	
Total number of sheets (including the sequence listing part of the description if **filed as an image file**)	513

(g) sequence listing part of the description

- ☐ filed in the form of an **Annex C/ST.25 text file**
- ☐ WILL BE filed separately on physical data carrier(s), on the same day and in the form of an **Annex C/ST.25 text file**

Indicate type and number of physical data carrier(s) .....

This international application is **accompanied by** the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item):*	Number of items
1. ☒ fee calculation sheet	1
2. ☐ original separate power of attorney	
3. ☐ original general power of attorney	
4. ☐ copy of general power of attorney; reference number:	
5. ☐ priority document(s) identified in Box No. VI as item(s)	
6. ☐ Translation of international application into *(language)*:	
7. ☐ separate indications concerning deposited microorganism or other biological material	
8. ☐ *(only where item (f) is marked in the left column)* copy of the sequence listing in electronic form (Annex C/ST.25 text file) not forming part of the international application but **furnished only for the purposes of international search** under Rule 13*ter*	
9. ☐ *(only where item (f) (in the left column) and item 8 (above) are marked)* a statement confirming that "the information recorded in electronic form submitted under Rule 13*ter* is identical to the sequence listing as contained in the international application" as filed via EFS-Web:	
10. ☐ copy of results of earlier search(es) (Rule 12*bis*.1(a))	
11. ☐ other *(specify)*:	

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

/Michael J. Belliveau, Ph.D./
Michael J. Belliveau, Ph.D., Agent for Applicant(s)
CLARK & ELBING LLP

Attorney Reg. No. (when applicable): 52,608

For receiving Office use only

1. Date of actual receipt of the purported international application: 29 January 2020 (29.01.2020)	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA / US	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PTO-1382 (Rev. 01-2017)
Approved for use through 08/31/2019. OMB 0651-0021
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL LETTER TO THE UNITED STATES RECEIVING OFFICE (RO/US)

Priority Mail Express Mailing Label No.:	Date of Deposit:
File Reference No.: 51121-027WO3	International Application No. (If known): Not Yet Assigned
Customer Number[1]: 21559	Earliest Priority Date Claimed (dd/mm/yyyy): 29/01/2019
Title of Invention: COMPOUNDS AND USES THEREOF	
Applicant: Foghorn Therapeutics Inc.	

[1]Customer Number will allow access to the application in Private PAIR but cannot be used to establish or change the correspondence address.

[X] This is a new International Application

SCREENING DISCLOSURE INFORMATION:

In order to assist in screening the accompanying international application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied. (check all boxes as apply):

[ ] The invention disclosed was **not** made in the United States of America.

[ ] There is no prior U.S. application relating to this invention.

[X] The following prior U.S. application(s) contain subject matter which is related to the invention disclosed in the attached international application. *(NOTE: priority to these applications may or may not be claimed on the Request (form PCT/RO/101) and this listing does not constitute a claim for priority.)*

application no.	62/881,195	filed on	31 July 2019
application no.	62/798,374	filed on	29 January 2019

[X] The present international application contains additional subject matter not found in the prior U.S. application(s) identified above.

The additional subject matter is found on pages throughout

and [X] DOES NOT ALTER [ ] MIGHT BE CONSIDERED TO ALTER the general nature of the invention in a manner which would require the U.S. application to have been made available for inspection by the appropriate defense agencies under 35 U.S.C. 181 and 37C.F.R. 5.15.

Itemized list of contents & entity status

Sheets of Request form: 5	Check no.:
Sheets of description (excluding sequence listing): 419	Return receipt postcard:
Sheets of claims: 74	Power of attorney:
Sheets of abstract: 1	Certified copy of priority document (specify): See Box VI
Sheets of drawings: 14	PTO/SB15A or B or equivalent:
Sheets (paper or pdf) of sequence listing:	Other (specify): PCT Fee Calculation Sheet
Sequence listing text file: [ ] CD or diskette [ ] via EFS-Web	

[X] Applicant asserts small entity status. See 37 CFR 1.27. If this written assertion is made by the applicant, all applicants must sign (37 C.F.R. §1.42)

[ ] Applicant certifies micro entity status. See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.

The person signing this form is:	[ ] Applicant	Michael J. Belliveau, Ph.D. Name of person signing
	[X] Attorney/Agent Registration No. 52,608	/Michael J. Belliveau, Ph.D./ Signature
	[ ] Common Representative	

COMPOUNDS AND USES THEREOF

Background

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

Summary

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

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

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

A-L-B

Formula I,

where

A is a BRD9 binding moiety;

B is a degradation moiety; and

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

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

Formula II

where

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

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

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

each of E^1 and E^2 is, independently, O, S, NR^N, optionally substituted $C_{1–10}$ alkylene, optionally substituted $C_{2–10}$ alkenylene, optionally substituted $C_{2–10}$ alkynylene, optionally substituted C_2-C_{10} polyethylene glycol, or optionally substituted $C_{1–10}$ heteroalkylene;

E^3 is optionally substituted C_1-C_6 alkylene, optionally substituted C_1-C_6 heteroalkylene, O, S, or NR^N;

C4 Therapeutics, Inc.
Exhibit 1005 Page 8 of 515

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

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

each of F^1, F^2, and F^3 is, independently, optionally substituted C_3-C_{10} carbocyclylene, optionally substituted C_{2-10} heterocyclylene, optionally substituted C_6-C_{10} arylene, or optionally substituted C_2-C_9 heteroarylene,

or a pharmaceutically acceptable salt thereof.

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

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

Formula IIa

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

$$A^1–(E^1)–(F^1)–(E^2)_p–A^2.$$

Formula IIb

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

$$A^1–(E^1)–(F^1)–A^2.$$

Formula IIc

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

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

Formula IId

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

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

Formula IIe

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

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

FormulaIIf

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

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

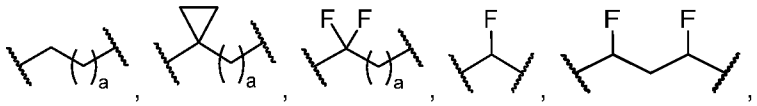
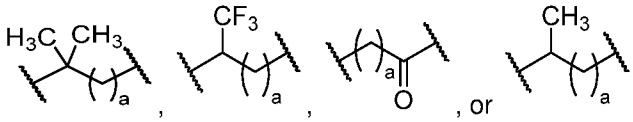
Formula IIg

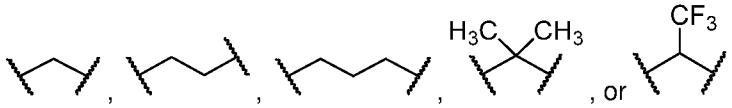
In some embodiments, each of E^1 and E^2 is, independently, NR^N, optionally substituted C_{1-10} alkylene, optionally substituted C_2-C_{10} polyethylene glycolene, or optionally substituted C_{1-10} heteroalkylene.

In some embodiments, E^3 is optionally substituted C_1-C_6 alkylene, O, S, or NR^N;

In some embodiments, E^3 is optionally substituted C_1-C_6 alkylene. In some embodiments, E^3 is optionally substituted C_1-C_3 alkylene. In some embodiments, E^3 is O, S, or NR^N.

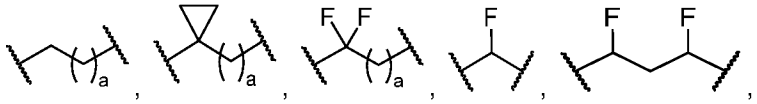
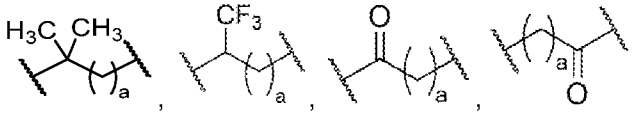
In some embodiments, E^3 is C_1-C_6 alkylene. In some embodiments, E^3 is C_1-C_3 alkylene. In some embodiments, E^3 is O.

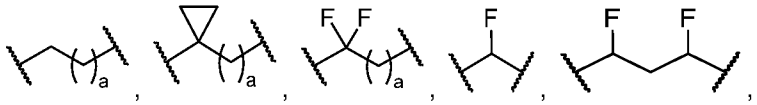
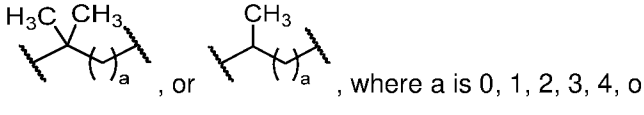
In some embodiments, E^3 is  ,  , or , where a is 0, 1, 2, 3, 4, or 5.

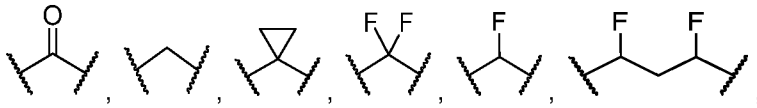
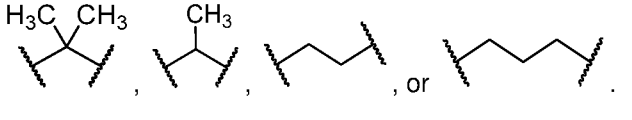
In some embodiments, E^3 is  .

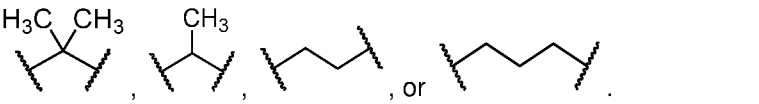
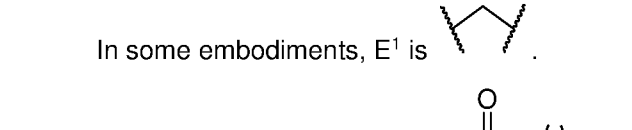
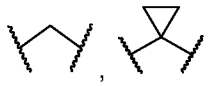
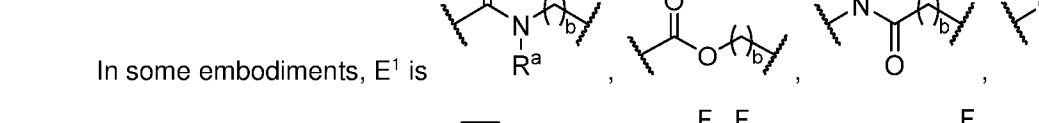
In some embodiments, each R^N is, independently, H or optionally substituted C_{1-4} alkyl.

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

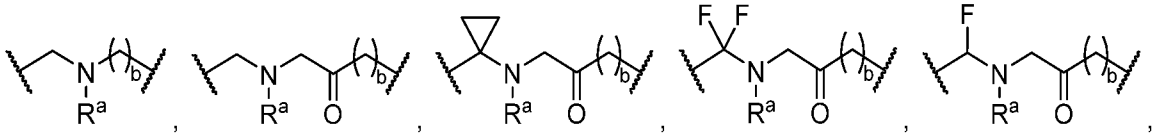
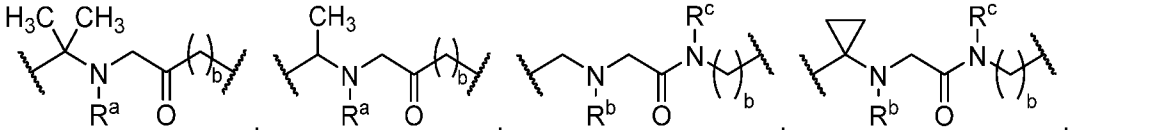
In some embodiments, E^1 is  ,  , or , where a is 0, 1, 2, 3, 4, or 5.

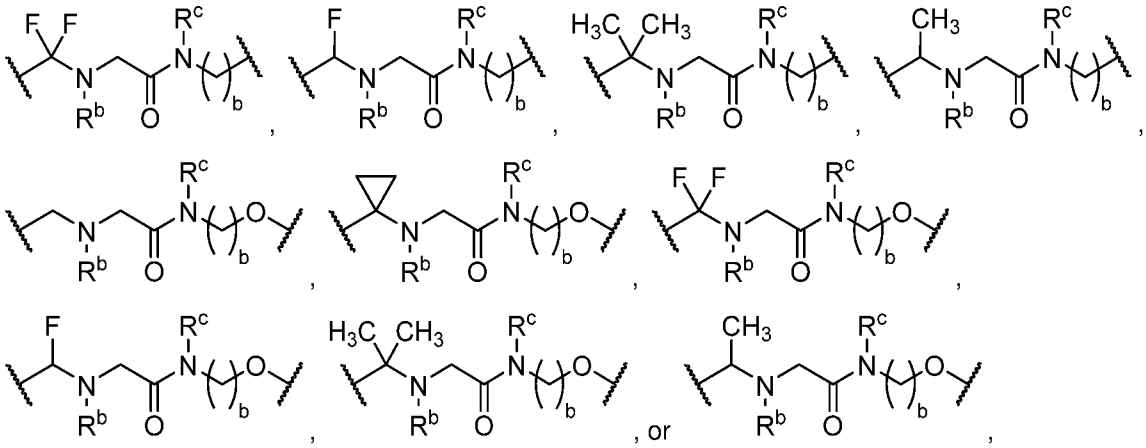
In some embodiments, E^1 is  ,  , or , where a is 0, 1, 2, 3, 4, or 5.

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

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

In some embodiments, E^1 is .

In some embodiments, E^1 is ,  ,  .



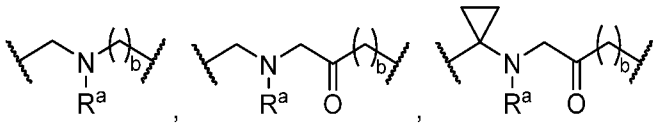
where

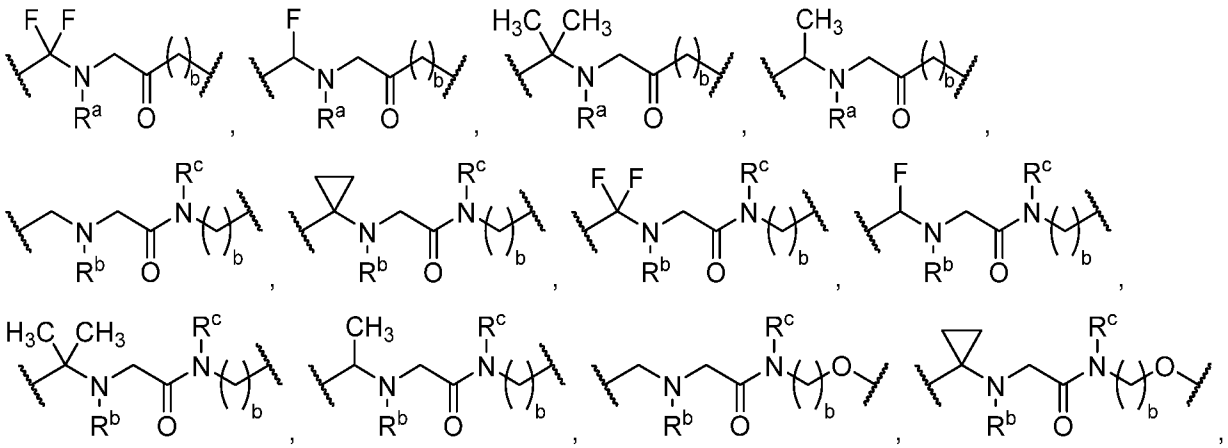
b is 0, 1, 2, 3, 4, 5, or 6;

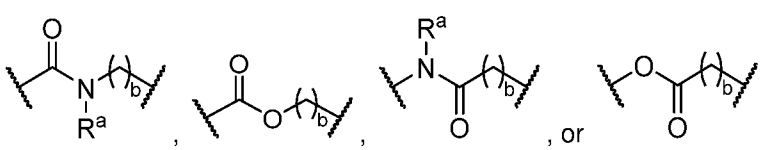
R^a is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_6 carbocyclyl;

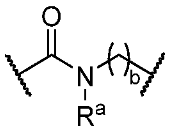
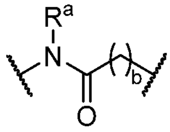
R^b is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_6 carbocyclyl; and

R^c is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_6 carbocyclyl.

In some embodiments, E^1 is 



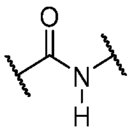
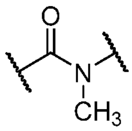
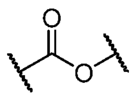
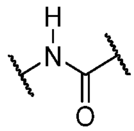
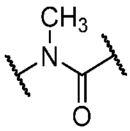
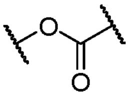
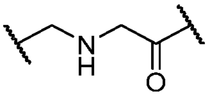
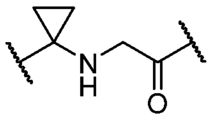
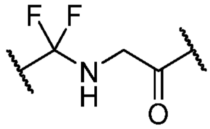
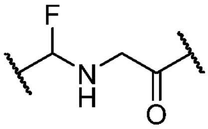
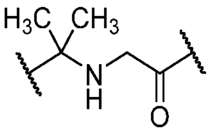
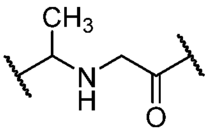
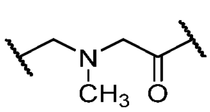
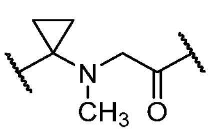
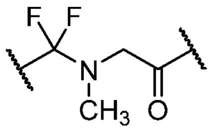
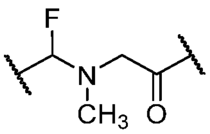
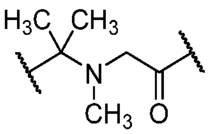
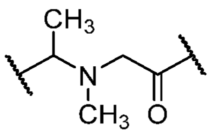
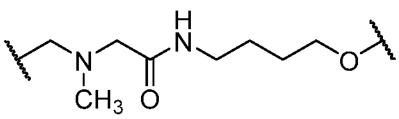
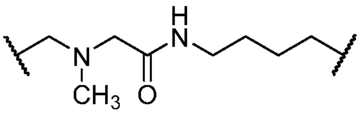
In some embodiments, E^1 is 

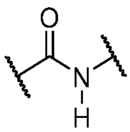
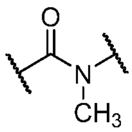
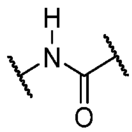
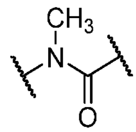
In some embodiments, E^1 is  or  .

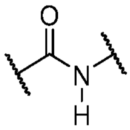
In some embodiments, R^a is H or optionally substituted C_1-C_6 alkyl. In some embodiments, R^b is H or optionally substituted C_1-C_6 alkyl. In some embodiments, R^c is H or optionally substituted C_1-C_6 alkyl.

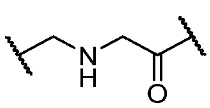
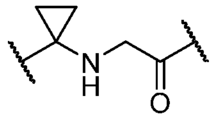
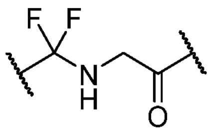
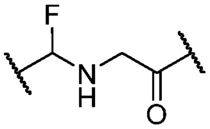
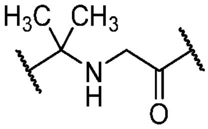
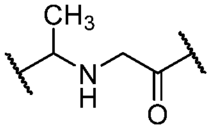
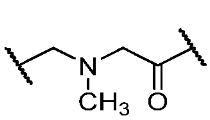
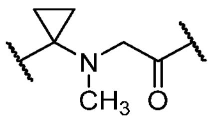
In some embodiments, R^a is H or methyl. In some embodiments, R^b is H or methyl. In some embodiments, R^c is H or methyl.

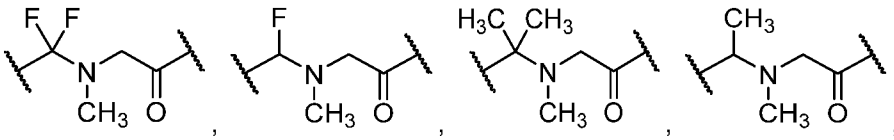
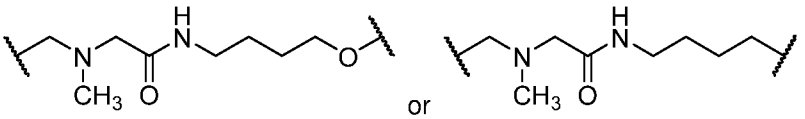
In some embodiments, b is 0, 1, 2, or 3. In some embodiments, b is 0. In some embodiments, b is 1. In some embodiments, b is 2. In some embodiments, b is 3.

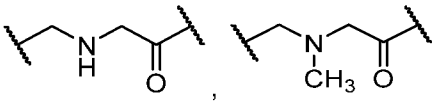
In some embodiments, E^1 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

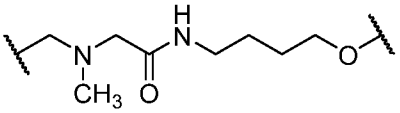
In some embodiments, E^1 is  ,  ,  , or  .

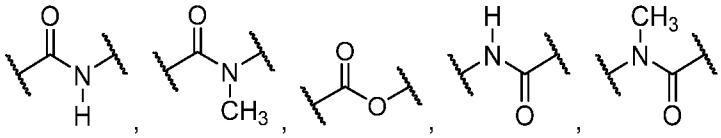
In some embodiments, E^1 is  .

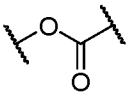
In some embodiments, E^1 is  ,  ,  ,  ,  ,  ,  ,  ,

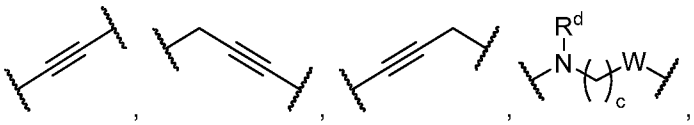



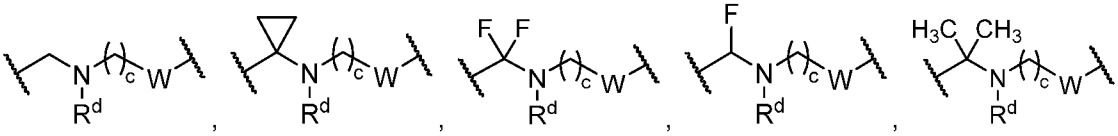
In some embodiments, E^1 is 

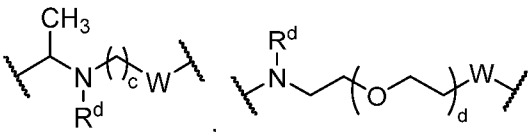


In some embodiments, E^1 is 



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





wherein

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

d is 0, 1, 2, or 3;

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

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

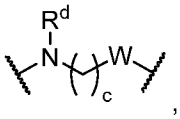
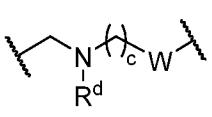
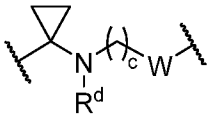
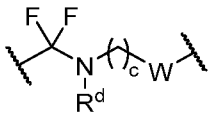
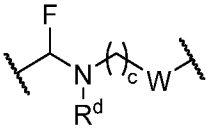
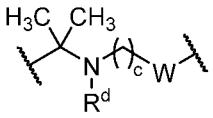
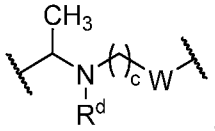
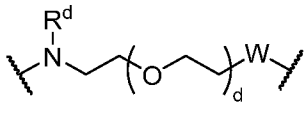
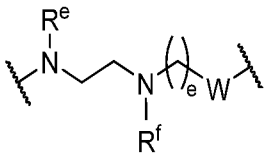
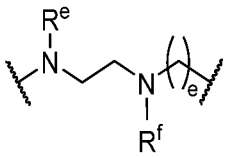
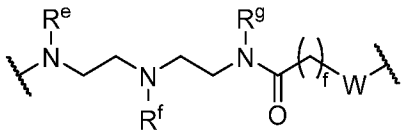
R^d is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_6 carbocyclyl;

R^e is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_6 carbocyclyl;

R^f is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_6 carbocyclyl;

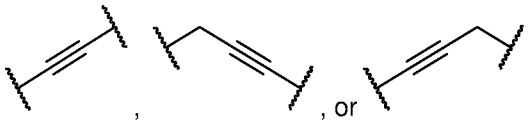
R^g is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_6 carbocyclyl; and

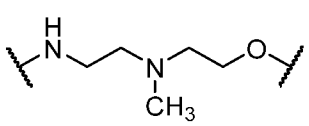
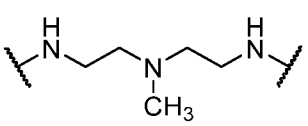
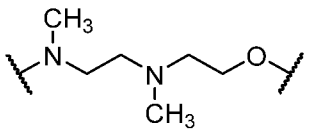
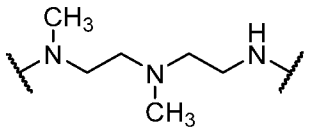
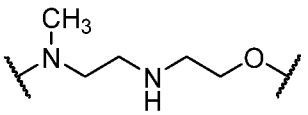
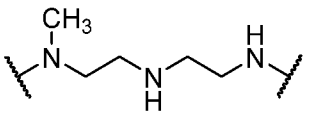
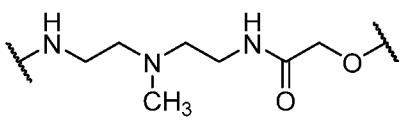
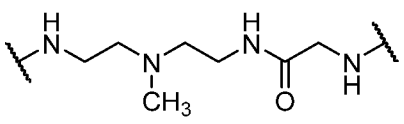
W is O or NR^w, wherein R^w is H or optionally substituted C_1-C_6 alkyl.

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

In some embodiments, R^d is H or optionally substituted C_1-C_6 alkyl. In some embodiments, R^e is H or optionally substituted C_1-C_6 alkyl. In some embodiments, R^f is H or optionally substituted C_1-C_6 alkyl. In some embodiments, R^g is H or optionally substituted C_1-C_6 alkyl. In some embodiments, R^w is H or optionally substituted C_1-C_6 alkyl.

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

In some embodiments, E^2 is  .

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

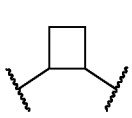
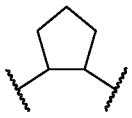
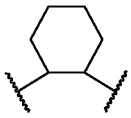
In some embodiments, each of F^1, F^2, or F^3 is, independently, optionally substituted C_3-C_{10} carbocyclylene.

C4 Therapeutics, Inc.
Exhibit 1005 Page 14 of 515

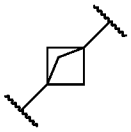
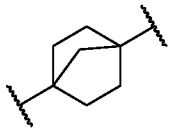
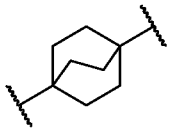
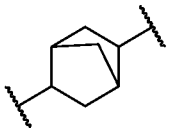
In some embodiments, the C_3-C_{10} carbocyclylene is monocyclic. In some embodiments, the C_3-C_{10} carbocyclylene is polycyclic.

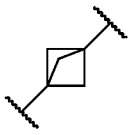
In some embodiments, the C_3-C_{10} carbocyclylene is bicyclic.

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

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

In some embodiments, F^2 is  .

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

In some embodiments, F^1 is  .

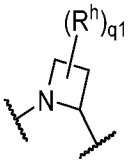
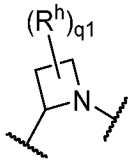
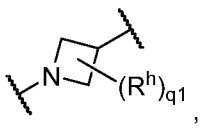
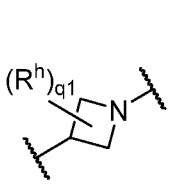
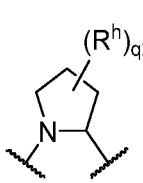
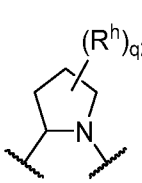
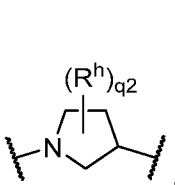
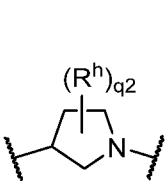
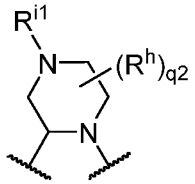
In some embodiments, each of F^1, F^2, or F^3 is, independently, optionally substituted C_2-C_9 heterocyclylene.

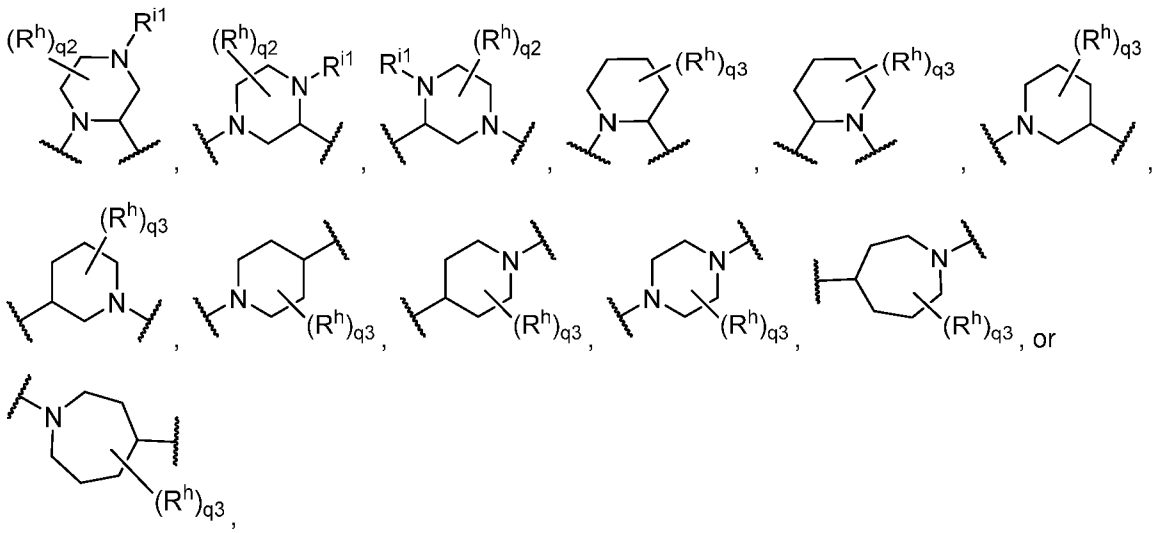
In some embodiments, the C_2-C_9 heterocyclylene is monocyclic. In some embodiments, the C_2-C_9 heterocyclylene is polycyclic.

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

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

In some embodiments, the C_2-C_9 heterocyclylene includes a quaternary amine.

In some embodiments, the C_2-C_9 heterocyclylene is  ,  ,  ,  ,  ,  ,  ,  ,  .



where

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

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

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

each R^h is, independently, ^2H, halogen, optionally substituted C_1-C_6 alkyl, OR^{i2}, or $NR^{i3}R^{i4}$; or two R^h groups, together with the carbon atom to which each is attached, combine to form optionally substituted C_3-C_{10} carbocyclyl or optionally substituted C_2-C_9 heterocyclyl; or two R^h groups, together with the carbon atoms to which each is attached, combine to form optionally substituted C_3-C_{10} carbocyclyl or optionally substituted C_2-C_9 heterocyclyl;

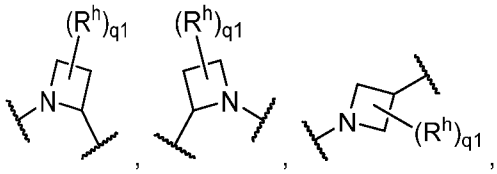
R^{i1} is H or optionally substituted C_1-C_6 alkyl;

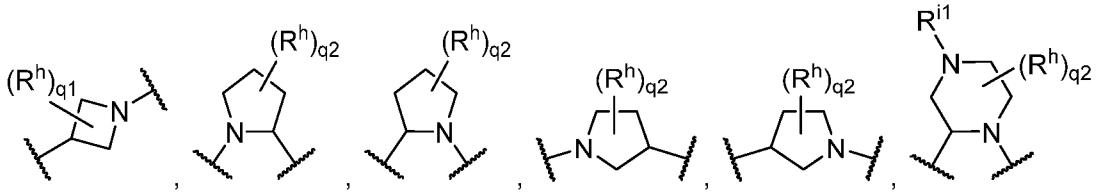
R^{i2} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_6 carbocyclyl;

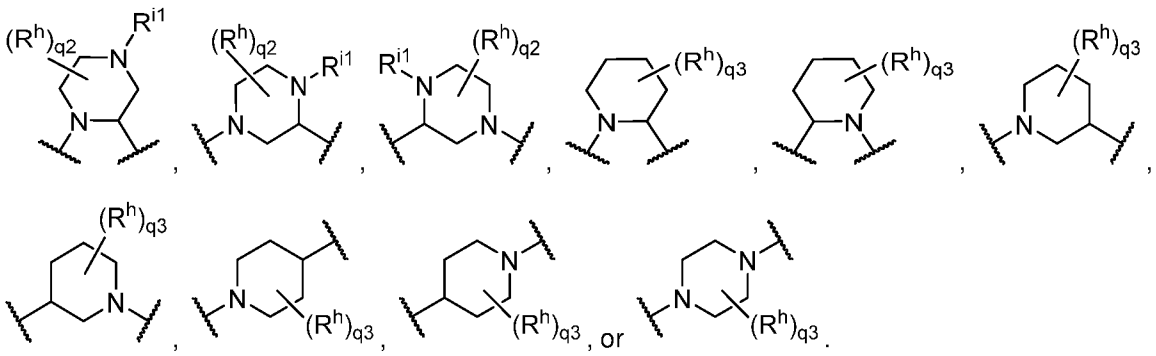
R^{i3} is H or optionally substituted C_1-C_6 alkyl; and

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

In some embodiments, each R^h is, independently, halogen, optionally substituted C_1-C_6 alkyl, OR^{i2}, or $NR^{i3}R^{i4}$. In some embodiments, R^{i1} is H or optionally substituted C_1-C_6 alkyl. In some embodiments, R^{i2} is H or optionally substituted C_1-C_6 alkyl. In some embodiments, R^{i3} is H or optionally substituted C_1-C_6 alkyl. In some embodiments, R^{i4} is H or optionally substituted C_1-C_6 alkyl.

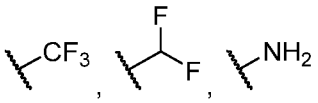
In some embodiments, the C_2-C_9 heterocyclylene is 

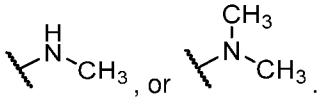




In some embodiments, each R^h is, independently, halogen, optionally substituted C_1-C_6 alkyl, OR^{i2}, or $NR^{i3}R^{i4}$. In some embodiments, each R^h is, independently, halogen, optionally substituted C_1-C_6 alkyl, or $NR^{i3}R^{i4}$.

In some embodiments, each R^h is, independently, ^2H, halogen, cyano, optionally substituted C_1-C_6 alkyl, OR^{i2}, or $NR^{i3}R^{i4}$. In some embodiments, two R^h groups, together with the carbon atom to which each is attached, combine to form optionally substituted C_3-C_{10} carbocyclyl or optionally substituted C_2-C_9 heterocyclyl. In some embodiments, two R^h groups, together with the carbon atoms to which each is attached, combine to form optionally substituted C_3-C_{10} carbocyclyl or optionally substituted C_2-C_9 heterocyclyl.

In some embodiments, each R^h is, independently, ^2H, F, methyl, 

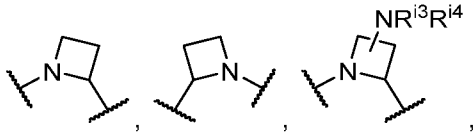


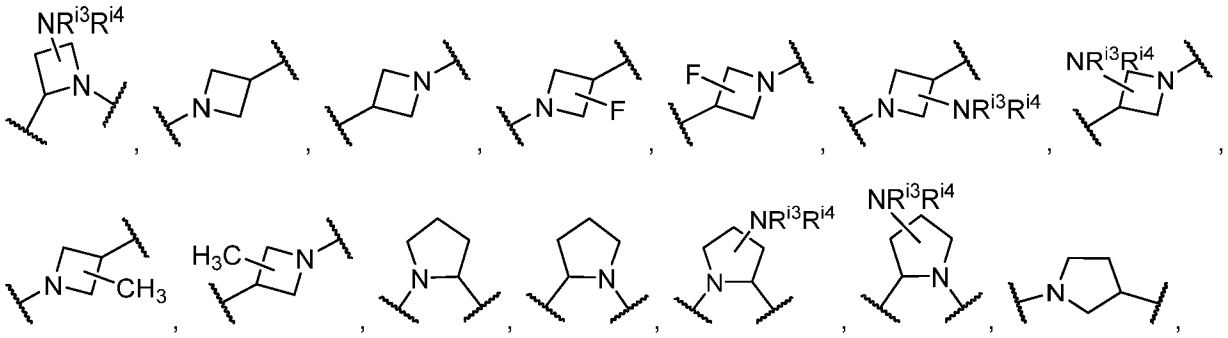
In some embodiments, each R^h is, independently, F, methyl, or $NR^{i3}R^{i4}$.

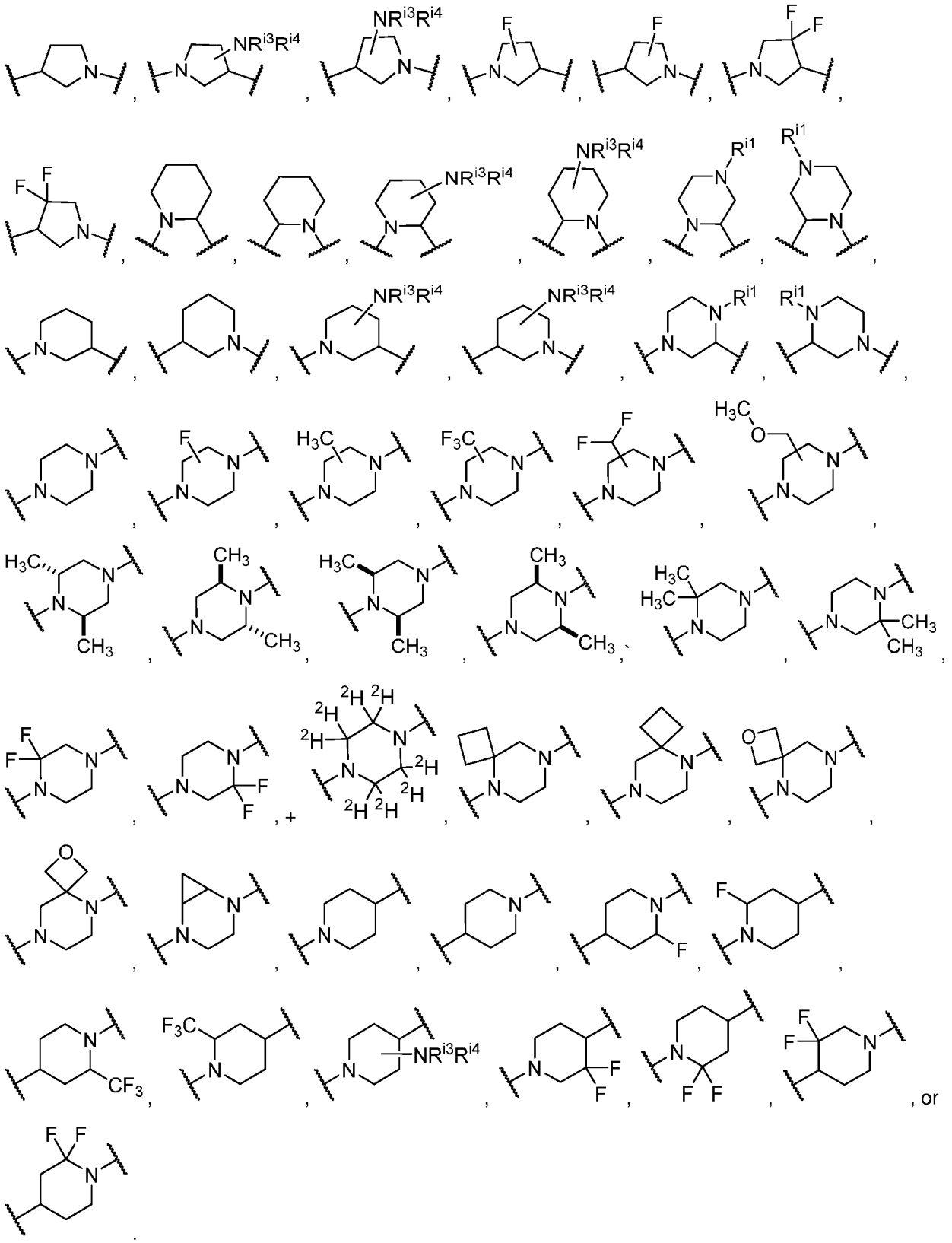
In some embodiments, q1 is 0, 1, or 2. In some embodiments, q1 is 0. In some embodiments, q1 is 1. In some embodiments, q1 is 2.

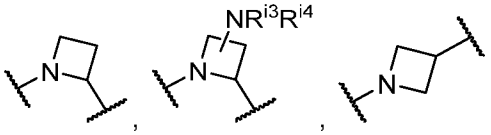
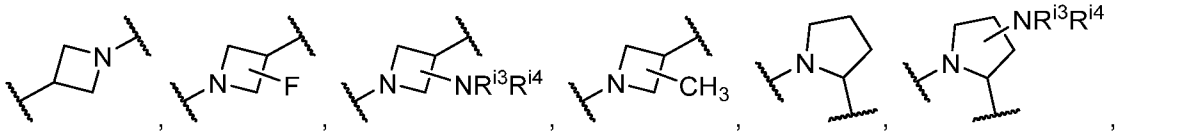
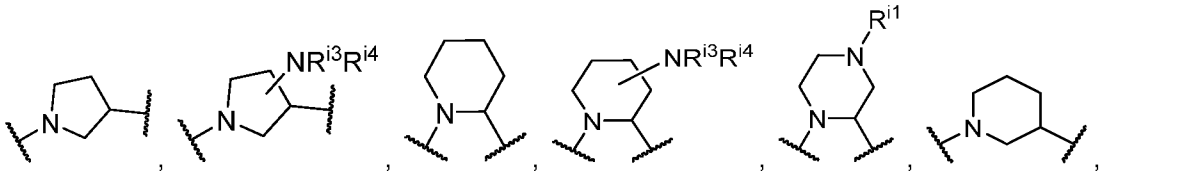
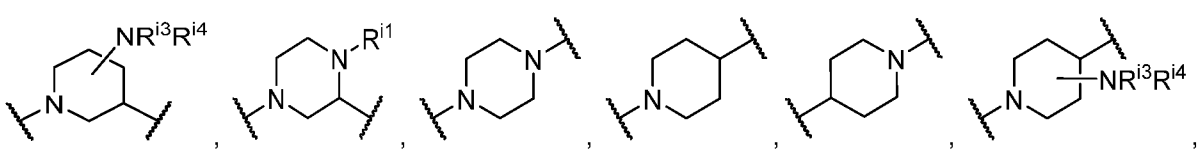
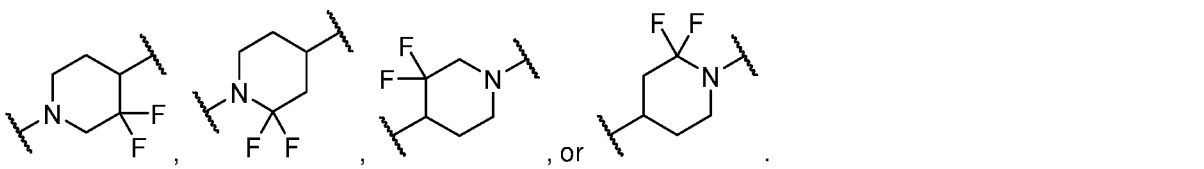
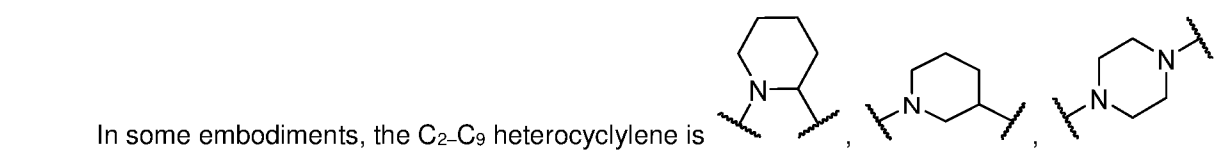
In some embodiments, q2 is 0, 1, or 2. In some embodiments, q2 is 0. In some embodiments, q2 is 1. In some embodiments, q2 is 2.

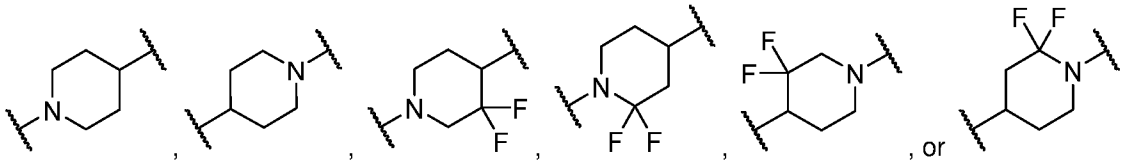
In some embodiments, q3 is 0, 1, or 2. In some embodiments, q3 is 0. In some embodiments, q3 is 1. In some embodiments, q3 is 2.

In some embodiments, the C_2-C_9 heterocyclylene is 

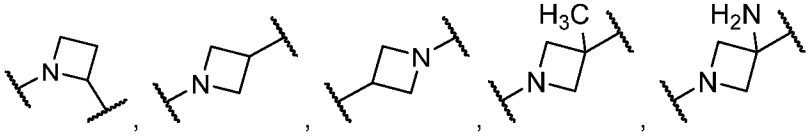
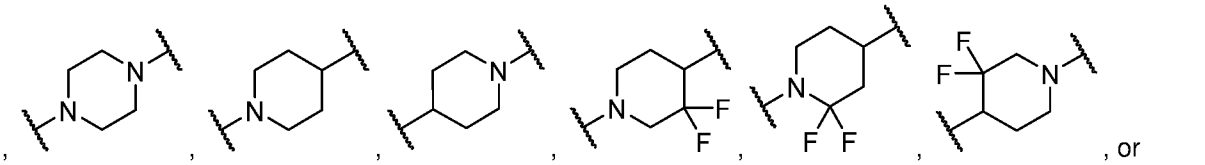
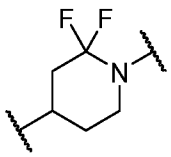


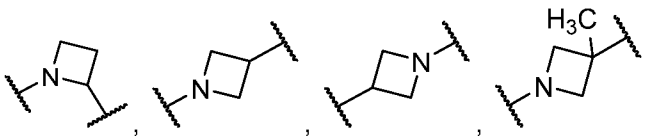
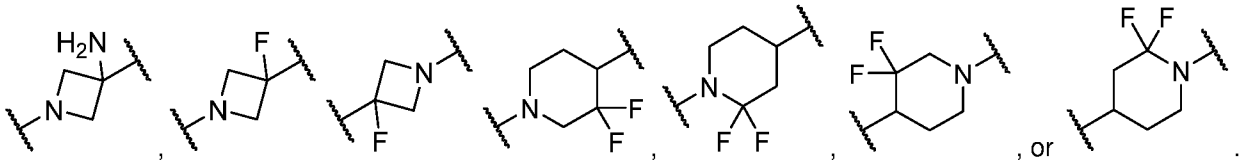


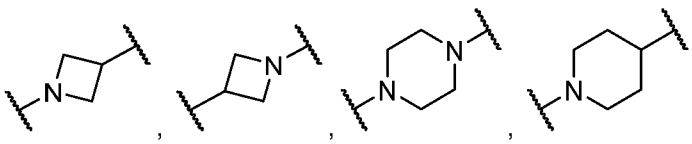
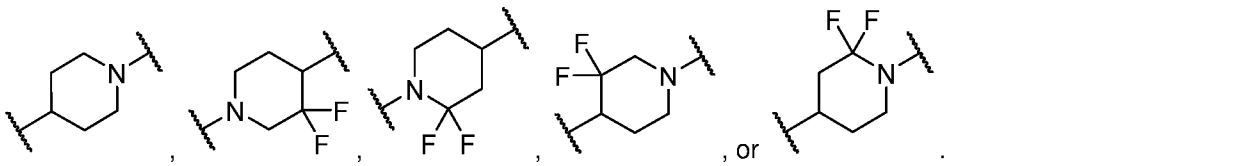
In some embodiments, the C_{2-9} heterocyclylene is  ,  ,  ,  ,  ,  , or .

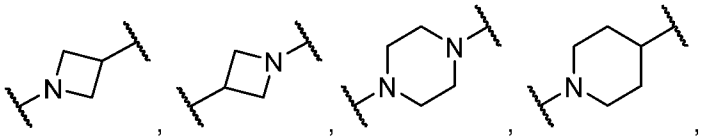
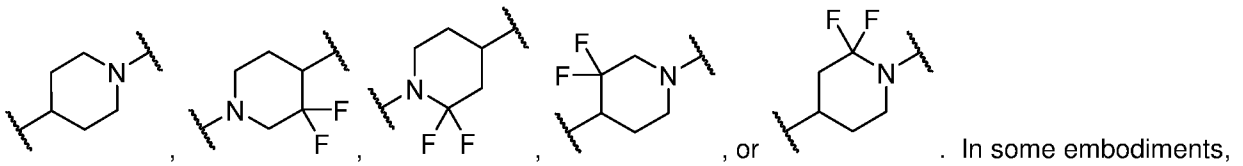
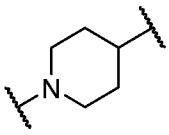
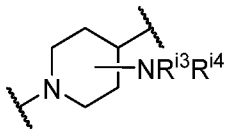
In some embodiments, the C_{2-9} heterocyclylene is ,  , or .

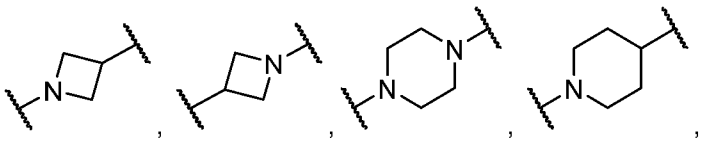
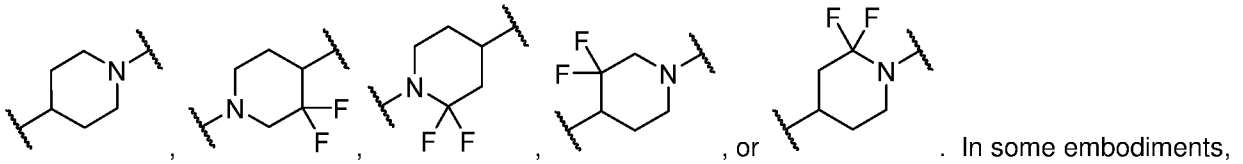
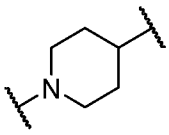
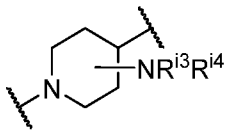
In some embodiments, the C_{2-9} heterocyclylene is  .

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

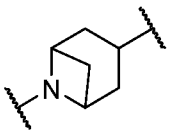
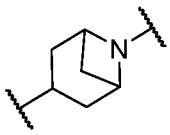
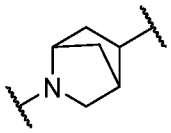
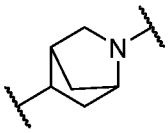
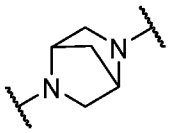
In some embodiments, F^1 is  ,  , or .

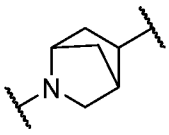
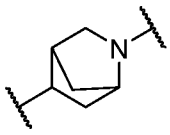
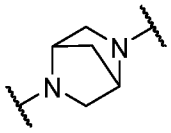
In some embodiments, F^1 is  ,  , or .

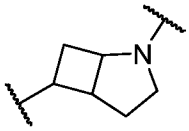
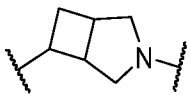
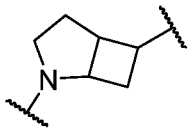
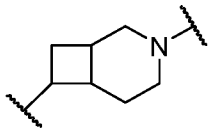
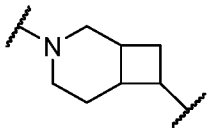
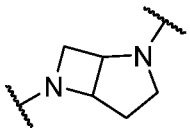
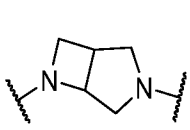
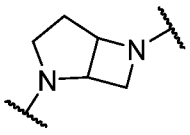
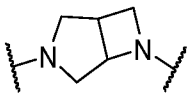
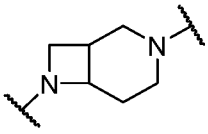
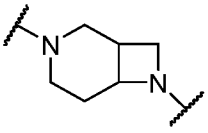
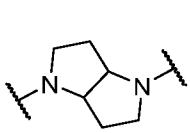
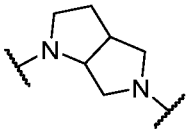
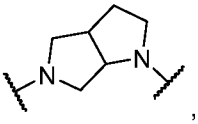
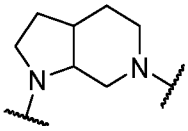
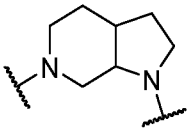
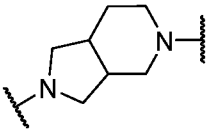
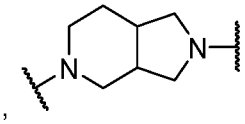
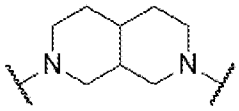
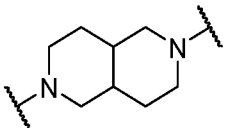
In some embodiments, F^2 is  ,  , or . In some embodiments, F^2 is  or  .

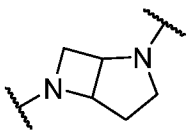
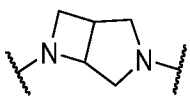
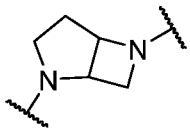
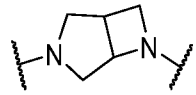
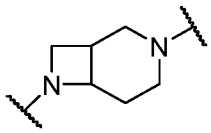
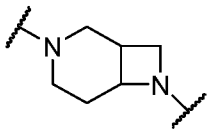
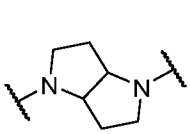
In some embodiments, F^3 is  ,  , or . In some embodiments, F^3 is  or  .

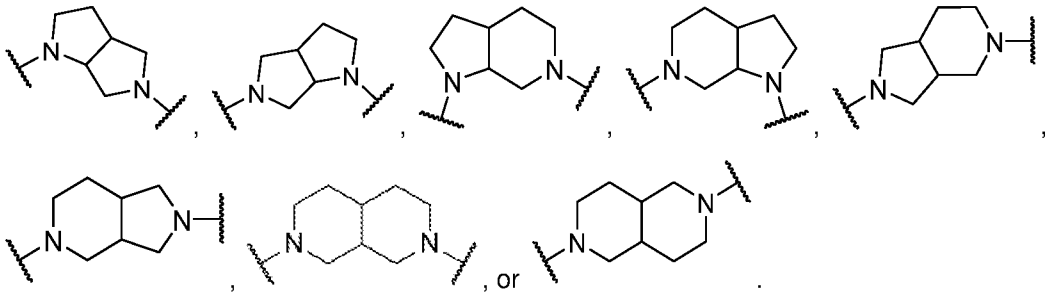
In some embodiments, R^{i1} is H or methyl. In some embodiments, R^{i2} is H or methyl. In some embodiments, R^{i3} is H or methyl. In some embodiments, R^{i4} is H or methyl.

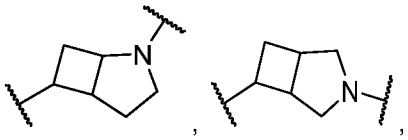
In some embodiments, the C_{2-9} heterocyclylene is  ,  ,  ,  , or  .

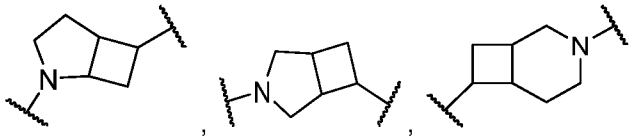
In some embodiments, the C_{2-9} heterocyclylene is  ,  , or  .

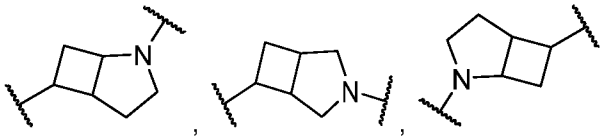
In some embodiments, the C_{2-9} heterocyclylene is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

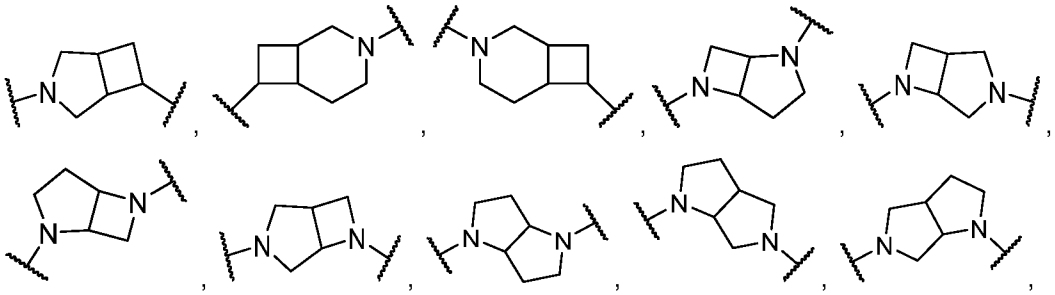
In some embodiments, the C_{2-9} heterocyclylene is  ,  ,  ,  ,  ,  ,  ,

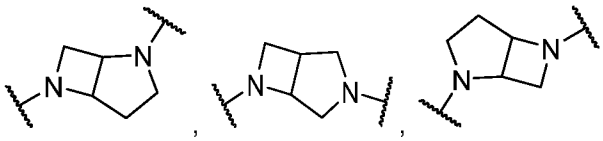


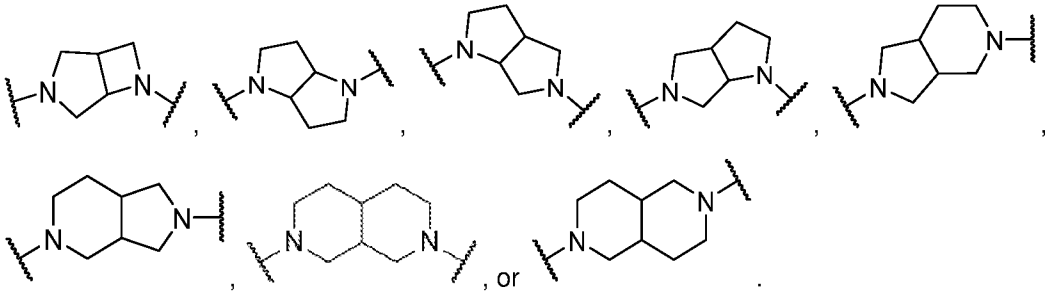
In some embodiments, the C_2–C_9 heterocyclylene is 

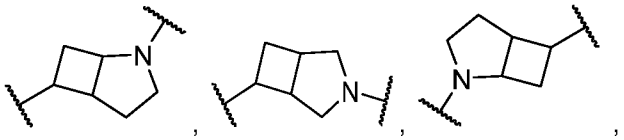
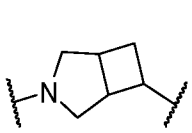
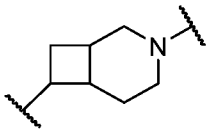
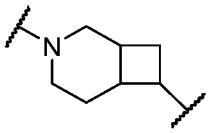


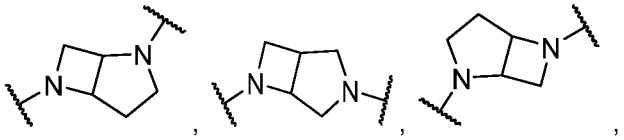
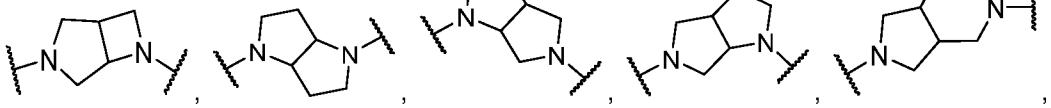
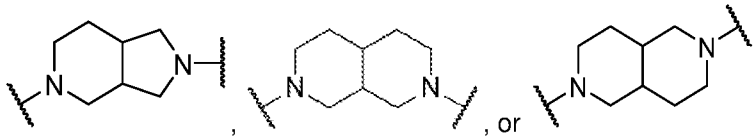
In some embodiments, F^1 is 

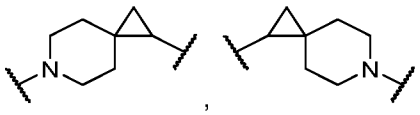
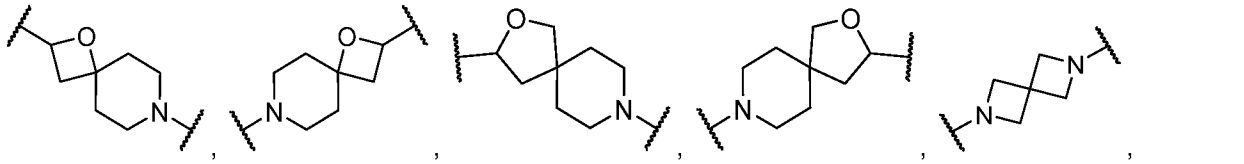
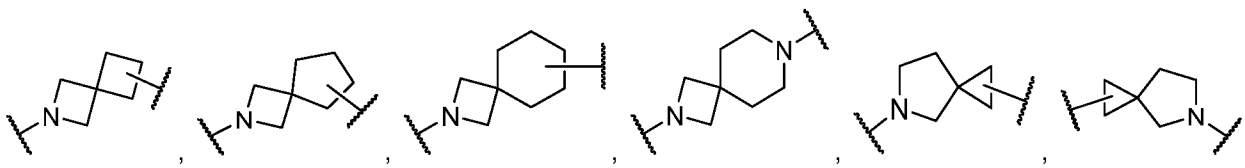
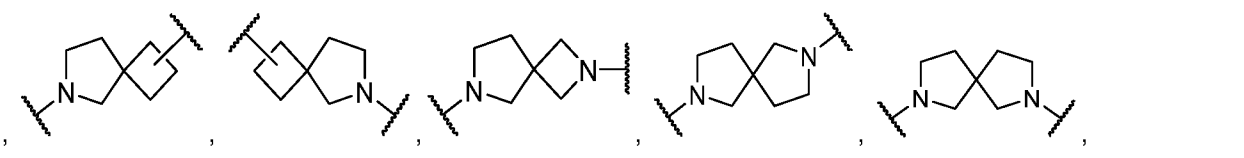
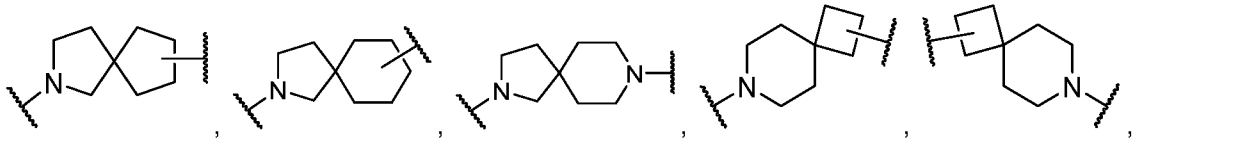


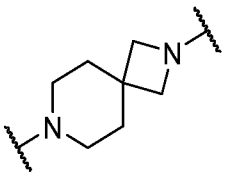
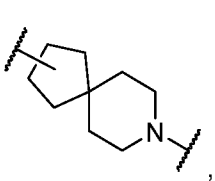
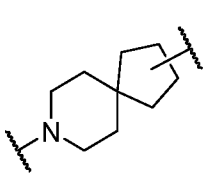
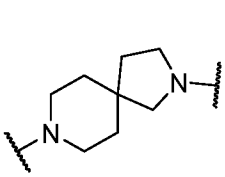
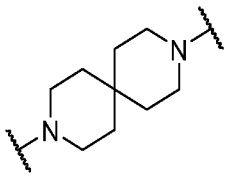
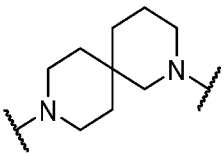
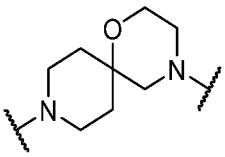
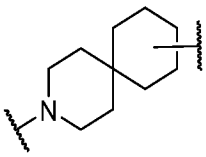
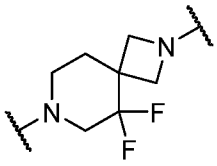
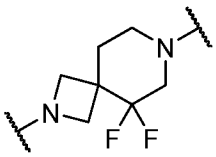
In some embodiments, F^1 is 

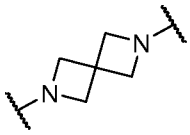
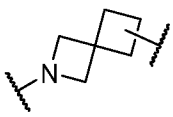
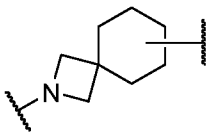
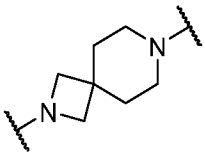
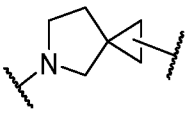
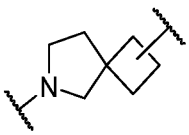
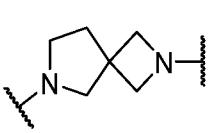
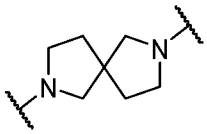
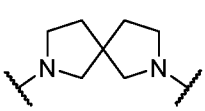
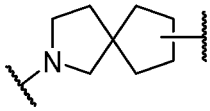
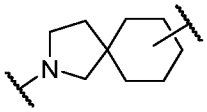
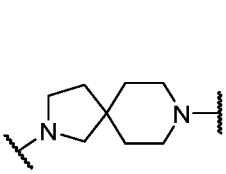
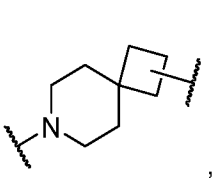
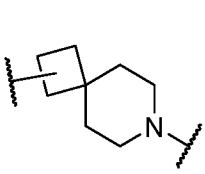
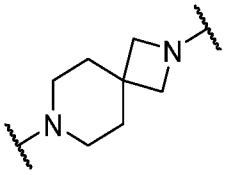
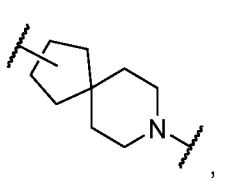
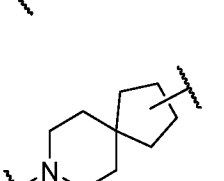
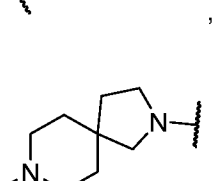
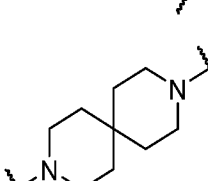
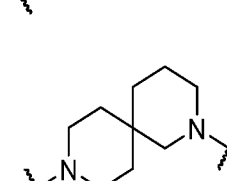
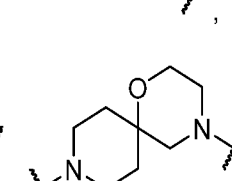
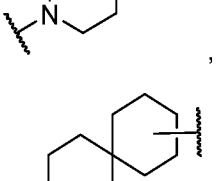
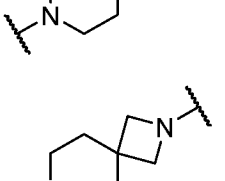
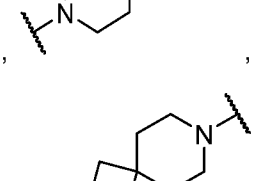
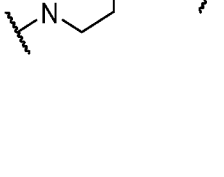
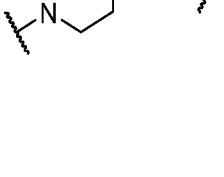
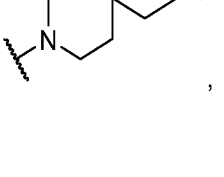
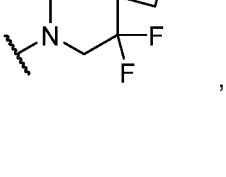
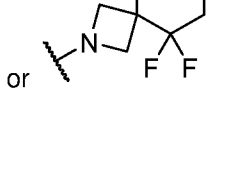


In some embodiments, F^1 is  ,  ,  , or  .

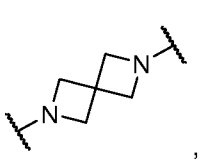
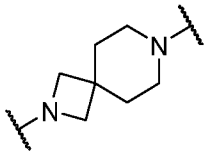
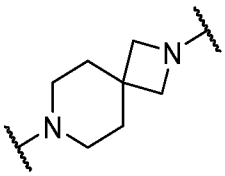
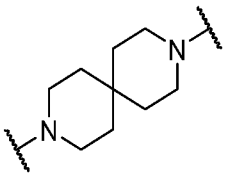
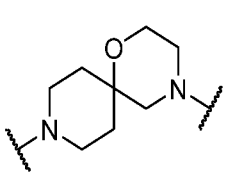
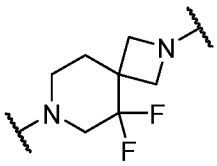
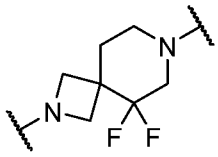
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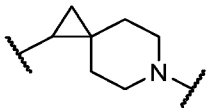
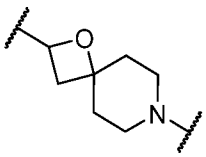
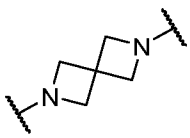
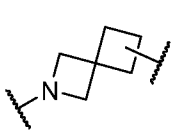
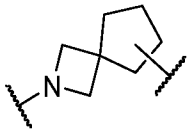
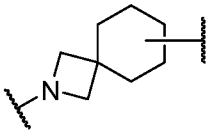
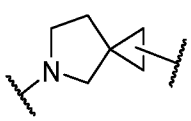
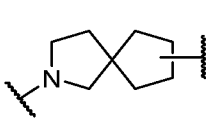
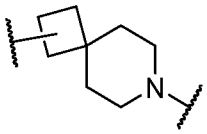
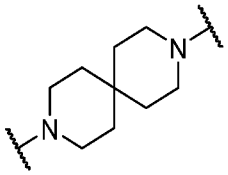
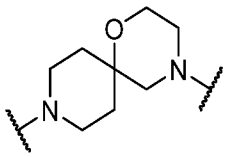
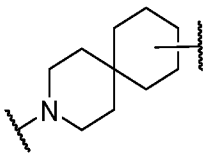
In some embodiments, the C_2-C_9 heterocyclyl is  ,  ,  ,  , or  .

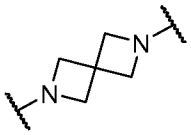
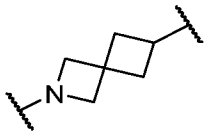
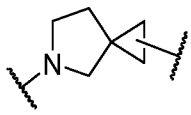
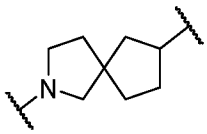
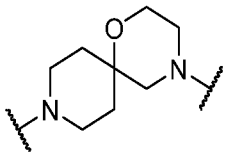
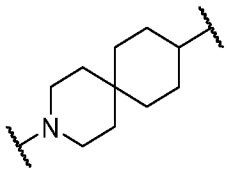
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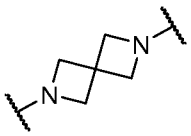
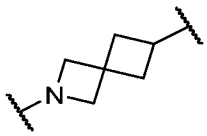
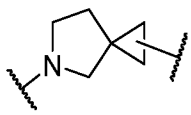
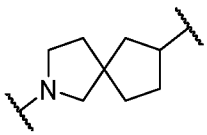
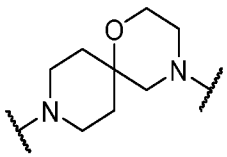
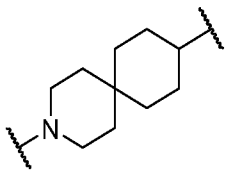
In some embodiments, the C_2-C_9 heterocyclyl is  ,  ,
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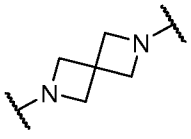
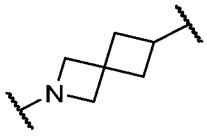
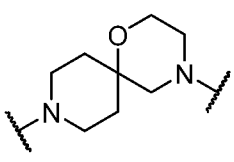
In some embodiments, the C_2-C_9 heterocyclyl is , ,
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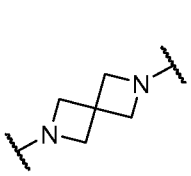
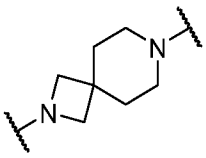
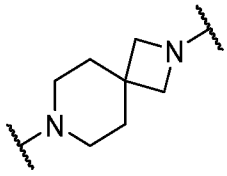
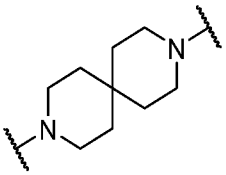
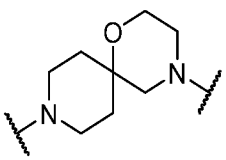
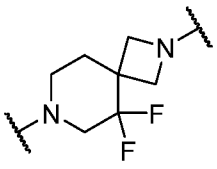
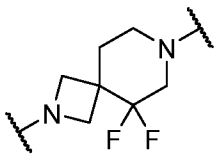
In some embodiments, the C_{2-9} heterocyclyl is  ,  ,  ,  ,  ,  , or  .

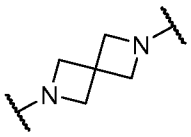
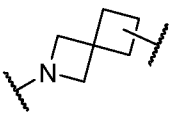
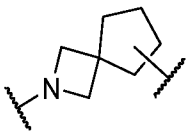
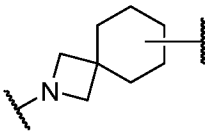
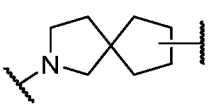
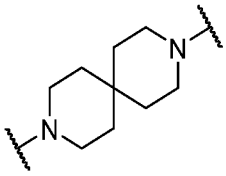
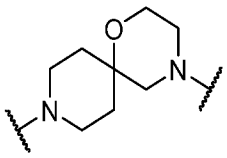
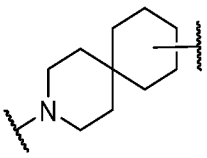
In some embodiments, F^1 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

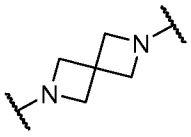
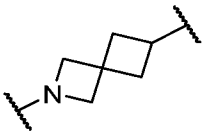
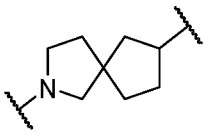
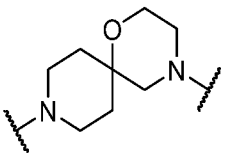
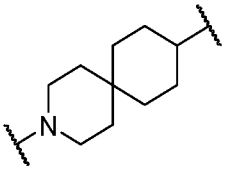
In some embodiments, F^1 is  ,  ,  ,  ,  , or  .

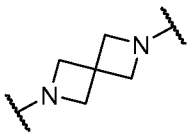
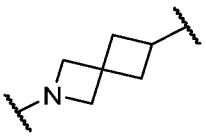
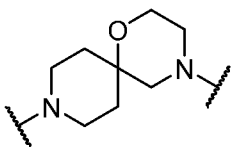
In some embodiments, F^1 is  ,  ,  ,  ,  , or  .

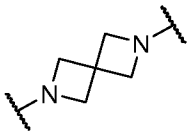
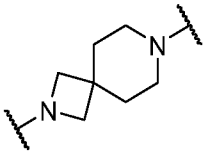
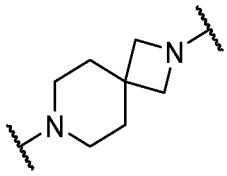
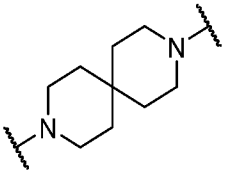
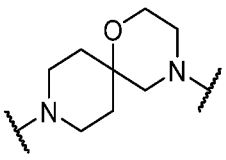
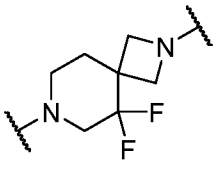
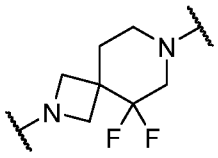
In some embodiments, F^1 is  ,  , or  .

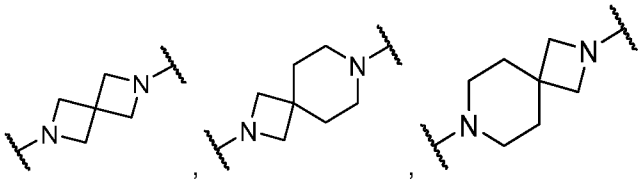
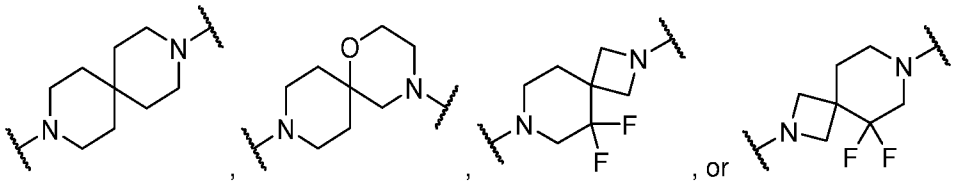
In some embodimetns, F^1 is  ,  ,  ,  ,  ,  , or  .

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

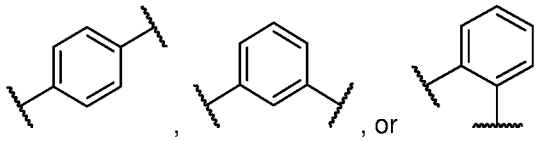
In some embodiments, F^2 is  ,  ,  ,  , or  .

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

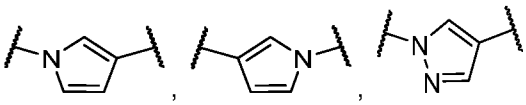
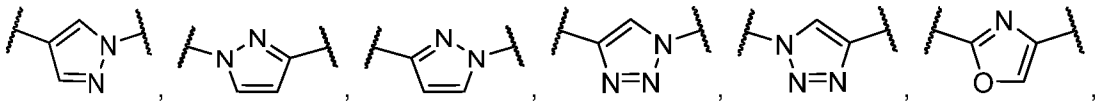
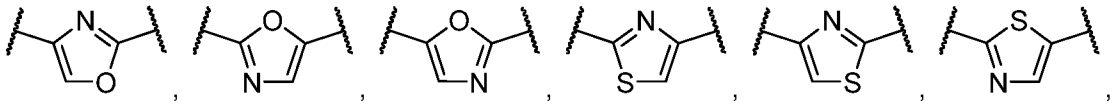
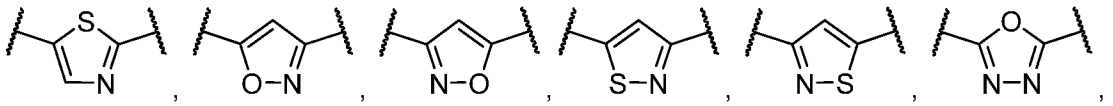
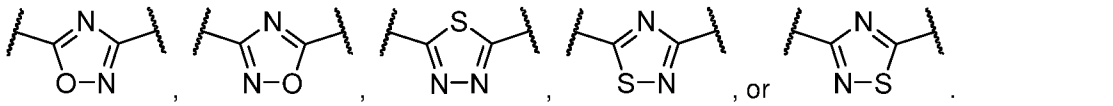
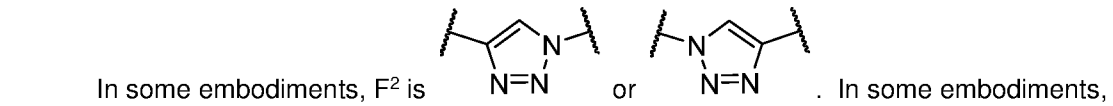
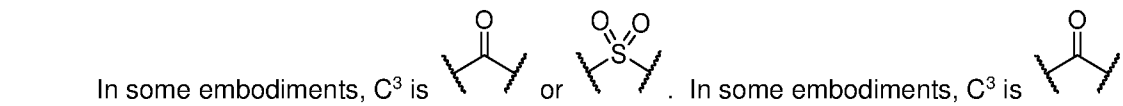
In some embodiments, F^2 is  ,  ,  ,  ,  ,  , or  .

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

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

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

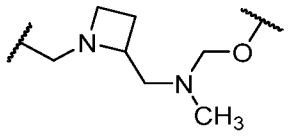
In some embodiments, each of F^1, F^2, or F^3 is, independently, optionally substituted C_2-C_9 heteroarylene.

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

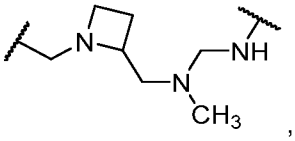
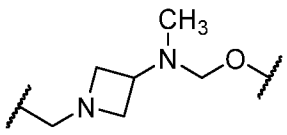
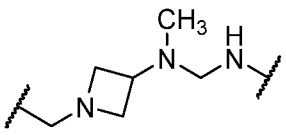
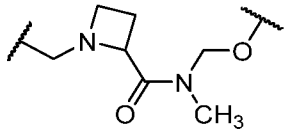
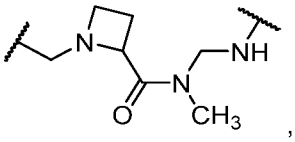
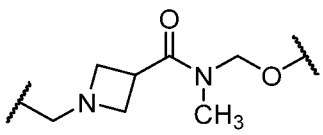
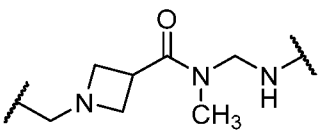
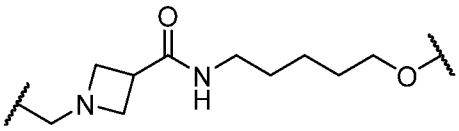
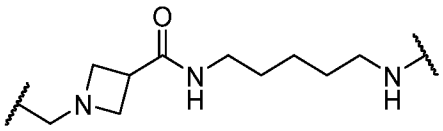
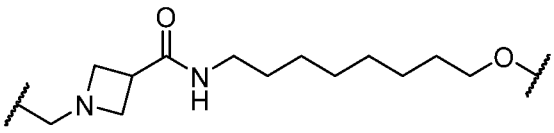
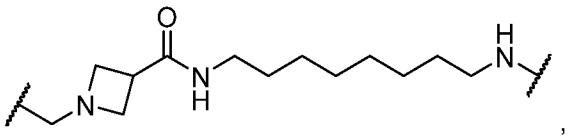
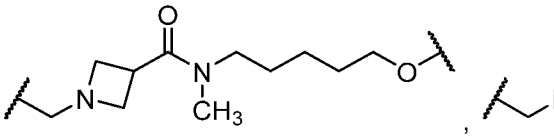
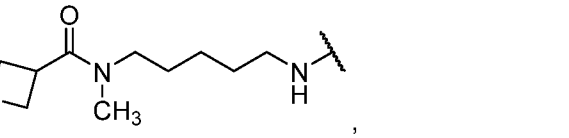
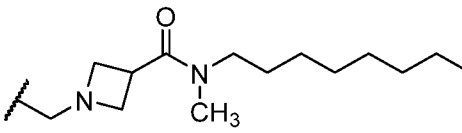
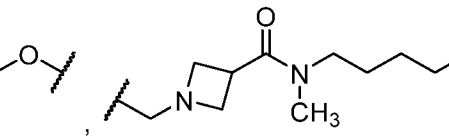
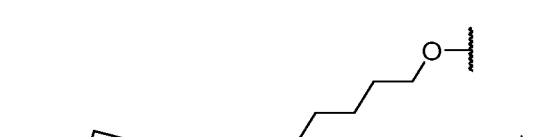
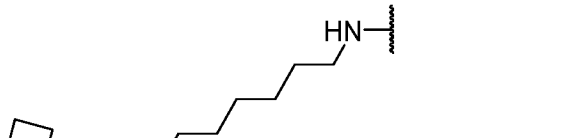
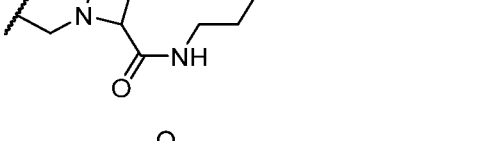
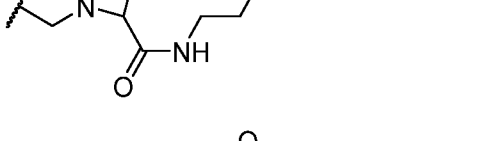
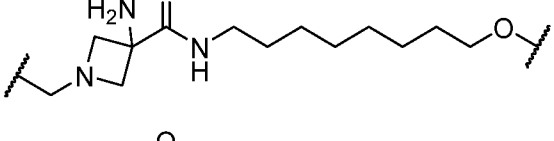
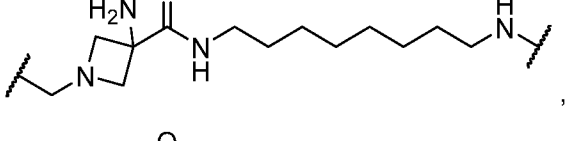
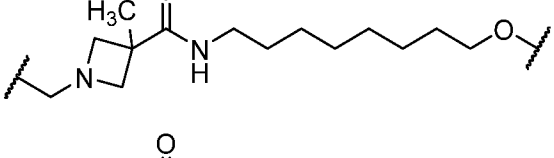
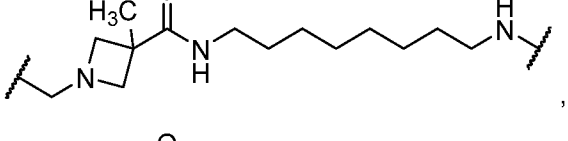
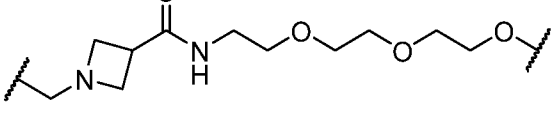
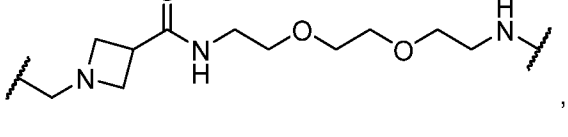
In some embodiments, F^2 is . In some embodiments, F^2 is .

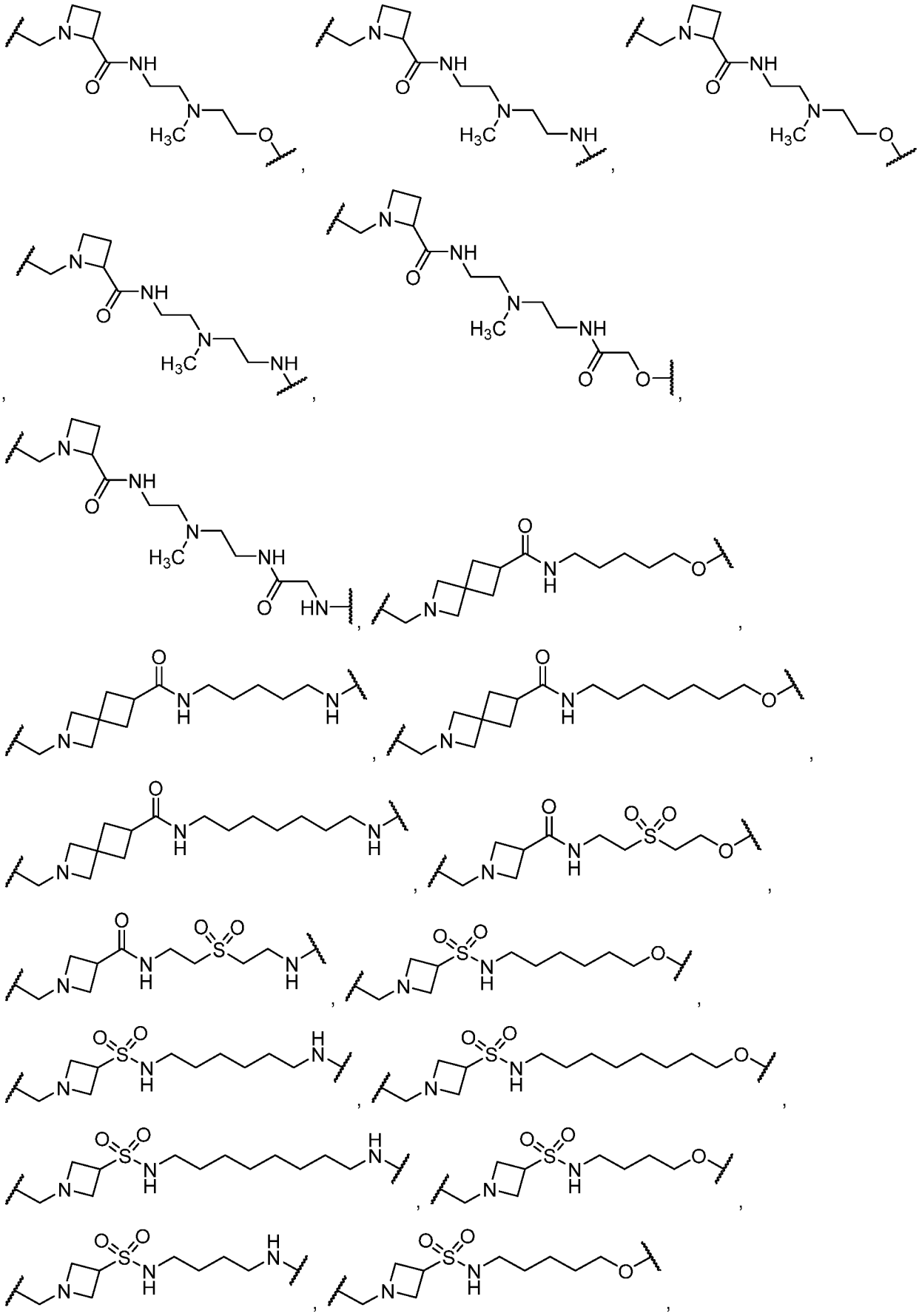
In some embodiments, C^3 is . In some embodiments, C^3 is .

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

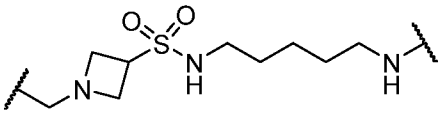
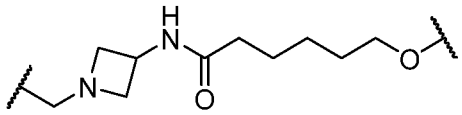
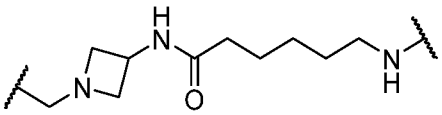
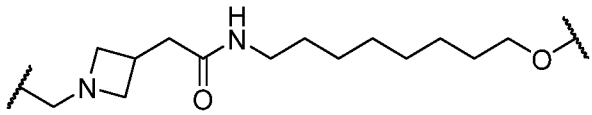
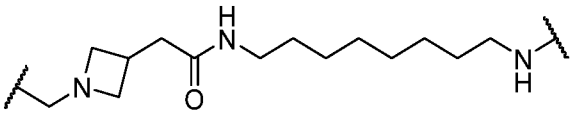
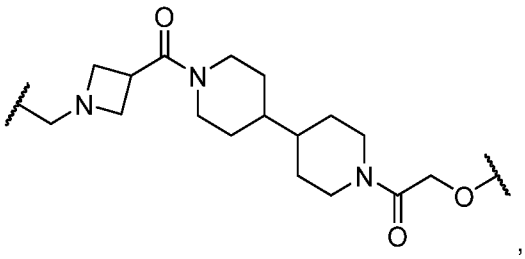
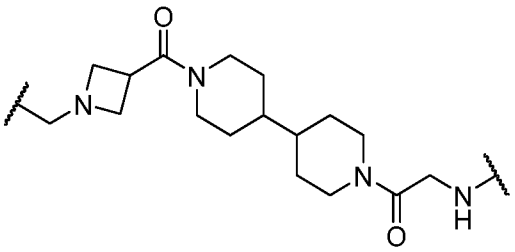
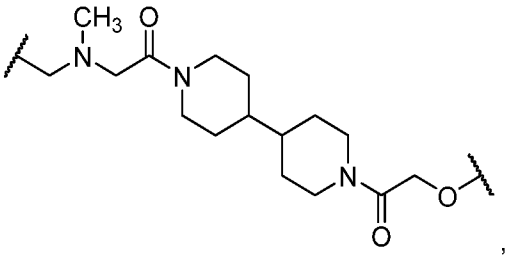
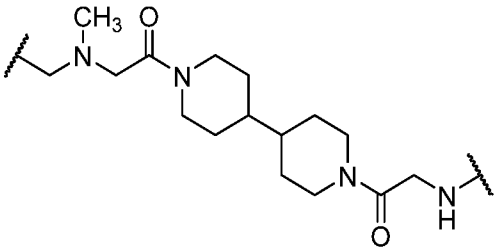
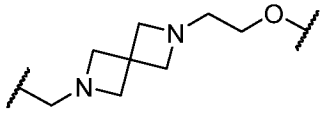
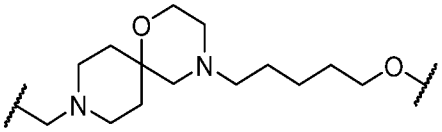
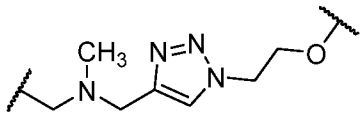
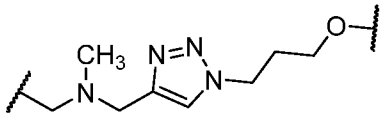
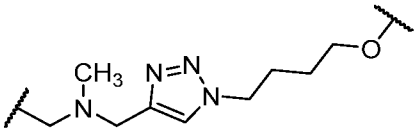
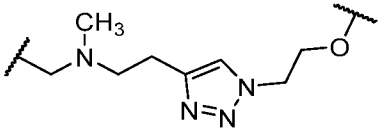
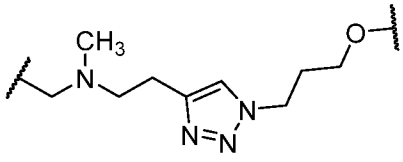
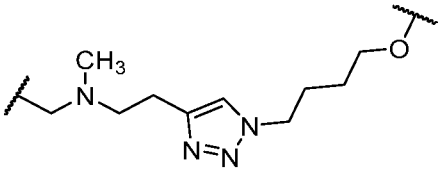
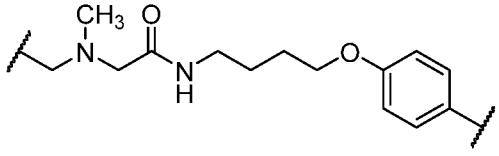
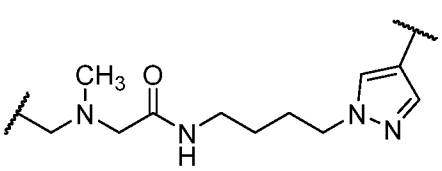
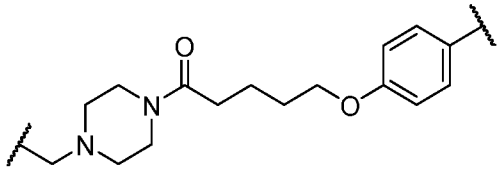


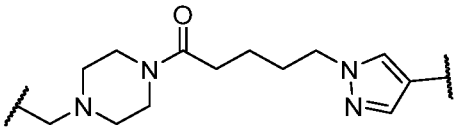
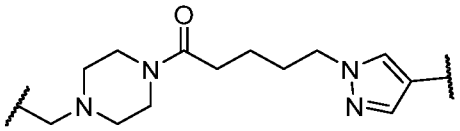
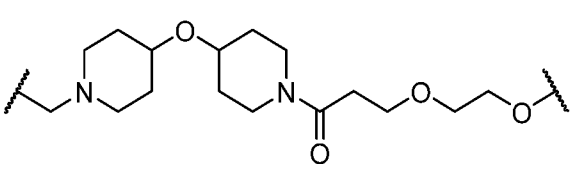
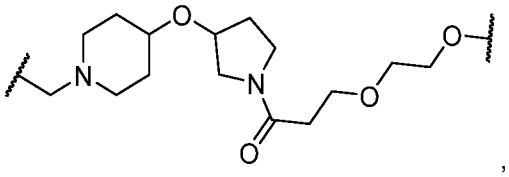
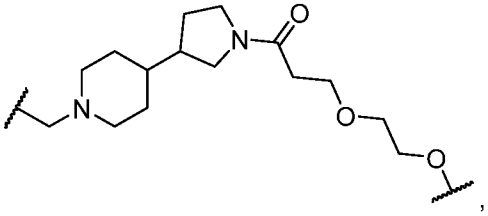
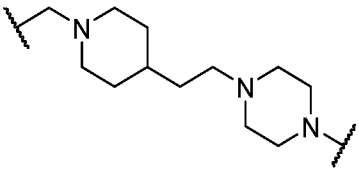
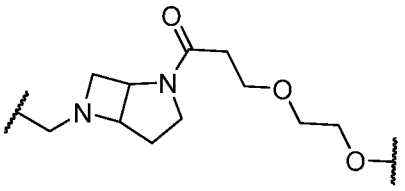
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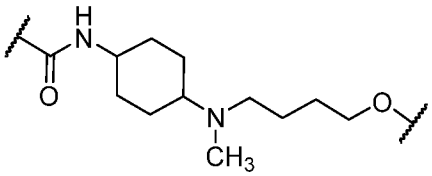

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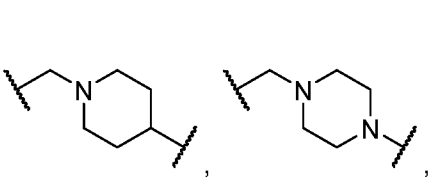
C4 Therapeutics, Inc.
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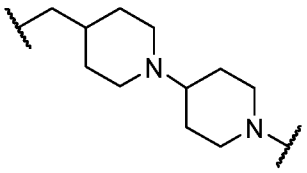
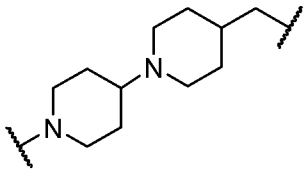
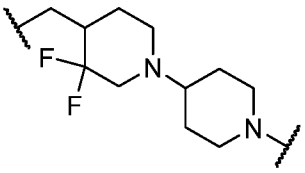
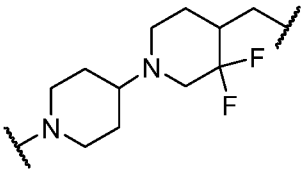
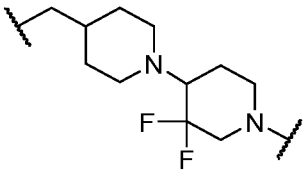
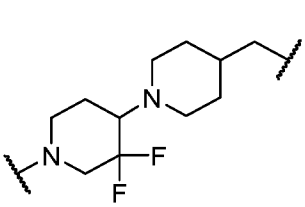
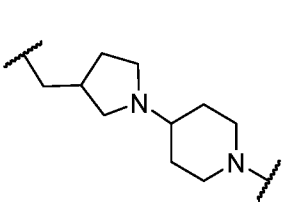
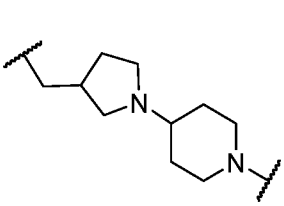
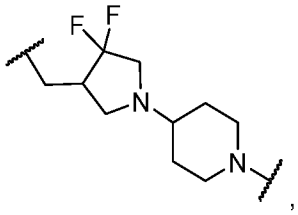
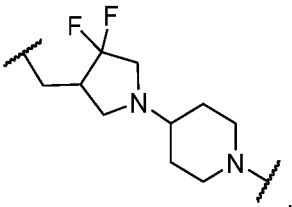
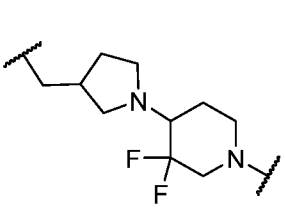
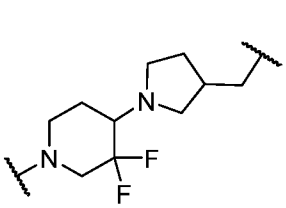
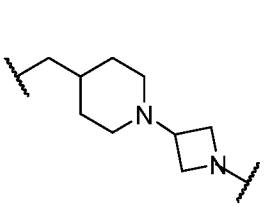

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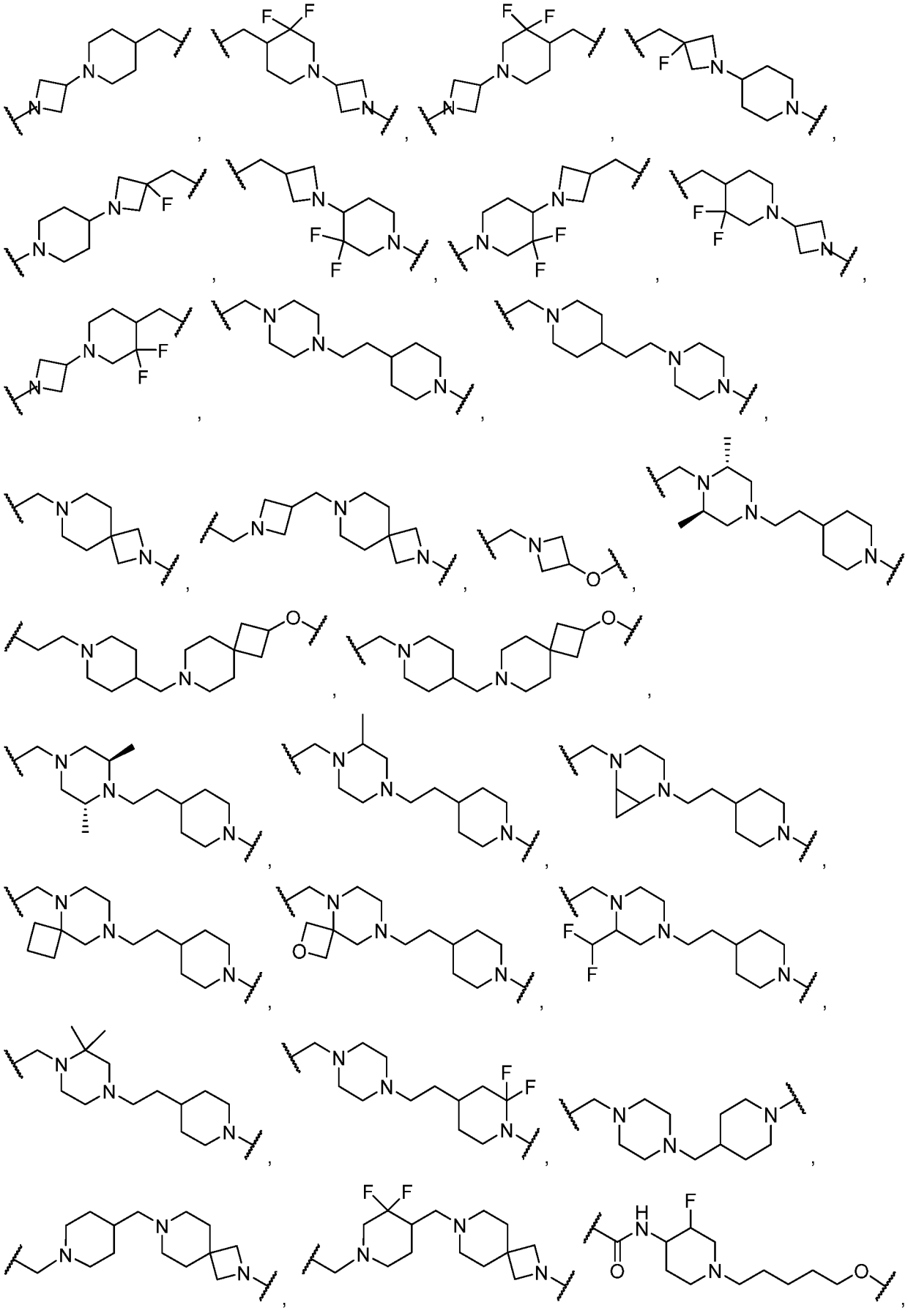

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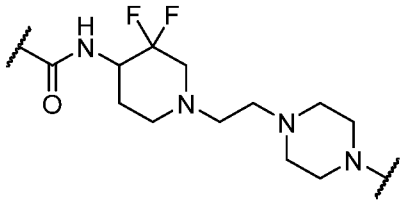
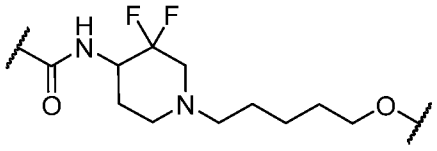
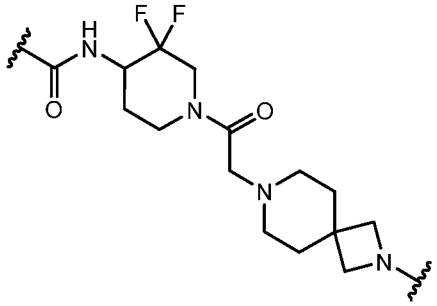
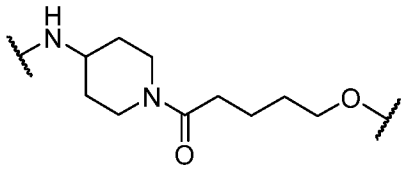
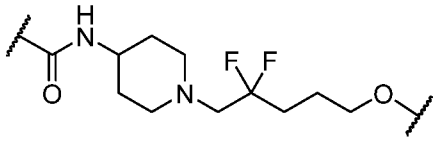
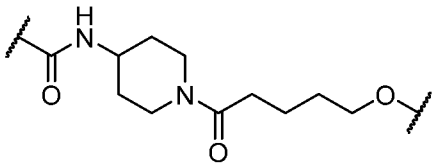
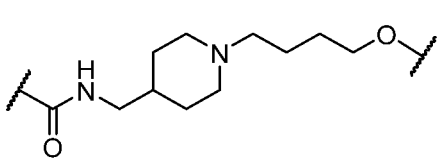
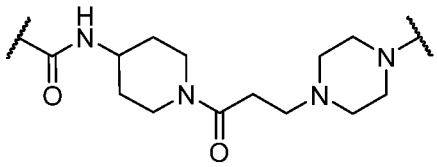
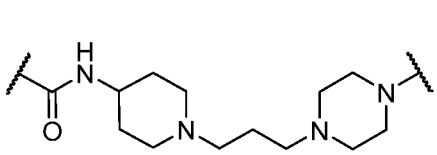
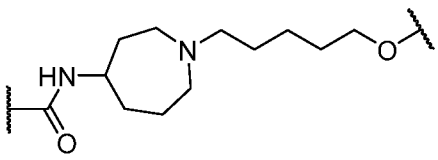

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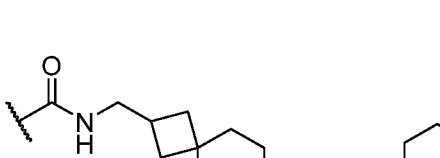
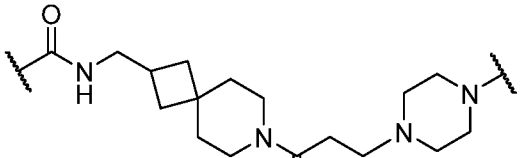

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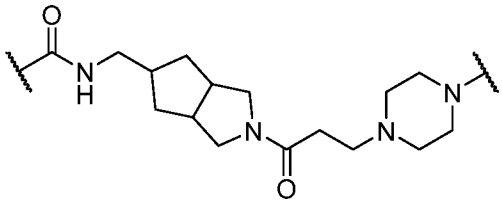
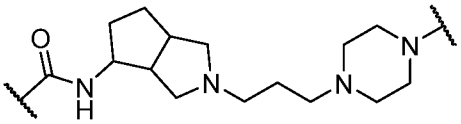
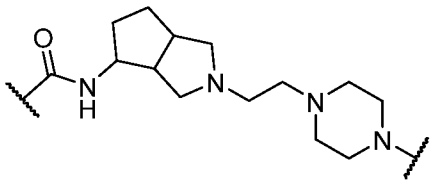
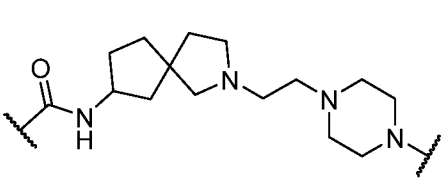



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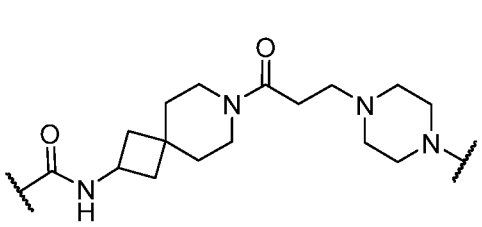
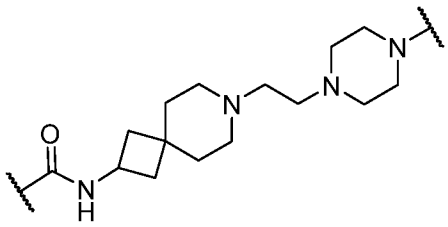
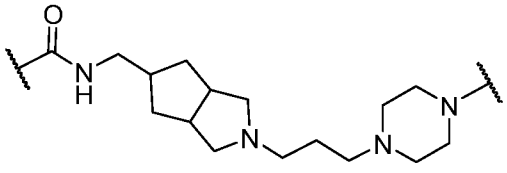
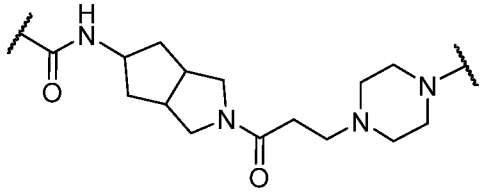
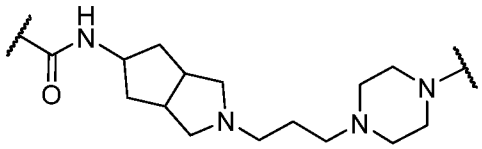
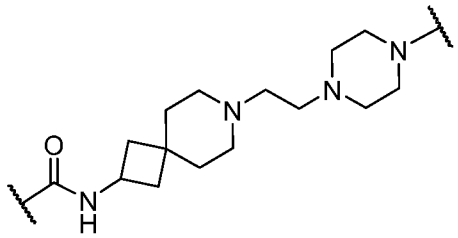
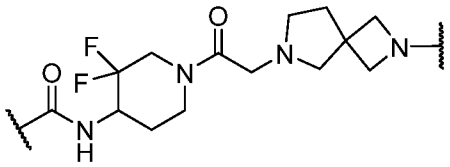
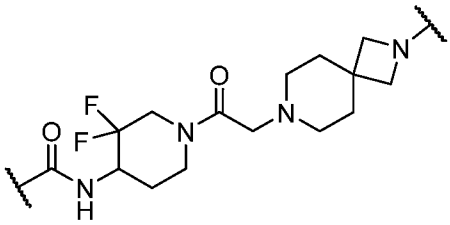
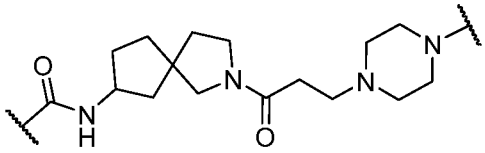
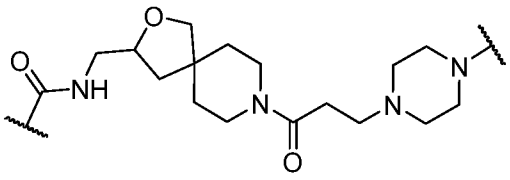
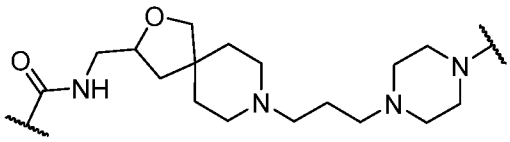
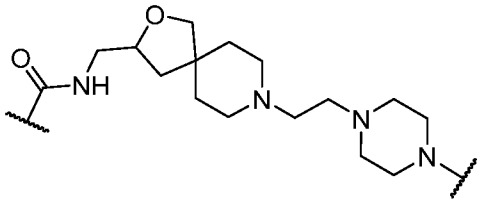
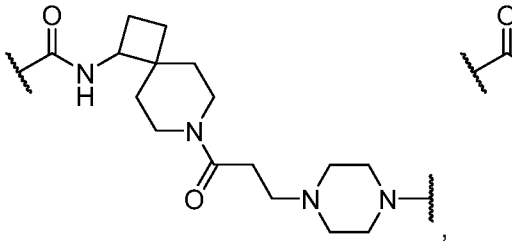
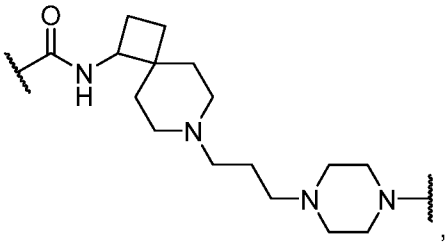
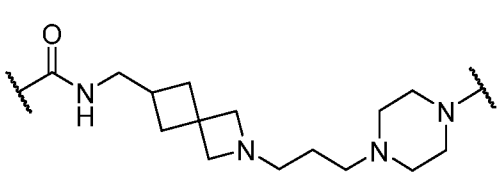
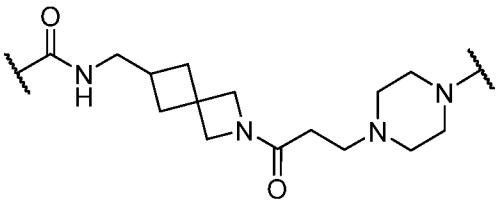
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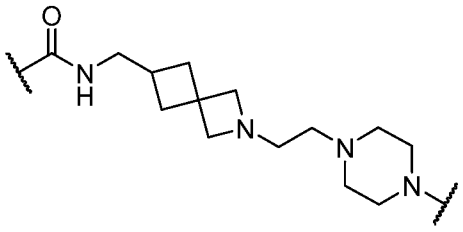
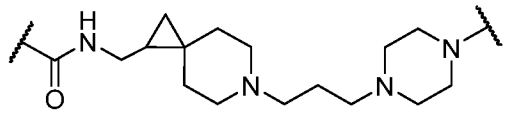
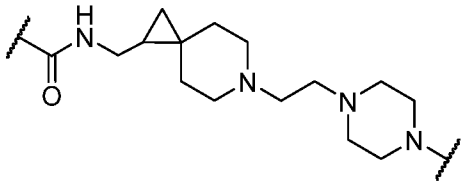
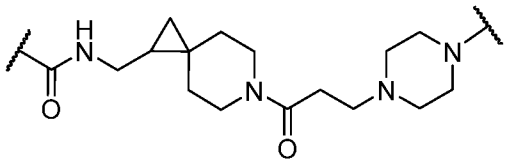
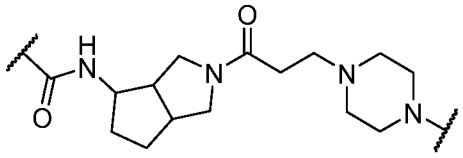
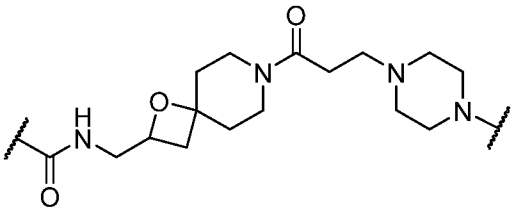
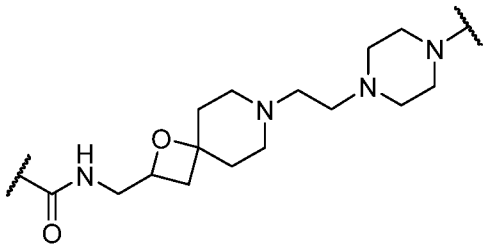
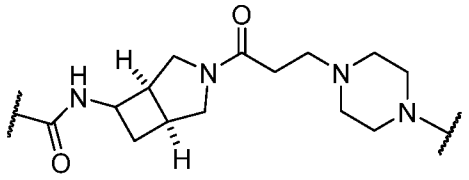
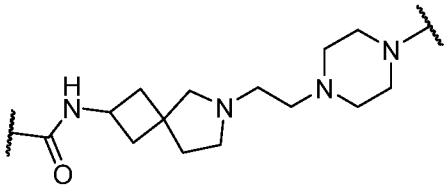
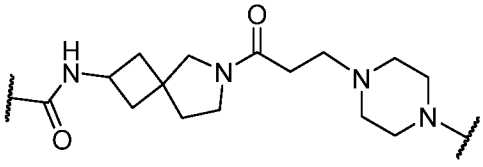
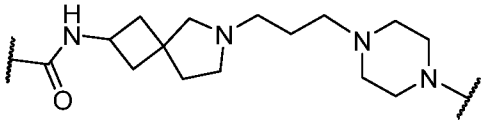
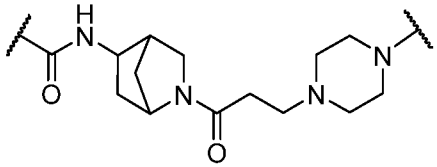
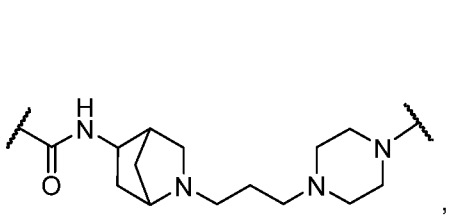
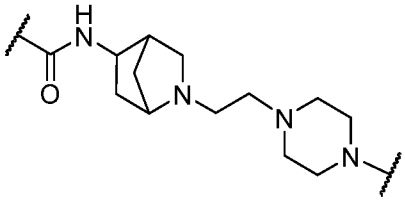
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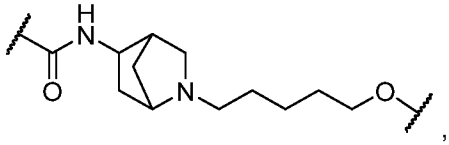
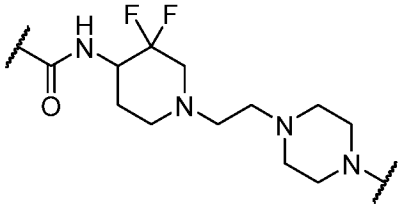
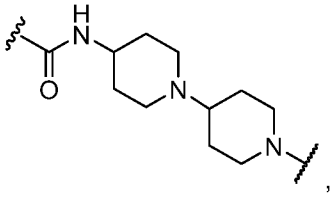
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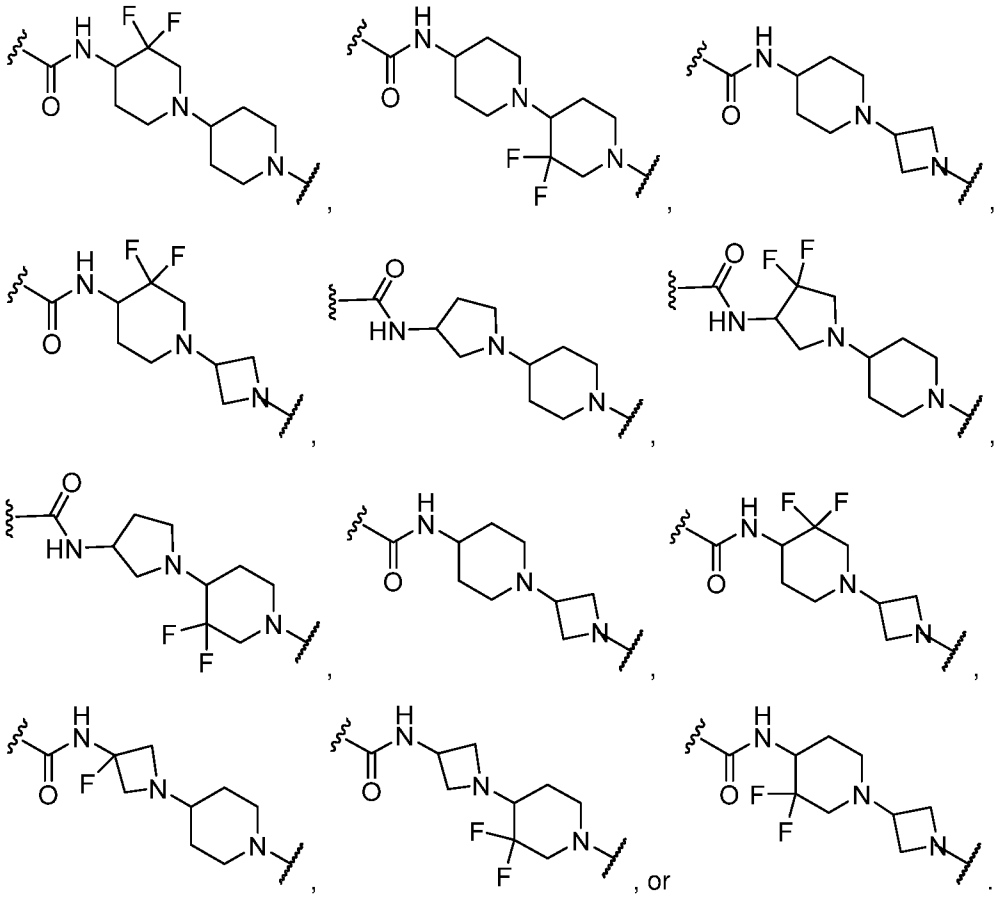
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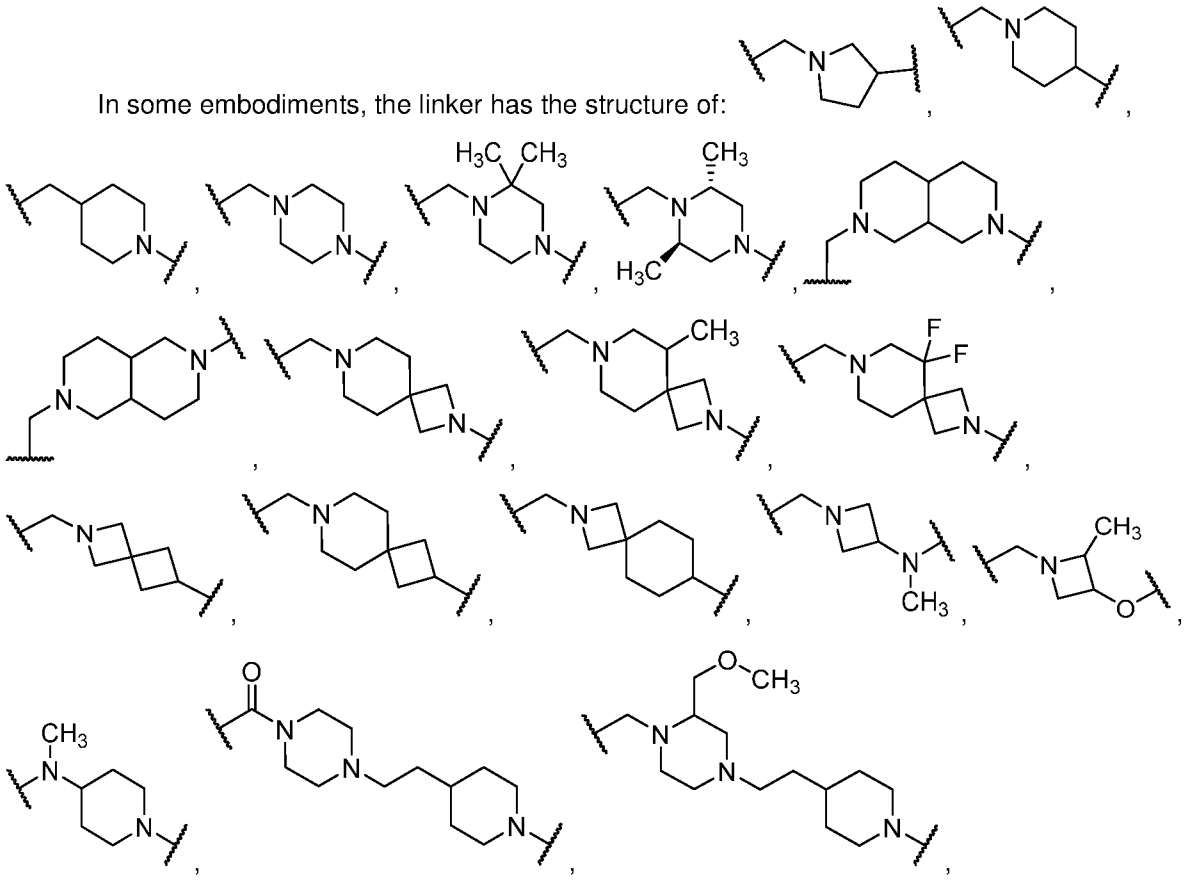

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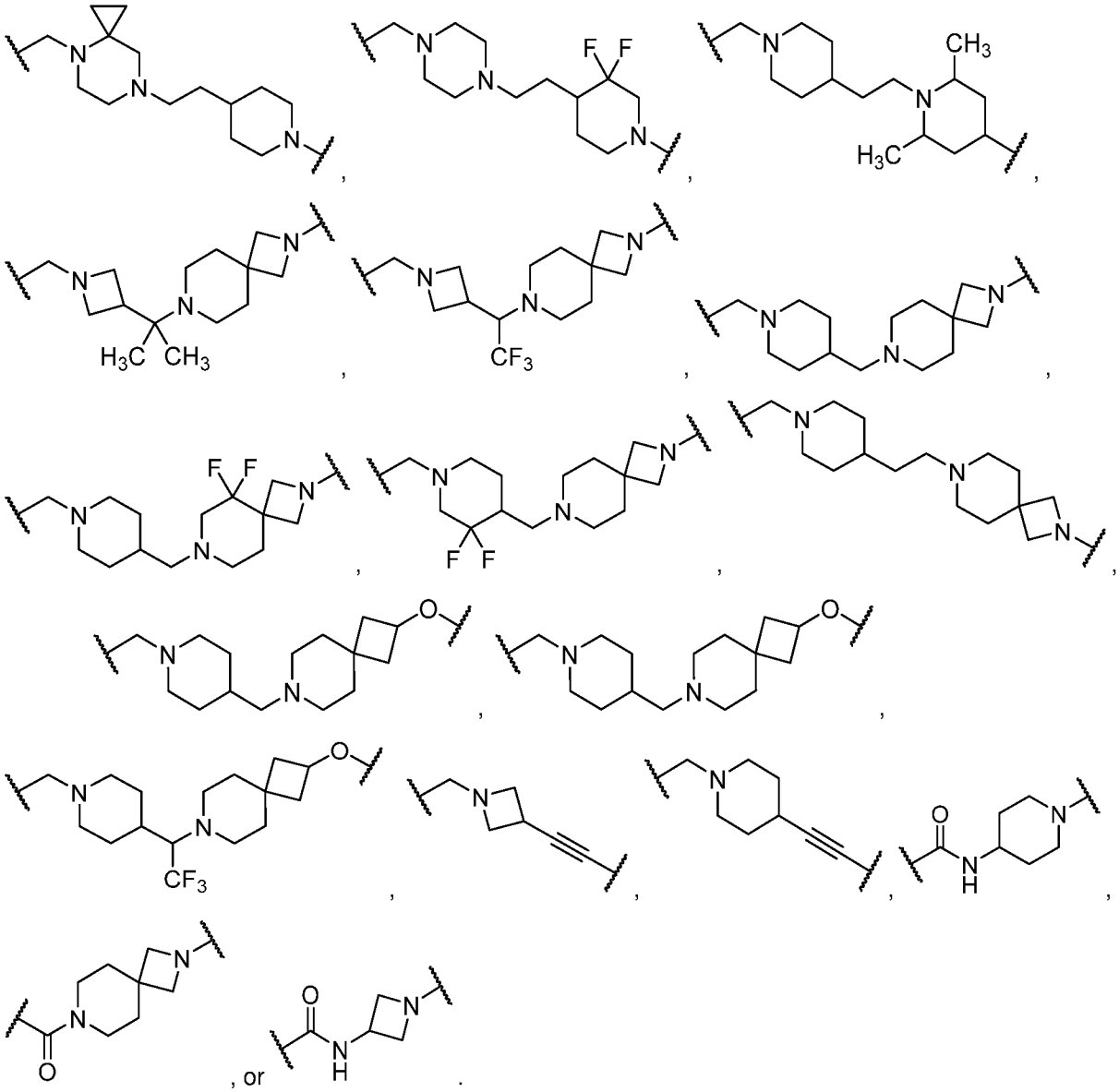
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In some embodiments, the linker has the structure of:





In some embodiments, the linker is absent.

In some embodiments, the linker is optionally substituted C_3-C_{10} carbocyclylene, optionally substituted C_{2-10} heterocyclylene, optionally substituted C_6-C_{10} arylene, or optionally substituted C_2-C_9 heteroarylene.

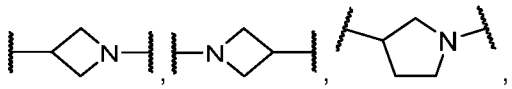
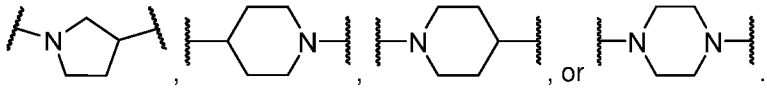
In some embodiments, the linker is optionally substituted C_3-C_{10} carbocyclylene or optionally substituted C_{2-10} heterocyclylene. In some embodiments, the linker is optionally substituted C_6-C_{10} arylene or optionally substituted C_2-C_9 heteroarylene.

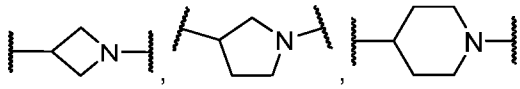
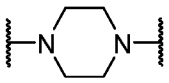
In some embodiments, the linker is optionally substituted C_{2-10} heterocyclylene.

In some embodiments, the $C_{2-}C_9$ heterocyclylene is monocyclic. In some embodiments, the $C_{2-}C_9$ heterocyclylene is polycyclic.

In some embodiments, the $C_{2-}C_9$ heterocyclylene is bicyclic.

In some embodiments, the $C_{2-}C_9$ heterocyclylene is bridged. In some embodiments, the $C_{2-}C_9$ heterocyclylene is fused. In some embodiments, the $C_{2-}C_9$ heterocyclylene is spirocyclic.

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

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

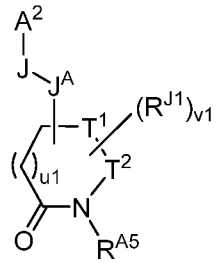
In some embodiments, the degradation moiety is a ubiquitin ligase binding moiety.

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

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

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

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



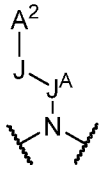
Formula Y,

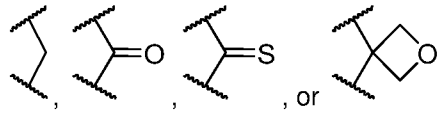
where

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

v1 is 0, 1, 2, 3, 4, or 5;

u1 is 1, 2, or 3;

T^1 is a bond or  ;

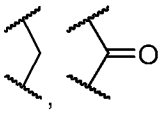
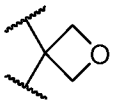
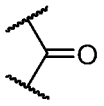
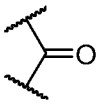
T^2 is  ;

R^{5A} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

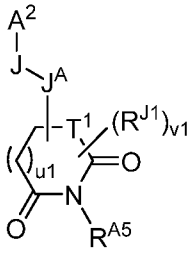
each R^{J1} is, independently, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

J^A is absent, O, optionally substituted amino, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl; and

J is absent, optionally substituted C_3-C_{10} carbocyclylene, optionally substituted C_6-C_{10} arylene, optionally substituted C_2-C_9 heterocyclylene, or optionally substituted C_2-C_9 heteroarylene, or a pharmaceutically acceptable salt thereof.

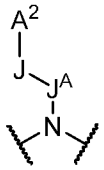
In some embodiments, T^2 is  , , or  . In some embodiments, T^2 is  or  . In some embodiments, T^2 is  . In some embodiments, T^2 is  .

In some embodiments, the structure of **Formula Y** has the structure of **Formula Y1**:

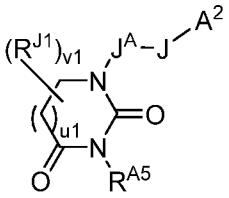


Formula Y1,

or a pharmaceutically acceptable salt thereof.

In some embodiments, T^1 is a bond. In some embodiments, T^1 is  .

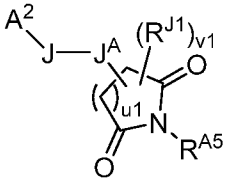
In some embodiments, the structure of **Formula Y** has the structure of **Formula Y2**:



Formula Y2,

or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of **Formula Y** has the structure of **Formula Z**:

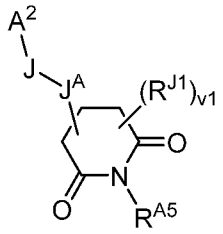


Formula Z,

or a pharmaceutically acceptable salt thereof.

In some embodiments, u1 is 1. In some embodiments, u1 is 2. In some embodiments u1 is 3.

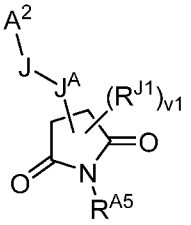
In some embodiments, the structure of **Formula Z** has the structure of **Formula AA0**:



Formula AA0,

or a pharmaceutically acceptable salt thereof.

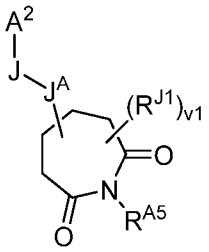
In some embodiments, the structure of **Formula Z** has the structure of **Formula AB**:



Formula AB,

or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of **Formula Z** has the structure of **Formula AC**:



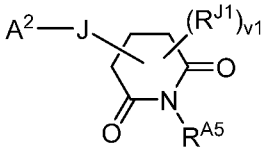
Formula AC,

or a pharmaceutically acceptable salt thereof.

In some embodiments, J^A is absent. In some embodiments, J^A is optionally substituted C_1-C_6 alkyl. In some embodiments, J^A is optionally substituted C_1-C_6 heteroalkyl. In some embodiments, J^A is O or optionally substituted amino.

In some embodiments, J^A is  .

In some embodiments, the structure of **Formula AA0** has the structure of **Formula AA0**:

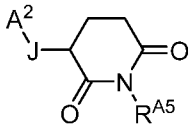


Formula AA,

or a pharmaceutically acceptable salt thereof.

In some embodiments, v1 is 0, 1, 2, or 3. In some embodiments, v1 is 0. In some embodiments, v1 is 1. In some embodiments, v1 is 2. In some embodiments, v1 is 3.

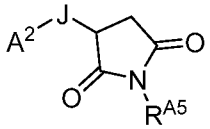
In some embodiments, the structure of **Formula AA** has the structure of **Formula AA1**:



Formula AA1,

or a pharmaceutically acceptable salt thereof.

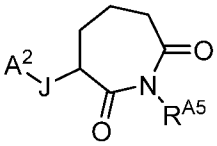
In some embodiments, the structure of **Formula AB** has the structure of **Formula AB1**:



Formula AB1,

or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of **Formula AC** has the structure of **Formula AC1**:

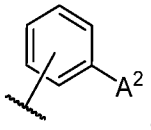


Formula AC1,

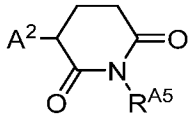
or a pharmaceutically acceptable salt thereof.

In some embodiments, J is absent. In some embodiments, J is optionally substituted C_3-C_{10} carbocyclylene or optionally substituted C_6-C_{10} arylene. In some embodiments, J is optionally substituted C_2-C_9 heterocyclylene or optionally substituted C_2-C_9 heteroarylene.

In some embodiments, J is optionally substituted heterocyclylene. In some embodiments, J is optionally substituted C_6-C_{10} arylene.

In some embodiments, J is  .

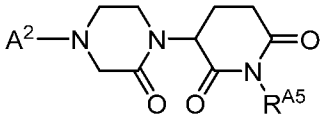
In some embodiments, the structure of **Formula AA** has the structure of **Formula AA2**:



Formula AA2,

or a pharmaceutically acceptable salt thereof.

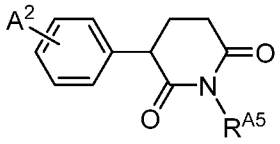
In some embodiments, the structure of **Formula AA** has the structure of **Formula AA3**:



Formula AA3,

or a pharmaceutically acceptable salt thereof.

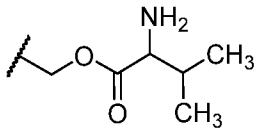
In some embodiments, the structure of **Formula AA** has the structure of **Formula AA4**:



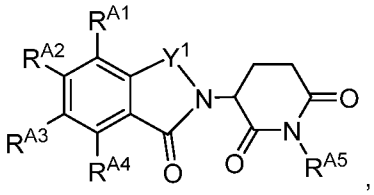
Formula AA4,

or a pharmaceutically acceptable salt thereof.

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

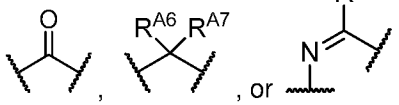
In some embodiments, R^{A5} is H or methyl. In some embodiments, R^{A5} is H. In some embodiments, R^{A5} is methyl. In some embodiments, R^{A5} is  .

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



Formula A

where

Y^1 is  ;

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

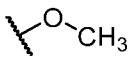
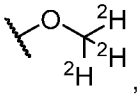
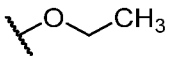
R^{A6} is H or optionally substituted C_1-C_6 alkyl; and R^{A7} is H or optionally substituted C_1-C_6 alkyl; or R^{A6} and R^{A7}, together with the carbon atom to which each is bound, combine to form optionally substituted C_3-C_6 carbocyclyl or optionally substituted C_2-C_5 heterocyclyl; or R^{A6}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

In some embodiments, 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, 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, or a pharmaceutically acceptable salt thereof.

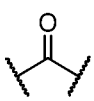
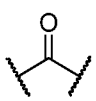
In some embodiments, each of R^{A1}, R^{A2}, R^{A3}, and R^{A4} is, H, A^2, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted -O-C_3-C_6 carbocyclyl, hydroxyl, optionally substituted amino; or R^{A1} and R^{A2}, R^{A2} and R^{A3}, or R^{A3} and R^{A4}, together with the carbon atoms to which each is attached, combine to form  ; and  is optionally substituted C_2-C_9 heterocyclyl, 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.

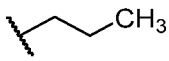
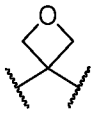
In some embodiments, each of R^{A1}, R^{A2}, R^{A3}, and R^{A4} is, independently, H, A^2, F,  ,  ,  , or  ; or R^{A1} and R^{A2}, R^{A2} and R^{A3}, or R^{A3} and R^{A4}, together with the carbon atoms to which each is attached, combine to form  ; and  is optionally substituted C_2-C_9 heterocyclyl, 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.

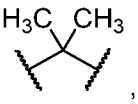
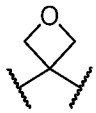
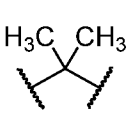
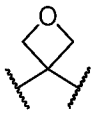
In some embodiments, R^{A1} is A^2. In some embodiments, R^{A2} is A^2. In some embodiments, R^{A3} is A^2. In some embodiments, R^{A4} is A^2. In some embodiments, R^{A5} is A^2.

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

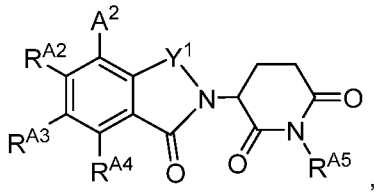
In some embodiments, R^{A5} is H or  . In some embodiments, R^{A5} is H. In some embodiments, R^{A5} is  .

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

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

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

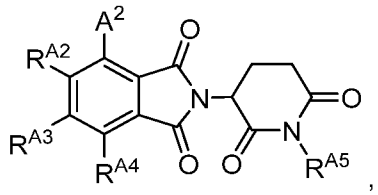
In some embodiments, the structure of **Formula A** has the structure of **Formula A1**:



Formula A1

or a pharmaceutically acceptable salt thereof.

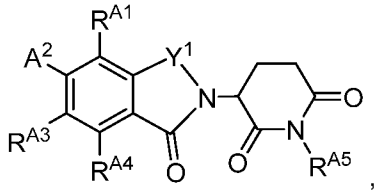
In some embodiments, the structure of **Formula A** has the structure of **Formula A2**:



Formula A2

or a pharmaceutically acceptable salt thereof.

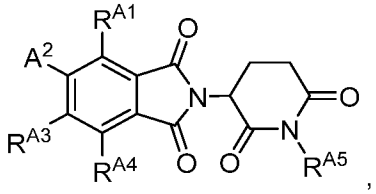
In some embodiments, the structure of **Formula A** has the structure of **Formula A3**:



Formula A3

or a pharmaceutically acceptable salt thereof.

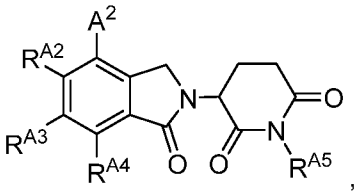
In some embodiments, the structure of **Formula A** has the structure of **Formula A4**:



Formula A4

or a pharmaceutically acceptable salt thereof.

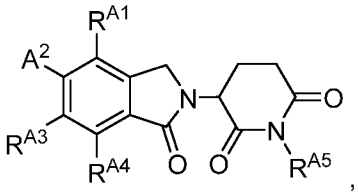
In some embodiments, the structure of **Formula A** has the structure of **Formula A5**:



Formula A5

or a pharmaceutically acceptable salt thereof.

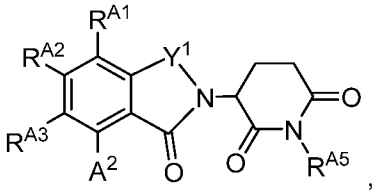
In some embodiments, the structure of **Formula A** has the structure of **Formula A6**:



Formula A6

or a pharmaceutically acceptable salt thereof.

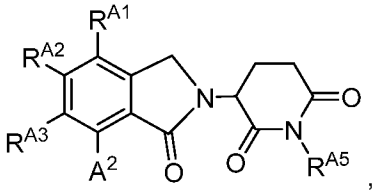
In some embodiments, the structure of **Formula A** has the structure of **Formula A7**:



Formula A7

or a pharmaceutically acceptable salt thereof.

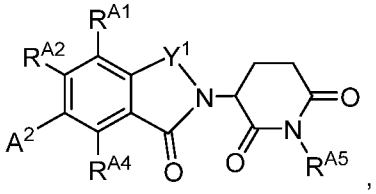
In some embodiments, the structure of **Formula A** has the structure of **Formula A8**:



Formula A8

or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of **Formula A** has the structure of **Formula A9**:

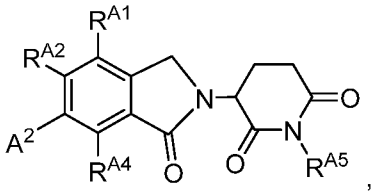


,

Formula A9

or a pharmaceutically acceptable salt thereof.

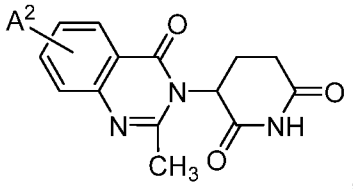
In some embodiments, the structure of **Formula A** has the structure of **Formula A10**:

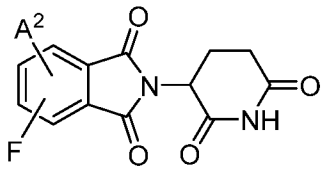
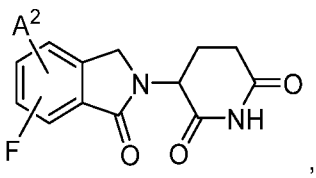
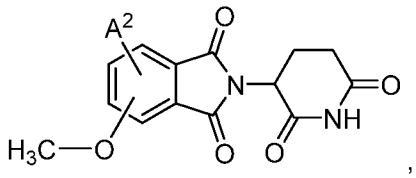


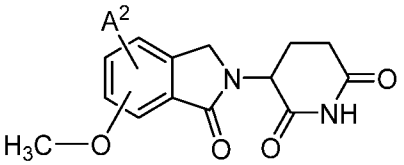
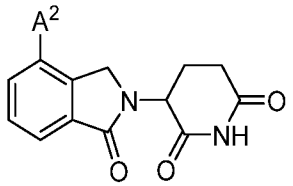
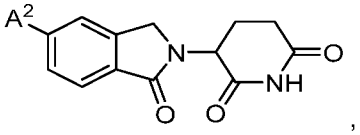
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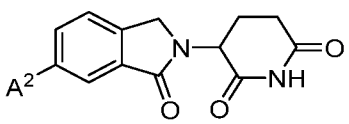
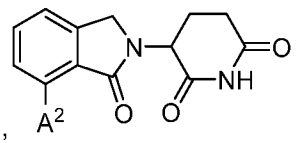
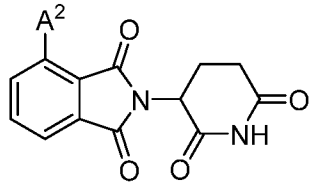
Formula A10

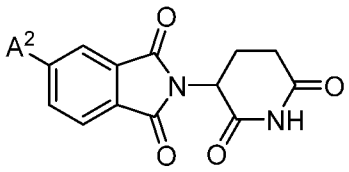
or a pharmaceutically acceptable salt thereof.

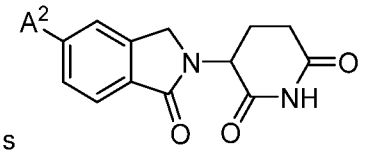
In some embodiments, wherein the structure of **Formula A** is  ,

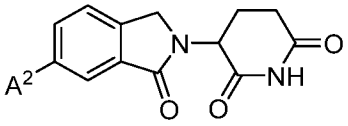
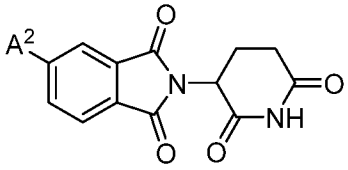
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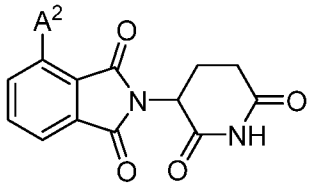
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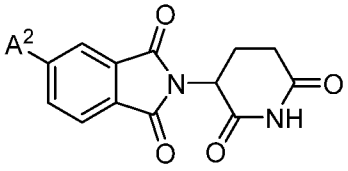
 ,  ,  , or

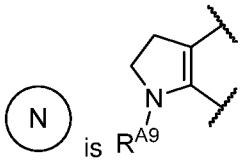
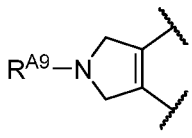
 , or derivative or analog thereof.

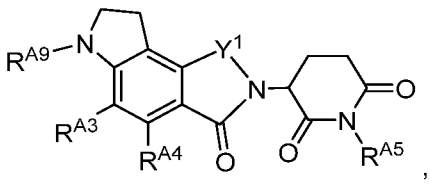
In some embodiments, the structure of **Formula A** is  ,

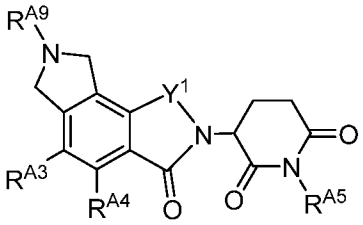
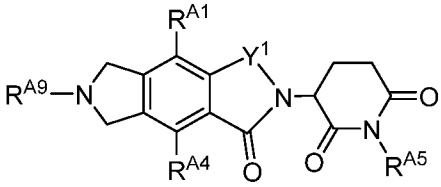
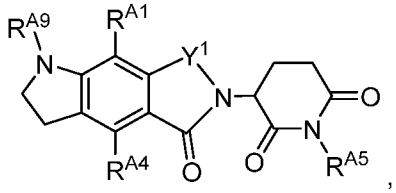
 , or  .

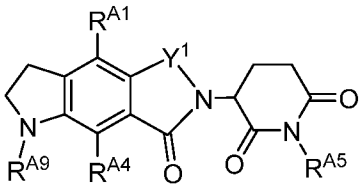
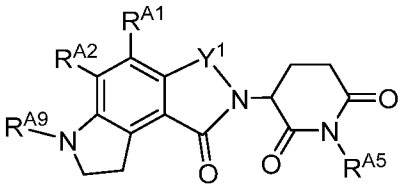
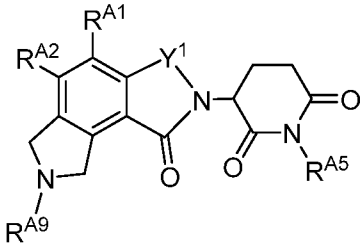
In some embodiments, the structure of **Formula A** is  or

 , or derivative or analog thereof.

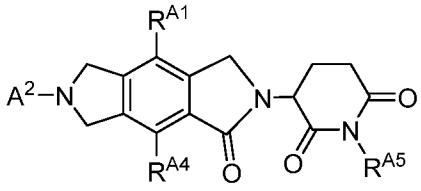
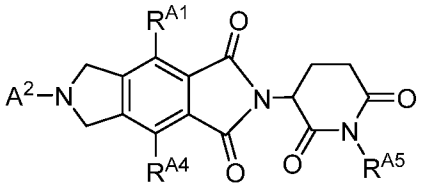
In some embodiments,  is or  , where R^{A9} is H, A^2, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl.

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

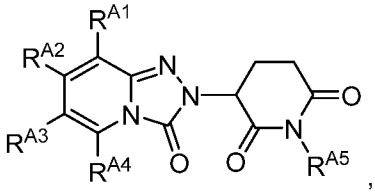
 ,  ,  ,

 ,  , or  .

In some embodiments, R^{A9} is H, A^2, or optionally substituted C_1-C_6 alkyl. In some embodiments, R^{A9} is H, A^2, or methyl. In some embodiments, R^{9A} is H. In some embodiments, R^{9A} is methyl. In some embodiments, R^{A9} is A^2.

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

In some embodiments, the structure of **Formula AA** has the structure of **Formula B**:

 ,

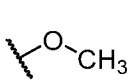
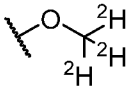
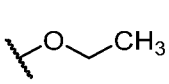
Formula B

where

R^{A5} 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, or a pharmaceutically acceptable salt thereof.

In some embodiments, each of R^{A1}, R^{A2}, R^{A3}, and R^{A4} is, H, A^2, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted -O-C_3-C_6 carbocyclyl, hydroxyl, optionally substituted amino; or R^{A1} and R^{A2}, R^{A2} and R^{A3}, or R^{A3} and R^{A4}, together with the carbon atoms to which each is attached, combine to form  ; and  is optionally substituted C_2-C_9 heterocyclyl, 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.

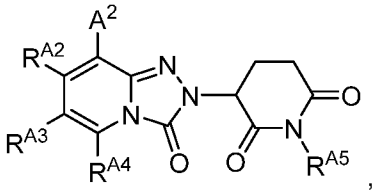
In some embodiments, each of R^{A1}, R^{A2}, R^{A3}, and R^{A4} is, independently, H, A^2, F,  ,  ,  , or  ; or R^{A1} and R^{A2}, R^{A2} and R^{A3}, or R^{A3} and R^{A4}, together with the carbon atoms to which each is attached, combine to form  ; and  is optionally substituted C_2-C_9 heterocyclyl, 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.

In some embodiments, R^{A1} is A^2. In some embodiments, R^{A2} is A^2. In some embodiments, R^{A3} is A^2. In some embodiments, R^{A4} is A^2. In some embodiments, R^{A5} is A^2.

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

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

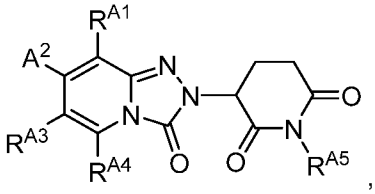
In some embodiments, the structure of **Formula B** has the structure of **Formula B1**:



Formula B1

or a pharmaceutically acceptable salt thereof.

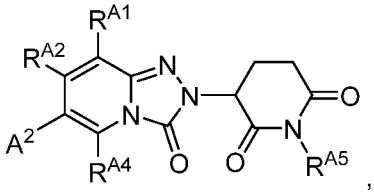
In some embodiments, the structure of **Formula B** has the structure of **Formula B2**:



Formula B2

or a pharmaceutically acceptable salt thereof.

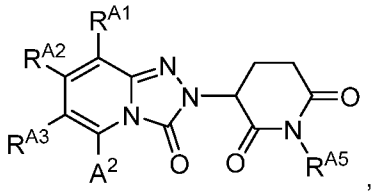
In some embodiments, the structure of **Formula B** has the structure of **Formula B3**:



Formula B3

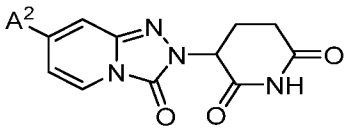
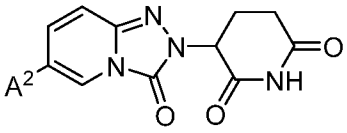
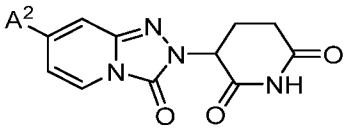
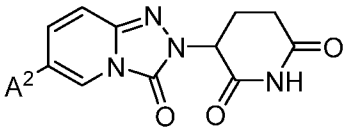
or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of **Formula B** has the structure of **Formula B4**:

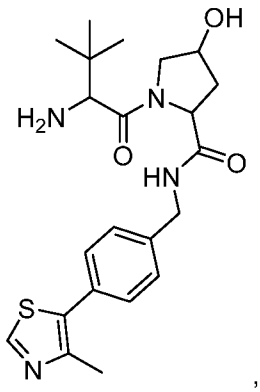


Formula B4

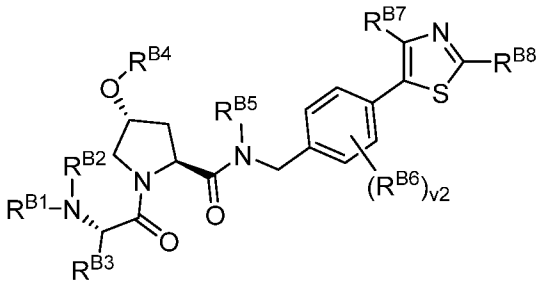
or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of **Formula B** is  or  . In some embodiments, the structure of **Formula B** is  . In some embodiments, the structure of **Formula B** is  .

In some embodiments, the ubiquitin ligase binding moiety comprises a von Hippel-Lindau ligand.

In some embodiments, the von Hippel-Lindau ligand has the structure of  , or derivative or analog thereof.

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



Formula C,

where

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;

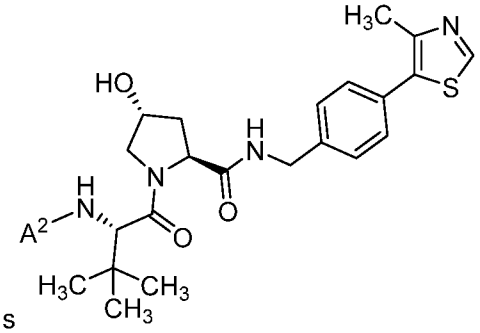
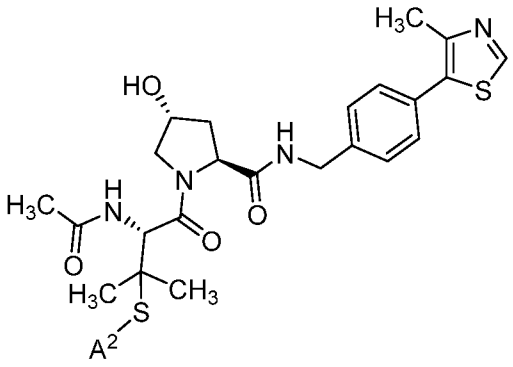
R^{B5} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

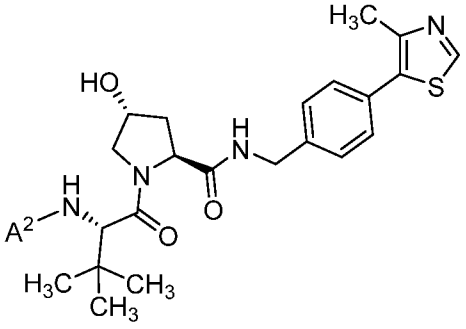
v2 is 0, 1, 2, 3, or 4;

each R^{B6} is, independently, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino; and

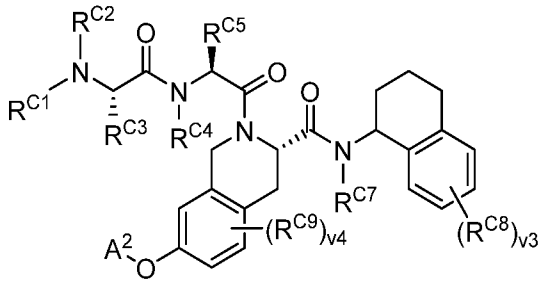
each of R^{B7} and R^{B8} is, independently, H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl,

where one of R^{B1} and R^{B3} is A^2, or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of **Formula C** is  or  , or derivative or analog thereof.

In some embodiments, the structure of **Formula C** is  .

In some embodiments, the degrader moiety includes the structure of **Formula D**:



Formula D,

where

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

each of R^{C1}, R^{C2}, and R^{C7} is, independently, H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

R^{C3} is 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;

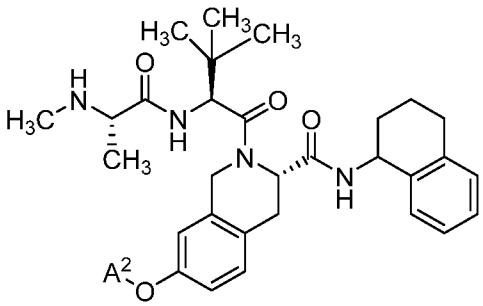
R^{C5} is optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_1-C_6 alkyl C_3-C_{10} carbocyclyl, or optionally substituted C_1-C_6 alkyl C_6-C_{10} aryl;

v3 is 0, 1, 2, 3, or 4;

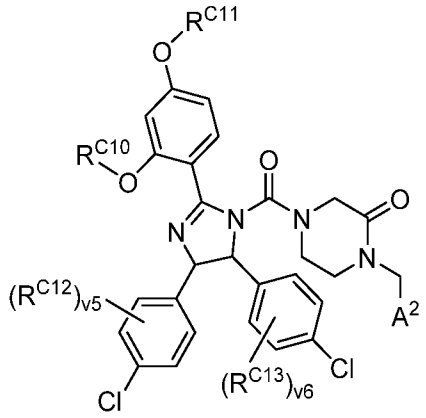
each R^{C8} is, independently, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

v4 is 0, 1, 2, 3, or 4; and

each R^{C9} is, independently, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino, or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of **Formula D** is  , or derivative or analog thereof.

In some embodiments, the degrader moiety includes the structure of **Formula E**:



Formula E,

where

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

each of R^{C10} and R^{C11} is, independently, 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;

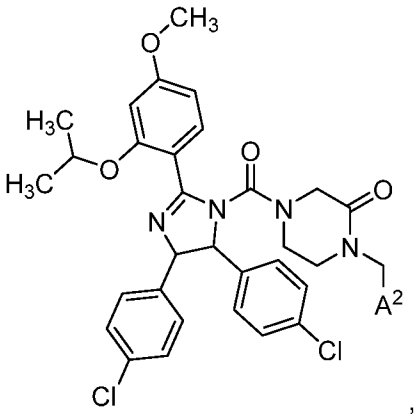
v5 is 0, 1, 2, 3, or 4;

each R^{C12} is, independently, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

v6 is 0, 1, 2, 3, or 4; and

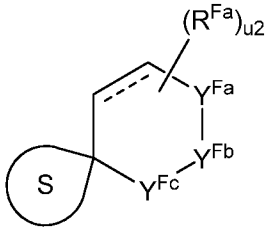
each R^{21} is, independently, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino, or a pharmaceutically acceptable salt thereof.

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



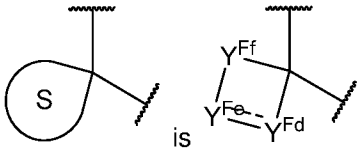
, or derivative or analog thereof.

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



Formula FA,

where



is , or a bicyclic moiety which is substituted with A^2 and substituted with one or more groups independently selected from H, R^{FF1}, and oxo;

==== is a single bond or a double bond;

u2 is 0, 1, 2, or 3;

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

Y^{Fa} is $CR^{Fb}R^{Fc}$, C=O, C=S, $C=CH_2$, SO_2, S(O), P(O)Oalkyl, P(O)NHalkyl, $P(O)N(alkyl)_2$, P(O)alkyl, P(O)OH, $P(O)NH_2$;

Y^{Fb} is NH, NR^{FF1}, CH_2, CHR^{FF1}, $C(R^{FF1})_2$, O, or S;

Y^{Fc} is $CR^{Fd}R^{Fe}$, C=O, C=S, $C=CH_2$, SO_2, S(O), P(O)Oalkyl, P(O)NHalkyl, $P(O)N(alkyl)_2$, P(O)alkyl, P(O)OH, $P(O)NH_2$;

each of R^{Fb}, R^{Fc}, R^{Fd}, and R^{Fe} is, independently, H, alkyl, aliphatic, heteroaliphatic, aryl, heteroaryl, carbocyclyl, hydroxyl, alkoxy, amino, —NHalkyl, or —$Nalkyl_2$;

or R^{Fb} and R^{Fc}, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclylene comprising 1 or 2 heteroatoms selected from N and O;

or R^{Fd} and R^{Fe}, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclylene comprising 1 or 2 heteroatoms selected from N and O; and

or R^{Fd} and R^{Fb}, together with the carbon atoms to which each is attached, combine to form a 1, 2, 3, or 4 carbon bridged ring;

each of Y^{Fd} and Y^{Ff} is, independently, CH_2, CHR^{FF2}, $C(R^{FF2})_2$, C(O), N, NH, NR^{FF3}, O, S, or S(O);

Y^{Fe} is a bond or a divalent moiety attached to Y^{Fd} and Y^{Ff} that contains 1 to 5 contiguous carbon atoms that form a 3 to 8-membered ring,

wherein 1, 2, or 3 carbon atoms can be replaced with a nitrogen, oxygen, or sulfur atom;

wherein one of the ring atoms is substituted with A^2 and the others are substituted with one or more groups independently selected from H and R^{FF1}; and

wherein the contiguous atoms of Y^{Fe} can be attached through a single or double bond;

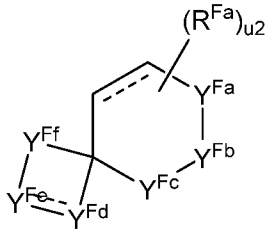
each R^{FF1} is, independently, H, alkyl, alkenyl, alkynyl, aliphatic, heteroaliphatic, carbocyclyl, halogen, hydroxyl, amino, cyano, alkoxy, aryl, heteroaryl, heterocyclyl, alkylamino, alkylhydroxyl, or haloalkyl;

each R^{FF2} is, independently, alkyl, alkene, alkyne, halogen, hydroxyl, alkoxy, azide, amino, —C(O)H, —C(O)OH, —C(O)(aliphatic, including alkyl), —C(O)O(aliphatic, including alkyl), —NH(aliphatic, including alkyl), —N(aliphatic including alkyl)(aliphatic including alkyl), —$NHSO_2$alkyl, —N(alkyl)SO_2alkyl, —$NHSO_2$aryl, —N(alkyl)SO_2aryl, —$NHSO_2$alkenyl, —N(alkyl)SO_2alkenyl, —$NHSO_2$alkynyl, —N(alkyl)SO_2alkynyl, aliphatic, heteroaliphatic, aryl, heteroaryl, hetercyclic, carbocyclic, cyano, nitro, nitroso, —SH, —Salkyl, or haloalkyl; and

R^{FF3} is alkyl, alkenyl, alkynyl, —C(O)H, —C(O)OH, —C(O)alkyl, or —C(O)Oalkyl,

wherein if Y^{Fd} or Y^{Ff} is substituted with A^2, then Y^{Fe} is a bond, or a pharmaceutically acceptable salt thereof.

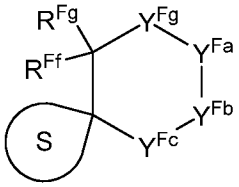
In some embodiments, the compound of **Formula FA** has the structure of **Formula FA1**:



Formula FA1,

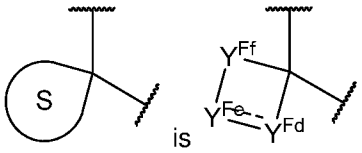
or a pharmaceutically acceptable salt thereof.

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



Formula FB,

where



is , or a bicyclic moiety which is substituted with A^2 and substituted with one or more groups independently selected from H, R^{FF1}, and oxo;

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

Y^{Fa} is $CR^{Fb}R^{Fc}$, C=O, C=S, $C=CH_2$, SO_2, S(O), P(O)Oalkyl, P(O)NHalkyl, P(O)N(alkyl)$_2$, P(O)alkyl, P(O)OH, $P(O)NH_2$;

each of Y^{Fb} and Y^{Fg} is, independently, NH, NR^{FF1}, CH_2, CHR^{FF1}, $C(R^{FF1})_2$, O, or S;

Y^{Fc} is $CR^{Fd}R^{Fe}$, C=O, C=S, $C=CH_2$, SO_2, S(O), P(O)Oalkyl, P(O)NHalkyl, P(O)N(alkyl)$_2$, P(O)alkyl, P(O)OH, $P(O)NH_2$;

each of R^{Fb}, R^{Fc}, R^{Fd}, R^{Fe}, R^{Ff}, and R^{Fg} is, independently, H, alkyl, aliphatic, heteroaliphatic, aryl, heteroaryl, carbocyclyl, hydroxyl, alkoxy, amino, —NHalkyl, or —Nalkyl$_2$;

or R^{Fb} and R^{Fc}, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclylene comprising 1 or 2 heteroatoms selected from N and O;

or R^{Fd} and R^{Fe}, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclylene comprising 1 or 2 heteroatoms selected from N and O;

or R^{Ff} and R^{Fg}, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclylene comprising 1 or 2 heteroatoms selected from N and O;

or R^{Fd} and R^{Fb}, together with the carbon atoms to which each is attached, combine to form a 1, 2, 3, or 4 carbon bridged ring;

or R^{Fd} and R^{Ff}, together with the carbon atoms to which each is attached, combine to form a 1, 2, 3, or 4 carbon bridged ring;

or R^{Fb} and R^{Fg}, together with the carbon atoms to which each is attached, combine to form a 1, 2, 3, or 4 carbon bridged ring;

each of Y^{Fd} and Y^{Ff} is, independently, CH_2, CHR^{FF2}, $C(R^{FF2})_2$, C(O), N, NH, NR^{FF3}, O, S, or S(O);

Y^{Fe} is a bond or a divalent moiety attached to Y^{Fd} and Y^{Ff} that contains 1 to 5 contiguous carbon atoms that form a 3 to 8-membered ring,

wherein 1, 2, or 3 carbon atoms can be replaced with a nitrogen, oxygen, or sulfur atom;

wherein one of the ring atoms is substituted with A^2 and the others are substituted with one or more groups independently selected from H and R^{FF1}; and

wherein the contiguous atoms of Y^{Fe} can be attached through a single or double bond;

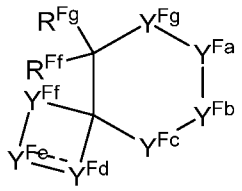
each R^{FF1} is, independently, H, alkyl, alkenyl, alkynyl, aliphatic, heteroaliphatic, carbocyclyl, halogen, hydroxyl, amino, cyano, alkoxy, aryl, heteroaryl, heterocyclyl, alkylamino, alkylhydroxyl, or haloalkyl;

each R^{FF2} is, independently, alkyl, alkene, alkyne, halogen, hydroxyl, alkoxy, azide, amino, —C(O)H, —C(O)OH, —C(O)(aliphatic, including alkyl), —C(O)O(aliphatic, including alkyl), —NH(aliphatic, including alkyl), —N(aliphatic including alkyl)(aliphatic including alkyl), —$NHSO_2$alkyl, —N(alkyl)SO_2alkyl, —$NHSO_2$aryl, —N(alkyl)SO_2aryl, —$NHSO_2$alkenyl, —N(alkyl)SO_2alkenyl, —$NHSO_2$alkynyl, —N(alkyl)SO_2alkynyl, aliphatic, heteroaliphatic, aryl, heteroaryl, hetercyclic, carbocyclic, cyano, nitro, nitroso, —SH, —Salkyl, or haloalkyl; and

R^{FF3} is alkyl, alkenyl, alkynyl, —C(O)H, —C(O)OH, —C(O)alkyl, or —C(O)Oalkyl,

wherein if Y^{Fd} or Y^{Ff} is substituted with A^2, then Y^{Fe} is a bond, or a pharmaceutically acceptable salt thereof.

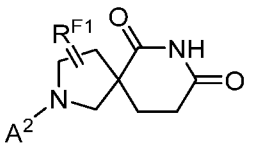
In some embodiments, the compound of **Formula FB** has the structure of **Formula FB1**:



Formula FB1,

or a pharmaceutically acceptable salt thereof.

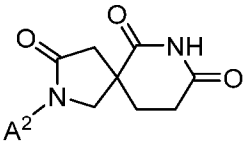
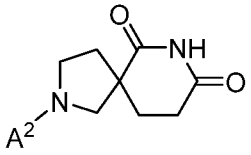
In some embodiments, the degradation moiety includes the structure of **Formula F1**:



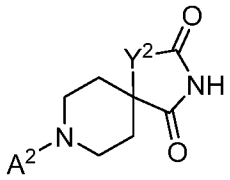
Formula F1,

where A^2 is a bond between the degrader and the linker; and R^{F1} is absent or O, or a pharmaceutically acceptable salt thereof.

In some embodiments, R^{F1} is absent. In some embodiments, R^{F1} is O.

In some embodiments, the structure of **Formula F1** is  or  .

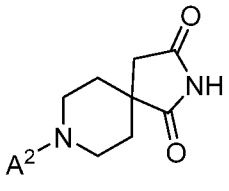
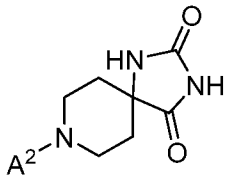
In some embodiments, the degradation moiety includes the structure **Formula F2**:



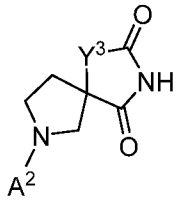
Formula F2,

where A^2 is a bond between the degrader and the linker; and Y^2 is CH_2 or NH, or a pharmaceutically acceptable salt thereof.

In some embodiments, Y^2 is NH. In some embodiments, Y^2 is CH_2.

In some embodiments, structure of **Formula F2** is  or  .

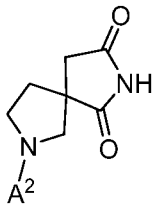
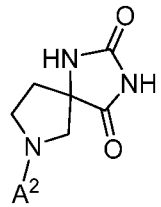
In some embodiments, the degradation moiety includes the structure **Formula G**:



Formula G,

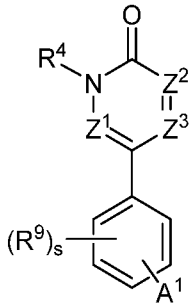
where A^2 is a bond between the degrader and the linker; and Y^3 is CH_2 or NH, or a pharmaceutically acceptable salt thereof.

In some embodiments, Y^3 is NH. In some embodiments, Y^3 is CH_2.

In some embodiments, structure of **Formula G** is  or  .

The degradation moiety may also include structures found in, e.g., WO2017/197036; WO2019/204354, WO2019/236483, WO2020/010177; and WO2020/010227, the structures of which are herein incorporated by reference.

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



Formula III,

where

R^4 is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_{10} carbocyclyl; Z^1 is N or CR^5;

Z^2 is N or CR^{6a};

Z^3 is N or CR^{6b};

R^5 is H, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, or optionally substituted C_6-C_{10} aryl;

R^{6a} is H, halogen, cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino; R^{6b} is H, halogen, cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino; or R^{6a} and R^{6b}, together with the carbon atoms to which each is attached, combine to form optionally substituted C_6-C_{10} aryl or optionally substituted C_2-C_9 heteroaryl;

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

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

A^1 is a bond between A and the linker, or a pharmaceutically acceptable salt thereof.

In some embodiments, Z^1 is N. In some embodiments, Z^1 is CR^5.

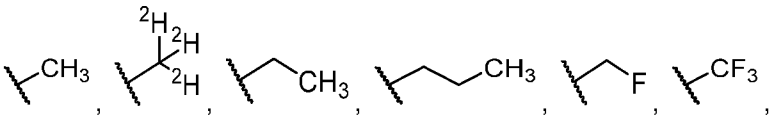
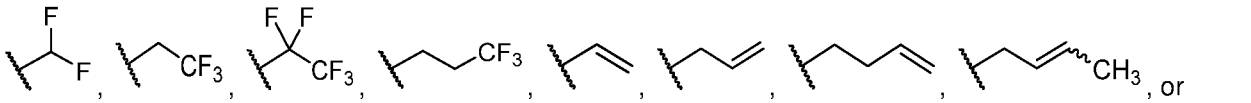
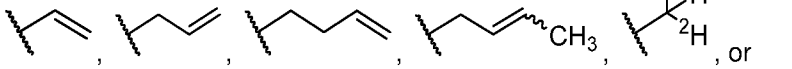
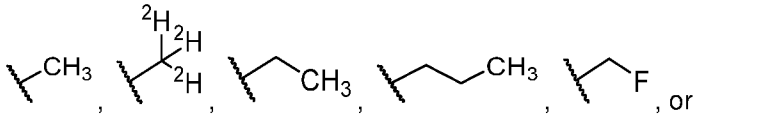
In some embodiments, Z^2 is N. In some embodiments, Z^2 is CR^{6a}.

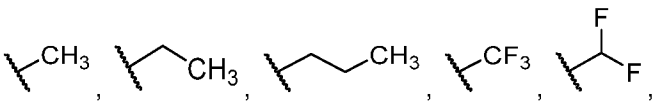
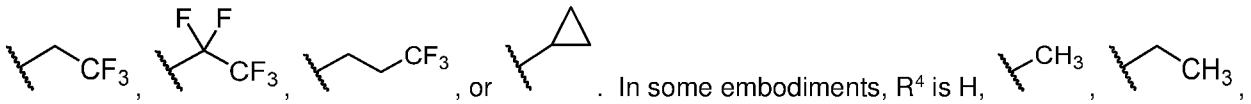
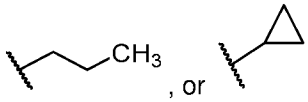
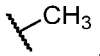
In some embodiments, Z^3 is N. In some embodiments, Z^3 is CR^{6b}.

In some embodiments, Z^1 is CR^5, Z^2 is CR^{6a}, and Z^3 is CR^{6b}. In some embodiments, Z^1 is N, Z^2 is CR^{6a}, and Z^2 is CR^{6b}. In some embodiments, Z^1 is CR^5, Z^2 is N, and Z^3 is CR^{6b}. In some embodiments, Z^1 is N, Z^2 is CR^{6a}, and Z^3 is N. In some embodiments, Z^1 is N, Z^2 is N, and Z^3 is CR^{6b}. In some embodiments, Z^1 is CR^5, Z^2 is N, and Z^3 is N.

In some embodiments, R^4 is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_{10} carbocyclyl. In some embodiments, R^4 is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, or optionally substituted C_3-C_{10} carbocyclyl. In some embodiments, R^4 is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_{10} carbocyclyl.

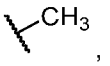
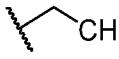
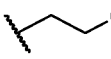
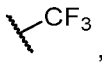
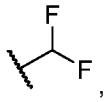
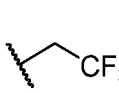
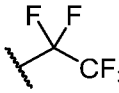
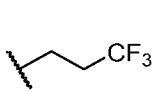
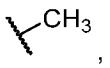
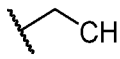
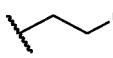
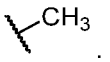
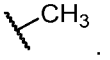
In some embodiments, optionally substituted C_1-C_6 alkyl is C_1-C_6 perfluoroalkyl.

In some embodiments, R^4 is H,  ,  ,  . In some embodiments, R^4 is  . In some embodiments, R^4 is H,  . In some embodiments, R^4 is H,  ,  .

In some embodiments, R^4 is H,  ,  . In some embodiments, R^4 is H, ,  . In some embodiments, R^4 is H or  . In some embodiments, R^4 is H. In some embodiments, R^4 is  .

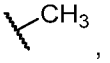
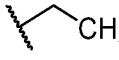
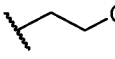
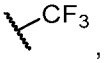
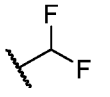
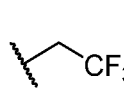
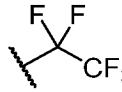
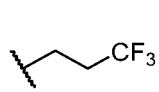
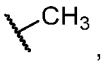
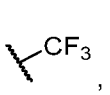
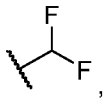
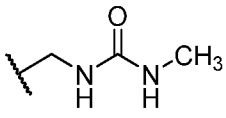
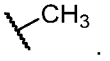
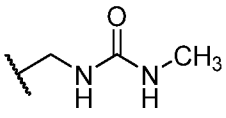
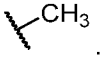
In some embodiments, R^5 is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl. In some embodiments, R^5 is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_{10} carbocyclyl. In some embodiments, R^5 is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_{10} carbocyclyl.

In some embodiments, optionally substituted C_1-C_6 alkyl is C_1-C_6 perfluoroalkyl.

In some embodiments, R^5 is H,  ,  ,  ,  ,  ,  ,  ,  , or  . In some embodiments, R^5 is H,  ,  ,  , or  . In some embodiments, R^5 is H or  . In some embodiments, R^5 is H. In some embodiments, R^5 is  .

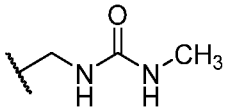
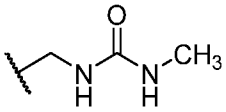
In some embodiments, R^{6a} is H, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino.

In some embodiments, R^{6a} is H, halogen, cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_{10} carbocyclyl. In some embodiments, R^{6a} is H, halogen, cyano, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl. In some embodiments, R^{6a} is H, halogen, cyano, or optionally substituted C_1-C_6 alkyl. In some embodiments, R^{6a} is optionally substituted C_1-C_6 heteroalkyl.

In some embodiments, R^{6a} is H, F, cyano,  ,  ,  ,  ,  ,  ,  ,  , or  . In some embodiments, R^{6a} is H, F, cyano,  ,  ,  , or  . In some embodiments, R^{6a} is H, F, cyano, or  . In some embodiments, R^{6a} is  . In some embodiments, R^{6a} is H or  . In some embodiments, R^{6a} is H. In some embodiments, R^{6a} is  .

In some embodiments, R^{6b} is H, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino.

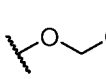
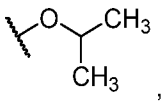
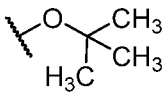
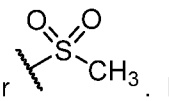
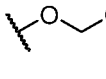
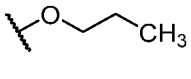
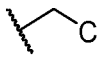
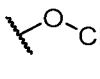
In some embodiments, R^{6b} is H, halogen, cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_{10} carbocyclyl. In some embodiments, R^{6b} is H, halogen, cyano, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl. In some embodiments, R^{6b} is H, halogen, cyano, or optionally substituted C_1-C_6 alkyl. In some embodiments, R^{6b} is optionally substituted C_1-C_6 heteroalkyl.

In some embodiments, R^{6b} is H, F, cyano,  ,  ,  ,  ,  ,  ,  ,  , or  . In some embodiments, R^{6b} is H, F, cyano,  ,  ,  , or  . In some embodiments, R^{6b} is H, F, cyano, or  . In some embodiments, R^{6b} is  . In some embodiments, R^{6b} is H or  . In some embodiments, R^{6b} is H. In some embodiments, R^{6b} is  .

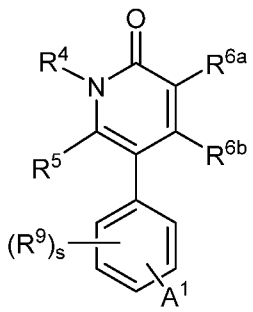
In some embodiments, R^{6a} and R^{6b}, together with the carbon atoms to which each is attached, combine to form optionally substituted C_6-C_{10} aryl or optionally substituted C_2-C_9 heteroaryl.

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

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

In some embodiments, R^9 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  . In some embodiments, each R^9 is, independently, halogen,  ,  ,  ,  ,  , or  . In some embodiments, each R^9 is, independently, F, Cl,  ,  , or  .

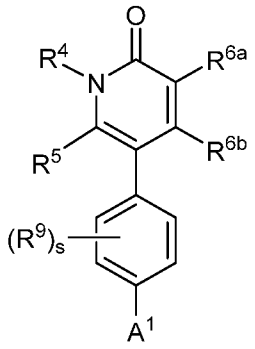
In some embodiments, the structure of **Formula III** has the structure of **Formula IIIa**:



Formula IIIa,

or a pharmaceutically acceptable salt thereof.

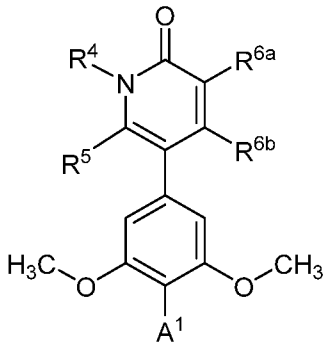
In some embodiments, the structure of **Formula III** has the structure of **Formula IIIb**:



Formula IIIb,

or a pharmaceutically acceptable salt thereof.

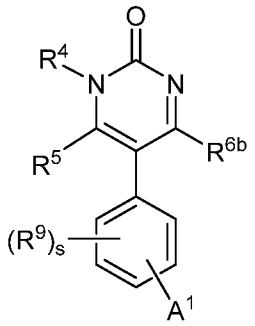
In some embodiments, the structure of **Formula III** has the structure of **Formula IIIc**:



Formula IIIc,

or a pharmaceutically acceptable salt thereof.

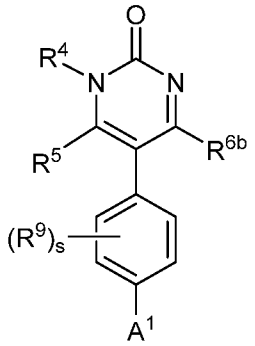
In some embodiments, the structure of **Formula III** has the structure of **Formula IIId**:



Formula IIId,

or a pharmaceutically acceptable salt thereof.

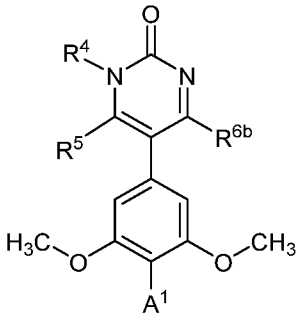
In some embodiments, the structure of **Formula III** has the structure of **Formula IIIe**:



Formula IIIe,

or a pharmaceutically acceptable salt thereof.

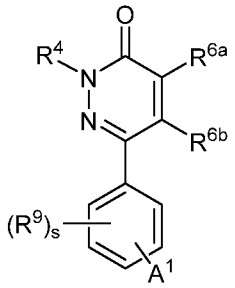
In some embodiments, the structure of **Formula III** has the structure of **Formula IIIf**:



Formula IIIf,

or a pharmaceutically acceptable salt thereof.

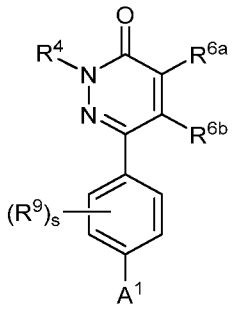
In some embodiments, the structure of **Formula III** has the structure of **Formula IIIg**:



Formula IIIg,

or a pharmaceutically acceptable salt thereof.

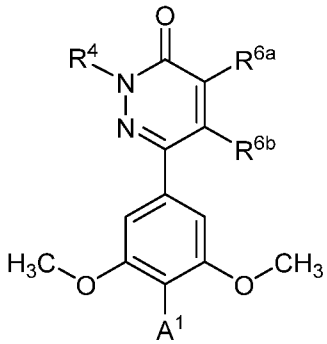
In some embodiments, the structure of **Formula III** has the structure of **Formula IIIh**:



Formula IIIh,

or a pharmaceutically acceptable salt thereof.

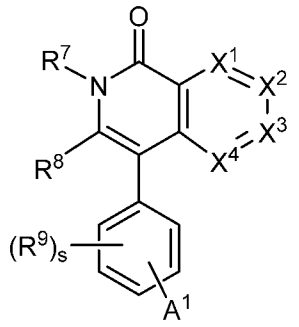
In some embodiments, the structure of **Formula III** has the structure of **Formula IIIi**:



Formula IIIi,

or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of **Formula III** has the structure of **Formula IV**:



Formula IV,

where

R^7 is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_{10} carbocyclyl;

R^8 is H, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, or optionally substituted C_6-C_{10} aryl;

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

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

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

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

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

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

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

A^1 is a bond between A and the linker, or a pharmaceutically acceptable salt thereof.

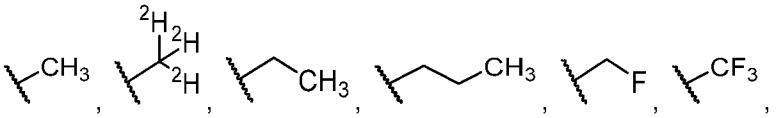
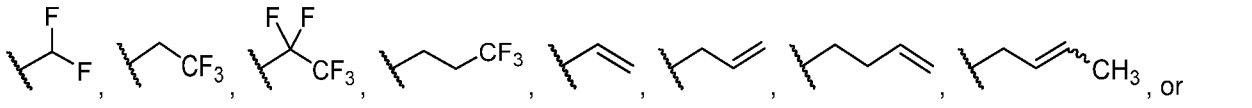
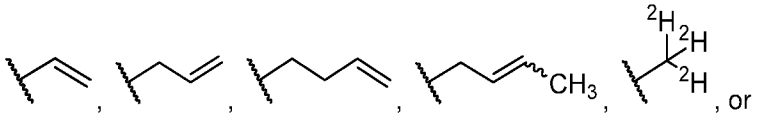
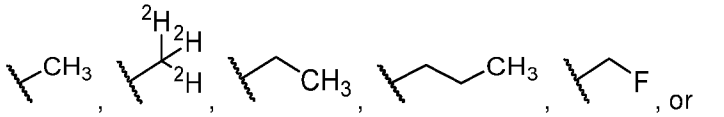
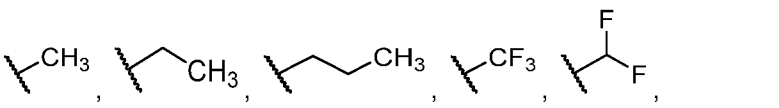
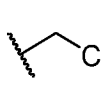
In some embodiments, X^1 is N. In some embodiments, X^1 is CR^{10a}. In some embodiments, X^2 is N. In some embodiments, X^2 is CR^{10b}. In some embodiments, X^3 is N. In some embodiments, X^3 is CR^{10c}. In some embodiments, X^4 is N. In some embodiments, X^1 is CR^{10d}.

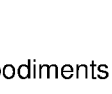
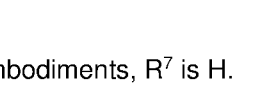
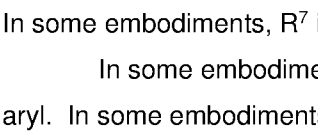
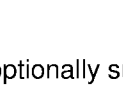
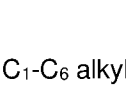
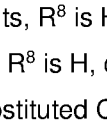
In some embodiments, X^1 is CR^{10a}, X^2 is CR^{10b}, X^3 is CR^{10c}, and X^4 is CR^{10d}. In some embodiments, X^1 is N, X^2 is CR^{10b}, X^3 is CR^{10c}, and X^4 is CR^{10d}. In some embodiments, X^1 is CR^{10a}, X^2 is N, X^3 is CR^{10c}, and X^4 is CR^{10d}. In some embodiments, X^1 is CR^{10a}, X^2 is CR^{10b}, X^3 is N, and X^4 is CR^{10d}. In some embodiments, X^1 is CR^{10a}, X^2 is CR^{10b}, X^3 is CR^{10c}, and X^4 is N. In some embodiments, X^1 is N, X^2 is N, X^3 is CR^{10c}, and X^4 is CR^{10d}. In some embodiments, X^1 is N, X^2 is CR^{10b}, X^3 is N, and X^4 is CR^{10d}. In some embodiments, X^1 is N, X^2 is CR^{10b}, X^3 is CR^{10c}, and X^4 is N. In some embodiments, X^1 is CR^{10a},

X^2 is N, X^3 is N, and X^4 is CR^{10d}. In some embodiments, X^1 is CR^{10a}, X^2 is N, X^3 is CR^{10c}, and X^4 is N. In some embodiments, X^1 is CR^{10a}, X^2 is CR^{10b}, X^3 is N, and X^4 is N.

In some embodiments, R^7 is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_{10} carbocyclyl. In some embodiments, R^7 is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, or optionally substituted C_3-C_{10} carbocyclyl. In some embodiments, R^7 is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_{10} carbocyclyl.

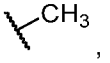
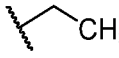
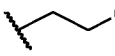
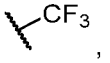
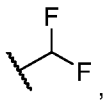
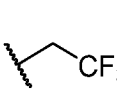
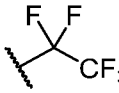
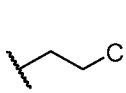
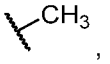
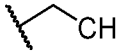
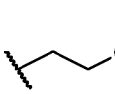
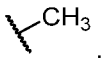
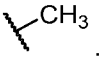
In some embodiments, optionally substituted C_1-C_6 alkyl is C_1-C_6 perfluoroalkyl.

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

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

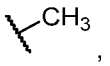
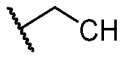
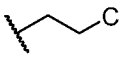
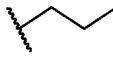
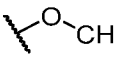
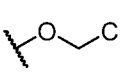
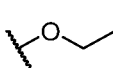
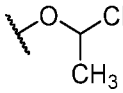
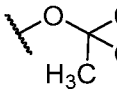
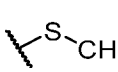
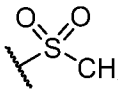
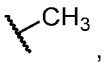
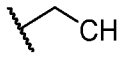
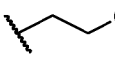
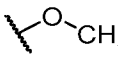
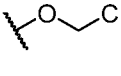
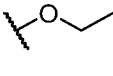
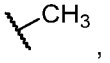
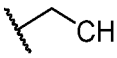
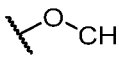
In some embodiments, R^8 is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl. In some embodiments, R^8 is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_{10} carbocyclyl. In some embodiments, R^8 is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_{10} carbocyclyl. In some embodiments, R^8 is H or optionally substituted C_1-C_6 alkyl.

In some embodiments, optionally substituted C_1-C_6 alkyl is C_1-C_6 perfluoroalkyl.

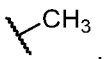
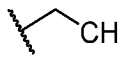
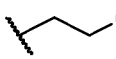
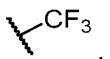
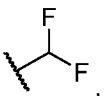
In some embodiments, R^8 is H,  ,  ,  ,  ,  ,  ,  ,  , or  . In some embodiments, R^8 is H,  ,  ,  , or  . In some embodiments, R^8 is H or  . In some embodiments, R^8 is H. In some embodiments, R^8 is  .

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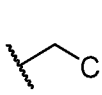
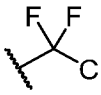
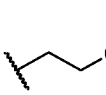
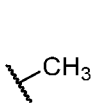
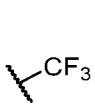
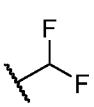
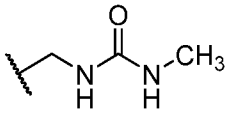
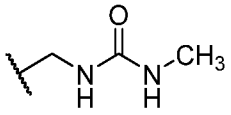
In some embodiments, each R^9 is, independently, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl. In some embodiments, each R^9 is, independently, optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_6 heteroalkyl.

In some embodiments, R^9 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  . In some embodiments, each R^9 is, independently, halogen,  ,  ,  ,  ,  , or  . In some embodiments, each R^9 is, independently, F, Cl,  ,  , or  .

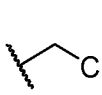
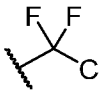
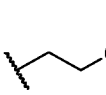
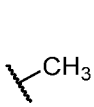
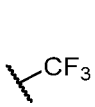
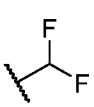
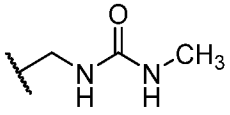
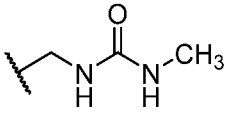
In some embodiments, R^{10a} is H, halogen, cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_{10} carbocyclyl. In some embodiments, R^{10a} is H, halogen, cyano, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl. In some embodiments, R^{10a} is H, halogen, cyano, or optionally substituted C_1-C_6 alkyl. In some embodiments, R^{10a} is optionally substituted C_1-C_6 heteroalkyl.

In some embodiments, R^{10a} is H, F, cyano,  ,  ,  ,  ,  , , , , or . In some embodiments, R^{10a} is H, F, cyano, , , , or . In some embodiments, R^{10a} is H, F, cyano, or . In some embodiments, R^{10a} is . In some embodiments, R^{10a} is H or . In some embodiments, R^{10a} is H. In some embodiments, R^{10a} is .

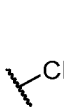
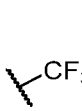
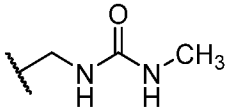
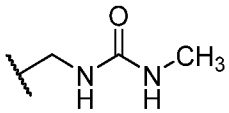
In some embodiments, R^{10b} is H, halogen, cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_{10} carbocyclyl. In some embodiments, R^{10b} is H, halogen, cyano, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl. In some embodiments, R^{10b} is H, halogen, cyano, or optionally substituted C_1-C_6 alkyl. In some embodiments, R^{10b} is optionally substituted C_1-C_6 heteroalkyl.

In some embodiments, R^{10b} is H, F, cyano,  ,  ,  ,  ,  ,  ,  ,  , or  . In some embodiments, R^{10b} is H, F, cyano,  ,  ,  , or  . In some embodiments, R^{10b} is H, F, cyano, or  . In some embodiments, R^{10b} is  . In some embodiments, R^{10b} is H or  . In some embodiments, R^{10b} is H. In some embodiments, R^{10b} is  .

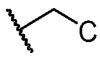
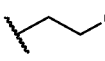
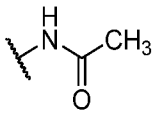
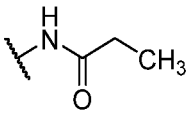
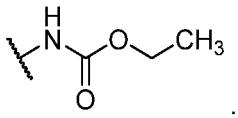
In some embodiments, R^{10c} is H, halogen, cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_{10} carbocyclyl. In some embodiments, R^{10c} is H, halogen, cyano, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl. In some embodiments, R^{10c} is H, halogen, cyano, or optionally substituted C_1-C_6 alkyl. In some embodiments, R^{10c} is optionally substituted C_1-C_6 heteroalkyl.

In some embodiments, R^{10c} is H, F, cyano,  ,  ,  ,  ,  ,  ,  ,  , or  . In some embodiments, R^{10c} is H, F, cyano,  ,  ,  , or  . In some embodiments, R^{10c} is H, F, cyano, or  . In some embodiments, R^{10c} is  . In some embodiments, R^{10c} is H or  . In some embodiments, R^{10c} is H. In some embodiments, R^{10c} is  .

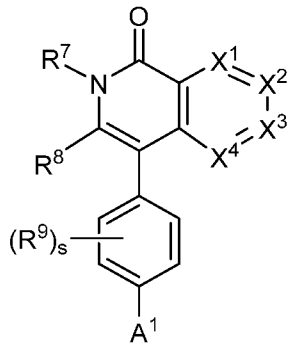
In some embodiments, R^{10d} is H, halogen, cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_{10} carbocyclyl. In some embodiments, R^{10d} is H, halogen, cyano, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl. In some embodiments, R^{10d} is H, halogen, cyano, or optionally substituted C_1-C_6 alkyl. In some embodiments, R^{10d} is optionally substituted C_1-C_6 heteroalkyl.

In some embodiments, R^{10d} is H, F, cyano,  ,  ,  ,  ,  ,  ,  ,  , or  . In some embodiments, R^{10d} is H, F, cyano,  ,  ,  , or  . In some embodiments, R^{10d} is H, F, cyano, or  . In some embodiments, R^{10d} is  . In some embodiments, R^{10d} is H or  . In some embodiments, R^{10d} is H. In some embodiments, R^{10d} is  .

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

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

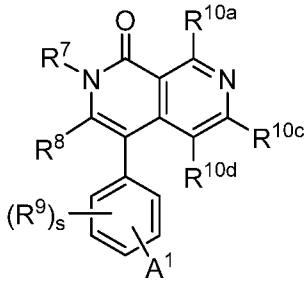
In some embodiments, A includes the structure of **Formula IVa**:



Formula IVa,

or a pharmaceutically acceptable salt thereof.

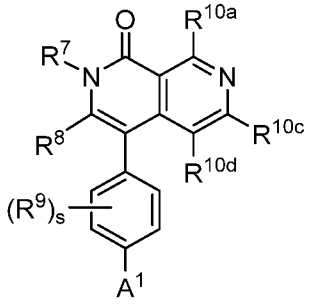
In some embodiments, A includes the structure of **Formula IVb**:



Formula IVb,

or a pharmaceutically acceptable salt thereof.

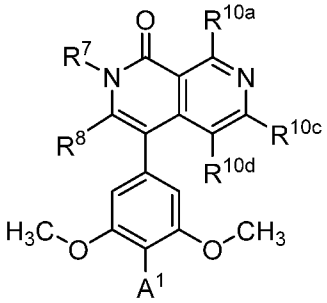
In some embodiments, A includes the structure of **Formula IVc**:



Formula IVc,

or a pharmaceutically acceptable salt thereof.

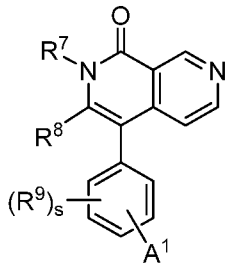
In some embodiments, A includes the structure of **Formula IVd**:



Formula IVd,

or a pharmaceutically acceptable salt thereof.

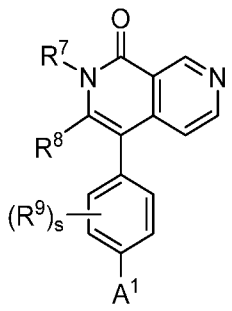
In some embodiments, A includes the structure of **Formula IVe**:



Formula IVe,

or a pharmaceutically acceptable salt thereof.

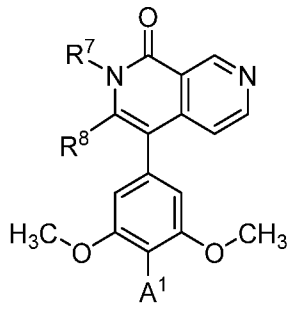
In some embodiments, A includes the structure of **Formula IVf**:



Formula IVf,

or a pharmaceutically acceptable salt thereof.

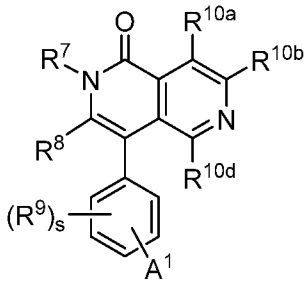
In some embodiments, A includes the structure of **Formula IVg**:



Formula IVg,

or a pharmaceutically acceptable salt thereof.

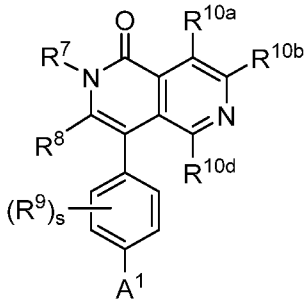
In some embodiments, A includes the structure of **Formula IVh**:



Formula IVh,

or a pharmaceutically acceptable salt thereof.

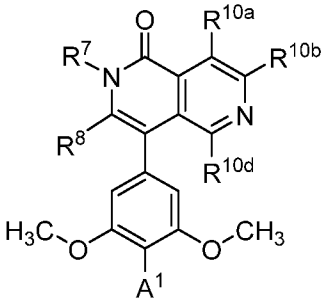
In some embodiments, A includes the structure of **Formula IVi**:



Formula IVi,

or a pharmaceutically acceptable salt thereof.

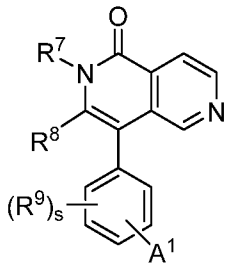
In some embodiments, A includes the structure of **Formula IVj**:



Formula IVj,

or a pharmaceutically acceptable salt thereof.

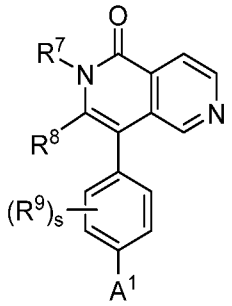
In some embodiments, A includes the structure of **Formula IVk**:



Formula IVk,

or a pharmaceutically acceptable salt thereof.

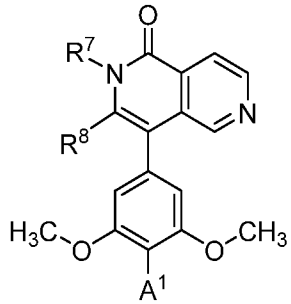
In some embodiments, A includes the structure of **Formula IVm**:



Formula IVm,

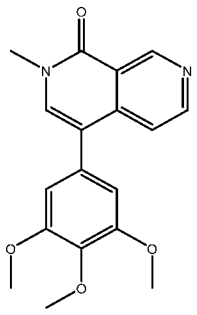
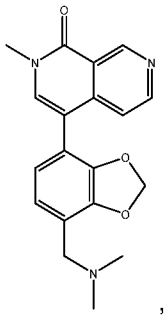
or a pharmaceutically acceptable salt thereof.

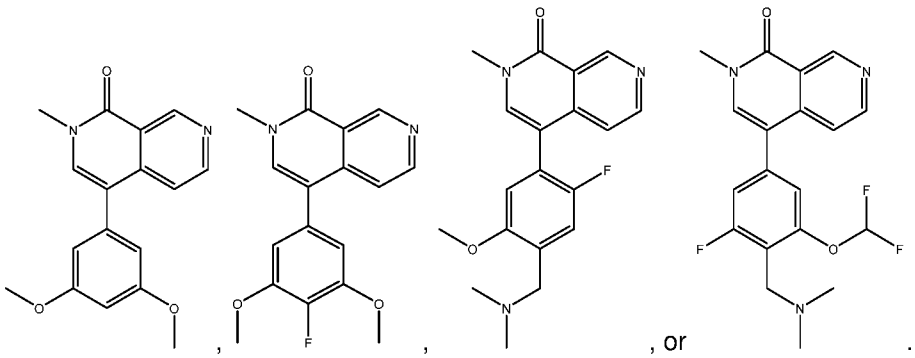
In some embodiments, A includes the structure of **Formula IVn**:



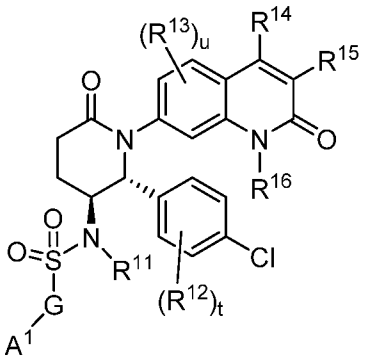
Formula IVn,

or a pharmaceutically acceptable salt thereof.

In some embodiments, A includes the structure of any one of  ,  ,



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



Formula V,

where

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

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

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

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

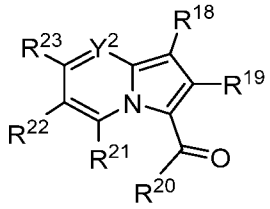
each R^{13} is, independently, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally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

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

G is optionally substituted C_1-C_6 alkylene, optionally substituted C_6-C_{10} arylene, or optionally substituted C_3-C_6 carbocyclylene; and

A^1 is a bond between A and the linker, or a pharmaceutically acceptable salt thereof.

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



Formula VI,

where

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

R^{18} is A^1, optionally substituted C_6-C_{10} aryl or C_2-C_9 heteroaryl;

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

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

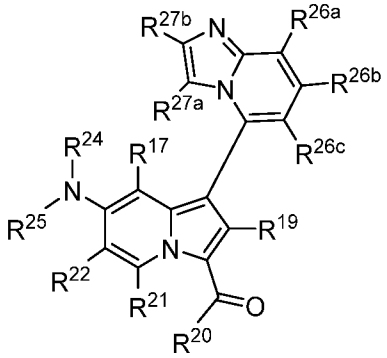
each R^{17}, R^{21}, and R^{22} is, independently, H, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9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

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

each of R^{24} and R^{25} is, independently, H, A^1, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl, or R^{24} and R^{25} combine to form optionally substituted C_2-C_9 heterocyclyl,

where one of R^{18}, R^{24}, or R^{25} is A^1, or a pharmaceutically acceptable salt thereof.

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



Formula VII,

where

each R^{26a}, R^{26b}, and R^{26c} is, independently, H, A^1, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

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

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

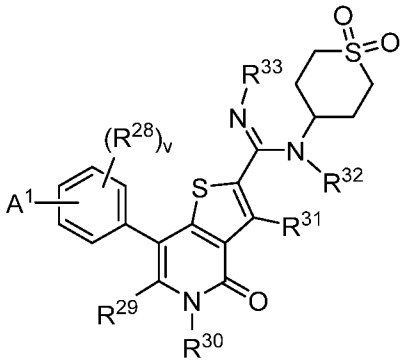
R^{20} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

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

each of R^{24} and R^{25} is, independently, H, A^1, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl, or R^{24} and R^{25} combine to form optionally substituted C_2-C_9 heterocyclyl,

where one of R^{26a}, R^{26b}, R^{26c}, R^{24}, or R^{25} is A^1, or a pharmaceutically acceptable salt thereof.

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



Formula VIII,

where

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

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

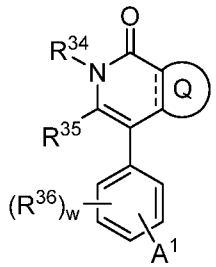
R^{29} is H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

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

each R^{30}, R^{32}, and R^{33} is, independently, H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl; and

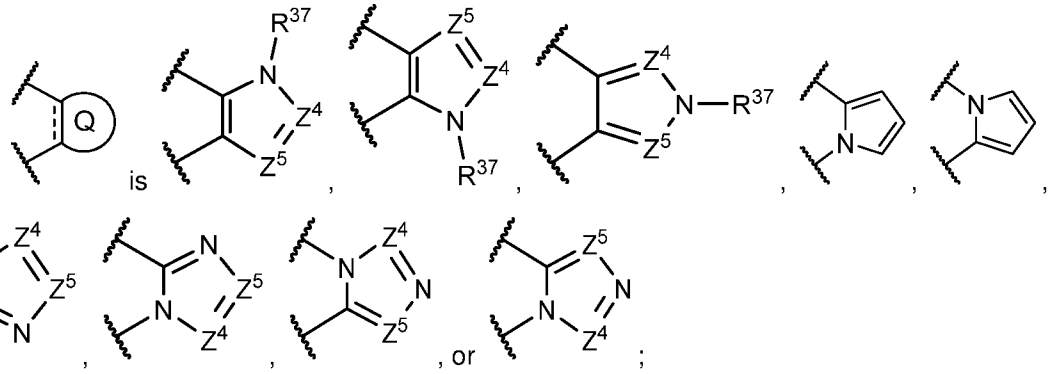
A^1 is a bond between A and the linker, or a pharmaceutically acceptable salt thereof.

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



Formula IX,

where



Z^4 is N or CR^{38};

Z^5 is N or CR^{39};

R^{34} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_{10} carbocyclyl;

R^{35} is H, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_6 carbocyclyl, or optionally substituted C_6-C_{10} aryl;

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

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

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

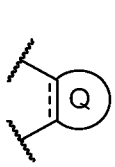
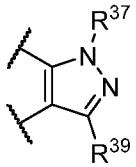
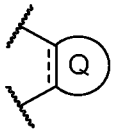
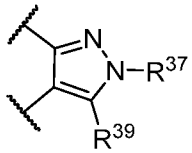
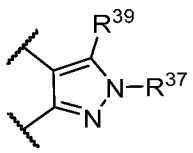
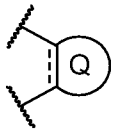
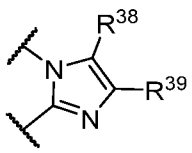
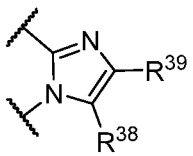
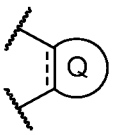
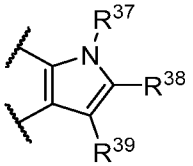
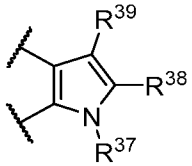
w is 0, 1, 2, 3, or 4;

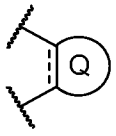
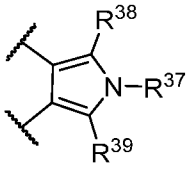
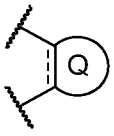
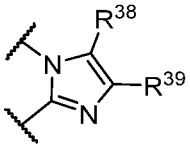
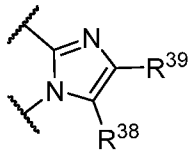
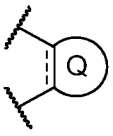
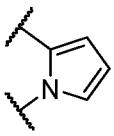
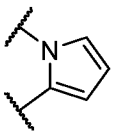
each R^{36} is, independently, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally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

A^1 is a bond between A and the linker, or a pharmaceutically acceptable salt thereof.

In some embodiments, Z^4 is N. In some embodiments, Z^4 is R^{38}. In some embodiments, Z^5 is N. In some embodiments, Z^5 is R^{39}.

In some embodiments, Z^4 is N and Z^5 is R^{39}. In some embodiments, Z^4 is R^{38} and Z^5 is N. In some embodiments, Z^4 is R^{38} and Z^5 is R^{39}.

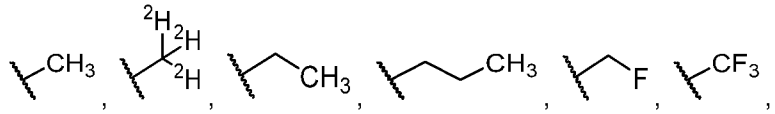
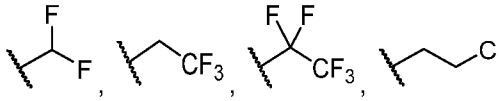
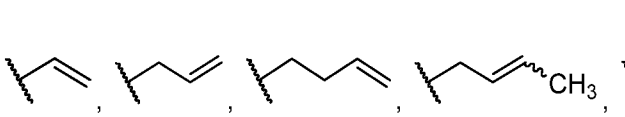
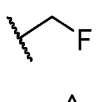
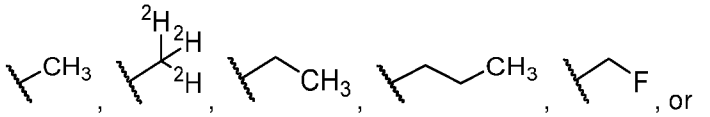
In some embodiments,  is  or  . In some embodiments,  is  or  . In some embodiments,  is  or  . In some embodiments,  is  or  . In some

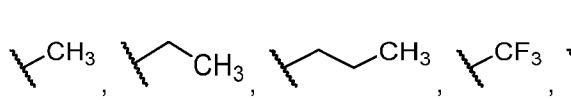
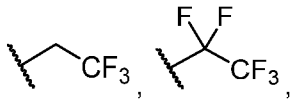
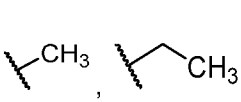
embodiments,  is  . In some embodiments,  is  or  . In some embodiments,  is  or  .

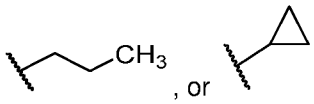
In some embodiments, R^{37} is H or optionally substituted C_1-C_6 alkyl. In some embodiments, R^{37} is H or  . In some embodiments, R^{38} is H or optionally substituted C_1-C_6 alkyl. In some embodiments, R^{38} is H or  . In some embodiments, R^{39} is H or optionally substituted C_1-C_6 alkyl. In some embodiments, R^{39} is H or  .

In some embodiments, R^{34} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_{10} carbocyclyl. In some embodiments, R^{34} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, or optionally substituted C_3-C_{10} carbocyclyl. In some embodiments, R^{34} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_{10} carbocyclyl.

In some embodiments, optionally substituted C_1-C_6 alkyl is C_1-C_6 perfluoroalkyl.

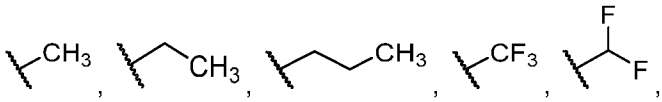
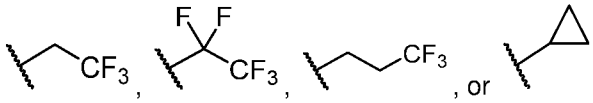
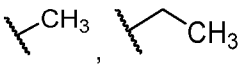
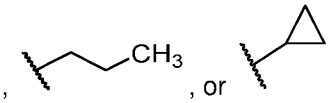
In some embodiments, R^{34} is H,  ,  , or  . In some embodiments, R^{34} is  , or  . In some embodiments, R^{34} is H,  , or  .

In some embodiments, R^{34} is H,  ,  , or  . In some embodiments, R^{34} is H, 

 , . In some embodiments, R^{34} is H or  . In some embodiments, R^{34} is H. In some embodiments, R^{34} is  .

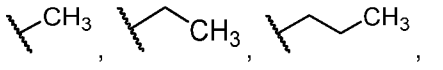
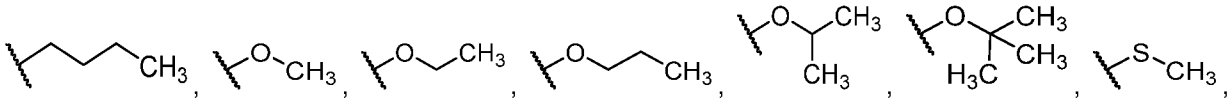
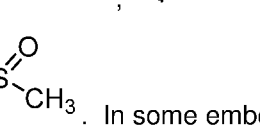
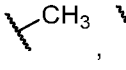
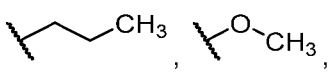
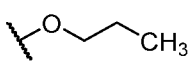
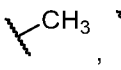
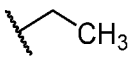
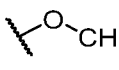
In some embodiments, R^{35} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl. In some embodiments, R^{35} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_{10} carbocyclyl. In some embodiments, R^{35} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_{10} carbocyclyl. In some embodiments, R^{35} is H or optionally substituted C_1-C_6 alkyl.

In some embodiments, optionally substituted C_1-C_6 alkyl is C_1-C_6 perfluoroalkyl.

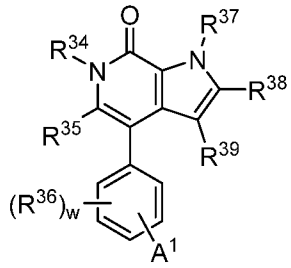
In some embodiments, R^{35} is H,  ,  , . In some embodiments, R^{35} is H,  ,  , . In some embodiments, R^{35} is H or  . In some embodiments, R^{35} is H. In some embodiments, R^{35} is  .

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

In some embodiments, each R^{36} is, independently, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl. In some embodiments, each R^{36} is, independently, optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_6 heteroalkyl.

In some embodiments, each R^{36} is, independently,  ,  ,  . In some embodiments, each R^{36} is, independently, halogen,  ,  , , or  . In some embodiments, each R^{36} is, independently, F, Cl,  ,  , or  .

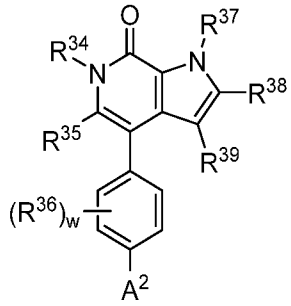
In some embodiments, the structure of **Formula IX** has the structure of **Formula IXa**:



Formula IXa,

or a pharmaceutically acceptable salt thereof.

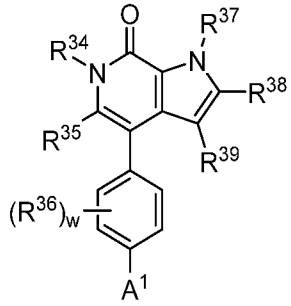
In some embodiments, the structure of **Formula IX** has the structure of **Formula IXb**:



Formula IXb,

or a pharmaceutically acceptable salt thereof.

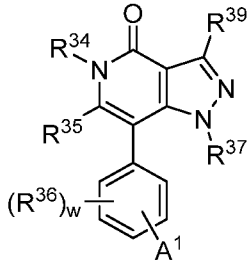
In some embodiments, the structure of **Formula IX** has the structure of **Formula IXc**:



Formula IXc,

or a pharmaceutically acceptable salt thereof.

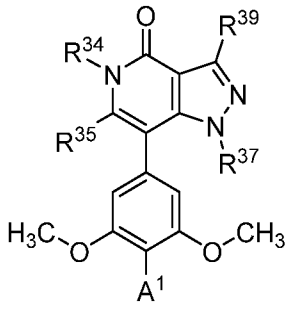
In some embodiments, the structure of **Formula IX** has the structure of **Formula IXd**:



Formula IXd,

or a pharmaceutically acceptable salt thereof.

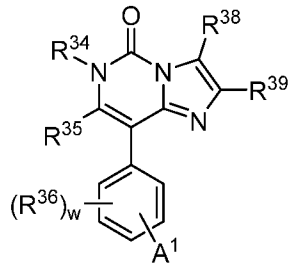
In some embodiments, the structure of **Formula IX** has the structure of **Formula IXe**:



Formula IXe,

or a pharmaceutically acceptable salt thereof.

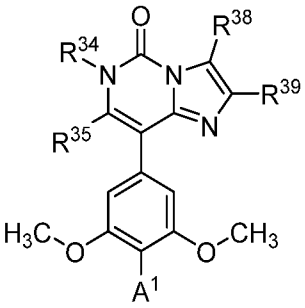
In some embodiments, the structure of **Formula IX** has the structure of **Formula IXf**:



Formula IXf,

or a pharmaceutically acceptable salt thereof.

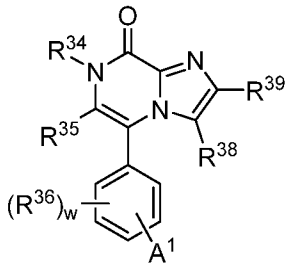
In some embodiments, the structure of **Formula IX** has the structure of **Formula IXg**:



Formula IXg,

or a pharmaceutically acceptable salt thereof.

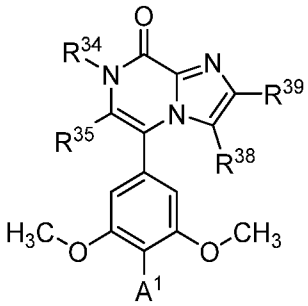
In some embodiments, the structure of **Formula IX** has the structure of **Formula IXh**:



Formula IXh,

or a pharmaceutically acceptable salt thereof.

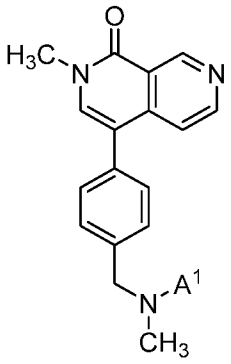
In some embodiments, the structure of **Formula IX** has the structure of **Formula IXi**:



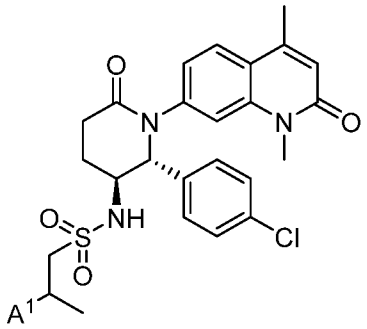
Formula IXi,

or a pharmaceutically acceptable salt thereof.

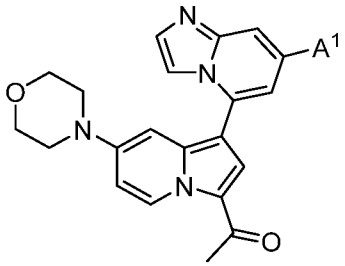
In some embodiments, A includes the structure of:



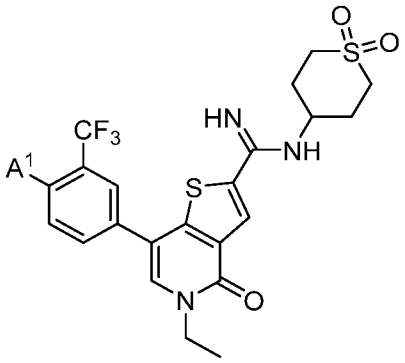
X2,



X3,

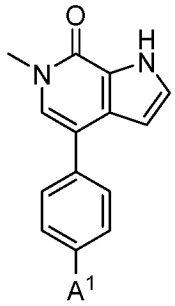


X4,



X5,

or



X6,

where A^1 is a bond between A and the linker, or derivative or analog thereof.

In some embodiments, the compound has the structure of any one of compounds D1-D177 in Table 1A, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D178-D371 in Table 1B, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D372-D476 in Table 1D, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound has the structure of any one of compounds D1, D3, D6, D9-D20, D23, D33, D33-D35, D37-D40, D42, D44-D47, D50-D53, D56-D60, D67, D69, D71-D73, D75, D76, D80, D81, D89, D92, D100, D108, D113, D122-D124, D128-D132, D143, D152, D157, D167, D168, D170, D171, D173, and D176 in Table 1A, or a pharmaceutically acceptable salt thereof. . In some embodiments, the compound has the structure of any one of compounds D178, D180, D184-D189, D191, D194, D197-D199, D201-D208, D211, D213-D230, D235-D244, D246, D247, D250-D263, D268, D269, D271-D275, D277, D279, D280, D287-D291, D297-D299, D300-D302, D304, D306-D308, D310, D312, D313, D315, D316, D318-D333, D335-D341, D343-D349, D353, D354, D356-D363, and D366-D371 in Table 1B, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D372-D379, D381, D382, D384-D388, D395-D428, D430, D431, D433, D434, D436, D438-D444, D448, D450, D453-D460, D462, D463, D465, D466, D471, and D476 in Table 1D, or a pharmaceutically acceptable salt thereof.

In an aspect, the disclosure features a compound having the structure of any one of compounds D1-D177 in Table 1A, or a pharmaceutically acceptable salt thereof.

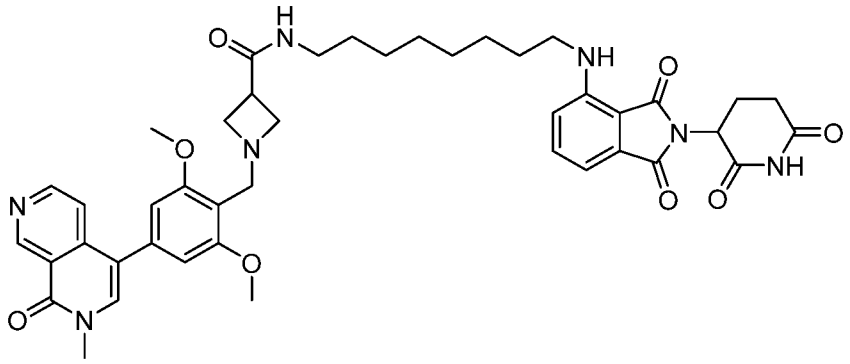
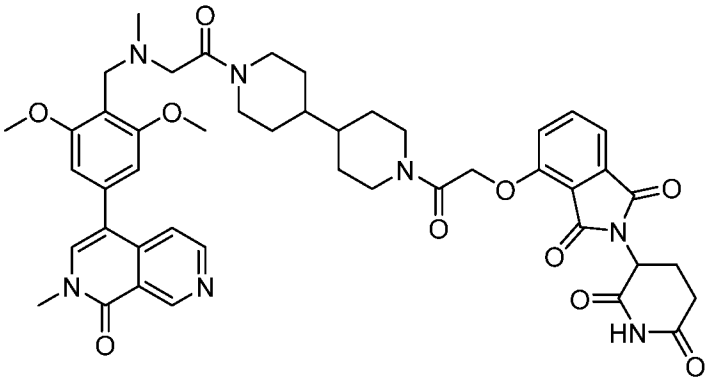
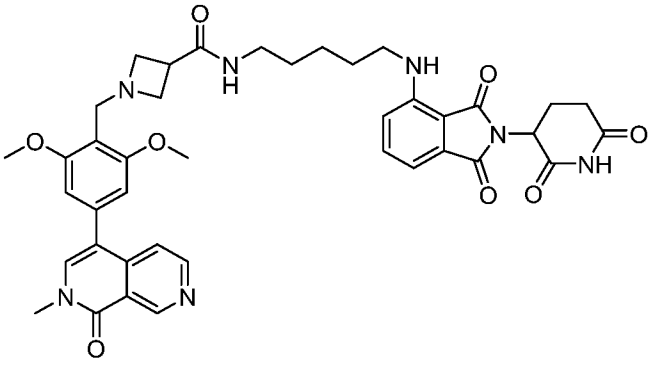
In another aspect, the disclosure features a compound having the structure of any one of compounds D178-D371 in Table 1B, or a pharmaceutically acceptable salt thereof.

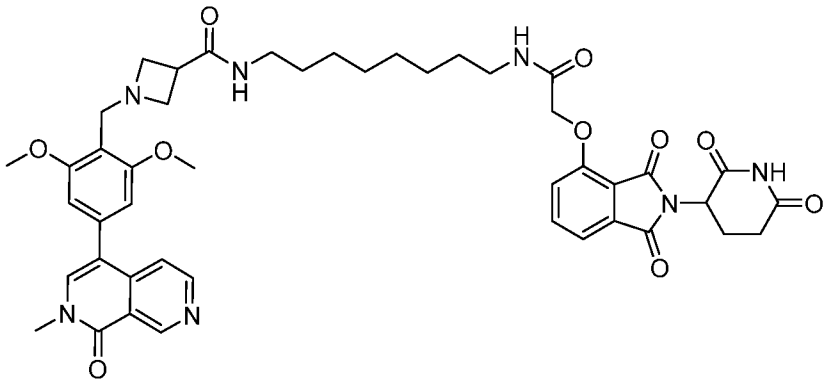
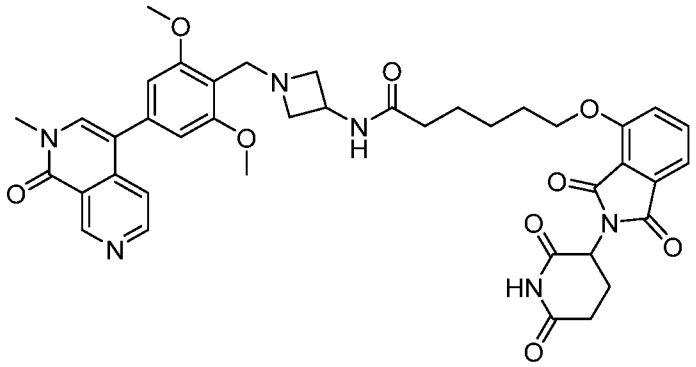
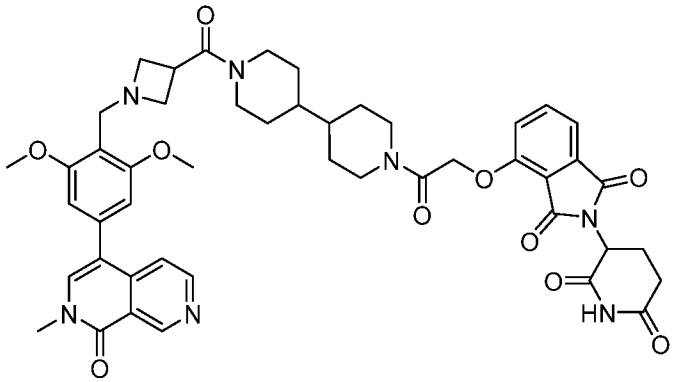
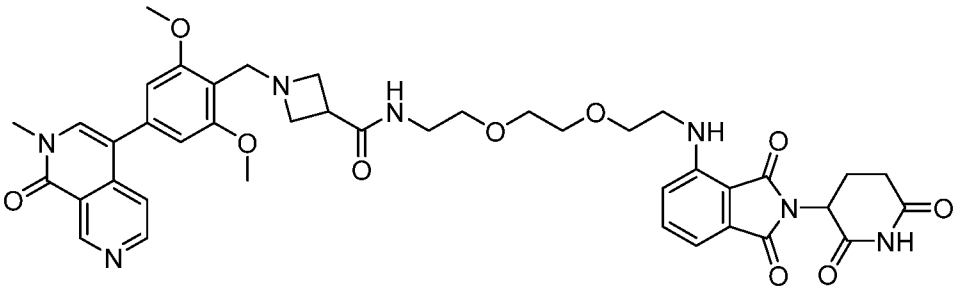
In another aspect, the disclosure features a compound having the structure of any one of compounds D372-D476 in Table 1D, or a pharmaceutically acceptable salt thereof.

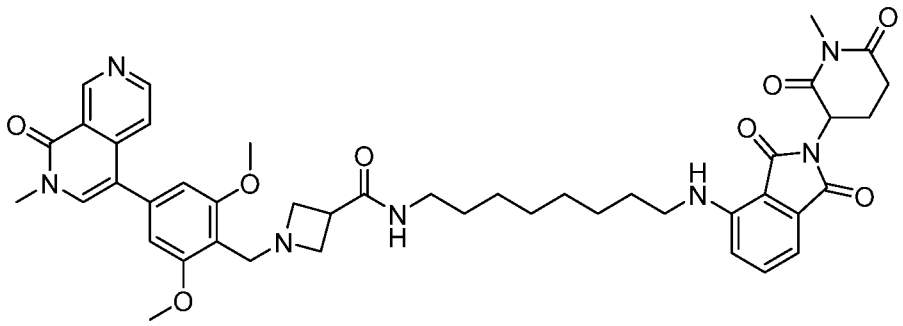
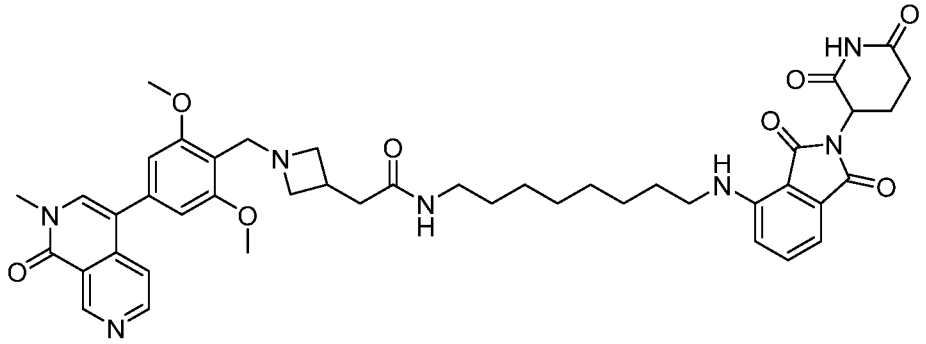
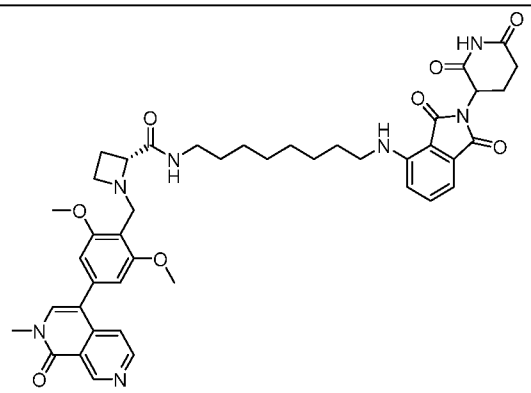
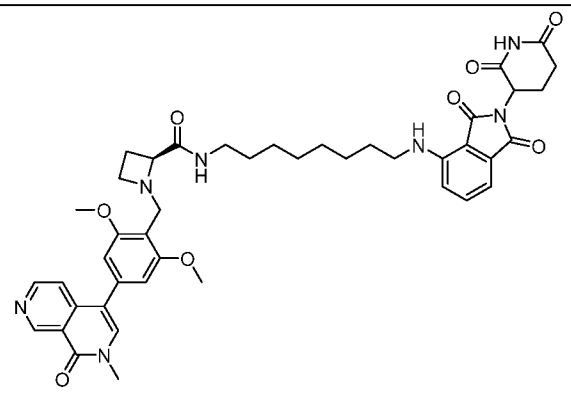
In another aspect, the disclosure features a compound having the structure of any one of compounds DD1-DD10 in Table 1C, or a pharmaceutically acceptable salt thereof.

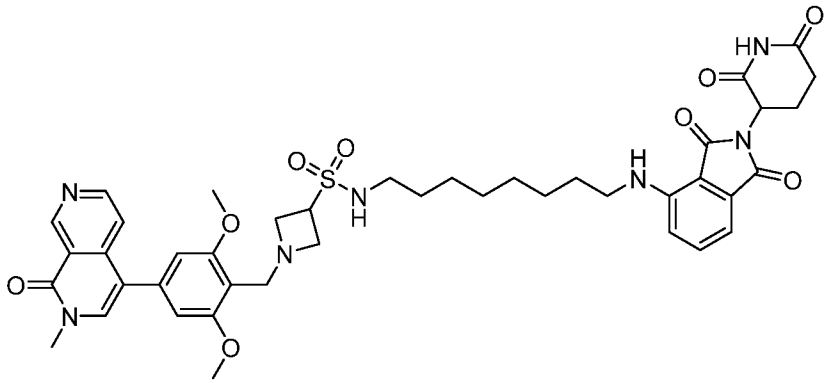
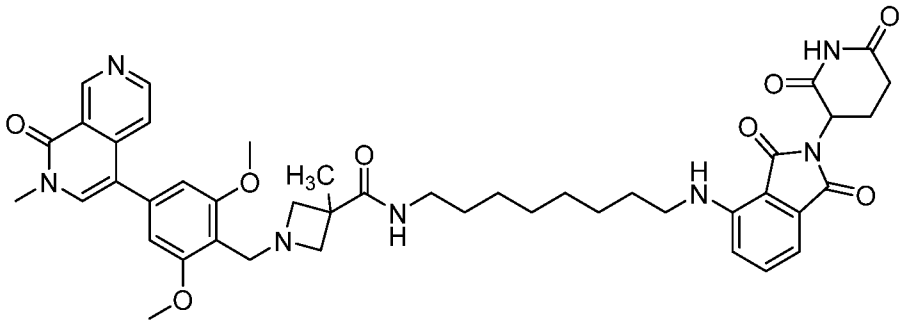
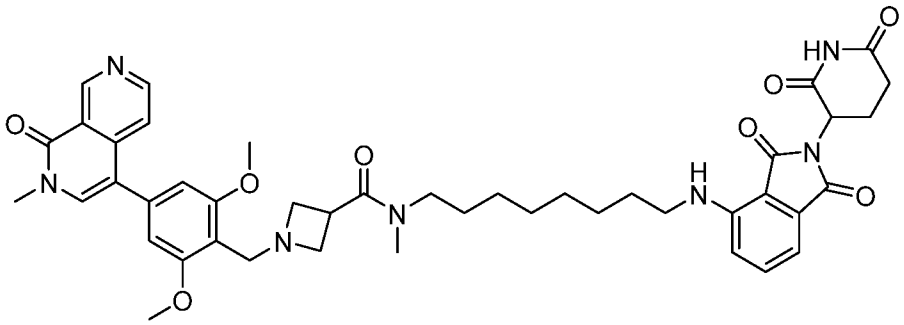
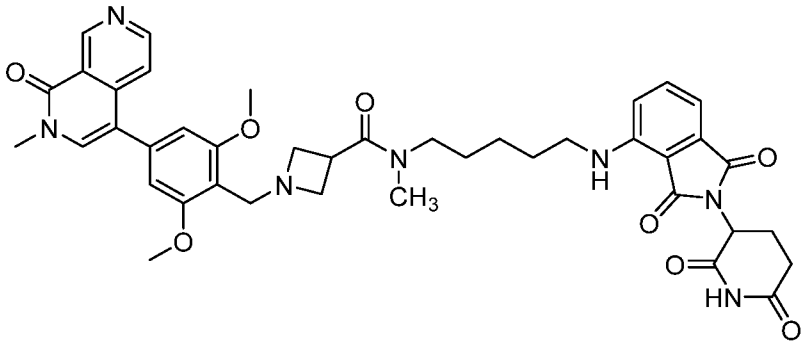
In another aspect, the disclosure features a compound having the structure of any one of compounds DD11-DD16 in Table 1E, or a pharmaceutically acceptable salt thereof.

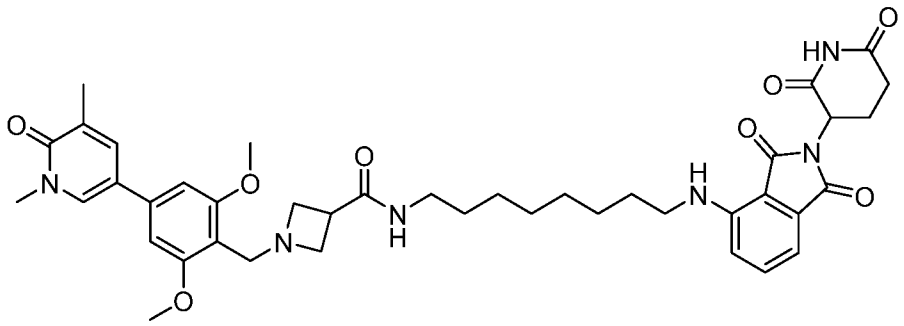
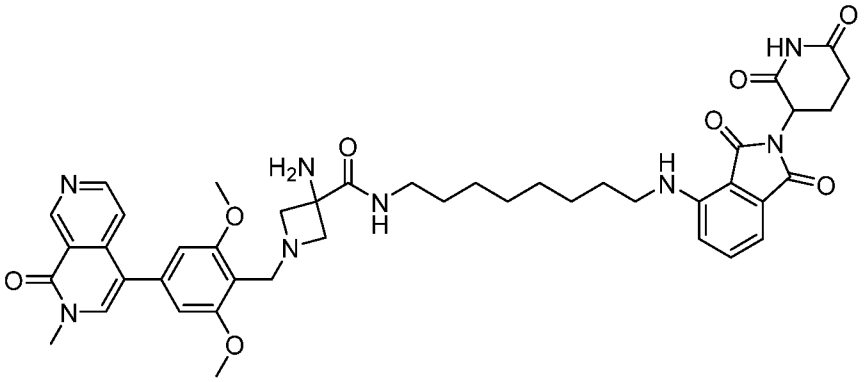
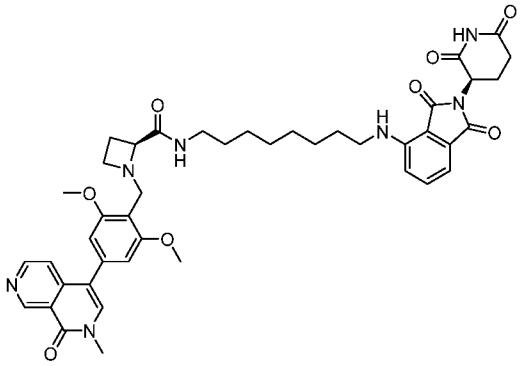
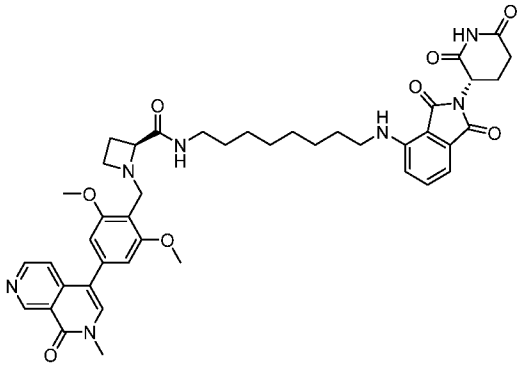
Table 1A. Compounds D1-D177 of the Disclosure

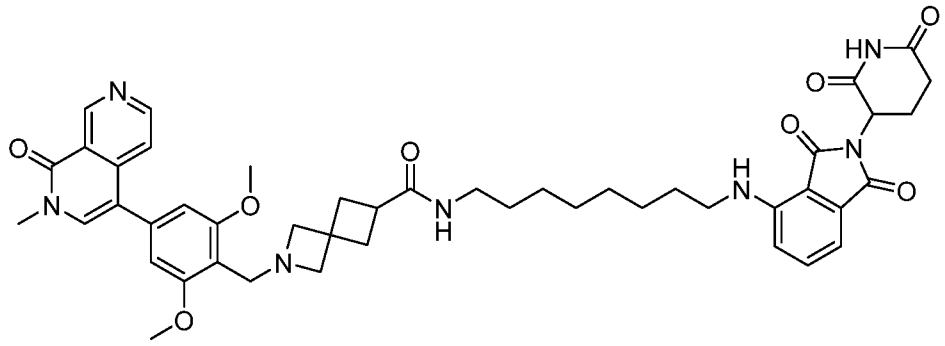
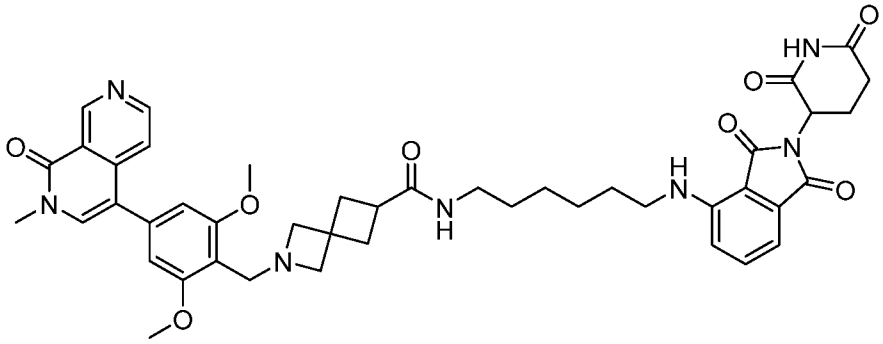
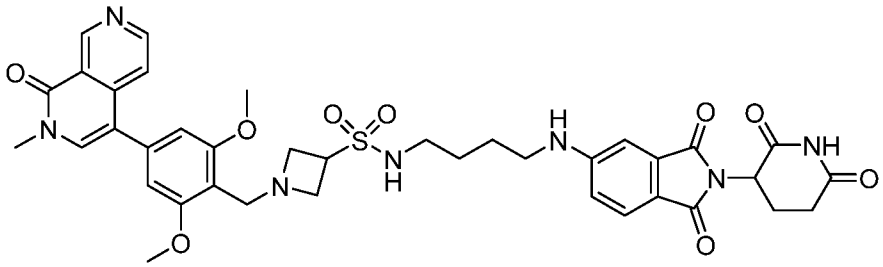
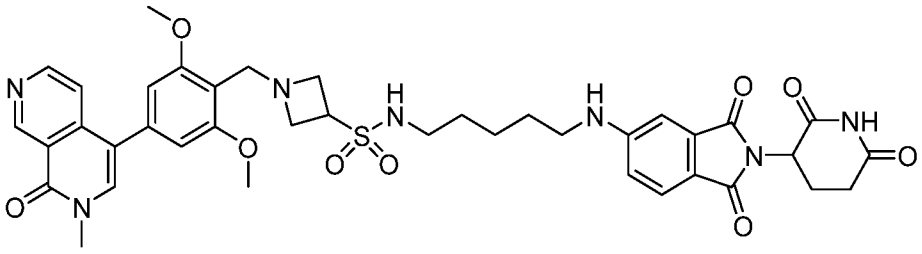
Compound No.	Structure
D1	
D2	
D3	

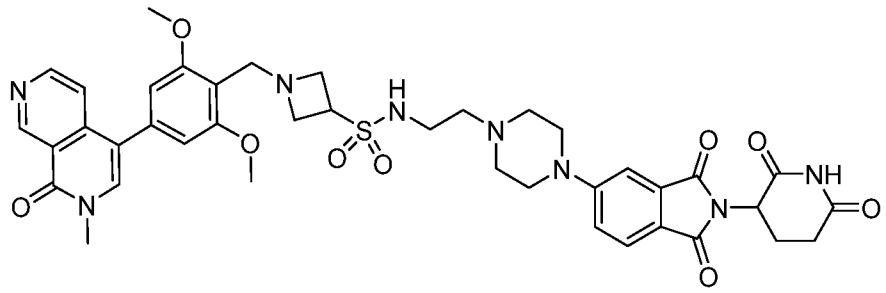
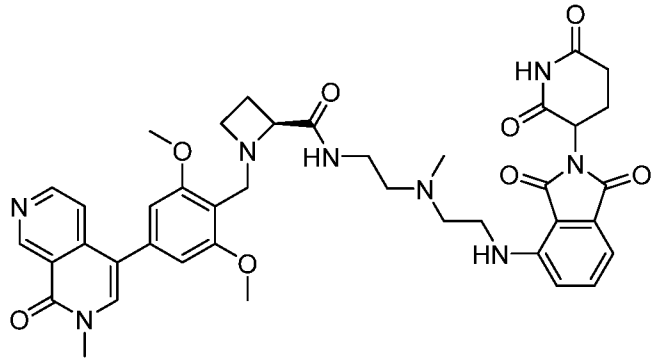
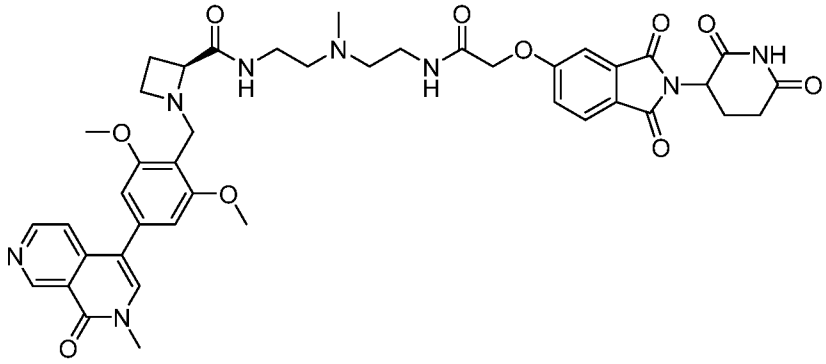
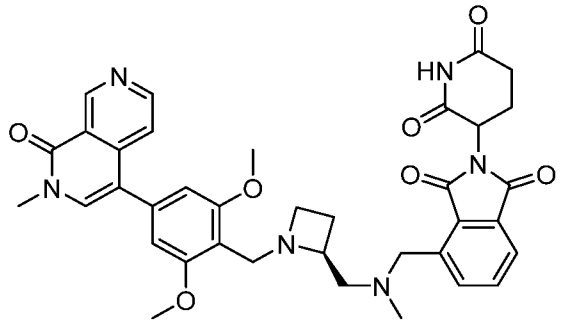
Compound No.	Structure
D4	
D5	
D6	
D7	

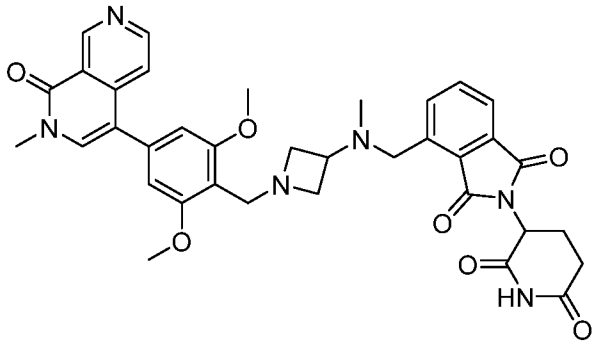
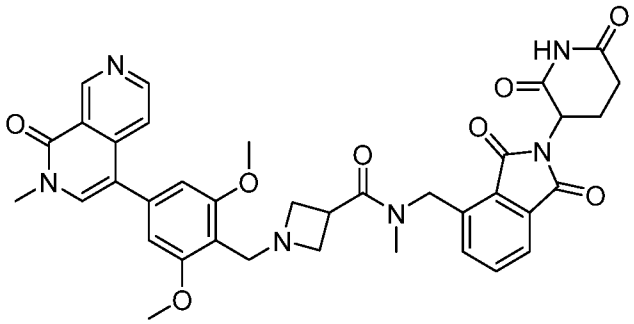
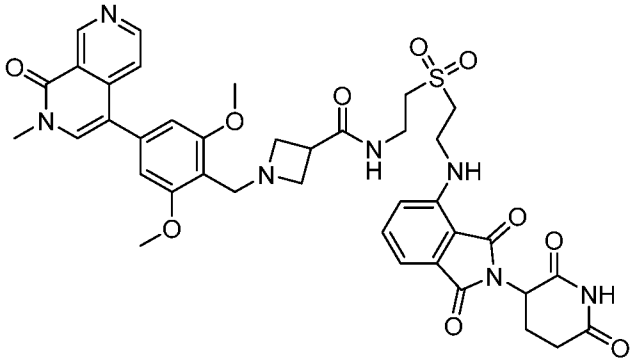
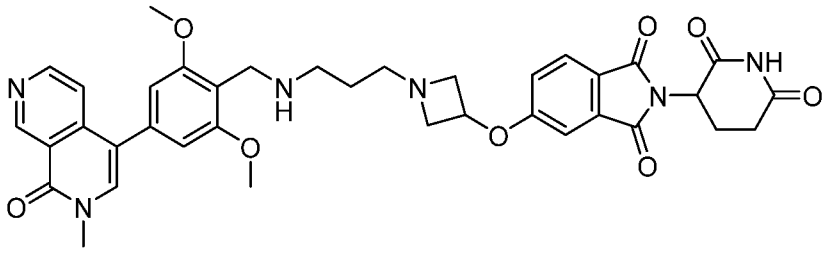
Compound No.	Structure
D8	
D9	
D10	
D11	

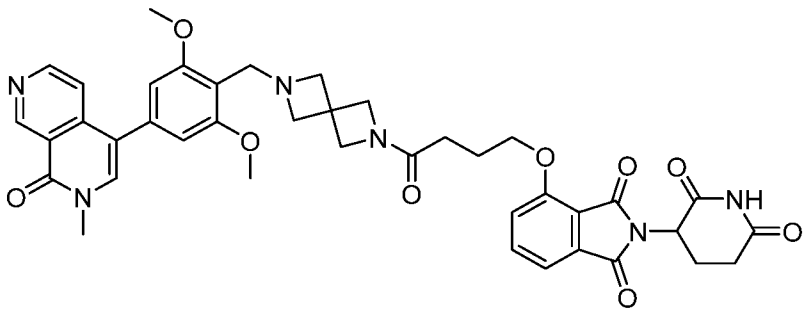
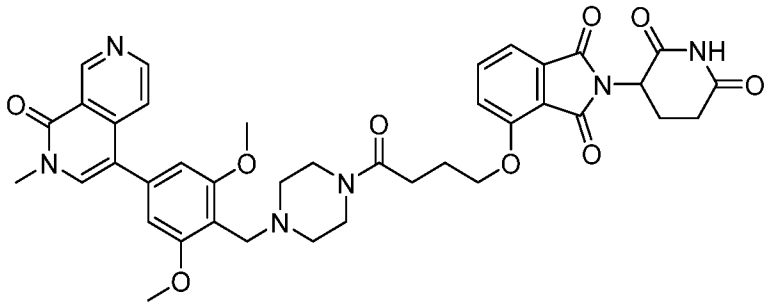
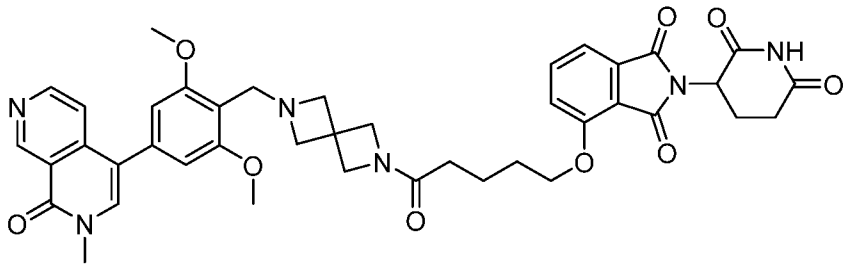
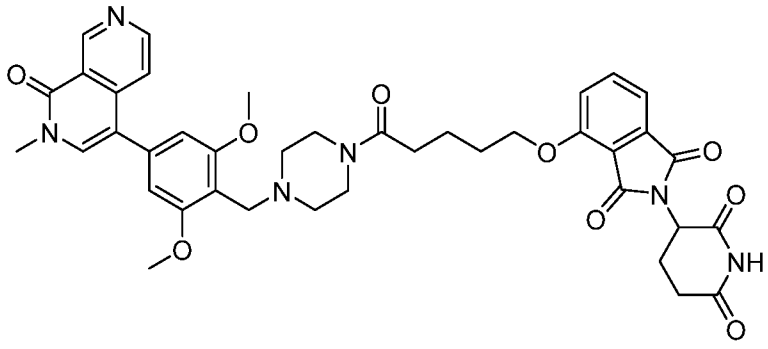
Compound No.	Structure
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D13	
D14	
D15	

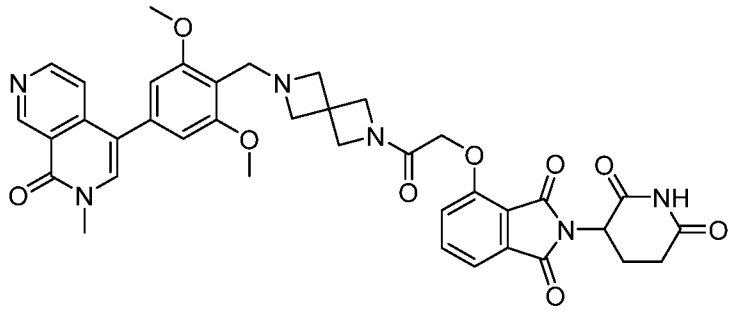
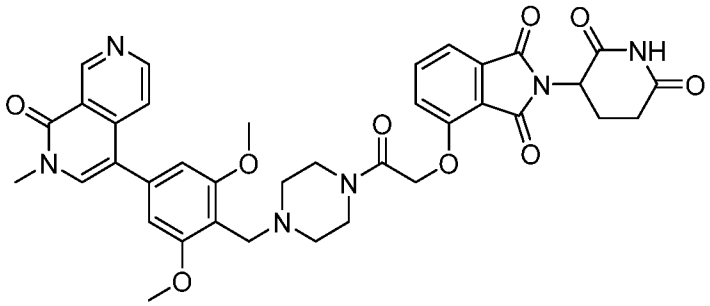
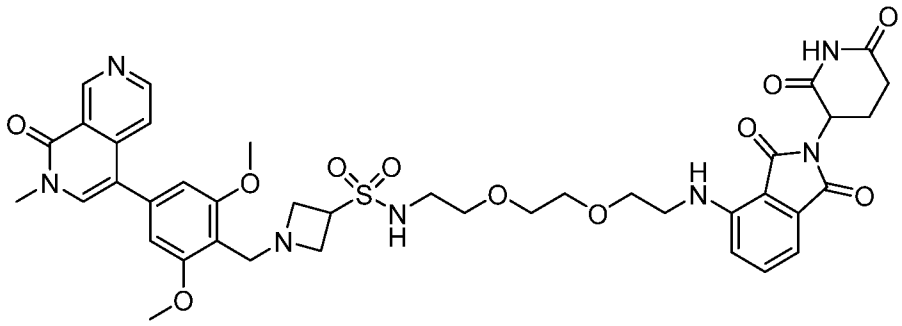
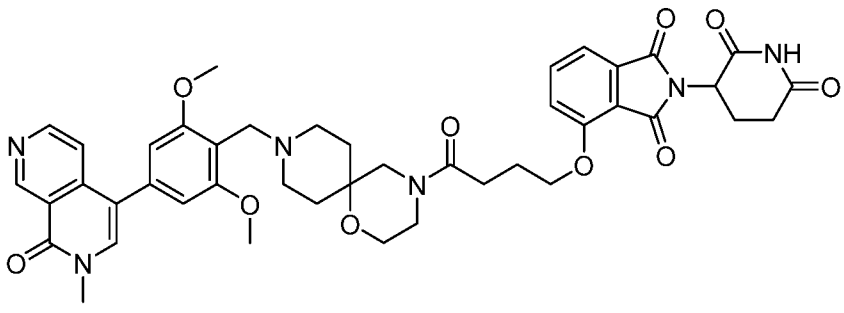
Compound No.	Structure
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D17	
D18	
D19	

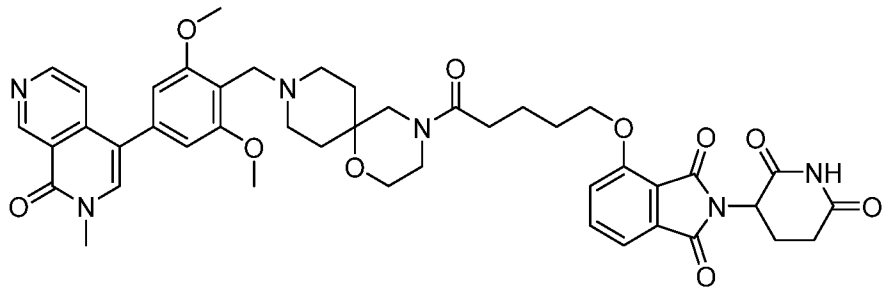
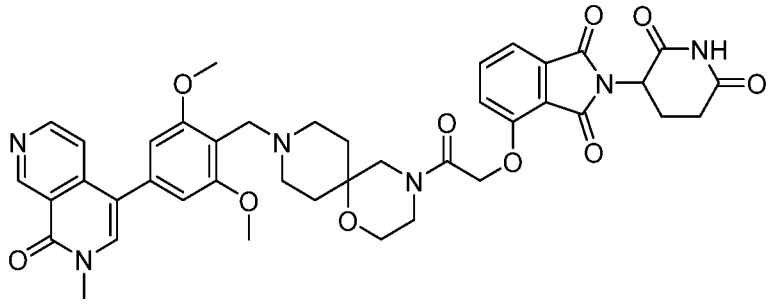
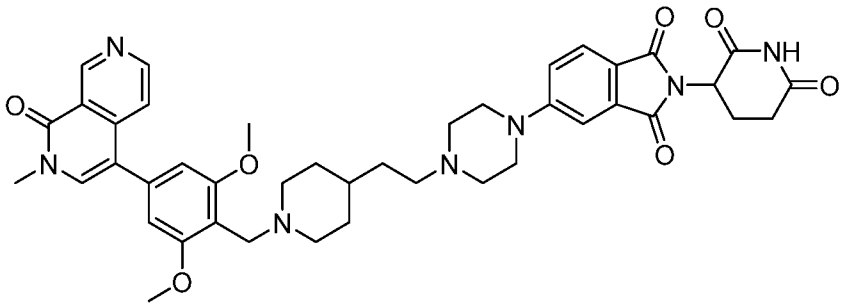
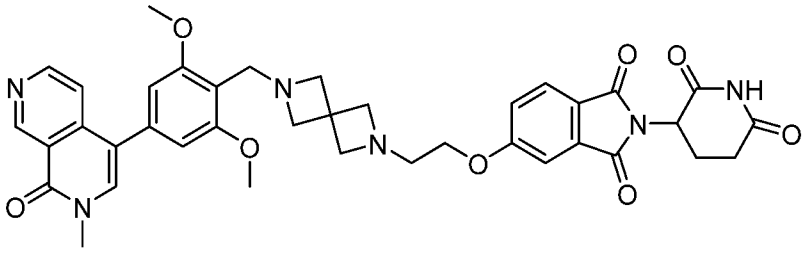
Compound No.	Structure
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D21	
D22	
D23	

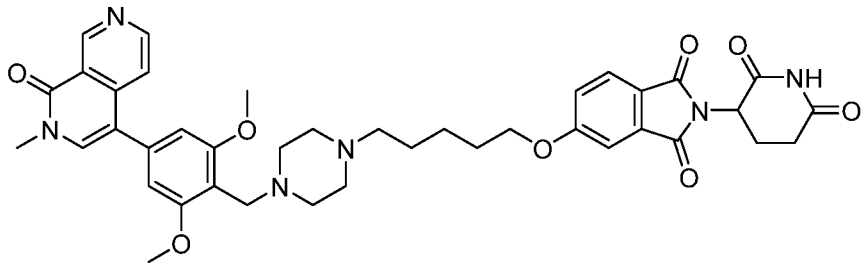
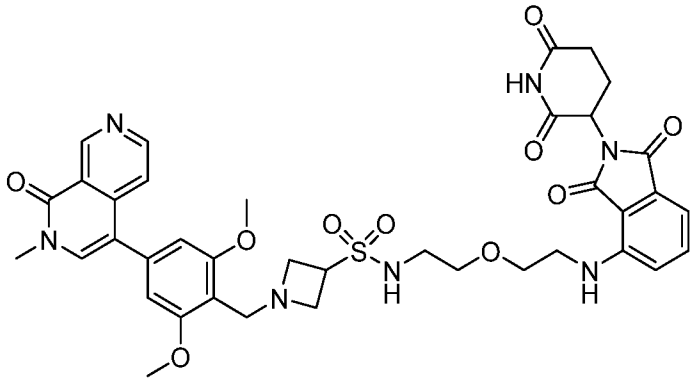
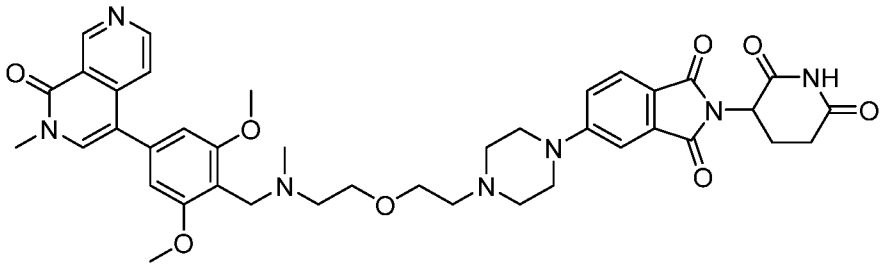
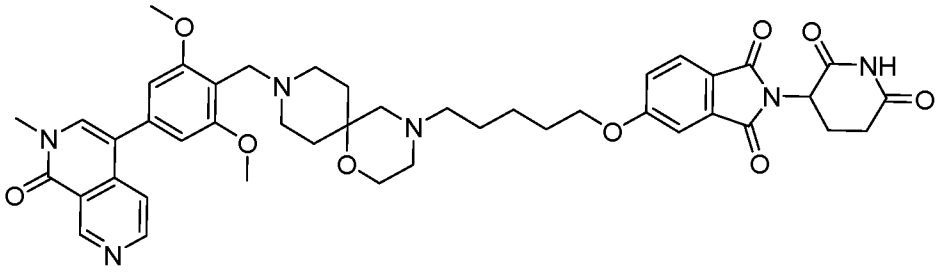
Compound No.	Structure
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D25	
D26	
D27	

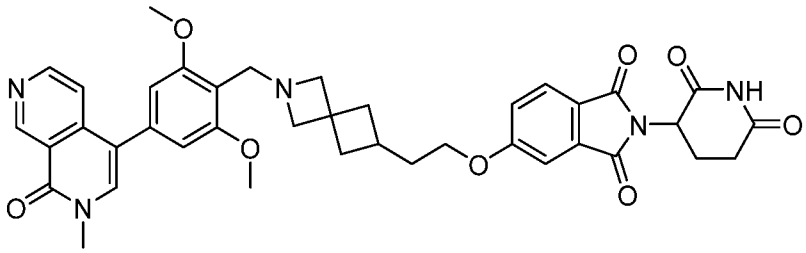
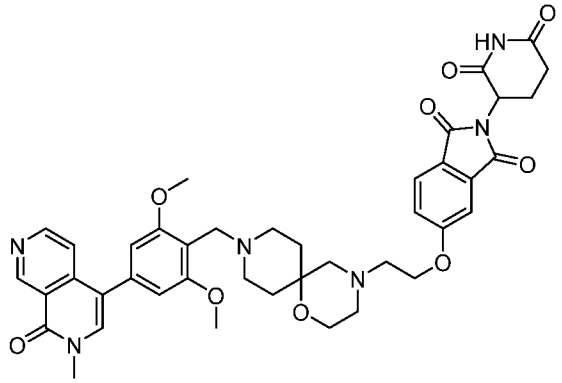
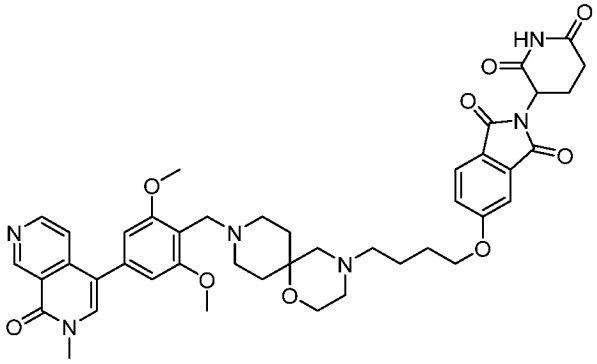
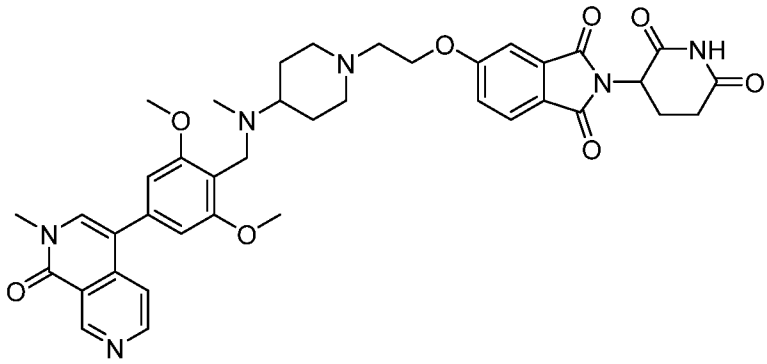
Compound No.	Structure
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D29	
D30	
D31	

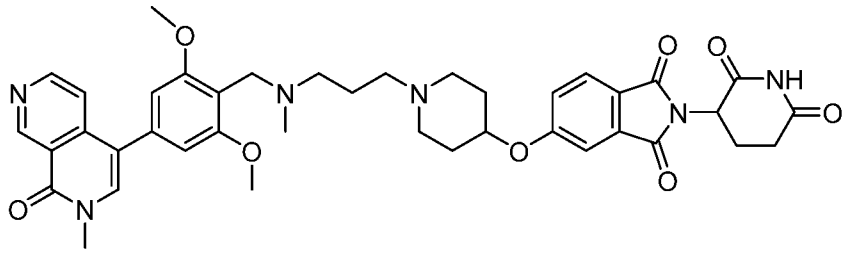
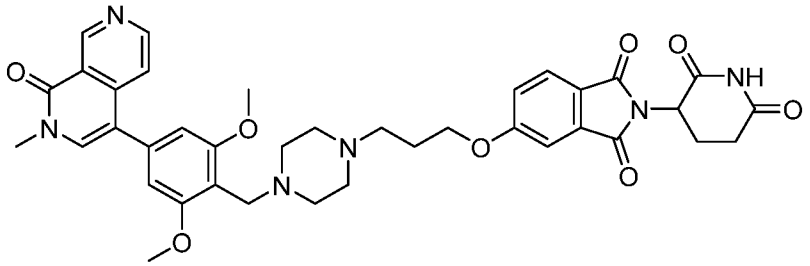
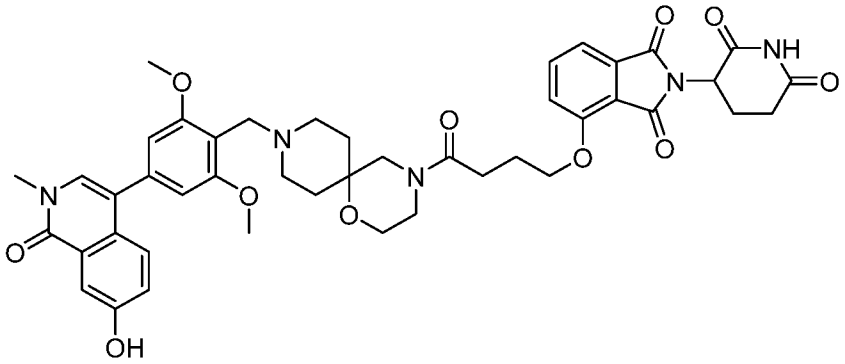
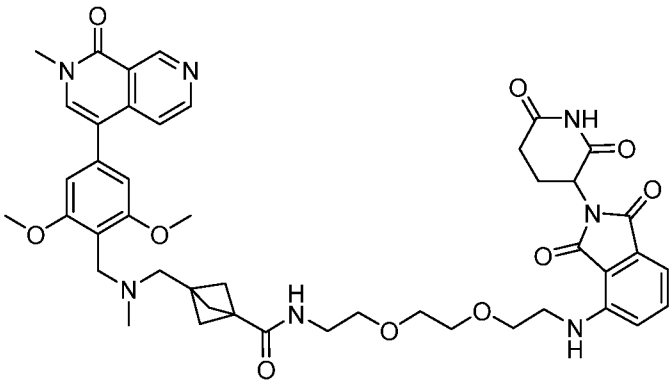
Compound No.	Structure
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D35	

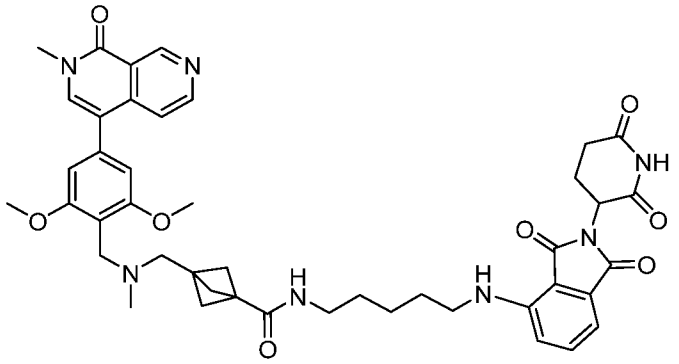
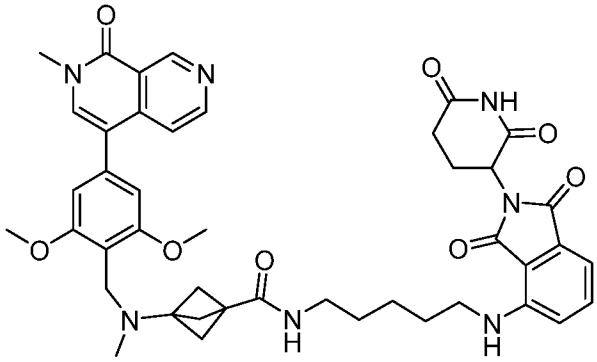
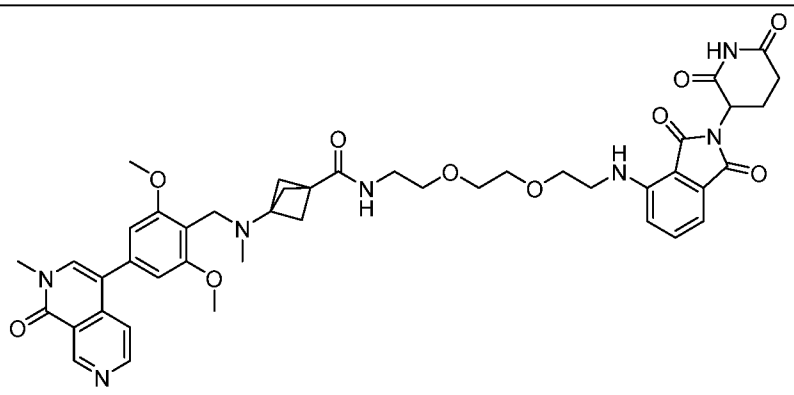
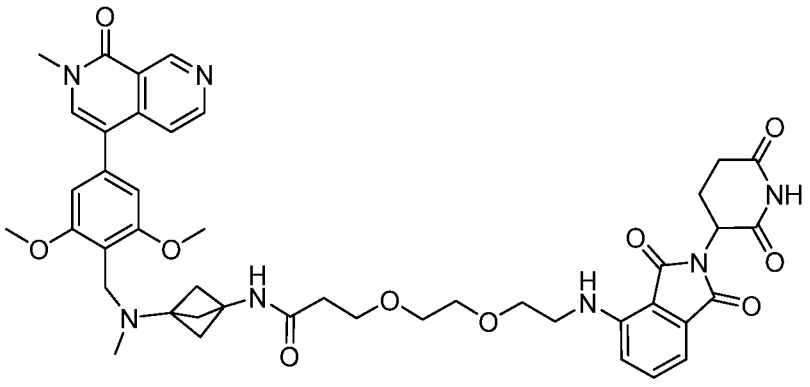
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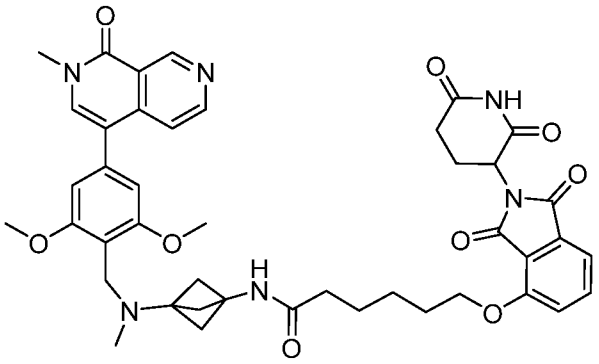
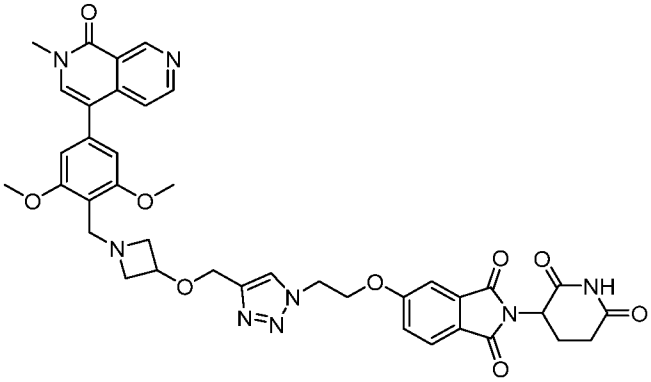
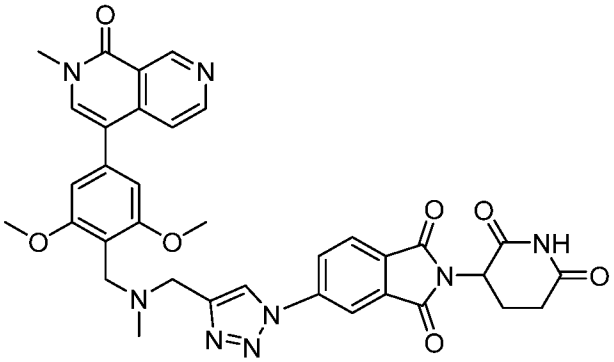
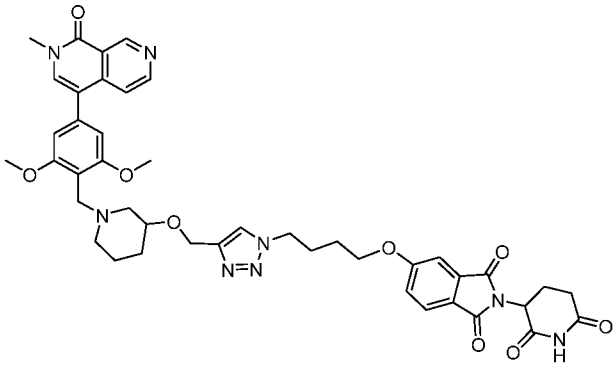
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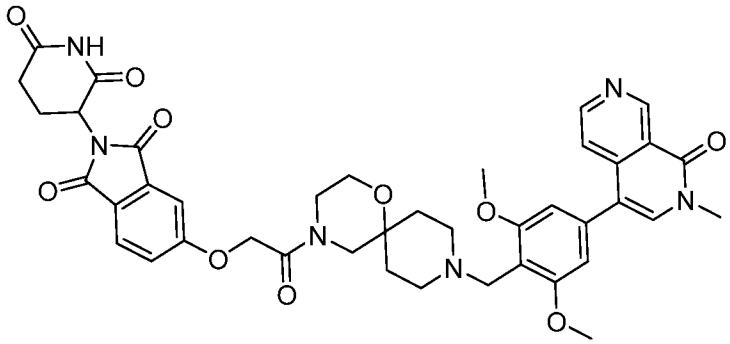
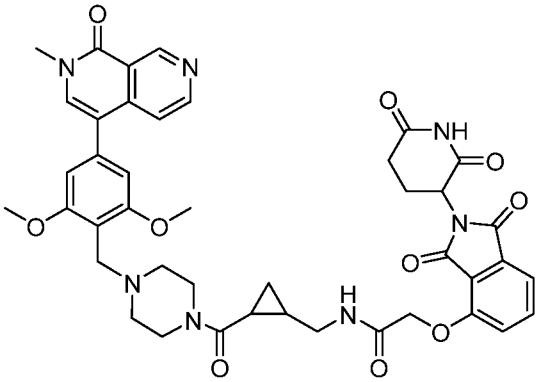
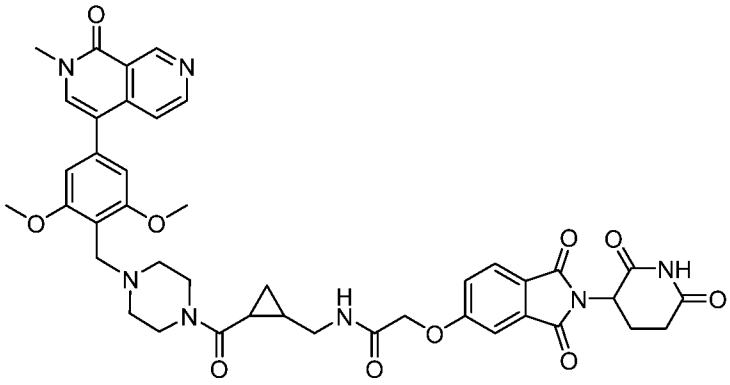
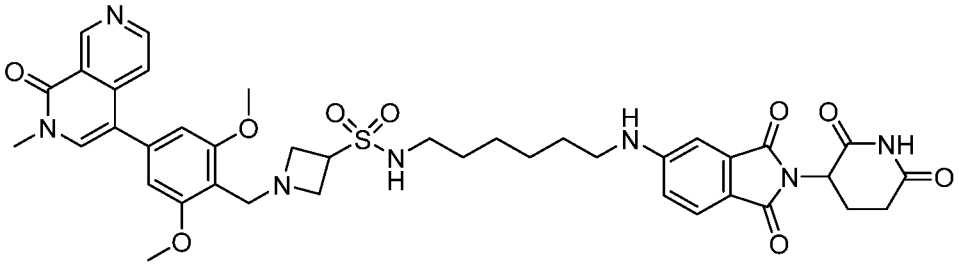
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D47	

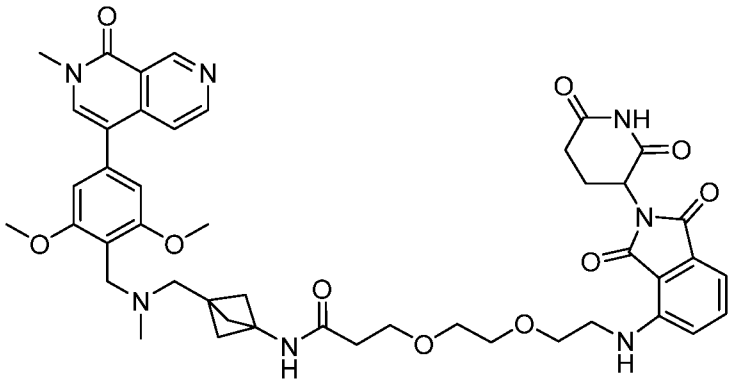
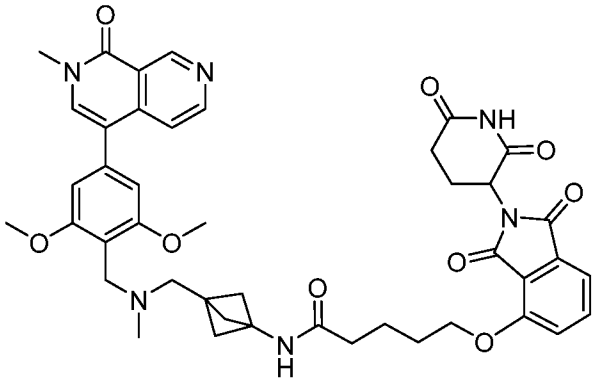
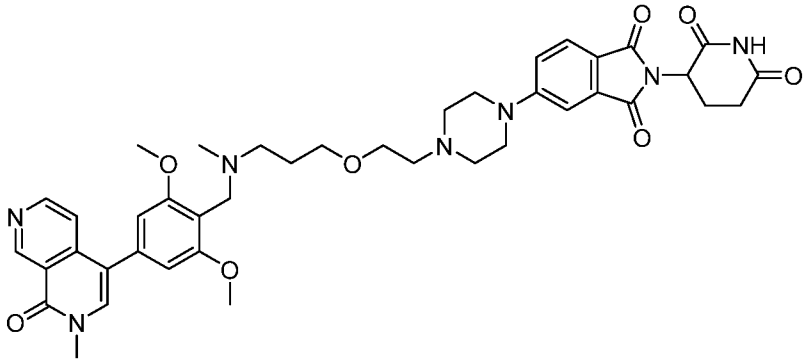
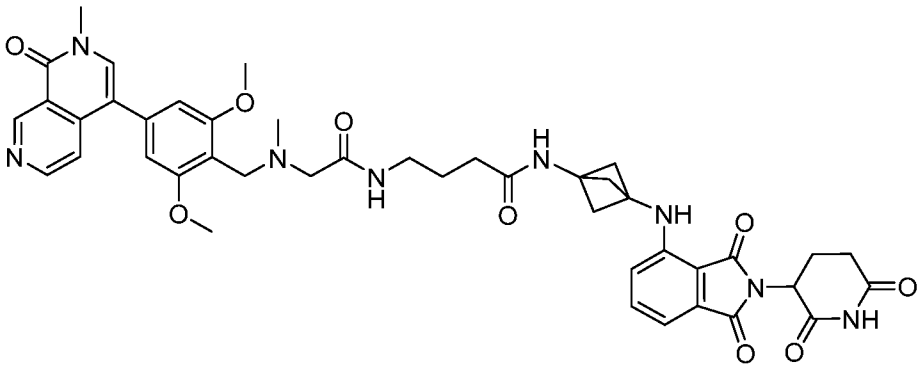
Compound No.	Structure
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D51	

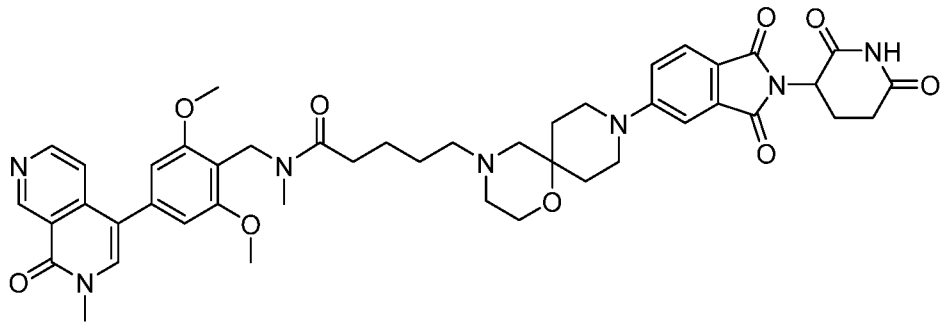
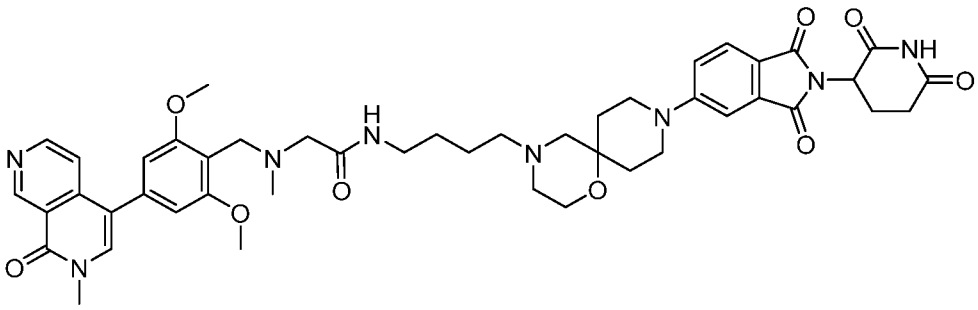
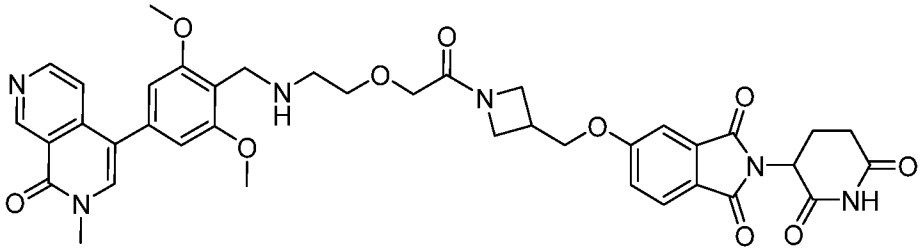
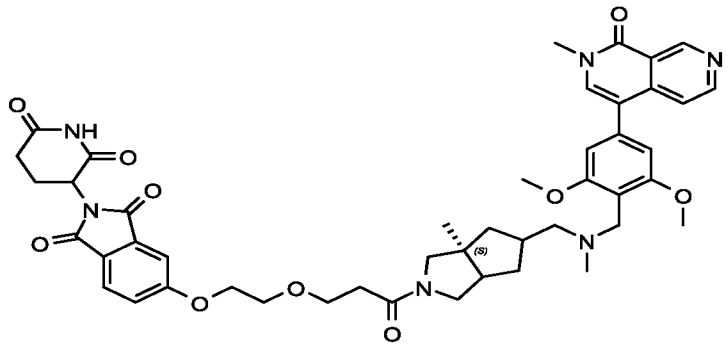
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D55	

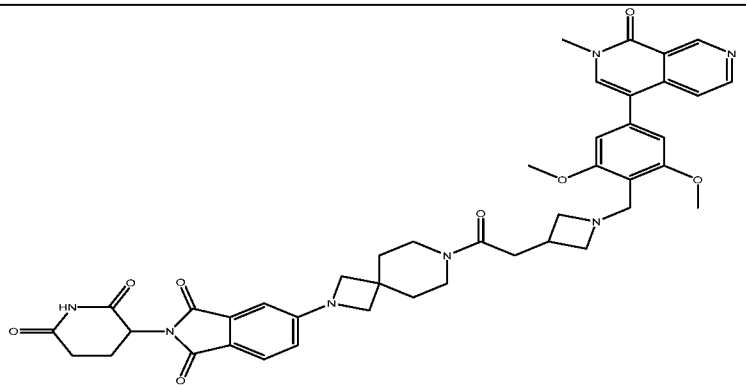
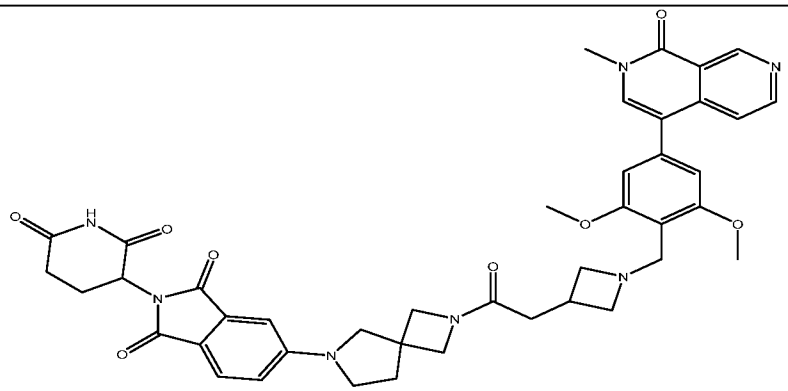
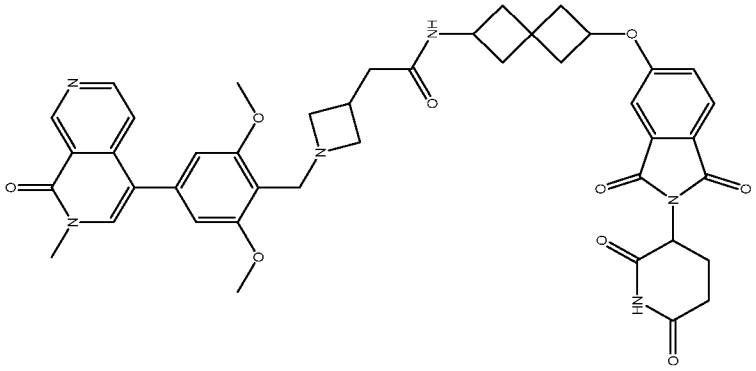
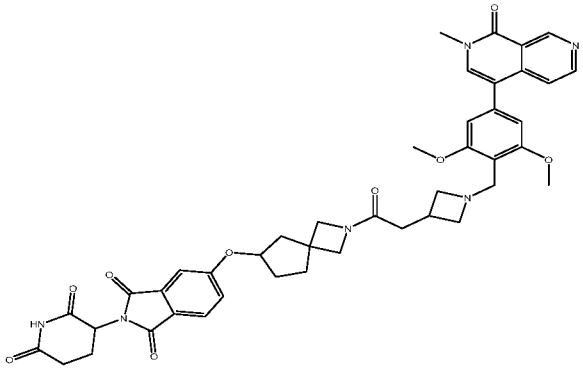
Compound No.	Structure
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D58	
D59	

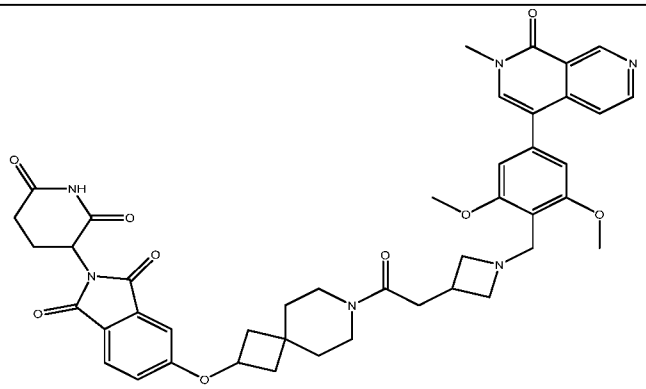
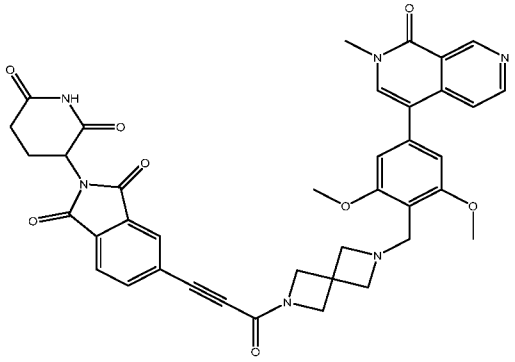
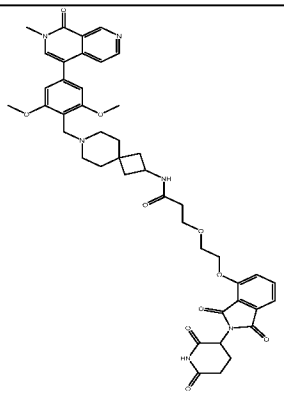
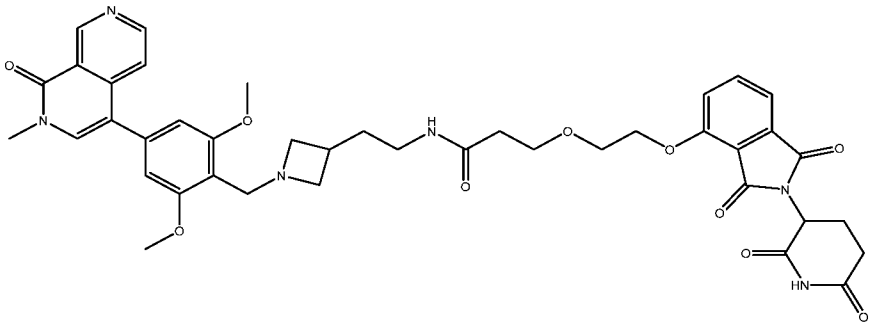
Compound No.	Structure
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D62	
D63	

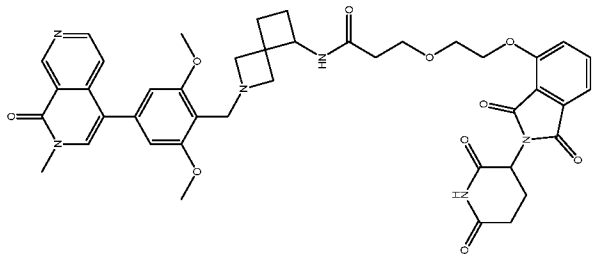
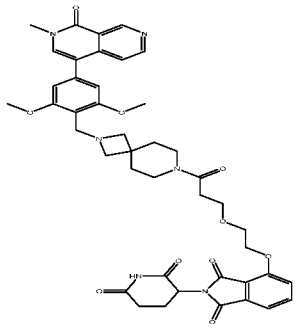
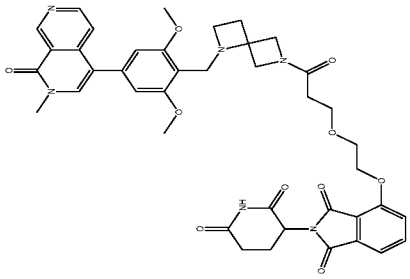
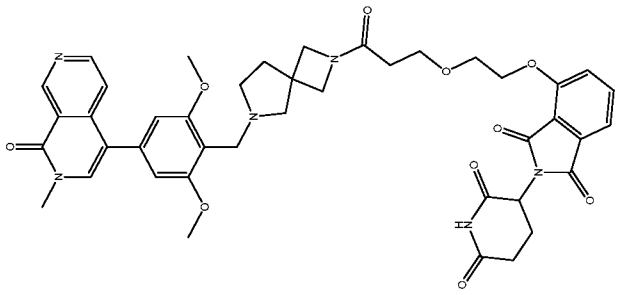
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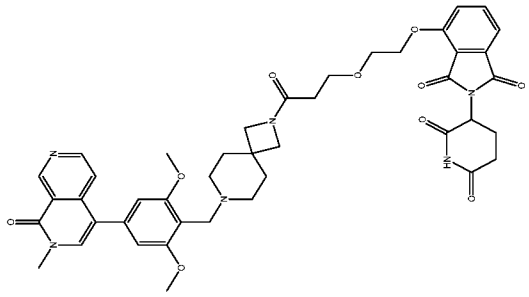
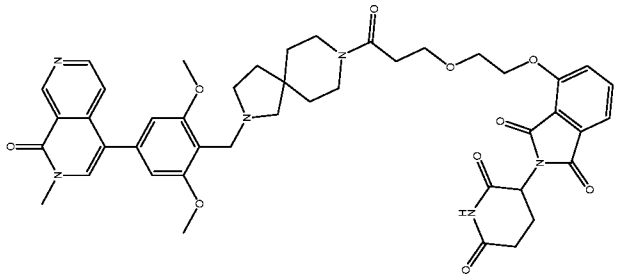
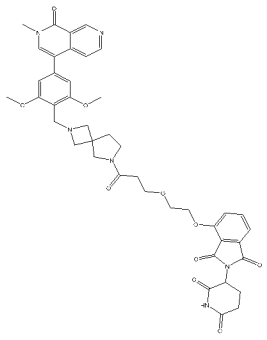
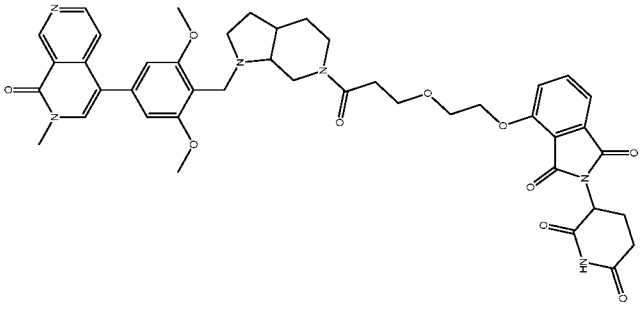
Compound No.	Structure
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D70	
D71	

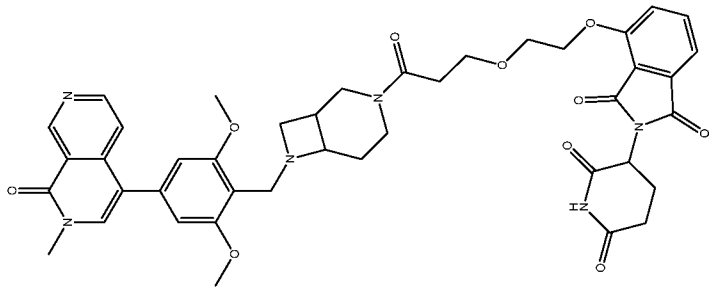
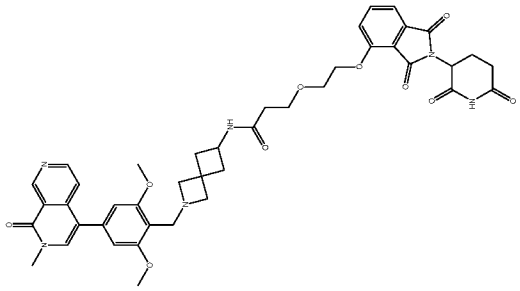
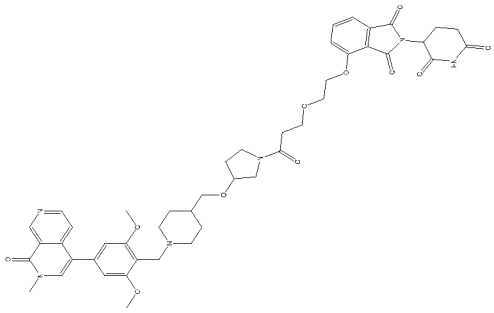
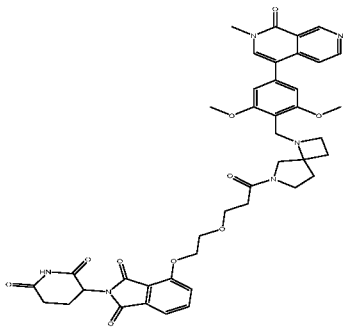
Compound No.	Structure
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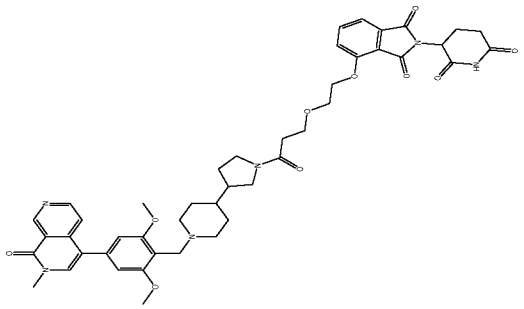
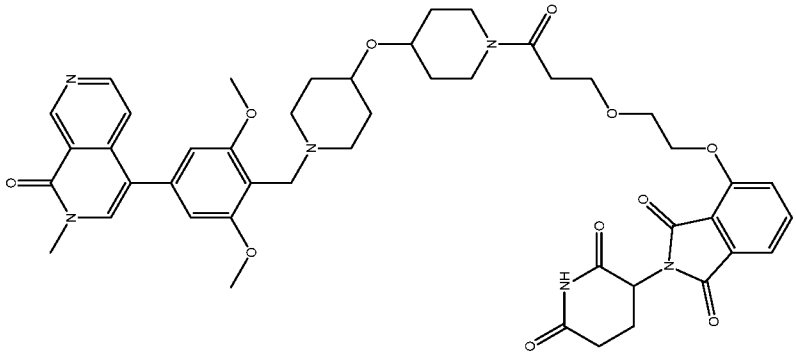
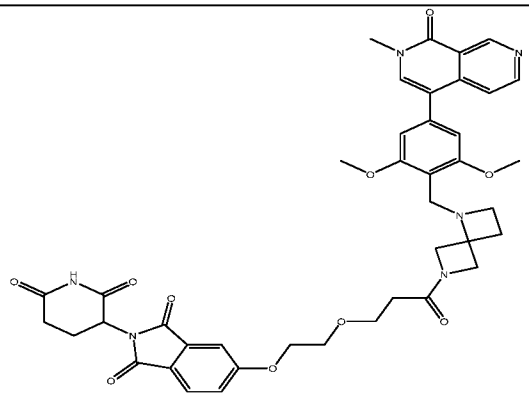
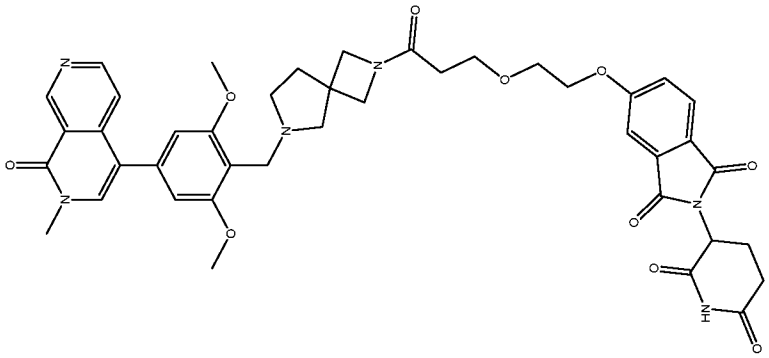
Compound No.	Structure
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D78	
D79	

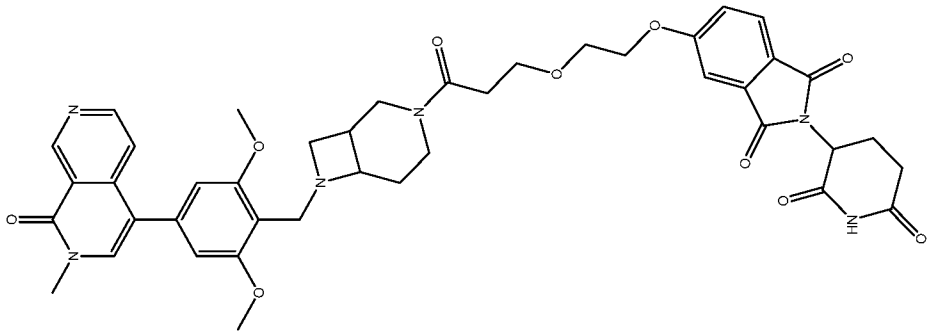
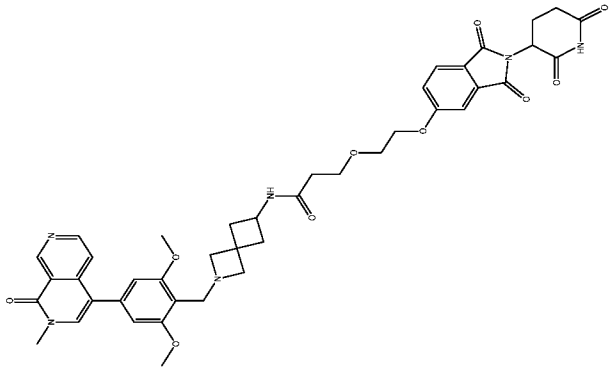
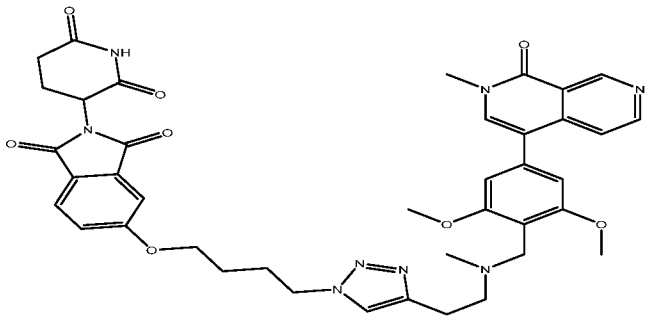
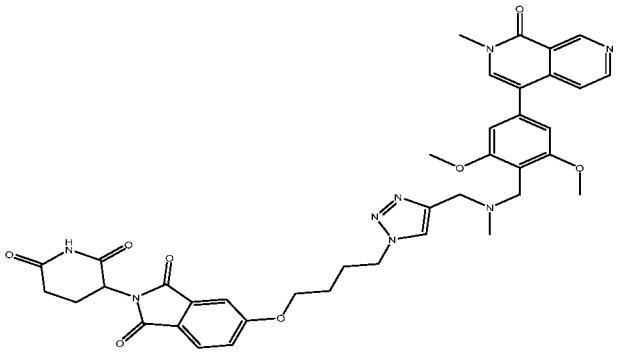
Compound No.	Structure
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D81	
D82	
D83	

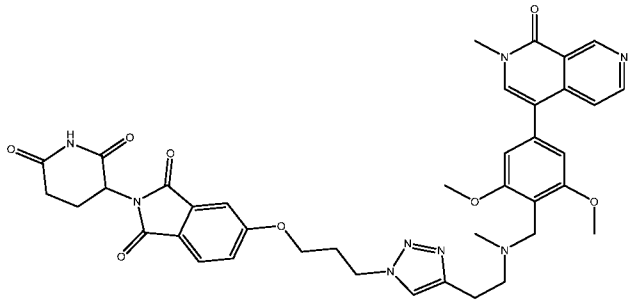
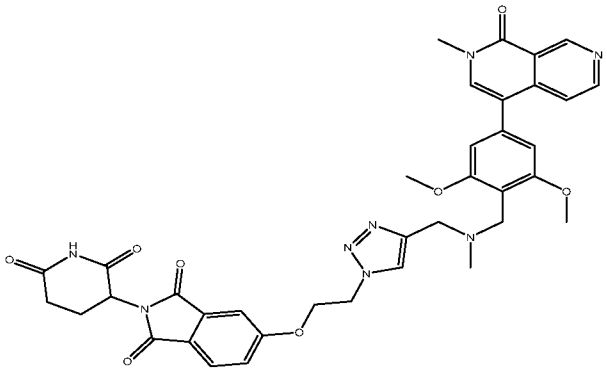
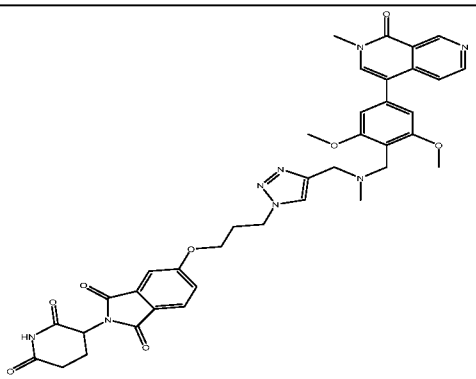
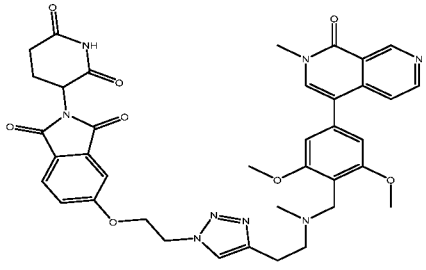
Compound No.	Structure
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D86	
D87	

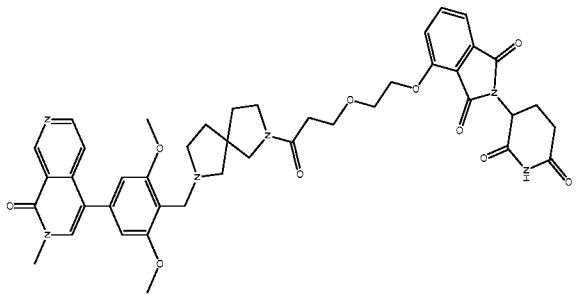
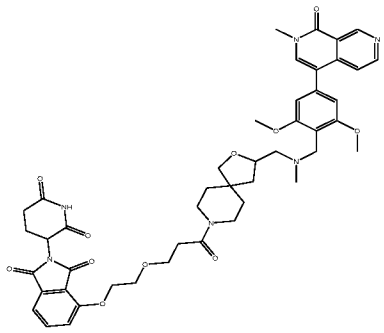
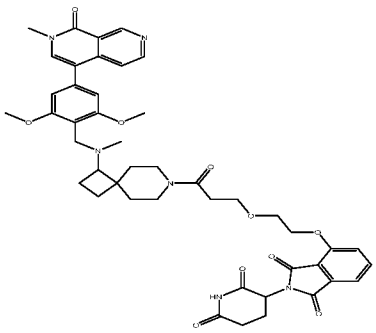
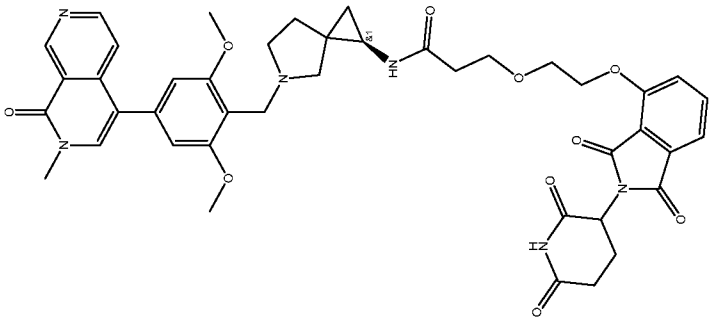
Compound No.	Structure
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D91	

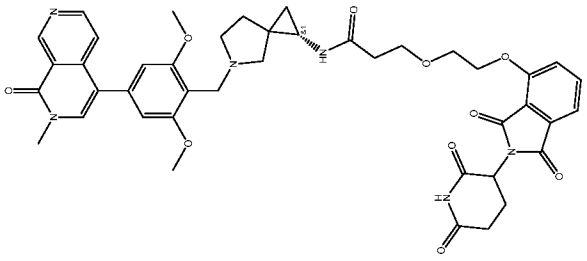
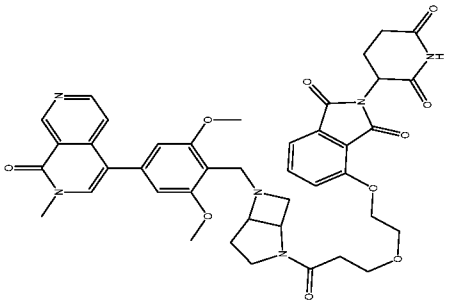
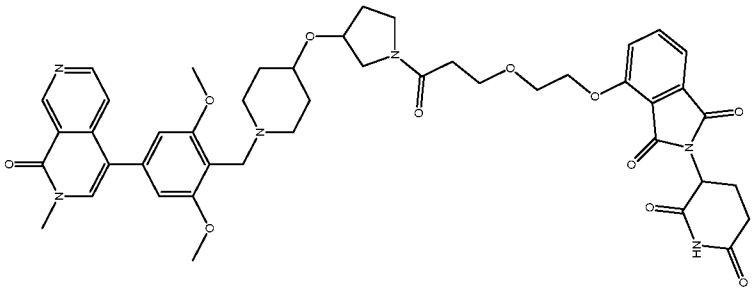
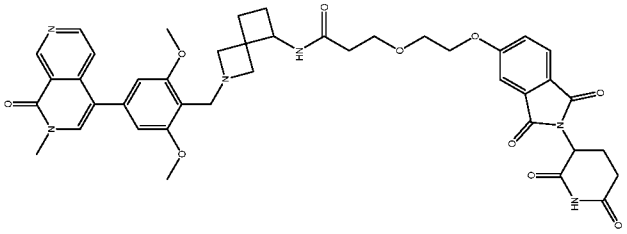
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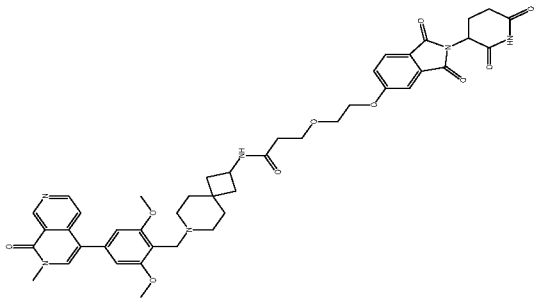
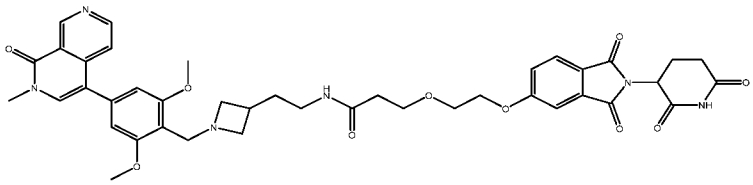
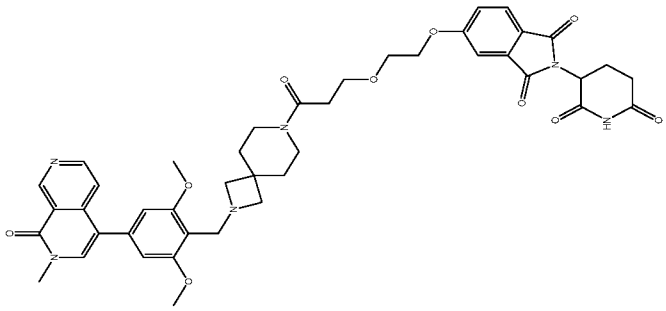
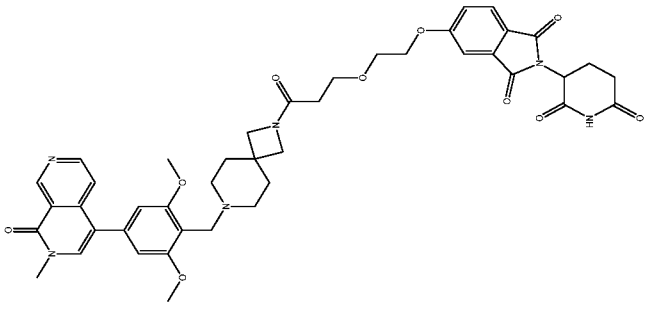
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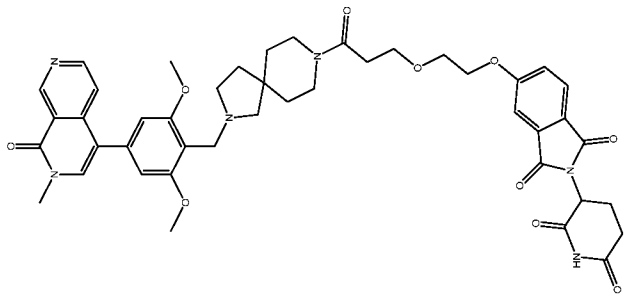
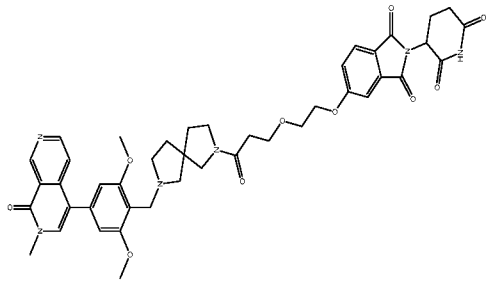
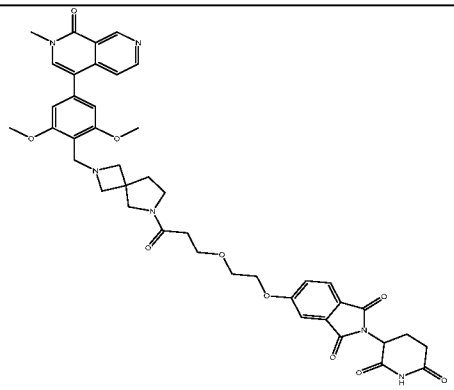
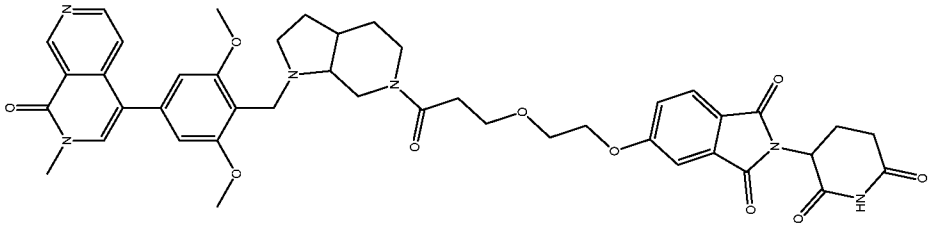
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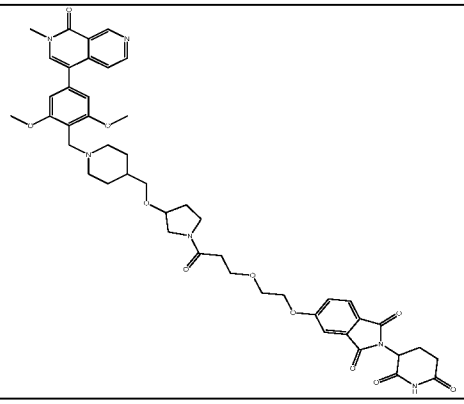
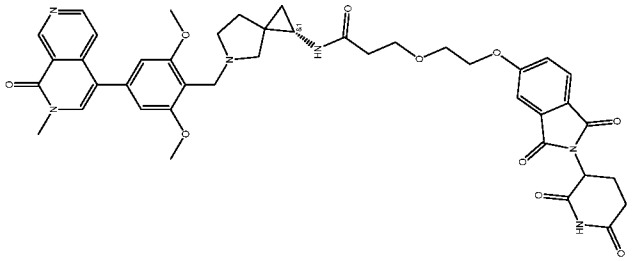
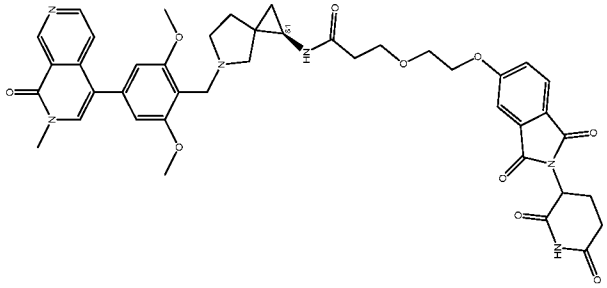
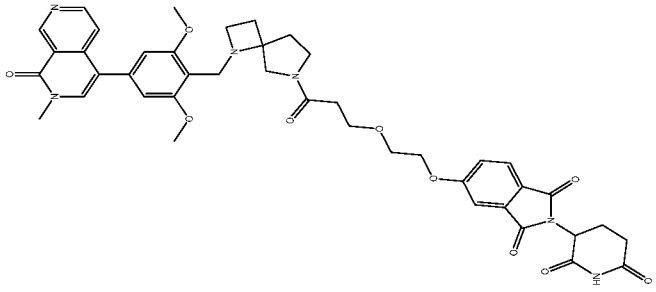
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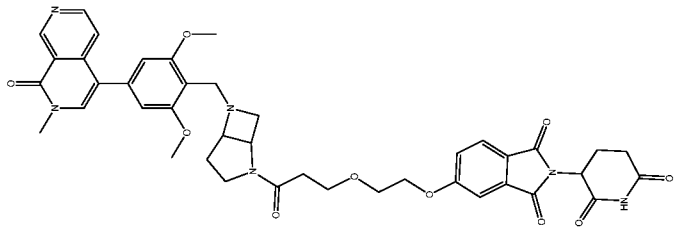
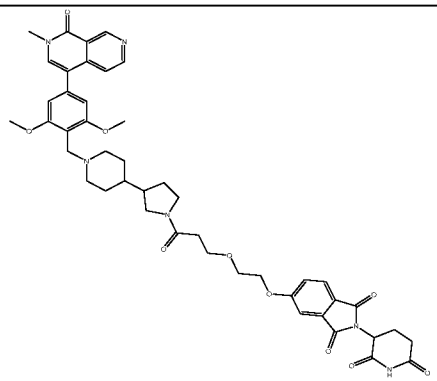
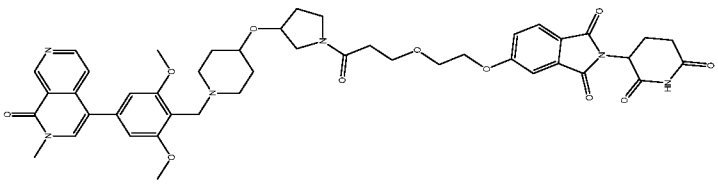
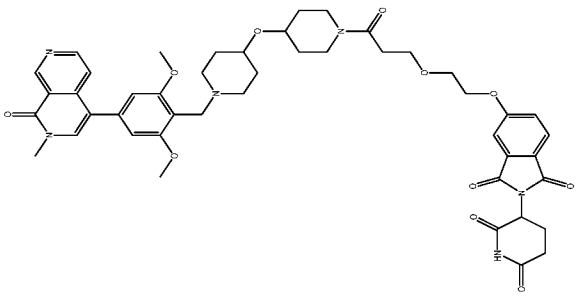
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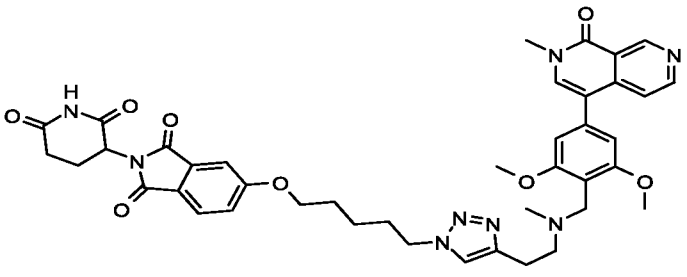
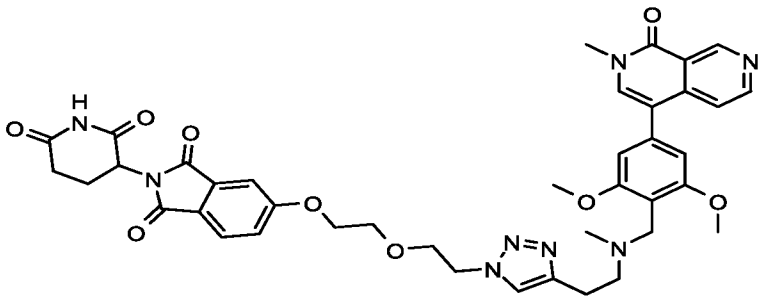
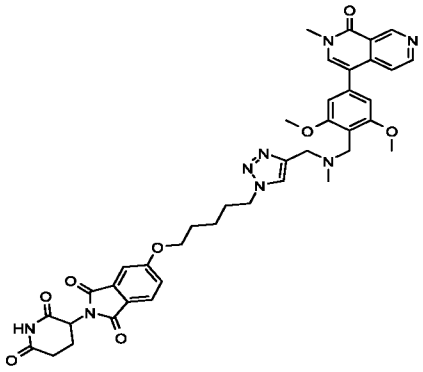
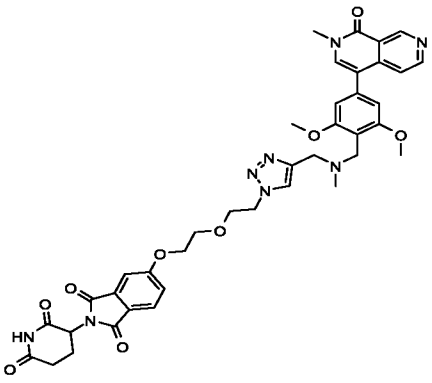
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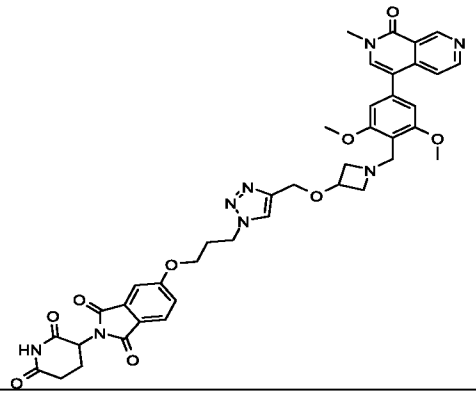
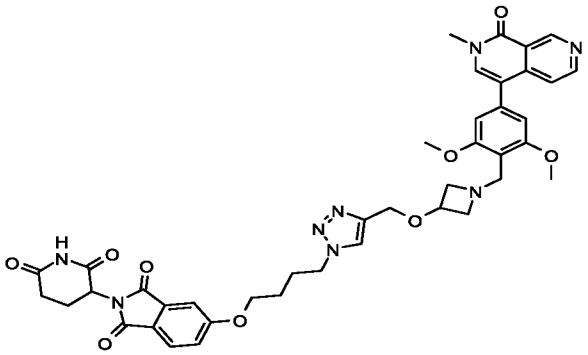
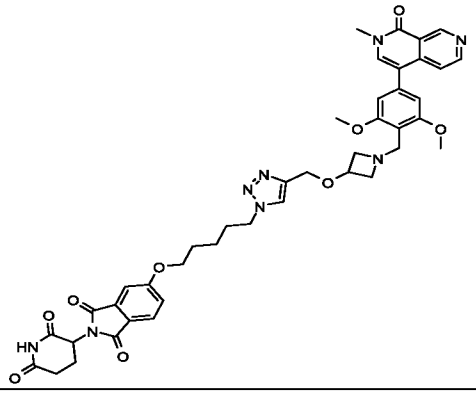
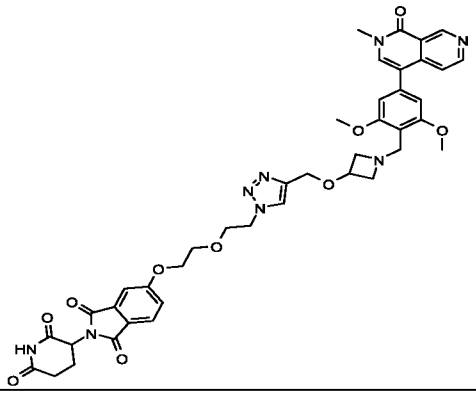
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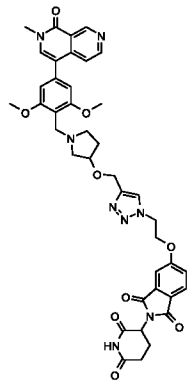
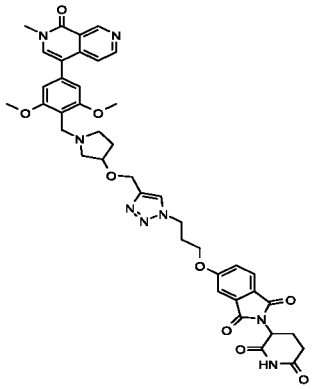
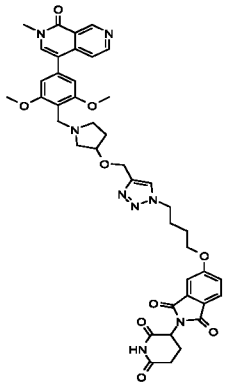
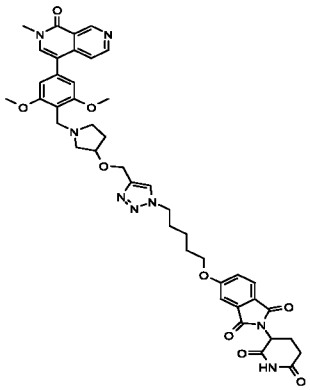
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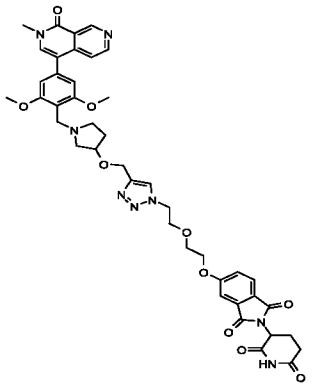
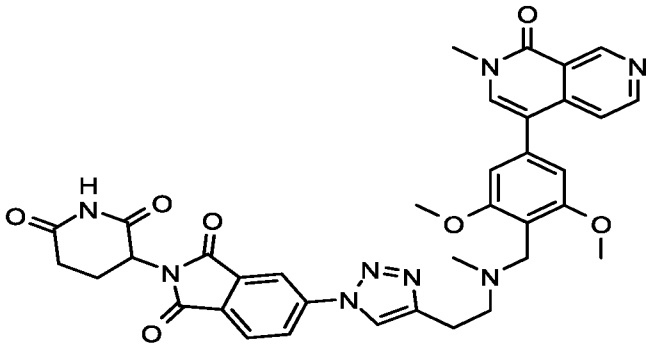
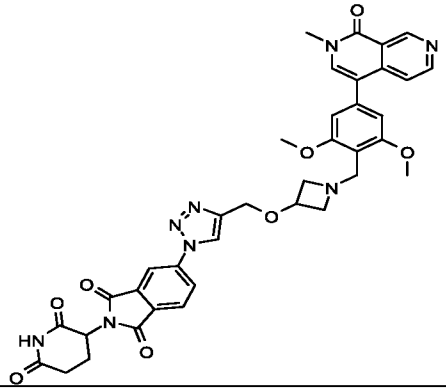
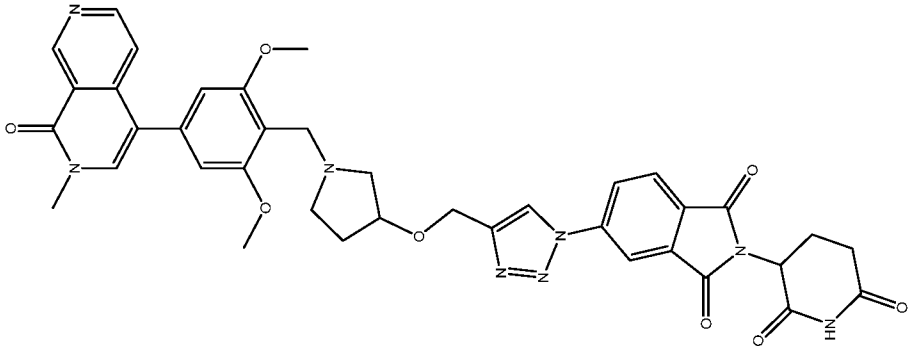
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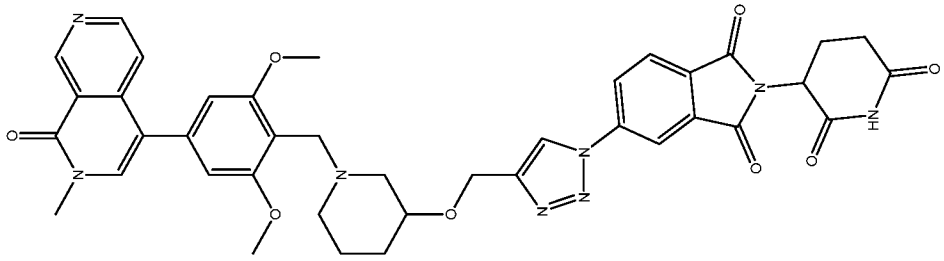
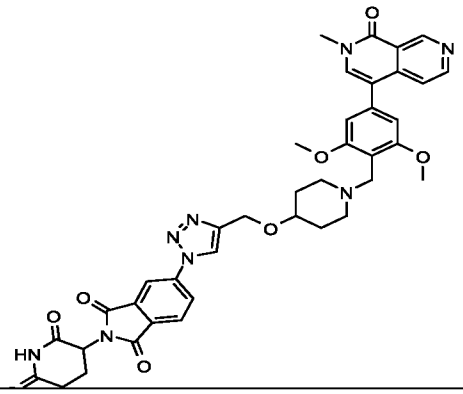
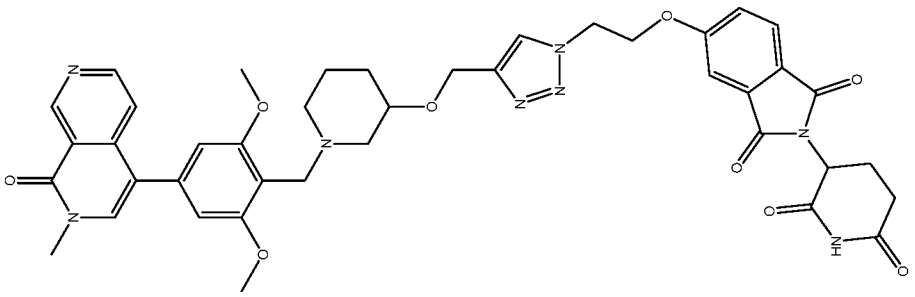
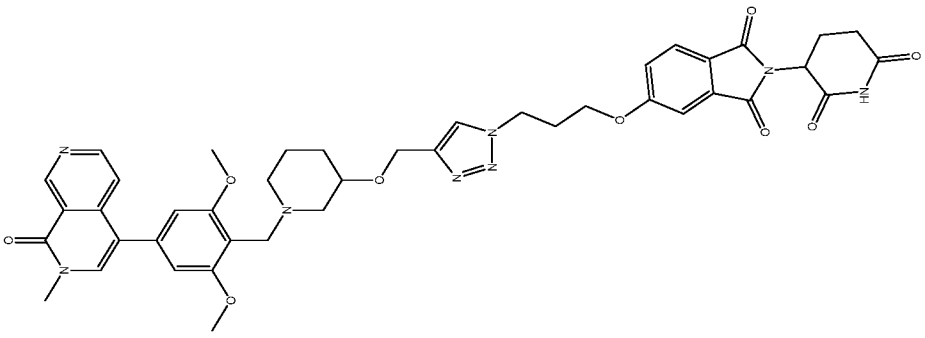
Compound No.	Structure
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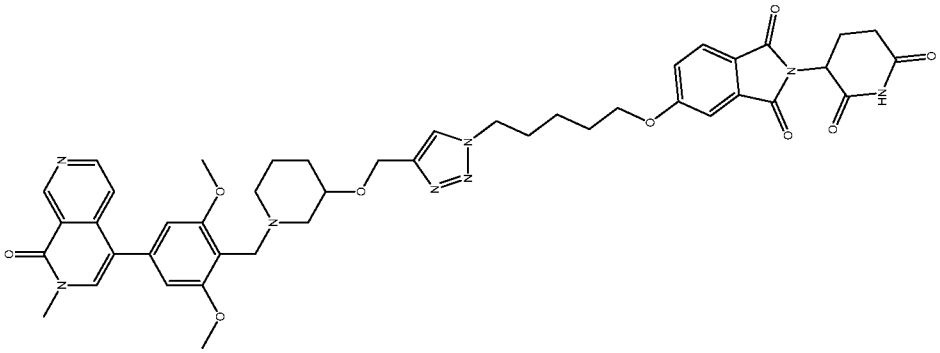
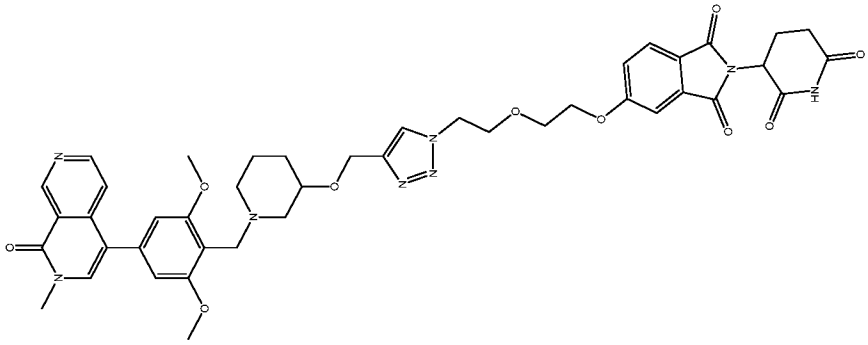
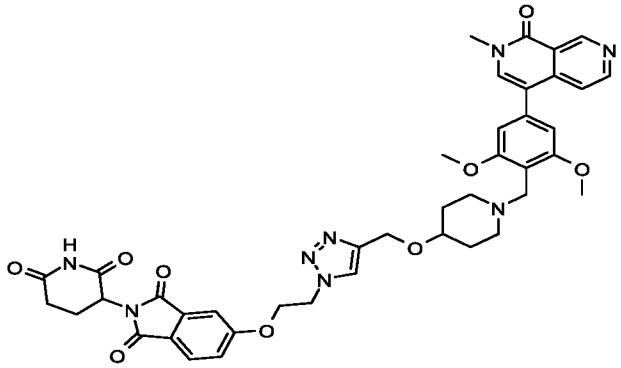
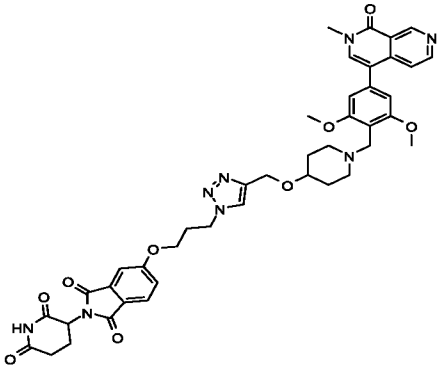
Compound No.	Structure
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D135	

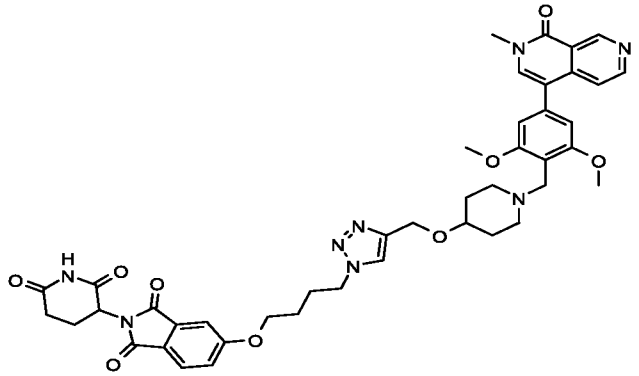
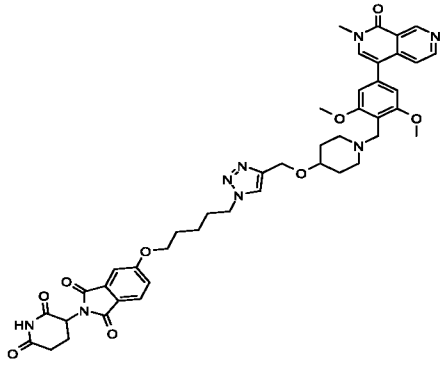
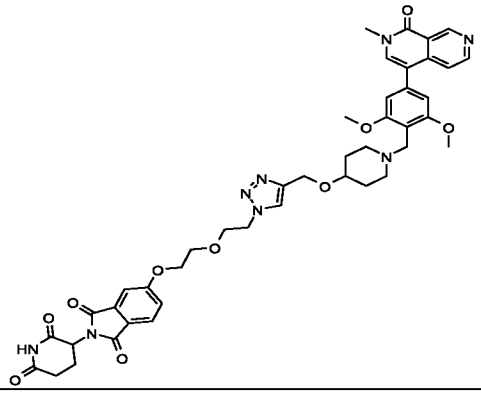
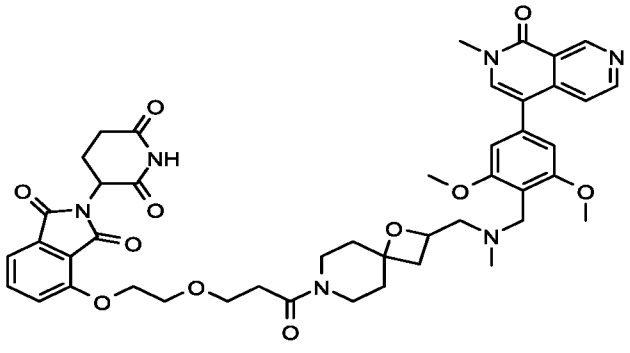
Compound No.	Structure
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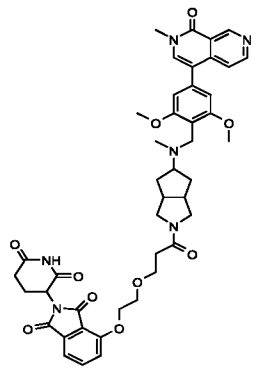
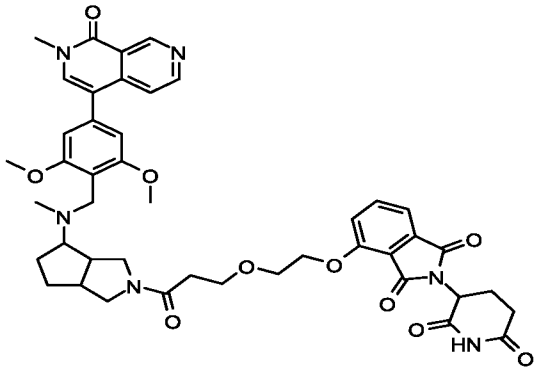
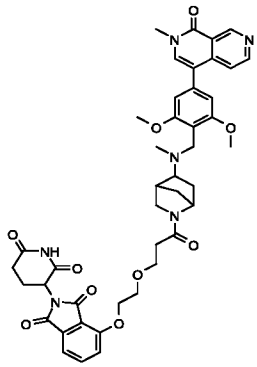
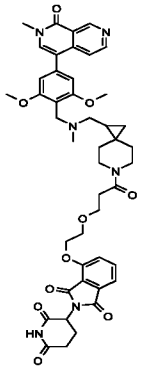
Compound No.	Structure
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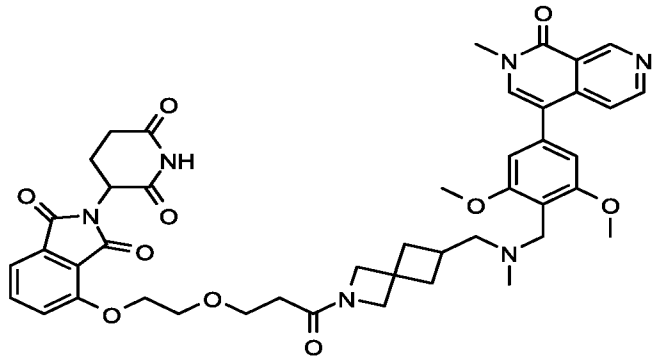
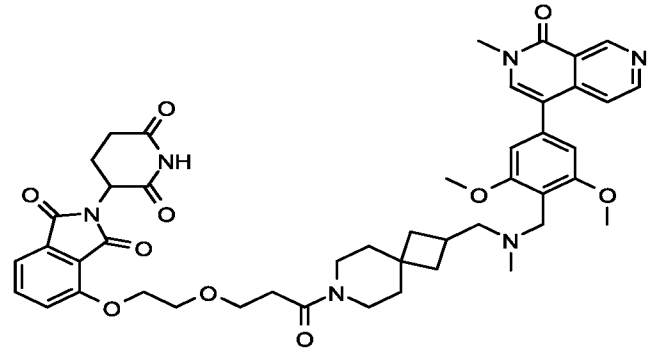
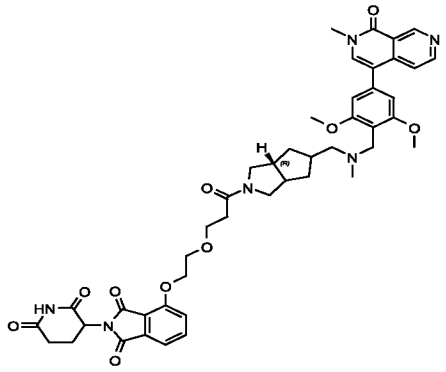
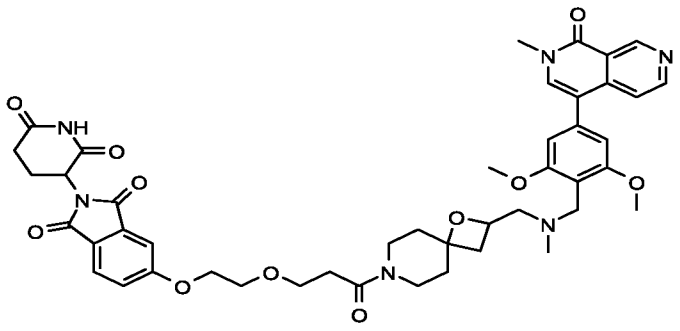
Compound No.	Structure
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D147	

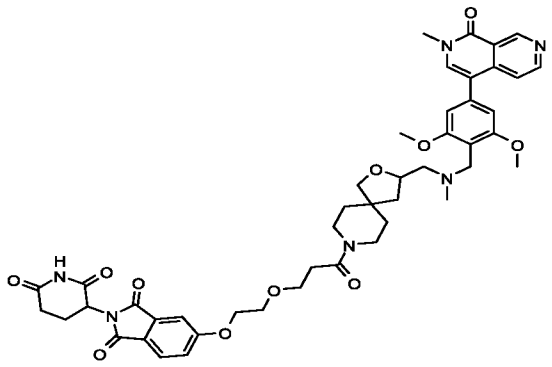
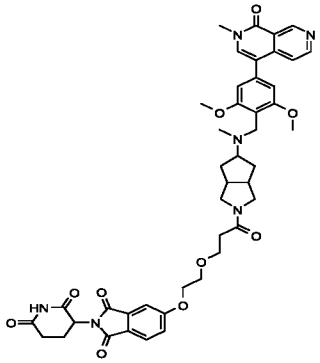
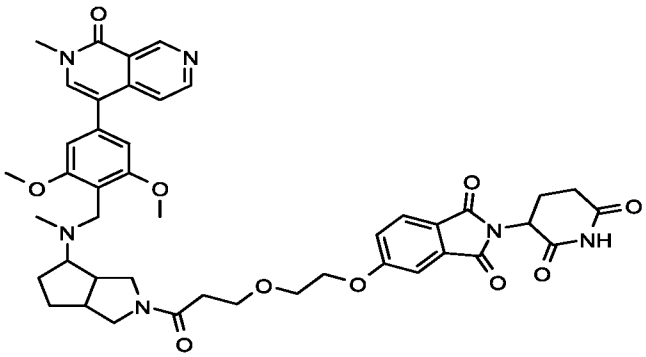
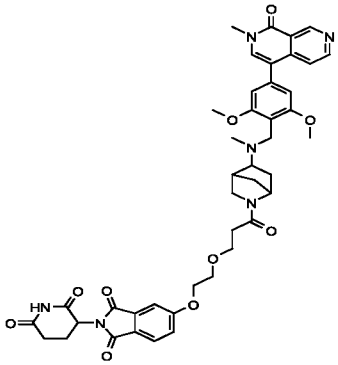
Compound No.	Structure
D148	
D149	
D150	
D151	

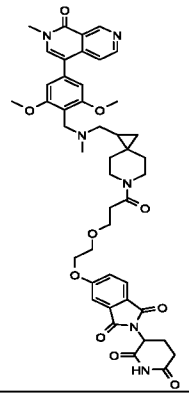
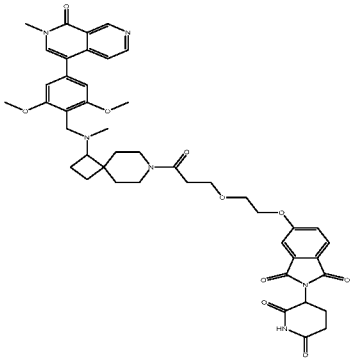
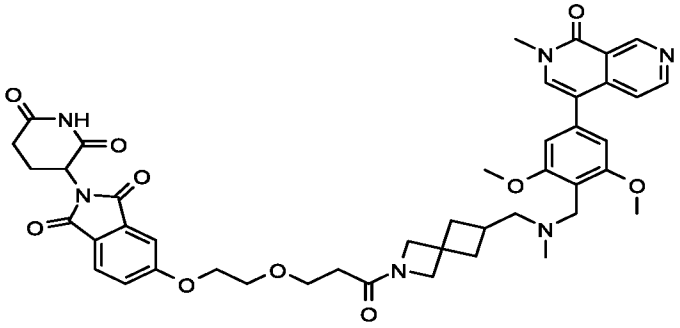
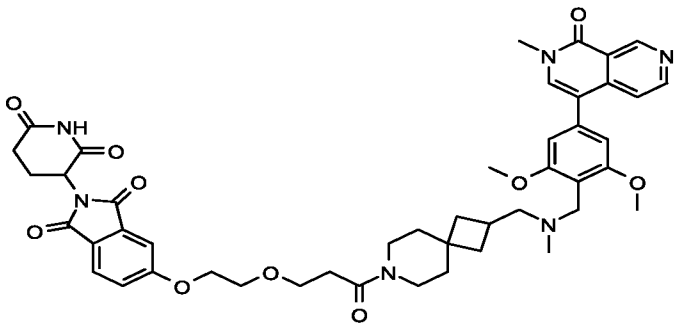
Compound No.	Structure
D152	
D153	
D154	
D155	

Compound No.	Structure
D156	
D157	
D158	
D159	

Compound No.	Structure
D160	
D161	
D162	
D163	

Compound No.	Structure
D164	
D165	
D166	
D167	

Compound No.	Structure
D168	
D169	
D170	
D171	

Compound No.	Structure
D172	
D173	
D174	
D175	

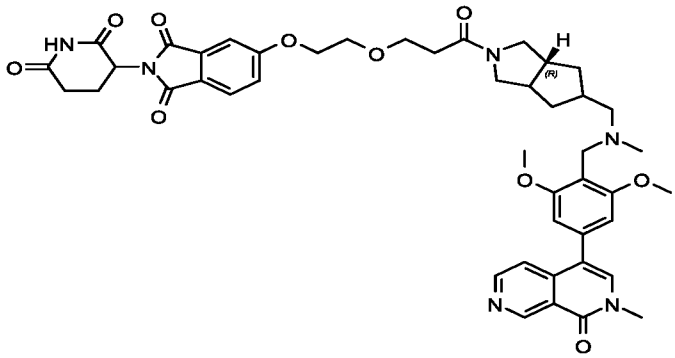
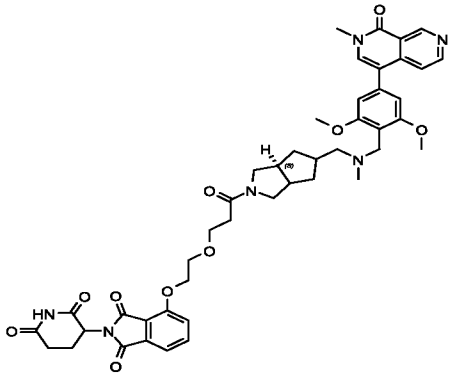
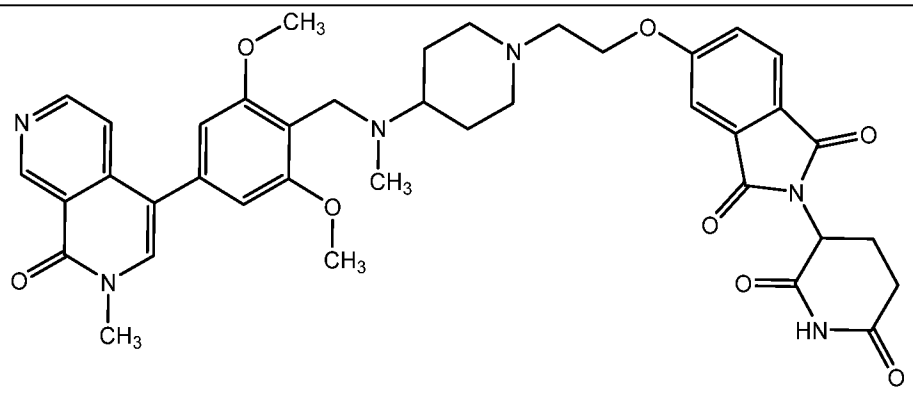
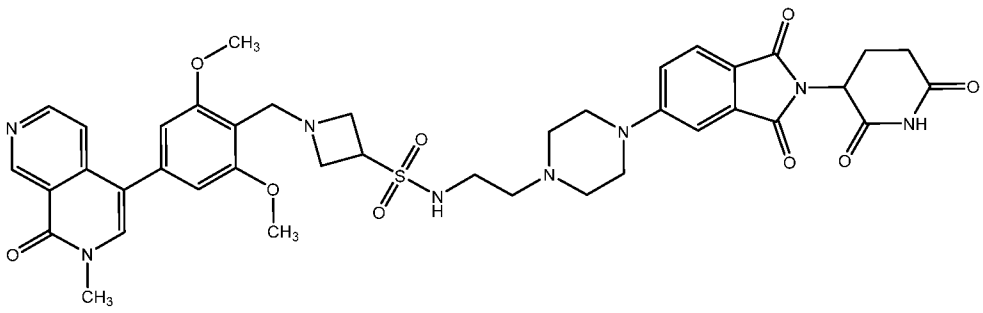
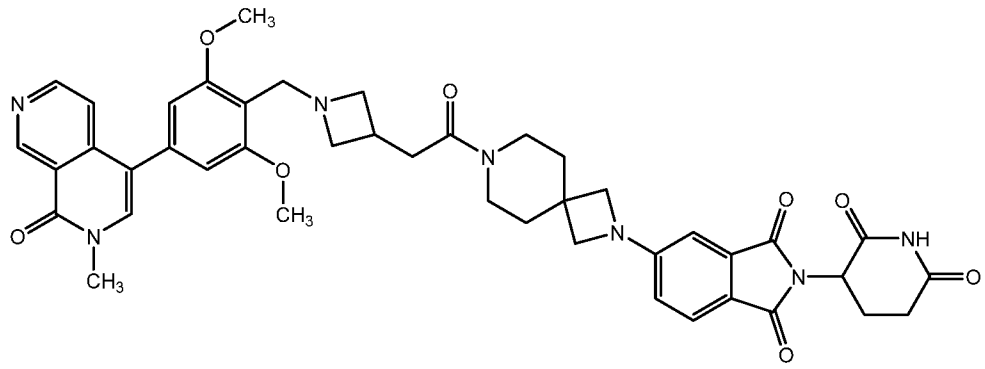
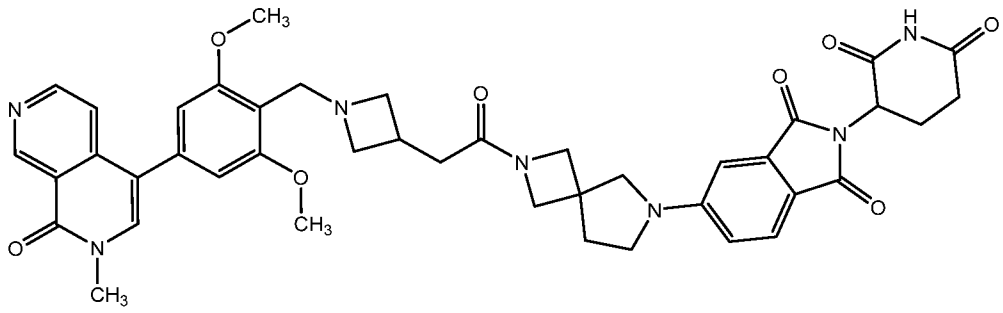
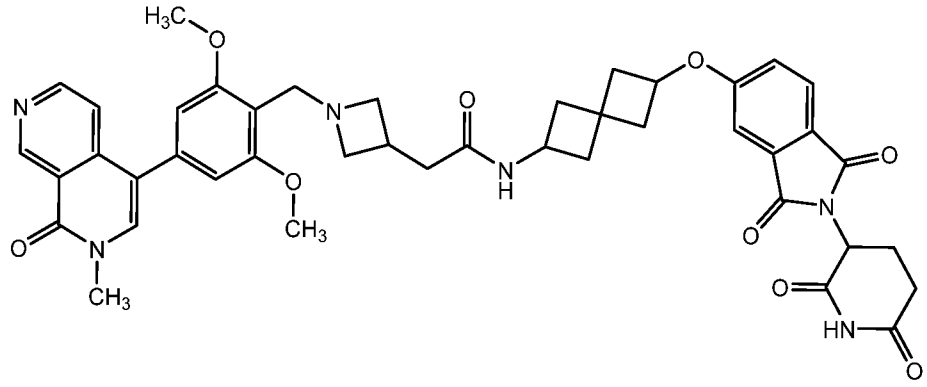
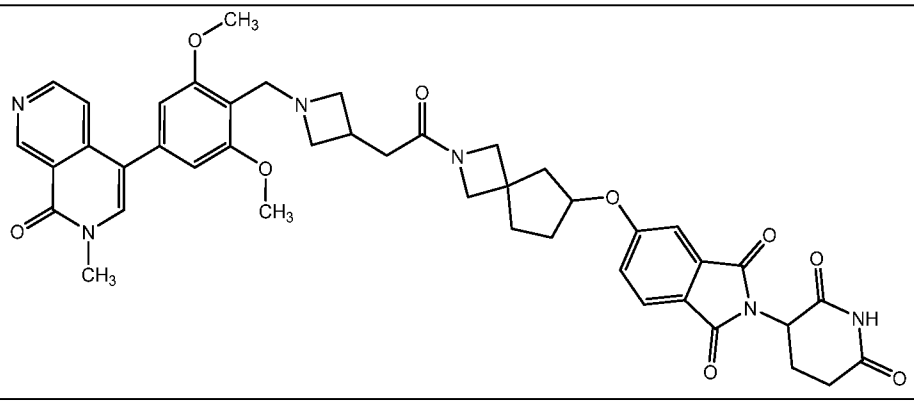
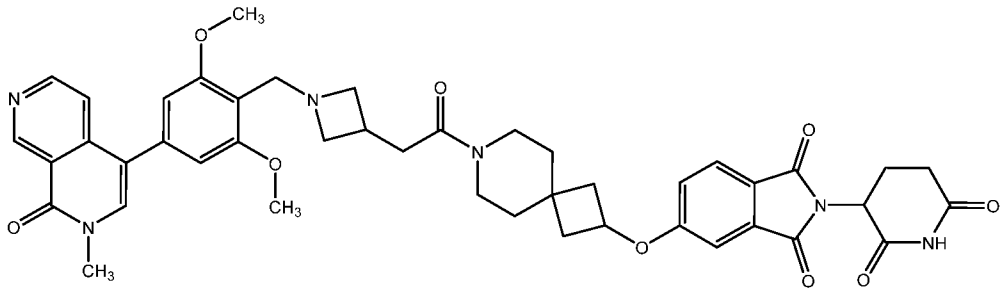
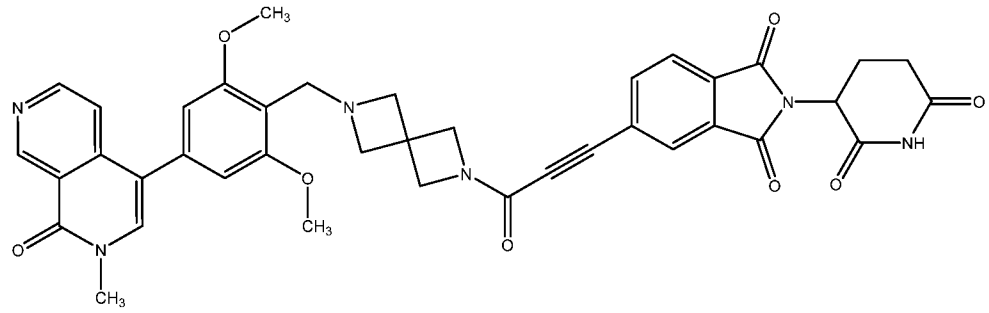
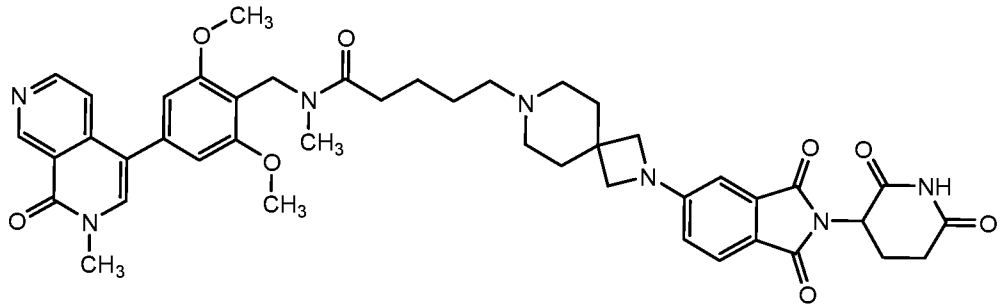
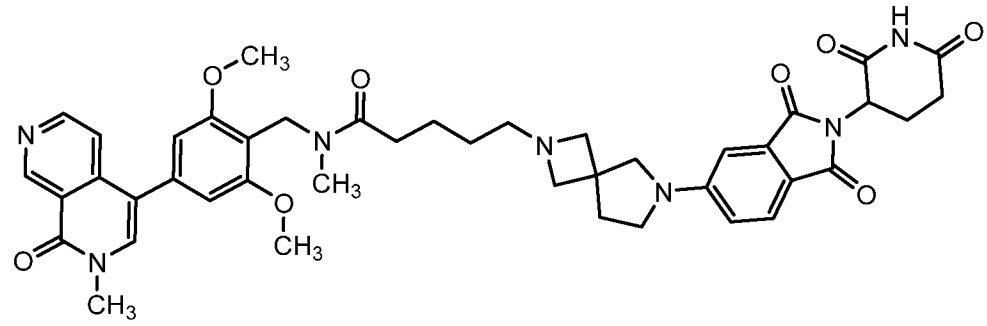
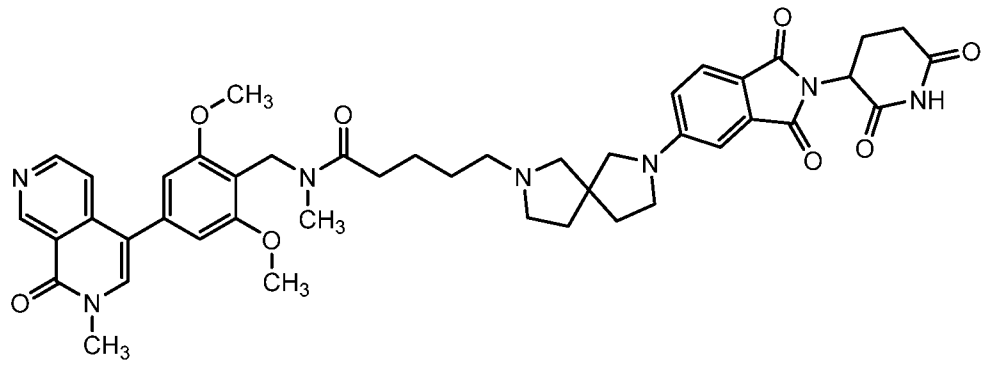
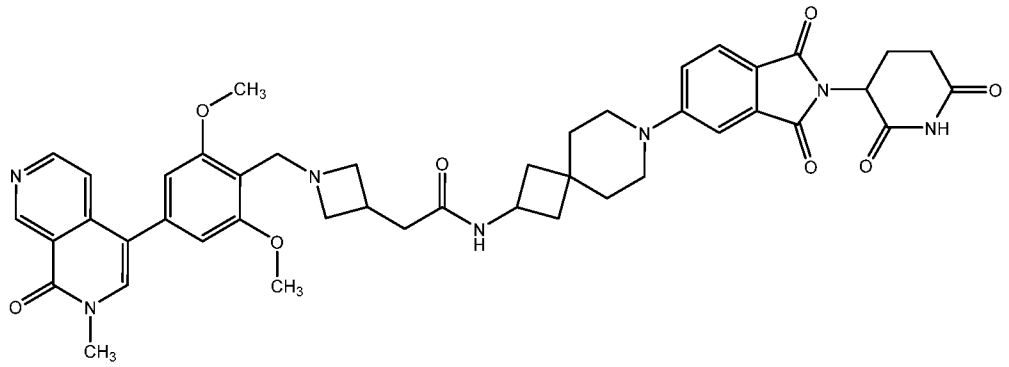
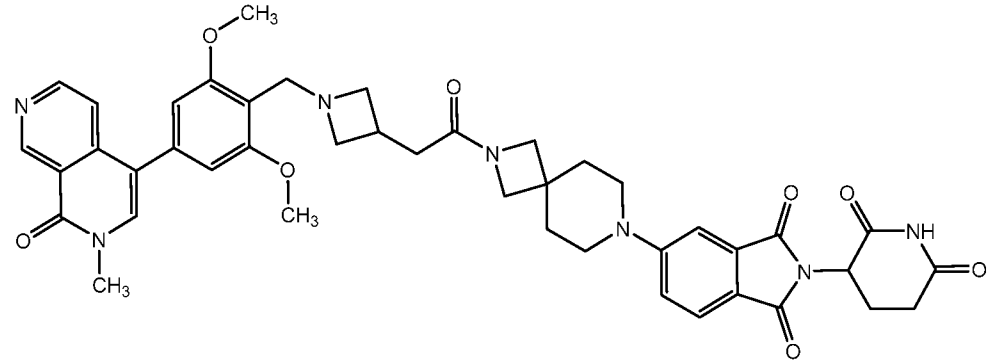
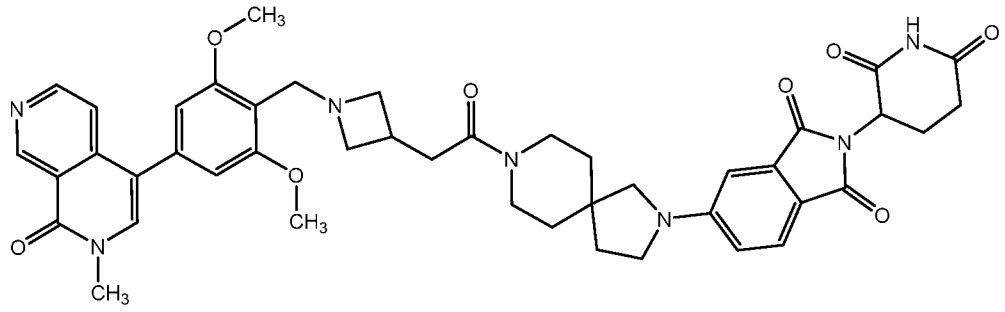
Compound No.	Structure
D176	
D177	

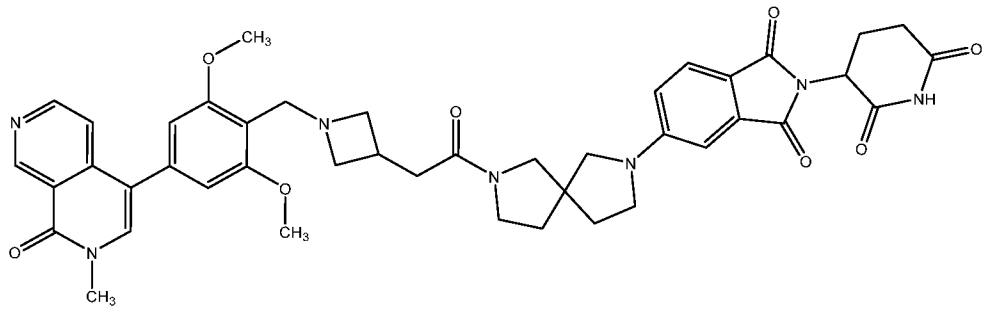
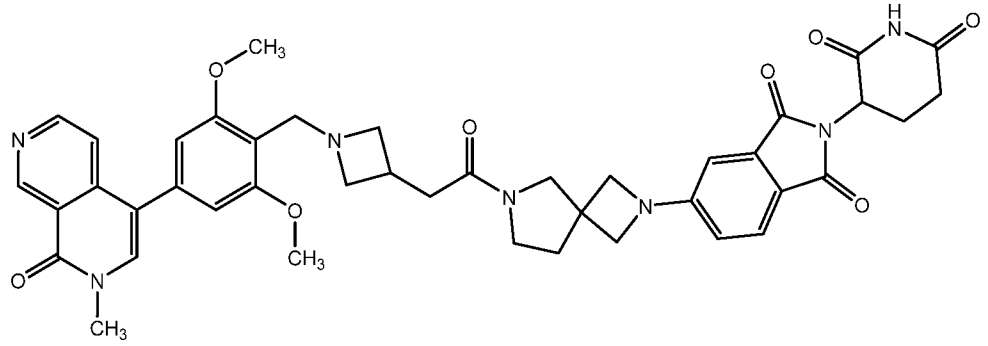
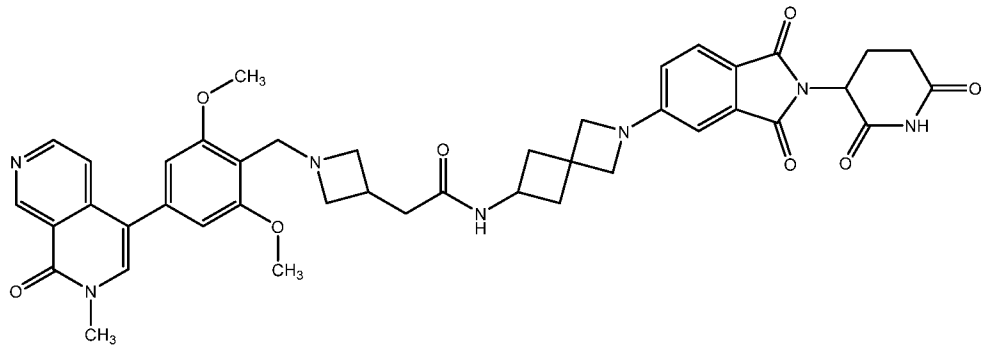
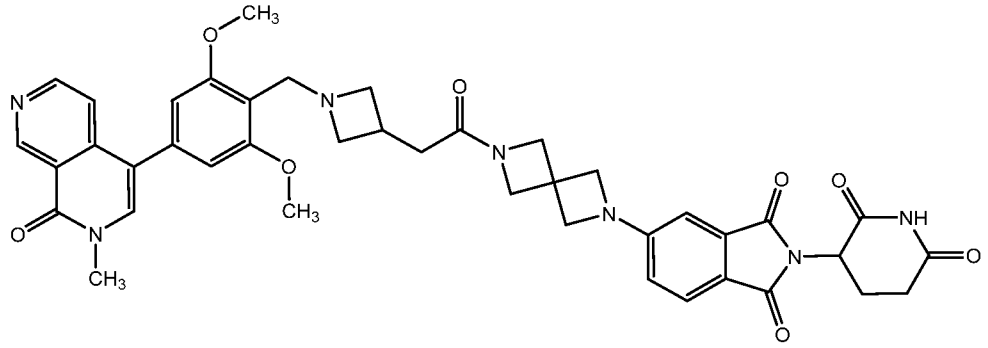
Table 1B. Compounds D178-D371 of the Disclosure

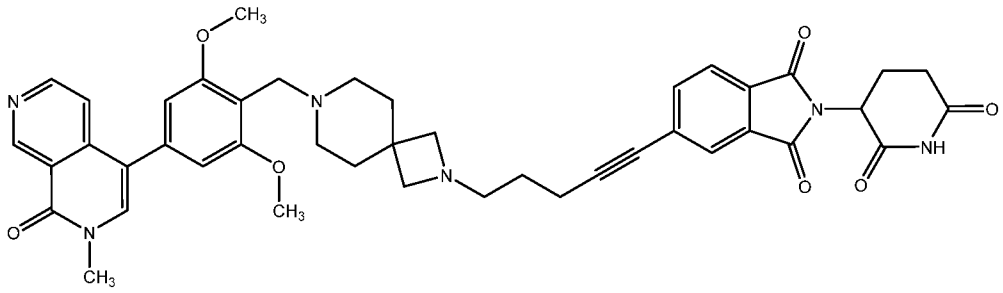
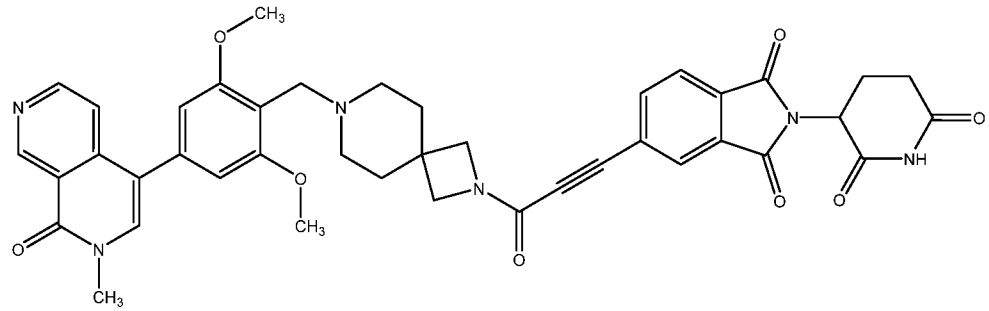
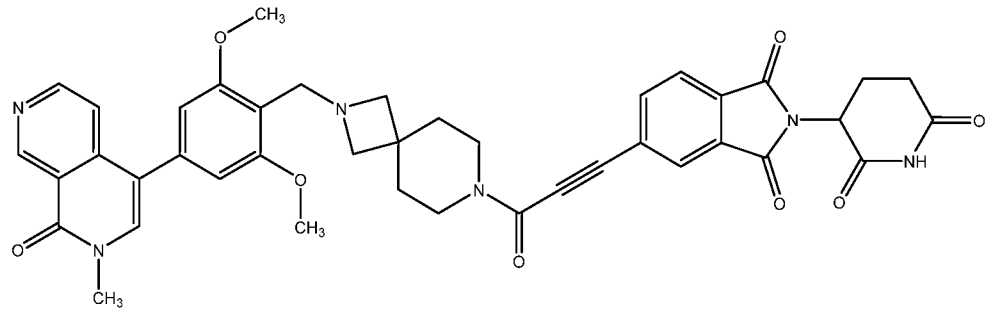
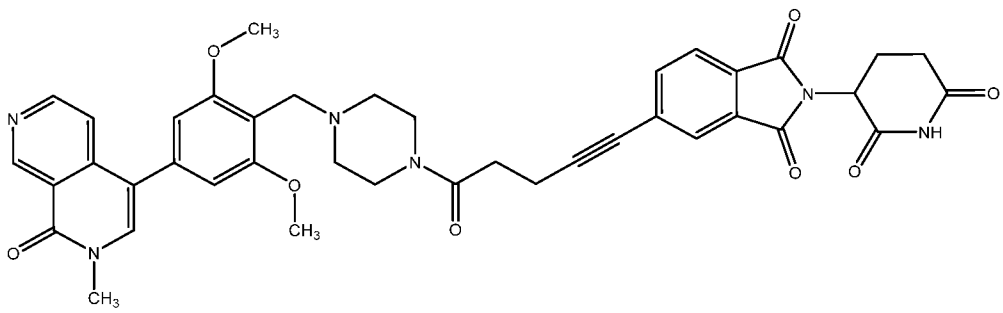
Compound No.	Structure
D178	
D179	

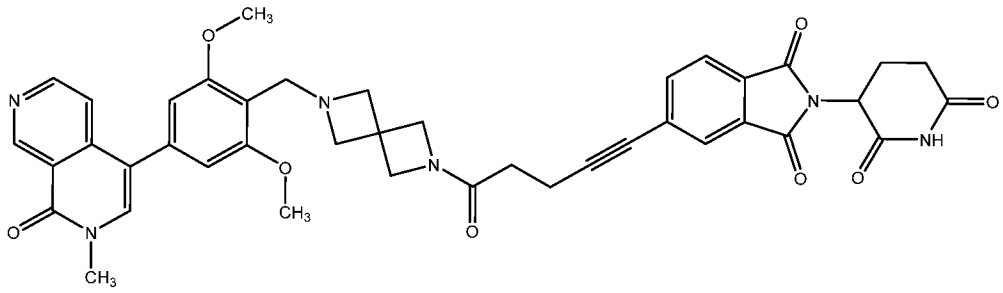
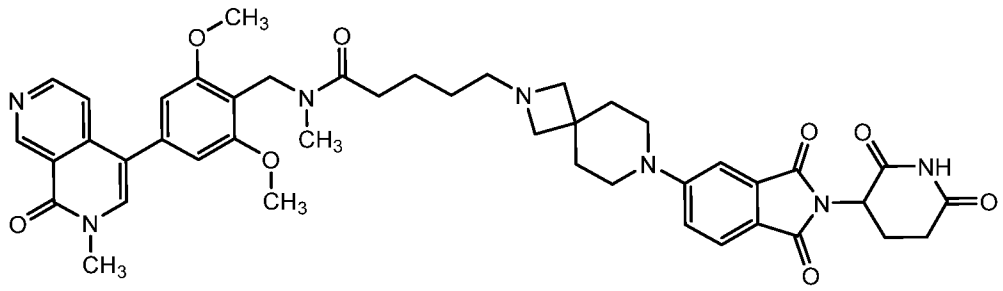
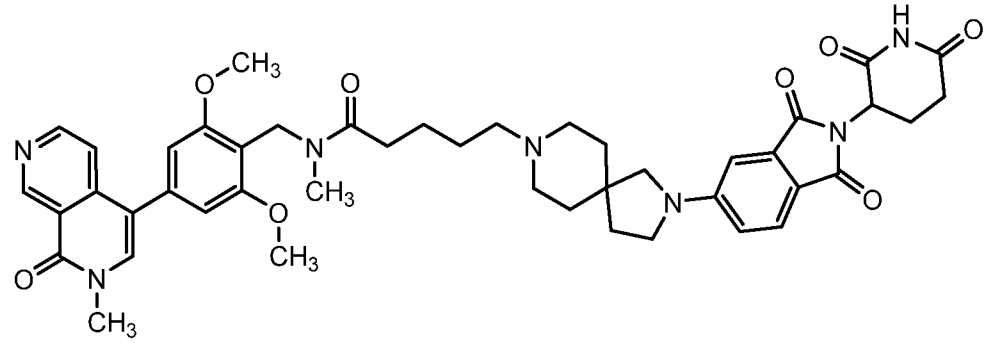
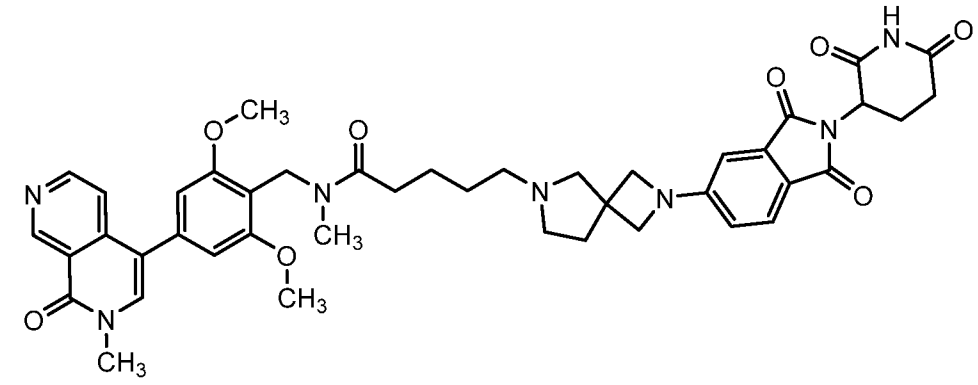
Compound No.	Structure
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D181	
D182	
D183	

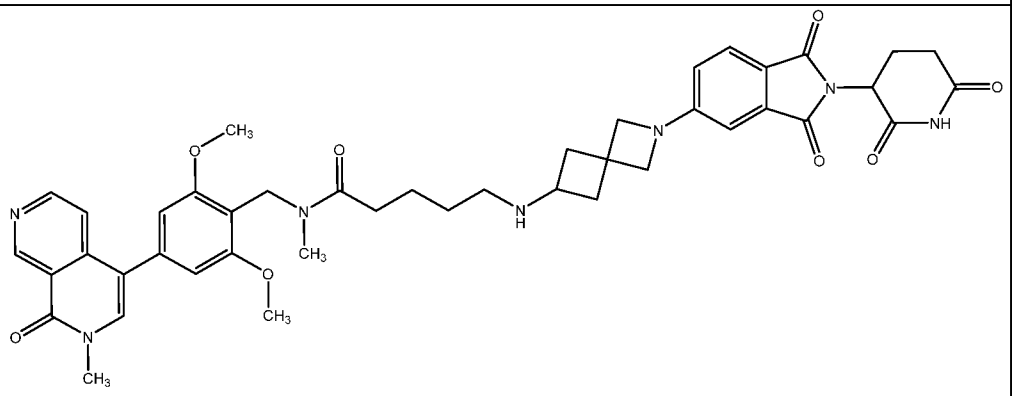
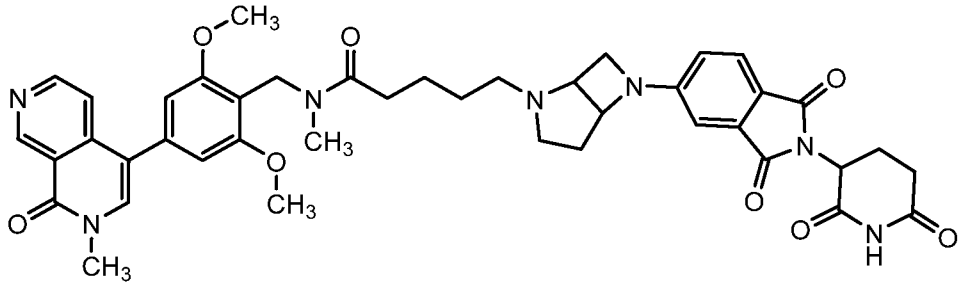
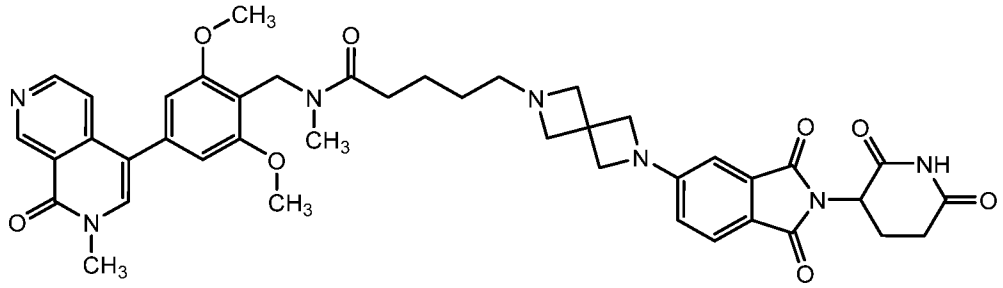
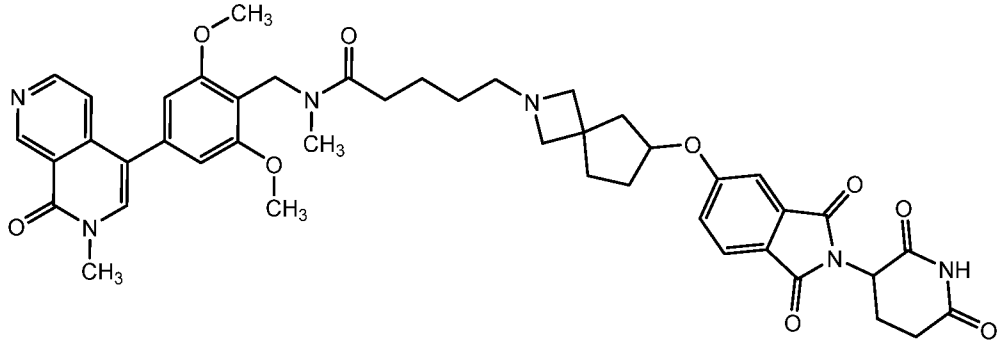
Compound No.	Structure
D184	
D185	
D186	
D187	

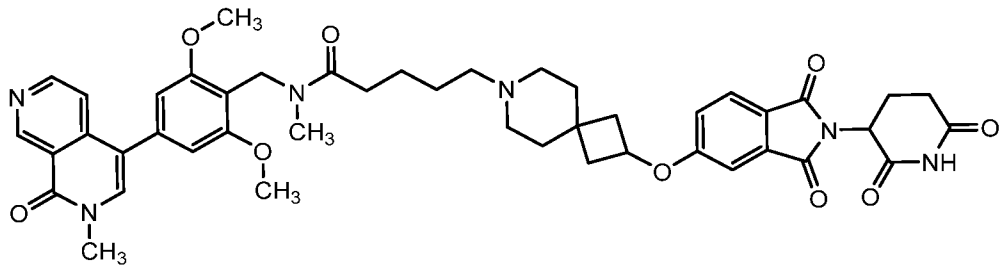
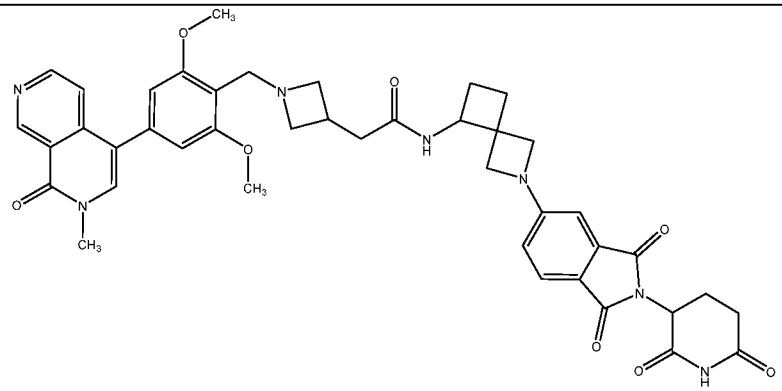
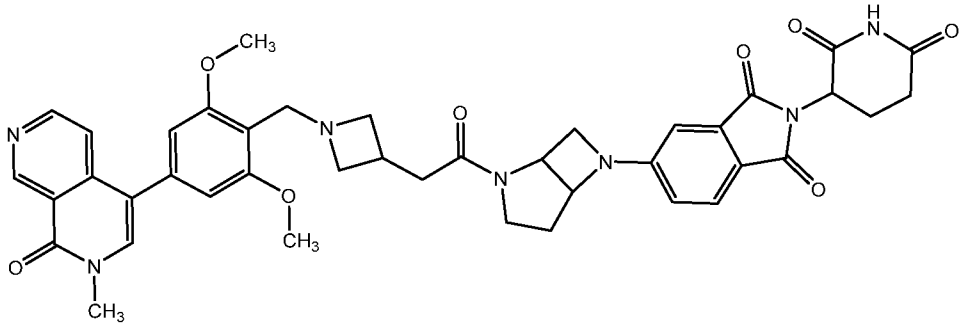
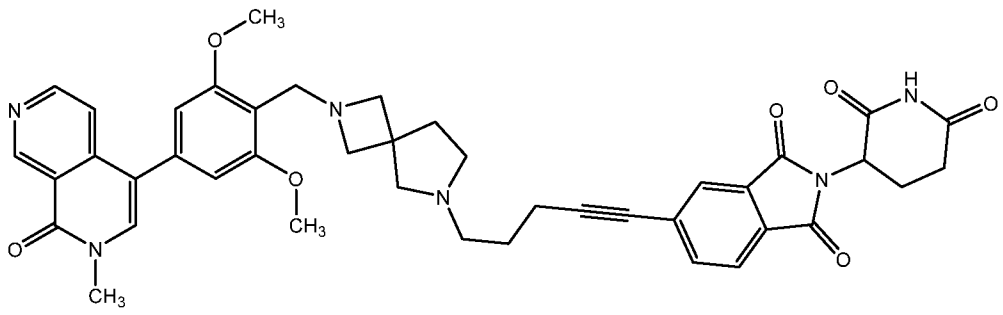
Compound No.	Structure
D188	
D189	
D190	
D191	

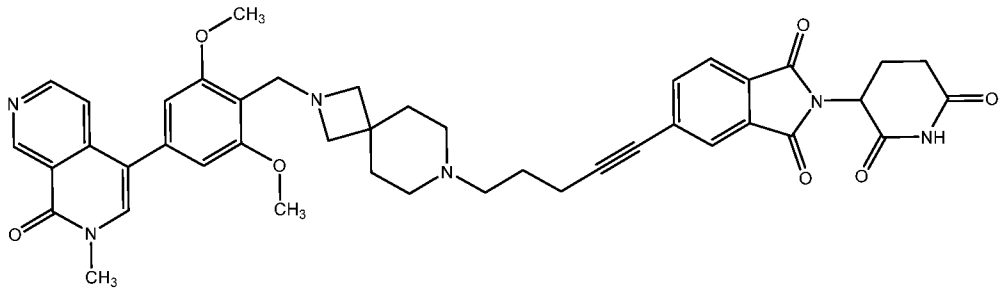
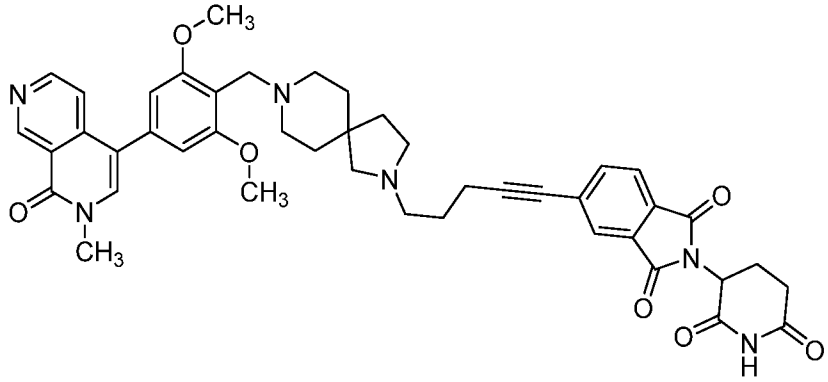
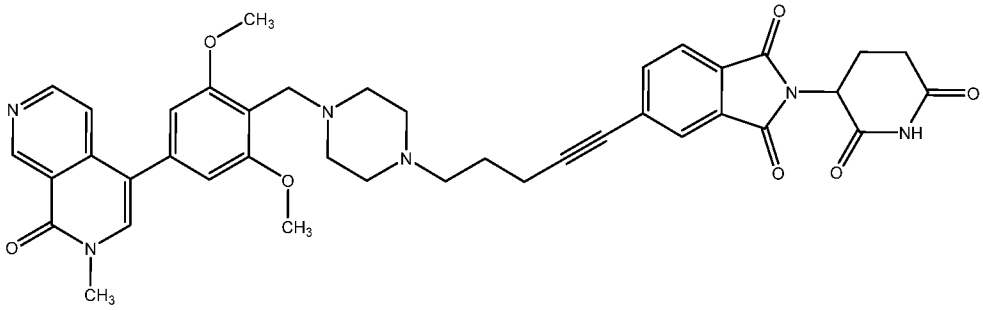
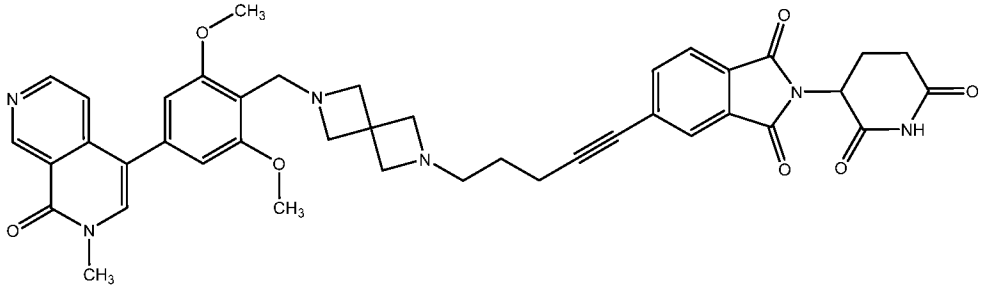
Compound No.	Structure
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D193	
D194	
D195	

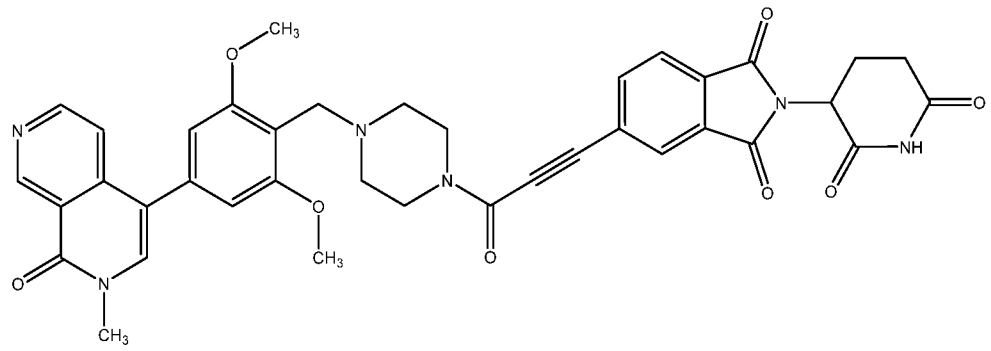
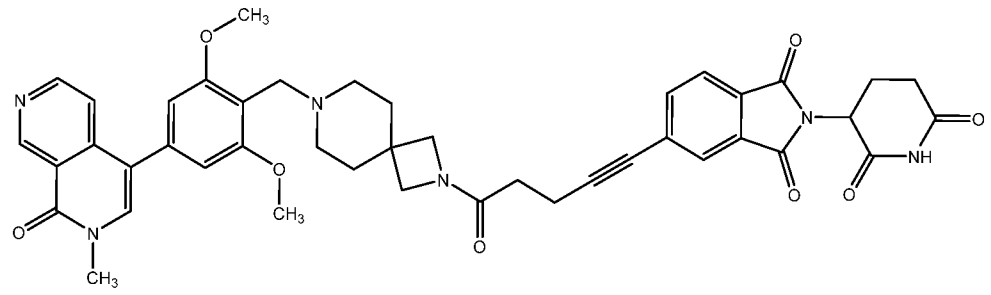
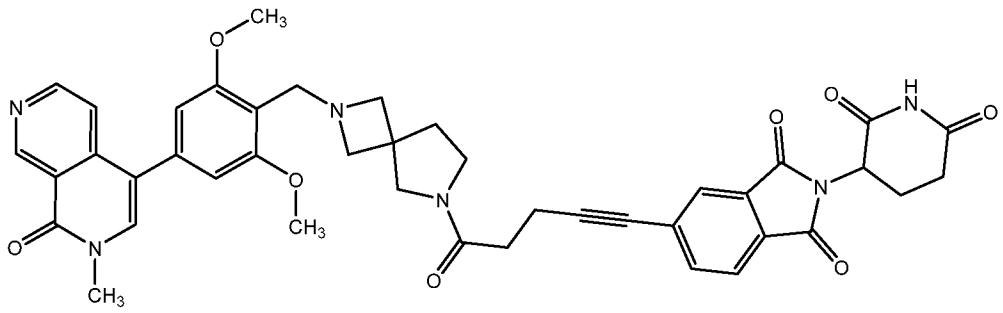
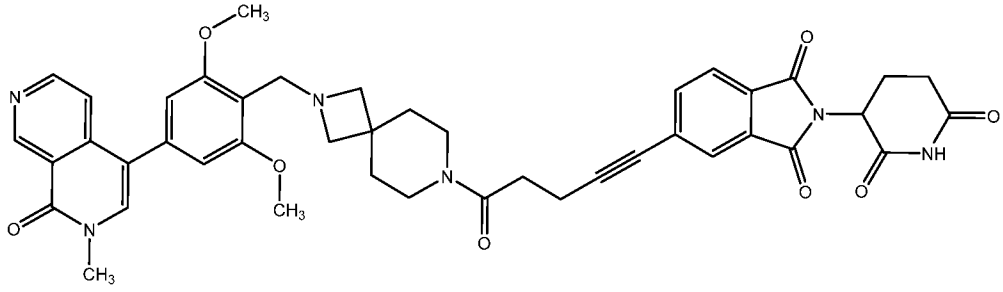
Compound No.	Structure
D196	
D197	
D198	
D199	

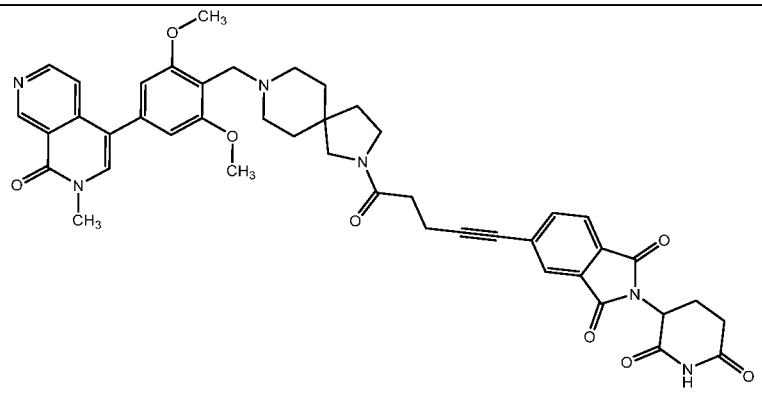
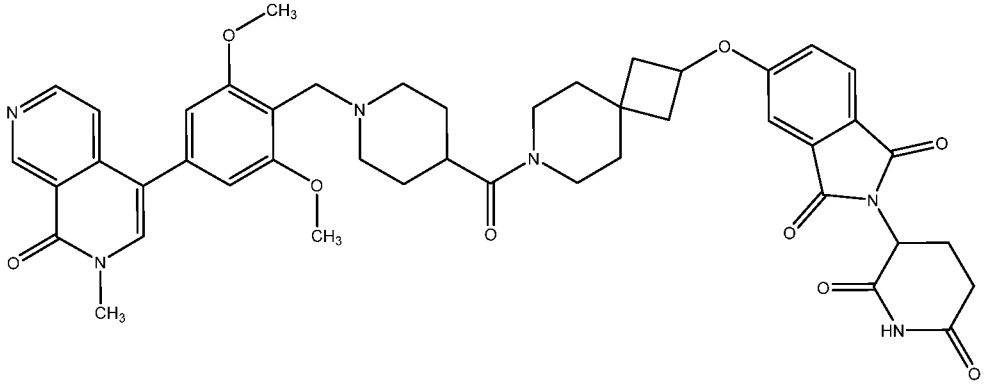
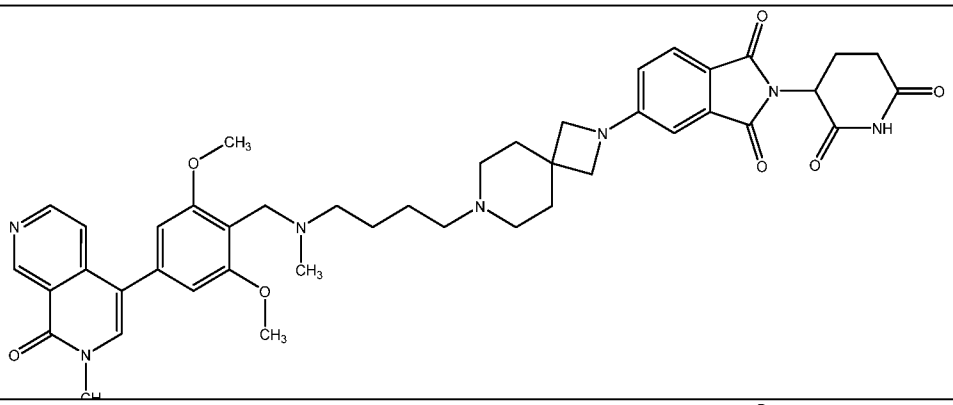
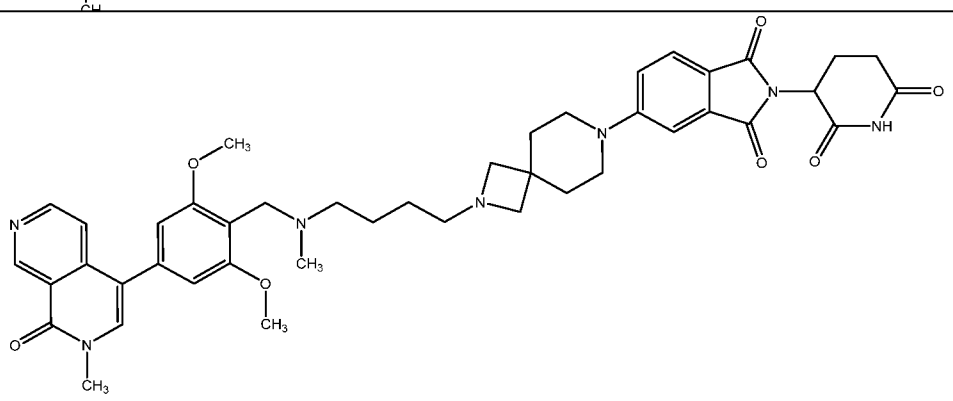
Compound No.	Structure
D200	
D201	
D202	
D203	

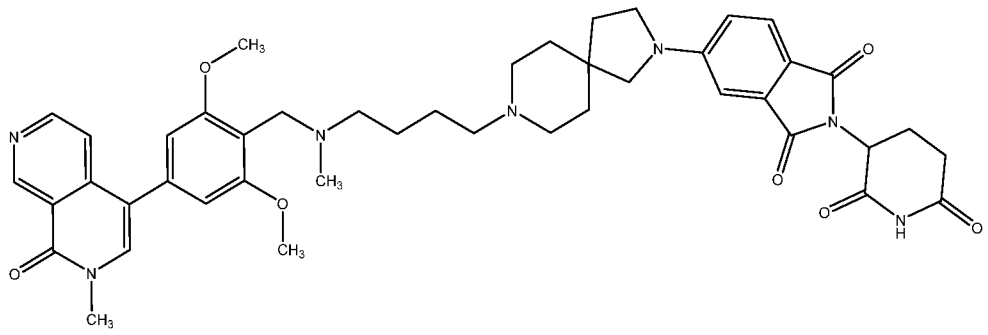
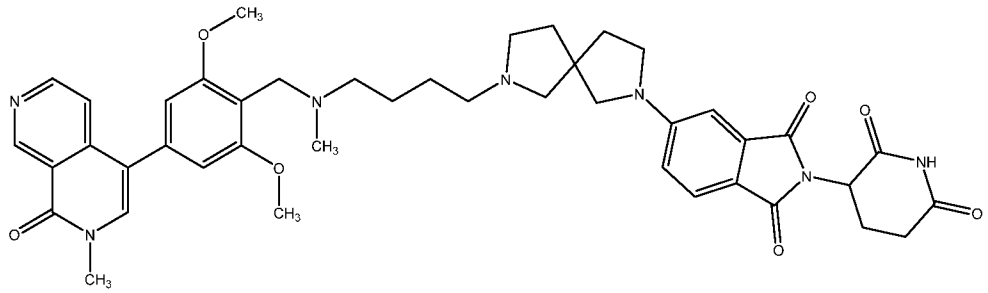
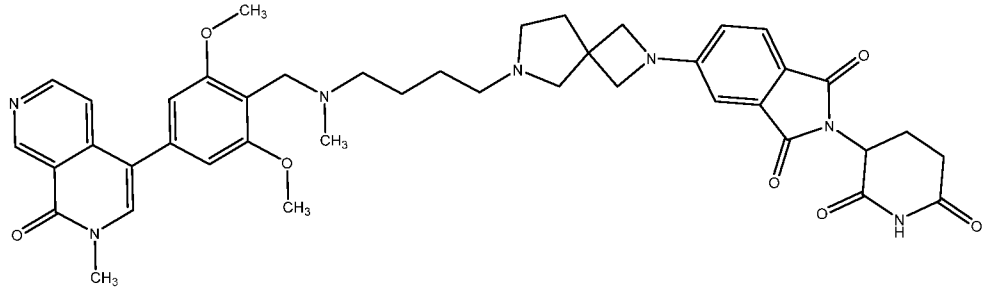
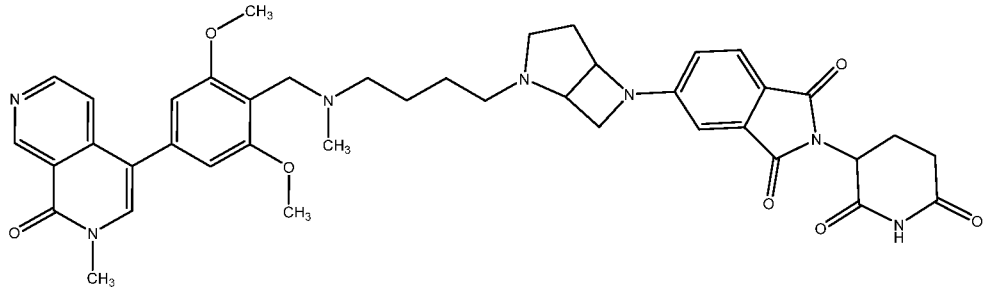
Compound No.	Structure
D204	
D205	
D206	
D207	

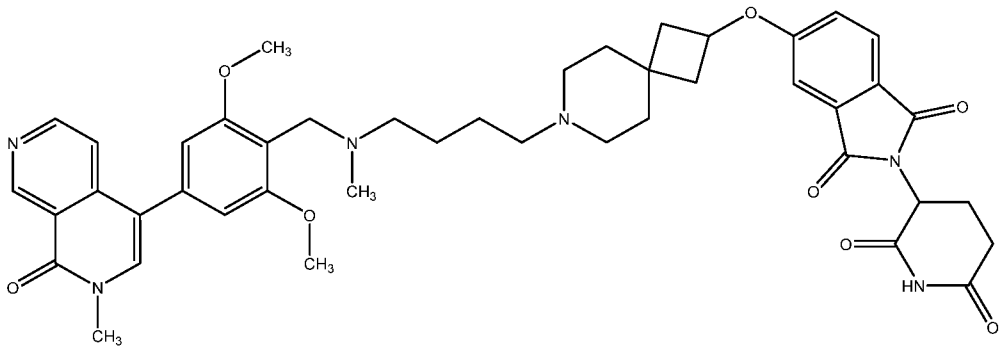
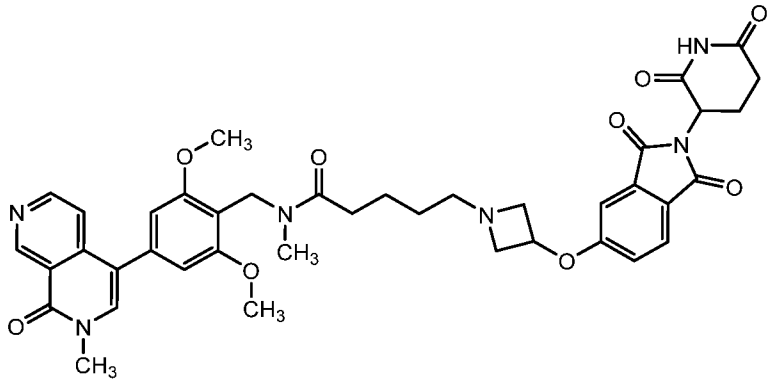
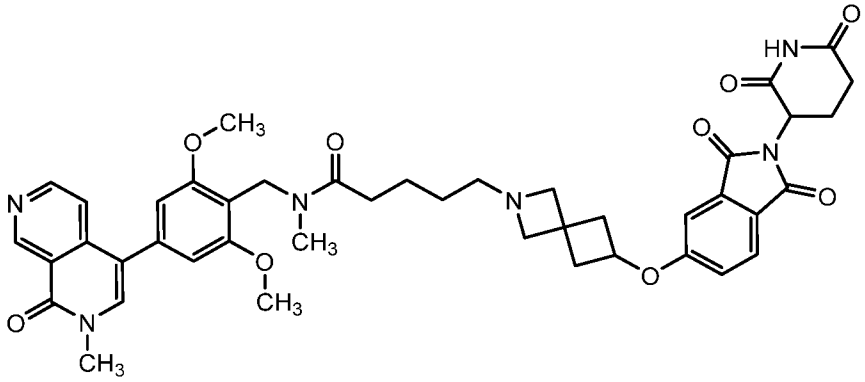
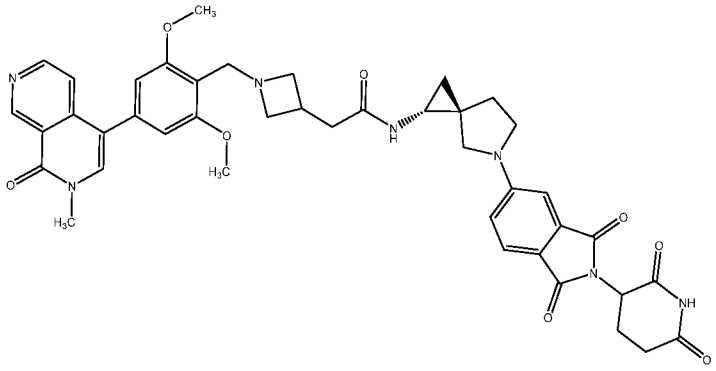
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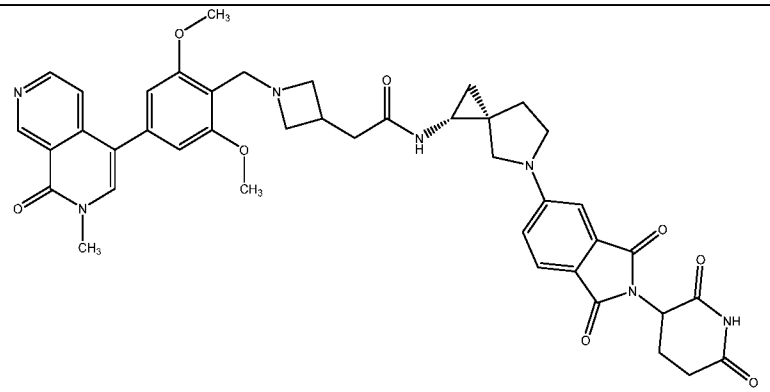
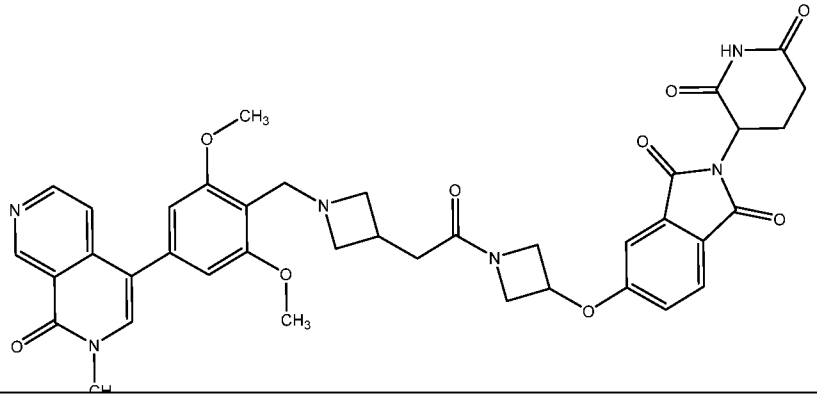
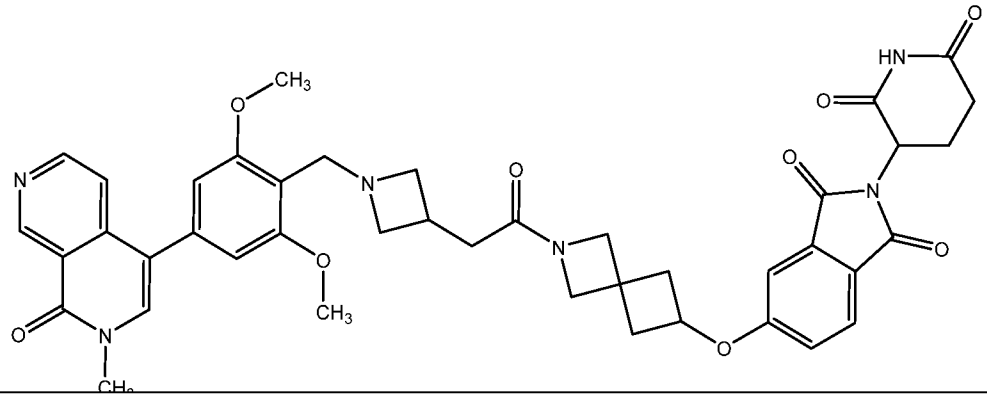
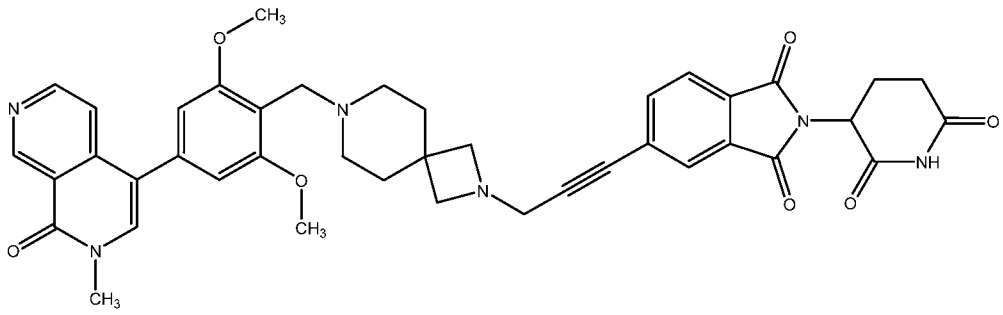
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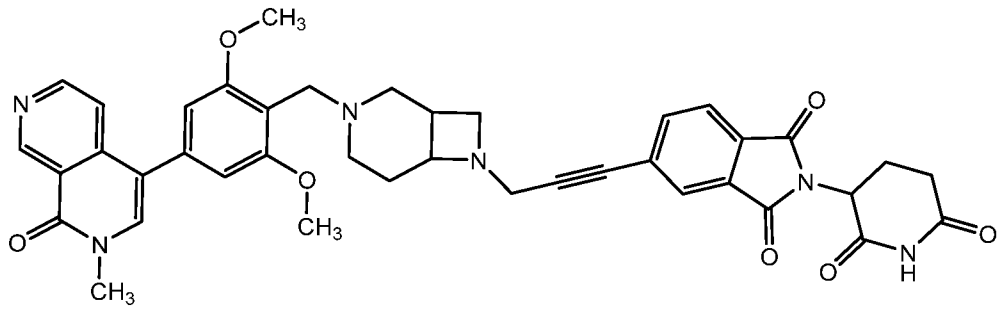
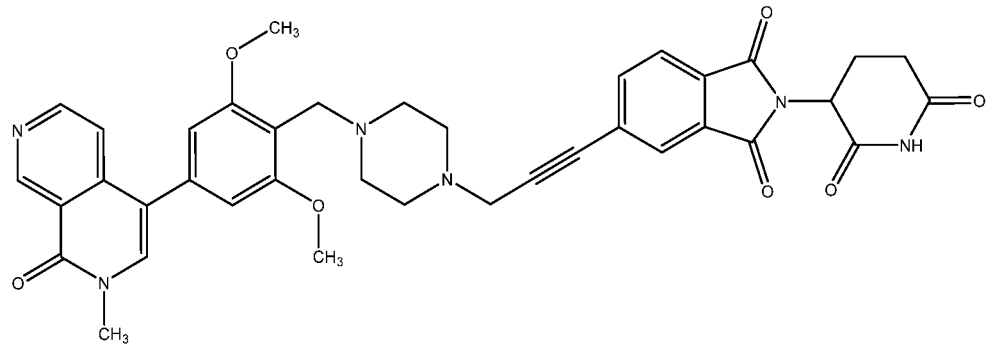
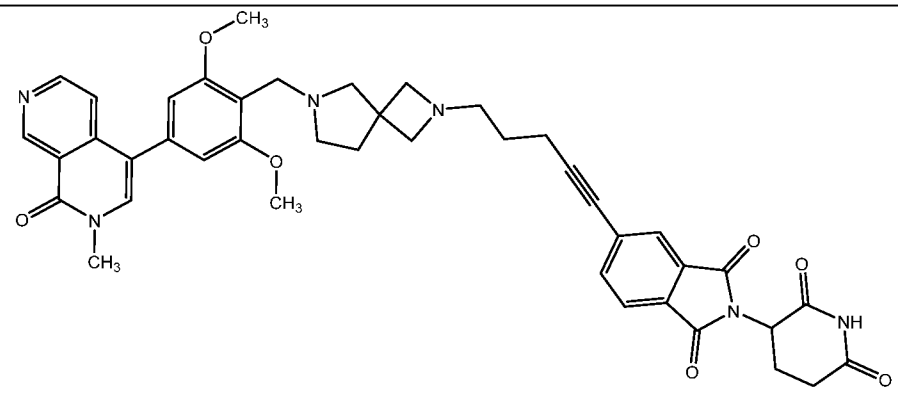
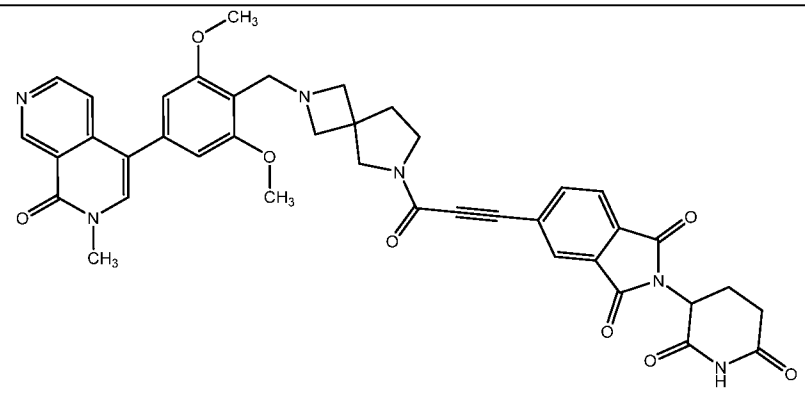
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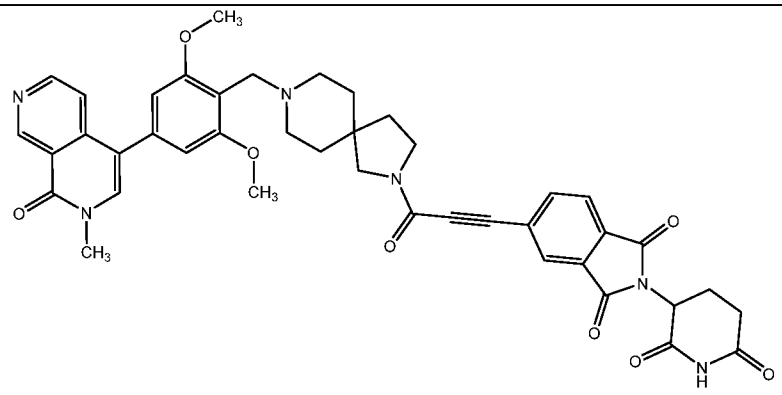
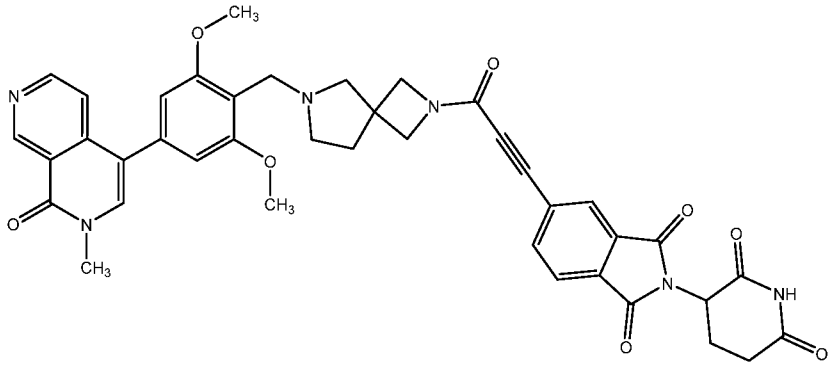
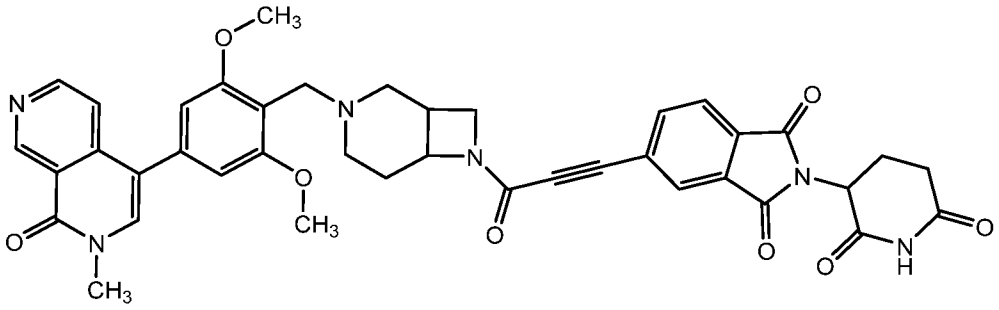
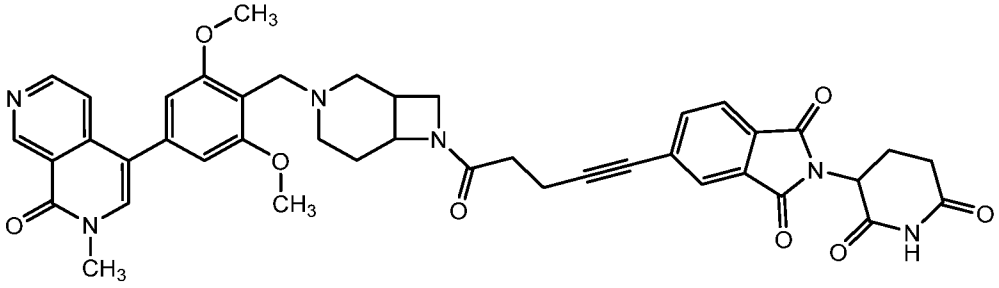
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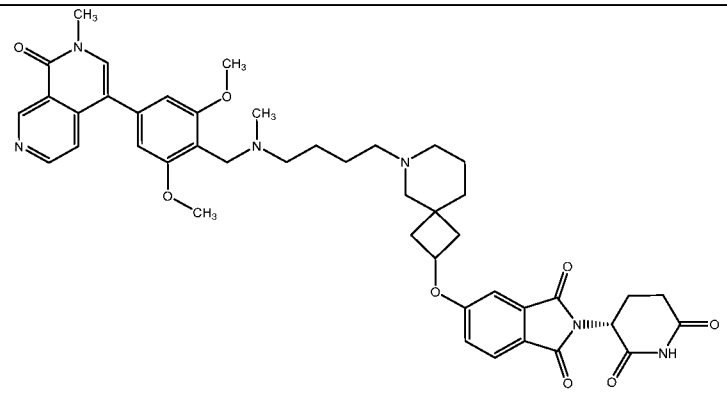
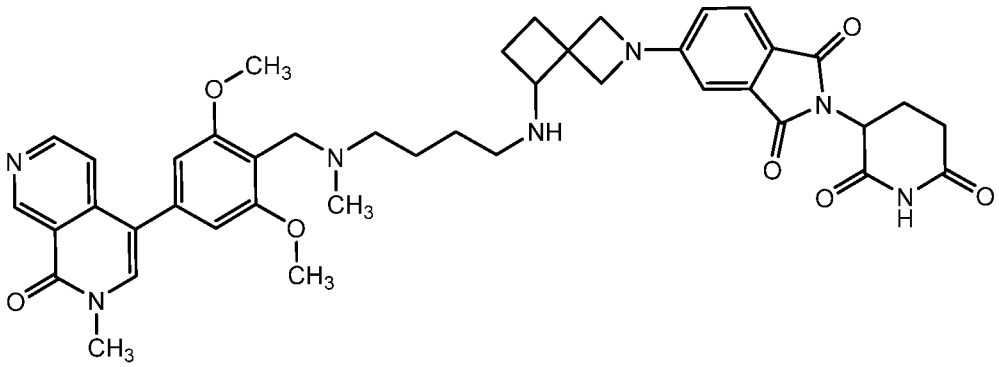
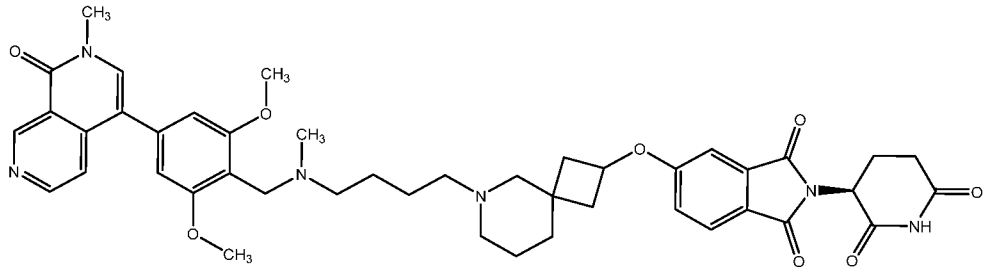
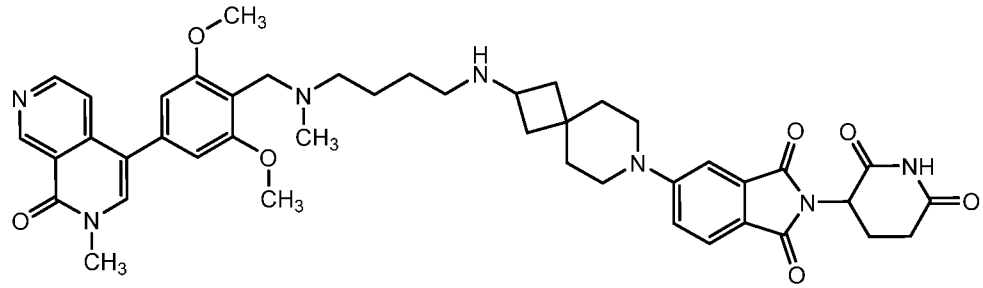
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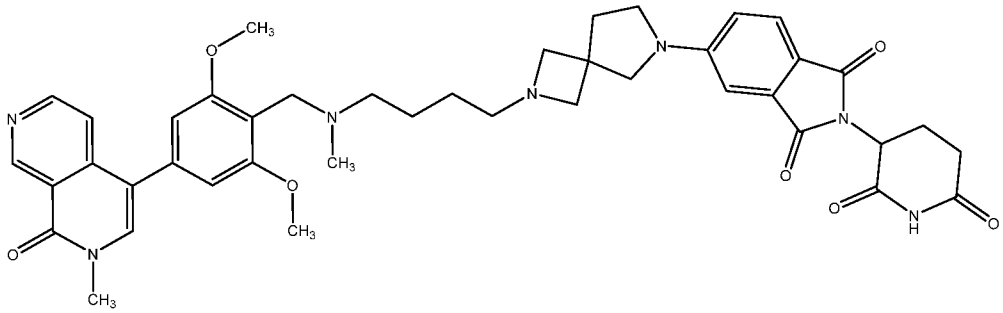
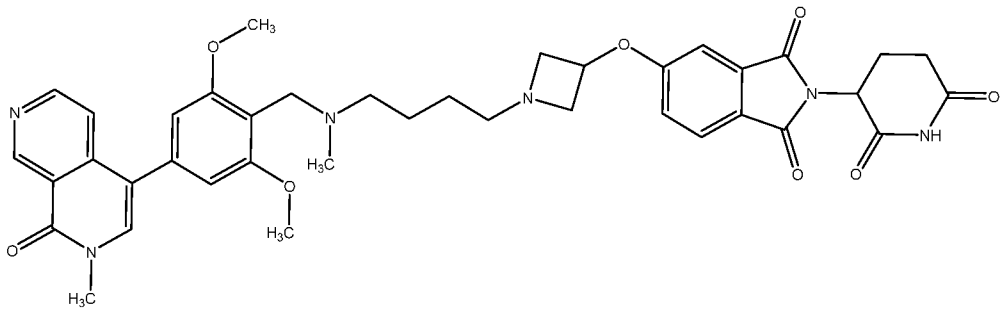
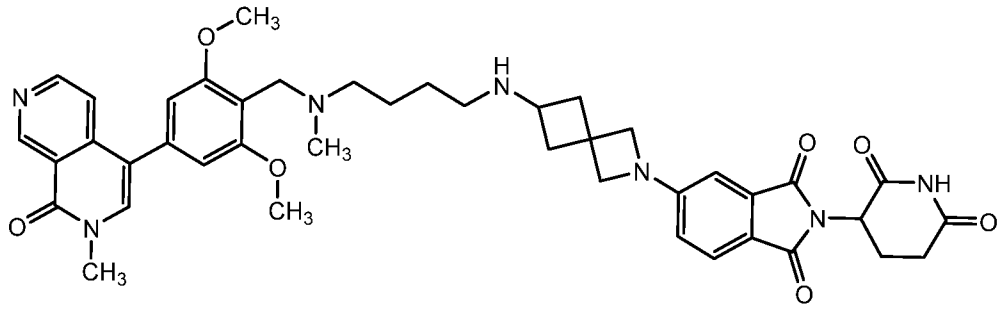
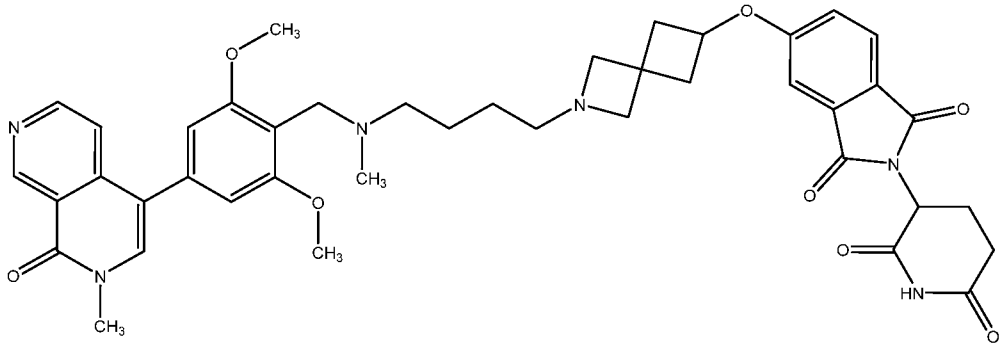
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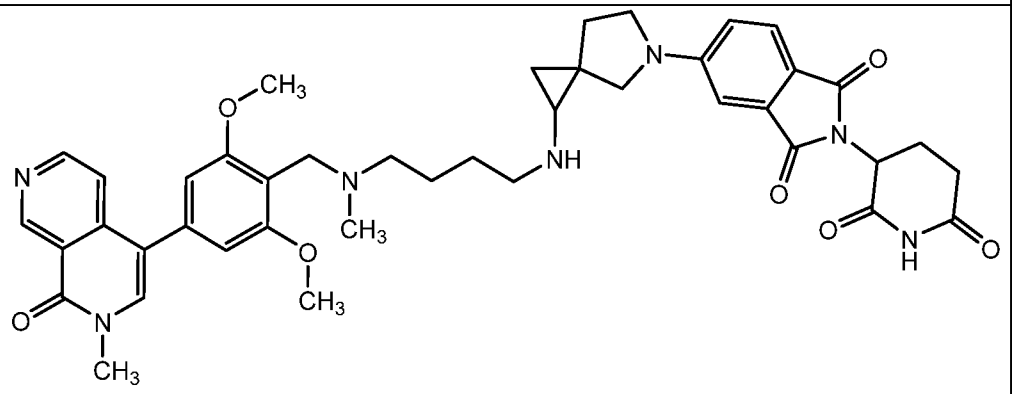
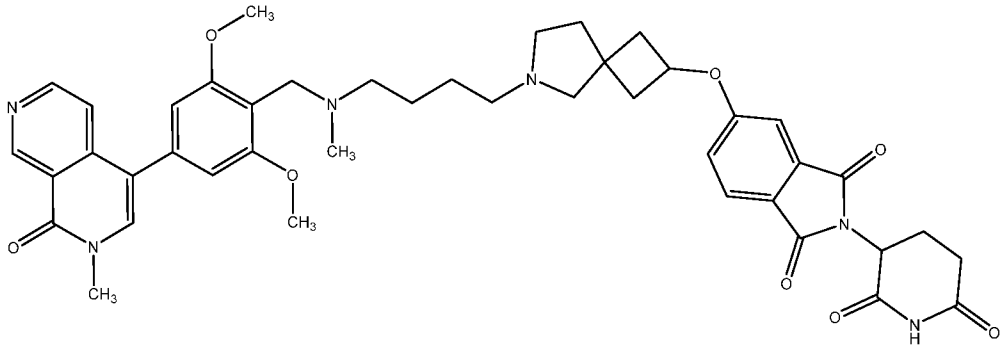
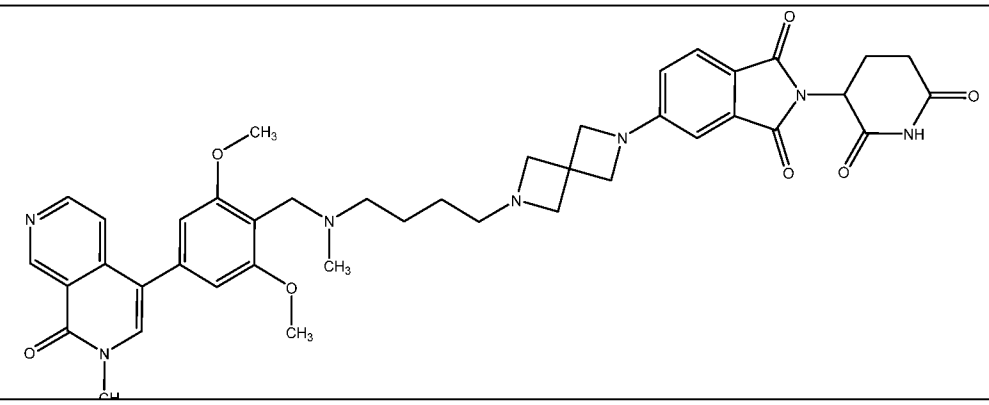
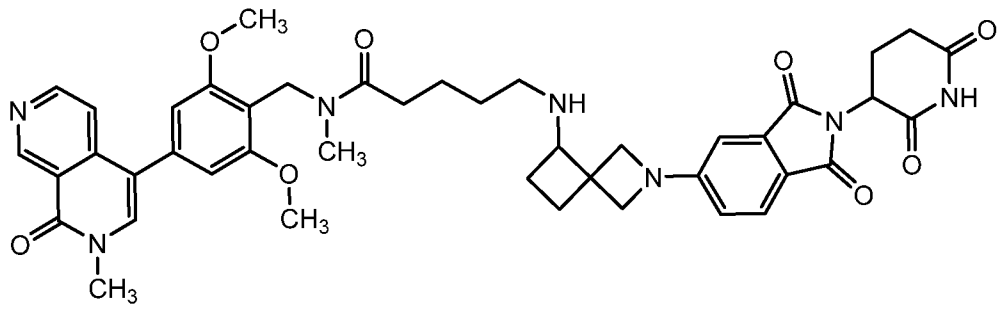
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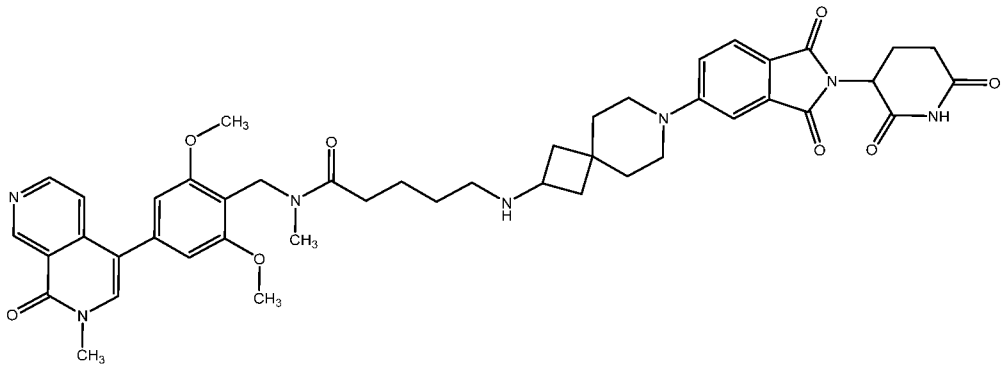
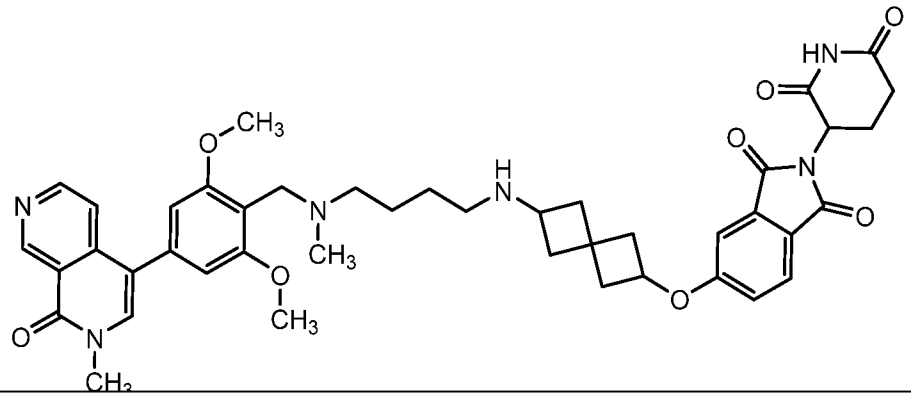
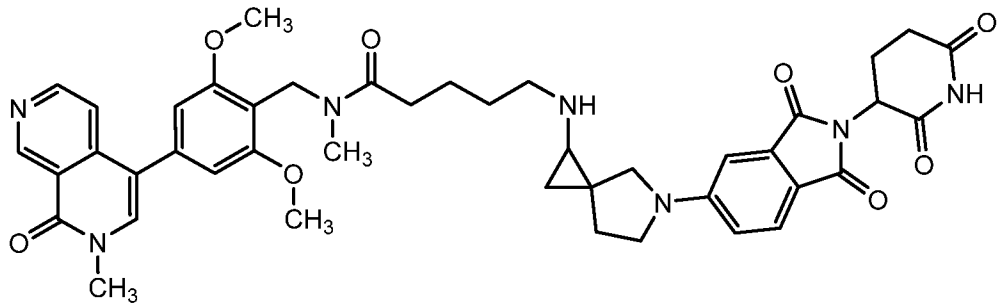
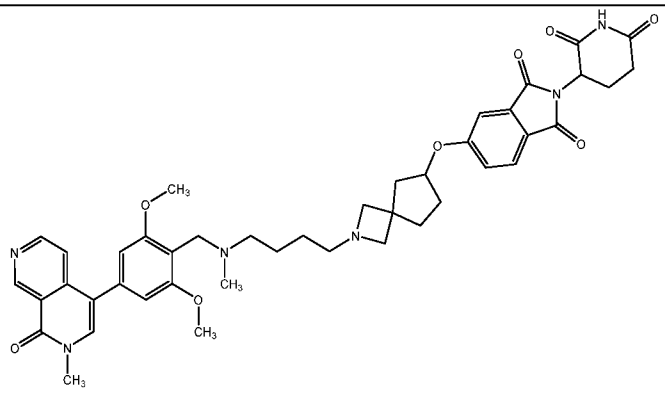
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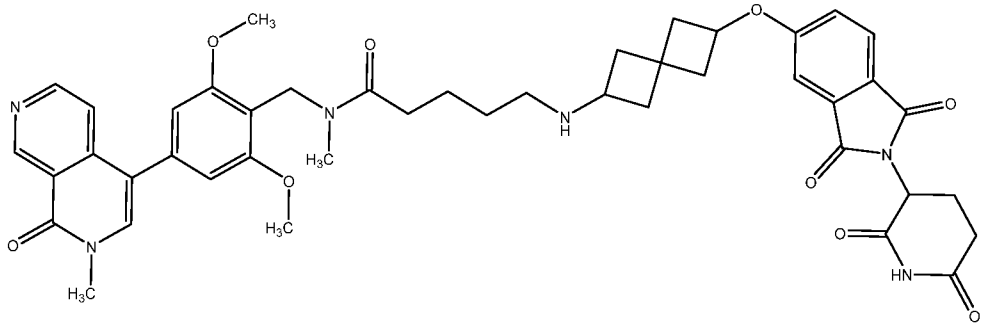
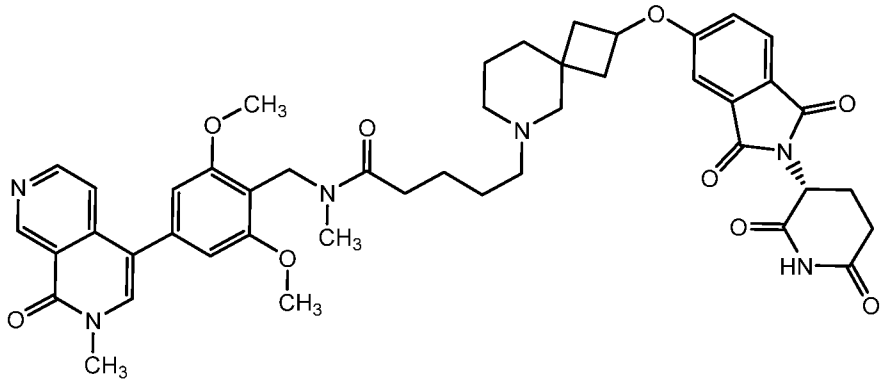
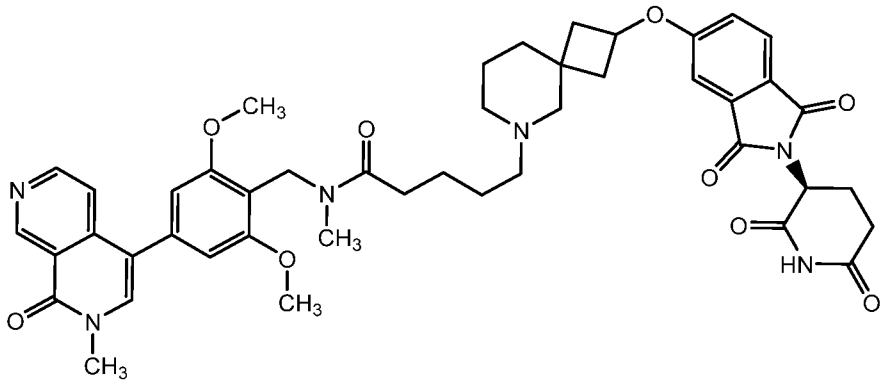
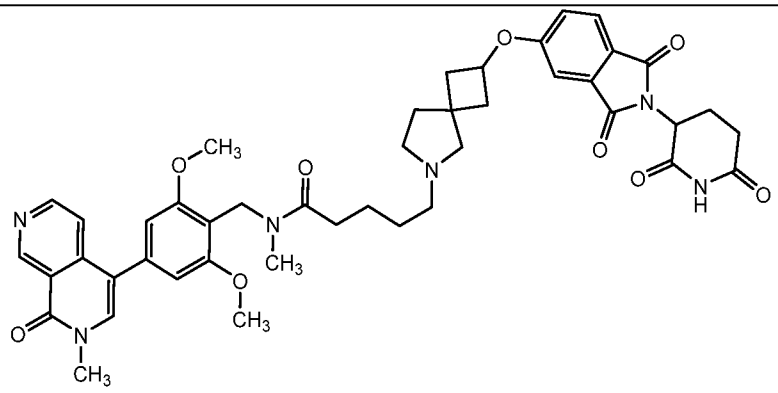
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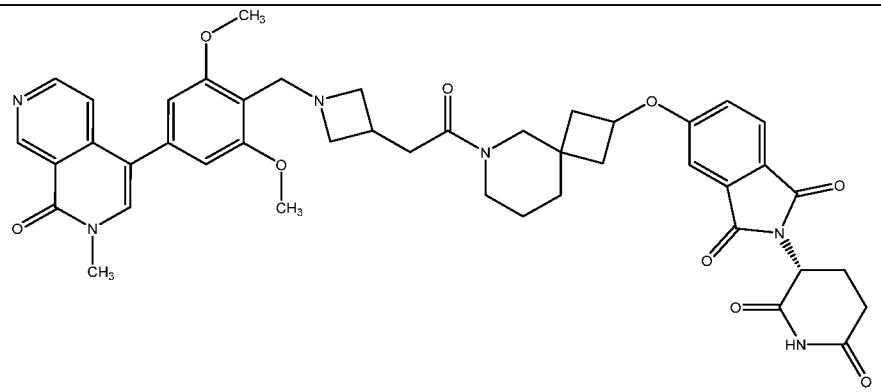
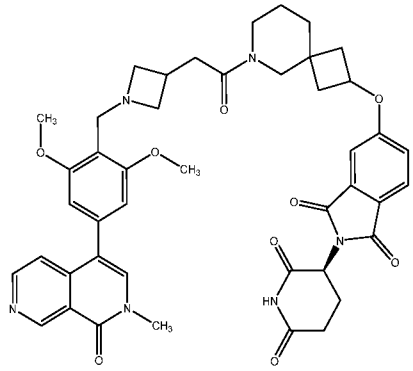
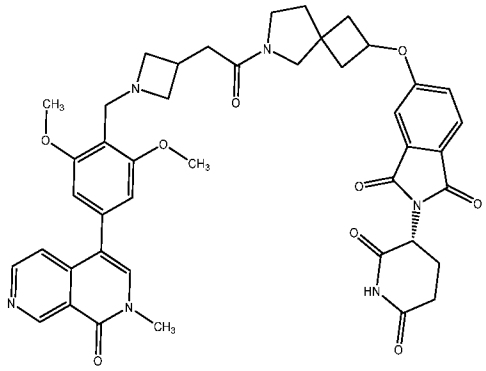
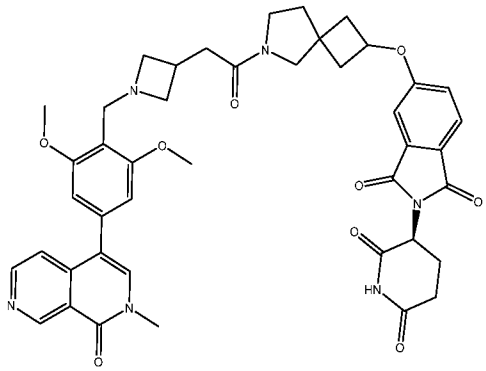
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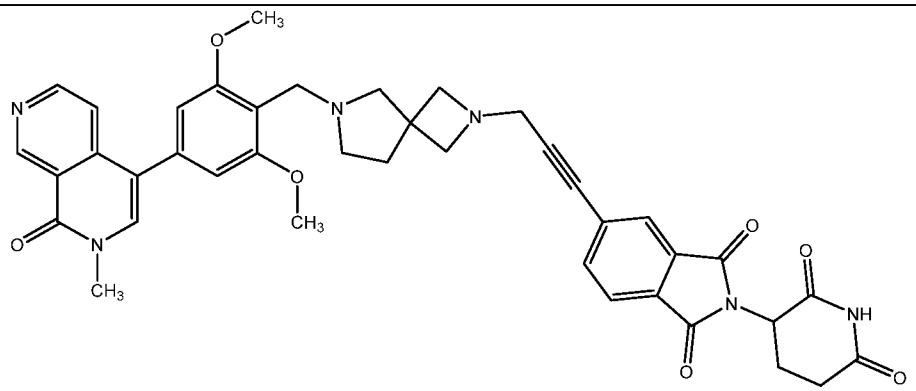
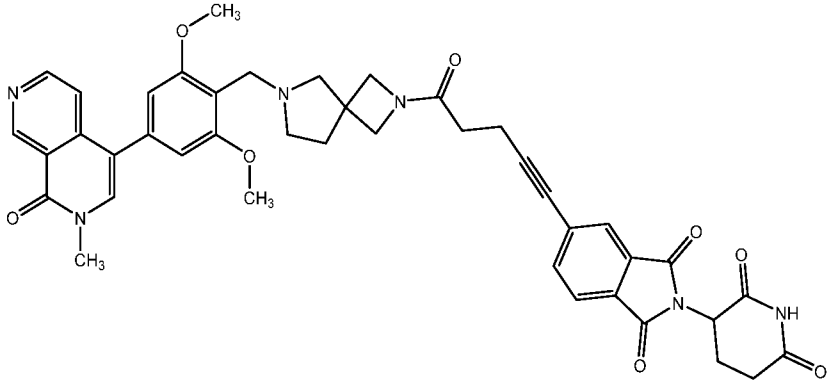
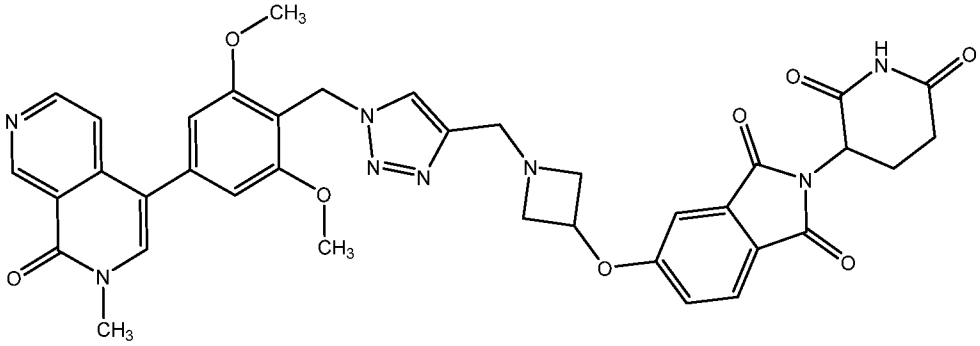
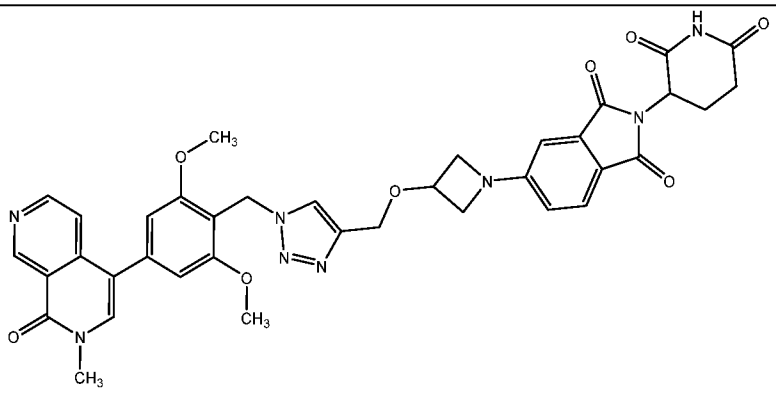
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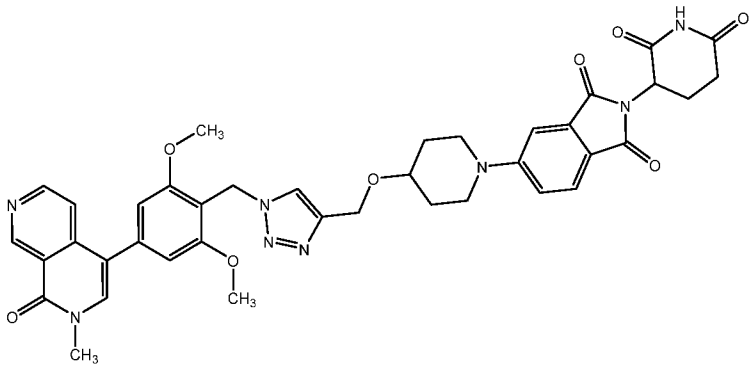
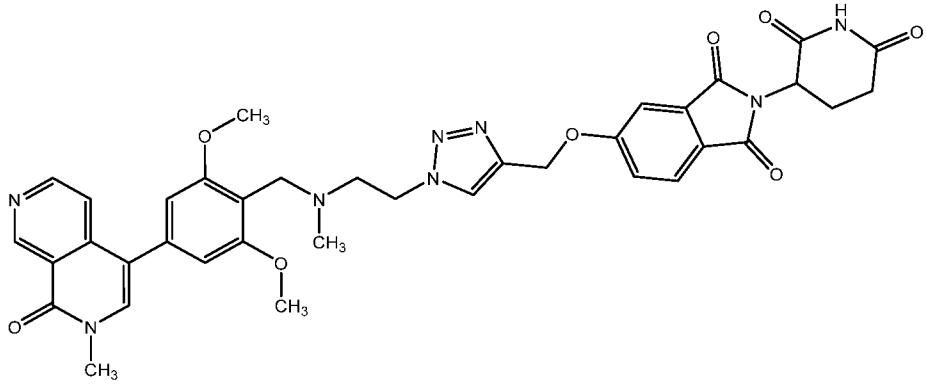
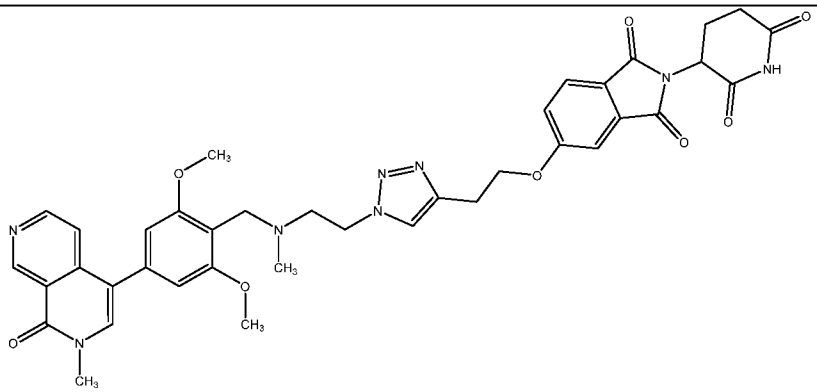
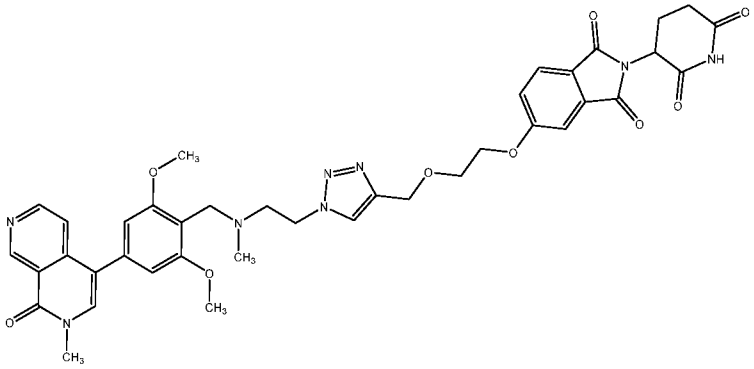
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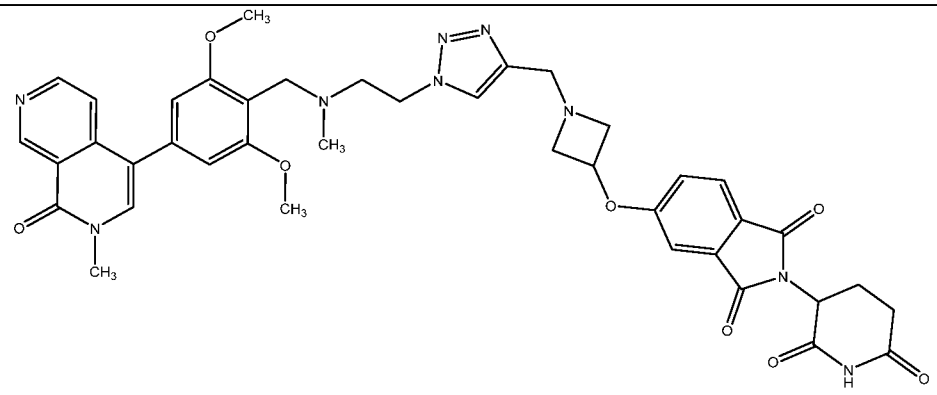
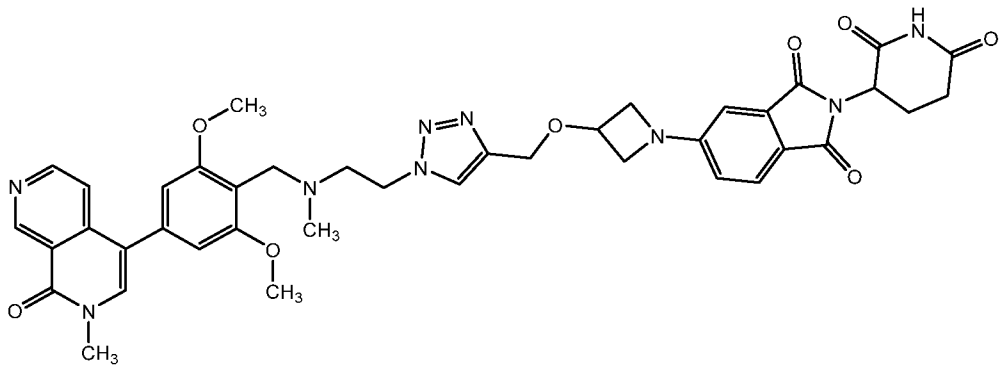
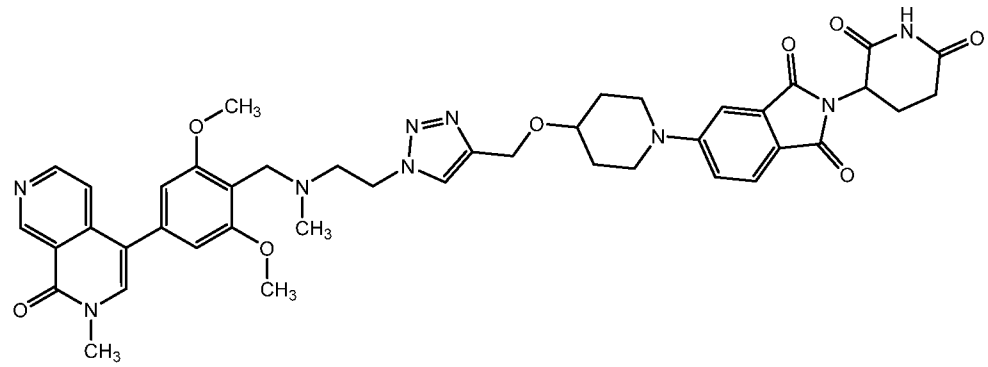
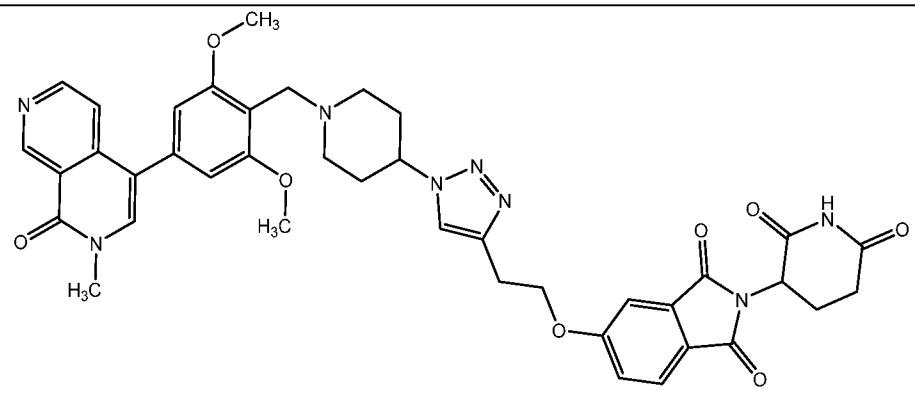
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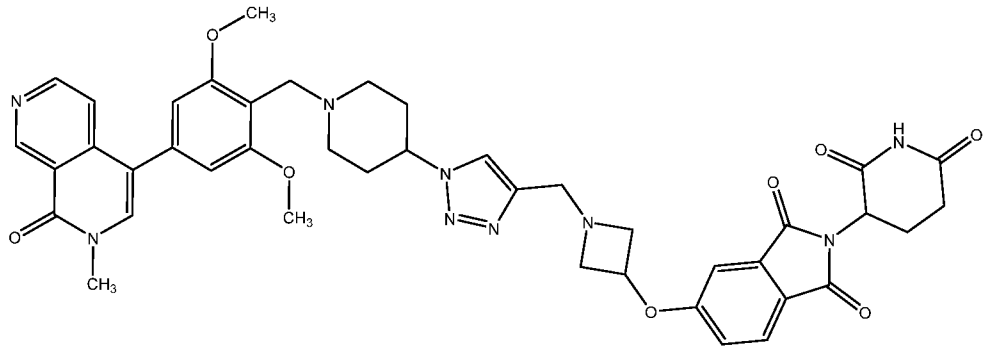
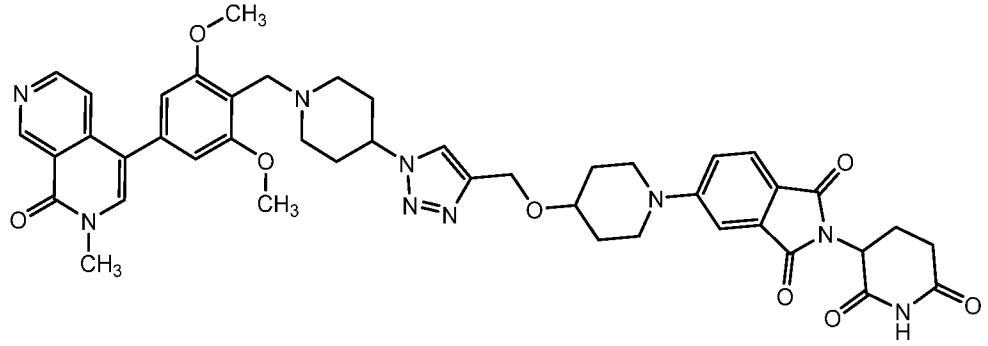
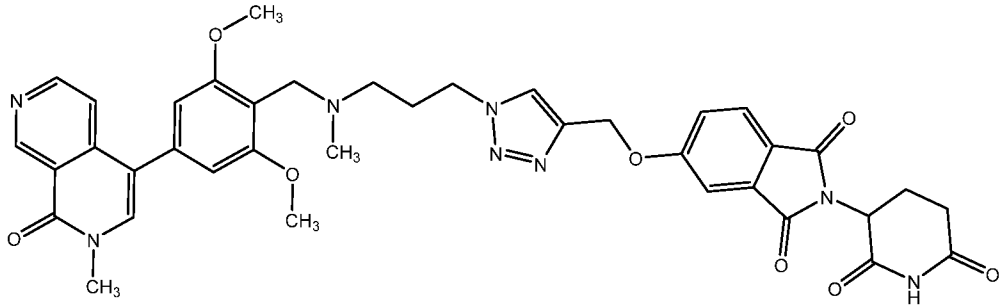
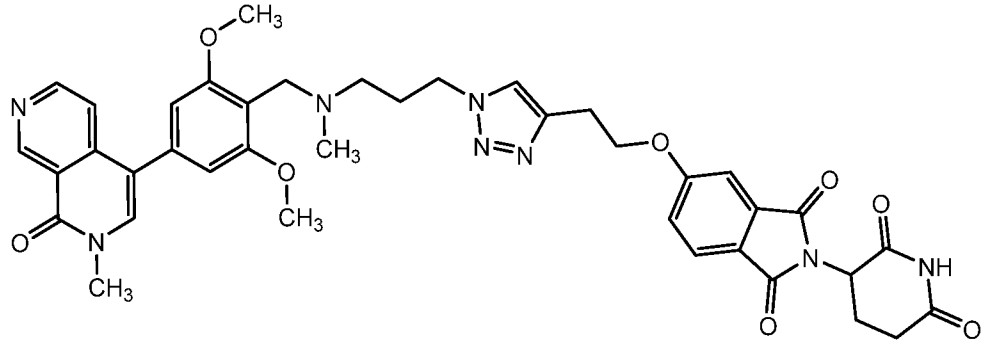
Compound No.	Structure
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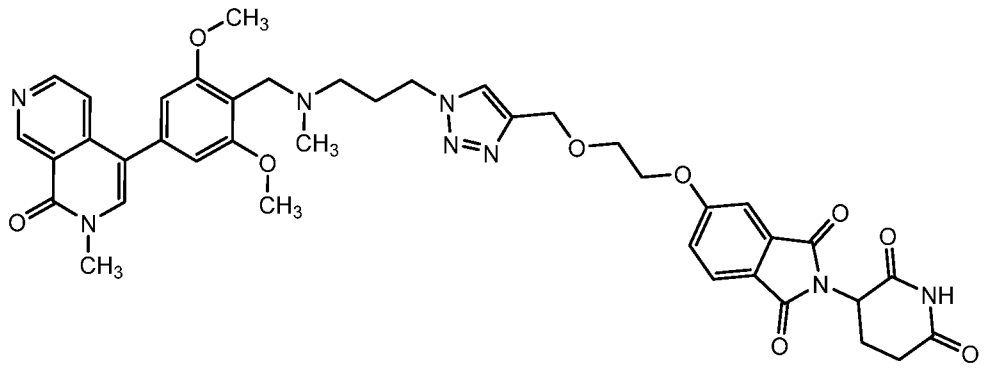
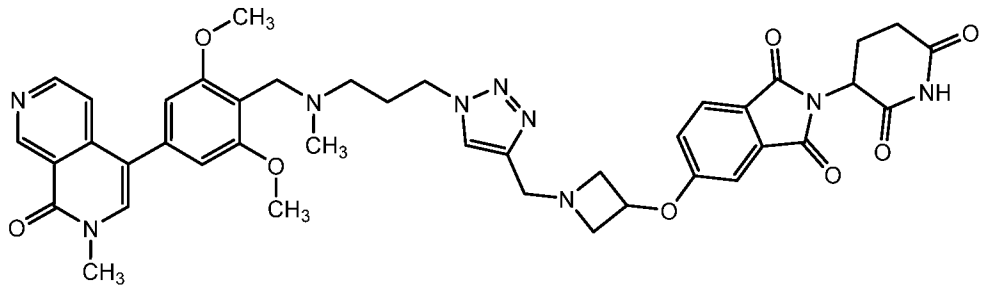
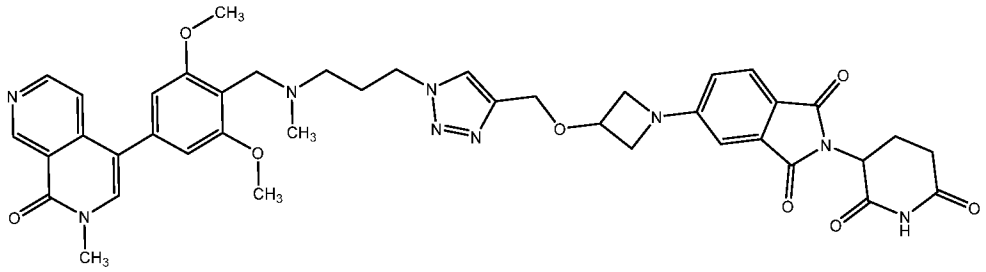
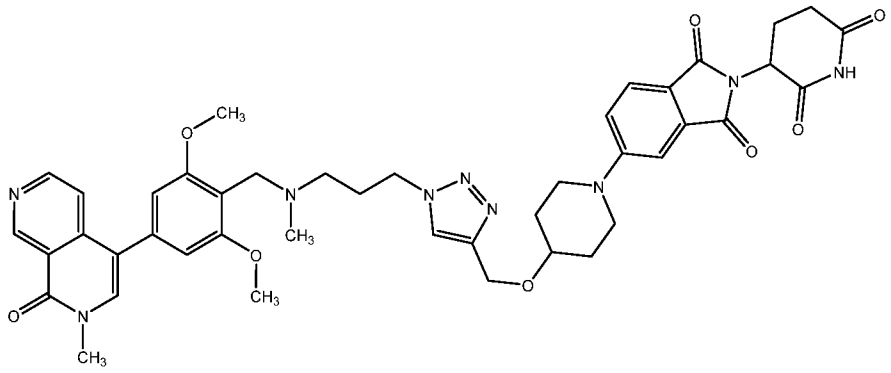
Compound No.	Structure
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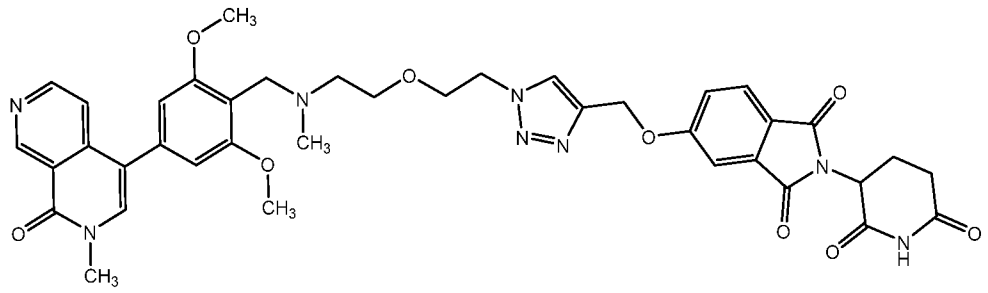
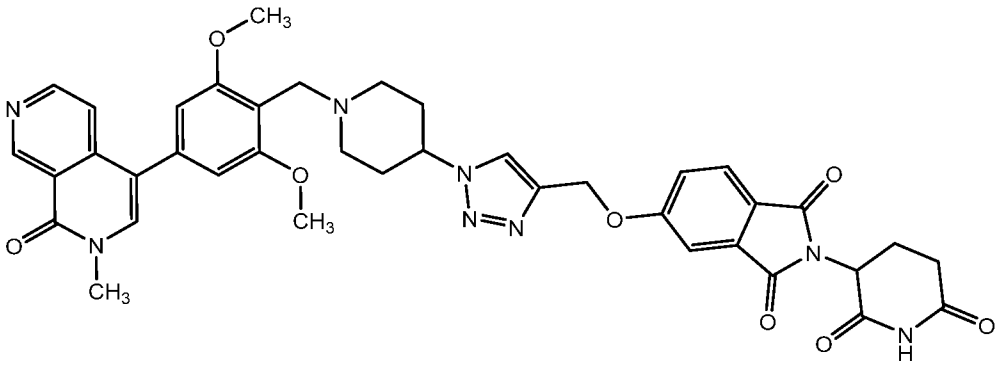
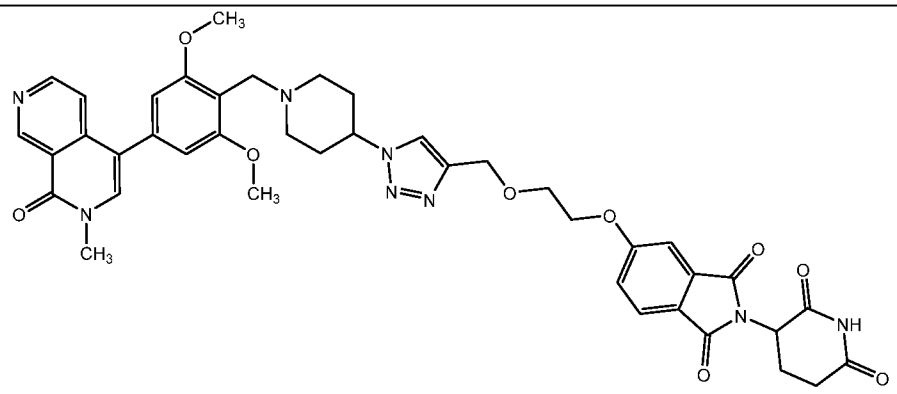
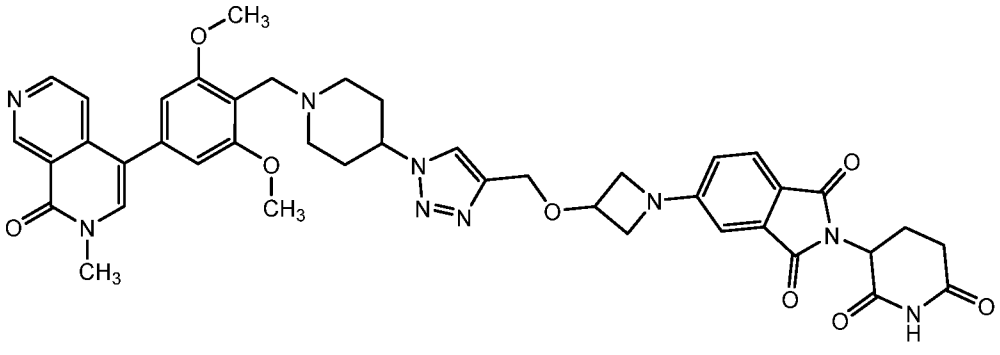
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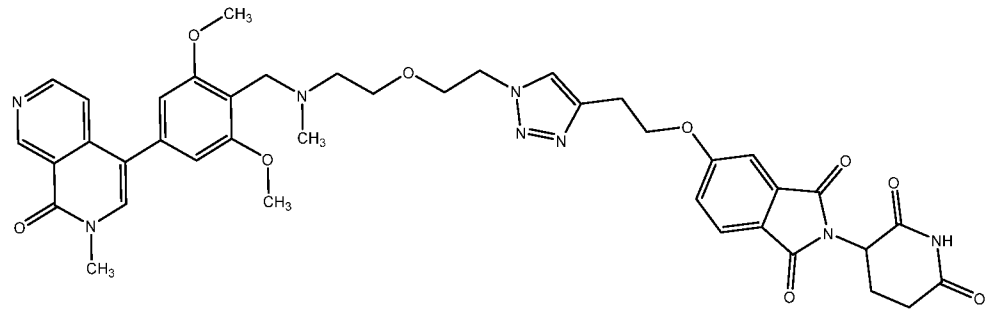
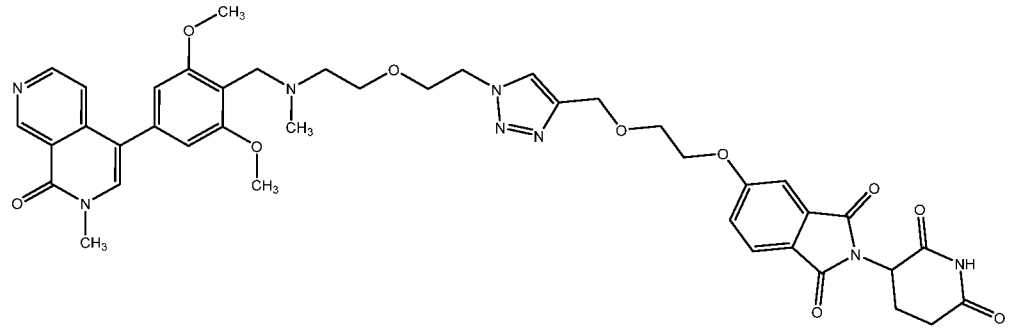
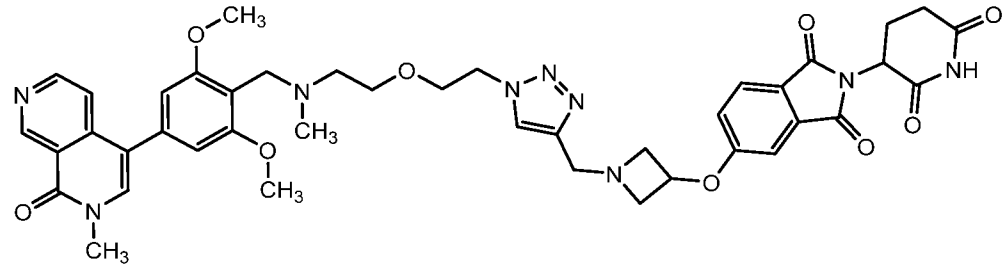
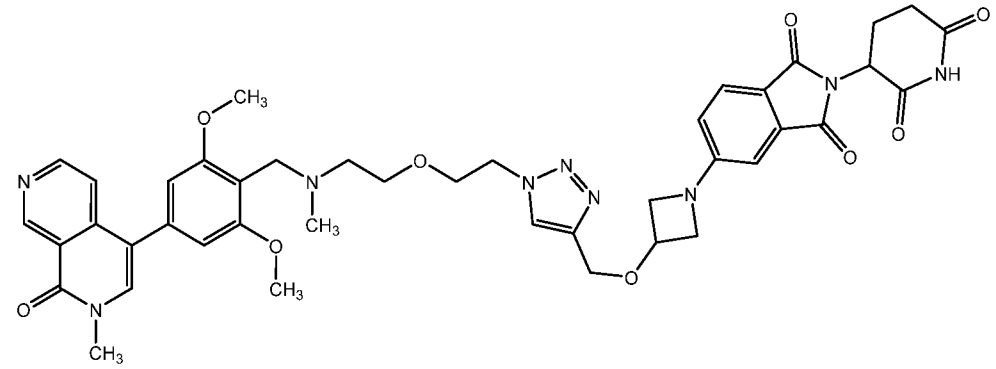
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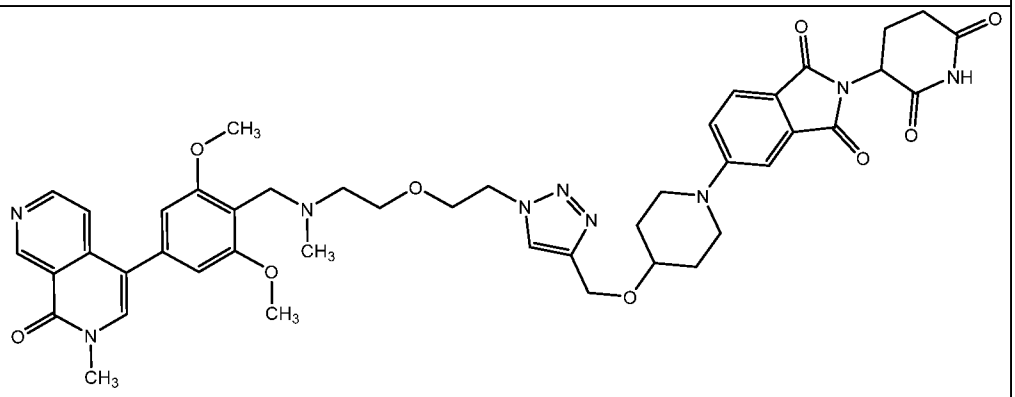
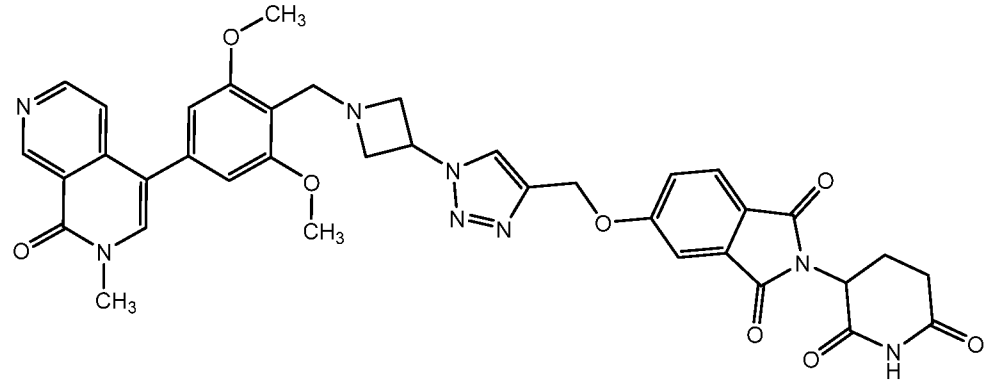
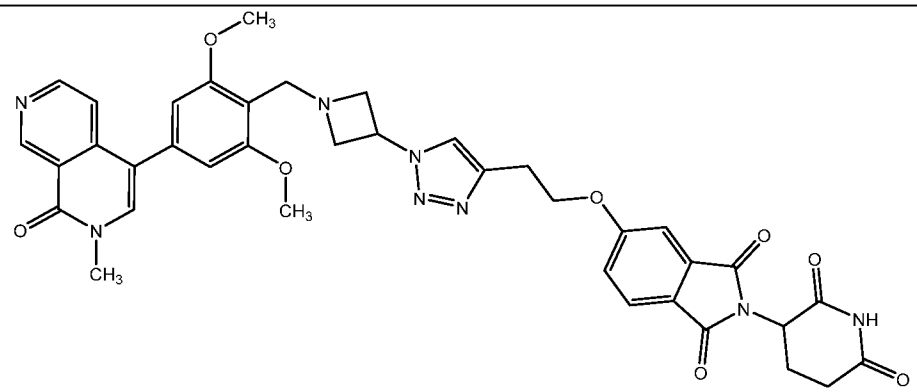
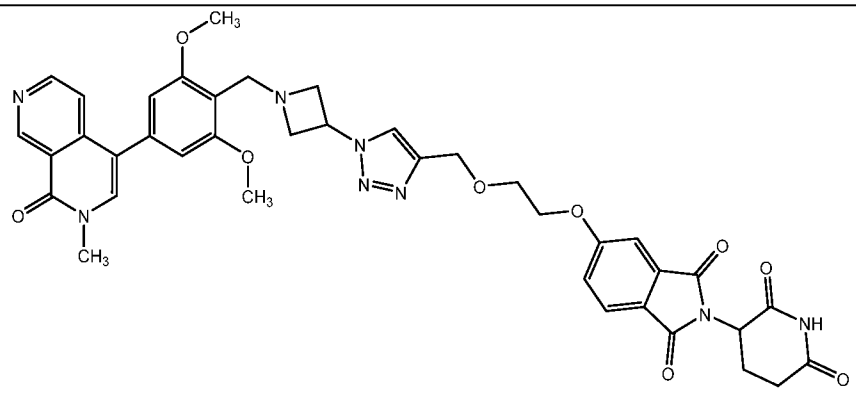
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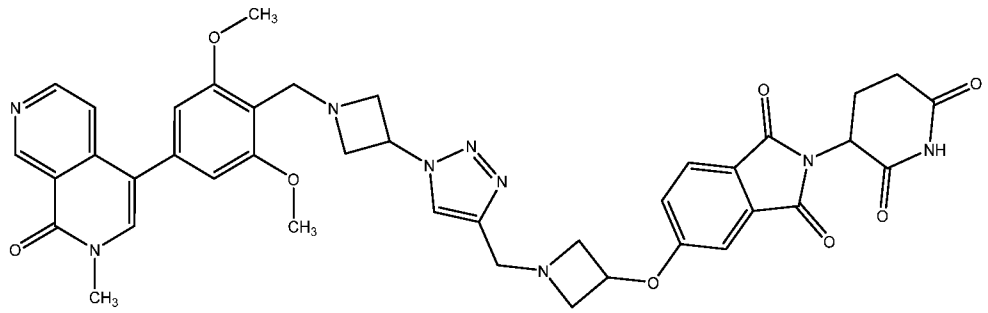
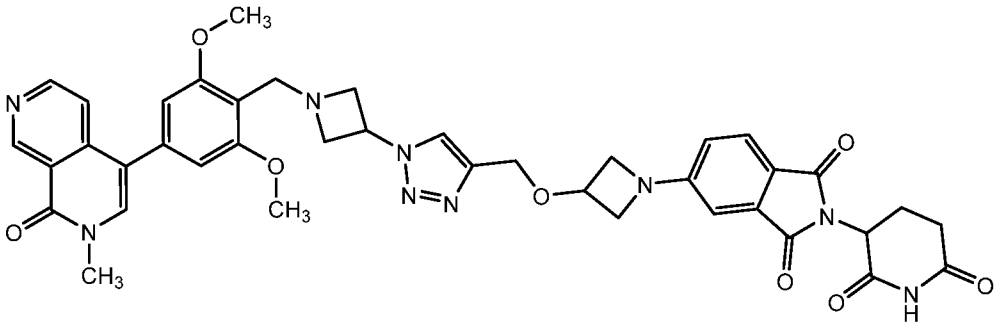
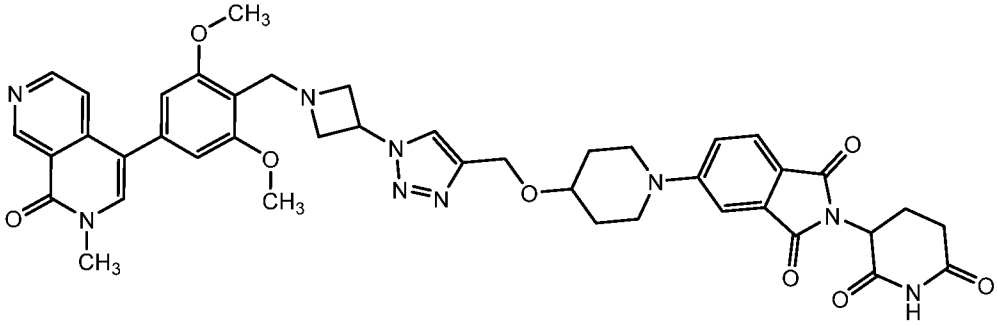
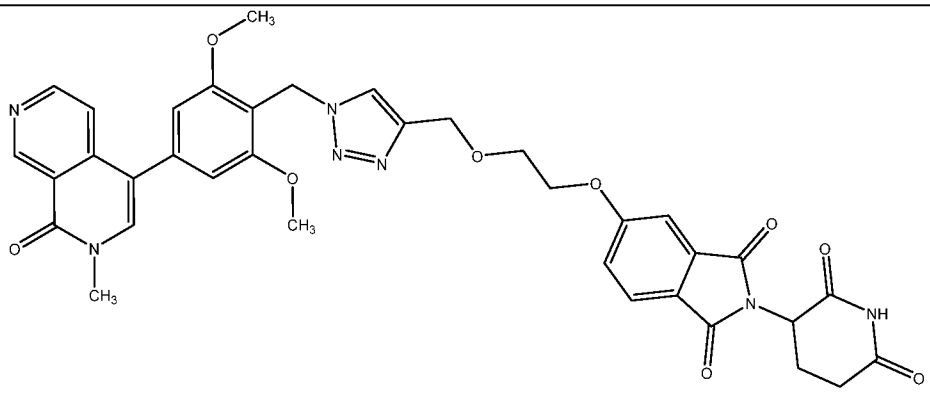
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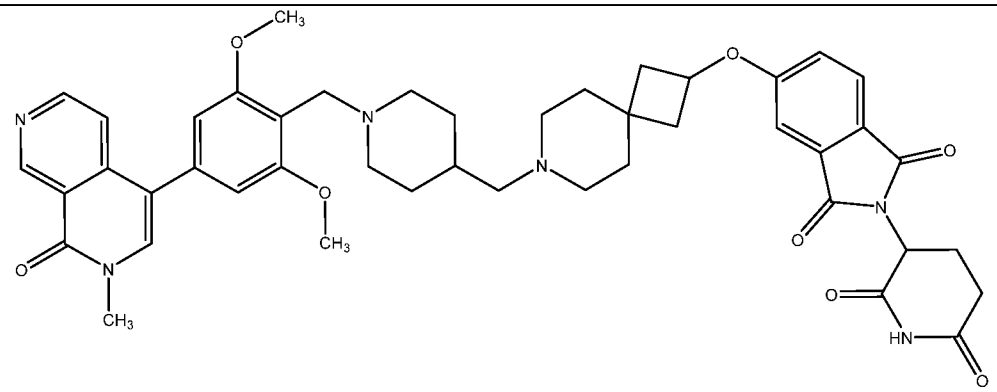
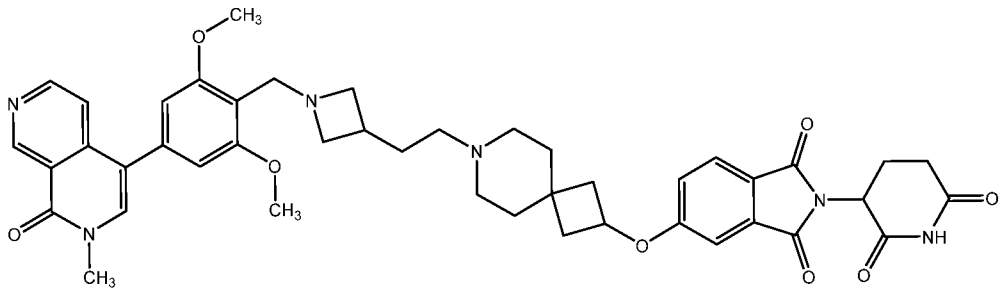
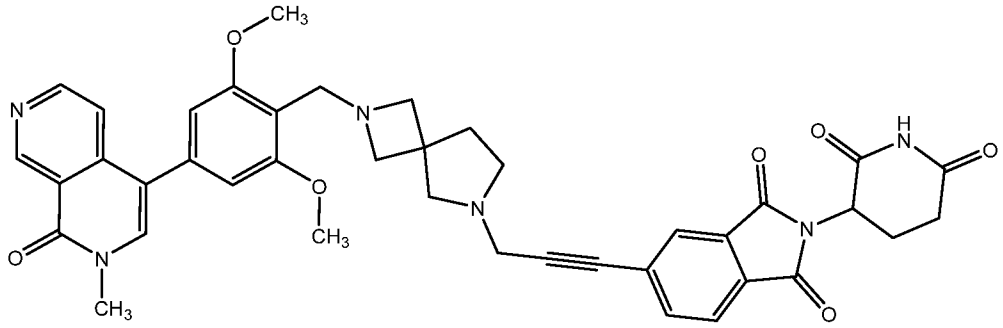
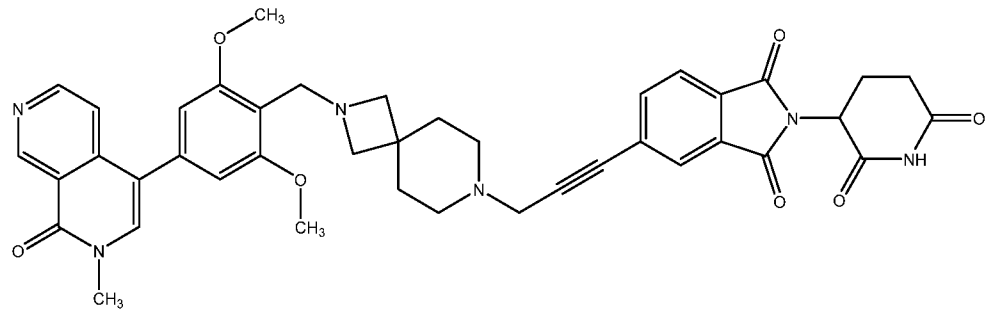
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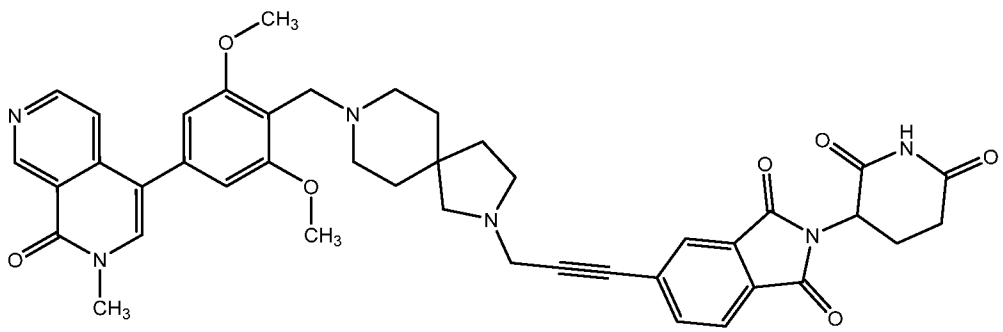
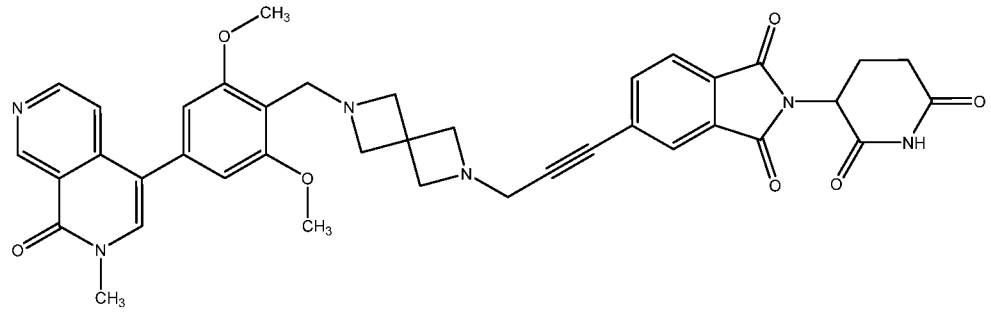
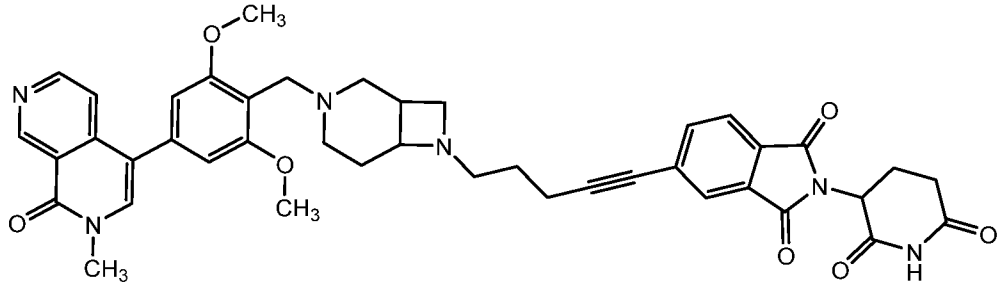
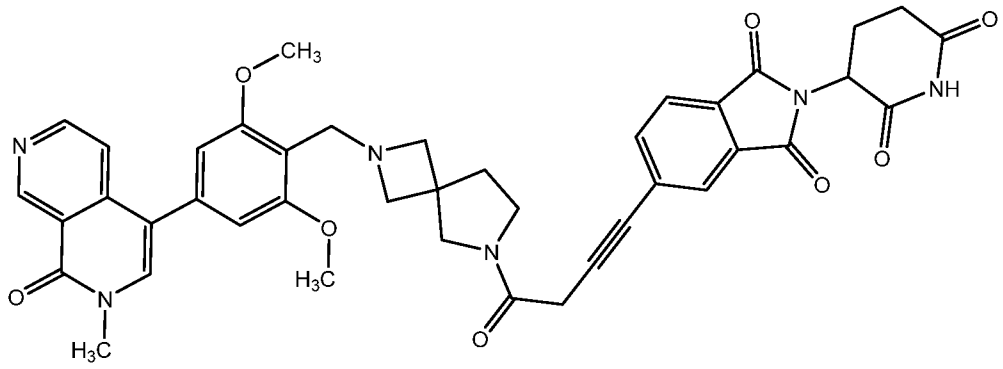
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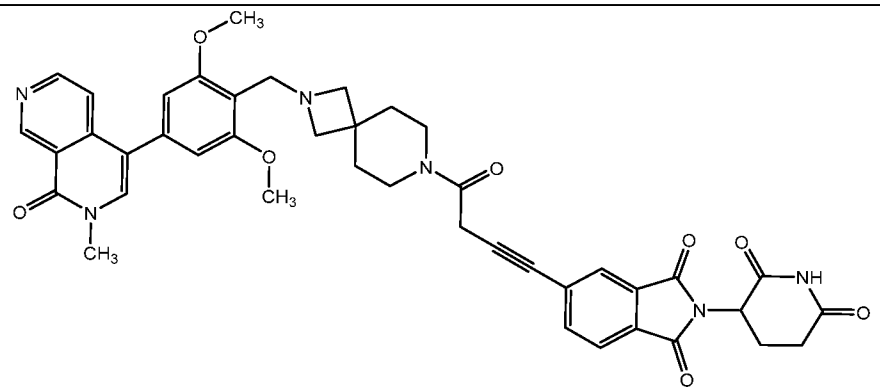
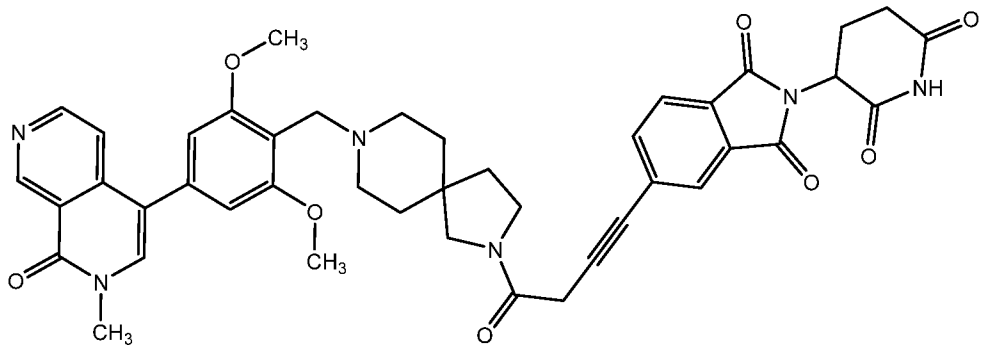
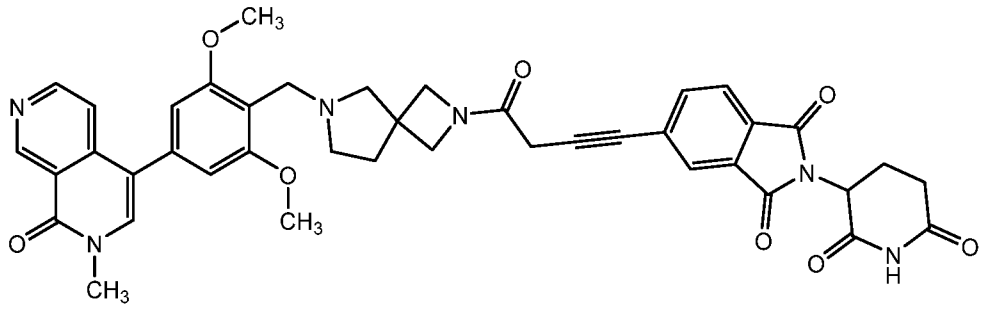
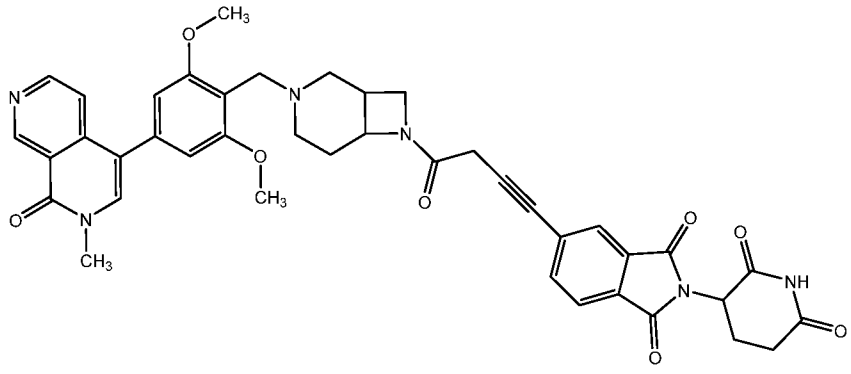
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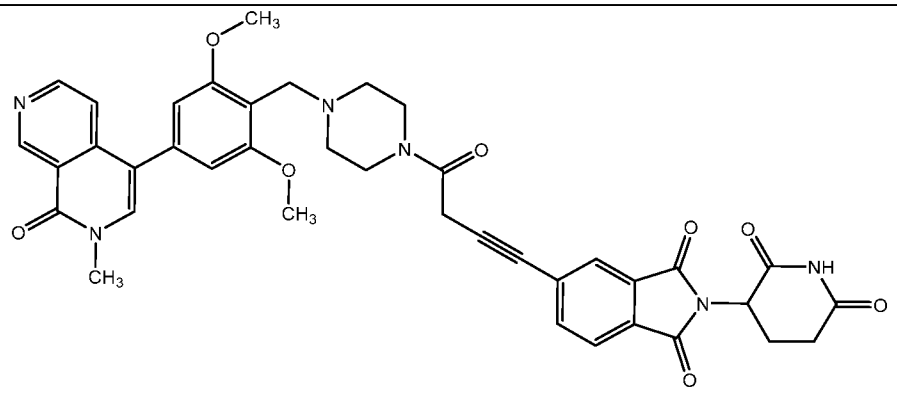
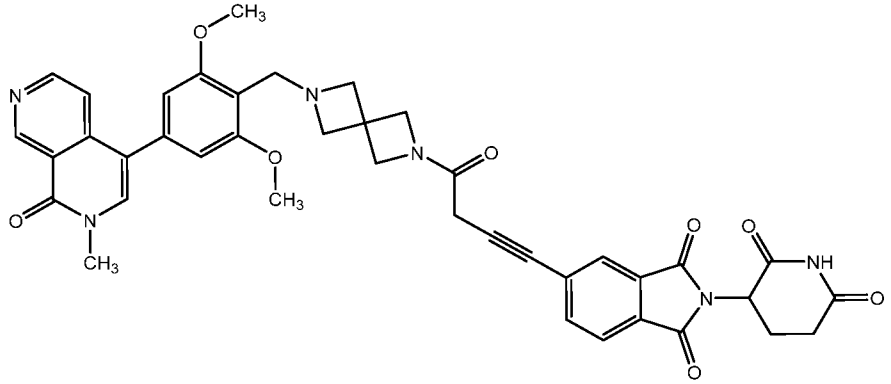
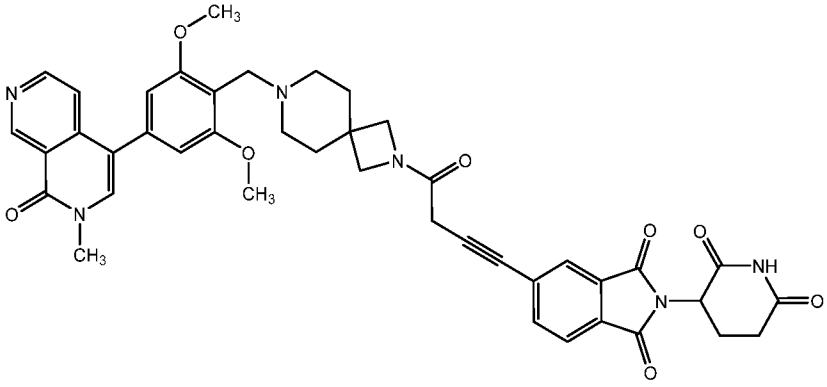
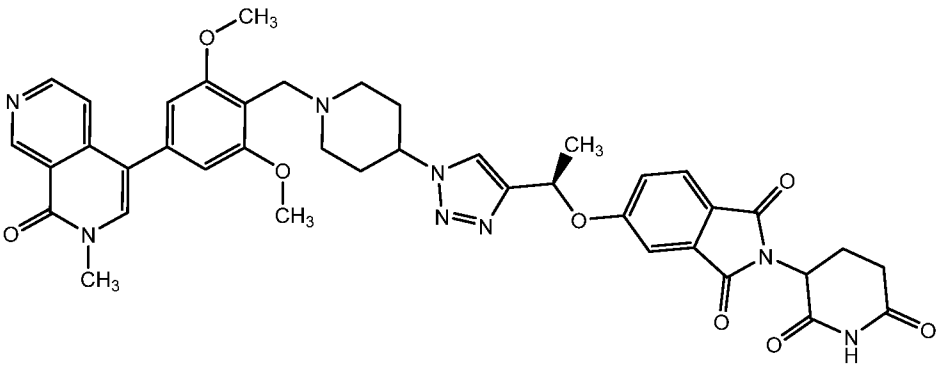
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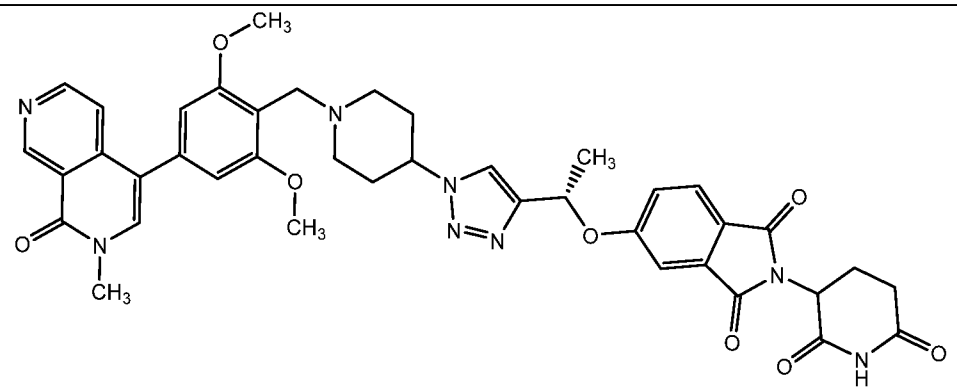
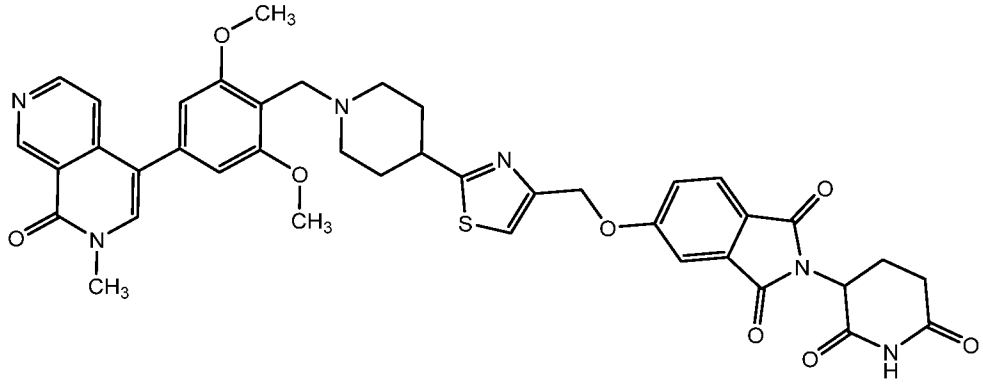
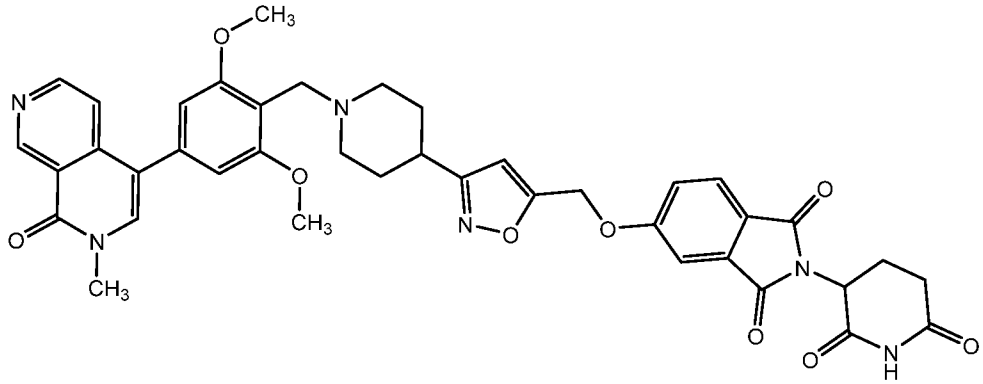
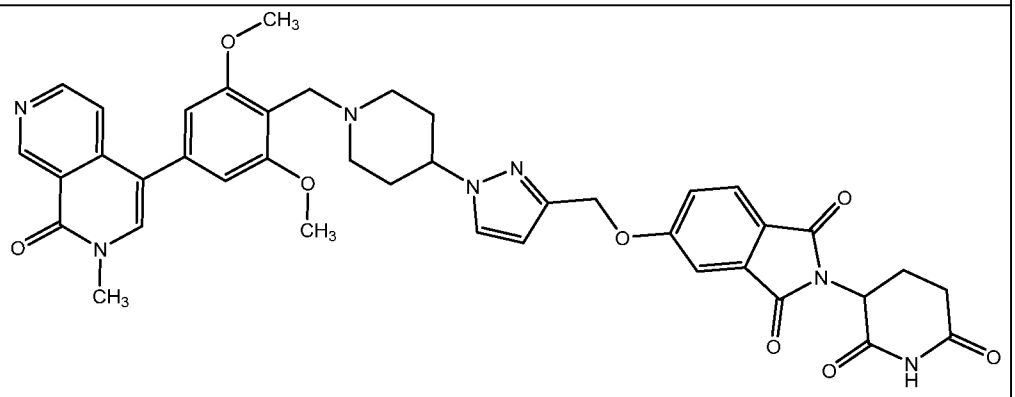
Compound No.	Structure
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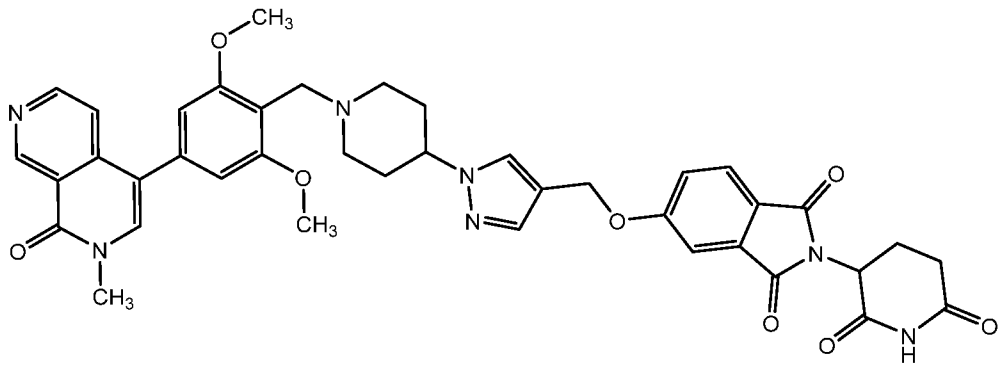
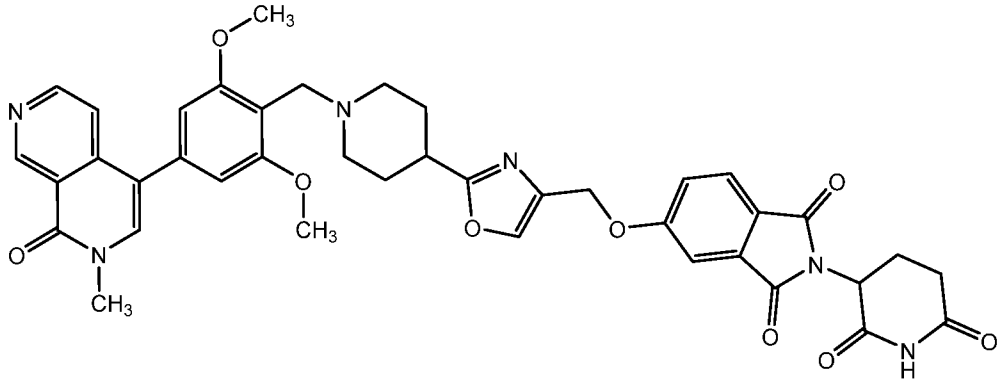
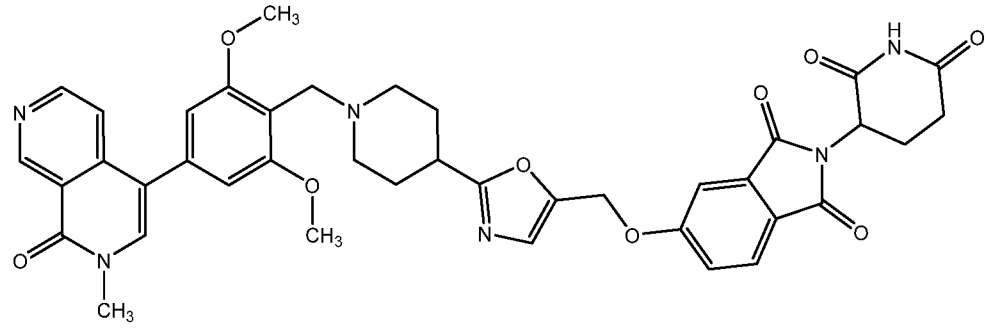
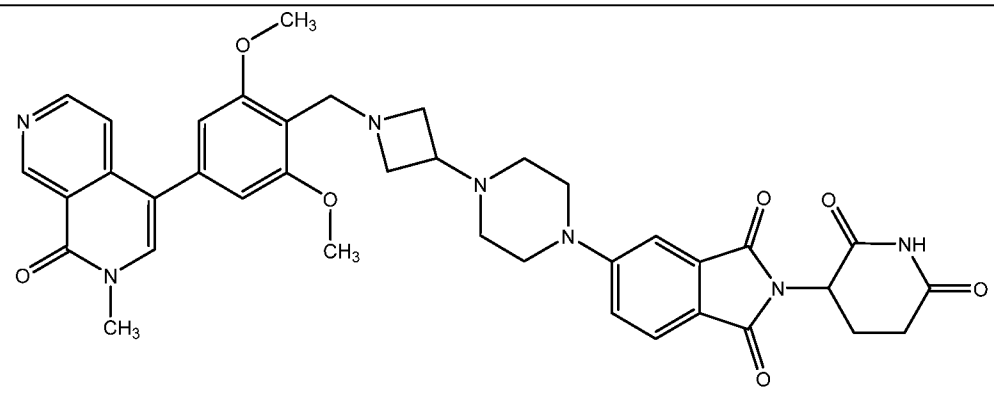
Compound No.	Structure
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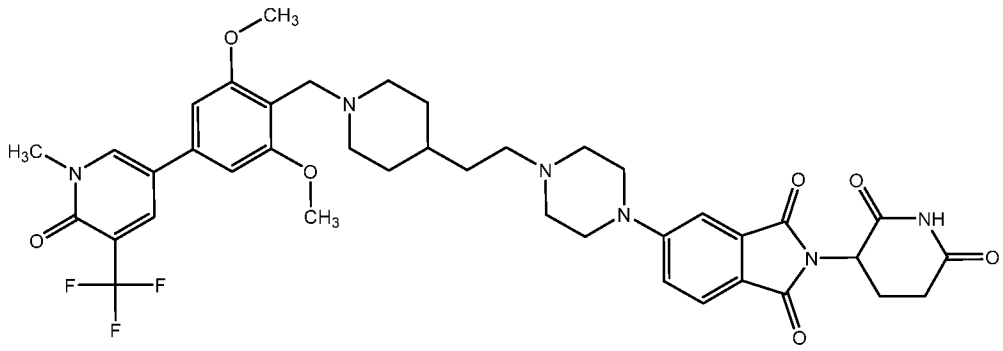
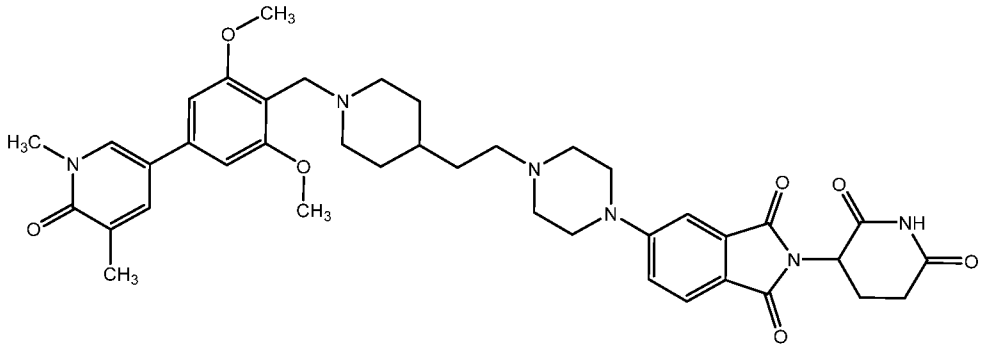
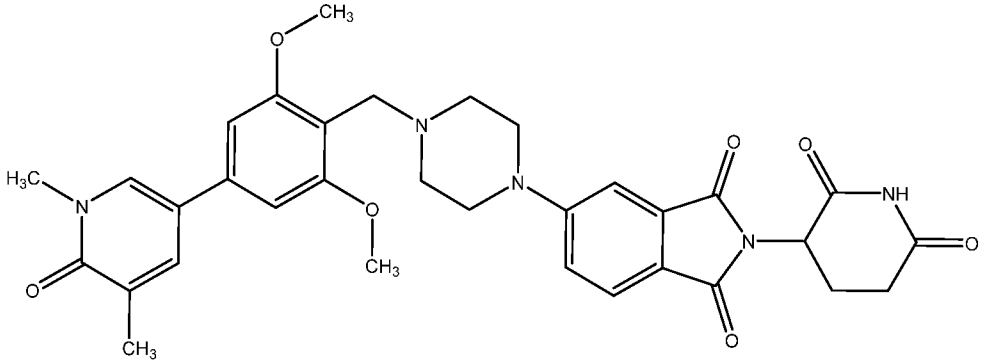
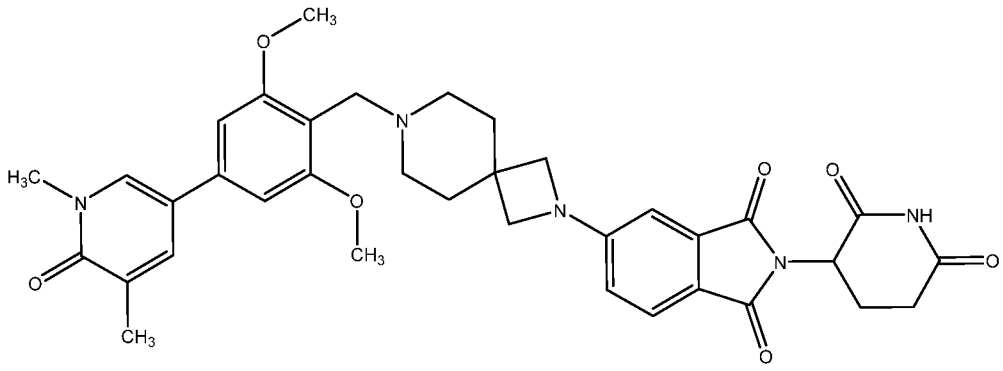
Compound No.	Structure
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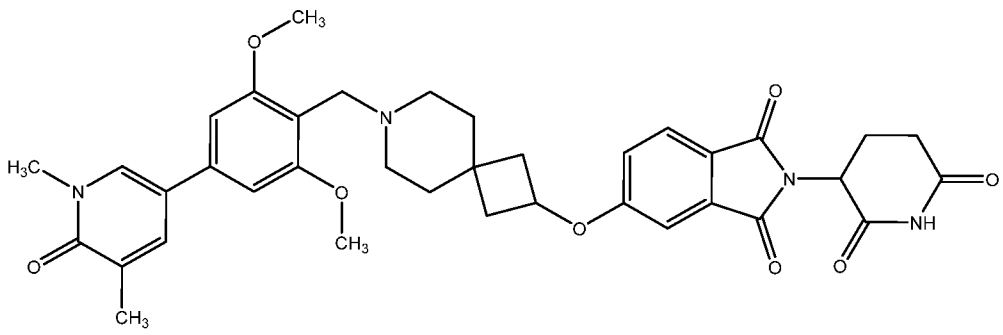
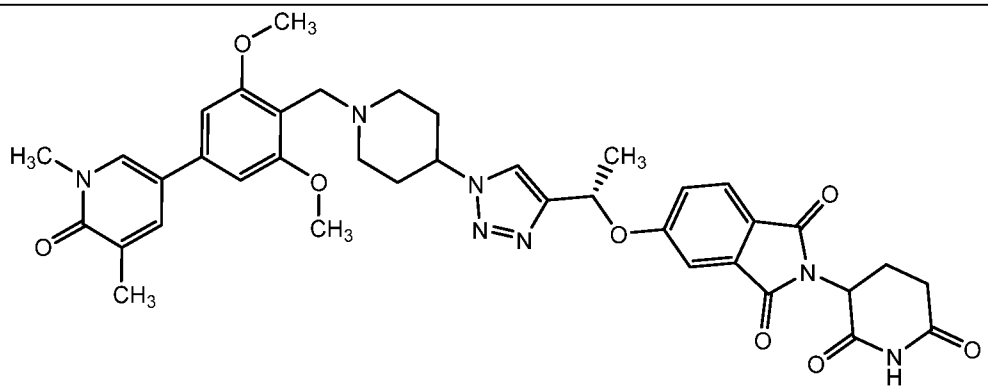
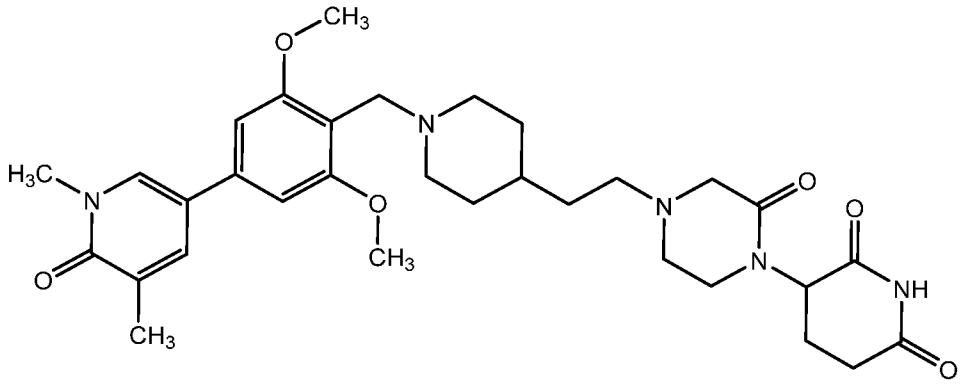
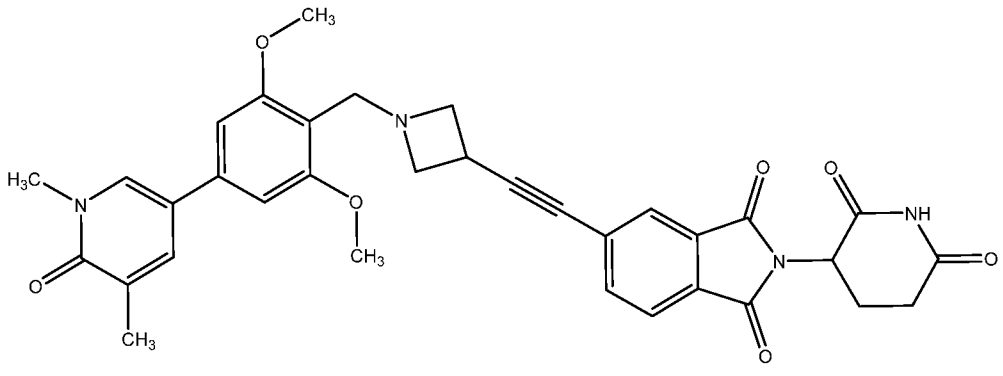
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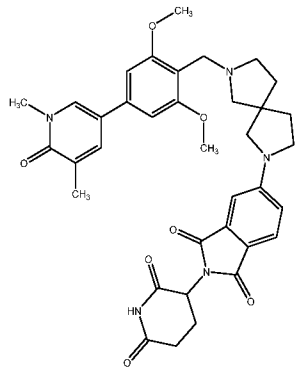
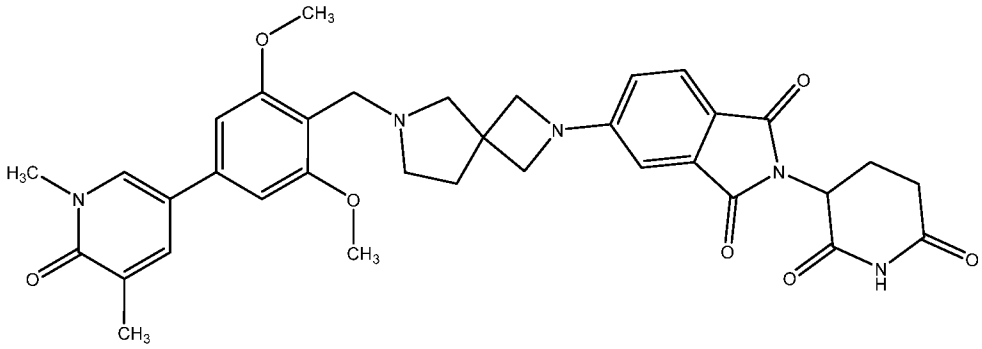
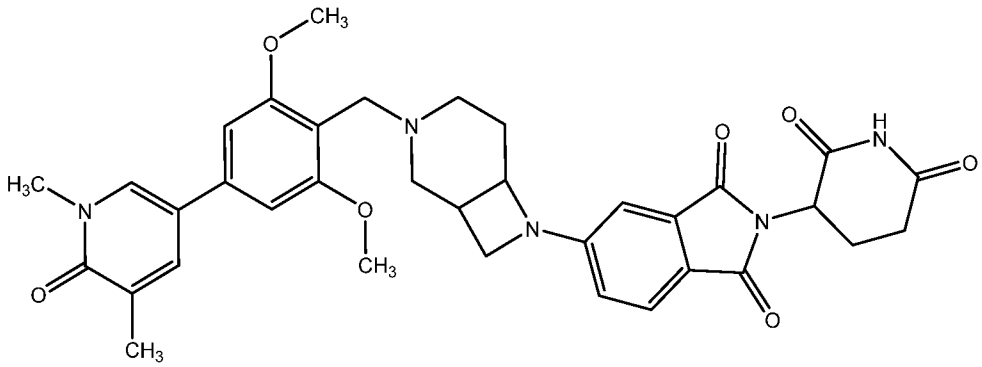
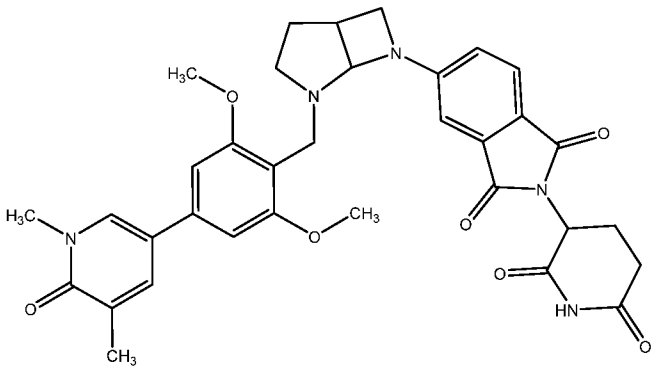
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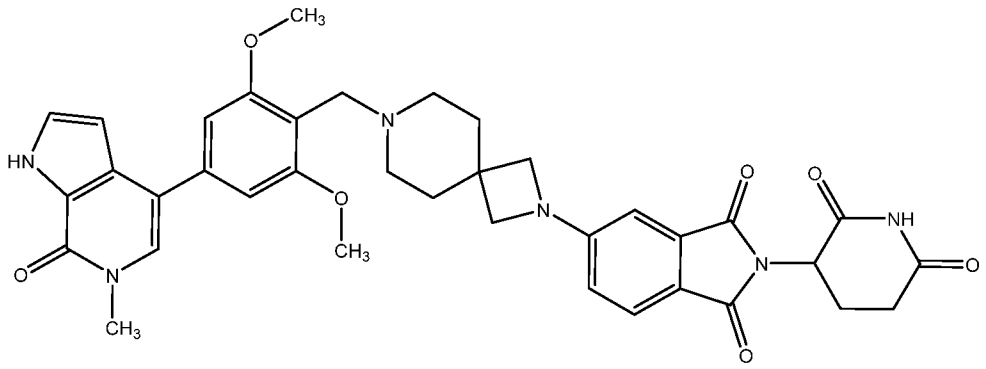
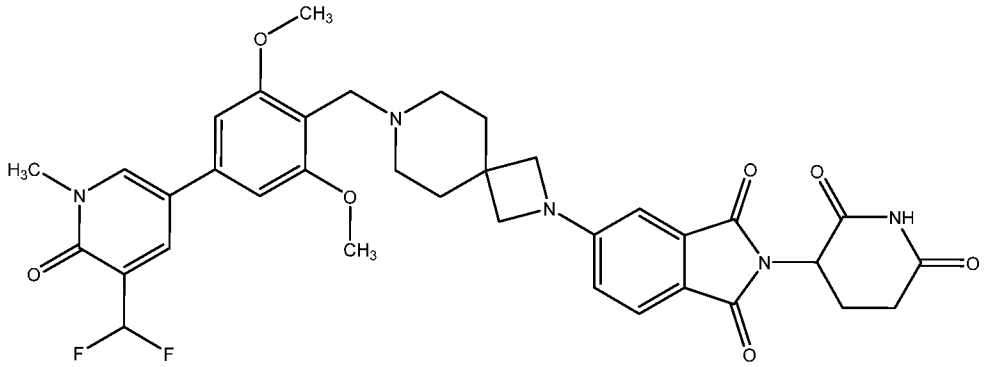
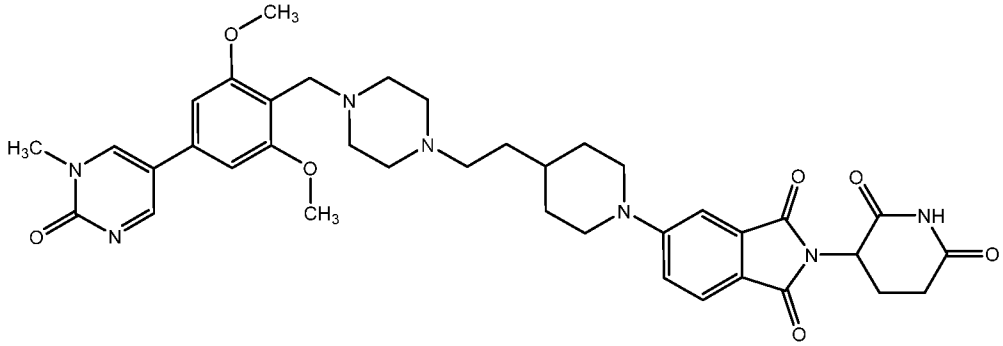
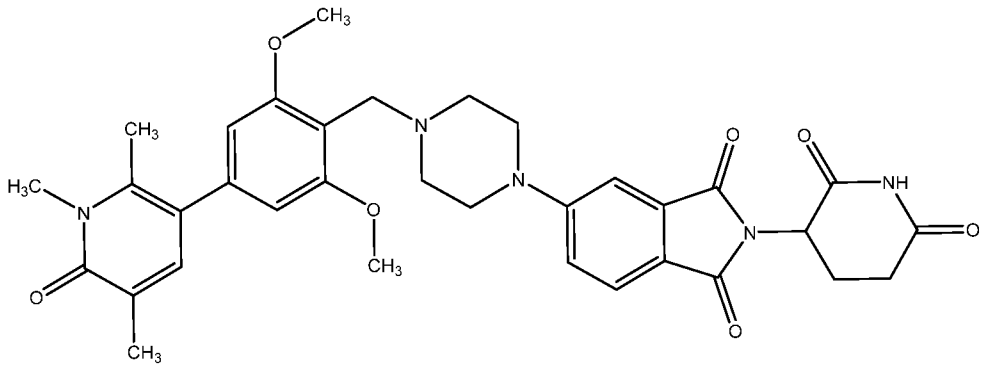
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D323	

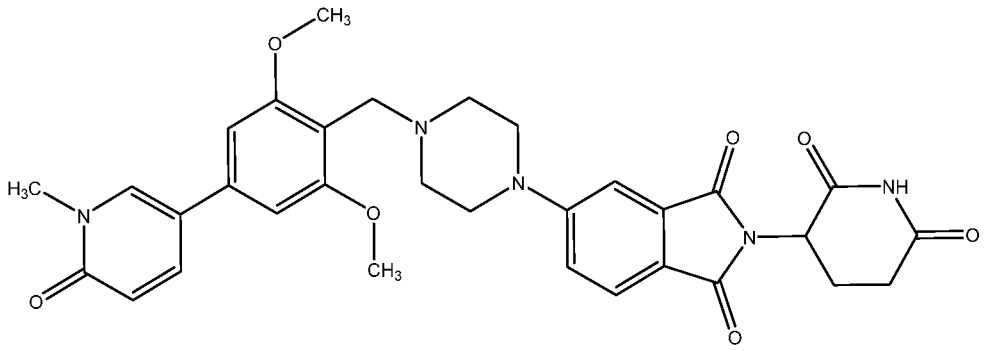
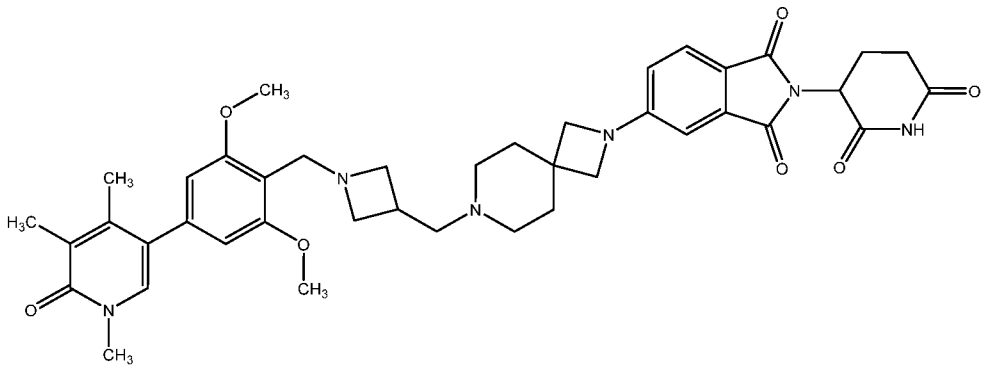
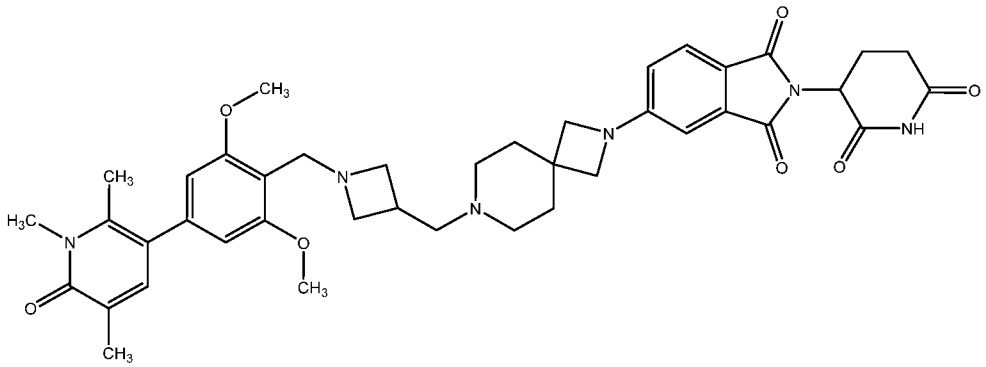
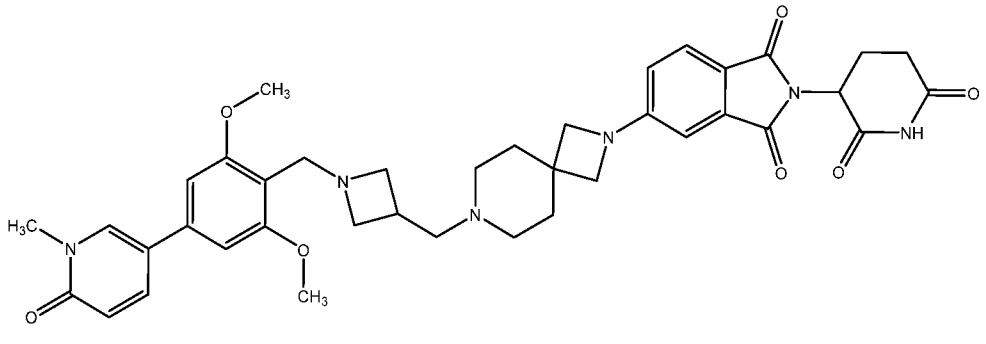
Compound No.	Structure
D324	
D325	
D326	
D327	

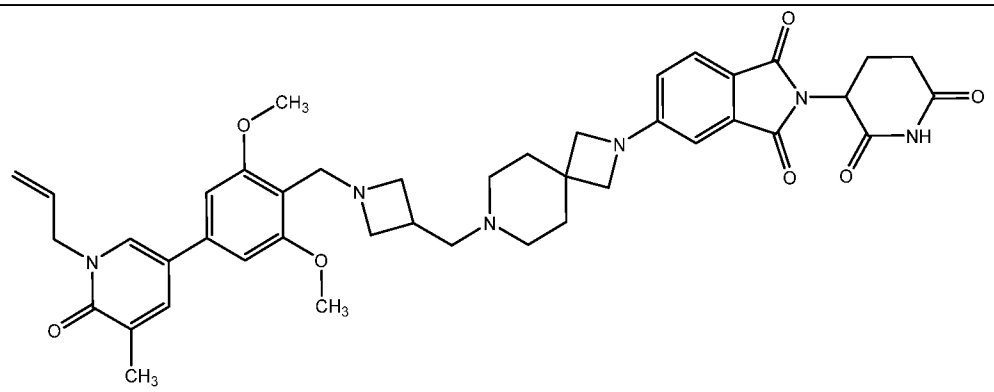
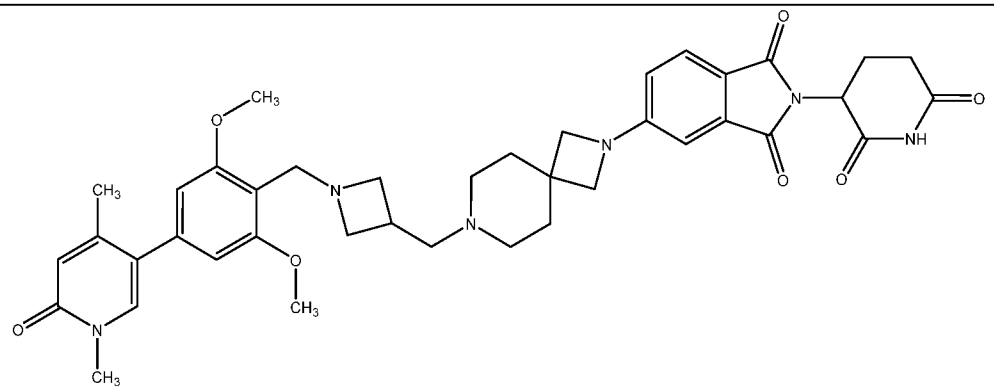
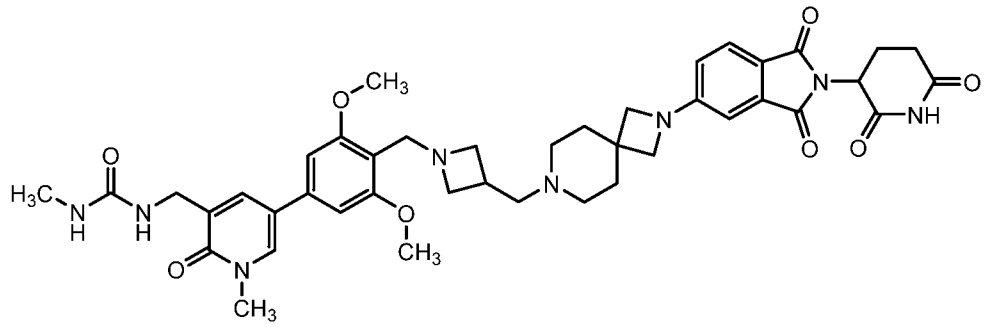
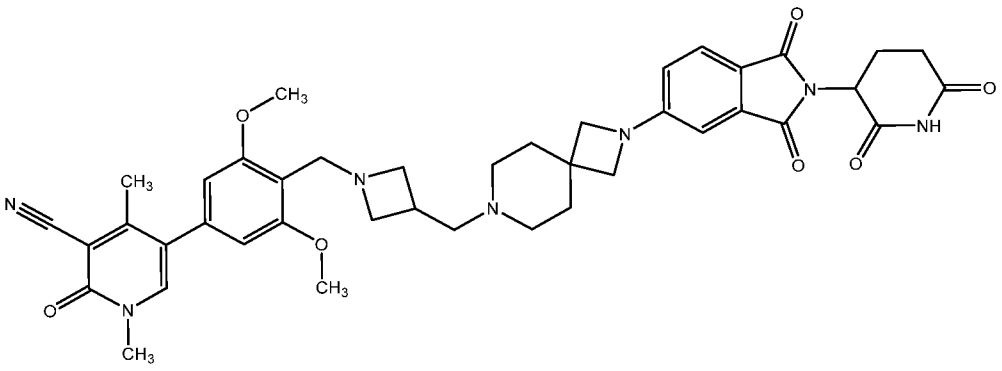
Compound No.	Structure
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D329	
D330	
D331	

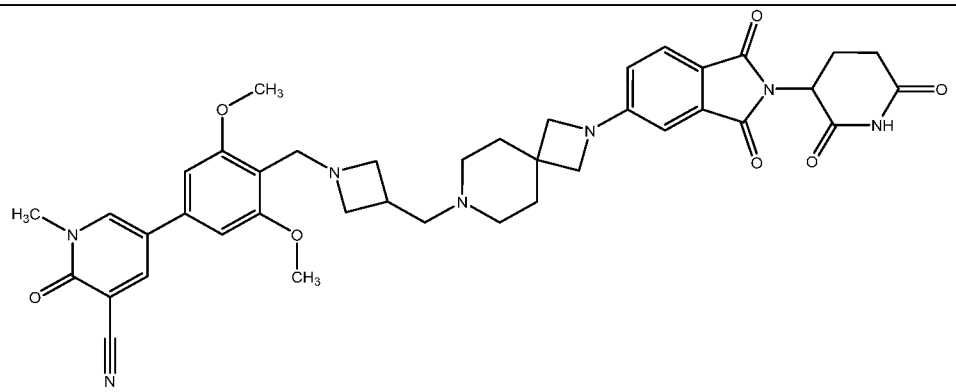
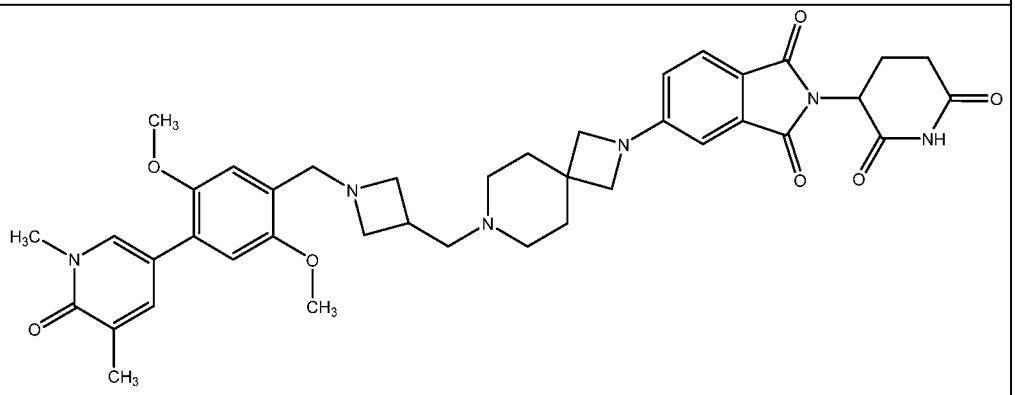
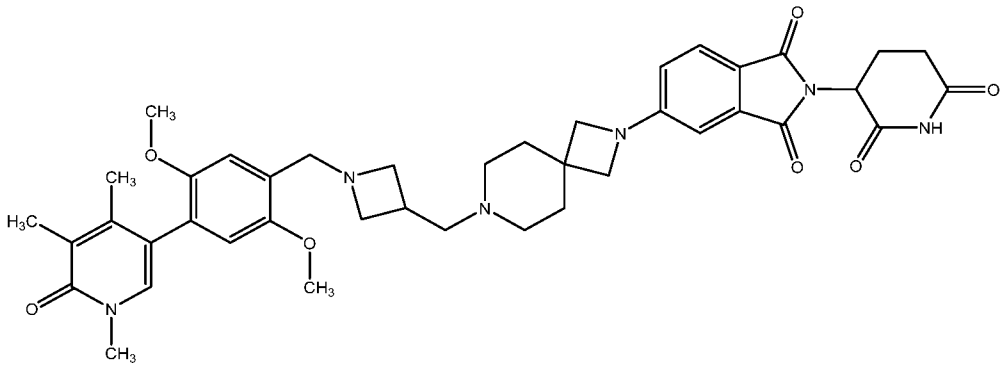
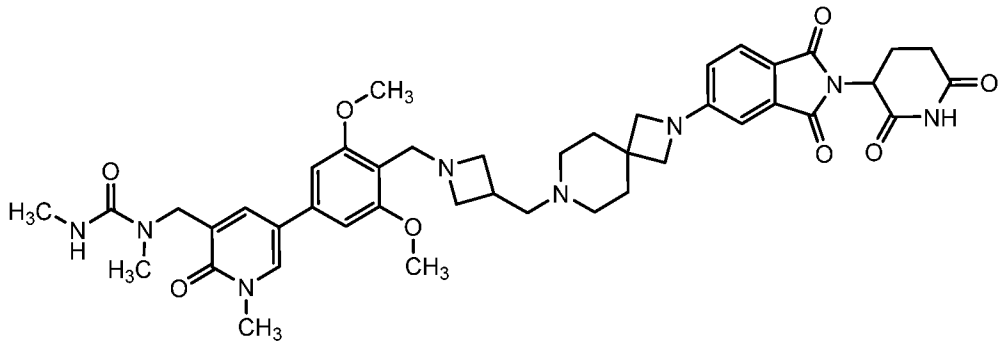
Compound No.	Structure
D332	
D333	
D334	
D335	

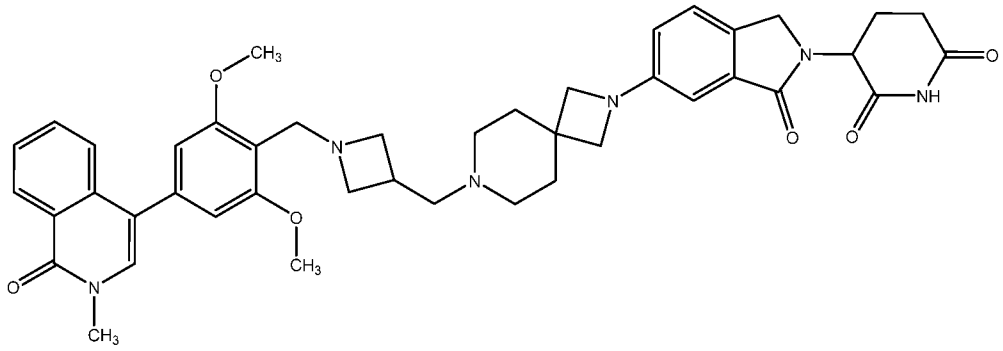
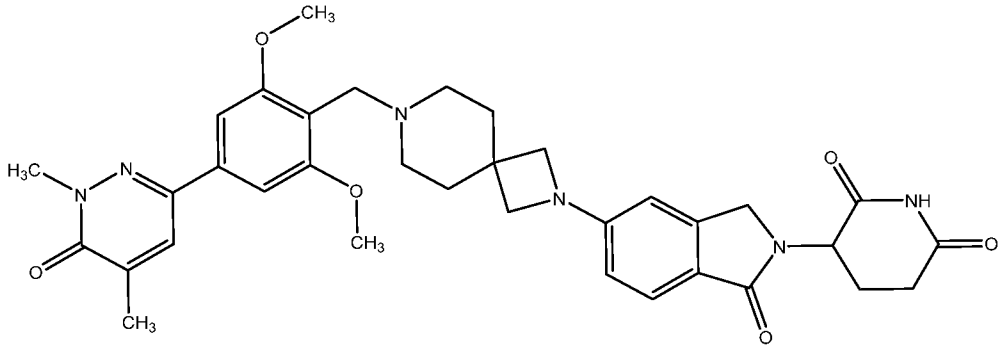
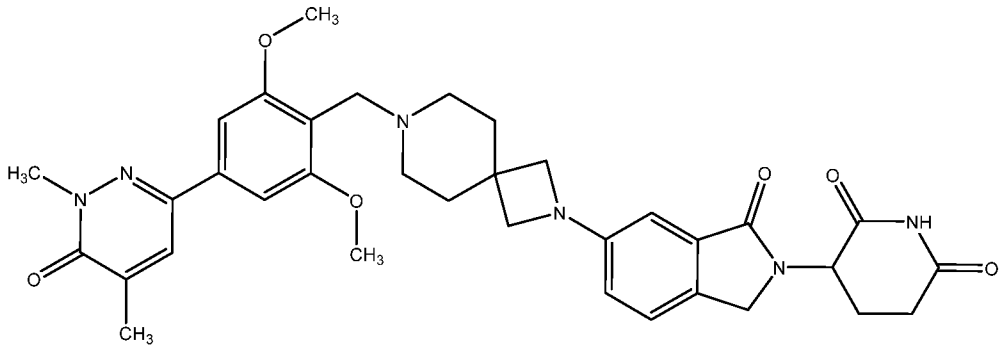
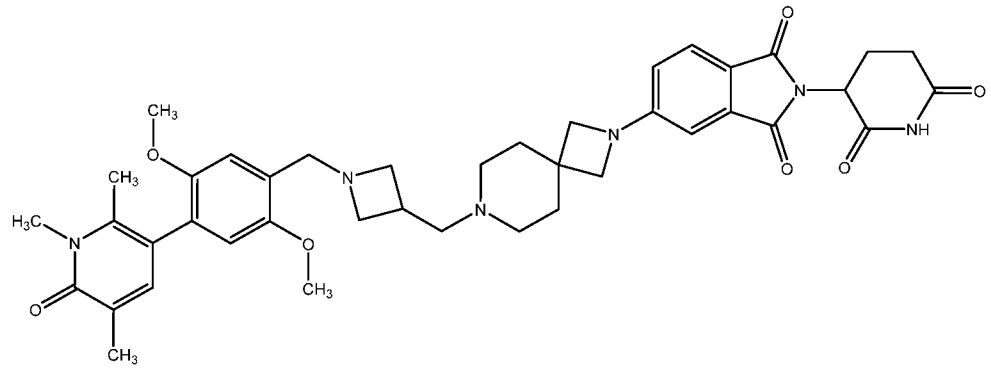
Compound No.	Structure
D336	
D337	
D338	
D339	

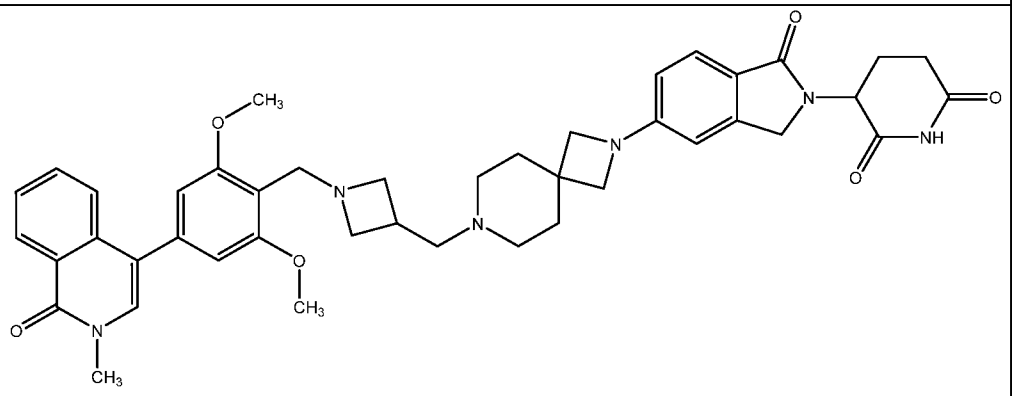
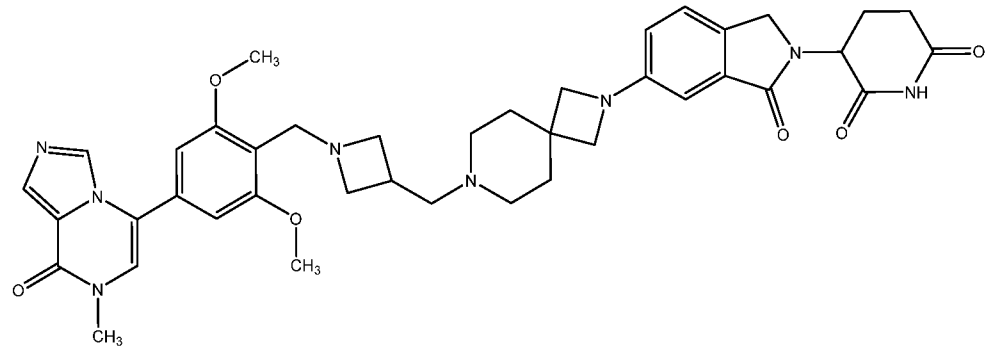
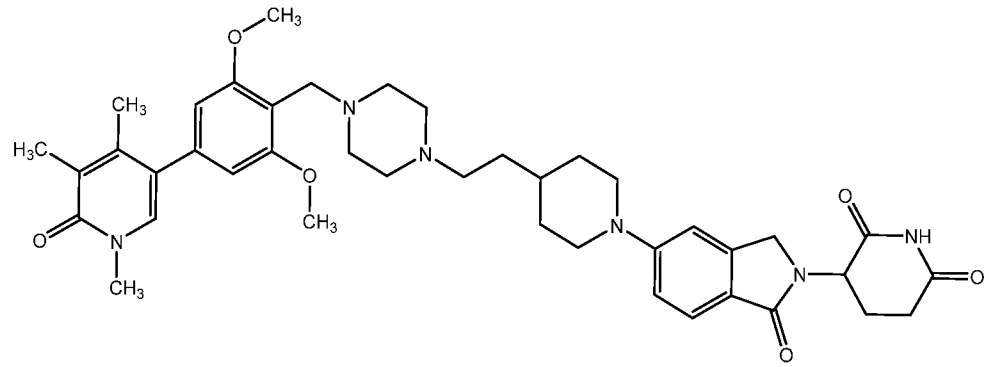
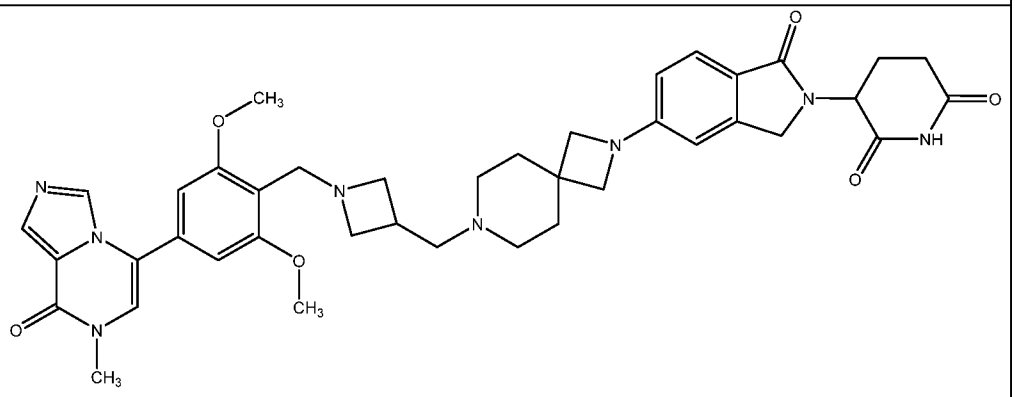
Compound No.	Structure
D340	
D341	
D342	
D343	

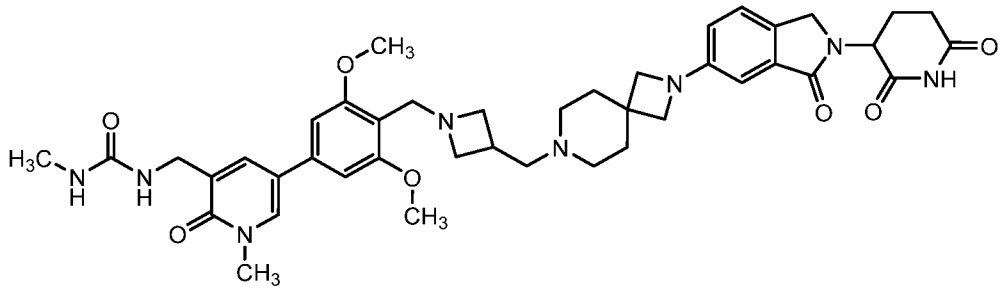
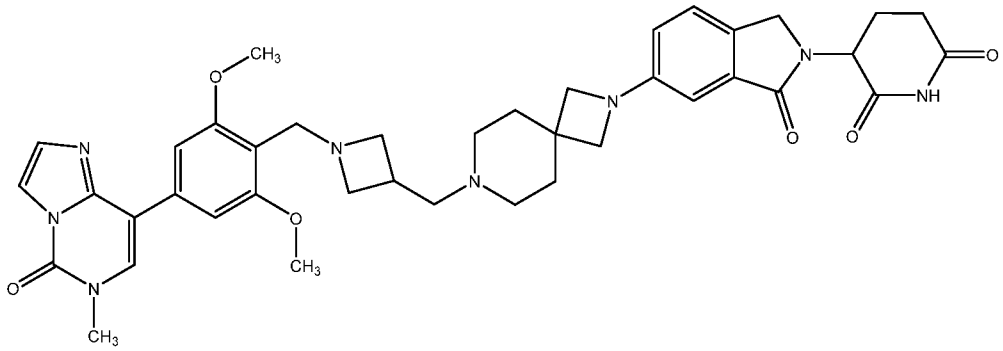
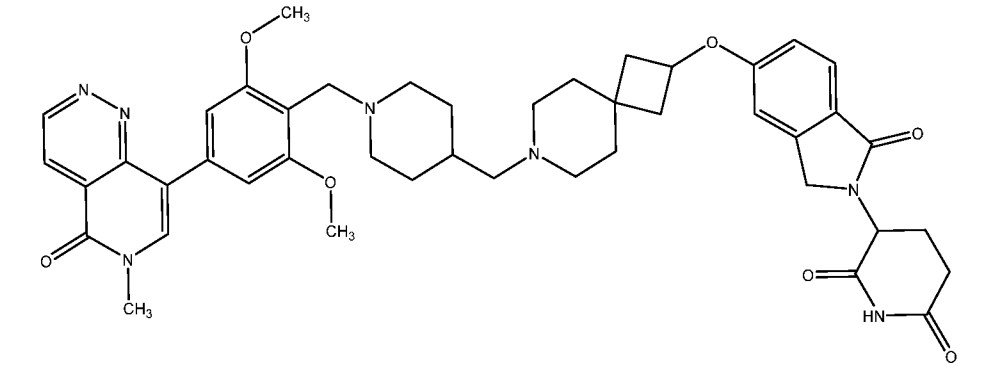
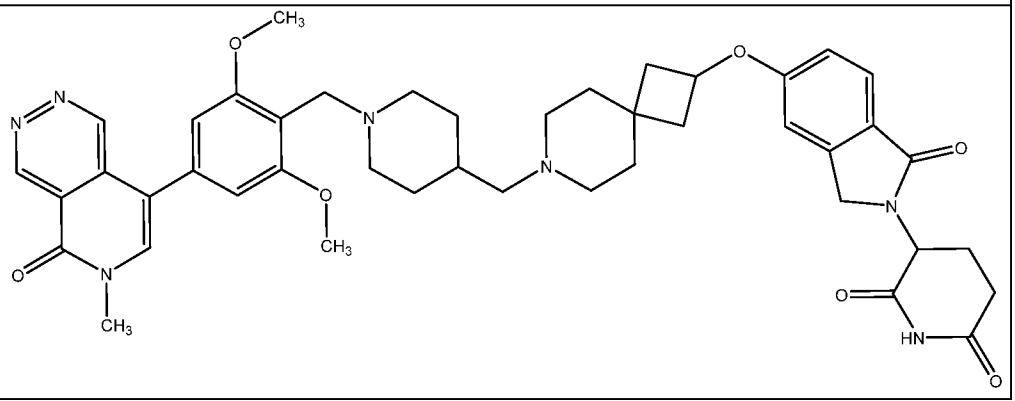
Compound No.	Structure
D344	
D345	
D346	
D347	

Compound No.	Structure
D348	
D349	
D350	
D351	

Compound No.	Structure
D352	
D353	
D354	
D355	

Compound No.	Structure
D356	
D357	
D358	
D359	

Compound No.	Structure
D360	
D361	
D362	
D363	

Compound No.	Structure
D364	
D365	
D366	
D367	

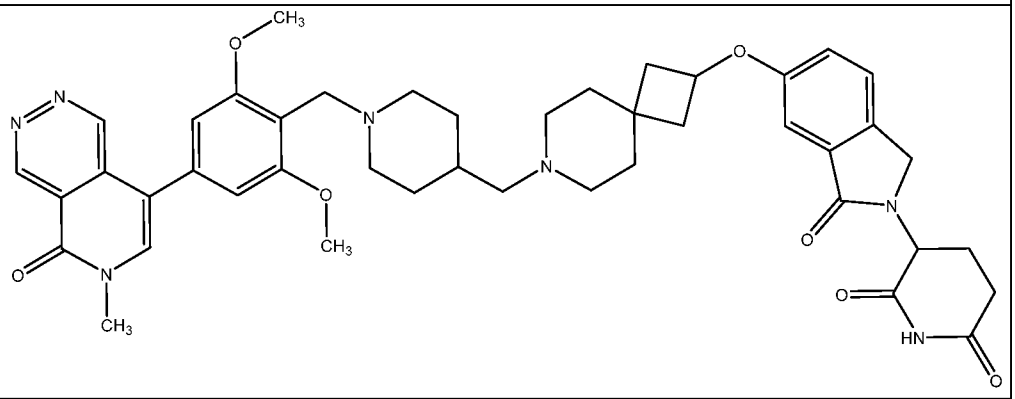
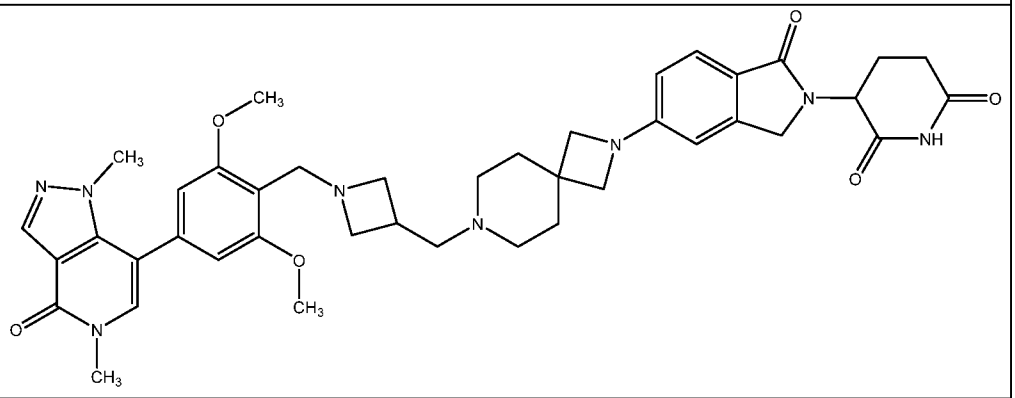
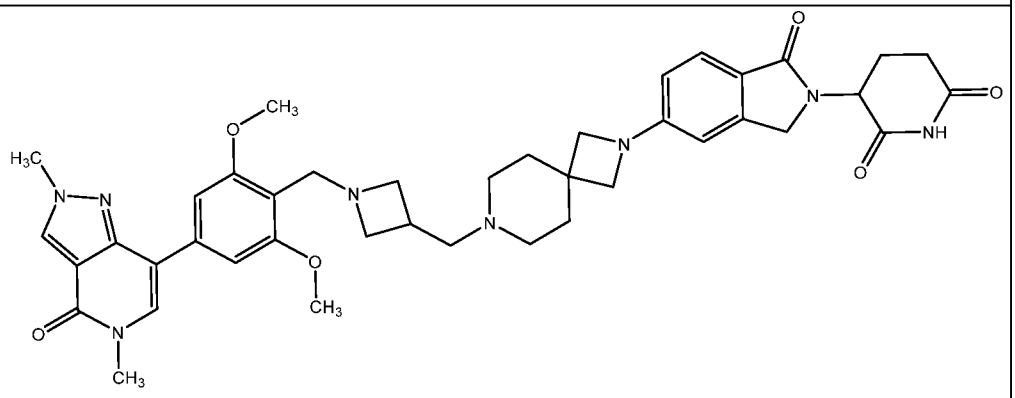
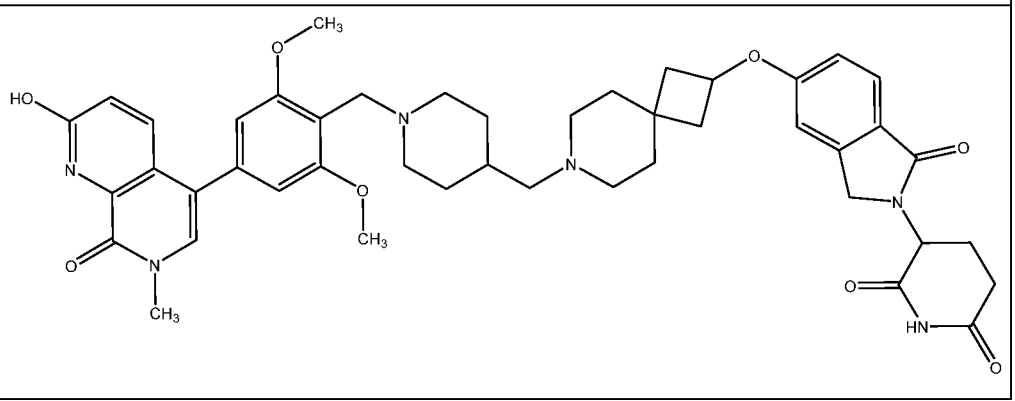
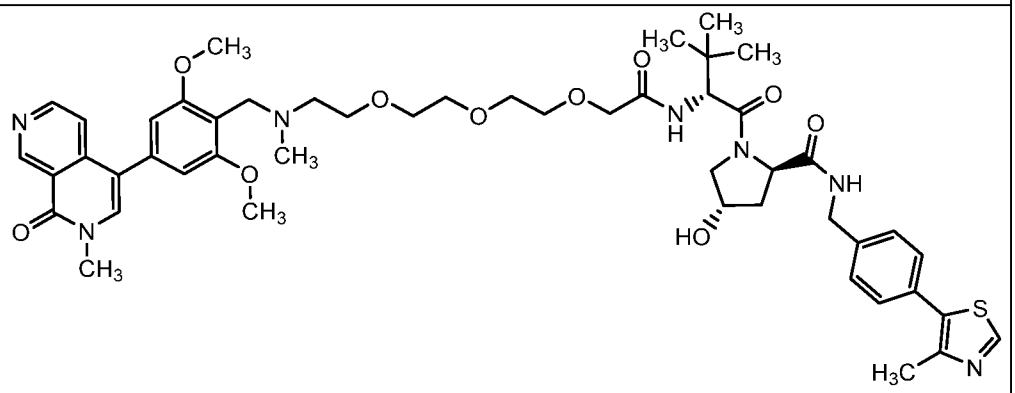
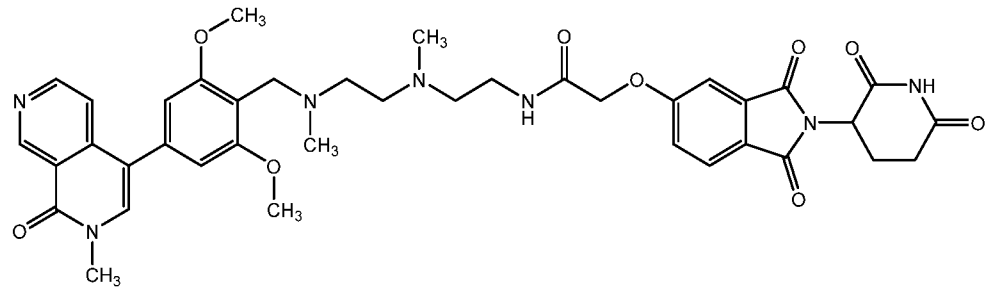
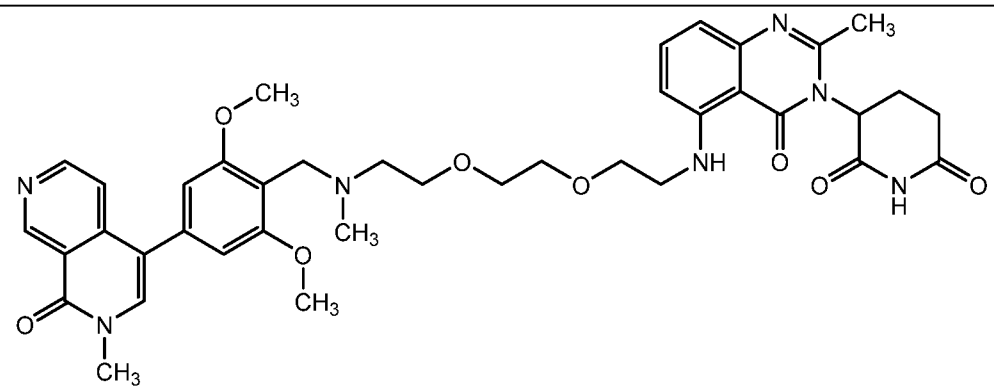
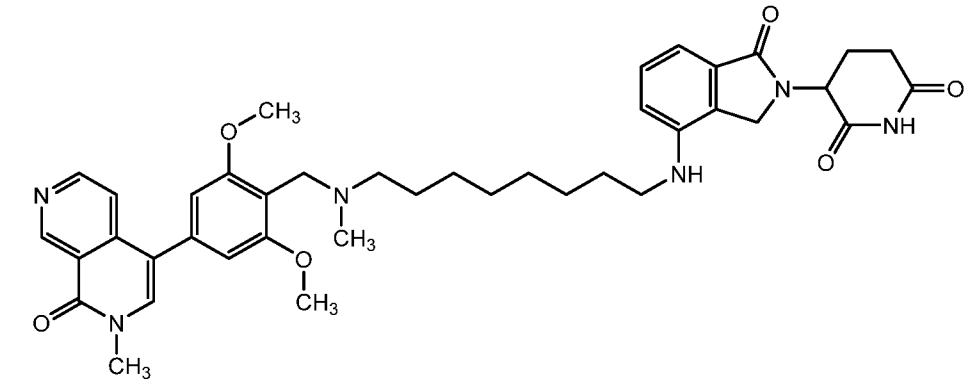
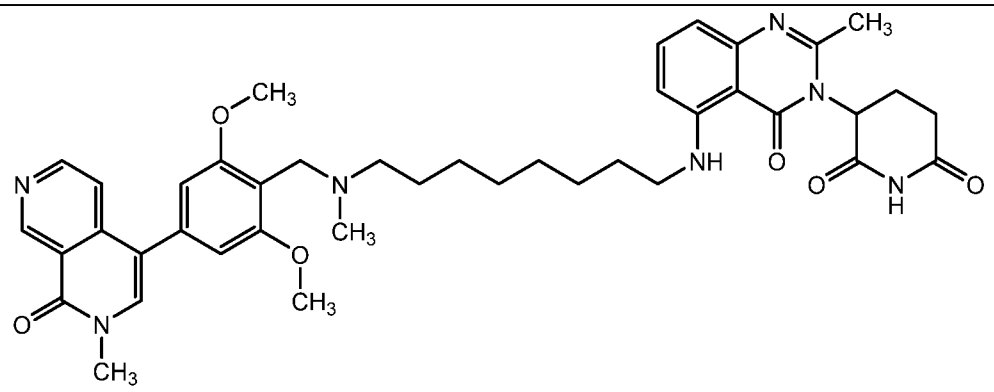
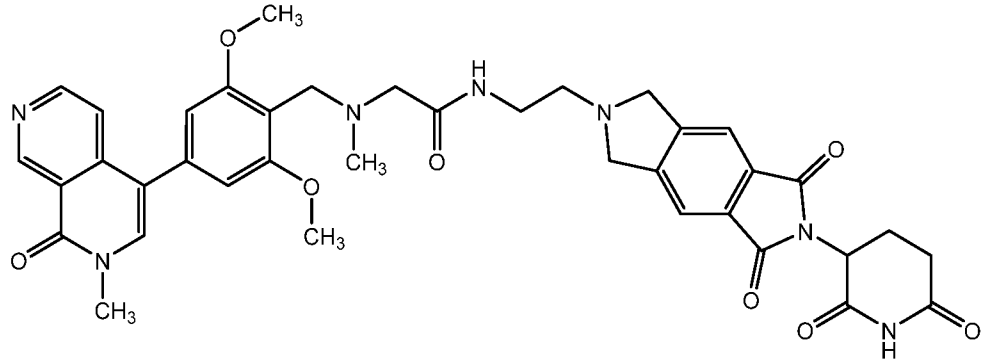
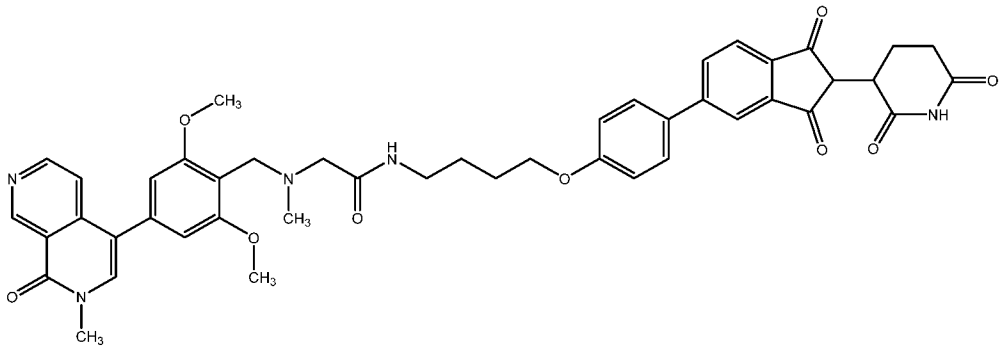
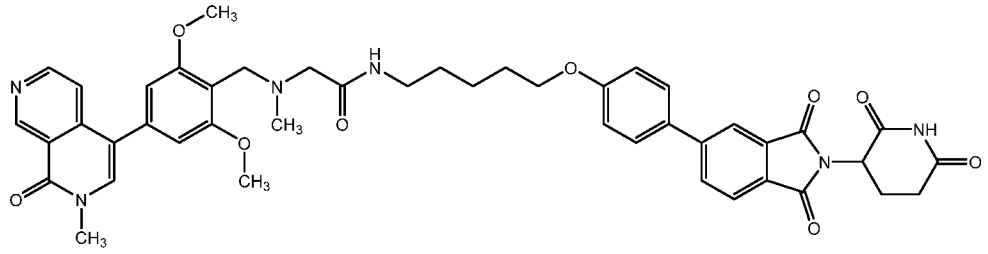
Compound No.	Structure
D368	
D369	
D370	
D371	

Table 1C. Compounds DD1-DD10 of the Disclosure

Compound No.	Structure
DD1	
DD2	
DD3	
DD4	

Compound No.	Structure
DD5	
DD6	
DD7	
DD8	

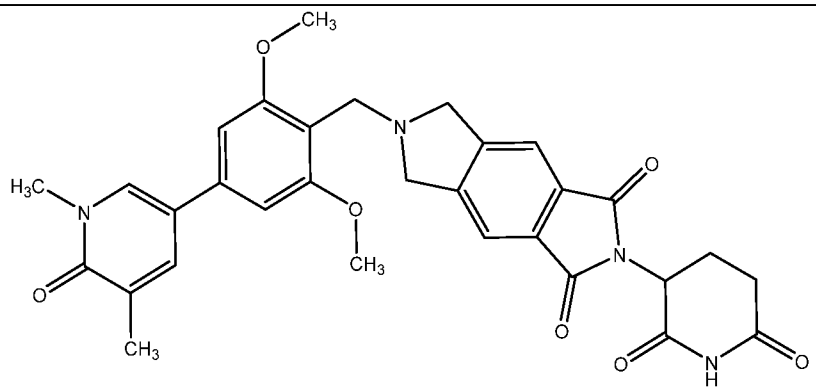
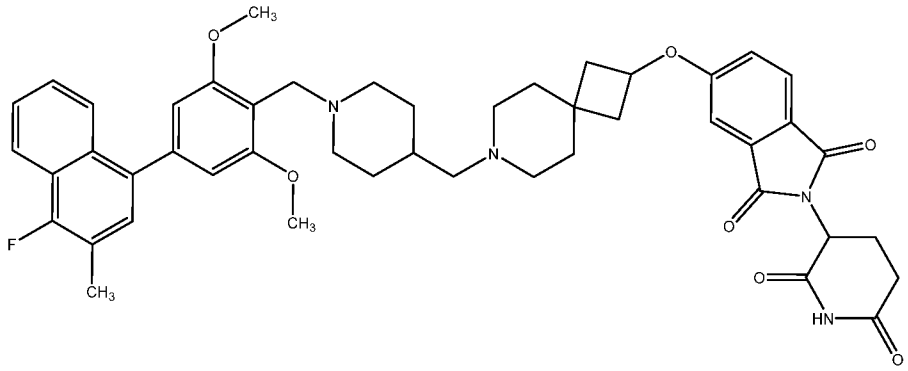
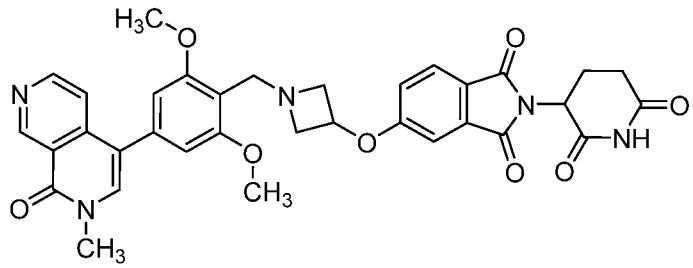
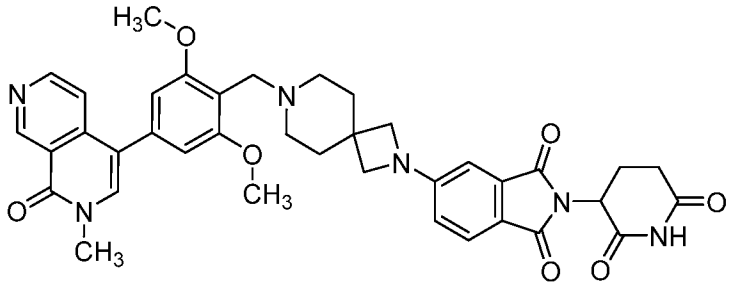
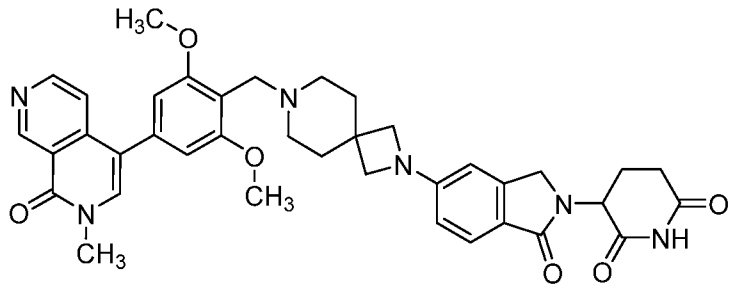
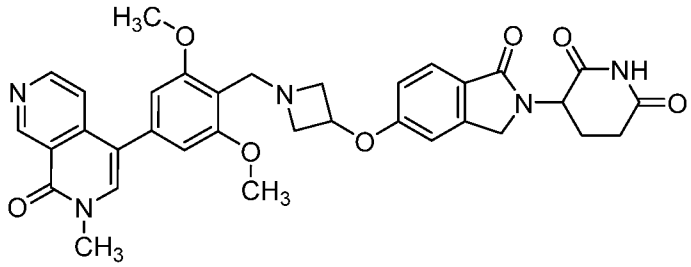
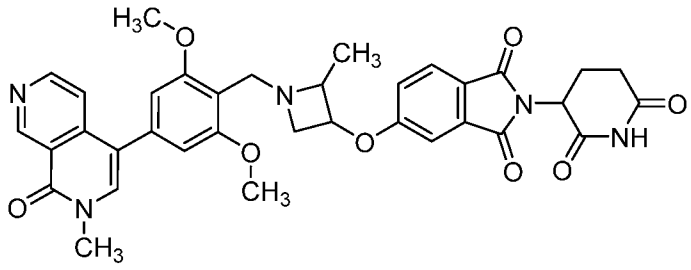
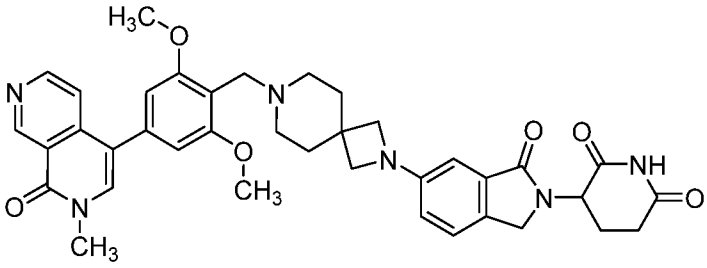
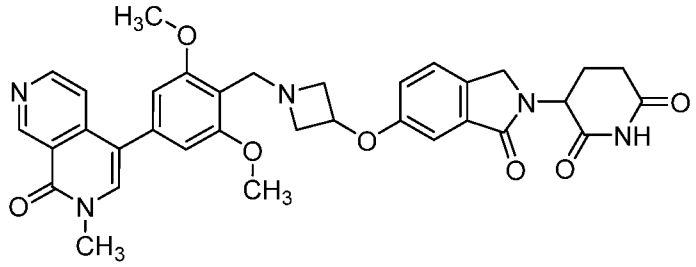
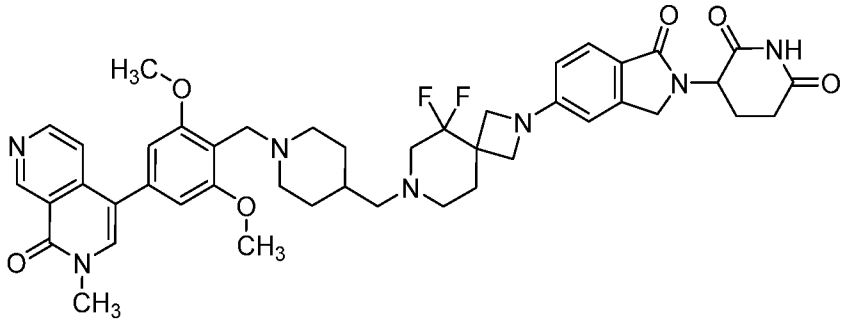
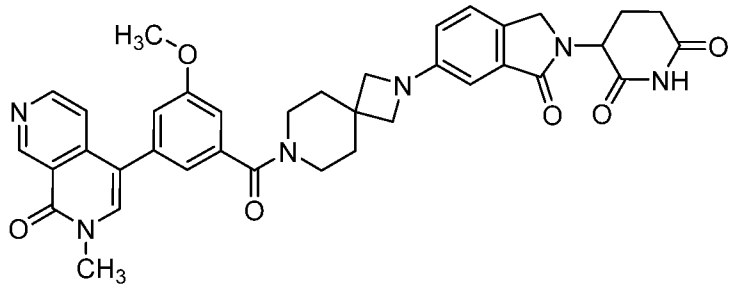
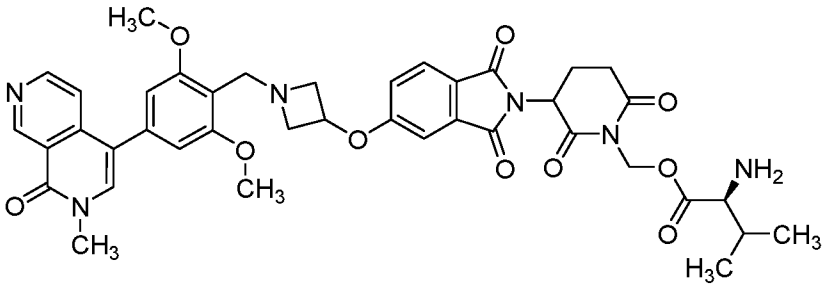
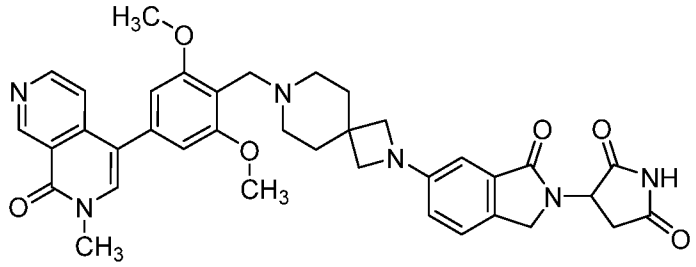
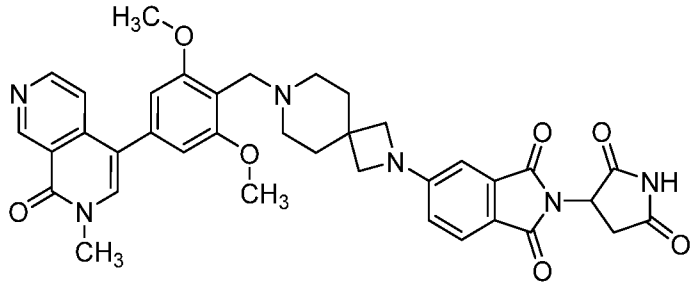
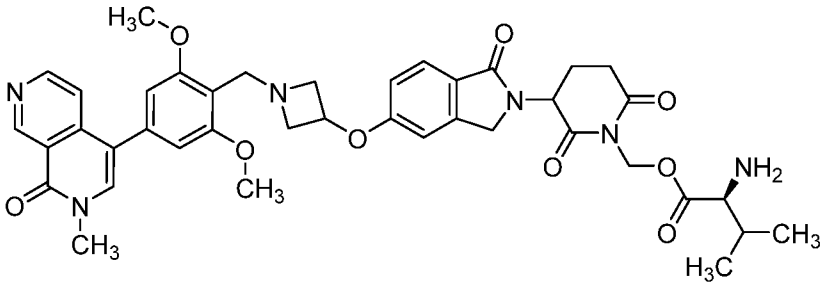
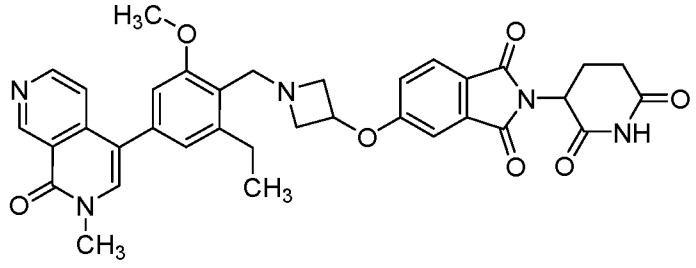
Compound No.	Structure
DD9	
DD10	

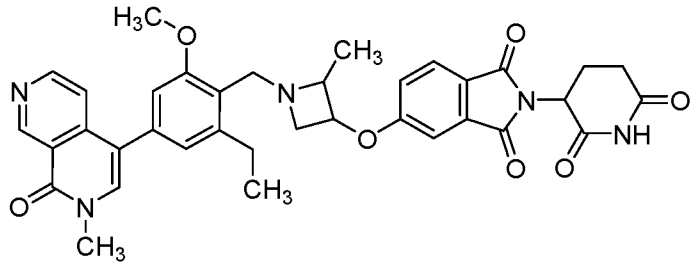
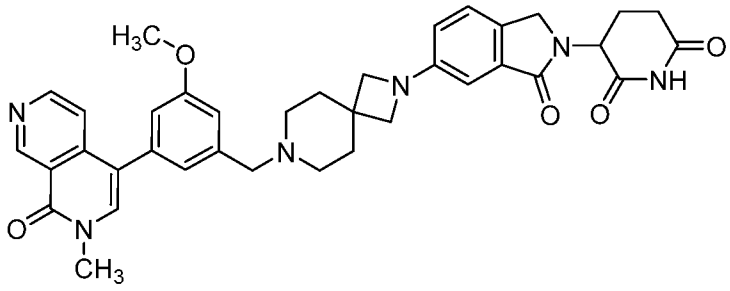
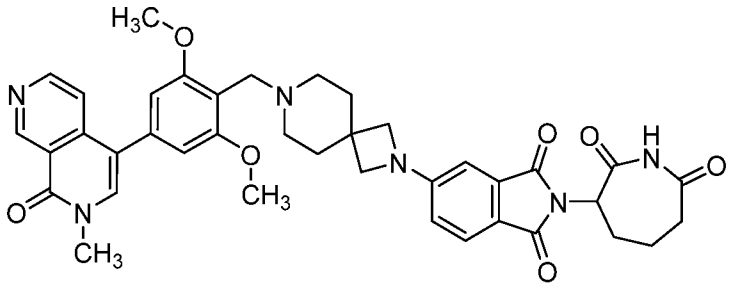
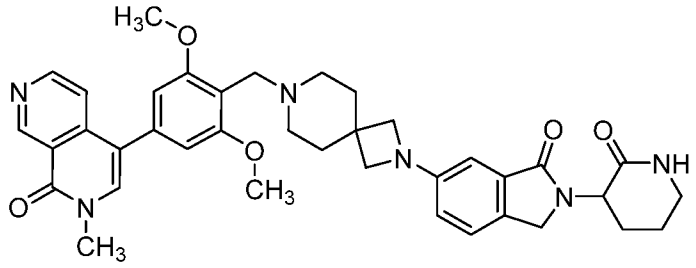
Table 1D. Compounds D372-D477 of the disclosure

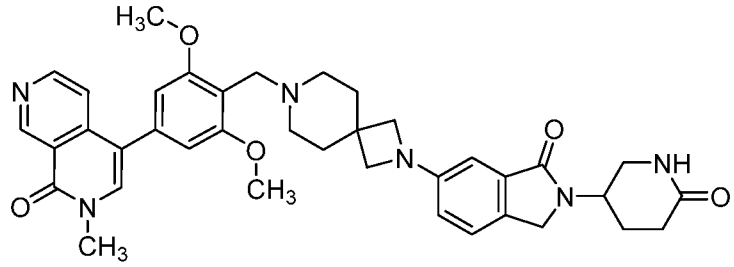
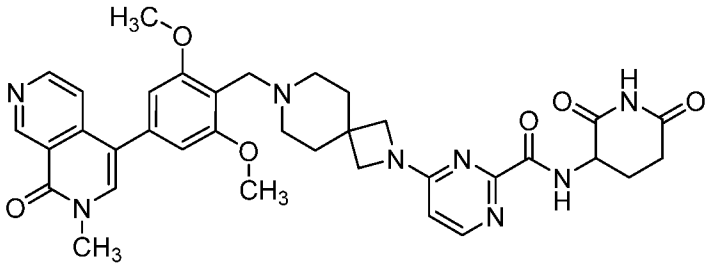
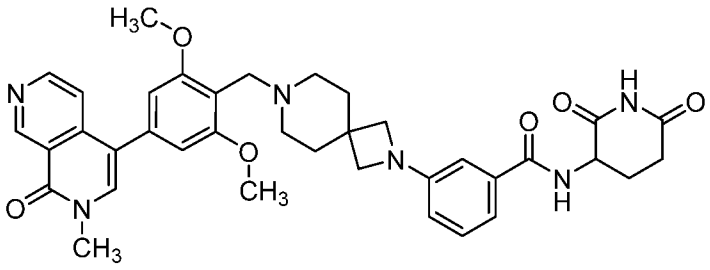
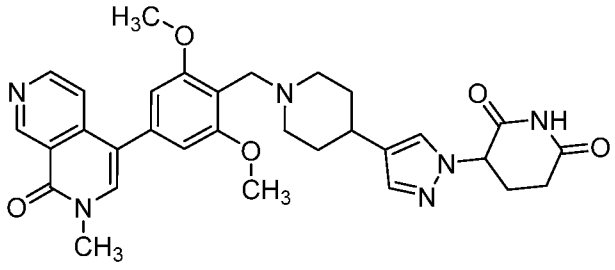
Compound No.	Structure
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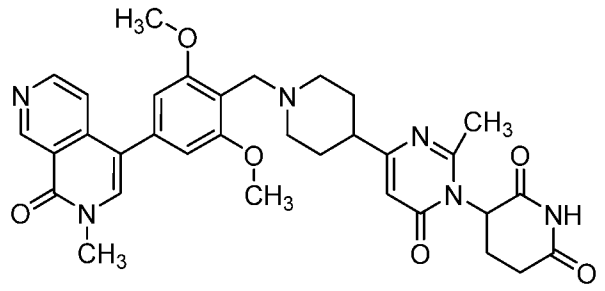
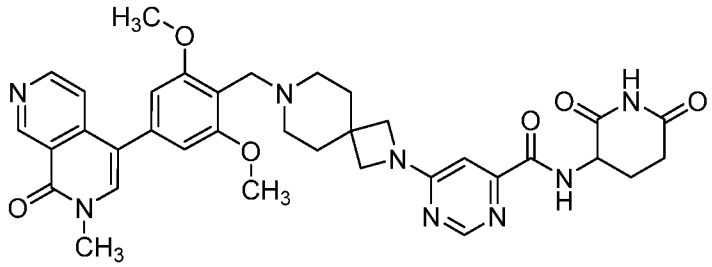
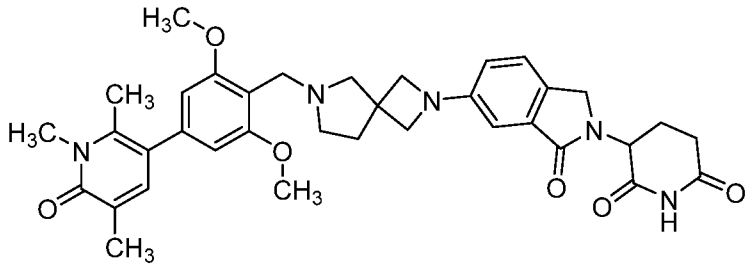
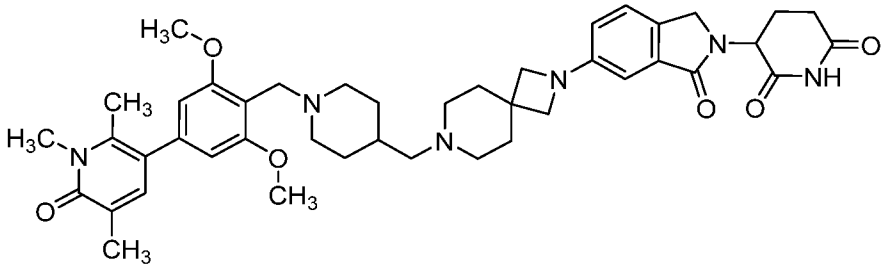
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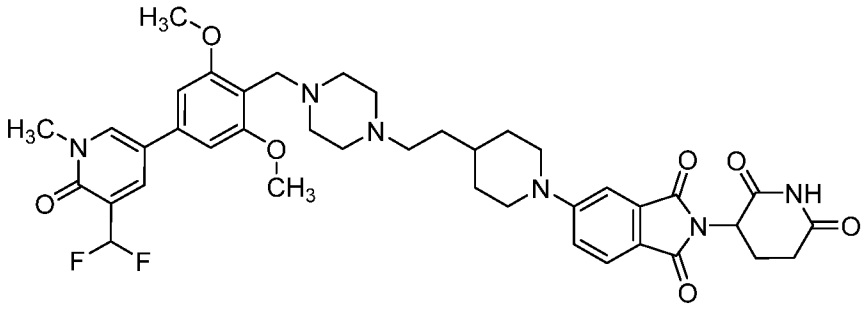
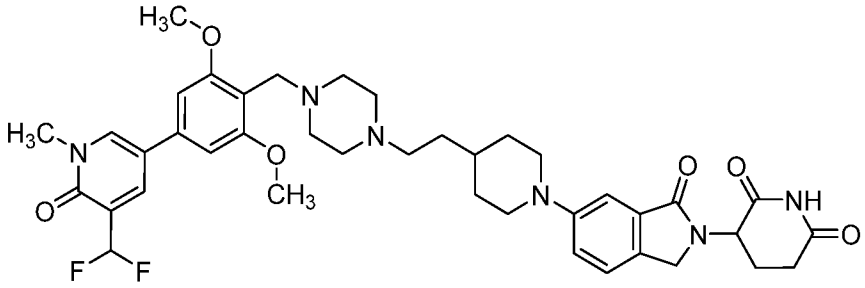
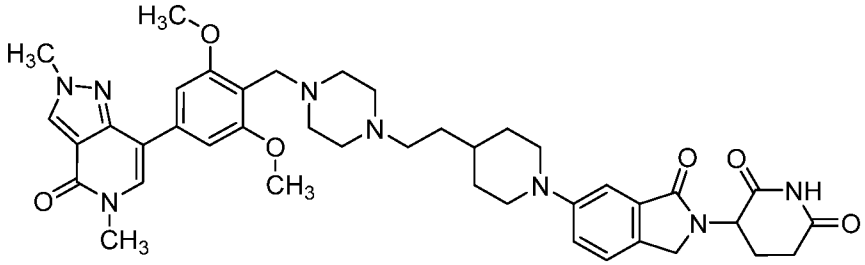
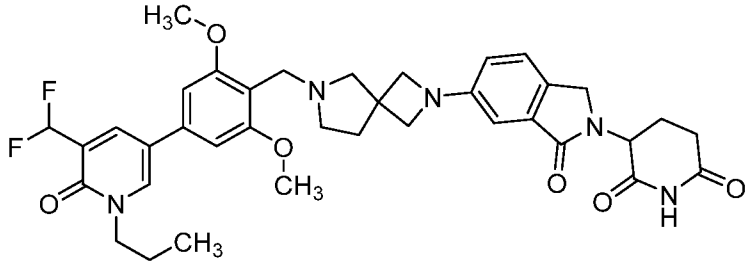
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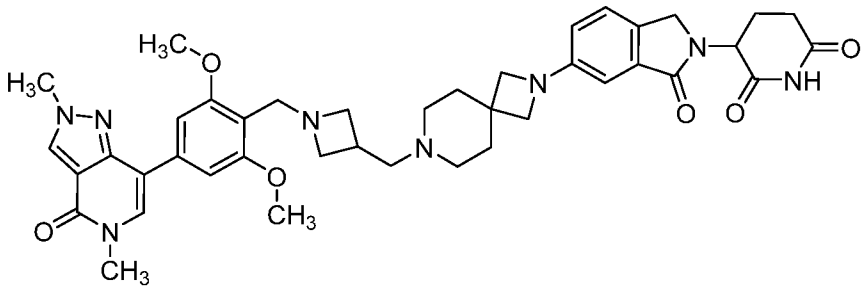
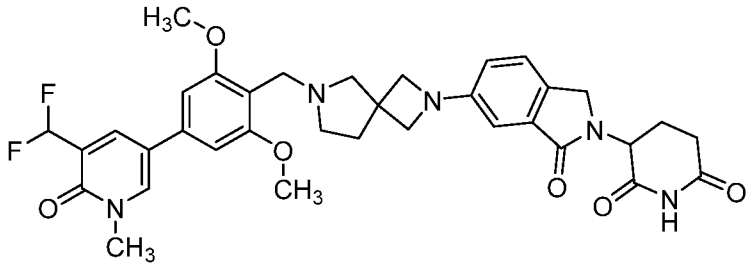
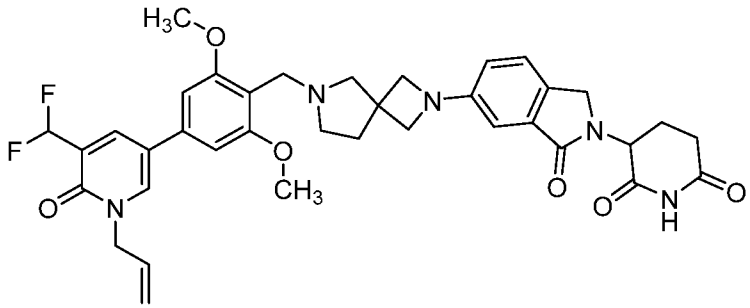
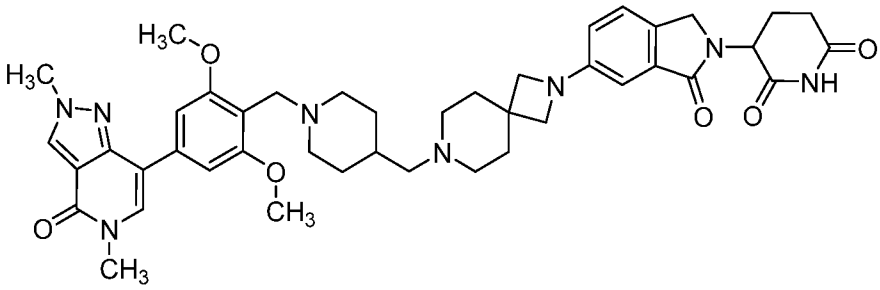
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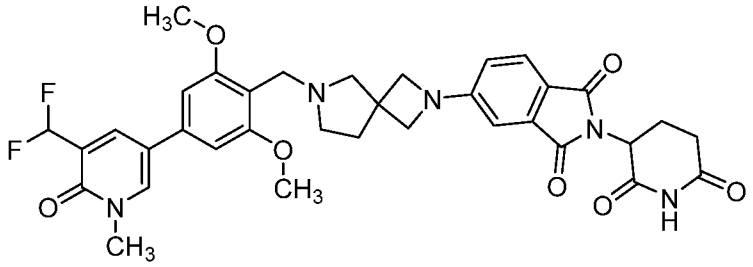
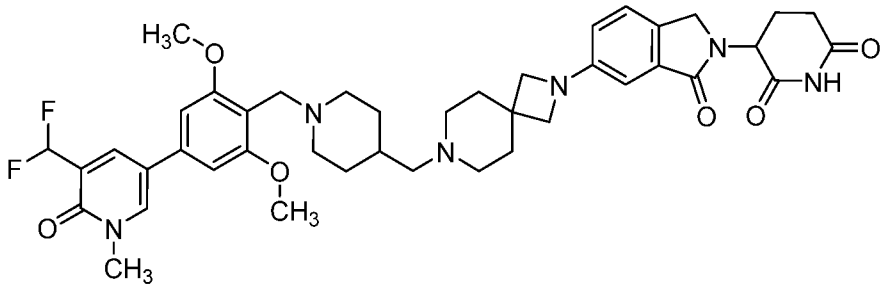
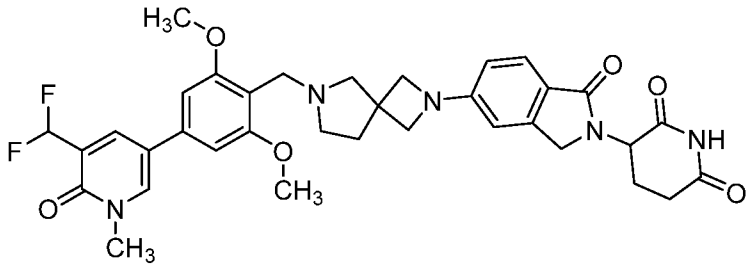
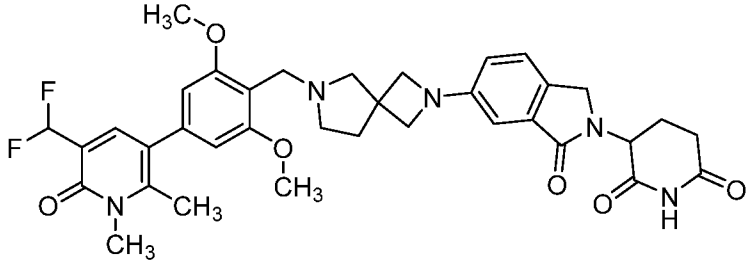
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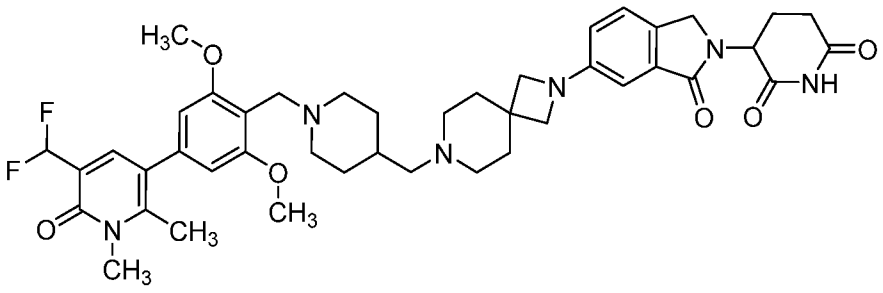
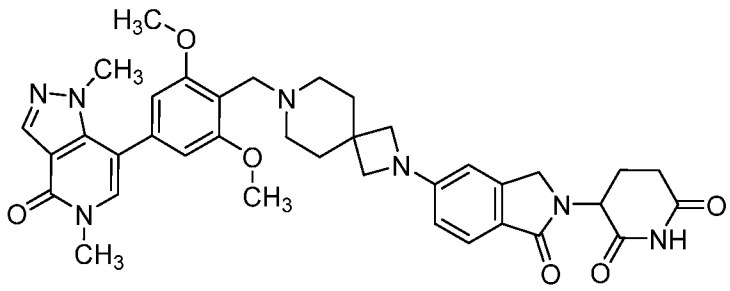
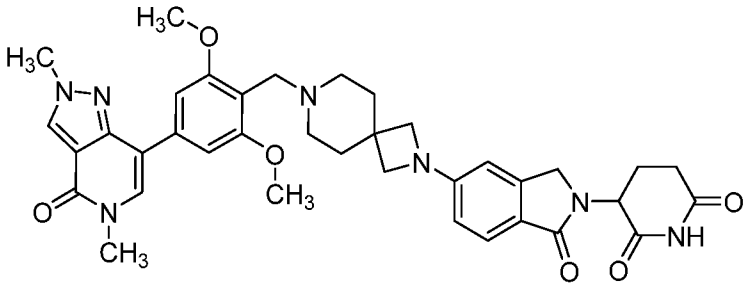
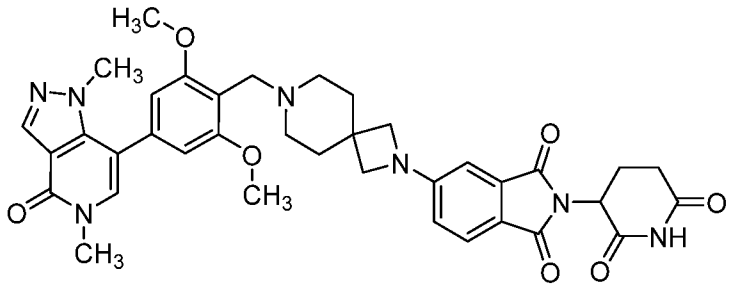
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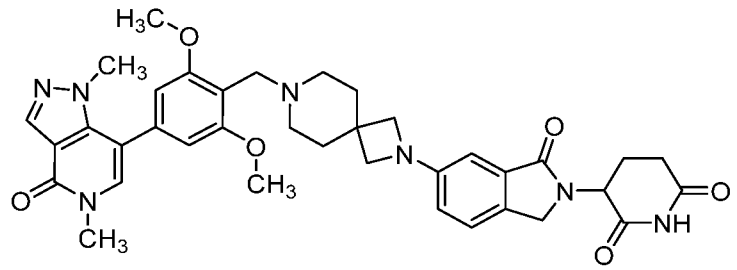
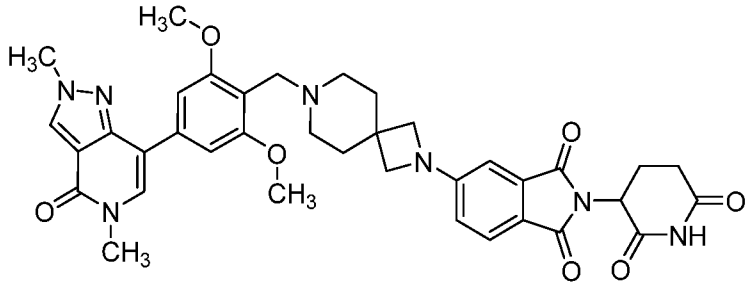
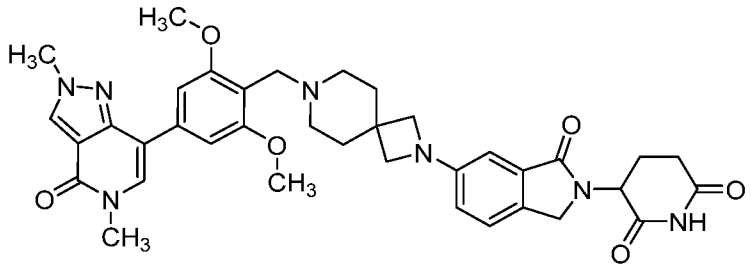
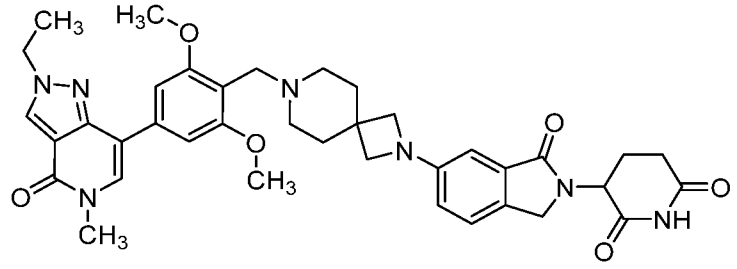
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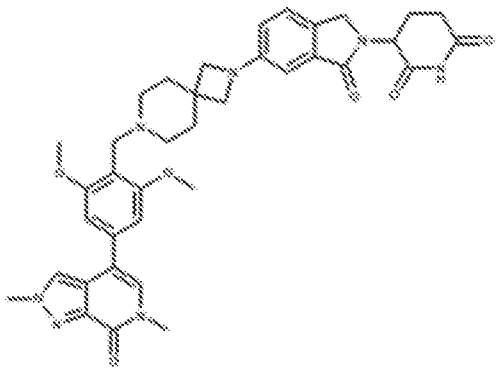
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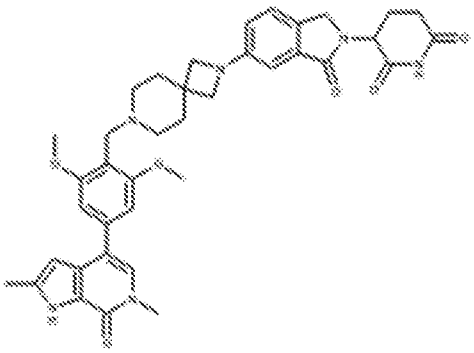
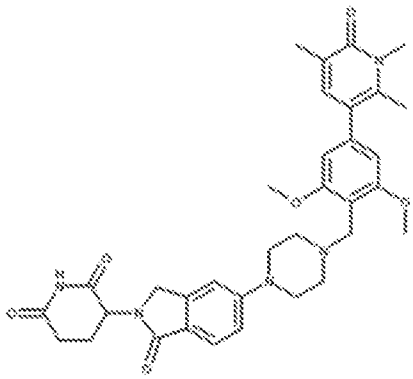
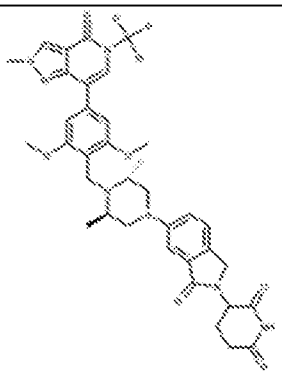
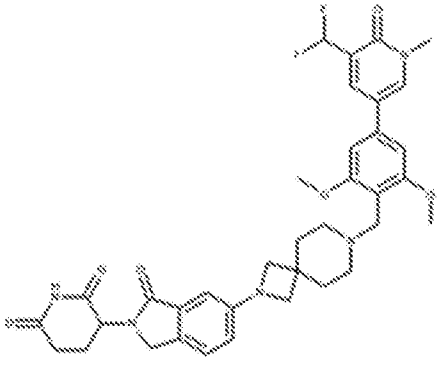
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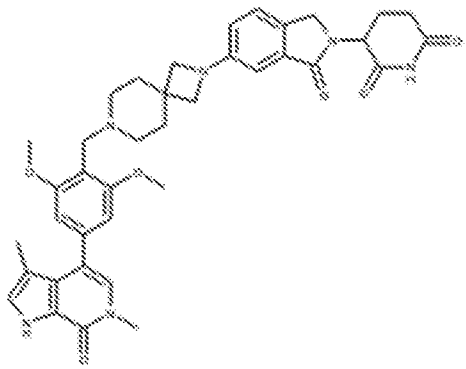
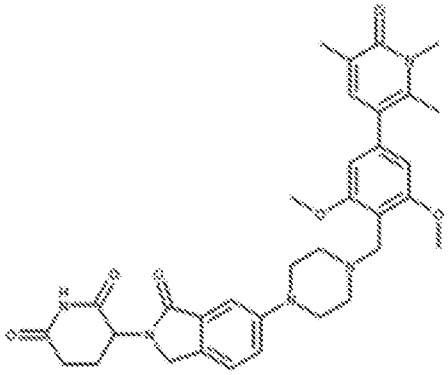
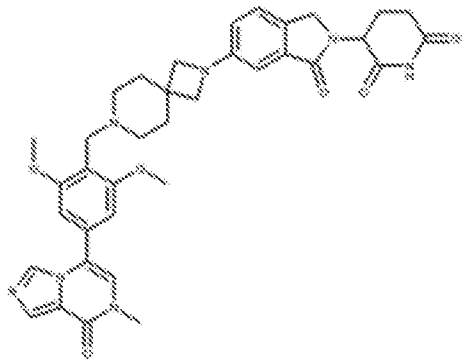
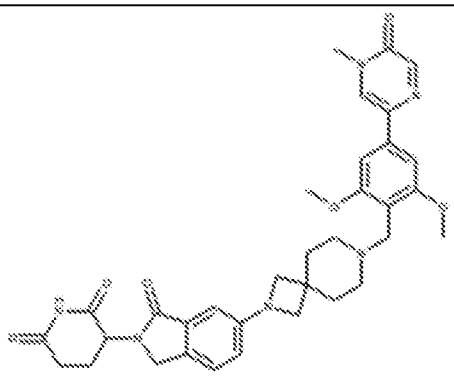
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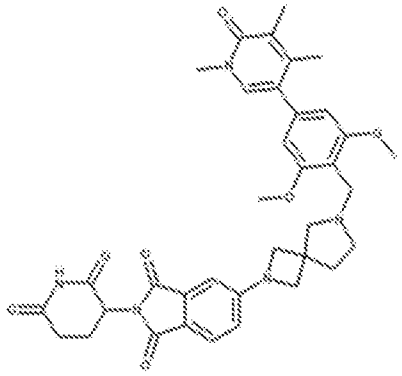
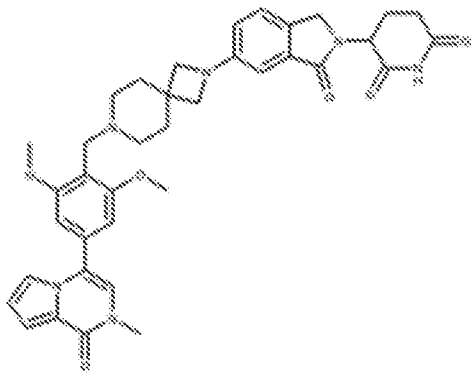
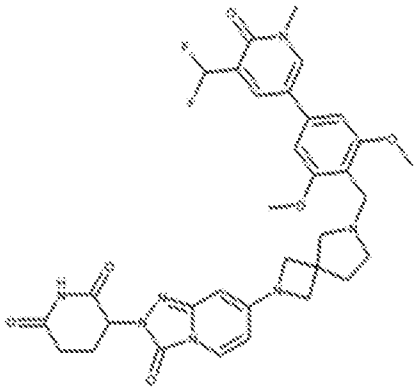
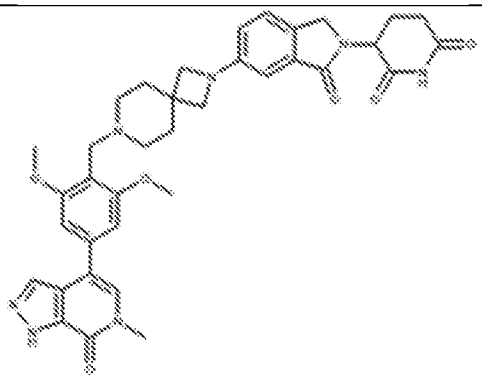
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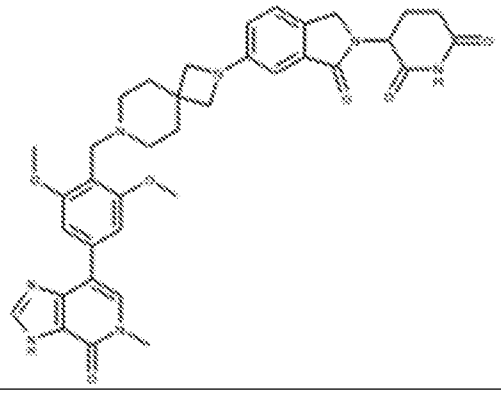
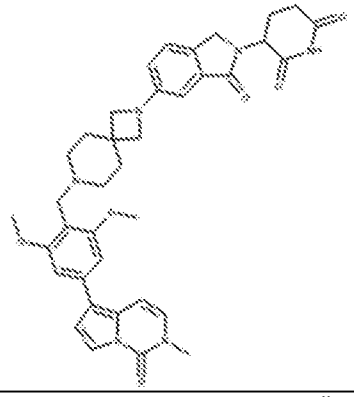
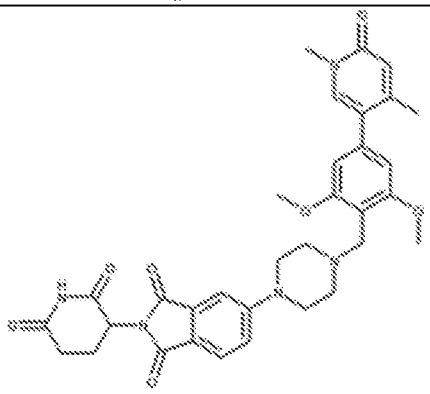
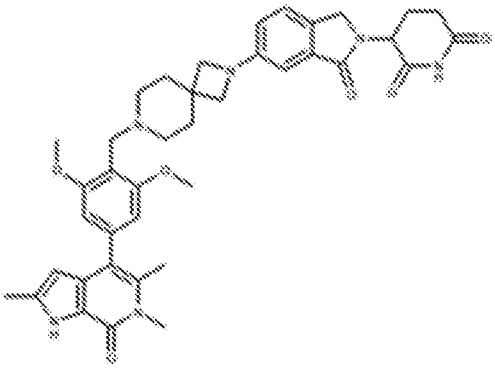
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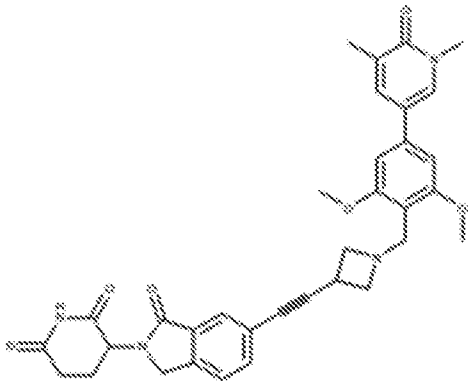
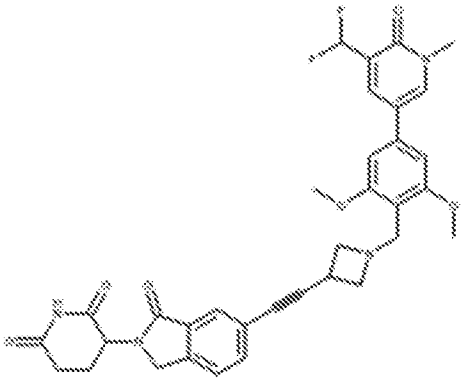
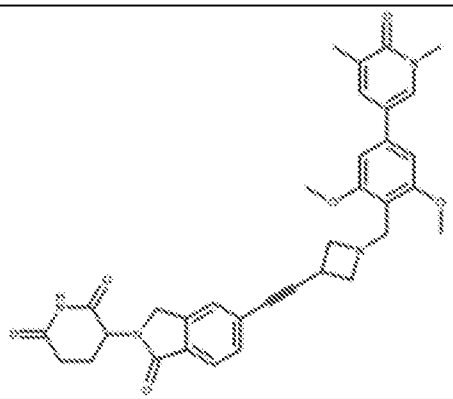
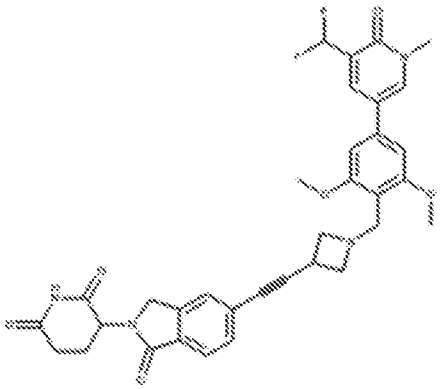
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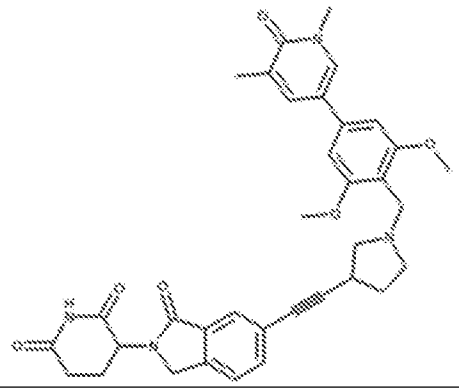
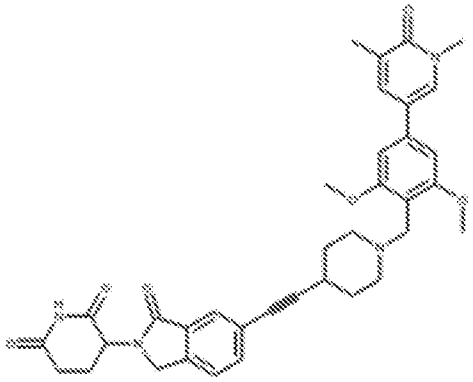
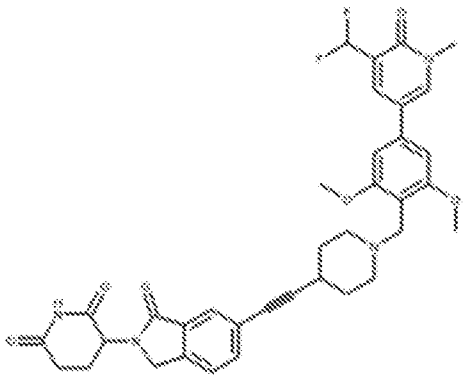
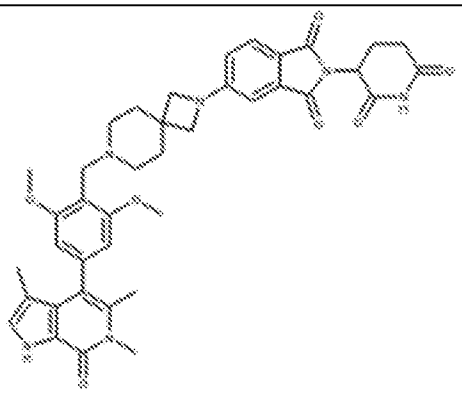
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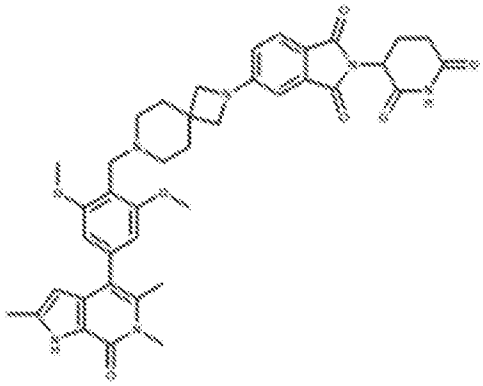
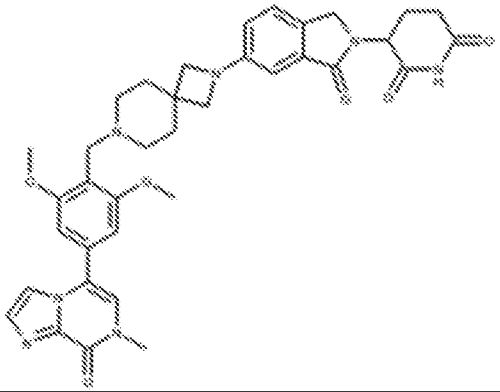
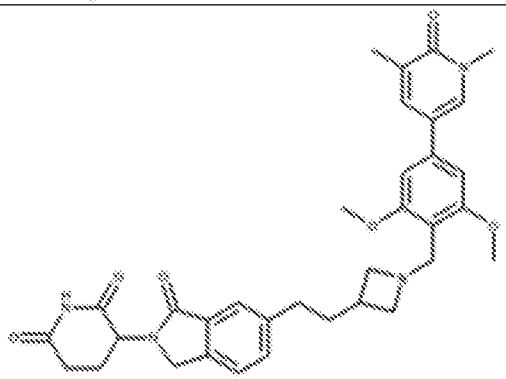
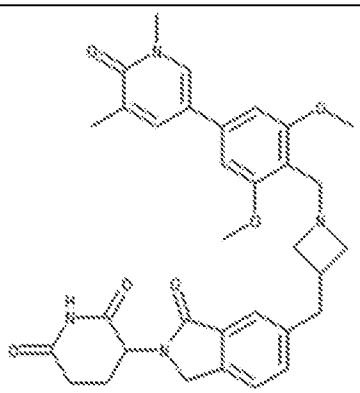
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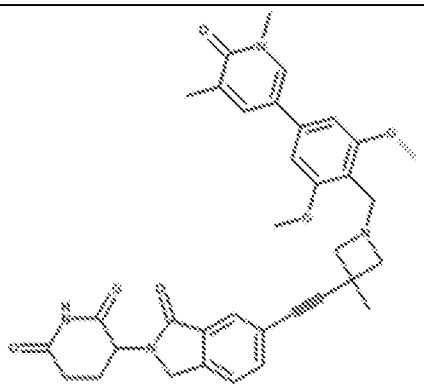
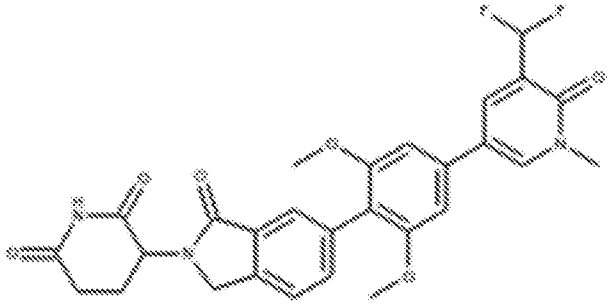
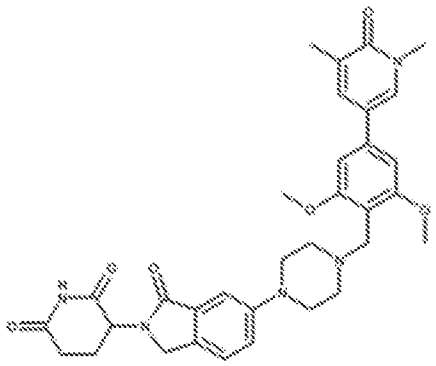
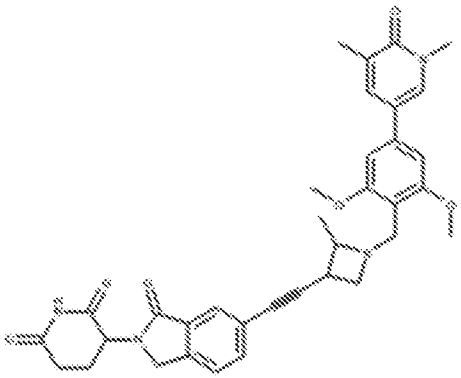
Compound No.	Structure
D430	
D431	
D432	
D433	

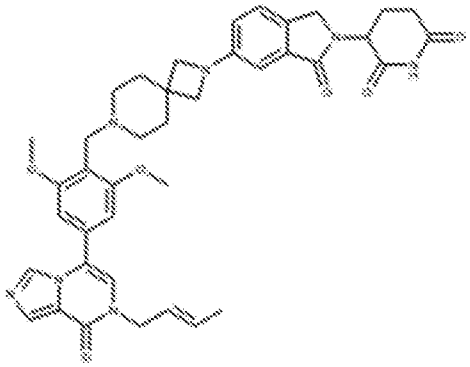
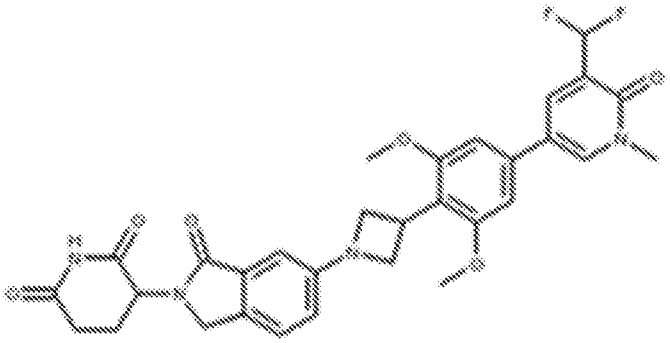
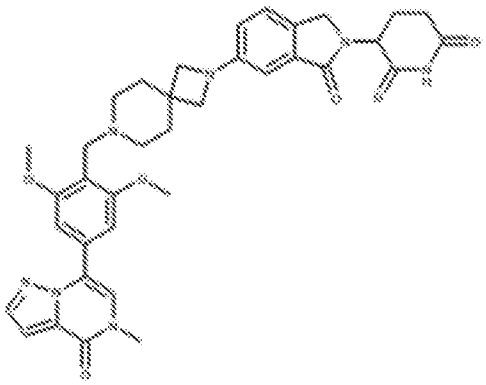
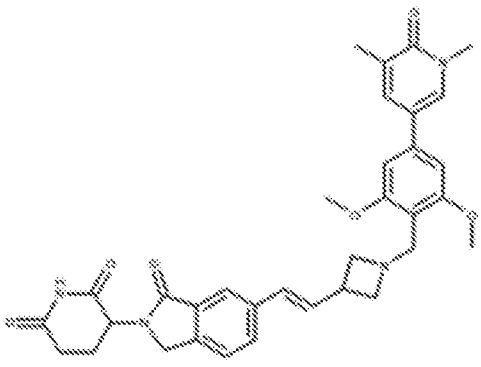
Compound No.	Structure
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D435	
D436	
D437	

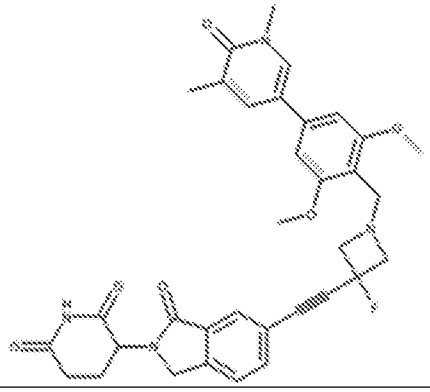
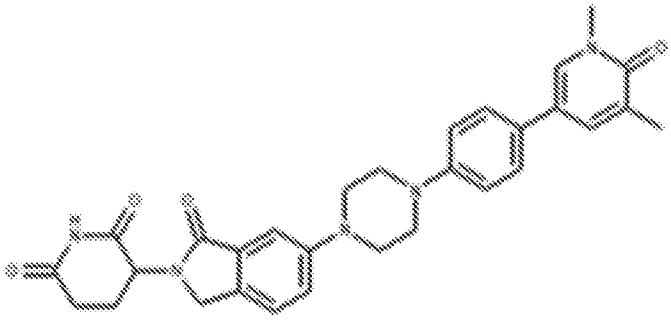
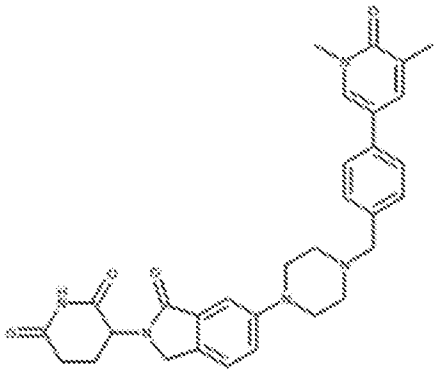
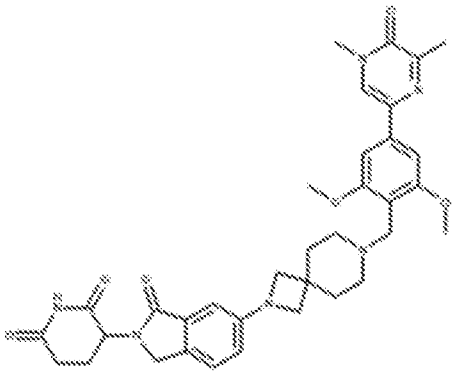
Compound No.	Structure
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D439	
D440	
D441	

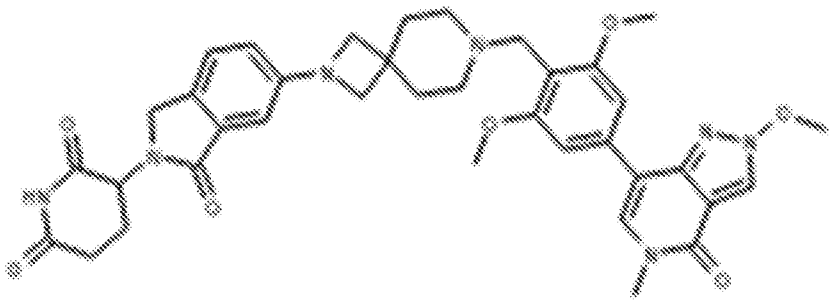
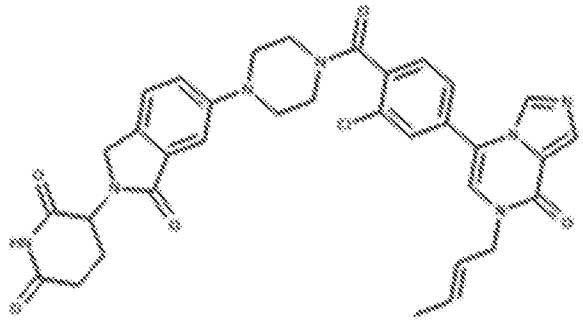
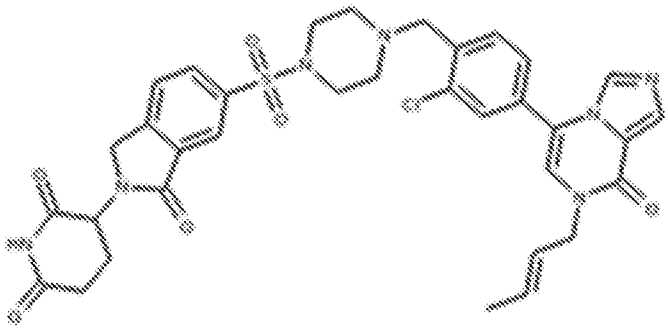
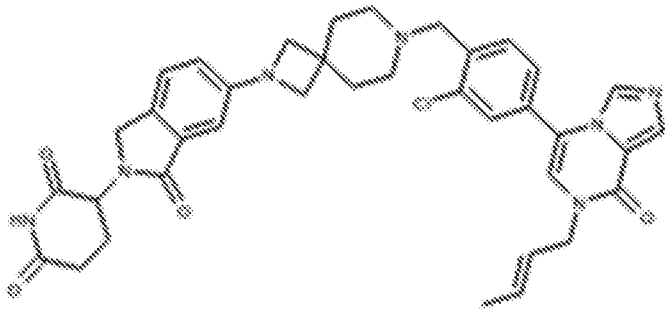
Compound No.	Structure
D442	
D443	
D444	
D445	

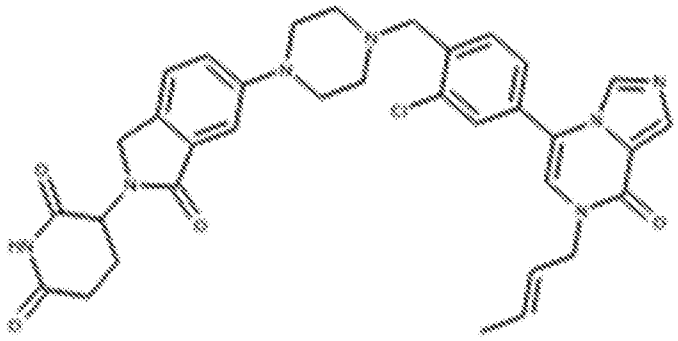
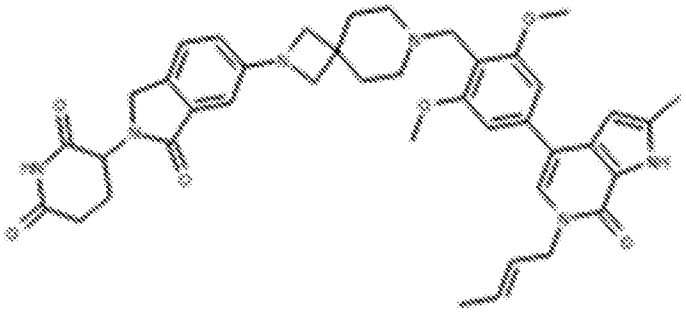
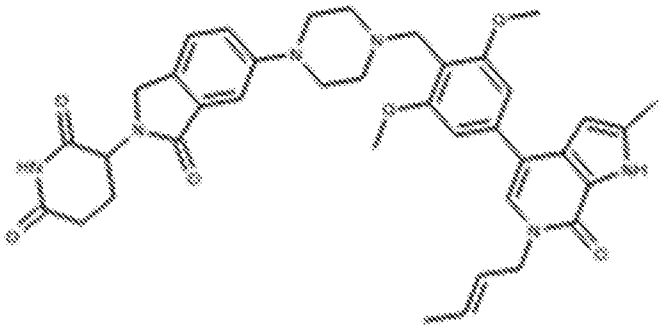
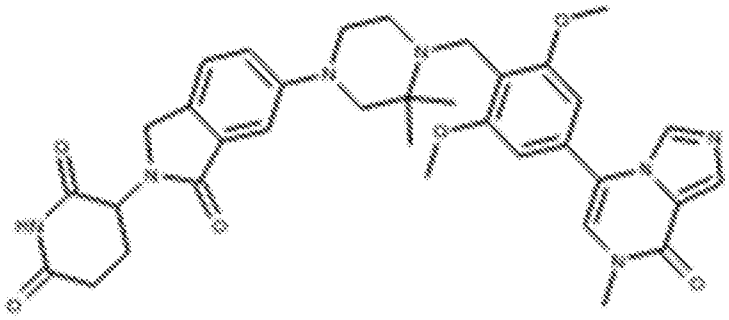
Compound No.	Structure
D446	
D447	
D448	
D449	

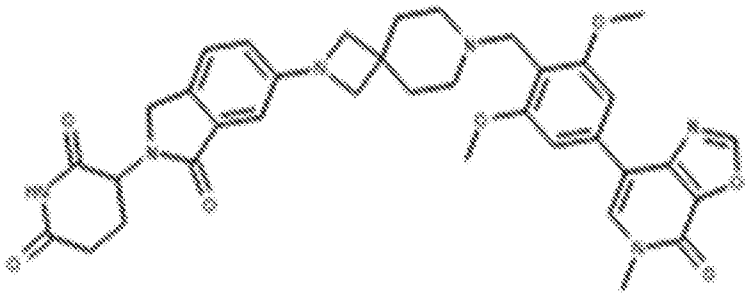
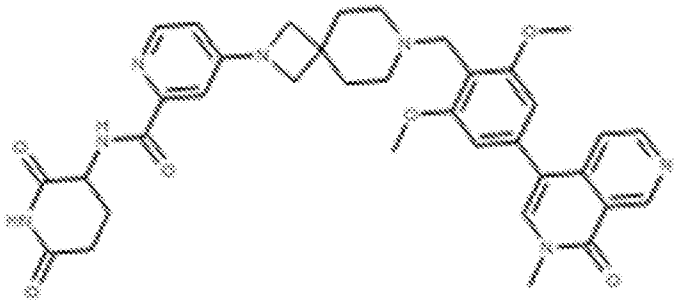
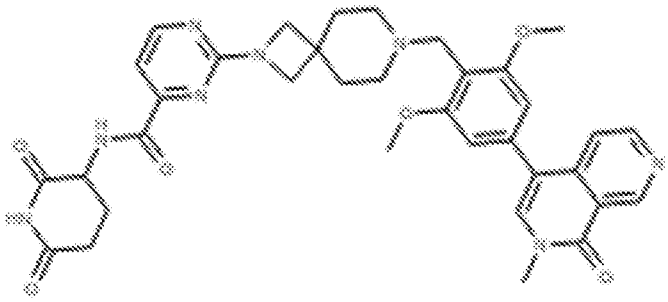
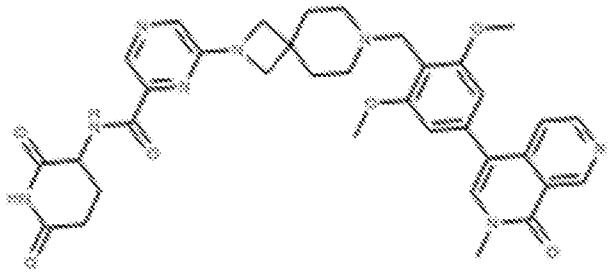
Compound No.	Structure
D450	
D451	
D452	
D453	

Compound No.	Structure
D454	
D455	
D456	
D457	

Compound No.	Structure
D458	
D459	
D460	
D461	

Compound No.	Structure
D462	
D463	
D464	
D465	

Compound No.	Structure
D466	
D467	
D468	
D469	

Compound No.	Structure
D470	
D471	
D472	
D473	

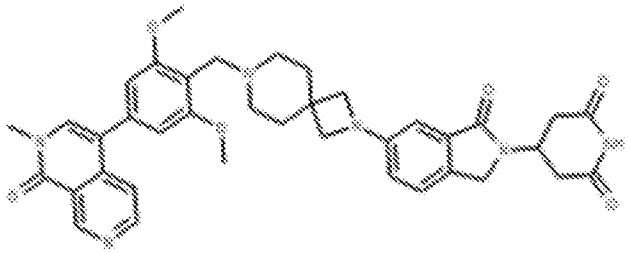
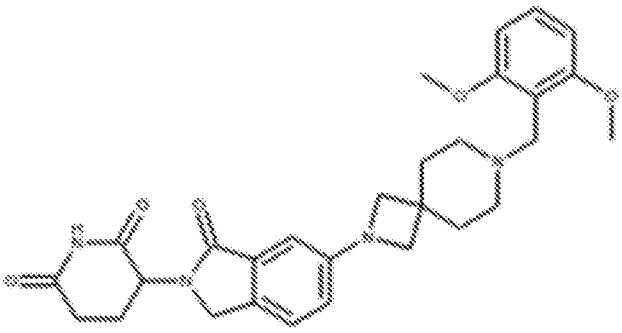
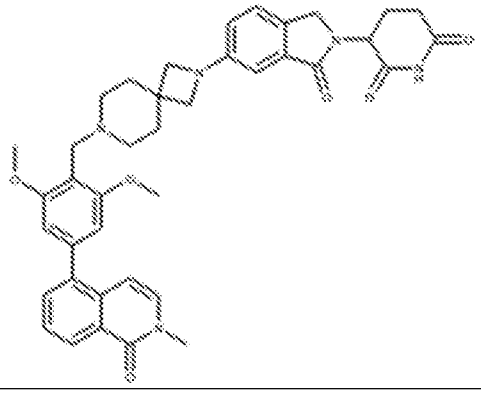
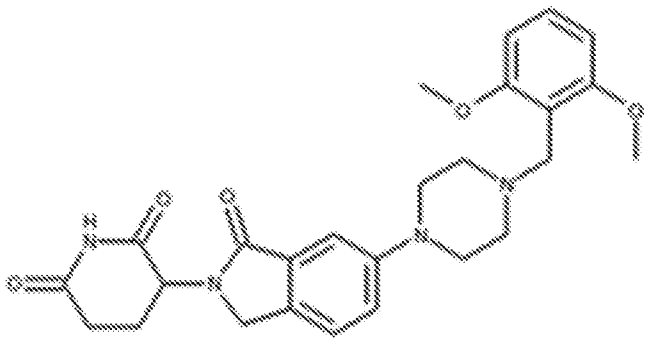
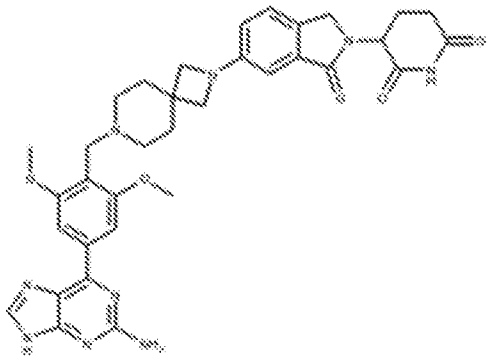
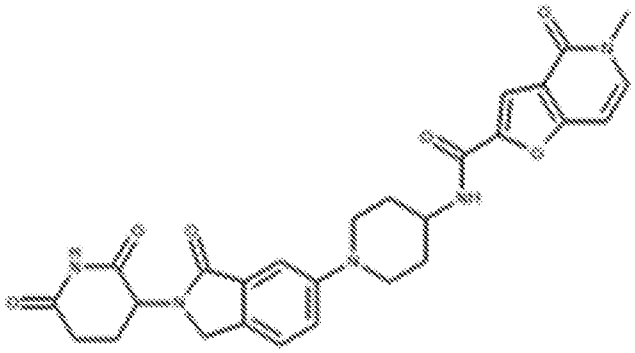
Compound No.	Structure
D474	

Table 1E. Compounds DD11-DD16 of the disclosure

Compound No.	Structure
DD11	
DD12	
DD13	

Compound No.	Structure
DD14	
DD15	
DD16	

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

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

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

In some embodiments, the cell is a cancer cell.

In some embodiments, the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer,

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

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

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

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

In some embodiments, the cancer is squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, hepatocellular carcinomas, and renal cell carcinomas, cancer of the bladder, bowel, breast, cervix, colon, esophagus, head, kidney, liver, lung, neck, ovary, pancreas, prostate, and stomach; leukemias; benign and malignant lymphomas, particularly Burkitt's lymphoma and Non-Hodgkin's lymphoma; benign and malignant melanomas; myeloproliferative diseases; sarcomas, including Ewing's sarcoma, hemangiosarcoma, Kaposi's sarcoma, liposarcoma, myosarcomas, peripheral neuroepithelioma, synovial sarcoma, gliomas, astrocytomas, oligodendrogliomas, ependymomas, gliobastomas, neuroblastomas, ganglioneuromas, gangliogliomas, medulloblastomas, pineal cell tumors, meningiomas, meningeal sarcomas, neurofibromas, and Schwannomas; bowel cancer, breast cancer, prostate cancer, cervical cancer, uterine cancer, lung cancer, ovarian cancer, testicular cancer, thyroid cancer, astrocytoma, esophageal cancer, pancreatic cancer, stomach cancer, liver cancer, colon cancer,

melanoma; carcinosarcoma, Hodgkin's disease, Wilms' tumor and teratocarcinomas. Additional cancers which may be treated using the disclosed compounds according to the present invention include, for example, acute granulocytic leukemia, acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), adenocarcinoma, adenosarcoma, adrenal cancer, adrenocortical carcinoma, anal cancer, anaplastic astrocytoma, angiosarcoma, appendix cancer, astrocytoma, Basal cell carcinoma, B-Cell lymphoma, bile duct cancer, bladder cancer, bone cancer, bone marrow cancer, bowel cancer, brain cancer, brain stem glioma, breast cancer, triple (estrogen, progesterone and HER-2) negative breast cancer, double negative breast cancer (two of estrogen, progesterone and HER-2 are negative), single negative (one of estrogen, progesterone and HER-2 is negative), estrogen-receptor positive, HER2-negative breast cancer, estrogen receptor-negative breast cancer, estrogen receptor positive breast cancer, metastatic breast cancer, luminal A breast cancer, luminal B breast cancer, Her2-negative breast cancer, HER2-positive or negative breast cancer, progesterone receptor-negative breast cancer, progesterone receptor-positive breast cancer, recurrent breast cancer, carcinoid tumors, cervical cancer, cholangiocarcinoma, chondrosarcoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), colon cancer, colorectal cancer, craniopharyngioma, cutaneous lymphoma, cutaneous melanoma, diffuse astrocytoma, ductal carcinoma in situ (DCIS), endometrial cancer, ependymoma, epithelioid sarcoma, esophageal cancer, ewing sarcoma, extrahepatic bile duct cancer, eye cancer, fallopian tube cancer, fibrosarcoma, gallbladder cancer, gastric cancer, gastrointestinal cancer, gastrointestinal carcinoid cancer, gastrointestinal stromal tumors (GIST), germ cell tumor glioblastoma multiforme (GBM), glioma, hairy cell leukemia, head and neck cancer, hemangioendothelioma, Hodgkin lymphoma, hypopharyngeal cancer, infiltrating ductal carcinoma (IDC), infiltrating lobular carcinoma (ILC), inflammatory breast cancer (IBC), intestinal Cancer, intrahepatic bile duct cancer, invasive/infiltrating breast cancer, Islet cell cancer, jaw cancer, Kaposi sarcoma, kidney cancer, laryngeal cancer, leiomyosarcoma, leptomeningeal metastases, leukemia, lip cancer, liposarcoma, liver cancer, lobular carcinoma in situ, low-grade astrocytoma, lung cancer, lymph node cancer, lymphoma, male breast cancer, medullary carcinoma, medulloblastoma, melanoma, meningioma, Merkel cell carcinoma, mesenchymal chondrosarcoma, mesenchymous, mesothelioma metastatic breast cancer, metastatic melanoma metastatic squamous neck cancer, mixed gliomas, monodermal teratoma, mouth cancer mucinous carcinoma, mucosal melanoma, multiple myeloma, Mycosis Fungoides, myelodysplastic syndrome, nasal cavity cancer, nasopharyngeal cancer, neck cancer, neuroblastoma, neuroendocrine tumors (NETs), non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), oat cell cancer, ocular cancer, ocular melanoma, oligodendroglioma, oral cancer, oral cavity cancer, oropharyngeal cancer, osteogenic sarcoma, osteosarcoma, ovarian cancer, ovarian epithelial cancer ovarian germ cell tumor, ovarian primary peritoneal carcinoma, ovarian sex cord stromal tumor, Paget's disease, pancreatic cancer, papillary carcinoma, paranasal sinus cancer, parathyroid cancer, pelvic cancer, penile cancer, peripheral nerve cancer, peritoneal cancer, pharyngeal cancer, pheochromocytoma, pilocytic astrocytoma, pineal region tumor, pineoblastoma, pituitary gland cancer, primary central nervous system (CNS) lymphoma, prostate cancer, rectal cancer, renal cell carcinoma, renal pelvis cancer, rhabdomyosarcoma, salivary gland cancer, soft tissue sarcoma, bone sarcoma, sarcoma, sinus cancer, skin cancer, small cell lung cancer (SCLC), small intestine cancer, spinal cancer, spinal column cancer, spinal cord cancer, squamous cell carcinoma, stomach cancer, synovial sarcoma, T-cell lymphoma,

testicular cancer, throat cancer, thymoma/thymic carcinoma, thyroid cancer, tongue cancer, tonsil cancer, transitional cell cancer, tubal cancer, tubular carcinoma, undiagnosed cancer, ureteral cancer, urethral cancer, uterine adenocarcinoma, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, T-cell lineage acute lymphoblastic leukemia (T-ALL), T-cell lineage lymphoblastic lymphoma (T-LL), peripheral T-cell lymphoma, Adult T-cell leukemia, Pre-B ALL, Pre-B lymphomas, large B-cell lymphoma, Burkitts lymphoma, B-cell ALL, Philadelphia chromosome positive ALL, Philadelphia chromosome positive CML, juvenile myelomonocytic leukemia (JMML), acute promyelocytic leukemia (a subtype of AML), large granular lymphocytic leukemia, Adult T-cell chronic leukemia, diffuse large B cell lymphoma, follicular lymphoma; Mucosa-Associated Lymphatic Tissue lymphoma (MALT), small cell lymphocytic lymphoma, mediastinal large B cell lymphoma, nodal marginal zone B cell lymphoma (NMZL); splenic marginal zone lymphoma (SMZL); intravascular large B-cell lymphoma; primary effusion lymphoma; or lymphomatoid granulomatosis;; B-cell prolymphocytic leukemia; splenic lymphoma/leukemia, unclassifiable, splenic diffuse red pulp small B-cell lymphoma; lymphoplasmacytic lymphoma; heavy chain diseases, for example, Alpha heavy chain disease, Gamma heavy chain disease, Mu heavy chain disease, plasma cell myeloma, solitary plasmacytoma of bone; extraosseous plasmacytoma; primary cutaneous follicle center lymphoma, T cell/histocyte rich large B-cell lymphoma, DLBCL associated with chronic inflammation; Epstein-Barr virus (EBV)+ DLBCL of the elderly; primary mediastinal (thymic) large B-cell lymphoma, primary cutaneous DLBCL, leg type, ALK+ large B-cell lymphoma, plasmablastic lymphoma; large B-cell lymphoma arising in HHV8-associated multicentric, Castleman disease; B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma, or B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma.

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

In some embodiments, the infection is viral infection (e.g., an infection with a virus of the Retroviridae family such as the lentiviruses (e.g. Human immunodeficiency virus (HIV) and deltaretroviruses (e.g., human T cell leukemia virus I (HTLV-I), human T cell leukemia virus II (HTLV-II)); Hepadnaviridae family (e.g. hepatitis B virus (HBV)); Flaviviridae family (e.g. hepatitis C virus (HCV)); Adenoviridae family (e.g. Human Adenovirus); Herpesviridae family (e.g. Human cytomegalovirus

(HCMV), Epstein-Barr virus, herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), human herpesvirus 6 (HHV-6), Herpesvitus K*, CMV, varicella-zoster virus); Papillomaviridae family (e.g. Human Papillomavirus (HPV, HPV E1)); Parvoviridae family (e.g. Parvovirus B19); Polyomaviridae family (e.g. JC virus and BK virus); Paramyxoviridae family (e.g. Measles virus); or Togaviridae family (e.g. Rubella virus)). In some embodiments, the disorder is Coffin Siris, Neurofibromatosis (e.g., NF-1, NF-2, or Schwannomatosis), or Multiple Meningioma.In an aspect, the disclosure features a method of treating a cancer in a subject in need thereof, the method including administering to the subject an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or any of the foregoing pharmaceutical compositions.

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

inflammatory breast cancer (IBC), intestinal Cancer, intrahepatic bile duct cancer, invasive/infiltrating breast cancer, Islet cell cancer, jaw cancer, Kaposi sarcoma, kidney cancer, laryngeal cancer, leiomyosarcoma, leptomeningeal metastases, leukemia, lip cancer, liposarcoma, liver cancer, lobular carcinoma in situ, low-grade astrocytoma, lung cancer, lymph node cancer, lymphoma, male breast cancer, medullary carcinoma, medulloblastoma, melanoma, meningioma, Merkel cell carcinoma, mesenchymal chondrosarcoma, mesenchymous, mesothelioma metastatic breast cancer, metastatic melanoma metastatic squamous neck cancer, mixed gliomas, monodermal teratoma, mouth cancer mucinous carcinoma, mucosal melanoma, multiple myeloma, Mycosis Fungoides, myelodysplastic syndrome, nasal cavity cancer, nasopharyngeal cancer, neck cancer, neuroblastoma, neuroendocrine tumors (NETs), non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), oat cell cancer, ocular cancer, ocular melanoma, oligodendroglioma, oral cancer, oral cavity cancer, oropharyngeal cancer, osteogenic sarcoma, osteosarcoma, ovarian cancer, ovarian epithelial cancer ovarian germ cell tumor, ovarian primary peritoneal carcinoma, ovarian sex cord stromal tumor, Paget's disease, pancreatic cancer, papillary carcinoma, paranasal sinus cancer, parathyroid cancer, pelvic cancer, penile cancer, peripheral nerve cancer, peritoneal cancer, pharyngeal cancer, pheochromocytoma, pilocytic astrocytoma, pineal region tumor, pineoblastoma, pituitary gland cancer, primary central nervous system (CNS) lymphoma, prostate cancer, rectal cancer, renal cell carcinoma, renal pelvis cancer, rhabdomyosarcoma, salivary gland cancer, soft tissue sarcoma, bone sarcoma, sarcoma, sinus cancer, skin cancer, small cell lung cancer (SCLC), small intestine cancer, spinal cancer, spinal column cancer, spinal cord cancer, squamous cell carcinoma, stomach cancer, synovial sarcoma, T-cell lymphoma, testicular cancer, throat cancer, thymoma/thymic carcinoma, thyroid cancer, tongue cancer, tonsil cancer, transitional cell cancer, tubal cancer, tubular carcinoma, undiagnosed cancer, ureteral cancer, urethral cancer, uterine adenocarcinoma, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, T-cell lineage acute lymphoblastic leukemia (T-ALL), T-cell lineage lymphoblastic lymphoma (T-LL), peripheral T-cell lymphoma, Adult T-cell leukemia, Pre-B ALL, Pre-B lymphomas, large B-cell lymphoma, Burkitts lymphoma, B-cell ALL, Philadelphia chromosome positive ALL, Philadelphia chromosome positive CML, juvenile myelomonocytic leukemia (JMML), acute promyelocytic leukemia (a subtype of AML), large granular lymphocytic leukemia, Adult T-cell chronic leukemia, diffuse large B cell lymphoma, follicular lymphoma; Mucosa-Associated Lymphatic Tissue lymphoma (MALT), small cell lymphocytic lymphoma, mediastinal large B cell lymphoma, nodal marginal zone B cell lymphoma (NMZL); splenic marginal zone lymphoma (SMZL); intravascular large B-cell lymphoma; primary effusion lymphoma; or lymphomatoid granulomatosis;; B-cell prolymphocytic leukemia; splenic lymphoma/leukemia, unclassifiable, splenic diffuse red pulp small B-cell lymphoma; lymphoplasmacytic lymphoma; heavy chain diseases, for example, Alpha heavy chain disease, Gamma heavy chain disease, Mu heavy chain disease, plasma cell myeloma, solitary plasmacytoma of bone; extraosseous plasmacytoma; primary cutaneous follicle center lymphoma, T cell/histocyte rich large B-cell lymphoma, DLBCL associated with chronic inflammation; Epstein-Barr virus (EBV)+ DLBCL of the elderly; primary mediastinal (thymic) large B-cell lymphoma, primary cutaneous DLBCL, leg type, ALK+ large B-cell lymphoma, plasmablastic lymphoma; large B-cell lymphoma arising in HHV8-associated multicentric, Castleman disease; B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma, or B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma.

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

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

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

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

In particular embodiments, the compound of the invention and the additional anticancer therapy and any of the foregoing compounds or pharmaceutical compositions are administered within 28 days of

each other (e.g., within 21, 14, 10, 7, 5, 4, 3, 2, or 1 days) or within 24 hours (e.g., 12, 6, 3, 2, or 1 hours; or concomitantly) each in an amount that together are effective to treat the subject.

Chemical Terms

The terminology employed herein is for the purpose of describing particular embodiments and is not intended to be limiting.

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

Herein a phrase of the form "optionally substituted X" (e.g., optionally substituted alkyl) is intended to be equivalent to "X, wherein X is optionally substituted" (e.g., "alkyl, wherein said alkyl is optionally substituted"). It is not intended to mean that the feature "X" (e.g., alkyl) *per se* is optional. As described herein, certain compounds of interest may contain one or more "optionally substituted" moieties. In general, the term "substituted", whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent, e.g., any of the substituents or groups described herein. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by the present disclosure are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable", as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

The term "aliphatic," as used herein, refers to a saturated or unsaturated, straight, branched, or cyclic hydrocarbon. "Aliphatic" is intended herein to include, but is not limited to, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, and cycloalkynyl moieties, and thus incorporates each of these definitions. In one embodiment, "aliphatic" is used to indicate those aliphatic groups having 1-20 carbon atoms. The aliphatic chain can be, for example, mono-unsaturated, di-unsaturated, tri-unsaturated, or polyunsaturated, or alkynyl. Unsaturated aliphatic groups can be in a cis or trans configuration. In one embodiment, the aliphatic group contains from 1 to about 12 carbon atoms, more generally from 1 to about 6 carbon atoms or from 1 to about 4 carbon atoms. In one embodiment, the aliphatic group contains from 1 to about 8 carbon atoms. In certain embodiments, the aliphatic group is C_1-C_2, C_1-C_3, C_1-C_4, C_1-C_5, or C_1-C_6. The specified ranges as used herein indicate an aliphatic group having each member of the range described as an independent species. For example, the term C_1-C_6 aliphatic as used herein indicates a straight or branched alkyl, alkenyl, or alkynyl group having from 1, 2, 3, 4, 5, or 6

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carbon atoms and is intended to mean that each of these is described as an independent species. For example, the term C_1-C_4 aliphatic as used herein indicates a straight or branched alkyl, alkenyl, or alkynyl group having from 1, 2, 3, or 4 carbon atoms and is intended to mean that each of these is described as an independent species. In one embodiment, the aliphatic group is substituted with one or more functional groups that results in the formation of a stable moiety.

The term "heteroaliphatic," as used herein, refers to an aliphatic moiety that contains at least one heteroatom in the chain, for example, an amine, carbonyl, carboxy, oxo, thio, phosphate, phosphonate, nitrogen, phosphorus, silicon, or boron atoms in place of a carbon atom. In one embodiment, the only heteroatom is nitrogen. In one embodiment, the only heteroatom is oxygen. In one embodiment, the only heteroatom is sulfur. "Heteroaliphatic" is intended herein to include, but is not limited to, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, and heterocycloalkynyl moieties. In one embodiment, "heteroaliphatic" is used to indicate a heteroaliphatic group (cyclic, acyclic, substituted, unsubstituted, branched or unbranched) having 1-20 carbon atoms. In one embodiment, the heteroaliphatic group is optionally substituted in a manner that results in the formation of a stable moiety. Nonlimiting examples of heteroaliphatic moieties are polyethylene glycol, polyalkylene glycol, amide, polyamide, polylactide, polyglycolide, thioether, ether, alkyl-heterocycle-alkyl, —O-alkyl-O-alkyl, and alkyl-O-haloalkyl.

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

The term "alkyl," as used herein, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of 1 to 20 carbon atoms (e.g., 1 to 16 carbon atoms, 1 to 10 carbon atoms, 1 to 6 carbon atoms, or 1 to 3 carbon atoms). An "alkylene" is a divalent alkyl group.

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

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

The term "amino," as used herein, represents $-N(R^{N1})_2$, wherein each R^{N1} is, independently, H, OH, NO_2, $N(R^{N2})_2$, SO_2OR^{N2}, SO_2R^{N2}, SOR^{N2}, an *N*-protecting group, alkyl, alkoxy, aryl, arylalkyl, cycloalkyl, acyl (e.g., acetyl, trifluoroacetyl, or others described herein), wherein each of these recited R^{N1} groups can be optionally substituted; or two R^{N1} combine to form an alkylene or heteroalkylene, and wherein each R^{N2} is, independently, H, alkyl, or aryl. The amino groups of the compounds described herein can be an unsubstituted amino (i.e., $-NH_2$) or a substituted amino (i.e., $-N(R^{N1})_2$).

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

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

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

The term "bridged cyclyl," as used herein, refers to a bridged polycyclic group of 5 to 20 atoms, containing from 1 to 3 bridges. Bridged cyclyl includes bridged carbocyclyl (e.g., norbornyl) and bridged heterocyclyl (e.g., 1,4-diazabicyclo[2.2.2]octane).

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

The term "carbocyclyl," as used herein, refers to a non-aromatic C_3-C_{12}, monocyclic or polycyclic (e.g., bicyclic or tricyclic) structure in which the rings are formed by carbon atoms. Carbocyclyl structures include cycloalkyl groups (e.g., cyclohexyl) and unsaturated carbocyclyl radicals (e.g., cyclohexenyl). Polycyclic carbocyclyl includes spirocyclic carbocyclyl, bridged carbocyclyl, and fused carbocyclyl. A "carbocyclylene" is a divalent carbocyclyl group.

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

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

The term "heteroalkyl," as used herein, refers to an alkyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkyl groups. Examples of heteroalkyl groups are an "alkoxy" which, as used herein, refers to alkyl–O– (e.g., methoxy and ethoxy), and an "alkylamino" which, as used herein, refers to $-N(alkyl)R^{Na}$, where R^{Na} is H or alkyl (e.g., methylamino). A "heteroalkylene" is a divalent heteroalkyl group.

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

The term "heteroalkynyl," as used herein, refers to an alkynyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkynyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkynyl groups. Examples of heteroalkynyl groups are an "alkynoxy" which, as used herein, refers to alkynyl–O–. A "heteroalkynylene" is a divalent heteroalkynyl group.

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

pyrazoyl, benzooxazolyl, benzoimidazolyl, benzothiazolyl, imidazolyl, oxaxolyl, and thiazolyl. A "heteroarylene" is a divalent heteroaryl group.

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

The term "heterocyclyl," as used herein, refers a monocyclic or polycyclic radical (e.g., bicyclic or tricyclic) having 3 to 12 atoms having at least one non-aromatic ring containing 1, 2, 3, or 4 ring atoms selected from N, O, or S, and no aromatic ring containing any N, O, or S atoms. Polycyclic heterocyclyl includes spirocyclic heterocyclyl, bridged heterocyclyl, and fused heterocyclyl. Examples of heterocyclyl groups include, but are not limited to, morpholinyl, thiomorpholinyl, furyl, piperazinyl, piperidinyl, pyranyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrofuranyl, and 1,3-dioxanyl. A "heterocyclylene" is a divalent heterocyclyl group.

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

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

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

The term "imine," as used herein, represents $=NR^N$ group, where R^N is, e.g., H or alkyl.

The term "*N*-protecting group," as used herein, represents those groups intended to protect an amino group against undesirable reactions during synthetic procedures. Commonly used *N*-protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis," 3rd Edition (John Wiley & Sons, New York, 1999). *N*-protecting groups include, but are not limited to, acyl, aryloyl, or carbamyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and chiral auxiliaries such as protected or unprotected D, L, or D, L-amino acids such as alanine, leucine, and phenylalanine; sulfonyl-containing groups such as benzenesulfonyl, and p-toluenesulfonyl; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4- dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxy carbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxy carbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, and phenylthiocarbonyl, arylalkyl groups such as benzyl, triphenylmethyl, and benzyloxymethyl, and silyl groups, such as trimethylsilyl. Preferred *N*-protecting

groups are alloc, formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, alanyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc), and benzyloxycarbonyl (Cbz).

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

The term "oxo," as used herein, represents an =O group.

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

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

Compounds described herein (e.g., compounds of the invention) can have one or more asymmetric carbon atoms and can exist in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, or mixtures of diastereoisomeric racemates. The optically active forms can be obtained for example by resolution of the racemates, by asymmetric synthesis or asymmetric chromatography (chromatography with a chiral adsorbent or eluant). That is, certain of the disclosed compounds may exist in various stereoisomeric forms. Stereoisomers are compounds that differ only in their spatial arrangement. Enantiomers are pairs of stereoisomers whose mirror images are not superimposable, most commonly because they contain an asymmetrically substituted carbon atom that acts as a chiral center. "Enantiomer" means one of a pair of molecules that are mirror images of each other and are not superimposable. Diastereomers are stereoisomers that are not related as mirror images, most commonly because they contain two or more asymmetrically substituted carbon atoms and represent the configuration of substituents around one or more chiral carbon atoms. Enantiomers of a compound can be prepared, for example, by separating an enantiomer from a racemate using one or more well-known techniques and methods, such as, for example, chiral chromatography and separation methods based thereon. The appropriate technique and/or method for separating an enantiomer of a compound described herein from a racemic mixture can be readily determined by those of skill in the art. "Racemate" or "racemic mixture" means a compound containing two enantiomers, wherein such mixtures exhibit no optical activity; i.e., they do not rotate the plane of polarized light. "Geometric isomer" means isomers that differ in the orientation of substituent atoms in relationship to a carbon-carbon double bond, to a cycloalkyl ring, or to a bridged bicyclic system. Atoms (other than H) on each side of a carbon- carbon double bond may be in an E (substituents are on opposite sides of the carbon- carbon double bond) or Z (substituents are oriented on the same side) configuration. "R," "S," "S*," "R*," "E," "Z," "cis," and "trans," indicate configurations relative to the core molecule. Certain of the disclosed compounds may exist in atropisomeric forms. Atropisomers are stereoisomers resulting from hindered rotation about single bonds where the steric strain barrier to

rotation is high enough to allow for the isolation of the conformers. The compounds described herein (e.g., the compounds of the invention) may be prepared as individual isomers by either isomer-specific synthesis or resolved from an isomeric mixture. Conventional resolution techniques include forming the salt of a free base of each isomer of an isomeric pair using an optically active acid (followed by fractional crystallization and regeneration of the free base), forming the salt of the acid form of each isomer of an isomeric pair using an optically active amine (followed by fractional crystallization and regeneration of the free acid), forming an ester or amide of each of the isomers of an isomeric pair using an optically pure acid, amine or alcohol (followed by chromatographic separation and removal of the chiral auxiliary), or resolving an isomeric mixture of either a starting material or a final product using various well known chromatographic methods. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by weight relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by weight optically pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by weight pure. Percent optical purity is the ratio of the weight of the enantiomer or over the weight of the enantiomer plus the weight of its optical isomer. Diastereomeric purity by weight is the ratio of the weight of one diastereomer or over the weight of all the diastereomers. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by mole fraction pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by mole fraction pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by mole fraction pure. Percent purity by mole fraction is the ratio of the moles of the enantiomer or over the moles of the enantiomer plus the moles of its optical isomer. Similarly, percent purity by moles fraction is the ratio of the moles of the diastereomer or over the moles of the diastereomer plus the moles of its isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry, and the compound has at least one chiral center, it is to be understood that the name or structure encompasses either enantiomer of the compound free from the corresponding optical isomer, a racemic mixture of the compound, or mixtures enriched in one enantiomer relative to its corresponding optical isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry and has two or more chiral centers, it is to be understood that the name or structure encompasses a diastereomer free of other diastereomers, a number of diastereomers free from other diastereomeric pairs, mixtures of diastereomers, mixtures of diastereomeric pairs, mixtures of diastereomers in which one diastereomer is enriched relative to the other diastereomer(s), or mixtures of diastereomers in which one or more diastereomer is enriched relative to the other diastereomers. The invention embraces all of these forms.

Compounds of the present disclosure also include all of the isotopes of the atoms occurring in the intermediate or final compounds. "Isotopes" refers to atoms having the same atomic number but different mass numbers resulting from a different number of neutrons in the nuclei. For example, isotopes of hydrogen include tritium and deuterium.

Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. Exemplary isotopes that can be incorporated into compounds of the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I and ^{125}I. Isotopically-labeled compounds (e.g., those labeled with ^{3}H and ^{14}C) can be useful in compound or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes can be useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements). In some embodiments, one or more hydrogen atoms are replaced by ^{2}H or ^{3}H, or one or more carbon atoms are replaced by ^{13}C- or ^{14}C-enriched carbon. Positron emitting isotopes such as ^{15}O, ^{13}N, ^{11}C, and ^{18}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Preparations of isotopically labelled compounds are known to those of skill in the art. For example, isotopically labeled compounds can generally be prepared by following procedures analogous to those disclosed for compounds of the present invention described herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

As is known in the art, many chemical entities can adopt a variety of different solid forms such as, for example, amorphous forms or crystalline forms (e.g., polymorphs, hydrates, solvate). In some embodiments, compounds of the present invention may be utilized in any such form, including in any solid form. In some embodiments, compounds described or depicted herein may be provided or utilized in hydrate or solvate form.

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

Definitions

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

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

As used herein, the term "administration" refers to the administration of a composition (e.g., a compound or a preparation that includes a compound as described herein) to a subject or system. Administration to an animal subject (e.g., to a human) may be by any appropriate route. For example, in some embodiments, administration may be bronchial (including by bronchial instillation), buccal, enteral,

interdermal, intra-arterial, intradermal, intragastric, intramedullary, intramuscular, intranasal, intraperitoneal, intrathecal, intratumoral, intravenous, intraventricular, mucosal, nasal, oral, rectal, subcutaneous, sublingual, topical, tracheal (including by intratracheal instillation), transdermal, vaginal, and vitreal.

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

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

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

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

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

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

As used herein, the term "BRD9" refers to bromodomain-containing protein 9, a component of the BAF (BRG1- or BRM-associated factors) complex, a SWI/SNF ATPase chromatin remodeling complex, and belongs to family IV of the bromodomain-containing proteins. BRD9 is encoded by the *BRD9* gene, the nucleic acid sequence of which is set forth in SEQ ID NO: 1. The term "BRD9" also refers to natural variants of the wild-type BRD9 protein, such as proteins having at least 85% identity (e.g., 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.9% identity, or more) to the amino acid sequence of wild-type BRD9, which is set forth in SEQ ID NO: 2.

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

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

A "compound of the present invention" and similar terms as used herein, whether explicitly noted or not, refers to compounds useful for treating BAF-related disorders (e.g., cancer or infection) described herein, including, e.g., compounds of **Formula I** (e.g., compounds of Table 1A, Table 1B, and Table 1D) and compounds of Table 1C and 1E, as well as salts (e.g., pharmaceutically acceptable salts), solvates, hydrates, stereoisomers (including atropisomers), and tautomers thereof. Those skilled in the art will appreciate that certain compounds described herein can exist in one or more different isomeric (e.g., stereoisomers, geometric isomers, atropisomers, and tautomers) or isotopic (e.g., in which one or more

atoms has been substituted with a different isotope of the atom, such as hydrogen substituted for deuterium) forms. Unless otherwise indicated or clear from context, a depicted structure can be understood to represent any such isomeric or isotopic form, individually or in combination. Compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present disclosure that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present disclosure. Cis and trans geometric isomers of the compounds of the present disclosure are described and may be isolated as a mixture of isomers or as separated isomeric forms. In some embodiments, one or more compounds depicted herein may exist in different tautomeric forms. As will be clear from context, unless explicitly excluded, references to such compounds encompass all such tautomeric forms. In some embodiments, tautomeric forms result from the swapping of a single bond with an adjacent double bond and the concomitant migration of a proton. In certain embodiments, a tautomeric form may be a prototropic tautomer, which is an isomeric protonation states having the same empirical formula and total charge as a reference form. Examples of moieties with prototropic tautomeric forms are ketone - enol pairs, amide - imidic acid pairs, lactam - lactim pairs, amide - imidic acid pairs, enamine - imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, such as, 1H- and 3H-imidazole, 1H-, 2H- and 4H-1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. In some embodiments, tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. In certain embodiments, tautomeric forms result from acetal interconversion.

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

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

By “determining the level of a protein” is meant the detection of a protein, or an mRNA encoding the protein, by methods known in the art either directly or indirectly. “Directly determining” means performing a process (e.g., performing an assay or test on a sample or “analyzing a sample” as that term is defined herein) to obtain the physical entity or value. “Indirectly determining” refers to receiving the physical entity or value from another party or source (e.g., a third-party laboratory that directly acquired the physical entity or value). Methods to measure protein level generally include, but are not limited to, western blotting, immunoblotting, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), immunoprecipitation, immunofluorescence, surface plasmon resonance, chemiluminescence, fluorescent polarization, phosphorescence, immunohistochemical analysis, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, liquid chromatography (LC)-mass spectrometry, microcytometry, microscopy, fluorescence activated cell sorting (FACS), and flow

cytometry, as well as assays based on a property of a protein including, but not limited to, enzymatic activity or interaction with other protein partners. Methods to measure mRNA levels are known in the art.

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

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

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

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

about 10-fold, about 15-fold, about 20-fold, about 30-fold, about 40-fold, about 50-fold, about 100-fold, about 1000-fold, or more). A level of a protein may be expressed in mass/vol (e.g., g/dL, mg/mL, µg/mL, ng/mL) or percentage relative to total protein or mRNA in a sample.

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

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

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

100 multiplied by (the fraction X/Y)

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

A "pharmaceutically acceptable excipient," as used herein, refers any ingredient other than the compounds described herein (for example, a vehicle capable of suspending or dissolving the active compound) and having the properties of being substantially nontoxic and non-inflammatory in a patient. Excipients may include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors,

fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspensing or dispersing agents, sweeteners, and waters of hydration. Exemplary excipients include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

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

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

The term "pharmaceutical composition," as used herein, represents a composition containing a compound described herein formulated with a pharmaceutically acceptable excipient, and manufactured or sold with the approval of a governmental regulatory agency as part of a therapeutic regimen for the

treatment of disease in a mammal. Pharmaceutical compositions can be formulated, for example, for oral administration in unit dosage form (e.g., a tablet, capsule, caplet, gelcap, or syrup); for topical administration (e.g., as a cream, gel, lotion, or ointment); for intravenous administration (e.g., as a sterile solution free of particulate emboli and in a solvent system suitable for intravenous use); or in any other pharmaceutically acceptable formulation.

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

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

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

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

The term "shRNA", as used herein, refers to an RNA agent having a stem-loop structure, comprising a first and second region of complementary sequence, the degree of complementarity and

orientation of the regions being sufficient such that base pairing occurs between the regions, the first and second regions being joined by a loop region, the loop resulting from a lack of base pairing between nucleotides (or nucleotide analogs) within the loop region.

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

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

As used herein, the terms "treat," "treated," or "treating" mean both therapeutic treatment and prophylactic or preventative measures wherein the object is to prevent or slow down (lessen) an undesired physiological condition, disorder, or disease, or obtain beneficial or desired clinical results. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of a condition, disorder, or disease; stabilized (i.e., not worsening) state of condition, disorder, or disease; delay in onset or slowing of condition, disorder, or disease progression; amelioration of the condition, disorder, or disease state or remission (whether partial or total), whether detectable or undetectable; an amelioration of at least one measurable physical parameter, not necessarily discernible by the patient; or enhancement or improvement of condition, disorder, or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment.

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

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

Brief Description of the Drawings

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Detailed Description

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

Compounds

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

Formula I is

A-L-B

Formula I,

where

A is a BRD9 binding moiety;

B is a degradation moiety; and

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

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

Formula II

wherein

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

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

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

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

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

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

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

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

Pharmaceutical Uses

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

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

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

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

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

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

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

Combination Therapies

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

In some embodiments, the second therapeutic agent is a chemotherapeutic agent (e.g., a cytotoxic agent or other chemical compound useful in the treatment of cancer). These include alkylating

agents, antimetabolites, folic acid analogs, pyrimidine analogs, purine analogs and related inhibitors, vinca alkaloids, epipodopyyllotoxins, antibiotics, L-Asparaginase, topoisomerase inhibitors, interferons, platinum coordination complexes, anthracenedione substituted urea, methyl hydrazine derivatives, adrenocortical suppressant, adrenocorticosteroides, progestins, estrogens, antiestrogen, androgens, antiandrogen, and gonadotropin-releasing hormone analog. Also included is 5-fluorouracil (5-FU), leucovorin (LV), irenotecan, oxaliplatin, capecitabine, paclitaxel, and doxetaxel. Non-limiting examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethiylenethiophosphoramide and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin gammall and calicheamicin omegall (see, e.g., *Agnew, Chem. Intl. Ed Engl.* 33:183-186 (1994)); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antiobiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, ADRIAMYCIN® (doxorubicin, including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5- FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine;

mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, e.g., TAXOL® (paclitaxel; Bristol-Myers Squibb Oncology, Princeton, NJ), ABRAXANE®, cremophor-free, albumin-engineered nanoparticle formulation of paclitaxel (American Pharmaceutical Partners, Schaumberg, IL), and TAXOTERE® doxetaxel (Rhone-Poulenc Rorer, Antony, France); chloranbucil; GEMZAR® gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum coordination complexes such as cisplatin, oxaliplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; NAVELBINE® vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; irinotecan (e.g., CPT-11); topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Two or more chemotherapeutic agents can be used in a cocktail to be administered in combination with the first therapeutic agent described herein. Suitable dosing regimens of combination chemotherapies are known in the art and described in, for example, Saltz et al., *Proc. Am. Soc. Clin. Oncol.* 18:233a (1999), and Douillard et al., *Lancet* 355(9209):1041-1047 (2000).

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

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

The second agent may be a checkpoint inhibitor. In one embodiment, the inhibitor of checkpoint is an inhibitory antibody (e.g., a monospecific antibody such as a monoclonal antibody). The antibody may be, e.g., humanized or fully human. In some embodiments, the inhibitor of checkpoint is a fusion protein, e.g., an Fc-receptor fusion protein. In some embodiments, the inhibitor of checkpoint is an agent, such as an antibody, that interacts with a checkpoint protein. In some embodiments, the inhibitor of checkpoint is an agent, such as an antibody, that interacts with the ligand of a checkpoint protein. In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or small

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

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

In any of the combination embodiments described herein, the first and second therapeutic agents are administered simultaneously or sequentially, in either order. The first therapeutic agent may be administered immediately, up to 1 hour, up to 2 hours, up to 3 hours, up to 4 hours, up to 5 hours, up to 6 hours, up to 7 hours, up to, 8 hours, up to 9 hours, up to 10 hours, up to 11 hours, up to 12 hours, up to 13 hours, 14 hours, up to hours 16, up to 17 hours, up 18 hours, up to 19 hours up to 20 hours, up to 21 hours, up to 22 hours, up to 23 hours up to 24 hours or up to 1-7, 1-14, 1-21 or 1-30 days before or after the second therapeutic agent.

Pharmaceutical Compositions

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

The compounds described herein may be used in the form of the free base, in the form of salts, solvates, and as prodrugs. All forms are within the methods described herein. In accordance with the methods of the invention, the described compounds or salts, solvates, or prodrugs thereof may be administered to a patient in a variety of forms depending on the selected route of administration, as will

be understood by those skilled in the art. The compounds described herein may be administered, for example, by oral, parenteral, buccal, sublingual, nasal, rectal, patch, pump, intratumoral, or transdermal administration and the pharmaceutical compositions formulated accordingly. Parenteral administration includes intravenous, intraperitoneal, subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary, intrathecal, rectal, and topical modes of administration. Parenteral administration may be by continuous infusion over a selected period of time.

A compound described herein may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, a compound described herein may be incorporated with an excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, and wafers. A compound described herein may also be administered parenterally. Solutions of a compound described herein can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, DMSO, and mixtures thereof with or without alcohol, and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington's Pharmaceutical Sciences (2012, 22nd ed.) and in The United States Pharmacopeia: The National Formulary (USP 41 NF36), published in 2018. The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that may be easily administered via syringe. Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels, and powders. Aerosol formulations typically include a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomizing device. Alternatively, the sealed container may be a unitary dispensing device, such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal after use. Where the dosage form includes an aerosol dispenser, it will contain a propellant, which can be a compressed gas, such as compressed air or an organic propellant, such as fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomizer. Compositions suitable for buccal or sublingual administration include tablets, lozenges, and pastilles, where the active ingredient is formulated with a carrier, such as sugar, acacia, tragacanth, gelatin, and glycerine. Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base, such as cocoa butter. A compound described herein may be administered intratumorally, for example, as an intratumoral injection. Intratumoral injection is injection directly into the tumor vasculature and is specifically contemplated for discrete, solid, accessible tumors. Local, regional, or systemic administration also may be appropriate. A compound described herein may advantageously be contacted by administering an injection or multiple injections to the tumor, spaced for example, at approximately, 1 cm intervals. In the case of surgical intervention, the present invention may be used preoperatively, such as to render an inoperable tumor

subject to resection. Continuous administration also may be applied where appropriate, for example, by implanting a catheter into a tumor or into tumor vasculature.

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

Dosages

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

Alternatively, the dosage amount can be calculated using the body weight of the patient. For example, the dose of a compound, or pharmaceutical composition thereof, administered to a patient may range from 0.1-100 mg/kg (e.g., 0.1-50 mg/kg (e.g., 0.25-25 mg/kg)). In exemplary, non-limiting embodiments, the dose may range from 0.5-5.0 mg/kg (e.g., 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, or 5.0 mg/kg) or from 5.0-20 mg/kg (e.g., 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mg/kg).

Kits

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

Examples

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

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

Procedure: To perform high density sgRNA tiling screen, an sgRNA library against BAF complex subunits was custom synthesized at Cellecta (Mountain View, CA). Sequences of DNA encoding the

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

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

Table 2: BRD9 sgRNA Library

SEQ ID NO	Nucleic Acid Sequence		SEQ ID NO	Nucleic Acid Sequence
203	CAAGAAGCACAAGAAGCACA		319	GCTCTACAGCGTGGTCAACA
204	CTTGTGCTTCTTGCCCATGG		320	CGGGAGCCTGCTCTACAGCG
205	CTTCTTGTGCTTCTTGCCCA		321	CGTGGTCAACACGGCCGAGC
206	ACAAGAAGCACAAGGCCGAG		322	CCCACCATCAGCGTCCGGCT
207	CTCGTAGGACGAGCGCCACT		323	ACGGCCGAGCCGGACGCTGA
208	CGAGTGGCGCTCGTCCTACG		324	GGGCACCCACCATCAGCGTC
209	GAGTGGCGCTCGTCCTACGA		325	GCCGAGCCGGACGCTGATGG
210	AGGCTTCTCCAGGGGCTTGT		326	CCATGTCCGTGTTGCAGAGG
211	AGATTATGCCGACAAGCCCC		327	CCGAGCCGGACGCTGATGGT
212	ACCTTCAGGACTAGCTTTAG		328	CGAGCTCAAGTCCACCGGGT
213	AGCTTTAGAGGCTTCTCCAG		329	GCGAGCTCAAGTCCACCGGG
214	CTAGCTTTAGAGGCTTCTCC		330	AGAGCGAGCTCAAGTCCACC
215	TAGCTTTAGAGGCTTCTCCA		331	GAGAGCGAGCTCAAGTCCAC
216	CTAAAGCTAGTCCTGAAGGT		332	GAAGCCTGGGAGTAGCTTAC
217	GCCTCTAAAGCTAGTCCTGA		333	CTCTCCAGTAAGCTACTCCC
218	CTTCACTTCCTCCGACCTTC		334	AGCCCAGCGTGGTGAAGCCT
219	AAGCTAGTCCTGAAGGTCGG		335	AAGCCCAGCGTGGTGAAGCC
220	AGTGAAGTGACTGAACTCTC		336	ACTCCCAGGCTTCACCACGC

SEQ ID NO	Nucleic Acid Sequence		SEQ ID NO	Nucleic Acid Sequence
221	GTGACTGAACTCTCAGGATC		337	CTCCCAGGCTTCACCACGCT
222	ATAGTAACTGGAGTCGTGGC		338	CTCGTCTTTGAAGCCCAGCG
223	CATCATAGTAACTGGAGTCG		339	CACTGGAGAGAAAGGTGACT
224	TGACCTGTCATCATAGTAAC		340	GCACTGGAGAGAAAGGTGAC
225	ACTCCAGTTACTATGATGAC		341	AGTAGTGGCACTGGAGAGAA
226	CTTTGTGCCTCTCTCGCTCA		342	CGAAAGCGCAGTAGTGGCAC
227	GGTCAGACCATGAGCGAGAG		343	CTGCATCGAAAGCGCAGTAG
228	GAAGAAGAAGAAGTCCGAGA		344	ATGCAGAATAATTCAGTATT
229	GTCCAGATGCTTCTCCTTCT		345	AGTATTTGGCGACTTGAAGT
230	GTCCGAGAAGGAGAAGCATC		346	CGACTTGAAGTCGGACGAGA
231	GGAGAAGCATCTGGACGATG		347	GAGCTGCTCTACTCAGCCTA
232	TGAGGAAAGAAGGAAGCGAA		348	CACGCCTGTCTCATCTCCGT
233	ATCTGGACGATGAGGAAAGA		349	TCAGCCTACGGAGATGAGAC
234	AGAAGAAGCGGAAGCGAGAG		350	CAGGCGTGCAGTGTGCGCTG
235	GAAGAAGCGGAAGCGAGAGA		351	CCGCGGCCCCTCTAGCCTGC
236	CCGCCCAGGAAGAGAAGAAG		352	CATCCTTCACAAACTCCTGC
237	AGAGAGGGAGCACTGTGACA		353	TAGCCTGCAGGAGTTTGTGA
238	AGGGAGCACTGTGACACGGA		354	CAGGAGTTTGTGAAGGATGC
239	GAGGGAGCACTGTGACACGG		355	AGGAGTTTGTGAAGGATGCT
240	GCACTGTGACACGGAGGGAG		356	TGGGAGCTACAGCAAGAAAG
241	GAGGCTGACGACTTTGATCC		357	GAGCTACAGCAAGAAAGTGG
242	AGGCTGACGACTTTGATCCT		358	GAAAGTGGTGGACGACCTCC
243	TCCACCTCCACCTTCTTCCC		359	CGCCTGTGATCTGGTCCAGG
244	CGACTTTGATCCTGGGAAGA		360	CTCCGCCTGTGATCTGGTCC
245	CTTTGATCCTGGGAAGAAGG		361	GACCTCCTGGACCAGATCAC
246	TGATCCTGGGAAGAAGGTGG		362	CTCCTGGACCAGATCACAGG
247	TCCTGGGAAGAAGGTGGAGG		363	GCTGGAAGAGCGTCCTAGAG
248	CGGACTGGCCGATCTGGGGG		364	TGCAGCCCACCTGCTTCAGC
249	ACGCTCGGACTGGCCGATCT		365	GACGCTCTTCCAGCTGAAGC
250	AGGTGGAGCCGCCCCCAGAT		366	CTCTTCCAGCTGAAGCAGGT
251	CGCTCGGACTGGCCGATCTG		367	GCTCTTCCAGCTGAAGCAGG
252	GCTCGGACTGGCCGATCTGG		368	CCTCCAGATGAAGCCAAGGT
253	CACGCTCGGACTGGCCGATC		369	GCTTCATCTGGAGGCTTCAT
254	TGTGTCCGGCACGCTCGGAC		370	GGCTTCATCTGGAGGCTTCA
255	CTGGCTGTGTCCGGCACGCT		371	CTTACCTTGGCTTCATCTGG
256	ATCGGCCAGTCCGAGCGTGC		372	AAACTTACCTTGGCTTCATC

SEQ ID NO	Nucleic Acid Sequence		SEQ ID NO	Nucleic Acid Sequence
257	CACCCTTGCCTGGCTGTGTC		373	GAAGCCTCCAGATGAAGCCA
258	CGAGCGTGCCGGACACAGCC		374	TCCTAGGGTGTCCCCAACCT
259	TGTTCCAGGAGTTGCTGAAT		375	CCTAGGGTGTCCCCAACCTG
260	CACACCTATTCAGCAACTCC		376	GTGTCTGTCTCCACAGGTTG
261	GCTGGCGGAGGAAGTGTTCC		377	TGTGTCTGTCTCCACAGGTT
262	TTTACCTCTGAAGCTGGCGG		378	CCACAGGTTGGGGACACCCT
263	CCCCGGTTTACCTCTGAAGC		379	AGAGCTGCTGCTGTCTCCTA
264	ACTTCCTCCGCCAGCTTCAG		380	CAGAGCTGCTGCTGTCTCCT
265	CAGGAAAAGCAAAAAATCCA		381	AGACAGCAGCAGCTCTGTTC
266	GCTTTCAGAAAAGATCCCCA		382	ATCCACAGAAACGTCGGGAT
267	AGGAAAAGCAAAAAATCCAT		383	GAGATATCCACAGAAACGTC
268	GGAAAAGCAAAAAATCCATG		384	GGAGATATCCACAGAAACGT
269	GGAGCAATTGCATCCGTGAC		385	GTCCTATCCCGACGTTTCTG
270	GTCACGGATGCAATTGCTCC		386	TCTCCATGCTCAGCTCTCTG
271	TTTATTATCATTGAATATCC		387	CTCACCCAGAGAGCTGAGCA
272	AATGATAATAAAACATCCCA		388	ATCTCCATGCTCAGCTCTCT
273	ATAAAACATCCCATGGATTT		389	TATCTCCATGCTCAGCTCTC
274	TTCATGGTGCCAAAATCCAT		390	ATGTCCTGTTTACACAGGGA
275	TTTCATGGTGCCAAAATCCA		391	TTACACAGGGAAGGTGAAGA
276	TAATGAATACAAGTCAGTTA		392	AGTTCAAATGGCTGTCGTCA
277	CAAGTCAGTTACGGAATTTA		393	TGACGACAGCCATTTGAACT
278	ATAATGCAATGACATACAAT		394	AAGTTCAAATGGCTGTCGTC
279	AACTTGTAGTACACGGTATC		395	TCGTCTCATCCAAGTTCAAA
280	CTTCGCCAACTTGTAGTACA		396	TGAGACGACGAAGCTCCTGC
281	AGATACCGTGTACTACAAGT		397	GTGCTTCGTGCAGGTCCTGC
282	GCGAAGAAGATCCTTCACGC		398	GCAGGACCTGCACGAAGCAC
283	TCATCTTAAAGCCTGCGTGA		399	GCTCCGCCTGTGCTTCGTGC
284	TTCTCAGCAGGCAGCTCTTT		400	GGACCTGCACGAAGCACAGG
285	CAATGAAGATACAGCTGTTG		401	CACGAAGCACAGGCGGAGCG
286	ACTGGTACAACTTCAGGGAC		402	AGGCGGAGCGCGGCGGCTCT
287	CTTGTACTGGTACAACTTCA		403	AGGGAGCTGAGGTTGGACGA
288	ACTTGTACTGGTACAACTTC		404	GTTGGACAGGGAGCTGAGGT
289	TTGGCAGTTTCTACTTGTAC		405	AGGCGTTGGACAGGGAGCTG
290	TACCTGATAACTTCTCTACT		406	CCCTCTCGGAGGCGTTGGAC
291	AGCCGAGTAGAGAAGTTATC		407	CCTCTCGGAGGCGTTGGACA
292	AGCTGCATGTTTGAGCCTGA		408	CTGGTCCCTCTCGGAGGCGT

SEQ ID NO	Nucleic Acid Sequence		SEQ ID NO	Nucleic Acid Sequence
293	GCTGCATGTTTGAGCCTGAA		409	CCCTGTCCAACGCCTCCGAG
294	AAGCTGCAGGCATTCCCTTC		410	CCTGTCCAACGCCTCCGAGA
295	GGTACTGTCCGTCAAGCTGC		411	GTGGTGCTGGTCCCTCTCGG
296	AGGGAATGCCTGCAGCTTGA		412	CAGGTGGTGCTGGTCCCTCT
297	CTTGACGGACAGTACCGCAG		413	GCATCTCACCCAGGTGGTGC
298	CGCCAGCACGTGCTCCTCTG		414	CGAGAGGGACCAGCACCACC
299	TACCGCAGAGGAGCACGTGC		415	GAGAGGGACCAGCACCACCT
300	AGAGGAGCACGTGCTGGCGC		416	GTGGGGGCATCTCACCCAGG
301	GGAGCACGTGCTGGCGCTGG		417	CCCCGACACTCAGGCGAGAA
302	AGCACGCAGCTGACGAAGCT		418	TCCCCGACACTCAGGCGAGA
303	GCACGCAGCTGACGAAGCTC		419	AGCCCTTCTCGCCTGAGTGT
304	CAGCTGACGAAGCTCGGGAC		420	CTGGCTGCTCCCCGACACTC
305	AAGCTCGGGACAGGATCAAC		421	CCCTTCTCGCCTGAGTGTCG
306	CCTTGCCGCCTGGGAGGAAC		422	GCCCTTCTCGCCTGAGTGTC
307	AGGATCAACCGGTTCCTCCC		423	TAGGGGTCGTGGGTGACGTC
308	ATCAACCGGTTCCTCCCAGG		424	AAGAAACTCATAGGGGTCGT
309	GCACTACCTTGCCGCCTGGG		425	GAAGAAACTCATAGGGGTCG
310	AGAGCACTACCTTGCCGCCT		426	GAGACTGAAGAAACTCATAG
311	CCGGTTCCTCCCAGGCGGCA		427	GGAGACTGAAGAAACTCATA
312	TCCTCTTCAGATAGCCCATC		428	TGGAGACTGAAGAAACTCAT
313	ATGGGCTATCTGAAGAGGAA		429	TCTTCAGTCTCCAGAGCCTG
314	GGGCTATCTGAAGAGGAACG		430	TTGGCAGAGGCCGCAGGCTC
315	TGGGCTATCTGAAGAGGAAC		431	TAGGTCTTGGCAGAGGCCGC
316	TATCTGAAGAGGAACGGGGA		432	CTAGAGTTAGGTCTTGGCAG
317	ATCTGAAGAGGAACGGGGAC		433	GGTGGTCTAGAGTTAGGTCT
318	TGTTGACCACGCTGTAGAGC			

Table 3: Control sgRNA Library

SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
434	1|sg_Non_Targeting_Human_0001|Non_Targeting_Human	Non_Targeting_Human	GTAGCGAACGTGTCCGGCGT
435	1|sg_Non_Targeting_Human_0002|Non_Targeting_Human	Non_Targeting_Human	GACCGGAACGATCTCGCGTA
436	1|sg_Non_Targeting_Human_0003|Non_Targeting_Human	Non_Targeting_Human	GGCAGTCGTTCGGTTGATAT

SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
437	1|sg_Non_Targeting_Human_0004|Non_Targeting_Human	Non_Targeting_Human	GCTTGAGCACATACGCGAAT
438	1|sg_Non_Targeting_Human_0005|Non_Targeting_Human	Non_Targeting_Human	GTGGTAGAATAACGTATTAC
439	1|sg_Non_Targeting_Human_0006|Non_Targeting_Human	Non_Targeting_Human	GTCATACATGGATAAGGCTA
440	1|sg_Non_Targeting_Human_0007|Non_Targeting_Human	Non_Targeting_Human	GATACACGAAGCATCACTAG
441	1|sg_Non_Targeting_Human_0008|Non_Targeting_Human	Non_Targeting_Human	GAACGTTGGCACTACTTCAC
442	1|sg_Non_Targeting_Human_0009|Non_Targeting_Human	Non_Targeting_Human	GATCCATGTAATGCGTTCGA
443	1|sg_Non_Targeting_Human_0010|Non_Targeting_Human	Non_Targeting_Human	GTCGTGAAGTGCATTCGATC
444	1|sg_Non_Targeting_Human_0011|Non_Targeting_Human	Non_Targeting_Human	GTTCGACTCGCGTGACCGTA
445	1|sg_Non_Targeting_Human_0012|Non_Targeting_Human	Non_Targeting_Human	GAATCTACCGCAGCGGTTCG
446	1|sg_Non_Targeting_Human_0013|Non_Targeting_Human	Non_Targeting_Human	GAAGTGACGTCGATTCGATA
447	1|sg_Non_Targeting_Human_0014|Non_Targeting_Human	Non_Targeting_Human	GCGGTGTATGACAACCGCCG
448	1|sg_Non_Targeting_Human_0015|Non_Targeting_Human	Non_Targeting_Human	GTACCGCGCCTGAAGTTCGC
449	1|sg_Non_Targeting_Human_0016|Non_Targeting_Human	Non_Targeting_Human	GCAGCTCGTGTGTCGTACTC
450	1|sg_Non_Targeting_Human_0017|Non_Targeting_Human	Non_Targeting_Human	GCGCCTTAAGAGTACTCATC
451	1|sg_Non_Targeting_Human_0018|Non_Targeting_Human	Non_Targeting_Human	GAGTGTCGTCGTTGCTCCTA
452	1|sg_Non_Targeting_Human_0019|Non_Targeting_Human	Non_Targeting_Human	GCAGCTCGACCTCAAGCCGT
453	1|sg_Non_Targeting_Human_0020|Non_Targeting_Human	Non_Targeting_Human	GTATCCTGACCTACGCGCTG
454	1|sg_Non_Targeting_Human_0021|Non_Targeting_Human	Non_Targeting_Human	GTGTATCTCAGCACGCTAAC

SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
455	1|sg_Non_Targeting_Human_0022|Non_Targeting_Human	Non_Targeting_Human	GTCGTCATACAACGGCAACG
456	1|sg_Non_Targeting_Human_0023|Non_Targeting_Human	Non_Targeting_Human	GTCGTGCGCTTCCGGCGGTA
457	1|sg_Non_Targeting_Human_0024|Non_Targeting_Human	Non_Targeting_Human	GCGGTCCTCAGTAAGCGCGT
458	1|sg_Non_Targeting_Human_0025|Non_Targeting_Human	Non_Targeting_Human	GCTCTGCTGCGGAAGGATTC
459	1|sg_Non_Targeting_Human_0026|Non_Targeting_Human	Non_Targeting_Human	GCATGGAGGAGCGTCGCAGA
460	1|sg_Non_Targeting_Human_0027|Non_Targeting_Human	Non_Targeting_Human	GTAGCGCGCGTAGGAGTGGC
461	1|sg_Non_Targeting_Human_0028|Non_Targeting_Human	Non_Targeting_Human	GATCACCTGCATTCGTACAC
462	1|sg_Non_Targeting_Human_0029|Non_Targeting_Human	Non_Targeting_Human	GCACACCTAGATATCGAATG
463	1|sg_Non_Targeting_Human_0030|Non_Targeting_Human	Non_Targeting_Human	GTTGATCAACGCGCTTCGCG
464	1|sg_Non_Targeting_Human_0031|Non_Targeting_Human	Non_Targeting_Human	GCGTCTCACTCACTCCATCG
465	1|sg_Non_Targeting_Human_0032|Non_Targeting_Human	Non_Targeting_Human	GCCGACCAACGTCAGCGGTA
466	1|sg_Non_Targeting_Human_0033|Non_Targeting_Human	Non_Targeting_Human	GGATACGGTGCGTCAATCTA
467	1|sg_Non_Targeting_Human_0034|Non_Targeting_Human	Non_Targeting_Human	GAATCCAGTGGCGGCGACAA
468	1|sg_Non_Targeting_Human_0035|Non_Targeting_Human	Non_Targeting_Human	GCACTGTCAGTGCAACGATA
469	1|sg_Non_Targeting_Human_0036|Non_Targeting_Human	Non_Targeting_Human	GCGATCCTCAAGTATGCTCA
470	1|sg_Non_Targeting_Human_0037|Non_Targeting_Human	Non_Targeting_Human	GCTAATATCGACACGGCCGC
471	1|sg_Non_Targeting_Human_0038|Non_Targeting_Human	Non_Targeting_Human	GGAGATGCATCGAAGTCGAT
472	1|sg_Non_Targeting_Human_0039|Non_Targeting_Human	Non_Targeting_Human	GGATGCACTCCATCTCGTCT

SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
473	1|sg_Non_Targeting_Human_0040|Non_Targeting_Human	Non_Targeting_Human	GTGCCGAGTAATAACGCGAG
474	1|sg_Non_Targeting_Human_0041|Non_Targeting_Human	Non_Targeting_Human	GAGATTCCGATGTAACGTAC
475	1|sg_Non_Targeting_Human_0042|Non_Targeting_Human	Non_Targeting_Human	GTCGTCACGAGCAGGATTGC
476	1|sg_Non_Targeting_Human_0043|Non_Targeting_Human	Non_Targeting_Human	GCGTTAGTCACTTAGCTCGA
477	1|sg_Non_Targeting_Human_0044|Non_Targeting_Human	Non_Targeting_Human	GTTCACACGGTGTCGGATAG
478	1|sg_Non_Targeting_Human_0045|Non_Targeting_Human	Non_Targeting_Human	GGATAGGTGACCTTAGTACG
479	1|sg_Non_Targeting_Human_0046|Non_Targeting_Human	Non_Targeting_Human	GTATGAGTCAAGCTAATGCG
480	1|sg_Non_Targeting_Human_0047|Non_Targeting_Human	Non_Targeting_Human	GCAACTATTGGAATACGTGA
481	1|sg_Non_Targeting_Human_0048|Non_Targeting_Human	Non_Targeting_Human	GTTACCTTCGCTCGTCTATA
482	1|sg_Non_Targeting_Human_0049|Non_Targeting_Human	Non_Targeting_Human	GTACCGAGCACCACAGGCCG
483	1|sg_Non_Targeting_Human_0050|Non_Targeting_Human	Non_Targeting_Human	GTCAGCCATCGGATAGAGAT
484	1|sg_Non_Targeting_Human_0051|Non_Targeting_Human	Non_Targeting_Human	GTACGGCACTCCTAGCCGCT
485	1|sg_Non_Targeting_Human_0052|Non_Targeting_Human	Non_Targeting_Human	GGTCCTGTCGTATGCTTGCA
486	1|sg_Non_Targeting_Human_0053|Non_Targeting_Human	Non_Targeting_Human	GCCGCAATATATGCGGTAAG
487	1|sg_Non_Targeting_Human_0054|Non_Targeting_Human	Non_Targeting_Human	GCGCACGTATAATCCTGCGT
488	1|sg_Non_Targeting_Human_0055|Non_Targeting_Human	Non_Targeting_Human	GTGCACAACACGATCCACGA
489	1|sg_Non_Targeting_Human_0056|Non_Targeting_Human	Non_Targeting_Human	GCACAATGTTGACGTAAGTG
490	1|sg_Non_Targeting_Human_0057|Non_Targeting_Human	Non_Targeting_Human	GTAAGATGCTGCTCACCGTG

SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
491	1|sg_Non_Targeting_Human_0058|Non_Targeting_Human	Non_Targeting_Human	GTCGGTGATCCAACGTATCG
492	1|sg_Non_Targeting_Human_0059|Non_Targeting_Human	Non_Targeting_Human	GAGCTAGTAGGACGCAAGAC
493	1|sg_Non_Targeting_Human_0060|Non_Targeting_Human	Non_Targeting_Human	GTACGTGGAAGCTTGTGGCC
494	1|sg_Non_Targeting_Human_0061|Non_Targeting_Human	Non_Targeting_Human	GAGAACTGCCAGTTCTCGAT
495	1|sg_Non_Targeting_Human_0062|Non_Targeting_Human	Non_Targeting_Human	GCCATTCGGCGCGGCACTTC
496	1|sg_Non_Targeting_Human_0063|Non_Targeting_Human	Non_Targeting_Human	GCACACGACCAATCCGCTTC
497	1|sg_Non_Targeting_Human_0064|Non_Targeting_Human	Non_Targeting_Human	GAGGTGATCGATTAAGTACA
498	1|sg_Non_Targeting_Human_0065|Non_Targeting_Human	Non_Targeting_Human	GTCACTCGCAGACGCCTAAC
499	1|sg_Non_Targeting_Human_0066|Non_Targeting_Human	Non_Targeting_Human	GCGCTACGGAATCATACGTT
500	1|sg_Non_Targeting_Human_0067|Non_Targeting_Human	Non_Targeting_Human	GGTAGGACCTCACGGCGCGC
501	1|sg_Non_Targeting_Human_0068|Non_Targeting_Human	Non_Targeting_Human	GAACTGCATCTTGTTGTAGT
502	1|sg_Non_Targeting_Human_0069|Non_Targeting_Human	Non_Targeting_Human	GATCCTGATCCGGCGGCGCG
503	1|sg_Non_Targeting_Human_0070|Non_Targeting_Human	Non_Targeting_Human	GGTATGCGCGATCCTGAGTT
504	1|sg_Non_Targeting_Human_0071|Non_Targeting_Human	Non_Targeting_Human	GCGGAGCTAGAGAGCGGTCA
505	1|sg_Non_Targeting_Human_0072|Non_Targeting_Human	Non_Targeting_Human	GAATGGCAATTACGGCTGAT
506	1|sg_Non_Targeting_Human_0073|Non_Targeting_Human	Non_Targeting_Human	GTATGGTGAGTAGTCGCTTG
507	1|sg_Non_Targeting_Human_0074|Non_Targeting_Human	Non_Targeting_Human	GTGTAATTGCGTCTAGTCGG
508	1|sg_Non_Targeting_Human_0075|Non_Targeting_Human	Non_Targeting_Human	GGTCCTGGCGAGGAGCCTTG

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510	1|sg_Non_Targeting_Human_0077|Non_Targeting_Human	Non_Targeting_Human	GTCGGCGTTCTGTTGTGACT
511	1|sg_Non_Targeting_Human_0078|Non_Targeting_Human	Non_Targeting_Human	GAGGCAAGCCGTTAGGTGTA
512	1|sg_Non_Targeting_Human_0079|Non_Targeting_Human	Non_Targeting_Human	GCGGATCCAGATCTCATTCG
513	1|sg_Non_Targeting_Human_0080|Non_Targeting_Human	Non_Targeting_Human	GGAACATAGGAGCACGTAGT
514	1|sg_Non_Targeting_Human_0081|Non_Targeting_Human	Non_Targeting_Human	GTCATCATTATGGCGTAAGG
515	1|sg_Non_Targeting_Human_0082|Non_Targeting_Human	Non_Targeting_Human	GCGACTAGCGCCATGAGCGG
516	1|sg_Non_Targeting_Human_0083|Non_Targeting_Human	Non_Targeting_Human	GGCGAAGTTCGACATGACAC
517	1|sg_Non_Targeting_Human_0084|Non_Targeting_Human	Non_Targeting_Human	GCTGTCGTGTGGAGGCTATG
518	1|sg_Non_Targeting_Human_0085|Non_Targeting_Human	Non_Targeting_Human	GCGGAGAGCATTGACCTCAT
519	1|sg_Non_Targeting_Human_0086|Non_Targeting_Human	Non_Targeting_Human	GACTAATGGACCAAGTCAGT
520	1|sg_Non_Targeting_Human_0087|Non_Targeting_Human	Non_Targeting_Human	GCGGATTAGAGGTAATGCGG
521	1|sg_Non_Targeting_Human_0088|Non_Targeting_Human	Non_Targeting_Human	GCCGACGGCAATCAGTACGC
522	1|sg_Non_Targeting_Human_0089|Non_Targeting_Human	Non_Targeting_Human	GTAACCTCTCGAGCGATAGA
523	1|sg_Non_Targeting_Human_0090|Non_Targeting_Human	Non_Targeting_Human	GACTTGTATGTGGCTTACGG
524	1|sg_Non_Targeting_Human_0091|Non_Targeting_Human	Non_Targeting_Human	GTCACTGTGGTCGAACATGT
525	1|sg_Non_Targeting_Human_0092|Non_Targeting_Human	Non_Targeting_Human	GTACTCCAATCCGCGATGAC
526	1|sg_Non_Targeting_Human_0093|Non_Targeting_Human	Non_Targeting_Human	GCGTTGGCACGATGTTACGG

SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
527	1|sg_Non_Targeting_Human_0094|Non_Targeting_Human	Non_Targeting_Human	GAACCAGCCGGCTAGTATGA
528	1|sg_Non_Targeting_Human_0095|Non_Targeting_Human	Non_Targeting_Human	GTATACTAGCTAACCACACG
529	1|sg_Non_Targeting_Human_0096|Non_Targeting_Human	Non_Targeting_Human	GAATCGGAATAGTTGATTCG
530	1|sg_Non_Targeting_Human_0097|Non_Targeting_Human	Non_Targeting_Human	GAGCACTTGCATGAGGCGGT
531	1|sg_Non_Targeting_Human_0098|Non_Targeting_Human	Non_Targeting_Human	GAACGGCGATGAAGCCAGCC
532	1|sg_Non_Targeting_Human_0099|Non_Targeting_Human	Non_Targeting_Human	GCAACCGAGATGAGAGGTTC
533	1|sg_Non_Targeting_Human_0100|Non_Targeting_Human	Non_Targeting_Human	GCAAGATCAATATGCGTGAT
534	1|sg_Non_Targeting_Human_GA_0101|Non_Targeting_Human	Non_Targeting_Human	ACGGAGGCTAAGCGTCGCAA
535	1|sg_Non_Targeting_Human_GA_0102|Non_Targeting_Human	Non_Targeting_Human	CGCTTCCGCGGCCCGTTCAA
536	1|sg_Non_Targeting_Human_GA_0103|Non_Targeting_Human	Non_Targeting_Human	ATCGTTTCCGCTTAACGGCG
537	1|sg_Non_Targeting_Human_GA_0104|Non_Targeting_Human	Non_Targeting_Human	GTAGGCGCGCCGCTCTCTAC
538	1|sg_Non_Targeting_Human_GA_0105|Non_Targeting_Human	Non_Targeting_Human	CCATATCGGGGCGAGACATG
539	1|sg_Non_Targeting_Human_GA_0106|Non_Targeting_Human	Non_Targeting_Human	TACTAACGCCGCTCCTACAG
540	1|sg_Non_Targeting_Human_GA_0107|Non_Targeting_Human	Non_Targeting_Human	TGAGGATCATGTCGAGCGCC
541	1|sg_Non_Targeting_Human_GA_0108|Non_Targeting_Human	Non_Targeting_Human	GGGCCCGCATAGGATATCGC
542	1|sg_Non_Targeting_Human_GA_0109|Non_Targeting_Human	Non_Targeting_Human	TAGACAACCGCGGAGAATGC
543	1|sg_Non_Targeting_Human_GA_0110|Non_Targeting_Human	Non_Targeting_Human	ACGGGCGGCTATCGCTGACT
544	1|sg_Non_Targeting_Human_GA_0111|Non_Targeting_Human	Non_Targeting_Human	CGCGGAAATTTTACCGACGA

SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
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546	1|sg_Non_Targeting_Human_GA_0113|Non_Targeting_Human	Non_Targeting_Human	GCGTGCGTCCCGGGTTACCC
547	1|sg_Non_Targeting_Human_GA_0114|Non_Targeting_Human	Non_Targeting_Human	CGGAGTAACAAGCGGACGGA
548	1|sg_Non_Targeting_Human_GA_0115|Non_Targeting_Human	Non_Targeting_Human	CGAGTGTTATACGCACCGTT
549	1|sg_Non_Targeting_Human_GA_0116|Non_Targeting_Human	Non_Targeting_Human	CGACTAACCGGAAACTTTTT
550	1|sg_Non_Targeting_Human_GA_0117|Non_Targeting_Human	Non_Targeting_Human	CAACGGGTTCTCCCGGCTAC
551	1|sg_Non_Targeting_Human_GA_0118|Non_Targeting_Human	Non_Targeting_Human	CAGGAGTCGCCGATACGCGT
552	1|sg_Non_Targeting_Human_GA_0119|Non_Targeting_Human	Non_Targeting_Human	TTCACGTCGTCTCGCGACCA
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555	1|sg_Non_Targeting_Human_GA_0122|Non_Targeting_Human	Non_Targeting_Human	CGCTAGTACGCTCCTCTATA
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557	1|sg_Non_Targeting_Human_GA_0124|Non_Targeting_Human	Non_Targeting_Human	CTATCTCGAGTGGTAATGCG
558	1|sg_Non_Targeting_Human_GA_0125|Non_Targeting_Human	Non_Targeting_Human	AATCGACTCGAACTTCGTGT
559	1|sg_Non_Targeting_Human_GA_0126|Non_Targeting_Human	Non_Targeting_Human	CCCGATGGACTATACCGAAC
560	1|sg_Non_Targeting_Human_GA_0127|Non_Targeting_Human	Non_Targeting_Human	ACGTTCGAGTACGACCAGCT
561	1|sg_Non_Targeting_Human_GA_0128|Non_Targeting_Human	Non_Targeting_Human	CGCGACGACTCAACCTAGTC
562	1|sg_Non_Targeting_Human_GA_0129|Non_Targeting_Human	Non_Targeting_Human	GGTCACCGATCGAGAGCTAG

SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
563	1|sg_Non_Targeting_Human_GA_0130|Non_Targeting_Human	Non_Targeting_Human	CTCAACCGACCGTATGGTCA
564	1|sg_Non_Targeting_Human_GA_0131|Non_Targeting_Human	Non_Targeting_Human	CGTATTCGACTCTCAACGCG
565	1|sg_Non_Targeting_Human_GA_0132|Non_Targeting_Human	Non_Targeting_Human	CTAGCCGCCCAGATCGAGCC
566	1|sg_Non_Targeting_Human_GA_0133|Non_Targeting_Human	Non_Targeting_Human	GAATCGACCGACACTAATGT
567	1|sg_Non_Targeting_Human_GA_0134|Non_Targeting_Human	Non_Targeting_Human	ACTTCAGTTCGGCGTAGTCA
568	1|sg_Non_Targeting_Human_GA_0135|Non_Targeting_Human	Non_Targeting_Human	GTGCGATGTCGCTTCAACGT
569	1|sg_Non_Targeting_Human_GA_0136|Non_Targeting_Human	Non_Targeting_Human	CGCCTAATTTCCGGATCAAT
570	1|sg_Non_Targeting_Human_GA_0137|Non_Targeting_Human	Non_Targeting_Human	CGTGGCCGGAACCGTCATAG
571	1|sg_Non_Targeting_Human_GA_0138|Non_Targeting_Human	Non_Targeting_Human	ACCCTCCGAATCGTAACGGA
572	1|sg_Non_Targeting_Human_GA_0139|Non_Targeting_Human	Non_Targeting_Human	AAACGGTACGACAGCGTGTG
573	1|sg_Non_Targeting_Human_GA_0140|Non_Targeting_Human	Non_Targeting_Human	ACATAGTCGACGGCTCGATT
574	1|sg_Non_Targeting_Human_GA_0141|Non_Targeting_Human	Non_Targeting_Human	GATGGCGCTTCAGTCGTCGG
575	1|sg_Non_Targeting_Human_GA_0142|Non_Targeting_Human	Non_Targeting_Human	ATAATCCGGAAACGCTCGAC
576	1|sg_Non_Targeting_Human_GA_0143|Non_Targeting_Human	Non_Targeting_Human	CGCCGGGCTGACAATTAACG
577	1|sg_Non_Targeting_Human_GA_0144|Non_Targeting_Human	Non_Targeting_Human	CGTCGCCATATGCCGGTGGC
578	1|sg_Non_Targeting_Human_GA_0145|Non_Targeting_Human	Non_Targeting_Human	CGGGCCTATAACACCATCGA
579	1|sg_Non_Targeting_Human_GA_0146|Non_Targeting_Human	Non_Targeting_Human	CGCCGTTCCGAGATACTTGA
580	1|sg_Non_Targeting_Human_GA_0147|Non_Targeting_Human	Non_Targeting_Human	CGGGACGTCGCGAAAATGTA

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

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599	1|sg_Non_Targeting_Human_GA_0166|Non_Targeting_Human	Non_Targeting_Human	AGCTCGCCATGTCGGTTCTC
600	1|sg_Non_Targeting_Human_GA_0167|Non_Targeting_Human	Non_Targeting_Human	AACTAGCCCGAGCAGCTTCG
601	1|sg_Non_Targeting_Human_GA_0168|Non_Targeting_Human	Non_Targeting_Human	CGCAAGGTGTCGGTAACCCT
602	1|sg_Non_Targeting_Human_GA_0169|Non_Targeting_Human	Non_Targeting_Human	CTTCGACGCCATCGTGCTCA
603	1|sg_Non_Targeting_Human_GA_0170|Non_Targeting_Human	Non_Targeting_Human	TCCTGGATACCGCGTGGTTA
604	1|sg_Non_Targeting_Human_GA_0171|Non_Targeting_Human	Non_Targeting_Human	ATAGCCGCCGCTCATTACTT
605	1|sg_Non_Targeting_Human_GA_0172|Non_Targeting_Human	Non_Targeting_Human	GTCGTCCGGGATTACAAAAT
606	1|sg_Non_Targeting_Human_GA_0173|Non_Targeting_Human	Non_Targeting_Human	TAATGCTGCACACGCCGAAT
607	1|sg_Non_Targeting_Human_GA_0174|Non_Targeting_Human	Non_Targeting_Human	TATCGCTTCCGATTAGTCCG
608	1|sg_Non_Targeting_Human_GA_0175|Non_Targeting_Human	Non_Targeting_Human	GTACCATACCGCGTACCCTT
609	1|sg_Non_Targeting_Human_GA_0176|Non_Targeting_Human	Non_Targeting_Human	TAAGATCCGCGGGTGGCAAC
610	1|sg_Non_Targeting_Human_GA_0177|Non_Targeting_Human	Non_Targeting_Human	GTAGACGTCGTGAGCTTCAC
611	1|sg_Non_Targeting_Human_GA_0178|Non_Targeting_Human	Non_Targeting_Human	TCGCGGACATAGGGCTCTAA
612	1|sg_Non_Targeting_Human_GA_0179|Non_Targeting_Human	Non_Targeting_Human	AGCGCAGATAGCGCGTATCA
613	1|sg_Non_Targeting_Human_GA_0180|Non_Targeting_Human	Non_Targeting_Human	GTTCGCTTCGTAACGAGGAA
614	1|sg_Non_Targeting_Human_GA_0181|Non_Targeting_Human	Non_Targeting_Human	GACCCCCGATAACTTTTGAC
615	1|sg_Non_Targeting_Human_GA_0182|Non_Targeting_Human	Non_Targeting_Human	ACGTCCATACTGTCGGCTAC
616	1|sg_Non_Targeting_Human_GA_0183|Non_Targeting_Human	Non_Targeting_Human	GTACCATTGCCGGCTCCCTA

SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
617	1|sg_Non_Targeting_Human_GA_0184|Non_Targeting_Human	Non_Targeting_Human	TGGTTCCGTAGGTCGGTATA
618	1|sg_Non_Targeting_Human_GA_0185|Non_Targeting_Human	Non_Targeting_Human	TCTGGCTTGACACGACCGTT
619	1|sg_Non_Targeting_Human_GA_0186|Non_Targeting_Human	Non_Targeting_Human	CGCTAGGTCCGGTAAGTGCG
620	1|sg_Non_Targeting_Human_GA_0187|Non_Targeting_Human	Non_Targeting_Human	AGCACGTAATGTCCGTGGAT
621	1|sg_Non_Targeting_Human_GA_0188|Non_Targeting_Human	Non_Targeting_Human	AAGGCGCGCGAATGTGGCAG
622	1|sg_Non_Targeting_Human_GA_0189|Non_Targeting_Human	Non_Targeting_Human	ACTGCGGAGCGCCCAATATC
623	1|sg_Non_Targeting_Human_GA_0190|Non_Targeting_Human	Non_Targeting_Human	CGTCGAGTGCTCGAACTCCA
624	1|sg_Non_Targeting_Human_GA_0191|Non_Targeting_Human	Non_Targeting_Human	TCGCAGCGGCGTGGGATCGG
625	1|sg_Non_Targeting_Human_GA_0192|Non_Targeting_Human	Non_Targeting_Human	ATCTGTCCTAATTCGGATCG
626	1|sg_Non_Targeting_Human_GA_0193|Non_Targeting_Human	Non_Targeting_Human	TGCGGCGTAATGCTTGAAAG
627	1|sg_Non_Targeting_Human_GA_0194|Non_Targeting_Human	Non_Targeting_Human	CGAACTTAATCCCGTGGCAA
628	1|sg_Non_Targeting_Human_GA_0195|Non_Targeting_Human	Non_Targeting_Human	GCCGTGTTGCTGGATACGCC
629	1|sg_Non_Targeting_Human_GA_0196|Non_Targeting_Human	Non_Targeting_Human	TACCCTCCGGATACGGACTG
630	1|sg_Non_Targeting_Human_GA_0197|Non_Targeting_Human	Non_Targeting_Human	CCGTTGGACTATGGCGGGTC
631	1|sg_Non_Targeting_Human_GA_0198|Non_Targeting_Human	Non_Targeting_Human	GTACGGGGCGATCATCCACA
632	1|sg_Non_Targeting_Human_GA_0199|Non_Targeting_Human	Non_Targeting_Human	AAGAGTAGTAGACGCCCGGG
633	1|sg_Non_Targeting_Human_GA_0200|Non_Targeting_Human	Non_Targeting_Human	AAGAGCGAATCGATTTCGTG
634	3|sg_hCDC16_CC_1|CDC16	CDC16	TCAACACCAGTGCCTGACGG
635	3|sg_hCDC16_CC_2|CDC16	CDC16	AAAGTAGCTTCACTCTCTCG

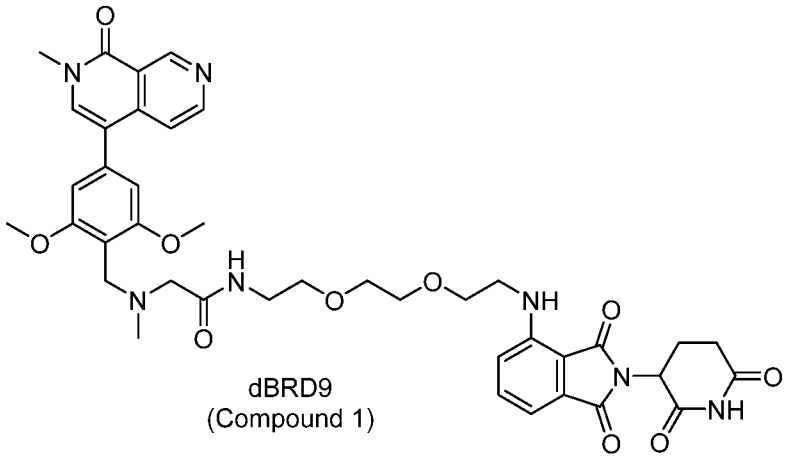
SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
636	3|sg_hCDC16_CC_3|CDC16	CDC16	GAGCCAACCAATAGATGTCC
637	3|sg_hCDC16_CC_4|CDC16	CDC16	GCGCCGCCATGAACCTAGAG
638	3|sg_hGTF2B_CC_1|GTF2B	GTF2B	ACAAAGGTTGGAACAGAACC
639	3|sg_hGTF2B_CC_2|GTF2B	GTF2B	GGTGACCGGGTTATTGATGT
640	3|sg_hGTF2B_CC_3|GTF2B	GTF2B	TTAGTGGAGGACTACAGAGC
641	3|sg_hGTF2B_CC_4|GTF2B	GTF2B	ACATATAGCCCGTAAAGCTG
642	3|sg_hHSPA5_CC_1|HSPA5	HSPA5	CGTTGGCGATGATCTCCACG
643	3|sg_hHSPA5_CC_2|HSPA5	HSPA5	TGGCCTTTTCTACCTCGCGC
644	3|sg_hHSPA5_CC_3|HSPA5	HSPA5	AATGGAGATACTCATCTGGG
645	3|sg_hHSPA5_CC_4|HSPA5	HSPA5	GAAGCCCGTCCAGAAAGTGT
646	3|sg_hHSPA9_CC_1|HSPA9	HSPA9	CAATCTGAGGAACTCCACGA
647	3|sg_hHSPA9_CC_2|HSPA9	HSPA9	AGGCTGCGGCGCCCACGAGA
648	3|sg_hHSPA9_CC_3|HSPA9	HSPA9	ACTTTGACCAGGCCTTGCTA
649	3|sg_hHSPA9_CC_4|HSPA9	HSPA9	ACCTTCCATAACTGCCACGC
650	3|sg_hPAFAH1B1_CC_1|PAFAH1B1	PAFAH1B1	CGAGGCGTACATACCCAAGG
651	3|sg_hPAFAH1B1_CC_2|PAFAH1B1	PAFAH1B1	ATGGTACGGCCAAATCAAGA
652	3|sg_hPAFAH1B1_CC_3|PAFAH1B1	PAFAH1B1	TCTTGTAATCCCATACGCGT
653	3|sg_hPAFAH1B1_CC_4|PAFAH1B1	PAFAH1B1	ATTCACAGGACACAGAGAAT
654	3|sg_hPCNA_CC_1|PCNA	PCNA	CCAGGGCTCCATCCTCAAGA
655	3|sg_hPCNA_CC_2|PCNA	PCNA	TGAGCTGCACCAAAGAGACG
656	3|sg_hPCNA_CC_3|PCNA	PCNA	ATGTCTGCAGATGTACCCCT

SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
657	3|sg_hPCNA_CC_4|PCNA	PCNA	CGAAGATAACGCGGATACCT
658	3|sg_hPOLR2L_CC_1|POLR2L	POLR2L	GCTGCAGGCCGAGTACACCG
659	3|sg_hPOLR2L_CC_2|POLR2L	POLR2L	ACAAGTGGGAGGCTTACCTG
660	3|sg_hPOLR2L_CC_3|POLR2L	POLR2L	GCAGCGTACAGGGATGATCA
661	3|sg_hPOLR2L_CC_4|POLR2L	POLR2L	GCAGTAGCGCTTCAGGCCCA
662	3|sg_hRPL9_CC_1|RPL9	RPL9	CAAATGGTGGGGTAACAGAA
663	3|sg_hRPL9_CC_2|RPL9	RPL9	GAAAGGAACTGGCTACCGTT
664	3|sg_hRPL9_CC_3|RPL9	RPL9	AGGGCTTCCGTTACAAGATG
665	3|sg_hRPL9_CC_4|RPL9	RPL9	GAACAAGCAACACCTAAAAG
666	3|sg_hSF3A3_CC_1|SF3A3	SF3A3	TGAGGAGAAGGAACGGCTCA
667	3|sg_hSF3A3_CC_2|SF3A3	SF3A3	GGAAGAATGCAGAGTATAAG
668	3|sg_hSF3A3_CC_3|SF3A3	SF3A3	GGAATTTGAGGAACTCCTGA
669	3|sg_hSF3A3_CC_4|SF3A3	SF3A3	GCTCACCGGCCATCCAGGAA
670	3|sg_hSF3B3_CC_1|SF3B3	SF3B3	ACTGGCCAGGAACGATGCGA
671	3|sg_hSF3B3_CC_2|SF3B3	SF3B3	GCAGCTCCAAGATCTTCCCA
672	3|sg_hSF3B3_CC_3|SF3B3	SF3B3	GAATGAGTACACAGAACGGA
673	3|sg_hSF3B3_CC_4|SF3B3	SF3B3	GGAGCAGGACAAGGTCGGGG

Example 2 – BRD9 degrader depletes BRD9 protein

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

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



dBRD9
(Compound 1)

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

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

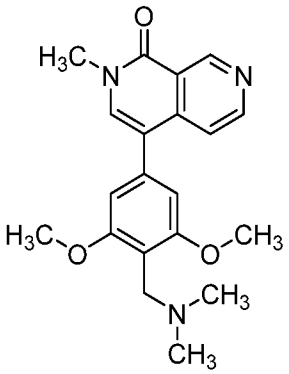
Example 3 – Inhibition of growth of synovial cell lines by BRD9 inhibitors and BRD9 degraders

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

Procedures:

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

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



BI-7273
(Compound 2)

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

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

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

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

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

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

Results: As shown in FIGS. 8 and 9, treatment of synovial sarcoma cell lines (SYO1, HS-SY-II, and ASKA) with Compound 1 or Compound 2 resulted in inhibition of the growth of the cells, but did not result in inhibition of the growth of non-synovial control cancer cell lines (RD, HCT116, and Calu6). Overall, Compound 1 showed most significant growth inhibition in all synovial cell lines.

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Example 5- Inhibition of cell growth in synovial sarcoma cells

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

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

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

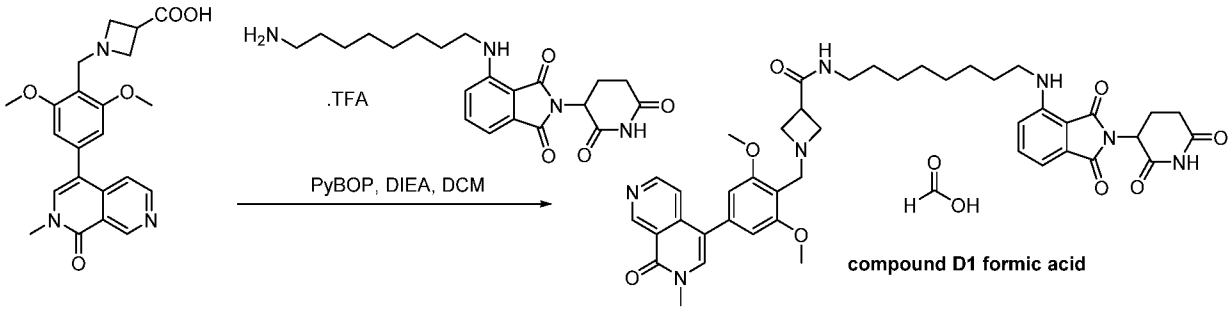
Example 6 – Composition for SS18-SSX1-BAF

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

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

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

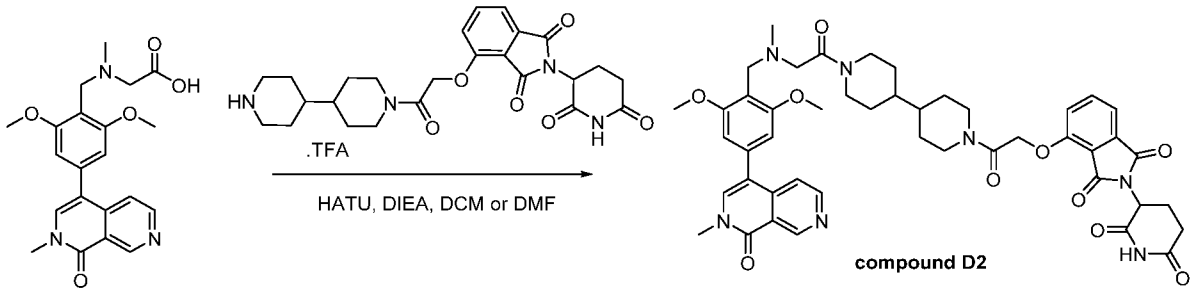
Example 7 – Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)azetidine-3-carboxamide formic acid (compound D1 formic acid)



To a stirred mixture of 4-[(8-aminooctyl)amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione trifluoroacetic acid salt (50 mg, 0.097 mmol, 1 equiv) and 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-3-carboxylic acid trifluoroacetic acid salt (50.87 mg, 0.097 mmol, 1 equiv) in DCM (2 mL, 31.460 mmol, 323.73 equiv) was added DIEA (37.68 mg, 0.292 mmol, 3 equiv) and PyBOP (75.86 mg, 0.146 mmol, 1.5 equiv). The mixture was stirred for 2 hours at room temperature, and then it was concentrated under vacuum. The residue was purified

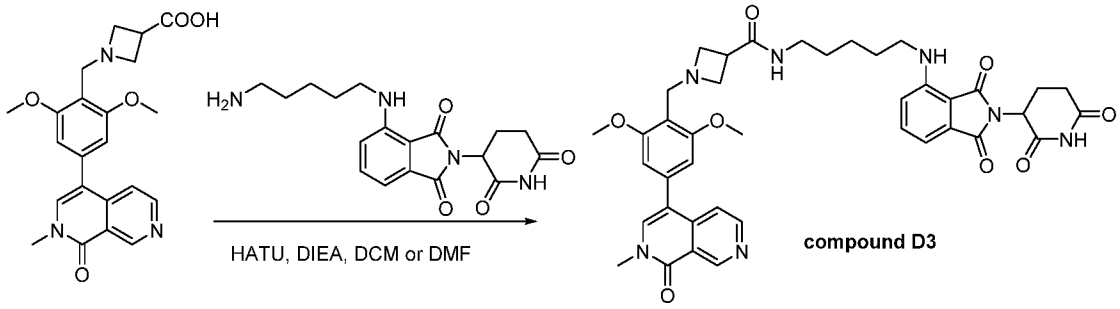
by Prep-HPLC (conditions: X Select CSH Prep C18 OBD Column, 5 µm, 19*150 mm; mobile phase, Water (0.1% FA) and ACN (25% Phase B up to 45% in 8 minutes); Detector, UV). This resulted in 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-*N*-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)azetidine-3-carboxamide formic acid (4 mg, 4.81%) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.54 (s, 1H), 8.69 (d, *J* = 5.7 Hz, 1H), 8.54 (s, 1H), 7.76 (s, 1H), 7.62 (d, *J* = 5.8 Hz, 1H), 7.60 – 7.51 (m, 1H), 7.04 (d, *J* = 7.8 Hz, 2H), 6.83 (s, 2H), 5.07 (dd, *J* = 12.5, 5.5 Hz, 1H), 4.31 (s, 2H), 4.05 (s, 4H), 3.94 (s, 6H), 3.71 (s, 3H), 3.52 - 3.45 (s, 2H), 3.22 (t, *J* = 7.0 Hz, 2H), 2.91 – 2.66 (m, 4H), 2.14 - 2.11 (m, 1H), 1.67 (q, *J* = 7.3 Hz, 2H), 1.54 (d, *J* = 7.3 Hz, 2H), 1.45 -1.38 (m, 8H). LCMS (ESI) m/z: [M+H]$^+$ = 792.36.

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



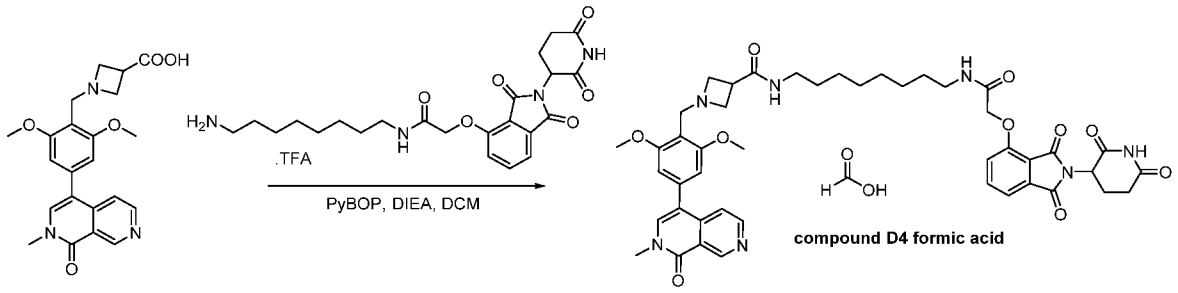
To a stirred solution of 2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)acetic acid (19.99 mg, 0.050 mmol, 1 equiv) and DIPEA (19.50 mg, 0.151 mmol, 3 equiv) in DMF (3 mL) was added PyBOP (28.68 mg, 0.075 mmol, 1.5 equiv) and 4-(2-[[4,4-bipiperidin]-1-yl]-2-oxoethoxy)-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione trifluoroacetic acid salt (30 mg, 0.050 mmol, 1 equiv). The solution was stirred for 2 hours at room temperature. The resulting mixture was purified by Prep-HPLC (conditions: XSelect CSH Prep C18 OBD Column, 5 µm, 19*150 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 5% B to 30% B in 8 minutes; 254 nm; R_t: 7.56 minutes) to afford 4-(2-[1-[2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)acetyl]-[4,4-bipiperidin]-1-yl]-2-oxoethoxy)-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (19 mg, 43.83%) as a white solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.53 (d, *J* = 0.8 Hz, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.56 (s, 0.3H), 7.76 (s, 2H), 7.64 (d, *J* = 5.7 Hz, 1H), 7.49 (d, *J* = 7.3 Hz, 1H),7.36 (d, *J* = 8.2 Hz, 1H), 6.80 (s, 2H), 5.14 (t, *J* = 15.7 Hz, 3H), 4.60 – 4.43 (m, 3H), 4.02 (d, *J* = 13.6 Hz, 4H), 3.91 (s, 6H), 3.71 (s, 3H), 3.58 (s, 2H), 3.15 -2.59 (m,6H), 2.53 (s, 3H),2.15 (s, 1H), 1.85 - 1.67 (m, 4H), 1.41 - 1.16 (m, 6H). LCMS (ESI) m/z: [M+H]+ = 862.

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



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

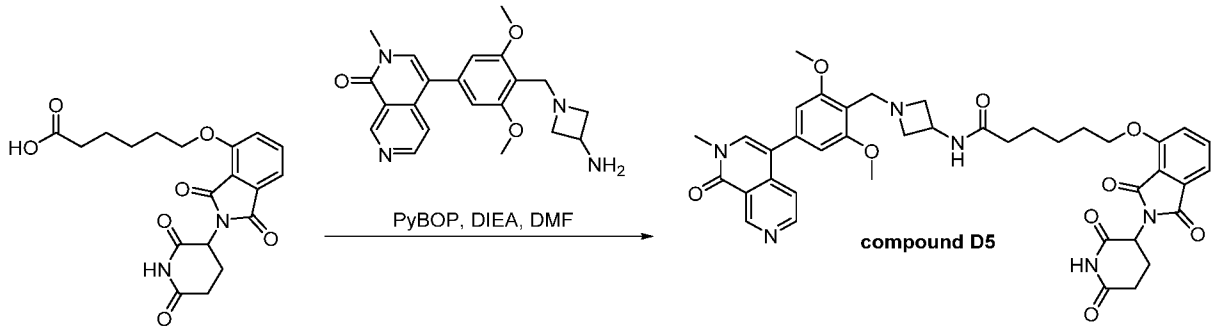
Example 10 – Preparation of N-[8-[(1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidin-3-yl)formamido]octyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy]acetamide formic acid (compound D4 formic acid)



To a stirred mixture of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl] methyl]azetidine-3-carboxylic acid; trifluoroacetic acid salt (68.57 mg, 0.131 mmol, 1.50 equiv) and *N*-(8-aminooctyl)-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetamide trifluoroacetic acid salt (50.00 mg, 0.087 mmol, 1.00 equiv) in DCM (2.00 mL) was added DIEA (67.72 mg, 0.524 mmol, 6.00 equiv) and PyBOP (68.17 mg, 0.131 mmol, 1.50 equiv). The mixture was stirred for 2 hours at room temperature, and then it was concentrated under vacuum. The residue was purified by Prep-HPLC

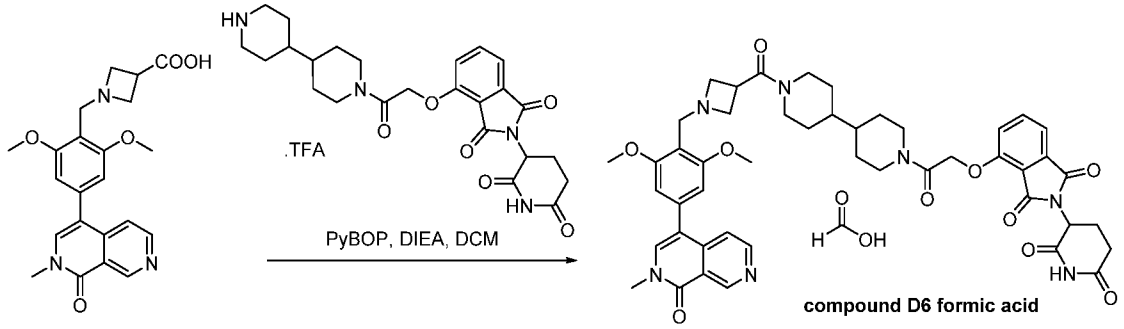
(conditions: X Bridge Shield RP18 OBD Column, 5 µm, 19*150 mm; mobile phase, Water (0.1% FA) and ACN (20% Phase B up to 32% in 7 minutes); Detector, UV). This resulted in *N*-[8-[(1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidin-3-yl)formamido]octyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3 -dihydro-1H-isoindol-4-yl]oxy]acetamide formic acid (12 mg, 14.77%) as a white solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.53 (s, 1H), 8.68 (d, *J* = 5.8 Hz, 1H), 7.87 – 7.78 (m, 1H), 7.75 (s, 1H), 7.63 (d, *J* = 5.8 Hz, 1H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 6.80 (s, 2H), 5.15 (dd, *J* = 12.6, 5.3 Hz, 1H), 4.76 (s, 2H), 4.14 (s, 2H), 3.92 (s, 6H), 3.80 (s, 4H), 3.71 (s, 3H), 3.20 (t, *J* = 7.0 Hz, 2H), 2.94 – 2.71 (m, 6H), 2.15 (s, 1H), 1.58 (d, *J* = 7.9 Hz, 2H), 1.51 (s, 2H), 1.35 (s, 8H). LCMS (ESI) m/z: $[M+H]^+$ = 850.37.

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



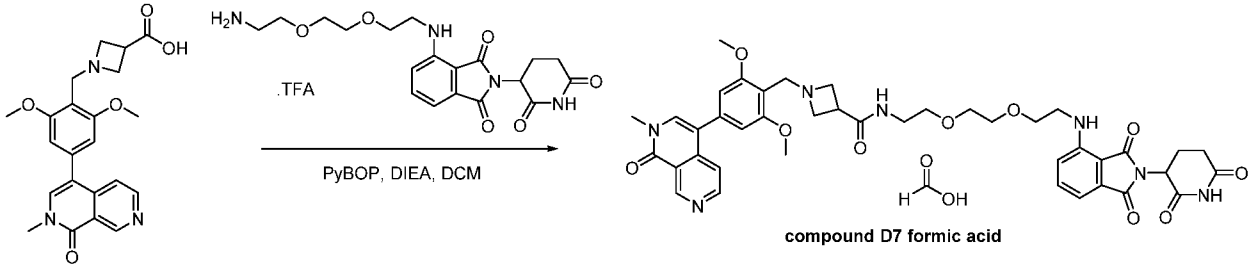
To a solution of 6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy]hexanoic acid (50.00 mg, 0.129 mmol, 1.00 eq.) and DIEA (49.92 mg, 0.386 mmol, 3 eq.) in DCM (2.00 mL, 31.460 mmol, 244.37 eq.) was added PyBOP (100.49 mg, 0.193 mmol, 1.5 eq.) and 4-[4-[(3-aminoazetidin-1-yl)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyri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

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



To a stirred mixture of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl] methyl]azetidine-3-carboxylic acid trifluoroacetic acid salt (26.32 mg, 0.050 mmol, 1.50 equiv) and 4-(2-[[4,4-bipiperidin]-1-yl]-2-oxoethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione trifluoroacetic acid salt (20.00 mg, 0.034 mmol, 1.00 equiv) in DCM (2 mL) was added DIEA (26.00 mg, 0.201 mmol, 6.00 equiv) and PyBOP (26.17 mg, 0.050 mmol, 1.50 equiv). The mixture was stirred for 2 hours at room temperature, and then it was concentrated under vacuum. The residue was purified was purified by Prep-HPLC (conditions: X Select CSH Prep C18 OBD Column, 5 μm, 19*150 mm; mobile phase, Water (0.1% FA) and ACN (8% Phase B up to 22% in 8 minutes); Detector, UV). This resulted in 4-[2-[1-(1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-3-carbonyl)-[4,4-bipiperidin]-1-yl]-2-oxoethoxy]-2-(2,6-dioxo piperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione formic acid (3.5 mg, 10.89%) as a white solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.54 (d, *J* = 0.8 Hz, 1H), 8.69 (d, *J* = 5.7 Hz, 1H), 8.56 (s, 1H), 7.84 – 7.72 (m, 2H), 7.63 (d, *J* = 5.8 Hz, 1H), 7.51 (d, *J* = 7.3 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 6.81 (s, 2H), 5.31 – 4.98 (m, 3H), 4.68 – 4.44 (m, 2H), 4.16 (s, 2H), 3.93 (s, 10H), 3.79 – 3.56 (m, 5H), 3.09 – 2.93 (m, 2H), 2.93 – 2.61 (m, 6H), 2.15 (d, *J* = 10.4 Hz, 1H), 1.86 – 1.67 (m, 4H), 1.50 – 1.25 (m, 3H), 1.23 – 1.04 (m, 2H). LCMS (ESI) m/z: $[M+H]^+$ = 874.37.

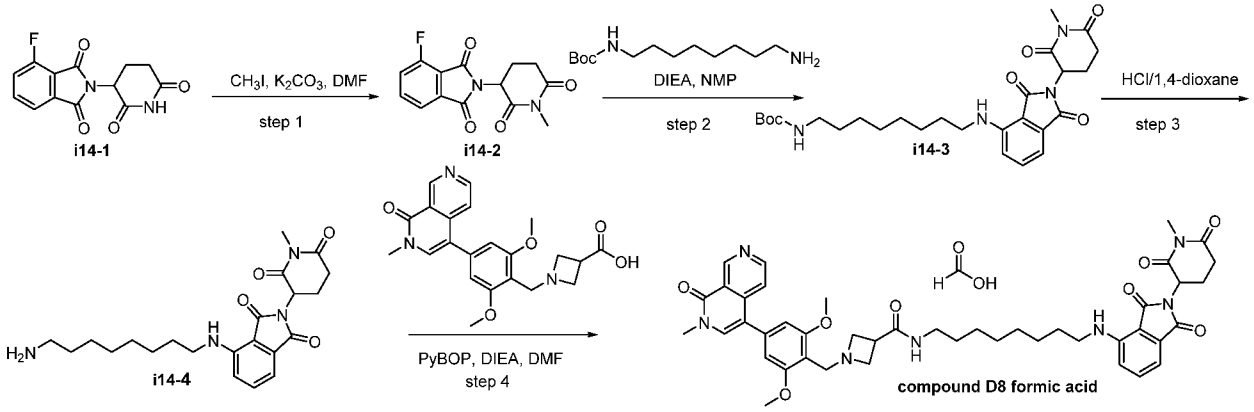
Example 13 – Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl] methyl]-N-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino] ethoxy)ethoxy]ethyl]azetidine-3-carboxamide formic acid (compound D7 formic acid)



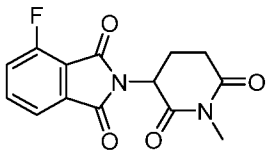
To a stirred mixture of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-3-carboxylic acid trifluoroacetic acid salt (75.73 mg, 0.145 mmol, 1.5 equiv) and 4-([2-[2-(2-aminoethoxy)ethoxy]ethyl]amino)-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione trifluoroacetic acid salt (50 mg, 0.096 mmol, 1 equiv) in DCM (2 mL) was added DIEA (74.79 mg, 0.579 mmol, 6 equiv) and PyBOP (75.28 mg, 0.145 mmol, 1.5 equiv). The mixture was stirred for 2 hours at room temperature, and then it was concentrated under vacuum. The residue was purified by Prep-

HPLC (conditions: X Select CSH Prep C18 OBD Column, 5 µm, 19*150 mm; mobile phase, Water (0.1% FA) and ACN (10% Phase B up to 32% in 8 minutes); Detector, UV). This resulted in 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]ethoxy)ethoxy]ethyl]azetidine-3-carboxamide formic acid (13.2 mg, 15.77%) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.53 (s, 1H), 8.68 (d, *J* = 5.8 Hz, 1H), 8.56 (s, 1H), 7.75 (s, 1H), 7.62 (d, *J* = 5.9 Hz, 1H), 7.55 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.07(dd, *J* = 11.7, 7.8 Hz, 2H), 6.80 (s, 2H), 5.07 (dd, *J* = 12.4, 5.5 Hz, 1H), 4.20 (s, 2H), 3.92 (s, 10H), 3.78 – 3.57 (m, 9H), 3.61 – 3.43 (m, 4H), 3.41 (td, *J* = 5.2, 1.6Hz, 2H), 2.88 (ddd, *J* = 19.0, 14.0, 5.0 Hz, 1H), 2.80 – 2.64 (m, 3H). 2.17 – 2.08 (m, 1H). LCMS (ESI) m/z: [M+H]$^+$ = 796.25.

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



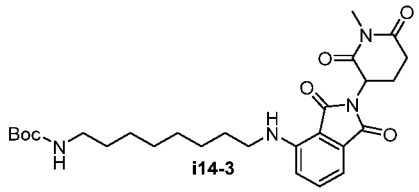
Step 1: Preparation of 4-fluoro-2-(1-methyl-2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (i14-2)



i14-2

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

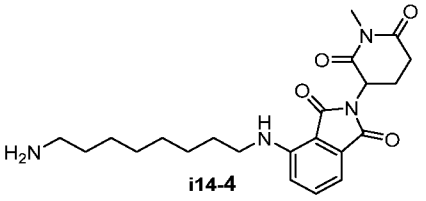
Step 2: Preparation of tert-butyl N-(8-[[2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)carbamate (i14-3)



i14-3

To a solution of 4-fluoro-2-(1-methyl-2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (480 mg, 1.654 mmol, 1 equiv) and *tert*-butyl *N*-(8-aminooctyl)carbamate (404.14 mg, 1.654 mmol, 1 equiv) in NMP (10 mL) was added DIEA (641.21 mg, 4.961 mmol, 3 equiv). The resulting solution was stirred for 6 hours at 90 °C. The resulting solution was diluted with 20 mL of water and extracted with ethyl acetate (2 x 20 mL), and the organic layers were combined and dried over anhydrous sodium sulfate and concentrated. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in *tert*-butyl *N*-(8-[[2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)carbamate (480 mg, 56.40%) as a green solid. LCMS (ESI) m/z: [M-H]+ = 515.

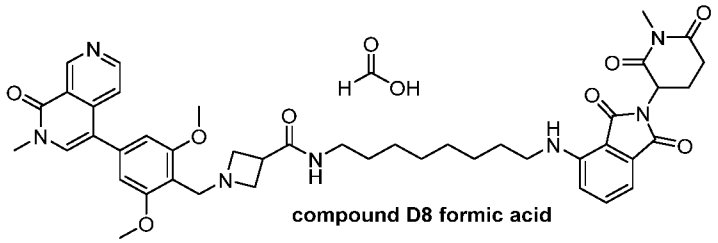
Step 3: Preparation of 4-[(8-aminooctyl)amino]-2-(1-methyl-2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (i14-4)



i14-4

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

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

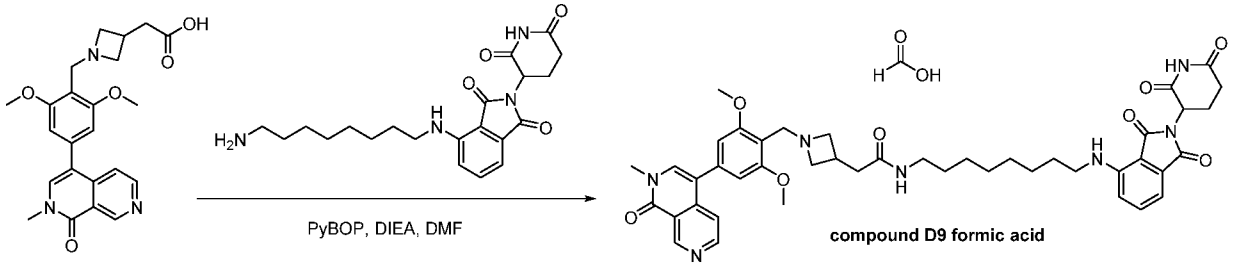


compound D8 formic acid

To a solution of 4-[(8-aminooctyl)amino]-2-(1-methyl-2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (80 mg, 0.193 mmol, 1 equiv) and 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-

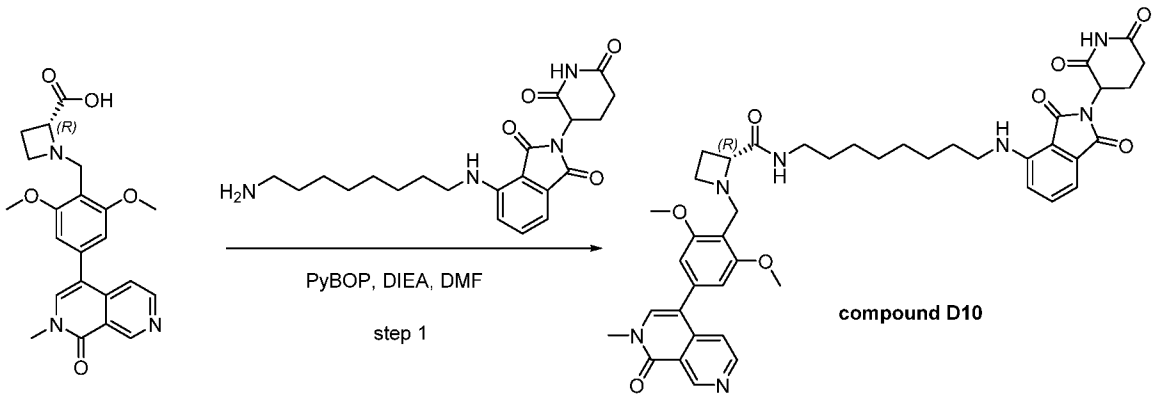
2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-3-carboxylic acid (79.02 mg, 0.193 mmol, 1 equiv) in DMF (3 mL) was added HATU (110.08 mg, 0.290 mmol, 1.5 equiv) and DIEA (49.89 mg, 0.386 mmol, 2 equiv). The resulting solution was stirred for 2 hours at 25 °C. The crude product was purified by Prep-HPLC (conditions: XBridge Prep C18 OBD Column, 5 μm, 19*150 mm; mobile phase, Water (0.1% FA) and ACN; Detector, UV 254nm). This resulted in 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-*N*-(8-[[2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)azetidine-3-carboxamide (15 mg, 9.64%) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.54 (d, *J* = 0.8 Hz, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.54 (s, 1.2H, FA), 7.77 (s, 1H), 7.65 – 7.52 (m, 2H), 7.10 – 7.01 (m, 2H), 6.84 (s, 2H), 5.10 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.39 (s, 2H), 4.14 (d, *J* = 8.2 Hz, 3H), 3.95 (s, 6H), 3.71 (s, 3H), 3.54 (d, *J* = 8.1 Hz, 1H), 3.22 (t, *J* = 7.0 Hz, 2H), 3.17 (d, *J* = 3.1 Hz, 1H), 3.15 (s, 3H), 2.99 (s, 1H), 2.96 – 2.86 (m, 2H), 2.69 (dt, *J* = 12.7, 6.3 Hz, 2H), 2.15 – 2.05 (m, 1H), 1.68 (p, *J* = 7.1 Hz, 2H), 1.52 (q, *J* = 7.1 Hz, 2H), 1.38 (s, 8H). LCMS (ESI) m/z: [M-H]+ = 806.40.

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



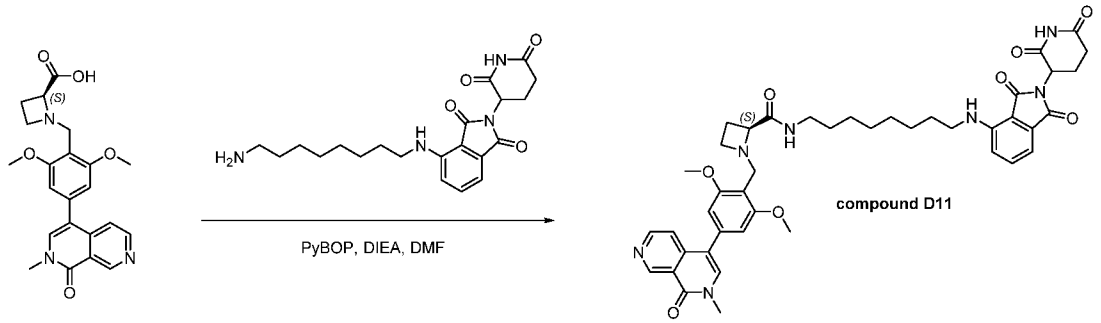
To a solution of 2-(1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidin-3-yl)acetic acid (110 mg, 0.260 mmol, 1 equiv) in DMF (3 mL) was added 4-[(8-aminooctyl)amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (104.03 mg, 0.260 mmol, 1.00 equiv),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

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



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

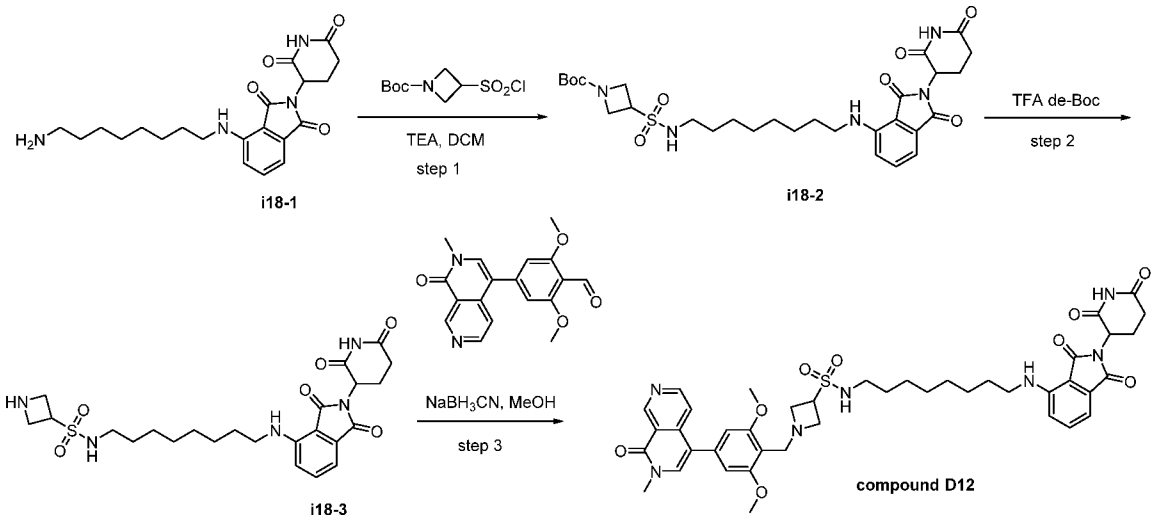
Example 17 – Preparation of (2S)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]octyl)azetidine-2-carboxamide (compound D11)



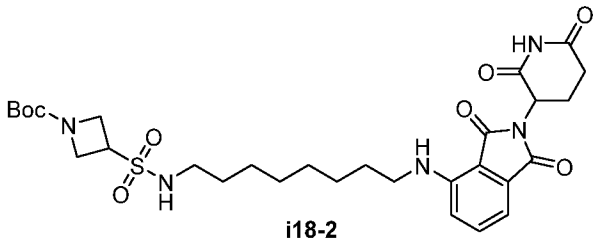
To a solution of (2*S*)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-2-carboxylic acid (50.00 mg, 0.122 mmol, 1.00 equiv) and 4-[(8-aminooctyl)amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (48.91 mg, 0.122 mmol,

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

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



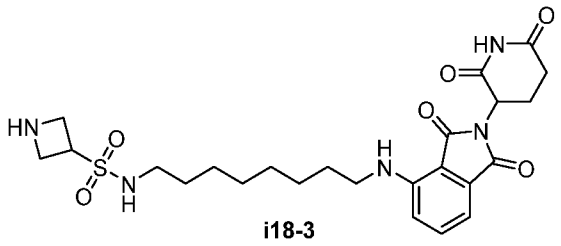
Step 1: Preparation of tert-butyl 3-[(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)sulfamoyl]azetidine-1-carboxylate (i18-2)



To a solution of 4-[(8-aminooctyl)amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-*1H*-isoindole-1,3-dione (100.00 mg, 0.250 mmol, 1.00 equiv) in DCM (2.00 mL) was added tert-butyl 3-(chlorosulfonyl)azetidine-1-carboxylate (95.78 mg, 0.375 mmol, 1.50 equiv) and TEA (50.53 mg, 0.499 mmol, 2.00 equiv) at 0 °C. The resulting solution was stirred for 2 hours at 25 °C. The reaction was then quenched by the addition of 5 mL of MeOH. The resulting mixture was concentrated. The residue was

applied onto a silica gel column with ethyl DCM/MeOH (20:1). This resulted in 110 mg (71.08%) of *tert*-butyl 3-[(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-*1H*-isoindol-4-yl]amino]octyl) sulfamoyl]azetidine-1-carboxylate as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 620.

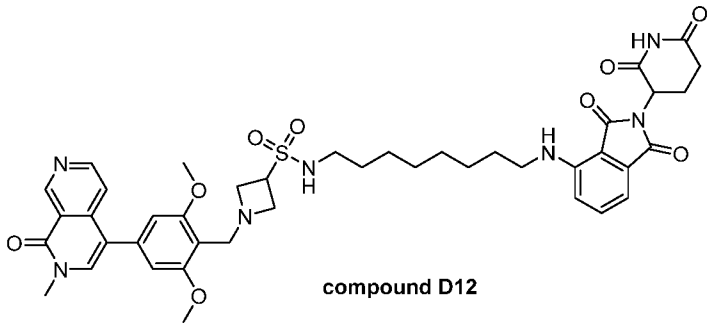
Step 2: Preparation of N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]octyl)azetidine-3-sulfonamide (i18-3)



i18-3

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

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

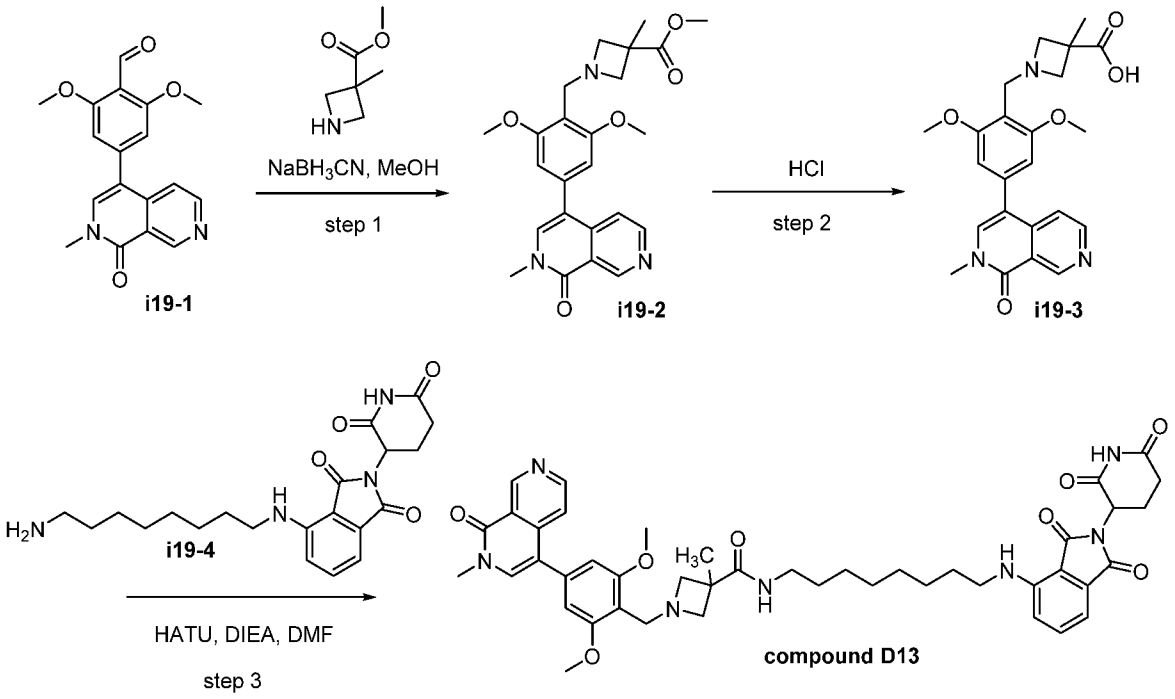


compound D12

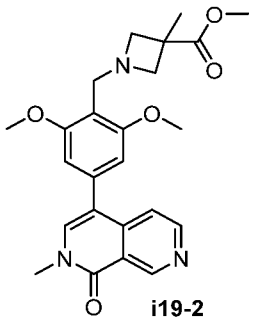
To a solution of *N*-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino]octyl)azetidine-3-sulfonamide (85.00 mg, 0.164 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (53.06 mg, 0.164 mmol, 1.00 equiv) in MeOH (2.00 mL)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

7.1 Hz, 1H), 7.03 (dd, *J* = 7.8, 4.8 Hz, 2H), 6.77 (s, 2H), 5.06 (dd, *J* = 12.5, 5.5 Hz, 1H), 4.03 (p, *J* = 8.2, 7.8 Hz, 1H), 3.91 (d, *J* = 4.1 Hz, 2H), 3.89 (s, 6H), 3.78 – 3.68 (m, 8H), 3.30 (d, *J* = 6.8 Hz, 1H), 3.03 (t, *J* = 7.0 Hz, 2H), 2.94 – 2.80 (m, 1H), 2.80 – 2.66 (m, 2H), 2.17 – 2.08 (m, 1H), 1.70 – 1.62 (m, 2H), 1.51 (d, *J* = 6.9 Hz, 2H), 1.44 -1.37 (m, 8H). LCMS (ESI) m/z: [M+H]+ = 828.35.

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

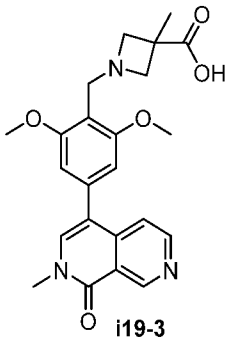


Step 1: Preparation of methyl 1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-3-methylazetidine-3-carboxylate (i19-2)



To a solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (200 mg, 0.617 mmol, 1 equiv) and methyl 3-methylazetidine-3-carboxylate (79.65 mg, 0.617 mmol, 1.00 equiv) in MeOH(2 mL) was added $NaBH_3CN$ (77.50 mg, 1.233 mmol, 2 equiv). The resulting solution was stirred at 25 °C for 1 hour. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (9:1) to afford methyl 1-[[2, 6-dimethoxy -4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl) phenyl] methyl]-3- methylazetidine-3-carboxylate (247 mg, 91.56%) as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 438.

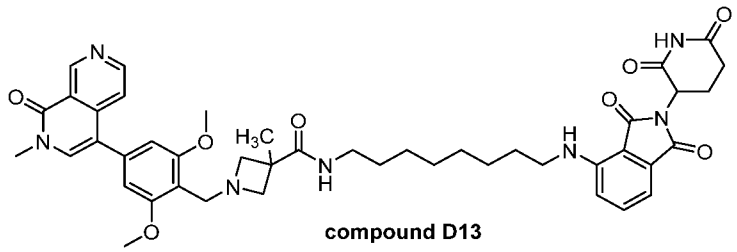
Step 2: Preparation of 1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-3-methylazetidine-3-carboxylic acid (i19-3)



i19-3

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

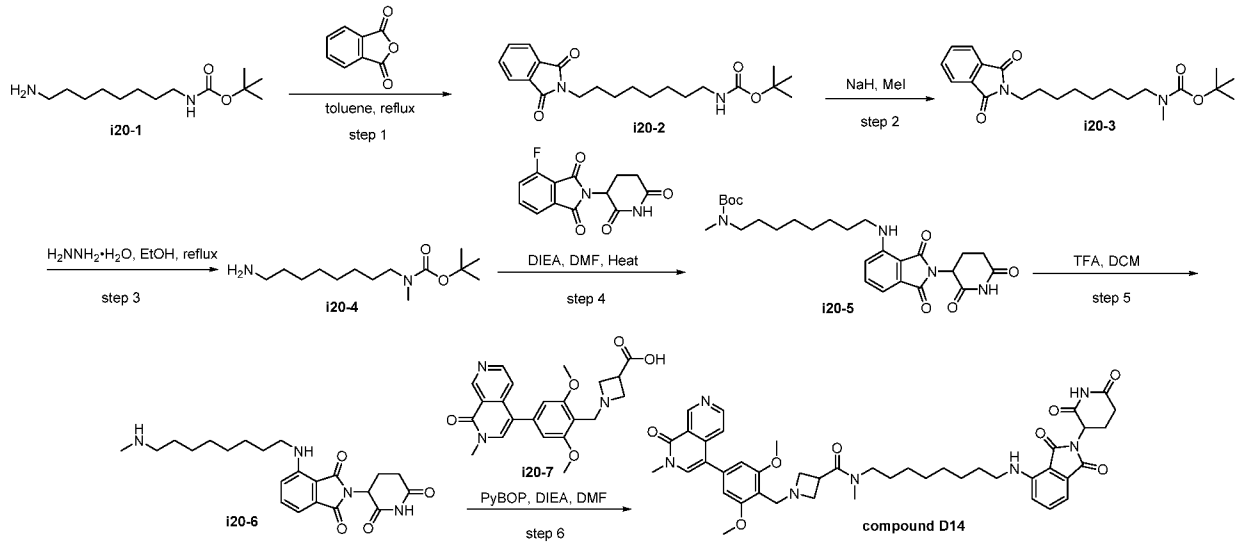
Step 3: Preparation of 1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-N-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octyl)-3-methylazetidine-3-carboxamide (compound D13)



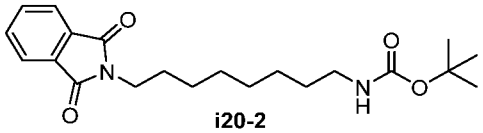
compound D13

To a solution of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl] -3-methylazetidine-3-carboxylic acid (50 mg, 0.118 mmol, 1 equiv), 4-[(8-aminooctyl)amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (94.57 mg, 0.236 mmol, 2 equiv) and Et_3N (119.48 mg, 1.181 mmol, 10.00 equiv) in DMF (3 mL), was added EDCI (27.16 mg, 0.142 mmol, 1.2 equiv) and HOBT (19.15 mg, 0.142 mmol, 1.2 equiv), the resulting solution was stirred at 25 °C for 24 hours. The crude product was purified by Prep-HPLC with the following conditions (condition: XBridge Prep C18 OBD Column, 5 μm, 19*150 mm; mobile phase, Water (0.1% FA) and ACN; Detector, UV) to give 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-*N*-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)-3-methylazetidine-3-carboxamide (21.7 mg, 22.80%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.53 (s, 1H), 8.69 (d, *J* = 5.7 Hz, 1H), 8.55 (s, 1H), 7.76 (s, 1H), 7.62 (d, *J* = 5.7 Hz, 1H), 7.59 – 7.49 (m, 1H), 7.07 – 6.98 (m, 2H), 6.81 (s, 2H), 5.06 (dd, *J* = 12.3, 5.4 Hz, 1H), 4.19 (s, 2H), 4.06 (s, 2H), 3.93 (s, 6H), 3.71 (s, 5H), 3.32 – 3.16 (m, 1H), 2.92 – 2.66 (m, 4H), 2.15 -2.06 (m, 1H), 1.64 (d, *J* = 7.4 Hz, 2H), 1.55 (s, 5H), 1.39 – 1.32 (m, 8H). LCMS (ESI) m/z: [M+H]+ = 806.50.

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

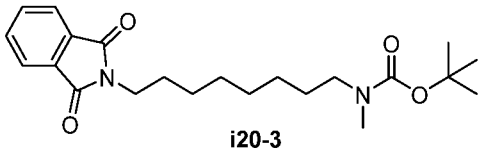


Step 1: preparation of tert-butyl N-[8-(1,3-dioxoisoindol-2-yl)octyl]carbamate (i20-2)



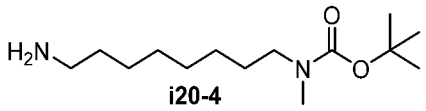
A mixture of tert-butyl *N*-(8-aminooctyl)carbamate (1.00 g, 4.092 mmol, 1.00 equiv) and phthalic anhydride (606.10 mg, 4.092 mmol, 1.00 equiv) in toluene (20.00 mL) was stirred for 2 hours at 130 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature and the solvent was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

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



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

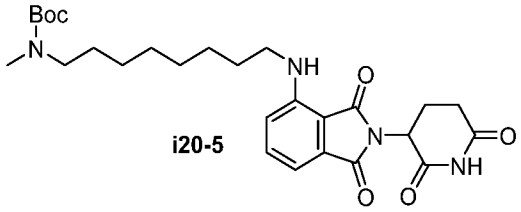
Step 3: Preparation of tert-butyl N-(8-aminooctyl)-N-methylcarbamate (i20-4)



i20-4

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

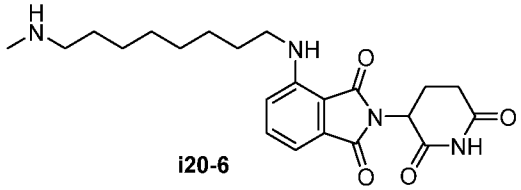
Step 4: Preparation of tert-butyl N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]octyl)-N-methylcarbamate (i20-5)



i20-5

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

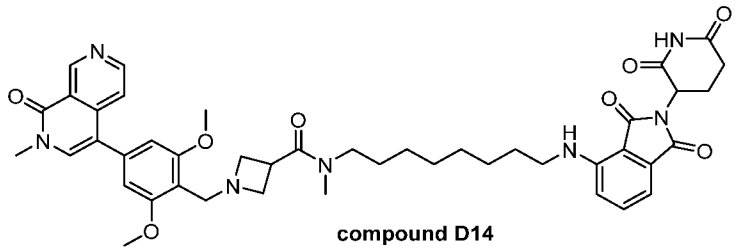
Step 5: Preparation of 2-(2,6-dioxopiperidin-3-yl)-4-[[8-(methylamino)octyl]amino]isoindole-1,3-dione (i20-6)



i20-6

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

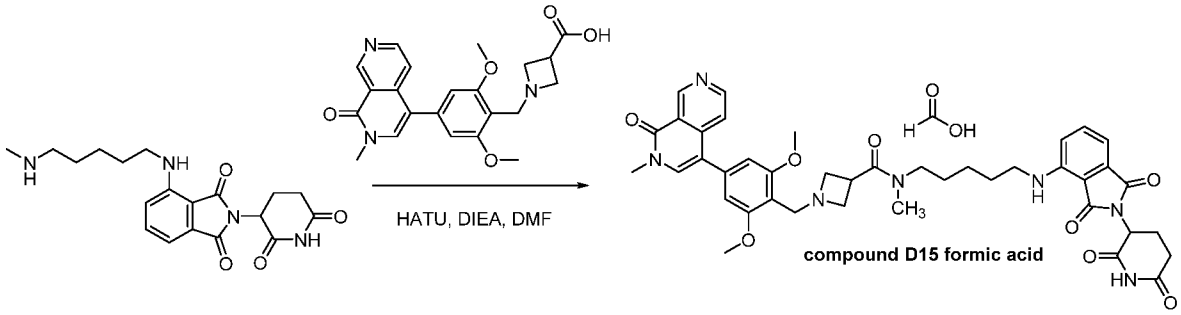
Step 6: Preparation of 1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)-N-methylazetidine-3-carboxamide (compound D14)



compound D14

To a stirred solution of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-3-carboxylic acid (30 mg, 0.073 mmol, 1 equiv) in DMF (0.5 mL), was added DIPEA (47.35 mg, 0.366 mmol, 5 equiv), HATU (55.72 mg, 0.147 mmol, 2 equiv), and 2-(2,6-dioxopiperidin-3-yl)-4-[[8-(methylamino)octyl]amino]-2,3-dihydro-1*H*-isoindole-1,3-dione (30.37 mg, 0.073 mmol, 1 equiv). The reaction was stirred at ambient atmosphere for 1 hour. The mixture was purified directly by Prep-HPLC (condition: SunFire C18 OBD Prep Column, 100 Å, 5 μm, 19 mm X 250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minuteutes; Gradient: 24% B to 36% B in 8 minutes; 254 nm; R_t: 7.9 minutes) to afford 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-*N*-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino]octyl)-*N*-methylazetidine-3-carboxamide formate (25 mg, 40.05%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.52 (dd, *J* = 4.5, 0.9 Hz, 1H), 8.68 (dd, *J* = 5.8, 2.5 Hz, 1H), 8.56 (s, 0.5H, FA), 7.75 (d, *J* = 2.0 Hz, 1H), 7.67 – 7.58 (m, 1H), 7.53 (ddd, *J* = 8.5, 7.1, 4.7 Hz, 1H), 7.07 – 6.95 (m, 2H), 6.81 (d, *J* = 1.8 Hz, 2H), 5.06 (ddd, *J* = 12.1, 5.4, 2.5 Hz, 1H), 4.21 (d, *J* = 4.7 Hz, 2H), 4.00 (dd, *J* = 17.1, 8.8 Hz, 4H), 3.93 (s, 6H), 3.80 (t, *J* = 8.2 Hz, 1H), 3.70 (d, *J* = 3.3 Hz, 3H), 3.45 – 3.19 (m, 2H), 2.94 (d, *J* = 4.3 Hz, 3H), 2.91 – 2.68 (m, 3H), 2.12 (s, 1H), 1.67 (s, 2H), 1.57 (d, *J* = 6.9 Hz, 2H), 1.41 - 1.33 (m, 8H). LCMS (ESI) m/z: [M+H]+ = 806.35.

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

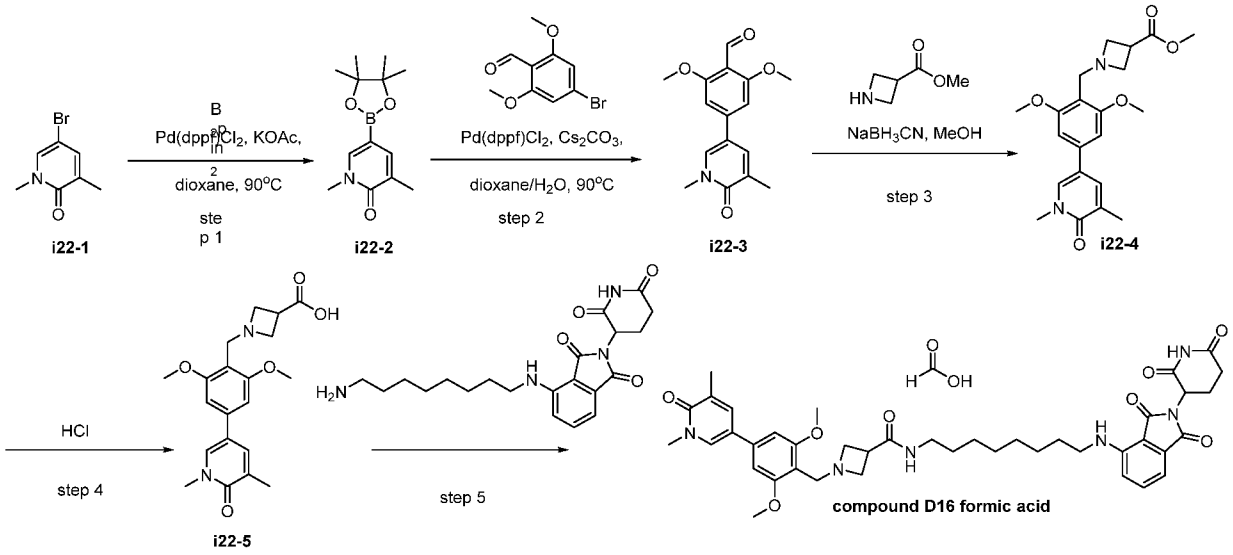


compound D15 formic acid

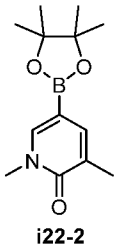
To a solution of 2-(2,6-dioxopiperidin-3-yl)-4-[[5-(methylamino)pentyl]amino]-2,3-dihydro-1*H*-isoindole-1,3-dione (60.00 mg, 0.161 mmol, 1.00 equiv), 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-3-carboxylic acid (65.96 mg, 0.161 mmol, 1.00 equiv), and DIEA (41.64 mg, 0.322 mmol, 2.00 equiv) in DMF (2.00 mL, 25.844 mmol, 160.41 equiv) was added HATU (91.89 mg, 0.242 mmol, 1.50 equiv). The resulting mixture was stirred at room temperature for 16 hours. Without workup, the crude product was purified by Prep-HPLC (condition: XBridge Shield RP18

OBD Column 30*150 mm, 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 40 mL/minuteute; Gradient: 18% B to 18% B in 2 minutes; 254/220 nm; R_t: 11.43 minutes) to afford 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino]pentyl)-N-methylazetidine-3-carboxamide; formic acid (25.1 mg) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.53 (dd, *J* = 5.4, 0.9 Hz, 1H), 8.68 (dd, *J* = 5.8, 1.2 Hz, 1H), 8.56 (s, 0.53H, FA), 7.79 – 7.73 (m, 1H), 7.67 – 7.50 (m, 2H), 7.09 – 6.99 (m, 2H), 6.80 (d, *J* = 3.2 Hz, 2H), 5.06 (ddd, *J* = 12.3, 5.4, 2.8 Hz, 1H), 4.17 (s, 2H), 3.92 - 3.90 (m, 10H), 3.78 (q, *J* = 9.0, 8.5 Hz, 1H), 3.71 (d, *J* = 2.2 Hz, 3H), 3.48 – 3.35 (m, 2H), 3.27 (t, *J* = 7.5 Hz, 1H), 2.98 – 2.85 (m, 3H), 2.89 – 2.64 (m, 4H), 2.22 – 2.08 (m, 1H), 1.75 -1.62 (m, 4H), 1.43 (s, 2H). LCMS (ESI) m/z: $[M+H]^+$ = 764.45.

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



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

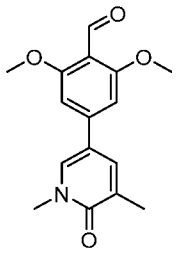


i22-2

To a solution of 5-bromo-1,3-dimethylpyridin-2-one(1.00 g, 4.949 mmol, 1.00 equiv) and bis(pinacolato)diboron (1508.17 mg, 5.939 mmol, 1.20 equiv) in dioxane (10.00 mL) was added KOAc (971.46 mg, 9.898 mmol, 2.00 equiv) and $Pd(dppf)Cl_2•CH_2Cl_2$ (404.18 mg, 0.495 mmol, 0.10 equiv). After stirring for 2 hours at 90 °C under a nitrogen atmosphere, the resulting mixture was concentrated under

reduced pressure. The crude product was used in the next step directly without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 250.

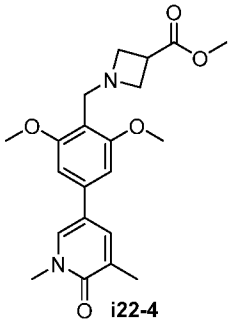
Step 2: Preparation of 4-(1,5-dimethyl-6-oxopyridin-3-yl)-2,6-dimethoxybenzaldehyde (i22-3)



i22-3

To a solution of 1,3-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-one (1.20 g, 4.817 mmol, 1.00 equiv) and 4-bromo-2,6-dimethoxybenzaldehyde (1.18 g, 4.817 mmol, 1.00 equiv) in 1,4-dioxane (40.00 mL) and H_2O (4.00 mL) was added CS_2CO_3 (3.14 g, 9.634 mmol, 2.00 equiv) and $Pd(dppf)Cl_2$ (0.35 g, 0.482 mmol, 0.10 equiv). After stirring for 2 hours at 80 °C under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH (18:1) to afford 4-(1,5-dimethyl-6-oxopyridin-3-yl)-2,6-dimethoxybenzaldehyde (1.43 g, 87.83%) as a brown syrup. LCMS (ESI) m/z: $[M+H]^+$ = 288.

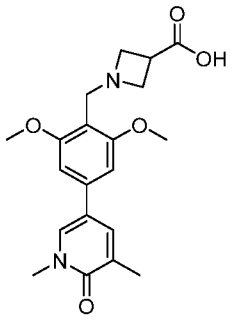
Step 3: Preparation of methyl 1-[[4-(1,5-dimethyl-6-oxopyridin-3-yl)-2,6-dimethoxyphenyl]methyl]azetidine-3-carboxylate (i22-4)



i22-4

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

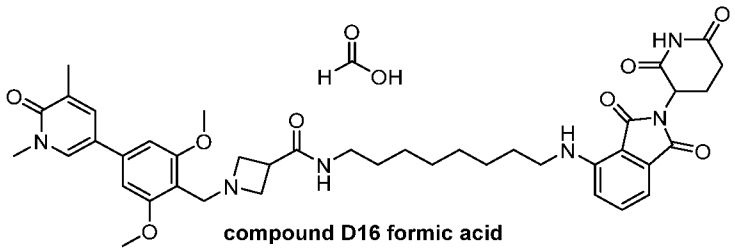
Step 4: Preparation of 1-[[4-(1,5-dimethyl-6-oxopyridin-3-yl)-2,6-dimethoxyphenyl]methyl]azetidine-3-carboxylic acid (i22-5)



i22-5

A mixture of methyl 1-[[4-(1,5-dimethyl-6-oxopyridin-3-yl)-2,6-dimethoxyphenyl]methyl]azetidine-3-carboxylate (203.00 mg, 0.525 mmol, 1.00 equiv) in HCl (12 N, 2.00 mL) was stirred for 2 hours at 90 °C. The resulting mixture was concentrated under reduced pressure to give 1-[[4-(1,5-dimethyl-6-oxopyridin-3-yl)-2,6-dimethoxyphenyl]methyl]azetidine-3-carboxylic acid (150 mg, 71.31%) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 373.

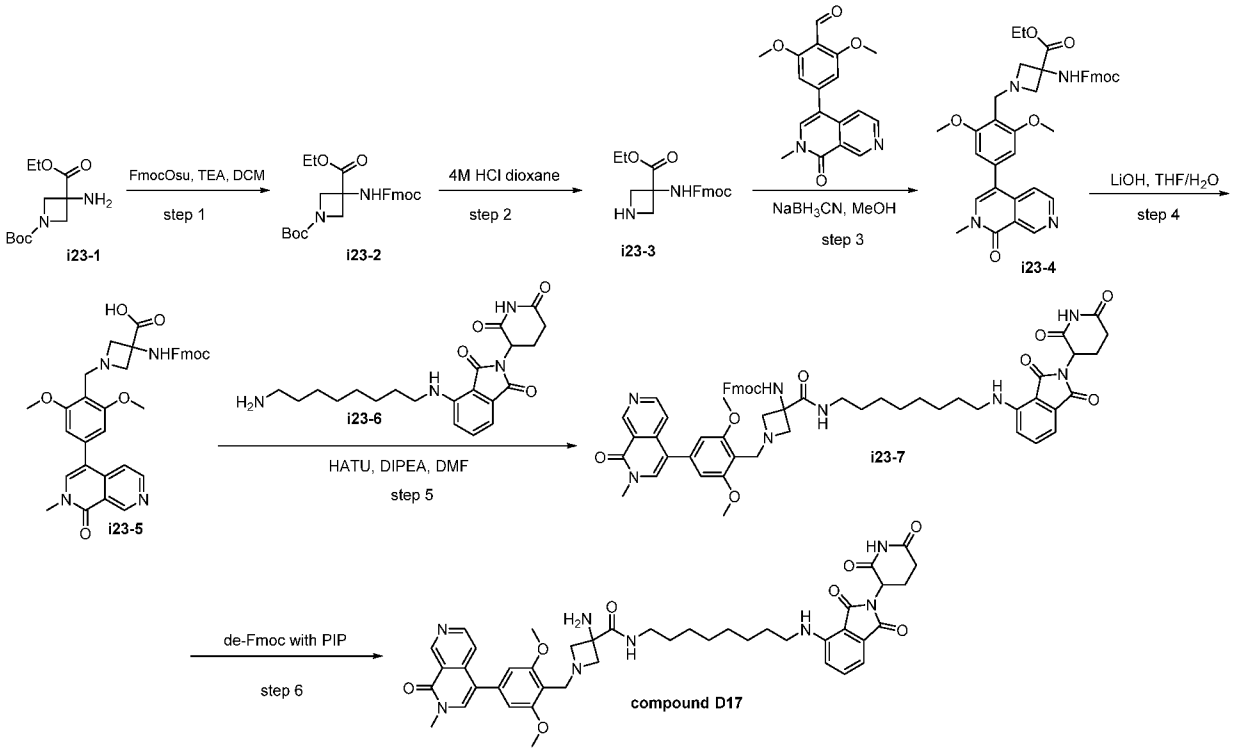
Step4: Preparation of 2-(2,6-dihydroxypiperidin-3-yl)-4-[(8-[[hydroxy(1-[[4-(6-hydroxy-1,5-dimethyl-1,6-dihydropyridin-3-yl)-2,6-dimethoxyphenyl]methyl]azetidin-3-yl)methyl]amino]octyl)amino]-2,3-dihydro-1H-isoindole-1,3-diol formic acid (compound D16 formic acid)



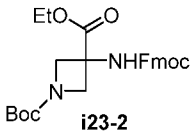
compound D16 formic acid

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

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

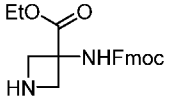


Step 1: Preparation of 1-tert-Butyl 3-ethyl 3-([[(9H-fluoren-9-yl)methoxy]carbonyl]amino)azetidine-1,3-dicarboxylate (i23-2)



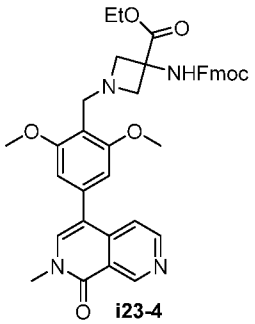
To a solution of 1-*tert*-butyl 3-ethyl 3-aminoazetidine-1,3-dicarboxylate (120 mg, 0.491 mmol, 1 equiv) and 2,5-dioxopyrrolidin-1-yl (9*H*-fluoren-9-yl)methyl carbonate (182.3 mg, 0.540 mmol, 1.1 equiv) in DCM (1 mL) was added TEA (149.1 mg, 1.474 mmol, 3 equiv). The resulting solution was stirred at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

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



A mixture of 1-tert-*butyl* 3-ethyl 3-([[(9*H*-fluoren-9-yl)methoxy]carbonyl]amino)azetidine-1,3-dicarboxylate (120.00 mg, 0.257 mmol, 1.00 equiv) and 4 M HCl in 1,4-dioxane (2 mL) was stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure to afford ethyl 3-([[(9*H*-fluoren-9-yl)methoxy]carbonyl]amino)azetidine-3-carboxylate (120 mg, 89%) as a white solid that was used directly without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 367.

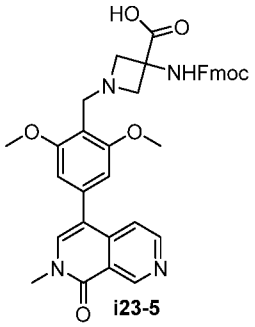
Step 3: Preparation of Ethyl 1-[[2,6-Dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-3-([[(9H-fluoren-9-yl)methoxy]carbonyl]amino)azetidine-3-carboxylate (i23-4)



i23-4

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

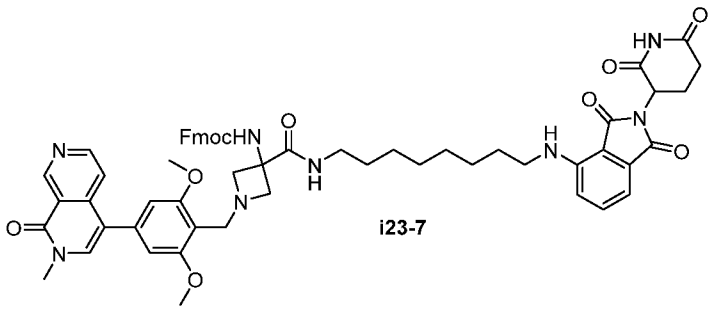
Step 4: Preparation of Ethyl 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-3-([[(9H-fluoren-9-yl)methoxy]carbonyl]amino)azetidine-3-carboxylic acid (i23-5)



i23-5

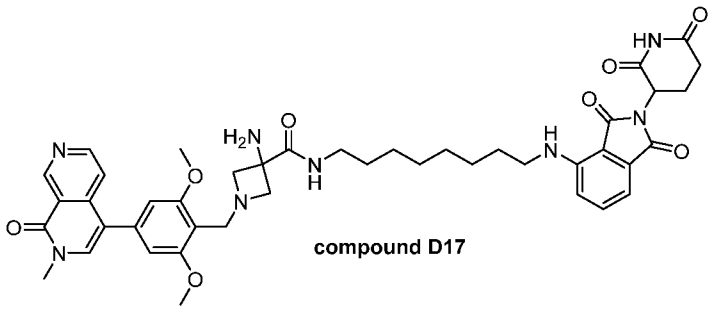
A solution of ethyl 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-3-([[(9*H*-fluoren-9-yl)methoxy]carbonyl]amino)azetidine-3-carboxylate (100 mg, 0.148 mmol, 1 equiv) in concentrated HCl (2 mL) was stirred at 90 °C for 1 hour. The resulting mixture was concentrated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

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



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

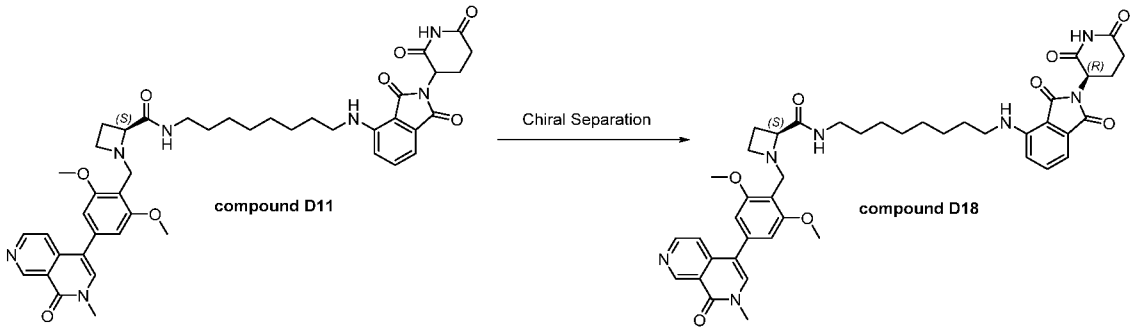
Step 6: Preparation of 3-Amino-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)azetidine-3-carboxamide (compound D17)



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

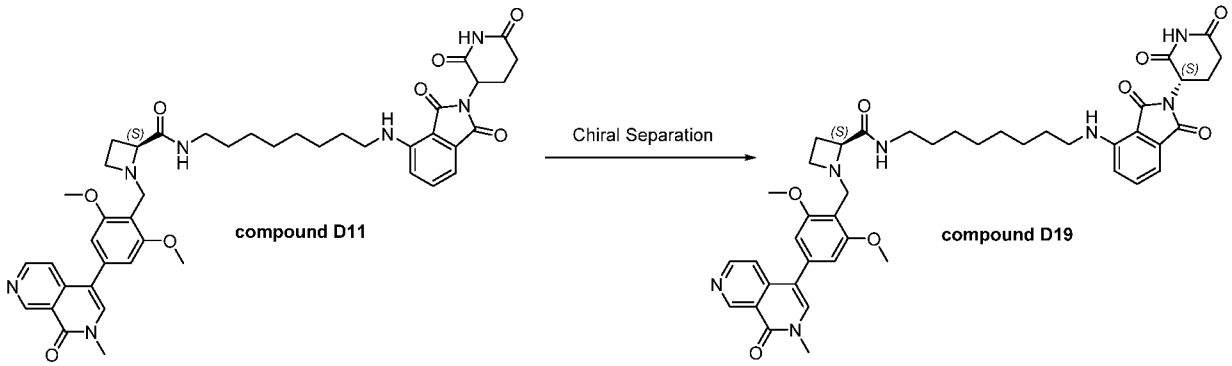
Hz, 2H), 6.75 (s, 2H), 6.30 (t, *J* = 5.9 Hz, 1H), 4.95 (dd, *J* = 12.4, 5.2 Hz, 1H), 4.10 (s, 2H), 3.95 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 6H), 3.50 (s, 3H), 3.24 (dq, *J* = 23.4, 6.6 Hz, 4H), 2.83-2.59 (m, 3H), 1.63 (s, 2H), 1.49 (s, 2H), 1.32 (d, *J* = 13.1 Hz, 10H). LCMS (ESI) m/z: [M+H]+ = 807.40.

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



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

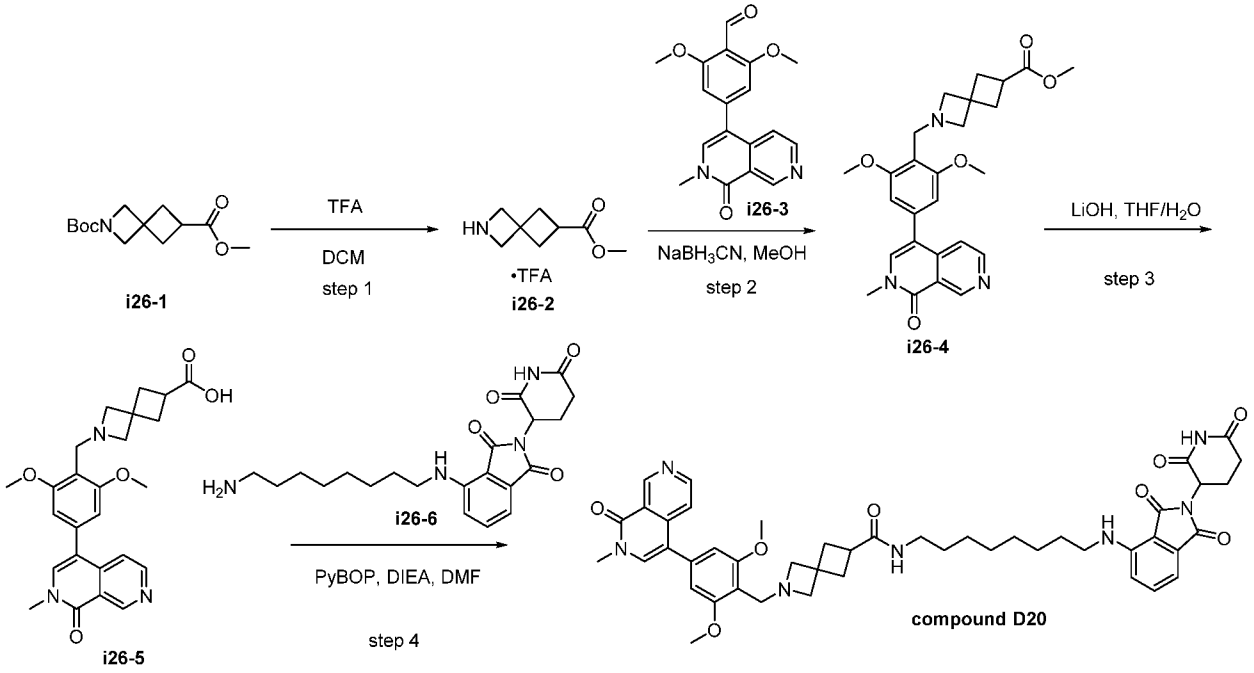
Example 25 – Preparation of (2S)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]octyl)azetidine-2-carboxamide (compound D19)



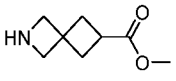
Compound D11 was further separated by chiral HPLC to afford (2*S*)-1-((2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl)methyl)-*N*-(8-((2-((*S*)-2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl)amino)octyl) azetidine-2-carboxamide (10 mg, 10.34%) as a yellow solid.^{1}H NMR (400 MHz, Methanol-*d4*)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

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

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

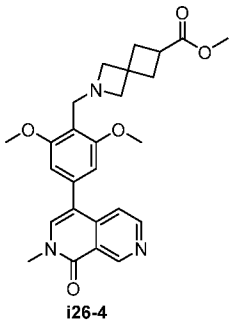


Step 1: Preparation of methyl 2-azaspiro[3.3]heptane-6-carboxylate trifluoroacetic acid (i26-2)



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

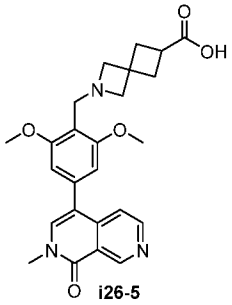
Step 2: Preparation of methyl 2-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-2-azaspiro[3.3]heptane-6-carboxylate (i26-4)



To a stirred solution of methyl 2-azaspiro[3.3]heptane-6-carboxylate trifluoroacetic acid (77.60 mg, 0.288 mmol, 1.00 equiv), Et_3N (116.67 mg, 1.153 mmol, 4 equiv), and 2,6-dimethoxy-4-(2-methyl-1-

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

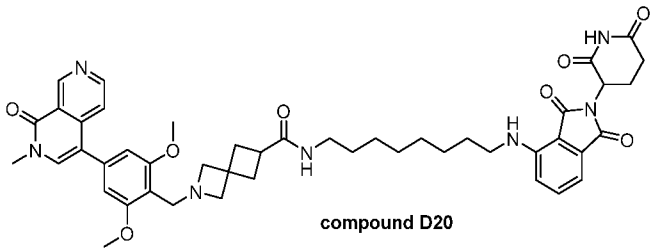
Step 3: Preparation of 2-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-2-azaspiro[3.3]heptane-6-carboxylic acid (i26-5)



i26-5

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

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

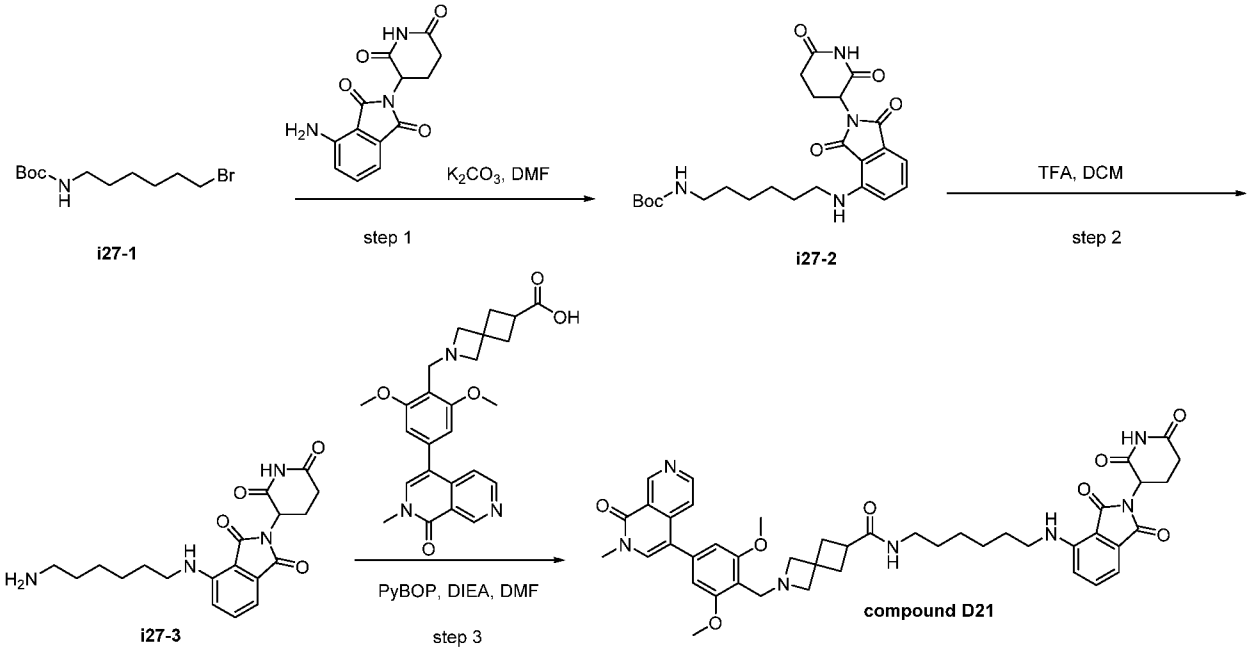


compound D20

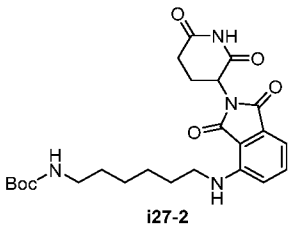
To a stirred solution of 6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2,4a,8a-tetrahydro-2,7-naphthyridin-4-yl)phenyl]methyl]spiro[3.3]heptane-2-carboxylic acid (45 mg, 0.100 mmol, 1 equiv) and 4-[(8-aminooctyl)amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (40.00 mg, 0.100 mmol, 1 equiv) in DMF (0.5 mL), was added DIEA (64.54 mg, 0.499 mmol, 5 equiv) and PyBOP (103.95 mg, 0.200 mmol, 2 equiv) at room temperature. The mixture was stirred for 1 h and directly purified by Prep-HPLC with the following conditions (conditions: SunFire C18 OBD Prep Column, 19 mm X 250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minuteute; Gradient: 29% B to 32% B in 8 minutes; 254 nm; R_t: 6.55 minutes) to afford 6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2,4a,8a-tetrahydro-2,7-naphthyridin-4-yl)phenyl]methyl]-*N*-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-

1H-isoindol-4-yl]amino]octyl)spiro[3.3]heptane-2-carboxamide (14.1 mg, 14.24%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.54 (d, *J* = 0.9 Hz, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 7.78 (s, 1H), 7.65 – 7.50 (m, 2H), 7.04 (d, *J* = 7.9 Hz, 2H), 6.86 (s, 2H), 5.05 (dd, *J* = 12.6, 5.7 Hz, 1H), 4.63 (s, 2H), 4.44 (s, 2H), 4.18 (s, 3H), 3.97 (s, 6H), 3.88 (s, 1H), 3.71 (s, 3H), 3.34 – 3.11 (m, 3H), 3.10 – 2.67 (m, 5H), 2.61 – 2.37 (m, 4H), 2.27 – 2.13 (m, 1H), 1.67 (q, *J* = 7.0 Hz, 2H), 1.59 – 1.26 (m, 10H). LCMS (ESI) m/z: [M+H]+ = 832.5.

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

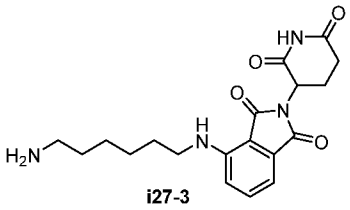


Step 1: preparation o tert-butyl N-(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]hexyl) carbamate (i27-2)



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

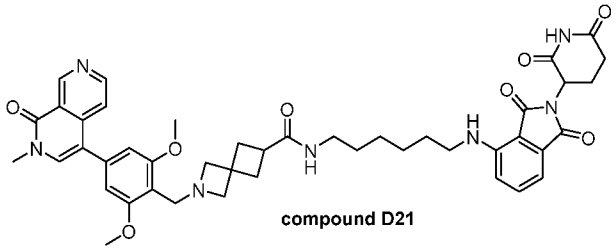
Step 2: Preparation of 4-[(6-aminohexyl)amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione trifluoroacetic acid (i27-3)



i27-3

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

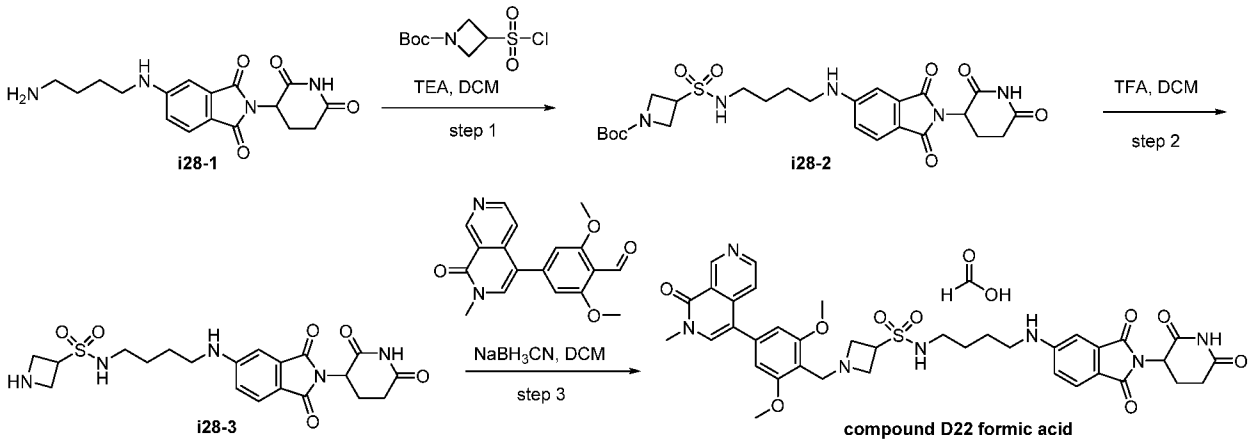
Step 3: Preparation of 6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2,4a,8a-tetrahydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]hexyl) spiro[3.3]heptane-2-carboxamide (compound D21)



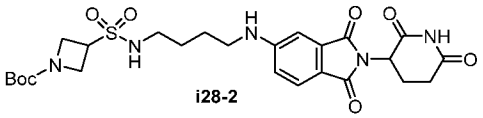
compound D21

To a stirred solution of 6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2,4a,8a-tetrahydro-2,7-naphthyridin-4-yl)phenyl]methyl]spiro[3.3]heptane-2-carboxylic acid (30 mg, 0.067 mmol, 1 equiv) in DMF (0.5 mL) was added DIEA (43.03 mg, 0.333 mmol, 5 equiv), PyBOP (69.30 mg, 0.133 mmol, 2 equiv), and 4-[(6-aminohexyl)amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1*H*-isoindole-1,3-dione(24.80 mg, 0.067 mmol, 1 equiv). The reaction was stirred at ambient atmosphere for 1 hour. The mixture was purified directly by Prep-HPLC (condition: SunFire C18 OBD Prep Column, 100 Å, 5 μm, 19 mm X 250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minuteute; Gradient: 12% B to 38% B in 8 minutes; 254 nm; R_t: 7.58 minutes), to afford 6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2,4a,8a-tetrahydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]hexyl)spiro[3.3]heptane-2-carboxamide(11.2mg,20.90%) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.52 (s, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 7.77 (s, 1H), 7.61 (d, *J* = 5.8 Hz, 1H), 7.50 – 7.39 (m, 1H), 7.01 (dd, *J* = 17.7, 7.7 Hz, 2H), 6.85 (s, 2H), 5.09 (dd, *J* = 12.9, 5.5 Hz, 1H), 4.42 (s, 2H), 4.16 (d, *J* = 3.1 Hz, 4H), 3.96 (s, 6H), 3.78 (t, *J* = 7.4 Hz, 2H), 3.71 (s, 3H), 3.50 (q, *J* = 7.3 Hz, 1H), 3.20 (qd, *J* = 7.3, 5.4 Hz, 9H), 2.99 – 2.87 (m, 2H), 2.91 – 2.83 (m, 1H), 2.75 – 2.61 (m, 1H), 2.53 (s, 2H), 2.53 – 2.47 (m, 1H), 2.47 – 2.37 (m, 2H), 2.22 - 2.09 (m, 2H), 1.94 (s, 2H), 1.93 (s, 6H), 1.61 (s, 1H), 1.51 (tt, *J* = 15.1, 8.0 Hz, 4H), 1.46 – 1.26 (m, 23H), 1.12 (t, *J* = 7.3 Hz, 10H), 0.91 (q, *J* = 9.7, 7.9 Hz, 3H). LCMS (ESI) m/z: [M+H]+ = 804.40.

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

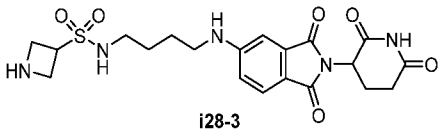


Step 1: Preparation of tert-butyl-3-[(4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]butyl)sulfamoyl]azetidine-1-carboxylate (i28-2)



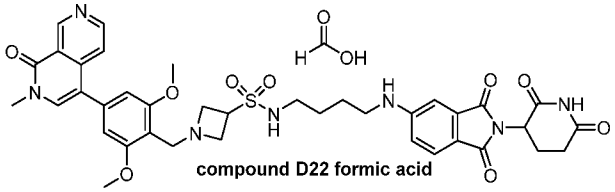
To a stirred mixture of 5-[(4-aminobutyl)amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (60.00 mg, 0.174 mmol, 1.00 equiv) and *tert*-butyl 3-(chlorosulfonyl)azetidine-1-carboxylate (111.38 mg, 0.436 mmol, 2.50 equiv) in DCM (2.00 mL) was added TEA (52.89 mg, 0.523 mmol, 3.00 equiv). After stirring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

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



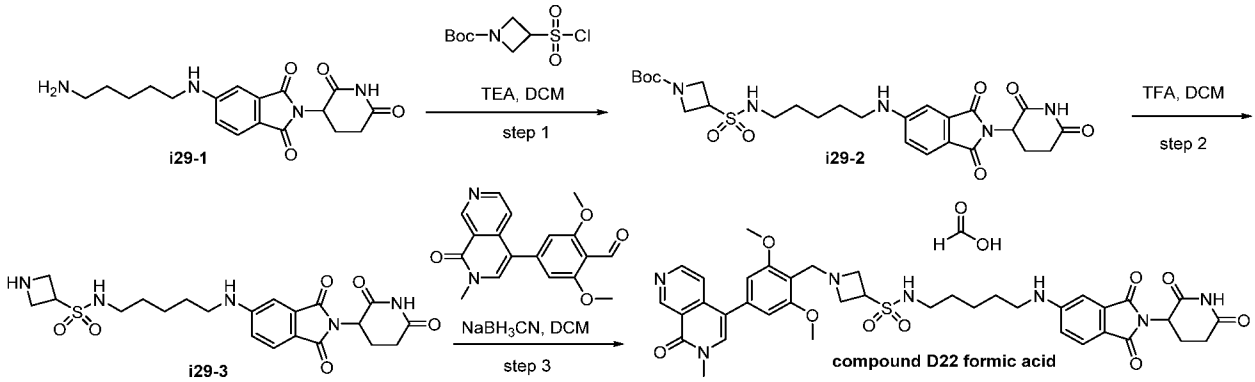
To a stirred mixture of *tert*-butyl-3-[(4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl] amino]butyl)sulfamoyl]azetidine-1-carboxylate (78.00 mg, 0.138 mmol, 1.00 equiv) in DCM (2.00 mL, 0.012 mmol, 0.10 equiv) was added TFA (0.40 mL, 5.385 mmol, 38.91 equiv). After stirring for 1 hour at room temperature, the resulting mixture was concentrated under reduced pressure. The residue was used in the next step directly without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 464.15.

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

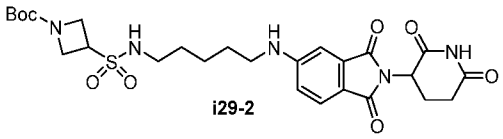


A mixture of *N*-(4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]amino]butyl) azetidine-3-sulfonamide (64.17 mg, 0.138 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (44.90 mg, 0.138 mmol, 1.00 equiv) in DMF (2 mL) was stirred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

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

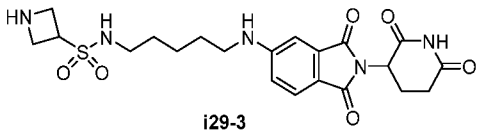


Step 1: Preparation of tert-butyl-3-[(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]pentyl) sulfamoyl]azetidine-1-carboxylate (i28-2)



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

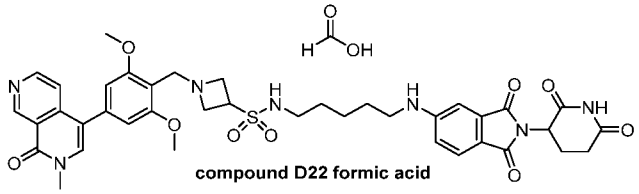
Step 2: Preparation of N-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)pentyl)azetidine-3-sulfonamide (i28-3)



i29-3

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

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

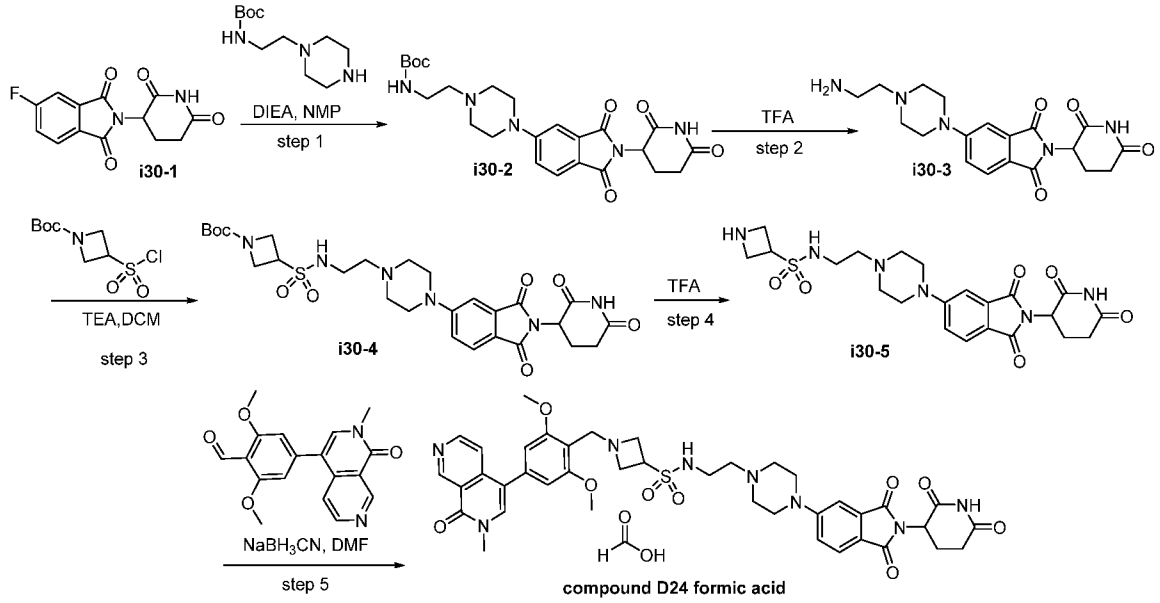


compound D22 formic acid

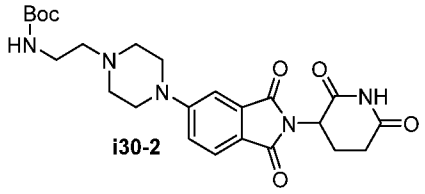
A mixture of *N*-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl]amino]pentyl) azetidine-3-sulfonamide (48.54 mg, 0.102 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (39.56 mg, 0.122 mmol, 1.20 equiv) in THF (2 mL) was stirred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

2.61 – 2.51 (m, 3H), 2.06 – 1.93 (t, *J* = 12.7 Hz, 1H), 1.60 – 1.51 (m, 2H), 1.50 – 1.42 (m, 2H), 1.42 – 1.32 (m, 2H). LCMS (ESI) m/z: $[M+H]^+$ = 786.28.

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

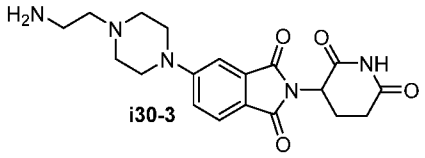


Step 1: Preparation of tert-butyl N-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)carbamate (i30-2)



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

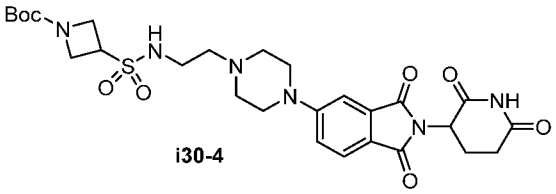
Step 2: Preparation of 5-*[4-(2-aminoethyl)piperazin-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (i30-3)*



i30-3

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

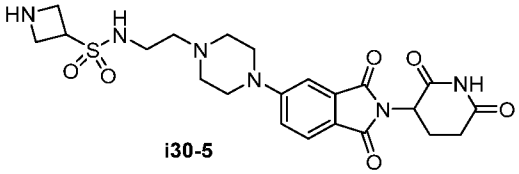
Step 3: Preparation of tert-butyl 3-[(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)sulfamoyl]azetidine-1-carboxylate (i30-4)



i30-4

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

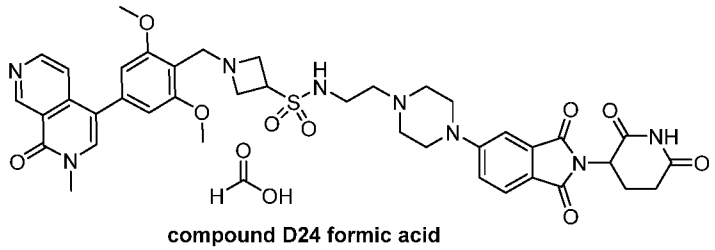
Step 4: Preparation of N-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)azetidine-3-sulfonamide (i30-5)



i30-5

A solution of *tert*-butyl 3-[(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl) sulfamoyl]azetidine-1-carboxylate (500.00 mg, 0.827 mmol, 1.00 equiv) and TFA (3.00 mL) in DCM (5.00 mL) was stirred for 1 hour at room temperature. The resulting mixture was concentrated under vacuum. This resulted in *N*-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)azetidine-3-sulfonamide (400 mg, 95.87%) as a green solid. LCMS (ESI) m/z: $[M+H]^+$ = 505.

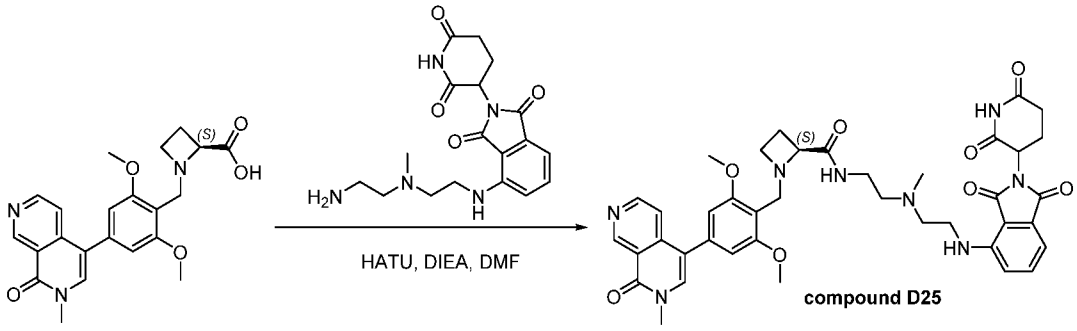
Step 5: Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)azetidine-3-sulfonamide formic acid (compound D24 formic acid)



compound D24 formic acid

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

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

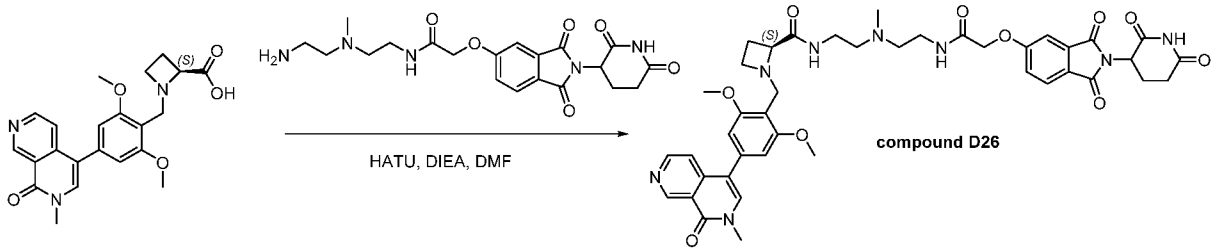


compound D25

To a solution of (2*S*)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-2-carboxylic acid (80 mg, 0.195 mmol, 1.00 equiv) and DIEA (75.8 mg, 0.586 mmol, 3.00 equiv) in DMF (1.50 mL) was added HATU (111.4 mg, 0.293 mmol, 1.50 equiv), and the resulting solution was stirred at room temperature for 1 hour. The crude mixture was directly purified by Prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100 Å, 5 μm, 19 mm X 250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minuteute; Gradient: 7% B to 22% B in 8

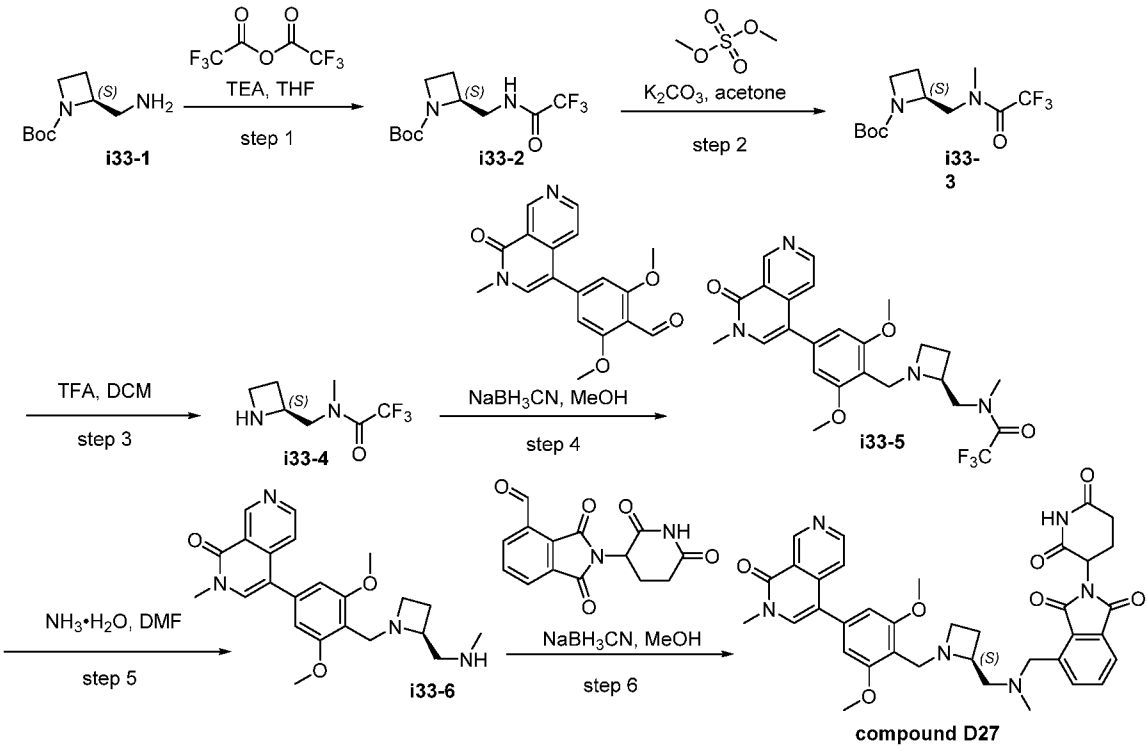
minutes; 254 nm; R_t: 7.75 minutes) to afford (2*S*)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-*N*-[2-[(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino]ethyl)(methyl)amino]ethyl]azetidine-2-carboxamide (5.5 mg, 3.5%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.45 (d, *J* = 1.1 Hz, 1H), 8.67 (d, *J* = 5.8 Hz, 1H), 7.72 (s, 1H), 7.63 (d, *J* = 5.9 Hz, 1H), 7.54-7.42 (m, 1H), 6.99 (d, *J* = 7.1 Hz, 1H), 6.91 (dd, *J* = 8.5, 3.1 Hz, 1H), 6.71 (d, *J* = 0.9 Hz, 2H), 5.13-5.02 (m, 1H), 3.86 (s, 8H), 3.66 (d, *J* = 1.0 Hz, 5H), 3.28 (s, 5H), 2.76-2.66 (m, 6H), 2.53-2.42 (m, 2H), 2.34 (s, 3H), 2.30-2.19 (m, 1H), 2.15 -1.94 (m, 2H). LCMS (ESI) m/z: [M+H]+ = 765.30.

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

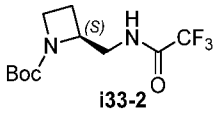


To a solution of (2*S*)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-2-carboxylic acid (30 mg, 0.073 mmol, 1.00 equiv) and DIEA (28.4 mg, 0.220 mmol, 3.00 equiv) in DMF (1.00 mL) was added HATU (41.8 mg, 0.110 mmol, 1.50 equiv) and *N*-[2-[(2-aminoethyl)(methyl)amino]ethyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl]oxy]acetamide (31.61 mg, 0.073 mmol, 1.00 equiv). The resulting solution was stirred at room temperature for 1 hour. The crude mixture was directly purified by Prep-HPLC (condition: SunFire C18 OBD Prep Column , 100 Å, 5 μm, 19 mm X 250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minuteute; Gradient: 5% B to 5% B in 2 minutes; 254 nm; R_t: 9.88 minutes) to afford *N*-[2-[(2-[[(2*S*)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidin-2-yl]formamido]ethyl)(methyl)amino]ethyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]oxy]acetamide (4.8 mg, 7.5%) as a yellow solid. ^{1}H NMR (300 MHz, Acetonitrile-*d3*) δ 9.52 (s, 1H), 9.11 (s, 1H), 8.70 (d, *J* = 5.7 Hz, 1H), 8.20-8.02 (m, 1H), 7.79 (t, *J* = 6.5 Hz, 2H), 7.57 (d, *J* = 5.0 Hz, 2H), 7.45-7.23 (m, 2H), 6.73 (s, 2H), 4.99 (dd, *J* = 12.1, 5.3 Hz, 1H), 4.63 (s, 2H), 4.38 (s, 1H), 4.11 (s, 2H), 3.87 (s, 6H), 3.72-3.60 (m, 5H), 3.59-3.49 (m, 2H), 3.45 (d, *J* = 5.6 Hz, 2H), 3.01 (dt, *J* = 11.1, 5.7 Hz, 4H), 2.83-2.72 (m, 2H), 2.72-2.60 (m, 5H), 2.13 (ddd, *J* = 10.6, 5.5, 3.1 Hz, 2H). LCMS (ESI) m/z: [M+H]+ = 823.45.

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

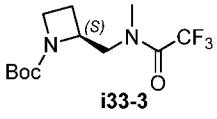


Step 1: Preparation of tert-butyl (2S)-2-((2,2,2-trifluoroacetamido)methyl)azetidine-1-carboxylate (i33-2)



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

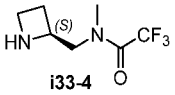
Step 2: Preparation of tert-butyl (2S)-2-[(2,2,2-trifluoro-N-methylacetamido)methyl]azetidine-1-carboxylate (i33-3)



To a solution of *tert*-butyl (2*S*)-2-[(2,2,2-trifluoroacetamido)methyl]azetidine-1-carboxylate (1270.00 mg, 4.499 mmol, 1.00 equiv) and dimethyl sulfate (681.00 mg, 5.399 mmol, 1.2 equiv) in acetone (15.00 mL) was added K_2CO_3 (621.83 mg, 4.499 mmol, 1 equiv). The mixture was stirred at 25 °C for 12 hours. The resulting mixture were evaporated to dryness to afford *tert*-butyl (2*S*)-2-[(2,2,2-

trifluoro-*N*-methylacetamido)methyl]azetidine-1-carboxylate (1640 mg,123.02%) as a yellow oil that was used directly without further purification. LCMS (ESI) m/z: [M+H]+ = 297.

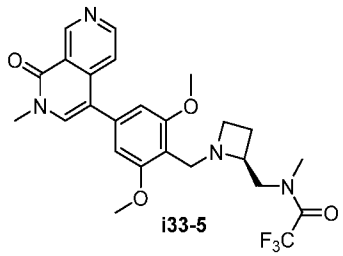
Step 3: Preparation of N-[(2S)-azetidin-2-ylmethyl]-2,2,2-trifluoro-N-methylacetamide (i33-4)



i33-4

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

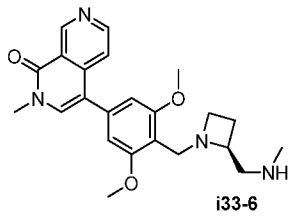
Step 4: Preparation of N-[[(2S)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] azetidin-2-yl]methyl]-2,2,2-trifluoro-N-methylacetamide (i33-5)



i33-5

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

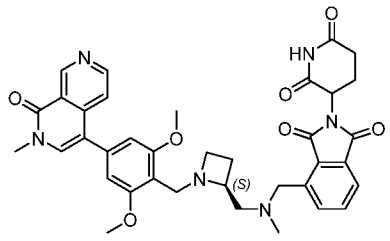
Step 5: Preparation of (S)-4-(3,5-dimethoxy-4-((2-((methylamino)methyl)azetidin-1-yl)methyl)phenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (i33-6)



i33-6

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

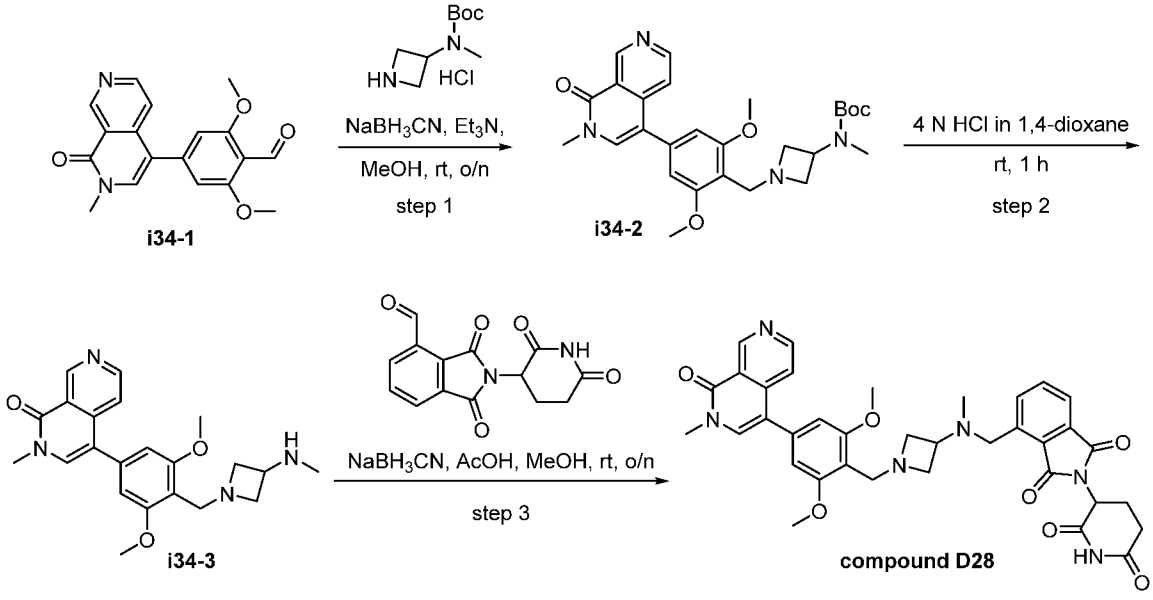
Step 6: Preparation of 4-(((((S)-1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)azetidin-2-yl)methyl)(methyl)amino)methyl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound D27)



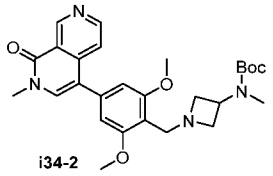
compound D27

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

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



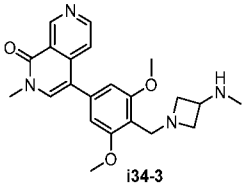
Step 1: Preparation of tert-butyl (1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)azetidin-3-yl)(methyl)carbamate (i34-2)



i34-2

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

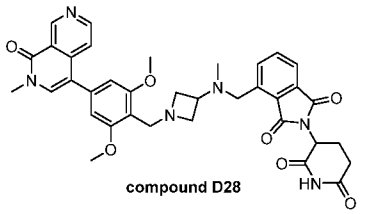
Step 2: Preparation of 4-(3,5-dimethoxy-4-((3-(methylamino)azetidin-1-yl)methyl)phenyl) -2-methyl-2,7-naphthyridin-1(2H)-one (i34-3)



i34-3

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

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

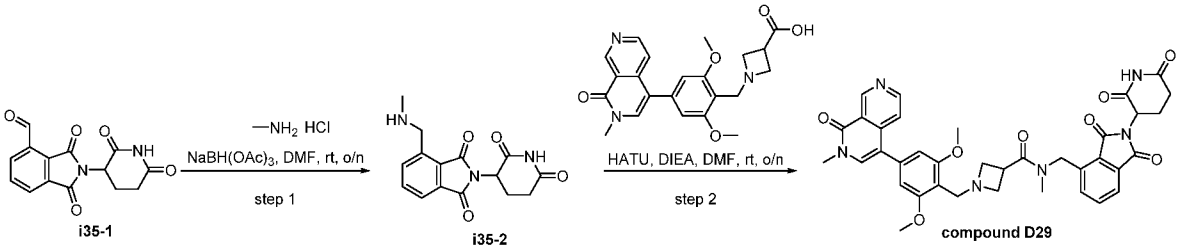


compound D28

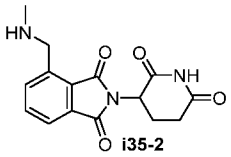
To a mixture of 4-(3,5-dimethoxy-4-[[3-(methylamino)azetidin-1-yl]methyl]phenyl)-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (30.00 mg, 0.076 mmol, 1.00 equiv) and 2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo- 2,3-dihydro-1H-isoindole-4-carbaldehyde (21.77 mg, 0.076 mmol, 1.00 equiv) in MeOH (2.00 mL) was added AcOH (0.05 mg, 0.001 mmol, 0.01 equiv). The mixture was stirred for 1 hour. $NaBH_3CN$ (9.56 mg, 0.152 mmol, 2.00 equiv) was added. The resulting mixture was stirred for 1

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

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

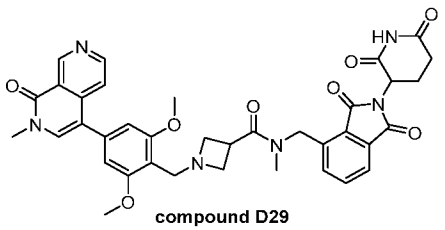


Step 1: Preparation of 2-(2,6-dioxopiperidin-3-yl)-4-((methylamino)methyl)isoindoline-1,3-dione (i35-2)



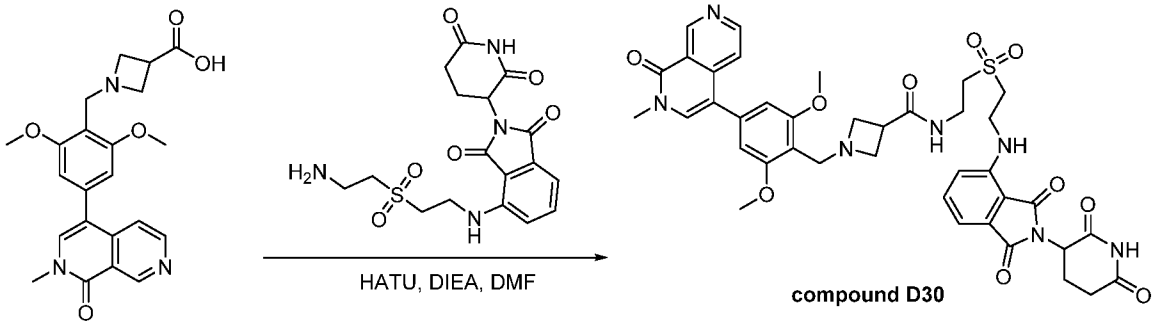
To a solution of 2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindoline-4-carbaldehyde (70.00 mg, 0.245 mmol, 1.00 equiv) in DMF (3.00 mL) was added methanamine hydrochloride (24.77 mg, 0.367 mmol, 1.50 equiv). The resulting mixture was stirred overnight at room temperature. Then $NaBH(OAc)_3$ (103.88 mg,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

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



To a mixture of 1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)azetidine-3-carboxylic acid (40.77 mg, 0.100 mmol, 1.00 equiv) in DMF (3.00 mL) was added HATU (94.65 mg, 0.250 mmol, 2.50 equiv) and DIEA (38.61 mg, 0.300 mmol, 3.00 equiv). The resulting mixture was stirred for 2 hours at room temperature. Then 2-(2,6-dioxopiperidin-3-yl)-4-((methylamino)methyl)isoindoline-1,3-dione (30.00 mg, 0.100 mmol, 1.00 equiv) was added. The resulting mixture was stirred for 1 hour. The crude product was purified by preparative HPLC (conditions: XSelect CSH Prep C_{18} OBD Column, 5 μm, 19*150 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minuteute; Gradient: 12% B to 12% B in 2 minutes; 254/220 nm; R_t: 13.57 min Fractions containing the desired compound were evaporated to dryness to afford 1-(2,6-dimethoxy-4-(2-methyl-1-oxo- 1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-*N*-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)methyl)-N-methylazetidine-3-carboxamide (17.10 mg, 24.25%) as a light yellow solid. ^{1}H-NMR (400 MHz, Methanol-*d4*) δ 9.58 (s, 1H), 8.69 (t, *J* = 7.8 Hz, 1H), 7.98–7.87 (m, 2H), 7.85 – 7.77 (m, 2H), 7.72 - 7.64 (m, 1H), 6.89 (d, *J* = 8.2 Hz, 2H), 5.22 – 5.01 (m, 3H), 4.65 – 4.36 (m, 5H), 4.34 - 4.21 (m, 1H), 4.20 - 4.07 (m, 1H), 4.01 – 3.92 (m, 6H), 3.74 (s, 3H), 3.02 (s, 3H), 2.96 – 2.84 (m, 1H), 2.80 – 2.71 (m, 2H), 2.24 – 2.12 (m, 1H). LCMS (ESI) m/z: $[M+H]^+$ =693.35.

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

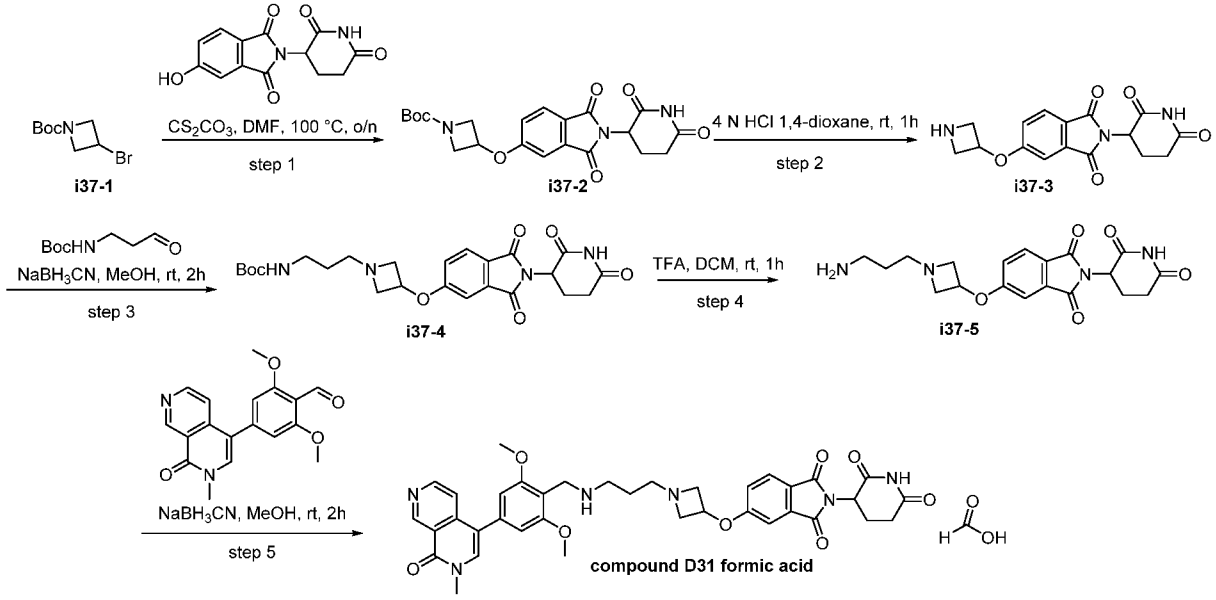


compound D30

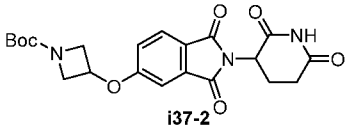
Into a stirred mixture of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] azetidine-3-carboxylic acid (53.00 mg, 0.129 mmol, 1.00 equiv) and DIEA (*N,N*-diisopropylamine) (50.19 mg, 0.388 mmol, 3.00 equiv) in DMF (dimethylformamide) (1.00 mL) was added 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium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

1H), 7.67-7.55 (m, 2H), 7.13 (t, *J* = 7 .6 Hz, 2H), 6.83 (s, 2H), 5.06 (dd, *J* = 12.3, 5.4 Hz, 1H), 4.37 (s, 2H), 4.23-4.06 (m, 4H), 3.95 (s, 6H), 3.89 (t, *J* = 6.3 Hz, 2H), 3.77-3.69 (m, 2H), 3.71 (s, 3H), 3.52 (q, *J* = 6.9, 6.3 Hz, 3H), 3.38 (t, *J* = 6.3 Hz, 2H), 2.62-2.93 (m, 3H), 2.07-2.17 (m, 1H). LCMS (ESI) m/z: $[M+H]^+$ = 800.35.

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

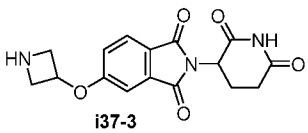


Step 1: Preparation of tert-butyl 3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)azetidine-1-carboxylate (i37-2)



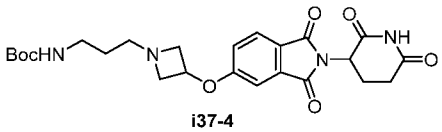
To a mixture of *tert*-butyl 3-bromoazetidine-1-carboxylate (2.00 g, 8.511 mmol, 1.00 equiv) and 2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindoline-1,3-dione (2.33 g, 8.511 mmol, 1.00 equiv) in DMF (30.00 mL) was added Cs_2CO_3 (5.53 g, 17.022 mmol, 2.00 equiv). The resulting mixture was stirred overnight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

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



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

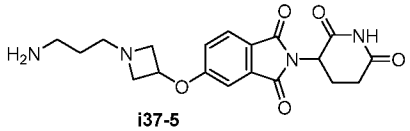
Step 3: Preparation of tert-butyl (3-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy) zetidin-1-yl)propyl)carbamate (i37-4)



i37-4

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

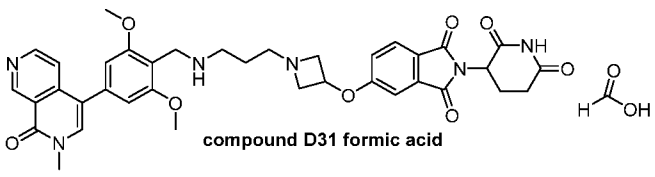
Step 4: Preparation of 5-((1-(3-aminopropyl)azetidin-3-yl)oxy)-2-(2,6-dioxopiperidin-3–yl) isoindoline-1,3-dione (i37-5)



i37-5

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

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

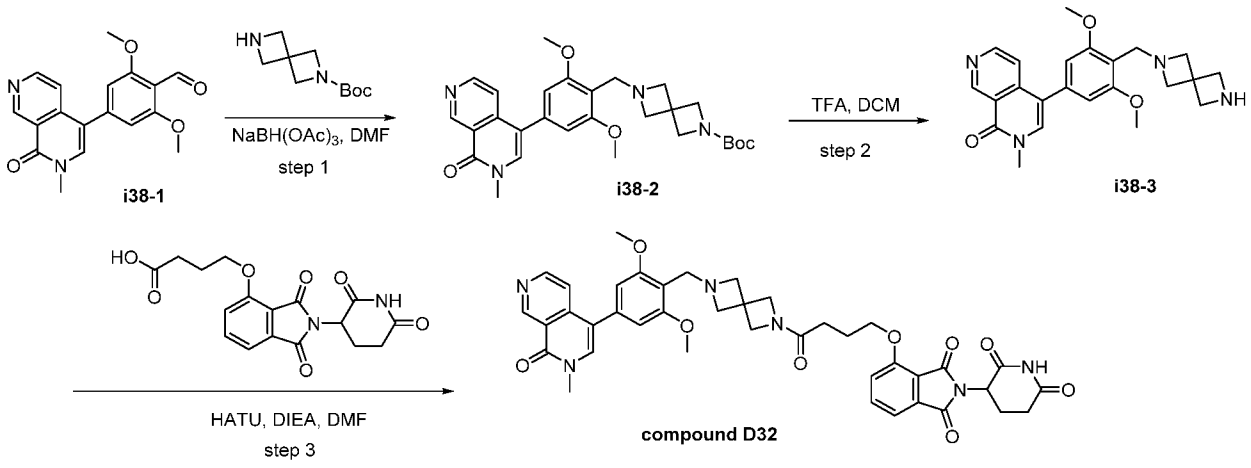


compound D31 formic acid

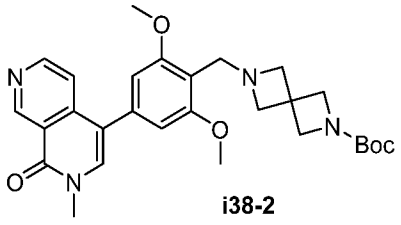
To a solution of 5-((1-(3-aminopropyl)azetidin-3-yl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline -1,3-dione (60.00 mg, 0.155 mmol, 1.00 equiv) in MeOH (5.00 mL, 123.495 mmol, 795.32 equiv) was added

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

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

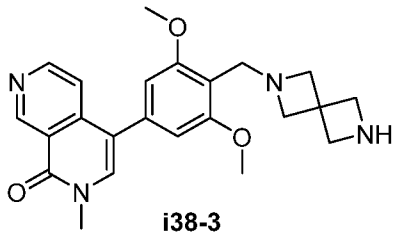


Step 1: Preparation of tert-butyl 6-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (i38-2)



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

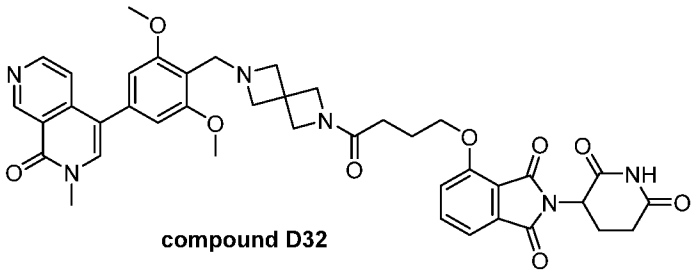
Step 2: Preparation of 4-(4-((2,6-diazaspiro[3.3]heptan-2-yl)methyl)-3,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (i38-3)



i38-3

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

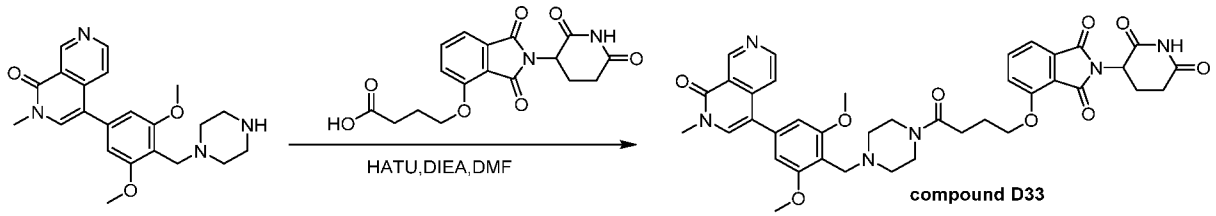
Step 3: Preparation of 4-(4-(6-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-2,6-diazaspiro[3.3]heptan-2-yl)-4-oxobutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound D32)



compound D32

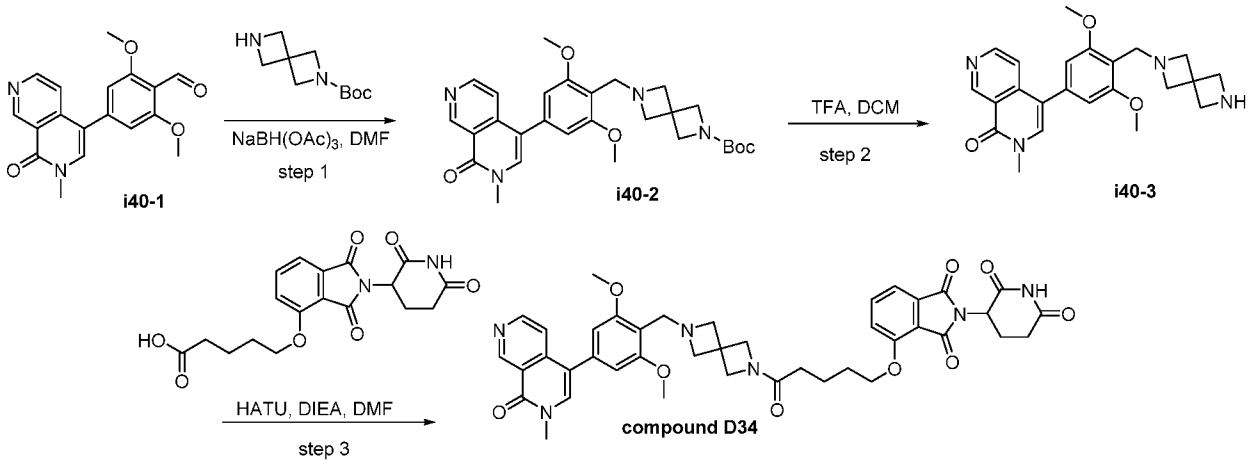
To a solution of 4-(4-[2,6-diazaspiro[3.3]heptan-2-ylmethyl]-3,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1-one (40.00 mg, 0.098 mmol, 1.00 equiv) and 4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]butanoic acid (35.46 mg, 0.098 mmol, 1.00 equiv) in DMF (1.0 mL) was added HATU (56.12 mg, 0.148 mmol, 1.5 equiv) and DIEA (31.80 mg, 0.246 mmol, 10 equiv). The mixture was stirred at 25 °C for 1 hour. The mixture was purified by prep-HPLC (conditions: Kinetex EVO C18 Column 21.2*150, 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 16% B to 26% B in 8 minutes; 254/220 nm; Rt: 7.03 minutes) to afford 4-[4-(6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-2,6-diazaspiro[3.3]heptan-2-yl)-4-oxobutoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (12 mg, 16.29%) as a white solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.53 (s, 1H), 8.70 (d, *J* = 5.8 Hz, 1H), 7.79 (dd, *J* = 8.5, 7.4 Hz, 1H), 7.78 (s, 1H), 7.62 (d, *J* = 5.8 Hz, 1H), 7.46 (dd, *J* = 14.7, 7.9 Hz, 2H), 6.86 (s, 2H), 5.13 (dd, *J* = 12.5, 5.4 Hz, 1H), 4.60 (s, 1H), 4.40 (d, *J* = 13.7 Hz, 4H), 4.32 – 4.19 (m, 6H), 4.14 (s, 2H), 3.96 (s, 6H), 3.71 (s, 3H), 2.95 – 2.68 (m, 3H), 2.53 – 2.34 (m, 2H), 2.20 – 2.10 (m, 3H). LCMS (ESI) m/z: [M+H]+ = 749.40.

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

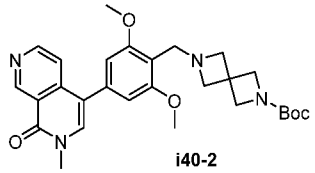


To a stirred mixture of 4-[3,5-dimethoxy-4-(piperazin-1-ylmethyl)phenyl]-2-methyl-2,7-naphthyridin-1-one (50.00 mg, 0.127 mmol, 1.00 equiv) and 4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]butanoic acid (45.67 mg, 0.127 mmol, 1.00 equiv) in DMF (2.00 mL) was added DIEA (163.82 mg, 1.268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

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



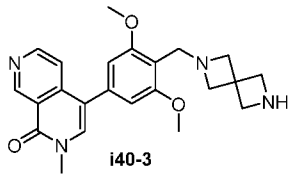
Step 1: Preparation of tert-butyl 6-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (i40-2)



i40-2

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

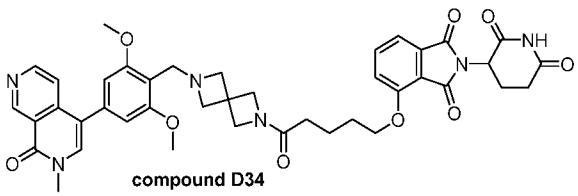
Step 2: Preparation of 4-(4-((2,6-diazaspiro[3.3]heptan-2-yl)methyl)-3,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (i40-3)



i40-3

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

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

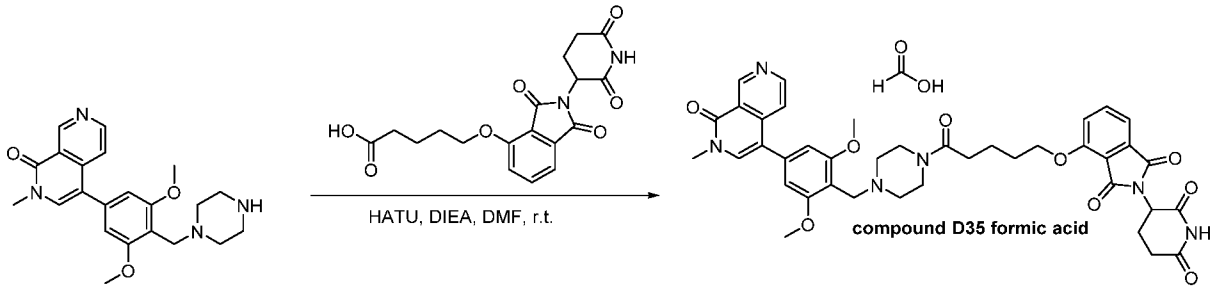


compound D34

To a solution of 4-(4-[2,6-diazaspiro[3.3]heptan-2-ylmethyl]-3,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1-one (40.00 mg, 0.098 mmol, 1.00 equiv) and 5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]pentanoic acid (36.84 mg, 0.098 mmol, 1 equiv) in DMF(1 mL) was added HATU (56.12 mg, 0.148 mmol, 1.5 equiv) and DIEA (31.80 mg, 0.246 mmol, 10 equiv). The mixture was stirred at 25 °C for 1 hour. The mixture was purified by prep-HPLC (conditions: XSelect CSH Prep C18 OBD

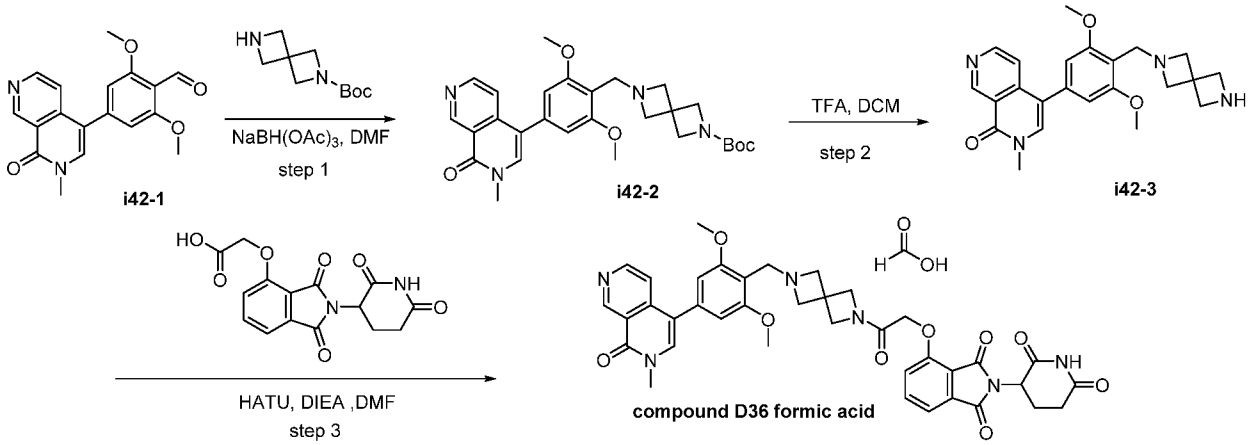
Column, 5 μm, 19*150 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 12% B to 22% B in 12 minutes; 254/220 nm; Rt: 10.52 minutes) to afford 4-[[5-(6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-2,6-diazaspiro[3.3]heptan-2-yl)-5-oxop entyl]oxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (10.1 mg, 13.46%) as a light yellow solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.58 (s, 1H), 8.73 – 8.67 (m, 1H), 7.92 (d, *J* = 6.9 Hz, 1H), 7.84 – 7.76 (m, 1H), 7.47 (t, *J* = 8.1 Hz, 2H), 6.89 (d, *J* = 3.5 Hz, 2H), 5.17 – 5.07 (m, 1H), 4.51 (d, *J* = 3.0 Hz, 2H), 4.45 – 4.31 (m, 6H), 4.27 (t, *J* = 5.5 Hz, 2H), 4.19 (s, 1H), 4.12 (s, 1H), 3.98 (d, *J* = 3.4 Hz, 6H), 3.74 (d, *J* = 1.7 Hz, 3H), 2.96 – 2.65 (m, 3H), 2.34 – 2.30 (m, 2H), 2.19 – 2.12 (m, 1H), 1.96 – 1.89 (m, 2H), 1.88 – 1.80 (m, 2H). LCMS (ESI) m/z: [M+H]+ = 763.40.

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

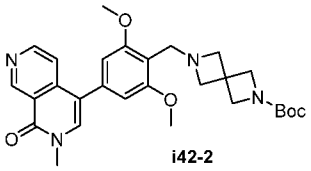


To a stirred solution of 4-[3,5-dimethoxy-4-(piperazin-1-ylmethyl)phenyl]-2-methyl-2,7-naphthyridin-1-one (50.0 mg, 0.127 mmol, 1.00 equiv) and 5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]pentanoic acid (47.5 mg, 0.127 mmol, 1.00 equiv) in DMF (1 mL) was added DIEA (163.8 mg, 1.268 mmol, 10.00 equiv) dropwise at room temperature. The resulting mixture was stirred for 10 min at room temperature. To the above mixture was added HATU (96.4 mg, 0.254 mmol, 2.00 equiv). The resulting mixture was stirred for additional 2 hours at room temperature. The residue was purified by reverse flash chromatography (conditions: SunFire C18 OBD Prep Column, 100Å, 5 μm, 19 mm X 250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 9 B to 27 B in 10 minutes; 254 nm; R_T: 10.12) to afford 4-[[5-(4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]piperazin-1-yl)-5-oxopentyl]oxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (6.6 mg, 6.7%) as a white solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.53 (d, *J* = 0.9 Hz, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.45 (br s, 0.13H, FA), 7.81 – 7.73 (m, 2H), 7.64 (dd, *J* = 5.8, 0.9 Hz, 1H), 7.45 (dd, *J* = 7.9, 6.2 Hz, 2H), 6.79 (s, 2H), 5.11 (dd, *J* = 12.5, 5.5 Hz, 1H), 4.28 (t, *J* = 5.7 Hz, 2H), 3.97 (s, 2H), 3.90 (s, 6H), 3.74 – 3.62 (m, 7H), 2.95 – 2.81 (m, 3H), 2.80 – 2.65 (m, 4H), 2.60 (t, *J* = 7.4 Hz, 2H), 2.17 – 2.07 (m, 1H), 1.99 – 1.83 (m, 4H). LCMS (ESI) m/z: [M+H]+ = 751.40

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

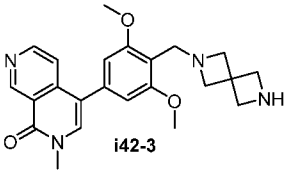


Step 1: Preparation of tert-butyl 6-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (i42-2)



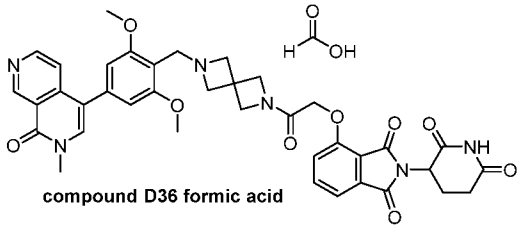
To a solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (700.00 mg, 2.158 mmol, 1.00 equiv) and *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate (427.91 mg, 2.158 mmol, 1.00 equiv) in DMF(10 mL) was added $NaBH(OAc)_3$ (914.85 mg, 4.317 mmol, 2.00 equiv). The resulting solution was stirred at 25 °C for 1 hour. The mixture was concentrated to give crude product that was purified by chromatography on silica gel eluted with MeOH]/DCM (6:94) to give *tert*-butyl 6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-2,6-diazaspiro[3.3]heptane-2-carboxylate (808mg, 73.90%) as an off-white solid. LCMS (ESI) m/z: [M+H]+ = 507.

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



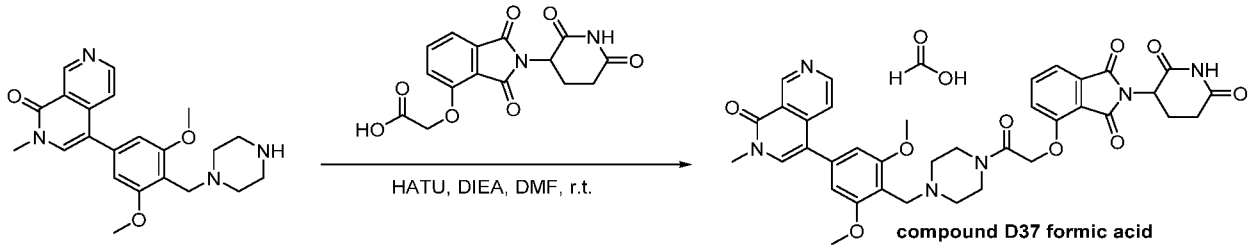
To a solution of *tert*-butyl 6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-2,6-diazaspiro[3.3]heptane-2-carboxylate (708.00 mg, 1.398 mmol, 1.00 equiv) and TFA (1.50 mL, 20.195 mmol, 14.45 equiv) in DCM (7 mL) was stirred at 25 °C for 1 hour. The mixture was concentrated to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

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



To a solution of 4-(4-[2,6-diazaspiro[3.3]heptan-2-ylmethyl]-3,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1-one (40.00 mg, 0.098 mmol, 1.00 equiv) and [[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetic acid (32.70 mg, 0.098 mmol, 1.00 equiv) in DMF (1 mL) was added HATU (56.12 mg, 0.148 mmol, 1.50 equiv) and DIEA (31.80 mg, 0.246 mmol, 10 equiv). The mixture was stirred at 25 °C for 1 hour. The mixture was purified by prep-HPLC (conditions: SunFire Prep C18 OBD Column 19×150 mm 5 μm 10 nm;Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 8% B to 21% B in 10 minutes; 254/220 nm; Rt: 8.20 minutes) to afford 4-[2-(6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-2,6-diazaspiro[3.3]heptan-2-yl)-2-oxoethoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (6.2 mg, 8.74%) as a white solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.51 (s, 1H), 8.68 (d, *J* = 5.8 Hz, 1H), 8.55 (br s, 0.46H, FA), 7.80 (s, 1H), 7.69 (t, *J* = 8.1 Hz, 1H), 7.62 (d, *J* = 5.7 Hz, 1H), 7.44 (dd, *J* = 11.8, 7.2 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 6.87 (s, 2H), 5.19 – 5.10 (m, 1H), 4.69 – 4.51 (m, 6H), 4.39 (s, 2H), 4.34 – 4.26 (m, 2H), 4.22 (s, 2H), 3.97 (s, 6H), 3.69 (s, 3H), 2.95 – 2.68 (m, 3H), 2.20 – 2.09 (m, 1H). LCMS (ESI) m/z: [M+H]+ = 721.35.

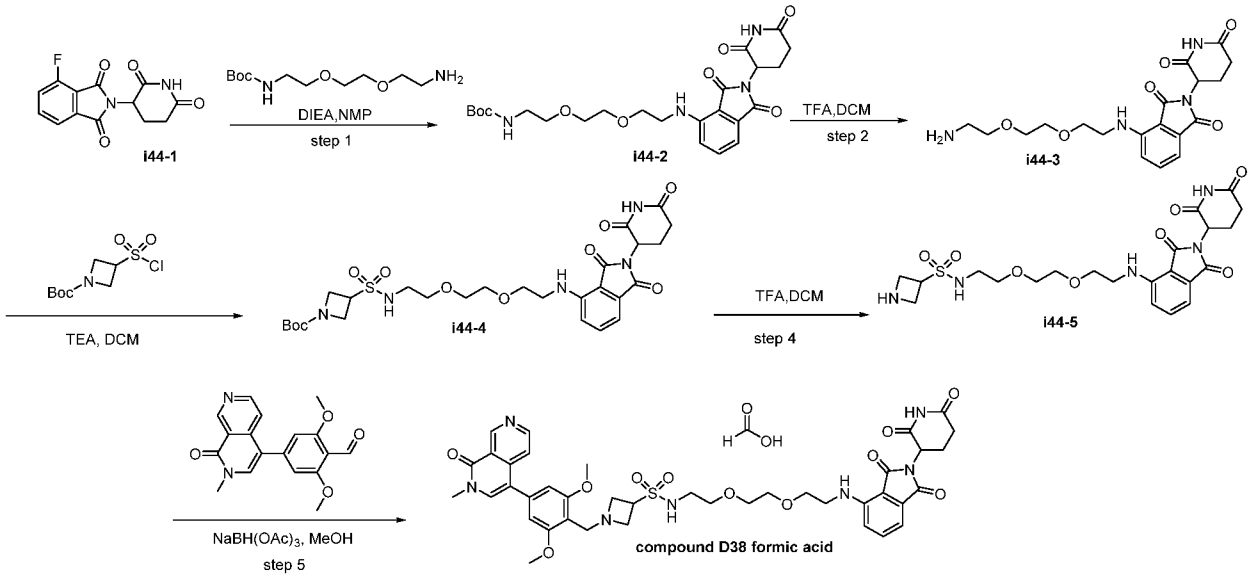
Example 43 – Preparation of 4-(2-(4-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)piperazin-1-yl)-2-oxoethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (compound D37 formic acid)



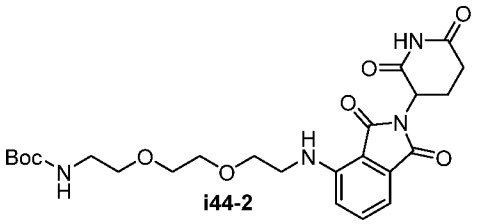
To a stirred solution of 4-[3,5-dimethoxy-4-(piperazin-1-ylmethyl)phenyl]-2-methyl-2,7-naphthyridin-1-one (50.0 mg, 0.127 mmol, 1.00 equiv) and [[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetic acid (42.1 mg, 0.127 mmol, 1.00 equiv) in DMF (1 mL) was added DIEA (163.8 mg, 1.268 mmol, 10.00 equiv) dropwise at room temperature. The resulting mixture was stirred for 10 minutes at room temperature. To the above mixture was added HATU (96.4 mg, 0.254 mmol, 2.00 equiv). The resulting mixture was stirred for additional 2 hours at room temperature. The residue was purified by reverse flash chromatography (conditions: SunFire C18 OBD Prep Column, 100Å, 5 μm, 19 mm X 250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 9 B to 27 B in 10 minutes; 254 nm; R_T: 10.12 minutes) to afford 4-[2-(4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]piperazin-1-yl)-2-oxoethoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione

formic acid (12.2 mg,13.6%) as a white solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.54 (s, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.34 (br s, 0.28H, FA), 7.83 – 7.73 (m, 2H), 7.67 – 7.61 (m, 1H), 7.52 (d, *J* = 7.1 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 6.81 (s, 2H), 5.15 – 5.09 (m, 3H), 4.08 (s, 2H), 3.92 (s, 6H), 3.83 – 3.73 (m, 4H), 3.72 (s, 3H), 3.05 – 2.96 (m, 2H), 2.96 – 2.80 (m, 3H), 2.77 – 2.69 (m, 2H), 2.17 – 2.11 (m, 1H). LCMS (ESI) m/z: [M+H]+ = 709.35.

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

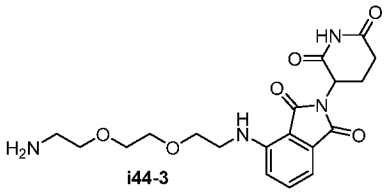


Step 1: Preparation of tert-butyl N-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]ethoxy)ethoxy]ethyl]carbamate (i44-2)



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

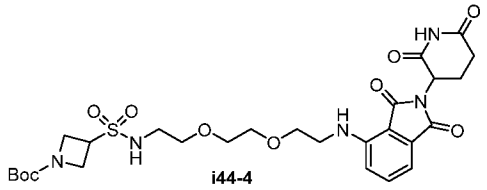
Step 2: Preparation of 4-([2-[2-(2-aminoethoxy)ethoxy]ethyl]amino)-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro -1H-isoindole-1,3-dione (i44-3)



i44-3

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

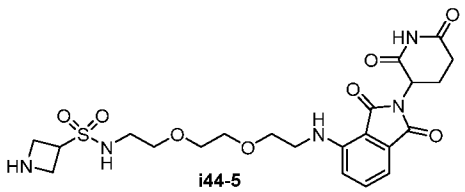
Step 3: Preparation of tert-butyl 3-([2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]eth oxy)ethoxy]ethyl]sulfamoyl)azetidine-1-carboxylate (i44-4)



i44-4

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

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

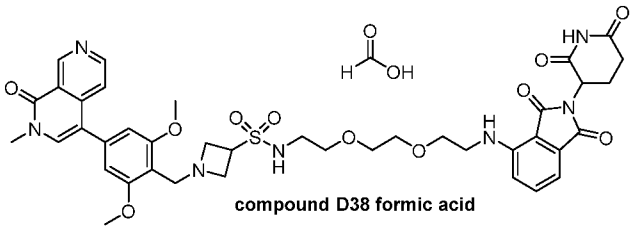


i44-5

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

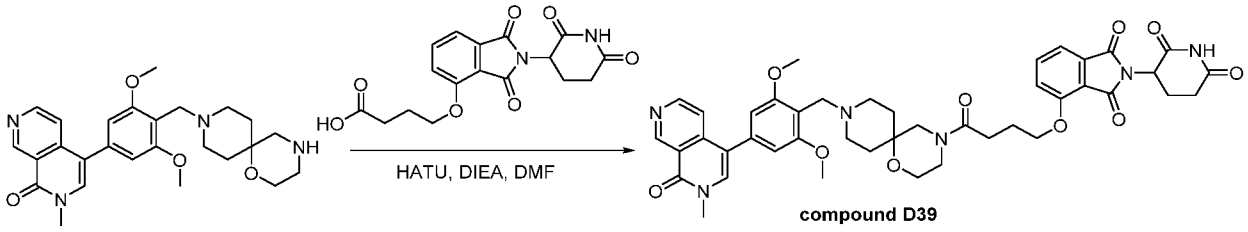
crude product 130 mg was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]+ = 524.

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



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

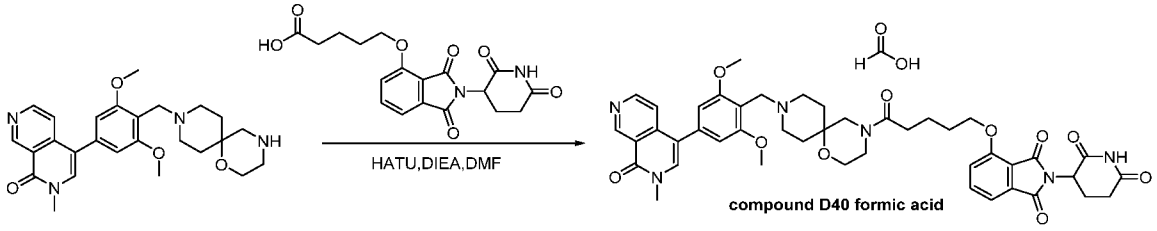
Example 45 – Preparation of 4-[4-(9-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-4-oxobutoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione. (compound D39)



To a stirred solution of 4-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-2-methyl -2,7naphthyridin-1-one (20.00 mg, 0.043 mmol, 1.00 equiv) and 4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]butanoic acid (15.00 mg, 0.042 mmol, 0.97 equiv) in DMF was added HATU (25.00 mg, 0.066 mmol, 1.53 equiv) and DIEA (60.00 mg, 0.464 mmol, 10.78 equiv) in portions at room temperature. The resulting mixture was stirred for 2 hours at room temperature. The crude product was purified by Prep-HPLC (conditions: Gemini-NX C18 AXAI Packed, 21.2*150 mm 5 μm; mobile phase, Water (0.1% FA) and ACN (14% Phase B up to 19% in 10 minutes); Detector, UV). This resulted in 4-[4-

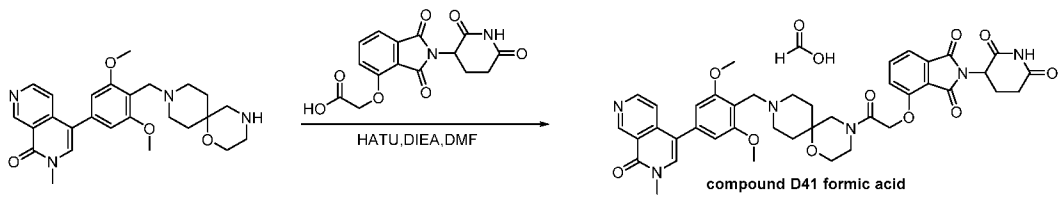
(9-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-1-oxa-4,9diaza spiro[5.5]undecan-4-yl)-4-oxobutoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (5.1 mg, 14.68%) as a white solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.55 (s, 1H), 8.70 (d, *J* = 5.6 Hz, 1H), 7.85 – 7.75 (m, 2H), 7.63 (d, *J* = 5.8 Hz, 1H), 7.57 – 7.43 (m, 2H), 6.87 (d, *J* = 5.2 Hz, 2H), 5.12 (d, *J* = 11.8 Hz, 1H), 4.41 (s, 2H), 4.37 – 4.27 (m, 2H), 3.96 (d, *J* = 8.2 Hz, 6H), 3.84 – 3.60 (m, 9H), 3.58 – 3.45 (m, 3H), 2.92 – 2.69 (m, 5H), 2.26 – 2.04 (m, 6H), 1.85 – 1.60 (m, 2H). LCMS (ESI) m/z: [M+H]+ = 807.40.

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



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

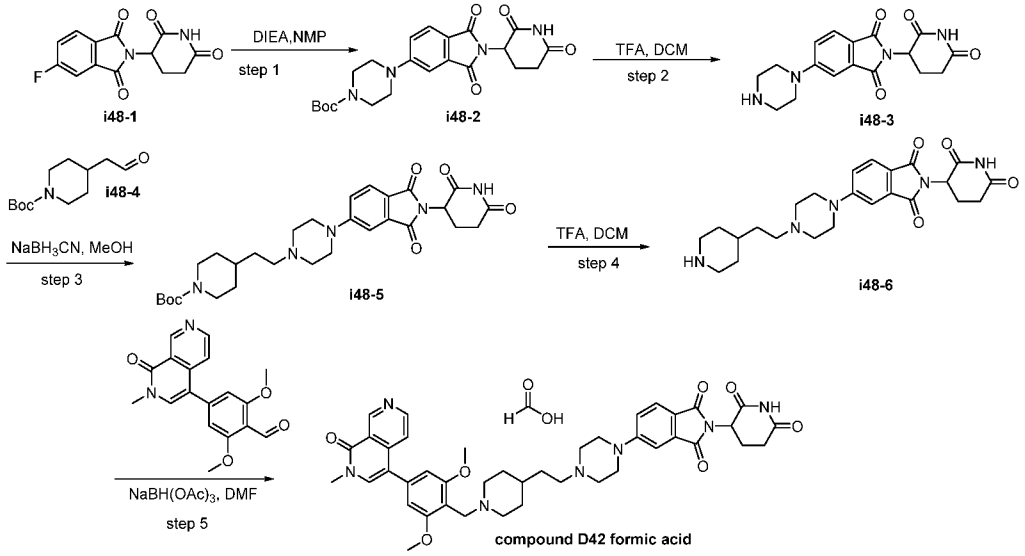
Example 47 – Preparation of 4-[2-(9-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2-oxoethoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (compound D41 formic acid)



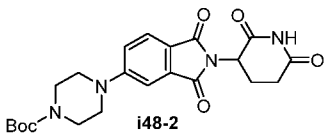
To a solution of 4-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-2-methyl-2,7-naphthyridin-1-one (30.00 mg, 0.065 mmol, 1.00 equiv) and [[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetic acid (21.46 mg, 0.065 mmol, 1.00 equiv) in DMF (1.00 mL) was added DIEA

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

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



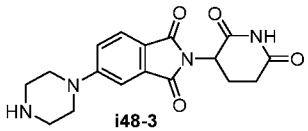
Step 1: Preparation of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)piperazine-1-carboxylate (i42-2)



To a solution of 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisoindole-1,3-dione (1.38 g, 4.996 mmol, 1.00 equiv) and *tert*-butyl piperazine-1-carboxylate (930.52 mg, 4.996 mmol, 1.00 equiv) in NMP (20 mL) was added DIPEA (1937.08 mg, 14.988 mmol, 3 equiv). The mixture was stirred at 90 °C for 2 hours (under nitrogen atmosphere). The reaction was monitored by LC-MS. The resulting mixture was diluted with water (70 mL) and then extracted with EA (3 x 25 mL). The combined organic layers were washed with water (2 x 25 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; mobile phase, 0.5% FA in water, 10%

to 90% gradient in 25 minutes; detector, UV 220 nm). The fractions were concentrated under reduced pressure afford *tert*-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)piperazine-1-carboxylate (700 mg, 31.67%) as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 443.

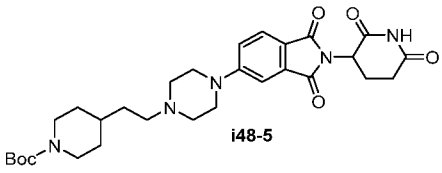
Step 2: Preparation of 2-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)isoindoline-1,3-dione (i42-3)



i48-3

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

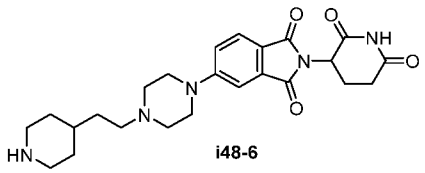
Step 3: Preparation of tert-butyl 4-(2-(4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)piperazin-1-yl)ethyl)piperidine-1-carboxylate (i42-5)



i48-5

To a solution of 2-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)isoindole-1,3-dione (200.00 mg, 0.584 mmol, 1.00 equiv) and *tert*-butyl 4-(2-oxoethyl)piperidine-1-carboxylate (132.79 mg, 0.584 mmol, 1 equiv) in DMF (3.00 mL) was added $NaBH(OAc)_3$ (247.63 mg, 1.168 mmol, 2 equiv). The resulting solution was stirred at 25 °C for 1 hour. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 10 minutes; detector, UV 254 nm) to give *tert*-butyl 4-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)piperidine-1-carboxylate (197.5 mg, 61.06%) as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 554.

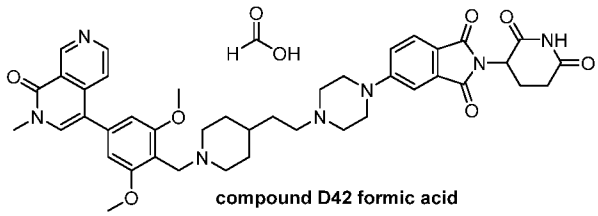
Step 4: Preparation of 2-(2,6-dioxopiperidin-3-yl)-5-(4-(2-(piperidin-4-yl)ethyl)piperazin-1-yl)isoindoline-1,3-dione (i42-6)



i48-6

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

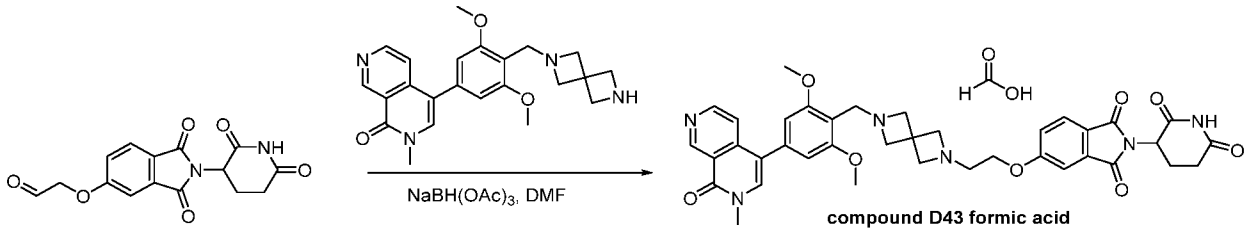
Step 5: Preparation of 5-(4-(2-(1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)piperidin-4-yl)ethyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (compound D42 formic acid)



compound D42 formic acid

To a solution of 2-(2,6-dioxopiperidin-3-yl)-5-[4-[2-(piperidin-4-yl)ethyl]piperazin-1-yl]isoindole-1,3-dione(100.68 mg, 0.222 mmol, 1.20 equiv) and 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (60.00 mg, 0.185 mmol, 1.00 equiv) in DMF(1.5mL) was added $NaBH(OAc)_3$ (78.42 mg, 0.370 mmol, 2 equiv). The mixture was stirred at 25 °C for 1 hour. The mixture was purified by prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100Å, 5 μm, 19 mm X 250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient:10 B to 12 B in 10 minutes; 254 nm; R_T: 8.7 minutes) to afford 5-[4-[2-(1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]piperidin-4-yl)ethyl]piperazin-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoi ndole-1,3-dione (24 mg, 17.03%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.55 (d, *J* = 0.9 Hz, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.15 (br s, 0.2H, FA), 7.80 – 7.71 (m, 2H), 7.63 (d, *J* = 5.8 Hz, 1H), 7.43 (s, 1H), 7.31 (d, *J* = 9.2 Hz, 1H), 6.89 (s, 2H), 5.10 (dd, *J* = 12.3, 5.4 Hz, 1H), 4.41 (s, 2H), 3.98 (s, 6H), 3.72 (s, 3H), 3.67 – 3.55 (m, 6H), 3.17 (d, *J* = 12.9 Hz, 2H), 3.05 – 2.92 (m, 4H), 2.90 – 2.70 (m, 5H), 2.17 – 2.00 (m, 3H), 1.81 – 1.51 (m, 5H). LCMS (ESI) m/z: [M+H]+ = 762.45.

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

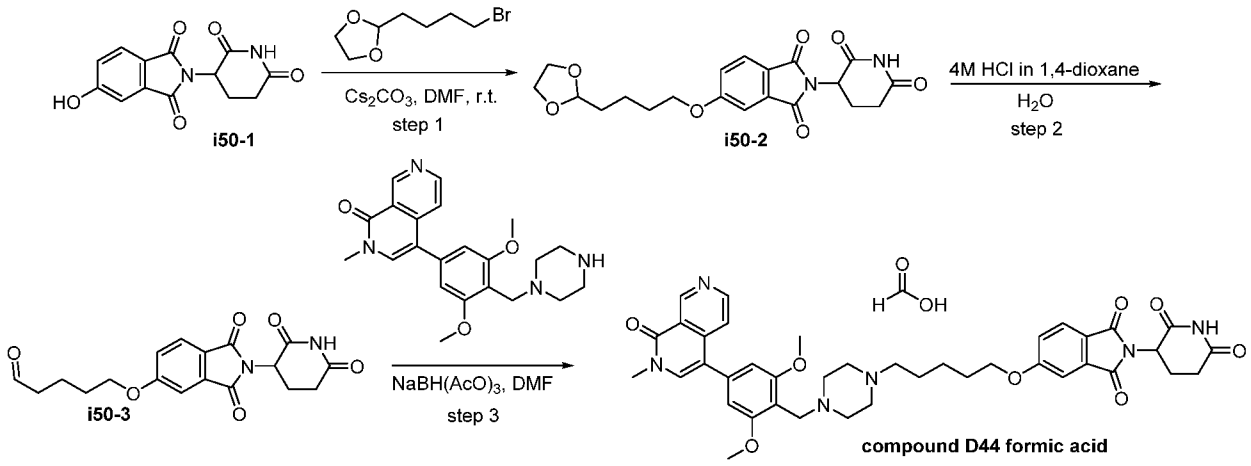


compound D43 formic acid

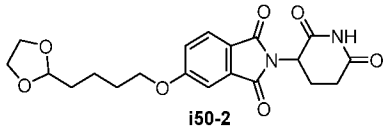
To a solution of 2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]acetaldehyde (60.00 mg, 0.190 mmol, 1.00 equiv) and 4-(4-[2,6-diazaspiro[3.3]heptan-2-ylmethyl]-3,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1-one (77.12 mg, 0.190 mmol, 1 equiv) in DMF(1.00 mL)was added $NaBH(OAc)_3$ (80.42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

(dd, *J* = 12.8, 5.4 Hz, 1H), 4.47 (s, 2H), 4.34 (s, 4H), 3.98 (s, 6H), 3.95-3.87 (m, 2H), 3.80 (s, 4H), 3.71 (s, 3H), 3.00-2.85 (m, 4H), 2.81-2.63 (m, 1H), 2.20-2.05 (m, 1H). LCMS (ESI) m/z: [M+H]+ = 707.5.

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

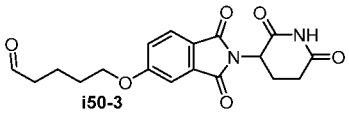


Step 1: 5-(4-(1,3-dioxolan-2-yl)butoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (i50-2)



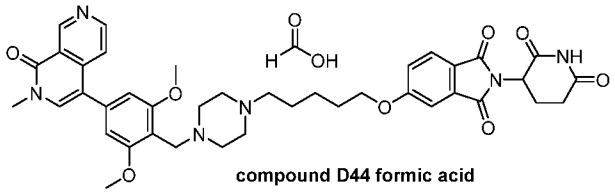
To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-hydroxy-2,3-dihydro-1H-isoindole-1,3-dione (400.0 mg, 1.459 mmol, 1.00 equiv) and 2-(4-bromobutyl)-1,3-dioxolane (305.0 mg, 1.459 mmol, 1.00 equiv) in DMF was added cesium carbonate (475.3 mg, 1.459 mmol, 1.00 equiv) at room temperature. The resulting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

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



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

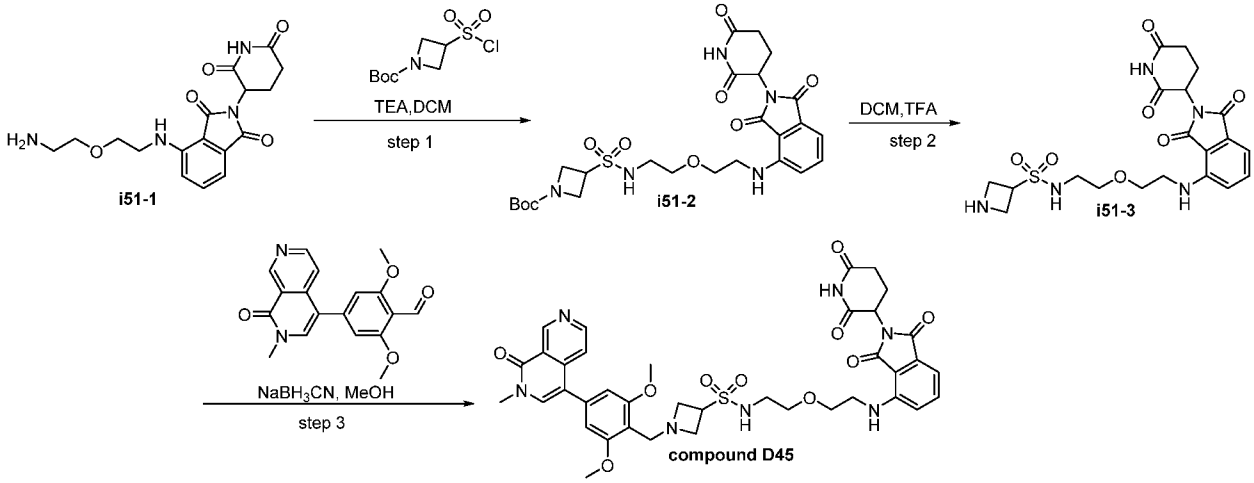
Step 3: Preparation of N-(6-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-3-methyl-[1,2,4]triazolo[4,3-a]pyridin-8-yl)acetamide formic acid (compound D44 formic acid)



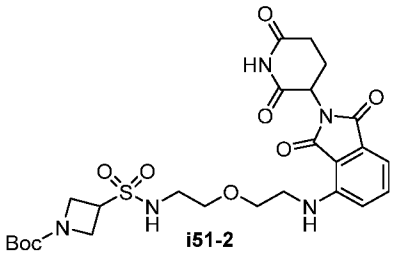
compound D44 formic acid

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

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

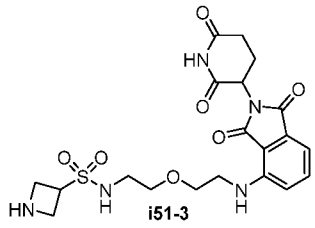


Step 1: Preparation of tert-butyl 3-[[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy) ethyl]sulfamoyl]azetidine-1-carboxylate (i51-2)



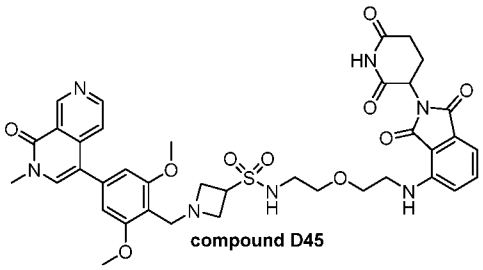
To a stirred solution of 4-[[2-(2-aminoethoxy)ethyl]amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (200.00 mg, 0.555 mmol, 1.00 equiv) and TEA (168.48 mg, 1.665 mmol, 3.00 equiv) in DCM (2mL) was added *tert*-butyl 3-(chlorosulfonyl)azetidine-1-carboxylate (170.30 mg, 0.666 mmol, 1.20 equiv) at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

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



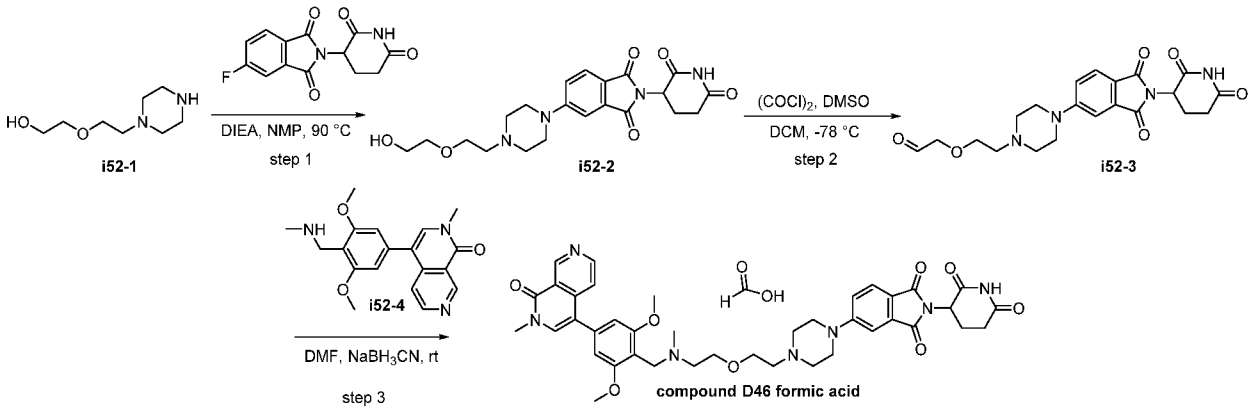
A solution of *tert*-butyl 3-[[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethyl] sulfamoyl]azetidine-1-carboxylate (100.00 mg, 0.173 mmol, 1.00 equiv) and TFA (1.00 mL) in DCM was stirred for 1 hour at room temperature. The resulting mixture was concentrated under vacuum.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

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

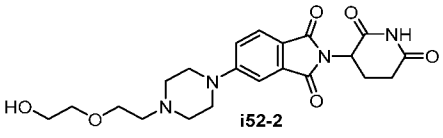


A solution of *N*-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethyl] azetidine-3-sulfonamide (30.00 mg, 0.063 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (26.38 mg, 0.081 mmol, 1.30 equiv) in DMF (2.00 mL) was stirred for 20 minutes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

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

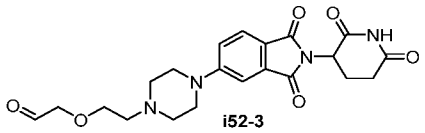


Step 1: Preparation of 2-(2,6-dioxopiperidin-3-yl)-5-(4-(2-(2-hydroxyethoxy)ethyl)piperazin-1-yl)isoindoline-1,3-dione (i52-2)



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

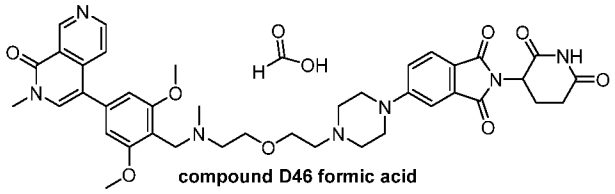
Step 2: Preparation of 2-(2-(4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)piperazin-1-yl)ethoxy)acetaldehyde (i52-3)



i52-3

A solution of DMSO (54.5 mg, 0.697 mmol, 1.00 equiv) in DCM (6.00 mL) was added slowly to a stirred solution of oxalyl chloride (176.9 mg, 1.394 mmol, 2.00 equiv) in DCM (6.00 mL) at -78 °C under nitrogen atmosphere. After 30 minutes 2-(2,6-dioxopiperidin-3-yl)-5-[4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl]isoindole-1,3-dione (300.0 mg, 0.697 mmol, 1.00 equiv) in DCM (6.00 mL) was added slowly. The resulting mixture was stirred for 2 hours at -78 °C and 1.5 hours at -55 °C. Et_3N (0.48 mL, 4.787 mmol, 5.00 equiv) was added slowly at -60 °C. After stirring for an additional 10 minutes, the reaction was allowed to warm to room temperature. The resulting mixture was quenched with saturated ammonium chloride aqueous solution (50 mL) and extracted with DCM (100 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by prep-TLC (EtOAc/PE = 1:1) to afford 2-(2-(4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)piperazin-1-yl)ethoxy)acetaldehyde (30.0 mg, 5.7%) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 429.

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

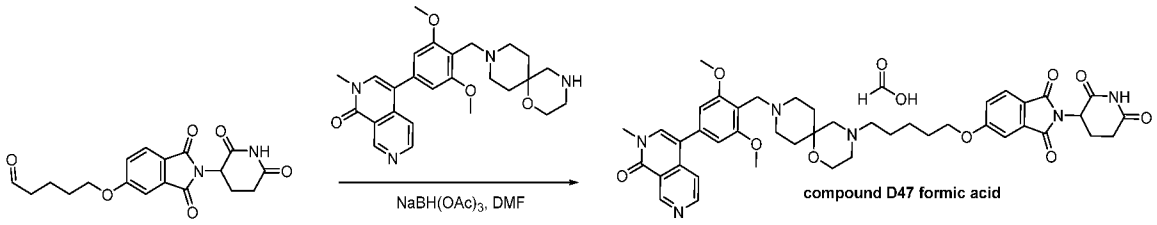


compound D46 formic acid

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

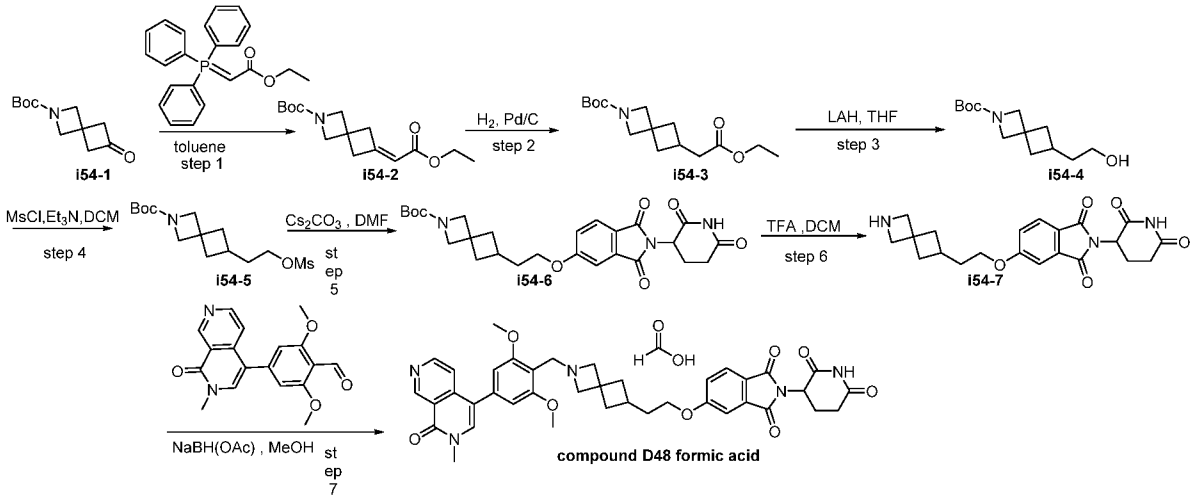
Hz, 1H), 4.53 (s, 2H), 3.99 (s, 6H), 3.91 (t, *J* = 4.7 Hz, 2H), 3.76 (t, *J* = 5.1 Hz, 2H), 3.67 (s, 3H), 3.53 – 3.40 (m, 6H), 2.91 (s, 4H), 2.81 – 2.67 (m, 8H), 2.18 – 2.05 (m, 1H).

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

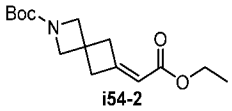


A solution of 5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]pentanal (25 mg, 0.070 mmol, 1.00 equiv) and 4-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-2-methyl-2,7-naph thyridin-1-one (32.4 mg, 0.070 mmol, 1.00 equiv) in DMF (0.8 mL) was stirred for 30 minutes at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

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



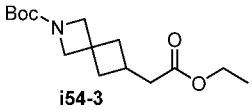
Step 1: Preparation of tert-butyl 6-(2-ethoxy-2-oxoethylidene)-2-azaspiro[3.3]heptane-2-carboxylate (i54-2)



i54-2

A solution of *tert*-butyl 6-oxo-2-azaspiro[3.3]heptane-2-carboxylate (2.0 g, 9.467 mmol, 1.00 equiv) and ethyl2-(triphenyl-lambda5-phosphanylidene)acetate (3.63 g, 10.414 mmol, 1.10 equiv) in toluene was stirred for 4 hours at 80 °C under nitrogen atmosphere. The resulting mixture was washed with water (3 x 30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford *tert*-butyl 6-(2-ethoxy-2-oxoethylidene)-2-azaspiro[3.3]heptane-2-carboxylate (2.51 g, 94.09%) as a light yellow oil. LCMS (ESI) m/z: [M+H]+ = 282.

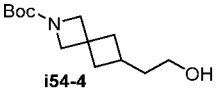
Step 2: Preparation of tert-butyl 6-(2-ethoxy-2-oxoethyl)-2-azaspiro[3.3]heptane-2-carboxylate (i54-3)



i54-3

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

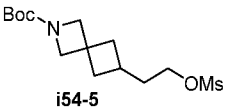
Step 3: Preparation of tert-butyl 6-(2-hydroxyethyl)-2-azaspiro[3.3]heptane-2-carboxylate (i54-4)



i54-4

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

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

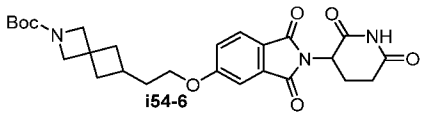


i54-5

A solution of *tert*-butyl 6-(2-hydroxyethyl)-2-azaspiro[3.3]heptane-2-carboxylate (537.00 mg, 2.225 mmol, 1.00 equiv), Et_3N (450.33 mg, 4.450 mmol, 2.00 equiv), and MsCl (280.38 mg, 2.448 mmol,

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

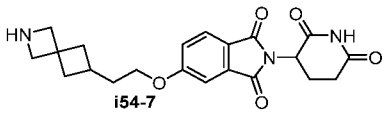
Step 5: Preparation of tert-butyl 6-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)ethyl)-2-azaspiro[3.3] heptane-2-carboxylate (i54-6)



i54-6

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

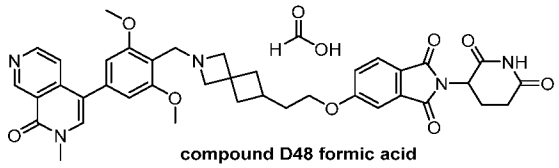
Step 6: Preparation of 5-(2-(2-azaspiro[3.3]heptan-6-yl)ethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (i54-7)



i54-7

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

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

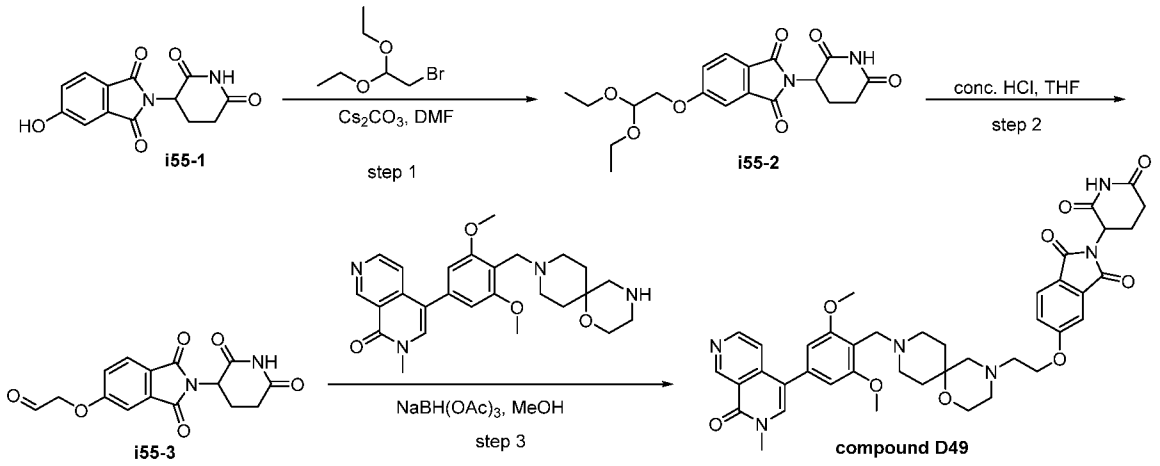


compound D48 formic acid

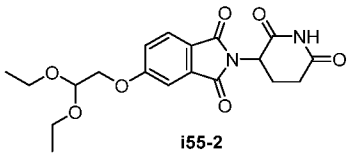
A solution of 5-(2-[2-azaspiro[3.3]heptan-6-yl]ethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (51.00 mg, 0.128 mmol, 1.00 equiv) in MeOH (1 mL) was treated with 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (41.62 mg, 0.128 mmol, 1.00 equiv) for 20 minutes at room

temperature under nitrogen atmosphere followed by the addition of $NaBH_3CN$ (16.13 mg, 0.257 mmol, 2.00 equiv) in portions at room temperature. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; mobile phase, MeOH in water, 10% to 50% gradient in 10 minutes; detector, UV 254 nm). This resulted in 5-(2-(2-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-2-azaspiro[3.3]heptan-6-yl)ethoxy)-2-(2,6-dioxopiperidin-3-yl)iso indoline-1,3-dione formic acid (2.4 mg, 2.2%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.54 (s, 1H), 8.68 (d, *J* = 5.7 Hz, 1H), 8.56 (brs, 1.1H, FA), 7.77 (s, 1H), 7.68 – 7.56 (m, 2H), 7.13 (d, *J* = 2.2 Hz, 1H), 7.05 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.85 (s, 2H), 5.10 (dd, *J* = 12.9, 5.5 Hz, 1H), 4.40 (s, 2H), 4.21 – 4.12 (m, 2H), 4.05 (s, 2H), 3.96 (s, 6H), 3.79 – 3.70 (m, 5H), 2.95 – 2.84 (m, 2H), 2.75 – 2.59 (m, 1H), 2.49 – 2.36 (m, 2H), 2.27 – 2.06 (m, 2H), 2.05 – 1.92 (m, 2H), 1.72 – 1.54 (m, 2H). LCMS (ESI) m/z: [M+H]+ =706.50 .

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

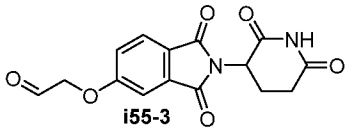


Step 1: Preparation of 5-(2,2-Diethoxyethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (i55-2)



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

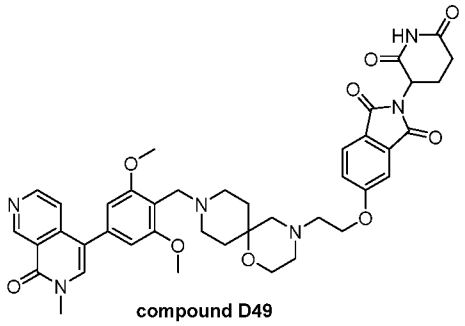
Step 2: Preparation of 2-[[2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]acetaldehyde (i55-3)



i55-3

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

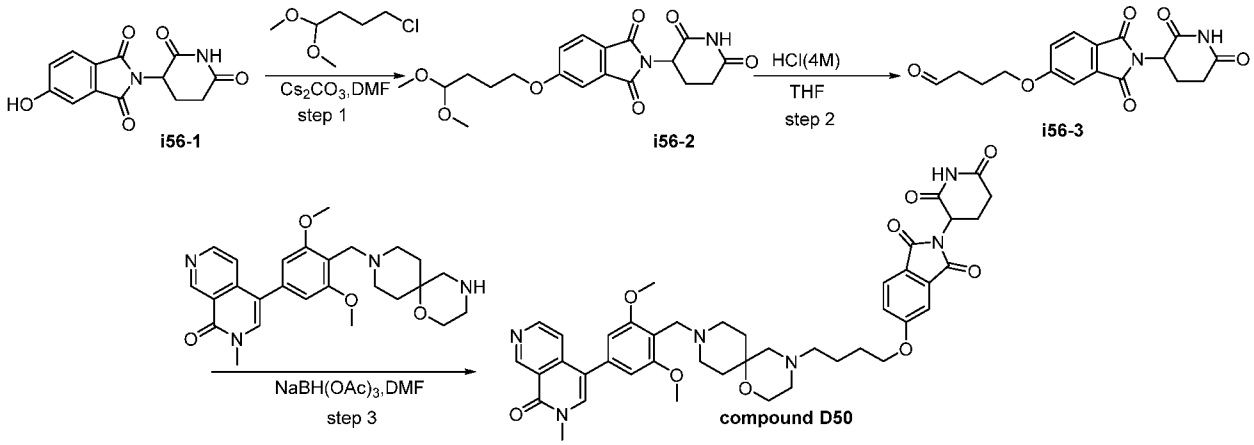
Step 3: Preparation of 5-[2-(9-[[2,6-Dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)ethoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (compound D49)



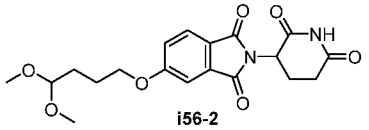
compound D49

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

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

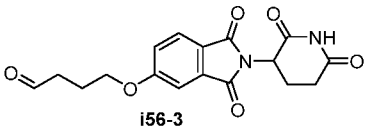


Step 1: Preparation of 5-(4,4-dimethoxybutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (i56-2)



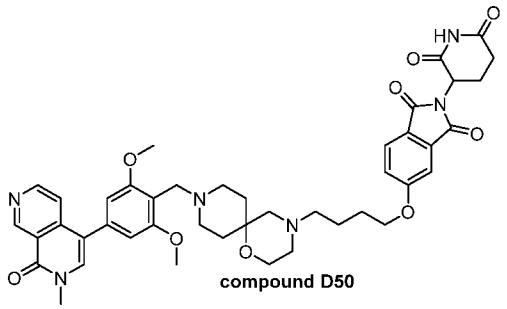
To a solution of 2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindole-1,3-dione (500.00 mg, 1.823 mmol, 1.00 equiv) and 4-chloro-1,1-dimethoxybutane (278.27 mg, 1.823 mmol, 1 equiv) in DMF (7.00 mL) was added K_2CO_3 (755.96 mg, 5.470 mmol, 3 equiv). The resulting solution was stirred at 80 °C for 12 hours.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

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



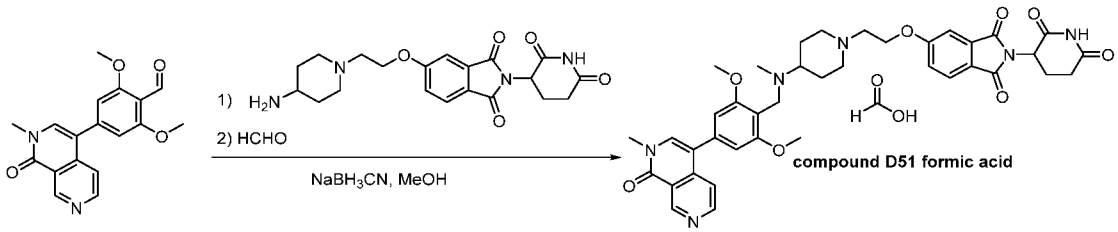
A solution of 5-(4,4-dimethoxybutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (43.60 mg, 0.112 mmol, 1.00 equiv) and HCl (1.00 mL, 4M) in THF (1.00 mL) was stirred at 25 °C for 1 hour. The resulting mixture was extracted with EA (50 mL x 2). The combined organic layers were washed with saturated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

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



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

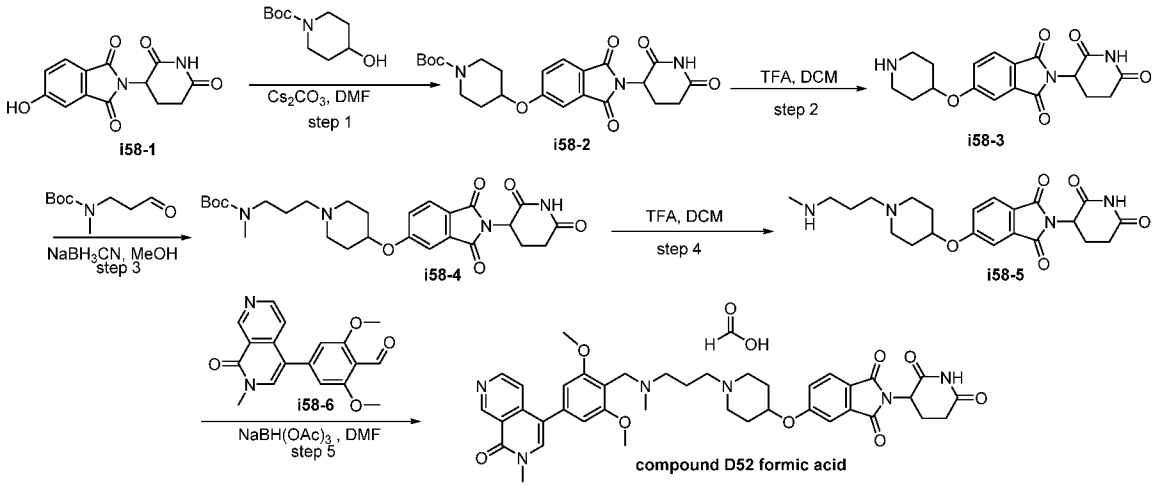
Example 57 – Preparation of 5-[2-[4-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] (methyl)amino)piperidin-1-yl]ethoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione; formic acid (compound D51 formic acid)



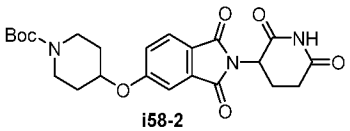
To a solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (30.00 mg, 0.092 mmol, 1.00 equiv) and 5-[2-(4-aminopiperidin-1-yl)ethoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (37.04 mg, 0.092 mmol, 1.00 equiv) in MeOH (1 mL) was stirred for 3 hours at room temperature under nitrogen atmosphere. To the above mixture was added $NaBH_3CN$ (11.63 mg, 0.185 mmol, 2.00 equiv), and the reaction was stirred for additional 1 hour at room temperature. To the above mixture was added HCHO (27.77 mg, 0.925 mmol, 10.00 equiv), and the reaction was stirred for 1 hour at room temperature under nitrogen atmosphere. Then $NaBH_3CN$ (11.63 mg, 0.185 mmol, 2.00 equiv) was added. The mixture was stirred for overnight at room temperature under nitrogen atmosphere. The crude product (40 mg) was purified by Prep-HPLC (conditions: Gemini-NX C18 AXAI Packed column,

21.2*150 mm 5 µm; Mobile Phase A: Water (0.1% FA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient:5 B to 17 B in 9 minutes; 254-220 nm; R_T: 8.30 minutes) to afford 5-[2-[4-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)piperidin-1-yl]ethoxy]-2-(2,6-dioxopiperidin-3-yl)iso indole-1,3-dione formic acid (7.8 mg) as a white solid. ^{1}H NMR (300 MHz, DMSO-d6) δ 1.55 (2H, d), 1.77 (2H, d), 2.03 (3H, d), 2.16 (3H, s), 2.44 (3H, d), 2.73 (2H, s), 2.88 – 3.08 (3H, m), 3.61 (5H, s), 3.80 (6H, s), 4.30 (2H, s), 5.12 (1H, m), 6.72 (2H, s), 7.38 (1H, m), 7.48 (1H, d), 7.57 (1H, d), 7.80 – 7.90 (2H, m), 8.23 (1H, s), 8.72 (1H, d), 9.45 (1H, s), 11.12 (1H, s). LCMS (ESI) m/z: [M+H]+ = 723.40.

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

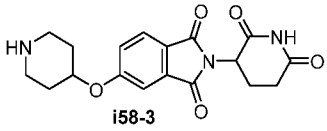


Step 1: Preparation of tert-butyl 4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)piperidine-1-carboxylate (i58-2)



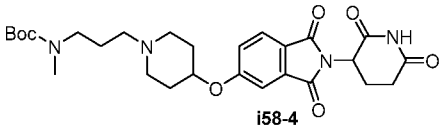
A mixture of 2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindole-1,3-dione (1.00 g, 3.647 mmol, 1.00 equiv), *tert*-butyl 4- bromopiperidine-1-carboxylate (0.96 g, 3.634 mmol, 1.00 equiv) and Cs_2CO_3 (2.38 g, 7.293 mmol, 2.00 equiv) in DMF (20.00 mL) was stirred for overnight at 90 °C under air atmosphere. The resulting mixture was filtered, and the filter cake was washed with EtOAc (3 x 10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (hexane/ EtOAc 1:1) to afford *tert*-butyl4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]piperidine-1-carboxylate (280 mg, 11.19%) as a yellow oil. LCMS (ESI) m/z: [M+H]+ = 458.19.

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



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

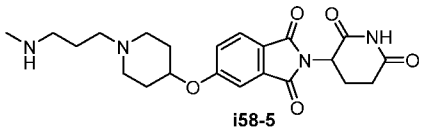
Step 3: Preparation of tert-butyl(3-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)piperidin-1-yl)propyl)(methyl) carbamate (i58-4)



i58-4

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

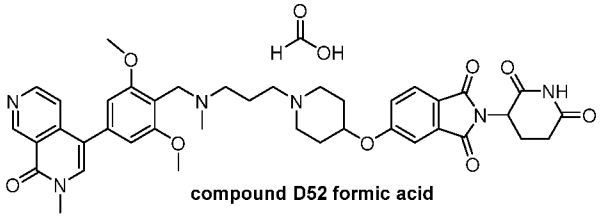
Step 4: Preparation of 2-(2,6-dioxopiperidin-3-yl)-5-((1-(3-(methylamino)propyl)piperidin-4-yl)oxy)isoindoline-1,3-dione (i58-5)



i58-5

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

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

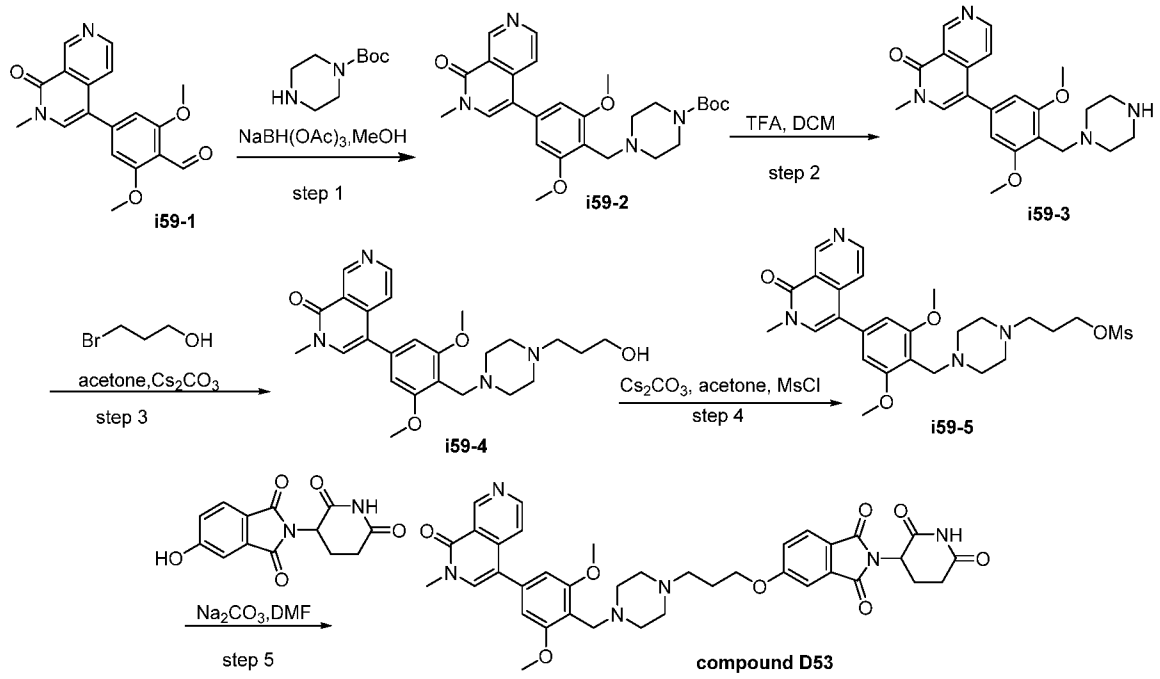


compound D52 formic acid

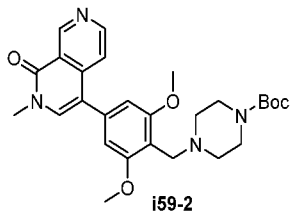
A solution of 2-(2,6-dioxopiperidin-3-yl)-5-([1-[3-(methylamino)propyl]piperidin-4-yl]oxy)isoindole-1,3-dione (70.00 mg, 0.163 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (52.99 mg, 0.163 mmol, 1.00 equiv) in DMF (3.00 mL) was stirred for 30 minutes at

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

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

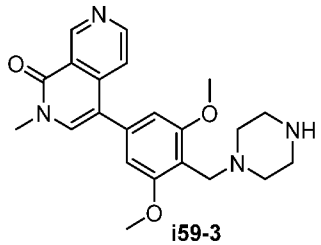


Step 1: Preparation of tert-butyl 4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] piperazine-1-carboxylate (i59-2)



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

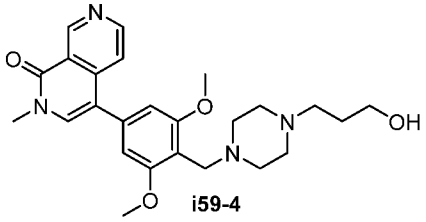
Step 2: Preparation of 4-(3, 5-dimethoxy-4-(piperazin-1-ylmethyl) phenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (i59-3)



i59-3

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

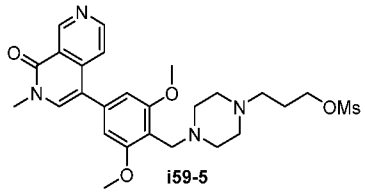
Step 3: Preparation of 4-(4-((4-(3-hydroxypropyl) piperazin-1-yl) methyl)-3, 5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (i59-4)



i59-4

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

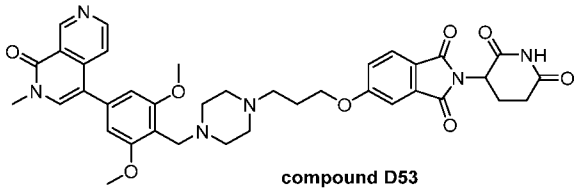
Step 4: Preparation of 3-(4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl) phenyl]methyl]pipera -zin-1-yl)propyl methanesulfonate (i59-5)



i59-5

To a stirred solution of 4-(4-[[4-(3-hydroxypropyl) piperazin-1-yl] methyl]-3, 5-dimethoxyphenyl)-2-methyl-2, 7-naphthyridin-1-one (200.00 mg, 0.442 mmol, 1.00 equiv) and Cs_2CO_3 (287.98 mg, 0.884 mmol, 2.00 equiv) in acetone was added MsCl (101.25 mg, 0.884 mmol, 2.00 equiv) in portions at room temperature. The resulting mixture was stirred for overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 3-(4-[[2, 6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl] methyl]piperazin-1-yl)propyl methanesulfonate (92 mg, 39.23%) as a light yellow oil. LCMS (ESI) m/z: [M+H]+ = 531.

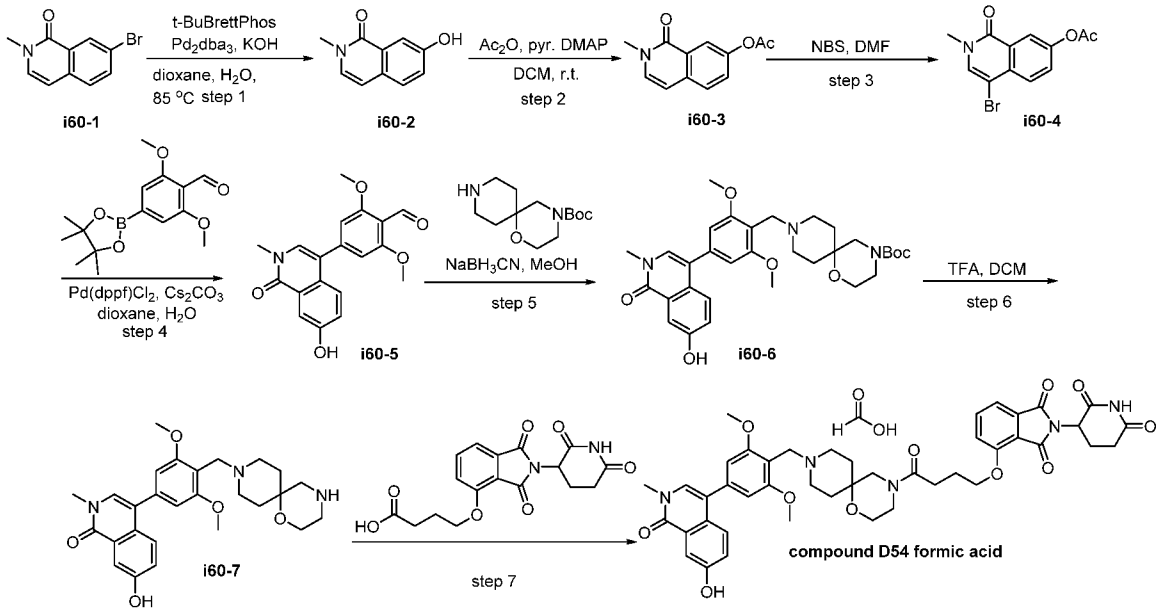
Step 5: Preparation of 5-[3-(4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]piper -azin-1-yl) propoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (compound D53)



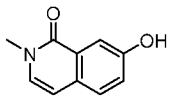
compound D53

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

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



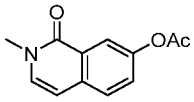
Step 1: Preparation of 7-hydroxy-2-methylisoquinolin-1-one (i60-2)



i60-2

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

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



i60-3

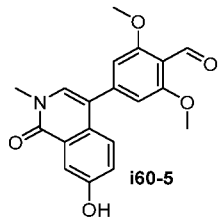
To a stirred solution/mixture of 7-hydroxy-2-methylisoquinolin-1-one (272 mg, 1.553 mmol, 1.00 equiv) and pyridine (614 mg, 7.763 mmol, 5.00 equiv) in DCM (6 mL) was added DMAP (10 mg, 0.082 mmol, 0.05 equiv) and Ac_2O (46.6 mg, 0.457 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred for 1 hour at room temperature. The resulting mixture was diluted with water (10 mL) and extracted with DCM (2 x 20 mL). The combined organic layers were washed with brine, dried over

anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 2-methyl-1-oxoisoquinolin-7-yl acetate (335 mg, 99%) as a light brown solid. LCMS (ESI) m/z: [M+H]+ = 218.

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

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

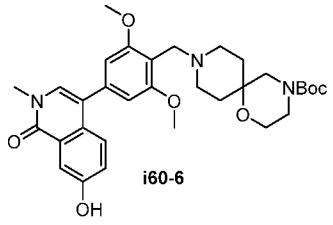
Step 4: Preparation of 4-(7-hydroxy-2-methyl-1-oxoisoquinolin-4-yl)-2,6-dimethoxybenzaldehyde (i60-5)



i60-5

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

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

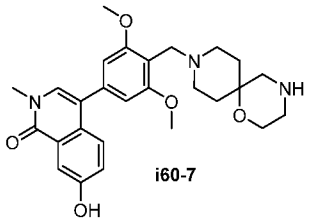


i60-6

A solution of 4-(7-hydroxy-2-methyl-1-oxoisoquinolin-4-yl)-2,6-dimethoxybenzaldehyde(100 mg, 0.295 mmol, 1.00 equiv) and *tert*-butyl 1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (83.1 mg, 0.324 mmol, 1.1 equiv) in MeOH (1.5 mL) was stirred for 30 minutes at room temperature. Then $NaBH_3CN$ (125 mg, 1.989 mmol, 6.75 equiv) was added. The resulting mixture was stirred for 2 hours at room

temperature. The reaction solution was purified by Prep-TLC (DCM/ MeOH 20:1) to afford *tert*-butyl 9-[[4-(7-hydroxy-2-methyl-1-oxoisoquinolin-4-yl)-2,6-dimethoxyphenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (134 mg, 78%) as a light brown foam. LCMS (ESI) m/z: [M+H]+ = 580.

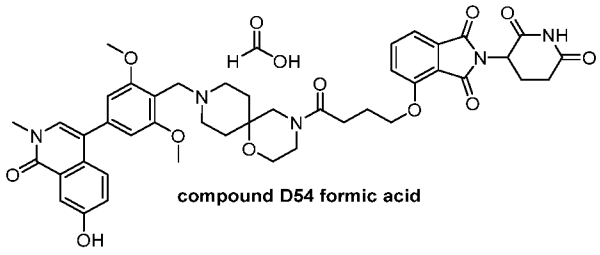
Step 6: Preparation of 4-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-7-hydroxy-2-methylisoquinolin-1-one (i60-7)



i60-7

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

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

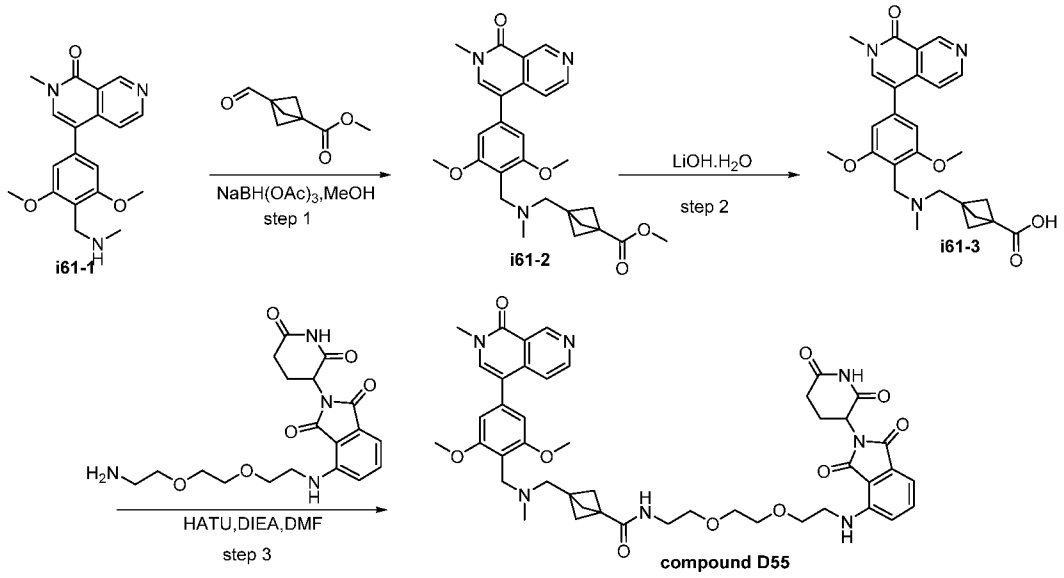


compound D54 formic acid

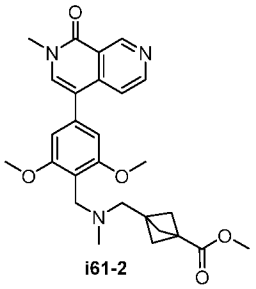
To a stirred solution of 4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]butanoic acid (33.8 mg, 0.094 mmol, 0.90 equiv) in DMF (1 mL) was added EDCI (40.0 mg, 0.209 mmol, 2.00 equiv) and HOBt (28.2 mg, 0.209 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred at room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

(m, 4H), 3.93 (d, *J* = 12.4 Hz, 6H), 3.78 – 3.62 (m, 7H), 3.58 – 3.48 (m, 2H), 3.30– 3.17 (m, 4H), 2.97 – 2.53 (m, 5H), 2.24 – 1.99 (m, 5H), 1.95 – 1.71 (s, 2H). LCMS (ESI) m/z: [M+H]+ = 822.40.

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

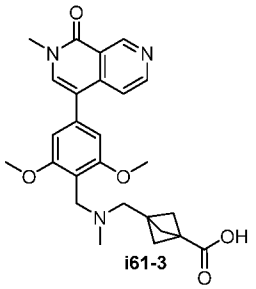


Step 1: Preparation of methyl 3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)methyl]bicyclo[1.1.1]pentane-1-carboxylate (i61-2)



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

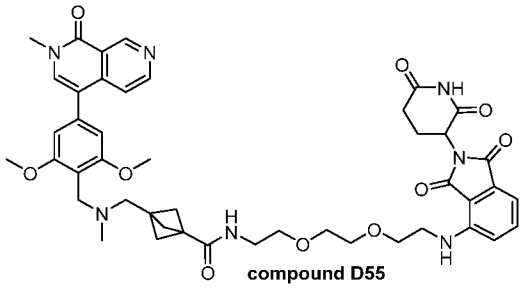
Step 2: Preparation of 3-(((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl) (methyl)amino)methyl)bicyclo[1.1.1]pentane-1-carboxylic acid (i61-3)



i61-3

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

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

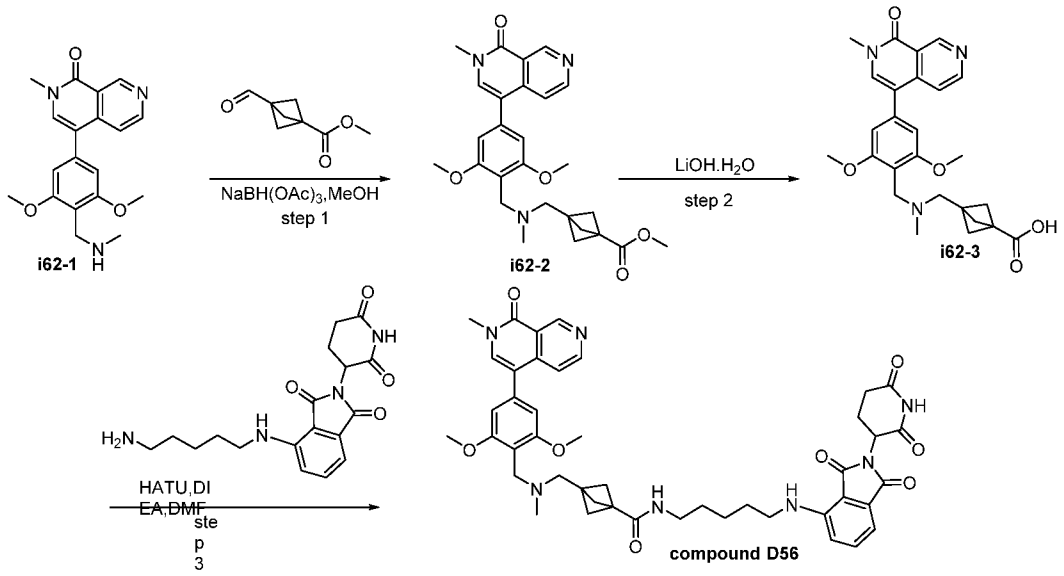


compound D55

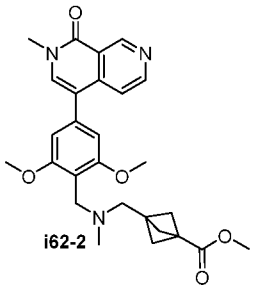
To a stirred solution of 3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] (methyl)amino)methyl]bicyclo[1.1.1]pentane-1-carboxylic acid (50.00 mg, 0.108 mmol, 1.00 equiv) and 4-([2-[2-(2-aminoethoxy)ethoxy]ethyl]amino)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (65.44 mg, 0.162 mmol, 1.50 equiv) in DMF were added DIEA (55.76 mg, 0.431 mmol, 4.00 equiv) and HATU (61.52 mg, 0.162 mmol, 1.50 equiv) in portions at room temperature. The resulting mixture was stirred for 3 h at room temperature. The crude product was purified by Prep-HPLC with the following conditions (NB-Prep-HPLC-01): Column, XSelect CSH Prep C18 OBD Column, 5 μm,19*150 mm; mobile phase, Water (0.05%TFA) and ACN (16% PhaseB up to 17% in 20 min ,hold 17% in 8 minutes); Detector, uv. This resulted in 3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)ami-no) methyl]-N-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]ethyl]bicyc-lo [1.1.1]pentane-1-carboxamide; formic acid (4.1 mg, 4.24%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.55 (s, 1H), 8.70 (d, *J* = 5.7 Hz, 1H), 8.55 (s, 1H), 7.78 (s, 1H), 7.65 (d, *J* = 5.9 Hz, 1H), 7.52 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 6.99 (d, *J* = 7.1 Hz, 1H), 6.84 (s, 2H), 5.07 (dd, *J* = 12.4, 5.4 Hz, 1H), 4.22 (s, 2H), 3.95 (s, 6H), 3.77 (t, *J* = 5.2 Hz, 2H),

3.73 (s, 3H), 3.71 – 3.65 (m, 4H), 3.59 (t, *J* = 5.4 Hz, 2H), 3.52 (t, *J* = 5.2 Hz, 2H), 3.44 – 3.38 (m, 2H), 3.28 – 3.24 (m, 1H), 2.91 – 2.81 (m, 1H), 2.80 – 2.77 (m, 1H), 2.75 – 2.69 (m, 1H), 2.66 (s, 3H), 2.20 (s, 6H), 2.17 – 2.05 (m, 2H). LCMS (ESI) m/z: [M+H]+ = 850.45.

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

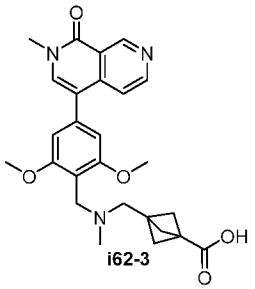


Step 1: Preparation of methyl 3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)methyl]bicyclo[1.1.1]pentane-1-carboxylate (i62-2)



To a stirred solution of 4-[3,5-dimethoxy-4-[(methylamino)methyl]phenyl]-2-methyl-2,7-naphthyridin-1-one (264.18 mg, 0.778 mmol, 1.20 equiv) and methyl 3-formylbicyclo[1.1.1]pentane-1-carboxylate (100.00 mg, 0.649 mmol, 1.00 equiv) in MeOH was added $NaBH(OAc)_3$ (549.91 mg, 2.595 mmol, 4.00 equiv) in portions at room temperature. The resulting solution was stirred for 4 hours at room temperature. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (8:1) to afford methyl3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)-methyl] bicyclo[1.1.1]pentane-1-carboxylate (220 mg, 71.02%) as a light yellow oil. LCMS (ESI) m/z: [M+H]+ = 478.

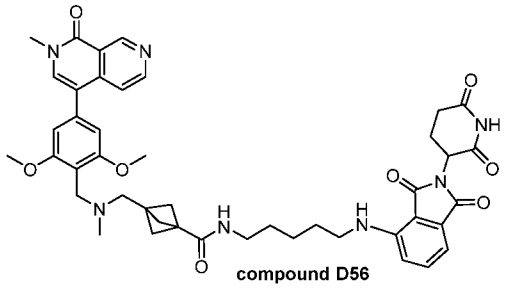
Step 2: Preparation of 3-(((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl) (methyl)amino)methyl)bicyclo[1.1.1]pentane-1-carboxylic acid (i62-3)



i62-3

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

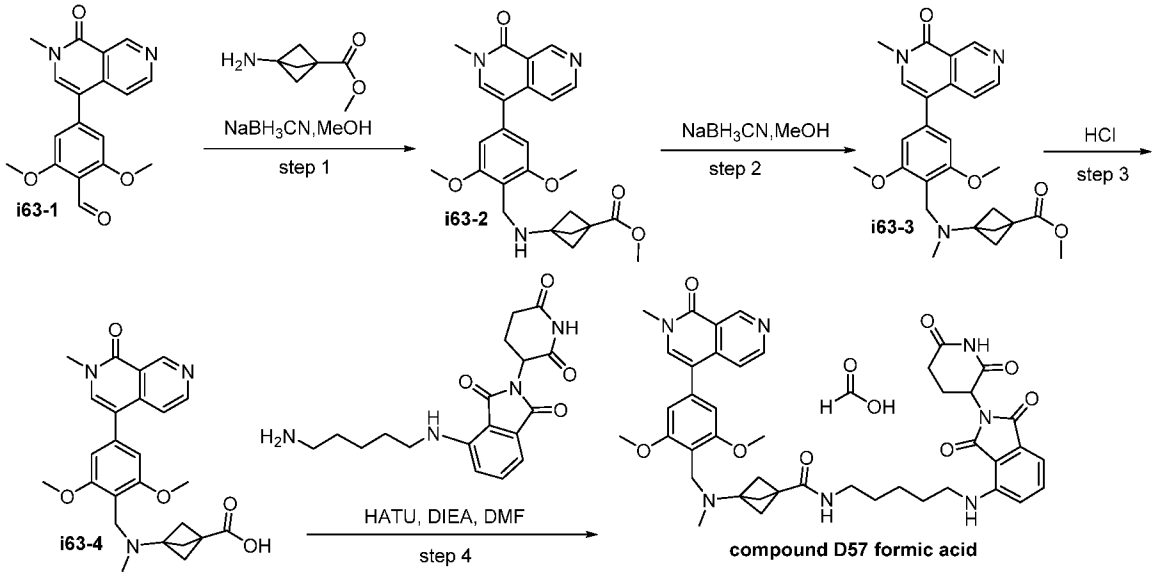
Step 3: Preparation of 3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] (methyl) amino)methyl]-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]pentyl)bicyclo[1.1.1] pentane -1-carboxamide (compound D56)



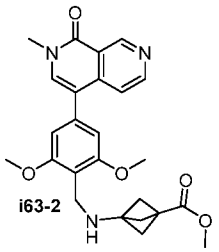
compound D56

To a stirred solution of 3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] (methyl)amino)methyl]bicyclo[1.1.1]pentane-1-carboxylic acid (50.00 mg, 0.108 mmol, 1.00 equiv) and 4-((5-aminopentyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (65.44 mg, 0.162 mmol, 1.50 equiv) in DMF was added DIEA (55.76 mg, 0.431 mmol, 4.00 equiv) and HATU (61.52 mg, 0.162 mmol, 1.50 equiv) in portions at room temperature. The resulting mixture was stirred for 3 hours at room temperature. The crude product was purified by Prep-HPLC (conditions: XSelect CSH Prep C18 OBD Column, 5 μm, 19*150 mm; mobile phase, Water (0.05%TFA) and ACN (16% Phase B up to 17% in 20 min ,hold 17% in 8 minutes); Detector, UV). This resulted in 3-(((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)(methyl)amino)-methyl)-*N*-(5-((2-(2,6-dioxopiperidin -3-yl)-1,3-dioxoisoindolin-4-yl)amino)pentyl)bicyclo[1.1.1]pentane-1-carboxamide (12.3 mg, 13.42%) as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 804.45.

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

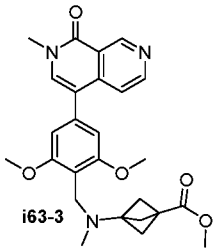


Step 1: Preparation of methyl-3-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)amino)bicyclo[1.1.1]pentane-1-carboxylate (i63-2)



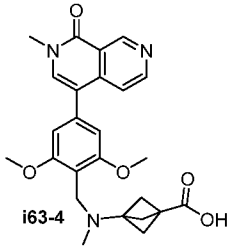
To a solution of methyl 3-aminobicyclo[1.1.1]pentane-1-carboxylate hydrochloride (195.2 mg, 1.099 mmol, 1.10 equiv) in MeOH (5.00 mL) was added Et_3N (111.0 mg, 1.099 mmol, 1.10 equiv), and then 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (324.0 mg, 0.999 mmol, 1.00 equiv) was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

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



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

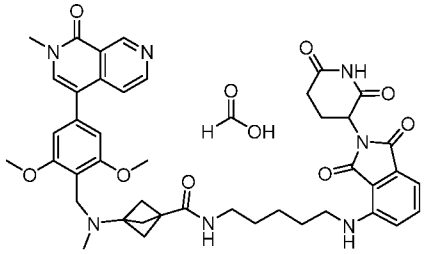
Step 3: Preparation of 3-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl) (methyl)amino)bicyclo[1.1.1]pentane-1-carboxylic acid (i63-4)



i63-4

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

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

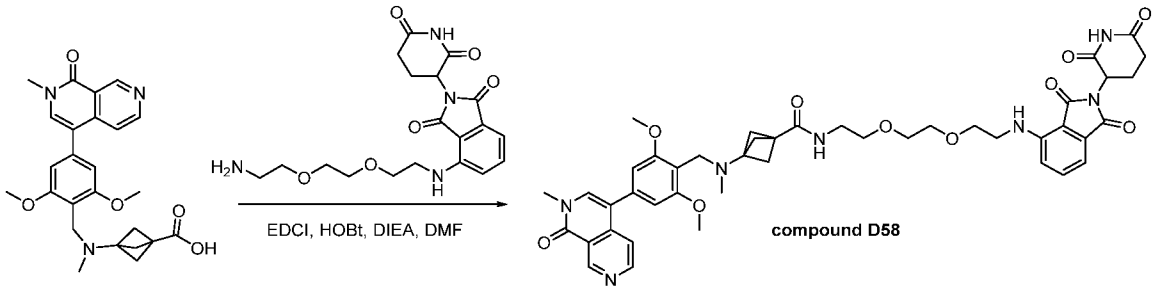


compound D57 formic acid

To a stirred mixture of 3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] (methyl)amino)bicyclo[1.1.1]pentane-1-carboxylic acid hydrochloride (50 mg, 0.103 mmol, 1.00 equiv) and 4-[(5-aminopentyl)amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione; trifluoroacetic acid (53.5 mg, 0.113 mmol, 1.10 equiv) in DMF (2.00 mL) was added DIEA (39.9 mg, 0.309 mmol, 3.00 equiv). The mixture was stirred at room temperature for 5 minutes, and then HATU (78.2 mg, 0.206 mmol, 2.00 equiv) was added. After stirring at room temperature for 2 hours, the mixture was purified by Prep-HPLC (conditions: X-select CSH F-Phenyl OBD Column 19*150 mm 5 μm, mobile phase, Water (0.05%TFA) and ACN (10% Phase B up to 26% in 15 minutes)). This resulted in of 3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)-*N*-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]pentyl)bicyclo[1.1.1]pentane-1-carboxamide formic acid (15.2 mg, 17.2%) as a

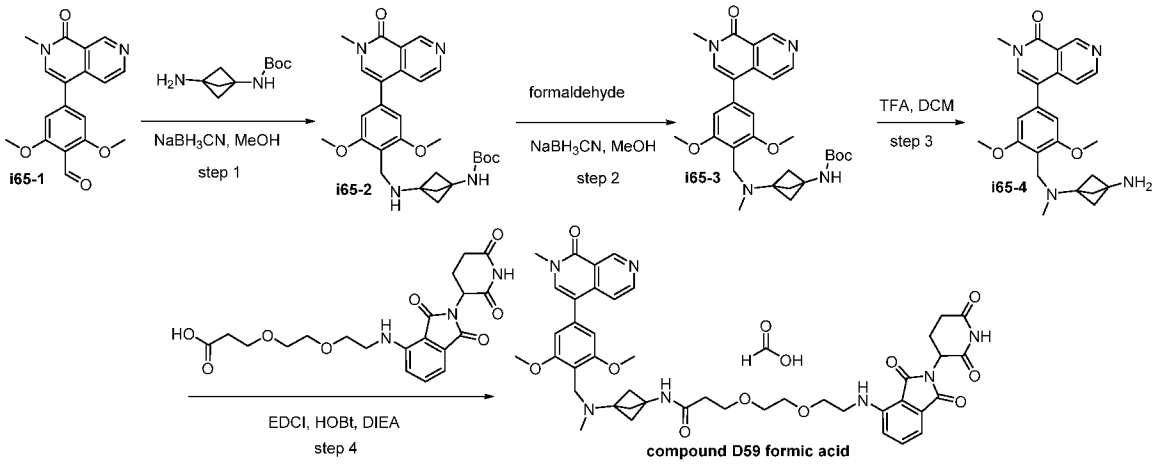
yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.57 (s, 1H), 8.71 (d, *J* = 5.9 Hz, 1H), 8.18 (brs, 0.4H, FA), 7.86 (s, 1H), 7.72 (s, 1H), 7.58 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.07 (dd, *J* = 7.8, 5.2 Hz, 2H), 6.90 (s, 2H), 5.06 (dd, *J* = 12.0, 5.4 Hz, 1H), 4.51 (s, 2H), 3.99 (s, 6H), 3.73 (s, 3H), 3.41 – 3.35 (m, 2H), 3.31 – 3.23 (m, 2H), 2.89 – 2.64 (m, 6H), 2.42 (s, 6H), 2.17 – 2.08 (m, 1H), 1.78 – 1.67 (m, 2H), 1.66 – 1.56 (m, 2H), 1.54 – 1.43 (m, 2H). LCMS (ESI) m/z: $[M+H]^+$ = 790.40.

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

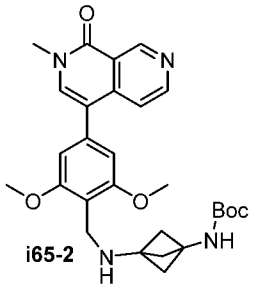


To a stirred mixture of 3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] (methyl)amino)bicyclo[1.1.1]pentane-1-carboxylic acid (50.0 mg, 0.111 mmol, 1.00 equiv) in DMF (2.00 mL) was added EDCI (42.7 mg, 0.222 mmol, 2.00 equiv) and 4-([2-[2-(2-aminoethoxy)ethoxy]ethyl]amino) -2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (49.5 mg, 0.122 mmol, 1.10 equiv). The mixture was stirred at room temperature for 30 minutes, and then DIEA (71.9 mg, 0.556 mmol, 5.00 equiv) and 4-([2-[2-(2-aminoethoxy)ethoxy]ethyl]amino)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (9.9 mg, 0.024 mmol, 1.10 equiv) were added. After stirring at room temperature for 2 hours, without any additional work-up, the mixture was purified by Prep-HPLC (conditions: column, Phenomenex Gemini C6-Phenyl, 21.2*250 mm, 5 μm; mobile phase, Water (0.05% FA) and ACN (11% Phase B up to 21% in 28 minutes). This resulted in 3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)-N-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino] ethoxy)ethoxy]ethyl]bicyclo[1.1.1]pentane-1-carboxamide (10.5 mg, 10.6%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.53 (s, 1H), 8.69 (d, *J* = 5.7 Hz, 1H), 7.75 (s, 1H), 7.64 (d, *J* = 5.7 Hz, 1H), 7.55 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.07 (dd, *J* = 19.4, 7.8 Hz, 2H), 6.74 (s, 2H), 5.07 (dd, *J* = 12.3, 5.4 Hz, 1H), 3.88 (s, 6H), 3.77 (t, *J* = 5.2 Hz, 2H), 3.73 – 3.63 (m, 9H), 3.59 (t, *J* = 5.5 Hz, 2H), 3.53 (t, *J* = 5.2 Hz, 2H), 3.41 (t, *J* = 5.5 Hz, 2H), 2.90 – 2.68 (m, 3H), 2.27 (s, 3H), 2.20 – 2.06 (m, 7H). LCMS (ESI) m/z: $[M+H]^+$ = 836.40.

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

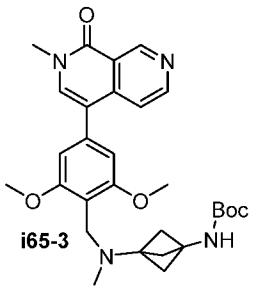


Step 1: Preparation of tert-butyl (3-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)amino)bicyclo[1.1.1]pentan-1-yl)carbamate (i65-2)



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

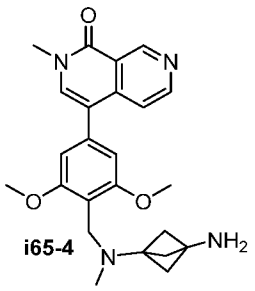
Step 2: Preparation of tert-butyl N-[3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl] methyl](methyl)amino)bicyclo[1.1.1]pentan-1-yl]carbamate (i65-3)



To a stirred solution of the product from step 1 was added $NaBH_3CN$ (49.62 mg, 0.790 mmol, 2.00 equiv) and formaldehyde (59.27 mg, 1.974 mmol, 5.00 equiv) in portions at room temperature. The resulting mixture was stirred for 2 hours at room temperature. Desired product could be detected by

LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (8:1) to afford *tert*-butyl *N*-[3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)bicyclo[1.1.1]pentan-1-yl]carbamate (146 mg, 71.03%) as a light yellow oil. LCMS (ESI) m/z: $[M+H]^+$ = 521.

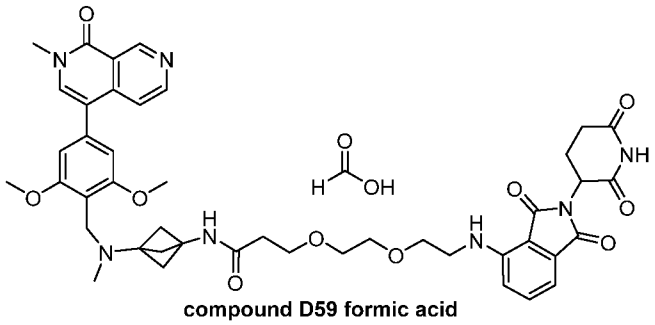
Step 3: Preparation of 4-(4-(((3-aminobicyclo[1.1.1]pentan-1-yl)(methyl)amino)methyl)-3,5-dimethoxy phenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (i65-4)



i65-4

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

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

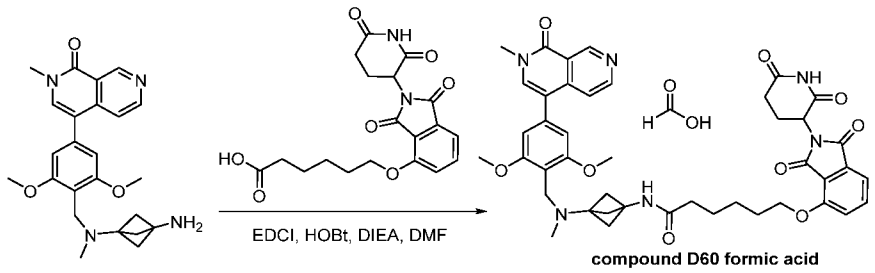


compound D59 formic acid

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

in 17 minutes; 254/220 nm; R_T:15.32 minutes) to afford *N*-[3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)bicyclo[1.1.1]pentan-1-yl]-3-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]propanamide formic acid (23.7 mg, 14.13%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.53 (s, 1H), 8.70 (d, *J* = 5.8 Hz, 1H), 8.20 (brs, 0.3H, FA), 7.78 (s, 1H), 7.63 (d, *J* = 5.7 Hz, 1H), 7.55 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 1H), 7.03 (d, *J* = 7.1 Hz, 1H), 6.85 (s, 2H), 5.08 (dd, *J* = 12.3, 5.4 Hz, 1H), 4.20 (s, 2H), 3.95 (s, 6H), 3.78 – 3.63 (m, 11H), 3.52 (t, *J* = 5.3 Hz, 2H), 2.99 – 2.66 (m, 6H), 2.52 – 2.34 (m, 8H), 2.18 – 2.08 (m, 1H). LCMS (ESI) m/z: $[M+H]^+$ = 836.65.

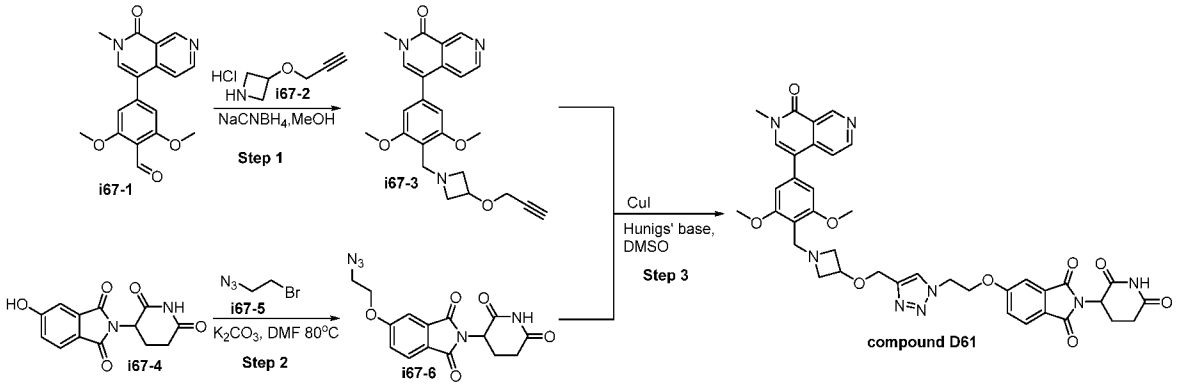
Example 66 – Preparation of N-[3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](me thyl)amino)bicyclo[1.1.1]pentan-1-yl]-6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]hex anamide formic acid (compound D60 formic acid)



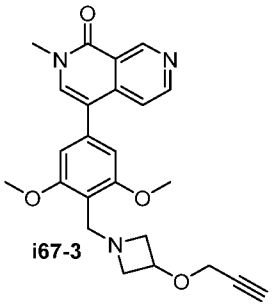
compound D60 formic acid

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

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

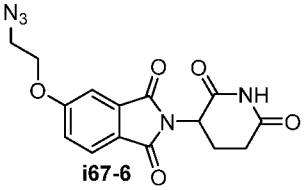


Step 1: Preparation of 4-(3,5-dimethoxy-4-((3-(prop-2-yn-1-yloxy)azetidin-1-yl)methyl)phenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (i67-3)



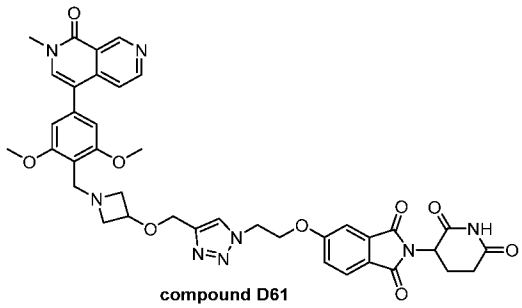
To a stirred solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (500 mg, 1.54 mmol, 1.00 equiv) in MeOH (15 mL) was added $NaBH_3CN$ (290 mg, 4.62 mmol, 3.00 equiv) and 3-(prop-2-yn-1-yloxy)azetidine hydrochloride (269 mg, 1.84 mmol, 1.20 equiv). The resulting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

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



2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindoline-1,3-dione (500 mg, 1.82 mmol, 1.0 equiv) was dissolved in DMF (15 mL). Potassium carbonate was then added (753 mg, 545 mmol, 3 equiv) followed by potassium iodide (451 mg, 2.72 mmol, 1.5 equiv) and 1-azido-2-bromoethane (286 mg, 1.91 mmol, 1.05 equiv). The mixture was then heated to 80 °C and stirred for 2 hours. The solvent was then removed and Flash column chromatography with EtOAc/PE (0-100%), to afford 5-(2-azidoethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (385 mg, 62%) as a solid. LCMS (ESI) m/z: $[M+H]^+$ = 344.4.

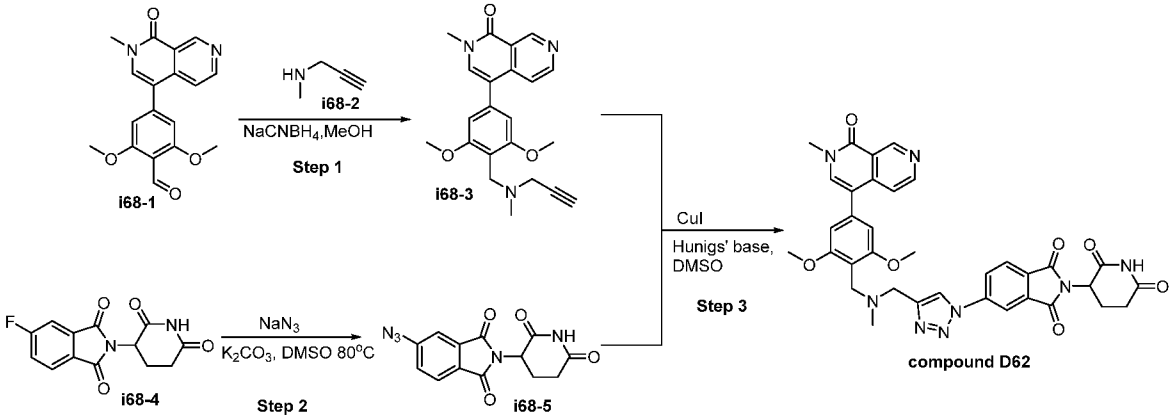
Step 3: Preparation of 5-(2-(4-(((1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)azetidin-3-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound D61)



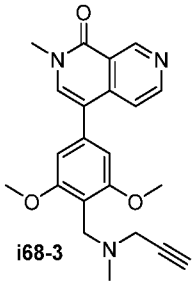
compound D61

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

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



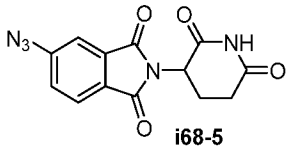
Step 1: Preparation of 4-(3,5-dimethoxy-4-((methyl(prop-2-yn-1-yl)amino)methyl)phenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (i68-3)



i68-3

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

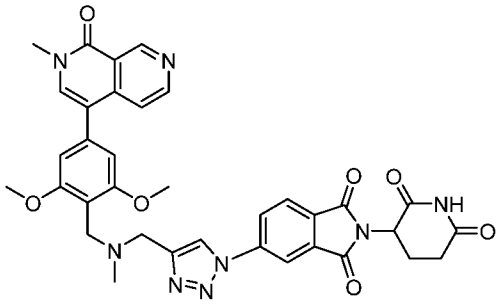
Step 2: Preparation of 5-azido-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (i68-5)



i68-5

2-(2,6-dioxopiperidin-3-yl)-5-fluoroisoindoline-1,3-dione (500 mg, 1.81 mmol, 1.0 equiv) was dissolved in DMSO (5 mL). Hünig's base was then added (0.944 mL, 5.43 mmol, 3 equiv) followed by sodium azide (176 mg, 2.71 mmol, 1.5 equiv) and 1-azido-2-bromoethane (286 mg, 1.91 mmol, 1.05 equiv). The mixture was then heated to 50 °C and stirred for 2 hours. The solution was then loaded directly onto silica gel and purified over silica gel with EtOAc/PE (0-100%) to afford 5-azido-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (480 mg, 89%) as a solid. LCMS (ESI) m/z: $[M+H]^+$ = 300.1.

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

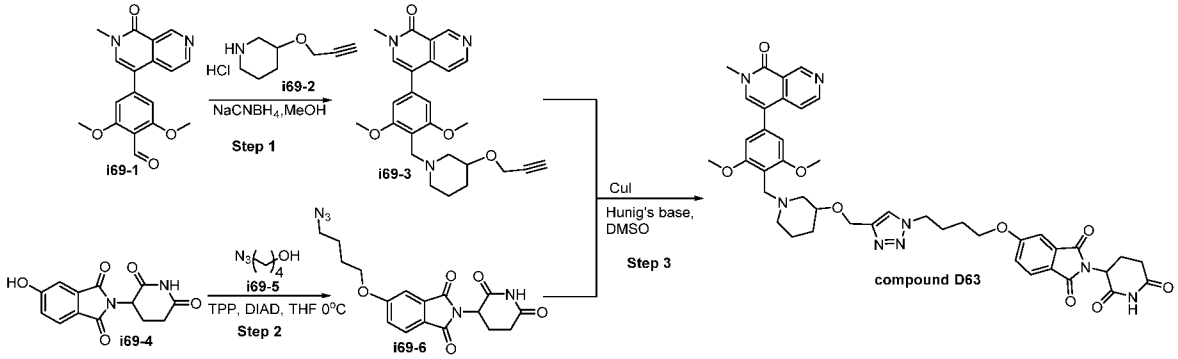


compound D62

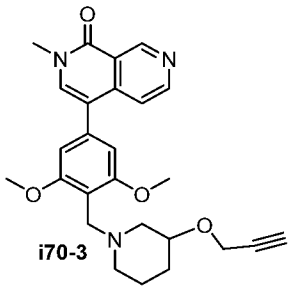
5-(2-azidoethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (19.8 mg, 0.0662 mmol, 1.0 equiv) and 4-(3,5-dimethoxy-4-((3-(prop-2-yn-1-yloxy)azetidin-1-yl)methyl)phenyl)-2-methyl-2,7-

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

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

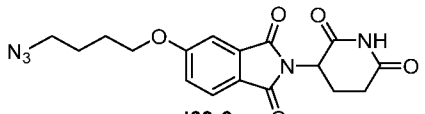


Step 1: Preparation of 4-(3,5-dimethoxy-4-((3-(prop-2-yn-1-yloxy)piperidin-1-yl)methyl)phenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (i69-3)



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

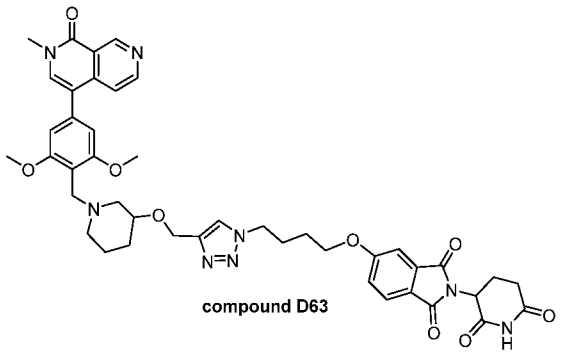
Step 2: Preparation of 5-(4-azidobutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (i69-6)



i69-6

2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindoline-1,3-dione (500 mg, 1.82 mmol, 1.0 equiv) was dissolved in THF (18 mL). Triphenylphosphine was then added (571 mg, 2.18 mmol, 1.2 equiv) followed by 4-azidobutan-1-ol (246 mg, 2.91 mmol, 1.05 equiv). The solution was cooled to 0 °C and 1-diisopropyl azodicarboxylate (358 mL, 1.82 mmol, 1.0 equiv) was added. The mixture was then warmed to room temperature and stirred for 2 hours. Water was added and the reaction extracted 3 times with ethyl acetate. The organics were dried over MgSO4, filtered, and evaporated. The resulting oil was columned over silica gel with EtOAc/PE (0-100%), to afford 5-(4-azidobutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (391 mg, 56%) as a solid. LCMS (ESI) m/z: $[M+H]^+$ = 372.4.

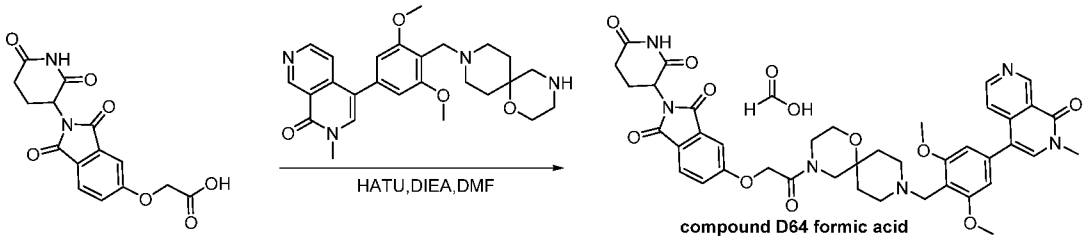
Step 3: 5-(4-(4-(((1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)piperidin-3-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)butoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound D63)



compound D63

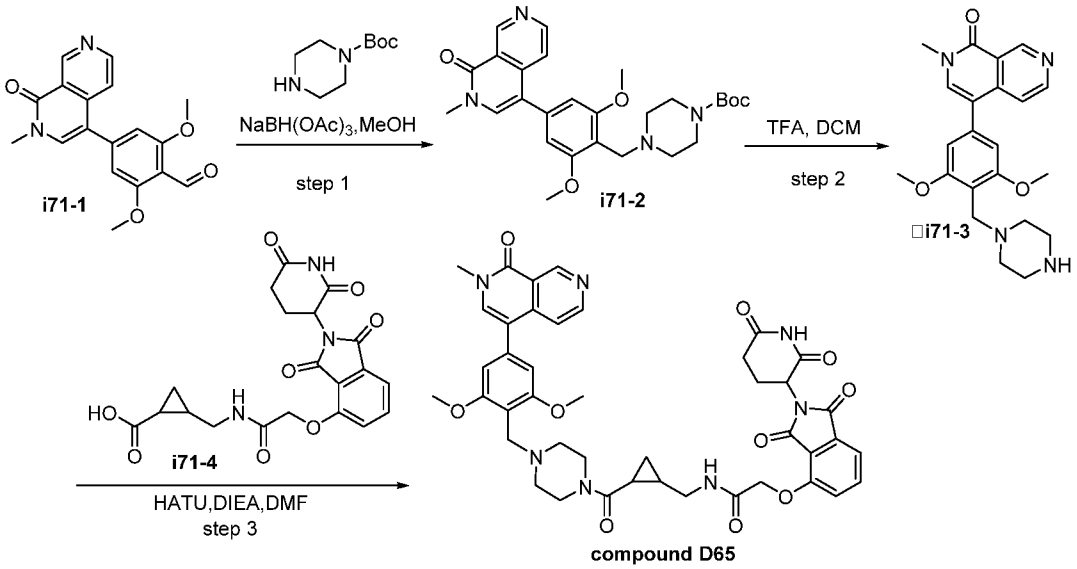
5-(4-azidobutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (21.5 mg, 0.0558 mmol, 1.0 equiv) and 4-(3,5-dimethoxy-4-((3-(prop-2-yn-1-yloxy)azetidin-1-yl)methyl)phenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (25 mg, 0.0558 mmol, 1.0 equiv) were dissolved in DMSO (1 mL). Hünig's base (0.0192 mL, 0.111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

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

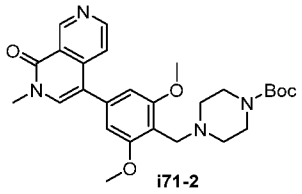


To a stirred solution of [[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]acetic acid (21.46 mg, 0.065 mmol,1.00 equiv) and 4-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-2-methyl-2,7-naphthyridin-1-one(30.00 mg,0.065 mmol,1.00 equiv) in DMF (1 mL) was added HATU (49.11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

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



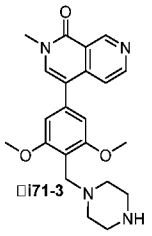
Step 1: Preparation of tert-butyl 4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl] methyl] piperazine-1-carboxylate (i71-2)



i71-2

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

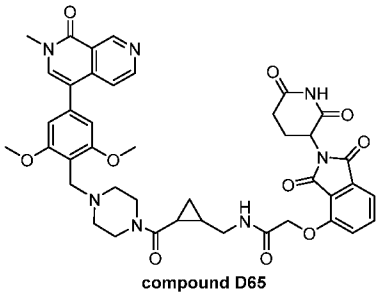
Step 2: Preparation of 4-[3,5-dimethoxy-4-(piperazin-1-ylmethyl)phenyl]-2-methyl-2,7-naphthyridin-1-one (i71-3)



□i71-3

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

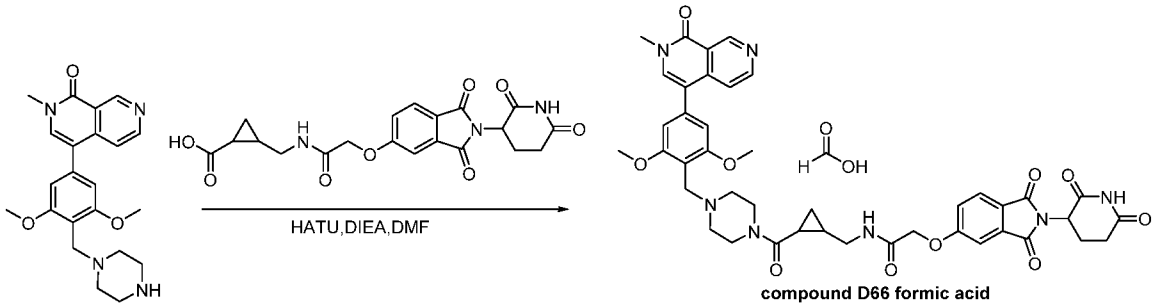
Step 3: Preparation of N-[[2-(4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] piperazine-1-carbonyl)cyclopropyl]methyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acet amide (compound D65)



compound D65

To a stirred mixture of 4-[3,5-dimethoxy-4-(piperazin-1-ylmethyl)phenyl]-2-methyl-2,7-naphthyridin-1-one (22.05 mg, 0.056 mmol, 1.20 equiv) and 2-[(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetamido)methyl]cyclopropane-1-carboxylic acid (20.00 mg, 0.047 mmol, 1.00 equiv) in DMF (1 mL) was added HATU (35.42 mg, 0.093 mmol, 2.00 equiv) and DIEA (12.04 mg, 0.093 mmol, 2.00 equiv) at room temperature. Without any additional work-up, the mixture was purified by prep-HPLC (conditions: XBridge Shield RP18 OBD Column, 30*150 mm, 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient:13 B to 22 B in 12 minutes; 254/220 nm; R_T: 9.45 minutes). Pure fractions were evaporated to dryness to afford *N*-[[2-(4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]piperazine-1-carbonyl)cyclopropyl]meth-yl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetamide (12.4 mg, 33.04%) as a white solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.52 (s, 1H), 8.68 (dd, *J* = 5.8, 1.8 Hz, 1H), 8.43 (brs, 0.5H, FA), 7.81 (ddd, *J* = 8.4, 7.3, 3.5 Hz, 1H), 7.75 (d, *J* = 3.7 Hz, 1H), 7.65 – 7.61 (m, 1H), 7.54 (dd, *J* = 6.9, 1.6 Hz, 1H), 7.45 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.76 (d, *J* = 2.5 Hz, 2H), 5.19 – 5.11 (m, 1H), 4.80 – 4.68 (m, 2H), 3.93 – 3.81 (m, 9H), 3.78 – 3.68 (m, 5H), 3.51 – 3.35 (m, 2H), 3.29 – 3.16 (m, 1H), 2.93 – 2.67 (m, 7H), 2.21 – 2.06 (m, 2H), 1.72 – 1.60 (m, 1H), 1.21 – 1.12 (m, 1H), 1.09 – 0.99 (m, 1H). LCMS (ESI) m/z: $[M+H]^+$ = 806.70.

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

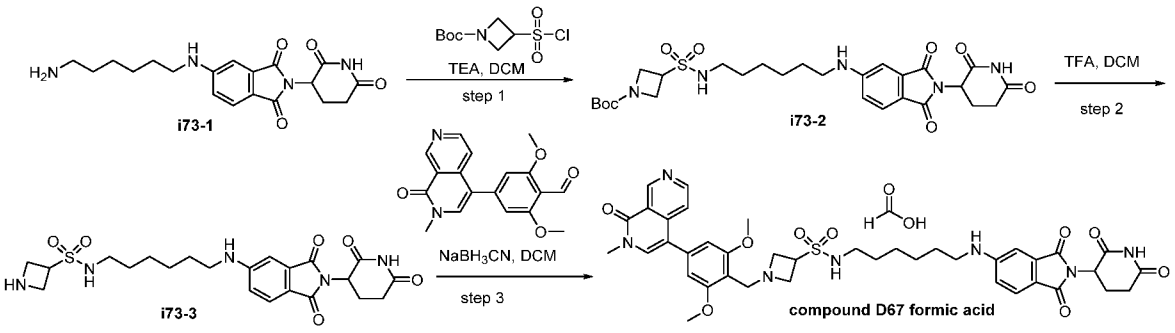


compound D66 formic acid

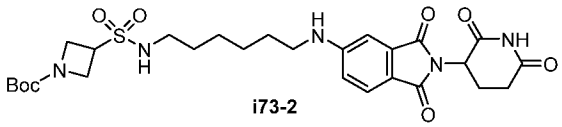
To a stirred mixture of 4-[3,5-dimethoxy-4-(piperazin-1-ylmethyl)phenyl]-2-methyl-2,7-naphthyridin-1-one (22.05 mg, 0.056 mmol, 1.20 equiv) and 2-[(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]ace tamido)methyl]cyclopropane-1-carboxylic acid (20.00 mg, 0.047 mmol, 1.00 equiv) in DMF(1 mL) was added HATU (35.42 mg, 0.093 mmol, 2.00 equiv) and DIEA (12.04 mg, 0.093 mmol, 2.00 equiv) at room temperature. Without any additional work-up, the mixture was purified by prep-HPLC (conditions: XBridge Shield RP18 OBD Column, 19*250 mm,10 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient:13 B to 22 B in 12 minutes; 254/220 nm; R_T: 10.22 minutes). Pure fractions were evaporated to dryness to afford *N*-[[2-(4-[[2,6-dimeth oxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]piperazine-1-carbonyl)cyclopropyl]methyl]-2-[[2-(2,6-dio xopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]acetamide (7.4 mg, 19.18%) as a white solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.52 (s, 1H), 8.68 (d, *J* = 5.8 Hz, 1H), 8.46 (brs, 1.0H, FA), 7.82 (d, *J* = 8.3 Hz, 1H), 7.73 (s, 1H), 7.63 (d, *J* = 5.8 Hz, 1H), 7.45 (d, *J* = 2.3 Hz, 1H), 7.40 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.78 (s, 2H), 5.11 (dd, *J* = 12.4, 5.4 Hz, 1H), 4.68 (s, 2H), 3.95 (s, 2H), 3.89 (s, 6H), 3.81 (s, 2H), 3.70 (s, 3H), 3.63 (s, 1H), 3.42 – 3.34 (m, 2H), 3.29 – 3.20 (m, 1H), 2.94 – 2.67 (m, 7H), 2.18 – 2.09 (m, 1H), 2.09 –

2.00 (m, 1H), 1.62 (q, *J* = 7.5 Hz, 1H), 1.11 (q, *J* = 5.5 Hz, 1H), 1.01 (td, *J* = 8.1, 4.5 Hz, 1H). LCMS (ESI) m/z: $[M+H]^+$ = 806.40.

Example 73 – Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl] methyl]-N-(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]amino]hexyl) azetidine-3-sulfonamide formic acid (compound D67 formic acid)

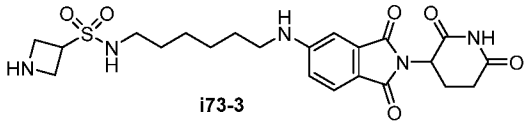


Step 1: Preparation of tert-butyl-3-[(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]hexyl) sulfamoyl]azetidine-1-carboxylate (i73-2)



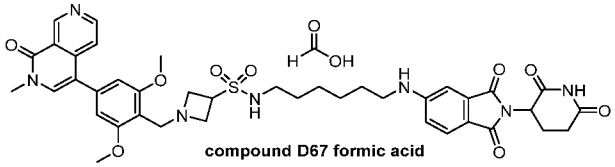
To a stirred mixture of 5-[(6-aminohexyl)amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione(60.00 mg, 0.161 mmol, 1.00 equiv) and *tert*-butyl 3-(chlorosulfonyl)azetidine-1-carboxylate(102.99 mg, 0.403 mmol, 2.50 equiv) in DCM(2.00 mL) was added TEA(48.91 mg, 0.483 mmol, 3.00 equiv). After stirring for 1.5 hours at room temperature, the resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/EA = 1:2) to afford *tert*-butyl-3-[(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]hexyl)sulfamoyl]azetidine-1-carboxylate (61.8 mg, 60.29%) as a light yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 592.

Step 2: Preparation of N-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)hexyl)azetidine-3-sulfonamide (i73-3)



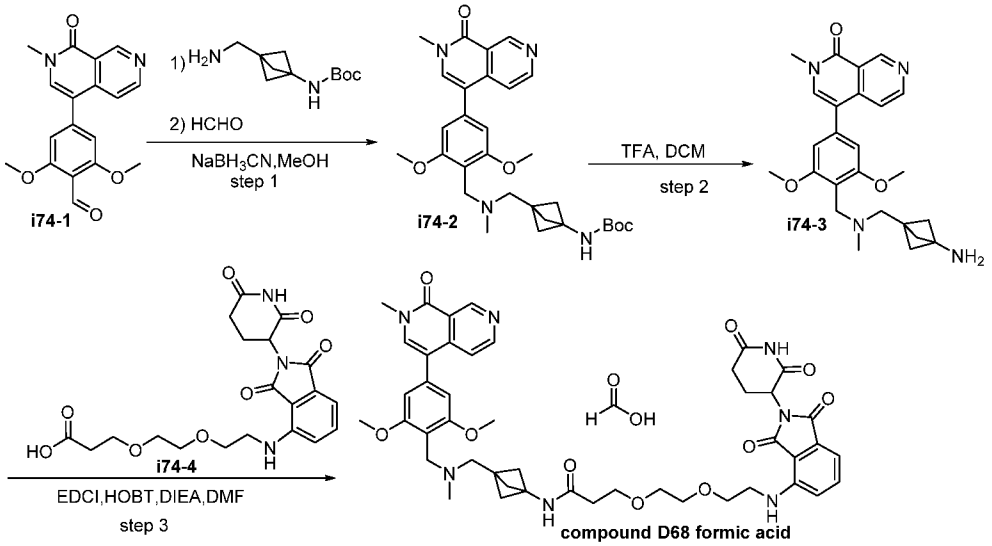
To a stirred mixture of *tert*-butyl 3-[(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino] hexyl)sulfamoyl]azetidine-1-carboxylate (61.8 mg, 0.104 mmol, 1.00 equiv) in DCM (2.00 mL) was added TFA (0.40 mL, 5.385 mmol, 51.56 equiv). After stirring for 1 hour at room temperature, the resulting mixture was concentrated under reduced pressure. The residue was used in the next step directly without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 492.

Step 3: Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl] methyl]-N-(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]amino]hexyl)azetidine-3-sulfonamide formic acid (compound D67 formic acid)

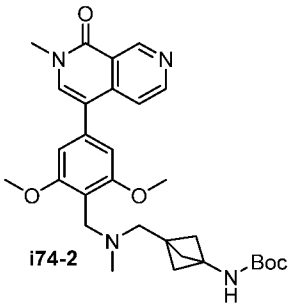


A mixture of *N*-(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]amino] hexyl)azetidine-3-sulfonamide(51.36 mg, 0.104 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (33.89 mg, 0.104 mmol, 1.00 equiv) in DMF(2 mL) was stirred at room temperature. The reaction mixture was then adjusted to pH 8-9 with TEA. To the above mixture was added $NaBH_3CN$ (19.70 mg, 0.313 mmol, 3.00 equiv) in portions, and the resulting mixture was stirred for 2 hours at room temperature. The resulting mixture was concentrated under reduced pressure, the residue was purified by Prep-HPLC (conditions: X Select CSH Prep C18 OBD Column, 5 μm, 19*150 mm; mobile phase, Water (0.1% FA) and ACN (15% Phase B up to 30% in 14 minutes); Detector, UV). This gave 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]amino]hexyl)azetidine-3-sulfonamide formic acid (13 mg, 14.12%) as a yellow solid. ^1H NMR (400 MHz, DMSO-d6) δ 9.45 (s, 1H), 8.73 (d, *J* = 5.7 Hz, 1H), 8.14 (s, 0.2H, FA), 7.87 (s, 1H), 7.56 (d, *J* = 5.7 Hz, 1H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.27 (br s, 1H), 6.94 (d, *J* = 2.0 Hz, 1H), 6.82 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.78 (s, 2H), 6.56 (d, *J* = 8.2 Hz, 2H), 5.10 (dd, *J* = 13.0, 5.4 Hz, 1H), 4.01 (br s, 2H), 3.84 (s, 7H), 3.60 (s, 6H), 3.47 – 3.35 (m, 2H), 3.05 – 2.83 (m, 3H), 2.77 – 2.65 (m, 1H), 2.49 – 2.41 (m, 2H), 2.03 – 1.96 (m, 1H), 1.39 (t, *J* = 7.0 Hz, 4H), 1.24 (s, 4H). LCMS (ESI) m/z: $[M+H]^+$ = 800.25.

Example 74 – Preparation of N-[3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](meth- yl)amino)methyl]bicyclo[1.1.1]pentan-1-yl]-3-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]propanamide formic acid (compound D68 formic acid)

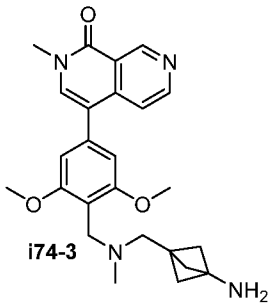


Step 1: Preparation of tert-butyl N-[3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]amino)methyl]bicyclo[1.1.1]pentan-1-yl]carbamate (i74-2)



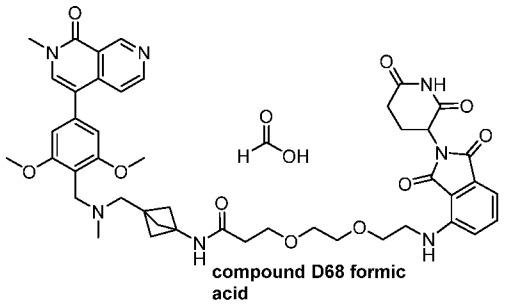
To a stirred mixture of 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (200.00 mg, 0.617 mmol, 1.00 equiv) and *tert*-butyl *N*-[3-(aminomethyl)bicyclo[1.1.1]pentan-1-yl]carbamate (144.00 mg, 0.678 mmol, 1.10 equiv) in MeOH (1 mL) was added $NaBH_3CN$ (77.50 mg, 1.233 mmol, 2.00 equiv) in portions at room temperature. The resulting mixture was stirred for 2 hours at room temperature. To the above mixture was added formaldehyde (0.50 mL). The resulting mixture was stirred for 1 hour at room temperature. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash silica chromatography, elution gradient 0 to 30% EtOAc in petroleum ether. Pure fractions was concentrated under vacuum to afford tert-butyl N-[3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]amino)methyl]bicyclo[1.1.1]pentan-1-yl] carbamate (284.8 mg) as a yellow gum. LCMS (ESI) m/z: $[M+H]^+$ = 535.

Step 2: Preparation of 4-(4-[[([3-aminobicyclo[1.1.1]pentan-1-yl]methyl)(methyl)amino]methyl]-3,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1-one (i74-3)



A mixture of *tert*-butyl *N*-[3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](me- thyl)amino)methyl]bicyclo[1.1.1]pentan-1-yl]carbamate (284.80 mg) and TFA (1.00 mL) in DCM (1 mL) was stirred for overnight at room temperature. The reaction mixture was concentrated under vacuum to afford 4-(4-[[([3-aminobicyclo[1.1.1]pentan-1-yl]methyl)(methyl)amino]methyl]-3,5-dimethoxyphenyl)-2-me thyl-2,7-naphthyridin-1-one (639.4 mg, crude) as a yellow gum. LCMS (ESI) m/z: $[M+H]^+$ = 435.

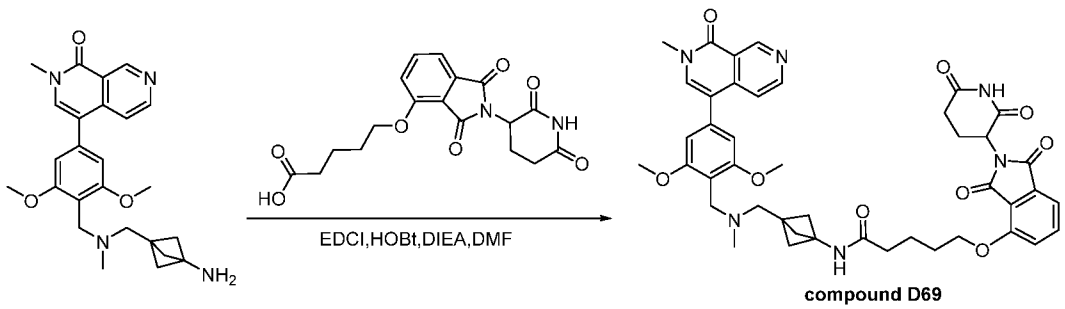
Step 3: Preparation of N-[3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)methyl]bicyclo[1.1.1]pentan-1-yl]-3-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]propanamide formic acid (compound D68 formic acid)



compound D68 formic acid

To a stirred solution of 4-(4-[[([3-aminobicyclo[1.1.1]pentan-1-yl]methyl)(methyl)amino]methyl]-3,5-dimet- hoxyphenyl)-2-methyl-2,7-naphthyridin-1-one (20.05 mg, 0.046 mmol, 1 equiv) and 3-[2-(2-[[2-(2,6-diox- opiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]propanoic acid (20.00 mg, 0.046 mmol, 1.00 equiv) in DMF (1 mL) was added EDCI (17.69 mg, 0.092 mmol, 2.00 equiv), HOBT (12.47 mg, 0.092 mmol, 2.00 equiv), and DIEA (23.86 mg, 0.185 mmol, 4.00 equiv). The resulting mixture was stirred overnight at room temperature. Without any additional work-up, the mixture was purified by prep-HPLC (conditions: Column: Gemini-NX C18 AXAI Packed, 21.2*150 mm 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient:8 B to 25 B in 12 minutes; 254/220 nm; R_T: 11.04 minutes) to afford *N*-[3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methy-l)amino)methyl]bicycle[1.1.1]pentan-1-yl]-3-[2-(2-[[2-(2,6-dioxopi peridin-3-yl)-1,3-dioxoisoindol-4-yl]amin-o]ethoxy)ethoxy]propanamide (3.4 mg, 8.67%) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 9.45 (s, 1H), 8.72 (d, *J* = 5.6 Hz, 1H), 8.29 (s, 1H), 8.23 (brs, 1.0H, FA), 7.87 (s, 1H), 7.58 (t, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 8.6 Hz, 1H), 7.03 (d, *J* = 7.1 Hz, 1H), 6.72 (s, 2H), 6.61 (t, *J* = 5.8 Hz, 1H), 5.06 (dd, *J* = 12.7, 5.4 Hz, 1H), 3.81 (s, 6H), 3.58 – 3.54 (m, 5H), 3.54 – 3.49 (m, 6H), 3.48 – 3.42 (m, 4H), 2.96 – 2.81 (m, 1H), 2.64 – 2.58 (m, 1H), 2.55 (s, 3H), 2.26 (t, *J* = 6.4 Hz, 2H), 2.12 (s, 3H), 2.08 – 1.98 (m, 1H), 1.92 (s, 6H). LCMS (ESI) m/z: $[M+H]^+$ = 850.50.

Example 75 – Preparation of N-[3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](meth- yl)amino)methyl]bicyclo[1.1.1]pentan-1-yl]-5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]ox- y]pentanamide (compound D69)

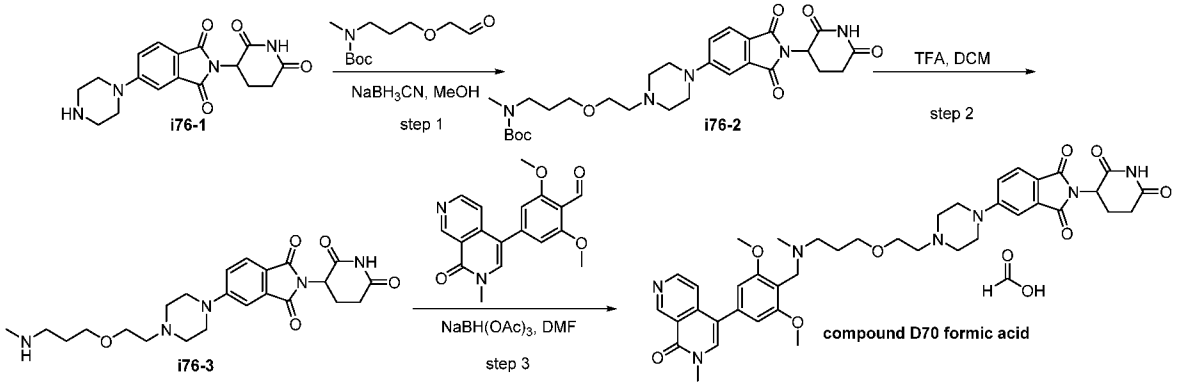


compound D69

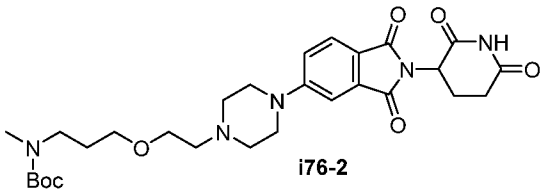
To a stirred solution of 4-(4-[[([3-aminobicyclo[1.1.1]pentan-1-yl]methyl)(methyl)amino]methyl]-3,5-dime thoxyphenyl)-2-methyl-2,7-naphthyridin-1-one (23.22 mg, 0.053 mmol, 1.00 equiv) and 5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]pentanoic acid (20.00 mg, 0.053 mmol, 1.00 equiv) in DMF (1 mL) was added EDCI (20.48 mg, 0.107 mmol, 2.00 equiv) and HOBT (14.44 mg, 0.107 mmol,

2.00 equiv) at room temperature. To the above mixture was added DIEA (27.62 mg, 0.214 mmol, 4.00 equiv). The resulting mixture was stirred for overnight at room temperature. Without any additional work-up, the mixture was purified by prep-HPLC (conditions: SunFire Prep C18 OBD Column, 19×150 mm 5 μm 10 nm; Mobile Phase A: Water (0.1% FA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient:13 B to 22 B in 13 minutes; 254/220 nm; R_T: 12.5 minutes) to afford *N*-[3-[([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)methy-l]bicyclo[1.1.1] pentan-1-yl]-5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]pentanamide (6.9 mg, 17.75%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d6) δ 11.10 (s, 1H), 9.46 (d, *J* = 0.8 Hz, 1H), 8.74 (d, *J* = 5.7 Hz, 1H), 8.36 (s, 1H), 7.88 (s, 1H), 7.82 (dd, *J* = 8.5, 7.2 Hz, 1H), 7.60 – 7.42 (m, 3H), 6.79 (s, 2H), 5.08 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.21 (t, *J* = 6.0 Hz, 2H), 3.86 (s, 6H), 3.61 (s, 3H), 3.40 (s, 2H), 2.98 – 2.80 (m, 2H), 2.62 (s, 2H), 2.46 – 2.30 (m, 4H), 2.15 – 2.00 (m, 9H), 1.78 – 1.64 (m, 4H). LCMS (ESI) m/z: $[M+H]^+$ = 791.40.

Example 76 – Preparation of 5-(4-[2-[3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]meth yl](methyl)amino)propoxy]ethyl]piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (compound D70 formic acid)

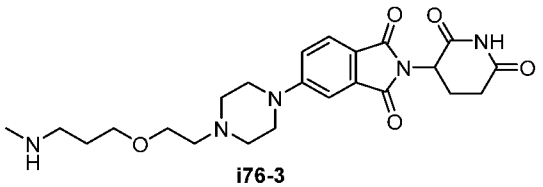


Step 1: Preparation of tert-butyl N-[3-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethoxy)propyl]-N-methylcarbamate (i76-2)



To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)isoindole-1,3-dione (250.00 mg, 0.730 mmol, 1.00 equiv) and *tert*-butyl *N*-methyl-*N*-[3-(2-oxoethoxy)propyl]carbamate (168.90 mg, 0.730 mmol, 1 equiv) in MeOH (3.00 mL) was added $NaBH_3CN$ (91.78 mg, 1.460 mmol, 2 equiv). The mixture was stirred at room temperature for 2 hours. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (Petroleum ether/EtOAc 1:3) to afford *tert*-butyl *N*-[3-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethoxy)propyl]-*N*-methylcarbamate (400 mg, crude) as a dark grey solid. LCMS (ESI) m/z: [M+H]+ = 558.

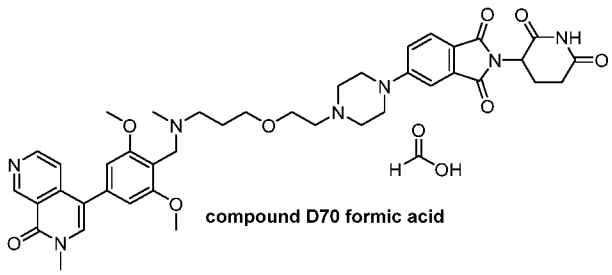
Step 2: Preparation of 2-(2,6-dioxopiperidin-3-yl)-5-(4-[2-[3-(methylamino)propoxy]ethyl]piperazin-1-yl)isoindole-1,3-dione *(i76-3)*



i76-3

To a stirred solution of *tert*-butyl *N*-[3-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethoxy)propyl]-*N*-methylcarbamate (200.00 mg, 0.359 mmol, 1.00 equiv) in DCM (4.00 mL, 62.920 mmol) was added TFA (1.00 mg, 0.009 mmol). The mixture was stirred at room temperature for 2 hours. The resulting mixture was concentrated under reduced pressure to afford 2-(2,6-dioxopiperidin-3-yl)-5-(4-[2-[3-(methylamino)propoxy]ethyl]piperazin-1-yl)isoindole-1,3-dione (280 mg, crude) as a dark grey solid. LCMS (ESI) m/z: [M+H]+ = 458.

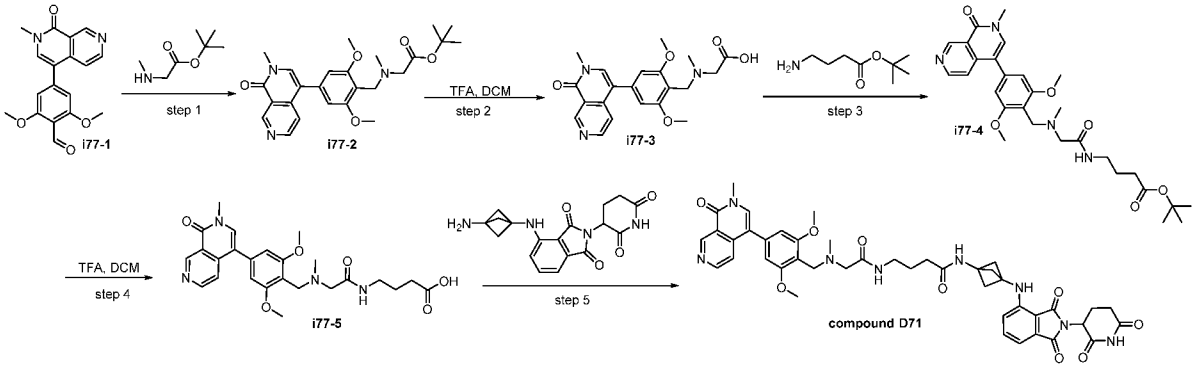
Step 3: Preparation of 5-(4-[2-[3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)propoxy]ethyl]piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (compound D70 formic acid)



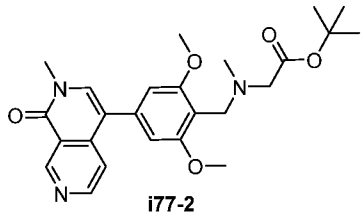
compound D70 formic acid

To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-(4-[2-[3-(methylamino)propoxy]ethyl]piperazin-1-yl)isoindole-1,3-dione (100.00 mg, 0.219 mmol, 1.00 equiv) and2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (70.89 mg, 0.219 mmol, 1 equiv) in DMF (1.50 mL) was added $NaBH(OAc)_3$ (92.65 mg, 0.437 mmol, 2 equiv). The mixture was stirred at room temperature for 2 hours. The crude product (100 mg) was purified by Prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100Å, 5 μm, 19 mm X 250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient:5 B to 13 B in 15 minutes; 254 nm; R_T: 12.23 minutes) to afford 5-(4-[2-[3-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)propoxy]ethyl]piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione; formic acid(10mg,5.38%) as a yellow solid. ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.51 (d, *J* = 18.3 Hz, 1H), 8.68 (d, *J* = 5.7 Hz, 1H), 8.53 (brs, 4.1H, FA), 7.76 (s, 1H), 7.64 (d, *J* = 7.4 Hz, 2H), 7.25 (s, 1H), 7.17 (d, *J* = 8.6 Hz, 1H), 6.90 (s, 2H), 5.11 – 5.04 (m, 2H), 4.69 – 4.53 (m, 2H), 4.47 (s, 2H), 4.00 (s, 6H), 3.74 – 3.62 (m, 7H), 3.40 (d, *J* = 5.5 Hz, 4H), 2.91 (s, 3H), 2.87 – 2.73 (m, 3H), 2.69 (s, 6H), 2.23 – 2.08 (m, 3H). LCMS (ESI) m/z: $[M+H]^+$ = 766.45.

Example 77 – Preparation of 4-[2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](meth yl)amino)acetamido]-N-(3-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]bicycle[1.1.1] pentan-1-yl)butanamide (compound D71)



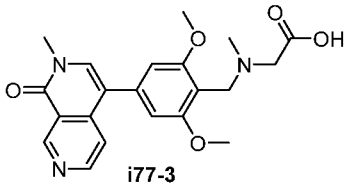
Step 1: Preparation of tert-butyl N-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl) benzyl)-N-methylglycinate (i77-2)



i77-2

To a stirred solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (250.00 mg, 0.771 mmol, 1.00 equiv) and *tert*-butyl 2-(methylamino)acetate (111.92 mg, 0.771 mmol, 1.00 equiv) in MeOH (10.00 mL) was added $NaBH_3CN$ (96.88 mg, 1.542 mmol, 2.00 equiv) in portions at 50 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched with Water at room temperature. The aqueous layer was extracted with EtOAc (3 x 30 mL). The resulting solid was dried under vacuum. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; mobile phase, MeOH in water, 10% to 50% gradient in 10 minutes; detector, UV 254 nm). This resulted in *tert*-butyl *N*-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-N-methylglycinate (101mg,28.92%) as a yellow oil. LCMS (ESI) m/z: [M+H]+ = 454.

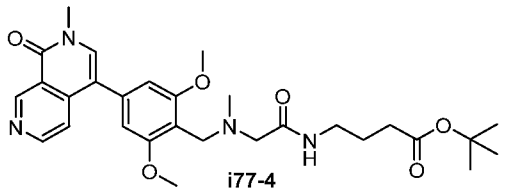
Step 2: Preparation of N-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-N-methylglycine *(i77-3)*



i77-3

A solution of *tert*-butyl 2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] (methyl) amino) acetate (101.00 mg, 0.223 mmol, 1.00 equiv) and TFA (7.21 mL, 63.270 mmol, 436.14 equiv) in DCM (29.00 mL) was stirred for 15 hours at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The residue (108 mg, crude) was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]+ = 398.

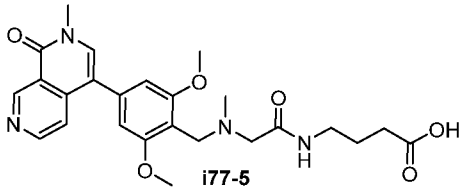
Step 3: Preparation of tert-butyl 4-(2-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)(methyl)amino)acetamido)butanoate (i77-4)



i77-4

A solution of ([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)acetic acid (108 mg (crude), 0.272 mmol, 1.00 equiv), DIEA (105.36 mg, 0.815 mmol, 3.00 equiv), and HATU (206.53 mg, 0.543 mmol, 2.00 equiv) in DMF (2.00 mL) was stirred for 30 minutes at room temperature under nitrogen atmosphere. To the above mixture was added *tert*-butyl 4-aminobutanoate (43.27 mg, 0.272 mmol, 1.00 equiv) at room temperature. The resulting mixture was stirred for additional 12 hours at room temperature. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; mobile phase, MeOH in water, 10% to 50% gradient in 10 minutes; detector, UV 254 nm). This resulted in *tert*-butyl 4-(2-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)(methyl)amino)acetamido) butanoate (75 mg, 62.33%) as a yellow oil. LCMS (ESI) m/z: [M+H]+ = 539.

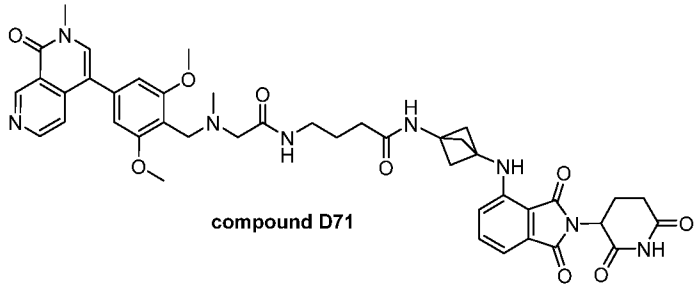
Step 4: Preparation of 4-(2-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)(m ethyl)amino)acetamido)butanoicacid (i77-5)



i77-5

A solution of *tert*-butyl 4-[2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](meth yl)amino) acetamido]butanoate (75.00 mg, 0.139 mmol, 1.00 equiv) and TFA (1 mL) in DCM (4.00 mL) was stirred for 2 hours at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The residue (73 mg, crude) was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]+ = 483.

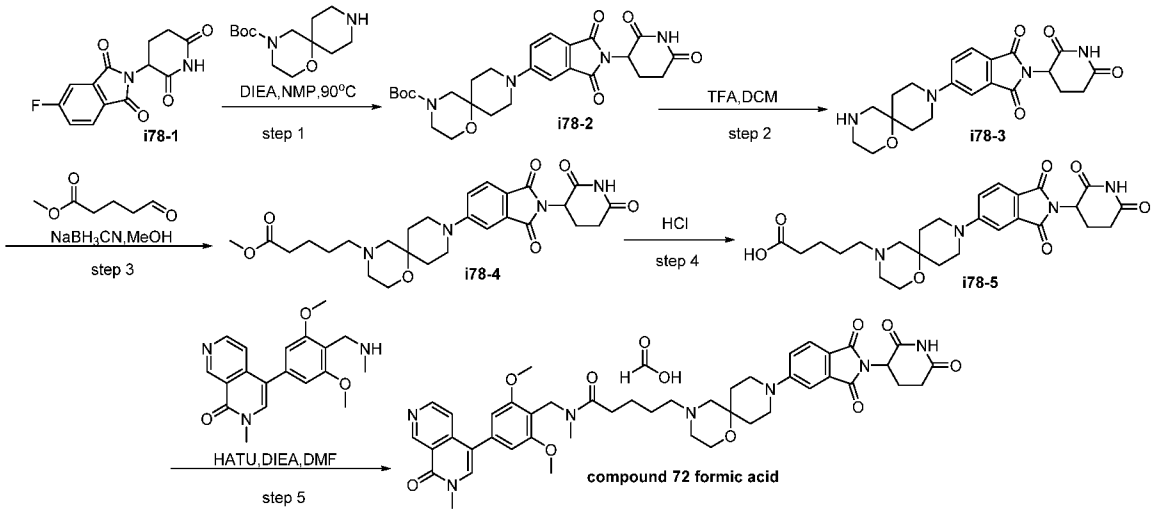
Step 5: Preparation of 4-(2-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)(methyl)amino)acetamido)-N-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)bicycle[1.1.1]pentan-1-yl)butanamide (compound D71)



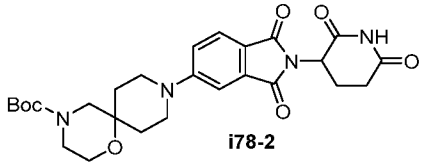
compound D71

To a stirred solution of 4-[2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] (methyl)amino) acetamido]butanoic acid (73.00 mg(crude), 0.151 mmol, 1.00 equiv) , DIEA (58.66 mg, 0.454 mmol, 3.00 equiv), and EDCI (58.00 mg, 0.303 mmol, 2.00 equiv) in DMF (2.00 mL) was added HOBT (40.88 mg, 0.303 mmol, 2.00 equiv) in portions at room temperature under nitrogen atmosphere. The reaction mixture was irradiated with microwave radiation for 1 hour at room temperature. To the above mixture was added 4-([3-aminobicyclo[1.1.1]pentan-1-yl]amino)-2-(2,6-dioxopiperidin-3-yl) isoindole-1,3-dione (53.61 mg, 0.151 mmol, 1.00 equiv) at room temperature. The resulting mixture was stirred for additional 2 days at room temperature. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; mobile phase, MeOH in water, 10% to 50% gradient in 10 minutes; detector, UV 254 nm). The crude product (70 mg) was purified by Prep-HPLC (conditions: Atlantis HILIC OBD Column 19*150 mm,5 μm ;Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 40 mL/minute; Gradient: 24% B to 24% B in 12 minutes; 254/220 nm; Rt: 11.43 minutes) to afford 4-[2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino) acetamido]-*N*-(3-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]bicyclo[1.1.1]pentan-1-yl)butane mide (10 mg, 8.07%) as a light yellow solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.56 (s, 1H), 8.70 (d, *J* = 6.0 Hz, 1H), 7.88 (d, *J* = 1.4 Hz, 1H), 7.75 (d, *J* = 5.9 Hz, 1H), 7.58 (dd, *J* = 9.5, 5.0 Hz, 1H), 7.27 (dd, *J* = 8.6, 3.5 Hz, 1H), 7.14 (d, *J* = 7.2 Hz, 1H), 6.89 (s, 2H), 5.08 (dd, *J* = 12.4, 5.4 Hz, 1H), 4.56 (d, *J* = 5.7 Hz, 2H), 4.01 – 3.97 (m, 7H), 3.93 – 3.87 (m, 1H), 3.73 (s, 3H), 3.29 – 3.23 (m, 2H), 2.97 (s, 3H), 2.90 – 2.83 (m, 1H), 2.80 – 2.68 (m, 2H), 2.43 (s, 6H), 2.22 (t, *J* = 7.3 Hz, 2H), 2.16 – 2.10 (m, 1H), 1.80 (p, *J* = 7.2 Hz, 2H). LCMS (ESI) m/z: $[M+H]^+$ = 819.35.

Example 78 – Preparation of N-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-5-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]-N-methyl pentanamide formic acid (compound D72 formic acid)

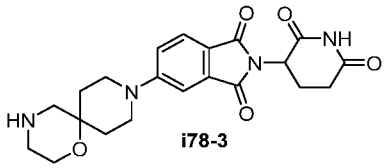


Step 1: Preparation of 2-(2,6-dioxopiperidin-3-yl)-5-[1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]isoindole-1,3-dione (i78-2)



To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisoindole-1,3-dione (1.50 g, 5.430 mmol, 1.00 equiv) and *tert*-butyl 1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (1.67 g, 6.516 mmol, 1.20 equiv) in NMP (10.00 mL) was added DIEA (1.40 g, 10.861 mmol, 2.00 equiv) dropwise at room temperature. The resulting mixture was stirred for 6 hours at 90 °C under nitrogen atmosphere. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 20 minutes; detector, UV 254 nm). This resulted in *tert*-butyl 9-(2-(2,6- dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (2 g, 72%) as a green oil. LCMS (ESI) m/z: [M+H]+ = 513.

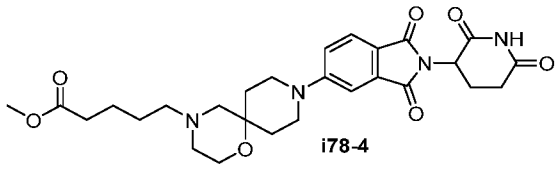
Step 2: Preparation of 2-(2,6-dioxopiperidin-3-yl)-5-[1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]isoindole-1,3-dione (*i78-3)*



i78-3

To a stirred solution of *tert*-butyl 9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (430.00 mg, 0.839 mmol, 1.00 equiv) in DCM (3.50 mL) was added TFA (1.00 mL). The mixture was stirred at room temperature for 1 hour. The resulting mixture was concentrated under reduced pressure to afford 2-(2,6-dioxopiperidin-3-yl)-5-[1-oxa-4,9-diazaspiro [5.5]undecan-9-yl]isoindole-1,3-dione (670 mg, crude) as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 413

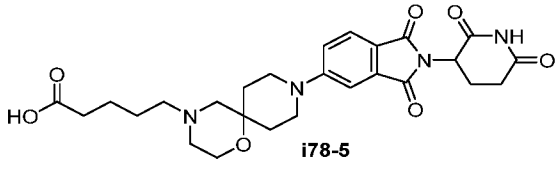
Step 3: Preparation of methyl 5-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]pentanoate (i78-4)



i78-4

To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-[1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]isoindole-1,3-dione (200.00 mg, 0.485 mmol, 1.00 equiv) and methyl 5-oxopentanoate (75.73 mg, 0.582 mmol, 1.2 equiv) in MeOH (2.00 mL) was added $NaBH_3CN$ (60.95 mg, 0.970 mmol, 2 equiv). The mixture was stirred at room temperature for 2 hours. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (Petroleum ether/EtOAc 1:3) to afford methyl 5-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]pentanoate (80 mg, 31.33%) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 527.

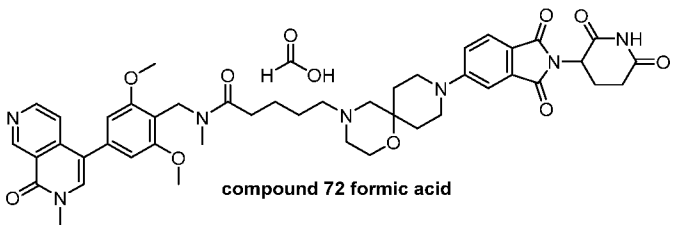
Step 4: Preparation of5-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro [5.5]undecan-4-yl]pentanoic acid (i78-5)



i78-5

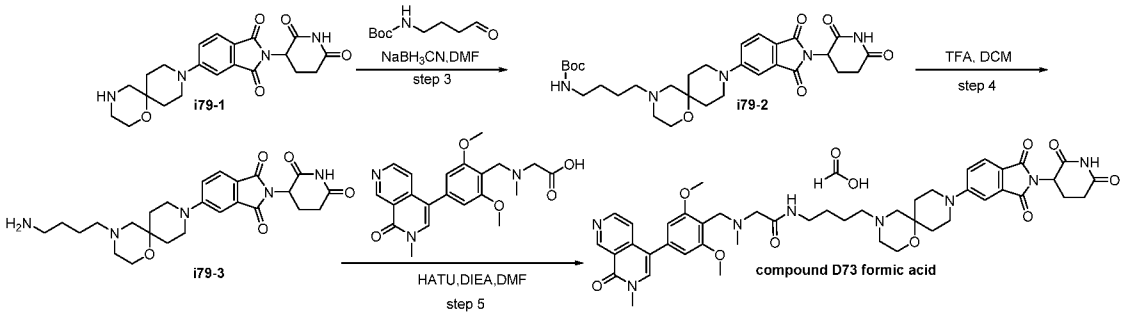
Methyl 5-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]pentanoate (70.00 mg, 0.133 mmol, 1.00 equiv) was stirred at room temperature with HCl (aq.) for 2 hours. The resulting mixture was concentrated under reduced pressure. This resulted in 5-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]pentanoic acid (70 mg, crude) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 513.

Step 5: Preparation of N-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-5-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]-N-methylpentanamide formic acid (compound D72 formic acid)

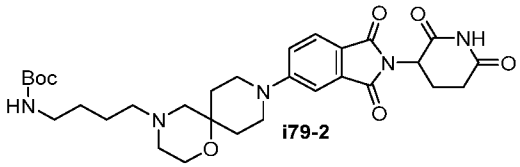


To a stirred solution of 5-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5] undecan-4-yl]pentanoic acid (55.00 mg, 0.107 mmol, 1.00 equiv) and 4-[3,5-dimethoxy-4-[(methylamino)methyl]phenyl]-2-methyl-2,7-naphthyridin-1-one (36.42 mg, 0.107 mmol, 1.00 equiv) in DMF (1.00 mL) was added DIEA (69.34 mg, 0.537 mmol, 5.00 equiv) and HATU (61.20 mg, 0.161 mmol, 1.50 equiv). The mixture was stirred at room temperature for 1 hours. The crude product (55 mg) was purified by Prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100Å, 5 μm, 19 mm X 250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient:9 B to 28 B in 13 minutes; 254 nm; R_T: 14.08 minutes) to afford *N*-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-5-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]-*N*-methylpentanamide formic acid (8.2 mg, 8.68%) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.50 (d, *J* = 3.4 Hz, 1H), 8.65 (dd, *J* = 12.4, 5.8 Hz, 1H), 8.39 (brs, 0.6H, FA), 7.74 (d, *J* = 4.5 Hz, 1H), 7.66 – 7.57 (m, 2H), 7.28 (dd, *J* = 12.7, 2.3 Hz, 1H), 7.22 – 7.14 (m, 1H), 6.80 (d, *J* = 20.6 Hz, 2H), 5.04 (dt, *J* = 12.8, 5.8 Hz, 1H), 4.75 (d, *J* = 16.1 Hz, 2H), 3.90 (d, *J* = 16.5 Hz, 6H), 3.87 – 3.82 (m, 2H), 3.74 – 3.63 (m, 5H), 3.32 – 3.26 (m, 2H), 2.92 – 2.82 (m, 2H), 2.78 (d, *J* = 6.8 Hz, 4H), 2.73 – 2.53 (m, 7H), 2.47 (t, *J* = 6.7 Hz, 1H), 2.17 – 2.01 (m, 3H), 1.82 – 1.62 (m, 6H). LCMS (ESI) m/z: $[M+H]^+$ = 834.40.

Example 79 – Preparation of 2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] (methyl)amino)-N-(4-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diaza spiro[5.5]undecan-4-yl]butyl)acetamide formic acid (compound D73 formic acid)

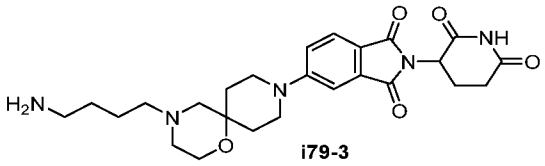


Step 1: Preparation of tert-butyl N-(4-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]butyl)carbamate (i79-2)



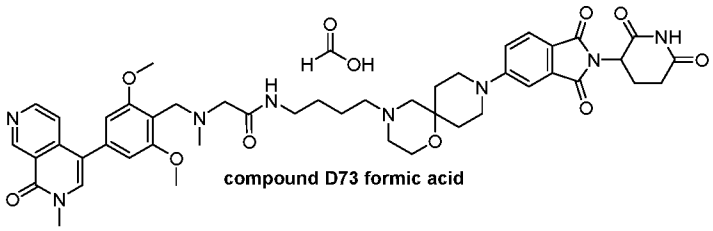
To a stirred solution of2-(2,6-dioxopiperidin-3-yl)-5-[1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]isoindole-1,3-dione (200.00 mg, 0.485 mmol, 1.00 equiv) and *tert*-butyl *N*-(4-oxobutyl)carbamate (907.94 mg, 4.849 mmol, 10.00 equiv) in DMF(1.50 mL) was added $NaBH_3CN$ (60.95 mg, 0.970 mmol, 2.00 equiv). The mixture was stirred at room temperature for 5 hours. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (Petroleum ether/EtOAc 1:3) to afford *tert*-butyl *N*-(4-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]butyl)carbamate(200 mg,crude) as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 584.

Step 2: Preparation of 5-[4-(4-aminobutyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione *(i79-3)*



To a stirred solution of *tert*-butyl *N*-(4-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]butyl)carbamate (200.00 mg, 0.343 mmol, 1.00 equiv) in DCM (3.00 mL) was added TFA (1.00 mL). The mixture was stirred at room temperature for 2 hours. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 5-[4-(4-aminobutyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (60 mg, 36.21%) as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 484.

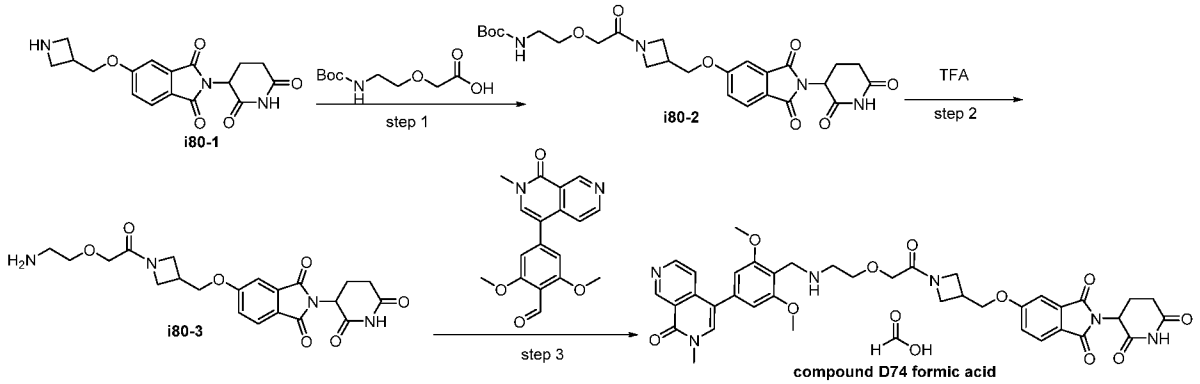
Step 3: Preparation of 2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)-N-(4-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]butyl)acetamide formic acid (compound D73 formic acid)



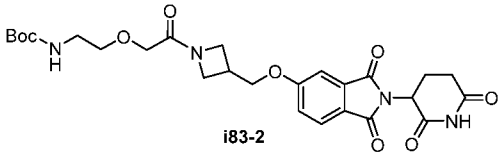
To a stirred solution of 5-[4-(4-aminobutyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (60.00 mg, 0.124 mmol, 1.00 equiv) and ([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)acetic acid (49.31 mg, 0.124 mmol, 1.00 equiv)in DMF (1.00 mg) was added DIEA (80.18 mg, 0.620 mmol, 5.00 equiv) and HATU (70.77 mg, 0.186 mmol, 1.50 equiv). The mixture was stirred at room temperature for 1 hour. The crude product

(60mg) was purified by Prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100Å, 5 µm, 19 mm X 250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B:ACN; Flow rate:25 mL/minute; Gradient:8 B to 17 B in 12 minutes; 254 nm; R_T: 11.87 minutes) to afford 2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)-*N*-(4-[9-[2-(2,6-dioxopip eridin-3-yl)-1,3-dioxoisoindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]butyl)acetamide formic acid (12. 6mg,10.72%) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.51 (s, 1H), 8.68 (d, *J* = 5.8 Hz, 1H), 8.53 (brs, 0.9H, FA), 7.74 (s, 1H), 7.62 (dd, *J* = 7.3, 6.3 Hz, 2H), 7.27 (d, *J* = 2.3 Hz, 1H), 7.16 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.82 (s, 2H), 5.05 (dd, *J* = 12.7, 5.5 Hz, 1H), 4.15 (s, 2H), 3.94 (s, 6H), 3.75 (t, *J* = 4.8 Hz, 2H), 3.69 (s, 3H), 3.64 (d, *J* = 13.0 Hz, 2H), 3.54 (s, 2H), 3.31 – 3.25 (m, 4H), 2.94 – 2.81 (m, 1H), 2.80 – 2.68 (m, 2H), 2.63 (s, 3H), 2.46 (s, 2H), 2.37 (t, *J* = 6.6 Hz, 2H), 2.32 (s, 2H), 2.17 – 2.00 (m, 3H), 1.68 – 1.51 (m, 6H). LCMS (ESI) m/z: $[M+H]^+$ = 863.50.

Example 80 – Preparation of 5-[(1-[2-[2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] amino)ethoxy]acetyl]azetidin-3-yl)methoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (compound D74 formic acid)

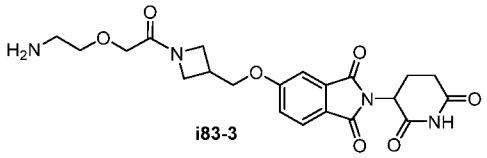


Step 1: Preparation of tert-butyl N-(2-[2-[3-([[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]methyl) azetidin-1-yl]-2-oxoethoxy]ethyl)carbamate (i80-2)



To a solution of [2-[(*tert*-butoxycarbonyl)amino]ethoxy]acetic acid (30.65 mg, 0.140 mmol, 1.20 equiv) and HATU (88.60 mg, 0.233 mmol, 2.00 equiv) in DMF (1.00 mL) was added 5-(azetidin-3-ylmethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (40.00 mg, 0.117 mmol, 1.00 equiv) and DIEA (45.17 mg, 0.350 mmol, 3.00 equiv), and the resulting solution was stirred at 25 °C for 2 hours. The resulting mixture was concentrated. The residue was applied onto a silica gel column with CH_2Cl_2/MeOH (20:1). This resulted in (50 mg, 78.81%) of *tert*-butyl *N*-(2-[2-[3-([[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]methyl)azetidin-1-yl]-2-oxoethoxy]ethyl)carbamate as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 545.30.

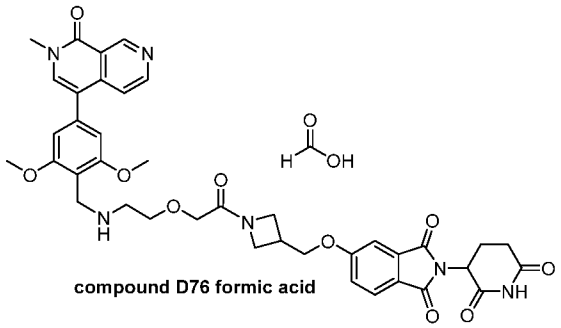
Step 2: Preparation of 5-([1-[2-(2-aminoethoxy)acetyl]azetidin-3-yl]methoxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (i80-3)



i83-3

To a solution of *tert*-butyl N-(2-[2-[3-([[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]methyl) azetidin-1-yl]-2-oxoethoxy]ethyl)carbamate (50.00 mg, 0.092 mmol, 1.00 equiv) in TFA (2.00 mL) and DCM (2.00 mL), and the resulting solution was stirred at 25 °C for 2 hours. The resulting mixture was concentrated and used directly without further purification. This resulted in (60 mg, crude) of 5-([1-[2-(2-aminoethoxy)acetyl]azetidin-3-yl]methoxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione as a yellow solid. LCMS (ESI) m/z: [M+H]+ = 445.50.

Step 3: Preparation of 5-[(1-[2-[2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] amino)ethoxy]acetyl]azetidin-3-yl)methoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (compound D74 formic acid)



compound D76 formic acid

To a solution of 5-([1-[2-(2-aminoethoxy)acetyl]azetidin-3-yl]methoxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (20 mg, 0.045 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (17.51 mg, 0.054 mmol, 1.20 equiv) in DMF (2.00 mL) was added $NaBH_3CN$ (5.66 mg, 0.090 mmol, 2.00 equiv). The resulting solution was stirred at 25 °C for 2 hours. The resulting mixture was concentrated. The crude product was purified by preparative HPLC Column: XSelect CSH Prep C18 OBD Column, 5 μm, 19*150 mm;Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 20% B to 55% B in 8 minutes; 254 nm; Rt: 7.12 minutes). This resulted in (10 mg, 27.82%) of 5-[(1-[2-[2-([[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] amino)ethoxy]acetyl]azetidin-3-yl)methoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione as an off-white solid. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.53 (s, 1H), 8.68 (d, *J* = 5.8 Hz, 1H), 8.57 (brs, 3.2H, FA), 7.82 (d, *J* = 8.3 Hz, 1H), 7.76 (s, 1H), 7.61 (d, *J* = 5.7 Hz, 1H), 7.43 (d, *J* = 2.3 Hz, 1H), 7.35 (dd, *J* = 8.1, 2.3 Hz, 1H), 6.84 (s, 2H), 5.12 (dd, *J* = 12.6, 5.4 Hz, 1H), 4.40 (t, *J* = 8.8 Hz, 1H), 4.35 (d, *J* = 3.8 Hz, 4H), 4.27 – 4.13 (m, 4H), 4.02 – 3.93 (m, 7H), 3.83 (t, *J* = 4.9 Hz, 2H), 3.71 (s, 3H), 3.27 – 3.21 (m, 3H), 2.94 – 2.83 (m, 1H), 2.82 – 2.67 (m, 2H), 2.20 – 2.10 (m, 1H). LCMS (ESI) m/z: [M+H]+ = 753.40.

Example 81 – Preparation of Compounds D75-D177

In analogy to the procedures described in the examples above, compounds D75-D177 were prepared using the appropriate starting materials.

Compound No.	Analytical Data
D75	LCMS: (ESI) m/z: $[M+H]^+$ = 835.70
D76	LCMS: (ESI) m/z: $[M+H]^+$ = 788.20
D77	LCMS: (ESI) m/z: $[M+H]^+$ = 774.10
D78	LCMS: 789.2; ^{1}H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.45 (s, 1H), 8.73 (d, J = 5.7 Hz, 1H), 8.21 (s, 0.7H, FA), 8.05 (d, J = 7.5 Hz, 1H), 7.87 (s, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.59 – 7.54 (m, 1H), 7.31 – 7.24 (m, 2H), 6.73 (s, 2H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 4.87 (t, J = 6.8 Hz, 1H), 4.14 – 3.99 (m, 1H), 3.81 (s, 6H), 3.66 (s, 2H), 3.61 (s, 3H), 3.44 – 3.35 (m, 3H), 2.98 (s, 2H), 2.92 – 2.83 (m, 1H), 2.73 – 2.55 (m, 4H), 2.44 – 2.32 (m, 1H), 2.25 (dd, J = 18.0, 6.8 Hz, 3H), 2.15 – 2.00 (m, 3H), 1.95 (td, J = 11.2, 8.4 Hz, 2H).
D79	LCMS: (ESI) m/z: $[M+H]^+$ = 789.20; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.11 (s, 1H), 9.45 (s, 1H), 8.73 (d, *J* = 5.7 Hz, 1H), 8.21 (s, 0.7H, FA), 8.05 (d, *J* = 7.5 Hz, 1H), 7.87 (s, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.59 – 7.54 (m, 1H), 7.31 – 7.24 (m, 2H), 6.73 (s, 2H), 5.12 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.87 (t, *J* = 6.8 Hz, 1H), 4.14 – 3.99 (m, 1H), 3.81 (s, 6H), 3.66 (s, 2H), 3.61 (s, 3H), 3.44 – 3.35 (m, 3H), 2.98 (s, 2H), 2.92 – 2.83 (m, 1H), 2.73 – 2.55 (m, 4H), 2.44 – 2.32 (m, 1H), 2.25 (dd, *J* = 18.0, 6.8 Hz, 3H), 2.15 – 2.00 (m, 3H), 1.95 (td, *J* = 11.2, 8.4 Hz, 2H).
D80	LCMS: (ESI) m/z: $[M+H]^+$ = 803.15; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.12 (s, 1H), 9.45 (s, 1H), 8.73 (d, *J* = 5.6 Hz, 1H), 8.21 (s, 0.6H, FA), 7.97 – 7.77 (m, 2H), 7.56 (d, *J* = 5.7 Hz, 1H), 7.37 – 7.20 (m, 2H), 6.74 (s, 2H), 5.12 (dd, *J* = 12.8, 5.4 Hz, 1H), 5.10 – 4.97 (m, 1H), 3.82 (d, *J* = 2.0 Hz, 6H), 3.70 (s, 2H), 3.61 (s, 3H), 3.36 (s, 5H), 3.09 – 2.95 (m, 2H), 2.88 (d, *J* = 13.9 Hz, 1H), 2.58 (d, *J* = 10.3 Hz, 8H), 2.16 – 1.99 (m, 1H), 1.87 (d, *J* = 9.8 Hz, 2H), 1.63 (s, 1H), 1.55 (s, 2H), 1.47 (s, 1H).
D81	LCMS: (ESI) m/z: $[M+H]^+$ = 715.20
D82	LCMS: (ESI) m/z: $[M+H]^+$ = 821.25; ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.54 (d, *J* = 0.9 Hz, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.54 (s, 0.4H, FA), 7.86 – 7.75 (m, 2H), 7.63 (dd, *J* = 5.8, 0.9 Hz, 1H), 7.50 (dd, *J* = 7.8, 5.7 Hz, 2H), 6.87 (s, 2H), 5.14 (dd, *J* = 12.3, 5.4 Hz, 1H), 4.44 – 4.32 (m, 4H), 4.24 (p, *J* = 8.3 Hz, 1H), 3.97 (s, 6H), 3.93 – 3.83 (m, 4H), 3.72 (s, 3H), 3.22 – 3.02 (m, 2H), 2.99 – 2.65 (m, 4H), 2.46 (t, *J* = 5.9 Hz, 2H), 2.27 (s, 2H), 2.22 – 2.09 (m, 2H), 1.91 (s, 2H), 1.76 (s, 4H).

Compound No.	Analytical Data
D83	LCMS: (ESI) m/z: $[M+H]^+$ = 781.55; ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.53 (s, 1H), 8.69 (d, *J* = 6.0 Hz, 1H), 7.85 (s, 1H), 7.82 – 7.66 (m, 2H), 7.50 – 7.36 (m, 2H), 6.85 (d, *J* = 1.2 Hz, 2H), 5.12 (dd, *J* = 12.5, 5.4 Hz, 1H), 4.50 (s, 1H), 4.42 (s, 1H), 4.35 – 4.11 (m, 4H), 4.02 (dd, *J* = 11.0, 6.7 Hz, 1H), 3.94 (d, *J* = 2.7 Hz, 6H), 3.91 – 3.76 (m, 5H), 3.71 (d, *J* = 1.5 Hz, 3H), 3.22 (t, *J* = 6.5 Hz, 2H), 3.08 – 2.59 (m, 4H), 2.46 (t, *J* = 5.8 Hz, 2H), 2.21 – 2.07 (m, 1H), 1.84 (p, *J* = 7.2, 6.7 Hz, 2H).
D84	LCMS: (ESI) m/z: $[M+H]^+$ = 793.55
D85	LCMS: (ESI) m/z: $[M+H]^+$ = 807.25
D86	LCMS: (ESI) m/z: $[M+H]^+$ = 779.20
D87	LCMS: (ESI) m/z: $[M+H]^+$ = 793.45
D88	LCMS: (ESI) m/z: $[M+H]^+$ = 807.90; ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.55 (d, *J* = 0.8 Hz, 1H), 8.69 (d, *J* = 5.7 Hz, 1H), 8.56 (s, 0.5H, FA), 7.86 – 7.73 (m, 2H), 7.63 (d, *J* = 5.8 Hz, 1H), 7.48 (dd, *J* = 7.9, 6.2 Hz, 2H), 6.85 (s, 2H), 5.24 – 5.02 (m, 1H), 4.38 (t, *J* = 4.3 Hz, 2H), 4.33 (s, 2H), 3.95 (s, 6H), 3.93 – 3.81 (m, 4H), 3.72 (s, 4H), 3.71 – 3.40 (m, 4H), 3.25 – 3.01 (m, 3H), 2.98 – 2.82 (m, 2H), 2.82 – 2.61 (m, 3H), 2.21 – 2.07 (m, 1H), 1.91 (s, 2H), 1.63 (d, *J* = 17.7 Hz, 4H).
D89	LCMS: (ESI) m/z: $[M+H]^+$ = 821.30
D90	LCMS: (ESI) m/z: $[M+H]^+$ = 793.45
D91	LCMS: (ESI) m/z: $[M+H]^+$ = 807.50
D92	LCMS: (ESI) m/z: $[M+H]^+$ = 793.60; ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.53 (s, 1H), 8.68 (dd, *J* = 5.8, 2.4 Hz, 1H), 8.52 (s, 0.5H, FA), 7.90 – 7.73 (m, 2H), 7.62 (s, 1H), 7.47 (dd, *J* = 9.3, 3.5 Hz, 2H), 6.89 – 6.74 (m, 2H), 5.24 – 5.04 (m, 1H), 4.31 (d, *J* = 33.1 Hz, 5H), 3.90 (dd, *J* = 6.6, 4.5 Hz, 12H), 3.78 – 3.58 (m, 7H), 3.00 – 2.48 (m, 6H), 2.26 – 1.78 (m, 3H).
D93	LCMS: (ESI) m/z: $[M+H]^+$ = 793.50
D94	LCMS: (ESI) m/z: $[M+H]^+$ = 865.55
D95	LCMS: (ESI) m/z: $[M+H]^+$ = 793.65
D96	LCMS: (ESI) m/z: $[M+H]^+$ = 835.45

Compound No.	Analytical Data
D97	LCMS: (ESI) m/z: $[M+H]^+$ = 865.50; ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.54 (d, *J* = 0.8 Hz, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.55 (s, 0.6H, FA), 7.90 – 7.71 (m, 2H), 7.64 (d, *J* = 5.8 Hz, 1H), 7.48 (dd, *J* = 7.9, 3.5 Hz, 2H), 6.87 (s, 2H), 5.12 (dd, *J* = 12.3, 5.4 Hz, 1H), 4.50 – 4.23 (m, 4H), 3.97 (s, 6H), 3.95 – 3.79 (m, 5H), 3.72 (s, 5H), 3.66 (dd, *J* = 5.8, 1.9 Hz, 1H), 3.59 – 3.32 (m, 3H), 3.30 – 2.98 (m, 2H), 2.98 – 2.59 (m, 6H), 2.25 – 1.70 (m, 7H), 1.49 (s, 2H).
D98	LCMS: (ESI) m/z: $[M+H]^+$ = 779.40; ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.51 (d, *J* = 1.5 Hz, 1H), 8.67 (d, *J* = 5.7 Hz, 1H), 7.69 (d, *J* = 1.8 Hz, 1H), 7.63 – 7.49 (m, 2H), 7.27 (dd, *J* = 5.8, 2.3 Hz, 1H), 7.16 (ddd, *J* = 11.0, 8.4, 2.3 Hz, 1H), 6.65 (d, *J* = 2.1 Hz, 2H), 5.04 (td, *J* = 12.4, 5.5 Hz, 1H), 4.80 (d, *J* = 10.2 Hz, 1H), 4.33 (d, *J* = 10.5 Hz, 2H), 4.25 (d, *J* = 16.3 Hz, 2H), 4.03 (d, *J* = 11.4 Hz, 1H), 3.95 – 3.74 (m, 12H), 3.74 (d, *J* = 1.3 Hz, 4H), 3.39– 3.30 (m, 1H), 2.80 (dt, *J* = 13.9, 4.7 Hz, 1H), 2.76 – 2.54 (m, 3H), 2.46 – 2.22 (m, 3H), 2.03 (td, *J* = 7.3, 6.8, 3.3 Hz, 1H).
D99	LCMS: (ESI) m/z: $[M+H]^+$ = 793.45
D100	LCMS: (ESI) m/z: $[M+H]^+$ = 793.35
D101	LCMS: (ESI) m/z: $[M+H]^+$ = 793.45; ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.53 (d, *J* = 0.8 Hz, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.56 (s, 0.7H, FA), 7.86 – 7.73 (m, 2H), 7.64 – 7.56 (m, 1H), 7.43 (d, *J* = 2.3 Hz, 1H), 7.34 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.84 (s, 2H), 5.12 (dd, *J* = 12.4, 5.4 Hz, 1H), 4.36 – 4.20 (m, 4H), 4.20 – 4.05 (m, 3H), 3.96 (d, *J* = 8.5 Hz, 8H), 3.90 – 3.75 (m, 4H), 3.71 (s, 3H), 2.97 – 2.55 (m, 5H), 2.43 (t, *J* = 5.9 Hz, 2H), 2.25 – 2.08 (m, 3H).
D102	LCMS: (ESI) m/z: $[M+H]^+$ = 761.2
D103	LCMS: (ESI) m/z: $[M+H]^+$ = 747.3
D104	LCMS: (ESI) m/z: $[M+H]^+$ = 747.3
D105	LCMS: (ESI) m/z: $[M+H]^+$ = 719.3
D106	LCMS: (ESI) m/z: $[M+H]^+$ = 733.4
D107	LCMS: (ESI) m/z: $[M+H]^+$ = 733.3
D108	LCMS: (ESI) m/z: $[M+H]^+$ = 807.45
D109	LCMS: (ESI) m/z: $[M+H]^+$ = 865.35
D110	LCMS: (ESI) m/z: $[M+H]^+$ = 835.75
D111	LCMS: (ESI) m/z: $[M+H]^+$ = 793.50
D112	LCMS: (ESI) m/z: $[M+H]^+$ = 793.50
D113	LCMS: (ESI) m/z: $[M+H]^+$ = 779.35

Compound No.	Analytical Data
D114	LCMS: (ESI) m/z: $[M+H]^+$ = 851.25
D115	LCMS: (ESI) m/z: $[M+H]^+$ = 793.45
D116	LCMS: (ESI) m/z: $[M+H]^+$ = 821.30
D117	LCMS: (ESI) m/z: $[M+H]^+$ = 781.60; ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.51 (s, 1H), 8.68 (d, *J* = 5.8 Hz, 1H), 8.56 (s, 0.7H, FA), 7.76 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 5.8 Hz, 1H), 7.39 (d, *J* = 2.2 Hz, 1H), 7.30 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.84 (s, 2H), 5.10 (dd, *J* = 12.5, 5.4 Hz, 1H), 4.37 (s, 2H), 4.33 – 4.24 (m, 2H), 4.22 – 4.08 (m, 2H), 3.95 (s, 6H), 3.85 (dq, *J* = 7.2, 5.7 Hz, 6H), 3.70 (s, 3H), 3.20 (t, *J* = 6.5 Hz, 2H), 3.02 – 2.62 (m, 4H), 2.47 (t, *J* = 5.8 Hz, 2H), 2.23 – 2.05 (m, 1H), 1.84 (q, *J* = 6.9 Hz, 2H).
D118	LCMS: (ESI) m/z: $[M+H]^+$ = 807.60; ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.53 (d, *J* = 0.8 Hz, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.55 (s, 0.7H, FA), 7.89 – 7.75 (m, 2H), 7.61 (dd, *J* = 5.8, 0.8 Hz, 1H), 7.44 (d, *J* = 2.2 Hz, 1H), 7.37 – 7.30 (m, 1H), 6.85 (s, 2H), 5.10 (dd, *J* = 12.4, 5.4 Hz, 1H), 4.41 (s, 2H), 4.35 – 4.25 (m, 2H), 3.95 (s, 6H), 3.91 – 3.77 (m, 8H), 3.72 (s, 3H), 3.54 (q, *J* = 5.6 Hz, 4H), 2.96 – 2.63 (m, 5H), 2.12 (dtd, *J* = 12.8, 4.8, 2.1 Hz, 1H), 1.83 (dt, *J* = 16.1, 5.8 Hz, 4H).
D119	LCMS: (ESI) m/z: $[M+H]^+$ = 807.45
D120	LCMS: (ESI) m/z: $[M+H]^+$ = 821.45
D121	LCMS: (ESI) m/z: $[M+H]^+$ = 807.40; ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.53 (d, *J* = 1.0 Hz, 1H), 8.69 (d, *J* = 5.7 Hz, 1H), 8.54 (s, 0.5H, FA), 7.88 – 7.73 (m, 2H), 7.66 – 7.59 (m, 1H), 7.41 (dd, *J* = 4.4, 2.3 Hz, 1H), 7.32 (ddd, *J* = 8.1, 6.0, 2.1 Hz, 1H), 6.84 (d, *J* = 7.6 Hz, 2H), 5.10 (dd, *J* = 6.9, 5.4 Hz, 1H), 4.38 (s, 1H), 4.30 (d, *J* = 4.9 Hz, 3H), 3.95 (d, *J* = 8.8 Hz, 6H), 3.87 (t, *J* = 4.6 Hz, 4H), 3.71 (d, *J* = 1.2 Hz, 3H), 3.71 – 3.56 (m, 2H), 3.55 – 3.37 (m, 3H), 3.33 – 3.26 (m, 3H), 2.97 – 2.52 (m, 5H), 2.21 – 1.92 (m, 5H).
D122	LCMS: (ESI) m/z: $[M+H]^+$ = 793.35; ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.53 (d, *J* = 2.5 Hz, 1H), 8.68 (dd, *J* = 5.7, 1.6 Hz, 1H), 8.54 (s, 0.6H, FA), 7.85 – 7.70 (m, 2H), 7.60 (dd, *J* = 6.0, 3.1 Hz, 1H), 7.42 (dd, *J* = 3.5, 2.2 Hz, 1H), 7.37 – 7.29 (m, 1H), 6.84 (d, *J* = 9.2 Hz, 2H), 5.11 (dd, *J* = 12.5, 5.4 Hz, 1H), 4.40 (s, 1H), 4.31 (dt, *J* = 6.1, 3.1 Hz, 3H), 4.08 – 4.00 (m, 2H), 3.99 – 3.91 (m, 8H), 3.90 – 3.82 (m, 4H), 3.81 (s, 1H), 3.71 (d, *J* = 1.2 Hz, 3H), 3.68 – 3.58 (m, 2H), 3.47 (t, *J* = 7.1 Hz, 1H), 2.96 – 2.81 (m, 1H), 2.74 (dtt, *J* = 12.1, 6.1, 3.4 Hz, 2H), 2.62 (dt, *J* = 11.5, 5.9 Hz, 2H), 2.25 (t, *J* = 7.0 Hz, 1H), 2.22 – 2.05 (m, 2H).
D123	LCMS: (ESI) m/z: $[M+H]^+$ = 807.30
D124	LCMS: (ESI) m/z: $[M+H]^+$ = 865.90

Compound No.	Analytical Data
D125	LCMS: (ESI) m/z: $[M+H]^+$ = 793.20
D126	LCMS: (ESI) m/z: $[M+H]^+$ = 793.20
D127	LCMS: (ESI) m/z: $[M+H]^+$ = 793.55
D128	LCMS: (ESI) m/z: $[M+H]^+$ = 779.40
D129	LCMS: (ESI) m/z: $[M+H]^+$ = 835.70
D130	LCMS: (ESI) m/z: $[M+H]^+$ = 851.40
D131	LCMS: (ESI) m/z: $[M+H]^+$ = 865.35
D132	LCMS: (ESI) m/z: $[M+H]^+$ = 775.3
D133	LCMS: (ESI) m/z: $[M+H]^+$ = 777.5
D134	LCMS: (ESI) m/z: $[M+H]^+$ = 761.4
D135	LCMS: (ESI) m/z: $[M+H]^+$ = 763.4
D136	LCMS: (ESI) m/z: $[M+H]^+$ = 775.2
D137	LCMS: (ESI) m/z: $[M+H]^+$ = 789.3
D138	LCMS: (ESI) m/z: $[M+H]^+$ = 803.5
D139	LCMS: (ESI) m/z: $[M+H]^+$ = 805.4
D140	LCMS: (ESI) m/z: $[M+H]^+$ = 775.2
D141	LCMS: (ESI) m/z: $[M+H]^+$ = 789.3
D142	LCMS: (ESI) m/z: $[M+H]^+$ = 803.5
D143	LCMS: (ESI) m/z: $[M+H]^+$ = 817.5
D144	LCMS: (ESI) m/z: $[M+H]^+$ = 819.3
D145	LCMS: (ESI) m/z: $[M+H]^+$ = 689.3
D146	LCMS: (ESI) m/z: $[M+H]^+$ = 717.3
D147	LCMS: (ESI) m/z: $[M+H]^+$ = 731.4
D148	LCMS: (ESI) m/z: $[M+H]^+$ = 745.2
D149	LCMS: (ESI) m/z: $[M+H]^+$ = 745.3
D150	LCMS: (ESI) m/z: $[M+H]^+$ = 789.5
D151	LCMS: (ESI) m/z: $[M+H]^+$ = 805.9
D152	LCMS: (ESI) m/z: $[M+H]^+$ = 831.4
D153	LCMS: (ESI) m/z: $[M+H]^+$ = 833.3
D154	LCMS: (ESI) m/z: $[M+H]^+$ = 789.3

Compound No.	Analytical Data
D155	LCMS: (ESI) m/z: $[M+H]^+$ = 803.2
D156	LCMS: (ESI) m/z: $[M+H]^+$ = 817.6
D157	LCMS: (ESI) m/z: $[M+H]^+$ = 831.6
D158	LCMS: (ESI) m/z: $[M+H]^+$ = 833.5
D159	LCMS: (ESI) m/z: $[M+H]^+$ = 851.25
D160	LCMS: (ESI) m/z: $[M+H]^+$ = 821.45
D161	LCMS: (ESI) m/z: $[M+H]^+$ = 821.35
D162	LCMS: (ESI) m/z: $[M+H]^+$ = 807.35
D163	LCMS: (ESI) m/z: $[M+H]^+$ = 835.50
D164	LCMS: (ESI) m/z: $[M+H]^+$ = 821.60
D165	LCMS: (ESI) m/z: $[M+H]^+$ = 849.60; ^{1}H NMR (300 MHz, Methanol-*d4*) δ 9.60 – 9.41 (m, 1H), 8.69 (dd, *J* = 5.6, 3.0 Hz, 1H), 8.53 (s, 0.6H, FA), 7.79 – 7.50 (m, 3H), 7.44 – 7.15 (m, 2H), 6.81 – 6.47 (m, 2H), 5.11 (dt, *J* = 11.6, 4.5 Hz, 1H), 4.57 – 4.07 (m, 5H), 4.05 – 3.76 (m, 13H), 3.74 – 3.66 (m, 3H), 3.64 – 3.44 (m, 1H), 3.05 – 2.65 (m, 5H), 2.64 – 2.02 (m, 6H).
D166	LCMS: (ESI) m/z: $[M+H]^+$ = 835.65
D167	LCMS: (ESI) m/z: $[M+H]^+$ = 851.25
D168	LCMS: (ESI) m/z: $[M+H]^+$ = 851.25
D169	LCMS: (ESI) m/z: $[M+H]^+$ = 821.35
D170	LCMS: (ESI) m/z: $[M+H]^+$ = 821.35
D171	LCMS: (ESI) m/z: $[M+H]^+$ = 807.35
D172	LCMS: (ESI) m/z: $[M+H]^+$ = 835.35
D173	LCMS: (ESI) m/z: $[M+H]^+$ = 835.60
D174	LCMS: (ESI) m/z: $[M+H]^+$ = 821.65
D175	LCMS: (ESI) m/z: $[M+H]^+$ = 849.80
D176	LCMS: (ESI) m/z: $[M+H]^+$ = 835.70
D177	LCMS: (ESI) m/z: $[M+H]^+$ = 835.65

Example 82 – Preparation of Compounds D178-D37

In analogy to the procedures described in the examples above, compounds D178-D371 were prepared using the appropriate starting materials.

Compound No.	LCMS	^{1}H NMR
D178	723.4	^{1}H NMR (300 MHz, DMSO-d6) δ 1.55 (2H, d), 1.77 (2H, d), 2.03 (3H, d), 2.16 (3H, s), 2.44 (3H, d), 2.73 (2H, s), 2.88 – 3.08 (3H, m), 3.61 (5H, s), 3.80 (6H, s), 4.30 (2H, s), 5.12 (1H, m), 6.72 (2H, s), 7.38 (1H, m), 7.48 (1H, d), 7.57 (1H, d), 7.80 – 7.90 (2H, m), 8.23 (1H, s), 8.72 (1H, d), 9.45 (1H, s), 11.12 (1H, s).
D179	813.3	^{1}H NMR(400 MHz, D .79 (brs, 0.8H, FA(COOH), 11.08 (s, 1H), 9.44 (s, 1H), 8.71 (d, *J* = 5.7 Hz, 1H), 8.14 (s, 0.8H, FA), 7.86 (s, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.56 (d, *J* = 5.8 Hz, 1H), 7.33 (d, *J* = 2.3 Hz, 1H), 7.24 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.11 (s, 1H), 6.73 (s, 2H), 5.07 (dd, *J* = 13.0, 5.4 Hz, 1H), 4.08 – 4.02 (m, 1H), 3.82 (s, 7H), 3.69 – 3.62 (m, 2H), 3.60 (s, 3H), 3.50 – 3.39 (m, 8H), 3.12 – 3.05 (m, 2H), 2.95 – 2.83 (m, 1H), 2.63 – 2.55 (m, 3H), 2.55 (s, 2H), 2.47 – 2.39 (m, 3H), 2.07 – 1.98 (m, 1H).
D180	788.2	
D181	774.7	
D182	789.2	^{1}H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.45 (s, 1H), 8.73 (d, *J* = 5.7 Hz, 1H), 8.21 (s, 0.7H, FA), 8.05 (d, *J* = 7.5 Hz, 1H), 7.87 (s, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.59 – 7.54 (m, 1H), 7.31 – 7.24 (m, 2H), 6.73 (s, 2H), 5.12 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.87 (t, *J* = 6.8 Hz, 1H), 4.14 – 3.99 (m, 1H), 3.81 (s, 6H), 3.66 (s, 2H), 3.61 (s, 3H), 3.44 – 3.35 (m, 3H), 2.98 (s, 2H), 2.92 – 2.83 (m, 1H), 2.73 – 2.55 (m, 4H), 2.44 – 2.32 (m, 1H), 2.25 (dd, *J* = 18.0, 6.8 Hz, 3H), 2.15 – 2.00 (m, 3H), 1.95 (td, *J* = 11.2, 8.4 Hz, 2H).
D183	789.5	
D184	803.15	
D185	715.2	
D186	804.65	^{1}H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.45 (d, *J* = 4.3 Hz, 1H), 8.73 (d, *J* = 5.7 Hz, 1H), 8.16 (s, 0.6H, FA), 7.90 (d, *J* = 6.4 Hz, 1H), 7.64 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.58 (d, *J* = 5.7 Hz, 1H), 6.90 – 6.72 (m, 3H), 6.65 (dd, *J* = 8.5, 2.3 Hz, 1H), 5.06 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.57 (d, *J* = 23.1 Hz, 2H), 3.83 (d, *J* = 18.2 Hz, 6H), 3.74 (s, 4H), 3.60 (d, *J* = 3.3 Hz, 3H), 2.88 (ddd, *J* = 17.7, 14.0, 5.4 Hz, 1H), 2.72 (s, 1H), 2.65 (s, 2H), 2.62 – 2.53 (m, 4H), 2.44 – 2.26 (m, 6H), 2.08 – 1.94 (m, 1H), 1.77 (d, *J* = 6.5 Hz, 4H), 1.53 (s, 4H).
D187	790.5	
D188	804.6	
D189	802.65	

Compound No.	LCMS	^{1}H NMR
D190	788.6	
D191	802.55	
D192	788.8	
D193	774.55	
D194	774.75	^{1}H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.45 (s, 1H), 8.73 (d, *J* = 5.7 Hz, 1H), 8.22 (s, 1H, FA), 8.12 (d, *J* = 7.4 Hz, 1H), 7.88 (s, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 5.7 Hz, 1H), 6.74 (d, *J* = 6.3 Hz, 3H), 6.67 – 6.56 (m, 1H), 5.06 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.08 (d, *J* = 10.2 Hz, 3H), 3.97 (s, 2H), 3.82 (s, 6H), 3.67 (s, 2H), 3.61 (s, 3H), 3.51 (s, 2H), 3.01 (d, *J* = 7.1 Hz, 2H), 2.95 – 2.80 (m, 1H), 2.65 – 2.53 (m, 5H), 2.29 (d, *J* = 7.6 Hz, 2H), 2.12 (t, *J* = 10.3 Hz, 2H), 2.07 – 1.93 (m, 1H).
D195	760.5	^{1}H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.45 (s, 1H), 8.74 (d, *J* = 5.6 Hz, 1H), 7.89 (s, 1H), 7.67 (d, *J* = 8.3 Hz, 1H), 7.56 (d, *J* = 5.6 Hz, 1H), 6.82 (d, *J* = 2.4 Hz, 3H), 6.68 (dd, *J* = 8.4, 2.1 Hz, 1H), 5.07 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.32 (s, 2H), 4.20 (s, 6H), 4.06 (s, 3H), 3.88 (s, 8H), 3.61 (s, 4H), 2.98 – 2.74 (m, 2H), 2.59 (d, *J* = 16.5 Hz, 2H), 2.44 (d, *J* = 7.2 Hz, 2H), 2.11 – 1.95 (m, 1H).
D196	757.5	
D197	743.35	
D198	743.25	
D199	731.35	^{1}H NMR (400 MHz, DMSO-d6) δ 11.15 (s, 1H), 9.52 (s, 1H), 8.77 (d, *J* = 6.0 Hz, 1H), 8.06 (s, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.85 (dd, *J* = 5.5, 1.6 Hz, 2H), 7.75 (d, *J* = 6.0 Hz, 1H), 6.87 (s, 2H), 5.16 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.43 (d, *J* = 13.9 Hz, 1H), 4.29 (s, 2H), 4.14 – 4.03 (m, 1H), 3.91 (s, 6H), 3.64 (s, 4H), 3.40 (t, *J* = 8.2 Hz, 2H), 3.18 (m, 2H), 3.23 - 3.13 (m, 2H), 3.02 – 2.72 (m, 4H), 2.68 – 2.56 (m, 2H), 2.12 – 1.99 (m, 1H).
D200	743.15	
D201	804.7	^{1}H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 9.45 (t, *J* = 1.4 Hz, 1H), 8.72 (d, *J* = 5.7 Hz, 1H), 8.23 (s, 0.8H, FA), 7.90 (d, *J* = 6.0 Hz, 1H), 7.76 – 7.56 (m, 2H), 7.40 – 7.16 (m, 2H), 6.77 (d, *J* = 10.7 Hz, 2H), 5.17 – 4.99 (m, 1H), 4.56 (d, *J* = 19.2 Hz, 2H), 3.83 (d, *J* = 13.5 Hz, 6H), 3.60 (d, *J* = 2.3 Hz, 3H), 3.43 (s, 6H), 3.01 (d, *J* = 5.0 Hz, 4H), 2.98 – 2.78 (m, 1H), 2.72 (d, *J* = 5.9 Hz, 1H), 2.65 (s, 2H), 2.63 – 2.55 (m, 1H), 2.47 (s, 2H), 2.27 (dd, *J* = 4.3, 2.4 Hz, 1H), 2.10 – 1.91 (m, 1H), 1.73 (d, *J* = 6.4 Hz, 4H), 1.62 – 1.47 (m, 2H), 1.44 – 1.26 (m, 2H).

Compound No.	LCMS	^{1}H NMR
D202	818.4	
D203	790.6	
D204	790.8	
D205	776.35	
D206	776.6	
D207	805.65	
D208	819.55	^{1}H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.45 (s, 1H), 8.72 (dd, *J* = 5.7, 2.2 Hz, 1H), 8.20 (s, 0.6H, FA), 7.90 (d, *J* = 3.6 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.58 (dt, *J* = 5.7, 1.2 Hz, 1H), 7.37 – 7.22 (m, 2H), 6.77 (d, *J* = 9.7 Hz, 2H), 5.12 (dd, *J* = 12.9, 5.4 Hz, 1H), 5.04 – 4.92 (m, 1H), 4.56 (d, *J* = 17.5 Hz, 2H), 3.82 (d, *J* = 13.3 Hz, 6H), 3.60 (s, 3H), 2.90 (ddd, *J* = 17.3, 13.9, 5.4 Hz, 1H), 2.71 (s, 1H), 2.61 (d, *J* = 20.0 Hz, 5H), 2.47 – 2.22 (m, 9H), 2.06 (d, *J* = 5.9 Hz, 1H), 1.80 (dd, *J* = 12.2, 6.3 Hz, 2H), 1.70 – 1.43 (m, 8H).
D209	774.6	
D210	760.7	
D211	743.35	^{1}H NMR (400 MHz, DMSO-d6) δ 11.15 (s, 1H), 9.44 (s, 1H), 8.72 (d, *J* = 5.7 Hz, 1H), 8.21 (s, 1H), 7.94 – 7.79 (m, 4H), 7.56 (d, *J* = 5.7 Hz, 1H), 6.75 (s, 2H), 5.16 (dd, *J* = 12.8, 5.4 Hz, 1H), 3.82 (d, *J* = 9.2 Hz, 8H), 3.60 (s, 4H), 3.46-3.40 (m, 6H), 2.90 (ddd, *J* = 16.9, 13.8, 5.4 Hz, 1H), 2.70 (s, 2H), 2.66 – 2.53 (m, 5H), 2.07 (ddd, *J* = 13.3, 5.6, 3.2 Hz, 1H), 1.94 (t, *J* = 7.0 Hz, 2H), 1.74 (p, *J* = 7.1 Hz, 2H).
D212	757.35	
D213	771.2	
D214	717.35	^{1}H NMR (400 MHz, DMSO-d6) δ 11.15 (s, 1H), 9.45 (s, 1H), 8.73 (d, *J* = 5.7 Hz, 1H), 8.19 (s, 1H FA), 7.87 (d, *J* = 9.1 Hz, 4H), 7.58 (d, *J* = 5.6 Hz, 1H), 6.74 (s, 2H), 5.16 (dd, *J* = 12.8, 5.4 Hz, 1H), 3.81 (s, 6H), 3.60 (s, 6H), 3.47 (s, 5H), 2.94 - 2.85 (m, 1H), 2.68 - 2.58 (m, 2H), 2.44 (t, *J* = 7.2 Hz, 6H), 2.12 – 2.01 (m, 1H), 1.73 (p, *J* = 7.1 Hz, 2H).
D215	729.35	
D216	703.15	
D217	771.15	^{1}H NMR (300 MHz, DMSO-d6) δ 11.15 (s, 1H), 9.47 (s, 1H), 8.75 (d, *J* = 5.7 Hz, 1H), 7.97 – 7.79 (m, 4H), 7.58 (d, *J* = 5.6 Hz, 1H), 6.87 (s, 2H), 5.16 (dd, *J* = 12.9, 5.3 Hz, 1H), 4.27 (d, *J* = 4.0 Hz, 2H), 4.02 (s, 1H), 3.90 (s, 7H), 3.75 (s, 1H), 3.62 (s, 4H), 3.11 (s,

Compound No.	LCMS	^{1}H NMR
		2H), 3.08 (s, 2H), 2.96 - 2.84 (m, 1H), 2.69 (dd, *J* = 7.2, 3.6 Hz, 2H), 2.66 – 2.54 (m, 2H), 2.47 – 2.39 (m, 2H), 2.13 – 2.00 (m, 3H), 1.92 (t, *J* = 12.4 Hz, 2H).
D218	757.35	
D219	771.35	^{1}H NMR (300 MHz, DMSO-d6) δ 11.15 (s, 1H), 9.45 (s, 1H), 8.73 (d, *J* = 5.7 Hz, 1H), 8.20 (s, 1H FA), 7.97 – 7.77 (m, 4H), 7.57 (d, *J* = 5.7 Hz, 1H), 6.74 (s, 2H), 5.24 – 5.08 (m, 1H), 3.82 (s, 6H), 3.71 (s, 3H), 3.61 (s, 4H), 3.11 (s, 4H), 2.98 – 2.80 (m, 2H), 2.76 – 2.62 (m, 6H), 2.15 – 2.01 (m, 1H), 1.61 (d, *J* = 27.8 Hz, 5H)
D220	785.15	^{1}H NMR (400 MHz, DMSO-d6) δ 11.15 (s, 1H), 9.45 (d, *J* = 2.0 Hz, 1H), 8.73 (dd, *J* = 5.6, 2.2 Hz, 1H), 7.94 – 7.87 (m, 2H), 7.84 (q, *J* = 2.9 Hz, 2H), 7.58 (dd, *J* = 5.7, 2.6 Hz, 1H), 6.74 (s, 2H), 5.16 (dd, *J* = 12.8, 5.4 Hz, 1H), 3.82 (s, 6H), 3.60 (d, *J* = 1.4 Hz, 5H), 3.52 (t, *J* = 7.0 Hz, 1H), 3.17 (s, 2H), 2.89 (ddd, *J* = 16.6, 13.6, 5.4 Hz, 1H), 2.70 (t, *J* = 7.0 Hz, 2H), 2.66 – 2.56 (m, 7H), 2.41 (s, 2H), 2.12 – 2.00 (m, 1H), 1.76 (t, *J* = 7.1 Hz, 1H), 1.67 (t, *J* = 7.2 Hz, 1H), 1.49 (s, 4H).
D221	817.35	^{1}H NMR (300 MHz, DMSO-d6) δ 11.13 (s, 1H), 9.45 (s, 1H), 8.73 (d, *J* = 5.7 Hz, 1H), 8.20 (s, 1H, FA), 7.92 – 7.80 (m, 2H), 7.60 (d, *J* = 5.7 Hz, 1H), 7.38 – 7.21 (m, 2H), 6.74 (s, 2H), 5.12 (dd, *J* = 12.9, 5.4 Hz, 1H), 5.03 (t, *J* = 6.9 Hz, 1H), 3.81 (s, 6H), 3.61 (s, 3H), 3.58 (s, 2H), 3.44 (s, 4H), 2.96 – 2.82 (m, 3H), 2.66 – 2.54 (m, 5H), 2.21 – 1.98 (m, 3H), 1.93 – 1.81 (m, 2H), 1.66 – 1.43 (m, 8H).
D222	776.4	
D223	776.35	
D224	790.4	
D225	776.35	
D226	762.8	
D227	748.3	^{1}H NMR (300 MHz, DMSO-d6) δ 11.07 (s, 1H), 9.44 (s, 1H), 8.72 (d, *J* = 5.7 Hz, 1H), 8.17 (s, 0.6H, FA), 7.88 (s, 1H), 7.59 (dd, *J* = 9.7, 7.0 Hz, 2H), 6.76 (d, *J* = 7.3 Hz, 3H), 6.61 (d, *J* = 8.4 Hz, 1H), 5.05 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.87 (t, *J* = 5.4 Hz, 1H), 4.15 – 3.95 (m, 2H), 3.84 (s, 6H), 3.67 (d, *J* = 15.2 Hz, 3H), 3.60 (s, 3H), 3.11 – 2.71 (m, 2H), 2.66 – 2.55 (m, 5H), 2.27 (s, 3H), 2.12 – 1.88 (m, 4H), 1.75 (d, *J* = 10.1 Hz, 1H), 1.64 – 1.36 (m, 4H).
D228	791.55	
D229	751.2	

Compound No.	LCMS	^{1}H NMR
D230	791.4	^{1}H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.45 (t, *J* = 1.2 Hz, 1H), 8.73 (dd, *J* = 5.7, 1.0 Hz, 1H), 8.19 (s, 0.3H, FA), 7.99 – 7.73 (m, 2H), 7.66 – 7.50 (m, 1H), 7.39 – 7.22 (m, 2H), 6.77 (d, *J* = 9.5 Hz, 2H), 5.12 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.87 (t, *J* = 6.8 Hz, 1H), 4.56 (d, *J* = 19.1 Hz, 2H), 3.82 (d, *J* = 13.1 Hz, 6H), 3.60 (d, *J* = 1.5 Hz, 3H), 3.26 (s, 2H), 3.17 (s, 2H), 2.89 (s, 1H), 2.78 – 2.61 (m, 6H), 2.61 – 2.52 (m, 2H), 2.48 – 2.33 (m, 2H), 2.28 (dd, *J* = 3.8, 1.9 Hz, 1H), 2.19 (dd, *J* = 11.7, 8.0 Hz, 2H), 2.04 (d, *J* = 11.6 Hz, 1H), 1.53 (d, *J* = 7.9 Hz, 2H), 1.42 – 1.19 (m, 2H).
D231	774.2	
D232	774.4	
D233	735.2	^{1}H NMR (300 MHz, DMSO-d6) δ 11.13 (s, 1H), 9.45 (d, *J* = 0.8 Hz, 1H), 8.72 (d, *J* = 5.7 Hz, 1H), 8.18 (s, 0.5H, FA), 7.93 – 7.79 (m, 2H), 7.56 (dd, *J* = 5.7, 0.9 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 2H), 6.74 (s, 2H), 5.27 (s, 1H), 5.14 (dd, *J* = 12.9, 5.3 Hz, 1H), 4.63 (t, *J* = 8.1 Hz, 1H), 4.34 (dd, *J* = 10.5, 6.5 Hz, 1H), 4.13 (d, *J* = 8.3 Hz, 1H), 3.82 (s, 7H), 3.73 (s, 2H), 3.60 (s, 3H), 3.50 (d, *J* = 9.7 Hz, 2H), 3.07 (s, 2H), 2.98 – 2.80 (m, 1H), 2.71 – 2.53 (m, 3H), 2.38 (d, *J* = 7.5 Hz, 2H), 2.17 – 1.97 (m, 1H).
D234	775.35	^{1}H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.45 (s, 1H), 8.73 (dd, *J* = 5.7, 1.2 Hz, 1H), 8.20 (s, 1H, FA), 7.96 – 7.76 (m, 2H), 7.69 – 7.54 (m, 1H), 7.42 – 7.19 (m, 2H), 6.75 (d, *J* = 1.7 Hz, 2H), 5.12 (dd, *J* = 12.9, 5.3 Hz, 1H), 4.90 (t, *J* = 6.7 Hz, 1H), 4.14 (d, *J* = 27.9 Hz, 2H), 3.92 (s, 1H), 3.83 (d, *J* = 2.2 Hz, 7H), 3.75 (s, 2H), 3.61 (s, 3H), 3.49 (t, *J* = 6.8 Hz, 3H), 3.08 (s, 2H), 2.99 – 2.70 (m, 4H), 2.68 – 2.55 (m, 3H), 2.40 – 2.19 (m, 4H), 2.15 – 1.94 (m, 1H).
D235	729.3	
D236	715.15	
D237	689.2	
D238	743.4	
D239	729.35	
D240	757.35	
D241	729.15	
D242	729.2	
D243	757.35	
D244	791.23	
D245	762.4	

Compound No.	LCMS	^{1}H NMR
D246	791.4	
D247	790.4	
D248	762.3	
D249	723.3	
D250	762.4	
D251	763.6	^{1}H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.45 (s, 1H), 8.73 (d, *J* = 5.7 Hz, 1H), 8.21 (s, 1.4H, FA), 7.88 (s, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 5.6 Hz, 1H), 7.28 (d, *J* = 2.2 Hz, 1H), 7.24 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.75 (s, 2H), 5.12 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.90 – 4.80 (m, 1H), 3.82 (s, 6H), 3.61 (d, *J* = 3.2 Hz, 5H), 3.36 (s, 2H), 3.27 (s, 2H), 2.89 (ddd, *J* = 16.7, 13.7, 5.3 Hz, 1H), 2.75 – 2.56 (m, 4H), 2.45 (q, *J* = 7.1, 6.7 Hz, 4H), 2.26 – 2.13 (m, 5H), 2.11 – 1.98 (m, 1H), 1.50 (t, *J* = 7.2 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 2H).
D252	762.4	
D253	777.35	
D254	748.4	
D255	790.25	
D256	818.2	
D257	777.7	
D258	790.4	
D259	777.2	
D260	805.35	
D261	819.2	
D262	819.25	
D263	805.35	
D264	803.2	
D265	803.15	
D266	789.3	
D267	789.3	
D268	715.3	
D269	757.35	
D270	719.35	
D271	719.28	^{1}H NMR (400 MHz, DMSO-d6) δ 11.03 (s, 1H), 9.42 (s, 1H), 8.68 (d, *J* = 5.6 Hz, 1H), 7.91 (s, 1H), 7.85 (s, 1H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.55 (d, *J* = 5.7 Hz, 1H), 6.80 (s, 2H), 6.75 (d, *J* = 2.1 Hz, 1H), 6.62 (dd, *J* = 8.4, 2.1 Hz, 1H), 5.53 (s, 2H), 5.02 (dd, *J* = 12.8, 5.4

Compound No.	LCMS	^{1}H NMR
		Hz, 1H), 4.57 (td, *J* = 6.3, 3.2 Hz, 1H), 4.53 (s, 2H), 4.24 – 4.15 (m, 2H), 3.86 (s, 6H), 3.79 (dd, *J* = 9.7, 3.9 Hz, 2H), 3.56 (s, 3H), 3.15 (d, *J* = 5.3 Hz, 1H), 2.85 (ddd, *J* = 16.8, 13.8, 5.3 Hz, 1H), 2.60 – 2.50 (m, 2H), 2.05 (s, 1H), 2.03 – 1.94 (m, 1H).
D272	747.28	
D273	720.03	
D274	735.52	
D275	765.06	
D276	776.47	
D277	776.33	
D278	804.19	
D279	761.28	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.08 (s, 1H), 9.43 (s, 1H), 8.71 (d, *J* = 5.6 Hz, 1H), 8.05 (s, 1H), 7.86 (s, 1H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.56 (d, *J* = 5.7 Hz, 1H), 7.45 (d, *J* = 2.3 Hz, 1H), 7.35 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.76 (s, 2H), 5.09 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.41 (t, *J* = 6.6 Hz, 2H), 3.83 (s, 5H), 3.59 (s, 2H), 3.15 (d, *J* = 5.1 Hz, 1H), 3.11 (d, *J* = 6.4 Hz, 1H), 2.87 (ddd, *J* = 17.2, 13.9, 5.3 Hz, 1H), 2.70 – 2.51 (m, 2H), 2.03 (d, *J* = 15.9 Hz, 5H).
D280	802.16	
D281	830.16	
D282	735.45	^{1}H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 7.97 (s, 1H), 7.86 (s, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.47 (d, *J* = 2.1 Hz, 1H), 7.32 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.71 (s, 2H), 5.26 (s, 2H), 4.40 (s, 1H), 3.78 (s, 5H), 3.55 (s, 3H), 2.88 (ddd, *J* = 18.2, 13.8, 5.4 Hz, 1H), 2.71 – 2.53 (m, 2H), 2.38 – 2.24 (m, 2H), 2.09 (d, *J* = 28.1 Hz, 4H).
D283	749.31	
D284	779.27	
D285	790.33	
D286	790.4	^{1}H NMR (400 MHz, DMSO-d6) δ 11.03 (s, 1H), 8.08 (s, 1H), 7.85 (s, 1H), 7.60 (d, *J* = 8.3 Hz, 1H), 6.72 (s, 2H), 5.03 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.55 (s, 2H), 4.20 (dd, *J* = 9.2, 6.3 Hz, 2H), 3.80 (s, 6H), 3.58 (s, 2H), 2.97 – 2.72 (m, 0H), 2.18 (s, 1H), 2.05 (s, 1H), 2.02 – 1.94 (m, 1H).
D287	818.26	
D288	765.27	
D289	747.35	
D290	791.24	
D291	802.37	

Compound No.	LCMS	^{1}H NMR
D292	779.2	
D293	809.16	
D294	820.29	
D295	820.08	
D296	847.22	
D297	719.28	
D298	733.49	
D299	763.31	
D300	774.44	
D301	774.02	
D302	802.58	
D303	708.22	
D304	803.4	^{1}H NMR (400 MHz, Methanol-d4) δ 9.58 (s, 1H), 8.70 (d, *J* = 6.0 Hz, 1H), 7.91 (d, *J* = 2.2 Hz, 1H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.78 (d, *J* = 6.1 Hz, 1H), 7.31 (d, *J* = 2.3 Hz, 1H), 7.26 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.89 (s, 2H), 5.13 (dd, *J* = 12.6, 5.4 Hz, 1H), 4.98 (t, *J* = 6.5 Hz, 1H), 4.43 (s, 2H), 3.98 (d, *J* = 4.3 Hz, 6H), 3.74 (s, 3H), 3.70 – 3.50 (m, 4H), 3.33 – 2.94 (m, 6H), 2.93 – 2.66 (m, 4H), 2.56 (s, 1H), 2.27 (s, 1H), 2.17 – 1.95 (m, 10H), 1.67 (q, *J* = 12.6 Hz, 1H).
D305	789.7	^{1}H NMR (400 MHz, Methanol-d4) δ 9.54 (s, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.50 (s, 2H, FA), 7.83 (d, *J* = 8.3 Hz, 1H), 7.75 (s, 1H), 7.62 (d, *J* = 5.7 Hz, 1H), 7.31 (d, *J* = 2.2 Hz, 1H), 7.26 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.82 (s, 2H), 5.13 (dd, *J* = 12.5, 5.4 Hz, 1H), 5.01 – 4.97 (m, 1H), 4.17 (s, 2H), 3.95 (s, 6H), 3.77 – 3.65 (m, 5H), 3.56 – 3.40 (m, 5H), 3.28 (s, 1H), 3.07 – 2.92 (m, 3H), 2.91 – 2.84 (m, 1H), 2.81 – 2.65 (m, 4H), 2.50 – 2.40 (m, 1H), 2.18 – 2.07 (m, 6H), 2.05 – 1.96 (m, 2H).
D306	715.3	^{1}H NMR (400 MHz, DMSO-d6) δ 11.15 (s, 1H), 9.45 (s, 1H), 8.72 (d, *J* = 5.6 Hz, 1H), 8.18 (s, 1H FA), 7.89 (d, *J* = 17.4 Hz, 4H), 7.56 (d, *J* = 5.6 Hz, 1H), 6.74 (s, 2H), 5.17 (dd, *J* = 12.8, 5.4 Hz, 1H), 3.82 (s, 6H), 3.74 (s, 2H), 3.63 (d, *J* = 19.3 Hz, 6H), 3.27 (s, 3H), 2.90 (ddd, *J* = 16.8, 13.7, 5.3 Hz, 1H), 2.78 (s, 2H), 2.66 – 2.57 (m, 3H), 2.55 (s, 1H), 2.11 – 2.02 (m, 1H), 1.96 (t, *J* = 6.9 Hz, 2H).
D307	729.3	^{1}H NMR (400 MHz, DMSO-d6) δ 11.15 (s, 1H), 9.45 (s, 1H), 8.72 (d, *J* = 5.7 Hz, 1H), 7.99 – 7.80 (m, 4H), 7.56 (d, *J* = 5.7 Hz, 1H), 6.73 (s, 2H), 5.16 (dd, *J* = 12.7, 5.4 Hz, 1H), 3.82 (s, 6H), 3.71 (s, 2H), 3.60 (s, 3H), 3.53 (s, 2H), 3.10 (s, 4H), 2.90 (ddd, *J* = 16.7,

Compound No.	LCMS	^{1}H NMR
		13.6, 5.4 Hz, 1H), 2.65 – 2.54 (m, 1H), 2.44 (s, 5H), 2.12 – 2.01 (m, 1H), 1.67 (t, *J* = 5.5 Hz, 4H).
D308	743.35	
D309	701.3	
D310	743.55	
D311	743.3	
D312	757.3	
D313	771.45	
D314	743.3	
D315	743.3	
D316	717.3	
D317	729.3	
D318	757.3	
D319	761.35	
D320	761.28	
D321	763.24	
D322	747.42	
D323	746.83	
D324	746.55	
D325	747.33	
D326	747.45	
D327	706.67	
D328	779.84	^{1}H NMR (400 MHz, DMSO-d6) δ 11.04 (s, 1H), 8.48 (d, *J* = 2.7 Hz, 1H), 8.25 (d, *J* = 2.7 Hz, 1H), 8.19 (s, 2H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.30 (d, *J* = 2.3 Hz, 1H), 7.22 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.85 (d, *J* = 5.6 Hz, 2H), 5.04 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.83 (d, *J* = 2.7 Hz, 7H), 3.59 (s, 3H), 3.48 (d, *J* = 5.0 Hz, 2H), 3.39 (t, *J* = 5.0 Hz, 4H), 2.81 (dd, *J* = 25.4, 11.4 Hz, 3H), 2.63 – 2.51 (m, 2H), 2.32 – 2.22 (m, 2H), 2.06 – 1.90 (m, 1H), 1.56 (s, 1H), 1.34 (d, *J* = 7.5 Hz, 2H), 1.09 (s, 1H)
D329	725.87	^{1}H NMR (400 MHz, DMSO-d6) δ 11.04 (s, 1H), 8.24 – 8.12 (m, 2H), 8.03 (d, *J* = 2.6 Hz, 1H), 7.88 – 7.72 (m, 1H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.30 (d, *J* = 2.2 Hz, 1H), 7.22 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.79 (s, 2H), 3.83 (s, 6H), 3.57 (s, 2H), 3.51 (s, 3H), 3.40 (t, *J* = 5.1 Hz, 4H), 2.91 – 2.78 (m, 3H), 2.66 – 2.50 (m, 2H), 2.36 – 2.24 (m,

Compound No.	LCMS	^{1}H NMR
		2H), 2.14 (t, *J* = 11.6 Hz, 2H), 2.08 (s, 3H), 1.99 (ddd, *J* = 11.5, 6.0, 3.7 Hz, 1H), 1.61 (d, *J* = 12.4 Hz, 2H), 1.35 (q, *J* = 7.0 Hz, 2H), 1.26 (s, 2H), 1.13 (q, *J* = 11.2, 10.7 Hz, 2H).
D330	614.68	^{1}H NMR (400 MHz, DMSO-d6) δ 11.04 (s, 1H), 8.15 (s, 1H), 8.02 (d, *J* = 2.7 Hz, 1H), 7.79 (dd, *J* = 2.8, 1.3 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.27 (d, *J* = 2.3 Hz, 1H), 7.20 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.80 (s, 2H), 5.04 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.84 (s, 6H), 3.55 (s, 2H), 3.37 (t, *J* = 5.1 Hz, 4H), 2.66 – 2.53 (m, 2H), 2.08 (s, 3H).
D331	654.74	^{1}H NMR (400 MHz, DMSO-d6) δ 11.03 (s, 1H), 8.12 (s, 1H), 8.04 (d, *J* = 2.6 Hz, 1H), 7.80 (dd, *J* = 2.7, 1.3 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 1H), 6.82 (s, 2H), 6.75 (d, *J* = 2.1 Hz, 1H), 5.02 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.85 (s, 6H), 3.72 (s, 5H), 3.52 (s, 3H), 2.93 – 2.74 (m, 1H), 2.08 (s, 3H), 1.98 (dd, *J* = 9.2, 4.2 Hz, 1H), 1.76 (s, 5H).
D332	669.75	
D333	724.79	
D334	594.73	^{1}H NMR (400 MHz, DMSO-d6) δ 10.81 (s, 1H), 8.13 (s, 1H), 8.05 (d, *J* = 2.7 Hz, 1H), 7.80 (dd, *J* = 2.8, 1.3 Hz, 1H), 6.82 (s, 2H), 5.73 (s, 1H), 3.85 (s, 6H), 3.71 (s, 2H), 3.52 (s, 3H), 3.08 – 2.85 (m, 4H), 2.79 – 2.53 (m, 3H), 2.38 – 2.28 (m, 3H), 2.08 (s, 3H), 1.86 – 1.74 (m, 1H), 1.65 (d, *J* = 12.7 Hz, 2H), 1.33 (s, 3H), 1.27 – 1.12 (m, 3H).
D335	609.66	
D336	654.74	
D337	640.72	
D338	640.72	
D339	626.69	
D340	679.75	^{1}H NMR (400 MHz, DMSO-d6) δ 12.12 (s, 1H), 11.03 (s, 1H), 8.14 (d, *J* = 1.1 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.45 (s, 1H), 7.34 (t, *J* = 2.8 Hz, 1H), 6.82 (s, 2H), 6.75 (d, *J* = 2.1 Hz, 1H), 6.62 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.54 (t, *J* = 2.4 Hz, 1H), 5.73 (s, 1H), 5.02 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.83 (s, 6H), 3.71 (s, 4H), 3.58 (s, 3H), 3.53 (s, 2H), 2.86 (ddd, *J* = 17.3, 13.9, 5.4 Hz, 1H), 2.64 – 2.50 (m, 1H), 1.98 (dd, *J* = 9.2, 4.0 Hz, 1H), 1.72 (d, *J* = 5.8 Hz, 4H).
D341	690.72	^{1}H NMR (400 MHz, DMSO-d6) δ 8.13 (dd, *J* = 9.6, 2.7 Hz, 2H), 6.83 (d, *J* = 0.9 Hz, 2H), 11.03 (s, 1H), 8.37 (d, *J* = 2.6 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 1H), 6.78 – 6.71 (m, 1H), 6.62 (dd, *J* = 8.4, 2.1 Hz, 1H), 5.02 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.84 (d, *J* = 0.8 Hz, 6H),

Compound No.	LCMS	^{1}H NMR
		3.69 (s, 4H), 3.57 (s, 3H), 3.50 (d, *J* = 4.1 Hz, 2H), 2.86 (ddd, *J* = 17.3, 13.9, 5.4 Hz, 1H), 2.38 (s, 5H), 1.69 (s, 4H).
D342	712.15	^{1}H NMR (400 MHz, DMSO-d6) δ 11.07 (s, 1H), 9.04 (d, *J* = 3.3 Hz, 1H), 8.66 (d, *J* = 3.4 Hz, 1H), 8.20 (s, 1H, FA), 7.64 (d, *J* = 8.5 Hz, 1H), 7.29 (s, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 6.88 (s, 2H), 5.06 (dd, *J* = 13.0, 5.3 Hz, 1H), 4.02 (d, *J* = 12.8 Hz, 2H), 3.84 (s, 6H), 3.57 – 3.47 (m, 5H), 2.91 (dt, *J* = 22.4, 13.1 Hz, 3H), 2.71 – 2.55 (m, 2H), 2.42 – 2.23 (m, 10H), 2.09 – 1.93 (m, 1H), 1.82 – 1.68 (m, 2H), 1.64 – 1.50 (m, 1H), 1.39 – 1.30 (m, 2H), 1.22 – 1.09 (m, 2H).
D343	628.5	^{1}H NMR (300 MHz, DMSO-d6) δ 11.10 (s, 1H), 9.47 (s, 1H, TFA), 7.77 (d, *J* = 8.5 Hz, 1H), 7.47 (d, *J* = 2.2 Hz, 1H), 7.38 – 7.23 (m, 2H), 6.69 (s, 2H), 5.10 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.33 (s, 2H), 4.18 (d, *J* = 12.1 Hz, 2H), 3.89 (s, 6H), 3.55 (s, 4H), 3.53 – 3.45 (m, 5H), 2.99 – 2.81 (m, 1H), 2.60 (d, *J* = 18.3 Hz, 2H), 2.35 (s, 3H), 2.05 (s, 4H).
D344	600.2	^{1}H NMR (400 MHz, DMSO-d6) δ 11.07 (s, 1H), 8.21 (d, *J* = 2.8 Hz, 1H), 8.14 (s, 1H FA), 7.97 – 7.88 (m, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.32 (d, *J* = 2.3 Hz, 1H), 7.26 – 7.21 (m, 1H), 6.85 (s, 2H), 6.50 (d, *J* = 9.4 Hz, 1H), 5.10 – 5.00 (m, 1H), 3.87 (s, 6H), 3.67 (s, 2H), 3.53 (s, 3H), 3.44 (d, 5H), 2.97 – 2.78 (m, 1H), 2.67 – 2.60 (m, 5H), 2.58 – 2.52 (m, 1H), 2.09 – 1.92 (m, 1H).
D345	737.3	^{1}H NMR (300 MHz, Methanol-d4) δ 8.31 (s, 1H FA), 7.65 (d, *J* = 8.3 Hz, 1H), 7.48 (s, 1H), 6.84 (d, *J* = 2.1 Hz, 1H), 6.72 – 6.63 (m, 3H), 5.07 (dd, *J* = 12.4, 5.4 Hz, 1H), 4.48 (s, 2H), 4.25 (s, 2H), 4.06 – 3.90 (m, 8H), 3.82 (s, 4H), 3.58 (d, *J* = 20.8 Hz, 4H), 2.97 – 2.66 (m, 5H), 2.63 (s,3H), 2.27 – 2.03 (m, 8H), 1.95 (s, 4H).
D346	737.7	^{1}H NMR (300 MHz, DMSO-d6) δ 11.07 (s, 1H), 8.16 (s, 1H, FA), 7.64 (d, *J* = 8.3 Hz, 1H), 7.28 (d, *J* = 1.2 Hz, 1H), 6.77 (d, *J* = 2.1 Hz, 1H), 6.69 – 6.53 (m, 3H), 5.05 (dd, *J* = 12.7, 5.4 Hz, 1H), 3.92 – 3.85 (m, 2H), 3.82 (s, 6H), 3.74 (s, 4H), 3.71 – 3.61 (m, 2H), 3.54 (s, 4H), 2.98 – 2.78 (m, 2H), 2.71 – 2.54 (m, 2H), 2.54 – 2.50 (m, 2H), 2.48 – 2.42 (m, 3H), 2.37 – 2.20 (m, 4H), 2.11 – 1.93 (m, 4H), 1.82 – 1.65 (m, 4H), 1.20 (d, *J* = 26.6 Hz, 1H).
D347	709.2	^{1}H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.23 (s, 1H), 8.17 (s, 1H, FA), 7.94 (d, *J* = 9.6 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 6.86 (d, *J* = 4.5 Hz, 2H), 6.77 (d, *J* = 2.1 Hz, 1H), 6.64 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.50 (d, *J* = 9.4 Hz, 1H), 5.05 (dd, *J* = 12.9, 5.3 Hz, 1H), 3.88 (t, *J* = 2.1 Hz, 7H), 3.79 (s, 2H), 3.73 (s, 5H), 3.54 (s, 6H), 3.19 (d, *J* = 29.3 Hz, 1H), 2.99 – 2.81 (m, 1H), 2.58 (d, *J* = 16.2 Hz,

Compound No.	LCMS	^{1}H NMR
		2H), 2.44 (s, 2H), 2.28 (s, 3H), 2.01 (d, *J* = 12.4 Hz, 1H), 1.73 (s, 4H).
D348	749.25	^{1}H NMR (300 MHz, DMSO-d6) δ 8.04 (d, *J* = 2.6 Hz, 1H), 7.88 (t, *J* = 1.8 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 6.90 (d, *J* = 2.1 Hz, 2H), 6.77 (d, *J* = 2.2 Hz, 1H), 6.66 (m, *J* = 8.3, 2.0 Hz, 1H), 6.09 - 5.91 (m, 1H), , 5.19 (m, *J* = 10.3, 1.5 Hz, 1H), 5.14 - 4.98 (m, 2H), 4.62 (d, *J* = 5.4 Hz, 2H), 4.34 (d, *J* = 16.5 Hz, 2H), 4.18 (s, 2H), 3.99 (d, *J* = 10.2 Hz, 2H), 3.92 (s, 6H), 3.87 (s, 2H), 3.81 (s, 2H), 3.41 (d, *J* = 6.6 Hz, 4H), 3.17 (d, *J* = 8.1 Hz, 1H), 2.94 (s, 3H), 2.89 - 2.78 (m, 1H), 2.65 - 2.54 (m, 1H), 2.40 - 2.23 (m, 1H), 2.11 (s, 4H), 2.06 - 1.83 (m, 3H).
D349	723.2	^{1}H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.78 (s, 2H, TFA), 7.69 (d, *J* = 8.2 Hz, 1H), 7.65 (s, 1H), 6.75 (dd, *J* = 21.5, 3.2 Hz, 3H), 6.66 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.38 (s, 1H), 5.06 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.39 (s, 1H), 4.34 (d, *J* = 5.5 Hz, 1H), 4.22 (s, 2H), 4.01 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 8H), 3.82 (s, 2H), 3.46 (s, 5H), 3.25 – 3.08 (m, 2H), 3.03 – 2.82 (m, 3H), 2.64 – 2.59 (m, 2H), 2.21 – 2.09 (m, 5H), 2.09 – 1.77 (m, 4H).
D350	795.4	^{1}H NMR (300 MHz, MeOD) δ 8.04 (d, 1H), 7.82 (d, 1H), 7.67 (d, 1H), 6.95 – 6.84 (m, 3H), 6.71 (dd, 1H), 5.08 (dd, 1H), 4.58 - 4.45 (m, 2H), 4.34 (t, 2H), 4.24 (s, 2H), 4.17 - 4.09 (m, 2H), 4.01 (s, 6H), 3.94 - 3.86 (m, 4H), 3.69 (s, 3H), 3.55 - 3.49 (m, 5H), 3.20 – 3.03 (m, 2H),2.91 - 2.77 (m, 2H), 2.72 (s, 4H), 2.35 – 2.00 (m, 5H).
D351	748.7	^{1}H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.94 (br s, 2H, TFA salt), 8.07 (s, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 6.77 (d, *J* = 3.7 Hz, 3H), 6.66 (dd, *J* = 8.4, 2.3 Hz, 1H), 5.06 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.40 (s, 1H), 4.35 (d, *J* = 5.6 Hz, 1H), 4.27 – 4.16 (m, 2H), 4.03 (q, *J* = 8.7, 7.5 Hz, 2H), 3.88 (s, 8H), 3.82 (s, 2H), 3.55 (s, 3H), 3.39 (s, 5H), 3.18 (s, 1H), 3.04 – 2.82 (m, 3H), 2.64 – 2.54 (m, 2H), 2.36 (s, 3H), 2.15 (d, *J* = 14.0 Hz, 2H), 2.02 (dd, *J* = 9.7, 4.6 Hz, 1H), 1.97 – 1.84 (m, 2H).
D352	734.45	^{1}H NMR (400 MHz, DMSO-d6) δ 11.07 (s, 1H), 8.77 (s, 1H), 8.69 (s, 1H), 8.14 (s, 0.4H, FA), 7.67 (d, *J* = 8.3 Hz, 1H), 7.02 (s, 2H), 6.77 (s, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 5.05 (dd, *J* = 12.6, 5.4 Hz, 1H), 4.30 (s, 2H), 4.14 (s, 3H), 3.95 (s, 7H), 3.91 – 3.78 (m, 6H), 3.63 (s, 4H), 2.96 – 2.80 (m, 2H), 2.97 – 2.79 (m, 5H), 2.05 – 1.79 (m, 5H).
D353	723.5	^{1}H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.16 (s, 1H FA), 7.72 (d, *J* = 2.5 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.52 (dd, *J* = 2.7,

Compound No.	LCMS	^{1}H NMR
		1.2 Hz, 1H), 6.99 (s, 1H), 6.88 (s, 1H), 6.78 (d, *J* = 2.1 Hz, 1H), 6.65 (dd, *J* = 8.5, 2.1 Hz, 1H), 5.05 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.78 (s, 3H), 3.74 (d, *J* = 2.8 Hz, 7H), 3.60 (s, 2H), 3.49 (s, 6H), 2.90 (s, 3H), 2.73 – 2.58 (m, 5H), 2.39 – 2.19 (m, 3H), 2.05 (s, 3H), 2.02 (d, *J* = 7.1 Hz, 1H), 1.74 (s, 4H).
D354	737.45	^{1}H NMR (400 MHz, Methanol-d4) δ 8.30 (s, 2H FA), 7.64 (d, *J* = 8.3 Hz, 1H), 7.35 (s, 1H), 7.15 (s, 1H), 6.95 (s, 1H), 6.83 (d, *J* = 2.0 Hz, 1H), 6.67 (dd, *J* = 8.3, 2.0 Hz, 1H), 5.07 (dd, *J* = 12.4, 5.5 Hz, 1H), 4.43 (s, 2H), 4.26 (s, 2H), 4.03 (s, 2H), 3.91 (s, 3H), 3.83 (s, 4H), 3.79 (s, 3H), 3.60 (s, 3H), 3.29 (s, 1H), 3.03 (s, 2H), 2.95 – 2.64 (m, 7H), 2.16 (s, 3H), 2.15 – 2.07 (m, 1H), 2.07 – 1.87 (m, 7H).
D355	809.5	^{1}H NMR (300 MHz, MeOD) δ 8.07 (d, 1H), 7.74 – 7.63 (m, 2H), 6.88 (d, 3H), 6.71 (dd, 1H), 5.08 (dd, 1H), 4.58 - 4.45 (m, 2H), 4.41 - 4.28 (m, 4H), 4.19 - 4.07 (m, 2H), 4.01 (s, 6H), 3.98 - 3.82 (m, 4H), 3.70 (s, 3H), 3.58 - 3.41 (m, 5H), 3.18 - 3.02(m, 2H), 2.98 (s, 3H), 2.93 – 2.79 (m, 2H), 2.76 (s, 3H), 2.77 – 2.66 (m, 1H), 2.40 - 2.01 (m, 5H).
D356	745.5	^{1}H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.93 (br s, 2H, TFA salt), 8.36 (d, *J* = 8.0 Hz, 1H), 7.78 – 7.53 (m, 4H), 7.41 (d, *J* = 8.5 Hz, 1H), 6.85 (s, 2H), 6.70 (s, 2H), 5.07 (dd, *J* = 13.2, 4.9 Hz, 1H), 4.50 – 3.96 (m, 8H), 3.90 (s, 6H), 3.78 – 3.55 (m, 8H), 3.53 – 3.49 (m, 1H), 3.28 – 3.12 (m, 2H), 3.09 – 2.82 (m, 3H), 2.75 – 2.56 (m, 1H), 2.43 – 2.24 (m, 2H), 2.19 – 1.83 (m, 5H)
D357	641.748028	
D358	641.748028	
D359	737.4	^{1}H NMR (300 MHz, DMSO-d6) δ 11.10 (s, 1H), 10.32 – 9.43 (m, 2H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.22 – 7.05 (m, 2H), 6.92 (s, 1H), 6.83 – 6.74 (m, 1H), 6.66 (dd, *J* = 8.2, 2.1 Hz, 1H), 5.17 – 4.99 (m, 1H), 4.57 – 4.33 (m, 2H), 4.34 – 4.15 (m, 2H), 4.15 – 3.94 (m, 2H), 3.90 (s, 2H), 3.82 (s, 6H), 3.73 (m, 3H), 3.52 (s, 4H), 3.25 – 3.10 (m, 2H), 3.08 – 2.79 (m, 4H), 2.62 (m, 2H), 2.59 – 2.54 (m, 1H), 2.54 – 2.41 (m, 1H), 2.23 – 2.06 (m, 3H), 2.02 (s, 4H), 2.00 – 1.83 (m, 2H).
D360	745.6	^{1}H NMR (300 MHz, DMSO-d6) δ 10.95 (s, 1H), 9.83 (br s, 2H, TFA salt), 8.36 (d, *J* = 7.9 Hz, 1H), 7.73 (t, *J* = 7.8 Hz, 1H), 7.66 – 7.48 (m, 4H), 6.85 (s, 2H), 6.55–6.44 (m, 2H), 5.04 (dd, *J* = 13.2, 4.8 Hz, 1H), 4.40 (t, *J* = 13.8 Hz, 2H), 4.32 – 4.13 (m, 4H), 4.05 (s, 2H), 3.90 (s, 6H), 3.81–3.65 (m, 5H), 3.60 (s, 4H), 3.55–3.50 (m, 2H),

Compound No.	LCMS	^{1}H NMR
		3.20 (s, 1H), 3.10 – 2.80 (m, 3H), 2.62 (s, 1H), 2.41 – 2.24 (m, 1H), 2.19 – 2.05 (m, 2H), 2.02–1.82 (m, 3H).
D361	735.4	^{1}H NMR (400 MHz, DMSO-d6) δ 8.33 (s, 1H), 8.14 (s, FA, 1H), 7.91 (s, 1H), 7.40 (d, *J* = 8.9 Hz, 1H), 7.13 (s, 1H), 7.03 (s, 2H), 6.73 – 6.67 (m, 2H), 5.06 (dd, *J* = 13.2, 5.1 Hz, 1H), 4.34 (s, *J* = 16.7 Hz, 3H), 4.30 (d, *J* = 16.7 Hz, 1H) 4.19 (d, *J* = 16.7 Hz, 1H), 4.14 (m, 2H), 3.92 (s, 6H), 3.90–3.80 (m, 2H), 3.63 (s, 4H), 3.06 (s, 2H), 2.96 – 2.82 (m, 3H), 2.74– 2.56 (m, 3H), 2.45–2.32 (m, 2H), 2.01–1.92 (m, 2H), 1.87 (s, 5H).
D362	725.3	^{1}H NMR (400 MHz, DMSO-d6) δ 10.95 (s, 1H), 8.17 (s, 1H, FA), 7.55 – 7.46 (m, 2H), 7.04 (s, 2H), 6.54 (s, 2H), 5.04 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.36 – 4.12 (m, 2H), 3.85 (d, *J* = 12.7 Hz, 2H), 3.77 (s, 6H), 3.53 (s, 2H), 3.46 (s, 3H), 2.97 – 2.74 (m, 3H), 2.61 (s, 1H), 2.47 – 2.28 (m, 11H), 2.06 (d, *J* = 2.7 Hz, 6H), 1.97 (s, 1H), 1.73 (d, *J* = 12.6 Hz, 2H), 1.50 (s, 1H), 1.36 (d, *J* = 7.5 Hz, 2H), 1.26 – 1.13 (m, 2H).
D363	735.6	^{1}H NMR (400 MHz, DMSO-d6) δ 10.94 (s, 1H), 8.33 (s, 1H), 8.22 (s, FA, 1H), 7.89 (s, 1H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.11 (s, 1H), 6.92 (s, 2H), 6.53 – 6.43 (t, 2H), 5.03 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.30 (d, *J* = 16.9 Hz, 1H), 4.17 (d, *J* = 16.9 Hz, 1H), 3.85 (s, 6H), 3.67 (s, 2H), 3.61 (s, *J* = 6.9 Hz, 6H), 3.47 (s, *J* = 6.9 Hz, 4H), 2.98 (m, *J* = 6.9 Hz, 4H), 2.60 (s, 1H), 2.46 – 2.34 (m, 3H), 2.28 (s, 3H), 1.99 – 1.89 (m, 1H), 1.72 (t, *J* = 5.2 Hz, 4H).
D364	781.2	^{1}H NMR (300 MHz, MeOD) δ 8.05 (d, *J* = 2.5 Hz, 1H), 7.83 (s, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 6.95 – 6.84 (m, 3H), 6.79 (d, *J* = 8.2 Hz, 1H), 5.14 (dd, *J* = 13.2, 5.1 Hz, 1H), 4.51 - 1.45 (m, 2H), 4.44 – 4.30 (m, 4H), 4.25 (s, 2H), 4.14 (s, 2H), 4.01 (s, 6H), 3.79 - 3.73 (m, 4H), 3.69 (s, 3H), 3.55 - 3.48 (m, 4H), 3.18 - 3.04 (m, 2H), 3.00 - 2.78 (m, 2H), 2.72 (s, 3H), 2.60 – 2.41 (m, 1H), 2.28 – 2.12 (m, 5H), 1.38 - 1.28 (m, 2H).
D365	735.45	^{1}H NMR (400 MHz, MeOD) δ 8.48 (s, FA, 1H), 7.93 (d, *J* = 1.6 Hz, 1H), 7.77 (s, 1H), 7.49 (d, *J* = 1.6 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.25 (s, 2H), 6.85 (d, *J* = 2.2 Hz, 1H), 6.77 (dd, *J* = 8.3, 2.2 Hz, 1H), 5.14 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.48 (s, 2H), 4.45 – 4.33 (m, 2H), 4.23 (s, 735.452H), 4.02 (s, 6H), 3.97 (s, 2H), 3.72 (s, 3H), 3.67 (s, 4H), 3.43 - 3.35 (m, 1H), 3.22 – 3.01 (m, 1H), 2.96 - 2.85 (m, 1H), 2.84 – 2.75 (m, 1H), 2.74 (s, 2H), 2.64 – 2.42 (m, 5H), 2.23 – 2.13 (m, 1H), 1.91 (s, 4H).

Compound No.	LCMS	^{1}H NMR
D366	790.2	^{1}H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.56 (d, *J* = 5.4 Hz, 1H), 9.29 (s, 2H, TFA), 8.39 (d, *J* = 5.4 Hz, 1H), 8.08 (s, 1H), 7.64 (dd, *J* = 8.4, 3.2 Hz, 1H), 7.17 – 7.04 (m, 3H), 7.02 – 6.95 (m, 1H), 5.08 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.88 (p, *J* = 6.7 Hz, 1H), 4.43 – 4.14 (m, 4H), 3.90 (s, 6H), 3.65 (s, 3H), 3.47 – 3.15 (m, 4H), 3.09 – 2.78 (m, 7H), 2.60 (d, *J* = 16.2 Hz, 2H), 2.46 – 2.34 (m, 2H), 2.17 – 2.08 (m, 1H), 1.98 – 1.87 (m, 6H), 1.86 – 1.82 (m, 3H), 1.49 (q, *J* = 12.7 Hz, 2H).
D367	790.5	^{1}H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.56 (d, *J* = 5.4 Hz, 1H), 9.29 (s, 2H, TFA), 8.39 (d, *J* = 5.4 Hz, 1H), 8.08 (s, 1H), 7.64 (dd, *J* = 8.4, 3.2 Hz, 1H), 7.17 – 7.04 (m, 3H), 7.02 – 6.95 (m, 1H), 5.08 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.88 (p, *J* = 6.7 Hz, 1H), 4.43 – 4.14 (m, 4H), 3.90 (s, 6H), 3.65 (s, 3H), 3.47 – 3.15 (m, 4H), 3.09 – 2.78 (m, 7H), 2.60 (d, *J* = 16.2 Hz, 2H), 2.46 – 2.34 (m, 2H), 2.17 – 2.08 (m, 1H), 1.98 – 1.87 (m, 6H), 1.86 – 1.82 (m, 3H), 1.49 (q, *J* = 12.7 Hz, 2H).
D368	790.65	^{1}H NMR (400 MHz, DMSO-d6) δ 11.00 (s, 1H), 9.75 (s, 1H), 9.55 (s, 1H), 9.32 (br s, 1H, TFA salt), 8.20 (s, 1H), 7.52 (dd, *J* = 8.4, 2.7 Hz, 1H), 7.19 – 7.09 (m, 2H), 6.97 (s, 2H), 5.11 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.93 – 4.85 (m, 1H), 4.38 (d, *J* = 16.9 Hz, 2H), 4.26 (d, *J* = 16.9 Hz, 2H), 3.92 (s, 6H), 3.68 (s, 3H), 3.54 – 3.38 (m, 4H), 3.25 – 3.21 (m, 1H), 3.06 – 2.82 (m, 6H), 2.67 – 2.56 (m, 2H), 2.44 – 2.38 (m, 2H), 2.18 – 1.73 (m, 10H), 1.54 – 1.46 (m, 2H).
D369	749.25	^{1}H NMR (400 MHz, DMSO-d6) δ 10.95 (s, 1H), 10.05 – 9.61 (m, 2H, TFA salt), 8.15 (s, 1H), 7.56 – 7.46 (m, 2H), 6.90 (d, *J* = 4.6 Hz, 2H), 6.54 – 6.45 (m, 2H), 5.05 (dd, *J* = 13.2, 5.1 Hz, 1H), 4.40 – 4.28 (m, 2H), 4.27 – 4.15 (m, 4H), 4.12 – 3.98 (m, 2H), 3.90 (s, 6H), 3.78 (s, 2H), 3.70 (s, 2H), 3.60 (d, *J* = 2.0 Hz, 3H), 3.52 (s, 3H), 3.41 (s, 3H), 3.17 (s, 1H), 2.99 – 2.90 (m, 3H), 2.68 – 2.52 (m, 2H), 2.47 – 2.28 (m, 1H), 2.13 (d, *J* = 13.9 Hz, 2H), 2.00 – 1.88 (m, 3H).
D370	749.4	^{1}H NMR (400 MHz, DMSO-d6) δ 10.95 (s, 1H), 9.99 – 9.58 (m, 2H, TFA salt), 8.63 (s, 1H), 7.92 (s, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.41 (s, 2H), 6.54 – 6.45 (m, 2H), 5.05 (dd, *J* = 13.2, 5.1 Hz, 1H), 4.42 – 4.27 (m, 2H), 4.25 – 4.14 (m, 4H), 4.08 (s, 3H), 4.05 – 3.95 (m, 2H), 3.94 (s, 6H), 3.77 (s, 2H), 3.69 (s, 2H), 3.54 (s, 3H), 3.38 (s, 3H), 3.17 (d, *J* = 6.7 Hz, 1H), 2.96 (s, 3H), 2.65 –2.51 (m, 2H), 2.43 – 2.36 (m, 1H), 2.12 (d, *J* = 14.3 Hz, 2H), 2.00 – 1.88 (m, 3H).

Compound No.	LCMS	^{1}H NMR
D371	805.45	1H NMR (400 MHz, Methanol-d4) δ 7.86 (d, J = 9.7 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.46 (s, 1H), 7.06 – 6.97 (m, 2H), 6.90 – 6.79 (m, 3H), 5.14 (dd, J = 13.3, 5.1 Hz, 1H), 4.55 – 4.39 (m, 4H), 4.01 – 3.86 (m, 6H), 3.74 (s, 3H), 3.69 – 3.52 (m, 3H), 3.41 – 3.36 (m, 1H), 3.28 – 3.16 (m, 2H), 3.13 – 2.98 (m, 4H), 2.96 – 2.86 (m, 2H), 2.85 – 2.75 (m, 1H), 2.74 – 2.65 (m, 1H), 2.60 – 2.43 (m, 2H), 2.27 (s, 1H), 2.22 – 2.15 (m, 1H), 2.14 – 1.92 (m, 8H), 1.73 – 1.59 (m, 2H).

Example 83 – Preparation of Compounds DD1-DD10

In analogy to the procedures described in the examples above, compounds DD1-DD10 were prepared using the appropriate starting materials.

Compound No.	LCMS	^{1}H NMR
DD1	942.5	^{1}H NMR (300 MHz, DMSO-d6) δ 9.45 (s, 1H), 8.98 (s, 1H), 8.72 (d, *J* = 5.7 Hz, 1H), 8.60 (t, *J* = 6.0 Hz, 1H), 8.19 (s, 1.0H, FA), 7.87 (s, 1H), 7.56 (d, *J* = 5.6 Hz, 1H), 7.47 – 7.35 (m, 5H), 6.72 (s, 2H), 4.57 (d, *J* = 9.5 Hz, 1H), 4.47 – 4.33 (m, 3H), 4.30 – 4.21 (m, 1H), 3.97 (s, 2H), 3.80 (s, 6H), 3.68 – 3.50 (m, 18H), 2.58 (t, *J* = 6.1 Hz, 2H), 2.44 (s, 3H), 2.18 (s, 3H), 2.11 – 2.00 (m, 1H), 1.97 – 1.85 (m, 1H), 0.95 (s, 9H).
DD2	754.2	^{1}H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.43 (s, 1H), 8.71 (d, *J* = 5.8 Hz, 1H), 8.22 (s, 1.5H, FA), 8.11 (s, 1H), 7.88 – 7.81 (m, 2H), 7.54 (d, *J* = 5.6 Hz, 1H), 7.40 (s, 1H), 7.35 (d, *J* = 8.6 Hz, 1H), 6.72 (s, 2H), 5.16 – 5.07 (m, 1H), 4.68 (s, 2H), 3.80 (s, 6H), 3.62 – 3.58 (m, 5H), 3.31 – 3.10 (m, 7H), 2.93 – 2.83 (m, 1H), 2.46 (s, 2H), 2.21 (s, 3H), 2.17 (s, 3H), 2.16 – 1.94 (m, 2H).
DD3	740.45	^{1}H NMR (300 MHz, Methanol-d4) δ 9.53 (s, 1H), 8.70 (d, *J* = 5.8 Hz, 1H), 8.55 (s, 1H, FA), 7.74 (s, 1H), 7.62 (d, *J* = 5.7 Hz, 1H), 7.38 (t, *J* = 8.1 Hz, 1H), 6.77 (s, 2H), 6.63 (d, *J* = 7.8 Hz, 1H), 6.44 (d, *J* = 8.4 Hz, 1H), 5.21 (dd, *J* = 10.9, 5.7 Hz, 1H), 4.52 – 4.25 (m, 2H), 4.12 – 4.00 (m, 1H), 3.90 (s, 8H), 3.85 – 3.75 (m, 6H), 3.71 (s, 3H), 3.53 – 3.42 (m, 2H), 2.93 – 2.70 (m, 7H), 2.64 (s, 3H), 2.26 – 2.17 (m, 1H).

Compound No.	LCMS	^{1}H NMR
DD4	709.4	^{1}H NMR (300 MHz, DMSO-d6) δ 11.02 (s, 1H), 9.48 (s, 1H), 8.75 (d, *J* = 5.7 Hz, 2H), 7.92 (s, 1H), 7.58 (d, *J* = 5.6 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 1H), 6.93 (d, *J* = 7.4 Hz, 1H), 6.87 (s, 2H), 6.74 (d, *J* = 8.0 Hz, 1H), 5.13 (dd, *J* = 13.2, 5.1 Hz, 1H), 4.37 – 4.26 (m, 2H), 4.22 – 4.13 (m, 2H), 3.89 (s, 7H), 3.62 (s, 3H), 3.21 – 3.03 (m, 4H), 2.98 – 2.84 (m, 1H), 2.77 – 2.63 (m, 3H), 2.30 – 2.23 (m, 1H), 2.10 – 1.98 (m, 1H), 1.84 – 1.66 (m, 2H), 1.66 – 1.53 (m, 2H), 1.44 – 1.29 (m, 8H).
DD5	736.45	^{1}H NMR (400 MHz, Methanol-d4) δ 9.51 (s, 1H), 8.69 (d, *J* = 5.7 Hz, 1H), 8.56 (s, 1H, FA), 7.76 (s, 1H), 7.61 (dd, *J* = 5.8, 0.9 Hz, 1H), 7.47 (t, *J* = 8.1 Hz, 1H), 6.87 (s, 2H), 6.67 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 8.4 Hz, 1H), 5.19 (dd, *J* = 11.0, 5.7 Hz, 1H), 4.29 (s, 2H), 3.96 (s, 6H), 3.68 (s, 3H), 3.37 – 3.36 (m, 1H), 3.14 – 3.02 (m, 3H), 2.91 – 2.70 (m, 6H), 2.63 (s, 3H), 2.24 – 2.17 (m, 1H), 1.87 – 1.76 (m, 2H), 1.74 – 1.64 (m, 2H), 1.54 – 1.36 (m, 8H).
DD6	722.54	^{1}H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.45 (s, 1H), 8.72 (d, *J* = 5.7 Hz, 1H), 7.91 (d, *J* = 44.8 Hz, 2H), 7.55 (d, *J* = 5.7 Hz, 1H), 6.84 (s, 2H), 5.22 – 5.02 (m, 0H), 4.98 (s, 1H), 4.71 (s, 1H), 4.35 (s, 2H), 3.94 – 3.78 (m, 6H), 3.59 (s, 3H), 3.13 – 2.80 (m, 2H), 2.73 (s, 2H), 2.67 – 2.53 (m, 1H), 2.05 (s, 2H).
DD7	800.3	1H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.40 (s, 1H), 8.68 (d, J = 5.6 Hz, 1H), 8.14 – 8.04 (m, 3H), 7.92 (d, J = 8.3 Hz, 1H), 7.83 (s, 1H), 7.72 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 5.6 Hz, 1H), 7.00 (d, J = 8.7 Hz, 2H), 6.74 (s, 2H), 5.15 (dd, J = 12.9, 5.4 Hz, 1H), 4.06 (q, J = 5.2 Hz, 1H), 4.02 (t, J = 6.4 Hz, 2H), 3.82 (s, 6H), 3.64 (s, 2H), 3.56 (s, 3H), 3.29 – 3.12 (m, 5H), 3.00 (s, 3H), 2.95 – 2.82 (m, 1H), 2.64 – 2.50 (m, 2H), 2.22 (s, 3H), 2.06 (d, J = 11.5 Hz, 1H), 1.71 (d, J = 15.0 Hz, 0H), 1.71 (s, 2H), 1.59 (q, J = 7.3 Hz, 2H).
DD8	814.3	1H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.40 (s, 1H), 8.68 (d, J = 5.6 Hz, 1H), 8.23 (s, 1H), 8.10 – 8.01 (m, 2H), 7.90 (d, J = 8.3 Hz, 1H), 7.83 (s, 1H), 7.76 – 7.64 (m, 3H), 7.52 (d, J = 6.2 Hz, 1H), 7.00 (d, J = 8.8 Hz, 2H), 6.72 (s, 2H), 5.15 (dd, J = 12.9, 5.4 Hz, 1H), 4.00 (t, J = 6.3 Hz, 2H), 3.81 (s, 6H), 3.58 (d, J = 14.7 Hz, 5H), 3.18 (d, J = 6.3 Hz, 1H), 3.15 (s, 5H), 2.94 (s, 2H), 2.92 – 2.82 (m, 1H), 2.62 (s, 1H), 2.59 – 2.50 (m, 1H), 2.16 (s, 3H), 2.07 (d, J = 11.7 Hz, 1H), 1.73 (t, J = 7.0 Hz, 2H), 1.49 (d, J = 5.5 Hz, 2H), 1.42 (d, J = 7.9 Hz, 3H).

Compound No.	LCMS	^{1}H NMR
DD9	571.61	^{1}H NMR (400 MHz, DMSO-d6) δ 8.32 (s, 1H), 8.09 – 8.02 (m, 1H), 7.82 – 7.77 (m, 1H), 7.73 (s, 1H), 7.63 (s, 0H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.82 (s, 2H), 5.09 (dt, *J* = 11.9, 5.8 Hz, 1H), 3.92 (d, *J* = 3.9 Hz, 5H), 3.86 (d, *J* = 3.7 Hz, 6H), 3.51 (d, *J* = 2.0 Hz, 4H), 3.15 (s, 1H), 2.08 (d, *J* = 2.6 Hz, 4H).
DD10	803.2	1H NMR (300 MHz, DMSO) δ 11.13 (s, 1H), 8.20 (s, FA, 1H), 8.09 (d, J = 8.3 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.69 – 7.59 (m, 1H), 7.58 - 7.49 (m, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.34 – 7.23 (m, 2H), 6.73 (s, 2H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 5.05 - 4.94 (m, 1H), 3.81 (s, 6H), 3.73 - 3.67 (m, 1H), 3.03 - 2.89 (m, 2H), 2.88 – 2.81 (m, 1H), 2.66 – 2.53 (m, 2H), 2.49 – 2.39 (m, 6H), 2.36 - 2.21 (m, 6H), 2.14 – 1.99 (m, 3H), 1.89 - 1.75 (m, 2H), 1.72 – 1.45 (m, 7H), 1.26 - 1.06 (m, 2H).

Example 84 – Preparation of Compounds D372-D476

In analogy to the procedures described in the examples above, compounds D372-D476 were prepared using the appropriate starting materials.

Compound No.	LCMS	^{1}H NMR
D372	638.25	^{1}H NMR (400 MHz, DMSO-d6) δ 11.13 (s, 1H), 9.45 (s, 1H), 8.73 (d, J = 5.7 Hz, 1H), 7.88 (d, J = 14.1 Hz, 2H), 7.57 (d, J = 5.6 Hz, 1H), 7.36 – 7.28 (m, 2H), 6.79 (s, 2H), 5.18 - 5.01 (m, 2H), 4.25 - 3.92 (m, 3H), 3.84 (s, 7H), 3.61 (s, 4H), 2.96 - 2.81 (m, 1H), 2.70 – 2.53 (m, 3H), 2.10 – 2.01 (m, 1H).
D373	691.30	^{1}H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.45 (d, J = 0.8 Hz, 1H), 8.73 (d, J = 5.7 Hz, 1H), 8.18 (s, FA, 1H), 7.89 (s, 1H), 7.67 – 7.57 (m, 2H), 6.81 – 6.72 (m, 3H), 6.66 (dd, J = 8.4, 2.1 Hz, 1H), 5.06 (dd, J = 12.9, 5.4 Hz, 1H), 3.82 (s, 6H), 3.74 (s, 4H), 3.58 (d, J = 20.8 Hz, 6H), 2.95 – 2.82 (m, 1H), 2.63 – 2.52 (m, 2H), 2.46 - 2.41 (m, 3H), 2.04 - 1.97 (m, 1H), 1.77 - 1.70 (m, 4H).
D374	677.30	^{1}H NMR (400 MHz, MeOD) δ 9.59 (s, 1H), 8.71 (d, J = 6.1 Hz, 1H), 7.94 (s, 1H), 7.81 (d, J = 6.0 Hz, 1H), 7.67 – 7.60 (m, 1H), 6.91 (s, 2H), 6.59 (d, J = 7.8 Hz, 2H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.47 (s, 2H), 4.40 (d, J = 7.0 Hz, 2H), 4.00 (s, 6H), 3.92 (s, 2H), 3.80 (s, 2H), 3.75 (s, 3H), 3.62 - 3.55 (m, 3H), 3.31 - 3.21 (m, 1H), 2.98 – 2.85 (m, 1H), 2.85 – 2.74 (m, 1H), 2.55 - 2.39 (m, 1H), 2.33 - 2.24 (m, 2H), 2.21 – 2.06 (m, 3H).

Compound No.	LCMS	^{1}H NMR
D375	624.25	^{1}H NMR (300 MHz, Methanol-d4) δ 9.57 (s, 1H), 8.70 (d, J = 6.0 Hz, 1H), 7.90 (s, 1H), 7.77 (dd, J = 14.9, 7.1 Hz, 2H), 7.09 (d, J = 10.5 Hz, 2H), 6.89 (s, 2H), 5.41 – 5.20 (m, 1H), 5.15 (dd, J = 13.3, 5.2 Hz, 1H), 4.86 – 4.60 (m, 4H), 4.49 (d, J = 4.5 Hz, 2H), 4.44 – 4.27 (m, 2H), 3.97 (d, J = 14.5 Hz, 6H), 3.73 (s, 3H), 3.01 – 2.74 (m, 2H), 2.60 – 2.41 (m, 1H), 2.25 – 2.13 (m, 1H).
D376	652.30	^{1}H NMR (400 MHz, DMSO-d6) δ 11.14 (s, 1H), 9.81 (s, TFA, 1H), 9.48 (d, J = 0.8 Hz, 1H), 8.75 (d, J = 5.7 Hz, 1H), 7.96 – 7.89 (m, 2H), 7.57 (d, J = 5.7 Hz, 1H), 7.44 – 7.34 (m, 2H), 6.88 (s, 2H), 5.15 (dd, J = 12.8, 5.4 Hz, 2H), 4.74 – 4.57 (m, 2H), 4.55 – 4.42 (m, 2H), 4.09 (s, 1H), 3.92 (s, 6H), 3.63 (s, 3H), 2.97 – 2.84 (m, 1H), 2.66 – 2.52 (m, 2H), 2.10 – 2.03 (m, 1H), 1.53 (d, J = 6.8 Hz, 3H).
D377	677.35	^{1}H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.16 (s, 1H), 7.73 (s, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.25 (dd, J = 8.5, 2.4 Hz, 1H), 7.14 (d, J = 2.3 Hz, 1H), 6.74 (d, J = 20.0 Hz, 3H), 5.10 (dd, J = 13.3, 5.1 Hz, 1H), 4.38 – 4.15 (m, 2H), 3.93 (s, 3H), 3.79 (s, 6H), 3.73 (d, J = 12.3 Hz, 3H), 3.57 – 3.52 (m, 5H), 2.97 – 2.84 (m, 1H), 2.75 – 2.64 (m, 2H), 2.64 – 2.55 (m, 1H), 2.48 – 2.38 (m, 4H), 2.38 – 2.20 (m, 6H), 2.03 – 1.94 (m, 1H), 1.74 (d, J = 12.4 Hz, 2H), 1.52 – 1.42 (m, 1H), 1.41 – 1.32 (m, 2H), 1.31 – 1.17 (m, 2H).
D378	624.30	^{1}H NMR (300 MHz, Methanol-d4) δ 9.56 (s, 1H), 8.69 (d, J = 5.9 Hz, 1H), 7.84 (s, 1H), 7.68 (s, 1H), 7.60 (d, J = 8.3 Hz, 1H), 7.33 – 7.16 (m, 2H), 6.89 (s, 2H), 5.40 – 5.07 (m, 2H), 4.84 – 4.61 (m, 4H), 4.59 – 4.44 (m, 2H), 4.44 – 4.28 (m, 2H), 4.07 – 3.85 (m, 6H), 3.73 (s, 3H), 3.01 – 2.86 (m, 1H), 2.86 – 2.75 (m, 1H), 2.61 – 2.43 (m, 1H), 2.25 – 2.14 (m, 1H).
D379	810.35	^{1}H NMR (400 MHz, Methanol-d4) δ 9.55 (s, 1H), 8.70 (d, J = 5.8 Hz, 1H), 8.56 (s, 1H, FA), 7.78 (s, 1H), 7.69 – 7.56 (m, 2H), 6.88 (s, 2H), 6.65 – 6.53 (m, 2H), 5.11 (dd, J = 13.3, 5.2 Hz, 1H), 4.53 – 4.24 (m, 4H), 4.06 (d, 2H), 3.98 (s, 6H), 3.76 (d, J = 8.0 Hz, 2H), 3.72 (s, 3H), 3.56 – 3.48 (m, 2H), 3.16 – 3.01 (m, 2H), 2.99 – 2.85 (m, 1H), 2.84 – 2.64 (m, 3H), 2.60 – 2.40 (m, 3H), 2.36 (s, 2H), 2.21 – 2.11 (m, 3H), 2.05 (d, J = 13.9 Hz, 2H), 1.92 (s, 1H), 1.59 – 1.38 (m, 2H).

Compound No.	LCMS	^{1}H NMR
D380	661.35	1H), 9.49 (s, 1H), 8.75 (d, J = 5.9 Hz, 1H), 7.99 (s, 1H), 7.56 (d, J = 5.9 Hz, 1H), 7.39 (d, J = 8.5 Hz, 1H), 7.12 (t, J = 2.0 Hz, 1H), 7.04 (d, J = 2.0 Hz, 2H), 6.74 - 6.67 (m, 2H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.32 (d, J = 16.6 Hz, 1H), 4.19 (d, J = 16.6 Hz, 1H), 3.86 (s, 3H), 3.67 (s, 6H), 3.61 (s, 3H), 3.39 (s, 2H), 2.98 - 2.84 (m, 1H), 2.63 - 2.59 (m, 1H), 2.42 - 2.33 (m, 1H), 2.02 - 1.95 (m, 1H), 1.90-1.72 (m, 4H).
D381	767.40	^{1}H NMR (400 MHz, DMSO-d6) δ 10.86 – 10.81 (m, HCl, 1H), 9.52 (s, 1H), 8.80 – 8.73 (m, 1H), 8.52 (s, 3H), 8.07 (s, 1H), 7.93 (d, J = 8.2 Hz, 1H), 7.72 (s, 1H), 7.44 – 7.34 (m, 2H), 6.88 (d, J = 6.1 Hz, 2H), 5.93 – 5.84 (m, 1H), 5.75 – 5.67 (m, 1H), 5.53 – 5.21 (m, 2H), 4.81 – 4.73 (m, 1H), 4.67 – 4.53 (m, 1H), 4.52 – 4.44 (m, 2H), 4.33 – 4.29 (m, 1H), 4.17 – 4.12 (m, 1H), 3.92 (s, 3H), 3.87 (s, 4H), 3.64 (s, 3H), 3.13 – 3.05 (m, 1H), 2.93 – 2.84 (m, 1H), 2.70 – 2.56 (m, 1H), 2.18 – 2.11 (m, 2H), 0.98 – 0.90 (m, 6H).
D382	663.35	^{1}H NMR (300 MHz, DMSO-d6) δ 11.51 (s, 1H), 9.47 (s, 1H), 8.92 (s, 1H, FA), 8.76 (d, J = 5.7 Hz, 1H), 7.90 (s, 1H), 7.59 (d, J = 5.7 Hz, 1H), 7.40 (d, J = 8.2 Hz, 1H), 6.87 (s, 2H), 6.75 – 6.52 (m, 2H), 5.19 (dd, J = 9.1, 6.3 Hz, 1H), 4.49 (d, J = 16.8 Hz, 1H), 4.38 – 4.15 (m, 3H), 3.91 (s, 7H), 3.76 (s, 2H), 3.62 (s, 6H), 3.21 – 3.04 (m, 2H), 3.04 – 2.79 (m, 2H), 2.21 – 1.90 (m, 4H).
D383	667.30	^{1}H NMR (400 MHz, DMSO-d6 with a drop of D_2O) δ 9.46 (s, 1H), 8.75 (d, J = 5.7 Hz, 1H), 7.88 (s, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.60 (d, J = 5.6 Hz, 1H), 6.86 (s, 2H), 6.78 (d, J = 2.0 Hz, 1H), 6.67 (dd, J = 8.4, 2.1 Hz, 1H), 5.21 (dd, J = 9.6, 5.6 Hz, 1H), 4.29 (s, 2H), 3.91 (d, J = 8.4 Hz, 8H), 3.81 (s, 2H), 3.61 (s, 3H), 3.38 (d, J = 12.6 Hz, 2H), 3.13 (t, J = 12.0 Hz, 2H), 3.05 – 2.95 (m, 1H), 2.82 (dd, J = 17.9, 5.5 Hz, 1H), 2.15 (d, J = 14.1 Hz, 2H), 2.01 (t, J = 12.8 Hz, 2H).
D384	753.40	^{1}H NMR (400 MHz, DMSO-d6) δ 10.71 (s, 1H, HCl salt), 9.49 (s, 1H), 8.79 – 8.72 (m, 1H), 8.51 (br s, 3H), 7.99 (s, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.67 – 7.59 (m, 1H), 7.39 – 7.01 (m, 3H), 6.87 (d, J = 5.1 Hz, 2H), 5.86 – 5.78 (m, 1H), 5.76 – 5.68 (m, 1H), 5.35 – 5.02 (m, 2H), 4.80 – 4.67 (m, 1H), 4.60 – 4.54 (m, 1H), 4.52 – 4.41 (m, 3H), 4.34 – 4.22 (m, 2H), 4.16 – 4.10 (m, 1H), 3.94 – 3.82 (m, 7H), 3.63 (s, 3H), 3.20 – 3.06 (m, 1H), 2.91 – 2.82 (m, 1H), 2.46 – 2.36 (m, 1H), 2.21 – 2.06 (m, 2H), 0.97 – 0.90 (m, 6H).

Compound No.	LCMS	^{1}H NMR
D385	636.35	^{1}H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.45 (s, 1H), 8.73 (d, J = 5.7 Hz, 1H), 8.13 (s, 0.1 H, FA salt), 7.90 – 7.81 (m, 2H), 7.51 (d, J = 5.7 Hz, 1H), 7.37 – 7.27 (m, 2H), 6.94 (s, 2H), 5.18 – 4.99 (m, 2H), 3.84 (s, 6H), 3.60 (s, 4H), 3.28 – 3.25 (m, 2H), 2.99 – 2.72 (m, 3H), 2.61 – 2.53 (m, 2H), 2.11–1.99 (m, 1H), 1.21 (t, J = 7.5 Hz, 3H).
D386	650.30	^{1}H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.45 (s, 1H), 8.73 (dd, J = 5.7, 2.3 Hz, 1H), 8.13 (s, 0.1H, FA salt), 7.89–7.80 (m, 2H), 7.49 (dd, J = 6.0, 2.1 Hz, 1H), 7.37–7.28 (m, 2H), 6.92 (s, 2H), 5.12 (dd, J = 12.9, 5.3 Hz, 1H), 4.63 (s, 1H), 3.90–3.68 (m, 6H), 3.60 (s, 4H), 3.44–3.37 (m, 1H), 2.99 – 2.72 (m, 3H), 2.62 – 2.52 (m, 2H), 2.11–1.95 (m, 1H), 1.29–1.12 (m, 6H).
D387	647.25	^{1}H NMR (300 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.45 (s, 1H), 8.73 (d, J = 5.7 Hz, 1H), 7.85 (s, 1H), 7.48 – 7.36 (m, 2H), 7.01 – 6.89 (m, 3H), 6.73 – 6.65 (m, 2H), 5.11 – 5.04 (m, 1H), 4.31 – 4.18 (m, 2H), 3.82 (s, 3H), 3.60 (s, 7H), 3.52 (s, 2H), 2.94 – 2.87 (m, 1H), 2.67 – 2.61 (m, 1H), 2.46 – 2.34 (m, 4H), 2.04 – 1.92 (m, 2H), 1.83 – 1.73 (m, 4H).
D388	705.45	^{1}H NMR (300 MHz, DMSO-d6) δ 10.78 (s, 1H), 9.48 (s, 1H), 9.07 (br s, 1H), 8.76 (d, J = 5.7 Hz, 1H), 7.92 (s, 1H), 7.68 (d, J = 8.2 Hz, 1H), 7.61 (d, J = 5.8 Hz, 1H), 6.88 (s, 2H), 6.78 (d, J = 2.1 Hz, 1H), 6.67 (dd, J = 8.3, 2.2 Hz, 1H), 5.14 (dd, 1H), 4.38 – 4.24 (m, 2H), 3.97 – 3.88 (m, 8H), 3.83 (s, 2H), 3.63 (s, 3H), 3.46 – 3.35 (m, 3H), 3.18 – 3.06 (m, 3H), 2.76 – 2.66 (m, 1H), 2.22 – 2.13 (m, 2H), 2.11 – 1.80 (m, 5H).
D389	663.30	^{1}H NMR (300 MHz, DMSO-d6) δ 9.45 (s, 1H), 8.74 (d, J = 5.7 Hz, 1H), 7.89 (s, 1H), 7.73 (s, 1H), 7.58 (d, J = 5.6 Hz, 1H), 7.36 (d, J = 8.7 Hz, 1H), 6.80 (s, 2H), 6.70 – 6.64 (m, 2H), 4.64 (dd, J = 10.8, 6.8 Hz, 1H), 4.38 – 4.25 (m, 1H), 4.21 – 4.07 (m, 1H), 3.96 – 3.80 (m, 8H), 3.66 – 3.59 (m, 7H), 3.23 – 3.11 (m, 3H), 2.94 – 2.74 (m, 3H), 2.09 – 1.80 (m, 8H).
D390	663.50	^{1}H NMR (300 MHz, DMSO-d6) δ 9.48 (s, 1H), 8.99 (s, 1H, TFA), 8.76 (d, J = 5.7 Hz, 1H), 7.91 (s, 1H), 7.60 (d, J = 5.7 Hz, 1H), 7.54 (d, J = 2.5 Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H), 6.88 (s, 2H), 6.73 – 6.64 (m, 2H), 4.41 – 4.27 (m, 5H), 3.92 (s, 6H), 3.76 (s, 3H), 3.64 (s, 4H), 3.45 – 3.34 (m, 2H), 3.34 – 3.06 (m, 4H), 2.44 – 2.29 (m, 2H), 2.19 – 1.85 (m, 6H).

Compound No.	LCMS	^{1}H NMR
D391	667.45	^{1}H NMR (300 MHz, DMSO-d6) δ 10.95 (s, 1H), 9.54 (s, 1H), 9.10 (s, 1H), 8.97 (d, J = 8.2 Hz, 1H), 8.82 (d, J = 5.7 Hz, 1H), 8.37 (d, J = 5.9 Hz, 1H), 7.96 (s, 1H), 7.65 (d, J = 5.7 Hz, 1H), 6.94 (s, 2H), 6.60 (d, J = 6.0 Hz, 1H), 4.85–4.71 (m, 1H), 4.42–4.32 (m, 2H), 4.12–3.89 (m, 11H), 3.69 (s, 3H), 3.27–3.15 (m, 3H), 2.98–2.78 (m, 1H), 2.71–2.60 (m, 1H), 2.32–1.99 (m, 6H).
D392	665.25	^{1}H NMR (300 MHz, Methanol-d4) δ 9.63 (s, 1H), 8.72 (d, J = 6.4 Hz, 1H), 8.08 (s, 1H), 7.95 (d, J = 6.3 Hz, 1H), 7.32 (t, J = 7.8 Hz, 1H), 7.23 (dt, J = 7.9, 1.2 Hz, 1H), 7.02 (t, J = 2.0 Hz, 1H), 6.91 (s, 2H), 6.71 (ddd, J = 8.0, 2.5, 1.1 Hz, 1H), 4.86 – 4.85 (m, 1H), 4.46 (s, 2H), 4.00 (s, 6H), 3.85 (s, 2H), 3.75 (d, J = 9.0 Hz, 5H), 3.58 (d, J = 12.9 Hz, 2H), 3.25 (t, J = 11.8 Hz, 2H), 2.95 – 2.65 (m, 2H), 2.34 – 2.05 (m, 6H).
D393	571.25	^{1}H NMR (300 MHz, DMSO-d6) δ 11.00 (s, 1H), 9.45 (d, J = 0.8 Hz, 1H), 8.73 (d, J = 5.7 Hz, 1H), 8.19 (.1.0 FA, s, 1H), 7.89 (s, 1H), 7.63 – 7.50 (m, 2H), 7.36 (s, 1H), 6.74 (s, 2H), 5.27 (dd, J = 11.5, 5.1 Hz, 1H), 3.83 (s, 6H), 3.60 (d, J = 4.2 Hz, 5H), 2.92 (d, J = 11.3 Hz, 2H), 2.84 – 2.68 (m, 1H), 2.68 – 2.53 (m, 1H), 2.49 – 2.35 (m, 2H), 2.24 – 2.09 (m, 3H), 1.80 (d, J = 12.8 Hz, 2H), 1.58 – 1.38 (m, 2H).
D394	613.25	^{1}H NMR (300 MHz, Methanol-d4) δ 9.60 (s, 1H), 8.71 (d, 1H), 7.97 (s, 1H), 7.85 (d, 1H), 6.91 (s, 2H), 6.70 (s, 1H), 6.12 (dd, 1H), 4.48 (s, 2H), 4.00 (s, 6H), 3.75 (s, 4H), 3.71 (s, 1H), 3.58 – 3.42 (m, 1H), 3.27 (s, 1H), 3.06 – 2.95 (m, 1H), 2.90 – 2.76 (m, 2H), 2.60 (d, 3H), 2.40 – 2.27 (m, 2H), 2.12 (dd, 4H).
D395	667.45	^{1}H NMR (300 MHz, DMSO-d6) δ 10.87 (s, 1H), 9.45 (s, 1H), 9.00 (d, J = 8.4 Hz, 1H), 8.73 (d, J = 5.6 Hz, 1H), 8.54 (d, J = 1.2 Hz, 1H), 8.17 (s, 1H, FA), 7.88 (s, 1H), 7.63 – 7.55 (m, 1H), 6.89 (d, J = 1.2 Hz, 1H), 6.74 (s, 2H), 4.76 (ddd, J = 12.9, 8.4, 5.3 Hz, 1H), 3.82 (d, J = 4.1 Hz, 10H), 3.61 (s, 3H), 3.58 (s, 2H), 2.84 – 2.74 (m, 1H), 2.55 (s, 2H), 2.48 – 2.40 (m, 3H), 2.25 – 2.13 (m, 1H), 2.05 – 1.93 (m, 1H), 1.75 (s, 4H).
D396	640.31	^{1}H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 8.19 (s, FA, 1H), 7.41 – 7.26 (m, 2H), 6.72 – 6.66 (m, 2H), 6.53 (s, 2H), 5.09 (dd, J = 13.2, 5.0 Hz, 1H), 4.31 (d, J = 16.6 Hz, 1H), 4.18 (d, J = 16.6 Hz, 1H), 3.79 (s, 6H), 3.77 (d, J = 7.1 Hz, 2H), 3.74 – 3.66 (m, 4H), 3.54 (s, 3H), 2.97 – 2.84 (m, 1H), 2.77 (s, 2H), 2.64 – 2.59 (m, 2H), 2.40 – 2.28 (m, 5H), 2.04 (s, 3H), 2.01 – 1.95 (m, 3H).

Compound No.	LCMS	^{1}H NMR
D397	751.4	^{1}H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.19 (br s, TFA salt, 2H), 7.45 – 7.38 (m, 1H), 7.28 (s, 1H), 6.74 – 6.66 (m, 4H), 5.07 (dd, J = 13.3, 5.1 Hz, 1H), 4.37 – 4.16 (m, 4H), 3.87 (s, 6H), 3.74 (d, J = 8.5 Hz, 2H), 3.67 (d, J = 6.9 Hz, 2H), 3.65 (s, 5H), 3.53 – 3.50 (m, 2H), 3.21 (s, 1H), 3.07 – 2.85 (m, 6H), 2.65 – 2.55 (m, 1H), 2.43 – 2.31 (m, 4H), 2.20–2.07 (m, 3H), 2.05 (s, 3H), 2.02 – 1.87 (m, 5H), 1.58 – 1.39 (m, 2H).
D398	761.2	1H), 8.40 (d, J = 2.6 Hz, 1H), 8.17 (s, 1H, FA), 8.15 (d, J = 2.5 Hz, 1H), 7.65 (d, J = 8.5 Hz, 1H), 7.30 (d, J = 2.2 Hz, 1H), 7.22 (dd, J = 8.7, 2.3 Hz, 1H), 7.14 – 6.71 (m, 3H), 5.06 (dd, J = 12.8, 5.3 Hz, 1H), 4.03 (d, J = 13.0 Hz, 2H), 3.85 (s, 6H), 3.59 (s, 3H), 3.54 (s, 2H), 3.00 – 2.80 (m, 3H), 2.65 – 2.52 (m, 2H), 2.48 – 2.24 (m, 10H), 2.06 – 1.96 (m, 1H), 1.73 (d, J = 12.6 Hz, 2H), 1.60 – 1.54 (m, 1H), 1.37 (t, J = 7.3 Hz, 2H), 1.16 (q, J = 11.6 Hz, 2H).
D399	747.3	^{1}H NMR (300 MHz, DMSO-d6) δ 10.99 (s, 1H), 8.40 (d, J = 2.6 Hz, 1H), 8.19 (s, 1H, FA), 8.15 (d, J = 2.6 Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H), 7.24 (dd, J = 8.6, 2.3 Hz, 1H), 7.14 (d, J = 2.3 Hz, 1H), 7.12 – 6.72 (m, 3H), 5.10 (dd, J = 13.2, 5.1 Hz, 1H), 4.33 (d, J = 16.7 Hz, 1H), 4.19 (d, J = 16.7 Hz, 1H), 3.85 (s, 6H), 3.72 (d, J = 12.1 Hz, 2H), 3.59 (s, 3H), 3.53 (s, 2H), 3.01 – 2.82 (m, 1H), 2.78 – 2.51 (m, 4H), 2.46 – 2.20 (m, 10H), 1.98 (d, J = 13.3 Hz, 1H), 1.73 (d, J = 12.4 Hz, 2H), 1.47 – 1.36 (m, 3H), 1.24 (q, J = 11.2 Hz, 2H).
D400	751.5	^{1}H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 8.63 (s, 1H), 7.91 (s, 1H), 7.47 – 7.39 (m, 3H), 7.29 (dd, J = 8.5, 2.4 Hz, 1H), 7.20 (d, J = 2.3 Hz, 1H), 5.09 (dd, J = 13.3, 5.1 Hz, 1H), 4.40 – 4.14 (m, 4H), 4.08 (s, 3H), 3.92 (s, 6H), 3.78 – 3.74 (m, 8H), 3.54 (s, 3H), 3.14 (s, 4H), 2.91 (ddd, J = 17.2, 13.6, 5.4 Hz, 1H), 2.75 (t, J = 11.8 Hz, 2H), 2.65 – 2.56 (m, 1H), 2.43 – 2.34 (m, 1H), 2.04 – 1.95 (m, 1H), 1.78 (d, J = 12.4 Hz, 2H), 1.64 – 1.46 (m, 3H), 1.38 – 1.23 (m, 2H).
D401	690.3	^{1}H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 8.37 (s, 1H), 8.24 (s, 1H), 8.15 (s, 1H, FA), 7.41 – 7.32 (m, 1H), 7.20 – 6.73 (m, 3H), 6.68 (dd, J = 5.1, 2.5 Hz, 2H), 5.09 (dd, J = 13.3, 5.0 Hz, 1H), 4.45 – 4.10 (m, 2H), 4.00 (t, J = 7.5 Hz, 2H), 3.87 (s, 6H), 3.81 – 3.66 (m, 6H), 2.94 – 2.83 (m, 1H), 2.75 (s, 2H), 2.64 – 2.52 (m, 2H), 2.42 – 2.25 (m, 2H), 1.98 (t, J = 7.0 Hz, 3H), 1.75 (q, J = 7.5 Hz, 2H), 0.91 (t, J = 7.3 Hz, 3H).

Compound No.	LCMS	^{1}H NMR
D402	749.35	^{1}H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.95 – 9.63 (m, 2H, TFA salt), 8.63 (s, 1H), 7.92 (s, 1H), 7.45 – 7.38 (m, 3H), 6.73 – 6.66 (m, 2H), 5.07 (dd, J = 13.3, 5.1 Hz, 1H), 4.43 – 4.28 (m, 3H), 4.24 – 4.15 (m, 3H), 4.08 (s, 3H), 4.03 – 3.98 (m, 2H), 3.94 (s, 6H), 3.76 – 3.62 (m, 4H), 3.54 (s, 3H), 3.22 – 3.12 (m, 2H), 2.97 – 2.88 (m, 4H), 2.70 – 2.56 (m, 2H), 2.44 – 2.30 (m, 2H), 2.12 (d, J = 14.1 Hz, 2H), 2.02 – 1.89 (m, 3H).
D403	662.15	^{1}H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 8.41 (s, J = 2.6 Hz, 1H), 8.16 (s, 1H, FA), 7.37 (d, J = 8.8 Hz, 1H), 6.86 - 7.08 (m, 3H), 6.72 – 6.65 (m, 2H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.31 (d, J = 16.6 Hz, 1H), 4.18 (d, J = 16.6 Hz, 1H), 3.87 (s, 6H), 3.79 – 3.67 (m, 6H), 3.60 (s, 3H), 2.97 – 2.84 (m, 2H), 2.76 (s, 2H), 2.63 – 2.55 (m, 3H), 2.31 – 2.42 (m, 2H), 2.02 – 1.94 (m, 3H).
D404	688.15	^{1}H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 8.34 (d, J = 2.6 Hz, 1H), 8.22 (s, 1H), 8.18 (s, 1H, FA), 7.37 (d, J = 8.8 Hz, 1H), 7.16 – 6.73 (m, 3H), 6.68 (dq, J = 4.0, 2.3 Hz, 2H), 6.03 (ddd, J = 17.2, 10.5, 5.3 Hz, 1H), 5.33 – 5.00 (m, 3H), 4.68 (d, J = 5.5 Hz, 2H), 4.31 (d, J = 16.7 Hz, 1H), 4.18 (d, J = 16.6 Hz, 1H), 3.90 – 3.79 (m, 7H), 3.77 – 3.71 (m, 2H), 3.72 – 3.63 (m, 3H), 3.00 – 2.82 (m, 1H), 2.76 (s, 2H), 2.59 (d, J = 17.1 Hz, 3H), 2.43 – 2.28 (m, 1H), 1.98 (t, J = 6.9 Hz, 3H).
D405	777.4	^{1}H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 8.61 (s, 1H), 8.19 – 8.14 (m, 1H, FA), 7.89 – 7.82 (m, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.36 – 7.29 (m, 2H), 6.72 – 6.65 (m, 2H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.31 (d, J = 16.6 Hz, 1H), 4.18 (d, J = 16.6 Hz, 1H), 4.08 (s, 3H), 3.87 (s, 6H), 3.79 (s, 2H), 3.58 (s, 4H), 3.53 (s, 3H), 3.08 – 3.01 (m, 2H), 2.98 – 2.84 (m, 1H), 2.68 – 2.55 (m, 2H), 2.43 – 2.30 (m, 6H), 2.11 (d, J = 7.0 Hz, 2H), 2.02 – 1.93 (m, 1H), 1.77 – 1.67 (m, 6H), 1.59 (s, 1H), 1.21 – 1.17 (m, 2H).
D406	676.3	^{1}H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.41 (d, J = 2.6 Hz, 1H), 8.19 (s, 1H, FA), 8.15 (d, J = 2.5 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.15 – 6.74 (m, 4H), 6.64 (dd, J = 8.3, 2.1 Hz, 1H), 5.06 (dd, J = 12.8, 5.4 Hz, 1H), 3.99 – 3.85 (m, 4H), 3.87 (s, 6H), 3.70 (s, 2H), 3.59 (s, 3H), 2.97 – 2.80 (m, 1H), 2.77 (s, 2H), 2.63 – 2.53 (m, 4H), 2.02 (t, J = 7.0 Hz, 3H).

Compound No.	LCMS	^{1}H NMR
D407	773.89	^{1}H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.42 (s, 1H, TFA), 9.25 (s, 1H, TFA), 8.50 (d, J = 2.7 Hz, 1H), 8.21 (d, J = 2.5 Hz, 1H), 7.44 – 7.38 (m, 1H), 7.11 – 6.79 (m, 3H), 6.70 (dd, J = 5.8, 2.4 Hz, 2H), 5.07 (dd, J = 13.3, 5.1 Hz, 1H), 4.38 – 4.14 (m, 4H), 3.95 (s, 6H), 3.66 (d, J = 7.8 Hz, 2H), 3.61 (s, 3H), 3.54 – 3.39 (m, 4H), 3.21 – 3.14 (m, 1H), 3.02 – 2.82 (m, 7H), 2.64 – 2.56 (m, 1H), 2.43 – 2.35 (m, 1H), 2.15 – 2.07 (m, 3H), 2.02 – 1.88 (m, 5H), 1.48 (q, J = 12.8 Hz, 2H), 1.26 (q, J = 7.2, 6.7 Hz, 1H).
D408	662.3	^{1}H NMR (300 MHz, DMSO-d6) δ 10.95 (s, 1H), 8.41 (d, J = 2.6 Hz, 1H), 8.21 (s, 1H, FA), 8.17 – 8.10 (m, 1H), 7.48 (d, J = 8.2 Hz, 1H), 7.18 – 6.73 (m, 3H), 6.54 – 6.42 (m, 2H), 5.03 (dd, J = 13.3, 5.1 Hz, 1H), 4.30 (d, J = 16.9 Hz, 1H), 4.16 (d, J = 16.9 Hz, 1H), 3.87 (s, 6H), 3.79 (q, J = 7.9 Hz, 4H), 3.70 (s, 2H), 3.59 (s, 3H), 2.99 – 2.81 (m, 1H), 2.80 – 2.74 (m, 2H), 2.63 – 2.52 (m, 2H), 2.41 – 2.29 (m, 2H), 2.05 – 1.89 (m, 3H).
D409	676.25	^{1}H NMR (300 MHz, Methanol-d4) δ 8.55 (s, 1H, FA), 7.68 (s, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.03 – 6.77 (m, 3H), 6.71 (s, 2H), 5.14 (dd, J = 13.3, 5.1 Hz, 1H), 4.48 – 4.33 (m, 4H), 4.03 – 3.89 (m, 10H), 3.71 (s, 3H), 3.64 – 3.54 (m, 2H), 3.47 – 3.37 (m, 2H), 3.00 – 2.85 (m, 1H), 2.85 – 2.74 (m, 1H), 2.58 – 2.41 (m, 6H), 2.23 – 2.13 (m, 1H).
D410	787.25	^{1}H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 8.17 (s, 1H, FA), 7.61 (s, 1H), 7.37 (d, J = 8.1 Hz, 1H), 6.91 (t, J = 55.2 Hz, 1H), 6.74 – 6.65 (m, 2H), 6.61 (s, 2H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.32 (d, J = 16.6 Hz, 1H), 4.18 (d, J = 16.6 Hz, 1H), 3.81 (s, 6H), 3.69 (s, 2H), 3.63 – 3.58 (m, 6H), 3.01 – 2.88 (m, 4H), 2.65 – 2.59 (m, 1H), 2.41 (s, 4H), 2.37 – 2.26 (m, 6H), 2.11 (d, J = 6.9 Hz, 2H), 2.02 – 1.95 (m, 1H), 1.79 – 1.64 (m, 6H), 1.54 (s, 1H), 1.21 – 1.08 (m, 2H).
D411	680.35	^{1}H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1H), 9.06 (s, 1H, TFA salt), 8.15 (s, 1H), 7.56 – 7.48 (m, 2H), 6.91 (s, 2H), 6.55 – 6.46 (m, 2H), 5.05 (dd, J = 13.3, 5.1 Hz, 1H), 4.37 – 4.25 (m, 3H), 4.19 (d, J = 16.9 Hz, 1H), 3.92 (s, 6H), 3.81 (s, 2H), 3.70 (s, 2H), 3.63 (s, 3H), 3.52 (s, 3H), 3.13 (q, J = 11.1 Hz, 2H), 2.91 (ddd, J = 17.1, 13.6, 5.3 Hz, 1H), 2.64 – 2.55 (m, 3H), 2.44 – 2.28 (m, 1H), 2.14 (d, J = 13.9 Hz, 2H), 2.05 – 1.92 (m, 3H). 19F NMR (377 MHz, DMSO-d6) δ -73.65.

Compound No.	LCMS	^{1}H NMR
D412	680.35	^{1}H NMR (400 MHz, DMSO-d6) δ 10.95 (s, 1H), 8.90 (s, 1H, TFA salt), 8.63 (s, 1H), 7.93 (s, 1H), 7.52 (d, J = 8.3 Hz, 1H), 7.43 (s, 2H), 6.55 – 6.46 (m, 2H), 5.05 (dd, J = 13.3, 5.1 Hz, 1H), 4.36 – 4.15 (m, 4H), 4.09 (s, 3H), 3.95 (s, 6H), 3.80 (s, 2H), 3.69 (s, 2H), 3.55 (s, 3H), 3.14 – 3.07 (m, 2H), 2.97 – 2.84 (m, 1H), 2.71 – 2.57 (m, 3H), 2.39 – 2.31 (m, 1H), 2.17 – 2.09 (m, 2H), 2.04 – 1.93 (m, 3H). 19F NMR (377 MHz, DMSO-d6) δ -73.66.
D413	694.45	^{1}H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.19 – 8.14 (m, 1H, FA), 8.12 (s, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.52 (s, 1H), 6.81 – 6.74 (m, 3H), 6.69 – 6.62 (m, 1H), 5.06 (dd, J = 12.9, 5.4 Hz, 1H), 3.82 (s, 6H), 3.74 (s, 4H), 3.61 – 3.54 (m, 5H), 3.51 (s, 3H), 2.95 – 2.82 (m, 1H), 2.63 – 2.52 (m, 2H), 2.46 – 2.39 (m, 4H), 2.06 – 1.97 (m, 1H), 1.78 – 1.69 (m, 4H).
D414	680.4	^{1}H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1H), 8.16 (s, 1H, FA), 8.12 (s, 1H), 7.51 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 6.76 (s, 2H), 6.72 – 6.65 (m, 2H), 5.08 (dd, J = 13.3, 5.2 Hz, 1H), 4.36 – 4.12 (m, 2H), 3.82 (s, 6H), 3.61 – 3.55 (m, 9H), 3.51 (s, 3H), 2.94 – 2.85 (m, 1H), 2.66 – 2.54 (m, 2H), 2.46 – 2.40 (m, 4H), 2.02 – 1.95 (m, 1H), 1.76 – 1.69 (m, 4H).
D415	694.3	^{1}H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.60 (s, 1H), 8.17 (s, 1H, FA), 7.80 (s, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.27 (s, 2H), 6.78 (d, J = 2.1 Hz, 1H), 6.68 – 6.61 (m, 1H), 5.05 (dd, J = 12.9, 5.3 Hz, 1H), 4.08 (s, 3H), 3.84 (s, 6H), 3.73 (s, 4H), 3.56 (s, 2H), 3.53 (s, 3H), 2.91 – 2.81 (m, 1H), 2.62 – 2.52 (m, 2H), 2.46 – 2.41 (m, 4H), 2.04 – 1.96 (m, 1H), 1.77 – 1.70 (m, 4H).
D416	680.4	^{1}H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1H), 8.59 (s, 1H), 8.18 (s, 1H, FA), 7.80 (s, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.27 (s, 2H), 6.72 – 6.65 (m, 2H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.35 – 4.13 (m, 2H), 4.08 (s, 3H), 3.85 (s, 6H), 3.59 – 3.50 (m, 9H), 2.96 – 2.84 (m, 1H), 2.64 – 2.53 (m, 2H), 2.48 – 2.36 (m, 4H), 2.02 – 1.94 (m, 1H), 1.76 – 1.69 (m, 4H).
D417	694.25	^{1}H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 8.65 (s, 1H), 8.20 (s, 1H FA), 7.83 (s, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.32 (s, 2H), 6.72 – 6.64 (m, 2H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.38 (q, J = 7.3 Hz, 2H), 4.31 (d, J = 16.6 Hz, 1H), 4.18 (d, J = 16.7 Hz, 1H), 3.85 (s, 6H), 3.57 (d, J = 4.1 Hz, 6H), 3.53 (s, 3H), 2.98 – 2.84 (m, 1H), 2.70 – 2.52 (m, 2H), 2.49 – 2.42 (m, 3H), 2.37 (dd, J = 13.2, 4.6 Hz, 1H), 2.03 – 1.94 (m, 1H), 1.74 (t, J = 5.5 Hz, 4H), 1.50 (t, J = 7.3 Hz, 3H).

Compound No.	LCMS	^{1}H NMR
D418	693.45	^{1}H NMR (400 MHz, DMSO-d6) δ 11.85 (d, J = 2.7 Hz, 1H), 11.09 (s, 1H), 7.66 (d, J = 8.3 Hz, 1H), 7.17 – 7.10 (m, 2H), 6.78 (d, J = 2.1 Hz, 1H), 6.70 (s, 2H), 6.65 (dd, J = 8.4, 2.1 Hz, 1H), 5.06 (dd, J = 12.9, 5.4 Hz, 1H), 3.82 (d, J = 22.7 Hz, 12H), 3.55 (s, 3H), 2.95 – 2.83 (m, 2H), 2.82 – 2.66 (m, 2H), 2.64 – 2.53 (m, 4H), 2.01 (dd, J = 9.4, 4.3 Hz, 1H), 1.87 (s, 6H).
D419	665.25	^{1}H NMR (300 MHz, DMSO-d6) δ 12.17 (s, 1H), 10.98 (s, 1H), 8.15 (s, 1H, FA), 7.48 (s, 1H), 7.38 – 7.36 (m, 2H), 6.85 (s, 2H), 6.71 – 6.68 (m, 2H), 6.58 – 6.55 (m, 1H), 5.11 – 5.05 (m, 1H), 4.34 – 4.15 (m, 2H), 3.85 (s, 6H), 3.60 (s, 3H), 3.58 (s, 6H), 2.97 – 2.89 (m ,1H), 2.74 – 2.72 (m, 3H), 2.40 – 2.34 (m, 2H), 2.00 – 1.97 (m, 1H), 1.73 (s, 4H), 1.35-1.24 (m, 1H).
D420	666.35	^{1}H NMR (400 MHz, DMSO-d6) δ 13.50 (s, 1H), 10.97 (s, 1H), 8.15 (s, 1H), 7.77 (s, 1H), 7.38 (d, J = 8.0 Hz, 1H), 6.88 (s, 2H), 6.73 – 6.65 (m, 2H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.31 (d, J = 16.6 Hz, 1H), 4.18 (d, J = 16.5 Hz, 1H), 3.89 (s, 6H), 3.69 (s, 2H), 3.60 (s, 4H), 3.55 (s, 3H), 2.96 – 2.84 (m, 1H), 2.64 – 2.55 (m, 4H), 2.42 – 2.22 (m, 2H), 1.98 (d, J = 12.9 Hz, 1H), 1.79 (s, 4H).
D421	680.45	^{1}H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 8.45 (s, 1H), 8.18 (s, 1H, FA), 7.47 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 6.83 (s, 2H), 6.72 – 6.64 (m, 2H), 5.08 (dd, J = 13.2, 5.1 Hz, 1H), 4.31 (d, J = 16.6 Hz, 1H), 4.18 (d, J = 16.6 Hz, 1H), 4.12 (s, 3H), 3.87 (s, 6H), 3.57 (s, 3H), 3.56 – 3.53 (m, 6H), 2.95 – 2.86 (m, 1H), 2.63 – 2.56 (m, 1H), 2.49 – 2.34 (m, 5H), 2.04 – 1.94 (m, 1H), 1.79 – 1.62 (m, 4H).
D422	679.25	^{1}H NMR (300 MHz, DMSO-d6) δ 11.99 (s, 1H), 10.99 (s, 1H), 9.05 – 8.75 (m, 1H, TFA), 7.51 (s, 1H), 7.41 (d, J = 8.8 Hz, 1H), 6.94 (s, 2H), 6.71 (d, J = 5.7 Hz, 2H), 6.30 (s, 1H), 5.08 (dd, J = 13.2, 5.1 Hz, 1H), 4.36 – 4.15 (m, 4H), 3.95 (s, 6H), 3.76 (s, 2H), 3.65 – 3.63 (m, 2H), 3.62 – 3.60 (m, 3H), 3.38 – 3.33 (m, 2H), 3.18 – 3.05 (m, 2H), 3.00 – 2.84 (m, 1H), 2.67 – 2.59 (m, 1H), 2.44 – 2.39 (m, 1H), 2.36 (s, 3H), 2.13 (d, J = 13.3 Hz, 2H), 2.01 (d, J = 11.3 Hz, 3H).
D423	614.35	^{1}H NMR (400 MHz, DMSO-d6) δ 7.53 (d, J = 8.5 Hz, 1H), 7.31 (d, J = 1.2 Hz, 1H), 7.05 (d, J = 8.3 Hz, 2H), 6.56 (s, 2H), 5.00 (dd, J = 13.3, 5.1 Hz, 1H), 4.39 – 4.15 (m, 2H), 3.77 (d, J = 18.2 Hz, 8H), 3.53 (s, 3H), 3.32 (t, J = 4.8 Hz, 4H), 2.94 – 2.81 (m, 1H), 2.79 – 2.67 (m, 4H), 2.65 – 2.55 (m, 1H), 2.43 – 2.28 (m, 4H), 2.03 (s, 3H), 2.01 – 1.92 (m, 1H).

Compound No.	LCMS	^{1}H NMR
D424	671.4	^{1}H NMR (300 MHz, DMSO-d6) δ 8.56 (s, 1H), 8.24 (s, 1H, FA), 7.77 (s, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.25 (s, 2H), 7.21 (d, J = 6.0 Hz, 1H), 7.15 (d, 1H), 5.05 (dd, J = 13.2, 5.0 Hz, 1H), 4.34 – 4.20 (m, 2H), 4.07 (s, 3H), 4.00 (d, J = 12.7 Hz, 1H), 3.86 (s, 6H), 3.83 – 3.77 (m, 1H), 3.28 – 3.14 (m, 4H), 3.06 – 2.96 (m, 2H), 2.91 – 2.79 (m, 1H), 2.66 – 2.55 (m, 1H), 2.43 – 2.20 (m, 1H), 2.00 (s, 1H), 1.26 (d, J = 6.1 Hz, 6H).
D425	676.35	^{1}H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 8.41 (d, J = 2.6 Hz, 1H), 8.19 (d, J = 6.8 Hz, 1H), 8.16 (d, J = 2.6 Hz, 1H, FA), 7.36 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 33.7 Hz, 3H), 6.72 – 6.64 (m, 2H), 5.13 – 5.04 (m, 1H), 4.31 (d, J = 16.5 Hz, 1H), 4.18 (d, J = 16.6 Hz, 1H), 3.87 (s, 6H), 3.60 (s, 3H), 3.54 (d, J = 15.6 Hz, 7H), 2.97 – 2.84 (m, 1H), 2.63 – 2.54 (m, 1H), 2.45 – 2.31 (m, 4H), 1.98 (d, J = 12.6 Hz, 1H), 1.71 (s, 4H).
D426	679.5	^{1}H NMR (300 MHz, DMSO-d6) δ 11.82 (s, 1H), 10.98 (s, 1H), 8.24 FA (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.20 – 7.06 (m, 2H), 6.76 – 6.54 (m, 4H), 5.09 (dd, J = 13.3, 5.0 Hz, 1H), 4.40 – 4.10 (m, 2H), 3.80 (s, 6H), 3.60 – 3.54 (m, 9H), 3.00 – 2.83 (m, 2H), 2.62 (s, 1H), 2.40 (s, 3H), 1.99 (s, 2H), 1.85 (s, 3H), 1.78 – 1.64 (m, 4H).
D427	614.35	^{1}H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 1.2 Hz, 1H), 7.25 (dd, J = 8.5, 2.4 Hz, 1H), 7.14 (d, J = 2.3 Hz, 1H), 6.59 – 6.52 (m, 2H), 5.09 (dd, J = 13.3, 5.1 Hz, 1H), 4.39 – 4.16 (m, 2H), 3.81 (s, 6H), 3.62 (s, 2H), 3.54 (s, 3H), 3.22 – 3.11 (m, 4H), 2.98 – 2.84 (m, 1H), 2.72 – 2.56 (m, 5H), 2.46 – 2.36 (m, 1H), 2.33 (s, 3H), 2.04 (s, 3H), 2.02 – 1.94 (m, 1H).
D428	666.35	^{1}H NMR (300 MHz, DMSO-d6) δ 10.97 (s, 1H), 8.36 (s, 1H), 8.15 (d, J = 0.9 Hz, 1H, FA), 7.89 (s, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.12 (s, 1H), 6.93 (s, 2H), 6.69 (d, J = 7.7 Hz, 2H), 5.08 (dd, J = 13.2, 5.1 Hz, 1H), 4.43 – 4.14 (m, 2H), 3.86 (s, 6H), 3.64 – 3.57 (m, 6H), 3.44 (s, 5H), 2.99 – 2.84 (m, 2H), 2.68 – 2.60 (m, 1H), 2.45 – 2.32 (m, 2H), 2.05 – 1.91 (m, 1H), 1.81 – 1.68 (m, 4H).
D429	627.35	^{1}H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 8.50 (d, J = 1.2 Hz, 1H), 8.14 (d, J = 1.1 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.18 (s, 2H), 6.68 (d, J = 7.7 Hz, 2H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.42 – 4.14 (m, 2H), 3.88 (s, 6H), 3.77 (s, 2H), 3.60 (s, 4H), 3.56 (s, 4H), 2.97 – 2.84 (m, 1H), 2.69 (s, 3H), 2.64 – 2.55 (m, 2H), 2.39 (td, J = 13.1, 4.4 Hz, 1H), 2.02 – 1.93 (m, 1H), 1.82 (s, 4H).

Compound No.	LCMS	^{1}H NMR
D430	654.3	^{1}H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 7.66 (d, J = 8.2 Hz, 1H), 7.53 (s, 1H), 6.82 (d, J = 2.1 Hz, 1H), 6.73 – 6.54 (m, 3H), 5.06 (dd, J = 12.8, 5.3 Hz, 1H), 4.14 – 3.94 (m, 5H), 3.85 (s, 6H), 3.49 – 3.46 (m, 5H), 3.14 – 2.97 (m, 2H), 2.96 – 2.70 (m, 2H), 2.68 – 2.58 (m, 1H), 2.36 – 2.17 (m, 2H), 2.14 – 1.95 (m, 7H).
D431	665.35	^{1}H NMR (300 MHz, DMSO-d6) δ 10.99 (s, 1H), 8.94 (s, 1H, TFA), 7.50 (d, J = 6.0 Hz, 1H), 7.41 (d, J = 8.9 Hz, 1H), 7.04 (d, J = 4.0 Hz, 1H), 6.92 (s, 2H), 6.87 (dd, J = 10.2, 5.1 Hz, 2H), 6.75 – 6.66 (m, 2H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.39 – 4.12 (m, 4H), 3.95 (s, 6H), 3.76 (s, 2H), 3.70 (s, 2H), 3.43 – 3.31 (m, 5H), 3.17 – 3.11 (m, 2H), 3.00 – 2.82 (m, 1H), 2.63 (s, 1H), 2.44 – 2.30 (m, 1H), 2.19 – 2.08 (m, 2H), 2.06 – 1.96 (m, 3H).
D432	664.3	^{1}H NMR (300 MHz, Methanol-d4) δ 8.30 (d, J = 2.6 Hz, 1H), 8.20 – 8.13 (m, 1H), 7.72 (d, J = 7.7 Hz, 1H), 7.10 – 6.61 (m, 3H), 6.26 (dd, J = 7.6, 2.0 Hz, 1H), 5.67 (d, J = 1.8 Hz, 1H), 5.25 (dd, J = 12.5, 5.3 Hz, 1H), 4.43 (s, 2H), 4.17 – 3.96 (m, 10H), 3.72 (s, 3H), 3.67 (s, 2H), 3.51 – 3.45 (m, 2H), 2.99 – 2.76 (m, 2H), 2.73 – 2.49 (m, 1H), 2.52 – 2.46 (m, 2H), 2.36 – 2.23 (m, 1H).
D433	666.25	^{1}H NMR (300 MHz, DMSO-d6) δ 14.27 (s, 1H), 10.98 (s, 1H), 8.24 (s, 1H, FA), 8.15 (s, 1H), 7.61 (s, 1H), 7.38 (d, J = 8.3 Hz, 1H), 6.90 (s, 2H), 6.74 – 6.64 (m, 2H), 5.08 (dd, J = 13.2, 5.1 Hz, 1H), 4.25 (dd, 2H), 3.90 (s, 6H), 3.74 (s, 2H), 3.61 (d, J = 6.9 Hz, 7H), 2.98 – 2.84 (m, 1H), 2.79 – 2.54 (m, 5H), 2.42 – 2.32 (m, 1H), 2.03 – 1.93 (m, 1H), 1.81 (s, 4H).
D434	666.25	^{1}H NMR (300 MHz, MeOD) δ 8.85 - 8.49 (m, 1H), 7.85 (d, J = 1.9 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.17 – 7.09 (m, 2H), 6.89 (d, J = 2.2 Hz, 1H), 6.81 (dd, J = 8.2, 2.3 Hz, 1H), 5.14 (dd, J = 13.2, 5.1 Hz, 1H), 4.49 – 4.31 (m, 4H), 4.04 (s, 6H), 3.85 (s, 2H), 3.78 (s, 3H), 3.73 (s, 2H), 3.56 (d, J = 12.7 Hz, 2H), 3.24 (t, J = 11.9, 11.9 Hz, 2H), 3.02 - 2.86 (m, 1H), 2.85 – 2.72 (m, 1H), 2.59 – 2.41 (m, 1H), 2.34 - 2.22 (m, 2H), 2.21 – 2.04 (m, 3H).
D435	665.35	^{1}H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1H), 8.23 (s, 1H, FA), 7.61 (d, J = 3.2 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 7.7 Hz, 1H), 7.03 (d, J = 3.2 Hz, 1H), 6.88 (d, J = 7.7 Hz, 1H), 6.77 (s, 2H), 6.70 – 6.67 (m, 2H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.34 – 4.14 (m, 2H), 3.85 (s, 6H), 3.56 (s, 3H), 3.51 – 3.50 (m, 6H), 2.98 – 2.83 (m, 1H), 2.68 – 2.57 (m, 1H), 2.48 – 2.22 (m, 5H), 2.06 – 1.91 (m, 1H), 1.72 – 1.70 (m, 4H).

Compound No.	LCMS	^{1}H NMR
D436	614.3	^{1}H NMR (300 MHz, Methanol-d4) δ 7.71 (d, J = 8.5 Hz, 1H), 7.60 (s, 1H), 7.39 (d, J = 2.2 Hz, 1H), 7.27 (dd, J = 8.6, 2.3 Hz, 1H), 6.65 (s, 2H), 6.52 (s, 1H), 5.09 (dd, J = 12.3, 5.4 Hz, 1H), 3.91 (d, 8H), 3.58 (d, J = 18.3 Hz, 7H), 2.99 – 2.89 (m, 4H), 2.87 – 2.66 (m, 3H), 2.21 (s, 3H), 2.18 – 2.07 (m, 1H).
D437	693.4	^{1}H NMR (300 MHz, Methanol-d4) 7.41 (d, J = 8.2 Hz, 1H), 6.99 – 6.78 (m, 2H), 6.70 (s, 2H), 5.86 (s, 1H), 5.29 – 5.05 (m, 1H), 4.52 – 4.29 (m, 2H), 4.22 – 3.98 (m, 5H), 3.91 (s, 6H), 3.74 (s, 4H), 3.21 – 2.72 (m, 6H), 2.66 – 2.40 (m, 1H), 2.35 (s, 3H), 2.27 – 2.15 (m, 4H), 2.15 – 1.94 (m, 4H).
D438	595.3	^{1}H NMR (400 MHz, DMSO-d6 with a drop of D_2O) δ 8.15 (s, 1H, FA), 8.05 (d, J = 2.7 Hz, 1H), 7.82 (dd, J = 2.7, 1.3 Hz, 1H), 7.70 – 7.59 (m, 3H), 6.82 (s, 2H), 5.10 (dd, J = 13.3, 5.1 Hz, 1H), 4.42 (dd, 2H), 3.86 (s, 6H), 3.66 (s, 2H), 3.65 – 3.56 (m, 2H), 3.53 (s, 3H), 3.34 (s, 1H), 3.28 (d, J = 7.7 Hz, 2H), 2.97 – 2.84 (m, 1H), 2.66 – 2.56 (m, 1H), 2.44 – 2.35 (m, 1H), 2.10 (s, 3H), 2.07 – 1.95 (m, 1H).
D439	631.3	^{1}H NMR (300 MHz, Methanol-d4) δ 8.25 (s, 1H), 8.11 (s, 1H), 7.79 (d, J = 1.2 Hz, 1H), 7.67 (dd, J = 7.9, 1.5 Hz, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.09 – 6.61 (m, 3H), 5.17 (dd, J = 13.3, 5.2 Hz, 1H), 4.61 – 4.42 (m, 2H), 4.23 (s, 2H), 4.16 (t, J = 8.8 Hz, 2H), 4.00 (s, 6H), 3.97 – 3.85 (m, 2H), 3.77 – 3.63 (m, 4H), 3.03 – 2.75 (m, 2H), 2.61 – 2.40 (m, 1H), 2.29 – 2.13 (m, 1H).
D440	595.3	^{1}H NMR (400 MHz, Methanol-d4) δ 7.99 – 7.90 (m, 1H), 7.84 – 7.74 (m, 2H), 7.72 – 7.49 (m, 2H), 6.91 (d, J = 2.6 Hz, 2H), 5.20 – 5.11 (m, 1H), 4.55 – 4.37 (m, 6H), 4.34 – 4.22 (m, 2H), 4.00 (s, 6H), 3.95 – 3.84 (m, 1H), 3.66 (d, J = 6.7 Hz, 3H), 2.98 – 2.85 (m, 1H), 2.81 (s, 1H), 2.54 – 2.40 (m, 1H), 2.20 (d, J = 5.0 Hz, 4H).
D441	631.5	^{1}H NMR (400 MHz, Methanol-d4) δ 8.32 – 8.07 (m, 2H), 7.77 (d, J = 7.8 Hz, 1H), 7.70 – 7.53 (m, 2H), 7.07 – 6.67 (m, 3H), 5.15 (dd, J = 13.3, 5.1 Hz, 1H), 4.62 – 4.39 (m, 6H), 4.35 – 4.23 (m, 2H), 4.17 – 3.83 (m, 7H), 3.68 (s, 3H), 2.98 – 2.84 (m, 1H), 2.78 (d, J = 17.4 Hz, 1H), 2.48 (qd, J = 13.1, 4.7 Hz, 1H), 2.22 – 2.14 (m, 1H).
D442	609.5	^{1}H NMR (300 MHz, Methanol-d4) δ 8.56 (s, FA, 1H), 7.96 (d, 1H), 7.85 -7.79 (m, 2H), 7.71 - 7.63 (m, 1H), 7.58 (d,1H), 6.90 (s, 2H), 5.23 - 5.11 (m, 1H), 4.52 (d, 2H), 4.41 (s, 2H), 4.00 (s, 6H), 3.69 (s, 3H), 3.63–3.50 (m, 2H), 3.48–3.36 (m, 3H), 3.00–2.73 (m, 2H), 2.61–2.39 (m, 2H), 2.31 - 2.11 (m, 5H).

Compound No.	LCMS	^{1}H NMR
D443	623.35	^{1}H NMR (300 MHz, DMSO-d6) δ 11.01 (s, 1H), 8.06 (d, J = 2.7 Hz, 1H), 7.89 – 7.75 (m, 1H), 7.69 – 7.54 (m, 3H), 6.82 (s, 2H), 5.11 (dd, J = 13.2, 5.1 Hz, 1H), 4.61 – 4.25 (m, 2H), 3.86 (s, 6H), 3.58 (s, 2H), 3.54 (s, 3H), 3.02 – 2.84 (m, 1H), 2.84 – 2.70 (m, 2H), 2.67 – 2.53 (m, 2H), 2.48 – 2.35 (m, 1H), 2.33 – 2.21 (m, 2H), 2.10 (s, 3H), 2.06 – 1.95 (m, 1H), 1.92 – 1.79 (m, 2H), 1.69 – 1.53 (m, 2H).
D444	659.3	^{1}H NMR (300 MHz, DMSO-d6) δ 11.01 (s, 1H), 8.40 (.1.0 FA, d, J = 2.6 Hz, 1H), 8.26 – 8.05 (m, 2H), 7.75 – 7.51 (m, 3H), 7.20 – 6.69 (m, 3H), 5.11 (dd, J = 13.2, 5.1 Hz, 1H), 4.61 – 4.21 (m, 2H), 3.87 (s, 6H), 3.60 (s, 3H), 3.56 (s, 2H), 3.00 – 2.83 (m, 1H), 2.82 – 2.69 (m, 2H), 2.68 – 2.53 (m, 2H), 2.48 – 2.32 (m, 1H), 2.32 – 2.18 (m, 2H), 2.08 – 1.93 (m, 1H), 1.84 (d, 2H), 1.70 – 1.49 (m, 2H).
D445	707.4	^{1}H NMR (300 MHz, DMSO-d6) δ 11.58 (s, 1H), 11.08 (s, 1H), 8.28 – 8.13 (m, 1H, FA), 7.64 (d, J = 8.3 Hz, 1H), 6.99 (d, J = 2.6 Hz, 1H), 6.77 (d, J = 2.1 Hz, 1H), 6.64 (dd, J = 8.4, 2.2 Hz, 1H), 6.51 (s, 2H), 5.06 (dd, J = 12.7, 5.2 Hz, 1H), 3.74 (d, J = 8.4 Hz, 10H), 3.58 (d, J = 3.6 Hz, 5H), 2.94 – 2.83 (m, 1H), 2.65 – 2.55 (m, 3H), 2.47 – 2.38 (m, 3H), 2.17 (s, 3H), 2.07 – 1.97 (m, 1H), 1.79 – 1.67 (m, 4H), 1.51 (s, 3H).
D446	707.4	^{1}H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 10.85 (s, 1H), 7.65 (d, J = 8.3 Hz, 1H), 6.79 (d, J = 2.1 Hz, 1H), 6.70 – 6.62 (m, 1H), 6.59 (s, 2H), 5.83 (s, 1H), 5.06 (dd, J = 12.7, 5.3 Hz, 1H), 4.00 (s, 3H), 3.89 – 3.72 (m, 10H), 3.68 (s, 2H), 3.00 – 2.78 (m, 1H), 2.70 – 2.53 (m, 6H), 2.27 (s, 3H), 2.14 (s, 3H), 2.09 – 1.96 (m, 1H), 1.81 (s, 4H).
D447	666.4	^{1}H NMR (300 MHz, Methanol-d4) δ 8.52 (br s, 0.2H, FA), 7.84 (d, J = 1.2 Hz, 1H), 7.64 (s, 1H), 7.48 (d, J = 8.2 Hz, 1H), 7.30 (s, 1H), 7.10 (s, 2H), 6.95 (d, J = 2.2 Hz, 1H), 6.87 (dd, J = 8.2, 2.2 Hz, 1H), 5.20 (dd, 1H), 4.47 (d, J = 5.4 Hz, 2H), 4.41 (s, 2H), 4.07 (s, 6H), 3.86 – 3.71 (m, 8H), 3.38 – 3.28 (m, 3H) 3.18 – 2.80 (m, 2H), 2.62 – 2.54 (m, 1H), 2.36 – 2.10 (m, 5H).
D448	599.35	^{1}H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 8.19 (s, 1H, FA), 8.06 (d, J = 2.6 Hz, 1H), 7.81 (d, J = 2.3 Hz, 1H), 7.54 (s, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.44 (dd, J = 7.8, 1.6 Hz, 1H), 6.81 (s, 2H), 5.10 (dd, J = 13.3, 5.2 Hz, 1H), 4.46 – 4.23 (m, 2H), 3.84 (s, 6H), 3.72 (d, J = 4.9 Hz, 2H), 3.53 (s, 3H), 3.46 (s, 2H), 3.07 (s, 2H), 2.96 – 2.85 (m, 1H), 2.64 – 2.56 (m, 4H), 2.39 (dd, J = 13.3, 4.7 Hz, 1H), 2.10 (s, 3H), 2.03 – 1.96 (m, 1H), 1.79 (q, J = 7.5 Hz, 2H).

Compound No.	LCMS	^{1}H NMR
D449	585.35	^{1}H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 8.19 (s, 1H, FA), 8.06 (d, J = 2.6 Hz, 1H), 7.81 (d, J = 2.3 Hz, 1H), 7.54 (s, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.44 (dd, J = 7.8, 1.6 Hz, 1H), 6.81 (s, 2H), 5.10 (dd, J = 13.3, 5.2 Hz, 1H), 4.46 – 4.23 (m, 2H), 3.84 (s, 6H), 3.72 (d, J = 4.9 Hz, 2H), 3.53 (s, 3H), 3.46 (s, 2H), 3.07 (s, 2H), 2.96 – 2.85 (m, 1H), 2.64 – 2.56 (m, 4H), 2.39 (dd, J = 13.3, 4.7 Hz, 1H), 2.10 (s, 3H), 2.03 – 1.96 (m, 1H), 1.79 (q, J = 7.5 Hz, 2H).
D450	609.30	^{1}H NMR (400 MHz, DMSO-d6) δ 8.22 (s, 1H, FA), 8.04 (d, J = 2.7 Hz, 1H), 7.86 – 7.80 (m, 1H), 7.70 – 7.57 (m, 3H), 6.82 (s, 2H), 5.09 (dd, J = 13.3, 5.1 Hz, 1H), 4.55 – 4.31 (m, 2H), 3.86 (s, 6H), 3.66 (s, 2H), 3.54 (s, 3H), 3.43 (d, J = 6.8 Hz, 2H), 3.27 (d, J = 6.8 Hz, 2H), 2.99 – 2.81 (m, 1H), 2.74 – 2.58 (m, 1H), 2.46 – 2.32 (m, 1H), 2.10 (s, 3H), 2.07 – 1.97 (m, 1H), 1.51 (s, 3H).
D451	538.25	^{1}H NMR (300 MHz, DMSO-d6) δ 11.02 (s, 1H), 8.48 (d, J = 2.4 Hz, 1H), 8.22 (s, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.54 – 7.45 (m, 2H), 7.18 – 6.74 (m, 3H), 5.14 (dd, J = 13.2, 5.0 Hz, 1H), 4.43 (dd, 2H), 3.79 (s, 6H), 3.62 (s, 3H), 3.04 – 2.91 (m, 1H), 2.67 – 2.59 (m, 1H), 2.47 – 2.34 (m, 1H), 2.07 – 1.97 (m, 1H).
D452	600.25	^{1}H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.39 (s, 1H), 8.16 (d, J = 2.7 Hz, 1H, FA), 7.88 (dd, J = 2.7, 1.3 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.31 (dd, J = 8.4, 2.4 Hz, 1H), 7.26 (d, J = 2.3 Hz, 1H), 6.96 (s, 2H), 5.10 (dd, J = 13.3, 5.1 Hz, 1H), 4.36 (d, J = 16.9 Hz, 1H), 4.31 (d, J = 4.2 Hz, 2H), 4.23 (d, J = 16.9 Hz, 1H), 3.96 (s, 6H), 3.88 (d, J = 13.1 Hz, 2H), 3.55 (s, 3H), 3.47 (d, J = 12.0 Hz, 2H), 3.33 – 3.20 (m, 2H), 3.12 (t, J = 12.4 Hz, 2H), 2.98 – 2.84 (m, 1H), 2.60 (d, J = 17.7 Hz, 1H), 2.43 – 2.32 (m, 1H), 2.11 (s, 3H), 2.04 – 1.94 (m, 1H).
D453	609.50	^{1}H NMR (400 MHz, DMSO-d6) δ 11.00 (s, 1H), 8.25 (s, 1H, FA salt), 8.05 (d, J = 2.7 Hz, 1H), 7.82 (d, J = 2.6 Hz, 1H), 7.63 – 7.56 (m, 3H), 6.82 (s, 2H), 5.10 (dd, J = 13.3, 5.2 Hz, 1H), 4.37 (dd, 2H), 3.86 (s, 6H), 3.62 – 3.58 (m, 2H), 3.53 (s, 3H), 3.15 – 3.13 (m, 1H), 2.96 – 2.89 (m, 2H), 2.86 – 2.83 (m, 2H), 2.62 – 2.58 (m, 1H), 2.41 – 2.35 (m, 1H), 2.09 (s, 3H), 2.03 – 1.98 (m, 1H), 1.11 (d, J = 5.9 Hz, 3H).

Compound No.	LCMS	^{1}H NMR
D454	706.4	^{1}H NMR (400 MHz, DMSO-d6) δ 10.89 (s, 1H), 8.28 (s, 1H), 7.82 (s, 1H), 7.30 (d, J = 8.0 Hz, 1H), 6.96 (s, 1H), 6.85 (s, 2H), 6.62 (d, J = 8.2 Hz, 2H), 5.73–5.62 (m, 1H), 5.59–5.48 (m, 1H), 5.00 (dd, J = 13.2, 5.1 Hz, 1H), 4.36 (d, J = 6.0 Hz, 2H), 4.28–4.07 (m, 2H), 3.79 (s, 6H), 3.61–3.49 (m, 8H), 2.91–2.77 (m, 1H), 2.54 (d, J = 3.7 Hz, 3H), 2.37–2.23 (m, 1H), 1.96–1.86 (m, 1H), 1.68 (t, J = 6.6 Hz, 4H), 1.60 (d, J = 6.3 Hz, 3H).
D455	593.25	^{1}H NMR (400 MHz, Methanol-d4) δ 8.16 (d, J = 2.6 Hz, 1H), 8.11 – 8.05 (m, 1H), 7.38 (d, J = 8.3 Hz, 1H), 6.99 – 6.78 (m, 3H), 6.76 (s, 2H), 5.12 (dd, J = 13.3, 5.1 Hz, 1H), 4.45 – 4.31 (m, 5H), 3.99 (q, J = 5.5, 4.1 Hz, 2H), 3.82 (s, 6H), 3.67 (s, 3H), 2.97 – 2.83 (m, 1H), 2.83 – 2.72 (m, 1H), 2.56 – 2.40 (m, 1H), 2.21 – 2.11 (m, 1H).
D456	666.5	^{1}H NMR (400 MHz, Methanol-d4) δ 8.52 (s, 0.67H, FA), 7.93 (d, J = 2.2 Hz, 1H), 7.39 (d, J = 8.2 Hz, 1H), 7.28 (s, 1H), 7.22 – 7.15 (m, 3H), 6.86 (d, J = 2.2 Hz, 1H), 6.81 – 6.74 (m, 1H), 5.16 – 5.07 (m, 1H), 4.45 – 4.30 (m, 4H), 3.97 (s, 6H), 3.75 (s, 4H), 3.63 (s, 3H),3.39 – 3.36 (m, 2H), 3.28 – 3.21 (m, 2H), 2.96 – 2.83 (m, 1H), 2.82 – 2.72 (m, 1H), 2.56 – 2.40 (m, 1H), 2.19 – 2.02 (m, 5H).
D457	597.35	^{1}H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 9.67 - 9.52 (m, 1H, TFA salt), 8.17 – 8.10 (m, 1H), 7.88 – 7.78 (m, 2H), 7.71 – 7.64 (m, 1H), 7.62 – 7.56 (m, 1H), 6.98 – 6.91 (m, 2H), 6.71 – 6.62 (m, 5.7 Hz, 2H), 5.17 – 5.06 (m, 1H), 4.49 – 4.41 (m, 1H), 4.41 – 4.27 (m, 3H), 4.27 – 4.22 (m, 2H), 4.16 – 4.15 (m, 2H), 3.95 (s, 6H), 3.54 (s, 3H), 2.97 – 2.85 (m, 1H), 2.61 (d, J = 17.1 Hz, 1H), 2.43 – 2.35 (m, 2H), 2.10 (s, 3H), 2.04 – 1.97 (m, 2H).
D458	613.35	^{1}H NMR (400 MHz, DMSO-d6) δ 8.08 (s, 1H), 7.89 (s, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 7.9 Hz, 1H), 6.92 (s, 2H), 5.09 (dd, J = 13.3, 5.1 Hz, 1H), 4.86 – 4.57 (m, 4H), 4.57 – 4.45 (m, 3H), 4.40 (d, J = 18.1 Hz, 1H), 3.94 (s, 6H), 3.54 (s, 3H), 2.97 – 2.83 (m, 1H), 2.71 – 2.59 (m, 1H), 2.47 – 2.33 (m, 1H), 2.16 – 2.01 (s, 4H).
D459	526.2	^{1}H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 7.87 (d, J = 2.7 Hz, 1H), 7.69 (dd, J = 2.7, 1.3 Hz, 1H), 7.46 (t, J = 8.7 Hz, 3H), 7.35 (dd, J = 8.4, 2.4 Hz, 1H), 7.25 (d, J = 2.4 Hz, 1H), 7.05 (d, J = 8.8 Hz, 2H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.46 – 4.19 (m, 2H), 3.50 (s, 3H), 3.35 (s, 8H), 2.98 – 2.85 (m, 1H), 2.60 (d, J = 17.0 Hz, 1H), 2.43 – 2.32 (m, 1H), 2.07 (s, 3H), 2.04 – 1.95 (m, 1H).

Compound No.	LCMS	^{1}H NMR
D460	540.25	^{1}H NMR (400 MHz, DMSO-d6) δ 7.99 (d, J = 2.7 Hz, 1H), 7.75 (d, J = 2.6 Hz, 1H), 7.57 (d, J = 7.7 Hz, 2H), 7.43 (dd, J = 11.4, 7.8 Hz, 3H), 7.27 (dd, J = 8.5, 2.4 Hz, 1H), 7.18 (s, 1H), 5.09 (dd, J = 13.3, 5.1 Hz, 1H), 4.44 – 4.17 (m, 2H), 3.66 (s, 3H), 3.52 (s, 3H), 3.24 (s, 3H), 2.97 – 2.84 (m, 1H), 2.77 – 2.64 (m, 1H), 2.67 (s, 4H), 2.45 – 2.33 (m, 1H), 2.09 (s, 3H), 2.04 – 1.95 (m, 1H).
D461	641.25	^{1}H NMR (300 MHz, DMSO-d6) δ 11.02 (s, 1H), 9.00 (s, 1H, TFA), 8.49 (s, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.32 (s, 2H), 6.77 (dt, J = 4.0, 2.0 Hz, 2H), 5.14 (dd, J = 13.2, 5.1 Hz, 1H), 4.46 – 4.21 (m, 4H), 4.02 (s, 6H), 3.81 (s, 2H), 3.71 (s, 2H), 3.62 (s, 3H), 3.43 (d, J = 12.6 Hz, 2H), 3.18 (t, J = 11.4 Hz, 2H), 3.07 – 2.89 (m, 1H), 2.67 (d, J = 17.2 Hz, 1H), 2.56 – 2.31 (m, 4H), 2.19 (d, J = 14.0 Hz, 2H), 2.12 – 1.98 (m, 3H), 0.08 (s, 1H).
D462	696.5	^{1}H NMR (400 MHz, DMSO-d6 with a drop of D2O) δ 8.75 (s, 1H), 8.26 (s, 1H, FA), 7.89 (s, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.24 (s, 2H), 6.74 – 6.67 (m, 2H), 5.05 (dd, J = 13.3, 5.1 Hz, 1H), 4.37 – 4.15 (m, 5H), 3.88 (s, 6H), 3.80 (s, 2H), 3.61 (s, 4H), 3.55 (s, 3H), 2.95 – 2.82 (m, 1H), 2.81 – 2.57 (m, 5H), 2.45 – 2.31 (m, 1H), 2.06 – 1.95 (m, 1H), 1.85 (t, J = 5.5 Hz, 4H).
D463	654.35	^{1}H NMR (400 MHz, Methanol-d4) δ 8.90 (s, 1H), 8.28 (d, J = 1.1 Hz, 1H), 7.87 (d, J = 1.7 Hz, 1H), 7.73 (dd, J = 7.9, 1.7 Hz, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.48 (d, J = 8.5 Hz, 1H), 7.39 – 7.31 (m, 2H), 7.15 (s, 1H), 5.95 – 5.80 (m, 1H), 5.71 – 5.54 (m, 1H), 5.13 (dd, J = 13.3, 5.1 Hz, 1H), 4.52 (d, J = 6.4 Hz, 2H), 4.48 – 4.34 (m, 2H), 4.01 (t, J = 5.3 Hz, 2H), 3.59 – 3.52 (m, 2H), 3.42 – 3.38 (m, 2H), 3.36 – 3.32 (m, 1H), 3.28 – 3.20 (m, 1H), 2.95 – 2.83 (m, 1H), 2.82 – 2.73 (m, 1H), 2.56 – 2.42 (m, 1H), 2.23 – 2.13 (m, 1H), 1.73 (dd, J = 6.5, 1.6 Hz, 3H).
D464	704.1	^{1}H NMR (300 MHz, DMSO-d6) δ 11.04 (s, 1H), 8.22 (s, 1H), 8.08 – 7.95 (m, 3H), 7.92 (s, 1H), 7.79 (s, 1H), 7.67 (s, 2H), 7.05 (s, 1H), 5.82 – 5.66 (m, 1H), 5.66 – 5.51 (m, 1H), 5.18 (dd, J = 13.2, 5.1 Hz, 1H), 4.68 – 4.46 (m, 3H), 4.41 (d, J = 6.0 Hz, 2H), 3.51 (s, 2H), 3.02 – 2.84 (m, 8H), 2.62 (d, J = 17.0 Hz, 1H), 2.49 – 2.34 (m, 1H), 2.05 (dd, J = 12.7, 6.4 Hz, 1H), 1.65 (dd, J = 6.3, 1.4 Hz, 3H).

Compound No.	LCMS	^{1}H NMR
D465	680.4	^{1}H NMR (400 MHz, Methanol-d4) δ 8.06 (s, 1H), 7.86 (s, 1H), 7.68 – 7.60 (m, 2H), 7.52 (dd, J = 7.9, 1.8 Hz, 1H), 7.27 (d, J = 8.2 Hz, 1H), 6.79–6.73 (m, 2H), 6.67 (dd, J = 8.2, 2.3 Hz, 1H), 5.82 – 5.68 (m, 1H), 5.61 – 5.47 (m, 1H), 5.02 (dd, J = 13.3, 5.2 Hz, 1H), 4.39 (d, J = 6.3 Hz, 2H), 4.34 – 4.20 (m, 2H), 3.71 (s, 2H), 3.59 (s, 4H), 2.87 – 2.74 (m, 1H), 2.72 – 2.65 (m, 1H), 2.62 – 2.51 (m, 4H), 2.45 – 2.31 (m, 1H), 2.10 – 2.03 (m, 1H), 1.87 – 1.81 (m, 4H), 1.63 (dd, J = 6.5, 1.5 Hz, 3H).
D466	640.4	^{1}H NMR (300 MHz, DMSO-d6) δ 11.05 (s, 1H), 8.32 (s, 1H), 8.02 – 7.76 (m, 4H), 7.61 – 7.49 (m, 1H), 7.43 – 7.27 (m, 2H), 7.16 (s, 1H), 5.90 – 5.76 (m, 1H), 5.74 – 5.60 (m, 1H), 5.18 (dd, J = 13.2, 5.1 Hz, 1H), 4.88 – 4.57 (m, 1H), 4.54 – 4.38 (m, 3H), 4.36 – 4.24 (m, 1H), 4.10 – 3.56 (m, 3H), 3.32 – 3.14 (m, 3H), 3.07 – 2.90 (m, 2H), 2.75 – 2.62 (m, 3H), 2.52 – 2.38 (m, 1H), 2.14 – 2.04 (m, 1H), 1.78 – 1.70 (m, 3H).
D467	719.45	^{1}H NMR (400 MHz, DMSO-d6) δ 11.18 (d, J = 6.1 Hz, 1H), 10.96 (s, 1H), 8.94 (s, 1H, TFA), 7.40 (d, J = 8.9 Hz, 1H), 7.11 (s, 1H), 6.89 (s, 2H), 6.70 (h, J = 2.3 Hz, 2H), 6.35 (s, 1H), 5.67 – 5.55 (m, 1H), 5.45 – 5.29 (m, 1H), 5.15 (d, J = 5.5 Hz, 2H), 5.07 (dd, J = 13.2, 5.1 Hz, 1H), 4.32 (d, J = 16.7 Hz, 1H), 4.25 (d, J = 4.6 Hz, 2H), 4.19 (d, J = 16.6 Hz, 1H), 3.93 (s, 6H), 3.75 (s, 2H), 3.64 (s, 2H), 3.41 – 3.33 (m, 2H), 3.11 (q, J = 11.1 Hz, 2H), 2.90 (ddd, J = 17.5, 13.4, 5.4 Hz, 1H), 2.70 – 2.52 (m, 1H), 2.39 (dd, J = 13.2, 8.5 Hz, 1H), 2.34 (s, 3H), 2.12 (d, J = 13.9 Hz, 2H), 2.04 – 1.94 (m, 3H), 1.62 (dd, J = 6.6, 1.6 Hz, 3H).
D468	679.5	^{1}H NMR (400 MHz, DMSO-d6) δ 11.19 (d, J = 6.2 Hz, 1H), 10.98 (s, 1H), 9.42 (s, 1H, TFA), 7.50 (d, J = 8.4 Hz, 1H), 7.32 (dd, J = 8.4, 2.4 Hz, 1H), 7.29 – 7.20 (m, 1H), 7.12 (d, J = 6.0 Hz, 1H), 6.90 (s, 2H), 6.36 (s, 1H), 5.66 – 5.54 (m, 1H), 5.45 – 5.29 (m, 1H), 5.15 (d, J = 5.6 Hz, 1H), 5.10 (dd, J = 13.3, 5.1 Hz, 1H), 4.36 (d, J = 16.8 Hz, 3H), 4.23 (d, J = 16.9 Hz, 1H), 3.94 (s, 6H), 3.89 (d, J = 12.9 Hz, 2H), 3.74 (d, J = 7.0 Hz, 1H), 3.54 – 3.46 (m, 2H), 3.29 (d, J = 11.7 Hz, 2H), 3.14 (t, J = 12.1 Hz, 2H), 2.91 (ddd, J = 17.6, 13.6, 5.4 Hz, 1H), 2.60 (d, J = 17.0 Hz, 1H), 2.46 – 2.33 (m, 1H), 2.34 (s, 3H), 2.03 – 1.95 (m, 1H), 1.81 – 1.59 (m, 3H).

Compound No.	LCMS	^{1}H NMR
D469	654.25	^{1}H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1H), 8.35 (s, 1H), 7.88 (s, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.29 – 7.20 (m, 1H), 7.20 – 7.06 (m, 2H), 6.92 (s, 2H), 5.09 (dd, J = 13.3, 5.1 Hz, 1H), 4.37 – 4.15 (m, 2H), 3.86 (s, 6H), 3.66 – 3.51 (m, 2H), 3.43 (s, 3H), 3.11 – 2.85 (m, 5H), 2.70 – 2.55 (m, 3H), 2.43 – 2.31 (m, 1H), 2.05 – 1.93 (m, 1H), 1.39 – 1.14 (m, 6H).
D470	666.735	
D471	666.45	^{1}H NMR (300 MHz, Methanol-d4) δ 9.62 (s, 1H), 8.72 (d, J = 6.3 Hz, 1H), 8.15 (d, J = 7.0 Hz, 1H), 8.05 (s, 1H), 7.93 (d, J = 6.3 Hz, 1H), 7.36 (d, J = 2.4 Hz, 1H), 6.90 (s, 2H), 6.79 (dd, J = 7.1, 2.4 Hz, 1H), 4.96 (d, J = 9.1 Hz, 1H), 4.47 (s, 2H), 4.27 (s, 2H), 4.15 (s, 2H), 3.99 (s, 6H), 3.76 (s, 3H), 3.63 (d, J = 13.1 Hz, 2H), 3.25 (t, J = 12.2 Hz, 2H), 2.94 – 2.70 (m, 2H), 2.27 (dt, J = 28.7, 13.5 Hz, 6H).
D472	667.20	^{1}H NMR (300 MHz, Methanol-d4) δ 9.55 (d, J = 0.8 Hz, 1H), 8.70 (d, J = 5.8 Hz, 1H), 8.56 (d, J = 5.0 Hz, 1H), 7.77 (s, 1H), 7.64 (d, J = 5.8, 0.9 Hz, 1H), 7.28 (d, J = 4.9 Hz, 1H), 6.85 (s, 2H), 4.82 (dd, J = 12.6, 5.4 Hz, 1H), 4.20 (s, 2H), 4.06 – 3.91 (m, 10H), 3.72 (s, 3H), 3.06 (d, J = 27.6 Hz, 4H), 2.95 – 2.65 (m, 2H), 2.43 – 2.27 (m, 1H), 2.20 (s, 1H), 2.14 – 1.99 (m, 4H).
D473	667.20	^{1}H NMR (400 MHz, DMSO-d6) δ 10.93 (s, 1H), 9.48 (s, 1H), 9.02 (d, J = 15.8 Hz, 1H), 8.73 (dd, J = 16.7, 7.0 Hz, 2H), 8.40 (s, 1H), 8.10 (s, 1H), 7.91 (s, 1H), 7.60 (d, J = 5.7 Hz, 1H), 6.88 (s, 2H), 4.84 – 4.73 (m, 1H), 4.30 (d, J = 4.6 Hz, 2H), 4.02 (s, 2H), 3.91 (s, 8H), 3.62 (s, 3H), 3.40 (d, J = 12.2 Hz, 2H), 3.21 – 3.02 (m, 2H), 2.82 (s, 1H), 2.55 (d, J = 3.7 Hz, 1H), 2.25 – 2.11 (m, 3H), 2.08 – 1.91 (m, 3H).
D474	677.45	^{1}H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.45 (s, 1H), 8.74 (d, J = 5.7 Hz, 1H), 7.89 (s, 1H), 7.59 (d, J = 5.6 Hz, 1H), 7.38 (d, J = 8.1 Hz, 1H), 6.76 (s, 2H), 6.70–6.61 (m, 2H), 4.80–4.67 (m, 1H), 4.33 (s, 2H), 3.83 (s, 6H), 3.67–3.53 (m, 9H), 3.03–2.88 (m, 2H), 2.78–2.64 (m, 2H), 2.60–2.53 (m, 4H), 1.82–1.69 (m, 4H).
D475	748.35	^{1}H NMR (400 MHz, Methanol-d4) δ 7.42 (d, J = 8.2 Hz, 1H), 7.21 (s, 1H), 7.03 (d, J = 3.2 Hz, 1H), 6.90 – 6.85 (m, 3H), 6.82 – 6.78 (m, 2H), 5.14 (dd, J = 13.2, 5.1 Hz, 1H), 4.64 – 4.49 (m, 2H), 4.45 – 4.34 (m, 4H), 4.25 – 4.13 (m, 2H), 3.97 (s, 6H), 3.87 – 3.71 (m, 4H), 3.66 (s, 3H), 3.62 – 3.46 (m, 5H), 3.44 – 3.38 (m, 4H), 3.16 – 3.05 (m, 1H), 2.98 – 2.86 (m, 1H), 2.85 – 2.75 (m, 1H), 2.56 – 2.42 (m, 1H), 2.32 – 2.06 (m, 5H).

Compound No.	LCMS	^{1}H NMR
D476	693.2	^{1}H NMR (400 MHz, DMSO-d6) δ 11.90 (s, 1H), 11.08 (s, 1H), 8.25 (s, 1H, FA), 7.63 (d, J = 8.3 Hz, 1H), 7.43 (s, 1H), 6.84 – 6.75 (m, 3H), 6.65 (dd, J = 8.5, 2.2 Hz, 1H), 6.29 (s, 1H), 5.05 (dd, J = 12.9, 5.4 Hz, 1H), 3.84 (s, 6H), 3.73 (s, 4H), 3.58 (s, 3H), 3.52 (s, 2H), 2.94 – 2.85 (m, 1H), 2.62 – 2.55 (m, 2H), 2.44 – 2.37 (m, 3H), 2.37 – 2.31 (m, 4H), 2.06 – 1.96 (m, 1H), 1.73 (t, J = 5.2 Hz, 4H).

Example 85 – Preparation of Compounds DD11-DD16

In analogy to the procedures described in the examples above, compounds DD11-DD16 were prepared using the appropriate starting materials.

Compound No.	LCMS	^{1}H NMR
DD11	785.35	^{1}H NMR (300 MHz, DMSO) δ 11.13 (s, 1H), 8.20 (s, FA, 1H), 8.09 (d, J = 8.3 Hz, 1H), 7.88 - 7.80 (m, 2H), 7.74 (s, 1H), 7.56 - 7.48 (m, 1H), 7.47 - 7.39 (m, 1H), 7.39 - 7.35 (m, 1H), 7.34 – 7.23 (m, 2H), 6.73 (s, 2H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 5.06 - 4.91 (m, 1H), 3.81 (s, 6H), 3.70 (s, 2H), 3.58 - 3.50 (m, 1H), 3.00 - 2.81 (m, 4H), 2.66 – 2.53 (m, 1H), 2.49 – 2.38 (m, 4H), 2.35 - 2.18 (m, 6H), 2.14 – 1.99 (m, 3H), 1.86 - 1.75 (m, 2H), 1.72 - 1.61 (m, 4H), 1.60 - 1.49 (m, 3H), 1.27 - 1.07 (m, 2H).
DD12	519.45	^{1}H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.28 (t, J = 8.3 Hz, 1H), 6.72 – 6.64 (m, 4H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.35 – 4.12 (m, 2H), 3.79 (s, 6H), 3.64 (s, 2H), 3.57 (s, 4H), 2.98 – 2.84 (m, 1H), 2.64 – 2.55 (m, 5H), 2.45 – 2.33 (m, 1H), 2.02 – 1.94 (m, 1H), 1.79 – 1.72 (m, 4H).
DD13	676.35	^{1}H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 8.30 (dd, J = 8.2, 1.4 Hz, 1H), 7.71 (dd, J = 7.4, 1.4 Hz, 1H), 7.58 (t, J = 7.7 Hz, 1H), 7.45 (d, J = 7.7 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 6.69 (d, J = 4.3 Hz, 4H), 6.56 (d, J = 7.6 Hz, 1H), 5.09 (dd, J = 13.3, 5.1 Hz, 1H), 4.36 – 4.13 (m, 2H), 3.82 (s, 7H), 3.60 (d, J = 4.4 Hz, 7H), 3.53 (s, 3H), 2.98 – 2.84 (m, 1H), 2.64 – 2.55 (m, 2H), 2.38 (dd, J = 13.2, 4.6 Hz, 2H), 2.03 – 1.94 (m, 1H), 1.75 (t, J = 5.4 Hz, 4H).
DD14	479.30	^{1}H NMR (300 MHz, Methanol-d4) δ 8.52 (s, 0.48H, FA), 7.53 – 7.40 (m, 2H), 7.40 – 7.32 (m, 2H), 6.78 (d, J = 8.4 Hz, 2H),, 5.15 (dd, J = 13.3, 5.1 Hz, 1H), 4.52 – 4.35 (m, 2H), 4.27 (s, 2H), 3.93 (s, 6H), 3.62 – 3.39 (m, 4H), 3.30 – 3.18 (m, 4H), 3.12 – 2.73 (m, 2H), 2.62 – 2.41 (m, 1H), 2.26 – 2.12 (m, 1H).

Compound No.	LCMS	^{1}H NMR
DD15	652.30	^{1}H NMR (300 MHz, DMSO-d6) δ 12.70 (s, 1H), 10.97 (s, 1H), 8.22 – 8.13 (m, 3H), 7.36 (d, J = 8.0 Hz, 1H), 6.74 – 6.34 (m, 4H), 5.07 (dd, J = 13.6, 5.2 Hz, 1H), 4.34 – 4.14 (m, 2H), 3.88 (s, 6H), 3.65 – 3.57 (m, 6H), 2.94 – 2.86 (m, 1H), 2.67 – 2.59 (m, 1H), 2.47 – 2.26 (m, 5H), 2.04 – 1.93 (m, 1H), 1.84 – 1.59 (m, 4H).
DD16	518.15	^{1}H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 8.47 (d, J = 7.9 Hz, 1H), 7.78 (d, J = 7.5 Hz, 1H), 7.66 – 7.53 (m, 1H), 7.45 (m, J = 8.4 Hz, 1H), 7.37 – 7.08 (m, 2H), 6.74 (m, J = 7.5, 0.9 Hz, 1H), 5.11 (dd, J = 13.2, 5.1 Hz, 1H), 4.44 – 4.13 (m, 2H), 4.00 (s, 1H), 3.89 – 3.67 (m, 2H), 3.52 (s, 3H), 3.00-2.91 (m, 3H), 2.63 (m, 1H), 2.45 – 2.23 (m, 1H), 2.11 – 1.94 (m, 1H), 1.95 – 1.81 (m, 2H), 1.71-1.61 (m, 2H).

Example 86 – BRD9 bromodomain TR-FRET Competition Binding Assay

This example demonstrates the ability of the compounds of the disclosure to biochemically inhibit BRD9 bromodomain in a competition binding assay.

Procedure: His-Flag-BRD9 (P133-K239; Swiss Prot Q9H8M2; SEQ ID NO:1 mgsshhhhhhenlyfq/gdykddddkgslevlfqg/PAENESTPIQQLLEHFLRQLQRKDPHGFFAFPVTDAIAPGYSMII KHPMDFGTMKDKIVANEYKSVTEFKADFKLMCDNAMTYNRPDTVYYKLAKKILHAGFKMMSK) was cloned, expressed, purified, and then treated with TEV protease. Cleaved His tag was removed by purification. The binding of a biotinylated small molecule ligand of BRD9 was assessed via the LANCE® TR-FRET platform (PerkinElmer), and the compounds were assayed for inhibitory activity against this interaction.

A mixture of biotinylated-ligand and SureLight™ Allophycocyanin-Streptavidin (APC-SA, PerkinElmer AD0201) in 50 mM HEPES (pH 7.4), 50 mM NaCl, 1 mM TCEP (pH 7), 0.01% (v/v) Tween-20, 0.01% (w/v) bovine serum albumin was added to a white 384-well PerkinElmer Proxiplate Plus plate. DMSO or 3-fold serially diluted compounds were then added to the Proxiplate followed by addition of Flag-BRD9. After a 10-minute incubation at room temperature, Eu-W1024 anti-FLAG (PerkinElmer, AD0273) was added. The final reaction mixture that contained 3.75 nM biotinylated ligand, 3 nM Flag-BRD9, 7.5 nM SureLight™ Allophycocyanin-Streptavidin, and 0.2 nM Eu-W1024 anti-FLAG was incubated at room temperature for 90 minutes.

Results: The plates were then read on a PerkinElmer Envision plate reader to determine the ratio of emission at 665 nm over 615 nm. Data was normalized to a DMSO control (100%) and a no protein control (0%) and then fit to a four parameter, non-linear curve fit to calculate IC_{50} (μM) values as shown in Table 4. As shown by the results in Table 4, a number of compounds of the present disclosure exhibit an IC_{50} value of < 1 μM for BRD9 binding, indicating their affinity for targeting BRD9.

Table 4. Bromodomain 9 (BRD9) TR-FRET Binding of Compounds of the Disclosure

Compound No.	Bromodomain TR-FRET BRD9 IC_{50} (nM)
D1	+++
D2	++++
D3	++++
D4	++++
D5	++++
D6	++++
D7	++++
D8	++++
D9	++++
D10	+++
D11	+++
D12	++++
D13	++++
D14	++++
D15	++++
D16	NT
D17	NT
D18	NT
D19	NT
D20	NT
D21	NT
D22	++++
D23	++++
D24	NT
D25	++++
D26	+++
D27	++++
D28	NT
D29	NT
D30	++++

Compound No.	Bromodomain TR-FRET BRD9 IC_{50} (nM)
D31	++++
D32	++++
D33	++++
D34	++++
D35	++++
D36	++++
D37	++++
D38	++++
D39	++++
D40	++++
D41	++++
D42	NT
D43	NT
D44	NT
D45	NT
D46	NT
D47	NT
D48	NT
D49	NT
D50	NT
D51	NT
D52	++++
D53	++++
D54	+++
D55	+++
D56	++++
D57	+++
D58	++++
D59	++++
D60	++++
D61	++++

Compound No.	Bromodomain TR-FRET BRD9 IC_{50} (nM)
D62	+++
D63	+++
D64	+++
D65	+++
D66	+++
D67	++++
D68	++++
D69	++++
D70	+++
D71	++++
D72	++++
D73	+++
D74	++++
D75	NT
D76	NT
D77	NT
D78	NT
D79	NT
D80	NT
D81	NT
D82	NT
D83	NT
D84	+++
D85	+++
D86	+++
D87	++++
D88	++++
D89	++++
D90	++++
D91	+++
D92	++++

Compound No.	Bromodomain TR-FRET BRD9 IC_{50} (nM)
D93	++++
D94	+++
D95	+++
D96	++++
D97	++++
D98	++
D99	+++
D100	++++
D101	++++
D102	++++
D103	+++
D104	+++
D105	+++
D106	+++
D107	+++
D108	++++
D109	++++
D110	+++
D111	++++
D112	++++
D113	++++
D114	++++
D115	+++
D116	++++
D117	++++
D118	++++
D119	++++
D120	+++
D121	+++
D122	++++
D123	++++

Compound No.	Bromodomain TR-FRET BRD9 IC_{50} (nM)
D124	++++
D125	++++
D126	+++
D127	++++
D128	+++
D129	++++
D130	++++
D131	++++
D132	++++
D133	++++
D134	+++
D135	+++
D136	++++
D137	++++
D138	++++
D139	++++
D140	++++
D141	+++
D142	+++
D143	++++
D144	+++
D145	+++
D146	++++
D147	+++
D148	+++
D149	++++
D150	++++
D151	++++
D152	++++
D153	+++
D154	++++

Compound No.	Bromodomain TR-FRET BRD9 IC_{50} (nM)
D155	++++
D156	++++
D157	+++
D158	++++
D159	++++
D160	++++
D161	++++
D162	+++
D163	++++
D164	++++
D165	+++
D166	++++
D167	++++
D168	++++
D169	++++
D170	+++
D171	+++
D172	++++
D173	+++
D174	+++
D175	+++
D176	++++
D177	++++

"+" indicates inhibitory effect of ≥ 1000 nM;

"++" indicates inhibitory effect of ≥ 100 nM;

"+++" indicates inhibitory effect of ≥ 10 nM;

"++++" indicates inhibitory effect of < 10 nM;

"NT" indicates not tested

Example 87 – SYO1 BRD9 NanoLuc Degradation Assay

This example demonstrates the ability of the compounds of the disclosure to degrade a Nanoluciferase-BRD9 fusion protein in a cell-based degradation assay.

Procedure: A stable SYO-1 cell line expressing 3xFLAG-NLuc-BRD9 was generated. On day 0 cells were seeded in 30 µL media into each well of 384-well cell culture plates. The seeding density was 8000 cells/well. On day 1, cells were treated with 30 nL DMSO or 30 nL of 3-fold serially DMSO-diluted compounds (10 points in duplicates with 1 µM as final top dose). Subsequently plates were incubated for 6 hours in a standard tissue culture incubator and equilibrated at room temperature for 15 minutes. Nanoluciferase activity was measured by adding 15 µL of freshly prepared Nano-Glo Luciferase Assay Reagent (Promega N1130), shaking the plates for 10 minutes and reading the bioluminescence using an EnVision reader.

Results: The Inhibition% was calculated using the following formula: %Inhibition = 100 x (Lum_{HC} – Lum_{Sample}) / (Lum_{HC} –Lum_{LC}). DMSO treated cells are employed as High Control (HC) and 1 µM of a known BRD9 degrader standard treated cells are employed as Low Control (LC). The data was fit to a four parameter, non-linear curve fit to calculate IC_{50} (µM) values as shown in Table 5A, Table 5B, and Table 5C. As shown by the results in Table 5A, Table 5B, and Table 5C, a number of compounds of the present disclosure exhibit an IC_{50} value of < 1 µM for the degradation of BRD9, indicating their use as compounds for reducing the levels and/or activity of BRD9 and their potential for treating BRD9-related disorders.

Table 5A. SYO1 Bromodomain 9-NanoLuc Degradation by Compounds of the Disclosure

Compound No.	SYO1 BRD9-NanoLuc degradation IC_{50} (nM)
D1	++++
D2	+++
D3	++++
D4	+++
D5	+++
D6	++++
D7	+++
D8	+
D9	++++
D10	++++
D11	++++
D12	++++
D13	++++
D14	++++
D15	++++
D16	++++
D17	++++

Compound No.	SYO1 BRD9-NanoLuc degradation IC_{50} (nM)
D18	++++
D19	++++
D20	++++
D21	+
D22	+++
D23	++++
D24	+++
D25	++
D26	+
D27	+++
D28	++
D29	+++
D30	+++
D31	+++
D32	+++
D33	++++
D34	++++
D35	++++
D36	++
D37	++++
D38	++++
D39	++++
D40	++++
D41	+++
D42	++++
D43	++
D44	++++
D45	++++
D46	++++
D47	++++
D48	+++

Compound No.	SYO1 BRD9-NanoLuc degradation IC_{50} (nM)
D49	+
D50	++++
D51	++++
D52	++++
D53	++++
D54	+++
D55	++
D56	++++
D57	++++
D58	++++
D59	++++
D60	++++
D61	+++
D62	++
D63	+++
D64	++
D65	++
D66	++
D67	++++
D68	++
D69	++++
D70	+++
D71	++++
D72	++++
D73	++++
D74	++
D75	++++
D76	++++
D77	++
D78	+++
D79	++

Compound No.	SYO1 BRD9-NanoLuc degradation IC_{50} (nM)
D80	++++
D81	++++
D82	+++
D83	++
D84	+
D85	++
D86	++
D87	+++
D88	+++
D89	++++
D90	+++
D91	+++
D92	++++
D93	+++
D94	+++
D95	++
D96	+++
D97	+++
D98	++
D99	+++
D100	++++
D101	++
D102	+++
D103	+++
D104	++
D105	++
D106	++
D107	+++
D108	++++
D109	+++
D110	+++

Compound No.	SYO1 BRD9-NanoLuc degradation IC_{50} (nM)
D111	+++
D112	++
D113	++++
D114	+++
D115	++
D116	+++
D117	++
D118	+++
D119	+++
D120	+++
D121	+++
D122	++++
D123	++++
D124	++++
D125	+++
D126	++
D127	++
D128	++++
D129	++++
D130	++++
D131	++++
D132	++++
D133	+++
D134	+++
D135	++
D136	++
D137	+++
D138	+++
D139	++
D140	+++
D141	++

Compound No.	SYO1 BRD9-NanoLuc degradation IC_{50} (nM)
D142	+++
D143	++++
D144	+++
D145	+++
D146	+++
D147	+++
D148	++
D149	+++
D150	+++
D151	+++
D152	++++
D153	+++
D154	+++
D155	+++
D156	+++
D157	++++
D158	+++
D159	+++
D160	+++
D161	+++
D162	+++
D163	+++
D164	+++
D165	+++
D166	+++
D167	++++
D168	++++
D169	+++
D170	++++
D171	++++
D172	+++

Compound No.	SYO1 BRD9-NanoLuc degradation IC_{50} (nM)
D173	++++
D174	++
D175	+++
D176	++++
D177	+++

"+" indicates inhibitory effect of ≥ 1000 nM;

"++" indicates inhibitory effect of ≥ 100 nM;

"+++" indicates inhibitory effect of ≥ 10 nM;

"++++" indicates inhibitory effect of < 10 nM;

"NT" indicates not tested

Table 5B. SYO1 Bromodomain 9-NanoLuc Degradation by Compounds of the Disclosure

Compound No.	SYO1 BRD9-NanoLuc degradation IC_{50} (nM)
D178	++++
D179	+++
D180	++++
D181	++
D182	+++
D183	++
D184	++++
D185	++++
D186	++++
D187	++++
D188	++++
D189	++++
D190	+++
D191	++++
D192	++
D193	++
D194	++++
D195	+++
D196	+++
D197	++++
D198	++++
D199	++++
D200	+++
D201	++++

Compound No.	SYO1 BRD9-NanoLuc degradation IC_{50} (nM)
D202	++++
D203	++++
D204	++++
D205	++++
D206	++++
D207	++++
D208	++++
D209	++
D210	+++
D211	++++
D212	+++
D213	++++
D214	++++
D215	++++
D216	++++
D217	++++
D218	++++
D219	++++
D220	++++
D221	++++
D222	++++
D223	++++
D224	++++
D225	++++
D226	++++
D227	++++
D228	++++
D229	++++
D230	++++
D231	++
D232	+++
D233	++
D234	+++
D235	++++
D236	++++
D237	++++
D238	++++
D239	++++
D240	++++

Compound No.	SYO1 BRD9-NanoLuc degradation IC_{50} (nM)
D241	++++
D242	++++
D243	++++
D244	++++
D245	+++
D246	++++
D247	++++
D248	+++
D249	+++
D250	++++
D251	++++
D252	++++
D253	++++
D254	++++
D255	++++
D256	++++
D257	++++
D258	++++
D259	++++
D260	++++
D261	++++
D262	++++
D263	++++
D264	+++
D265	++
D266	+++
D267	+++
D268	++++
D269	++++
D270	+++
D271	++++
D272	++++
D273	++++
D274	++++
D275	++++
D276	+++
D277	++++
D278	+++
D279	++++

Compound No.	SYO1 BRD9-NanoLuc degradation IC_{50} (nM)
D280	++++
D281	+++
D282	++
D283	++
D284	+++
D285	++
D286	+++
D287	++++
D288	++++
D289	++++
D290	++++
D291	++++
D292	++
D293	+++
D294	++
D295	++
D296	++
D297	++++
D298	++++
D299	++++
D300	++++
D301	++++
D302	++++
D303	+++
D304	++++
D305	++
D306	++++
D307	++++
D308	++++
D309	+++
D310	++++
D311	+++
D312	++++
D313	++++
D314	+++
D315	++++
D316	++++
D317	+++
D318	++++

Compound No.	SYO1 BRD9-NanoLuc degradation IC_{50} (nM)
D319	++++
D320	++++
D321	++++
D322	++++
D323	++++
D324	++++
D325	++++
D326	++++
D327	++++
D328	++++
D329	++++
D330	++++
D331	++++
D332	++++
D333	++++
D334	+
D335	++++
D336	++++
D337	++++
D338	++++
D339	++++
D340	++++
D341	++++
D342	+
D343	++++
D344	++++
D345	++++
D346	++++
D347	++++
D348	++++
D349	++++
D350	++
D351	+
D352	+
D353	++++
D354	++++
D355	+
D356	++++
D357	++++

Compound No.	SYO1 BRD9-NanoLuc degradation IC_{50} (nM)
D358	++++
D359	++++
D360	++++
D361	++++
D362	++++
D363	++++
D364	++
D365	+++
D366	++++
D367	++++
D368	++++
D369	++++
D370	++++
D371	++++
DD1	+
DD2	++
DD3	+
DD4	++++
DD5	+++
DD6	+++
DD7	++++
DD8	++++
DD9	++++
DD10	++

"+" indicates inhibitory effect of ≥ 1000 nM;

"++" indicates inhibitory effect of ≥ 100 nM;

"+++" indicates inhibitory effect of ≥ 10 nM;

"++++" indicates inhibitory effect of < 10 nM;

"NT" indicates not tested

Table 5C. SYO1 Bromodomain 9-NanoLuc Degradation by Compounds of the Disclosure

Compound No.	SYO1 BRD9-NanoLuc degradation IC_{50} (nM)
D372	++++
D373	++++
D374	++++
D375	++++
D376	++++
D377	++++
D378	++++

Compound No.	SYO1 BRD9-NanoLuc degradation IC_{50} (nM)
D379	++++
D380	+++
D381	++++
D382	++++
D383	+
D384	++++
D385	++++
D386	++++
D387	++++
D388	++++
D389	+
D390	+
D391	++
D392	+++
D393	+++
D394	+
D395	++++
D396	++++
D397	++++
D398	++++
D399	++++
D400	++++
D401	++++
D402	++++
D403	++++
D404	++++
D405	++++
D406	++++
D407	++++
D408	++++
D409	++++
D410	++++
D411	++++
D412	++++
D413	++++
D414	++++
D415	++++
D416	++++
D417	++++

Compound No.	SYO1 BRD9-NanoLuc degradation IC_{50} (nM)
D418	++++
D419	++++
D420	++++
D421	++++
D422	++++
D423	++++
D424	++++
D425	++++
D426	++++
D427	++++
D428	++++
D429	+
D430	++++
D431	++++
D432	+++
D433	++++
D434	++++
D435	+
D436	++++
D437	+
D438	++++
D439	++++
D440	++++
D441	++++
D442	++++
D443	++++
D444	++++
D445	+
D446	+
D447	++
D448	++++
D449	+++
D450	++++
D451	+++
D452	++++
D453	++++
D454	++++
D455	++++
D456	++++

Compound No.	SYO1 BRD9-NanoLuc degradation IC_{50} (nM)
D457	++++
D458	++++
D459	++++
D460	++++
D461	+++
D462	++++
D463	++++
D464	+
D465	++++
D466	++++
D467	+
D468	+
D469	NT
D470	NT
D471	++++
D472	+
D473	+
D474	+
D475	+++
D476	++++
DD11	+
DD12	+
DD13	+++
DD14	+
DD15	+++
DD16	+++

"+" indicates inhibitory effect of ≥ 1000 nM;

"++" indicates inhibitory effect of ≥ 100 nM;

"+++" indicates inhibitory effect of ≥ 10 nM;

"++++" indicates inhibitory effect of < 10 nM;

"NT" indicates not tested

Other Embodiments

All publications, patents, and patent applications mentioned in this specification are incorporated herein by reference in their entirety to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference in its entirety. Where a term in the present application is found to be defined differently in a document incorporated herein by reference, the definition provided herein is to serve as the definition for the term.

While the invention has been described in connection with specific embodiments thereof, it will be

understood that invention is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure that come within known or customary practice within the art to which the invention pertains and may be applied to the essential features hereinbefore set forth, and follows in the scope of the claims.

Other embodiments are in the claims.

C4 Therapeutics, Inc.
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Claims

1. A compound having the structure of **Formula I**:

A-L-B

Formula I,

wherein

A is a BRD9 binding moiety;

B is a degradation moiety; and

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

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

Formula II

wherein

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

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

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

each of E^1 and E^2 is, independently, O, S, NR^N, optionally substituted $C_{1–10}$ alkylene, optionally substituted $C_{2–10}$ alkenylene, optionally substituted $C_{2–10}$ alkynylene, optionally substituted C_2-C_{10} polyethylene glycol, or optionally substituted $C_{1–10}$ heteroalkylene;

E^3 is optionally substituted C_1-C_6 alkylene, optionally substituted C_1-C_6 heteroalkylene, O, S, or NR^N;

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

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

each of F^1, F^2, and F^3 is, independently, optionally substituted C_3-C_{10} carbocyclylene, optionally substituted $C_{2–10}$ heterocyclylene, optionally substituted C_6-C_{10} arylene, or optionally substituted C_2-C_9 heteroarylene,

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein the linker has the structure of **Formula IIa** :

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

Formula IIa

3. The compound of claim 1, wherein the linker has the structure of **Formula IIb**:

$$A^1–(E^1)–(F^1)–(E^2)_p–A^2.$$

Formula IIb

4. The compound of claim 1, wherein the linker has the structure of **Formula IIc**:

$$A^1–(E^1)–(F^1)–A^2.$$

Formula IIc

5. The compound of claim 1, wherein the linker has the structure of **Formula IId**:

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

Formula IId

6. The compound of claim 1, wherein the linker has the structure of **Formula IIe** :

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

Formula IIe

7. The compound of claim 1, wherein the linker has the structure of **Formula IIf**:

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

Formula IIf

8. The compound of claim 1, wherein the linker has the structure of **Formula Vg**:

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

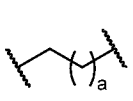
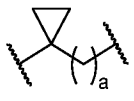
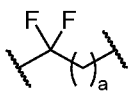
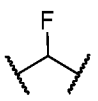
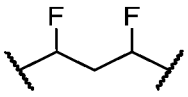
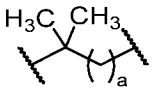
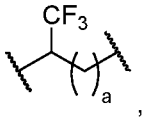
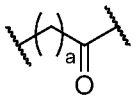
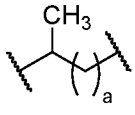
Formula IIg

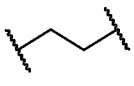
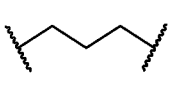
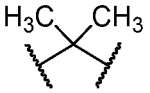
9. The compound of any one of claims 1 to 8, wherein each of E^1 and E^2 is, independently, NR^N, optionally substituted $C_{1–10}$ alkylene, optionally substituted C_2-C_{10} polyethylene glycolene, or optionally substituted $C_{1–10}$ heteroalkylene.

10. The compound of any one of claims 1 to 9, wherein E^3 is optionally substituted C_1-C_6 alkylene, O, S, or NR^N.

11. The compound of claim 10, wherein E^3 is optionally substituted C_1-C_6 alkylene.

12. The compound of claim 10, wherein E^3 is optionally substituted C_1-C_3 alkylene.

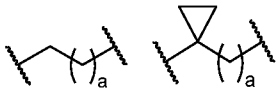
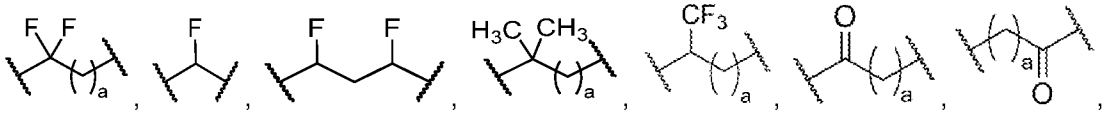
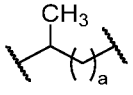
13. The compound of claim 10, wherein E^3 is  ,  ,  ,  ,  ,  ,  ,  , or  , where a is 0, 1, 2, 3, 4, or 5.

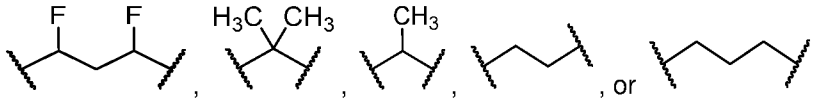
14. The compound of claim 10, wherein E^3 is  ,  ,  ,  , or  .

15. The compound of claim 10, wherein E^3 is O.

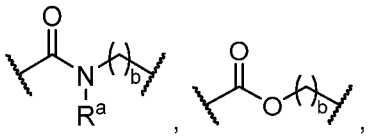
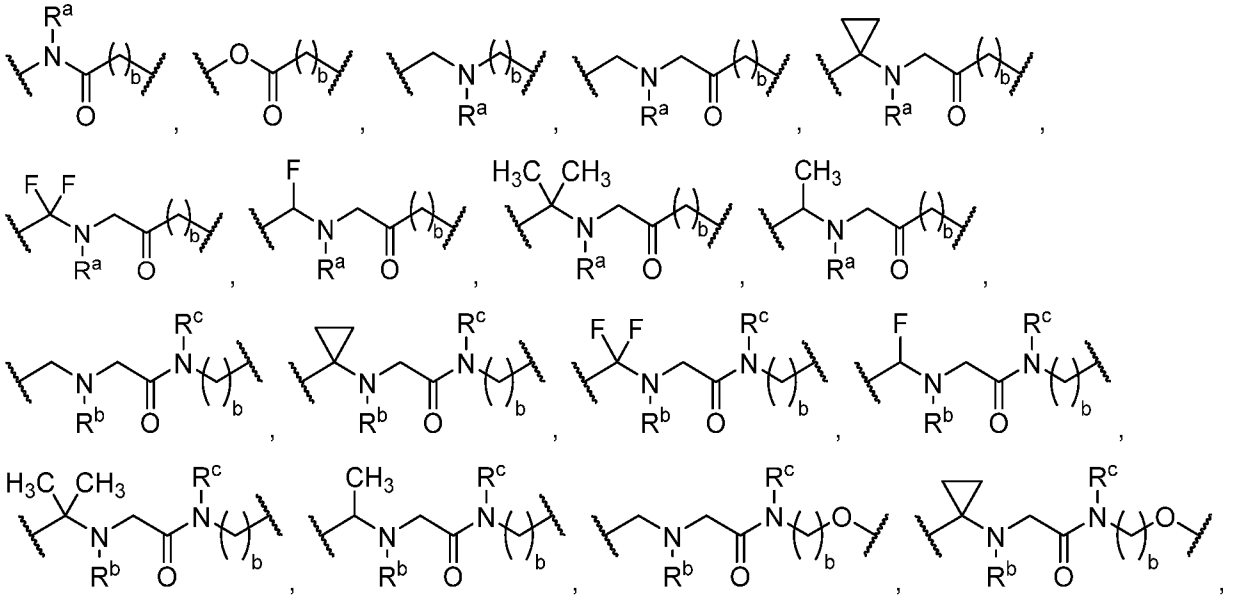
16. The compound of any one of claims 1 to 15, wherein each R^N is, independently, H or optionally substituted C_{1-4} alkyl.

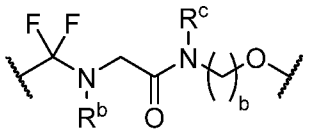
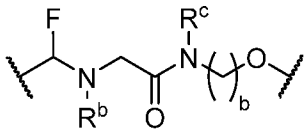
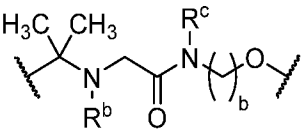
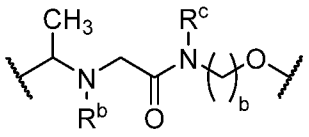
17. The compound of claim 16, wherein each R^N is, independently, H or methyl.

18. The compound of any one of claims 1 to 17, wherein E^1 is  ,  , or  , where a is 0, 1, 2, 3, 4, or 5.

19. The compound of claim 18, wherein E^1 is  ,  , or .

20. The compound of claim 19, wherein E^1 is  .

21. The compound of any one of claims 1 to 20, wherein E^1 is  , 


,

,

, or

,

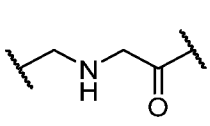
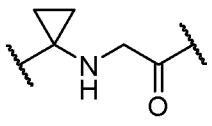
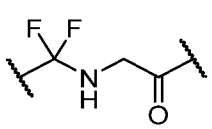
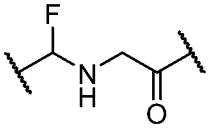
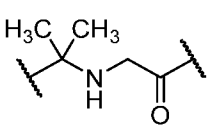
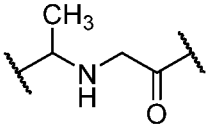
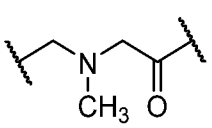
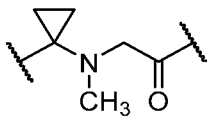
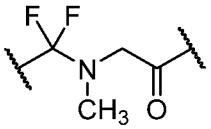
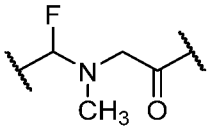
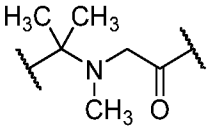
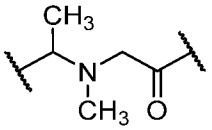
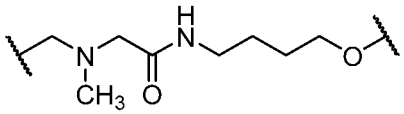
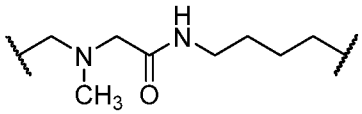
wherein

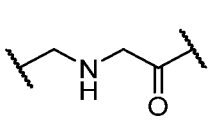
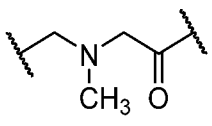
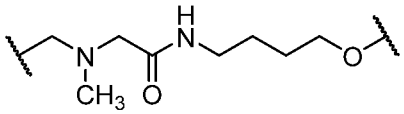
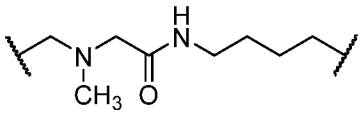
b is 0, 1, 2, 3, 4, 5, or 6;

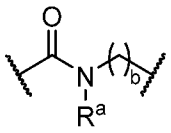
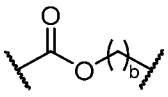
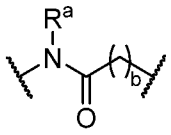
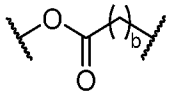
R^a is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_6 carbocyclyl;

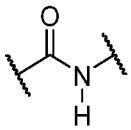
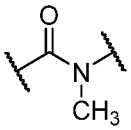
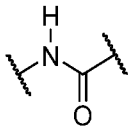
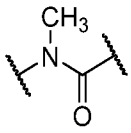
R^b is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_6 carbocyclyl; and

R^c is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_6 carbocyclyl.

22. The compound of claim 21, wherein E^1 is 
,

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or

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23. The compound of claim 22, wherein E^1 is 
,

,

, or

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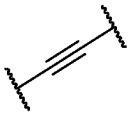
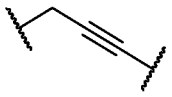
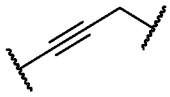
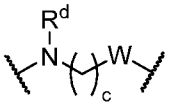
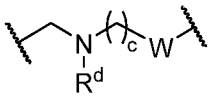
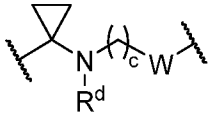
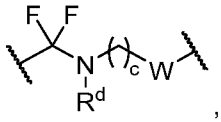
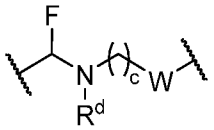
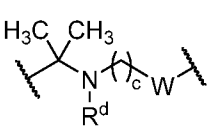
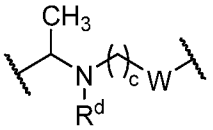
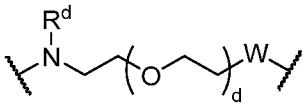
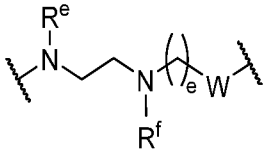
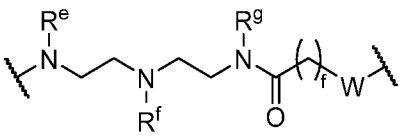
24. The compound of claim 21, wherein E^1 is  ,  ,  ,  or .

25. The compound of claim 24, wherein E^1 is  ,  ,  , or  .

26. The compound of any one of claims 21 to 25, wherein R^a is H or methyl.

27. The compound of claim 26, wherein R^a is H.

28. The compound of claim 26, wherein R^a is methyl.

29. The compound of any one of claims 1 to 28, wherein E^2 is O, NR^w,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  ,

wherein

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

d is 0, 1, 2, or 3;

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

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

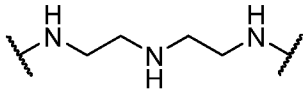
R^d is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_6 carbocyclyl;

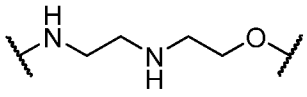
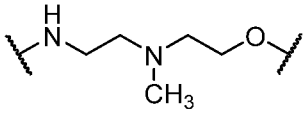
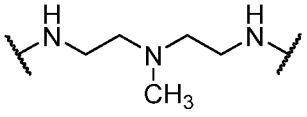
R^e is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_6 carbocyclyl;

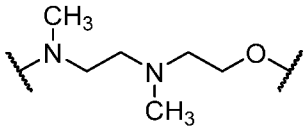
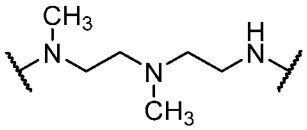
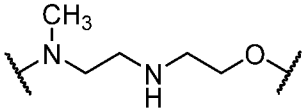
R^f is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_6 carbocyclyl;

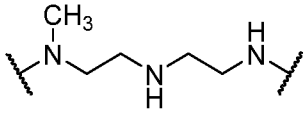
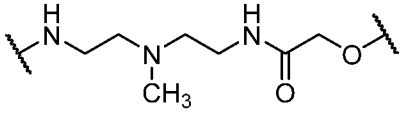
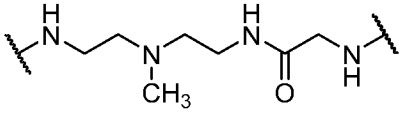
R^g is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_6 carbocyclyl; and

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

30. The compound of claim 29, wherein E^2 is O,  ,

 ,  ,  ,

 ,  ,  ,

 ,  , or  .

31. The compound of any one of claims 1 to 30, wherein each of F^1, F^2, or F^3 is, independently, optionally substituted C_3-C_{10} carbocyclylene.

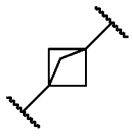
32. The compound of claim 31, wherein the C_3-C_{10} carbocyclylene is monocyclic.

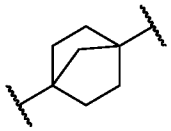
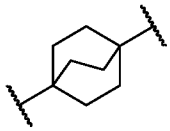
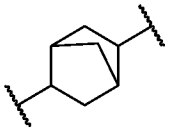
33. The compound of claim 31, wherein the C_3-C_{10} carbocyclylene is polycyclic.

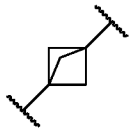
34. The compound of claim 33, wherein the C_3-C_{10} carbocyclylene is fused.

35. The compound of claim 33, wherein the C_3-C_{10} carbocyclylene is spirocyclic.

36. The compound of claim 33, wherein the C_3-C_{10} carbocyclylene is bridged.

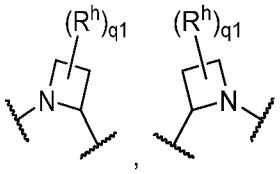
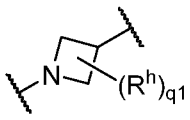
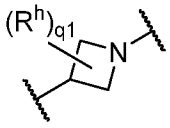
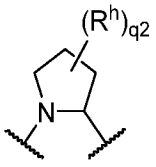
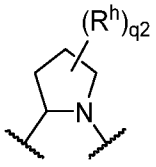
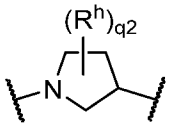
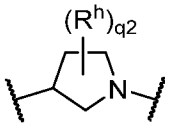
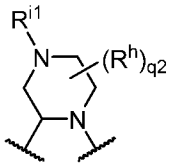
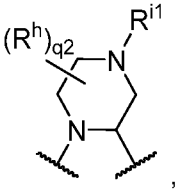
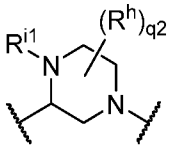
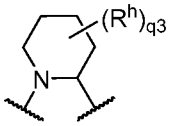
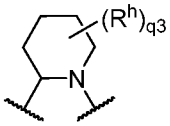
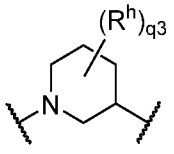
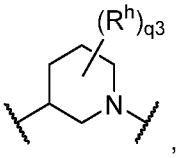
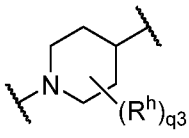
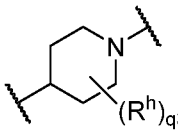
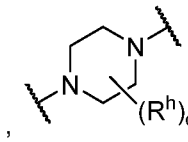
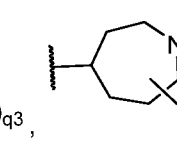
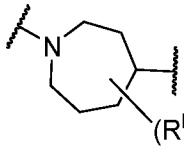
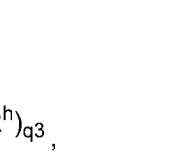
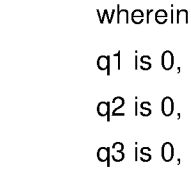
37. The compound of claim 36, wherein the C_3-C_{10} carbocyclylene is  ,

 ,  , or  .

38. The compound of claim 37, wherein the C_3-C_{10} carbocyclylene is  .

39. The compound of any one of claims 1 to 30, wherein each of F^1, F^2, or F^3 is, independently, optionally substituted C_2-C_6 heterocyclylene.

40. The compound of claim 39, wherein the C_2-C_6 heterocyclylene is monocyclic.

41. The compound of claim 40, wherein the C_2-C_6 heterocyclylene is  , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , , , ,  , or ,

wherein

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

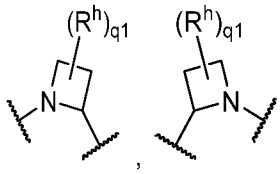
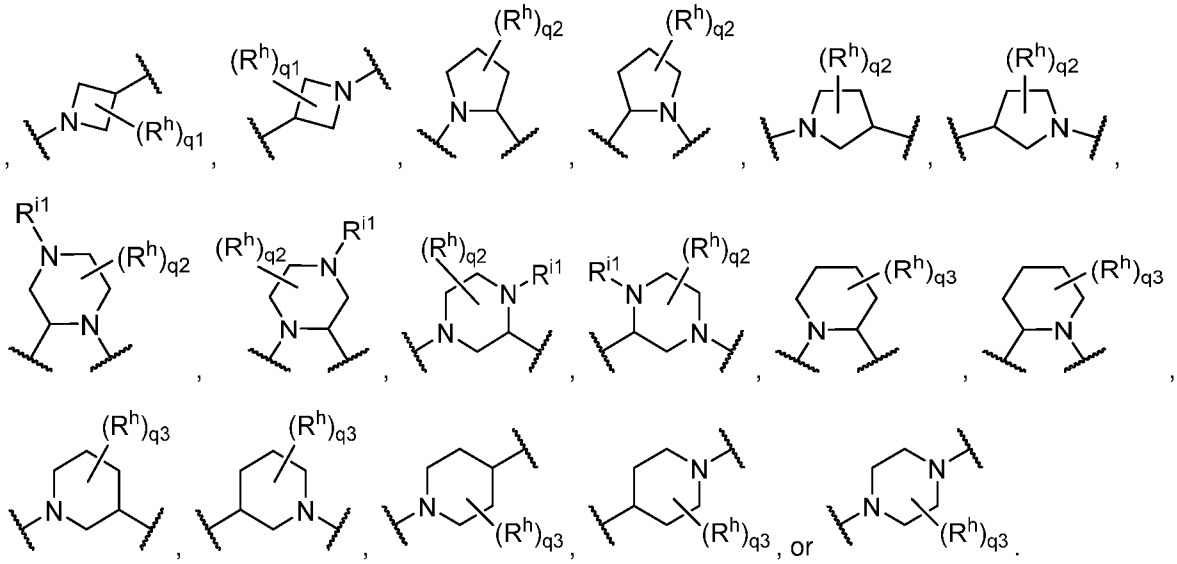
q2 is 0, 1, 2, 3, 4, 5, or 6;

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

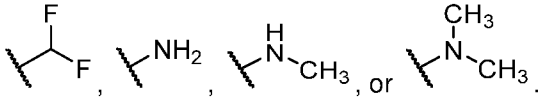
each R^h is, independently, ^2H, halogen, optionally substituted C_1-C_6 alkyl, OR^{i2}, or $NR^{i3}R^{i4}$; or two R^h groups, together with the carbon atom to which each is attached, combine to form optionally substituted C_3-C_{10} carbocyclyl or optionally substituted C_2-C_9 heterocyclyl; or two R^h groups, together with the carbon atoms to which each is attached, combine to form optionally substituted C_3-C_{10} carbocyclyl or optionally substituted C_2-C_9 heterocyclyl;

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

R^{i2} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_6 carbocyclyl;

42. The compound of claim 41, wherein the C_2–C_9 heterocyclylene is  ,  .

43. The compound of claim 41 or 42, wherein each R^h is, independently, ^2H, halogen, cyano, optionally substituted C_1-C_6 alkyl, OR^{i2}, or $NR^{i3}R^{i4}$.

44. The compound of claim 43, wherein each R^h is, independently, ^2H, F, methyl,  ,  .

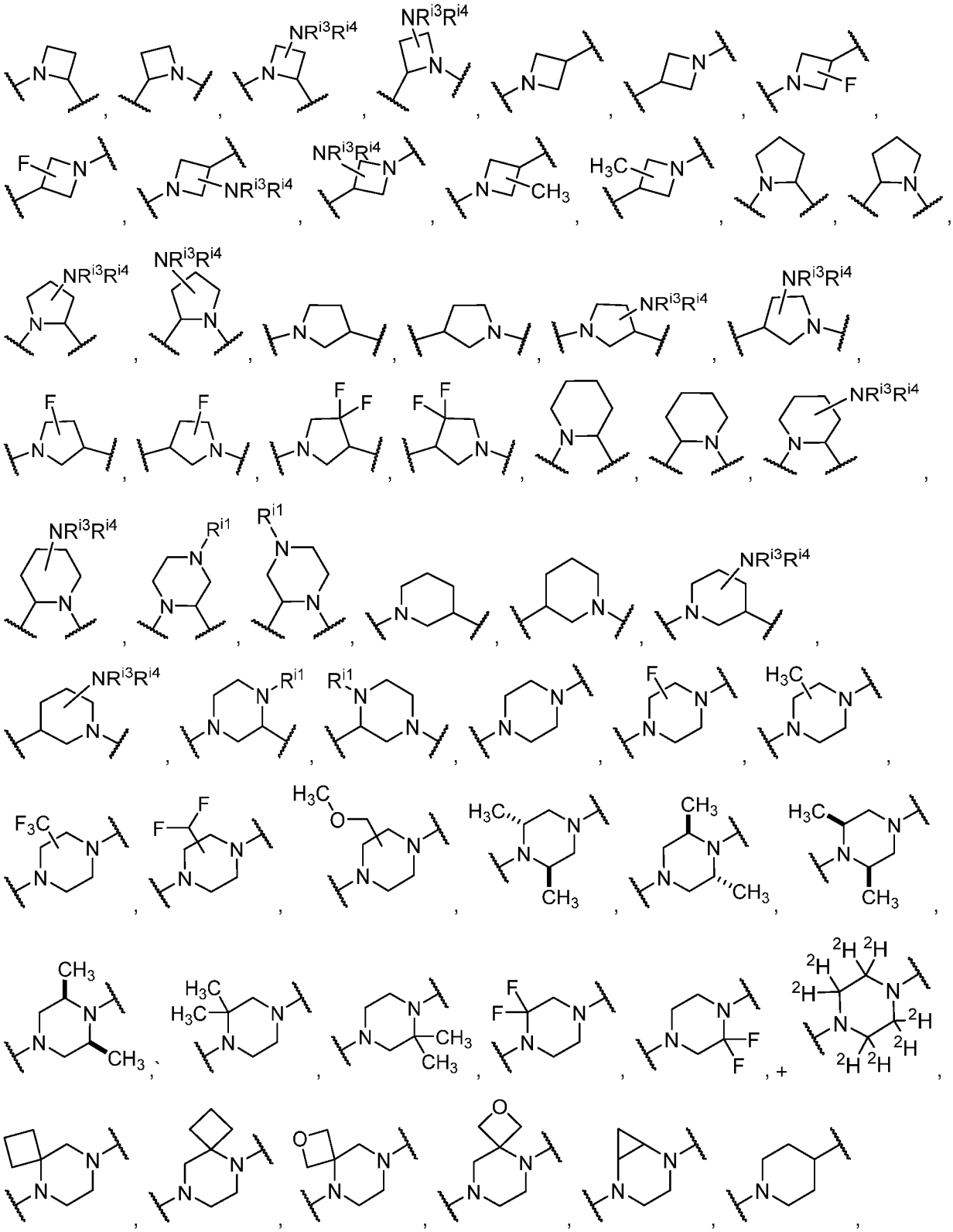
45. The compound of claim 44, wherein each R^h is, independently, F, methyl, or $NR^{i3}R^{i4}$.

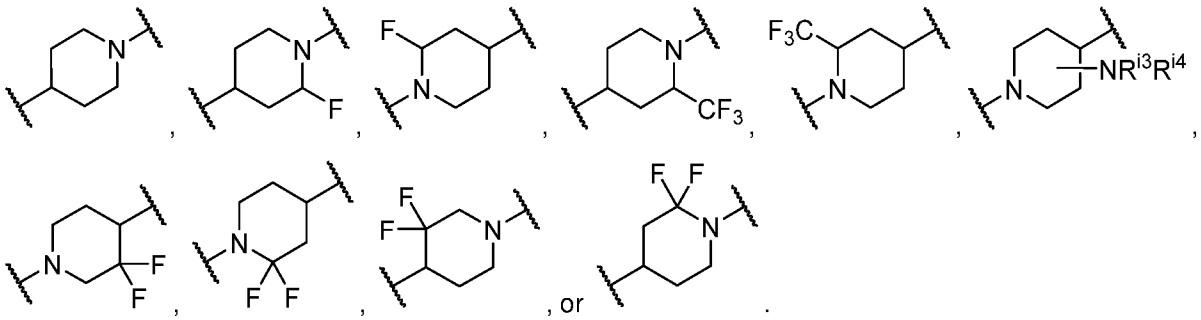
46. The compound of any one of claims 41 to 45, wherein q1 is 0, 1, or 2.

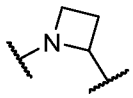
47. The compound of any one of claims 41 to 46, wherein q2 is 0, 1, or 2.

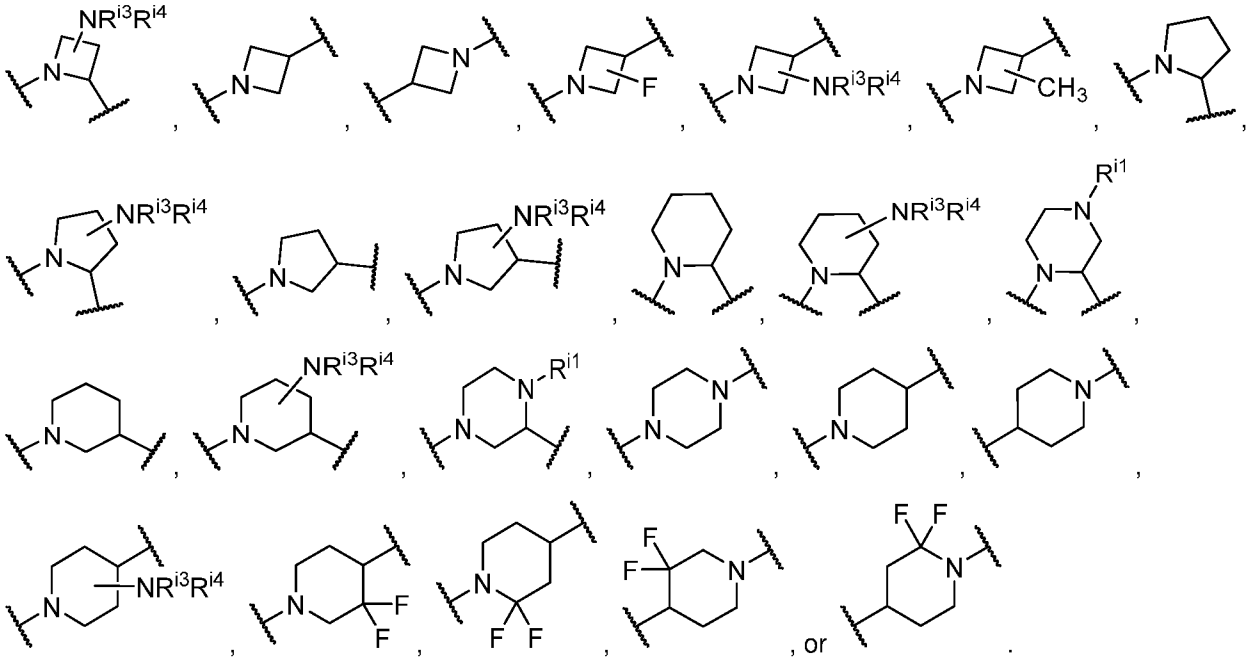
48. The compound of any one of claims 41 to 47, wherein q3 is 0, 1, or 2.

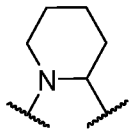
49. The compound of any one of claims 41 to 48, wherein the C_2-C_9 heterocyclylene is

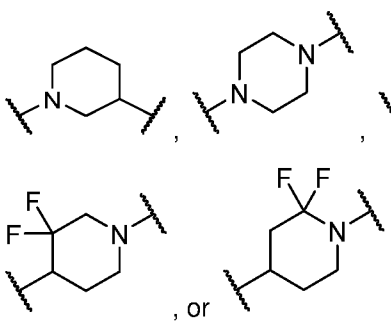


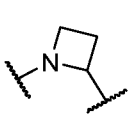
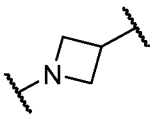
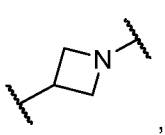
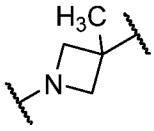
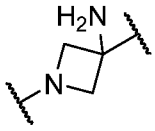
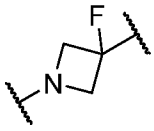
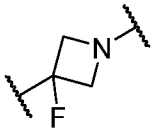
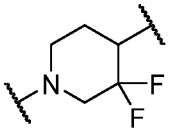
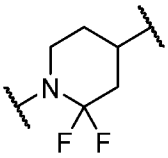
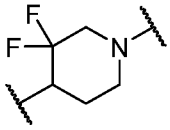
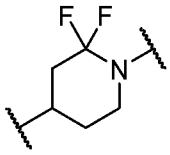


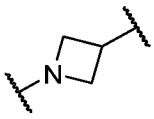
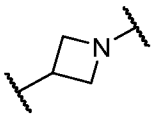
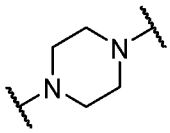
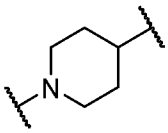
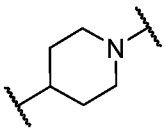
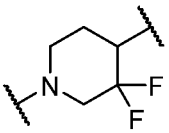
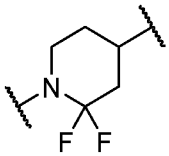
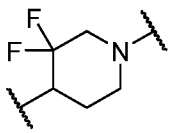
50. The compound of claim 49, wherein the C_{2-9} heterocyclylene is  ,

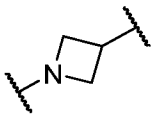
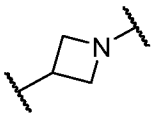
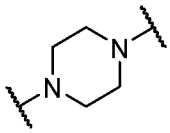
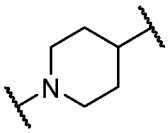
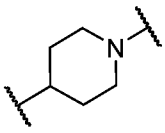
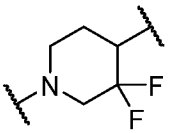
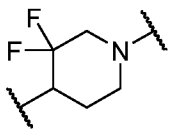
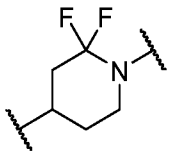


51. The compound of claim 50, wherein the C_{2-9} heterocyclylene is  ,



52. The compound of any one of claims 41 to 51, wherein F^1 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

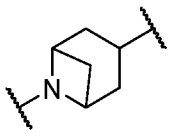
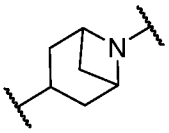
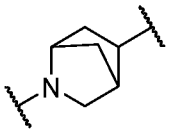
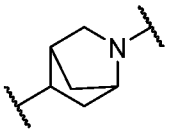
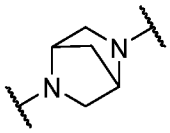
53. The compound of any one of claims 41 to 52, wherein F^2 is  ,  ,  ,  ,  ,  ,  ,  , , or  .

54. The compound of any one of claims 41 to 52, wherein F^3 is  ,  ,  ,  ,  ,  ,  ,  , , or  .

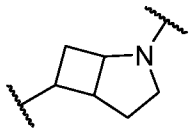
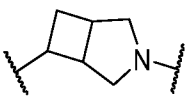
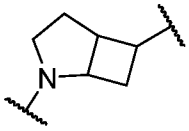
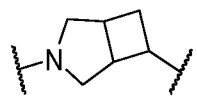
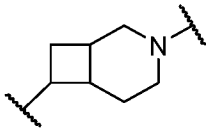
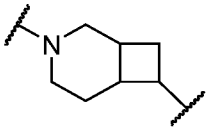
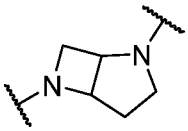
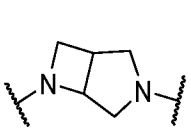
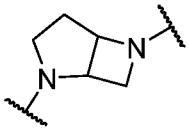
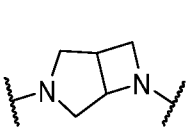
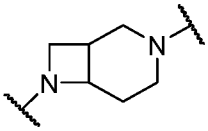
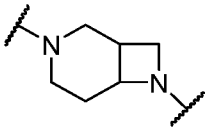
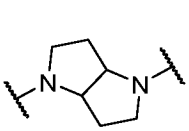
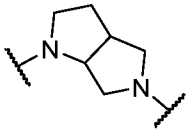
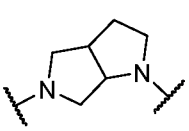
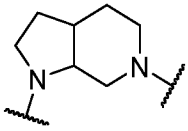
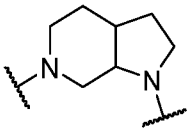
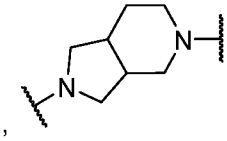
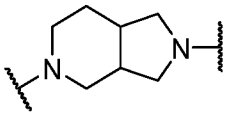
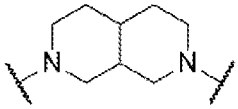
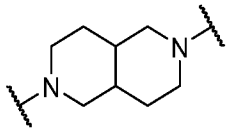
55. The compound of claim 39, wherein the C_2-C_6 heterocyclylene is polycyclic.

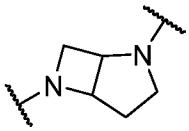
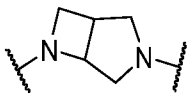
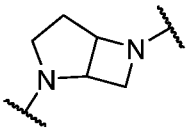
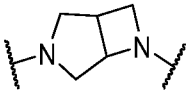
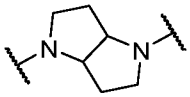
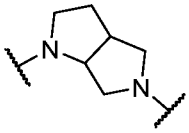
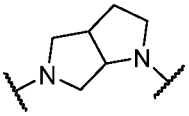
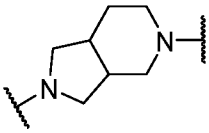
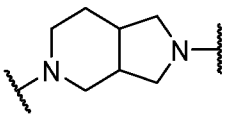
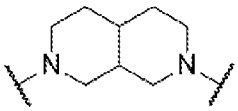
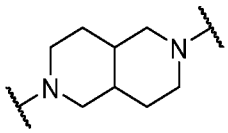
56. The compound of claim 55, wherein the C_2-C_6 heterocyclylene is bicyclic.

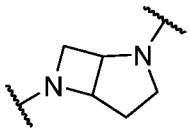
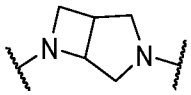
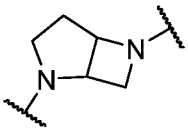
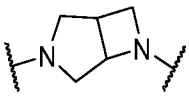
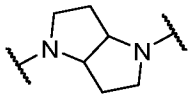
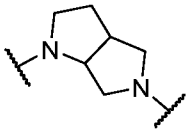
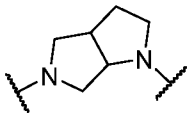
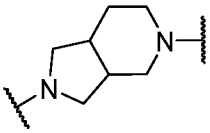
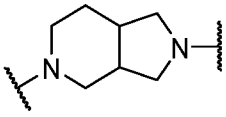
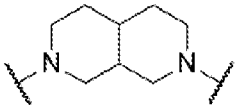
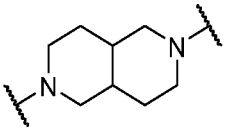
57. The compound of claim 55 or 56, wherein the C_2-C_6 heterocyclylene is bridged.

58. The compound of claim 57, wherein the C_2-C_6 heterocyclylene is  ,  ,  ,  , or  .

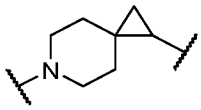
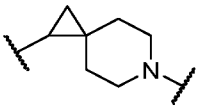
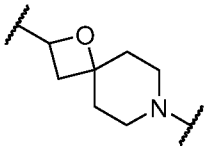
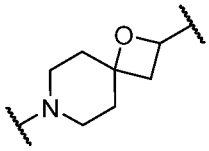
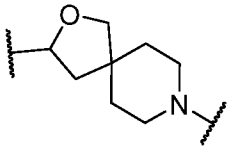
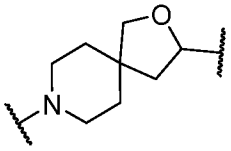
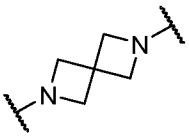
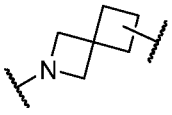
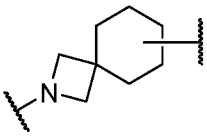
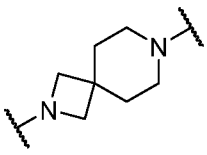
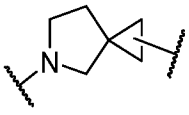
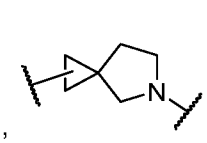
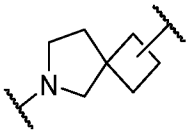
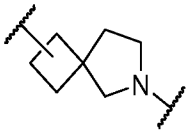
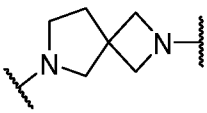
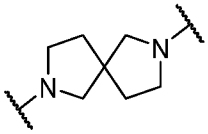
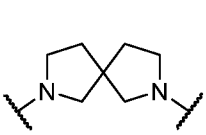
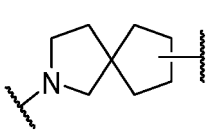
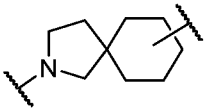
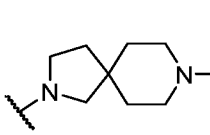
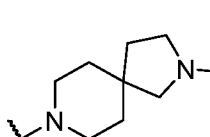
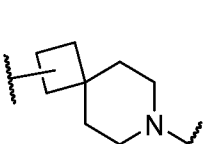
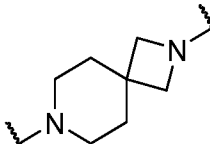
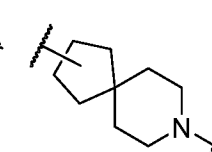
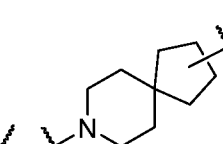
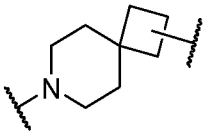
59. The compound of claim 55 or 56, wherein the C_2-C_6 heterocyclylene is fused.

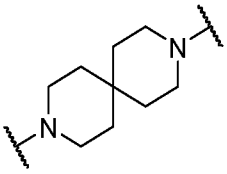
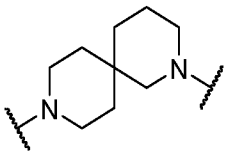
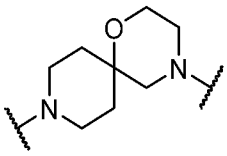
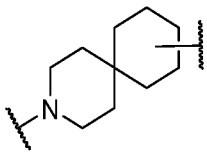
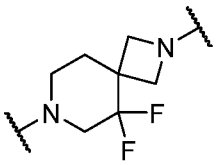
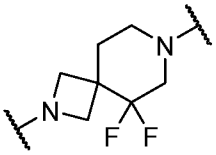
60. The compound of claim 59, wherein the C_2-C_9 heterocyclylene is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

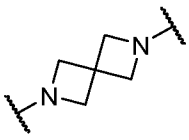
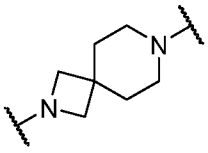
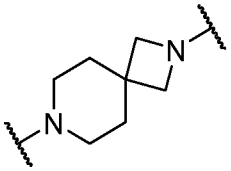
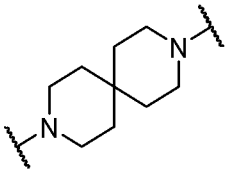
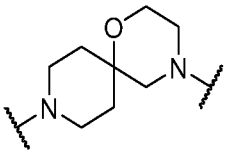
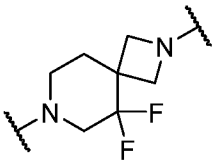
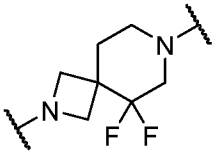
61. The compound of claim 60, wherein F^1 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

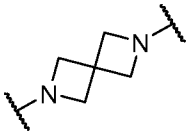
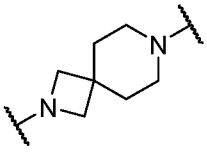
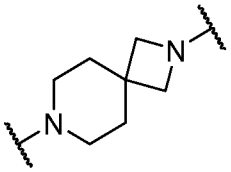
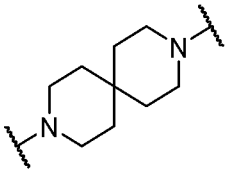
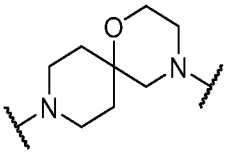
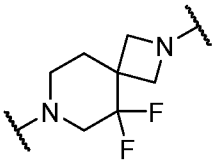
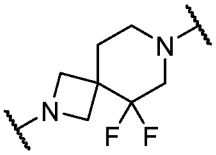
62. The compound of claim 60 or 61, wherein F^2 is   ,  ,  ,  ,  ,  ,  ,  ,  , or  .

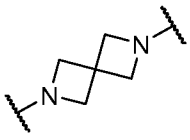
63. The compound of claim 55 or 56, wherein the C_2-C_6 heterocyclylene is spirocyclic.

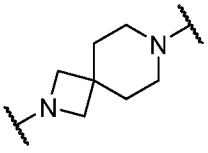
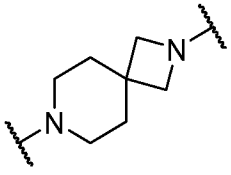
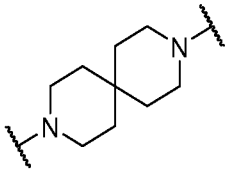
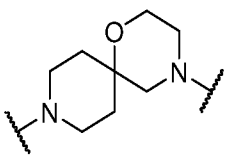
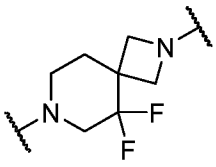
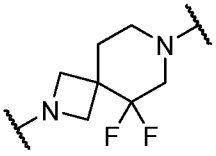
64. The compound of claim 63, wherein the C_2-C_6 heterocyclylene is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , , , , .


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65. The compound of claim 64, wherein F^1 is 
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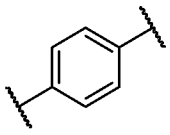
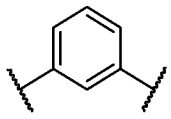
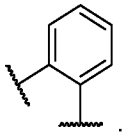
66. The compound of claim 64 or 65, wherein F^2 is 
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67. The compound of any one of claims 64 to 66, wherein F^3 is 
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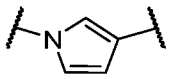
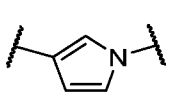
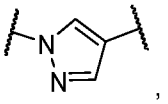
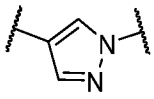
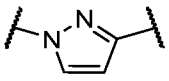
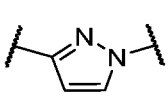
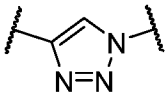
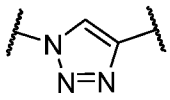
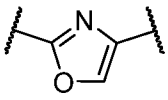
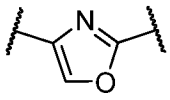
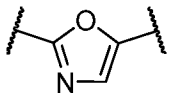
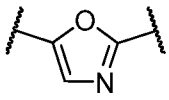
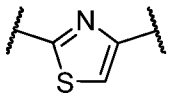
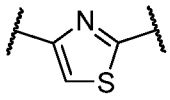
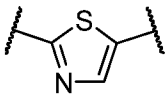
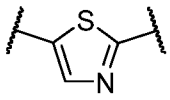
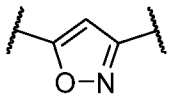
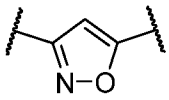
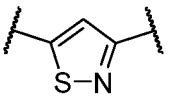
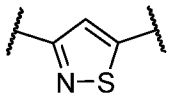
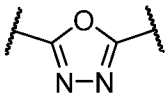
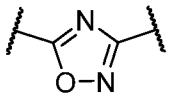
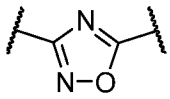
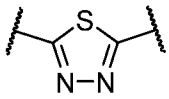
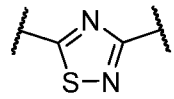
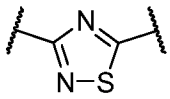

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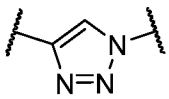
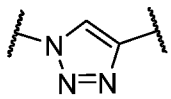
68. The compound of any one of claims 39 to 67 wherein the C_2-C_9 heterocyclylene comprises a quaternary amine.

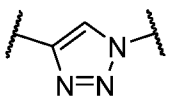
69. The compound of any one of claims 1 to 30, wherein each of F^1, F^2, or F^3 is, independently, optionally substituted C_6-C_{10} arylene.

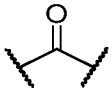
70. The compound of claim 69, wherein the C_6-C_{10} arylene is  ,  , or  .

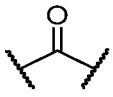
71. The compound of any one of claims 1 to 30, wherein each of F^1, F^2, or F^3 is, independently, optionally substituted C_2-C_9 heteroarylene.

72. The compound of claim 71, wherein the C_2-C_9 heteroarylene is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

73. The compound of claim 72, wherein F^2 is  or  .

74. The compound of claim 73, wherein F^2 is  .

75. The compound of any one of claims 1 to 74, C^3 is  or  .

76. The compound of claim 75, wherein C^3 is  .

77. The compound of any one of claims 1 to 76, wherein m is 1.

78. The compound of any one of claims 1 to 76, wherein m is 0.

79. The compound of any one of claims 1 to 78, wherein p is 1.

80. The compound of any one of claims 1 to 78, wherein p is 0.

81. The compound of any one of claims 1 to 80, wherein o1 is 1.

82. The compound of any one of claims 1 to 80, wherein o1 is 0.

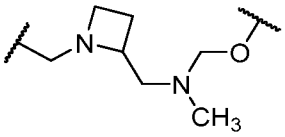
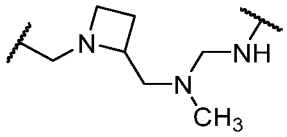
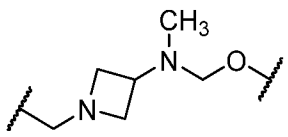
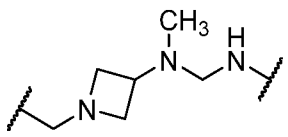
83. The compound of any one of claims 1 to 82, wherein o2 is 1.

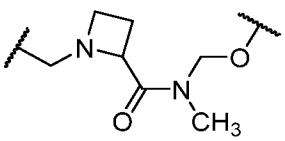
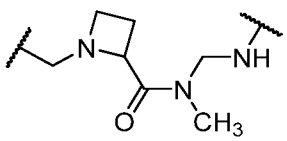
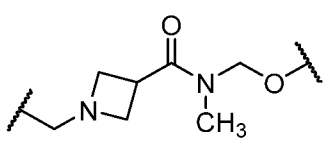
84. The compound of any one of claims 1 to 82, wherein o2 is 0.

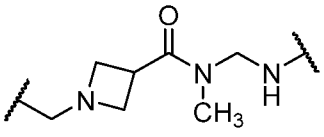
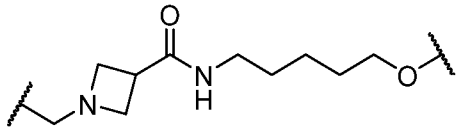
85. The compound of any one of claims 1 to 84, wherein n is 1.

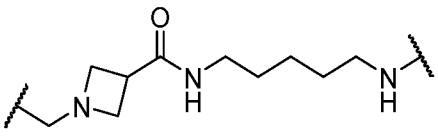
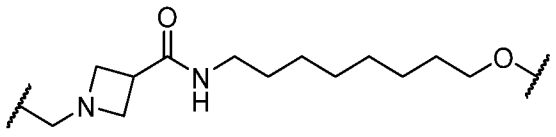
86. The compound of any one of claims 1 to 84, wherein n is 0.

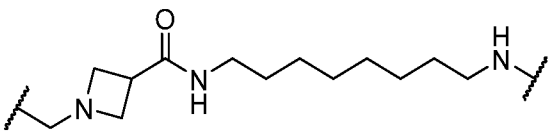
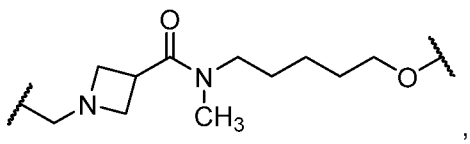
87. The compound of any one of claims 1 to 86, wherein the linker has the structure of

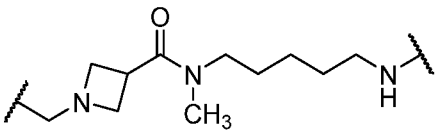
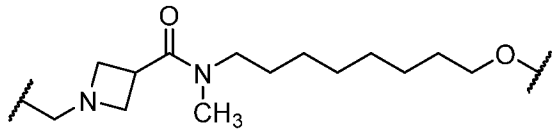
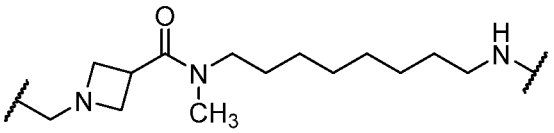
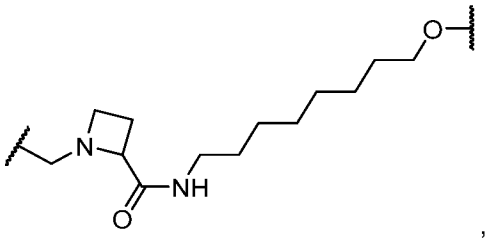
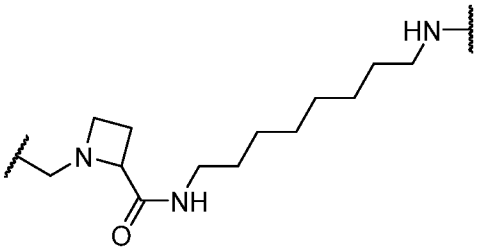
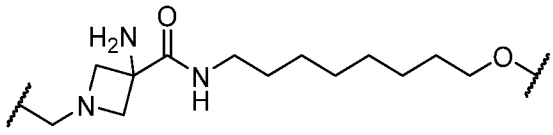
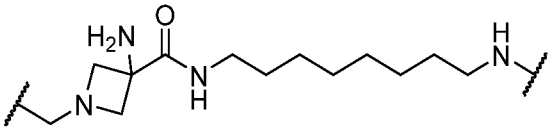
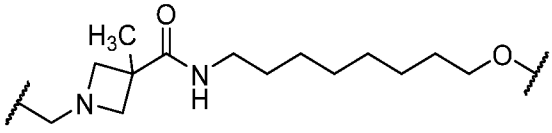
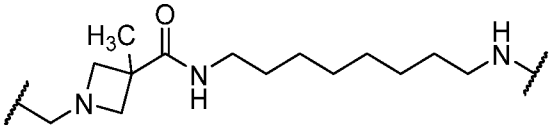
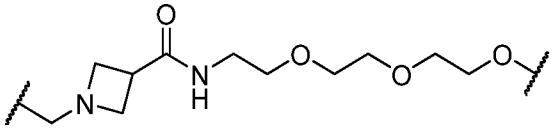
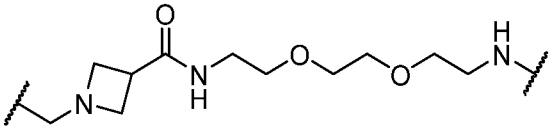
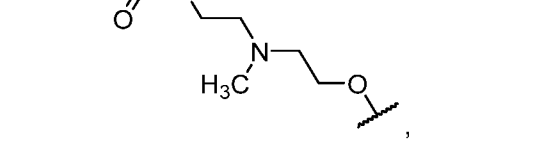
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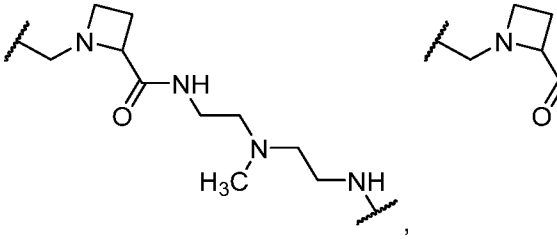
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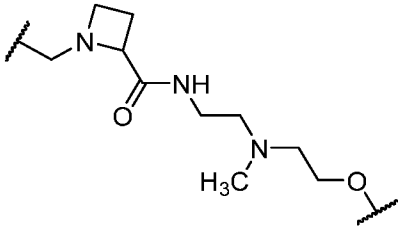
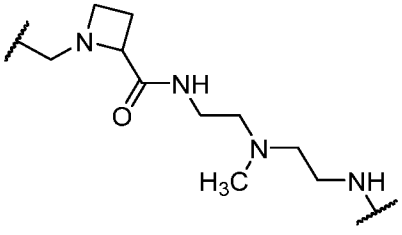
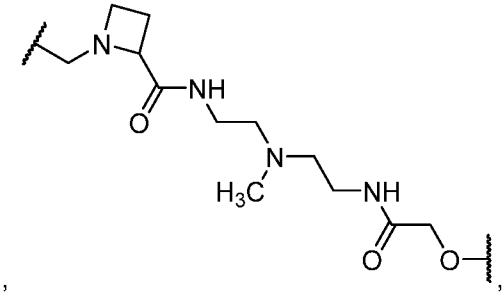
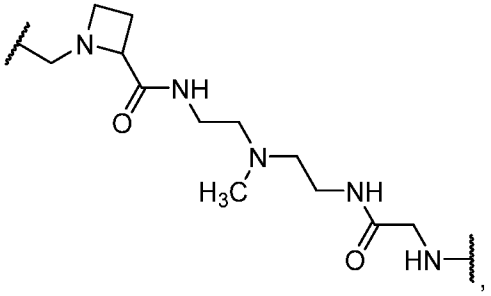
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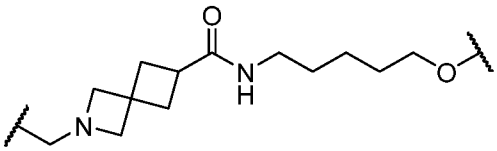
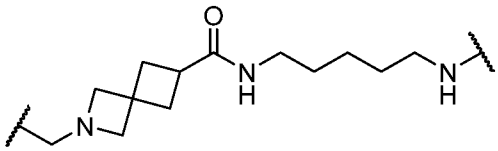
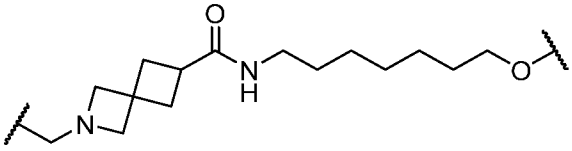
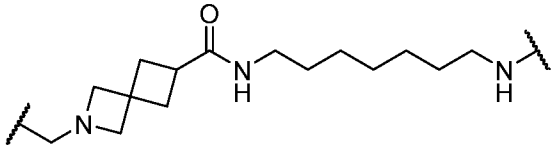
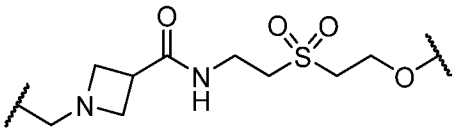
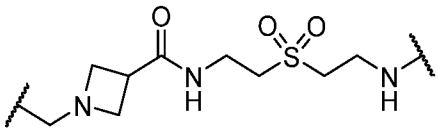
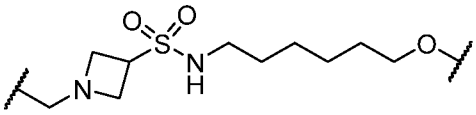
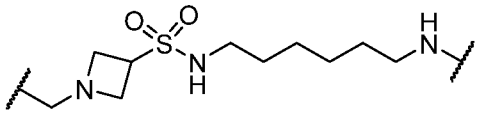
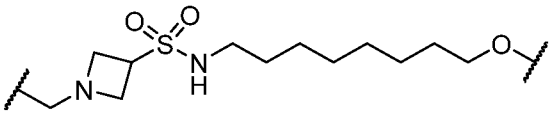
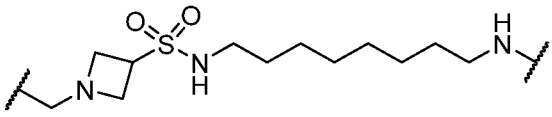
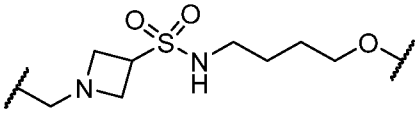
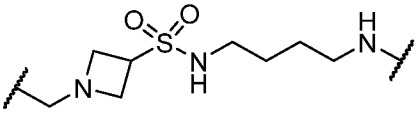
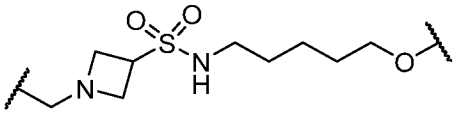
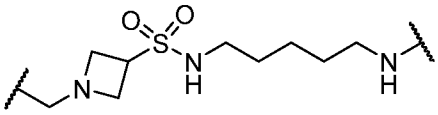
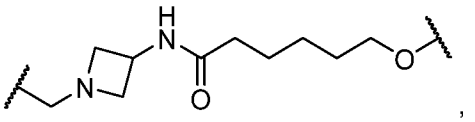
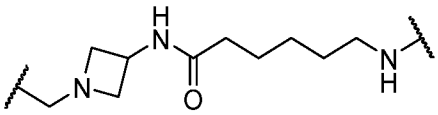
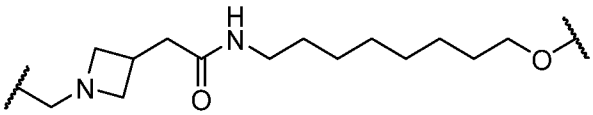
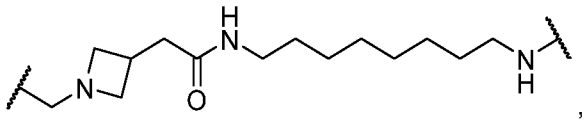
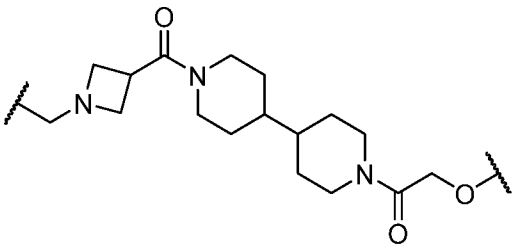
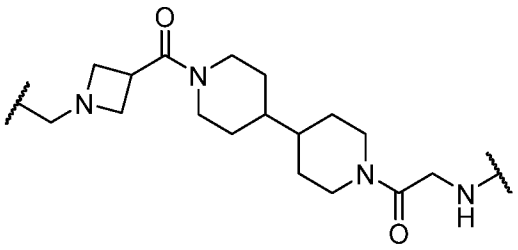
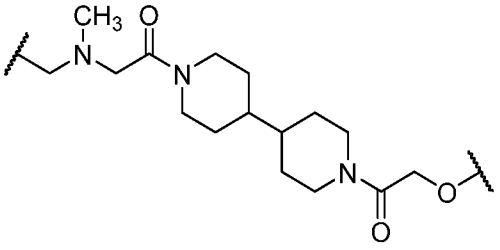
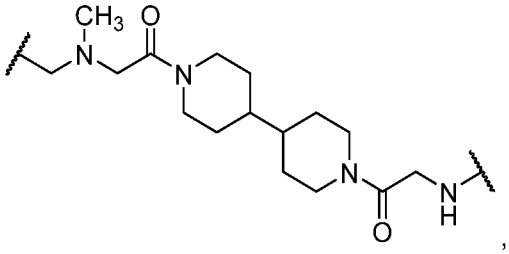
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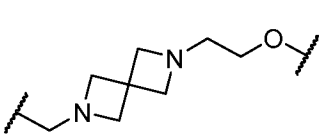
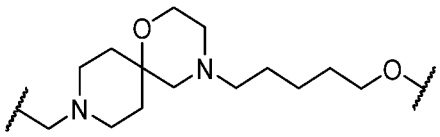
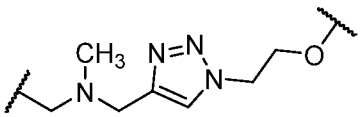
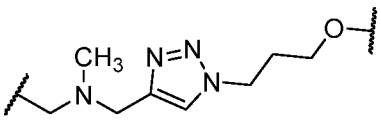
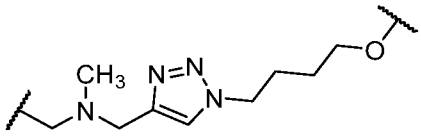
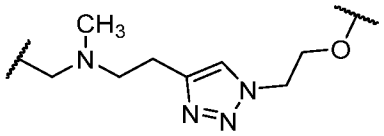
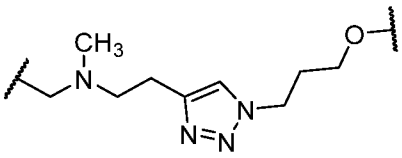
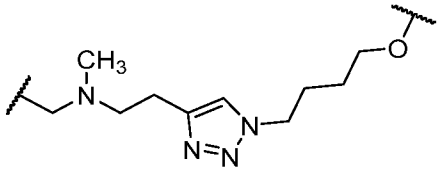
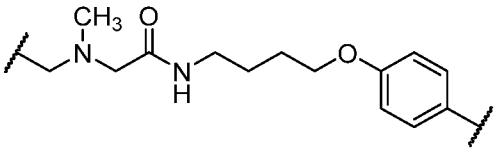
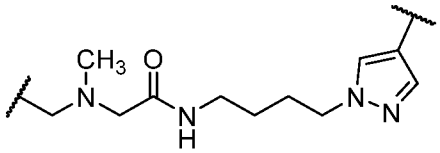
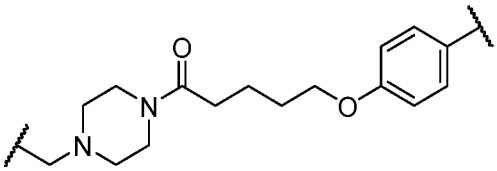
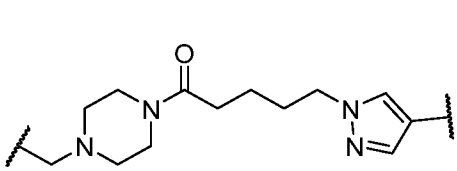
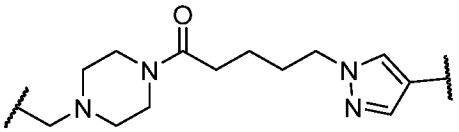
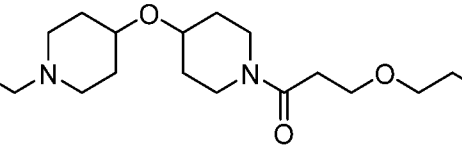
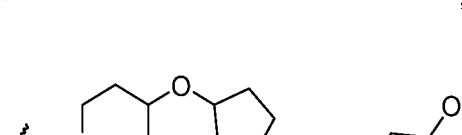
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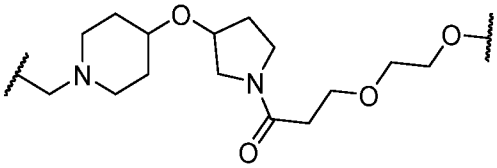
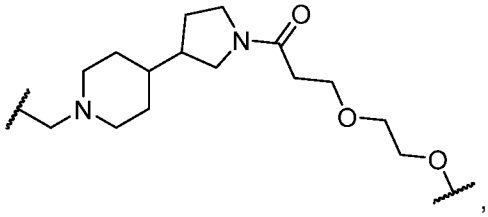
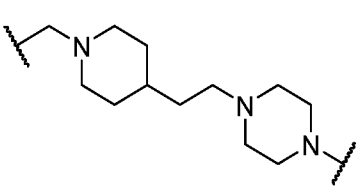
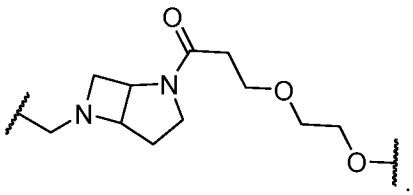

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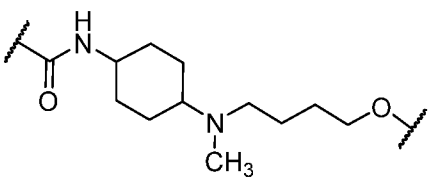
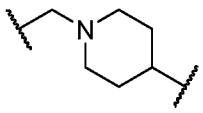
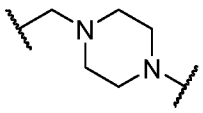
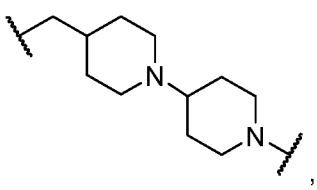
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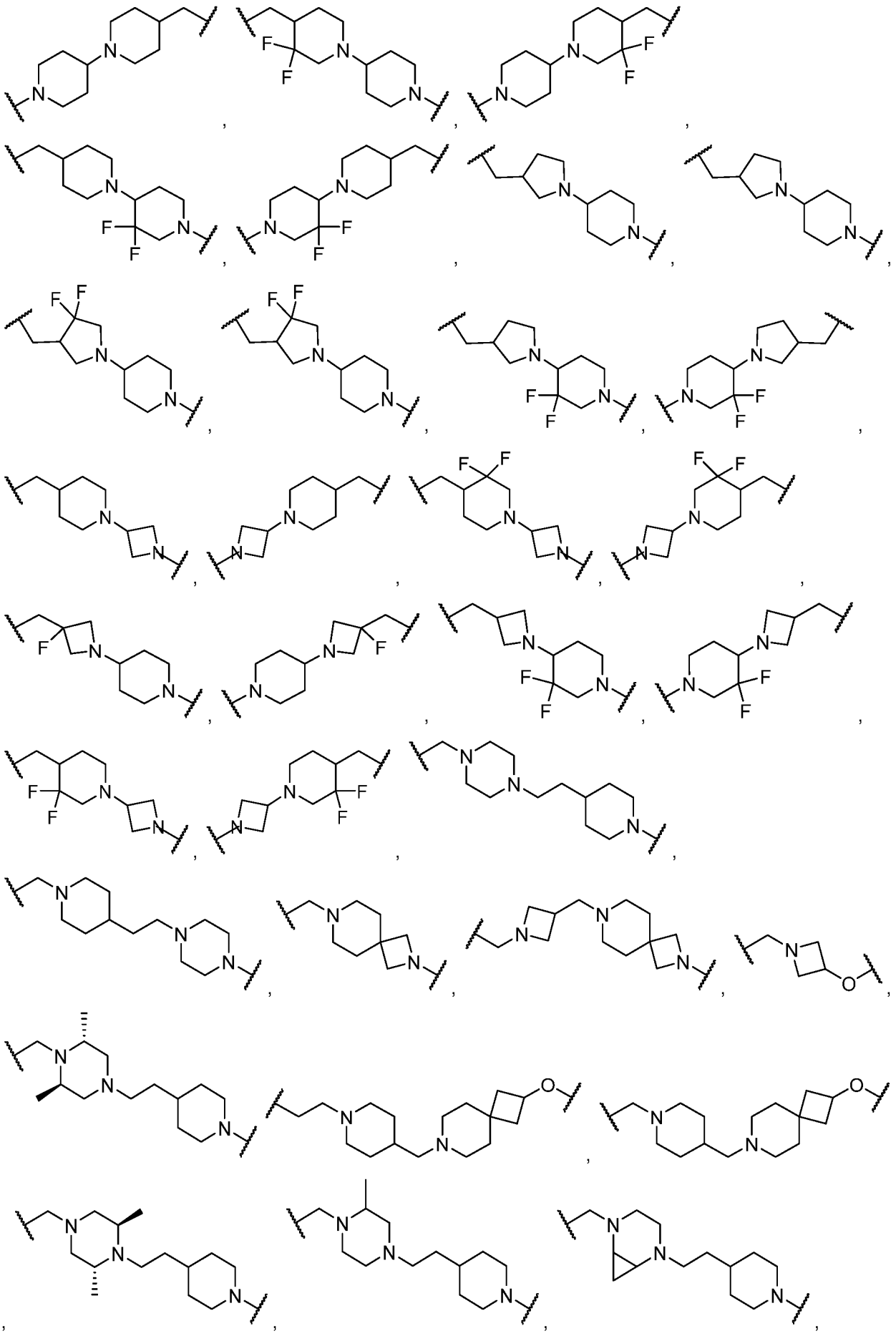

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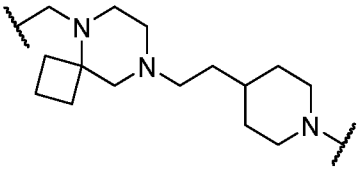
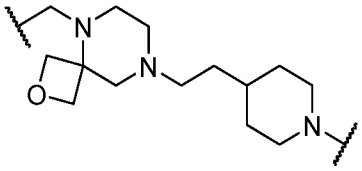
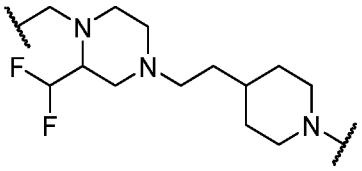
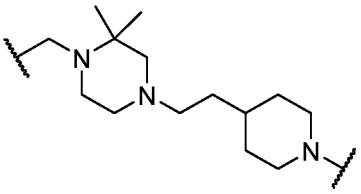
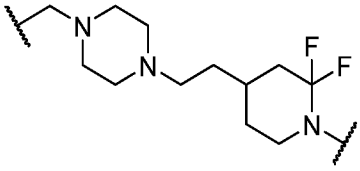
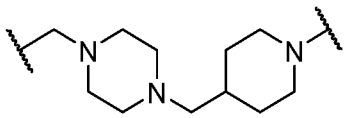
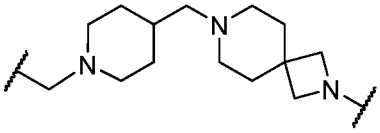
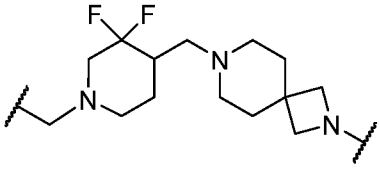
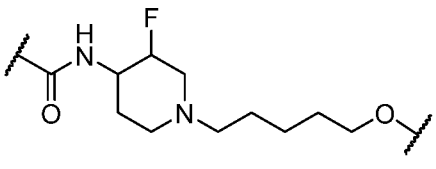
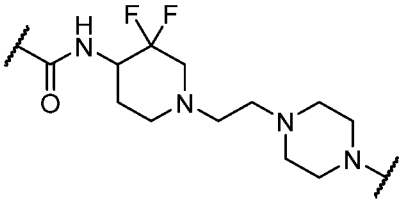
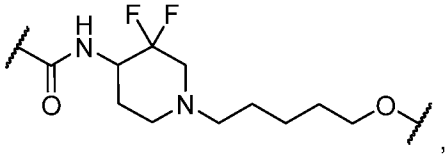

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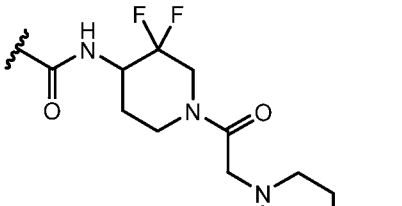
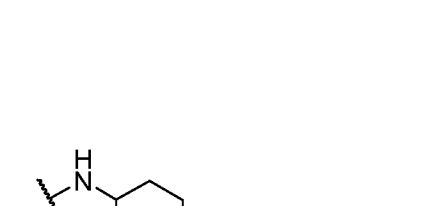
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88. The compound of any one of claims 1 to 86, wherein the linker has the structure of


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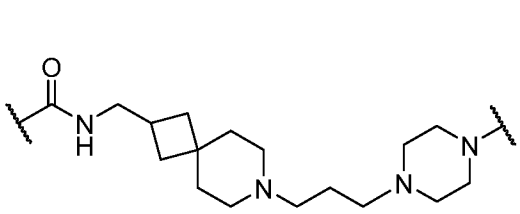
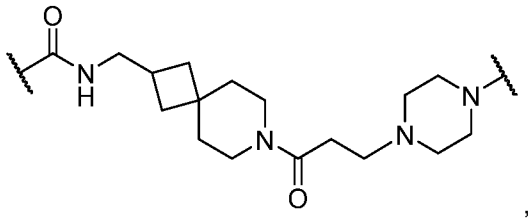
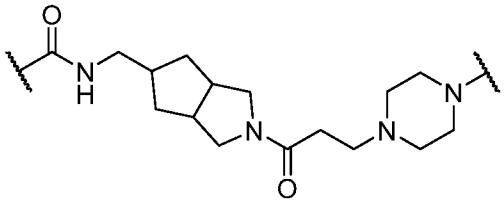
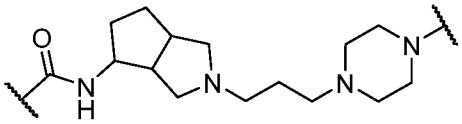
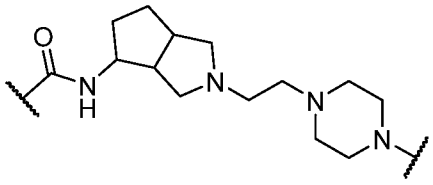
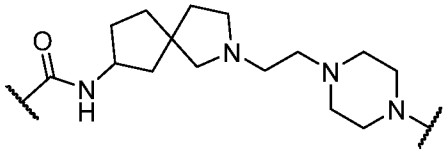
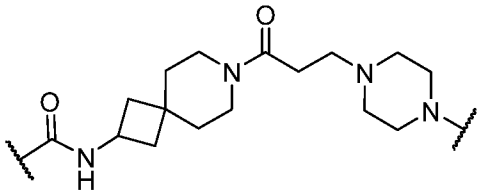
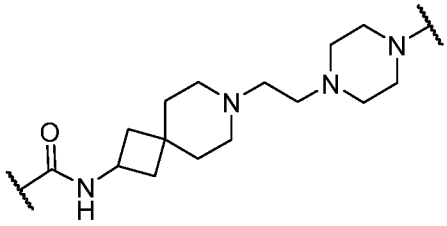
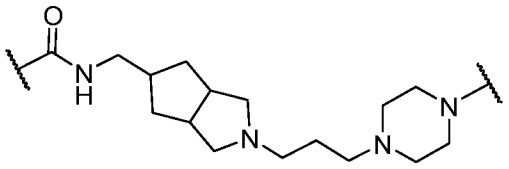
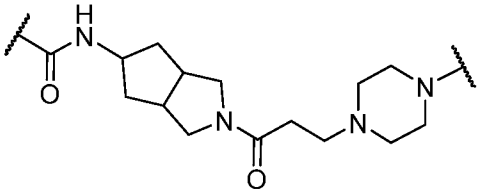
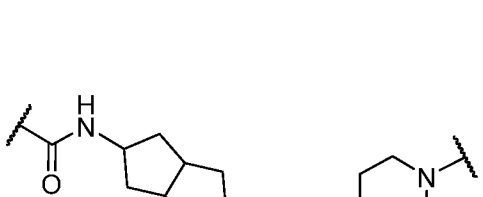
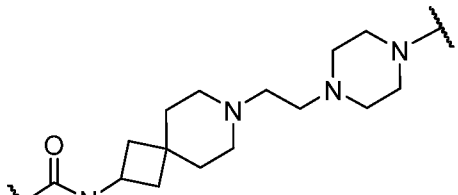
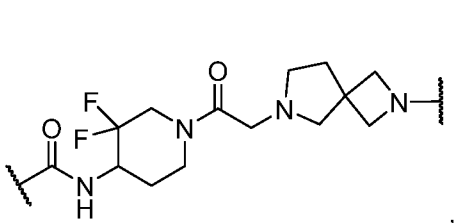
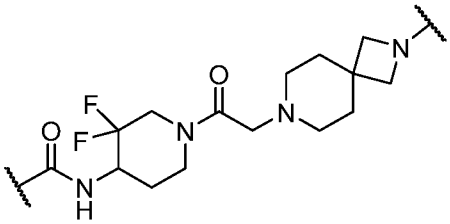
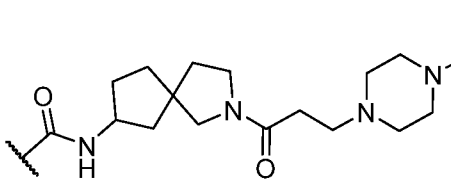
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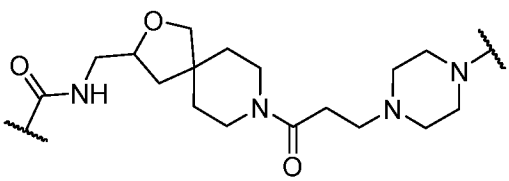
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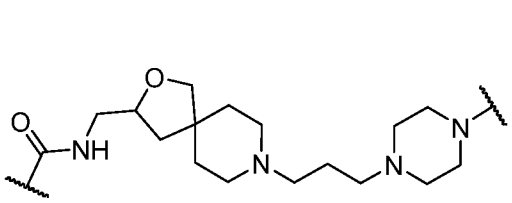
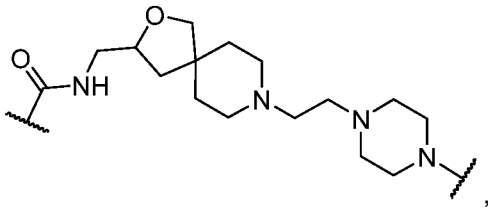
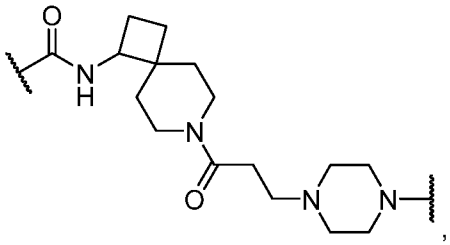
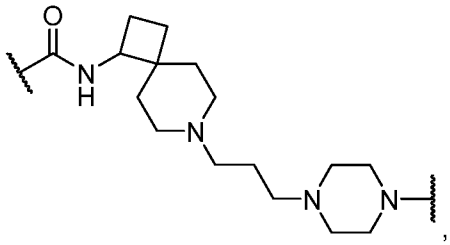
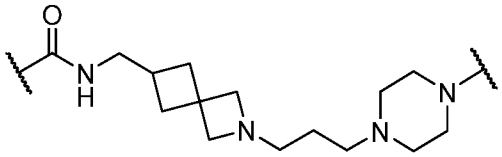
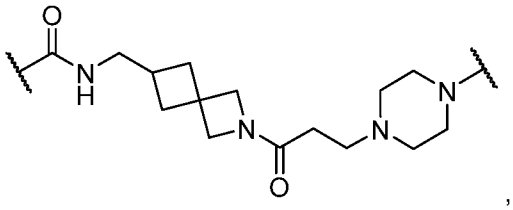
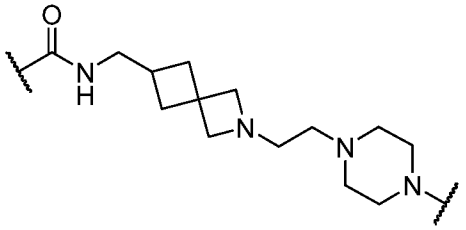
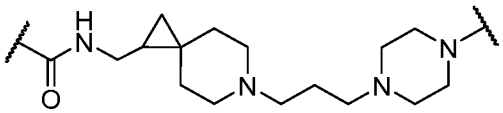
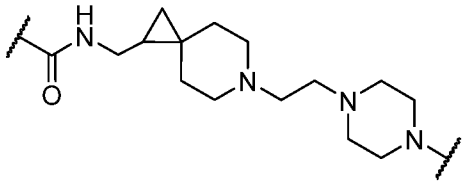
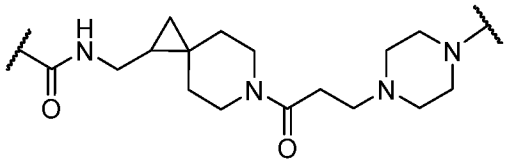
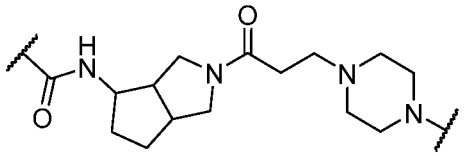
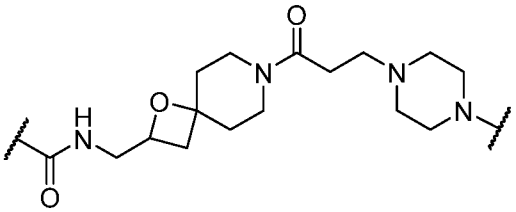
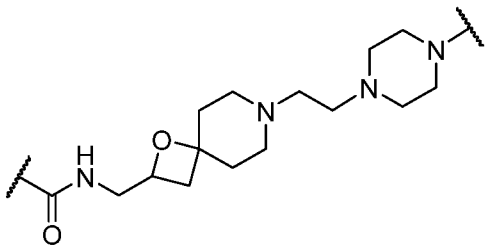
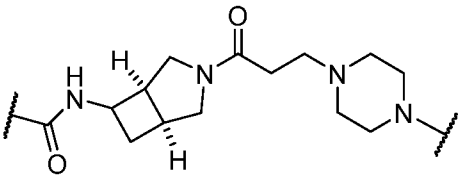
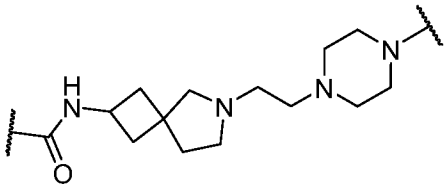
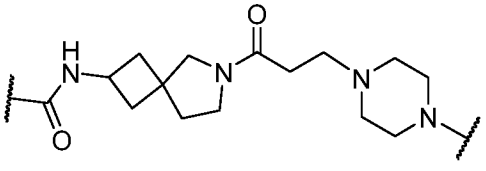
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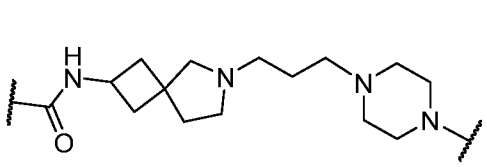
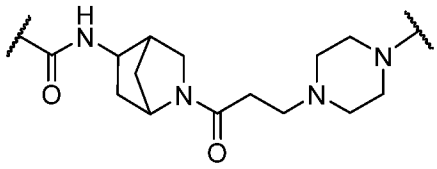
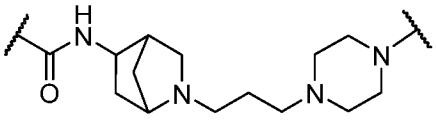
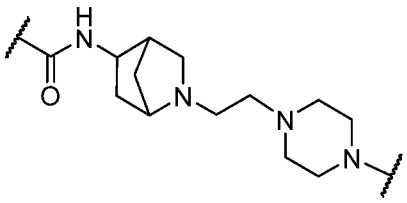
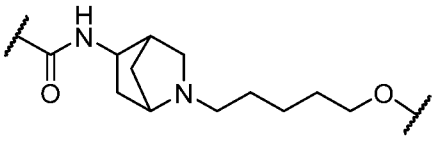
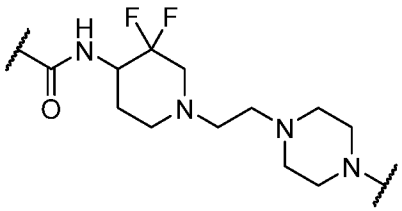
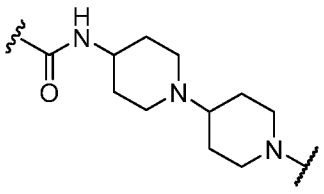
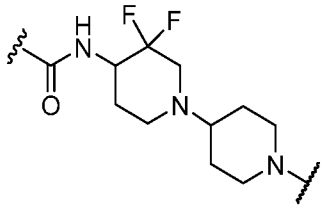
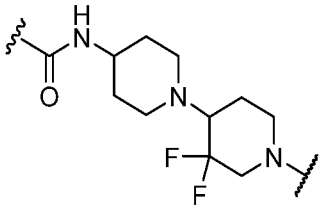
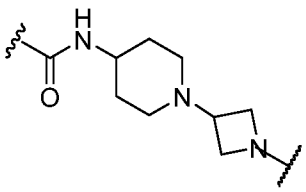
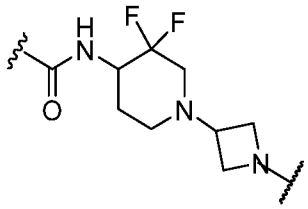
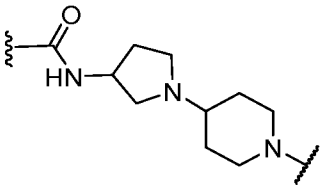
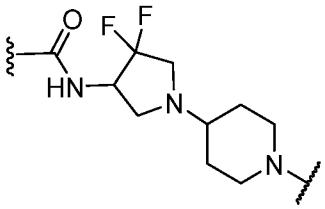
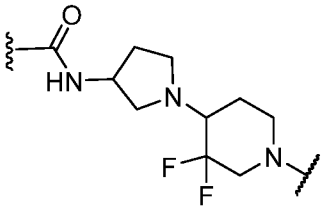
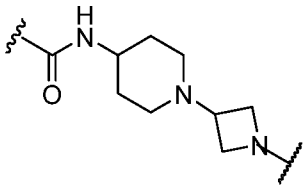
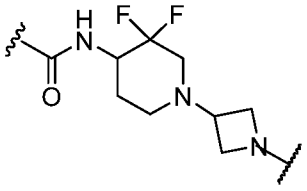
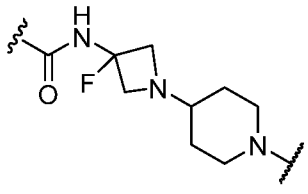
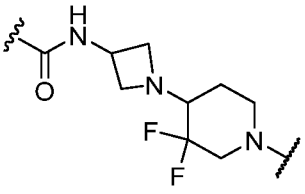
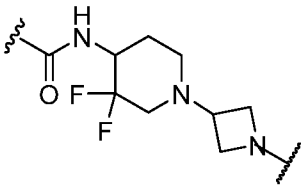
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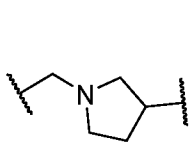
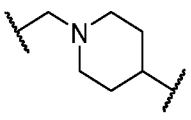
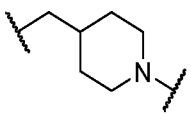
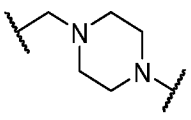
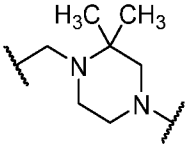
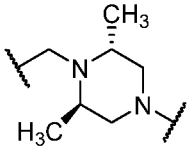
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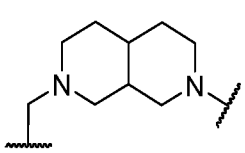
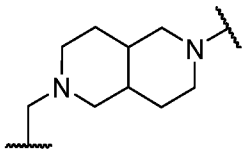
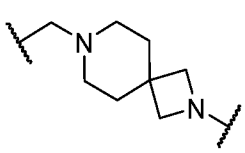
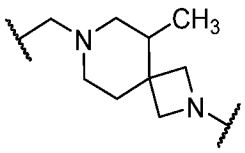
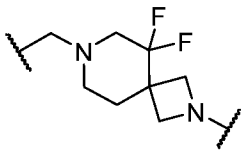
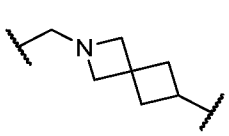
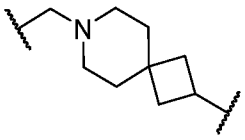
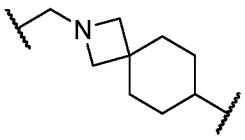
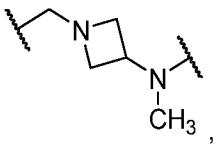
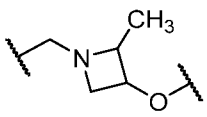
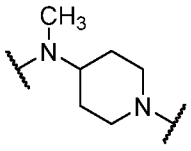
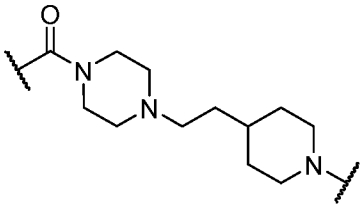
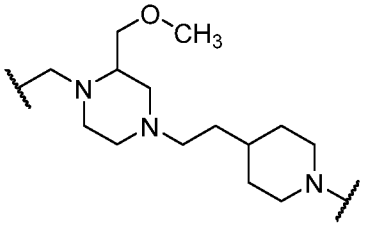
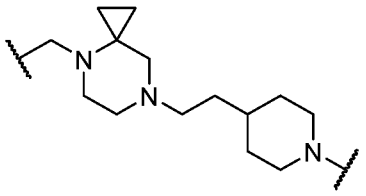
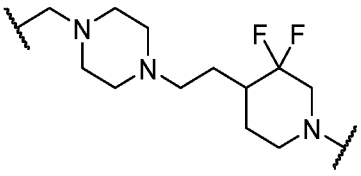
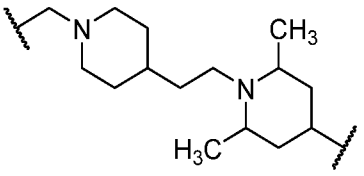
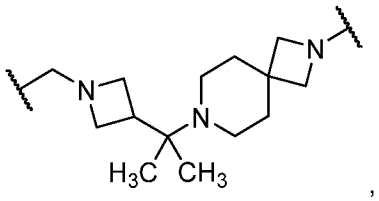
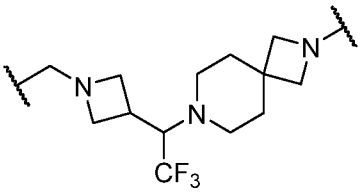
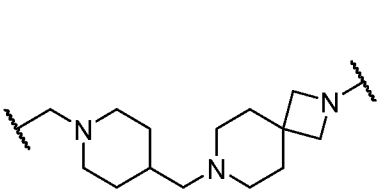
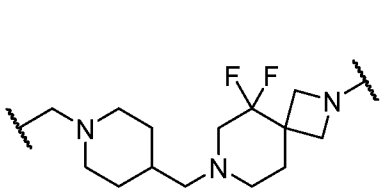
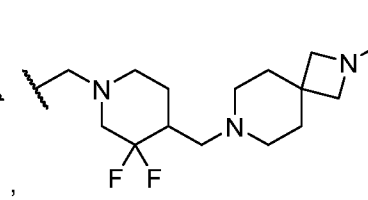
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89. The compound of any one of claims 1 to 86, wherein the linker has the structure of:

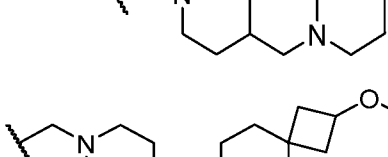
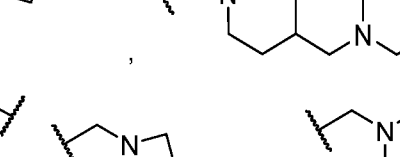
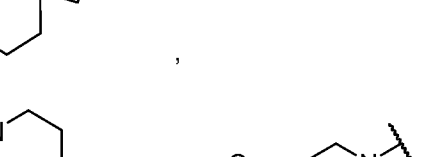
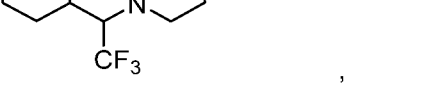

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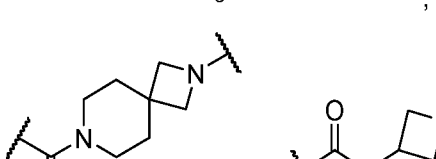
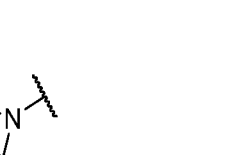

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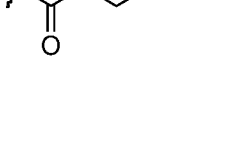
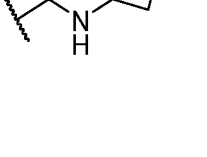
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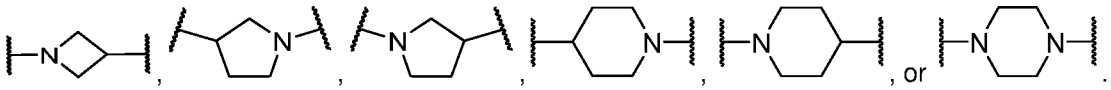
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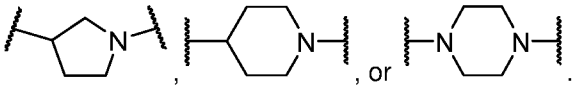
90. The compound of claim 1, wherein the linker is optionally substituted C_3-C_{10} carbocyclylene, optionally substituted C_{2-10} heterocyclylene, optionally substituted C_6-C_{10} arylene, or optionally substituted C_2-C_9 heteroarylene.

91. The compound of claim 90, wherein the linker is optionally substituted C_{2-10} heterocyclylene

92. The compound of claim 91, wherein the linker has the structure of  ,



93. The compound of claim 92, wherein the linker has the structure of  ,

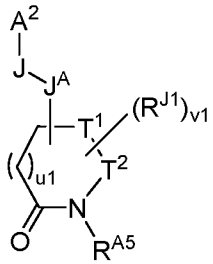


94. The compound of claim 1, wherein the linker is absent.

95. The compound of any one of claims 1 to 94, wherein the degradation moiety is a ubiquitin ligase binding moiety.

96. The compound of claim 95, wherein the ubiquitin ligase binding moiety comprises Cereblon ligands, IAP (Inhibitors of Apoptosis) ligands, mouse double minute 2 homolog (MDM2), or von Hippel-Lindau (VHL) ligands, or derivatives or analogs thereof.

97. The compound of claim 95 or 96, wherein the degradation moiety comprises the structure of **Formula Y**:



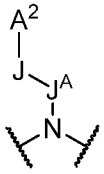
Formula Y,

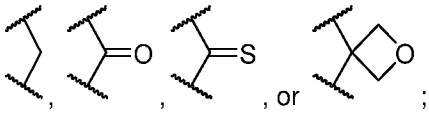
where

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

v1 is 0, 1, 2, 3, 4, or 5;

u1 is 1, 2, or 3;

T^1 is a bond or  ;

T^2 is  ;

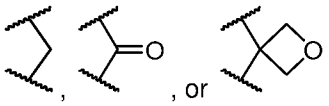
R^{5A} is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

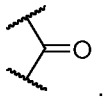
each R^{J1} is, independently, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

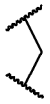
J^A is absent, O, optionally substituted amino, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl; and

J is absent, optionally substituted C_3-C_{10} carbocyclylene, optionally substituted C_6-C_{10} arylene, optionally substituted C_2-C_9 heterocyclylene, or optionally substituted C_2-C_9 heteroarylene,

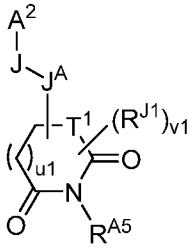
or a pharmaceutically acceptable salt thereof.

98. The compound of claim 97, wherein T^2 is  .

99. The compound of claim 98, wherein T^2 is  .

100. The compound of claim 98, wherein T^2 is 

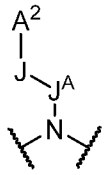
101. The compound of any one of claims 97 to 100, wherein the structure of **Formula Y** has the structure of **Formula Y1**:



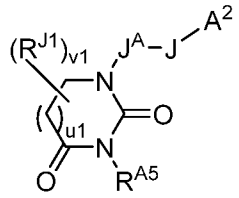
Formula Y1,

or a pharmaceutically acceptable salt thereof.

102. The compound of claim 101, wherein T^1 is a bond.

103. the compound of claim 101, wherein T^1 is  .

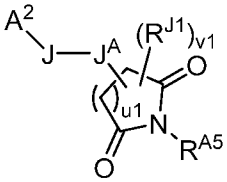
104. The compound of any one of claims 97 to 103, wherein the structure of **Formula Y** has the structure of **Formula Y2**:



Formula Y2,

or a pharmaceutically acceptable salt thereof.

105. The compound of any one of claims 97 to 103, wherein the structure of **Formula Y** has the structure of **Formula Z**:

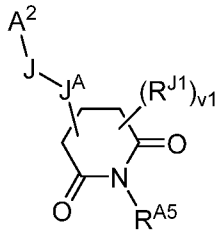


Formula Z,

or a pharmaceutically acceptable salt thereof.

106. The compound of any one of claims 97 to 105, wherein u1 is 2.

107. The compound of claim 106, wherein the structure of **Formula Z** has the structure of **Formula AA0**:

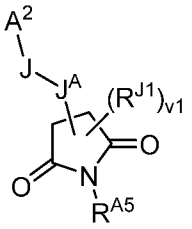


Formula AA0,

or a pharmaceutically acceptable salt thereof.

108. The compound of any one of claims 97 to 105, wherein u1 is 1.

109. The compound of claim 108, wherein the structure of **Formula Z** has the structure of **Formula AB**:

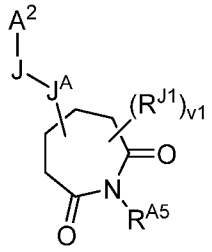


Formula AB,

or a pharmaceutically acceptable salt thereof.

110. The compound of any one of claims 97 to 105, wherein u1 is 3.

111. The compound of claim 110, wherein the structure of **Formula Z** has the structure of **Formula AC**:



Formula AC,

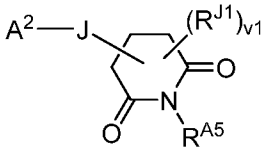
or a pharmaceutically acceptable salt thereof.

112. The compound of any one of claims 97 to 111, wherein J^A is absent.

113. The compound of any one of claims 97 to 111, wherein J^A is optionally substituted C_1-C_6 alkyl.

114. The compound of claim 113, wherein J^A is  .

115. The compound of claim 114, wherein the structure of **Formula AA0** has the structure of **Formula AA0**:



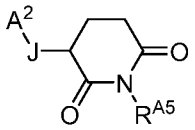
Formula AA,

or a pharmaceutically acceptable salt thereof.

116. The compound of any one of claims 97 to 115, wherein v1 is 0, 1, 2, or 3.

117. The compound of claim 116, wherein v1 is 0.

118. The compound of claim 117, wherein the structure of **Formula AA** has the structure of **Formula AA1**:



Formula AA1,

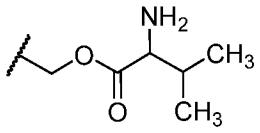
or a pharmaceutically acceptable salt thereof.

119. The compound of any one of claims 97 to 118, wherein R^{A5} is H or optionally substituted C_1-C_6 alkyl.

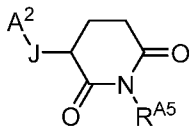
120. The compound of claim 119, wherein R^{A5} is H.

121. The compound of claim 119, wherein R^{A5} is methyl.

122. The compound of any one of claims 97 to 118, wherein R^{A5} is optionally substituted C_1-C_6 heteroalkyl.

123. The compound of claim 122, wherein R^{A5} is  .

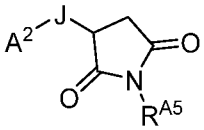
124. The compound of claim 115, wherein the structure of **Formula AA** has the structure of **Formula AA1**:



Formula AA1,

or a pharmaceutically acceptable salt thereof.

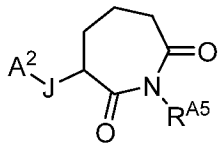
125. The compound of claim 109, wherein the structure of **Formula AB** has the structure of **Formula AB1**:



Formula AB1,

or a pharmaceutically acceptable salt thereof.

126. The compound of claim 111, wherein the structure of **Formula AC** has the structure of **Formula AC1**:

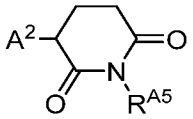


Formula AC1,

or a pharmaceutically acceptable salt thereof.

127. The compound of any one of claims 97 to 126, wherein J is absent.

128. The compound of claim 127, wherein the structure of **Formula AA1** has the structure of **Formula AA2**:

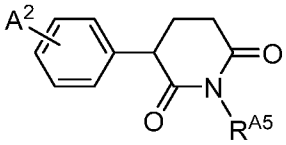


Formula AA2,

or a pharmaceutically acceptable salt thereof.

129. The compound of any one of claims 97 to 126, wherein J is optionally substituted C_3-C_{10} carbocyclylene or optionally substituted C_6-C_{10} arylene.

130. The compound of claim 129, wherein the structure of **Formula AA** has the structure of **Formula AA4**:

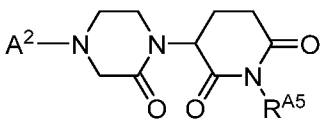


Formula AA4,

or a pharmaceutically acceptable salt thereof.

131. The compound of any one of claims 97 to 126, wherein J is optionally substituted C_2-C_9 heterocyclylene or optionally substituted C_2-C_9 heteroarylene.

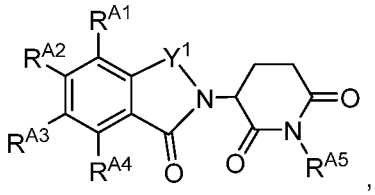
132. The compound of claim 131, wherein the structure of **Formula AA** has the structure of **Formula AA3**:



Formula AA3,

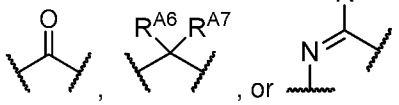
or a pharmaceutically acceptable salt thereof.

133. The compound of claim 131, wherein the structure of **Formula AA** has the structure of **Formula A**:



Formula A

wherein in

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,

wherein one of R^{A1}, R^{A2}, R^{A3}, and R^{A4} is A^2, or  is substituted with A^2, or a pharmaceutically acceptable salt thereof.

134. The compound of claim 133, 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, 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

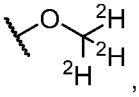
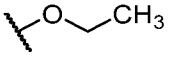
 is optionally substituted C_6-C_{10} aryl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heteroaryl, or C_2-C_9 heterocyclyl, any of which is optionally substituted with A^2,

wherein one of R^{A1}, R^{A2}, R^{A3}, and R^{A4} is A^2, or  is substituted with A^2, or a pharmaceutically acceptable salt thereof.

135. The compound of claim 134, wherein each of R^{A1}, R^{A2}, R^{A3}, and R^{A4} is, H, A^2, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted -O-C_3-C_6 carbocyclyl, hydroxyl, optionally substituted amino; or R^{A1} and R^{A2}, R^{A2} and R^{A3}, or R^{A3} and R^{A4}, together with the carbon atoms to which each is attached, combine to form  ; and

 is optionally substituted C_2-C_9 heterocyclyl, which is optionally substituted with A^2,

wherein one of R^{A1}, R^{A2}, R^{A3}, and R^{A4} is A^2, or  is substituted with A^2.

136. The compound of claim 135, wherein each of R^{A1}, R^{A2}, R^{A3}, and R^{A4} is, independently, H, A^2, F,  ,  ,  , or  ; or R^{A1} and R^{A2}, R^{A2} and R^{A3}, or R^{A3} and R^{A4}, together with the carbon atoms to which each is attached, combine to form  ; and

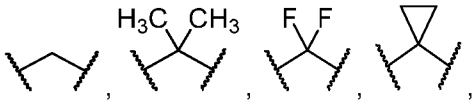
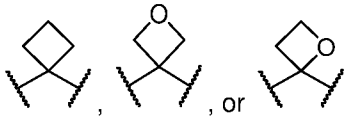
 is optionally substituted C_2-C_9 heterocyclyl, which is optionally substituted with A^2,

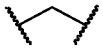
wherein one of R^{A1}, R^{A2}, R^{A3}, and R^{A4} is A^2, or  is substituted with A^2.

137. The compound of any one of claims 133 to 136, wherein Y^1 is  or  .

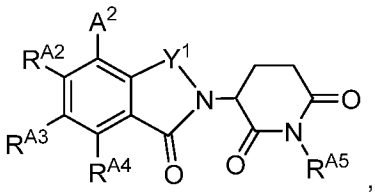
138. The compound of claim 137, wherein Y^1 is  .

139. The compound of claim 137, wherein Y^1 is  .

140. The compound of claim 139, wherein Y^1 is  ,  , or .

141. The compound of claim 140, wherein Y^1 is  .

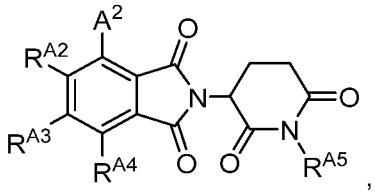
142. The compound of any one of claims 133 to 141, wherein the structure of **Formula A** has the structure of **Formula A1**:



Formula A1

or a pharmaceutically acceptable salt thereof.

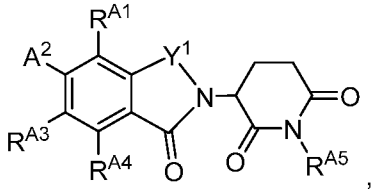
143. The compound of any one of claims 133 to 141, wherein the structure of **Formula A** has the structure of **Formula A2**:



Formula A2

or a pharmaceutically acceptable salt thereof.

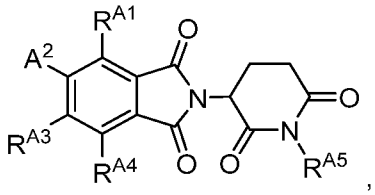
144. The compound of any one of claims 133 to 141, wherein the structure of **Formula A** has the structure of **Formula A3**:



Formula A3

or a pharmaceutically acceptable salt thereof.

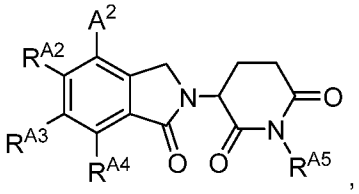
145. The compound of any one of claims 133 to 141, wherein the structure of **Formula A** has the structure of **Formula A4**:



Formula A4

or a pharmaceutically acceptable salt thereof.

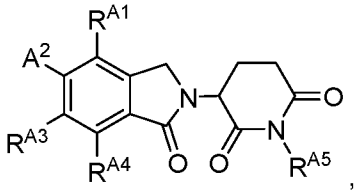
146. The compound of any one of claims 133 to 141, wherein the structure of **Formula A** has the structure of **Formula A5**:



Formula A5

or a pharmaceutically acceptable salt thereof.

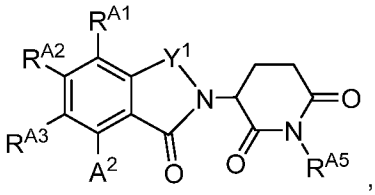
147. The compound of any one of claims 133 to 141, wherein the structure of **Formula A** has the structure of **Formula A6**:



Formula A6

or a pharmaceutically acceptable salt thereof.

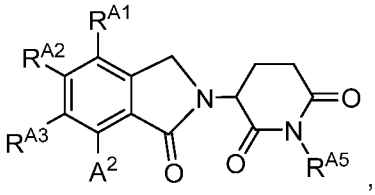
148. The compound of any one of claims 133 to 141, wherein the structure of **Formula A** has the structure of **Formula A7**:



Formula A7

or a pharmaceutically acceptable salt thereof.

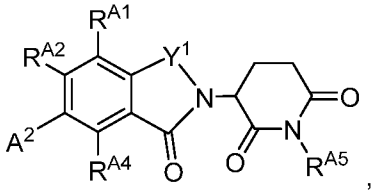
149. The compound of any one of claims 133 to 141, wherein the structure of **Formula A** has the structure of **Formula A8**:



Formula A8

or a pharmaceutically acceptable salt thereof.

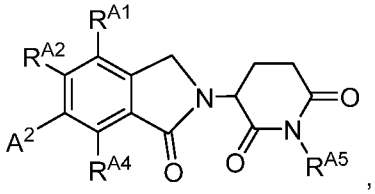
150. The compound of any one of claims 133 to 141, wherein the structure of **Formula A** has the structure of **Formula A9**:



Formula A9

or a pharmaceutically acceptable salt thereof.

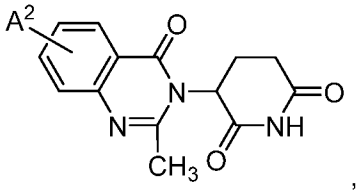
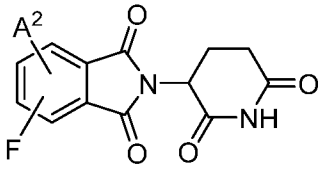
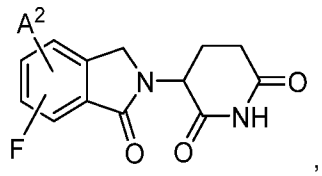
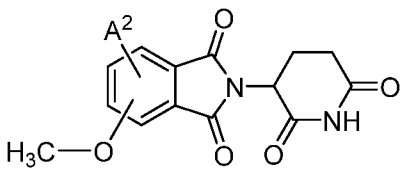
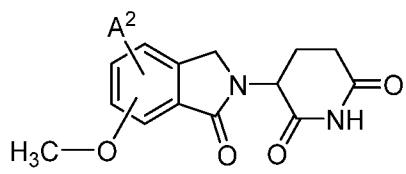
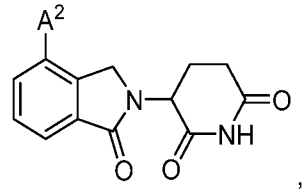
151. The compound of any one of claims 133 to 141, wherein the structure of **Formula A** has the structure of **Formula A10**:

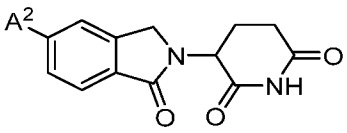
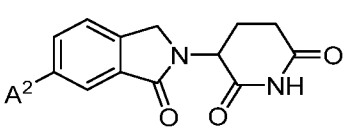
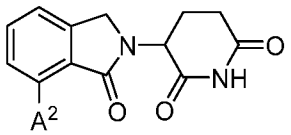
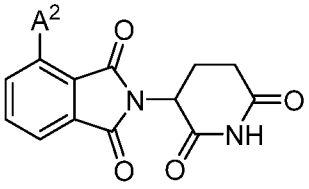
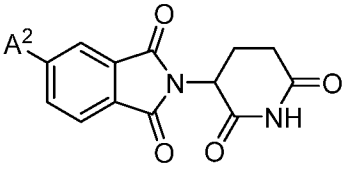


Formula A10

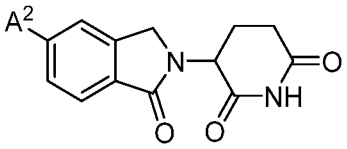
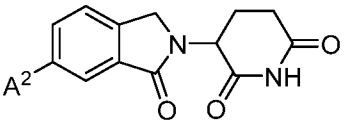
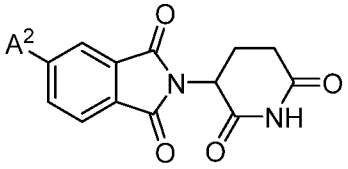
or a pharmaceutically acceptable salt thereof.

152. The compound of any one of claims 133 to 151, wherein the structure of **Formula A** is

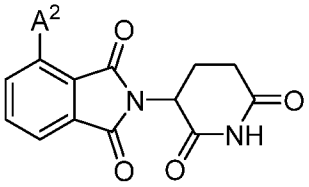
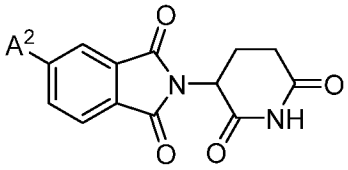







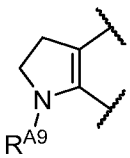
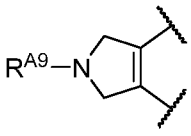

,

,

,

, or

, or derivative or analog thereof.

153. The compound of claim 152, wherein the structure of **Formula A** is


,

, or

.

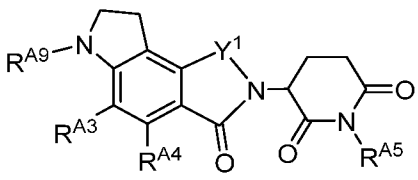
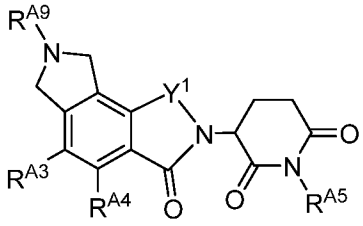
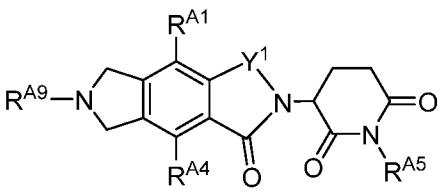
154. The compound of claim 153, wherein the structure of **Formula A** is

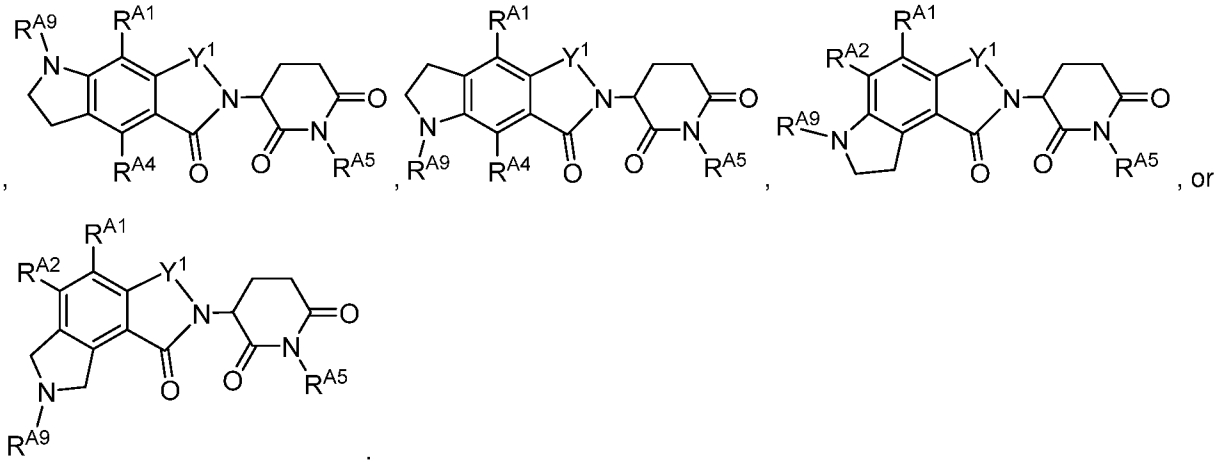

or

, or derivative or analog thereof.

155. The compound of any one of claims 133 to 151, wherein  is  or  ,

wherein R^{A9} is H, A^2, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl.

156. The compound of claim 155, wherein the structure of **Formula A** is

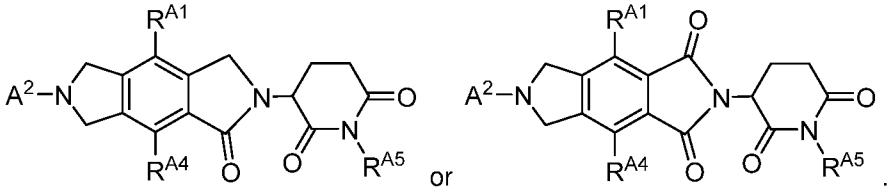

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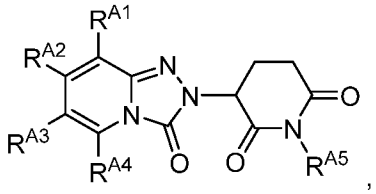
157. The compound of claim 156, wherein R^{A9} is H.

158. The compound of claim 156, wherein R^{A9} is A^2.

159. The compound of claim 158, wherein the structure of **Formula A** is



160. The compound of claim 129, wherein the structure of **Formula AA** has the structure of **Formula B**:



Formula B

wherein

R^{A5} 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,

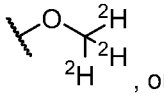
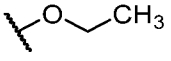
wherein one of R^{A1}, R^{A2}, R^{A3}, and R^{A4} is A^2, or  is substituted with A^2,

or a pharmaceutically acceptable salt thereof.

161. The compound of claim 160, wherein each of R^{A1}, R^{A2}, R^{A3}, and R^{A4} is, H, A^2, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted -O-C_3-C_6 carbocyclyl, hydroxyl, optionally substituted amino; or R^{A1} and R^{A2}, R^{A2} and R^{A3}, or R^{A3} and R^{A4}, together with the carbon atoms to which each is attached, combine to form  ; and

 is optionally substituted C_2-C_9 heterocyclyl, which is optionally substituted with A^2,

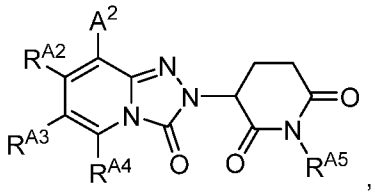
wherein one of R^{A1}, R^{A2}, R^{A3}, and R^{A4} is A^2, or  is substituted with A^2.

162. The compound of claim 161, wherein each of R^{A1}, R^{A2}, R^{A3}, and R^{A4} is, independently, H, A^2, F,  ,  ,  , or  ; or R^{A1} and R^{A2}, R^{A2} and R^{A3}, or R^{A3} and R^{A4}, together with the carbon atoms to which each is attached, combine to form  ; and

 is optionally substituted C_2-C_9 heterocyclyl, which is optionally substituted with A^2,

wherein one of R^{A1}, R^{A2}, R^{A3}, and R^{A4} is A^2, or  is substituted with A^2.

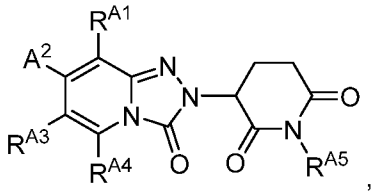
163. The compound of any one of claims 160 to 162, wherein the structure of **Formula B** has the structure of **Formula B1**:



Formula B1

or a pharmaceutically acceptable salt thereof.

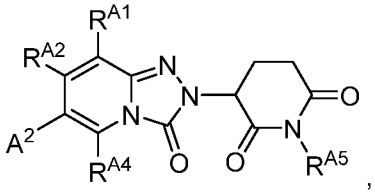
164. The compound of any one of claims 160 to 162, wherein the structure of **Formula B** has the structure of **Formula B2**:



Formula B2

or a pharmaceutically acceptable salt thereof.

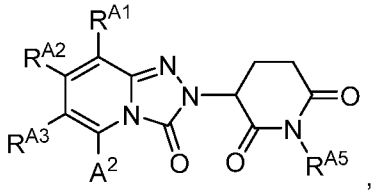
165. The compound of any one of claims 160 to 162, wherein the structure of **Formula B** has the structure of **Formula B3**:



Formula B3

or a pharmaceutically acceptable salt thereof.

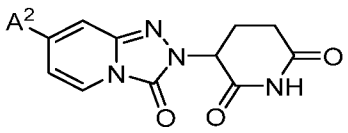
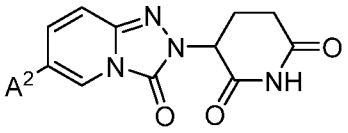
166. The compound of any one of claims 160 to 162, wherein the structure of **Formula B** has the structure of **Formula B4**:



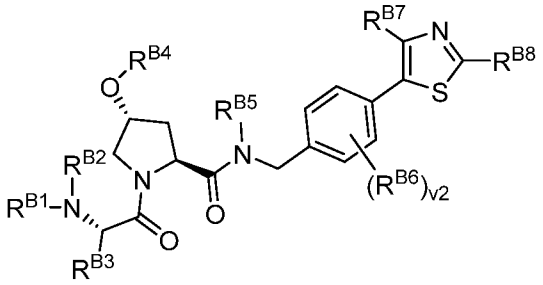
Formula B4

or a pharmaceutically acceptable salt thereof.

167. The compound of any one of claims 160 to 162, wherein the structure of **Formula B** is

 or  .

168. The compound of any one of claims 1 to 94, wherein the degradation moiety comprises the structure of **Formula C**:



Formula C,

wherein

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;

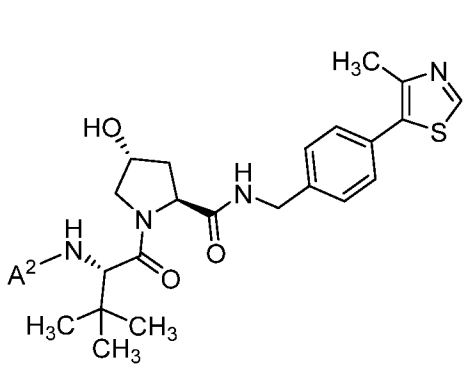
each R^{B6} is, independently, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino; and

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

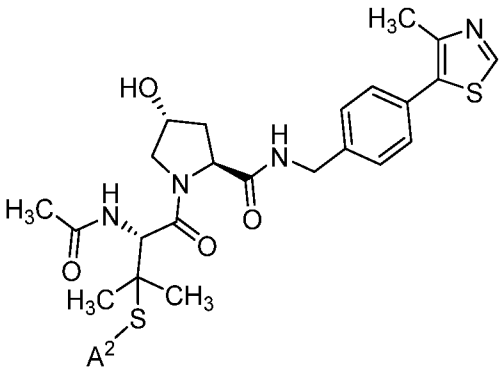
wherein one of R^{B1} and R^{B3} is A^2,

or a pharmaceutically acceptable salt thereof.

169. The compound of claim 168, wherein the structure of **Formula C** is

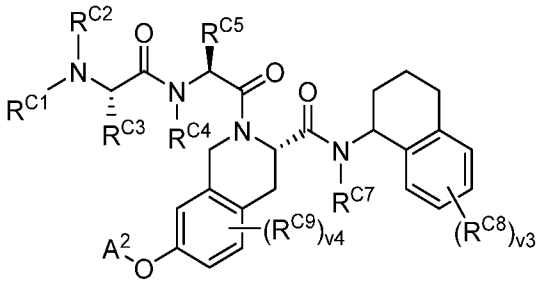


or



, or derivative or analog thereof.

170. The compound of any one of claims 1 to 94, wherein the degradation moiety comprises the structure of **Formula D**:



Formula D,

wherein

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

each of R^{C1}, R^{C2}, and R^{C7} is, independently, H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

R^{C3} is 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^{C5} is 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;

v3 is 0, 1, 2, 3, or 4;

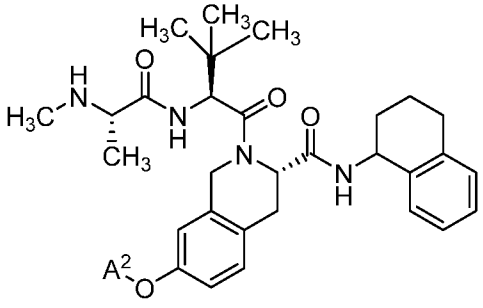
each R^{C8} is, independently, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

v4 is 0, 1, 2, 3, or 4; and

each R^{C9} is, independently, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino,

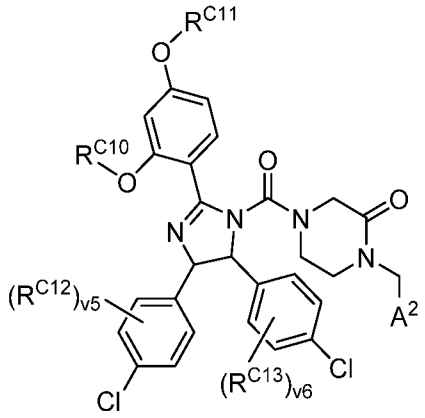
or a pharmaceutically acceptable salt thereof.

171. The compound of claim 170, wherein the structure of **Formula D** is



, or derivative or analog thereof.

172. The compound of any one of claims 1 to 94, wherein the degradation moiety comprises the structure of **Formula E**:



Formula E,

wherein

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

each of R^{C10} and R^{C11} is, independently, 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;

v5 is 0, 1, 2, 3, or 4;

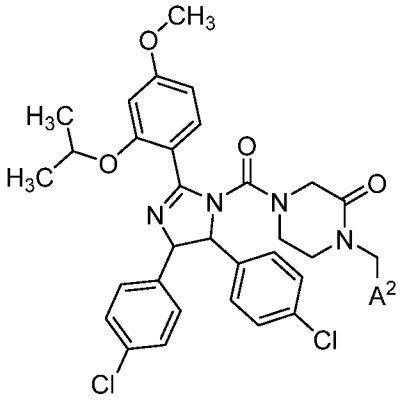
each R^{C12} is, independently, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

v6 is 0, 1, 2, 3, or 4; and

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

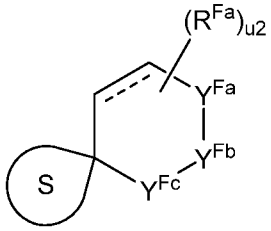
or a pharmaceutically acceptable salt thereof.

173. The compound of claim 172, wherein the structure of **Formula E** is



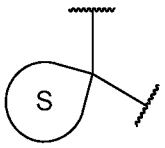
, or derivative or analog thereof.

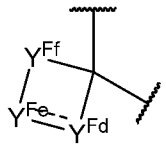
174. The compound of any one of claims 1 to 94, wherein the degradation moiety comprises the structure of **Formula FA**:



Formula FA,

where



is 

, or a bicyclic moiety which is substituted with A^2 and substituted with one or more groups independently selected from H, R^{FF1}, and oxo;

==== is a single bond or a double bond;

u2 is 0, 1, 2, or 3;

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

Y^{Fa} is $CR^{Fb}R^{Fc}$, C=O, C=S, $C=CH_2$, SO_2, S(O), P(O)Oalkyl, P(O)NHalkyl, $P(O)N(alkyl)_2$, P(O)alkyl, P(O)OH, $P(O)NH_2$;

Y^{Fb} is NH, NR^{FF1}, CH_2, CHR^{FF1}, $C(R^{FF1})_2$, O, or S;

Y^{Fc} is $CR^{Fd}R^{Fe}$, C=O, C=S, $C=CH_2$, SO_2, S(O), P(O)Oalkyl, P(O)NHalkyl, $P(O)N(alkyl)_2$, P(O)alkyl, P(O)OH, $P(O)NH_2$;

each of R^{Fb}, R^{Fc}, R^{Fd}, and R^{Fe} is, independently, H, alkyl, aliphatic, heteroaliphatic, aryl, heteroaryl, carbocyclyl, hydroxyl, alkoxy, amino, —NHalkyl, or —$Nalkyl_2$;

or R^{Fb} and R^{Fc}, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclylene comprising 1 or 2 heteroatoms selected from N and O;

or R^{Fd} and R^{Fe}, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclylene comprising 1 or 2 heteroatoms selected from N and O; and

or R^{Fd} and R^{Fb}, together with the carbon atoms to which each is attached, combine to form a 1, 2, 3, or 4 carbon bridged ring;

each of Y^{Fd} and Y^{Ff} is, independently, CH_2, CHR^{FF2}, $C(R^{FF2})_2$, C(O), N, NH, NR^{FF3}, O, S, or S(O);

Y^{Fe} is a bond or a divalent moiety attached to Y^{Fd} and Y^{Ff} that contains 1 to 5 contiguous carbon atoms that form a 3 to 8-membered ring,

wherein 1, 2, or 3 carbon atoms can be replaced with a nitrogen, oxygen, or sulfur atom;

wherein one of the ring atoms is substituted with A^2 and the others are substituted with one or more groups independently selected from H and R^{FF1}; and

wherein the contiguous atoms of Y^{Fe} can be attached through a single or double bond;

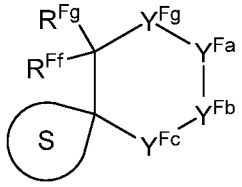
each R^{FF1} is, independently, H, alkyl, alkenyl, alkynyl, aliphatic, heteroaliphatic, carbocyclyl, halogen, hydroxyl, amino, cyano, alkoxy, aryl, heteroaryl, heterocyclyl, alkylamino, alkylhydroxyl, or haloalkyl;

each R^{FF2} is, independently, alkyl, alkene, alkyne, halogen, hydroxyl, alkoxy, azide, amino, —C(O)H, —C(O)OH, —C(O)(aliphatic, including alkyl), —C(O)O(aliphatic, including alkyl), —NH(aliphatic, including alkyl), —N(aliphatic including alkyl)(aliphatic including alkyl), —$NHSO_2$alkyl, —N(alkyl)SO_2alkyl, —$NHSO_2$aryl, —N(alkyl)SO_2aryl, —$NHSO_2$alkenyl, —N(alkyl)SO_2alkenyl, —$NHSO_2$alkynyl, —N(alkyl)SO_2alkynyl, aliphatic, heteroaliphatic, aryl, heteroaryl, hetercyclic, carbocyclic, cyano, nitro, nitroso, —SH, —Salkyl, or haloalkyl; and

R^{FF3} is alkyl, alkenyl, alkynyl, —C(O)H, —C(O)OH, —C(O)alkyl, or —C(O)Oalkyl,

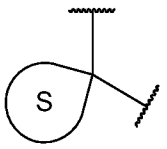
wherein if Y^{Fd} or Y^{Ff} is substituted with A^2, then Y^{Fe} is a bond, or a pharmaceutically acceptable salt thereof.

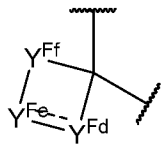
175. The compound of any one of claims 1 to 94, wherein the degradation moiety comprises the structure of **Formula FB**:



Formula FB,

where



is 

, or a bicyclic moiety which is substituted with A^2 and substituted with one or more groups independently selected from H, R^{FF1}, and oxo;

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

Y^{Fa} is $CR^{Fb}R^{Fc}$, C=O, C=S, $C=CH_2$, SO_2, S(O), P(O)Oalkyl, P(O)NHalkyl, P(O)N(alkyl)$_2$, P(O)alkyl, P(O)OH, $P(O)NH_2$;

each of Y^{Fb} and Y^{Fg} is, independently, NH, NR^{FF1}, CH_2, CHR^{FF1}, $C(R^{FF1})_2$, O, or S;

Y^{Fc} is $CR^{Fd}R^{Fe}$, C=O, C=S, $C=CH_2$, SO_2, S(O), P(O)Oalkyl, P(O)NHalkyl, P(O)N(alkyl)$_2$, P(O)alkyl, P(O)OH, $P(O)NH_2$;

each of R^{Fb}, R^{Fc}, R^{Fd}, R^{Fe}, R^{Ff}, and R^{Fg} is, independently, H, alkyl, aliphatic, heteroaliphatic, aryl, heteroaryl, carbocyclyl, hydroxyl, alkoxy, amino, —NHalkyl, or —Nalkyl$_2$;

or R^{Fb} and R^{Fc}, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclylene comprising 1 or 2 heteroatoms selected from N and O;

or R^{Fd} and R^{Fe}, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclylene comprising 1 or 2 heteroatoms selected from N and O;

or R^{Ff} and R^{Fg}, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclylene comprising 1 or 2 heteroatoms selected from N and O;

or R^{Fd} and R^{Fb}, together with the carbon atoms to which each is attached, combine to form a 1, 2, 3, or 4 carbon bridged ring;

or R^{Fd} and R^{Ff}, together with the carbon atoms to which each is attached, combine to form a 1, 2, 3, or 4 carbon bridged ring;

or R^{Fb} and R^{Fg}, together with the carbon atoms to which each is attached, combine to form a 1, 2, 3, or 4 carbon bridged ring;

each of Y^{Fd} and Y^{Ff} is, independently, CH_2, CHR^{FF2}, $C(R^{FF2})_2$, C(O), N, NH, NR^{FF3}, O, S, or S(O);

Y^{Fe} is a bond or a divalent moiety attached to Y^{Fd} and Y^{Ff} that contains 1 to 5 contiguous carbon atoms that form a 3 to 8-membered ring,

wherein 1, 2, or 3 carbon atoms can be replaced with a nitrogen, oxygen, or sulfur atom;

wherein one of the ring atoms is substituted with A^2 and the others are substituted with one or more groups independently selected from H and R^{FF1}; and

wherein the contiguous atoms of Y^{Fe} can be attached through a single or double bond;

each R^{FF1} is, independently, H, alkyl, alkenyl, alkynyl, aliphatic, heteroaliphatic, carbocyclyl, halogen, hydroxyl, amino, cyano, alkoxy, aryl, heteroaryl, heterocyclyl, alkylamino, alkylhydroxyl, or haloalkyl;

each R^{FF2} is, independently, alkyl, alkene, alkyne, halogen, hydroxyl, alkoxy, azide, amino, —C(O)H, —C(O)OH, —C(O)(aliphatic, including alkyl), —C(O)O(aliphatic, including alkyl), —NH(aliphatic, including alkyl), —N(aliphatic including alkyl)(aliphatic including alkyl), —$NHSO_2$alkyl, —N(alkyl)SO_2alkyl, —$NHSO_2$aryl, —N(alkyl)SO_2aryl, —$NHSO_2$alkenyl, —N(alkyl)SO_2alkenyl, —$NHSO_2$alkynyl, —N(alkyl)SO_2alkynyl, aliphatic, heteroaliphatic, aryl, heteroaryl, hetercyclic, carbocyclic, cyano, nitro, nitroso, —SH, —Salkyl, or haloalkyl; and

R^{FF3} is alkyl, alkenyl, alkynyl, —C(O)H, —C(O)OH, —C(O)alkyl, or —C(O)Oalkyl,

wherein if Y^{Fd} or Y^{Ff} is substituted with A^2, then Y^{Fe} is a bond, or a pharmaceutically acceptable salt thereof.

176. The compound of any one of claims 1 to 94, wherein the degradation moiety comprises the structure of **Formula F1**:



Formula F1,

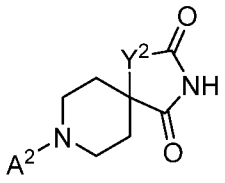
wherein

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

R^{F1} is absent or O,

or a pharmaceutically acceptable salt thereof.

177. The compound of any one of claims 1 to 94, wherein the degradation moiety comprises the structure of **Formula F2**:



Formula F2,

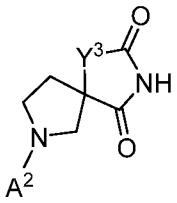
wherein

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

R^{F1} is absent or O,

or a pharmaceutically acceptable salt thereof.

178. The compound of any one of claims 1 to 94, wherein the degradation moiety comprises the structure of **Formula G**:



Formula G,

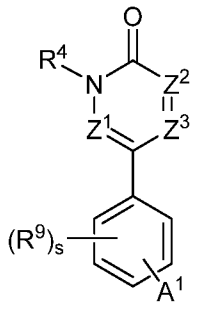
wherein

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

R^{F1} is absent or O,

or a pharmaceutically acceptable salt thereof.

179. The compound of any one of claims 1 to 178, wherein the BRD9 binding moiety comprises the structure of **Formula III**:



Formula III,

wherein

R^4 is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_{10} carbocyclyl; Z^1 is N or CR^5;

Z^2 is N or CR^{6a};

Z^3 is N or CR^{6b};

R^5 is H, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, or optionally substituted C_6-C_{10} aryl;

R^{6a} is H, halogen, cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino; R^{6b} is H, halogen, cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino; or R^{6a} and R^{6b}, together with the carbon atoms to which each is attached, combine to form optionally substituted C_6-C_{10} aryl or optionally substituted C_2-C_9 heteroaryl;

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

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

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

or a pharmaceutically acceptable salt thereof.

180. The compound of claim 179, wherein Z^1 is CR^5.

181. The compound of claim 179 or 180, wherein Z^2 is N.

182. The compound of claim 179 or 181, wherein Z^2 is CR^{6a}.

183. The compound of any one of claims 179 to 182, wherein Z^3 is N.

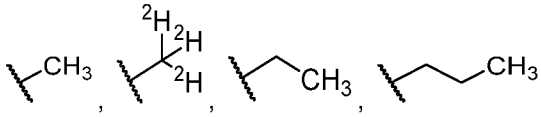
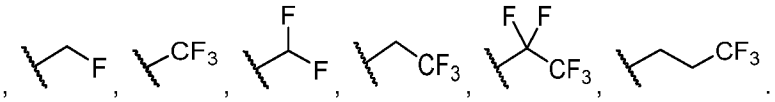
184. The compound of any one of claims 179 to 182, wherein Z^3 is CR^{6b}.

185. The compound of any one of claims 179 to 182, wherein R^4 is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, or optionally substituted C_3-C_{10} carbocyclyl.

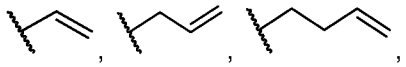
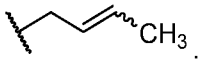
186. The compound of any one of claims 179 to 182, wherein R^4 is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, or optionally substituted C_3-C_{10} carbocyclyl.

187. The compound of claim 186, wherein R^4 is H.

188. The compound of claim 186, wherein R^4 is optionally substituted C_1-C_6 alkyl.

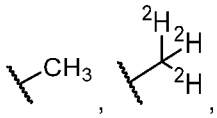
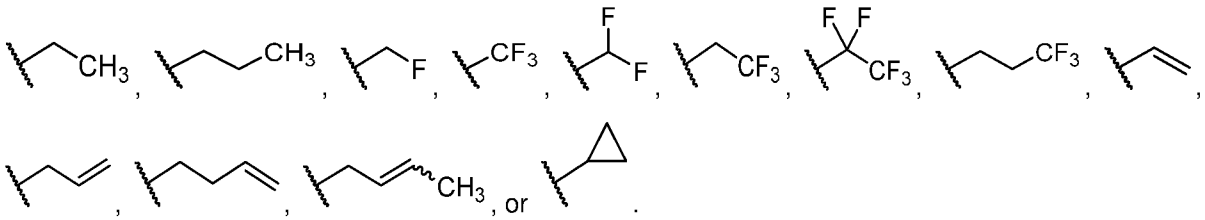
189. The compound of claim 188, wherein R^4 is  ,  .

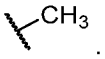
190. The compound of claim 186, wherein R^4 is optionally substituted C_2-C_6 alkenyl.

191. The compound of claim 190, wherein R^4 is  ,  .

192. The compoundof claim 186, wherein R^4 is optionally substituted C_3-C_{10} carbocyclyl.

193. The compound of claim 192, wherein R^4 is  .

194. The compound of any one of claims 186 to 193, wherein R^4 is H,  ,  , , or .

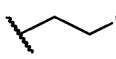
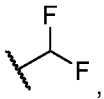
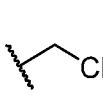
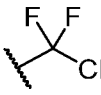
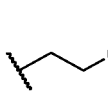
195. The compound of claim 194, wherein R^4 is H or  .

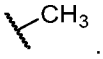
196. The compound of claim 195, wherein R^4 is  .

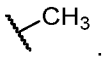
197. The compound of claim 195, wherein R^4 is H.

198. The compound of any one of claims 187 to 197, wherein R^5 is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl.

199. The compound of any one of claims 187 to 197, wherein R^5 is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_{10} carbocyclyl.

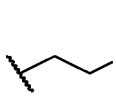
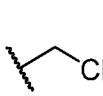
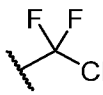
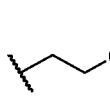
200. The compound of claim 199, wherein R^5 is H,  ,  ,  ,  ,  ,  ,  ,  , or  .

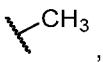
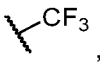
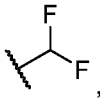
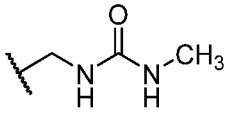
201. The compound of claim 200, wherein R^5 is H or  .

202. The compound of claim 201, wherein R^5 is  .

203. The compound of any one of claims 187 to 202, wherein R^{6a} is H, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino.

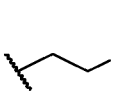
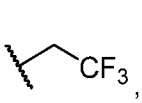
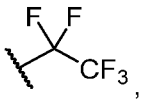
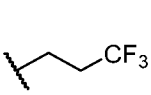
204. The compound of any one of claims 187 to 202, wherein R^{6a} is H, halogen, cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_{10} carbocyclyl. In some embodiments, R^{6a} is H, halogen, cyano, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl. In some embodiments, R^{6a} is H, halogen, cyano, or optionally substituted C_1-C_6 alkyl. In some embodiments, R^{6a} is optionally substituted C_1-C_6 heteroalkyl.

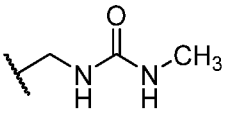
205. The compound of claim 204, wherein R^{6a} is H, F, cyano,  ,  ,  ,  ,  ,  ,  ,  , or  ..

206. The compound of claim 204, wherein R^{6a} is H, F, cyano,  ,  ,  , or  .

207. The compound of any one of claims 187 to 206, wherein R^{6b} is H, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino.

208. The compound of any one of claims 187 to 206, wherein R^{6b} is H, halogen, cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_{10} carbocyclyl. In some embodiments, R^{6a} is H, halogen, cyano, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl. In some embodiments, R^{6a} is H, halogen, cyano, or optionally substituted C_1-C_6 alkyl. In some embodiments, R^{6a} is optionally substituted C_1-C_6 heteroalkyl.

209. The compound of claim 208, wherein R^{6b} is H, F, cyano,  ,  ,  ,  ,  ,  ,  ,  , or  .

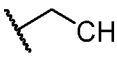
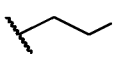
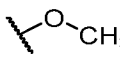
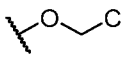
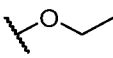
210. The compound of claim 208, wherein R^{6b} is H, F, cyano,  ,  ,  , or  .

211. The compound of any one of claims 187 to 210, wherein s is 0, 1, or 2.

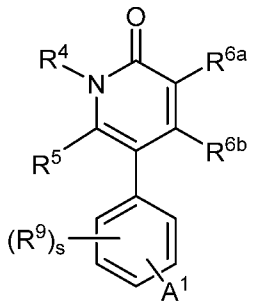
212. The compound of claim 211, wherein s is 2.

213. The compound of claim 211, wherein s is 1.

214. The compound of any one of claims 187 to 213, wherein each R^9 is, independently, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl. In some embodiments, each R^9 is, independently, optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_6 heteroalkyl.

215. The compound of claim 214, wherein each R^9 is, independently, halogen,  ,  ,  ,  ,  , or  .

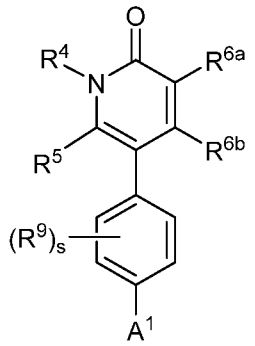
216. The compound of claim 187, wherein A comprises the structure of **Formula IIIa**:



Formula IIIa,

or a pharmaceutically acceptable salt thereof.

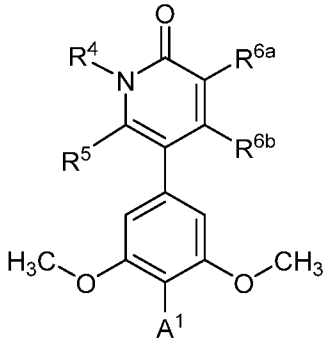
217. The compound of claim 187, wherein A comprises the structure of **Formula IIIb**:



Formula IIIb,

or a pharmaceutically acceptable salt thereof.

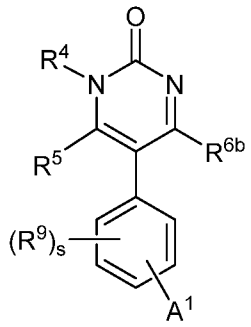
218. The compound of claim 187, wherein A comprises the structure of **Formula IIIc**:



Formula IIIc,

or a pharmaceutically acceptable salt thereof.

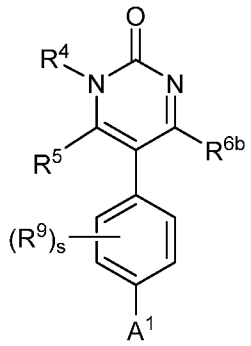
219. The compound of claim 187, wherein A comprises the structure of **Formula IIId**:



Formula IIId,

or a pharmaceutically acceptable salt thereof.

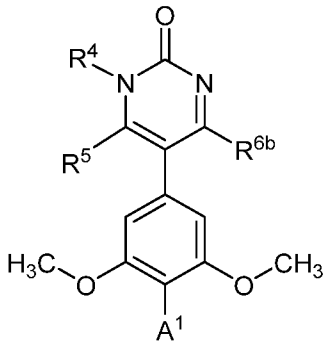
220. The compound of claim 187, wherein A comprises the structure of **Formula IIIe**:



Formula IIIe,

or a pharmaceutically acceptable salt thereof.

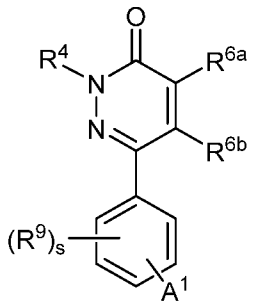
221. The compound of claim 187, wherein A comprises the structure of **Formula IIIf**:



Formula IIIf,

or a pharmaceutically acceptable salt thereof.

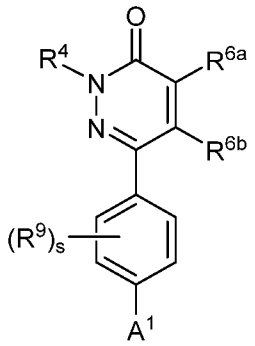
222. The compound of claim 187, wherein A comprises the structure of **Formula IIIg**:



Formula IIIg,

or a pharmaceutically acceptable salt thereof.

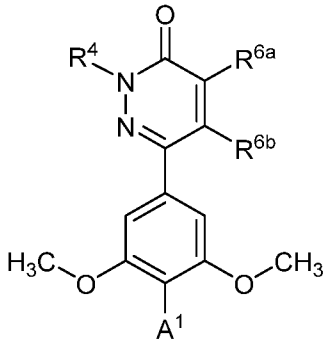
223. The compound of claim 187, wherein A comprises the structure of **Formula IIIh**:



Formula IIIh,

or a pharmaceutically acceptable salt thereof.

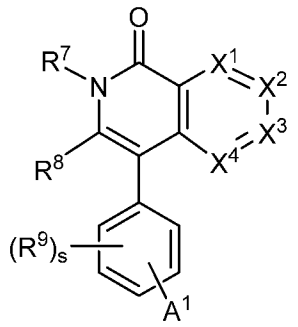
224. The compound of claim 187, wherein A comprises the structure of **Formula IIIi**:



Formula IIIi,

or a pharmaceutically acceptable salt thereof.

225. The compound of any one of claims 1 to 186, wherein A comprises the structure of **Formula IV**:



Formula IV,

wherein

R^7 is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_{10} carbocyclyl;

R^8 is H, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, or optionally substituted C_6-C_{10} aryl;

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

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

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

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

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

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

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

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

or a pharmaceutically acceptable salt thereof.

226. The compound of claim 225, wherein X^1 is CR^{10a}.

227. The compound of claim 225 or 226, wherein X^2 is N.

228. The compound of claim 225 or 226, wherein X^2 is CR^{10b}.

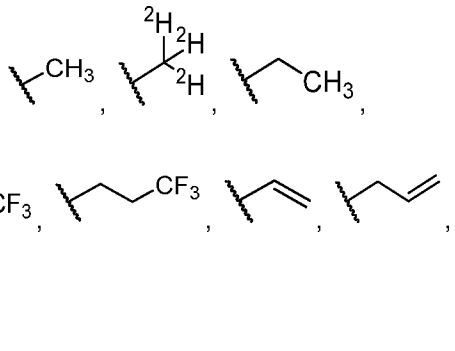
229. The compound of any one of claims 225 to 228, wherein X^3 is N.

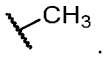
230. The compound of any one of claims 225 to 228, wherein X^3 is CR^{10c}.

231. The compound of any one of claims 225 to 230, wherein X^4 is CR^{10d}.

232. The compound of any one of claims 225 to 231, wherein R^7 is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_{10} carbocyclyl.

233. The compound of any one of claims 225 to 231, wherein R^7 is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 carbocyclyl.

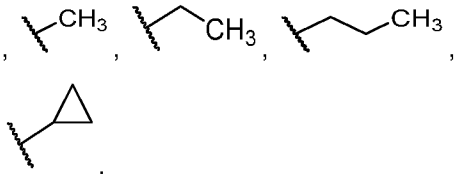
234. The compound of claim 233, wherein R^7 is H,  .

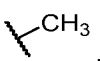
235. The compound of claim 234, wherein R^7 is H or  .

236. The compound of claim 235, wherein R^7 is  .

237. The compound of any one of claims 225 to 236, wherein R^8 is H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl.

238. The compound of any one of claims 225 to 236, wherein R^8 is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl.

239. The compound of claim 238, wherein R^8 is H,  .

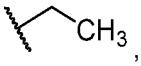
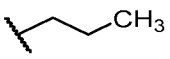
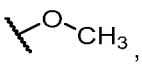
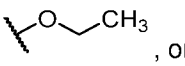
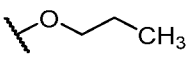
240. The compound of claim 239, wherein R^8 is H or  .

241. The compound of claim 240, wherein R^8 is  .

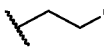
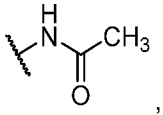
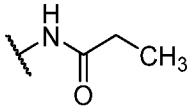
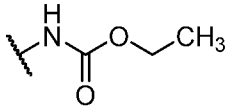
242. The compound of any one of claims 225 to 241, wherein s is 0, 1, or 2.

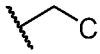
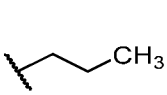
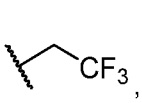
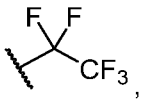
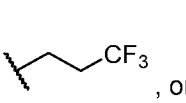
243. The compound of claim 242, wherein s is 2.

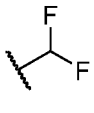
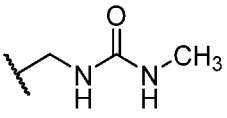
244. The compound of any one of claims 225 to 243, wherein each R^9 is, independently, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl. In some embodiments, each R^9 is, independently, optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_6 heteroalkyl.

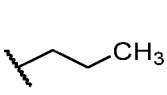
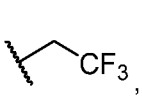
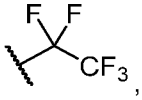
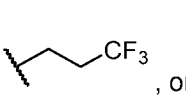
245. The compound of claim 244, wherein each R^9 is, independently, halogen,  ,  ,  ,  ,  , or  .

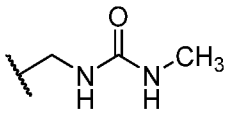
246. The compound of any one of claims 225 to 245, wherein each of R^{10a}, R^{10b}, R^{10c}, and R^{10d} is, independently, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted amino.

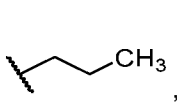
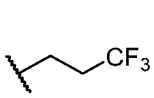
247. The compound of claim 246, wherein each of R^{10a}, R^{10b}, R^{10c}, and R^{10d} is, independently, -NH_2,  ,  ,  ,  ,  , or  .

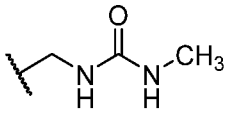
248. The compound of claim 246, wherein R^{10a} is H, F, cyano,  ,  ,  ,  ,  ,  ,  ,  , or  .

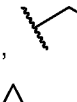
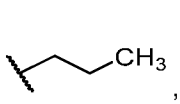
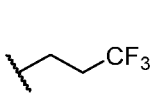
249. The compound of claim 246, wherein R^{10a} is H, F, cyano,  ,  ,  , or  .

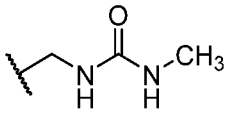
250. The compound of claim 246, wherein R^{10b} is H, F, cyano,  ,  ,  ,  ,  ,  ,  ,  , or  .

251. The compound of claim 246, wherein R^{10b} is H, F, cyano,  ,  ,  , or  .

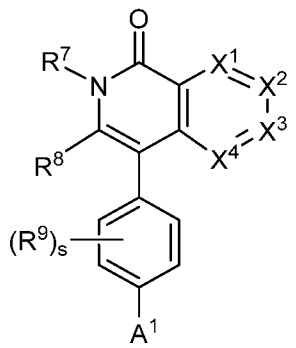
252. The compound of claim 246, wherein R^{10c} is H, F, cyano,  ,  ,  ,  ,  ,  ,  ,  , or  .

253. The compound of claim 246, wherein R^{10c} is H, F, cyano,  ,  ,  , or  .

254. The compound of claim 246, wherein R^{10d} is H, F, cyano,  ,  ,  ,  ,  ,  ,  ,  , or  .

255. The compound of claim 246, wherein R^{10d} is H, F, cyano,  ,  ,  , or  .

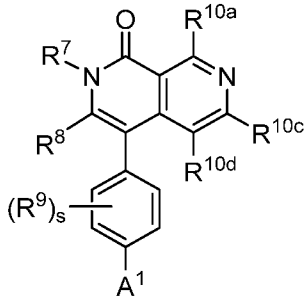
256. The compound of claim 225, wherein A comprises the structure of **Formula IVa**:



Formula IVa,

or a pharmaceutically acceptable salt thereof.

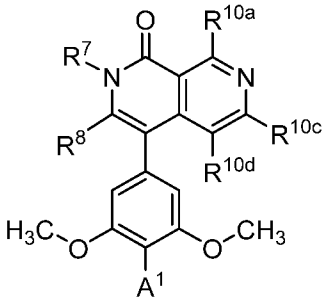
257. The compound of claim 225, wherein A comprises the structure of **Formula IVc**:



Formula IVc,

or a pharmaceutically acceptable salt thereof.

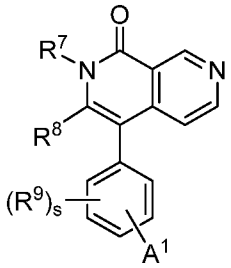
258. The compound of claim 225, wherein A comprises the structure of **Formula IVd**:



Formula IVd,

or a pharmaceutically acceptable salt thereof.

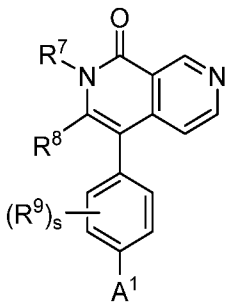
259. The compound of claim 225, wherein A comprises the structure of **Formula IVe**:



Formula IVe,

or a pharmaceutically acceptable salt thereof.

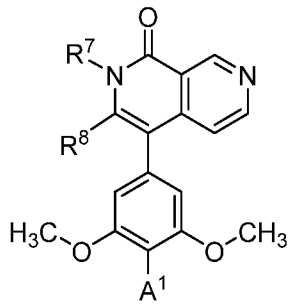
260. The compound of claim 225, wherein A comprises the structure of **Formula IVf**:



Formula IVf,

or a pharmaceutically acceptable salt thereof.

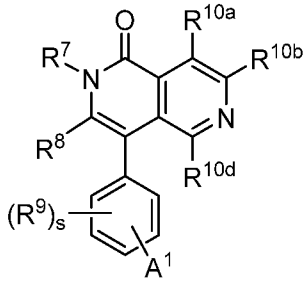
261. The compound of claim 225, wherein A comprises the structure of **Formula IVg**:



Formula IVg,

or a pharmaceutically acceptable salt thereof.

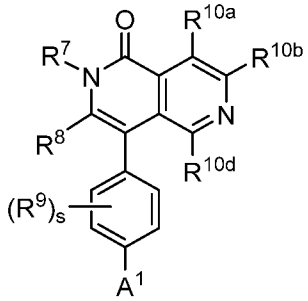
262. The compound of claim 225, wherein A comprises the structure of **Formula IVh**:



Formula IVh,

or a pharmaceutically acceptable salt thereof.

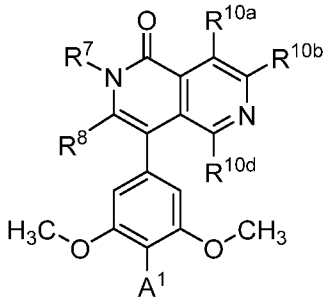
263. The compound of claim 225, wherein A comprises the structure of **Formula IVi**:



Formula IVi,

or a pharmaceutically acceptable salt thereof.

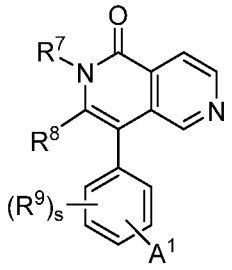
264. The compound of claim 225, wherein A comprises the structure of **Formula IVj**:



Formula IVj,

or a pharmaceutically acceptable salt thereof.

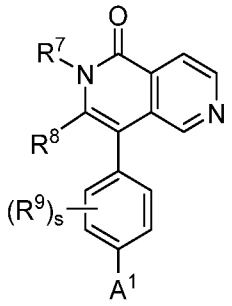
265. The compound of claim 225, wherein A comprises the structure of **Formula IVk**:



Formula IVk,

or a pharmaceutically acceptable salt thereof.

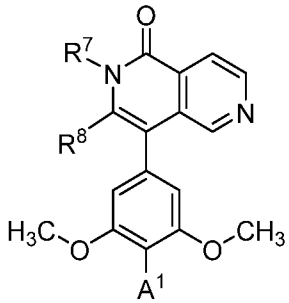
266. The compound of claim 225, wherein A comprises the structure of **Formula IVm**:



Formula IVm,

or a pharmaceutically acceptable salt thereof.

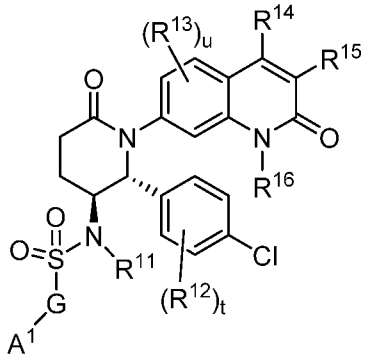
267. The compound of claim 225, wherein A comprises the structure of **Formula IVn**:



Formula IVn,

or a pharmaceutically acceptable salt thereof.

268. The compound of any one of claims 1 to 267, wherein the BRD9 binding moiety comprises the structure of **Formula V**



Formula V,

wherein

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

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

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

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

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

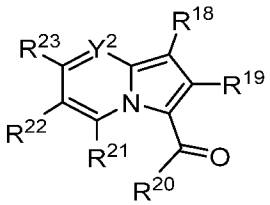
each R^{14} and R^{15} is, independently, selected form the group consisting of H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

G is optionally substituted C_1-C_6 alkylene, optionally substituted C_6-C_{10} arylene, or optionally substituted C_3-C_6 carbocyclylene; and

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

or a pharmaceutically acceptable salt thereof.

269. The compound of any one of claims 1 to 268, wherein the BRD9 binding moiety comprises the structure of **Formula VI**:



Formula VI,

wherein

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

R^{18} is A^1, optionally substituted C_6-C_{10} aryl or C_2-C_9 heteroaryl;

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

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

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

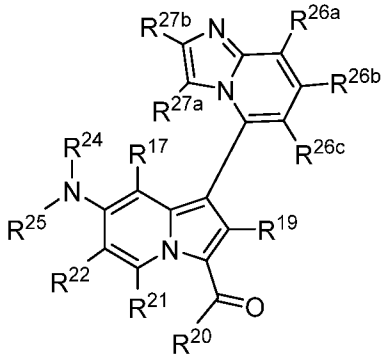
R^{23} is H or $-NR^{24}R^{25}$; and

each of R^{24} and R^{25} is, independently, H, A^1, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl, or R^{24} and R^{25} combine to form optionally substituted C_2-C_9 heterocyclyl,

where one of R^{18}, R^{24}, or R^{25} is A^1,

or a pharmaceutically acceptable salt thereof.

270. The compound of any one of claims 1 to 267, wherein the BRD9 binding moiety comprises the structure of **Formula VII**:



Formula VII,

wherein

each R^{26a}, R^{26b}, and R^{26c} is, independently, H, A^1, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

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

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

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

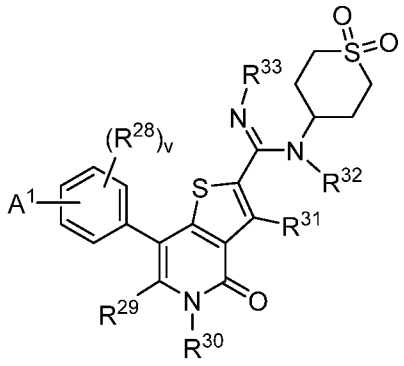
each R^{17}, R^{21}, and R^{22} is, independently, H, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9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

each of R^{24} and R^{25} is, independently, H, A^1, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl, or R^{24} and R^{25} combine to form optionally substituted C_2-C_9 heterocyclyl,

where one of R^{26a}, R^{26b}, R^{26c}, R^{24}, or R^{25} is A^1,

or a pharmaceutically acceptable salt thereof.

271. The compound of any one of claims 1 to 267, wherein the BRD9 binding moiety comprises the structure of **Formula VIII**:



Formula VIII,

wherein

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

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

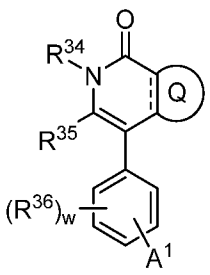
R^{29} is H, halogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_6-C_{10} aryl;

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

each R^{30}, R^{32}, and R^{33} is, independently, H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl,

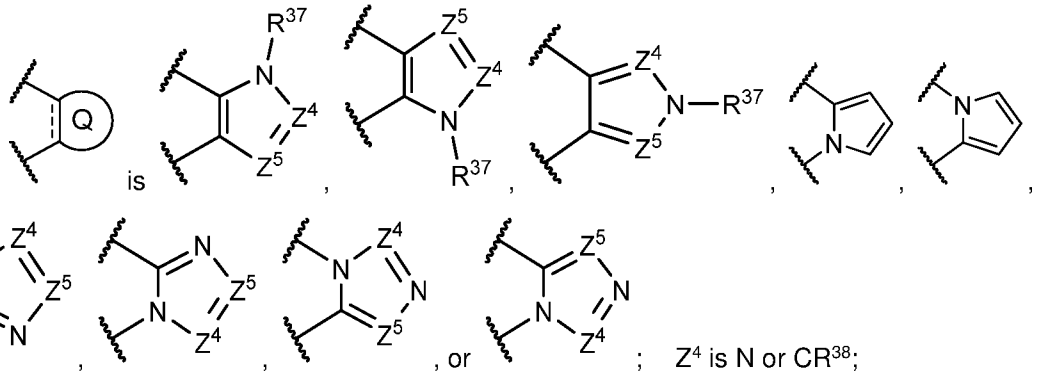
or a pharmaceutically acceptable salt thereof.

272. The compound of any one of claims 1 to 267, wherein the BRD9 binding moiety comprises the structure of **Formula IX**:



Formula IX,

wherein



; Z^4 is N or CR^{38};

Z^5 is N or CR^{39};

R^{34} is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_{10} carbocyclyl;

R^{35} is H, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_6 carbocyclyl, or optionally substituted C_6-C_{10} aryl;

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

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

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

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

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

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

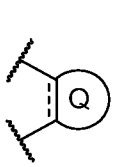
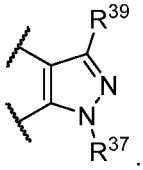
or a pharmaceutically acceptable salt thereof.

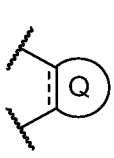
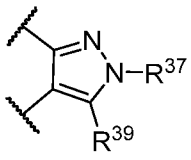
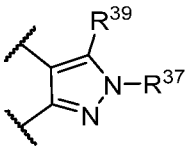
273. The compound of claim 272, wherein Z^4 is N.

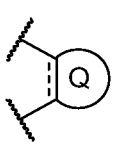
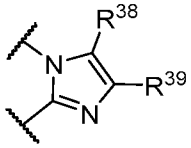
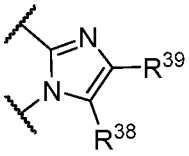
274. The compound of claim 272, wherein Z^4 is R^{38}.

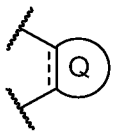
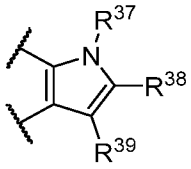
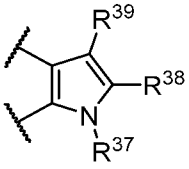
275. The compound of any one of claims 272 to 274, wherein Z^5 is N.

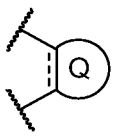
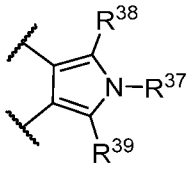
276. The compound of any one of claims 272 to 274, wherein Z^5 is R^{39}.

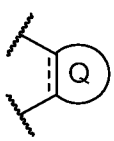
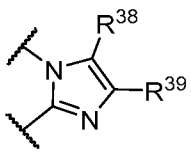
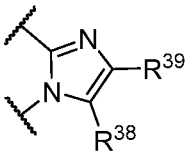
277. The compound of any one of claims 272 to 276, wherein  is  or  .

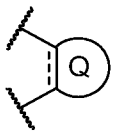
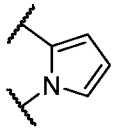
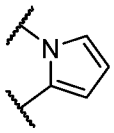
278. The compound of any one of claims 272 to 276, wherein  is  or  .

279. The compound of any one of claims 272 to 276, wherein  is  or  .

280. The compound of any one of claims 272 to 276, wherein  is  or  .

281. The compound of any one of claims 272 to 276, wherein  is  .

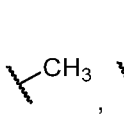
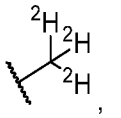
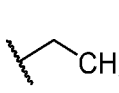
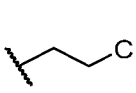
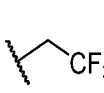
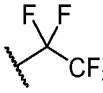
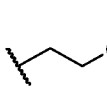
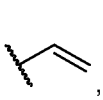
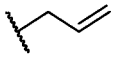
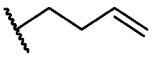
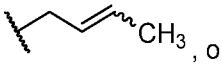
282. The compound of any one of claims 272 to 276, wherein  is  or  .

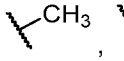
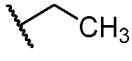
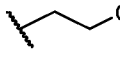
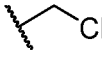
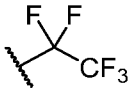
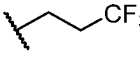
283. The compound of any one of claims 272 to 276, wherein  is  or  .

284. The compound of any one of claims 272 to 283, wherein R^{37} is H or  .

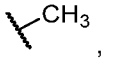
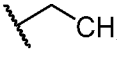
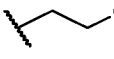
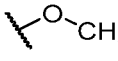
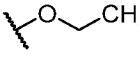
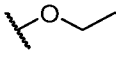
285. The compound of any one of claims 272 to 284, wherein R^{38} is H or  .

286. The compound of any one of claims 272 to 285, wherein R^{39} is H or  .

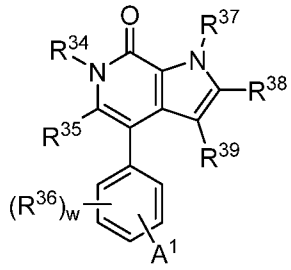
287. The compound of any one of claims 272 to 286, wherein R^{34} is H,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

288. The compound of any one of claims 272 to 287, wherein R^{35} is H,  ,  ,  ,  ,  ,  ,  ,  , or  .

289. The compound of any one of claims 272 to 288, wherein s is 0, 1, or 2.

290. The compound of any one of claims 272 to 289, wherein each R^{36} is, independently, halogen,  ,  ,  ,  ,  , or  .

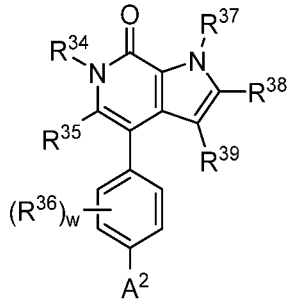
291. The compound of any one of claims 272 to 276, wherein A comprises the structure of **Formula IXa**:



Formula IXa,

or a pharmaceutically acceptable salt thereof.

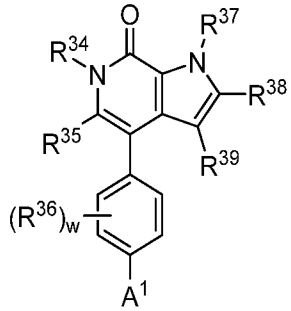
292. The compound of any one of claims 272 to 276, wherein A comprises the structure of **Formula IXb**:



Formula IXb,

or a pharmaceutically acceptable salt thereof.

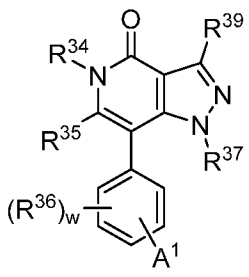
293. The compound of any one of claims 272 to 276, wherein A comprises the structure of **Formula IXc**:



Formula IXc,

or a pharmaceutically acceptable salt thereof.

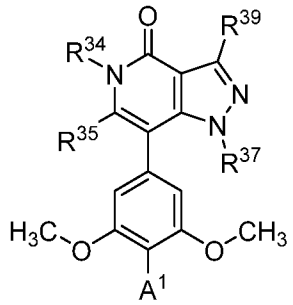
294. The compound of any one of claims 272 to 276, wherein A comprises the structure of **Formula IXd**:



Formula IXd,

or a pharmaceutically acceptable salt thereof.

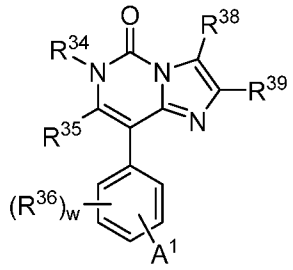
295. The compound of any one of claims 272 to 276, wherein A comprises the structure of **Formula IXe**:



Formula IXe,

or a pharmaceutically acceptable salt thereof.

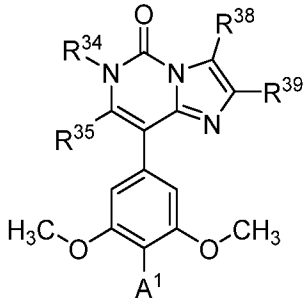
296. The compound of any one of claims 272 to 276, wherein A comprises the structure of **Formula IXf**:



Formula IXf,

or a pharmaceutically acceptable salt thereof.

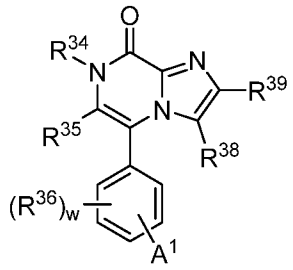
297. The compound of any one of claims 272 to 276, wherein A comprises the structure of **Formula IXg**:



Formula IXg,

or a pharmaceutically acceptable salt thereof.

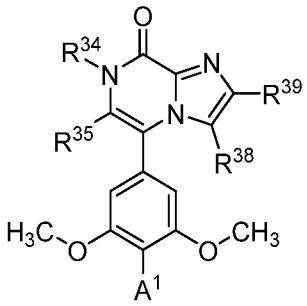
298. The compound of any one of claims 272 to 276, wherein A comprises the structure of **Formula IXh**:



Formula IXh,

or a pharmaceutically acceptable salt thereof.

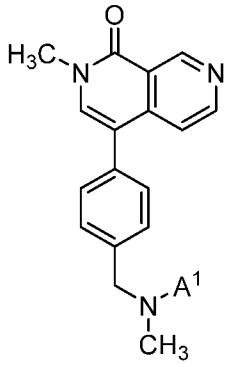
299. The compound of any one of claims 272 to 276, wherein A comprises the structure of **Formula IXi**:



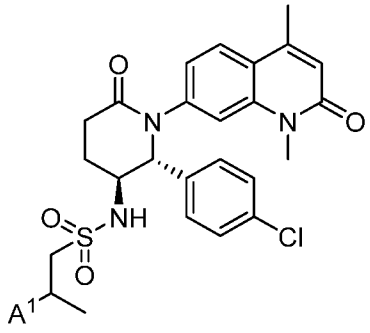
Formula IXi,

or a pharmaceutically acceptable salt thereof.

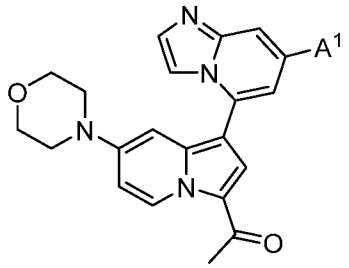
300. The compound of any one of claims 1 to 268, wherein A includes the structure of:



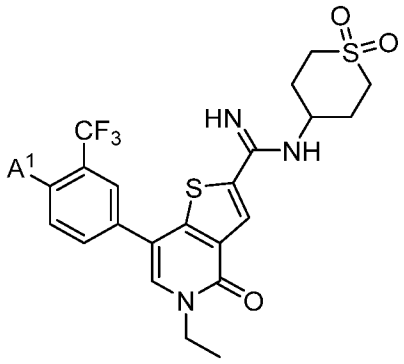
X2,



X3,

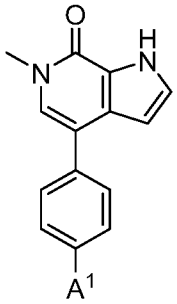


X4,



X5,

or



X6,

wherein A^1 is a bond between A and the linker, or derivative or analog thereof.

301. The compound of any one of claims 1 to 300, wherein the compound has the structure of any one of compounds D1-D259 in Table 1A.

302. The compound of any one of claims 1 to 300, wherein the compound has the structure of any one of compounds D260-D371 in Table 1B.

303. The compound of any one of claims 1 to 300, wherein the compound has the structure of any one of compounds D372-D476 in Table 1D.

304. A compound having the structure of any one of compounds DD1-DD10 in Table 1C.

305. A compound having the structure of any one of compounds DD11-DD16 in Table 1E.

306. A pharmaceutical composition comprising the compound of any one of claims 1 to 305 and a pharmaceutically acceptable excipient.

307. A method of inhibiting the level of BRD9 in a cell, the method involving contacting the cell with an effective amount of a compound of any one of claims 1 to 305, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 306.

308. A method of inhibiting the activity of BRD9 in a cell, the method involving contacting the cell with an effective amount of a compound of any one of claims 1 to 305, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 306.

309. The method of claim 307 or 308, wherein the cell is a cancer cell.

310. The method of claim 309, wherein the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, colorectal cancer, a sarcoma, non-small cell lung cancer, stomach cancer, or breast cancer.

311. The method of claim 310, wherein the cancer is a sarcoma.

312. The method of claim 311, wherein the sarcoma is a soft tissue sarcoma, synovial sarcoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, adult fibrosarcoma, alveolar soft-part sarcoma, angiosarcoma, clear cell sarcoma, desmoplastic small round cell tumor, epithelioid sarcoma, fibromyxoid sarcoma, gastrointestinal stromal tumor, Kaposi sarcoma, liposarcoma, leiomyosarcoma, malignant mesenchymoma malignant peripheral nerve sheath tumors, myxofibrosarcoma, or low-grade rhabdomyosarcoma.

313. The method of claim 312, wherein the sarcoma is synovial sarcoma.

314. A method of treating a BAF complex-related disorder in a subject in need thereof, the method involving administering to the subject an effective amount of a compound of any one of claims 1 to 305, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 306.

315. A method of treating an SS18-SSX fusion protein-related disorder in a subject in need thereof, the method involving administering to the subject an effective amount of a compound of any one of claims 1 to 305, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 306.

316. A method of treating a BRD9-related disorder in a subject in need thereof, the method involving administering to the subject an effective amount of a compound of any one of claims 1 to 305, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 306.

317. The method of any one of claims 314 to 316, wherein the disorder is cancer.

318. A method of treating a cancer in a subject in need thereof, the method including administering to the subject an effective amount of a compound of any one of claims 1 to 305, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 306.

319. The method of claim 317 or 318, wherein the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, colorectal cancer, a sarcoma, non-small cell lung cancer, stomach cancer, or breast cancer.

320. The method of claim 319, wherein the cancer is a sarcoma.

321. The method of claim 320, wherein the sarcoma is a soft tissue sarcoma, synovial sarcoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, adult fibrosarcoma, alveolar soft-part sarcoma, angiosarcoma, clear cell sarcoma, desmoplastic small round cell tumor, epithelioid sarcoma, fibromyxoid sarcoma, gastrointestinal stromal tumor, Kaposi sarcoma, liposarcoma, leiomyosarcoma, malignant mesenchymoma malignant peripheral nerve sheath tumors, myxofibrosarcoma, or low-grade rhabdomyosarcoma.

322. The method of claim 321, wherein the sarcoma is synovial sarcoma.

323. The method of any one of claims 314 to 316, wherein the disorder is infection.

324. A method of treating infection in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of any one of claims 1 to 305, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 306.

325. The method of claim 323 or 324, wherein the infection is viral infection.

326. The method of claim 325, wherein the viral infection is an infection with a virus of the Retroviridae family, Hepadnaviridae family, Flaviviridae family, Adenoviridae family, Herpesviridae family, Papillomaviridae family, Parvoviridae family, Polyomaviridae family, Paramyxoviridae family, or Togaviridae family.

327. The method of claim 325 or 326, wherein the viral infection is Coffin Siris, Neurofibromatosis, or Multiple Meningioma.

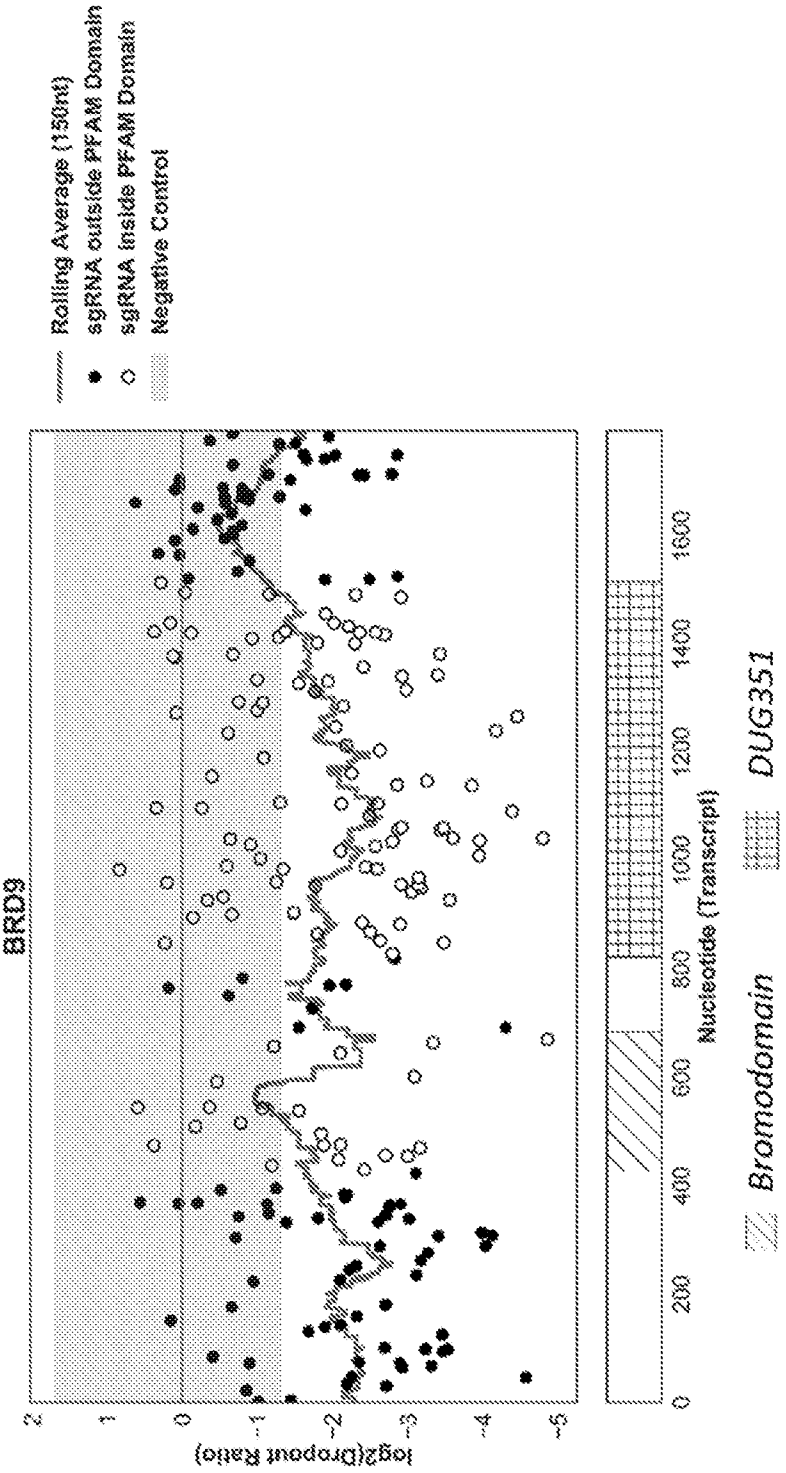
C4 Therapeutics, Inc.
Exhibit 1005 Page 500 of 515

Abstract

The present invention relates to compositions and methods for the treatment of BAF-related disorders, such as cancers and viral infections.

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FIG. 1


Rolling Average (150nt)
sgRNA outside PFAM Domain
sgRNA inside PFAM Domain
Negative Control
BRD9
log2(Dropout Ratio)
2
1
0
-1
-2
-3
-4
-5
0
200
400
600
800
1000
1200
1400
1600
Nucleotide (Transcript)
Bromodomain
DUG351

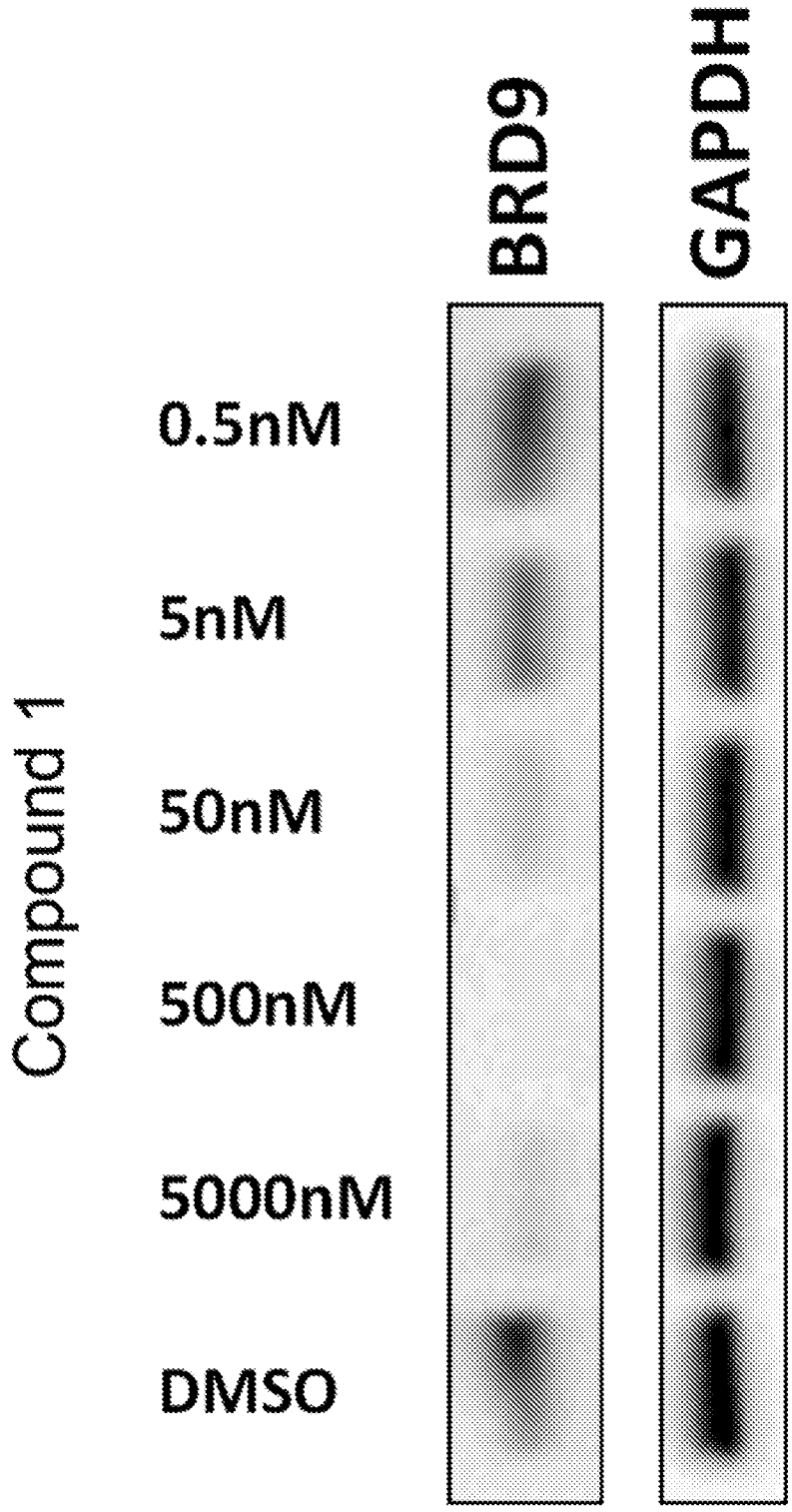


FIG. 2

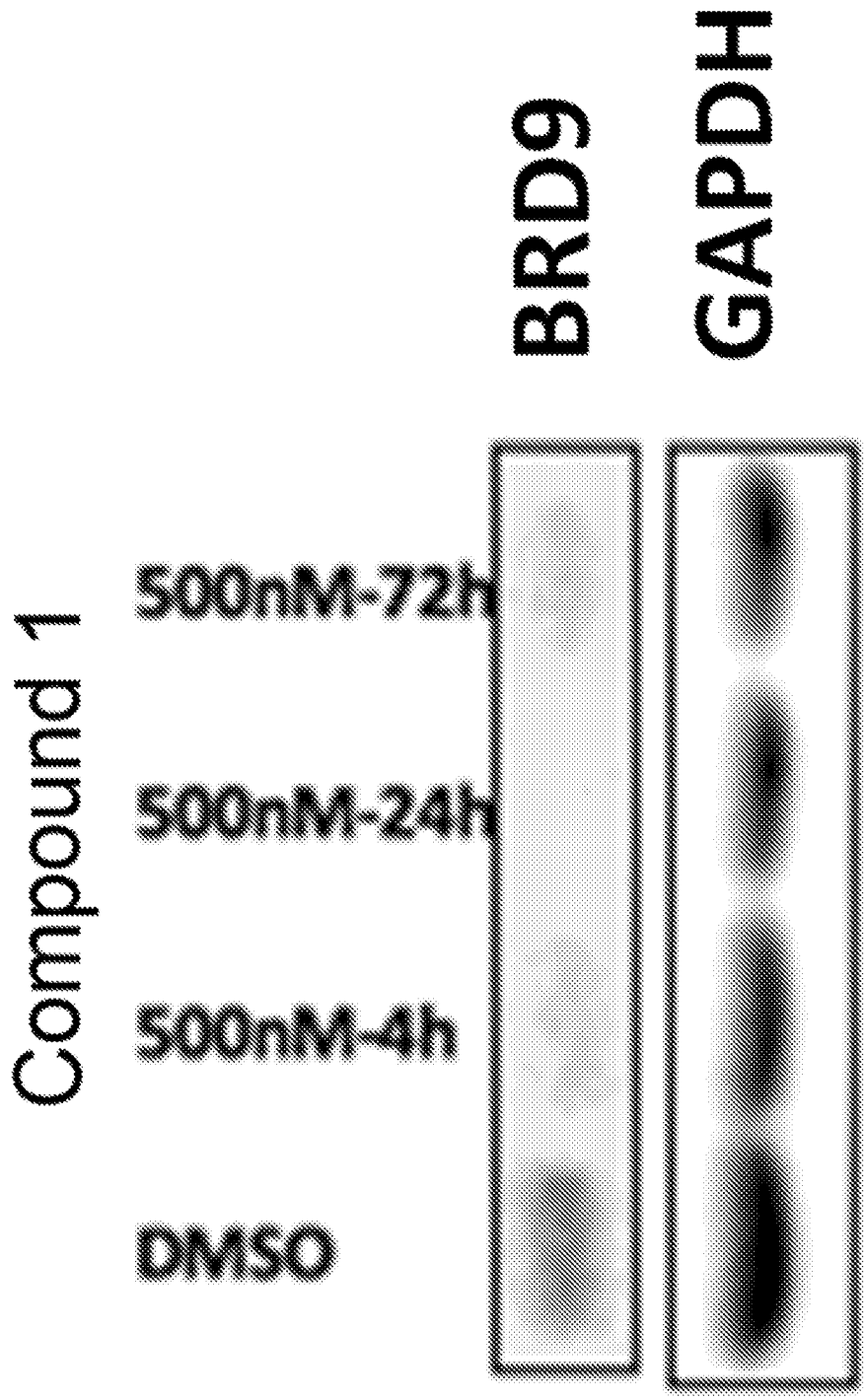


FIG. 3

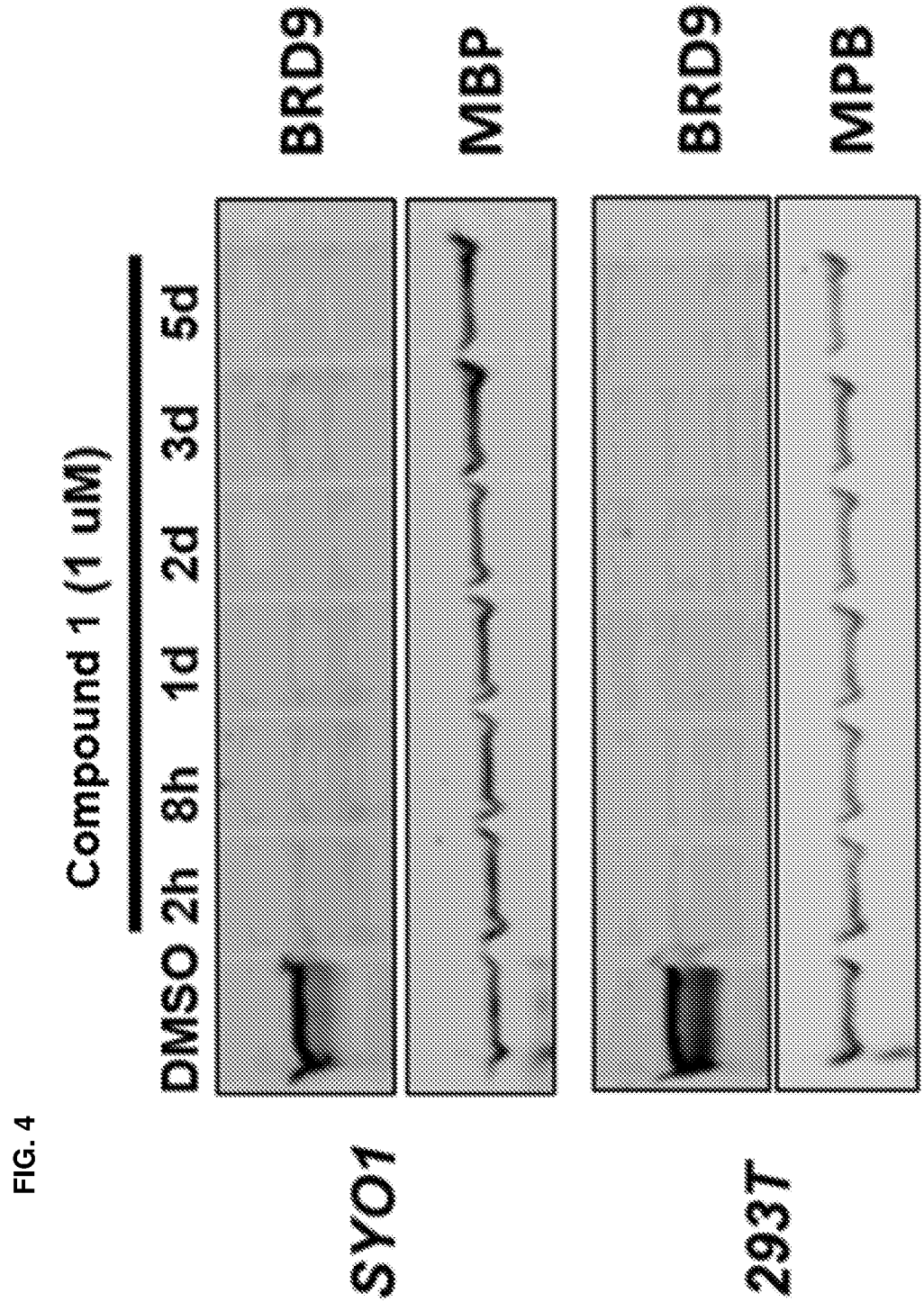

Compound 1 (1 uM)
DMSO 2h 8h 1d 2d 3d 5d
BRD9
MBP
BRD9
MPB
SYO1
293T

FIG. 4

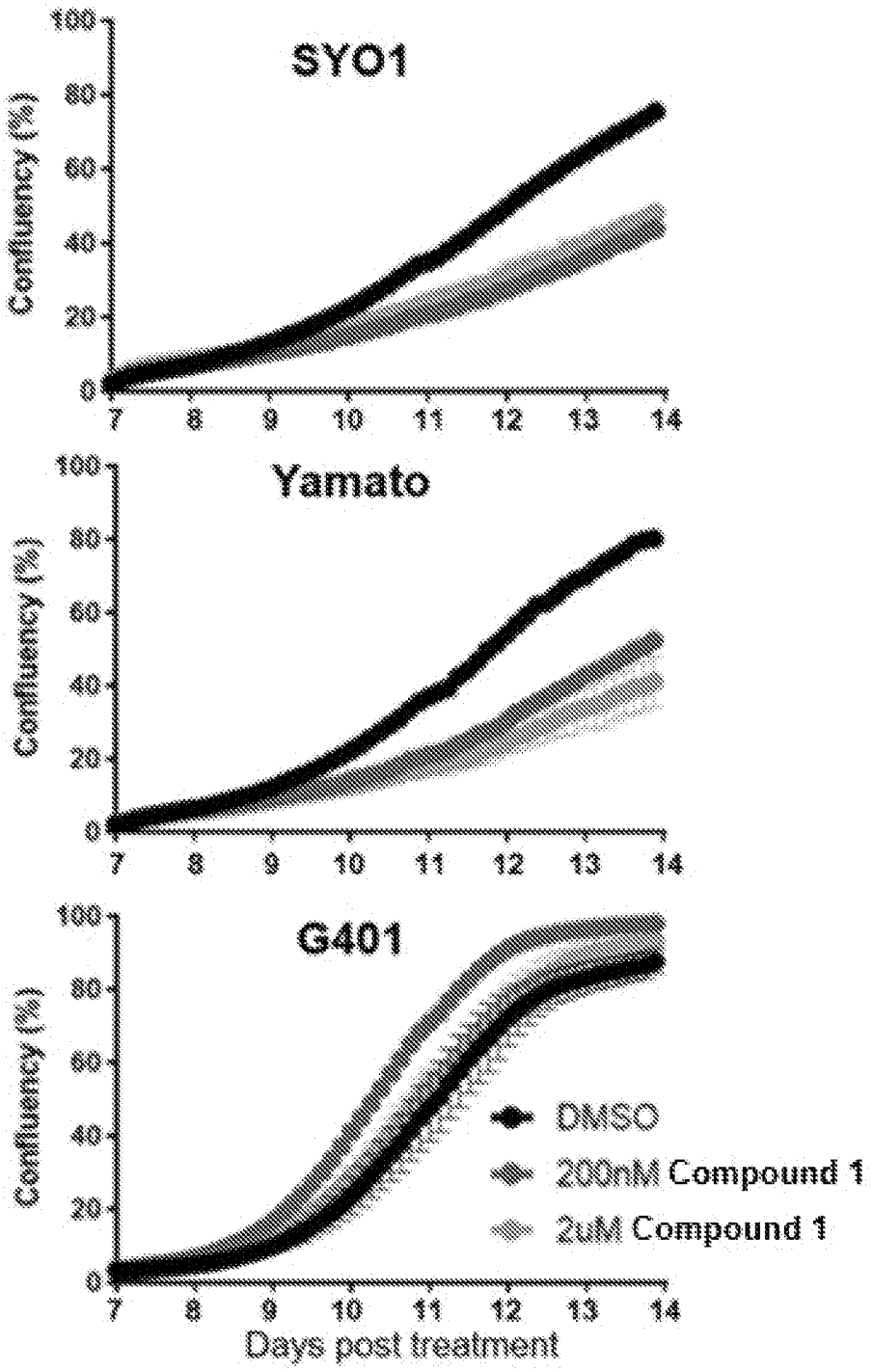

SYO1
Yamato
G401
Confluency (%)
100
80
60
40
20
0
7
8
9
10
11
12
13
14
DMSO
200nM Compound 1
2uM Compound 1
Days post treatment

FIG. 5

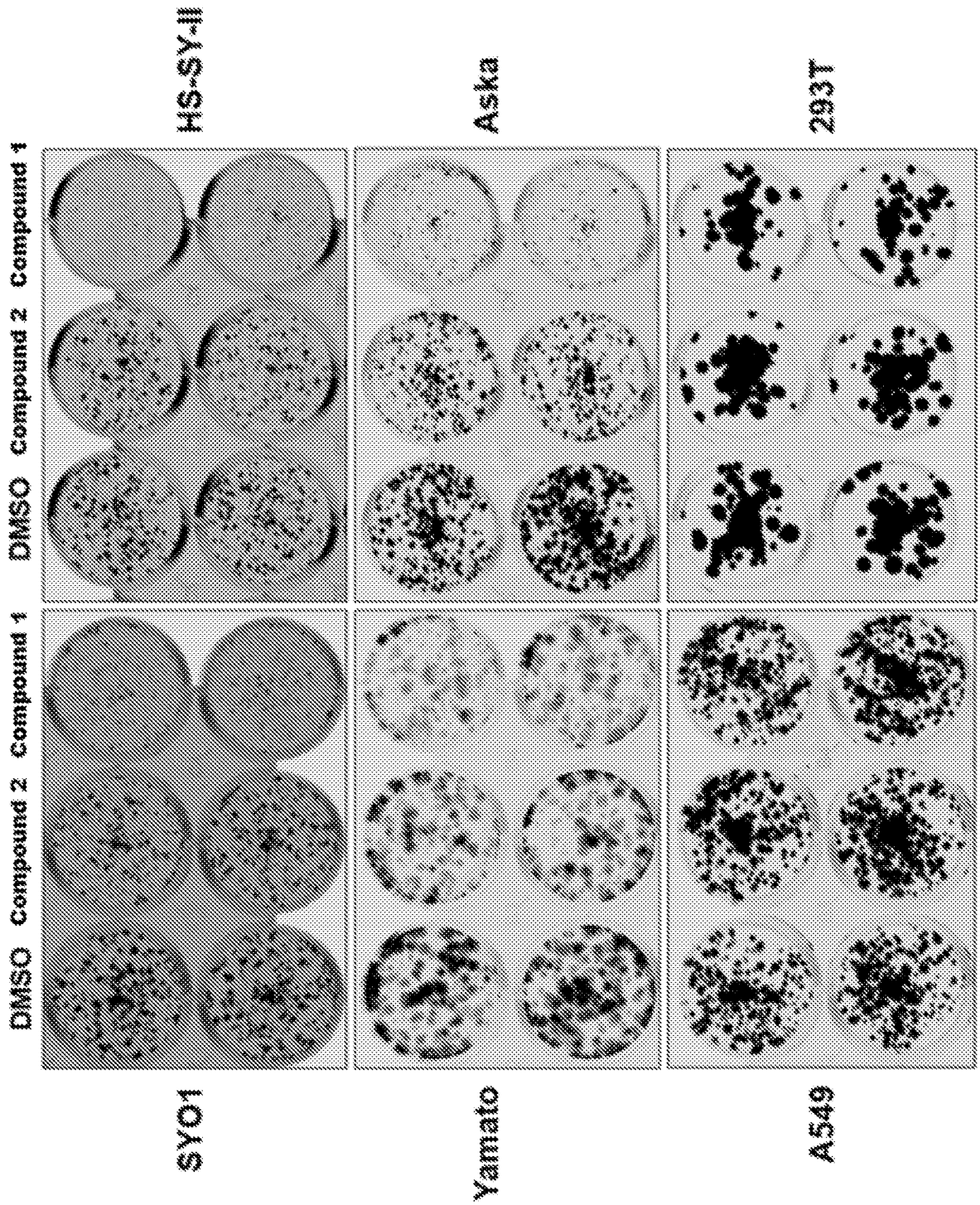

HS-SY-II
Aska
293T
DMSO
Compound 2
Compound 1
SYO1
Yamato
A549

FIG. 6

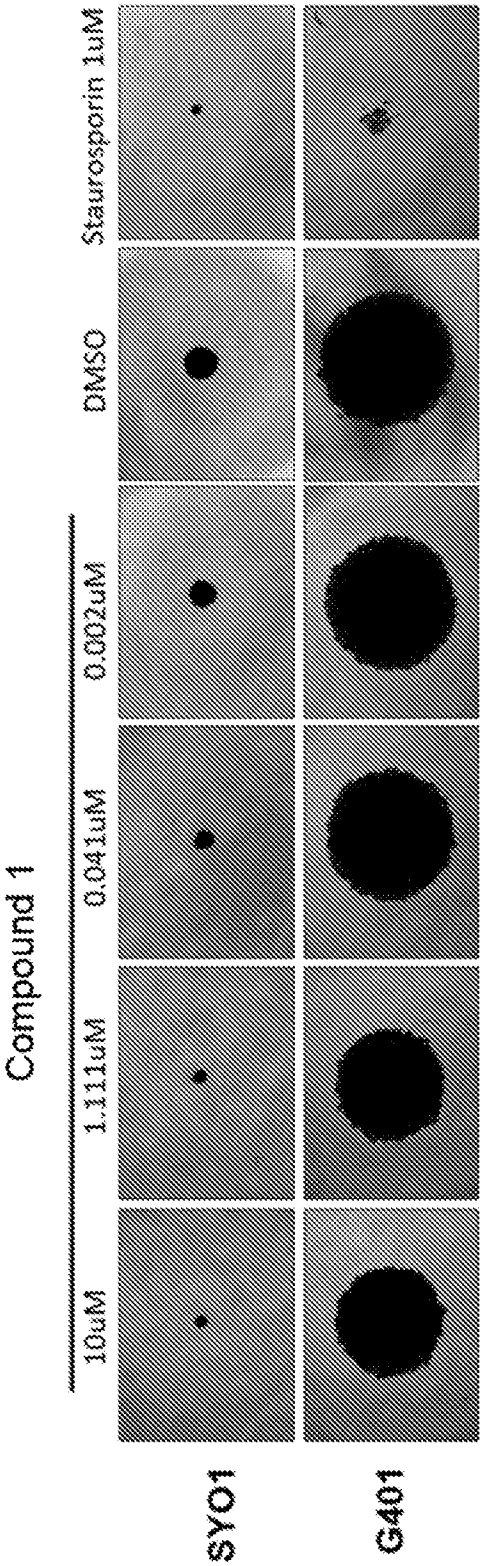
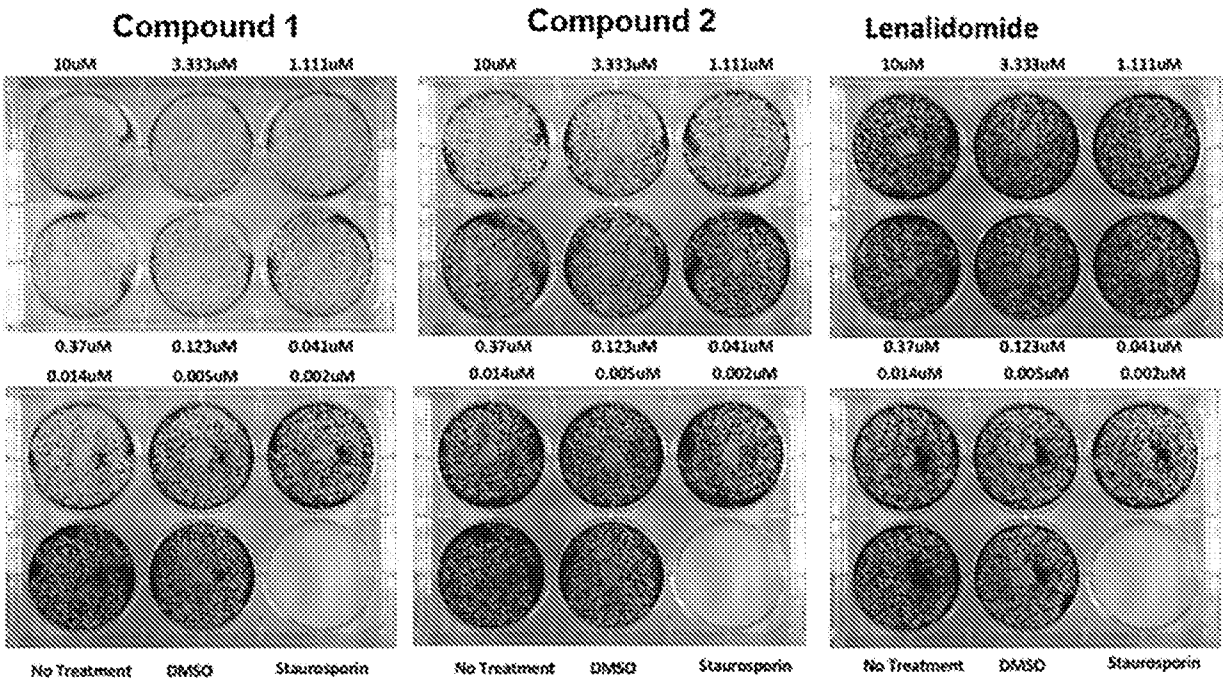

Compound 1
10uM
1.111uM
0.041uM
0.002uM
DMSO
Staurosporin 1uM
SYO1
G401

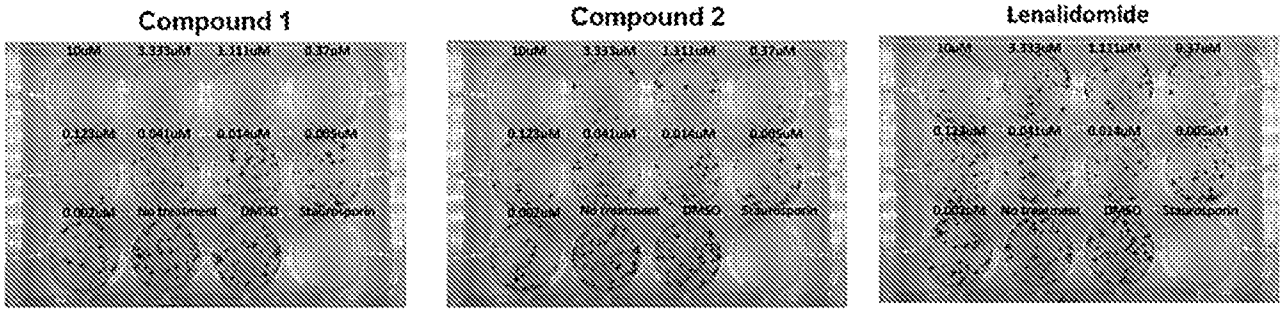
FIG. 7

FIG. 8

SYO1



HS-SY-II



ASKA

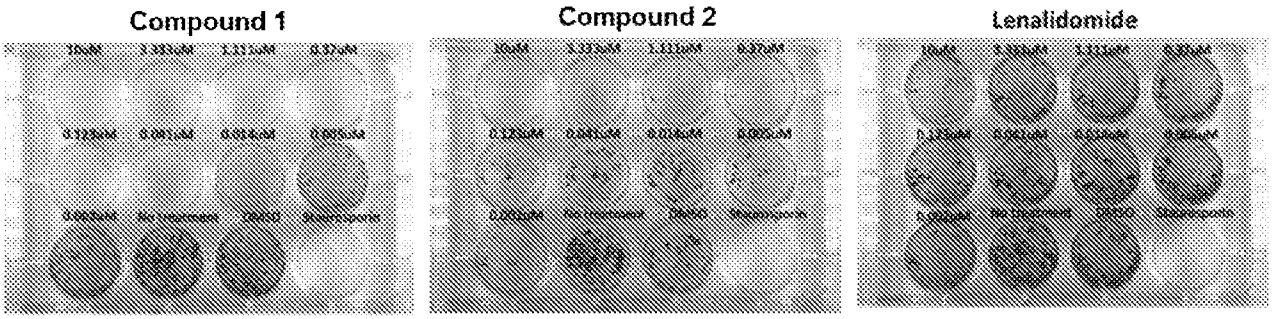
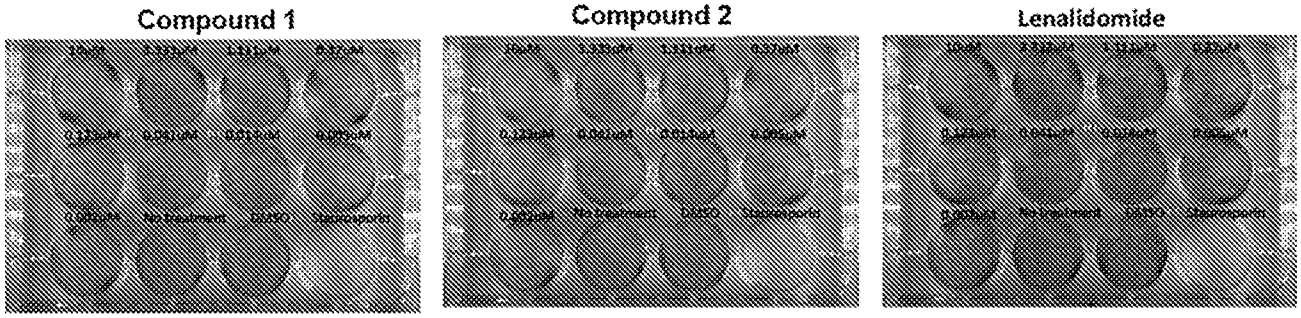
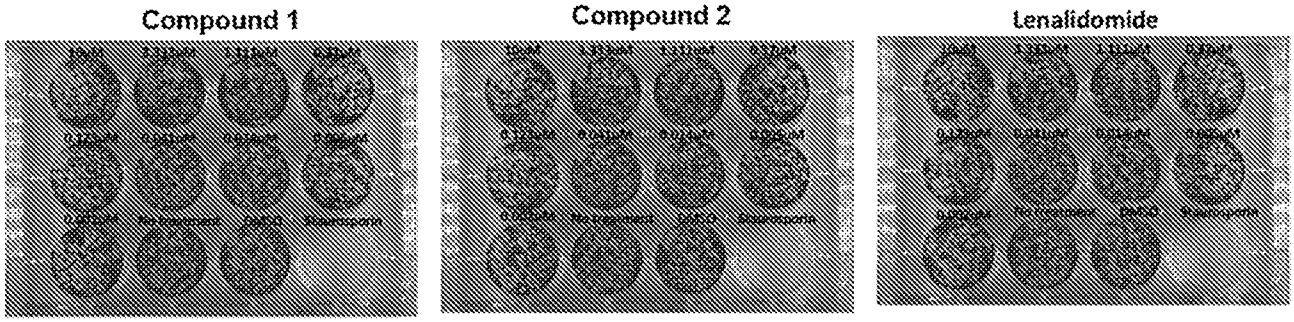


FIG. 9

RD



HCT116



Calu6

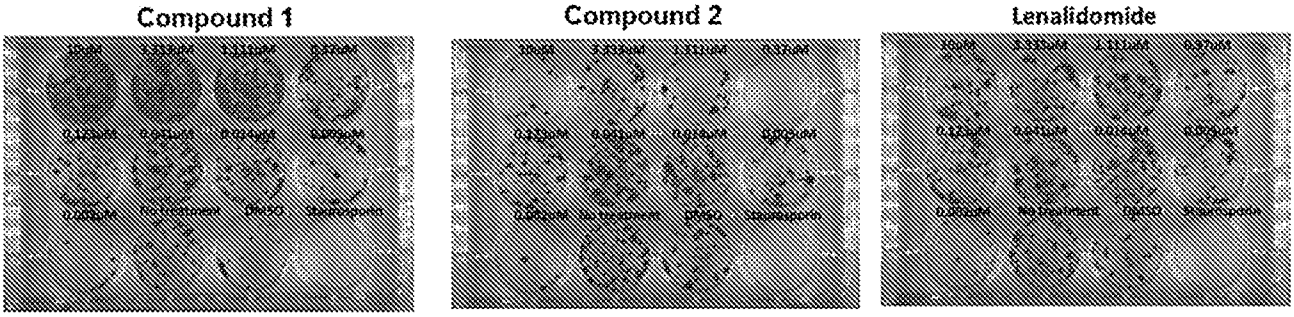


FIG. 10

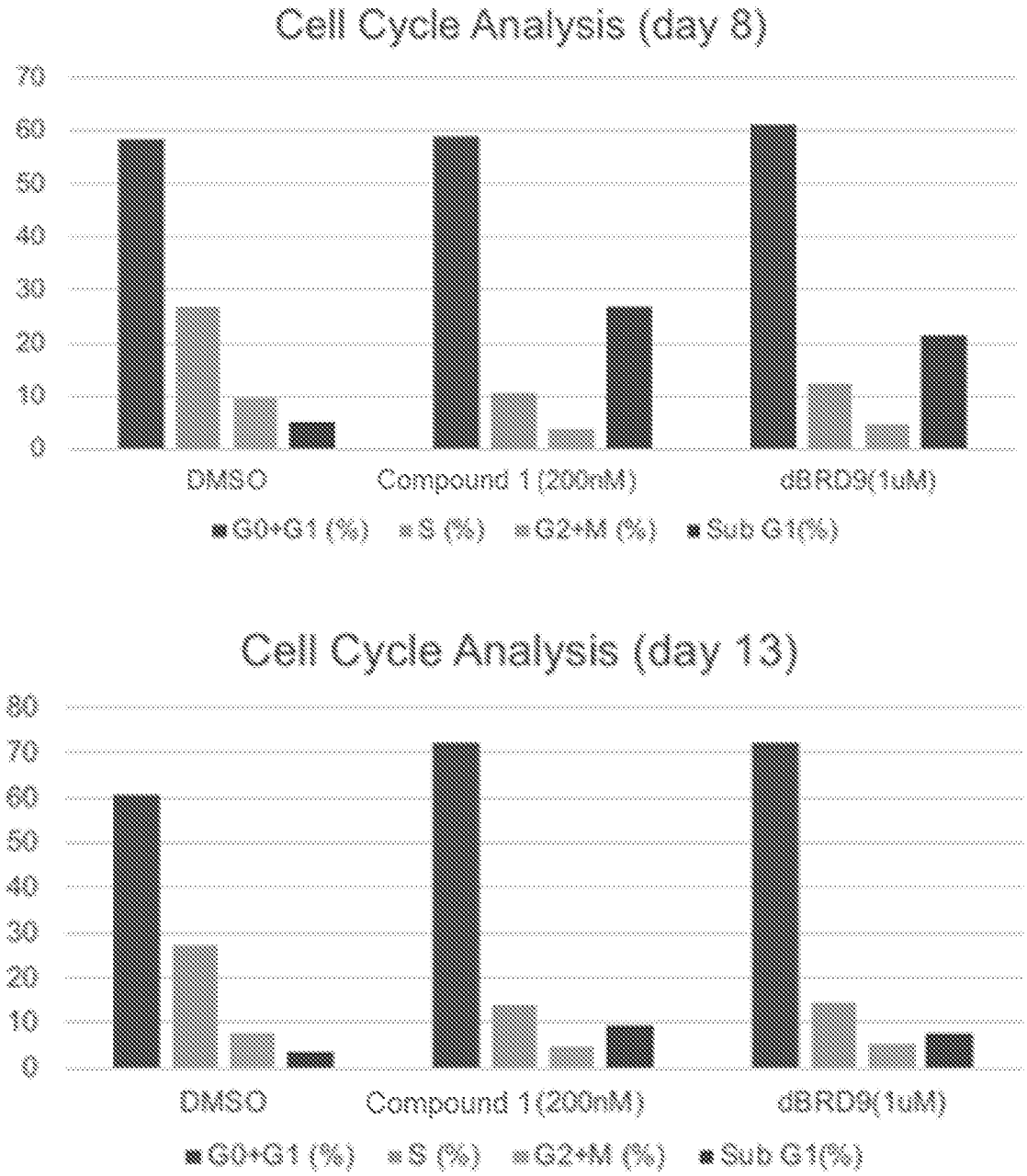
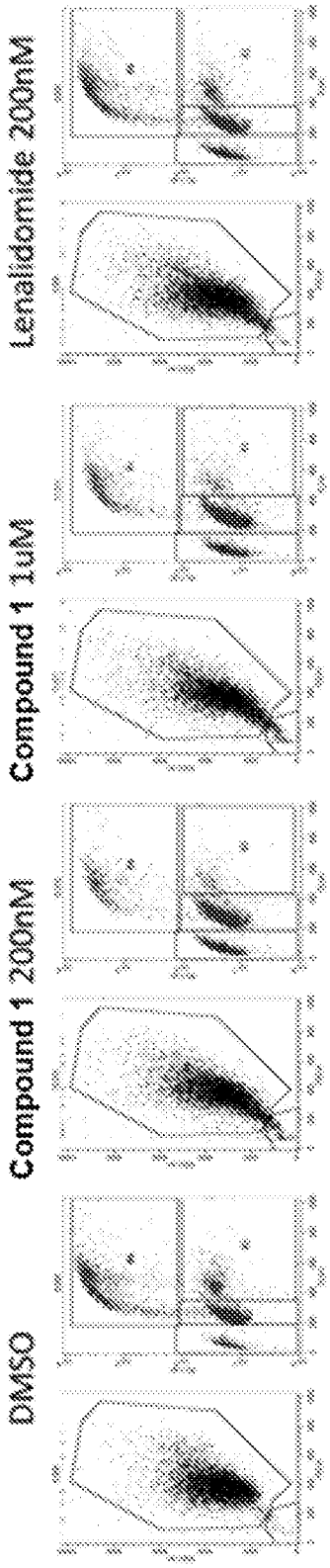
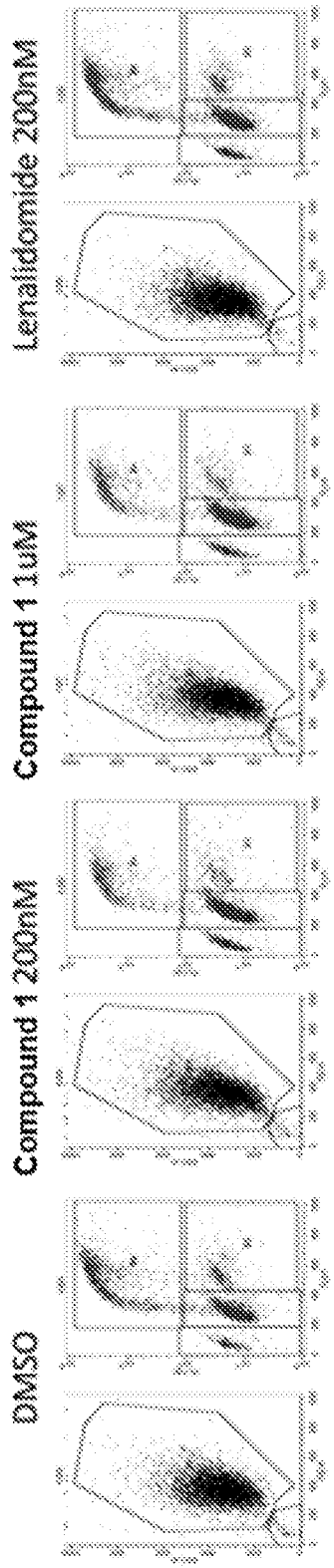

Cell Cycle Analysis (day 8)
70
60
50
40
30
20
10
0
DMSO
Compound 1 (200nM)
dBRD9(1uM)
G0+G1 (%)
S (%)
G2+M (%)
Sub G1(%)
Cell Cycle Analysis (day 13)
80
70
60
50
40
30
20
10
0
DMSO
Compound 1 (200nM)
dBRD9(1uM)
G0+G1 (%)
S (%)
G2+M (%)
Sub G1(%)

FIG. 11



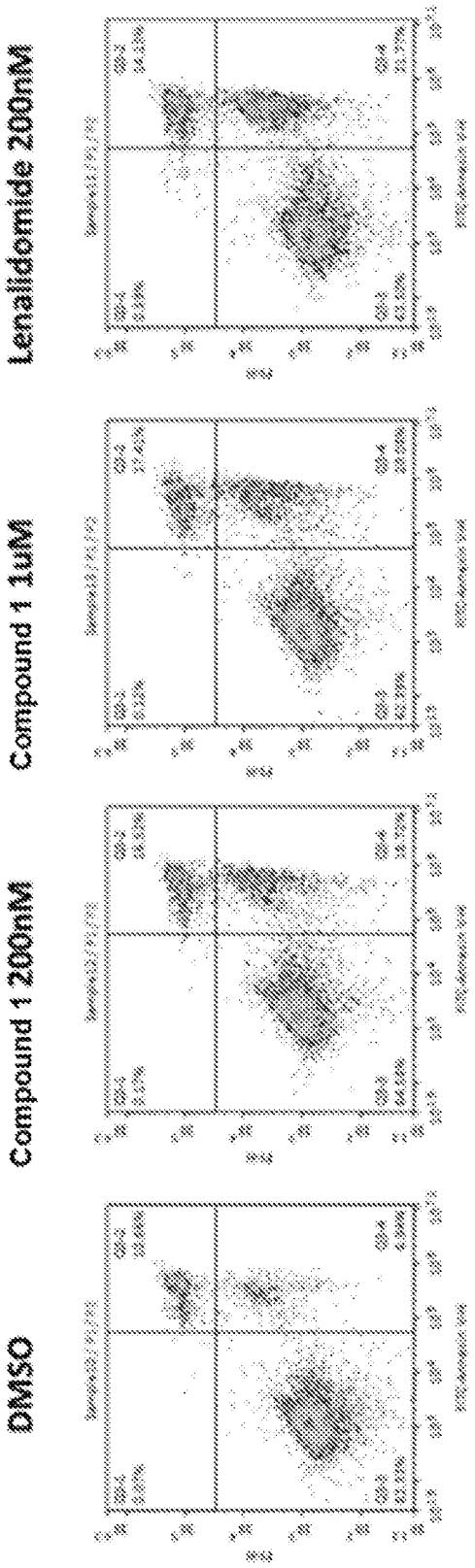
	G0-G1 (%)	S (%)	G2+M (%)	Sub G1(%)
DMSO	58.22	27.03	9.43	5.17
Compound 1 (200nM)	58.9	10.3	3.95	26.61
Compound 1 (1μM)	61.08	12.36	4.8	21.46
Lenalidomide (200nM)	50.45	22.27	8.61	18.43

FIG. 12



	G0+G1 (%)	S (%)	G2+M (%)	Sub G1 (%)
DMSO	60.83	27.29	7.53	3.88
Compound 1 (200nM)	71.9	14.06	4.76	9.1
Compound 1 (1μM)	72.21	14.33	5.08	7.91
Lenalidomide(200nM)	58.67	27.38	6.71	7.11

FIG. 13



	DMSO	Compound 1 (200nM)	Compound 1 (1uM)	Lenalidomide(200nM)
Early Apoptosis Cell	6.94	18.72	20.08	21.77
Late Apoptosis Cell	10.66	16.52	17.41	14.13

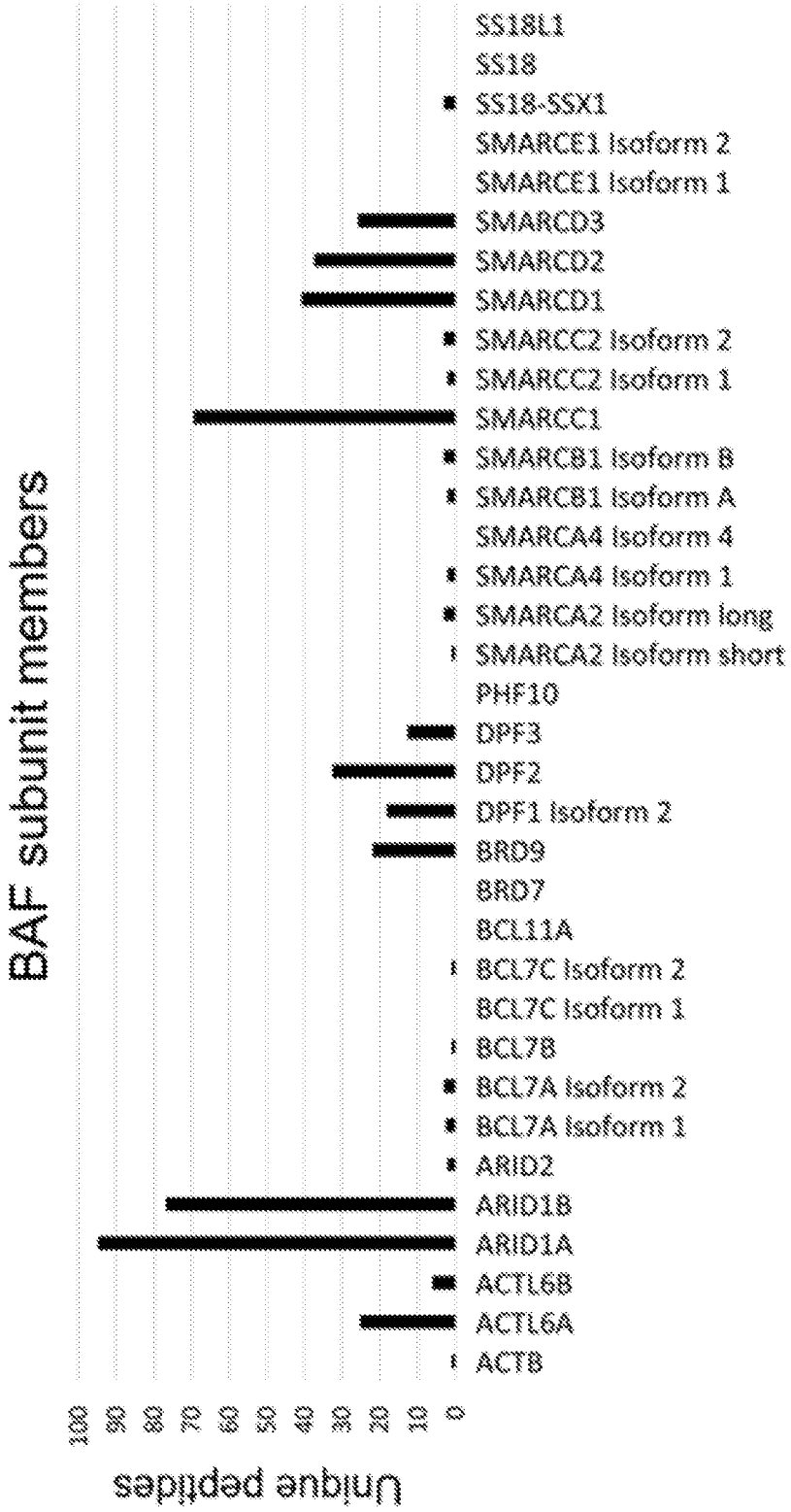

BAF subunit members
SS18L1
SS18
SS18-SSX1
SMARCE1 Isoform 2
SMARCE1 Isoform 1
SMARCD3
SMARCD2
SMARCD1
SMARCC2 Isoform 2
SMARCC2 Isoform 1
SMARCC1
SMARCB1 Isoform B
SMARCB1 Isoform A
SMARCA4 Isoform 4
SMARCA4 Isoform 1
SMARCA2 Isoform long
SMARCA2 Isoform short
PHF10
DPF3
DPF2
DPF1 Isoform 2
BRD9
BRD7
BCL11A
BCL7C Isoform 2
BCL7C Isoform 1
BCL7B
BCL7A Isoform 2
BCL7A Isoform 1
ARID2
ARID1B
ARID1A
ACTL6B
ACTL6A
ACTB
100
90
80
70
60
50
40
30
20
10
0
Unique peptides

FIG. 14