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United States Patent and Trademark Office

June 10, 2020

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APPLICATION NUMBER: 62/854,597

FILING DATE: *May 30, 2019*

RELATED PCT APPLICATION NUMBER: *PCT/US20/34746*

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS *US62/854,597*



Certified by

Anders Ivarsson

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	ALIG.026PR
		Application Number	
Title of Invention	TRICYCLIC COMPOUNDS		
The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76. This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.			

Secrecy Order 37 CFR 5.2:

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

Inventor	1				Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Sandrine		Vendeville		
Residence Information (Select One) US Residency • Non US Residency Active US Military Service					
City	Brussels		Country of Residence ⁱ	BE	
Mailing Address of Inventor:					
Address 1	1 Corporate Drive				
Address 2	2nd Floor				
City	South San Francisco		State/Province	CA	
Postal Code	94080		Country ⁱ	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.			
Customer Number	20995		
Email Address	efiling@knobbe.com	Add Email	Remove Email

Application Information:

Title of the Invention	TRICYCLIC COMPOUNDS		
Attorney Docket Number	ALIG.026PR	Small Entity Status Claimed	☒
Application Type	Provisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		Suggested Figure for Publication (if any)	

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	ALIG.026PR
		Application Number	
Title of Invention	TRICYCLIC COMPOUNDS		

Filing By Reference:

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

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

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

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

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

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	☒ Customer Number	☐ US Patent Practitioner	☐ Limited Recognition (37 CFR 11.9)
Customer Number	20995		

Domestic Benefit/National Stage Information:

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

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

Prior Application Status		Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button. Add			

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	ALIG.026PR
		Application Number	
Title of Invention	TRICYCLIC COMPOUNDS		

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.

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

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013. NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	ALIG.026PR
		Application Number	
Title of Invention	TRICYCLIC COMPOUNDS		

Authorization or Opt-Out of Authorization to Permit Access:

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

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

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

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

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

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

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

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

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

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

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

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

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	ALIG.026PR
		Application Number	
Title of Invention	TRICYCLIC COMPOUNDS		

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
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If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

[Clear](#)

☒ Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.		Person who shows sufficient proprietary interest

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	ALIGOS THERAPEUTICS, INC.		
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Mailing Address Information For Applicant:

Address 1	1 Corporate Drive		
Address 2	2nd Floor		
City	South San Francisco	State/Province	CA
Country	US	Postal Code	94080
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.

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	ALIG.026PR
		Application Number	
Title of Invention	TRICYCLIC COMPOUNDS		

Assignee	1
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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.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	Given Name	Middle Name	Family Name	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1				
Address 2				
City		State/Province		
Country i		Postal Code		
Phone Number		Fax Number		
Email Address				

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

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Signature:

Remove

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	/Kimberly J. Miller/		Date (YYYY-MM-DD)	2019-05-30
First Name	Kimberly J.	Last Name	Miller	Registration Number
				61749

Additional Signature may be generated within this form by selecting the Add button.

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	ALIG.026PR
		Application Number	
Title of Invention	TRICYCLIC COMPOUNDS		

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.

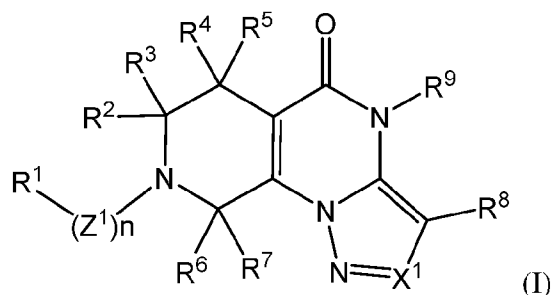
ABSTRACT OF THE DISCLOSURE

Provided herein are compounds of Formula (I), or pharmaceutically acceptable salts thereof, pharmaceutical compositions that include a compound described herein (including pharmaceutically acceptable salts of a compound described herein) and methods of synthesizing the same. Also provided herein are methods of treating diseases and/or conditions with a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

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WHAT IS CLAIMED IS:

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



wherein:

n is 0 or 1;

Z¹ is -C(=O)-, -NH-C(=O)- or -O-C(=O)-;

R¹ is selected from the group consisting of an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted aryl(C₁₋₄ alkyl), an optionally substituted heteroaryl(C₁₋₄ alkyl) and an optionally substituted heterocyclyl(C₁₋₄ alkyl);

R² and R³ are independently selected from the group consisting of hydrogen, an unsubstituted C₁₋₄ alkyl, an unsubstituted C₁₋₄ haloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted aryl(C₁₋₄ alkyl), an optionally substituted heteroaryl(C₁₋₄ alkyl) and an optionally substituted heterocyclyl(C₁₋₄ alkyl);

R⁴ and R⁵ are independently selected from the group consisting of hydrogen, an unsubstituted C₁₋₄ alkyl, an unsubstituted C₁₋₄ haloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted aryl(C₁₋₄ alkyl), an optionally substituted heteroaryl(C₁₋₄ alkyl) and an optionally substituted heterocyclyl(C₁₋₄ alkyl);

R⁶ and R⁷ are independently selected from the group consisting of hydrogen, an unsubstituted C₁₋₄ alkyl and an unsubstituted C₁₋₄ haloalkyl;

R⁸ is selected from the group consisting of hydrogen, an unsubstituted C₁₋₄ alkyl, an unsubstituted C₁₋₄ haloalkyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally

substituted heterocyclyl, an optionally substituted cycloalkyl(C₁₋₄ alkyl), an optionally substituted cycloalkenyl(C₁₋₄ alkyl), an optionally substituted aryl(C₁₋₄ alkyl), an optionally substituted heteroaryl(C₁₋₄ alkyl), an optionally substituted heterocyclyl(C₁₋₄ alkyl), $-NR^{10}R^{11}$ and $-C(=O)NR^{12}R^{13}$;

R^9 is selected from the group consisting of hydrogen, an unsubstituted C₁₋₄ alkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted aryl(C₁₋₄ alkyl), an optionally substituted heteroaryl(C₁₋₄ alkyl) and an optionally substituted heterocyclyl(C₁₋₄ alkyl);

R^{10} and R^{12} are independently hydrogen or an unsubstituted C₁₋₄ alkyl;

R^{11} and R^{13} are independently selected from the group consisting of hydrogen, an unsubstituted C₁₋₄ alkyl, an unsubstituted C₁₋₄ haloalkyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted cycloalkyl(C₁₋₄ alkyl), an optionally substituted cycloalkenyl(C₁₋₄ alkyl), an optionally substituted aryl(C₁₋₄ alkyl), an optionally substituted heteroaryl(C₁₋₄ alkyl) and an optionally substituted heterocyclyl(C₁₋₄ alkyl); or

R^{10} and R^{11} are taken together along with the nitrogen to which R^{10} and R^{11} are attached to form an optionally substituted 4- to 8-membered monocyclic heterocyclyl, an optionally substituted 8- to 13-membered fused-bicyclic heterocyclyl or an optionally substituted 7- to 13-membered spiro-bicyclic heterocyclyl;

R^{12} and R^{13} are taken together along with the nitrogen to which R^{12} and R^{13} are attached to form an optionally substituted 4- to 8-membered monocyclic heterocyclyl, an optionally substituted 8- to 13-membered fused-bicyclic heterocyclyl or an optionally substituted 7- to 13-membered spiro-bicyclic heterocyclyl;

R^2 and R^3 are taken together along with the carbon to which R^2 and R^3 are attached to form an optionally substituted monocyclic C₃₋₆ cycloalkyl or an optionally substituted 3 to 6 member monocyclic heterocyclyl; or

R^4 and R^5 are taken together along with the carbon to which R^4 and R^5 are attached to form an optionally substituted monocyclic C₃₋₆ cycloalkyl or an optionally substituted 3 to 6 member monocyclic heterocyclyl; or

R² and R⁴ are taken together along with the carbons to which R² and R⁴ are each attached to form an optionally monocyclic C₅₋₇ cycloalkyl or an optionally substituted 5 to 7 member monocyclic heterocyclyl; or

R³ and R⁵ are taken together along with the carbons to which R³ and R⁵ are each attached to form an optionally monocyclic C₅₋₇ cycloalkyl or an optionally substituted 5 to 7 member monocyclic heterocyclyl; or

R⁶ and R⁷ are taken together along with the carbon to which R⁶ and R⁷ are attached to form an optionally substituted monocyclic C₃₋₄ cycloalkyl, an optionally substituted oxetane or an optionally substituted thietane; and

X¹ is N or CR¹⁴, wherein R¹⁴ is hydrogen, cyano, an unsubstituted C₁₋₄ alkyl, a substituted C₁₋₄ alkyl or an optionally substituted aryl(C₁₋₄ alkyl), wherein the substituted C₁₋₄ alkyl is substituted one or more times with a substituents selected from the group consisting of cyano, halogen, hydroxy and an unsubstituted C₁₋₄ alkoxy.

2. The compound of Claim 1, wherein n is 1.
3. The compound of Claim 2, wherein Z¹ is -C(=O)-.
4. The compound of Claim 2, wherein Z¹ is -NH-C(=O)-.
5. The compound of Claim 2, wherein Z¹ is -O-C(=O)-.
6. The compound of Claim 1, wherein n is 0.
7. The compound of any one of Claims 1-6, wherein R¹ is an optionally substituted aryl.
8. The compound of Claim 7, wherein R¹ is an optionally substituted phenyl.
9. The compound of any one of Claims 1-6, wherein R¹ is an optionally substituted heteroaryl.
10. The compound of Claim 9, wherein R¹ is an optionally substituted monocyclic heteroaryl.
11. The compound of Claim 9, wherein R¹ is an optionally substituted bicyclic heteroaryl.
12. The compound of any one of Claims 1-6, wherein R¹ is an optionally substituted heterocyclyl.

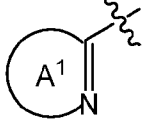
13. The compound of Claim 12, wherein R^1 is an optionally substituted monocyclic heterocyclyl.

14. The compound of Claim 12, wherein R^1 is an optionally substituted bicyclic heterocyclyl.

15. The compound of any one of Claims 1-6, wherein R^1 is an optionally substituted aryl(C_{1-4} alkyl).

16. The compound of any one of Claims 1-6, wherein R^1 is an optionally substituted heteroaryl(C_{1-4} alkyl).

17. The compound of any one of Claims 1-6, wherein R^1 is an optionally substituted heterocyclyl(C_{1-4} alkyl).

18. The compound of Claim 1, wherein n is 0; and R^1 is , wherein Ring A^1 is an optionally substituted bicyclic heteroaryl or an optionally substituted bicyclic heterocyclyl.

19. The compound of any one of Claims 1-18, wherein R^1 is substituted with one or more substituents independently selected from the group consisting of deuterium, halogen, cyano, an unsubstituted C_{1-6} alkyl, an unsubstituted C_{1-6} haloalkyl, an unsubstituted C_{1-6} alkoxy, an unsubstituted acyl, an unsubstituted C-amido, an unsubstituted sulfonyl, an unsubstituted amino, a mono-substituted amine and a di-substituted amine.

20. The compound of Claim 19, wherein Ring A^1 is an optionally substituted bicyclic heteroaryl.

21. The compound of Claim 20, wherein Ring A^1 is an optionally substituted nitrogen-containing bicyclic heteroaryl.

22. The compound of Claim 21, wherein Ring A^1 is an optionally substituted nitrogen-containing, 9-membered bicyclic heteroaryl.

23. The compound of Claim 21, wherein Ring A^1 is an optionally substituted nitrogen-containing, 10-membered bicyclic heteroaryl.

24. The compound of Claim 19, wherein Ring A^1 is an optionally substituted bicyclic heterocyclyl.

25. The compound of Claim 24, wherein Ring A¹ is an optionally substituted nitrogen-containing bicyclic heterocyclyl.

26. The compound of Claim 25, wherein Ring A¹ is an optionally substituted nitrogen-containing, 9-membered bicyclic heterocyclyl.

27. The compound of Claim 25, wherein Ring A¹ is an optionally substituted nitrogen-containing, 10-membered bicyclic heterocyclyl.

28. The compound of any one of Claims 1-27, wherein R² is hydrogen.

29. The compound of any one of Claims 1-27, wherein R² is an unsubstituted C₁₋₄ alkyl.

30. The compound of any one of Claims 1-27, wherein R² is an unsubstituted C₁₋₄ haloalkyl.

31. The compound of any one of Claims 1-27, wherein R² is an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted heterocyclyl.

32. The compound of Claim 31, wherein R² is an optionally substituted phenyl, an optionally substituted monocyclic heteroaryl or an optionally substituted monocyclic heterocyclyl.

33. The compound of any one of Claims 1-27, wherein R² is an optionally substituted aryl(C₁₋₄ alkyl), an optionally substituted heteroaryl(C₁₋₄ alkyl) or an optionally substituted heterocyclyl(C₁₋₄ alkyl).

34. The compound of any one of Claims 1-33, wherein R³ is hydrogen.

35. The compound of any one of Claims 1-33, wherein R³ is an unsubstituted C₁₋₄ alkyl.

36. The compound of any one of Claims 1-33, wherein R³ is an unsubstituted C₁₋₄ haloalkyl.

37. The compound of any one of Claims 1-33, wherein R³ is an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted heterocyclyl.

38. The compound of Claim 37, wherein R³ is an optionally substituted phenyl, an optionally substituted monocyclic heteroaryl or an optionally substituted monocyclic heterocyclyl.

39. The compound of any one of Claims 1-33, wherein R^3 is an optionally substituted aryl(C_{1-4} alkyl), an optionally substituted heteroaryl(C_{1-4} alkyl) or an optionally substituted heterocyclyl(C_{1-4} alkyl).

40. The compound of any one of Claims 1-27, wherein R^2 and R^3 are taken together along with the carbon to which R^2 and R^3 are attached to form an optionally substituted monocyclic C_{3-6} cycloalkyl or an optionally substituted 3 to 6 member monocyclic heterocyclyl.

41. The compound of any one of Claims 1-40, wherein R^4 is hydrogen.

42. The compound of any one of Claims 1-40, wherein R^4 is an unsubstituted C_{1-4} alkyl.

43. The compound of any one of Claims 1-40, wherein R^4 is an unsubstituted C_{1-4} haloalkyl.

44. The compound of any one of Claims 1-40, wherein R^4 is an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted heterocyclyl.

45. The compound of Claim 44, wherein R^4 is an optionally substituted phenyl, an optionally substituted monocyclic heteroaryl or an optionally substituted monocyclic heterocyclyl.

46. The compound of any one of Claims 1-40, wherein R^4 is an optionally substituted aryl(C_{1-4} alkyl), an optionally substituted heteroaryl(C_{1-4} alkyl) or an optionally substituted heterocyclyl(C_{1-4} alkyl).

47. The compound of any one of Claims 1-46, wherein R^5 is hydrogen.

48. The compound of any one of Claims 1-46, wherein R^5 is an unsubstituted C_{1-4} alkyl.

49. The compound of any one of Claims 1-46, wherein R^5 is an unsubstituted C_{1-4} haloalkyl.

50. The compound of any one of Claims 1-46, wherein R^5 is an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted heterocyclyl.

51. The compound of Claim 50, wherein R^5 is an optionally substituted phenyl, an optionally substituted monocyclic heteroaryl or an optionally substituted monocyclic heterocyclyl.

52. The compound of any one of Claims 1-46, wherein R^5 is an optionally substituted aryl(C_{1-4} alkyl), an optionally substituted heteroaryl(C_{1-4} alkyl) or an optionally substituted heterocyclyl(C_{1-4} alkyl).

53. The compound of any one of Claims 1-40, wherein R^4 and R^5 are taken together along with the carbon to which R^4 and R^5 are attached to form an optionally substituted monocyclic C_{3-6} cycloalkyl or an optionally substituted 3 to 6 member monocyclic heterocyclyl.

54. The compound of any one of Claims 1-27, 34-39 or 47-52, wherein R^2 and R^4 are taken together along with the carbons to which R^2 and R^4 are each attached to form an optionally monocyclic C_{5-7} cycloalkyl or an optionally substituted 5 to 7 member monocyclic heterocyclyl.

55. The compound of any one of Claims 1-33 or 41-46, wherein R^3 and R^5 are taken together along with the carbons to which R^3 and R^5 are each attached to form an optionally monocyclic C_{5-7} cycloalkyl or an optionally substituted 5 to 7 member monocyclic heterocyclyl.

56. The compound of any one of Claims 1-55, wherein R^6 is hydrogen.

57. The compound of any one of Claims 1-55, wherein R^6 is an unsubstituted C_{1-4} alkyl.

58. The compound of any one of Claims 1-55, wherein R^6 is an unsubstituted C_{1-4} haloalkyl.

59. The compound of any one of Claims 1-58, wherein R^7 is hydrogen.

60. The compound of any one of Claims 1-58, wherein R^7 is an unsubstituted C_{1-4} alkyl.

61. The compound of any one of Claims 1-58, wherein R^7 is an unsubstituted C_{1-4} haloalkyl.

62. The compound of any one of Claims 1-55, wherein R^6 and R^7 are taken together along with the carbon to which R^6 and R^7 are attached to form an optionally substituted monocyclic C_{3-4} cycloalkyl.

63. The compound of any one of Claims 1-55, wherein R^6 and R^7 are taken together along with the carbon to which R^6 and R^7 are attached to form an optionally substituted octane or an optionally substituted thietane.
64. The compound of any one of Claims 1-63, wherein X^1 is N.
65. The compound of any one of Claims 1-63, wherein X^1 is CR^{14} .
66. The compound of Claim 65, wherein R^{14} is hydrogen.
67. The compound of Claim 65, wherein R^{14} is cyano.
68. The compound of Claim 65, wherein R^{14} is an unsubstituted C_{1-4} alkyl.
69. The compound of Claim 65, wherein R^{14} is a substituted C_{1-4} alkyl.
70. The compound of Claim 65, wherein R^{14} is an optionally substituted aryl(C_{1-4} alkyl).
71. The compound of any one of Claims 1-70, wherein R^8 is hydrogen.
72. The compound of any one of Claims 1-70, wherein R^8 is an unsubstituted C_{1-4} alkyl.
73. The compound of any one of Claims 1-70, wherein R^8 is an unsubstituted C_{1-4} haloalkyl.
74. The compound of any one of Claims 1-70, wherein R^8 is an optionally substituted cycloalkyl or an optionally substituted cycloalkenyl.
75. The compound of any one of Claims 1-70, wherein R^8 is an optionally substituted aryl.
76. The compound of any one of Claims 1-70, wherein R^8 is an optionally substituted heteroaryl.
77. The compound of any one of Claims 1-70, wherein R^8 is an optionally substituted heterocyclyl.
78. The compound of any one of Claims 1-70, wherein R^8 is an optionally substituted cycloalkyl(C_{1-4} alkyl) or an optionally substituted cycloalkenyl(C_{1-4} alkyl).
79. The compound of any one of Claims 1-70, wherein R^8 is an optionally substituted aryl(C_{1-4} alkyl).
80. The compound of any one of Claims 1-70, wherein R^8 is an optionally substituted heteroaryl(C_{1-4} alkyl).

81. The compound of any one of Claims 1-70, wherein R^8 is an optionally substituted heterocyclyl(C_{1-4} alkyl),

82. The compound of any one of Claims 1-70, wherein R^8 is $-NR^{10}R^{11}$.

83. The compound of Claim 82, wherein R^{10} is hydrogen.

84. The compound of Claim 82, wherein R^{10} is an unsubstituted C_{1-4} alkyl.

85. The compound of any one of Claims 82-84, wherein R^{11} is hydrogen.

86. The compound of any one of Claims 82-84, wherein R^{11} is an unsubstituted C_{1-4} alkyl or an unsubstituted C_{1-4} haloalkyl.

87. The compound of any one of Claims 82-84, wherein R^{11} is an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted heterocyclyl.

88. The compound of any one of Claims 82-84, wherein R^{11} is an optionally substituted cycloalkyl(C_{1-4} alkyl), an optionally substituted cycloalkenyl(C_{1-4} alkyl), an optionally substituted aryl(C_{1-4} alkyl), an optionally substituted heteroaryl(C_{1-4} alkyl) or an optionally substituted heterocyclyl(C_{1-4} alkyl).

89. The compound of Claim 82, wherein R^{10} and R^{11} are taken together along with the nitrogen to which R^{10} and R^{11} are attached to form an optionally substituted 4- to 8-membered monocyclic heterocyclyl, an optionally substituted 8- to 13-membered fused-bicyclic heterocyclyl or an optionally substituted 7- to 13-membered spiro-bicyclic heterocyclyl.

90. The compound of any one of Claims 1-70, wherein R^8 is $-C(=O)NR^{12}R^{13}$.

91. The compound of Claim 90, wherein R^{12} is hydrogen.

92. The compound of Claim 90, wherein R^{12} is an unsubstituted C_{1-4} alkyl.

93. The compound of any one of Claims 90-92, wherein R^{13} is hydrogen.

94. The compound of any one of Claims 90-92, wherein R^{13} is an unsubstituted C_{1-4} alkyl or an unsubstituted C_{1-4} haloalkyl.

95. The compound of any one of Claims 90-92, wherein R^{13} is an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted heterocyclyl.

96. The compound of any one of Claims 90-92, wherein R¹³ is an optionally substituted cycloalkyl(C₁₋₄ alkyl), an optionally substituted cycloalkenyl(C₁₋₄ alkyl), an optionally substituted aryl(C₁₋₄ alkyl), an optionally substituted heteroaryl(C₁₋₄ alkyl) or an optionally substituted heterocyclyl(C₁₋₄ alkyl).

97. The compound of Claim 90, wherein R¹² and R¹³ are taken together along with the nitrogen to which R¹² and R¹³ are attached to form an optionally substituted 4- to 8-membered monocyclic heterocyclyl, an optionally substituted 8- to 13-membered fused-bicyclic heterocyclyl or an optionally substituted 7- to 13-membered spiro-bicyclic heterocyclyl;

98. The compound of any one of Claims 1-97, wherein R⁹ is hydrogen.

99. The compound of any one of Claims 1-97, wherein R⁹ is an unsubstituted C₁₋₄ alkyl.

100. The compound of any one of Claims 1-97, wherein R⁹ is an optionally substituted aryl.

101. The compound of Claim 100, wherein R⁹ is an unsubstituted phenyl or a substituted phenyl.

102. The compound of Claim 101, wherein R⁹ is a substituted phenyl, wherein the phenyl is substituted with one or more substituents selected from the group consisting of halogen, cyano, an unsubstituted C₁₋₄ alkoxy, an unsubstituted acyl, an unsubstituted C-amido, an unsubstituted sulfonyl and an unsubstituted S-sulfonamido.

103. The compound of any one of Claims 1-97, wherein R⁹ is an optionally substituted heteroaryl.

104. The compound of any one of Claims 1-97, wherein R⁹ is an optionally substituted heterocyclyl.

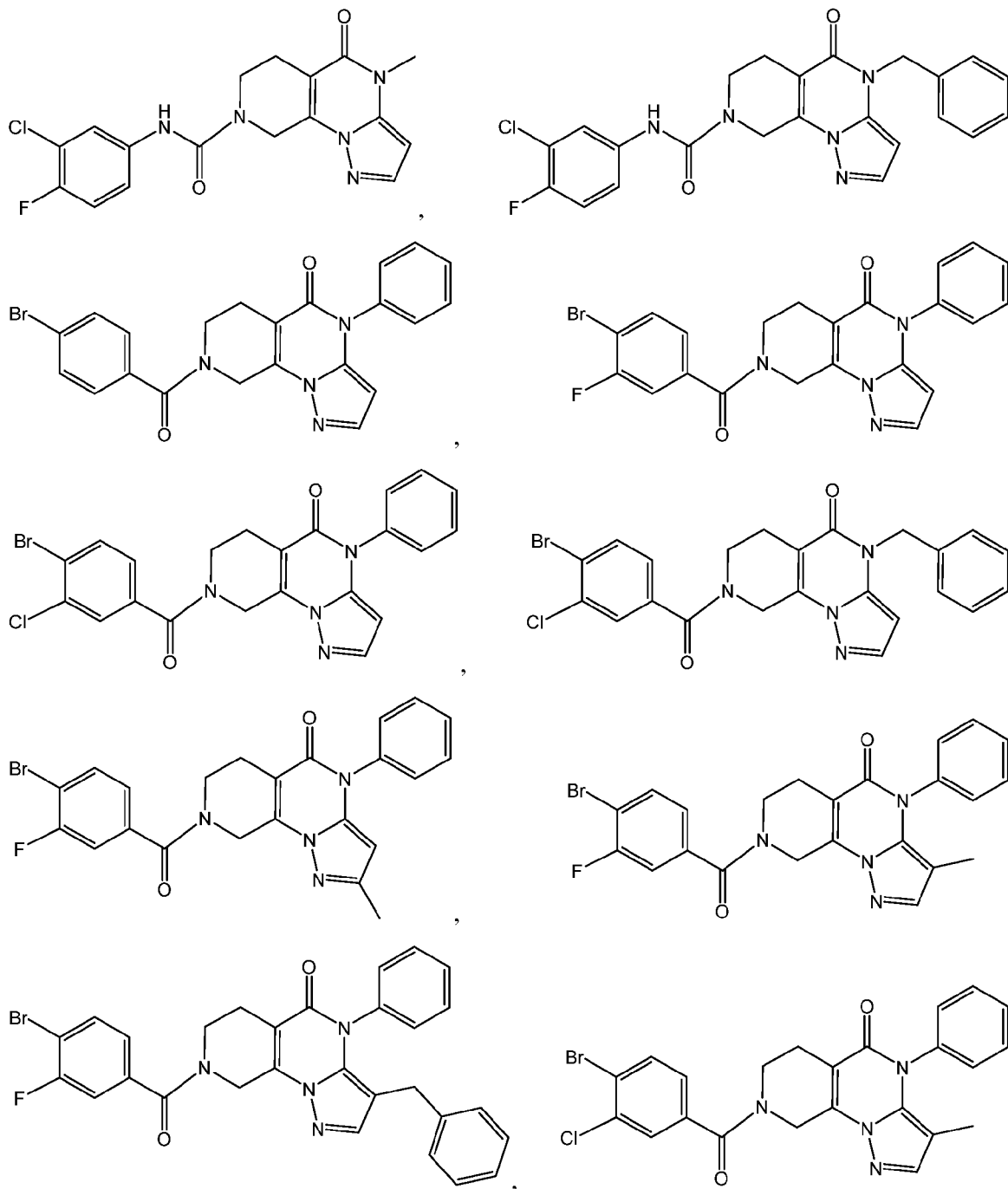
105. The compound of Claim 104, wherein R⁹ is an unsubstituted monocyclic heterocyclyl or a substituted monocyclic heterocyclyl.

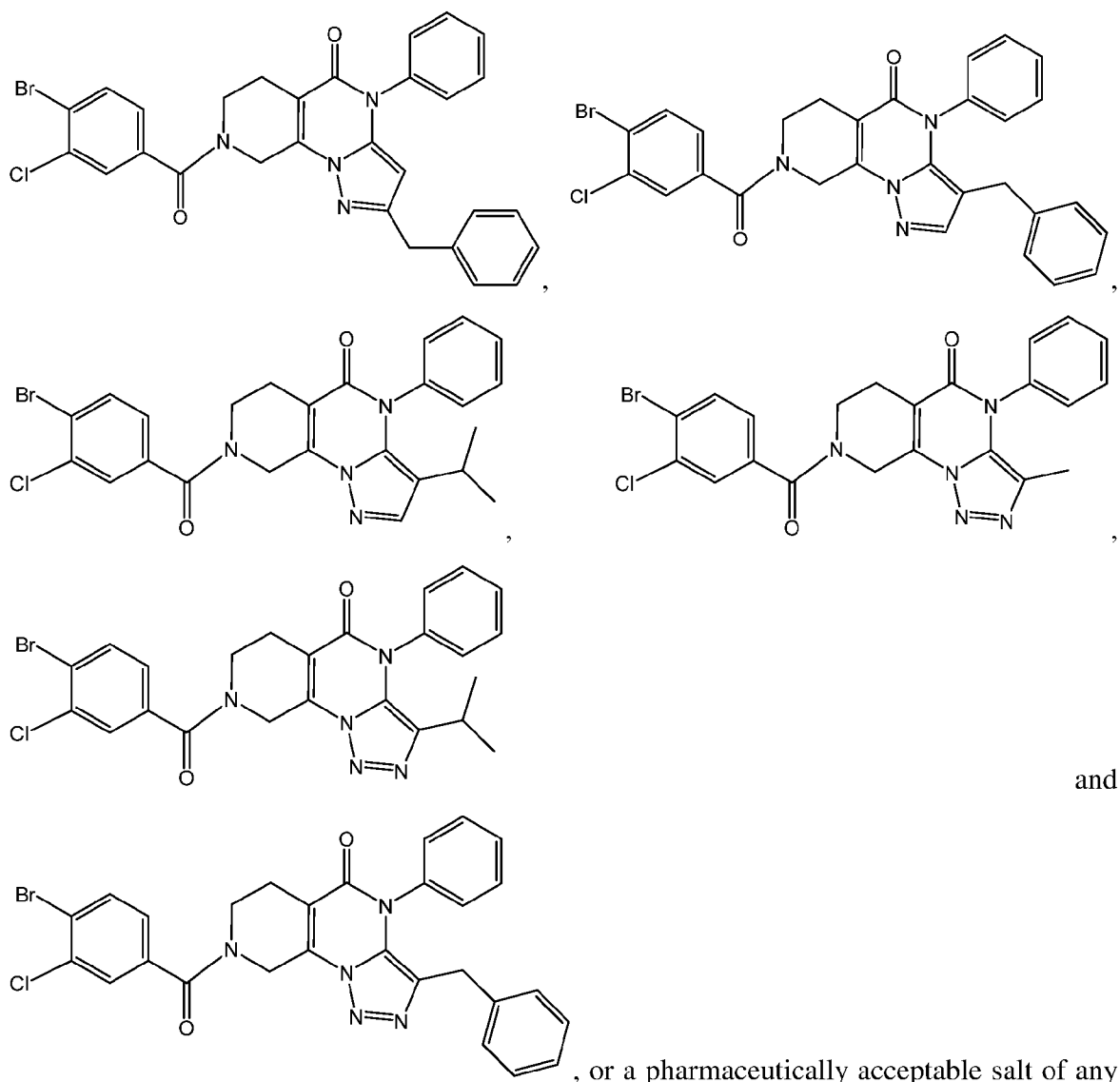
106. The compound of any one of Claims 1-97, wherein R⁹ is an optionally substituted aryl(C₁₋₄ alkyl).

107. The compound of any one of Claims 1-97, wherein R⁹ is an optionally substituted heteroaryl(C₁₋₄ alkyl).

108. The compound of any one of Claims 1-97, wherein R⁹ is an optionally substituted heterocyclyl(C₁₋₄ alkyl)

109. The compound of Claim 1, wherein the compound is selected from the group consisting of:





of the foregoing.

110. A pharmaceutical composition comprising an effective amount of a compound of any one of Claims 1-109, or a pharmaceutically acceptable salt thereof, and excipient.

111. Use of the compound of any one of Claims 1-109 in the preparation of a medicament for the treatment of hepatitis B.

112. Use of the compound of any one of Claims 1-109 in the preparation of a medicament for the treatment of hepatitis D.

113. The use of any one of Claims 111-112, wherein the use further comprises the use of an additional agent selected from the group consisting of an interferon, a nucleoside

analog, a nucleotide analog, a sequence specific oligonucleotide, a nucleic acid polymer, an entry inhibitor and a small molecule immunomodulator.

114. The use of Claim 113, wherein the additional agent selected from the group consisting of recombinant interferon alpha 2b, IFN- α , PEG-IFN- α -2a, lamivudine, telbivudine, adefovir dipivoxil, clevudine, entecavir, tenofovir alafenamide and tenofovir disoproxil.

TRICYCLIC COMPOUNDS**BACKGROUND**Field

[0001] The present application relates to the fields of chemistry, biochemistry and medicine. Disclosed herein are compounds of Formula (I), or pharmaceutically acceptable salt thereof, pharmaceutical compositions that include a compound described herein (including pharmaceutically acceptable salts of a compound described herein) and methods of synthesizing the same. Also disclosed herein are methods of treating diseases and/or conditions with a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

Description

[0002] The hepatitis B virus (HBV) is a DNA virus and a member of the *Hepadnaviridae* family. HBV infects more than 300 million worldwide, and is a causative agent of liver cancer and liver disease such as chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Although there are approved drugs for treating HBV, by either boosting the immune system or slowing down the replication of the HBV virus, HBV continues to be a problem due to the drawbacks associated with each of the approved drugs.

SUMMARY

[0003] Some embodiments disclosed herein relate to a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0004] Some embodiments disclosed herein relate to a pharmaceutical composition that can contain an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0005] Some embodiments described herein relate to a method of treating a HBV and/or HDV infection that can include administering to a subject identified as suffering from the HBV and/or HDV infection an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described

herein. Other embodiments described herein relate to a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the use of treating a HBV and/or HDV infection.

[0006] Some embodiments disclosed herein relate to a method of inhibiting replication of HBV and/or HDV that can include contacting a cell infected with the HBV and/or HDV with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the use of inhibiting the replication HBV and/or HDV.

[0007] These are other embodiments are described in greater detail below.

DETAILED DESCRIPTION

[0008] HBV is a partially double-stranded circular DNA of about 3.2 kilobase (kb) pairs, and is classified into eight genotypes, A to H. The HBV replication pathway has been studied in great detail. T.J. Liang, Hepatology (2009) 49(5 Suppl):S13-S21. On part of replication includes the formation of the covalently closed circular (cccDNA) form. The presence of the cccDNA gives rise to the risk of viral reemergence throughout the life of the host organism. HBV carriers can transmit the disease for many years. An estimated 300 million people are living with hepatitis B virus infection, and it is estimated that over 750,000 people worldwide die of hepatitis B each year. In addition, immunosuppressed individuals or individuals undergoing chemotherapy are especially at risk for reactivation of a HBV infection. HBV can be acute and/or chronic. Acute HBV infection can be either asymptomatic or present with symptomatic acute hepatitis.

[0009] HBV can be transmitted by blood, semen, and/or another body fluid. This can occur through direct blood-to-blood contact, unprotected sex, sharing of needles, and from an infected mother to her baby during the delivery process. The HBV surface antigen

(HBsAg) is most frequently used to screen for the presence of this infection. Currently available medications do not cure a HBV and/or HDV infection. Rather, the medications suppress replication of the virus.

[0010] The hepatitis D virus (HDV) is a DNA virus, also in the Hepadnaviridae family of viruses. HDV can propagate only in the presence of HBV. The routes of transmission of HDV are similar to those for HBV. Transmission of HDV can occur either via simultaneous infection with HBV (coinfection) or in addition to chronic hepatitis B or hepatitis B carrier state (superinfection). Both superinfection and coinfection with HDV results in more severe complications compared to infection with HBV alone. These complications include a greater likelihood of experiencing liver failure in acute infections and a rapid progression to liver cirrhosis, with an increased risk of developing liver cancer in chronic infections. In combination with hepatitis B, hepatitis D has the highest fatality rate of all the hepatitis infections, at 20%. There is currently no cure or vaccine for hepatitis D.

Definitions

[0011] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications referenced herein are incorporated by reference in their entirety unless stated otherwise. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0012] Whenever a group is described as being “optionally substituted” that group may be unsubstituted or substituted with one or more of the indicated substituents. Likewise, when a group is described as being “unsubstituted or substituted” if substituted, the substituent(s) may be selected from one or more of the indicated substituents. If no substituents are indicated, it is meant that the indicated “optionally substituted” or “substituted” group may be substituted with one or more group(s) individually and independently selected from deuterium, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, nitro, azido, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy,

trihalomethanesulfonyl, trihalomethanesulfonamido, an amino, a mono-substituted amino group and a di-substituted amino group.

[0013] As used herein, “C_a to C_b” in which “a” and “b” are integers refer to the number of carbon atoms in an alkyl, alkenyl or alkynyl group, or the number of carbon atoms in the ring of a cycloalkyl, cycloalkenyl, aryl, heteroaryl or heterocyclyl group. That is, the alkyl, alkenyl, alkynyl, ring of the cycloalkyl, ring of the cycloalkenyl, ring of the aryl, ring of the heteroaryl or ring of the heterocyclyl can contain from “a” to “b”, inclusive, carbon atoms. Thus, for example, a “C₁ to C₄ alkyl” group refers to all alkyl groups having from 1 to 4 carbons, that is, CH₃-, CH₃CH₂-, CH₃CH₂CH₂-, (CH₃)₂CH-, CH₃CH₂CH₂CH₂-, CH₃CH₂CH(CH₃)-, (CH₃)₂CHCH₂- and (CH₃)₃C-. If no “a” and “b” are designated with regard to an alkyl, alkenyl, alkynyl, cycloalkyl cycloalkenyl, aryl, heteroaryl or heterocyclyl group, the broadest range described in these definitions is to be assumed.

[0014] As used herein, “alkyl” refers to a straight or branched hydrocarbon chain that comprises a fully saturated (no double or triple bonds) hydrocarbon group. The alkyl group may have 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as “1 to 20” refers to each integer in the given range; *e.g.*, “1 to 20 carbon atoms” means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 20 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 10 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 6 carbon atoms. The alkyl group of the compounds may be designated as “C₁-C₄ alkyl” or similar designations. By way of example only, “C₁-C₄ alkyl” indicates that there are one to four carbon atoms in the alkyl chain, *i.e.*, the alkyl chain is selected from methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and t-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl and hexyl. The alkyl group may be substituted or unsubstituted.

[0015] As used herein, “alkenyl” refers to an alkyl group that contains in the straight or branched hydrocarbon chain one or more double bonds. The length of an alkenyl can vary. For example, the alkenyl can be a C₂₋₄ alkenyl, C₂₋₆ alkenyl or C₂₋₈ alkenyl.

Examples of alkenyl groups include allenyl, vinylmethyl and ethenyl. An alkenyl group may be unsubstituted or substituted.

[0016] As used herein, “alkynyl” refers to an alkyl group that contains in the straight or branched hydrocarbon chain one or more triple bonds. The length of an alkynyl can vary. For example, the alkynyl can be a C₂₋₄ alkynyl, C₂₋₆ alkynyl or C₂₋₈ alkynyl. Examples of alkynyls include ethynyl and propynyl. An alkynyl group may be unsubstituted or substituted.

[0017] As used herein, “cycloalkyl” refers to a completely saturated (no double or triple bonds) mono- or multi- cyclic hydrocarbon ring system. When composed of two or more rings, the rings may be joined together in a fused fashion. Cycloalkyl groups can contain 3 to 10 atoms in the ring(s). 3 to 8 atoms in the ring(s) or 3 to 6 atoms in the ring(s). A cycloalkyl group may be unsubstituted or substituted. Typical cycloalkyl groups include, but are in no way limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

[0018] As used herein, “cycloalkenyl” refers to a mono- or multi- cyclic hydrocarbon ring system that contains one or more double bonds in at least one ring; although, if there is more than one, the double bonds cannot form a fully delocalized pi-electron system throughout all the rings (otherwise the group would be “aryl,” as defined herein). When composed of two or more rings, the rings may be connected together in a fused fashion. A cycloalkenyl can contain 3 to 10 atoms in the ring(s) or 3 to 8 atoms in the ring(s). A cycloalkenyl group may be unsubstituted or substituted.

[0019] As used herein, “aryl” refers to a carbocyclic (all carbon) monocyclic or polycyclic aromatic ring system (including fused ring systems where two carbocyclic rings share a chemical bond) that has a fully delocalized pi-electron system throughout all the rings. The number of carbon atoms in an aryl group can vary. For example, the aryl group can be a C₆-C₁₄ aryl group, a C₆-C₁₀ aryl group, or a C₆ aryl group. Examples of aryl groups include, but are not limited to, benzene, naphthalene and azulene. An aryl group may be substituted or unsubstituted.

[0020] As used herein, “heteroaryl” refers to a monocyclic, bicyclic and tricyclic aromatic ring system (a ring system with fully delocalized pi-electron system) that contain(s)

one or more heteroatoms (for example, 1 to 5 heteroatoms), that is, an element other than carbon, including but not limited to, nitrogen, oxygen and sulfur. The number of atoms in the ring(s) of a heteroaryl group can vary. For example, the heteroaryl group can contain 4 to 14 atoms in the ring(s), 5 to 10 atoms in the ring(s) or 5 to 6 atoms in the ring(s). Furthermore, the term “heteroaryl” includes fused ring systems where two rings, such as at least one aryl ring and at least one heteroaryl ring, or at least two heteroaryl rings, share at least one chemical bond. Examples of heteroaryl rings include, but are not limited to, furan, furazan, thiophene, benzothiophene, phthalazine, pyrrole, oxazole, benzoxazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, thiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, benzothiazole, imidazole, benzimidazole, indole, indazole, pyrazole, benzopyrazole, isoxazole, benzoisoxazole, isothiazole, triazole, benzotriazole, thiadiazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, purine, pteridine, quinoline, isoquinoline, quinazoline, quinoxaline, cinnoline and triazine. A heteroaryl group may be substituted or unsubstituted.

[0021] As used herein, “heterocyclyl” refers to a monocyclic, bicyclic and tricyclic ring system wherein carbon atoms together with from 1 to 5 heteroatoms constitute said ring system. A heterocycle may optionally contain one or more unsaturated bonds situated in such a way, however, that a fully delocalized pi-electron system does not occur throughout all the rings. The number of atoms in the ring(s) of a heterocyclyl group can vary. For example, the heterocyclyl group can contain 4 to 14 atoms in the ring(s), 5 to 10 atoms in the ring(s) or 5 to 6 atoms in the ring(s). The heteroatom(s) is an element other than carbon including, but not limited to, oxygen, sulfur and nitrogen. A heterocycle may further contain one or more carbonyl or thiocarbonyl functionalities, so as to make the definition include oxo-systems and thio-systems such as lactams, lactones, cyclic imides, cyclic thioimides and cyclic carbamates. When composed of two or more rings, the rings may be joined together in a fused fashion. Additionally, any nitrogens in a heterocyclyl may be quaternized. Heterocyclyl groups may be unsubstituted or substituted. Examples of such “heterocyclyl groups include but are not limited to, 1,3-dioxin, 1,3-dioxane, 1,4-dioxane, 1,2-dioxolane, 1,3-dioxolane, 1,4-dioxolane, 1,3-oxathiane, 1,4-oxathiin, 1,3-oxathiolane, 1,3-dithiole, 1,3-dithiolane, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2H-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouracil, trioxane,

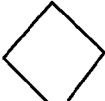
hexahydro-1,3,5-triazine, imidazoline, imidazolidine, isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, morpholine, oxirane, piperidine *N*-Oxide, piperidine, piperazine, pyrrolidine, pyrrolidone, pyrrolidione, 4-piperidone, pyrazoline, pyrazolidine, 2-oxopyrrolidine, tetrahydropyran, 4H-pyran, tetrahydrothiopyran, thiamorpholine, thiamorpholine sulfoxide, thiamorpholine sulfone and their benzo-fused analogs (e.g., benzimidazolidinone, tetrahydroquinoline and 3,4-methylenedioxyphenyl).

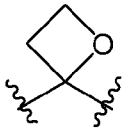
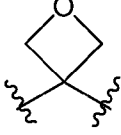
[0022] As used herein, “aryl(alkyl)” refer to an aryl group connected, as a substituent, via a lower alkylene group. The lower alkylene and aryl group of an aryl(alkyl) may be substituted or unsubstituted. Examples include but are not limited to benzyl, 2-phenyl(alkyl), 3-phenyl(alkyl), and naphthyl(alkyl).

[0023] As used herein, “heteroaryl(alkyl)” refer to a heteroaryl group connected, as a substituent, via a lower alkylene group. The lower alkylene and heteroaryl group of heteroaryl(alkyl) may be substituted or unsubstituted. Examples include but are not limited to 2-thienyl(alkyl), 3-thienyl(alkyl), furyl(alkyl), thienyl(alkyl), pyrrolyl(alkyl), pyridyl(alkyl), isoxazolyl(alkyl), imidazolyl(alkyl), and their benzo-fused analogs.

[0024] A “(heterocyclyl)alkyl” refer to a heterocyclic group connected, as a substituent, via a lower alkylene group. The lower alkylene and heterocyclyl of a heterocyclyl(alkyl) may be substituted or unsubstituted. Examples include but are not limited tetrahydro-2H-pyran-4-yl(methyl), piperidin-4-yl(ethyl), piperidin-4-yl(propyl), tetrahydro-2H-thiopyran-4-yl(methyl) and 1,3-thiazinan-4-yl(methyl).

[0025] “Lower alkylene groups” are straight-chained -CH₂- tethering groups, forming bonds to connect molecular fragments via their terminal carbon atoms. Examples include but are not limited to methylene (-CH₂-), ethylene (-CH₂CH₂-), propylene (-CH₂CH₂CH₂-) and butylene (-CH₂CH₂CH₂CH₂-). A lower alkylene group can be substituted by replacing one or more hydrogen of the lower alkylene group with a substituent(s) listed under the definition of “optionally substituted” and/or by substituting both hydrogens on the

same carbon with a cycloalkyl group (e.g.,  and ) or a monocyclic

heterocyclyl (such as  and ).

[0026] As used herein, “alkoxy” refers to the formula –OR wherein R is an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl) is defined herein. A non-limiting list of alkoxy groups are methoxy, ethoxy, n-propoxy, 1-methylethoxy (isopropoxy), n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, phenoxy and benzyloxy. An alkoxy may be substituted or unsubstituted.

[0027] As used herein, “acyl” refers to a hydrogen an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl) connected, as substituents, via a carbonyl group. Examples include formyl, acetyl, propanoyl, benzoyl, and acrylyl. An acyl may be substituted or unsubstituted.

[0028] As used herein, “hydroxyalkyl” refers to an alkyl group in which one or more of the hydrogen atoms are replaced by a hydroxy group. Exemplary hydroxyalkyl groups include but are not limited to, 2-hydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl and 2,2-dihydroxyethyl. A hydroxyalkyl may be substituted or unsubstituted.

[0029] As used herein, “alkoxyalkyl” refers to an alkyl group in which one or more of the hydrogen atoms are replaced by an alkoxy group. Exemplary alkoxyalkyl groups include but are not limited to, methoxymethyl, ethoxymethyl, methoxyethyl and ethoxyethyl. An alkoxyalkyl may be substituted or unsubstituted.

[0030] As used herein, “haloalkyl” refers to an alkyl group in which one or more of the hydrogen atoms are replaced by a halogen (e.g., mono-haloalkyl, di-haloalkyl and tri-haloalkyl). Such groups include but are not limited to, chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1-chloro-2-fluoromethyl and 2-fluoroisobutyl. A haloalkyl may be substituted or unsubstituted.

[0031] As used herein, “haloalkoxy” refers to a O-alkyl group in which one or more of the hydrogen atoms are replaced by a halogen (e.g., mono-haloalkoxy, di- haloalkoxy and tri- haloalkoxy). Such groups include but are not limited to, chloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 1-chloro-2-fluoromethoxy and 2-fluoroisobutoxy. A haloalkoxy may be substituted or unsubstituted.

[0032] A “sulfenyl” group refers to an “-SR” group in which R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A sulfenyl may be substituted or unsubstituted.

[0033] A “sulfinyl” group refers to an “-S(=O)-R” group in which R can be the same as defined with respect to sulfenyl. A sulfinyl may be substituted or unsubstituted.

[0034] A “sulfonyl” group refers to an “SO₂R” group in which R can be the same as defined with respect to sulfenyl. A sulfonyl may be substituted or unsubstituted.

[0035] An “O-carboxy” group refers to a “RC(=O)O-” group in which R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl), as defined herein. An O-carboxy may be substituted or unsubstituted.

[0036] The terms “ester” and “C-carboxy” refer to a “-C(=O)OR” group in which R can be the same as defined with respect to O-carboxy. An ester and C-carboxy may be substituted or unsubstituted.

[0037] A “thiocarbonyl” group refers to a “-C(=S)R” group in which R can be the same as defined with respect to O-carboxy. A thiocarbonyl may be substituted or unsubstituted.

[0038] A “trihalomethanesulfonyl” group refers to an “X₃CSO₂-” group wherein each X is a halogen.

[0039] A “trihalomethanesulfonamido” group refers to an “X₃CS(O)₂N(R_A)-” group wherein each X is a halogen, and R_A is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl).

[0040] The term “amino” as used herein refers to a -NH₂ group.

[0041] As used herein, the term “hydroxy” refers to a -OH group.

- [0042] A “cyano” group refers to a “-CN” group.
- [0043] The term “azido” as used herein refers to a $-N_3$ group.
- [0044] An “isocyanato” group refers to a “-NCO” group.
- [0045] A “thiocyanato” group refers to a “-CNS” group.
- [0046] An “isothiocyanato” group refers to an “-NCS” group.
- [0047] A “mercapto” group refers to an “-SH” group.
- [0048] A “carbonyl” group refers to a C=O group.
- [0049] An “S-sulfonamido” group refers to a “-SO₂N(R_AR_B)” group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An S-sulfonamido may be substituted or unsubstituted.
- [0050] An “N-sulfonamido” group refers to a “RSO₂N(R_A)-” group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-sulfonamido may be substituted or unsubstituted.
- [0051] An “O-carbamyl” group refers to a “-OC(=O)N(R_AR_B)” group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An O-carbamyl may be substituted or unsubstituted.
- [0052] An “N-carbamyl” group refers to an “ROC(=O)N(R_A)-” group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-carbamyl may be substituted or unsubstituted.
- [0053] An “O-thiocarbamyl” group refers to a “-OC(=S)-N(R_AR_B)” group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An O-thiocarbamyl may be substituted or unsubstituted.
- [0054] An “N-thiocarbamyl” group refers to an “ROC(=S)N(R_A)-” group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl,

cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-thiocarbamyl may be substituted or unsubstituted.

[0055] A “C-amido” group refers to a “-C(=O)N(R_AR_B)” group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A C-amido may be substituted or unsubstituted.

[0056] An “N-amido” group refers to a “RC(=O)N(R_A)” group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-amido may be substituted or unsubstituted.

[0057] The term “halogen atom” or “halogen” as used herein, means any one of the radio-stable atoms of column 7 of the Periodic Table of the Elements, such as, fluorine, chlorine, bromine and iodine.

[0058] Where the numbers of substituents is not specified (e.g. haloalkyl), there may be one or more substituents present. For example “haloalkyl” may include one or more of the same or different halogens. As another example, “C₁-C₃ alkoxyphenyl” may include one or more of the same or different alkoxy groups containing one, two or three atoms.

[0059] As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (See, Biochem. 11:942-944 (1972)).

[0060] The term “pharmaceutically acceptable salt” refers to a salt of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, the salt is an acid addition salt of the compound. Pharmaceutical salts can be obtained by reacting a compound with inorganic acids such as hydrohalic acid (e.g., hydrochloric acid or hydrobromic acid), sulfuric acid, nitric acid and phosphoric acid. Pharmaceutical salts can also be obtained by reacting a compound with an organic acid such as aliphatic or aromatic carboxylic or sulfonic acids, for example formic, acetic, succinic, lactic, malic, tartaric, citric, ascorbic, nicotinic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, salicylic or

naphthalenesulfonic acid. Pharmaceutical salts can also be obtained by reacting a compound with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, C₁-C₇ alkylamine, cyclohexylamine, triethanolamine, ethylenediamine, and salts with amino acids such as arginine and lysine.

[0061] Terms and phrases used in this application, and variations thereof, especially in the appended claims, unless otherwise expressly stated, should be construed as open ended as opposed to limiting. As examples of the foregoing, the term ‘including’ should be read to mean ‘including, without limitation,’ ‘including but not limited to,’ or the like; the term ‘comprising’ as used herein is synonymous with ‘including,’ ‘containing,’ or ‘characterized by,’ and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; the term ‘having’ should be interpreted as ‘having at least;’ the term ‘includes’ should be interpreted as ‘includes but is not limited to;’ the term ‘example’ is used to provide exemplary instances of the item in discussion, not an exhaustive or limiting list thereof. In addition, the term “comprising” is to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a compound or composition, the term "comprising" means that the compound or composition includes at least the recited features or components, but may also include additional features or components.

[0062] With respect to the use of substantially any plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may be expressly set forth herein for sake of clarity. The indefinite article “a” or “an” does not exclude a plurality.

[0063] It is understood that, in any compound described herein having one or more chiral centers, if an absolute stereochemistry is not expressly indicated, then each center may independently be of (R)-configuration or (S)-configuration or a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, enantiomerically enriched, racemic mixture, diastereomerically pure, diastereomerically enriched, or a stereoisomeric

mixture. In addition it is understood that, in any compound described herein having one or more double bond(s) generating geometrical isomers that can be defined as E or Z, each double bond may independently be E or Z a mixture thereof. Likewise, it is understood that, in any compound described, all tautomeric forms are also intended to be included.

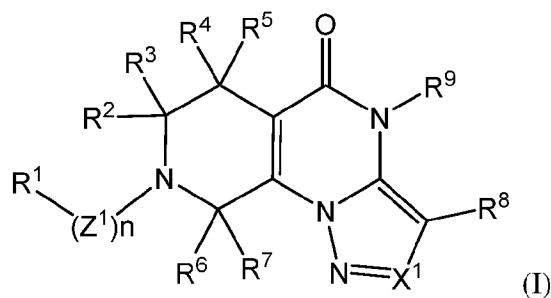
[0064] It is to be understood that where compounds disclosed herein have unfilled valencies, then the valencies are to be filled with hydrogens or isotopes thereof, e.g., hydrogen-1 (protium) and hydrogen-2 (deuterium).

[0065] It is understood that the compounds described herein can be labeled isotopically. Substitution with isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements. Each chemical element as represented in a compound structure may include any isotope of said element. For example, in a compound structure a hydrogen atom may be explicitly disclosed or understood to be present in the compound. At any position of the compound that a hydrogen atom may be present, the hydrogen atom can be any isotope of hydrogen, including but not limited to hydrogen-1 (protium) and hydrogen-2 (deuterium). Thus, reference herein to a compound encompasses all potential isotopic forms unless the context clearly dictates otherwise.

[0066] Where a range of values is provided, it is understood that the upper and lower limit, and each intervening value between the upper and lower limit of the range is encompassed within the embodiments.

Compounds

[0067] Some embodiments disclosed herein relate to a compound of Formula (I), or a pharmaceutically acceptable salt thereof:

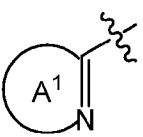


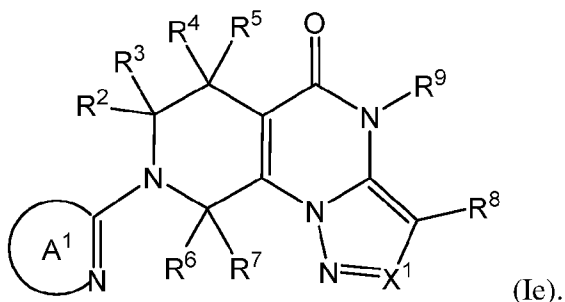
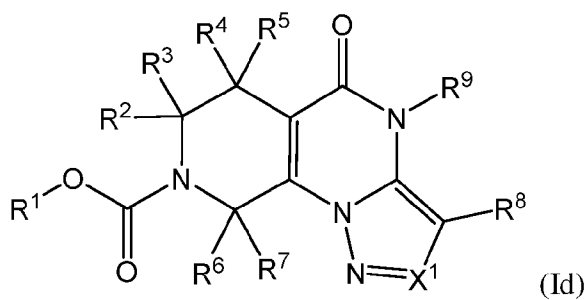
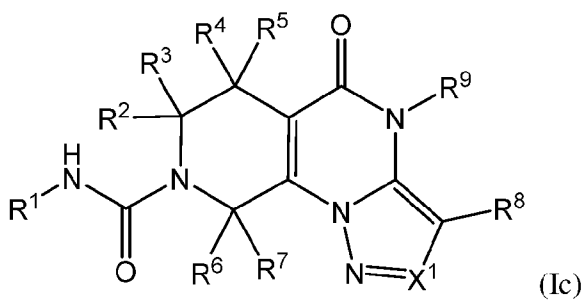
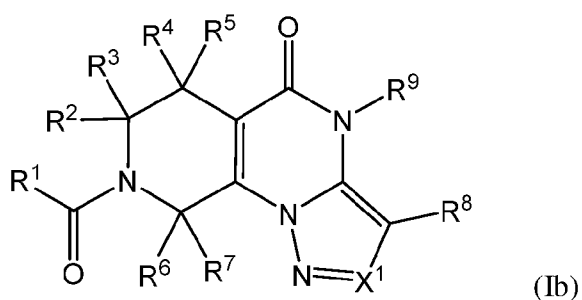
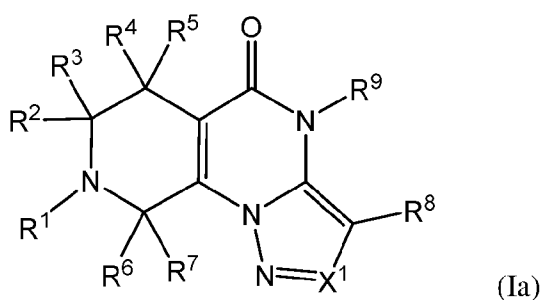
wherein: n can be 0 or 1; Z^1 can be $-C(=O)-$, $-NH-C(=O)-$ or $-O-C(=O)-$; R^1 can be selected from an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted aryl(C_{1-4} alkyl), an optionally substituted heteroaryl(C_{1-4} alkyl) and an optionally substituted heterocyclyl(C_{1-4} alkyl); R^2 and R^3 can be independently selected from hydrogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted aryl(C_{1-4} alkyl), an optionally substituted heteroaryl(C_{1-4} alkyl) and an optionally substituted heterocyclyl(C_{1-4} alkyl); R^4 and R^5 can be independently selected from hydrogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted aryl(C_{1-4} alkyl), an optionally substituted heteroaryl(C_{1-4} alkyl) and an optionally substituted heterocyclyl(C_{1-4} alkyl); R^6 and R^7 can be independently selected from hydrogen, an unsubstituted C_{1-4} alkyl and an unsubstituted C_{1-4} haloalkyl; R^8 can be selected from hydrogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted cycloalkyl(C_{1-4} alkyl), an optionally substituted cycloalkenyl(C_{1-4} alkyl), an optionally substituted aryl(C_{1-4} alkyl), an optionally substituted heteroaryl(C_{1-4} alkyl), an optionally substituted heterocyclyl(C_{1-4} alkyl), $-NR^{10}R^{11}$ and $-C(=O)NR^{12}R^{13}$; R^9 can be selected from hydrogen, an unsubstituted C_{1-4} alkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted aryl(C_{1-4} alkyl), an optionally substituted heteroaryl(C_{1-4} alkyl) and an optionally substituted heterocyclyl(C_{1-4} alkyl); R^{10} and R^{12} can be independently hydrogen or an unsubstituted C_{1-4} alkyl; R^{11} and R^{13} can be independently selected from hydrogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted cycloalkyl(C_{1-4} alkyl), an optionally substituted cycloalkenyl(C_{1-4} alkyl), an optionally substituted aryl(C_{1-4} alkyl), an optionally substituted heteroaryl(C_{1-4} alkyl) and an optionally substituted heterocyclyl(C_{1-4} alkyl); or R^{10} and R^{11} can be taken

together along with the nitrogen to which R^{10} and R^{11} are attached to form an optionally substituted 4- to 8-membered monocyclic heterocyclyl, an optionally substituted 8- to 13-membered fused-bicyclic heterocyclyl or an optionally substituted 7- to 13-membered spiro-bicyclic heterocyclyl; R^{12} and R^{13} can be taken together along with the nitrogen to which R^{12} and R^{13} are attached to form an optionally substituted 4- to 8-membered monocyclic heterocyclyl, an optionally substituted 8- to 13-membered fused-bicyclic heterocyclyl or an optionally substituted 7- to 13-membered spiro-bicyclic heterocyclyl; R^2 and R^3 can be taken together along with the carbon to which R^2 and R^3 are attached to form an optionally substituted monocyclic C_{3-6} cycloalkyl or an optionally substituted 3 to 6 member monocyclic heterocyclyl; or R^4 and R^5 can be taken together along with the carbon to which R^4 and R^5 are attached to form an optionally substituted monocyclic C_{3-6} cycloalkyl or an optionally substituted 3 to 6 member monocyclic heterocyclyl; or R^2 and R^4 can be taken together along with the carbons to which R^2 and R^4 are each attached to form an optionally monocyclic C_{5-7} cycloalkyl or an optionally substituted 5 to 7 member monocyclic heterocyclyl; or R^3 and R^5 can be taken together along with the carbons to which R^3 and R^5 are each attached to form an optionally monocyclic C_{5-7} cycloalkyl or an optionally substituted 5 to 7 member monocyclic heterocyclyl; or R^6 and R^7 can be taken together along with the carbon to which R^6 and R^7 are attached to form an optionally substituted monocyclic C_{3-4} cycloalkyl, an optionally substituted oxetane or an optionally substituted thietane; and X^1 can be N or CR^{14} , wherein R^{14} can be hydrogen, cyano, an unsubstituted C_{1-4} alkyl, a substituted C_{1-4} alkyl or an optionally substituted aryl(C_{1-4} alkyl), wherein the substituted C_{1-4} alkyl is substituted one or more times with a substituents selected from cyano, halogen, hydroxy and an unsubstituted C_{1-4} alkoxy.

[0068] A variety of moieties can be present for Z^1 and R^1 . In some embodiments, n can be 0; and R^1 can be selected from an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted aryl(C_{1-4} alkyl), an optionally substituted heteroaryl(C_{1-4} alkyl) and an optionally substituted heterocyclyl(C_{1-4} alkyl) such that Formula (I), and pharmaceutically acceptable salts thereof can be Formula (Ia), or a pharmaceutically acceptable salt thereof. In other embodiments, n can be 1; Z^1 can be $-C(=O)-$, $-NH-C(=O)-$ or $-O-C(=O)-$; and R^1 can be selected from an

optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted aryl(C₁₋₄ alkyl), an optionally substituted heteroaryl(C₁₋₄ alkyl) and an optionally substituted heterocyclyl(C₁₋₄ alkyl). As shown below, when Z¹ is -C(=O)-, -NH-C(=O)- or -O-C(=O)-, Formula (I) can be Formula (Ib), (Ic) or (Id), or a pharmaceutically acceptable salt thereof, respectively. As described herein, n can be 0 and R¹ can be an optionally substituted heteroaryl or an optionally substituted heterocyclyl. An example of n being 0; and R¹ being an optionally substituted heteroaryl or

an optionally substituted heterocyclyl is , wherein Ring A¹ can be an optionally substituted bicyclic heteroaryl or an optionally substituted bicyclic heterocyclyl such that Formula (I), and pharmaceutically acceptable salts thereof can be Formula (Ie), or a pharmaceutically acceptable salt thereof.



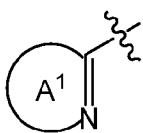
[0069] In some embodiments, X^1 can be N (nitrogen). In other embodiments, X^1 can be CH. In still other embodiments, X^1 can be CR^{14} , wherein R^{14} can be cyano, an unsubstituted C_{1-4} alkyl or a substituted C_{1-4} alkyl, wherein the substituted C_{1-4} alkyl is substituted one or more times with a substituents selected from cyano, halogen, hydroxy and an unsubstituted C_{1-4} alkoxy. In still other embodiments, X^1 can be CR^{14} , wherein R^{14} can be an optionally substituted aryl(C_{1-4} alkyl).

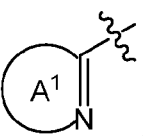
[0070] Various cyclic moieties can be present for R^1 . In some embodiments, R^1 can be an optionally substituted aromatic carbocyclic moiety, for example an optionally substituted aryl. For example, R^1 can be an optionally substituted phenyl. In some embodiments, R^1 can be an unsubstituted phenyl. In other embodiments, R^1 can be a substituted phenyl. When R^1 is a substituted phenyl, the phenyl can be mono-substituted. The mono-substituted phenyl can be a para-substituted phenyl, a meta-substituted phenyl or an ortho-substituted phenyl. The substituted phenyl can be substituted by multiple moieties, such as 2, 3 or 4 or more times. In some embodiments, R^1 can be a di-substituted phenyl. When more than one moiety is present, the moieties can be the same or different moieties can be different. In some embodiments, R^1 can be an unsubstituted or substituted naphthyl.

[0071] As described herein, R^1 can be a monocyclic or multicyclic (for example, a bicyclic) moiety that includes one or more heteroatoms in the ring(s). In some embodiments, R^1 can be an optionally substituted heteroaryl. In some embodiments, R^1 can be an unsubstituted or a substituted monocyclic heteroaryl. For example, R^1 can be a 5-membered or 6-membered monocyclic heteroaryl, wherein the heteroaryl ring can be unsubstituted or substituted. In other embodiments, R^1 can be an unsubstituted or a substituted bicyclic heteroaryl. The bicyclic heteroaryl can be an unsubstituted or a substituted 9-membered or an unsubstituted or a substituted 10-membered heteroaryl. The heteroaryl can include one or more heteroatoms, such as N (nitrogen), O (oxygen) and/or S (sulfur).

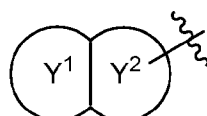
[0072] In some embodiments, R^1 can be an optionally substituted heterocyclyl. The heterocyclyl can be a monocyclic heterocyclyl or a bicyclic heterocyclyl. In some embodiments, R^1 can be an unsubstituted or a substituted monocyclic heterocyclyl, such as an unsubstituted or a substituted 5-membered or an unsubstituted or a substituted 6-membered monocyclic heterocyclyl. In other embodiments, R^1 can be an unsubstituted or a substituted

bicyclic heterocyclyl, including an unsubstituted or a substituted 9-membered or an unsubstituted or a substituted 10-membered heterocyclyl. The number and types of heteroatoms that can be present in a heterocyclyl for R^1 can vary. For example, 1, 2, 3 or more than 3 heteroatoms, such as N (nitrogen), O (oxygen) and/or S (sulfur), can be present in a heterocyclyl of R^1 .

[0073] In some embodiments, n can be 0; and R^1 can be , wherein Ring A^1 can be an optionally substituted bicyclic heteroaryl. In other embodiments, R^1 can

be , wherein Ring A^1 can be an optionally substituted bicyclic heterocyclyl. In some embodiments, Ring A^1 can be an optionally substituted nitrogen-containing, 9-membered bicyclic heteroaryl. In other embodiments, Ring A^1 can be an optionally substituted nitrogen-containing, 10-membered bicyclic heteroaryl. In still other embodiments, Ring A^1 can be an optionally substituted nitrogen-containing, 9-membered bicyclic heterocyclyl. In yet still other embodiments, Ring A^1 can be an optionally substituted nitrogen-containing, 10-membered bicyclic heterocyclyl.

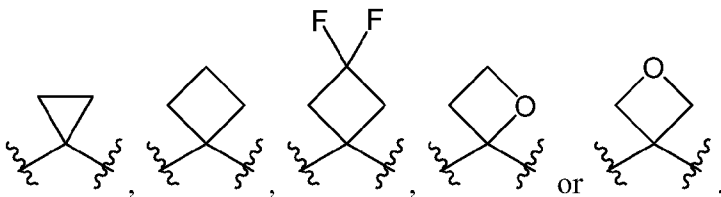
[0074] In some embodiments, R^1 can be a nitrogen-containing, bicyclic heteroaryl or a nitrogen-containing, bicyclic heterocyclyl. In some embodiments, R^1 can be selected from an unsubstituted or a substituted [5,5] bicyclic heteroaryl, an unsubstituted or a substituted [5,6] bicyclic heteroaryl, an unsubstituted or a substituted [6,5] bicyclic heteroaryl, an unsubstituted or a substituted [6,6] bicyclic heteroaryl, an unsubstituted or a substituted [5,5] bicyclic heterocyclyl, an unsubstituted or a substituted [5,6] bicyclic heterocyclyl, an unsubstituted or a substituted [6,5] bicyclic heterocyclyl and an unsubstituted or a substituted [6,6] bicyclic heterocyclyl. In some embodiments, R^1 can have the general

structure , wherein Ring Y^2 indicates the point of attachment to the remaining portion of Formula (I); and wherein Ring Y^1 and Ring Y^2 can be independently selected from phenyl, furan, furazan, thiophene, phthalazine, pyrrole, oxazole, 1,2,3-

oxadiazole, 1,2,4-oxadiazole, thiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, imidazole, pyrazole, isoxazole, isothiazole, triazole, thiadiazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,2,3,4-tetrazine, 2H-1,2-oxazine, hexahydro-1,3,5-triazine, imidazoline, imidazolidine, isoxazoline, isoxazolidine, oxazoline, oxazolidine, thiazoline, thiazolidine, morpholine, piperidine, piperazine, pyrrolidine, pyrazoline, pyrazolidine and thiamorpholine, wherein Ring Y¹ and Ring Y² can be each optionally substituted. In some embodiments, Ring Y¹ can be selected from an optionally substituted phenyl, an optionally substituted pyridine, an optionally substituted pyridazine, an optionally substituted pyrimidine, an optionally substituted pyrazine, an optionally substituted 1,2,3-triazine, an optionally substituted 1,2,4-triazine and an optionally substituted 1,2,3,4-tetrazine. In some embodiments, Ring Y² can be selected from an optionally substituted phenyl, an optionally substituted pyridine, an optionally substituted pyridazine, an optionally substituted pyrimidine, an optionally substituted pyrazine, an optionally substituted 1,2,3-triazine, an optionally substituted 1,2,4-triazine and an optionally substituted 1,2,3,4-tetrazine. In other embodiments, Ring Y² can be selected from an optionally substituted furan, an optionally substituted thiophene, an optionally substituted pyrrole, an optionally substituted oxazole, an optionally substituted thiazole, an optionally substituted imidazole, an optionally substituted pyrazole, an optionally substituted isoxazole and an optionally substituted isothiazole.

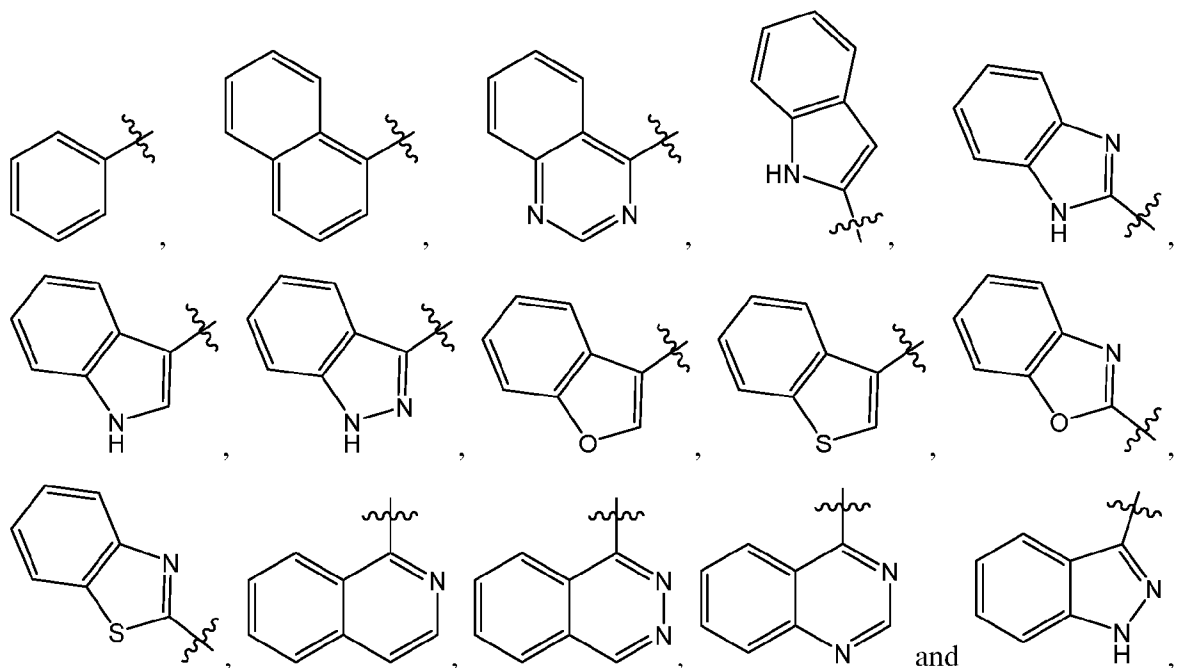
[0075] A variety of cyclic groups described herein for R¹ can be attached via a C₁₋₄ alkyl linker. In some embodiments, R¹ can be an optionally substituted aryl(C₁₋₄ alkyl), for example, an optionally substituted benzyl. In other embodiments, R¹ can be an optionally substituted heteroaryl(C₁₋₄ alkyl). In still other embodiments, R¹ can be an optionally substituted heterocyclyl(C₁₋₄ alkyl). Examples of heteroaryls and heterocyclyls are described herein, and include those of the previous paragraph. As described herein, the linker can include 1 to 4 carbons. The aryl, heteroaryl, heterocyclyl and C₁₋₄ alkyl of aryl(C₁₋₄ alkyl), heteroaryl(C₁₋₄ alkyl) and heterocyclyl(C₁₋₄ alkyl) can be each unsubstituted or unsubstituted. When the C₁₋₄ alkyl linker is substituted, one or more hydrogens can be replaced with a moiety, such as those provided in the definition of “optionally substituted,” and/or two or more hydrogens can be taken together along with the carbon to which the hydrogens are

attached to form an optionally substituted C₃₋₄ cycloalkyl or an optionally substituted 3-, 4- or 5-membered heterocyclyl. In some embodiments, the C₁₋₄ alkyl linker of aryl(C₁₋₄ alkyl), heteroaryl(C₁₋₄ alkyl) and heterocyclyl(C₁₋₄ alkyl) can be substituted with one or more moieties selected from halogen (such as F), cyano, C₁₋₂ haloalkyl (for example, CF₃), OH, an unsubstituted C₁₋₄ alkoxy and an unsubstituted C-amido (such as -C(=O)NH₂, -C(=O)NH(C₁₋₄ alkyl) and -C(=O)N(C₁₋₄ alkyl)₂). In some embodiments, the C₁₋₄ alkyl linker for R¹ can be -CH₂-, -CH₂CH₂-, -CH(CH₃)CH₂-, -CH₂CH₂CH₂-, -CH₂CH₂CH₂CH₂-,

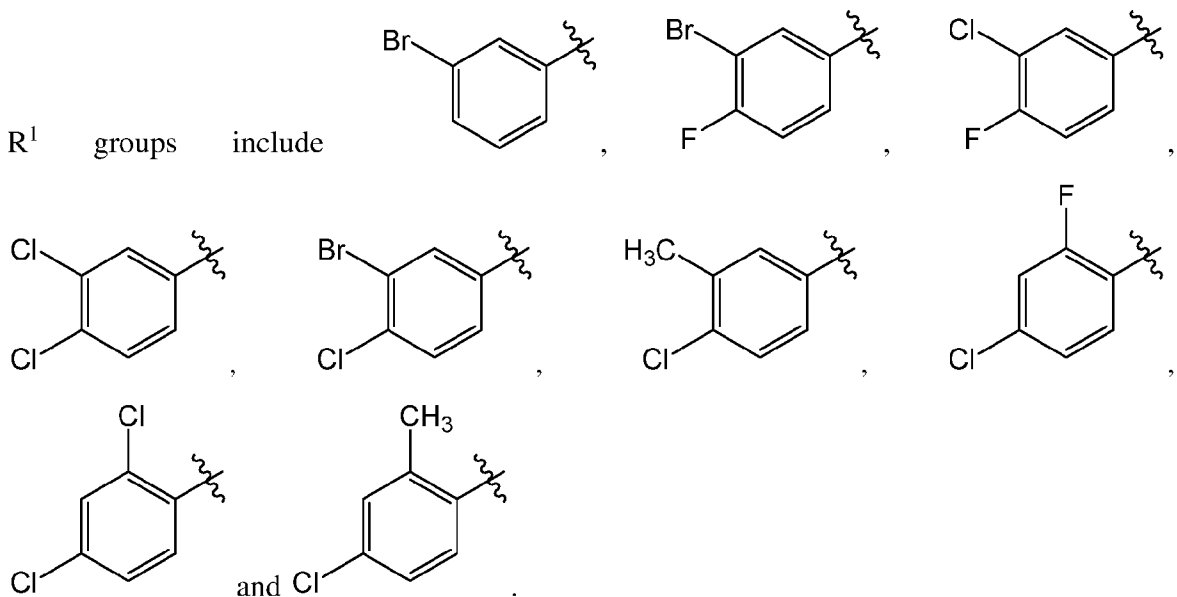


[0076] As described herein, the R¹ groups can be unsubstituted or substituted. When R¹ is substituted, a variety of substituents can be present on a R¹ group described herein. In some embodiments, R¹ can be substituted with one or more substituents selected from deuterium, halogen (such as F, Cl and/or Br), cyano, an unsubstituted C₁₋₆ alkyl (for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl (straight-chained or branched) and hexyl (straight-chained or branched)), an unsubstituted C₁₋₆ haloalkyl (such as -CHF₂, -CH₂F, -CF₃, -CHClF, -CH₂Cl, -CHCl₂ and -CCl₃), an unsubstituted C₁₋₆ alkoxy (for example, methoxy, ethoxy, isopropoxy, n-butoxy, sec-butoxy, isobutoxy and tert-butoxy), an unsubstituted acyl (for example, -C(=O)-C₁₋₄ alkyl), an unsubstituted C-amido (such as -C(=O)NH₂, -C(=O)NH(C₁₋₄ alkyl) and -C(=O)N(C₁₋₄ alkyl)₂), an unsubstituted sulfonyl (such as -S(=O)₂-C₁₋₄ alkyl), an unsubstituted amino, a mono-substituted amine (for example, an mono-alkyl substituted amine) and a di-substituted amine (such as a di-alkyl substituted amine).

[0077] Exemplary R¹ groups include, but are not limited to, the following:



wherein each of these moieties can be unsubstituted or substituted. Examples of substituted



[0078] As provided herein, R⁸ can be selected from hydrogen, an unsubstituted C₁₋₄ alkyl, an unsubstituted C₁₋₄ haloalkyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted cycloalkyl(C₁₋₄ alkyl), an optionally substituted cycloalkenyl(C₁₋₄ alkyl), an optionally substituted aryl(C₁₋₄ alkyl), an

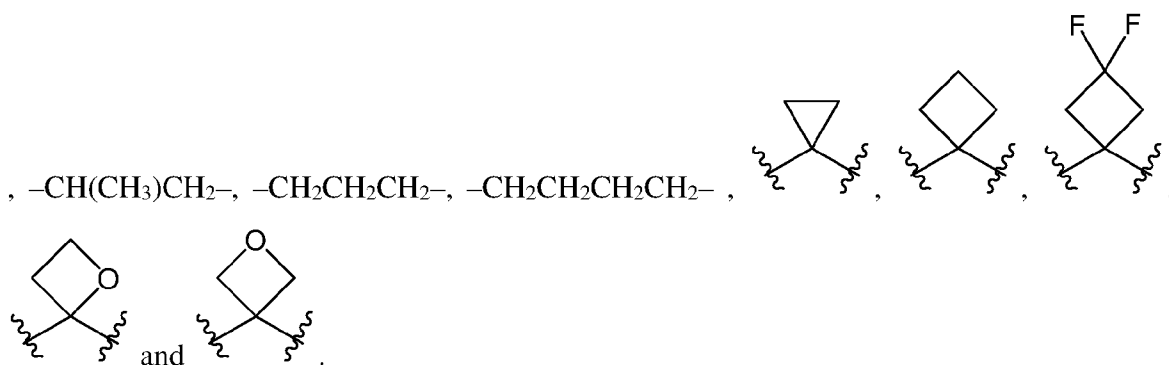
optionally substituted heteroaryl(C₁₋₄ alkyl), an optionally substituted heterocyclyl(C₁₋₄ alkyl), -NR¹⁰R¹¹ and -C(=O)NR¹²R¹³. In some embodiments, R⁸ can be hydrogen. In other embodiments, R⁸ can be an unsubstituted C₁₋₄ alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl. In still other embodiments, R⁸ can be an unsubstituted C₁₋₄ haloalkyl. Exemplary unsubstituted C₁₋₄ haloalkyls include -CF₃, -CHF₂, -CHClF, -CCl₃ and -CHCl₂.

[0079] Several cyclic moieties can be present at R⁸. For example, in some embodiments, R⁸ can be an optionally substituted cycloalkyl or an optionally substituted cycloalkenyl. The optionally substituted cycloalkyl and the optionally substituted cycloalkenyl can be monocyclic, such as an optionally substituted C₃₋₆ cycloalkyl or an optionally substituted C₃₋₆ cycloalkenyl. Alternatively, the optionally substituted cycloalkyl and/or the optionally substituted cycloalkenyl can be multicyclic, for example, an optionally substituted fused-bicyclic cycloalkyl, an optionally substituted fused-bicyclic cycloalkenyl, an optionally substituted spiro-bicyclic cycloalkyl and an optionally substituted spiro-bicyclic cycloalkenyl. In other embodiments, R⁸ can be an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted heterocyclyl. Exemplary R⁸ aryls, heteroaryls and heterocyclyls include, but are not limited to, phenyl, 5-membered monocyclic heteroaryls, 6-membered monocyclic heteroaryls, 5-membered monocyclic heterocyclyls and 6-membered monocyclic heterocyclyls, wherein each of the aforementioned moieties can be unsubstituted or substituted. The heteroatom(s) that can be present in an optionally substituted heteroaryl and an optionally substituted heterocyclyl for R⁸ include N (nitrogen), O (oxygen) and/or S (sulfur).

[0080] The cyclic moieties described herein for R⁸ can be attached via a C₁₋₄ alkyl linker, such as those described herein. In some embodiments, R⁸ can be an optionally substituted cycloalkyl(C₁₋₄ alkyl). In other embodiments, R⁸ can be an optionally substituted cycloalkenyl(C₁₋₄ alkyl). In still other embodiments, R⁸ can be an optionally substituted aryl(C₁₋₄ alkyl). In yet still other embodiments, R⁸ can be an optionally substituted heteroaryl(C₁₋₄ alkyl). In some embodiments, R⁸ can be an optionally substituted heterocyclyl(C₁₋₄ alkyl). The cycloalkyls, cycloalkenyls, aryls, heteroaryls and heterocyclyls can be monocyclic or bicyclic (for example, fused bicyclic). For example, R⁸ can be an

optionally substituted monocyclic C₃₋₆ cycloalkyl(C₁₋₄ alkyl), an optionally substituted monocyclic C₃₋₆ cycloalkenyl(C₁₋₄ alkyl), an optionally substituted benzyl, an optionally substituted monocyclic heteroaryl(C₁₋₄ alkyl) (such as a 5-membered monocyclic heteroaryl(C₁₋₄ alkyl) or 6-membered monocyclic heteroaryl(C₁₋₄ alkyl)) or an optionally substituted monocyclic heterocyclyl(C₁₋₄ alkyl) (such as a 5-membered monocyclic heterocyclyl(C₁₋₄ alkyl) or 6-membered monocyclic heterocyclyl(C₁₋₄ alkyl)).

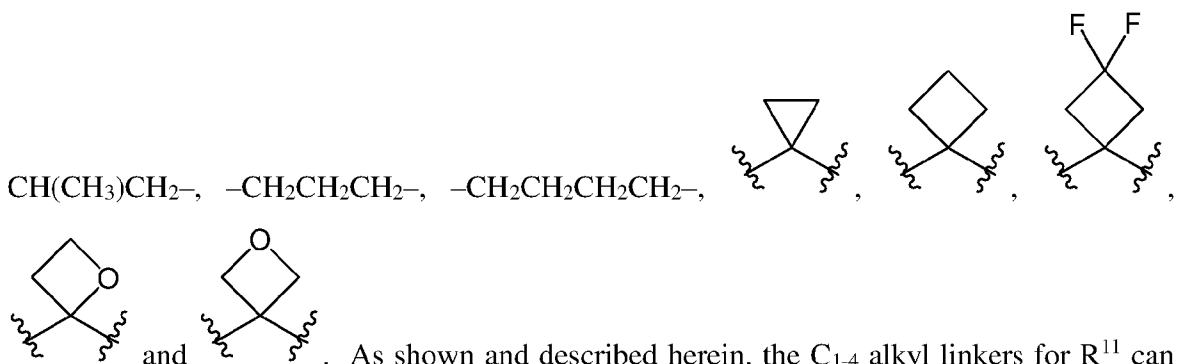
[0081] The C₁₋₄ alkyls of cycloalkyl(C₁₋₄ alkyl), cycloalkenyl(C₁₋₄ alkyl), aryl(C₁₋₄ alkyl), heteroaryl(C₁₋₄ alkyl) and heterocyclyl(C₁₋₄ alkyl) can be unsubstituted or substituted. When the C₁₋₄ alkyl is substituted, one or more hydrogens can be replaced with a moiety, such as those provided in the definition of “optionally substituted,” and/or two or more hydrogens can be taken together along with the carbon to which the hydrogens are attached to form an optionally substituted C₃₋₄ cycloalkyl or an optionally substituted 3-, 4- or 5-membered heterocyclyl. In some embodiments, the C₁₋₄ alkyl linker of cycloalkyl(C₁₋₄ alkyl), cycloalkenyl(C₁₋₄ alkyl), aryl(C₁₋₄ alkyl), heteroaryl(C₁₋₄ alkyl) and heterocyclyl(C₁₋₄ alkyl) can be substituted with one or more moieties selected from halogen (such as F), cyano, C₁₋₂ haloalkyl (for example, CF₃), OH, an unsubstituted C₁₋₄ alkoxy and an unsubstituted C-amido (such as -C(=O)NH₂, -C(=O)NH(C₁₋₄ alkyl) and -C(=O)N(C₁₋₄ alkyl)₂). Exemplary linkers that can attached the cyclic moieties for R⁸ include, but are not limited to, -CH₂-, -CH₂CH₂-



[0082] In some embodiments, R⁸ can be -NR¹⁰R¹¹. In other embodiments, R⁸ can be -C(=O)NR¹²R¹³. In some embodiments, R¹⁰ can be hydrogen. In other embodiments, R¹⁰ can be optionally substituted C₁₋₄ alkyl. In some embodiments, R¹² can be hydrogen. In other embodiments, R¹² can be optionally substituted C₁₋₄ alkyl. For example, R¹⁰ and/or R¹² can be methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl or tert-butyl.

[0083] In some embodiments, R^{11} can be hydrogen. In other embodiments, R^{11} can be an unsubstituted C_{1-4} alkyl. In still other embodiments, R^{11} can be an unsubstituted C_{1-4} haloalkyl. As described herein, R^{11} can be various carbocyclic, heteroaryl or heterocyclic groups. In some embodiments, R^{11} can be an optionally substituted cycloalkyl, for example, an optionally substituted C_{3-8} cycloalkyl. In other embodiments, R^{11} can be an optionally substituted cycloalkenyl, such as an optionally substituted C_{3-8} cycloalkenyl. In some embodiments, R^{11} can be an optionally substituted aryl. For example, R^{11} can be an unsubstituted or a substituted phenyl. In still other embodiments, R^{11} can be an optionally substituted heteroaryl. The heteroaryl for R^{11} can be an optionally substituted monocyclic heteroaryl (such as an optionally substituted 5- or 6-membered monocyclic heteroaryl) or an optionally substituted bicyclic heteroaryl (for example, an optionally substituted 9- or 10-membered bicyclic heteroaryl). In some embodiments, R^{11} can be an optionally substituted heterocyclyl.

[0084] A variety cyclic groups can be attached via a C_{1-4} alkyl linker for R^{11} . Examples of C_{1-4} alkyl linkers are described herein and include $-CH_2-$, $-CH_2CH_2-$, $-$



As shown and described herein, the C_{1-4} alkyl linkers for R^{11} can be unsubstituted or substituted. When the C_{1-4} alkyls for R^{11} are substituted, one or more hydrogens can be replaced with a moiety, such as those provided in the definition of “optionally substituted,” and/or two or more hydrogens can be taken together along with the carbon to which the hydrogens are attached to form an optionally substituted C_{3-4} cycloalkyl or an optionally substituted 3-, 4- or 5-membered heterocyclyl. In some embodiments, the C_{1-4} alkyl linker for the R^{11} groups can be substituted with one or more moieties selected from halogen (such as F), cyano, C_{1-2} haloalkyl (for example, CF_3), OH, an unsubstituted C_{1-4} alkoxy and an unsubstituted C-amido (such as $-C(=O)NH_2$, $-C(=O)NH(C_{1-4} \text{ alkyl})$ and $-$

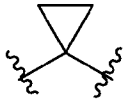
C(=O)N(C₁₋₄ alkyl)₂). In some embodiments, R¹¹ can be an optionally substituted cycloalkyl(C₁₋₄ alkyl), such as an optionally substituted monocyclic C₃₋₈ cycloalkyl(C₁₋₄ alkyl). In other embodiments, R¹¹ can be an optionally substituted cycloalkenyl(C₁₋₄ alkyl), such as an optionally substituted monocyclic C₃₋₈ cycloalkenyl(C₁₋₄ alkyl). In still other embodiments, R¹¹ can be an optionally substituted aryl(C₁₋₄ alkyl). As an example, R¹¹ can be an optionally substituted benzyl. In yet still other embodiments, R¹¹ can be an optionally substituted heteroaryl(C₁₋₄ alkyl). In some embodiments, R¹¹ can be an optionally substituted heterocyclyl(C₁₋₄ alkyl). The heteroaryl of the optionally substituted heteroaryl(C₁₋₄ alkyl) can be an optionally substituted monocyclic heteroaryl (such as a 5- or 6-membered monocyclic heteroaryl) or an optionally substituted bicyclic heteroaryl (such as a 9- or 10-membered bicyclic heteroaryl).

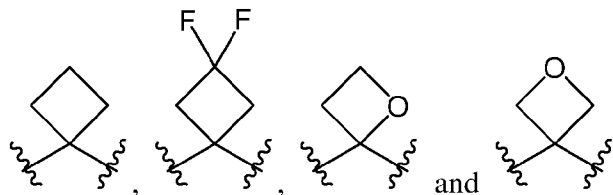
[0085] In some embodiments, R¹⁰ and R¹¹ can be taken together along with the nitrogen to which R¹⁰ and R¹¹ are attached to form an optionally substituted 4 to 8 member monocyclic heterocyclyl. In other embodiments, R¹⁰ and R¹¹ can be taken together along with the nitrogen to which R¹⁰ and R¹¹ are attached to form an optionally substituted 8 to 13 membered fused-bicyclic heterocyclyl. In still other embodiments, R¹⁰ and R¹¹ can be taken together along with the nitrogen to which R¹⁰ and R¹¹ are attached to form an optionally substituted 7 to 13 membered spiro-bicyclic heterocyclyl. The 4 to 8 member monocyclic heterocyclyl, 8 to 13 membered fused-bicyclic heterocyclyl and/or 7 to 13 membered spiro-bicyclic heterocyclyl can include one or more ring nitrogens.

[0086] As described herein, R¹³ can be cyclic and non-cyclic moieties. In some embodiments, R¹³ can be hydrogen. In other embodiments, R¹³ can be an unsubstituted C₁₋₄ alkyl. In still other embodiments, R¹³ can be an unsubstituted C₁₋₄ haloalkyl. Various carbocyclic, heteroaryl or heterocyclic groups are suitable for R¹³. In some embodiments, R¹³ can be an optionally substituted cycloalkyl, for example, an optionally substituted C₃₋₈ cycloalkyl. In other embodiments, R¹³ can be an optionally substituted cycloalkenyl, such as an optionally substituted C₃₋₈ cycloalkenyl. In some embodiments, R¹³ can be an optionally substituted aryl. For example, R¹³ can be an unsubstituted or a substituted phenyl. In still other embodiments, R¹³ can be an optionally substituted heteroaryl. The heteroaryl for R¹³ can be an optionally substituted monocyclic heteroaryl (such as an optionally substituted 5- or

6-membered monocyclic heteroaryl) or an optionally substituted bicyclic heteroaryl (for example, an optionally substituted 9- or 10-membered bicyclic heteroaryl). In some embodiments, R¹³ can be an optionally substituted heterocyclyl.

[0087] As described herein, R¹³ can be an optionally substituted cycloalkyl(C₁₋₄ alkyl), an optionally substituted cycloalkenyl(C₁₋₄ alkyl), an optionally substituted aryl(C₁₋₄ alkyl), an optionally substituted heteroaryl(C₁₋₄ alkyl) or an optionally substituted heterocyclyl(C₁₋₄ alkyl). Various C₁₋₄ alkyls are described herein for an optionally substituted cycloalkyl(C₁₋₄ alkyl), an optionally substituted cycloalkenyl(C₁₋₄ alkyl), an optionally substituted aryl(C₁₋₄ alkyl), an optionally substituted heteroaryl(C₁₋₄ alkyl) and/or an optionally substituted heterocyclyl(C₁₋₄ alkyl) are described herein. For example, the C₁₋₄ alkyl of an optionally substituted cycloalkyl(C₁₋₄ alkyl), an optionally substituted cycloalkenyl(C₁₋₄ alkyl), an optionally substituted aryl(C₁₋₄ alkyl), an optionally substituted heteroaryl(C₁₋₄ alkyl) and/or an optionally substituted heterocyclyl(C₁₋₄ alkyl) can be selected

from $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$, ,



As shown and described herein, the C₁₋₄ alkyl linkers for R¹³ can be unsubstituted or substituted. When the C₁₋₄ alkyls for R¹³ are substituted, one or more hydrogens can be replaced with a moiety, such as those provided in the definition of “optionally substituted,” and/or two or more hydrogens can be taken together along with the carbon to which the hydrogens are attached to form an optionally substituted C₃₋₄ cycloalkyl or an optionally substituted 3-, 4- or 5-membered heterocyclyl. In some embodiments, the C₁₋₄ alkyl linker for the R¹³ groups can be substituted with one or more moieties selected from halogen (such as F), cyano, C₁₋₂ haloalkyl (for example, CF₃), OH, an unsubstituted C₁₋₄ alkoxy and an unsubstituted C-amido (such as $-\text{C}(=\text{O})\text{NH}_2$, $-\text{C}(=\text{O})\text{NH}(\text{C}_{1-4} \text{ alkyl})$ and $-\text{C}(=\text{O})\text{N}(\text{C}_{1-4} \text{ alkyl})_2$).

[0088] In some embodiments, R¹³ can be an optionally substituted cycloalkyl(C₁₋₄ alkyl), such as an optionally substituted monocyclic C₃₋₈ cycloalkyl(C₁₋₄ alkyl). In other

embodiments, R^{13} can be an optionally substituted cycloalkenyl(C_{1-4} alkyl), such as an optionally substituted monocyclic C_{3-8} cycloalkenyl(C_{1-4} alkyl). In some embodiments, R^{13} can be an optionally substituted aryl(C_{1-4} alkyl). As an example, R^{13} can be an optionally substituted benzyl. In other embodiments, R^{13} can be an optionally substituted heteroaryl(C_{1-4} alkyl). In still other embodiments, R^{13} can be an optionally substituted heterocyclyl(C_{1-4} alkyl). The heteroaryl of the optionally substituted heteroaryl(C_{1-4} alkyl) can be an optionally substituted monocyclic heteroaryl (such as a 5- or 6-membered monocyclic heteroaryl) or an optionally substituted bicyclic heteroaryl (such as a 9- or 10-membered bicyclic heteroaryl).

[0089] In some embodiments, R^{12} and R^{13} can be taken together along with the nitrogen to which R^{12} and R^{13} are attached to form an optionally substituted 4 to 8 member monocyclic heterocyclyl. In other embodiments, R^{12} and R^{13} can be taken together along with the nitrogen to which R^{10} and R^{11} are attached to form an optionally substituted 8 to 13 membered fused-bicyclic heterocyclyl. In still other embodiments, R^{12} and R^{13} can be taken together along with the nitrogen to which R^{10} and R^{11} are attached to form an optionally substituted 7 to 13 membered spiro-bicyclic heterocyclyl. The 4 to 8 member monocyclic heterocyclyl, 8 to 13 membered fused-bicyclic heterocyclyl and/or 7 to 13 membered spiro-bicyclic heterocyclyl can include one or more ring nitrogens.

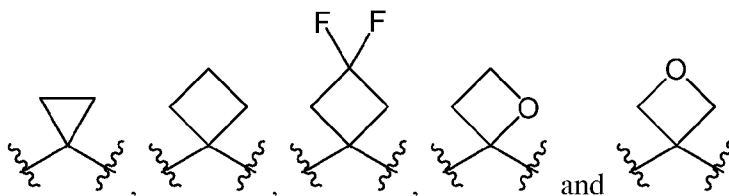
[0090] In some embodiments, R^{10} can be hydrogen; and R^{11} can be a non-hydrogen moiety described herein. For example, R^8 can be $-NH$ (an unsubstituted C_{1-4} alkyl) or $-NH$ (an optionally substituted phenyl). In some embodiments, when X^1 is CR^{14} , then R^8 can be $-NR^{10}R^{11}$. In other embodiments, when X^1 is CR^{14} , then R^8 can be $-C(=O)NR^{12}R^{13}$. As an example, X^1 can be CR^{14} , wherein R^8 can be $-C(=O)NHR^{13}$ and R^{13} can be a group described herein. In still other embodiments, when X^1 is N, then R^8 can be an unsubstituted C_{1-4} alkyl or an unsubstituted C_{1-4} haloalkyl. In yet still other embodiments, when X^1 is N, then R^8 can be an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted cycloalkyl(C_{1-4} alkyl), an optionally substituted cycloalkenyl(C_{1-4} alkyl), an optionally substituted aryl(C_{1-4} alkyl), an optionally substituted heteroaryl(C_{1-4} alkyl) or an optionally substituted heterocyclyl(C_{1-4} alkyl).

[0091] Various groups can be present for R⁹, including hydrogen, an unsubstituted C₁₋₄ alkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted aryl(C₁₋₄ alkyl), an optionally substituted heteroaryl(C₁₋₄ alkyl) and an optionally substituted heterocyclyl(C₁₋₄ alkyl). In some embodiment, R⁹ can be hydrogen. In other embodiments, R⁹ can be an unsubstituted C₁₋₄ alkyl, including methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

[0092] A variety of cyclic groups can be directly attached to the nitrogen to which R⁹ is attached or the cyclic groups can be attached via a C₁₋₄ linker. In some embodiment, R⁹ can be an optionally substituted aryl, for example, an optionally substituted phenyl or an optionally substituted naphthyl. In some embodiment, R⁹ can be an optionally substituted heteroaryl. In other embodiments, R⁹ can be an optionally substituted heterocyclyl. The heteroaryl can be a monocyclic or bicyclic heteroaryl (such as a fused bicyclic heteroaryl). For example, R⁹ can be an unsubstituted or a substituted monocyclic 5-membered heteroaryl, an unsubstituted or a substituted monocyclic 6-membered heteroaryl, an unsubstituted or a substituted bicyclic 9-membered heteroaryl or an unsubstituted or a substituted bicyclic 10-membered heteroaryl. As additional examples, R⁹ can be an unsubstituted or a substituted monocyclic 5-membered heterocyclyl, an unsubstituted or a substituted monocyclic 6-membered heterocyclyl, an unsubstituted or a substituted bicyclic 9-membered heterocyclyl or an unsubstituted or a substituted bicyclic 10-membered heterocyclyl.

[0093] In some embodiments, R⁹ can be an optionally substituted aryl(C₁₋₄ alkyl). In other embodiments, R⁹ can be an optionally substituted heteroaryl(C₁₋₄ alkyl). In still other embodiments, R⁹ can be an optionally substituted heterocyclyl(C₁₋₄ alkyl). The C₁₋₄ alkyl linkers for R⁹ can be unsubstituted or substituted. When the C₁₋₄ alkyl linkers are substituted, one or more hydrogens can be replaced with a moiety, such as those provided in the definition of “optionally substituted,” and/or two or more hydrogens can be taken together along with the carbon to which the hydrogens are attached to form an optionally substituted C₃₋₄ cycloalkyl or an optionally substituted 3-, 4- or 5-membered heterocyclyl. In some embodiments, the C₁₋₄ alkyl linker for the R⁹ groups can be substituted with one or more moieties selected from halogen (such as F), cyano, C₁₋₂ haloalkyl (for example, CF₃), OH, an

unsubstituted C₁₋₄ alkoxy and an unsubstituted C-amido (such as $-\text{C}(=\text{O})\text{NH}_2$, $-\text{C}(=\text{O})\text{NH}(\text{C}_{1-4} \text{ alkyl})$ and $-\text{C}(=\text{O})\text{N}(\text{C}_{1-4} \text{ alkyl})_2$). Exemplary C₁₋₄ alkyl linkers include, but are not limited to, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2-$,



. In some embodiments, R⁹ can be an unsubstituted benzyl. In other embodiments, R⁹ can be a substituted benzyl. The heteroaryls and heterocyclyls that can be present for R⁹ and attached via a C₁₋₄ alkyl linker include monocyclic and bicyclic heteroaryls and heterocyclyls. In some embodiments, R⁹ can be an unsubstituted or a substituted monocyclic 5-membered heteroaryl or an unsubstituted or a substituted monocyclic 6-membered heteroaryl. In other embodiments, R⁹ can be an unsubstituted or a substituted bicyclic 9-membered heteroaryl or an unsubstituted or a substituted bicyclic 10-membered heteroaryl. In still other embodiments, R⁹ can be an unsubstituted or a substituted monocyclic 5-membered heterocyclyl or an unsubstituted or a substituted monocyclic 6-membered heterocyclyl. In yet still other embodiments, R⁹ can be an unsubstituted or a substituted bicyclic 9-membered heterocyclyl or an unsubstituted or a substituted bicyclic 10-membered heterocyclyl, for example, an unsubstituted or a substituted fused-bicyclic 9-membered heterocyclyl or an unsubstituted or a substituted fused-bicyclic 10-membered heterocyclyl.

[0094] A variety of groups can substitute a R⁹ group described herein. For example, R⁹ can be substituted one or more times with a group selected from deuterium, halogen (such as F, Cl and/or Br), cyano, an unsubstituted C₁₋₆ alkyl (for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl (straight-chained or branched) and hexyl (straight-chained or branched)), an unsubstituted C₁₋₆ haloalkyl (such as $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{CF}_3$, $-\text{CHClF}$, $-\text{CH}_2\text{Cl}$, $-\text{CHCl}_2$ and $-\text{CCl}_3$), an unsubstituted C₁₋₆ alkoxy (for example, methoxy, ethoxy, isopropoxy, n-butoxy, sec-butoxy, isobutoxy and tert-butoxy), an unsubstituted acyl (such as $-\text{C}(=\text{O})-\text{C}_{1-4} \text{ alkyl}$), an unsubstituted C-amido (such as $-\text{C}(=\text{O})\text{NH}_2$, $-\text{C}(=\text{O})\text{NH}(\text{C}_{1-4} \text{ alkyl})$ and $-\text{C}(=\text{O})\text{N}(\text{C}_{1-4} \text{ alkyl})_2$), an unsubstituted sulfonyl (such as $-\text{S}(=\text{O})_2-\text{C}_{1-4} \text{ alkyl}$), an unsubstituted S-sulfonamido (such as $-\text{S}(=\text{O})_2\text{NH}_2$, $-\text{S}(=\text{O})_2\text{NH}(\text{C}_{1-4} \text{ alkyl})$ and $-\text{S}(=\text{O})_2\text{N}(\text{C}_{1-4} \text{ alkyl})_2$).

[illegible]

[0096] As provided herein, both hydrogen and non-hydrogen moieties can be present on the piperazine ring of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, R^2 can be hydrogen. In other embodiments, R^2 can be an unsubstituted C_{1-4} alkyl. In still other embodiments, R^2 can be an unsubstituted C_{1-4} haloalkyl. For example, R^2 can be methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, $-CHF_2$, $-CH_2F$, $-CF_3$, $-CH_2Cl$, $-CHCl_2$ and $-CCl_3$. In yet still other embodiments, R^2 can be an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted heterocyclyl. In some embodiments, R^2 can be an optionally substituted aryl(C_{1-4} alkyl), an optionally substituted heteroaryl(C_{1-4} alkyl) or an optionally substituted heterocyclyl(C_{1-4} alkyl). Exemplary R^2 groups include, but are not limited to, an optionally substituted phenyl, an optionally substituted benzyl, an optionally substituted monocyclic heteroaryl (an optionally substituted 5- or 6-membered monocyclic heteroaryl) or an optionally substituted monocyclic heterocyclyl (an optionally substituted 5- or 6-membered monocyclic heterocyclyl).

[0097] As with R^2 , R^3 can be hydrogen or non-hydrogen moieties as described herein. In some embodiments, R^3 can be hydrogen. In other embodiments, R^3 can be an unsubstituted C_{1-4} alkyl, such as those described herein. In still other embodiments, R^3 can be an unsubstituted C_{1-4} haloalkyl, for example, $-CHF_2$, $-CH_2F$, $-CF_3$, $-CH_2Cl$, $-CHCl_2$ and $-CCl_3$. In yet still other embodiments, R^3 can be an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted heterocyclyl. In some embodiments, R^3 can be an optionally substituted aryl(C_{1-4} alkyl), an optionally substituted heteroaryl(C_{1-4} alkyl) or an optionally substituted heterocyclyl(C_{1-4} alkyl). In other embodiments, R^3 can be an optionally substituted phenyl, an optionally substituted monocyclic heteroaryl or an optionally substituted monocyclic heterocyclyl. In other embodiments, R^2 and R^3 can be taken together along with the carbon to which R^2 and R^3 are attached to form an optionally substituted monocyclic C_{3-6} cycloalkyl or an optionally substituted 3 to 6 member monocyclic heterocyclyl. For example, R^2 and R^3 can be taken together along with the carbon to which R^2 and R^3 are attached to form an optionally substituted cyclopropyl, an optionally substituted cyclobutyl, an optionally substituted cyclopentyl, an optionally substituted

cyclohexyl, an optionally substituted oxetane, an optionally substituted thietane, an optionally substituted thietane oxide or an optionally substituted thietane dioxide.

[0098] Each of R^4 and R^5 can be independently hydrogen or selected from the non-hydrogen moieties described herein. In some embodiments, R^4 can be hydrogen. In other embodiments, R^4 can be an unsubstituted C_{1-4} alkyl, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and tert-butyl. In still other embodiments, R^4 can be an unsubstituted C_{1-4} haloalkyl. Exemplary unsubstituted C_{1-4} haloalkyls are described herein, and include $-CHF_2$, $-CH_2F$, $-CF_3$, $-CH_2Cl$, $-CHCl_2$ and $-CCl_3$. In yet still other embodiments, R^4 can be an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted heterocyclyl. In some embodiments, R^4 can be an optionally substituted aryl(C_{1-4} alkyl), an optionally substituted heteroaryl(C_{1-4} alkyl) or an optionally substituted heterocyclyl(C_{1-4} alkyl). For example, R^4 can be an optionally substituted phenyl, an optionally substituted benzyl, an optionally substituted monocyclic heteroaryl (an optionally substituted 5- or 6-membered monocyclic heteroaryl) or an optionally substituted monocyclic heterocyclyl (an optionally substituted 5- or 6-membered monocyclic heterocyclyl).

[0099] In some embodiments, R^5 can be hydrogen. In other embodiments, R^5 can be an unsubstituted C_{1-4} alkyl. In still other embodiments, R^5 can be an unsubstituted C_{1-4} haloalkyl. Exemplary unsubstituted C_{1-4} alkyls and unsubstituted C_{1-4} haloalkyls are described herein and include those described with respect to R^4 . In yet still other embodiments, R^5 can be an optionally substituted aryl (such as an optionally phenyl), an optionally substituted heteroaryl (such as an optionally substituted monocyclic heteroaryl) or an optionally substituted heterocyclyl (for example, an optionally substituted monocyclic heterocyclyl). The heteroaryl and heterocyclyl can include 3, 4, 5 or 6 ring(s) atoms and include 1, 2 or 3 heteroatoms such as N (nitrogen), O (oxygen) and S (sulfur). In some embodiments, R^5 can be an optionally substituted aryl(C_{1-4} alkyl), an optionally substituted heteroaryl(C_{1-4} alkyl) or an optionally substituted heterocyclyl(C_{1-4} alkyl). For example, R^5 can be an unsubstituted or a substituted benzyl, an unsubstituted or a substituted 5-membered monocyclic heteroaryl, an unsubstituted or a substituted 6-membered monocyclic heteroaryl, an unsubstituted or a substituted 5-membered monocyclic heterocyclyl or an

unsubstituted or a substituted 6-membered monocyclic heterocyclyl. In some embodiments, R^4 and R^5 can be taken together along with the carbon to which R^4 and R^5 are attached to form an optionally substituted monocyclic C_{3-6} cycloalkyl or an optionally substituted 3 to 6 member monocyclic heterocyclyl. Exemplary monocyclic C_{3-6} cycloalkyls and 3 to 6 member monocyclic heterocyclyls include, but are limited to, the following: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, oxetane, thietane, thietane oxide and thietane dioxide, each of the aforementioned can be optionally substituted.

[0100] In some embodiments, R^3 and R^5 can be taken together along with the carbons to which R^3 and R^5 are each attached to form an optionally substituted monocyclic C_{5-7} cycloalkyl. In other embodiments, R^3 and R^5 can be taken together along with the carbons to which R^3 and R^5 are each attached to form an optionally substituted 5 to 7 member monocyclic heterocyclyl. In some embodiments, R^2 and R^4 can be taken together along with the carbons to which R^2 and R^4 are each attached to form an optionally substituted monocyclic C_{5-7} cycloalkyl. In other embodiments, R^2 and R^4 can be taken together along with the carbons to which R^2 and R^4 are each attached to form an optionally substituted 5 to 7 member monocyclic heterocyclyl. Exemplary 5 to 7 member monocyclic heterocyclyls include, but are not limited to, tetrahydrofuran, pyrrolidine, piperidine and tetrahydro-2H-pyran.

[0101] In some embodiments, R^6 can be hydrogen. In other embodiments, R^6 can be an unsubstituted C_{1-4} alkyl. In still other embodiments, R^6 can be an unsubstituted C_{1-4} haloalkyl. Suitable unsubstituted C_{1-4} alkyls and unsubstituted C_{1-4} haloalkyls include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, $-CHF_2$, $-CH_2F$, $-CF_3$, $-CH_2Cl$, $-CHCl_2$ and $-CCl_3$.

[0102] In some embodiments, R^7 can be hydrogen. In other embodiments, R^7 can be an unsubstituted C_{1-4} alkyl, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl or tert-butyl. In still other embodiments, R^7 can be an unsubstituted C_{1-4} haloalkyl, for example, $-CHF_2$, $-CH_2F$, $-CF_3$, $-CH_2Cl$, $-CHCl_2$ and $-CCl_3$. In some embodiments, R^6 and R^7 are taken together along with the carbon to which R^6 and R^7 are attached to form an unsubstituted monocyclic C_{3-4} cycloalkyl. In other embodiments, R^6 and R^7 are taken together along with the carbon to which R^6 and R^7 are attached to form a substituted monocyclic C_{3-4} cycloalkyl. In still other embodiments, R^6 and R^7 are taken together along

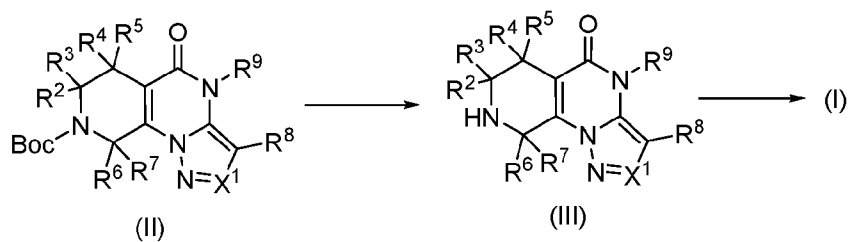
with the carbon to which R⁶ and R⁷ are attached to form an unsubstituted oxetane or an unsubstituted thietane. In yet still other embodiments, R⁶ and R⁷ are taken together along with the carbon to which R⁶ and R⁷ are attached to form a substituted oxetane or a substituted thietane.

[0103] In some embodiments, R², R³, R⁴, R⁵, R⁶ and R⁷ can be each hydrogen. In other embodiments, at least one of R², R³, R⁴, R⁵, R⁶ and R⁷ can be a non-hydrogen group, such as those described herein in the previous paragraphs. In other embodiments, R², R³, R⁴ and R⁵ can be each hydrogen, and R⁶ and R⁷ are taken together along with the carbon to which R⁶ and R⁷ are attached to form an optionally substituted monocyclic C₃₋₄ cycloalkyl. In still other embodiments, R², R³, R⁴ and R⁵ can be each hydrogen, and R⁶ and R⁷ are taken together along with the carbon to which R⁶ and R⁷ are attached to form an unsubstituted or a substituted oxetane or an unsubstituted or a substituted thietane.

Synthesis

[0104] Compounds of Formula (I) along with those described herein may be prepared in various ways. General synthetic routes for preparing compounds of Formula (I) are shown and described herein along with some examples of starting materials used to synthesize compounds described herein. The routes shown and described herein are illustrative only and are not intended, nor are they to be construed, to limit the scope of the claims in any manner whatsoever. Those skilled in the art will be able to recognize modifications of the disclosed syntheses and to devise alternate routes based on the disclosures herein; all such modifications and alternate routes are within the scope of the claims.

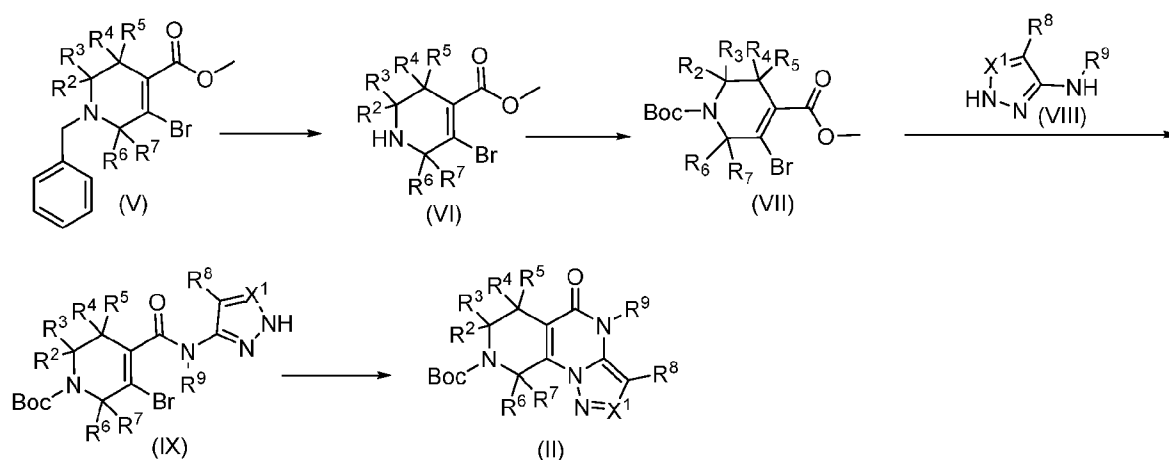
Scheme 1



[0105] Compounds of Formula (I) can be prepared from a Boc intermediate of Formula (II). The Boc group can be cleaved using acidic conditions, for example, in presence of HCl in a suitable solvent (such as 1,4-dioxane) or in presence of copper triflate. The coupling of the intermediate of Formula (III) with a suitable agent can afford a compound of Formula (I), or a pharmaceutically acceptable salt thereof. As an example, compounds of Formula (I) along with pharmaceutically acceptable salts thereof, wherein Z^1 represents $-\text{NH}-\text{C}(=\text{O})-$ and $n = 1$, can be obtained by reacting a compound of Formula (III) with a phenyl carbamate of formula $\text{R}^1\text{-NH}-\text{C}(=\text{O})\text{-O-phenyl}$ or with an isocyanate of general formula $\text{R}^1\text{-N}=\text{C}=\text{O}$, in presence of a suitable base in a suitable solvent. An example of a suitable base is triethylamine and an example of suitable solvent is acetonitrile.

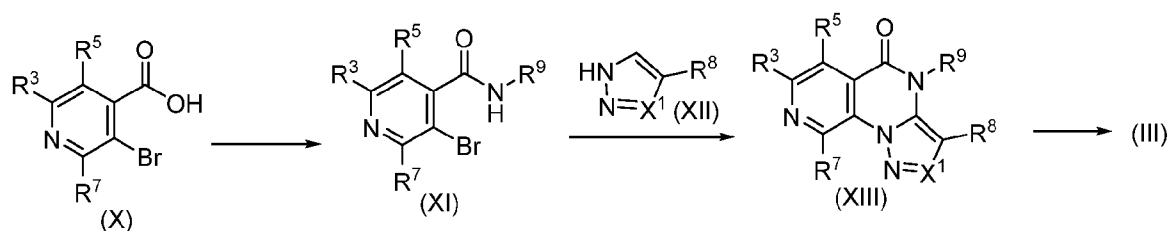
[0106] Other compounds of Formula (I) along with pharmaceutically acceptable salts thereof, wherein Z^1 represents $-\text{C}(=\text{O})-$ and $n = 1$, can be obtained by reacting a compound of Formula (III) with an acyl chloride of general formula $\text{R}^1\text{-C}(=\text{O})\text{-Cl}$ in presence of a base in a suitable solvent. Other compounds of Formula (I) and pharmaceutically acceptable salts thereof, wherein Z^1 represents $-\text{C}(=\text{O})-$ and $n = 1$, can be obtained by reacting compound of Formula (III) with a carboxylic acid of formula $\text{R}^1\text{-C}(=\text{O})\text{-OH}$ in presence of an amide coupling agent (such as HATU) in a suitable solvent. Other compounds of Formula (I) together with pharmaceutically acceptable salts thereof can be prepared from a compound of Formula (III) using methods known in the art.

Scheme 2



[0107] Compounds of Formula (II) can be prepared by various methods known in the art. As an example, a general synthesis of compounds of Formula (II) is depicted in Scheme 2. The benzyl derivative of Formula (V) can be debenzylated by methods known in the art, for example, using chloroethylchloroformate in a suitable solvent (such as dichloroethane) followed by treatment with methanol to give a compound of Formula (VI). A Boc group can be introduced on the nitrogen of a compound of Formula (VI) using (Boc)₂O in the presence of a suitable base (such as trimethylamine) in a suitable solvent (such as dichloromethane) to afford a compound of Formula (VII). If desired, protecting groups can be introduced and cleaved appropriately during the synthetic steps of Scheme 2. The coupling of the ester of Formula (VII) with a heterocycle of Formula (VIII) can be achieved in presence of a base, for example, lithium hexamethyldisilazide in a suitable solvent (such as tetrahydrofuran) to obtain a compound of Formula (IX). In some embodiments, a compound of Formula (VIII) (wherein X¹ can be CR¹⁴) can be an optionally substituted amino pyrazole. Cyclisation of a compound of Formula (IX) can be achieved by using methods known in the art. For example, a compound of Formula (IX) can be reacted with a base (such as potassium carbonate) in presence of copper in a suitable solvent (such as DMF) to afford a compound of Formula (II).

Scheme 3

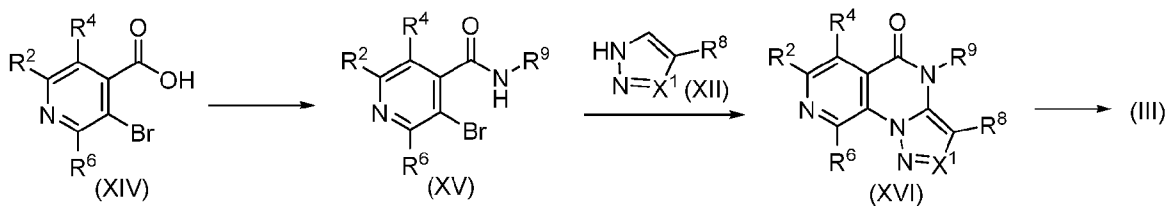


[0108] A compound of Formula (III) in which R², R⁴ and R⁶ each represents H can be prepared from a pyridine-4-carboxylic acid derivative of Formula (X) as shown in Scheme 3. An amine of general formula R⁹-NH₂, can be introduced on the acid of a compound of Formula (X) using amide coupling reactions known to those skilled in the art. For example, EDC/HOBt, in presence of a base (such as diisopropylethylamine) in a suitable solvent (for example, DMF) to afford a compound of Formula (XI). The coupling of a compound of Formula (XII) with a compound of Formula (XI) can be achieved by methods

known in the art. As an example, a compound of Formula (XII) can be reacted with a compound of Formula (XI) to yield a compound of Formula (XIII) utilizing the following conditions: 1,10-phenanthroline, CuI and a base (such as sodium ethoxide) in a suitable solvent (such as DMF) in the presence of oxygen. A compound of Formula (XII), wherein X^1 can be CR^{14} , can be an optionally substituted pyrazole. The reduction of the pyridyl cycle in a compound of Formula (XIII) can be achieved by hydrogenation in presence of a suitable catalyst, such as platinum dioxide, in a suitable solvent, such as methanol, to afford a compound of Formula (III) in which R^2 , R^4 and R^6 each represent H.

[0109] Alternatively, the reduction of the pyridyl moiety of a compound of Formula (XIII) can be achieved in several steps. For example, a compound of Formula (XIII) can be alkylated with 3,4-dimethoxy benzylbromide in a suitable solvent (such as acetonitrile) to afford a pyridinium intermediate that can be isolated, and then reduced with sodium triacetoxyborohydride in a suitable solvent (such as 1,2-dichloroethane). The dimethoxybenzyl group can be cleaved using procedures known to those skilled in the art. Exemplary procedures include using chloroethylchloroformate in a suitable solvent (such as 1,2-dichloroethane) followed by a treatment with methanol to obtain a compound of Formula (III) in which R^2 , R^4 and R^6 each represent H.

Scheme 4



[0110] A compound of Formula (III), wherein R^3 , R^5 and R^7 each represent H, can be prepared from a compound of Formula (XIV) as shown in Scheme 4 using methods known to those skilled in the art.

Pharmaceutical Compositions

[0111] Some embodiments described herein relate to a pharmaceutical composition, that can include an effective amount of a compound described herein (e.g., a

compound, or a pharmaceutically acceptable salt thereof, as described herein) and a pharmaceutically acceptable carrier, excipient or combination thereof. A pharmaceutical composition described herein is suitable for human and/or veterinary applications.

[0112] As used herein, a “carrier” refers to a compound that facilitates the incorporation of a compound into cells or tissues. For example, without limitation, dimethyl sulfoxide (DMSO) is a commonly utilized carrier that facilitates the uptake of many organic compounds into cells or tissues of a subject.

[0113] As used herein, a “diluent” refers to an ingredient in a pharmaceutical composition that lacks pharmacological activity but may be pharmaceutically necessary or desirable. For example, a diluent may be used to increase the bulk of a potent drug whose mass is too small for manufacture and/or administration. It may also be a liquid for the dissolution of a drug to be administered by injection, ingestion or inhalation. A common form of diluent in the art is a buffered aqueous solution such as, without limitation, phosphate buffered saline that mimics the composition of human blood.

[0114] As used herein, an “excipient” refers to an inert substance that is added to a pharmaceutical composition to provide, without limitation, bulk, consistency, stability, binding ability, lubrication, disintegrating ability etc., to the composition. A “diluent” is a type of excipient.

[0115] Proper formulation is dependent upon the route of administration chosen. Techniques for formulation and administration of the compounds described herein are known to those skilled in the art. Multiple techniques of administering a compound exist in the art including, but not limited to, oral, rectal, topical, aerosol, injection and parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, intrathecal, direct intraventricular, intraperitoneal, intranasal and intraocular injections. Pharmaceutical compositions will generally be tailored to the specific intended route of administration.

[0116] One may also administer the compound in a local rather than systemic manner, for example, via injection of the compound directly into the infected area, often in a depot or sustained release formulation. Furthermore, one may administer the compound in a targeted drug delivery system, for example, in a liposome coated with a tissue-specific antibody. The liposomes may be targeted to and taken up selectively by the organ.

[0117] The pharmaceutical compositions disclosed herein may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tableting processes. As described herein, compounds used in a pharmaceutical composition may be provided as salts with pharmaceutically compatible counterions.

Methods of Use

[0118] Some embodiments described herein relate to a method of treating a HBV and/or HDV infection that can include administering to a subject identified as suffering from the HBV and/or HDV infection an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for treating a HBV and/or HDV infection. Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein or a pharmaceutical composition that includes a compound, or a pharmaceutically acceptable salt thereof, as described herein for treating a HBV and/or HDV infection.

[0119] Some embodiments disclosed herein relate to a method of treating a HBV and/or HDV infection that can include contacting a cell infected with the HBV and/or HDV with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for treating a HBV and/or HDV infection. Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein described herein, or a pharmaceutical composition that includes an effective amount of a compound, or

a pharmaceutically acceptable salt thereof, as described herein for treating a HBV and/or HDV infection.

[0120] Some embodiments disclosed herein relate to a method of inhibiting replication of HBV and/or HDV that can include contacting a cell infected with the HBV and/or HDV with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for inhibiting replication of HBV and/or HDV. Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, for inhibiting replication of HBV and/or HDV.

[0121] In some embodiments, the HBV infection can be an acute HBV infection. In some embodiments, the HBV infection can be a chronic HBV infection.

[0122] Some embodiments disclosed herein relate to a method of treating liver cirrhosis that is developed because of a HBV and/or HDV infection that can include administering to a subject suffering from liver cirrhosis and/or contacting a cell infected with the HBV and/or HDV in a subject suffering from liver cirrhosis with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for treating liver cirrhosis with an effective amount of the compound, or a pharmaceutically acceptable salt thereof. Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for treating liver cirrhosis.

[0123] Some embodiments disclosed herein relate to a method of treating liver cancer (such as hepatocellular carcinoma) that is developed because of a HBV and/or HDV infection that can include administering to a subject suffering from the liver cancer and/or contacting a cell infected with the HBV and/or HDV in a subject suffering from the liver cancer with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for treating liver cancer (such as hepatocellular carcinoma). Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for treating liver cancer (such as hepatocellular carcinoma).

[0124] Some embodiments disclosed herein relate to a method of treating liver failure that is developed because of a HBV and/or HDV infection that can include administering to a subject suffering from liver failure and/or contacting a cell infected with the HBV and/or HDV in a subject suffering from liver failure with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for treating liver failure. Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for treating liver failure.

[0125] Various indicators for determining the effectiveness of a method for treating an HBV and/or HDV infection are also known to those skilled in the art. Examples of suitable indicators include, but are not limited to, a reduction in viral load indicated by

reduction in HBV DNA (or load) (e.g., reduction $<10^5$ copies/mL in serum), HBV surface antigen (HBsAg) and HBV e-antigen (HBeAg), a reduction in plasma viral load, a reduction in viral replication, a reduction in time to seroconversion (virus undetectable in patient serum), an increase in the rate of sustained viral response to therapy, an improvement in hepatic function, and/or a reduction of morbidity or mortality in clinical outcomes.

[0126] As used herein, the terms “treat,” “treating,” “treatment,” “therapeutic,” and “therapy” do not necessarily mean total cure or abolition of the disease or condition. Any alleviation of any undesired signs or symptoms of a disease or condition, to any extent can be considered treatment and/or therapy. Furthermore, treatment may include acts that may worsen the subject’s overall feeling of well-being or appearance.

[0127] As used herein, a “subject” refers to an animal that is the object of treatment, observation or experiment. “Animal” includes cold- and warm-blooded vertebrates and invertebrates such as fish, shellfish, reptiles and, in particular, mammals. “Mammal” includes, without limitation, mice, rats, rabbits, guinea pigs, dogs, cats, sheep, goats, cows, horses, primates, such as monkeys, chimpanzees, and apes, and, in particular, humans. In some embodiments, the subject is human.

[0128] The term “effective amount” is used to indicate an amount of an active compound, or pharmaceutical agent, that elicits the biological or medicinal response indicated. For example, an effective amount of compound can be the amount needed to alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. This response may occur in a tissue, system, animal or human and includes alleviation of the signs or symptoms of the disease being treated. Determination of an effective amount is well within the capability of those skilled in the art, in view of the disclosure provided herein. The effective amount of the compounds disclosed herein required as a dose will depend on the route of administration, the type of animal, including human, being treated, and the physical characteristics of the specific animal under consideration. The dose can be tailored to achieve a desired effect, but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize.

[0129] In some embodiments, an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein is an amount that is effective to achieve a sustained virologic response, for example, a sustained viral response 12 month after completion of treatment.

[0130] Subjects who are clinically diagnosed with a HBV and/or HDV infection include “naïve” subjects (e.g., subjects not previously treated for HBV and/or HDV) and subjects who have failed prior treatment for HBV and/or HDV (“treatment failure” subjects). Treatment failure subjects include “non-responders” (subjects who did not achieve sufficient reduction in ALT (alanine aminotransferase) levels, for example, subject who failed to achieve more than 1 log₁₀ decrease from base-line within 6 months of starting an anti-HBV and/or anti-HDV therapy) and “relapsers” (subjects who were previously treated for HBV and/or HDV whose ALT levels have increased, for example, ALT > twice the upper normal limit and detectable serum HBV DNA by hybridization assays). Further examples of subjects include subjects with a HBV and/or HDV infection who are asymptomatic.

[0131] In some embodiments, a compound, or a pharmaceutically acceptable salt thereof, as described herein can be provided to a treatment failure subject suffering from HBV and/or HDV. In some embodiments, a compound, or a pharmaceutically acceptable salt thereof, as described herein can be provided to a non-responder subject suffering from HBV and/or HDV. In some embodiments, a compound, or a pharmaceutically acceptable salt thereof, as described herein can be provided to a relapser subject suffering from HBV and/or HDV. In some embodiments, the subject can have HBeAg positive chronic hepatitis B. In some embodiments, the subject can have HBeAg negative chronic hepatitis B. In some embodiments, the subject can have liver cirrhosis. In some embodiments, the subject can be asymptomatic, for example, the subject can be infected with HBV and/or HDV but does not exhibit any symptoms of the viral infection. In some embodiments, the subject can be immunocompromised. In some embodiments, the subject can be undergoing chemotherapy.

[0132] Examples of agents that have been used to treat HBV and/or HDV include immunomodulating agents, and nucleosides/nucleotides. Examples of immunomodulating agents include interferons (such as IFN- α and pegylated interferons that include PEG-IFN- α -2a); and examples of nucleosides/nucleotides include lamivudine, telbivudine, adefovir

dipivoxil, clevudine, entecavir, tenofovir alafenamide and tenofovir disoproxil. However, some of the drawbacks associated with interferon treatment are the adverse side effects, the need for subcutaneous administration and high cost. Potential advantages of a compound of Formula (I) and/or (II), or a pharmaceutically acceptable salt of any of the foregoing, can be less adverse side effects, delay in the onset of an adverse side effect and/or reduction in the severity of an adverse side effect. A drawback with nucleoside/nucleotide treatment can be the development of resistance, including cross-resistance.

[0133] Resistance can be a cause for treatment failure. The term “resistance” as used herein refers to a viral strain displaying a delayed, lessened and/or null response to an anti-viral agent. In some embodiments, a compound, or a pharmaceutically acceptable salt thereof, as described herein can be provided to a subject infected with an HBV and/or HDV strain that is resistant to one or more anti-HBV and/or anti-HDV agents. Examples of anti-viral agents wherein resistance can develop include lamivudine, telbivudine, adefovir dipivoxil, clevudine, entecavir, tenofovir alafenamide and tenofovir disoproxil. In some embodiments, development of resistant HBV and/or HDV strains is delayed when a subject is treated with a compound, or a pharmaceutically acceptable salt thereof, as described herein compared to the development of HBV and/or HDV strains resistant to other HBV and/or HDV anti-viral agents, such as those described.

[0134] Previously known compounds, such as those provided in WO 2017/156255, were shown to form adducts with glutathione in *in vitro* assays. Formation of glutathione adducts can be a signal that a compound has the potential to induce liver injury. Thus, the formation of glutathione adducts can be used as a signal to predict safety. Unexpectedly, compounds described herein, such as many compounds of Formula (I), and pharmaceutically acceptable salts thereof, have been shown not to form adducts with glutathione in *in vitro* assays. Further, known compounds (for example, those described in WO 2017/156255), have demonstrated potency in a HepG2.2.15 cell based assay with an EC₅₀ of >1000 pM. Many compounds described herein, such as compounds of Formula (I), and pharmaceutically acceptable salts thereof, unexpectedly show improved potency in a HepG2.2.15 cell based assay with an EC₅₀ <1000 pM range. Thus, compounds described herein, including compounds of Formula (I), and pharmaceutically acceptable salts thereof,

can be at least 16 times more potent than previously known compounds. In some embodiments, improved potency can lead to a significantly lower dose requirement and therefore improve daily dose burden as well as lead to improved safety margins.

Combination Therapies

[0135] In some embodiments, a compound, or a pharmaceutically acceptable salt thereof, as described herein can be used in combination with one or more additional agent(s) for treating and/or inhibiting replication HBV and/or HDV. Additional agents include, but are not limited to, an interferon, nucleoside/nucleotide analogs, a sequence specific oligonucleotide (such as anti-sense oligonucleotide and siRNA), nucleic acid polymers (NAPs, such as nucleic acid polymers that reduce HBsAg levels) an entry inhibitor and/or a small molecule immunomodulator. Examples of additional agents include recombinant interferon alpha 2b, IFN- α , PEG-IFN- α -2a, lamivudine, telbivudine, adefovir dipivoxil, clevudine, entecavir, tenofovir alafenamide and tenofovir disoproxil. Examples of NAPs include, but are not limited to, REP 2139, REP 2165 and those described in U.S. Application No. 62/757632, filed November 8, 2018, which is hereby incorporated by reference for the purpose of the NAPs described therein.

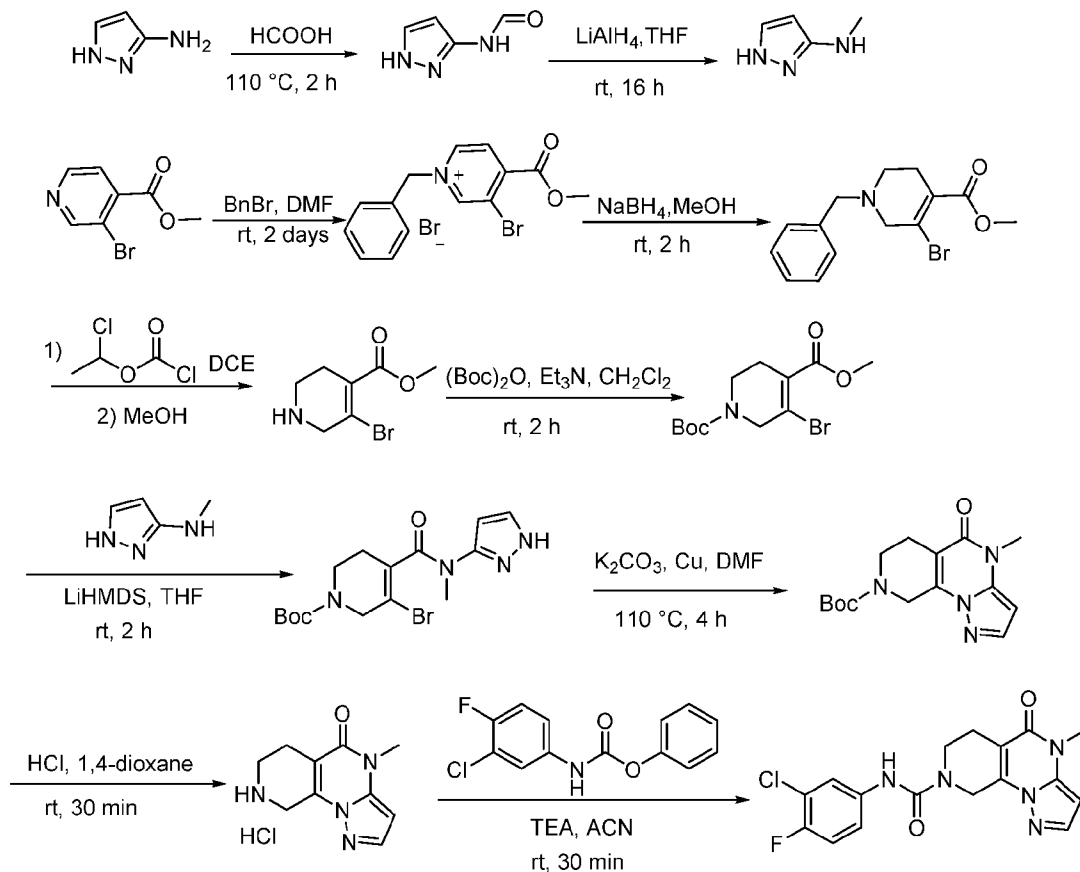
[0136] In some embodiments, a compound, or a pharmaceutically acceptable salt thereof, as described herein can be administered with one or more additional agent(s) together in a single pharmaceutical composition. In some embodiments, a compound, or a pharmaceutically acceptable salt thereof, can be administered with one or more additional agent(s) as two or more separate pharmaceutical compositions. Further, the order of administration of a compound, or a pharmaceutically acceptable salt thereof, as described herein with one or more additional agent(s) can vary.

EXAMPLES

[0137] Additional embodiments are disclosed in further detail in the following examples, which are not in any way intended to limit the scope of the claims.

Example 1

N-(3-chloro-4-fluorophenyl)-4-methyl-5-oxo-5,6,7,9-tetrahydropyrazolo[1,5-a]pyrido[4,3-e]pyrimidine-8(4H)-carboxamide (1)



[0138] A solution of 1H-pyrazol-3-amine (500 mg, 6.02 mmol, 1.00 eq.) in formic acid (3 mL) was stirred for 2 h at 110 °C and then concentrated under reduced pressure. The solution was triturated in cyclohexane (50 mL). The solids were collected by filtration to afford N-(1H-pyrazol-3-yl)formamide (700 mg, crude) as a white solid. LCMS (ESI, m/z): 112 [M+H]⁺, RT: 0.384 min.

[0139] To a stirred solution of N-(1H-pyrazol-3-yl)formamide (1.40 g, 12.6 mmol, 1.00 eq.) in THF (50 mL) was added lithium aluminum hydride (1.43 g, 37.8 mmol, 3.00 eq.) in batches with stirring at 0 °C. The solution was stirred for 16 h at room temperature (rt). The reaction was then quenched with sodium sulfate decahydrate and stirred for 30 min. The mixture was diluted with ethyl acetate (50 mL), and the solids were filtered off. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography with CH₂Cl₂:CH₃OH (10:1) to afford N-methyl-1H-

pyrazol-3-amine (700 mg, 57% yield) as a light yellow oil. LCMS (ESI, m/z): 98 [M+H]⁺, RT: 0.167 min.

[0140] To a stirred solution of methyl 3-bromopyridine-4-carboxylate (10.0 g, 46.3 mmol, 1.00 eq.) in N,N-dimethylformamide (100 mL) was added benzyl bromide (8.71 g, 50.9 mmol, 1.10 eq.). The solution was stirred for 2 days at rt. The solution was triturated in acetone (300 mL) and stirred at 0 °C for 0.5 h. The solids were collected by filtration to afford product 1-benzyl-3-bromo-4-(methoxycarbonyl)pyridin-1-ium bromide (12.0 g, 67% yield) as a white solid. LCMS (ESI, m/z): 306 [M-Br]⁺, RT: 0.618 min.

[0141] To a stirred solution of 1-benzyl-3-bromo-4-(methoxycarbonyl)pyridin-1-ium bromide (5.00 g, 12.9 mmol, 1.00 eq.) in CH₃OH (50 mL) was added sodium borohydride (2.44 g, 64.6 mmol, 5.00 eq.) in batches with stirring at 0 °C. The solution was stirred for 2 h at rt, and the reaction was quenched with water (30 mL). The mixture was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with ethyl acetate (EA):petroleum ether (PE) (1:50) to afford methyl 1-benzyl-3-bromo-5,6-dihydro-2H-pyridine-4-carboxylate 2.50 g (62% yield) as a light yellow oil. LCMS (ESI, m/z): 310 [M+H]⁺, RT: 0.754 min.

[0142] To a stirred solution of methyl 1-benzyl-3-bromo-5,6-dihydro-2H-pyridine-4-carboxylate (2.40 g, 7.74 mmol, 1.00 eq.) in 1,2-dichloroethane (50 mL) was added chloroethyl chloroformate (1.22 g, 8.53 mmol, 1.10 eq.) dropwise with stirring at 0 °C. The solution was stirred for 1 h at 84 °C and then concentrated. Methanol (50 mL) was added to the mixture at rt. The solution was stirring for an additional 1 h at 65 °C and then concentrated. The residue was purified by silica gel column chromatography with CH₂Cl₂:CH₃OH (10:1) to afford methyl 3-bromo-1,2,5,6-tetrahydropyridine-4-carboxylate (1.20 g, 70% yield) as a yellow oil. LCMS (ESI, m/z): 220 [M+H]⁺, RT: 0.613 min.

[0143] To a stirred solution of methyl 3-bromo-1,2,5,6-tetrahydropyridine-4-carboxylate (2.90 g, 13.2 mmol, 1.00 eq.) in CH₂Cl₂ (20 mL) was added triethylamine (4.00 g, 39.5 mmol, 3.00 eq.). A solution of di-tert-butyl dicarbonate (3.16 g, 14.5 mmol, 1.10 eq.) in dichloromethane (1 mL) was then added dropwise with stirring at 0 °C. The solution was

stirred for 2 h at rt and then concentrated. The residue was purified by silica gel column chromatography with EA:PE (1:9) to afford 1-tert-butyl 4-methyl 3-bromo-5,6-dihydro-2H-pyridine-1,4-dicarboxylate 3.00 g (71% yield) as a light yellow oil. LCMS (ESI, m/z): 320 [M+H]⁺, RT: 1.228 min.

[0144] To a stirred solution of 1-tert-butyl 4-methyl 3-bromo-5,6-dihydro-2H-pyridine-1,4-dicarboxylate (500 mg, 1.56 mmol, 1.00 eq.) in tetrahydrofuran (10 mL) was added lithium hexamethyldisilazide (4.7 mL, 4.70 mmol, 3.00 eq., 1 mol/L in THF) and N-methyl-1H-pyrazol-3-amine (167 mg, 1.72 mmol, 1.10 eq.). The solution was stirred for 2 h at rt. The reaction was quenched with CH₃OH (15 mL), and then the mixture was concentrated under reduced pressure. The crude product was purified by reverse flash chromatography with the following gradient conditions: column C₁₈; mobile phase, ACN:H₂O = (40%:60%); detector, 254 nm to afford tert-butyl 3-bromo-4-[methyl(1H-pyrazol-3-yl)carbamoyl]-5,6-dihydro-2H-pyridine-1-carboxylate (240 mg, 40% yield) as a light yellow oil. LCMS (ESI, m/z): 385 [M+H]⁺, RT: 1.063 min.

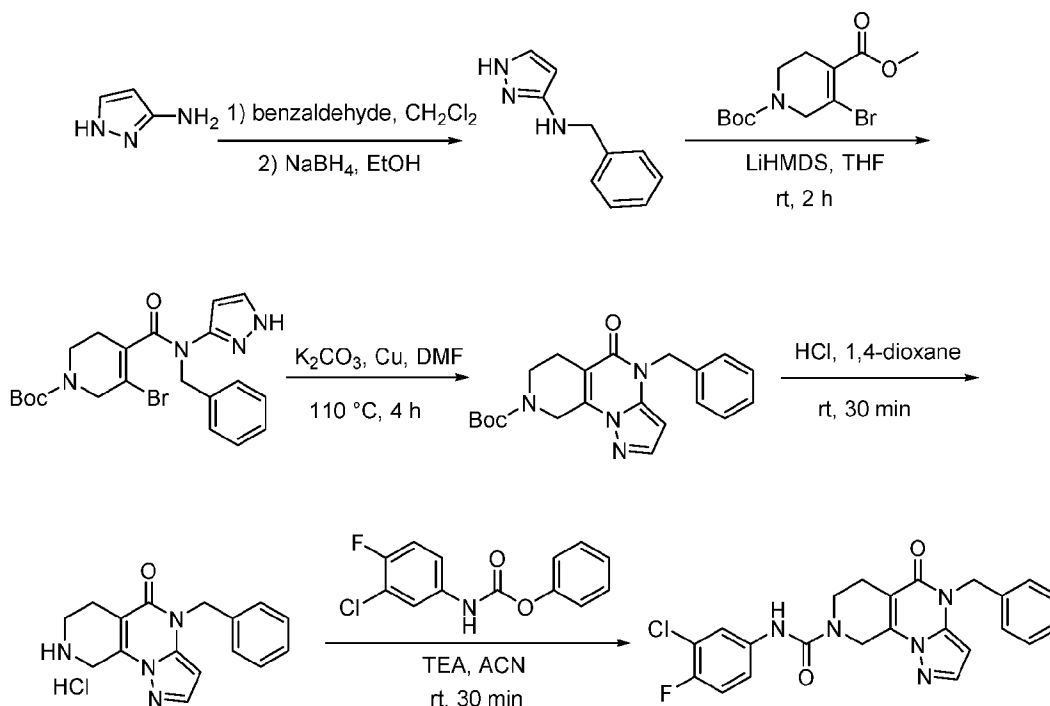
[0145] To a solution of tert-butyl 3-bromo-4-[methyl(1H-pyrazol-3-yl)carbamoyl]-5,6-dihydro-2H-pyridine-1-carboxylate (380 mg, 0.986 mmol, 1.00 eq.) in N,N-dimethylformamide (5.00 mL) was added potassium carbonate (273 mg, 1.97 mmol, 2.00 eq.) and copper (125 mg, 1.97 mmol, 2.00 eq.). The solution was stirred for 4 h at 110 °C. The solids were filtered off, and the filtration was concentrated under reduced pressure. The crude product was purified by reverse flash chromatography with the following gradient conditions: column C₁₈; mobile phase, ACN:H₂O = (40%:60%); detector, 254 nm to afford tert-butyl 7-methyl-8-oxo-2,3,7,12-tetraazatricyclo[7.4.0.0^{2,6}]trideca-1(9),3,5-triene-12-carboxylate (130 mg, 43% yield) as a light yellow oil. LCMS (ESI, m/z): 305 [M+H]⁺, RT: 1.112 min.

[0146] The mixture of tert-butyl 7-methyl-8-oxo-2,3,7,12-tetraazatricyclo[7.4.0.0^{2,6}]trideca-1(9),3,5-triene-12-carboxylate (130 mg, 0.427 mmol, 1.00 eq.) in HCl in 1,4-dioxane (2.00 mL, 4 mol/L) was stirred for 30 min at rt and then concentrated under reduced pressure to afford 7-methyl-2,3,7,12-tetraazatricyclo[7.4.0.0^{2,6}]trideca-1(9),3,5-trien-8-one hydrochloride salt (120 mg, crude) as a light yellow solid. LCMS (ESI, m/z): 205 [M+H-HCl]⁺, RT: 0.648 min.

[0147] To a stirred solution of 7-methyl-2,3,7,12-tetraazatricyclo[7.4.0.0^{2,6}]trideca-1(9),3,5-triene-8-one hydrochloride salt (150 mg, 0.623 mmol, 1.00 eq.) in acetonitrile (8 mL) was added phenyl N-(3-chloro-4-fluorophenyl)carbamate (215 mg, 0.808 mmol, 1.30 eq.) and triethylamine (743 mg, 7.345 mmol, 11.8 eq.). The solution was stirred for 30 min at rt and then concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C₁₈ Column, 30 x 150 mm 5 μ m; Mobile Phase A: Water (10 mmol/L NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 45% B in 10 min; 254&220 nm to afford N-(3-chloro-4-fluorophenyl)-7-methyl-8-oxo-2,3,7,12-tetraazatricyclo[7.4.0.0^{2,6}]trideca-1(9),3,5-triene-12-carboxamide (compound 1, 28.0 mg, 10% yield) as a white solid. LCMS (ESI, m/z): 376 [M+H]⁺, RT: 1.608 min. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.04 (s, 1H), 7.87 (d, *J* = 2.0 Hz, 1H), 7.75 (dd, *J* = 6.8, 2.6 Hz, 1H), 7.48-7.40 (m, 1H), 7.31 (t, *J* = 9.1 Hz, 1H), 6.23 (d, *J* = 2.1 Hz, 1H), 4.83 (s, 2H), 3.75 (t, *J* = 5.7 Hz, 2H), 3.47 (s, 3H), 2.53-2.50 (s, 2H).

Example 2

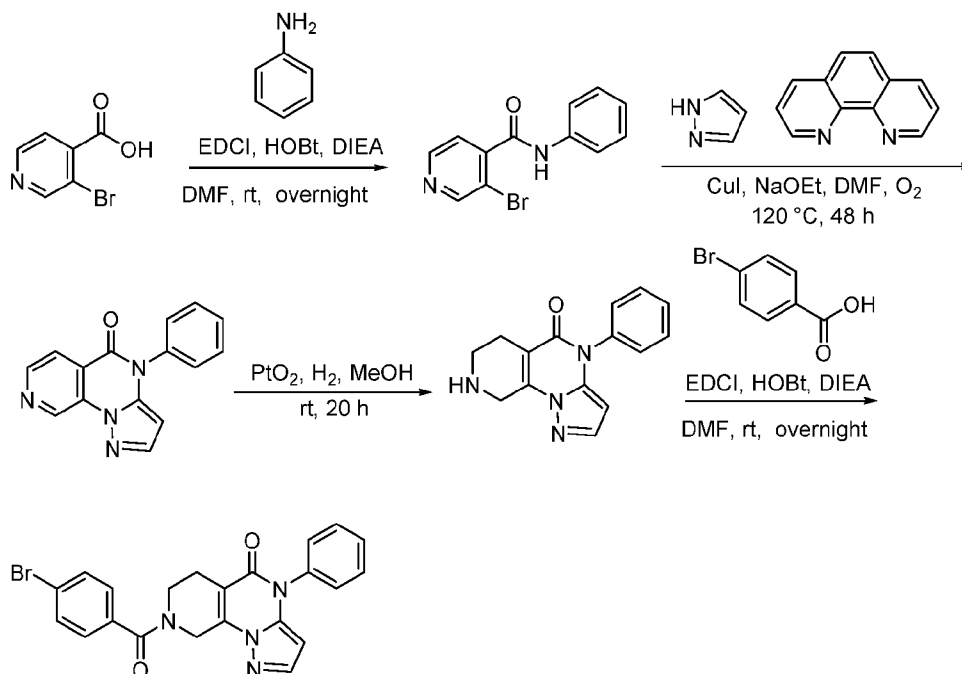
4-benzyl-N-(3-chloro-4-fluorophenyl)-5-oxo-5,6,7,9-tetrahydropyrazolo[1,5-a]pyrido[4,3-e]pyrimidine-8(4H)-carboxamide (2)



[0148] To a stirred solution of 1H-pyrazol-3-amine (1.50 g, 18.1 mmol, 1.00 eq.) in CH₂Cl₂ (20 mL) was added benzaldehyde (2.11 g, 19.9 mmol, 1.10 eq.), triethylamine (2.01 g, 19.9 mmol, 1.10 eq.). The solution was stirred overnight at rt and then concentrated under reduced pressure. The residue was dissolved in EtOH (30 mL), and sodium borohydride (1.02 g, 27.1 mmol, 1.50 eq.) was then added in batches at 0 °C. The solution was allowed to react for 2 h at rt. The reaction was then quenched with water (30 mL), and the mixture was extracted with EA (2 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with CH₂Cl₂:CH₃OH (40:1) to afford N-benzyl-1H-pyrazol-3-amine (1.70 g, 54% yield) as a white solid. LCMS (ESI, m/z): 174 [M+H]⁺, RT: 0.649 min.

[0149] 4-benzyl-N-(3-chloro-4-fluorophenyl)-5-oxo-5,6,7,9-tetrahydropyrazolo[1,5-a]pyrido[4,3-e]pyrimidine-8(4H)-carboxamide, compound 2, was prepared as a white solid according to the procedures of Example 1 g) to j) by substituting N-benzyl-1H-pyrazol-3-amine for N-methyl-1H-pyrazol-3-amine. LCMS (ESI, m/z): 452 [M+H]⁺, RT: 1.630 min. ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.04 (s, 1H), 7.87-7.72 (m, 2H), 7.45 (s, 1H), 7.38-7.25 (m, 6H), 6.22 (d, *J* = 2.2 Hz, 1H), 5.24 (s, 2H), 4.85 (s, 2H), 3.77 (d, *J* = 5.9 Hz, 2H), 2.59 (s, 2H).

Example 3
8-(4-bromobenzoyl)-4-phenyl-6,7,8,9-tetrahydropyrazolo[1,5-a]pyrido[4,3-e]pyrimidin-5(4H)-one (3)



[0150] A solution of 3-bromopyridine-4-carboxylic acid (20.0 g, 99.0 mmol, 1.00 eq.), aniline (10.1 g, 108 mmol, 1.10 eq.), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (22.7 g, 118 mmol, 1.20 eq.), 1-hydroxybenzotriazole (16.0 g, 118 mmol, 1.20 eq.) and N,N-diisopropylethylamine (38.3 g, 297 mmol, 3.00 eq.) in N,N-dimethylformamide (200 mL) was stirred overnight at rt, and then the reaction was quenched with water (200 mL). The mixture was extracted with EA (3 x 500 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EA:PE (45:55) to afford 3-bromo-N-phenylpyridine-4-carboxamide (21.7 g, 79% yield) as an off-white solid. LCMS (ESI, m/z): 277 [M+H]⁺, RT: 0.824 min.

[0151] To a stirred mixture of 3-bromo-N-phenylpyridine-4-carboxamide (2.00 g, 7.21 mmol, 1.00 eq.), pyrazole (0.490 g, 7.217 mmol, 1.00 eq.), 1,10-phenanthroline (0.520 g, 2.88 mmol, 0.40 eq.) and sodium ethoxide (0.980 g, 14.4 mmol, 2.00 eq.) in N,N-dimethylformamide (20 mL) was added cuprous iodide (0.270 g, 1.44 mmol, 0.20 eq.). The mixture was stirred for 48 h at 120 °C under an oxygen atmosphere. The reaction was

quenched with water (100 mL). The mixture was extracted with CH₂Cl₂ (3 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EA:PE (6:4) to afford 7-phenyl-2,3,7,12-tetraazatricyclo[7.4.0.0[^][2,6]]trideca-1(9),3,5,10,12-pentaen-8-one (1.10 g, 58% yield) as a yellow solid. LCMS (ESI, m/z): 263 [M+H]⁺, RT: 0.845 min.

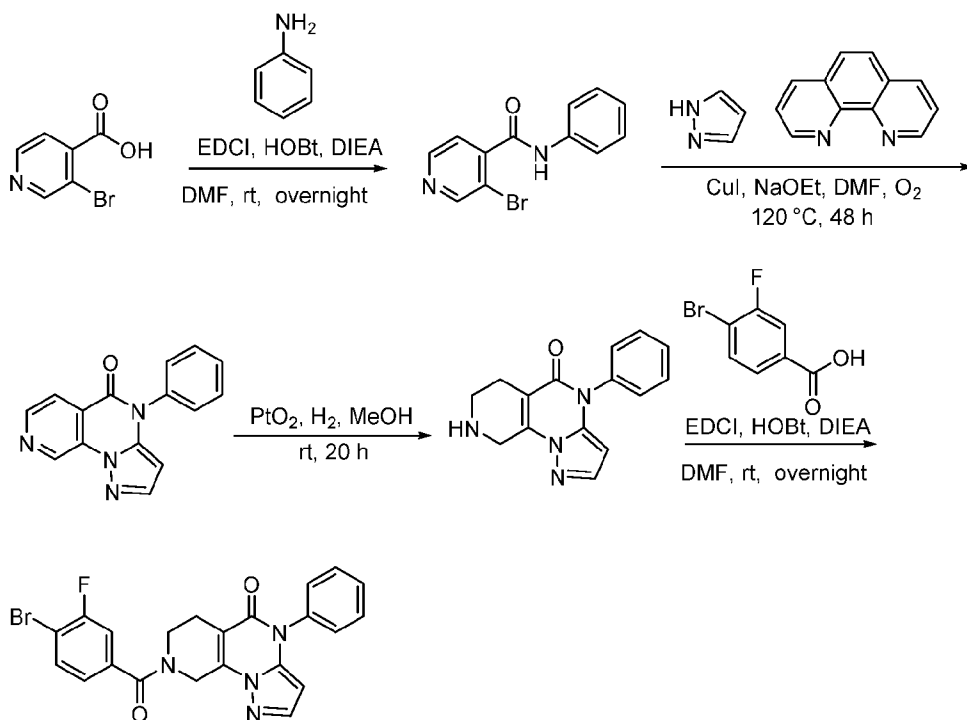
[0152] To a stirred mixture of 4-phenylpyrazolo[1,5-a]pyrido[4,3-e]pyrimidin-5(4H)-one (340 mg, 0.915 mmol, 1.00 eq.) in MeOH (60 mL) was added platinum dioxide (34.0 mg) under H₂ atmosphere (3 atm). The mixture was stirred overnight at rt. The solid was filtered off, and the filtrate was concentrated under reduced pressure to afford 4-phenyl-6,7,8,9-tetrahydropyrazolo[1,5-a]pyrido[4,3-e]pyrimidin-5(4H)-one (330 mg, 96% yield) as a yellow solid. LCMS (ESI, m/z): 267 [M+H]⁺, RT: 0.647 min.

[0153] To a stirred mixture of 7-phenyl-2,3,7,12-tetraazatricyclo[7.4.0.0[^][2,6]]trideca-1(9),3,5-trien-8-one (165 mg, 0.620 mmol, 1.00 eq.), 4-bromobenzoic acid (137 mg, 0.682 mmol, 1.10 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (142 mg, 0.744 mmol, 1.20 eq.) and 1-hydroxybenzotriazole (100 mg, 0.744 mmol, 1.20 eq.) in N,N-dimethylformamide (5.0 mL) was added N,N-diisopropylethylamine (240 mg, 1.86 mmol, 3.00 eq.). The mixture was stirred overnight at rt, and then diluted with water (15 mL). The mixture was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by Prep-HPLC: Column: XBridge Prep C₁₈ OBD Column, 19 x 150 mm 5 μm; Mobile Phase A: Water (10 mmol/L NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 35% B to 65% B in 7 min; 220 nm to afford the final compound. The final compound was repurified by Prep A Chiral_SFC: Column: DAICEL DCpak P4VP, 20 mm x 250 mm, 5 μm; Mobile Phase A: CO₂, Mobile Phase B: IPA (8 mmol/L NH₃.MeOH)--HPLC; Flow rate: 40 mL/min; Gradient: 30% B; 254 nm to afford 8-(4-bromobenzoyl)-4-phenyl-6,7,8,9-tetrahydropyrazolo[1,5-a]pyrido[4,3-e]pyrimidin-5(4H)-one (compound 3, 72.5 mg, 26% yield) as a white solid. LCMS (ESI, m/z): 449 [M+H]⁺,

RT: 1.591 min. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.87-7.58 (m, 5H), 7.57-7.38 (m, 5H), 5.52-5.32 (m, 1H), 5.09-4.73(m, 2H), 4.02-3.52 (m, 2H), 2.51 (s, 2H).

Example 4

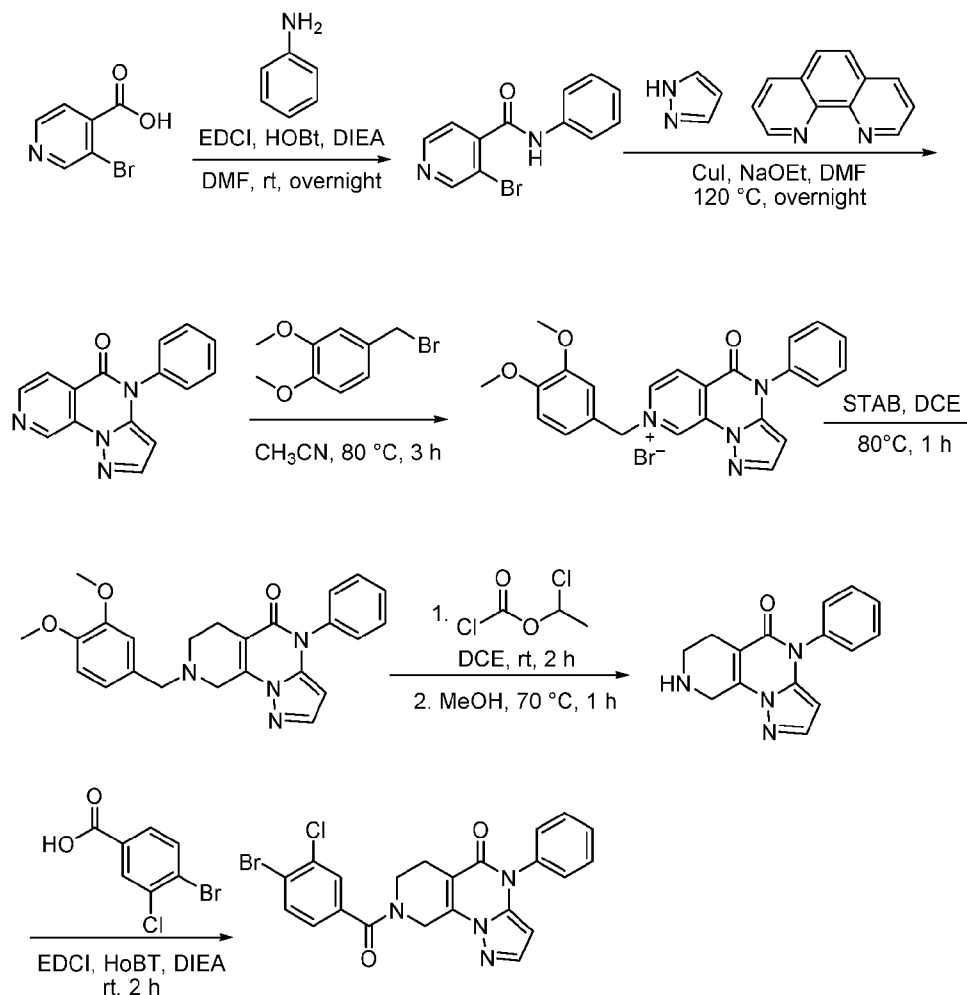
8-(4-bromo-3-fluorobenzoyl)-4-phenyl-6,7,8,9-tetrahydropyrazolo[1,5-a]pyrido[4,3-e]pyrimidin-5(4H)-one (4)



[0154] Compound 4 was prepared as a white solid according to the procedures of Example 3 a) to d) by substituting 4-bromo-3-fluorobenzoic acid for 4-bromobenzoic acid. LCMS (ESI, m/z): 467 $[\text{M}+\text{H}]^+$, RT: 1.632 min. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.97-7.83 (m, 1H), 7.82 -7.52 (m, 5H), 7.51-7.41 (m, 2H), 7.40-7.19 (m, 1H), 5.53-5.37 (m, 1H), 5.15-4.70 (m, 2H), 4.01-3.52 (m, 2H), 2.62-2.54 (m, 2H).

Example 5

12-(4-bromo-3-chlorobenzoyl)-7-phenyl-2,3,7,12-tetraazatricyclo[7.4.0.0^{2,6}]trideca-1(9),3,5-trien-8-one (5)



[0155] A solution of 3-bromopyridine-4-carboxylic acid (20.0 g, 99.0 mmol, 1.00 eq.), aniline (10.1 g, 108 mmol, 1.10 eq.), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (22.7 g, 118 mmol, 1.20 eq.), 1-hydroxybenzotriazole (16.0 g, 118 mmol, 1.20 eq.) and N,N-diisopropylethylamine (38.3 g, 297 mmol, 3.00 eq.) in N,N-dimethylformamide (200 mL) was stirred overnight at rt, and the reaction was then quenched with water (500 mL). The mixture was extracted with EA (3 x 500 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EA:PE (45:55) to afford 3-bromo-N-phenylpyridine-4-carboxamide (21.7 g, 79% yield) as an off-white solid. LCMS (ESI, m/z): 277 [M+H]⁺, RT: 0.824 min.

[0156] To a stirred mixture of 3-bromo-N-phenylpyridine-4-carboxamide (2.00 g, 7.21 mmol, 1.00 eq.), pyrazole (0.49 g, 7.217 mmol, 1.00 eq.), 1,10-phenanthroline (0.520 g, 2.88 mmol, 0.400 eq.) and sodium ethoxide (0.980 g, 14.4 mmol, 2.00 eq.) in N,N-dimethylformamide (20 mL) was added cuprous iodide (0.270 g, 1.44 mmol, 0.200 eq.). The mixture was stirred for 48 h at 120 °C under an oxygen atmosphere. The reaction was quenched with water (100 mL), and the mixture was extracted with CH₂Cl₂ (3 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EA:PE (6:4) to afford 7-phenyl-2,3,7,12-tetraazatricyclo[7.4.0.0[^][2,6]]trideca-1(9),3,5,10,12-pentaen-8-one (1.10 g, 58% yield) as a yellow solid. LCMS (ESI, m/z): 263 [M+H]⁺, RT: 0.845 min.

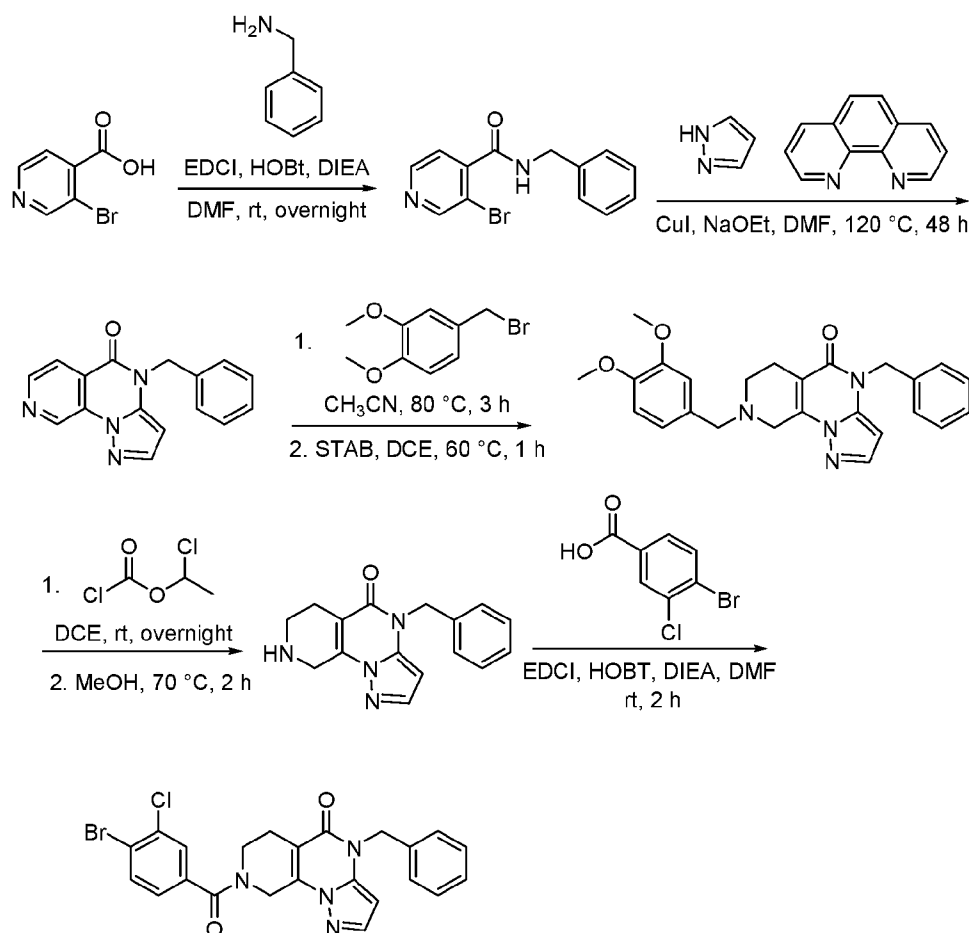
[0157] Into a round-bottom flask were added 7-phenyl-2,3,7,12-tetraazatricyclo[7.4.0.0[^][2,6]]trideca-1(9),3,5,10,12-pentaen-8-one (500 mg, 1.90 mmol, 1.00 eq.), 4-(bromomethyl)-1,2-dimethoxybenzene (616 mg, 2.66 mmol, 1.40 eq.) and acetonitrile (5 mL) at rt. The mixture was stirred for 3 h at 80 °C and then concentrated under reduced pressure. The residue was purified by trituration with diethyl ether (10 mL). The precipitated solids were collected by filtration, washed with diethyl ether (3 x 5 mL) and dried to afford 12-[(3,4-dimethoxyphenyl)methyl]-8-oxo-7-phenyl-2,3,7,12-tetraazatricyclo[7.4.0.0[^][2,6]]trideca-1(9),3,5,10,12-pentaen-12-ium bromide 900 mg (crude) as a yellow solid. LCMS (ESI, m/z): 413 [M-Br]⁺, RT: 0.796 min.

[0158] Into a round-bottom flask were added 12-[(3,4-dimethoxyphenyl)methyl]-8-oxo-7-phenyl-2,3,7,12-tetraazatricyclo[7.4.0.0[^][2,6]]trideca-1(9),3,5,10,12-pentaen-12-ium bromide (900 mg, 1.82 mmol, 1.00 eq.), sodium triacetoxyborohydride (2.76 g, 13.1 mmol, 7.20 eq.) and 1,2-dichloroethane (10 mL) at rt. The mixture was stirred for 1 h at 80 °C, and the reaction was quenched with water (10 mL). The mixture was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by Prep-TLC (silica, PE:EA (1:1)) to afford 12-[(3,4-dimethoxyphenyl)methyl]-7-phenyl-2,3,7,12-tetraazatricyclo[7.4.0.0[^][2,6]]trideca-1(9),3,5-trien-8-one (300 mg, 40% yield) as a white solid. LCMS (ESI, m/z): 417 [M+H]⁺, RT: 0.773 min.

[0159] Into a round-bottom flask were added 7-benzyl-12-[(3,4-dimethoxyphenyl)methyl]-2,3,7,12-tetraazatricyclo[7.4.0.0[^][2,6]]trideca-1(9),3,5-trien-8-one (300 mg, 0.697 mmol, 1.00 eq.), chloroethyl chloroformate (119 mg, 0.836 mmol, 1.20 eq.) and 1,2-dichloroethane (4 mL) at rt. The mixture was stirred for 2 h at rt and then concentrated under reduced pressure. The mixture was dissolved in MeOH (4 mL) and stirred for 1 h at 70 °C. The mixture was concentrated under reduced pressure to afford 7-benzyl-2,3,7,12-tetraazatricyclo[7.4.0.0[^][2,6]]trideca-1(9),3,5-trien-8-one 440 mg (crude) as a brown oil. LCMS (ESI, m/z): 267 [M+H]⁺, RT: 0.647 min.

[0160] Into a round-bottom flask were added 7-phenyl-2,3,7,12-tetraazatricyclo[7.4.0.0[^][2,6]]trideca-1(9),3,5-trien-8-one (440 mg, 1.65 mmol, 1.00 eq.), 4-bromo-3-chlorobenzoic acid (466 mg, 1.98 mmol, 1.20 eq.), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (475 mg, 2.47 mmol, 1.50 eq.), 1-hydroxybenzotriazole (335 mg, 2.47 mmol, 1.50 eq.), N,N-diisopropylethylamine (641 mg, 4.95 mmol, 3.00 eq.) and N,N-dimethylformamide (5 mL) at rt. The mixture was stirred for 2 h at rt. The reaction was quenched with water (20 mL), and the mixture was extracted with EA (3 x 30 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C₁₈ Column, 30 x 150 mm 5 µm; Mobile Phase A: Water (10 mmol/L NH₄HCO₃+0.1%NH₃.H₂O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 35% B in 7 min; 254 nm to afford 12-(4-bromo-3-chlorobenzoyl)-7-phenyl-2,3,7,12-tetraazatricyclo[7.4.0.0[^][2,6]]trideca-1(9),3,5-trien-8-one (compound 5, 125.8 mg, 15% yield) as a white solid. LCMS (ESI, m/z): 483 [M+H]⁺, RT: 1.724 min. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 8.4 Hz, 1H), 7.66-7.49 (m, 5H), 7.39 (d, *J* = 7.6 Hz, 2H), 7.26-7.25 (m, 1H), 5.51 (br, 1H), 5.15 (br, 2H), 3.73 (br, 2H), 2.76 (br, 2H).

Example 6
7-benzyl-12-(4-bromo-3-chlorobenzoyl)-2,3,7,12-tetraazatricyclo[7.4.0.0^{2,6}]trideca-
1(9),3,5-trien-8-one (6)



[0161] Into a 100-mL round-bottom flask, was placed benzylamine (1.00 g, 9.33 mmol, 1.00 eq.), 3-bromopyridine-4-carboxylic acid (2.07 g, 10.3 mmol, 1.10 eq.), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.15 g, 11.2 mmol, 1.20 eq.), 1-hydroxybenzotriazole (1.51 g, 11.2 mmol, 1.20 eq.), N,N-dimethylformamide (20 mL), N,N-diisopropylethylamine (3.62 g, 28.0 mmol, 3.00 eq.). The solution was stirred overnight at rt, and the reaction was then quenched with water (100 mL). The mixture was extracted with EA (3 x 500 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EA:PE (45:55) to afford N-benzyl-3-bromopyridine-4-carboxamide (1.00 g, 37% yield) as a white solid. LCMS (ESI, m/z): 291 [M+H]⁺, RT: 0.666 min.

[0162] To a stirred solution of N-benzyl-3-bromopyridine-4-carboxamide (1.00 g, 3.44 mmol, 1.00 eq.), 1,10-phenanthroline (0.120 g, 0.666 mmol, 0.19 eq.), pyrazole (0.280 g, 4.12 mmol, 1.20 eq.) and sodium ethoxide (0.470 g, 6.86 mmol, 2.00 eq.) in N,N-dimethylformamide (15 mL) was added cuprous iodide (0.130 g, 0.687 mmol, 0.200 eq.). The mixture was stirred for 48 h at 120 °C under an oxygen atmosphere. The reaction was quenched with water (100 mL), and the mixture was extracted with EA (3 x 40 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EA:PE (2:1) to afford 7-benzyl-2,3,7,12-tetraazatricyclo[7.4.0.0[^][2,6]]trideca-1(9),3,5,10,12-pentaen-8-one (410 mg, 43% yield) as a yellow green solid. LCMS (ESI, m/z): 277 [M+H]⁺, RT: 0.937 min.

[0163] A solution of 7-benzyl-2,3,7,12-tetraazatricyclo[7.4.0.0[^][2,6]]trideca-1(9),3,5,10,12-pentaen-8-one (230 mg, 0.832 mmol, 1.00 eq.) and 4-(bromomethyl)-1,2-dimethoxybenzene (269 mg, 1.16 mmol, 1.40 eq.) in acetonitrile (6 mL) was stirred for 3 h at 80 °C. The mixture was concentrated under reduced pressure. The residue was washed with diethyl ether (3 x 10 mL) and then dissolved in 1,2-dichloroethane (6 mL). Sodium triacetoxyborohydride (1.06 g, 4.99 mmol, 6.00 eq.) was added. The mixture was stirred for 1 h at 60 °C, and the reaction was then quenched with water (10 mL). The mixture was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by Prep-TLC (silica, PE:EA (1:1)) to afford 7-benzyl-12-[(3,4-dimethoxyphenyl)methyl]-2,3,7,12-tetraazatricyclo[7.4.0.0[^][2,6]]trideca-1(9),3,5-trien-8-one (240 mg, 67% yield) as a white solid. LCMS (ESI, m/z): 431 [M+H]⁺, RT: 0.640 min.

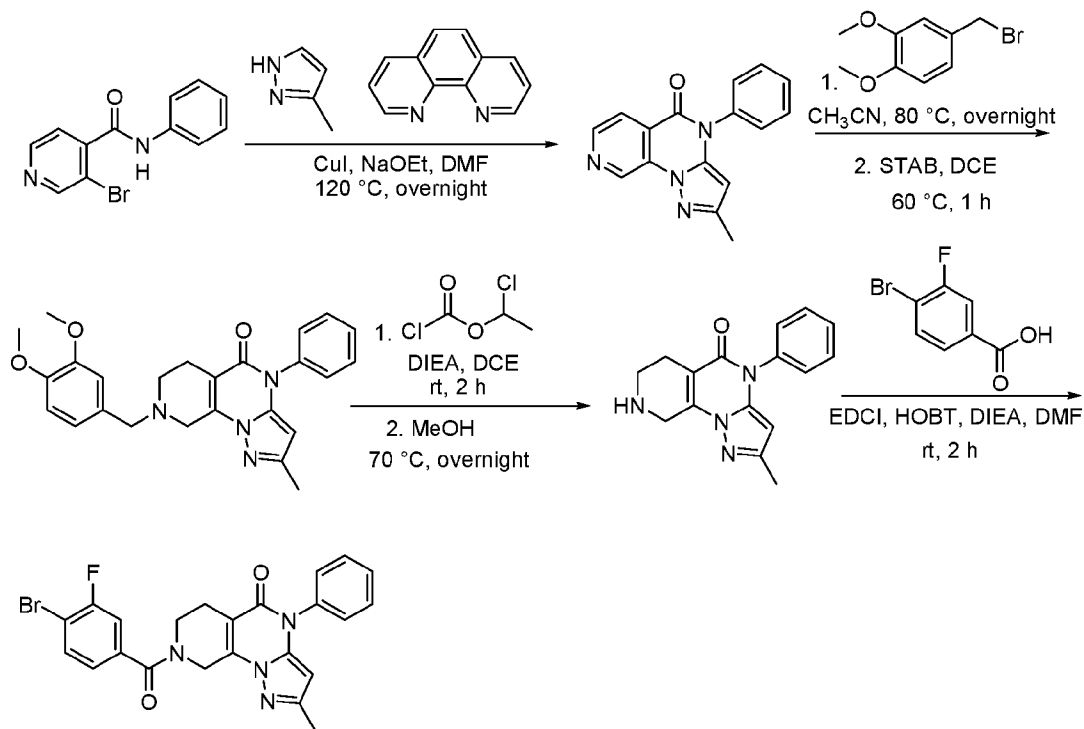
[0164] Into a round-bottom flask were added 7-benzyl-12-[(3,4-dimethoxyphenyl)methyl]-2,3,7,12-tetraazatricyclo[7.4.0.0[^][2,6]]trideca-1(9),3,5-trien-8-one (100 mg, 0.232 mmol, 1.00 eq.), chloroethyl chloroformate (39.8 mg, 0.279 mmol, 1.20 eq.) and 1,2-dichloroethane (3 mL) at rt. The mixture was stirred overnight at rt and then concentrated under reduced pressure. The residue was dissolved in methanol (3 mL) and stirred for 2 h at 70 °C. The mixture was concentrated under reduced pressure to afford 7-

benzyl-2,3,7,12-tetraazatricyclo[7.4.0.0^{2,6}]trideca-1(9),3,5-trien-8-one 70 mg (crude) as a brown oil. LCMS (ESI, m/z): 281 [M+H]⁺, RT: 0.573 min.

[0165] Into a round-bottom flask were added 7-benzyl-2,3,7,12-tetraazatricyclo[7.4.0.0^{2,6}]trideca-1(9),3,5-trien-8-one (70.0 mg, 0.250 mmol, 1.00 eq.), 4-bromo-3-chlorobenzoic acid (70.5 mg, 0.300 mmol, 1.20 eq.), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (71.8 mg, 0.375 mmol, 1.50 eq.), 1-hydroxybenzotriazole (50.6 mg, 0.375 mmol, 1.50 eq.), N,N-diisopropylethylamine (96.8 mg, 0.749 mmol, 3.00 eq.) and N,N-dimethylformamide (2 mL) at rt. The mixture was stirred for 2 h at rt, and the reaction was quenched with water (10 mL). The mixture was extracted with EA (3 x 30 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C₁₈ Column, 30 x 150 mm 5 μ m; Mobile Phase A: Water (10 mmol/L NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 46% B to 76% B in 7 min; 220 nm to afford 7-benzyl-12-(4-bromo-3-chlorobenzoyl)-2,3,7,12-tetraazatricyclo[7.4.0.0^{2,6}]trideca-1(9),3,5-trien-8-one (compound 6, 39.9 mg, 32% yield) as an off-white solid. LCMS (ESI, m/z): 497 [M+H]⁺, RT: 1.605 min. ¹H NMR (300 MHz, Chloroform-*d*) δ 7.75-7.61 (m, 3H), 7.36-7.30 (m, 5H), 7.25 (d, *J* = 1.8 Hz, 1H) 5.91 (d, *J* = 1.8 Hz, 1H), 5.25 (s, 2H), 5.10-4.76 (m, 2H), 4.04-3.72(m, 2H), 2.79 (br, 2H).

Example 7

12-(4-bromo-3-fluorobenzoyl)-4-methyl-7-phenyl-2,3,7,12-tetraazatricyclo[7.4.0.0[^][2,6]]trideca-1(9),3,5-trien-8-one (7)



[0166] A solution of 3-bromo-N-phenylpyridine-4-carboxamide (1.00 g, 3.61 mmol, 1.00 eq.), 3-methyl-1H-pyrazole (0.300 g, 3.61 mmol, 1.00 eq.), 1,10-phenanthroline (0.260 g, 1.44 mmol, 0.40 eq.), sodium ethoxide (0.490 g, 7.22 mmol, 2.00 eq.) and cuprous iodide (0.140 g, 0.722 mmol, 0.20 eq.) in N,N-dimethylformamide (15 mL) was stirred overnight at 120 °C under an oxygen atmosphere. The reaction was quenched with water (50 mL), and the mixture was extracted with EA (3 x 50 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by Prep-TLC (silica, EA) to afford 5-methyl-7-phenyl-2,3,7,12-tetraazatricyclo[7.4.0.0[^][2,6]]trideca-1(9),3,5,10,12-pentaen-8-one (440 mg, 44% yield) as a light yellow solid. LCMS (ESI, m/z): 277 [M+H]⁺, RT: 0.639 min.

[0167] A mixture of 4-methyl-7-phenyl-2,3,7,12-tetraazatricyclo[7.4.0.0[^][2,6]]trideca-1(9),3,5,10,12-pentaen-8-one (0.440 g, 1.59 mmol, 1.00 eq.) and 4-(bromomethyl)-1,2-dimethoxybenzene (0.478 g, 2.07 mmol, 1.30 eq.) in

acetonitrile (5 mL) was stirred overnight at 80 °C and concentrated under reduced pressure. The residue was triturated in diethyl ether (50 mL). The solid was collected by filtration and then dissolved in 1,2-dichloroethane (5 mL). Sodium triacetoxyborohydride (2.03 g, 9.55 mmol, 6.00 eq.) was added, and the mixture was stirred for 1 h at 60 °C. The reaction was quenched with water (10 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by Prep-TLC (silica, EA 100%) to afford 12-[(3,4-dimethoxyphenyl)methyl]-4-methyl-7-phenyl-2,3,7,12-tetraazatricyclo[7.4.0.0^{2,6}]trideca-1(9),3,5-trien-8-one (170 mg, 24% yield) as an off-white solid. LCMS (ESI, m/z): 431 [M+H]⁺, RT: 0.631 min.

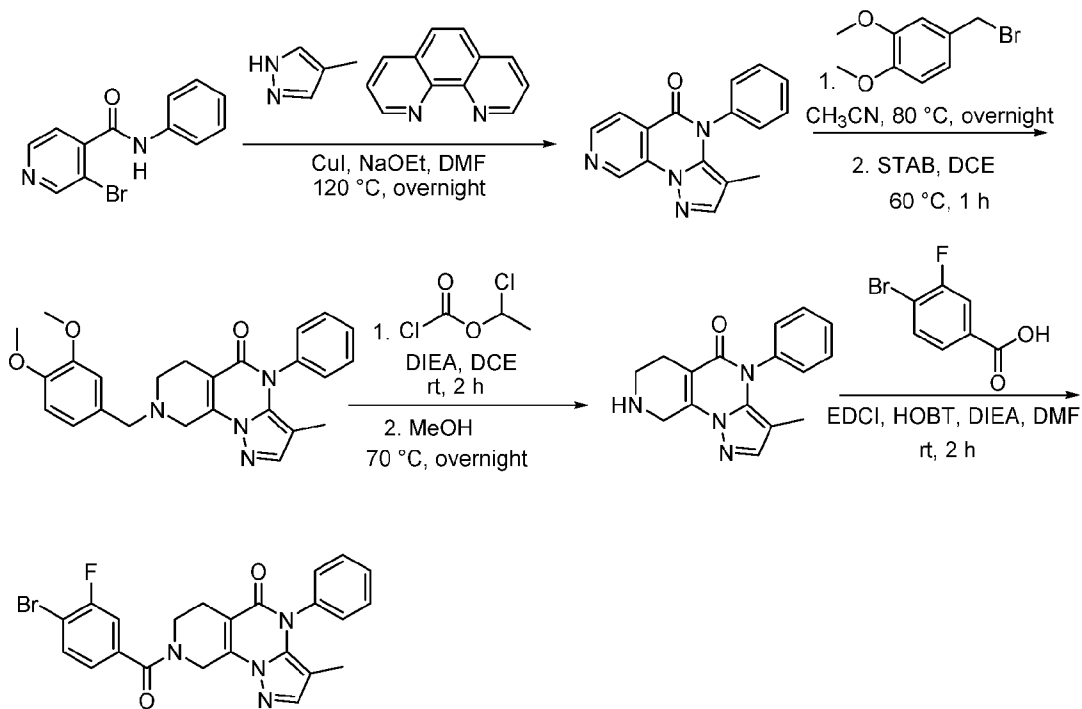
[0168] A solution of 12-[(3,4-dimethoxyphenyl)methyl]-4-methyl-7-phenyl-2,3,7,12-tetraazatricyclo[7.4.0.0^{2,6}]trideca-1(9),3,5-trien-8-one (170 mg, 0.395 mmol, 1.00 eq.), chloroethyl chloroformate (67.7 mg, 0.474 mmol, 1.20 eq.) and N,N-diisopropylethylamine (5.10 mg, 0.0390 mmol, 0.10 eq.) in 1,2-dichloroethane (3 mL) was stirred for 2 h at rt and then concentrated under reduced pressure. The residue was dissolved in methanol (3 mL). The mixture was stirred for overnight at 70 °C and then concentrated under reduced pressure to afford 4-methyl-7-phenyl-2,3,7,12-tetraazatricyclo[7.4.0.0^{2,6}]trideca-1(9),3,5-trien-8-one 250 mg (crude) as a brown oil. LCMS (ESI, m/z): 281 [M+H]⁺, RT: 0.706 min.

[0169] A solution of 4-methyl-7-phenyl-2,3,7,12-tetraazatricyclo[7.4.0.0^{2,6}]trideca-1(9),3,5-trien-8-one (250 mg, 0.892 mmol, 1.00 eq.), 4-bromo-3-fluorobenzoic acid (234 mg, 1.07 mmol, 1.20 eq.), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (205 mg, 1.07 mmol, 1.20 eq.), 1-hydroxybenzotriazole (144 mg, 1.07 mmol, 1.20 eq.) and N,N-diisopropylethylamine (345 mg, 2.67 mmol, 3.00 eq.) in N,N-dimethylformamide (5 mL) was stirred for 2 h at rt. The reaction was quenched with water (30 mL), and the mixture was extracted with EA (3 x 25 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions: Column: XBridge Shield RP₁₈ OBD Column, 19 mm x 250 mm, 10 μm; Mobile Phase A: Water (10 mmol/L NH₄HCO₃), Mobile Phase B: ACN; Flow rate:

25 mL/min; Gradient: 39% B to 59% B in 12 min; 220 nm to afford 12-(4-bromo-3-fluorobenzoyl)-4-methyl-7-phenyl-2,3,7,12-tetraazatricyclo[7.4.0.0[^][2,6]]trideca-1(9),3,5-trien-8-one (compound 7, 59.9 mg, 13% yield) as a white solid. LCMS (ESI, m/z): 481 [M+H]⁺, RT: 1.515 min. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.85 (d, *J* = 6.8 Hz, 1H), 7.61-7.51 (m, 4H), 7.45-7.30 (m, 3H), 5.30-5.25 (m, 1H), 4.98-4.94 (m, 2H), 3.91-3.60 (m, 2H), 2.56 (s, 2H), 2.15 (s, 3H).

Example 8

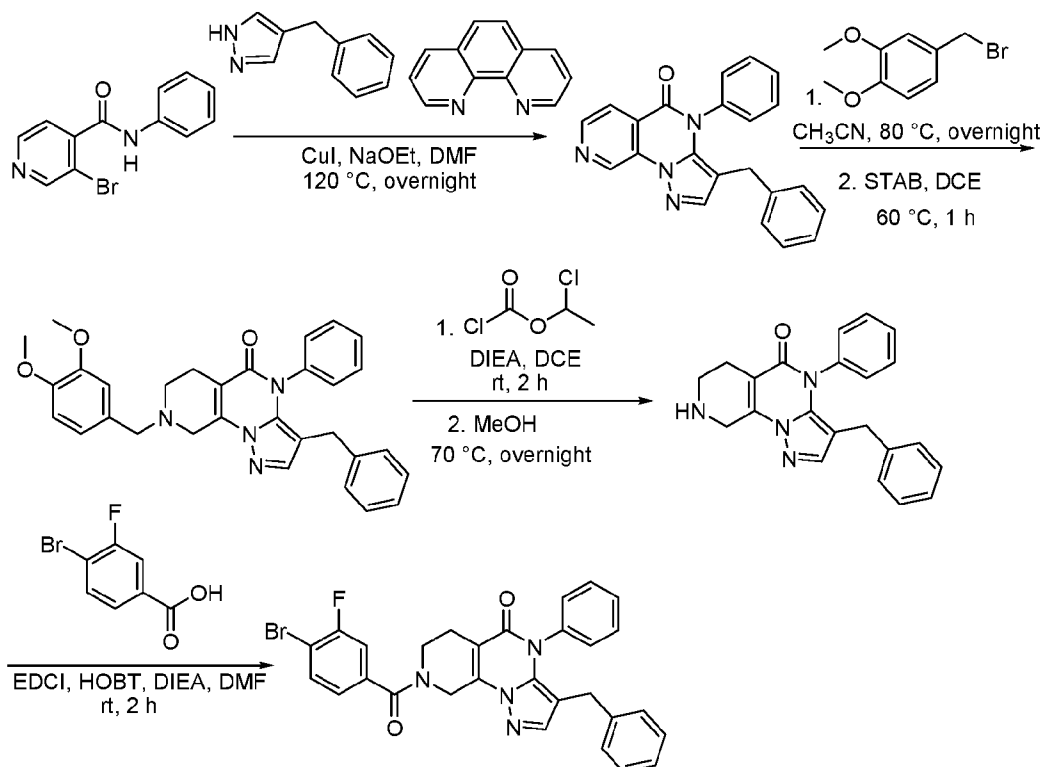
12-(4-bromo-3-fluorobenzoyl)-5-methyl-7-phenyl-2,3,7,12-tetraazatricyclo[7.4.0.0[^][2,6]]trideca-1(9),3,5-trien-8-one (8)



[0170] Compound 8 was prepared as a white solid according to the procedures of Example 11 a) to d) by substituting 4-methyl-1H-pyrazole for 3-methyl-1H-pyrazole. LCMS (ESI, m/z): 481 [M+H]⁺, RT: 1.509 min. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.86 (t, *J* = 6.6 Hz, 1H), 7.67-7.56 (m, 5H), 7.43-7.30 (m, 3H), 4.96-4.74 (m, 2H), 3.92-3.60 (m, 2H), 2.56 (s, 2H), 1.20 (s, 3H).

Example 9

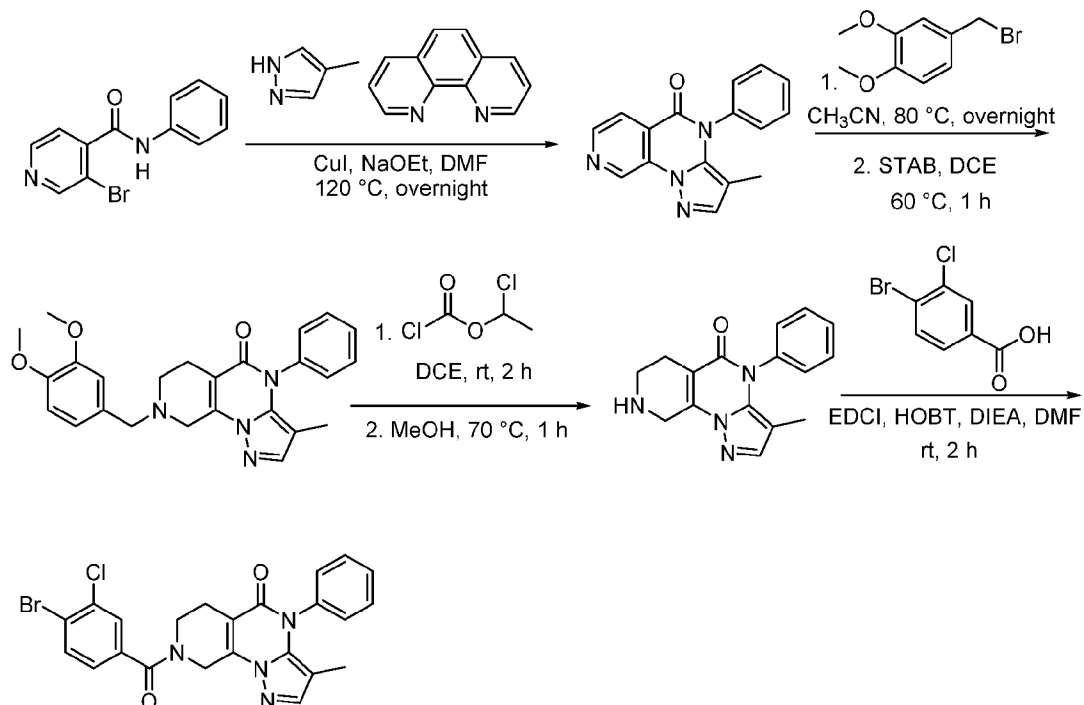
5-benzyl-12-(4-bromo-3-fluorobenzoyl)-7-phenyl-2,3,7,12-tetraazatricyclo[7.4.0.0^{2,6}]]trideca-1(9),3,5-trien-8-one (9)



[0171] Compound 9 was prepared as an off-white solid according to the procedures of Example 11 a) to d) by substituting 4-benzyl-1H-pyrazole for 3-methyl-1H-pyrazole. LCMS (ESI, m/z): 557 $[\text{M}+\text{H}]^+$, RT: 1.646 min. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.87 (t, $J = 7.6$ Hz, 1H), 7.61 (s, 2H), 7.49-7.42 (m, 3H), 7.40-7.33 (m, 3H), 7.14 (d, $J = 8.6$ Hz, 3H), 6.75 (br, 2H), 4.89 (m, 2H), 3.78 (m, 2H), 2.94 (s, 2H), 2.57 (s, 2H).

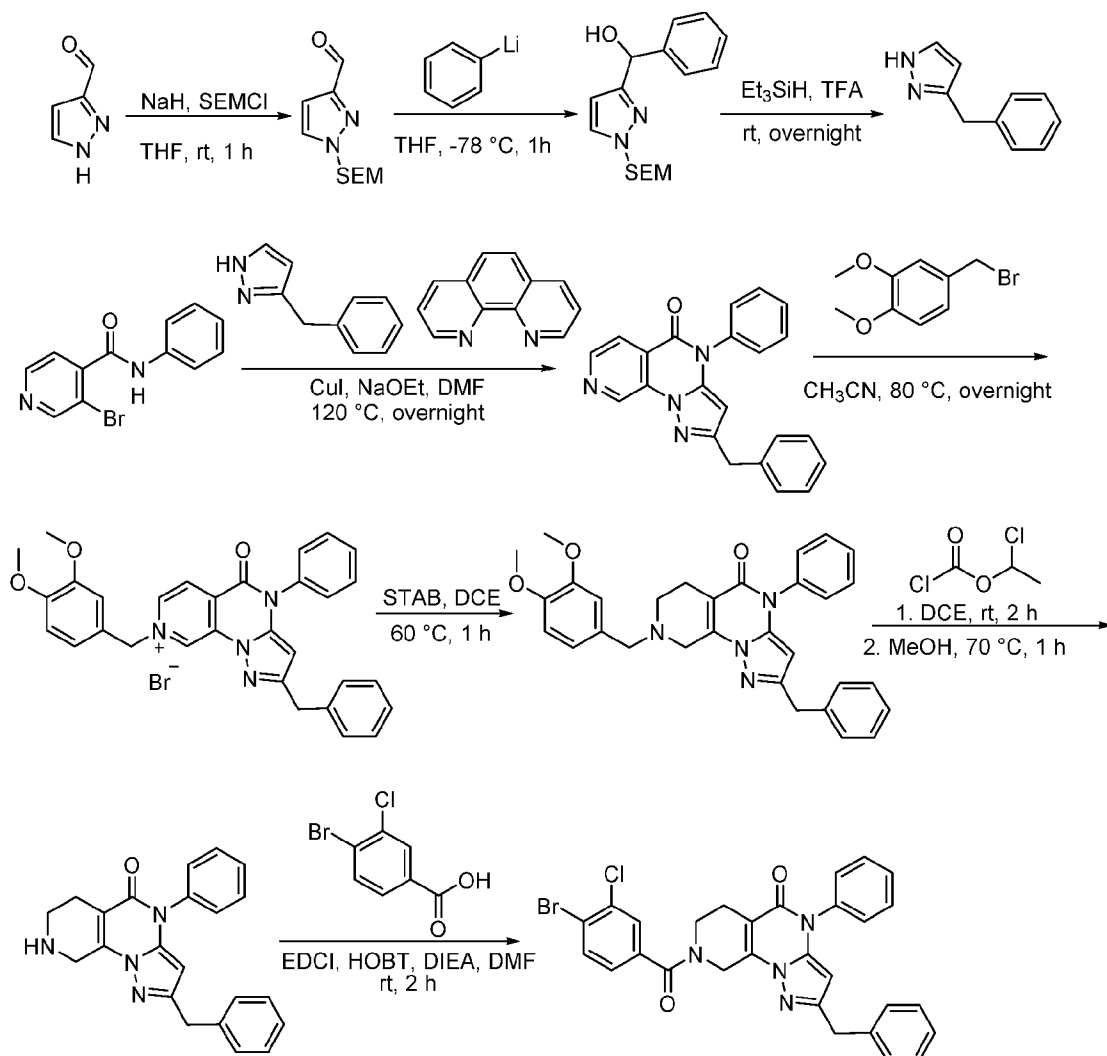
Example 10

12-(4-bromo-3-chlorobenzoyl)-5-methyl-7-phenyl-2,3,7,12-tetraazatricyclo[7.4.0.0[^][2,6]]trideca-1(9),3,5-trien-8-one (10)



[0172] Compound 10 was prepared as an off-white solid according to the procedures of Example 5 b) to f) by substituting 4-methyl-1H-pyrazole for pyrazole. LCMS (ESI, m/z): 497 [M+H]⁺, RT: 2.473 min. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.92 (d, *J* = 8.2 Hz, 1H), 7.81 (m, 1H), 7.67 (br, 1H), 7.56 (t, *J* = 9.2 Hz, 3H), 7.42 (s, 3H), 4.96-4.74 (m, 2H), 3.91-3.61 (m, 2H), 2.55 (s, 2H), 1.21 (s, 3H).

4-benzyl-12-(4-bromo-3-chlorobenzoyl)-7-phenyl-2,3,7,12-
tetraazatricyclo[7.4.0.0[^]2,6]]trideca-1(9),3,5-trien-8-one (**11**)



-65-

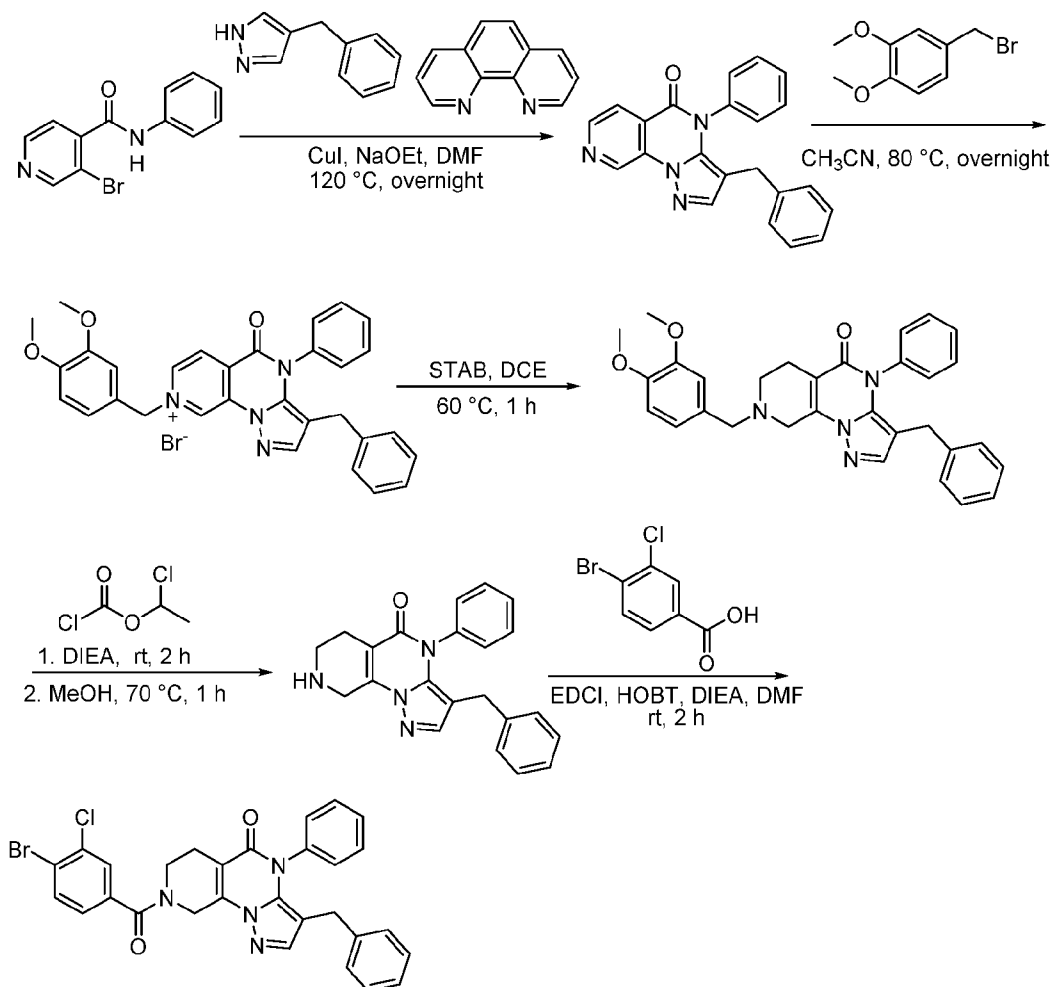
[0174] Into a 100 mL round-bottom flask were added 1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazole-3-carbaldehyde (4.00 g, 17.6 mmol, 1.00 eq.) and tetrahydrofuran (40 mL) at rt. To the above mixture was added phenyllithium (21.2 mL, 21.2 mmol, 1.20 eq., 1M in THF) dropwise over 10 min at -78 °C. The mixture was stirred for 3 h at rt, and the reaction was quenched with water (50 mL). The mixture was extracted with EA (3 x 100 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous sodium sulfate, filtrated and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with PE:EA (1:1) to afford phenyl(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-3-yl)methanol (2.64 g, 49% yield) as a light yellow solid. LCMS (ESI, m/z): 305 [M+H]⁺, RT: 1.267 min.

[0175] Into a 100 mL round-bottom flask was added phenyl(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-3-yl)methanol (2.60 g, 8.54 mmol, 1.00 eq.), triethylsilane (2.98 g, 25.6 mmol, 3.00 eq.) and trifluoroacetic acid (25 mL) at rt. The mixture was stirred overnight at rt and then concentrated under reduced pressure. The reaction was quenched with water (10 mL), and the mixture was extracted with EA (3 x 50 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtrated and concentrated under reduced pressure. The residue was purified by Prep-TLC (silica, EA) to afford 3-benzyl-1H-pyrazole 1.25 g (crude) as a yellow solid. LCMS (ESI, m/z): 159 [M+H]⁺, RT: 0.588 min.

[0176] 4-benzyl-12-(4-bromo-3-chlorobenzoyl)-7-phenyl-2,3,7,12-tetraazatricyclo[7.4.0.0[^][2,6]]trideca-1(9),3,5-trien-8-one, compound 11, was prepared as an off-white solid according to the procedures of Example 5 b) to f) by substituting 3-benzyl-1H-pyrazole for pyrazole. LCMS (ESI, m/z): 573 [M+H]⁺, RT: 2.737 min. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 8.0 Hz, 1H), 7.61 (s, 1H), 7.57-7.44 (m, 3H), 7.41 (d, *J* = 6.8 Hz, 2H), 7.33 (d, *J* = 7.2 Hz, 2H), 7.28-7.17 (m, 4H), 5.26 (s, 1H), 5.12 (br, 2H) 3.94-3.60 (m, 4H), 2.73 (s, 2H).

Example 12

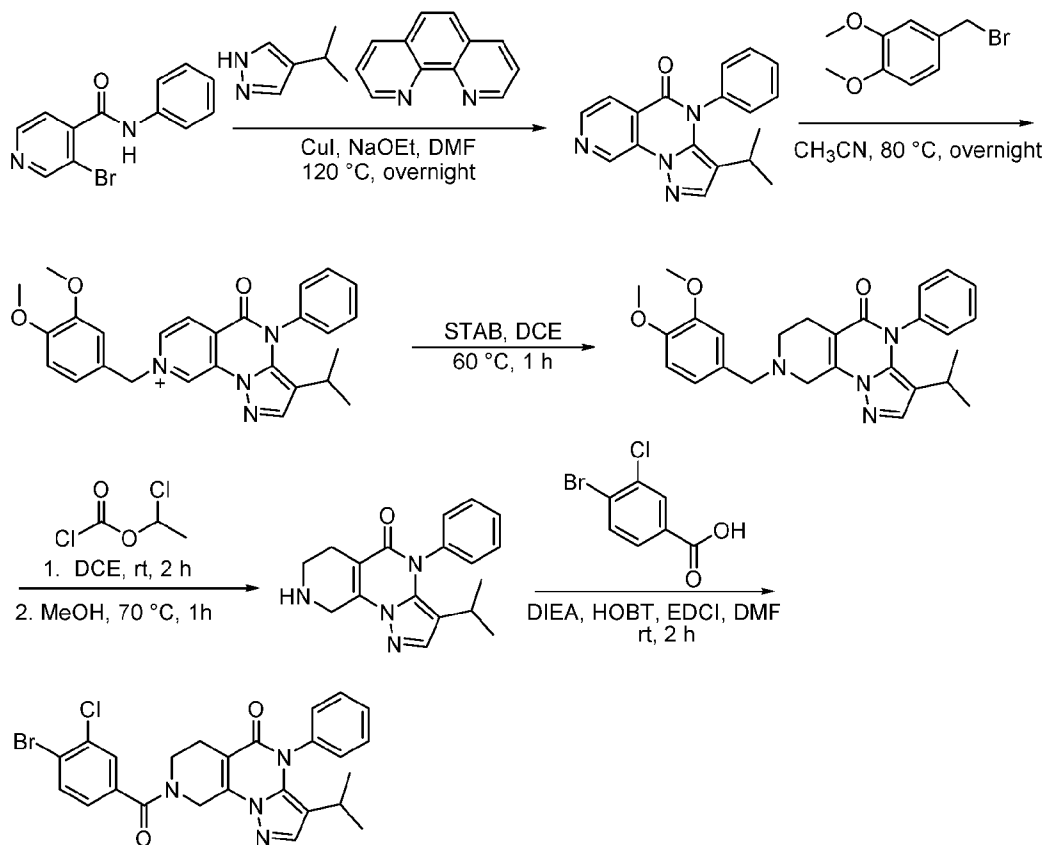
5-benzyl-12-(4-bromo-3-chlorobenzoyl)-7-phenyl-2,3,7,12-tetraazatricyclo[7.4.0.0^{2,6}][trideca-1(9),3,5-trien-8-one (**12**)



[0177] Compound **12** was prepared as a white solid according to the procedures of Example 5 b) to f) by substituting 4-benzyl-1H-pyrazole for pyrazole. LCMS (ESI, m/z): 573 $[\text{M}+\text{H}]^+$, RT: 1.734 min. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.92 (d, $J = 8.2\text{ Hz}$, 1H), 7.81 (d, $J = 19.2\text{ Hz}$, 1H), 7.60-7.40 (m, 5H), 7.33 -7.29 (m, 2H), 7.18-7.10 (m, 3H), 6.79-6.72 (m, 2H), 4.98-4.76 (m, 2H), 3.91-3.61 (m, 2H), 2.93 (d, $J = 14.8\text{ Hz}$, 2H), 2.56 (s, 2H).

Example 13

12-(4-bromo-3-chlorobenzoyl)-5-isopropyl-7-phenyl-2,3,7,12-tetraazatricyclo[7.4.0.0^{2,6}]]trideca-1(9),3,5-trien-8-one (13)



[0178] Compound 13 was prepared as a white solid according to the procedures of Example 5 b) to f) by substituting 4-isopropyl-1H-pyrazole for pyrazole. LCMS (ESI, m/z): 525 $[M+H]^+$, RT: 1.659 min. ^1H NMR (400 MHz, $DMSO-d_6$) δ 7.92 (d, $J = 8.0$ Hz, 1H), 7.85-7.77 (m, 2H), 7.57 (d, $J = 4.4$ Hz, 3H), 7.45 (s, 3H), 4.95-4.73 (m, 2H), 3.90-3.60 (m, 2H), 2.54 (s, 2H), 1.42 (br, 1H), 0.83 (d, $J = 7.2$ Hz, 6H).

EXAMPLE A

HBV-DNA Antiviral Assay using HepG2.117 cells

[0179] The following assay procedure describes the HBV antiviral assay, using HepG2.117 cells, which carry a stably integrated genotype D HBV genome under the control of a Tet-off promoter, and intracellular HBV DNA quantification as endpoint. Cell viability is assessed in parallel by measuring the intracellular ATP content using ATPlite (Perkin Elmer).

[0180] On day 0, HepG2.117 cells (which are maintained in routine cell culture with doxycycline present in the medium at a final concentration of 1 µg/mL) were seeded in 96-well plates (white with clear bottom) at a density of 2.0×10^4 cells/well (0.1 mL/well) in medium without doxycycline to induce pgRNA transcription and subsequent formation of HBV particles. The cells were incubated at 37 °C and 5% CO₂.

[0181] On day 1, medium was removed from each well, the test articles were diluted in culture medium without doxycycline and 100 µL was added to cell culture wells (9 concentrations, 4-fold dilution). For each plate, 6 untreated (merely DMSO) wells were included. The final concentration of DMSO in the culture medium was 2%. Each plate was prepared in duplicate (one for HBV DNA extraction, one for ATPlite measurement). The cells were incubated at 37 °C and 5% CO₂ for 3 days.

[0182] On day 4, cell viability was assessed using ATPlite and cell lysates were prepared for HBV DNA extraction and subsequent quantification by qPCR.

HBV DNA quantification by qPCR

[0183] Medium was removed from each well and 100 µL of 0.33% NP-40 in H₂O was added to each well. Plates were sealed, incubated at 4 °C for 5 mins, vortexed extensively and centrifuged briefly. Next, 35 µL of lysate was added to 65 µL QuickExtract DNA Extraction Solution (Epicentre) in a PCR plate for each well. PCR plate was incubated at 65 °C for 6 mins, 98 °C for 2 mins and finally cooled to 4 °C. HBV DNA was then quantified by qPCR with HBV-specific primers and probes as specified in Table 1 using the Bio-Rad SSOAdvanced Universal Probes Supermix on a CFX96 machine (Bio-Rad). The PCR cycle program consisted of 95 °C for 3 mins, followed by 40 cycles at 95 °C for 10 sec and 60 °C for 30 sec.

Table 1: HBV DNA Primers and Probe for HepG2.117 assay

Items	Name	Sequence (5'→3')
HBV Primer	HBV-forward	GTGTCTGCGGCGTTTTATCA
	HBV-reverse	GACAAACGGGCAACATACCTT
HBV Probe	HBV probe	FAM/CCTCTKCAT/ZEN/CCTGCTGCTATGCCTCATC/3IABk FQ/

[0184] A DNA standard was prepared by dilution of an IDT gBlock corresponding to the amplicon with concentrations ranging from 10^2 to 10^8 copies/input (i.e. per 4 μ L) and used to generate a standard curve by plotting Cq values vs. HBV DNA standard concentration. The quantity of HBV DNA in each sample was determined by interpolating from the standard curve.

Cell viability

[0185] Using the other plates, the cell viability was quantified by ATPlite according to the manufacturer's manual. In brief, 50 μ L of cell lysis solution was added to the culture plates and shaken for 5', followed by addition of 50 μ L substrate into each well and further shaking. The plates were incubated at room temperature for 10 mins and luminescence signal was subsequently measured on a VarioSkan Lux (ThermoFisher) plate reader.

Data analysis

[0186] Cell viability was calculated as follows: % Cell viability = (luminescence value of test sample) / (average luminescence value of 2% DMSO control) x 100%. HBV DNA inhibition was calculated as follows: $100 - (\text{HBV DNA copy number of test sample}) / (\text{average HBV DNA copy number of 2\% DMSO control}) \times 100\%$. No normalization to entecavir was required due to the excellent dynamic window of this assay. The CC₅₀, EC₅₀ and EC₉₀ values were determined by dose-response curves fitted by GraphPad Prism using "log (agonist) vs. response -- Variable slope".

[0187] Compounds of Formula (I) are active against HBV as shown in Table 2, where 'A' indicates an EC₅₀ < 1 nM, 'B' indicates an EC₅₀ of ≥ 1 nM and < 10 nM, 'C' indicates an EC₅₀ ≥ 10 nM and < 100 nM, 'D' indicates an EC₅₀ ≥ 100 nM and < 1000 nM, and 'E' indicates an EC₅₀ > 1000 nM.

Table 2

Compound	EC50 – HepG2.117
1	NA
2	NA
3	E
4	E

Compound	EC50 – HepG2.117
5	E
6	D
7	E
8	E

Compound	EC50 – HepG2.117
9	D
10	D
11	E

Compound	EC50 – HepG2.117
12	D
13	D

[0188] Although the foregoing has been described in some detail by way of illustrations and examples for purposes of clarity and understanding, it will be understood by those of skill in the art that numerous and various modifications can be made without departing from the spirit of the present disclosure. Therefore, it should be clearly understood that the forms disclosed herein are illustrative only and are not intended to limit the scope of the present disclosure, but rather to also cover all modification and alternatives coming with the true scope and spirit of the invention.

Electronic Acknowledgement Receipt

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First Named Inventor/Applicant Name:	Sandrine Vendeville
Customer Number:	20995
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The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	ADS_026PR.pdf	1255908	no	8
			79950e479a11ea3b7d3729aa4dfe2172b7920564		
Warnings:					
Information:					
2		App_026PR.pdf	627013	yes	85
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	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Abstract		85	85	
	Claims		72	84	
	Specification		1	71	
Warnings:					
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3	Fee Worksheet (SB06)	fee-info.pdf	29344	no	2
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