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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
17/478,505	09/17/2021	1629	1880	51121-027004	15	1

CONFIRMATION NO. 1099

172056
CLARK+ELBING LLP/FOGHORN THERAPEUTICS
101 FEDERAL STREET
BOSTON, MA 02110

FILING RECEIPT



0000000128806327

Date Mailed: 10/01/2021

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Sabine K. RUPPEL, Cambridge, MA;
Zhaoxia YANG, Belmont, MA;
Jason T. LOWE, East Bridgewater, MA;
Johannes H. VOIGT, Cambridge, MA;
Matthew NETHERTON, Cambridge, MA;

Applicant(s)

Foghorn Therapeutics Inc., Cambridge, MA;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 17/425,153
which is a 371 of PCT/US2020/015746 01/29/2020
which claims benefit of 62/881,195 07/31/2019
and claims benefit of 62/798,374 01/29/2019

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 09/30/2021

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 17/478,505**

Projected Publication Date: 01/06/2022

Non-Publication Request: No

Early Publication Request: No

**** SMALL ENTITY ****

Title

COMPOUNDS AND USES THEREOF

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative,

page 2 of 4

this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER
Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop

technology, manufacture products, deliver services, and grow your business, visit <http://www.SelectUSA.gov> or call +1-202-482-6800.

Electronic Acknowledgement Receipt

EFS ID:	43796633
Application Number:	17478505
International Application Number:	
Confirmation Number:	1099
Title of Invention:	COMPOUNDS AND USES THEREOF
First Named Inventor/Applicant Name:	Sabine K. RUPPEL
Customer Number:	172056
Filer:	Michael J. Belliveau/Elicia Niland
Filer Authorized By:	Michael J. Belliveau
Attorney Docket Number:	51121-027004
Receipt Date:	17-SEP-2021
Filing Date:	
Time Stamp:	17:14:54
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$4050
RAM confirmation Number	E20219GH15193077
Deposit Account	032095
Authorized User	Elicia Niland

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.21 (Miscellaneous fees and charges)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.19 (Document supply fees)
37 CFR 1.17 (Patent application and reexamination processing fees)
37 CFR 1.16 (National application filing, search, and examination fees)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Sequence Listing (Text File)	51121-027004_- _Sequence_Listing_from_Parent.TXT	99431	no	-
Warnings:					
Information:					
2	Application Data Sheet	51121-027004_- _Application_Data_Sheet_Fillable_PDF.pdf	1256044	no	10
			ef711e768f5e88c0dd32e0d5104a72ed792515ea		
Warnings:					
Information:					
3		51121-027004_- _Application3.pdf	12712302	yes	426
			64c55ea4988d350d27c6e14b6cb6a737f83b62eb		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Specification		1	419	
	Claims		420	425	
	Abstract		426	426	
Warnings:					
Information:					
4	Transmittal of New Application	51121-027004_- _Transmittal_-_Utility_Patent_Application_PTO_AIA-15.pdf	32215	no	1
			643d7513ea11b9092b34f3a613f9362cd9225dd2		
Warnings:					
Information:					
5	TrackOne Request	51121-027004_- _Certification_and_Request_for_Prioritized_Exam_37_CFR_1102e_PTO_AIA-4.pdf	34337	no	1
			7875c7346bbcc6987bef2b0bcc83de64fa523ceb8		

Warnings:					
Information:					
6	Oath or Declaration filed	51121-027004_- _Executed_Declaration.PDF	308159 6de6d5ccc1d17064f2193948e1de04618c185fa0	no	5
Warnings:					
The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.					
Information:					
7	CRF Statement Paper and CRF are the same	51121-027004_- _Sequence_Statement.pdf	18549 9a315ab491b00a963d22113159c4b7710bc014dd	no	1
Warnings:					
Information:					
8	Drawings-only black and white line drawings	Drawings.pdf	1757517 e8be2c8059f53d9ad9a24ce1cb40121d7c6e8a1d	no	14
Warnings:					
Information:					
9	Fee Worksheet (SB06)	fee-info.pdf	53097 34eae9388fa3a643d8ef8064639359c1c9d3fbc0	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			16271651		
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>					

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	51121-027004
		Application Number	
Title of Invention	COMPOUNDS AND USES THEREOF		
<p>The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.</p> <p>This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.</p>			

Secrecy Order 37 CFR 5.2:

☐	Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)
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Inventor Information:

Inventor	1				Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Sabine	K.	RUPPEL		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					
City	Cambridge	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	c/o Foghorn Therapeutics Inc.				
Address 2	500 Technology Square, Suite 700				
City	Cambridge	State/Province	MA		
Postal Code	02139	Country	US		

Inventor	2				Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Zhaoxia		YANG		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					
City	Belmont	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	c/o Foghorn Therapeutics Inc.				
Address 2	500 Technology Square, Suite 700				
City	Cambridge	State/Province	MA		
Postal Code	02139	Country	US		

Inventor	3				Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Jason	T.	LOWE		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	51121-027004
		Application Number	
Title of Invention	COMPOUNDS AND USES THEREOF		

City	East Bridgewater	State/Province	MA	Country of Residence	US
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Mailing Address of Inventor:

Address 1	c/o Foghorn Therapeutics Inc.				
Address 2	500 Technology Square, Suite 700				
City	Cambridge	State/Province	MA		
Postal Code	02139	Country	US		
Inventor	4				Remove
Legal Name					

Prefix	Given Name	Middle Name	Family Name	Suffix	
	Johannes	H.	VOIGT		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					
City	Cambridge	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	c/o Foghorn Therapeutics Inc.				
Address 2	500 Technology Square, Suite 700				
City	Cambridge	State/Province	MA		
Postal Code	02139	Country	US		
Inventor	5				Remove
Legal Name					

Prefix	Given Name	Middle Name	Family Name	Suffix	
	Matthew		NETHERTON		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					
City	Cambridge	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	c/o Foghorn Therapeutics Inc.				
Address 2	500 Technology Square, Suite 700				
City	Cambridge	State/Province	MA		
Postal Code	02139	Country	US		
All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button. Add					

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).	
☐ An Address is being provided for the correspondence information of this application.	

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	51121-027004
		Application Number	
Title of Invention	COMPOUNDS AND USES THEREOF		

Customer Number	172056		
Email Address		<input type="button" value="Add Email"/>	<input type="button" value="Remove Email"/>

Application Information:

Title of the Invention	COMPOUNDS AND USES THEREOF		
Attorney Docket Number	51121-027004	Small Entity Status Claimed	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	14	Suggested Figure for Publication (if any)	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐ Request Not to Publish. I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

<p>Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.</p>			
Please Select One:	☒ Customer Number	☐ US Patent Practitioner	☐ Limited Recognition (37 CFR 11.9)
Customer Number	21559		

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	51121-027004
		Application Number	
Title of Invention	COMPOUNDS AND USES THEREOF		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	17/425153	2021-07-22
Prior Application Status		Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
17/425153	a 371 of international	PCT/US2020/015746	2020-01-29
Prior Application Status	Expired	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2020/015746	Claims benefit of provisional	62/881195	2019-07-31
Prior Application Status	Expired	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2020/015746	Claims benefit of provisional	62/798374	2019-01-29
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.			Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)ⁱ the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Application Number	Country ⁱ	Filing Date (YYYY-MM-DD)	Access Code ⁱ (if applicable)	Remove
Additional Foreign Priority Data may be generated within this form by selecting the Add button.				Add

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	51121-027004
		Application Number	
Title of Invention	COMPOUNDS AND USES THEREOF		

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐	<p>This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.</p> <p>NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.</p>
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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	51121-027004
		Application Number	
Title of Invention	COMPOUNDS AND USES THEREOF		

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	51121-027004
		Application Number	
Title of Invention	COMPOUNDS AND USES THEREOF		

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant	1	Remove
<p>If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.</p> <p style="text-align: right;">Clear</p>		
☒ Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.		Person who shows sufficient proprietary interest
If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:		
<div style="border: 1px solid black; height: 20px; width: 100%;"></div>		
Name of the Deceased or Legally Incapacitated Inventor: <div style="border: 1px solid black; height: 20px; width: 100%;"></div>		
If the Applicant is an Organization check here. ☒		
Organization Name	Foghorn Therapeutics Inc.	
Mailing Address Information For Applicant:		
Address 1	500 Technology Square, Suite 700	
Address 2		
City	Cambridge	State/Province MA
Country	US	Postal Code 02139
Phone Number		Fax Number
Email Address		
Additional Applicant Data may be generated within this form by selecting the Add button. Add		

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	51121-027004
		Application Number	
Title of Invention	COMPOUNDS AND USES THEREOF		

Assignee	1			
Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.				
				<input type="button" value="Remove"/>
If the Assignee or Non-Applicant Assignee is an Organization check here.				☐
Prefix	Given Name	Middle Name	Family Name	Suffix
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Mailing Address Information For Assignee including Non-Applicant Assignee:				
Address 1	<input type="text"/>			
Address 2	<input type="text"/>			
City	<input type="text"/>	State/Province	<input type="text"/>	
Country ⁱ	<input type="text"/>	Postal Code	<input type="text"/>	
Phone Number	<input type="text"/>	Fax Number	<input type="text"/>	
Email Address	<input type="text"/>			
Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.				<input type="button" value="Add"/>

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). However, if this Application Data Sheet is submitted with the **INITIAL** filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Michael J. Belliveau, Ph.D./		Date (YYYY-MM-DD)	2021-09-17
First Name	Michael	Last Name	Belliveau	Registration Number
				52,608
Additional Signature may be generated within this form by selecting the Add button.				<input type="button" value="Add"/>

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	51121-027004
		Application Number	
Title of Invention	COMPOUNDS AND USES THEREOF		

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

- 1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
- 2 A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
- 3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
- 4 A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
- 5 A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
- 6 A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
- 7 A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
- 8 A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
- 9 A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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.

UTILITY PATENT APPLICATION TRANSMITTAL		Attorney Docket No. 51121-027004	
		First Named Inventor Sabine K. RUPPEL	
		Title COMPOUNDS AND USES THEREOF	
(Only for new nonprovisional applications under 37 CFR 1.53(b))		Priority Mail Express® Label No.	

APPLICATION ELEMENTS See MPEP chapter 600 concerning utility patent application contents.	ADDRESS TO: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450
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1. ☐ Fee Transmittal Form (PTO/SB/17 or equivalent) 2. ☒ Applicant asserts small entity status. See 37 CFR 1.27 3. ☐ Applicant certifies micro entity status. See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent. 4. ☒ Specification [Total Pages <u>426</u>] Both the claims and abstract must start on a new page. (See MPEP § 608.01(a) for information on the preferred arrangement) 5. ☒ Drawing(s) (35 U.S.C. 113) [Total Sheets <u>14</u>] 6. Inventor's Oath or Declaration [Total Pages <u>5</u>] (including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e)) a. ☐ Newly executed (original or copy) b. ☒ A copy from a prior application (37 CFR 1.63(d)) 7. ☒ Application Data Sheet * See note below. See 37 CFR 1.76 (PTO/AIA/14 or equivalent) 8. CD-ROM or CD-R in duplicate, large table, or Computer Program (Appendix) ☐ Landscape Table on CD 9. Nucleotide and/or Amino Acid Sequence Submission (if applicable, items a. – c. are required) a. ☒ Computer Readable Form (CRF) b. ☐ Specification Sequence Listing on: i. ☐ CD-ROM or CD-R (2 copies); or ii. ☐ Paper c. ☒ Statements verifying identity of above copies	ACCOMPANYING APPLICATION PAPERS 10. ☐ Assignment Papers (cover sheet & document(s)) Name of Assignee <div style="border: 1px solid black; height: 30px; width: 100%;"></div> 11. ☐ 37 CFR 3.73(c) Statement (when there is an assignee) ☐ Power of Attorney 12. ☐ English Translation Document (if applicable) 13. ☐ Information Disclosure Statement (PTO/SB/08 or PTO-1449) ☐ Copies of citations attached 14. ☐ Preliminary Amendment 15. ☐ Return Receipt Postcard (MPEP § 503) (Should be specifically itemized) 16. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed) 17. ☐ Nonpublication Request Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent. 18. ☒ Other: Certification and Request for Prioritized Examination Under 37 CFR 1.102(e)
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***Note:** (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must** be included in an Application Data Sheet (ADS).
 (2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

19. CORRESPONDENCE ADDRESS			
☒ The address associated with Customer Number: <u>21559</u> OR ☐ Correspondence address below			
Name			
Address			
City	State	Zip Code	
Country	Telephone	Email	
Signature	/Michael J. Belliveau, Ph.D./		Date
Name (Print/Type)	Michael J. Belliveau, Ph.D.		Registration No. (Attorney/Agent)
		September 17, 2021	
		52,608	

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)			
First Named Inventor:	Sabine K. RUPPEL	Nonprovisional Application Number (if known):	Not Yet Assigned
Title of Invention:	COMPOUNDS AND USES THEREOF		
<p>APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.</p> <p>1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently \$0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.</p> <p>2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.</p> <p>3. The applicable box is checked below:</p> <p style="margin-left: 20px;">I. ☒ <u>Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)</u></p> <p style="margin-left: 40px;">i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web. ---OR---</p> <p style="margin-left: 40px;">(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.</p> <p style="margin-left: 40px;">ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, or the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.</p> <p style="margin-left: 20px;">II. ☐ <u>Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)</u></p> <p style="margin-left: 40px;">i. A request for continued examination has been filed with, or prior to, this form.</p> <p style="margin-left: 40px;">ii. If the application is a utility application, this certification and request is being filed via EFS-Web.</p> <p style="margin-left: 40px;">iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.</p> <p style="margin-left: 40px;">iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.</p> <p style="margin-left: 40px;">v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).</p>			
Signature /Michael J. Belliveau, Ph.D./		Date September 17, 2021	
Name (Print/Typed) Michael J. Belliveau, Ph.D.		Practitioner Registration Number 52,608	
<small>Note: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.*</small>			
<div style="display: flex; align-items: center;">☐ *Total of <u> 1 </u> forms are submitted.</div>			

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

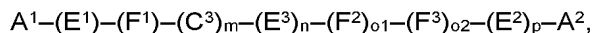
Formula I,

where

A is a BRD9 binding moiety;

B is a degradation moiety; and

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



Formula II

where

A¹ is a bond between the linker and A;

A² is a bond between B and the linker;

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

each of E¹ and E² is, independently, O, S, NR^N, optionally substituted C₁₋₁₀ alkylene, optionally substituted C₂₋₁₀ alkenylene, optionally substituted C₂₋₁₀ alkynylene, optionally substituted C₂₋₁₀ polyethylene glycol, or optionally substituted C₁₋₁₀ heteroalkylene;

E³ is optionally substituted C_{1-C₆} alkylene, optionally substituted C_{1-C₆} heteroalkylene, O, S, or NR^N;

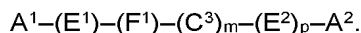
each R^N is, independently, H, optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, optionally substituted C_{2-6} heterocyclyl, optionally substituted C_{6-12} aryl, or optionally substituted C_{1-7} heteroalkyl;

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,

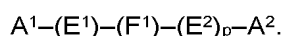
or a pharmaceutically acceptable salt thereof.

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



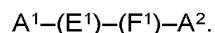
Formula IIa

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



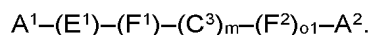
Formula IIb

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



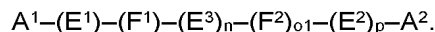
Formula IIc

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



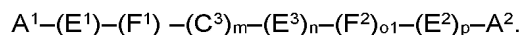
Formula IId

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



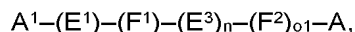
Formula IIe

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



Formula IIff

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



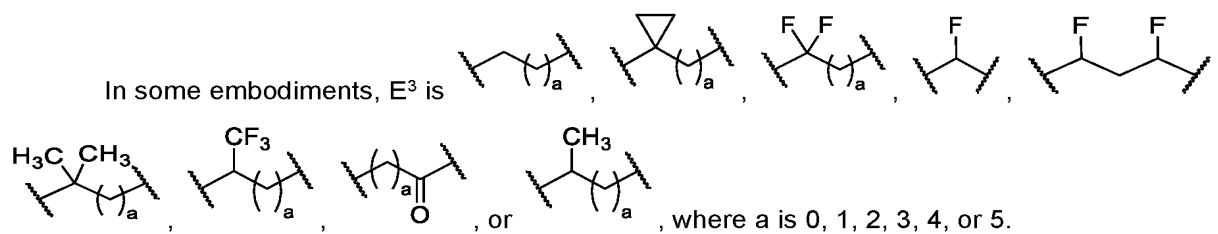
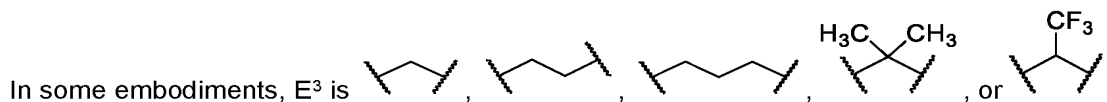
Formula IIg

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 ;

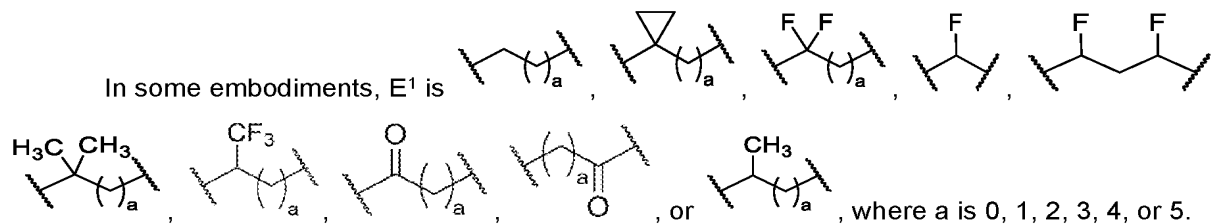
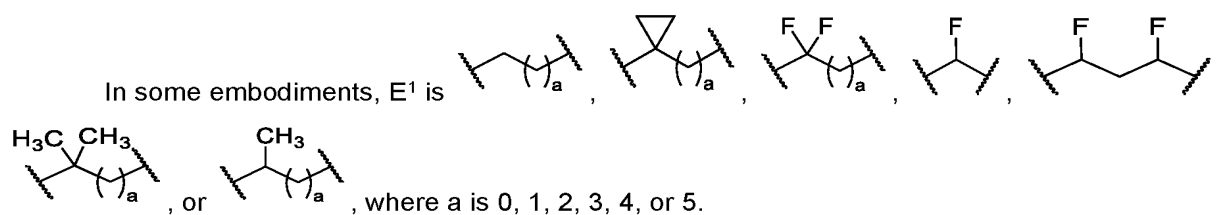
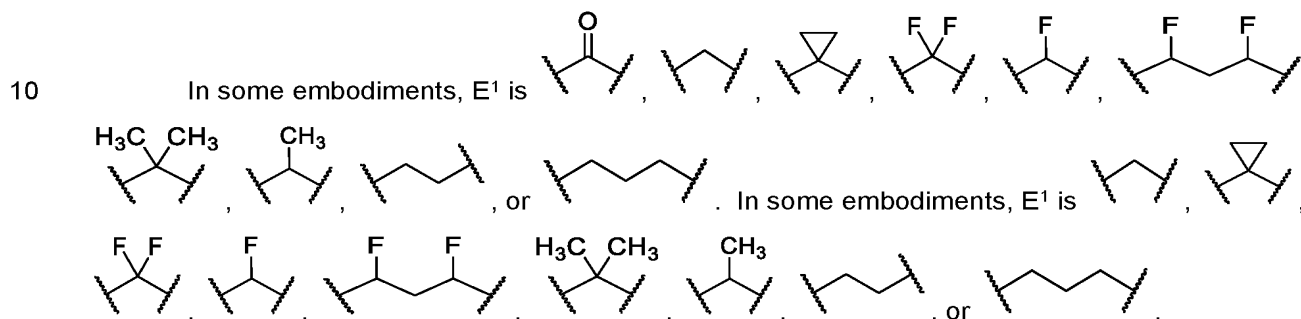
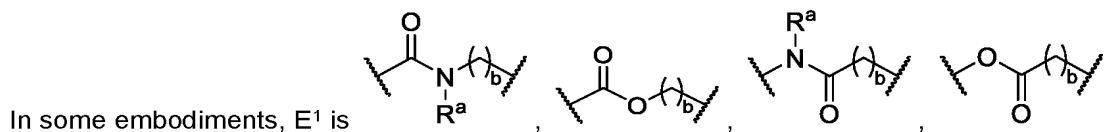
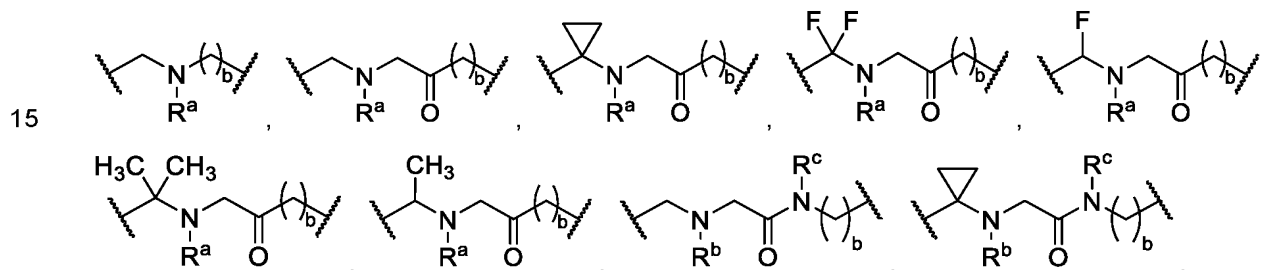
In some embodiments, E^3 is optionally substituted C_1-C_6 alkylene. In some embodiments, E^3 is optionally substituted C_1-C_3 alkylene. In some embodiments, E^3 is O, S, or NR^N .

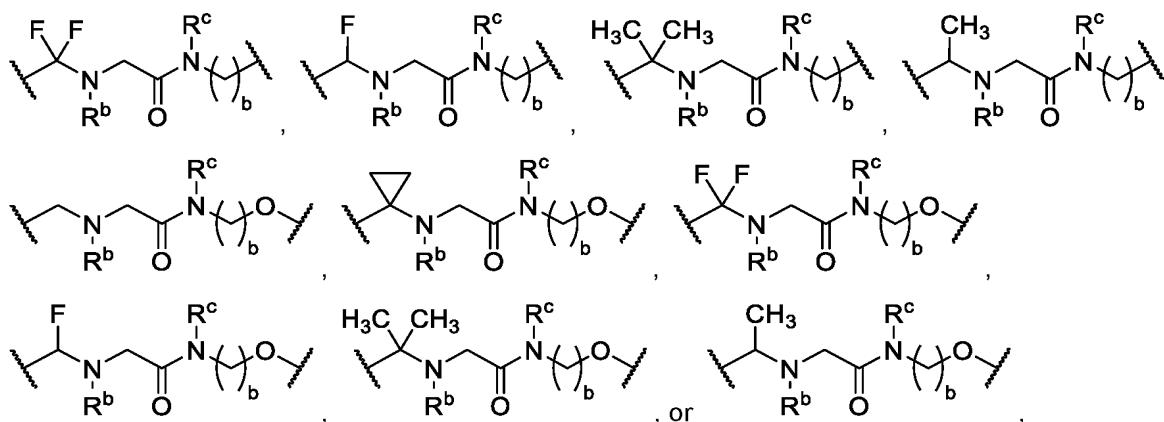
In some embodiments, E^3 is C_1-C_6 alkylene. In some embodiments, E^3 is C_1-C_3 alkylene. In some embodiments, E^3 is O.



In some embodiments, each R^N is, independently, H or optionally substituted C₁₋₄ alkyl.

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





where

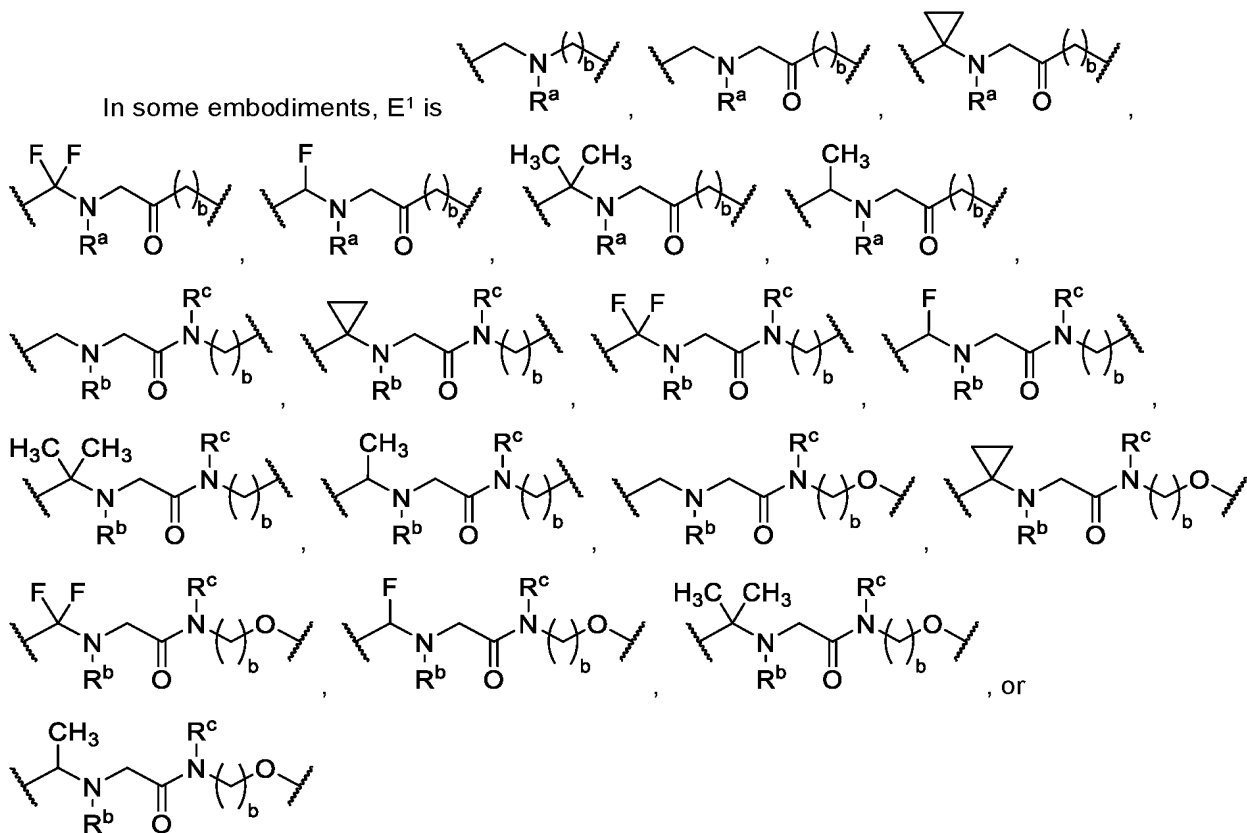
b is 0, 1, 2, 3, 4, 5, or 6;

R^a is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₆ carbocyclyl;

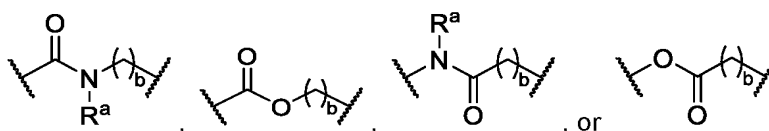
R^b is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₆ carbocyclyl; and

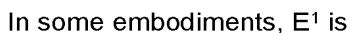
R^c is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₆ carbocyclyl.

In some embodiments, E¹ is



In some embodiments, E¹ is





or

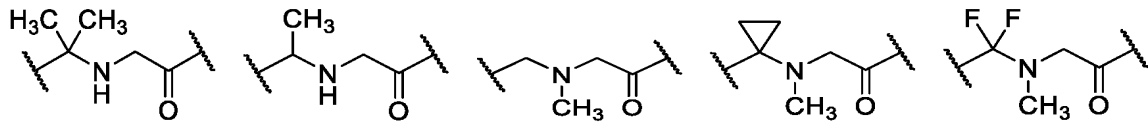
In some embodiments, R^a is H or optionally substituted C₁-C₆ alkyl. In some embodiments, R^b is

5

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



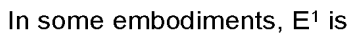
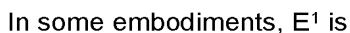
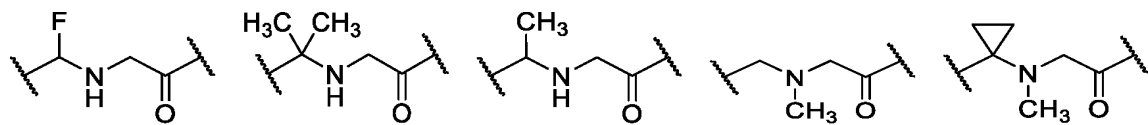
In some embodiments, E^1 is

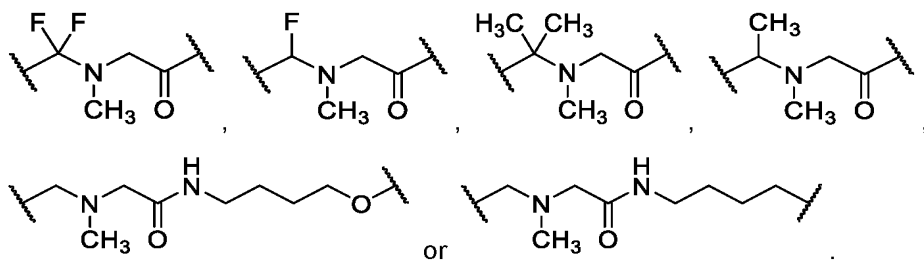


On

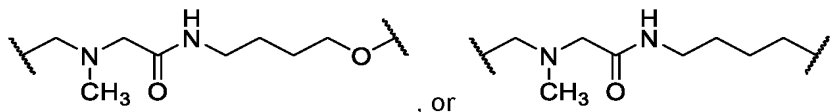


In some embodiments, E^1 is

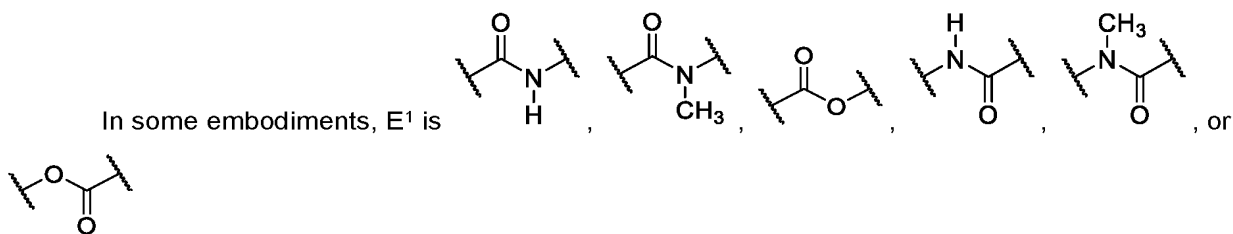




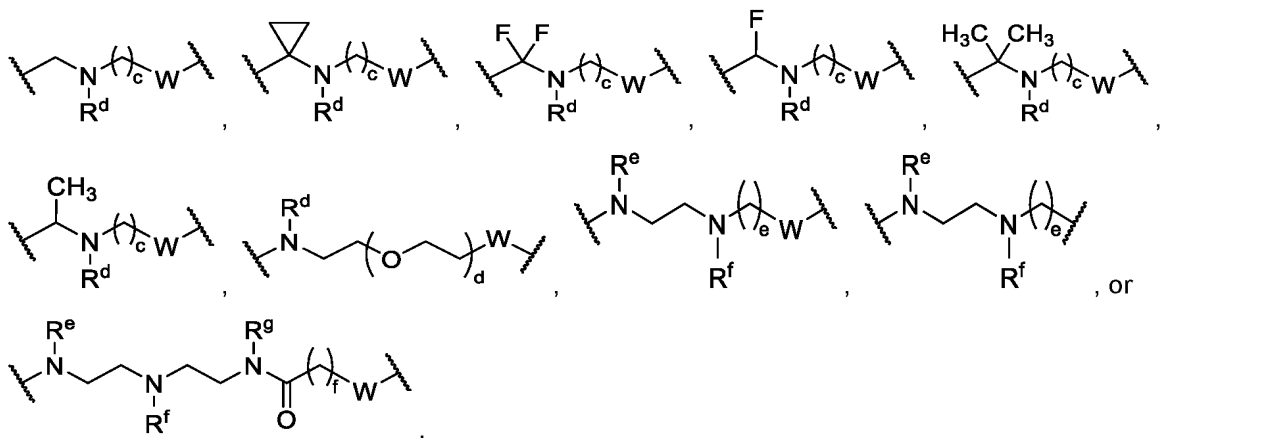
In some embodiments, E^1 is



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;

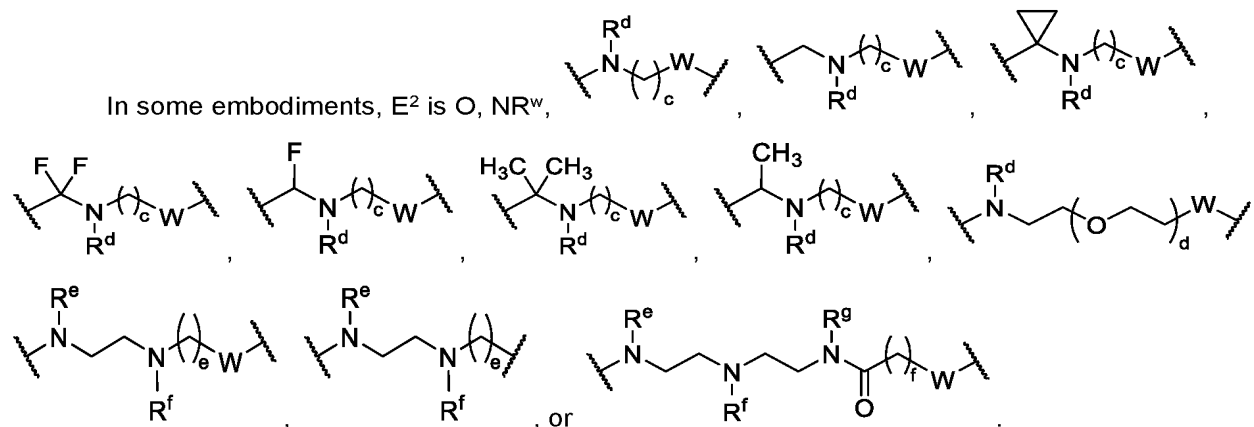
R^d is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₈ carbocyclyl;

R^e is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₆ carbocyclyl;

R^f is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₆ carbocyclyl;

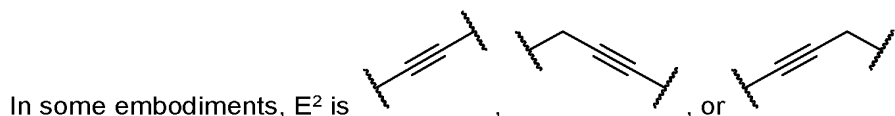
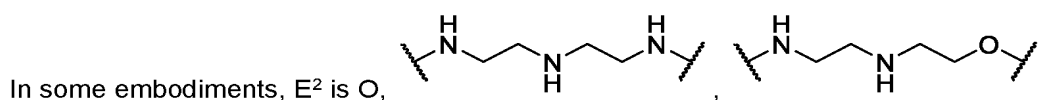
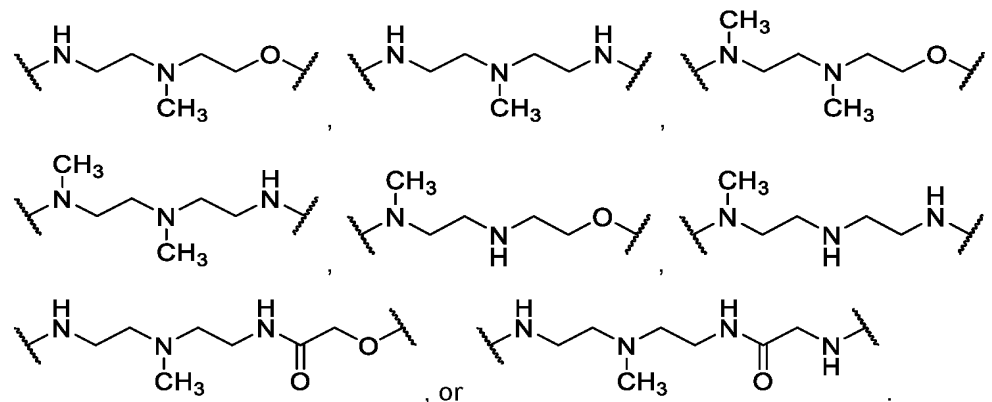
R^g is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₆ carbocyclyl; and

5 W is O or NR^w, wherein R^w is H or optionally substituted C₁-C₆ alkyl.



10 In some embodiments, R^d is H or optionally substituted C₁-C₆ alkyl. In some embodiments, R^e is H or optionally substituted C₁-C₆ alkyl. In some embodiments, R^f is H or optionally substituted C₁-C₆ alkyl. In some embodiments, R^g is H or optionally substituted C₁-C₆ alkyl. In some embodiments, R^w is H or optionally substituted C₁-C₆ alkyl.

15 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.

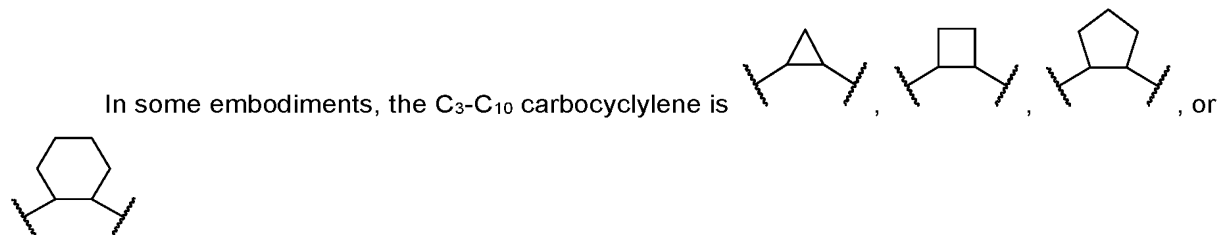
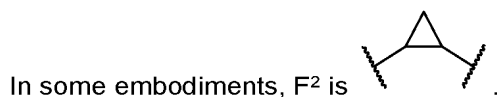
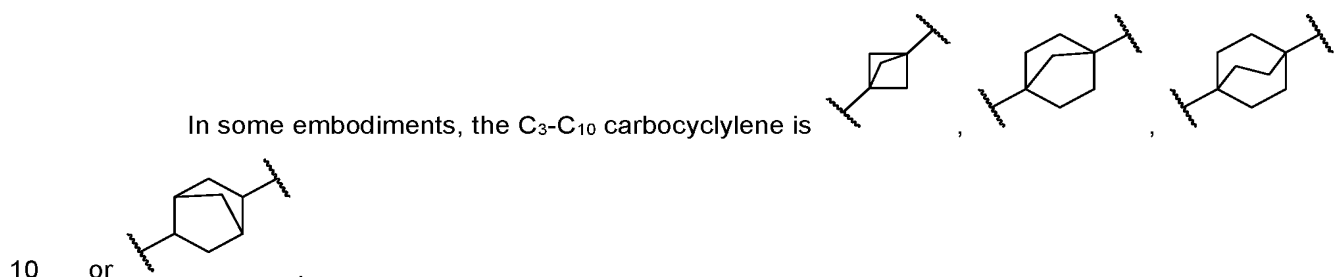


20 In some embodiments, each of F¹, F², or F³ is, independently, optionally substituted C₃-C₁₀ carbocyclene.

In some embodiments, the C₃-C₁₀ carbocyclylene is monocyclic. In some embodiments, the C₃-C₁₀ carbocyclylene is polycyclic.

In some embodiments, the C₃-C₁₀ carbocyclylene is bicyclic.

In some embodiments, the C₃-C₁₀ carbocyclylene is bridged. In some embodiments, the C₃-C₁₀ carbocyclylene is fused. In some embodiments, the C₃-C₁₀ carbocyclylene is spirocyclic.



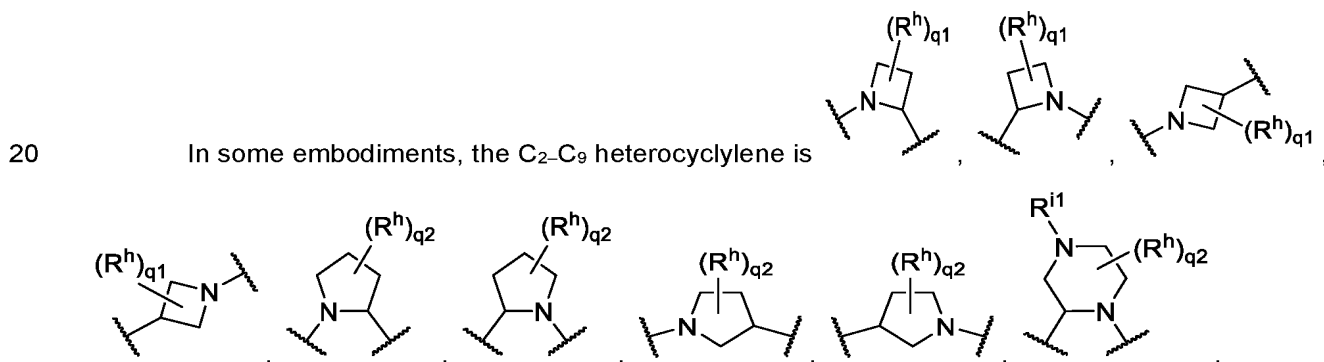
In some embodiments, each of F¹, F², or F³ is, independently, optionally substituted C₂-C₉ heterocyclylene.

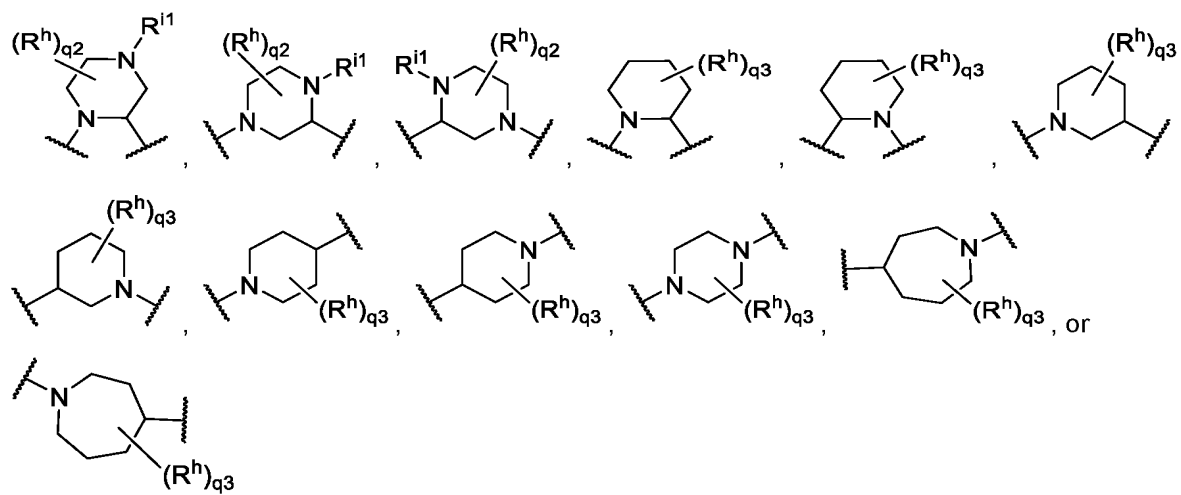
In some embodiments, the C₂-C₉ heterocyclylene is monocyclic. In some embodiments, the C₂-C₉ heterocyclylene is polycyclic.

In some embodiments, the C₂-C₉ heterocyclylene is bicyclic.

In some embodiments, the C₂-C₉ heterocyclylene is bridged. In some embodiments, the C₂-C₉ heterocyclylene is fused. In some embodiments, the C₂-C₉ heterocyclylene is spirocyclic.

In some embodiments, the C₂-C₉ heterocyclylene includes a quaternary amine.





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 C₁-C₆ alkyl, ORⁱ², or NRⁱ³Rⁱ⁴; or two R^h groups, together with the carbon atom to which each is attached, combine to form optionally substituted C₃-C₁₀ carbocyclyl or optionally substituted C₂-C₉ heterocyclyl; or two R^h groups, together with the carbon atoms to which each is attached, combine to form optionally substituted C₃-C₁₀ carbocyclyl or optionally substituted C₂-C₉ heterocyclyl;

Rⁱ¹ is H or optionally substituted C₁-C₆ alkyl;

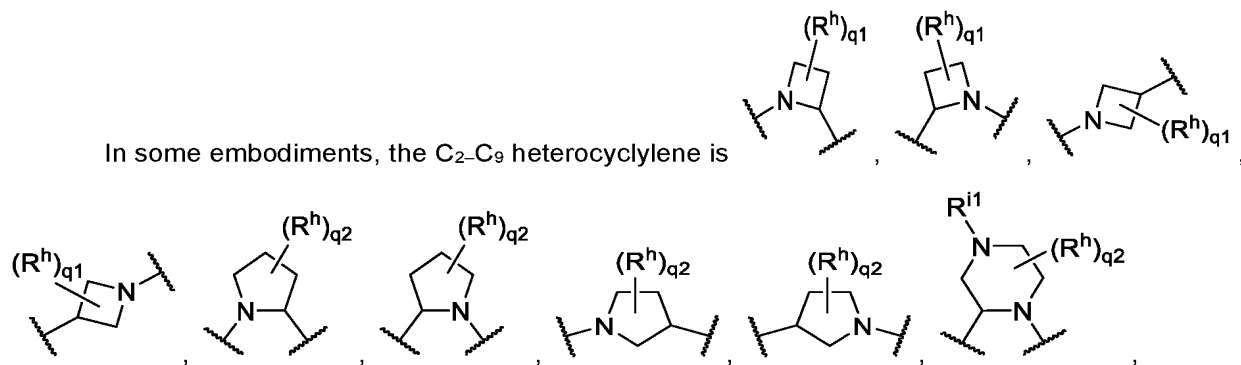
Rⁱ² is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₆ carbocyclyl;

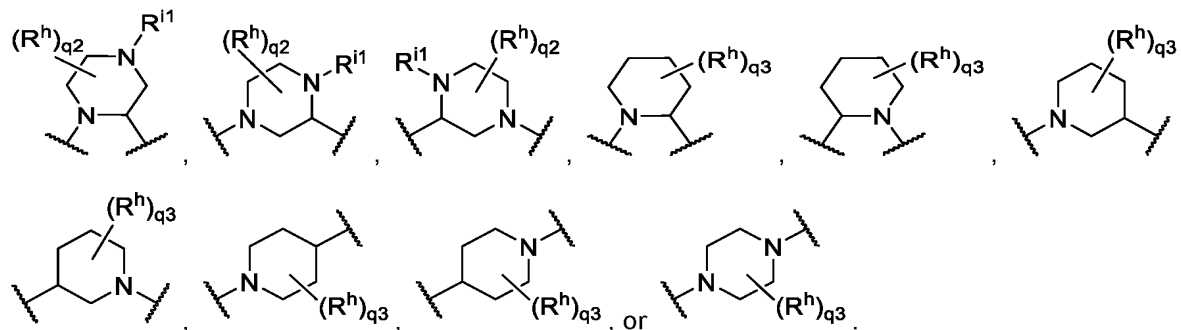
Rⁱ³ is H or optionally substituted C₁-C₆ alkyl; and

Rⁱ⁴ is H or optionally substituted C₁-C₆ alkyl.

In some embodiments, each R^h is, independently, halogen, optionally substituted C₁-C₆ alkyl, ORⁱ², or NRⁱ³Rⁱ⁴. In some embodiments, Rⁱ¹ is H or optionally substituted C₁-C₆ alkyl. In some embodiments, Rⁱ² is H or optionally substituted C₁-C₆ alkyl. In some embodiments, Rⁱ³ is H or optionally substituted C₁-C₆ alkyl. In some embodiments, Rⁱ⁴ is H or optionally substituted C₁-C₆ alkyl.

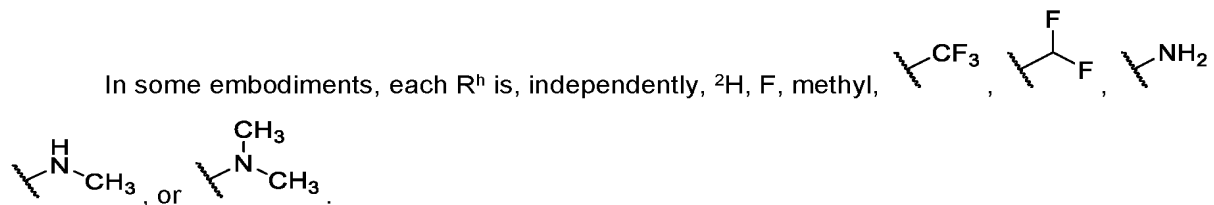
In some embodiments, the C₂-C₉ heterocyclylene is





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.

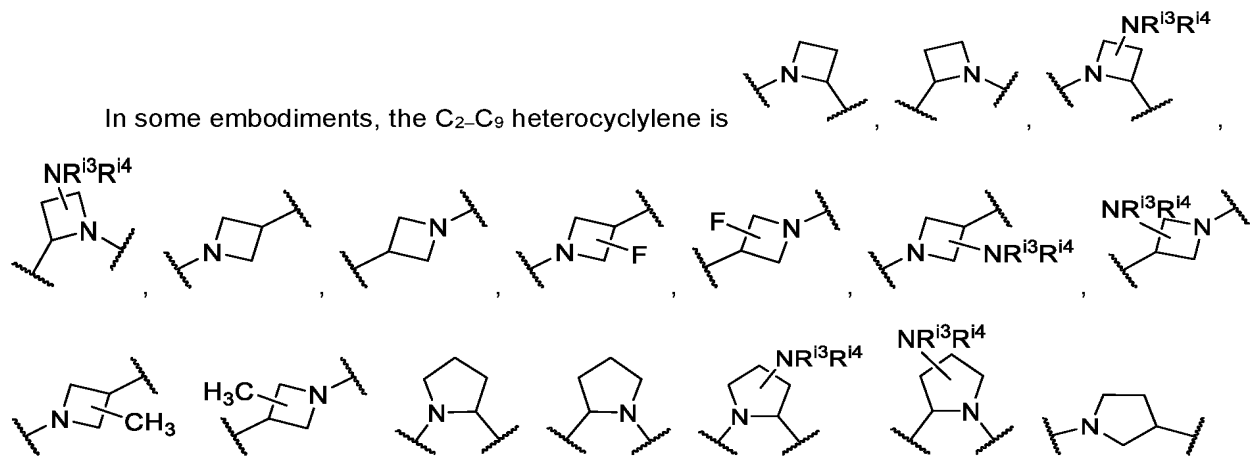


In some embodiments, each R^h is, independently, F, methyl, or $NR^{i3}R^{i4}$.

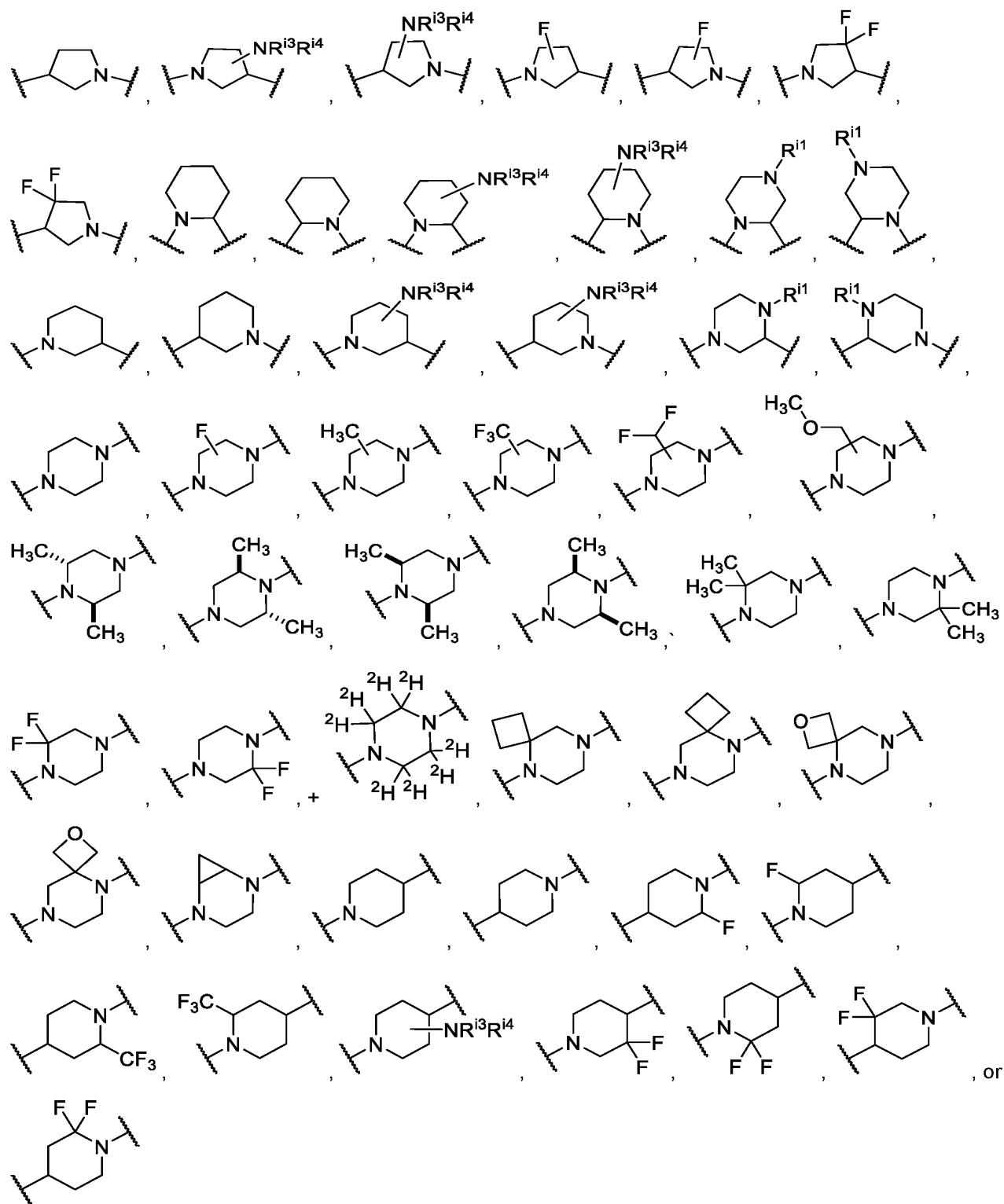
In some embodiments, q_1 is 0, 1, or 2. In some embodiments, q_1 is 0. In some embodiments, q_1 is 1. In some embodiments, q_1 is 2.

In some embodiments, q_2 is 0, 1, or 2. In some embodiments, q_2 is 0. In some embodiments, q_2 is 1. In some embodiments, q_2 is 2.

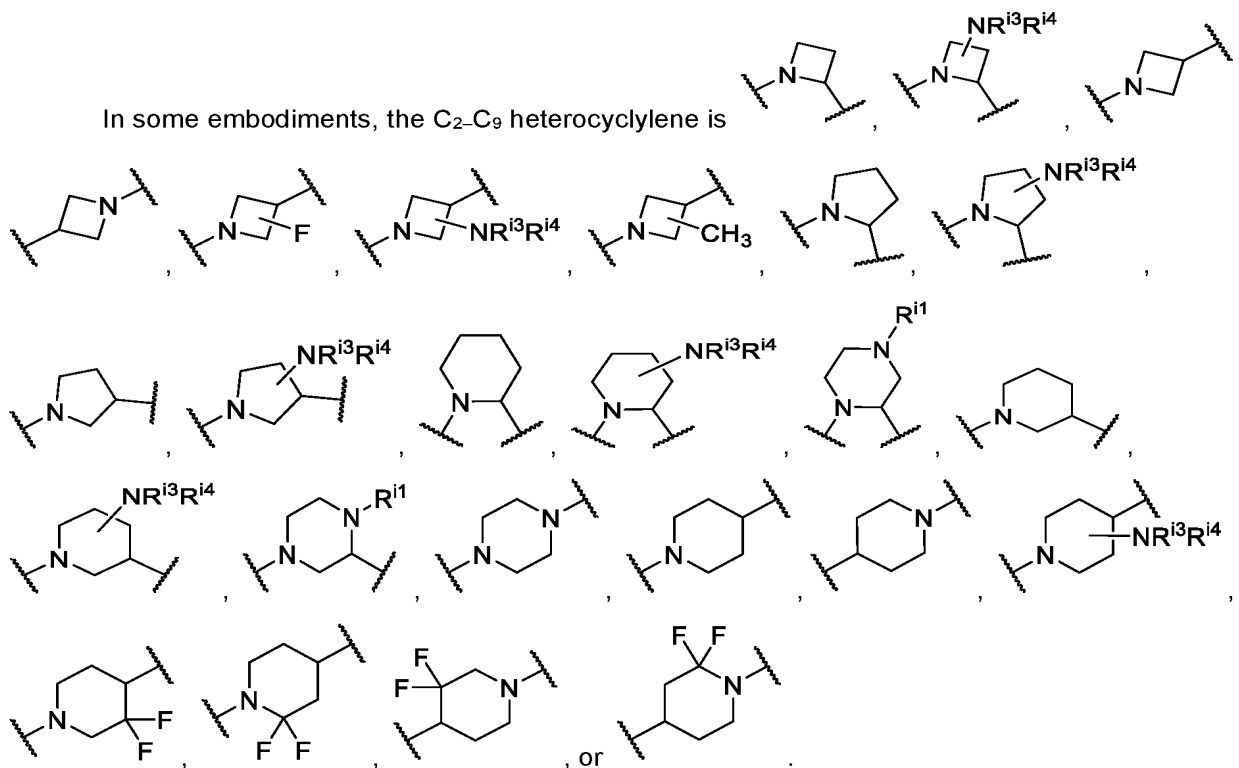
In some embodiments, q_3 is 0, 1, or 2. In some embodiments, q_3 is 0. In some embodiments, q_3 is 1. In some embodiments, q_3 is 2.



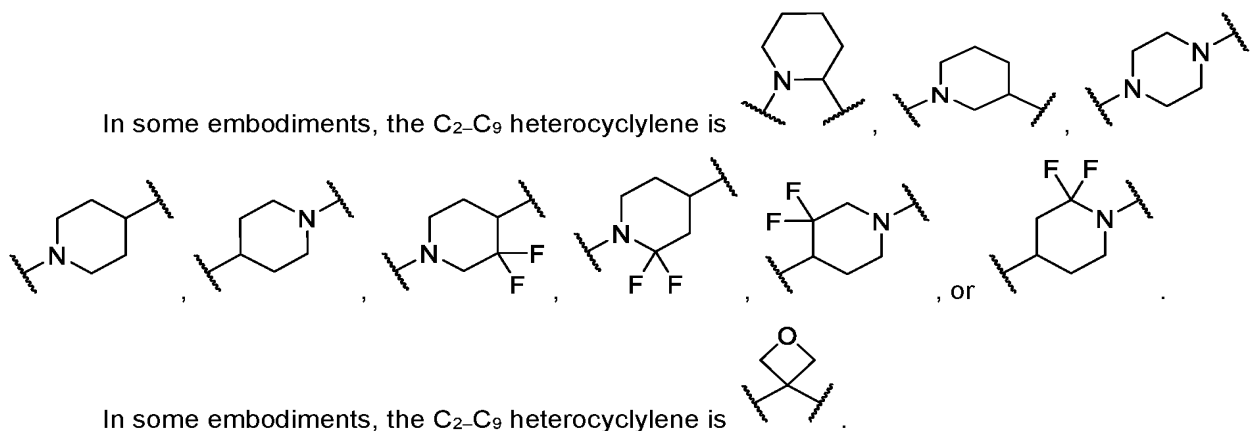
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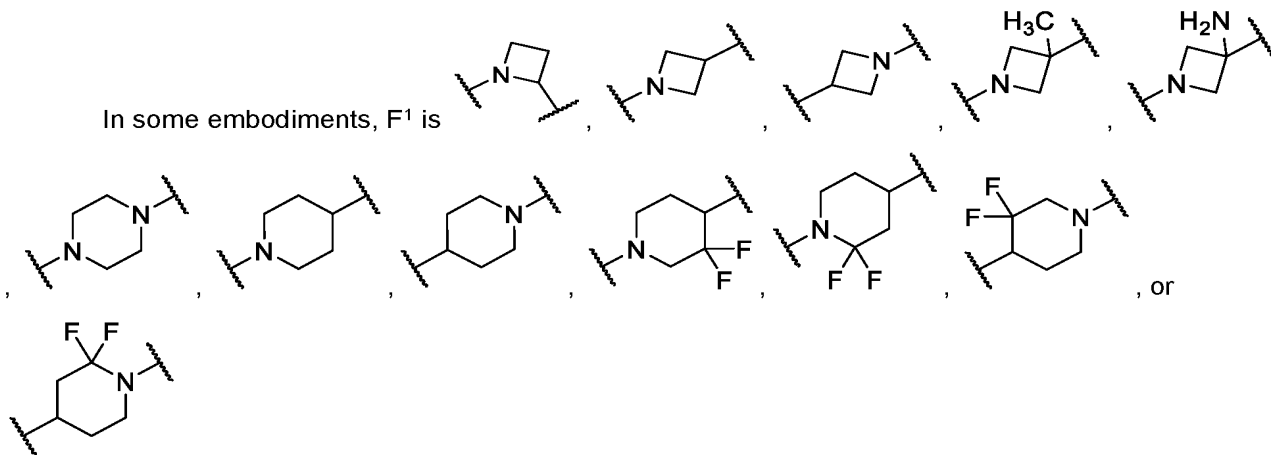
In some embodiments, the C₂-C₉ heterocyclylene is



In some embodiments, the C₂-C₉ heterocyclylene is



In some embodiments, F¹ is



In some embodiments, F¹ is



In some embodiments, F¹ is



In some embodiments, F² is

In some embodiments, F² is

F^2 is  or 

In some embodiments, F^3 is

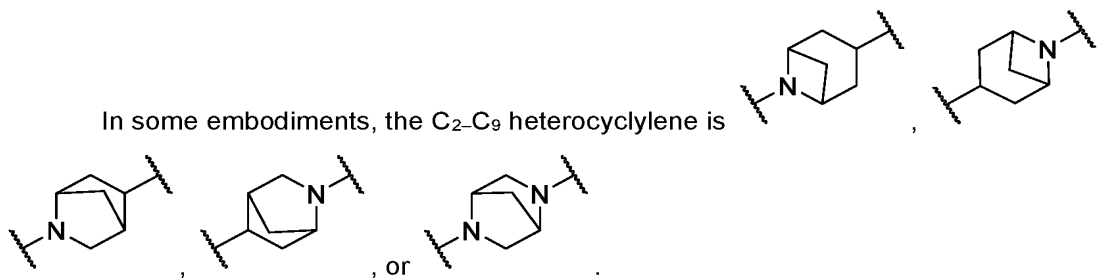


In some embodiments

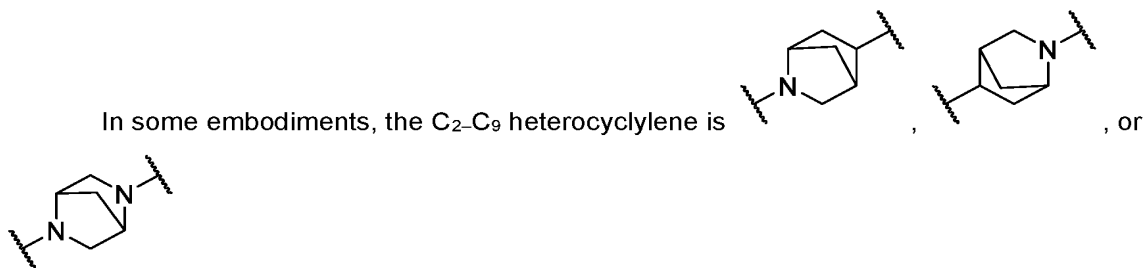
F^3 is  or 

10

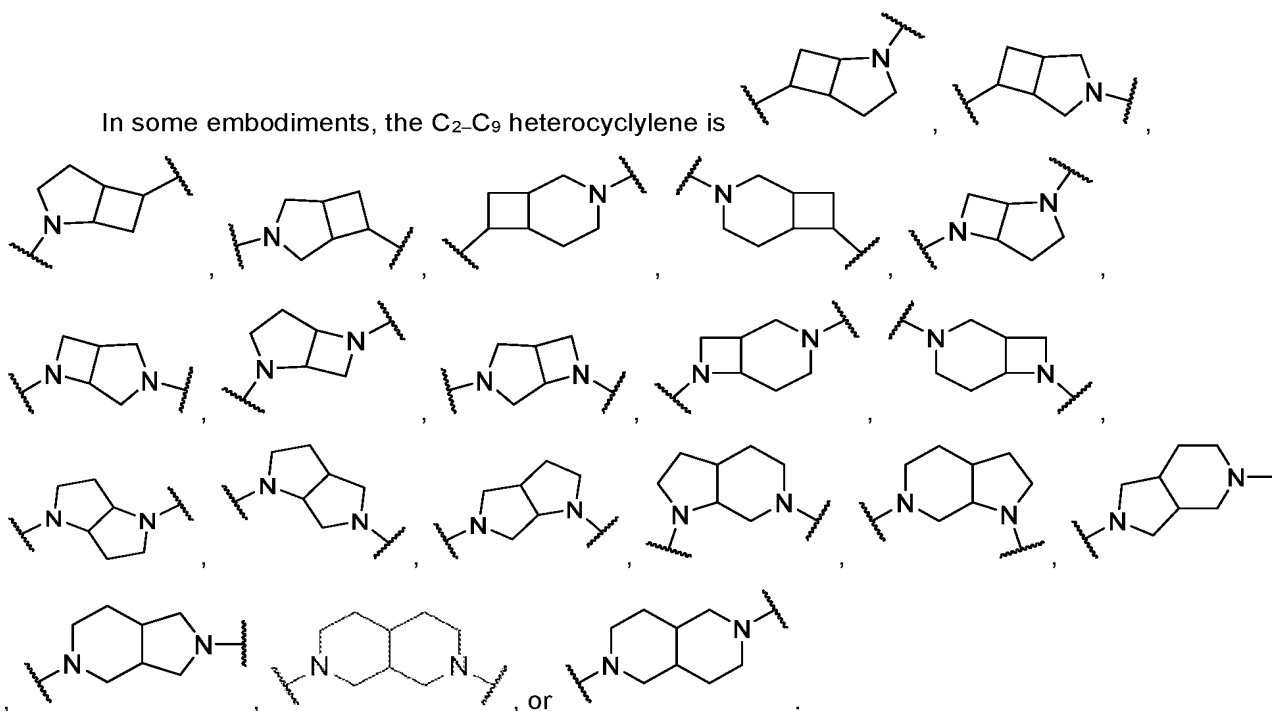
In some embodiments, the C₂-C₉ heterocyclylene is



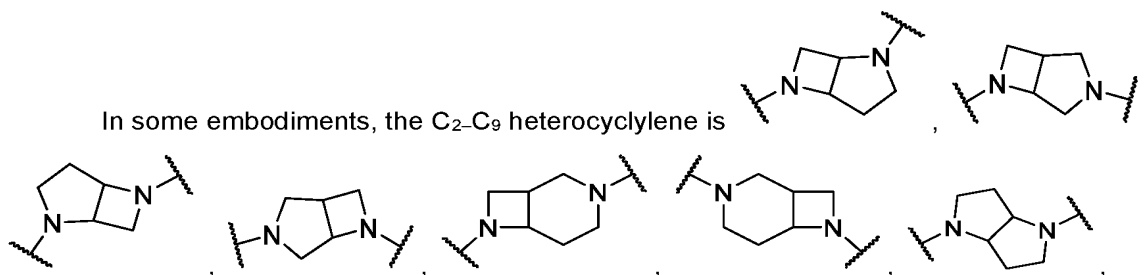
In some embodiments, the C₂-C₉ heterocyclylene is

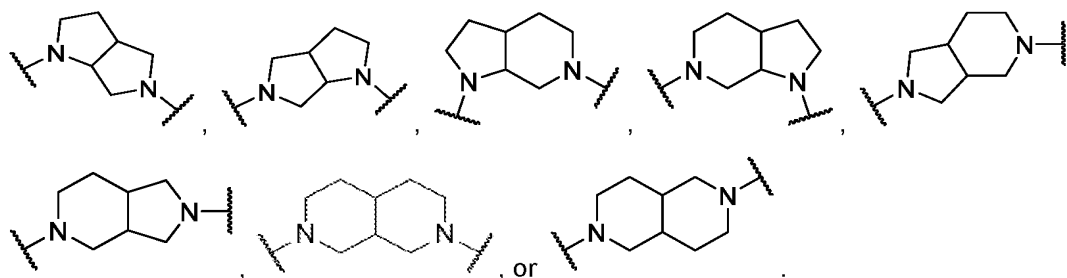


5 In some embodiments, the C₂-C₉ heterocyclylene is

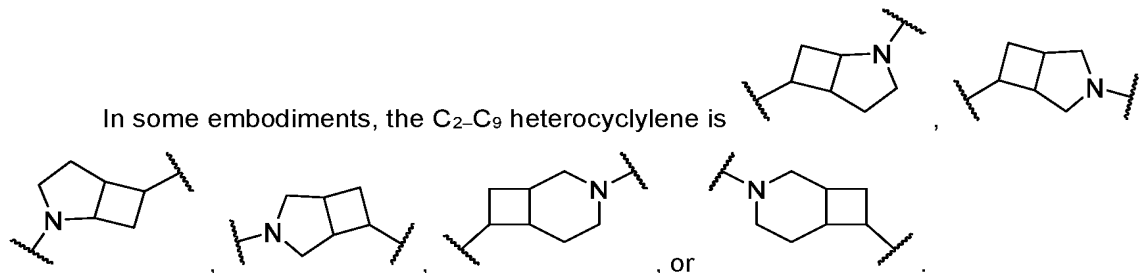


10 In some embodiments, the C₂-C₉ heterocyclylene is

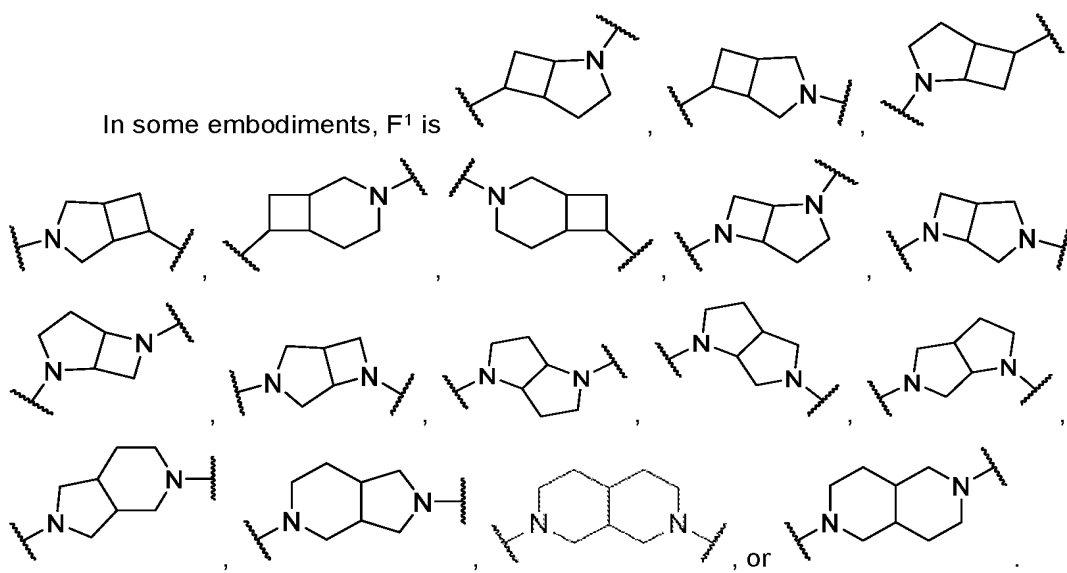




In some embodiments, the C₂-C₉ heterocyclylene is

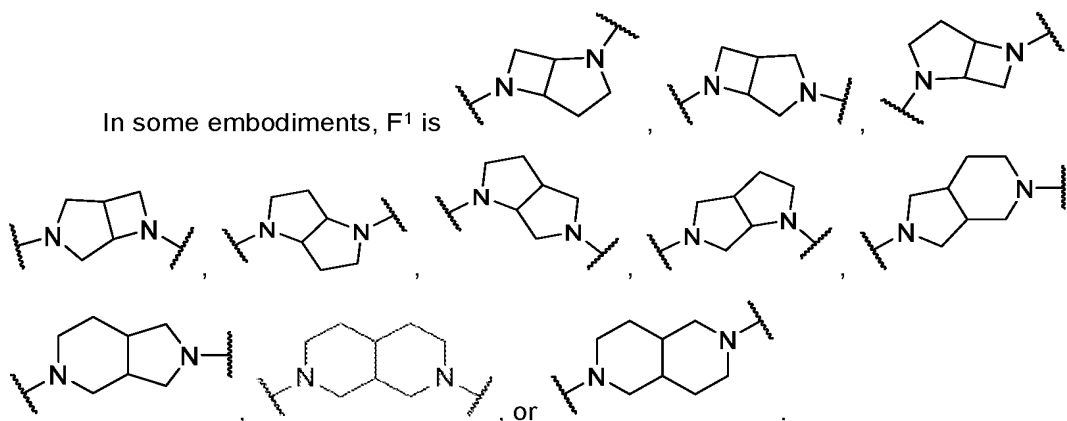


5 In some embodiments, F¹ is

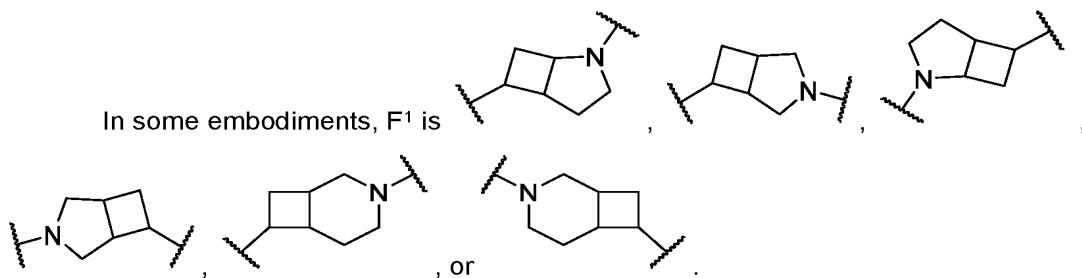


In some embodiments, F¹ is

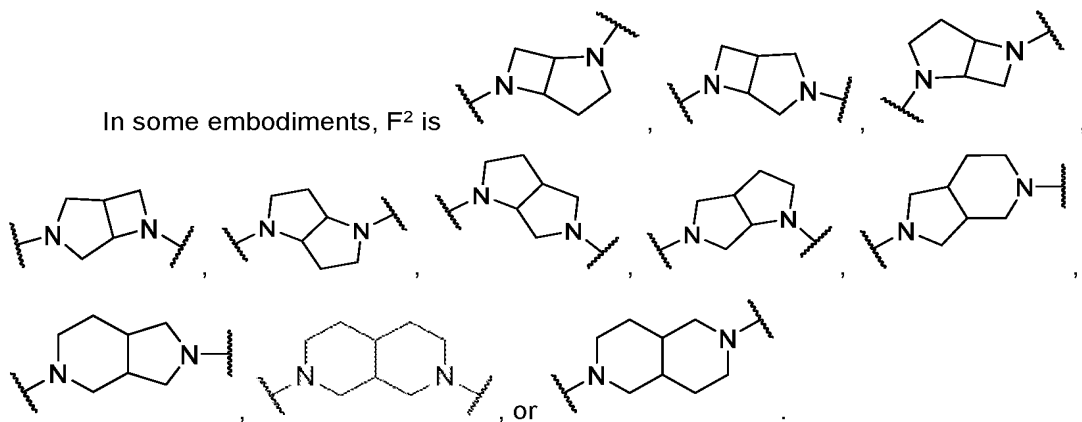
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In some embodiments, F¹ is

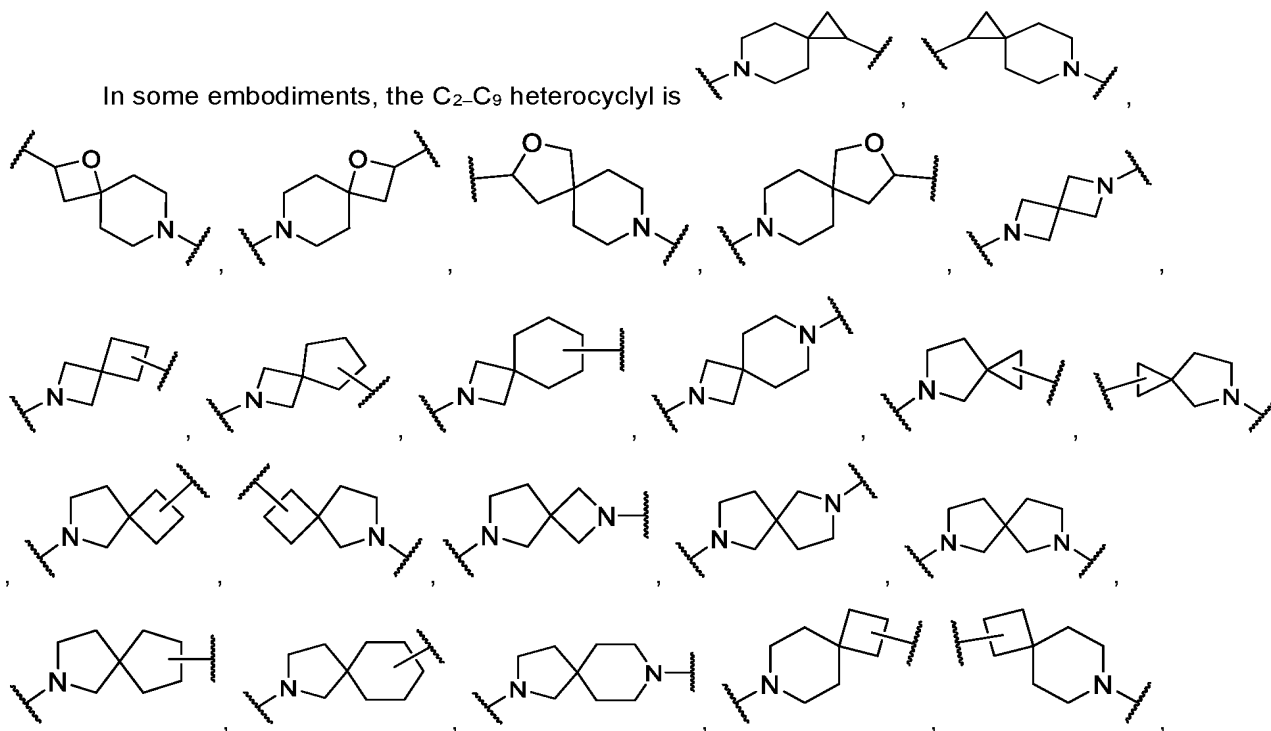


In some embodiments, F² is

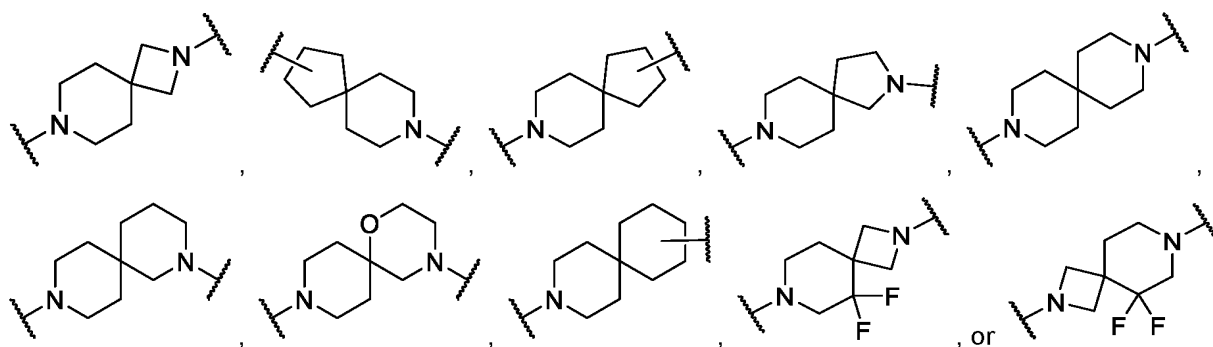


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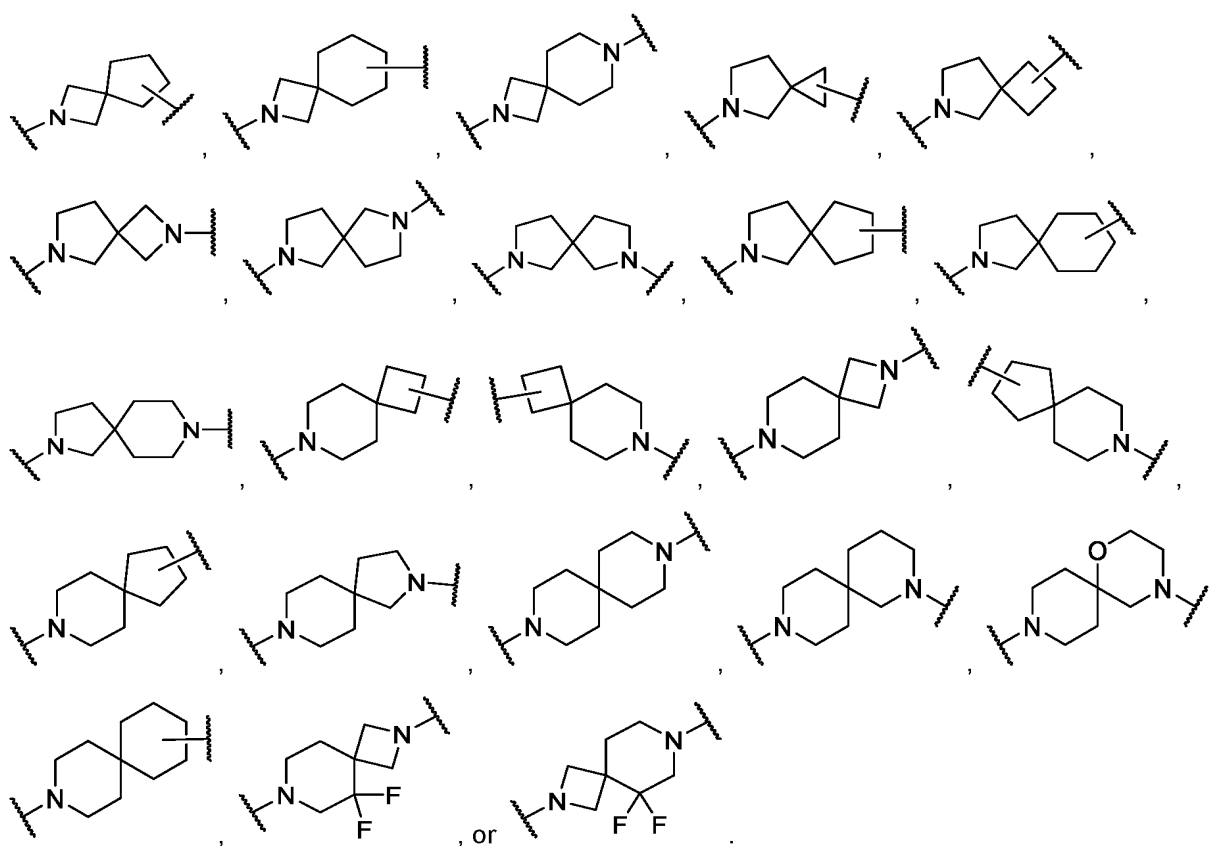
In some embodiments, the C₂-C₉ heterocyclyl is



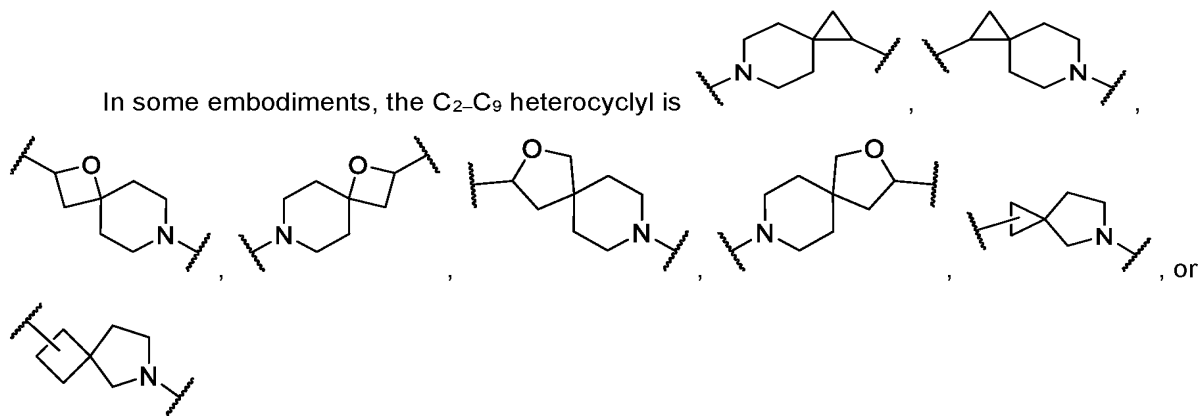
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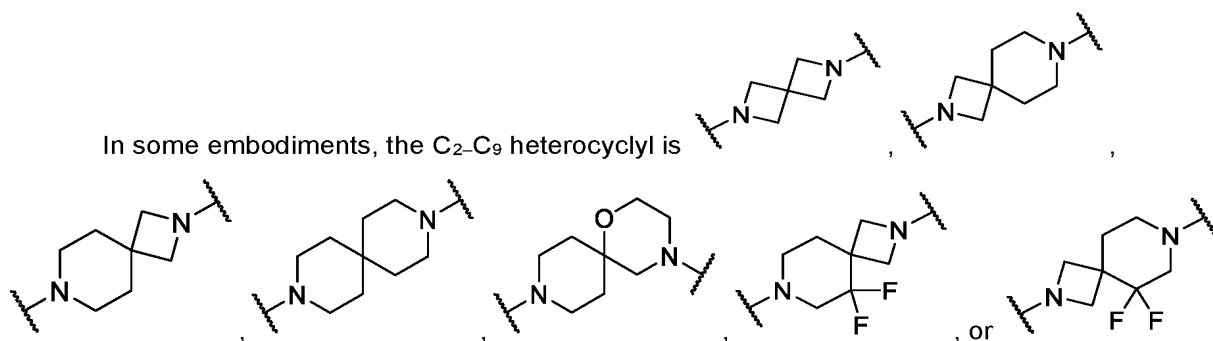
In some embodiments, the C₂-C₉ heterocyclyl is



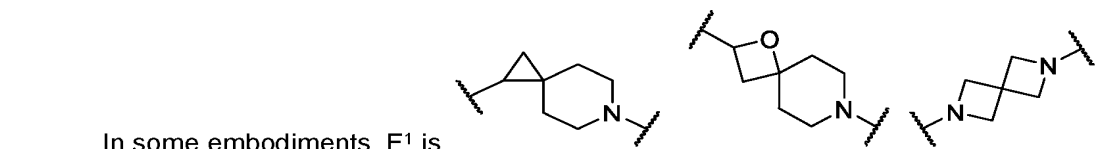
In some embodiments, the C₂-C₉ heterocyclyl is



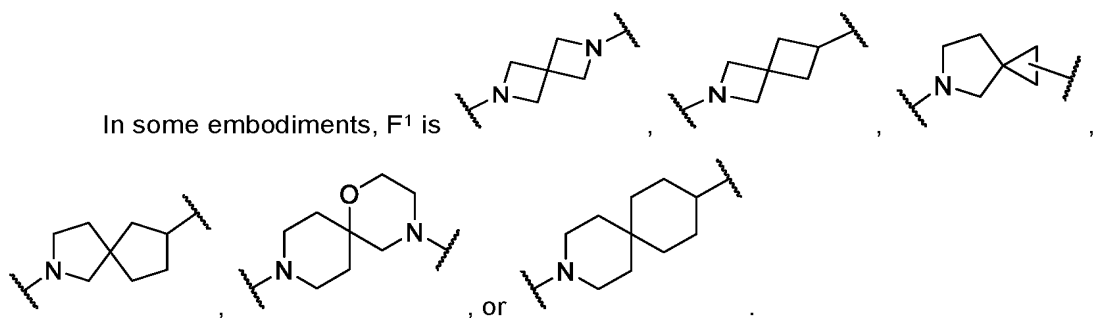
In some embodiments, the C₂-C₉ heterocyclyl is



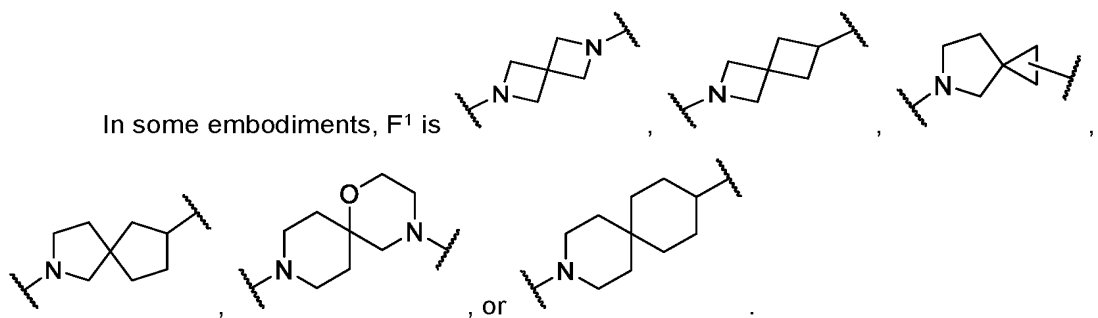
In some embodiments, F¹ is



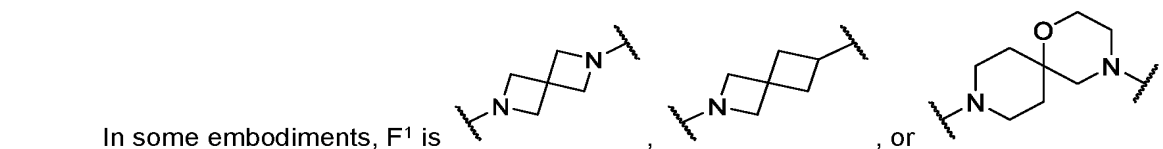
In some embodiments, F¹ is



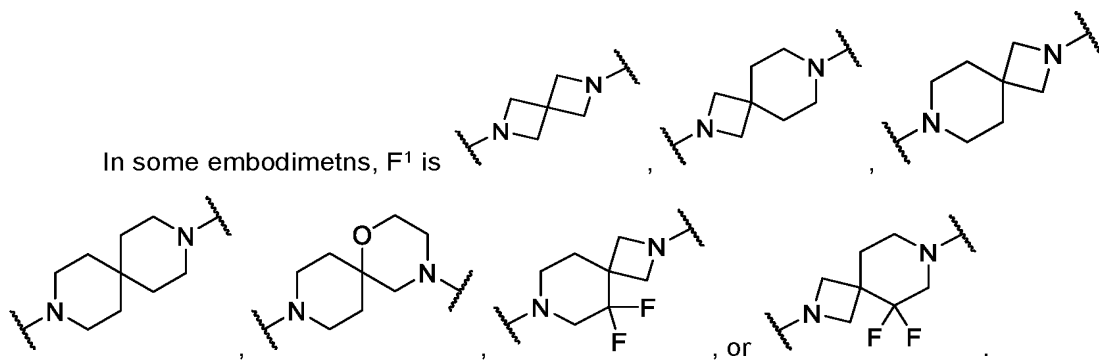
In some embodiments, F¹ is



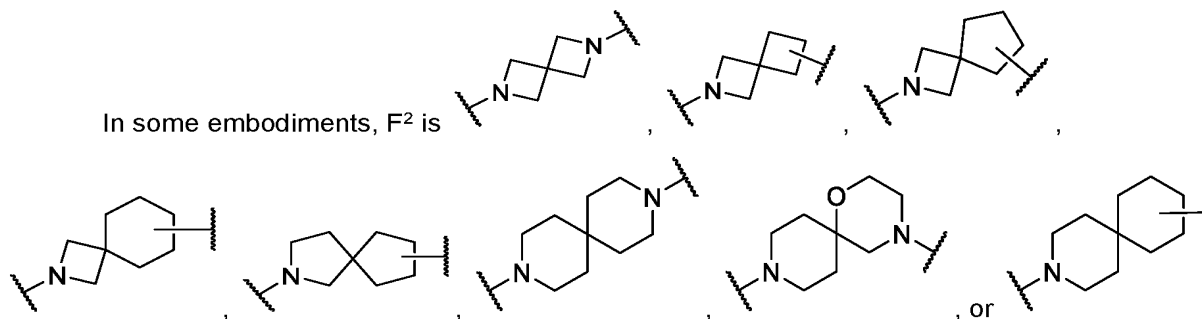
In some embodiments, F¹ is



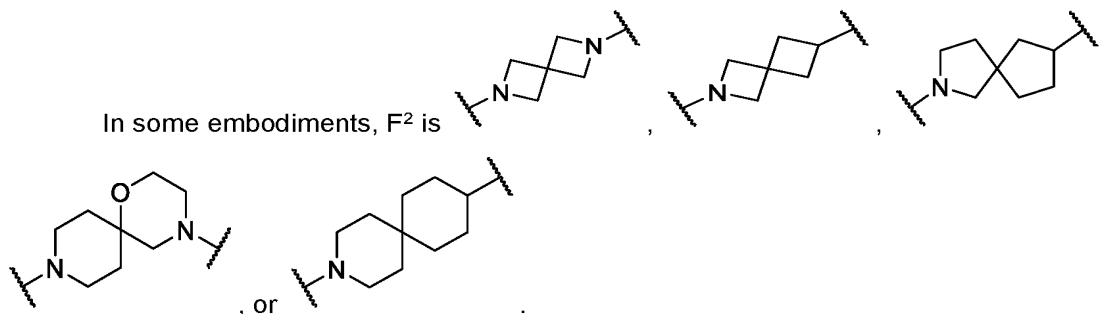
In some embodiments, F^1 is



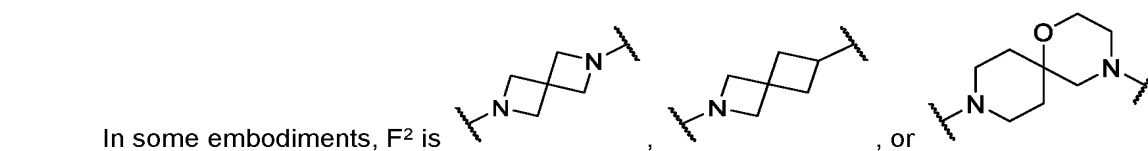
In some embodiments, F^2 is



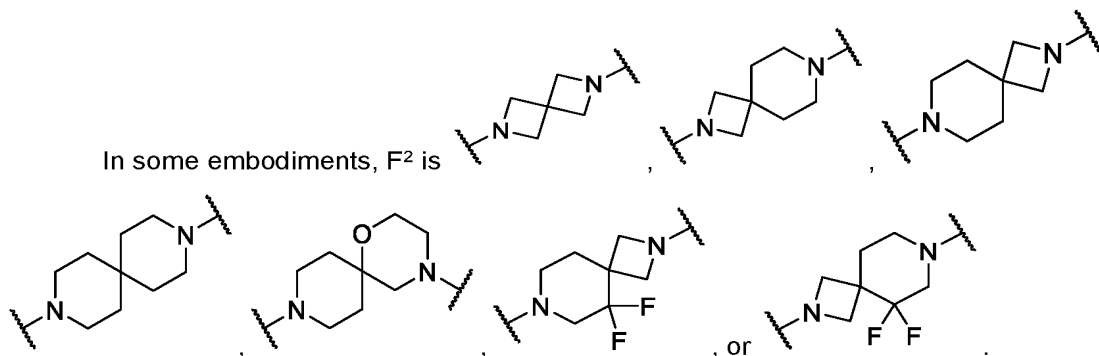
In some embodiments, F^2 is



In some embodiments, F^2 is

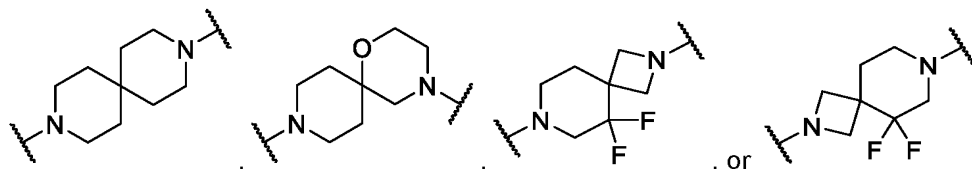


In some embodiments, F^2 is



The image displays three chemical structures of bicyclic polyimides, each with a central nitrogen atom and two phenyl rings. The structures are:

- 1,3-bis(4-aminophenyl)isobenzofuran:** A bicyclic system consisting of a benzene ring fused to a five-membered ring containing a nitrogen atom. The nitrogen atom is substituted with a 4-aminophenyl group.
- 1,3-bis(4-aminophenyl)isindole:** A bicyclic system consisting of a benzene ring fused to a six-membered ring containing a nitrogen atom. The nitrogen atom is substituted with a 4-aminophenyl group.
- 1,3-bis(4-aminophenyl)indole:** A bicyclic system consisting of a benzene ring fused to a five-membered ring containing a nitrogen atom. The nitrogen atom is substituted with a 4-aminophenyl group.



In some embodiments, each of F¹, F², or F³ is, independently, optionally substituted C₆-C₁₀ arylene.

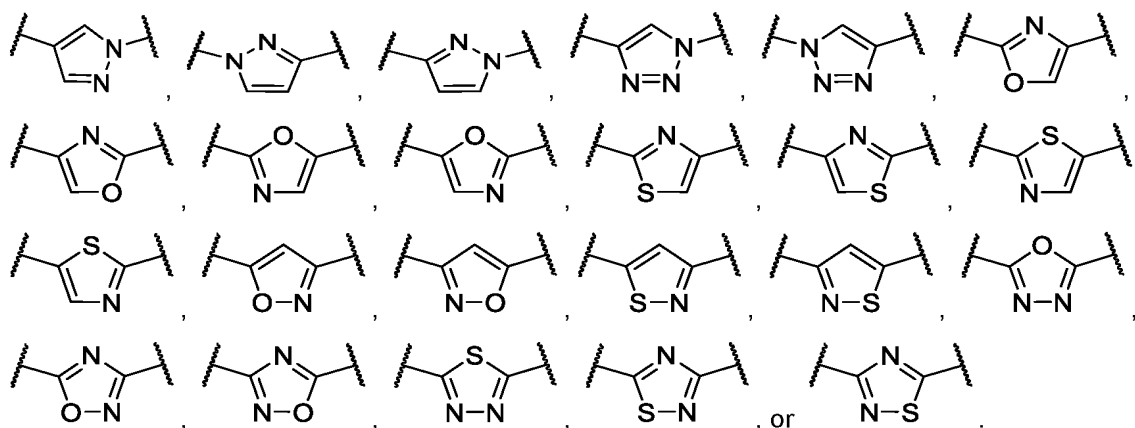


 , or
 

In some embodiments, each of F¹, F², or F³ is, independently, optionally substituted C₂-C₉ heteroaryl.

Chemical structures of three pyrazole isomers are shown, each with two phenyl groups attached at the 2 and 5 positions (or equivalent):

- Structure 1: 2,5-diphenylpyrazole (SMILES: c1cc(ccc1)-n2cc(ccc2)-c3cc(ccc3))
- Structure 2: 2,6-diphenylpyrazole (SMILES: c1cc(ccc1)-n2cc(ccc2)-c3cc(ccc3))
- Structure 3: 3,5-diphenylpyrazole (SMILES: c1cc(ccc1)-n2cc(ccc2)-c3cc(ccc3))

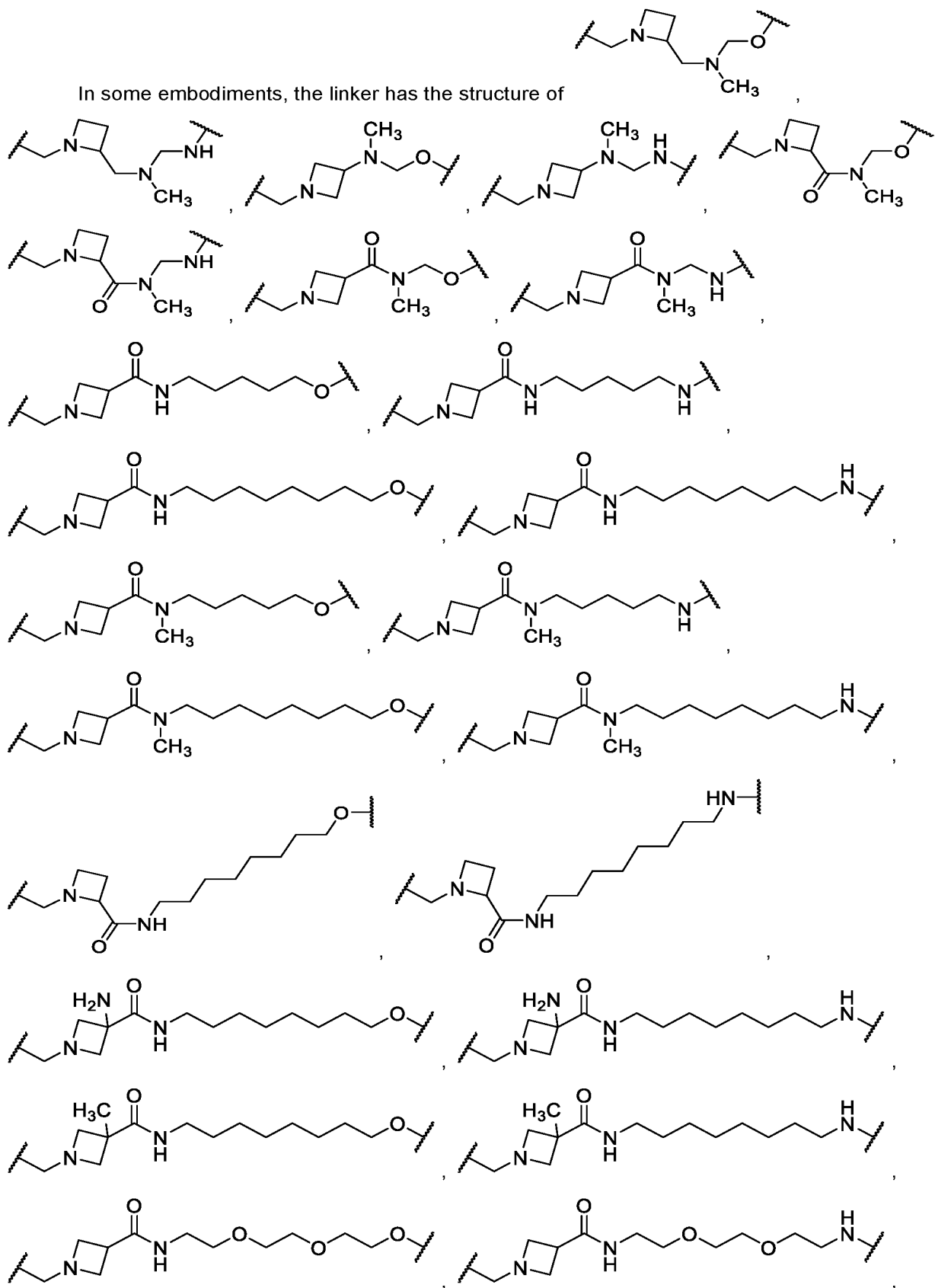


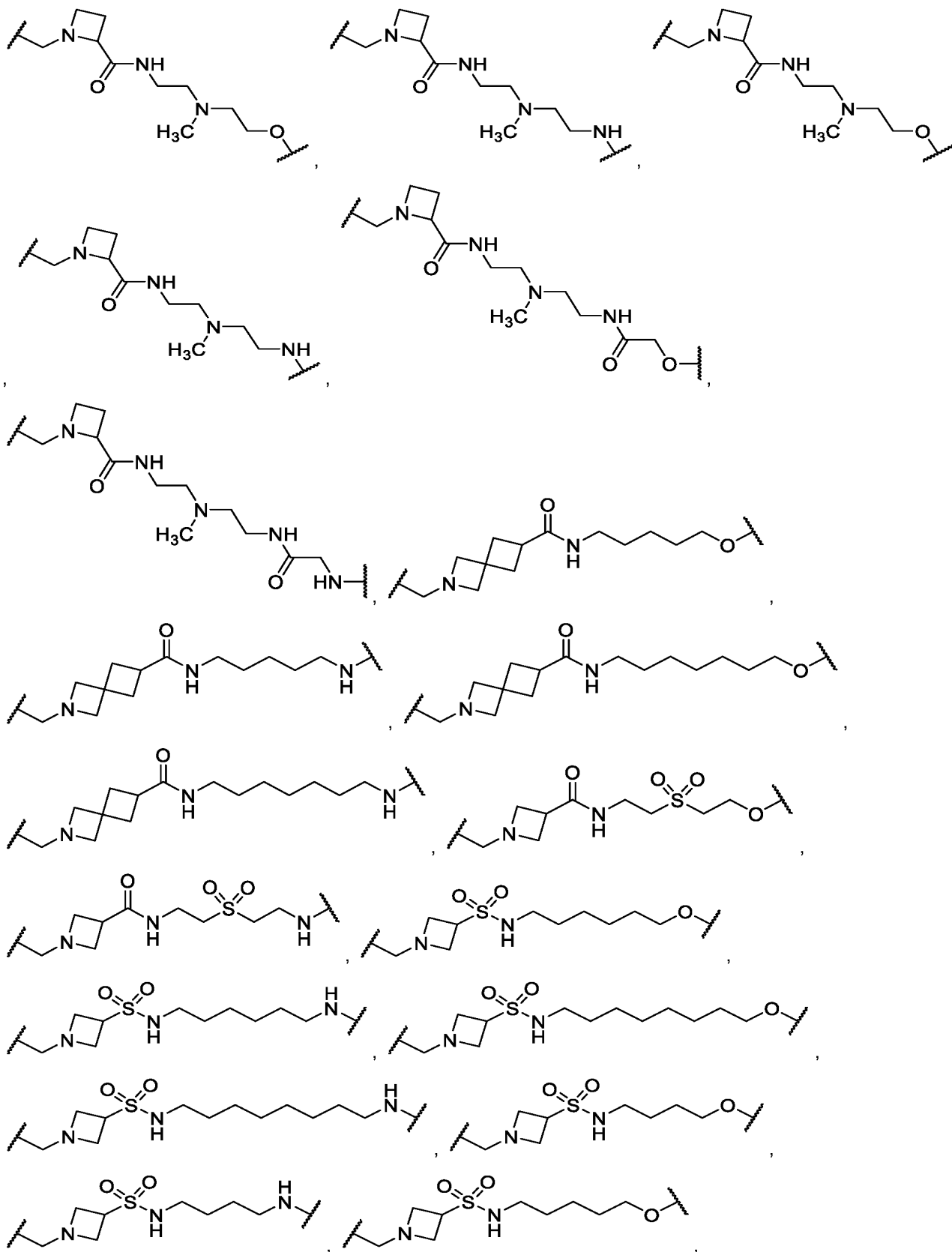
Chemical structures of 1,2,4-triazole and 1,3,4-triazole, separated by the word "or".

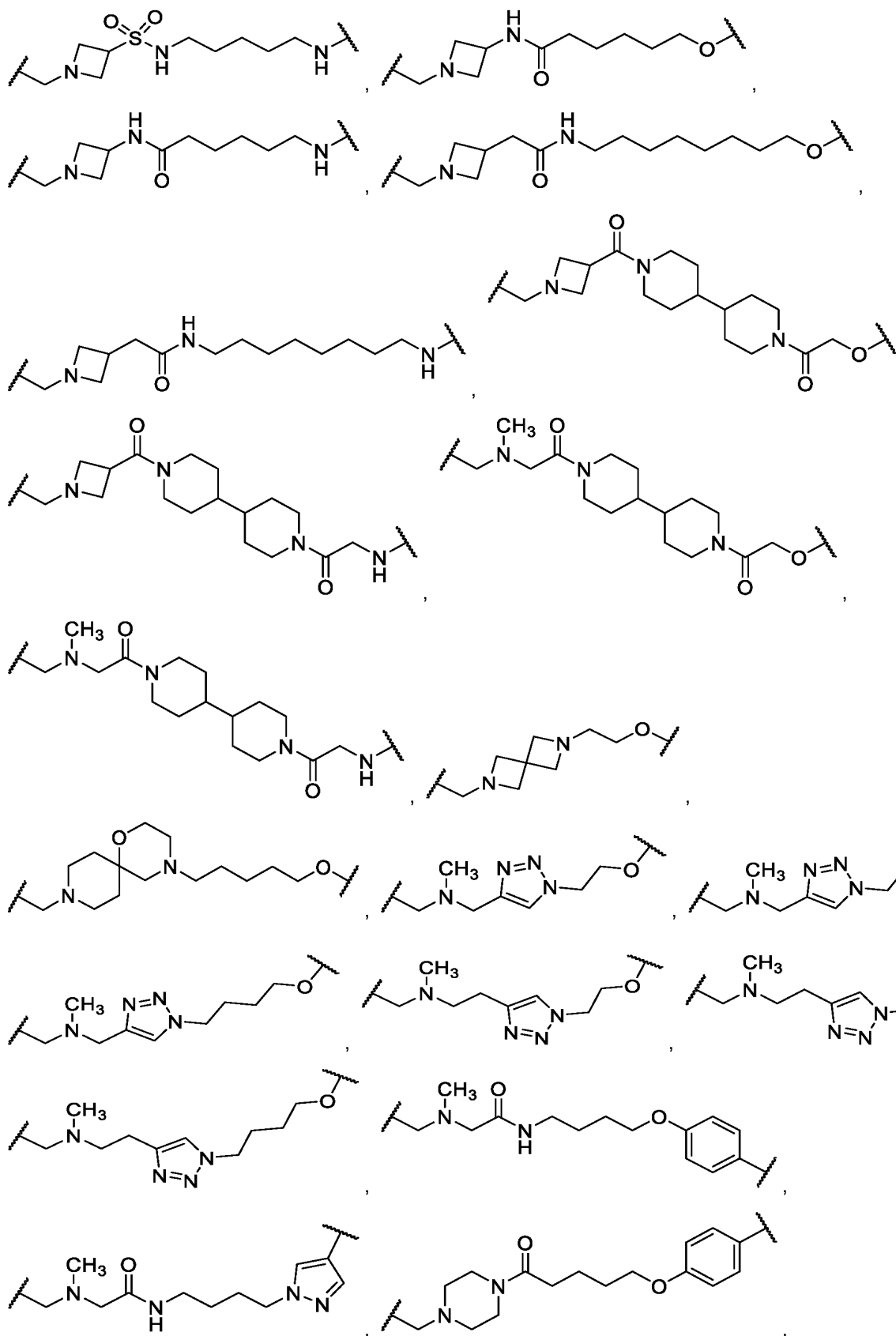
$$\begin{array}{c} \text{O} \\ \parallel \\ \diagup \quad \diagdown \end{array} \quad \text{or} \quad \begin{array}{c} \text{O} \quad \text{O} \\ \diagup \quad \diagdown \\ \text{S} \\ \diagup \quad \diagdown \end{array}$$

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

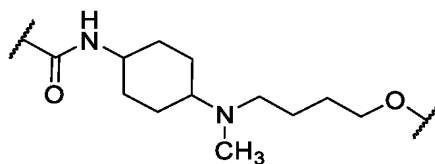
In some embodiments, the linker has the structure of





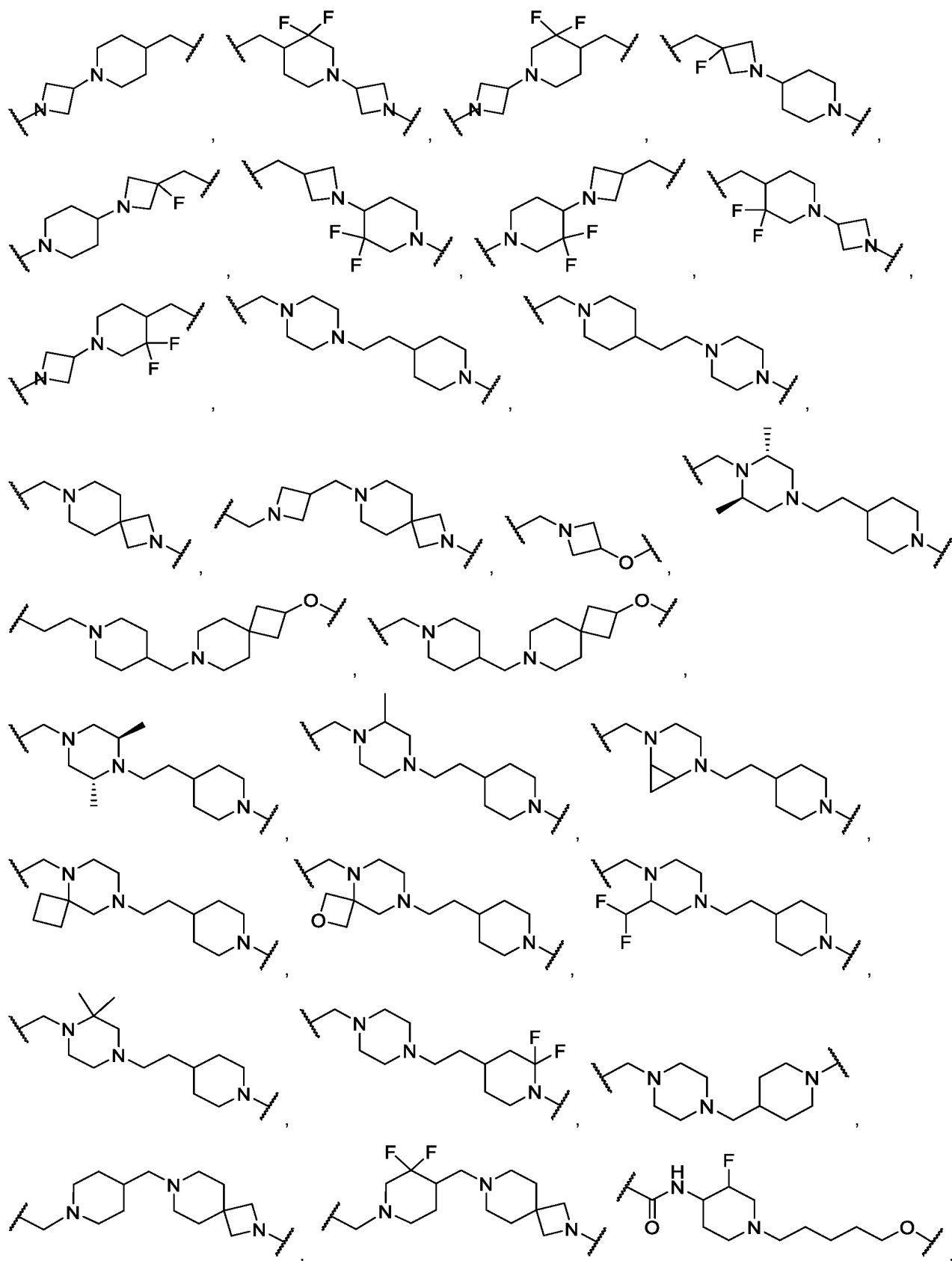


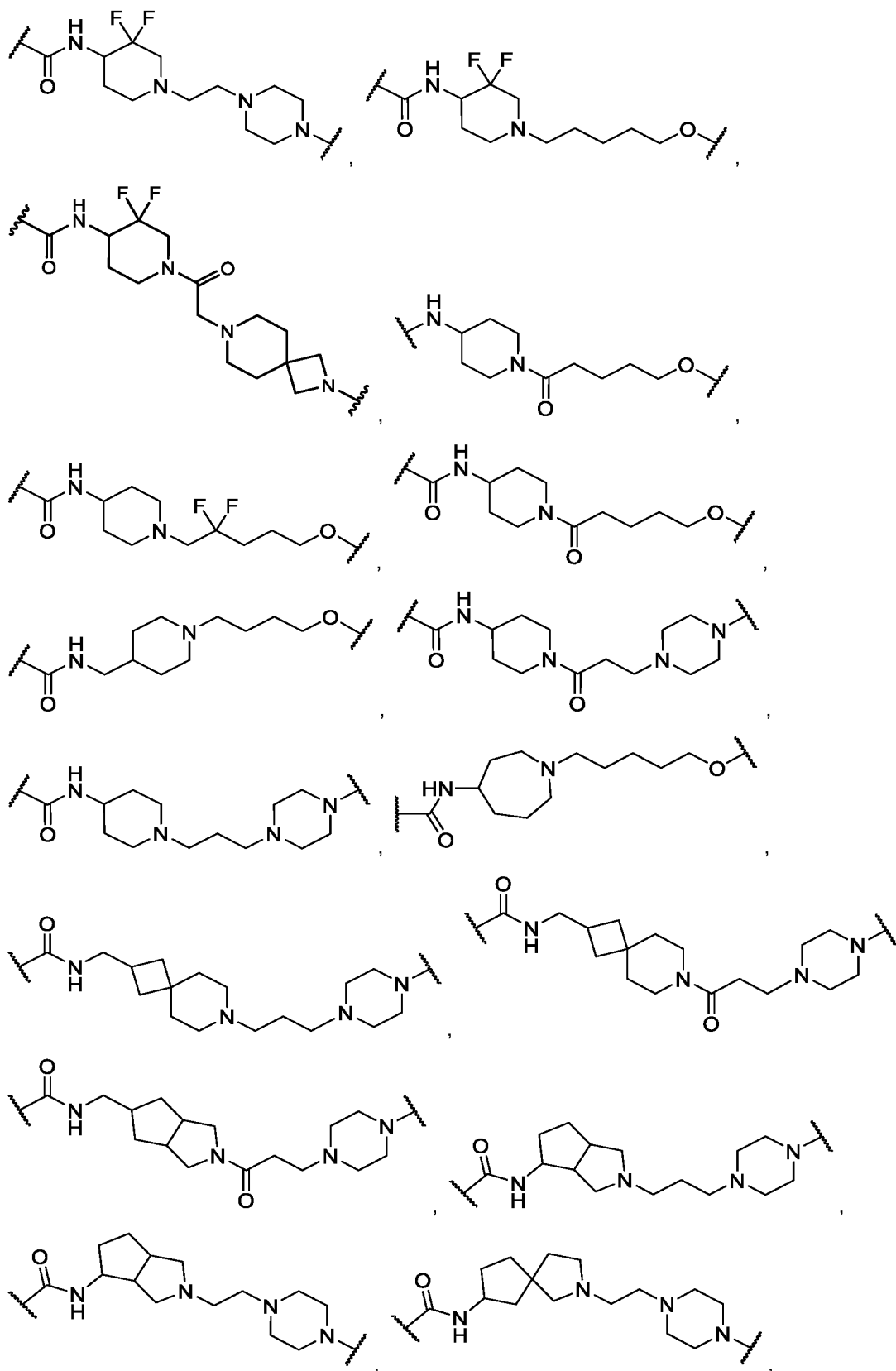
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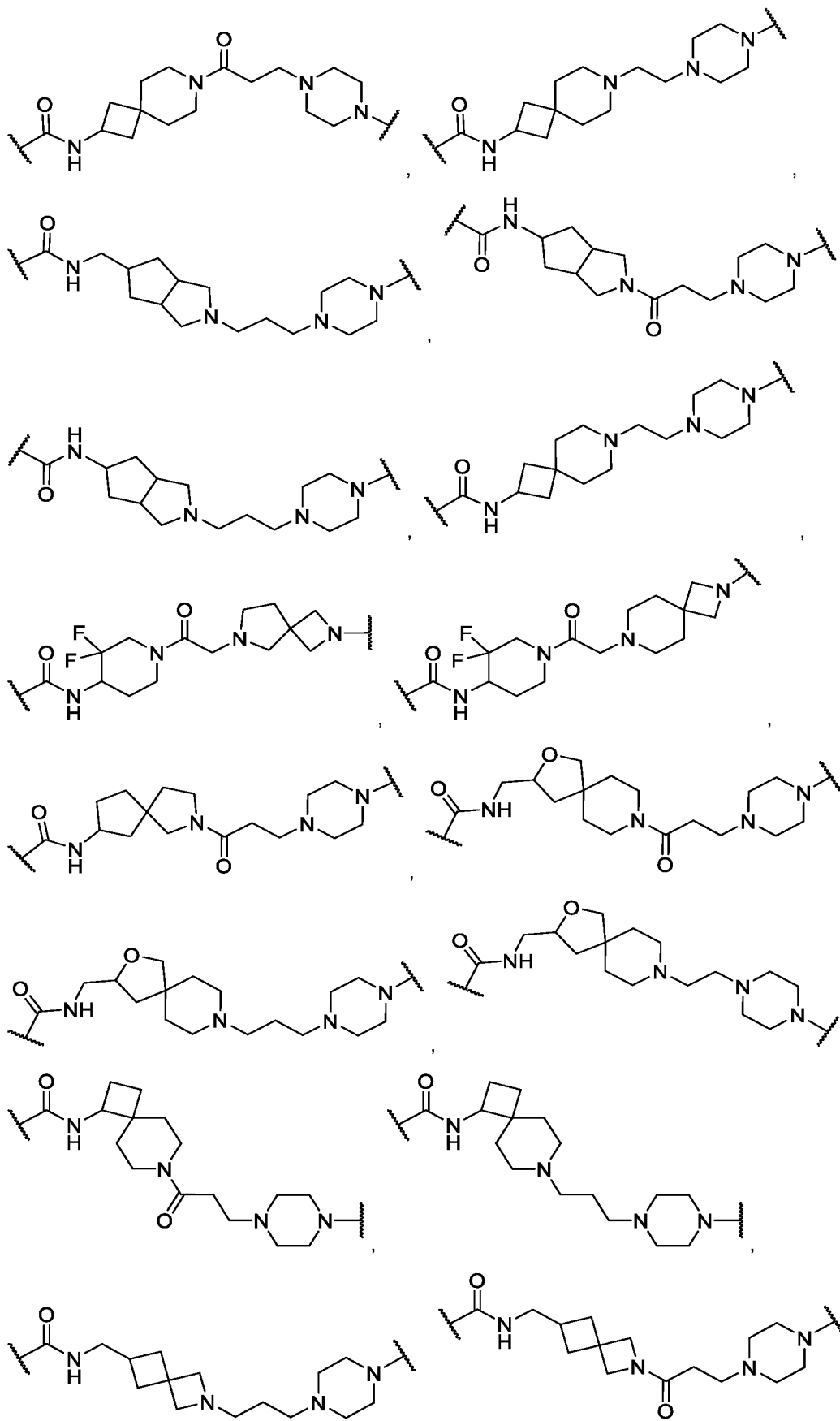
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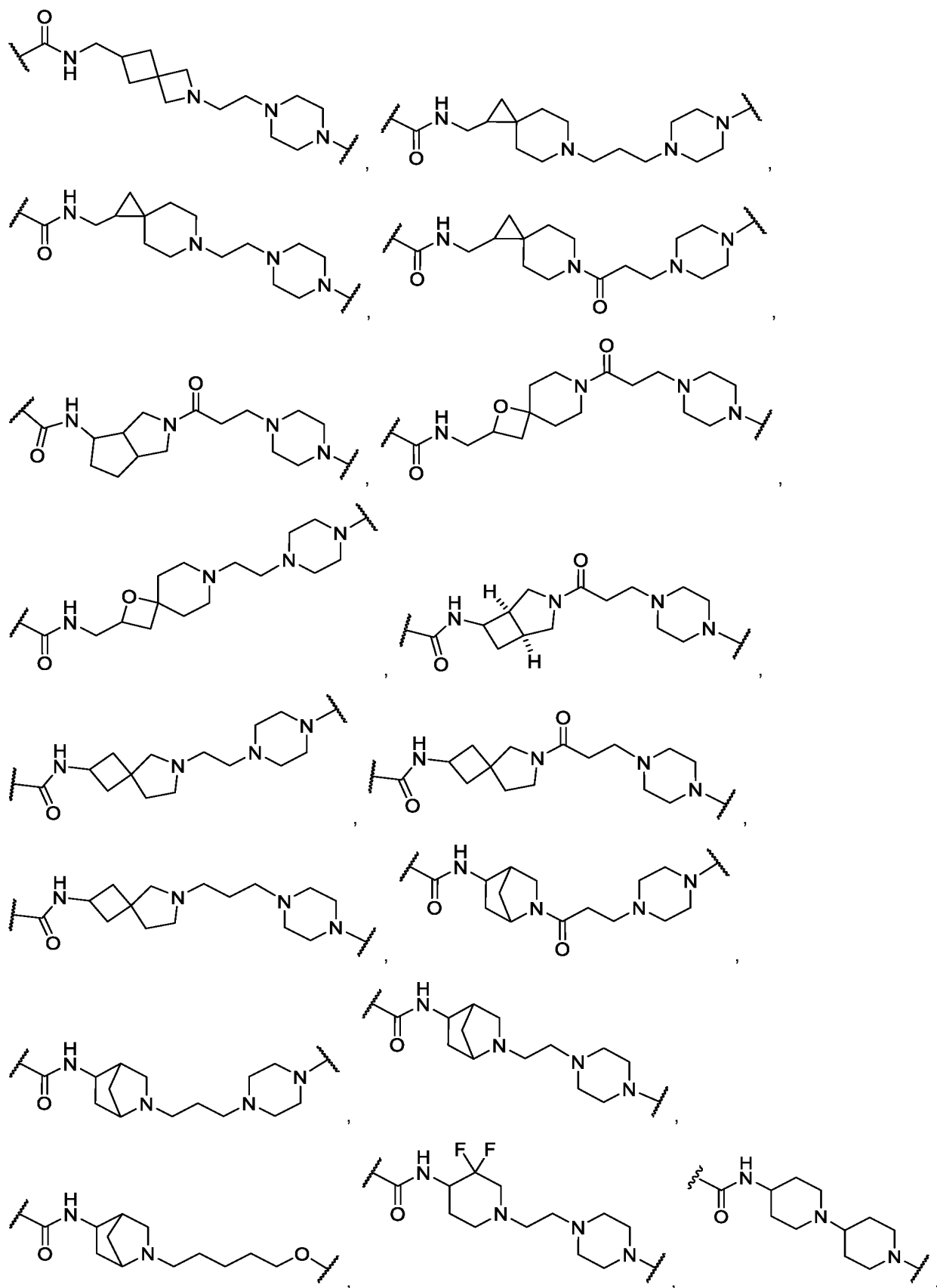


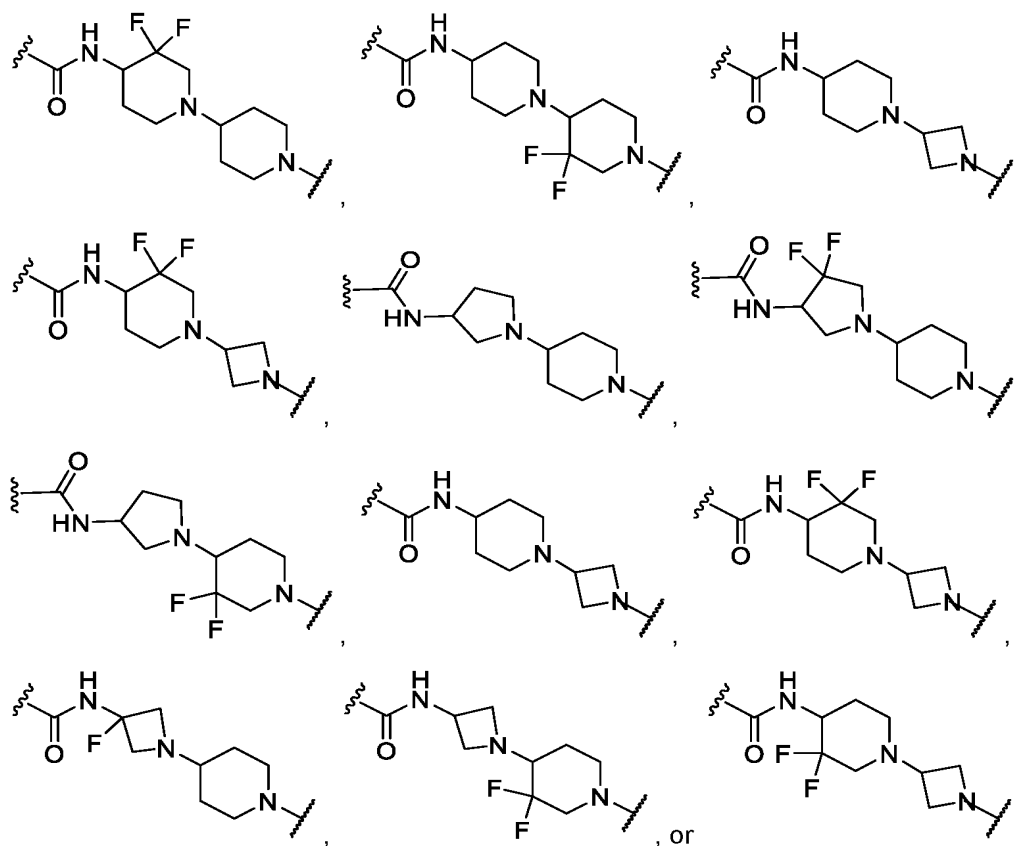




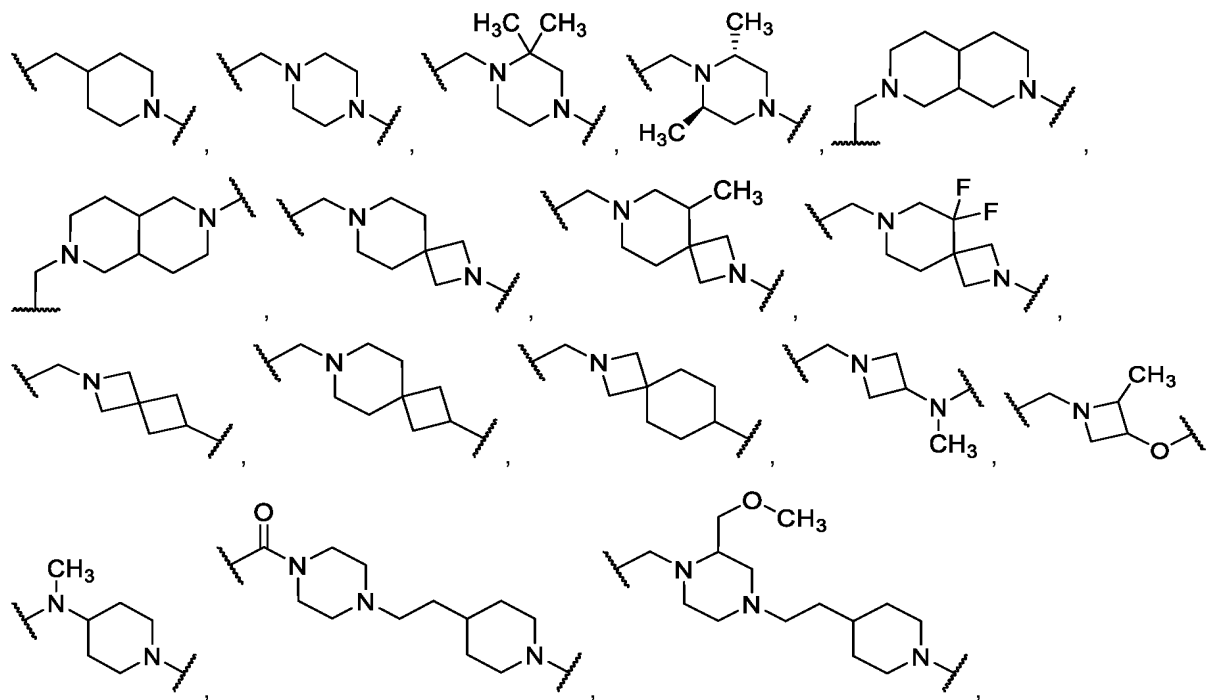
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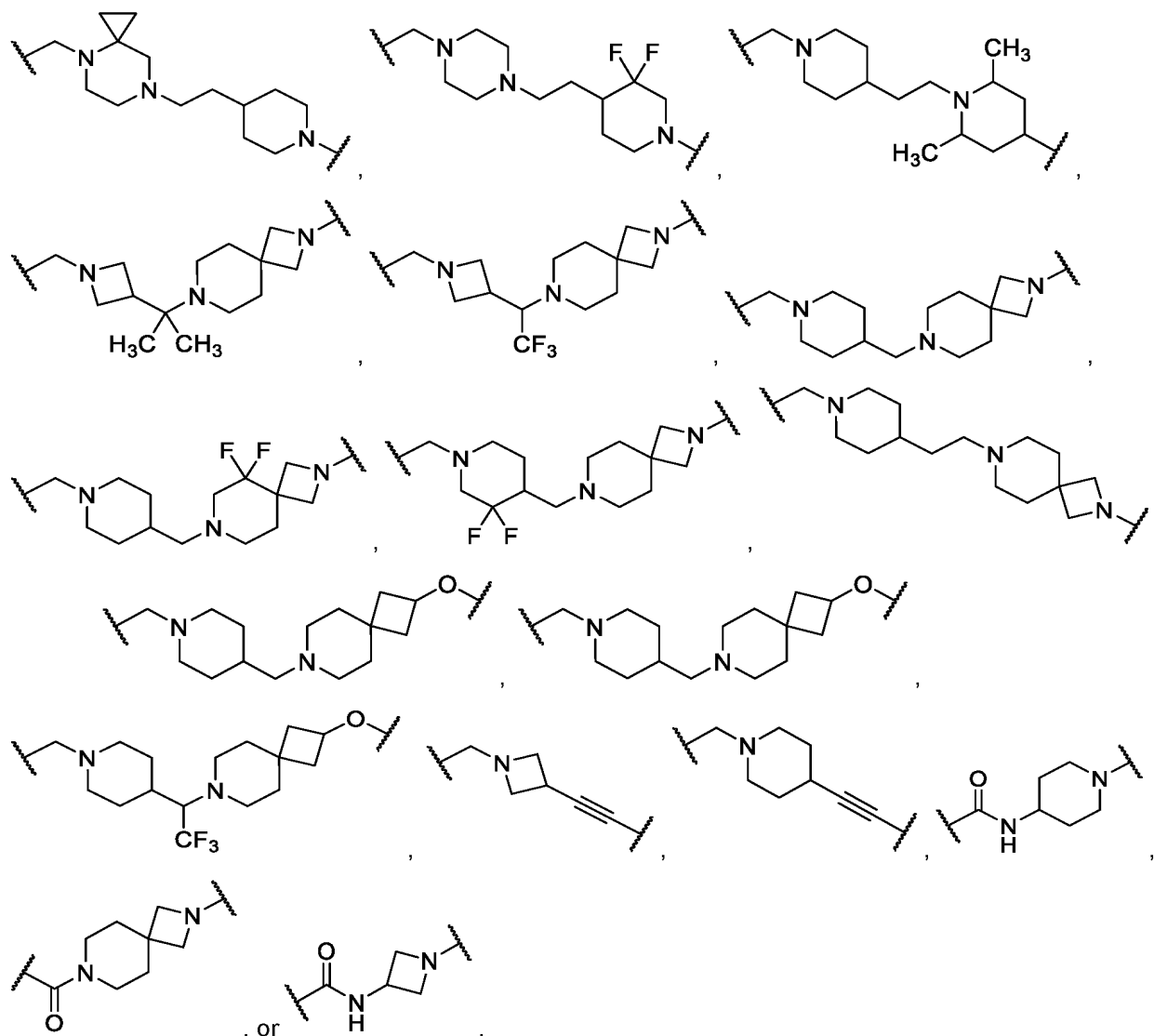






5 In some embodiments, the linker has the structure of:





In some embodiments, the linker is absent.

In some embodiments, the linker is optionally substituted C₃-C₁₀ carbocyclylene, optionally substituted C₂-C₁₀ heterocyclylene, optionally substituted C₆-C₁₀ arylene, or optionally substituted C₂-C₉ heteroarylene.

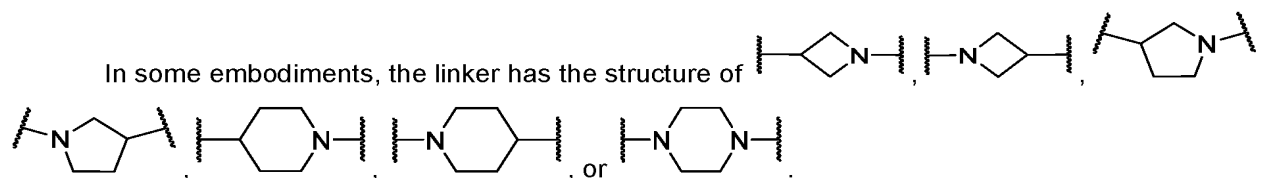
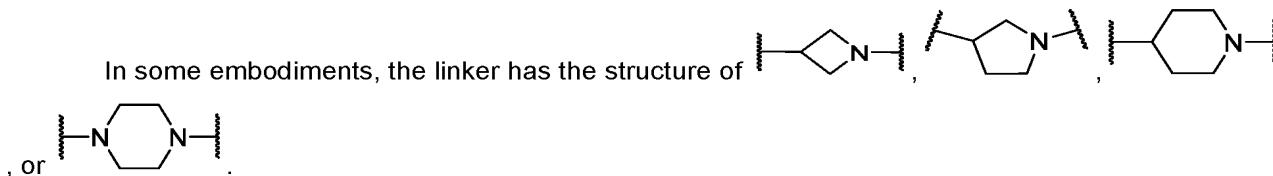
In some embodiments, the linker is optionally substituted C₃-C₁₀ carbocyclylene or optionally substituted C₂-C₁₀ heterocyclylene. In some embodiments, the linker is optionally substituted C₆-C₁₀ arylene or optionally substituted C₂-C₉ heteroarylene.

In some embodiments, the linker is optionally substituted C₂-C₁₀ heterocyclylene.

In some embodiments, the C₂-C₉ heterocyclylene is monocyclic. In some embodiments, the C₂-C₉ heterocyclylene is polycyclic.

In some embodiments, the C₂-C₉ heterocyclylene is bicyclic.

In some embodiments, the C₂-C₉ heterocyclylene is bridged. In some embodiments, the C₂-C₉ heterocyclylene is fused. In some embodiments, the C₂-C₉ heterocyclylene is spirocyclic.



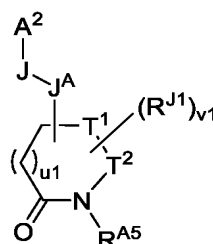
In some embodiments, the degradation moiety is a ubiquitin ligase binding moiety.

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.

5 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**:



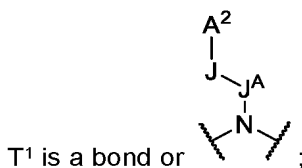
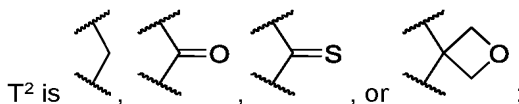
Formula Y,

where

A² 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;



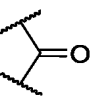
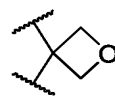
R^{A5} is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl;

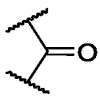
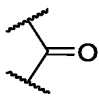
each R^{J1} is, independently, halogen, optionally substituted C₁-C₆ alkyl, or optionally substituted

C₁-C₆ heteroalkyl;

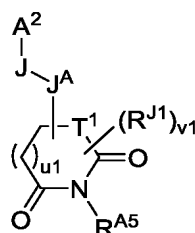
J^A is absent, O, optionally substituted amino, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl; and

J is absent, optionally substituted C₃-C₁₀ carbocyclylene, optionally substituted C₆-C₁₀ arylene, optionally substituted C₂-C₉ heterocyclylene, or optionally substituted C₂-C₉ heteroarylene, or a pharmaceutically acceptable salt thereof.

In some embodiments, T² is , , or . In some embodiments, T² is  or

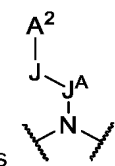
5 . In some embodiments, T² is . In some embodiments, T² is .

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

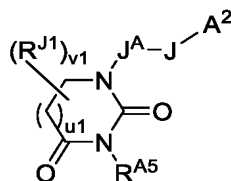


Formula Y1,

or a pharmaceutically acceptable salt thereof.

10 In some embodiments, T¹ is a bond. In some embodiments, T¹ is .

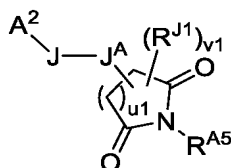
In some embodiments, the structure of **Formula Y** has the structure of **Formula Y2**:



Formula Y2,

or a pharmaceutically acceptable salt thereof.

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

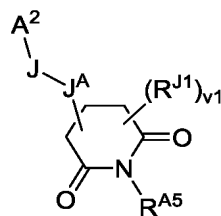


Formula Z,

or a pharmaceutically acceptable salt thereof.

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

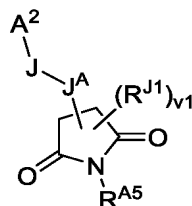
20 In some embodiments, the structure of **Formula Z** has the structure of **Formula AA0**:



Formula AA0,

or a pharmaceutically acceptable salt thereof.

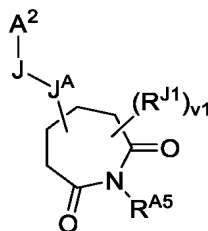
In some embodiments, the structure of **Formula Z** has the structure of **Formula AB**:



Formula AB,

or a pharmaceutically acceptable salt thereof.

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



Formula AC,

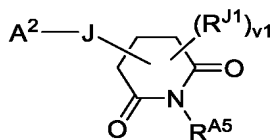
or a pharmaceutically acceptable salt thereof.

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**:

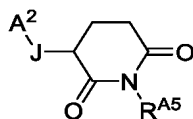


Formula AA,

or a pharmaceutically acceptable salt thereof.

In some embodiments, v_1 is 0, 1, 2, or 3. In some embodiments, v_1 is 0. In some embodiments, v_1 is 1. In some embodiments, v_1 is 2. In some embodiments, v_1 is 3.

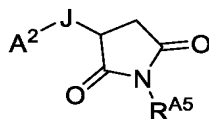
In some embodiments, the structure of **Formula AA** has the structure of **Formula AA1**:



Formula AA1,

or a pharmaceutically acceptable salt thereof.

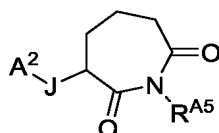
In some embodiments, the structure of **Formula AB** has the structure of **Formula AB1**:



Formula AB1,

or a pharmaceutically acceptable salt thereof.

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

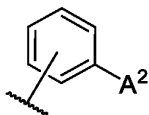


Formula AC1,

or a pharmaceutically acceptable salt thereof.

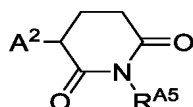
In some embodiments, J is absent. In some embodiments, J is optionally substituted C₃-C₁₀ carbocyclylene or optionally substituted C₆-C₁₀ arylene. In some embodiments, J is optionally substituted C₂-C₉ heterocyclylene or optionally substituted C₂-C₉ heteroarylene.

In some embodiments, J is optionally substituted heterocyclylene. In some embodiments, J is optionally substituted C₆-C₁₀ arylene.



In some embodiments, J is

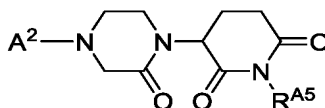
In some embodiments, the structure of **Formula AA** has the structure of **Formula AA2**:



Formula AA2,

or a pharmaceutically acceptable salt thereof.

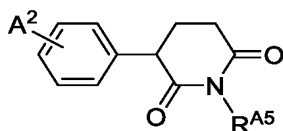
In some embodiments, the structure of **Formula AA** has the structure of **Formula AA3**:



Formula AA3,

or a pharmaceutically acceptable salt thereof.

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

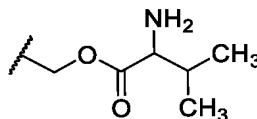


Formula AA4,

or a pharmaceutically acceptable salt thereof.

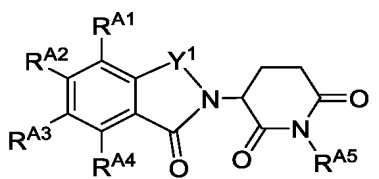
In some embodiments, R^{A5} is H or optionally substituted C_1 - C_6 alkyl. In some embodiments, R^{A5} is optionally substituted C_1 - C_6 heteroalkyl.

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



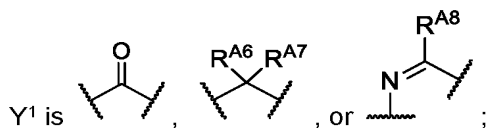
embodiments, R^{A5} is methyl. In some embodiments, R^{A5} is

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



Formula A

where



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 N ; and N 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 N 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,

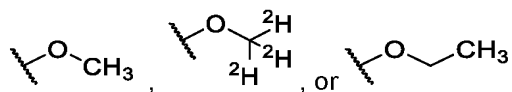
any of which is optionally substituted with A^2 , where one of R^{A1} , R^{A2} , R^{A3} , and R^{A4} is A^2 , or  is substituted with A^2 , or a pharmaceutically acceptable salt thereof.

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 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 .

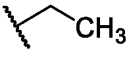
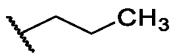
In some embodiments, R^{A5} is H or optionally substituted C_1 - C_6 alkyl.

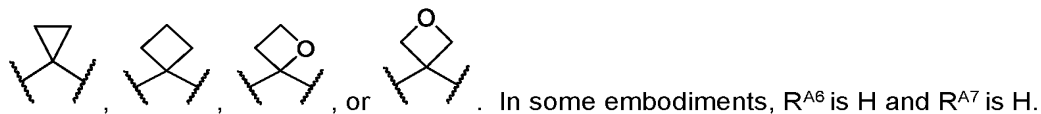
In some embodiments, R^{A5} is H or . In some embodiments, R^{A5} is H. In some

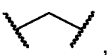
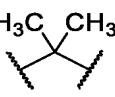
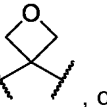
embodiments, R^{A5} is .

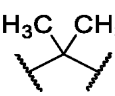
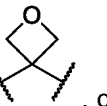
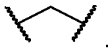
In some embodiments, Y^1 is  or . In some embodiments, Y^1 is . In

some embodiments, Y^1 is .

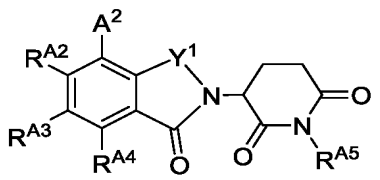
In some embodiments, each of R^{A6} and R^{A7} is, independently, H, F, , , or ; or R^{A6} and R^{A7} , together with the carbon atom to which each is bound, combine to form



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

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

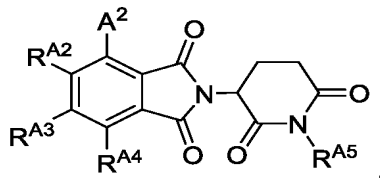
In some embodiments, the structure of **Formula A** has the structure of **Formula A1**:



Formula A1

10 or a pharmaceutically acceptable salt thereof.

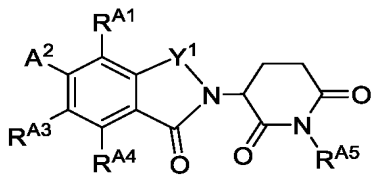
In some embodiments, the structure of **Formula A** has the structure of **Formula A2**:



Formula A2

or a pharmaceutically acceptable salt thereof.

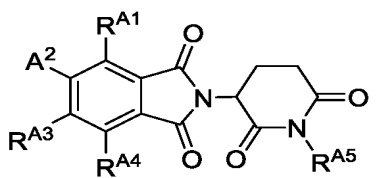
15 In some embodiments, the structure of **Formula A** has the structure of **Formula A3**:



Formula A3

or a pharmaceutically acceptable salt thereof.

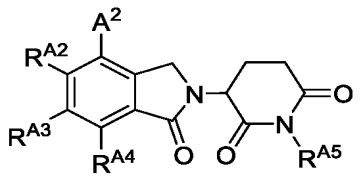
In some embodiments, the structure of **Formula A** has the structure of **Formula A4**:



Formula A4

or a pharmaceutically acceptable salt thereof.

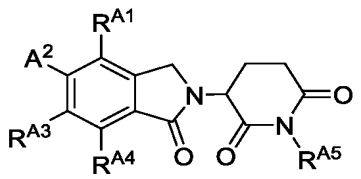
5 In some embodiments, the structure of **Formula A** has the structure of **Formula A5**:



Formula A5

or a pharmaceutically acceptable salt thereof.

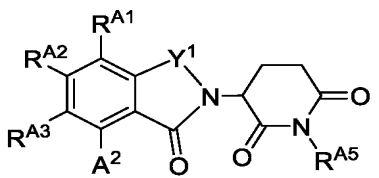
In some embodiments, the structure of **Formula A** has the structure of **Formula A6**:



Formula A6

or a pharmaceutically acceptable salt thereof.

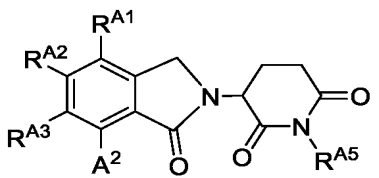
In some embodiments, the structure of **Formula A** has the structure of **Formula A7**:



Formula A7

or a pharmaceutically acceptable salt thereof.

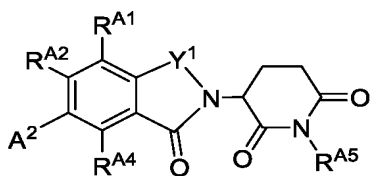
In some embodiments, the structure of **Formula A** has the structure of **Formula A8**:



Formula A8

or a pharmaceutically acceptable salt thereof.

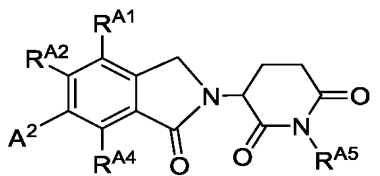
In some embodiments, the structure of **Formula A** has the structure of **Formula A9**:



Formula A9

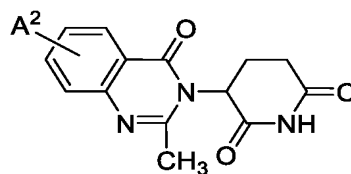
or a pharmaceutically acceptable salt thereof.

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



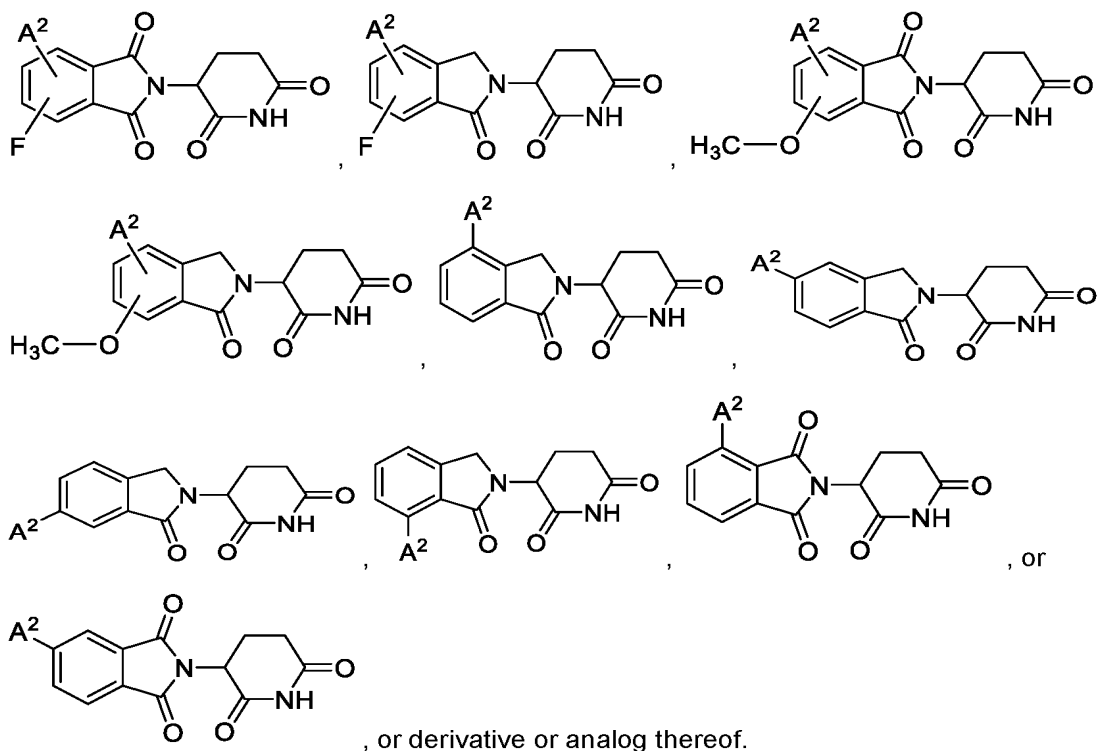
Formula A10

or a pharmaceutically acceptable salt thereof.

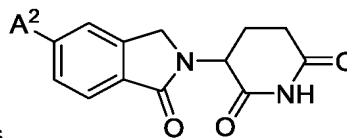


In some embodiments, wherein the structure of **Formula A** is

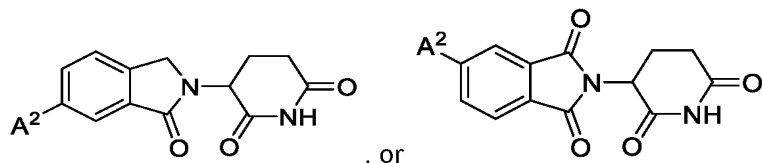
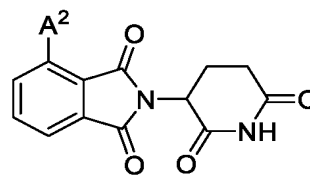
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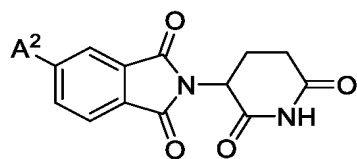
, or derivative or analog thereof.



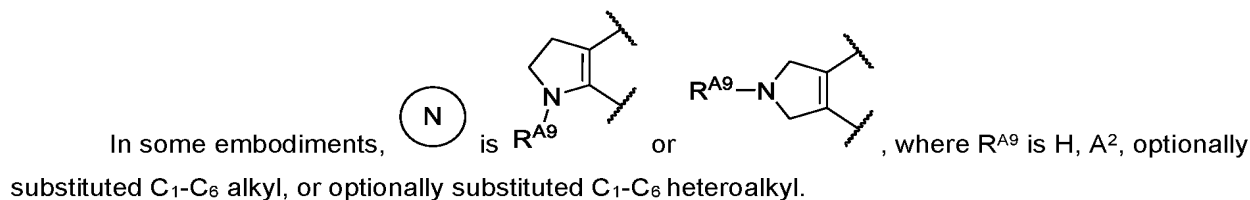
In some embodiments, the structure of **Formula A** is



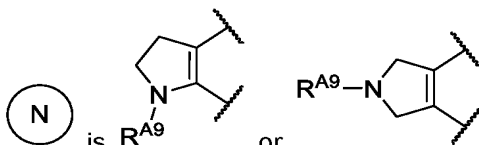
In some embodiments, the structure of **Formula A** is



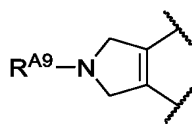
5, or derivative or analog thereof.



In some embodiments,

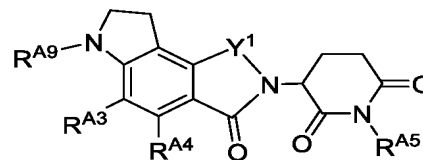
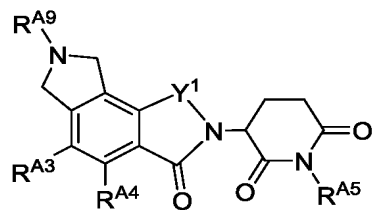
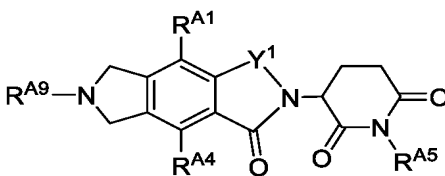
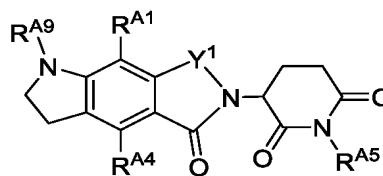
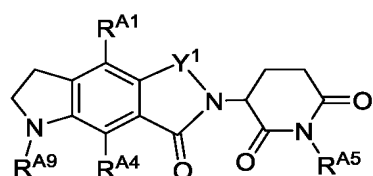
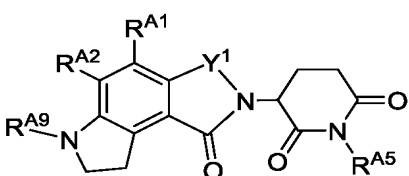
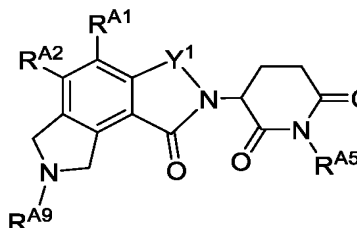


or



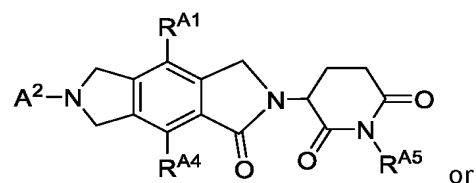
, where R^{A9} is H, A^2 , optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl.

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

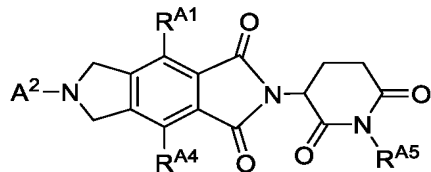


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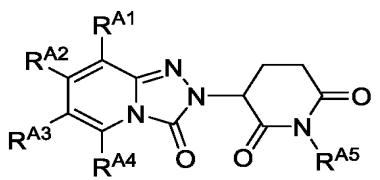
In some embodiments, R^{A9} is H, A^2 , or optionally substituted C_1 - C_6 alkyl. In some embodiments, R^{A9} is H, A^2 , or methyl. In some embodiments, R^{9A} is H. In some embodiments, R^{9A} is methyl. In some embodiments, R^{A9} is A^2 .



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



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



Formula B

5

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.

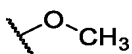
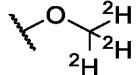
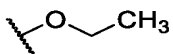
In some embodiments, each of R^{A1} , R^{A2} , R^{A3} , and R^{A4} is, H, A^2 , halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted $-O-C_3-C_6$ carbocyclyl, hydroxyl, optionally substituted amino; or R^{A1} and R^{A2} , R^{A2} and R^{A3} , 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 .

20

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

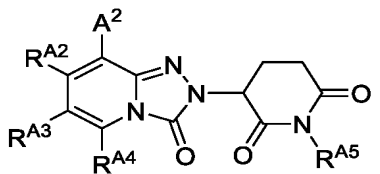
5  is substituted with A^2 .

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.

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

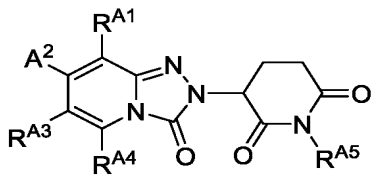
In some embodiments, the structure of **Formula B** has the structure of **Formula B1**:



Formula B1

or a pharmaceutically acceptable salt thereof.

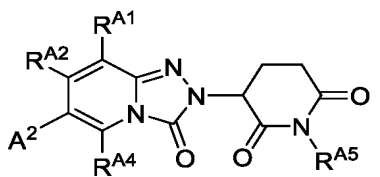
15 In some embodiments, the structure of **Formula B** has the structure of **Formula B2**:



Formula B2

or a pharmaceutically acceptable salt thereof.

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

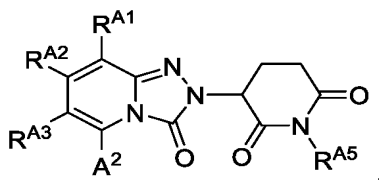


Formula B3

or a pharmaceutically acceptable salt thereof.

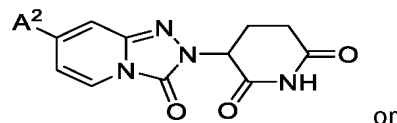
In some embodiments, the structure of **Formula B** has the structure of **Formula B4**:

20

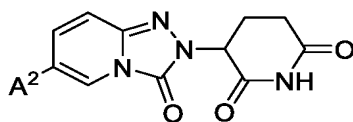


Formula B4

or a pharmaceutically acceptable salt thereof.

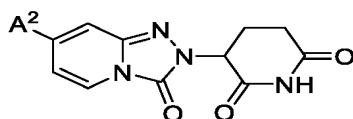


In some embodiments, the structure of **Formula B** is

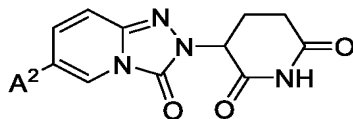


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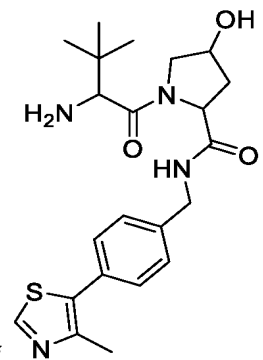
. In some embodiments, the structure of **Formula B** is



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



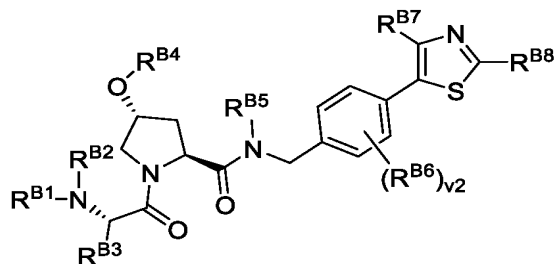
In some embodiments, the ubiquitin ligase binding moiety comprises a von Hippel-Lindau ligand.



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

10

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



Formula C,

where

R^{B1} is H, A², optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl;

15

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;

5 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;

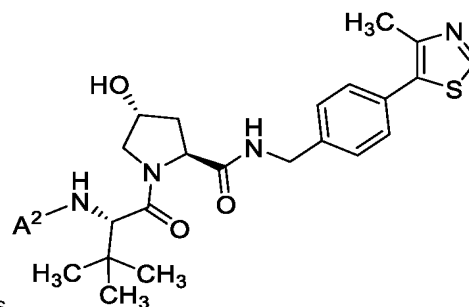
R^{B5} is H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl;

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

10 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

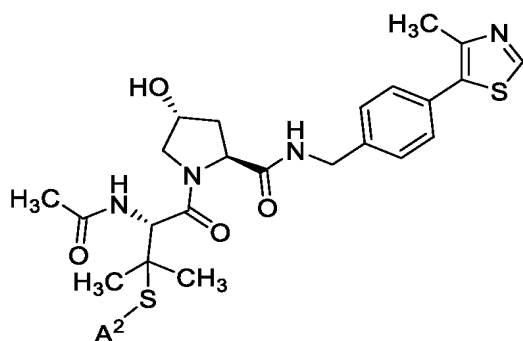
15 each of R^{B7} and R^{B8} is, independently, H, halogen, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_6 - C_{10} aryl,

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

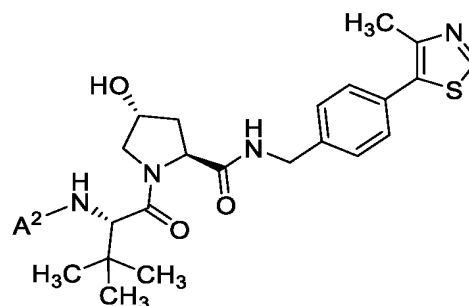


In some embodiments, the structure of **Formula C** is

or

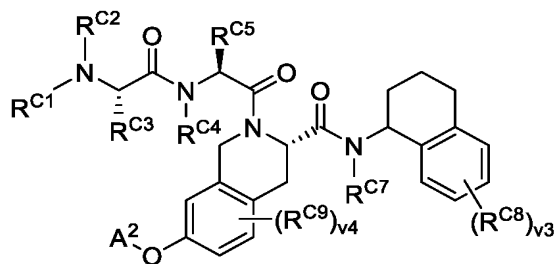


, or derivative or analog thereof.



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

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



Formula D,

where

A² is a bond between B and the linker;

each of R^{C1}, R^{C2}, and R^{C7} is, independently, H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl;

R^{C3} is optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₁-C₆ alkyl C₃-C₁₀ carbocyclyl, or optionally substituted C₁-C₆ alkyl C₆-C₁₀ aryl;

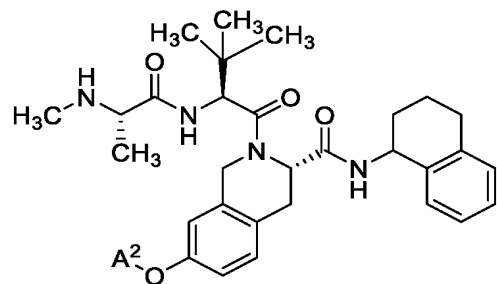
R^{C5} is optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₁-C₆ alkyl C₃-C₁₀ carbocyclyl, or optionally substituted C₁-C₆ alkyl C₆-C₁₀ aryl;

v₃ is 0, 1, 2, 3, or 4;

each R^{C8} is, independently, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

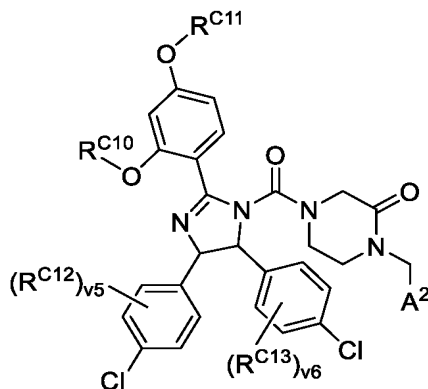
v₄ is 0, 1, 2, 3, or 4; and

each R^{C9} is, independently, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxy, thiol, or optionally substituted amino, or a pharmaceutically acceptable salt thereof.



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

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



Formula E,

where

A² is a bond between B and the linker;

each of R^{C10} and R^{C11} is, independently, H, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₁-C₆ alkyl C₃-C₁₀ carbocyclyl, or optionally substituted C₁-C₆ alkyl C₆-C₁₀ aryl;

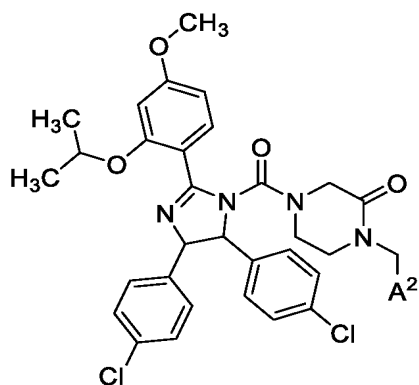
v₅ is 0, 1, 2, 3, or 4;

each R^{C12} is, independently, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

v₆ is 0, 1, 2, 3, or 4; and

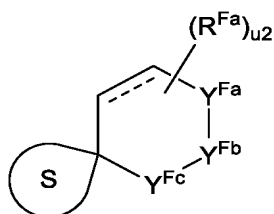
each R^{C13} is, independently, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxy, thiol, or optionally substituted amino, or a pharmaceutically acceptable salt thereof.

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



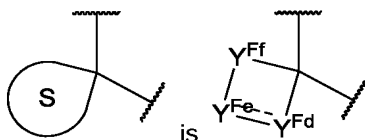
, or derivative or analog thereof.

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



Formula FA,

where



5 is 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;

u_2 is 0, 1, 2, or 3;

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

10 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 , $S(O)$, $P(O)Oalkyl$, $P(O)NHalkyl$, $P(O)N(alkyl)_2$, $P(O)alkyl$, $P(O)OH$, $P(O)NH_2$;

15 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 spirocarbocyclene, or a 4-, 5-, or 6-membered spiroheterocyclene comprising 1 or 2 heteroatoms selected from N and O;

20 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 spirocarbocyclene, or a 4-, 5-, or 6-membered spiroheterocyclene 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;

25 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

30 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;

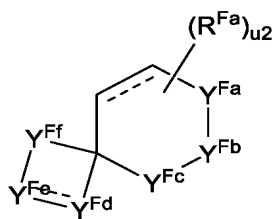
each R^{FF1} is, independently, H, alkyl, alkenyl, alkynyl, aliphatic, heteroaliphatic, carbocyclyl, halogen, hydroxyl, amino, cyano, alkoxy, aryl, heteroaryl, heterocyclyl, alkylamino, alkylhydroxyl, or haloalkyl;

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), —NHSO₂alkyl, —N(alkyl)SO₂alkyl, —NHSO₂aryl, —N(alkyl)SO₂aryl, —NHSO₂alkenyl, —N(alkyl)SO₂alkenyl, —NHSO₂alkynyl, —N(alkyl)SO₂alkynyl, aliphatic, heteroaliphatic, aryl, heteroaryl, heterocyclic, 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.

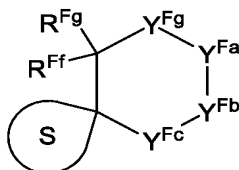
In some embodiments, the compound of **Formula FA** has the structure of **Formula FA1**:



Formula FA1,

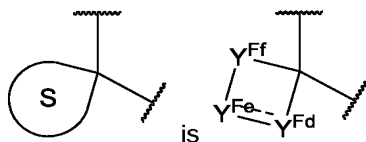
or a pharmaceutically acceptable salt thereof.

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 —Nalkyl₂;

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 , $CH(R^{FF2})$, $C(R^{FF2})_2$, $C(O)$, 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;

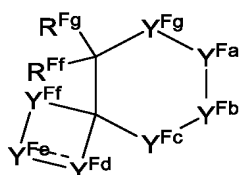
each R^{FF1} is, independently, H, alkyl, alkenyl, alkynyl, aliphatic, heteroaliphatic, carbocyclyl, halogen, hydroxyl, amino, cyano, alkoxy, aryl, heteroaryl, heterocyclyl, alkylamino, alkylhydroxyl, or haloalkyl;

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, $-N(alkyl)SO_2$ alkyl, $-NHSO_2$ aryl, $-N(alkyl)SO_2$ aryl, $-NHSO_2$ alkenyl, $-N(alkyl)SO_2$ alkenyl, $-NHSO_2$ alkynyl, $-N(alkyl)SO_2$ alkynyl, aliphatic, heteroaliphatic, aryl, heteroaryl, heterocyclic, carbocyclic, cyano, nitro, nitroso, $-SH$, $-S$ alkyl, or haloalkyl; and

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

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

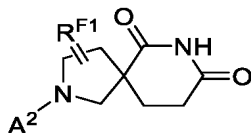
In some embodiments, the compound of **Formula FB** has the structure of **Formula FB1**:



Formula FB1,

or a pharmaceutically acceptable salt thereof.

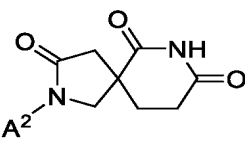
In some embodiments, the degradation moiety includes the structure of **Formula F1**:

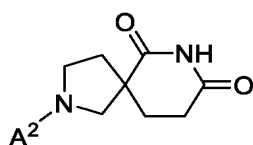


Formula F1,

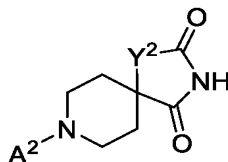
where A² is a bond between the degrader and the linker; and R^{F1} is absent or O, or a pharmaceutically acceptable salt thereof.

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

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



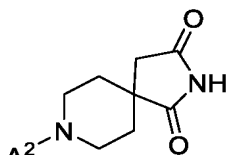
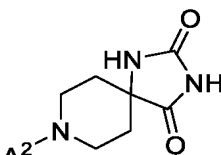
In some embodiments, the degradation moiety includes the structure **Formula F2**:



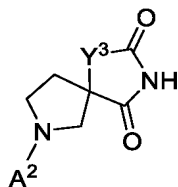
Formula F2,

10 where A² is a bond between the degrader and the linker; and Y² is CH₂ or NH, or a pharmaceutically acceptable salt thereof.

In some embodiments, Y² is NH. In some embodiments, Y² is CH₂.

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

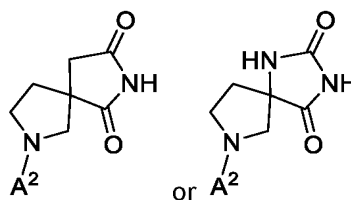
15 In some embodiments, the degradation moiety includes the structure **Formula G**:



Formula G,

where A² is a bond between the degrader and the linker; and Y³ is CH₂ or NH, or a pharmaceutically acceptable salt thereof.

20 In some embodiments, Y³ is NH. In some embodiments, Y³ is CH₂.

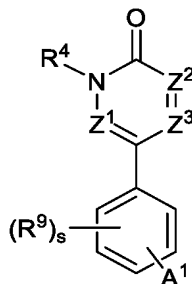


In some embodiments, structure of **Formula G** is

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.

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



Formula III,

where

10 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;

15 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;

25 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

30 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, Z² is N. In some embodiments, Z² is CR^{6a}.

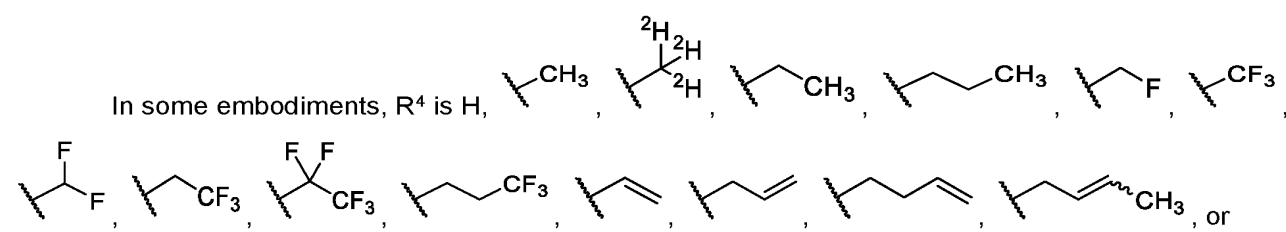
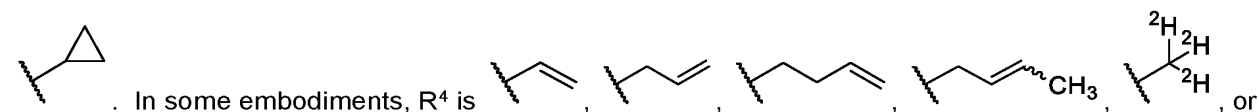
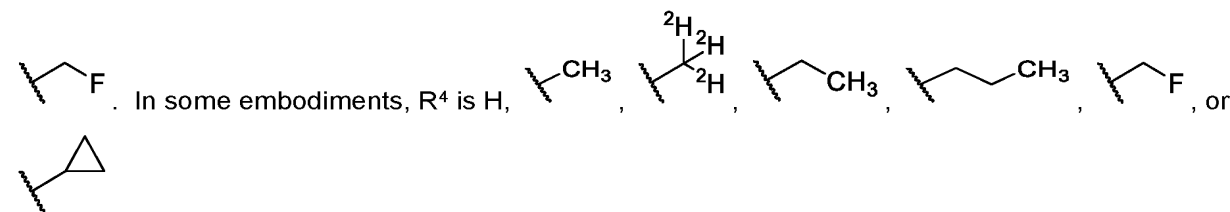
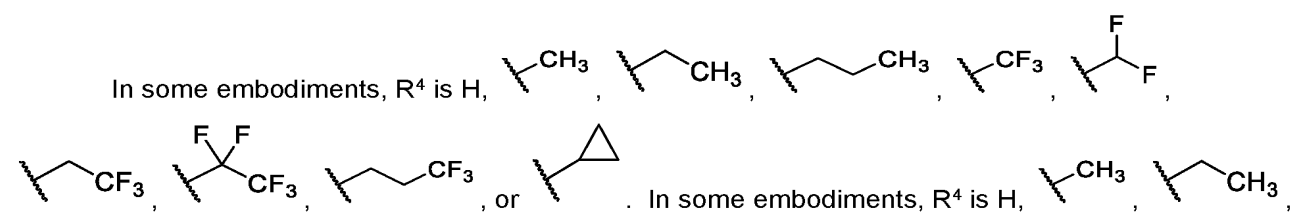
In some embodiments, Z³ is N. In some embodiments, Z³ is CR^{6b}.

In some embodiments, Z¹ is CR⁵, Z² is CR^{6a}, and Z³ is CR^{6b}. In some embodiments, Z¹ is N, Z² is CR^{6a}, and Z³ is CR^{6b}. In some embodiments, Z¹ is CR⁵, Z² is N, and Z³ is CR^{6b}. In some embodiments, Z¹ is N, Z² is CR^{6a}, and Z³ is N. In some embodiments, Z¹ is N, Z² is N, and Z³ is CR^{6b}. In some
5 embodiments, Z¹ is CR⁵, Z² is N, and Z³ is N.

In some embodiments, R⁴ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl. In some embodiments, R⁴ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, or optionally substituted C₃-C₁₀ carbocyclyl.

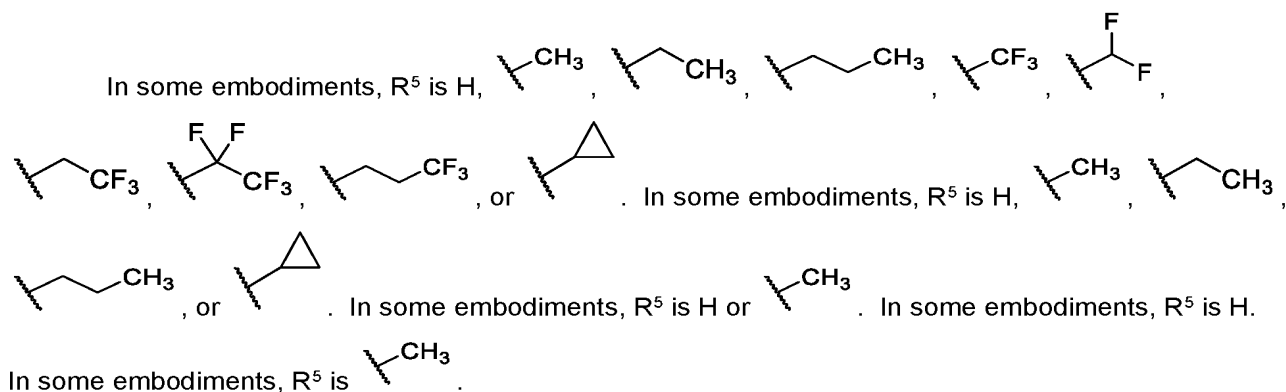
10 In some embodiments, R⁴ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₃-C₁₀ carbocyclyl.

In some embodiments, optionally substituted C₁-C₆ alkyl is C₁-C₆ perfluoroalkyl.



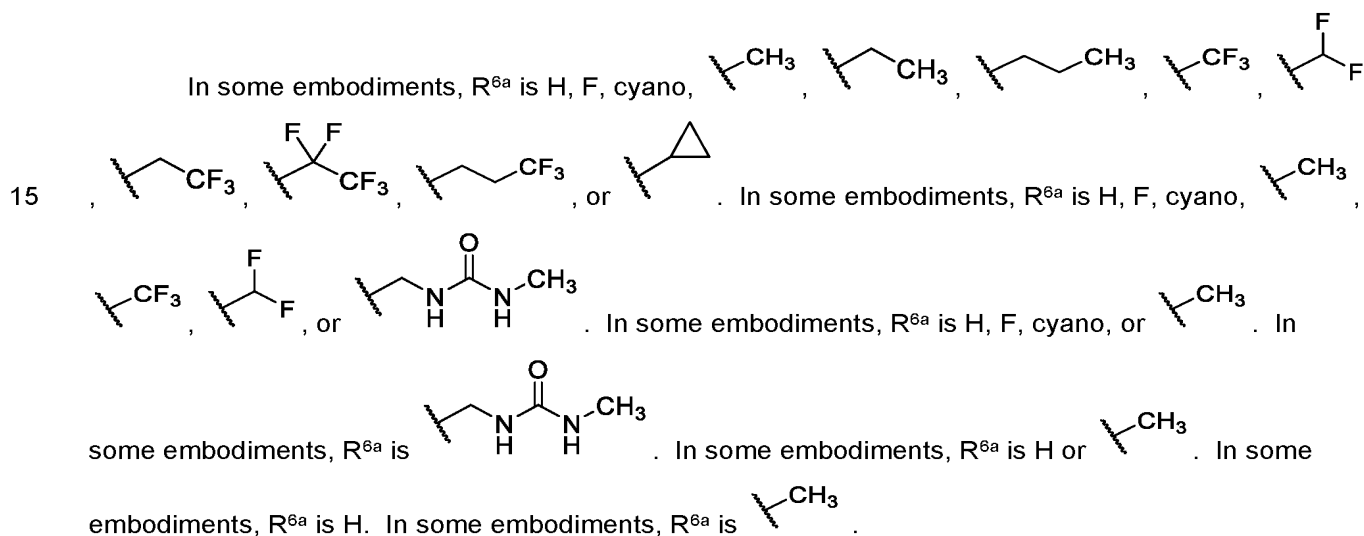
In some embodiments, R⁵ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₆-C₁₀ aryl. In some embodiments, R⁵ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl. In some embodiments, R⁵ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₃-C₁₀ carbocyclyl.
25

In some embodiments, optionally substituted C₁-C₆ alkyl is C₁-C₆ perfluoroalkyl.



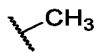
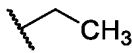
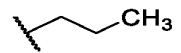
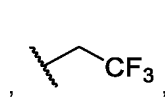
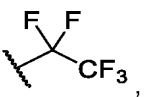
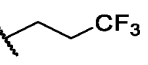
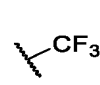
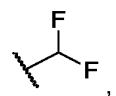
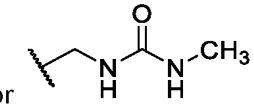
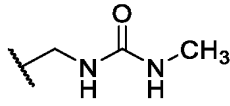
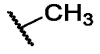
5 In some embodiments, R^{6a} is H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxy, thiol, or optionally substituted amino.

10 In some embodiments, R^{6a} is H, halogen, cyano, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl. In some embodiments, R^{6a} is H, halogen, cyano, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl. In some embodiments, R^{6a} is H, halogen, cyano, or optionally substituted C₁-C₆ alkyl. In some embodiments, R^{6a} is optionally substituted C₁-C₆ heteroalkyl.



20 In some embodiments, R^{6b} is H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxy, thiol, or optionally substituted amino.

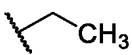
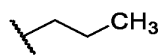
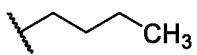
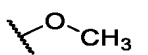
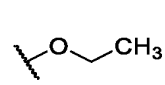
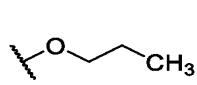
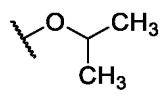
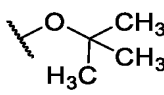
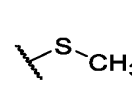
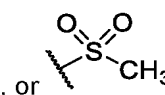
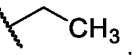
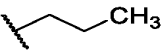
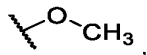
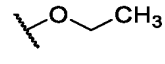
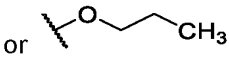
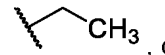
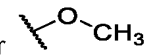
25 In some embodiments, R^{6b} is H, halogen, cyano, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl. In some embodiments, R^{6b} is H, halogen, cyano, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl. In some embodiments, R^{6b} is H, halogen, cyano, or optionally substituted C₁-C₆ alkyl. In some embodiments, R^{6b} is optionally substituted C₁-C₆ 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 .

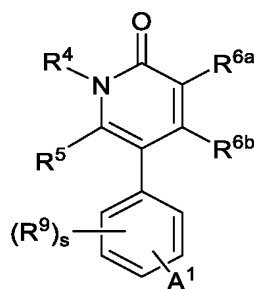
In some embodiments, R^{6a} and R^{6b} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_6 - C_{10} aryl or optionally substituted C_2 - C_9 heteroaryl.

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

10 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 .

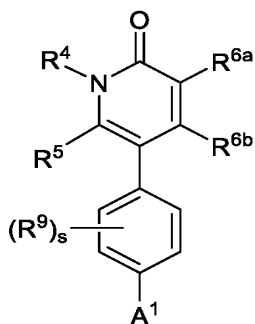
In some embodiments, the structure of **Formula III** has the structure of **Formula IIIa**:



Formula IIIa,

or a pharmaceutically acceptable salt thereof.

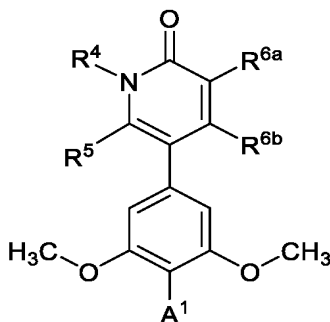
In some embodiments, the structure of **Formula III** has the structure of **Formula IIIb**:



Formula IIIb,

or a pharmaceutically acceptable salt thereof.

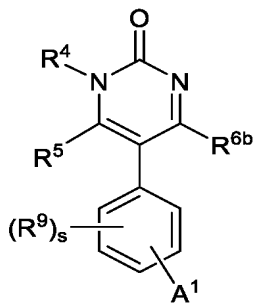
In some embodiments, the structure of **Formula III** has the structure of **Formula IIIc**:



Formula IIIc,

or a pharmaceutically acceptable salt thereof.

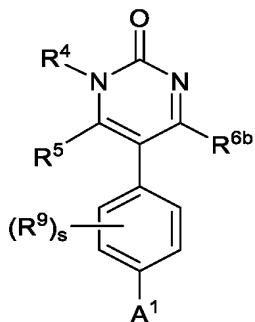
In some embodiments, the structure of **Formula III** has the structure of **Formula IIId**:



Formula IIId,

or a pharmaceutically acceptable salt thereof.

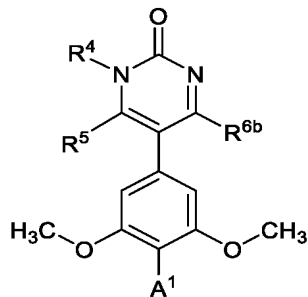
In some embodiments, the structure of **Formula III** has the structure of **Formula IIle**:



Formula IIle,

or a pharmaceutically acceptable salt thereof.

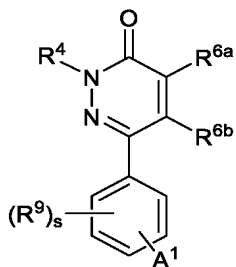
In some embodiments, the structure of **Formula III** has the structure of **Formula IIIf**:



Formula IIIf,

5 or a pharmaceutically acceptable salt thereof.

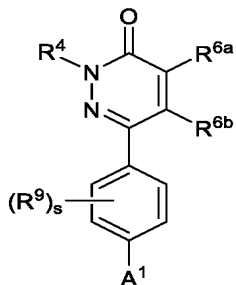
In some embodiments, the structure of **Formula III** has the structure of **Formula IIIg**:



Formula IIIg,

or a pharmaceutically acceptable salt thereof.

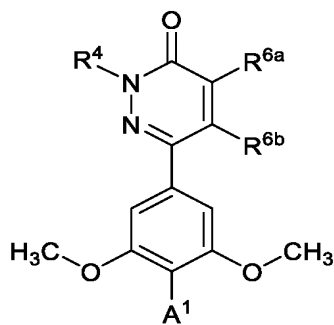
10 In some embodiments, the structure of **Formula III** has the structure of **Formula IIIh**:



Formula IIIh,

or a pharmaceutically acceptable salt thereof.

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

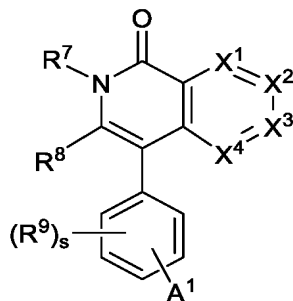


Formula IIIi,

15

or a pharmaceutically acceptable salt thereof.

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



Formula IV,

5 where

R⁷ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl;

10 R⁸ is H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, or optionally substituted C₆-C₁₀ aryl;

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

15 each R⁹ is, independently, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

X¹ is N or CR^{10a};

X² is N or CR^{10b};

X³ is N or CR^{10c};

X⁴ is N or CR^{10d};

20 each of R^{10a}, R^{10b}, R^{10c}, and R^{10d} is, independently, H, halogen, hydroxy, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxy, thiol, or optionally substituted amino; and

25 A¹ is a bond between A and the linker, or a pharmaceutically acceptable salt thereof.

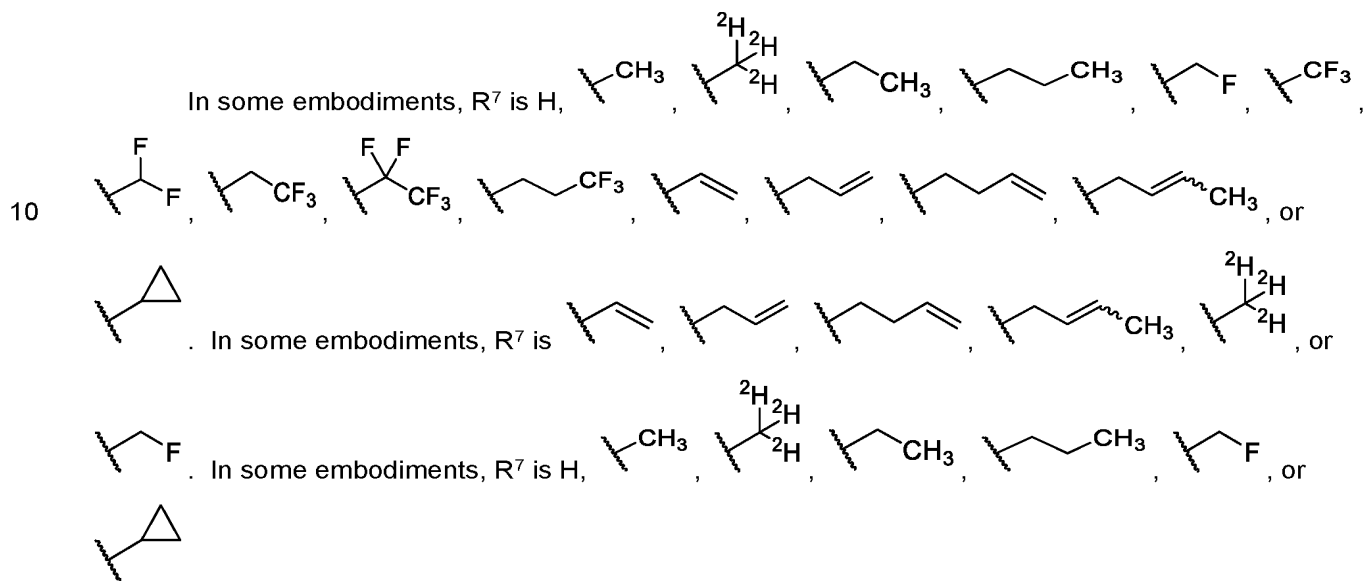
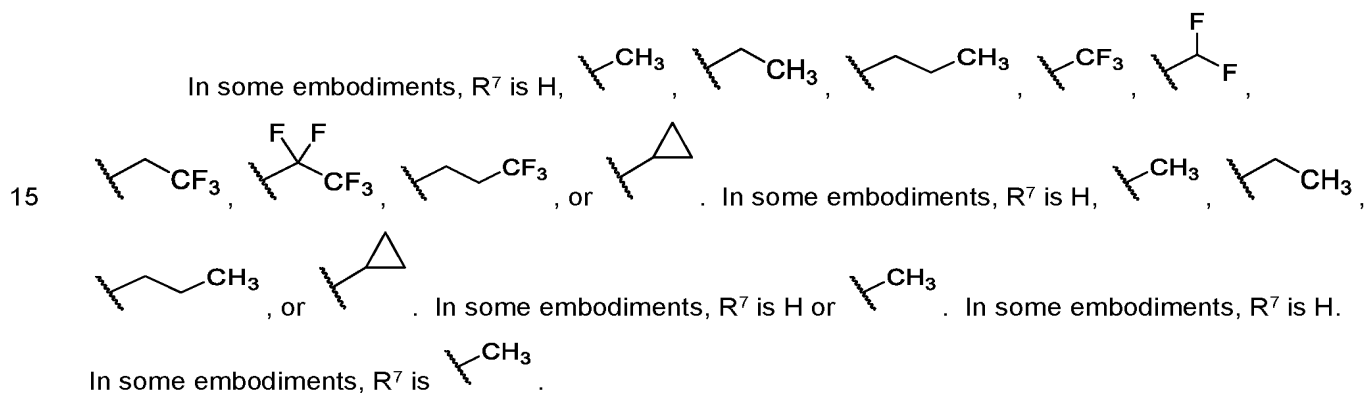
In some embodiments, X¹ is N. In some embodiments, X¹ is CR^{10a}. In some embodiments, X² is N. In some embodiments, X² is CR^{10b}. In some embodiments, X³ is N. In some embodiments, X³ is CR^{10c}. In some embodiments, X⁴ is N. In some embodiments, X⁴ is CR^{10d}.

30 In some embodiments, X¹ is CR^{10a}, X² is CR^{10b}, X³ is CR^{10c}, and X⁴ is CR^{10d}. In some embodiments, X¹ is CR^{10a}, X² is N, X³ is CR^{10c}, and X⁴ is CR^{10d}. In some embodiments, X¹ is CR^{10a}, X² is CR^{10b}, X³ is N, and X⁴ is CR^{10d}. In some embodiments, X¹ is CR^{10a}, X² is CR^{10b}, X³ is CR^{10c}, and X⁴ is N. In some embodiments, X¹ is N, X² is N, X³ is CR^{10c}, and X⁴ is CR^{10d}. In some embodiments, X¹ is N, X² is CR^{10b}, X³ is N, and X⁴ is CR^{10d}. In some embodiments, X¹ is N, X² is CR^{10b}, X³ is CR^{10c}, and X⁴ is N. In some embodiments, X¹ is CR^{10a},

X² is N, X³ is N, and X⁴ is CR^{10d}. In some embodiments, X¹ is CR^{10a}, X² is N, X³ is CR^{10c}, and X⁴ is N. In some embodiments, X¹ is CR^{10a}, X² is CR^{10b}, X³ is N, and X⁴ is N.

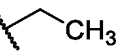
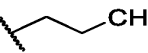
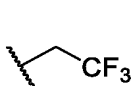
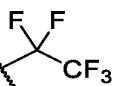
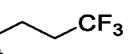
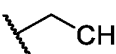
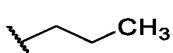
In some embodiments, R⁷ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl. In some embodiments, R⁷ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, or optionally substituted C₃-C₁₀ carbocyclyl. In some embodiments, R⁷ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₃-C₁₀ carbocyclyl.

In some embodiments, optionally substituted C₁-C₆ alkyl is C₁-C₆ perfluoroalkyl.



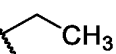
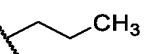
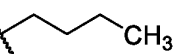
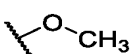
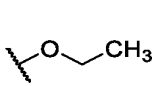
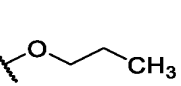
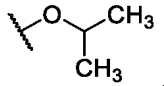
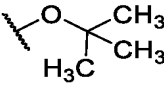
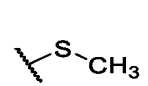
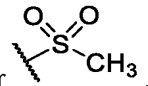
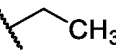
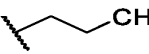
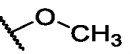
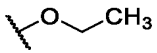
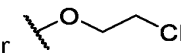
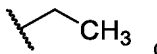
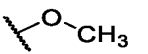
In some embodiments, R⁸ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₆-C₁₀ aryl. In some embodiments, R⁸ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl. In some embodiments, R⁸ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₃-C₁₀ carbocyclyl. In some embodiments, R⁸ is H or optionally substituted C₁-C₆ alkyl.

In some embodiments, optionally substituted C₁-C₆ alkyl is C₁-C₆ perfluoroalkyl.

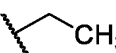
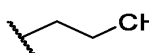
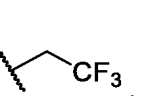
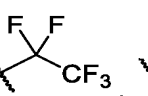
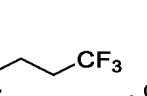
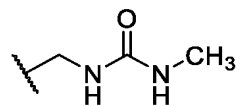
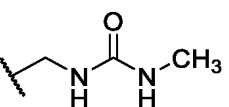
In some embodiments, R^8 is H, , , , , , , , , or . In some embodiments, R^8 is H, , , , or . In some embodiments, R^8 is H or . In some embodiments, R^8 is H. In some embodiments, R^8 is .

5 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, s is 1.

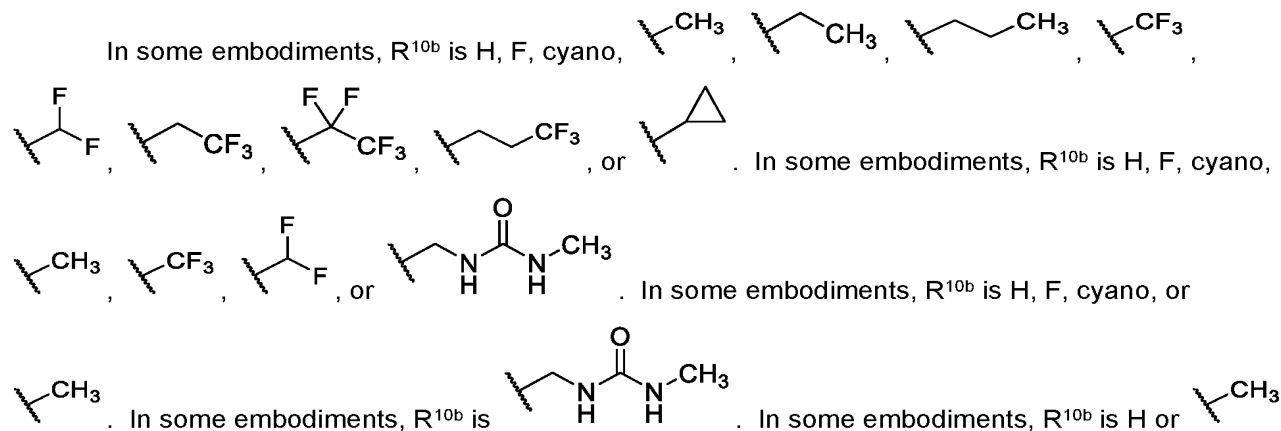
In some embodiments, each R^9 is, independently, halogen, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl. In some embodiments, each R^9 is, independently, optionally substituted C_1 - C_6 alkyl or optionally substituted C_1 - C_6 heteroalkyl.

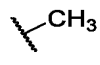
10 In some embodiments, R^9 is , , , , , , , , , , or . In some embodiments, each R^9 is, independently, halogen, , , , , , or . In some embodiments, each R^9 is, independently, F, Cl, , , or .

15 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.

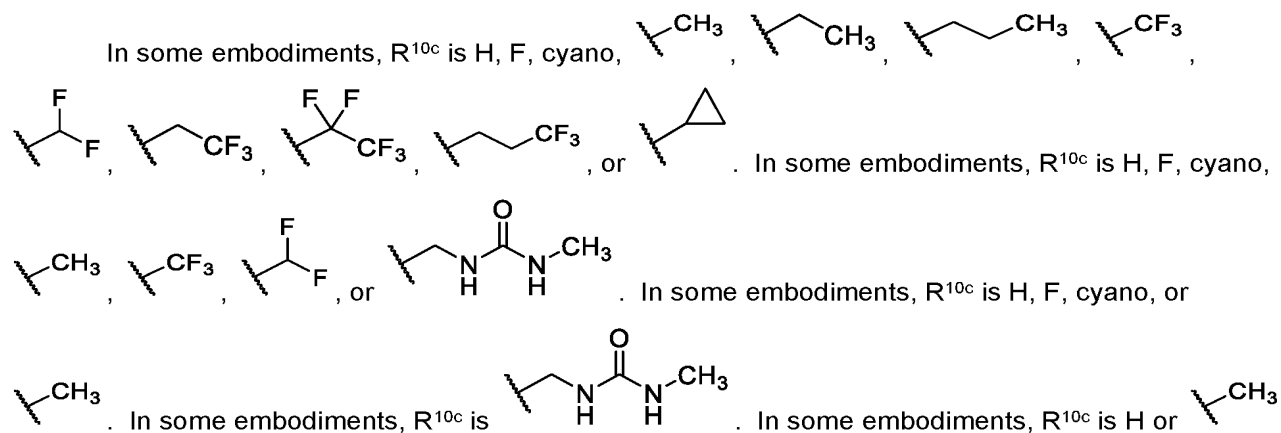
20 In some embodiments, R^{10a} is H, F, cyano, , , , , , , , , or . In some embodiments, R^{10a} is H, F, cyano, , , , or . In some embodiments, R^{10a} is H, F, cyano, or . In some embodiments, R^{10a} is . In some embodiments, R^{10a} is H or . In some embodiments, R^{10a} is H. In some embodiments,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

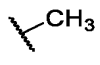
In some embodiments, R^{10b} is H, halogen, cyano, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl. In some embodiments, R^{10b} is H, halogen, cyano, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl. In some embodiments, R^{10b} is H, halogen, cyano, or optionally substituted C₁-C₆ alkyl. In some embodiments, R^{10b} is optionally substituted C₁-C₆ heteroalkyl.



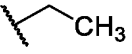
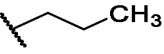
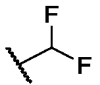
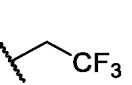
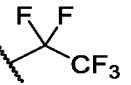
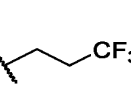
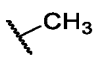
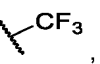
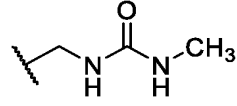
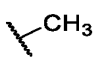
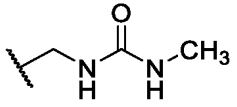
10 . In some embodiments, R^{10b} is H. In some embodiments, R^{10b} is .

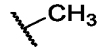
In some embodiments, R^{10c} is H, halogen, cyano, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl. In some embodiments, R^{10c} is H, halogen, cyano, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl. In some embodiments, R^{10c} is H, halogen, cyano, or optionally substituted C₁-C₆ alkyl. In some embodiments, R^{10c} is optionally substituted C₁-C₆ heteroalkyl.



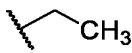
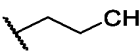
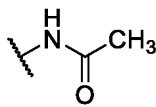
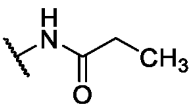
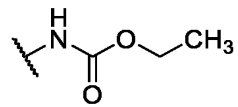
20 . In some embodiments, R^{10c} is H. In some embodiments, R^{10c} is .

In some embodiments, R^{10d} is H, halogen, cyano, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl. In some embodiments, R^{10d} is H, halogen, cyano, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl. In some embodiments, R^{10d} is H, halogen, cyano, or optionally substituted C₁-C₆ alkyl. In some embodiments, R^{10d} is optionally substituted C₁-C₆ 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 .

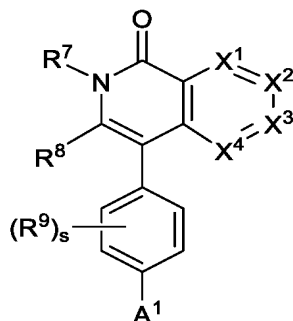
5 . In some embodiments, R^{10d} is H. In some embodiments, R^{10d} is .

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 .

10

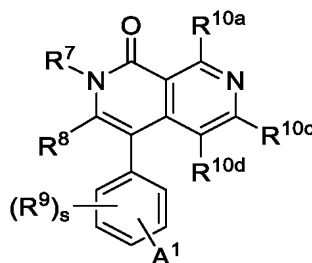
In some embodiments, A includes the structure of **Formula IVa**:



Formula IVa,

or a pharmaceutically acceptable salt thereof.

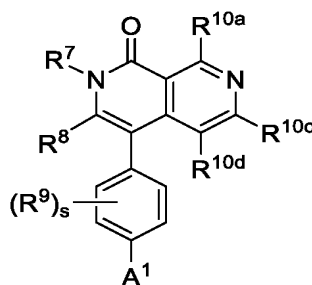
15 In some embodiments, A includes the structure of **Formula IVb**:



Formula IVb,

or a pharmaceutically acceptable salt thereof.

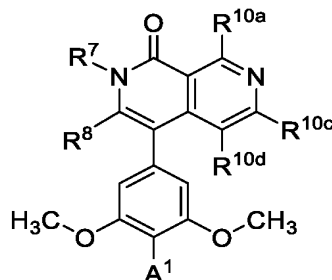
In some embodiments, A includes the structure of **Formula IVc**:



Formula IVc,

or a pharmaceutically acceptable salt thereof.

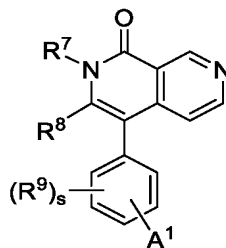
5 In some embodiments, A includes the structure of **Formula IVd**:



Formula IVd,

or a pharmaceutically acceptable salt thereof.

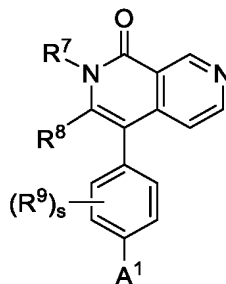
In some embodiments, A includes the structure of **Formula IVe**:



Formula IVe,

or a pharmaceutically acceptable salt thereof.

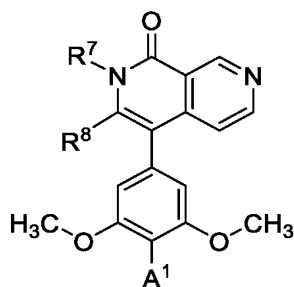
In some embodiments, A includes the structure of **Formula IVf**:



Formula IVf,

or a pharmaceutically acceptable salt thereof.

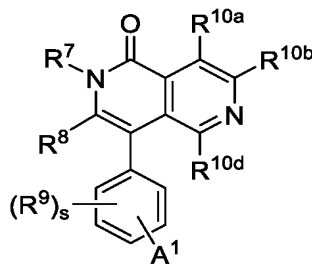
In some embodiments, A includes the structure of **Formula IVg**:



Formula IVg,

or a pharmaceutically acceptable salt thereof.

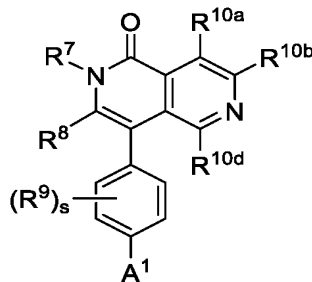
5 In some embodiments, A includes the structure of **Formula IVh**:



Formula IVh,

or a pharmaceutically acceptable salt thereof.

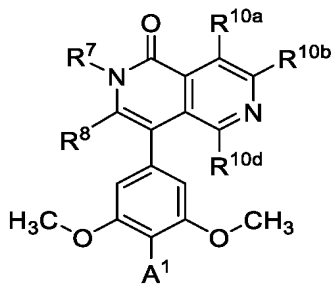
In some embodiments, A includes the structure of **Formula IVi**:



Formula IVi,

or a pharmaceutically acceptable salt thereof.

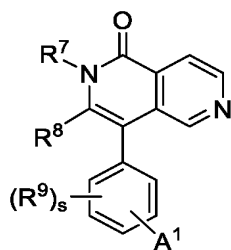
In some embodiments, A includes the structure of **Formula IVj**:



Formula IVj,

or a pharmaceutically acceptable salt thereof.

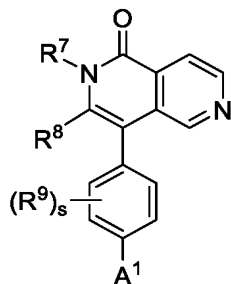
In some embodiments, A includes the structure of **Formula IVk**:



Formula IVk,

or a pharmaceutically acceptable salt thereof.

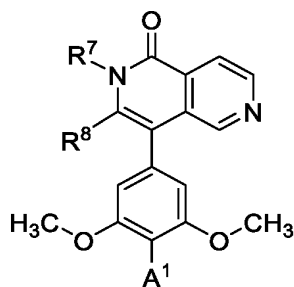
5 In some embodiments, A includes the structure of **Formula IVm**:



Formula IVm,

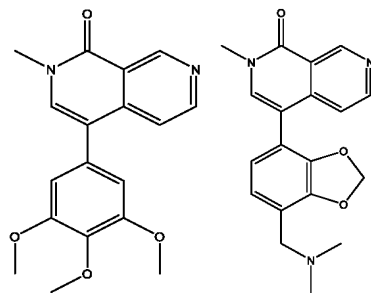
or a pharmaceutically acceptable salt thereof.

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

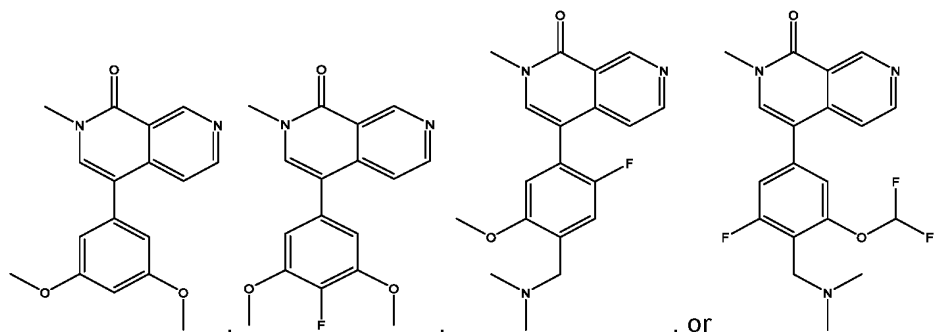


Formula IVn,

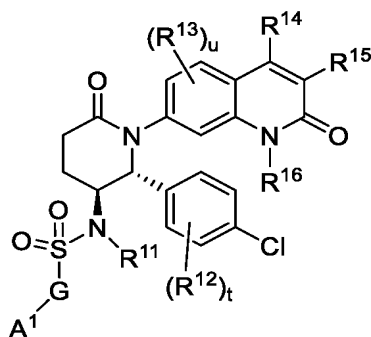
or a pharmaceutically acceptable salt thereof.



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

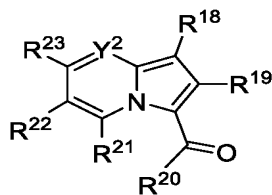


In some embodiments, A includes the structure of **Formula V**



Formula V,

- 5 where
- each R¹¹ and R¹⁶ is, independently, H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl;
- t is 0, 1, 2, 3, or 4;
- each R¹² is, independently, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl,
- 10 optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxy, thiol, or optionally substituted amino;
- u is 0, 1, 2, 3, or 4;
- each R¹³ is, independently, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl,
- 15 optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxy, thiol, or optionally substituted amino;
- each R¹⁴ and R¹⁵ is, independently, selected from the group consisting of H, halogen, optionally substituted C₁-C₆ alkyl, or optionally substituted C₆-C₁₀ aryl;
- 20 G is optionally substituted C₁-C₆ alkylene, optionally substituted C₆-C₁₀ arylene, or optionally substituted C₃-C₆ carbocyclylene; and
- A¹ 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

Y² is CR¹⁷ or N;

R¹⁸ is A¹, optionally substituted C₆-C₁₀ aryl or C₂-C₉ heteroaryl;

R¹⁹ is H, halogen, optionally substituted C₁-C₆ alkyl, or optionally substituted C₆-C₁₀ aryl;

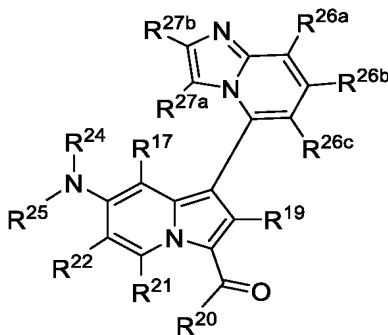
R²⁰ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₆-C₁₀ aryl;

each R¹⁷, R²¹, and R²² is, independently, H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

R²³ is H or -NR²⁴R²⁵; and

each of R²⁴ and R²⁵ is, independently, H, A¹, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl, or R²⁴ and R²⁵ combine to form optionally substituted C₂-C₉ heterocyclyl, where one of R¹⁸, R²⁴, or R²⁵ is A¹, 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, A¹, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

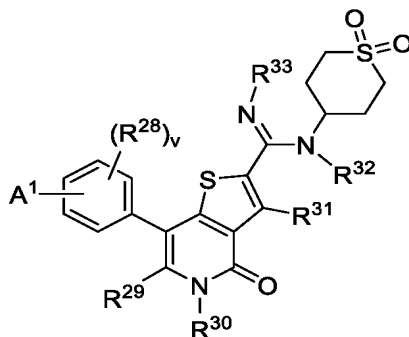
each R^{27a} and R^{27b} is, independently, H, halogen, optionally substituted C₁-C₆ alkyl, or optionally substituted C₆-C₁₀ aryl;

R¹⁹ is H, halogen, optionally substituted C₁-C₆ alkyl, or optionally substituted C₆-C₁₀ aryl;

R²⁰ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₆-C₁₀ aryl;

each R¹⁷, R²¹, and R²² is, independently, H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxy, thiol, or optionally substituted amino; and

each of R²⁴ and R²⁵ is, independently, H, A¹, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl, or R²⁴ and R²⁵ combine to form optionally substituted C₂-C₉ heterocyclyl, where one of R^{26a}, R^{26b}, R^{26c}, R²⁴, or R²⁵ is A¹, 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 R²⁸ is, independently, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

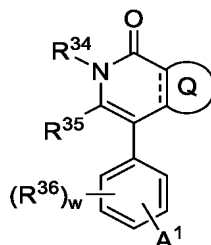
R²⁹ is H, halogen, optionally substituted C₁-C₆ alkyl, or optionally substituted C₆-C₁₀ aryl;

R³¹ is H, halogen, optionally substituted C₁-C₆ alkyl, or optionally substituted C₆-C₁₀ aryl;

each R³⁰, R³², and R³³ is, independently, H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl; and

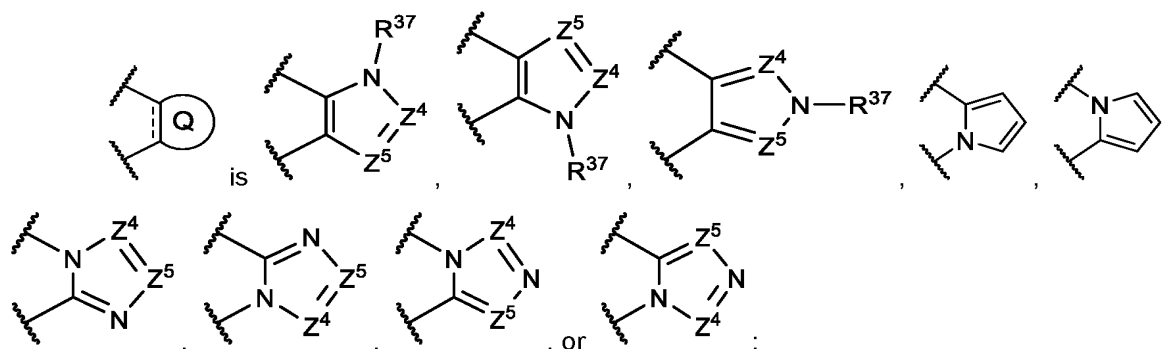
A¹ is a bond between A and the linker, or a pharmaceutically acceptable salt thereof.

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} ;

5 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;

10 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;

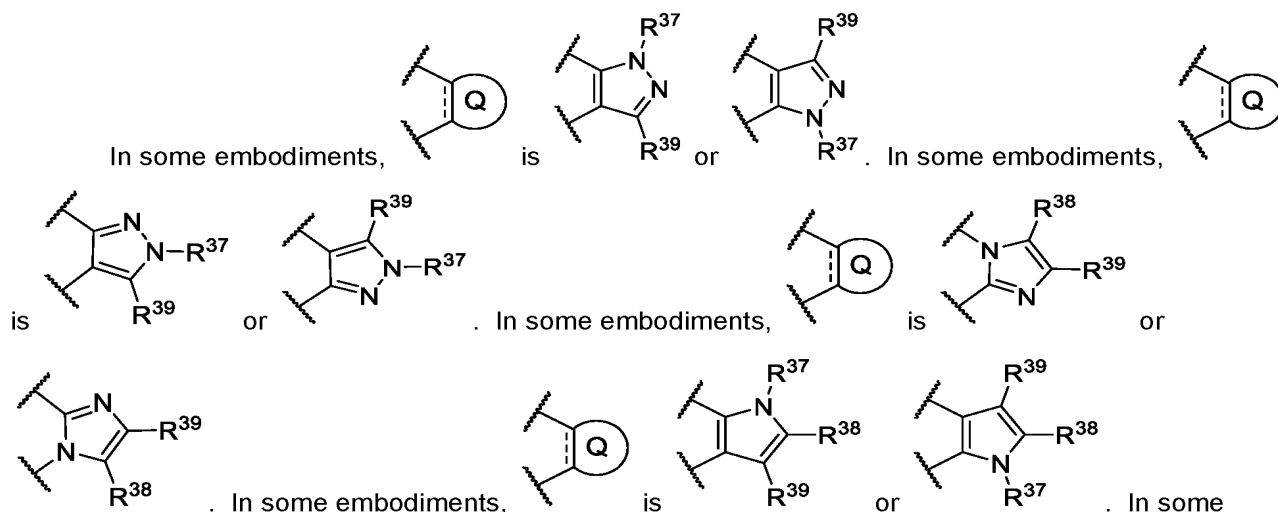
w is 0, 1, 2, 3, or 4;

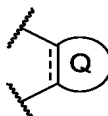
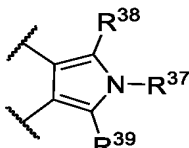
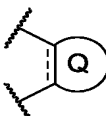
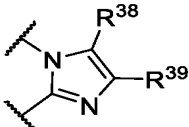
15 each R^{36} is, independently, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl,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

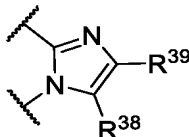
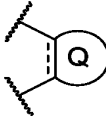
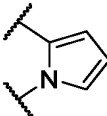
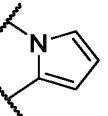
A^1 is a bond between A and the linker, or a pharmaceutically acceptable salt thereof.

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} .

20 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} .



embodiments,  is . In some embodiments,  is  or

. In some embodiments,  is  or .

In some embodiments, R³⁷ is H or optionally substituted C₁-C₆ alkyl. In some embodiments, R³⁷ is H or .

5 In some embodiments, R³⁸ is H or . In some embodiments, R³⁹ is H or optionally substituted C₁-C₆ alkyl.

In some embodiments, R³⁹ is H or .

In some embodiments, R³⁴ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl. In some embodiments, R³⁴ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, or optionally substituted C₃-C₁₀ carbocyclyl.

10 In some embodiments, R³⁴ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₃-C₁₀ carbocyclyl.

In some embodiments, optionally substituted C₁-C₆ alkyl is C₁-C₆ perfluoroalkyl.

In some embodiments, R³⁴ is H, , , , , , ,

, , , , , , , , , or

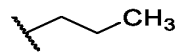
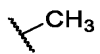
15 . In some embodiments, R³⁴ is , , , , , , or

. In some embodiments, R³⁴ is H, , , , , , or

.

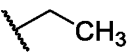
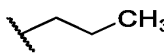
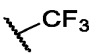
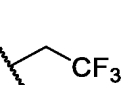
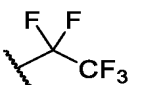
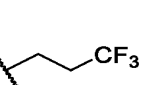
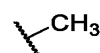
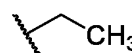
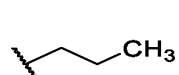
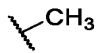
In some embodiments, R³⁴ is H, , , , , ,

, , , or . In some embodiments, R³⁴ is H, , .

, , or . In some embodiments, R³⁴ is H or . In some embodiments, R³⁴ is H. In some embodiments, R³⁴ is .

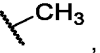
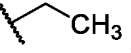
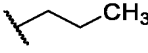
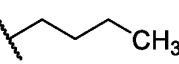
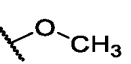
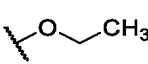
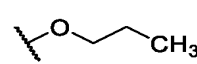
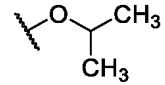
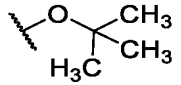
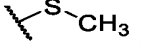
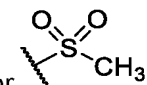
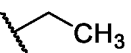
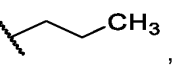
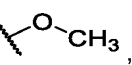
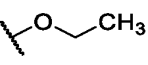
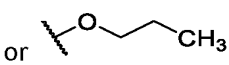
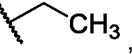
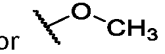
In some embodiments, R³⁵ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₆-C₁₀ aryl. In some embodiments, R³⁵ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl. In some embodiments, R³⁵ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₃-C₁₀ carbocyclyl. In some embodiments, R³⁵ is H or optionally substituted C₁-C₆ alkyl.

In some embodiments, optionally substituted C₁-C₆ alkyl is C₁-C₆ perfluoroalkyl.

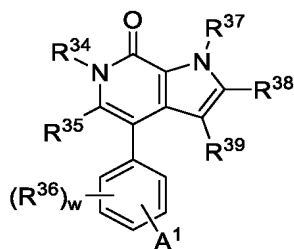
In some embodiments, R³⁵ is H, , , , , , , , , or . In some embodiments, R³⁵ is H, , , , or . In some embodiments, R³⁵ is H or . In some embodiments, R³⁵ is H. In some embodiments, R³⁵ is .

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 R³⁶ is, independently, halogen, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl. In some embodiments, each R³⁶ is, independently, optionally substituted C₁-C₆ alkyl or optionally substituted C₁-C₆ heteroalkyl.

In some embodiments, each R³⁶ is, independently, , , , , , , , , , , or . In some embodiments, each R³⁶ is, independently, halogen, , , , , , or . In some embodiments, each R³⁶ is, independently, F, Cl, , , or .

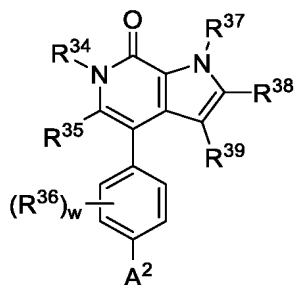
In some embodiments, the structure of **Formula IX** has the structure of **Formula IXa**:



Formula IXa,

or a pharmaceutically acceptable salt thereof.

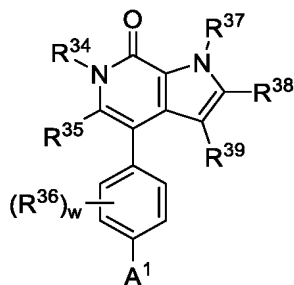
In some embodiments, the structure of **Formula IX** has the structure of **Formula IXb**:



Formula IXb,

or a pharmaceutically acceptable salt thereof.

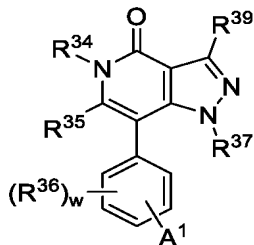
In some embodiments, the structure of **Formula IX** has the structure of **Formula IXc**:



Formula IXc,

or a pharmaceutically acceptable salt thereof.

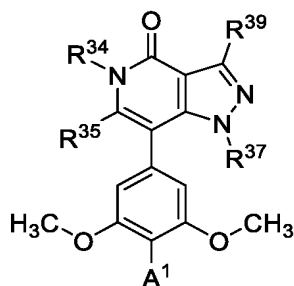
In some embodiments, the structure of **Formula IX** has the structure of **Formula IXd**:



Formula IXd,

or a pharmaceutically acceptable salt thereof.

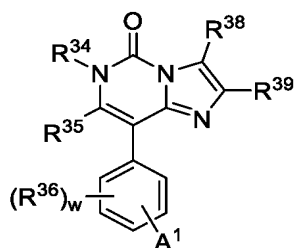
In some embodiments, the structure of **Formula IX** has the structure of **Formula IXe**:



Formula IXe,

or a pharmaceutically acceptable salt thereof.

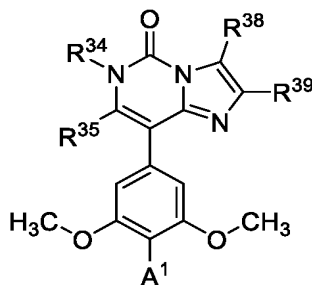
In some embodiments, the structure of **Formula IX** has the structure of **Formula IXf**:



Formula IXf,

or a pharmaceutically acceptable salt thereof.

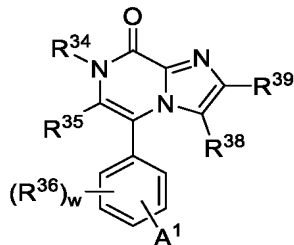
In some embodiments, the structure of **Formula IX** has the structure of **Formula IXg**:



Formula IXg,

or a pharmaceutically acceptable salt thereof.

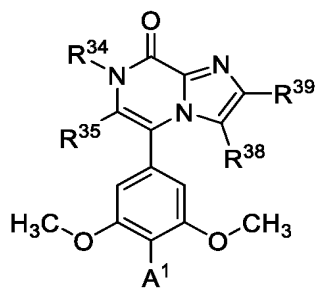
In some embodiments, the structure of **Formula IX** has the structure of **Formula IXh**:



Formula IXh,

or a pharmaceutically acceptable salt thereof.

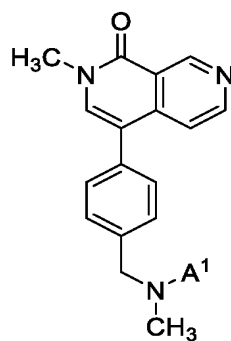
In some embodiments, the structure of **Formula IX** has the structure of **Formula IXi**:



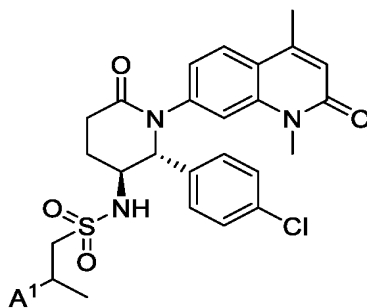
Formula IXi,

or a pharmaceutically acceptable salt thereof.

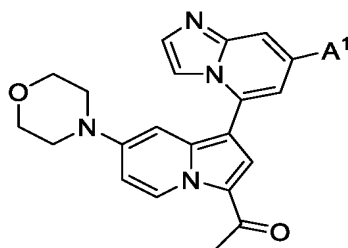
In some embodiments, A includes the structure of:



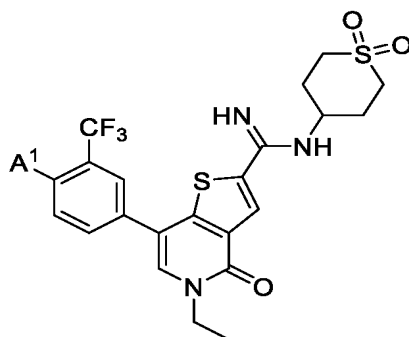
X2,



X3,

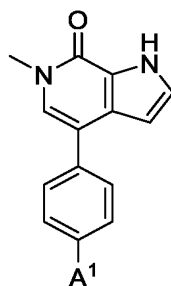


X4,



X5,

or



X6,

where A¹ 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.

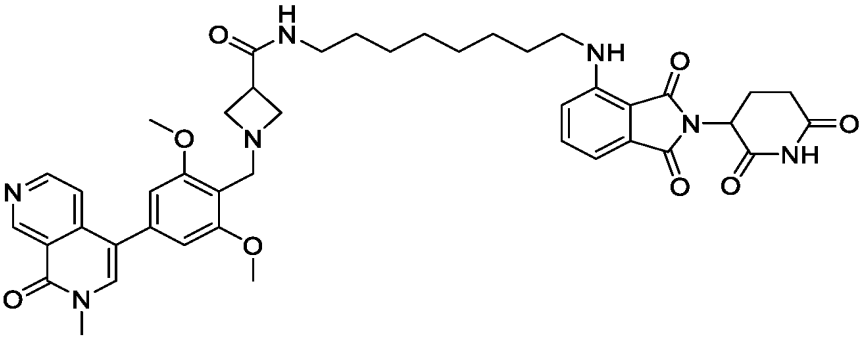
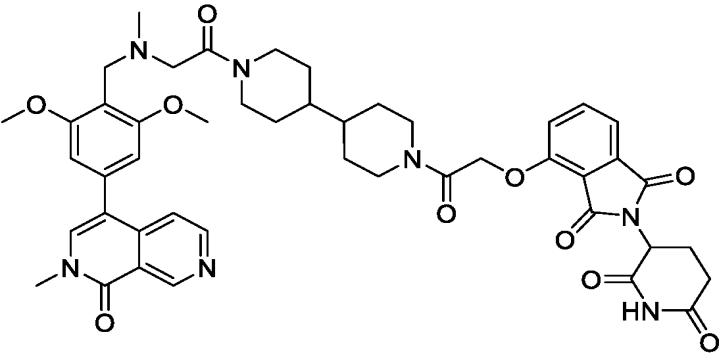
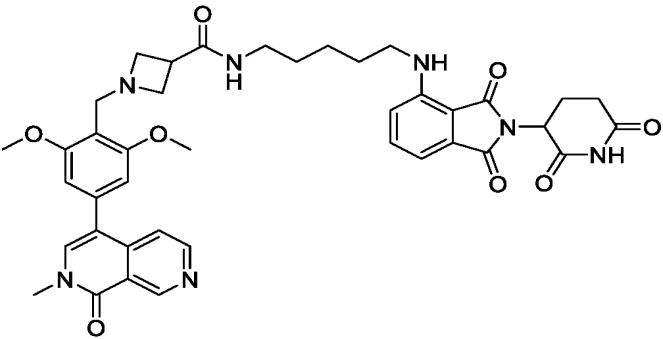
In another aspect, the disclosure features a compound having the structure of any one of compounds D178-D371 in Table 1B, or a pharmaceutically acceptable salt thereof.

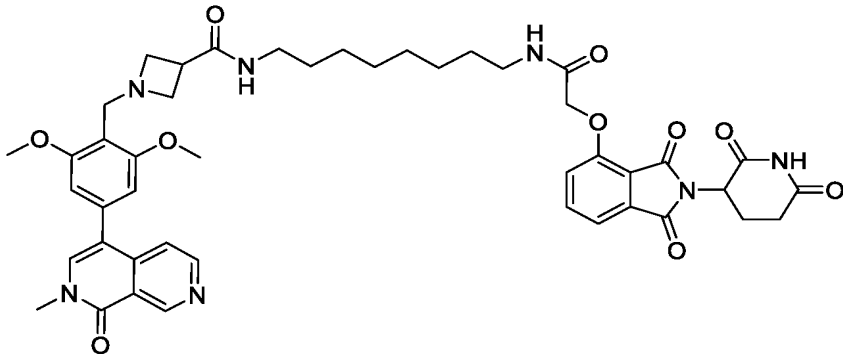
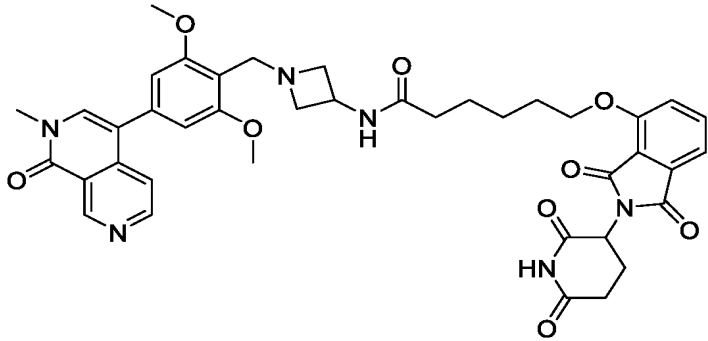
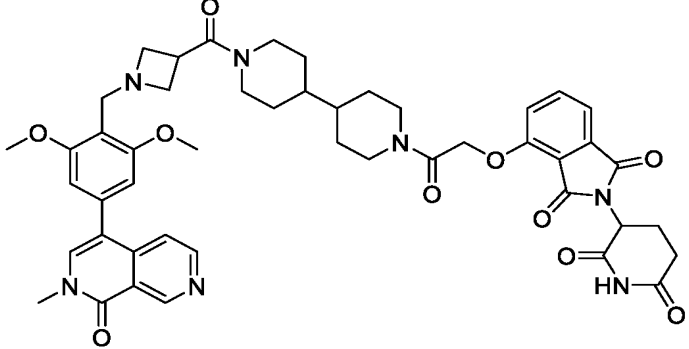
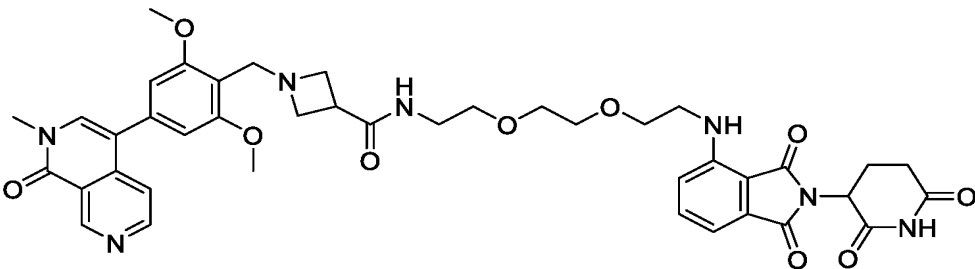
In another aspect, the disclosure features a compound having the structure of any one of compounds D372-D476 in Table 1D, or a pharmaceutically acceptable salt thereof.

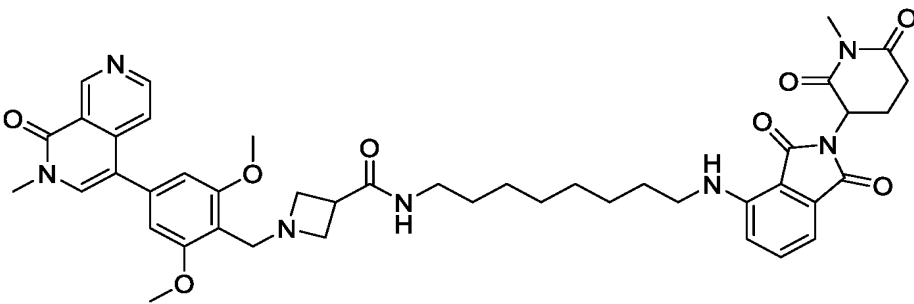
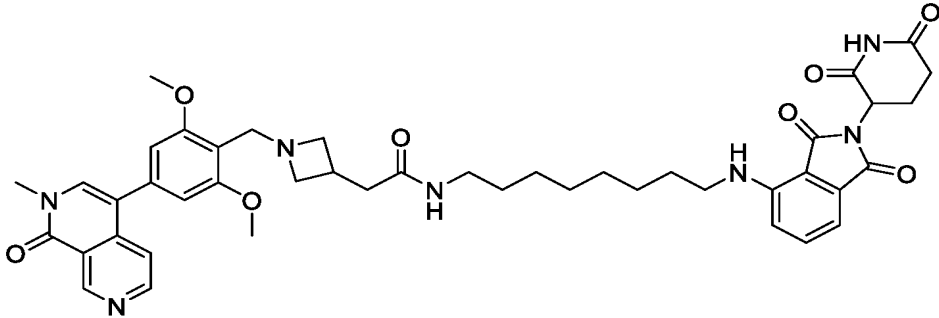
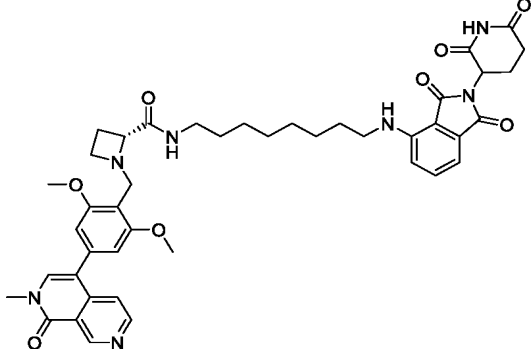
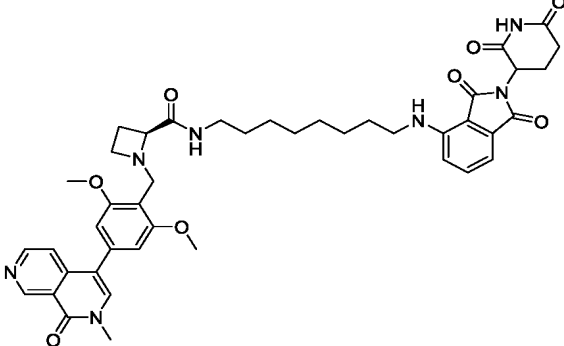
In another aspect, the disclosure features a compound having the structure of any one of compounds DD1-DD10 in Table 1C, or a pharmaceutically acceptable salt thereof.

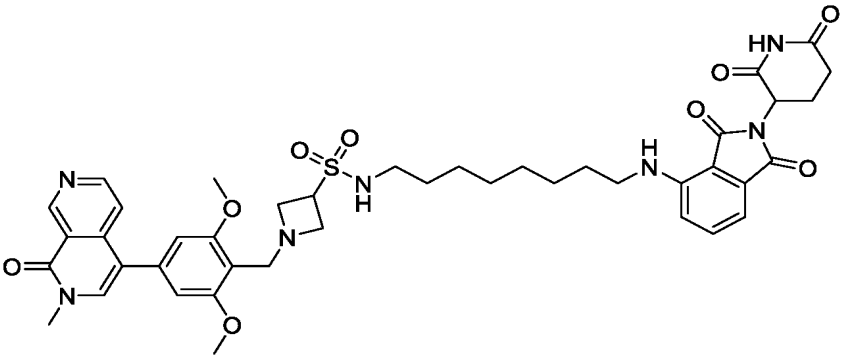
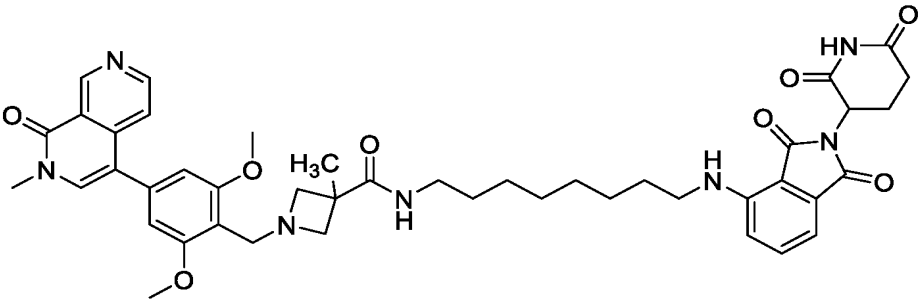
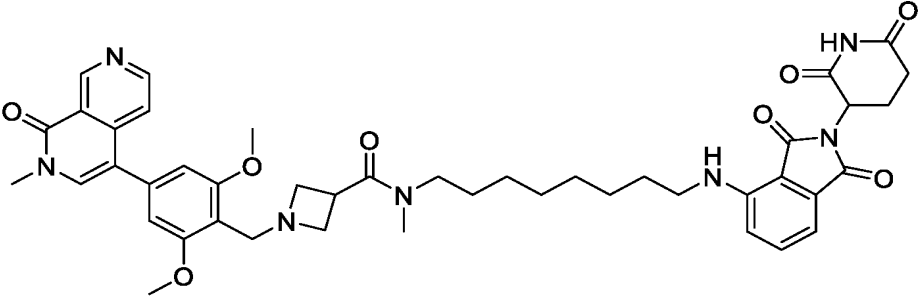
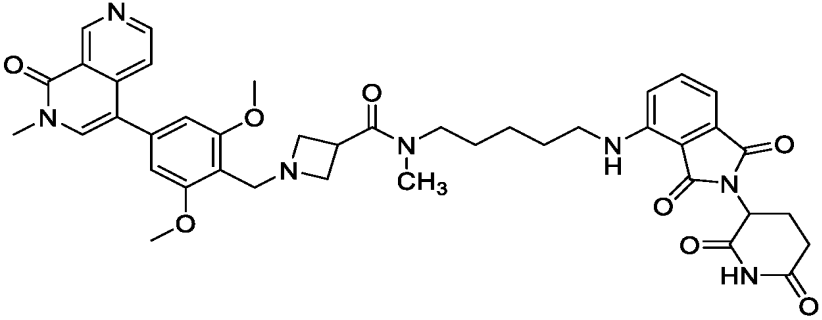
5 In another aspect, the disclosure features a compound having the structure of any one of compounds DD11-DD16 in Table 1E, or a pharmaceutically acceptable salt thereof.

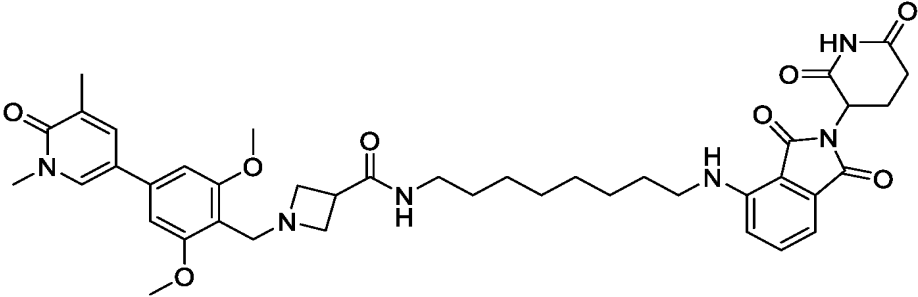
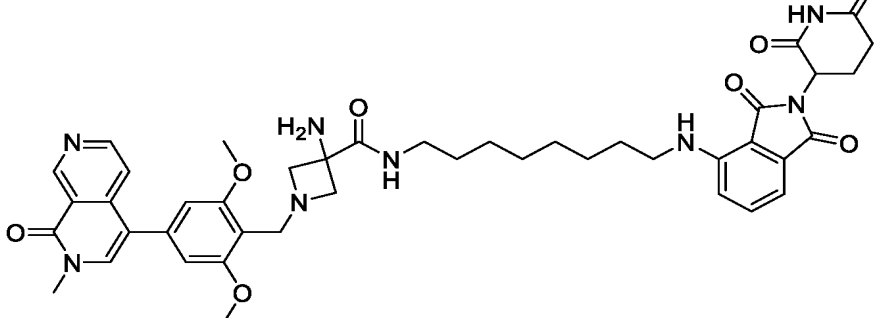
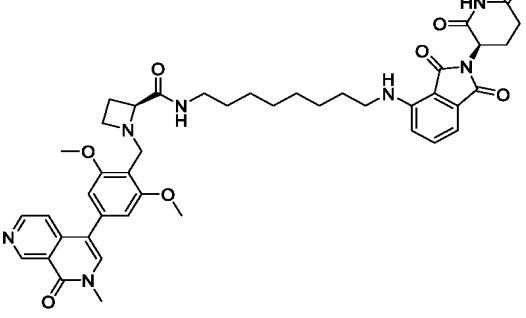
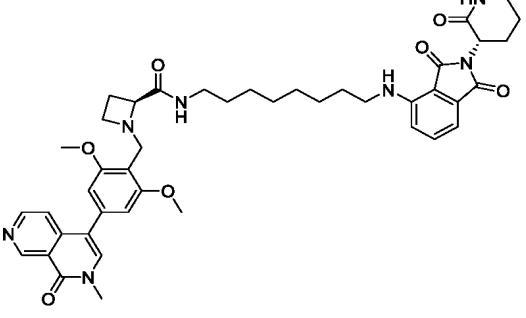
Table 1A. Compounds D1-D177 of the Disclosure

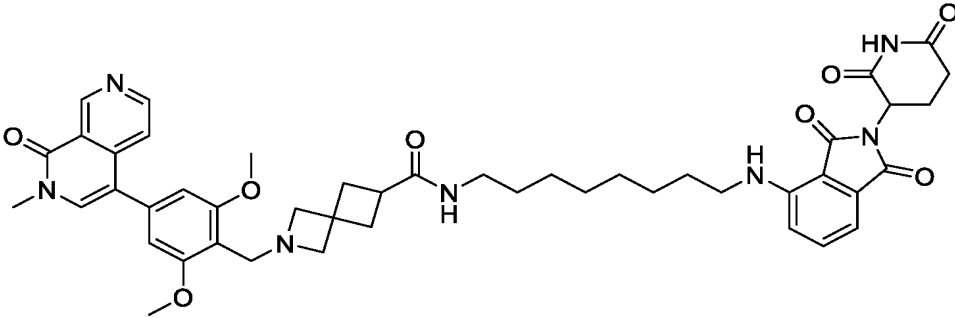
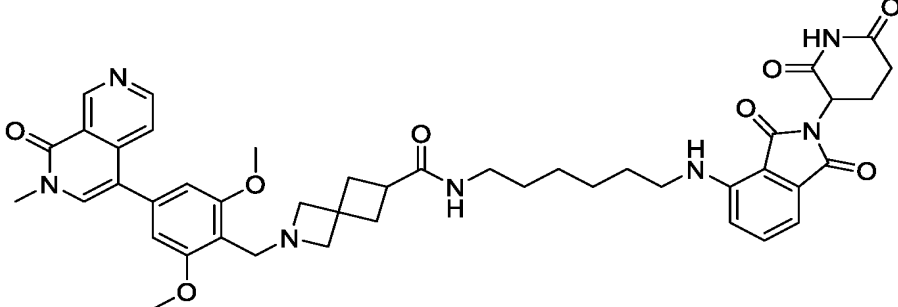
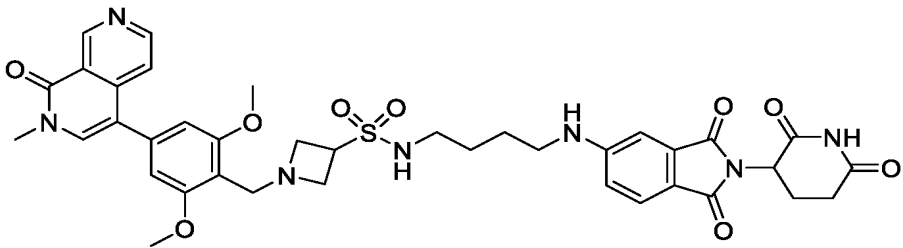
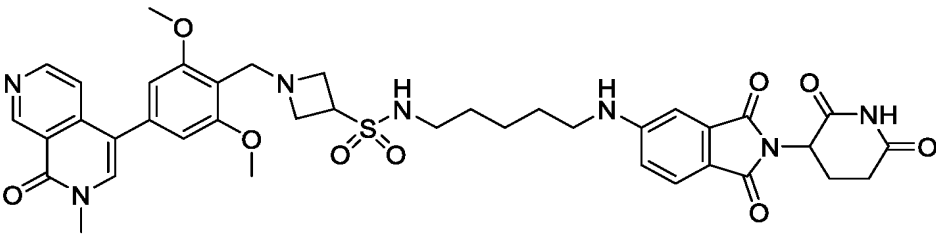
Compound No.	Structure
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D2	
D3	

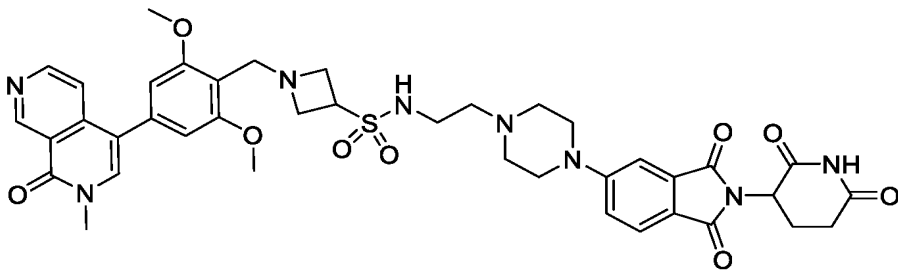
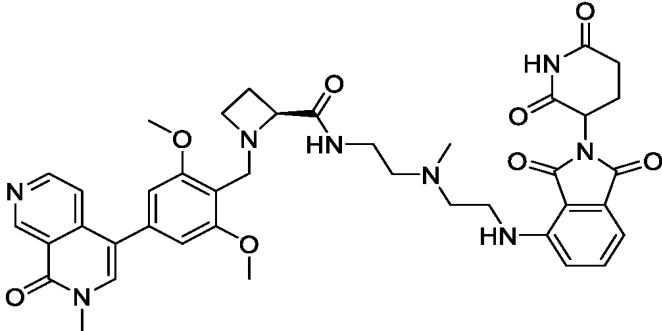
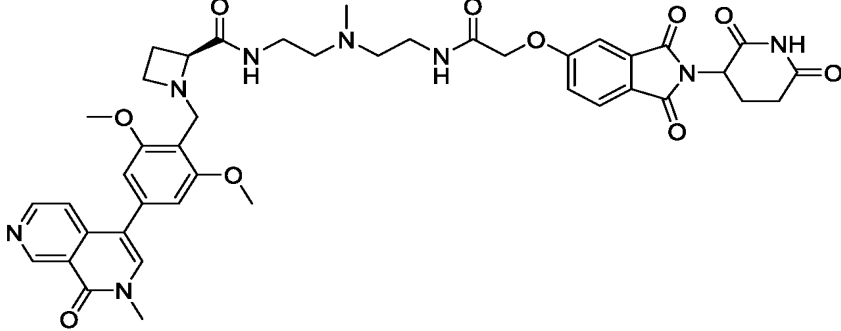
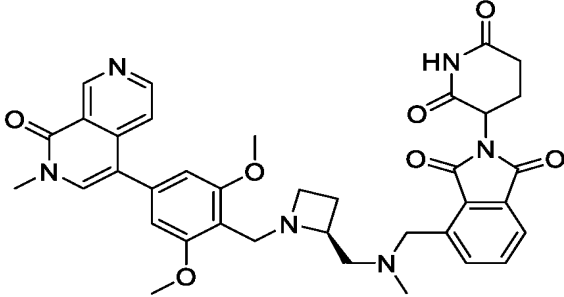
Compound No.	Structure
D4	
D5	
D6	
D7	

Compound No.	Structure
D8	
D9	
D10	
D11	

Compound No.	Structure
D12	
D13	
D14	
D15	

Compound No.	Structure
D16	
D17	
D18	
D19	

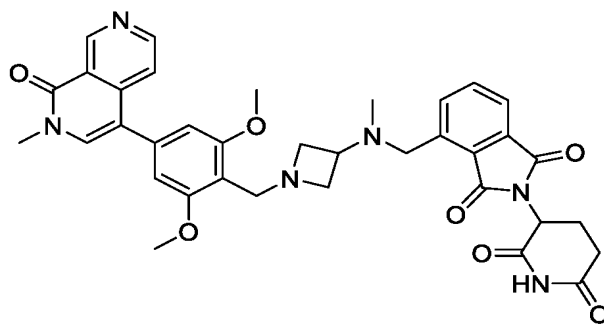
Compound No.	Structure
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D21	
D22	
D23	

Compound No.	Structure
D24	
D25	
D26	
D27	

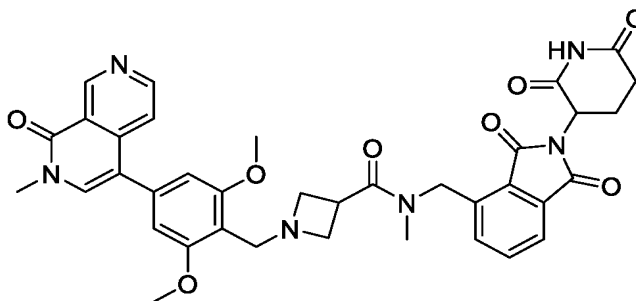
Compound No.

D28

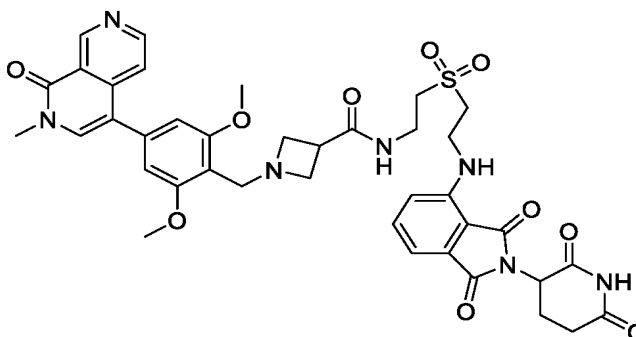
Structure



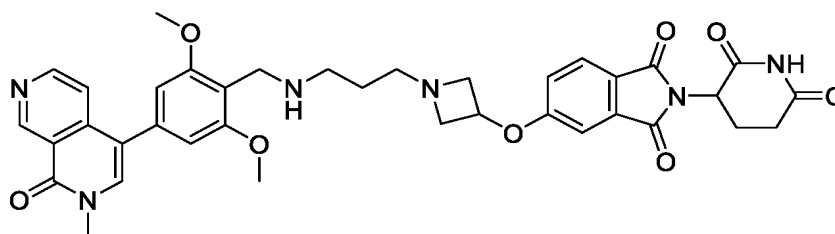
D29

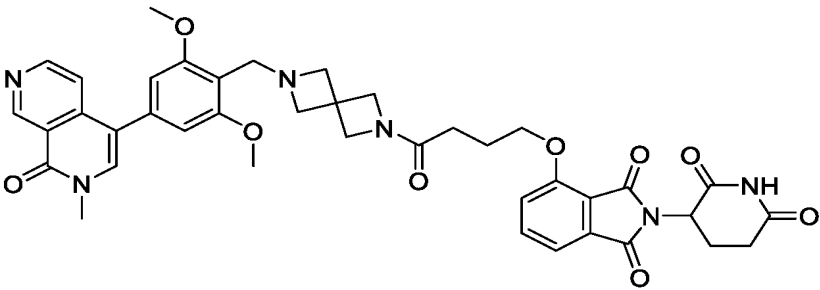
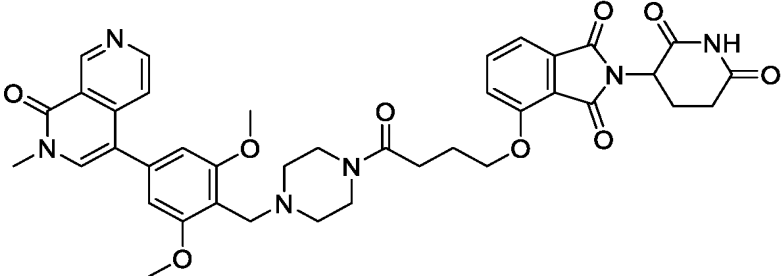
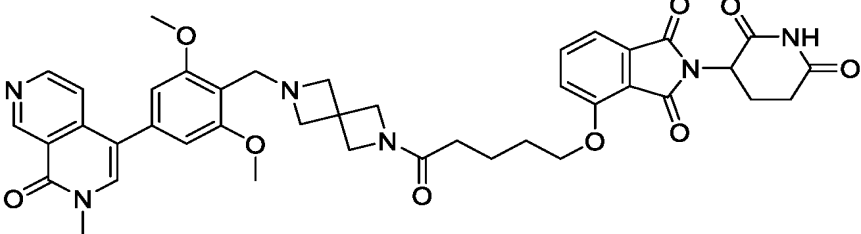
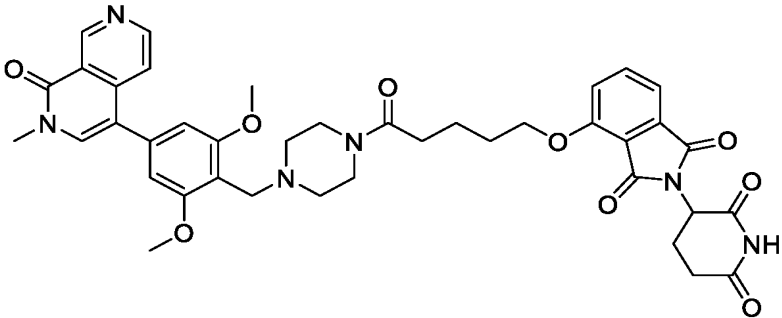


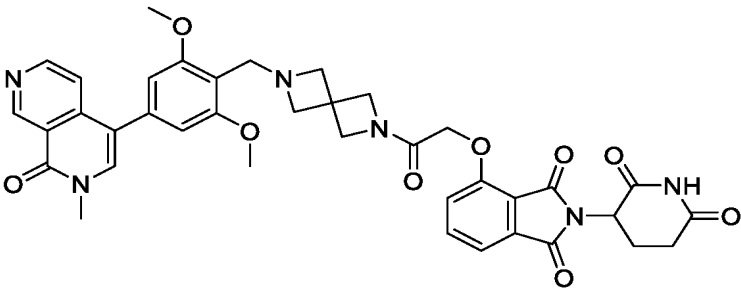
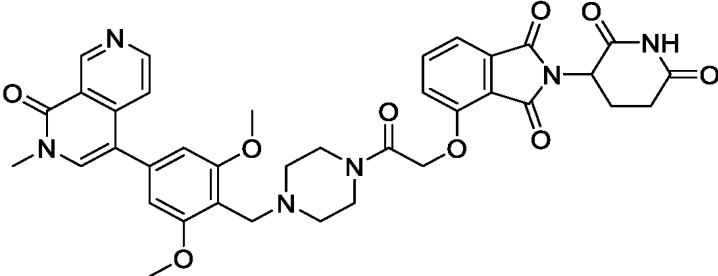
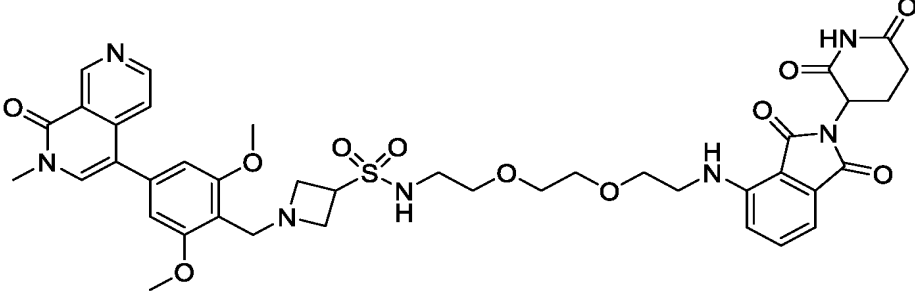
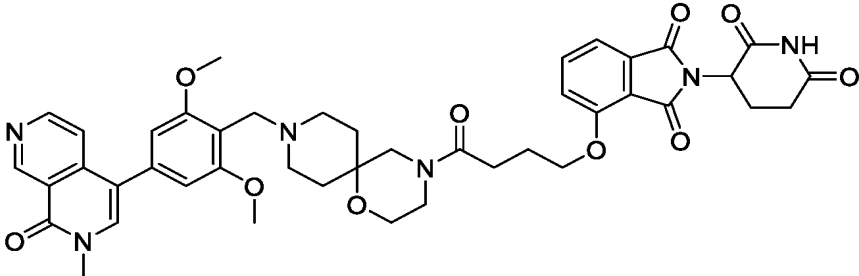
D30



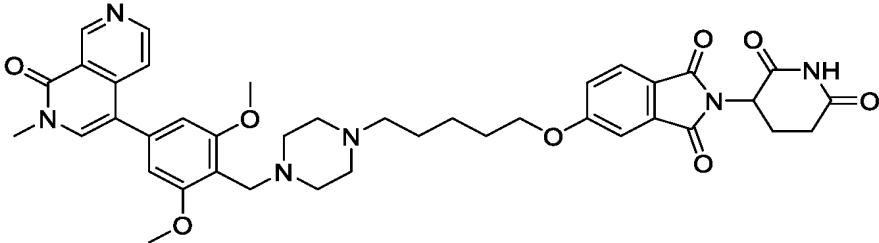
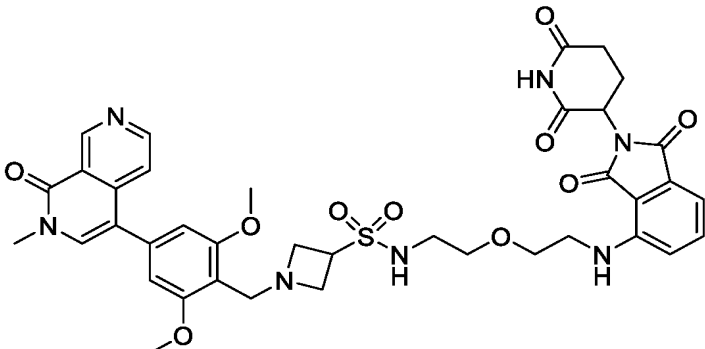
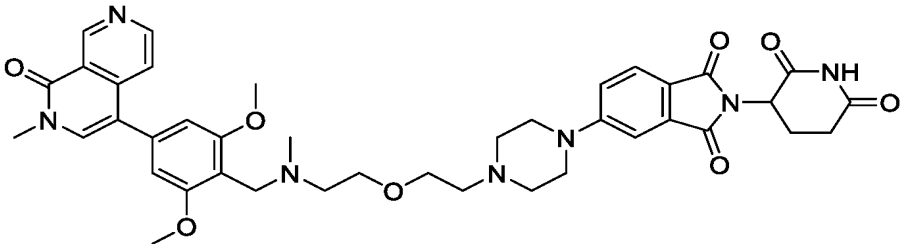
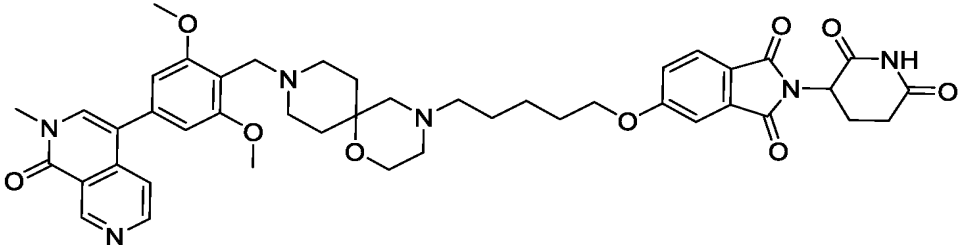
D31

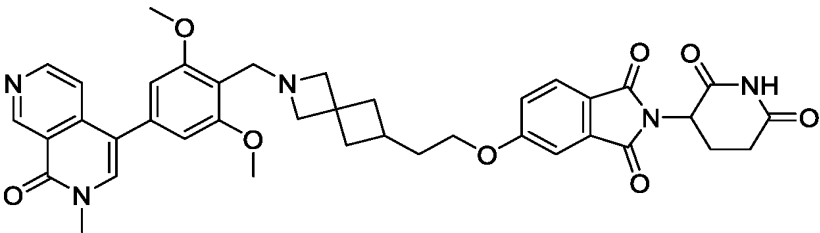
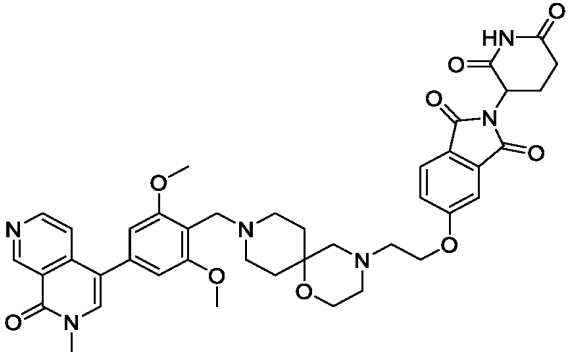
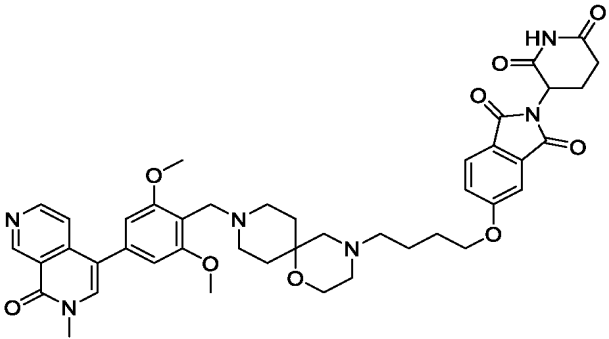
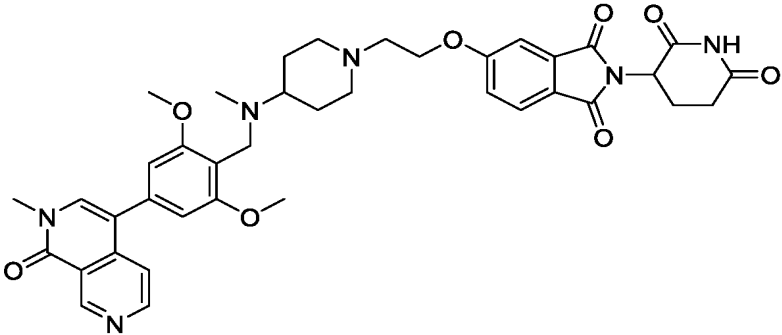


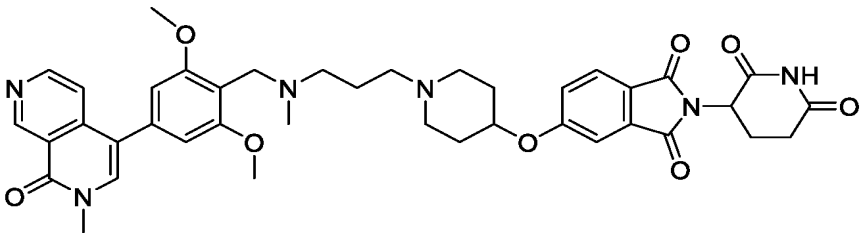
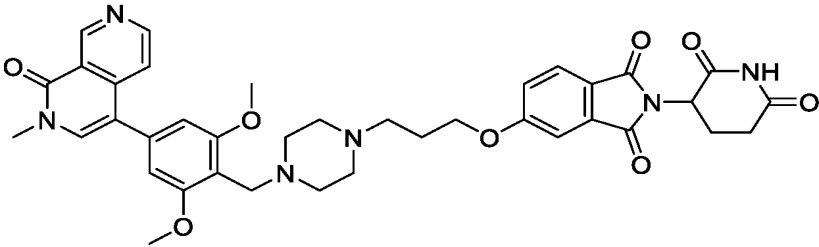
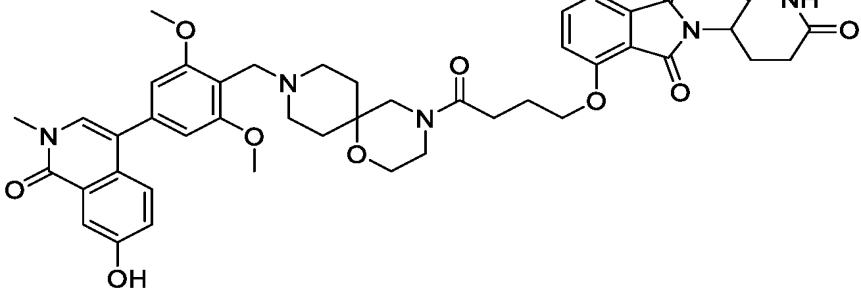
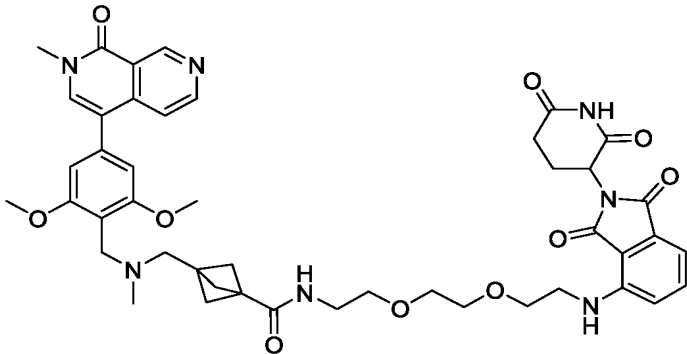
Compound No.	Structure
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D33	
D34	
D35	

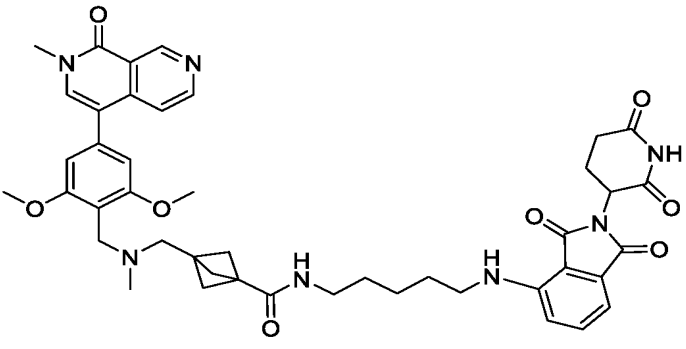
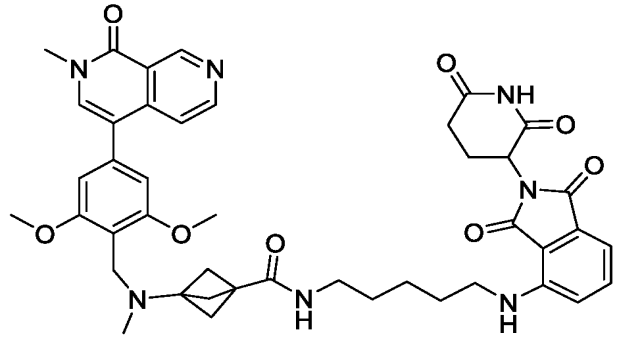
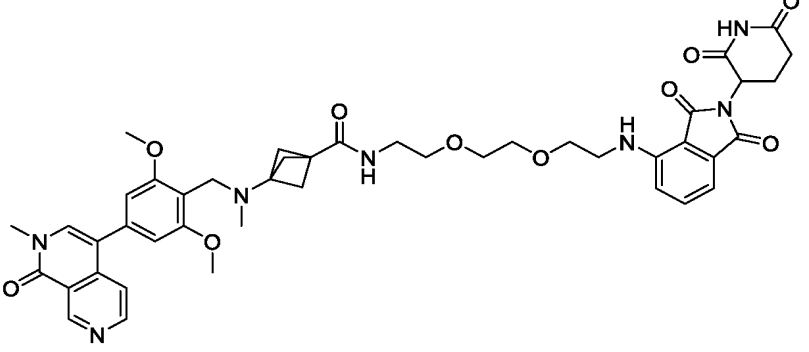
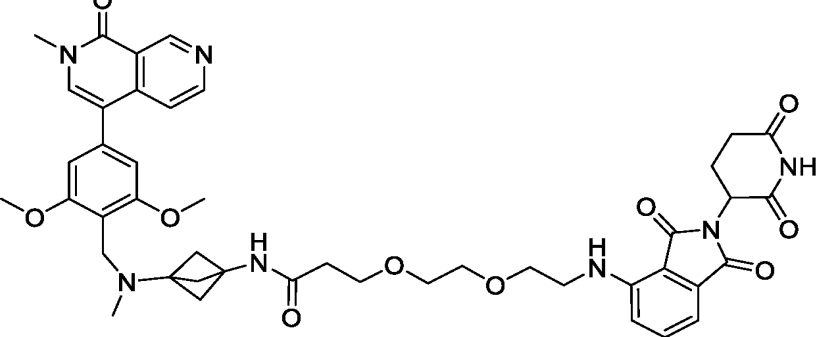
Compound No.	Structure
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D37	
D38	
D39	

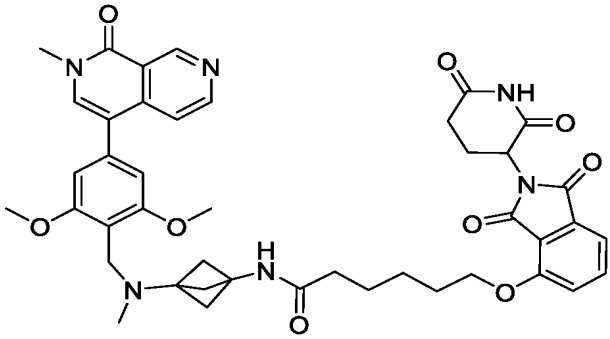
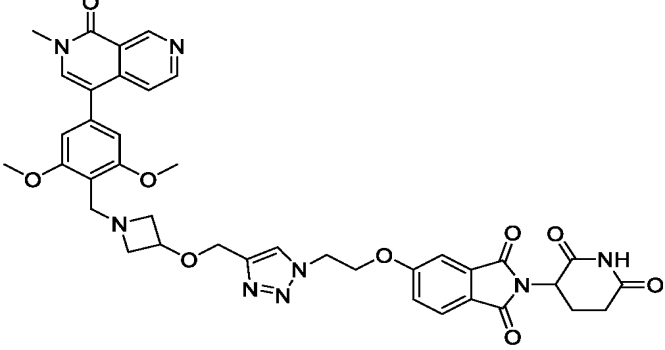
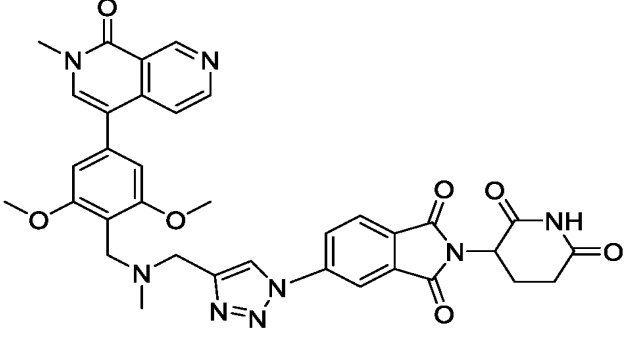
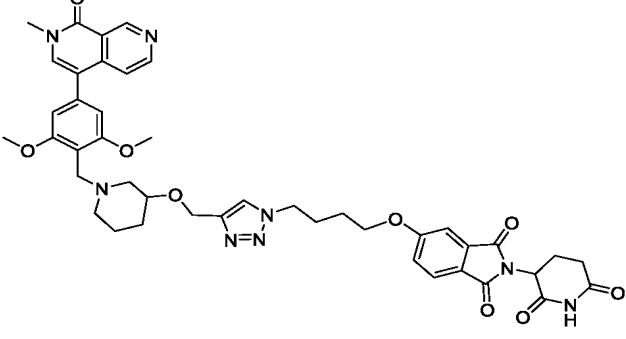
Compound No.	Structure
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D41	
D42	
D43	

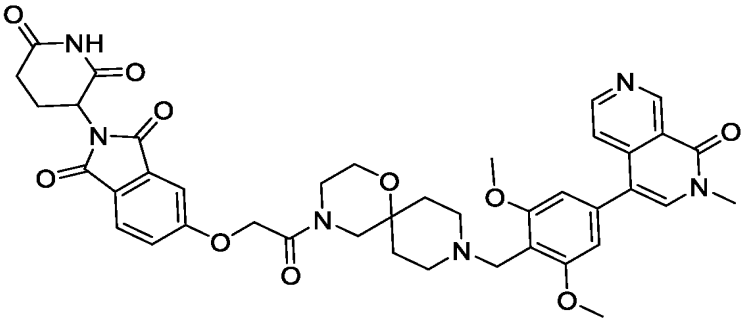
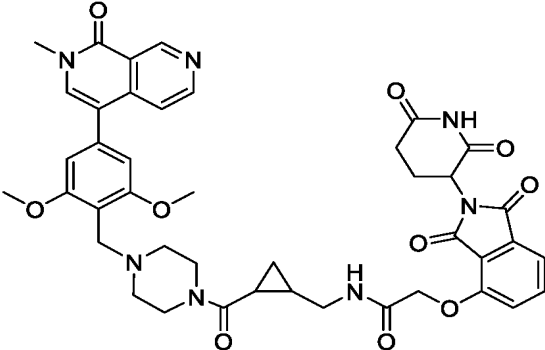
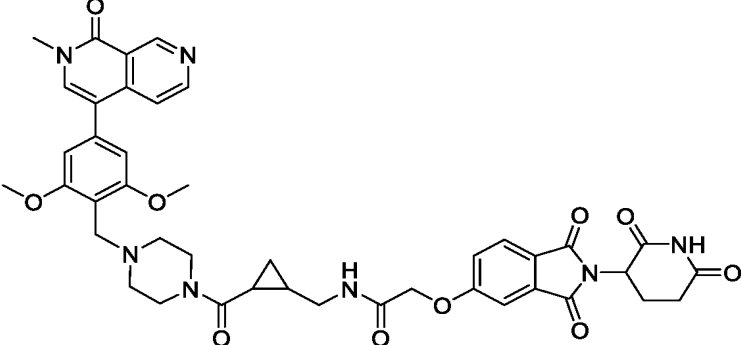
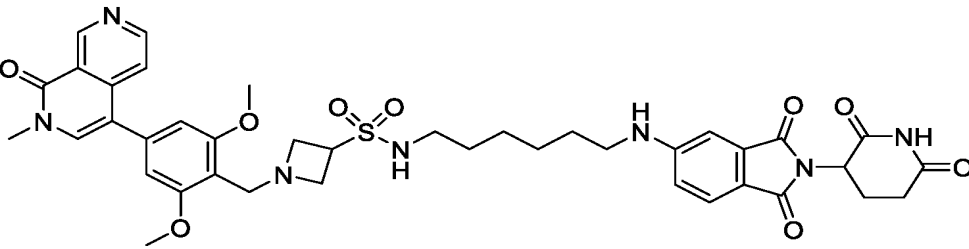
Compound No.	Structure
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D45	
D46	
D47	

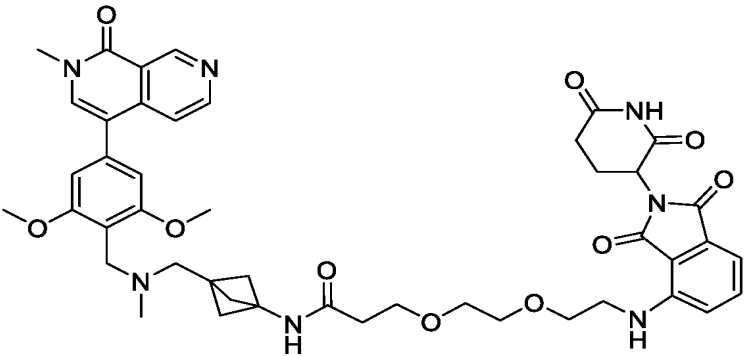
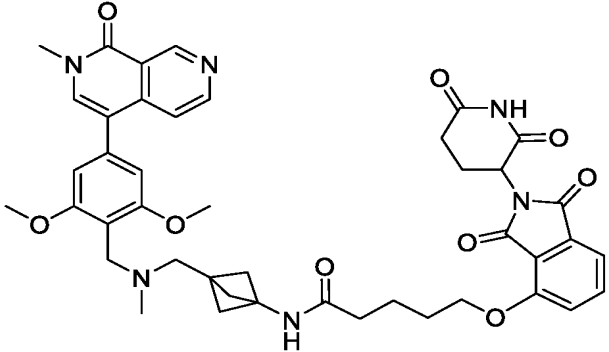
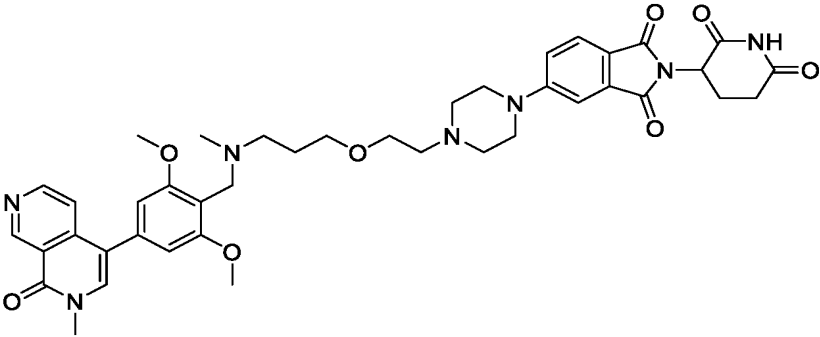
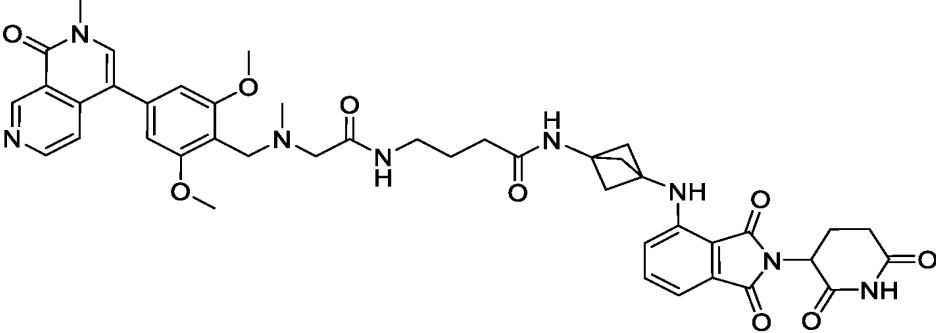
Compound No.	Structure
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D49	
D50	
D51	

Compound No.	Structure
D52	
D53	
D54	
D55	

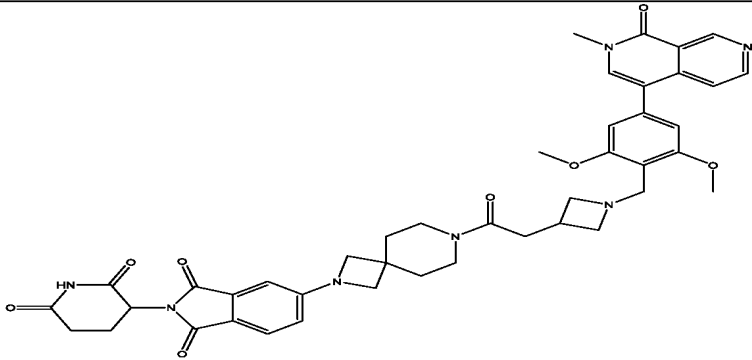
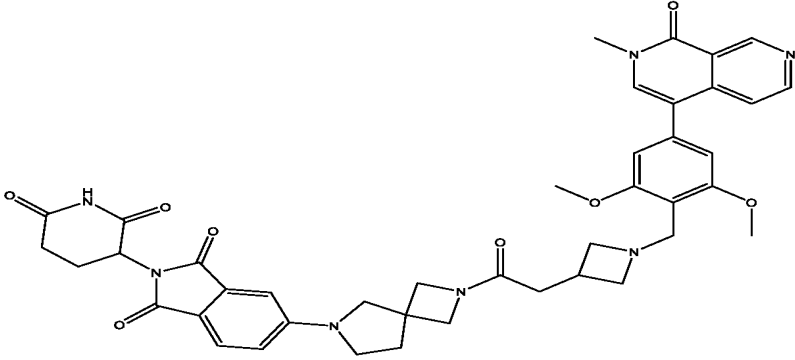
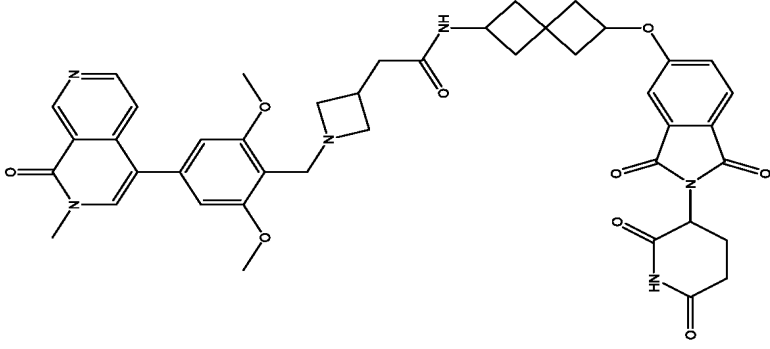
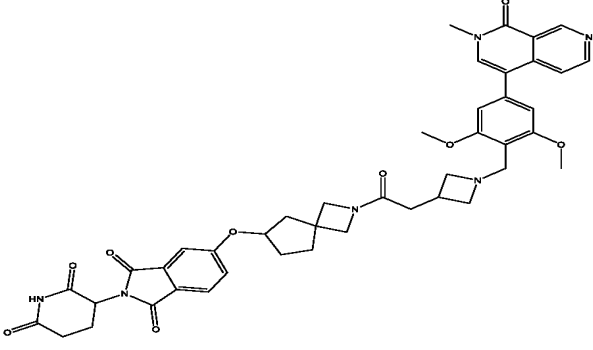
Compound No.	Structure
D56	
D57	
D58	
D59	

Compound No.	Structure
D60	 <p>Chemical structure of compound D60: A 4-methoxy-2-methyl-6-(2-methoxy-5-((2-methyl-1H-indolizin-5-ylideneamino)oxy)methyl)phenyl)-1H-imidazo[1,2-a]pyridine-3-carboxamide derivative. The structure features a central benzene ring substituted with a methoxy group, a methyl group, and a complex side chain. The side chain includes a 1H-imidazo[1,2-a]pyridine-3-carboxamide moiety linked via an amide bond to a 2-methyl-1H-imidazo[1,2-a]pyridine-3-carboxamide moiety, which is further linked via an amide bond to a 2-methyl-1H-imidazo[1,2-a]pyridine-3-carboxamide moiety.</p>
D61	 <p>Chemical structure of compound D61: A 4-methoxy-2-methyl-6-(2-methoxy-5-((2-methyl-1H-imidazo[1,2-a]pyridine-3-carboxamido)methyl)phenyl)-1H-imidazo[1,2-a]pyridine-3-carboxamide derivative. The structure features a central benzene ring substituted with a methoxy group, a methyl group, and a complex side chain. The side chain includes a 1H-imidazo[1,2-a]pyridine-3-carboxamide moiety linked via an amide bond to a 2-methyl-1H-imidazo[1,2-a]pyridine-3-carboxamide moiety, which is further linked via an amide bond to a 2-methyl-1H-imidazo[1,2-a]pyridine-3-carboxamide moiety.</p>
D62	 <p>Chemical structure of compound D62: A 4-methoxy-2-methyl-6-(2-methoxy-5-((2-methyl-1H-imidazo[1,2-a]pyridine-3-carboxamido)methyl)phenyl)-1H-imidazo[1,2-a]pyridine-3-carboxamide derivative. The structure features a central benzene ring substituted with a methoxy group, a methyl group, and a complex side chain. The side chain includes a 1H-imidazo[1,2-a]pyridine-3-carboxamide moiety linked via an amide bond to a 2-methyl-1H-imidazo[1,2-a]pyridine-3-carboxamide moiety, which is further linked via an amide bond to a 2-methyl-1H-imidazo[1,2-a]pyridine-3-carboxamide moiety.</p>
D63	 <p>Chemical structure of compound D63: A 4-methoxy-2-methyl-6-(2-methoxy-5-((2-methyl-1H-imidazo[1,2-a]pyridine-3-carboxamido)methyl)phenyl)-1H-imidazo[1,2-a]pyridine-3-carboxamide derivative. The structure features a central benzene ring substituted with a methoxy group, a methyl group, and a complex side chain. The side chain includes a 1H-imidazo[1,2-a]pyridine-3-carboxamide moiety linked via an amide bond to a 2-methyl-1H-imidazo[1,2-a]pyridine-3-carboxamide moiety, which is further linked via an amide bond to a 2-methyl-1H-imidazo[1,2-a]pyridine-3-carboxamide moiety.</p>

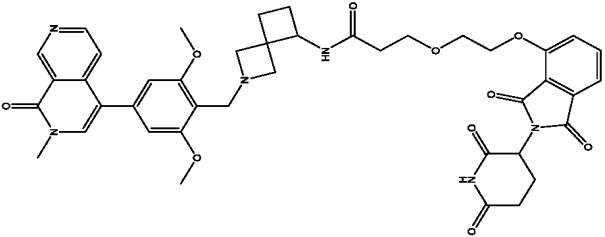
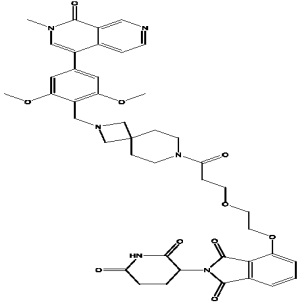
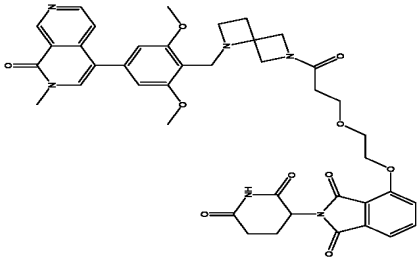
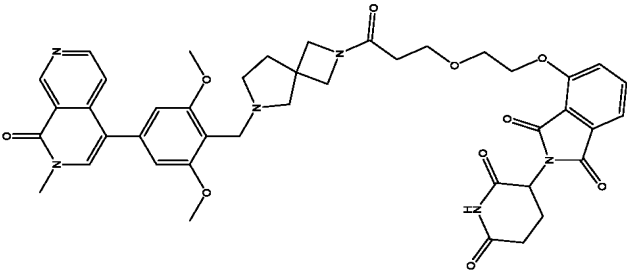
Compound No.	Structure
D64	
D65	
D66	
D67	

Compound No.	Structure
D68	
D69	
D70	
D71	

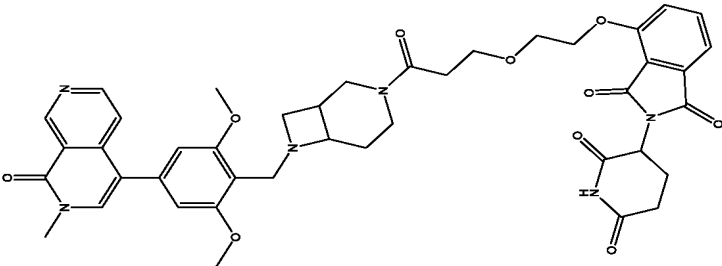
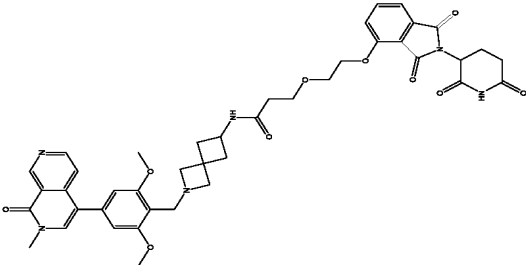
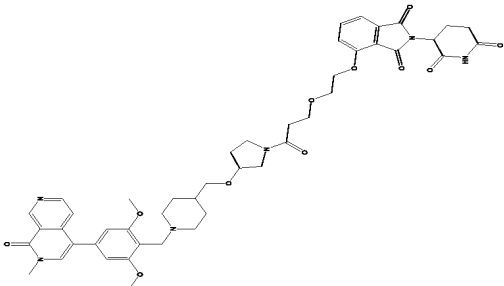
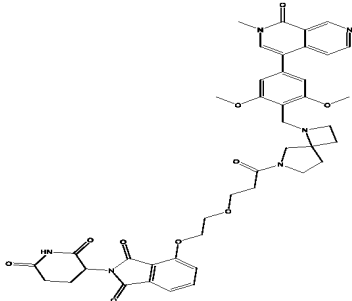
Compound No.	Structure
D72	
D73	
D74	
D75	

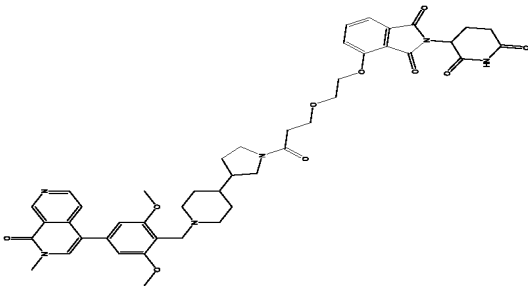
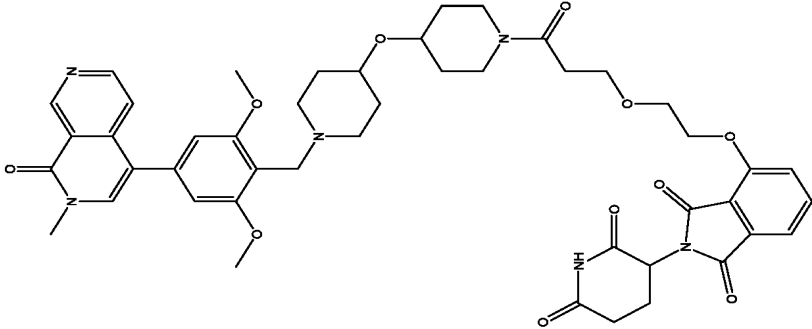
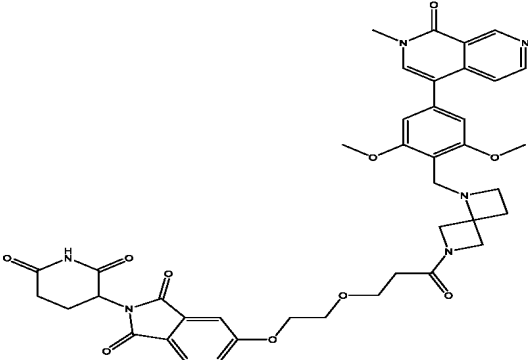
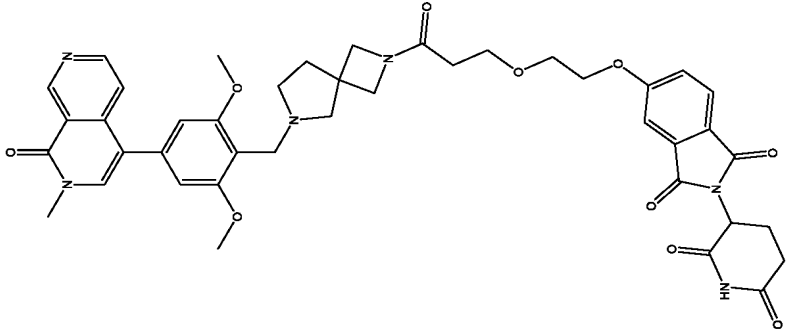
Compound No.	Structure
D76	 <p>Chemical structure of compound D76: A complex molecule featuring a 1,2,3,4-tetrahydroquinolin-5(1H)-one core. This core is linked via a nitrogen atom to a 1,4-dioxane ring, which is further connected to a 1,4-dioxane-2-carboxamide group. The amide group is linked to a 1,4-dioxane ring, which is connected to a 1,4-dioxane-2-carboxamide group. The amide group is linked to a 1,4-dioxane ring, which is connected to a 1,4-dioxane-2-carboxamide group. The amide group is linked to a 1,4-dioxane ring, which is connected to a 1,4-dioxane-2-carboxamide group.</p>
D77	 <p>Chemical structure of compound D77: A complex molecule featuring a 1,2,3,4-tetrahydroquinolin-5(1H)-one core. This core is linked via a nitrogen atom to a 1,4-dioxane ring, which is further connected to a 1,4-dioxane-2-carboxamide group. The amide group is linked to a 1,4-dioxane ring, which is connected to a 1,4-dioxane-2-carboxamide group. The amide group is linked to a 1,4-dioxane ring, which is connected to a 1,4-dioxane-2-carboxamide group. The amide group is linked to a 1,4-dioxane ring, which is connected to a 1,4-dioxane-2-carboxamide group.</p>
D78	 <p>Chemical structure of compound D78: A complex molecule featuring a 1,2,3,4-tetrahydroquinolin-5(1H)-one core. This core is linked via a nitrogen atom to a 1,4-dioxane ring, which is further connected to a 1,4-dioxane-2-carboxamide group. The amide group is linked to a 1,4-dioxane ring, which is connected to a 1,4-dioxane-2-carboxamide group. The amide group is linked to a 1,4-dioxane ring, which is connected to a 1,4-dioxane-2-carboxamide group. The amide group is linked to a 1,4-dioxane ring, which is connected to a 1,4-dioxane-2-carboxamide group.</p>
D79	 <p>Chemical structure of compound D79: A complex molecule featuring a 1,2,3,4-tetrahydroquinolin-5(1H)-one core. This core is linked via a nitrogen atom to a 1,4-dioxane ring, which is further connected to a 1,4-dioxane-2-carboxamide group. The amide group is linked to a 1,4-dioxane ring, which is connected to a 1,4-dioxane-2-carboxamide group. The amide group is linked to a 1,4-dioxane ring, which is connected to a 1,4-dioxane-2-carboxamide group. The amide group is linked to a 1,4-dioxane ring, which is connected to a 1,4-dioxane-2-carboxamide group.</p>

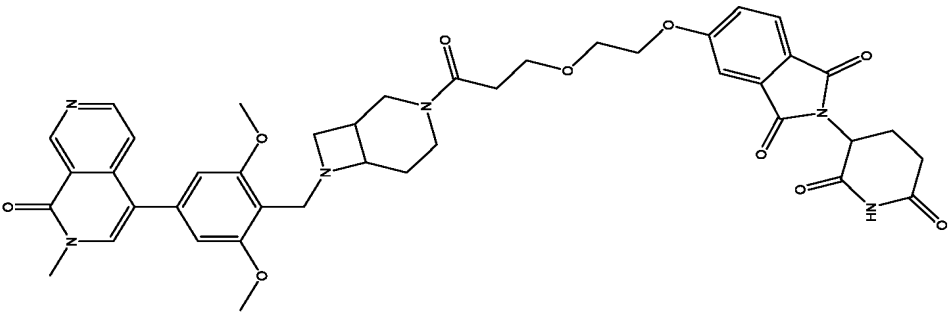
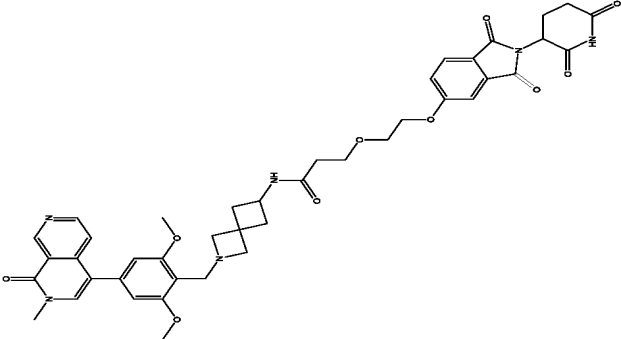
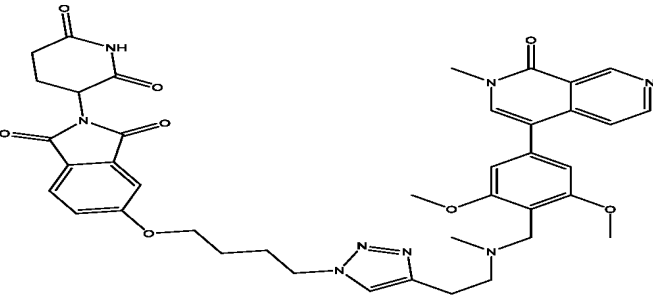
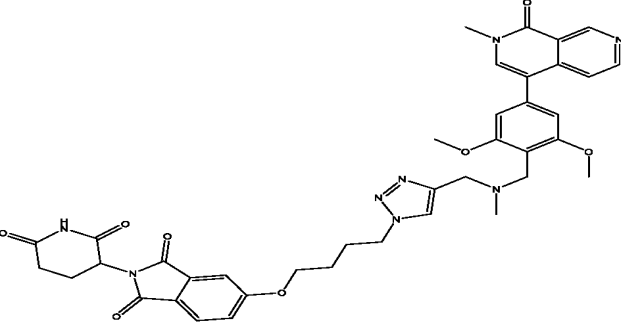
Compound No.	Structure
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D81	
D82	
D83	

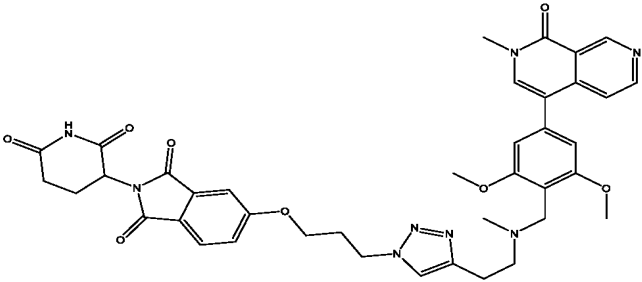
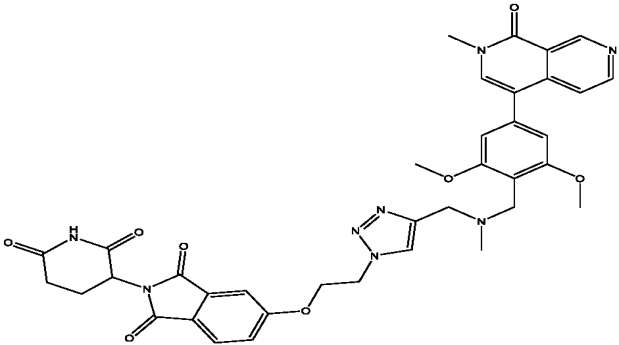
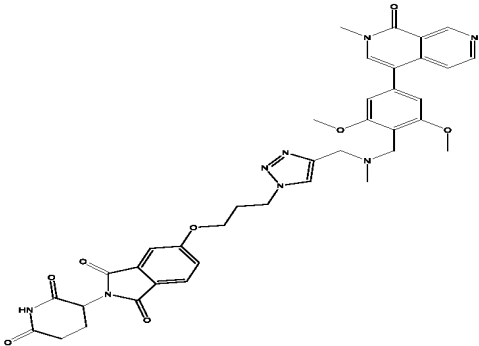
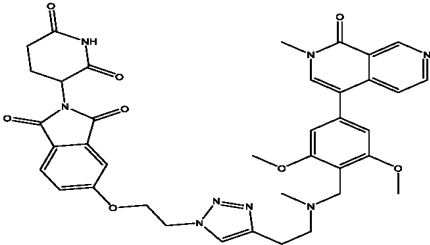
Compound No.	Structure
D84	 <p>Chemical structure of compound D84. It features a 4-methoxyphenyl ring substituted with a 2-methyl-4-oxoquinoline-3-yl group and a 1,4-dioxane-5-carbonyl group. The 1,4-dioxane ring is further substituted with a 2-methyl-4-oxoquinoline-3-yl group. The 4-methoxyphenyl ring is also substituted with a 2-methyl-4-oxoquinoline-3-yl group.</p>
D85	 <p>Chemical structure of compound D85. It features a 4-methoxyphenyl ring substituted with a 2-methyl-4-oxoquinoline-3-yl group and a 1,4-dioxane-5-carbonyl group. The 1,4-dioxane ring is further substituted with a 2-methyl-4-oxoquinoline-3-yl group. The 4-methoxyphenyl ring is also substituted with a 2-methyl-4-oxoquinoline-3-yl group.</p>
D86	 <p>Chemical structure of compound D86. It features a 4-methoxyphenyl ring substituted with a 2-methyl-4-oxoquinoline-3-yl group and a 1,4-dioxane-5-carbonyl group. The 1,4-dioxane ring is further substituted with a 2-methyl-4-oxoquinoline-3-yl group. The 4-methoxyphenyl ring is also substituted with a 2-methyl-4-oxoquinoline-3-yl group.</p>
D87	 <p>Chemical structure of compound D87. It features a 4-methoxyphenyl ring substituted with a 2-methyl-4-oxoquinoline-3-yl group and a 1,4-dioxane-5-carbonyl group. The 1,4-dioxane ring is further substituted with a 2-methyl-4-oxoquinoline-3-yl group. The 4-methoxyphenyl ring is also substituted with a 2-methyl-4-oxoquinoline-3-yl group.</p>

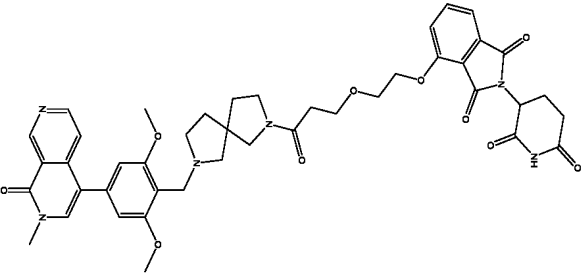
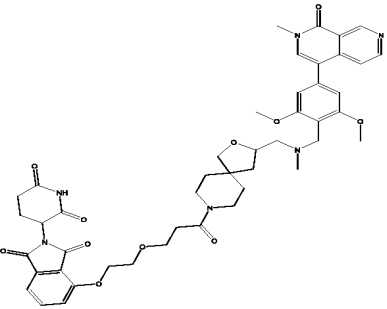
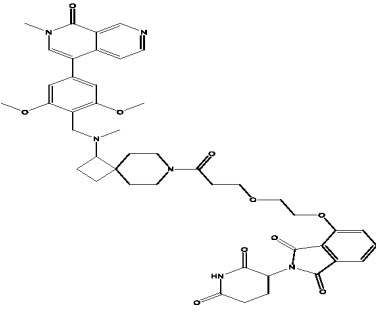
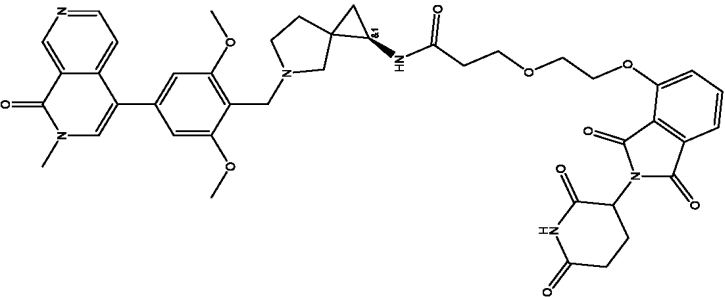
Compound No.	Structure
D88	
D89	
D90	
D91	

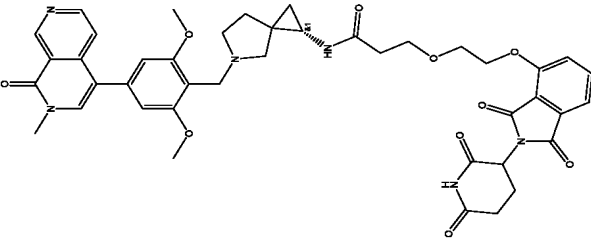
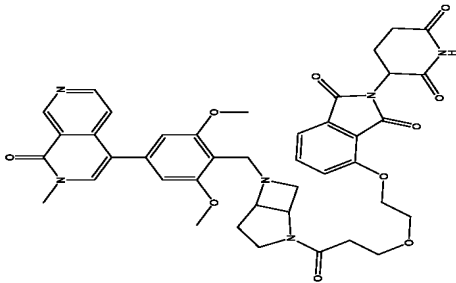
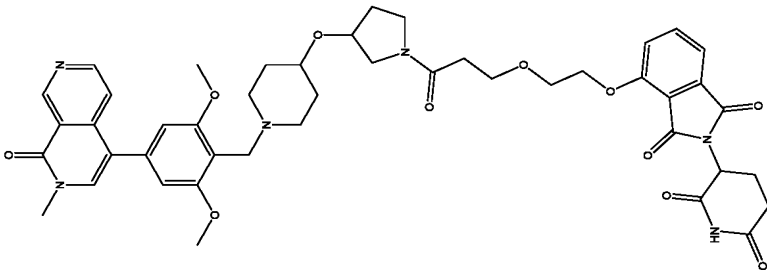
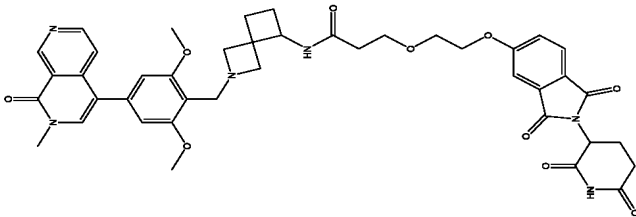
Compound No.	Structure
D92	 <p>Chemical structure of compound D92. It features a 7-methoxy-2-methyl-1H-benzimidazole-5-carbonyl group connected via a methylene bridge to a 2,6-dimethoxyphenyl ring. This phenyl ring is further connected via a methylene bridge to a bicyclic amine system (8-azabicyclo[3.2.1]octane). The nitrogen of this bicyclic system is linked via a carbonyl group to a 3-(2-(2-(2-oxo-2,3,4,5-tetrahydro-1H-benzimidazol-5-yl)ethoxy)propyl)propanoate chain.</p>
D93	 <p>Chemical structure of compound D93. It features a 7-methoxy-2-methyl-1H-benzimidazole-5-carbonyl group connected via a methylene bridge to a 2,6-dimethoxyphenyl ring. This phenyl ring is further connected via a methylene bridge to a bicyclic amine system (8-azabicyclo[3.2.1]octane). The nitrogen of this bicyclic system is linked via a carbonyl group to a 3-(2-(2-(2-oxo-2,3,4,5-tetrahydro-1H-benzimidazol-5-yl)ethoxy)propyl)propanoate chain.</p>
D94	 <p>Chemical structure of compound D94. It features a 7-methoxy-2-methyl-1H-benzimidazole-5-carbonyl group connected via a methylene bridge to a 2,6-dimethoxyphenyl ring. This phenyl ring is further connected via a methylene bridge to a bicyclic amine system (8-azabicyclo[3.2.1]octane). The nitrogen of this bicyclic system is linked via a carbonyl group to a 3-(2-(2-(2-oxo-2,3,4,5-tetrahydro-1H-benzimidazol-5-yl)ethoxy)propyl)propanoate chain.</p>
D95	 <p>Chemical structure of compound D95. It features a 7-methoxy-2-methyl-1H-benzimidazole-5-carbonyl group connected via a methylene bridge to a 2,6-dimethoxyphenyl ring. This phenyl ring is further connected via a methylene bridge to a bicyclic amine system (8-azabicyclo[3.2.1]octane). The nitrogen of this bicyclic system is linked via a carbonyl group to a 3-(2-(2-(2-oxo-2,3,4,5-tetrahydro-1H-benzimidazol-5-yl)ethoxy)propyl)propanoate chain.</p>

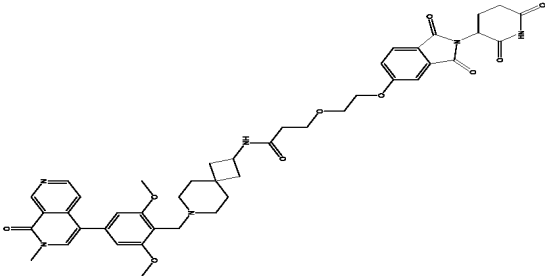
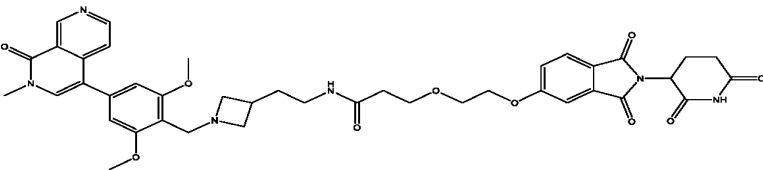
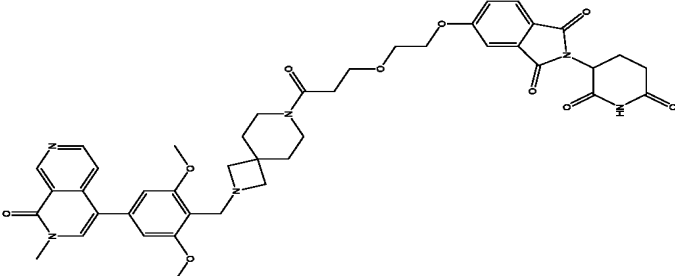
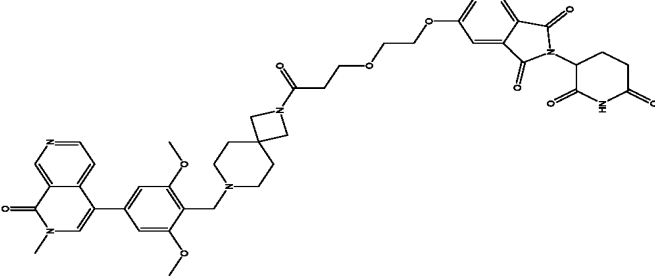
Compound No.	Structure
D96	 <p>Chemical structure of compound D96, featuring a 3,4-dimethoxyphenyl group connected via a methylene bridge to a 1,4-dioxane ring, which is further linked to a 1,4-dioxane ring containing a carbonyl group, and finally to a 1,4-dioxane ring with a carbonyl group.</p>
D97	 <p>Chemical structure of compound D97, featuring a 3,4-dimethoxyphenyl group connected via a methylene bridge to a 1,4-dioxane ring, which is further linked to a 1,4-dioxane ring containing a carbonyl group, and finally to a 1,4-dioxane ring with a carbonyl group.</p>
D98	 <p>Chemical structure of compound D98, featuring a 3,4-dimethoxyphenyl group connected via a methylene bridge to a 1,4-dioxane ring, which is further linked to a 1,4-dioxane ring containing a carbonyl group, and finally to a 1,4-dioxane ring with a carbonyl group.</p>
D99	 <p>Chemical structure of compound D99, featuring a 3,4-dimethoxyphenyl group connected via a methylene bridge to a 1,4-dioxane ring, which is further linked to a 1,4-dioxane ring containing a carbonyl group, and finally to a 1,4-dioxane ring with a carbonyl group.</p>

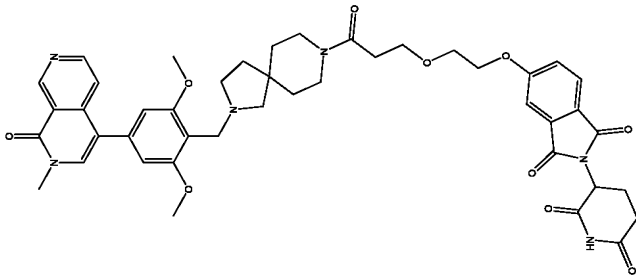
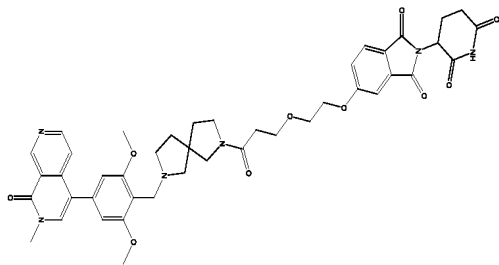
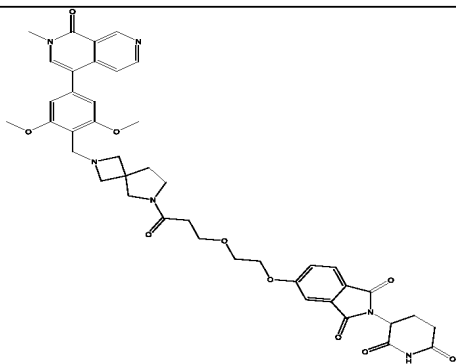
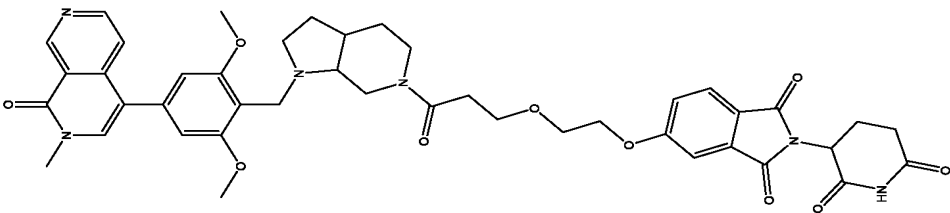
Compound No.	Structure
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D101	
D102	
D103	

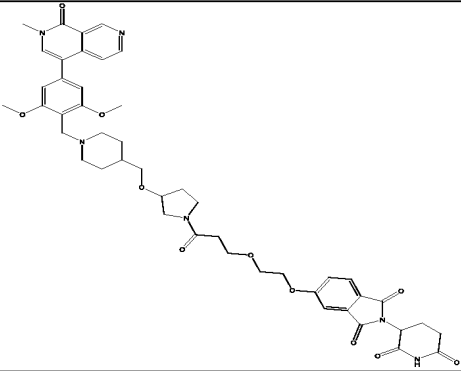
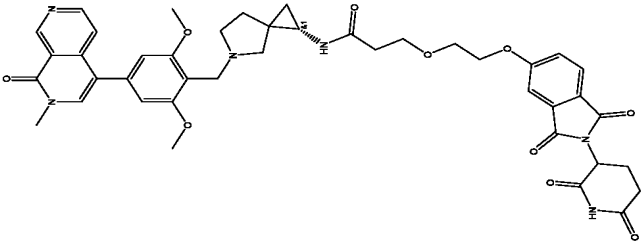
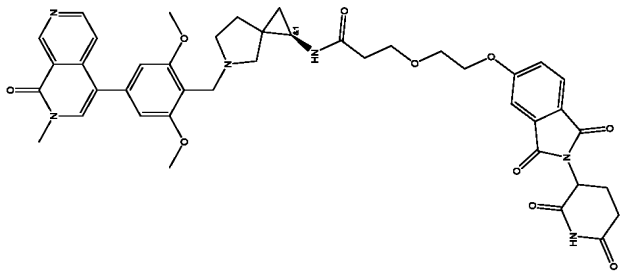
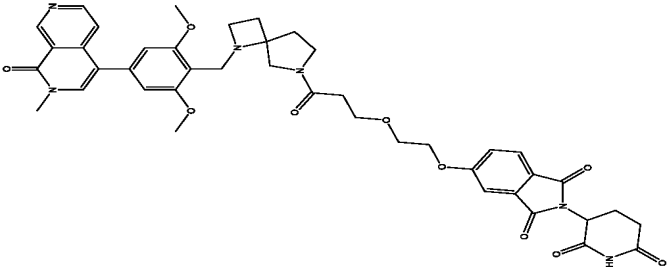
Compound No.	Structure
D104	
D105	
D106	
D107	

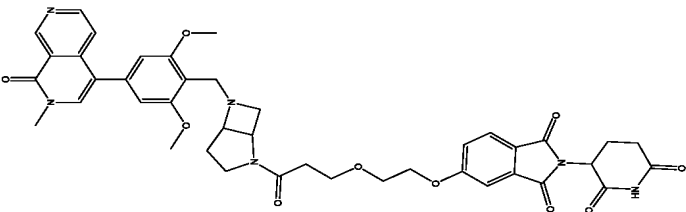
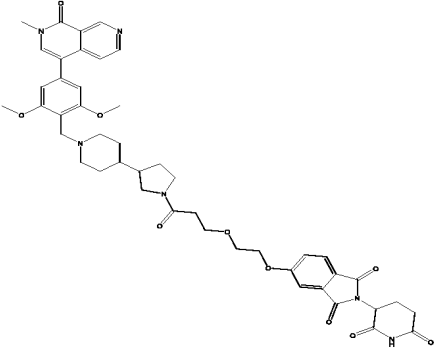
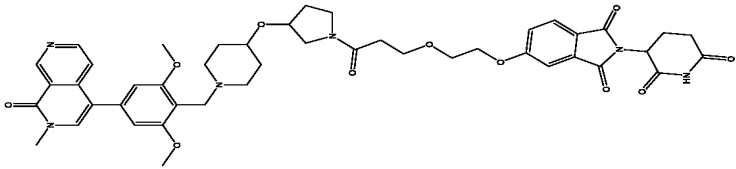
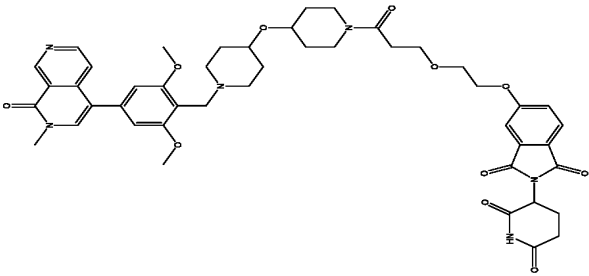
Compound No.	Structure
D108	
D109	
D110	
D111	

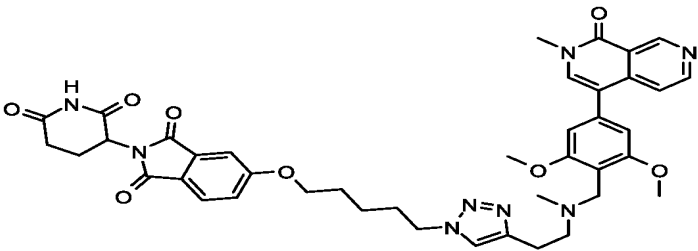
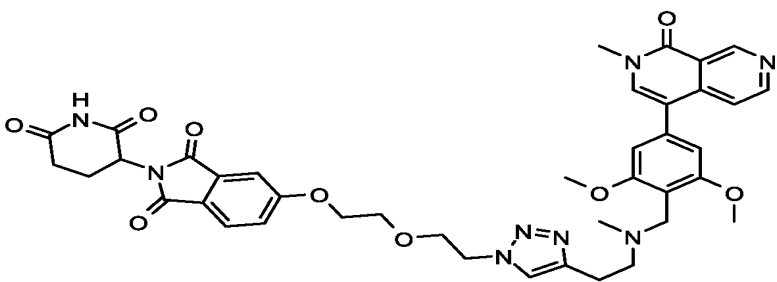
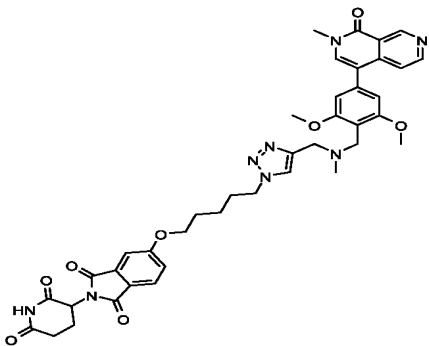
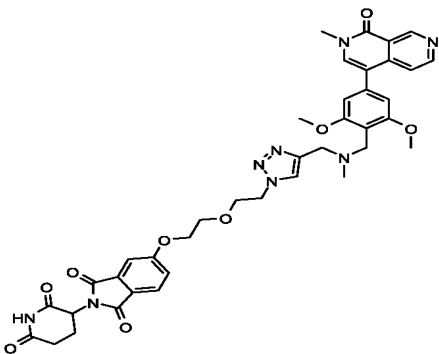
Compound No.	Structure
D112	 <p>Chemical structure of compound D112. It features a 2,6-dimethyl-4-(3,4,5-trimethoxyphenyl)quinazolin-4(1H)-one moiety connected via a methylene group to a 1,3-dioxolane ring. This ring is further connected to a 1,3-bis(2-methoxyethyl)urea linker, which is then connected to a 1,3-bis(2-methoxyethyl)urea moiety. The terminal part of the molecule is a 1,3-bis(2-methoxyethyl)urea moiety connected to a 1,3-bis(2-methoxyethyl)urea moiety.</p>
D113	 <p>Chemical structure of compound D113. It features a 2,6-dimethyl-4-(3,4,5-trimethoxyphenyl)quinazolin-4(1H)-one moiety connected via a methylene group to a 1,3-dioxolane ring. This ring is further connected to a 1,3-bis(2-methoxyethyl)urea linker, which is then connected to a 1,3-bis(2-methoxyethyl)urea moiety. The terminal part of the molecule is a 1,3-bis(2-methoxyethyl)urea moiety connected to a 1,3-bis(2-methoxyethyl)urea moiety.</p>
D114	 <p>Chemical structure of compound D114. It features a 2,6-dimethyl-4-(3,4,5-trimethoxyphenyl)quinazolin-4(1H)-one moiety connected via a methylene group to a 1,3-dioxolane ring. This ring is further connected to a 1,3-bis(2-methoxyethyl)urea linker, which is then connected to a 1,3-bis(2-methoxyethyl)urea moiety. The terminal part of the molecule is a 1,3-bis(2-methoxyethyl)urea moiety connected to a 1,3-bis(2-methoxyethyl)urea moiety.</p>
D115	 <p>Chemical structure of compound D115. It features a 2,6-dimethyl-4-(3,4,5-trimethoxyphenyl)quinazolin-4(1H)-one moiety connected via a methylene group to a 1,3-dioxolane ring. This ring is further connected to a 1,3-bis(2-methoxyethyl)urea linker, which is then connected to a 1,3-bis(2-methoxyethyl)urea moiety. The terminal part of the molecule is a 1,3-bis(2-methoxyethyl)urea moiety connected to a 1,3-bis(2-methoxyethyl)urea moiety.</p>

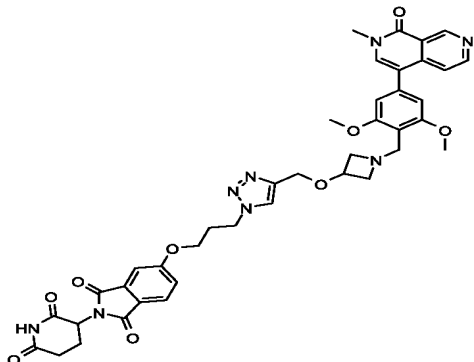
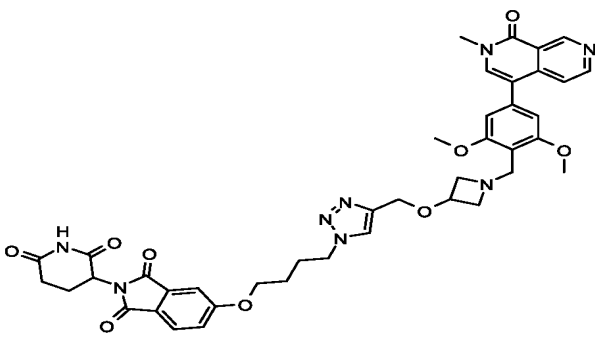
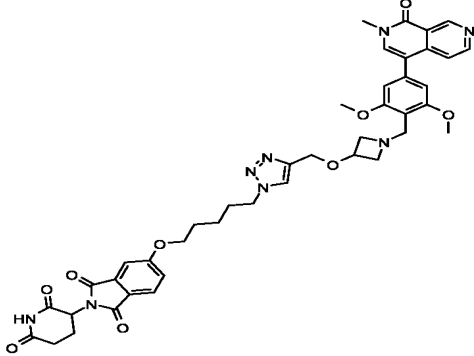
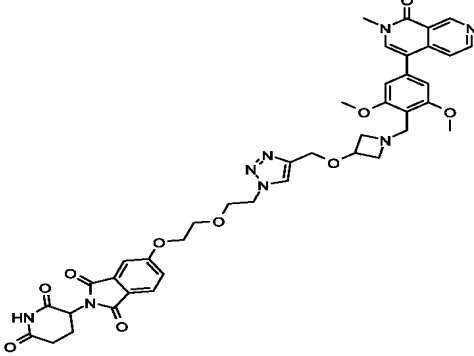
Compound No.	Structure
D116	 <p>Chemical structure of compound D116: A complex molecule featuring a 4-methoxyphenyl ring substituted with a 2-methyl-4-oxoquinoline-3-yl group and a 4-methoxyphenyl group. This is linked via a methylene bridge to a 1,4-dioxane ring, which is further connected to a 4-oxo-1,4-dihydroquinoline-3-yl group through a 4-oxo-1,4-dihydroquinoline-3-yl group.</p>
D117	 <p>Chemical structure of compound D117: A complex molecule featuring a 4-methoxyphenyl ring substituted with a 2-methyl-4-oxoquinoline-3-yl group and a 4-methoxyphenyl group. This is linked via a methylene bridge to a 1,4-dioxane ring, which is further connected to a 4-oxo-1,4-dihydroquinoline-3-yl group through a 4-oxo-1,4-dihydroquinoline-3-yl group.</p>
D118	 <p>Chemical structure of compound D118: A complex molecule featuring a 4-methoxyphenyl ring substituted with a 2-methyl-4-oxoquinoline-3-yl group and a 4-methoxyphenyl group. This is linked via a methylene bridge to a 1,4-dioxane ring, which is further connected to a 4-oxo-1,4-dihydroquinoline-3-yl group through a 4-oxo-1,4-dihydroquinoline-3-yl group.</p>
D119	 <p>Chemical structure of compound D119: A complex molecule featuring a 4-methoxyphenyl ring substituted with a 2-methyl-4-oxoquinoline-3-yl group and a 4-methoxyphenyl group. This is linked via a methylene bridge to a 1,4-dioxane ring, which is further connected to a 4-oxo-1,4-dihydroquinoline-3-yl group through a 4-oxo-1,4-dihydroquinoline-3-yl group.</p>

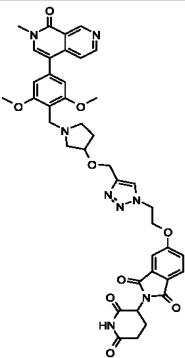
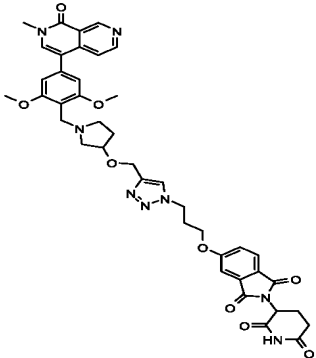
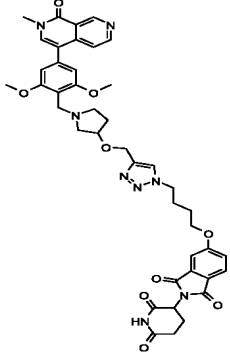
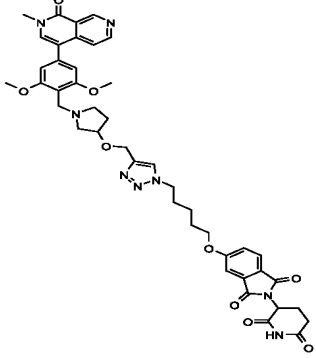
Compound No.	Structure
D120	
D121	
D122	
D123	

Compound No.	Structure
D124	
D125	
D126	
D127	

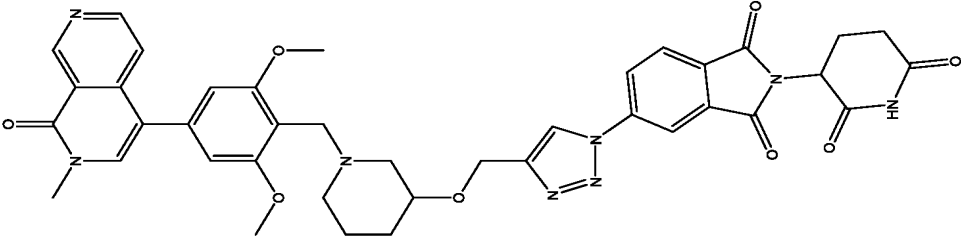
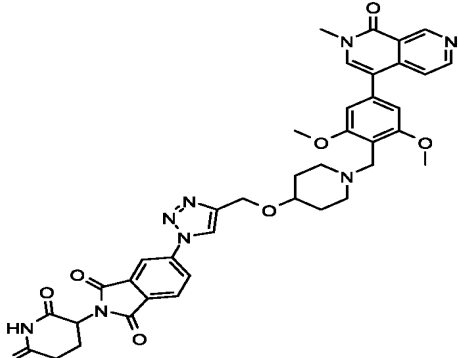
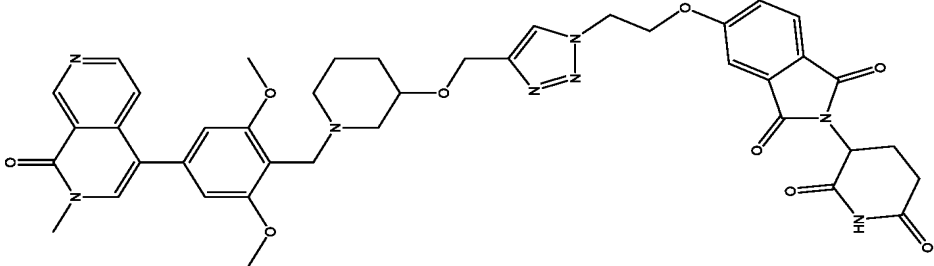
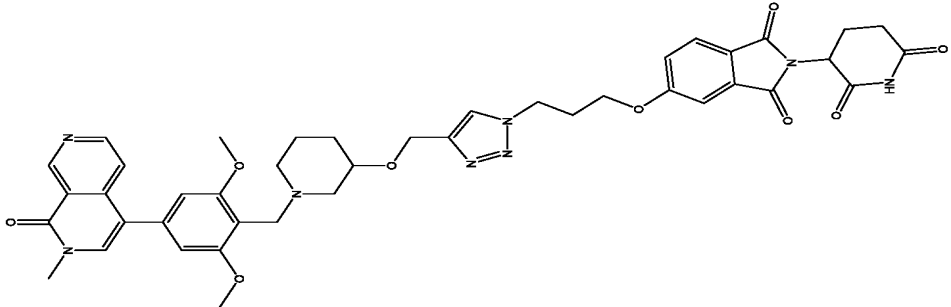
Compound No.	Structure
D128	
D129	
D130	
D131	

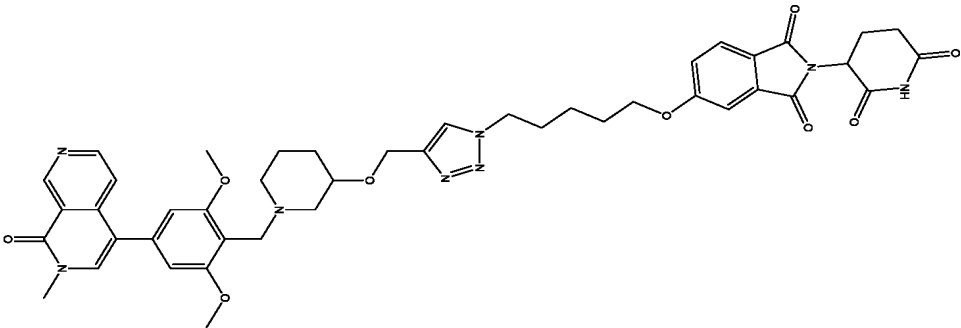
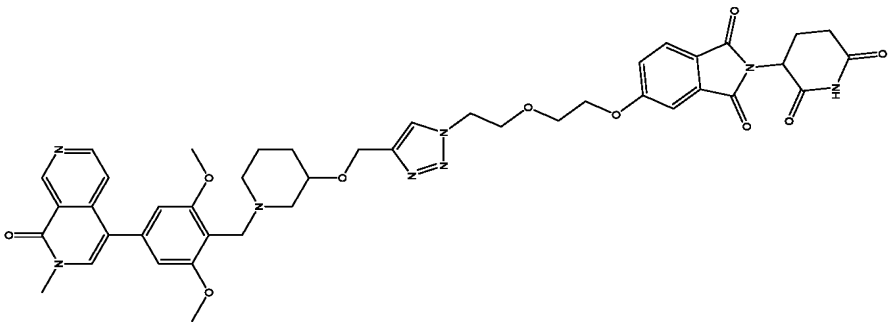
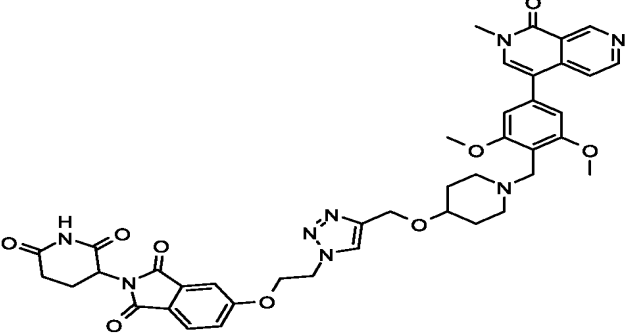
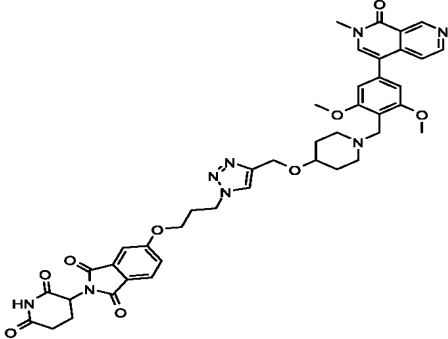
Compound No.	Structure
D132	
D133	
D134	
D135	

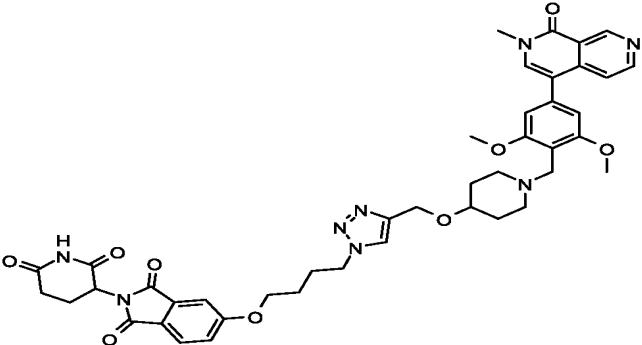
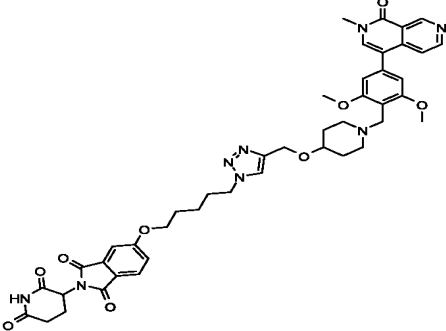
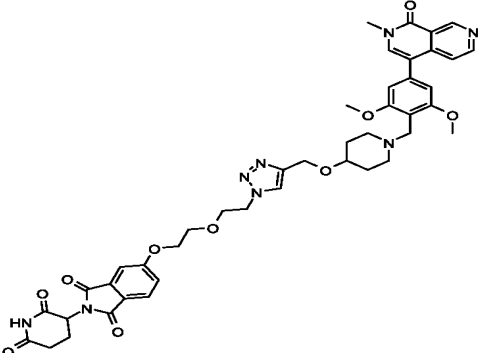
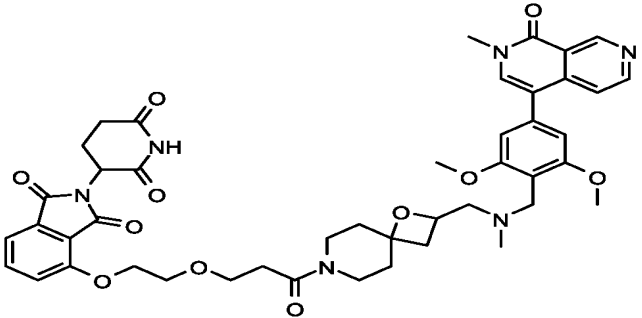
Compound No.	Structure
D136	
D137	
D138	
D139	

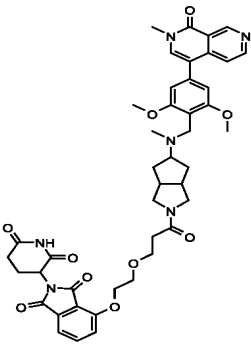
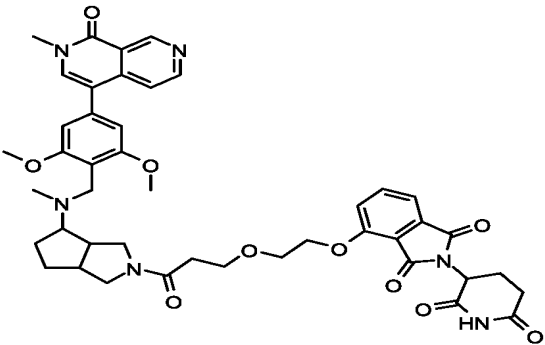
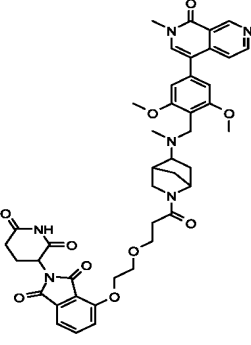
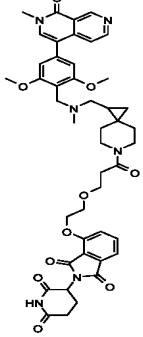
Compound No.	Structure
D140	
D141	
D142	
D143	

[illegible]

Compound No.	Structure
D148	
D149	
D150	
D151	

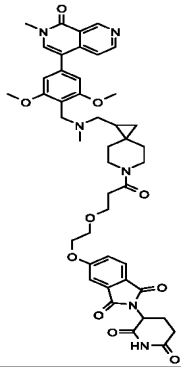
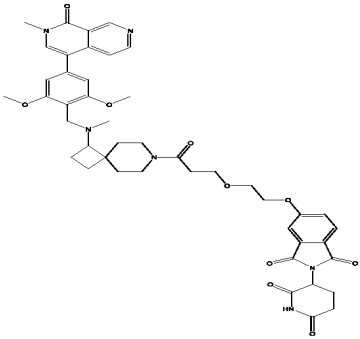
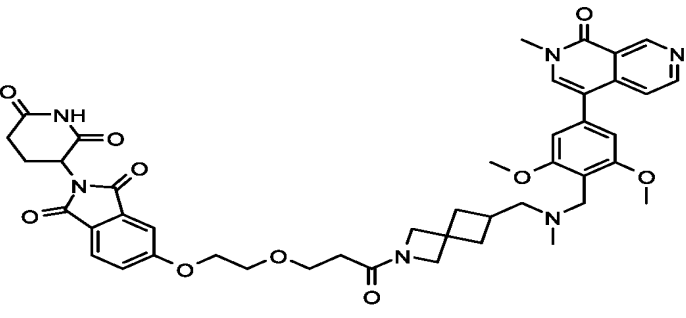
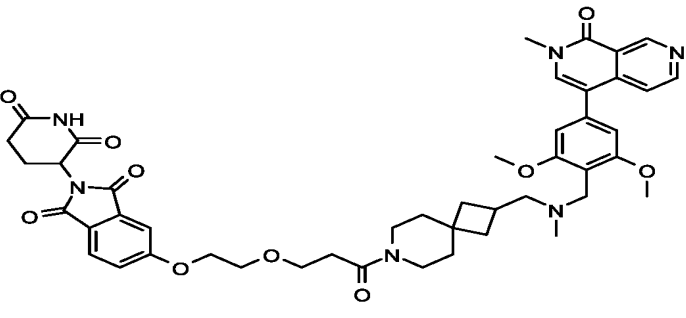
Compound No.	Structure
D152	
D153	
D154	
D155	

Compound No.	Structure
D156	
D157	
D158	
D159	

Compound No.	Structure
D160	
D161	
D162	
D163	

[illegible]

Compound No.	Structure
D168	
D169	
D170	
D171	

Compound No.	Structure
D172	
D173	
D174	
D175	

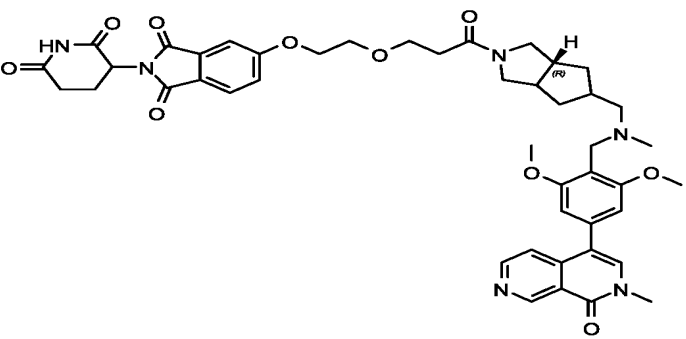
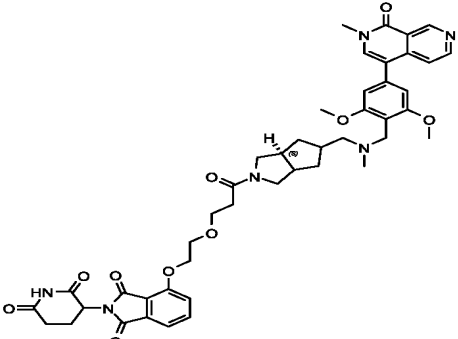
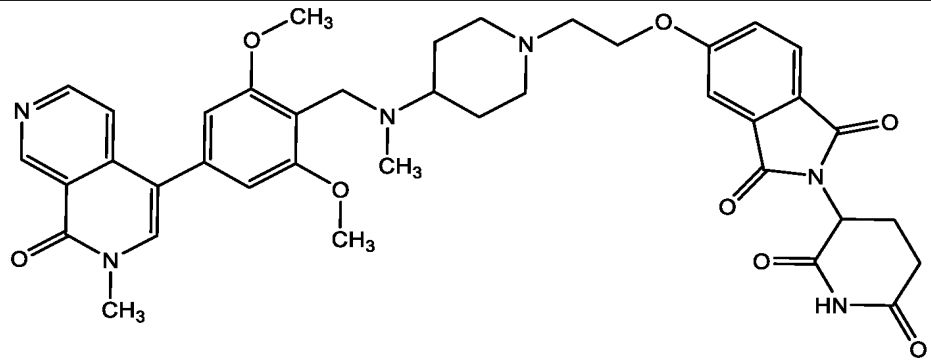
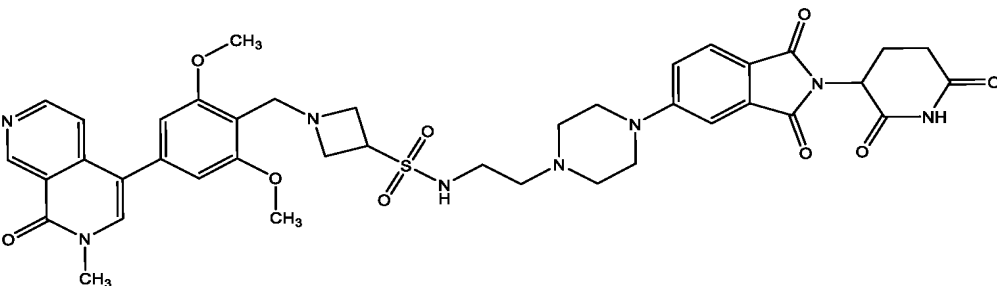
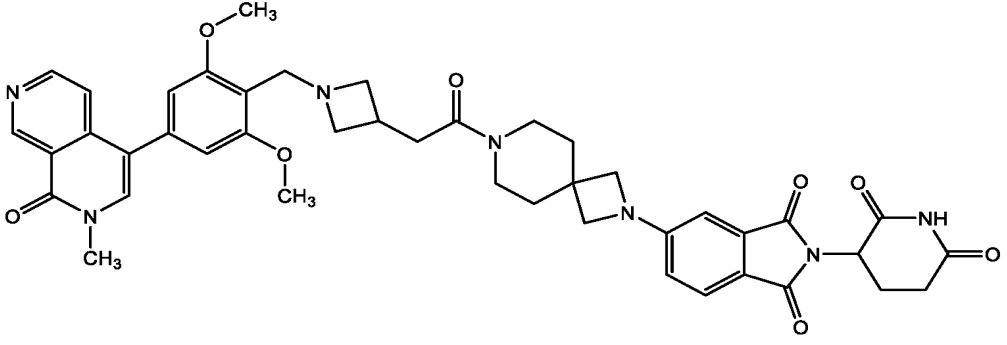
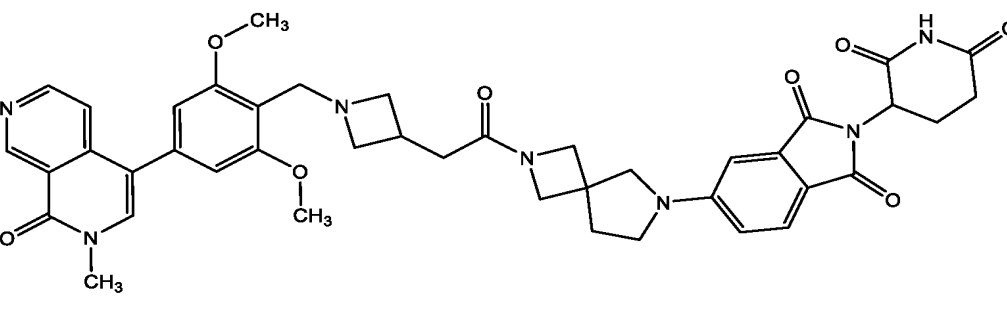
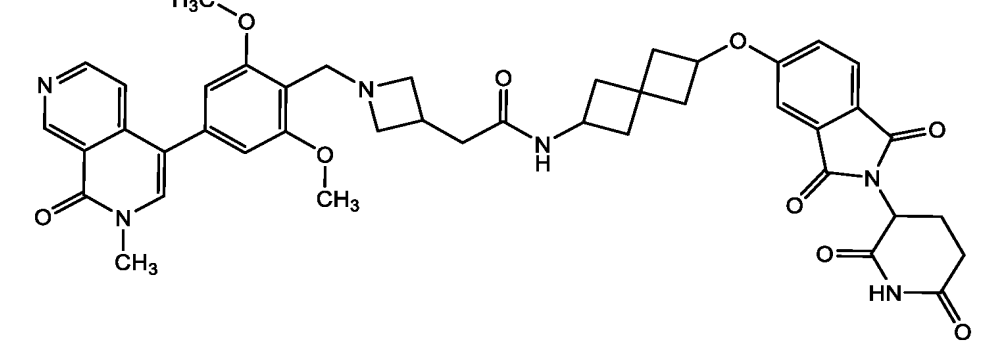
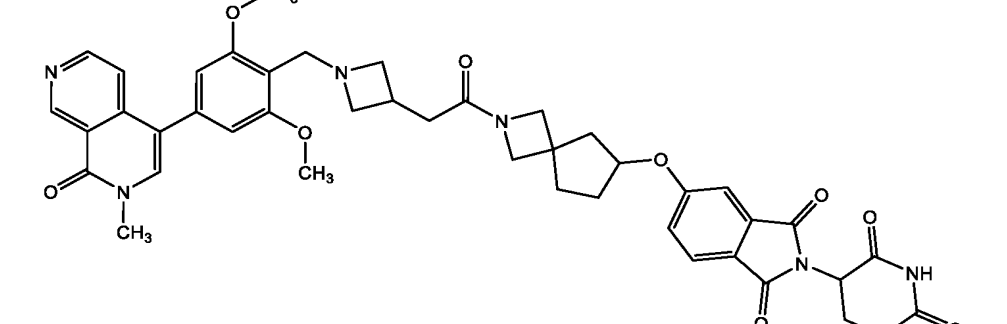
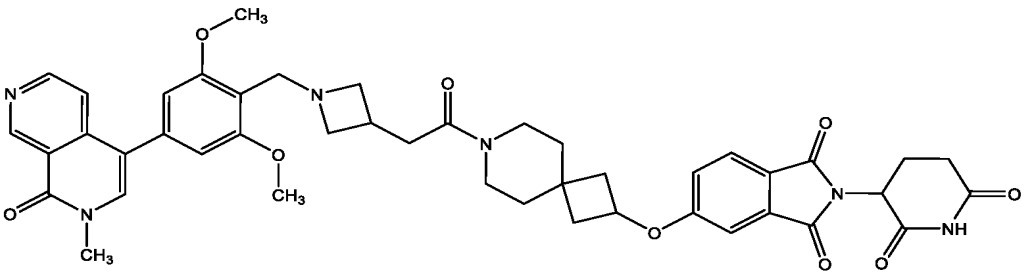
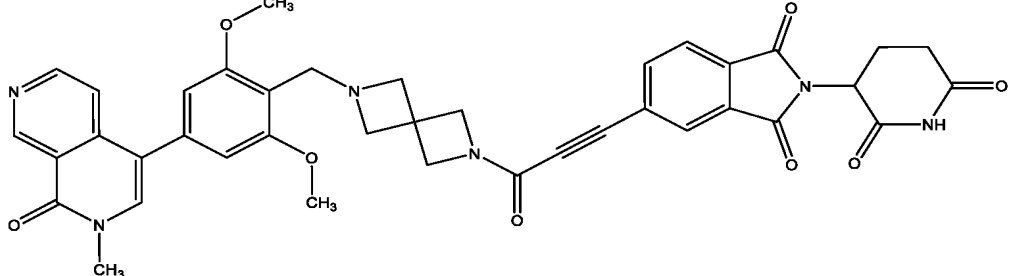
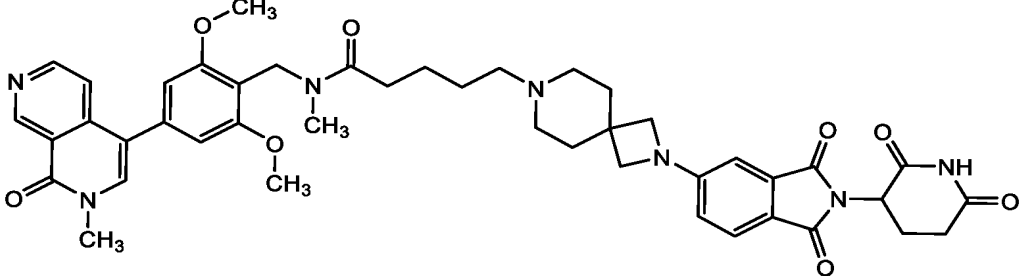
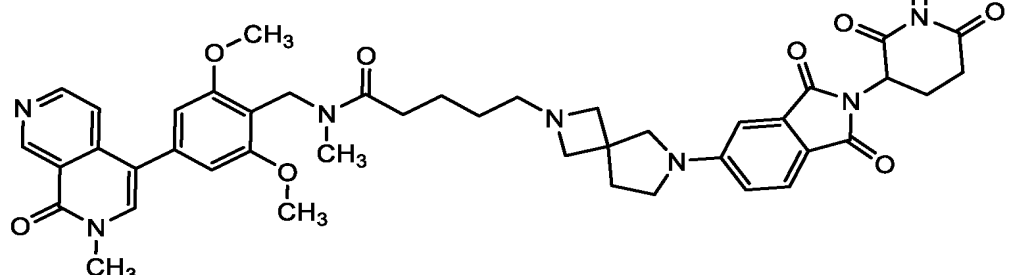
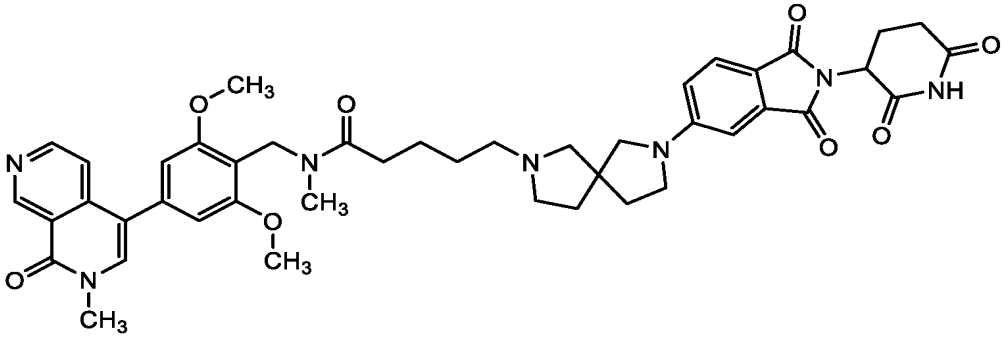
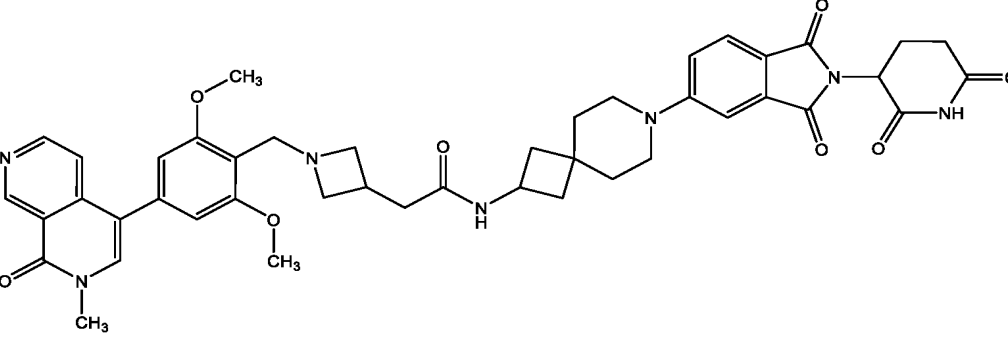
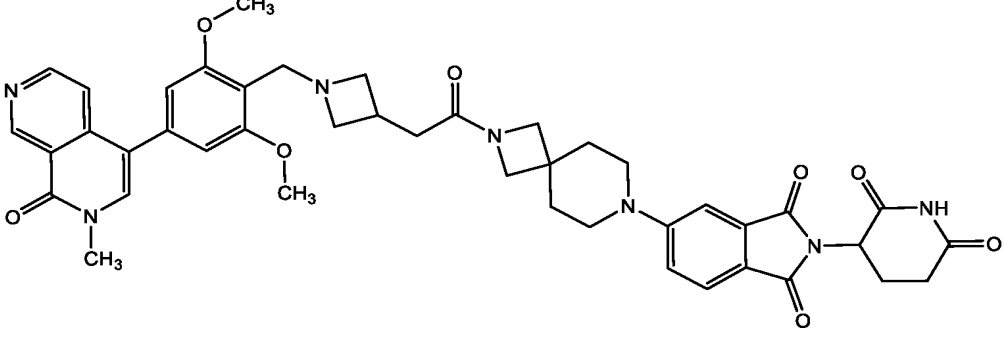
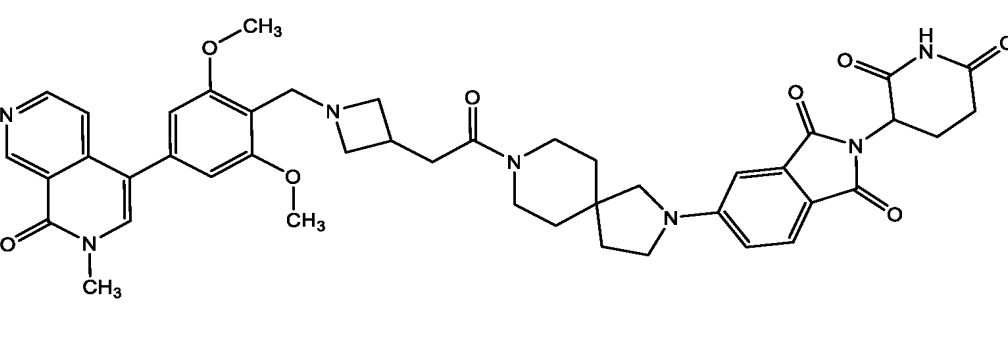
Compound No.	Structure
D176	
D177	

Table 1B. Compounds D178-D371 of the Disclosure

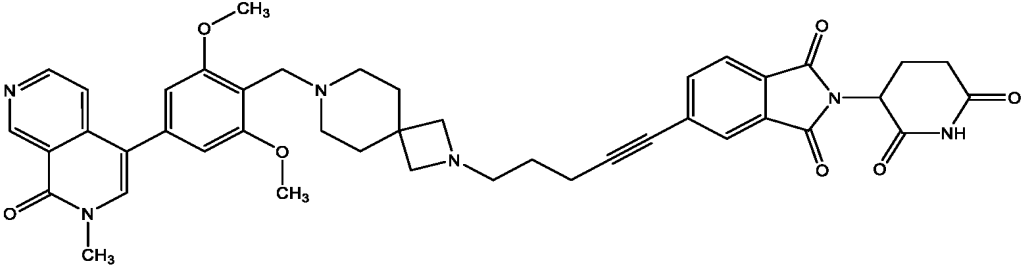
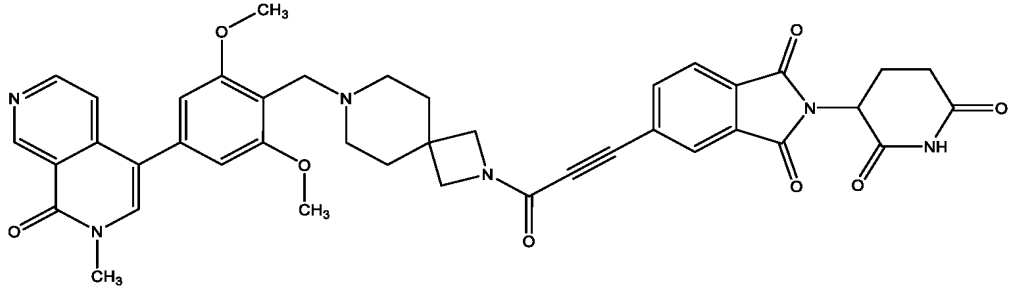
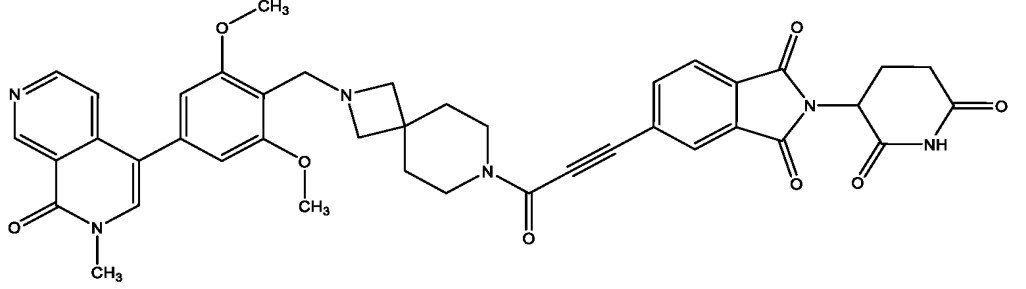
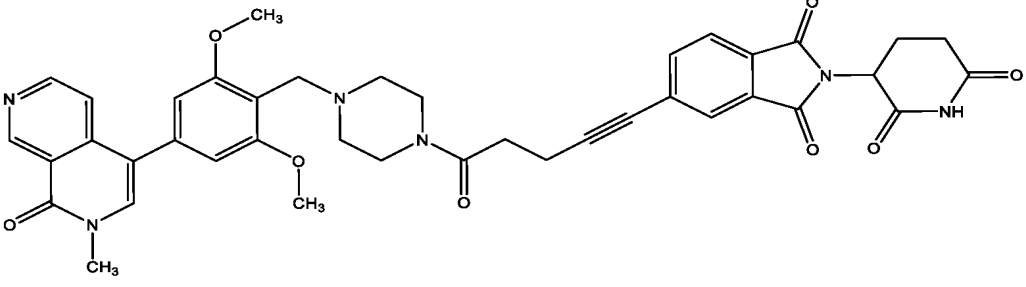
Compound No.	Structure
D178	
D179	

Compound No.	Structure
D180	
D181	
D182	
D183	

Compound No.	Structure
D184	
D185	
D186	
D187	

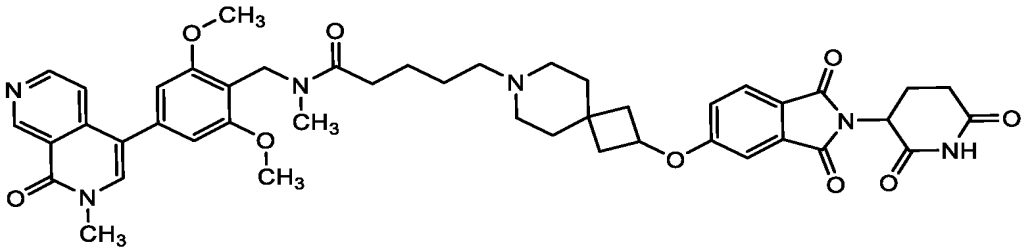
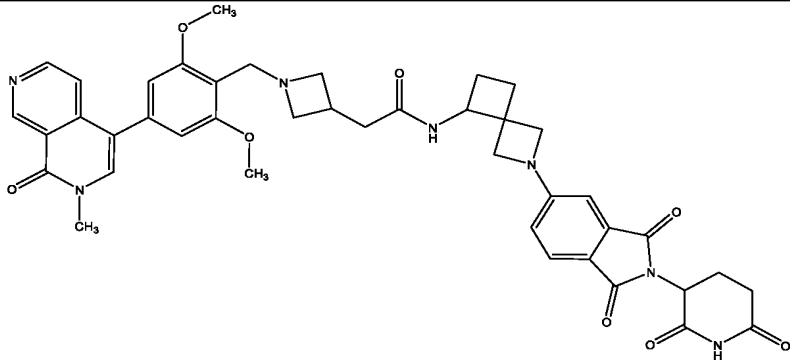
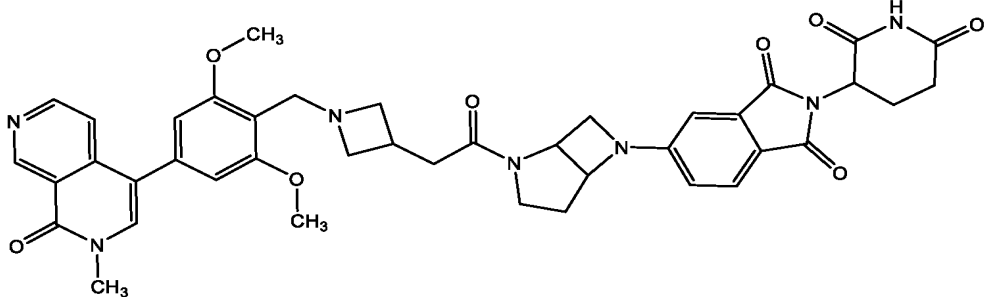
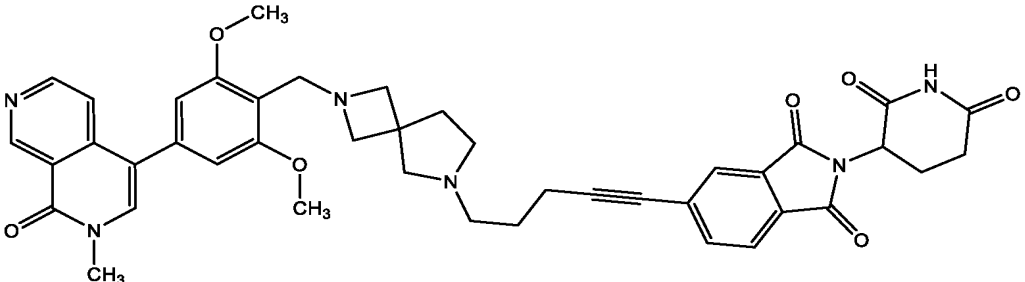
Compound No.	Structure
D188	
D189	
D190	
D191	

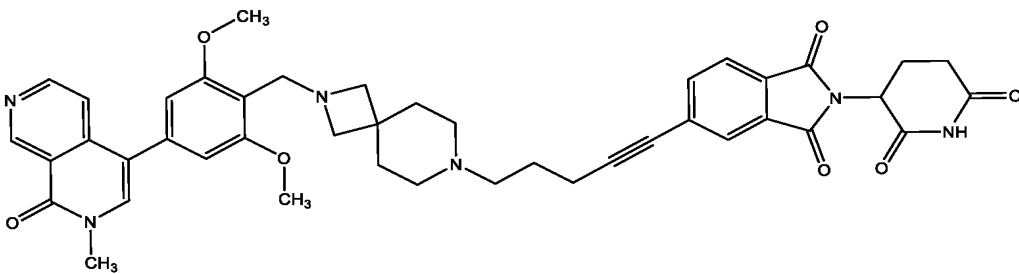
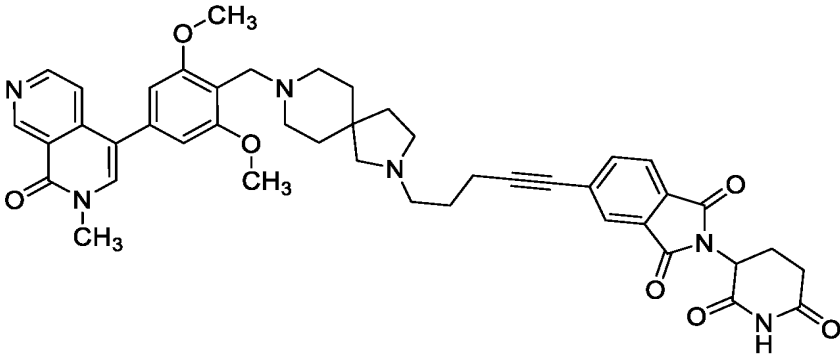
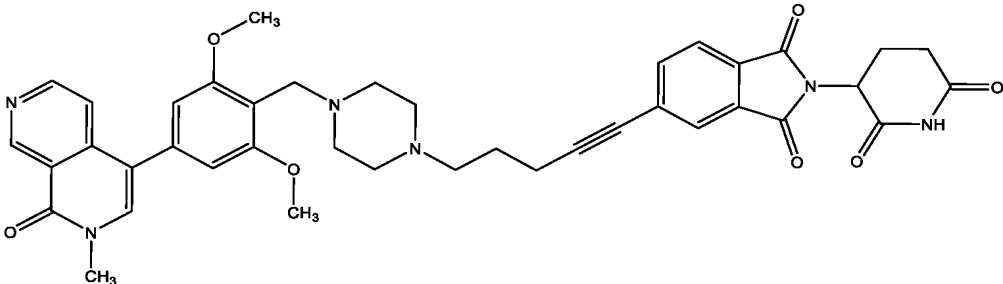
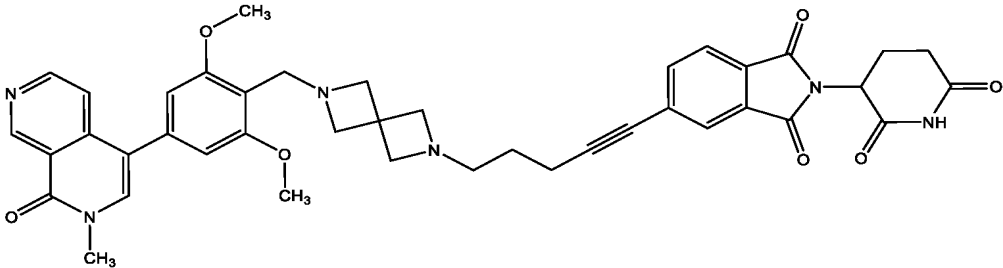
[illegible]

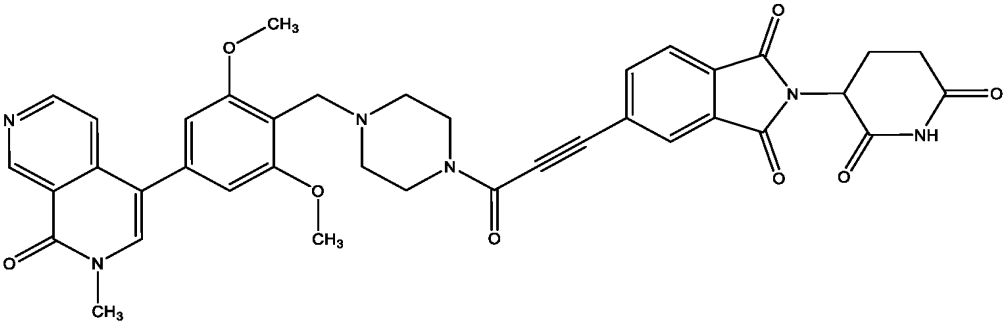
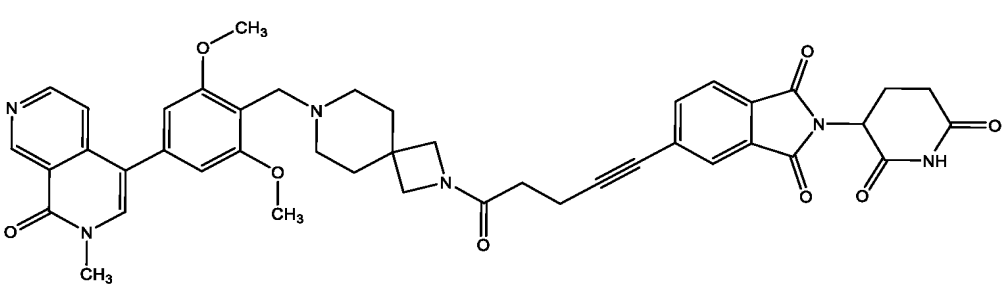
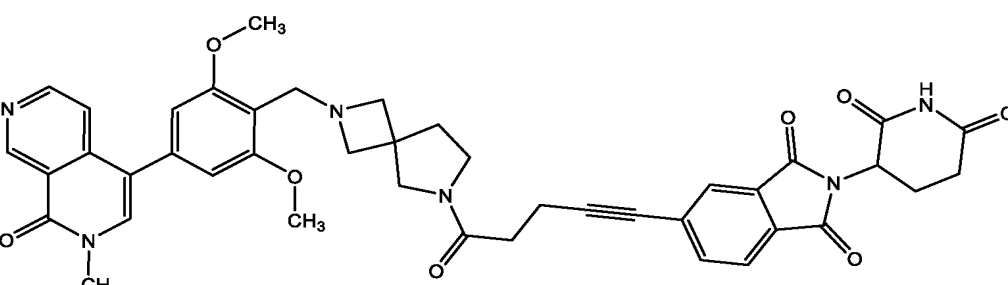
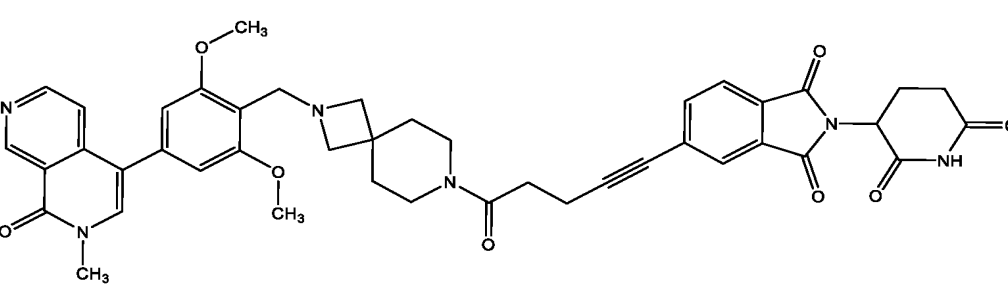
Compound No.	Structure
D196	
D197	
D198	
D199	

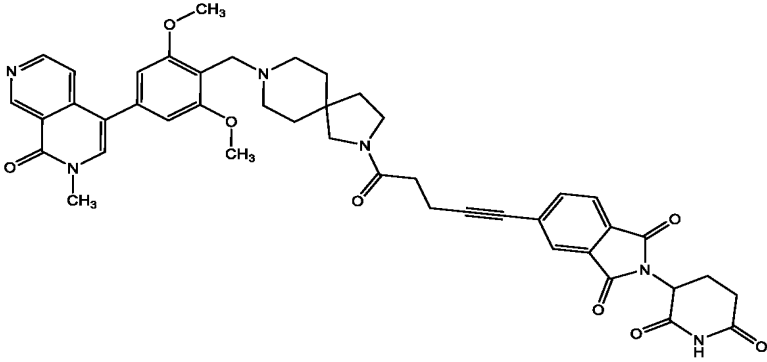
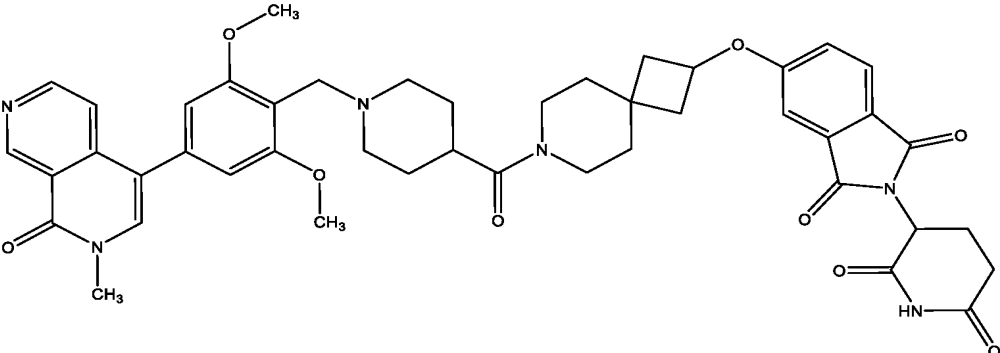
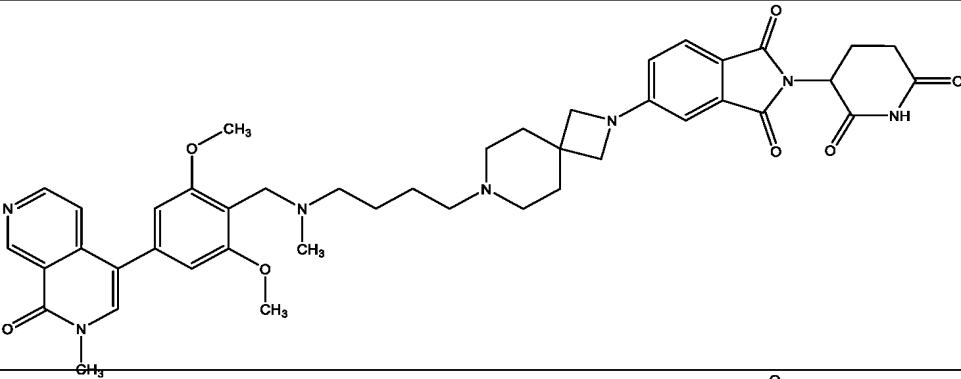
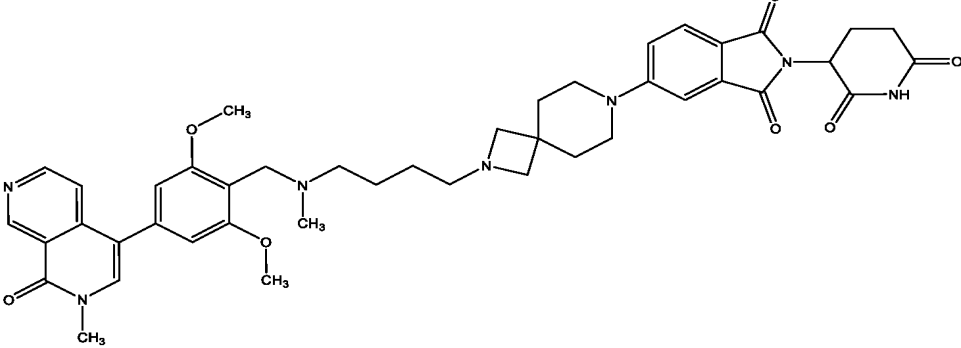
Compound No.	Structure
D200	
D201	
D202	
D203	

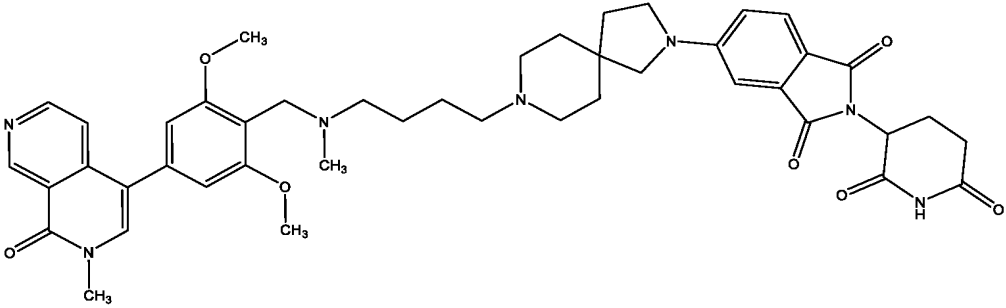
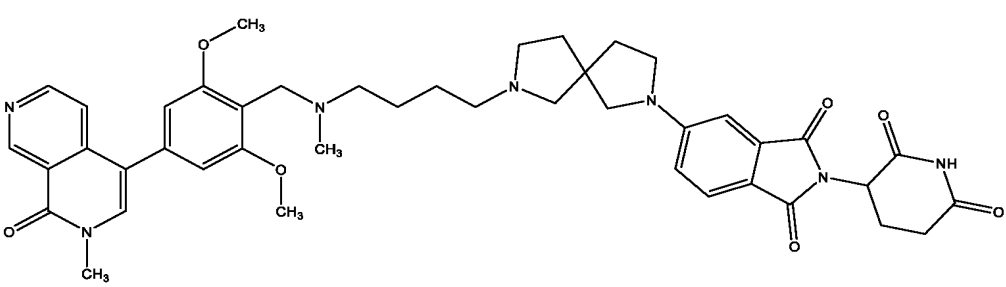
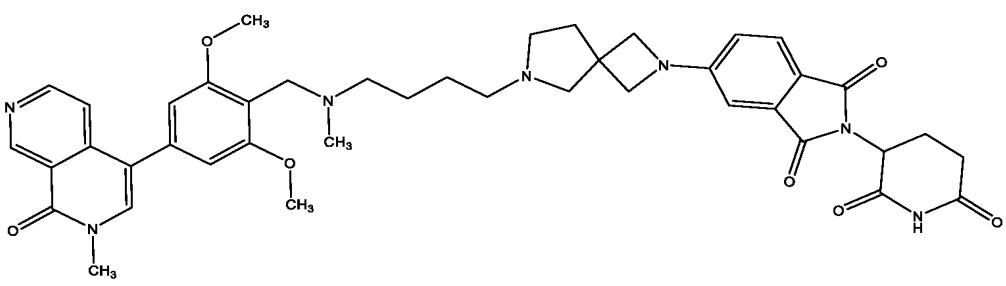
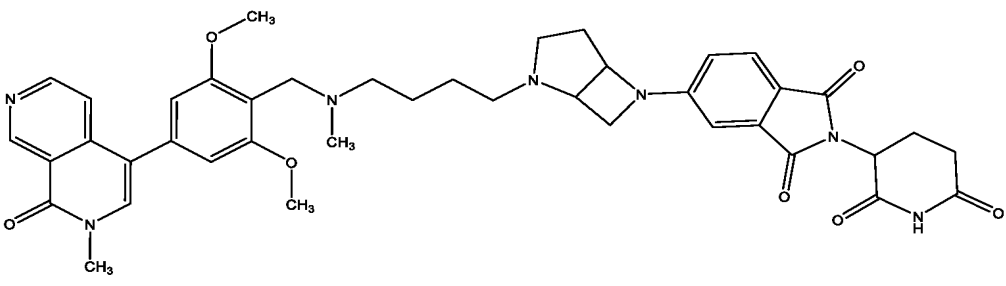
Compound No.	Structure
D204	
D205	
D206	
D207	

Compound No.	Structure
D208	
D209	
D210	
D211	

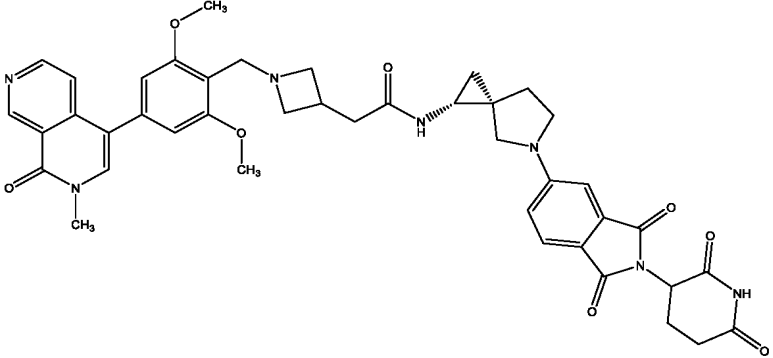
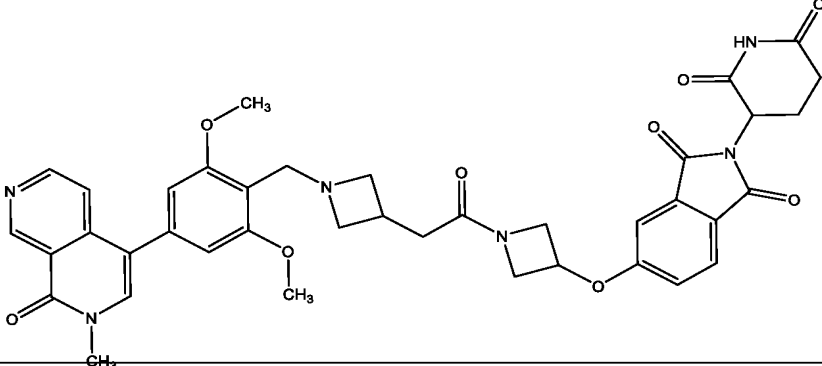
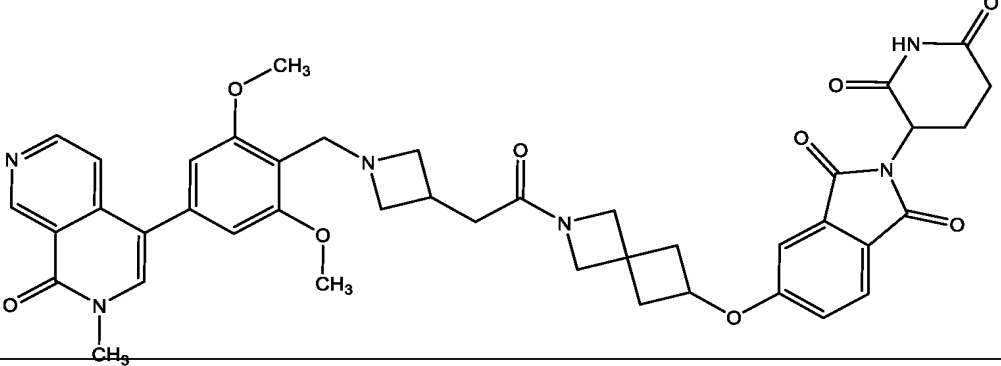
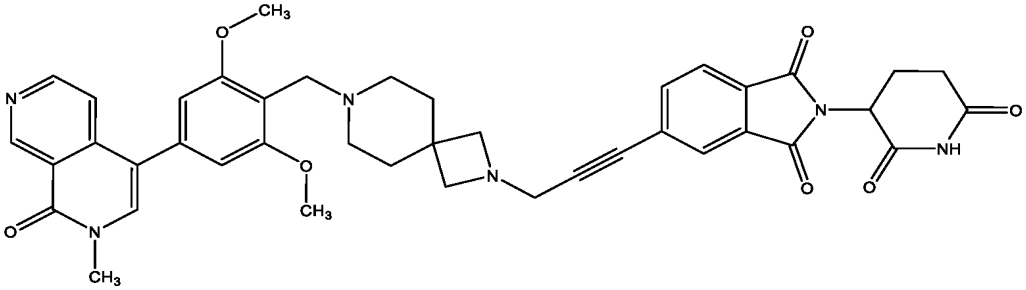
Compound No.	Structure
D212	
D213	
D214	
D215	

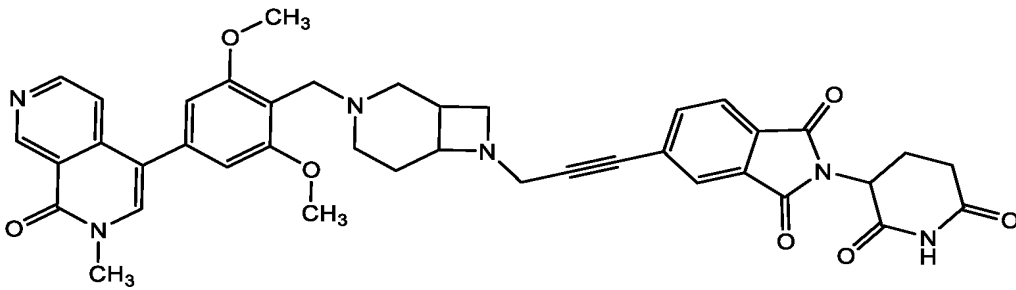
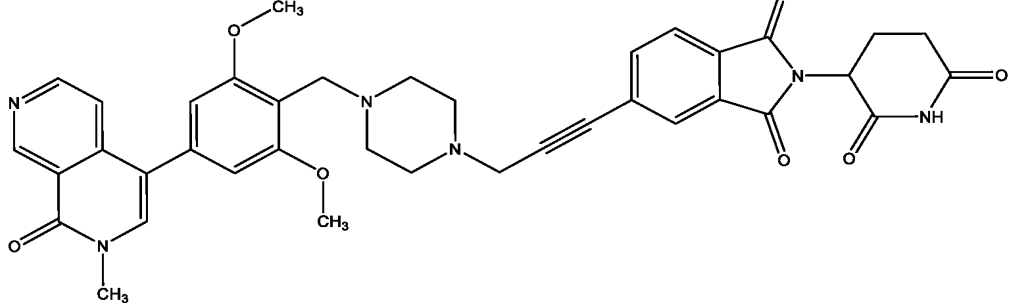
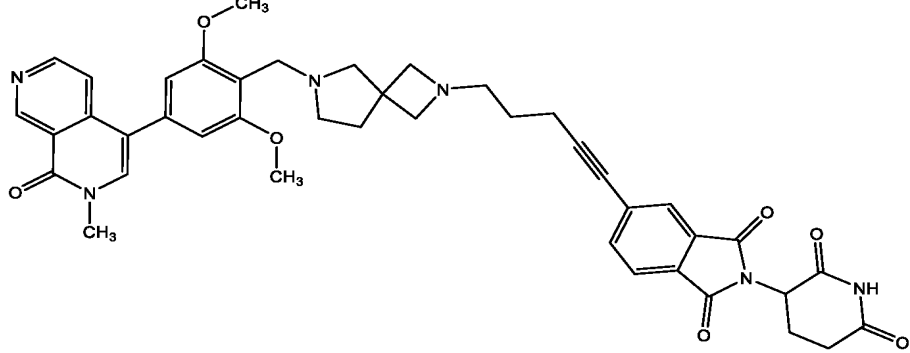
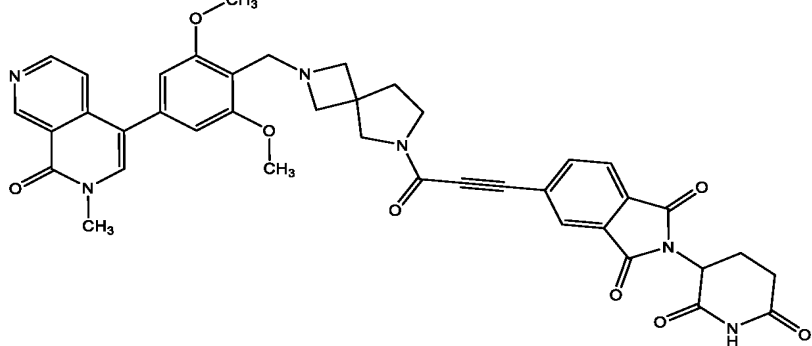
Compound No.	Structure
D216	
D217	
D218	
D219	

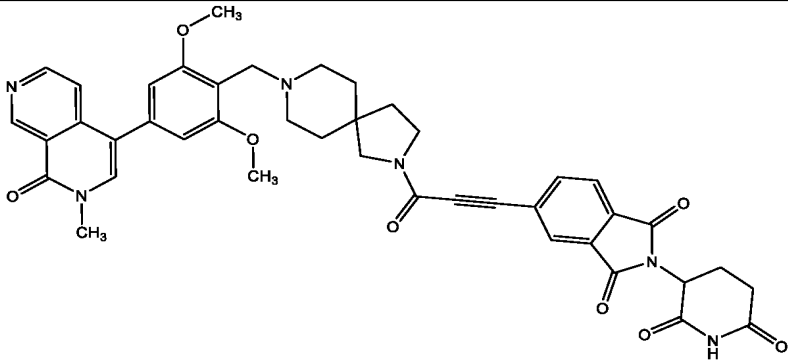
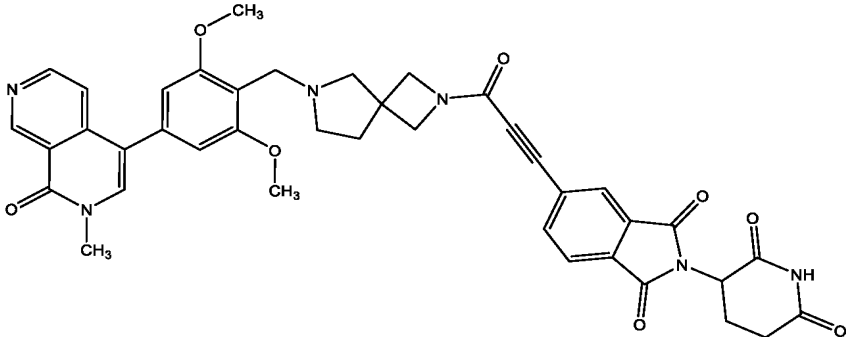
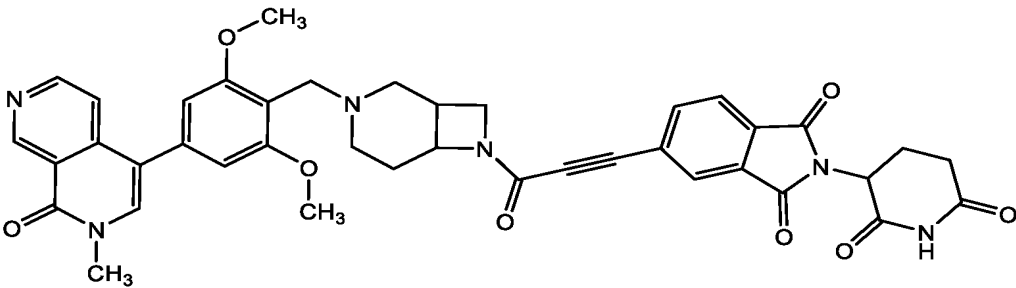
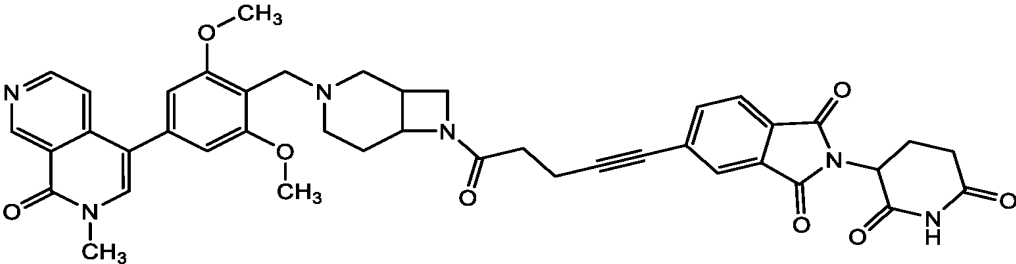
Compound No.	Structure
D220	
D221	
D222	
D223	

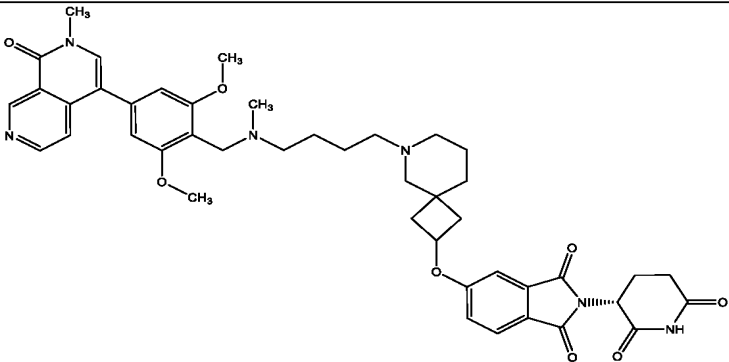
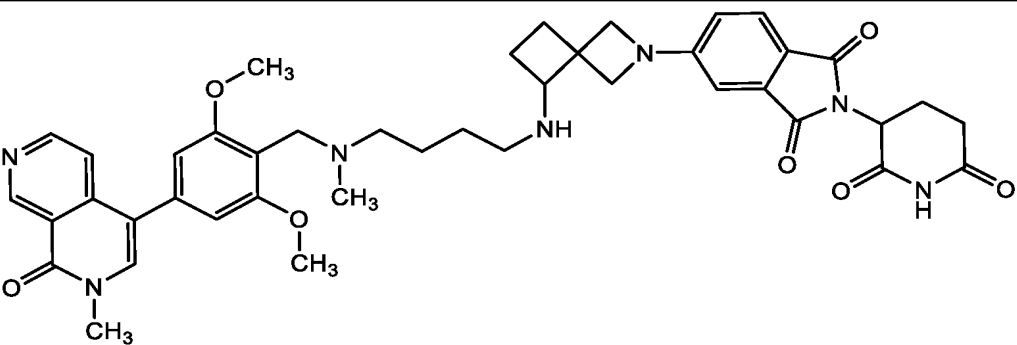
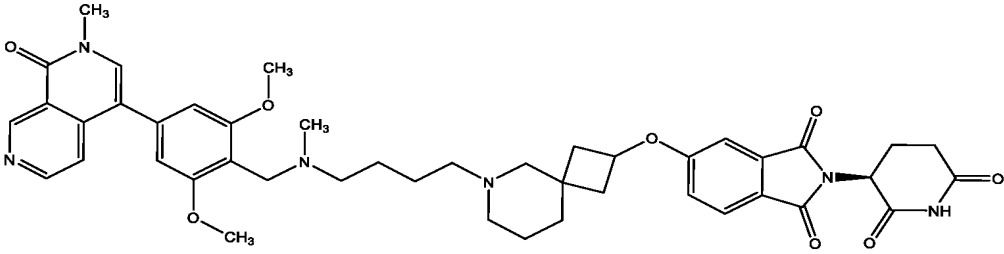
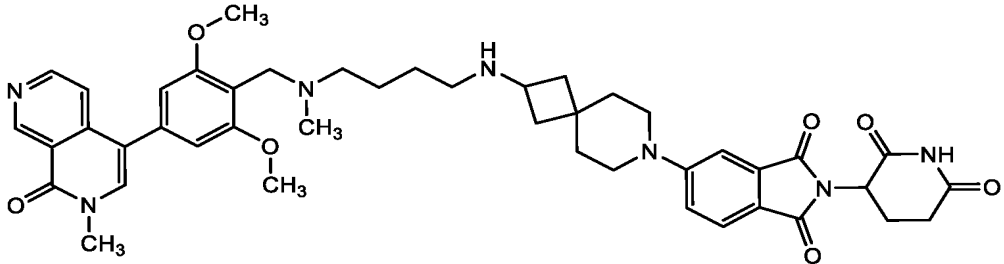
Compound No.	Structure
D224	
D225	
D226	
D227	

Compound No.	Structure
D228	
D229	
D230	
D231	

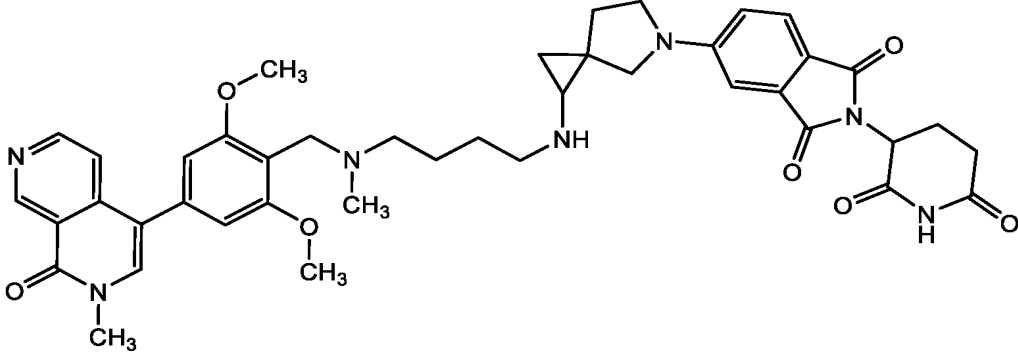
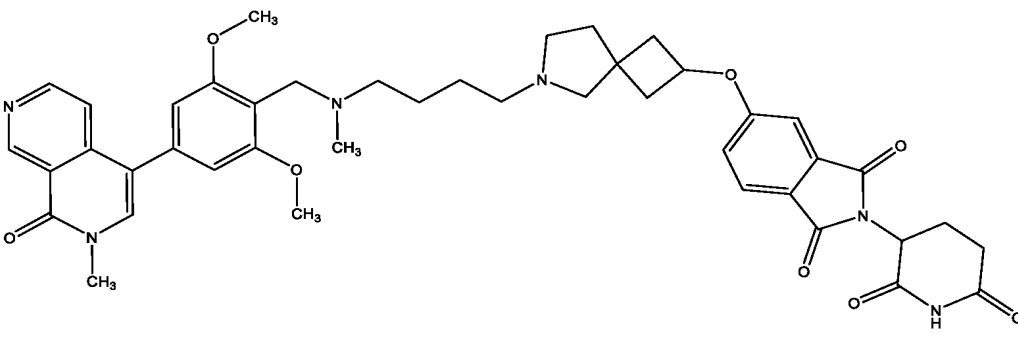
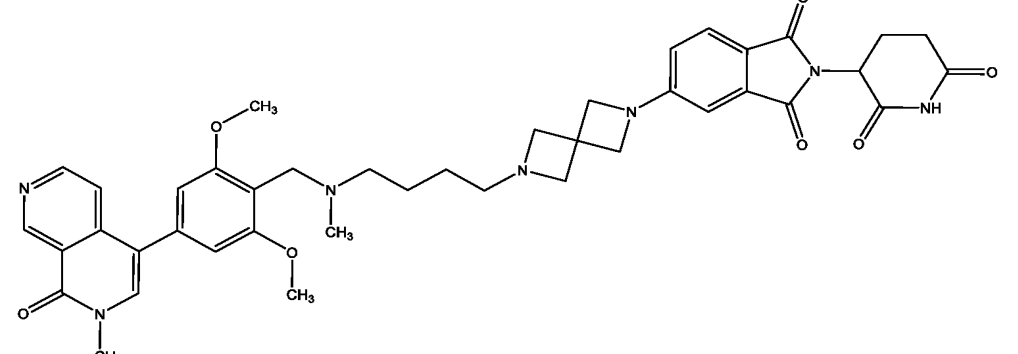
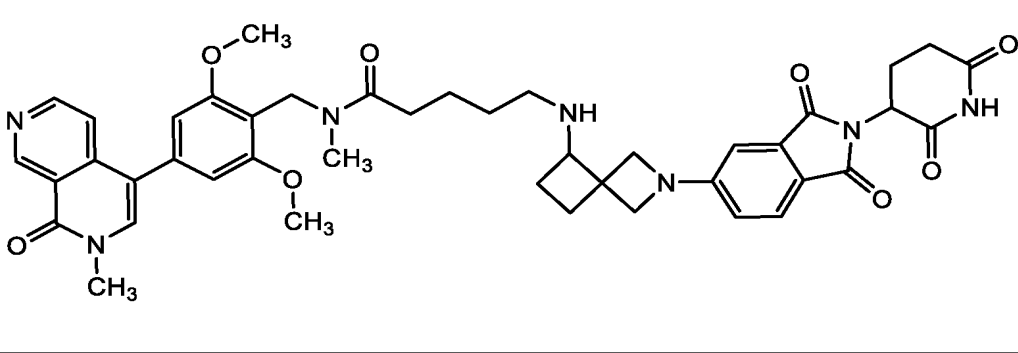
Compound No.	Structure
D232	
D233	
D234	
D235	

Compound No.	Structure
D236	
D237	
D238	
D239	

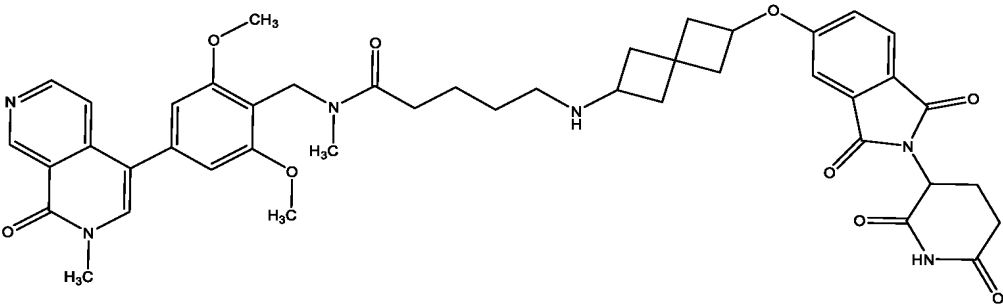
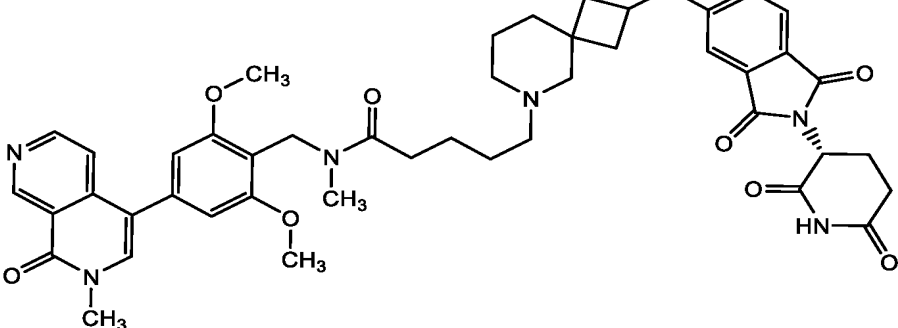
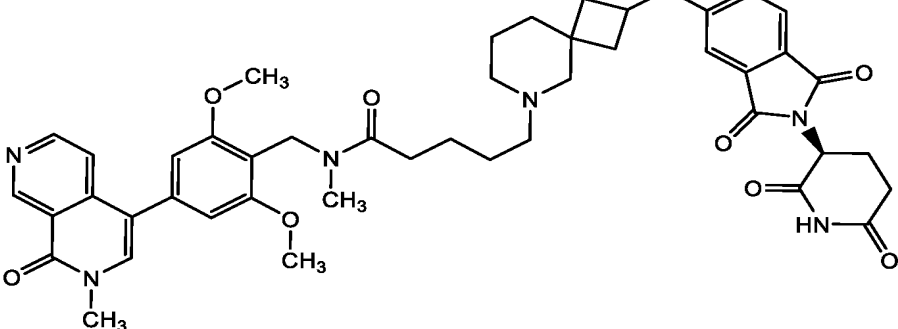
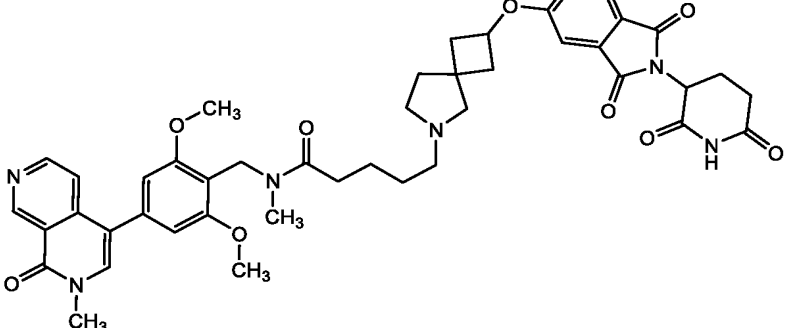
Compound No.	Structure
D240	
D241	
D242	
D243	

Compound No.	Structure
D244	
D245	
D246	
D247	

Compound No.	Structure
D248	
D249	
D250	
D251	

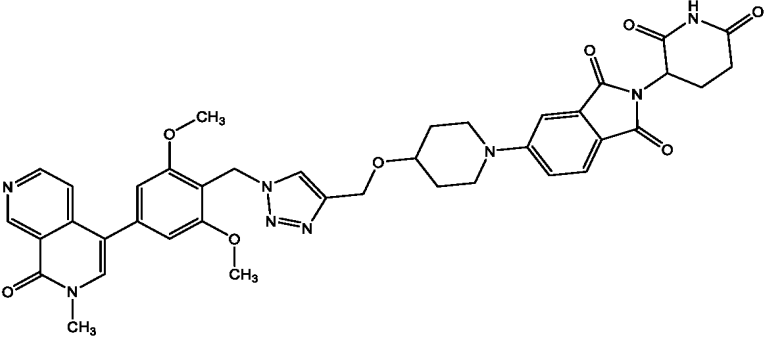
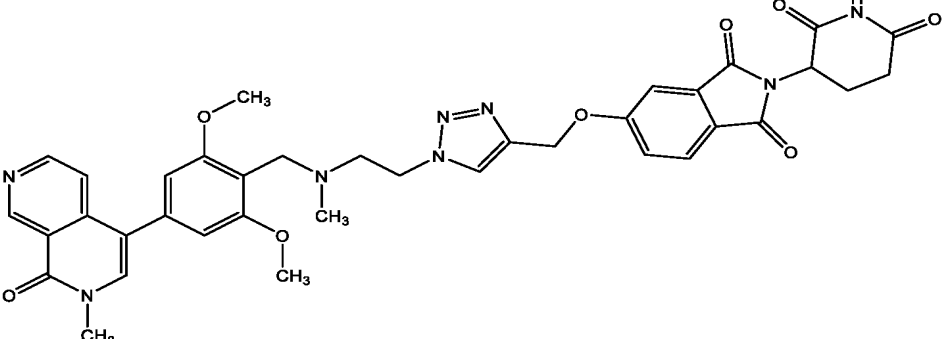
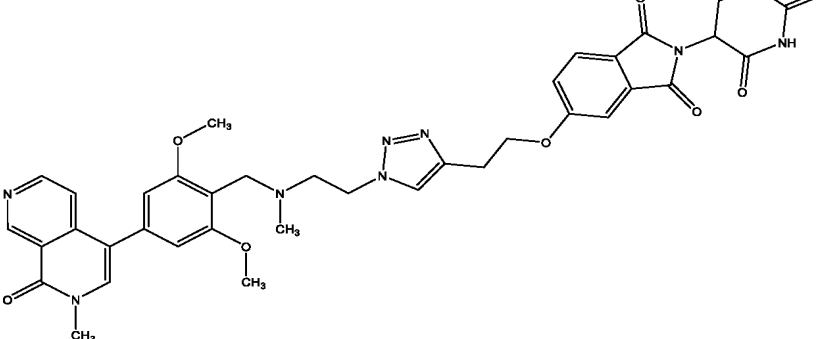
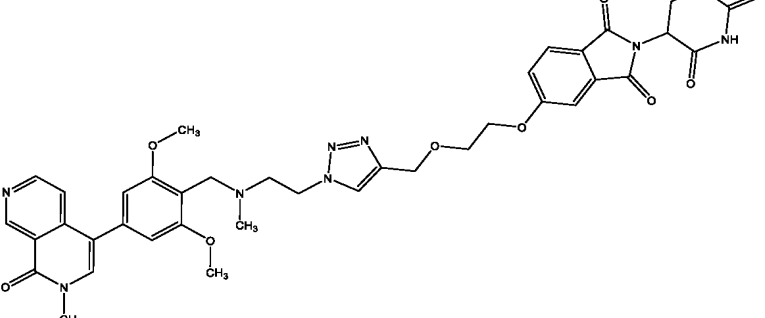
Compound No.	Structure
D252	
D253	
D254	
D255	

Compound No.	Structure
D256	
D257	
D258	
D259	

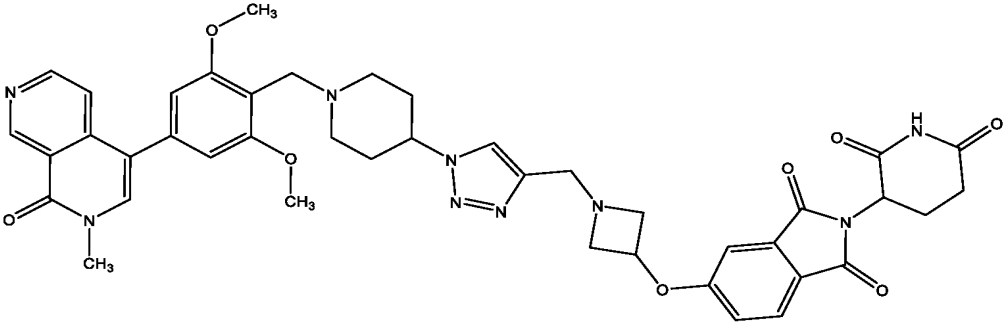
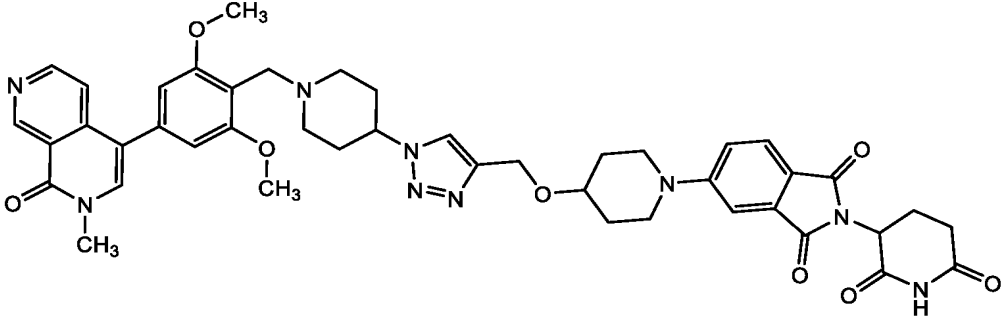
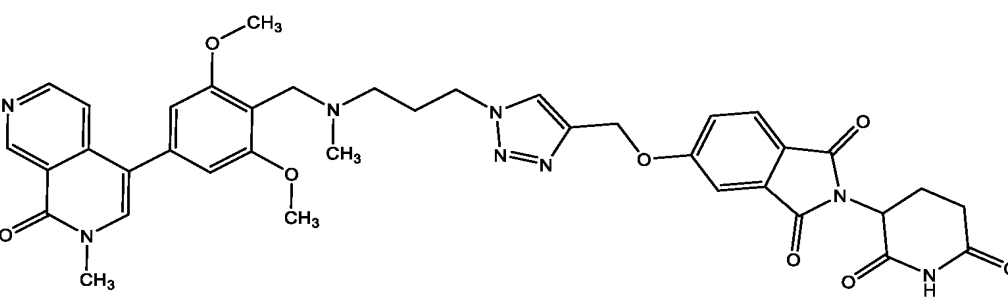
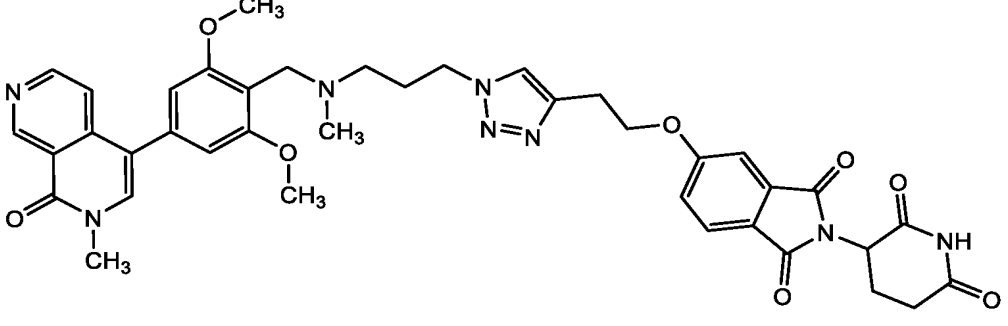
Compound No.	Structure
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D261	
D262	
D263	

Compound No.	Structure
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D265	
D266	
D267	

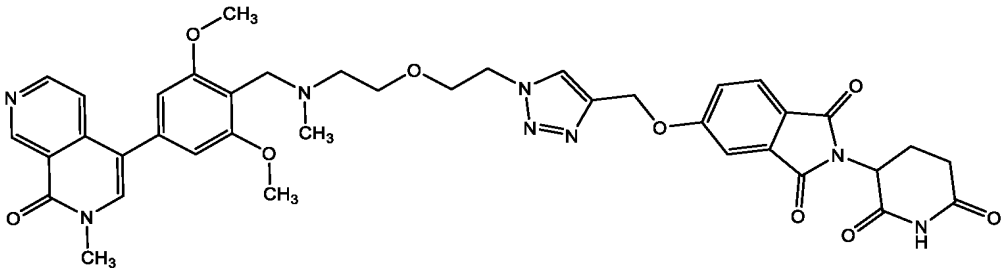
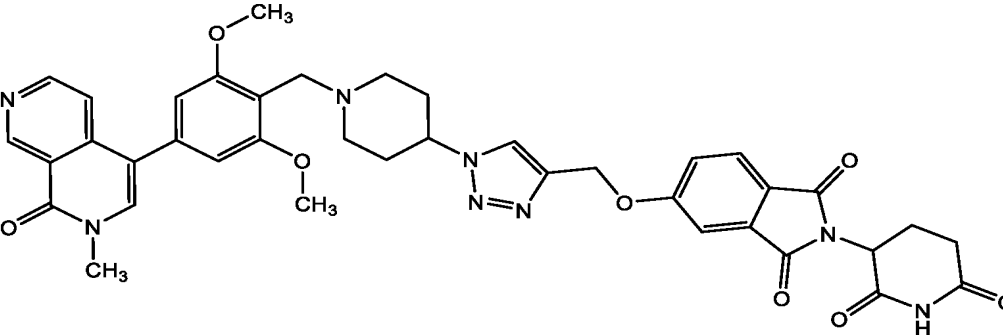
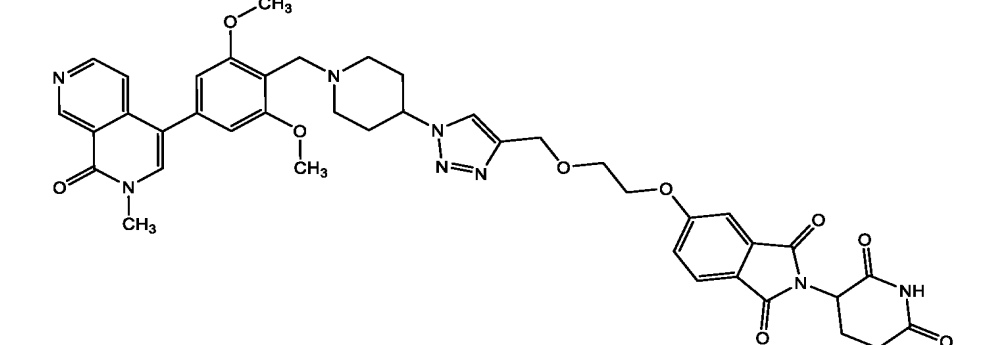
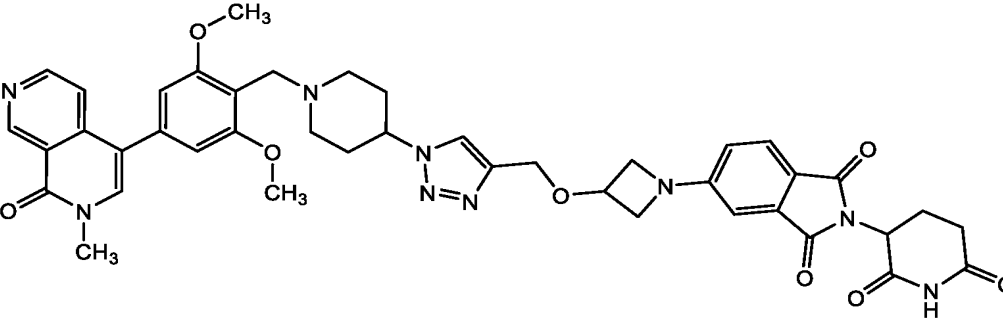
[illegible]

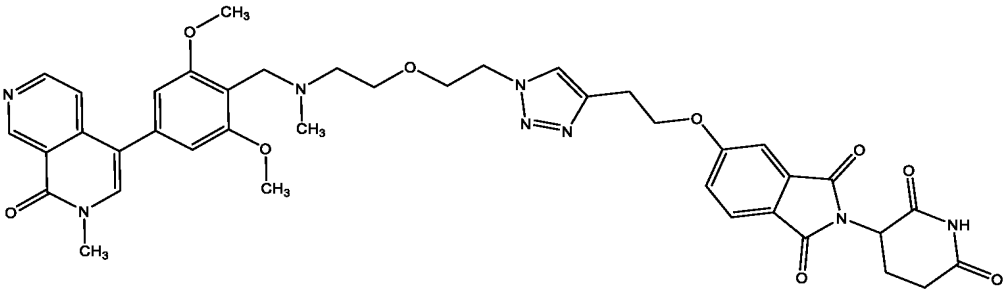
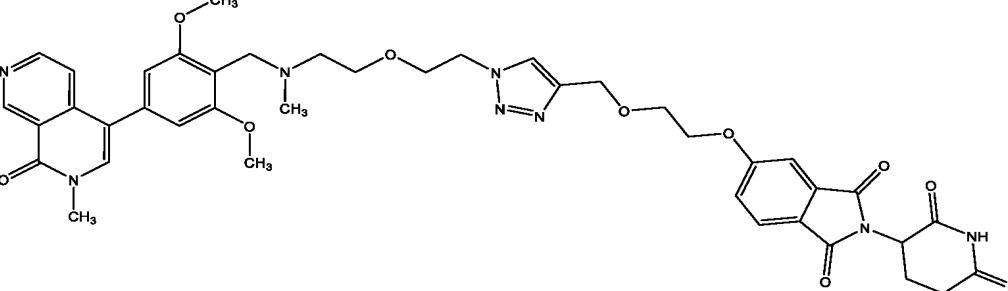
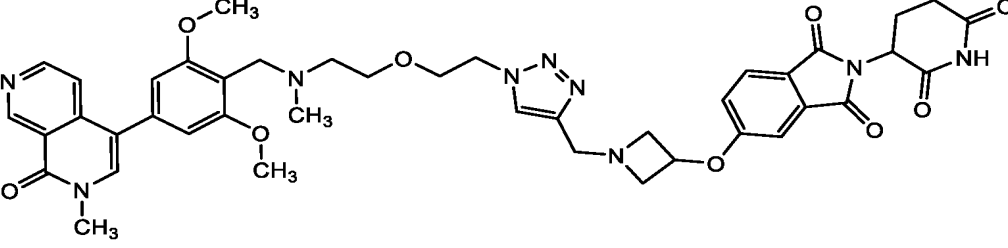
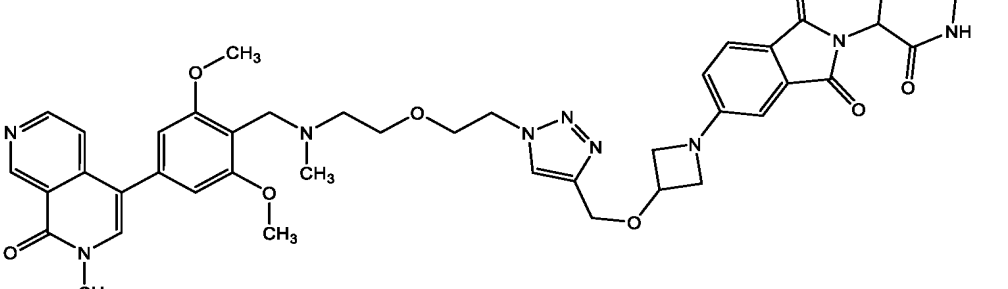
Compound No.	Structure
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D273	
D274	
D275	

Compound No.	Structure
D276	
D277	
D278	
D279	

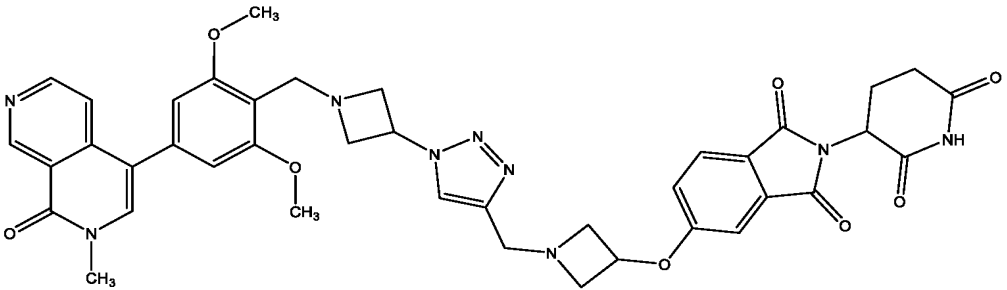
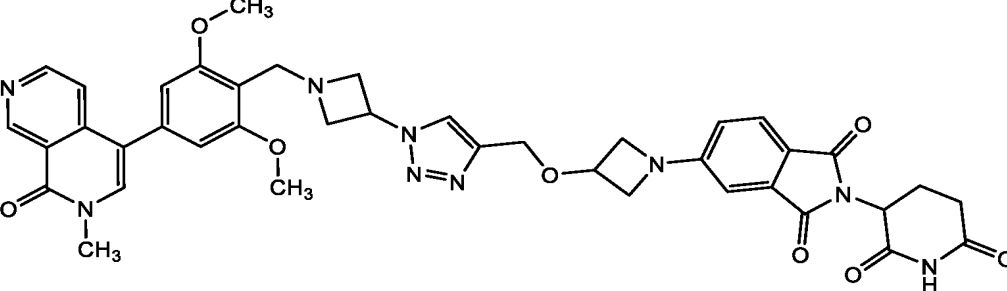
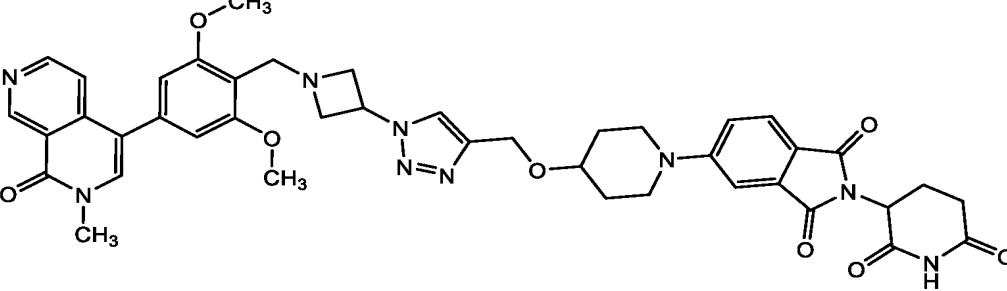
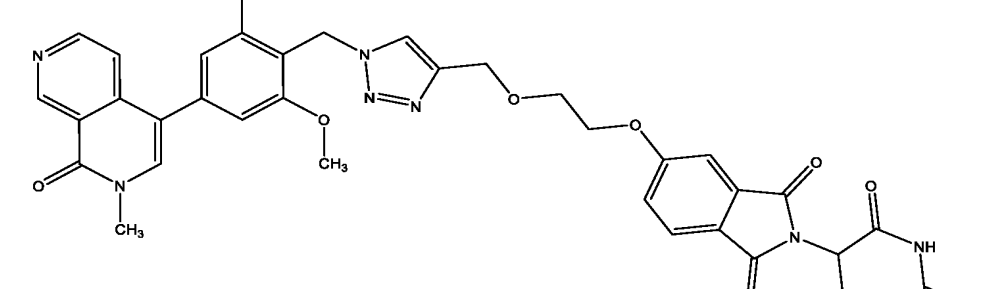
Compound No.	Structure
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D283	

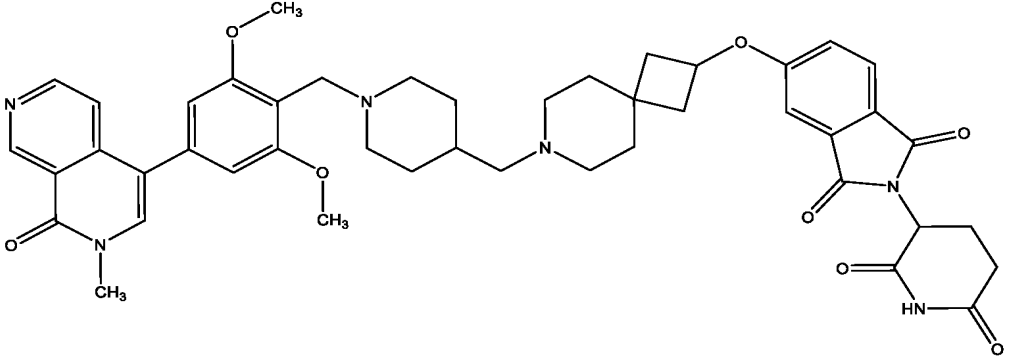
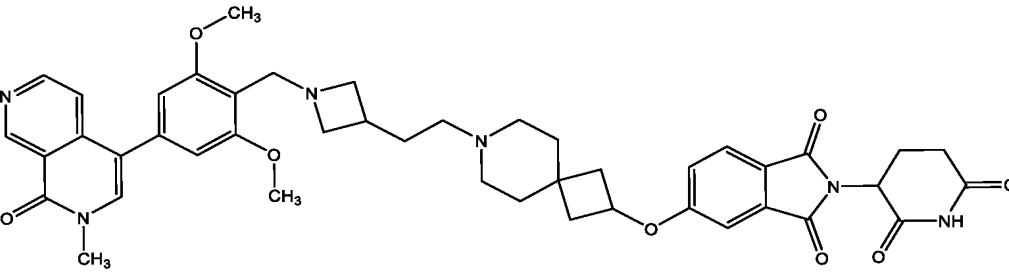
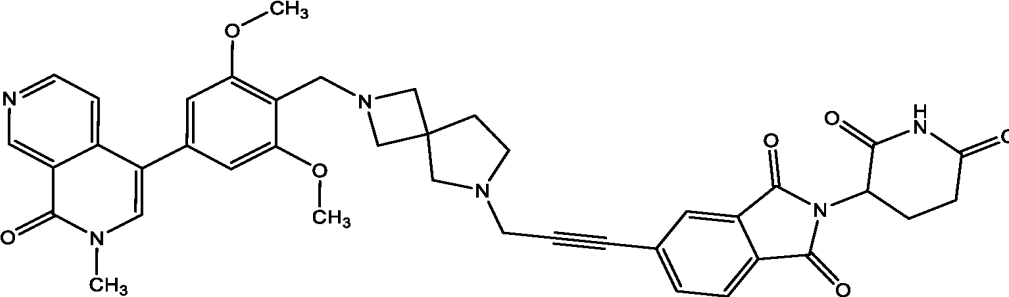
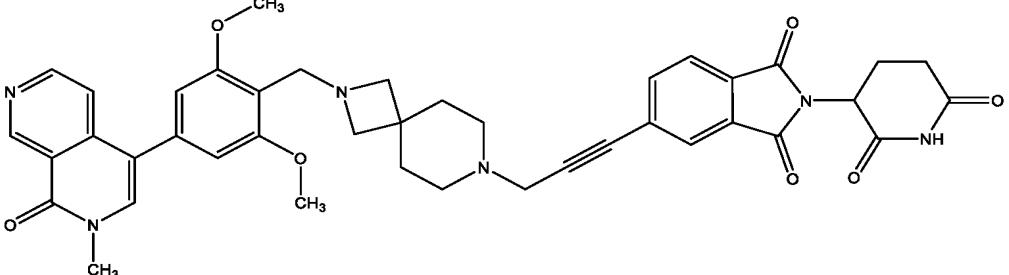
Compound No.	Structure
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D286	
D287	

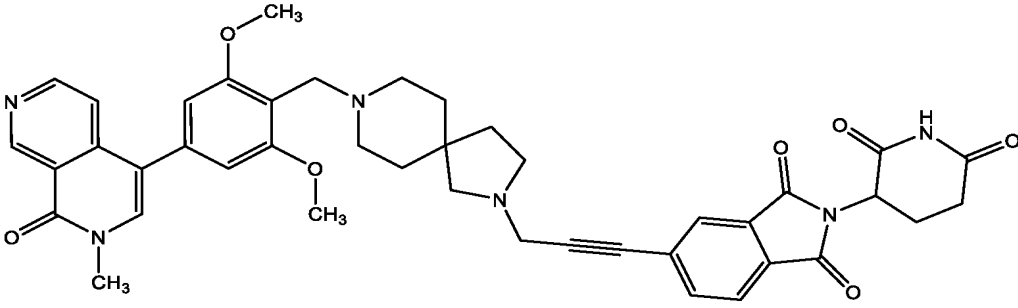
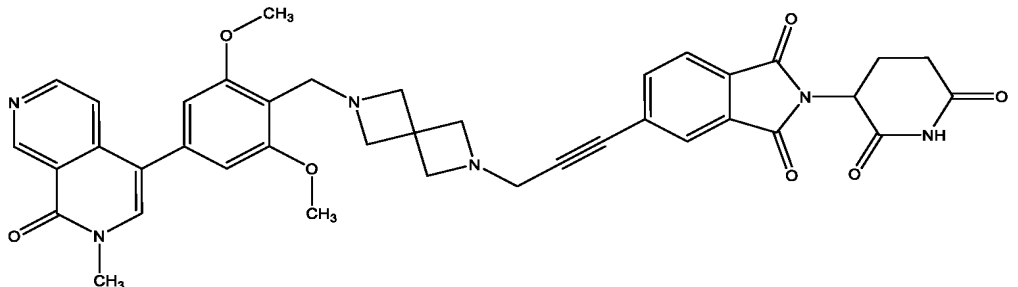
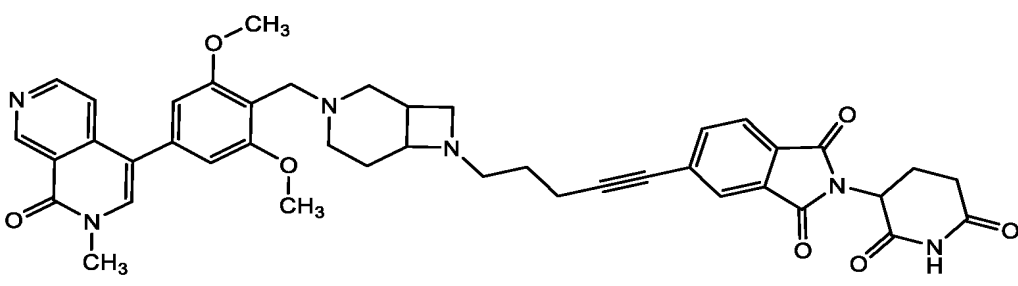
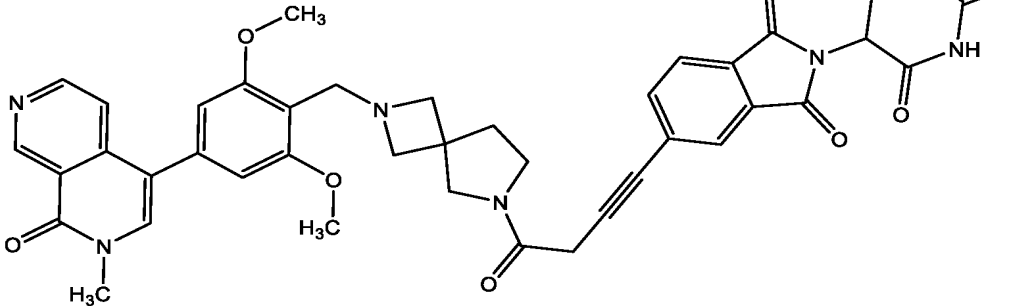
Compound No.	Structure
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D289	
D290	
D291	

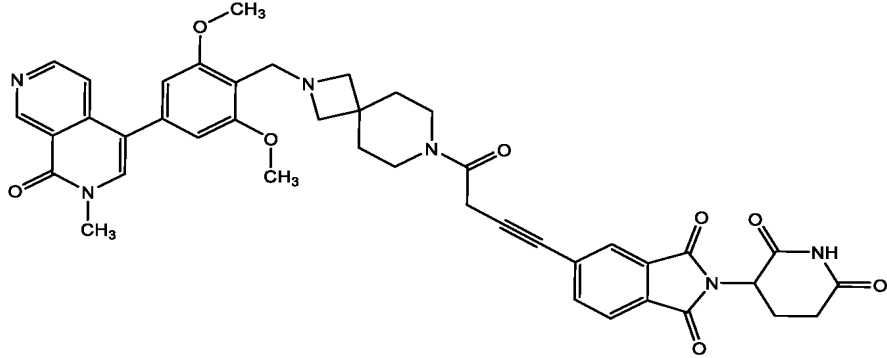
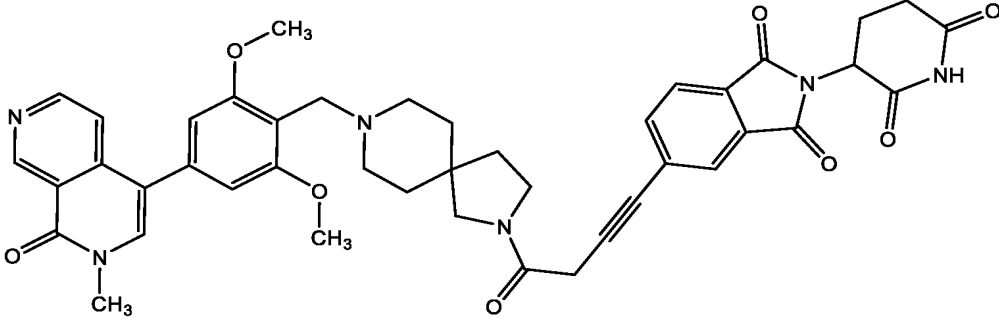
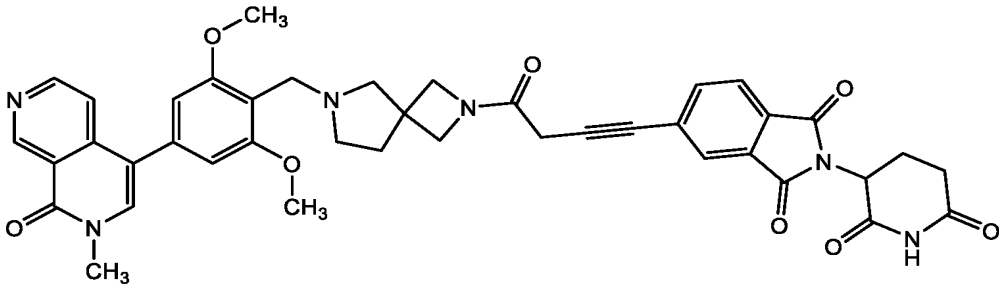
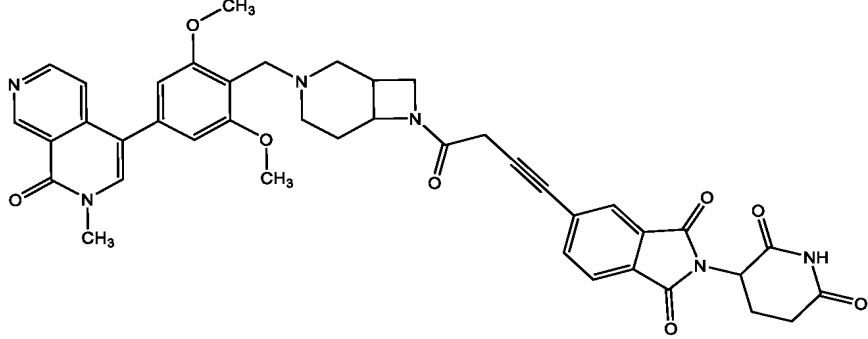
Compound No.	Structure
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D293	
D294	
D295	

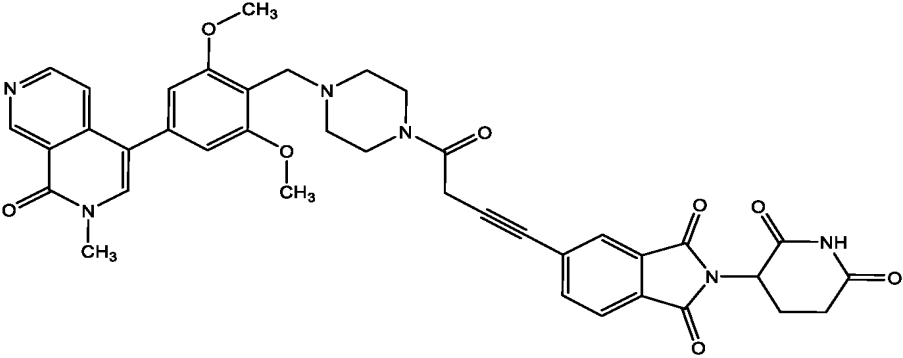
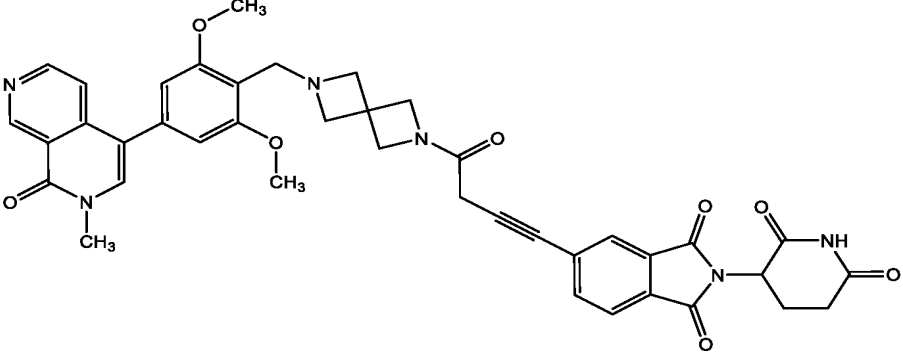
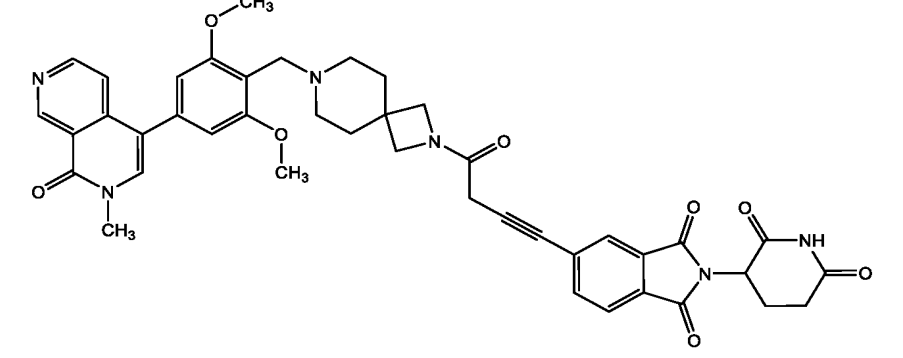
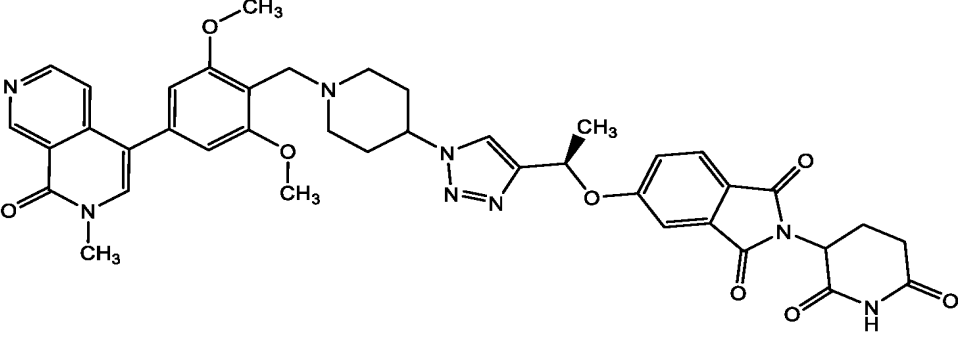
Compound No.	Structure
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D297	
D298	
D299	

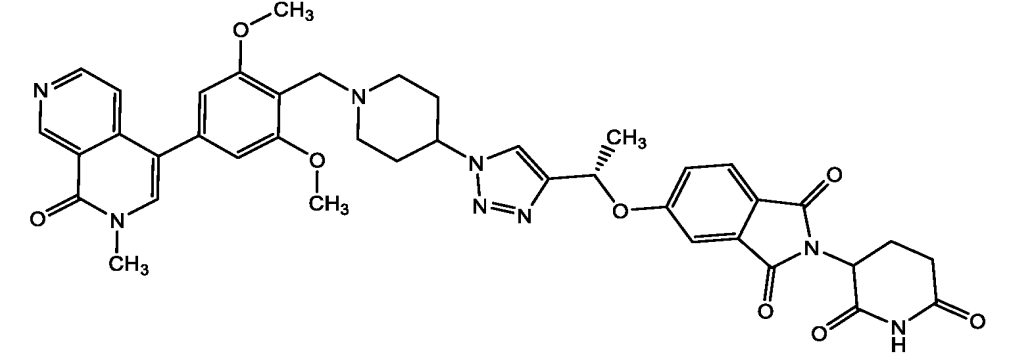
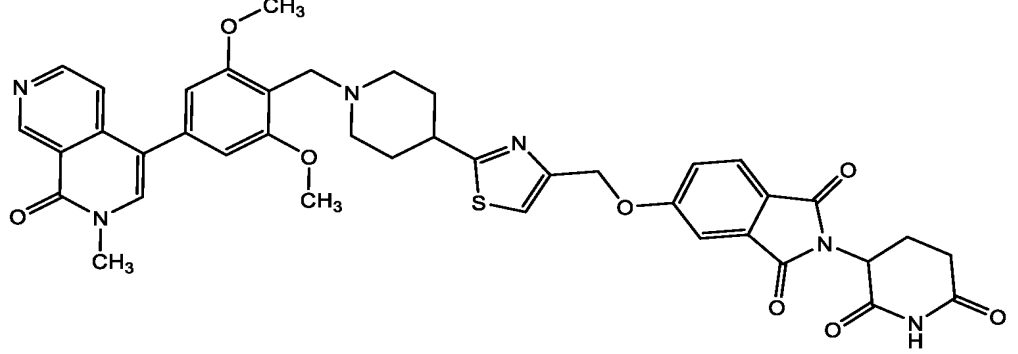
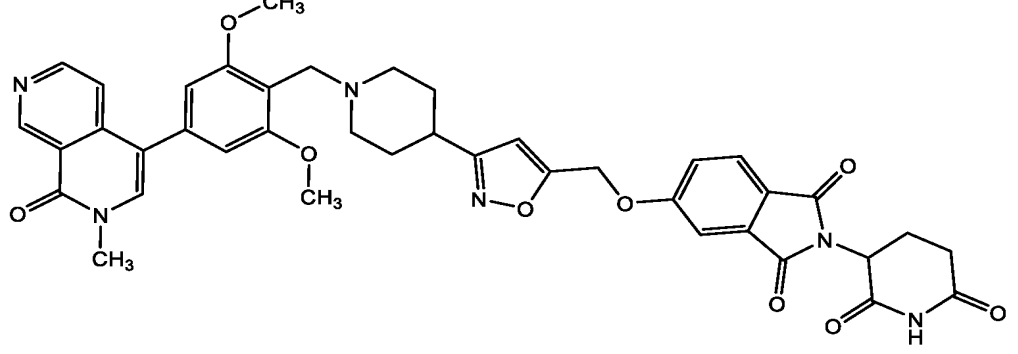
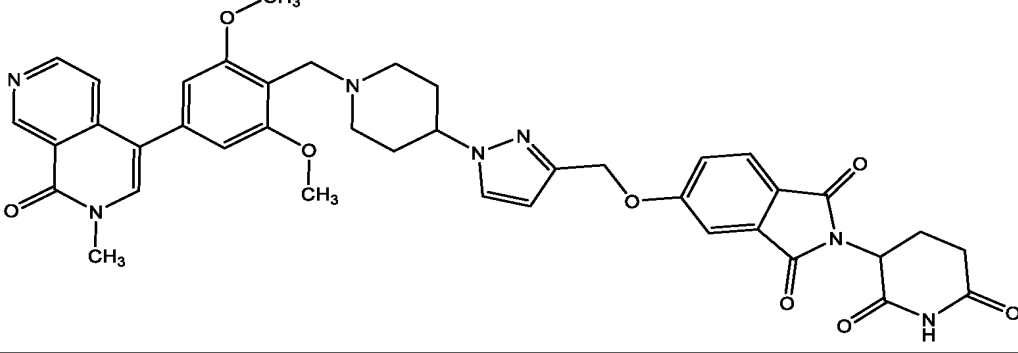
Compound No.	Structure
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D302	
D303	

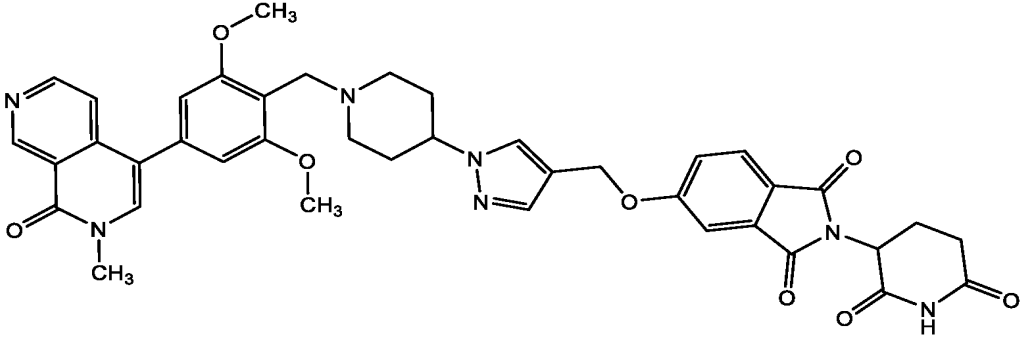
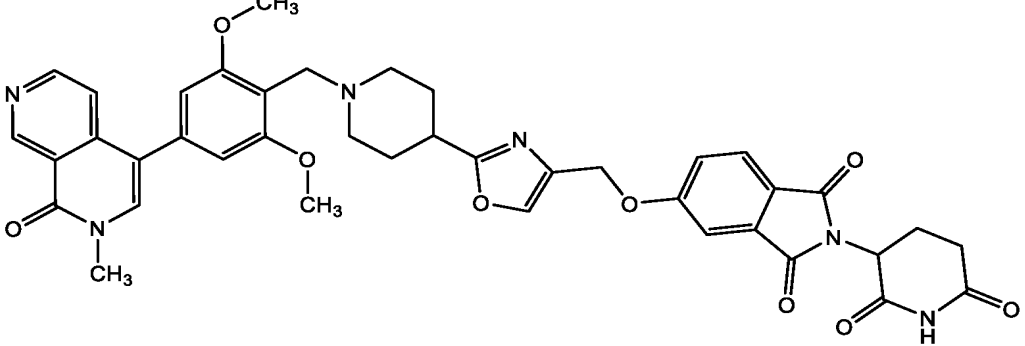
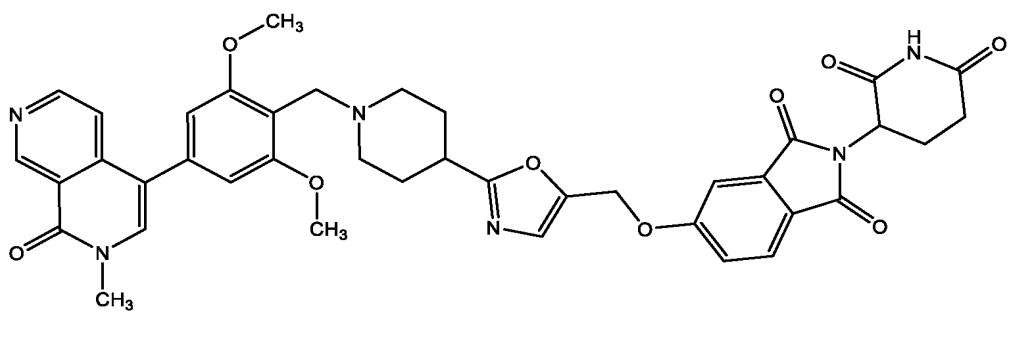
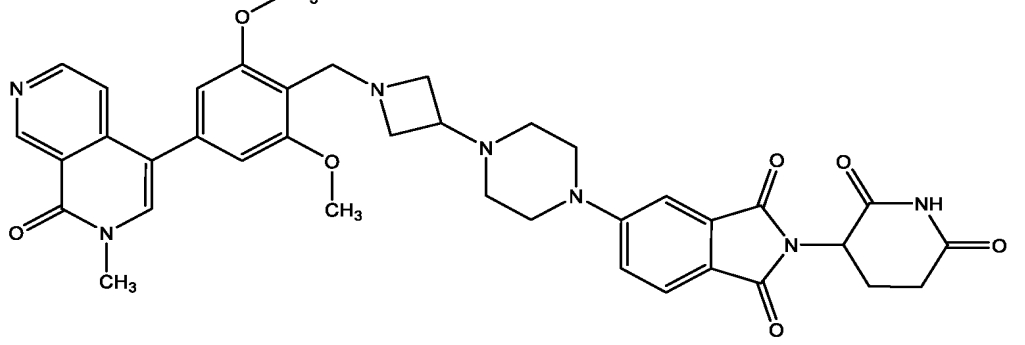
Compound No.	Structure
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D305	
D306	
D307	

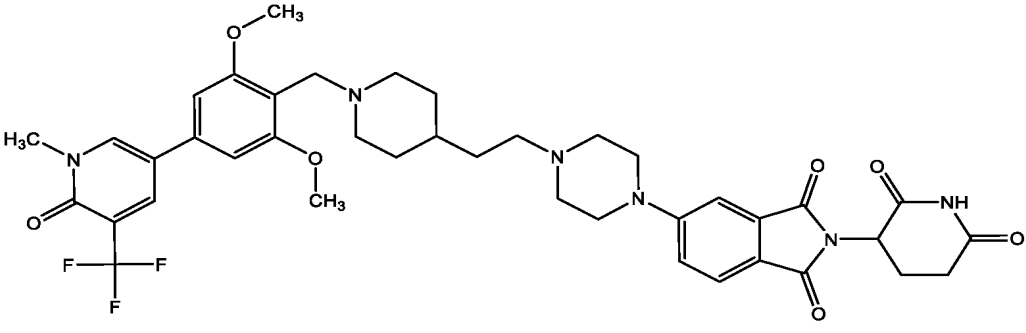
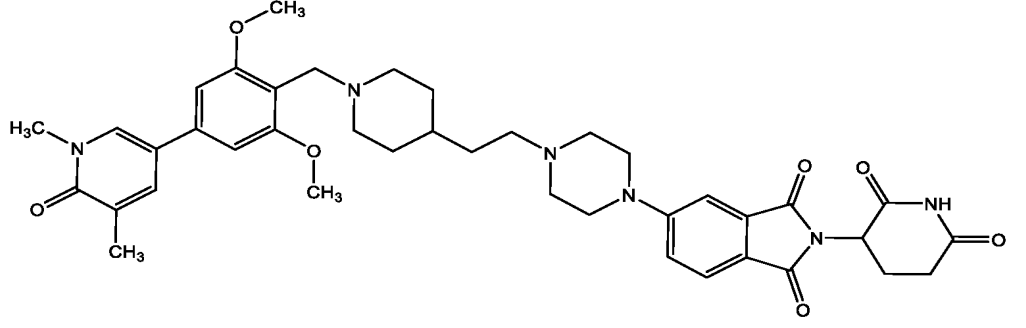
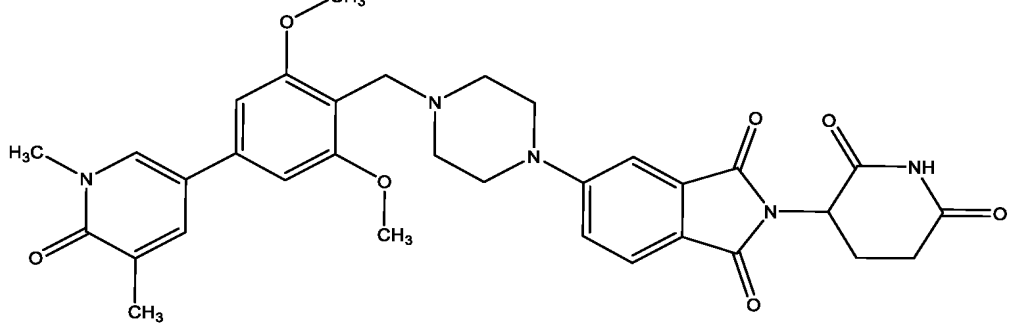
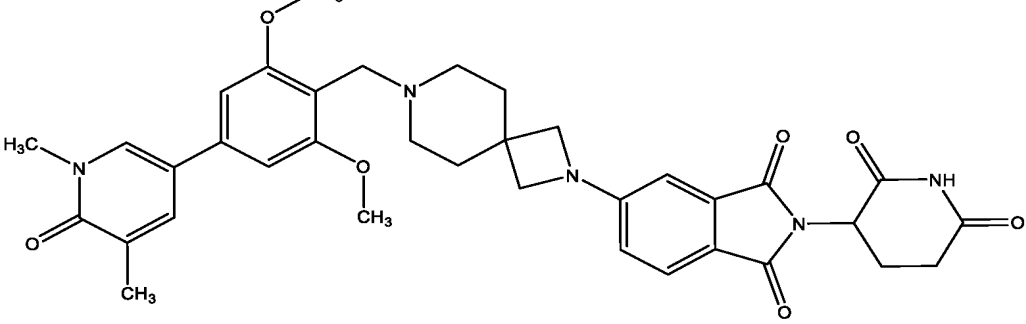
Compound No.	Structure
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D311	

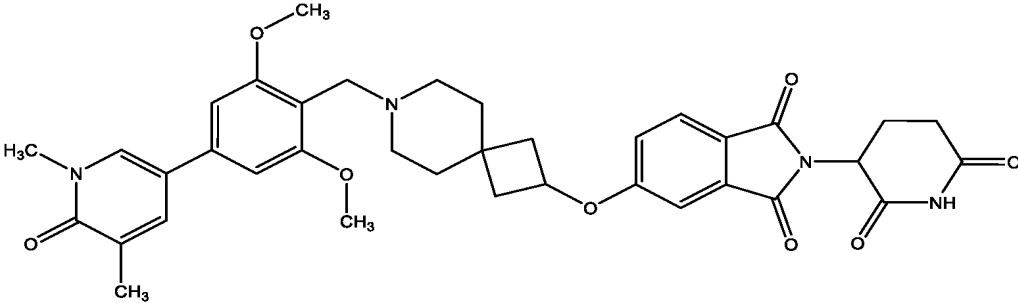
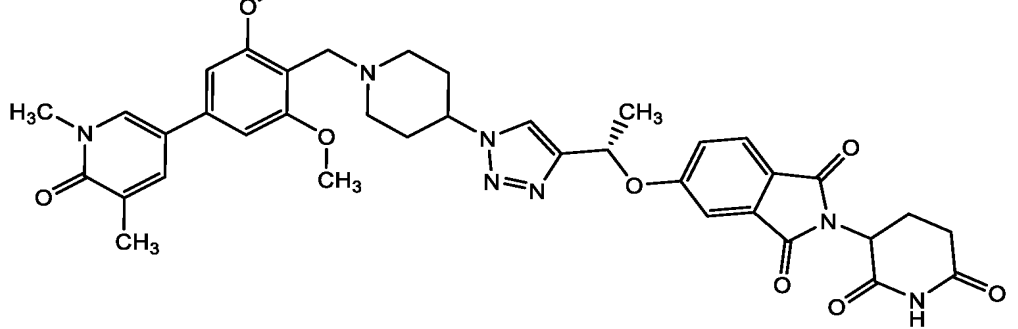
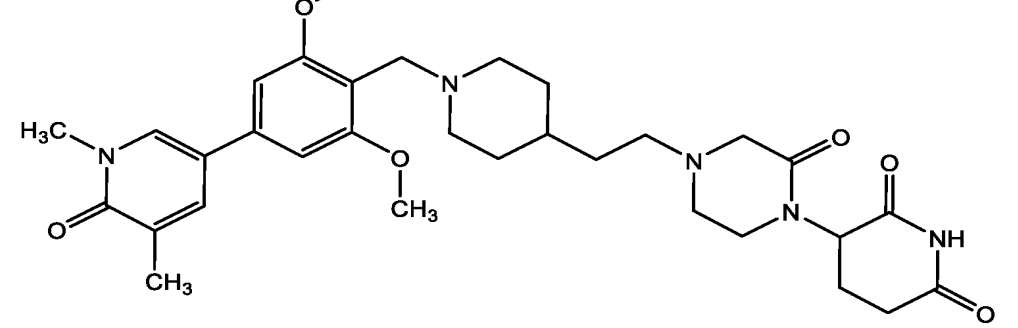
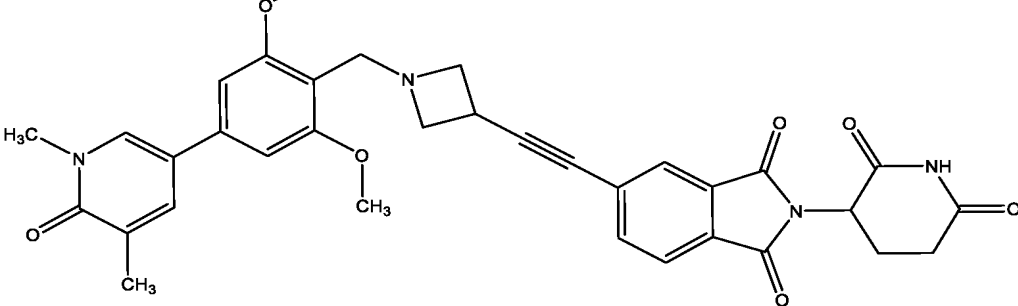
Compound No.	Structure
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D315	

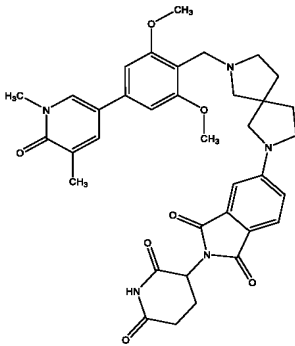
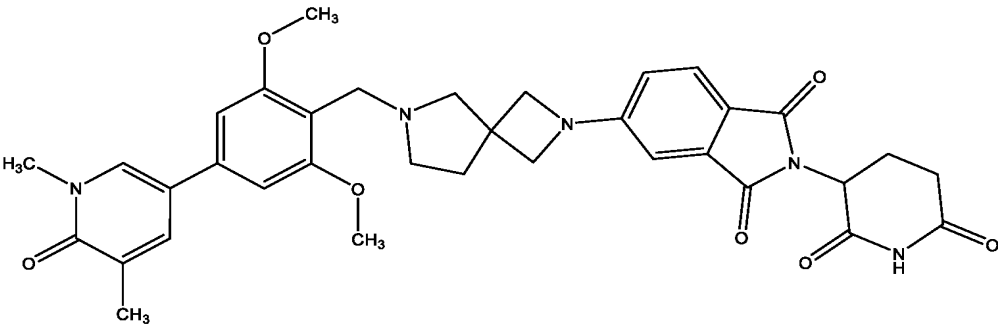
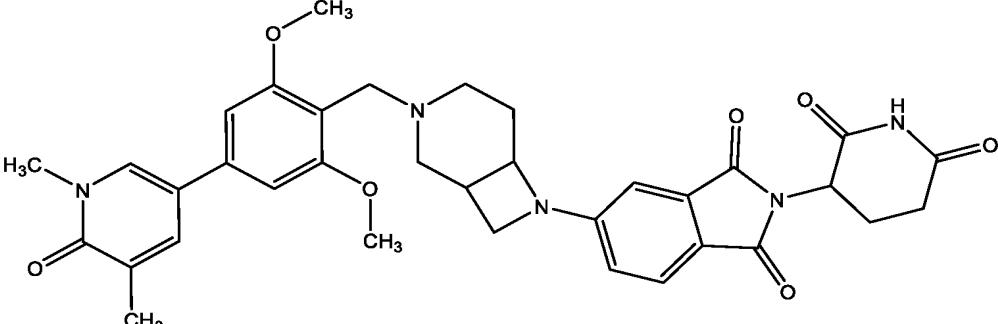
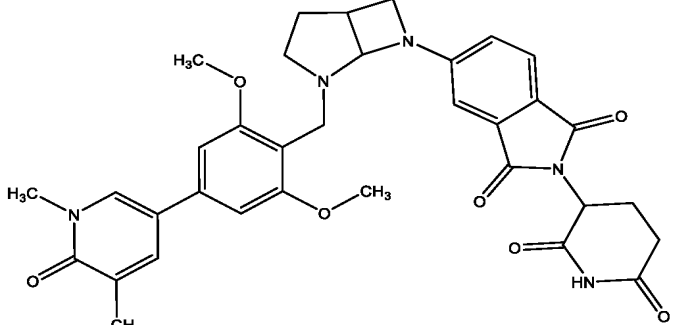
Compound No.	Structure
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D318	
D319	

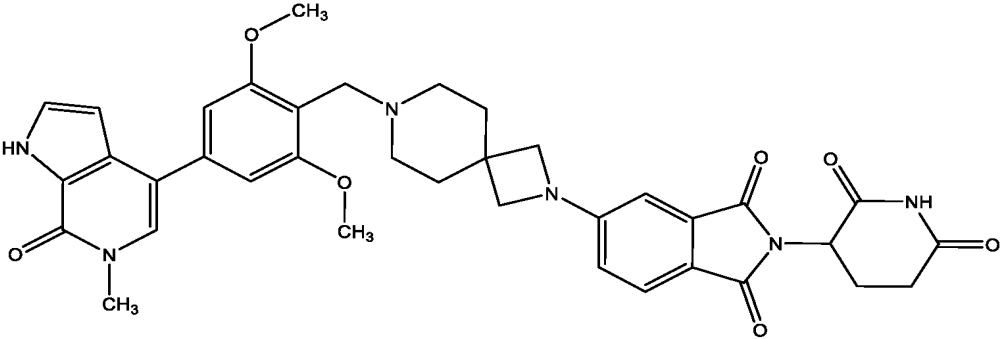
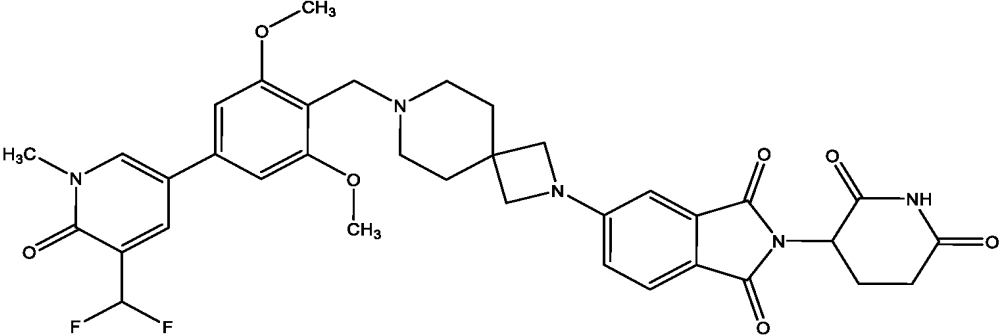
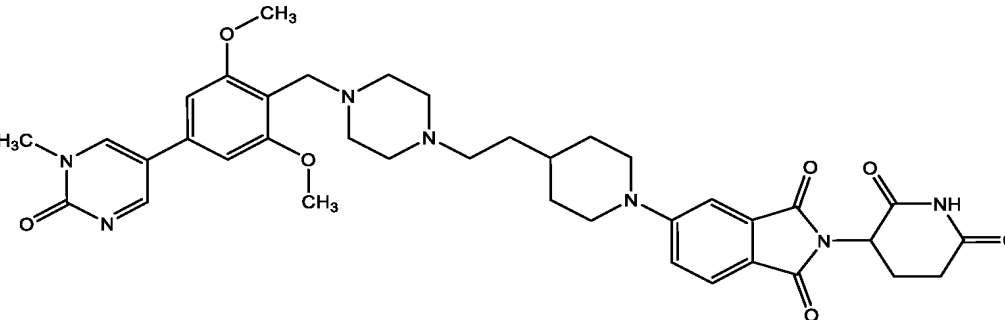
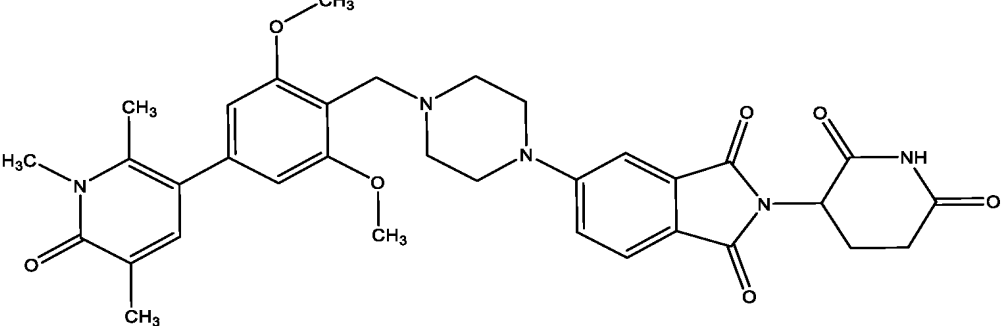
Compound No.	Structure
D320	
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D322	
D323	

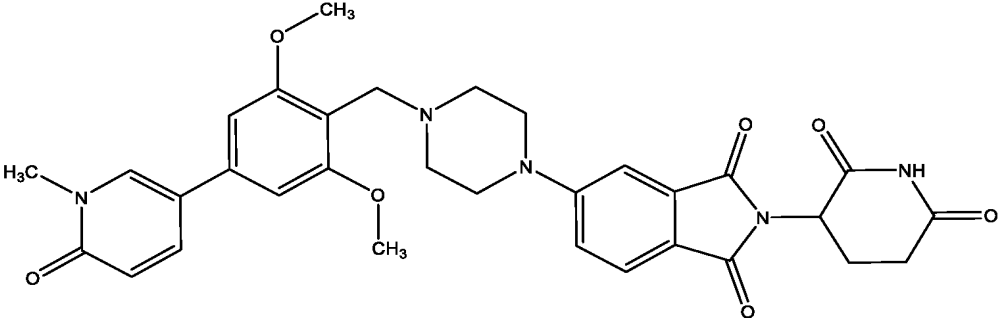
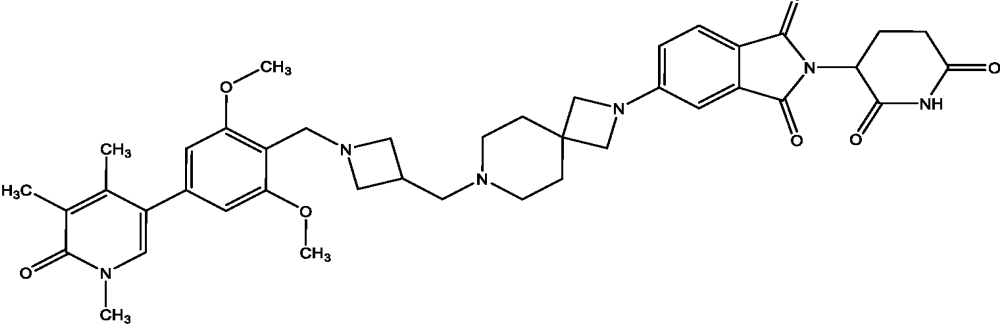
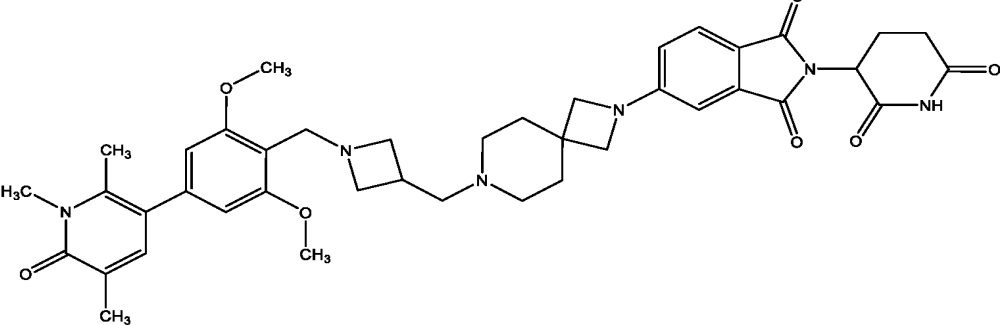
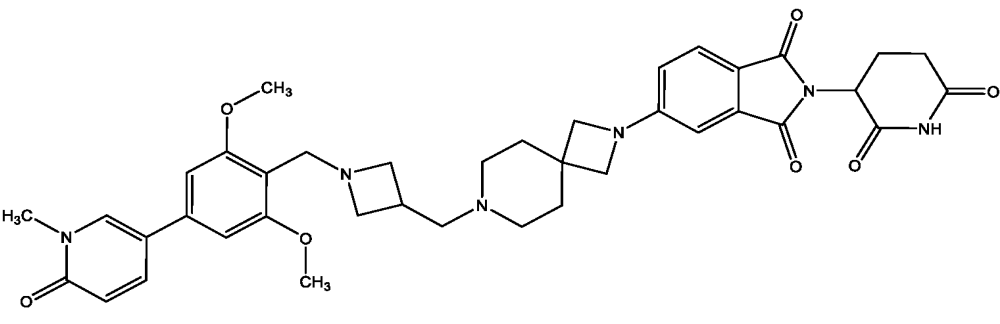
Compound No.	Structure
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D326	
D327	

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	

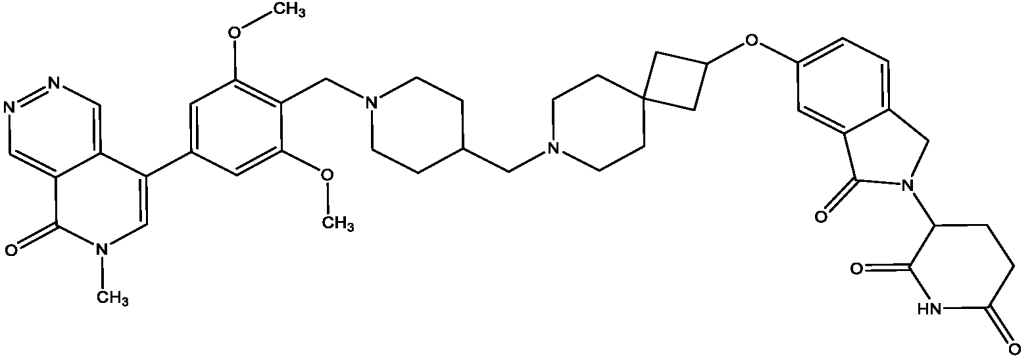
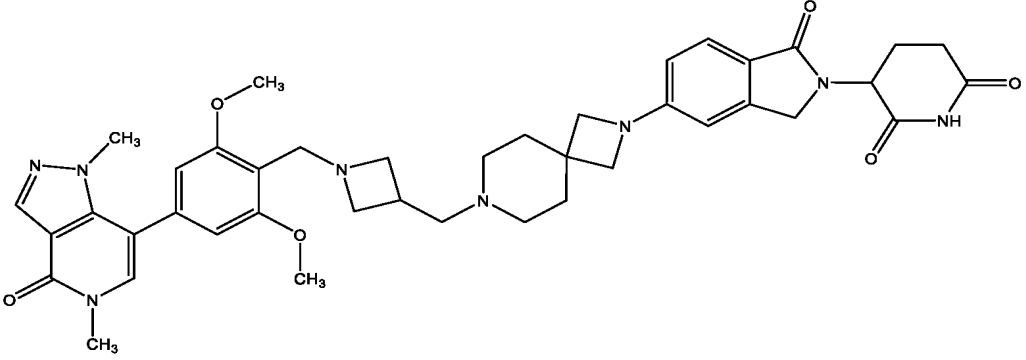
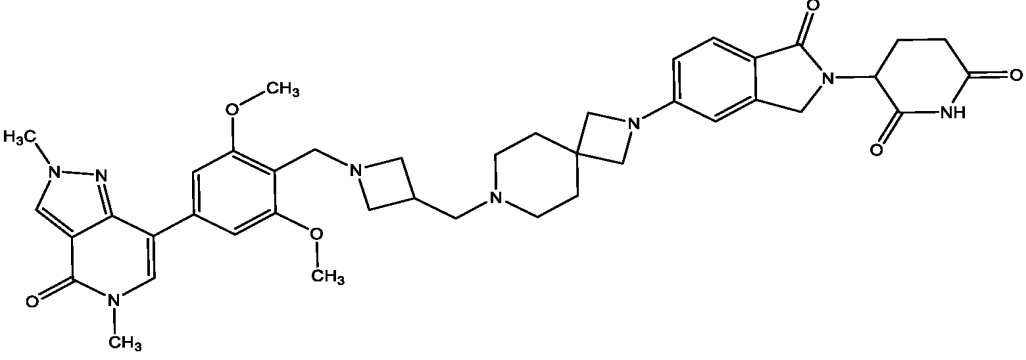
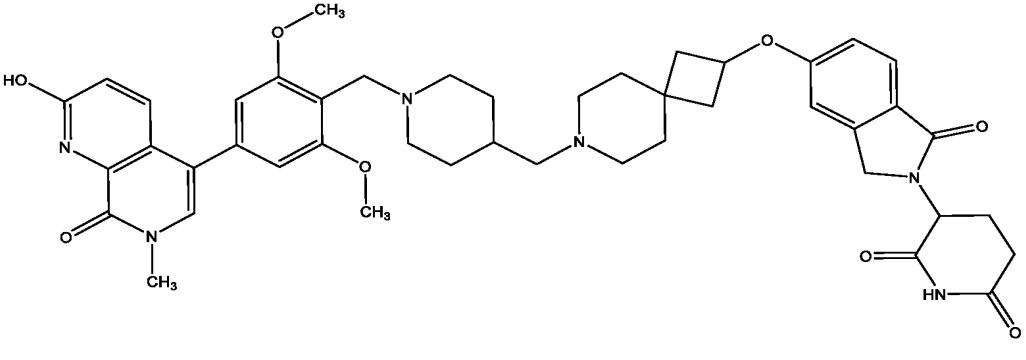
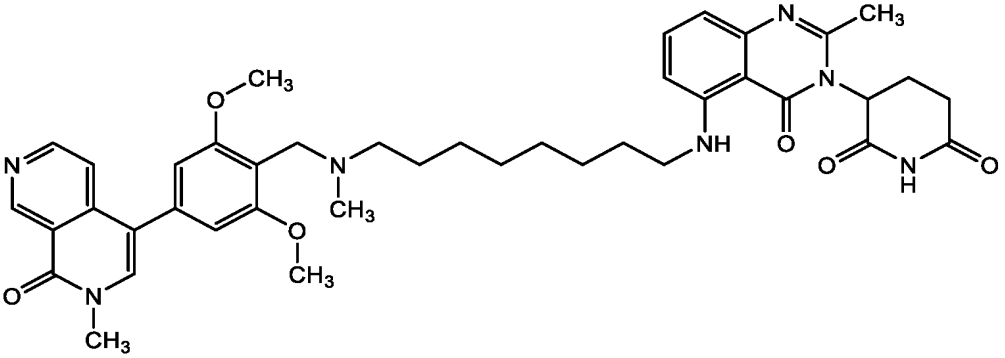
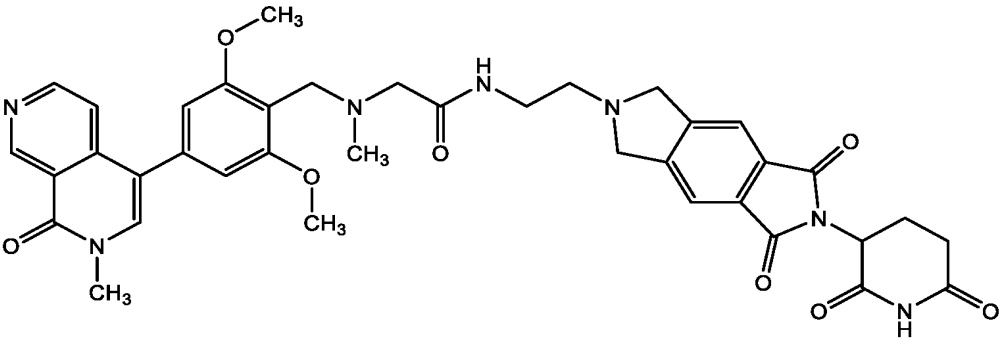
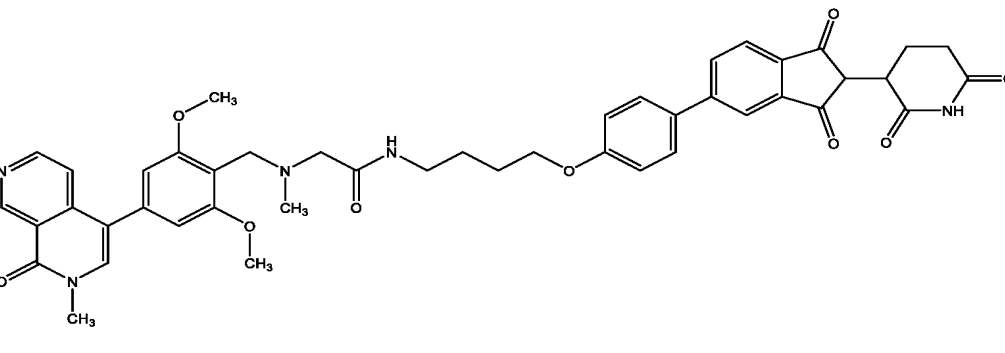
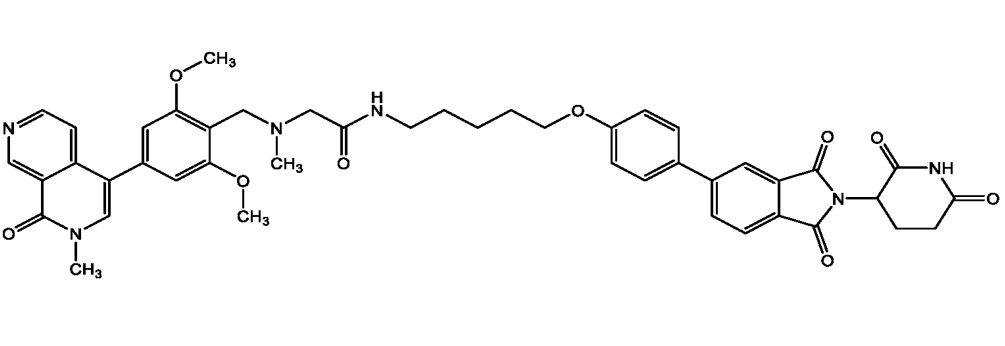
Compound No.	Structure
D368	
D369	
D370	
D371	

Table 1C. Compounds DD1-DD10 of the Disclosure

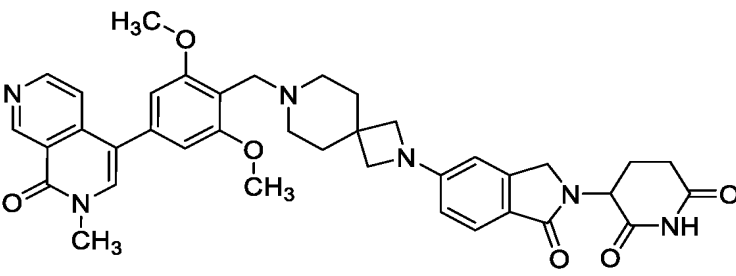
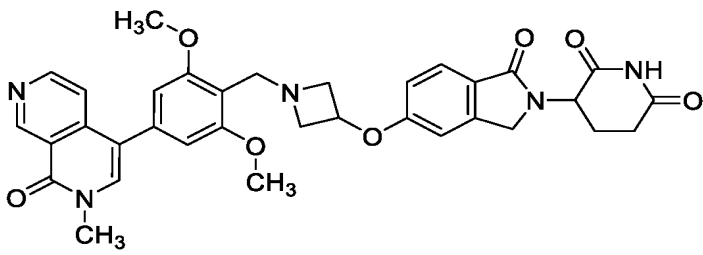
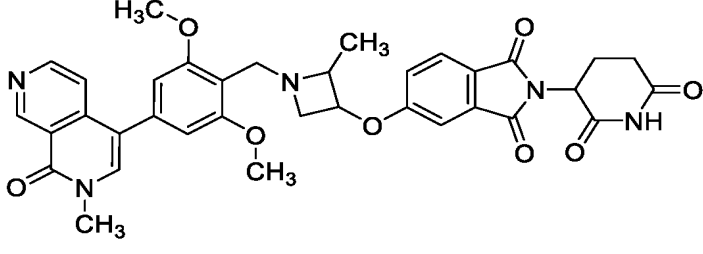
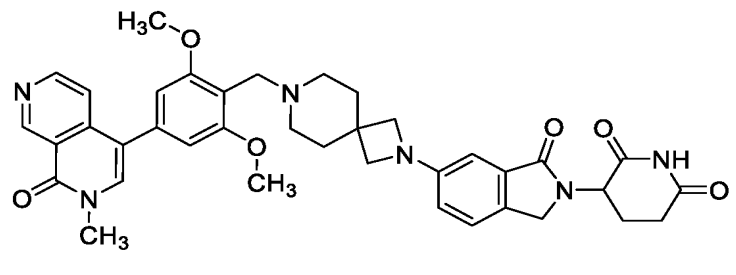
Compound No.	Structure
DD1	
DD2	
DD3	
DD4	

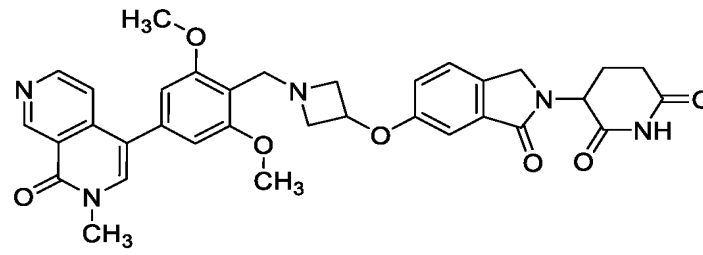
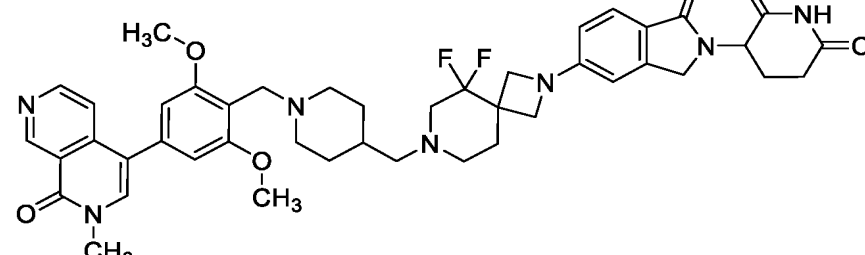
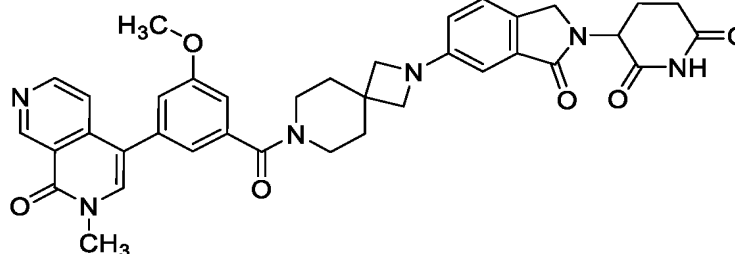
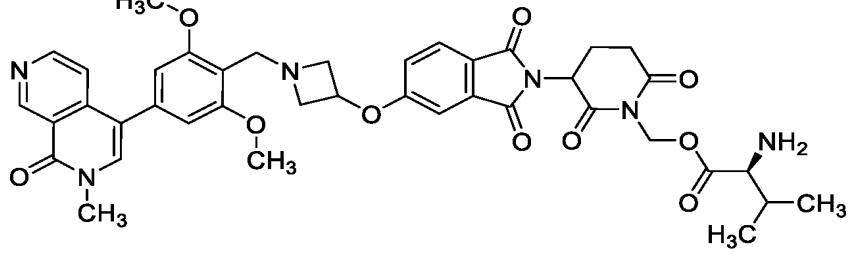
Compound No.	Structure
DD5	
DD6	
DD7	
DD8	

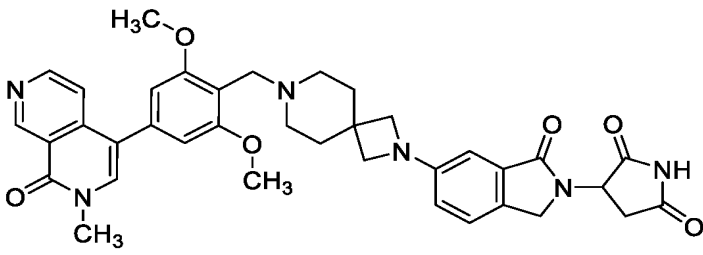
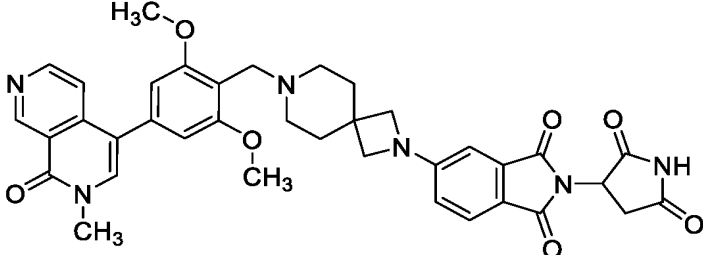
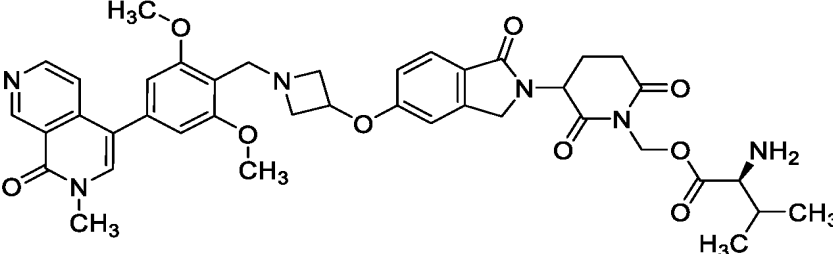
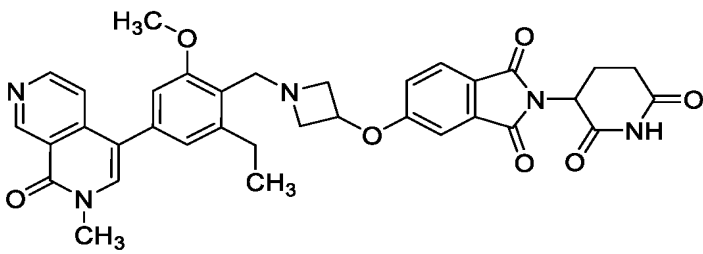
Compound No.	Structure
DD9	
DD10	

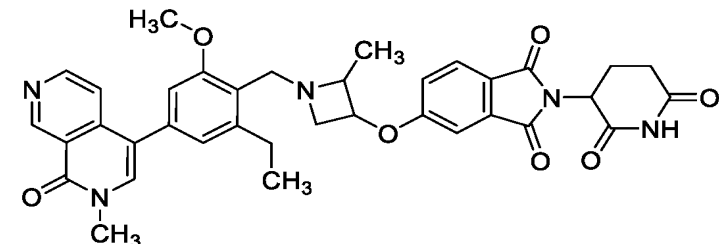
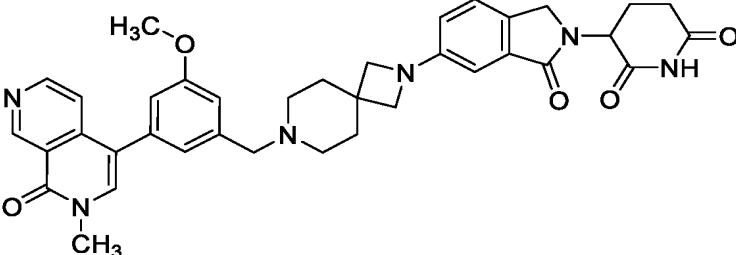
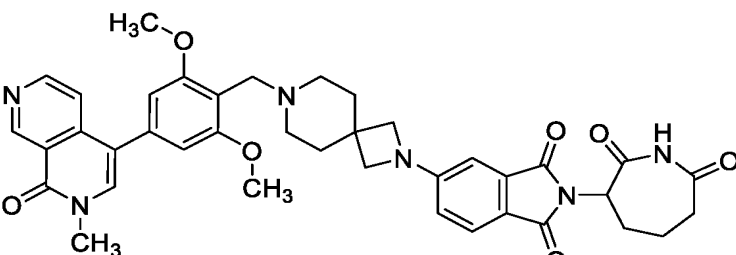
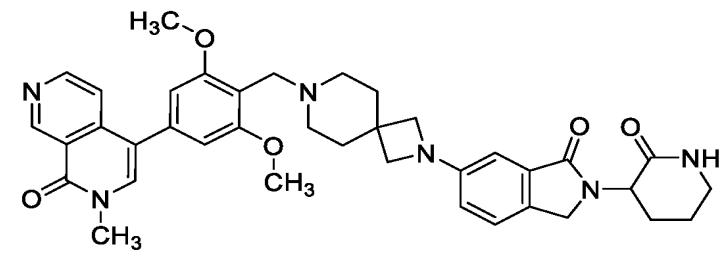
Table 1D. Compounds D372-D477 of the disclosure

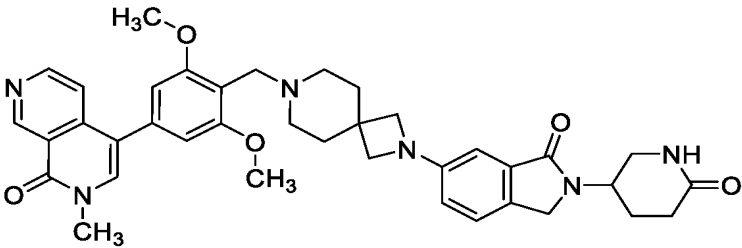
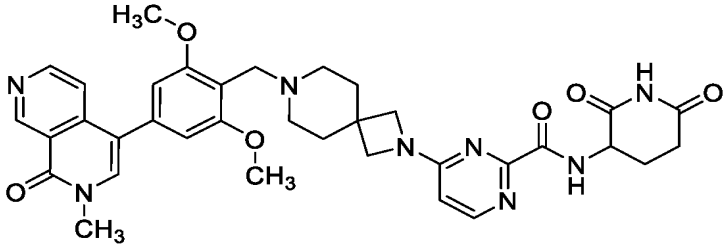
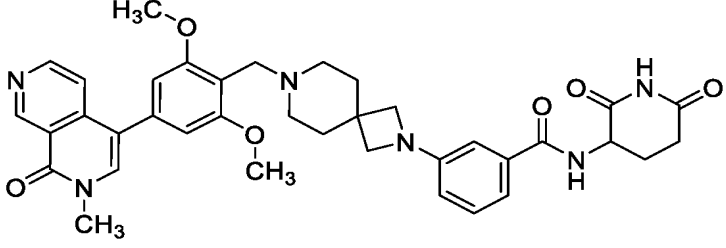
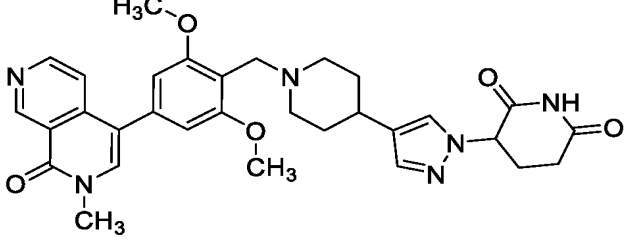
Compound No.	Structure
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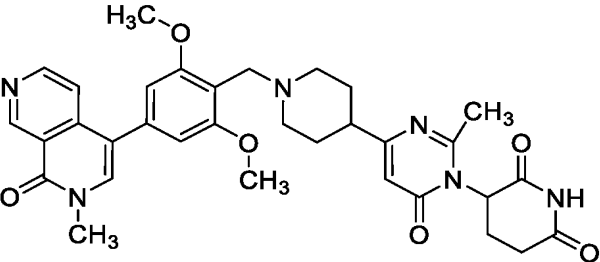
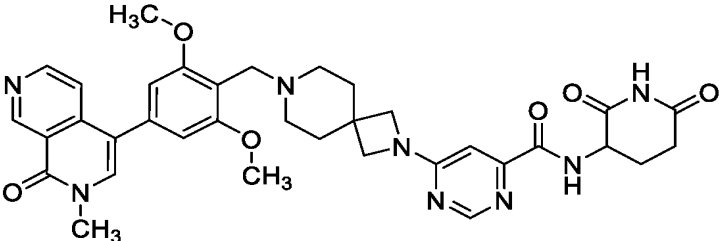
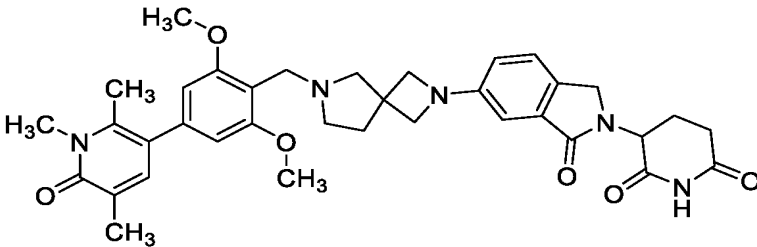
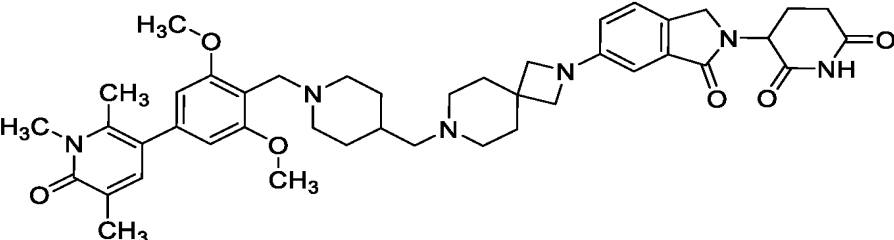
Compound No.	Structure
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D376	
D377	

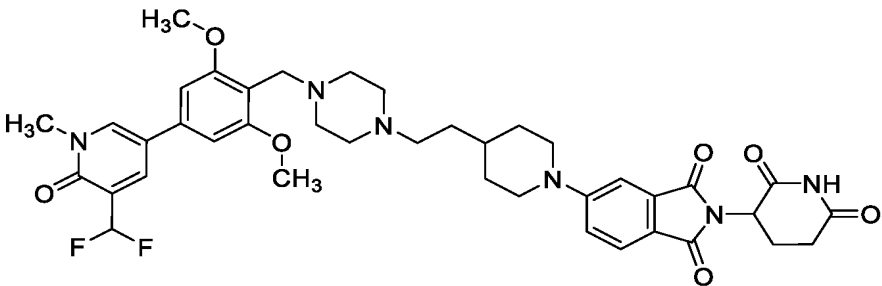
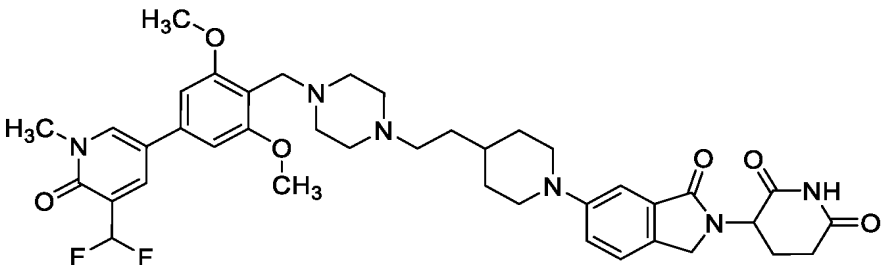
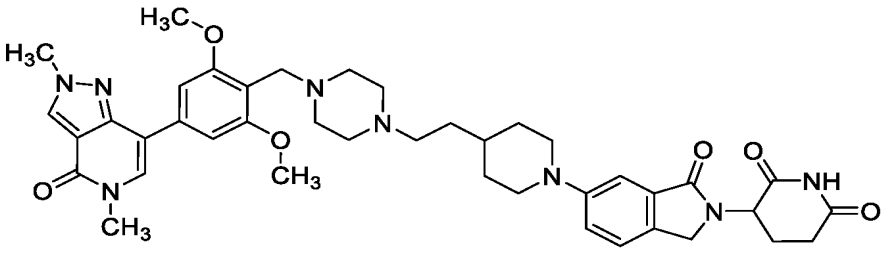
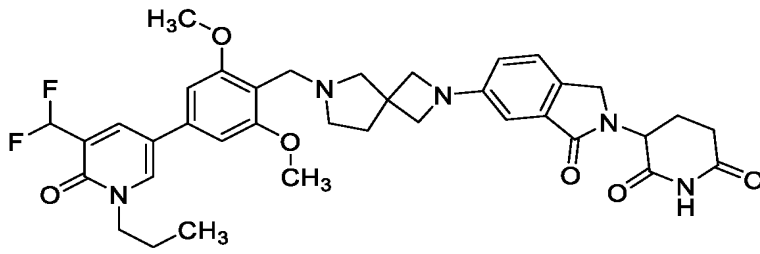
Compound No.	Structure
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D381	

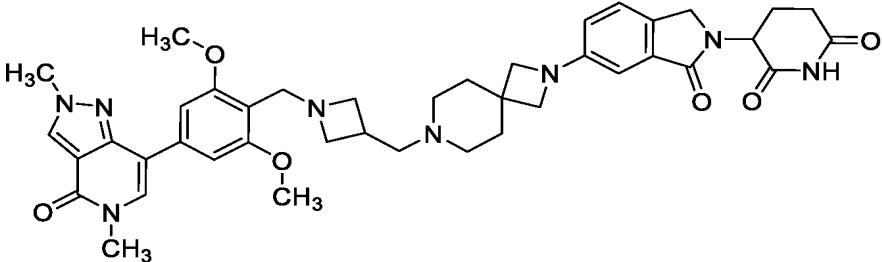
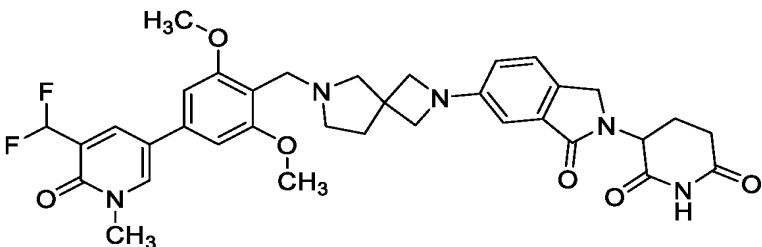
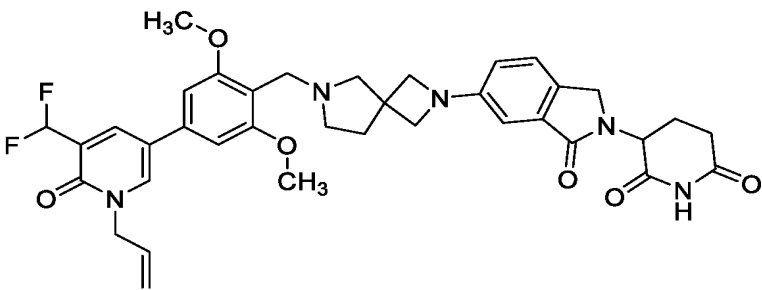
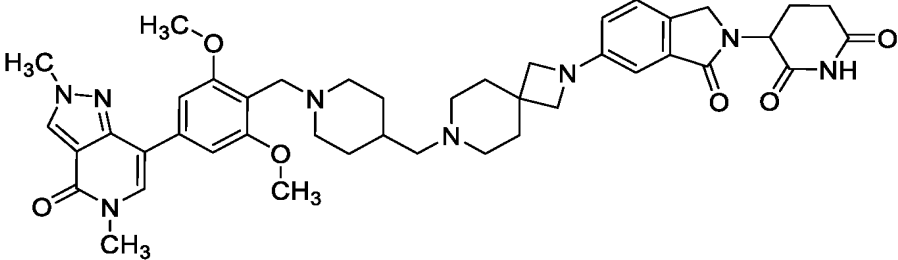
Compound No.	Structure
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D385	

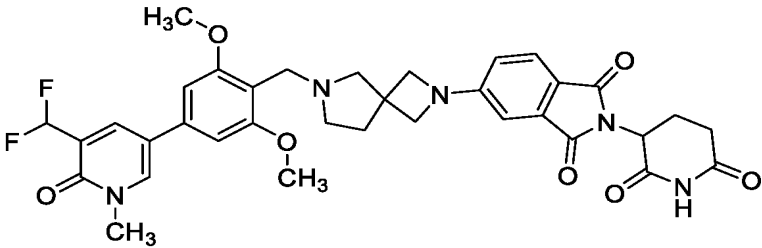
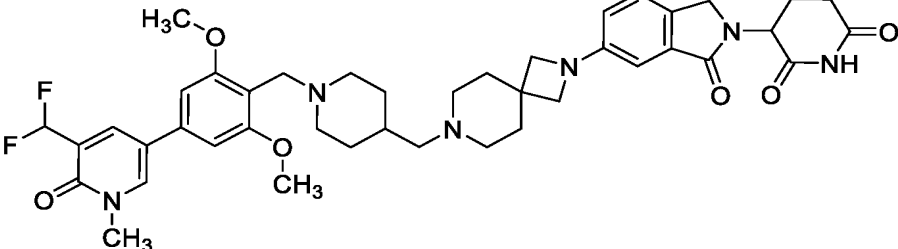
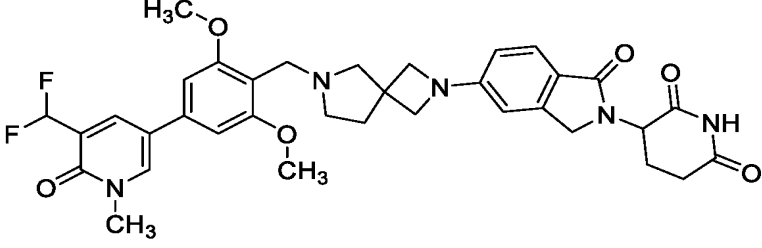
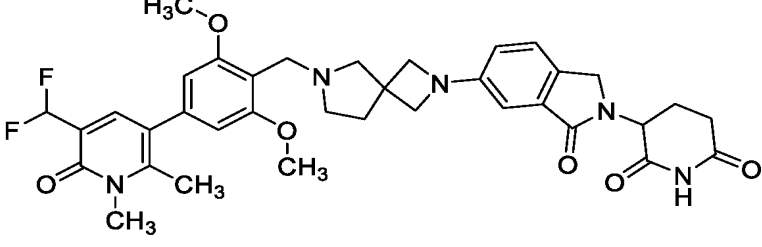
Compound No.	Structure
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D388	
D389	

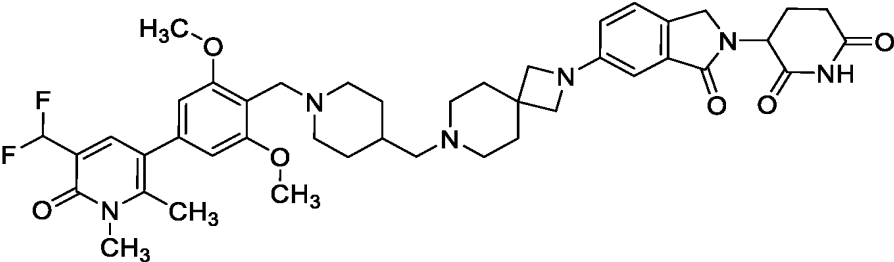
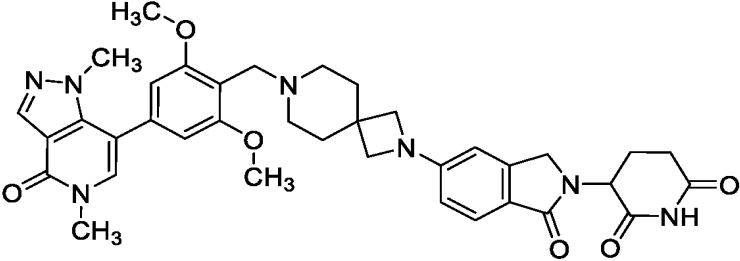
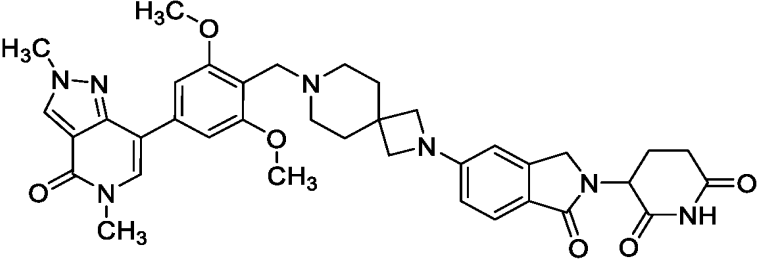
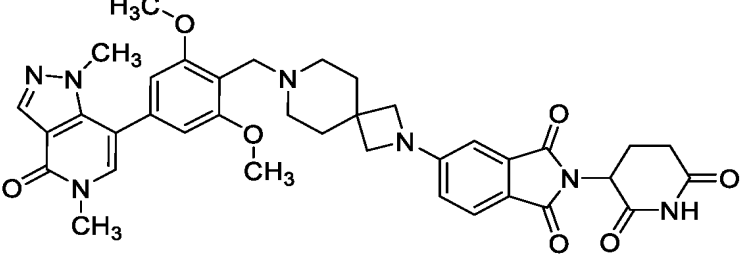
Compound No.	Structure
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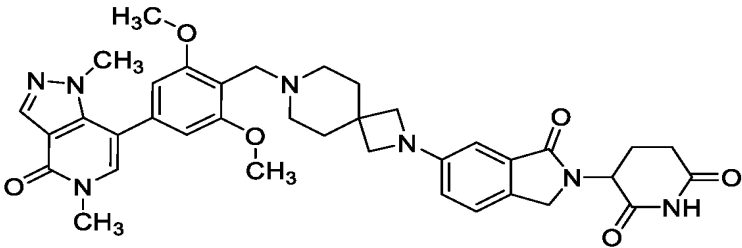
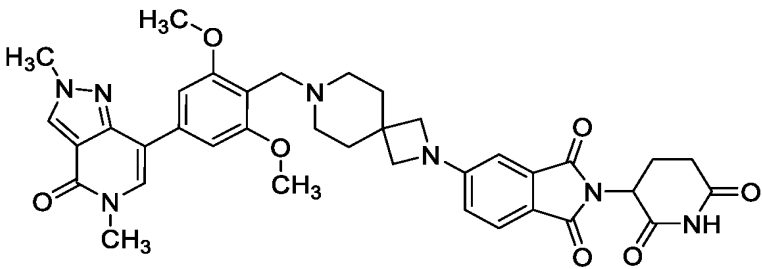
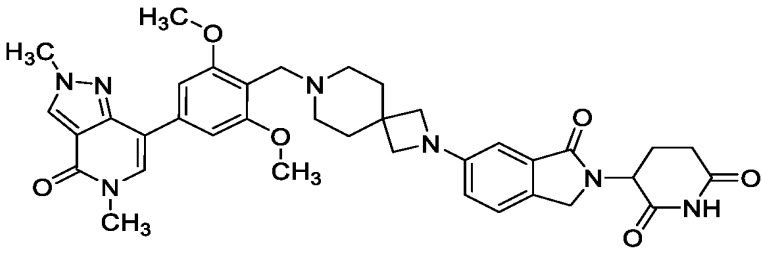
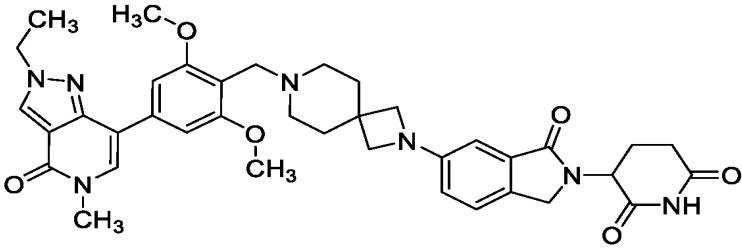
Compound No.	Structure
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D396	
D397	

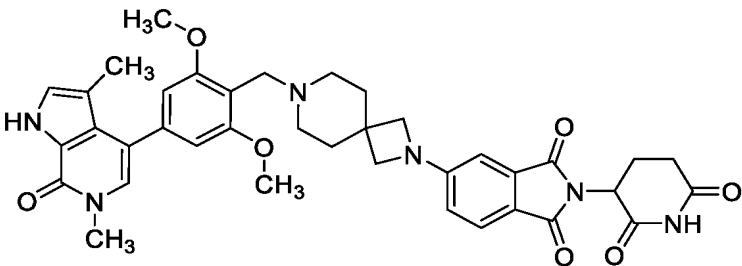
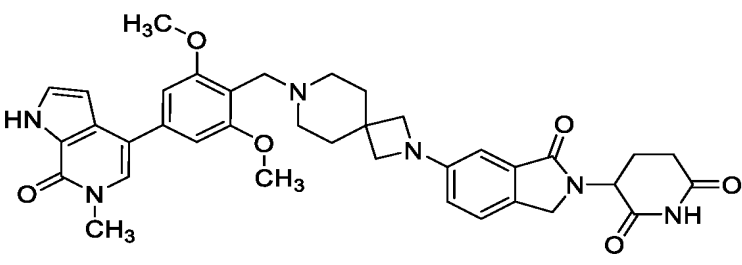
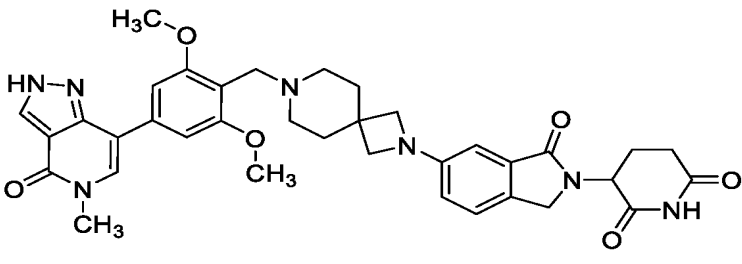
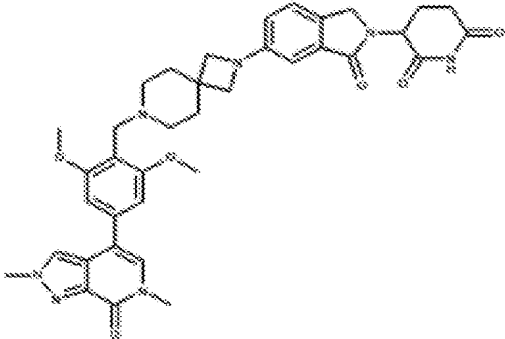
Compound No.	Structure
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D401	

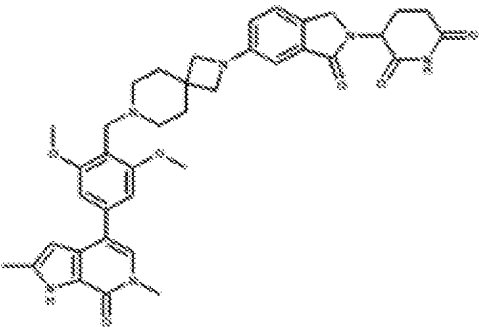
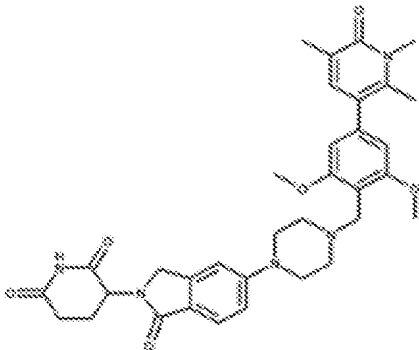
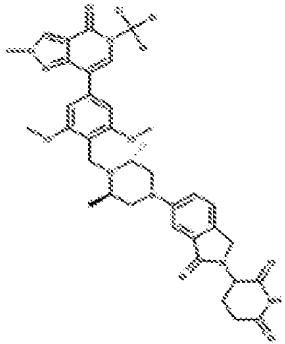
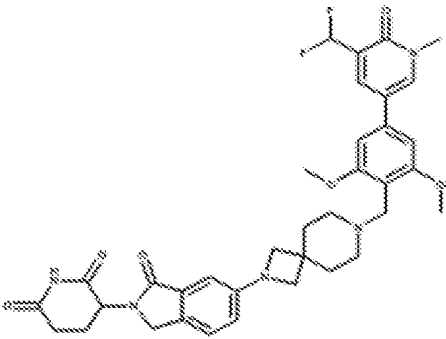
Compound No.	Structure
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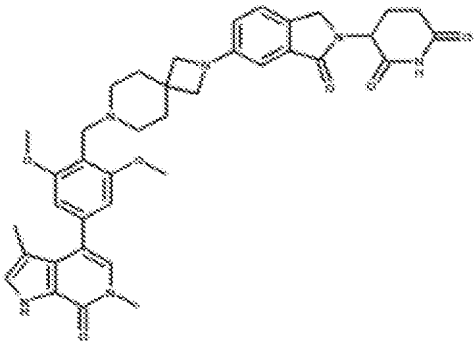
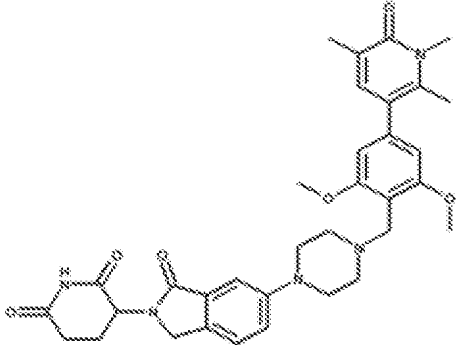
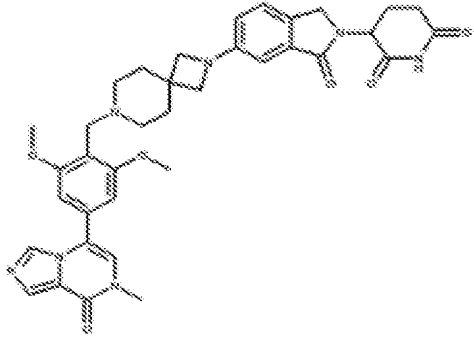
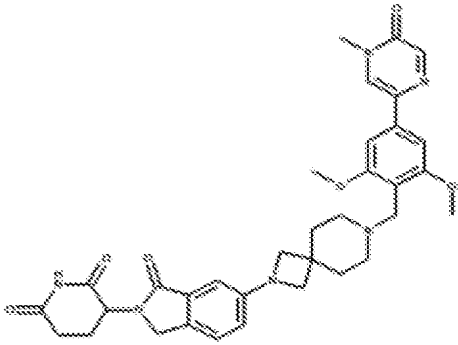
Compound No.	Structure
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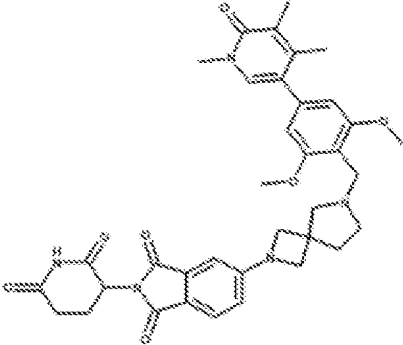
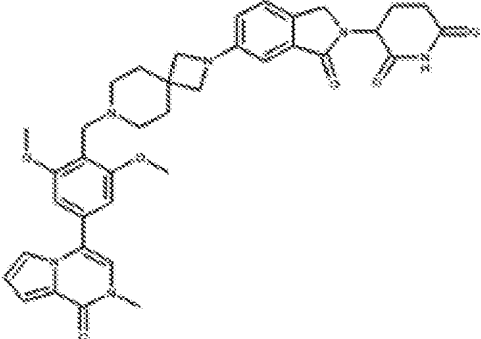
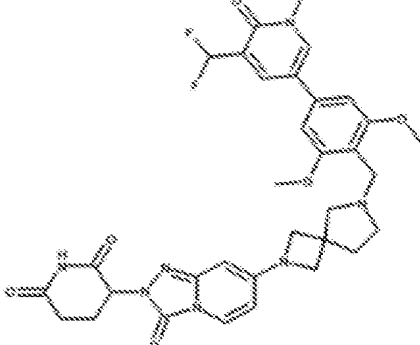
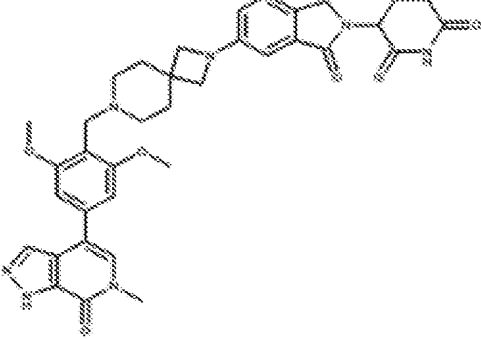
Compound No.	Structure
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D413	

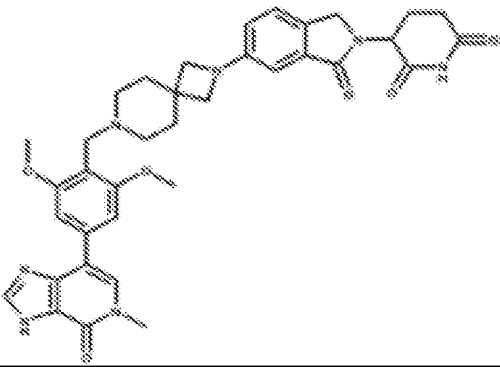
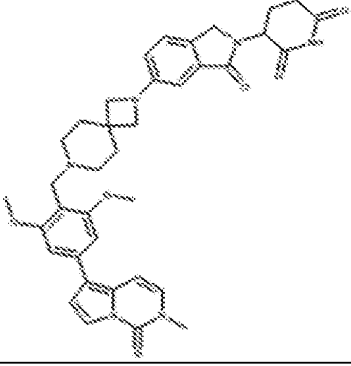
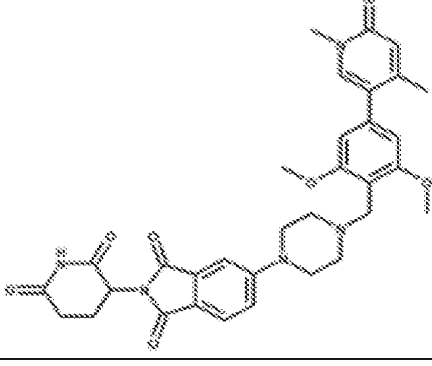
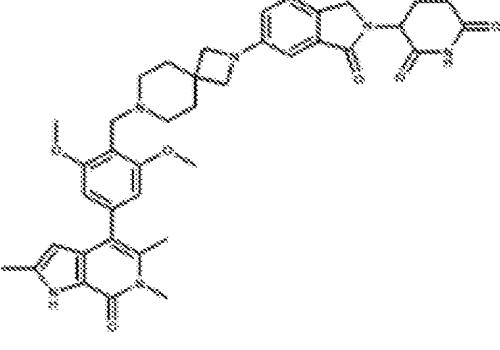
Compound No.	Structure
D414	 <p>Chemical structure of compound D414: A pyrimidine ring substituted with a methyl group at the 2-position and a methyl group at the 4-position. The pyrimidine ring is connected at the 6-position to a benzene ring. The benzene ring has methoxy groups at the 3 and 5 positions. The benzene ring is connected at the 1-position to a piperidine ring. The piperidine ring is connected at the 4-position to a cyclopropane ring. The cyclopropane ring is connected at the 1-position to an indole ring. The indole ring is connected at the 3-position to a pyridine ring. The pyridine ring is substituted with a methyl group at the 2-position and a methyl group at the 4-position.</p>
D415	 <p>Chemical structure of compound D415: A pyrimidine ring substituted with a methyl group at the 2-position and a methyl group at the 4-position. The pyrimidine ring is connected at the 6-position to a benzene ring. The benzene ring has methoxy groups at the 3 and 5 positions. The benzene ring is connected at the 1-position to a piperidine ring. The piperidine ring is connected at the 4-position to a cyclopropane ring. The cyclopropane ring is connected at the 1-position to an indole ring. The indole ring is connected at the 3-position to a pyridine ring. The pyridine ring is substituted with a methyl group at the 2-position and a methyl group at the 4-position.</p>
D416	 <p>Chemical structure of compound D416: A pyrimidine ring substituted with a methyl group at the 2-position and a methyl group at the 4-position. The pyrimidine ring is connected at the 6-position to a benzene ring. The benzene ring has methoxy groups at the 3 and 5 positions. The benzene ring is connected at the 1-position to a piperidine ring. The piperidine ring is connected at the 4-position to a cyclopropane ring. The cyclopropane ring is connected at the 1-position to an indole ring. The indole ring is connected at the 3-position to a pyridine ring. The pyridine ring is substituted with a methyl group at the 2-position and a methyl group at the 4-position.</p>
D417	 <p>Chemical structure of compound D417: A pyrimidine ring substituted with a methyl group at the 2-position and a methyl group at the 4-position. The pyrimidine ring is connected at the 6-position to a benzene ring. The benzene ring has methoxy groups at the 3 and 5 positions. The benzene ring is connected at the 1-position to a piperidine ring. The piperidine ring is connected at the 4-position to a cyclopropane ring. The cyclopropane ring is connected at the 1-position to an indole ring. The indole ring is connected at the 3-position to a pyridine ring. The pyridine ring is substituted with a methyl group at the 2-position and a methyl group at the 4-position.</p>

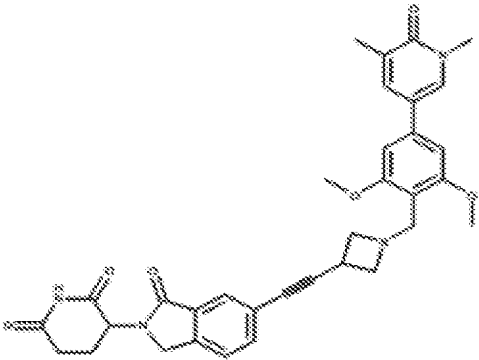
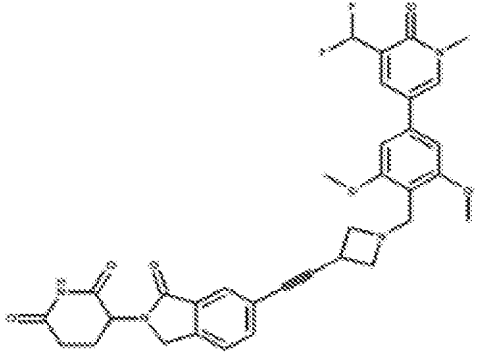
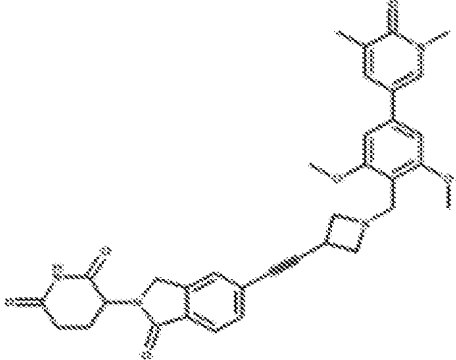
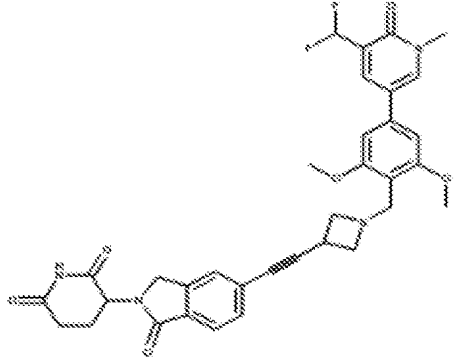
Compound No.	Structure
D418	 <p>Chemical structure of Compound D418: A complex molecule featuring a 4-methoxyphenyl ring substituted with a 1-methyl-4-oxo-1H-pyridine-2-yl group and a 2-methoxy-4-((1-methyl-4-oxo-1H-pyridine-2-yl)methyl)phenyl group. This is connected via a piperidine ring to a 1-methyl-4-oxo-1H-pyridine-2-yl group, which is further connected to a 1-methyl-4-oxo-1H-pyridine-2-yl group.</p>
D419	 <p>Chemical structure of Compound D419: A complex molecule featuring a 4-methoxyphenyl ring substituted with a 1-methyl-4-oxo-1H-pyridine-2-yl group and a 2-methoxy-4-((1-methyl-4-oxo-1H-pyridine-2-yl)methyl)phenyl group. This is connected via a piperidine ring to a 1-methyl-4-oxo-1H-pyridine-2-yl group, which is further connected to a 1-methyl-4-oxo-1H-pyridine-2-yl group.</p>
D420	 <p>Chemical structure of Compound D420: A complex molecule featuring a 4-methoxyphenyl ring substituted with a 1-methyl-4-oxo-1H-pyridine-2-yl group and a 2-methoxy-4-((1-methyl-4-oxo-1H-pyridine-2-yl)methyl)phenyl group. This is connected via a piperidine ring to a 1-methyl-4-oxo-1H-pyridine-2-yl group, which is further connected to a 1-methyl-4-oxo-1H-pyridine-2-yl group.</p>
D421	 <p>Chemical structure of Compound D421: A complex molecule featuring a 4-methoxyphenyl ring substituted with a 1-methyl-4-oxo-1H-pyridine-2-yl group and a 2-methoxy-4-((1-methyl-4-oxo-1H-pyridine-2-yl)methyl)phenyl group. This is connected via a piperidine ring to a 1-methyl-4-oxo-1H-pyridine-2-yl group, which is further connected to a 1-methyl-4-oxo-1H-pyridine-2-yl group.</p>

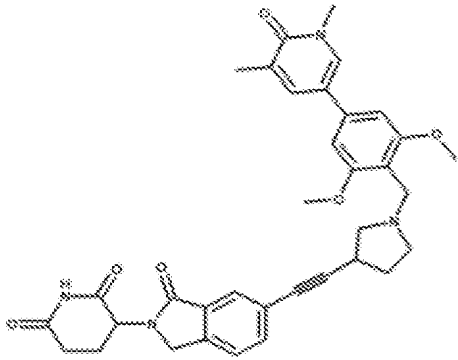
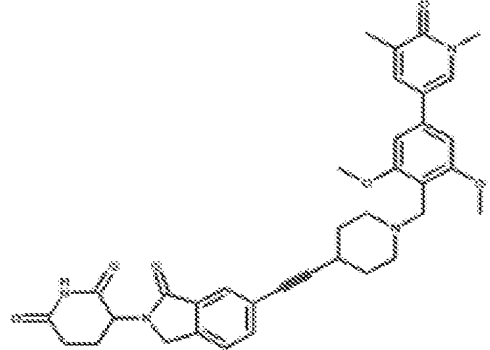
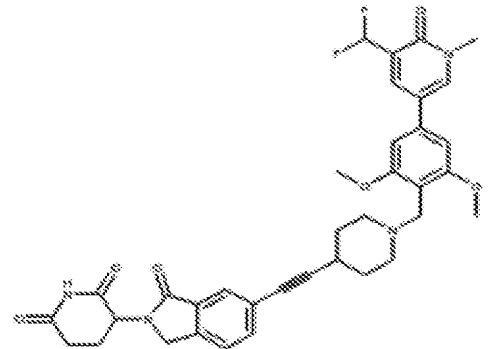
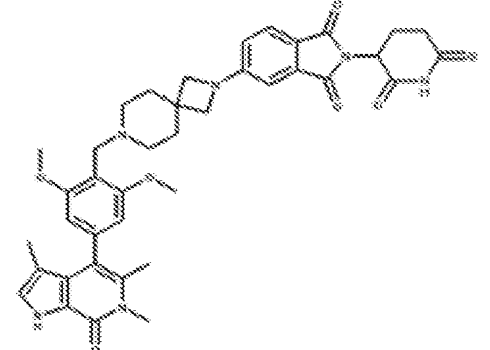
Compound No.	Structure
D422	 <p>The chemical structure of D422 is a complex molecule featuring a central benzene ring. This ring is substituted with a 1-methyl-2-(methylamino)pyridin-4-yl group at the 1-position, a 4-methoxyphenyl group at the 3-position, and a 4-methoxyphenyl group at the 4-position. The 4-methoxyphenyl group at the 4-position is further substituted with a 1-methyl-2-(methylamino)pyridin-4-yl group at its 4-position. The central benzene ring is also connected to a 1-methyl-2-(methylamino)pyridin-4-yl group at its 2-position.</p>
D423	 <p>The chemical structure of D423 is a complex molecule featuring a central benzene ring. This ring is substituted with a 1-methyl-2-(methylamino)pyridin-4-yl group at the 1-position, a 4-methoxyphenyl group at the 3-position, and a 4-methoxyphenyl group at the 4-position. The 4-methoxyphenyl group at the 4-position is further substituted with a 1-methyl-2-(methylamino)pyridin-4-yl group at its 4-position. The central benzene ring is also connected to a 1-methyl-2-(methylamino)pyridin-4-yl group at its 2-position.</p>
D424	 <p>The chemical structure of D424 is a complex molecule featuring a central benzene ring. This ring is substituted with a 1-methyl-2-(methylamino)pyridin-4-yl group at the 1-position, a 4-methoxyphenyl group at the 3-position, and a 4-methoxyphenyl group at the 4-position. The 4-methoxyphenyl group at the 4-position is further substituted with a 1-methyl-2-(methylamino)pyridin-4-yl group at its 4-position. The central benzene ring is also connected to a 1-methyl-2-(methylamino)pyridin-4-yl group at its 2-position.</p>
D425	 <p>The chemical structure of D425 is a complex molecule featuring a central benzene ring. This ring is substituted with a 1-methyl-2-(methylamino)pyridin-4-yl group at the 1-position, a 4-methoxyphenyl group at the 3-position, and a 4-methoxyphenyl group at the 4-position. The 4-methoxyphenyl group at the 4-position is further substituted with a 1-methyl-2-(methylamino)pyridin-4-yl group at its 4-position. The central benzene ring is also connected to a 1-methyl-2-(methylamino)pyridin-4-yl group at its 2-position.</p>

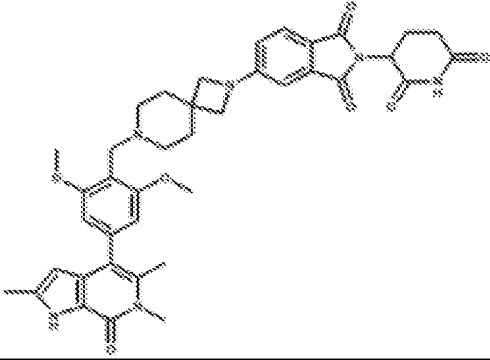
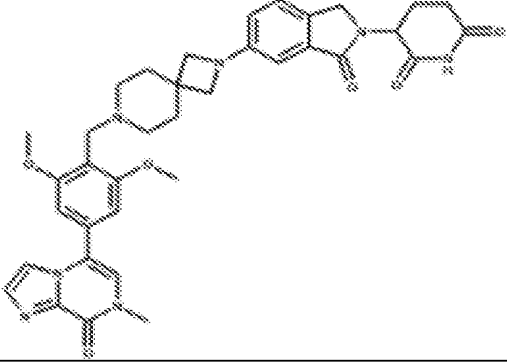
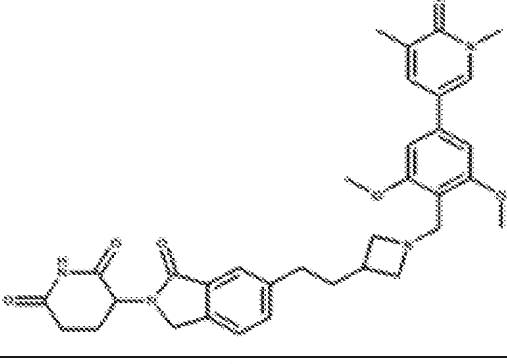
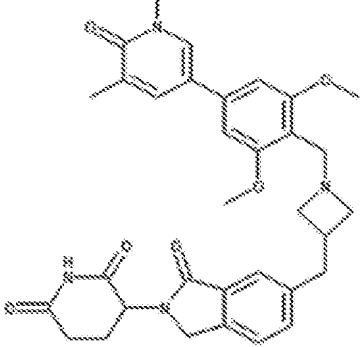
Compound No.	Structure
D426	 <p>Chemical structure of Compound D426: A complex molecule featuring a central benzene ring substituted with a 1,2,4-triazole-5-yl group, a 4-ethoxyphenyl group, and a 4-(2-ethoxyphenyl)phenyl group. This central ring is connected via a 1,4-bis(methylene)benzene linker to a 1,4-bis(methylene)piperidine ring, which is further connected to a 1,4-bis(methylene)benzene ring. This latter ring is substituted with a 1,2,4-triazole-5-yl group and a 4-ethoxyphenyl group.</p>
D427	 <p>Chemical structure of Compound D427: A complex molecule featuring a central benzene ring substituted with a 1,2,4-triazole-5-yl group, a 4-ethoxyphenyl group, and a 4-(2-ethoxyphenyl)phenyl group. This central ring is connected via a 1,4-bis(methylene)benzene linker to a 1,4-bis(methylene)piperidine ring, which is further connected to a 1,4-bis(methylene)benzene ring. This latter ring is substituted with a 1,2,4-triazole-5-yl group and a 4-ethoxyphenyl group.</p>
D428	 <p>Chemical structure of Compound D428: A complex molecule featuring a central benzene ring substituted with a 1,2,4-triazole-5-yl group, a 4-ethoxyphenyl group, and a 4-(2-ethoxyphenyl)phenyl group. This central ring is connected via a 1,4-bis(methylene)benzene linker to a 1,4-bis(methylene)piperidine ring, which is further connected to a 1,4-bis(methylene)benzene ring. This latter ring is substituted with a 1,2,4-triazole-5-yl group and a 4-ethoxyphenyl group.</p>
D429	 <p>Chemical structure of Compound D429: A complex molecule featuring a central benzene ring substituted with a 1,2,4-triazole-5-yl group, a 4-ethoxyphenyl group, and a 4-(2-ethoxyphenyl)phenyl group. This central ring is connected via a 1,4-bis(methylene)benzene linker to a 1,4-bis(methylene)piperidine ring, which is further connected to a 1,4-bis(methylene)benzene ring. This latter ring is substituted with a 1,2,4-triazole-5-yl group and a 4-ethoxyphenyl group.</p>

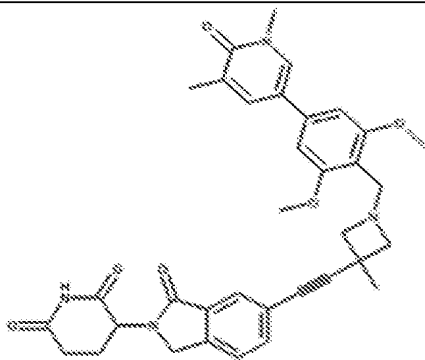
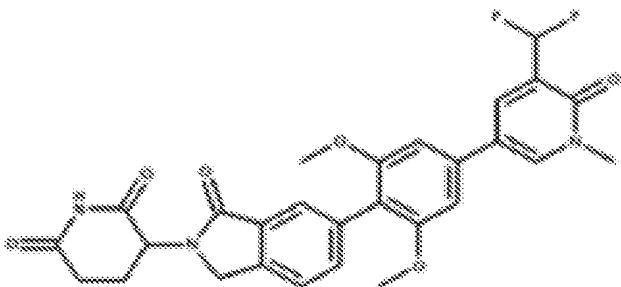
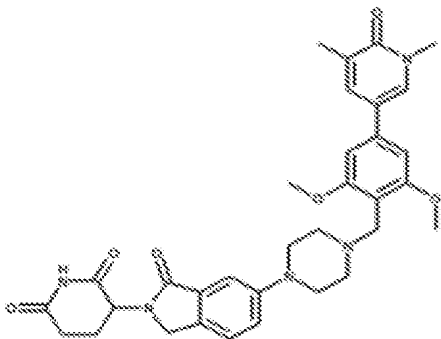
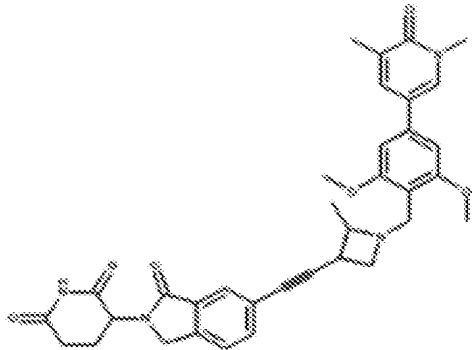
Compound No.	Structure
D430	 <p>Chemical structure of Compound D430: A complex molecule featuring a central benzene ring substituted with a 1,4-dioxane-2,5-dione ring, a 1,4-dioxane ring, and a 1,4-dioxane-2,5-dione ring. The structure is highly symmetrical and includes multiple oxygen atoms and a central nitrogen atom.</p>
D431	 <p>Chemical structure of Compound D431: A complex molecule featuring a central benzene ring substituted with a 1,4-dioxane-2,5-dione ring, a 1,4-dioxane ring, and a 1,4-dioxane-2,5-dione ring. The structure is highly symmetrical and includes multiple oxygen atoms and a central nitrogen atom.</p>
D432	 <p>Chemical structure of Compound D432: A complex molecule featuring a central benzene ring substituted with a 1,4-dioxane-2,5-dione ring, a 1,4-dioxane ring, and a 1,4-dioxane-2,5-dione ring. The structure is highly symmetrical and includes multiple oxygen atoms and a central nitrogen atom.</p>
D433	 <p>Chemical structure of Compound D433: A complex molecule featuring a central benzene ring substituted with a 1,4-dioxane-2,5-dione ring, a 1,4-dioxane ring, and a 1,4-dioxane-2,5-dione ring. The structure is highly symmetrical and includes multiple oxygen atoms and a central nitrogen atom.</p>

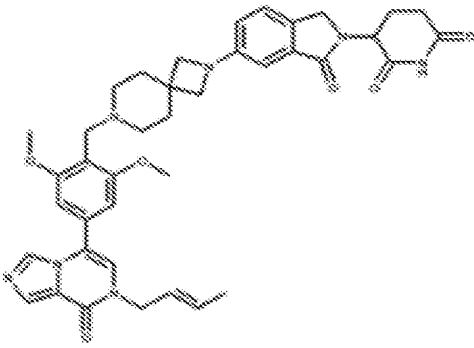
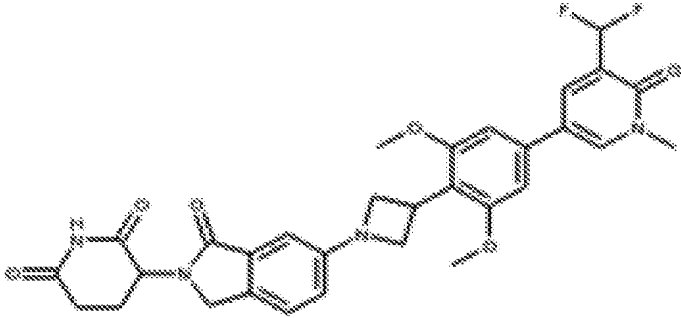
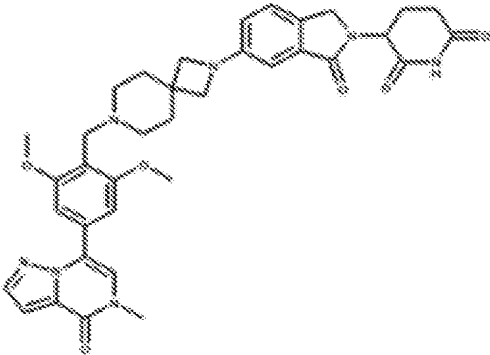
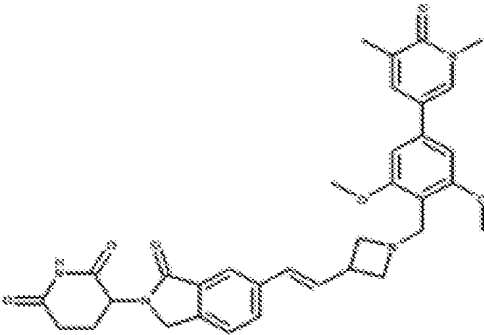
Compound No.	Structure
D434	
D435	
D436	
D437	

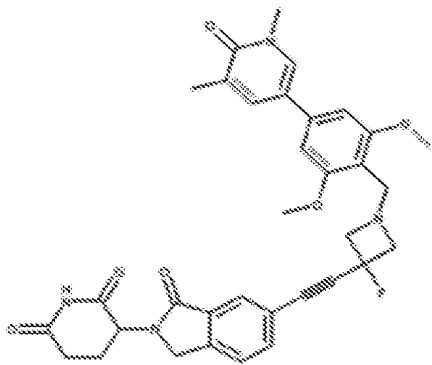
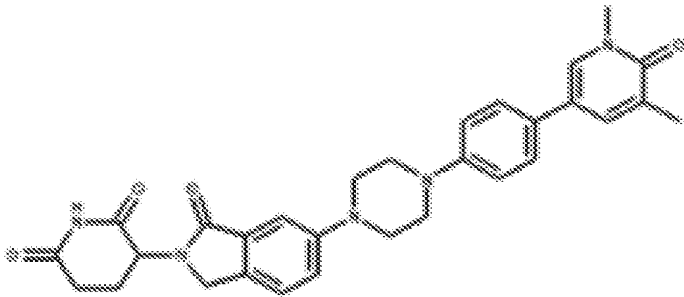
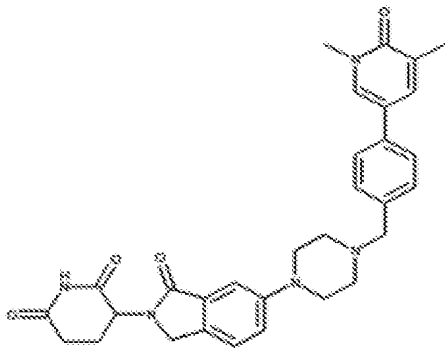
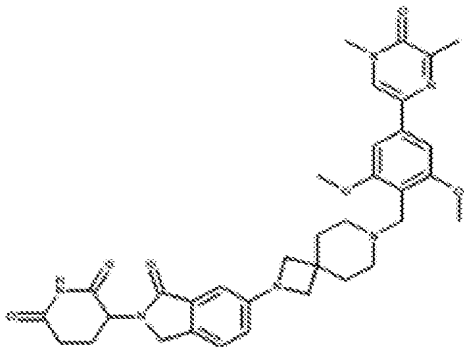
Compound No.	Structure
D438	 <p>The chemical structure of compound D438 features a 6,7-bis(methylidene)-5,6,7,8-tetrahydro-2H-pyrido[4,3-b]indole (A831007) moiety. This is connected via a propargyl linker to a cyclobutyl ring, which is further linked to a 2,6-dimethyl-4-(2,4,6-trimethylphenyl)phenyl group.</p>
D439	 <p>The chemical structure of compound D439 is identical to D438, featuring the A831007 moiety connected via a propargyl linker to a cyclobutyl ring, which is further linked to a 2,6-dimethyl-4-(2,4,6-trimethylphenyl)phenyl group.</p>
D440	 <p>The chemical structure of compound D440 is identical to D438, featuring the A831007 moiety connected via a propargyl linker to a cyclobutyl ring, which is further linked to a 2,6-dimethyl-4-(2,4,6-trimethylphenyl)phenyl group.</p>
D441	 <p>The chemical structure of compound D441 is identical to D438, featuring the A831007 moiety connected via a propargyl linker to a cyclobutyl ring, which is further linked to a 2,6-dimethyl-4-(2,4,6-trimethylphenyl)phenyl group.</p>

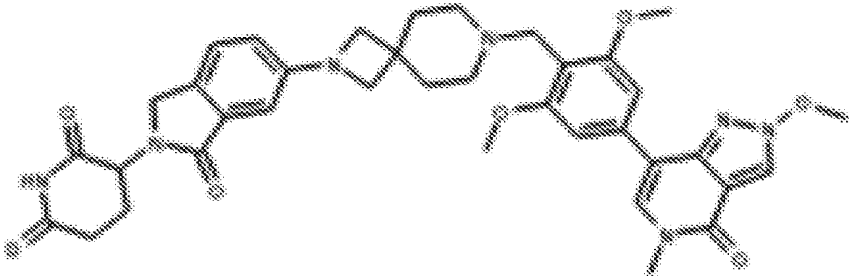
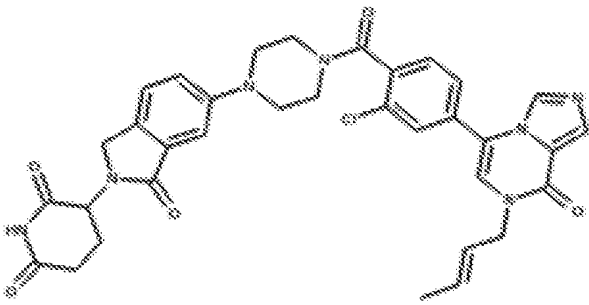
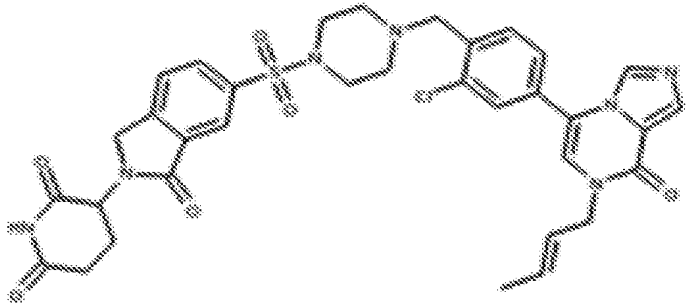
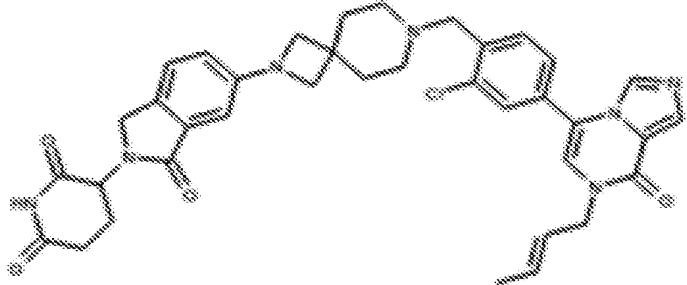
Compound No.	Structure
D442	 <p>Chemical structure of compound D442: A complex molecule featuring a central benzene ring substituted with a 2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-yl group, a 2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-yl group, and a 2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-yl group. The central benzene ring is also substituted with a 2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-yl group.</p>
D443	 <p>Chemical structure of compound D443: A complex molecule featuring a central benzene ring substituted with a 2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-yl group, a 2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-yl group, and a 2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-yl group. The central benzene ring is also substituted with a 2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-yl group.</p>
D444	 <p>Chemical structure of compound D444: A complex molecule featuring a central benzene ring substituted with a 2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-yl group, a 2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-yl group, and a 2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-yl group. The central benzene ring is also substituted with a 2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-yl group.</p>
D445	 <p>Chemical structure of compound D445: A complex molecule featuring a central benzene ring substituted with a 2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-yl group, a 2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-yl group, and a 2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-yl group. The central benzene ring is also substituted with a 2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-yl group.</p>

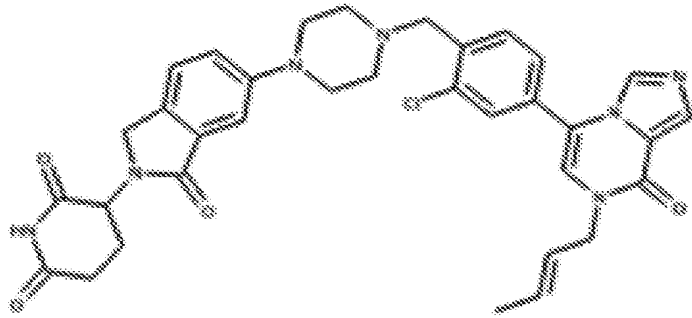
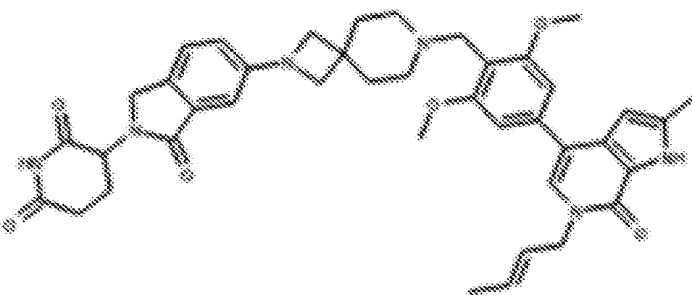
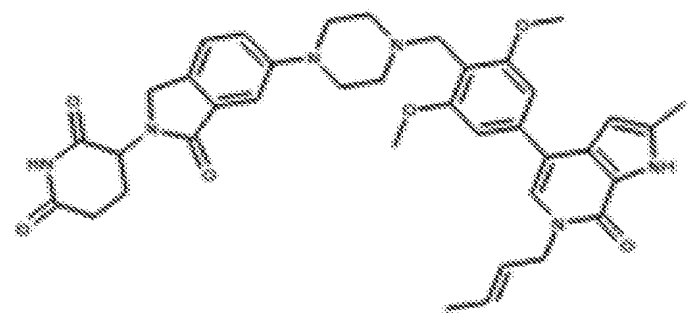
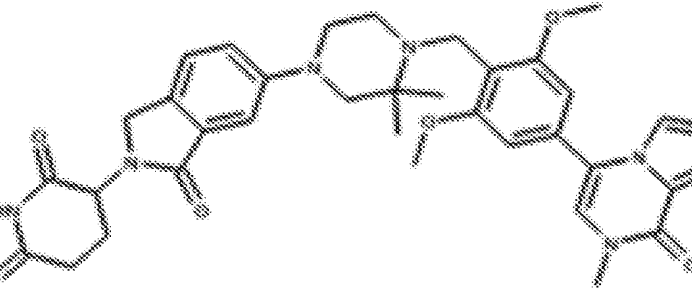
Compound No.	Structure
D446	 <p>Chemical structure of Compound D446: A complex molecule featuring a central benzene ring substituted with a 4-methoxyphenyl group, a 4-methoxyphenyl group, and a 4-methoxyphenyl group. It is connected via a cyclobutane ring to a 4-methoxyphenyl group, which is further connected to a 4-methoxyphenyl group.</p>
D447	 <p>Chemical structure of Compound D447: A complex molecule featuring a central benzene ring substituted with a 4-methoxyphenyl group, a 4-methoxyphenyl group, and a 4-methoxyphenyl group. It is connected via a cyclobutane ring to a 4-methoxyphenyl group, which is further connected to a 4-methoxyphenyl group.</p>
D448	 <p>Chemical structure of Compound D448: A complex molecule featuring a central benzene ring substituted with a 4-methoxyphenyl group, a 4-methoxyphenyl group, and a 4-methoxyphenyl group. It is connected via a cyclobutane ring to a 4-methoxyphenyl group, which is further connected to a 4-methoxyphenyl group.</p>
D449	 <p>Chemical structure of Compound D449: A complex molecule featuring a central benzene ring substituted with a 4-methoxyphenyl group, a 4-methoxyphenyl group, and a 4-methoxyphenyl group. It is connected via a cyclobutane ring to a 4-methoxyphenyl group, which is further connected to a 4-methoxyphenyl group.</p>

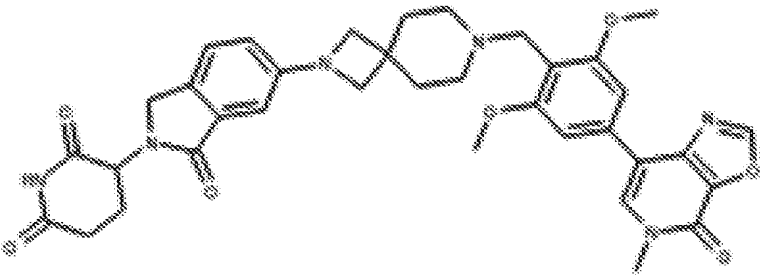
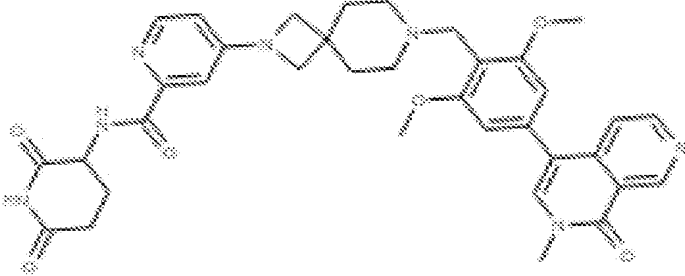
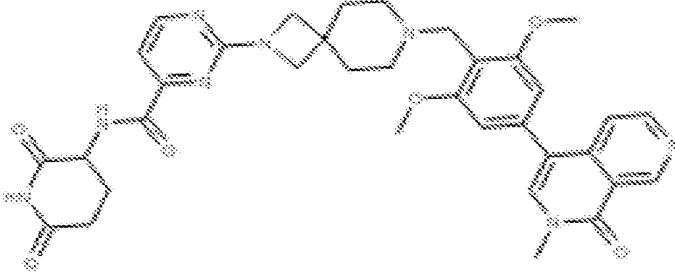
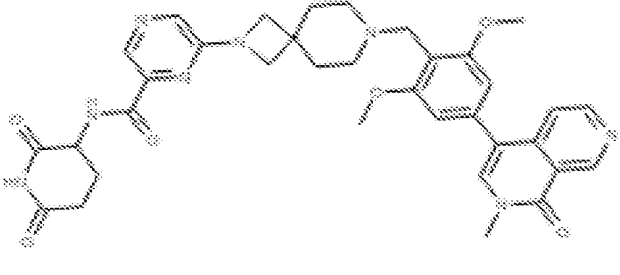
Compound No.	Structure
D450	
D451	
D452	
D453	

Compound No.	Structure
D454	 <p>Chemical structure of compound D454: A complex molecule featuring a central benzene ring substituted with a 2-ethyl-5-methylphenyl group, a 2-ethyl-5-methylphenyl group, and a 2-ethyl-5-methylphenyl group. It also includes a 2-ethyl-5-methylphenyl group and a 2-ethyl-5-methylphenyl group.</p>
D455	 <p>Chemical structure of compound D455: A complex molecule featuring a central benzene ring substituted with a 2-ethyl-5-methylphenyl group, a 2-ethyl-5-methylphenyl group, and a 2-ethyl-5-methylphenyl group. It also includes a 2-ethyl-5-methylphenyl group and a 2-ethyl-5-methylphenyl group.</p>
D456	 <p>Chemical structure of compound D456: A complex molecule featuring a central benzene ring substituted with a 2-ethyl-5-methylphenyl group, a 2-ethyl-5-methylphenyl group, and a 2-ethyl-5-methylphenyl group. It also includes a 2-ethyl-5-methylphenyl group and a 2-ethyl-5-methylphenyl group.</p>
D457	 <p>Chemical structure of compound D457: A complex molecule featuring a central benzene ring substituted with a 2-ethyl-5-methylphenyl group, a 2-ethyl-5-methylphenyl group, and a 2-ethyl-5-methylphenyl group. It also includes a 2-ethyl-5-methylphenyl group and a 2-ethyl-5-methylphenyl group.</p>

Compound No.	Structure
D458	 <p>Chemical structure of Compound D458: A complex molecule featuring a central benzene ring substituted with a 1,4-dimethyl-5-oxo-1,4-dihydro-2H-pyridin-2-yl group, a 1,4-dimethyl-5-oxo-1,4-dihydro-2H-pyridin-2-yl group, and a 1,4-dimethyl-5-oxo-1,4-dihydro-2H-pyridin-2-yl group. The central benzene ring is also substituted with a 1,4-dimethyl-5-oxo-1,4-dihydro-2H-pyridin-2-yl group.</p>
D459	 <p>Chemical structure of Compound D459: A complex molecule featuring a central benzene ring substituted with a 1,4-dimethyl-5-oxo-1,4-dihydro-2H-pyridin-2-yl group, a 1,4-dimethyl-5-oxo-1,4-dihydro-2H-pyridin-2-yl group, and a 1,4-dimethyl-5-oxo-1,4-dihydro-2H-pyridin-2-yl group. The central benzene ring is also substituted with a 1,4-dimethyl-5-oxo-1,4-dihydro-2H-pyridin-2-yl group.</p>
D460	 <p>Chemical structure of Compound D460: A complex molecule featuring a central benzene ring substituted with a 1,4-dimethyl-5-oxo-1,4-dihydro-2H-pyridin-2-yl group, a 1,4-dimethyl-5-oxo-1,4-dihydro-2H-pyridin-2-yl group, and a 1,4-dimethyl-5-oxo-1,4-dihydro-2H-pyridin-2-yl group. The central benzene ring is also substituted with a 1,4-dimethyl-5-oxo-1,4-dihydro-2H-pyridin-2-yl group.</p>
D461	 <p>Chemical structure of Compound D461: A complex molecule featuring a central benzene ring substituted with a 1,4-dimethyl-5-oxo-1,4-dihydro-2H-pyridin-2-yl group, a 1,4-dimethyl-5-oxo-1,4-dihydro-2H-pyridin-2-yl group, and a 1,4-dimethyl-5-oxo-1,4-dihydro-2H-pyridin-2-yl group. The central benzene ring is also substituted with a 1,4-dimethyl-5-oxo-1,4-dihydro-2H-pyridin-2-yl group.</p>

Compound No.	Structure
D462	
D463	
D464	
D465	

Compound No.	Structure
D466	 <p>Chemical structure of compound D466: A complex molecule featuring a central cyclohexane ring connected via a methylene bridge to a 1,4-dihydroquinoline-2,8-dione system. This system is further connected to a 1,4-dihydroquinoline-2,8-dione system, which is linked to a 1,4-dihydroquinoline-2,8-dione system, and finally to a 1,4-dihydroquinoline-2,8-dione system with a vinyl group.</p>
D467	 <p>Chemical structure of compound D467: A complex molecule featuring a central cyclohexane ring connected via a methylene bridge to a 1,4-dihydroquinoline-2,8-dione system. This system is further connected to a 1,4-dihydroquinoline-2,8-dione system, which is linked to a 1,4-dihydroquinoline-2,8-dione system, and finally to a 1,4-dihydroquinoline-2,8-dione system with a vinyl group.</p>
D468	 <p>Chemical structure of compound D468: A complex molecule featuring a central cyclohexane ring connected via a methylene bridge to a 1,4-dihydroquinoline-2,8-dione system. This system is further connected to a 1,4-dihydroquinoline-2,8-dione system, which is linked to a 1,4-dihydroquinoline-2,8-dione system, and finally to a 1,4-dihydroquinoline-2,8-dione system with a vinyl group.</p>
D469	 <p>Chemical structure of compound D469: A complex molecule featuring a central cyclohexane ring connected via a methylene bridge to a 1,4-dihydroquinoline-2,8-dione system. This system is further connected to a 1,4-dihydroquinoline-2,8-dione system, which is linked to a 1,4-dihydroquinoline-2,8-dione system, and finally to a 1,4-dihydroquinoline-2,8-dione system with a vinyl group.</p>

Compound No.	Structure
D470	
D471	
D472	
D473	

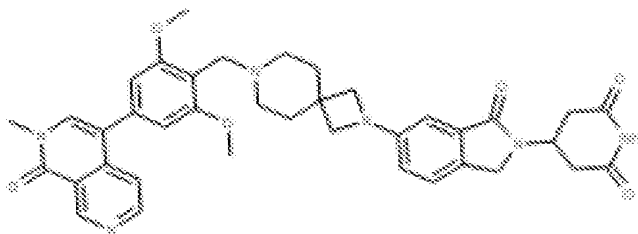
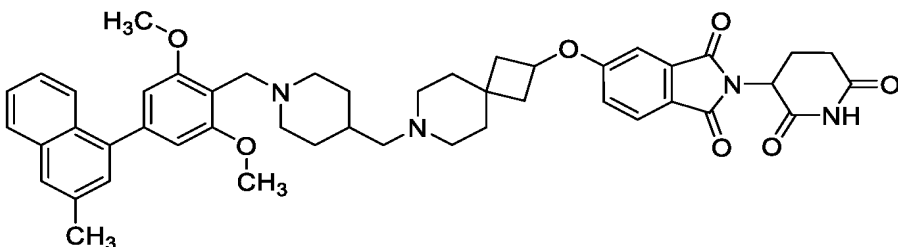
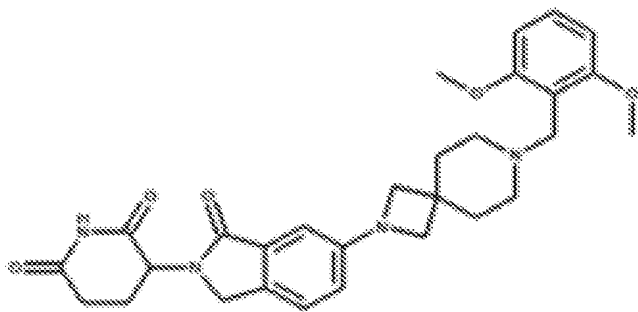
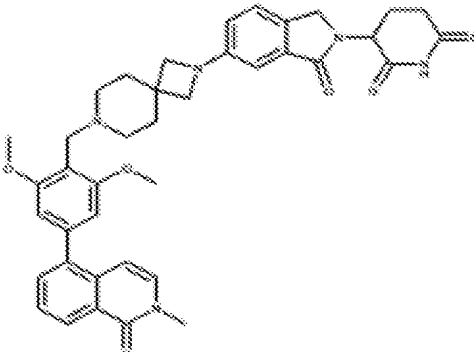
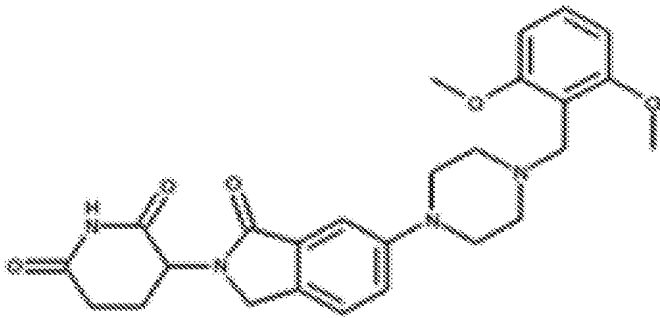
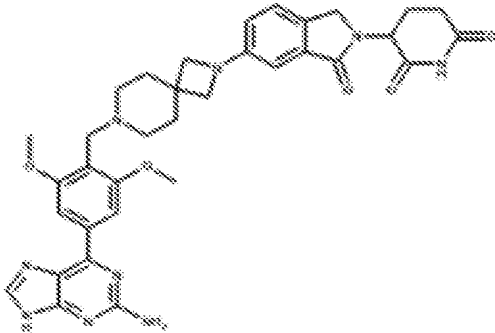
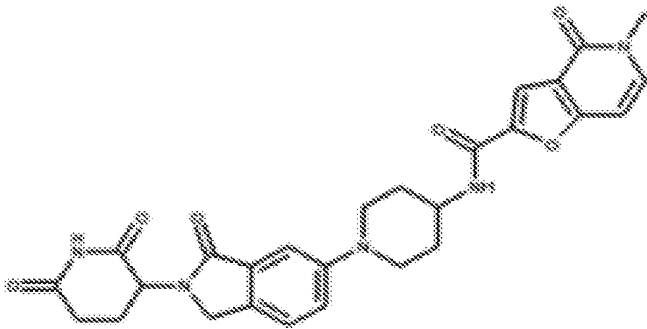
Compound No.	Structure
D474	

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.

5 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.

10 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, glioblastomas, 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,

5 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-

10 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

15 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

20 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

25 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

30 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

35 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,

40 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
5 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,
10 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
15 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,
20 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.,
25 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
30 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,
35 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));
40 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), Herpesvirus 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, glioblastomas, 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

5 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

10 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,

15 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,

20 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

25 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,

30 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

35 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,

40 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
5 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,
10 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
15 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
20 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
25 herpesvirus 6 (HHV-6), Herpesvirus 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
30 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,
35 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
40 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 C₂ alkyl group has the formula –CH₂CH₃. 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 C₁-C₂, C₁-C₃, C₁-C₄, C₁-C₅, or C₁-C₆. 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 C₁-C₆ aliphatic as used herein indicates a straight or branched alkyl, alkenyl, or alkynyl group having from 1, 2, 3, 4, 5, or 6

carbon atoms and is intended to mean that each of these is described as an independent species. For example, the term C₁-C₄ 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, NO₂, N(R^{N2})₂, SO₂OR^{N2}, SO₂R^{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., —NH₂) 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 C₁-C₆ alkyl C₆-C₁₀ aryl, C₁-C₁₀ alkyl C₆-C₁₀ aryl, or C₁-C₂₀ alkyl C₆-C₁₀ 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 -N₃ 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 C₃-C₁₂, 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, oxazolyl, 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 C₁-C₆ alkyl C₂-C₉ heteroaryl, C₁-C₁₀ alkyl C₂-C₉ heteroaryl, or C₁-C₂₀ alkyl C₂-C₉ 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 C₁-C₆ alkyl C₂-C₉ heterocyclyl, C₁-C₁₀ alkyl C₂-C₉ heterocyclyl, or C₁-C₂₀ alkyl C₂-C₉ 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-butyloxy, 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-biphenyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxy carbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropylloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxy carbonyl, fluorenyl-9-methoxycarbonyl, cyclopentylloxycarbonyl, adamantylloxycarbonyl, cyclohexylloxycarbonyl, 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.

5 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
10 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
15 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
20 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
25 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
30 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
35 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
40 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 ^2H , ^3H , ^{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 ^3H and ^{14}C) can be useful in compound or substrate tissue distribution assays. Tritiated (i.e., ^3H) 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., ^2H) 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 ^2H or ^3H , 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.

5 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, 10 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 15 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 20 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 25 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 30 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 35 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 40 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:

$$100 \text{ multiplied by (the fraction } X/Y \text{)}$$

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 (diluent), film formers or coatings, flavors,

fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspending 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 shown 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 μ M 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 μ M, 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 μ M, 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 μ M, 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

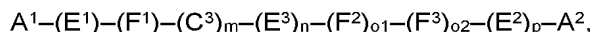
Formula I,

where

A is a BRD9 binding moiety;

B is a degradation moiety; and

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



Formula II

wherein

A¹ is a bond between the linker and A;

10 A² is a bond between B and the linker;

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

each of E¹ and E² is, independently, O, S, NR^N, optionally substituted C₁₋₁₀ alkyl, optionally substituted C₂₋₁₀ alkenyl, optionally substituted C₂₋₁₀ alkynyl, optionally substituted C_{2-C10} polyethylene glycol, or optionally substituted C₁₋₁₀ heteroalkyl;

15 E³ is O, S, or NR^N;

each R^N is, independently, H, optionally substituted C₁₋₄ alkyl, optionally substituted C₂₋₄ alkenyl, optionally substituted C₂₋₄ alkynyl, optionally substituted C₂₋₆ heterocyclyl, optionally substituted C₆₋₁₂ aryl, or optionally substituted C₁₋₇ heteroalkyl;

C³ is carbonyl, thiocarbonyl, sulphonyl, or phosphoryl; and

20 each of F¹, F², and F³ is, independently, optionally substituted C_{3-C10} carbocyclyl, optionally substituted C_{2-C9} heterocyclyl, optionally substituted C_{6-C10} aryl, or optionally substituted C_{2-C9} heteroaryl, or a pharmaceutically acceptable salt thereof.

Pharmaceutical Uses

25 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.

30 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
35 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
40 of the tumor.

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

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

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

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

Combination Therapies

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

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

agents, antimetabolites, folic acid analogs, pyrimidine analogs, purine analogs and related inhibitors, vinca alkaloids, epipodopyllotoxins, 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), irinotecan, oxaliplatin, capecitabine, paclitaxel, and doxorubicin. Non-limiting examples of chemotherapeutic agents include alkylating agents such as thiopeta and cyclophosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide 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 ranimustine; 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 antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabycin, 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, mepitiothane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestabucil; 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, Schaumburg, IL), and TAXOTERE® doxorubicin (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	CTTCTTGCTTCTTGCCCA	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	CCGCGGCCCCCTCTAGCCTGC
236	CCGCCCAGGAAGAGAAGAAG	352	CATCCTTCACAACTCCTGC
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	AGGTGGAGCCGCCCCAGAT	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	GCTGGCGGAGGAAGTGTTC	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	AACTTGTA GTACACGGTATC	395	TCGTCTCATCCAAGTTCAA
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	ACTGGTACAACCTCAGGGAC	402	AGGCGGAGCGCGGCGGCTCT
287	CTTGTA CTGGTACAACCTCA	403	AGGGAGCTGAGGTTGGACGA
288	ACTTGTA CTGGTACAACCTTC	404	GTTGGACAGGGAGCTGAGGT
289	TTGGCAGTTTCTACTTGTA C	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	CCCTTCTCGCCTGAGTGTG
306	CCTTGCCGCCTGGGAGGAAC	422	GCCCTTCTCGCCTGAGTGTG
307	AGGATCAACCGGTTCTCTCC	423	TAGGGGTCGTGGGTGACGTC
308	ATCAACCGGTTCTCTCCAGG	424	AAGAACTCATAGGGGTCTG
309	GCACTACCTTGCCGCCTGGG	425	GAAGAACTCATAGGGGTCTG
310	AGAGCACTACCTTGCCGCCT	426	GAGACTGAAGAACTCATAG
311	CCGGTTCCTCCAGGCGGCA	427	GGAGACTGAAGAACTCATA
312	TCCTCTTCAGATAGCCCATC	428	TGGAGACTGAAGAACTCAT
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	GGCAGTCGTTCCGTTGATAT

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	GTCGTGAAGTGCATTTCGATC
444	1 sg_Non_Targeting_Human_0011 Non_Targeting_Human	Non_Targeting_Human	GTTCTGACTCGCGTGACCGTA
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	GAAGTGACGTCGATTTCGATA
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	GCAGCTCGTGTGTCGTA
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	GAGTGTGTCGTCGTTGCTCCTA
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	GCCATTTCGGCGCGGCACTTC
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	GAAGTGCATCTTGTTGTAGT
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

SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
509	1 sg_Non_Targeting_Human_0076 Non_Targeting_Human	Non_Targeting_Human	GAAGATAAGTCGCTGTCTCG
510	1 sg_Non_Targeting_Human_0077 Non_Targeting_Human	Non_Targeting_Human	GTCGGCGTTCTGTTGTGACT
511	1 sg_Non_Targeting_Human_0078 Non_Targeting_Human	Non_Targeting_Human	GAGGCAAGCCGTTAGGTGTA
512	1 sg_Non_Targeting_Human_0079 Non_Targeting_Human	Non_Targeting_Human	GCGGATCCAGATCTCATTCG
513	1 sg_Non_Targeting_Human_0080 Non_Targeting_Human	Non_Targeting_Human	GGAACATAGGAGCACGTAGT
514	1 sg_Non_Targeting_Human_0081 Non_Targeting_Human	Non_Targeting_Human	GTCATCATTATGGCGTAAGG
515	1 sg_Non_Targeting_Human_0082 Non_Targeting_Human	Non_Targeting_Human	GCGACTAGCGCCATGAGCGG
516	1 sg_Non_Targeting_Human_0083 Non_Targeting_Human	Non_Targeting_Human	GGCGAAGTTCGACATGACAC
517	1 sg_Non_Targeting_Human_0084 Non_Targeting_Human	Non_Targeting_Human	GCTGTCGTGTGGAGGCTATG
518	1 sg_Non_Targeting_Human_0085 Non_Targeting_Human	Non_Targeting_Human	GCGGAGAGCATTGACCTCAT
519	1 sg_Non_Targeting_Human_0086 Non_Targeting_Human	Non_Targeting_Human	GACTAATGGACCAAGTCAGT
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	GTACTIONCAATCCGCGATGAC
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	GAATCGGAATAGTTGATTCTG
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
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SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
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549	1 sg_Non_Targeting_Human_GA_0116 Non_Targeting_Human	Non_Targeting_Human	CGACTAACCGGAAACTTTTT
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551	1 sg_Non_Targeting_Human_GA_0118 Non_Targeting_Human	Non_Targeting_Human	CAGGAGTCGCCGATACGCGT
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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
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561	1 sg_Non_Targeting_Human_GA_0128 Non_Targeting_Human	Non_Targeting_Human	CGCGACGACTCAACCTAGTC
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564	1 sg_Non_Targeting_Human_G A_0131 Non_Targeting_Human	Non_Targeting_Human	CGTATTCGACTCTCAACGCG
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SEQ ID NO.	gRNA Label	Gene	Nucleic Acid Sequence
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587	1 sg_Non_Targeting_Human_G A_0154 Non_Targeting_Human	Non_Targeting_Human	TGAACGCGTGTTTCCTTGCA
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596	1 sg_Non_Targeting_Human_G A_0163 Non_Targeting_Human	Non_Targeting_Human	TTATCGCGTAGTGCTGACGT
597	1 sg_Non_Targeting_Human_G A_0164 Non_Targeting_Human	Non_Targeting_Human	TACGCTTGCGTTTAGCGTCC
598	1 sg_Non_Targeting_Human_G A_0165 Non_Targeting_Human	Non_Targeting_Human	CGCGGCCACGCGTCATCGC

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599	1 sg_Non_Targeting_Human_G A_0166 Non_Targeting_Human	Non_Targeting_Human	AGCTCGCCATGTCGGTTCTC
600	1 sg_Non_Targeting_Human_G A_0167 Non_Targeting_Human	Non_Targeting_Human	AACTAGCCCGAGCAGCTTCG
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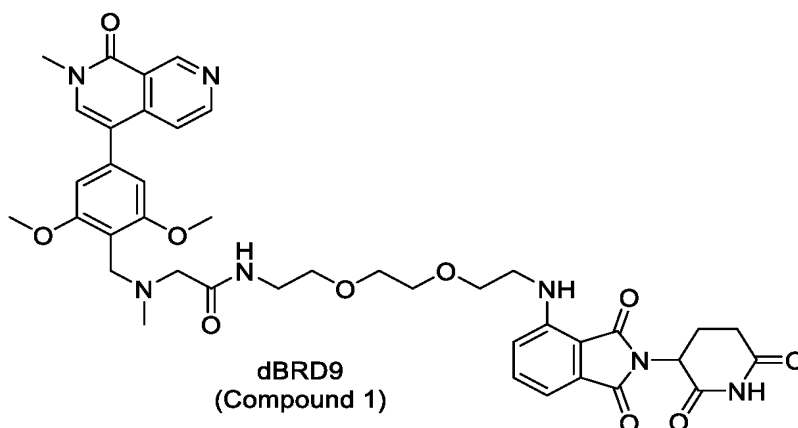
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639	3 sg_hGTF2B_CC_2 GTF2B	GTF2B	GGTGACCGGGTTATTGATGT
640	3 sg_hGTF2B_CC_3 GTF2B	GTF2B	TTAGTGAGGACTACAGAGC
641	3 sg_hGTF2B_CC_4 GTF2B	GTF2B	ACATATAGCCCGTAAAGCTG
642	3 sg_hHSPA5_CC_1 HSPA5	HSPA5	CGTTGGCGATGATCTCCACG
643	3 sg_hHSPA5_CC_2 HSPA5	HSPA5	TGGCCTTTTCTACCTCGCGC
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645	3 sg_hHSPA5_CC_4 HSPA5	HSPA5	GAAGCCCGTCCAGAAAGTGT
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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
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660	3 sg_hPOLR2L_CC_3 POLR2L	POLR2L	GCAGCGTACAGGGATGATCA
661	3 sg_hPOLR2L_CC_4 POLR2L	POLR2L	GCAGTAGCGCTTCAGGCCCA
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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.

- 5 **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.



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.

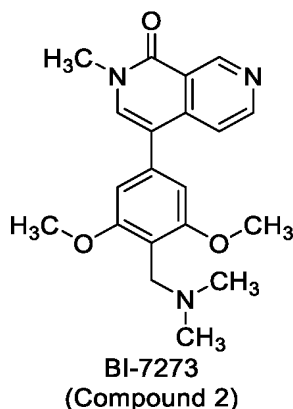
Example 3 – Inhibition of growth of synovial cell lines by BRD9 inhibitors and BRD9 degraders

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 μ M 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 μ M BRD9 degrader, Compound 1.



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 dH2O 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 μ L complete media and treated at day 2 with DMSO, Staurosporin, or BRD9 degrader, 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 μ L of 0.005% (w/v) crystal violet solution in 25% (v/v) methanol for at least 1 hour at room temperature. Subsequently plates were scanned on an Odyssey CLx Imaging system.

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

Overall, Compound 1 showed most significant growth inhibition in all synovial cell lines.

Example 5- Inhibition of cell growth in synovial sarcoma cells

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

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

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

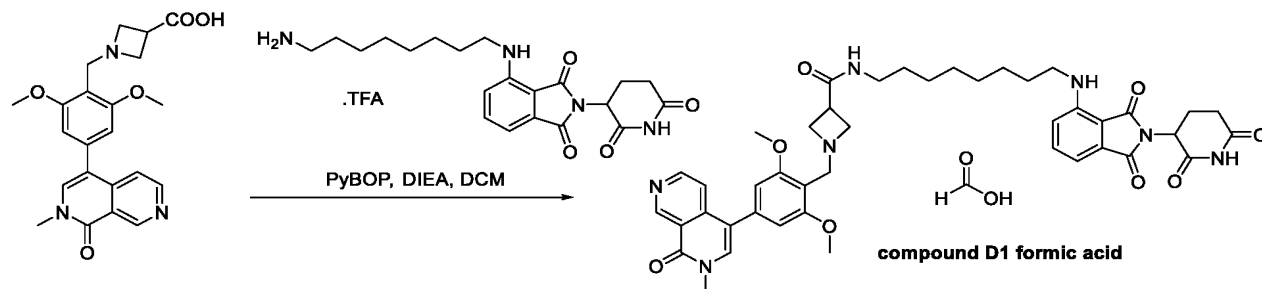
Example 6 – Composition for SS18-SSX1-BAF

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

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

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

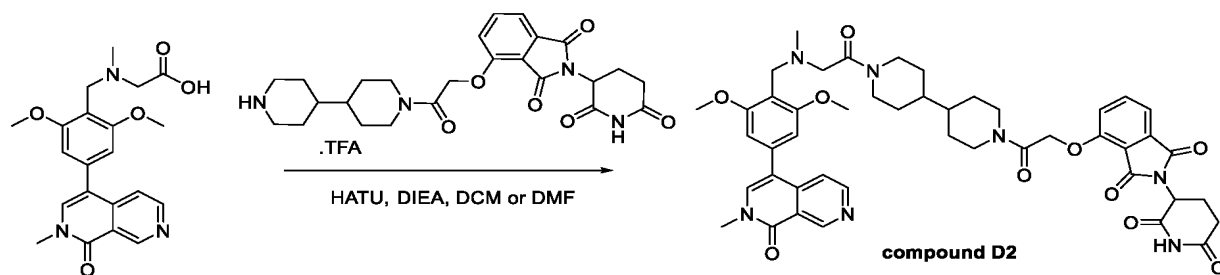
Example 7 – Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)azetidine-3-carboxamide formic acid (compound D1 formic acid)



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

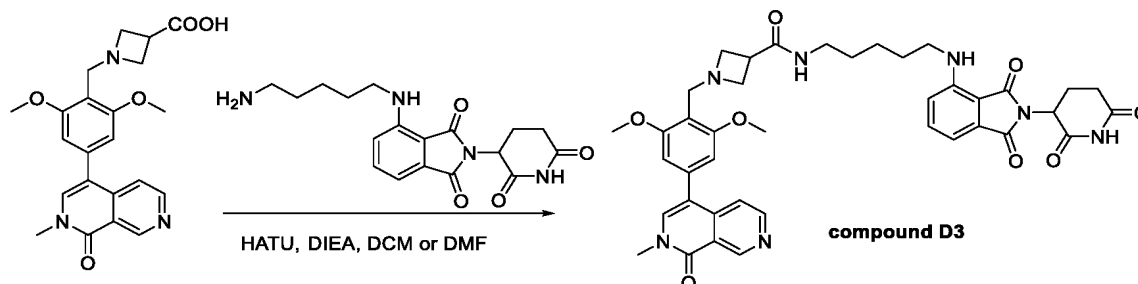
by Prep-HPLC (conditions: X Select CSH Prep C18 OBD Column, 5 μ m, 19*150 mm; mobile phase, Water (0.1% FA) and ACN (25% Phase B up to 45% in 8 minutes); Detector, UV). This resulted in 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)azetidine-3-carboxamide formic acid (4 mg, 4.81%) as a yellow solid. ¹H NMR (400 MHz, Methanol-*d*₄) 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)(methylamino)acetyl]-[4,4-bipiperidin]-1-yl]-2-oxoethoxy)-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (compound D2)



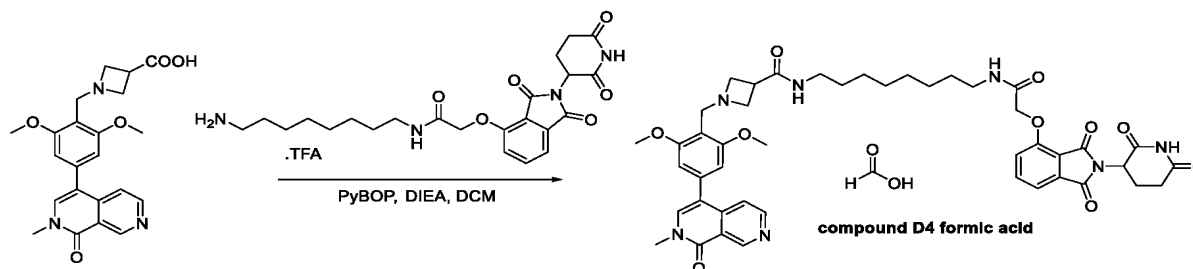
To a stirred solution of 2-([2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl)(methylamino)acetic acid (19.99 mg, 0.050 mmol, 1 equiv) and DIPEA (19.50 mg, 0.151 mmol, 3 equiv) in DMF (3 mL) was added PyBOP (28.68 mg, 0.075 mmol, 1.5 equiv) and 4-(2-[4,4-bipiperidin]-1-yl)-2-oxoethoxy)-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-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 μ m, 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)(methylamino)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. ¹H NMR (300 MHz, Methanol-*d*₄) 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 μ m, 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. ¹H NMR (400 MHz, Methanol-*d*₄) 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.

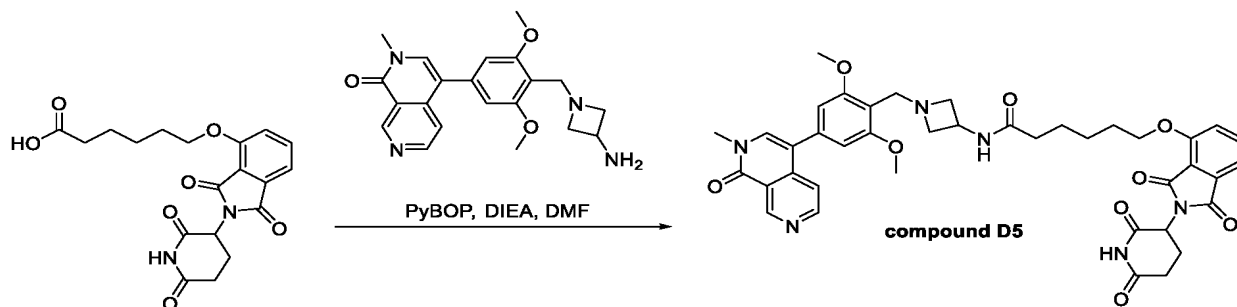
Example 10 – Preparation of N-[8-[(1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidin-3-yl)formamido]octyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy]acetamide formic acid (compound D4 formic acid)



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

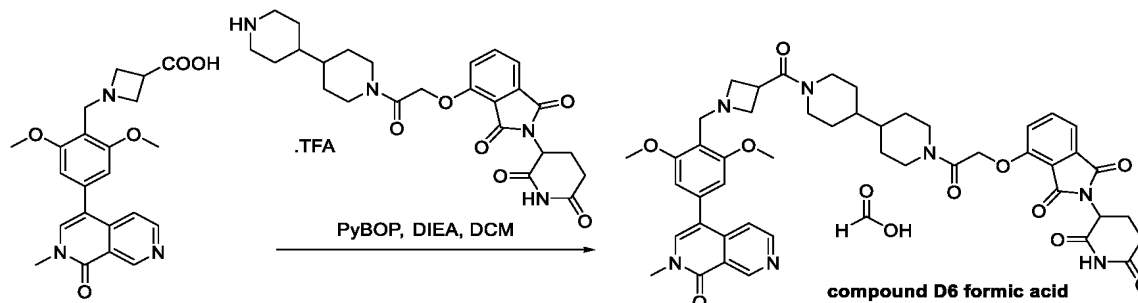
(conditions: X Bridge Shield RP18 OBD Column, 5 μ m, 19*150 mm; mobile phase, Water (0.1% FA) and ACN (20% Phase B up to 32% in 7 minutes); Detector, UV). This resulted in *N*-[8-[(1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidin-3-yl)formamido]octyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy]acetamide formic acid (12 mg, 14.77%) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) 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]azetidin-3-yl)-6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy]hexanamide (compound D5)



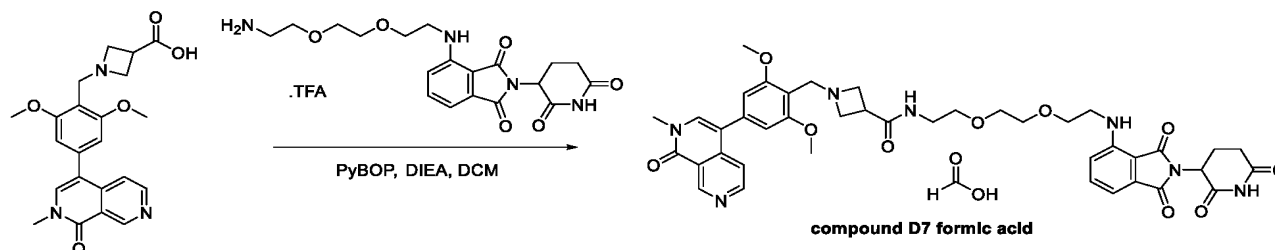
To a solution of 6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy]hexanoic acid (50.00 mg, 0.129 mmol, 1.00 eq.) and DIEA (49.92 mg, 0.386 mmol, 3 eq.) in DCM (2.00 mL, 31.460 mmol, 244.37 eq.) was added PyBOP (100.49 mg, 0.193 mmol, 1.5 eq.) and 4-[4-[(3-aminoazetidin-1-yl)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyridin-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 μ m, 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. ¹H NMR (400 MHz, Methanol-*d*₄) 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 by Prep-HPLC (conditions: X Select CSH Prep C18 OBD Column, 5 μ m, 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. ^1H NMR (300 MHz, Methanol- d_4) 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 : $[\text{M}+\text{H}]^+ = 874.37$.

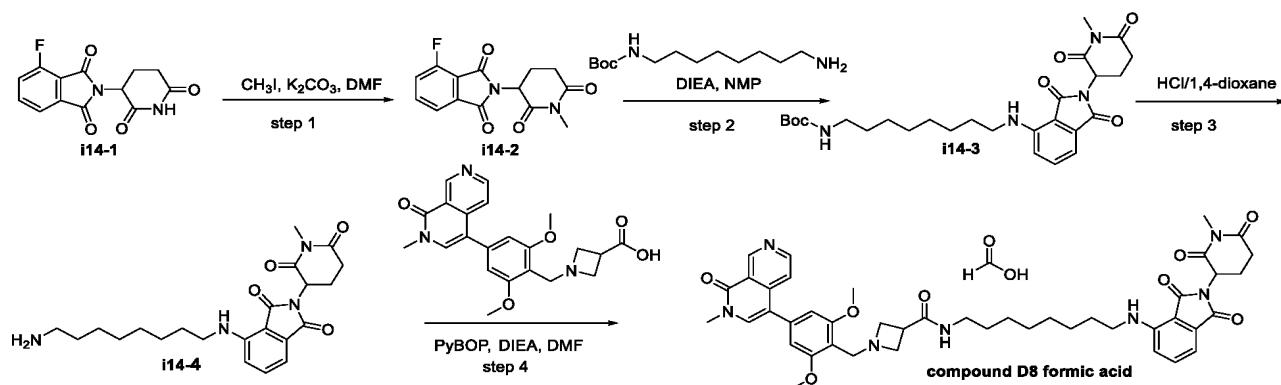
Example 13 – Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)]phenyl] methyl]-N-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino] ethoxy)ethoxy]ethyl]azetidine-3-carboxamide formic acid (compound D7 formic acid)



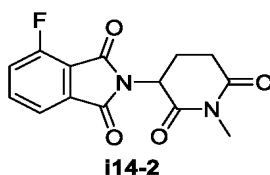
To a stirred mixture of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)]phenyl]methyl]azetidine-3-carboxylic acid trifluoroacetic acid salt (75.73 mg, 0.145 mmol, 1.5 equiv) and 4-([2-[2-(2-aminoethoxy)ethoxy]ethyl]amino)-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione 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 μ m, 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. ¹H NMR (400 MHz, Methanol-*d*₄) 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, 1.6 Hz, 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)

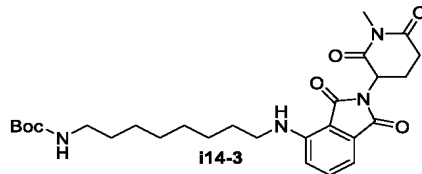


Step 1: Preparation of 4-fluoro-2-(1-methyl-2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (i14-2)



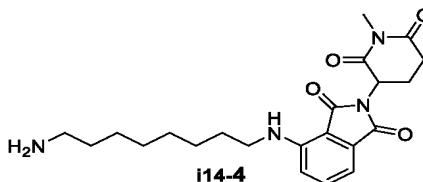
To a solution of 2-(2,6-dioxopiperidin-3-yl)-4-fluoro-2,3-dihydro-1H-isoindole-1,3-dione (500 mg, 1.810 mmol, 1 equiv) in DMF (10 mL) was added CH₃I (385.39 mg, 2.715 mmol, 1.5 equiv) and K₂CO₃ (750.51 mg, 5.430 mmol, 3 equiv). The resulting solution was stirred for overnight at 25 °C. The solids were 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)



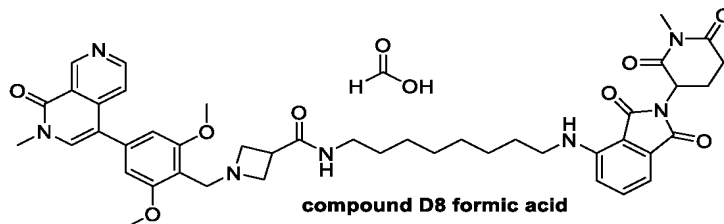
To a solution of 4-fluoro-2-(1-methyl-2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (480 mg, 1.654 mmol, 1 equiv) and *tert*-butyl *N*-(8-aminooctyl)carbamate (404.14 mg, 1.654 mmol, 1 equiv) in NMP (10 mL) was added DIEA (641.21 mg, 4.961 mmol, 3 equiv). The resulting solution was stirred 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)



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.

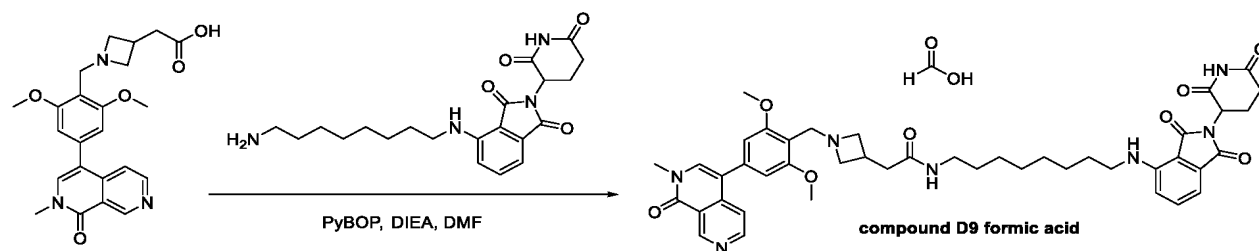
Step 4: Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)azetidine-3-carboxamide formic acid (compound D8 formic acid)



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-

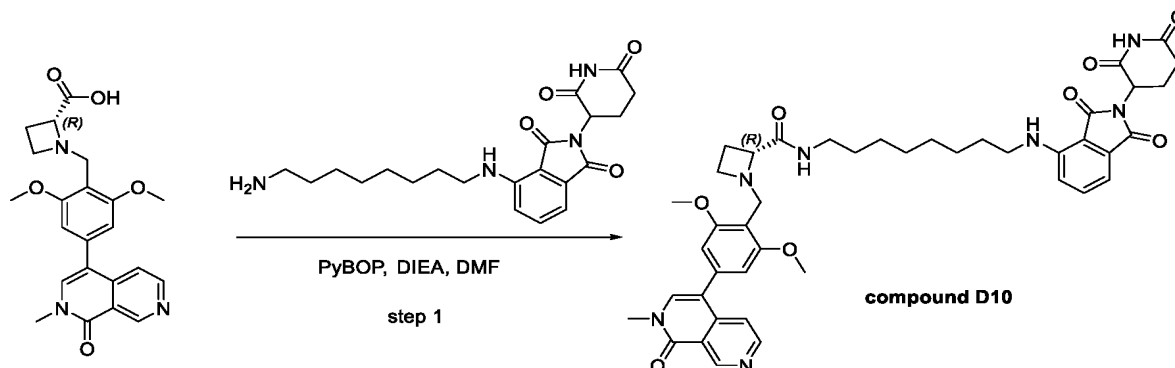
2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-3-carboxylic acid (79.02 mg, 0.193 mmol, 1 equiv) in DMF (3 mL) was added HATU (110.08 mg, 0.290 mmol, 1.5 equiv) and DIEA (49.89 mg, 0.386 mmol, 2 equiv). The resulting solution was stirred for 2 hours at 25 °C. The crude product was purified by Prep-HPLC (conditions: XBridge Prep C18 OBD Column, 5 µm, 19*150 mm; mobile phase, Water (0.1% FA) and
5 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. ¹H NMR (400 MHz, Methanol-*d*₄) 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* =
10 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)



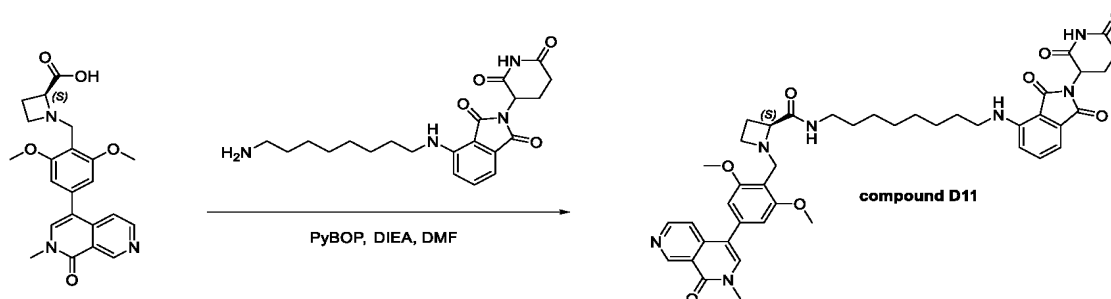
To a solution of 2-(1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidin-3-yl)acetic acid (110 mg, 0.260 mmol, 1 equiv) in DMF (3 mL) was added 4-[(8-aminooctyl)amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (104.03 mg, 0.260 mmol, 1.00 equiv), 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. ¹H NMR (300 MHz, Methanol-*d*₄) 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 μ m, 19*150 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; 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. ¹H NMR (300 MHz, Methanol-*d*₄) 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.

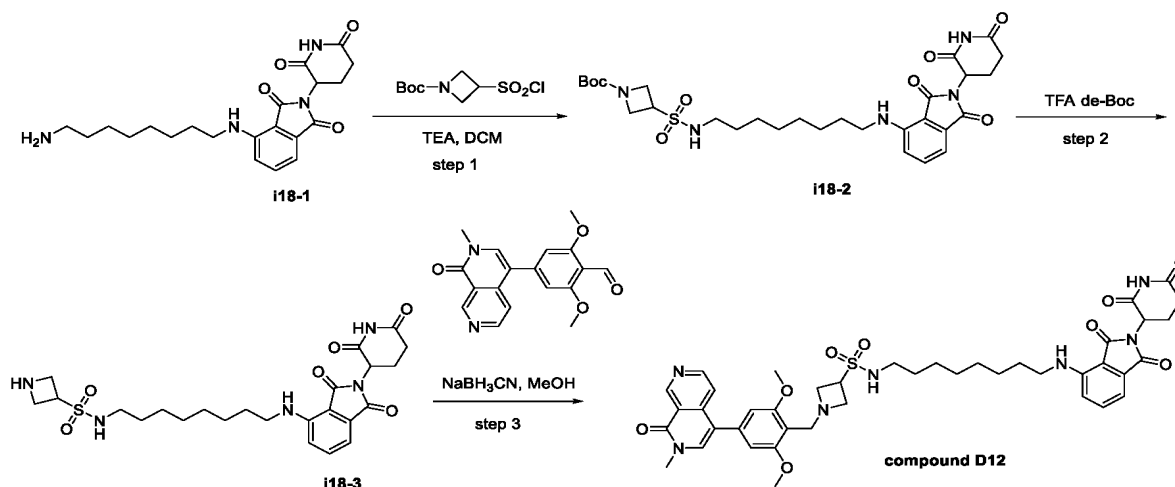
Example 17 – Preparation of (2S)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]octyl)azetidine-2-carboxamide (compound D11)



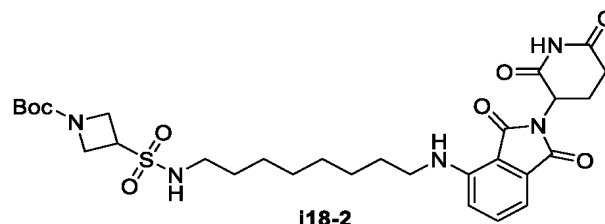
To a solution of (2S)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-2-carboxylic acid (50.00 mg, 0.122 mmol, 1.00 equiv) and 4-[(8-aminooctyl)amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (48.91 mg, 0.122 mmol,

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/minute; 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 (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-dioxoisindol-4-yl]amino]octyl)azetidine-2-carboxamide (35 mg, 35.47%) as a yellow solid. ¹H NMR (400 MHz, Methanol-*d*₄) 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)



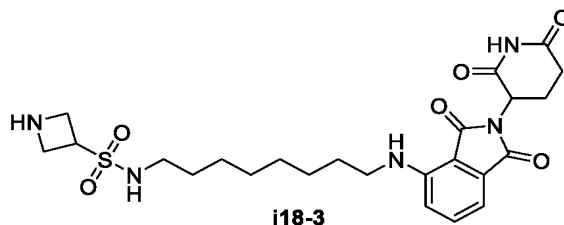
Step 1: Preparation of tert-butyl 3-[(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)sulfamoyl]azetidine-1-carboxylate (I18-2)



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)azetidin-1-yl]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

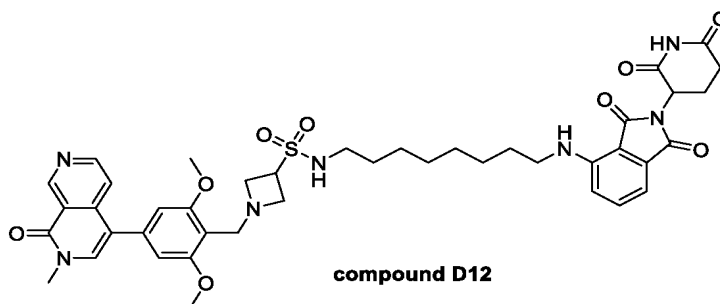
applied onto a silica gel column with ethyl DCM/MeOH (20:1). This resulted in 110 mg (71.08%) of *tert*-butyl 3-[(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino]octyl)sulfamoyl]azetidine-1-carboxylate as a yellow solid. LCMS (ESI) *m/z*: [M+H]⁺ = 620.

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



- 10 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 CH₂Cl₂ (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.

- 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*-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino]octyl)azetidine-3-sulfonamide (compound D12)

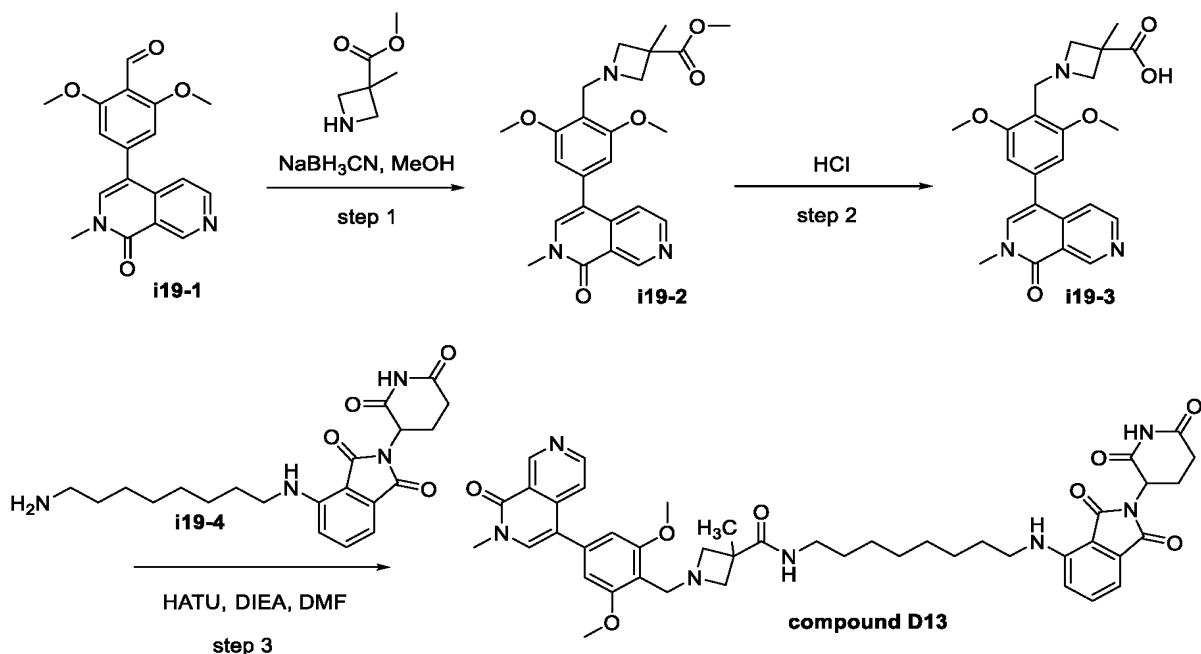


- 20 To a solution of *N*-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino]octyl)azetidine-3-sulfonamide (85.00 mg, 0.164 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (53.06 mg, 0.164 mmol, 1.00 equiv) in MeOH (2.00 mL) was added NaBH₃CN (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/minute; 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 (50 mg, 36.92%) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) 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,
- 30

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 : $[M+H]^+ = 828.35$.

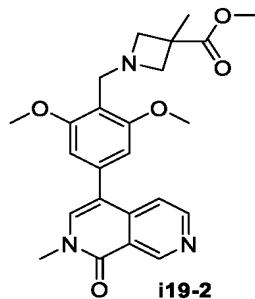
5

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-dioxoisindolin-4-yl)amino)octyl)-3-methylazetididine-3-carboxamide (compound D13)



10

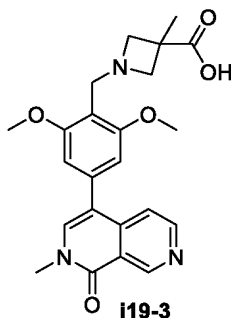
Step 1: Preparation of methyl 1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-3-methylazetididine-3-carboxylate (i19-2)



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

20

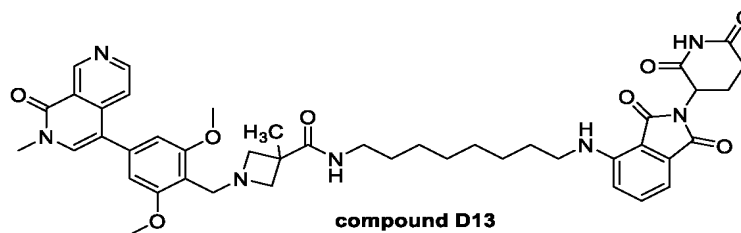
Step 2: Preparation of 1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-3-methylazetidine-3-carboxylic acid (119-3)



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-methylazetidine-3-carboxylic acid (185 mg, 81.33%) as a brown solid, that was used directly without further purification.

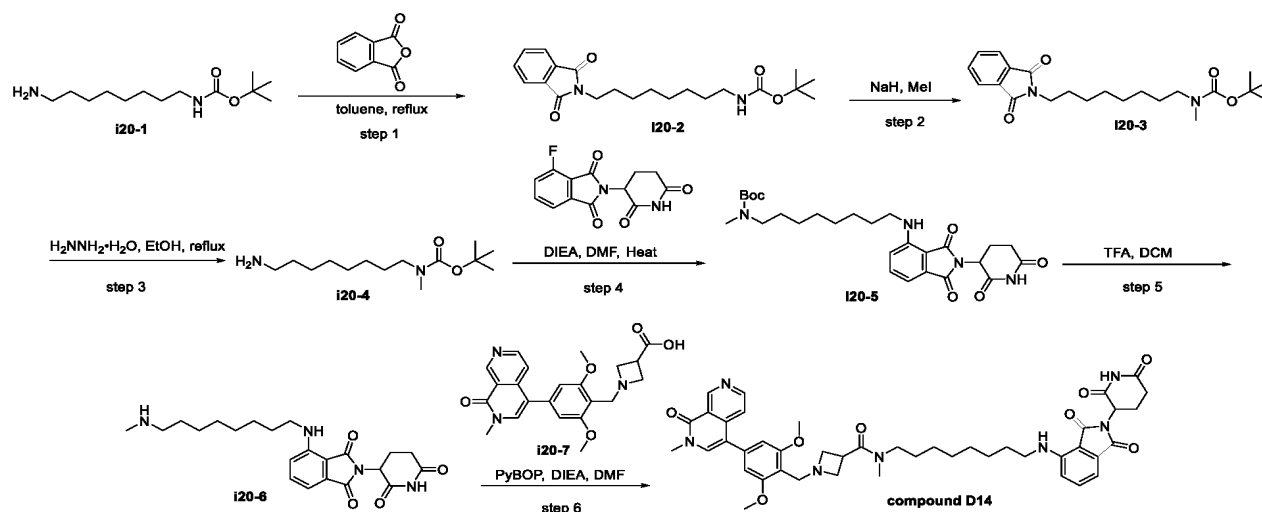
LCMS (ESI) m/z: [M+H]⁺ = 424.

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-dioxoisindolin-4-yl)amino)octyl)-3-methylazetidine-3-carboxamide (compound D13)

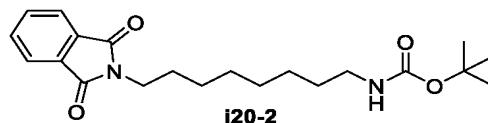


To a solution of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-3-methylazetidine-3-carboxylic acid (50 mg, 0.118 mmol, 1 equiv), 4-[(8-amino)octyl]amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isindole-1,3-dione (94.57 mg, 0.236 mmol, 2 equiv) and Et₃N (119.48 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-isindol-4-yl]amino]octyl)-3-methylazetidine-3-carboxamide (21.7 mg, 22.80%) as a yellow solid. ¹H 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)

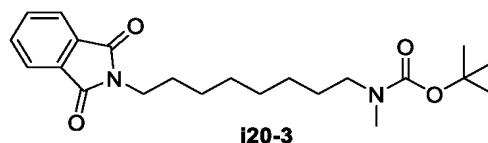


Step 1: preparation of tert-butyl N-[8-(1,3-dioxoisindol-2-yl)octyl]carbamate (i20-2)



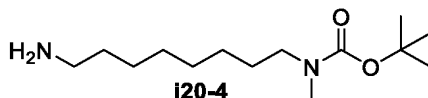
A mixture of tert-butyl N-(8-aminoctyl)carbamate (1.00 g, 4.092 mmol, 1.00 equiv) and phthalic anhydride (606.10 mg, 4.092 mmol, 1.00 equiv) in toluene (20.00 mL) was stirred for 2 hours at 130 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature and the solvent was 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-dioxoisindol-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-dioxoisindol-2-yl)octyl]-N-methylcarbamate (i20-3)



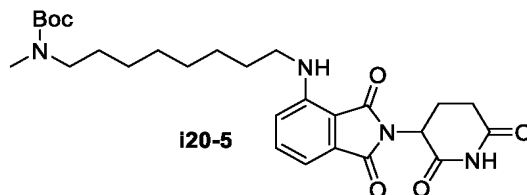
To a stirred solution of tert-butyl N-[8-(1,3-dioxoisindol-2-yl)octyl]carbamate (1.24 g, 3.311 mmol, 1.00 equiv) in DMF (1.00 mL) was added NaH (0.16 g, 6.622 mmol, 2 equiv) in portions at 0 °C under nitrogen atmosphere. Then CH₃I (1.88 g, 13.245 mmol, 4 equiv) was added. The resulting mixture was stirred 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-dioxoisindol-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 (*i*20-4)



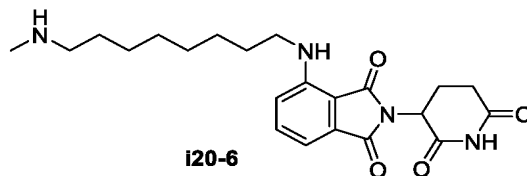
A solution of *tert*-butyl *N*-[8-(1,3-dioxoisindol-2-yl)octyl]-*N*-methylcarbamate (700.00 mg, 1.802 mmol, 1.00 equiv) and NH_2NH_2 (259.84 mg, 3.604 mmol, 2 equiv) in EtOH (5.00 mL) was stirred for 1 hour at 90 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. 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 : $[\text{M}+\text{H}]^+ = 259$.

Step 4: Preparation of *tert*-butyl *N*-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino]octyl)-*N*-methylcarbamate (*i*20-5)



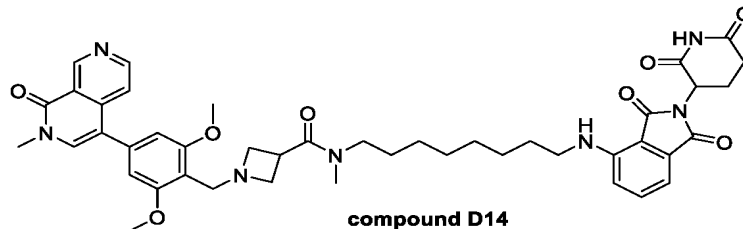
To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisindole-1,3-dione (520.00 mg, 1.883 mmol, 1.00 equiv) and *tert*-butyl *N*-(8-aminooctyl)-*N*-methylcarbamate (486.46 mg, 1.883 mmol, 1 equiv) in DMF (5.00 mL) was added DIPEA (1216.53 mg, 9.413 mmol, 5 equiv). The solution was stirred for 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-dioxoisindol-4-yl]amino]octyl)-*N*-methylcarbamate (260 mg, 26.84%) as a yellow solid. LCMS (ESI) m/z : $[\text{M}+\text{H}]^+ = 515$.

Step 5: Preparation of 2-(2,6-dioxopiperidin-3-yl)-4-[[8-(methylamino)octyl]amino]isindole-1,3-dione (*i*20-6)



A solution of *tert*-butyl *N*-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-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]isindole-1,3-dione (170 mg, 95.94%) as a dark yellow oil. LCMS (ESI) m/z : $[\text{M}+\text{H}]^+ = 415$.

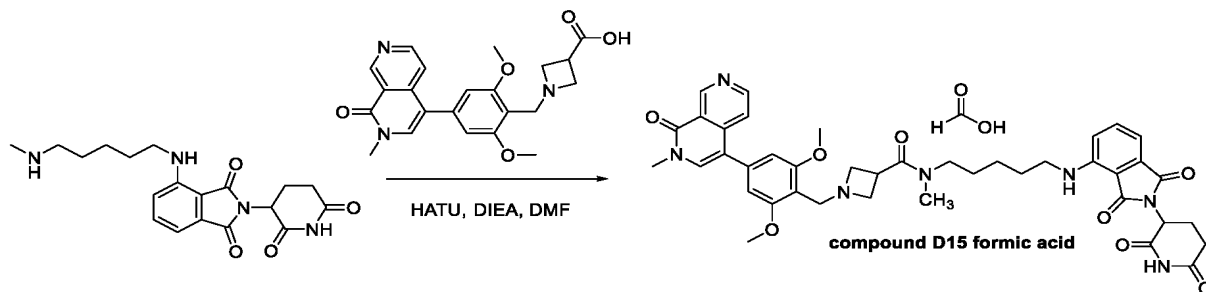
Step 6: Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-3-carboxylic acid (30 mg, 0.073 mmol, 1 equiv) in DMF (0.5 mL), was added



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-1H-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/minute; 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-1H-isoindol-4-yl]amino]octyl)-N-methylazetidine-3-carboxamide formate (25 mg, 40.05%) as a yellow solid.

¹H NMR (300 MHz, Methanol-*d*₄) δ 9.52 (dd, *J* = 4.5, 0.9 Hz, 1H), 8.68 (dd, *J* = 5.8, 2.5 Hz, 1H), 8.56 (s, 0.5H, FA), 7.75 (d, *J* = 2.0 Hz, 1H), 7.67 – 7.58 (m, 1H), 7.53 (ddd, *J* = 8.5, 7.1, 4.7 Hz, 1H), 7.07 – 6.95 (m, 2H), 6.81 (d, *J* = 1.8 Hz, 2H), 5.06 (ddd, *J* = 12.1, 5.4, 2.5 Hz, 1H), 4.21 (d, *J* = 4.7 Hz, 2H), 4.00 (dd, *J* = 17.1, 8.8 Hz, 4H), 3.93 (s, 6H), 3.80 (t, *J* = 8.2 Hz, 1H), 3.70 (d, *J* = 3.3 Hz, 3H), 3.45 – 3.19 (m, 2H), 2.94 (d, *J* = 4.3 Hz, 3H), 2.91 – 2.68 (m, 3H), 2.12 (s, 1H), 1.67 (s, 2H), 1.57 (d, *J* = 6.9 Hz, 2H), 1.41 – 1.33 (m, 8H). LCMS (ESI) *m/z*: [M+H]⁺ = 806.35.

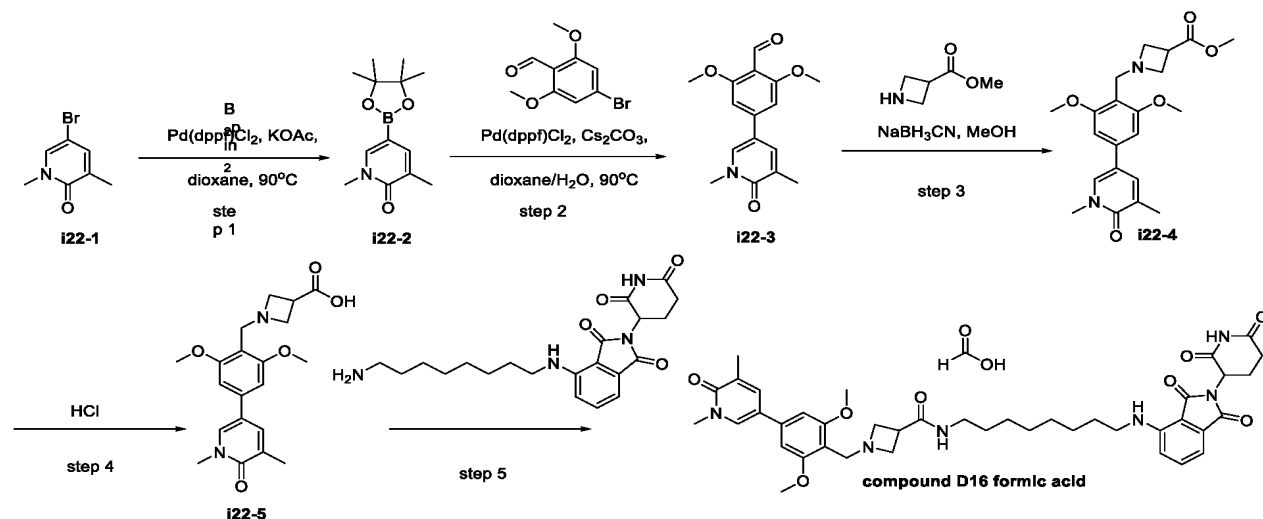
Example 21 – Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]pentyl)-N-methylazetidine-3-carboxamide formic acid (compound D15 formic acid)



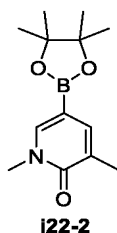
To a solution of 2-(2,6-dioxopiperidin-3-yl)-4-[[5-(methylamino)pentyl]amino]-2,3-dihydro-1H-isoindole-1,3-dione (60.00 mg, 0.161 mmol, 1.00 equiv), 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-3-carboxylic acid (65.96 mg, 0.161 mmol, 1.00 equiv), and 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 μ m; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 40 mL/minute; 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-1H-isoindol-4-yl]amino]pentyl)-N-methylazetidine-3-carboxamide; formic acid (25.1 mg) as a yellow solid. ^1H NMR (400 MHz, Methanol- d_4) 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)



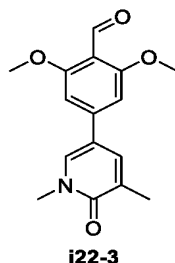
Step 1: Preparation of 1,3-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-one (I22-2)



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 $\text{Pd(dppf)Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (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

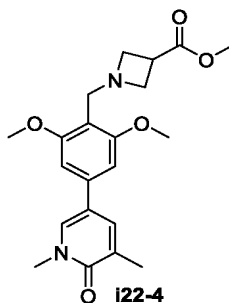
reduced pressure. The crude product was used in the next step directly without further purification.
LCMS (ESI) m/z: $[M+H]^+ = 250$.

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



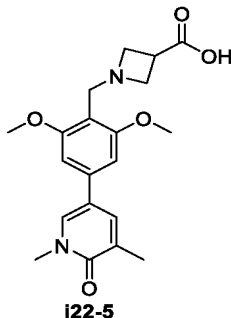
To a solution of 1,3-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-one (1.20 g, 4.817 mmol, 1.00 equiv) and 4-bromo-2,6-dimethoxybenzaldehyde (1.18 g, 4.817 mmol, 1.00 equiv) in 1,4-dioxane (40.00 mL) and H₂O (4.00 mL) was added CS₂CO₃ (3.14 g, 9.634 mmol, 2.00 equiv) and Pd(dppf)Cl₂ (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 CH₂Cl₂/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)



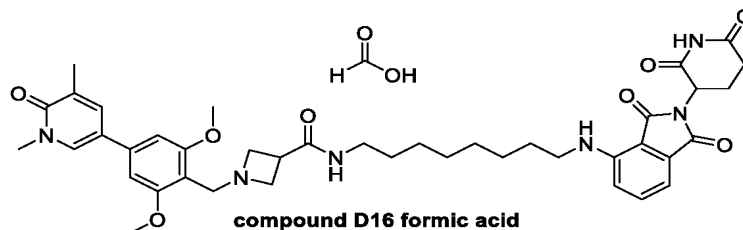
To a solution of methyl azetidine-3-carboxylate hydrochloride (1.13 g, 7.466 mmol, 1.50 equiv) in MeOH (10.00 mL) was added Et₃N to pH 7-8. Then 4-(1,5-dimethyl-6-oxopyridin-3-yl)-2,6-dimethoxybenzaldehyde (1.43 g, 4.977 mmol, 1.00 equiv) was added. After stirring for 5-10 minutes, NaBH₃CN (0.63 g, 9.954 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 CH₂Cl₂ / 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)



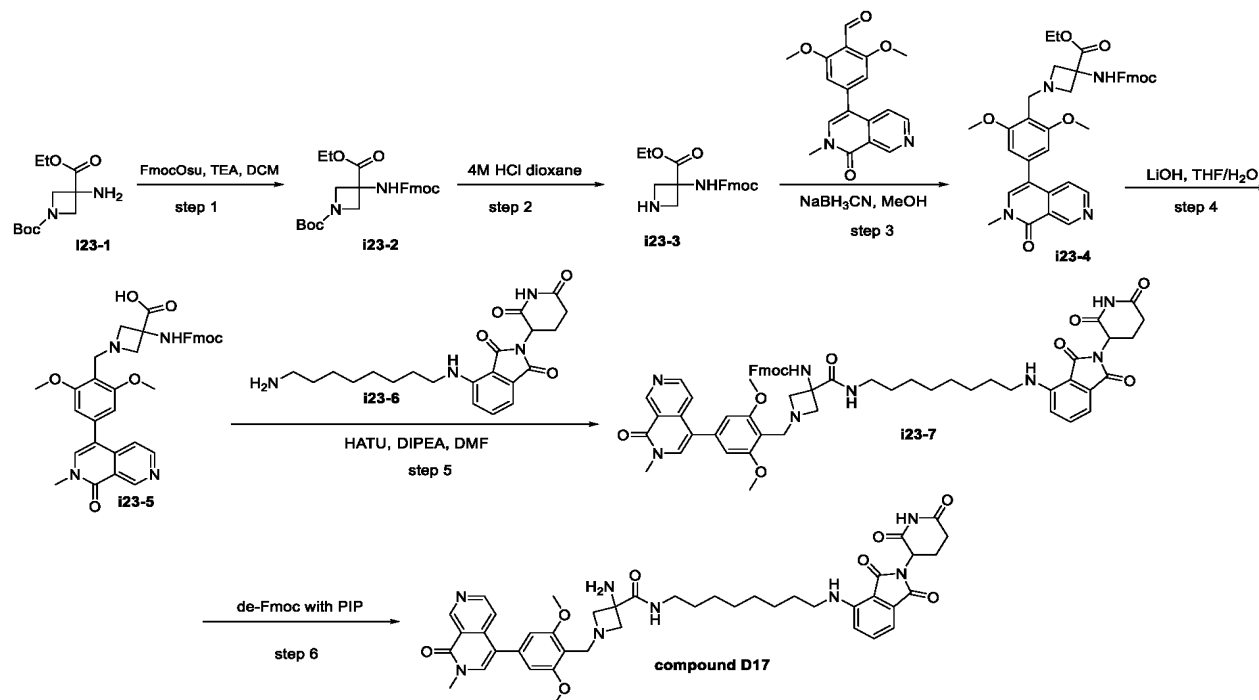
A mixture of methyl 1-[[4-(1,5-dimethyl-6-oxopyridin-3-yl)-2,6-dimethoxyphenyl]methyl]azetidine-3-carboxylate (203.00 mg, 0.525 mmol, 1.00 equiv) in HCl (12 N, 2.00 mL) was stirred for 2 hours at 90 °C. The resulting mixture was concentrated under reduced pressure to give 1-[[4-(1,5-dimethyl-6-oxopyridin-3-yl)-2,6-dimethoxyphenyl]methyl]azetidine-3-carboxylic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

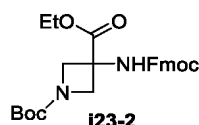


To a stirred mixture of 1-[[4-(1,5-dimethyl-6-oxo-1,6-dihydropyridin-3-yl)-2,6-dimethoxyphenyl]methyl]azetidine-3-carboxylic acid trifluoroacetic acid(50 mg, 0.103 mmol, 1 equiv) and 4-[(8-aminooctyl)amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione hydrochloride (44.91 mg, 0.103 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. ¹H NMR (300 MHz, Methanol-*d*₄) 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)

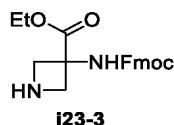


- 5 **Step 1: Preparation of 1-tert-Butyl 3-ethyl 3-([[(9H-fluoren-9-yl)methoxy]carbonyl]amino)azetidine-1,3-dicarboxylate (i23-2)**



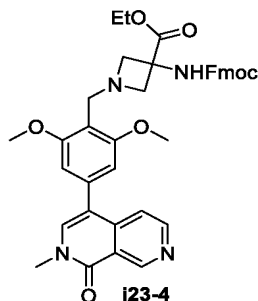
To a solution of 1-tert-butyl 3-ethyl 3-aminoazetidine-1,3-dicarboxylate (120 mg, 0.491 mmol, 1 equiv) and 2,5-dioxopyrrolidin-1-yl (9H-fluoren-9-yl)methyl carbonate (182.3 mg, 0.540 mmol, 1.1 equiv) in DCM (1 mL) was added TEA (149.1 mg, 1.474 mmol, 3 equiv). The resulting solution was stirred at room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

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



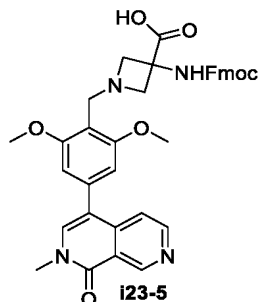
A mixture of 1-tert-butyl 3-ethyl 3-([[(9H-fluoren-9-yl)methoxy]carbonyl]amino)azetidine-1,3-dicarboxylate (120.00 mg, 0.257 mmol, 1.00 equiv) and 4 M HCl in 1,4-dioxane (2 mL) was stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure to afford ethyl 3-([[(9H-fluoren-9-yl)methoxy]carbonyl]amino)azetidine-3-carboxyl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



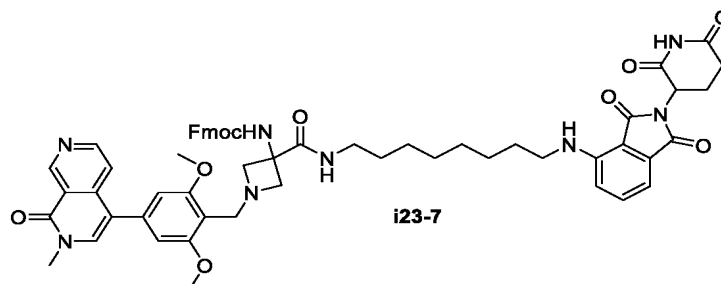
5 To a solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (127.5 mg, 0.393 mmol, 1.20 equiv) and ethyl 3-([[(9H-fluoren-9-yl)methoxy]carbonyl]amino)azetidine-3-carboxylate (120 mg, 0.327 mmol, 1 equiv) in MeOH (1 mL) was added NaBH₃CN (41.2 mg, 0.655 mmol, 2 equiv). 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
10 Prep-TLC (CH₂Cl₂ / 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-([[(9H-fluoren-9-yl)methoxy]carbonyl]amino)azetidine-3-carboxylate (100 mg, 45%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺ = 675.

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



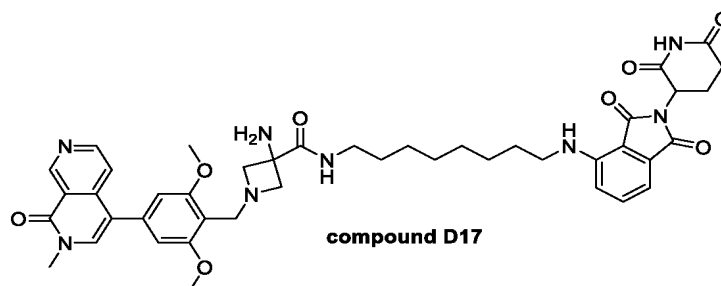
A solution of ethyl 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-3-([[(9H-fluoren-9-yl)methoxy]carbonyl]amino)azetidine-3-carboxylate (100 mg, 0.148 mmol, 1 equiv) in concentrated HCl (2 mL) was stirred at 90 °C for 1 hour. The resulting mixture was
20 concentrated 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-([[(9H-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-[[[(9H-fluoren-9-yl)methoxy]carbonyl]amino]azetidine-3-carboxylic acid (100 mg, 0.155 mmol, 1 equiv) and 4-[(8-amino)octyl]amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-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 (CH₂Cl₂ / MeOH 12:1) to afford (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 (90 mg, 51%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺ = 1029.

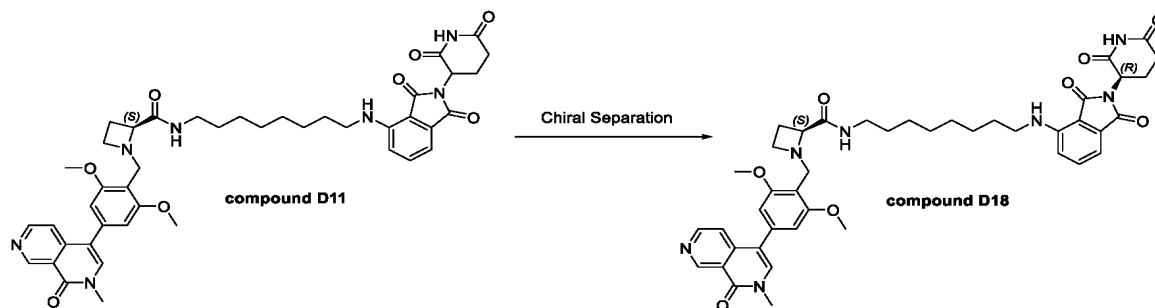
Step 6: Preparation of 3-Amino-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)azetidine-3-carboxamide (compound D17)



A solution of (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 (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/minute; 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-1H-isoindol-4-yl]amino]octyl)azetidine-3-carboxamide (3.8 mg, 5.2%) as a yellow solid. ¹H 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

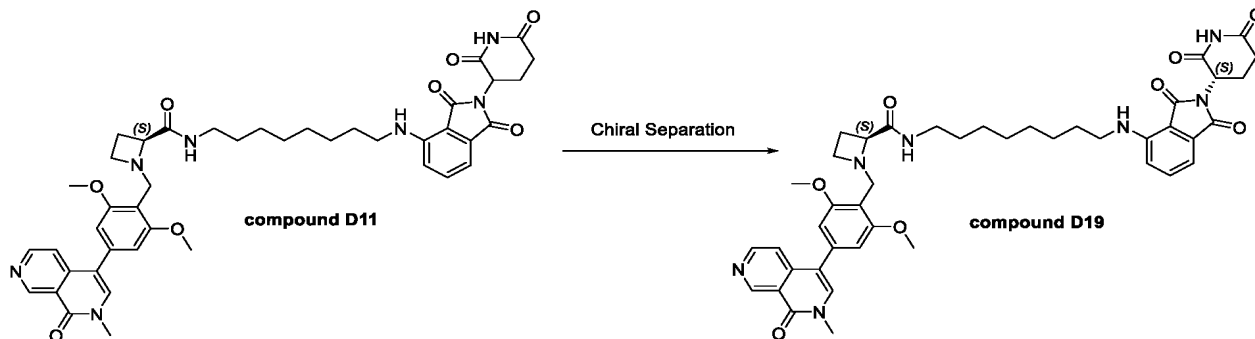
Hz, 2H), 6.75 (s, 2H), 6.30 (t, $J = 5.9$ Hz, 1H), 4.95 (dd, $J = 12.4, 5.2$ Hz, 1H), 4.10 (s, 2H), 3.95 (d, $J = 8.8$ Hz, 2H), 3.87 (s, 6H), 3.50 (s, 3H), 3.24 (dq, $J = 23.4, 6.6$ Hz, 4H), 2.83-2.59 (m, 3H), 1.63 (s, 2H), 1.49 (s, 2H), 1.32 (d, $J = 13.1$ Hz, 10H). LCMS (ESI) m/z : $[M+H]^+ = 807.40$.

5 **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-dioxoisindol-4-yl]amino]octyl)azetidine-2-carboxamide (compound D18)**



10 Compound D11 was further separated by chiral HPLC to afford (2S)-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-dioxoisindol-4-yl)amino)octyl) azetidine-2-carboxamide (10 mg, 10.34%) as a yellow solid. ^1H NMR (400 MHz, Methanol- d_4) 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 : $[M+H]^+ = 792.60$.

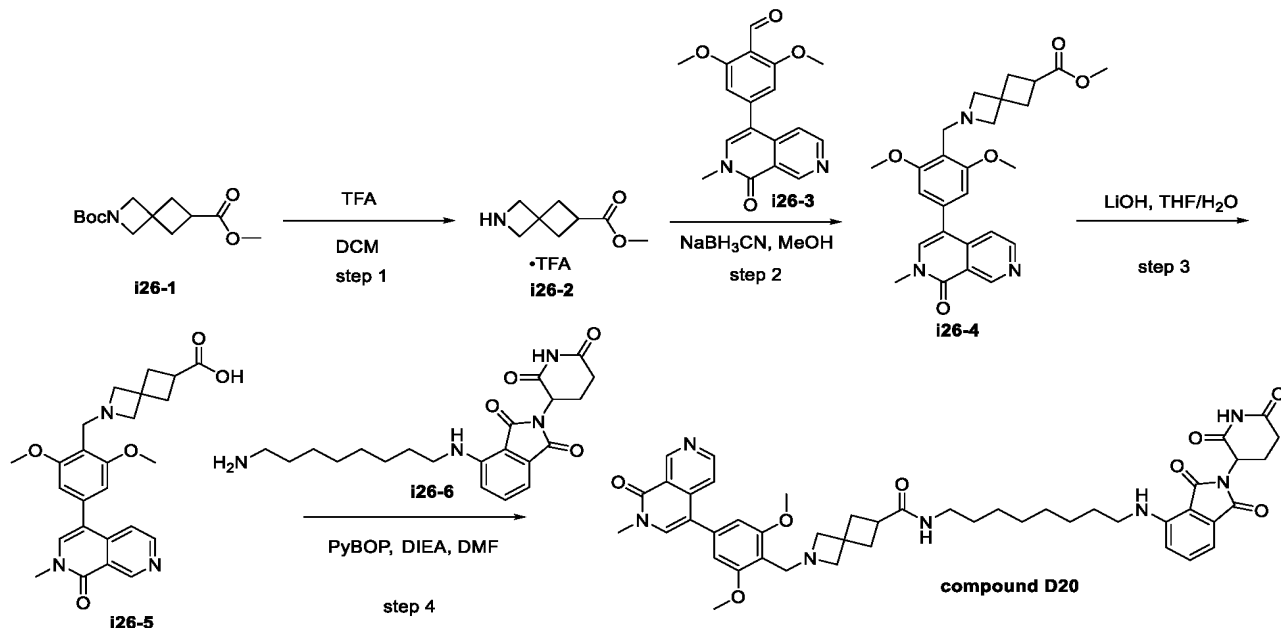
20 **Example 25 – Preparation of (2S)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino]octyl)azetidine-2-carboxamide (compound D19)**



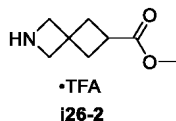
25 Compound D11 was further separated by chiral HPLC to afford (2S)-1-((2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl)methyl)-N-(8-((2-((S)-2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl)amino)octyl) azetidine-2-carboxamide (10 mg, 10.34%) as a yellow solid. ^1H NMR (400 MHz, Methanol- d_4) 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)

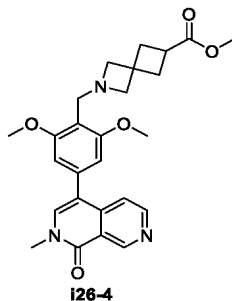


Step 1: Preparation of methyl 2-azaspiro[3.3]heptane-6-carboxylate trifluoroacetate (i26-2)



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.

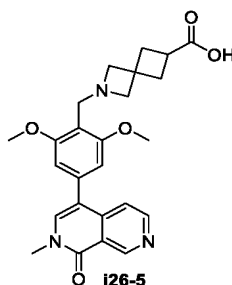
Step 2: Preparation of methyl 2-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-2-azaspiro[3.3]heptane-6-carboxylate (i26-4)



To a stirred solution of methyl 2-azaspiro[3.3]heptane-6-carboxylate trifluoroacetate (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-

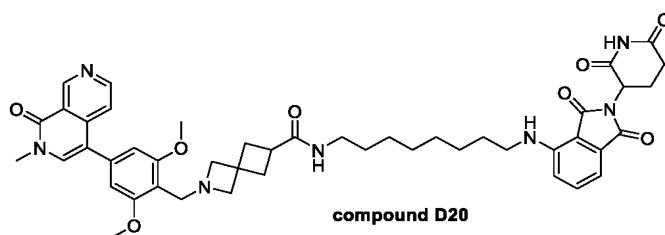
oxo-2,7-naphthyridin-4-yl)benzaldehyde (93.49 mg, 0.288 mmol, 1 equiv) in MeOH (2.00 mL) was added NaBH₃CN (36.23 mg, 0.576 mmol, 2 equiv) in portions at room temperature. After the solvent was evaporated, the residue was purified by silica gel column chromatography, eluted with CH₂Cl₂ / MeOH (12:1) 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)



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 H₂O (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.

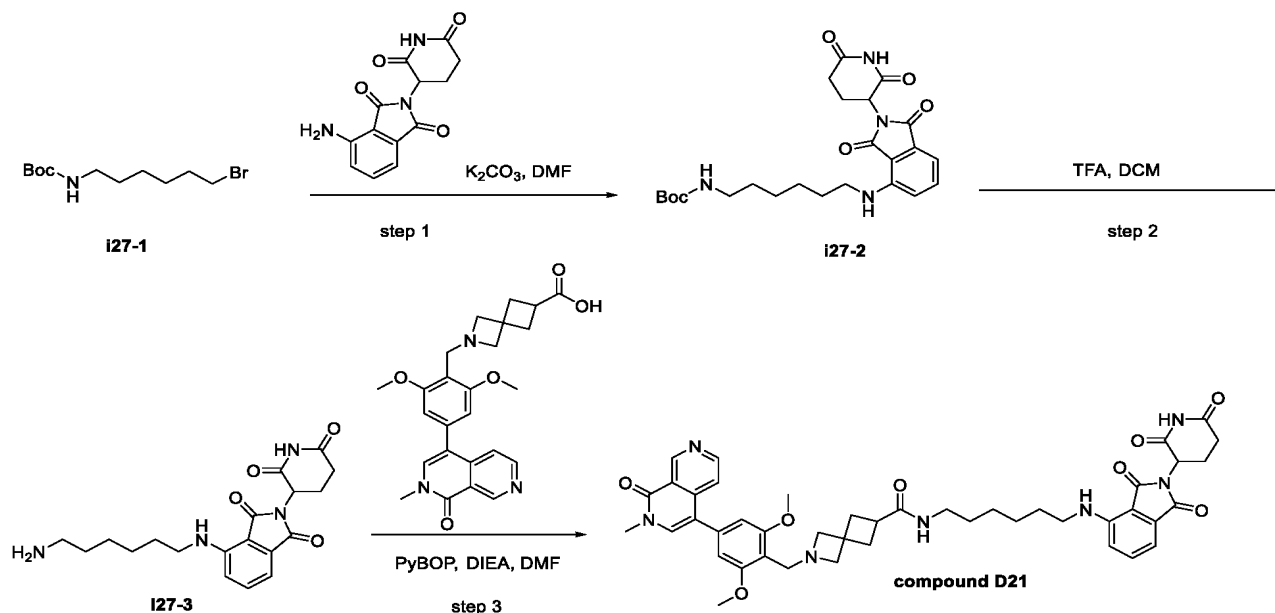
Step 4: Preparation of 6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2,4a,8a-tetrahydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(8-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]octyl)spiro[3.3]heptane-2-carboxamide (compound D20)



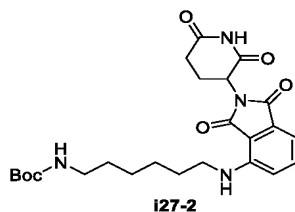
To a stirred solution of 6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2,4a,8a-tetrahydro-2,7-naphthyridin-4-yl)phenyl]methyl]spiro[3.3]heptane-2-carboxylic acid (45 mg, 0.100 mmol, 1 equiv) and 4-[(8-aminooctyl)amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (40.00 mg, 0.100 mmol, 1 equiv) 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/minute; 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. ¹H NMR (300 MHz, Methanol-*d*₄) 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)

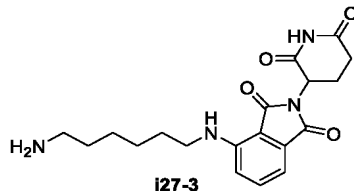


Step 1: preparation of tert-butyl N-(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]hexyl) carbamate (I27-2)



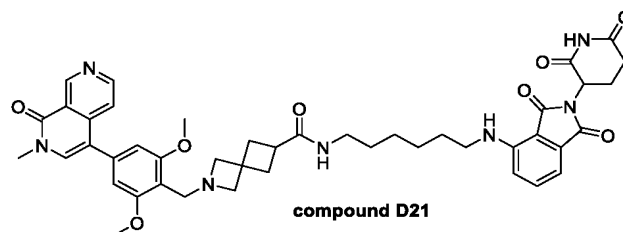
To a stirred solution of pomalidomide (150.30 mg, 0.550 mmol, 1.00 equiv) and *tert*-butyl *N*-(6-bromohexyl)carbamate (154.13 mg, 0.550 mmol, 1 equiv) in DMF (1.00 mL) was added K₂CO₃ (152.04 mg, 1.100 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature, and then it was concentrated and purified by silica gel column chromatography, eluting 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)



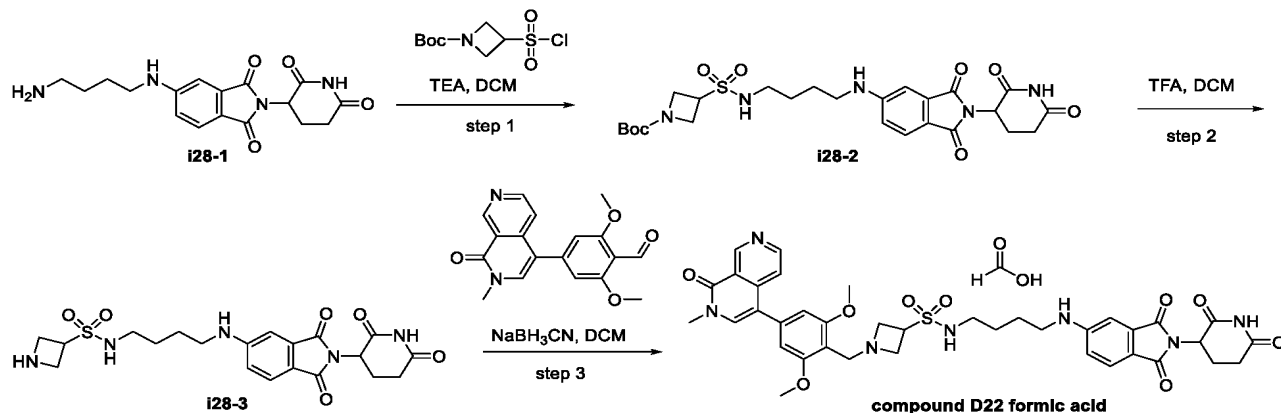
A solution of *tert*-butyl *N*-(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]hexyl) carbamate (293.00 mg, 0.620 mmol, 1.00 equiv) and TFA (2.0 mL) in DCM (5.00 mL) was stirred for 1 h at room temperature. The mixture was then concentrated to afford 4-[(6-aminohexyl)amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (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)

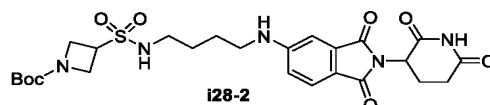


To a stirred solution of 6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2,4a,8a-tetrahydro-2,7-naphthyridin-4-yl)phenyl]methyl]spiro[3.3]heptane-2-carboxylic acid (30 mg, 0.067 mmol, 1 equiv) in DMF (0.5 mL) was added DIEA (43.03 mg, 0.333 mmol, 5 equiv), PyBOP (69.30 mg, 0.133 mmol, 2 equiv), and 4-[(6-aminohexyl)amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-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/minute; 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. ¹H NMR (400 MHz, Methanol-*d*₄) 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)

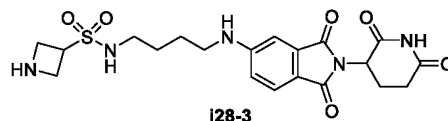


- 5 **Step 1: Preparation of tert-butyl-3-[[4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]butyl]sulfamoyl]azetidine-1-carboxylate (i28-2)**



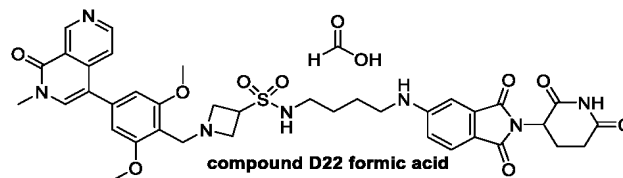
To a stirred mixture of 5-[(4-aminobutyl)amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (60.00 mg, 0.174 mmol, 1.00 equiv) and *tert*-butyl 3-(chlorosulfonyl)azetidine-1-carboxylate (111.38 mg, 0.436 mmol, 2.50 equiv) in DCM (2.00 mL) was added TEA (52.89 mg, 0.523 mmol, 3.00 equiv). After stirring for 1.5 hours at room temperature, the resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH₂Cl₂ / 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.

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



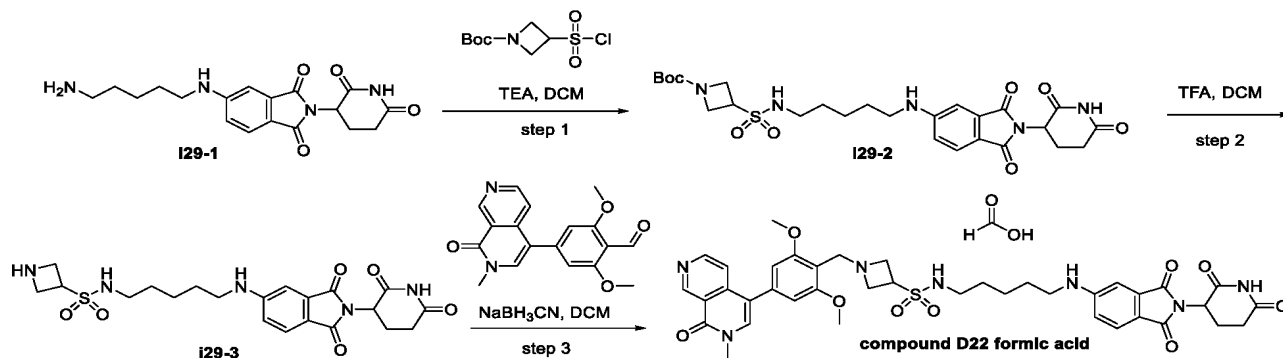
To a stirred mixture of *tert*-butyl-3-[[4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]butyl]sulfamoyl]azetidine-1-carboxylate (78.00 mg, 0.138 mmol, 1.00 equiv) in DCM (2.00 mL, 0.012 mmol, 0.10 equiv) was added TFA (0.40 mL, 5.385 mmol, 38.91 equiv). After stirring for 1 hour at room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

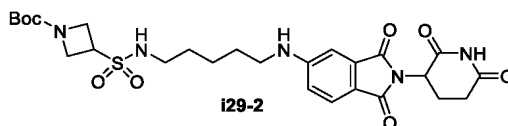


A mixture of *N*-(4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]amino]butyl)azetidine-3-sulfonamide (64.17 mg, 0.138 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (44.90 mg, 0.138 mmol, 1.00 equiv) in DMF (2 mL) was stirred at room temperature, then adjusted to pH 8~9 by addition of TEA. The above mixture was added NaBH₃CN (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. ¹H NMR (400 MHz, DMSO-*d*₆) 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)

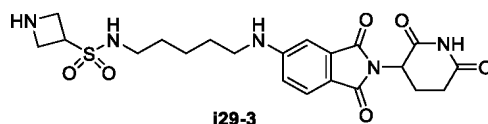


Step 1: Preparation of tert-butyl-3-[(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]pentyl)sulfamoyl]azetidine-1-carboxylate (I28-2)



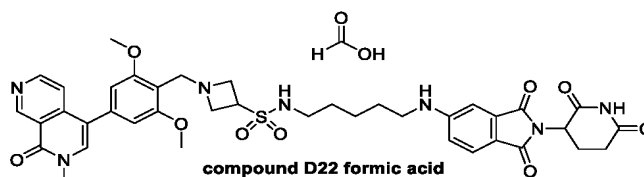
To a stirred mixture of 5-[(5-aminopentyl)amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (100.00 mg, 0.279 mmol, 1.00 equiv) and *tert*-butyl 3-(chlorosulfonyl)azetidine-1-carboxylate (178.37 mg, 0.698 mmol, 2.50 equiv) in DCM (2.00 mL) was added TEA (84.70 mg, 0.837 mmol, 3.00 equiv). After stirring for 1.5 hours at room temperature, the resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH₂Cl₂/EA (1:2)) to afford *tert*-butyl-3-[(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]pentyl)sulfamoyl]azetidine-1-carboxylate (58.7mg, 33.87%) as a yellow solid. LCMS (ESI) *m/z*: [M+H]⁺ = 578.

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



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

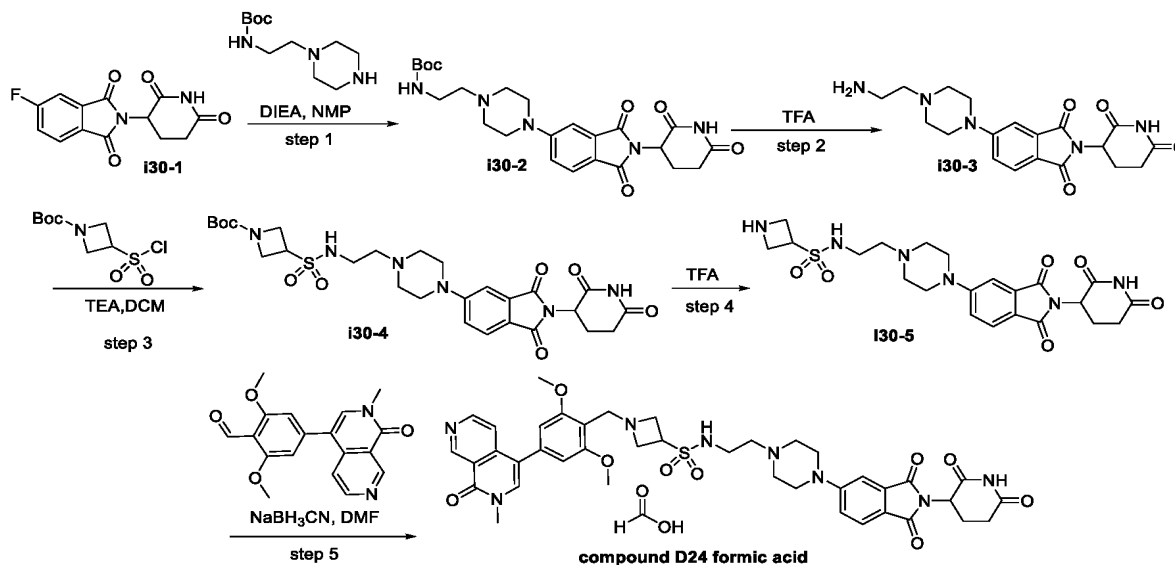
Step 3: Preparation of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]amino]pentyl)azetidine-3-sulfonamide formic acid (compound D22 formic acid)



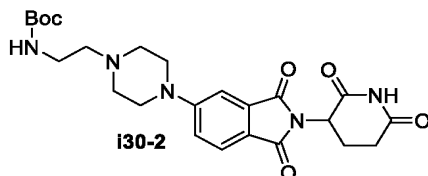
A mixture of *N*-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]amino]pentyl)azetidine-3-sulfonamide (48.54 mg, 0.102 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (39.56 mg, 0.122 mmol, 1.20 equiv) in THF (2 mL) was stirred at room temperature, then adjusted to pH 8--~9 with TEA. To the above mixture was added NaBH₃CN (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. ¹H NMR (400 MHz, DMSO-*d*₆) 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-dioxoisindol-5-yl]piperazin-1-yl]ethyl)azetidine-3-sulfonamide formic acid (compound D24 formic acid)

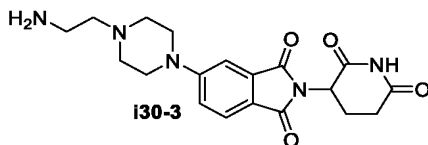


Step 1: Preparation of *tert*-butyl *N*-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]piperazin-1-yl]ethyl)carbamate (I30-2)



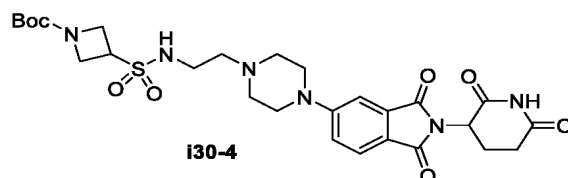
To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisindole-1,3-dione (1.50 g, 5.430 mmol, 1.00 equiv) and *tert*-butyl *N*-[2-(piperazin-1-yl)ethyl]carbamate (1.49 g, 6.516 mmol, 1.20 equiv) in NMP (10.00 mL) was added DIEA (1.40 g, 10.861 mmol, 2.00 equiv) dropwise at room temperature. The 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-dioxoisindol-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)



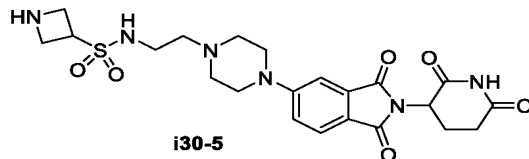
A solution of *tert*-butyl *N*-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl) carbamate (2.00 g, 4.119 mmol, 1.00 equiv) and TFA (2.00 mL, 26.926 mmol, 6.54 equiv) in DCM (5.00 mL, 78.650 mmol, 19.09 equiv) was stirred for 1 hours at room temperature. The resulting mixture 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)



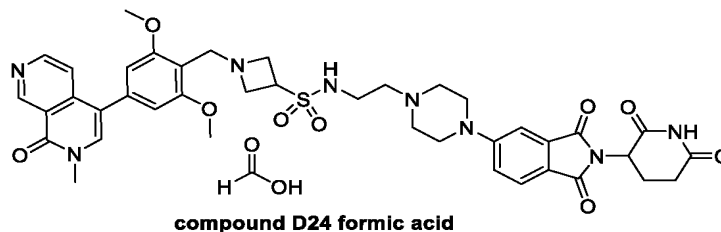
To a stirred solution of 5-[4-(2-aminoethyl)piperazin-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (400.00 mg, 1.038 mmol, 1.00 equiv) and *tert*-butyl 3-(chlorosulfonyl)azetidine-1-carboxylate (318.46 mg, 1.245 mmol, 1.20 equiv) in DCM (10.00 mL) was added TEA (210.03 mg, 2.076 mmol, 2.00 equiv) 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)



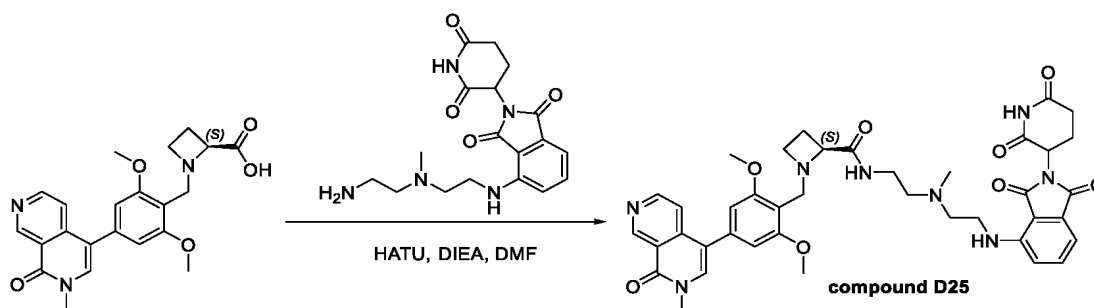
A solution of *tert*-butyl 3-[(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl) sulfamoyl]azetidine-1-carboxylate (500.00 mg, 0.827 mmol, 1.00 equiv) and TFA (3.00 mL) in DCM (5.00 mL) was stirred for 1 hour at room temperature. The resulting mixture was concentrated under 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-dioxoisindol-5-yl]piperazin-1-yl]ethyl)azetidine-3-sulfonamide formic acid (compound D24 formic acid)



5 A solution of *N*-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-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 NaBH₃CN (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-dioxoisindol-5-yl]piperazin-1-yl]ethyl)azetidine-3-sulfonamide (9.4 mg, 9.72%) as a green solid. ¹H 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.

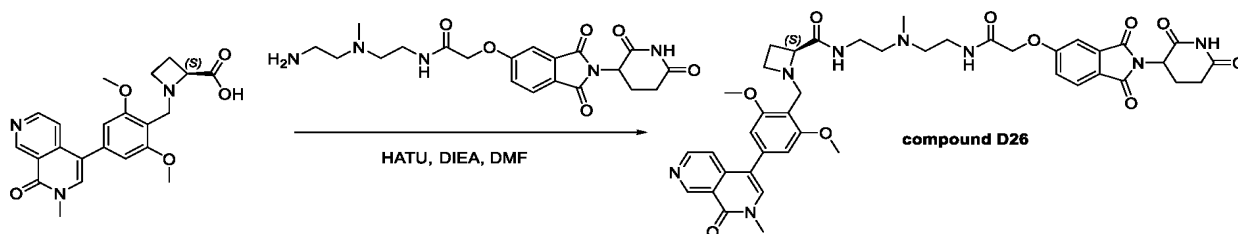
Example 31 – Preparation of (2S)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-N-[2-[(2-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]ethyl)(methyl)amino]ethyl]azetidine-2-carboxamide (compound D25)



25 To a solution of (2S)-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/minute; Gradient: 7% B to 22% B in 8

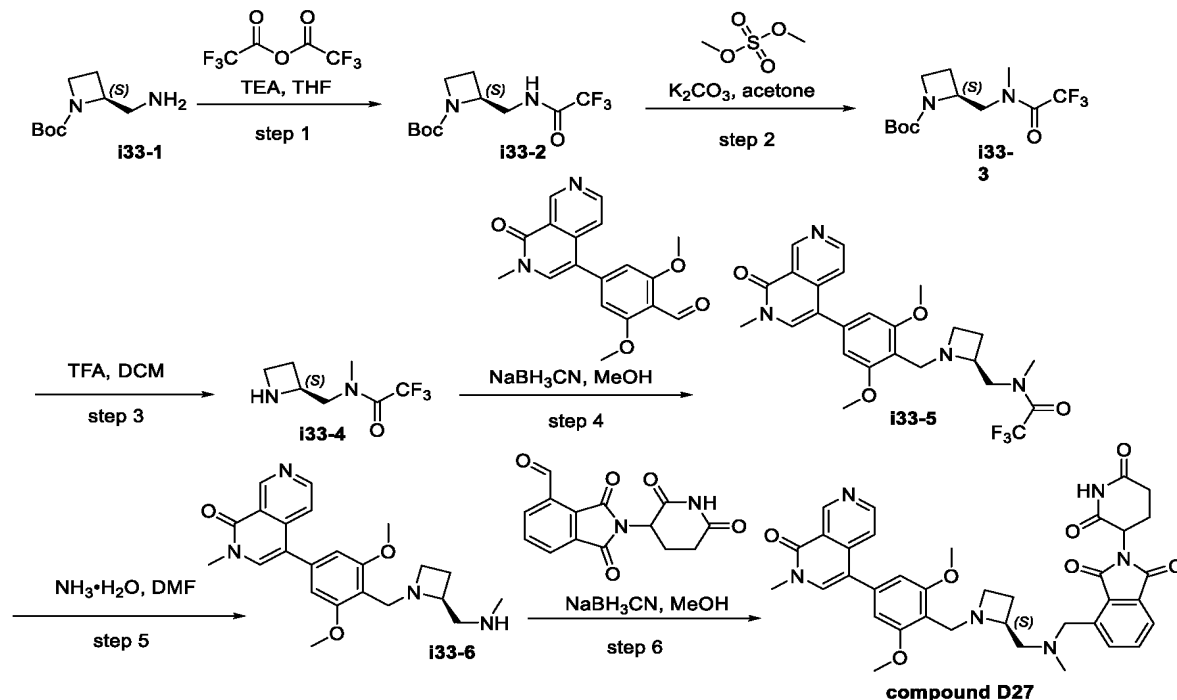
minutes; 254 nm; R_t: 7.75 minutes) to afford (2*S*)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]-*N*-[2-[(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl]amino]ethyl)(methyl)amino]ethyl]azetidine-2-carboxamide (5.5 mg, 3.5%) as a yellow solid. ¹H NMR (300 MHz, Methanol-*d*₄) 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)

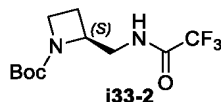


To a solution of (2*S*)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-2-carboxylic acid (30 mg, 0.073 mmol, 1.00 equiv) and DIEA (28.4 mg, 0.220 mmol, 3.00 equiv) in DMF (1.00 mL) was added HATU (41.8 mg, 0.110 mmol, 1.50 equiv) and *N*-[2-[(2-aminoethyl)(methyl)amino]ethyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-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/minute; 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-1*H*-isoindol-5-yl]oxy]acetamide (4.8 mg, 7.5%) as a yellow solid. ¹H NMR (300 MHz, Acetonitrile-*d*₃) 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)

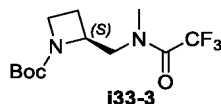


- 5 **Step 1: Preparation of tert-butyl (2S)-2-((2,2,2-trifluoroacetamido)methyl)azetidine-1-carboxylate (i33-2)**



To a solution of tert-butyl (2S)-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 (2S)-2-[(2,2,2-trifluoroacetamido) methyl]azetidine-1-carboxylate (1270 mg, 93.11%) as a yellow oil. LCMS (ESI) m/z: [M+H]⁺ = 283.

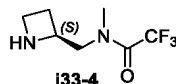
- 15 **Step 2: Preparation of tert-butyl (2S)-2-[(2,2,2-trifluoro-N-methylacetamido)methyl]azetidine-1-carboxylate (i33-3)**



To a solution of tert-butyl (2S)-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 K₂CO₃ (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 (2S)-2-[(2,2,2-

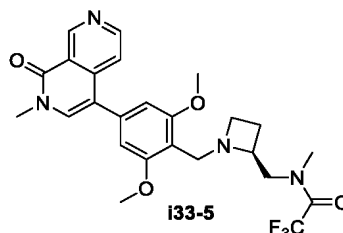
trifluoro-*N*-methylacetamido)methyl]azetidine-1-carboxylate (1640 mg, 123.02%) as a yellow oil that was used directly without further purification. LCMS (ESI) *m/z*: [M+H]⁺ = 297.

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



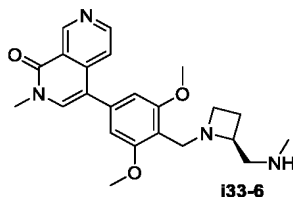
A solution of *tert*-butyl (2*S*)-2-[(2,2,2-trifluoro-*N*-methylacetamido)methyl]azetidine-1-carboxylate (1.64 g, 5.535 mmol, 1.00 equiv) and TFA (3.50 mL, 47.121 mmol, 8.51 equiv) in DCM (16.00 mL) was stirred for 1 hour at 25 °C. The mixture was concentrated to give *N*-[(2*S*)-azetidin-2-ylmethyl]-2,2,2-trifluoro-*N*-methylacetamide (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)



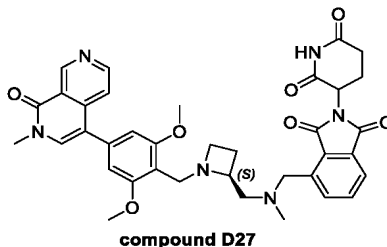
To a solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (552.00 mg, 1.702 mmol, 1.00 equiv) and *N*-[(2*S*)-azetidin-2-ylmethyl]-2,2,2-trifluoro-*N*-methylacetamide (500.81 mg, 2.553 mmol, 1.50 equiv) in DMF (6.00 mL) was added NaBH(OAc)₃ (721.42 mg, 3.404 mmol, 2.00 equiv). 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*-[[[(2*S*)-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)



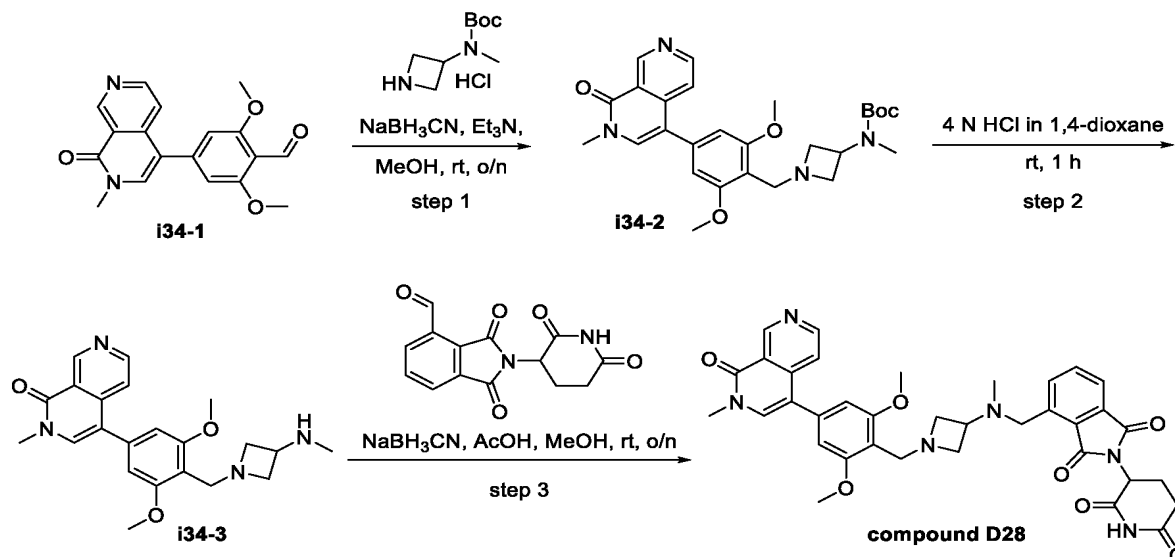
A solution of *N*-[[[(2*R*)-1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]azetidin-2-yl]methyl]-2,2,2-trifluoro-*N*-methylacetamide (230 mg, 0.456 mmol, 1.00 equiv) and NH₃·H₂O (1 mL, 0.008 mmol, 0.05 equiv) in DMF (2.50 mL) was stirred at 25 °C for 1 hour. The resulting mixture were evaporated to dryness to afford 4-(3,5-dimethoxy-4-[[[(2*R*)-2-[(methylamino)methyl]azetidin-1-yl]methyl]phenyl)-2-methyl-2,7-naphthyridin-1-one (219 mg) 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)

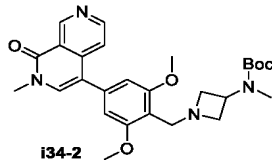


5 To a stirred solution of 4-(3,5-dimethoxy-4-[(2*R*)-2-[(methylamino)methyl]azetidin-1-yl]methyl]phenyl)-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (150.00 mg, 0.367 mmol, 1.00 equiv) and 2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindole-4-carbaldehyde (105.11 mg, 0.367 mmol, 1.00 equiv) in MeOH (2.00 mL) was added NaBH₃CN (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
10 (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. ¹H NMR (400 MHz, Methanol-*d*₄) 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.

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

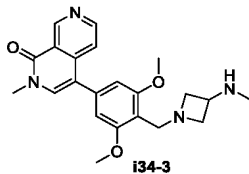


Step 1: Preparation of *tert*-butyl (1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)azetidin-3-yl)(methyl)carbamate (i34-2)



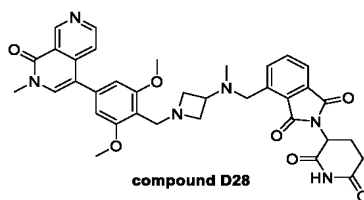
To a solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl) benzaldehyde (250.00 mg, 0.772 mmol, 1.00 equiv) and *tert*-butyl azetidin-3-yl(methyl) carbamate hydrochloride (171.38 mg, 0.772 mmol, 1.00 equiv), was added Et₃N (77.97 mg, 0.772 mmol, 1.00 equiv) and NaBH₃CN (97.27 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)



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(2H)-one (180 mg, crude) as a white solid, that was used directly without further purification. LCMS (ESI) m/z: [M+H]⁺ = 395.

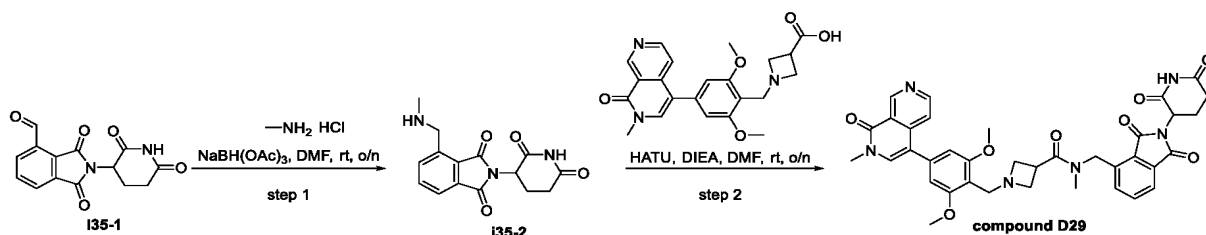
Step 3: Preparation of 4-(((1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)azetidin-3-yl)(methyl)amino)methyl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound D28)



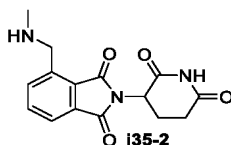
To a mixture of 4-(3,5-dimethoxy-4-[[3-(methylamino)azetidin-1-yl]methyl]phenyl)-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (30.00 mg, 0.076 mmol, 1.00 equiv) and 2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindole-4-carbaldehyde (21.77 mg, 0.076 mmol, 1.00 equiv) in MeOH (2.00 mL) was added AcOH (0.05 mg, 0.001 mmol, 0.01 equiv). The mixture was stirred for 1 hour. NaBH₃CN (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 C₁₈ 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/minute; Gradient: 5% B to 5% B in 2 minutes; 254 nm; R_t: 12.63 minutes. This afforded 4-[[[(1-
5 [[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. ¹H NMR (400 MHz, Methanol-*d*₄) 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-dioxoisindolin-4-yl)methyl)-N-methylazetidine-3-carboxamide (compound D29)

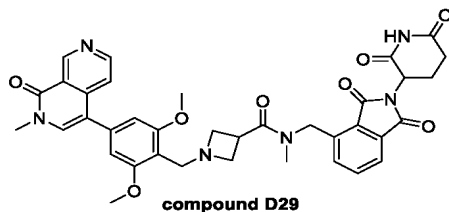


Step 1: Preparation of 2-(2,6-dioxopiperidin-3-yl)-4-((methylamino)methyl)isoindoline-1,3-dione (135-2)



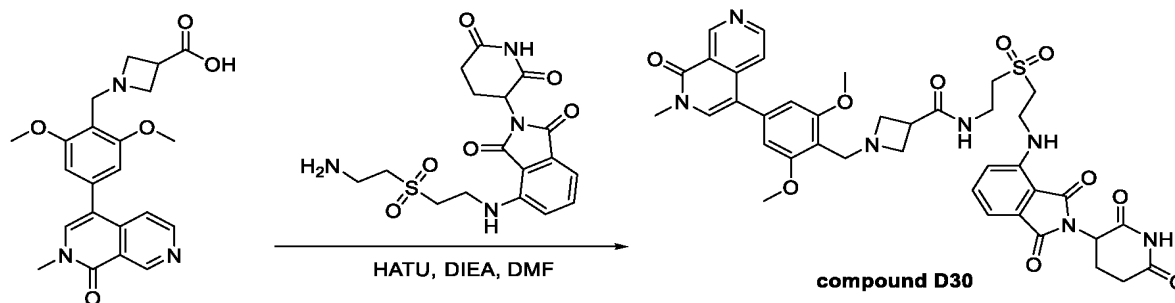
To a solution of 2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindoline-4-carbaldehyde (70.00 mg, 0.245 mmol, 1.00 equiv) in DMF (3.00 mL) was added methanamine hydrochloride (24.77 mg, 0.367 mmol, 1.50 equiv). The resulting mixture was stirred overnight at room temperature. Then NaBH(OAc)₃ (103.88 mg, 0.490 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-dioxoisindolin-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)isoindolin-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 C₁₈ OBD Column, 5 μ m, 19*150 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; 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. ¹H-NMR (400 MHz, Methanol-*d*₄) 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-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)sulfonyl)ethyl)azetidine-3-carboxamide (compound D30)

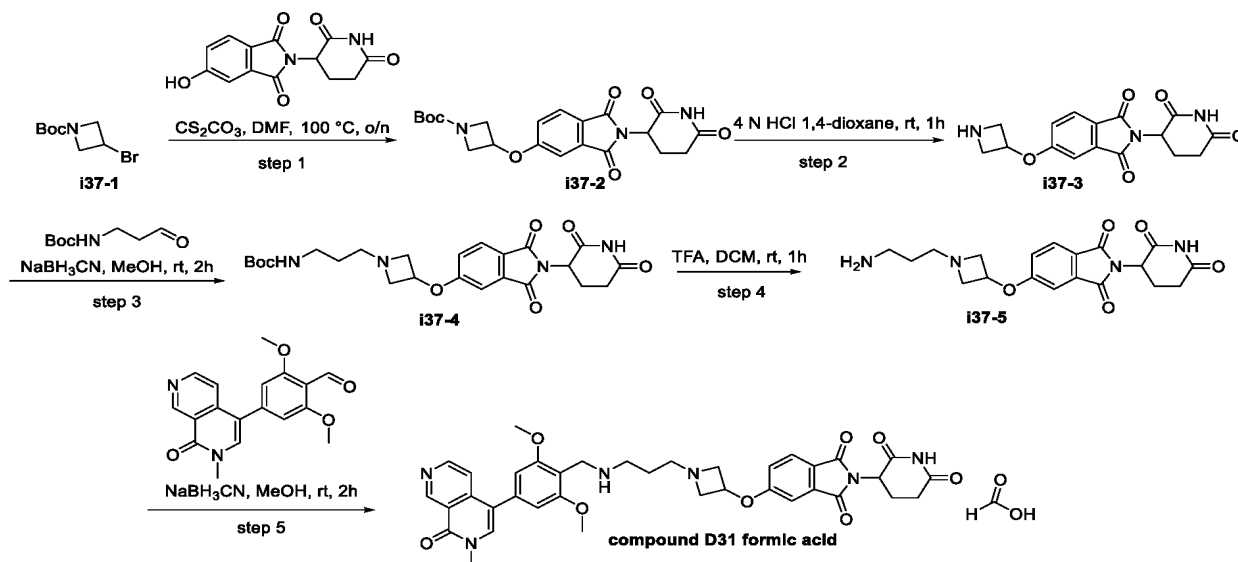


Into a stirred mixture of 1-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]azetidine-3-carboxylic acid (53.00 mg, 0.129 mmol, 1.00 equiv) and DIEA (*N,N*-diisopropylamine) (50.19 mg, 0.388 mmol, 3.00 equiv) in DMF (dimethylformamide) (1.00 mL) was added 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate, *N*-[(Dimethylamino)-1H-1,2,3-triazolo[4,5-*b*]pyridin-1-yl]methylene]-*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 N₂ atmosphere. The crude product was purified by Prep-HPLC (conditions: Sunfire C₁₈ OBD Prep Column, 5 μ m, 19mm*250 mm; Mobile Phase A: Water (0.05% TFA, trifluoroacetic acid), Mobile Phase B: acetonitrile (MeCN or ACN); Flow rate: 25 mL/minute; 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-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)sulfonyl)ethyl)azetidine-3-carboxamide 18.4 mg (16.47%) as a yellow solid. ¹H NMR (300 MHz, Methanol-*d*₄) 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,

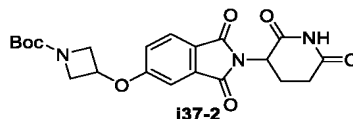
1H), 7.67-7.55 (m, 2H), 7.13 (t, $J = 7.6$ Hz, 2H), 6.83 (s, 2H), 5.06 (dd, $J = 12.3, 5.4$ Hz, 1H), 4.37 (s, 2H), 4.23-4.06 (m, 4H), 3.95 (s, 6H), 3.89 (t, $J = 6.3$ Hz, 2H), 3.77-3.69 (m, 2H), 3.71 (s, 3H), 3.52 (q, $J = 6.9, 6.3$ Hz, 3H), 3.38 (t, $J = 6.3$ Hz, 2H), 2.62-2.93 (m, 3H), 2.07-2.17 (m, 1H). LCMS (ESI) m/z : $[M+H]^+ = 800.35$.

5

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)



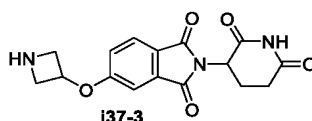
10 **Step 1: Preparation of tert-butyl 3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)azetidine-1-carboxylate (i37-2)**



15 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 : $[M+H]^+ = 430$.

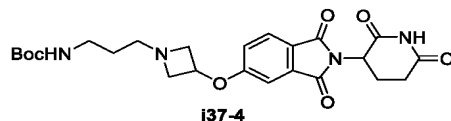
20

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



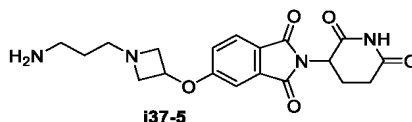
To a solution of *tert*-butyl 3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)oxy)azetidine -1-carboxylate (400.00 mg, 0.932 mmol, 1.00 equiv) in 1,4-dioxane (5 mL) was added HCl (4 N in 1,4-dioxane) (5 mL, 20.000 mmol, 21.46 equiv). The resulting solution was stirred for 1 hour at room temperature. 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-dioxoisindolin-5-yl)oxy)azetidin-1-yl)propyl)carbamate (i37-4)



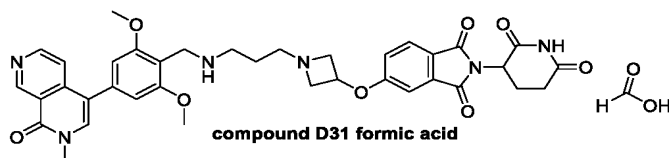
A mixture of 5-(azetidin-3-yloxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (200.00 mg, 0.608 mmol, 1.00 equiv) and *tert*-butyl (3-oxopropyl)carbamate (105.18 mg, 0.608 mmol, 1.00 equiv) in MeOH (5.00 mL) was stirred for 1.5 hours at room temperature. Then NaBH₃CN (75.39 mg, 1.216 mmol, 2.00 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 chromatography, eluted with EA in PE from 0% to 50% to afford *tert*-butyl (3-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)oxy)azetidin-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)



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

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



To a solution of 5-((1-(3-aminopropyl)azetidin-3-yl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline -1,3-dione (60.00 mg, 0.155 mmol, 1.00 equiv) in MeOH (5.00 mL, 123.495 mmol, 795.32 equiv) was added

2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (50.36 mg, 0.155 mmol, 1 equiv).

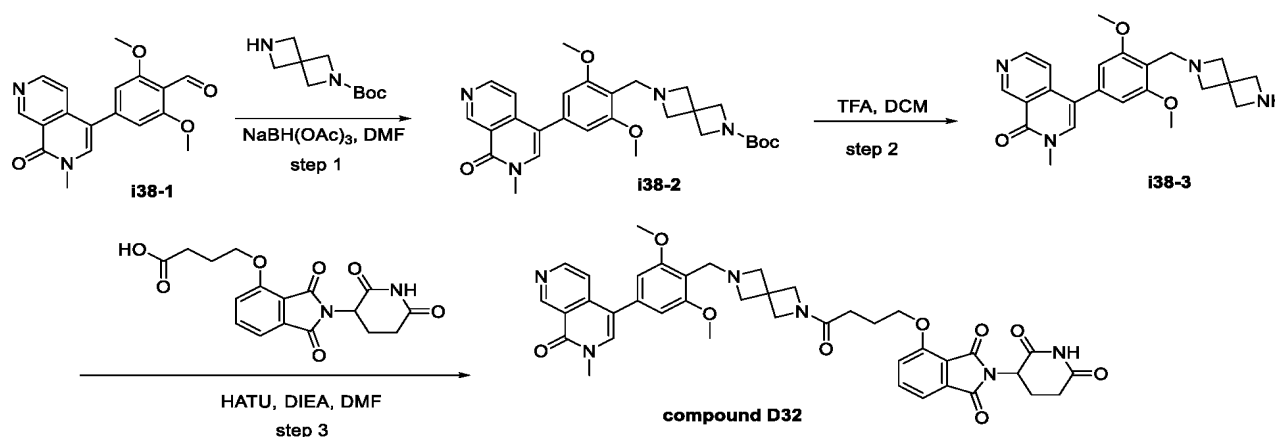
The resulting mixture was stirred for 1 hour. Then NaBH₃CN (19.52 mg, 0.311 mmol, 2 equiv) was

added. The resulting mixture was stirred for 1 hour. The resulting mixture was filtered, and the filtrate

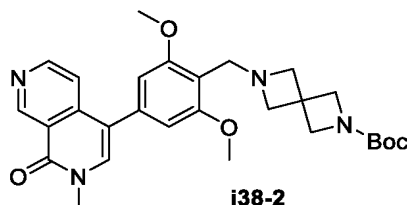
was purified by prep-HPLC (conditions: SunFire C₁₈ OBD Prep Column, 100Å, 5 µm, 19 mm X 250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 5% B to 5% B in 2 minutes; 254 nm; Rt: 9.75 minutes) to afford 5-((1-(3-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-

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. ¹H NMR (400 MHz, Methanol-*d*₄) 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)

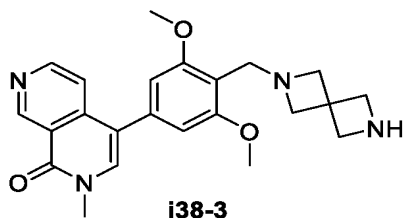


Step 1: Preparation of tert-butyl 6-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (i38-2)



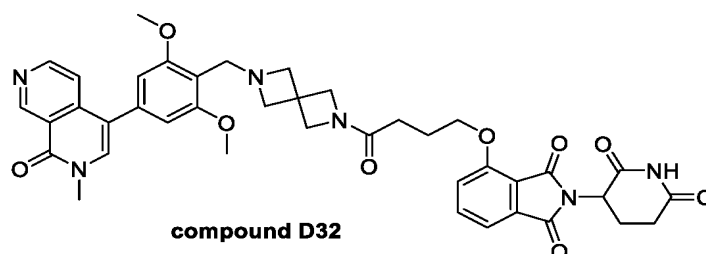
To a solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (700.00 mg, 2.158 mmol, 1.00 equiv) and *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate (427.91 mg, 2.158 mmol, 1.00 equiv) in DMF (10.00 mL, 129.218 mmol, 59.87 equiv) was added NaBH(OAc)₃ (914.85 mg, 4.317 mmol, 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*-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 (808 mg, 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)



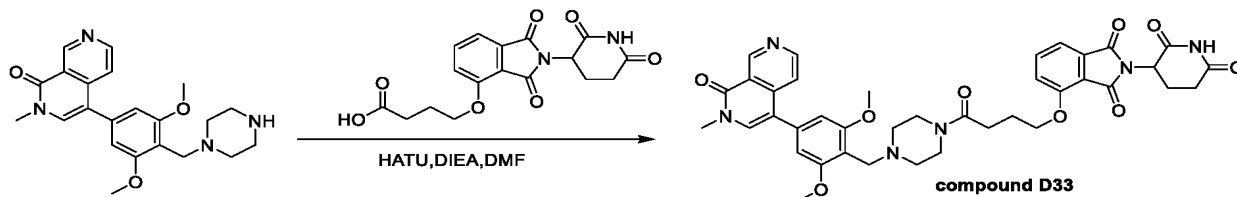
5 A solution of *tert*-butyl 6-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl] methyl]-2,6-diazaspiro[3.3]heptane-2-carboxylate (708.00 mg, 1.398 mmol, 1.00 equiv) and TFA (1.50 mL, 20.195 mmol, 14.45 equiv) in DCM (7.00 mL, 110.110 mmol, 78.79 equiv) was stirred at 25 °C for 1 hour. 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
10 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)



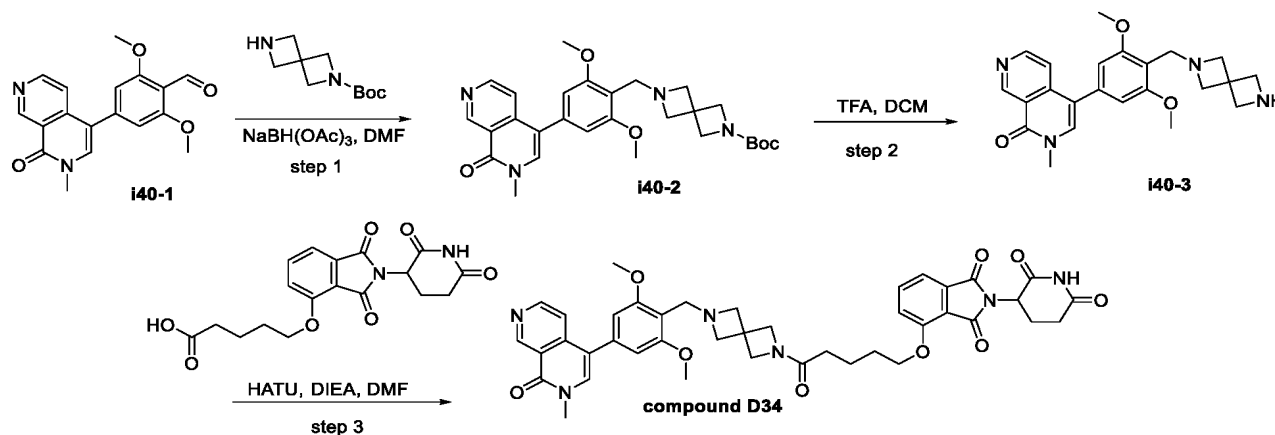
15 To a solution of 4-(4-[2,6-diazaspiro[3.3]heptan-2-ylmethyl]-3,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1-one (40.00 mg, 0.098 mmol, 1.00 equiv) and 4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]butanoic acid (35.46 mg, 0.098 mmol, 1.00 equiv) in DMF (1.0 mL) was added HATU (56.12 mg, 0.148 mmol, 1.5 equiv) and DIEA (31.80 mg, 0.246 mmol, 10 equiv). The mixture was stirred
20 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. ¹H NMR (400 MHz,
25 Methanol-*d*₄) 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)

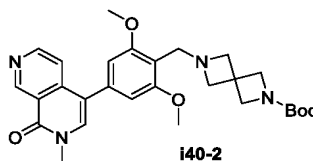


5 To a stirred mixture of 4-[3,5-dimethoxy-4-(piperazin-1-ylmethyl)phenyl]-2-methyl-2,7-naphthyridin-1-one (50.00 mg, 0.127 mmol, 1.00 equiv) and 4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]butanoic acid (45.67 mg, 0.127 mmol, 1.00 equiv) in DMF (2.00 mL) was added DIEA (163.82 mg, 1.268 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
10 preparative HPLC (conditions: XBridge Shield RP18 OBD Column, 5 μ m, 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. ¹H NMR (300 MHz, Methanol-*d*₄) 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)

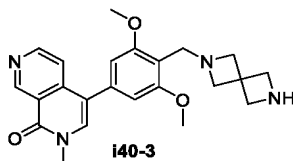


Step 1: Preparation of *tert*-butyl 6-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (*i*40-2)



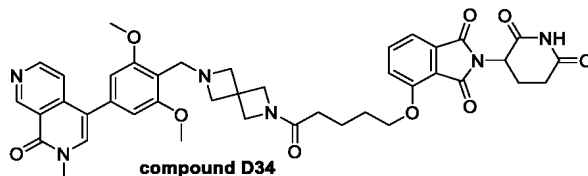
To a solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (700.00 mg, 2.158 mmol, 1.00 equiv) and *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate (427.91 mg, 2.158 mmol, 1.00 equiv) in DMF (10.00 mL, 129.218 mmol, 59.87 equiv) was added NaBH(OAc)₃ (914.85 mg, 4.317 mmol, 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 (*i*40-3)



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)

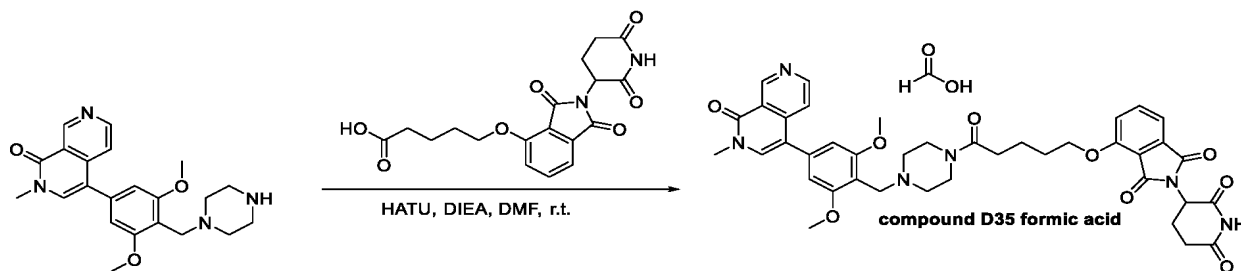


To a solution of 4-(4-[2,6-diazaspiro[3.3]heptan-2-ylmethyl]-3,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1-one (40.00 mg, 0.098 mmol, 1.00 equiv) and 5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]pentanoic acid (36.84 mg, 0.098 mmol, 1 equiv) in DMF (1 mL) was added HATU (56.12 mg, 0.148 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 μ m, 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-oxopentyl]oxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (10.1 mg, 13.46%) as a light yellow solid.

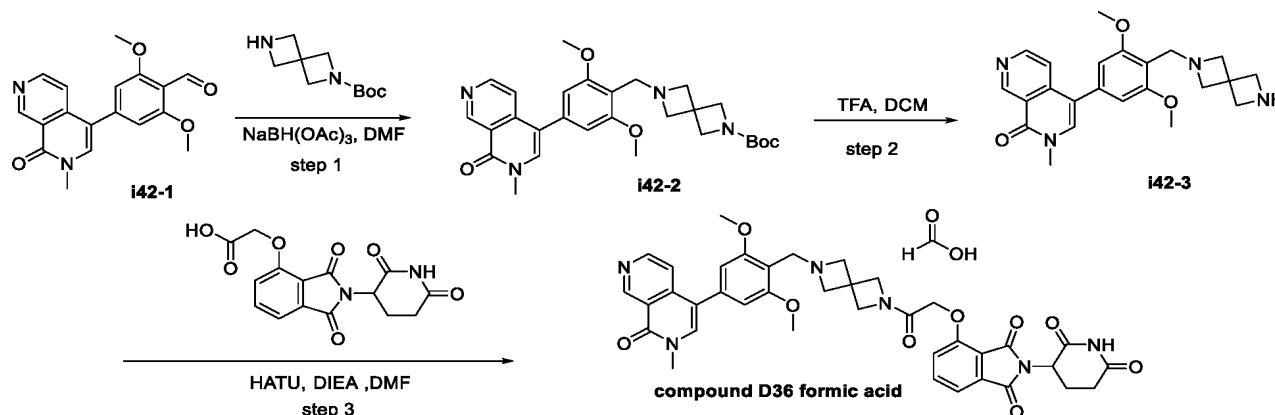
¹H NMR (400 MHz, Methanol-*d*₄) δ 9.58 (s, 1H), 8.73 – 8.67 (m, 1H), 7.92 (d, *J* = 6.9 Hz, 1H), 7.84 – 7.76 (m, 1H), 7.47 (t, *J* = 8.1 Hz, 2H), 6.89 (d, *J* = 3.5 Hz, 2H), 5.17 – 5.07 (m, 1H), 4.51 (d, *J* = 3.0 Hz, 2H), 4.45 – 4.31 (m, 6H), 4.27 (t, *J* = 5.5 Hz, 2H), 4.19 (s, 1H), 4.12 (s, 1H), 3.98 (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)

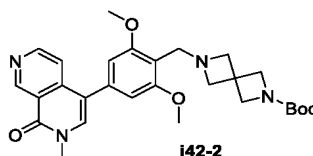


To a stirred solution of 4-[3,5-dimethoxy-4-(piperazin-1-ylmethyl)phenyl]-2-methyl-2,7-naphthyridin-1-one (50.0 mg, 0.127 mmol, 1.00 equiv) and 5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]pentanoic acid (47.5 mg, 0.127 mmol, 1.00 equiv) in DMF (1 mL) was added DIEA (163.8 mg, 1.268 mmol, 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 μ m, 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. ¹H NMR (400 MHz, Methanol-*d*₄) 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)

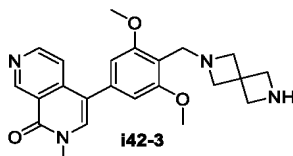


- 5 **Step 1: Preparation of tert-butyl 6-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (i42-2)**



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.

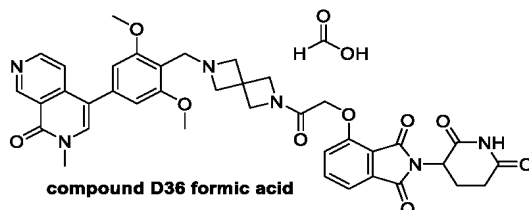
- 15 **Step 2: Preparation of 4-(4-((2,6-diazaspiro[3.3]heptan-2-yl)methyl)-3,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (i42-3)**



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-yl)methyl]-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.

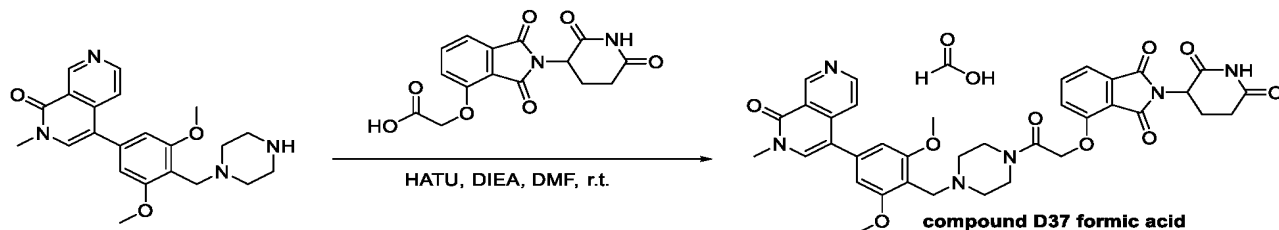
25

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)



5 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-dioxoisindol-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
10 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. ¹H NMR (300 MHz, Methanol-*d*₄) 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),
15 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.

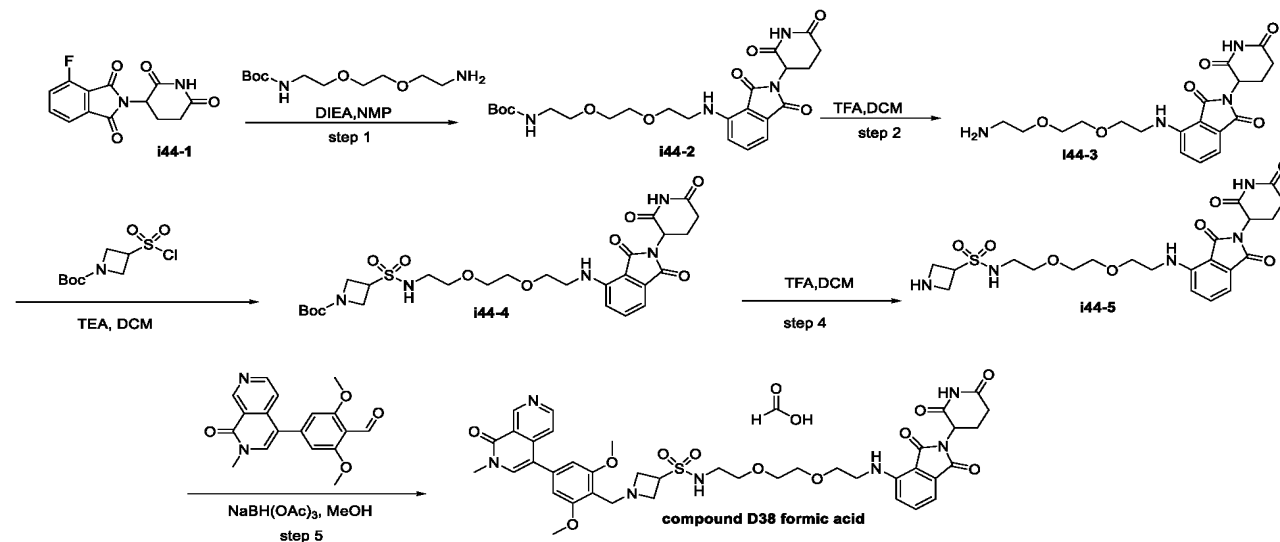
Example 43 – Preparation of 4-(2-(4-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)piperazin-1-yl)-2-oxoethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (compound D37 formic acid)



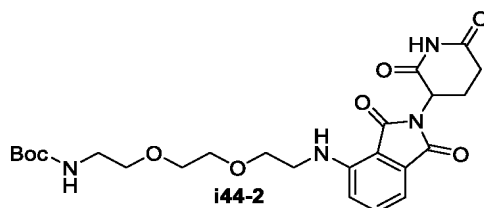
To a stirred solution of 4-[3,5-dimethoxy-4-(piperazin-1-ylmethyl)phenyl]-2-methyl-2,7-naphthyridin-1-one (50.0 mg, 0.127 mmol, 1.00 equiv) and [[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]acetic acid (42.1 mg, 0.127 mmol, 1.00 equiv) in DMF (1 mL) was added DIEA (163.8 mg, 1.268 mmol, 10.00 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
25 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
30

formic acid (12.2 mg, 13.6%) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) 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-dioxoisindol-4-yl]amino]ethoxy)ethoxy]ethyl]azetidine-3-sulfonamide formic acid (compound D38 formic acid)

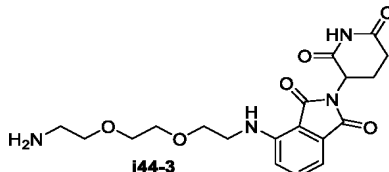


Step 1: Preparation of tert-butyl N-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isindol-4-yl]amino]ethoxy)ethoxy]ethyl]carbamate (i44-2)



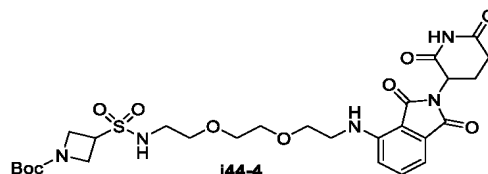
To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-4-fluoro-2,3-dihydro-1H-isindole-1,3-dione (1.0 g, 3.620 mmol, 1.00 equiv) in NMP (15.00 mL) was added DIEA (940.47 mg, 7.277 mmol, 2.01 equiv) and tert-butyl N-[2-[2-(2-aminoethoxy)ethoxy]ethyl]carbamate (988.89 mg, 3.982 mmol, 1.10 equiv) in portions 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-isindol-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)



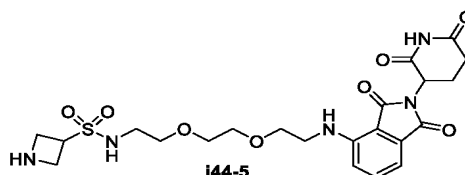
To a stirred solution of *tert*-butyl *N*-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]ethoxy)ethoxy]ethyl]carbamate (1.2 g, 2.378 mmol, 1.00 equiv) in DCM (40 mL) was added TFA (10 mL) in portions at room temperature. The resulting solution was stirred for 4 hours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

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



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 CH₂Cl₂ / 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.

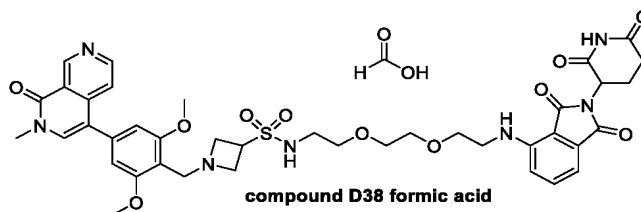
Step 4: Preparation of *N*-(2-(2-(2-([2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino)ethoxy)ethoxy)ethyl)azetidine-3-sulfonamide (i44-5)



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

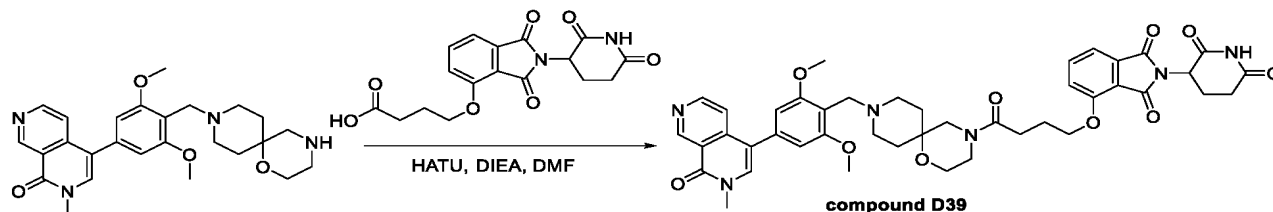
crude product 130 mg was used in the next step directly without further purification. LCMS (ESI) m/z:
[M+H]⁺ = 524.

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-dioxoisindol-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-dioxoisindol-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-dioxoisindol-4-yl]amino]ethoxy)ethoxy]ethyl]azetidine-3-sulfonamide formic acid (8.1 mg, 8.05%) as a yellow solid. ¹H 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.

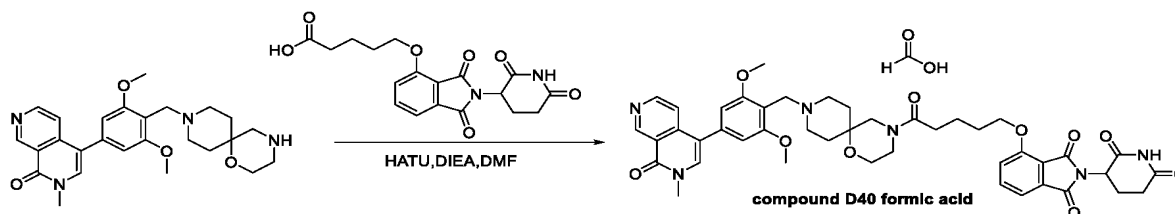
Example 45 – Preparation of 4-[4-(9-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-4-oxobutoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione. (compound D39)



To a stirred solution of 4-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-2-methyl-2,7-naphthyridin-1-one (20.00 mg, 0.043 mmol, 1.00 equiv) and 4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-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-4,9-diazaspiro[5.5]undecan-4-yl)-4-oxobutoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (compound D39).

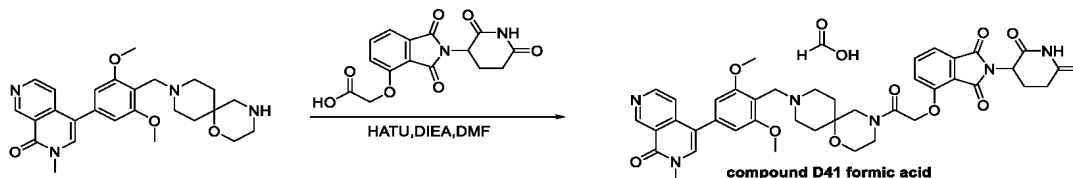
(9-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-4-oxobutoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (5.1 mg, 14.68%) as a white solid. ¹H NMR (300 MHz, Methanol-*d*₄) δ 9.55 (s, 1H), 8.70 (d, *J* = 5.6 Hz, 1H), 7.85 – 7.75 (m, 2H), 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-dioxoisindol-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. ¹H NMR (300 MHz, Methanol-*d*₄) 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.

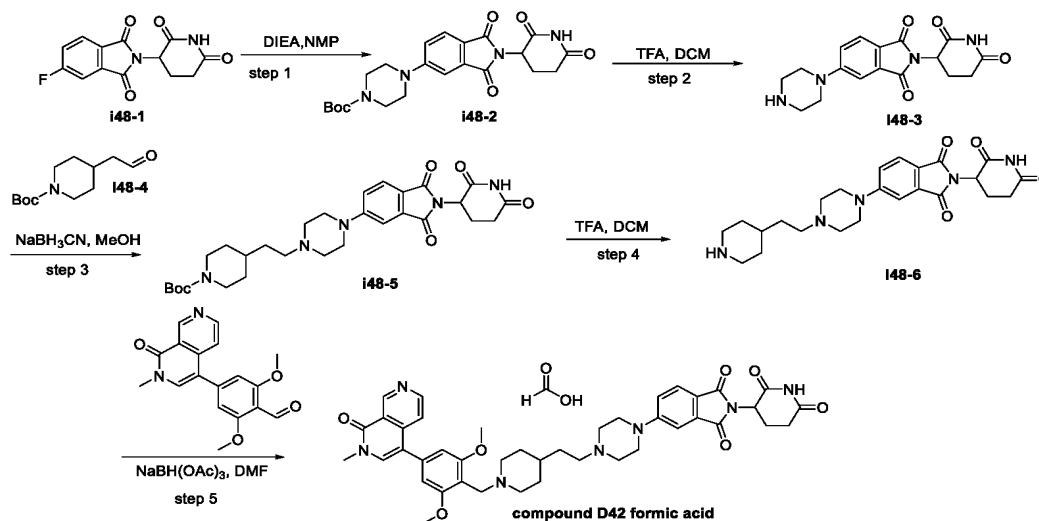
Example 47 – Preparation of 4-[2-(9-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2-oxoethoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (compound D41 formic acid)



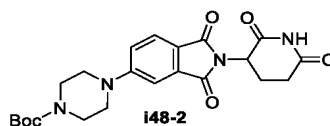
To a solution of 4-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-2-methyl-2,7-naphthyridin-1-one (30.00 mg, 0.065 mmol, 1.00 equiv) and [[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]acetic acid (21.46 mg, 0.065 mmol, 1.00 equiv) in DMF (1.00 mL) was added DIEA

(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-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (3.7 mg, 6.80%) as a white solid. ¹H NMR (300 MHz, Methanol-*d*₄) 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)



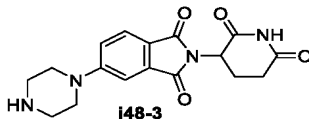
Step 1: Preparation of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)piperazine-1-carboxylate (i42-2)



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 Na₂SO₄. 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%

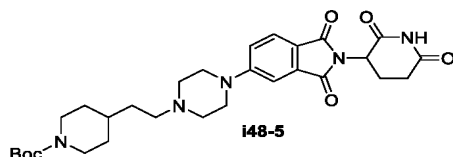
to 90% gradient in 25 minutes; detector, UV 220 nm). The fractions were concentrated under reduced pressure afford *tert*-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)piperazine-1-carboxylate (700 mg, 31.67%) as a yellow solid. LCMS (ESI) *m/z*: [M+H]⁺ = 443.

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



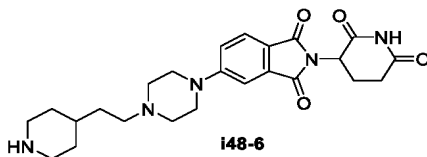
A solution of *tert*-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]piperazine-1-carboxylate (500.00 mg, 1.130 mmol, 1.00 equiv) and TFA (1.50 mL, 20.195 mmol, 17.87 equiv) in DCM (5.00 mL) was stirred at 25 °C for 1 hour. The resulting mixture was evaporated to dryness to afford 2-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)isoindole-1,3-dione (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-dioxoisindolin-5-yl)piperazin-1-yl)ethyl)piperidine-1-carboxylate (i42-5)



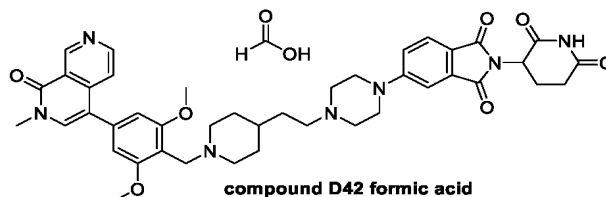
To a solution of 2-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)isoindole-1,3-dione (200.00 mg, 0.584 mmol, 1.00 equiv) and *tert*-butyl 4-(2-oxoethyl)piperidine-1-carboxylate (132.79 mg, 0.584 mmol, 1 equiv) in DMF (3.00 mL) was added NaBH(OAc)₃ (247.63 mg, 1.168 mmol, 2 equiv). The resulting solution 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-dioxoisindol-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.

25 *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)*



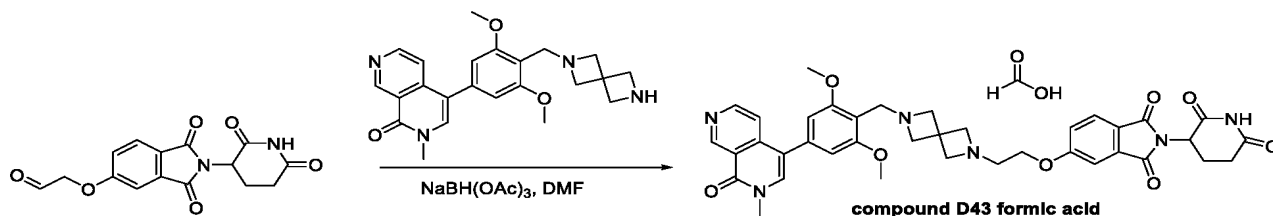
To a solution of *tert*-butyl 4-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]piperazin-1-yl]ethylpiperidine-1-carboxylate (197.00 mg, 0.356 mmol, 1.00 equiv) and TFA (0.50 mL, 6.732 mmol, 18.92 equiv) in DCM (2.00 mL) was stirred at 25 °C for 1 hour. The mixture was concentrated to give crude 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)



5 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 (1.5 mL) was added $\text{NaBH}(\text{OAc})_3$ (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)isoindole-1,3-dione (24 mg, 17.03%) as a yellow solid. ^1H NMR (300 MHz, Methanol- d_4) 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 : $[\text{M}+\text{H}]^+ = 762.45$.

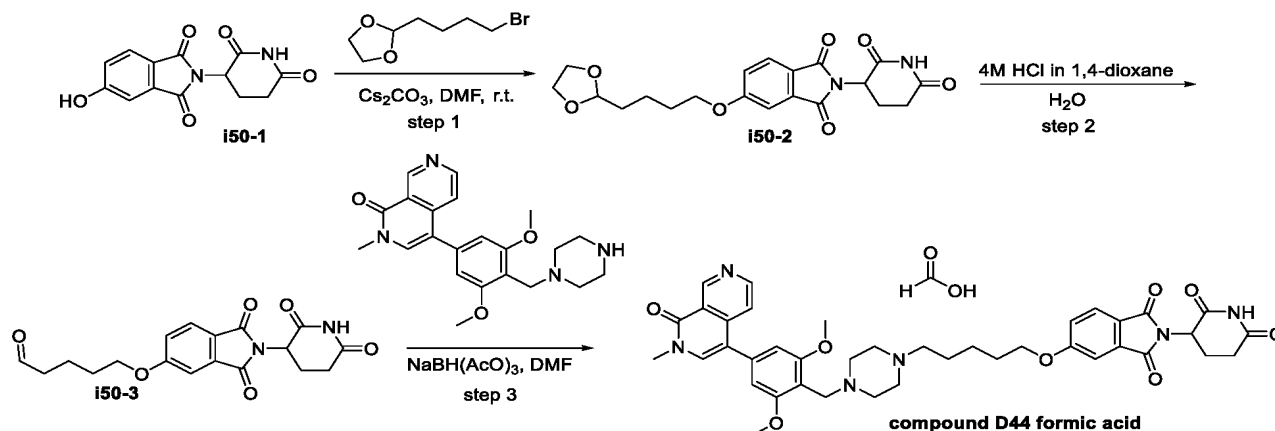
Example 49 – Preparation of 5-[2-(6-[[2,6-Dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]-2,6-diazaspiro[3.3]heptan-2-yl)ethoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (compound D43 formic acid)



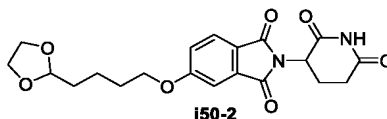
To a solution of 2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]acetaldehyde (60.00 mg, 0.190 mmol, 1.00 equiv) and 4-(4-[2,6-diazaspiro[3.3]heptan-2-ylmethyl]-3,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1-one (77.12 mg, 0.190 mmol, 1 equiv) in DMF (1.00 mL) was added $\text{NaBH}(\text{OAc})_3$ (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; R_t : 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. ^1H NMR (300 MHz, Methanol- d_4) 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)

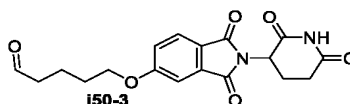


Step 1: 5-(4-(1,3-dioxolan-2-yl)butoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (i50-2)



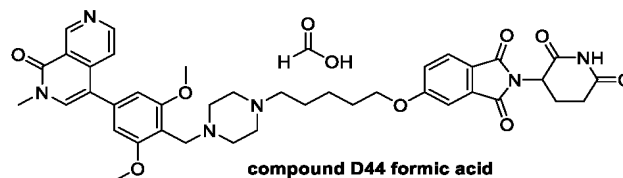
To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-hydroxy-2,3-dihydro-1H-isoindole-1,3-dione (400.0 mg, 1.459 mmol, 1.00 equiv) and 2-(4-bromobutyl)-1,3-dioxolane (305.0 mg, 1.459 mmol, 1.00 equiv) in DMF was added cesium carbonate (475.3 mg, 1.459 mmol, 1.00 equiv) at room temperature. The resulting 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)



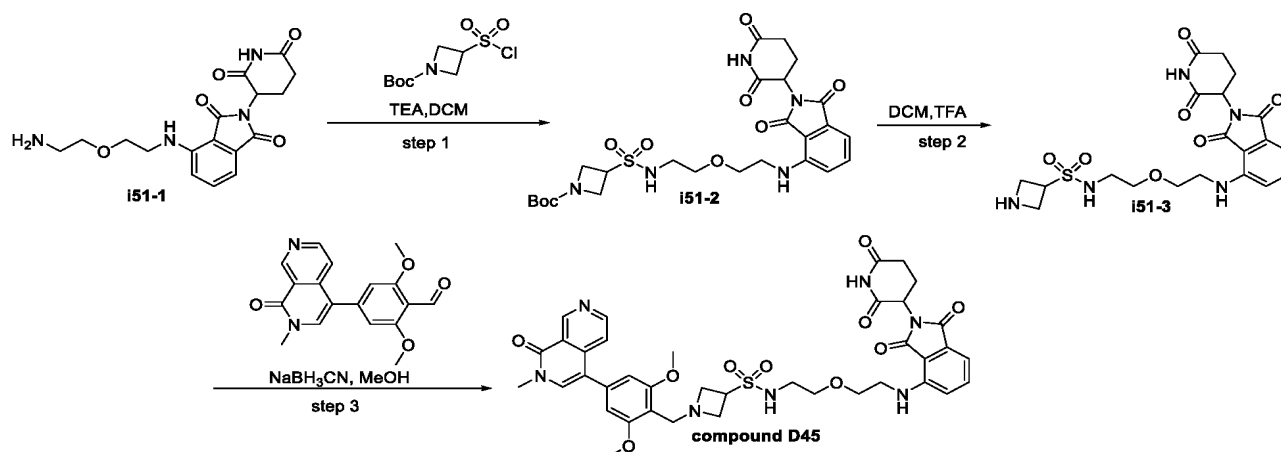
To a stirred mixture of 5-[4-(1,3-dioxolan-2-yl)butoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (40.0 mg, 0.099 mmol, 1.00 equiv) in water (1.50 mL) was added HCl in 1,4-dioxane (4 M, 3.00 mL) at room temperature. The resulting mixture was stirred for 2 hours at room temperature. The resulting 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)

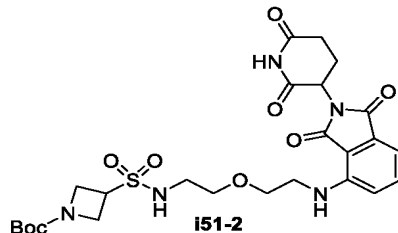


To a stirred solution/mixture of 5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]oxy]pentanal (20 mg, 0.056 mmol, 1.00 equiv) in DMF (1 mL) was added 4-[3,5-dimethoxy-4-(piperazin-1-ylmethyl)phenyl]-2-methyl-2,7-naphthyridin-1-one (22.0 mg, 0.056 mmol, 1 equiv) at room temperature. The resulting 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. ¹H NMR (400 MHz, Methanol-*d*₄) 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-dioxoisindol-4-yl]amino]ethoxy)ethyl]azetidine-3-sulfonamide (compound D45)

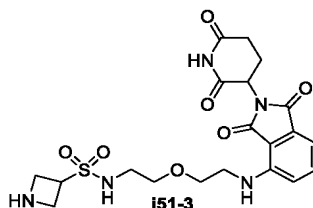


Step 1: Preparation of *tert*-butyl 3-[[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino]ethoxy)ethyl]sulfamoyl]azetidine-1-carboxylate (i51-2)



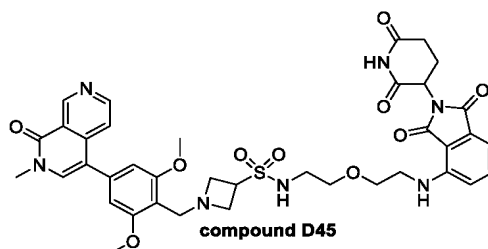
To a stirred solution of 4-[[2-(2-aminoethoxy)ethyl]amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (200.00 mg, 0.555 mmol, 1.00 equiv) and TEA (168.48 mg, 1.665 mmol, 3.00 equiv) in DCM (2mL) was added *tert*-butyl 3-(chlorosulfonyl)azetidine-1-carboxylate (170.30 mg, 0.666 mmol, 1.20 equiv) at 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 CH₂Cl₂ / MeOH (7:1) to afford *tert*-butyl 3-[[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-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-dioxoisindol-4-yl]amino]ethoxy)ethyl]azetidine-3-sulfonamide (i51-3)



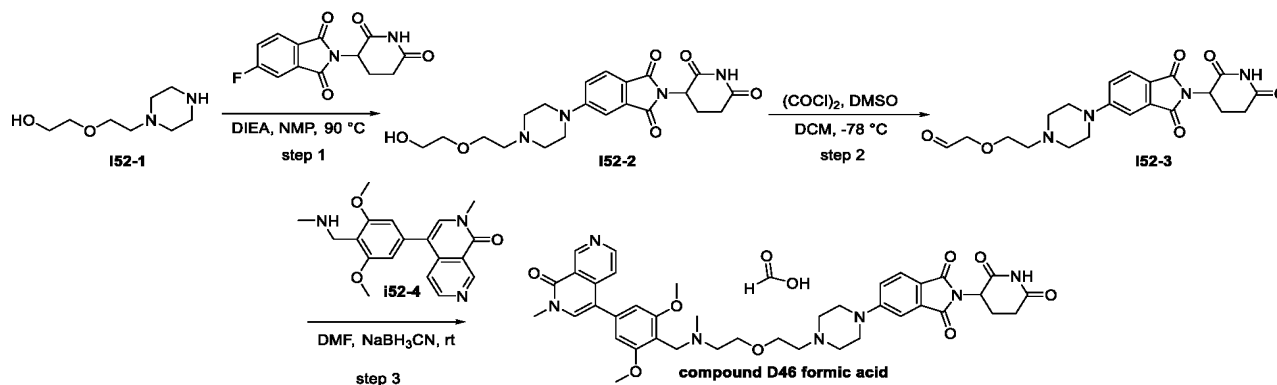
A solution of *tert*-butyl 3-[[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino]ethoxy)ethyl] sulfamoyl]azetidine-1-carboxylate (100.00 mg, 0.173 mmol, 1.00 equiv) and TFA (1.00 mL) in DCM was stirred for 1 hour at room temperature. The resulting mixture was concentrated under vacuum. This resulted in *N*-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-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-dioxoisindol-4-yl]amino]ethoxy)ethyl]azetidine-3-sulfonamide (compound D45)

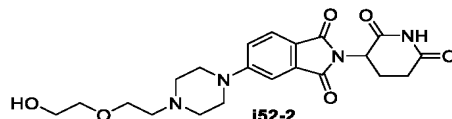


A solution of *N*-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino]ethoxy)ethyl]azetidine-3-sulfonamide (30.00 mg, 0.063 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (26.38 mg, 0.081 mmol, 1.30 equiv) in DMF (2.00 mL) was stirred for 20 minutes 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-dioxoisindol-4-yl]amino]ethoxy)ethyl]azetidine-3-sulfonamide (7.9 mg, 16.03%) as a green solid. ¹H NMR (400 MHz, Methanol-*d*₄) 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)(methylamino)ethoxy)ethyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (compound D46 formic acid)

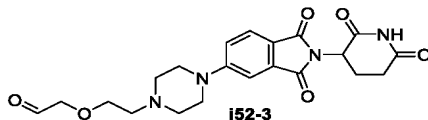


Step 1: Preparation of 2-(2,6-dioxopiperidin-3-yl)-5-(4-(2-(2-hydroxyethoxy)ethyl)piperazin-1-yl)isoindoline-1,3-dione (i52-2)



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-1H-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-dioxoisindolin-5-yl)piperazin-1-yl)ethoxy)acetaldehyde (i52-3)

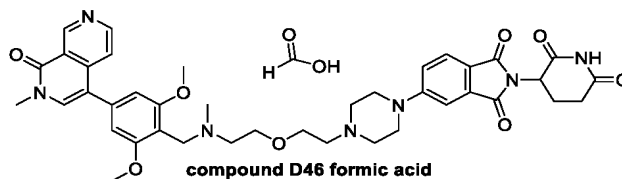


5 A solution of DMSO (54.5 mg, 0.697 mmol, 1.00 equiv) in DCM (6.00 mL) was added slowly to a stirred solution of oxalyl chloride (176.9 mg, 1.394 mmol, 2.00 equiv) in DCM (6.00 mL) at -78 °C under nitrogen atmosphere. After 30 minutes 2-(2,6-dioxopiperidin-3-yl)-5-[4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl]isoindole-1,3-dione (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.

10 Et₃N (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-dioxoisindolin-5-yl)piperazin-1-yl)ethoxy)acetaldehyde (30.0 mg, 5.7%) as a

15 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)(methylamino)ethoxy)ethyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (compound D46 formic acid)



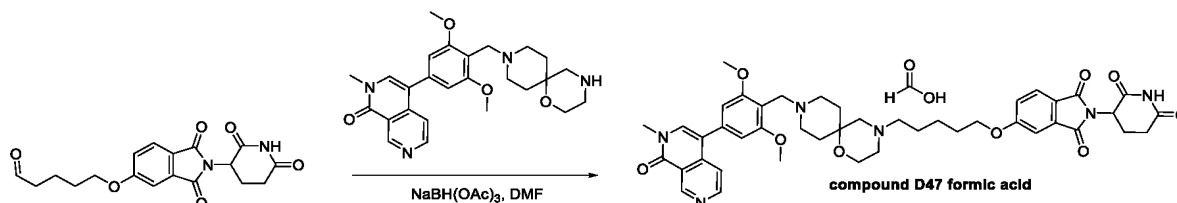
To a mixture of 2-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]piperazin-1-yl]ethoxy)acetaldehyde (30.0 mg, 0.070 mmol, 1.00 equiv) in DMF (2.00 mL) was added 4-[3,5-dimethoxy-4-[(methylamino)methyl]phenyl]-2-methyl-2,7-naphthyridin-1-one (23.7 mg, 0.070 mmol, 1.00 equiv). The resulting mixture 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 work-up, 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 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)(methylamino)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-*d*₄) 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

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30

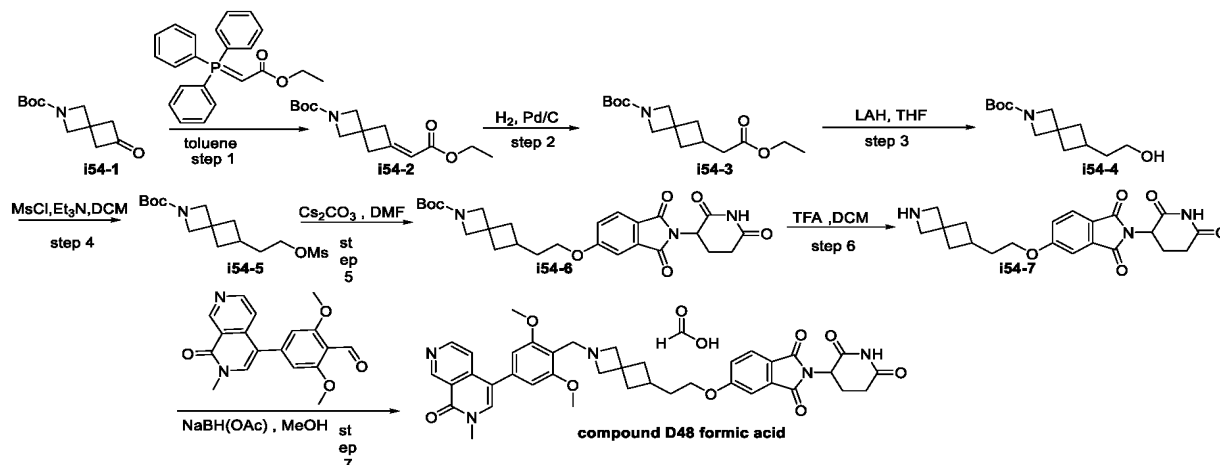
Hz, 1H), 4.53 (s, 2H), 3.99 (s, 6H), 3.91 (t, $J = 4.7$ Hz, 2H), 3.76 (t, $J = 5.1$ Hz, 2H), 3.67 (s, 3H), 3.53 – 3.40 (m, 6H), 2.91 (s, 4H), 2.81 – 2.67 (m, 8H), 2.18 – 2.05 (m, 1H).

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)

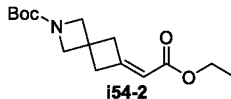


A solution of 5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]oxy]pentanal (25 mg, 0.070 mmol, 1.00 equiv) and 4-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-2-methyl-2,7-naphthyridin-1-one (32.4 mg, 0.070 mmol, 1.00 equiv) in DMF (0.8 mL) was stirred for 30 minutes at 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. ¹H NMR (300 MHz, Methanol-*d*₄) δ 9.55 (s, 1H), 8.69 (d, $J = 5.8$ Hz, 1H), 8.50 (br s, 1H, FA), 7.86 – 7.75 (m, 2H), 7.63 (d, $J = 5.8$ Hz, 1H), 7.40 (d, $J = 2.2$ Hz, 1H), 7.32 (dd, $J = 8.3, 2.3$ Hz, 1H), 6.88 (s, 2H), 5.11 (dd, $J = 12.3, 5.4$ Hz, 1H), 4.42 (s, 2H), 4.19 (t, $J = 6.2$ Hz, 2H), 3.98 (s, 6H), 3.76 (t, $J = 4.9$ Hz, 2H), 3.72 (s, 3H), 3.44 – 3.35 (3H), 2.93 – 2.67 (m, 3H), 2.53 – 2.10 (m, 10H), 1.98 – 1.51 (m, 8H). LCMS (ESI) m/z : [M+H]⁺ = 807.50.

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

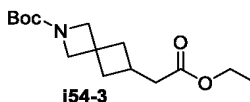


Step 1: Preparation of tert-butyl 6-(2-ethoxy-2-oxoethylidene)-2-azaspiro[3.3]heptane-2-carboxylate (i54-2)



A solution of *tert*-butyl 6-oxo-2-azaspiro[3.3]heptane-2-carboxylate (2.0 g, 9.467 mmol, 1.00 equiv) and ethyl2-(triphenyl-lambda5-phosphanylidene)acetate (3.63 g, 10.414 mmol, 1.10 equiv) in toluene was stirred for 4 hours at 80 °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)



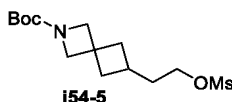
To a solution of *tert*-butyl 6-(2-ethoxy-2-oxoethylidene)-2-azaspiro[3.3]heptane-2-carboxylate (2506.00 mg, 8.907 mmol, 1.00 equiv) in MeOH (25 mL) was added Pd/C (10%, 1g) under nitrogen atmosphere. The mixture was hydrogenated at room temperature for 1 day under hydrogen atmosphere using a hydrogen 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)



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 Na₂SO₄•10H₂O 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 : $[M+H]^+ = 242$.

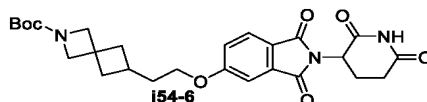
Step 4: Preparation of tert-butyl 6-(2-((methylsulfonyl)oxy)ethyl)-2-azaspiro[3.3]heptane-2-carboxylate (i54-5)



A solution of *tert*-butyl 6-(2-hydroxyethyl)-2-azaspiro[3.3]heptane-2-carboxylate (537.00 mg, 2.225 mmol, 1.00 equiv), Et₃N (450.33 mg, 4.450 mmol, 2.00 equiv), and MsCl (280.38 mg, 2.448 mmol,

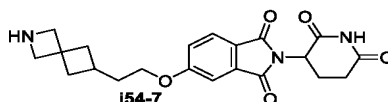
1.10 equiv) in DCM (5 mL) was stirred for 3 hours at room temperature under nitrogen atmosphere. The resulting mixture was extracted with EtOAc (1 x 20mL). The combined organic layers were washed with water (3 x 10 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂/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-dioxoisindolin-5-yl)oxy)ethyl)-2-azaspiro[3.3] heptane-2-carboxylate (i54-6)



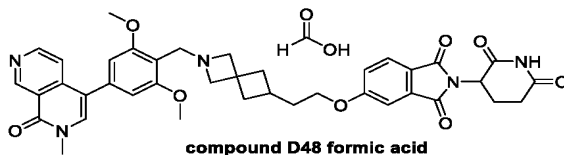
A solution of *tert*-butyl 6-[2-(methanesulfonyloxy)ethyl]-2-azaspiro[3.3]heptane-2-carboxylate (320.00 mg, 1.002 mmol, 1.00 equiv), Cs₂CO₃ (652.82 mg, 2.004 mmol, 2.00 equiv), and 2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisindole-1,3-dione (274.73 mg, 1.002 mmol, 1.00 equiv) in DMF (3 mL) was stirred for 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 Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford *tert*-butyl 6-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-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)isindoline-1,3-dione (i54-7)



A solution of *tert*-butyl 6-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-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 (CH₂Cl₂ / EtOAc 1:1) to afford 5-(2-[2-azaspiro[3.3]heptan-6-yl]ethoxy)-2-(2,6-dioxopiperidin-3-yl)isindole -1,3-dione (200 mg, 94.48%) as a yellow oil. LCMS (ESI) m/z: [M+H]⁺ = 398.

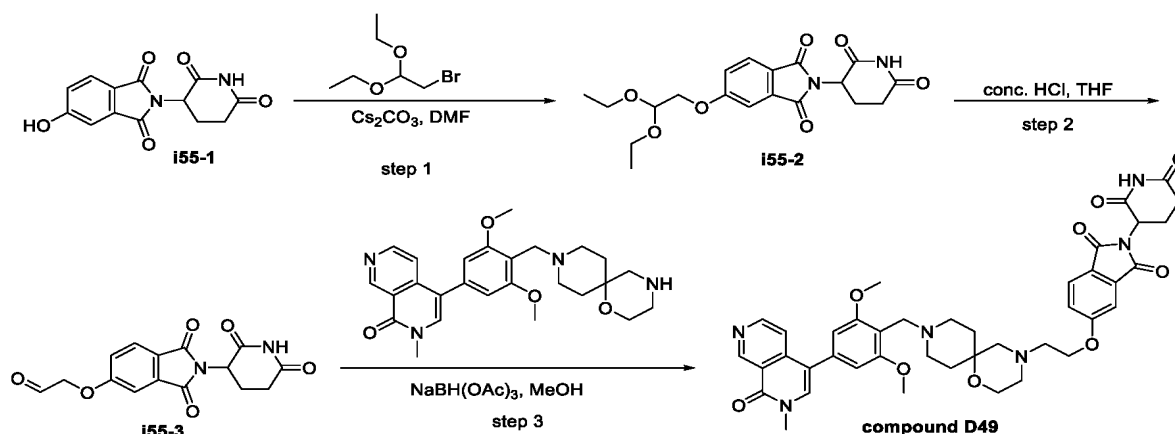
Step 7: Preparation of 5-(2-(2-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-2-azaspiro[3.3] heptan-6-yl)ethoxy)-2-(2,6-dioxopiperidin-3-yl)isindoline-1,3-dione formic acid (compound D48 formic acid)



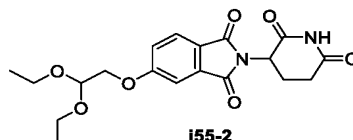
A solution of 5-(2-[2-azaspiro[3.3]heptan-6-yl]ethoxy)-2-(2,6-dioxopiperidin-3-yl)isindole-1,3-dione (51.00 mg, 0.128 mmol, 1.00 equiv) in MeOH (1 mL) was treated with 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (41.62 mg, 0.128 mmol, 1.00 equiv) for 20 minutes at room

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)isoindole-1,3-dione formic acid (2.4 mg, 2.2%) as a yellow solid. ^1H NMR (300 MHz, Methanol- d_4) 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 : $[\text{M}+\text{H}]^+ = 706.50$.

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)

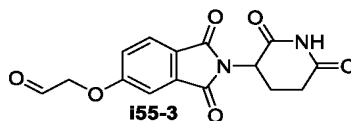


Step 1: Preparation of 5-(2,2-Diethoxyethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (i55-2)



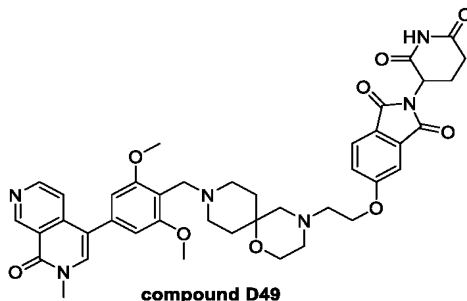
To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindole-1,3-dione (500.00 mg, 1.823 mmol, 1.00 equiv) and Cs_2CO_3 (980.20 mg, 3.008 mmol, 3 equiv) in DMF (10.00 mL) was added 2-bromo-1,1-diethoxyethane (538.97 mg, 2.735 mmol, 1.5 equiv). The mixture was stirred at 80 °C for 16 hours. 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 (110 mg, 15.45%) as a yellow solid. LCMS (ESI) m/z : $[\text{M}+\text{H}]^+ = 391$.

Step 2: Preparation of 2-[[2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]oxy]acetaldehyde (I55-3)



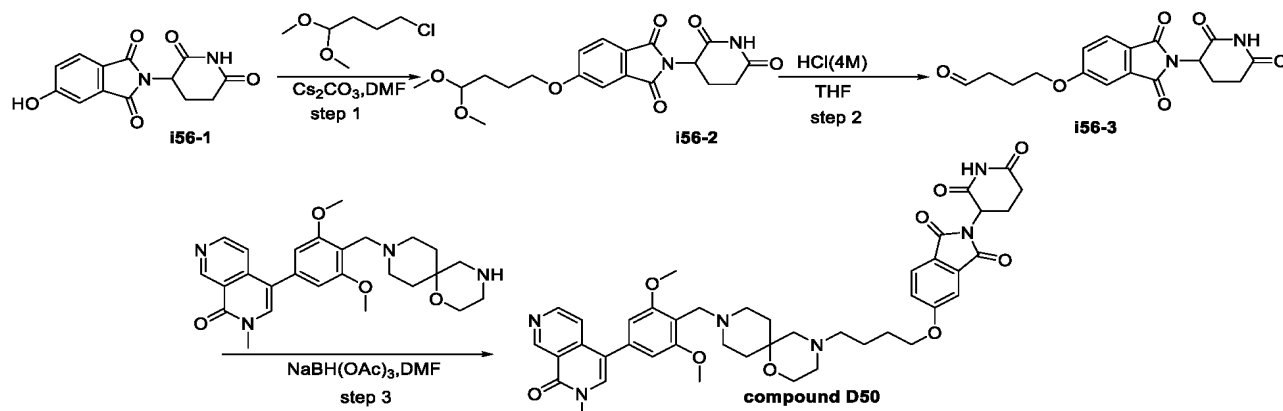
To a stirred solution of 5-(2,2-diethoxyethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (100.00 mg, 0.256 mmol, 1.00 equiv) in THF (2.00 mL) was added HCl (4 M) (2.00 mL). The mixture was stirred at room temperature for 4 hours. The mixture was diluted with water (20 mL) and extracted with EtOAc/DCM (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-dioxoisindol-5-yl]oxy]acetaldehyde (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)

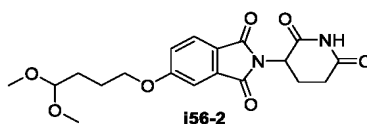


To a stirred solution of 2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]oxy]acetaldehyde (60.00 mg, 0.190 mmol, 1.00 equiv) and 4-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-2-methyl-2,7-naphthyridin-1-one (88.13 mg, 0.190 mmol, 1.00 equiv) in DMF (1.50 mL) was added 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: Xselect CSH F-phenyl 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, 5.5%) as a yellow solid. ¹H 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)

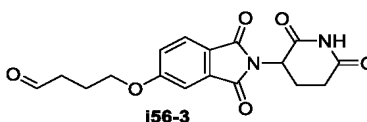


5 Step 1: Preparation of 5-(4,4-dimethoxybutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (i56-2)



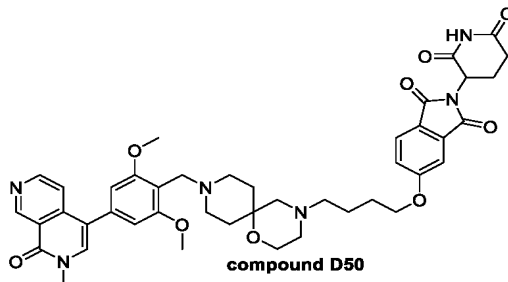
To a solution of 2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindole-1,3-dione (500.00 mg, 1.823 mmol, 1.00 equiv) and 4-chloro-1,1-dimethoxybutane (278.27 mg, 1.823 mmol, 1 equiv) in DMF (7.00 mL) was added K_2CO_3 (755.96 mg, 5.470 mmol, 3 equiv). The resulting solution was stirred at 80 °C for 12 hours. 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 : $[M+H]^+ = 391$.

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



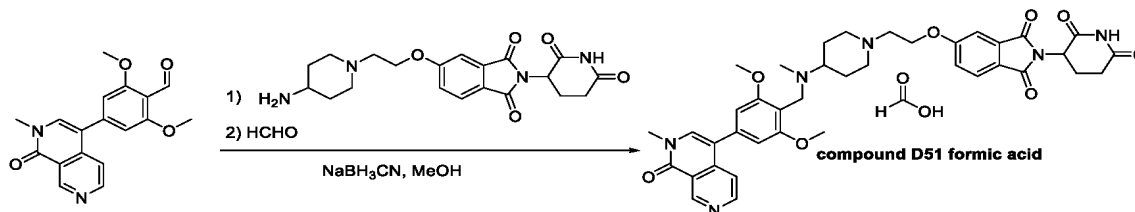
A solution of 5-(4,4-dimethoxybutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (43.60 mg, 0.112 mmol, 1.00 equiv) and HCl (1.00 mL, 4M) in THF (1.00 mL) was stirred at 25 °C for 1 hour. The resulting mixture was extracted with EA (50 mL x 2). The combined organic layers were washed with saturated 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-dioxoisindol-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)



5 To a solution of 4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-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. ¹H NMR (300 MHz, Methanol-*d*₄) 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.

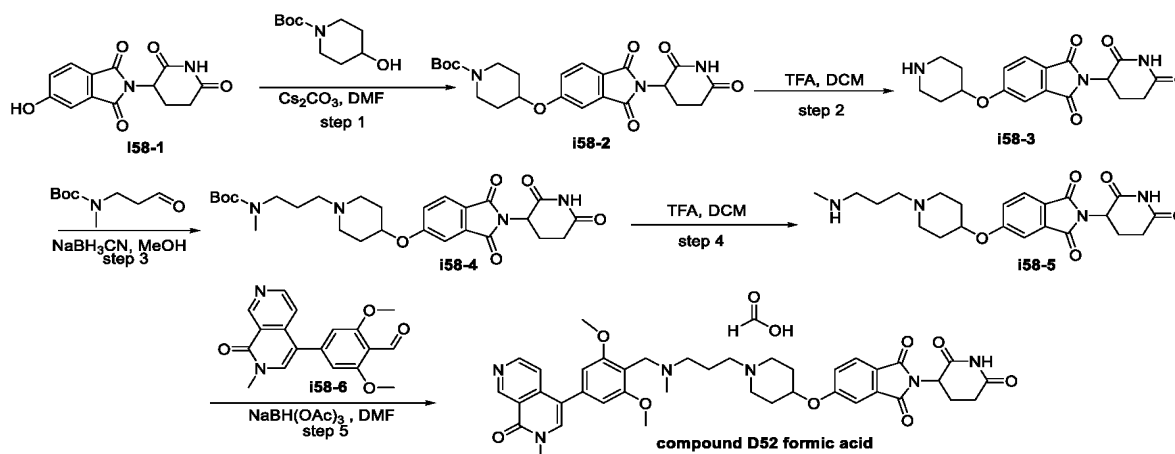
Example 57 – Preparation of 5-[2-[4-([2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl) (methyl)amino)piperidin-1-yl]ethoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione; formic acid (compound D51 formic acid)



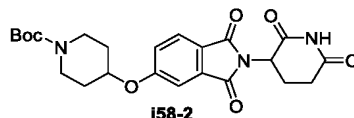
To a solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (30.00 mg, 0.092 mmol, 1.00 equiv) and 5-[2-(4-aminopiperidin-1-yl)ethoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (37.04 mg, 0.092 mmol, 1.00 equiv) in MeOH (1 mL) was stirred for 3 hours at room temperature under nitrogen atmosphere. To the above mixture was added NaBH₃CN (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 NaBH₃CN (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 μ m; 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. ^1H NMR (300 MHz, DMSO-
5 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 : $[\text{M}+\text{H}]^+ = 723.40$.

10 **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)**

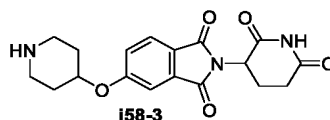


Step 1: Preparation of tert-butyl 4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl)oxy)piperidine-1-
15 carboxylate (i58-2)



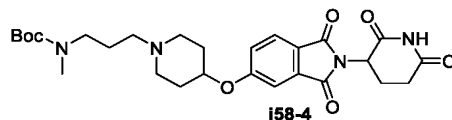
A mixture of 2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindole-1,3-dione (1.00 g, 3.647 mmol, 1.00 equiv), tert-butyl 4- bromopiperidine-1-carboxylate (0.96 g, 3.634 mmol, 1.00 equiv) and Cs_2CO_3 (2.38 g, 7.293 mmol, 2.00 equiv) in DMF (20.00 mL) was stirred for overnight at 90 $^\circ\text{C}$ under air atmosphere. The
20 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-butyl 4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]oxy]piperidine-1-carboxylate (280 mg, 11.19%) as a yellow oil. LCMS (ESI) m/z : $[\text{M}+\text{H}]^+ = 458.19$.

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



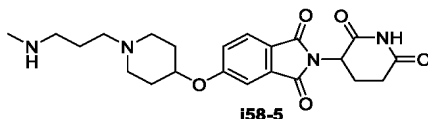
A solution of TFA (1.00 mL) and *tert*-butyl 4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]oxy]piperidine-1-carboxylate (200.00 mg, 0.437 mmol, 1.00 equiv) in DCM (4.00 mL) was stirred for 2 hours at room temperature under air atmosphere. The resulting mixture was concentrated under reduced pressure 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-dioxoisindolin-5-yl)oxy)piperidin-1-yl)propyl)(methyl) carbamate (i58-4)



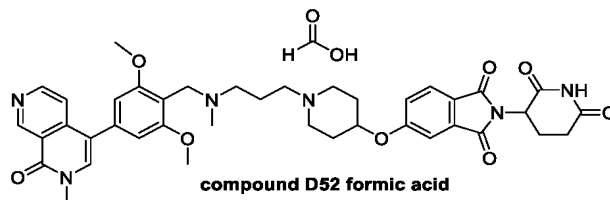
To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-(piperidin-4-yloxy)isoindole-1,3-dione (120.00 mg, 0.336 mmol, 1.00 equiv) and *tert*-butyl *N*-methyl-*N*-(3-oxopropyl)carbamate (62.87 mg, 0.336 mmol, 1.00 equiv) in MeOH (1.50 mL) was added NaBH_3CN (42.20 mg, 0.672 mmol, 2.00 equiv) in portions 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-dioxoisindol-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)



A solution of *tert*-butyl *N*-[3-(4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-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 : $[M+H]^+ = 429.21$.

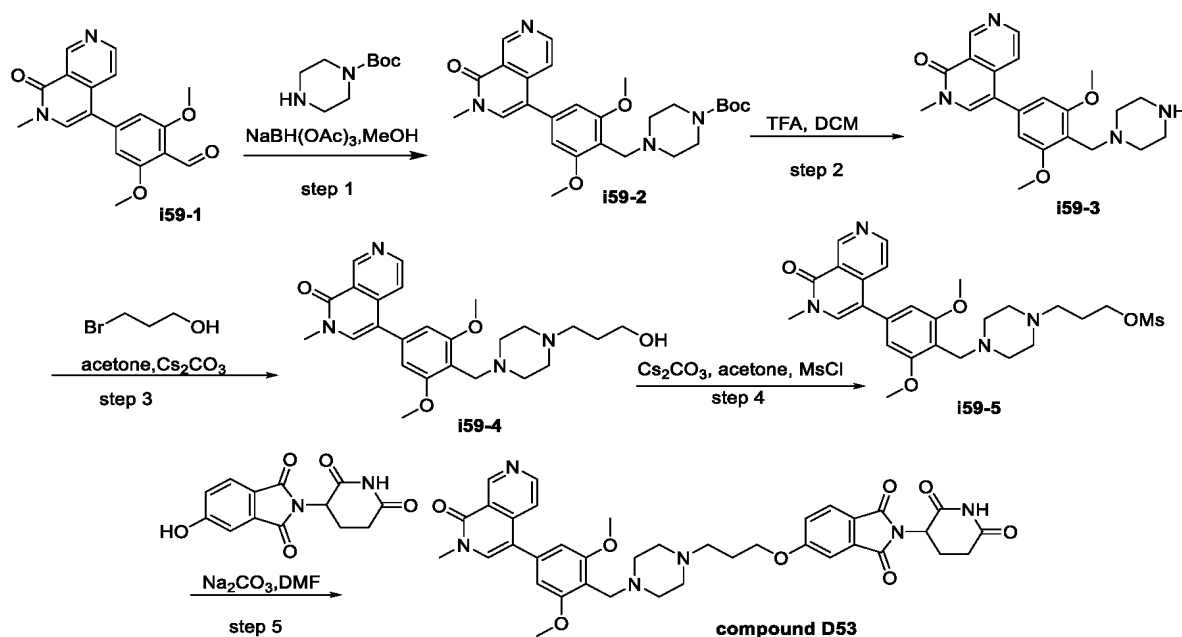
Step 5: Preparation of 5-((1-(3-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)(methyl)amino)propyl)piperidin-4-yl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (compound D52 formic acid)



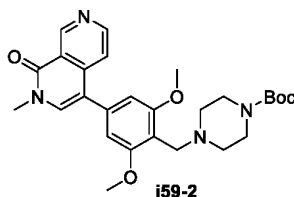
A solution of 2-(2,6-dioxopiperidin-3-yl)-5-([1-[3-(methylamino)propyl]piperidin-4-yl]oxy)isoindole-1,3-dione (70.00 mg, 0.163 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (52.99 mg, 0.163 mmol, 1.00 equiv) in DMF (3.00 mL) was stirred for 30 minutes at

room temperature. To the above mixture was added $\text{NaBH}(\text{AcO})_3$ (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. ^1H NMR (400 MHz, Methanol- d_4) 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 : $[\text{M}+\text{H}]^+ = 737.40$.

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)

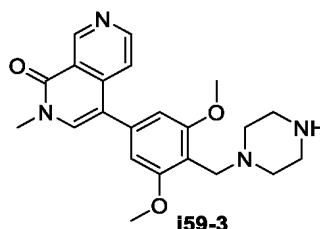


Step 1: Preparation of tert-butyl 4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]piperazine-1-carboxylate (i59-2)



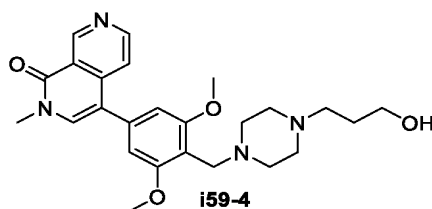
To a stirred solution of 2, 6-dimethoxy-4-(2-methyl-1-oxo-2, 7-naphthyridin-4-yl) benzaldehyde (200.00 mg, 0.617 mmol, 1.00 equiv) and *tert*-butyl piperazine-1-carboxylate (173.00 mg, 0.929 mmol, 1.51 equiv) in MeOH was added NaBH(OAc)₃ (527.00 mg, 2.487 mmol, 4.03 equiv) in portions at room temperature. The resulting mixture was stirred for 3 hours at room temperature. The residue was
5 purified by silica gel column chromatography, eluted with CH₂Cl₂ / 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)
10



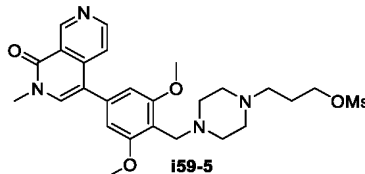
To a stirred solution of *tert*-butyl 4-[[2, 6-dimethoxy-4-(2-methyl-1-oxo-2, 7-naphthyridin-4-yl) phenyl] methyl] piperazine-1-carboxylate (204.00 mg, 0.412 mmol, 1.00 equiv) in DCM was added TFA
15 (1.00 mL) dropwise at room temperature. The resulting mixture was stirred for 1 hour at room temperature. 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)
20



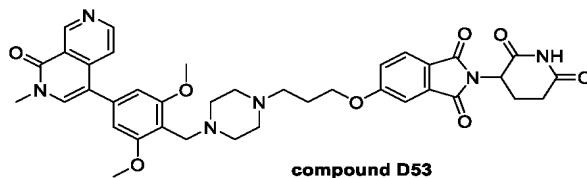
To a stirred solution of 4-[3,5-dimethoxy-4-(piperazin-1-ylmethyl)phenyl]-2-methyl-2,7-
25 naphthyridin-1-one (200.00 mg, 0.507 mmol, 1.00 equiv) and 3-bromopropanol (140.94 mg, 1.014 mmol, 2.00 equiv) in acetone was added Cs₂CO₃ (330.38 mg, 1.014 mmol, 2.00 equiv) in portions at room temperature. The 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]piperazin-1-yl)propyl methanesulfonate (i59-5)



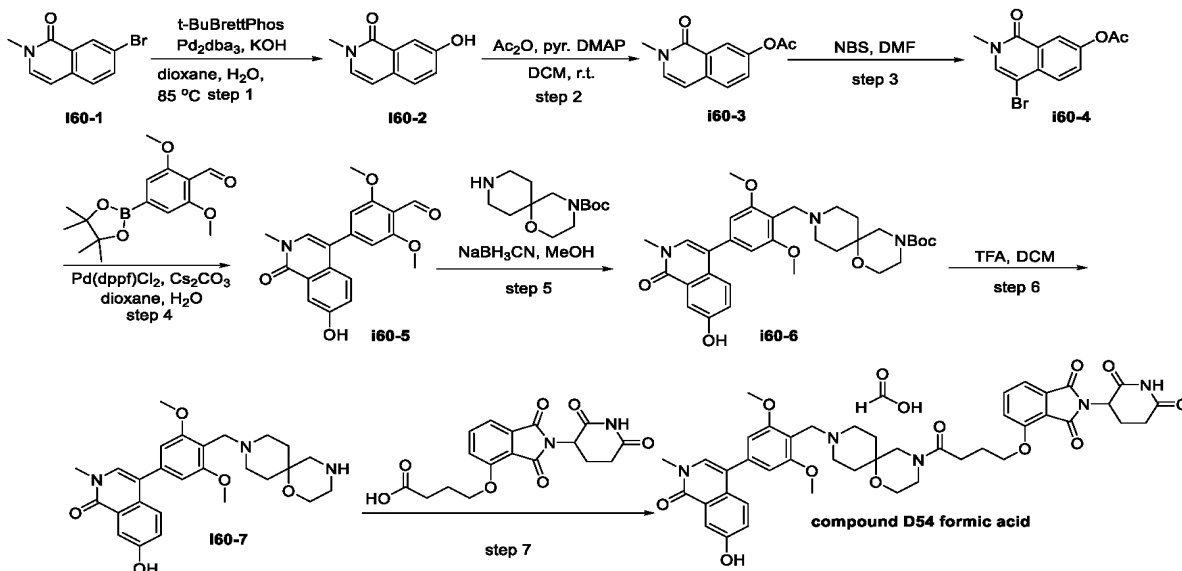
To a stirred solution of 4-(4-[[4-(3-hydroxypropyl) piperazin-1-yl] methyl]-3, 5-dimethoxyphenyl)-2-methyl-2, 7-naphthyridin-1-one (200.00 mg, 0.442 mmol, 1.00 equiv) and Cs_2CO_3 (287.98 mg, 0.884 mmol, 2.00 equiv) in acetone was added MsCl (101.25 mg, 0.884 mmol, 2.00 equiv) in portions at room temperature. The resulting mixture was stirred for overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 3-(4-[[2, 6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]piperazin-1-yl)propyl methanesulfonate (92 mg, 39.23%) as a light yellow oil. LCMS (ESI) m/z : $[\text{M}+\text{H}]^+ = 531$.

Step 5: 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)



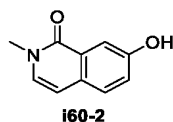
To a stirred solution of 3-(4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]piperazin-1-yl)propyl methanesulfonate (90.00 mg, 0.170 mmol, 1.00 equiv) and 2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindole-1,3-dione (47.00 mg, 0.171 mmol, 1.01 equiv) in DMF was added Na_2CO_3 (36.00 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-dioxopiperidin-3-yl)isoindole-1,3-dione (28.1 mg, 23.38%) as an off-white solid. ^1H NMR (300 MHz, $\text{Methanol-}d_4$) 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 : $[\text{M}+\text{H}]^+ = 709.35$.

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)



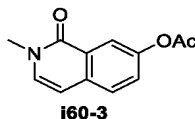
5

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



To a mixture of 7-bromo-2-methylisoquinolin-1-one (500 mg, 2.100 mmol, 1.00 equiv), $\text{Pd}_2(\text{dba})_3$ (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). The 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 : $[\text{M}+\text{H}]^+ = 176$.

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



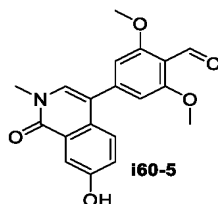
To a stirred solution/mixture of 7-hydroxy-2-methylisoquinolin-1-one (272 mg, 1.553 mmol, 1.00 equiv) and pyridine (614 mg, 7.763 mmol, 5.00 equiv) in DCM (6 mL) was added DMAP (10 mg, 0.082 mmol, 0.05 equiv) and Ac_2O (46.6 mg, 0.457 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred 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 Na₂SO₄. 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.

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

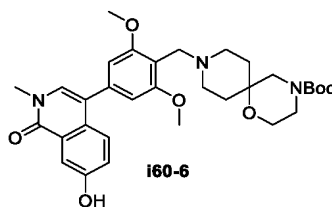
To a stirred solution/mixture of 2-methyl-1-oxoisoquinolin-7-yl acetate (325 mg, 1.496 mmol, 1.00 equiv) in ACN (10 mL) was added NBS (292.9 mg, 1.646 mmol, 1.10 equiv) at room temperature. The resulting mixture was stirred for 0.5 h at room temperature. The resulting mixture was diluted with DCM (30 mL) and washed with 10 mL of water and 10 mL of brine. The organic layer was dried over anhydrous Na₂SO₄. 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)



15 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)Cl₂.CH₂Cl₂ (59.8 mg, 0.073 mmol, 0.10 equiv), and Cs₂CO₃ (716.3 mg, 2.198 mmol, 3.00 equiv) was added dioxane (4 mL) and water (1 mL) at room temperature under N₂ atmosphere. The resulting mixture was stirred overnight at 80 °C. The resulting mixture was diluted with sat. NH₄Cl solution (10 mL) and extracted with DCM/i-PrOH (3/1) (5 x 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄. 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.

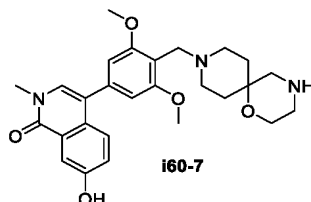
Step 5: Preparation of tert-butyl 9-[[4-(7-hydroxy-2-methyl-1-oxoisoquinolin-4-yl)-2,6-dimethoxyphenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (i60-6)



30 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 NaBH₃CN (125 mg, 1.989 mmol, 6.75 equiv) was added. The resulting mixture was stirred for 2 hours at room

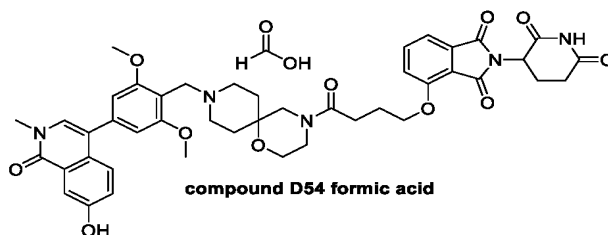
temperature. The reaction solution was purified by Prep-TLC (DCM/ MeOH 20:1) to afford *tert*-butyl 9-[[4-(7-hydroxy-2-methyl-1-oxoisoquinolin-4-yl)-2,6-dimethoxyphenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (134 mg, 78%) as a light brown foam. LCMS (ESI) *m/z*: [M+H]⁺ = 580.

5
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)



10 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.

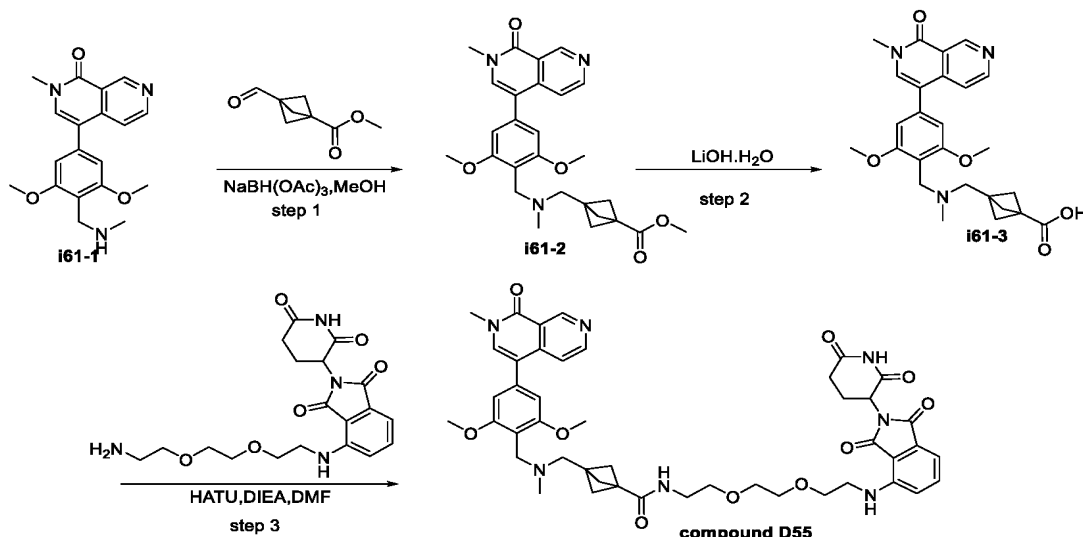
15
Step 7: Preparation of 2-(2,6-dioxopiperidin-3-yl)-4-[4-(9-[[4-(7-hydroxy-2-methyl-1-oxoisoquinolin-4-yl)-2,6-dimethoxyphenyl]methyl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-4-oxobutoxy]isoindole-1,3-dione formic acid (compound D54 formic acid)



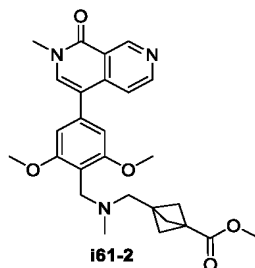
20 To a stirred solution of 4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]butanoic acid (33.8 mg, 0.094 mmol, 0.90 equiv) in DMF (1 mL) was added EDCI (40.0 mg, 0.209 mmol, 2.00 equiv) and HOBt (28.2 mg, 0.209 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred at room 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)
25 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. ¹H NMR (400 MHz, Methanol-*d*₄) 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](methylamino)methyl]-N-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino]ethoxy)ethoxy]ethyl]bicyclo[1.1.1]pentane-1-carboxamide (compound D55)

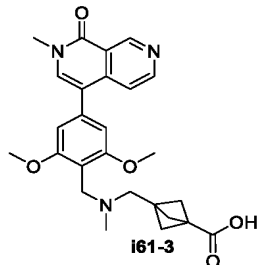


Step 1: Preparation of methyl 3-[[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methylamino)methyl]bicyclo[1.1.1]pentane-1-carboxylate (i61-2)



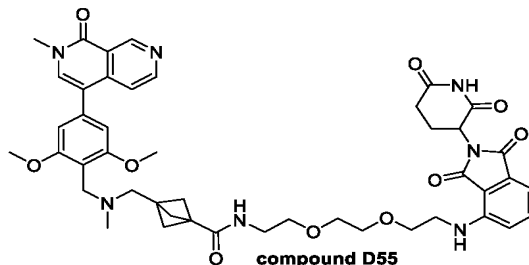
To a stirred solution of 4-[3,5-dimethoxy-4-((methylamino)methyl)phenyl]-2-methyl-2,7-naphthyridin-1-one (264.00 mg, 0.778 mmol, 1.20 equiv) and methyl 3-formylbicyclo[1.1.1]pentane-1-carboxylate (100.00 mg, 0.649 mmol, 1.00 equiv) in MeOH was added $\text{NaBH}(\text{OAc})_3$ (549.91 mg, 2.595 mmol, 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 methyl 3-[[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methylamino)-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)



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·H₂O (35.15 mg, 0.838 mmol, 2.00 equiv) in THF (6 mL) was added H₂O (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.

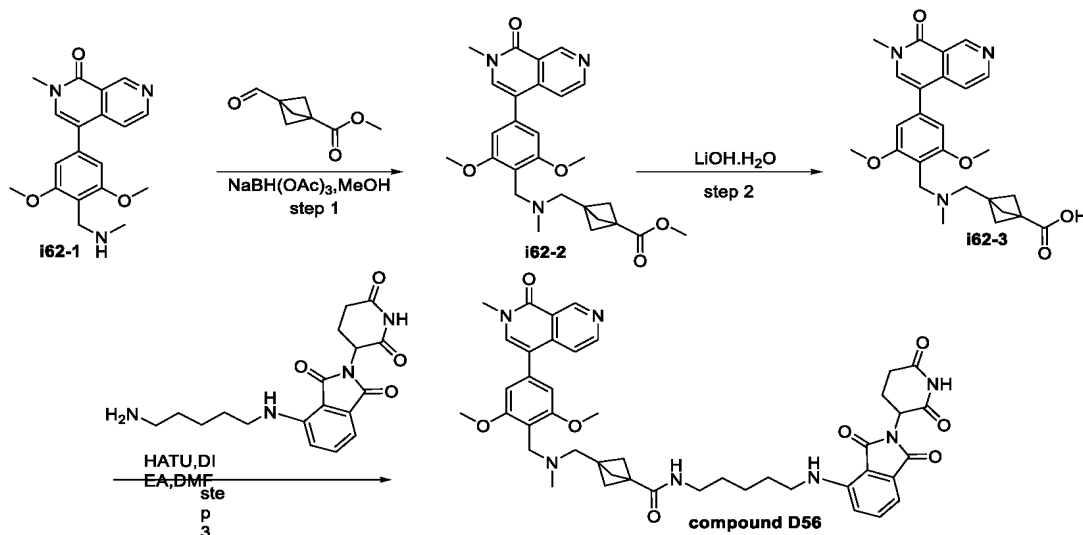
Step 3: Preparation of 3-([[(2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl)methyl](methyl)-amino)methyl]-N-[2-[2-(2-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino)ethoxy]ethoxy]ethyl]bicyclo[1.1.1]pentane-1-carboxamide (compound D55)



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% 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-2,7-naphthyridin-4-yl)phenyl)methyl](methyl)amino)methyl]-N-[2-[2-(2-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino)ethoxy]ethoxy]ethyl]bicyclo[1.1.1]pentane-1-carboxamide; formic acid (4.1 mg, 4.24%) as a yellow solid. ¹H NMR (300 MHz, Methanol-*d*₄) 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),

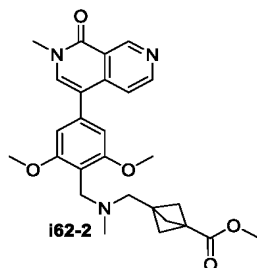
3.73 (s, 3H), 3.71 – 3.65 (m, 4H), 3.59 (t, $J = 5.4$ Hz, 2H), 3.52 (t, $J = 5.2$ Hz, 2H), 3.44 – 3.38 (m, 2H), 3.28 – 3.24 (m, 1H), 2.91 – 2.81 (m, 1H), 2.80 – 2.77 (m, 1H), 2.75 – 2.69 (m, 1H), 2.66 (s, 3H), 2.20 (s, 6H), 2.17 – 2.05 (m, 2H). LCMS (ESI) m/z : $[M+H]^+ = 850.45$.

5 **Example 62 – Preparation of 3-[[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methylamino)methyl]-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-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](methylamino)methyl]bicyclo[1.1.1]pentane-1-carboxylate (i62-2)

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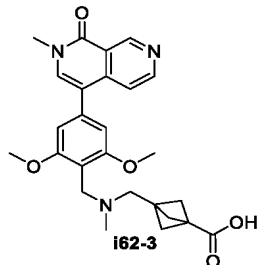


To a stirred solution of 4-[3,5-dimethoxy-4-[(methylamino)methyl]phenyl]-2-methyl-2,7-naphthyridin-1-one (264.18 mg, 0.778 mmol, 1.20 equiv) and methyl 3-formylbicyclo[1.1.1]pentane-1-carboxylate (100.00 mg, 0.649 mmol, 1.00 equiv) in MeOH was added $\text{NaBH}(\text{OAc})_3$ (549.91 mg, 2.595 mmol, 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 methyl 3-[[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methylamino)-methyl] bicyclo[1.1.1]pentane-1-carboxylate (220 mg, 71.02%) as a light yellow oil. LCMS (ESI) m/z : $[M+H]^+ = 478$.

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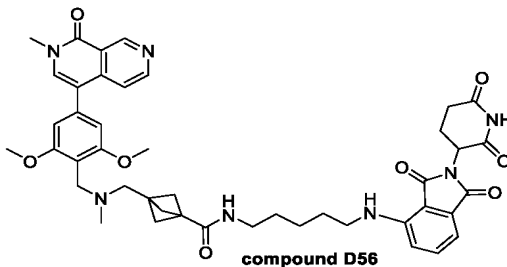
20

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)



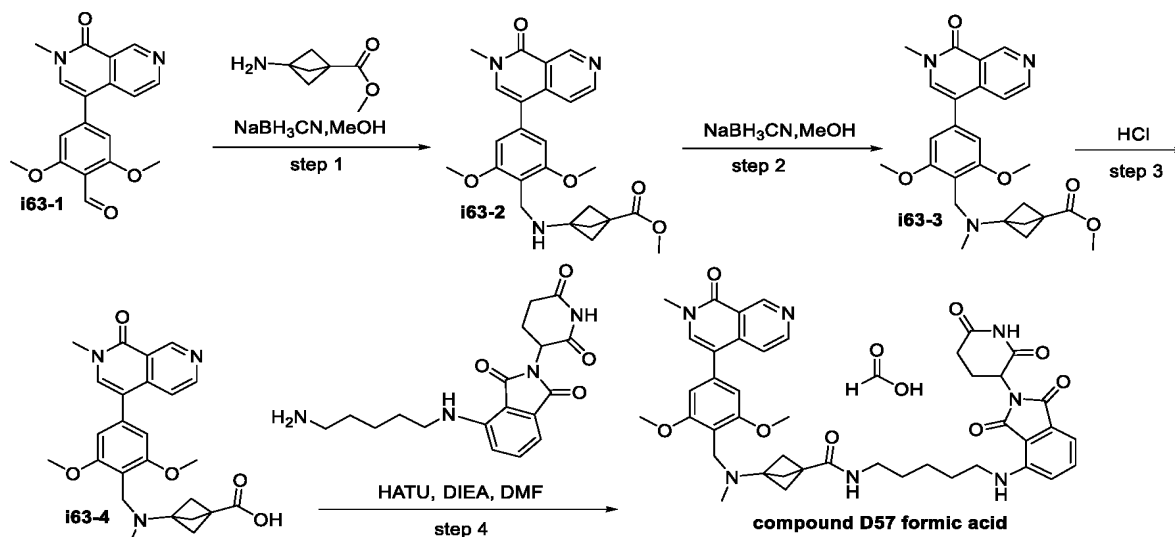
To a stirred solution of methyl 3-([[(2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)methyl)bicyclo[1.1.1]pentane-1-carboxylate (200.00 mg, 0.419 mmol, 1.00 equiv) and LiOH·H₂O (35.15 mg, 0.838 mmol, 2.00 equiv) in THF (6 mL) was added H₂O (2.00 mL) dropwise at room 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-dioxoisindol-4-yl]amino]pentyl)bicyclo[1.1.1]pentane-1-carboxamide (compound D56)



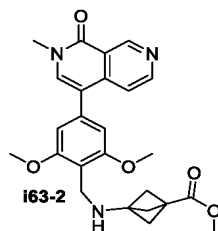
To a stirred solution of 3-([[(2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)methyl)bicyclo[1.1.1]pentane-1-carboxylic acid (50.00 mg, 0.108 mmol, 1.00 equiv) and 4-((5-aminopentyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (65.44 mg, 0.162 mmol, 1.50 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-dioxoisindolin-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-dioxoisindol-4-yl]amino]pentyl)bicyclo[1.1.1]pentane -1-carboxamide; formic acid (compound D57 formic acid)



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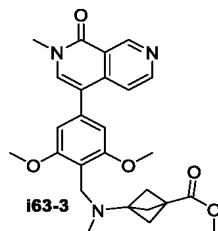
Step 1: Preparation of methyl-3-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)amino)bicyclo[1.1.1]pentane-1-carboxylate (i63-2)



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 Et₃N (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, NaBH₃CN (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.

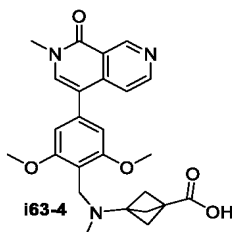
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Step 2: Preparation of methyl-3-([2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl) (methyl)amino)bicyclo[1.1.1]pentane-1-carboxylate (i63-3)



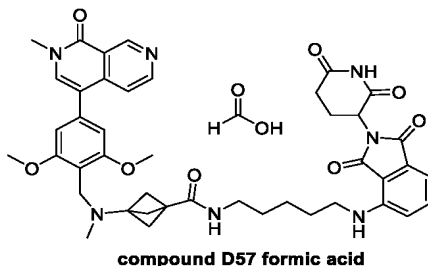
To a solution of crude methyl-3-([2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] amino)bicyclo[1.1.1]pentane-1-carboxylate obtained last step in MeOH (5.00 mL, 12.349 mmol) was added formaldehyde in water (226.0 µL). After 10 min stirring, NaBH₃CN (125.8 mg, 2.002 mmol, 2.00 equiv) was added in portions at ambient atmosphere. The resulting mixture was concentrated after stirring for 1 hour at room temperature. The mixture was purified by Prep-TLC (EtOAc) to afford methyl-3-([2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)bicyclo[1.1.1]pentane-1-carboxylate (120 mg, 24.8%) as a light yellow solid. LCMS (ESI) m/z: [M+H]⁺ = 464.

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



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

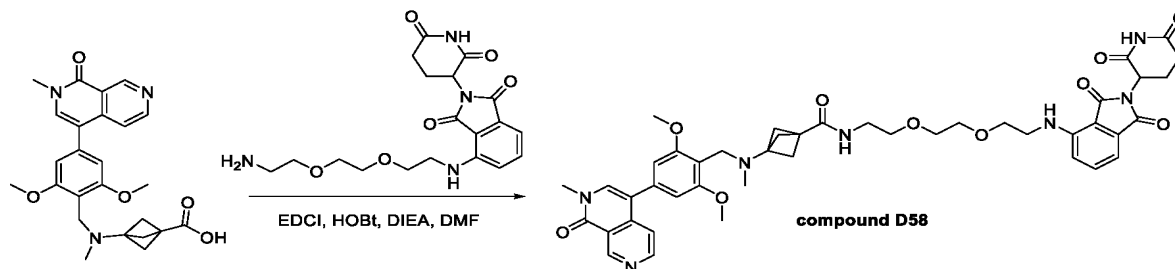
Step 4: Preparation of 3-([2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl] (methyl)amino)-N-(5-([2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino]pentyl)bicyclo[1.1.1]pentane-1-carboxamide formic acid (compound D57 formic acid)



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)isindole-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 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-dioxoisindol-4-yl]amino]pentyl)bicyclo[1.1.1]pentane-1-carboxamide formic acid (15.2 mg, 17.2%) as a

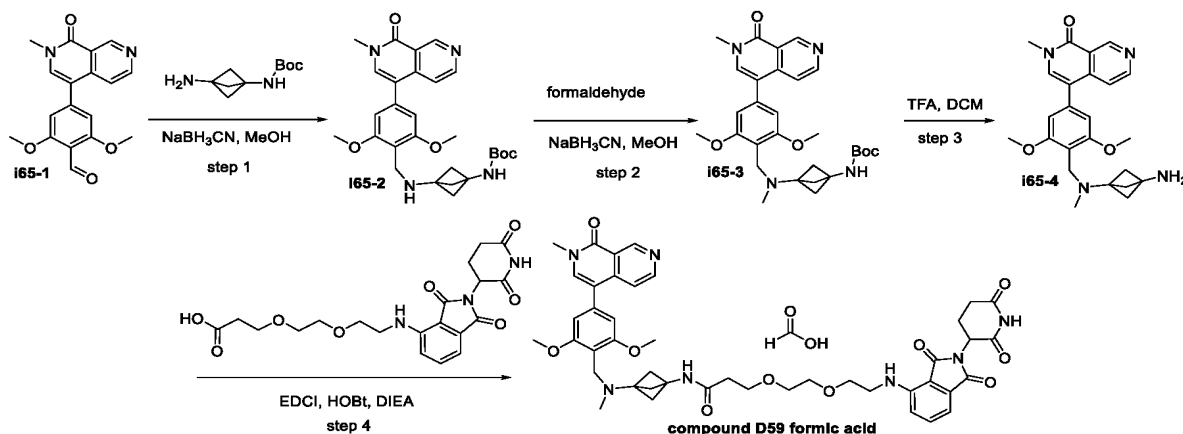
yellow solid. ¹H NMR (300 MHz, Methanol-*d*₄) δ 9.57 (s, 1H), 8.71 (d, *J* = 5.9 Hz, 1H), 8.18 (brs, 0.4H, FA), 7.86 (s, 1H), 7.72 (s, 1H), 7.58 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.07 (dd, *J* = 7.8, 5.2 Hz, 2H), 6.90 (s, 2H), 5.06 (dd, *J* = 12.0, 5.4 Hz, 1H), 4.51 (s, 2H), 3.99 (s, 6H), 3.73 (s, 3H), 3.41 – 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)(methylamino)-N-[2-[2-(2-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino)ethoxy]ethoxy]ethyl]bicyclo[1.1.1]pentane-1-carboxamide (compound D58)



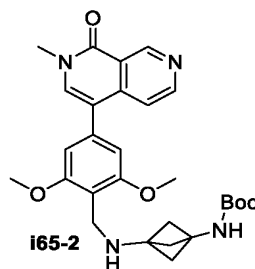
To a stirred mixture of 3-([2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl)(methylamino)bicyclo[1.1.1]pentane-1-carboxylic acid (50.0 mg, 0.111 mmol, 1.00 equiv) in DMF (2.00 mL) was added EDCI (42.7 mg, 0.222 mmol, 2.00 equiv) and 4-([2-[2-(2-aminoethoxy)ethoxy]ethyl]amino)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (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)(methylamino)-N-[2-[2-(2-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino)ethoxy]ethoxy]ethyl]bicyclo[1.1.1]pentane-1-carboxamide (10.5 mg, 10.6%) as a yellow solid. ¹H NMR (300 MHz, Methanol-*d*₄) 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-dioxoisindol-4-yl]amino)ethoxy]ethoxy]propanamide formic acid (compound D59 formic acid)



5

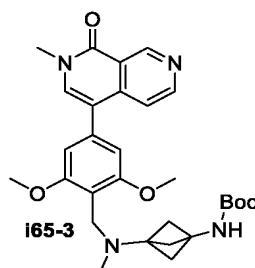
Step 1: Preparation of tert-butyl (3-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)amino)bicyclo[1.1.1]pentan-1-yl)carbamate (i65-2)



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 NaBH₃CN (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.

15

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)

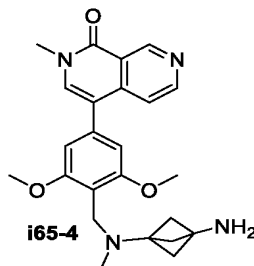


To a stirred solution of the product from step 1 was added NaBH₃CN (49.62 mg, 0.790 mmol, 2.00 equiv) and formaldehyde (59.27 mg, 1.974 mmol, 5.00 equiv) in portions at room temperature. The resulting mixture was stirred for 2 hours at room temperature. Desired product could be detected by

LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂ / 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.

5

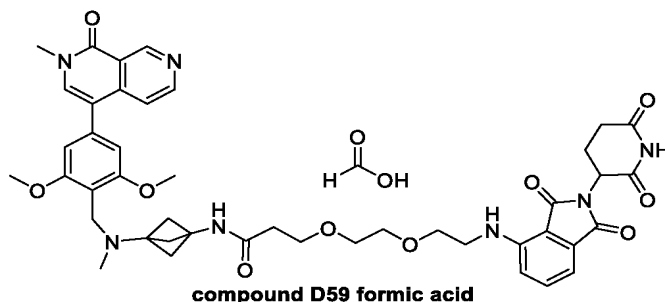
Step 3: Preparation of 4-(4-(((3-aminobicyclo[1.1.1]pentan-1-yl)(methyl)amino)methyl)-3,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (i65-4)



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(2H)-one (210 mg crude), which was used in the next step directly without further purification. LCMS (ESI) *m/z*: [M+H]⁺ = 421.

15

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-dioxoisindol-4-yl]amino)ethoxy]ethoxy]propanamide formic acid (compound D59 formic acid).



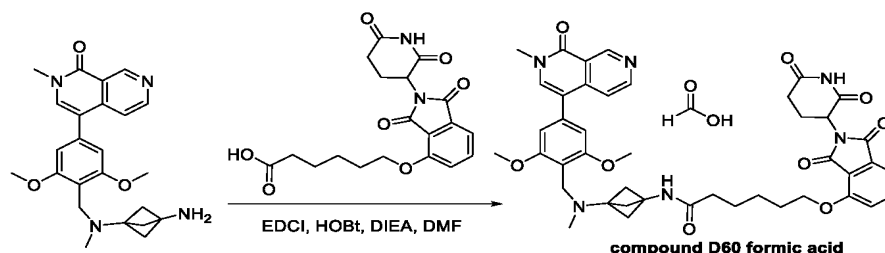
20

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-dioxoisindol-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

25

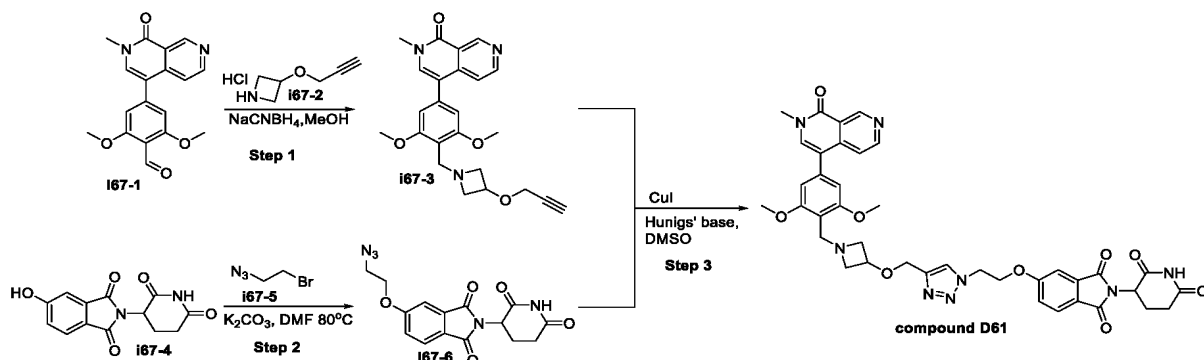
in 17 minutes; 254/220 nm; R_T :15.32 minutes) to afford *N*-[3-([2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl)(methyl)amino)bicyclo[1.1.1]pentan-1-yl]-3-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino]ethoxy)ethoxy]propanamide formic acid (23.7 mg, 14.13%) as a yellow solid. ^1H NMR (300 MHz, Methanol- d_4) 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 : $[\text{M}+\text{H}]^+ = 836.65$.

Example 66 – 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]-6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]hexanamide formic acid (compound D60 formic acid)



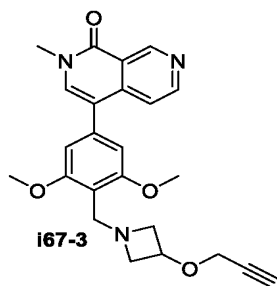
To a stirred solution of 4-[4-([3-aminobicyclo[1.1.1]pentan-1-yl](methyl)amino)methyl]-3,5-dimethoxyphenyl]-2-methyl-2,7-naphthyridin-1-one (80.00 mg, 0.190 mmol, 1.00 equiv) and EDCI (72.94 mg, 0.380 mmol, 2.00 equiv) in DMF (1 mL) was added HOBT (51.41 mg, 0.380 mmol, 2.00 equiv) at room temperature. 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)bicyclo[1.1.1]pentan-1-yl]-6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]hexanamide formic acid (14.9 mg, 9.36%) as a white solid. ^1H NMR (300 MHz, Methanol- d_4) 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 : $[\text{M}+\text{H}]^+ = 791.40$.

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)



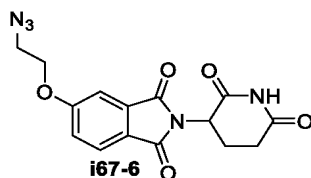
5

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)



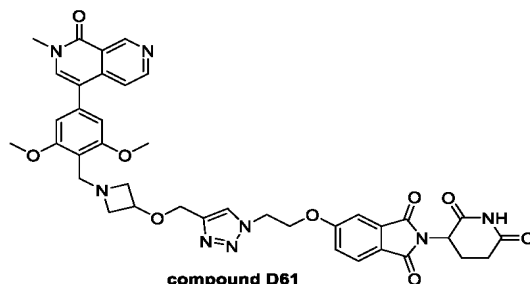
To a stirred solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (500 mg, 1.54 mmol, 1.00 equiv) in MeOH (15 mL) was added NaBH₃CN (290 mg, 4.62 mmol, 3.00 equiv) and 3-(prop-2-yn-1-yloxy)azetidine hydrochloride (269 mg, 1.84 mmol, 1.20 equiv). The resulting mixture 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)



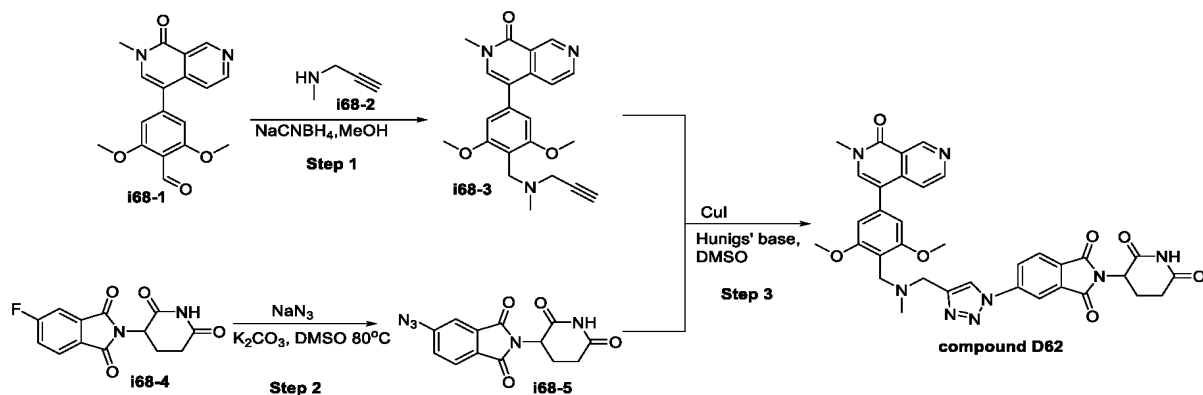
2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindoline-1,3-dione (500 mg, 1.82 mmol, 1.0 equiv) was dissolved in DMF (15 mL). Potassium carbonate was then added (753 mg, 5.45 mmol, 3 equiv) followed by potassium iodide (451 mg, 2.72 mmol, 1.5 equiv) and 1-azido-2-bromoethane (286 mg, 1.91 mmol, 1.05 equiv). 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)

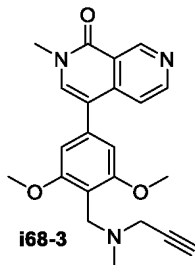


5-(2-azidoethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (20 mg, 0.0595 mmol, 1.0 equiv) and 4-(3,5-dimethoxy-4-((3-(prop-2-yn-1-yloxy)azetidin-1-yl)methyl)phenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (25 mg, 0.0595 mmol, 1.0 equiv) were dissolved in DMSO (1 mL). Hünig's base (0.020 mL, 0.119 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. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.08 (s, 1H), 9.42 (s, 1H), 8.70 (s, 1H), 8.18 (s, 1H), 7.85 (s, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.52 (d, *J* = 5.8 Hz, 1H), 7.46 (d, *J* = 2.3 Hz, 1H), 7.31 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.69 (s, 2H), 5.09 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.79 (t, *J* = 4.9 Hz, 2H), 4.60 (t, *J* = 5.0 Hz, 2H), 4.39 (s, 2H), 4.00 (t, *J* = 6.1 Hz, 1H), 3.83 – 3.76 (m, 1H), 3.76 (s, 6H), 3.57 (d, *J* = 4.2 Hz, 5H), 2.93 – 2.84 (m, 1H), 2.83 (s, 3H), 2.68 – 2.63 (m, 2H), 2.59 (s, 1H), 2.54 (s, 1H), 2.08 – 1.95 (m, 2H). LCMS (ESI) *m/z*: [M+H]⁺ = 761.4.

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

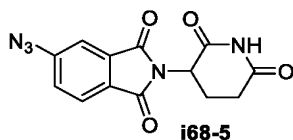


Step 1: Preparation of 4-(3,5-dimethoxy-4-((methyl(prop-2-yn-1-yl)amino)methyl)phenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (i68-3)



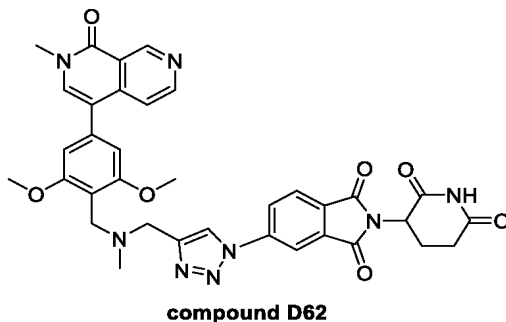
To a stirred solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (500 mg, 1.54 mmol, 1.00 equiv) in MeOH (15 mL) was added NaBH₃CN (290 mg, 4.62 mmol, 3.00 equiv) and *N*-methylprop-2-yn-1-amine (127 mg, 1.84 mmol, 1.20 equiv). The resulting mixture was stirred 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(2H)-one (390 mg, 67 %) as a solid. LCMS (ESI) *m/z*: [M+H]⁺ = 378.7.

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



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

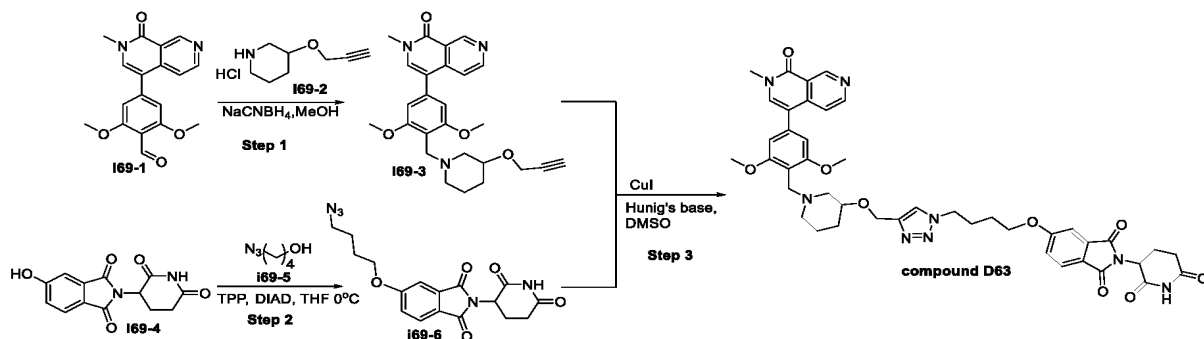
Step 3: 5-(4-(((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)(methyl)amino)methyl)-1H-1,2,3-triazol-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound D62)



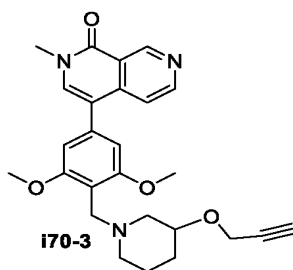
5-(2-azidoethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (19.8 mg, 0.0662 mmol, 1.0 equiv) and 4-(3,5-dimethoxy-4-((3-(prop-2-yn-1-yloxy)azetidin-1-yl)methyl)phenyl)-2-methyl-2,7-

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. ¹H 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-(((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)

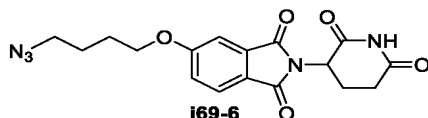


Step 1: Preparation of 4-(3,5-dimethoxy-4-((3-(prop-2-yn-1-yloxy)piperidin-1-yl)methyl)phenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (i69-3)



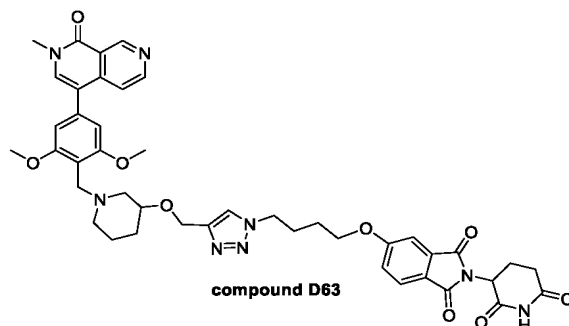
To a stirred solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (500 mg, 1.54 mmol, 1.00 equiv) in MeOH (15 mL) was added NaBH₃CN (290 mg, 4.62 mmol, 3.00 equiv) and 3-(prop-2-yn-1-yloxy)piperidine hydrochloride (321 mg, 1.84 mmol, 1.20 equiv). The resulting mixture was stirred for 2 hours at room temperature. Solvent was removed and the residue was purified by Flash column chromatography with EtOAc/PE (0-100%) to afford 4-(3,5-dimethoxy-4-((3-(prop-2-yn-1-yloxy)piperidin-1-yl)methyl)phenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (323 mg, 47 %) as a solid. LCMS (ESI) *m/z*: [M+H]⁺ = 448.5.

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



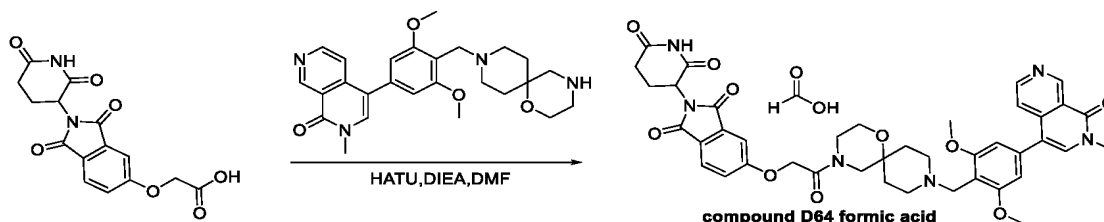
2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindoline-1,3-dione (500 mg, 1.82 mmol, 1.0 equiv) was dissolved in THF (18 mL). Triphenylphosphine was then added (571 mg, 2.18 mmol, 1.2 equiv) followed by 4-azidobutan-1-ol (246 mg, 2.91 mmol, 1.05 equiv). The solution was cooled to 0 °C and 1-diisopropyl azodicarboxylate (358 mL, 1.82 mmol, 1.0 equiv) was added. The mixture was then warmed to room temperature and stirred for 2 hours. Water was added and the reaction extracted 3 times with ethyl acetate. The organics were dried over MgSO₄, filtered, and evaporated. The resulting oil was columned over silica gel with EtOAc/PE (0-100%), to afford 5-(4-azidobutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (391 mg, 56%) as a solid. LCMS (ESI) m/z: [M+H]⁺ = 372.4.

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



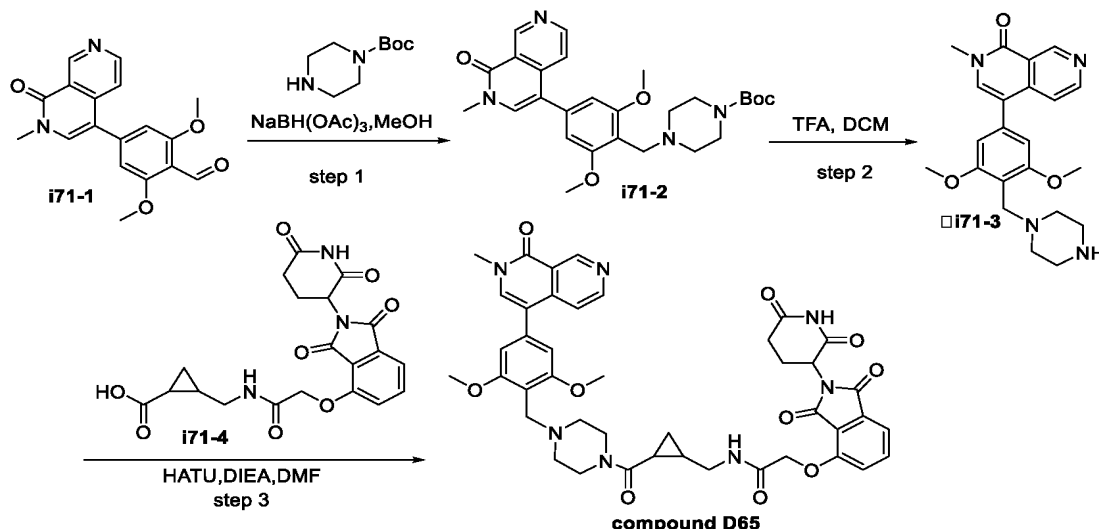
5-(4-azidobutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (21.5 mg, 0.0558 mmol, 1.0 equiv) and 4-(3,5-dimethoxy-4-((3-(prop-2-yn-1-yloxy)azetidin-1-yl)methyl)phenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (25 mg, 0.0558 mmol, 1.0 equiv) were dissolved in DMSO (1 mL). Hünig's base (0.0192 mL, 0.111 mmol, 2 equiv) was then added followed by CuI (5.31 mg, 0.0279 mmol, 0.5 equiv). The mixture was stirred for 1 hour at room temperature. The solution was submitted directly for HPLC purification to give 5-(4-(4-(((1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)piperidin-3-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)butoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (6.2 mg, 12%) as a solid. ¹H 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-oxa-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)

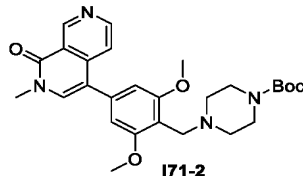


To a stirred solution of [[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]oxy]acetic acid (21.46 mg, 0.065 mmol, 1.00 equiv) and 4-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-2-methyl-2,7-naphthyridin-1-one (30.00 mg, 0.065 mmol, 1.00 equiv) in DMF (1 mL) was added HATU (49.11 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%). ¹H NMR (400 MHz, Methanol-*d*₄) 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-dioxoisindol-4-yl]oxy]acetamide (compound D65)

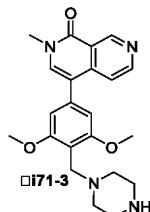


Step 1: Preparation of *tert*-butyl 4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl] methyl] piperazine-1-carboxylate (i71-2)



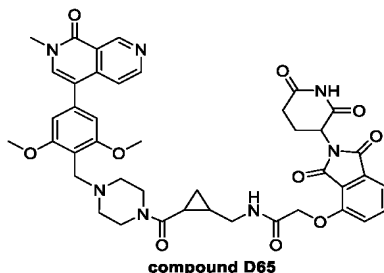
To a stirred solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (100.00 mg, 0.308 mmol, 1.00 equiv) and *tert*-butyl piperazine-1-carboxylate (86.14 mg, 0.462 mmol, 1.50 equiv) in MeOH (1 mL) was added NaBH(OAc)₃ (261.38 mg, 1.233 mmol, 4.00 equiv) at room temperature. The 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)



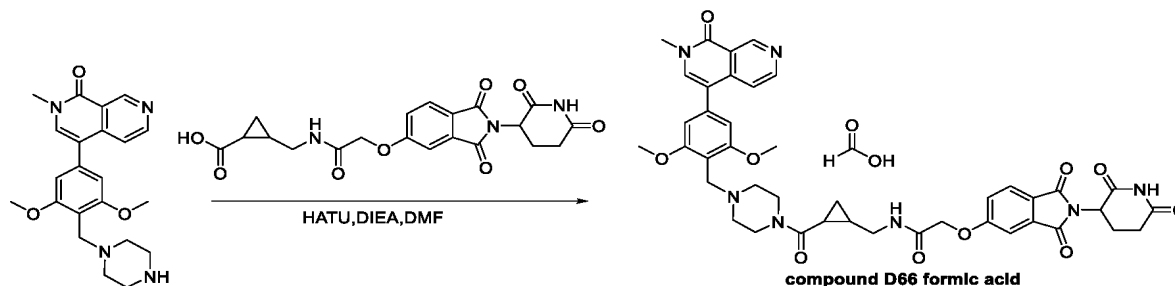
A solution of *tert*-butyl 4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]piperazine-1-carboxylate (115.00 mg) and TFA (1.00 mL) in DCM (1.00 mL) was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure to afford 4-[3,5-dimethoxy-4-(piperazin-1-ylmethyl)phenyl]-2-methyl-2,7-naphthyridin-1-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-dioxoisindol-4-yl]oxy]acetamide (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-dioxoisindol-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 μ m; 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]methyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]acetamide (12.4 mg, 33.04%) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) 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.

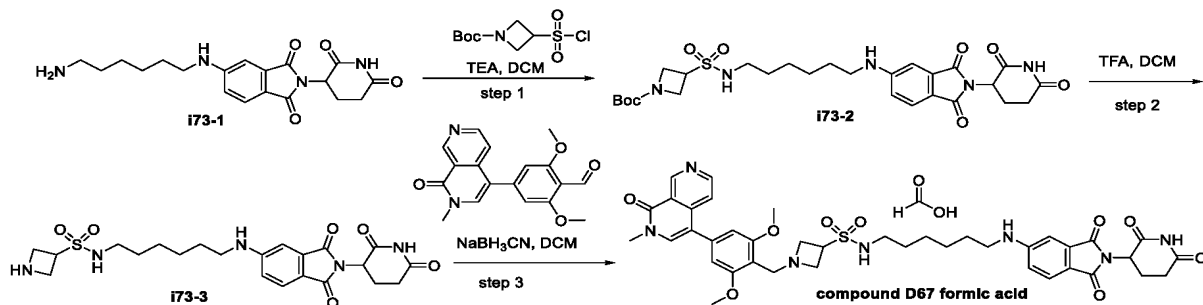
Example 72 – Preparation of *N*-[[2-(4-[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]piperazine-1-carbonyl)cyclopropyl]methyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]oxy]acetamide formic acid (compound D66 formic acid)



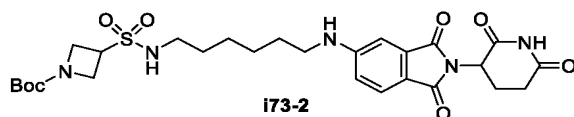
To a stirred mixture of 4-[3,5-dimethoxy-4-(piperazin-1-ylmethyl)phenyl]-2-methyl-2,7-naphthyridin-1-one (22.05 mg, 0.056 mmol, 1.20 equiv) and 2-[(2-[(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]oxy)acetamido)methyl]cyclopropane-1-carboxylic acid (20.00 mg, 0.047 mmol, 1.00 equiv) in DMF (1 mL) 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, 19*250 mm, 10 μ m; 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-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-dioxoisindol-5-yl]oxy]acetamide (7.4 mg, 19.18%) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) 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)

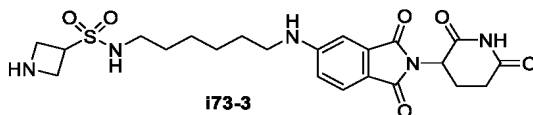


Step 1: Preparation of tert-butyl 3-[(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]hexyl)sulfamoyl]azetidine-1-carboxylate (i73-2)



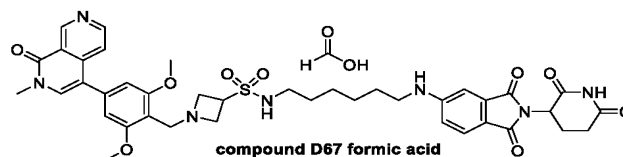
To a stirred mixture of 5-[(6-aminohexyl)amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (60.00 mg, 0.161 mmol, 1.00 equiv) and *tert*-butyl 3-(chlorosulfonyl)azetidine-1-carboxylate (102.99 mg, 0.403 mmol, 2.50 equiv) in DCM (2.00 mL) was added TEA (48.91 mg, 0.483 mmol, 3.00 equiv). After stirring for 1.5 hours at room temperature, the resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC ($\text{CH}_2\text{Cl}_2/\text{EA} = 1:2$) 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)



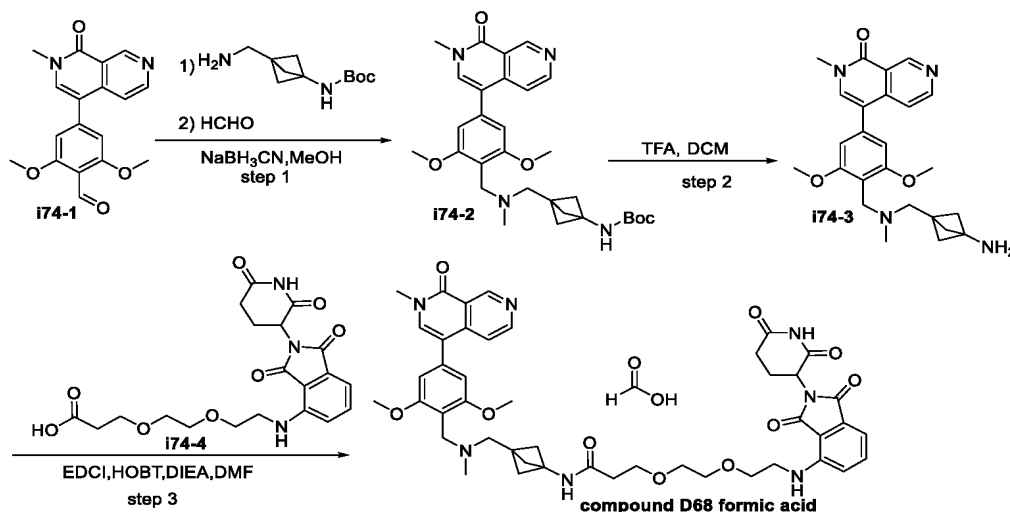
To a stirred mixture of *tert*-butyl 3-[(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]hexyl)sulfamoyl]azetidine-1-carboxylate (61.8 mg, 0.104 mmol, 1.00 equiv) in DCM (2.00 mL) was added TFA (0.40 mL, 5.385 mmol, 51.56 equiv). After stirring for 1 hour at room temperature, the resulting 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)

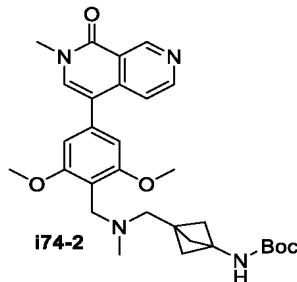


5 A mixture of *N*-(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]amino]hexyl)azetidine-3-sulfonamide (51.36 mg, 0.104 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (33.89 mg, 0.104 mmol, 1.00 equiv) in DMF (2 mL) was stirred at room temperature. The reaction mixture was then adjusted to pH 8-9 with TEA. To the above mixture was added NaBH₃CN (19.70 mg, 0.313 mmol, 3.00 equiv) in portions, and the resulting mixture
10 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-*d*₆) 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, 20 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-dioxoisindol-4-yl]amino]ethoxy)ethoxy]propanamide formic acid (compound D68 formic acid)

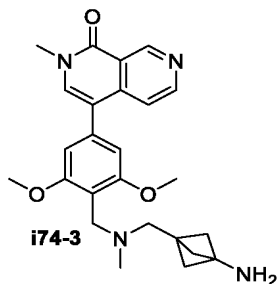


Step 1: Preparation of *tert*-butyl *N*-[3-[[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]amino)methyl]bicyclo[1.1.1]pentan-1-yl]carbamate (*i*74-2)



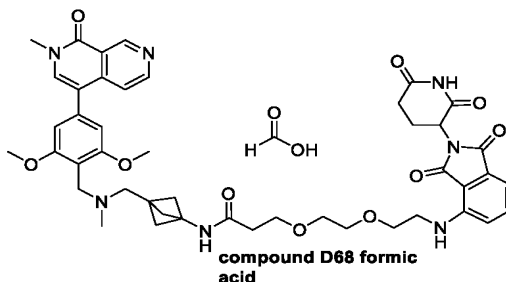
To a stirred mixture of 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (200.00 mg, 0.617 mmol, 1.00 equiv) and *tert*-butyl *N*-[3-(aminomethyl)bicyclo[1.1.1]pentan-1-yl]carbamate (144.00 mg, 0.678 mmol, 1.10 equiv) in MeOH (1 mL) was added NaBH₃CN (77.50 mg, 1.233 mmol, 2.00 equiv) 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 were 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 (*i*74-3)



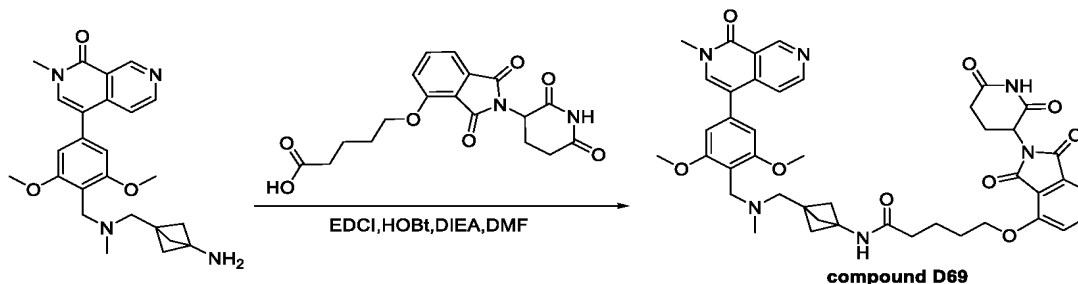
A mixture of *tert*-butyl *N*-[3-[[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methyl)amino)methyl]bicyclo[1.1.1]pentan-1-yl]carbamate (284.80 mg) and TFA (1.00 mL) in DCM (1 mL) was stirred for overnight at room temperature. The reaction mixture was concentrated under vacuum to afford 4-(4-[[[3-aminobicyclo[1.1.1]pentan-1-yl]methyl](methyl)amino]methyl)-3,5-dimethoxyphenyl)-2-methyl-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](methylamino)methyl]bicyclo[1.1.1]pentan-1-yl]-3-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino]ethoxy)ethoxy]propanamide formic acid (compound D68 formic acid)



5 To a stirred solution of 4-(4-[[[3-aminobicyclo[1.1.1]pentan-1-yl]methyl](methylamino)methyl]-3,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1-one (20.05 mg, 0.046 mmol, 1 equiv) and 3-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-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 μ m; 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](methylamino)methyl]bicyclo[1.1.1]pentan-1-yl]-3-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino]ethoxy)ethoxy]propanamide (3.4 mg, 8.67%) as a yellow solid. ¹H NMR (300 MHz, DMSO-*d*₆) 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.

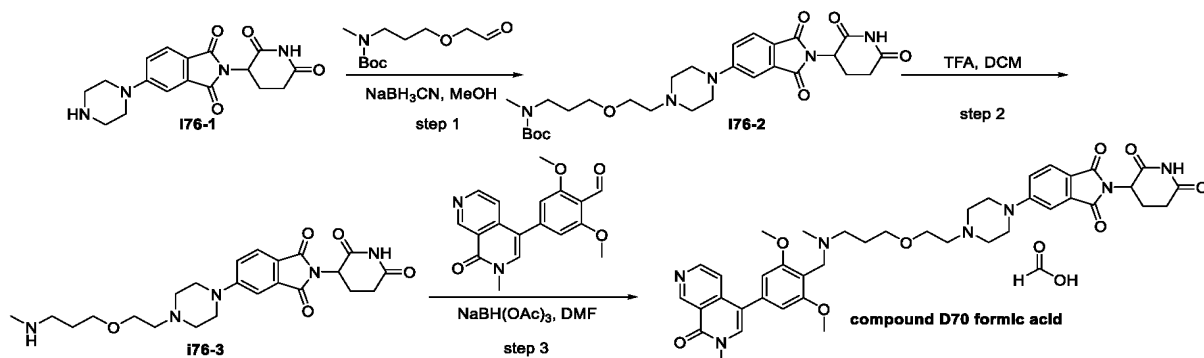
Example 75 – Preparation of *N*-[3-[[[2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl](methylamino)methyl]bicyclo[1.1.1]pentan-1-yl]-5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]pentanamide (compound D69)



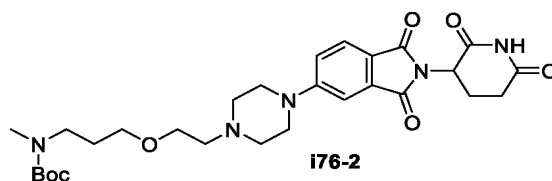
25 To a stirred solution of 4-(4-[[[3-aminobicyclo[1.1.1]pentan-1-yl]methyl](methylamino)methyl]-3,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1-one (23.22 mg, 0.053 mmol, 1.00 equiv) and 5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]pentanoic acid (20.00 mg, 0.053 mmol, 1.00 equiv) in DMF (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)methyl]bicyclo[1.1.1]pentan-1-yl]-5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]pentanamide (6.9 mg, 17.75%) as a white solid. ¹H 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)

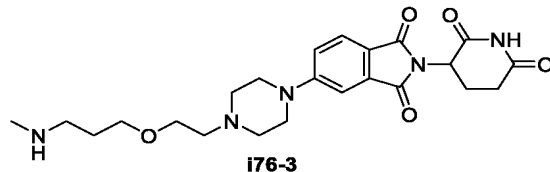


Step 1: Preparation of tert-butyl N-[3-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]piperazin-1-yl]ethoxy)propyl]-N-methylcarbamate (I76-2)



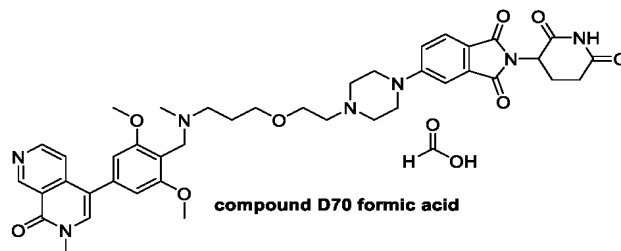
To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)isoindole-1,3-dione (250.00 mg, 0.730 mmol, 1.00 equiv) and *tert*-butyl *N*-methyl-*N*-[3-(2-oxoethoxy)propyl]carbamate (168.90 mg, 0.730 mmol, 1 equiv) in MeOH (3.00 mL) was added NaBH₃CN (91.78 mg, 1.460 mmol, 2 equiv). The mixture 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-dioxoisindol-5-yl]piperazin-1-yl]ethoxy)propyl]-*N*-methylcarbamate (400 mg, crude) as a dark grey solid. LCMS (ESI) *m/z*: [M+H]⁺ = 558.

Step 2: Preparation of 2-(2,6-dioxopiperidin-3-yl)-5-(4-[2-[3-(methylamino)propoxy]ethyl]piperazin-1-yl)isoindole-1,3-dione (I76-3)



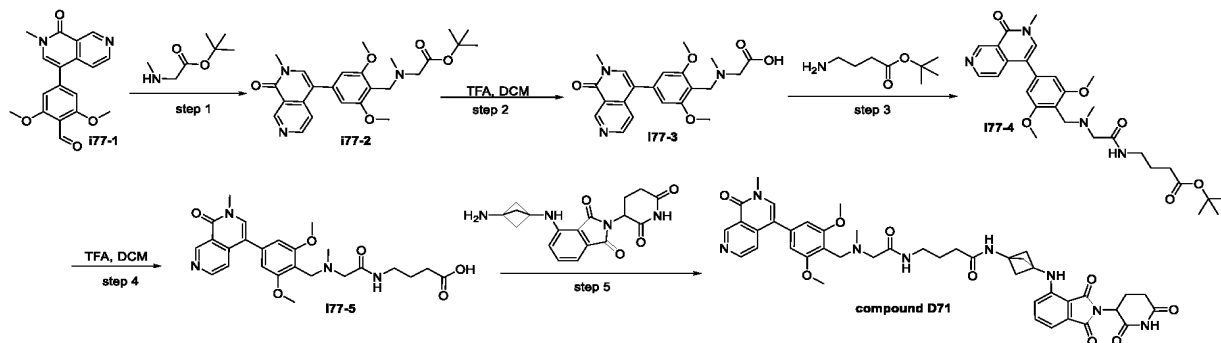
To a stirred solution of *tert*-butyl *N*-[3-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]piperazin-1-yl]ethoxy)propyl]-*N*-methylcarbamate (200.00 mg, 0.359 mmol, 1.00 equiv) in DCM (4.00 mL, 62.920 mmol) was added TFA (1.00 mg, 0.009 mmol). The mixture was stirred at room temperature for 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](methylamino)propoxy]ethyl]piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (compound D70 formic acid)

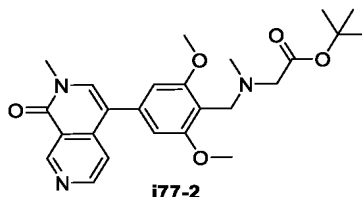


To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-(4-[2-[3-(methylamino)propoxy]ethyl]piperazin-1-yl)isoindole-1,3-dione (100.00 mg, 0.219 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (70.89 mg, 0.219 mmol, 1 equiv) in DMF (1.50 mL) was added NaBH(OAc)₃ (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](methylamino)propoxy]ethyl]piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione; formic acid (10 mg, 5.38%) as a yellow solid. ¹H NMR (300 MHz, Methanol-*d*₄) 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](methyl amino)acetamido]-N-(3-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino]bicycle[1.1.1] pentan-1-yl)butanamide (compound D71)

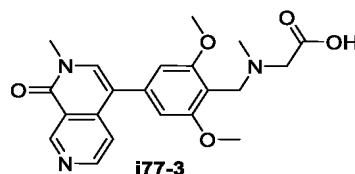


- 5 **Step 1: Preparation of *tert*-butyl N-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-N-methylglycinate (i77-2)**



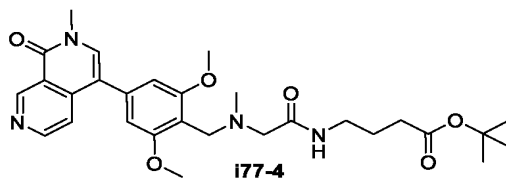
To a stirred solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (250.00 mg, 0.771 mmol, 1.00 equiv) and *tert*-butyl 2-(methylamino)acetate (111.92 mg, 0.771 mmol, 1.00 equiv) in MeOH (10.00 mL) was added NaBH₃CN (96.88 mg, 1.542 mmol, 2.00 equiv) in portions at 50 °C under 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.

- 20 **Step 2: Preparation of N-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)-N-methylglycine (i77-3)**



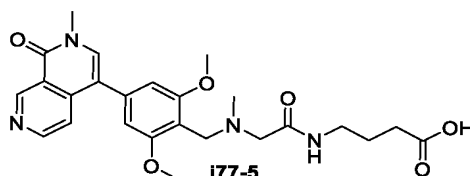
A solution of *tert*-butyl 2-([2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl)(methyl amino) acetate (101.00 mg, 0.223 mmol, 1.00 equiv) and TFA (7.21 mL, 63.270 mmol, 436.14 equiv) in DCM (29.00 mL) was stirred for 15 hours at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The residue (108 mg, crude) was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]⁺ = 398.

Step 3: Preparation of *tert*-butyl 4-(2-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)(methyl)amino)acetamido)butanoate (i77-4)



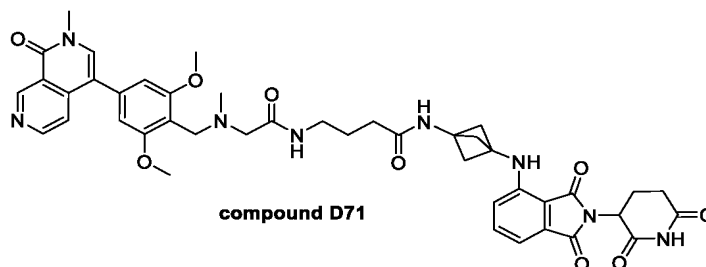
A solution of ([2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl)(methyl)amino)acetic acid (108 mg (crude), 0.272 mmol, 1.00 equiv), DIEA (105.36 mg, 0.815 mmol, 3.00 equiv), and HATU (206.53 mg, 0.543 mmol, 2.00 equiv) in DMF (2.00 mL) was stirred for 30 minutes at room temperature under nitrogen atmosphere. To the above mixture was added *tert*-butyl 4-aminobutanoate (43.27 mg, 0.272 mmol, 1.00 equiv) at room temperature. The resulting mixture was stirred for additional 12 hours at room temperature. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; mobile phase, MeOH in water, 10% to 50% gradient in 10 minutes; detector, UV 254 nm). This resulted in *tert*-butyl 4-(2-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)(methyl)amino)acetamido)butanoate (75 mg, 62.33%) as a yellow oil. LCMS (ESI) *m/z*: [M+H]⁺ = 539.

Step 4: Preparation of 4-(2-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)(methyl)amino)acetamido)butanoic acid (i77-5)



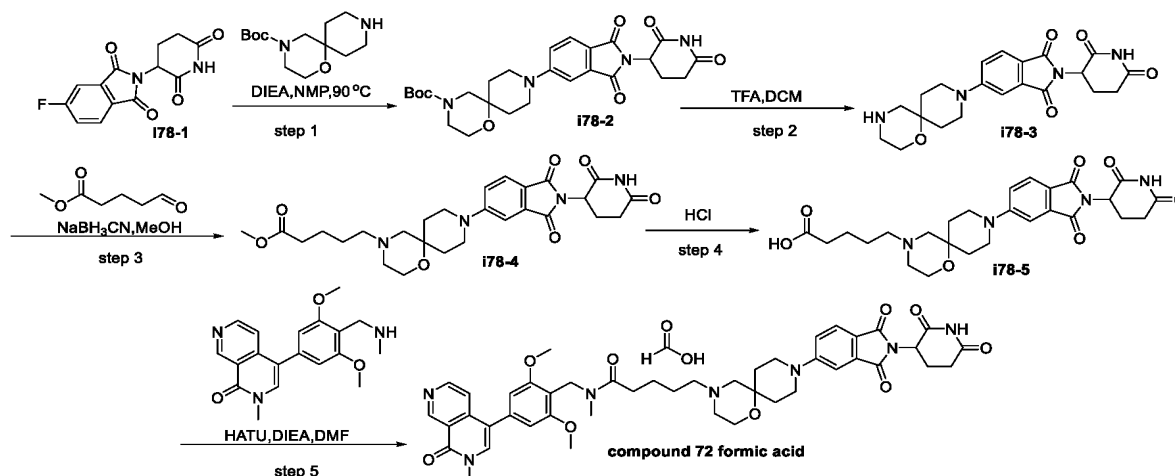
A solution of *tert*-butyl 4-[2-([2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl)(methyl)amino)acetamido]butanoate (75.00 mg, 0.139 mmol, 1.00 equiv) and TFA (1 mL) in DCM (4.00 mL) was stirred for 2 hours at room temperature under nitrogen atmosphere. The resulting mixture was concentrated 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-dioxoisindolin-4-yl)amino)bicyclo[1.1.1]pentan-1-yl)butanamide (compound D71)

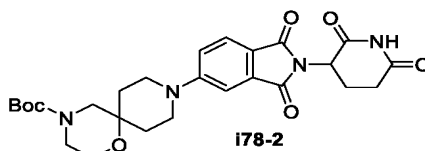


To a stirred solution of 4-[2-([2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl)(methyl)amino]acetamido]butanoic acid (73.00 mg(crude), 0.151 mmol, 1.00 equiv), DIEA (58.66 mg, 0.454 mmol, 3.00 equiv), and EDCI (58.00 mg, 0.303 mmol, 2.00 equiv) in DMF (2.00 mL) was added HOBT (40.88 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 μ m; 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-dioxoisindol-4-yl]amino)bicyclo[1.1.1]pentan-1-yl]butane mide (10 mg, 8.07%) as a light yellow solid. ¹H NMR (400 MHz, Methanol-*d*₄) 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-dioxoisindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]-N-methyl pentanamide formic acid (compound D72 formic acid)

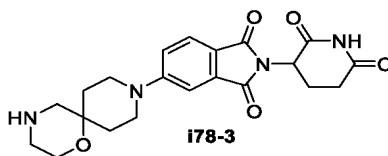


Step 1: Preparation of 2-(2,6-dioxopiperidin-3-yl)-5-[1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]isoindole-1,3-dione (178-2)



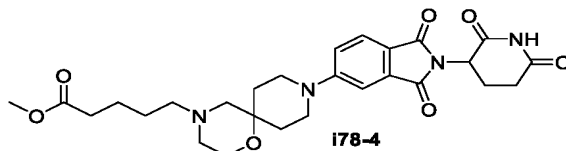
To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisindole-1,3-dione (1.50 g, 5.430 mmol, 1.00 equiv) and *tert*-butyl 1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (1.67 g, 6.516 mmol, 1.20 equiv) in NMP (10.00 mL) was added DIEA (1.40 g, 10.861 mmol, 2.00 equiv) dropwise at room temperature. 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-dioxoisindol-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.

- 10 *Step 2: Preparation of 2-(2,6-dioxopiperidin-3-yl)-5-[1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]isindole-1,3-dione (i78-3)*



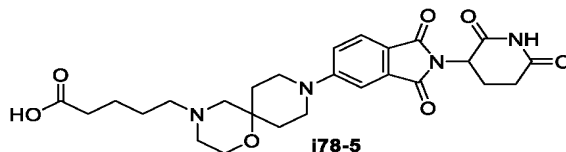
- 15 To a stirred solution of *tert*-butyl 9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (430.00 mg, 0.839 mmol, 1.00 equiv) in DCM (3.50 mL) was added TFA (1.00 mL). The mixture was stirred at room temperature for 1 hour. The resulting mixture was concentrated under reduced pressure to afford 2-(2,6-dioxopiperidin-3-yl)-5-[1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]isindole-1,3-dione (670 mg, crude) as a yellow solid. LCMS (ESI) *m/z*: [M+H]⁺ = 413

- 20 *Step 3: Preparation of methyl 5-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]pentanoate (i78-4)*



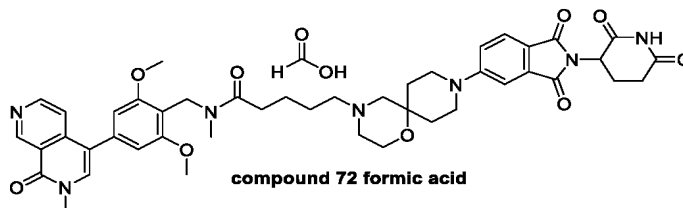
- 25 To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-[1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]isindole-1,3-dione (200.00 mg, 0.485 mmol, 1.00 equiv) and methyl 5-oxopentanoate (75.73 mg, 0.582 mmol, 1.2 equiv) in MeOH (2.00 mL) was added NaBH₃CN (60.95 mg, 0.970 mmol, 2 equiv). The mixture was stirred 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-dioxoisindol-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.

- 30 *Step 4: Preparation of 5-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]pentanoic acid (i78-5)*



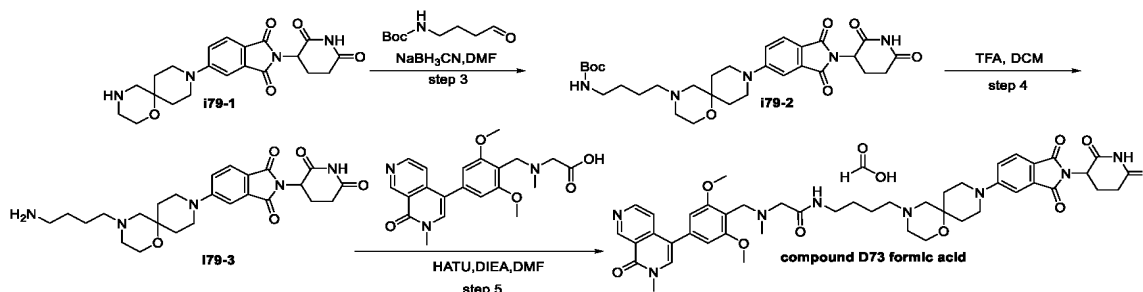
Methyl 5-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]pentanoate (70.00 mg, 0.133 mmol, 1.00 equiv) was stirred at room temperature with HCl (aq.) for 2 hours. The resulting mixture was concentrated under reduced pressure. This resulted in 5-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]-1-oxa-4,9-diazaspiro[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-dioxoisindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]-N-methylpentanamide formic acid (compound D72 formic acid)

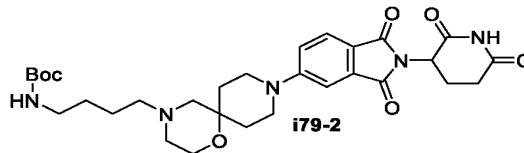


To a stirred solution of 5-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]pentanoic acid (55.00 mg, 0.107 mmol, 1.00 equiv) and 4-[3,5-dimethoxy-4-[(methylamino)methyl]phenyl]-2-methyl-2,7-naphthyridin-1-one (36.42 mg, 0.107 mmol, 1.00 equiv) in DMF (1.00 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-dioxoisindol-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. ^1H NMR (400 MHz, Methanol- d_4) 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-dioxoisindol-5-yl]-1-oxa-4,9-diaza spiro[5.5]undecan-4-yl]butyl)acetamide formic acid (compound D73 formic acid)

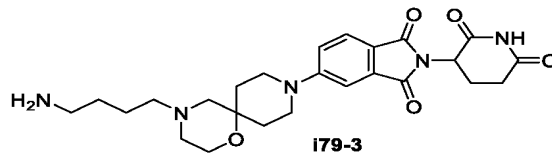


Step 1: Preparation of *tert*-butyl *N*-(4-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]butyl)carbamate (*i*79-2)



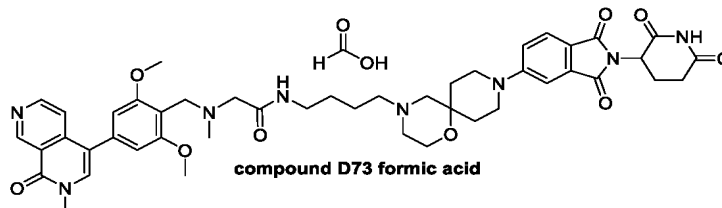
To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-[1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]isoindole-1,3-dione (200.00 mg, 0.485 mmol, 1.00 equiv) and *tert*-butyl *N*-(4-oxobutyl)carbamate (907.94 mg, 4.849 mmol, 10.00 equiv) in DMF (1.50 mL) was added NaBH₃CN (60.95 mg, 0.970 mmol, 2.00 equiv). 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-dioxoisindol-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 (*i*79-3)



To a stirred solution of *tert*-butyl *N*-(4-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-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 (CH₂Cl₂ / 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.

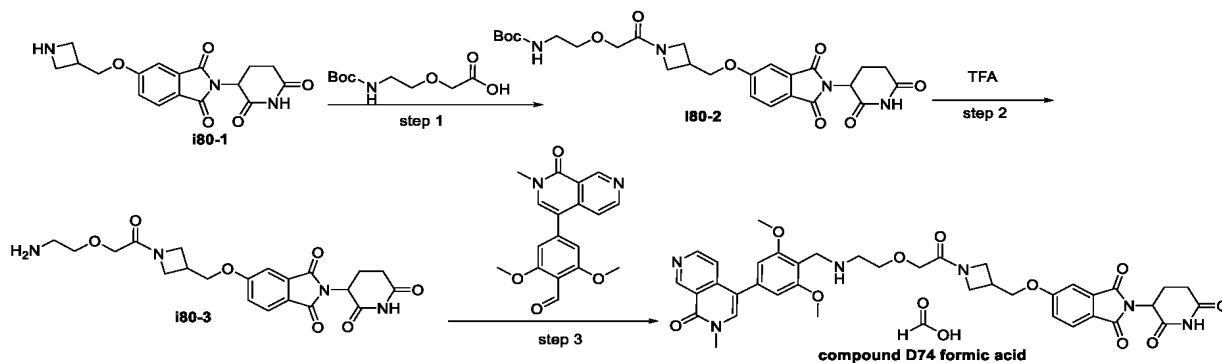
Step 3: Preparation of 2-([2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl)(methylamino)-*N*-(4-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]butyl)acetamide formic acid (compound D73 formic acid)



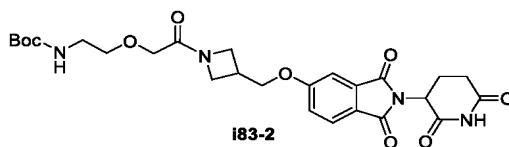
To a stirred solution of 5-[4-(4-aminobutyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (60.00 mg, 0.124 mmol, 1.00 equiv) and ([2,6-dimethoxy-4-(2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl)(methylamino)acetic acid (49.31 mg, 0.124 mmol, 1.00 equiv) in 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)(methylamino)-*N*-(4-[9-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]butyl)acetamide formic acid (12.6mg,10.72%) as a yellow solid. ¹H NMR (400 MHz, Methanol-*d*₄) 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)

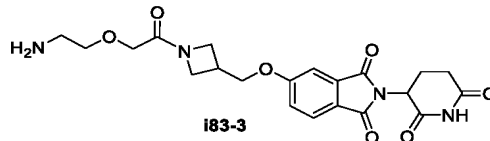


Step 1: Preparation of tert-butyl N-(2-[2-[3-([2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]oxy)methyl]azetidin-1-yl]-2-oxoethoxy)ethyl)carbamate (180-2)



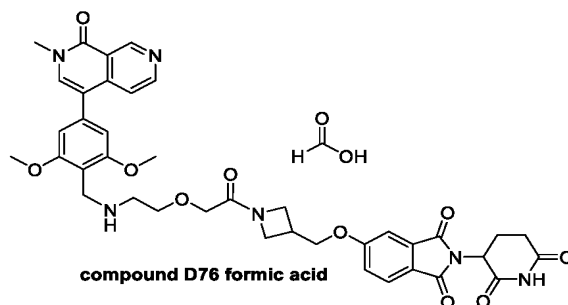
To a solution of [2-[(*tert*-butoxycarbonyl)amino]ethoxy]acetic acid (30.65 mg, 0.140 mmol, 1.20 equiv) and HATU (88.60 mg, 0.233 mmol, 2.00 equiv) in DMF (1.00 mL) was added 5-(azetidin-3-ylmethoxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (40.00 mg, 0.117 mmol, 1.00 equiv) and DIEA (45.17 mg, 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 CH₂Cl₂/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-dioxoisindol-5-yl]oxy)methyl]azetidin-1-yl]-2-oxoethoxy)ethyl)carbamate as a yellow solid. LCMS (ESI) *m/z*: [M+H]⁺ = 545.30.

Step 2: Preparation of 5-([1-[2-(2-aminoethoxy)acetyl]azetidin-3-yl]methoxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (i80-3)



To a solution of *tert*-butyl N-(2-[2-[3-([2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-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)



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 NaBH₃CN (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. ¹H NMR (400 MHz, Methanol-*d*₄) 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- <i>d</i> ₆) δ 11.11 (s, 1H), 9.45 (s, 1H), 8.73 (d, <i>J</i> = 5.7 Hz, 1H), 8.21 (s, 0.7H, FA), 8.05 (d, <i>J</i> = 7.5 Hz, 1H), 7.87 (s, 1H), 7.82 (d, <i>J</i> = 8.2 Hz, 1H), 7.59 – 7.54 (m, 1H), 7.31 – 7.24 (m, 2H), 6.73 (s, 2H), 5.12 (dd, <i>J</i> = 12.8, 5.4 Hz, 1H), 4.87 (t, <i>J</i> = 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, <i>J</i> = 18.0, 6.8 Hz, 3H), 2.15 – 2.00 (m, 3H), 1.95 (td, <i>J</i> = 11.2, 8.4 Hz, 2H).
D79	LCMS: (ESI) m/z: [M+H] ⁺ = 789.20; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.11 (s, 1H), 9.45 (s, 1H), 8.73 (d, <i>J</i> = 5.7 Hz, 1H), 8.21 (s, 0.7H, FA), 8.05 (d, <i>J</i> = 7.5 Hz, 1H), 7.87 (s, 1H), 7.82 (d, <i>J</i> = 8.2 Hz, 1H), 7.59 – 7.54 (m, 1H), 7.31 – 7.24 (m, 2H), 6.73 (s, 2H), 5.12 (dd, <i>J</i> = 12.8, 5.4 Hz, 1H), 4.87 (t, <i>J</i> = 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, <i>J</i> = 18.0, 6.8 Hz, 3H), 2.15 – 2.00 (m, 3H), 1.95 (td, <i>J</i> = 11.2, 8.4 Hz, 2H).
D80	LCMS: (ESI) m/z: [M+H] ⁺ = 803.15; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.12 (s, 1H), 9.45 (s, 1H), 8.73 (d, <i>J</i> = 5.6 Hz, 1H), 8.21 (s, 0.6H, FA), 7.97 – 7.77 (m, 2H), 7.56 (d, <i>J</i> = 5.7 Hz, 1H), 7.37 – 7.20 (m, 2H), 6.74 (s, 2H), 5.12 (dd, <i>J</i> = 12.8, 5.4 Hz, 1H), 5.10 – 4.97 (m, 1H), 3.82 (d, <i>J</i> = 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, <i>J</i> = 13.9 Hz, 1H), 2.58 (d, <i>J</i> = 10.3 Hz, 8H), 2.16 – 1.99 (m, 1H), 1.87 (d, <i>J</i> = 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- <i>d</i> ₄) δ 9.54 (d, <i>J</i> = 0.9 Hz, 1H), 8.69 (d, <i>J</i> = 5.8 Hz, 1H), 8.54 (s, 0.4H, FA), 7.86 – 7.75 (m, 2H), 7.63 (dd, <i>J</i> = 5.8, 0.9 Hz, 1H), 7.50 (dd, <i>J</i> = 7.8, 5.7 Hz, 2H), 6.87 (s, 2H), 5.14 (dd, <i>J</i> = 12.3, 5.4 Hz, 1H), 4.44 – 4.32 (m, 4H), 4.24 (p, <i>J</i> = 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, <i>J</i> = 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- <i>d</i> ₄) δ 9.53 (s, 1H), 8.69 (d, <i>J</i> = 6.0 Hz, 1H), 7.85 (s, 1H), 7.82 – 7.66 (m, 2H), 7.50 – 7.36 (m, 2H), 6.85 (d, <i>J</i> = 1.2 Hz, 2H), 5.12 (dd, <i>J</i> = 12.5, 5.4 Hz, 1H), 4.50 (s, 1H), 4.42 (s, 1H), 4.35 – 4.11 (m, 4H), 4.02 (dd, <i>J</i> = 11.0, 6.7 Hz, 1H), 3.94 (d, <i>J</i> = 2.7 Hz, 6H), 3.91 – 3.76 (m, 5H), 3.71 (d, <i>J</i> = 1.5 Hz, 3H), 3.22 (t, <i>J</i> = 6.5 Hz, 2H), 3.08 – 2.59 (m, 4H), 2.46 (t, <i>J</i> = 5.8 Hz, 2H), 2.21 – 2.07 (m, 1H), 1.84 (p, <i>J</i> = 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- <i>d</i> ₄) δ 9.55 (d, <i>J</i> = 0.8 Hz, 1H), 8.69 (d, <i>J</i> = 5.7 Hz, 1H), 8.56 (s, 0.5H, FA), 7.86 – 7.73 (m, 2H), 7.63 (d, <i>J</i> = 5.8 Hz, 1H), 7.48 (dd, <i>J</i> = 7.9, 6.2 Hz, 2H), 6.85 (s, 2H), 5.24 – 5.02 (m, 1H), 4.38 (t, <i>J</i> = 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, <i>J</i> = 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- <i>d</i> ₄) δ 9.53 (s, 1H), 8.68 (dd, <i>J</i> = 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, <i>J</i> = 9.3, 3.5 Hz, 2H), 6.89 – 6.74 (m, 2H), 5.24 – 5.04 (m, 1H), 4.31 (d, <i>J</i> = 33.1 Hz, 5H), 3.90 (dd, <i>J</i> = 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- <i>d</i> ₄) δ 9.54 (d, <i>J</i> = 0.8 Hz, 1H), 8.69 (d, <i>J</i> = 5.8 Hz, 1H), 8.55 (s, 0.6H, FA), 7.90 – 7.71 (m, 2H), 7.64 (d, <i>J</i> = 5.8 Hz, 1H), 7.48 (dd, <i>J</i> = 7.9, 3.5 Hz, 2H), 6.87 (s, 2H), 5.12 (dd, <i>J</i> = 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, <i>J</i> = 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- <i>d</i> ₄) δ 9.51 (d, <i>J</i> = 1.5 Hz, 1H), 8.67 (d, <i>J</i> = 5.7 Hz, 1H), 7.69 (d, <i>J</i> = 1.8 Hz, 1H), 7.63 – 7.49 (m, 2H), 7.27 (dd, <i>J</i> = 5.8, 2.3 Hz, 1H), 7.16 (ddd, <i>J</i> = 11.0, 8.4, 2.3 Hz, 1H), 6.65 (d, <i>J</i> = 2.1 Hz, 2H), 5.04 (td, <i>J</i> = 12.4, 5.5 Hz, 1H), 4.80 (d, <i>J</i> = 10.2 Hz, 1H), 4.33 (d, <i>J</i> = 10.5 Hz, 2H), 4.25 (d, <i>J</i> = 16.3 Hz, 2H), 4.03 (d, <i>J</i> = 11.4 Hz, 1H), 3.95 – 3.74 (m, 12H), 3.74 (d, <i>J</i> = 1.3 Hz, 4H), 3.39– 3.30 (m, 1H), 2.80 (dt, <i>J</i> = 13.9, 4.7 Hz, 1H), 2.76 – 2.54 (m, 3H), 2.46 – 2.22 (m, 3H), 2.03 (td, <i>J</i> = 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- <i>d</i> ₄) δ 9.53 (d, <i>J</i> = 0.8 Hz, 1H), 8.69 (d, <i>J</i> = 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, <i>J</i> = 2.3 Hz, 1H), 7.34 (dd, <i>J</i> = 8.3, 2.3 Hz, 1H), 6.84 (s, 2H), 5.12 (dd, <i>J</i> = 12.4, 5.4 Hz, 1H), 4.36 – 4.20 (m, 4H), 4.20 – 4.05 (m, 3H), 3.96 (d, <i>J</i> = 8.5 Hz, 8H), 3.90 – 3.75 (m, 4H), 3.71 (s, 3H), 2.97 – 2.55 (m, 5H), 2.43 (t, <i>J</i> = 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- <i>d</i> ₄) δ 9.51 (s, 1H), 8.68 (d, <i>J</i> = 5.8 Hz, 1H), 8.56 (s, 0.7H, FA), 7.76 (d, <i>J</i> = 8.6 Hz, 2H), 7.60 (d, <i>J</i> = 5.8 Hz, 1H), 7.39 (d, <i>J</i> = 2.2 Hz, 1H), 7.30 (dd, <i>J</i> = 8.3, 2.3 Hz, 1H), 6.84 (s, 2H), 5.10 (dd, <i>J</i> = 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, <i>J</i> = 7.2, 5.7 Hz, 6H), 3.70 (s, 3H), 3.20 (t, <i>J</i> = 6.5 Hz, 2H), 3.02 – 2.62 (m, 4H), 2.47 (t, <i>J</i> = 5.8 Hz, 2H), 2.23 – 2.05 (m, 1H), 1.84 (q, <i>J</i> = 6.9 Hz, 2H).
D118	LCMS: (ESI) m/z: [M+H] ⁺ = 807.60; ¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 9.53 (d, <i>J</i> = 0.8 Hz, 1H), 8.69 (d, <i>J</i> = 5.8 Hz, 1H), 8.55 (s, 0.7H, FA), 7.89 – 7.75 (m, 2H), 7.61 (dd, <i>J</i> = 5.8, 0.8 Hz, 1H), 7.44 (d, <i>J</i> = 2.2 Hz, 1H), 7.37 – 7.30 (m, 1H), 6.85 (s, 2H), 5.10 (dd, <i>J</i> = 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, <i>J</i> = 5.6 Hz, 4H), 2.96 – 2.63 (m, 5H), 2.12 (dtd, <i>J</i> = 12.8, 4.8, 2.1 Hz, 1H), 1.83 (dt, <i>J</i> = 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- <i>d</i> ₄) δ 9.53 (d, <i>J</i> = 1.0 Hz, 1H), 8.69 (d, <i>J</i> = 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, <i>J</i> = 4.4, 2.3 Hz, 1H), 7.32 (ddd, <i>J</i> = 8.1, 6.0, 2.1 Hz, 1H), 6.84 (d, <i>J</i> = 7.6 Hz, 2H), 5.10 (dd, <i>J</i> = 6.9, 5.4 Hz, 1H), 4.38 (s, 1H), 4.30 (d, <i>J</i> = 4.9 Hz, 3H), 3.95 (d, <i>J</i> = 8.8 Hz, 6H), 3.87 (t, <i>J</i> = 4.6 Hz, 4H), 3.71 (d, <i>J</i> = 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- <i>d</i> ₄) δ 9.53 (d, <i>J</i> = 2.5 Hz, 1H), 8.68 (dd, <i>J</i> = 5.7, 1.6 Hz, 1H), 8.54 (s, 0.6H, FA), 7.85 – 7.70 (m, 2H), 7.60 (dd, <i>J</i> = 6.0, 3.1 Hz, 1H), 7.42 (dd, <i>J</i> = 3.5, 2.2 Hz, 1H), 7.37 – 7.29 (m, 1H), 6.84 (d, <i>J</i> = 9.2 Hz, 2H), 5.11 (dd, <i>J</i> = 12.5, 5.4 Hz, 1H), 4.40 (s, 1H), 4.31 (dt, <i>J</i> = 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, <i>J</i> = 1.2 Hz, 3H), 3.68 – 3.58 (m, 2H), 3.47 (t, <i>J</i> = 7.1 Hz, 1H), 2.96 – 2.81 (m, 1H), 2.74 (dtt, <i>J</i> = 12.1, 6.1, 3.4 Hz, 2H), 2.62 (dt, <i>J</i> = 11.5, 5.9 Hz, 2H), 2.25 (t, <i>J</i> = 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- <i>d</i> ₄) δ 9.60 – 9.41 (m, 1H), 8.69 (dd, <i>J</i> = 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, <i>J</i> = 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-d ₆) 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 ₂ O) δ 7.9 (brs, 0.8H, FA(COOH)), 11.08 (s, 1H), 9.44 (s, 1H), 8.71 (d, <i>J</i> = 5.7 Hz, 1H), 8.14 (s, 0.8H, FA), 7.86 (s, 1H), 7.66 (d, <i>J</i> = 8.5 Hz, 1H), 7.56 (d, <i>J</i> = 5.8 Hz, 1H), 7.33 (d, <i>J</i> = 2.3 Hz, 1H), 7.24 (dd, <i>J</i> = 8.8, 2.3 Hz, 1H), 7.11 (s, 1H), 6.73 (s, 2H), 5.07 (dd, <i>J</i> = 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-d ₆) δ 11.11 (s, 1H), 9.45 (s, 1H), 8.73 (d, <i>J</i> = 5.7 Hz, 1H), 8.21 (s, 0.7H, FA), 8.05 (d, <i>J</i> = 7.5 Hz, 1H), 7.87 (s, 1H), 7.82 (d, <i>J</i> = 8.2 Hz, 1H), 7.59 – 7.54 (m, 1H), 7.31 – 7.24 (m, 2H), 6.73 (s, 2H), 5.12 (dd, <i>J</i> = 12.8, 5.4 Hz, 1H), 4.87 (t, <i>J</i> = 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, <i>J</i> = 18.0, 6.8 Hz, 3H), 2.15 – 2.00 (m, 3H), 1.95 (td, <i>J</i> = 11.2, 8.4 Hz, 2H).
D183	789.5	
D184	803.15	
D185	715.2	
D186	804.65	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.08 (s, 1H), 9.45 (d, <i>J</i> = 4.3 Hz, 1H), 8.73 (d, <i>J</i> = 5.7 Hz, 1H), 8.16 (s, 0.6H, FA), 7.90 (d, <i>J</i> = 6.4 Hz, 1H), 7.64 (dd, <i>J</i> = 8.3, 2.2 Hz, 1H), 7.58 (d, <i>J</i> = 5.7 Hz, 1H), 6.90 – 6.72 (m, 3H), 6.65 (dd, <i>J</i> = 8.5, 2.3 Hz, 1H), 5.06 (dd, <i>J</i> = 12.9, 5.4 Hz, 1H), 4.57 (d, <i>J</i> = 23.1 Hz, 2H), 3.83 (d, <i>J</i> = 18.2 Hz, 6H), 3.74 (s, 4H), 3.60 (d, <i>J</i> = 3.3 Hz, 3H), 2.88 (ddd, <i>J</i> = 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, <i>J</i> = 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-d ₆) δ 11.08 (s, 1H), 9.45 (s, 1H), 8.73 (d, <i>J</i> = 5.7 Hz, 1H), 8.22 (s, 1H, FA), 8.12 (d, <i>J</i> = 7.4 Hz, 1H), 7.88 (s, 1H), 7.64 (d, <i>J</i> = 8.2 Hz, 1H), 7.57 (d, <i>J</i> = 5.7 Hz, 1H), 6.74 (d, <i>J</i> = 6.3 Hz, 3H), 6.67 – 6.56 (m, 1H), 5.06 (dd, <i>J</i> = 12.8, 5.4 Hz, 1H), 4.08 (d, <i>J</i> = 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, <i>J</i> = 7.1 Hz, 2H), 2.95 – 2.80 (m, 1H), 2.65 – 2.53 (m, 5H), 2.29 (d, <i>J</i> = 7.6 Hz, 2H), 2.12 (t, <i>J</i> = 10.3 Hz, 2H), 2.07 – 1.93 (m, 1H).
D195	760.5	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.08 (s, 1H), 9.45 (s, 1H), 8.74 (d, <i>J</i> = 5.6 Hz, 1H), 7.89 (s, 1H), 7.67 (d, <i>J</i> = 8.3 Hz, 1H), 7.56 (d, <i>J</i> = 5.6 Hz, 1H), 6.82 (d, <i>J</i> = 2.4 Hz, 3H), 6.68 (dd, <i>J</i> = 8.4, 2.1 Hz, 1H), 5.07 (dd, <i>J</i> = 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, <i>J</i> = 16.5 Hz, 2H), 2.44 (d, <i>J</i> = 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-d ₆) δ 11.15 (s, 1H), 9.52 (s, 1H), 8.77 (d, <i>J</i> = 6.0 Hz, 1H), 8.06 (s, 1H), 7.91 (d, <i>J</i> = 8.1 Hz, 1H), 7.85 (dd, <i>J</i> = 5.5, 1.6 Hz, 2H), 7.75 (d, <i>J</i> = 6.0 Hz, 1H), 6.87 (s, 2H), 5.16 (dd, <i>J</i> = 12.8, 5.4 Hz, 1H), 4.43 (d, <i>J</i> = 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, <i>J</i> = 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-d ₆) δ 11.09 (s, 1H), 9.45 (t, <i>J</i> = 1.4 Hz, 1H), 8.72 (d, <i>J</i> = 5.7 Hz, 1H), 8.23 (s, 0.8H, FA), 7.90 (d, <i>J</i> = 6.0 Hz, 1H), 7.76 – 7.56 (m, 2H), 7.40 – 7.16 (m, 2H), 6.77 (d, <i>J</i> = 10.7 Hz, 2H), 5.17 – 4.99 (m, 1H), 4.56 (d, <i>J</i> = 19.2 Hz, 2H), 3.83 (d, <i>J</i> = 13.5 Hz, 6H), 3.60 (d, <i>J</i> = 2.3 Hz, 3H), 3.43 (s, 6H), 3.01 (d, <i>J</i> = 5.0 Hz, 4H), 2.98 – 2.78 (m, 1H), 2.72 (d, <i>J</i> = 5.9 Hz, 1H), 2.65 (s, 2H), 2.63 – 2.55 (m, 1H), 2.47 (s, 2H), 2.27 (dd, <i>J</i> = 4.3, 2.4 Hz, 1H), 2.10 – 1.91 (m, 1H), 1.73 (d, <i>J</i> = 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-d ₆) δ 11.12 (s, 1H), 9.45 (s, 1H), 8.72 (dd, <i>J</i> = 5.7, 2.2 Hz, 1H), 8.20 (s, 0.6H, FA), 7.90 (d, <i>J</i> = 3.6 Hz, 1H), 7.83 (d, <i>J</i> = 8.2 Hz, 1H), 7.58 (dt, <i>J</i> = 5.7, 1.2 Hz, 1H), 7.37 – 7.22 (m, 2H), 6.77 (d, <i>J</i> = 9.7 Hz, 2H), 5.12 (dd, <i>J</i> = 12.9, 5.4 Hz, 1H), 5.04 – 4.92 (m, 1H), 4.56 (d, <i>J</i> = 17.5 Hz, 2H), 3.82 (d, <i>J</i> = 13.3 Hz, 6H), 3.60 (s, 3H), 2.90 (ddd, <i>J</i> = 17.3, 13.9, 5.4 Hz, 1H), 2.71 (s, 1H), 2.61 (d, <i>J</i> = 20.0 Hz, 5H), 2.47 – 2.22 (m, 9H), 2.06 (d, <i>J</i> = 5.9 Hz, 1H), 1.80 (dd, <i>J</i> = 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-d ₆) δ 11.15 (s, 1H), 9.44 (s, 1H), 8.72 (d, <i>J</i> = 5.7 Hz, 1H), 8.21 (s, 1H), 7.94 – 7.79 (m, 4H), 7.56 (d, <i>J</i> = 5.7 Hz, 1H), 6.75 (s, 2H), 5.16 (dd, <i>J</i> = 12.8, 5.4 Hz, 1H), 3.82 (d, <i>J</i> = 9.2 Hz, 8H), 3.60 (s, 4H), 3.46-3.40 (m, 6H), 2.90 (ddd, <i>J</i> = 16.9, 13.8, 5.4 Hz, 1H), 2.70 (s, 2H), 2.66 – 2.53 (m, 5H), 2.07 (ddd, <i>J</i> = 13.3, 5.6, 3.2 Hz, 1H), 1.94 (t, <i>J</i> = 7.0 Hz, 2H), 1.74 (p, <i>J</i> = 7.1 Hz, 2H).
D212	757.35	
D213	771.2	
D214	717.35	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.15 (s, 1H), 9.45 (s, 1H), 8.73 (d, <i>J</i> = 5.7 Hz, 1H), 8.19 (s, 1H FA), 7.87 (d, <i>J</i> = 9.1 Hz, 4H), 7.58 (d, <i>J</i> = 5.6 Hz, 1H), 6.74 (s, 2H), 5.16 (dd, <i>J</i> = 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, <i>J</i> = 7.2 Hz, 6H), 2.12 – 2.01 (m, 1H), 1.73 (p, <i>J</i> = 7.1 Hz, 2H).
D215	729.35	
D216	703.15	
D217	771.15	¹ H NMR (300 MHz, DMSO-d ₆) δ 11.15 (s, 1H), 9.47 (s, 1H), 8.75 (d, <i>J</i> = 5.7 Hz, 1H), 7.97 – 7.79 (m, 4H), 7.58 (d, <i>J</i> = 5.6 Hz, 1H), 6.87 (s, 2H), 5.16 (dd, <i>J</i> = 12.9, 5.3 Hz, 1H), 4.27 (d, <i>J</i> = 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, <i>J</i> = 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, <i>J</i> = 12.4 Hz, 2H).
D218	757.35	
D219	771.35	¹ H NMR (300 MHz, DMSO-d ₆) δ 11.15 (s, 1H), 9.45 (s, 1H), 8.73 (d, <i>J</i> = 5.7 Hz, 1H), 8.20 (s, 1H FA), 7.97 – 7.77 (m, 4H), 7.57 (d, <i>J</i> = 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, <i>J</i> = 27.8 Hz, 5H)
D220	785.15	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.15 (s, 1H), 9.45 (d, <i>J</i> = 2.0 Hz, 1H), 8.73 (dd, <i>J</i> = 5.6, 2.2 Hz, 1H), 7.94 – 7.87 (m, 2H), 7.84 (q, <i>J</i> = 2.9 Hz, 2H), 7.58 (dd, <i>J</i> = 5.7, 2.6 Hz, 1H), 6.74 (s, 2H), 5.16 (dd, <i>J</i> = 12.8, 5.4 Hz, 1H), 3.82 (s, 6H), 3.60 (d, <i>J</i> = 1.4 Hz, 5H), 3.52 (t, <i>J</i> = 7.0 Hz, 1H), 3.17 (s, 2H), 2.89 (ddd, <i>J</i> = 16.6, 13.6, 5.4 Hz, 1H), 2.70 (t, <i>J</i> = 7.0 Hz, 2H), 2.66 – 2.56 (m, 7H), 2.41 (s, 2H), 2.12 – 2.00 (m, 1H), 1.76 (t, <i>J</i> = 7.1 Hz, 1H), 1.67 (t, <i>J</i> = 7.2 Hz, 1H), 1.49 (s, 4H).
D221	817.35	¹ H NMR (300 MHz, DMSO-d ₆) δ 11.13 (s, 1H), 9.45 (s, 1H), 8.73 (d, <i>J</i> = 5.7 Hz, 1H), 8.20 (s, 1H, FA), 7.92 – 7.80 (m, 2H), 7.60 (d, <i>J</i> = 5.7 Hz, 1H), 7.38 – 7.21 (m, 2H), 6.74 (s, 2H), 5.12 (dd, <i>J</i> = 12.9, 5.4 Hz, 1H), 5.03 (t, <i>J</i> = 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-d ₆) δ 11.07 (s, 1H), 9.44 (s, 1H), 8.72 (d, <i>J</i> = 5.7 Hz, 1H), 8.17 (s, 0.6H, FA), 7.88 (s, 1H), 7.59 (dd, <i>J</i> = 9.7, 7.0 Hz, 2H), 6.76 (d, <i>J</i> = 7.3 Hz, 3H), 6.61 (d, <i>J</i> = 8.4 Hz, 1H), 5.05 (dd, <i>J</i> = 12.8, 5.4 Hz, 1H), 4.87 (t, <i>J</i> = 5.4 Hz, 1H), 4.15 – 3.95 (m, 2H), 3.84 (s, 6H), 3.67 (d, <i>J</i> = 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, <i>J</i> = 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-d ₆) δ 11.12 (s, 1H), 9.45 (t, <i>J</i> = 1.2 Hz, 1H), 8.73 (dd, <i>J</i> = 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, <i>J</i> = 9.5 Hz, 2H), 5.12 (dd, <i>J</i> = 12.9, 5.4 Hz, 1H), 4.87 (t, <i>J</i> = 6.8 Hz, 1H), 4.56 (d, <i>J</i> = 19.1 Hz, 2H), 3.82 (d, <i>J</i> = 13.1 Hz, 6H), 3.60 (d, <i>J</i> = 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, <i>J</i> = 3.8, 1.9 Hz, 1H), 2.19 (dd, <i>J</i> = 11.7, 8.0 Hz, 2H), 2.04 (d, <i>J</i> = 11.6 Hz, 1H), 1.53 (d, <i>J</i> = 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-d ₆) δ 11.13 (s, 1H), 9.45 (d, <i>J</i> = 0.8 Hz, 1H), 8.72 (d, <i>J</i> = 5.7 Hz, 1H), 8.18 (s, 0.5H, FA), 7.93 – 7.79 (m, 2H), 7.56 (dd, <i>J</i> = 5.7, 0.9 Hz, 1H), 7.31 (d, <i>J</i> = 7.8 Hz, 2H), 6.74 (s, 2H), 5.27 (s, 1H), 5.14 (dd, <i>J</i> = 12.9, 5.3 Hz, 1H), 4.63 (t, <i>J</i> = 8.1 Hz, 1H), 4.34 (dd, <i>J</i> = 10.5, 6.5 Hz, 1H), 4.13 (d, <i>J</i> = 8.3 Hz, 1H), 3.82 (s, 7H), 3.73 (s, 2H), 3.60 (s, 3H), 3.50 (d, <i>J</i> = 9.7 Hz, 2H), 3.07 (s, 2H), 2.98 – 2.80 (m, 1H), 2.71 – 2.53 (m, 3H), 2.38 (d, <i>J</i> = 7.5 Hz, 2H), 2.17 – 1.97 (m, 1H).
D234	775.35	¹ H NMR (300 MHz, DMSO-d ₆) δ 11.12 (s, 1H), 9.45 (s, 1H), 8.73 (dd, <i>J</i> = 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, <i>J</i> = 1.7 Hz, 2H), 5.12 (dd, <i>J</i> = 12.9, 5.3 Hz, 1H), 4.90 (t, <i>J</i> = 6.7 Hz, 1H), 4.14 (d, <i>J</i> = 27.9 Hz, 2H), 3.92 (s, 1H), 3.83 (d, <i>J</i> = 2.2 Hz, 7H), 3.75 (s, 2H), 3.61 (s, 3H), 3.49 (t, <i>J</i> = 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-d ₆) δ 11.12 (s, 1H), 9.45 (s, 1H), 8.73 (d, <i>J</i> = 5.7 Hz, 1H), 8.21 (s, 1.4H, FA), 7.88 (s, 1H), 7.82 (d, <i>J</i> = 8.2 Hz, 1H), 7.57 (d, <i>J</i> = 5.6 Hz, 1H), 7.28 (d, <i>J</i> = 2.2 Hz, 1H), 7.24 (dd, <i>J</i> = 8.3, 2.3 Hz, 1H), 6.75 (s, 2H), 5.12 (dd, <i>J</i> = 12.8, 5.4 Hz, 1H), 4.90 – 4.80 (m, 1H), 3.82 (s, 6H), 3.61 (d, <i>J</i> = 3.2 Hz, 5H), 3.36 (s, 2H), 3.27 (s, 2H), 2.89 (ddd, <i>J</i> = 16.7, 13.7, 5.3 Hz, 1H), 2.75 – 2.56 (m, 4H), 2.45 (q, <i>J</i> = 7.1, 6.7 Hz, 4H), 2.26 – 2.13 (m, 5H), 2.11 – 1.98 (m, 1H), 1.50 (t, <i>J</i> = 7.2 Hz, 2H), 1.32 (t, <i>J</i> = 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-d ₆) δ 11.03 (s, 1H), 9.42 (s, 1H), 8.68 (d, <i>J</i> = 5.6 Hz, 1H), 7.91 (s, 1H), 7.85 (s, 1H), 7.61 (d, <i>J</i> = 8.3 Hz, 1H), 7.55 (d, <i>J</i> = 5.7 Hz, 1H), 6.80 (s, 2H), 6.75 (d, <i>J</i> = 2.1 Hz, 1H), 6.62 (dd, <i>J</i> = 8.4, 2.1 Hz, 1H), 5.53 (s, 2H), 5.02 (dd, <i>J</i> = 12.8, 5.4

Compound No.	LCMS	¹ H NMR
		Hz, 1H), 4.57 (td, <i>J</i> = 6.3, 3.2 Hz, 1H), 4.53 (s, 2H), 4.24 – 4.15 (m, 2H), 3.86 (s, 6H), 3.79 (dd, <i>J</i> = 9.7, 3.9 Hz, 2H), 3.56 (s, 3H), 3.15 (d, <i>J</i> = 5.3 Hz, 1H), 2.85 (ddd, <i>J</i> = 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- <i>d</i> ₆) δ 11.08 (s, 1H), 9.43 (s, 1H), 8.71 (d, <i>J</i> = 5.6 Hz, 1H), 8.05 (s, 1H), 7.86 (s, 1H), 7.82 (d, <i>J</i> = 8.3 Hz, 1H), 7.56 (d, <i>J</i> = 5.7 Hz, 1H), 7.45 (d, <i>J</i> = 2.3 Hz, 1H), 7.35 (dd, <i>J</i> = 8.4, 2.3 Hz, 1H), 6.76 (s, 2H), 5.09 (dd, <i>J</i> = 12.9, 5.4 Hz, 1H), 4.41 (t, <i>J</i> = 6.6 Hz, 2H), 3.83 (s, 5H), 3.59 (s, 2H), 3.15 (d, <i>J</i> = 5.1 Hz, 1H), 3.11 (d, <i>J</i> = 6.4 Hz, 1H), 2.87 (ddd, <i>J</i> = 17.2, 13.9, 5.3 Hz, 1H), 2.70 – 2.51 (m, 2H), 2.03 (d, <i>J</i> = 15.9 Hz, 5H).
D280	802.16	
D281	830.16	
D282	735.45	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.08 (s, 1H), 7.97 (s, 1H), 7.86 (s, 1H), 7.75 (d, <i>J</i> = 8.2 Hz, 1H), 7.47 (d, <i>J</i> = 2.1 Hz, 1H), 7.32 (dd, <i>J</i> = 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, <i>J</i> = 18.2, 13.8, 5.4 Hz, 1H), 2.71 – 2.53 (m, 2H), 2.38 – 2.24 (m, 2H), 2.09 (d, <i>J</i> = 28.1 Hz, 4H).
D283	749.31	
D284	779.27	
D285	790.33	
D286	790.4	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.03 (s, 1H), 8.08 (s, 1H), 7.85 (s, 1H), 7.60 (d, <i>J</i> = 8.3 Hz, 1H), 6.72 (s, 2H), 5.03 (dd, <i>J</i> = 12.9, 5.4 Hz, 1H), 4.55 (s, 2H), 4.20 (dd, <i>J</i> = 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-d ₄) δ 9.58 (s, 1H), 8.70 (d, <i>J</i> = 6.0 Hz, 1H), 7.91 (d, <i>J</i> = 2.2 Hz, 1H), 7.82 (d, <i>J</i> = 8.3 Hz, 1H), 7.78 (d, <i>J</i> = 6.1 Hz, 1H), 7.31 (d, <i>J</i> = 2.3 Hz, 1H), 7.26 (dd, <i>J</i> = 8.3, 2.3 Hz, 1H), 6.89 (s, 2H), 5.13 (dd, <i>J</i> = 12.6, 5.4 Hz, 1H), 4.98 (t, <i>J</i> = 6.5 Hz, 1H), 4.43 (s, 2H), 3.98 (d, <i>J</i> = 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, <i>J</i> = 12.6 Hz, 1H).
D305	789.7	¹ H NMR (400 MHz, Methanol-d ₄) δ 9.54 (s, 1H), 8.69 (d, <i>J</i> = 5.8 Hz, 1H), 8.50 (s, 2H, FA), 7.83 (d, <i>J</i> = 8.3 Hz, 1H), 7.75 (s, 1H), 7.62 (d, <i>J</i> = 5.7 Hz, 1H), 7.31 (d, <i>J</i> = 2.2 Hz, 1H), 7.26 (dd, <i>J</i> = 8.3, 2.2 Hz, 1H), 6.82 (s, 2H), 5.13 (dd, <i>J</i> = 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-d ₆) δ 11.15 (s, 1H), 9.45 (s, 1H), 8.72 (d, <i>J</i> = 5.6 Hz, 1H), 8.18 (s, 1H FA), 7.89 (d, <i>J</i> = 17.4 Hz, 4H), 7.56 (d, <i>J</i> = 5.6 Hz, 1H), 6.74 (s, 2H), 5.17 (dd, <i>J</i> = 12.8, 5.4 Hz, 1H), 3.82 (s, 6H), 3.74 (s, 2H), 3.63 (d, <i>J</i> = 19.3 Hz, 6H), 3.27 (s, 3H), 2.90 (ddd, <i>J</i> = 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, <i>J</i> = 6.9 Hz, 2H).
D307	729.3	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.15 (s, 1H), 9.45 (s, 1H), 8.72 (d, <i>J</i> = 5.7 Hz, 1H), 7.99 – 7.80 (m, 4H), 7.56 (d, <i>J</i> = 5.7 Hz, 1H), 6.73 (s, 2H), 5.16 (dd, <i>J</i> = 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, <i>J</i> = 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, <i>J</i> = 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-d ₆) δ 11.04 (s, 1H), 8.48 (d, <i>J</i> = 2.7 Hz, 1H), 8.25 (d, <i>J</i> = 2.7 Hz, 1H), 8.19 (s, 2H), 7.65 (d, <i>J</i> = 8.5 Hz, 1H), 7.30 (d, <i>J</i> = 2.3 Hz, 1H), 7.22 (dd, <i>J</i> = 8.6, 2.3 Hz, 1H), 6.85 (d, <i>J</i> = 5.6 Hz, 2H), 5.04 (dd, <i>J</i> = 12.9, 5.4 Hz, 1H), 3.83 (d, <i>J</i> = 2.7 Hz, 7H), 3.59 (s, 3H), 3.48 (d, <i>J</i> = 5.0 Hz, 2H), 3.39 (t, <i>J</i> = 5.0 Hz, 4H), 2.81 (dd, <i>J</i> = 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, <i>J</i> = 7.5 Hz, 2H), 1.09 (s, 1H)
D329	725.87	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.04 (s, 1H), 8.24 – 8.12 (m, 2H), 8.03 (d, <i>J</i> = 2.6 Hz, 1H), 7.88 – 7.72 (m, 1H), 7.65 (d, <i>J</i> = 8.5 Hz, 1H), 7.30 (d, <i>J</i> = 2.2 Hz, 1H), 7.22 (dd, <i>J</i> = 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, <i>J</i> = 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, <i>J</i> = 11.6 Hz, 2H), 2.08 (s, 3H), 1.99 (ddd, <i>J</i> = 11.5, 6.0, 3.7 Hz, 1H), 1.61 (d, <i>J</i> = 12.4 Hz, 2H), 1.35 (q, <i>J</i> = 7.0 Hz, 2H), 1.26 (s, 2H), 1.13 (q, <i>J</i> = 11.2, 10.7 Hz, 2H).
D330	614.68	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.04 (s, 1H), 8.15 (s, 1H), 8.02 (d, <i>J</i> = 2.7 Hz, 1H), 7.79 (dd, <i>J</i> = 2.8, 1.3 Hz, 1H), 7.63 (d, <i>J</i> = 8.5 Hz, 1H), 7.27 (d, <i>J</i> = 2.3 Hz, 1H), 7.20 (dd, <i>J</i> = 8.7, 2.3 Hz, 1H), 6.80 (s, 2H), 5.04 (dd, <i>J</i> = 12.9, 5.4 Hz, 1H), 3.84 (s, 6H), 3.55 (s, 2H), 3.37 (t, <i>J</i> = 5.1 Hz, 4H), 2.66 – 2.53 (m, 2H), 2.08 (s, 3H).
D331	654.74	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.03 (s, 1H), 8.12 (s, 1H), 8.04 (d, <i>J</i> = 2.6 Hz, 1H), 7.80 (dd, <i>J</i> = 2.7, 1.3 Hz, 1H), 7.61 (d, <i>J</i> = 8.3 Hz, 1H), 6.82 (s, 2H), 6.75 (d, <i>J</i> = 2.1 Hz, 1H), 5.02 (dd, <i>J</i> = 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, <i>J</i> = 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-d ₆) δ 10.81 (s, 1H), 8.13 (s, 1H), 8.05 (d, <i>J</i> = 2.7 Hz, 1H), 7.80 (dd, <i>J</i> = 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, <i>J</i> = 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-d ₆) δ 12.12 (s, 1H), 11.03 (s, 1H), 8.14 (d, <i>J</i> = 1.1 Hz, 1H), 7.60 (d, <i>J</i> = 8.3 Hz, 1H), 7.45 (s, 1H), 7.34 (t, <i>J</i> = 2.8 Hz, 1H), 6.82 (s, 2H), 6.75 (d, <i>J</i> = 2.1 Hz, 1H), 6.62 (dd, <i>J</i> = 8.4, 2.2 Hz, 1H), 6.54 (t, <i>J</i> = 2.4 Hz, 1H), 5.73 (s, 1H), 5.02 (dd, <i>J</i> = 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, <i>J</i> = 17.3, 13.9, 5.4 Hz, 1H), 2.64 – 2.50 (m, 1H), 1.98 (dd, <i>J</i> = 9.2, 4.0 Hz, 1H), 1.72 (d, <i>J</i> = 5.8 Hz, 4H).
D341	690.72	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.13 (dd, <i>J</i> = 9.6, 2.7 Hz, 2H), 6.83 (d, <i>J</i> = 0.9 Hz, 2H), 11.03 (s, 1H), 8.37 (d, <i>J</i> = 2.6 Hz, 1H), 7.60 (d, <i>J</i> = 8.3 Hz, 1H), 6.78 – 6.71 (m, 1H), 6.62 (dd, <i>J</i> = 8.4, 2.1 Hz, 1H), 5.02 (dd, <i>J</i> = 12.9, 5.4 Hz, 1H), 3.84 (d, <i>J</i> = 0.8 Hz, 6H),

Compound No.	LCMS	¹ H NMR
		3.69 (s, 4H), 3.57 (s, 3H), 3.50 (d, <i>J</i> = 4.1 Hz, 2H), 2.86 (ddd, <i>J</i> = 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-d ₆) δ 11.07 (s, 1H), 9.04 (d, <i>J</i> = 3.3 Hz, 1H), 8.66 (d, <i>J</i> = 3.4 Hz, 1H), 8.20 (s, 1H, FA), 7.64 (d, <i>J</i> = 8.5 Hz, 1H), 7.29 (s, 1H), 7.22 (d, <i>J</i> = 8.8 Hz, 1H), 6.88 (s, 2H), 5.06 (dd, <i>J</i> = 13.0, 5.3 Hz, 1H), 4.02 (d, <i>J</i> = 12.8 Hz, 2H), 3.84 (s, 6H), 3.57 – 3.47 (m, 5H), 2.91 (dt, <i>J</i> = 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-d ₆) δ 11.10 (s, 1H), 9.47 (s, 1H, TFA), 7.77 (d, <i>J</i> = 8.5 Hz, 1H), 7.47 (d, <i>J</i> = 2.2 Hz, 1H), 7.38 – 7.23 (m, 2H), 6.69 (s, 2H), 5.10 (dd, <i>J</i> = 12.8, 5.4 Hz, 1H), 4.33 (s, 2H), 4.18 (d, <i>J</i> = 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, <i>J</i> = 18.3 Hz, 2H), 2.35 (s, 3H), 2.05 (s, 4H).
D344	600.2	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.07 (s, 1H), 8.21 (d, <i>J</i> = 2.8 Hz, 1H), 8.14 (s, 1H FA), 7.97 – 7.88 (m, 1H), 7.67 (d, <i>J</i> = 8.5 Hz, 1H), 7.32 (d, <i>J</i> = 2.3 Hz, 1H), 7.26 – 7.21 (m, 1H), 6.85 (s, 2H), 6.50 (d, <i>J</i> = 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-d ₄) δ 8.31 (s, 1H FA), 7.65 (d, <i>J</i> = 8.3 Hz, 1H), 7.48 (s, 1H), 6.84 (d, <i>J</i> = 2.1 Hz, 1H), 6.72 – 6.63 (m, 3H), 5.07 (dd, <i>J</i> = 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, <i>J</i> = 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-d ₆) δ 11.07 (s, 1H), 8.16 (s, 1H, FA), 7.64 (d, <i>J</i> = 8.3 Hz, 1H), 7.28 (d, <i>J</i> = 1.2 Hz, 1H), 6.77 (d, <i>J</i> = 2.1 Hz, 1H), 6.69 – 6.53 (m, 3H), 5.05 (dd, <i>J</i> = 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, <i>J</i> = 26.6 Hz, 1H).
D347	709.2	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.08 (s, 1H), 8.23 (s, 1H), 8.17 (s, 1H, FA), 7.94 (d, <i>J</i> = 9.6 Hz, 1H), 7.64 (d, <i>J</i> = 8.3 Hz, 1H), 6.86 (d, <i>J</i> = 4.5 Hz, 2H), 6.77 (d, <i>J</i> = 2.1 Hz, 1H), 6.64 (dd, <i>J</i> = 8.4, 2.2 Hz, 1H), 6.50 (d, <i>J</i> = 9.4 Hz, 1H), 5.05 (dd, <i>J</i> = 12.9, 5.3 Hz, 1H), 3.88 (t, <i>J</i> = 2.1 Hz, 7H), 3.79 (s, 2H), 3.73 (s, 5H), 3.54 (s, 6H), 3.19 (d, <i>J</i> = 29.3 Hz, 1H), 2.99 – 2.81 (m, 1H), 2.58 (d, <i>J</i> = 16.2 Hz,

Compound No.	LCMS	¹ H NMR
		2H), 2.44 (s, 2H), 2.28 (s, 3H), 2.01 (d, <i>J</i> = 12.4 Hz, 1H), 1.73 (s, 4H).
D348	749.25	¹ H NMR (300 MHz, DMSO-d ₆) δ 8.04 (d, <i>J</i> = 2.6 Hz, 1H), 7.88 (t, <i>J</i> = 1.8 Hz, 1H), 7.67 (d, <i>J</i> = 8.2 Hz, 1H), 6.90 (d, <i>J</i> = 2.1 Hz, 2H), 6.77 (d, <i>J</i> = 2.2 Hz, 1H), 6.66 (m, <i>J</i> = 8.3, 2.0 Hz, 1H), 6.09 - 5.91 (m, 1H), , 5.19 (m, <i>J</i> = 10.3, 1.5 Hz, 1H), 5.14 - 4.98 (m, 2H), 4.62 (d, <i>J</i> = 5.4 Hz, 2H), 4.34 (d, <i>J</i> = 16.5 Hz, 2H), 4.18 (s, 2H), 3.99 (d, <i>J</i> = 10.2 Hz, 2H), 3.92 (s, 6H), 3.87 (s, 2H), 3.81 (s, 2H), 3.41 (d, <i>J</i> = 6.6 Hz, 4H), 3.17 (d, <i>J</i> = 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-d ₆) δ 11.08 (s, 1H), 9.78 (s, 2H, TFA), 7.69 (d, <i>J</i> = 8.2 Hz, 1H), 7.65 (s, 1H), 6.75 (dd, <i>J</i> = 21.5, 3.2 Hz, 3H), 6.66 (dd, <i>J</i> = 8.3, 2.4 Hz, 1H), 6.38 (s, 1H), 5.06 (dd, <i>J</i> = 12.9, 5.4 Hz, 1H), 4.39 (s, 1H), 4.34 (d, <i>J</i> = 5.5 Hz, 1H), 4.22 (s, 2H), 4.01 (d, <i>J</i> = 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-d ₆) δ 11.08 (s, 1H), 9.94 (br s, 2H, TFA salt), 8.07 (s, 1H), 7.69 (d, <i>J</i> = 8.2 Hz, 1H), 6.77 (d, <i>J</i> = 3.7 Hz, 3H), 6.66 (dd, <i>J</i> = 8.4, 2.3 Hz, 1H), 5.06 (dd, <i>J</i> = 12.8, 5.4 Hz, 1H), 4.40 (s, 1H), 4.35 (d, <i>J</i> = 5.6 Hz, 1H), 4.27 - 4.16 (m, 2H), 4.03 (q, <i>J</i> = 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, <i>J</i> = 14.0 Hz, 2H), 2.02 (dd, <i>J</i> = 9.7, 4.6 Hz, 1H), 1.97 - 1.84 (m, 2H).
D352	734.45	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.07 (s, 1H), 8.77 (s, 1H), 8.69 (s, 1H), 8.14 (s, 0.4H, FA), 7.67 (d, <i>J</i> = 8.3 Hz, 1H), 7.02 (s, 2H), 6.77 (s, 1H), 6.65 (d, <i>J</i> = 8.4 Hz, 1H), 5.05 (dd, <i>J</i> = 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-d ₆) δ 11.08 (s, 1H), 8.16 (s, 1H FA), 7.72 (d, <i>J</i> = 2.5 Hz, 1H), 7.64 (d, <i>J</i> = 8.3 Hz, 1H), 7.52 (dd, <i>J</i> = 2.7,

Compound No.	LCMS	¹ H NMR
		1.2 Hz, 1H), 6.99 (s, 1H), 6.88 (s, 1H), 6.78 (d, <i>J</i> = 2.1 Hz, 1H), 6.65 (dd, <i>J</i> = 8.5, 2.1 Hz, 1H), 5.05 (dd, <i>J</i> = 12.9, 5.4 Hz, 1H), 3.78 (s, 3H), 3.74 (d, <i>J</i> = 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, <i>J</i> = 7.1 Hz, 1H), 1.74 (s, 4H).
D354	737.45	¹ H NMR (400 MHz, Methanol-d ₄) δ 8.30 (s, 2H FA), 7.64 (d, <i>J</i> = 8.3 Hz, 1H), 7.35 (s, 1H), 7.15 (s, 1H), 6.95 (s, 1H), 6.83 (d, <i>J</i> = 2.0 Hz, 1H), 6.67 (dd, <i>J</i> = 8.3, 2.0 Hz, 1H), 5.07 (dd, <i>J</i> = 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-d ₆) δ 10.98 (s, 1H), 9.93 (br s, 2H, TFA salt), 8.36 (d, <i>J</i> = 8.0 Hz, 1H), 7.78 – 7.53 (m, 4H), 7.41 (d, <i>J</i> = 8.5 Hz, 1H), 6.85 (s, 2H), 6.70 (s, 2H), 5.07 (dd, <i>J</i> = 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-d ₆) δ 11.10 (s, 1H), 10.32 – 9.43 (m, 2H), 7.69 (d, <i>J</i> = 8.3 Hz, 1H), 7.22 – 7.05 (m, 2H), 6.92 (s, 1H), 6.83 – 6.74 (m, 1H), 6.66 (dd, <i>J</i> = 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-d ₆) δ 10.95 (s, 1H), 9.83 (br s, 2H, TFA salt), 8.36 (d, <i>J</i> = 7.9 Hz, 1H), 7.73 (t, <i>J</i> = 7.8 Hz, 1H), 7.66 – 7.48 (m, 4H), 6.85 (s, 2H), 6.55–6.44 (m, 2H), 5.04 (dd, <i>J</i> = 13.2, 4.8 Hz, 1H), 4.40 (t, <i>J</i> = 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-d ₆) δ 8.33 (s, 1H), 8.14 (s, FA, 1H), 7.91 (s, 1H), 7.40 (d, <i>J</i> = 8.9 Hz, 1H), 7.13 (s, 1H), 7.03 (s, 2H), 6.73 – 6.67 (m, 2H), 5.06 (dd, <i>J</i> = 13.2, 5.1 Hz, 1H), 4.34 (s, <i>J</i> = 16.7 Hz, 3H), 4.30 (d, <i>J</i> = 16.7 Hz, 1H) 4.19 (d, <i>J</i> = 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-d ₆) 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, <i>J</i> = 13.3, 5.1 Hz, 1H), 4.36 – 4.12 (m, 2H), 3.85 (d, <i>J</i> = 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, <i>J</i> = 2.7 Hz, 6H), 1.97 (s, 1H), 1.73 (d, <i>J</i> = 12.6 Hz, 2H), 1.50 (s, 1H), 1.36 (d, <i>J</i> = 7.5 Hz, 2H), 1.26 – 1.13 (m, 2H).
D363	735.6	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.94 (s, 1H), 8.33 (s, 1H), 8.22 (s, FA, 1H), 7.89 (s, 1H), 7.48 (d, <i>J</i> = 8.3 Hz, 1H), 7.11 (s, 1H), 6.92 (s, 2H), 6.53 – 6.43 (t, 2H), 5.03 (dd, <i>J</i> = 13.3, 5.1 Hz, 1H), 4.30 (d, <i>J</i> = 16.9 Hz, 1H), 4.17 (d, <i>J</i> = 16.9 Hz, 1H), 3.85 (s, 6H), 3.67 (s, 2H), 3.61 (s, <i>J</i> = 6.9 Hz, 6H), 3.47 (s, <i>J</i> = 6.9 Hz, 4H), 2.98 (m, <i>J</i> = 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, <i>J</i> = 5.2 Hz, 4H).
D364	781.2	¹ H NMR (300 MHz, MeOD) δ 8.05 (d, <i>J</i> = 2.5 Hz, 1H), 7.83 (s, 1H), 7.41 (d, <i>J</i> = 8.2 Hz, 1H), 6.95 – 6.84 (m, 3H), 6.79 (d, <i>J</i> = 8.2 Hz, 1H), 5.14 (dd, <i>J</i> = 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, <i>J</i> = 1.6 Hz, 1H), 7.77 (s, 1H), 7.49 (d, <i>J</i> = 1.6 Hz, 1H), 7.39 (d, <i>J</i> = 8.2 Hz, 1H), 7.25 (s, 2H), 6.85 (d, <i>J</i> = 2.2 Hz, 1H), 6.77 (dd, <i>J</i> = 8.3, 2.2 Hz, 1H), 5.14 (dd, <i>J</i> = 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-d ₆) δ 10.98 (s, 1H), 9.56 (d, <i>J</i> = 5.4 Hz, 1H), 9.29 (s, 2H, TFA), 8.39 (d, <i>J</i> = 5.4 Hz, 1H), 8.08 (s, 1H), 7.64 (dd, <i>J</i> = 8.4, 3.2 Hz, 1H), 7.17 – 7.04 (m, 3H), 7.02 – 6.95 (m, 1H), 5.08 (dd, <i>J</i> = 13.3, 5.1 Hz, 1H), 4.88 (p, <i>J</i> = 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, <i>J</i> = 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, <i>J</i> = 12.7 Hz, 2H).
D367	790.5	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.98 (s, 1H), 9.56 (d, <i>J</i> = 5.4 Hz, 1H), 9.29 (s, 2H, TFA), 8.39 (d, <i>J</i> = 5.4 Hz, 1H), 8.08 (s, 1H), 7.64 (dd, <i>J</i> = 8.4, 3.2 Hz, 1H), 7.17 – 7.04 (m, 3H), 7.02 – 6.95 (m, 1H), 5.08 (dd, <i>J</i> = 13.3, 5.1 Hz, 1H), 4.88 (p, <i>J</i> = 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, <i>J</i> = 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, <i>J</i> = 12.7 Hz, 2H).
D368	790.65	¹ H NMR (400 MHz, DMSO-d ₆) 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, <i>J</i> = 8.4, 2.7 Hz, 1H), 7.19 – 7.09 (m, 2H), 6.97 (s, 2H), 5.11 (dd, <i>J</i> = 13.3, 5.1 Hz, 1H), 4.93 – 4.85 (m, 1H), 4.38 (d, <i>J</i> = 16.9 Hz, 2H), 4.26 (d, <i>J</i> = 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-d ₆) 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, <i>J</i> = 4.6 Hz, 2H), 6.54 – 6.45 (m, 2H), 5.05 (dd, <i>J</i> = 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, <i>J</i> = 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, <i>J</i> = 13.9 Hz, 2H), 2.00 – 1.88 (m, 3H).
D370	749.4	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.95 (s, 1H), 9.99 – 9.58 (m, 2H, TFA salt), 8.63 (s, 1H), 7.92 (s, 1H), 7.52 (d, <i>J</i> = 8.2 Hz, 1H), 7.41 (s, 2H), 6.54 – 6.45 (m, 2H), 5.05 (dd, <i>J</i> = 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, <i>J</i> = 6.7 Hz, 1H), 2.96 (s, 3H), 2.65 – 2.51 (m, 2H), 2.43 – 2.36 (m, 1H), 2.12 (d, <i>J</i> = 14.3 Hz, 2H), 2.00 – 1.88 (m, 3H).

Compound No.	LCMS	¹ H NMR
D371	805.45	¹ H NMR (400 MHz, Methanol-d ₄) 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-d ₆) 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-d ₆) 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-d ₄) 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-d ₆) 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-d ₄) 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-d ₆) 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	¹ H NMR (400 MHz, DMSO-d ₆) 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	¹ H NMR (400 MHz, DMSO-d ₆) 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-d ₆) 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, <i>J</i> = 8.0 Hz, 1H), 6.82 (s, 2H), 5.09 (dt, <i>J</i> = 11.9, 5.8 Hz, 1H), 3.92 (d, <i>J</i> = 3.9 Hz, 5H), 3.86 (d, <i>J</i> = 3.7 Hz, 6H), 3.51 (d, <i>J</i> = 2.0 Hz, 4H), 3.15 (s, 1H), 2.08 (d, <i>J</i> = 2.6 Hz, 4H).
DD10	803.2	¹ H NMR (300 MHz, DMSO) δ 11.13 (s, 1H), 8.20 (s, FA, 1H), 8.09 (d, <i>J</i> = 8.3 Hz, 1H), 7.90 (d, <i>J</i> = 8.4 Hz, 1H), 7.83 (d, <i>J</i> = 8.1 Hz, 1H), 7.69 – 7.59 (m, 1H), 7.58 - 7.49 (m, 1H), 7.43 (d, <i>J</i> = 7.5 Hz, 1H), 7.34 – 7.23 (m, 2H), 6.73 (s, 2H), 5.12 (dd, <i>J</i> = 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-d ₆) δ 11.13 (s, 1H), 9.45 (s, 1H), 8.73 (d, <i>J</i> = 5.7 Hz, 1H), 7.88 (d, <i>J</i> = 14.1 Hz, 2H), 7.57 (d, <i>J</i> = 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-d ₆) δ 11.08 (s, 1H), 9.45 (d, <i>J</i> = 0.8 Hz, 1H), 8.73 (d, <i>J</i> = 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, <i>J</i> = 8.4, 2.1 Hz, 1H), 5.06 (dd, <i>J</i> = 12.9, 5.4 Hz, 1H), 3.82 (s, 6H), 3.74 (s, 4H), 3.58 (d, <i>J</i> = 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, <i>J</i> = 6.1 Hz, 1H), 7.94 (s, 1H), 7.81 (d, <i>J</i> = 6.0 Hz, 1H), 7.67 – 7.60 (m, 1H), 6.91 (s, 2H), 6.59 (d, <i>J</i> = 7.8 Hz, 2H), 5.11 (dd, <i>J</i> = 13.3, 5.1 Hz, 1H), 4.47 (s, 2H), 4.40 (d, <i>J</i> = 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-d ₄) 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-d ₆) 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-d ₆) 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-d ₄) 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-d ₄) 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	¹ H), 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-d ₆) 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-d ₆) 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-d ₆ with a drop of D ₂ O) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₄) 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-d ₆) 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-d ₄) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₄) 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-d ₆) 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-d ₆) 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). ¹⁹ F NMR (377 MHz, DMSO-d ₆) δ - 73.65.

Compound No.	LCMS	¹ H NMR
D412	680.35	¹ H NMR (400 MHz, DMSO-d ₆) 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). ¹⁹ F NMR (377 MHz, DMSO-d ₆) δ -73.66.
D413	694.45	¹ H NMR (400 MHz, DMSO-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₄) 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-d ₆) 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-d ₆) 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-d ₄) 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-d ₄) 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-d ₆ with a drop of D ₂ O) 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-d ₄) 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-d ₄) 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-d ₄) 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-d ₄) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₄) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₄) 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-d ₄) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆ with a drop of D ₂ O) 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-d ₄) 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-d ₆) 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-d ₄) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₄) 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-d ₄) 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-d ₆) 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-d ₆) 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-d ₄) 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-d ₆) 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-d ₆) 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-d ₆) 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-d ₄) 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-d ₆) 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-d ₆) 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.

5 **Procedure:** His-Flag-BRD9 (P133-K239; Swiss Prot Q9H8M2; SEQ ID NO:1 mgssshhhhhhenlyfq/gdykdddkgslevlfqg/PAENESTPIQQLLEHFLRQLQRKDPHGFFAFPVTDIAIPGYSMII 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®
10 TR-FRET platform (PerkinElmer), and the compounds were assayed for inhibitory activity against this interaction.

15 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.

20 **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 IC₅₀ (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 IC₅₀ value of < 1 μM for BRD9 binding, indicating their affinity for targeting BRD9.

25

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

5

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 μ L 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 μ M 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 μ L 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 = $100 \times (\text{Lum}_{\text{HC}} - \text{Lum}_{\text{Sample}}) / (\text{Lum}_{\text{HC}} - \text{Lum}_{\text{LC}})$. DMSO treated cells are employed as High Control (HC) and 1 μ M 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} (μ M) 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 μ M 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

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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

5

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

5

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.

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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.

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Other embodiments are in the claims.

Claims

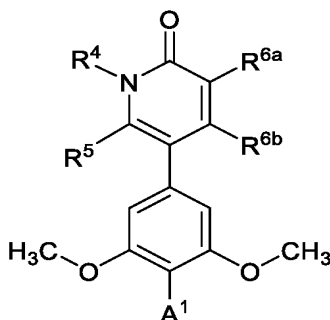
1. A compound having the structure of **Formula I**:

A-L-B

Formula I,

wherein

A is:



Formula IIIc,

wherein

A¹ is a bond between A and L;

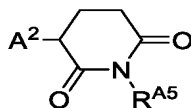
R⁴ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl;

R⁵ is H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, or optionally substituted C₆-C₁₀ aryl;

R^{6a} is H, halogen, cyano, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

R^{6b} is H, halogen, cyano, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ 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 C₆-C₁₀ aryl or optionally substituted C₂-C₉ heteroaryl;

B is:



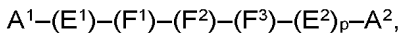
Formula AA2,

wherein

A² is a bond between B and L; and

R^{A5} is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl;

L is:



Formula II

wherein

A¹ is a bond between the linker and A:

A² is a bond between B and the linker:

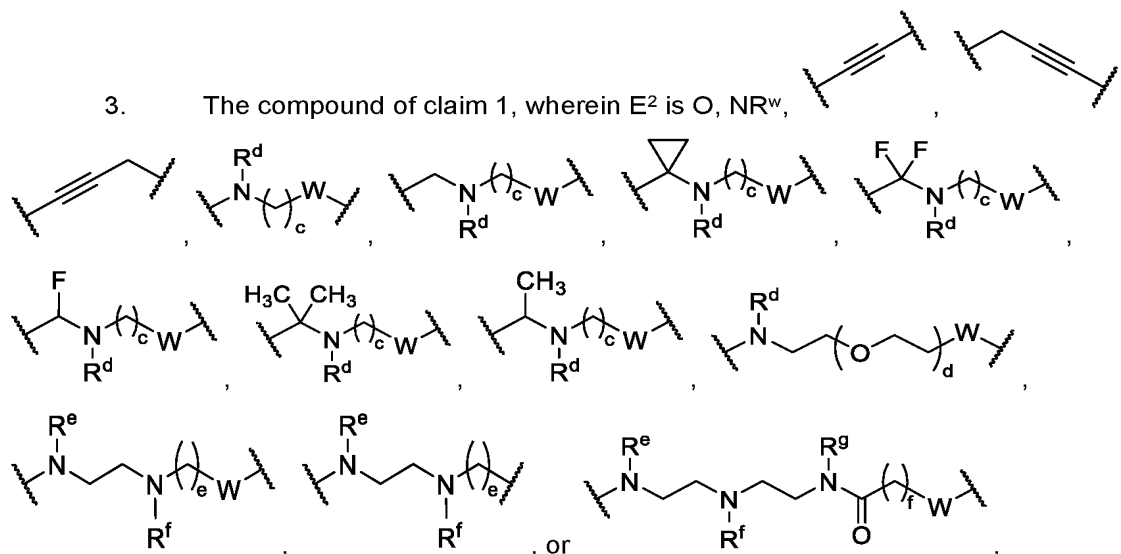
each of E¹ and E² is, independently, O, S, NR^N, optionally substituted C₁₋₁₀ alkylene, optionally substituted C₂₋₁₀ alkenylene, optionally substituted C₂₋₁₀ alkynylene, optionally substituted C₂-C₁₀ polyethylene glycol, or optionally substituted C₁₋₁₀ heteroalkylene;

each R^N is, independently, H, optionally substituted C₁₋₄ alkyl, optionally substituted C₂₋₄ alkenyl, optionally substituted C₂₋₄ alkynyl, optionally substituted C₂₋₆ heterocyclyl, optionally substituted C₆₋₁₂ aryl, or optionally substituted C₁₋₇ heteroalkyl; and

each of F¹, F², and F³ is, independently, optionally substituted C₃-C₁₀ carbocyclylene, optionally substituted C₂₋₁₀ heterocyclylene, optionally substituted C₆-C₁₀ arylene, or optionally substituted C₂-C₉ heteroarylene,

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein E¹ is -CH₂-.



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 C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₆ carbocyclyl;

R^e is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₆ carbocyclyl;

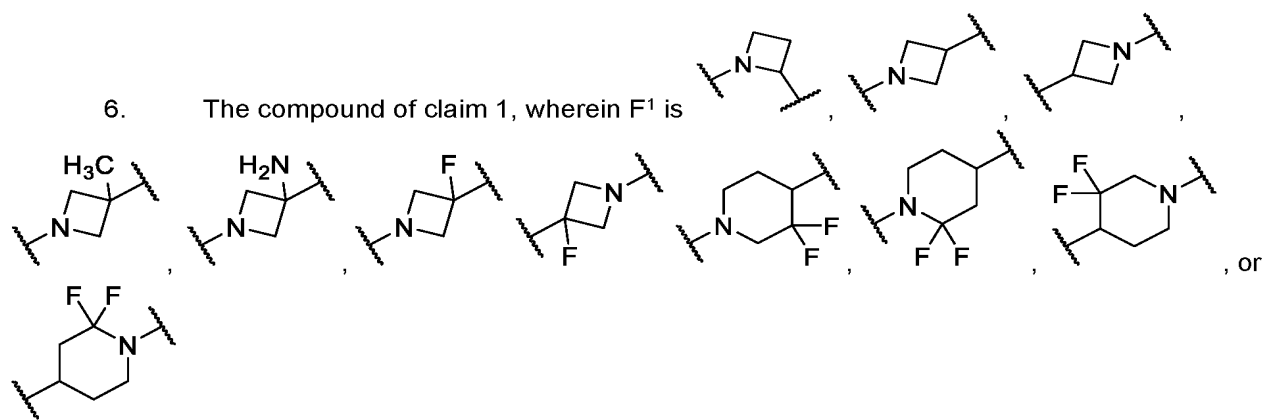
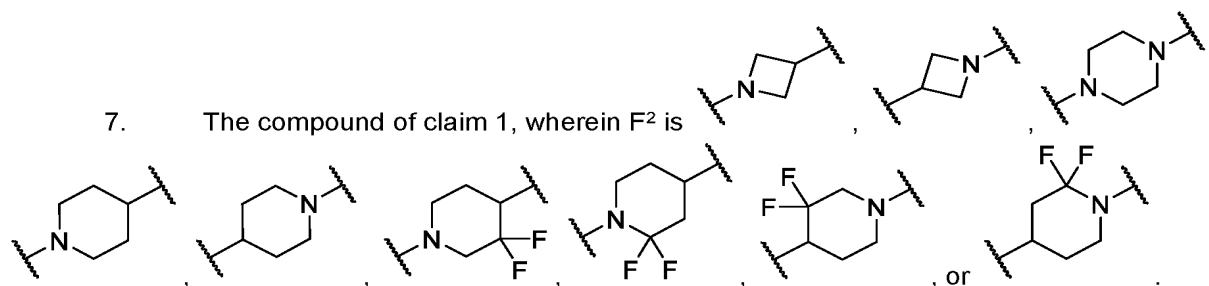
R^f is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_6 carbocyclyl;

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.

4. The compound of claim 3, wherein E^2 is $-NR^N-$.

5. The compound of claim 4, wherein E^2 is $-NH-$.

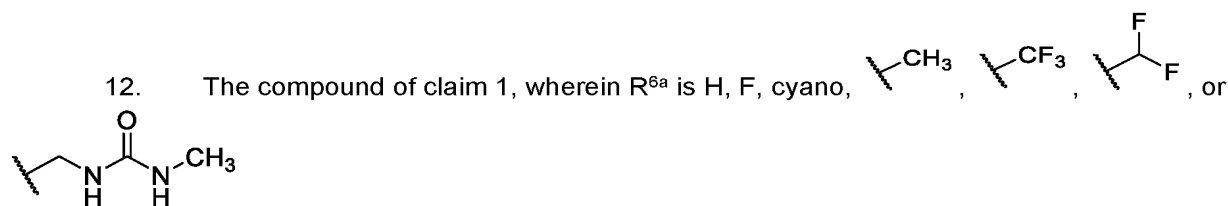
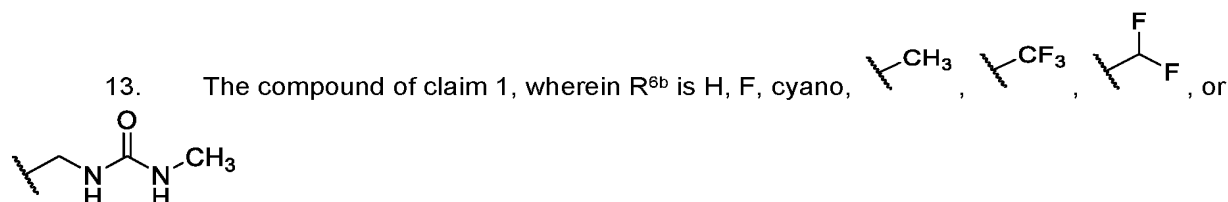


8. The compound of claim 1, wherein F^3 is optionally substituted C_6 - C_{10} arylene.

9. The compound of claim 1, wherein R^{A5} is H.

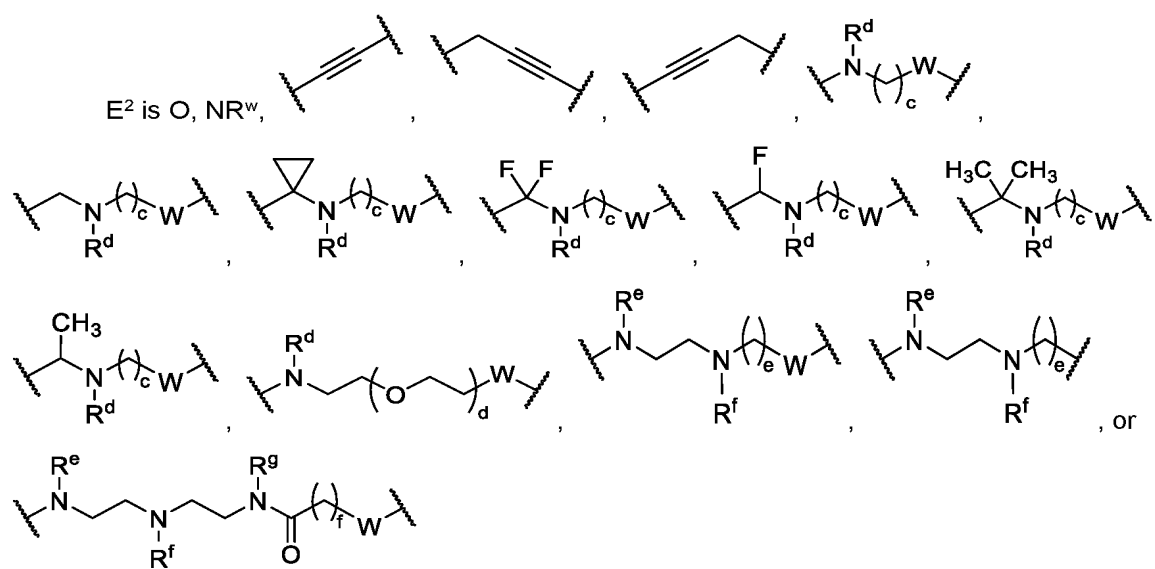
10. The compound of claim 1, wherein R^4 is $-CH_3$.

11. The compound of claim 1, wherein R^5 is H or $-CH_3$.



14. The compound of claim 1, wherein:

E¹ is -CH₂-;



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;

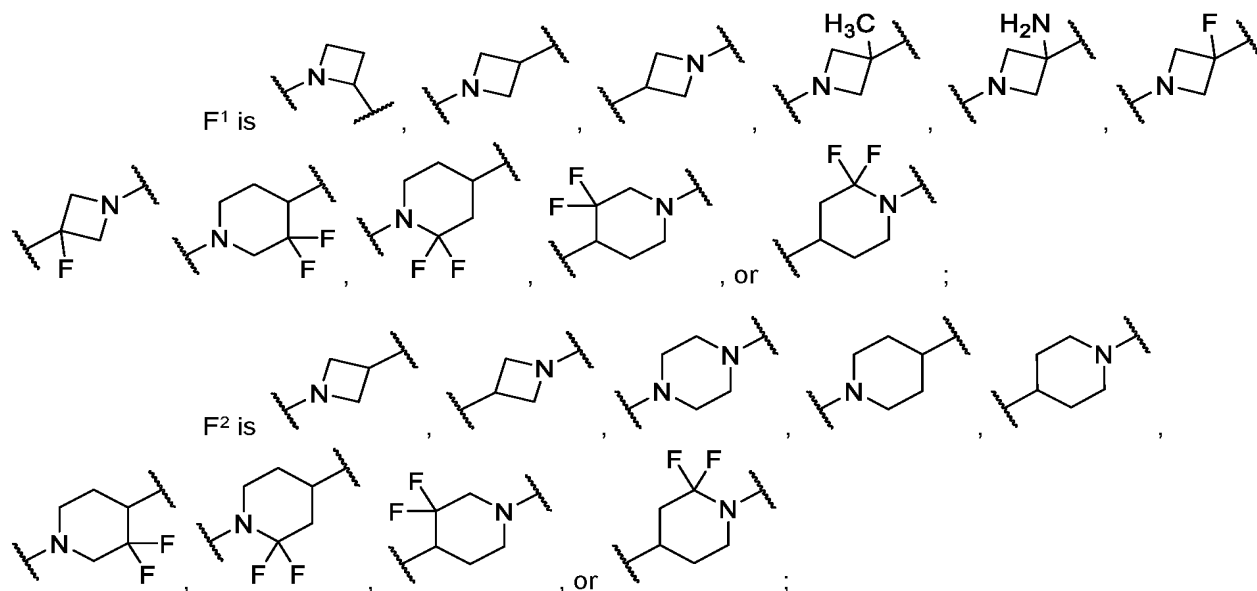
R^d is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₆ carbocyclyl;

R^e is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₆ carbocyclyl;

R^f is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₆ carbocyclyl;

R⁹ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₆ carbocyclyl; and

W is O or NR^w, wherein R^w is H or optionally substituted C₁-C₆ alkyl;

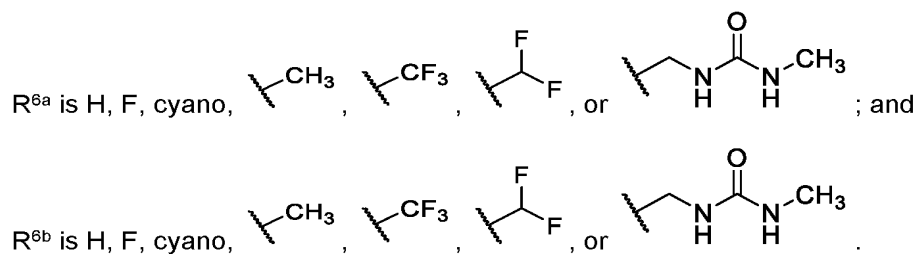


F³ is optionally substituted C₆-C₁₀ arylene;

R^{A5} is H;

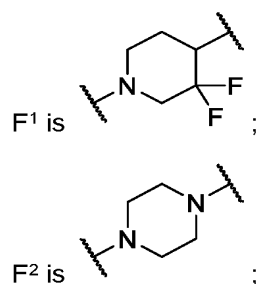
R⁴ is -CH₃;

R⁵ is H or -CH₃;



15. The compound of claim 14, wherein:

E² is -NR^N-;



R^5 is H;

R^{6a} is -CH₃; and

R^{6b} is -CH₃.

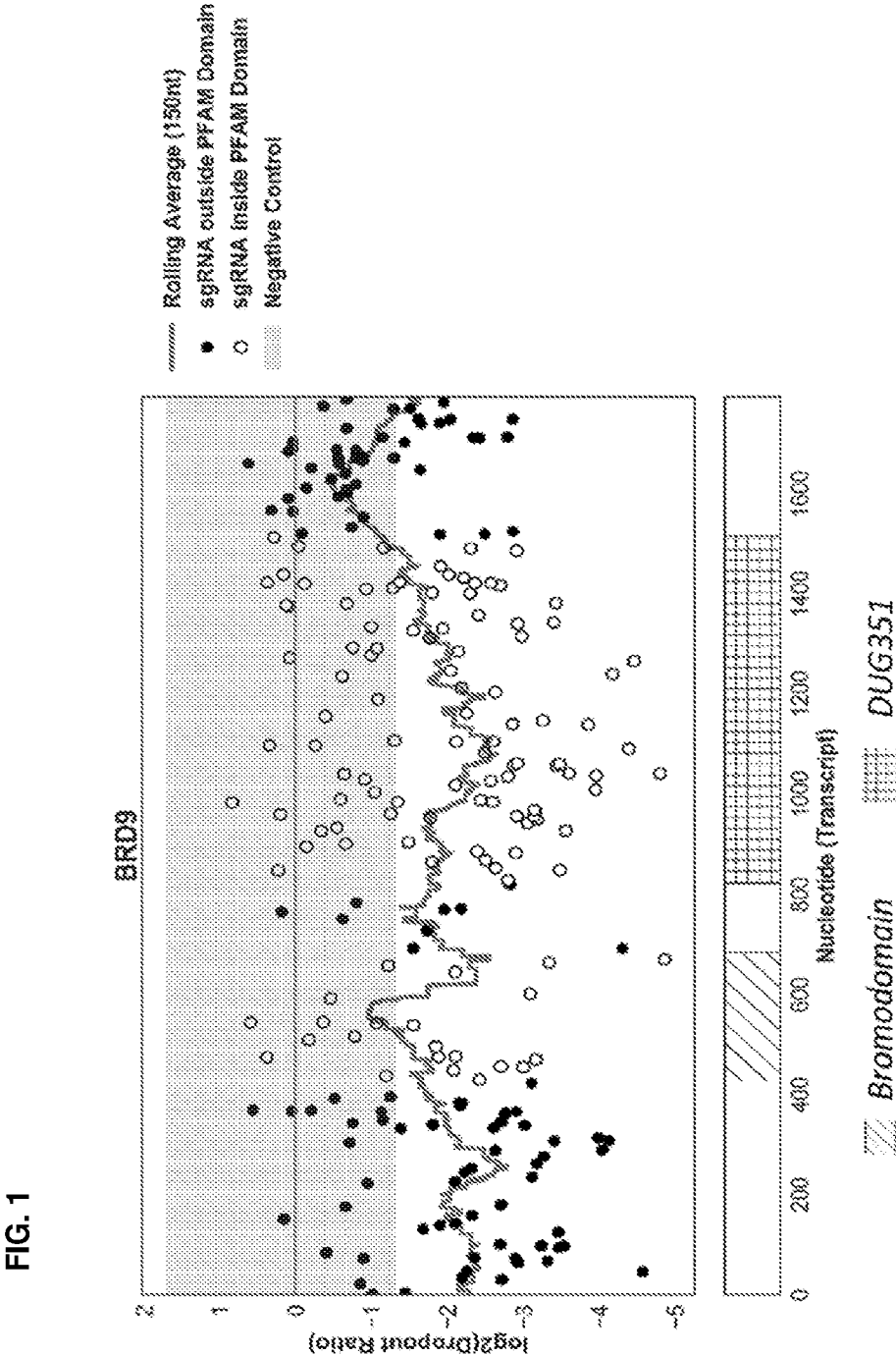


FIG. 2

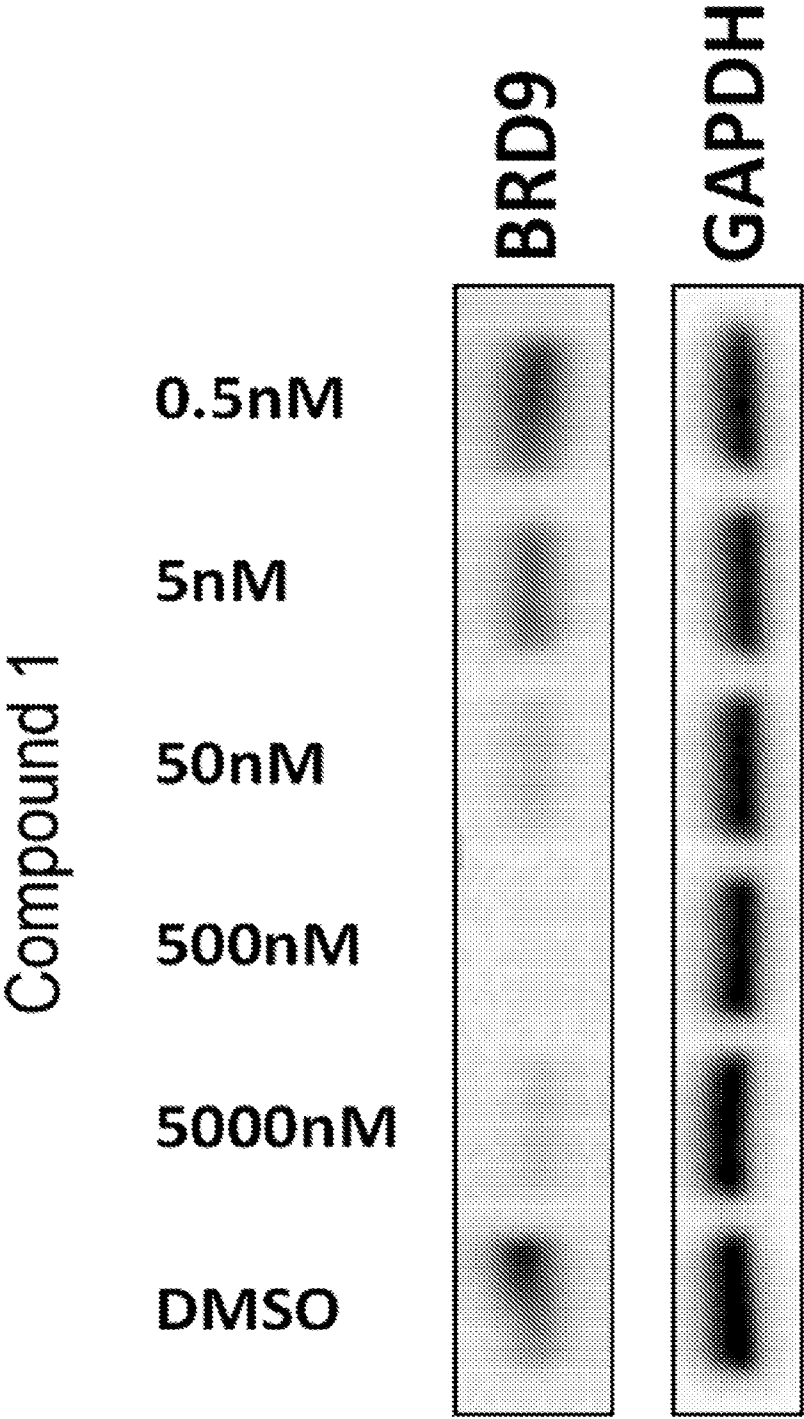
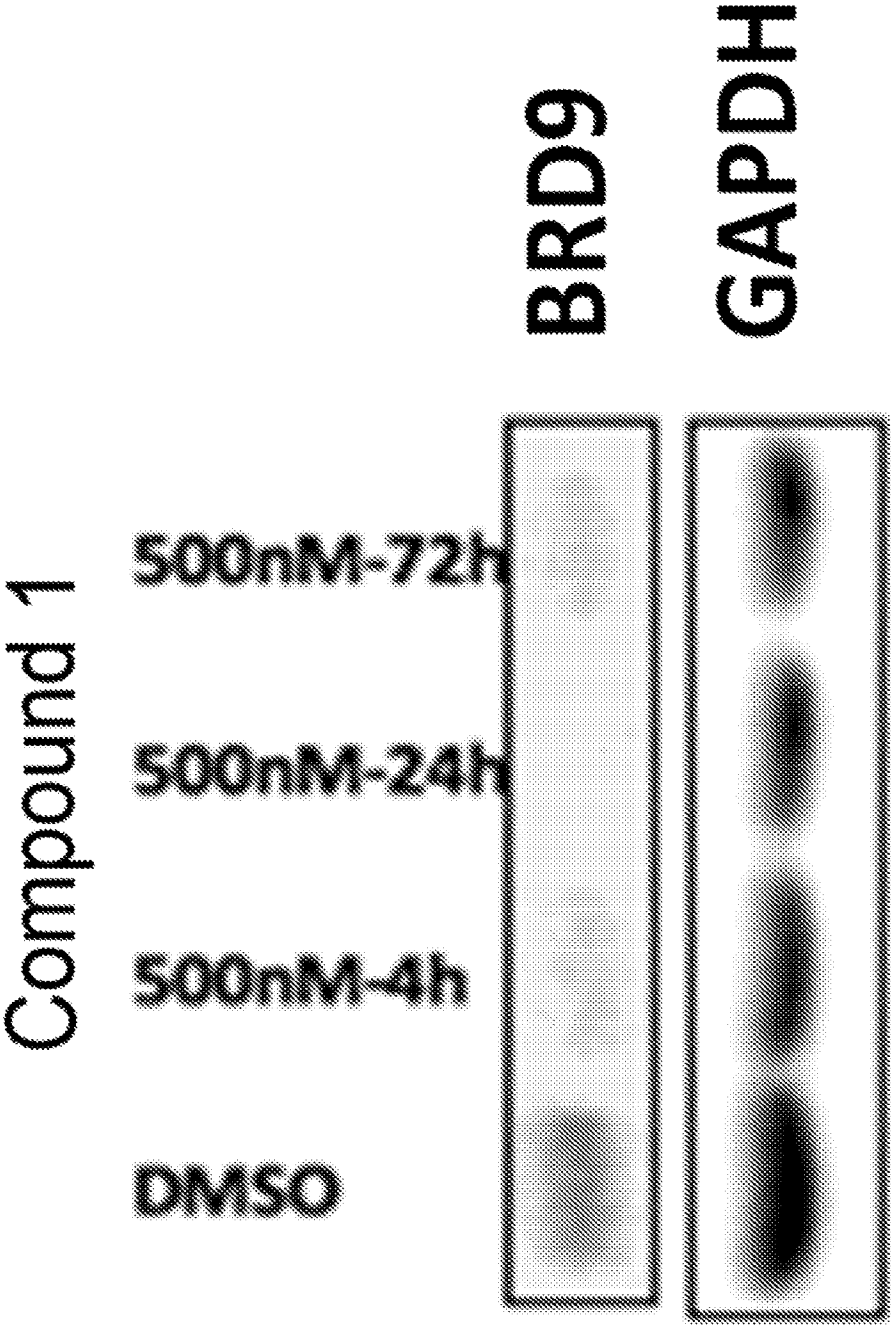
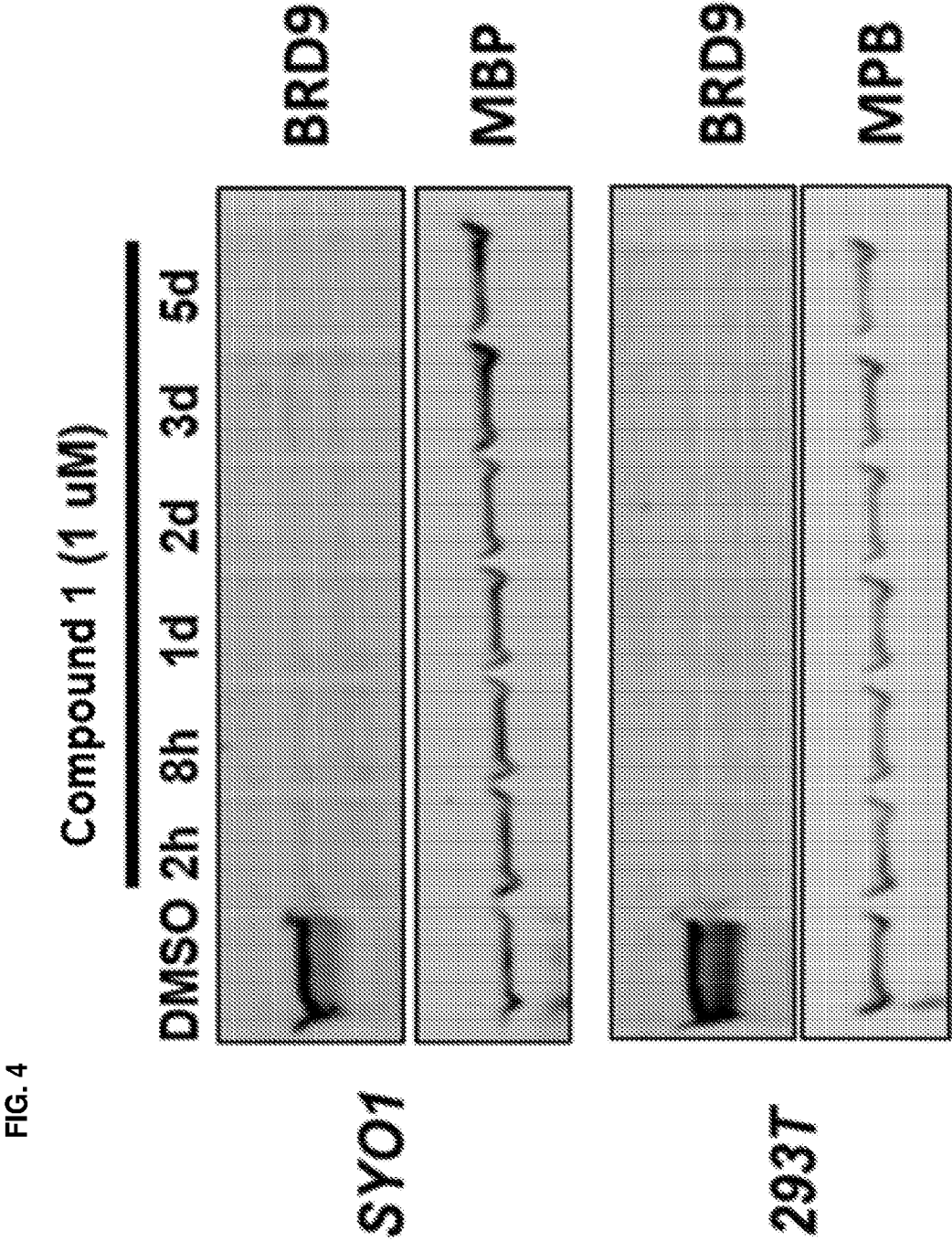


FIG. 3





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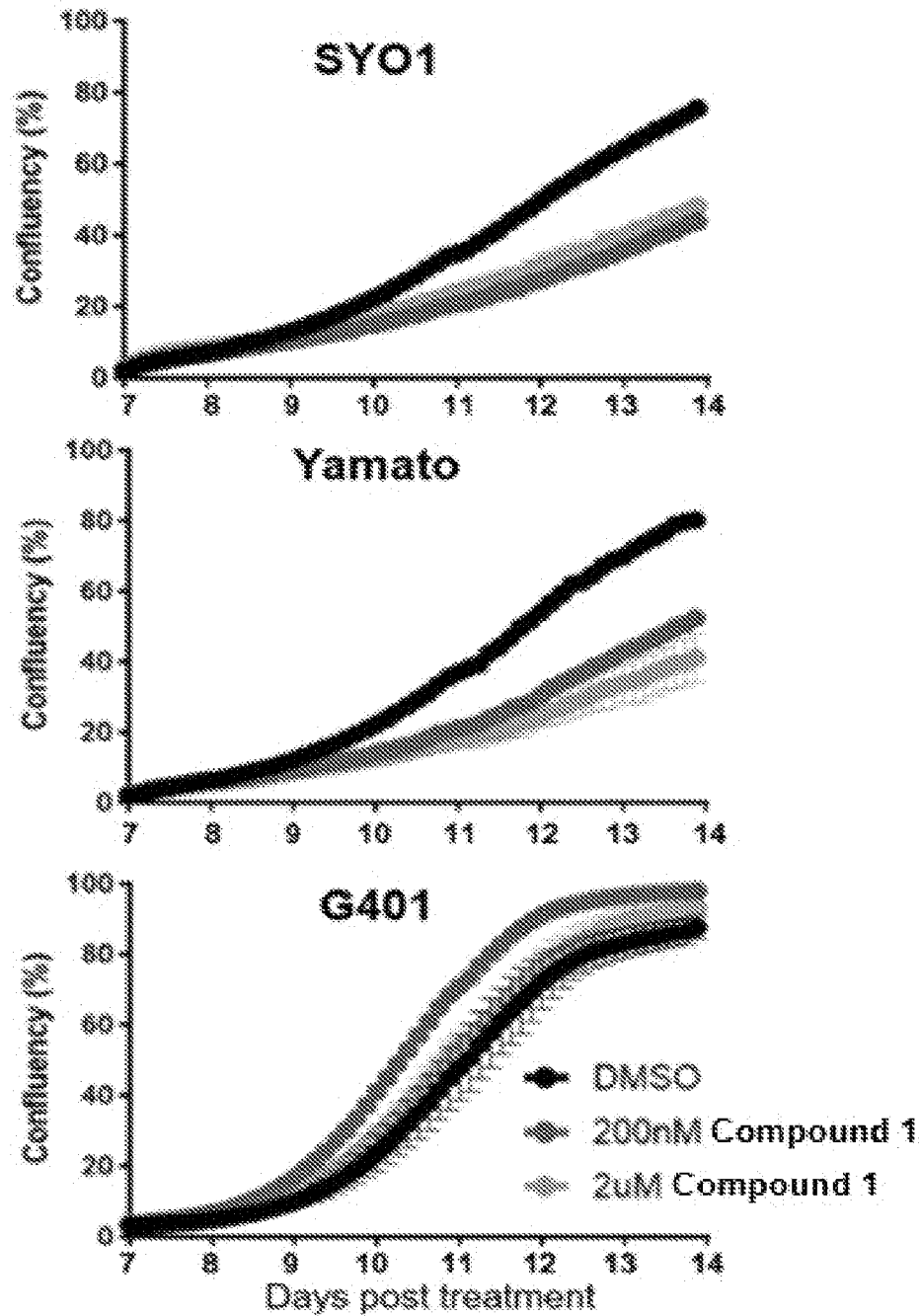


FIG. 5

FIG. 6

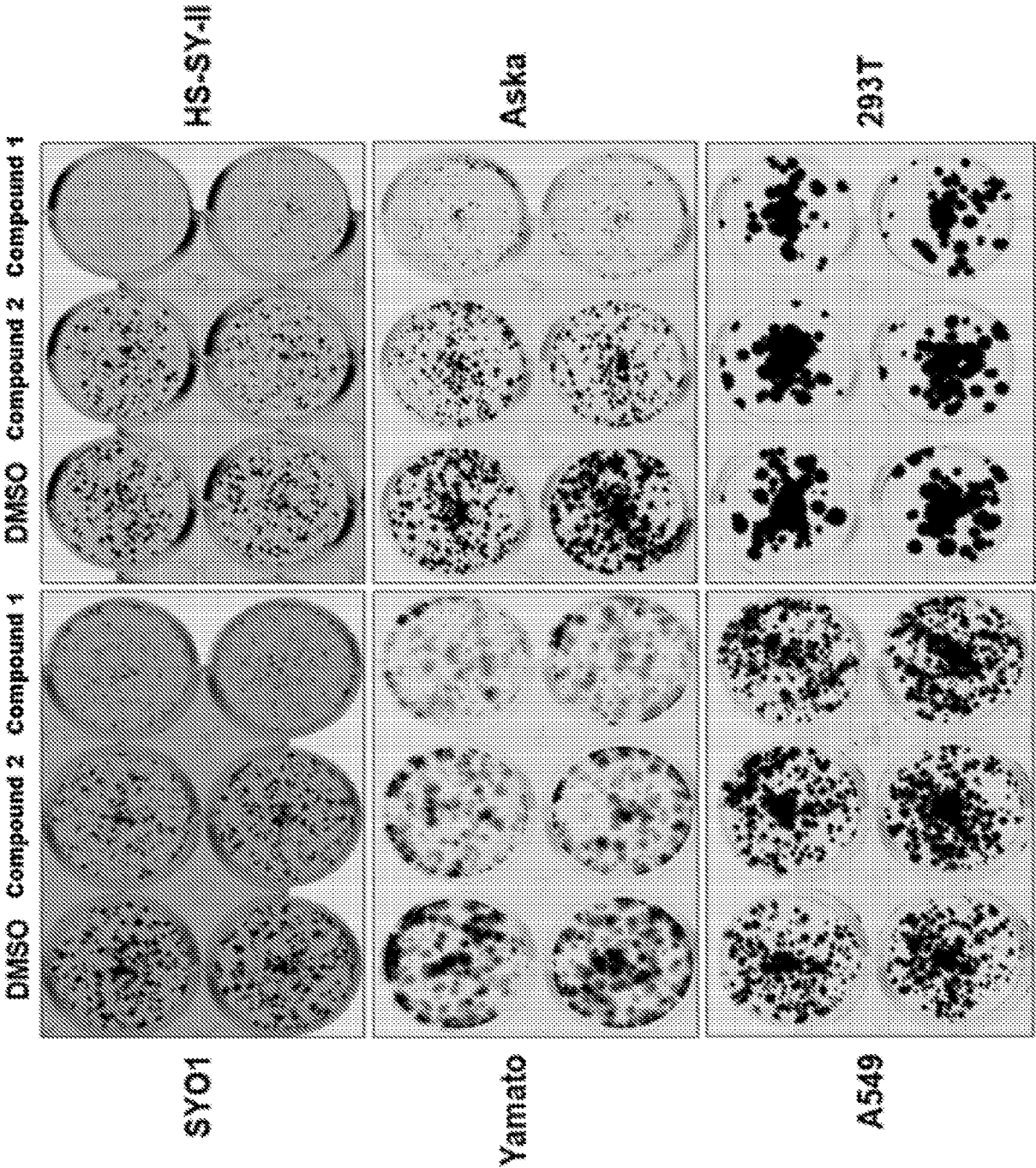
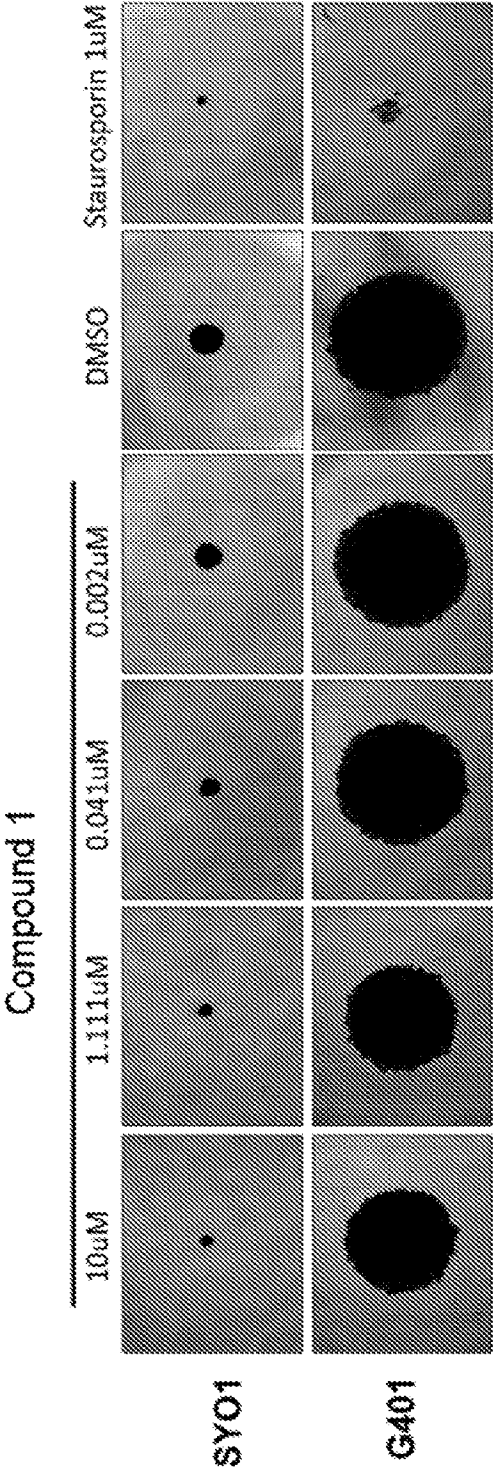


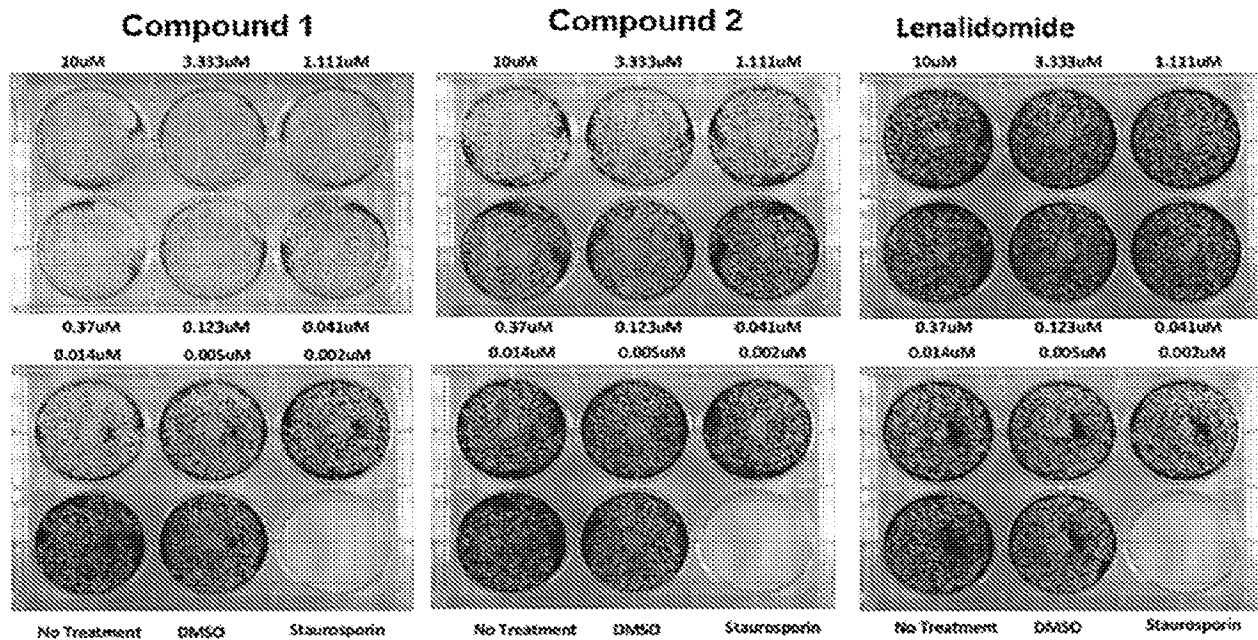
FIG. 7



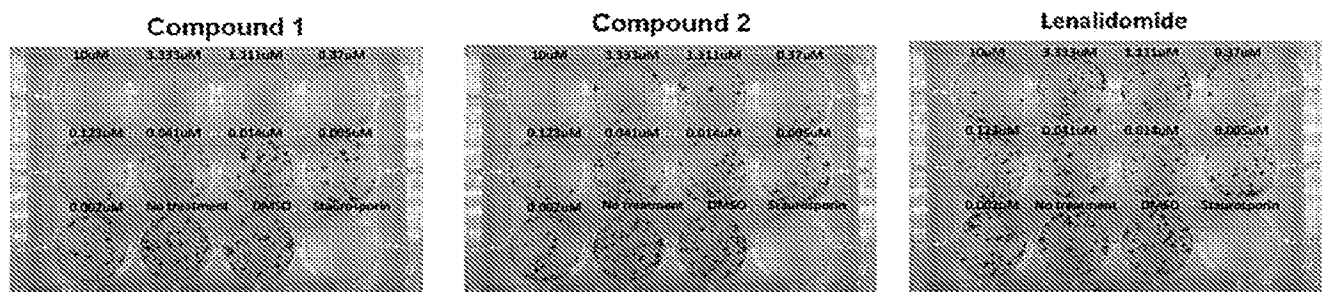
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FIG. 8

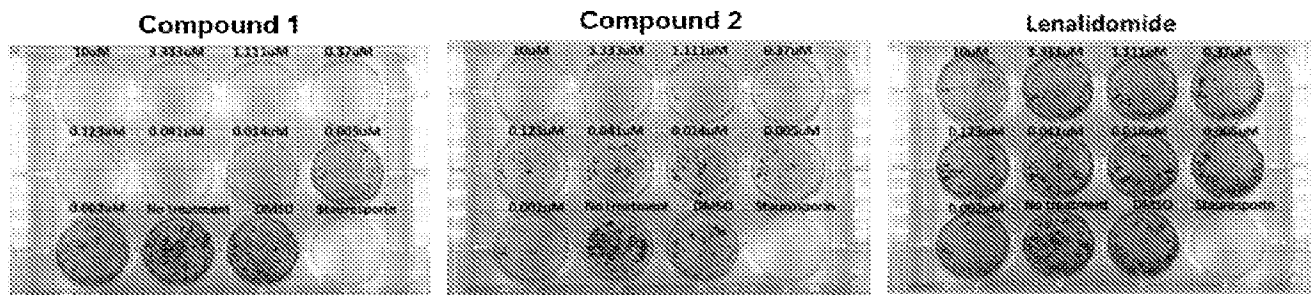
SYO1



HS-SY-II



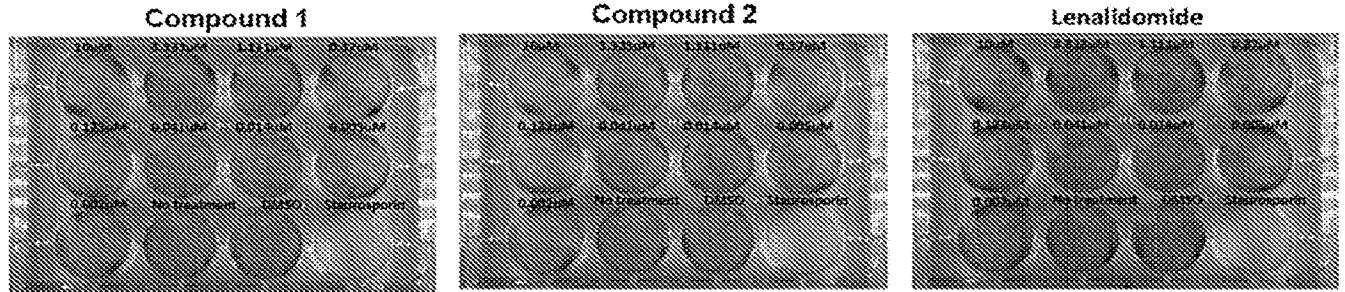
ASKA



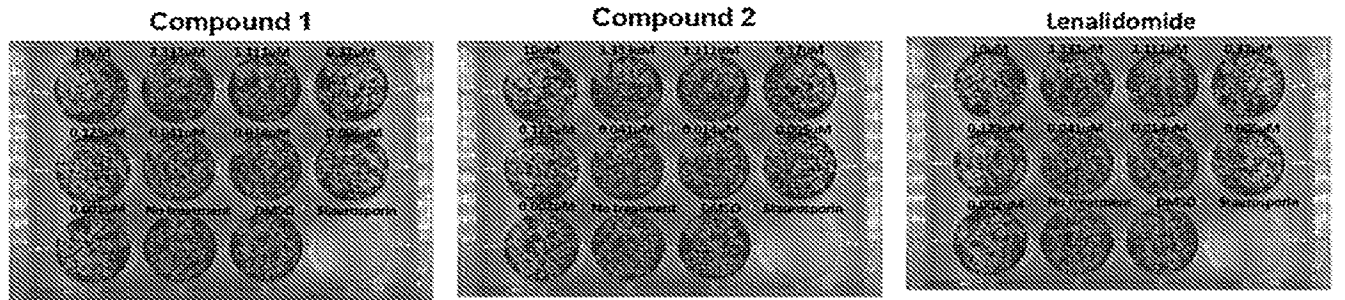
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FIG. 9

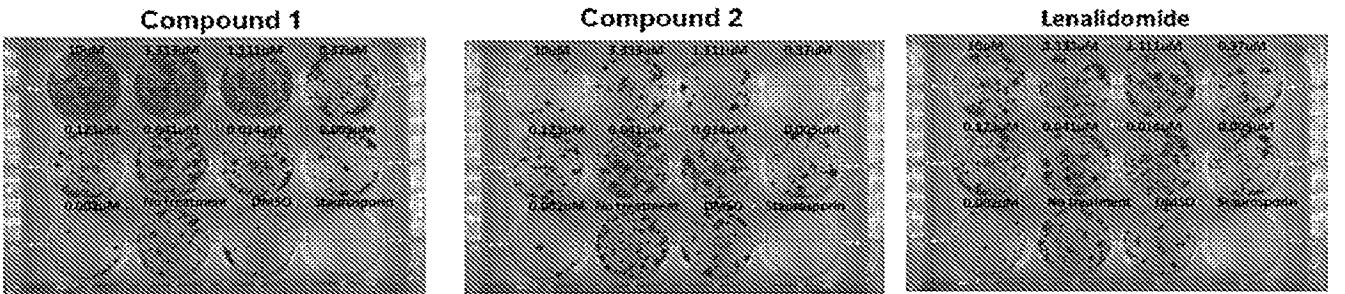
RD



HCT116



Calu6



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FIG. 10

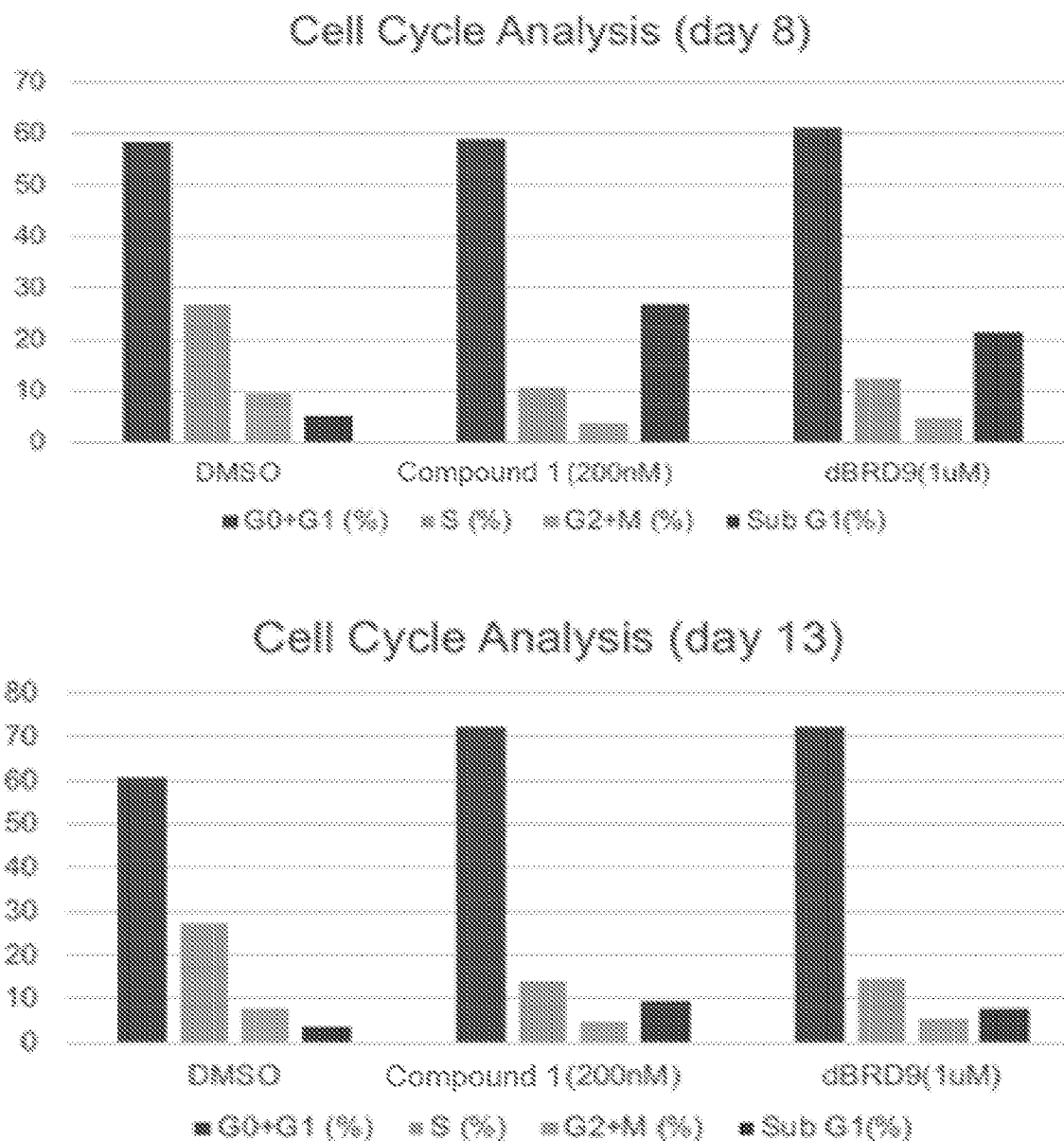


FIG. 11

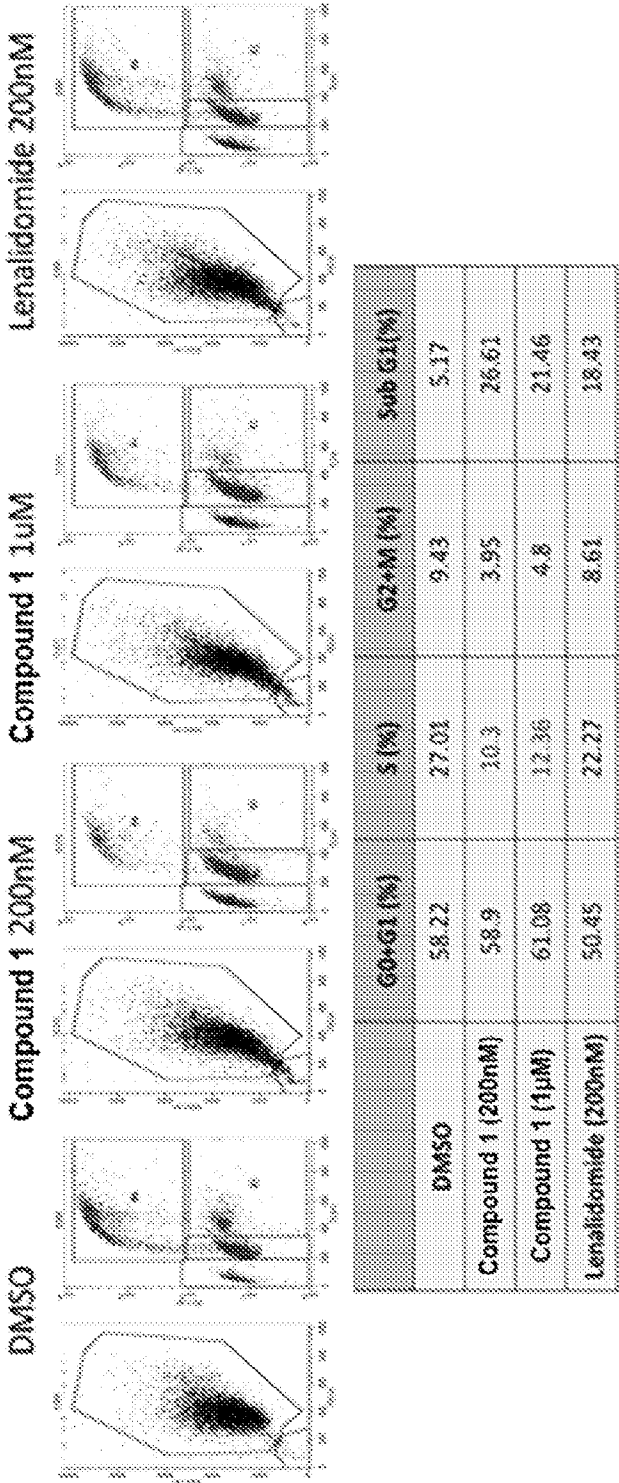
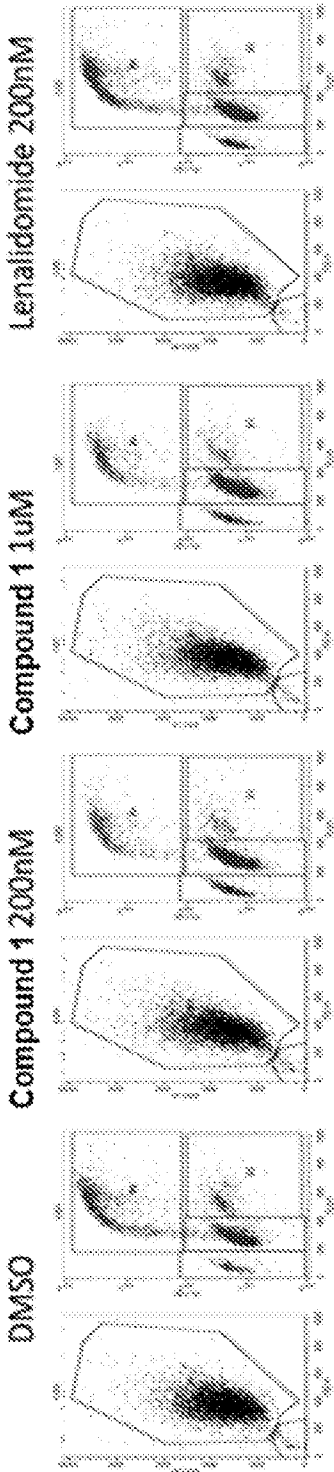
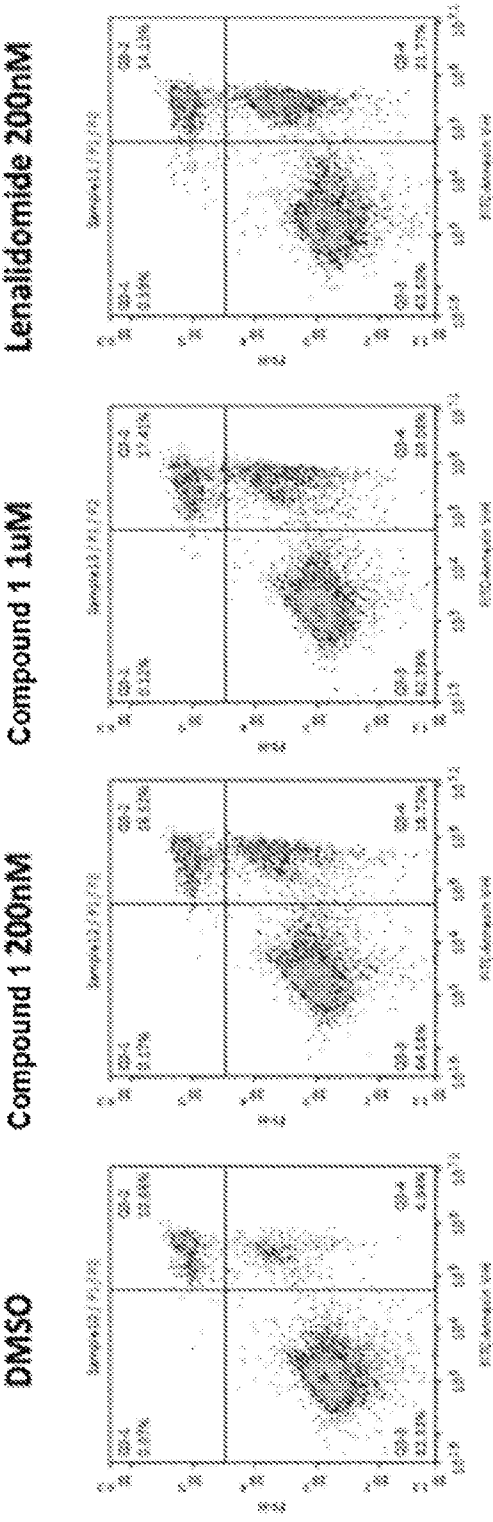


FIG. 12



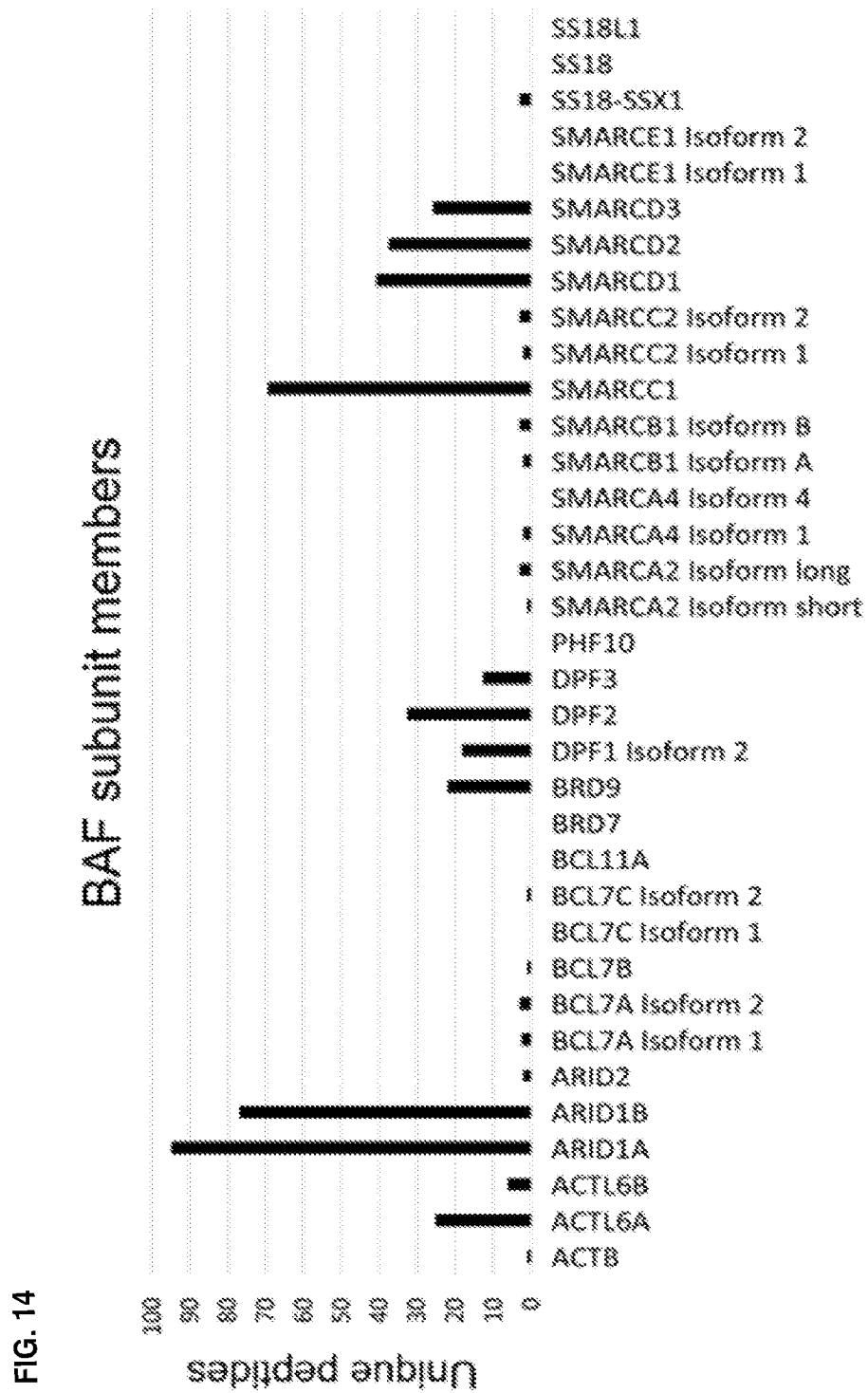
	G0+G1 (%)	S (%)	G2+M (%)	Sub G1 (%)
DMSO	60.83	27.29	7.53	3.88
Compound 1 (200nM)	71.9	14.06	4.76	9.1
Compound 1 (1uM)	72.21	14.53	5.08	7.91
Lenalidomide(200nM)	58.67	27.28	6.71	7.11

FIG. 13



	DMSO	Compound 1 (200nM)	Compound 1 (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

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Abstract

The present invention relates to compositions and methods for the treatment of BAF-related disorders, such as cancers and viral infections.