



(12) **DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION**

(13) **A1**

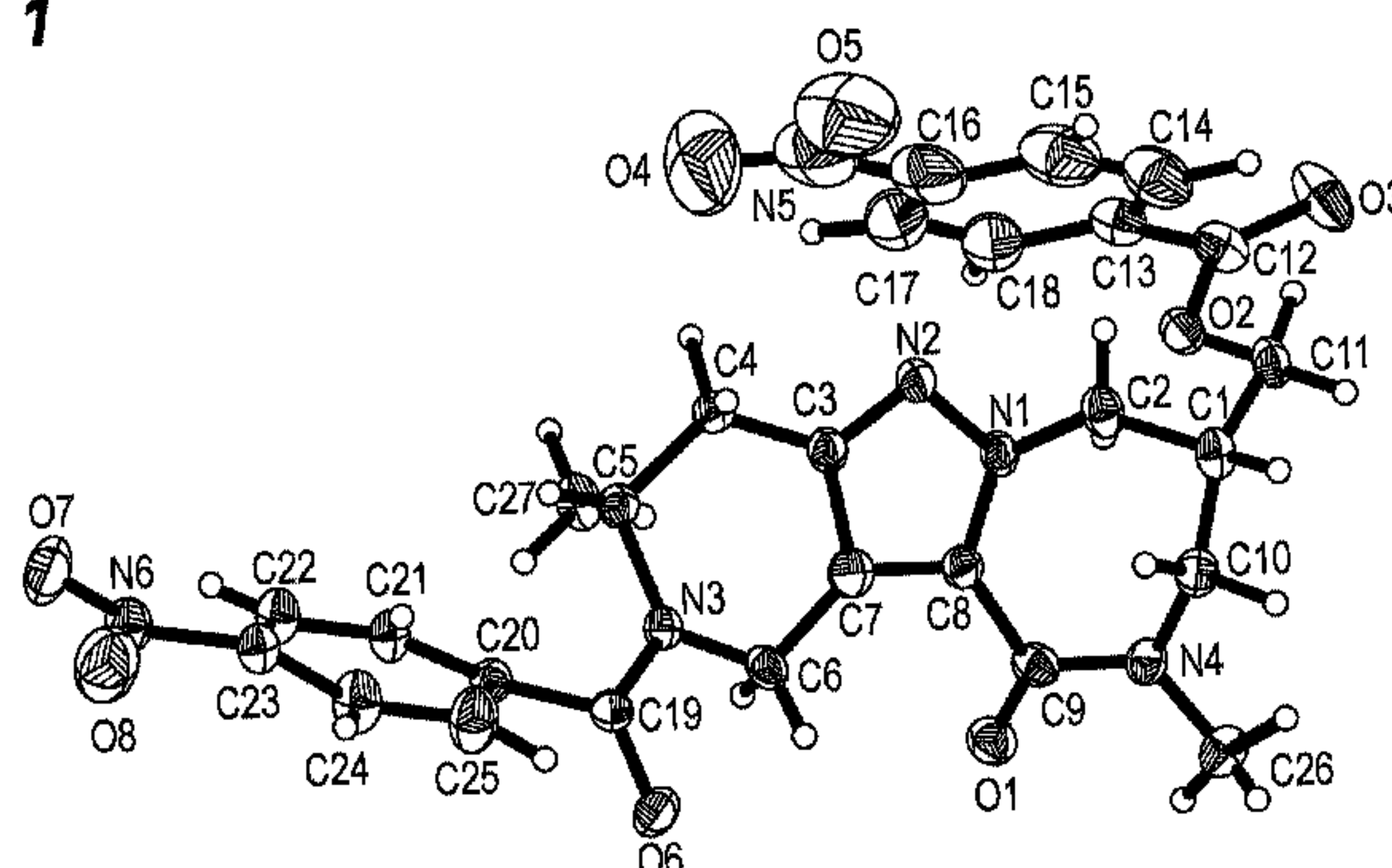
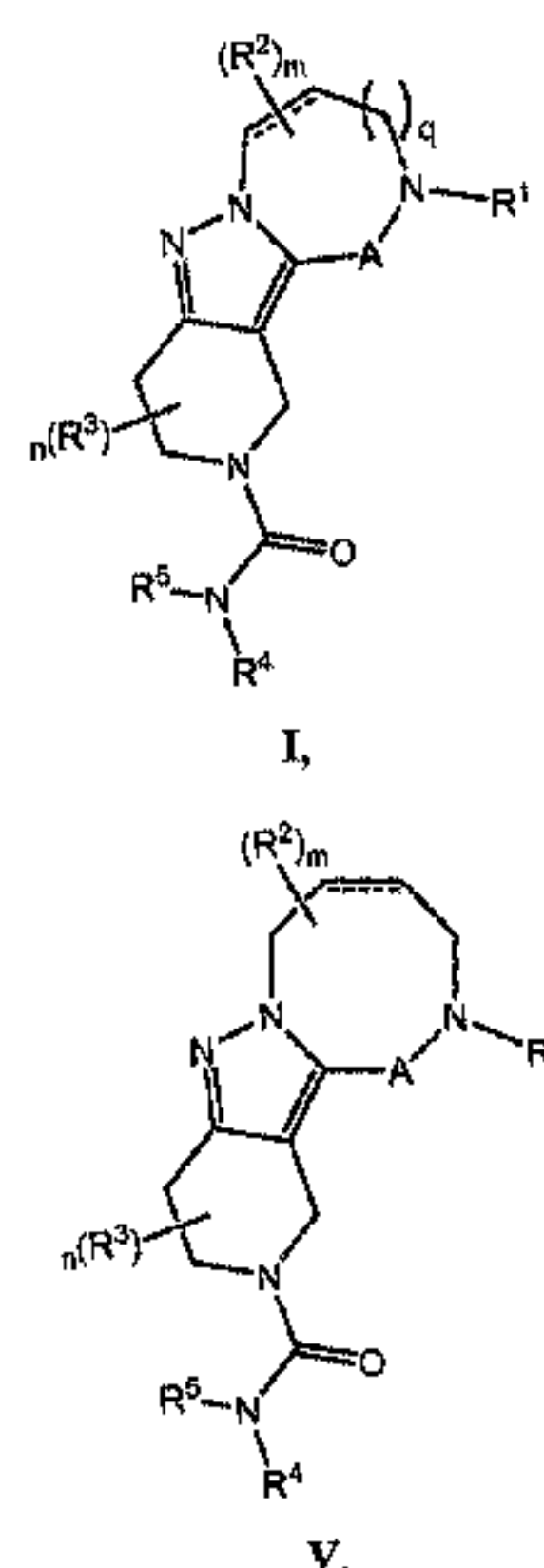
(86) Date de dépôt PCT/PCT Filing Date: 2017/06/29
(87) Date publication PCT/PCT Publication Date: 2018/01/04
(85) Entrée phase nationale/National Entry: 2018/12/28
(86) N° demande PCT/PCT Application No.: US 2017/040132
(87) N° publication PCT/PCT Publication No.: 2018/005883
(30) Priorités/Priorities: 2016/06/29 (US62/356,489);
2017/05/26 (US62/511,573)

(51) Cl.Int./Int.Cl. *C07D 471/04* (2006.01),
A61K 31/551 (2006.01), *A61P 31/12* (2006.01)
(71) Demandeur/Applicant:
NOVIRA THERAPEUTICS, INC., US
(72) Inventeurs/Inventors:
KUDUK, SCOTT, US;
HARTMAN, GEORGE D., US
(74) Agent: NORTON ROSE FULBRIGHT CANADA
LLP/S.E.N.C.R.L., S.R.L.

(54) Titre : DERIVES DE DIAZEPINONE ET LEUR UTILISATION DANS LE TRAITEMENT DES INFECTIONS PAR
L'HEPATITE B

(54) Title: DIAZEPINONE DERIVATIVES AND THEIR USE IN THE TREATMENT OF HEPATITIS B INFECTIONS

Fig. 1



(57) **Abrégé/Abstract:**

Provided herein are compounds of formula (I) and (V) useful for the treatment of HBV infection in a subject in need thereof, pharmaceutical compositions thereof, and methods of inhibiting, suppressing, or preventing HBV infection in the subject.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau

(43) International Publication Date
04 January 2018 (04.01.2018)



(10) International Publication Number
WO 2018/005883 A1

(51) International Patent Classification:

C07D 471/04 (2006.01) *A61P 31/12* (2006.01)
A61K 31/551 (2006.01)

(21) International Application Number:

PCT/US2017/040132

(22) International Filing Date:

29 June 2017 (29.06.2017)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/356,489	29 June 2016 (29.06.2016)	US
62/511,573	26 May 2017 (26.05.2017)	US

(71) Applicant: NOVIRA THERAPEUTICS, INC. [US/US];
3805 Old Easton Road, Doylestown, PA 18902 (US).

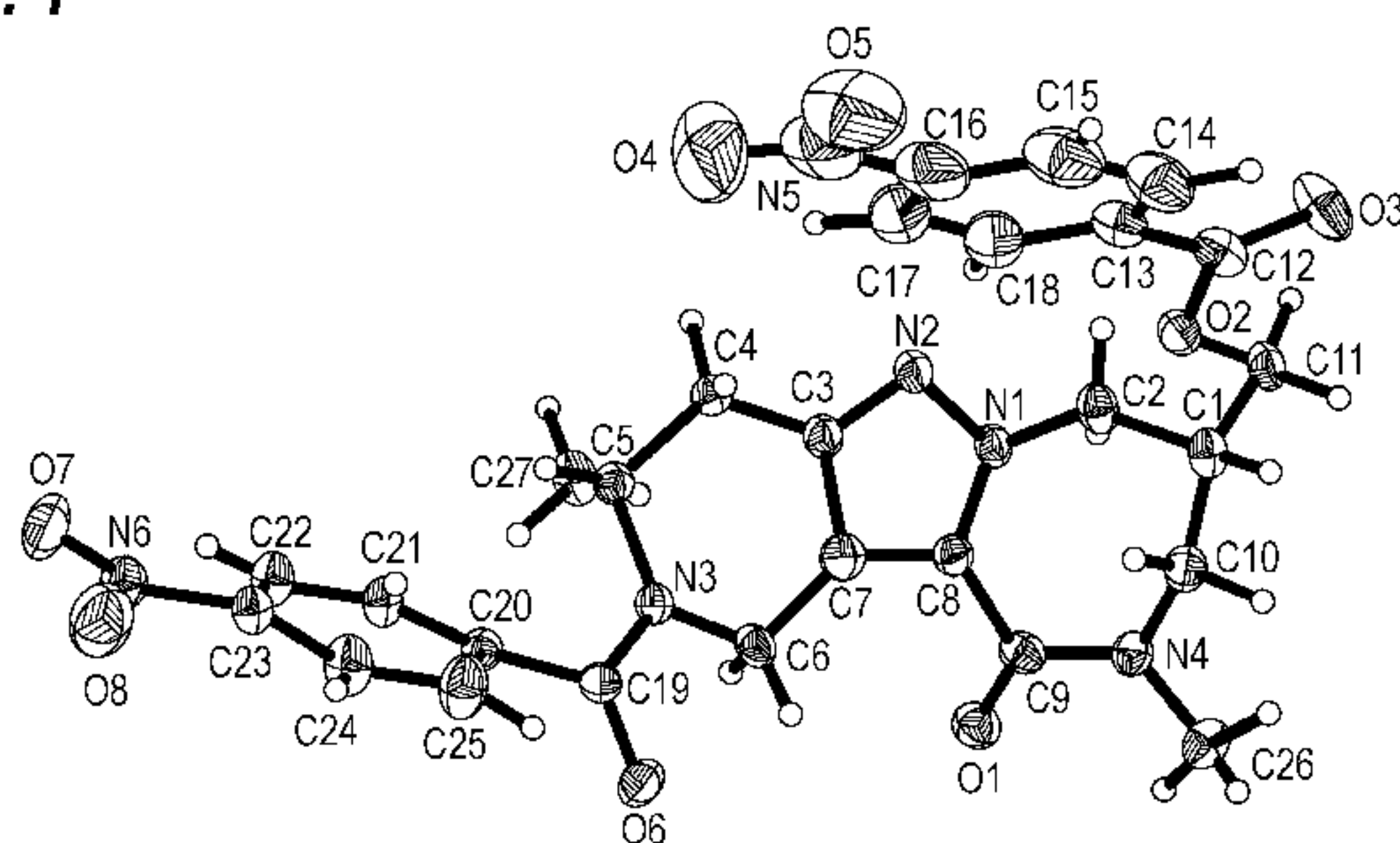
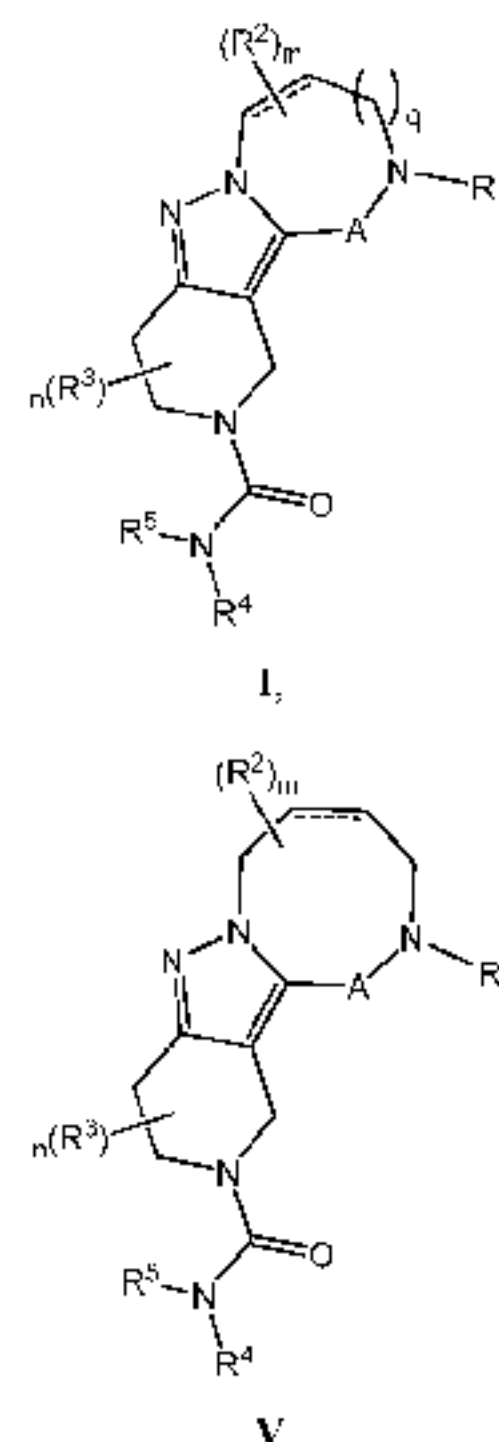
(72) Inventors: KUDUK, Scott; 219 Summerwind Lane,
Harleysville, PA 19438 (US). **HARTMAN, George, D.;**
1529 Tennis Circle, Lansdale, PA 19446 (US).

(74) Agent: SHIRTZ, Joseph, F. et al.; Johnson & Johnson,
One Johnson & Johnson Plaza, New Brunswick, NJ 08933
(US).

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(54) Title: DIAZEPINONE DERIVATIVES AND THEIR USE IN THE TREATMENT OF HEPATITIS B INFECTIONS

Fig. 1

(57) Abstract: Provided herein are compounds of formula (I) and (V) useful for the treatment of HBV infection in a subject in need thereof, pharmaceutical compositions thereof, and methods of inhibiting, suppressing, or preventing HBV infection in the subject.

WO 2018/005883 A1

Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

- *with international search report (Art. 21(3))*

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 353

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 353

NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

DIAZEPINONE DERIVATIVES AND THEIR USE IN THE TREATMENT OF HEPATITIS B INFECTIONS

RELATED APPLICATIONS

5 This application claims benefit of United States provisional patent application no. 62/356,489, filed June 29, 2016; and United States provisional patent application no. 62/511,573, filed May 26, 2017; the entire contents of each of which are incorporated herein by reference.

BACKGROUND

10 Chronic hepatitis B virus (HBV) infection is a significant global health problem, affecting over 5% of the world population (over 350 million people worldwide and 1.25 million individuals in the U.S.).

 Despite the availability of a prophylactic HBV vaccine, the burden of chronic HBV infection continues to be a significant unmet worldwide medical problem, due to suboptimal
15 treatment options and sustained rates of new infections in most parts of the developing world. Current treatments do not provide a cure and are limited to only two classes of agents (interferon alpha and nucleoside analogues/inhibitors of the viral polymerase); drug resistance, low efficacy, and tolerability issues limit their impact. The low cure rates of HBV are attributed at least in part to the fact that complete suppression of virus production is difficult to achieve with a single
20 antiviral agent. However, persistent suppression of HBV DNA slows liver disease progression and helps to prevent hepatocellular carcinoma. Current therapy goals for HBV-infected patients are directed to reducing serum HBV DNA to low or undetectable levels, and to ultimately reducing or preventing the development of cirrhosis and hepatocellular carcinoma.

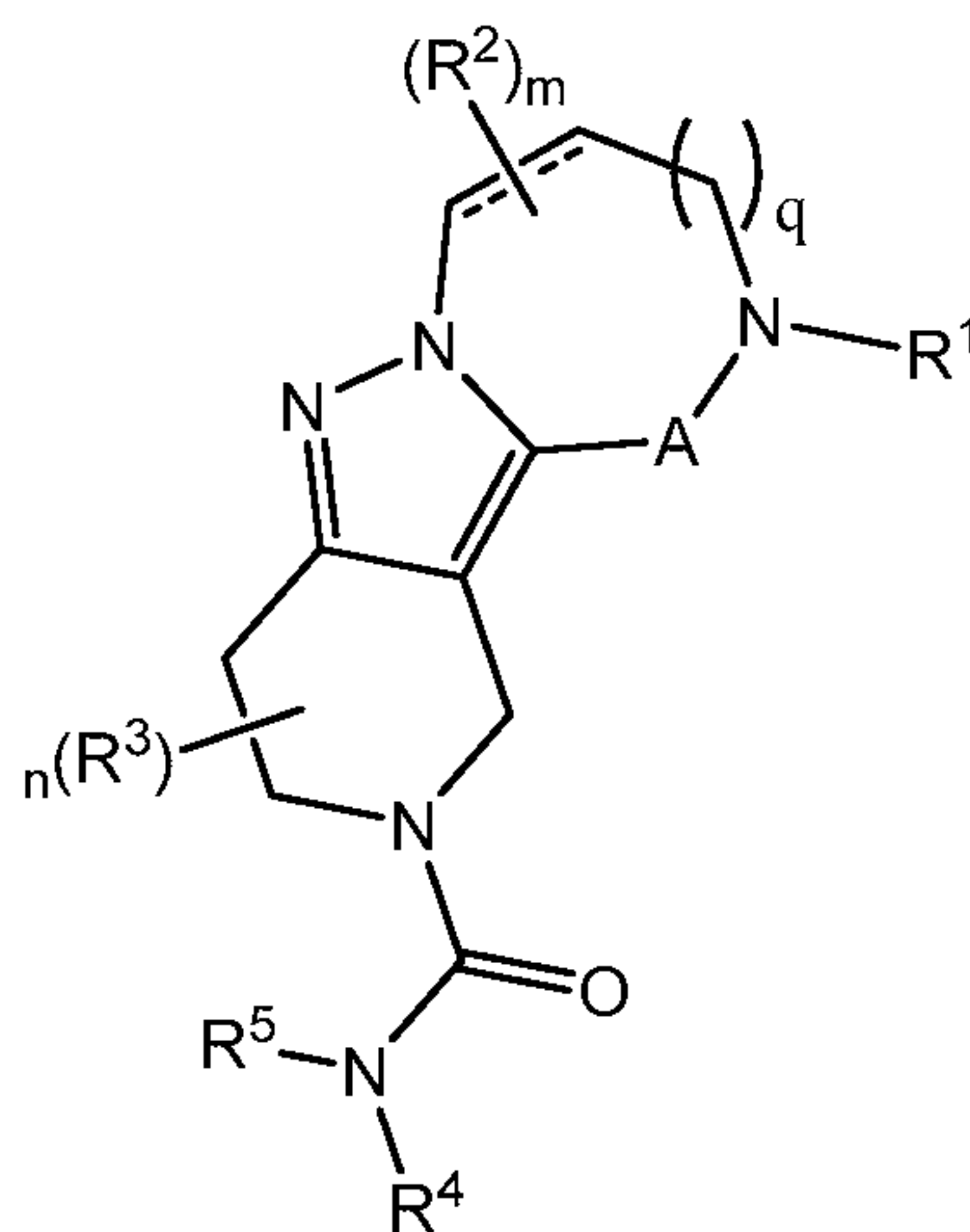
 The HBV capsid protein plays essential functions during the viral life cycle. HBV
25 capsid/core proteins form metastable viral particles or protein shells that protect the viral genome during intercellular passage, and also play a central role in viral replication processes, including genome encapsidation, genome replication, and virion morphogenesis and egress. Capsid structures also respond to environmental cues to allow un-coating after viral entry. Consistently, the appropriate timing of capsid assembly and dis-assembly, the appropriate capsid stability and
30 the function of core protein have been found to be critical for viral infectivity.

There is a need in the art for therapeutic agents that can increase the suppression of virus production and that can treat, ameliorate, or prevent HBV infection. Administration of such therapeutic agents to an HBV infected patient, either as monotherapy or in combination with other HBV treatments or ancillary treatments, will lead to significantly reduced virus burden, improved prognosis, diminished progression of the disease and enhanced seroconversion rates.

SUMMARY

Provided herein are compounds useful for the treatment of HBV infection in a subject in need thereof.

Thus, in an aspect, provided herein is a compound of Formula I:



I,

or a pharmaceutically acceptable salt thereof, wherein

A is CH₂ or C=O;

R¹ is H, C₁-C₆-alkyl, C₁-C₆-alkenyl, C₁-C₆-alkyl-OH, or C₁-C₆-haloalkyl;

R² is, at each occurrence, independently selected from -OH, halo, C₁-C₆-alkyl, C₁-C₆-alkylene, C₀-C₆-alkyl-C₃-C₆-cycloalkyl, C₀-C₆-alkyl-C₂-C₆-heterocycloalkyl, C₀-C₆-alkyl-OR⁶, C₀-C₆-alkyl-N(R⁷)₂, C₀-C₆-alkyl-SR⁸, C₀-C₆-alkyl-S(O)R⁸, C₀-C₆-alkyl-S(O)₂R⁸, C₀-C₆-alkyl-C(O)OR⁹, C₀-C₆-alkyl-OC(O)R⁹, C₀-C₆-alkyl-OC(O)OR⁹, C₀-C₆-alkyl-OC(O)N(R⁷)₂, and C₀-C₆-alkyl-C(O)N(R⁷)₂, wherein alkyl, alkylene, cycloalkyl, and heterocycloalkyl are optionally substituted with 1, 2, or 3 groups, each independently selected from -OH and halo; or

two R² groups together form a C₃-C₆ spiro cycloalkyl, wherein the cycloalkyl is optionally

substituted with 1, 2, or 3 groups, each individually selected from –OH and halo;

R^3 is, at each occurrence, independently selected from –OH, halo, C₁-C₆-alkyl, C₁-C₆-haloalkyl, –O-C₁-C₆-alkyl, and C₁-C₆-alkyl-OH;

R^4 is selected from (CR^aR^b)_p-C₁-C₉-heteroaryl, (CR^aR^b)_p-C₆-C₁₂-aryl, (CR^aR^b)_p-C₃-C₇-
5 cycloalkyl, and (CR^aR^b)_p-C₂-C₆-heterocycloalkyl, wherein heteroaryl, aryl, cycloalkyl, and heterocycloalkyl are optionally substituted with 1, 2, 3, or 4 groups, each independently selected from –OH, halo, –CN, –SF₅, C₁-C₆-alkyl, C₁-C₆-haloalkyl, –O-C₁-C₆-alkyl, and C₁-C₆-alkyl-OH;

R^5 is selected from H, C₁-C₆-alkyl, and C₁-C₆-alkyl-OH;

R^6 is selected from H, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkenyl, and C₀-C₆-alkyl-C₃-
10 C₆-cycloalkyl;

R^7 is, at each occurrence, independently selected from H, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C(O) C₁-C₆-alkyl and C₁-C₆-alkyl-OH;

R^8 is selected from H and C₁-C₆-alkyl;

R^9 is selected from H and C₁-C₆-alkyl;

15 R^a is, at each occurrence, independently selected from H, –OH, halo, C₁-C₆-alkyl, C₁-C₆-haloalkyl, –O-C₁-C₆-alkyl, and C₁-C₆-alkyl-OH;

R^b is, at each occurrence, independently selected from H and C₁-C₆-alkyl;

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

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

20 p is 0, 1, 2, 3, or 4;

q is 0 or 1; and

a ---- line denotes an optionally double bond.

In an embodiment, provided herein is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein

25 A is CH₂ or C=O;

R^1 is H, C₁-C₆-alkyl, C₁-C₆-alkenyl, C₁-C₆-alkyl-OH, or C₁-C₆-haloalkyl;

R^2 is, at each occurrence, independently selected from –OH, halo, C₁-C₆-alkyl, C₁-C₆-alkylene, C₀-C₆-alkyl-C₃-C₆-cycloalkyl, C₀-C₆-alkyl-C₂-C₆-heterocycloalkyl, C₀-C₆-alkyl-OR⁶, C₀-C₆-alkyl-N(R⁷)₂, C₀-C₆-alkyl-SR⁸, C₀-C₆-alkyl-S(O)R⁸, C₀-C₆-alkyl-S(O)₂R⁸, C₀-C₆-alkyl-C(O)OR⁹, C₀-C₆-alkyl-OC(O)R⁹, C₀-C₆-alkyl-OC(O)OR⁹, C₀-C₆-alkyl-OC(O)N(R⁷)₂, and C₀-C₆-alkyl-C(O)N(R⁷)₂, wherein alkyl, cycloalkyl, and heterocycloalkyl are
30

optionally substituted with 1, 2, or 3 groups, each independently selected from $-\text{OH}$ and halo;

R^3 is, at each occurrence, independently selected from $-\text{OH}$, halo, $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_1\text{-C}_6\text{-haloalkyl}$, $-\text{O-C}_1\text{-C}_6\text{-alkyl}$, and $\text{C}_1\text{-C}_6\text{-alkyl-OH}$;

R^4 is selected from $(\text{CR}^a\text{R}^b)_p\text{-C}_1\text{-C}_9\text{-heteroaryl}$, $(\text{CR}^a\text{R}^b)_p\text{-C}_6\text{-C}_{12}\text{-aryl}$, $(\text{CR}^a\text{R}^b)_p\text{-C}_3\text{-C}_7\text{-cycloalkyl}$, and $(\text{CR}^a\text{R}^b)_p\text{-C}_2\text{-C}_6\text{-heterocycloalkyl}$, wherein heteroaryl, aryl, cycloalkyl, and heterocycloalkyl are optionally substituted with 1, 2, 3, or 4 groups, each independently selected from $-\text{OH}$, halo, $-\text{CN}$, $-\text{SF}_5$, $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_1\text{-C}_6\text{-haloalkyl}$, $-\text{O-C}_1\text{-C}_6\text{-alkyl}$, and $\text{C}_1\text{-C}_6\text{-alkyl-OH}$;

R^5 is selected from H, $\text{C}_1\text{-C}_6\text{-alkyl}$, and $\text{C}_1\text{-C}_6\text{-alkyl-OH}$;

R^6 is selected from H, $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_1\text{-C}_6\text{-haloalkyl}$, $\text{C}_1\text{-C}_6\text{-alkenyl}$, and $\text{C}_0\text{-C}_6\text{-alkyl-C}_3\text{-C}_6\text{-cycloalkyl}$;

R^7 is, at each occurrence, independently selected from H, $\text{C}_1\text{-C}_6\text{-alkyl}$, and $\text{C}_1\text{-C}_6\text{-alkyl-OH}$;

R^8 is selected from H and $\text{C}_1\text{-C}_6\text{-alkyl}$;

R^9 is selected from H and $\text{C}_1\text{-C}_6\text{-alkyl}$;

R^a is, at each occurrence, independently selected from H, $-\text{OH}$, halo, $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_1\text{-C}_6\text{-haloalkyl}$, $-\text{O-C}_1\text{-C}_6\text{-alkyl}$, and $\text{C}_1\text{-C}_6\text{-alkyl-OH}$;

R^b is, at each occurrence, independently selected from H and $\text{C}_1\text{-C}_6\text{-alkyl}$;

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

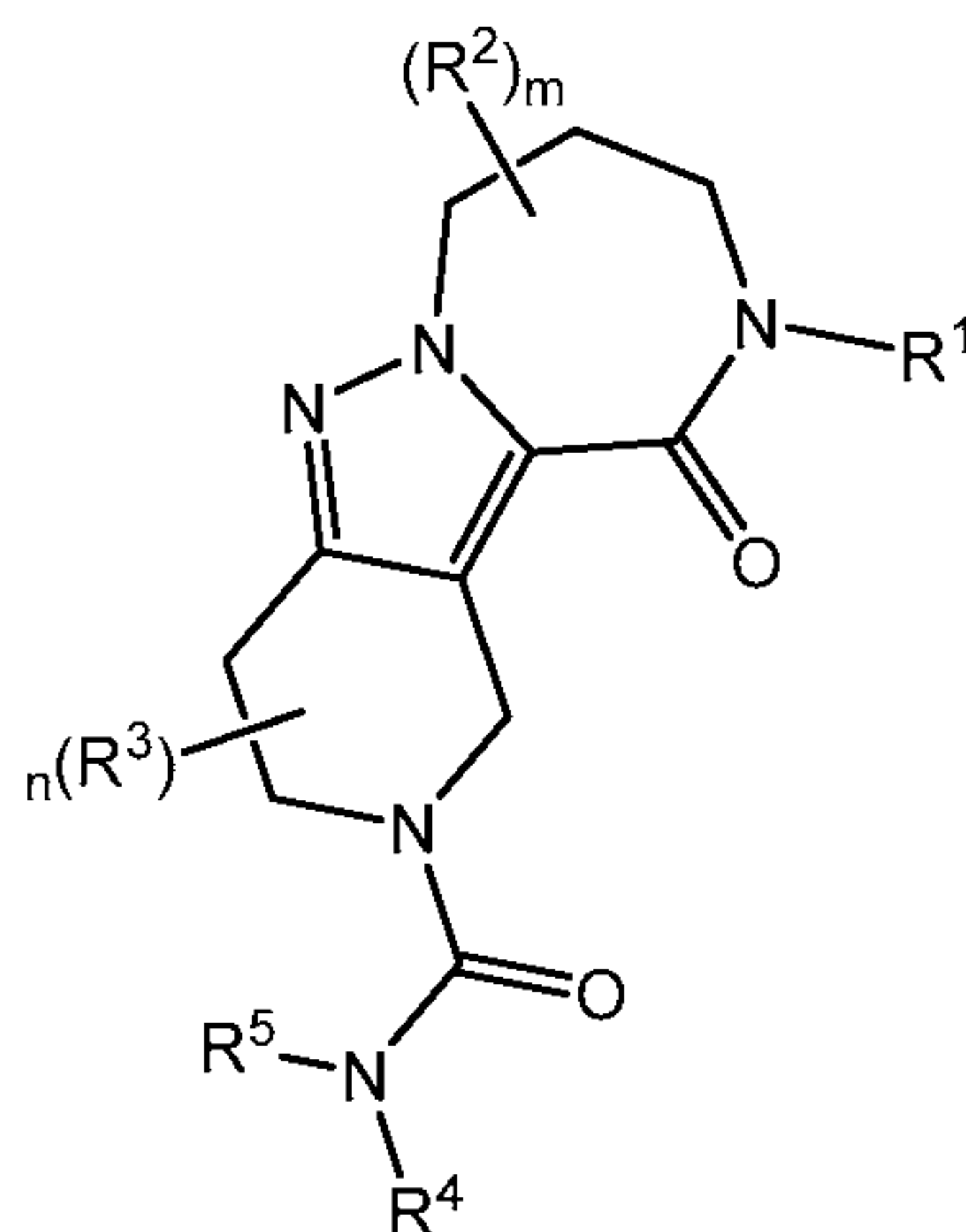
n is 0, 1, 2, 3, or 4;

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

q is 0 or 1; and

a ---- line denotes an optionally double bond.

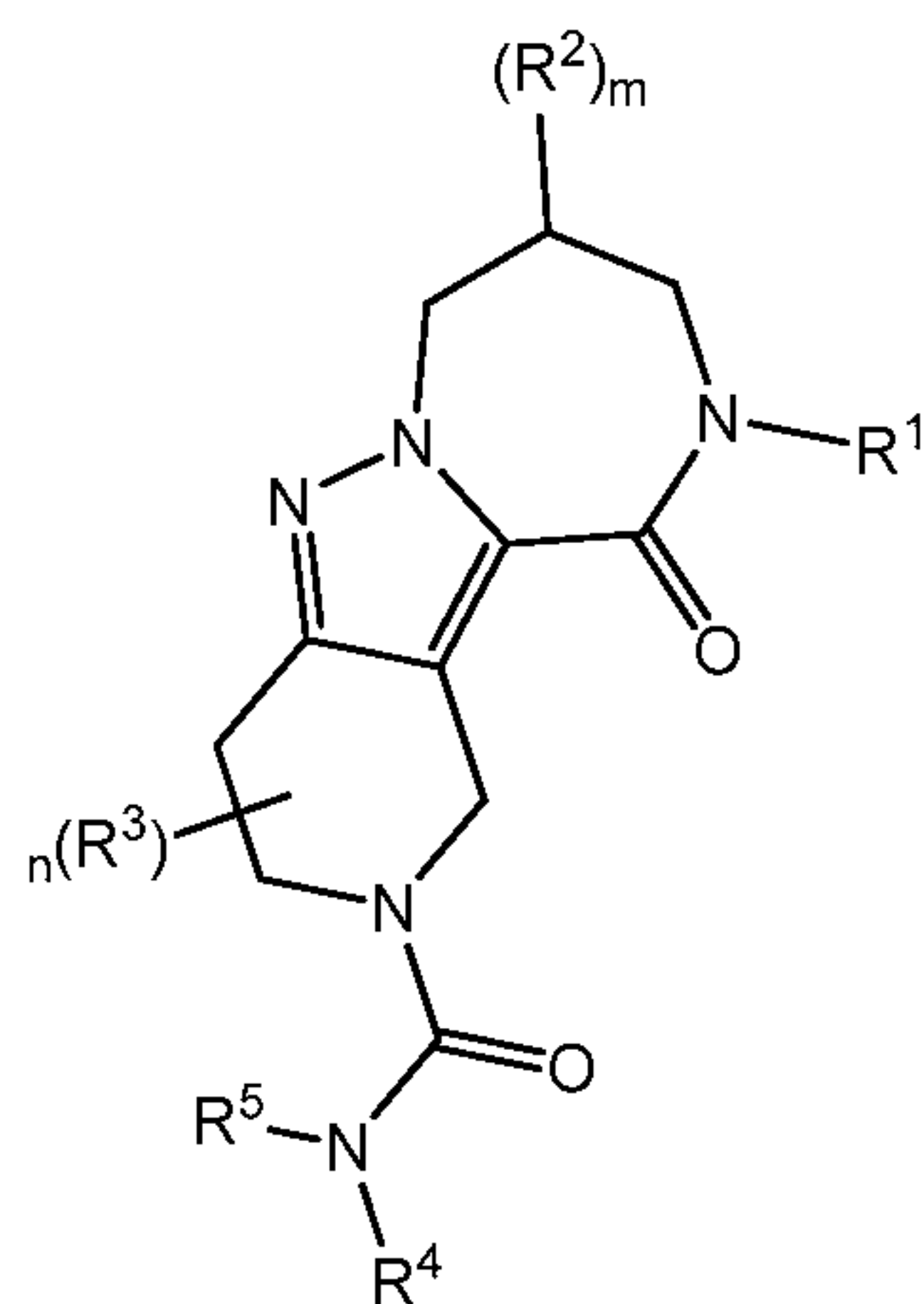
In an embodiment, the compound of Formula I has the structure of Formula II:



II,

or a pharmaceutically acceptable salt thereof.

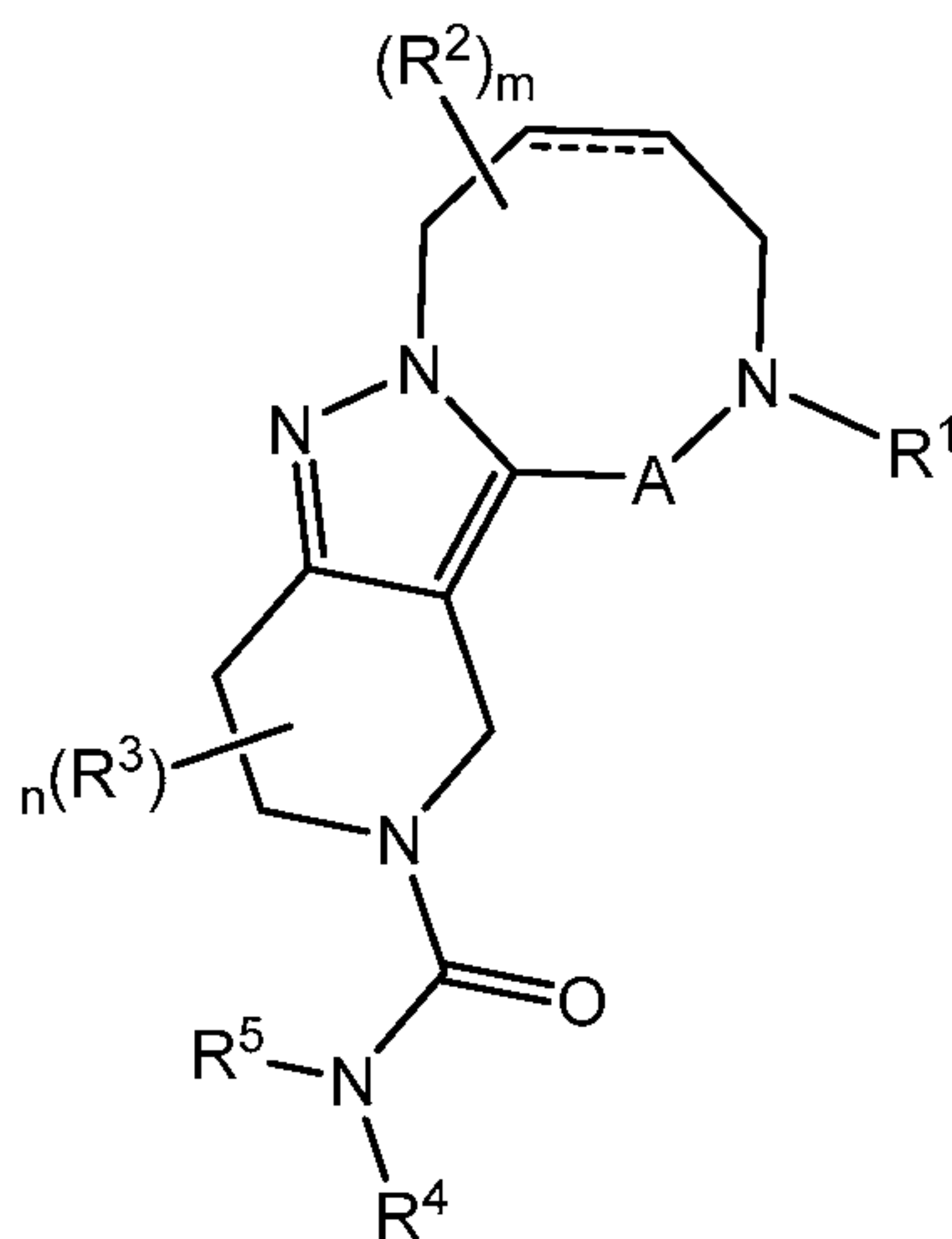
In another embodiment, the compound of Formula I or Formula II has the structure of Formula III:



III,

or a pharmaceutically acceptable salt thereof.

In another embodiment, provided herein is a compound of Formula V:



V,

or a pharmaceutically acceptable salt thereof, wherein

A is CH₂ or C=O;

R¹ is H, C₁-C₆-alkyl, C₁-C₆-alkenyl, C₁-C₆-alkyl-OH, or C₁-C₆-haloalkyl;

R² is, at each occurrence, independently selected from -OH, halo, C₁-C₆-alkyl, C₁-C₆-alkylene, C₀-C₆-alkyl-C₃-C₆-cycloalkyl, C₀-C₆-alkyl-C₂-C₆-heterocycloalkyl, C₀-C₆-alkyl-OR⁶, C₀-C₆-alkyl-N(R⁷)₂, C₀-C₆-alkyl-SR⁸, C₀-C₆-alkyl-S(O)R⁸, C₀-C₆-alkyl-

$S(O)_2R^8$, C_0 - C_6 -alkyl- $C(O)OR^9$, C_0 - C_6 -alkyl- $OC(O)R^9$, C_0 - C_6 -alkyl- $OC(O)OR^9$, C_0 - C_6 -alkyl- $OC(O)N(R^7)_2$, and C_0 - C_6 -alkyl- $C(O)N(R^7)_2$, wherein alkyl, alkylene, cycloalkyl, and heterocycloalkyl are optionally substituted with 1, 2, or 3 groups, each independently selected from $-OH$ and halo; or

5 two R^2 groups together form a C_3 - C_6 spiro cycloalkyl, wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups, each individually selected from $-OH$ and halo;

R^3 is, at each occurrence, independently selected from $-OH$, halo, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, $-O$ - C_1 - C_6 -alkyl, and C_1 - C_6 -alkyl- OH ;

10 R^4 is selected from $(CR^aR^b)_p$ - C_1 - C_9 -heteroaryl, $(CR^aR^b)_p$ - C_6 - C_{12} -aryl, $(CR^aR^b)_p$ - C_3 - C_7 -cycloalkyl, and $(CR^aR^b)_p$ - C_2 - C_6 -heterocycloalkyl, wherein heteroaryl, aryl, cycloalkyl, and heterocycloalkyl are optionally substituted with 1, 2, 3, or 4 groups, each independently selected from $-OH$, halo, $-CN$, $-SF_5$, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, $-O$ - C_1 - C_6 -alkyl, and C_1 - C_6 -alkyl- OH ;

R^5 is selected from H , C_1 - C_6 -alkyl, and C_1 - C_6 -alkyl- OH ;

15 R^6 is selected from H , C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 - C_6 -alkenyl, and C_0 - C_6 -alkyl- C_3 - C_6 -cycloalkyl;

R^7 is, at each occurrence, independently selected from H , C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, $C(O)$ C_1 - C_6 -alkyl and C_1 - C_6 -alkyl- OH ;

R^8 is selected from H and C_1 - C_6 -alkyl;

R^9 is selected from H and C_1 - C_6 -alkyl;

20 R^a is, at each occurrence, independently selected from H , $-OH$, halo, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, $-O$ - C_1 - C_6 -alkyl, and C_1 - C_6 -alkyl- OH ;

R^b is, at each occurrence, independently selected from H and C_1 - C_6 -alkyl;

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

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

25 p is 0, 1, 2, 3, or 4; and

a ---- line denotes an optionally double bond.

In another aspect, provided herein is a pharmaceutical composition comprising a compound of Formula I, II, III, IV, or V, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

30 In another aspect, provided herein is a pharmaceutical composition comprising a disclosed compound and a pharmaceutically acceptable carrier.

In another aspect, provided herein is a method of treating an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of Formula I, II, III, IV, or V, or a pharmaceutically acceptable salt thereof.

5 In another aspect, provided herein is a method of inhibiting or reducing the formation or presence of HBV DNA-containing particles or HBV RNA-containing particles in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of Formula, I, II, III, IV, or V, or a pharmaceutically acceptable salt thereof.

10 In an embodiment, any of the methods provided herein can further comprising administering to the individual at least one additional therapeutic agent selected from the group consisting of an HBV polymerase inhibitor, immunomodulatory agents, interferon, viral entry inhibitor, viral maturation inhibitor, capsid assembly modulator, reverse transcriptase inhibitor, a cyclophilin/TNF inhibitor, a TLR-agonist, an HBV vaccine, and any combination thereof.

15 BRIEF DESCRIPTION OF THE DRAWING

Figure 1 shows the X-ray crystal structure of the di p-nitro-benzoic acid analogue of Intermediate 16, also referred to as compound 151.

DETAILED DESCRIPTION

20 Provided herein are compounds, e.g., the compounds of Formulas I, II, III, IV, or V, or pharmaceutically acceptable salts thereof, that are useful in the treatment and prevention of HBV infection in subject.

Without being bound to any particular mechanism of action, these compounds are believed to modulate or disrupt HBV assembly and other HBV core protein functions necessary
25 for HBV replication or the generation of infectious particles. In addition, or alternatively, the compounds may disrupt HBV capsid assembly to induce production of defective viral particles with greatly reduced infectivity or replication capacity. In other words, the compounds provided herein may act as capsid assembly modulators by modulating (e.g., accelerating, delaying, inhibiting, disrupting or reducing) normal viral capsid assembly or disassembly, binding
30 capsids, and/or altering metabolism of cellular polyproteins and precursors. The modulation may

occur when the capsid protein is mature, or during viral infectivity. The disclosed compounds can be used in methods of modulating the activity or properties of HBV cccDNA, or the generation or release of HBV RNA particles from within an infected cell.

5 In one embodiment, the compounds described herein are suitable for monotherapy and are effective against natural or native HBV strains and against HBV strains resistant to currently known drugs. In another embodiment, the compounds described herein are suitable for use in combination therapy.

Definitions

10 Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification and claims, unless otherwise limited in specific instances, either individually or as part of a larger group.

Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this invention
15 belongs. Generally, the nomenclature used herein and the laboratory procedures in cell culture, molecular genetics, organic chemistry, and peptide chemistry are those well-known and commonly employed in the art.

As used herein, the articles “a” and “an” refer to one or to more than one (i.e. to at least one) of the grammatical object of the article. By way of example, “an element” means one
20 element or more than one element. Furthermore, use of the term “including” as well as other forms, such as “include”, “includes,” and “included,” is not limiting.

As used herein, the term “about” will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. As used herein when referring to a measurable value such as an amount, a temporal duration, and the like, the term “about” is
25 meant to encompass variations of $\pm 20\%$ or $\pm 10\%$, including $\pm 5\%$, $\pm 1\%$, and $\pm 0.1\%$ from the specified value, as such variations are appropriate to perform the disclosed methods.

As used herein, the term “capsid assembly modulator” refers to a compound that disrupts or accelerates or inhibits or hinders or delays or reduces or modifies normal capsid assembly (e.g., during maturation) or normal capsid disassembly (e.g., during infectivity) or perturbs
30 capsid stability, thereby inducing aberrant capsid morphology and function. In one embodiment, a capsid assembly modulator accelerates capsid assembly or disassembly, thereby inducing

aberrant capsid morphology. In another embodiment, a capsid assembly modulator interacts (e.g. binds at an active site, binds at an allosteric site, modifies or hinders folding and the like) with the major capsid assembly protein (CA), thereby disrupting capsid assembly or disassembly. In yet another embodiment, a capsid assembly modulator causes a perturbation in structure or function of CA (e.g., ability of CA to assemble, disassemble, bind to a substrate, fold into a suitable conformation, or the like), which attenuates viral infectivity or is lethal to the virus.

As used herein, the term “treatment” or “treating” is defined as the application or administration of a therapeutic agent, i.e., a disclosed compound (alone or in combination with another pharmaceutical agent), to a patient, or application or administration of a therapeutic agent to an isolated tissue or cell line from a patient (e.g., for diagnosis or ex vivo applications), who has an HBV infection, a symptom of HBV infection or the potential to develop an HBV infection, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect the HBV infection, the symptoms of HBV infection, or the potential to develop an HBV infection. Such treatments may be specifically tailored or modified, based on knowledge obtained from the field of pharmacogenomics.

As used herein, the term “prevent” or “prevention” means no disorder or disease development if none had occurred, or no further disorder or disease development if there had already been development of the disorder or disease. Also considered is the ability of one to prevent some or all of the symptoms associated with the disorder or disease.

As used herein, the term “patient,” “individual” or “subject” refers to a human or a non-human mammal. Non-human mammals include, for example, livestock and pets, such as ovine, bovine, porcine, canine, feline and murine mammals. Preferably, the patient, subject, or individual is human.

As used herein, the terms “effective amount,” “pharmaceutically effective amount,” and “therapeutically effective amount” refer to a nontoxic but sufficient amount of an agent to provide the desired biological result. That result may be reduction or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. An appropriate therapeutic amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

As used herein, the term “pharmaceutically acceptable” refers to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively non-toxic, i.e., the material may be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

As used herein, the term “pharmaceutically acceptable salt” refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and Journal of Pharmaceutical Science, 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

As used herein, the term “composition” or “pharmaceutical composition” refers to a mixture of at least one compound useful within the invention with a pharmaceutically acceptable carrier. The pharmaceutical composition facilitates administration of the compound to a patient or subject. Multiple techniques of administering a compound exist in the art including, but not limited to, intravenous, oral, aerosol, parenteral, ophthalmic, pulmonary, and topical administration.

As used herein, the term “pharmaceutically acceptable carrier” means a pharmaceutically acceptable material, composition or carrier, such as a liquid or solid filler, stabilizer, dispersing agent, suspending agent, diluent, excipient, thickening agent, solvent or encapsulating material, involved in carrying or transporting a compound useful within the invention within or to the patient such that it may perform its intended function. Typically, such constructs are carried or

transported from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation, including the compound useful within the invention, and not injurious to the patient. Some examples of materials that may serve as pharmaceutically acceptable carriers

5 include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol,

10 mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; surface active agents; alginic acid; pyrogen-free water; isotonic saline; Ringer’s solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations.

As used herein, “pharmaceutically acceptable carrier” also includes any and all coatings,

15 antibacterial and antifungal agents, and absorption delaying agents, and the like that are compatible with the activity of the compound useful within the invention, and are physiologically acceptable to the patient. Supplementary active compounds may also be incorporated into the compositions. The “pharmaceutically acceptable carrier” may further include a pharmaceutically acceptable salt of the compound useful within the invention. Other

20 additional ingredients that may be included in the pharmaceutical compositions used in the practice of the invention are known in the art and described, for example in Remington's Pharmaceutical Sciences (Genaro, Ed., Mack Publishing Co., 1985, Easton, PA), which is incorporated herein by reference.

As used herein, the term “alkyl,” by itself or as part of another substituent means, unless

25 otherwise stated, a straight or branched chain hydrocarbon having the number of carbon atoms designated (i.e., C₀-C₆-alkyl means null or an alkyl having one to six carbon atoms) and includes straight and branched chains. Examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, and hexyl. Other examples of C₁-C₆-alkyl include ethyl, methyl, isopropyl, isobutyl, n-pentyl, and n-hexyl.

As used herein, the term “alkenyl,” denotes a monovalent group derived from a

30 hydrocarbon moiety containing at least two carbon atoms and at least one carbon-carbon double

bond. The double bond may or may not be the point of attachment to another group. Alkenyl groups (e.g., C₂-C₈-alkenyl) include, but are not limited to, for example, ethenyl, propenyl, prop-1-en-2-yl, butenyl, 1-methyl-2-buten-1-yl, heptenyl, octenyl and the like.

As used herein, the term “halo” or “halogen” alone or as part of another substituent means, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom, preferably, fluorine, chlorine, or bromine, more preferably, fluorine or chlorine.

As used herein, the term “haloalkyl” refers to alkyl radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Haloalkyl embraces monohaloalkyl, dihaloalkyl, and polyhaloalkyl radicals. The term “haloalkyl” includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, and pentafluoroethyl.

As used herein, the term “cycloalkyl” refers to a mono cyclic or polycyclic non-aromatic radical, wherein each of the atoms forming the ring (i.e., skeletal atoms) is a carbon atom. In one embodiment, the cycloalkyl group is saturated or partially unsaturated. In another embodiment, the cycloalkyl group is fused with an aromatic ring. Cycloalkyl groups include groups having 3 to 10 ring atoms (C₃-C₁₀-cycloalkyl), groups having 3 to 8 ring atoms (C₃-C₈-cycloalkyl), groups having 3 to 7 ring atoms (C₃-C₇-cycloalkyl), and groups having 3 to 6 ring atoms (C₃-C₆-cycloalkyl). Monocyclic cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Dicyclic cycloalkyls include, but are not limited to, tetrahydronaphthyl, indanyl, and tetrahydropentalene. Polycyclic cycloalkyls include adamantane and norbornane. The term cycloalkyl includes unsaturated nonaromatic cyclic groups, which contain at least one carbon carbon double bond or one carbon carbon triple bond.

As used herein, the term “heterocycloalkyl” or “heterocyclyl” refers to a heteroalicyclic group containing one to four ring heteroatoms each selected from O, S, and N. In one embodiment, each heterocyclyl group has from 3 to 10 atoms in its ring system, with the proviso that the ring of said group does not contain two adjacent O or S atoms. Heterocyclyl substituents may be alternatively defined by the number of carbon atoms, e.g., C₂-C₈-heterocyclyl indicates the number of carbon atoms contained in the heterocyclic group without including the number of heteroatoms. For example, a C₂-C₈-heterocyclyl will include an additional one to four heteroatoms. Preferably, the heterocyclyl group has less than three heteroatoms. More preferably, the heterocyclyl group has one to two heteroatoms. In another embodiment, the

heterocycloalkyl group is fused with an aromatic ring. In one embodiment, the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen atom may be optionally quaternized. The heterocyclic system may be attached, unless otherwise stated, at any heteroatom or carbon atom that affords a stable structure.

5 An example of a 3-membered heterocyclyl group includes, and is not limited to, aziridine. Examples of 4-membered heterocycloalkyl groups include, and are not limited to, azetidine and a beta lactam. Examples of 5-membered heterocyclyl groups include, and are not limited to, pyrrolidine, oxazolidine and thiazolidinedione. Examples of 6-membered heterocycloalkyl groups include, and are not limited to, piperidine, morpholine, and piperazine.

10 Other non-limiting examples of heterocyclyl groups include monocyclic groups such as aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, pyrroline, pyrazolidine, imidazoline, dioxolane, sulfolane, 2,3-dihydrofuran, 2,5-dihydrofuran, tetrahydrofuran, thiophane, piperidine, 1,2,3,6-tetrahydropyridine, 1,4-dihydropyridine, piperazine, morpholine, thiomorpholine, pyran, 2,3-dihydropyran, tetrahydropyran, 1,4-dioxane, 1,3-dioxane,
15 homopiperazine, homopiperidine, 1,3-dioxepane, 4,7-dihydro-1,3-dioxepin, and hexamethyleneoxide.

As used herein, the term “aromatic” refers to a carbocycle or heterocycle with one or more polyunsaturated rings and having aromatic character, i.e., having $(4n + 2)$ delocalized π (pi) electrons, where n is an integer.

20 As used herein, the term “aryl,” employed alone or in combination with other terms, means, unless otherwise stated, a carbocyclic aromatic system containing one or more rings (typically one, two, or three rings), wherein such rings may be attached together in a pendent manner, such as a biphenyl, or may be fused, such as naphthalene. Examples of aryl groups include phenyl, anthracyl, and naphthyl. Preferred examples are phenyl (e.g., C₆-aryl) and
25 biphenyl (e.g., C₁₂-aryl). In some embodiments, aryl groups have from six to sixteen carbon atoms. In some embodiments, aryl groups have from six to twelve carbon atoms (e.g., C₆-C₁₂-aryl). In some embodiments, aryl groups have six carbon atoms (e.g., C₆-aryl).

As used herein, the term “heteroaryl” or “heteroaromatic” refers to a heterocycle having aromatic character. Heteroaryl substituents may be defined by the number of carbon atoms, e.g.,
30 C₁-C₉-heteroaryl indicates the number of carbon atoms contained in the heteroaryl group without including the number of heteroatoms. For example, a C₁-C₉-heteroaryl will include an additional

one to four heteroatoms. Preferably, the heteroaryl group has less than three heteroatoms.

More preferably, the heteroaryl group has one to two heteroatoms. A polycyclic heteroaryl may include one or more rings that are partially saturated. Non-limiting examples of heteroaryls include pyridyl, pyrazinyl, pyrimidinyl (including, e.g., 2- and 4-pyrimidinyl), pyridazinyl, thienyl, furyl, pyrrolyl (including, e.g., 2-pyrrolyl), imidazolyl, thiazolyl, oxazolyl, pyrazolyl (including, e.g., 3- and 5-pyrazolyl), isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3,4-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,3,4-thiadiazolyl and 1,3,4-oxadiazolyl.

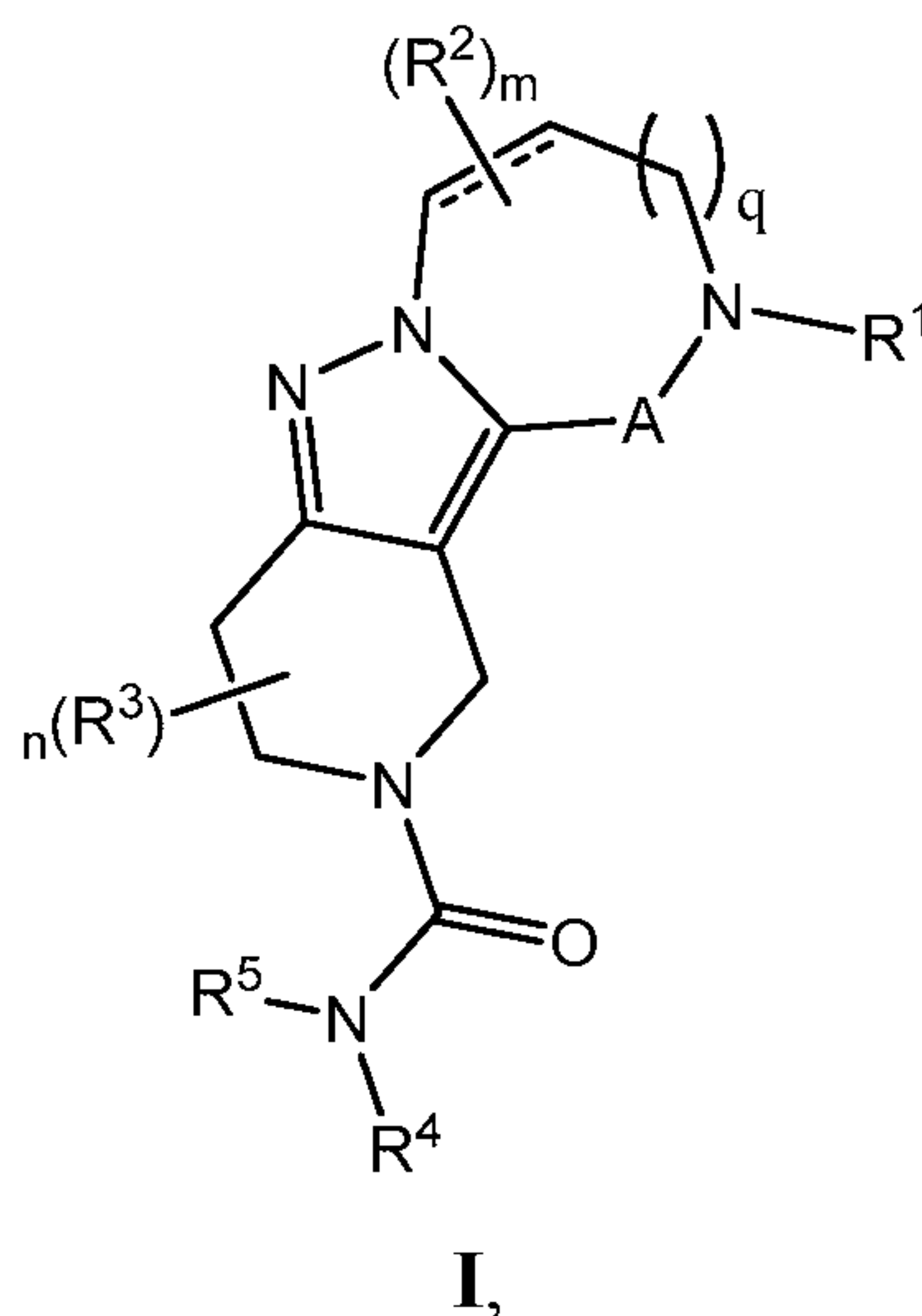
Non-limiting examples of polycyclic heterocycles and heteroaryls include indolyl (including, e.g., 3-, 4-, 5-, 6- and 7-indolyl), indolinyl, quinolyl, tetrahydroquinolyl, isoquinolyl (including, e.g., 1- and 5-isoquinolyl), 1,2,3,4-tetrahydroisoquinolyl, cinnolinyl, quinoxalinyl (including, e.g., 2- and 5-quinoxalinyl), quinazolinyl, phthalazinyl, 1,8-naphthyridinyl, 1,4-benzodioxanyl, coumarin, dihydrocoumarin, 1,5-naphthyridinyl, benzofuryl (including, e.g., 3-, 4-, 5-, 6- and 7-benzofuryl), 2,3-dihydrobenzofuryl, 1,2-benzisoxazolyl, benzothienyl (including, e.g., 3-, 4-, 5-, 6-, and 7-benzothienyl), benzoxazolyl, benzothiazolyl (including, e.g., 2-benzothiazolyl and 5-benzothiazolyl), purinyl, benzimidazolyl (including, e.g., 2-benzimidazolyl), benzotriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, pyrrolizidinyl, and quinolizidinyl.

As used herein, the term “substituted” means that an atom or group of atoms has replaced hydrogen as the substituent attached to another group.

As used herein, the terminology “selected from...” (e.g., “R⁴ is selected from A, B and C”) is understood to be equivalent to the terminology “selected from the group consisting of...” (e.g., “R⁴ is selected from the group consisting of A, B and C”).

Compounds

Provided herein are compounds having the structure of Formula I:



or a pharmaceutically acceptable salt thereof.

In embodiments, A is CH₂ or C=O. In embodiments, A is CH₂. In other embodiments, A is C=O.

R¹ may be H, C₁-C₆-alkyl, C₁-C₆-alkenyl, C₁-C₆-alkyl-OH, or C₁-C₆-haloalkyl. In embodiments, R¹ is H. In embodiments, R¹ is C₁-C₆-alkyl. In particular embodiments, R¹ is –CH₃. In embodiments, R¹ is C₁-C₆-alkenyl. In embodiments, R¹ is C₁-C₆-alkyl-OH. In embodiments, R¹ is C₁-C₆-haloalkyl.

In embodiments, there may be 0, 1, 2, 3, or 4 R² substituents: m is 0, 1, 2, 3, or 4. Each R² may be independently selected from –OH, halo, C₁-C₆-alkyl, C₁-C₆-alkylene, C₀-C₆-alkyl-C₃-C₆-cycloalkyl, C₀-C₆-alkyl-C₂-C₆-heterocycloalkyl, C₀-C₆-alkyl-OR⁶, C₀-C₆-alkyl-N(R⁷)₂, C₀-C₆-alkyl-SR⁸, C₀-C₆-alkyl-S(O)R⁸, C₀-C₆-alkyl-S(O)₂R⁸, C₀-C₆-alkyl-C(O)OR⁹, C₀-C₆-alkyl-OC(O)R⁹, C₀-C₆-alkyl-OC(O)OR⁹, C₀-C₆-alkyl-OC(O)N(R⁷)₂, and C₀-C₆-alkyl-C(O)N(R⁷)₂, wherein alkyl, alkylene, cycloalkyl, and heterocycloalkyl are optionally substituted with 1, 2, or 3 groups, each independently selected from –OH and halo; or

two R² groups together form a C₃-C₆ spiro cycloalkyl, wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups, each individually selected from –OH and halo.

In certain embodiments, m is 0 and there is no R² substitution. In certain embodiments, m is 1 and there is one R² substitution. In certain embodiments, m is 2 and there are two R² substitutions. In certain embodiments, m is 3 and there are three R² substitutions. In certain embodiments, m is 4 and there are four R² substitutions.

In certain embodiments, at least one R^2 is $-OH$. In certain embodiments, at least one R^2 is halo. In certain embodiments, at least one R^2 is C_1-C_6 -alkyl. In certain embodiments, at least one R^2 is C_1-C_6 -alkylene. In certain embodiments, at least one R^2 is C_0-C_6 -alkyl- C_3-C_6 -cycloalkyl. In certain embodiments, at least one R^2 is C_0-C_6 -alkyl- C_2-C_6 -heterocycloalkyl. In certain embodiments, at least one R^2 is C_0-C_6 -alkyl- OR^6 . In certain embodiments, at least one R^2 is C_0-C_6 -alkyl- $N(R^7)_2$. In certain embodiments, at least one R^2 is C_0-C_6 -alkyl- SR^8 . In certain embodiments, at least one R^2 is C_0-C_6 -alkyl- $S(O)R^8$. In certain embodiments, at least one R^2 is C_0-C_6 -alkyl- $S(O)_2R^8$. In certain embodiments, at least one R^2 is C_0-C_6 -alkyl- $C(O)OR^9$. In certain embodiments, at least one R^2 is C_0-C_6 -alkyl- $OC(O)R^9$. In certain embodiments, at least one R^2 is C_0-C_6 -alkyl- $OC(O)OR^9$. In certain embodiments, at least one R^2 is C_0-C_6 -alkyl- $OC(O)N(R^7)_2$. In certain embodiments, at least one R^2 is C_0-C_6 -alkyl- $C(O)N(R^7)_2$. In certain embodiments, two R^2 groups together form a C_3-C_6 spiro cycloalkyl, wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups, each individually selected from $-OH$ and halo.

In certain embodiments, R^2 is substituted with 1, 2 or 3 groups. Each occurrence of R^2 as alkyl, alkylene, cycloalkyl or heterocycloalkyl optionally may be substituted with $-OH$ or halo. For example, R^2 may be alkyl, and the alkyl is substituted with $-OH$; or R^2 may be alkyl, and the alkyl is substituted with at least one fluorine atom. In a particular embodiment, R^2 may be CH_2OH . R^2 may be alkylene, and the alkylene group is substituted with $-OH$; or R^2 may be alkylene, and the alkylene group is substituted with at least one fluorine atom. R^2 may be cycloalkyl, and the cycloalkyl is substituted with $-OH$; or R^2 may be cycloalkyl, and the cycloalkyl is substituted with at least one fluorine atom. R^2 may be heterocycloalkyl, and the heterocycloalkyl is substituted with $-OH$; or R^2 may be heterocycloalkyl, and the heterocycloalkyl is substituted with at least one fluorine atom. In certain embodiments, two R^2 groups together form a C_3-C_6 spiro cycloalkyl, wherein the cycloalkyl is substituted with at least 1 $-OH$. In certain embodiments, two R^2 groups together form a C_3-C_6 spiro cycloalkyl, wherein the cycloalkyl is substituted with at least 1 halogen.

In certain embodiments, R^2 may be C_1-C_6 -alkyl optionally substituted with 1, 2, or 3 halo groups. In certain embodiments, R^2 may be C_0-C_6 -alkyl- OR^6 , wherein R^6 is C_1-C_6 -haloalkyl. In certain embodiments, R^2 may be $(CH_2)_{1-2}-O-C_1-C_3$ -alkyl, wherein C_1-C_3 -alkyl is optionally substituted with 1, 2, or 3 halo groups. In certain embodiments, m is 1 or 2.

In embodiments, there may be 0, 1, 2, 3, or 4 R^3 substituents: n is 0, 1, 2, 3, or 4. In

certain embodiments, n is 0 and there is no R^3 substitution. In certain embodiments, n is 1 and there is one R^3 substitution. In certain embodiments, n is 2 and there are two R^3 substitutions. In certain embodiments, n is 3 and there are three R^3 substitutions. In certain embodiments, n is 4 and there are four R^3 substitutions.

Each R^3 may be independently selected from $-OH$, halo, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, $-O$ - C_1 - C_6 -alkyl, and C_1 - C_6 -alkyl- OH . In certain embodiments, at least one R^3 is $-OH$. In certain embodiments, at least one R^3 is halo. In certain embodiments, at least one R^3 is C_1 - C_6 -alkyl. In certain embodiments, at least one R^3 is C_1 - C_6 -haloalkyl. In certain embodiments, at least one R^3 is $-O$ - C_1 - C_6 -alkyl. In certain embodiments, at least one R^3 is C_1 - C_6 -alkyl- OH .

R^4 is selected from $(CR^aR^b)_p$ - C_1 - C_9 -heteroaryl, $(CR^aR^b)_p$ - C_6 - C_{12} -aryl, $(CR^aR^b)_p$ - C_3 - C_7 -cycloalkyl, and $(CR^aR^b)_p$ - C_2 - C_6 -heterocycloalkyl, wherein heteroaryl, aryl, cycloalkyl, and heterocycloalkyl are optionally substituted with 1, 2, 3, or 4 groups, each independently selected from $-OH$, halo, $-CN$, $-SF_5$, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, $-O$ - C_1 - C_6 -alkyl, and C_1 - C_6 -alkyl- OH . In certain embodiments, R^4 is $(CR^aR^b)_p$ - C_1 - C_9 -heteroaryl optionally substituted with 1, 2, 3, or 4 groups, each independently selected from $-OH$, halo, $-CN$, $-SF_5$, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, $-O$ - C_1 - C_6 -alkyl, and C_1 - C_6 -alkyl- OH . In certain embodiments, R^4 is $(CR^aR^b)_p$ - C_6 - C_{12} -aryl optionally substituted with 1, 2, 3, or 4 groups, each independently selected from $-OH$, halo, $-CN$, $-SF_5$, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, $-O$ - C_1 - C_6 -alkyl, and C_1 - C_6 -alkyl- OH . In certain embodiments, R^4 is $(CR^aR^b)_p$ - C_3 - C_7 -cycloalkyl optionally substituted with 1, 2, 3, or 4 groups, each independently selected from $-OH$, halo, $-CN$, $-SF_5$, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, $-O$ - C_1 - C_6 -alkyl, and C_1 - C_6 -alkyl- OH . In certain embodiments, R^4 is $(CR^aR^b)_p$ - C_2 - C_6 -heterocycloalkyl optionally substituted with 1, 2, 3, or 4 groups, each independently selected from $-OH$, halo, $-CN$, $-SF_5$, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, $-O$ - C_1 - C_6 -alkyl, and C_1 - C_6 -alkyl- OH . In certain embodiments, R^4 is phenyl or pyridyl, wherein said phenyl or pyridyl is optionally substituted with 1, 2, 3, or 4 groups, each independently selected from halo, $-CN$, C_1 - C_6 -alkyl and C_1 - C_6 -haloalkyl. In a particular embodiment, R^4 is phenyl, wherein the phenyl is substituted with 1, 2, 3, or 4 groups, each independently selected from halo, $-CN$, C_1 - C_6 -alkyl and C_1 - C_6 -haloalkyl. In another particular embodiment, R^4 is pyridyl, wherein the pyridyl is substituted with 1, 2, 3, or 4 groups, each independently selected from halo, $-CN$, C_1 - C_6 -alkyl and C_1 - C_6 -haloalkyl.

R^5 may be selected from H , C_1 - C_6 -alkyl, and C_1 - C_6 -alkyl- OH . In a particular embodiment, R^5 is H .

R^6 may be selected from H, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkenyl, and C₀-C₆-alkyl-C₃-C₆-cycloalkyl. In a particular embodiment, R^6 is selected from H, C₁-C₆-alkyl, and C₁-C₆-haloalkyl.

R^7 may be independently selected from H, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C(O) C₁-C₆-alkyl and C₁-C₆-alkyl-OH. In a particular embodiment, R^7 is, at each occurrence, independently selected from H, and C₁-C₆-alkyl. In another embodiment, R^7 is, at each occurrence, independently selected from C₁-C₆-haloalkyl, and C(O) C₁-C₆-alkyl.

R^8 may be selected from H and C₁-C₆-alkyl.

R^9 may be selected from H and C₁-C₆-alkyl.

R^a may be independently selected from H, -OH, halo, C₁-C₆-alkyl, C₁-C₆-haloalkyl, -O-C₁-C₆-alkyl, and C₁-C₆-alkyl-OH.

R^b may be independently selected from H and C₁-C₆-alkyl.

m may be 0, 1, 2, 3, or 4.

n may be 0, 1, 2, 3, or 4.

p may be 0, 1, 2, 3, or 4.

q may be 0 or 1.

a ---- line denotes an optionally double bond.

In embodiments, A is CH₂ or C=O. In embodiments, A is CH₂. In other embodiments, A is C=O.

R^1 may be H, C₁-C₆-alkyl, C₁-C₆-alkenyl, C₁-C₆-alkyl-OH, or C₁-C₆-haloalkyl. In embodiments, R^1 is H. In embodiments, R^1 is C₁-C₆-alkyl. In embodiments, R^1 is C₁-C₆-alkenyl. In embodiments, R^1 is C₁-C₆-alkyl-OH. In embodiments, R^1 is C₁-C₆-haloalkyl.

In embodiments, there may be 0, 1, 2, 3, or 4 R^2 substituents: m is 0, 1, 2, 3, or 4.

Each R^2 may be independently selected from -OH, halo, C₁-C₆-alkyl, C₁-C₆-alkylene, C₀-C₆-alkyl-C₃-C₆-cycloalkyl, C₀-C₆-alkyl-C₂-C₆-heterocycloalkyl, C₀-C₆-alkyl-OR⁶, C₀-C₆-alkyl-N(R^7)₂, C₀-C₆-alkyl-SR⁸, C₀-C₆-alkyl-S(O)R⁸, C₀-C₆-alkyl-S(O)₂R⁸, C₀-C₆-alkyl-C(O)OR⁹, C₀-C₆-alkyl-OC(O)R⁹, C₀-C₆-alkyl-OC(O)OR⁹, C₀-C₆-alkyl-OC(O)N(R^7)₂, or C₀-C₆-alkyl-C(O)N(R^7)₂. In certain embodiments, m is 0 and there is no R^2 substitution. In certain embodiments, m is 1 and there is one R^2 substitution. In certain embodiments, m is 2 and there are two R^2 substitutions. In certain embodiments, m is 3 and there are three R^2 substitutions. In certain embodiments, m is 4 and there are four R^2 substitutions.

In certain embodiments, at least one R^2 is $-OH$. In certain embodiments, at least one R^2 is halo. In certain embodiments, at least one R^2 is C_1-C_6 -alkyl. In certain embodiments, at least one R^2 is C_1-C_6 -alkylene. In certain embodiments, at least one R^2 is C_0-C_6 -alkyl- C_3-C_6 -cycloalkyl. In certain embodiments, at least one R^2 is C_0-C_6 -alkyl- C_2-C_6 -heterocycloalkyl. In certain embodiments, at least one R^2 is C_0-C_6 -alkyl- OR^6 . In certain embodiments, at least one R^2 is C_0-C_6 -alkyl- $N(R^7)_2$. In certain embodiments, at least one R^2 is C_0-C_6 -alkyl- SR^8 . In certain embodiments, at least one R^2 is C_0-C_6 -alkyl- $S(O)R^8$. In certain embodiments, at least one R^2 is C_0-C_6 -alkyl- $S(O)_2R^8$. In certain embodiments, at least one R^2 is C_0-C_6 -alkyl- $C(O)OR^9$. In certain embodiments, at least one R^2 is C_0-C_6 -alkyl- $OC(O)R^9$. In certain embodiments, at least one R^2 is C_0-C_6 -alkyl- $OC(O)OR^9$. In certain embodiments, at least one R^2 is C_0-C_6 -alkyl- $OC(O)N(R^7)_2$. In certain embodiments, at least one R^2 is C_0-C_6 -alkyl- $C(O)N(R^7)_2$.

In certain embodiments, R^2 is substituted with 1, 2 or 3 groups. Each occurrence of R^2 as alkyl, cycloalkyl or heterocycloalkyl optionally may be substituted with $-OH$ or halo. For example, R^2 may be alkyl, and the alkyl is substituted with $-OH$; or R^2 may be alkyl, and the alkyl is substituted with at least one fluorine atom. R^2 may be cycloalkyl, and the cycloalkyl is substituted with $-OH$; or R^2 may be cycloalkyl, and the cycloalkyl is substituted with at least one fluorine atom. R^2 may be heterocycloalkyl, and the heterocycloalkyl is substituted with $-OH$; or R^2 may be heterocycloalkyl, and the heterocycloalkyl is substituted with at least one fluorine atom.

In embodiments, there may be 0, 1, 2, 3, or 4 R^3 substituents: n is 0, 1, 2, 3, or 4. In certain embodiments, n is 0 and there is no R^3 substitution. In certain embodiments, n is 1 and there is one R^3 substitution. In certain embodiments, n is 2 and there are two R^3 substitutions. In certain embodiments, n is 3 and there are three R^3 substitutions. In certain embodiments, n is 4 and there are four R^3 substitutions.

Each R^3 may be independently selected from $-OH$, halo, C_1-C_6 -alkyl, C_1-C_6 -haloalkyl, $-O-C_1-C_6$ -alkyl, and C_1-C_6 -alkyl- OH . In certain embodiments, at least one R^3 is $-OH$. In certain embodiments, at least one R^3 is halo. In certain embodiments, at least one R^3 is C_1-C_6 -alkyl. In certain embodiments, at least one R^3 is C_1-C_6 -haloalkyl. In certain embodiments, at least one R^3 is $-O-C_1-C_6$ -alkyl. In certain embodiments, at least one R^3 is C_1-C_6 -alkyl- OH .

R^4 is selected from $(CR^aR^b)_p-C_1-C_9$ -heteroaryl, $(CR^aR^b)_p-C_6-C_{12}$ -aryl, $(CR^aR^b)_p-C_3-C_7$ -cycloalkyl, and $(CR^aR^b)_p-C_2-C_6$ -heterocycloalkyl, wherein heteroaryl, aryl, cycloalkyl, and

heterocycloalkyl are optionally substituted with 1, 2, 3, or 4 groups, each independently selected from $-\text{OH}$, halo, $-\text{CN}$, $-\text{SF}_5$, $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_1\text{-C}_6\text{-haloalkyl}$, $-\text{O-C}_1\text{-C}_6\text{-alkyl}$, and $\text{C}_1\text{-C}_6\text{-alkyl-OH}$. In certain embodiments, R^4 is $(\text{CR}^a\text{R}^b)_p\text{-C}_1\text{-C}_9\text{-heteroaryl}$ optionally substituted with 1, 2, 3, or 4 groups, each independently selected from $-\text{OH}$, halo, $-\text{CN}$, $-\text{SF}_5$, $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_1\text{-C}_6\text{-haloalkyl}$, $-\text{O-C}_1\text{-C}_6\text{-alkyl}$, and $\text{C}_1\text{-C}_6\text{-alkyl-OH}$. In certain
 5 $\text{O-C}_1\text{-C}_6\text{-alkyl}$, and $\text{C}_1\text{-C}_6\text{-alkyl-OH}$. In certain embodiments, R^4 is $(\text{CR}^a\text{R}^b)_p\text{-C}_6\text{-C}_{12}\text{-aryl}$ optionally substituted with 1, 2, 3, or 4 groups, each independently selected from $-\text{OH}$, halo, $-\text{CN}$, $-\text{SF}_5$, $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_1\text{-C}_6\text{-haloalkyl}$, $-\text{O-C}_1\text{-C}_6\text{-alkyl}$, and $\text{C}_1\text{-C}_6\text{-alkyl-OH}$. In certain
 10 $\text{C}_6\text{-alkyl}$, and $\text{C}_1\text{-C}_6\text{-alkyl-OH}$. In certain embodiments, R^4 is $(\text{CR}^a\text{R}^b)_p\text{-C}_3\text{-C}_7\text{-cycloalkyl}$ optionally substituted with 1, 2, 3, or 4 groups, each independently selected from $-\text{OH}$, halo, $-\text{CN}$, $-\text{SF}_5$, $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_1\text{-C}_6\text{-haloalkyl}$, $-\text{O-C}_1\text{-C}_6\text{-alkyl}$, and $\text{C}_1\text{-C}_6\text{-alkyl-OH}$. In certain
 15 $\text{C}_6\text{-alkyl}$, and $\text{C}_1\text{-C}_6\text{-alkyl-OH}$. In certain embodiments, R^4 is phenyl or pyridyl, wherein said phenyl or pyridyl is optionally substituted with 1, 2, 3, or 4 groups, each independently selected from halo, $-\text{CN}$, $\text{C}_1\text{-C}_6\text{-alkyl}$ and $\text{C}_1\text{-C}_6\text{-haloalkyl}$. In a particular embodiment, R^4 is phenyl, wherein the phenyl is substituted with 1, 2, 3, or 4 groups, each independently selected from halo, $-\text{CN}$, $\text{C}_1\text{-C}_6\text{-alkyl}$ and $\text{C}_1\text{-C}_6\text{-haloalkyl}$. In another particular embodiment, R^4 is pyridyl, wherein the pyridyl is substituted with 1, 2, 3, or 4 groups, each independently selected from halo, $-\text{CN}$, $\text{C}_1\text{-C}_6\text{-alkyl}$ and $\text{C}_1\text{-C}_6\text{-haloalkyl}$.

R^5 may be selected from H, $\text{C}_1\text{-C}_6\text{-alkyl}$, and $\text{C}_1\text{-C}_6\text{-alkyl-OH}$. In a particular
 20 embodiment, R^5 is H.

R^6 may be selected from H, $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_1\text{-C}_6\text{-haloalkyl}$, $\text{C}_1\text{-C}_6\text{-alkenyl}$, and $\text{C}_0\text{-C}_6\text{-alkyl-C}_3\text{-C}_6\text{-cycloalkyl}$. In a particular embodiment, R^6 is selected from H, $\text{C}_1\text{-C}_6\text{-alkyl}$, and $\text{C}_1\text{-C}_6\text{-haloalkyl}$.

R^7 may be independently selected from H, $\text{C}_1\text{-C}_6\text{-alkyl}$, and $\text{C}_1\text{-C}_6\text{-alkyl-OH}$. In a
 25 particular embodiment, R^7 is, at each occurrence, independently selected from H, and $\text{C}_1\text{-C}_6\text{-alkyl}$.

R^8 may be selected from H and $\text{C}_1\text{-C}_6\text{-alkyl}$.

R^9 may be selected from H and $\text{C}_1\text{-C}_6\text{-alkyl}$.

R^a may be independently selected from H, $-\text{OH}$, halo, $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_1\text{-C}_6\text{-haloalkyl}$, $-\text{O-C}_1\text{-C}_6\text{-alkyl}$, and $\text{C}_1\text{-C}_6\text{-alkyl-OH}$.
 30

R^b may be independently selected from H and $\text{C}_1\text{-C}_6\text{-alkyl}$.

m may be 0, 1, 2, 3, or 4.

n may be 0, 1, 2, 3, or 4.

p may be 0, 1, 2, 3, or 4.

q may be 0 or 1.

5 A ---- line denotes an optionally double bond.

In an embodiment of the compound of Formula I, A is C=O.

In another embodiment of the compound of Formula I, A is CH₂. In an embodiment of the compound of Formula I, q is 1.

10 In another embodiment of the compound of Formula I, R¹ is H, C₁-C₆-alkyl, or C₁-C₆-haloalkyl. In a particular embodiment, R¹ is C₁-C₆-alkyl. In another particular embodiment, R¹ is -CH₃ or -CH₂CHF₂. In a more particular embodiment, R¹ is -CH₃

In another embodiment of the compound of Formula I, R⁴ is phenyl or pyridyl, wherein said phenyl or pyridyl is optionally substituted with 1, 2, 3, or 4 groups, each independently selected from halo, -CN, C₁-C₆-alkyl and C₁-C₆-haloalkyl, and R⁵ is H.

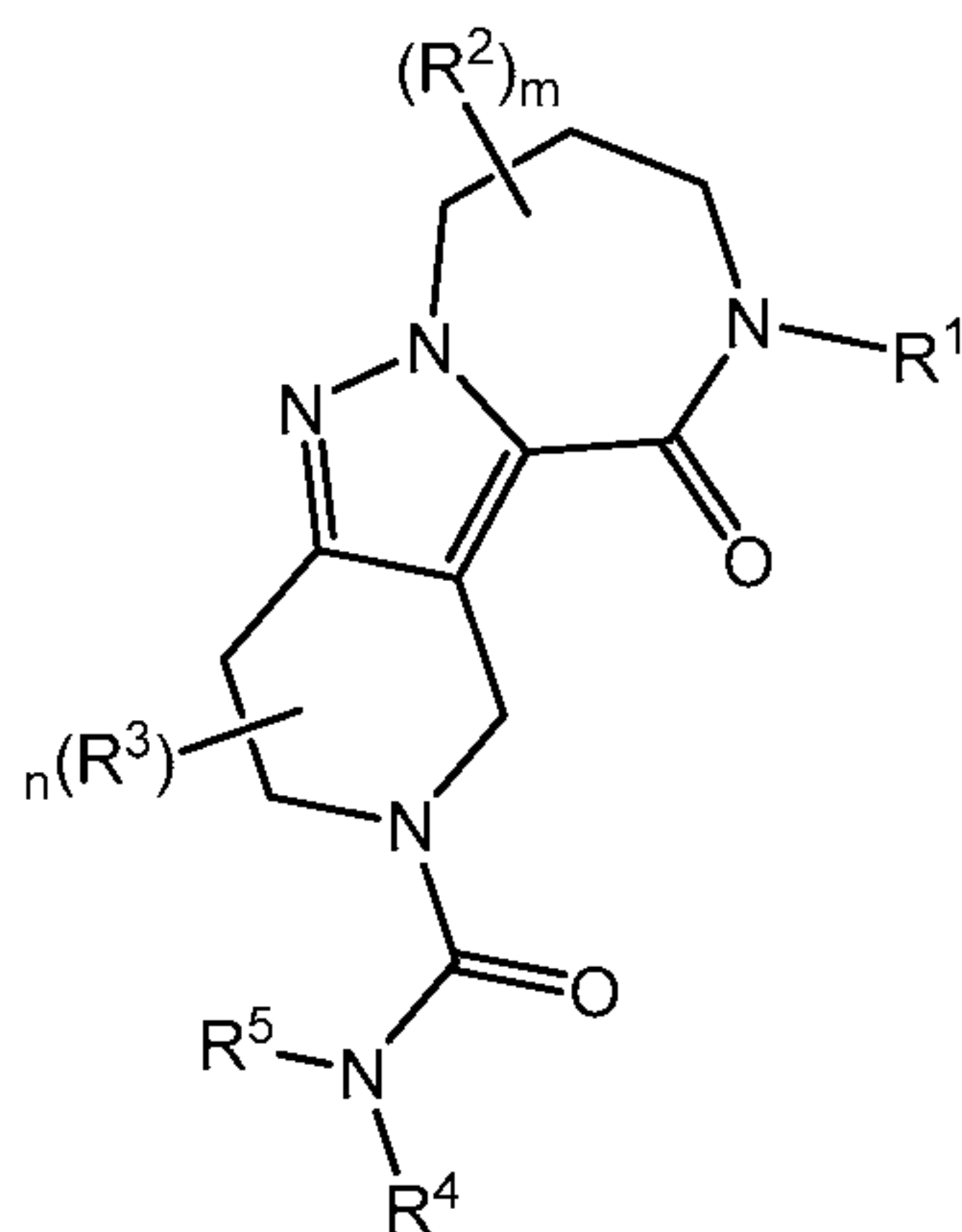
15 In another particular embodiment of Formula I, R¹ is C₁-C₆-alkyl; R² is C₁-C₆-alkyl or C₀-C₆-alkyl-OR⁶, wherein alkyl is substituted with halo, and R⁶ is H or C₁-C₆-haloalkyl; R³ is C₁-C₆-alkyl; R⁴ is phenyl substituted with 1 or 2 groups, each independently selected from halo and -CN; R⁵ is H; m is 1; and n is 1.

20 In another particular embodiment of Formula I, R¹ is methyl; R² is -CH₂F or CH₂-O-CH₂CHF₂; R³ is methyl; R⁴ is phenyl substituted with 1 or 2 groups, each independently selected from F and -CN; R⁵ is H; m is 1; and n is 1.

In another particular embodiment of Formula I, R¹ is C₁-C₆-alkyl, R² is -CH₂F, R⁴ is phenyl or pyridyl, wherein the phenyl or pyridyl is substituted with 1-3 groups independently selected from halo, -CN, -SF₅, C₁-C₆-alkyl, and C₁-C₆-haloalkyl, R⁵ is H, and n is 0.

25 In another particular embodiment of Formula I, R¹ is C₁-C₆-alkyl, R² is -CH₂OCH₂CHF₂, R⁴ is phenyl or pyridyl, wherein the phenyl or pyridyl is substituted with 1-3 groups independently selected from halo, -CN, -SF₅, C₁-C₆-alkyl, and C₁-C₆-haloalkyl, R⁵ is H, n is 1, and R³ is C₁-C₆-alkyl.

In another embodiment, the compound of Formula I has the structure of Formula II:

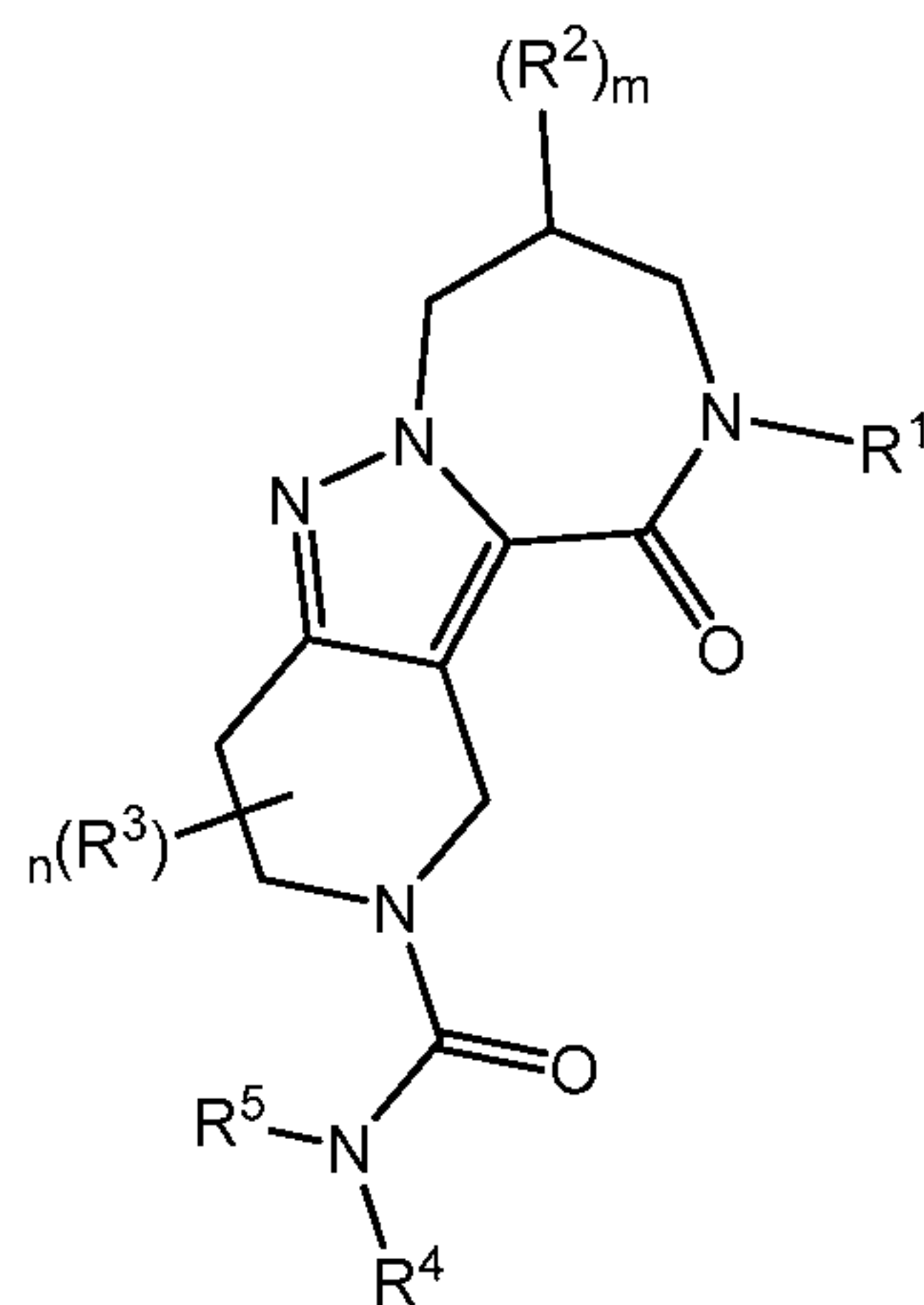
**II,**

or a pharmaceutically acceptable salt thereof.

In one embodiment of the compound of Formula II, R¹ is H, C₁-C₆-alkyl, or C₁-C₆-haloalkyl. In a particular embodiment, R¹ is C₁-C₆-alkyl. In another particular embodiment, R¹ is -CH₃ or -CH₂CHF₂. In a more particular embodiment, R¹ is -CH₃.

In another embodiment of the compound of Formula II, R⁴ is phenyl or pyridyl, wherein said phenyl or pyridyl is optionally substituted with 1, 2, 3, or 4 groups, each independently selected from halo, -CN, C₁-C₆-alkyl and C₁-C₆-haloalkyl, and R⁵ is H.

In another embodiment, the compound of Formula I or Formula II has the structure of Formula III:

**III,**

or a pharmaceutically acceptable salt thereof,

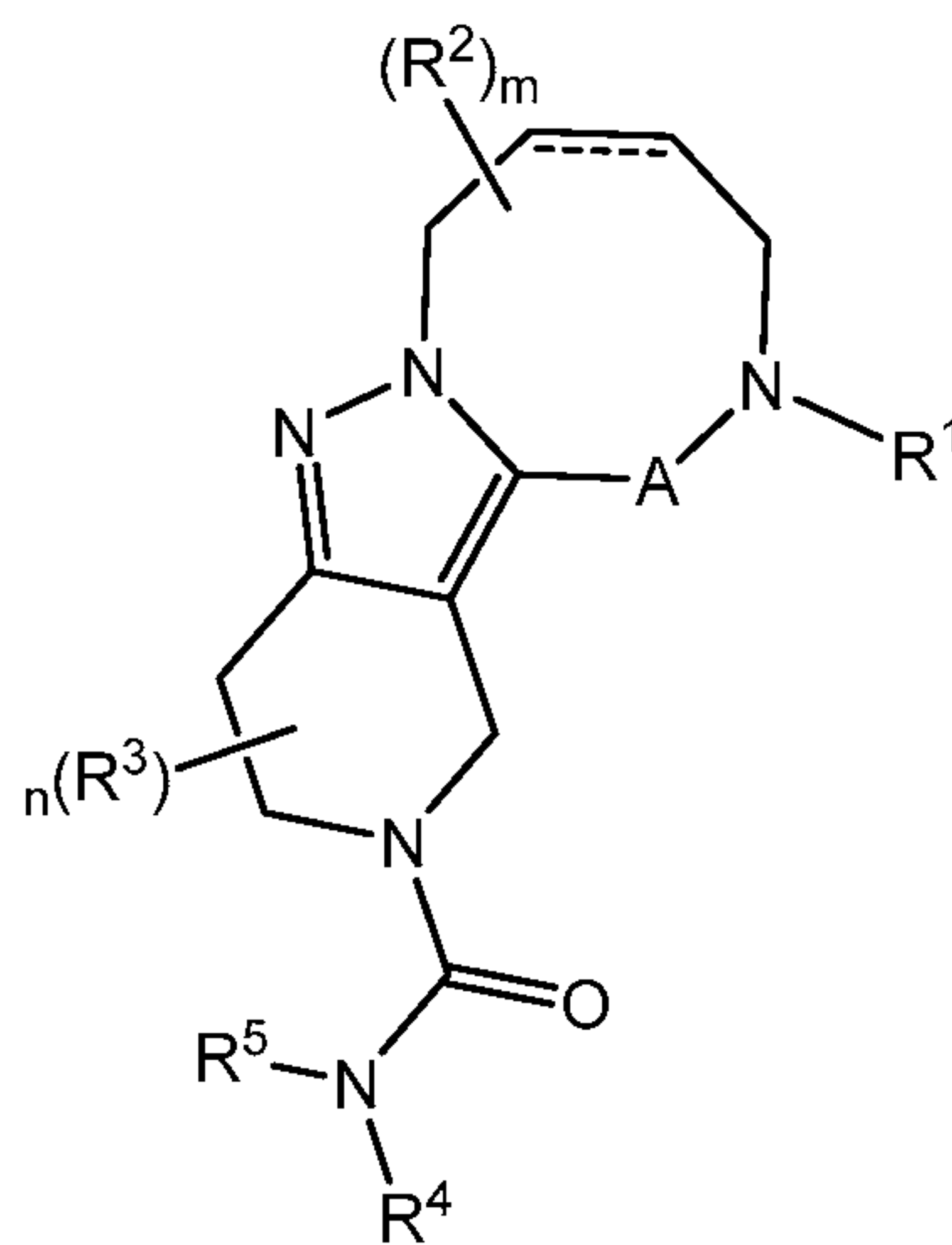
wherein m is 0, 1, or 2.

In one embodiment of the compound of Formula III, R¹ is H, C₁-C₆-alkyl, or C₁-C₆-haloalkyl. In a particular embodiment, R¹ is C₁-C₆-alkyl. In another particular embodiment, R¹

is $-\text{CH}_3$ or $-\text{CH}_2\text{CHF}_2$. In a more particular embodiment, R^1 is $-\text{CH}_3$

In another embodiment of the compound of Formula III, R^4 is phenyl or pyridyl, wherein said phenyl or pyridyl is optionally substituted with 1, 2, 3, or 4 groups, each independently selected from halo, $-\text{CN}$, $\text{C}_1\text{-C}_6\text{-alkyl}$ and $\text{C}_1\text{-C}_6\text{-haloalkyl}$, and R^5 is H.

5 In another embodiment, provided herein are compounds having the structure of Formula V:



V,

or a pharmaceutically acceptable salt thereof, wherein

10 A is CH_2 or $\text{C}=\text{O}$;

R^1 is H, $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_1\text{-C}_6\text{-alkenyl}$, $\text{C}_1\text{-C}_6\text{-alkyl-OH}$, or $\text{C}_1\text{-C}_6\text{-haloalkyl}$;

R^2 is, at each occurrence, independently selected from $-\text{OH}$, halo, $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_1\text{-C}_6\text{-alkylene}$, $\text{C}_0\text{-C}_6\text{-alkyl-C}_3\text{-C}_6\text{-cycloalkyl}$, $\text{C}_0\text{-C}_6\text{-alkyl-C}_2\text{-C}_6\text{-heterocycloalkyl}$, $\text{C}_0\text{-C}_6\text{-alkyl-OR}^6$, $\text{C}_0\text{-C}_6\text{-alkyl-N(R}^7)_2$, $\text{C}_0\text{-C}_6\text{-alkyl-SR}^8$, $\text{C}_0\text{-C}_6\text{-alkyl-S(O)R}^8$, $\text{C}_0\text{-C}_6\text{-alkyl-S(O)}_2\text{R}^8$, $\text{C}_0\text{-C}_6\text{-alkyl-C(O)OR}^9$, $\text{C}_0\text{-C}_6\text{-alkyl-OC(O)R}^9$, $\text{C}_0\text{-C}_6\text{-alkyl-OC(O)OR}^9$, $\text{C}_0\text{-C}_6\text{-alkyl-OC(O)N(R}^7)_2$, and $\text{C}_0\text{-C}_6\text{-alkyl-C(O)N(R}^7)_2$, wherein alkyl, alkylene, cycloalkyl, and heterocycloalkyl are optionally substituted with 1, 2, or 3 groups, each independently selected from $-\text{OH}$ and halo; or

two R^2 groups together form a $\text{C}_3\text{-C}_6$ spiro cycloalkyl, wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups, each individually selected from $-\text{OH}$ and halo;

R^3 is, at each occurrence, independently selected from $-\text{OH}$, halo, $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_1\text{-C}_6\text{-haloalkyl}$, $-\text{O-C}_1\text{-C}_6\text{-alkyl}$, and $\text{C}_1\text{-C}_6\text{-alkyl-OH}$;

R^4 is selected from $(\text{CR}^a\text{R}^b)_p\text{-C}_1\text{-C}_9\text{-heteroaryl}$, $(\text{CR}^a\text{R}^b)_p\text{-C}_6\text{-C}_{12}\text{-aryl}$, $(\text{CR}^a\text{R}^b)_p\text{-C}_3\text{-C}_7\text{-}$

cycloalkyl, and $(CR^aR^b)_p$ -C₂-C₆-heterocycloalkyl, wherein heteroaryl, aryl, cycloalkyl, and heterocycloalkyl are optionally substituted with 1, 2, 3, or 4 groups, each independently selected from -OH, halo, -CN, -SF₅, C₁-C₆-alkyl, C₁-C₆-haloalkyl, -O-C₁-C₆-alkyl, and C₁-C₆-alkyl-OH;

R⁵ is selected from H, C₁-C₆-alkyl, and C₁-C₆-alkyl-OH;

5 R⁶ is selected from H, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkenyl, and C₀-C₆-alkyl-C₃-C₆-cycloalkyl;

R⁷ is, at each occurrence, independently selected from H, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C(O) C₁-C₆-alkyl and C₁-C₆-alkyl-OH;

R⁸ is selected from H and C₁-C₆-alkyl;

10 R⁹ is selected from H and C₁-C₆-alkyl;

R^a is, at each occurrence, independently selected from H, -OH, halo, C₁-C₆-alkyl, C₁-C₆-haloalkyl, -O-C₁-C₆-alkyl, and C₁-C₆-alkyl-OH;

R^b is, at each occurrence, independently selected from H and C₁-C₆-alkyl;

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

15 n is 0, 1, 2, 3, or 4;

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

a ---- line denotes an optionally double bond.

In one embodiment of the compound of Formula V, A is C=O. In another embodiment, R¹ is H or C₁-C₆-alkyl. In another embodiment, R¹ is -CH₃. In a further embodiment, m is 0.

20 In another embodiment of the compound of Formula V, R⁴ is $(CR^aR^b)_p$ -C₁-C₅-heteroaryl or $(CR^aR^b)_p$ -C₆-aryl, wherein heteroaryl and aryl are optionally substituted with 1, 2, 3, or 4 groups, each independently selected from -OH, halo, -CN, -SF₅, C₁-C₆-alkyl, C₁-C₆-haloalkyl, -O-C₁-C₆-alkyl, and C₁-C₆-alkyl-OH;

R^a is H or C₁-C₆-alkyl;

25 R^b is H or C₁-C₆-alkyl; and

p is 0 or 1.

In a further embodiment of the compound of Formula V, A is C=O;

R¹ is -CH₃;

30 R⁴ is $(CR^aR^b)_p$ -C₆-C₁₂-aryl, wherein aryl is optionally substituted with 1, 2, 3, or 4 groups, each independently selected from halo, -CN, and C₁-C₆-alkyl;

R⁵ is H;

m is 0;

n is 0; and

p is 0.

In an embodiment of the compound of any one of Formulas I, II, III, or V, m is 0, 1, or 2;

5 and

R^2 is, at each occurrence, independently selected from $-OH$, halo, C_1-C_6 -alkyl, C_1-C_6 -alkenyl, C_0-C_6 -alkyl- OR^6 , C_0-C_6 -alkyl- $N(R^7)_2$, C_0-C_6 -alkyl- C_3-C_6 -cycloalkyl, C_0-C_6 -alkyl- C_2-C_6 -heterocycloalkyl, C_0-C_6 -alkyl- SR^8 , C_0-C_6 -alkyl- $S(O)R^8$, C_0-C_6 -alkyl- $S(O)_2R^8$, C_0-C_6 -alkyl- $C(O)OR^9$, and C_0-C_6 -alkyl- $C(O)N(R^7)_2$, wherein alkyl, alkylene, cycloalkyl, and

10 heterocycloalkyl are optionally substituted with 1 or 2 groups, each independently selected from $-OH$ and halo; or

two R^2 groups together form a C_3-C_6 spiro cycloalkyl, wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups, each individually selected from $-OH$ and halo.

In an embodiment of the compound of any one of Formulas I, II, III, or V, m is 1 or 2;

15 and

R^2 is, at each occurrence, independently selected from $-CH_2N(H)(C(O)-CH_3)$, $-CH_2N(H)CH_2CHF_2$, $CH_2N(H)CH_2CF_3$, or $CH(OH)CH=CH_2$; or two R^2 groups together form a spiro-cyclobutyl, which is substituted with $-OH$.

In an embodiment of the compound of any one of Formulas I, II, III, or V, m is 0, 1, or 2;

20 and

R^2 is, at each occurrence, independently selected from $-OH$, halo, C_1-C_6 -alkyl, C_1-C_6 -alkenyl, C_0-C_6 -alkyl- OR^6 , C_0-C_6 -alkyl- $N(R^7)_2$, C_0-C_6 -alkyl- C_3-C_6 -cycloalkyl, C_0-C_6 -alkyl- C_2-C_6 -heterocycloalkyl, C_0-C_6 -alkyl- SR^8 , C_0-C_6 -alkyl- $S(O)R^8$, C_0-C_6 -alkyl- $S(O)_2R^8$, C_0-C_6 -alkyl- $C(O)OR^9$, and C_0-C_6 -alkyl- $C(O)N(R^7)_2$, wherein alkyl, cycloalkyl, and heterocycloalkyl are

25 optionally substituted with 1 or 2 groups, each independently selected from $-OH$ and halo.

In an embodiment of the compound of any one of Formulas I, II, III, or V, m is 1 or 2;

and

R^2 is, at each occurrence, independently selected from $=CH_2$, $-CH_2OH$, $-OH$, $-F$, $-CH_3$, $-CHF_2$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CHF_2$, $-NH_2$, $-N(CH_3)_2$, morpholinyl, azetidiny, pyrrolidinyl, $-SCH_3$, $-S(O)CH_3$, $-S(O)_2CH_3$, $-CH_2C(O)OCH_3$, $-CH_2CH_2OH$, $-C(O)OH$, $-C(O)OCH_3$, $-C(O)OCH_2CH_3$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-C(OH)(CH_3)_2$, $-CH(OH)CH_3$, $-$

30

CH(OH)CH₂CH₃, and –CH(OH)-cyclopropyl, wherein morpholinyl, azetidiny, and pyrrolidinyl are optionally substituted with 1 or 2 groups, each independently selected from –OH and halo.

In an embodiment of the compound of any one of Formulas I, II, or III, m is 0, 1, or 2; and

R² is, at each occurrence, independently selected from –OH, halo, C₁-C₆-alkyl, C₁-C₆-alkenyl, C₀-C₆-alkyl-OR⁶, C₀-C₆-alkyl-N(R⁷)₂, C₀-C₆-alkyl-C₃-C₆-cycloalkyl, C₀-C₆-alkyl-C₂-C₆-heterocycloalkyl, C₀-C₆-alkyl-SR⁸, C₀-C₆-alkyl-S(O)R⁸, C₀-C₆-alkyl-S(O)₂R⁸, C₀-C₆-alkyl-C(O)OR⁹, and C₀-C₆-alkyl-C(O)N(R⁷)₂, wherein alkyl, cycloalkyl, and heterocycloalkyl are optionally substituted with 1 or 2 groups, each independently selected from –OH and halo.

In an embodiment of the compound of any one of Formulas I, II, or III, m is 1 or 2; and

R² is, at each occurrence, independently selected from =CH₂, –CH₂OH, –OH, –F, –CH₃, –CHF₂, –OCH₃, –OCH₂CH₃, –OCH₂CHF₂, –NH₂, –N(CH₃)₂, morpholinyl, azetidiny, pyrrolidinyl, –SCH₃, –S(O)CH₃, –S(O)₂CH₃, –CH₂C(O)OCH₃, –CH₂CH₂OH, –C(O)OH, –C(O)OCH₃, –C(O)OCH₂CH₃, –C(O)NHCH₃, –C(O)N(CH₃)₂, –C(OH)(CH₃)₂, –CH(OH)CH₃, –CH(OH)CH₂CH₃, and –CH(OH)-cyclopropyl, wherein morpholinyl, azetidiny, and pyrrolidinyl are optionally substituted with 1 or 2 groups, each independently selected from –OH and halo.

In an embodiment of the compound of any one of Formulas I, II, or III, n is 0, 1, or 2; and R³ is, at each occurrence, selected from –OH, halo, and C₁-C₆-alkyl.

In an embodiment of the compound of any one of Formula V, n is 0, 1, or 2; and R³ is, at each occurrence, selected from –OH, halo, and C₁-C₆-alkyl.

In an embodiment of the compound of any one of Formulas I, II, III, or V, R⁴ is (CR^aR^b)_p-C₁-C₅-heteroaryl or (CR^aR^b)_p-C₆-aryl, wherein heteroaryl and aryl are optionally substituted with 1, 2, or 3 groups, each independently selected from –OH, halo, –CN, –SF₅, C₁-C₆-alkyl, C₁-C₆-haloalkyl, –O-C₁-C₆-alkyl, and C₁-C₆-alkyl-OH;

R^a is H or C₁-C₆-alkyl;

R^b is H or C₁-C₆-alkyl; and

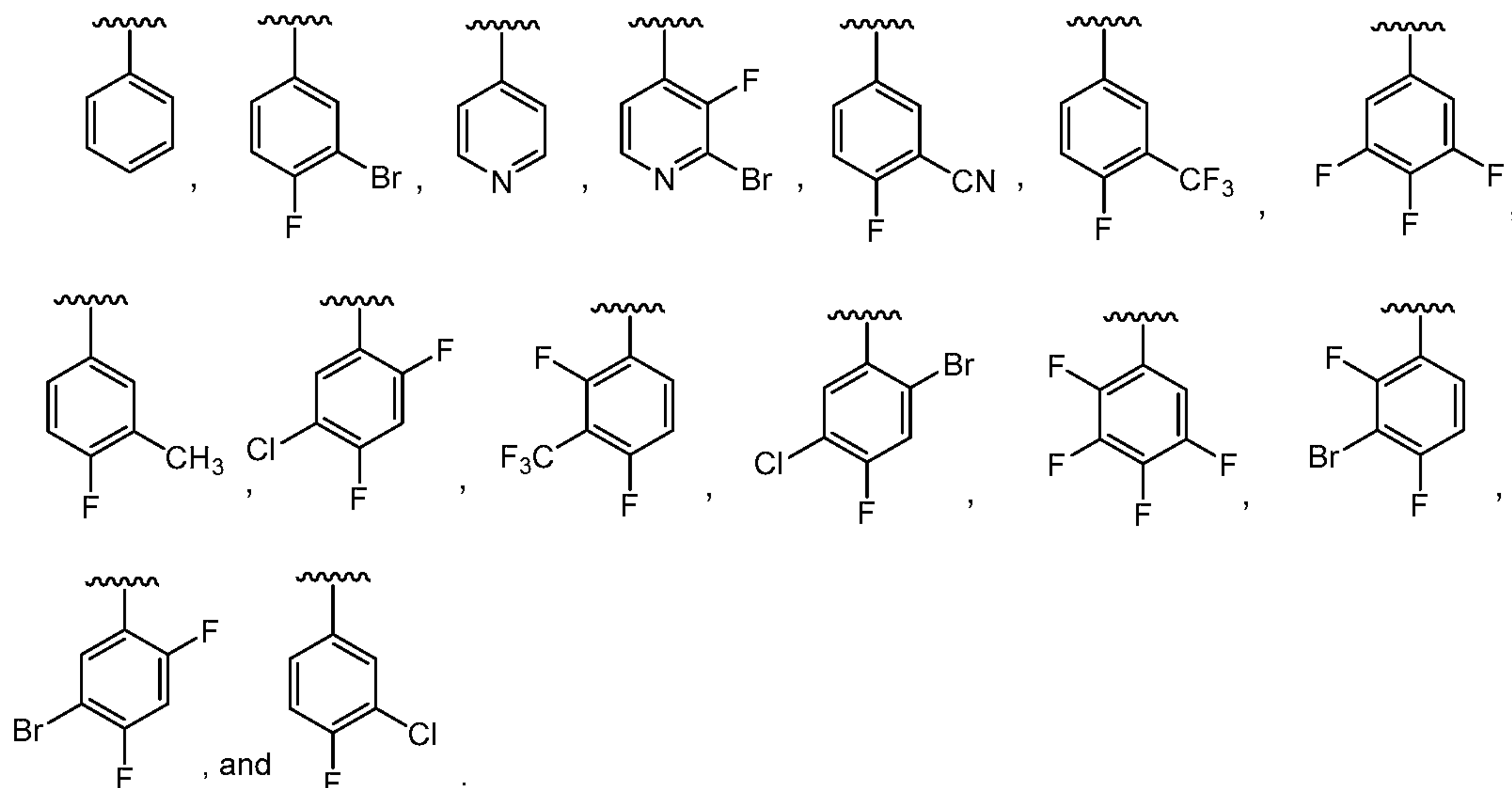
p is 0 or 1.

In an embodiment of the compound of any one of Formulas I, II, III, or V, R⁴ is C₁-C₅-heteroaryl or C₆-aryl, any of which is optionally substituted with 1, 2, or 3 groups, each independently selected from halo, –CN, C₁-C₆-alkyl, and C₁-C₆-haloalkyl.

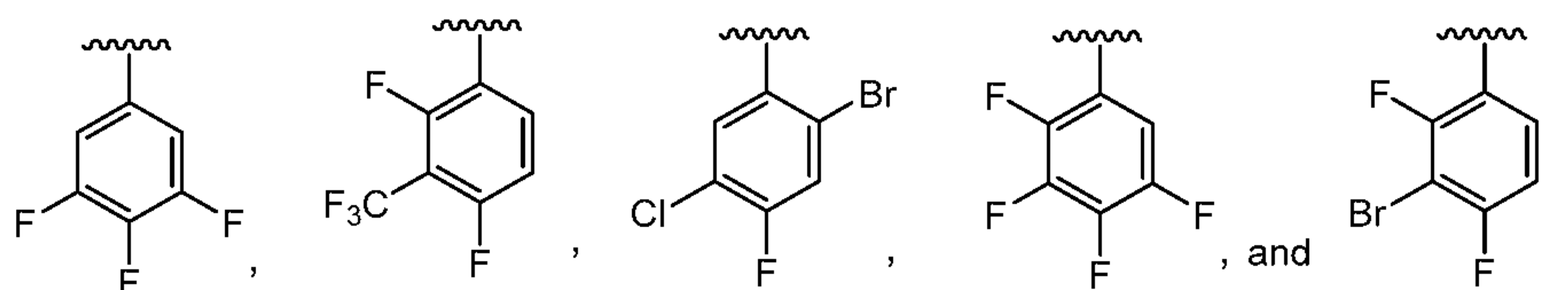
In a further embodiment of the compound of any one of Formulas I, II, III, or V, R⁴ is phenyl or pyridinyl, any of which is optionally substituted with 1, 2, or 3 groups, each

independently selected from halo, $-\text{CN}$, $\text{C}_1\text{-C}_6\text{-alkyl}$, and $\text{C}_1\text{-C}_6\text{-haloalkyl}$.

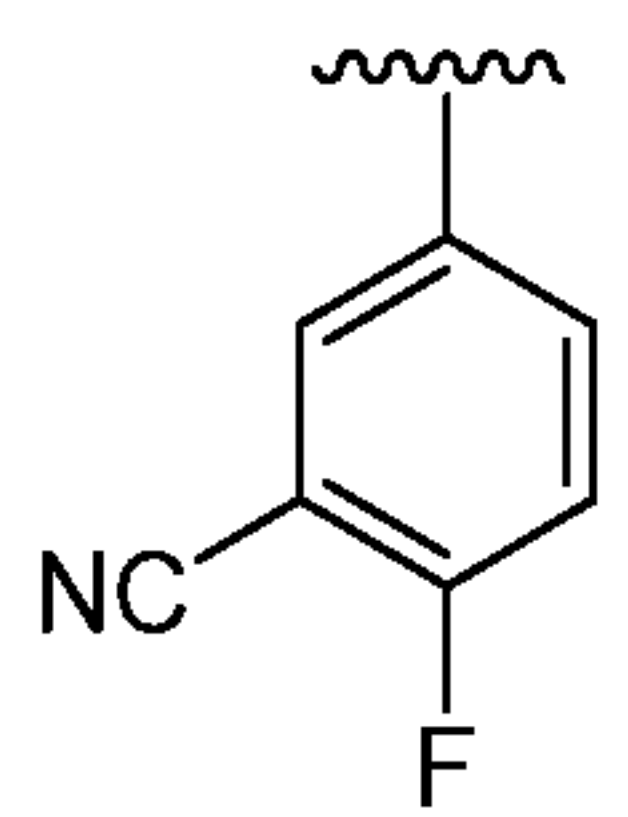
In an embodiment of the compound of any one of Formulas I, II, III, or V, R^4 is selected from the group consisting of:



5 In another embodiment of the compound of any one of Formulas I, II, III, or V, R^4 is selected from the group consisting of:



In another embodiment of the compound of any one of Formulas I, II, III, or V, R^4 is



10 In an embodiment of the compound of any one of Formulas I, II, or III, R^4 is $(\text{CR}^a\text{R}^b)_p\text{-C}_1\text{-C}_5\text{-heteroaryl}$ or $(\text{CR}^a\text{R}^b)_p\text{-C}_6\text{-aryl}$, wherein heteroaryl and aryl are optionally substituted with 1, 2, or 3 groups, each independently selected from $-\text{OH}$, halo, $-\text{CN}$, $-\text{SF}_5$, $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_1\text{-C}_6\text{-haloalkyl}$, $-\text{O-C}_1\text{-C}_6\text{-alkyl}$, and $\text{C}_1\text{-C}_6\text{-alkyl-OH}$;

R^a is H or $\text{C}_1\text{-C}_6\text{-alkyl}$;

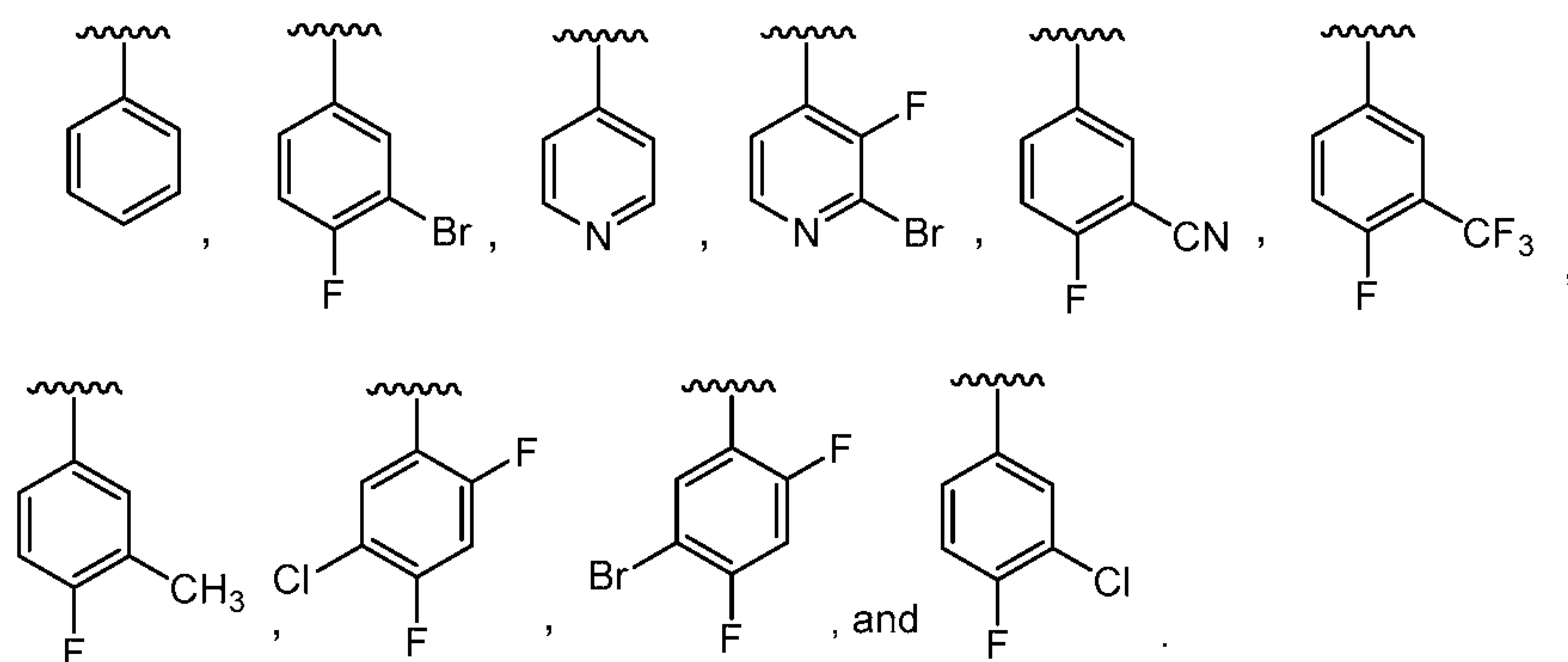
15 R^b is H or $\text{C}_1\text{-C}_6\text{-alkyl}$; and

p is 0 or 1.

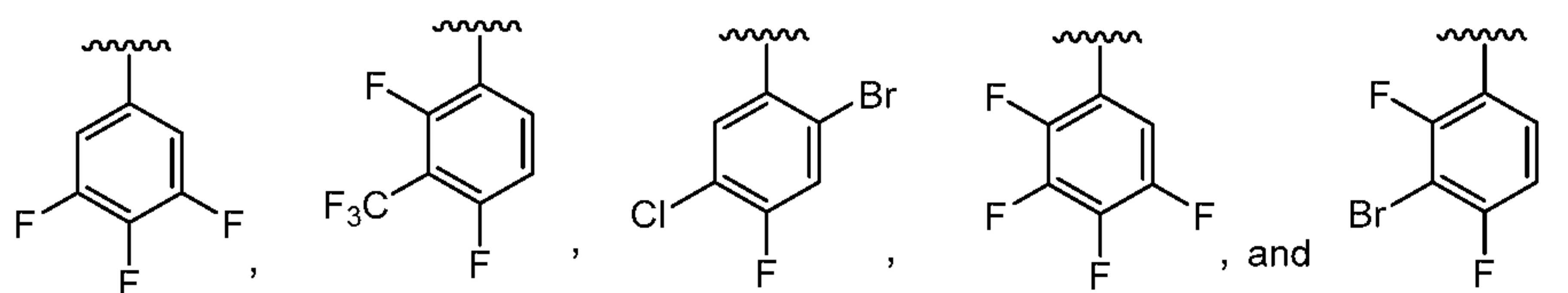
In an embodiment of the compound of any one of Formulas I, II, or III, R^4 is C_1 - C_5 -heteroaryl or C_6 -aryl, any of which is optionally substituted with 1, 2, or 3 groups, each independently selected from halo, $-CN$, C_1 - C_6 -alkyl, and C_1 - C_6 -haloalkyl.

5 In a further embodiment of the compound of any one of Formulas I, II, or III, R^4 is phenyl or pyridinyl, any of which is optionally substituted with 1, 2, or 3 groups, each independently selected from halo, $-CN$, C_1 - C_6 -alkyl, and C_1 - C_6 -haloalkyl.

In an embodiment of the compound of any one of Formulas I, II, or III, R^4 is selected from the group consisting of:



10 In another embodiment of the compound of any one of Formulas I, II, or III, R^4 is selected from the group consisting of:



In an embodiment of the compound of any one of Formulas I, II, or III, R^5 is H or C_1 - C_6 -alkyl.

15 In an embodiment of the compound of any one of Formulas I, II, or III, R^5 is H.

In an embodiment of the compound of any one of Formula V, R^5 is H or C_1 - C_6 -alkyl.

In an embodiment of the compound of any one of Formula V, R^5 is H. In an embodiment of the compound of any one of Formulas I, II, or III,

A is $C=O$;

20 R^1 is C_1 - C_6 -alkyl;

R^2 is, at each occurrence, independently selected from $-OH$, halo, C_1 - C_6 -alkyl, C_1 - C_6 -alkylene, C_0 - C_6 -alkyl- C_3 - C_6 -cycloalkyl, C_0 - C_6 -alkyl- C_2 - C_6 -heterocycloalkyl,

C₀-C₆-alkyl-OR⁶, C₀-C₆-alkyl-N(R⁷)₂, C₀-C₆-alkyl-SR⁸, C₀-C₆-alkyl-S(O)R⁸, C₀-C₆-alkyl-S(O)₂R⁸, C₀-C₆-alkyl-C(O)OR⁹, C₀-C₆-alkyl-OC(O)R⁹, C₀-C₆-alkyl-OC(O)OR⁹, C₀-C₆-alkyl-OC(O)N(R⁷)₂, and C₀-C₆-alkyl-C(O)N(R⁷)₂, wherein alkyl, alkylene, cycloalkyl, and heterocycloalkyl are optionally substituted with 1, 2, or 3 groups, each independently selected from -OH and halo; or

two R² groups together form a C₃-C₆ spiro cycloalkyl, wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups, each individually selected from -OH and halo;

R⁴ is (CR^aR^b)_p-C₆-C₁₂-aryl, wherein aryl is optionally substituted with 1, 2, 3, or 4 groups, each independently selected from halo, -CN, and C₁-C₆-alkyl;

R⁵ is H;

R⁶ is selected from H, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkenyl, and C₀-C₆-alkyl-C₃-C₆-cycloalkyl;

R⁷ is, at each occurrence, independently selected from H, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C(O) C₁-C₆-alkyl and C₁-C₆-alkyl-OH;

R⁸ is selected from H and C₁-C₆-alkyl;

R⁹ is selected from H and C₁-C₆-alkyl;

m is 0, 1 or 2;

n is 0;

p is 0; and

q is 1.

In another embodiment of the compound of any one of Formulas I, II, or III,

A is C=O;

R¹ is C₁-C₆-alkyl;

R² is, at each occurrence, independently selected from -OH, halo, C₁-C₆-alkyl, C₁-C₆-alkylene, C₀-C₆-alkyl-C₃-C₆-cycloalkyl, C₀-C₆-alkyl-C₂-C₆-heterocycloalkyl, C₀-C₆-alkyl-OR⁶, C₀-C₆-alkyl-N(R⁷)₂, C₀-C₆-alkyl-SR⁸, C₀-C₆-alkyl-S(O)R⁸, C₀-C₆-alkyl-S(O)₂R⁸, C₀-C₆-alkyl-C(O)OR⁹, and C₀-C₆-alkyl-C(O)N(R⁷)₂, wherein alkyl, alkylene, cycloalkyl, and heterocycloalkyl are optionally substituted with 1, 2, or 3 groups, each independently selected from -OH and halo; or

two R² groups together form a C₃-C₆ spiro cycloalkyl, wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups, each individually selected from -OH and halo;

R^4 is $(CR^aR^b)_p$ -C₆-C₁₂-aryl, wherein aryl is optionally substituted with 1, 2, 3, or 4 groups, each independently selected from halo, -CN, and C₁-C₆-alkyl;

R^5 is H;

R^6 is selected from H, C₁-C₆-alkyl, and C₁-C₆-haloalkyl;

5 R^7 is, at each occurrence, independently selected from H, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C(O) C₁-C₆-alkyl and C₁-C₆-alkyl-OH;

R^8 is C₁-C₆-alkyl;

R^9 is selected from H and C₁-C₆-alkyl;

m is 0, 1 or 2;

10 n is 0;

p is 0; and

q is 1.

In an embodiment of the compound of any one of Formulas I, II, or III,

A is C=O;

15 R^1 is C₁-C₆-alkyl;

R^2 is, at each occurrence, independently selected from -OH, halo, C₁-C₆-alkyl, C₁-C₆-alkylene, C₀-C₆-alkyl-C₃-C₆-cycloalkyl, C₀-C₆-alkyl-C₂-C₆-heterocycloalkyl, C₀-C₆-alkyl-OR⁶, C₀-C₆-alkyl-N(R⁷)₂, C₀-C₆-alkyl-SR⁸, C₀-C₆-alkyl-S(O)R⁸, C₀-C₆-alkyl-S(O)₂R⁸, C₀-C₆-alkyl-C(O)OR⁹, C₀-C₆-alkyl-OC(O)R⁹, C₀-C₆-alkyl-OC(O)OR⁹, C₀-C₆-alkyl-OC(O)N(R⁷)₂, and C₀-C₆-alkyl-C(O)N(R⁷)₂, wherein alkyl, cycloalkyl, and heterocycloalkyl are optionally substituted with 1, 2, or 3 groups, each independently selected from -OH and halo;

R^4 is $(CR^aR^b)_p$ -C₆-C₁₂-aryl, wherein aryl is optionally substituted with 1, 2, 3, or 4 groups, each independently selected from halo, -CN, and C₁-C₆-alkyl;

R^5 is H;

25 R^6 is selected from H, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkenyl, and C₀-C₆-alkyl-C₃-C₆-cycloalkyl;

R^7 is, at each occurrence, independently selected from H, C₁-C₆-alkyl, and C₁-C₆-alkyl-OH;

R^8 is selected from H and C₁-C₆-alkyl;

30 R^9 is selected from H and C₁-C₆-alkyl;

m is 0, 1 or 2;

n is 0;

p is 0; and

q is 1.

In another embodiment of the compound of any one of Formulas I, II, or III,

5 A is C=O;

R¹ is C₁-C₆-alkyl;

R² is, at each occurrence, independently selected from –OH, halo, C₁-C₆-alkyl, C₁-C₆-alkylene, C₀-C₆-alkyl-C₃-C₆-cycloalkyl, C₀-C₆-alkyl-C₂-C₆-heterocycloalkyl, C₀-C₆-alkyl-OR⁶, C₀-C₆-alkyl-N(R⁷)₂, C₀-C₆-alkyl-SR⁸, C₀-C₆-alkyl-S(O)R⁸, C₀-C₆-alkyl-S(O)₂R⁸, C₀-C₆-alkyl-C(O)OR⁹, and C₀-C₆-alkyl-C(O)N(R⁷)₂, wherein alkyl, cycloalkyl, and heterocycloalkyl are optionally substituted with 1, 2, or 3 groups, each independently selected from –OH and halo;

R⁴ is (CR^aR^b)_p-C₆-C₁₂-aryl, wherein aryl is optionally substituted with 1, 2, 3, or 4 groups, each independently selected from halo, –CN, and C₁-C₆-alkyl;

15 R⁵ is H;

R⁶ is selected from H, C₁-C₆-alkyl, and C₁-C₆-haloalkyl;

R⁷ is, at each occurrence, independently selected from H, and C₁-C₆-alkyl;

R⁸ is C₁-C₆-alkyl;

R⁹ is selected from H and C₁-C₆-alkyl;

20 m is 0, 1 or 2;

n is 0;

p is 0; and

q is 1.

In an embodiment of the compound of any one of Formulas I, II, or III,

25 A is C=O;

R¹ is C₁-C₆-alkyl;

R² is, at each occurrence, independently selected from –OH, halo, C₁-C₆-alkyl, C₁-C₆-alkylene, C₀-C₆-alkyl-C₃-C₆-cycloalkyl, C₀-C₆-alkyl-C₂-C₆-heterocycloalkyl, C₀-C₆-alkyl-OR⁶, C₀-C₆-alkyl-N(R⁷)₂, C₀-C₆-alkyl-SR⁸, C₀-C₆-alkyl-S(O)R⁸, C₀-C₆-alkyl-S(O)₂R⁸, C₀-C₆-alkyl-C(O)OR⁹, C₀-C₆-alkyl-OC(O)R⁹, C₀-C₆-alkyl-OC(O)OR⁹, C₀-C₆-alkyl-OC(O)N(R⁷)₂, and C₀-C₆-alkyl-C(O)N(R⁷)₂, wherein alkyl, cycloalkyl, and heterocycloalkyl are

optionally substituted with 1, 2, or 3 groups, each independently selected from –OH and halo;

R^4 is $(CR^aR^b)_p$ -C₆-C₁₂-aryl, wherein aryl is optionally substituted with 1, 2, 3, or 4 groups, each independently selected from halo, –CN, and C₁-C₆-alkyl;

R^5 is H;

5 R^6 is selected from H, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkenyl, and C₀-C₆-alkyl-C₃-C₆-cycloalkyl;

R^7 is, at each occurrence, independently selected from H, C₁-C₆-alkyl, and C₁-C₆-alkyl-OH;

R^8 is selected from H and C₁-C₆-alkyl;

10 R^9 is selected from H and C₁-C₆-alkyl;

m is 0, 1 or 2;

n is 0;

p is 0; and

q is 1.

15 In another embodiment of the compound of any one of Formulas I, II, or III,

A is C=O;

R^1 is C₁-C₆-alkyl;

R^2 is, at each occurrence, independently selected from –OH, halo, C₁-C₆-alkyl, C₁-C₆-alkylene, C₀-C₆-alkyl-C₃-C₆-cycloalkyl, C₀-C₆-alkyl-C₂-C₆-heterocycloalkyl,

20 C₀-C₆-alkyl-OR⁶, C₀-C₆-alkyl-N(R⁷)₂, C₀-C₆-alkyl-SR⁸, C₀-C₆-alkyl-S(O)R⁸, C₀-C₆-alkyl-S(O)₂R⁸, C₀-C₆-alkyl-C(O)OR⁹, and C₀-C₆-alkyl-C(O)N(R⁷)₂, wherein alkyl, cycloalkyl, and heterocycloalkyl are optionally substituted with 1, 2, or 3 groups, each independently selected from –OH and halo;

R^4 is $(CR^aR^b)_p$ -C₆-C₁₂-aryl, wherein aryl is optionally substituted with 1, 2, 3, or 4 groups, each independently selected from halo, –CN, and C₁-C₆-alkyl;

25 R^5 is H;

R^6 is selected from H, C₁-C₆-alkyl, and C₁-C₆-haloalkyl;

R^7 is, at each occurrence, independently selected from H, and C₁-C₆-alkyl;

R^8 is C₁-C₆-alkyl;

30 R^9 is selected from H and C₁-C₆-alkyl;

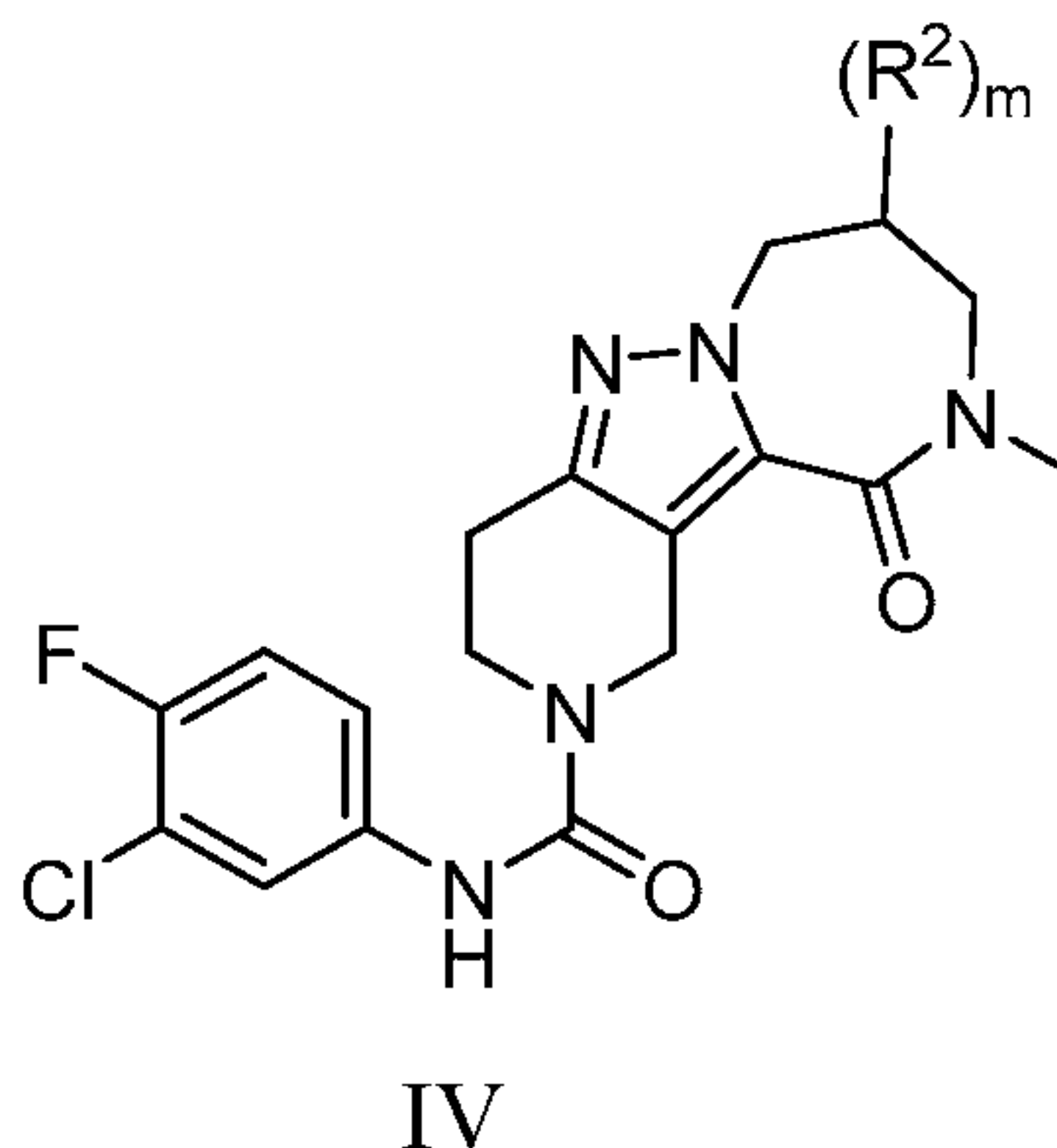
m is 0, 1 or 2;

n is 0;

p is 0; and

q is 1.

In another embodiment, the compound of Formula III has the structure of Formula IV



wherein

m is 1 or 2; and

R^2 is, at each occurrence, independently selected from $-\text{CH}_2\text{N}(\text{H})(\text{C}(\text{O})-\text{CH}_3)$, $-\text{CH}_2\text{N}(\text{H})\text{CH}_2\text{CHF}_2$, $-\text{CH}_2\text{N}(\text{H})\text{CH}_2\text{CF}_3$, and $-\text{CH}(\text{OH})\text{CH}=\text{CH}_2$; or two R^2 groups together form a spiro-cyclobutyl, which is substituted with $-\text{OH}$. In another embodiment, R^2 is, at each occurrence, independently selected from $=\text{CH}_2$, $-\text{CH}_2\text{OH}$, $-\text{OH}$, $-\text{F}$, $-\text{CH}_3$, $-\text{CHF}_2$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{OCH}_2\text{CHF}_2$, $-\text{NH}_2$, $-\text{N}(\text{CH}_3)_2$, morpholinyl, azetidiny, pyrrolidinyl, $-\text{SCH}_3$, $-\text{S}(\text{O})\text{CH}_3$, $-\text{S}(\text{O})_2\text{CH}_3$, $-\text{CH}_2\text{C}(\text{O})\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OCH}_3$, $-\text{C}(\text{O})\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{NHCH}_3$, $-\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{OH})(\text{CH}_3)_2$, $-\text{CH}(\text{OH})\text{CH}_3$, $-\text{CH}(\text{OH})\text{CH}_2\text{CH}_3$, and $-\text{CH}(\text{OH})$ -cyclopropyl, wherein morpholinyl, azetidiny, and pyrrolidinyl are optionally substituted with 1 or 2 groups, each independently selected from $-\text{OH}$ and halo.

In another embodiment of Formula IV,

m is 1 or 2; and

R^2 is, at each occurrence, independently selected from $=\text{CH}_2$, $-\text{CH}_2\text{OH}$, $-\text{OH}$, $-\text{F}$, $-\text{CH}_3$, $-\text{CHF}_2$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{OCH}_2\text{CHF}_2$, $-\text{NH}_2$, $-\text{N}(\text{CH}_3)_2$, morpholinyl, azetidiny, pyrrolidinyl, $-\text{SCH}_3$, $-\text{S}(\text{O})\text{CH}_3$, $-\text{S}(\text{O})_2\text{CH}_3$, $-\text{CH}_2\text{C}(\text{O})\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OCH}_3$, $-\text{C}(\text{O})\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{NHCH}_3$, $-\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{OH})(\text{CH}_3)_2$, $-\text{CH}(\text{OH})\text{CH}_3$, $-\text{CH}(\text{OH})\text{CH}_2\text{CH}_3$, and $-\text{CH}(\text{OH})$ -cyclopropyl, wherein morpholinyl, azetidiny, and pyrrolidinyl are optionally substituted with 1 or 2 groups, each independently selected from $-\text{OH}$ and halo.

Provided herein are compounds according to the following embodiments:

In one embodiment of Formula I, A is C=O; R¹ is C₁-C₆-alkyl; R⁴ is (CR^aR^b)_p-C₆-C₁₂-aryl substituted with at least one halo; R⁵ is H; n is 0; p is 0; m is 1 or 2; and each R² is independently selected from -OH, halo, C₁-C₆-alkyl, C₁-C₆-alkylene, C₀-C₆-alkyl-C₃-C₆-cycloalkyl, C₀-C₆-alkyl-C₂-C₆-heterocycloalkyl, C₀-C₆-alkyl-OR⁶, C₀-C₆-alkyl-N(R⁷)₂, C₀-C₆-alkyl-SR⁸, C₀-C₆-alkyl-S(O)R⁸, C₀-C₆-alkyl-S(O)₂R⁸, C₀-C₆-alkyl-C(O)OR⁹, C₀-C₆-alkyl-OC(O)R⁹, C₀-C₆-alkyl-OC(O)OR⁹, C₀-C₆-alkyl-OC(O)N(R⁷)₂, or C₀-C₆-alkyl-C(O)N(R⁷)₂. In such an embodiment, if R² is alkyl, alkylene, cycloalkyl or heterocycloalkyl, R² may be substituted with -OH or halo.

In an embodiment of Formula III, R¹ is C₁-C₆-alkyl, R² is -CH₂N(H)(C(O)CH₃), R⁴ is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R⁵ is H, m is 1, and n is 0.

In an embodiment of Formula III, R¹ is C₁-C₆-alkyl, R² is -CH₂N(H)(CH₂CHF₂), R⁴ is phenyl substituted with 1-2 groups independently selected from fluorine and CN, R⁵ is H, m is 1, and n is 0.

In an embodiment of Formula III, R¹ is C₁-C₆-alkyl, R² is -CH₂N(H)(CH₂CHF₂), R⁴ is phenyl substituted with 1-2 groups independently selected from fluorine and CF₃, R⁵ is H, m is 1, and n is 0.

In an embodiment of Formula III, R¹ is C₁-C₆-alkyl, R² is -CH₂N(H)(CH₂CF₃), R⁴ is phenyl substituted with 1-2 groups independently selected from fluorine and CN, R⁵ is H, m is 1, and n is 0.

In an embodiment of Formula III, R¹ is C₁-C₆-alkyl, R² is -CH₂N(H)(CH₂CF₃), R⁴ is phenyl substituted with 1-2 groups independently selected from fluorine and CF₃, R⁵ is H, m is 1, and n is 0.

In an embodiment of Formula III, R¹ is C₁-C₆-alkyl, R² is -CH(OH)CH=CH₂, R³ is C₁-C₆-alkyl, R⁴ is phenyl substituted with 1-2 groups independently selected from fluorine and CF₃, R⁵ is H, m is 1, and n is 1. In a more particular embodiment, R³ is (*R*)-methyl.

In an embodiment of Formula III, R¹ is C₁-C₆-alkyl, R² is -CH(OH)CH=CH₂, R³ is C₁-C₆-alkyl, R⁴ is phenyl substituted with 1-2 groups independently selected from fluorine and CN, R⁵ is H, m is 1, and n is 1. In a more particular embodiment, R³ is (*R*)-methyl.

In an embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-\text{CH}(\text{OH})\text{CH}=\text{CH}_2$, R^3 is C_1 - C_6 -alkyl, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and bromine, R^5 is H, m is 1, and n is 1. In a more particular embodiment, R^3 is (*R*)-methyl.

5 In an embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-\text{CH}_2\text{N}(\text{H})(\text{CH}_2\text{CHF}_2)$, R^4 is phenyl substituted with 1-3 groups independently selected from fluorine and CN, R^5 is H, m is 1, and n is 0.

In an embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-\text{CH}_2\text{N}(\text{H})(\text{CH}_2\text{CHF}_2)$, R^4 is phenyl substituted with 1-3 groups independently selected from fluorine and CF_3 , R^5 is H, m is 1, and n is 0.

10 In an embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-\text{CH}_2\text{N}(\text{H})(\text{CH}_2\text{CHF}_2)$, R^4 is phenyl substituted with 1-3 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

In an embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-\text{CH}_2\text{N}(\text{H})(\text{CH}_2\text{CHF}_2)$, R^4 is phenyl substituted with 1-3 halogen atoms independently selected from fluorine and bromine, R^5 is H, m is 1, and n is 0.

In an embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-\text{CH}_2\text{N}(\text{H})(\text{CH}_2\text{CHF}_2)$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and bromine, R^5 is H, m is 1, and n is 0.

20 In an embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, two R^2 groups together form a spiro-cyclobutyl, which is substituted with $-\text{OH}$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 2, and n is 0.

In one embodiment of Formula I, A is $\text{C}=\text{O}$; R^1 is C_1 - C_6 -alkyl; R^4 is $(\text{CR}^a\text{R}^b)_p\text{-C}_6\text{-C}_{12}\text{-aryl}$ substituted with at least one halo; R^5 is H; n is 0; p is 0; m is 1 or 2; and each R^2 is independently selected from $-\text{OH}$, halo, C_1 - C_6 -alkyl, C_1 - C_6 -alkylene, C_0 - C_6 -alkyl- C_3 - C_6 -cycloalkyl, C_0 - C_6 -alkyl- C_2 - C_6 -heterocycloalkyl, C_0 - C_6 -alkyl- OR^6 , C_0 - C_6 -alkyl- $\text{N}(\text{R}^7)_2$, C_0 - C_6 -alkyl- SR^8 , C_0 - C_6 -alkyl- $\text{S}(\text{O})\text{R}^8$, C_0 - C_6 -alkyl- $\text{S}(\text{O})_2\text{R}^8$, C_0 - C_6 -alkyl- $\text{C}(\text{O})\text{OR}^9$, C_0 - C_6 -alkyl- $\text{OC}(\text{O})\text{R}^9$, C_0 - C_6 -alkyl- $\text{OC}(\text{O})\text{OR}^9$, C_0 - C_6 -alkyl- $\text{OC}(\text{O})\text{N}(\text{R}^7)_2$, or C_0 - C_6 -alkyl- $\text{C}(\text{O})\text{N}(\text{R}^7)_2$. In such an embodiment, if R^2 is alkyl, cycloalkyl or heterocycloalkyl, R^2 may be substituted with $-\text{OH}$ or halo.

30 In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-\text{CH}(\text{OH})\text{CH}_2$ -cyclopropyl, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

In another embodiment of Formula III, R^1 is C_1 - C_6 -haloalkyl, R^2 is $-CH_2OH$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

5 In a further embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-N(H)(C_1-C_6-alkyl)$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

In yet another embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, one instance of R^2 is C_1 - C_6 -alkyl and the other instance of R^2 is $-C(O)OCH_2CH_3$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 2, and n is 0.

10 In yet another embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, one instance of R^2 is C_1 - C_6 -alkyl and the other instance of R^2 is $-CH_2OH$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 2, and n is 0.

15 In a further embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is C_2 - C_6 -heterocycloalkyl which is substituted with two fluorine groups, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

In a another embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is C_2 - C_6 -heterocycloalkyl, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

20 In a another embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH_2-C_2-C_6$ -heterocycloalkyl, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

In a another embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH_2-C_2-C_6$ -heterocycloalkyl which is substituted with two fluorine groups, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

25 In a further embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH_2N(C_1-C_6-alkyl)(C_1-C_6-alkyl)$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

30 In another embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH_2NH_2$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

In yet another embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, one instance of R^2 is $-CH_2CHF_2$ and the other instance of R^2 is $-CH_2OH$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 2, and n is 0.

5 In another embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH(OH)CH_2CH_2CH_3$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

In another embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH(OH)CH_2CH_2F$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

10 In another embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH(OH)CH_2CHF_2$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

15 In another embodiment of Formula II, R^1 is C_1 - C_6 -alkyl, R^2 is $-C(O)OCH_3$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

In a further embodiment of Formula II, R^1 is C_1 - C_6 -alkyl, R^2 is $-C(O)N(C_1-C_6-alkyl)(C_1-C_6-alkyl)$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

20 In yet another embodiment of Formula II, R^1 is C_1 - C_6 -alkyl, R^2 is CH_2OH , R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

In another embodiment of Formula II, R^1 is C_1 - C_6 -alkyl, one instance of R^2 is C_1 - C_6 -alkyl and the other instance of R^2 is $-CH_2OH$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 2, and n is 0.

25 In another embodiment of Formula II, R^1 is C_1 - C_6 -alkyl, one instance of R^2 is C_1 - C_6 -alkyl and the other instance of R^2 is $-C(O)OH$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 2, and n is 0.

30 In a further embodiment of Formula II, R^1 is C_1 - C_6 -alkyl, R^2 is $-C(O)OH$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

In another particular embodiment of Formula II, R^1 is C_1 - C_6 -alkyl; R^2 is C_1 - C_6 -alkyl or C_0 - C_6 -alkyl- OR^6 , wherein alkyl is substituted with halo, and R^6 is H or C_1 - C_6 -haloalkyl; R^3 is C_1 - C_6 -alkyl; R^4 is phenyl substituted with 1 or 2 groups, each independently selected from halo and $-CN$; R^5 is H; m is 1; and n is 1.

5 In another particular embodiment of Formula II, R^1 is methyl; R^2 is $-CH_2F$ or $CH_2-O-CH_2CHF_2$; R^3 is methyl; R^4 is phenyl substituted with 1 or 2 groups, each independently selected from F and $-CN$; R^5 is H; m is 1; and n is 1.

10 In another particular embodiment of Formula II, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH_2F$, R^4 is phenyl or pyridyl, wherein the phenyl or pyridyl is substituted with 1-3 groups independently selected from halo, $-CN$, $-SF_5$, C_1 - C_6 -alkyl, and C_1 - C_6 -haloalkyl, R^5 is H, and n is 0.

In another particular embodiment of Formula II, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH_2OCH_2CHF_2$, R^4 is phenyl or pyridyl, wherein the phenyl or pyridyl is substituted with 1-3 groups independently selected from halo, $-CN$, $-SF_5$, C_1 - C_6 -alkyl, and C_1 - C_6 -haloalkyl, R^5 is H, n is 1, and R^3 is C_1 - C_6 -alkyl.

15 In a another embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH_2-C_2-C_6$ -heterocycloalkyl which is substituted with two fluorine groups, R^4 is phenyl substituted with 1-2 groups independently selected from fluorine and CF_3 , R^5 is H, m is 1, and n is 0.

20 In another embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH_2NH_2$, R^4 is phenyl substituted with 1-2 groups independently selected from fluorine and CF_3 , R^5 is H, m is 1, and n is 0.

In a further embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-N(H)(C_1-C_6-alkyl)$, R^4 is phenyl substituted with 1-2 groups independently selected from fluorine and CF_3 , R^5 is H, m is 1, and n is 0.

25 In a further embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH(OH)CH_2CH_3$, R^4 is phenyl substituted with 1-2 groups independently selected from fluorine and CF_3 , R^5 is H, m is 1, and n is 0.

In a another embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH_2-C_2-C_6$ -heterocycloalkyl which is substituted with two fluorine groups, R^4 is phenyl substituted with 1-2 groups independently selected from fluorine and CN, R^5 is H, m is 1, and n is 0.

In another embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH_2NH_2$, R^4 is phenyl substituted with 1-2 groups independently selected from fluorine and CN, R^5 is H, m is 1, and n is 0.

5 In a further embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH(OH)CH_2CH_3$, R^4 is phenyl substituted with 1-2 groups independently selected from fluorine and CN, R^5 is H, m is 1, and n is 0.

In a further embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH(OH)CH_2CHF_2$, R^4 is phenyl substituted with 1-2 groups independently selected from fluorine and CN, R^5 is H, m is 1, and n is 0.

10 In a further embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH(OH)CH_2CH_3$, R^4 is phenyl substituted with 1-3 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

15 In a further embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH(OH)CH_2CH_3$, R^4 is phenyl substituted with 1-3 groups independently selected from fluorine and CN, R^5 is H, m is 1, and n is 0.

In another embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH(OH)CH_2CH_3$, R^4 is phenyl substituted with 1-3 halogen atoms independently selected from fluorine and bromine, R^5 is H, m is 1, and n is 0.

20 In another embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH(OH)CH_2CH_3$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and bromine, R^5 is H, m is 1, and n is 0.

In another embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH(OH)CH_2CH_3$, R^4 is phenyl substituted with 1-3 groups independently selected from fluorine and CF_3 , R^5 is H, m is 1, and n is 0.

25 In another embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH(OH)CH_2CH_3$, R^4 is phenyl substituted with 1-3 fluorine groups, R^5 is H, m is 1, and n is 0.

In another embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH(OH)CH_2CH_3$, R^4 is phenyl substituted with 1-4 fluorine groups, R^5 is H, m is 1, and n is 0.

30 In an embodiment of Formula III, R^1 is C_1 - C_6 -alkyl-OH, R^3 is C_1 - C_6 -alkyl, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 0, and n is 1. In a more particular embodiment, R^3 is (*R*)-methyl.

In another embodiment of Formula III, R^1 is C_1 - C_6 -haloalkyl, R^3 is C_1 - C_6 -alkyl, R^4 is phenyl substituted with 1-3 halogen atoms independently selected from fluorine, bromine, and chlorine, R^5 is H, m is 0, and n is 1. In a more particular embodiment, R^3 is (*R*)-methyl.

5 In an embodiment of Formula III, R^1 is C_1 - C_6 -haloalkyl, R^3 is C_1 - C_6 -alkyl, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 0, and n is 1. In a more particular embodiment, R^3 is (*R*)-methyl.

In an embodiment of Formula III, R^1 is C_1 - C_6 -haloalkyl, R^3 is C_1 - C_6 -alkyl, R^4 is phenyl substituted with 1-2 groups independently selected from fluorine and CF_3 , R^5 is H, m is 0, and n is 1. In a more particular embodiment, R^3 is (*R*)-methyl.

10 In an embodiment of Formula III, R^1 is C_1 - C_6 -haloalkyl, R^3 is C_1 - C_6 -alkyl, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and bromine, R^5 is H, m is 0, and n is 1. In a more particular embodiment, R^3 is (*R*)-methyl.

In an embodiment of Formula III, R^1 is C_1 - C_6 -haloalkyl, R^3 is C_1 - C_6 -alkyl, R^4 is pyridine substituted with 1-2 halogen atoms independently selected from fluorine and bromine, R^5 is H, m is 0, and n is 1. In a more particular embodiment, R^3 is (*R*)-methyl.

In an embodiment of Formula III, R^1 is C_1 - C_6 -haloalkyl, R^3 is C_1 - C_6 -alkyl, R^4 is phenyl substituted with 1-2 groups independently selected from fluorine and CN, R^5 is H, m is 0, and n is 1. In a more particular embodiment, R^3 is (*R*)-methyl.

20 In an embodiment of Formula III, R^1 is C_1 - C_6 -haloalkyl, R^3 is C_1 - C_6 -alkyl, R^4 is phenyl substituted with 1-2 groups independently selected from fluorine and Me, R^5 is H, m is 0, and n is 1. In a more particular embodiment, R^3 is (*R*)-methyl.

In an embodiment of Formula III, R^1 is C_1 - C_6 -haloalkyl, R^3 is C_1 - C_6 -alkyl, R^4 is phenyl substituted with 1-3 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 0, and n is 1. In a more particular embodiment, R^3 is (*R*)-methyl.

25 In an embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, one instance of R^2 is methyl and the other instance of R^2 is fluorine, R^3 is C_1 - C_6 -alkyl, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 2, and n is 1. In a more particular embodiment, R^3 is (*R*)-methyl.

30 In an embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is methyl, R^3 is C_1 - C_6 -alkyl, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 1. In a more particular embodiment, R^3 is (*R*)-methyl.

In an embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is CH_2OH , R^3 is C_1 - C_6 -alkyl, R^4 is phenyl substituted with 1-2 groups independently selected from fluorine and CF_3 , R^5 is H, m is 1, and n is 1. In a more particular embodiment, R^3 is (*R*)-methyl.

5 In an embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is CH_2OH , R^3 is C_1 - C_6 -alkyl, R^4 is phenyl substituted with 1-3 groups independently selected from fluorine and CF_3 , R^5 is H, m is 1, and n is 1. In a more particular embodiment, R^3 is (*R*)-methyl.

In an embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is CH_2OH , R^3 is C_1 - C_6 -alkyl, R^4 is phenyl substituted with 1-3 halogen atoms independently selected from fluorine and bromine, R^5 is H, m is 1, and n is 1. In a more particular embodiment, R^3 is (*R*)-methyl.

10 In an embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is CH_2OH , R^3 is C_1 - C_6 -alkyl, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and bromine, R^5 is H, m is 1, and n is 1. In a more particular embodiment, R^3 is (*R*)-methyl.

15 In an embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is CH_2OH , R^3 is C_1 - C_6 -alkyl, R^4 is phenyl substituted with 1-2 groups independently selected from fluorine and CN, R^5 is H, m is 1, and n is 1. In a more particular embodiment, R^3 is (*R*)-methyl.

In an embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is CH_2OH , R^3 is C_1 - C_6 -alkyl, R^4 is phenyl substituted with 1-3 groups independently selected from fluorine and CN, R^5 is H, m is 1, and n is 1. In a more particular embodiment, R^3 is (*R*)-methyl.

20 In an embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is CH_2OH , R^3 is C_1 - C_6 -alkyl, R^4 is phenyl substituted with 1-3 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 1. In a more particular embodiment, R^3 is (*R*)-methyl.

In an embodiment of Formula III, R^1 is C_1 - C_6 -haloalkyl, R^2 is CH_2OH , R^3 is C_1 - C_6 -alkyl, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 1. In a more particular embodiment, R^3 is (*R*)-methyl.

25 In an embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $CH(OH)CH_2CH_3$, R^3 is C_1 - C_6 -alkyl, R^4 is phenyl substituted with 1-2 groups independently selected from fluorine and CF_3 , R^5 is H, m is 1, and n is 1. In a more particular embodiment, R^3 is (*R*)-methyl.

30 In an embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $CH(OH)CH_2CH_3$, R^3 is C_1 - C_6 -alkyl, R^4 is phenyl substituted with 1-2 groups independently selected from fluorine and CN, R^5 is H, m is 1, and n is 1. In a more particular embodiment, R^3 is (*R*)-methyl.

In an embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $CH(OH)CH_2CH_3$, R^3 is C_1 - C_6 -alkyl, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and bromine, R^5 is H, m is 1, and n is 1. In a more particular embodiment, R^3 is (*R*)-methyl

5 In one embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

In another embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is fluorine, R^5 is H, m is 1, and n is 0.

10 In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $=CH_2$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

In another particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH_2OH$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

15 In another particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, one instance of R^2 is $-OH$ and the other instance of R^2 is $-CH_2OH$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 2, and n is 0.

In another particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-OH$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

20 In another particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, both instances of R^2 are fluorine, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 2, and n is 0.

25 In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is fluorine, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

In another particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is fluorine, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and bromine, R^5 is H, m is 1, and n is 0.

30 In another particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is fluorine, R^4 is pyridyl substituted with 1-2 halogen atoms independently selected from fluorine and bromine, R^5 is H, m is 1, and n is 0.

In another particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is fluorine, R^4 is phenyl substituted with 1-2 substituents independently selected from fluorine and $-CN$, R^5 is H, m is 1, and n is 0.

5 In another particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is fluorine, R^4 is phenyl substituted with 1-2 substituents independently selected from fluorine and $-CH_3$, R^5 is H, m is 1, and n is 0.

In another particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is fluorine, R^4 is phenyl substituted with 1-2 substituents independently selected from fluorine and $-CF_3$, R^5 is H, m is 1, and n is 0.

10 In another particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is fluorine, R^4 is pyridyl substituted with 1-3 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

In another particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is fluorine, R^4 is pyridyl substituted with 1-3 halogen atoms independently selected from fluorine and bromine, R^5 is H, m is 1, and n is 0.

15 In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH_3$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

20 In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 0, and n is 0.

In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-OCH_3$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

25 In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-OCH_2CH_3$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

30 In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-OCH_2CHF_2$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-NH_2$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

5 In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-N(CH_3)_2$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is morpholin-1-yl, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

10 In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is 3,3-difluoroazetidin-1-yl, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is azetidin-1-yl, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is pyrrolidin-1-yl, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

20 In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-SCH_3$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-S(O)CH_3$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

25 In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-S(O)_2CH_3$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH_2C(O)OCH_3$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH_2CH_2OH$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

5 In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-C(O)OCH_3$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-C(OH)(CH_3)_2$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

10 In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-C(O)NHCH_3$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-C(O)N(CH_3)_2$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH(OH)$ -cyclopropyl, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

20 In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CHF_2$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

In a particular embodiment of Formula III, R^1 is C_1 - C_6 -alkyl, R^2 is $-CHF_2$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

25 In another embodiment of Formula III, R^1 is C_1 - C_6 -haloalkyl, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 0, and n is 0.

In an embodiment of Formula I, R^1 is C_1 - C_6 -alkyl, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 0, n is 0, and q is 0.

30 0.

In an embodiment of Formula II, R^1 is C₁-C₆-alkyl, R^2 is $-CH_3$, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 1, and n is 0.

5 In another particular embodiment of Formula III, R^1 is C₁-C₆-alkyl; R^2 is C₁-C₆-alkyl or C₀-C₆-alkyl-OR⁶, wherein alkyl is substituted with halo, and R^6 is H or C₁-C₆-haloalkyl; R^3 is C₁-C₆-alkyl; R^4 is phenyl substituted with 1 or 2 groups, each independently selected from halo and $-CN$; R^5 is H; m is 1; and n is 1.

10 In another particular embodiment of Formula III, R^1 is methyl; R^2 is $-CH_2F$ or $CH_2-O-CH_2CHF_2$; R^3 is methyl; R^4 is phenyl substituted with 1 or 2 groups, each independently selected from F and $-CN$; R^5 is H; m is 1; and n is 1.

In another particular embodiment of Formula III, R^1 is C₁-C₆-alkyl, R^2 is $-CH_2F$, R^4 is phenyl or pyridyl, wherein the phenyl or pyridyl is substituted with 1-3 groups independently selected from halo, $-CN$, $-SF_5$, C₁-C₆-alkyl, and C₁-C₆-haloalkyl, R^5 is H, and n is 0.

15 In another particular embodiment of Formula III, R^1 is C₁-C₆-alkyl, R^2 is $-CH_2OCH_2CHF_2$, R^4 is phenyl or pyridyl, wherein the phenyl or pyridyl is substituted with 1-3 groups independently selected from halo, $-CN$, $-SF_5$, C₁-C₆-alkyl, and C₁-C₆-haloalkyl, R^5 is H, n is 1, and R^3 is C₁-C₆-alkyl.

In an embodiment of Formula V, R^1 is C₁-C₆-alkyl, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 0, and n is 0.

20 In an embodiment of Formula V, R^1 is C₁-C₆-alkyl, R^4 is phenyl substituted with 1-2 halogen atoms independently selected from fluorine and chlorine, R^5 is H, m is 0, n is 0, and --- is a double bond.

25 In another particular embodiment of Formula V, R^1 is C₁-C₆-alkyl; R^2 is C₁-C₆-alkyl or C₀-C₆-alkyl-OR⁶, wherein alkyl is substituted with halo, and R^6 is H or C₁-C₆-haloalkyl; R^3 is C₁-C₆-alkyl; R^4 is phenyl substituted with 1 or 2 groups, each independently selected from halo and $-CN$; R^5 is H; m is 1; and n is 1.

In another particular embodiment of Formula V, R^1 is methyl; R^2 is $-CH_2F$ or $CH_2-O-CH_2CHF_2$; R^3 is methyl; R^4 is phenyl substituted with 1 or 2 groups, each independently selected from F and $-CN$; R^5 is H; m is 1; and n is 1.

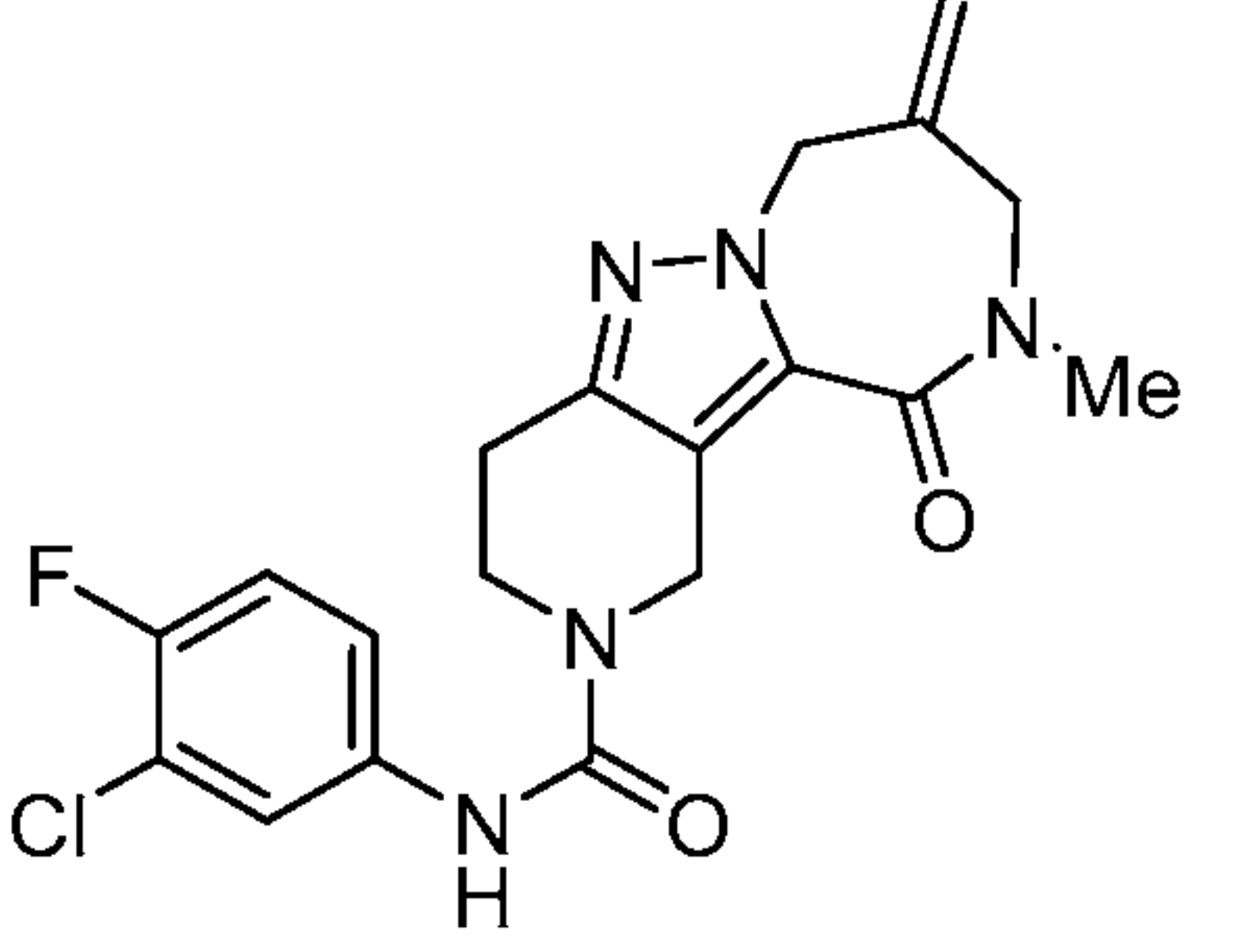
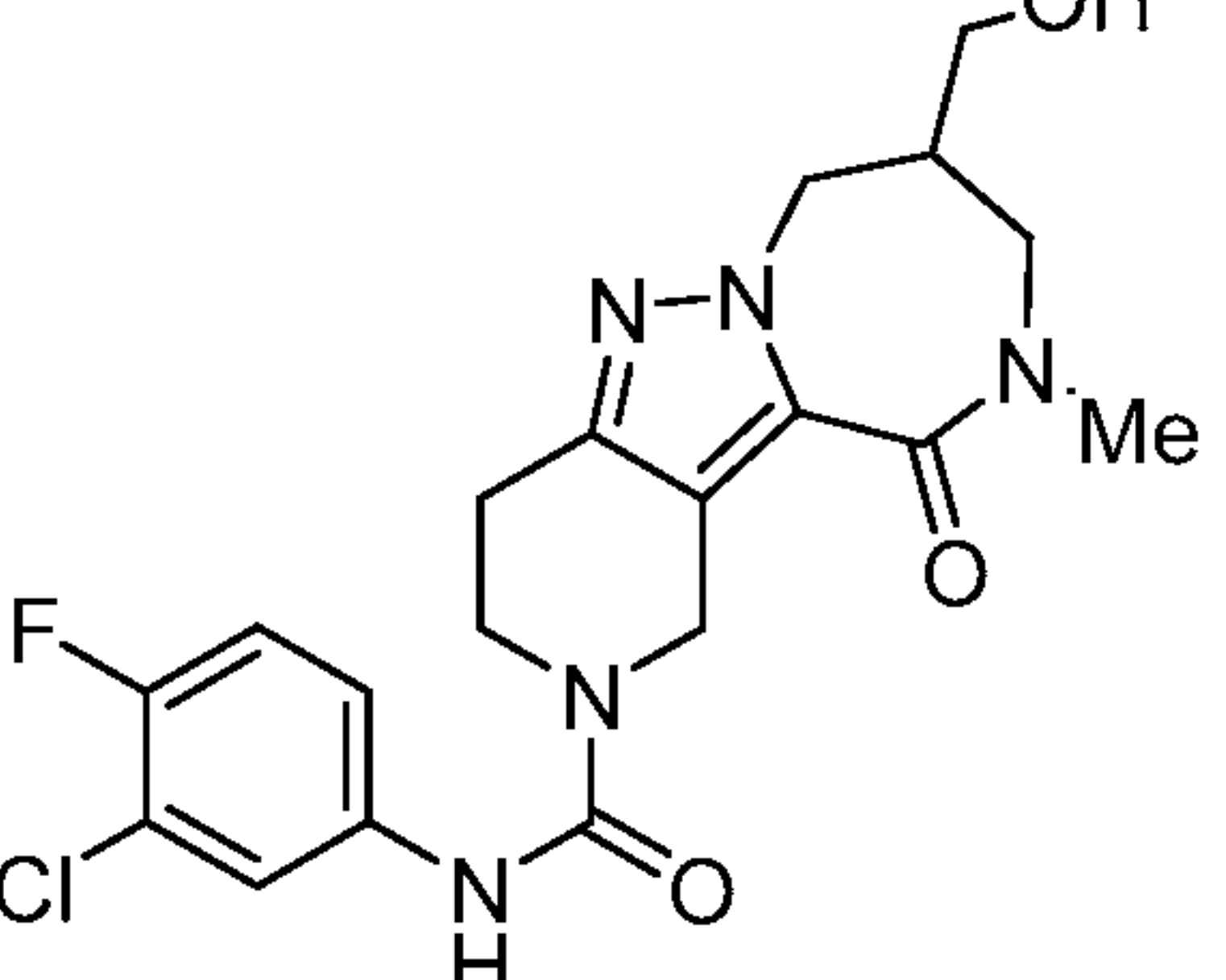
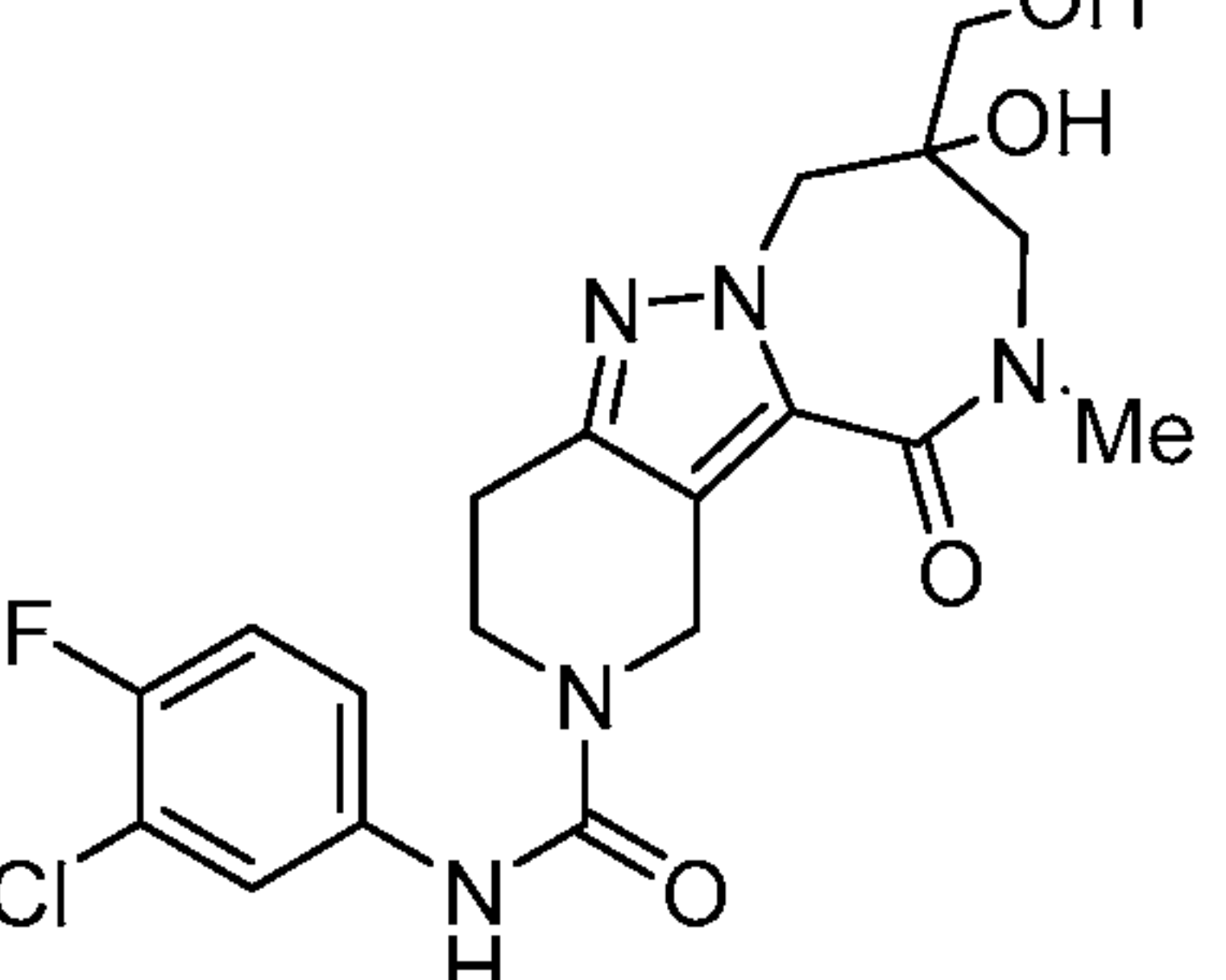
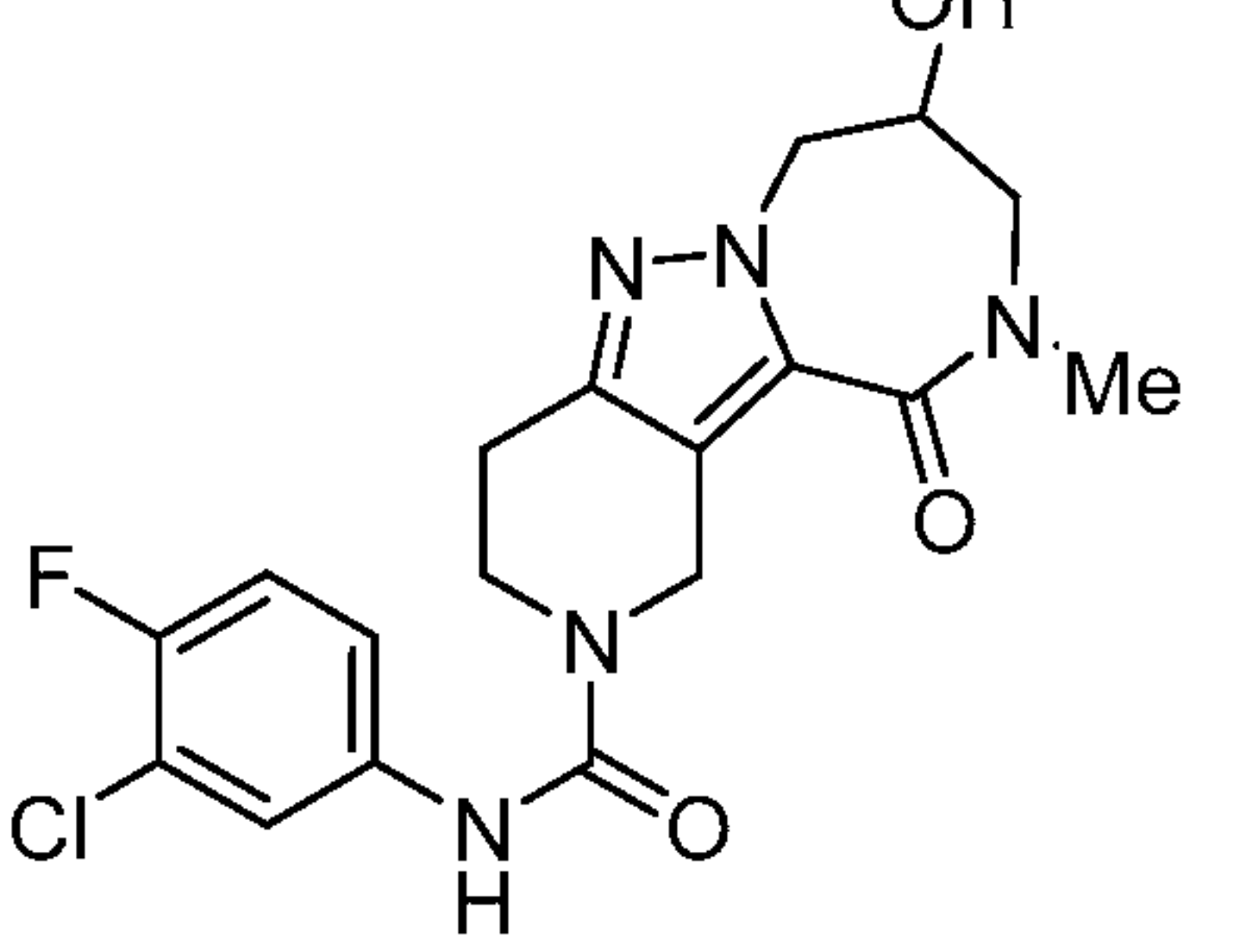
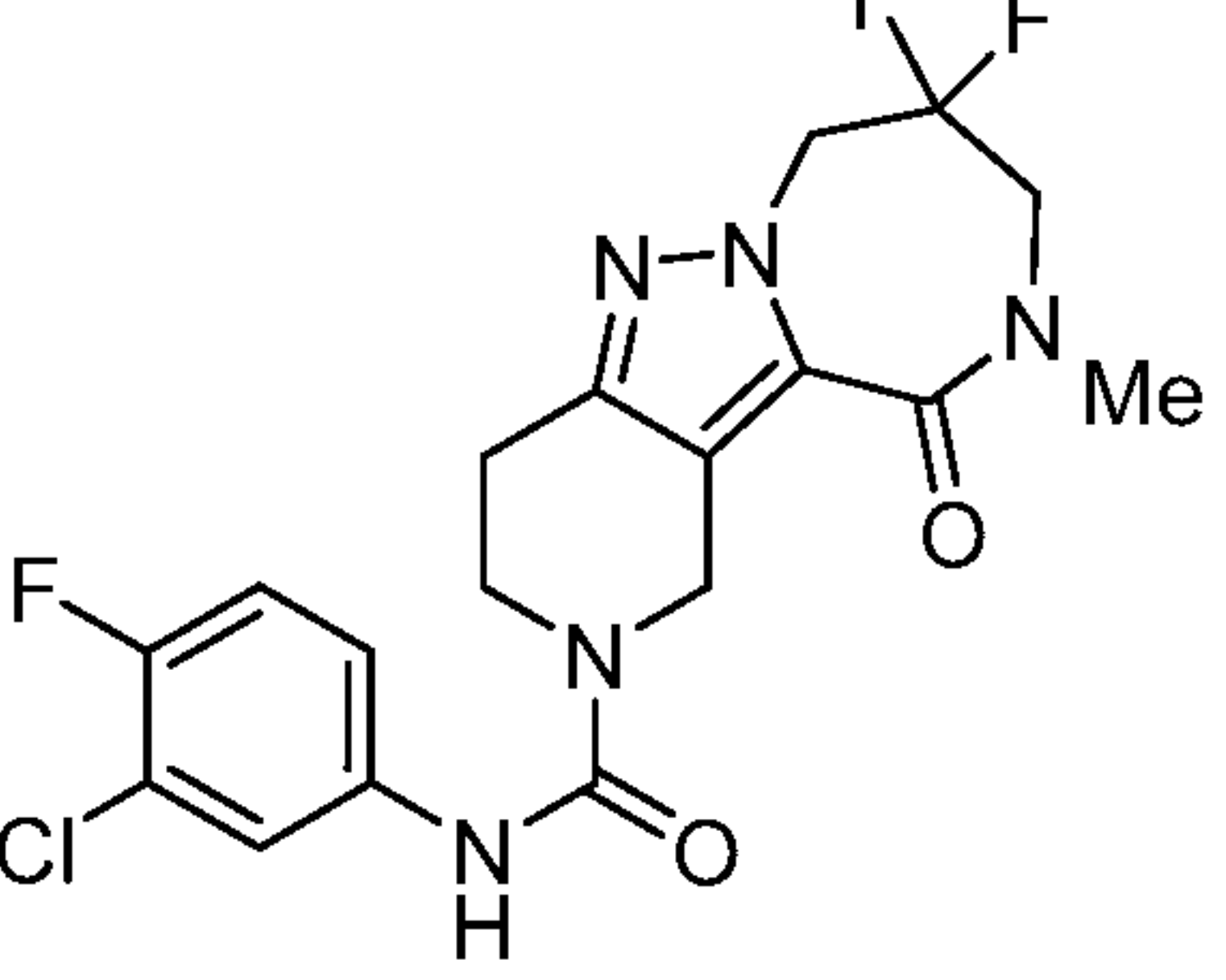
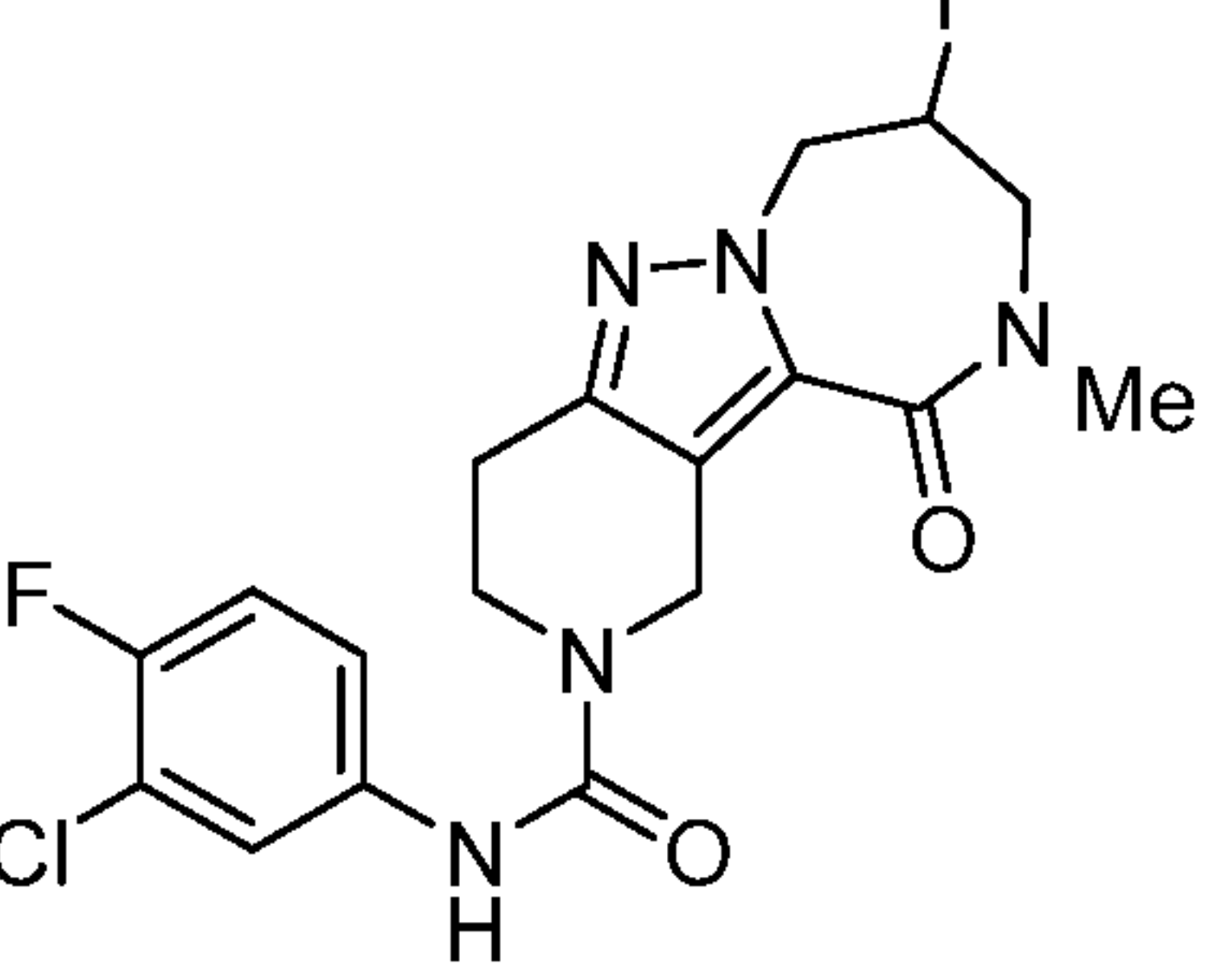
In another particular embodiment of Formula V, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH_2F$, R^4 is phenyl or pyridyl, wherein the phenyl or pyridyl is substituted with 1-3 groups independently selected from halo, $-CN$, $-SF_5$, C_1 - C_6 -alkyl, and C_1 - C_6 -haloalkyl, R^5 is H, and n is 0.

- 5 In another particular embodiment of Formula V, R^1 is C_1 - C_6 -alkyl, R^2 is $-CH_2OCH_2CHF_2$, R^4 is phenyl or pyridyl, wherein the phenyl or pyridyl is substituted with 1-3 groups independently selected from halo, $-CN$, $-SF_5$, C_1 - C_6 -alkyl, and C_1 - C_6 -haloalkyl, R^5 is H, n is 1, and R^3 is C_1 - C_6 -alkyl.

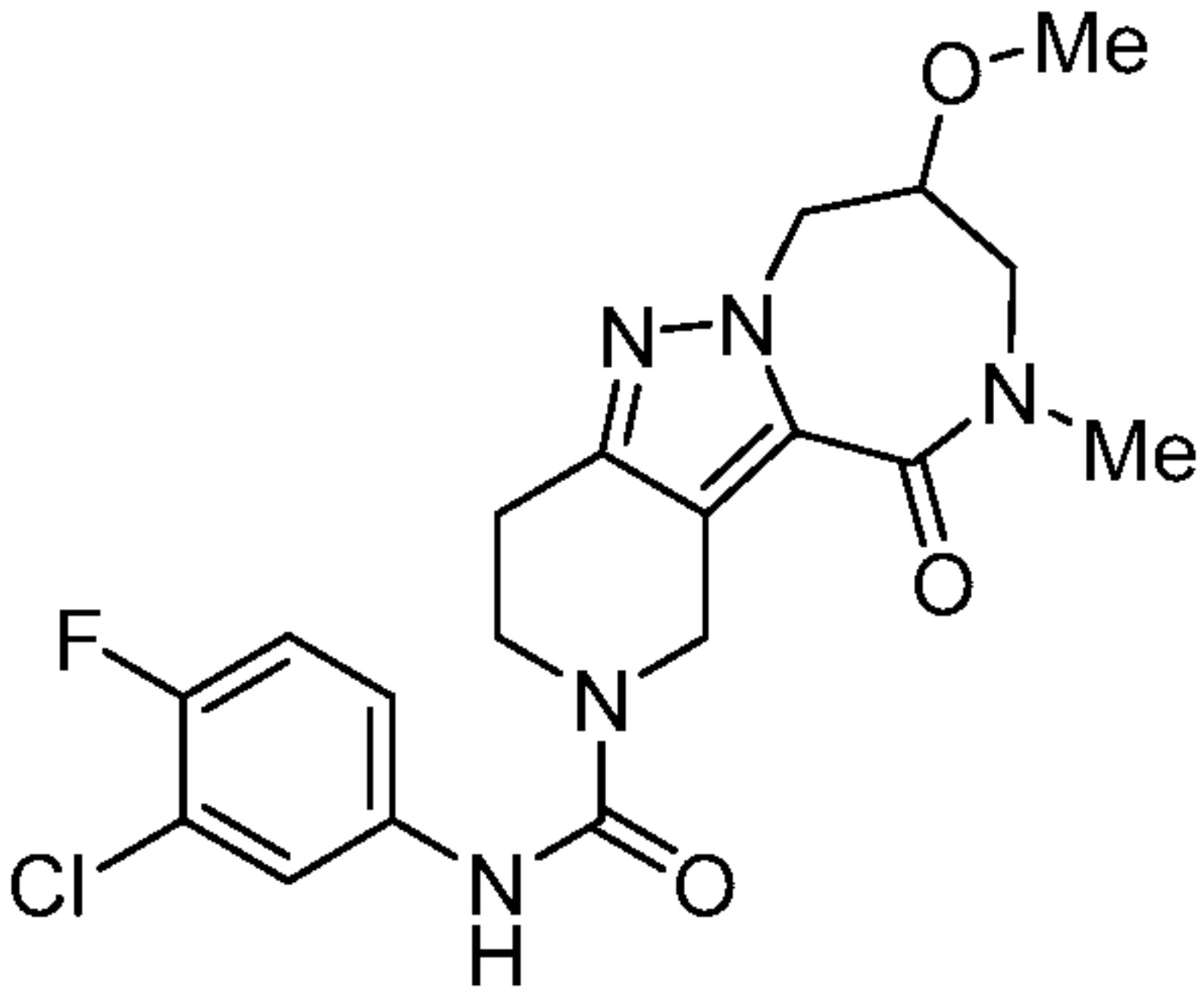
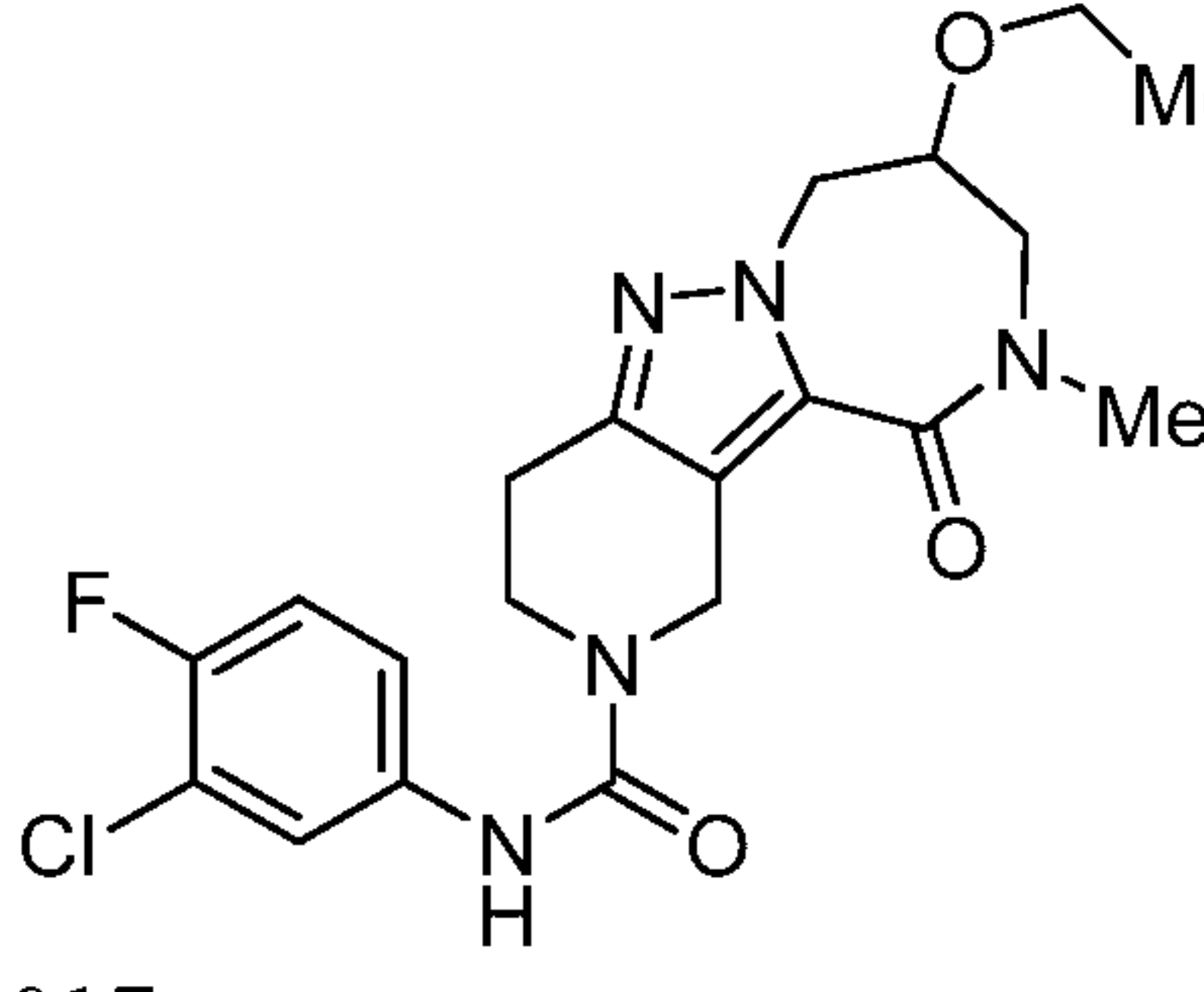
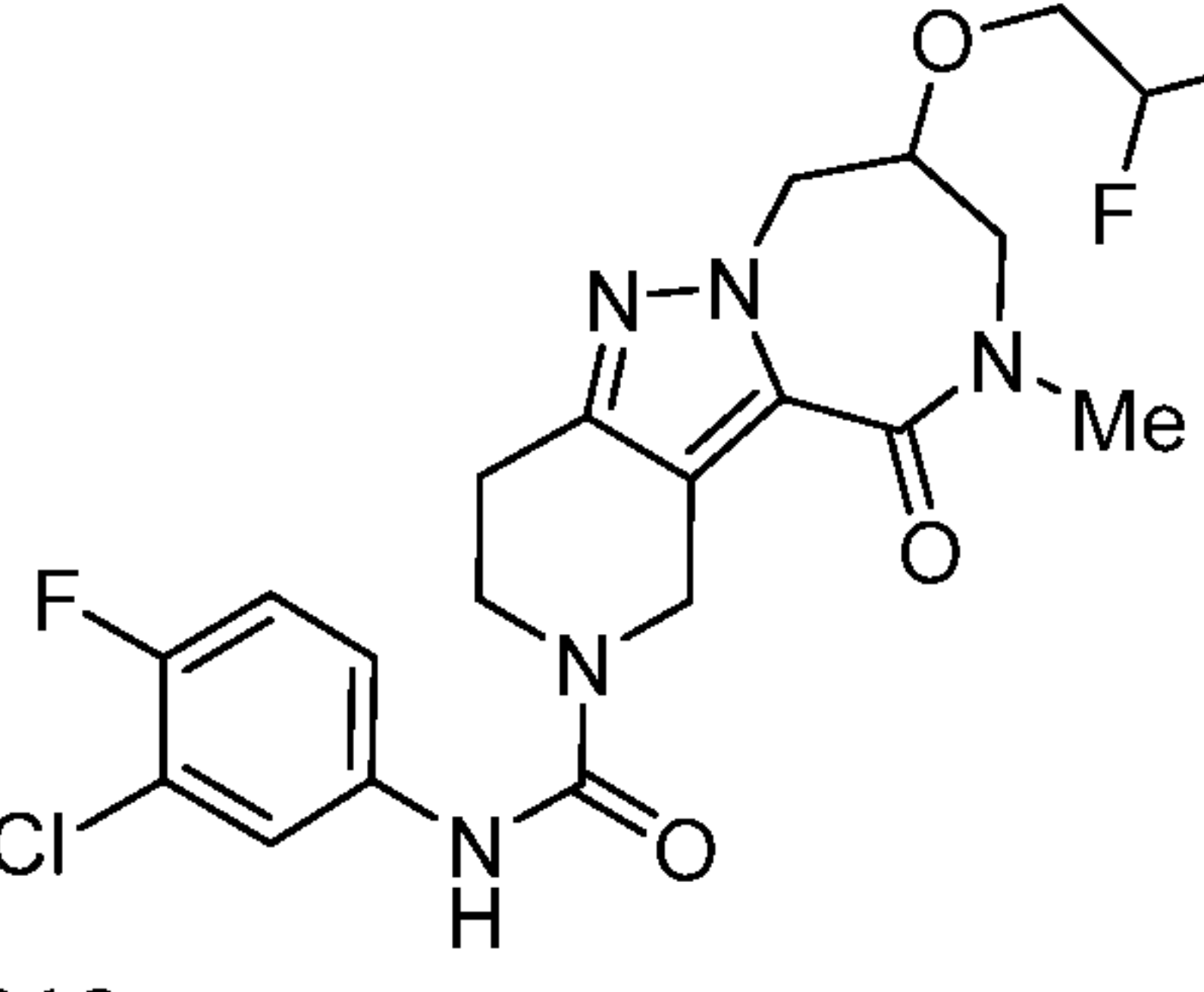
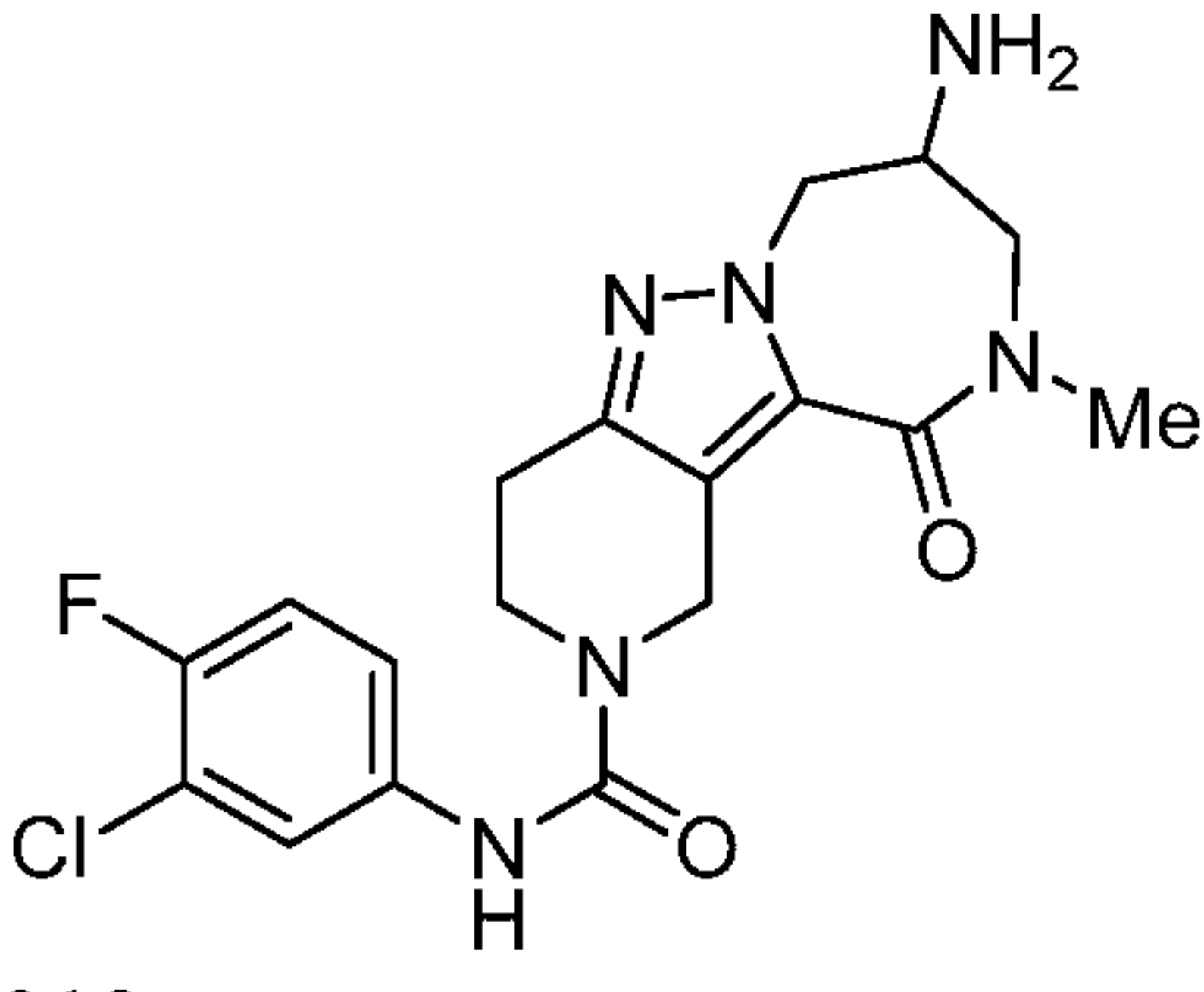
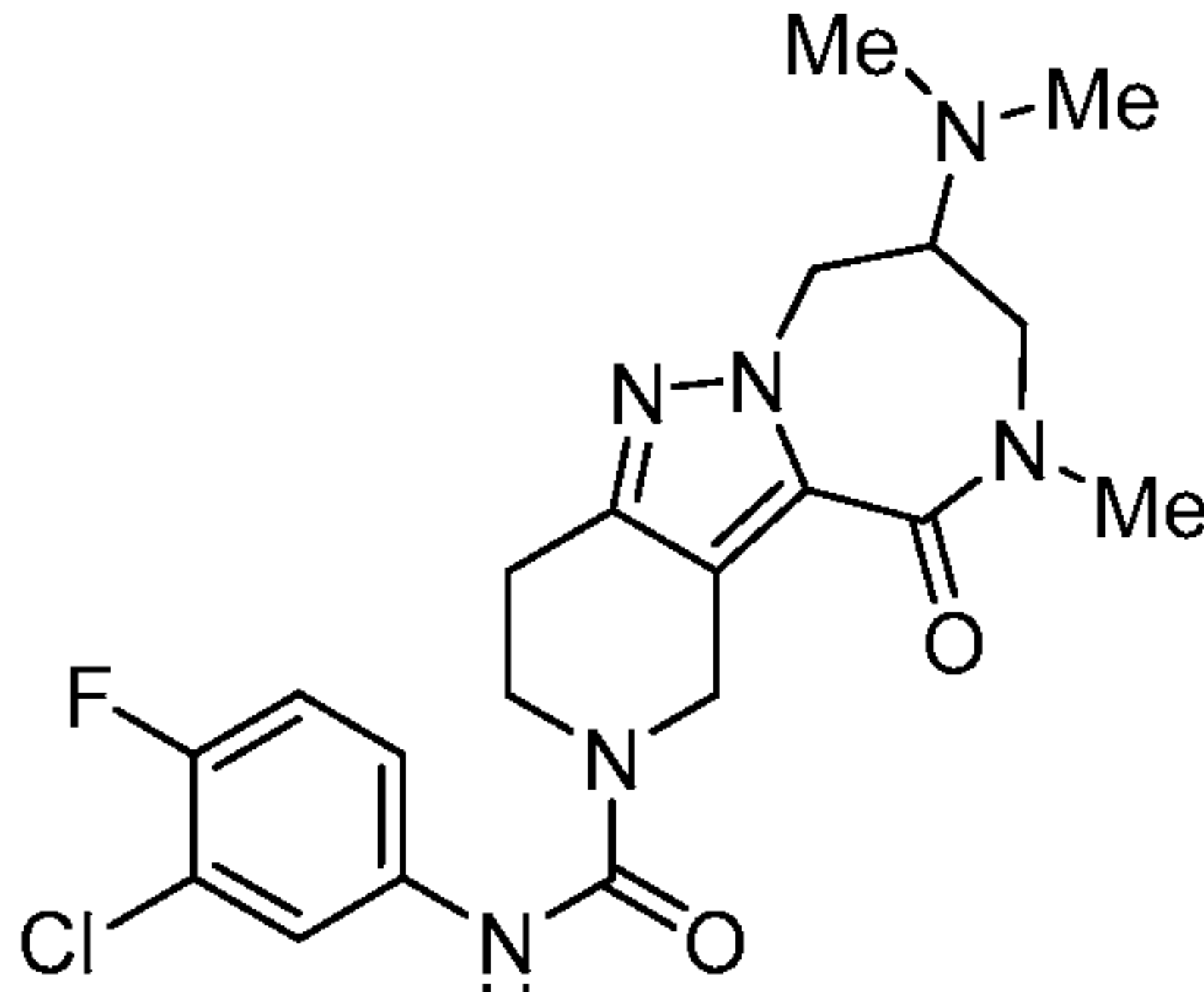
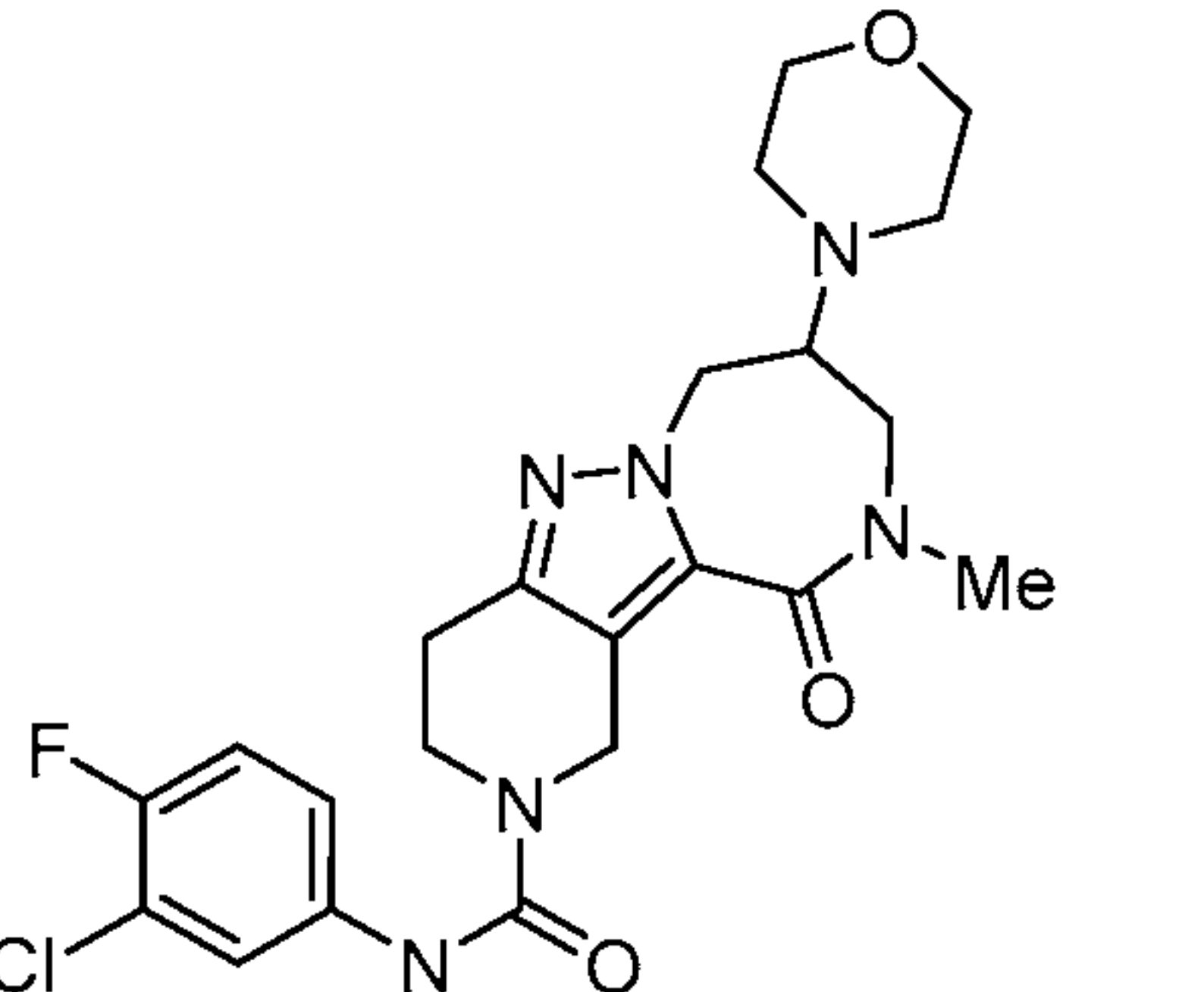
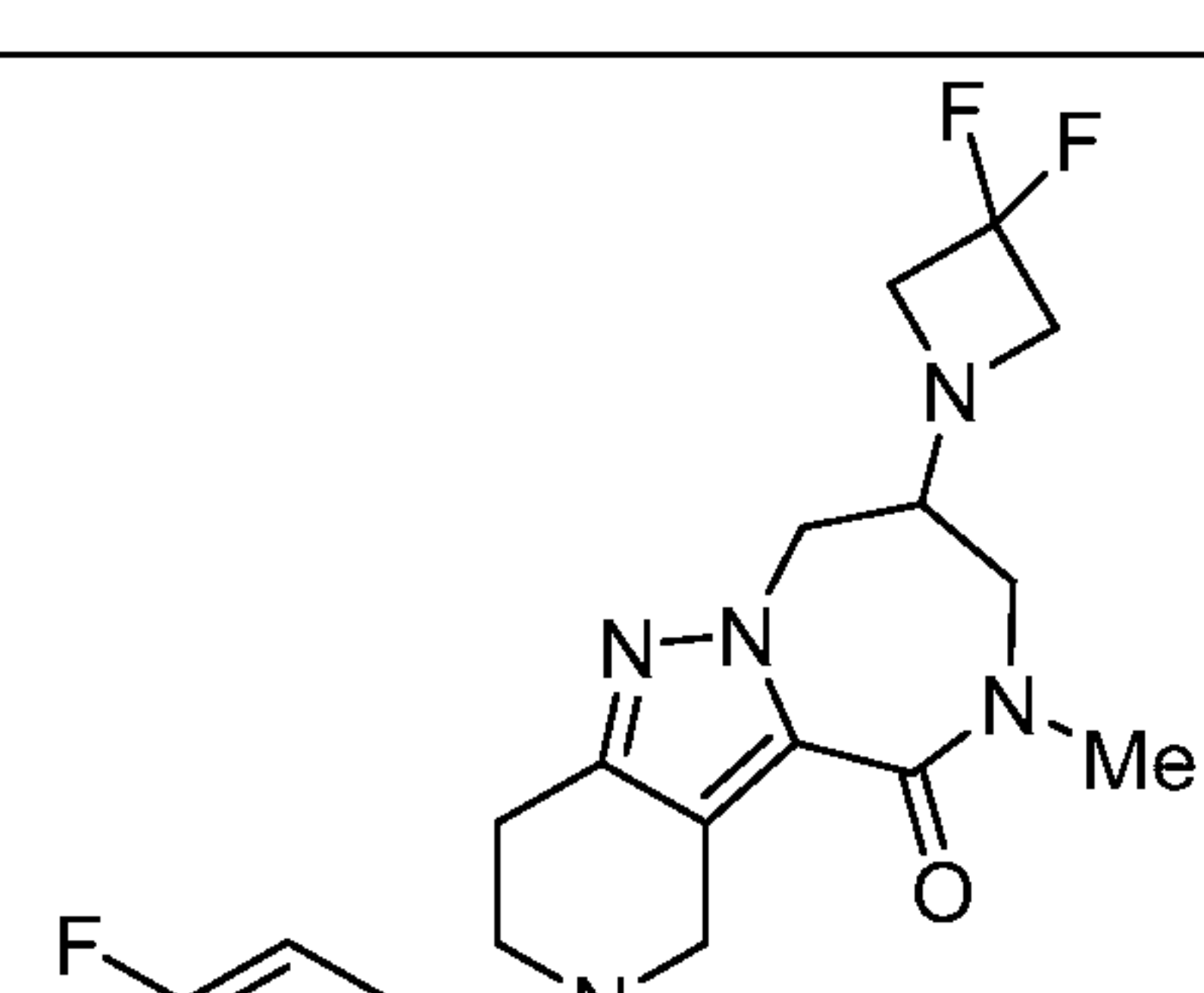
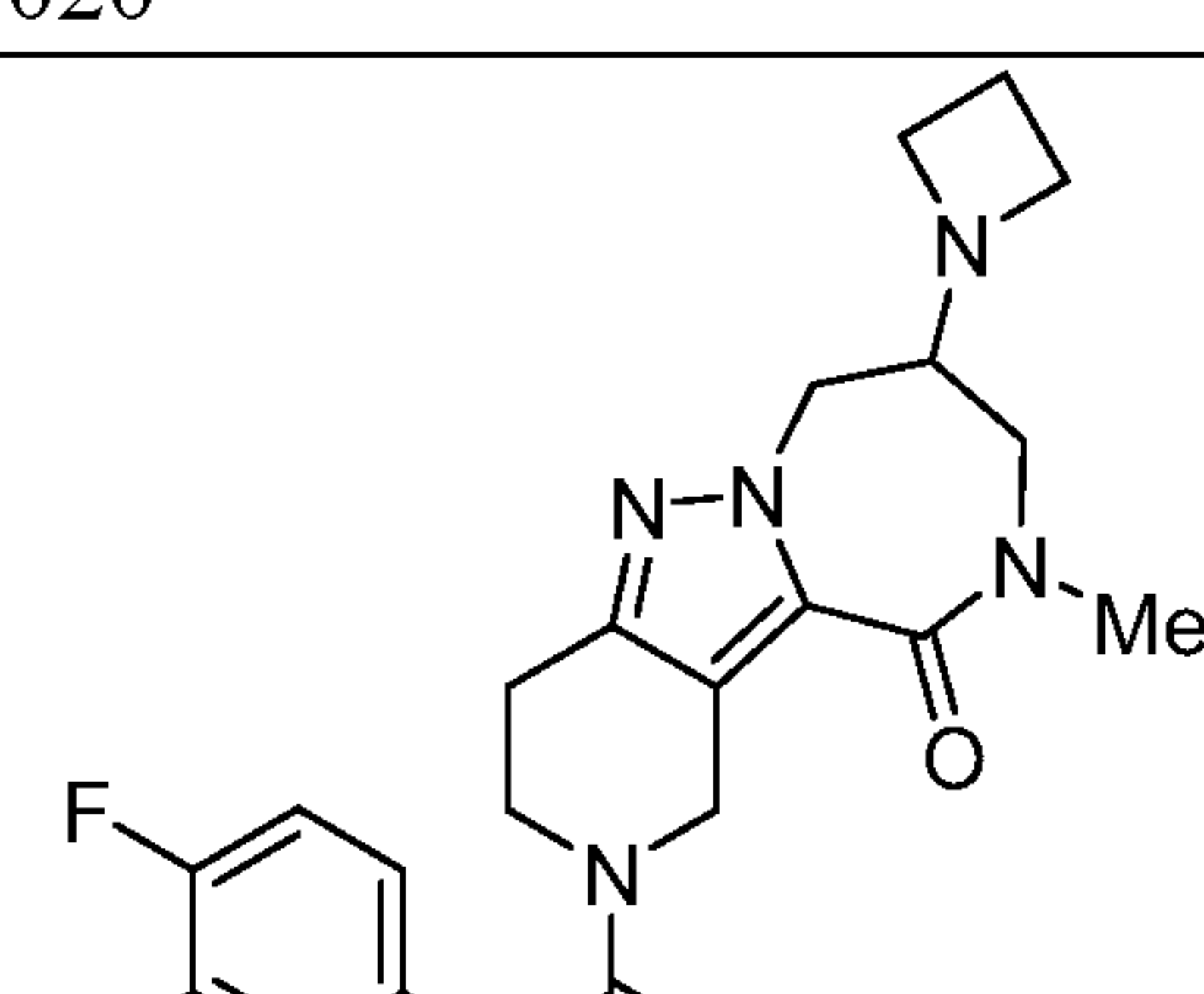
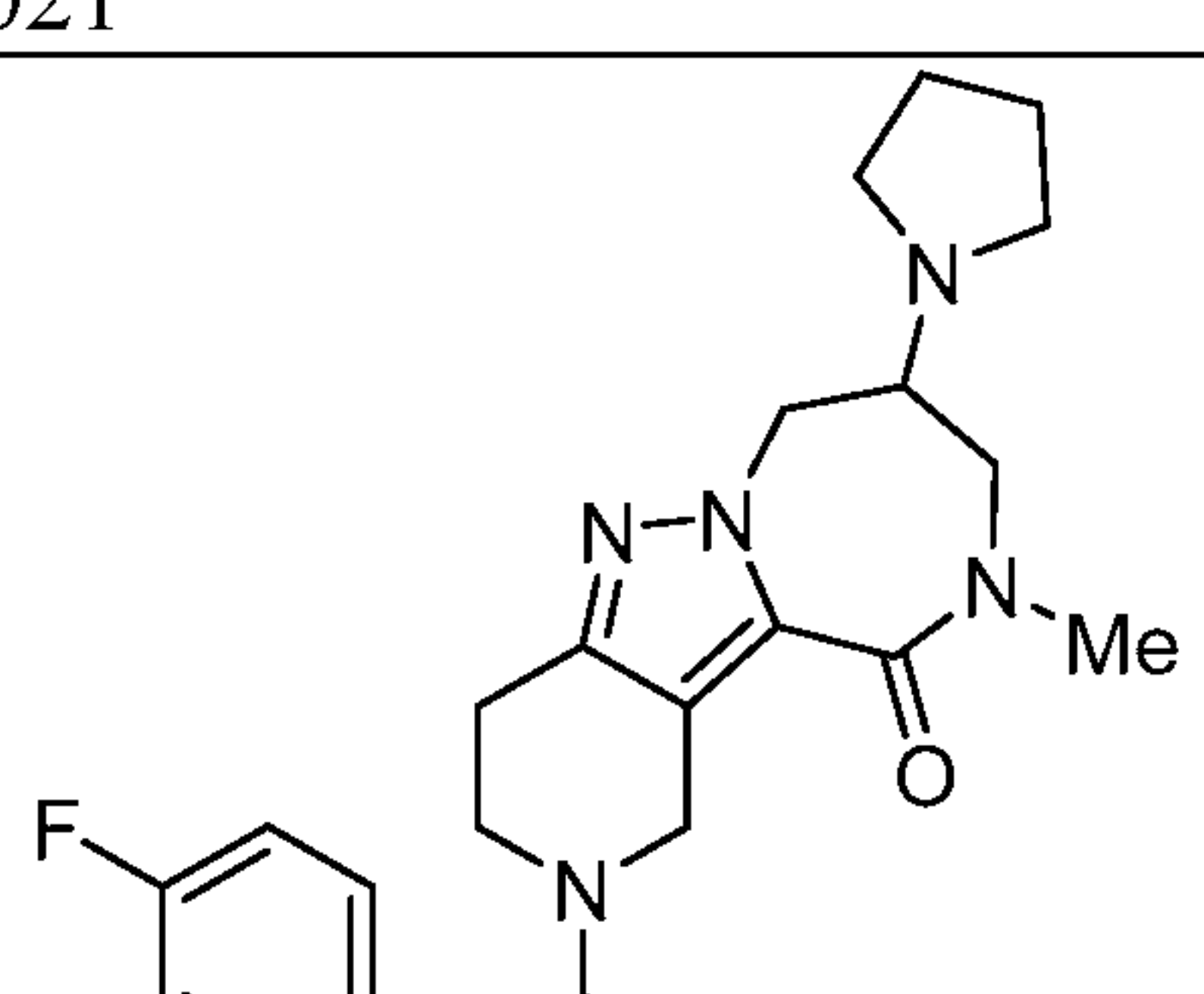
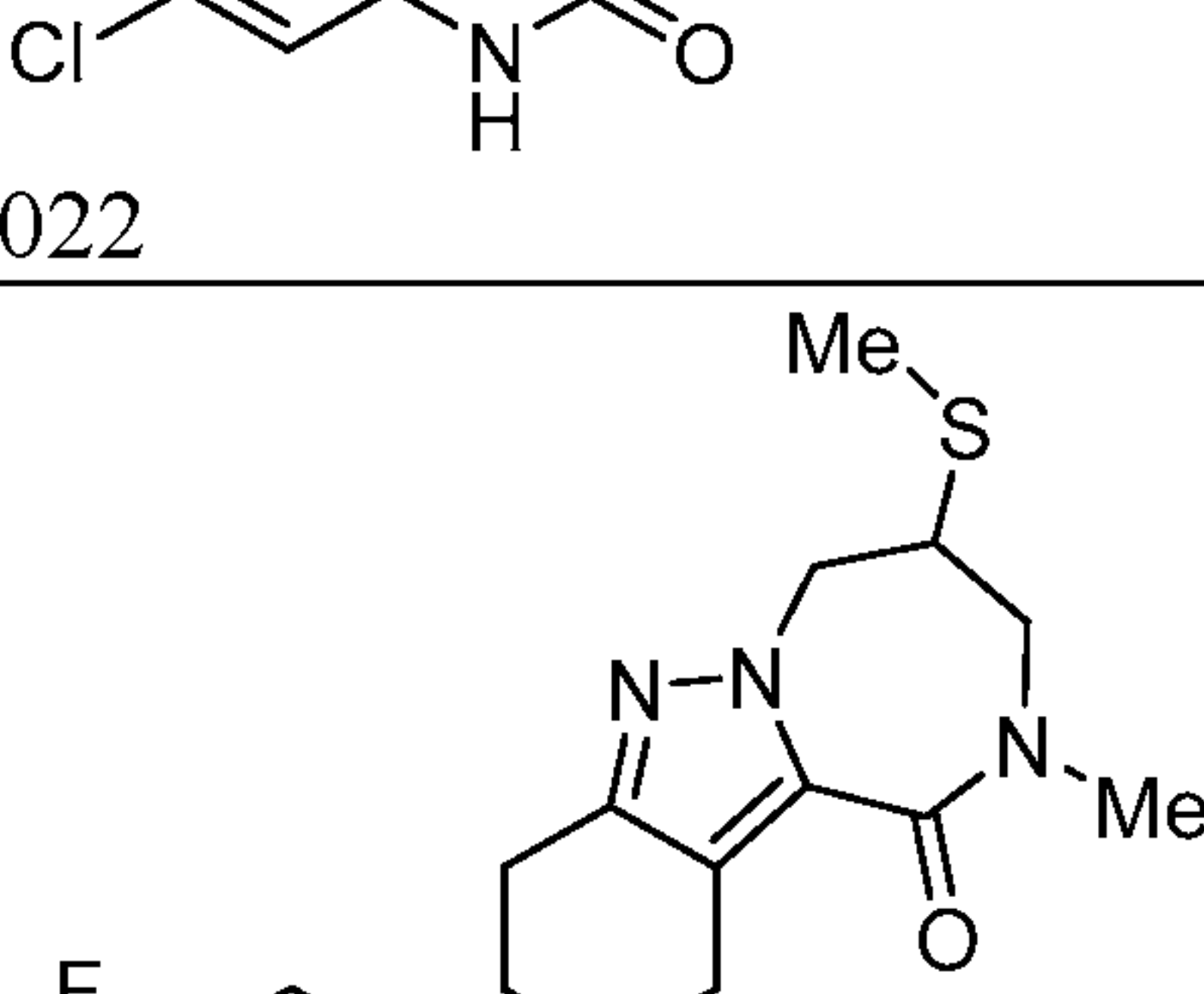
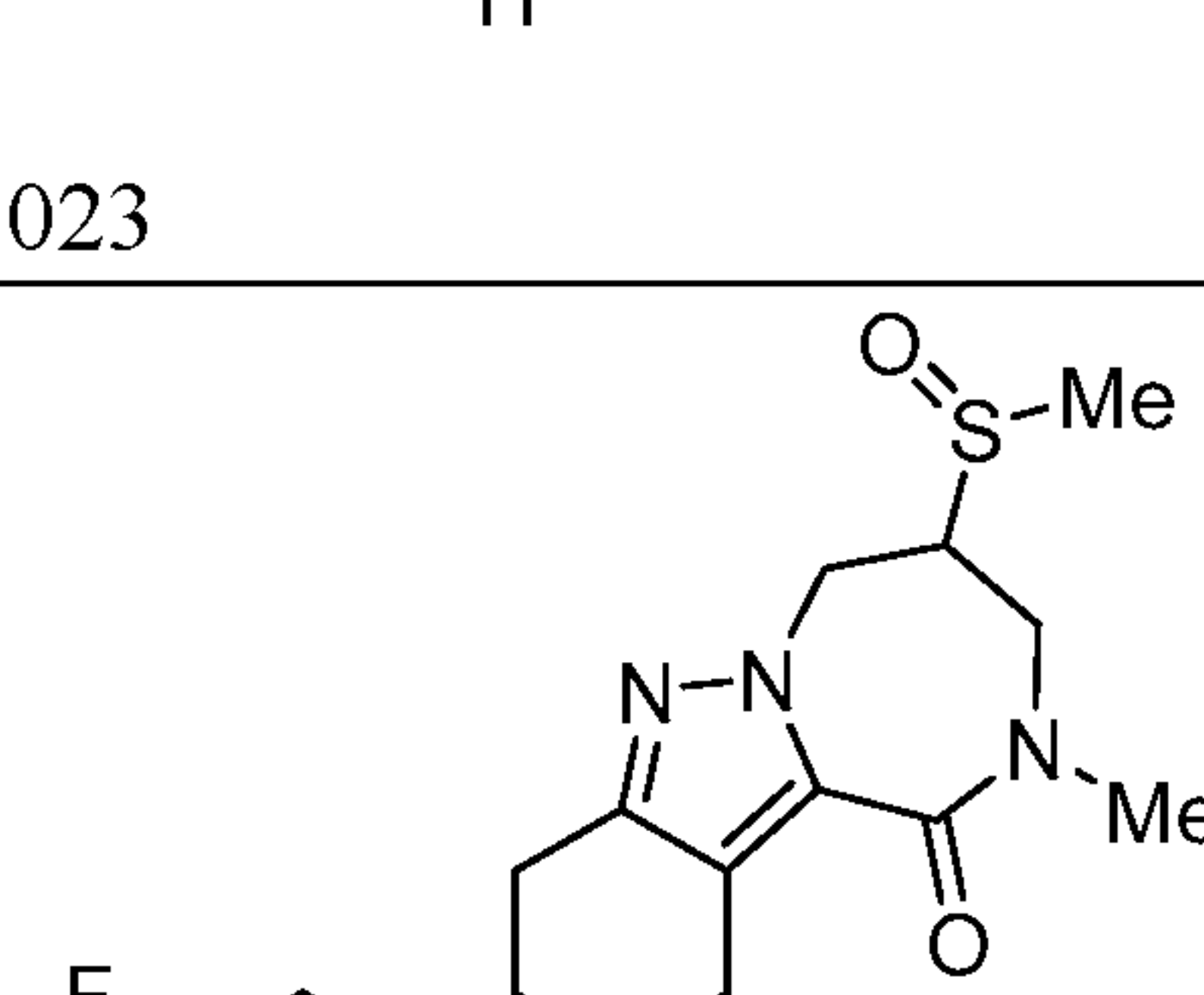
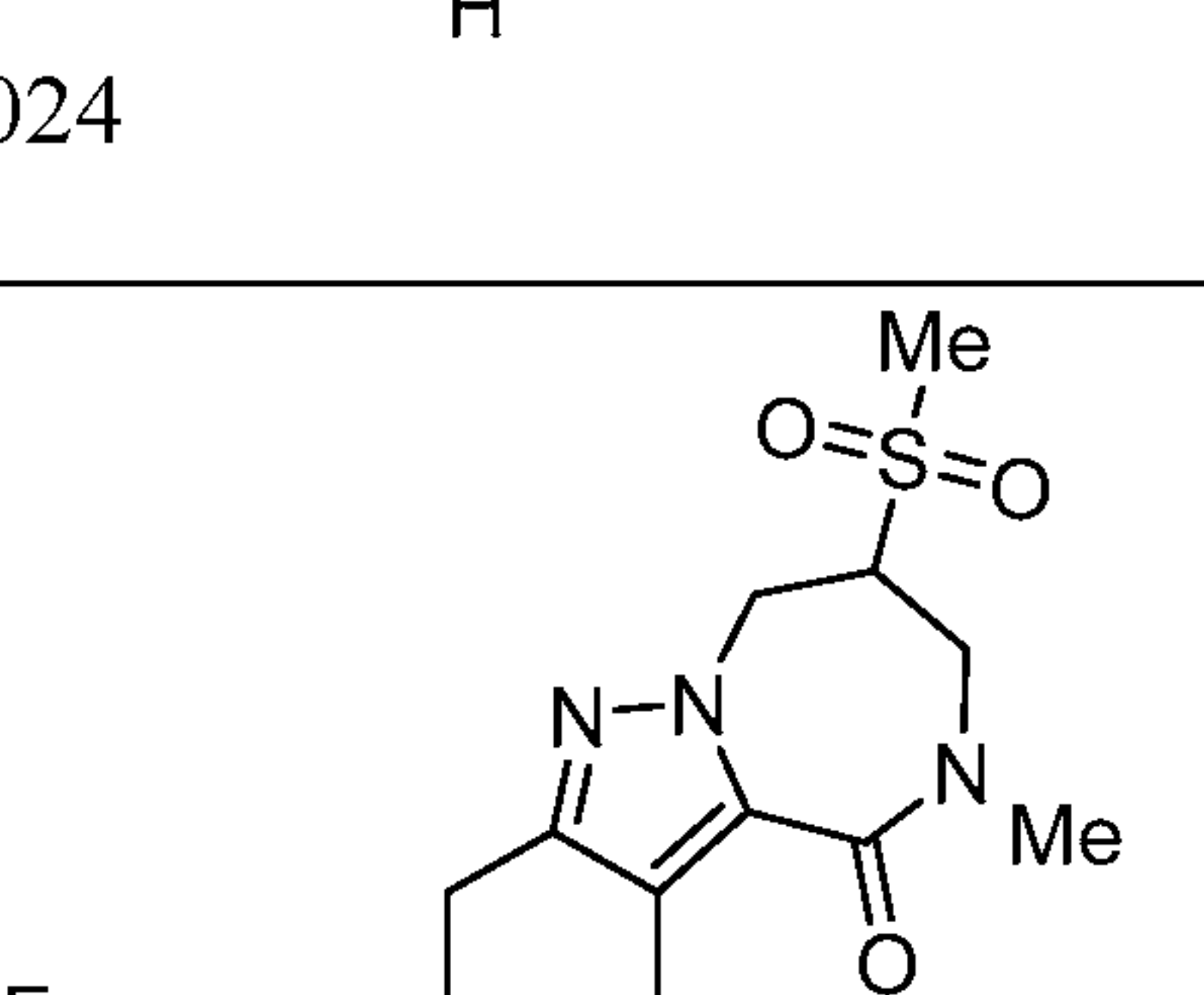
Certain embodiments of Formulas I, II, III and IV are shown below in **Table 1**.
disclosed compounds.

10

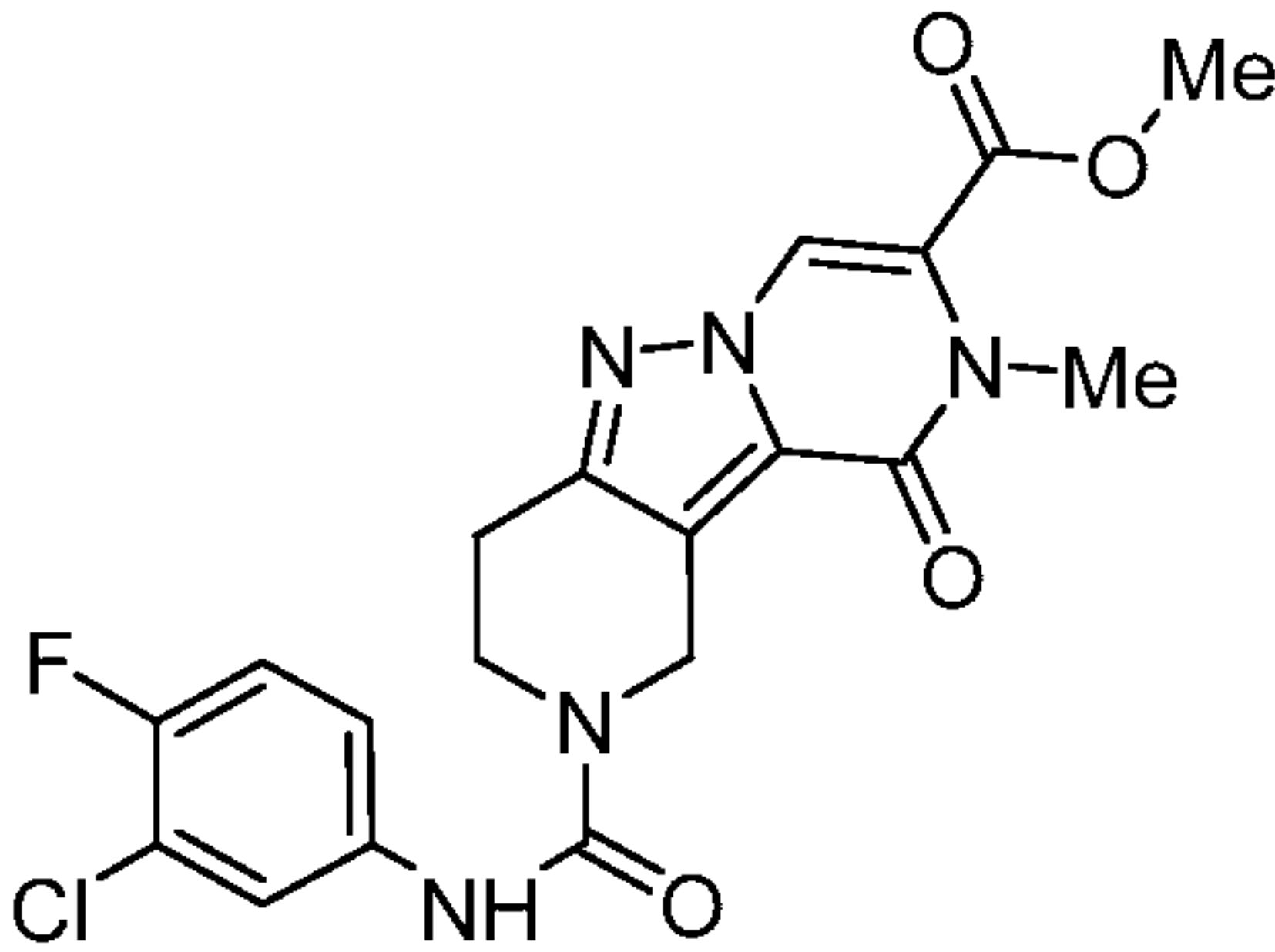
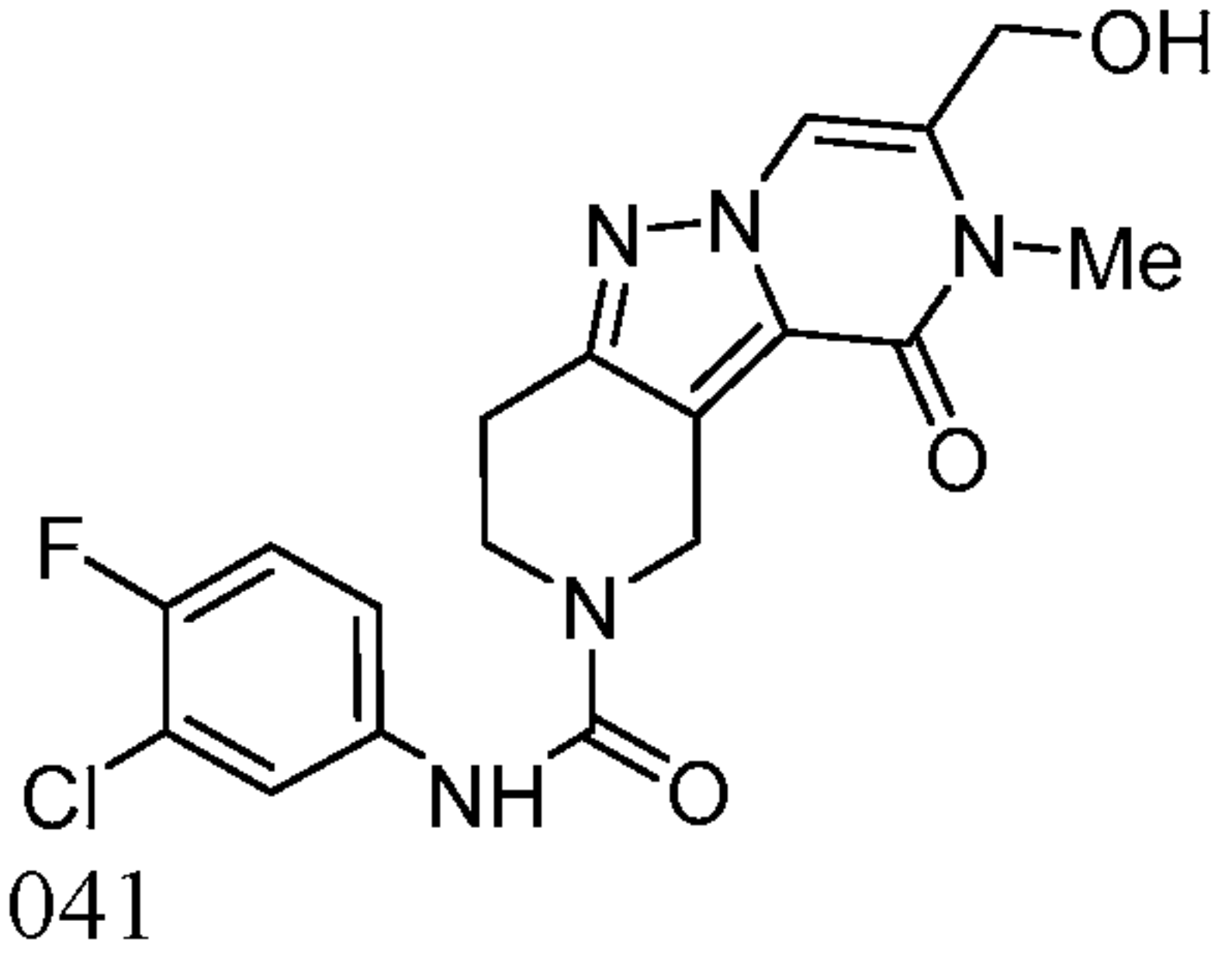
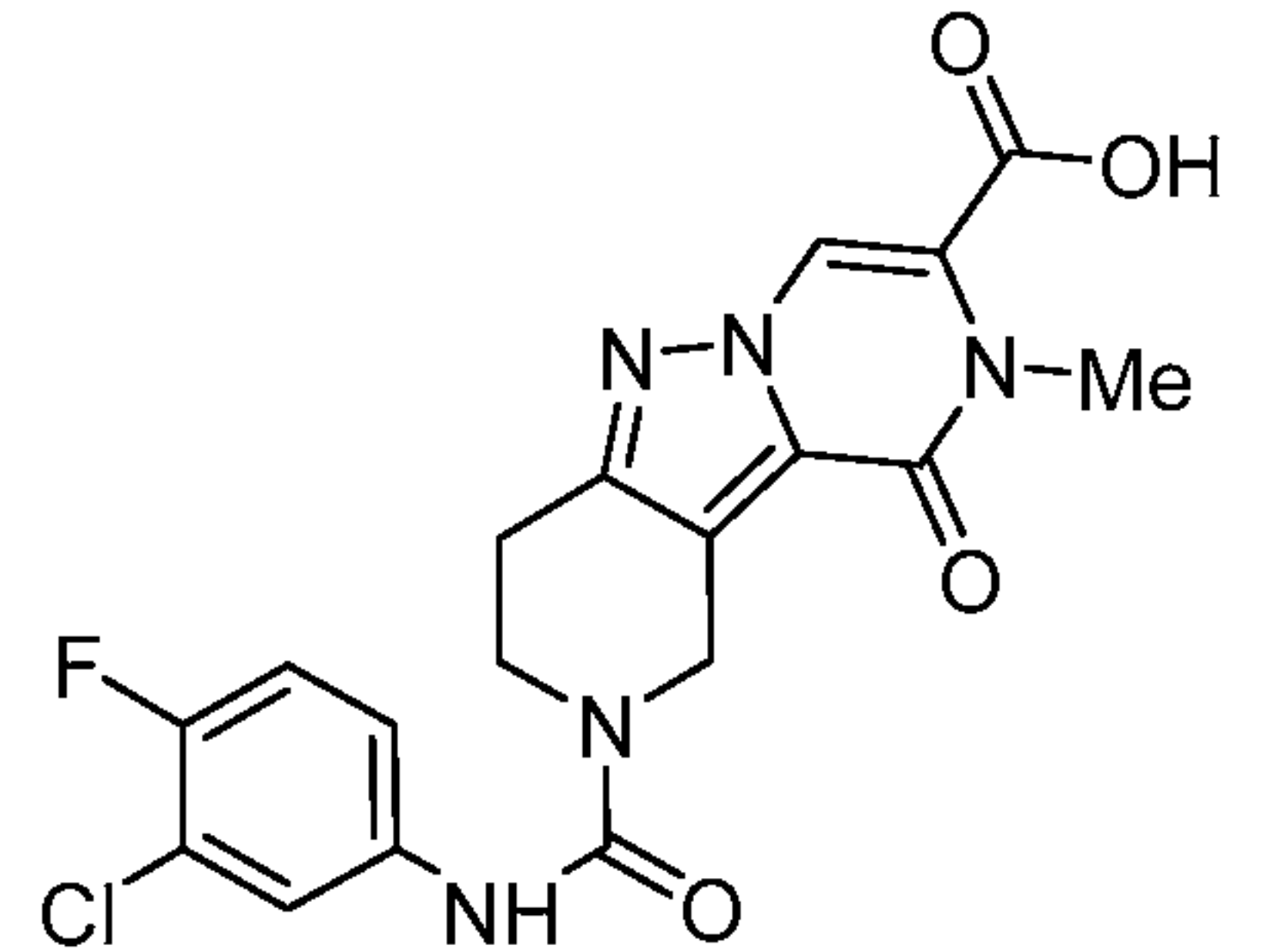
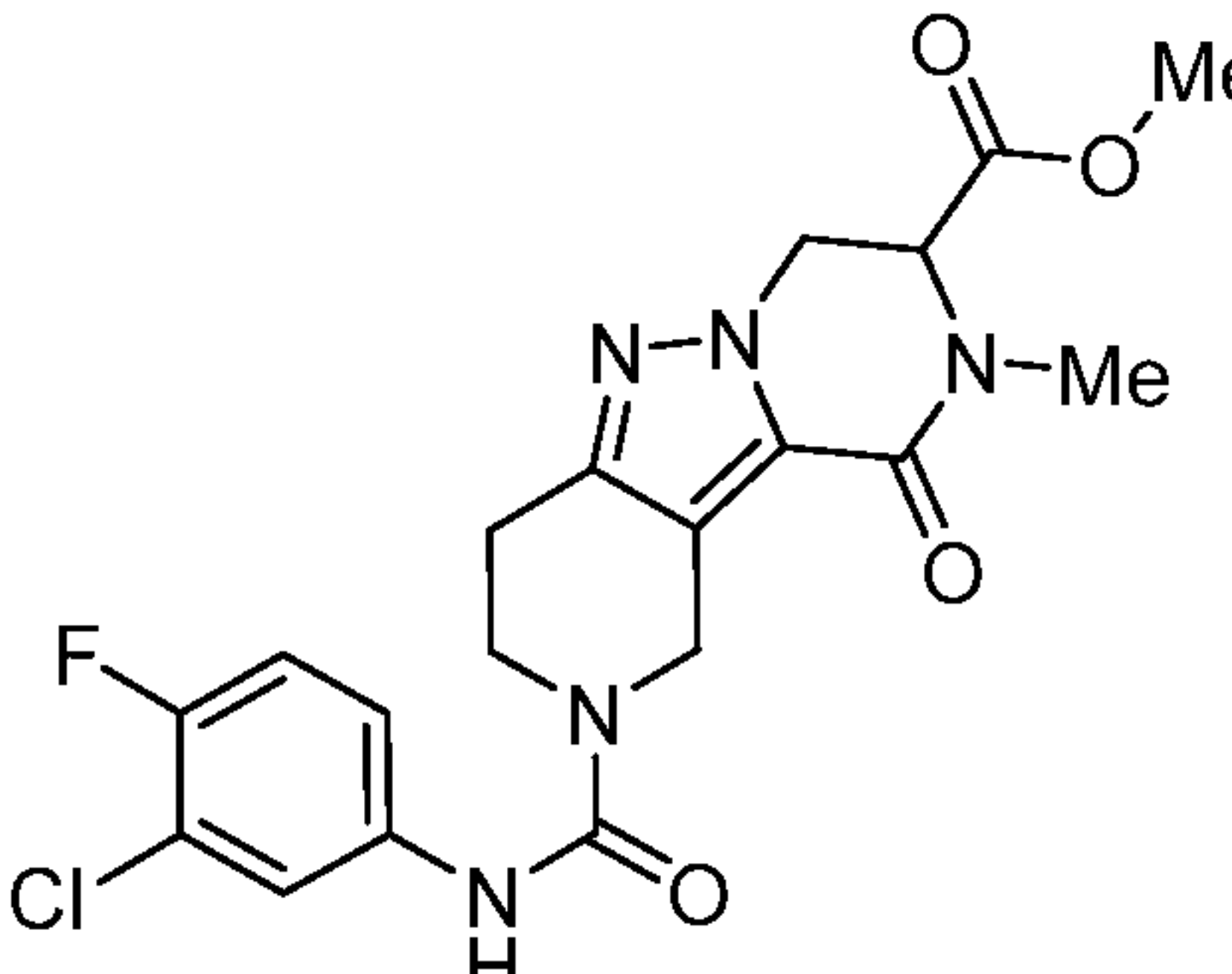
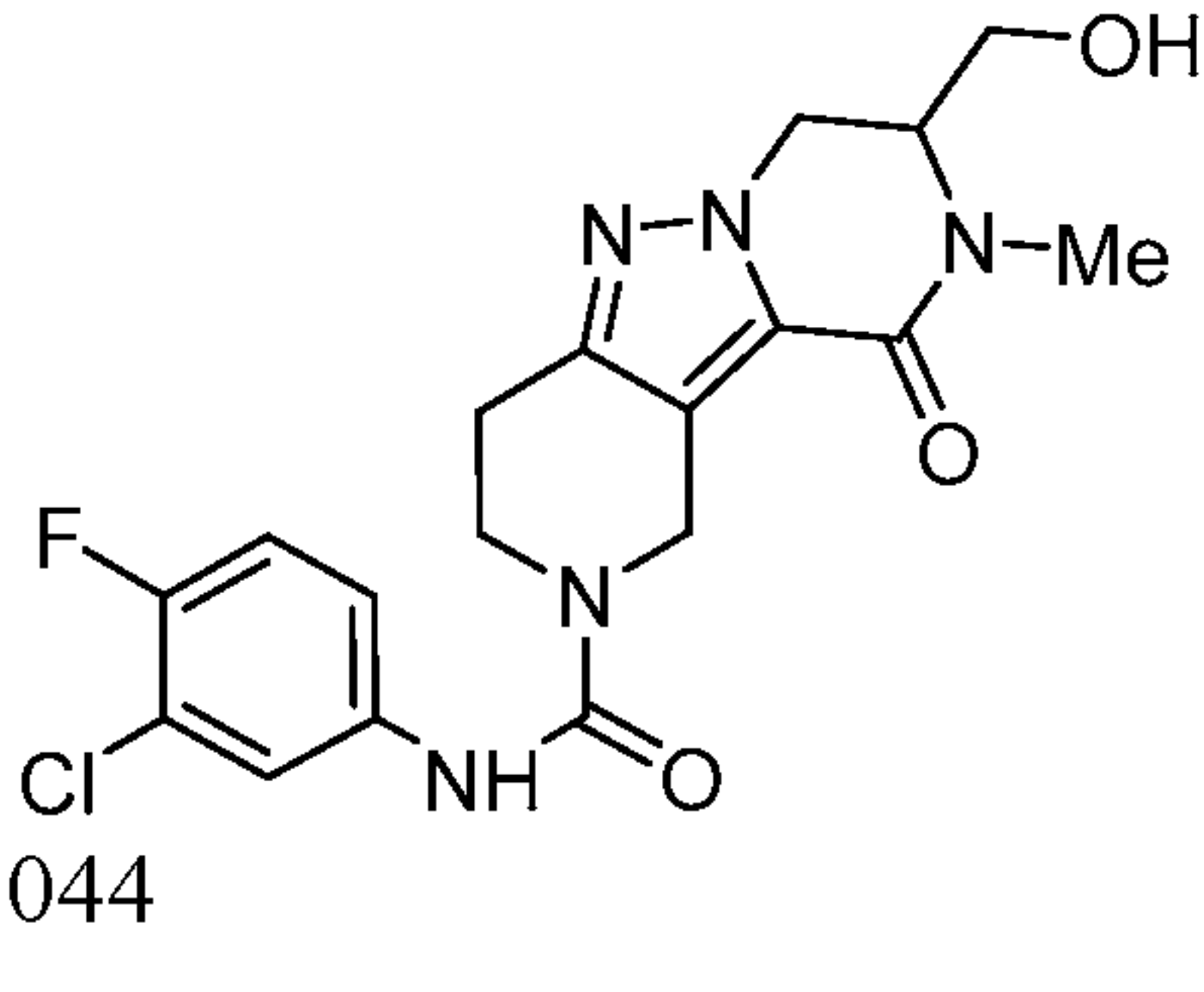
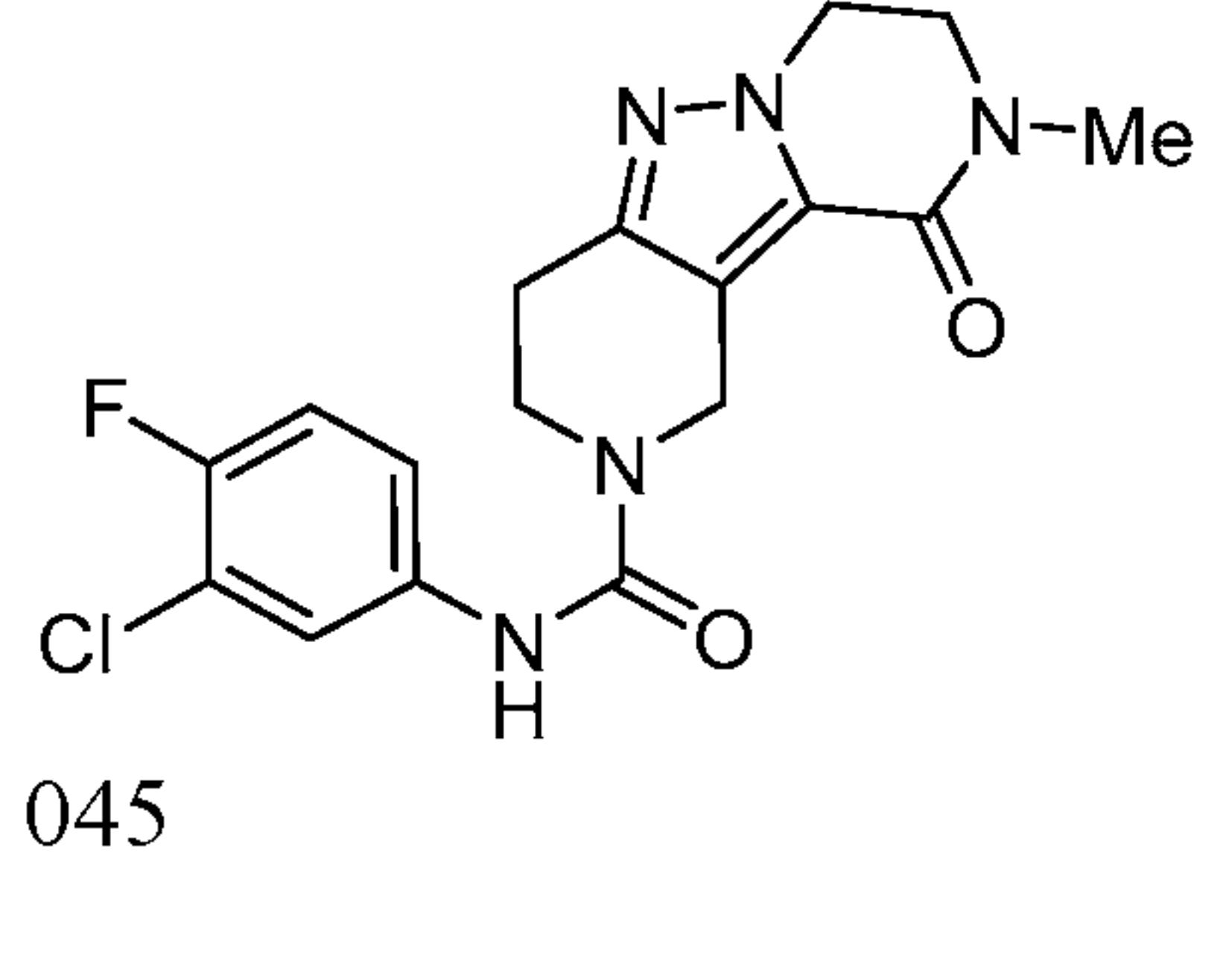
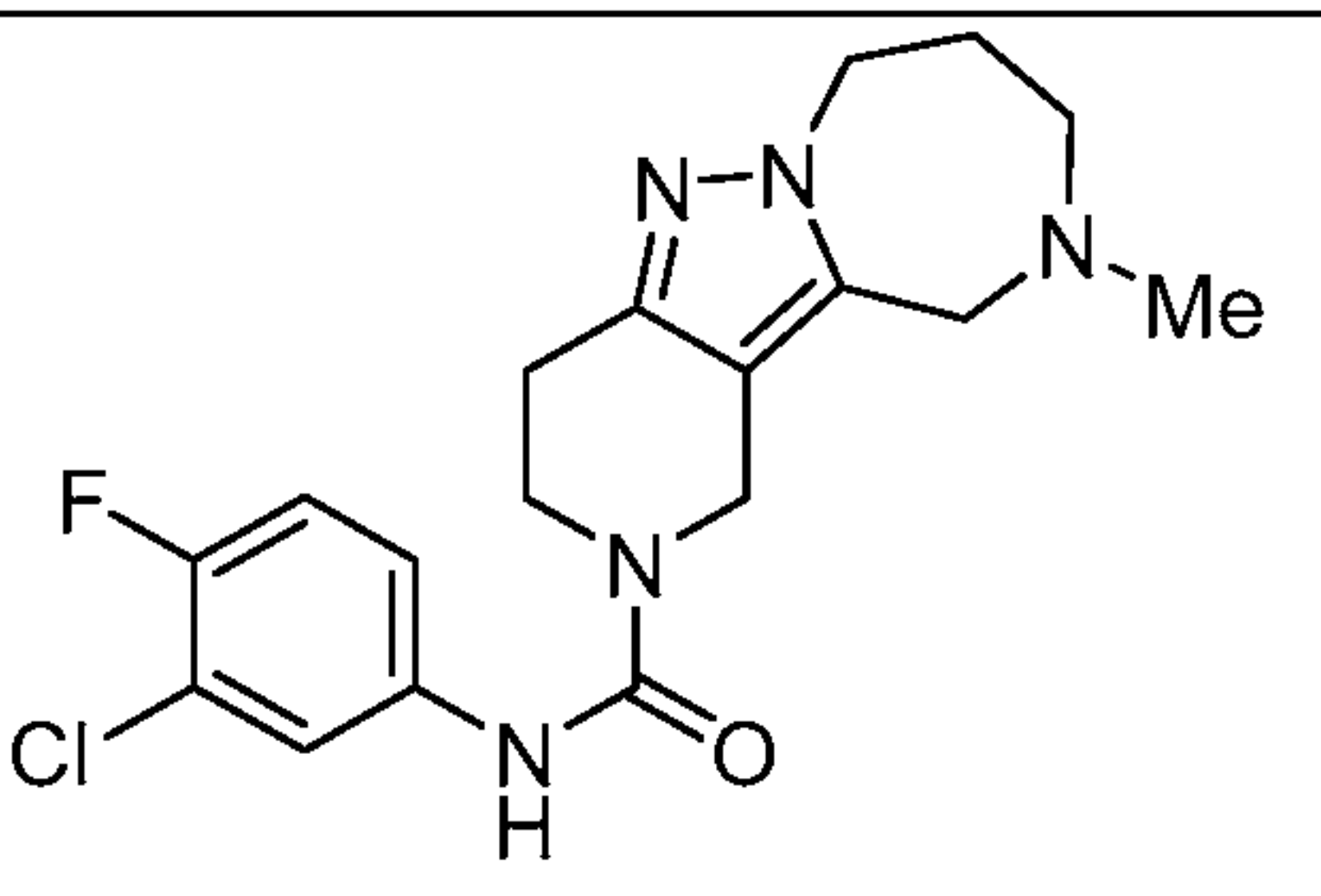
Table 1.

 <p>001</p>	 <p>002</p>	 <p>003</p>
 <p>004</p>	 <p>005</p>	 <p>006</p>

 007	 008	 009
 010	 011	 012
 013	 014	 015

 016	 017	 018
 019	 020	 021
 022	 023	 024
 025	 026	 027

 028	 029	 030
 031	 032	 033
 034	 035	 036
 037	 038	 039

 040	 041	 042
 043	 044	 045
 046		

In an embodiment, compounds of Formulas I, II, III and IV are selected from:

Compound ID	Compound Name
001	N-(3-chloro-4-fluorophenyl)-10-methyl-8-methylene-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
002	N-(3-chloro-4-fluorophenyl)-8-(hydroxymethyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
003	N-(3-chloro-4-fluorophenyl)-8-hydroxy-8-(hydroxymethyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

Compound ID	Compound Name
004	N-(3-chloro-4-fluorophenyl)-8-hydroxy-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
005	N-(3-chloro-4-fluorophenyl)-8,8-difluoro-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
006	N-(3-chloro-4-fluorophenyl)-8-fluoro-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
007	N-(3-bromo-4-fluorophenyl)-8-fluoro-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
008	N-(2-bromo-3-fluoropyridin-4-yl)-8-fluoro-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
009	N-(3-cyano-4-fluorophenyl)-8-fluoro-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
010	8-fluoro-N-(4-fluoro-3-methylphenyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
011	8-fluoro-N-(4-fluoro-3-(trifluoromethyl)phenyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
012	N-(5-chloro-2,4-difluorophenyl)-8-fluoro-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
013	N-(5-bromo-2,4-difluorophenyl)-8-fluoro-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
014	N-(3-chloro-4-fluoro-phenyl)-8,10-dimethyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide
015	N-(3-chloro-4-fluoro-phenyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide
016A	(S*)-N-(3-chloro-4-fluorophenyl)-8-methoxy-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
016B	(R*)-N-(3-chloro-4-fluorophenyl)-8-methoxy-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide

Compound ID	Compound Name
017	N-(3-chloro-4-fluorophenyl)-8-ethoxy-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
018	N-(3-chloro-4-fluorophenyl)-8-(2,2-difluoroethoxy)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
019	8-amino-N-(3-chloro-4-fluorophenyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
020	N-(3-chloro-4-fluorophenyl)-8-(dimethylamino)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
021	N-(3-chloro-4-fluorophenyl)-10-methyl-8-morpholino-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
022	N-(3-chloro-4-fluorophenyl)-8-(3,3-difluoroazetidin-1-yl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
023	8-(azetidin-1-yl)-N-(3-chloro-4-fluorophenyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
024	N-(3-chloro-4-fluorophenyl)-10-methyl-11-oxo-8-(pyrrolidin-1-yl)-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
025	N-(3-chloro-4-fluorophenyl)-10-methyl-8-(methylthio)-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
026A	N-(3-chloro-4-fluorophenyl)-10-methyl-8-(methylsulfinyl)-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
026B	N-(3-chloro-4-fluorophenyl)-10-methyl-8-(methylsulfinyl)-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
027	N-(3-chloro-4-fluoro-phenyl)-10-methyl-8- methylsulfonyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide
028	methyl 2-(2-((3-chloro-4-fluorophenyl)carbamoyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-8-yl)acetate
029	N-(3-chloro-4-fluorophenyl)-8-(2-hydroxyethyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

Compound ID	Compound Name
030	ethyl 2-((3-chloro-4-fluorophenyl)carbamoyl)-10-methyl-11-oxo-2,3,4,7,8,9,10,11-octahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-8-carboxylate
031	N2-(3-chloro-4-fluorophenyl)-N8,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2,8-dicarboxamide
032	N2-(3-chloro-4-fluorophenyl)-N8,N8,10-trimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2,8-dicarboxamide
033	N-(3-chloro-4-fluorophenyl)-8-(2-hydroxypropan-2-yl)-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
034	N-(3-chloro-4-fluorophenyl)-8-(1-hydroxyethyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
035	N-(3-chloro-4-fluorophenyl)-8-(1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
036	N-(3-chloro-4-fluorophenyl)-8-(cyclopropyl(hydroxy)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
037	N-(3-chloro-4-fluorophenyl)-8-(difluoromethyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
038	N-(3-chloro-4-fluorophenyl)-10-(2,2-difluoroethyl)-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
039	N-(3-chloro-4-fluorophenyl)-9,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
040	methyl 2-((3-chloro-4-fluorophenyl)carbamoyl)-9-methyl-10-oxo-1,2,3,4,9,10-hexahydropyrido[4',3':3,4]pyrazolo[1,5-a]pyrazine-8-carboxylate
041	N-(3-chloro-4-fluorophenyl)-8-(hydroxymethyl)-9-methyl-10-oxo-3,4,9,10-tetrahydropyrido[4',3':3,4]pyrazolo[1,5-a]pyrazine-2(1H)-carboxamide
042	2-((3-chloro-4-fluorophenyl)carbamoyl)-9-methyl-10-oxo-1,2,3,4,9,10-hexahydropyrido[4',3':3,4]pyrazolo[1,5-a]pyrazine-8-carboxylic acid
043	methyl 2-((3-chloro-4-fluorophenyl)carbamoyl)-9-methyl-10-oxo-1,2,3,4,7,8,9,10-octahydropyrido[4',3':3,4]pyrazolo[1,5-a]pyrazine-8-carboxylate

Compound ID	Compound Name
044	N-(3-chloro-4-fluorophenyl)-8-(hydroxymethyl)-9-methyl-10-oxo-3,4,7,8,9,10-hexahydropyrido[4',3':3,4]pyrazolo[1,5-a]pyrazine-2(1H)-carboxamide
045	N-(3-chloro-4-fluorophenyl)-9-methyl-10-oxo-3,4,7,8,9,10-hexahydropyrido[4',3':3,4]pyrazolo[1,5-a]pyrazine-2(1H)-carboxamide
046	N-(3-chloro-4-fluorophenyl)-10-methyl-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

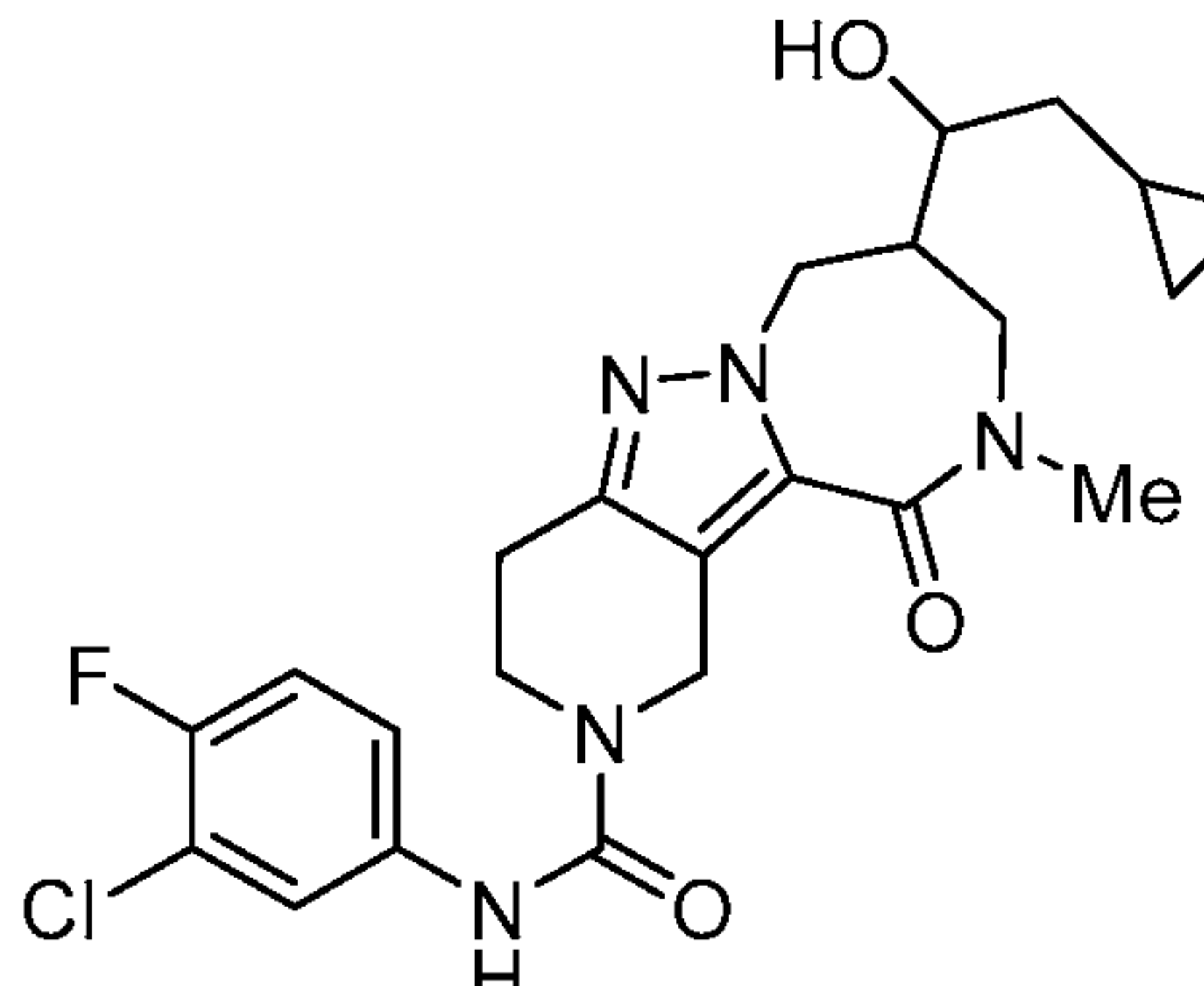
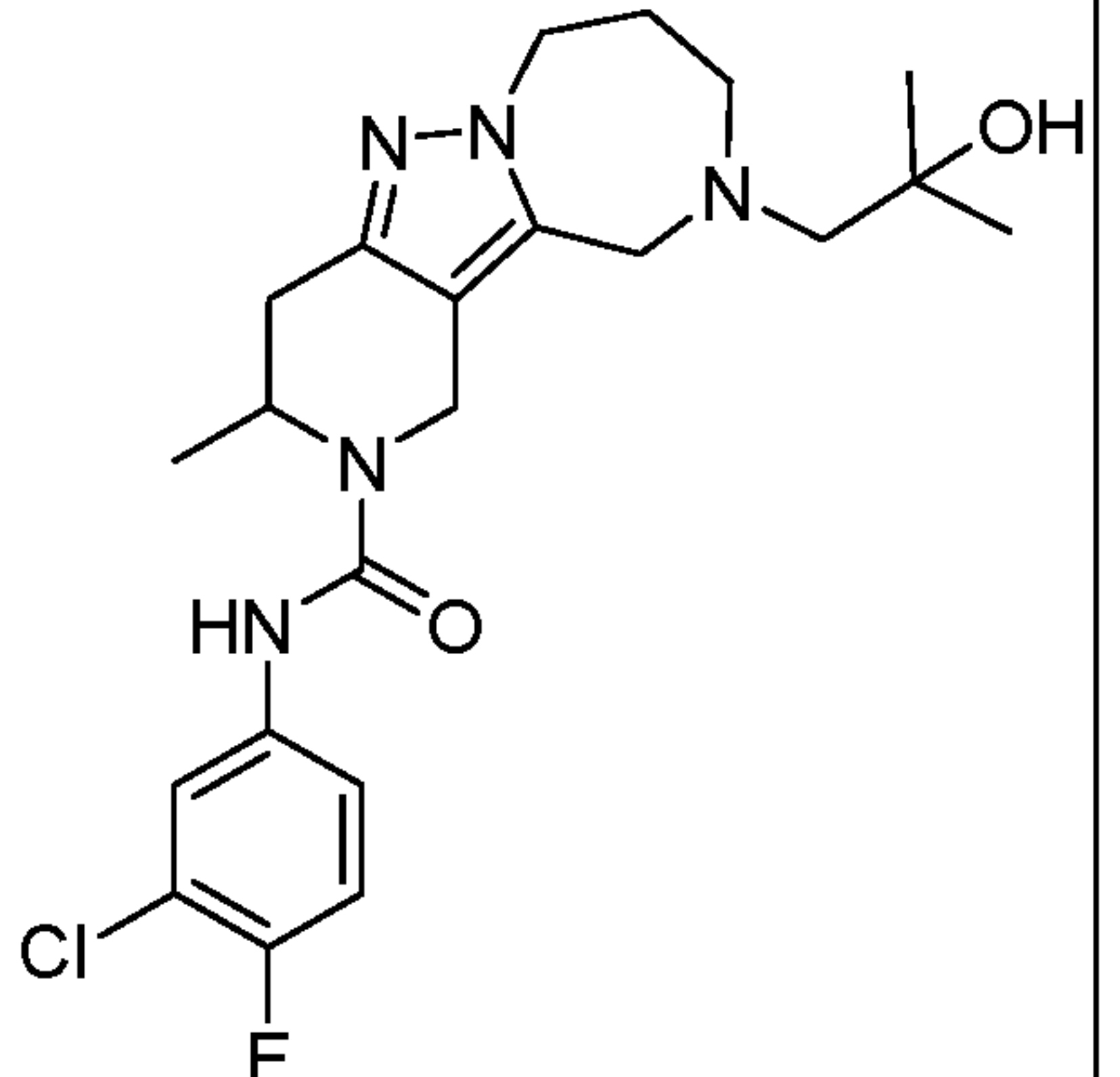
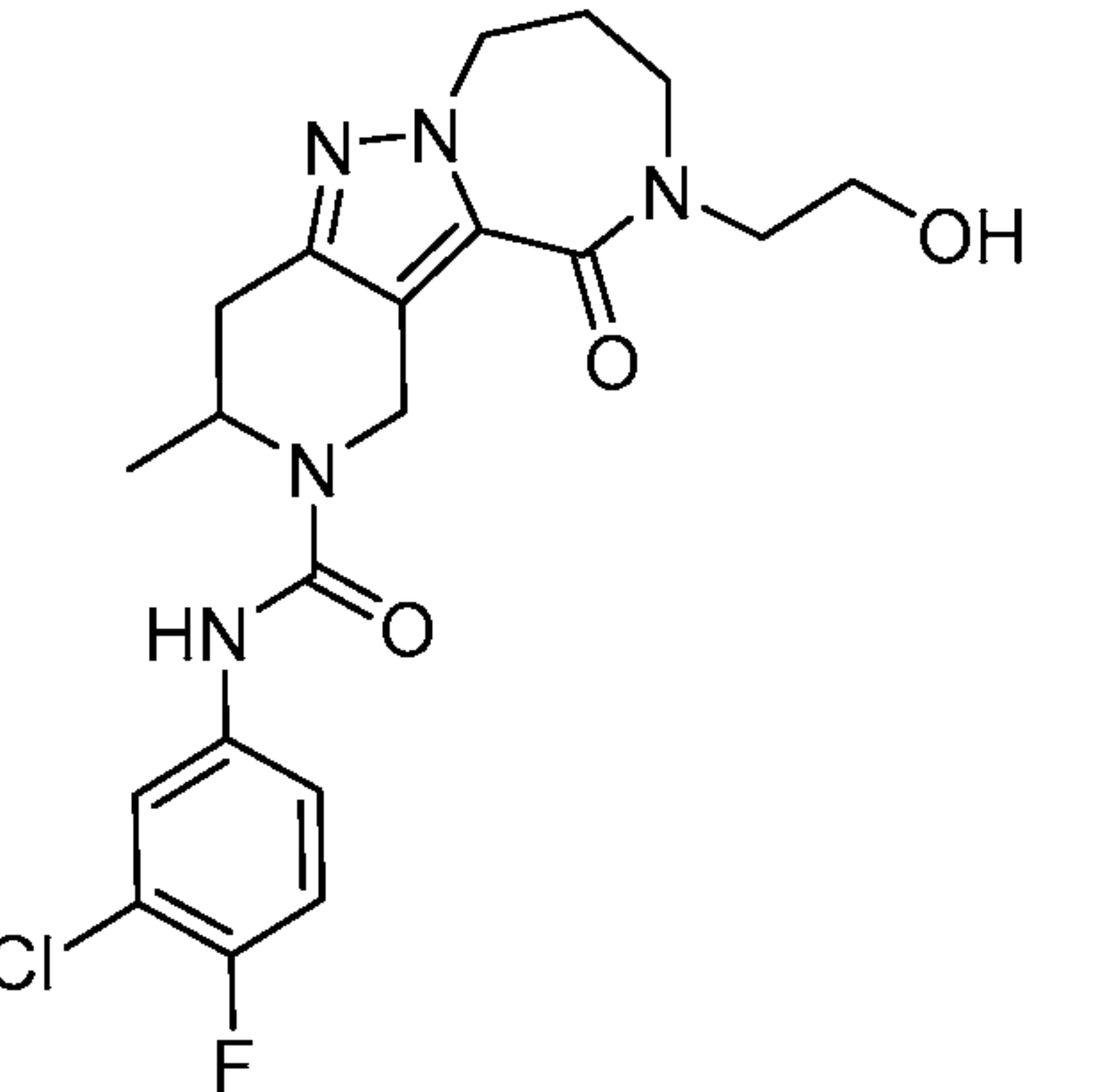
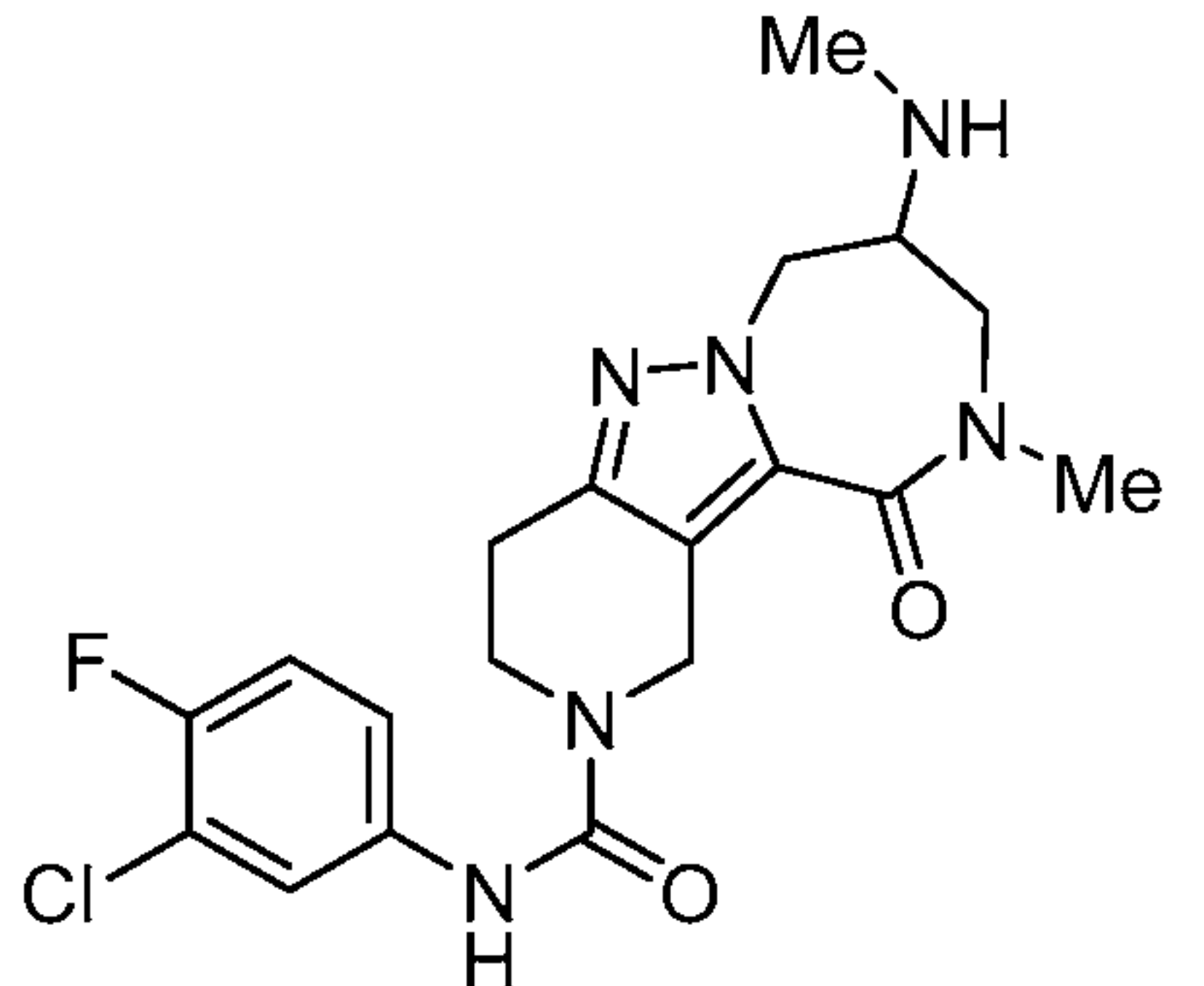
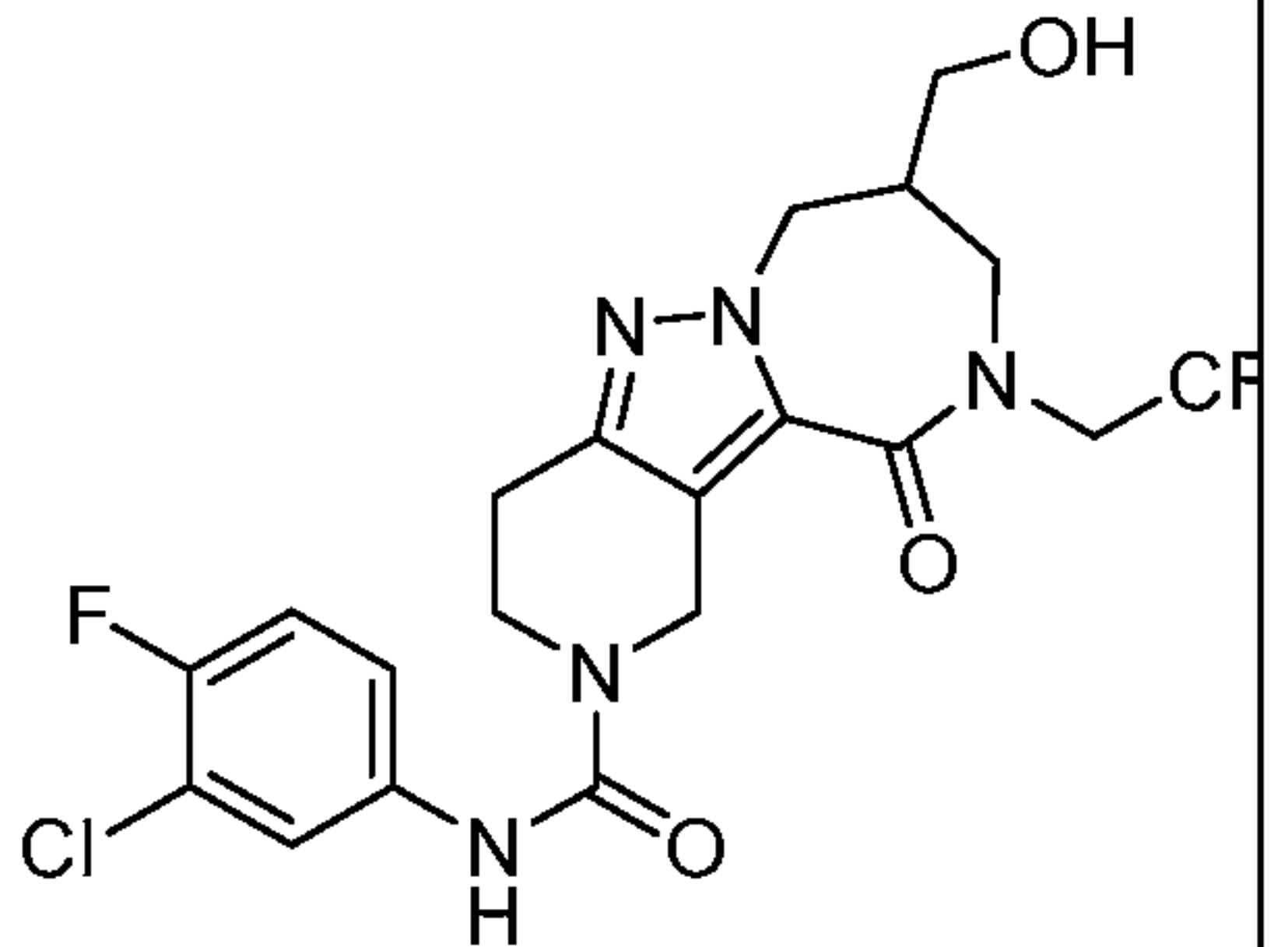
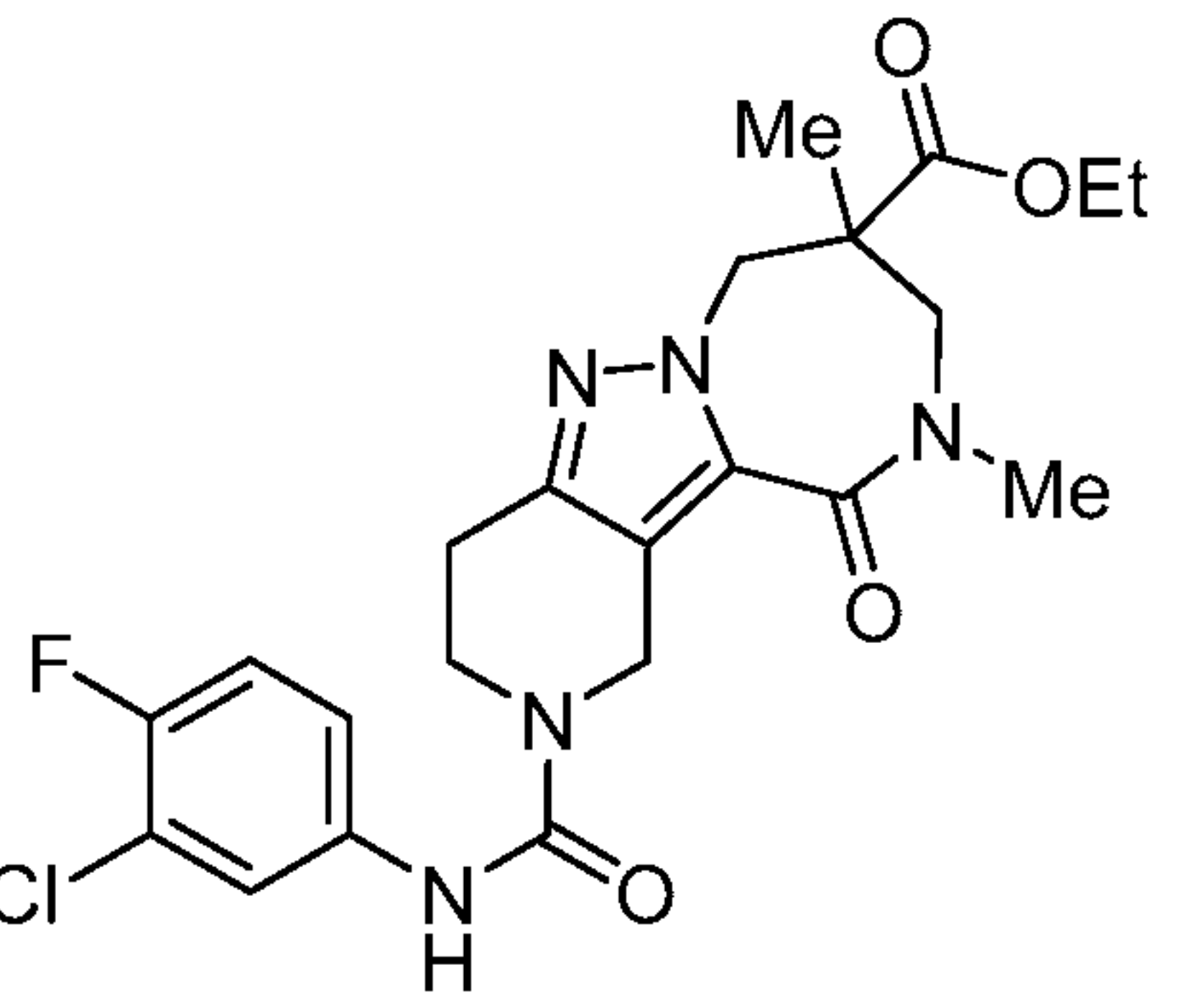
*Pure but unknown enantiomer or diastereomer.

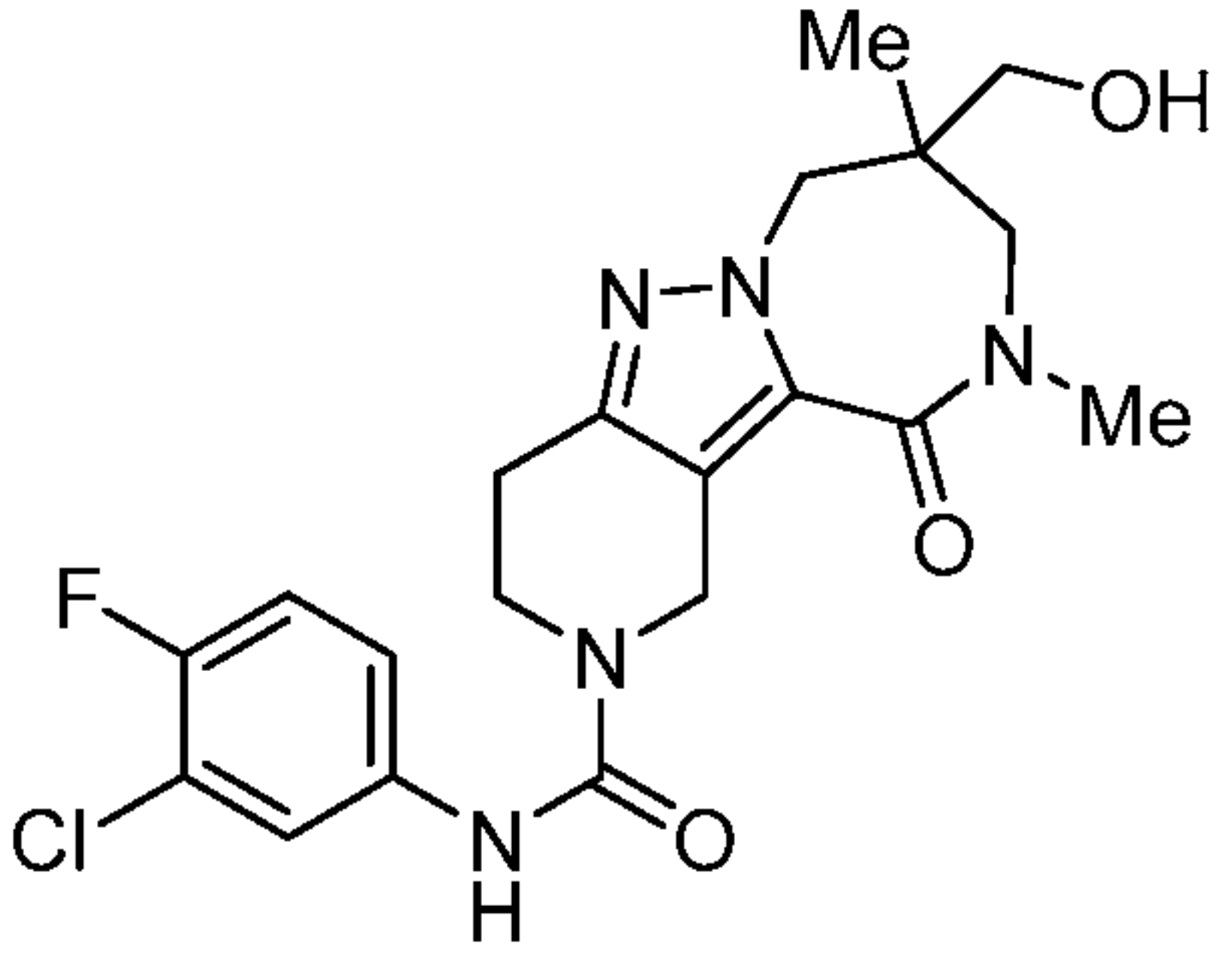
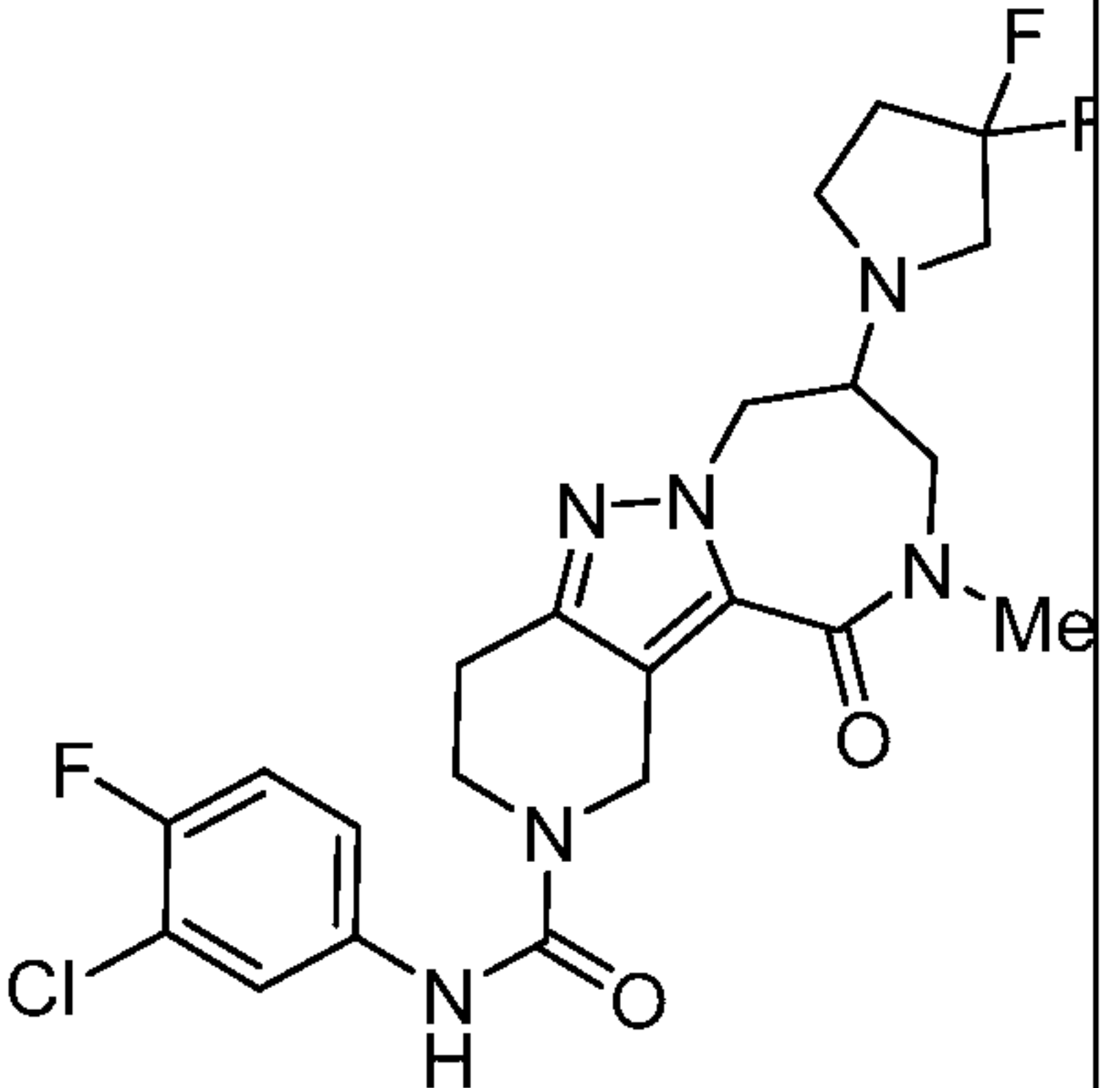
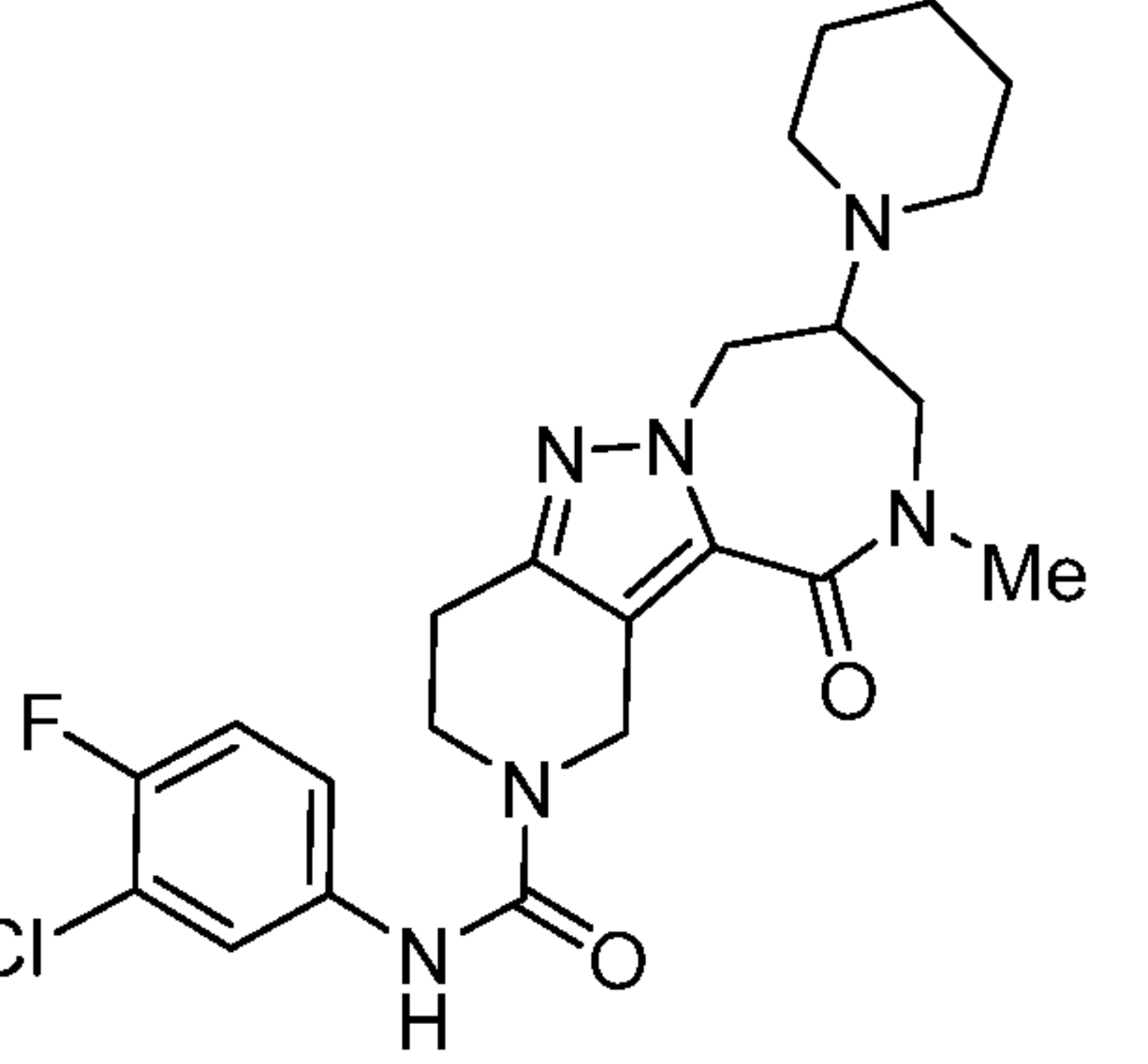
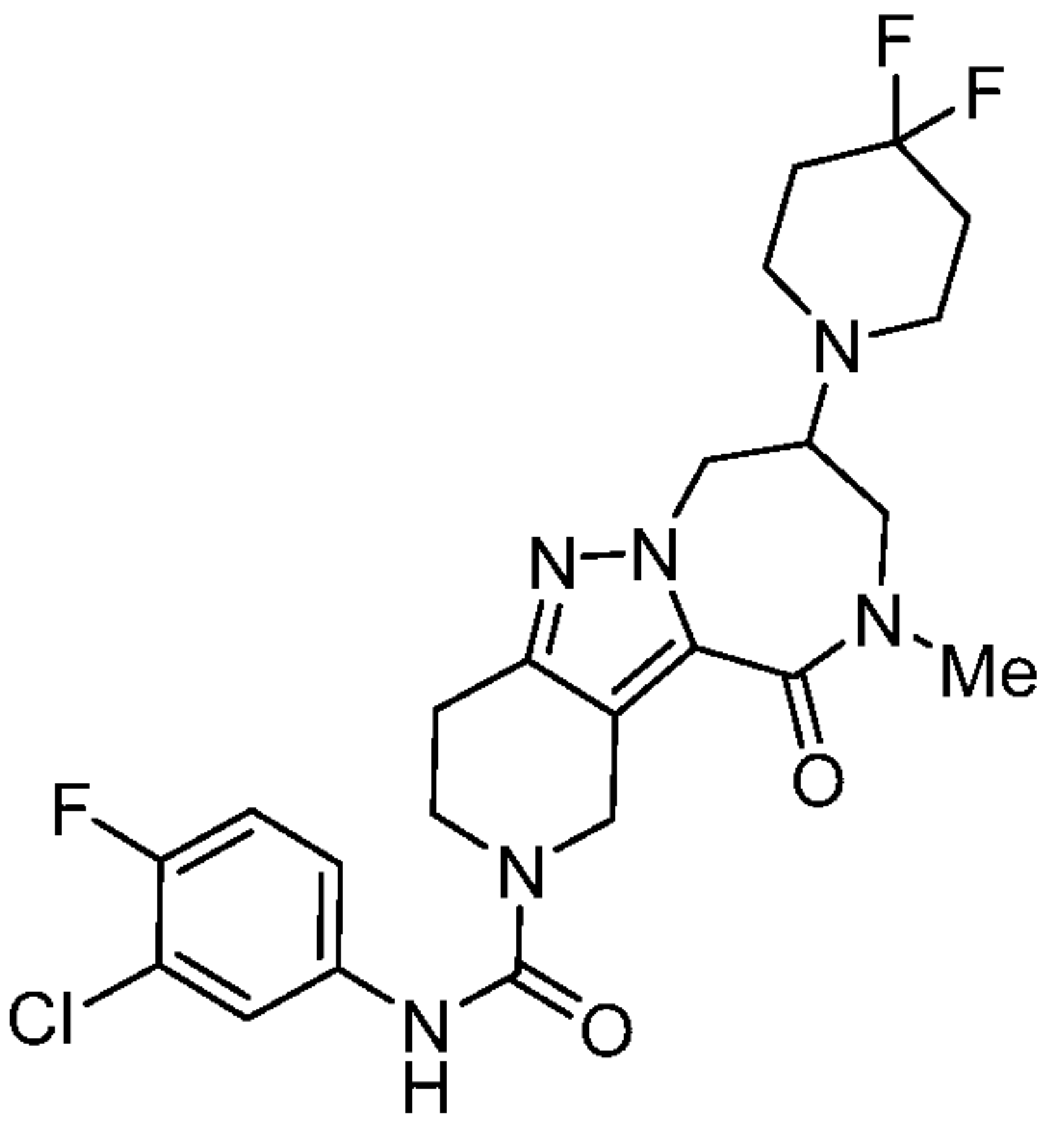
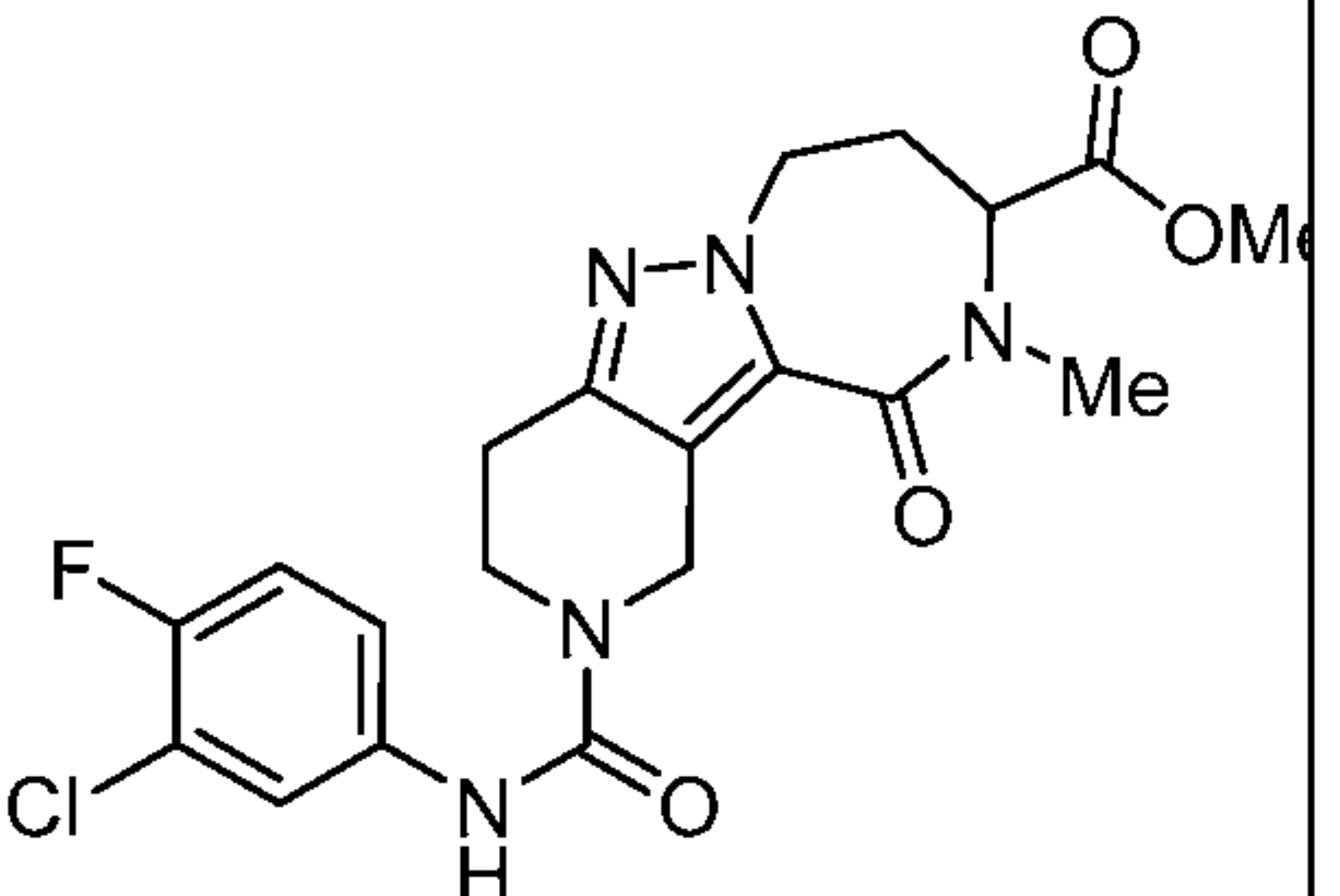
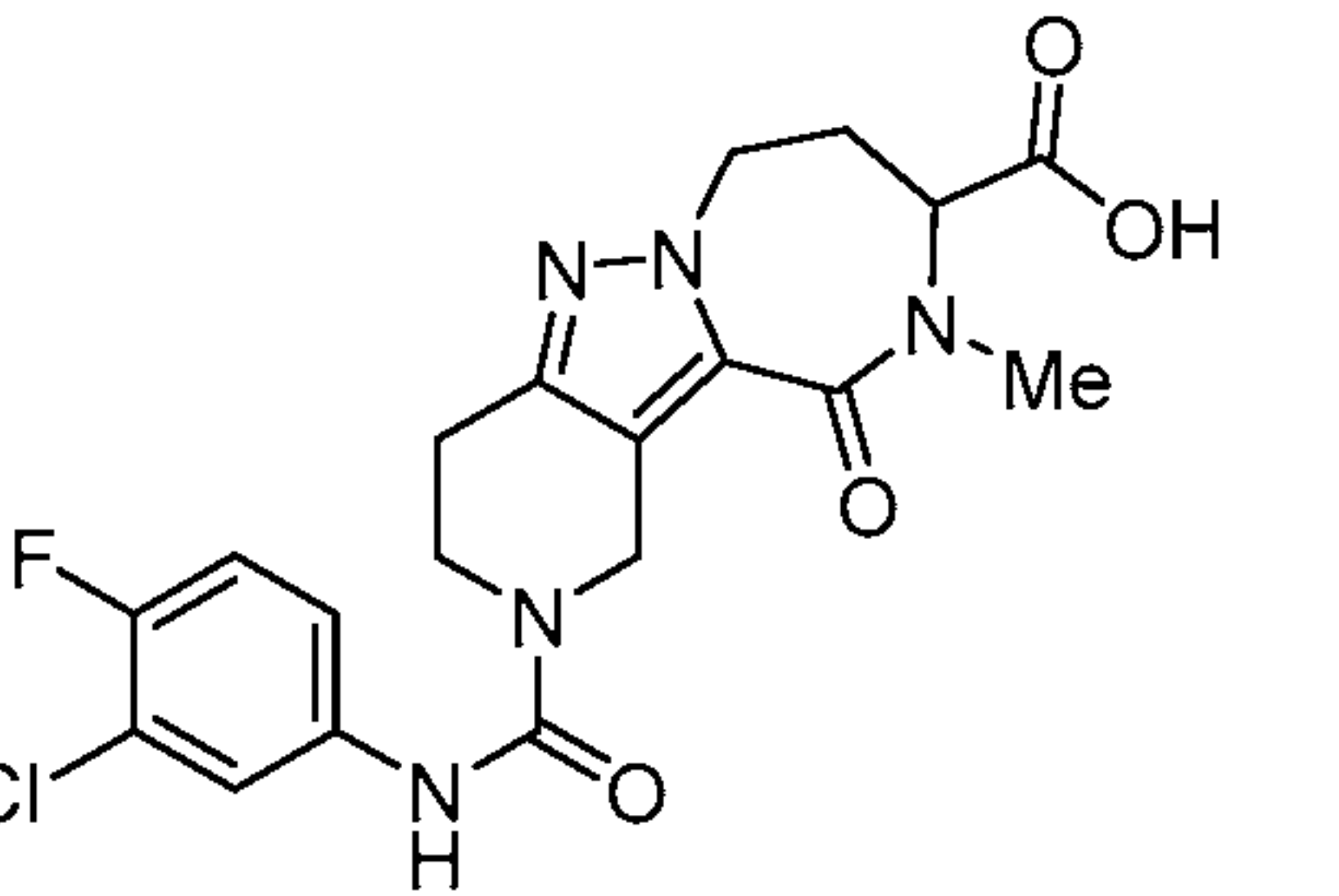
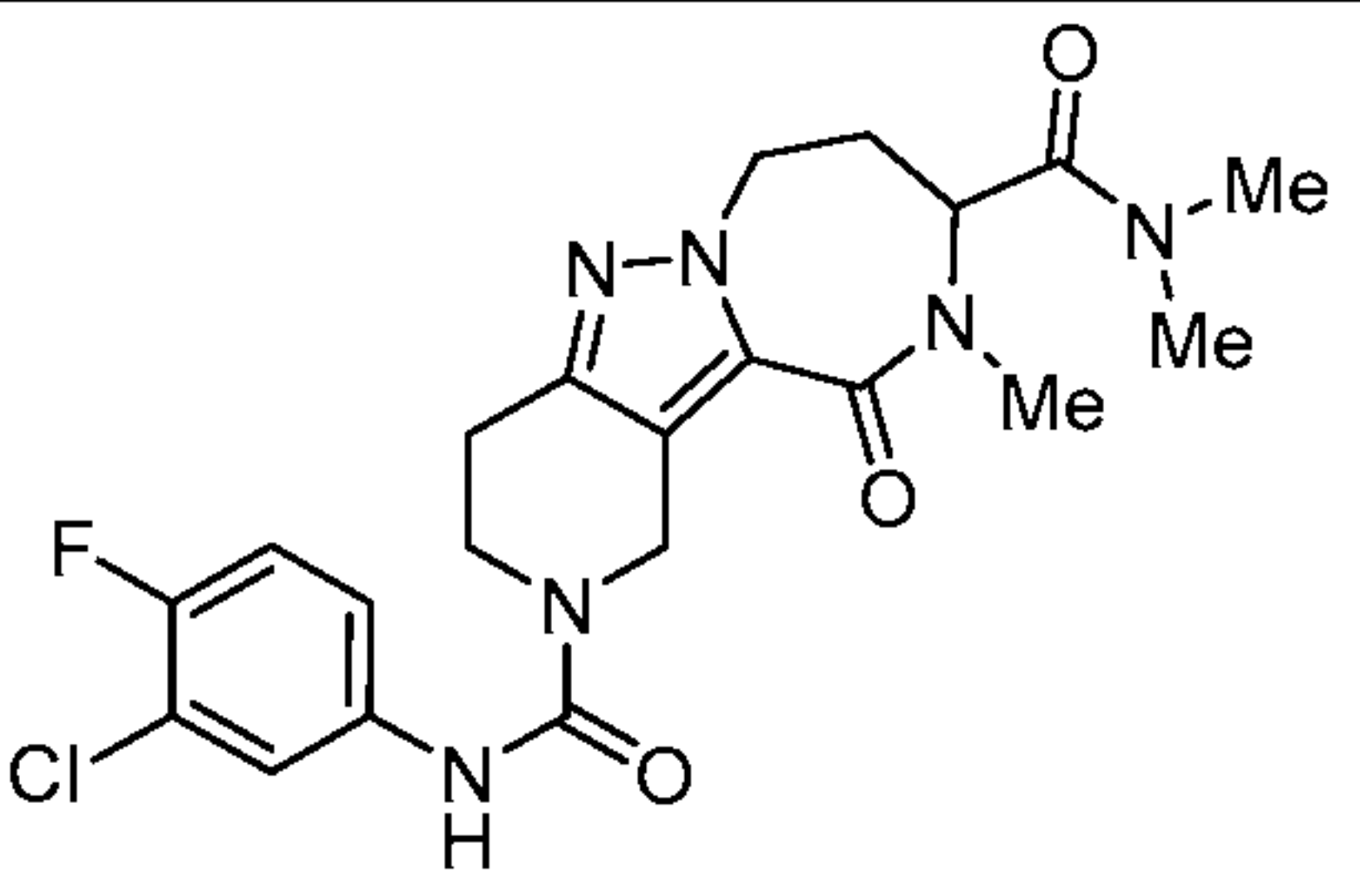
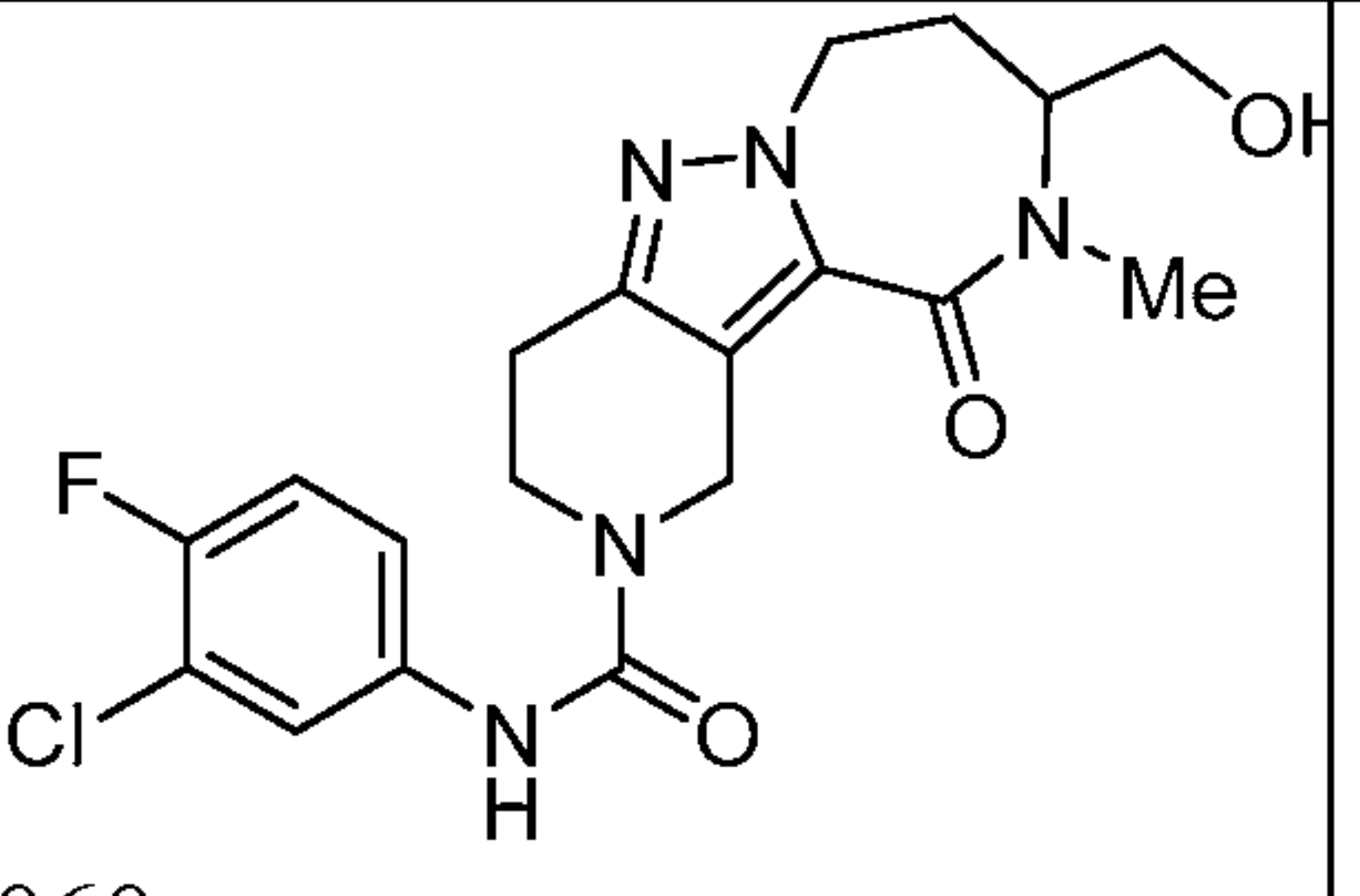
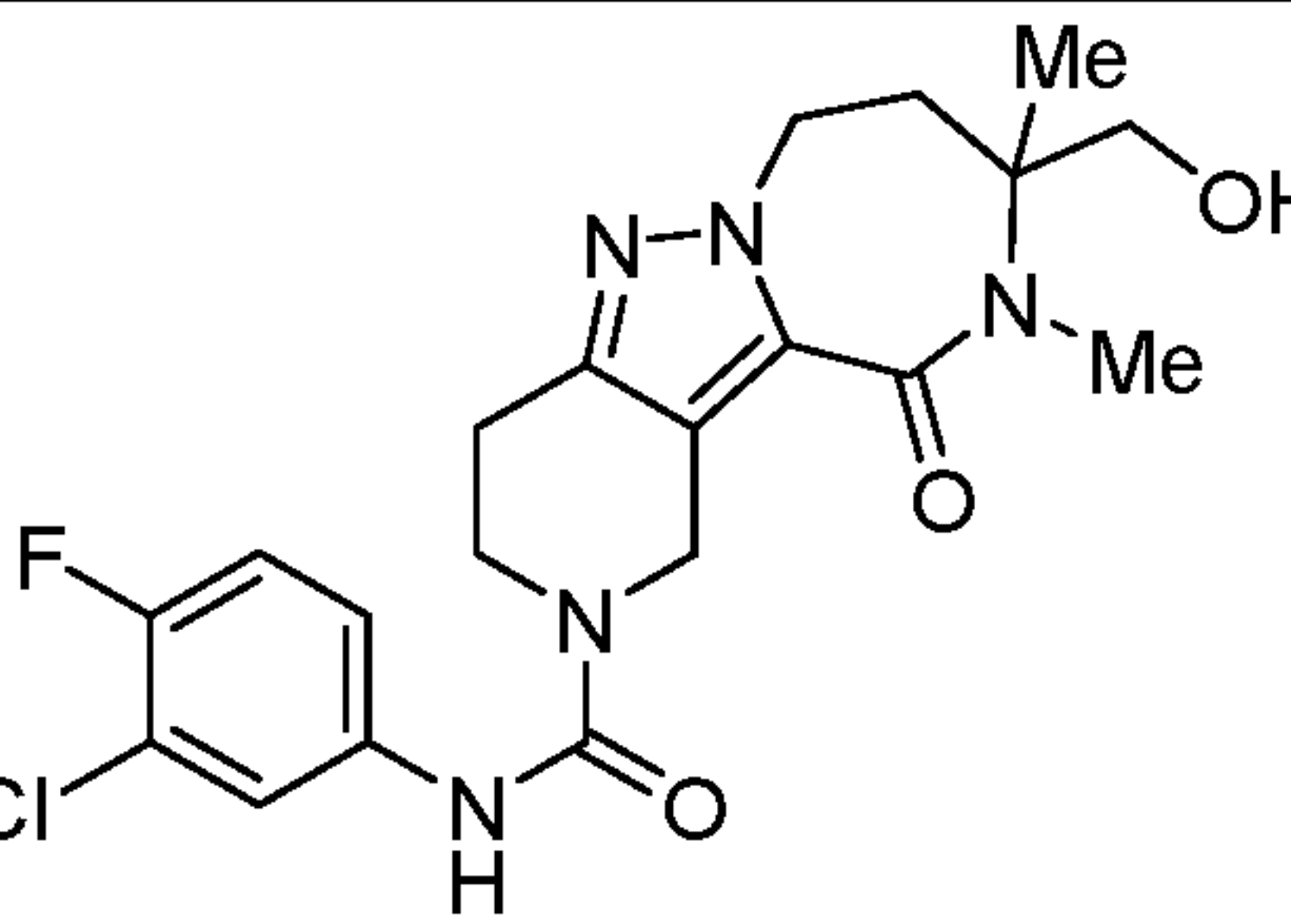
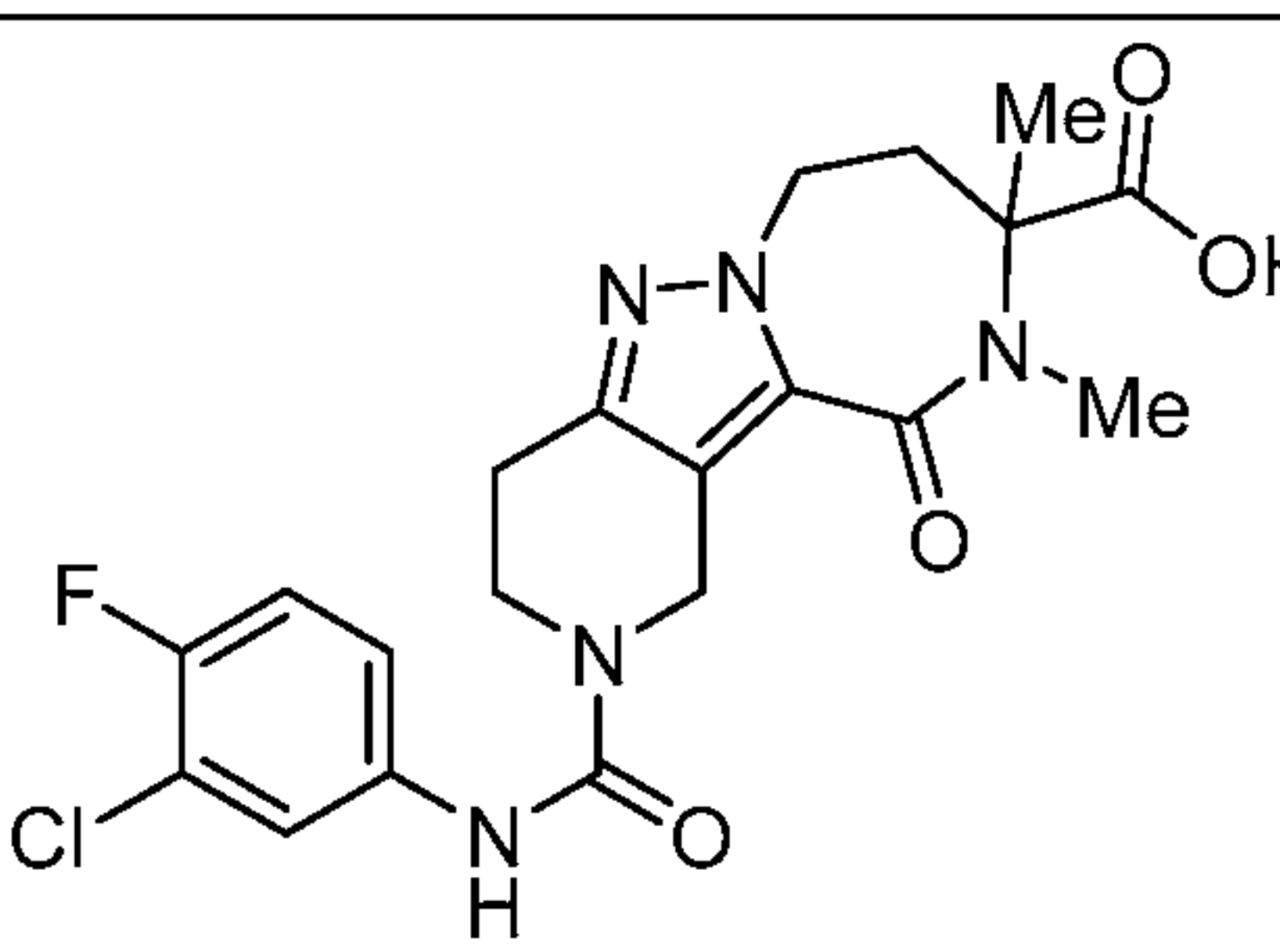
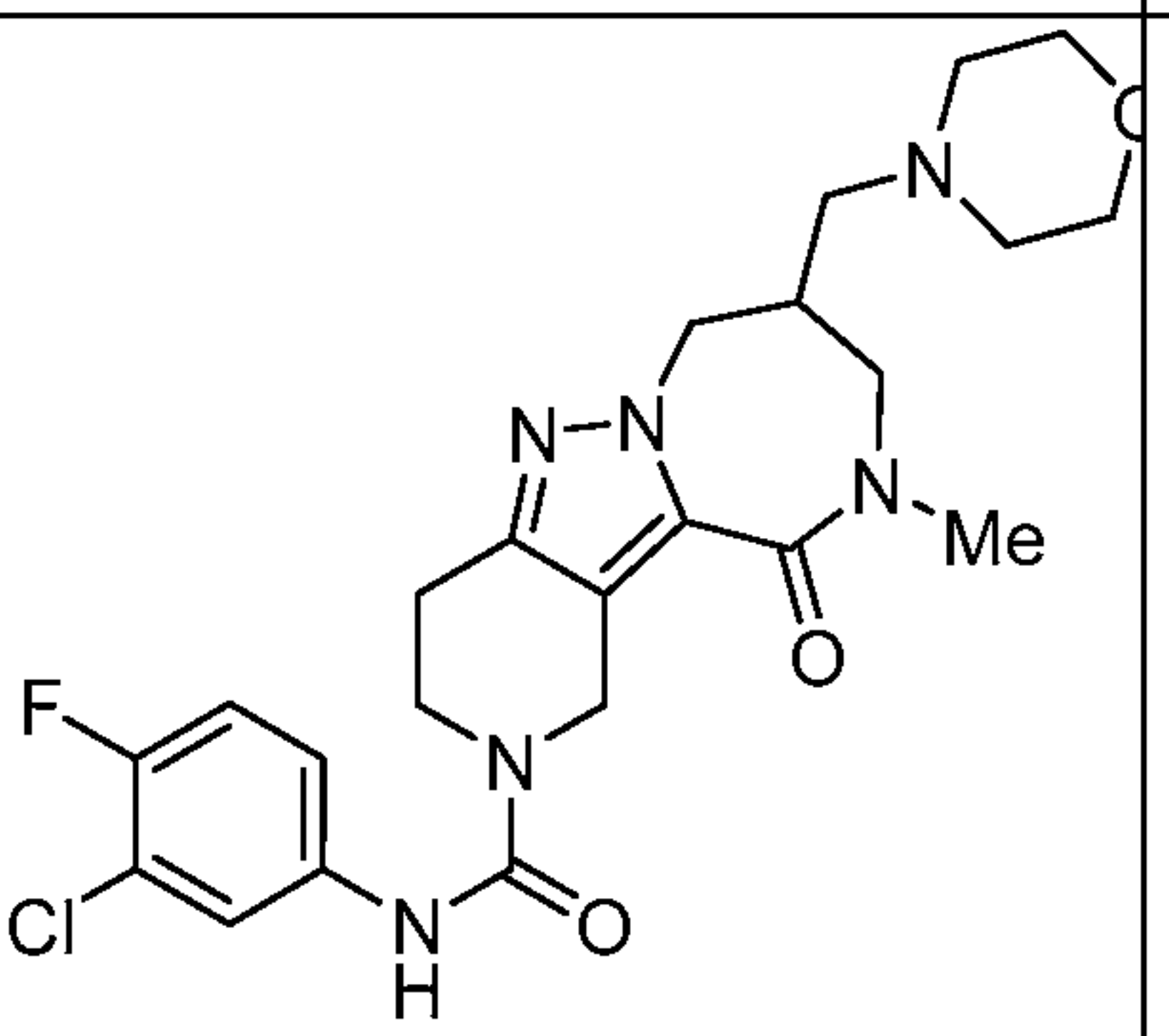
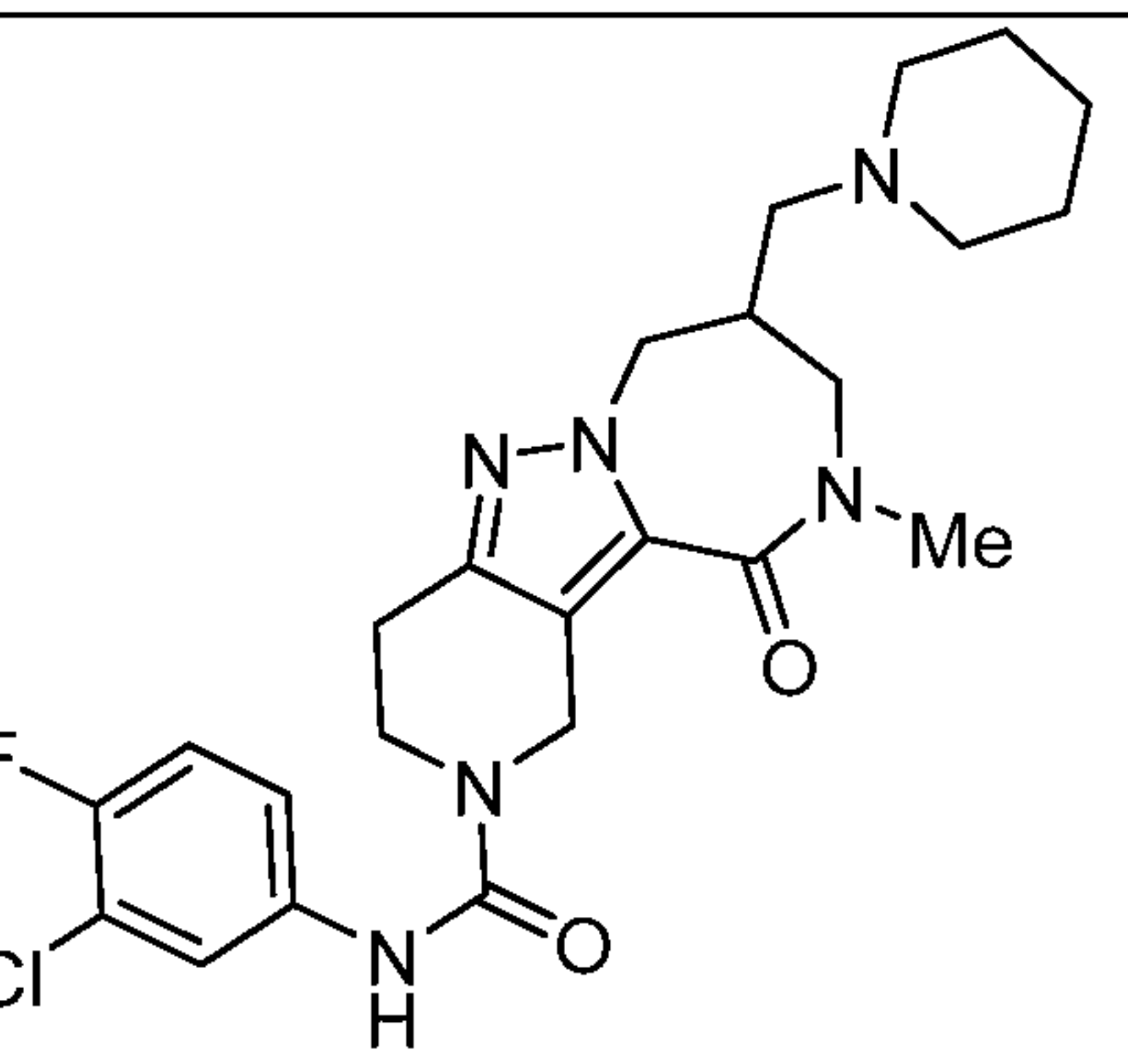
and pharmaceutically acceptable salts thereof.

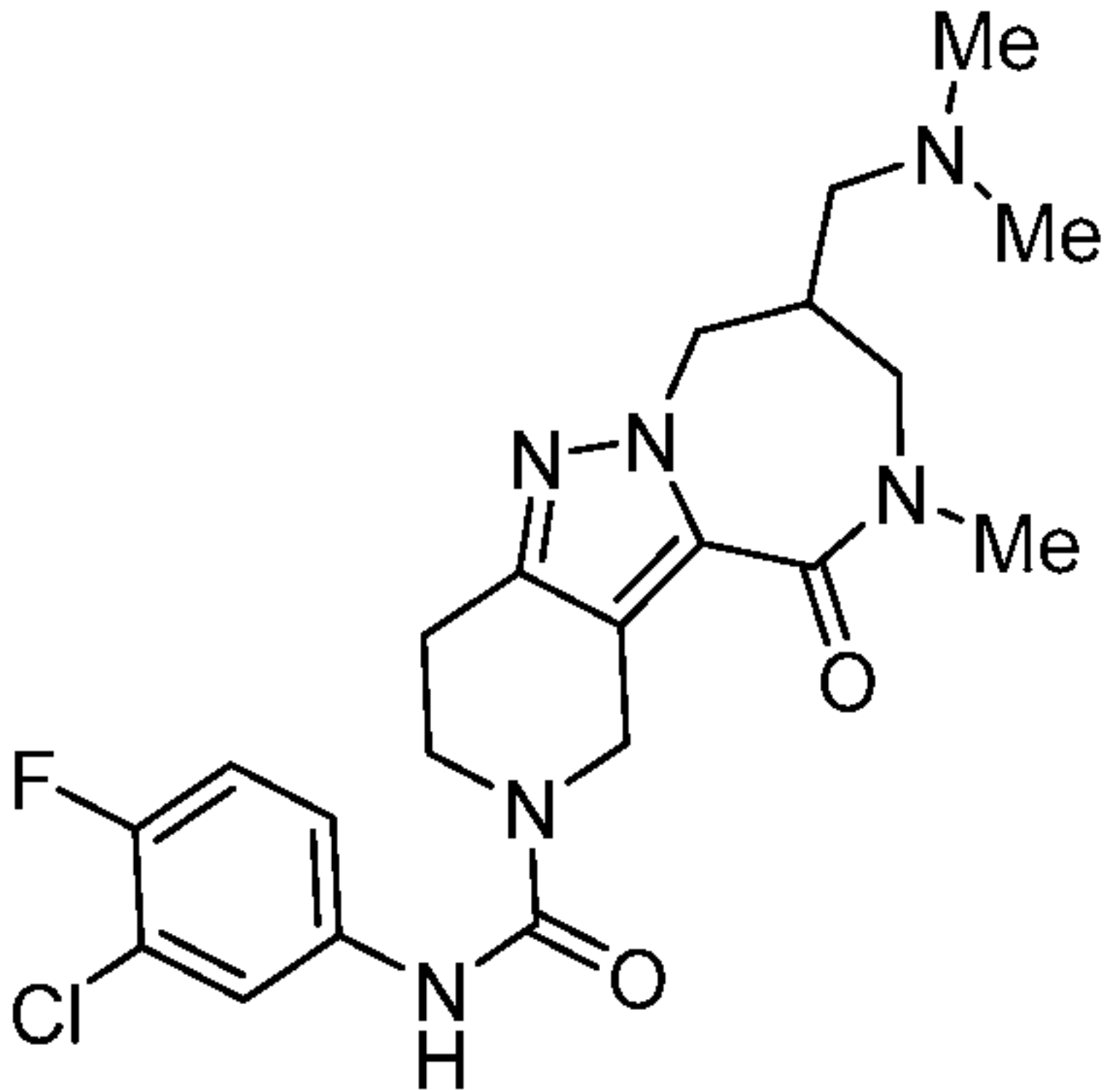
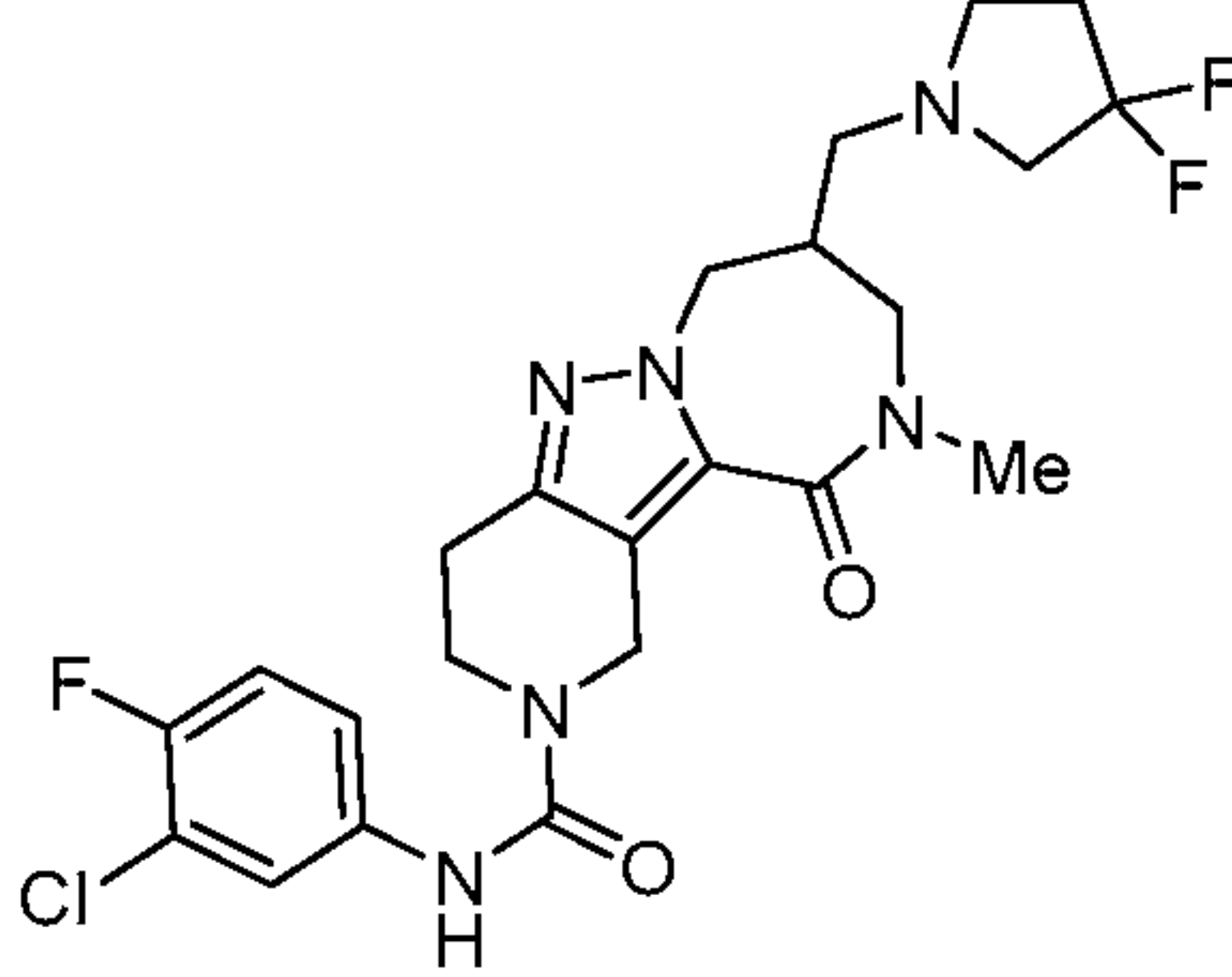
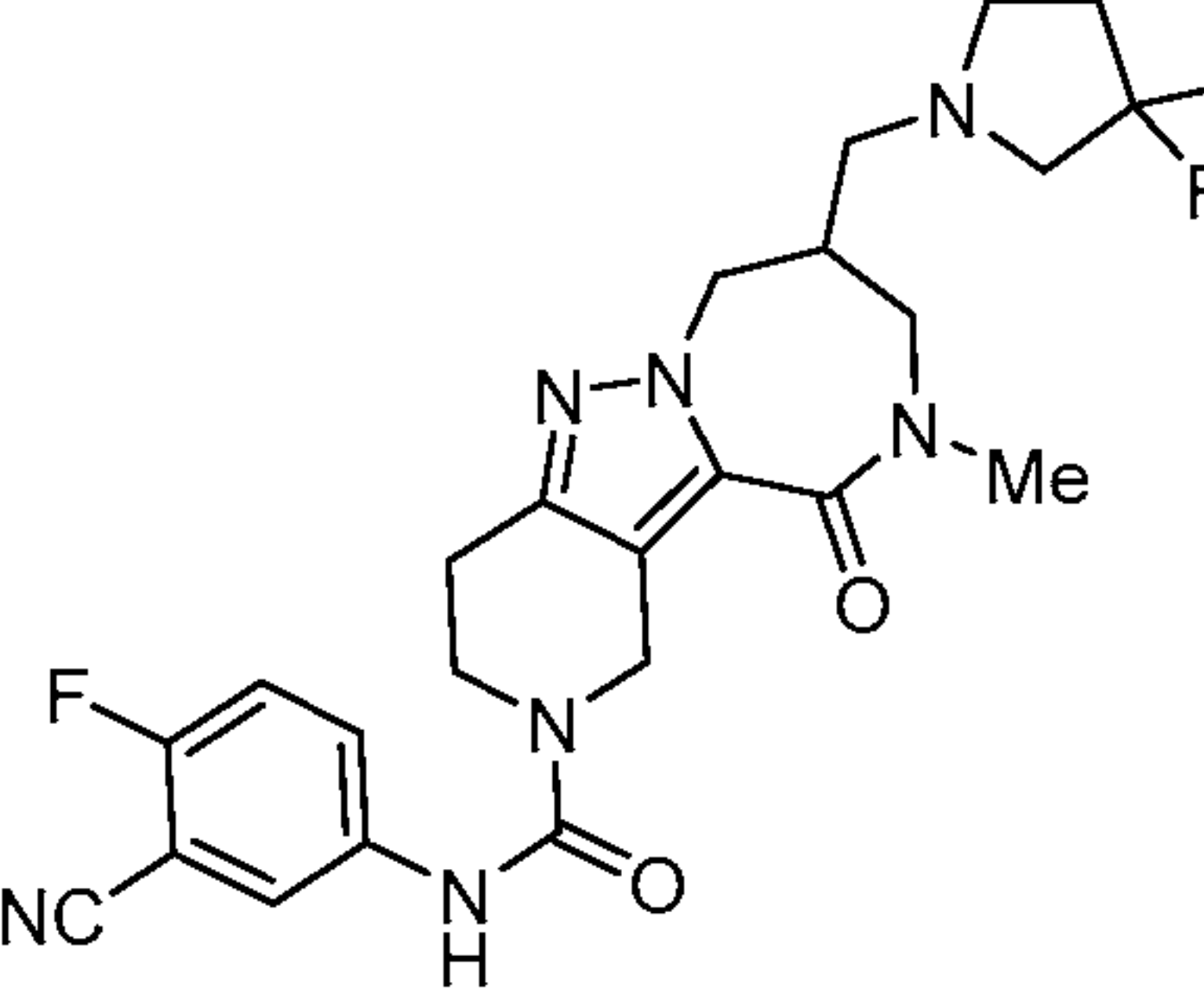
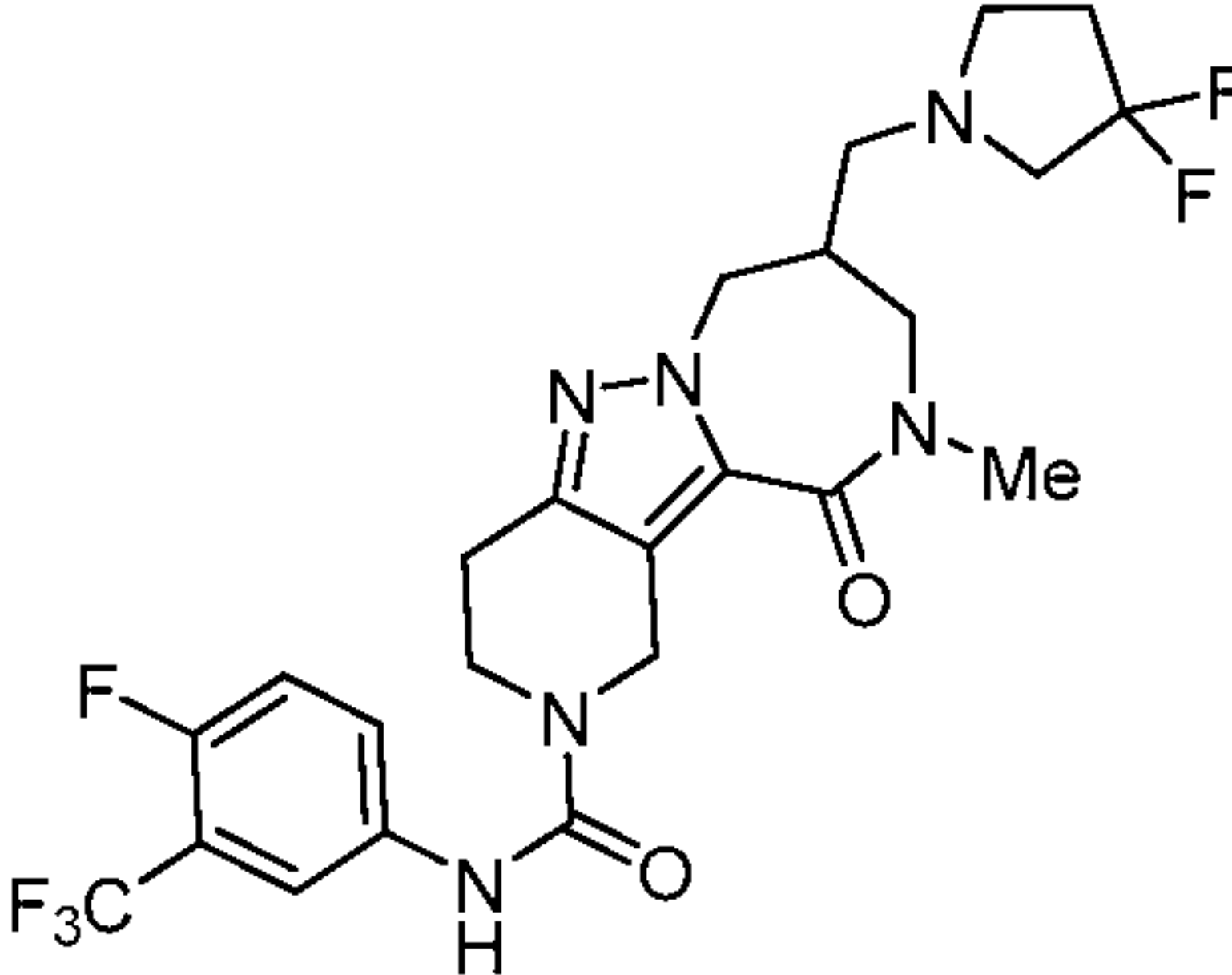
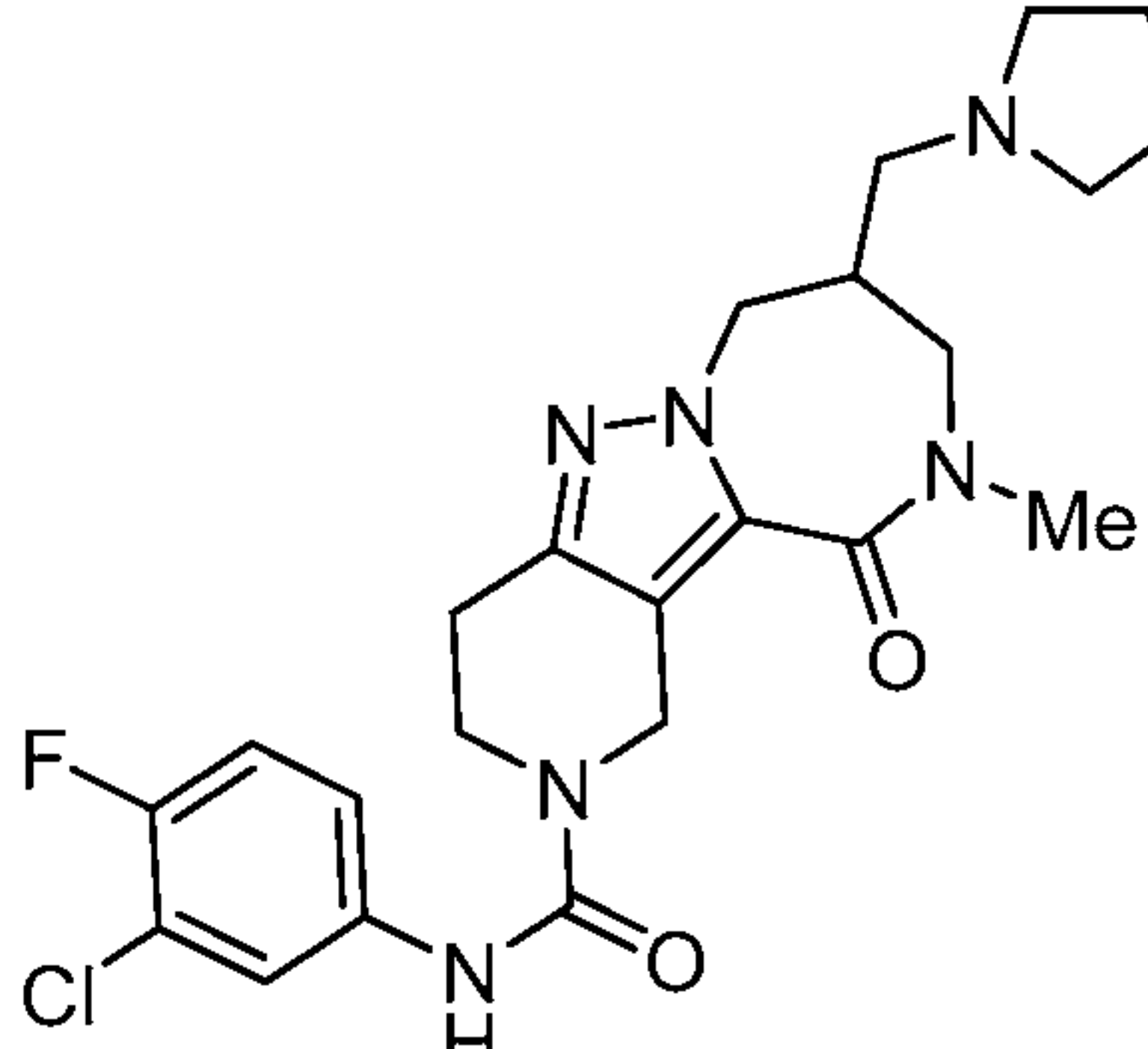
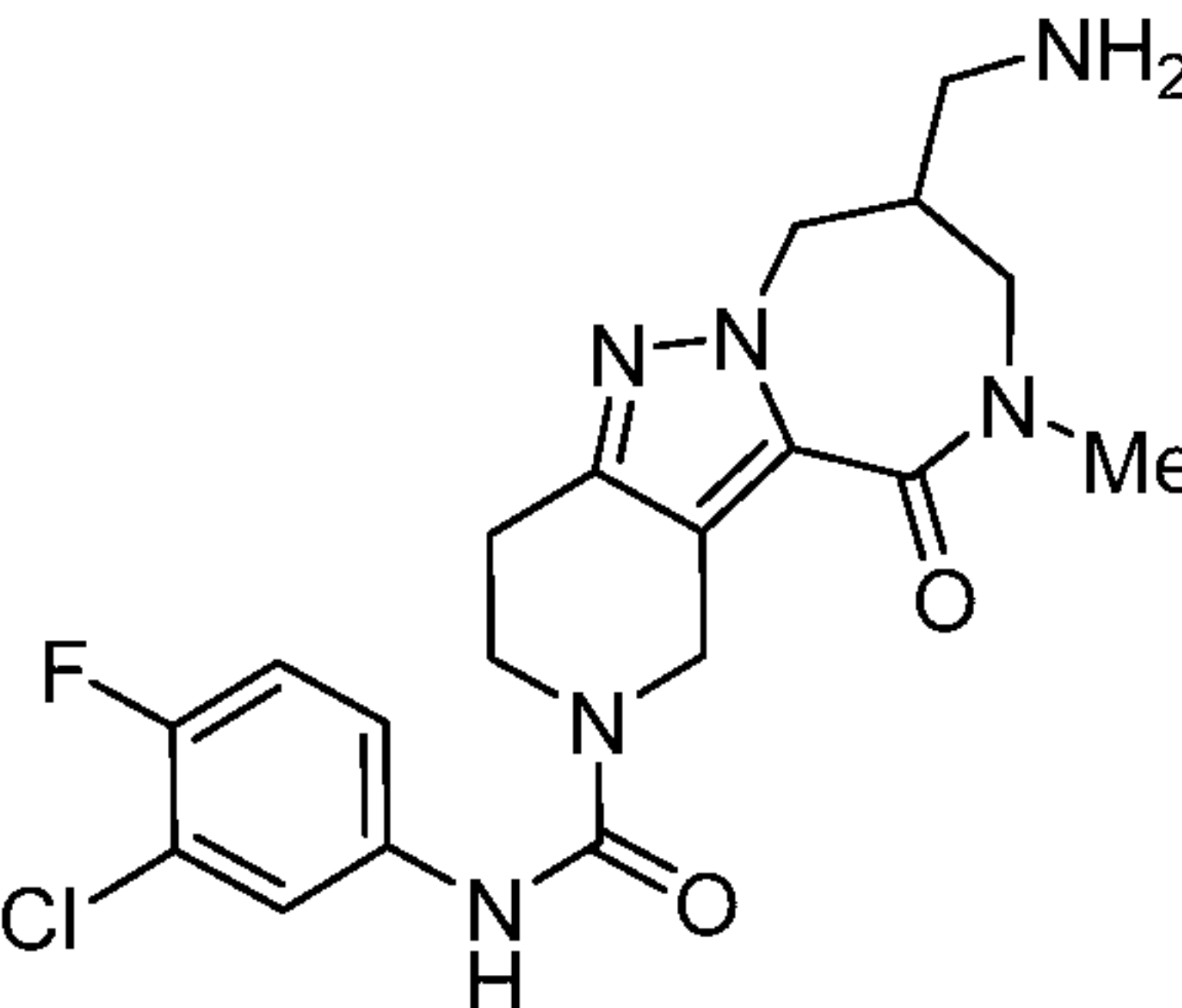
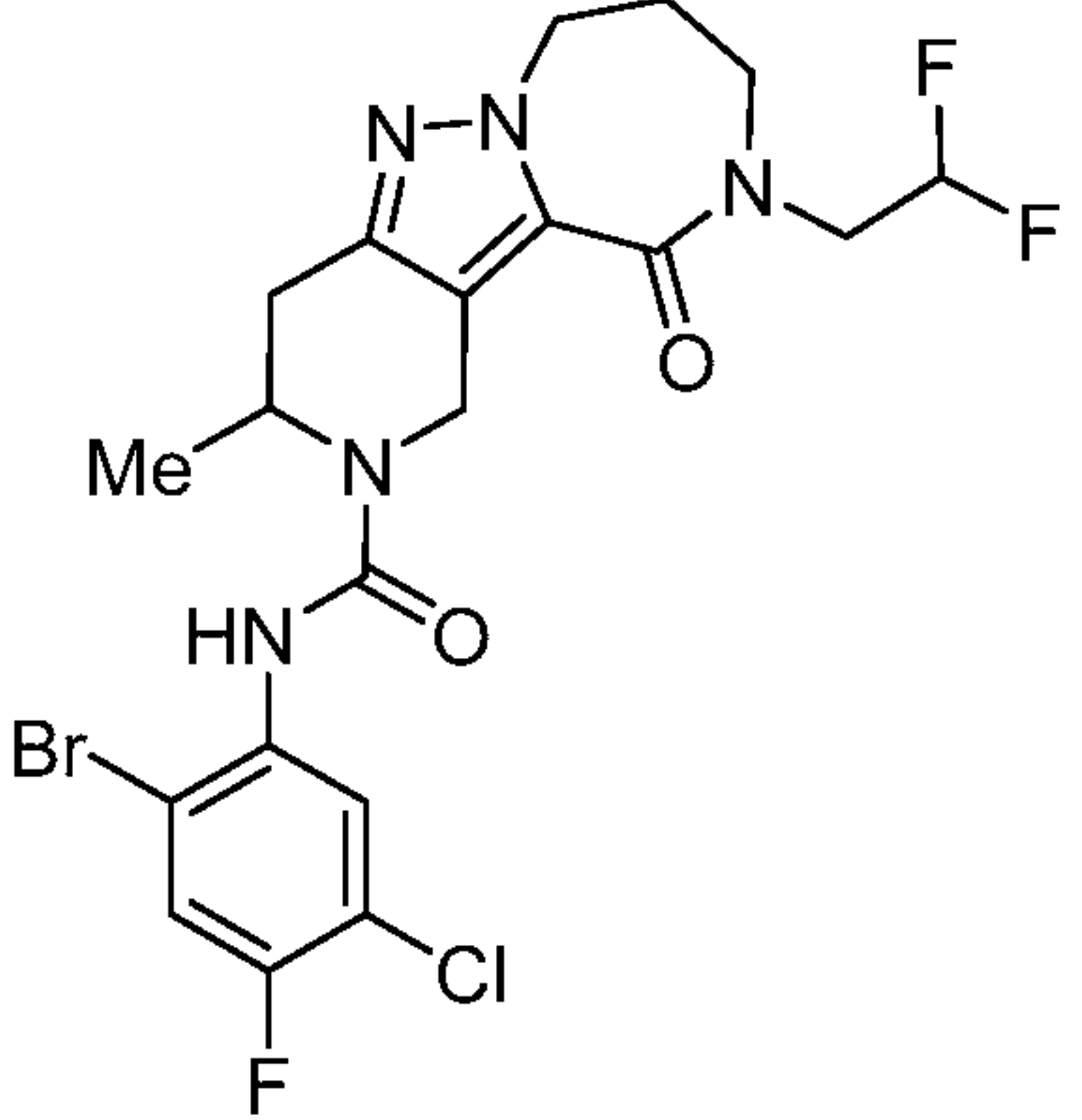
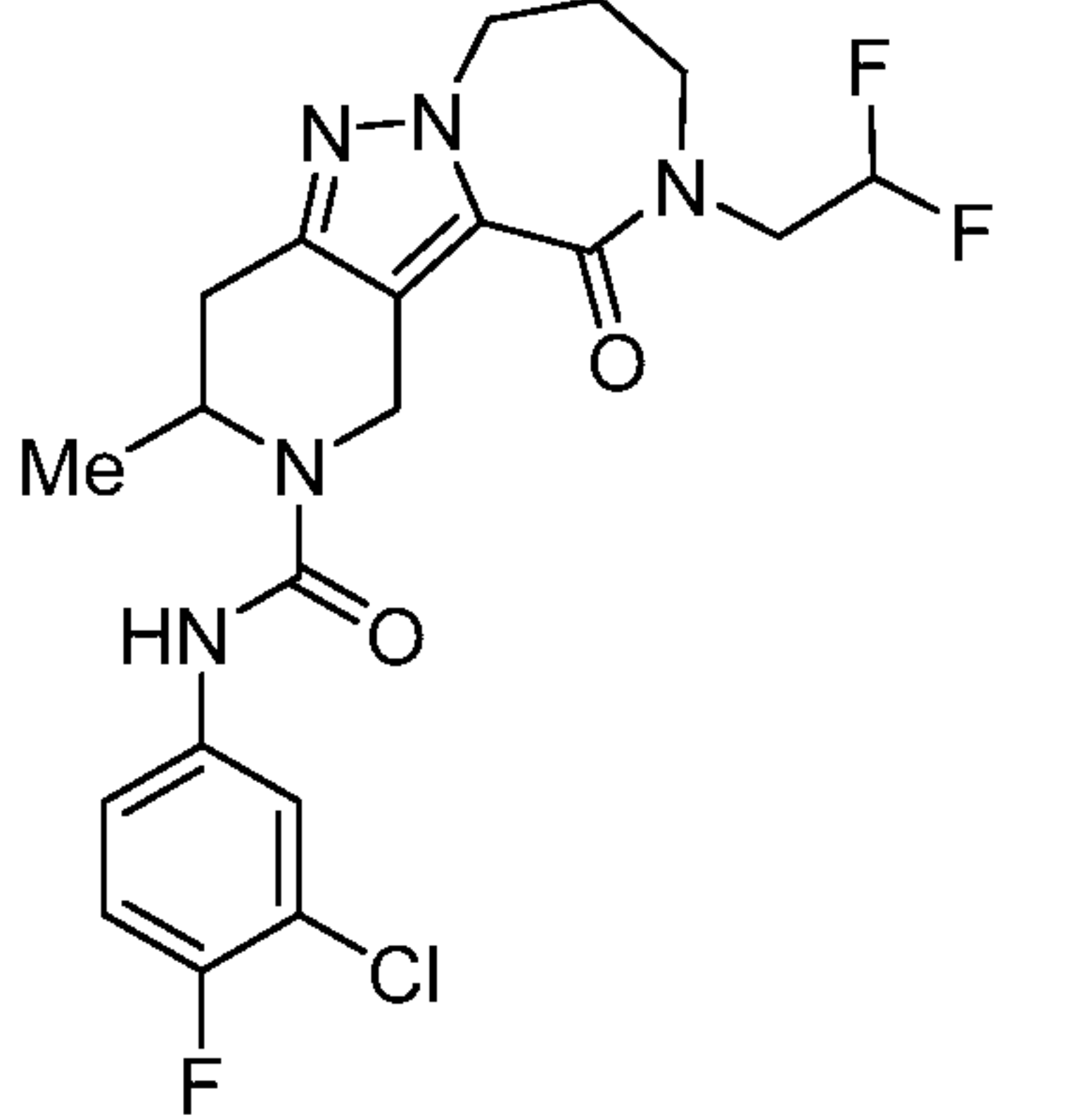
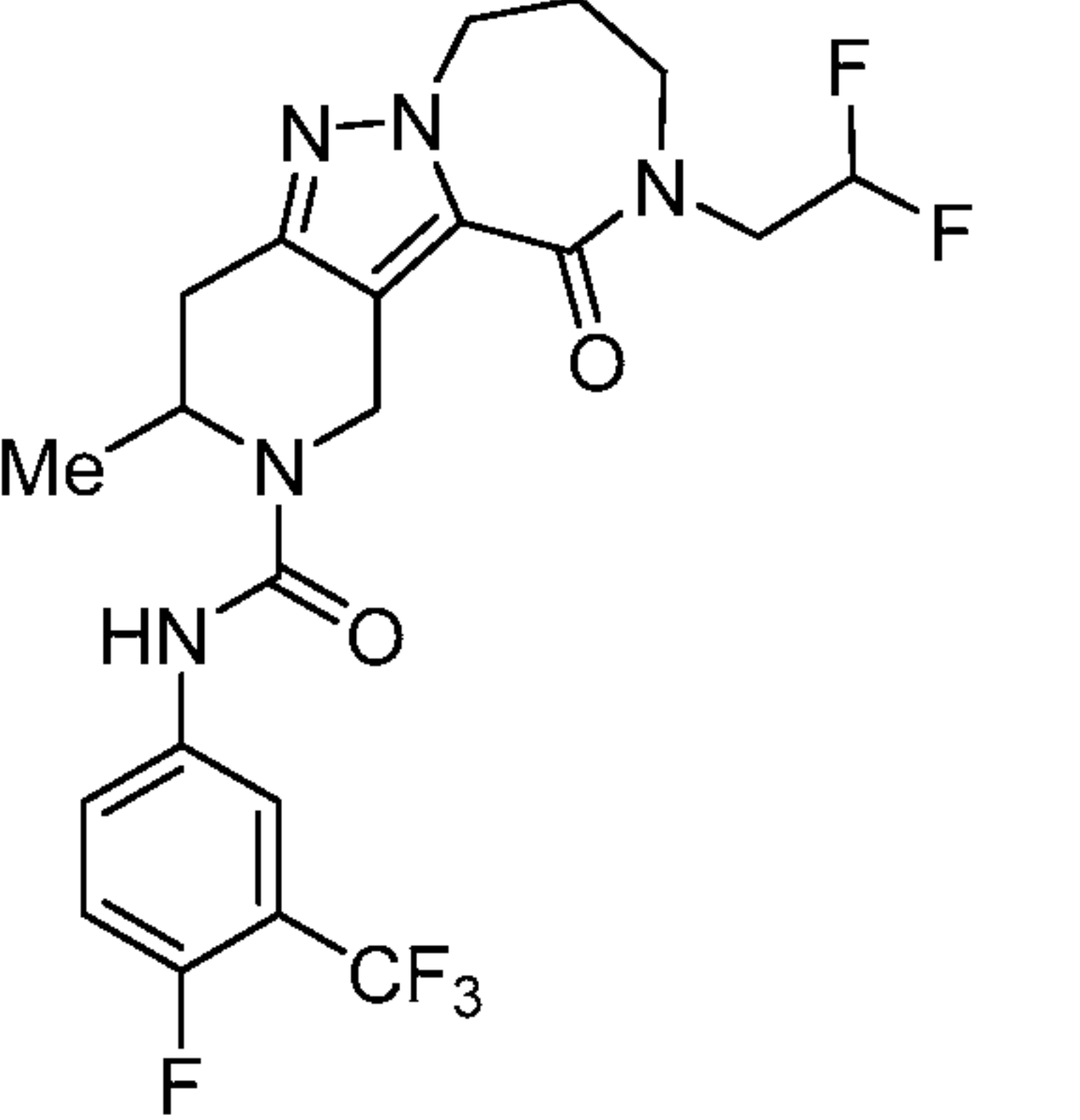
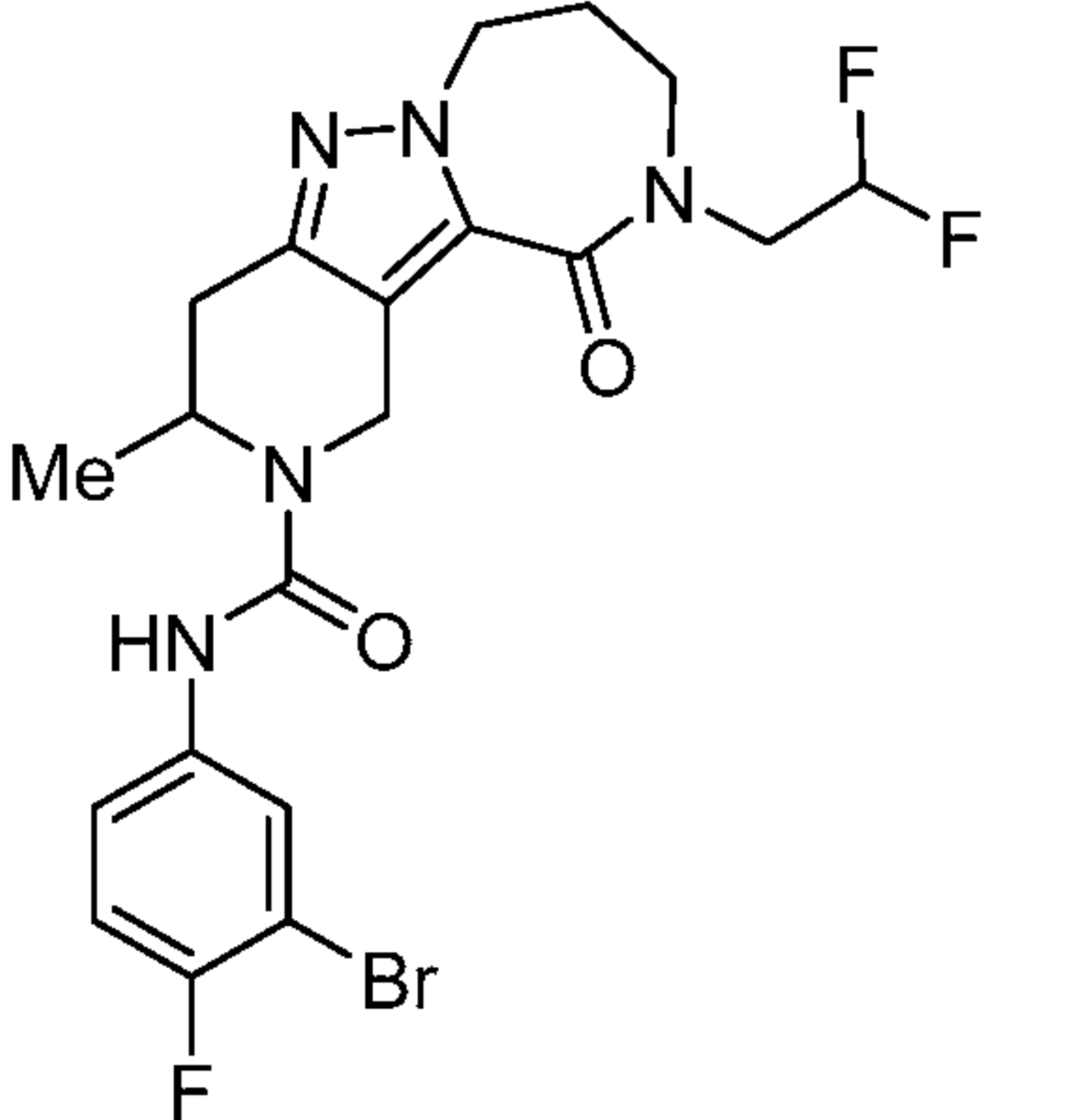
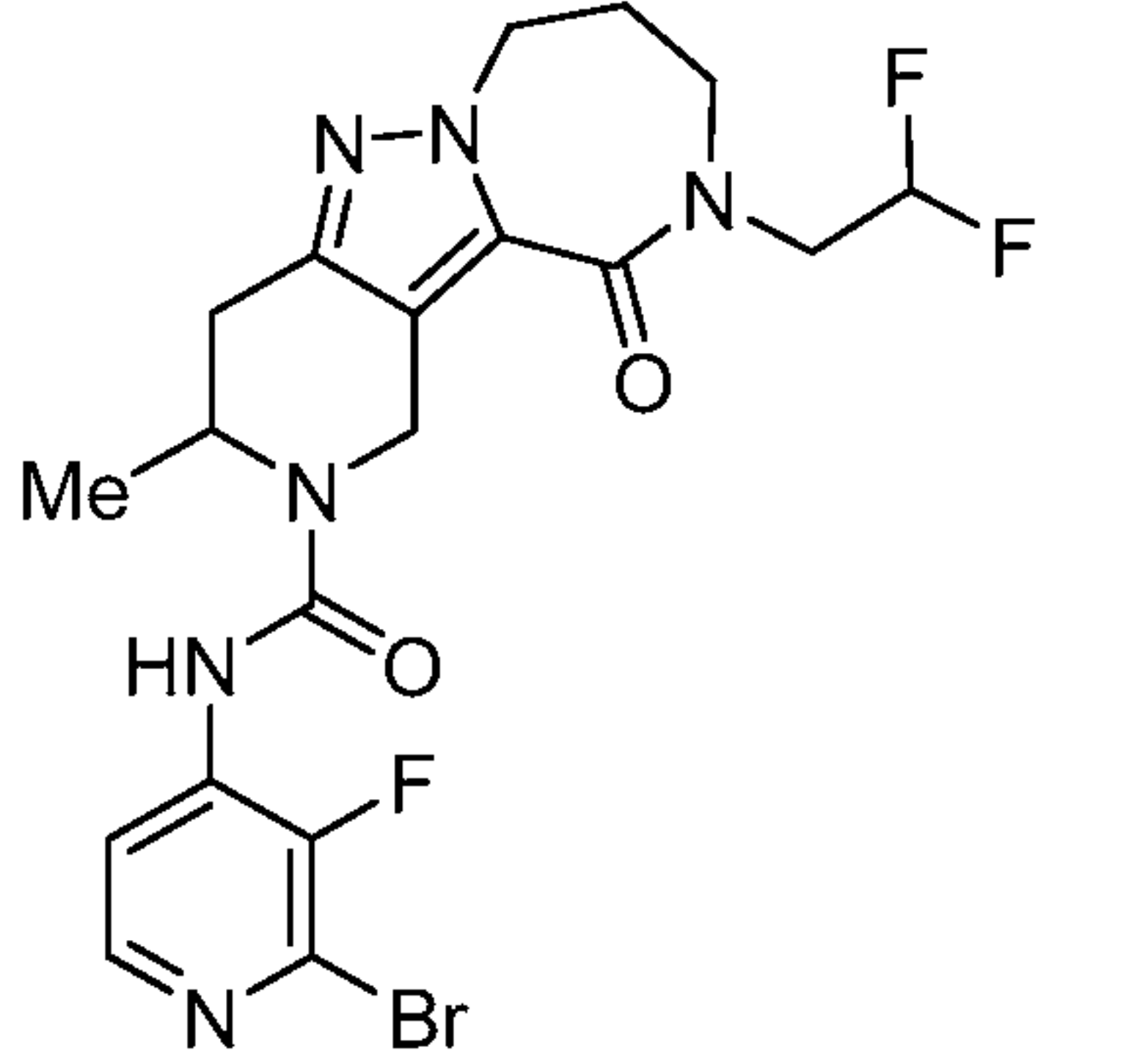
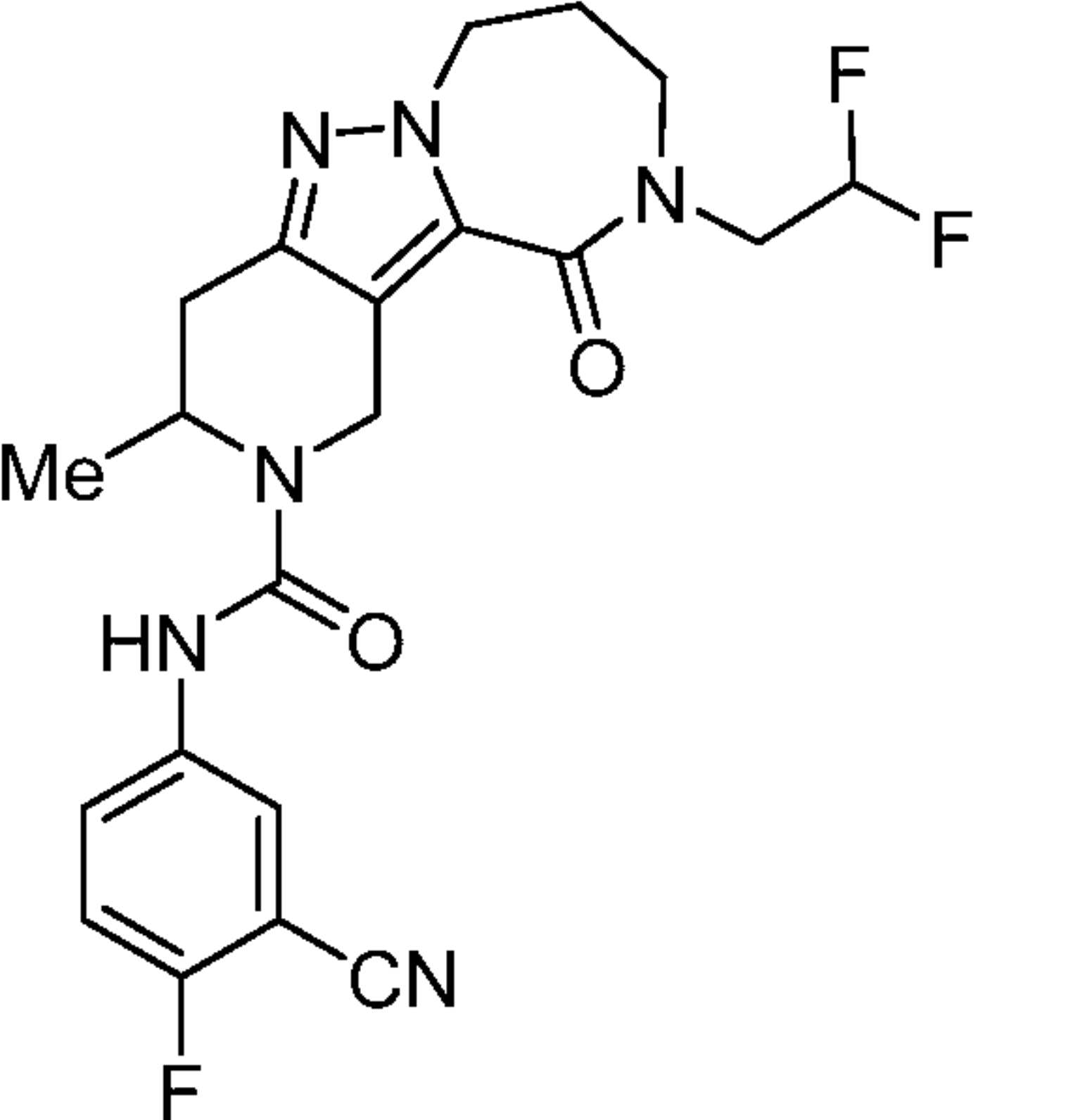
Certain embodiments of Formulas I, II, III and IV are shown below in **Table 2**.

disclosed compounds.

5 **Table 2.**

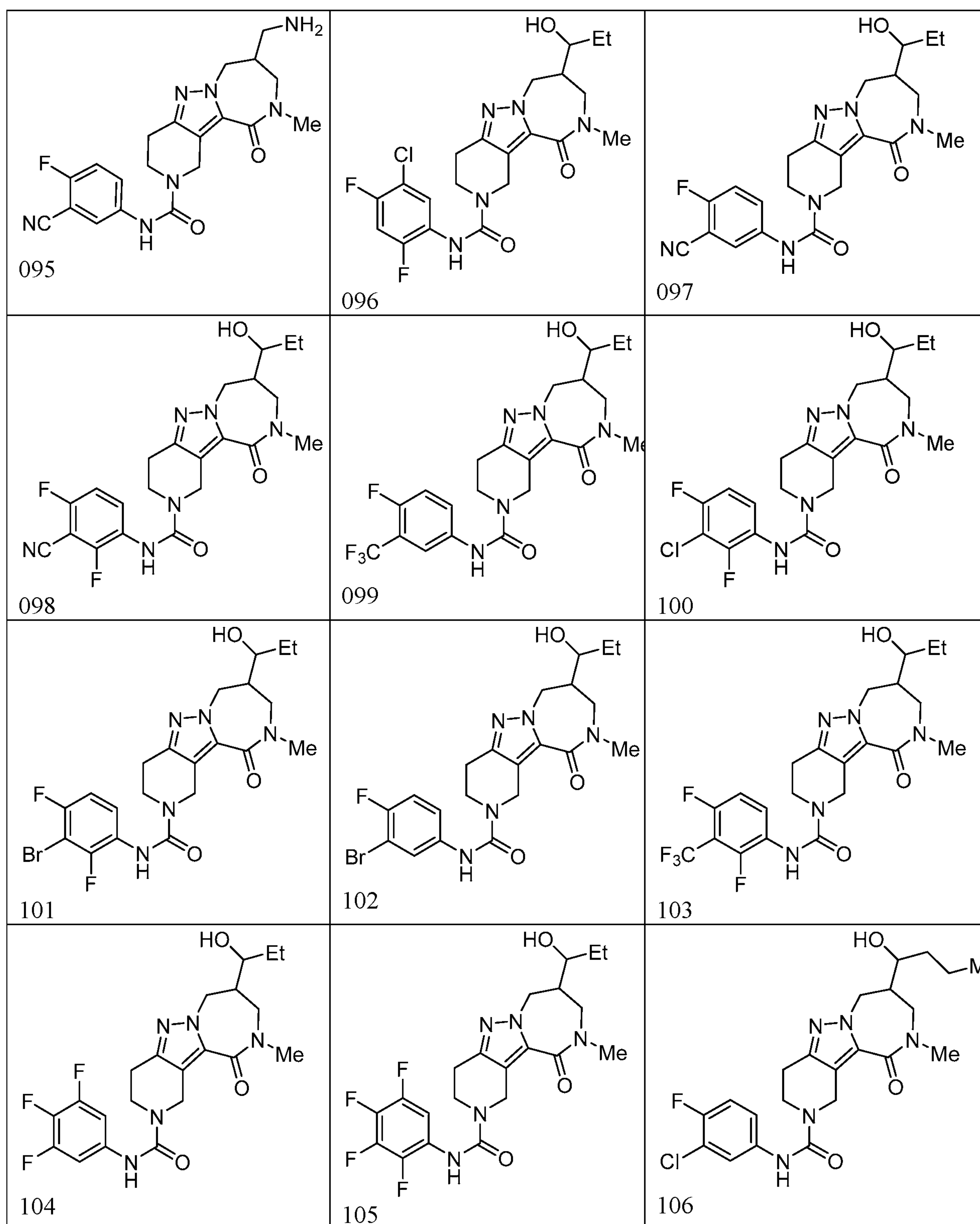
 <p>047</p>	 <p>048</p>	 <p>049</p>
 <p>050</p>	 <p>051</p>	 <p>052</p>

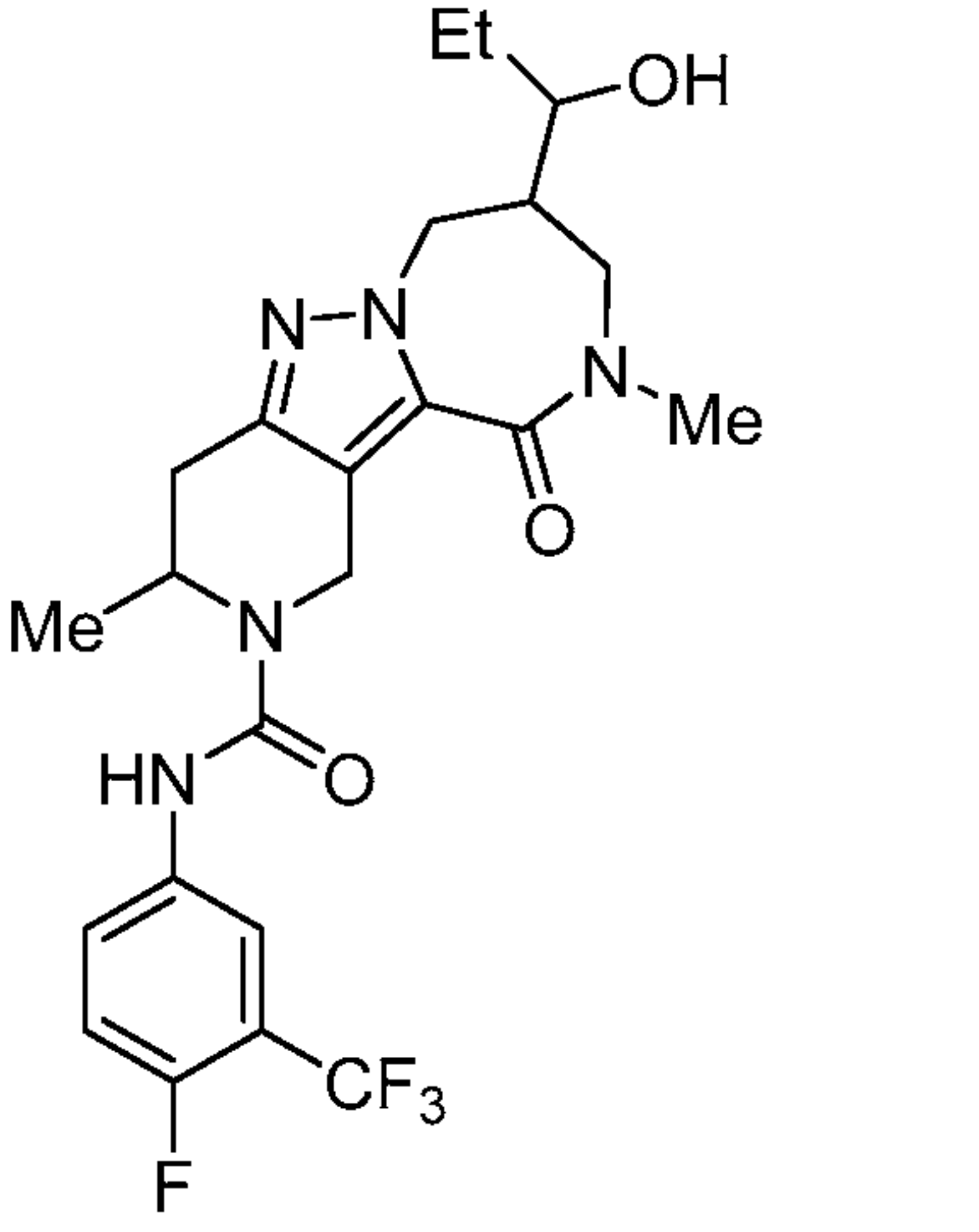
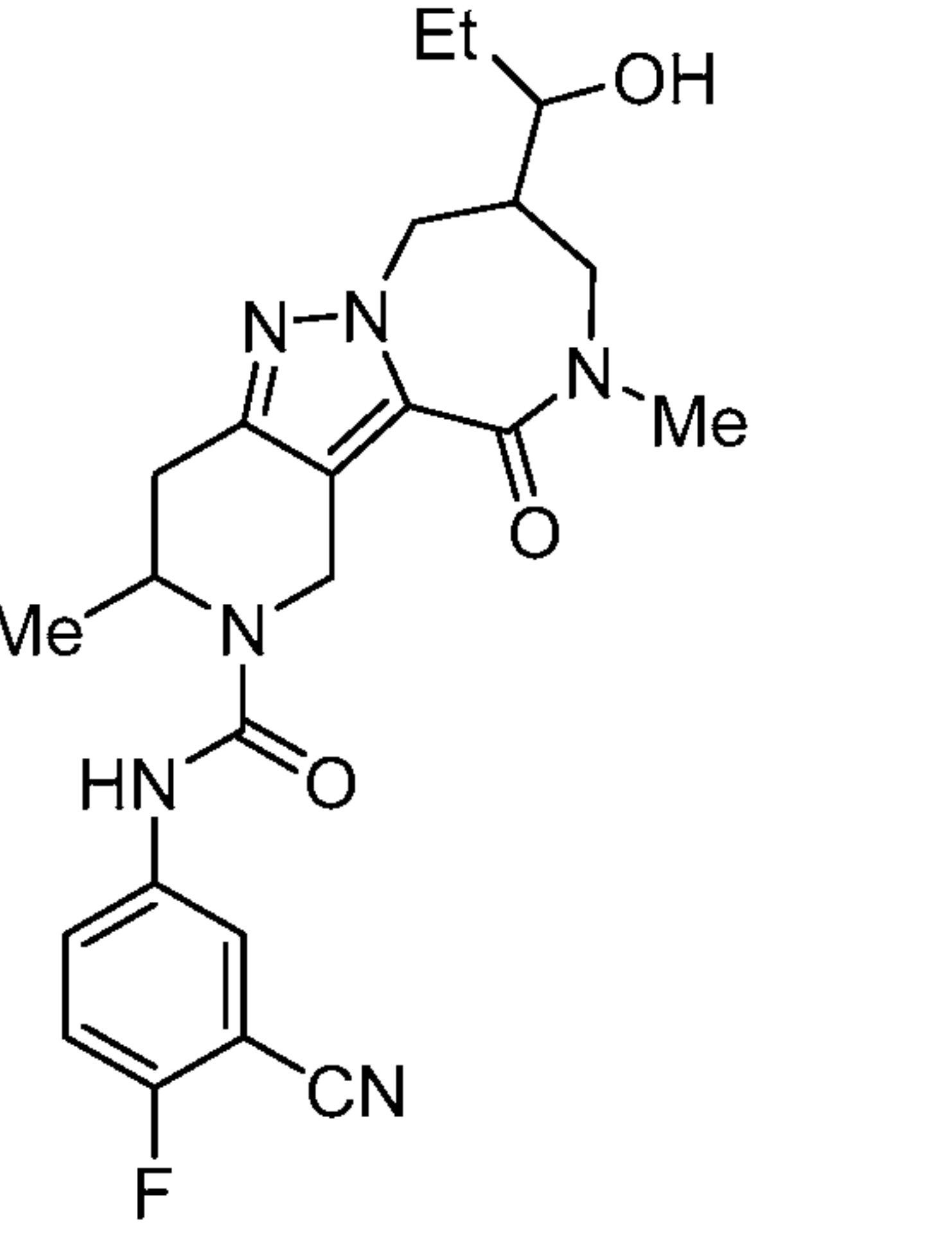
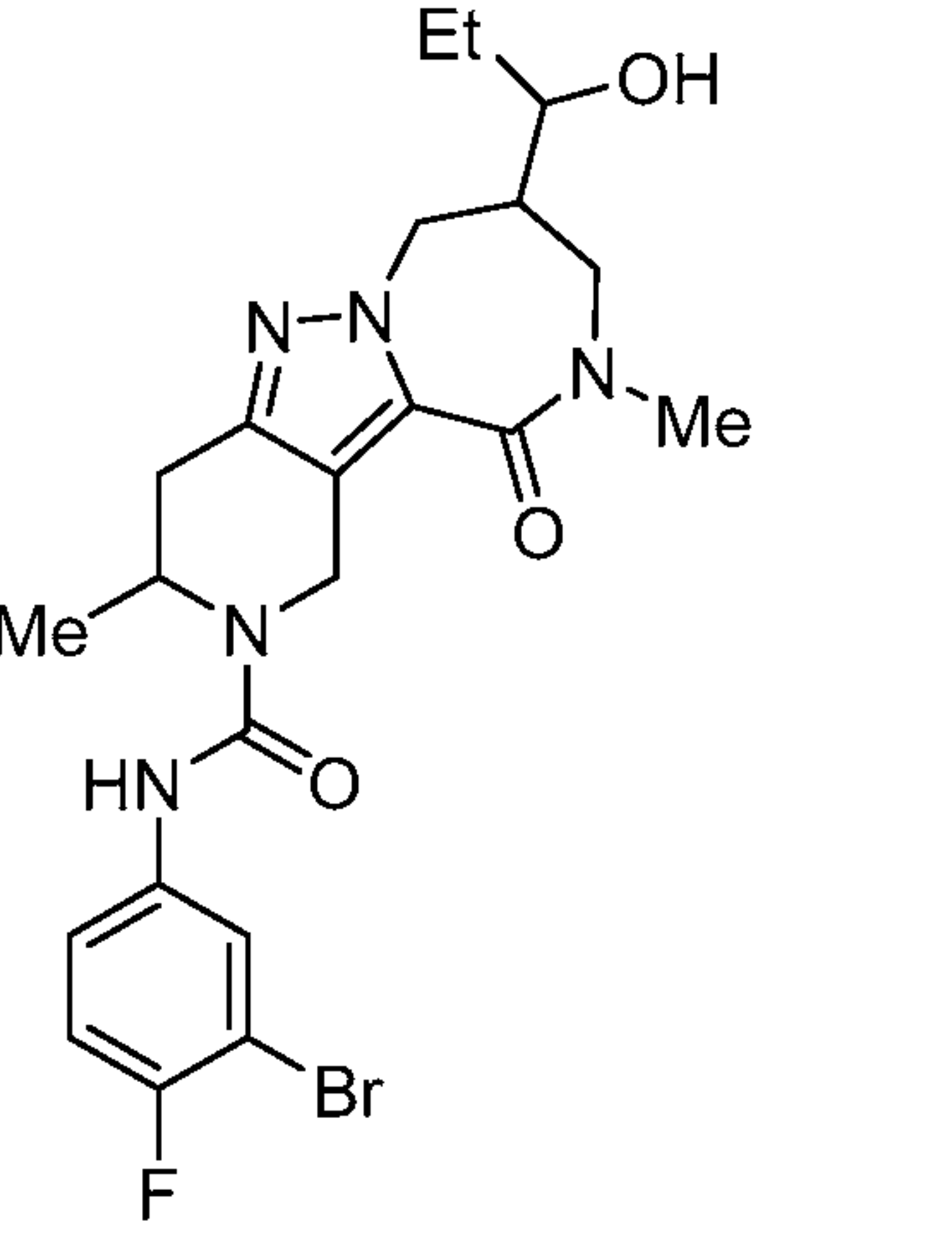
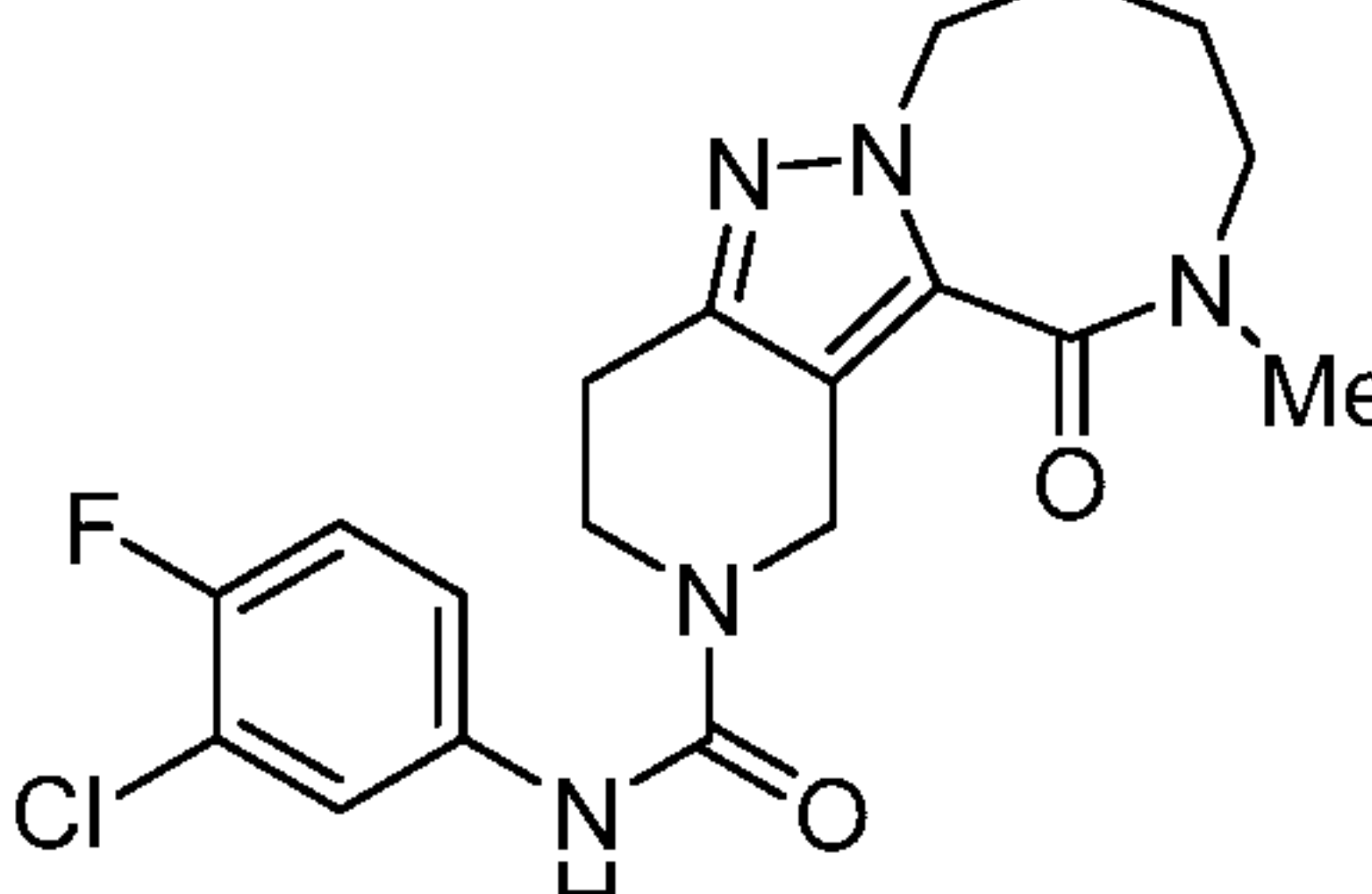
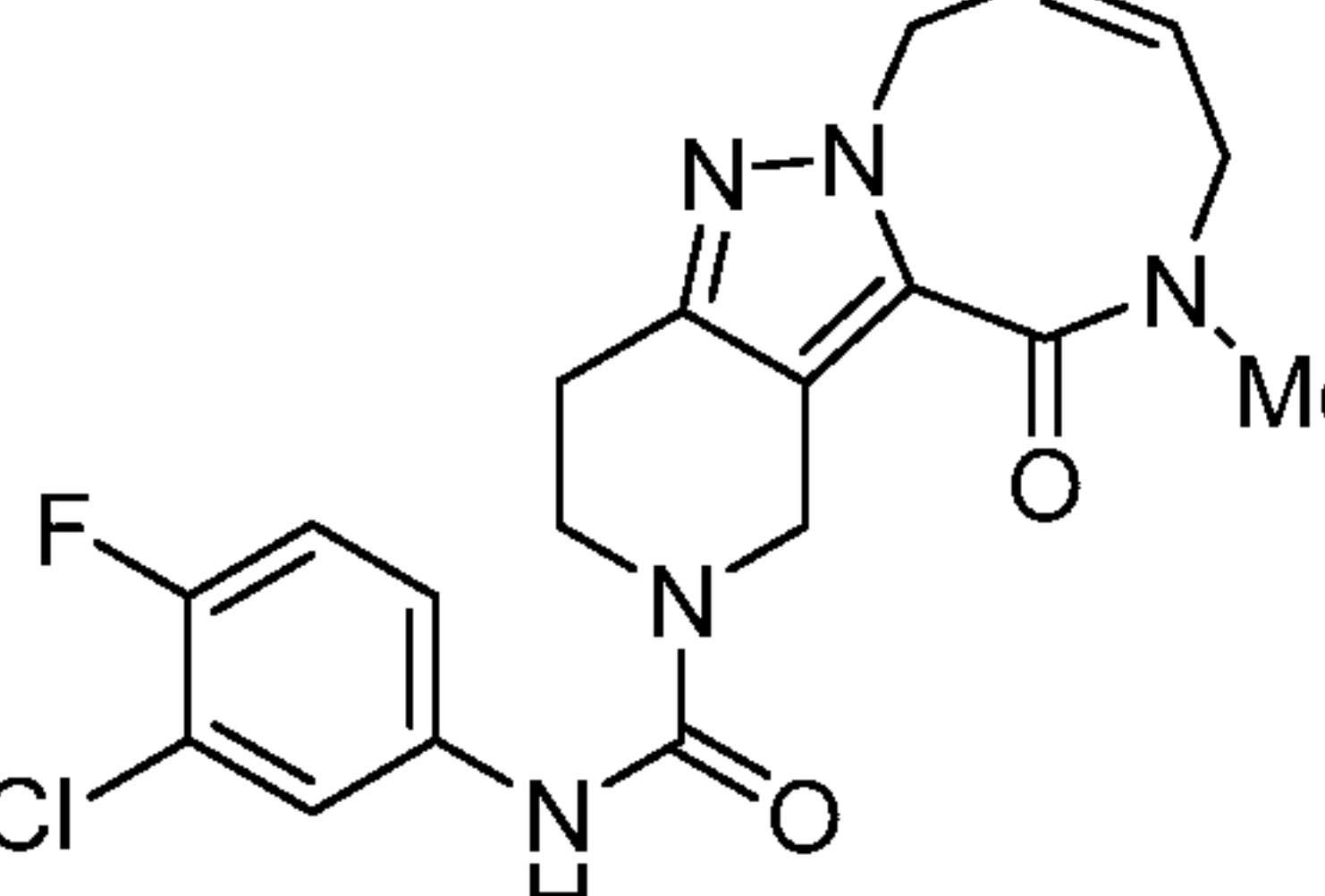
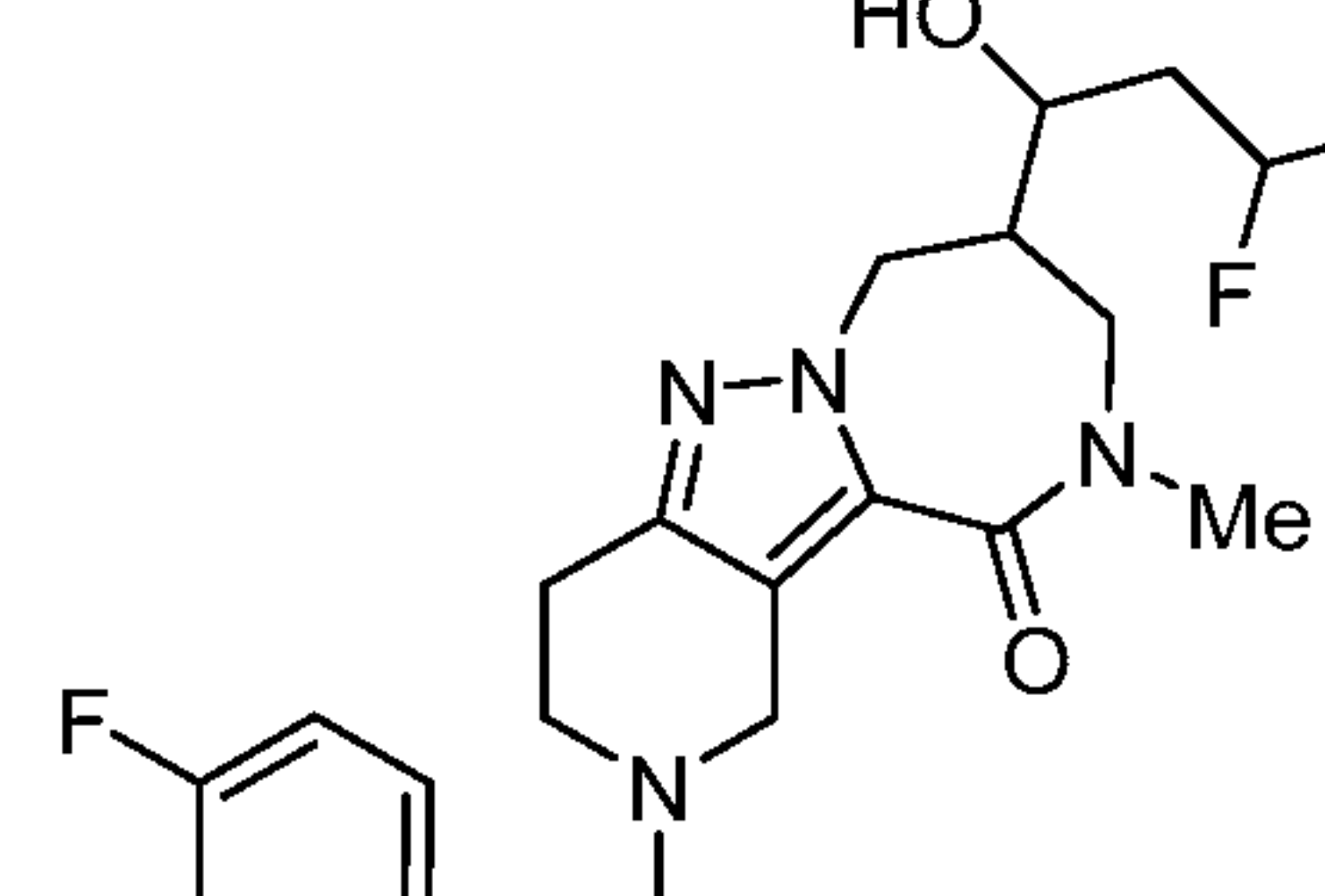
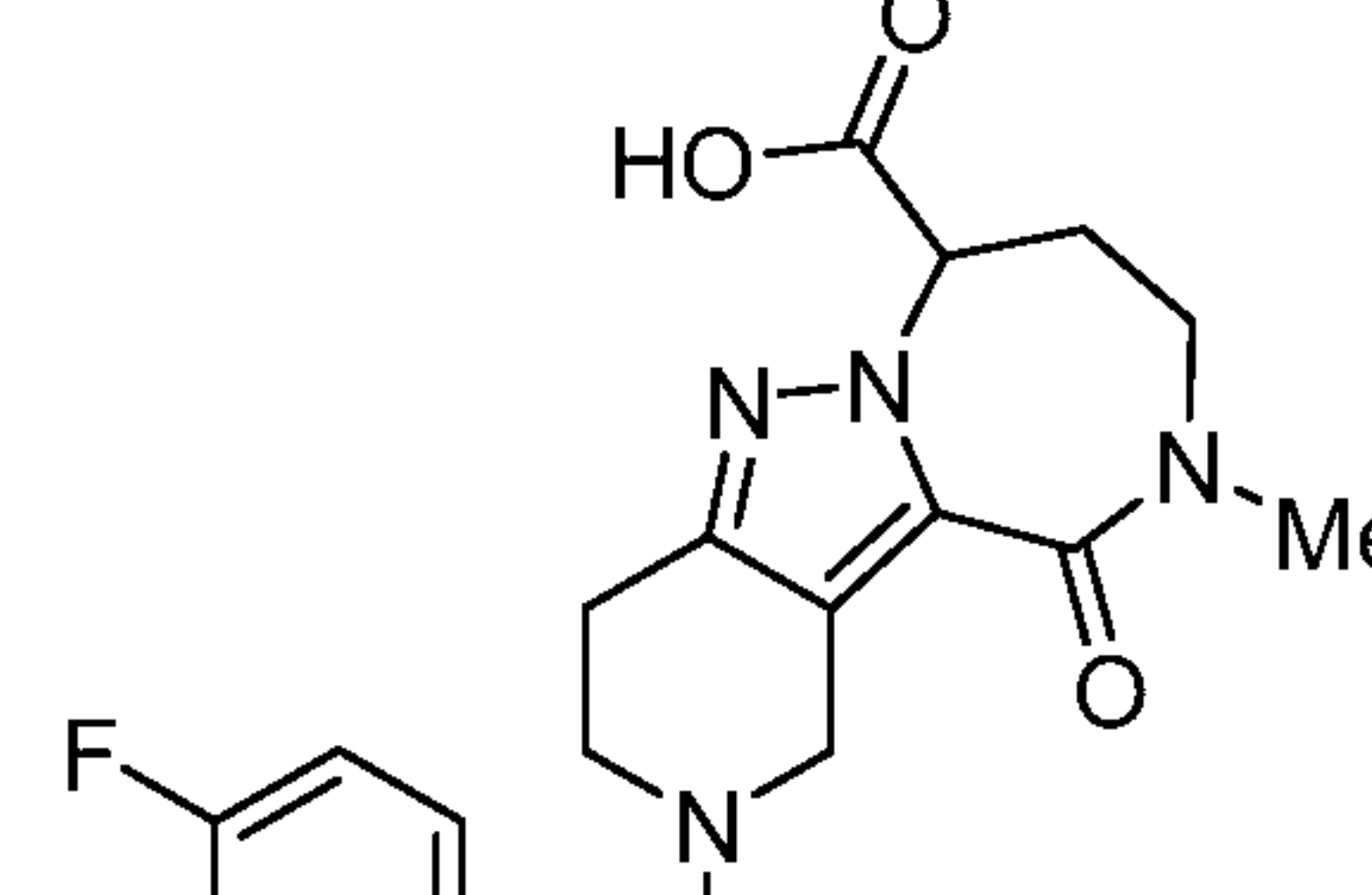
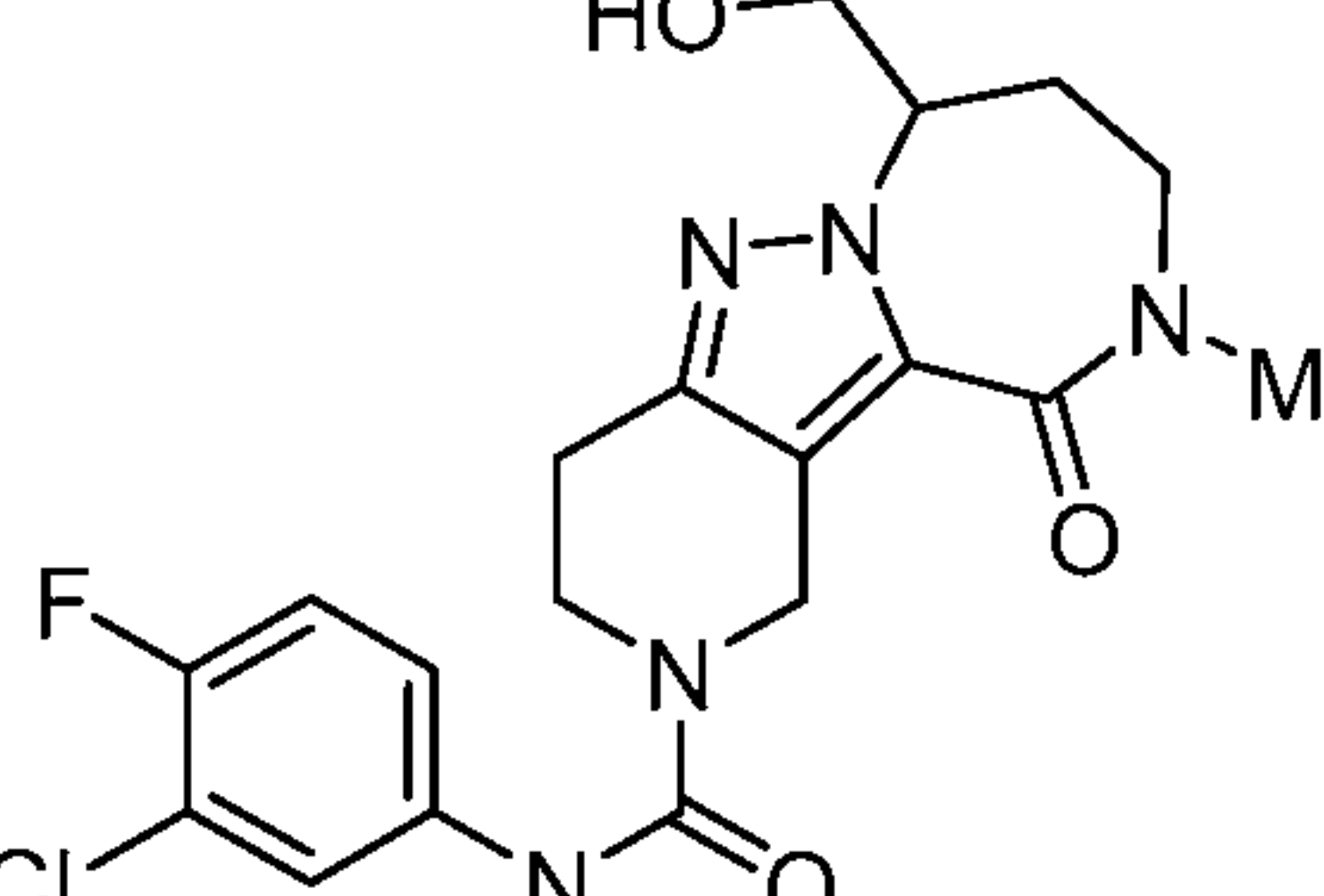
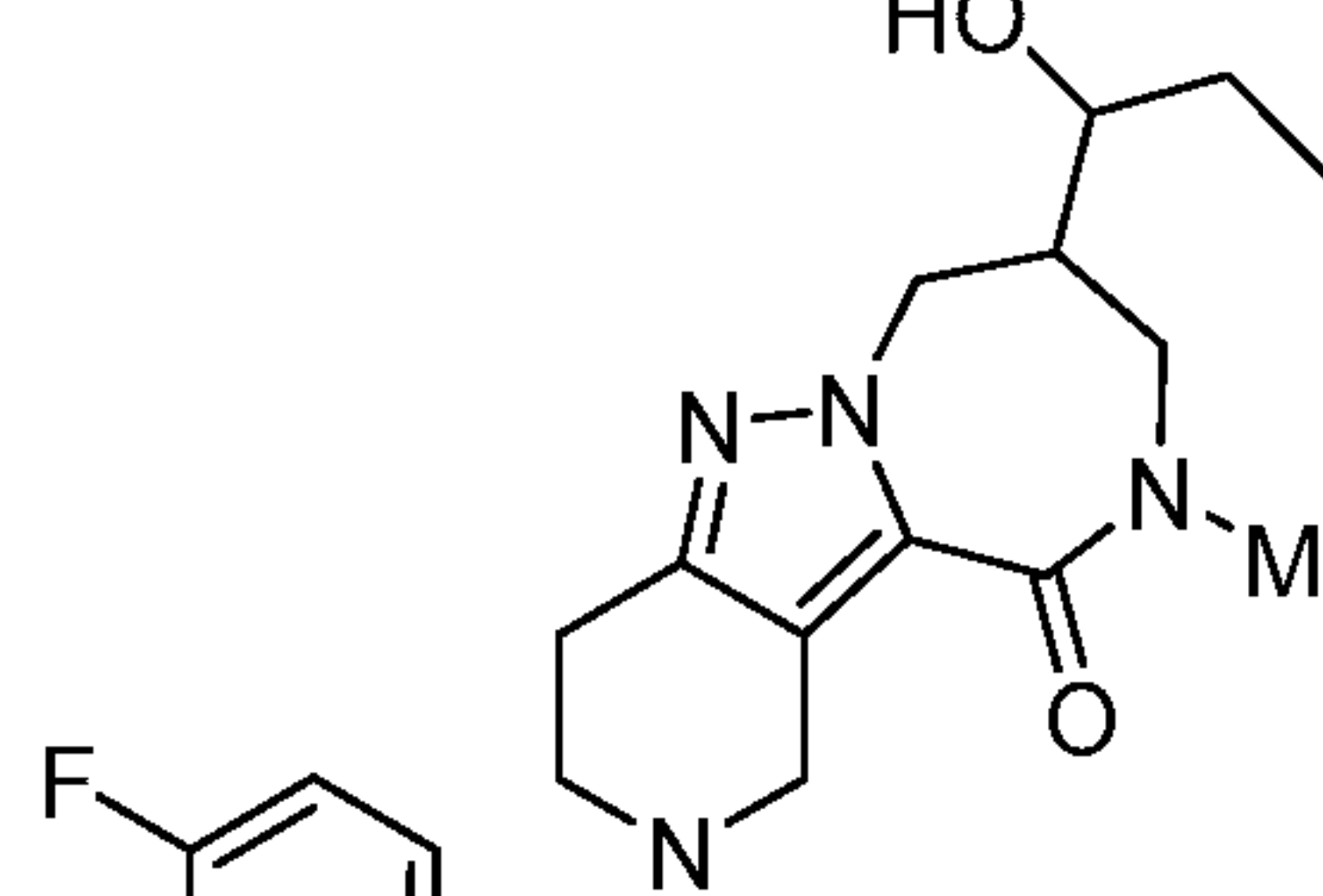
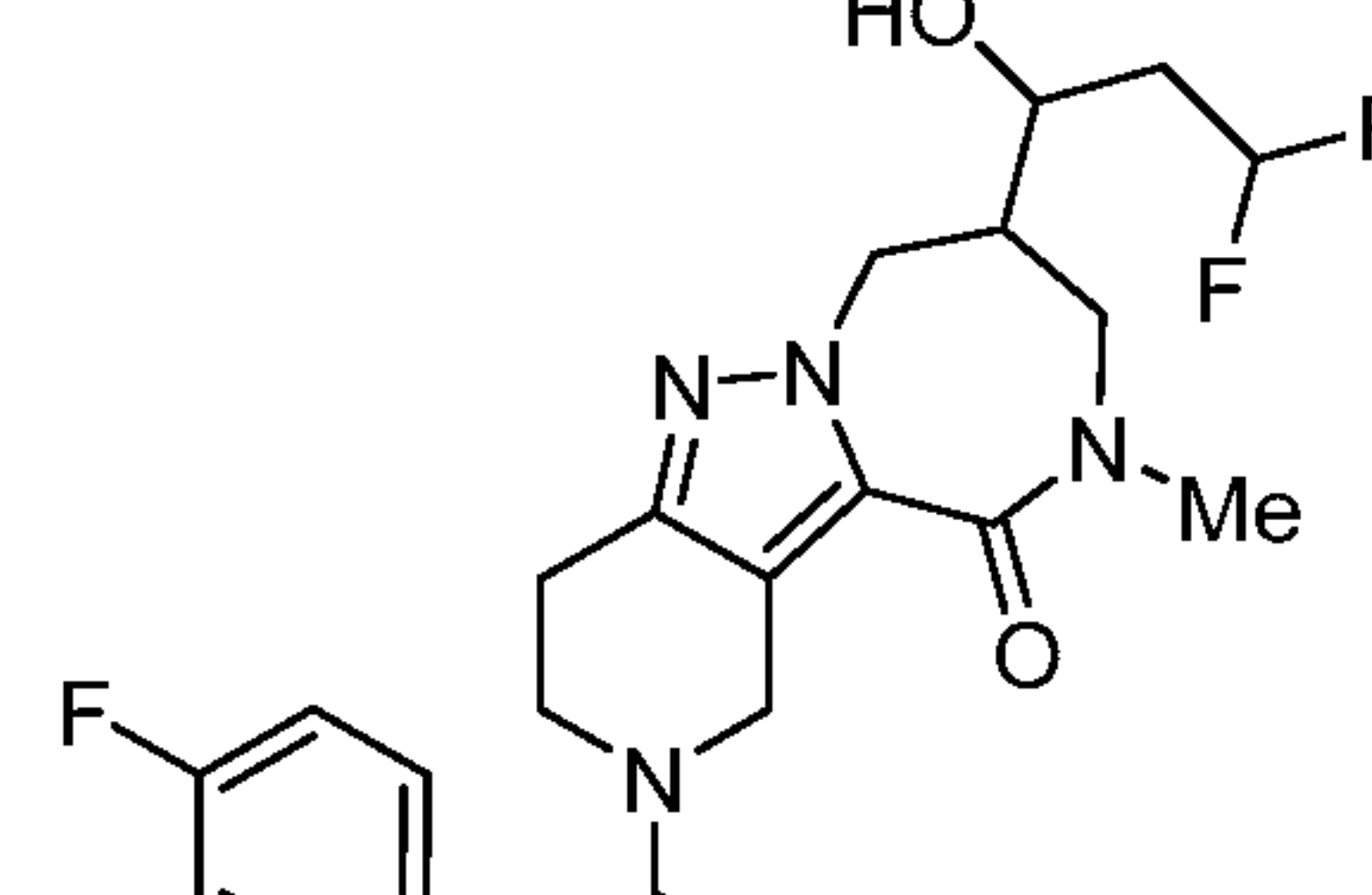
 053	 054	 055
 056	 057	 058
 059	 060	 061
 062	 063	 064

 065	 066	 067
 068	 069	 070
 071	 072	 073
 074	 075	 076

<p>077</p>	<p>078</p>	<p>079</p>
<p>080</p>	<p>081</p>	<p>082</p>
<p>083</p>	<p>084</p>	<p>085</p>

<p>086</p>	<p>087</p>	<p>088</p>
<p>089</p>	<p>090</p>	<p>091</p>
<p>092</p>	<p>093</p>	<p>094</p>



 <p>107</p>	 <p>108</p>	 <p>109</p>
 <p>110</p>	 <p>111</p>	 <p>112</p>
 <p>113</p>	 <p>114</p>	 <p>115</p>
 <p>116</p>		

In an embodiment, compounds of Formulas I, II, III and IV are selected from:

Compound ID	Compound Name
047	N-(3-chloro-4-fluorophenyl)-8-(2-cyclopropyl-1-hydroxyethyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
048	(3R)-N-(3-chloro-4-fluorophenyl)-10-(2-hydroxy-2-methylpropyl)-3-methyl-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
049	(3R)- N-(3-chloro-4-fluorophenyl)-10-(2-hydroxyethyl)-3-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
050	N-(3-chloro-4-fluorophenyl)-10-methyl-8-(methylamino)-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
051	N-(3-chloro-4-fluorophenyl)-8-(hydroxymethyl)-11-oxo-10-(2,2,2-trifluoroethyl)-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
052	ethyl 2-((3-chloro-4-fluorophenyl)carbamoyl)-8,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-8-carboxylate
053	N-(3-chloro-4-fluorophenyl)-8-(hydroxymethyl)-8,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
054	N-(3-chloro-4-fluorophenyl)-8-(3,3-difluoropyrrolidin-1-yl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
055	N-(3-chloro-4-fluorophenyl)-10-methyl-11-oxo-8-(piperidin-1-yl)-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
056	N-(3-chloro-4-fluorophenyl)-8-(4,4-difluoropiperidin-1-yl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
057	methyl 2-((3-chloro-4-fluorophenyl)carbamoyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-9-carboxylate
058	2-((3-chloro-4-fluorophenyl)carbamoyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-9-carboxylic acid
059	N2-(3-chloro-4-fluorophenyl)-N9,N9,10-trimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2,9-dicarboxamide
060	N-(3-chloro-4-fluorophenyl)-9-(hydroxymethyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

Compound ID	Compound Name
061	N-(3-chloro-4-fluorophenyl)-9-(hydroxymethyl)-9,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
062	2-((3-chloro-4-fluorophenyl)carbamoyl)-9,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-9-carboxylic acid
063	N-(3-chloro-4-fluorophenyl)-10-methyl-8-(morpholinomethyl)-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
064	N-(3-chloro-4-fluorophenyl)-10-methyl-11-oxo-8-(piperidin-1-ylmethyl)-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
065	N-(3-chloro-4-fluorophenyl)-8-((dimethylamino)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
066	N-(3-chloro-4-fluorophenyl)-8-((3,3-difluoropyrrolidin-1-yl)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
067	N-(3-cyano-4-fluorophenyl)-8-((3,3-difluoropyrrolidin-1-yl)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
068	8-((3,3-difluoropyrrolidin-1-yl)methyl)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
069	N-(3-chloro-4-fluorophenyl)-10-methyl-11-oxo-8-(pyrrolidin-1-ylmethyl)-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
070	8-(aminomethyl)-N-(3-chloro-4-fluorophenyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
071	(R)-N-(2-bromo-5-chloro-4-fluorophenyl)-10-(2,2-difluoroethyl)-3-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
072	(3R)-N-(3-chloro-4-fluorophenyl)-10-(2,2-difluoroethyl)-3-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
073	(R)-10-(2,2-difluoroethyl)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-3-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
074	(R)-N-(3-bromo-4-fluorophenyl)-10-(2,2-difluoroethyl)-3-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide

Compound ID	Compound Name
075	(R)-N-(2-bromo-3-fluoropyridin-4-yl)-10-(2,2-difluoroethyl)-3-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
076	(R)-N-(3-cyano-4-fluorophenyl)-10-(2,2-difluoroethyl)-3-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
077	(R)-10-(2,2-difluoroethyl)-N-(4-fluoro-3-methylphenyl)-3-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
078	(R)-N-(5-chloro-2,4-difluorophenyl)-10-(2,2-difluoroethyl)-3-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
079_D1	(3R,8R*)-N-(3-chloro-4-fluorophenyl)-8-fluoro-3,8,10-trimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
079_D2	(3R,8S*)-N-(3-chloro-4-fluorophenyl)-8-fluoro-3,8,10-trimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
080_D1	(3R,8S*)-N-(3-chloro-4-fluorophenyl)-3,8,10-trimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
080_D2	(3R,8R*)-N-(3-chloro-4-fluorophenyl)-3,8,10-trimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
081_D1	(3R,8S*)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
081_D2	(3R,8R*)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
082_D1	(3R,8S*)-N-(2,4-difluoro-5-(trifluoromethyl)phenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
082_D2	(3R,8R*)-N-(2,4-difluoro-5-(trifluoromethyl)phenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
083_D1	(3R,8S*)-N-(2,4-difluoro-3-(trifluoromethyl)phenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
083_D2	(3R,8R*)-N-(2,4-difluoro-3-(trifluoromethyl)phenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide

Compound ID	Compound Name
084_D1	(3R,8S*)-N-(3-bromo-2,4-difluorophenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
084_D2	(3R,8R*)-N-(3-bromo-2,4-difluorophenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
085_D1	(3R,8S*)-N-(5-bromo-2,4-difluorophenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
085_D2	(3R,8R*)-N-(5-bromo-2,4-difluorophenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
086_D1	(3R,8S*)-N-(3-bromo-4-fluorophenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
086_D2	(3R,8R*)-N-(3-bromo-4-fluorophenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
087_D1	(3R,8S*)-N-(3-cyano-4-fluorophenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
087_D2	(3R,8R*)-N-(3-cyano-4-fluorophenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
088_D1	(3R,8S*)-N-(3-cyano-2,4-difluorophenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
088_D2	(3R,8R*)-N-(3-cyano-2,4-difluorophenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
089_D1	(3R,8S*)-N-(3-chloro-2,4-difluorophenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
089_D2	(3R,8R*)-N-(3-chloro-2,4-difluorophenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
090_D1	(3R,8S*)-N-(5-chloro-2,4-difluorophenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
090_D2	(3R,8R*)-N-(5-chloro-2,4-difluorophenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide

Compound ID	Compound Name
091	N-(3-chloro-4-fluorophenyl)-8-(2,2-difluoroethyl)-8-(hydroxymethyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
092_D1	(3R,8R*)-N-(3-chloro-4-fluorophenyl)-10-(2,2-difluoroethyl)-8-(hydroxymethyl)-3-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
092_D2	(3R,8S*)-N-(3-chloro-4-fluorophenyl)-10-(2,2-difluoroethyl)-8-(hydroxymethyl)-3-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
093	8-(aminomethyl)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
094	N-(4-fluoro-3-(trifluoromethyl)phenyl)-10-methyl-8-((methylamino)methyl)-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
095	8-(aminomethyl)-N-(3-cyano-4-fluorophenyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
096_E1	(R*)-N-(5-chloro-2,4-difluorophenyl)-8-((S*)-1-hydroxypropyl)-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
096_E2	(S*)-N-(5-chloro-2,4-difluorophenyl)-8-((R*)-1-hydroxypropyl)-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
096_E3	(S*)-N-(5-chloro-2,4-difluorophenyl)-8-((S*)-1-hydroxypropyl)-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
096_E4	(R*)-N-(5-chloro-2,4-difluorophenyl)-8-((R*)-1-hydroxypropyl)-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
097_E1	(R*)-N-(3-cyano-4-fluorophenyl)-8-((S*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
097_E2	(S*)-N-(3-cyano-4-fluorophenyl)-8-((R*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
097_E3	(S*)-N-(3-cyano-4-fluorophenyl)-8-((S*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
097_E4	(R*)-N-(3-cyano-4-fluorophenyl)-8-((R*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

Compound ID	Compound Name
098_E1	(R*)-N-(3-cyano-2,4-difluorophenyl)-8-((S*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
098_E2	(S*)-N-(3-cyano-2,4-difluorophenyl)-8-((R*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
098_E3	(S*)-N-(3-cyano-2,4-difluorophenyl)-8-((S*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
098_E4	(R*)-N-(3-cyano-2,4-difluorophenyl)-8-((R*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
099_E1	(R*)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-((S*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
099_E2	(S*)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-((R*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
099_E3	(S*)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-((S*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
099_E4	(R*)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-((R*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
100_E1	N-(3-chloro-2,4-difluorophenyl)-8-(1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
101_E1	N-(3-bromo-2,4-difluorophenyl)-8-(1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
102_E1	N-(3-bromo-4-fluorophenyl)-8-(1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
103_E1	N-(2,4-difluoro-3-(trifluoromethyl)phenyl)-8-(1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
104_E1	8-(1-hydroxypropyl)-10-methyl-11-oxo-N-(3,4,5-trifluorophenyl)-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
105_E1	8-(1-hydroxypropyl)-10-methyl-11-oxo-N-(2,3,4,5-tetrafluorophenyl)-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

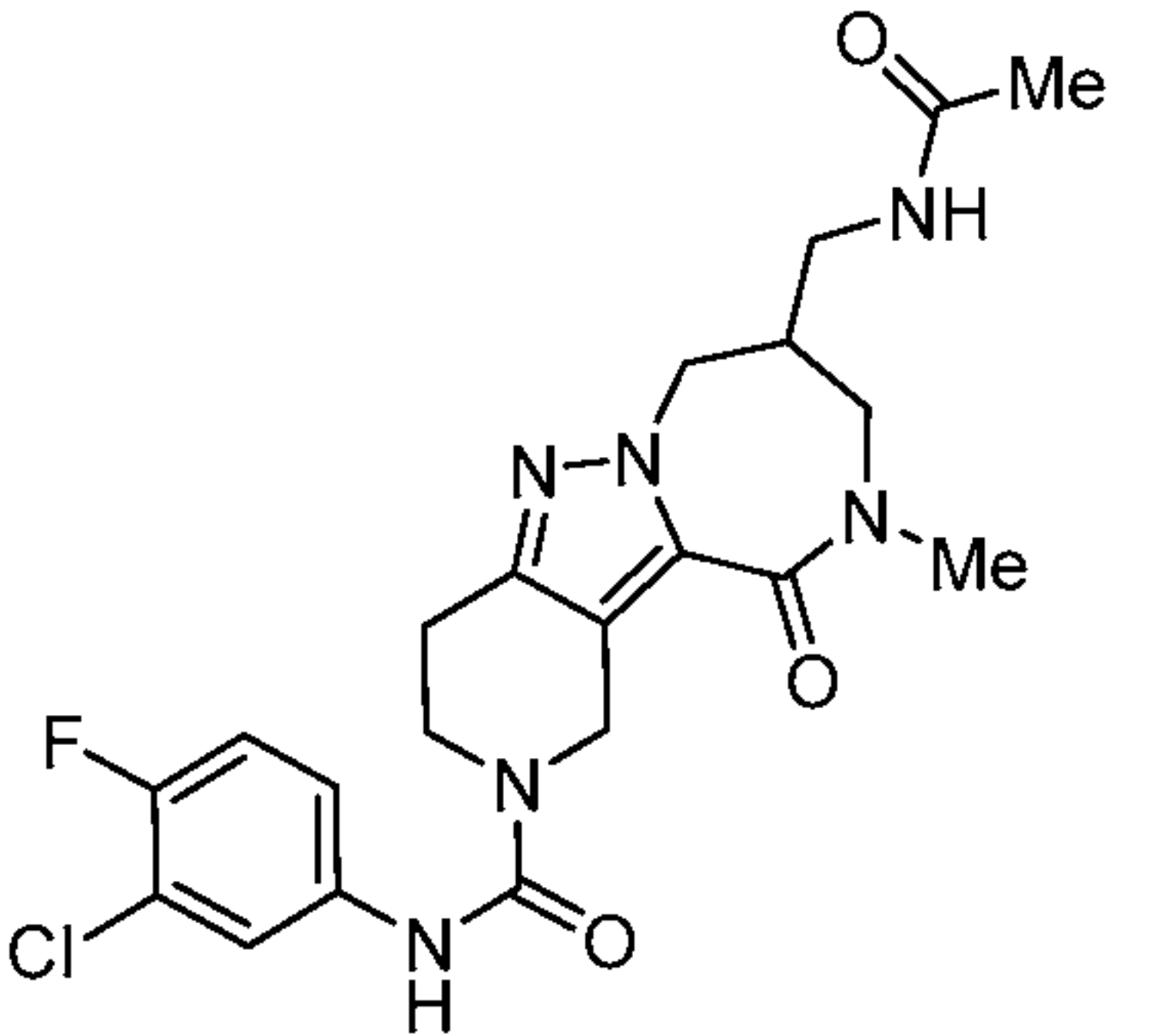
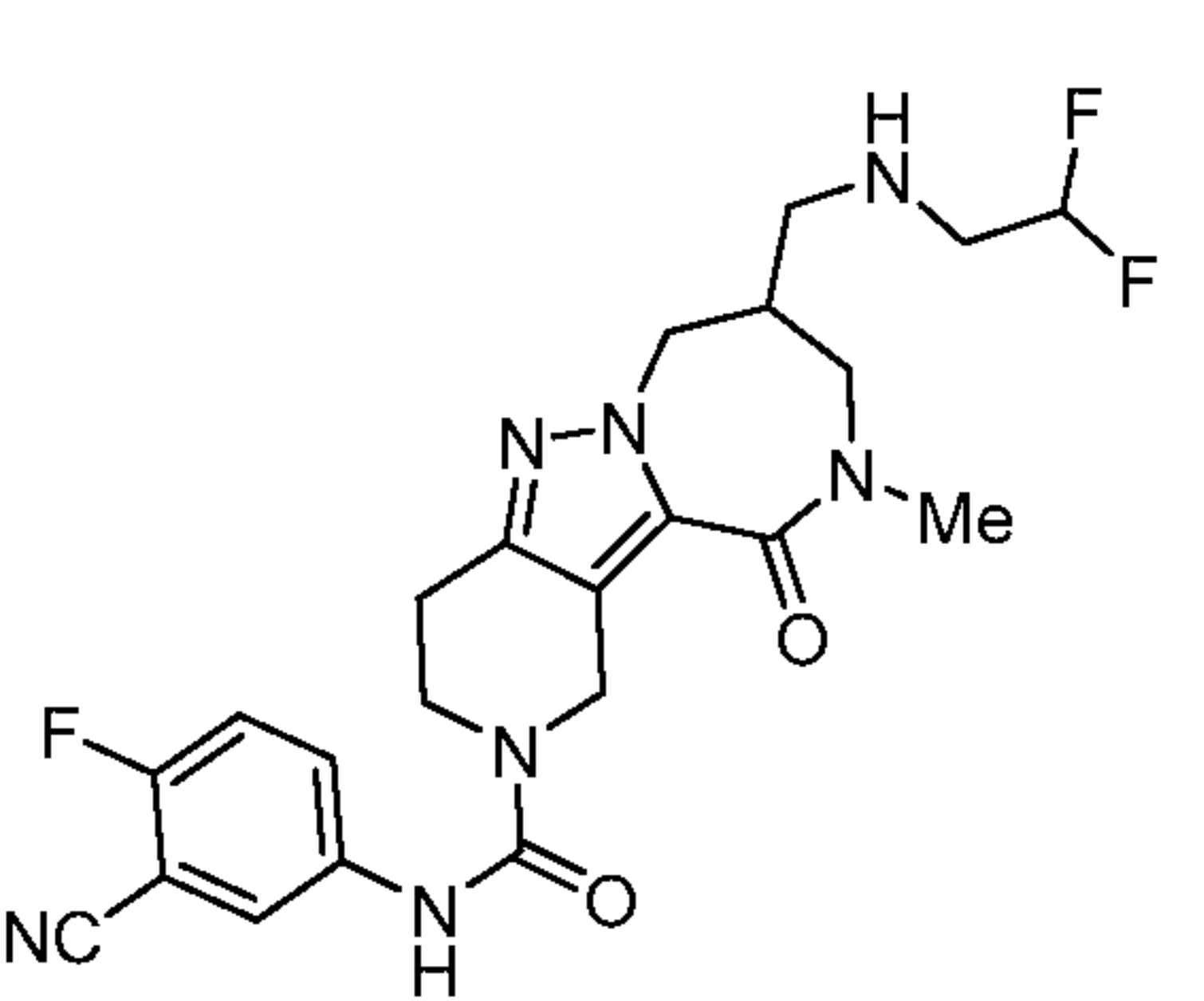
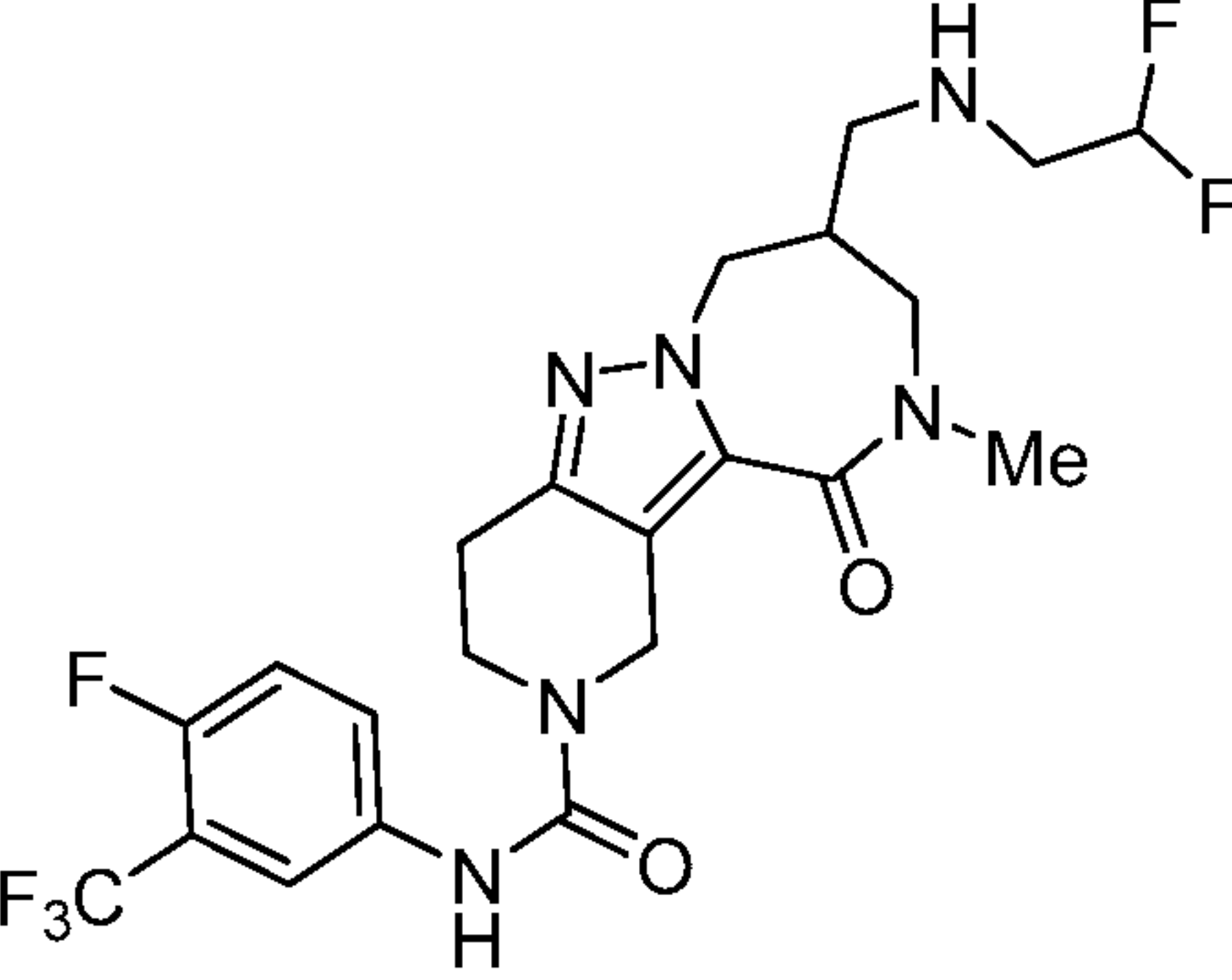
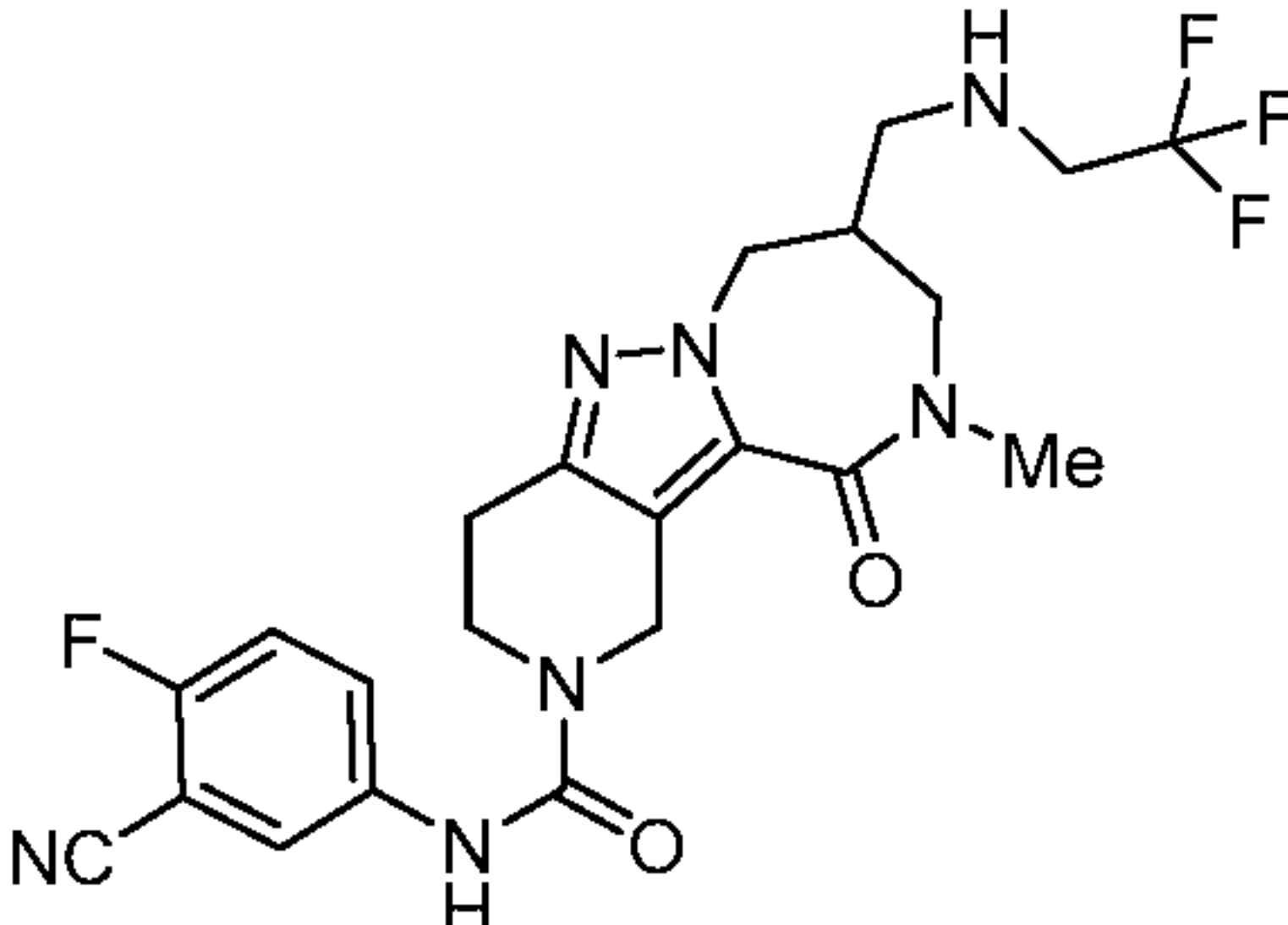
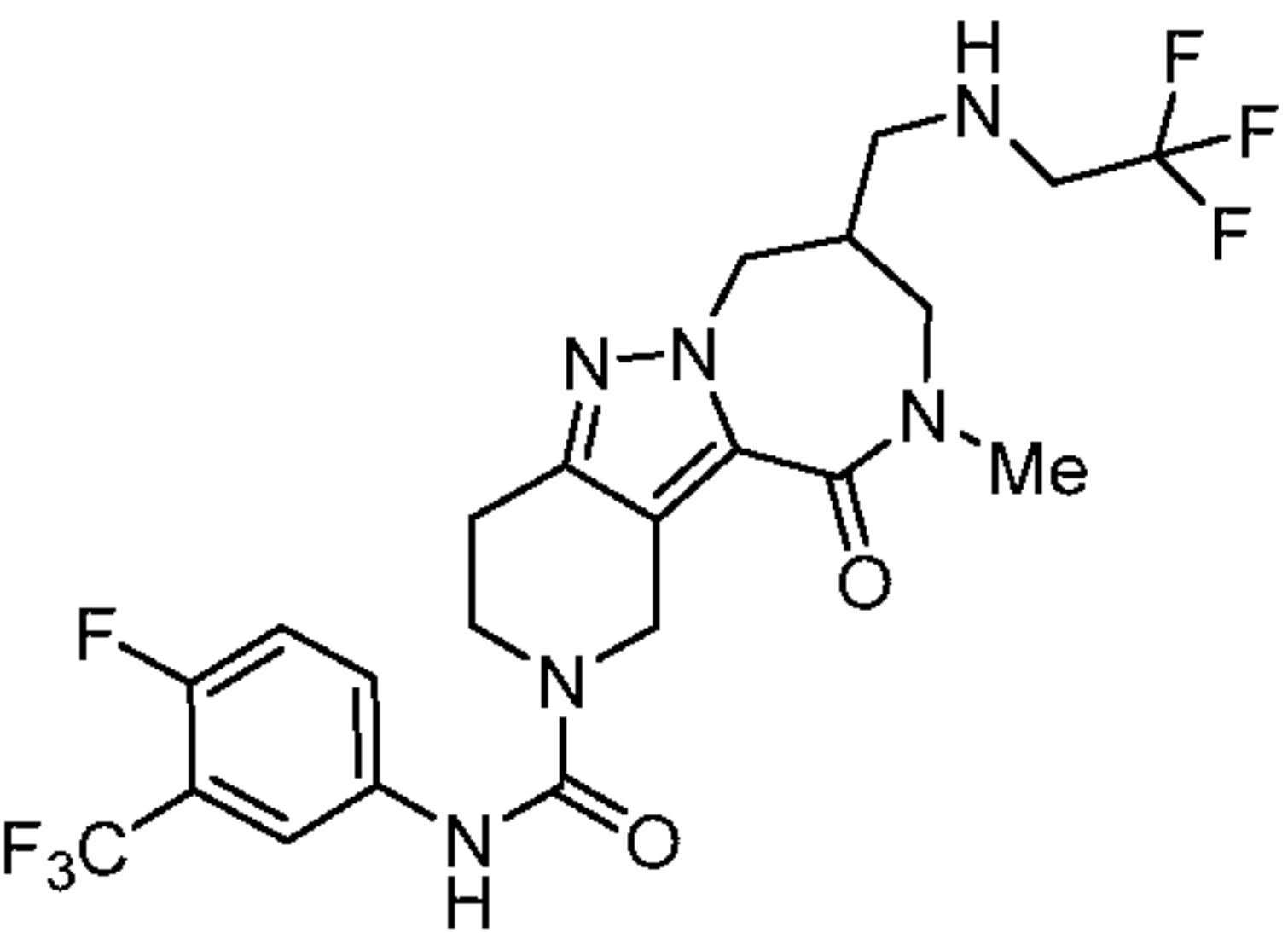
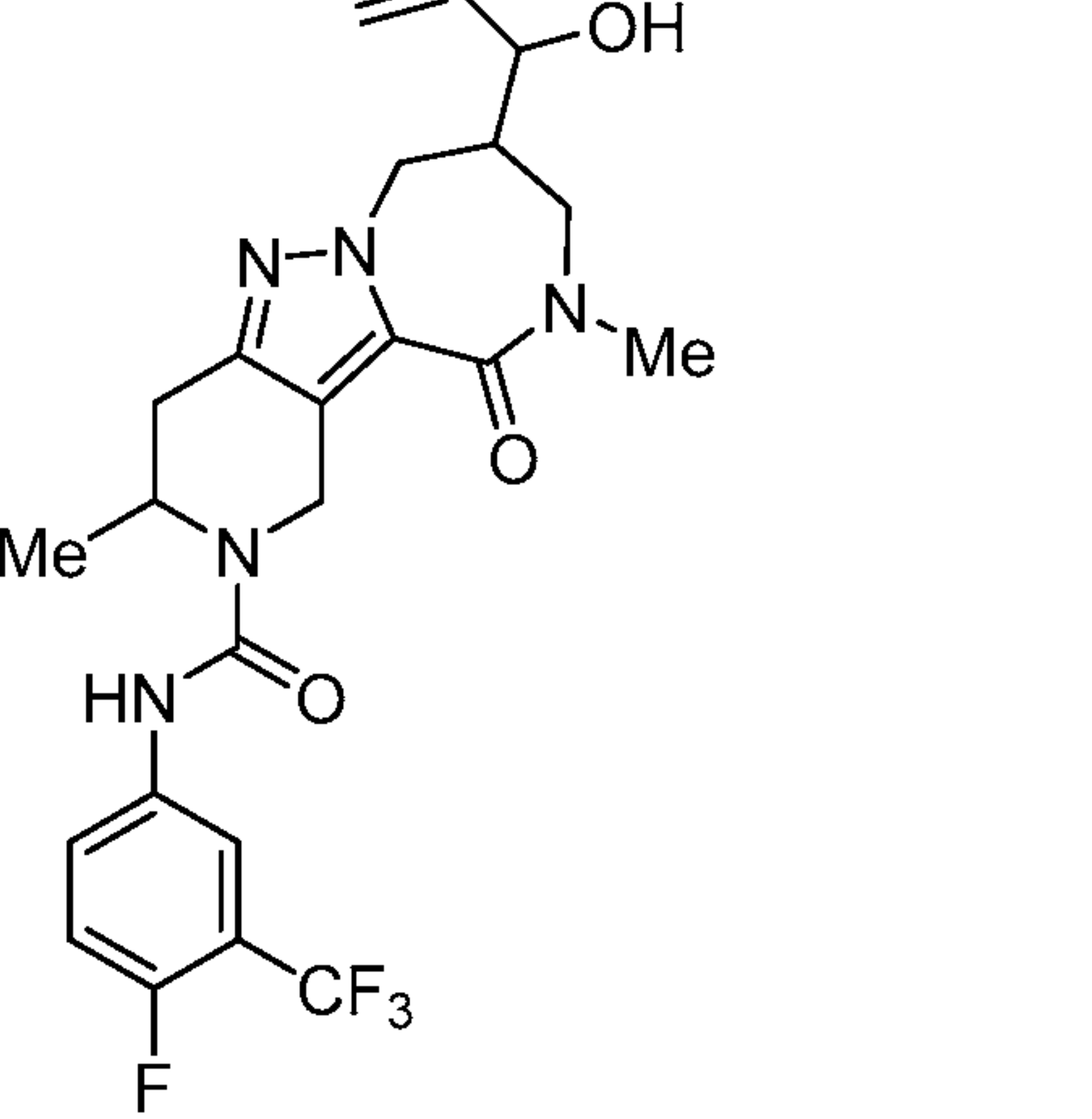
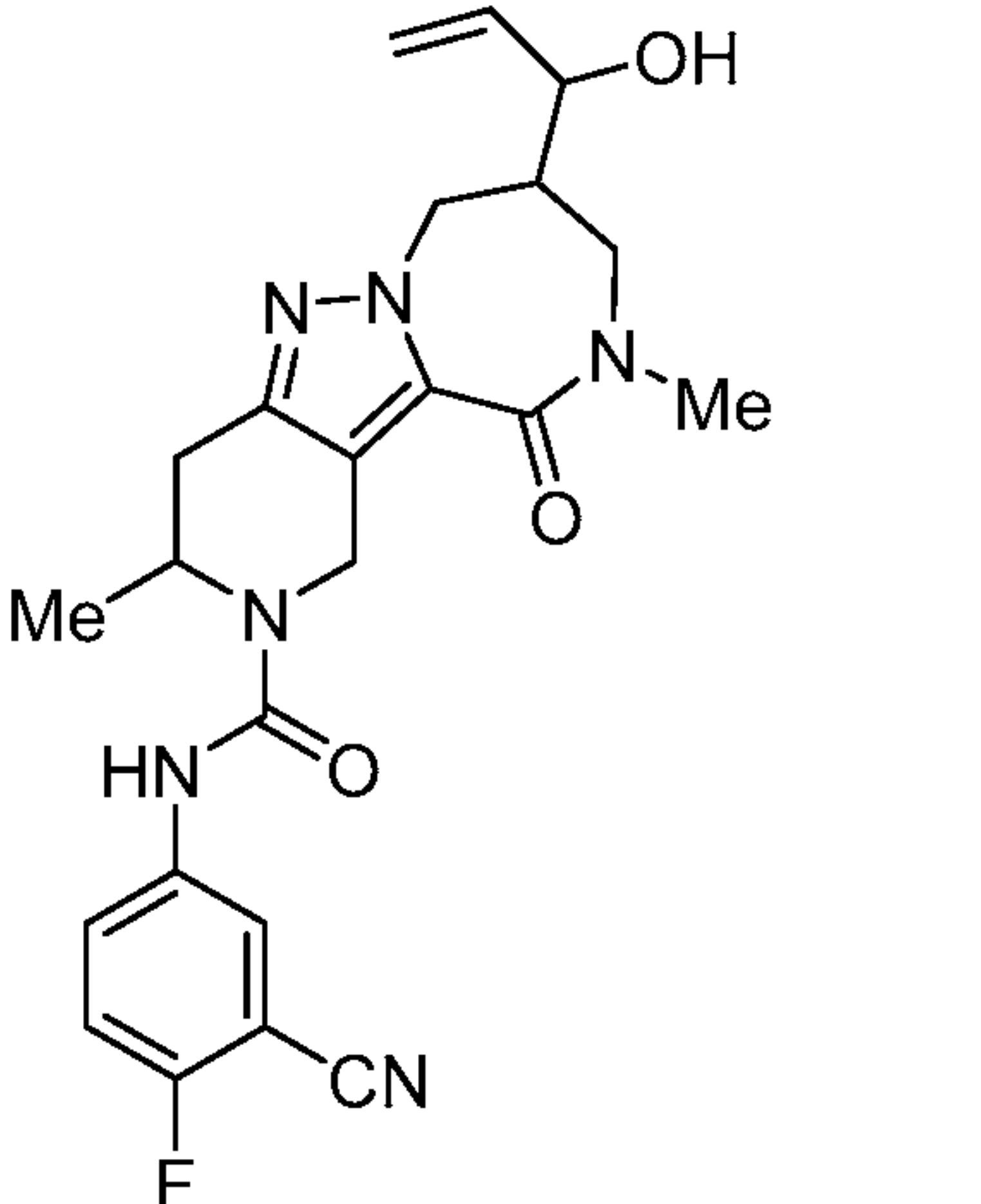
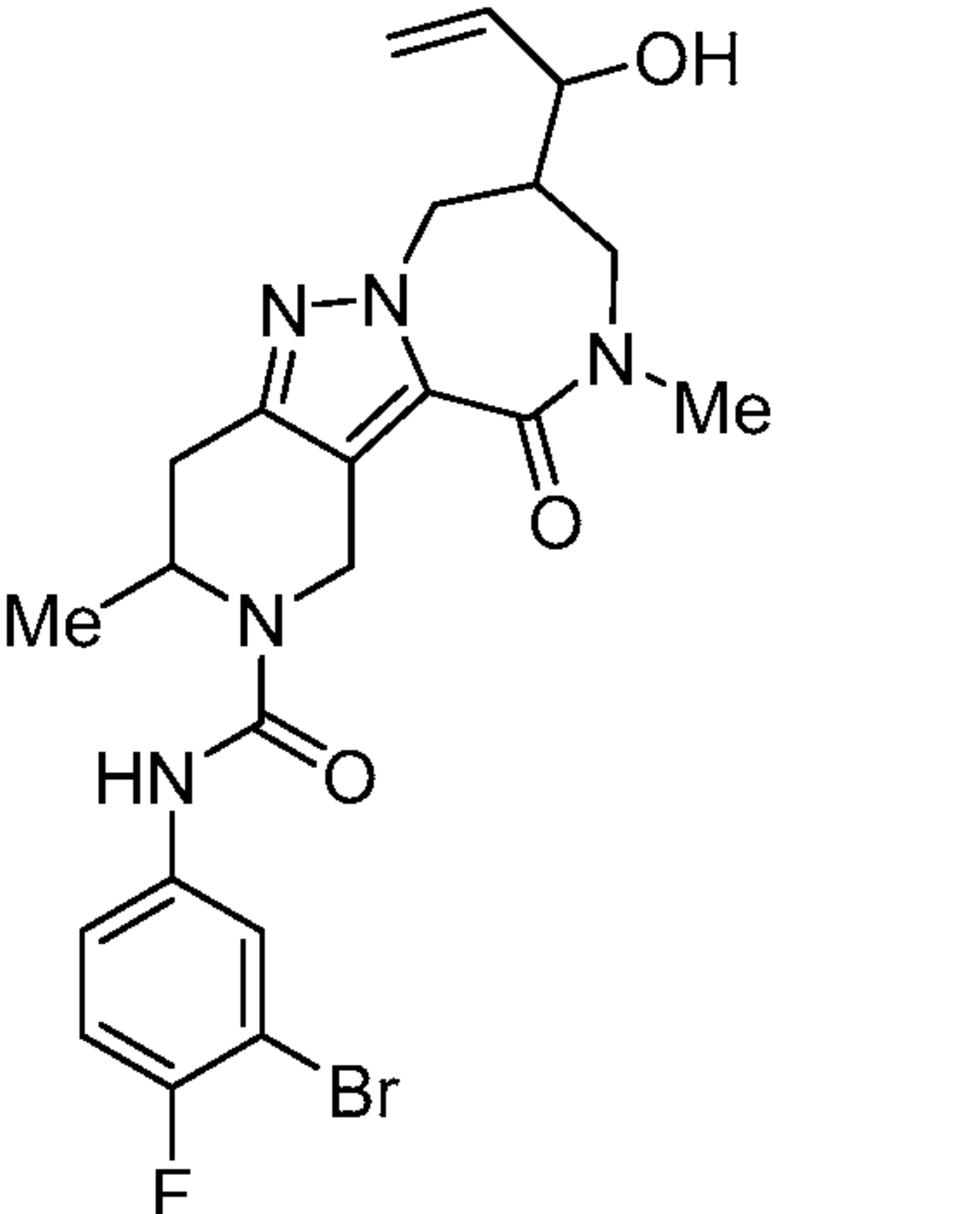
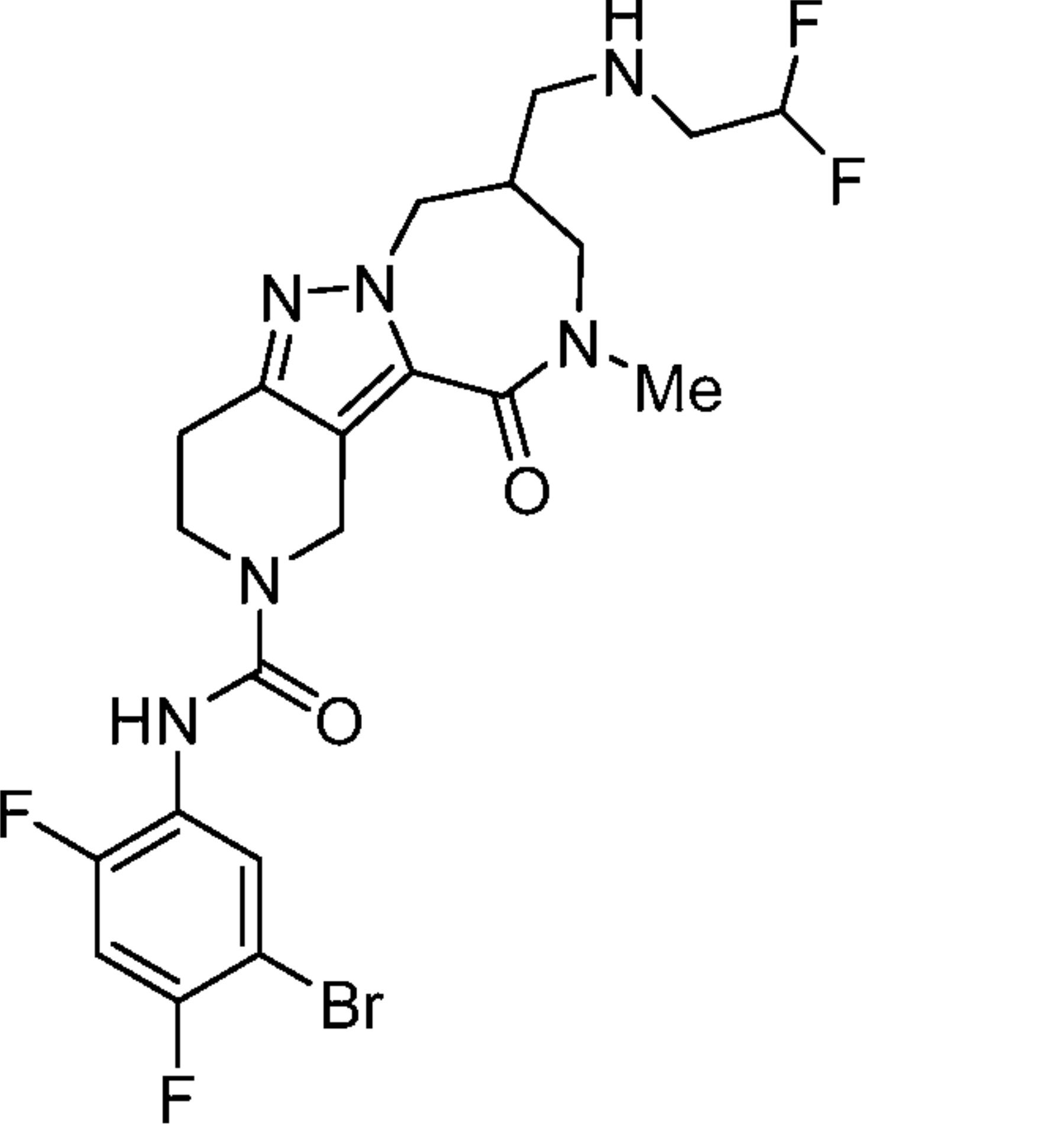
Compound ID	Compound Name
106	N-(3-chloro-4-fluorophenyl)-8-(1-hydroxybutyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
107_D1	(3R,8S*)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-((R)-1-hydroxypropyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
107_D2	(3R,8R*)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-((R)-1-hydroxypropyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
108_D1	(3R,8S*)-N-(3-cyano-4-fluorophenyl)-8-((R)-1-hydroxypropyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
108_D2	(3R,8R*)-N-(3-cyano-4-fluorophenyl)-8-((R)-1-hydroxypropyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
109_D1	(3R,8S*)-N-(3-bromo-4-fluorophenyl)-8-((R)-1-hydroxypropyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
109_D2	(3R,8R*)-N-(3-bromo-4-fluorophenyl)-8-((R)-1-hydroxypropyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
110	N-(3-chloro-4-fluorophenyl)-11-methyl-12-oxo-3,4,7,8,9,10,11,12-octahydropyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazocine-2(1H)-carboxamide
111	(Z)-N-(3-chloro-4-fluorophenyl)-11-methyl-12-oxo-3,4,7,10,11,12-hexahydropyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazocine-2(1H)-carboxamide
112	N-(3-cyano-4-fluorophenyl)-8-(3,3-difluoro-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
113	2-((3-chloro-4-fluorophenyl)carbonyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-7-carboxylic acid
114	N-(3-chloro-4-fluorophenyl)-7-(hydroxymethyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
115	N-(3-chloro-4-fluorophenyl)-8-(3-fluoro-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
116	N-(3-chloro-4-fluorophenyl)-8-(3,3-difluoro-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

*Pure but unknown enantiomer or diastereomer.

and pharmaceutically acceptable salts thereof.

Certain embodiments of Formulas I, II, III, and IV are shown below in **Table 3**.
disclosed compounds.

Table 3.

 <p>117</p>	 <p>118</p>	 <p>119</p>
 <p>120</p>	 <p>121</p>	 <p>122</p>
 <p>123</p>	 <p>124</p>	 <p>125</p>

<p>126</p>	<p>127</p>	<p>128</p>
<p>129</p>	<p>130</p>	<p>131</p>
<p>132</p>		

In an embodiment, compounds of Formulas I, II, III, and IV are selected from:

Compound ID	Compound Name
117	8-(acetamidomethyl)-N-(3-chloro-4-fluorophenyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
118	N-(3-cyano-4-fluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
118_E1	(R*)-N-(3-cyano-4-fluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
118_E2	(S*)-N-(3-cyano-4-fluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
119	8-(((2,2-difluoroethyl)amino)methyl)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
119_E1	(R*)-8-(((2,2-difluoroethyl)amino)methyl)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
119_E2	(S*)-8-(((2,2-difluoroethyl)amino)methyl)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
120	N-(3-cyano-4-fluorophenyl)-10-methyl-11-oxo-8-(((2,2,2-trifluoroethyl)amino)methyl)-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
121	N-(4-fluoro-3-(trifluoromethyl)phenyl)-10-methyl-11-oxo-8-(((2,2,2-trifluoroethyl)amino)methyl)-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
122_D1	(3R,8S*)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-((R)-1-hydroxyallyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
122_D2	(3R,8R*)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-((R)-1-hydroxyallyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide

Compound ID	Compound Name
123_D1	(3R,8S*)-N-(3-cyano-4-fluorophenyl)-8-((R)-1-hydroxyallyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
123_D2	(3R,8R*)-N-(3-cyano-4-fluorophenyl)-8-((R)-1-hydroxyallyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
124_D1	(3R,8S*)-N-(3-bromo-4-fluorophenyl)-8-((R)-1-hydroxyallyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
124_D2	(3R,8R*)-N-(3-bromo-4-fluorophenyl)-8-((R)-1-hydroxyallyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
125_E1	(R*)-N-(5-bromo-2,4-difluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
125_E2	(S*)-N-(5-bromo-2,4-difluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
126_E1	(R*)-N-(5-chloro-2,4-difluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
126_E2	(S*)-N-(5-chloro-2,4-difluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
127_E1	(R*)-N-(3-cyano-2,4-difluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
127_E2	(S*)-N-(3-cyano-2,4-difluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
128_E1	(R*)-N-(3-chloro-2,4-difluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-3,4,8,9,10,11-

Compound ID	Compound Name
	hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
128_E2	(S*)-N-(3-chloro-2,4-difluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
129_E1	(R*)-N-(3-bromo-2,4-difluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
129_E2	(S*)-N-(3-bromo-2,4-difluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
130_E1	(R*)-N-(3-bromo-4-fluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
130_E2	(S*)-N-(3-bromo-4-fluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
131_E1	(R*)-N-(2,4-difluoro-3-(trifluoromethyl)phenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
131_E2	(S*)-N-(2,4-difluoro-3-(trifluoromethyl)phenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide
132	N-(3-chloro-4-fluorophenyl)-3-hydroxy-10'-methyl-11'-oxo-1',3',4',9',10',11'-hexahydro-2'H,7'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine]-2'-carboxamide

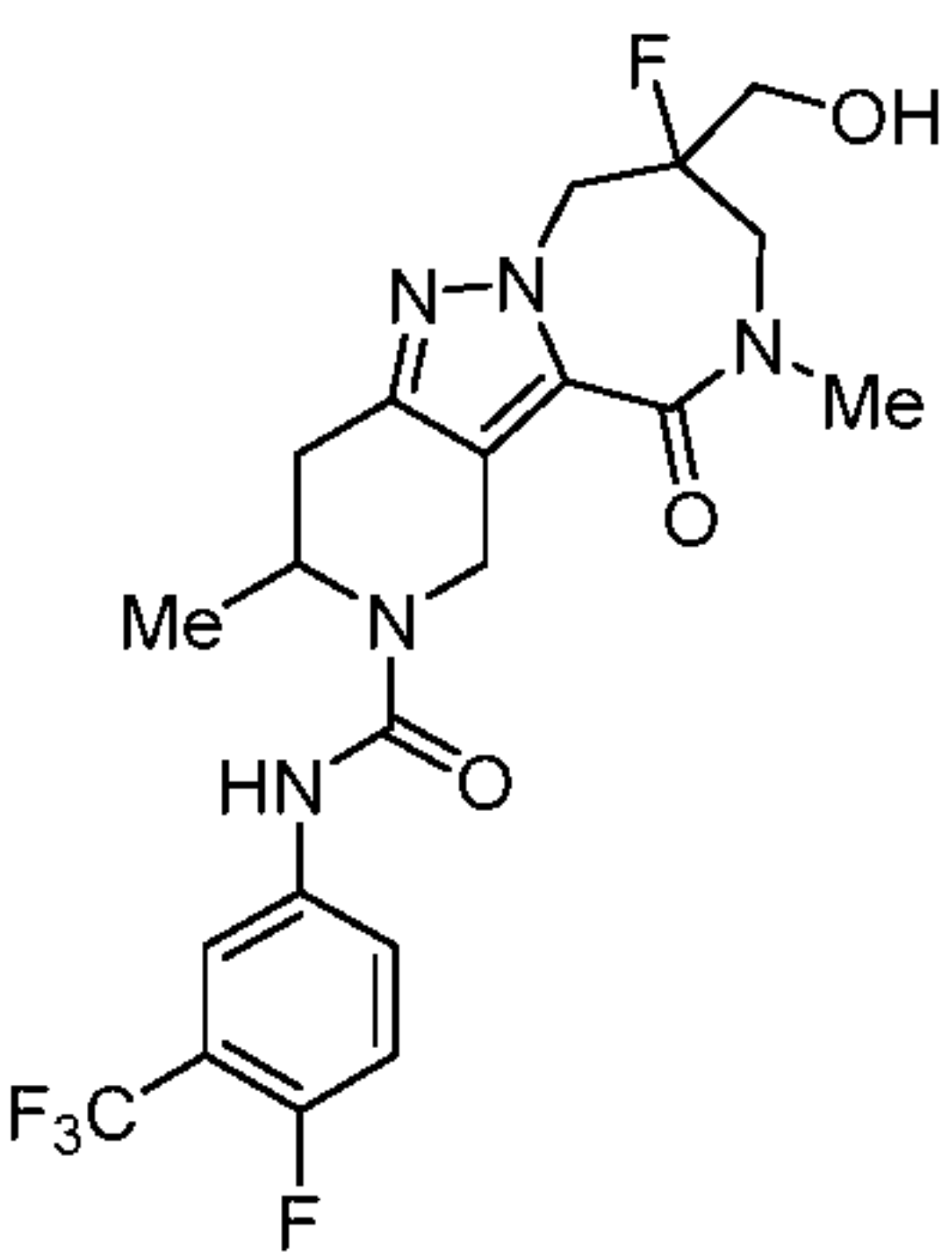
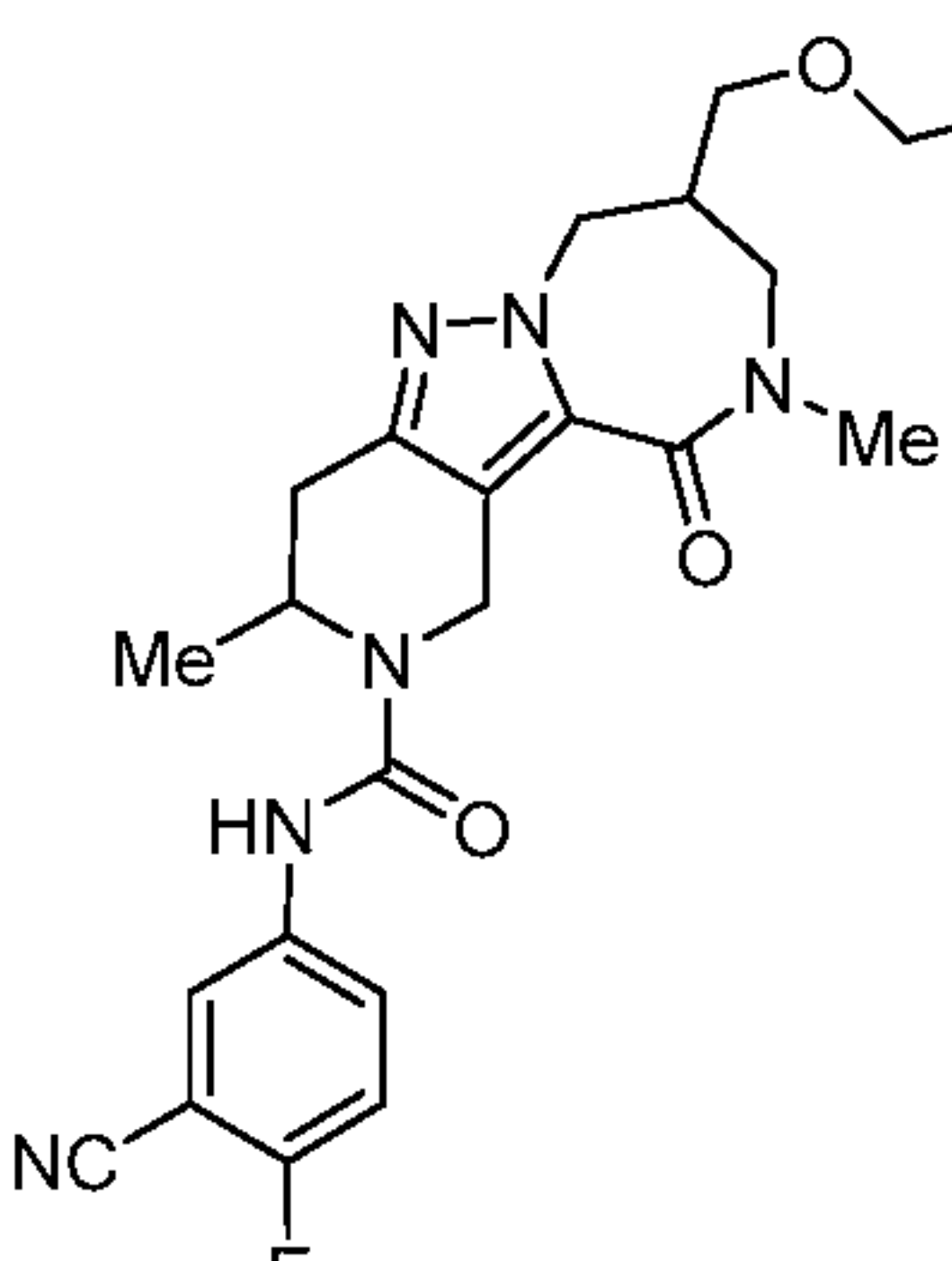
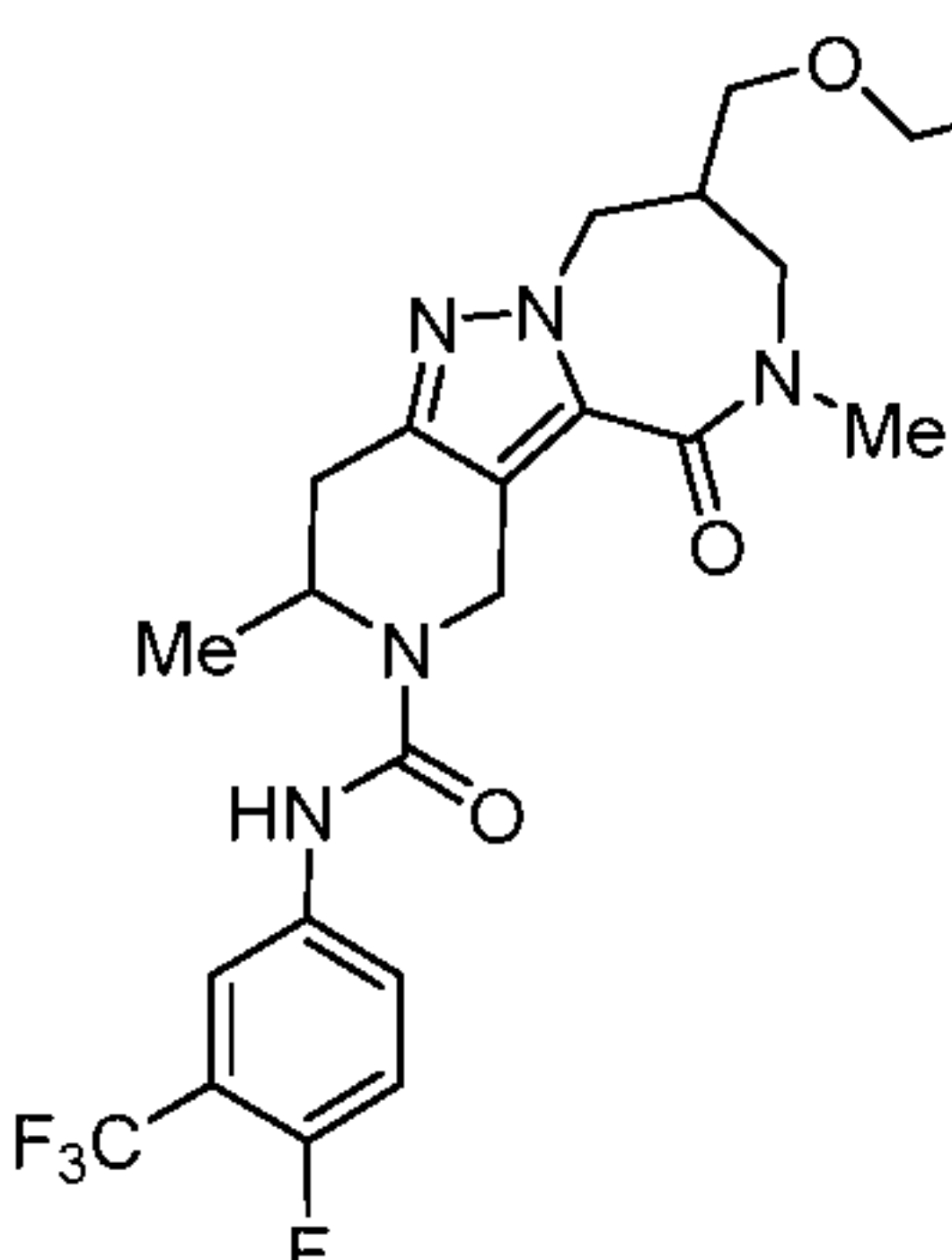
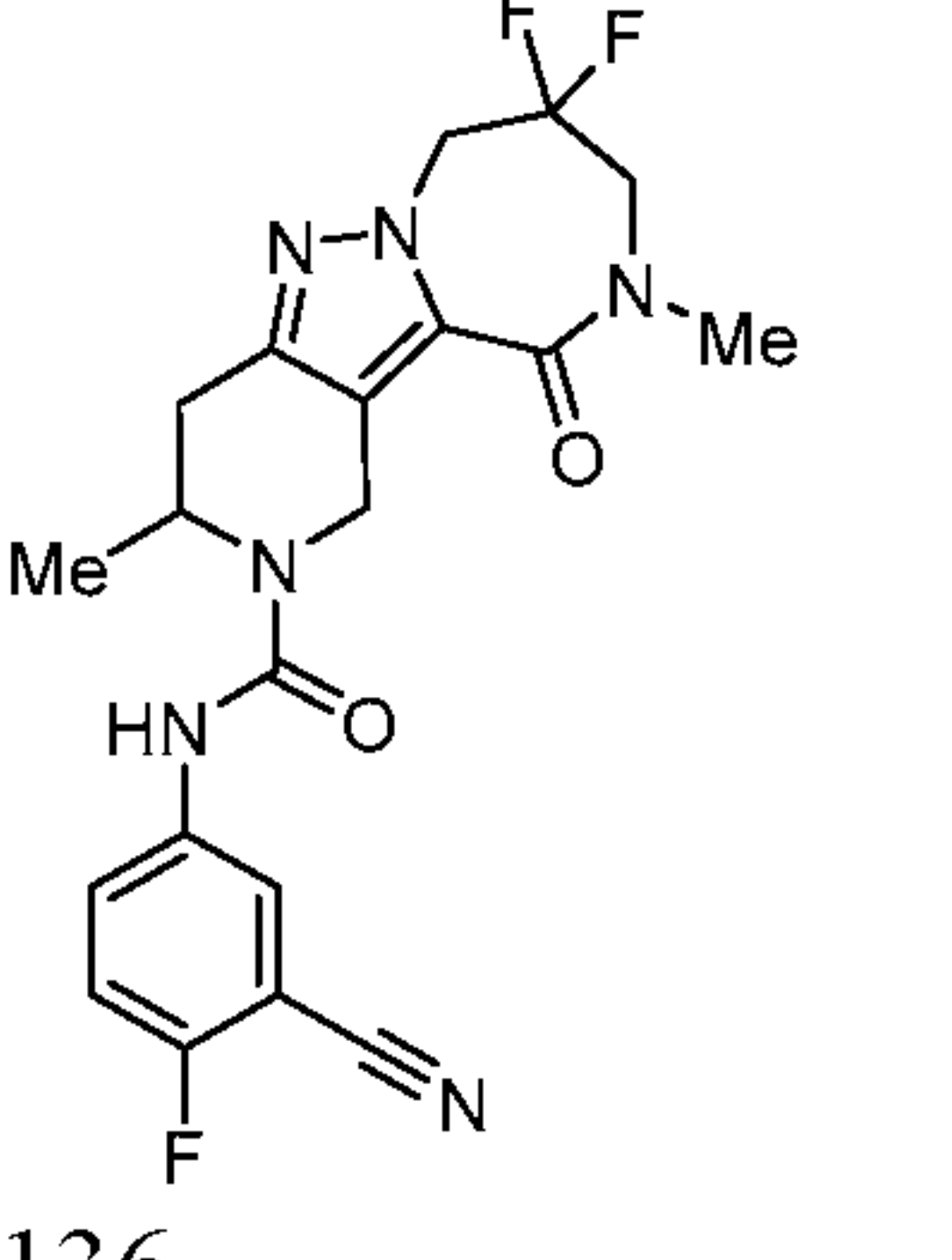
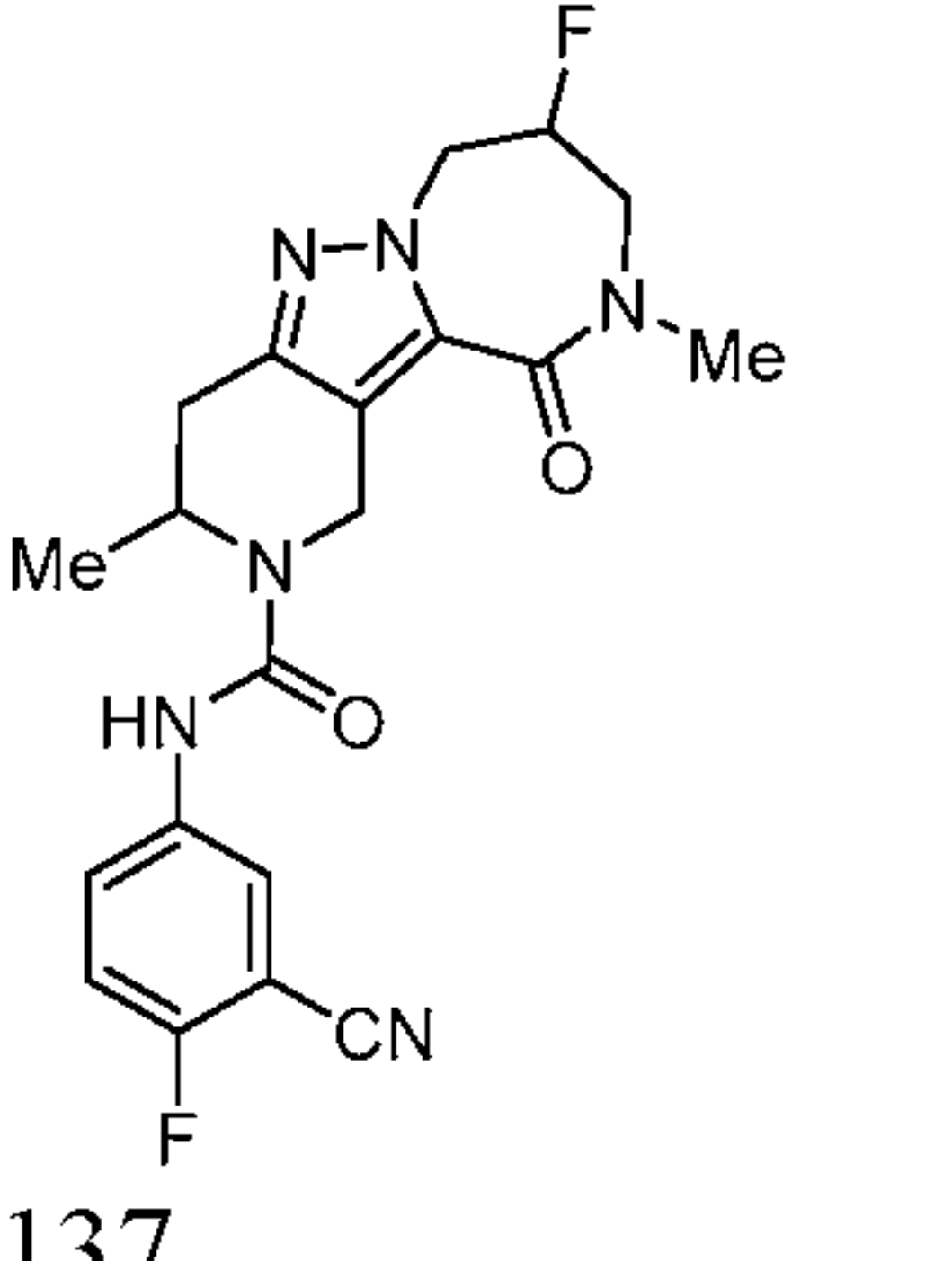
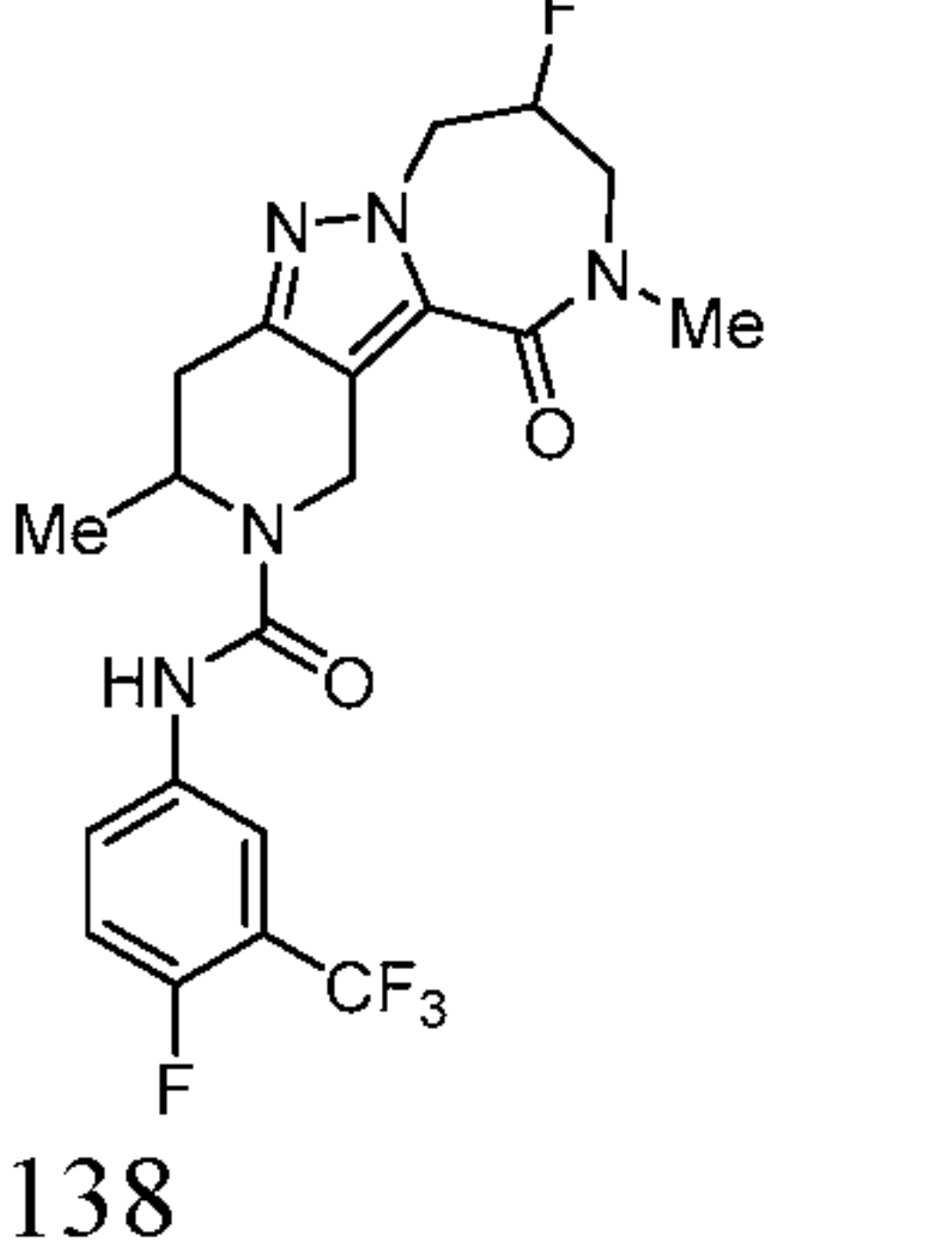
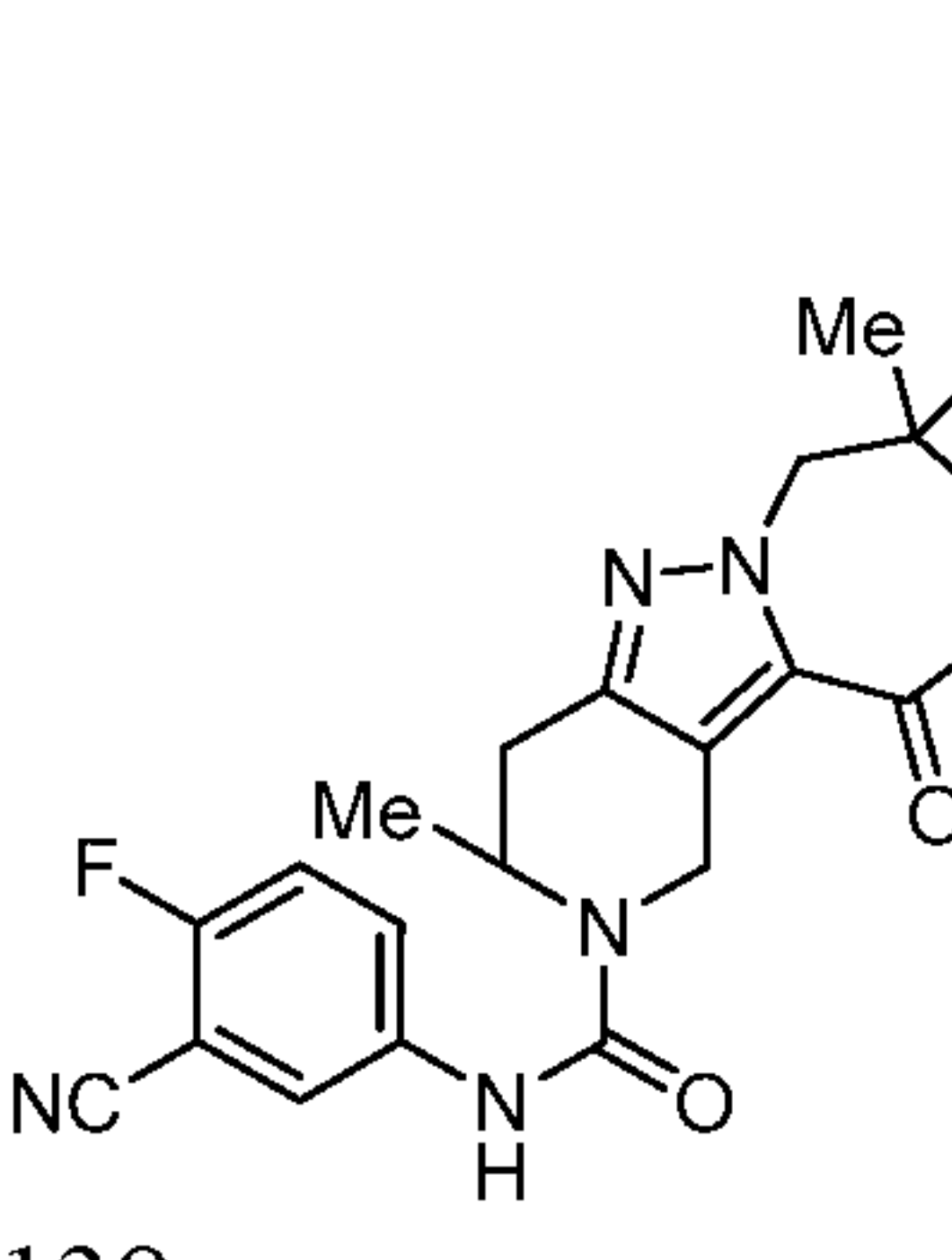
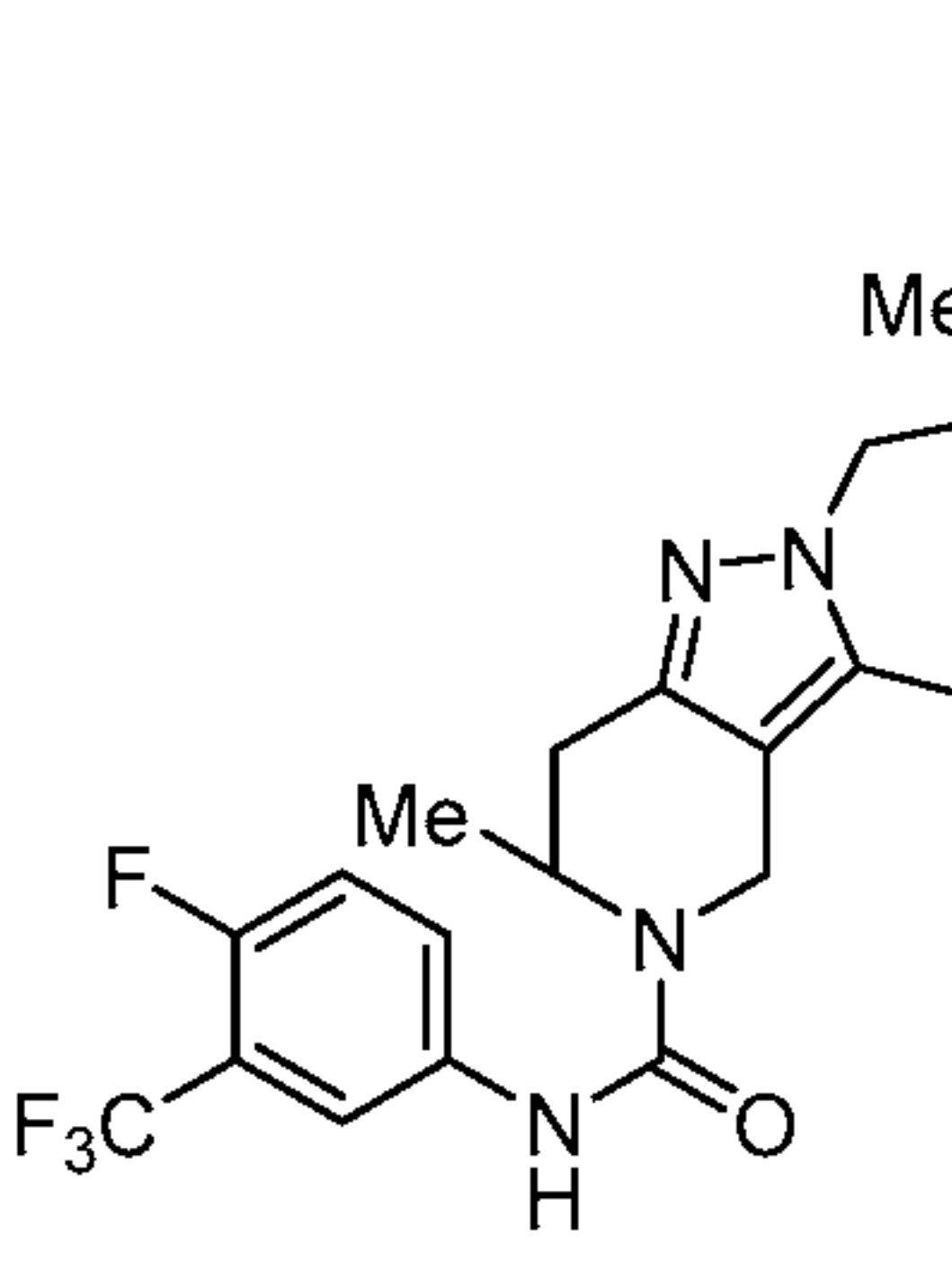
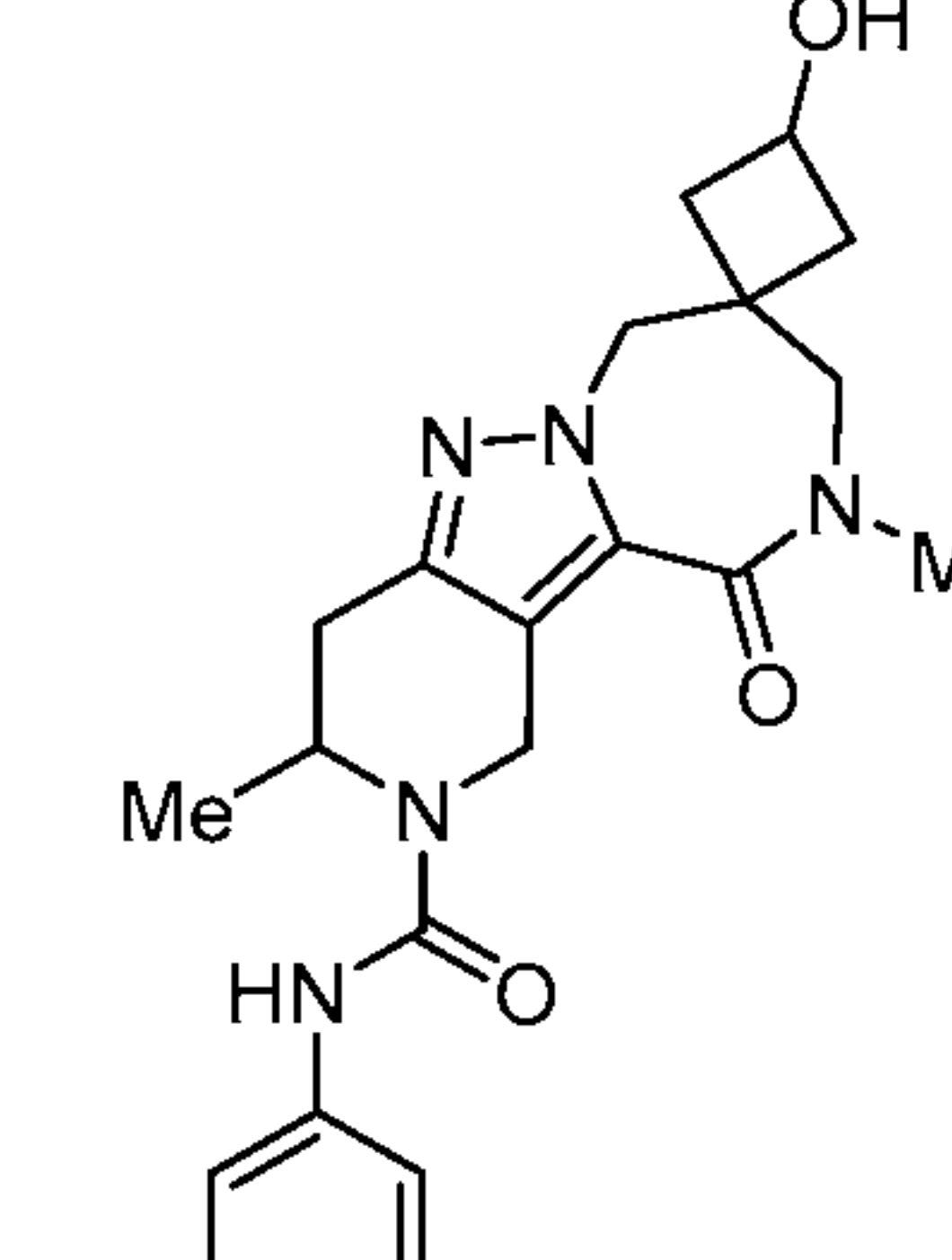
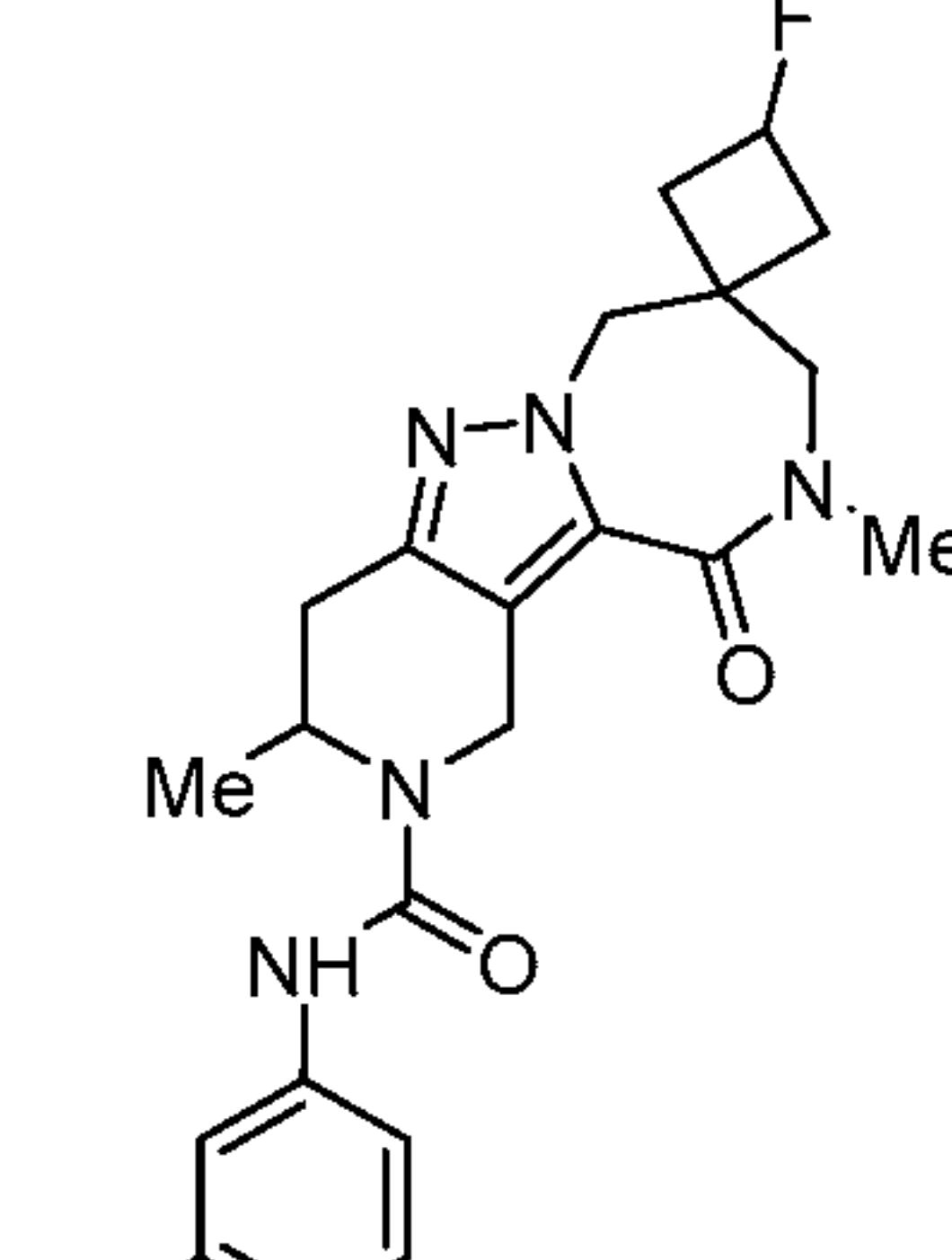
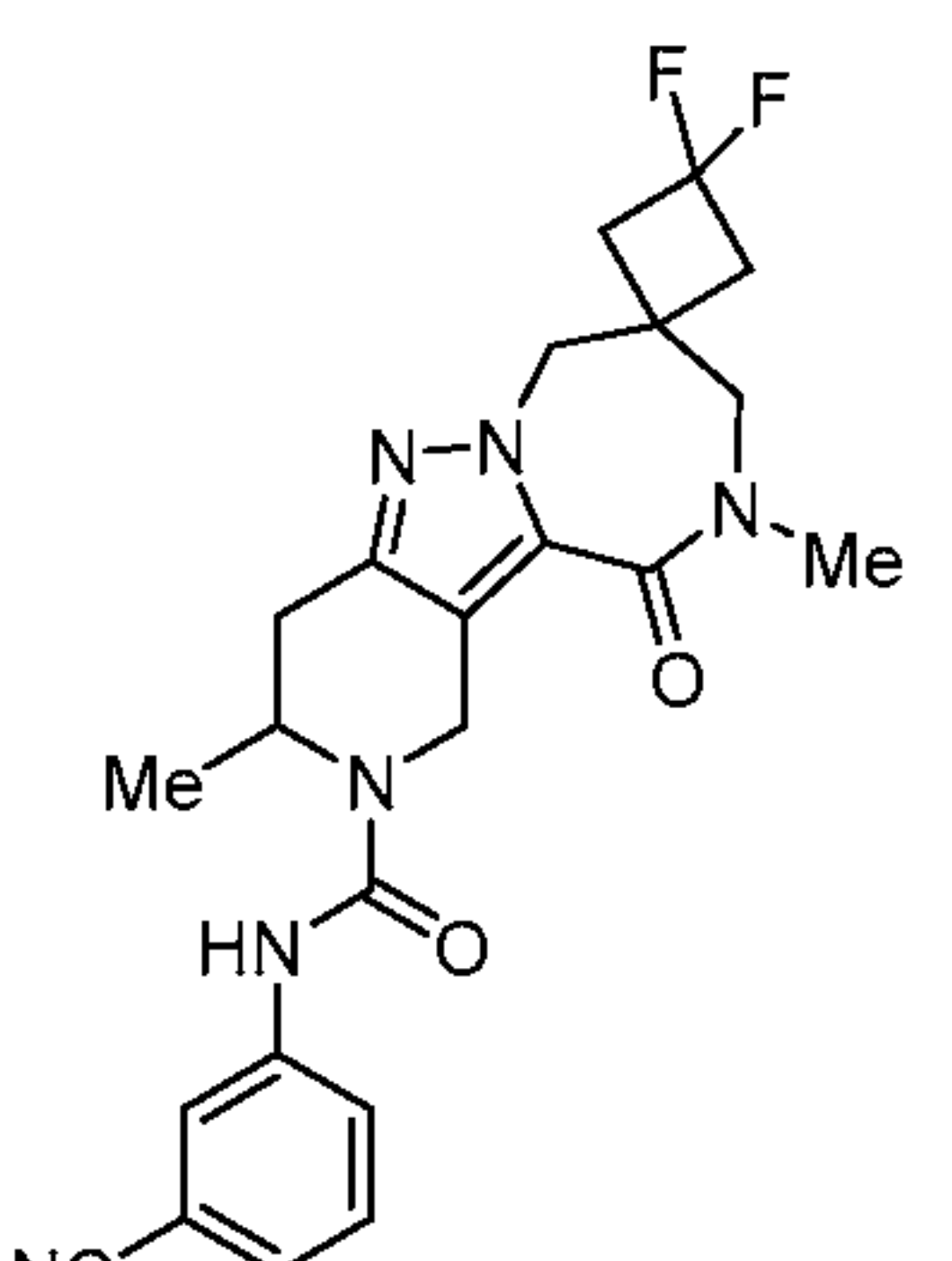
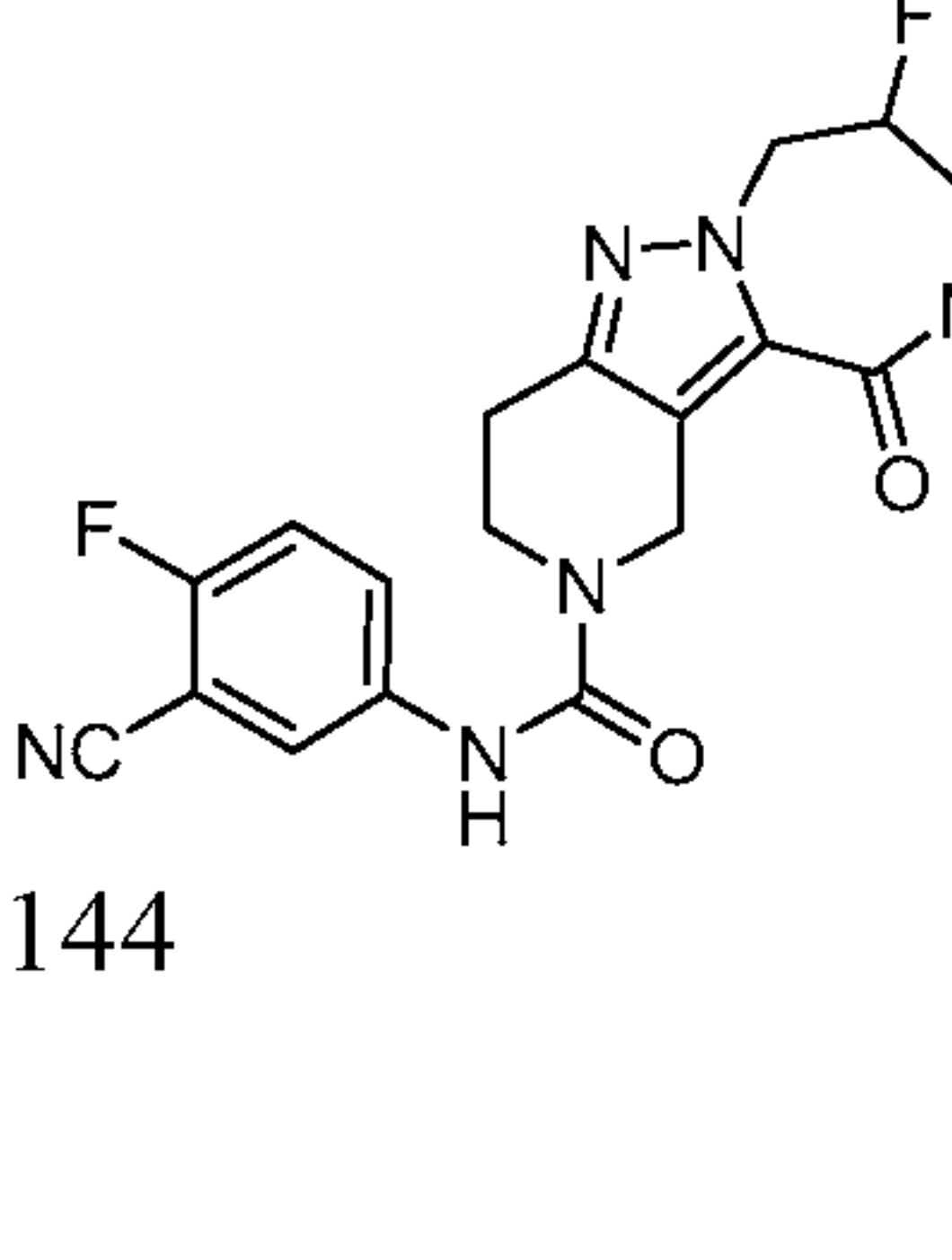
*Pure but unknown enantiomer or diastereomer.

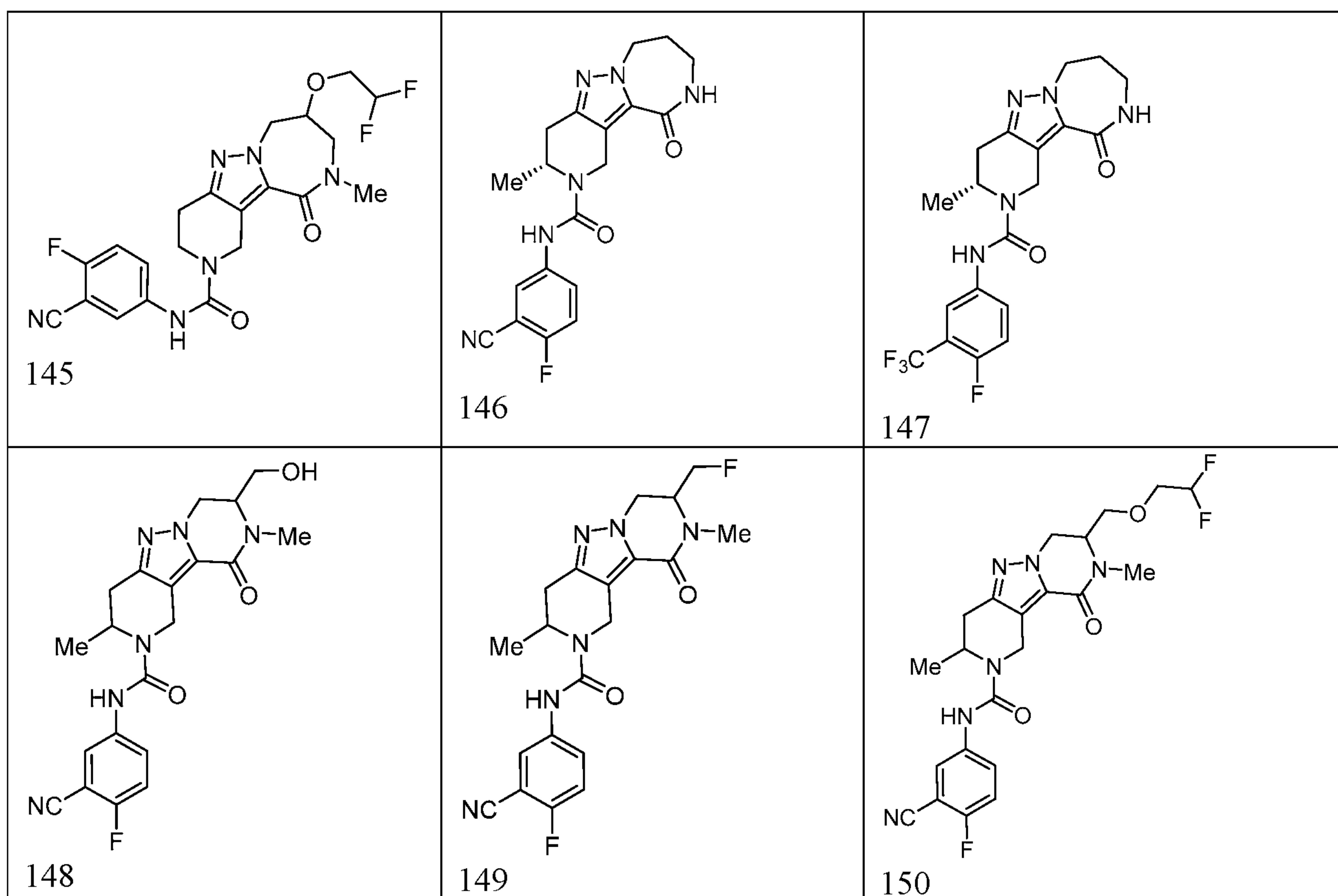
and pharmaceutically acceptable salts thereof.

Certain embodiments of Formulas I, II, III, and IV are shown below in **Table 4**.

5 disclosed compounds.

Table 4.

 <p>133</p>	 <p>134</p>	 <p>135</p>
 <p>136</p>	 <p>137</p>	 <p>138</p>
 <p>139</p>	 <p>140</p>	 <p>141</p>
 <p>142</p>	 <p>143</p>	 <p>144</p>



In an embodiment, compounds of Formulas I, II, III, and IV are selected from:

Compound ID	Compound Name
133_D1	(3R,8R*)-8-fluoro-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
133_D2	(3R,8S*)-8-fluoro-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
134_D1	(3R,8R)-N-(3-Cyano-4-fluorophenyl)-8-((2,2-difluoroethoxy)methyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
135_D1	(3R,8R)-8-((2,2-difluoroethoxy)methyl)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

Compound ID	Compound Name
134_D2	(3R,8S)-N-(3-cyano-4-fluorophenyl)-8-((2,2-difluoroethoxy)methyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
135_D2	(3R,8S)-8-((2,2-difluoroethoxy)methyl)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
136	(R)-N-(3-cyano-4-fluorophenyl)-8,8-difluoro-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.
137_D1	(3R,8R*)-N-(3-cyano-4-fluorophenyl)-8-fluoro-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
137_D2	(3R,8S*)-N-(3-Cyano-4-fluorophenyl)-8-fluoro-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
138	(3R,8R*)-8-fluoro-N-(4-fluoro-3-(trifluoromethyl)phenyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
139	(R)-N-(3-cyano-4-fluorophenyl)-3,8,8,10-tetramethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
140	(R)-N-(4-Fluoro-3-(trifluoromethyl)phenyl)-3,8,8,10-tetramethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
141	(R)-N-(3-Cyano-4-fluorophenyl)-3-hydroxy-3',10'-dimethyl-11'-oxo-1',3',4',9',10',11'-hexahydro-2'H,7'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine]-2'-carboxamide
142	(R)-N-(3-Cyano-4-fluorophenyl)-3-fluoro-3',10'-dimethyl-11'-oxo-1',3',4',9',10',11'-hexahydro-2'H,7'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine]-2'-carboxamide
143	(R)-N-(3-Cyano-4-fluorophenyl)-3,3-difluoro-3',10'-dimethyl-11'-oxo-1',3',4',9',10',11'-hexahydro-2'H,7'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine]-2'-carboxamide
144_E1	(S)-N-(3-Cyano-4-fluorophenyl)-8-fluoro-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

Compound ID	Compound Name
144_E2	(R)-N-(3-Cyano-4-fluorophenyl)-8-fluoro-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
145_D1	(R)-N-(3-Cyano-4-fluorophenyl)-8-(2,2-difluoroethoxy)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
145_D2	(S)-N-(3-Cyano-4-fluorophenyl)-8-(2,2-difluoroethoxy)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
146	(R)-N-(3-Cyano-4-fluorophenyl)-3-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
147	(R)-N-(4-Fluoro-3-(trifluoromethyl)phenyl)-3-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide
148	(3R,8S)-N-(3-Cyano-4-fluorophenyl)-8-(hydroxymethyl)-3,9-dimethyl-10-oxo-3,4,7,8,9,10-hexahydropyrido[4',3':3,4]pyrazolo[1,5-a]pyrazine-2(1H)-carboxamide
149	(3R,8S)-N-(3-cyano-4-fluorophenyl)-8-(fluoromethyl)-3,9-dimethyl-10-oxo-3,4,7,8,9,10-hexahydropyrido[4',3':3,4]pyrazolo[1,5-a]pyrazine-2(1H)-carboxamide
150	(3R,8S)-N-(3-cyano-4-fluorophenyl)-8-((2,2-difluoroethoxy)methyl)-3,9-dimethyl-10-oxo-3,4,7,8,9,10-hexahydropyrido[4',3':3,4]pyrazolo[1,5-a]pyrazine-2(1H)-carboxamide

*Pure but unknown enantiomer or diastereomer.

and pharmaceutically acceptable salts thereof.

The disclosed disclosed compounds may possess one or more stereocenters, and each stereocenter may exist independently in either the R or S configuration. In one embodiment, compounds described herein are present in optically active or racemic forms. It is to be understood that the compounds described herein encompass racemic, optically-active, regioisomeric and stereoisomeric forms, or combinations thereof that possess the therapeutically useful properties described herein.

Preparation of optically active forms is achieved in any suitable manner, including by way of non-limiting example, by resolution of the racemic form with recrystallization

techniques, synthesis from optically-active starting materials, chiral synthesis, or chromatographic separation using a chiral stationary phase. In one embodiment, a mixture of one or more isomer is utilized as the disclosed compound described herein. In another embodiment, compounds described herein contain one or more chiral centers. These compounds are prepared by any means, including stereoselective synthesis, enantioselective synthesis or separation of a mixture of enantiomers or diastereomers. Resolution of compounds and isomers thereof is achieved by any means including, by way of non-limiting example, chemical processes, enzymatic processes, fractional crystallization, distillation, and chromatography.

It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers." Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers," for example, diastereomers, enantiomers, and atropisomers.

Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers." When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R-and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (*i.e.*, as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture."

Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. Within the present disclosure, any open valency appearing on a carbon, oxygen, or nitrogen atom in any structure described herein indicates the presence of a hydrogen atom. Where a chiral center exists in a structure, but no specific stereochemistry is shown for that center, both enantiomers, separately or as a mixture, are encompassed by that structure. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art.

In embodiments, the disclosed compounds may exist as tautomers. All tautomers are included within the scope of the compounds presented herein.

Compounds described herein also include isotopically-labeled compounds wherein one or more atoms is replaced by an atom having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds described herein include and are not limited to ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{36}Cl , ^{18}F , ^{123}I , ^{125}I , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{32}P , and ^{35}S . In one embodiment, isotopically-labeled compounds are useful in drug or substrate tissue distribution studies. In another embodiment, substitution with heavier isotopes such as deuterium affords greater metabolic stability (for example, increased in vivo half-life or reduced dosage requirements).

In yet another embodiment, substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , is useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds are prepared by any suitable method or by processes using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

In one embodiment, the compounds described herein are labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

The compounds described herein, and other related compounds having different substituents are synthesized using techniques and materials described herein and as described, for example, in Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989), March, Advanced Organic Chemistry 4th Ed., (Wiley 1992); Carey and Sundberg, Advanced Organic Chemistry 4th Ed., Vols. A and B (Plenum 2000, 2001), and Green and Wuts, Protective Groups in Organic Synthesis 3rd Ed., (Wiley 1999) (all of which are incorporated by reference for such disclosure). General methods for the preparation of compound as described herein are modified by the use of appropriate reagents and conditions, for the introduction of the various moieties found in the formula as provided herein.

Compounds described herein are synthesized using any suitable procedures starting from compounds that are available from commercial sources, or are prepared using procedures described herein.

Methods of Use

Provided herein is a method of treating an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a disclosed compound.

Also provided herein is a method of eradicating an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a disclosed compound.

Provided herein is a method of reducing HBV viral load associated with an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a disclosed compound.

Further, provided herein is a method of reducing reoccurrence of an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a disclosed compound.

Provided herein is a method of inhibiting or reducing the formation or presence of HBV DNA-containing particles or HBV RNA-containing particles in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a disclosed compound.

In certain aspects, the methods and/or compositions described herein are effective for inhibiting or reducing the formation or presence of HBV-associated particles *in vitro* or *in vivo* (e.g., in a cell, in a tissue, in an organ (e.g., in the liver), in an organism or the like). HBV-associated particles may contain HBV DNA (i.e., linear and/or covalently closed circular DNA (cccDNA)) and/or HBV RNA (i.e., pre-genomic RNA and/or sub-genomic RNA). Accordingly, HBV-associated particles include HBV DNA-containing particles or HBV RNA-containing particles.

As used herein, “HBV-associated particles” refer to both infectious HBV virions (i.e., Dane particles) and non-infectious HBV subviral particles (i.e., HBV filaments and/or HBV spheres). HBV virions comprise an outer envelope including surface proteins, a nucleocapsid comprising core proteins, at least one polymerase protein, and an HBV genome. HBV filaments and HBV spheres comprise HBV surface proteins, but lack core proteins, polymerase and an HBV genome. HBV filaments and HBV spheres are also known collectively as surface antigen (HBsAg)

particles. HBV spheres comprise middle and small HBV surface proteins. HBV filaments also include middle, small and large HBV surface proteins. HBV subviral particles can include the nonparticulate or secretory HBeAg, which serves as a marker for active replication of HBV.

5 Provided herein is a method of reducing an adverse physiological impact of an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a disclosed compound.

Also provided herein is a method of reducing, slowing, or inhibiting an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a disclosed compound.

10 Provided herein is a method of inducing reversal of hepatic injury from an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a disclosed compound.

15 Provided herein is a method of reducing the physiological impact of long-term antiviral therapy for HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a disclosed compound.

Provided herein is a method of prophylactically treating an HBV infection in an individual in need thereof, wherein the individual is afflicted with a latent HBV infection, comprising administering to the individual a therapeutically effective amount of a disclosed compound.

20 In one embodiment, the individual is refractory to other therapeutic classes of HBV drugs (e.g, HBV polymerase inhibitors, interferons, viral entry inhibitors, viral maturation inhibitors, literature-described capsid assembly modulators, antiviral compounds of distinct or unknown mechanism, and the like, or combinations thereof). In another embodiment, the disclosed method reduces viral load in an individual suffering from an HBV infection to a greater extent or
25 at a faster rate compared to the extent that other therapeutic classes of HBV drugs reduce viral load in the individual.

In one embodiment, the administering of a disclosed compound, or a pharmaceutically acceptable salt thereof, allows for administering of the at least one additional therapeutic agent at a lower dose or frequency as compared to the administering of the at least one additional
30 therapeutic agent alone that is required to achieve similar results in prophylactically treating an HBV infection in an individual in need thereof.

In one embodiment, the administering of a disclosed compound, or a pharmaceutically acceptable salt thereof, reduces the viral load in the individual to a greater extent or at a faster rate compared to the administering of a compound selected from the group consisting of an HBV polymerase inhibitor, interferon, viral entry inhibitor, viral maturation inhibitor, distinct capsid assembly modulator, antiviral compounds of distinct or unknown mechanism, and any combination thereof.

In one embodiment, the disclosed method reduces HBV viral load in an individual suffering from an HBV infection, thus allowing lower doses or varying regimens of combination therapies to be used.

In one embodiment, the disclosed method causes a lower incidence of HBV viral mutation or HBV viral resistance compared to other classes of HBV drugs, thereby allowing for long term therapy and minimizing the need for changes in treatment regimens.

In one embodiment, the administering of a compound the invention, or a pharmaceutically acceptable salt thereof, causes a lower incidence of viral mutation or viral resistance than the administering of a compound selected from the group consisting of an HBV polymerase inhibitor, interferon, viral entry inhibitor, viral maturation inhibitor, distinct capsid assembly modulator, antiviral compounds of distinct or unknown mechanism, and combination thereof.

In one embodiment, the disclosed method increases the seroconversion rate from HBV infected to non-HBV infected or from detectable HBV viral load to non-detectable HBV viral load beyond that of current treatment regimens. As used herein, “seroconversion” refers to the period of time during which HBV antibodies develop and become detectable.

In one embodiment, the disclosed method increases or normalizes or restores normal health, elicits full recovery of normal health, restores life expectancy, or resolves the viral infection in the individual in need thereof.

In one embodiment, the disclosed method eliminates or decreases the number of HBV RNA particles that are released from HBV infected cells thus enhancing, prolonging, or increasing the therapeutic benefit of the disclosed disclosed compounds.

In one embodiment, the disclosed method eradicates HBV from an individual infected with HBV, thereby obviating the need for long term or life-long treatment, or shortening the duration of treatment, or allowing for reduction in dosing of other antiviral agents.

In another embodiment, the disclosed method further comprises monitoring or detecting the HBV viral load of the subject, and wherein the method is carried out for a period of time

In one embodiment, provided herein is a method of treating an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective
5 amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

In another embodiment, provided herein is a method of treating an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of Formula II, or a pharmaceutically acceptable salt thereof.

In another embodiment, provided herein is a method of treating an HBV infection in an
10 individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of Formula III, or a pharmaceutically acceptable salt thereof.

In another embodiment, provided herein is a method of treating an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of Formula IV, or a pharmaceutically acceptable salt thereof.

15 In another embodiment, provided herein is a method of treating an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of Formula V, or a pharmaceutically acceptable salt thereof.

In another embodiment, provided herein is a method of treating an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective
20 amount of a compound of Table 1, or a pharmaceutically acceptable salt thereof.

In another embodiment, provided herein is a method of treating an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of Table 2, or a pharmaceutically acceptable salt thereof.

In another embodiment, provided herein is a method of treating an HBV infection in an
25 individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of Table 3, or a pharmaceutically acceptable salt thereof.

In another embodiment, provided herein is a method of treating an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of Table 4, or a pharmaceutically acceptable salt thereof.

Any of the methods provided herein can further comprise monitoring or detecting the HBV viral load of the subject, wherein the method is carried out for a period of time including until such time that the HBV virus is undetectable.

5 Combination Therapies

The disclosed compounds may be useful in combination with one or more additional compounds useful for treating HBV infection. These additional compounds may comprise other disclosed compounds and/or compounds known to treat, prevent, or reduce the symptoms or effects of HBV infection. Such compounds include, but are not limited to, HBV polymerase
10 inhibitors, interferons, viral entry inhibitors, viral maturation inhibitors, literature-described capsid assembly modulators, reverse transcriptase inhibitors, immunomodulatory agents, TLR-agonists, and other agents with distinct or unknown mechanisms that affect the HBV life cycle or affect the consequences of HBV infection.

In non-limiting examples, the disclosed compounds may be used in combination with one
15 or more drugs (or a salt thereof) selected from the group comprising:

HBV reverse transcriptase inhibitors, and DNA and RNA polymerase inhibitors including, but not limited to, lamivudine (3TC, Zeffix, Heptovir, Epivir, and Epivir-HBV), entecavir (Baraclude, Entavir), adefovir dipivoxil (Hepsara, Preveon, bis-POM PMEA), tenofovir disoproxil fumarate (Viread, TDF or PMPA);
20 interferons including, but not limited to, interferon alpha (IFN- α), interferon beta (IFN- β), interferon lambda (IFN- λ), and interferon gamma (IFN- γ);
viral entry inhibitors;
viral maturation inhibitors;
literature-described capsid assembly modulators, such as, but not limited to, BAY 41-
25 4109;
reverse transcriptase inhibitors;
immunomodulatory agents such as TLR-agonists; and
agents of distinct or unknown mechanisms, such as but not limited to AT-61 ((E)-N-(1-chloro-3-oxo-1-phenyl-3-(piperidin-1-yl)prop-1-en-2-yl)benzamide), AT-130 ((E)-N-(1-bromo-1-(2-methoxyphenyl)-3-oxo-3-(piperidin-1-yl)prop-1-en-2-yl)-4-nitrobenzamide), and similar
30 analogs.

In one embodiment, the additional therapeutic agent is an interferon. The term “interferon” or “IFN” refers to any member of the family of highly homologous species-specific proteins that inhibit viral replication and cellular proliferation and modulate immune response. Human interferons are grouped into three classes: Type I, which includes interferon-alpha (IFN- α), interferon-beta (IFN- β), and interferon-omega (IFN- ω), Type II, which includes interferon-gamma (IFN- γ), and Type III, which includes interferon-lambda (IFN- λ). Recombinant forms of interferons that have been developed and are commercially available are encompassed by the term “interferon” as used herein. Subtypes of interferons, such as chemically modified or mutated interferons, are also encompassed by the term “interferon” as used herein. Chemically modified interferons may include pegylated interferons and glycosylated interferons. Examples of interferons also include, but are not limited to, interferon-alpha-2a, interferon-alpha-2b, interferon-alpha-n1, interferon-beta-1a, interferon-beta-1b, interferon-lambda-1, interferon-lambda-2, and interferon-lambda-3. Examples of pegylated interferons include pegylated interferon-alpha-2a and pegylated interferon alpha-2b.

Accordingly, in one embodiment, the compounds of Formula I, II, III, IV or V can be administered in combination with an interferon selected from the group consisting of interferon alpha (IFN- α), interferon beta (IFN- β), interferon lambda (IFN- λ), and interferon gamma (IFN- γ). In one specific embodiment, the interferon is interferon-alpha-2a, interferon-alpha-2b, or interferon-alpha-n1. In another specific embodiment, the interferon-alpha-2a or interferon-alpha-2b is pegylated. In a preferred embodiment, the interferon-alpha-2a is pegylated interferon-alpha-2a (PEGASYS). In another embodiment, the additional therapeutic agent is selected from immune modulator or immune stimulator therapies, which includes biological agents belonging to the interferon class.

Further, the additional therapeutic agent may be an agent of distinct or unknown mechanism including agents that disrupt the function of other essential viral protein(s) or host proteins required for HBV replication or persistence.

In another embodiment, the additional therapeutic agent is an antiviral agent that blocks viral entry or maturation or targets the HBV polymerase such as nucleoside or nucleotide or non-nucleos(t)ide polymerase inhibitors. In a further embodiment of the combination therapy, the reverse transcriptase inhibitor or DNA or RNA polymerase inhibitor is Zidovudine, Didanosine, Zalcitabine, ddA, Stavudine, Lamivudine, Abacavir, Emtricitabine, Entecavir, Apricitabine,

Atevirapine, ribavirin, acyclovir, famciclovir, valacyclovir, ganciclovir, valganciclovir, Tenofovir, Adefovir, PMPA, cidofovir, Efavirenz, Nevirapine, Delavirdine, or Etravirine.

In an embodiment, the additional therapeutic agent is an immunomodulatory agent that induces a natural, limited immune response leading to induction of immune responses against
5 unrelated viruses. In other words, the immunomodulatory agent can effect maturation of antigen presenting cells, proliferation of T-cells and cytokine release (e.g., IL-12, IL-18, IFN-alpha, -beta, and -gamma and TNF-alpha among others),

In a further embodiment, the additional therapeutic agent is a TLR modulator or a TLR agonist, such as a TLR-7 agonist or TLR-9 agonist. In further embodiment of the combination
10 therapy, the TLR-7 agonist is selected from the group consisting of SM360320 (9-benzyl-8-hydroxy-2-(2-methoxy-ethoxy)adenine) and AZD 8848 (methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9H-purin-9-yl)propyl][3-(4-morpholinyl)propyl]amino}methyl)phenyl]acetate).

In any of the methods provided herein, the method may further comprise administering to the individual at least one HBV vaccine, a nucleoside HBV inhibitor, an interferon or any
15 combination thereof. In an embodiment, the HBV vaccine is at least one of RECOMBIVAX HB, ENGERIX-B, ELOVAC B, GENEVAC-B, or SHANVAC B.

In one embodiment, the methods described herein further comprise administering at least one additional therapeutic agent selected from the group consisting of nucleotide/nucleoside analogs, entry inhibitors, fusion inhibitors, and any combination of these or other antiviral
20 mechanisms.

In another aspect, provided herein is method of treating an HBV infection in an individual in need thereof, comprising reducing the HBV viral load by administering to the individual a therapeutically effective amount of a disclosed compound alone or in combination with a reverse transcriptase inhibitor; and further administering to the individual a therapeutically
25 effective amount of HBV vaccine. The reverse transcriptase inhibitor may be at least one of Zidovudine, Didanosine, Zalcitabine, ddA, Stavudine, Lamivudine, Abacavir, Emtricitabine, Entecavir, Apricitabine, Atevirapine, ribavirin, acyclovir, famciclovir, valacyclovir, ganciclovir, valganciclovir, Tenofovir, Adefovir, PMPA, cidofovir, Efavirenz, Nevirapine, Delavirdine, or Etravirine.

30 In another aspect, provided herein is a method of treating an HBV infection in an individual in need thereof, comprising reducing the HBV viral load by administering to the

individual a therapeutically effective amount of a disclosed compound alone or in combination with a antisense oligonucleotide or RNA interference agent that targets HBV nucleic acids; and further administering to the individual a therapeutically effective amount of HBV vaccine. The antisense oligonucleotide or RNA interference agent possesses sufficient complementarity to the
5 the target HBV nucleic acids to inhibit replication of the viral genome, transcription of viral RNAs, or translation of viral proteins.

In another embodiment, the disclosed compound and the at least one additional therapeutic agent are co-formulated. In yet another embodiment, the disclosed compound and the at least one additional therapeutic agent are co-administered. For any combination therapy
10 described herein, synergistic effect may be calculated, for example, using suitable methods such as the Sigmoid- $E_{\max}$ equation (Holford & Scheiner, 19981, Clin. Pharmacokinet. 6: 429-453), the equation of Loewe additivity (Loewe & Muischnek, 1926, Arch. Exp. Pathol Pharmacol. 114: 313-326) and the median-effect equation (Chou & Talalay, 1984, Adv. Enzyme Regul. 22: 27-55). Each equation referred to above may be applied to experimental data to generate a
15 corresponding graph to aid in assessing the effects of the drug combination. The corresponding graphs associated with the equations referred to above are the concentration-effect curve, isobologram curve and combination index curve, respectively.

In an embodiment of any of the methods of administering combination therapies provided herein, the method can further comprise monitoring or detecting the HBV viral load of the
20 subject, wherein the method is carried out for a period of time including until such time that the HBV virus is undetectable.

Administration/Dosage/Formulations

In another aspect, provided herein is a pharmaceutical composition comprising a at least
25 one disclosed compound, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of
30 administration, without being toxic to the patient.

In particular, the selected dosage level will depend upon a variety of factors including the activity of the particular compound employed, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds or materials used in combination with the compound, the age, sex, weight, condition, general health and prior
5 medical history of the patient being treated, and like factors well, known in the medical arts.

A medical doctor, e.g., physician or veterinarian, having ordinary skill in the art may readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could begin administration of the pharmaceutical composition to dose the disclosed compound at levels lower than that required in
10 order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In particular embodiments, it is especially advantageous to formulate the compound in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the patients to be treated;
15 each unit containing a predetermined quantity of the disclosed compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical vehicle. The dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the disclosed compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding/formulating such a disclosed
20 compound for the treatment of HBV infection in a patient.

In one embodiment, the compositions of the invention are formulated using one or more pharmaceutically acceptable excipients or carriers. In one embodiment, the pharmaceutical compositions of the invention comprise a therapeutically effective amount of a disclosed compound and a pharmaceutically acceptable carrier.

25 In some embodiments, the dose of a disclosed compound is from about 1 mg to about 2,500 mg. In some embodiments, a dose of a disclosed compound used in compositions described herein is less than about 10,000 mg, or less than about 8,000 mg, or less than about 6,000 mg, or less than about 5,000 mg, or less than about 3,000 mg, or less than about 2,000 mg, or less than about 1,000 mg, or less than about 500 mg, or less than about 200 mg, or less than
30 about 50 mg. Similarly, in some embodiments, a dose of a second compound (i.e., another drug for HBV treatment) as described herein is less than about 1,000 mg, or less than about 800 mg,

or less than about 600 mg, or less than about 500 mg, or less than about 400 mg, or less than about 300 mg, or less than about 200 mg, or less than about 100 mg, or less than about 50 mg, or less than about 40 mg, or less than about 30 mg, or less than about 25 mg, or less than about 20 mg, or less than about 15 mg, or less than about 10 mg, or less than about 5 mg, or less than about 2 mg, or less than about 1 mg, or less than about 0.5 mg, and any and all whole or partial increments thereof.

In one embodiment, the present invention is directed to a packaged pharmaceutical composition comprising a container holding a therapeutically effective amount of a disclosed compound, alone or in combination with a second pharmaceutical agent; and instructions for using the compound to treat, prevent, or reduce one or more symptoms of HBV infection in a patient.

Routes of administration of any of the compositions of the invention include oral, nasal, rectal, intravaginal, parenteral, buccal, sublingual or topical. The compounds for use in the invention may be formulated for administration by any suitable route, such as for oral or parenteral, for example, transdermal, transmucosal (e.g., sublingual, lingual, (trans)buccal, (trans)urethral, vaginal (e.g., trans- and perivaginally), (intra)nasal and (trans)rectal), intravesical, intrapulmonary, intraduodenal, intragastrical, intrathecal, subcutaneous, intramuscular, intradermal, intra-arterial, intravenous, intrabronchial, inhalation, and topical administration.

Suitable compositions and dosage forms include, for example, tablets, capsules, caplets, pills, gel caps, troches, dispersions, suspensions, solutions, syrups, granules, beads, transdermal patches, gels, powders, pellets, magmas, lozenges, creams, pastes, plasters, lotions, discs, suppositories, liquid sprays for nasal or oral administration, dry powder or aerosolized formulations for inhalation, compositions and formulations for intravesical administration and the like. It should be understood that the formulations and compositions that would be useful in the present invention are not limited to the particular formulations and compositions that are described herein.

For oral application, particularly suitable are tablets, dragees, liquids, drops, suppositories, or capsules, caplets and gelcaps. The compositions intended for oral use may be prepared according to any method known in the art and such compositions may contain one or more agents selected from the group consisting of inert, non-toxic pharmaceutically excipients

that are suitable for the manufacture of tablets. Such excipients include, for example an inert diluent such as lactose; granulating and disintegrating agents such as cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate. The tablets may be uncoated or they may be coated by known techniques for elegance or to delay the release of the active ingredients. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert diluent.

For parenteral administration, the disclosed compounds may be formulated for injection or infusion, for example, intravenous, intramuscular or subcutaneous injection or infusion, or for administration in a bolus dose or continuous infusion. Suspensions, solutions or emulsions in an oily or aqueous vehicle, optionally containing other formulatory agents such as suspending, stabilizing or dispersing agents may be used.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures, embodiments, claims, and examples described herein. Such equivalents were considered to be within the scope of this invention and covered by the claims appended hereto. For example, it should be understood, that modifications in reaction conditions, including but not limited to reaction times, reaction size/volume, and experimental reagents, such as solvents, catalysts, pressures, atmospheric conditions, e.g., nitrogen atmosphere, and reducing/oxidizing agents, with art-recognized alternatives and using no more than routine experimentation, are within the scope of the present application.

It is to be understood that wherever values and ranges are provided herein, all values and ranges encompassed by these values and ranges, are meant to be encompassed within the scope of the present invention. Moreover, all values that fall within these ranges, as well as the upper or lower limits of a range of values, are also contemplated by the present application.

The following examples further illustrate aspects of the present invention. However, they are in no way a limitation of the teachings or disclosure of the present invention as set forth herein.

EXAMPLES

Exemplary compounds useful in methods of the invention will now be described by reference to the illustrative synthetic schemes for their general preparation below and the specific

examples that follow. Artisans will recognize that, to obtain the various compounds herein, starting materials may be suitably selected so that the ultimately desired substituents will be carried through the reaction scheme with or without protection as appropriate to yield the desired product. Alternatively, it may be necessary or desirable to employ, in the place of the ultimately desired substituent, a suitable group that may be carried through the reaction scheme and replaced as appropriate with the desired substituent. Unless otherwise specified, the variables are as defined above in reference to Formula (I). Reactions may be performed between the melting point and the reflux temperature of the solvent, and preferably between 0 °C and the reflux temperature of the solvent. Reactions may be heated employing conventional heating or microwave heating. Reactions may also be conducted in sealed pressure vessels above the normal reflux temperature of the solvent.

Abbreviations and acronyms used herein include the following:

Table 5:

Term	Acronym
Acetonitrile	ACN or MeCN
Aqueous	aq
Atmosphere	atm
tert-Butylcarbamoyl	Boc
Boron-dipyrromethene	BODIPY
Benzyl	Bn
Broad	br
Capside assembly	CA
Carboxybenzyl	CBz
Diatomaceous Earth	Celite [®]
1,1'-Carbonyldiimidazole	CDI
Doublet of doublets	dd
Diethylaminosulfur trifluoride	DAST
Di- <i>tert</i> -butyl azodicarboxylate	DBAD
1,8-Diazabicyclo[5.4.0]undec-7-ene	DBU

Term	Acronym
Dichloroethane	DCE
Dichloromethane	DCM
Bis(2-methoxyethyl)aminosulfur trifluoride	Deoxo-Fluor®
Diethyl azodicarboxylate	DEAD
Diisopropyl azodicarboxylate	DIAD
Diisopropylethylamine	DIPEA, DIEA, or Hunig's base
4-Dimethylaminopyridine	DMAP
1,2-Dimethoxyethane	DME
<i>N,N</i> -Dimethylformamide	DMF
Dimethyl sulfide	DMS
Dimethylsulfoxide	DMSO
Deoxyribonucleic Acid	DNA
1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide	EDCI, EDAC, or EDC
Diethyl ether	Ether, Et ₂ O
Ethyl Acetate	EtOAc, or EA
Ethanol	EtOH
Electrospray ionization	ESI
Normal-phase silica gel chromatography	FCC
Grams	g
Hours	h or hr
(1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate)	HATU
Hepatitis B Virus	HBV
Acetic acid	HOAc
1-Hydroxy-7-azabenzotriazole	HOAt
Hydroxybenzotriazole	HOBt
High-pressure liquid chromatography	HPLC
Hertz	Hz

Term	Acronym
Isopropyl alcohol	<i>i</i> PrOH, IPA
Potassium <i>tert</i> -butoxide	KO <i>t</i> Bu
Lithium aluminum hydride	LAH
Liquid chromatography and mass spectrometry	LCMS
Lithium diisopropylamide	LDA
Lithium bis(trimethylsilyl)amide	LHMDS
Molar	M
multiplet	m
Mass to charge ratio	m/z
meta-Chloroperoxybenzoic acid	<i>m</i> CPBA
Methyl Iodide	MeI
Methanol	MeOH
Milligrams	mg
Megahertz	MHz
Minute	min
Milliliter	mL
Microliter	μL
Millimole	mmol
Micromole	μmol
Mass spectrometry	MS
Mesityl chloride	MsCl
Normal	N
Sodium acetate	NaOAc
Sodium <i>tert</i> -butoxide	NaO <i>t</i> -Bu
N-Methylmorpholine N-oxide	NMO
Nuclear magnetic resonance	NMR
CF ₃ SO ₃ [−] or triflate	OTf
Polymerase chain reaction	PCR

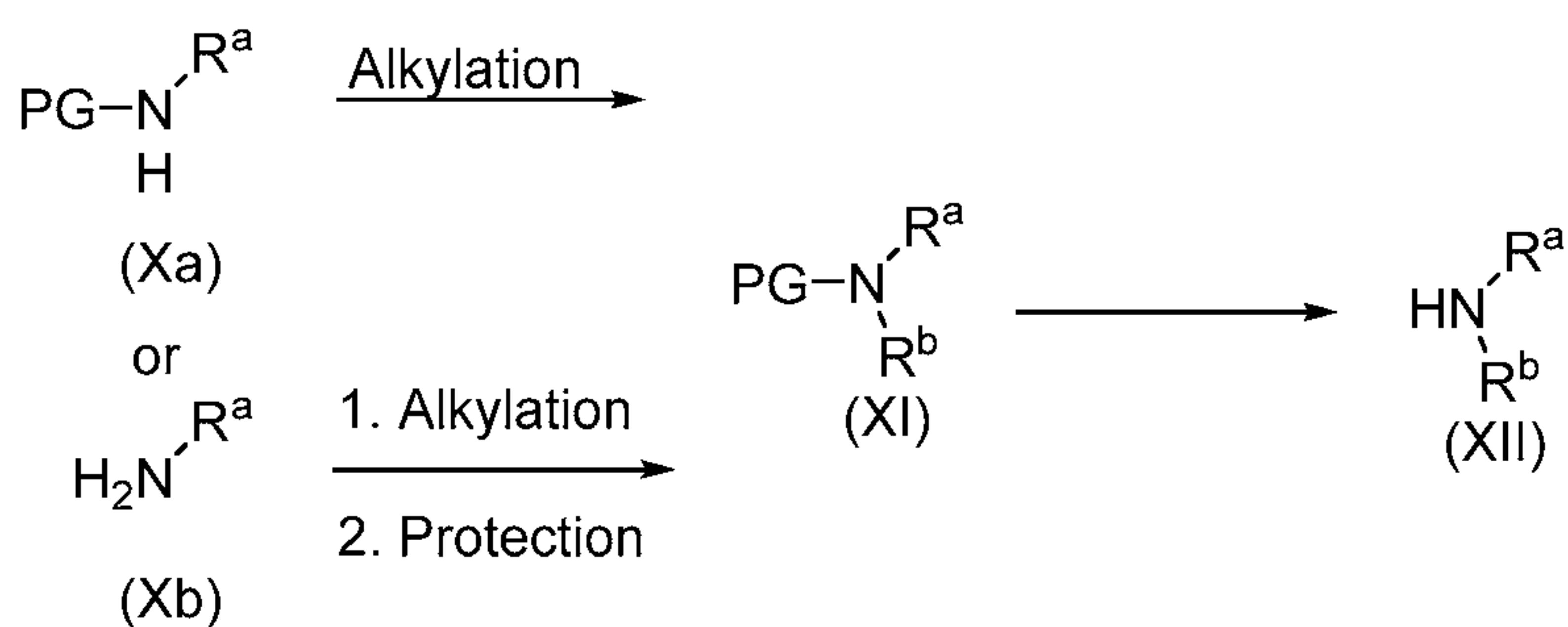
Term	Acronym
Petroleum ether	PE
Palladium (II) acetate	Pd(OAc) ₂
Palladium(II)bis(triphenylphosphine) dichloride	Pd(PPh ₃) ₂ Cl ₂
Tetrakis(triphenylphosphine)palladium(0)	Pd(PPh ₃) ₄
[1,1'-Bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II)	PdCl ₂ (dtbpf) or Pd(dtbpf) ₂ Cl ₂
[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)	PdCl ₂ (dppf) or Pd(dppf) ₂ Cl ₂
9-(2-Phosphonyl-methoxypropyl)adenine	MPA
Parts per million	ppm
Precipitate	ppt
Polytetrafluoroethylene	PTFE
Pyridine	Py
Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate	PyBOP
Retention time	R _t
Ribonucleic Acid	RNA
Room temperature	rt
singlet	s
Saturated	sat
1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)	Selectfluor [®]
[2-(Trimethylsilyl)ethoxy]methyl acetal	SEM
Supercritical Fluid Chromatography	SFC
Temperature	T
triplet	t
Propylphosphonic anhydride	T ₃ P
<i>Tert</i> -Butyl alcohol	<i>t</i> BuOH, t-BuOH
Tetra-n-butylammonium fluoride	TBAF
Tetra-n-butylammonium iodide	TBAI

Term	Acronym
Tert-butyldiphenylsilyl chloride	TBDPSCI
Triethylamine	TEA
Trifluoroacetic acid	TFA
Tetrahydrofuran	THF
Thin layer chromatography	TLC
Toll-like receptor	TLR
Tumor necrosis factor	TNF
Volume in milliliters of solvent per gram of substrate	V, or volumes
(Diethylamino)difluorosulfonium tetrafluoroborate	XtalFluor®

PREPARATIVE EXAMPLES

Exemplary compounds useful in methods of the invention will now be described by reference to the illustrative synthetic schemes for their general preparation below and the specific examples to follow.

SCHEME 1



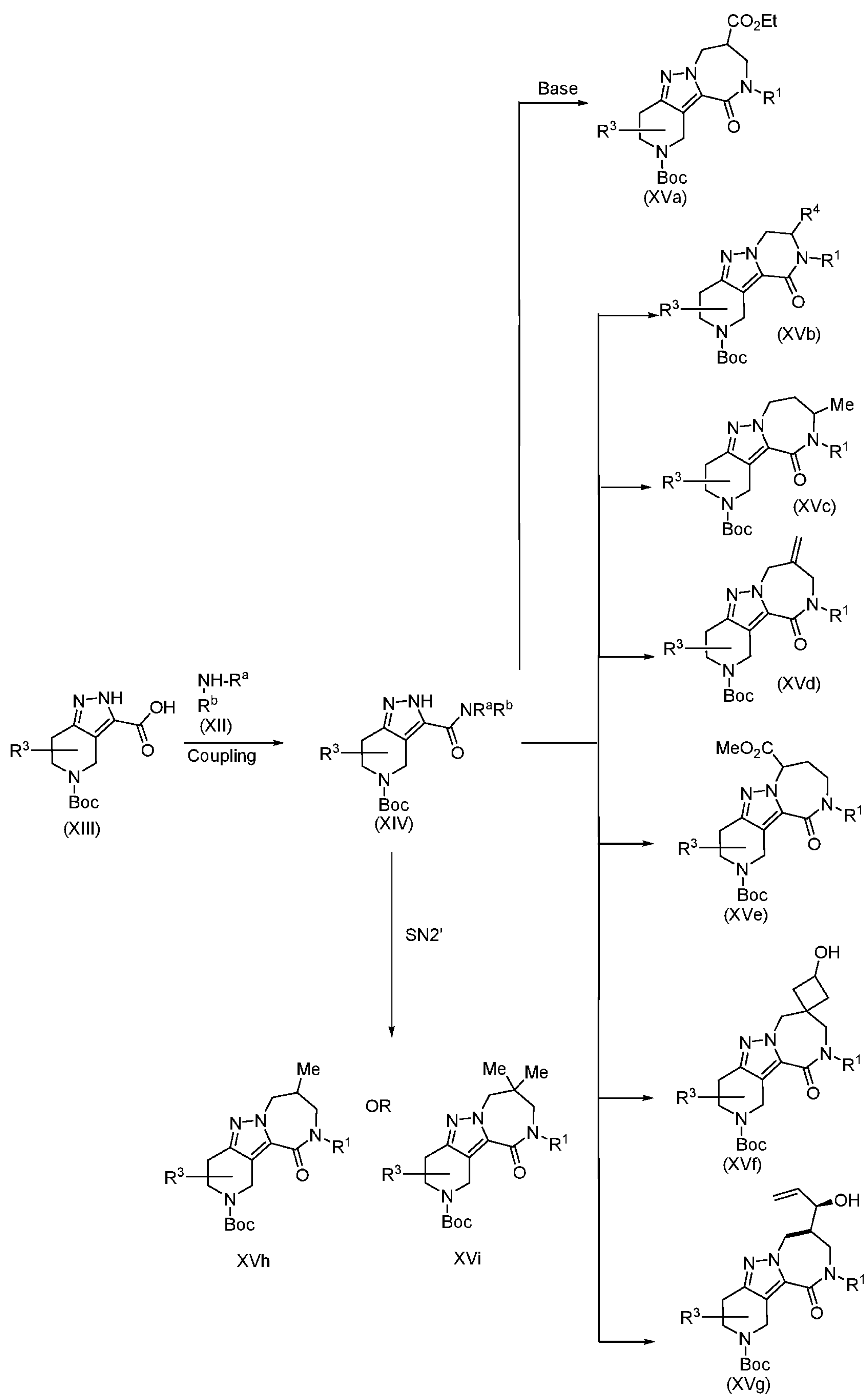
According to SCHEME 1, a commercially available or synthetically accessible compound of formula (Xa), where R^a is C₁₋₆alkyl or C₁₋₆haloalkyl, and PG is a suitable nitrogen protecting group such as BOC, Bn, and the like, is alkylated with an alkylating agent such as ethyl prop-2-enoate, ethyl 2-(bromomethyl)prop-2-enoate, and the like, to provide a compound

of formula (XI), where R^b is C_{2-6} alkylene optionally substituted with CO_2Et . A compound of formula (Xa), where R^a is CH_3 or CH_2CHF_2 , and PG is BOC, is alkylated under conditions known to one skilled in the art, for example, reaction with or without a base such as NaH, CS_2CO_3 , K_2CO_3 , and the like, in a suitable solvent such as THF, DMF and the like, with an alkylating agent such as ethyl 2-(bromomethyl)prop-2-enoate and the like, at temperatures ranging from 0 °C to 80 °C, for a period of 12-24 h, to provide a compound of formula (XI), where R^b is $CH_2(C=CH_2)CO_2Et$. In an alternate method, a compound of formula (Xb), is first alkylated under conditions previously described, then protected with a suitable nitrogen protecting group, to provide a compound of formula (XI). For example, a compound of formula (Xb), where R^a is C_{1-6} alkyl, is alkylated with an alkylating agent such as 5-methylene-1,3,2-dioxathiane 2-oxide, in a solvent such as THF, and the like, at a temperature of about 50-80 °C, subsequent protection with di-tert-butyl dicarbonate, provides a compound of formula (XI), where R^b is $CH_2(C=CH_2)CH_2OH$, and PG is BOC.

Deprotection of the nitrogen protecting group, employing conditions known to one skilled in the art provides a compound of formula (XII). For example the BOC protecting group is removed with acid such as TFA, HCl, and the like, in a suitable solvent such as DCM, and the like.

20

SCHEME 2



According to SCHEME 2, a commercially available or synthetically accessible compound of formula (XIII), where R^3 is H or C_{1-6} alkyl, is coupled with a compound of formula (XII), where R^a is C_{1-6} alkyl or C_{1-6} haloalkyl, and R^b is CH_2CH_2OH , $CH(CH_3)CH_2CH_2OH$, $CH(C=CH_2)CO_2Et$, $CH_2CH(C=CH_2)CH_2OH$, $CH_2CH_2CH(OPG)CO_2Me$, $CH_2CH(CH_2OH)CH(OTBDPS)CH=CH_2$, $CH_2C(CH_2OH)(CH_2CH(OBn)CH_2)$, $CH_2CH_2CH(OH)CO_2Me$, $CH_2C(Me)_2CH_2OH$, $CH(CH_2OTBS)(CH_2OCH_2CH=CH_2)$, and the like, under amide bond coupling conditions to provide a compound of formula (XIV). For example, an acid compound of formula (XIII) is reacted with an amine of formula (XII), in the presence of a dehydrating agent such as HOBt/EDAC, CDI, PyBOP, HATU, HOAT, propylphosphonic anhydride (T_3P), a suitably selected base such as DIPEA, TEA, and the like, in a solvent such as toluene, MeCN, EtOAc, DMF, THF, DCM, or a mixture thereof, to afford a compound of formula (XIV).

A compound of formula (XIV), where R^3 is H or C_{1-6} alkyl, R^a is C_{1-6} alkyl or C_{1-6} haloalkyl, and R^b is $CH(C=CH_2)CO_2Et$, is reacted with a base such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), in a solvent such as ACN, at a temperature of about 40-60 °C for a period of 1-3 h provides a compound of formula (XVa).

A compound of formula (XIV) is cyclized under Mitsunobu conditions, to provide a compound of formulas (XVb) where R^4 is H, (XVc), and (XVd). For example, a compound of formula (XIV), where R^3 is H or C_{1-6} alkyl, R^a is C_{1-6} alkyl or C_{1-6} haloalkyl, and R^b is CH_2CH_2OH is reacted with a trisubstituted phosphane such as triphenylphosphane, tributylphosphane, and the like, and an azodicarboxylate such as diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD), and the like, in a suitable solvent such as THF, and the like, at temperatures ranging from 70- 100 °C, for a period of 10-16 hours, to provide a compound of formula (XVb), where R^1 and R^3 are C_{1-6} alkyl or C_{1-6} haloalkyl.

A compound of formula (XIV), where R^3 is H or C_{1-6} alkyl, R^a is C_{1-6} alkyl or C_{1-6} haloalkyl, and R^b is $CH_2CH_2CH(OH)CO_2Me$, is reacted with a base such as TEA, and a sulfonyl such as MsCl, in a solvent such as DCM, at a temperature of about 0 °C for a period of 1-3 h. This is followed by a base such as NaH in a solvent such as THF to provide a compound of formula (XVe).

A compound of formula (XIV), where R^3 is H or C_{1-6} alkyl, R^a is C_{1-6} alkyl or C_{1-6} haloalkyl, and R^b is $CH_2C(CH_2OH)(CH_2CH(OBn)CH_2)$, is reacted with a base such as TEA, and a sulfonyl such as MsCl, in a solvent such as DCM, at a temperature of about 0 °C for a period of 1-3 h. This is followed by a base such as NaH in a solvent such as THF to provide a compound
5 of formula (XVf).

A compound of formula (XIV), where R^3 is H or C_{1-6} alkyl, R^a is C_{1-6} alkyl or C_{1-6} haloalkyl, and R^b is $CH_2CH(CH_2OH)CH(OTBDPS)CH=CH_2$, is reacted with a base such as TEA, and a sulfonyl such as MsCl, in a solvent such as DCM, at a temperature of about 0 °C for a period of 1-3 h. This is followed by a base such as NaH in a solvent such as THF to provide a
10 compound of formula (XVg).

A compound of formula (XIV), where R^3 is H or C_{1-6} alkyl, R^a is C_{1-6} alkyl or C_{1-6} haloalkyl, and R^b is $CH_2CH(C=CH_2)CH_2OH$, is reacted with a base such as TEA, and a sulfonyl such as MsCl, in a solvent such as DCM, at a temperature of about 0 °C for a period of 1-3 h. This is followed by a base such as potassium tert-butoxide in a solvent such as DMF. Followed
15 by a reducing agent such palladium on carbon in the presence of hydrogen gas in a solvent such as methanol, at a temperature of about 30 °C, for about 15-45 minutes provides a compound of formula (XVh).

A compound of formula (XIV), where R^3 is H or C_{1-6} alkyl, R^a is C_{1-6} alkyl or C_{1-6} haloalkyl, and R^b is $CH_2C(Me)_2CH_2OH$, is reacted with a base such as TEA, and a sulfonyl such
20 as MsCl, in a solvent such as DCM, at a temperature of about 0 °C for a period of 1-3 h. This is followed by a base such as sodium hydride in a solvent such as THF to provide a compound of formula (XVi).

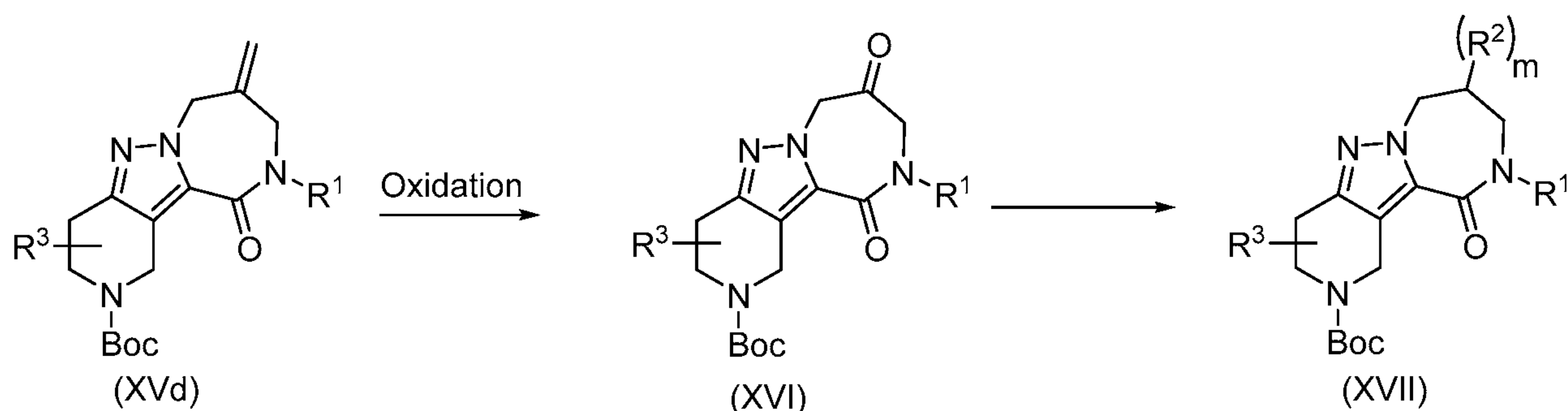
A compound of formula (XVb), where R^3 is H or C_{1-6} alkyl, R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl, and R^4 is CH_2OH , is prepared in three steps. First, a compound of formula (XIV) where R^b is $CH(CH_2OTBS)(CH_2OCH_2CH=CH_2)$ is deprotected using a suitable reagent such as TBAF, in a solvent such as THF, to provide a compound of formula (XIV) where R^b is $CH(CH_2OH)(CH_2OCH_2CH=CH_2)$. Second, cyclized under the Mitsunobu conditions described
25 above. Third, removal of the allyl group using suitable reagents such as osmium oxide, with sodium periodate, and with NMO, in a solvent such as THF, to provide a compound of formula
30 (XVb), where R^3 is H or C_{1-6} alkyl, R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl, and R^4 is CH_2OH .

A compound of formula (XVb), where where R^3 is H or C_{1-6} alkyl, R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl, and R^4 is CH_2OH , is reacted with a fluorinating reagent such as DAST, in a solvent such as DCM, to provide a compound of formula (XVb), where where R^3 is H or C_{1-6} alkyl, R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl, and R^4 is CH_2F .

5 A compound of formula (XVb), where where R^3 is H or C_{1-6} alkyl, R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl, and R^4 is CH_2OH , is reacted with an alkylating reagent such as CF_2HCH_2OTf , using a base such as sodium hydride, in a solvent such as THF, to provide a compound of formula (XVb), where where R^3 is H or C_{1-6} alkyl, R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl, and R^4 is $CH_2OCH_2CHF_2$.

10

SCHEME 3



According to SCHEME 3, a compound of formula (XVd) is oxidized, employing oxidation conditions known to one skilled in the art, for example OsO_4 and $NaIO_4$.

15 A compound of formula (XVI), where R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl and R^3 is H or C_{1-6} alkyl, is reduced with a reducing agent such as $NaBH_4$, and the like, in a suitable solvent such as MeOH, THF, and the like, to provide a compound of formula (XVII), where R^2 is OH, and m is 1.

20 A compound of formula (XVII), where R^2 is OH, and m is 1, is alkylated with an alkylating agent such as a C_{1-6} alkylhalide or C_{1-6} haloalkyl halide, and the like, a base such as NaH, and the like, in a suitable solvent such as THF, DMF, and the like, to provide a compound of formula (XVII), where R^2 is OC_{1-6} alkyl or $O-C_{1-6}$ haloalkyl, and m is 1.

25 A compound of formula (XVII), where R^2 is OH, and m is 1, is fluorinated with a fluorinating agent such as, DAST, XtalFluor®, Deoxo-Fluor®, and the like, in a suitable solvent such as DCM, and the like, at temperatures ranging from $-78\text{ }^{\circ}C$ to $50\text{ }^{\circ}C$, for a period of 2-16 h, to provide a compound of formula (XVII), where R^2 is F, and m is 1.

A compound of formula (XVII), where R^2 is S-C₁₋₆alkyl, and m is 1, is preped in three steps from a compound of formula (XVII) where R^2 is OH, and m is 1. In a first step, mesylation of a compound of formula (XVII) where R^2 is OH, with mesyl chloride, a base such as TEA, in a solvent such as DCM, to provide a compound of formula (XVII), where R^2 is O-SO₂CH₃.

5 Subsequent reaction of the mesylated compound of formula (XVII) with sodium methanethiolate, in a solvent such as DMF, at temperatures ranging from 0 °C to 20 °C, provides a compound of formula (XVII), where R^2 is S(C=O)CH₃. Reaction of a compound of formula (XVII), where R^2 is S(C=O)CH₃ with a base such as K₂CO₃, and the like, and an C₁₋₆alkylhalide such as MeI, provides a compound of formula (XVII), where R_2 is S-C₁₋₆alkyl.

10 A carbonyl compound of formula (XVI), where R^1 is C₁₋₆alkyl or C₁₋₆haloalkyl and R^3 is H or C₁₋₆alkyl, is fluorinated with a fluorinating agent such as, DAST, XtalFluor®, Deoxo-Fluor®, and the like, in a suitable solvent such as DCM, and the like, at temperatures ranging from -78 °C to 50 °C, for a period of 2-16 h, to provide a compound of formula (XVII), where R^2 is F, and m is 2.

15 A carbonyl compound of formula (XVI), where R^1 is C₁₋₆alkyl or C₁₋₆haloalkyl and R^3 is H or C₁₋₆alkyl, is reacted with an alkyl amine of formula N(C₁₋₆alkyl)₁₋₂ such as NH(CH₃)₂, or an optionally substituted C₂-C₆-heterocycloalkyl such as morpholine, azetidine, difluoroazetidine, pyrrolidine, and the like, under reductive amination conditions, to provide a compound of formula (XVII), where R^2 is an optionally substituted C₂-C₆-heterocycloalkyl, or N(C₁₋₆alkyl)₂.

20 For example, a carbonyl compound of formula (XVI), where R^1 is C₁₋₆alkyl or C₁₋₆haloalkyl and R^3 is H or C₁₋₆alkyl, is reacted with NH(CH₃)₂, a reducing agent such as NaCNBH₃, NaBH₃, sodium triacetyborohydride, and the like, with or without a dehydrating agent such as molecular sieves, with or without HOAc, or NaOAc, in a suitable solvent such as DCM, THF, DCE, and the like, provides a compound of formula (XVI) where R^2 is N(CH₃)₂.

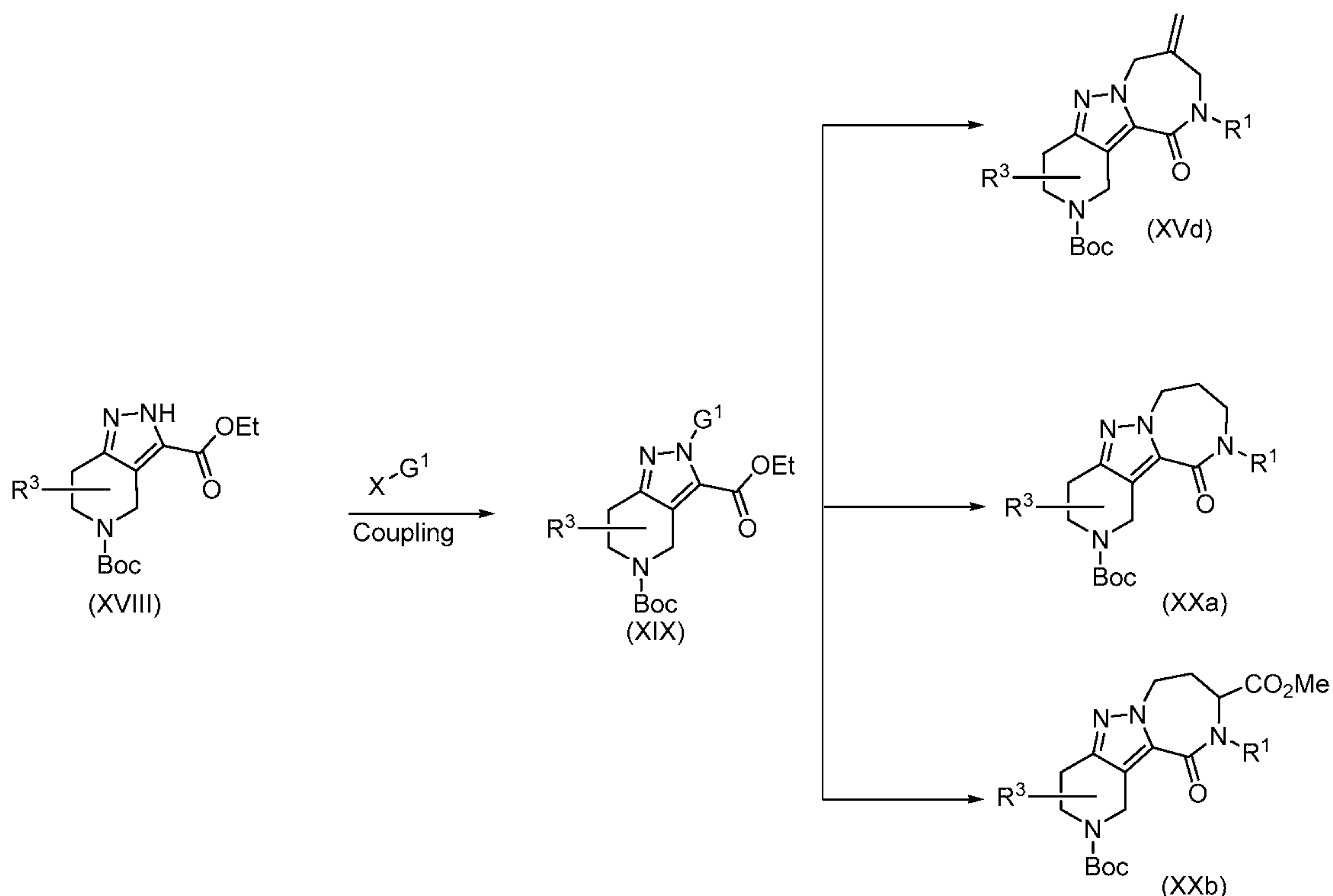
25 A compound of formula (XVII), where R^2 is CH₂CO₂C₁₋₆alkyl, is prepared in two steps from a carbonyl compound of formula (XVI), where R^1 is C₁₋₆alkyl or C₁₋₆haloalkyl and R^3 is H or C₁₋₆alkyl. In a first step, carbonyl compound of formula (XVI) is reacted with methyl 2-dimethoxyphosphorylacetate, a base such as potassium 2-methylpropan-2-olate, in a solvent such as THF, and the like, at temperatures ranging from 0 °C to 20 °C. In a second step, reduction of
30 the alkene under hydrogenation conditions, for example, Pd/C and H₂, in a solvent such as EtOH, MeOH, and the like, provides a compound of formula (XVII), where R^2 is CH₂CO₂CH₃.

A compound of formula (XVII), where R^2 is $\text{CH}_2\text{N}(\text{C}_{1-6}\text{alkyl})_{1-2}$ such as $\text{NH}(\text{CH}_3)_2$, $\text{CH}_2\text{N}(\text{C}_{1-6}\text{haloalkyl})_{1-2}$, or an optionally substituted $\text{CH}_2\text{C}_2\text{-C}_6\text{-heterocycloalkyl}$ such as morpholine, azetidine, difluoroazetidine, pyrrolidine, and the like, is prepared in three steps from a carbonyl compound of formula (XVI), where R^1 is $\text{C}_{1-6}\text{alkyl}$ or $\text{C}_{1-6}\text{haloalkyl}$ and R^3 is H or $\text{C}_{1-6}\text{alkyl}$. In a first step, carbonyl compound of formula (XVI) is reacted with a hydroboration reagent such as wilkinson's catalyst and catecholborane, a base such as sodium hydroxide, in a solvent such as hydrogen peroxide, at temperatures ranging from $-30\text{ }^\circ\text{C}$ to $20\text{ }^\circ\text{C}$. In a second step, mesylation of a compound of formula (XVII) where R^2 is CH_2OH , with mesyl chloride, a base such as TEA, in a solvent such as DCM, to provide a compound of formula (XVII), where R^2 is $\text{CH}_2\text{O-SO}_2\text{CH}_3$. Subsequent reaction of the mesylated compound of formula (XVII) with a $\text{C}_2\text{-C}_6\text{-heterocycloalkyl}$, in a solvent such as DMSO, at temperatures ranging from $80\text{ }^\circ\text{C}$ to $90\text{ }^\circ\text{C}$, provides a compound of formula (XVII), where R^2 is $\text{CH}_2\text{N}(\text{C}_{1-6}\text{alkyl})_{1-2}$ such as $\text{NH}(\text{CH}_3)_2$, $\text{CH}_2\text{N}(\text{C}_{1-6}\text{haloalkyl})_{1-2}$, or an optionally substituted $\text{CH}_2\text{C}_2\text{-C}_6\text{-heterocycloalkyl}$ such as morpholine, azetidine, difluoroazetidine, pyrrolidine, and the like.

A compound of formula (XVII), where R^2 is F and $\text{C}_{1-6}\text{alkyl}$, and m is 2, is prepared from a compound of formula (XVII) where R^2 is OH and $\text{C}_{1-6}\text{alkyl}$, and m is 2 with a fluorinating agent such as, DAST, XtalFluor®, Deoxo-Fluor®, and the like, in a suitable solvent such as DCM, and the like, at temperatures ranging from $-78\text{ }^\circ\text{C}$ to $50\text{ }^\circ\text{C}$, for a period of 2-16 h, to provide a compound of formula (XVII), where R^2 is F and $\text{C}_{1-6}\text{alkyl}$, and m is 2.

A compound of formula (XVII), where R^2 is $\text{CH}_2\text{N}(\text{C}_{1-6}\text{haloalkyl})(\text{COC}_{1-6}\text{haloalkyl})$, and m is 1, is prepared from a compound of formula (XVII), where R^2 is $\text{CH}_2\text{N}(\text{C}_{1-6}\text{haloalkyl})\text{H}$ by reacting with an acylating reagent such as trifluoroacetic anhydride, a base such as triethyl amine, in a solvent such as DCM, at a temperature between the range of $0\text{ }^\circ\text{C}$ to $20\text{ }^\circ\text{C}$, for a period of 2-4 hours, to provide a compound of formula (XVII), where R^2 is $\text{CH}_2\text{N}(\text{C}_{1-6}\text{haloalkyl})(\text{COC}_{1-6}\text{haloalkyl})$, and m is 1.

SCHEME 4



According to SCHEME 4, a commercially available or synthetically accessible alkyl
 5 halide, where X is a halide and G^1 is $CH_2C(CH_2Cl)=CH_2$, $CH_2CH_2CH_2N(H)(Boc)$, and
 $CH_2CH_2CH(NHCbz)CO_2Me$ and the like, is coupled with a compound of formula (XVIII),
 where R^3 is H or C_{1-6} alkyl, under coupling conditions to provide a compound of formula (XIX).
 For example, a compound of formula (XVIII) is reacted with an alkyl halide, a suitably selected
 base such as potassium carbonate and the like, in a solvent such as DMF or THF, to afford a
 10 compound of formula (XIX).

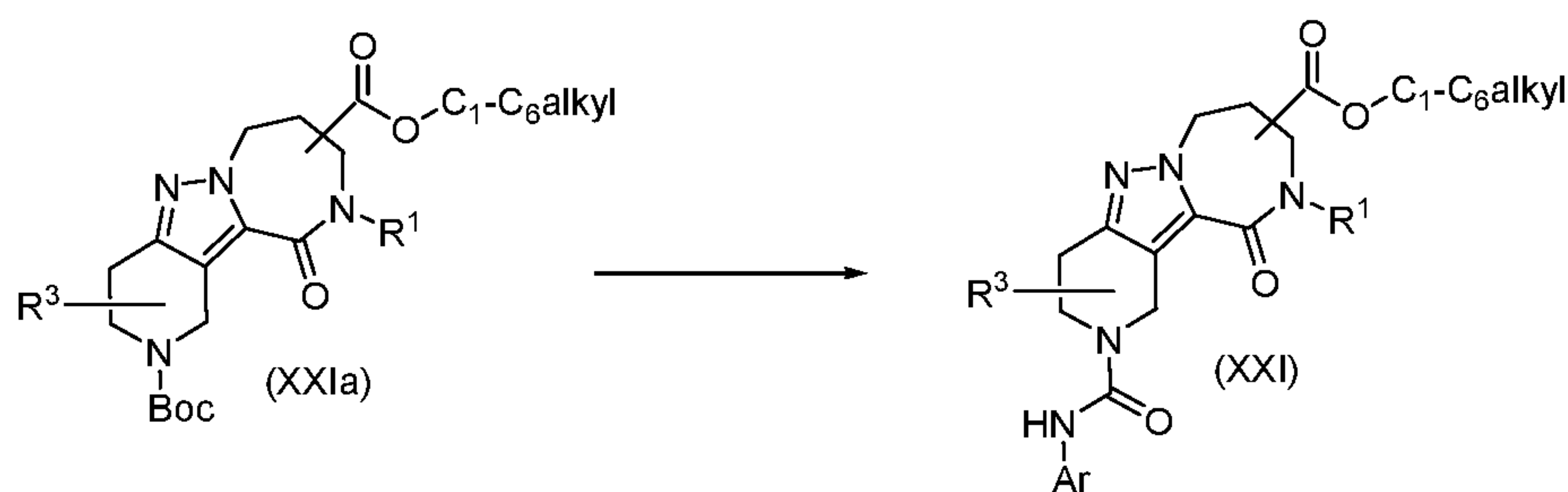
A compound of formula (XIX), where R^3 is H or C_{1-6} alkyl, is reacted with a primary a C_{1-6} alkyl or C_{1-6} haloalkyl amine such as methyl amine, in a solvent such as EtOH, at a temperature
 of about 80 °C for a period of 16 h provides a compound of formula (XVd) where R^1 is C_{1-6} alkyl
 or C_{1-6} haloalkyl.

15 A compound of formula (XXa), where R^3 is H or C_{1-6} alkyl, and R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl, is made in three steps. The first being global deprotection of BOC protecting groups
 of a compound of Formula (XIX) where G^1 is $CH_2CH_2CH_2N(H)(Boc)$, using suitable conditions
 such as TFA in DCM. Second, cyclizing by forming an amide bond using a suitable base such

as potassium carbonate, in a solvent such as EtOH, and reprotecting with boc anhydride to form a compound of Formula (XXa) where R^1 is H. Third, reacting a C_{1-6} alkyl or C_{1-6} haloalkyl halide, using a base such as NaH, in a solvent such as THF, to provide a compound of Formula (XXa) where R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl.

5 A compound of formula (XXb), where R^3 is H or C_{1-6} alkyl, and R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl, is made in four steps. The first being deprotection of the Cbz protecting group of a compound of Formula (XIX) where G^1 is $CH_2CH_2CH(NHCbz)CO_2Me$, using suitable deprotection conditions such as Pd/C in the presense of H_2 , in a solvent such as MeOH. Second, cyclizing by forming an amide bond and subsequent hydrolysis, using a base such as sodium methoxide, and a solvent such as methanol. Third, esterification of the carboxylic acid, using a base such as NaH, alkyl halide such as methyl iodide, and a solvent such as DMF. Fourth, reacting a C_{1-6} alkyl or C_{1-6} haloalkyl halide, using a base such as NaH, in a solvent such as THF, to provide a compound of Formula (XXb) where R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl.

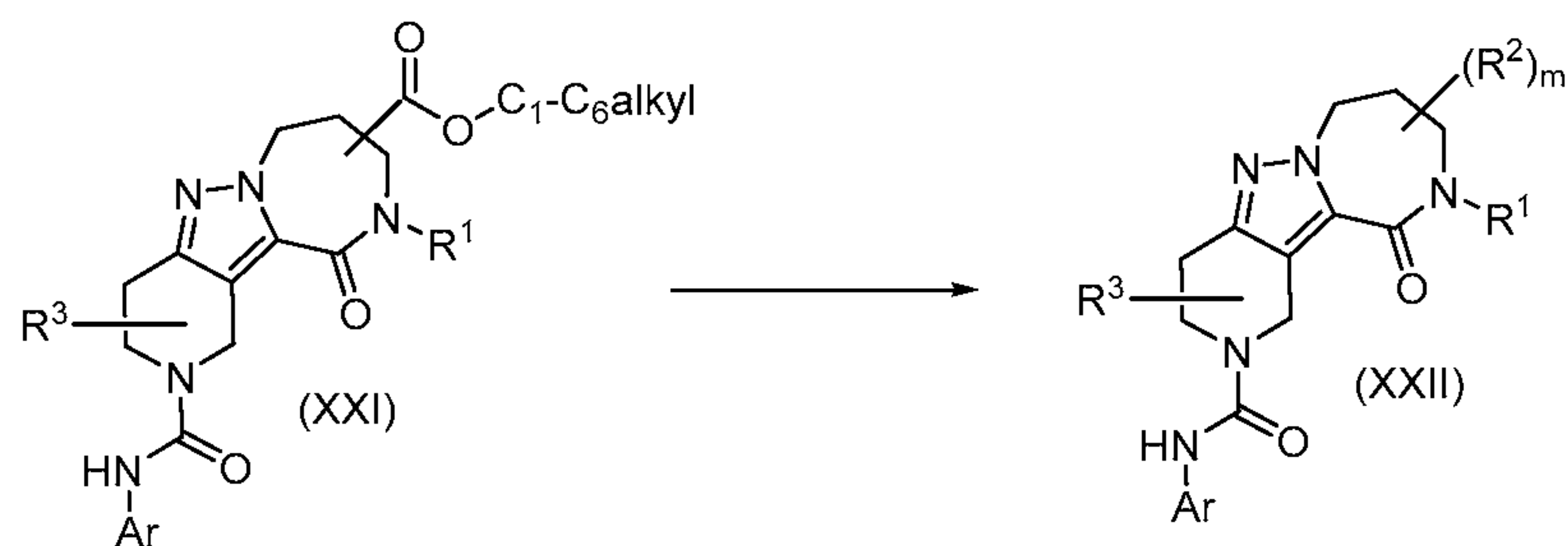
SCHEME 5



15 According to SCHEME 5, a compound of Formula (XXI) where R^3 is H or C_{1-6} alkyl, R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl, and Ar is an optionally substituted aryl ring can be prepared in two steps. For example, the Boc protecting group can be removed from a compound of Formula (XXIa) using suitable conditions such as trifluoroacetic acid in DCM. The resulting product can then be reacted with an aryl carbamate such as N-Aryl-phenylcarbamate, a base such as TEA, and a solvent such as DCM to provide a compound of Formula (XXI) where R^3 is H or C_{1-6} alkyl, R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl, and Ar is an optionally substituted aryl ring. Wherein, a compound of Formula (XXIa) is a compound of Formula (XXb), Formula (XVa), or Formula (XVe).

25

SCHEME 6



According to SCHEME 6, a compound of Formula (XXI) where R^3 is H or C_{1-6} alkyl, R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl, and Ar is 4-fluoro-2-chloro-benzene, is reacted with a Grignard reagent such as methyl magnesium bromide, in a solvent such as THF to provide a compound of Formula (XXII) where R^2 is an optionally substituted C_{1-6} alkyl, and m is 1.

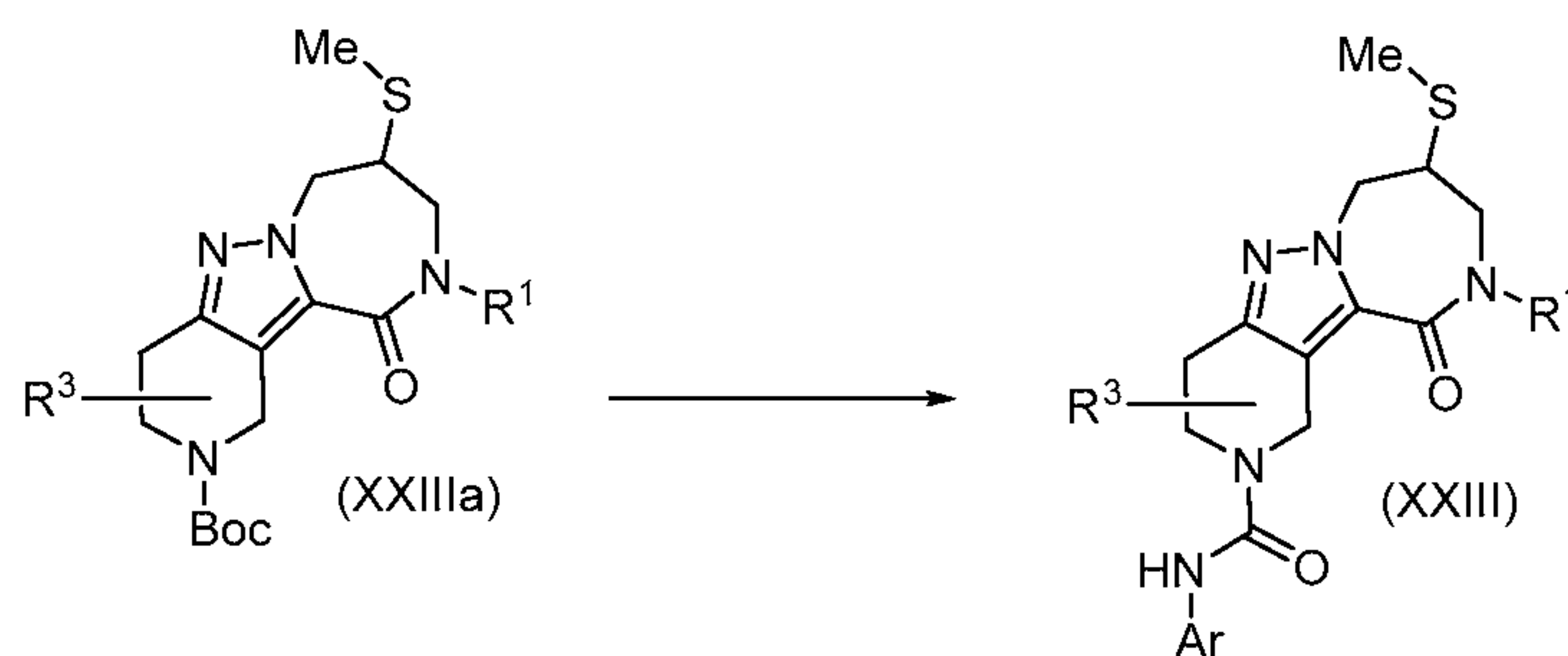
A compound of Formula (XXI) where R^3 is H or C_{1-6} alkyl, R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl, and Ar is 4-fluoro-2-chloro-benzene, is reacted with an alkyl amine of formula $N(C_{1-6}alkyl)_{1-2}$ such as $NH(CH_3)_2$, in a solvent such as DMF, with a base such as DIPEA, and a coupling agent such as HATU to provide a compound of Formula (XXII) where R^2 is $CO N(C_{1-6}alkyl)_{1-2}$, and m is 1.

A compound of Formula (XXII) where R^3 is H or C_{1-6} alkyl, R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl, and Ar is 4-fluoro-2-chloro-benzene, R^2 is $CH(OH)C_{1-6}alkyl$ or $CH(OH)C_{3-6}cycloalkyl$, and m is 1, was prepared from a compound of Formula (XXI) in 4 steps. First, a compound of Formula (XXI) was hydrolyzed, using a base such as sodium hydroxide, in a solvent such as water, MeOH or a mix of both to provide a compound of Formula (XXII) where R^2 is $COOH$. Second, reacting with an alkyl alkoxy amide such as MeNHOMe, a coupling reagent such as HATU, a base such as DIPEA, and a solvent such as DMF to provide a compound of Formula (XXII) where R^2 is a Weinreb amide. Third, reacting with a Grignard such as methyl magnesium bromide, ethyl magnesium bromide or cyclopropyl magnesium bromide, and a solvent such as THF to provide a compound of Formula (XXII) where R^2 is $C=OMe$. Fourth, reacting with a reducing reagent such as $NaBH_4$, and a solvent such as EtOH to provide a compound of Formula (XXII) where R^2 is $CH(OH)C_{1-6}alkyl$ or $CH(OH)C_{3-6}cycloalkyl$, and m is 1.

A compound of Formula (XXII) where R^3 is H or C_{1-6} alkyl, R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl, and Ar is 4-fluoro-2-chloro-benzene, R^2 is CHF_2 , and m is 1, was prepared from a compound of Formula (XXI) in 3 steps. First, a compound of Formula (XXI) was reduced, using

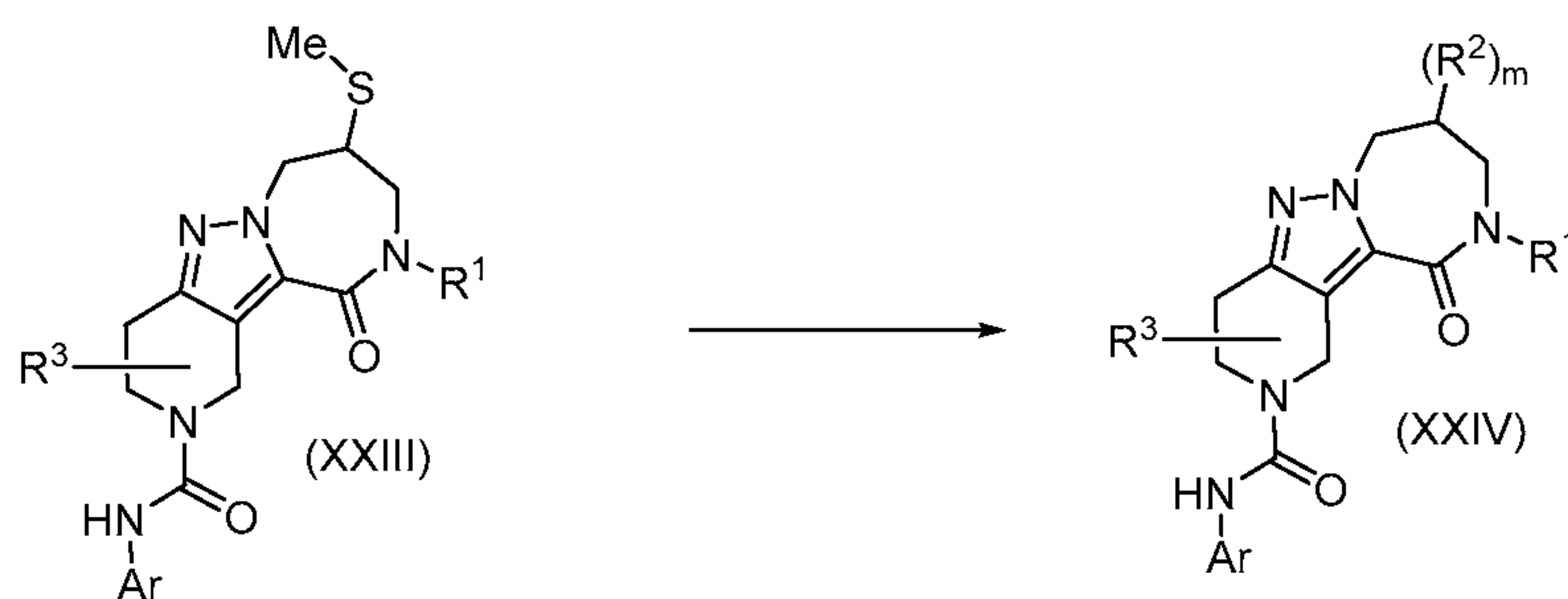
a reducing reagent such as LiAlH_4 , in a solvent such as THF to provide a compound of Formula (XXII) where R^2 is CH_2OH . Second, reacting with an oxidant such DMP, in a solvent such as DCM to provide a compound of Formula (XXII) where R^2 is CHO . Third, reacting with a fluorinating agent such as DAST, in a solvent such as DCM to provide a compound of Formula (XXII) where R^2 is CHF_2 , and m is 1.

SCHEME 7



According to SCHEME 7, a compound of Formula (XXIII) where R^3 is H or C_{1-6} alkyl, R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl, and Ar is an optionally substituted aryl ring can be prepared in two steps. For example, the Boc protecting group can be removed from a compound of Formula (XXIIIa) using suitable conditions such as trifluoroacetic acid in DCM. The resulting product can then be reacted with an aryl carbamate such as N-Aryl-phenylcarbamate, a base such as TEA, and a solvent such as DCM to provide a compound of Formula (XXIII) where R^3 is H or C_{1-6} alkyl, R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl, and Ar is an optionally substituted aryl ring. Wherein, a compound of Formula (XXIIIa) is prepared as described in SCHEME 3.

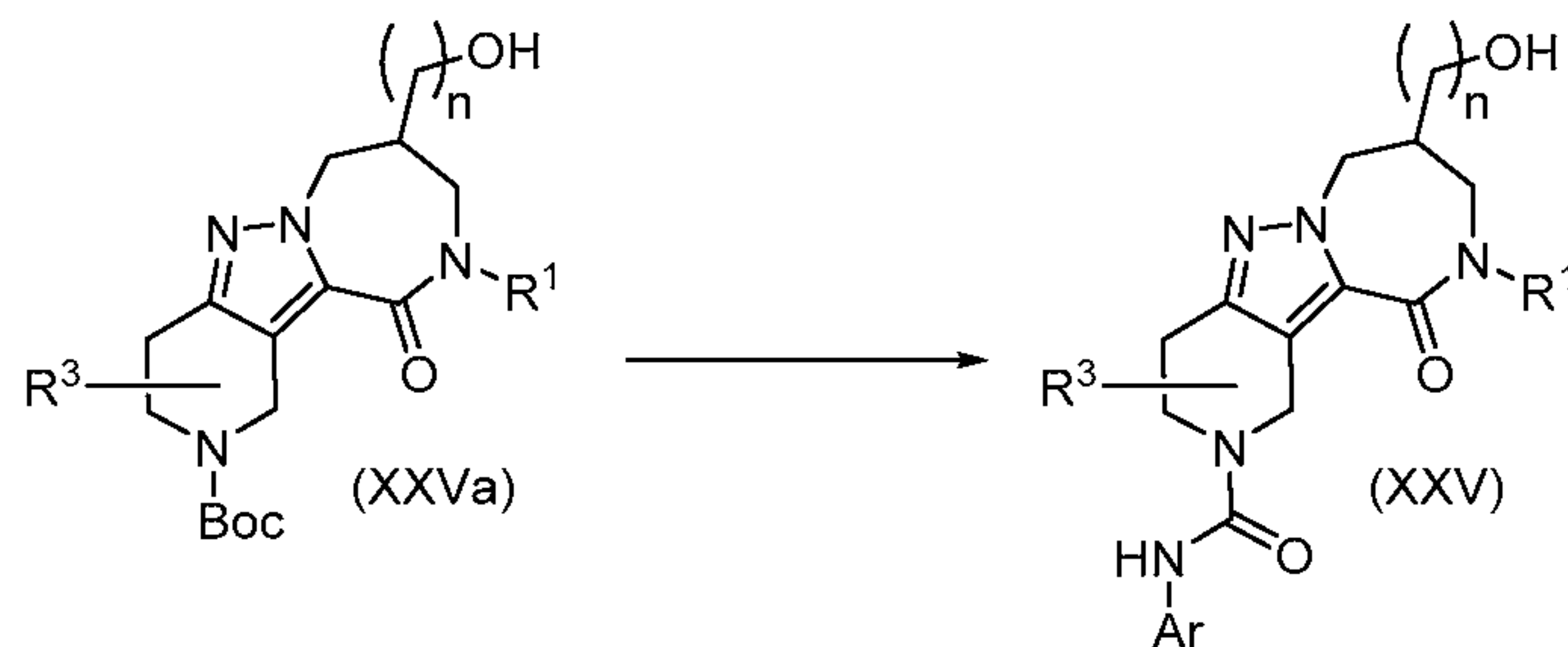
SCHEME 8



According to SCHEME 8, a compound of Formula (XXIII) where R^3 is H or C_{1-6} alkyl, R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl, and Ar is 4-fluoro-2-chloro-benzene, is reacted with an oxidant

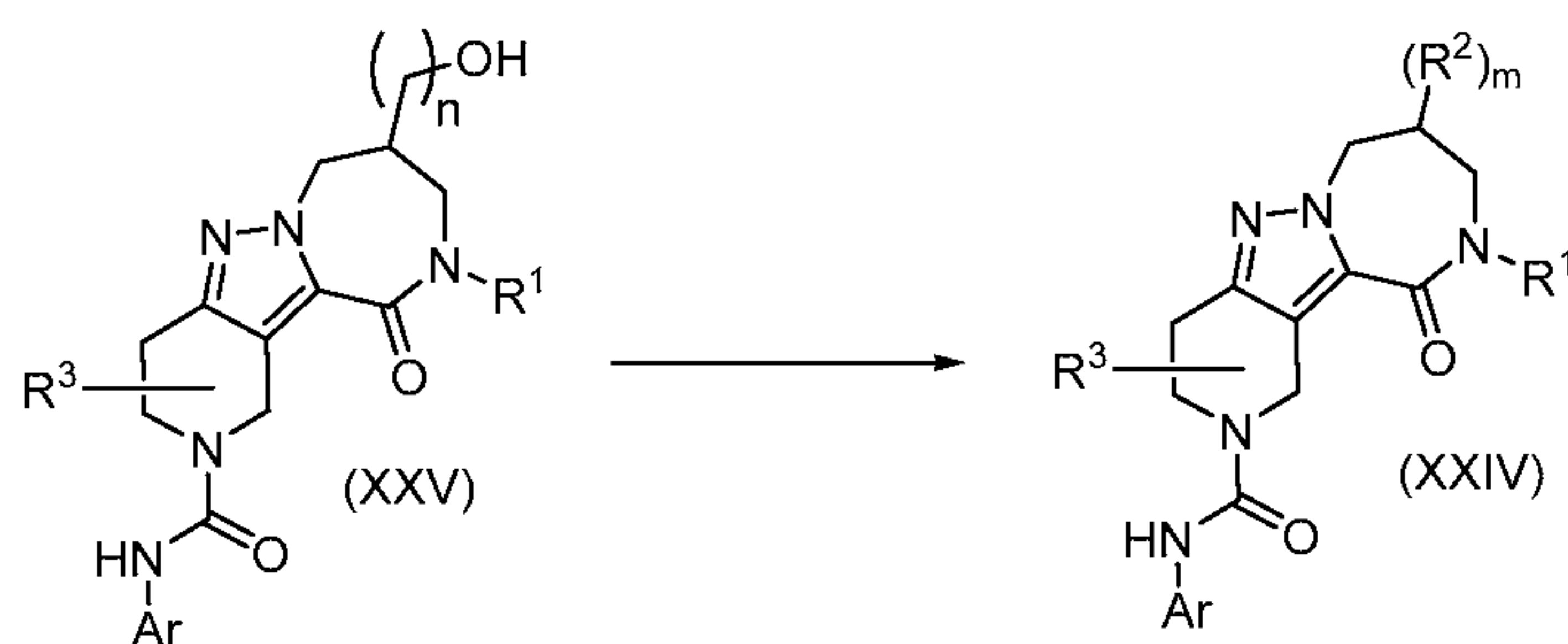
such as $(\text{Bu}_3\text{Sn})_2\text{O}$ and Bromide or *m*-CPBA, in a solvent such as DCM to provide a compound of Formula (XXIV) where R^2 is a sulfonate or sulfoxide, and *m* is 1.

SCHEME 9



5 According to SCHEME 9, a compound of Formula (XXV) where R^3 is H or C_{1-6} alkyl, R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl, and Ar is an optionally substituted aryl ring can be prepared in two steps. For example, the Boc protecting group can be removed from a compound of Formula (XXVa) using suitable conditions such as trifluoroacetic acid in DCM. The resulting product can then be reacted with an aryl carbamate such as N-Aryl-phenylcarbamate, a base such as
 10 TEA, and a solvent such as DCM to provide a compound of Formula (XXV) where R^3 is H or C_{1-6} alkyl, R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl, and Ar is an optionally substituted aryl ring. Wherein, a compound of Formula (XXVa) is prepared as described in SCHEME 3.

SCHEME 10

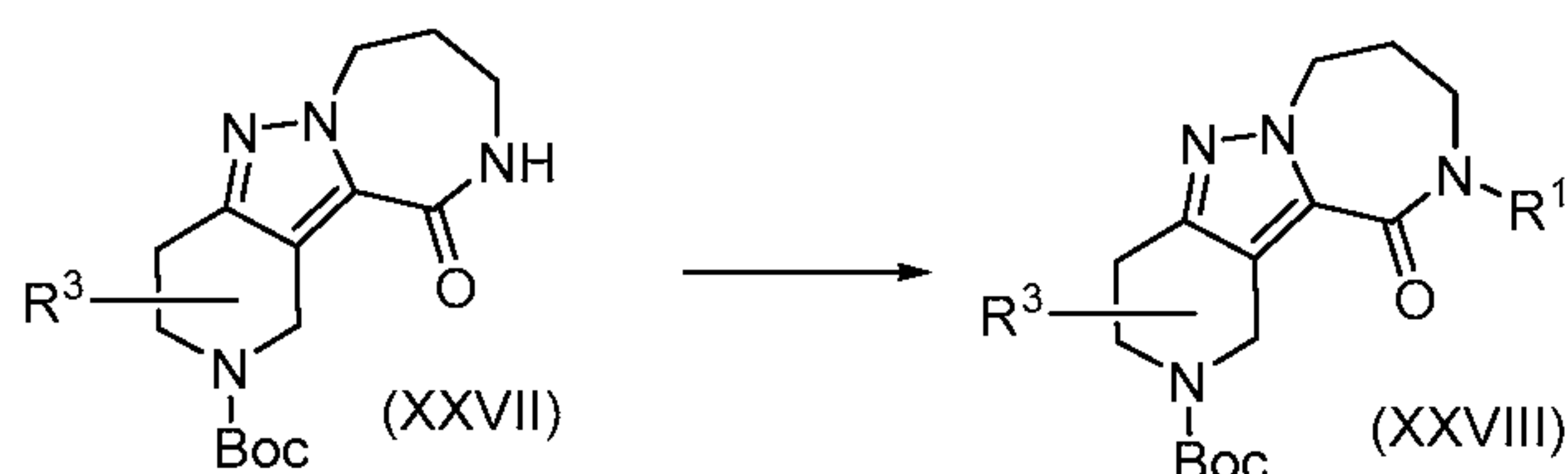


15 According to SCHEME 10, a compound of Formula (XXIV) where R^3 is H or C_{1-6} alkyl, R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl, and Ar is 4-fluoro-2-chloro-benzene, R^2 is $\text{N}(\text{C}_{1-6}\text{alkyl})_{0-2}$, and *m* is 1, was prepared from a compound of Formula (XXV) in 3 steps. First, a compound of Formula (XXV) where *n* is 0 was reacted with, sulfonating reagent such as MSCl , using a base
 20 such as TEA, in a solvent such as DCM to provide a compound of Formula (XXIV) where R^2 is OM_s. Second, reacting with a nucleophilic azide such as sodium azide, in a solvent such as DMF to provide a compound of Formula (XXIV) where R^2 is N_3 . Third, reacting with a reducing

agent such as zinc/ammoniumchloride or Pd/C and hydrogen, in a solvent such as MeOH, EtOH, water, or a mixture of any to provide a compound of Formula (XXII) where R^2 is $N(C_{1-6}alkyl)_0-2$, and m is 1.

A compound of Formula (XXIV) where R^3 is H or $C_{1-6}alkyl$, R^1 is $C_{1-6}alkyl$ or $C_{1-6}haloalkyl$, and Ar is 4-fluoro-2-chloro-benzene, R^2 is $N(C_{1-6}alkyl)_0-2$, and m is 1, was prepared from a compound of Formula (XXV) in 3 steps. First, a compound of Formula (XXV) where n is 1 was reacted with, sulfonating reagent such as MSO_3H , using a base such as TEA, in a solvent such as DCM to provide a compound of Formula (XXIV) where R^2 is CH_2OMs . Second, reacting with a nucleophilic azide such as sodium azide, in a solvent such as DMF to provide a compound of Formula (XXIV) where R^2 is CH_2N_3 . Third, reacting with a reducing agent such as zinc/ammoniumchloride or Pd/C and hydrogen, in a solvent such as MeOH, EtOH, water, or a mixture of any to provide a compound of Formula (XXIV) where R^2 is $CH_2N(C_{1-6}alkyl)_0-2$, and m is 1.

SCHEME 11

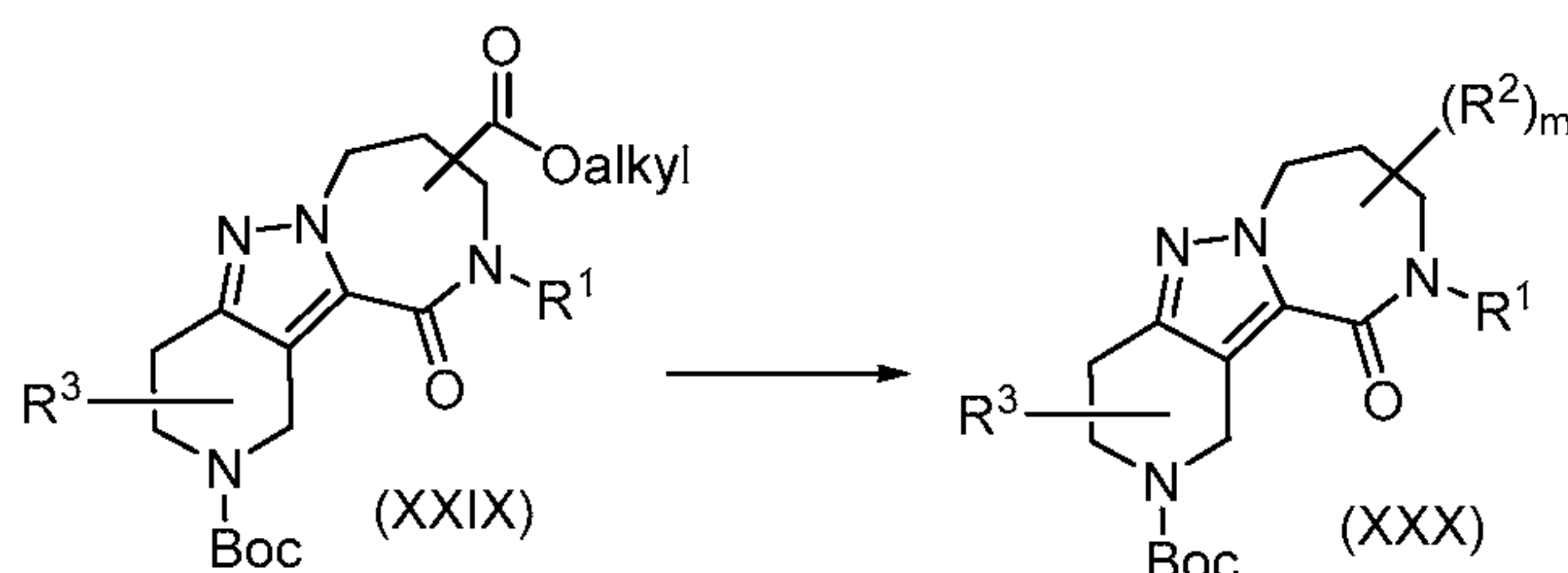


According to SCHEME 11, a compound of Formula (XXVIII) where R^3 is H or $C_{1-6}alkyl$, R^1 is $C_{1-6}alkyl-OH$ was prepared from a compound of Formula (XXVII) in 2 steps. First, a compound of Formula (XXVII) where was reacted with, alkylating reagent with a terminal ester such as $BrCH_2COOMe$, using a base such as NaH, in a solvent such as THF to provide a compound of Formula (XXVI) where R^1 is a C_1-C_6alkyl ester. Second, reacting with a Grignard such as methyl magnesium bromide, in a solvent such as THF to provide a compound of Formula (XXVI) where R^2 is $C_1-C_6alkyl-OH$.

A compound of Formula (XXVIII) where R^3 is H or $C_{1-6}alkyl$, R^1 is $C_{1-6}alkyl-OH$ was prepared from a compound of Formula (XXVII) in 2 steps. First, a compound of Formula (XXVII) where was reacted with, alkylating reagent with a terminal ester such as $BrCH_2COOMe$, using a base such as NaH, in a solvent such as THF to provide a compound of Formula (XXVI) where R^1 is a C_1-C_6alkyl ester. Second, reacting with a reducing reagent such

as LiAlH_4 , in a solvent such as THF to provide a compound of Formula (XXVI) where R^2 is C_1 - C_6 alkyl-OH.

SCHEME 12



According to SCHEME 12, a compound of Formula (XXIX) where R^3 is H or C_1 - C_6 alkyl, and R^1 is C_1 - C_6 alkyl or C_1 - C_6 haloalkyl, is reacted with a strong base such as LDA, an alkylating agent such as MeI or $\text{CHF}_2\text{CH}_2\text{OTf}$, in a solvent such as THF to provide a compound of Formula (XXX) where R^2 is C_1 - C_6 alkyl or C_1 - C_6 haloalkyl and COOalkyl , and m is 2.

A compound of Formula (XXX) where R^3 is H or C_1 - C_6 alkyl, R^1 is C_1 - C_6 alkyl or C_1 - C_6 haloalkyl, R^2 is $\text{CH}(\text{OH})\text{Et}$, and m is 1 was prepared from a compound of Formula (XXIX) in 5 steps. First, a compound of Formula (XXIX) where was hydrolyzed using suitable conditions such as NaOH in MeOH/water to provide a compound of Formula (XXX) where R^2 is COOH . Second, reacting with an alkyl alkoxy amide such MeNHOMe, a coupling reagent such as HATU, a base such as DIPEA, and a solvent such as DMF to provide a compound of Formula (XXX) where R^2 is a Weinreb amide. Third, reacting with a grignard such as vinyl magnesium bromide, in a solvent such as THF to provide a compound of Formula (XXX) where R^2 is $\text{C}(\text{O})\text{CH}=\text{CH}_2$. Fourth, reacting with a reducing reagent such as $\text{NaBH}_4/\text{CeCl}_3$, in a solvent such as MeOH to provide a compound of Formula (XXX) where R^2 is $\text{CH}(\text{OH})\text{CH}=\text{CH}_2$. Fifth, reacting with a reducing reagent such as Pd/C, in a solvent such as MeOH to provide a compound of Formula (XXX) where R^2 is $\text{CH}(\text{OH})\text{CH}_2\text{CH}_3$, and m is 1.

A compound of Formula (XXX) where R^3 is H or C_1 - C_6 alkyl, R^1 is C_1 - C_6 alkyl or C_1 - C_6 haloalkyl, R^2 is $\text{CH}(\text{OH})\text{C}_1$ - C_6 alkyl, and m is 1 was prepared from a compound of Formula (XXX) where R^2 is a Weinreb amide in 2 steps. First, reacting with a C_1 - C_6 alkyl Grignard such as n-propyl magnesium bromide, in a solvent such as THF to provide a compound of Formula (XXX) where R^2 is $\text{C}(\text{O})\text{C}_1$ - C_6 alkyl. Second, reacting with a reducing reagent such as NaBH_4 , in a

solvent such as MeOH to provide a compound of Formula (XXX) where R^2 is $CH(OH)C_{1-6}alkyl$.

A compound of Formula (XXX) where R^3 is H or $C_{1-6}alkyl$, R^1 is $C_{1-6}alkyl$ or $C_{1-6}haloalkyl$, R^2 is $CH(OH)CH_2-cyclopropyl$, and m is 1 was prepared from a compound of Formula (XXX) where R^2 is a Weinreb amide in 3 steps. First, reacting with a grignard such as allyl magnesium bromide, in a solvent such as THF to provide a compound of Formula (XXX) where R^2 is $C(O)CH_2CH=CH_2$. Second, reacting with a reducing reagent such as $NaBH_4$, in a solvent such as MeOH to provide a compound of Formula (XXX) where R^2 is $CH(OH)CH_2CH=CH_2$. Third, reacting with an alkyl halide such as ICH_2Cl , a zincate such as diethyl zinc, in a solvent such as DCM to provide a compound of Formula (XXX) where R^2 is $CH(OH)CH_2-cyclopropyl$.

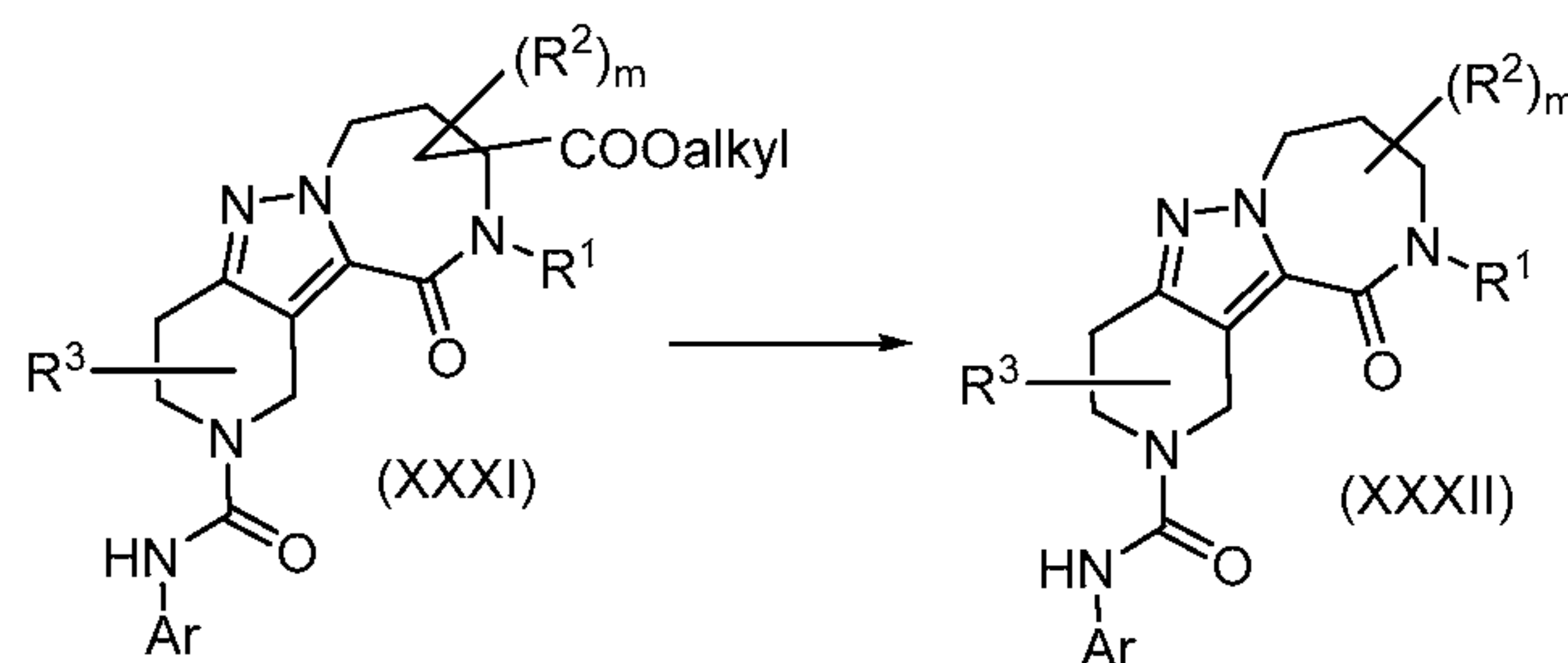
A compound of Formula (XXX) where R^3 is H or $C_{1-6}alkyl$, R^1 is $C_{1-6}alkyl$ or $C_{1-6}haloalkyl$, R^2 is CH_2OH and F, and m is 2 was prepared from a compound of Formula (XXIX) in 2 steps. First, reacting with a fluorinating reagent such as NFSI with LDA, in a solvent such as THF to provide a compound of Formula (XXX) where R^2 is $C(O)C_{1-6}alkyl$ and F, and m is 2. Second, reacting with a reducing reagent such as $LiBH_4$, in a solvent such as THF to provide a compound of Formula (XXX) where R^2 is CH_2OH and F, and m is 2.

A compound of Formula (XXX) where R^3 is H or $C_{1-6}alkyl$, R^1 is $C_{1-6}alkyl$ or $C_{1-6}haloalkyl$, R^2 is $CH_2OC_{1-6}haloalkyl$, and m is 1 was prepared from a compound of Formula (XXX) where R^2 is a Weinreb amide in 2 steps. First, reacting with a reducing agent such as $NaBH_4$, in a solvent such as THF to provide a compound of Formula (XXX) where R^2 is CH_2OH . Second, reacting with an alkylating reagent such as CHF_2CH_2OTf , using a suitable base such as NaH , in a solvent such as THF to provide a compound of Formula (XXX) where R^2 is $CH_2OC_{1-6}haloalkyl$.

25

30

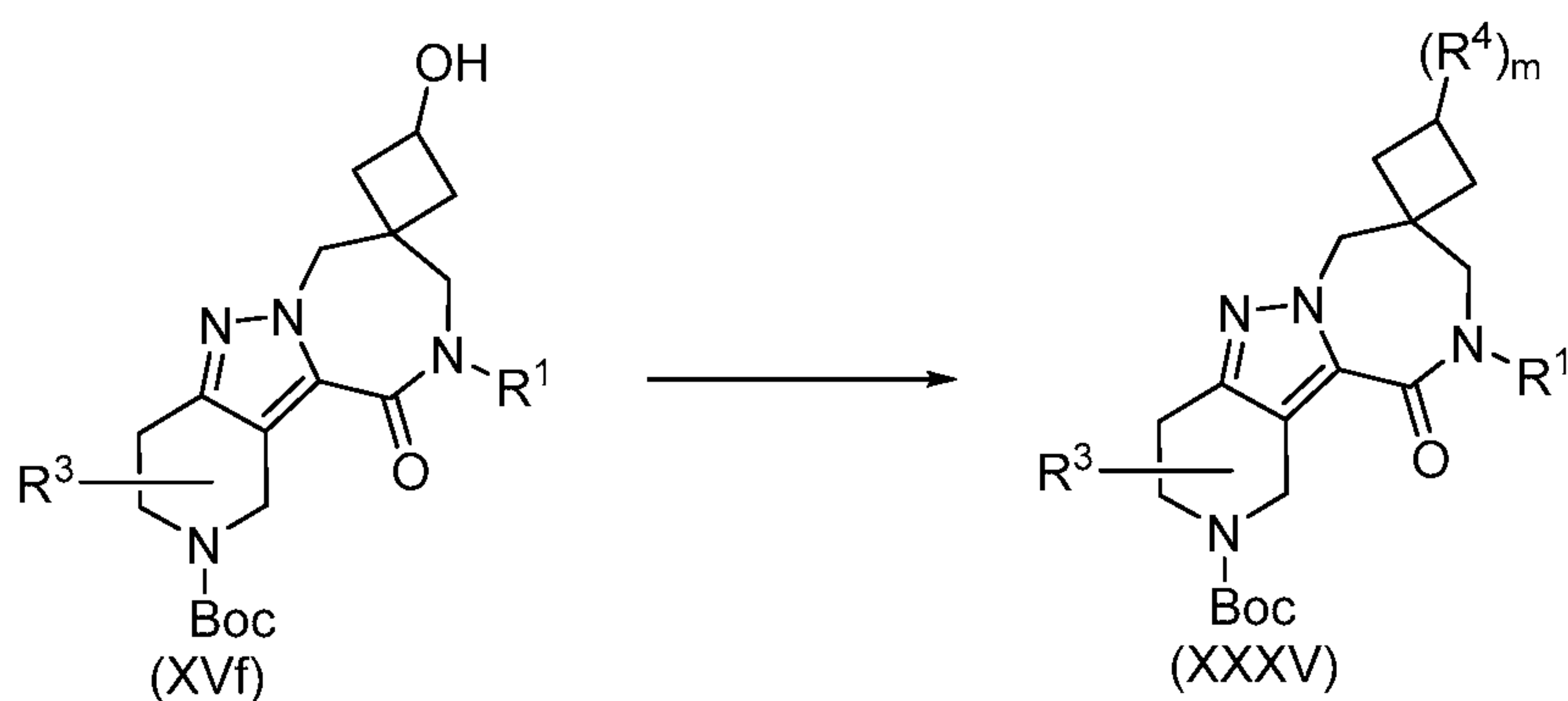
SCHEME 13



5 According to SCHEME 13, a compound of Formula (XXXI) where R^3 is H or C_{1-6} alkyl, R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl, and R^2 is C_{1-6} alkyl or C_{1-6} haloalkyl, is reacted with a reducing agent such as $LiBH_4$, in a solvent such as THF to provide a compound of Formula (XXXII) where R^2 is C_{1-6} alkyl or C_{1-6} haloalkyl and CH_2OH , and m is 2.

10 A compound of Formula (XXXI) where R^3 is H or C_{1-6} alkyl, R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl, and R^2 is C_{1-6} alkyl or C_{1-6} haloalkyl, is hydrolyzed using suitable conditions such as NaOH in MeOH/water to provide a compound of Formula (XXXII) where R^2 is C_{1-6} alkyl or C_{1-6} haloalkyl and $COOH$, and m is 2.

SCHEME 14



15

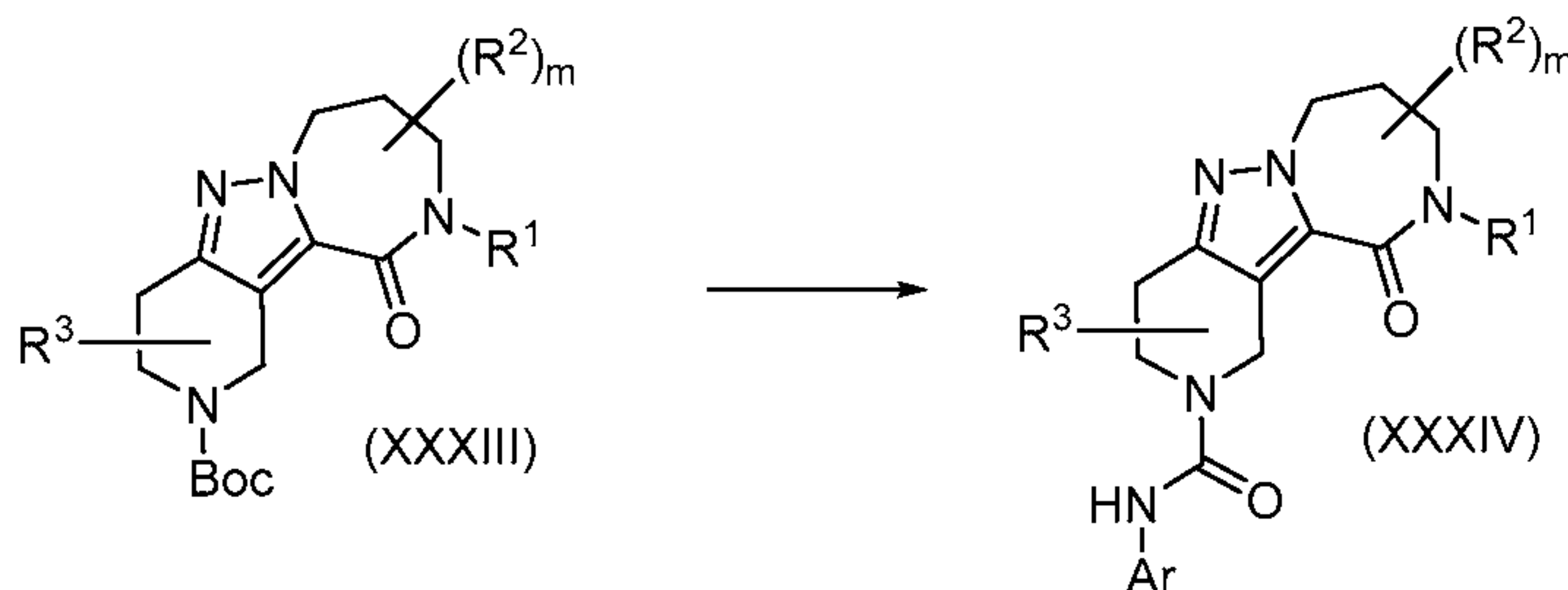
According to SCHEME 13, a compound of Formula (XVf) where R^3 is H or C_{1-6} alkyl, and R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl, is reacted with a fluorinating agent such as DAST, in a solvent such as DCM to provide a compound of Formula (XXXV) where R^4 is F, and m is 1.

20 A compound of Formula (XXXV) where R^3 is H or C_{1-6} alkyl, and R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl, and R^4 is F and F, and m is 2, is prepared in two steps. First, a compound of Formula (XVf) is oxidized using a suitable reagent such as DMP, in a solvent such as DCM, to provide a

compound of Formula (XXXV) where R^4 is =O. Second, reacting with a fluorinating agent such as DAST, in a solvent such as DCM to provide a compound of Formula (XXXV) where R^4 is F and F, and m is 2.

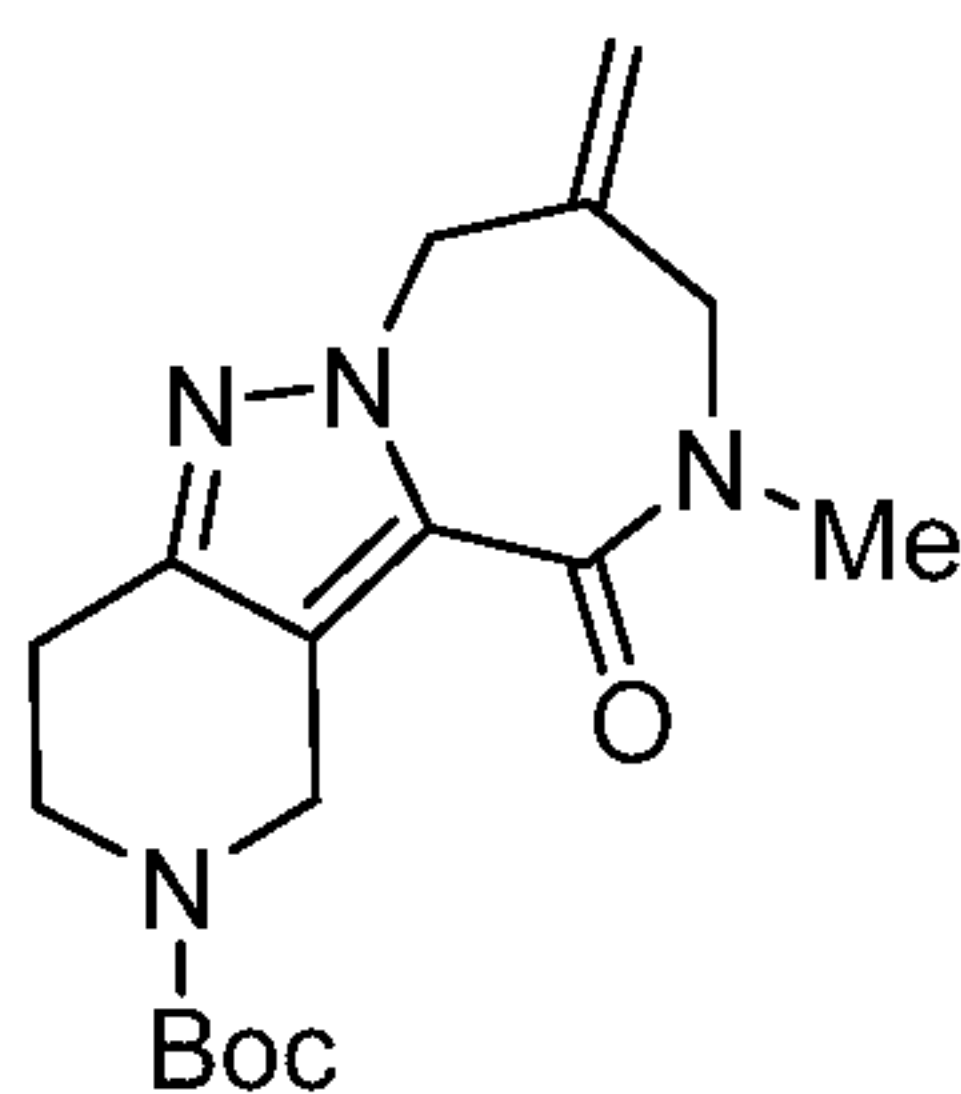
5

SCHEME 15



According to SCHEME 15, a compound of Formula (XXXIV) where R^3 is H or C_{1-6} alkyl, R^1 is as described by the schemes above, R^2 is described as the schemes above, Ar is an optionally substituted aryl ring, and m is 0, 1, or 2 is prepared in two steps. First, removal of the Boc protecting group from a compound of Formula (XXXIII) using suitable conditions such as trifluoroacetic acid in DCM. Second, reaction with a aryl carbamate such as N-Aryl-phenylcarbamate, a base such as TEA, and a solvent such as DCM to provide a compound of Formula (XXXIV) where R^3 is H or C_{1-6} alkyl, R^1 is as described by the schemes above, R^2 is described as the schemes above, Ar is an optionally substituted aryl ring, and m is 0, 1, or 2.

Intermediate 1. tert-butyl 10-methyl-8-methylene-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate.



Method A

20 Step 1. 5-methylene-1,3,2-dioxathiane 2-oxide. To a solution of 2-methylenepropane-1,3-diol (5.00 g, 56.75 mmol, 4.63 mL, 1.00 eq) in CCl_4 (50.00 mL) was added a solution of $SOCl_2$ (10.13 g, 85.13 mmol, 6.18 mL, 1.50 eq) in CCl_4 (10.00 mL) at 0 °C under N_2 , and the mixture was stirred at 0 °C for 45 mins. The mixture was concentrated under reduced pressure to afford

5-methylene-1,3,2-dioxathiane 2-oxide (6.90 g, 51.43 mmol, 90.63% yield) as yellow oil, which was used directly for the next step. ¹H NMR (400 MHz, CDCl₃) δ 5.36 - 5.39 (m, 2 H), 5.16 (s, 2 H), 4.22 - 4.28 (m, 2 H).

Step 2. 2-((methylamino)methyl)prop-2-en-1-ol. A solution of 5-methylene-1,3,2-dioxathiane 2-oxide (1.00 g, 7.45 mmol, 1.00 *eq*) and methanamine (2 M, 11.18 mL, 3.00 *eq*) in THF (2.00 mL) was heated to 70 °C for 16 h. TLC (DCM/MeOH = 20/1) showed the starting material was consumed completely and one major new spot with larger polarity was detected. The mixture was filtered and the filtrate was concentrated in vacuo to afford the title compound (750.00 mg, 7.41 mmol, 99.46% yield) as yellow oil, which was used directly for the next step.

Step 3. tert-butyl (2-(hydroxymethyl)allyl)(methyl)carbamate. To a solution of 2-(methylaminomethyl)prop-2-en-1-ol (750.00 mg, 7.41 mmol, 1.00 *eq*) in dioxane (5.00 mL)/H₂O (5.00 mL) was added Boc₂O (1.94 g, 8.89 mmol, 2.04 mL, 1.20 *eq*) and NaHCO₃ (622.40 mg, 7.41 mmol, , 1.00 *eq*). The mixture was stirred at 30 °C for 16 h. The mixture with was diluted with EA (50 mL) and washed with brine (50 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated to give yellow oil, which was purified by silica gel column to afford the title compound (710.00 mg, 3.53 mmol, 47.61% yield) as yellow oil. ¹H NMR (400 MHz, CD₃OD) δ 5.10 (s, 1 H), 4.97 (s, 1 H), 3.91 - 4.10 (m, 4 H), 2.81 (s, 3 H), 1.50 (s, 9 H).

Step 4. 2-((methylamino)methyl)prop-2-en-1-ol hydrochloride. To a solution of tert-butyl N-[2-(hydroxymethyl)allyl]-N-methyl-carbamate (710.00 mg, 3.53 mmol, 1.00 *eq*) in dioxane (3.00 mL) was added HCl/dioxane (4 M, 5.00 mL, 5.67 *eq*) and the mixture was stirred at 15 °C for 1 h. TLC (PE/ EtOAc = 2/1) showed the starting material was consumed completely and one major new spot with larger polarity was detected. The mixture was concentrated in vacuo to afford the title compound (480.00 mg, 3.49 mmol, 98.81% yield, HCl) as yellow oil, which was used directly for the next step. ¹H NMR (400 MHz, CD₃OD) δ 5.46 (s, 1 H), 5.32 (s, 1 H), 4.20 (s, 2 H), 3.71 (s, 2 H), 2.73 (s, 3 H).

Step 5. tert-butyl 3-((2-(hydroxymethyl)allyl)(methyl)carbamoyl)-6,7-dihydro-2H-pyrazolo[4,3-c]pyridine-5(4H)-carboxylate. A mixture of 5-tert-butoxycarbonyl-1,4,6,7- tetrahydropyrazolo [4,3-c]pyridine-3- carboxylic acid (550.00 mg, 2.06 mmol, 1.00 *eq*), DIPEA (798.70 mg, 6.18 mmol, 1.08 mL, 3.00 *eq*), HATU (939.93 mg, 2.47 mmol, 1.20 *eq*) and 2-(methylaminomethyl)prop-2-en-1-ol (425.21 mg, 3.09 mmol, 1.50 *eq*, HCl) in DMF (6.00 mL) was heated to 80 °C for 16 h. The mixture was diluted with EtOAc (80 mL) and washed with

brine (80 mL *3). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give yellow oil. The yellow oil was purified by silica gel column to afford the title compound (390.00 mg, 1.11 mmol, 54.03% yield) as yellow solid. LCMS: 351 [M+1].

Step 6. tert-butyl 10-methyl-8-methylene-11-oxo-3,4,8,9,10,11-hexahydro-1H-

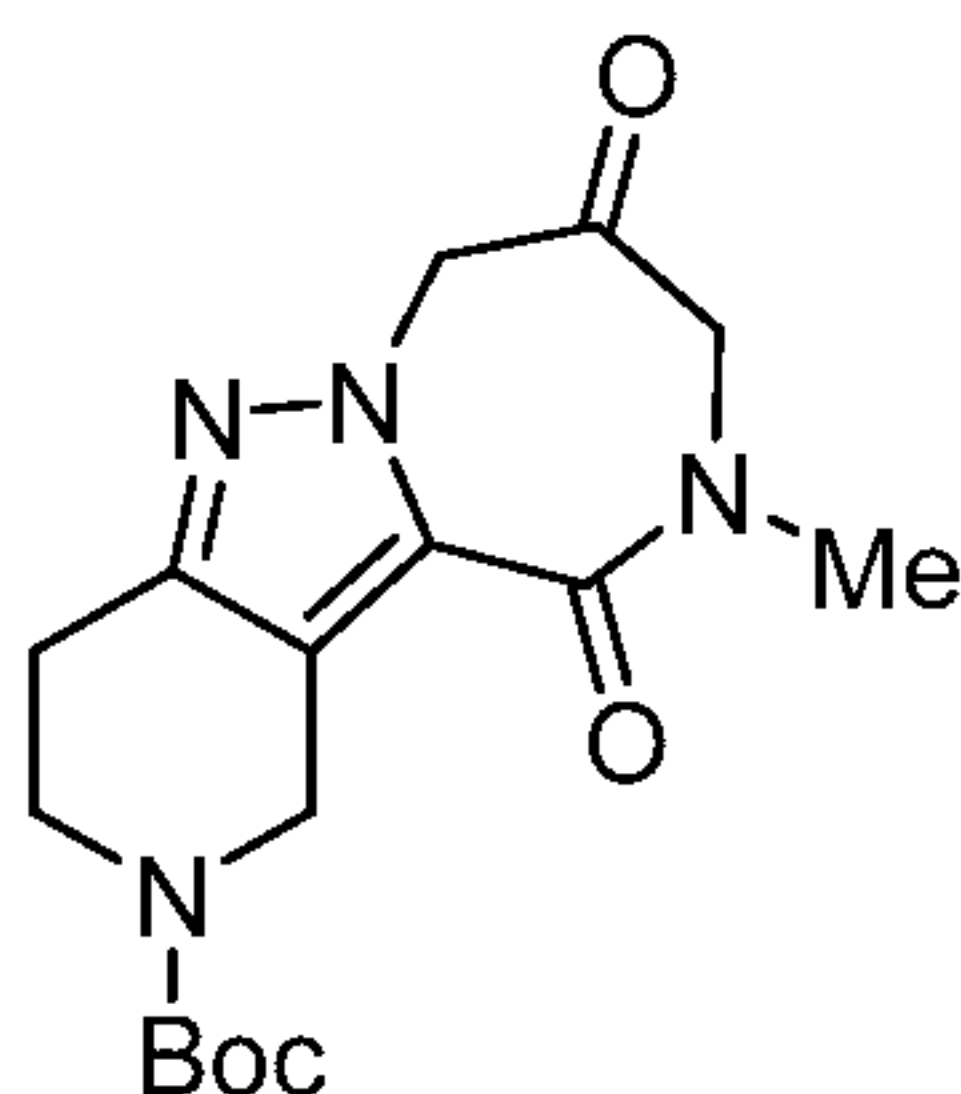
5 pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxylate. To a solution of tert-butyl 3-[2-(hydroxymethyl)allyl-methyl-carbamoyl]-2,4,6,7- tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (200.00 mg, 570.76 μmol, 1.00 *eq*) and triphenylphosphane (194.62 mg, 741.99 μmol, 1.30 *eq*) in THF (3.00 mL) was added DIAD (150.04 mg, 741.99 μmol, 144.27 μL, 1.30 *eq*) and the mixture was stirred at 30 °C for 4 h. The mixture was diluted with EtOAc (50 mL) and washed with HCl (1 M, 50 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo to give oil. The oil was purified by silica gel column to afford the title compound as impure product (320.00 mg, crude, containing Ph₃PO) as yellow oil. LCMS: 355 [M+23].

Method B

15 Step 1. 5-tert-butyl 3-ethyl 2-(2-(chloromethyl)allyl)-6,7-dihydro-2H-pyrazolo[4,3-c]pyridine-3,5(4H)-dicarboxylate. To a solution of 3-chloro-2-(chloromethyl)prop-1-ene (7.62 g, 60.95 mmol, 7.05 mL, 3.00 *eq*) in DMF (100.00 mL) was added 5-tert-butyl 3-ethyl 2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-3,5-dicarboxylate (6.00 g, 20.32 mmol, 1.00 *eq*) and K₂CO₃ (3.65 g, 26.41 mmol, 1.30 *eq*). The mixture was stirred at 25 °C for 6 h and then heated to 75 °C for 16 h. TLC showed the starting material was consumed completely. The mixture was diluted with EtOAc (80 mL), washed with HCl (1M, 80 mL) and brine (80 mL*2). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo to give yellow oil. The oil was purified by silica gel column to afford the title compound (2.90 g, 7.55 mmol, 37.18% yield) as colorless oil.

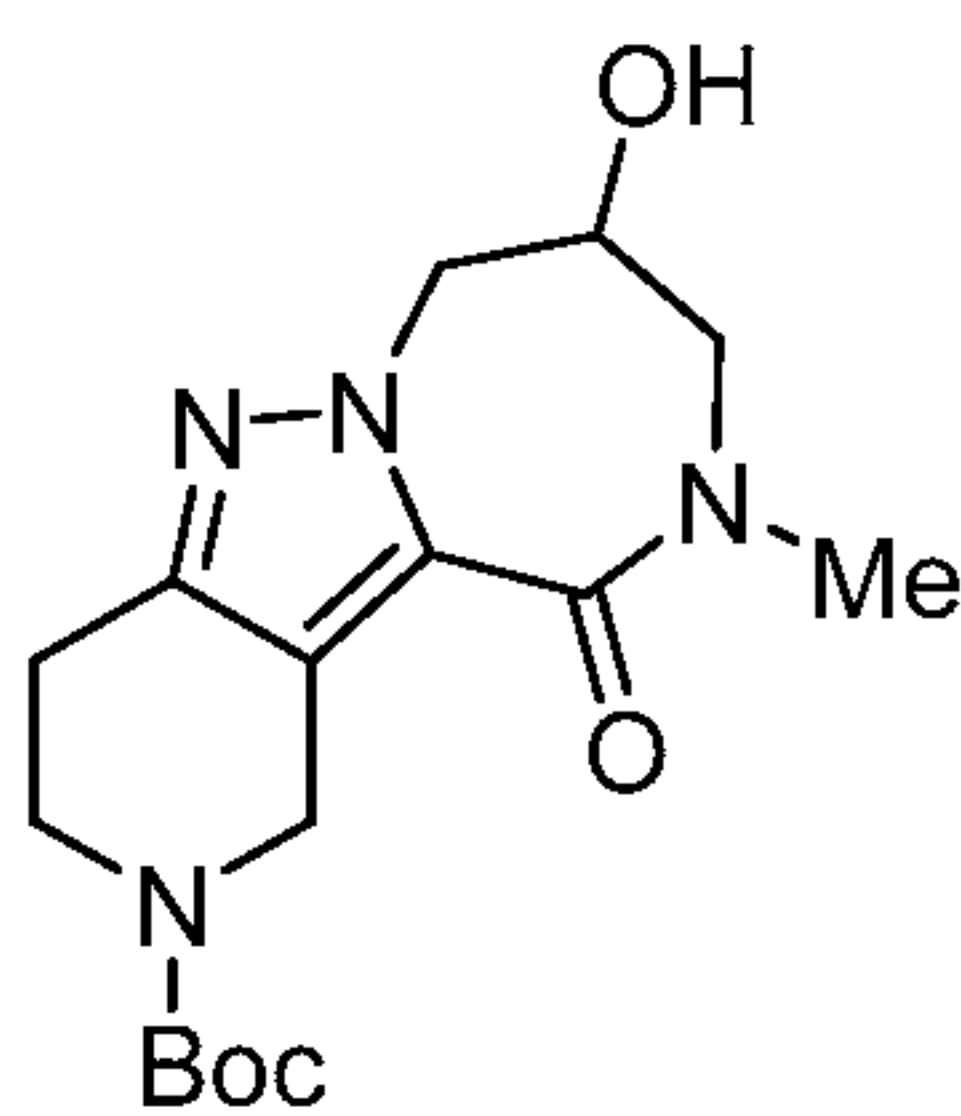
25 Step 2. tert-butyl 10-methyl-8-methylene-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxylate. A solution of 5-tert-butyl 3-ethyl 2-(2-(chloromethyl)allyl)-6,7-dihydro-2H-pyrazolo[4,3-c]pyridine-3,5(4H)-dicarboxylate (1.00 g, 2.61 mmol, 1.00 *eq*) and methanamine (7.5 M, 40.00 mL, 33% purity, 114.94 *eq*) in EtOH (30.00 mL) was heated to 80 °C in sealed tube for 16 h. The mixture was concentrated in vacuo to give yellow oil. The yellow oil was purified by silica gel column to afford the title compound (560.00 mg, 1.68 mmol, 64.37% yield) as yellow oil. LCMS: 333 [M+1].

Intermediate 2: tert-butyl 10-methyl-8,11-dioxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxylate.



- 5 To a solution of tert-butyl 10-methyl-8-methylene-11-oxo-3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (150.00 mg, 451.26 μmol , 1.00 *eq*) in THF (3.00 mL) and H₂O (1.50 mL) was added OsO₄ (5.74 mg, 22.56 μmol , 1.17 μL , 0.05 *eq*) and NaIO₄ (386.08 mg, 1.81 mmol, 100.02 μL , 4.00 *eq*) at 0 °C. The mixture was stirred at 15 °C for 16 hr. The mixture was diluted with EtOAc (40 mL) and washed with brine (40 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo to give yellow oil. The yellow oil was purified by silica gel column to afford the title compound (102.00 mg, 305.05 μmol , 67.60% yield) as yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 5.01 (s, 2 H), 4.67 (s, 2 H), 4.05 (s, 2 H), 3.73 (s, 2 H), 3.20 (s, 3 H), 2.76 (s, 2 H), 1.49 (s, 9 H).

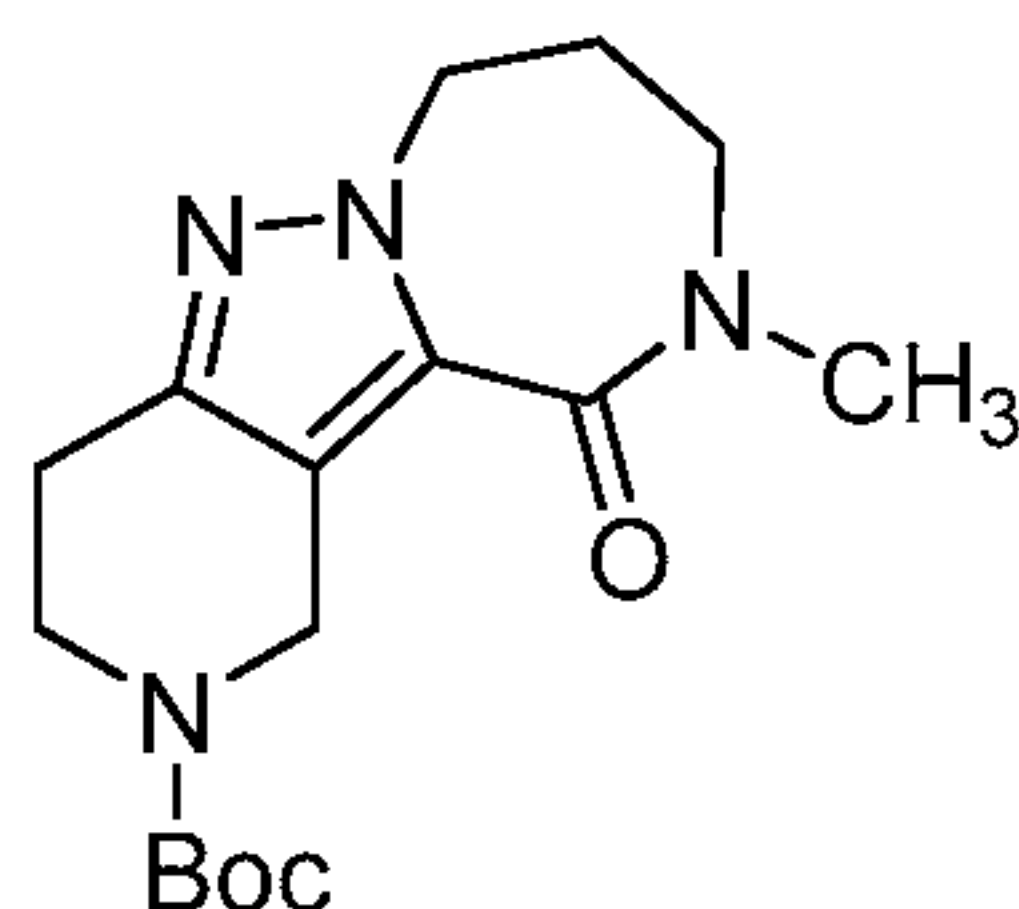
- 15 Intermediate 3: tert-butyl 8-hydroxy-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxylate.



- To a solution of tert-butyl 10-methyl-8,11-dioxo-3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (60.00 mg, 179.44 μmol , 1.00 *eq*) (60.00 mg, 179.44 μmol , 1.00 *eq*) in MeOH (4.00 mL) was added NaBH₄ (13.58 mg, 358.88 μmol , 2.00 *eq*). The mixture was stirred at 15 °C for 1 h. The mixture was diluted with brine (30 mL), extracted with EtOAc (30 mL *2) and DCM (30 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated

in vacuo to afford the title compound (51.00 mg, 136.45 μ mol, 76.04% yield, 90% purity) as yellow solid, which was used directly for the next step. LCMS: 337 [M+1].

Intermediate 4: tert-butyl 10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate.



Step 1. 5-tert-butyl 3-ethyl 2-(3-((tert-butoxycarbonyl)amino)propyl)-6,7-dihydro-2H-pyrazolo[4,3-c]pyridine-3,5(4H)-dicarboxylate. To a solution of O5-tert-butyl O3-ethyl 2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine -3,5-dicarboxylate (500.00 mg, 1.69 mmol, 1.00 *eq*) in THF (5.00 mL) was added tert-butyl N-(3-bromopropyl)carbamate (482.91 mg, 2.03 mmol, 1.20 *eq*) followed by DBU (385.93 mg, 2.54 mmol, 382.11 μ L, 1.50 *eq*). The mixture was heated to 50 °C for 16 hr. TLC (PE:EA = 1:1) showed the starting material consumed and two main spots appeared. The mixture was extracted with EtOAc (100 mL*2) and H₂O (50 mL). The combined organic layer was dried with Na₂SO₄, filtrated. The filtrate was concentrated in vacuum. The residue was purified by flash chromatography (PE:EA=20%~50%) to afford the title compound (400.00 mg, 875.06 μ mol, 51.78% yield, 99% purity) as colorless oil. ¹H NMR (400MHz, CDCl₃) δ = 4.97 (brs, 1 H), 4.49 - 4.65 (m, 4 H), 4.34 (q, *J* = 7.0 Hz, 2 H), 3.69 (brs, 2 H), 3.08 (d, *J* = 5.9 Hz, 2 H), 2.74 (brs, 2 H), 1.99 (quin, *J* = 6.3 Hz, 2 H), 1.49 (s, 9 H), 1.44 (s, 9 H), 1.39 (t, *J* = 7.2 Hz, 4 H).

Step 2. ethyl 2-(3-aminopropyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-3-carboxylate.

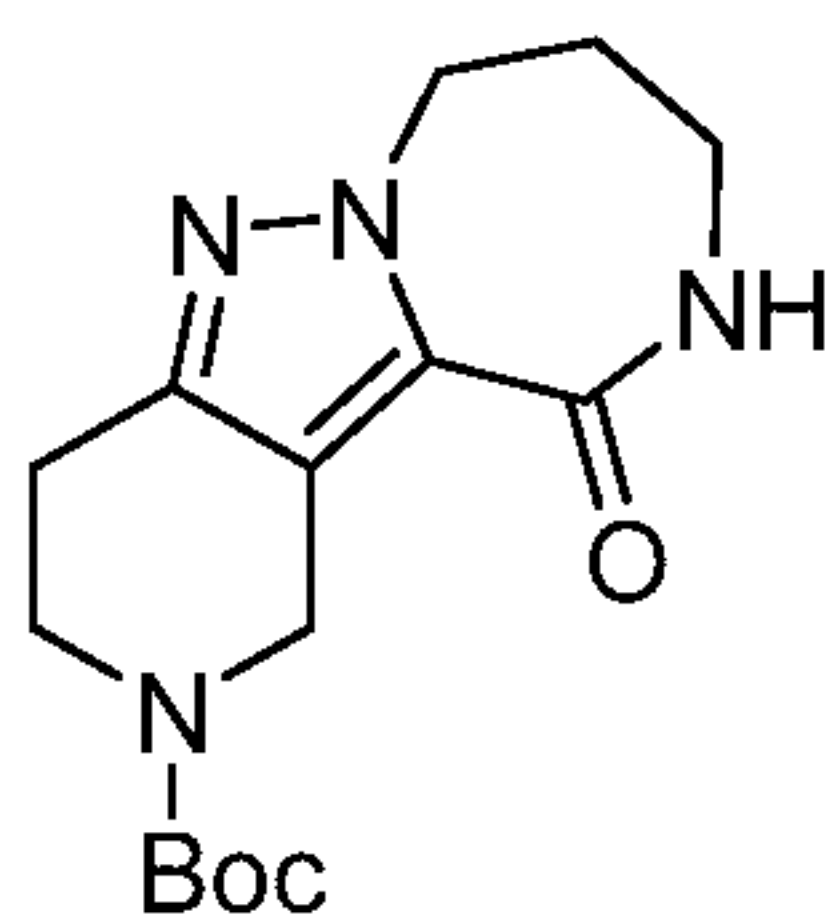
To a solution of O5-tert-butyl O3-ethyl 2-[3-(tert-butoxycarbonylamino)propyl]- 6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-3,5-dicarboxylate (400.00 mg, 883.90 μ mol, 1.00 *eq*) in DCM (2.00 mL) was added TFA (6.16 g, 54.02 mmol, 4.00 mL, 61.12 *eq*). The mixture was stirred at 10 °C for 1 hr. The mixture was concentrated in vacuum to afford the title compound (430.00 mg, crude, as brown oil.

Step 3. tert-butyl 11-oxo-3,4,7,8,9,10- hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of ethyl 2-(3-aminopropyl)-4,5,6,7-tetrahydropyrazolo[4,3-

c]pyridine -3-carboxylate (400.00 mg, 832.71 μmol , 1.00 *eq*, in EtOH (50.00 mL) was added K_2CO_3 (460.35 mg, 3.33 mmol, 4.00 *eq*). The mixture was stirred at 70~80 °C for 32 hr. The mixture was cooled to 10 °C and Boc_2O (363.48 mg, 1.67 mmol, 382.61 μL , 2.00 *eq*) was added. The mixture was stirred at 10 °C for 1 hr. TLC (DCM:MeOH = 10:1) showed one main spot appeared. The mixture was concentrated in vacuum. The residue was extracted with EtOAc (50 mL*2) and H_2O (20 mL). The combined organic layer was dried over Na_2SO_4 , filtrated. The filtrate was concentrated in vacuum. The residue was purified by flash chromatography (DCM:MeOH:0%~7%) to afford the title compound (155.00 mg, 505.94 μmol , 60.76% yield) as white solid.

Step 4. tert-butyl 10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of tert-butyl 11-oxo-3,4,7,8,9,10-hexahydro-1H-pyrido[2,3]pyrazolo [2,4-b][1,4]diazepine-2-carboxylate (100.00 mg, 326.41 μmol , 1.00 *eq*) in THF (2.00 mL) was added NaH (19.58 mg, 489.61 μmol , 60% purity, 1.50 *eq*). The mixture was stirred at 0 °C for 30 min. CH_3I (69.50 mg, 489.61 μmol , 30.48 μL , 1.50 *eq*) was added. The mixture was stirred at 10 °C for 1 hr. LCMS showed one main peak with desired Ms detected. The mixture was poured into H_2O (10 mL) and extracted with EtOAc (10 mL*2). The combined organic layer was dried with Na_2SO_4 , filtrated. The filtrates was concentrated in vacuum to afford the title compound (90.00 mg, crude) as colorless oil.

Intermediate 5: tert-butyl 11-oxo-3,4,7,8,9,10-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate.



Step 1. 5-tert-butyl 3-ethyl 2-[3-(tert-butoxycarbonylamino)propyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-3,5-dicarboxylate. To a solution of O5-tert-butyl O3-ethyl 2,4,6,7-

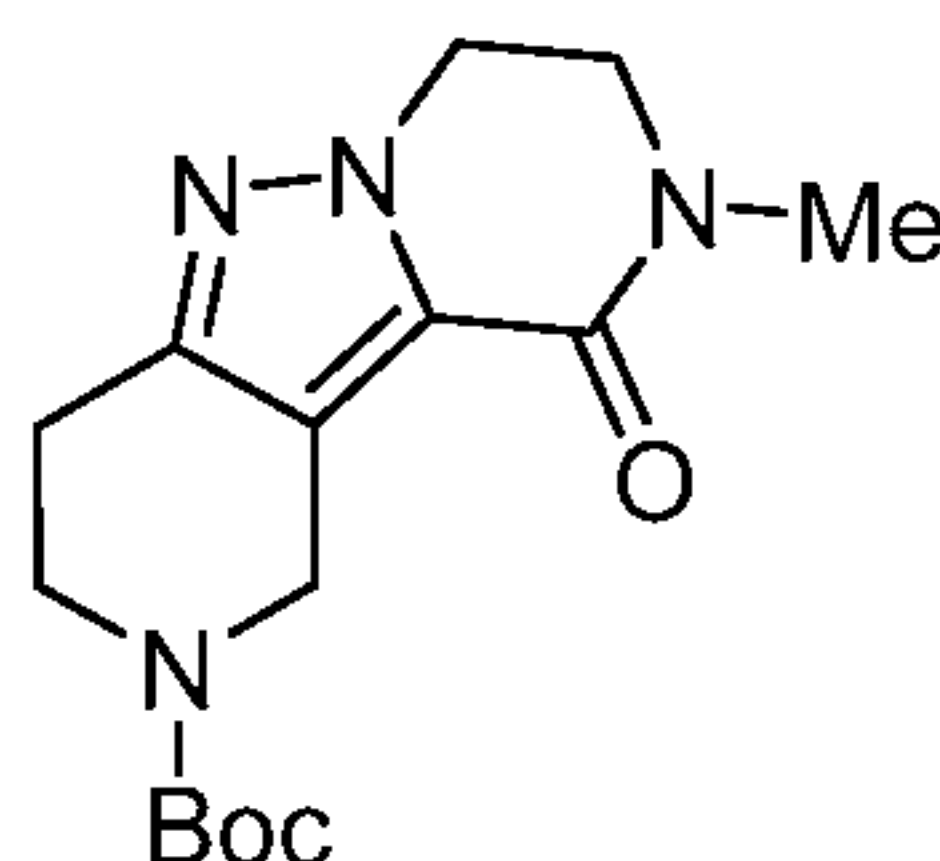
tetrahydropyrazolo[4,3-c]pyridine-3,5- dicarboxylate (2.00 g, 6.77 mmol, 1.00 *eq*) in THF (20.00 mL) was added tert-butyl N-(3-bromopropyl)carbamate (1.93 g, 8.12 mmol, 1.20 *eq*), followed by DBU (1.55 g, 10.16 mmol, 1.53 mL, 1.50 *eq*), the reaction mixture was stirred at 50 °C for 16

hours. Several new peaks were shown on LCMS and about 30% of desired product was detected. The reaction mixture was diluted with EtOAc (150 mL) and washed with water (50 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to afford the title compound (1.70 g, 3.76 mmol, 55.49% yield) as white solid. ¹H NMR (400 MHz, CDCl₃) δ = 4.94 (brs, 1 H) 4.54 - 4.85 (m, 4 H) 4.30 - 4.35 (m, 2 H) 3.67 (br s, 2 H) 3.06 - 3.08 (br d, *J* = 5.90 Hz, 2 H) 2.72 (br s, 2 H) 1.94 - 2.01 (m, *J* = 6.43 Hz, 2 H) 1.47 (s, 9 H) 1.42 (s, 9 H) 1.36 - 1.39 (t, *J* = 7.15 Hz, 3 H). LCMS: 453 [M+1].

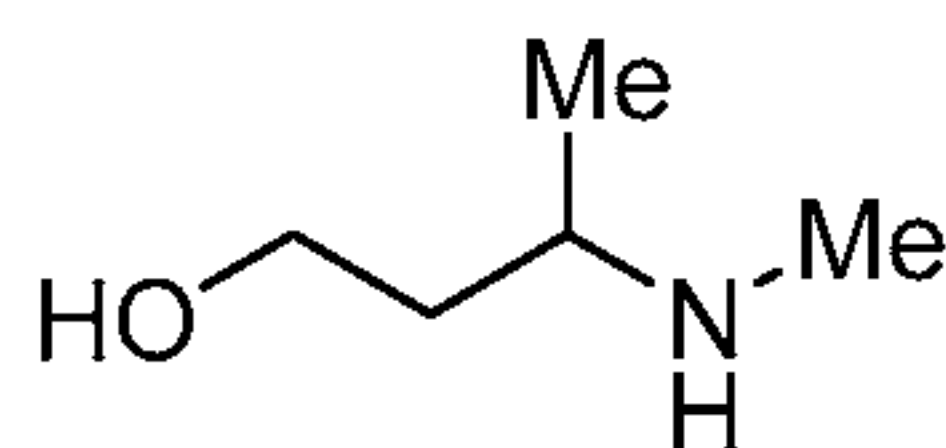
Step 2. ethyl 2-(3-aminopropyl)-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridine-3-carboxylate. To a solution of O5-tert-butyl O3-ethyl 2-[3-(tert-butoxycarbonylamino)propyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-3,5-dicarboxylate (1.70 g, 3.76 mmol, 1.00 *eq*) in dioxane (10.00 mL) was added HCl/dioxane (4 M, 20.00 mL, 21.28 *eq*). The reaction mixture was stirred at 20 °C for 2 hours. TLC indicated compound 3 was consumed completely, and one major new spot with larger polarity was detected. The solvent was removed on a rotary evaporator to afford the title compound (1.10 g, crude, as white solid. ¹H NMR (400 MHz, METHANOL-d₄) δ = 4.65 - 4.68 (t, *J* = 6.65 Hz, 2 H) 4.38 - 4.44 (m, 4 H) 3.53 - 3.56 (t, *J* = 6.27 Hz, 2 H) 3.03 - 3.07 (t, *J* = 6.21 Hz, 2 H) 2.94 - 2.98 (br t, *J* = 7.65 Hz, 2 H) 2.17 - 2.24 (m, 2 H) 1.39 - 1.42 (t, *J* = 7.09 Hz, 3 H)

Step 3. tert-butyl 11-oxo-3,4,7,8,9,10-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of ethyl 2-(3-aminopropyl)-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridine-3-carboxylate (900.00 mg, 2.77 mmol, 1.00 *eq*,) in EtOH (10.00 mL) was added NaOMe (597.95 mg, 11.07 mmol, 4.00 *eq*) under N₂. The reaction mixture was stirred at 20 °C for 3 hours. LCMS showed compound 4 was consumed completely. The solvent was removed on a rotary evaporator. To the residue, was added THF (10.00 mL), followed by a solution of NaHCO₃ (697.44 mg, 8.30 mmol, 322.89 μL, 3.00 *eq*) in H₂O (2.00 mL) and (Boc)₂O (905.94 mg, 4.15 mmol, 953.62 μL, 1.50 *eq*). The reaction mixture was stirred at 20 °C for one hour. LCMS showed one main peak with desired MS was detected. The reaction mixture was diluted with EtOAc (50 mL) and washed with water (30 mL*2), the organic phase was dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to afford the title compound (600.00 mg, 1.96 mmol, 70.70% yield) was obtained as white solid. LCMS: 329 [M+23].

Intermediate 6: tert-butyl 9-methyl-10-oxo-3,4,7,8-tetrahydro-1H-pyrido [2,3]pyrazolo[2,4-b]pyrazine-2-carboxylate.

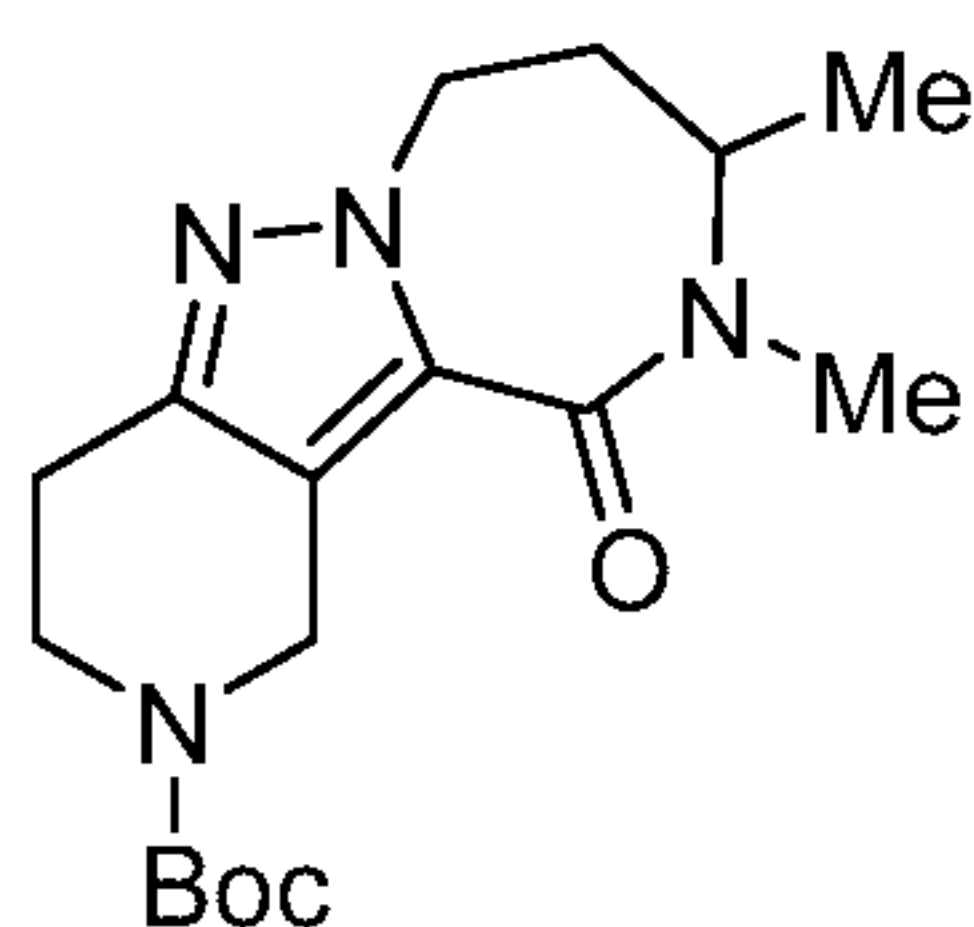


- 5 Step 1. tert-butyl 3-[2-hydroxyethyl(methyl) carbamoyl]-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate. To a mixture of 5-tert-butoxycarbonyl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-3-carboxylic acid (1.00 g, 3.74 mmol, 1.00 *eq*) and 2-(methylamino)ethanol (1.41 g, 18.71 mmol, 1.49 mL, 5.00 *eq*) in DMF (5.00 mL) was added HATU (2.13 g, 5.61 mmol, 1.50 *eq*) and DIPEA (7.25 g, 56.12 mmol, 9.80 mL, 15.00 *eq*) in one portion under N₂. The
- 10 mixture was stirred at 80 °C for 10 hours. LCMS and TLC (Dichloromethane : Methanol=10:1) showed the reaction was completed. The residue was poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (50 mL*2). The combined organic phase was washed with brine (50 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Petroleum
- 15 ether/Ethyl acetate=1/1, Dichloromethane:Methanol=20:1) to afford the title compound (750.00 mg, 2.31 mmol, 61.82% yield, 100% purity) as white solid. LCMS: 325 [M+1].
- Step 2. tert-butyl 9-methyl-10-oxo-3,4,7,8-tetrahydro-1H-pyrido [2,3]pyrazolo[2,4-b]pyrazine-2-carboxylate. To a mixture of tert-butyl 3-[2-hydroxyethyl(methyl)carbamoyl]-1,4,6,7-
- 20 tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (100.00 mg, 308.29 μmol, 1.00 *eq*) in THF (3.00 mL) was added tributylphosphane (81.09 mg, 400.78 μmol, 98.88 μL, 1.30 *eq*) and DIAD (81.04 mg, 400.78 μmol, 77.92 μL, 1.30 *eq*) under N₂. The mixture was stirred at 80 °C for 4 hours. TLC (Dichloromethane:Methanol=10:1) showed the reaction was completed. The mixture was poured into water (10 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (10 mL*2). The combined organic phase was washed with brine (10 mL*2),
- 25 dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-TLC (Dichloromethane: Methanol=10:1) to afford the title compound (70.00 mg, 228.49 μmol, 74.12% yield) as yellow solid. LCMS: 307 [M+1].

Intermediate 7: 3-(methylamino)butan-1-ol.

Step 1. N-(3-hydroxy-1-methyl-propyl)formamide. To a mixture of 3-aminobutan-1-ol (5.00 g, 56.09 mmol, 1.00 *eq*) and ethyl acetate (9.88 g, 112.18 mmol, 10.98 mL, 2.00 *eq*) in EtOH (30.00 mL) was added ethyl formate (9.88 g, 112.18 mmol, 10.98 mL, 2.00 *eq*) in one portion under N₂. The mixture was stirred at 80 °C for 12 hours. TLC (dichloromethane: methanol=10:1) showed the reaction was completed. The mixture was concentrated in vacuum to afford the title compound (6.00 g, 51.22 mmol, 91.31% yield) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 8.17 (s, 1H), 5.75-5.97 (m, 1H), 4.13-4.43 (m, 1H), 3.53-3.68 (m, 2H), 3.27 (br s, 1H), 1.74-1.97 (m, 1H), 1.34-1.52 (m, 1H), 1.15-1.31 (m, 3H).

Step 2. 3-(methylamino)butan-1-ol. To a mixture of N-(3-hydroxy-1-methyl-propyl)formamide (2.00 g, 17.07 mmol, 1.00 *eq*) in THF (10.00 mL) was added LiAlH₄ (1.30 g, 34.14 mmol, 2.00 *eq*) in one portion at -10 °C under N₂. The mixture was stirred at -10 °C for 30 min, then heated to 20 °C and stirred for 12 hours, then heated to 80 °C and stirred for 3 hours. TLC (dichloromethane: methanol=10:1) showed the reaction was completed. The mixture was quenched with 1.3 mL of H₂O, followed by 1.3 mL of NaOH(15%) and 3.9 mL of H₂O. The mixture was dried with anhydrous MgSO₄, filtered and concentrated in vacuum to afford the title compound (1.20 g, 11.63 mmol, 68.15% yield) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 3.71 - 3.93 (m, 2 H), 2.83 (ddd, *J* = 3.30, 6.39, 8.28 Hz, 1 H), 2.43 (s, 3 H), 1.66 - 1.74 (m, 1 H), 1.53 (s, 1 H), 1.15 (d, *J* = 6.36 Hz, 3 H).

Intermediate 8: tert-butyl 9,10-dimethyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo [2,4-c][1,4]diazepine-2-carboxylate.

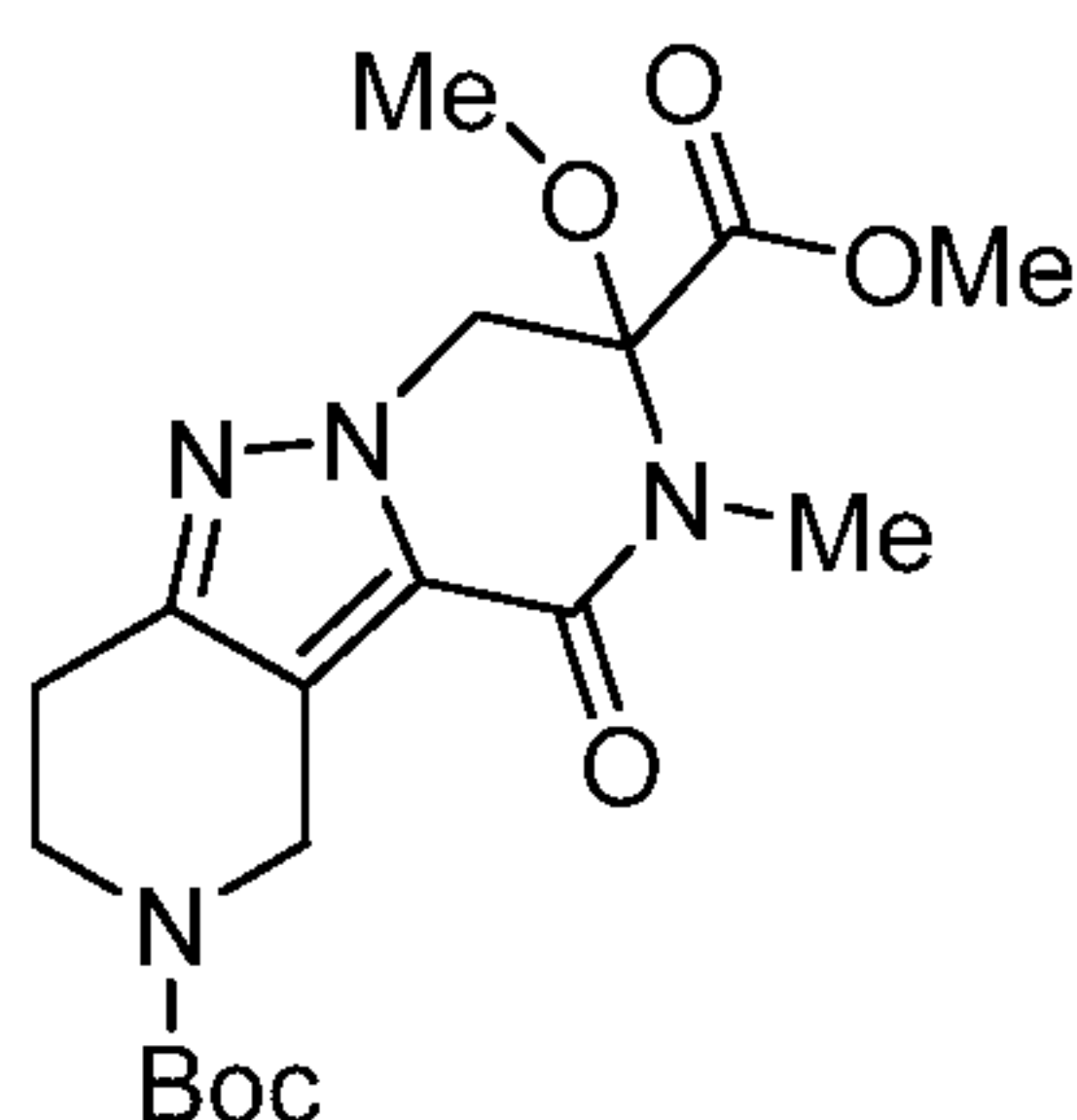
Step 1. tert-butyl 3-[(3-hydroxy-1-methyl-propyl)-methyl-carbamoyl]-1,4,6,7-

tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate. To a mixture of 5-tert-butoxycarbonyl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-3-carboxylic acid (500.00 mg, 1.87 mmol, 1.00 *eq*) and 3-(methylamino)butan-1-ol (Intermediate 7, 771.92 mg, 7.48 mmol, 4.00 *eq*) in DMF (5.00 mL) was added HATU (1.07 g, 2.81 mmol, 1.50 *eq*) and DIPEA (3.63 g, 28.06 mmol, 4.90 mL, 15.00 *eq*) in one portion under N₂. The mixture was stirred at 80 °C for 10 hours. LCMS and TLC (dichloromethane: methanol=10:1) showed Desired product was detected. The residue was poured into water (10 mL). The aqueous phase was extracted with ethyl acetate (10 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate=1/1, dichloromethane: methanol=20:1) to afford the title compound (300.00 mg, 510.74 μmol, 27.31% yield, 60% purity) as yellow solid. LCMS: 353 [M+1].

Step 2. tert-butyl 9,10-dimethyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo [2,4-

c][1,4]diazepine-2-carboxylate. To a mixture of tert-butyl 3-[(3-hydroxy-1-methyl-propyl)-methyl-carbamoyl]-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (300.00 mg, 851.23 μmol, 1.00 *eq*) in THF (10.00 mL) was added tributylphosphane (223.89 mg, 1.11 mmol, 273.03 μL, 1.30 *eq*) and DIAD (223.77 mg, 1.11 mmol, 215.16 μL, 1.30 *eq*) in one portion under N₂. The mixture was stirred at 80 °C for 12 hours. LCMS and TLC (Dichloromethane : Methanol=10:1) showed the desired product was detected. The mixture was poured into water (10 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (10 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-HPLC(FA) to afford the title compound (66.00 mg, 197.36 μmol, 23.19% yield) as yellow solid. LCMS: 335 [M+1].

Intermediate 9: 2-tert-butyl8-methyl8-methoxy-9-methyl-10-oxo-1,3,4,7-tetrahydro pyrido[2,3]pyrazolo[2,4-c]pyrazine-2,8-dicarboxylate.



Step 1. tert-butyl 3-[(hydroxy(methyl)carbamoyl)-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate. Na (7.78 g, 338.60 mmol, 8.02 mL, 10.00 *eq*) was added to MeOH (100.00 mL) portionwise at 0 °C, and the mixture was stirred at 15 °C for 0.5 hr under N₂. Then N-methylhydroxylamine (8.48 g, 101.58 mmol, 3.00 *eq*, HCl) was added to the mixture and the mixture was stirred at 15 °C for 0.5 hr under N₂. Then 5-tert-butyl 3-ethyl 1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-3,5-dicarboxylate (Intermediate 30, 10.00 g, 33.86 mmol, 1.00 *eq*) was added, the mixture was stirred at 70 °C for 16 hr under N₂ atmosphere. TLC (PE/EA=1/1) showed the starting material was consumed completely and a new spot was detected mainly. The mixture was poured into ice-water (300 mL) and stirred for 5 min. Then the mixture was concentrated to remove MeOH. The aqueous phase was adjusted to pH =6 with HCl (1 N, aq) and then extracted with ethyl acetate (100 mL x 3). The combined organic phase was washed with brine (300 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to afford the title compound (8.00 g, 27.00 mmol, 79.73% yield) as a yellow solid. LCMS: 297 [M+1]. ¹H NMR (400 MHz, METHANOL-d₄) δ = 4.62 (brs, 2 H) 3.70 (t, *J* = 5.52 Hz, 2 H) 3.31 - 3.58 (m, 3 H) 2.74 (s, 2 H) 1.48 (s, 9 H).

Step 2. tert-butyl 4- (hydroxymethyl)-2-methyl-1-oxo- 5,8,9,11-tetrahydro-4H-pyrido[2,3]pyrazolo[2,4-d][1,2,5]oxadiazepine-10-carboxylate. A mixture of tert-butyl 3-[(hydroxy(methyl)carbamoyl)-1,4,6,7-tetrahydropyrazolo [4,3-c]pyridine-5-carboxylate (8.00 g, 27.00 mmol, 1.00 *eq*), 3-bromooxetane (4.07 g, 29.70 mmol, 1.10 *eq*), TBAI (997.22 mg, 2.70 mmol, 0.10 *eq*) and Cs₂CO₃ (13.19 g, 40.50 mmol, 1.50 *eq*) in DMF (80.00 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 70 °C for 3 hr under N₂ atmosphere. TLC (DCM/MeOH=10/1) showed the starting material was consumed completely and the title compound was major. The mixture was poured into water (200 mL) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (100 mL x 3). The combined organic phase was washed with brine (300 mL x 2), dried with anhydrous Na₂SO₄, filtered and

concentrated in vacuum. The residue was purified by column chromatography (SiO₂, PE/EA = 100/1 to 1/2) to afford the title compound (4.50 g, 12.39 mmol, 45.88% yield, 97% purity) as a yellow solid. LCMS: 353 [M+1]. ¹H NMR (400 MHz, CDCl₃/CDCl₃) δ = 4.62 (brs, 2 H) 4.53 (brs, 2 H) 4.32 - 4.42 (m, 1 H) 3.57 - 3.88 (m, 4 H) 3.29 (br. s., 3 H) 2.68 - 2.79 (m, 2 H) 1.41 - 1.53 (m, 9 H).

Step 3. 10-tert-butoxycarbonyl-2-methyl-1-oxo-5,8,9,11-tetrahydro-4H-

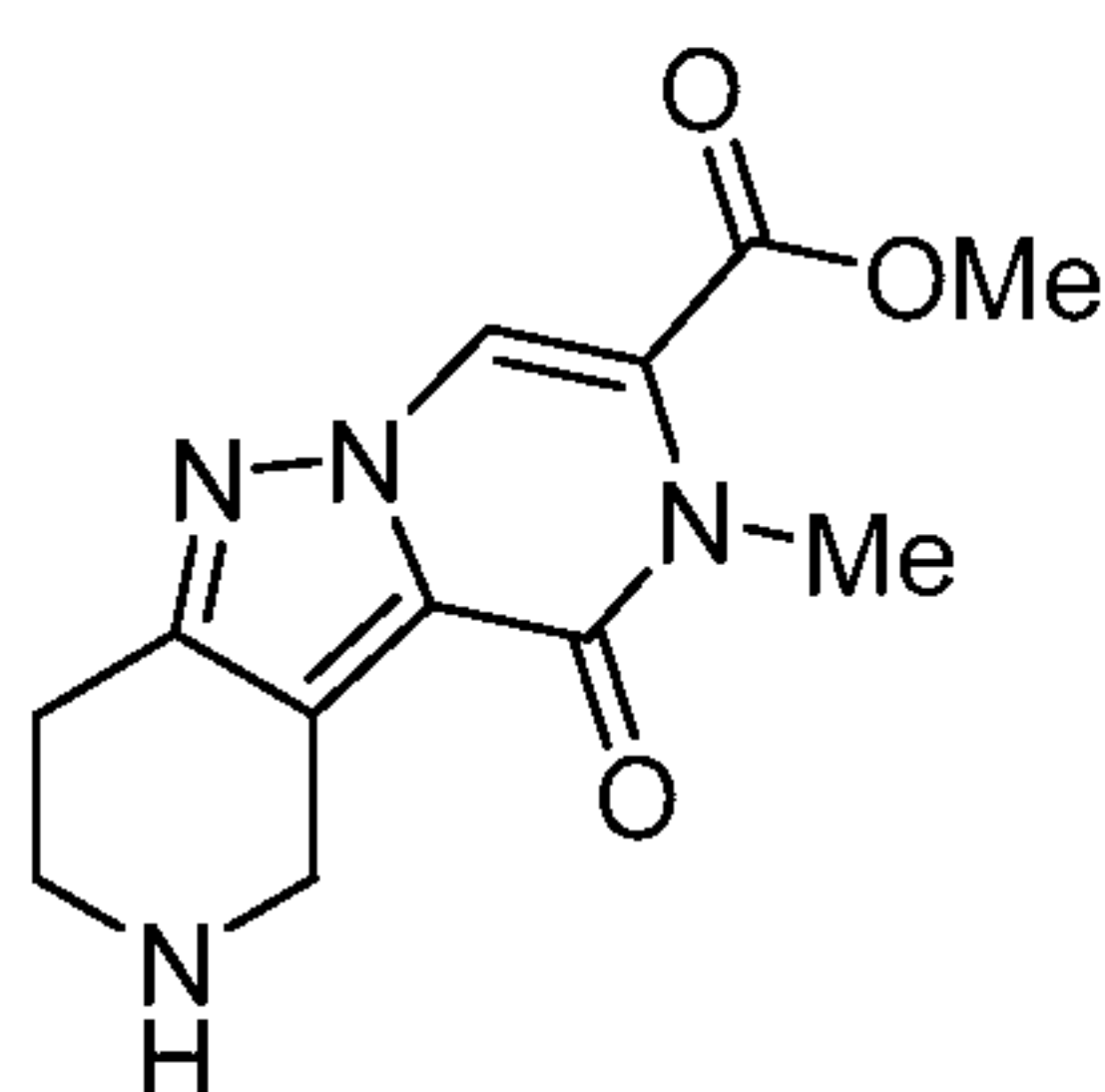
pyrido[2,3]pyrazolo[2,4-d][1,2,5]oxadiazepine-4-carboxylic acid. To a mixture of tert-butyl 4-(hydroxymethyl)-2-methyl-1-oxo-5,8,9,11-tetrahydro-4H-pyrido[2,3]pyrazolo[2,4-d][1,2,5]oxadiazepine-10-carboxylate (1.00 g, 2.84 mmol, 1.00 *eq*) and NMO (2.50 g, 21.30 mmol, 2.25 mL, 7.50 *eq*) in MeCN (30.00 mL) was added TPAP (199.61 mg, 568.00 μmol, 0.20 *eq*) in one portion at 0 °C under N₂. The mixture was stirred at 0 °C for 2 hr. LCMS showed the reaction was completed. The mixture was concentrated in vacuum to afford the title compound (1.04 g, crude) as black brown solid. LCMS: 367 [M+1].

Step 4. 2-tert-butyl 8-methyl 8-methoxy-9-methyl-10-oxo-1,3,4,7-

tetrahydropyrido[2,3]pyrazolo[2,4-c]pyrazine-2,8-dicarboxylate. To a mixture of 10-tert-butoxycarbonyl-2-methyl-1-oxo-5,8,9,11-tetrahydro-4H-pyrido[2,3]pyrazolo[2,4-d][1,2,5]oxadiazepine-4-carboxylic acid (1.04 g crude, 2.84 mmol, 1.00 *eq*) and K₂CO₃ (1.18 g, 8.52 mmol, 3.00 *eq*) in MeCN (20.00 mL) was added MeI (1.21 g, 8.52 mmol, 530.70 μL, 3.00 *eq*) in one portion at 25 °C under N₂. The mixture was stirred at 25 °C 12 hours. LCMS showed the reaction didn't react. The starting material was recovered: the reaction mixture was neutralized with HCl (1 N, aq) to pH=3, then extracted with ethyl acetate (20 mL x 2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to dryness. The reaction was performed again. To the recovered starting material and K₂CO₃ (1.18 g, 8.52 mmol, 3.00 *eq*) in MeCN (20.00 mL) was added MeI (1.21 g, 8.52 mmol, 530.70 μL, 3.00 *eq*) in one portion at 25 °C under N₂. The mixture was stirred at 25 °C for 12 hours. LCMS and TLC (EA/PE=2/1) showed the reaction was completed, 50% of the title compound was detected. The residue was poured into water (20 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (20 mL x 2). The combined organic phase was washed with brine (20 mL x 2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (PE/EA=10/1, 2/1) to the title compound (200.00 mg,

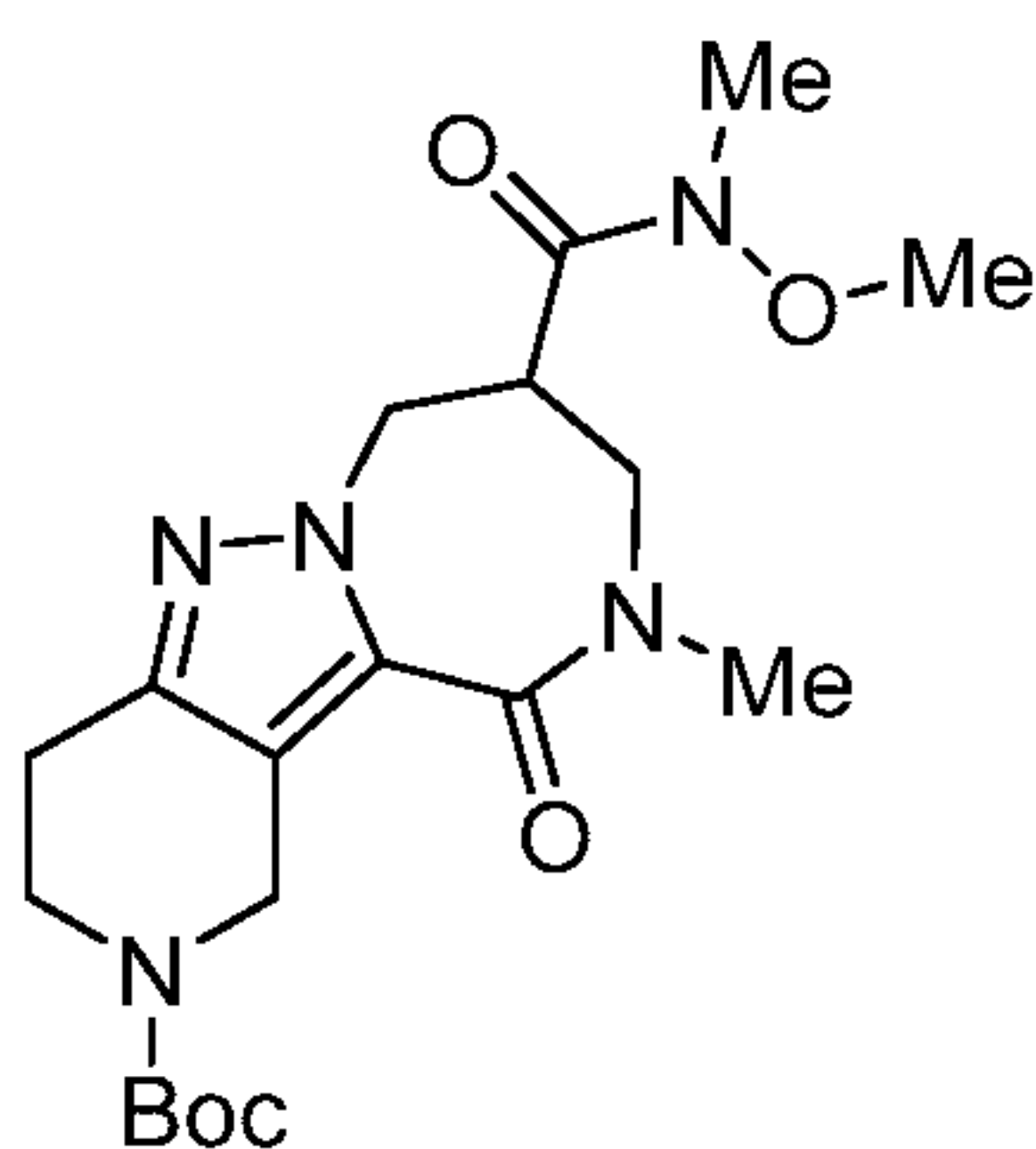
507.07 μmol , 17.85% yield, 100% purity) as yellow oil. LCMS: 395 [M+1]. ^1H NMR (400 MHz, CDCl_3) 4.64 - 4.80 (m, 3 H), 4.51 - 4.62 (m, 1 H), 3.88 (s, 3 H), 3.60 - 3.79 (m, 2 H), 3.38 (s, 3 H), 3.05 (s, 3 H), 2.78 (br. s., 2 H), 1.49 (s, 9 H).

5 Intermediate 10: methyl 9-methyl-10-oxo-1,2,3,4-tetrahydropyrido[2,3]pyrazolo[2,4-b]pyrazine-8-carboxylate



A mixture of 2-tert-butyl-8-methyl-8-methoxy-9-methyl-10-oxo-1,3,4,7-tetrahydropyrido[2,3]pyrazolo[2,4-c]pyrazine-2,8-dicarboxylate (20.00 mg, 50.71 μmol , 1.00 *eq*) in HCl/dioxane (4 M, 20.00 mL, 1577.60 *eq*) was stirred at 20 °C for 2 hours. LCMS showed the reaction was completed. The residue was concentrated in vacuum to afford the title compound as the HCl salt (15.15 mg, 50.71 μmol , 100.00% yield) as yellow solid. LCMS: 263 [M+1].

15 Intermediate 11: tert-butyl 8-[methoxy(methyl)carbamoyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate.

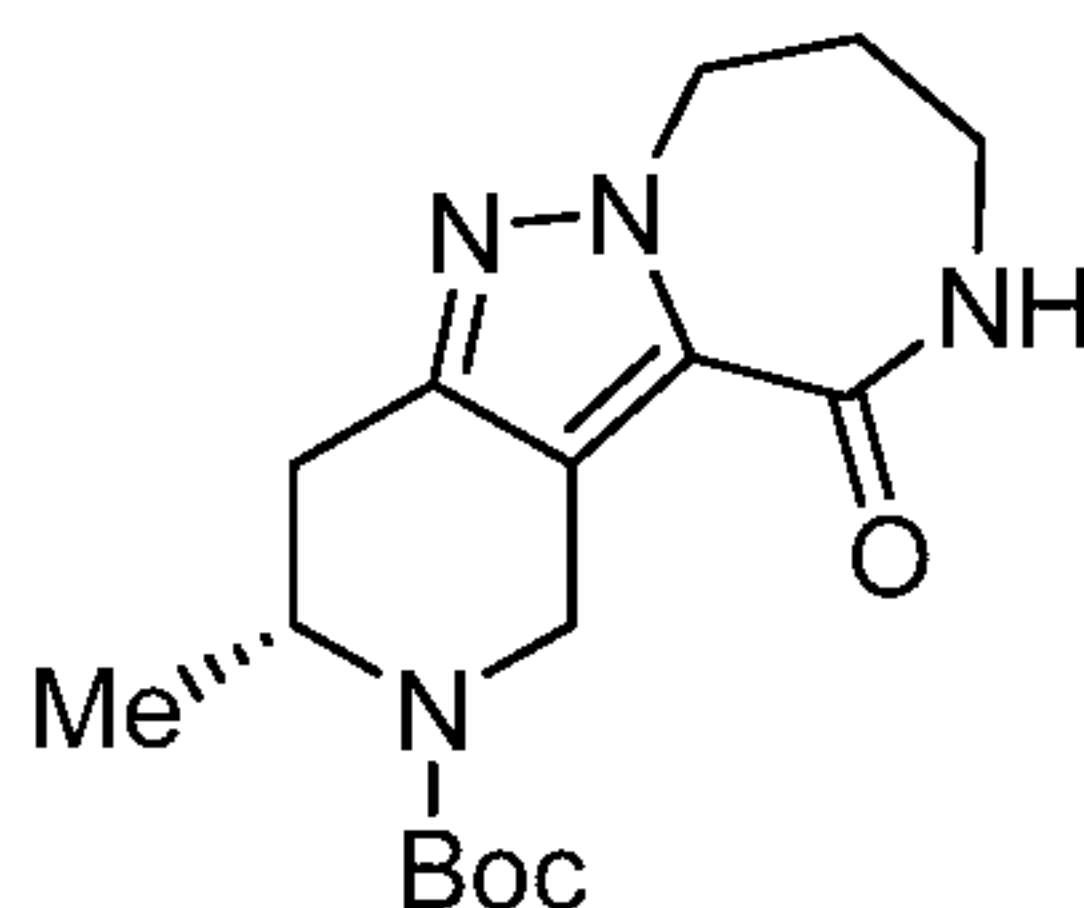


To a mixture of 2-tert-butoxycarbonyl-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-8-carboxylic acid (500.00 mg, 1.37 mmol, 1.00 *eq*) and N-methoxymethanamine hydrochloride (534.52 mg, 5.48 mmol, 4.00 *eq*) in THF (10.00 mL) was added T₃P (1.74 g, 2.74 mmol, 1.63 mL, 50% purity, 2.00 *eq*) and TEA (2.08 g,

20.55 mmol, 2.85 mL, 15.00 *eq*) in one portion under N₂. The mixture was stirred at 30 °C for 12 hours. LCMS and TLC (Dichloromethane : Methanol=10:1) showed the reaction was completed. The mixture was poured into water (15 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (20 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Dichloromethane : Methanol=50:1~20:1) to afford the title compound (510.00 mg, 1.24 mmol, 90.45% yield, 99% purity) as white solid.

LCMS[M+1]: 408.

10 Intermediate 12: tert-butyl (3R)-3-methyl-11-oxo-3,4,7,8,9,10-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate.



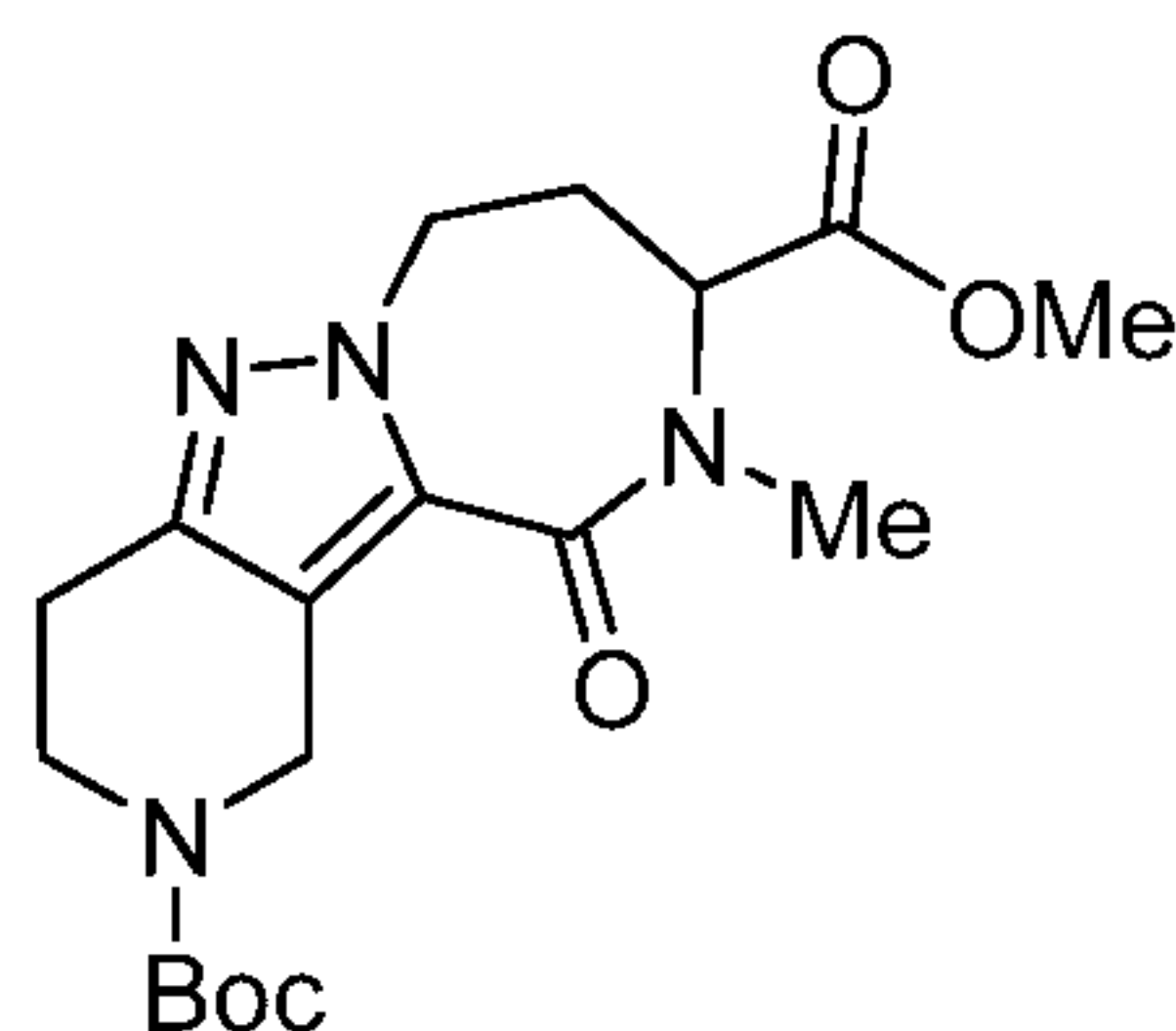
15 Step 1. 5-tert-butyl 3-ethyl (6R)-2-[3-(tert-butoxycarbonylamino)propyl]-6-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-3,5-dicarboxylate. To a solution of 5-tert-butyl 3-ethyl (6R)-6-methyl-2,4,6,7-tetrahydropyrazolo [4,3-c]pyridine-3,5-dicarboxylate (4.50 g, 14.55 mmol, 1.00 *eq*) in THF (50.00 mL) was added tert-butyl N-(3-bromopropyl)carbamate (4.16 g, 17.46 mmol, 1.20 *eq*) followed by DBU (3.32 g, 21.83 mmol, 3.29 mL, 1.50 *eq*). The mixture was heated to 60 °C for 16 hr. TLC (PE: EtOAc = 1:1) showed the starting material consumed and two new main spots appeared. The mixture was extracted with EtOAc (200 mL*2) and H₂O (50 mL). The combined organic layer was dried with Na₂SO₄, filtrated. The filtrate was concentrated in vacuum. The residue was purified by flash chromatography (PE:EtOAc = 20%~50%) to afford the title compound (4.50 g, 9.64 mmol, 66.29% yield) as colorless oil.

25 Step 2. ethyl (6R)-2-(3-aminopropyl)-6- methyl-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridine-3-carboxylate. 5-tert-butyl 3-ethyl (6R)-2-[3-(tert-butoxycarbonylamino)propyl]-6-methyl -6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-3,5-dicarboxylate (4.50 g, 9.64 mmol, 1.00 *eq*) was dissolved in HCl/dioxane (4 M, 50.00 mL, 20.75 *eq*). The mixture was stirred at 20 °C for 2 hr.

LCMS showed one main peak with desired Ms detected. The mixture was concentrated in vacuum to afford the title compound as the HCl salt (3.30 g, crude) as white solid.

Step 3. tert-butyl (3R)-3-methyl-11-oxo-3,4,7,8,9,10-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of ethyl (6R)-2-(3-aminopropyl)-6-methyl-4,5,6,7-tetrahydro pyrazolo[4,3-c]pyridine-3-carboxylate (3.27 g, 9.64 mmol, 1.00 *eq*) in MeOH (4.00 mL) was added CH₃ONa (2.08 g, 38.55 mmol, 4.00 *eq*). The mixture was stirred at 20 °C for 2 hr. LCMS showed one main peak with desired Ms detected. The mixture was concentrated in vacuum. The residue was dissolved in THF (8.00 mL) and H₂O (4.00 mL). NaHCO₃ (1.62 g, 19.28 mmol, 749.76 μL, 2.00 *eq*) and Boc₂O (2.52 g, 11.57 mmol, 2.66 mL, 1.20 *eq*) was added. The mixture was stirred at 20 °C for 16 hr. TLC (PE:EtOAc = 0:1) showed one main spot appeared. The mixture was diluted with saturated NH₄Cl (100 mL) and extracted with EtOAc (200 mL*2). The combined organic layer was dried over Na₂SO₄, filtrated. The filtrate was concentrated in vacuum. The residue was purified by column chromatography (PE:EtOAc = 50%~100%) to afford the title compound (2.40 g, 7.49 mmol, 77.71% yield) as white solid.

Intermediate 13: 2-(tert-butyl) 9-methyl 11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2,9-dicarboxylate.



Step 1. 3-aminotetrahydrofuran-2-one. To a solution of 2-amino-4-hydroxy-butanoic acid (5.50 g, 46.17 mmol, 1.00 *eq*) in H₂O (50.00 mL) was added HCl (12 M, 50.02 mL, 13.00 *eq*), the mixture was stirred at 120 °C for 3 hr. TLC (Dichloromethane : Methanol=10:1) showed the reactant consumed. The mixture was concentrated to give the residue, most of the solvent was removed azeotropically with ethanol. Following crystal formation the solution was cooled on ice. The resulting solid was filtered and rinsed three times with cold ethanol (20 mL). The filtrate was concentrated and cooled, producing additional homoserine lactone. The process was repeated 2 more times to afford the title compound as the HCl salt (4.20 g, 30.53 mmol, 66.13%

yield) as white solid. ¹H NMR (400 MHz, d₆-DMSO) δ 4.52 - 4.63 (m, 1 H), 4.32 - 4.49 (m, 2 H), 2.68 - 2.84 (m, 1 H), 2.31 - 2.46 (m, 1 H).

Step 2. 2-amino-4-bromo-butanoic acid. A mixture of 3-aminotetrahydrofuran-2-one (4.00 g, 29.08 mmol, 1.00 *eq*) in HBr (103.67 g, 615.00 mmol, 69.57 mL, 48% purity, 21.15 *eq*) was stirred at 100 °C for 6 hr. TLC (Dichloromethane: Methanol=10:1) showed the reaction was completed. The mixture was filtered to give the solid which was washed with methyl tertiary-butyl ether (50 mL) to afford the title compound (6.30 g, 23.96 mmol, 82.40% yield, HBr) as red solid

Step 3. methyl 2-amino-4-bromo-butanoate. To a solution of 2-amino-4-bromo-butanoic acid (6.30 g, 23.96 mmol, 1.00 *eq*, HBr) in MeOH (50.00 mL) was added SOCl₂ (5.70 g, 47.92 mmol, 3.48 mL, 2.00 *eq*) at 0 °C, the mixture was stirred at 20 °C for 12 hr. TLC (Petroleum ether: Ethyl acetate=1:1) showed the reaction was completed. The mixture was concentrated in vacuum to afford the title compound (6.30 g, 22.75 mmol, 94.94% yield, HBr) as the red solid ¹H NMR (400 MHz, DEUTERIUM OXIDE) δ 4.34 (t, *J* = 6.65 Hz, 1 H), 3.84 (s, 3 H), 3.54 - 3.68 (m, 2 H), 2.58 (qd, *J* = 6.53, 15.29 Hz, 1 H), 2.29 - 2.47 (m, 1 H).

Step 4. methyl 2-(benzyloxycarbonylamino)-4-bromo-butanoate. To a solution of methyl 2-amino-4-bromo-butanoate (6.30 g, 22.75 mmol, 1.00 *eq*, HBr) in H₂O (50.00 mL) was added NaHCO₃ (4.78 g, 56.87 mmol, 2.21 mL, 2.50 *eq*) and CbzCl (4.66 g, 27.30 mmol, 3.88 mL, 1.20 *eq*) at 0 °C, the mixture was stirred at 20 °C for 16 hr. TLC (Petroleum ether: Ethyl acetate=1:1) showed the reaction was completed. The mixture was extracted with ethyl acetate (200 mL*2), the organic layer was washed with brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated in vacuum. The crude was triturated with Petroleum ether (30 mL) to afford the title compound (3.60 g, 10.79 mmol, 47.45% yield, 99% purity) as white solid.

Step 5. 5-tert-butyl 3-ethyl 2-[3-(benzyloxycarbonylamino)-4-methoxy-4-oxo-butyl]-6,7-

dihydro-4H-pyrazolo[4,3-c]pyridine-3,5-dicarboxylate. To a solution of 5-tert-butyl 3-ethyl 2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-3,5-dicarboxylate (3.60 g, 12.19 mmol, 1.00 *eq*) and methyl 2-(benzyloxycarbonylamino)-4-bromo-butanoate (4.31 g, 13.04 mmol, 1.07 *eq*) in THF (50.00 mL) was added DBU (5.57 g, 36.57 mmol, 5.51 mL, 3.00 *eq*), the mixture was stirred at 20 °C for 16 hr. TLC (Petroleum ether : Ethyl acetate=1:1) showed the reaction was complete. The mixture was poured into water (20 mL), extracted with Ethyl acetate (20 mL*2), the organic layer was washed with brine (20 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuum.

The crude was purified by prep.TLC (Petroleum ether : Ethyl acetate=1:1) to afford the title compound (3.60 g, 6.28 mmol, 51.52% yield, 95% purity) as colorless oil.

Step 6. 5-tert-butyl 3-ethyl 2-(3-amino-4-methoxy-4-oxo-butyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-3,5-dicarboxylate. To a solution of 5-tert-butyl 3-ethyl 2-[3-

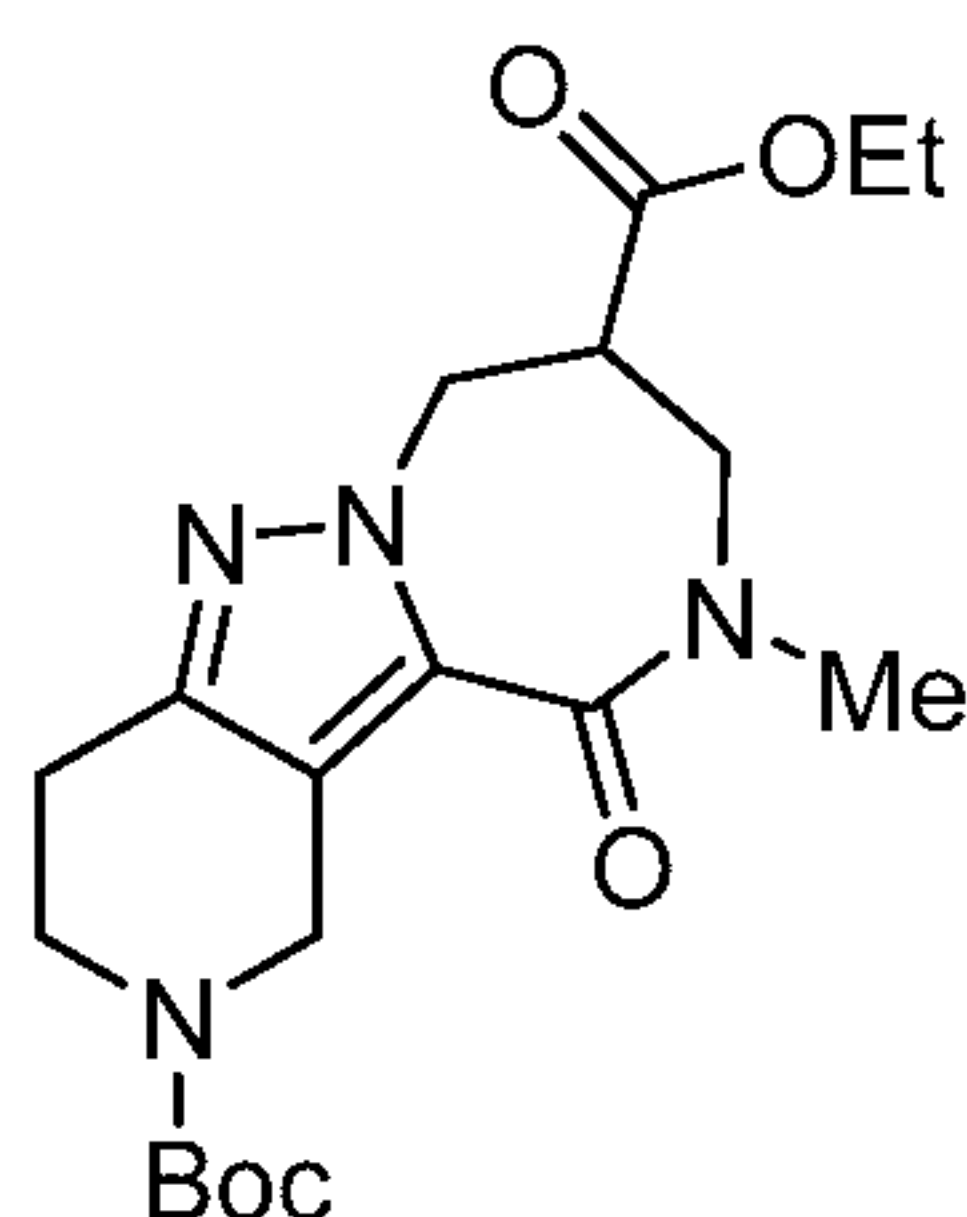
5 (benzyloxycarbonylamino)-4-methoxy-4-oxo-butyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-3,5-dicarboxylate (3.60 g, 6.61 mmol, 1.00 *eq*) in MeOH (40.00 mL) was added Pd/C (700.00 mg, 6.61 mmol, 10% purity, 1.00 *eq*). The mixture was stirred under H₂ (15 Psi) at 20 °C for 2 hr. LCMS showed the reaction completed. The mixture was filtered and concentrated in vacuo to afford the title compound (2.60 g, 6.33 mmol, 95.83% yield) as colorless oil.

10 Step 7. 2-tert-butoxycarbonyl-11-oxo-3,4,7,8,9,10-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-9-carboxylic acid. To a solution of 5-tert-butyl 3-ethyl 2-(3-amino-4-methoxy-4-oxo-butyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-3,5-dicarboxylate (2.60 g, 6.33 mmol, 1.00 *eq*) in MeOH (3.00 mL) was added NaOMe (631.72 mg, 11.69 mmol, 3.00 *eq*). The mixture was stirred at 20 °C for 16 hr. LCMS showed the reaction complete. The solvent was evaporated to
15 give the residue which was poured into aqueous HCl (0.5 M, 50 mL), extracted with DCM (30 mL*4), the organic layer was washed with brine (20 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuum to afford the title compound (1.10 g, 3.14 mmol, 80.50% yield) as yellow solid.

Step 8. 2-tert-butyl 9-methyl 11-oxo-3,4,7,8,9,10-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-2,9-dicarboxylate. To a solution of 2-tert-butoxycarbonyl-11-oxo-3,4,7,8,9,10-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-9-carboxylic acid (1.10 g, 3.14 mmol, 1.00 *eq*) in DMF (20.00 mL) was added K₂CO₃ (650.87 mg, 4.71 mmol, 1.50 *eq*) and MeI (1.34 g, 9.42 mmol, 586.44 μL, 3.00 *eq*). The mixture was stirred at 20 °C for 16 hr. LCMS showed the reaction was complete. The mixture was poured into water (100 mL), extracted with ethyl
25 acetate (50 mL*2), the combined organic layer was washed with brine (30 mL*2), dried over anhydrous Na₂SO₄ and concentrated in vacuum to afford the title compound (1.10 g, 3.02 mmol, 96.18% yield) as colorless oil.

Intermediate 14: 2-tert-butyl 8-ethyl 10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2,8-dicarboxylate.

30



Step 1. ethyl 2-[[tert-butoxycarbonyl(methyl)amino]methyl]prop-2-enoate. A mixture of tert-butyl N-methylcarbamate (200.00 mg, 1.52 mmol, 1.00 *eq*) in THF (5.00 mL) was added NaH (91.20 mg, 2.28 mmol, 60% purity, 1.50 *eq*) at 0 °C for 0.5 hr under N₂, then ethyl 2-

(bromomethyl)prop-2-enoate (352.10 mg, 1.82 mmol, 1.20 *eq*) was added to the mixture dropwise at 0 °C, and the mixture was stirred at 15 °C for 2 hr under N₂ atmosphere. TLC (PE/EA=10/1) the starting material was consumed completely and two new spots appeared. The mixture was poured into ice-water (10 mL) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (5 mL x 3). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 5/1) to afford the title compound (112.00 mg, 460.34 μmol, 30.29% yield) as colorless oil. ¹H NMR (400MHz, CDCl₃) δ 6.28 (s, 1 H), 5.55 (s, 1 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 4.07 (br s, 2 H), 2.88 (br s, 3 H), 1.45 (br s, 9 H), 1.31 (br s, 3 H).

Step 2. ethyl 2-(methylaminomethyl)prop-2-enoate. A mixture of ethyl 2-[[tert-butoxycarbonyl(methyl)amino]methyl]prop-2-enoate (112.00 mg, 460.34 μmol, 1.00 *eq*) in dioxane (1.00 mL) was added HCl/dioxane (4 M, 5.00 mL, 43.45 *eq*), and then the mixture was stirred at 15 °C for 0.5 hour. TLC (PE/EA=10/1) showed the starting material was consumed completely, a new spot was major. The mixture was concentrated in vacuum to afford the title compound (82.50 mg, 459.25 μmol, 99.76% yield, HCl) as a white solid, which was used directly for the next step.

Step 3. tert-butyl 3-[2-ethoxycarbonylallyl (methyl) carbamoyl]-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate. A mixture of 5-tert-butoxycarbonyl-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-3-carboxylic acid (80.00 mg, 299.31 μmol, 1.00 *eq*), ethyl 2-(methylaminomethyl)prop-2-enoate (59.14 mg, 329.24 μmol, 1.10 *eq*, HCl), T₃P (285.70 mg, 897.93 μmol, 267.01 μL, 3.00 *eq*) and TEA (151.44 mg, 1.50 mmol, 207.45 μL, 5.00 *eq*) in THF (3.00 mL) was

degassed and purged with N₂ for 3 times, and then the mixture was stirred at 15 °C for 16 hours under N₂ atmosphere. TLC (DCM/MeOH=10/1) the starting material was consumed completely and a new spot appeared. The mixture was poured into water (10 mL) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (5 mL x 3). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum.

The residue was purified by prep-TLC (DCM/MeOH=10/1) to afford the title compound (46.00 mg, 105.49 μmol, 35.24% yield, 90% purity) as a white solid. LCMS: 393 [M+1]. ¹H NMR (400MHz, CDCl₃) δ 6.35 (s, 1 H), 5.67 (br s, 1 H), 4.63 (s, 4 H), 4.18 - 4.30 (m, 2 H), 3.71 (br s, 2 H), 2.91 - 3.47 (m, 3 H), 2.74 (br t, *J* = 5.4 Hz, 2 H), 1.48 (s, 9 H), 1.31 (t, *J* = 7.2 Hz, 3 H).

Step 4. tert-butyl 8-ethyl 10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3] pyrazolo[2,4-b][1,4]diazepine-2,8-dicarboxylate. A mixture of tert-butyl 3-[2-

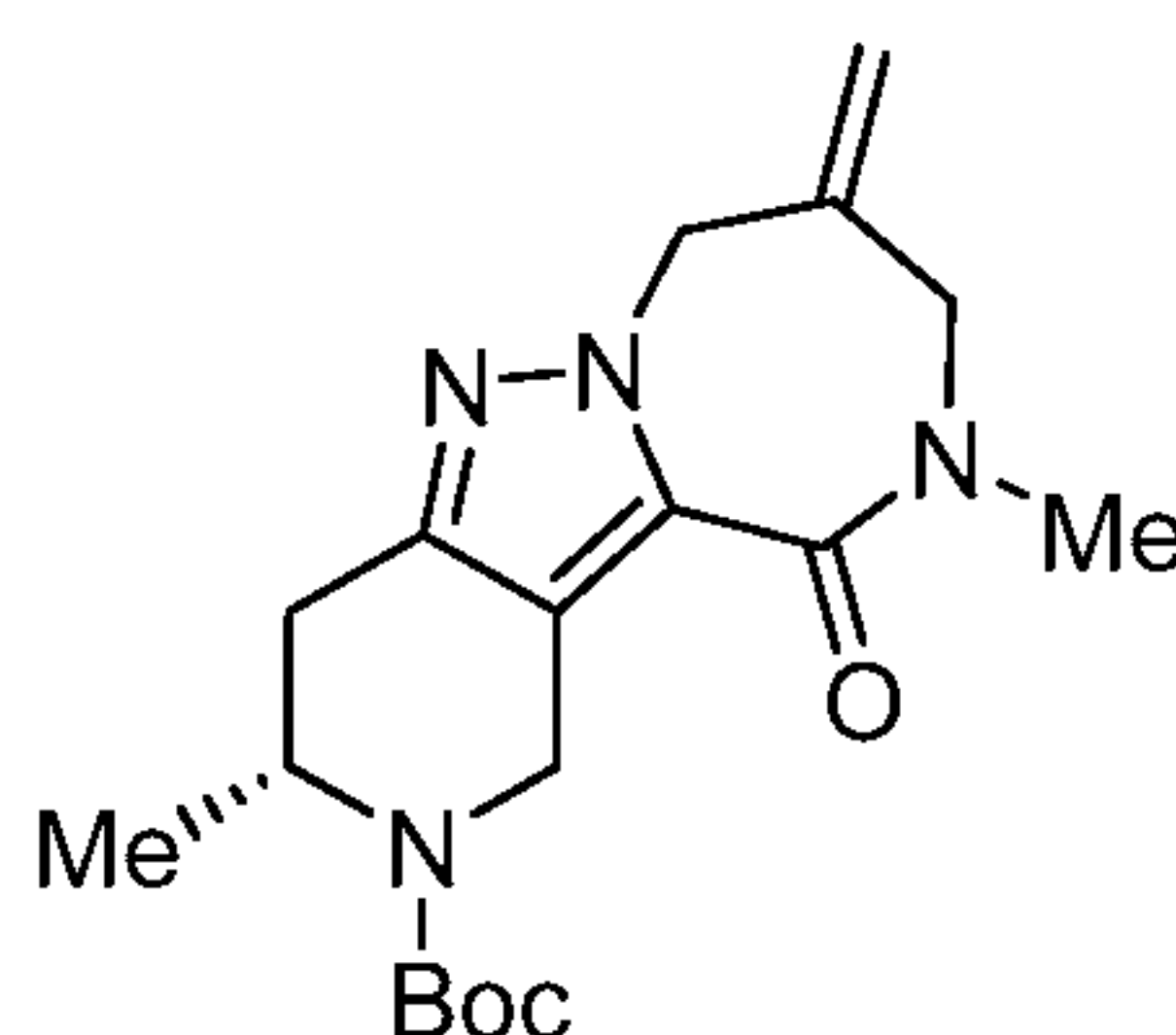
ethoxycarbonylallyl(methyl)carbamoyl]-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (36.00 mg, 91.73 μmol, 1.00 *eq*), DBU (6.98 mg, 45.87 μmol, 6.91 μL, 0.50 *eq*)

in MeCN (1.00 mL) was degassed and purged with N₂ for 3 times, and then the mixture was

stirred at 50 °C for 2 hour under N₂ atmosphere. TLC (DCM/MeOH=20/1) showed starting material was consumed completely and the title compound was major. The mixture were poured into water (5 mL) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (3 mL x 3). The combined organic phase was washed with brine (5 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-TLC

(DCM/MeOH=20/1) to afford the title compound (20.00 mg, 50.96 μmol, 55.56% yield) as a white solid. LCMS: 393 [M+1]

Intermediate 15: tert-butyl (3R)-3,10-dimethyl-8-methylene-11-oxo-3,4,7,9-tetrahydro-1H-pyrido[2,3] pyrazolo[2,4-b][1,4]diazepine-2-carboxylate

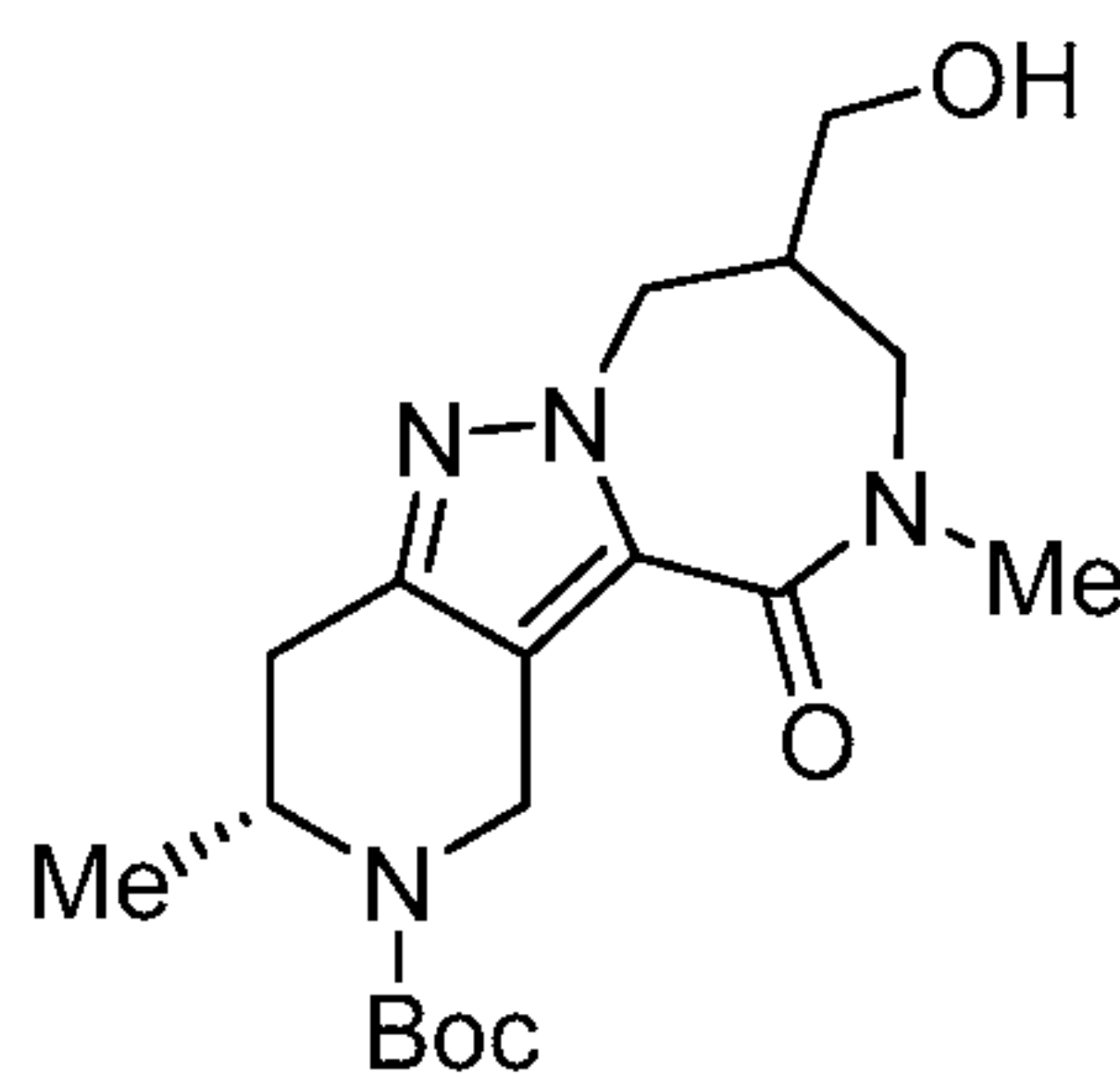


Step 1. 5-tert-butyl 3-ethyl (6R)-2-[2-(chloromethyl)allyl]-6-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-3,5-dicarboxylate. To a solution of 5-tert-butyl 3-ethyl (6R)-6-methyl-

1,4,6,7-tetrahydropyrazolo [4,3-c]pyridine-3,5-dicarboxylate (15.00 g, 48.49 mmol, 1.00 *eq*) in DMF (4.00 mL) was added Cs₂CO₃ (23.70 g, 72.73 mmol, 1.50 *eq*), followed by 3-chloro-2-(chloromethyl)prop-1-ene (12.12 g, 96.97 mmol, 11.22 mL, 2.00 *eq*). The mixture was heated to 50°C for 16 hr. TLC (PE:EtOAc=4:1) showed four spots appeared. The mixture was diluted with H₂O (300 mL) and extracted with EtOAc(500 mL*2). The combined organic layer was washed with H₂O (300 mL*3), dried over Na₂SO₄ and filtrated. The filtrate was concentrated in vacuum. The reissue was purified by flash chromatography (PE:EtOAc=0%~30%) to afford the title compound (7.00 g, 17.59 mmol, 36.28% yield) as colorless oil.

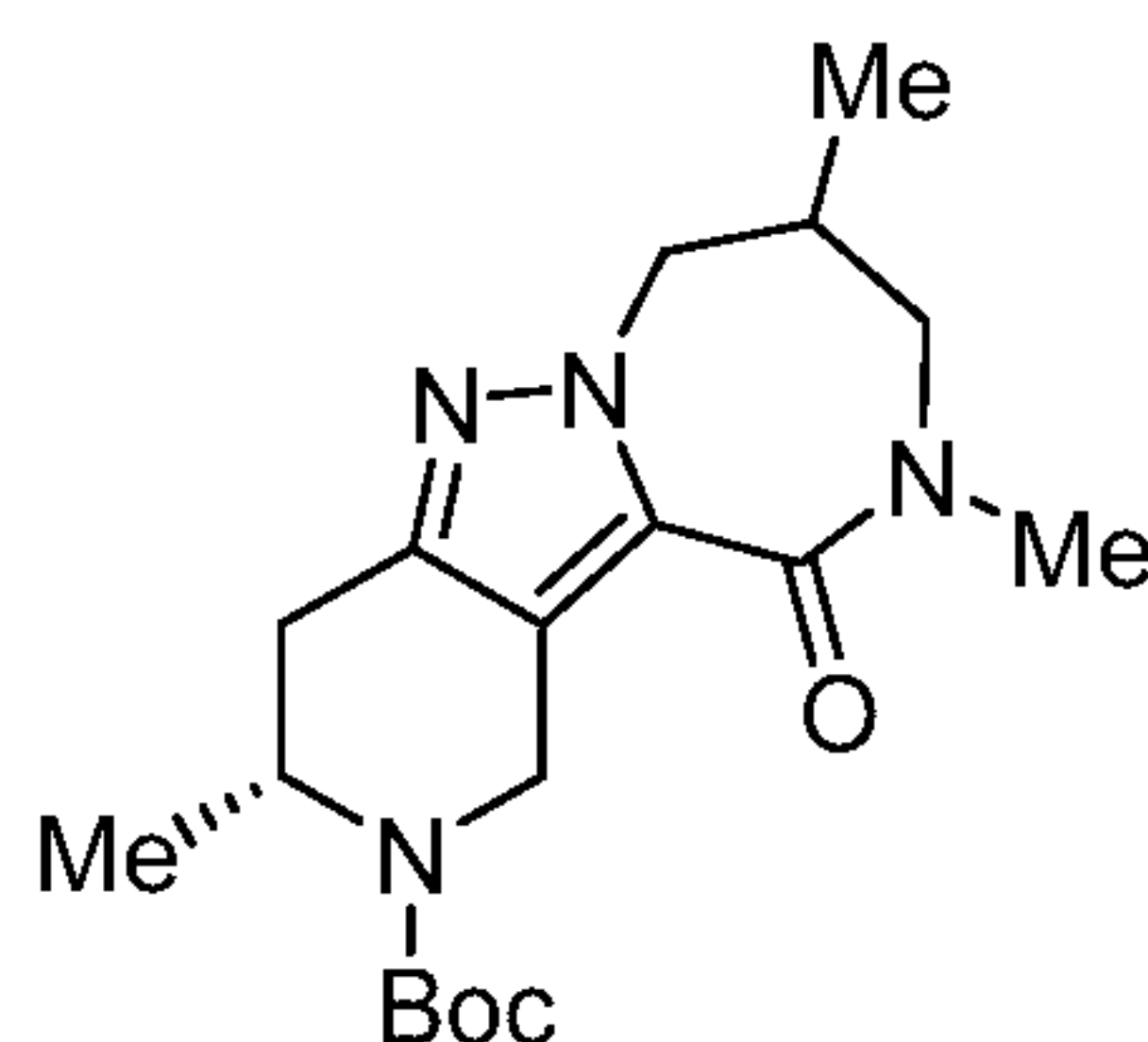
Step 2. tert-butyl (3R)-3,10-dimethyl-8-methylene-11-oxo-3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate and by-product tert-butyl (6R)-6-methyl-2-[2-(methylaminomethyl)allyl]-3-(methylcarbamoyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate. To a solution of 5-tert-butyl 3-ethyl (6R)-2-[2-(chloromethyl)allyl]-6-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-3,5-dicarboxylate (7.00 g, 17.59 mmol, 1.00 *eq*) in EtOH (28.00 mL) was added methanamine (54.63 g, 527.70 mmol, 120.00 mL, 30.00 *eq*, 30 % EtOH solution). The mixture was heated to 80 °C for 16 hr in sealed tube. TLC (PE: EtOAc = 1:1) showed that starting material consumed completely and two new spots formed mainly. The mixture was concerned and purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 10/1 to 1/1) to afford the title compound (3.00 g, 6.36 mmol, 36.15% yield, 80% purity) as yellow gum.

Intermediate 16: tert-butyl (3R)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate.



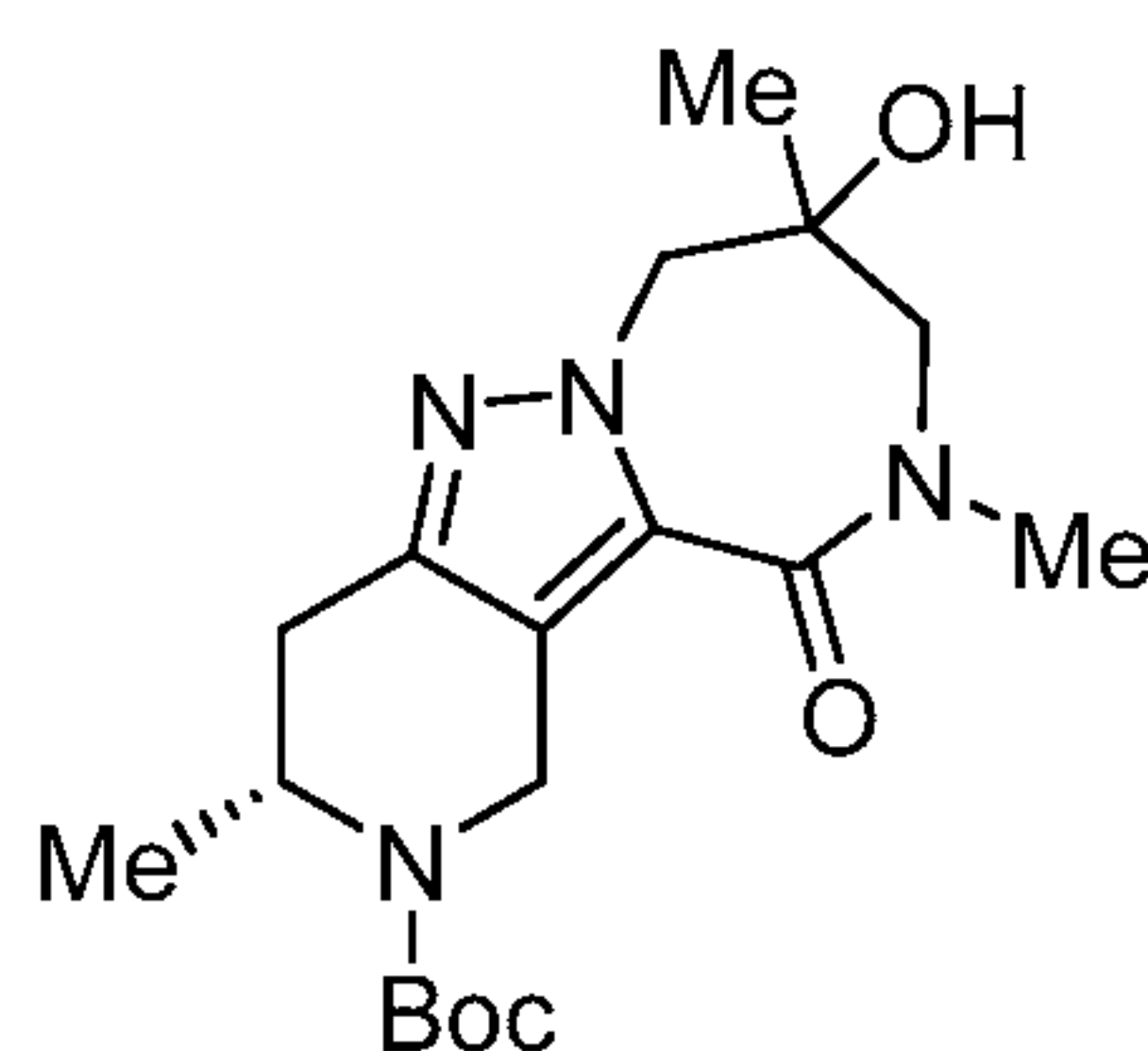
Step 1. tert-butyl (3R)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate, tert-butyl(3R)-8-hydroxy-3,8,10-trimethyl- 11-oxo-3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (Intermediate 17), and tert-butyl (3R)-3,8,10-trimethyl-11-oxo-1,3,4,7,8,9-

- hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (Intermediate 18). To a solution of tert-butyl (3R)-3,10-dimethyl-8-methylene-11-oxo-3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (Intermediate 15, 3.20 g, 9.24 mmol, 1.00 *eq*) in THF (50.00 mL) was added BH₃•DMS (10 M, 3.70 mL, 4.00 *eq*) at 0 °C under N₂.
- 5 The mixture was stirred at 20 °C for 2 h. TLC (PE: EtOAc=1:2, showed that starting material consumed. A solution of NaOH (2.59 g, 64.68 mmol, 7.00 *eq*) in H₂O (10.00 mL) was added at -30 °C dropwise, then H₂O₂ (6.28 g, 55.44 mmol, 5.32 mL, 30% purity, 6.00 *eq*) was added slowly. The mixture was stirred at 20 °C for 16 h. LC-MS indicated that 8% of tert-butyl (3R)-3,10-dimethyl-8-methylene-11-oxo-3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-
- 10 b][1,4]diazepine-2-carboxylate was still remained and ~54% of tert-butyl (3R)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate and ~17% of tert-butyl (3R)-3,8,10-trimethyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate were detected. The mixture was extracted with ethyl acetate (30 mL*3) and H₂O (20 mL). The combined organic layer was
- 15 washed with brine (20 mL*1), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=50/1 to 1/5, Plate 1), followed by prep-TLC to afford tert-butyl (3R)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (2.00 g, 5.48 mmol, 59.27% yield, 99.8% purity) as off-white gum, tert-butyl(3R)-8-hydroxy-3,8,10-
- 20 trimethyl-11-oxo-3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (150.00 mg, 382.78 μmol, 4.14% yield, 93% purity) as off-white gum and tert-butyl (3R)-3,8,10-trimethyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (250.00 mg, 645.74 μmol, 6.99% yield, 90% purity) as off-white gum.
- 25 Intermediate 17: tert-butyl(3R)-8-hydroxy-3,8,10-trimethyl-11-oxo-3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate.



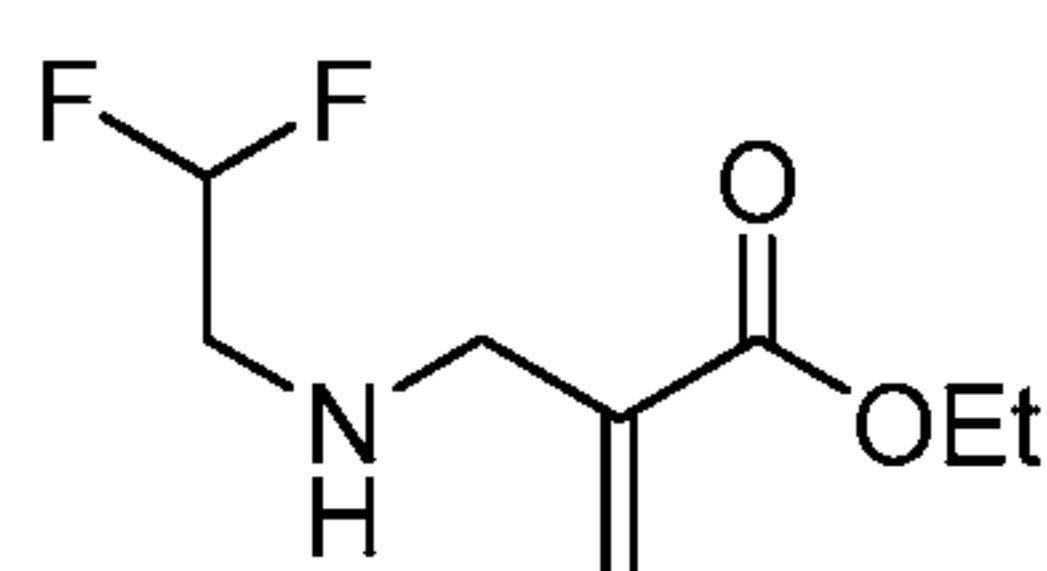
Isolated from Intermediate 16 (150.00 mg, 382.78 μ mol, 4.14% yield, 93% purity) as off-white gum.

- 5 Intermediate 18: tert-butyl (3R)-3,8,10-trimethyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate.



Isolated from Intermediate 16 (250.00 mg, 645.74 μ mol, 6.99% yield, 90% purity) as off-white gum.

- 10 Intermediate 19: ethyl 2-[(2,2-difluoroethylamino)methyl]prop-2-enoate.



- 15 Step 1. tert-butyl N-(2,2-difluoroethyl)carbamate. To a mixture of 2,2-difluoroethanamine (10.00 g, 123.37 mmol, 1.00 *eq*) and Et₃N (24.97 g, 246.74 mmol, 34.21 mL, 2.00 *eq*) in DCM (100.00 mL) was added Boc₂O (29.62 g, 135.71 mmol, 31.18 mL, 1.10 *eq*), and the mixture was stirred at 25 °C for 16 h. TLC indicated no starting material and one major new spot with lower polarity was detected. The mixture was diluted with DCM (150 mL) and washed with brine (150 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by silica gel column to afford the title compound (17.90 g, 98.80 mmol, 80.08%

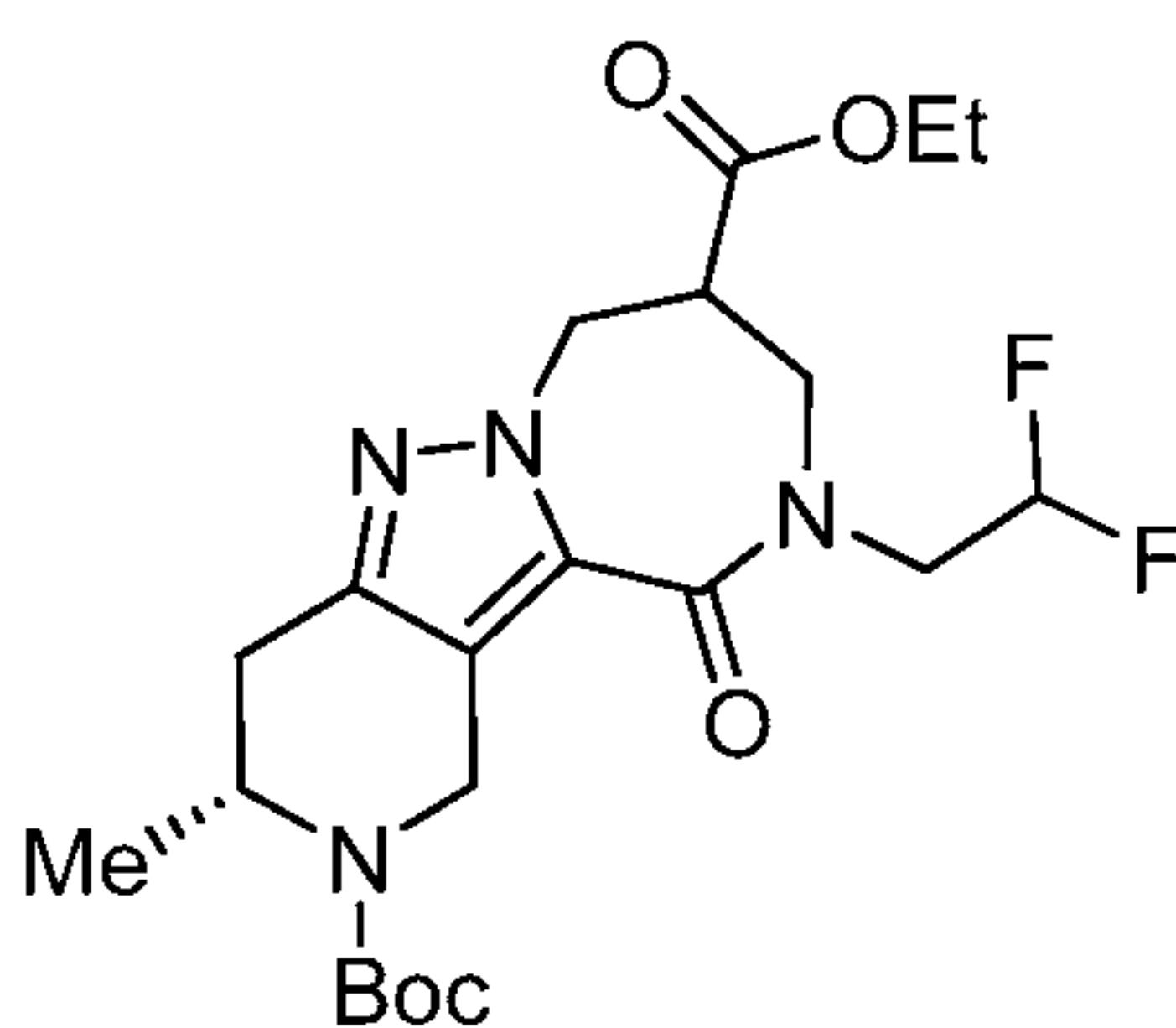
yield) as colorless solid. ^1H NMR (400 MHz, CDCl_3) δ 5.55 - 6.02 (m, 1 H), 4.58 - 4.88 (m, 1 H), 3.26 - 3.58 (m, 2 H), 1.38 (s, 9 H).

Step 2. ethyl 2-[[tert-butoxycarbonyl (2,2-difluoroethyl)amino]methyl]prop-2-enoate. To a solution of tert-butyl N-(2,2-difluoroethyl)carbamate (2.00 g, 11.04 mmol, 1.00 *eq*) in THF (30.00 mL) was added NaH (574.08 mg, 14.35 mmol, 60% purity, 1.30 *eq*) at 0 °C under N_2 , followed by ethyl 2-(bromomethyl)prop-2-enoate (3.20 g, 16.56 mmol, 1.50 *eq*) after 0.5 h, and the mixture was stirred at 25 °C for 16 h. LCMS showed desired product was detected mainly. The mixture was quenched with H_2O (100 mL) and extracted with EtOAc (100 mL). The organic phase was concentrated in vacuo, which was purified by silica gel column to afford the title compound (2.30 g, 7.14 mmol, 64.64% yield, 91% purity) as colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 6.30 – 6.32 (m, 1 H), 5.70 - 6.15 (m, 1 H), 5.30 – 5.60 (m, 1 H), 4.14 - 4.27 (m, 4 H), 3.55 – 3.59 (m, 2 H), 1.44 – 1.48 (m, 9 H), 1.28 – 1.34 (m, 3 H).

Step 3. ethyl 2-[(2,2-difluoroethylamino)methyl]prop-2-enoate. A solution of ethyl 2-[[tert-butoxycarbonyl(2,2-difluoroethyl)amino] methyl] prop-2- enoate (600.00 mg, 2.05 mmol, 1.00 *eq*) in HCl/dioxane (4 M, 6.00 mL, 11.71 *eq*) was stirred at 25 °C for 2 h. TLC showed no starting material and one new major spot was detected. The mixture was concentrated in vacuo to afford the title compound as the HCl salt (469.00 mg, 2.04 mmol, 99.62% yield) as colorless solid. ^1H NMR (400 MHz, CDCl_3) δ 10.08 - 10.26 (m, 1 H), 6.60 (m, 1 H), 6.31 (m, 2 H), 4.24 (m, 2 H), 3.91 - 4.01 (m, 2 H), 3.28 - 3.45 (m, 2 H), 1.28 (t, $J = 7.2$ Hz, 3H).

Intermediate 20: 2-tert-butyl 8-ethyl (3R)-10-(2,2-difluoroethyl)-3-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido [2,3]pyrazolo[2,4-b][1,4]diazepine-2,8-dicarboxylate.



Step 1. tert-butyl (6R)-3-[2,2-difluoroethyl (2-ethoxycarbonylallyl)carbamoyl]-6-methyl-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate. A mixture of ethyl 2-[(2,2-difluoroethylamino)methyl]prop-2-enoate (Intermediate 19, 456.54 mg, 1.99 mmol, 1.40 *eq*),

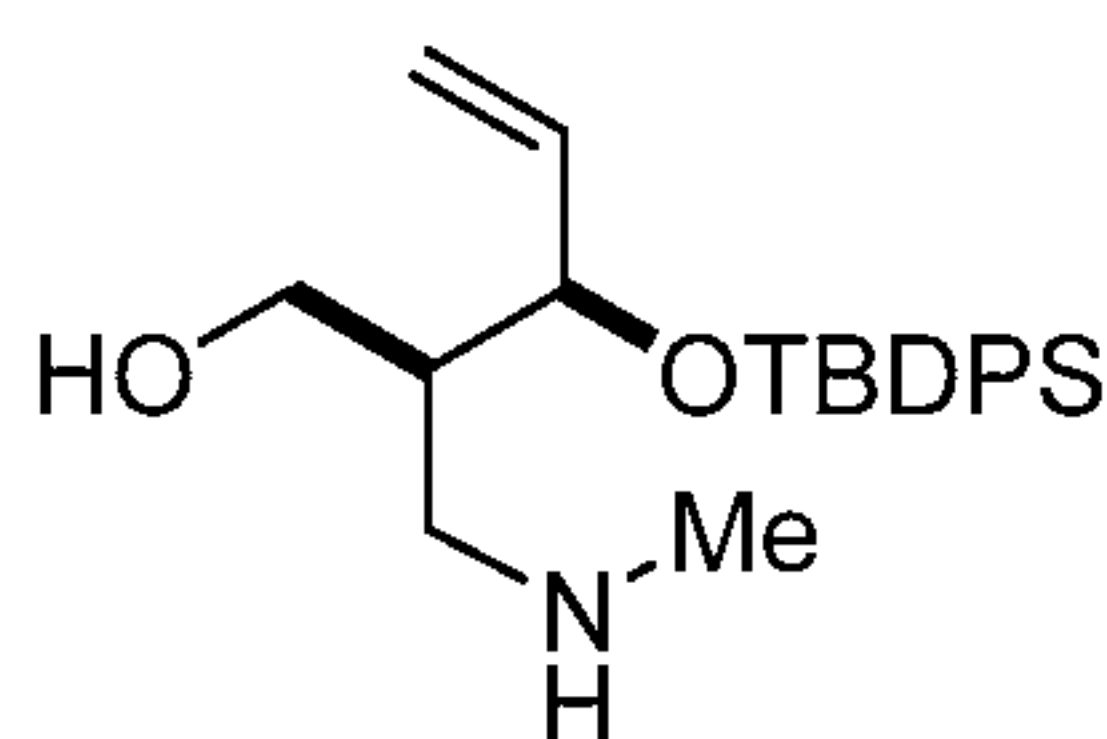
(6R)-5-tert-butoxycarbonyl-6-methyl-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-3-carboxylic acid (400.00 mg, 1.42 mmol, 1.00 *eq*), T₃P (904.85 mg, 2.84 mmol, 845.66 μ L, 2.00 *eq*) and Et₃N (719.42 mg, 7.11 mmol, 985.51 μ L, 5.00 *eq*) in THF (10.00 mL) was heated to 70 °C for 16 h. The mixture was diluted with EtOAc (60 mL) and washed with HCl (1 M, 60 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo, which was purified by prep-HPLC (FA) to afford the title compound (165.00 mg, 339.77 μ mol, 23.93% yield, 94% purity) as colorless oil. LCMS: 457 [M+1].

Step 2. 2-tert-butyl 8-ethyl (3R)-10-(2,2-difluoroethyl)-3-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido [2,3]pyrazolo[2,4-b][1,4]diazepine-2,8-dicarboxylate. To a solution of tert-

butyl (6R)-3-[2,2-difluoroethyl(2-ethoxycarbonylallyl) carbamoyl]-6-methyl-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (165.00 mg, 361.46 μ mol, 1.00 *eq*) in MeCN (6.00 mL) was added DBU (27.51 mg, 180.73 μ mol, 27.24 μ L, 0.50 *eq*), and the mixture was heated to 50 °C for 2 h. TLC showed no starting material and major desired product. The mixture was diluted with EtOAc (30 mL) and washed with brine (30 mL). The organic phase was concentrated in vacuo, which was purified by prep-TLC to afford the title compound (103.00 mg, 218.87 μ mol, 60.55% yield, 97% purity) as colorless oil.

LCMS: 457 [M+1].

Intermediate 21: (2S,3R)-3-((tert-butyldiphenylsilyl)oxy)-2-((methylamino)methyl)pent-4-en-1-ol.



Step 1. ethyl 3-[benzyl(methyl)amino]propanoate. To a solution of N-methyl-1-phenylmethanamine (50.00 g, 412.61 mmol, 53.19 mL, 1.00 *eq*) in EtOH (200.00 mL) was added ethyl prop-2-enoate (49.57 g, 495.13 mmol, 53.88 mL, 1.20 *eq*) under N₂, the reaction mixture was stirred at 20 °C for 16 hours. TLC indicated N-methyl-1-phenylmethanamine was consumed completely, and one major new spot with lower polarity was detected. The reaction mixture was concentrated on a rotary evaporator to afford the title compound (87.00 g, crude) as yellow oil,

used in next step directly. ^1H NMR (400 MHz, CDCl_3) δ = 7.21 - 7.35 (m, 5 H), 4.15 (q, J = 7.17 Hz, 2 H), 3.52 (s, 2 H), 2.72 - 2.80 (m, 2 H), 2.48 - 2.56 (m, 2 H), 2.22 (s, 3 H), 1.26 (t, J = 7.15 Hz, 3 H).

Step 2. ethyl 3-[tert-butoxycarbonyl(methyl)amino]propanoate. To a mixture of ethyl 3-[benzyl(methyl)amino]propanoate (33.00 g, 149.12 mmol, 1.00 *eq*) and $(\text{Boc})_2\text{O}$ (32.55 g, 149.12 mmol, 34.26 mL, 1.00 *eq*) in EtOH (200.00 mL) was added Pd/C (3.50 g, 10% purity) under N_2 , the suspension was degassed under vacuum and purged with H_2 three times, the mixture was stirred under H_2 (50 psi) at 40 °C for 16 hours. TLC indicated starting material was consumed completely and one major new spot with lower polarity was detected. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by flash silica gel chromatography to afford the title compound (24.00 g, 103.77 mmol, 69.59% yield) as yellow oil. ^1H NMR (400 MHz, CDCl_3) δ = 4.12 (q, J = 7.15 Hz, 2 H), 3.48 (brs, 2 H), 2.85 (s, 3 H), 2.52 (t, J = 6.78 Hz, 2 H), 1.44 (s, 9 H), 1.21 - 1.29 (m, 3 H).

Step 3. ethyl 2-[[tert-butoxycarbonyl(methyl)amino]methyl]-3-hydroxy-pent-4-enoate. To a solution of ethyl 3-[tert-butoxycarbonyl(methyl)amino]propanoate (25.00 g, 108.09 mmol, 1.00 *eq*) in THF (200.00 mL) was added LDA (1 M, 162.14 mL, 1.50 *eq*) dropwise at -78 °C under N_2 , the reaction mixture was stirred at -78 °C for 30 minutes, then a solution of prop-2-enal (7.88 g, 140.52 mmol, 9.38 mL, 1.30 *eq*) in THF (20.00 mL) was added dropwise, and the reaction mixture was stirred at 25 °C for another 2 hours. TLC indicated starting material was consumed completely and multiple new spots formed. The reaction was added into aqueous solution of NH_4Cl (200 mL) and then extracted with ethyl acetate (200 mL*2), the combined organic phase was dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to afford the title compound (18.00 g, 62.64 mmol, 57.95% yield) as yellow oil.

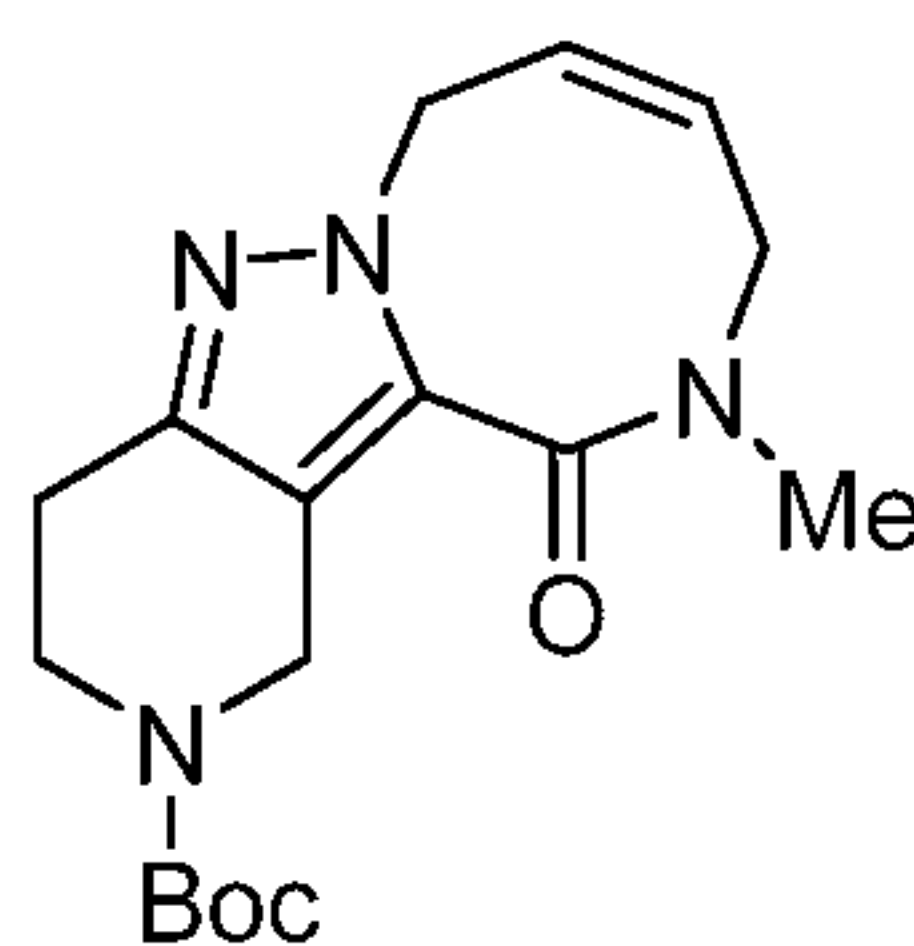
Step 4. ethyl 2-[[tert-butoxycarbonyl(methyl)amino]methyl]-3-[tert-butyl(diphenyl)silyl]oxy-pent-4-enoate. To a mixture of ethyl 2-[[tert-butoxycarbonyl(methyl)amino]methyl]-3-hydroxy-pent-4-enoate (25.50 g, 88.74 mmol, 1.00 *eq*) in DCM (200.00 mL) was added imidazole (6.65 g, 97.62 mmol, 1.10 *eq*), DMAP (1.08 g, 8.87 mmol, 0.10 *eq*) and TBDPSCl (26.83 g, 97.62 mmol, 25.08 mL, 1.10 *eq*) in one portion at 0 °C under N_2 . The mixture was stirred at 30 °C for 12 hours. TLC showed 30% of starting material was remained. Then added TBDPSCl (24.39 g, 88.74 mmol, 22.80 mL, 1.00 *eq*) and stirred at 30 °C for another 12 hours. TLC showed the

reaction completed. The mixture was poured into water (200 mL). The aqueous phase was extracted with DCM (100 mL*2). The combined organic phase was washed with brine (100 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to afford the title compound (49.00 g, crude) as yellow oil.

5 Step 5. tert-butyl ((2S,3S)-3-((tert-butyldiphenylsilyl)oxy)-2-(hydroxymethyl)pent-4-en-1-yl)(methyl)carbamate and tert-butyl ((2S,3R)-3-((tert-butyldiphenylsilyl)oxy)-2-(hydroxymethyl)pent-4-en-1-yl)(methyl)carbamate. To a mixture of ethyl 2-[[tert-butoxycarbonyl(methyl)amino]methyl]-3-[tert-butyl (diphenyl)silyl]oxy-pent-4-enoate (17.00 g, 32.33 mmol, 1.00 *eq*) in THF (200.00 mL) was added LiBH₄ (4.22 g, 193.98 mmol, 6.00 *eq*) in
10 one portion at 0 °C under N₂. The mixture was stirred at 30 °C for 60 hours. TLC showed the reaction completed, and two spots were detected. The mixture was poured into water (300 mL). The aqueous phase was extracted with DCM (100 mL*2). The combined organic phase was washed with brine (50 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to afford tert-butyl ((2S,3S)-3-
15 ((tert-butyldiphenylsilyl)oxy)-2-(hydroxymethyl)pent-4-en-1-yl)(methyl)carbamate (3.88 g, 8.02 mmol, 24.81% yield) as yellow oil and tert-butyl ((2S,3R)-3-((tert-butyldiphenylsilyl)oxy)-2-(hydroxymethyl)pent-4-en-1-yl)(methyl)carbamate (940.00 mg, 1.94 mmol, 6.01% yield) as yellow oil.

Step 6. (2S,3R)-3-((tert-butyldiphenylsilyl)oxy)-2-((methylamino)methyl)pent-4-en-1-ol. To a
20 solution of tert-butyl ((2S,3R)-3-((tert-butyldiphenylsilyl)oxy)-2-(hydroxymethyl)pent-4-en-1-yl)(methyl)carbamate (1.35 g, 2.79 mmol, 1.00 *eq*) in DCM (10.00 mL) was added TFA (7.70 g, 67.53 mmol, 5.00 mL, 24.21 *eq*), the reaction mixture was stirred at 25 °C for 30 minutes. TLC indicated starting material was consumed completely. The reaction mixture was concentrated on a rotary evaporator to afford the title compound (1.35 g, crude, TFA) as yellow oil, used in next
25 step directly. ¹H NMR (400 MHz, METHANOL-d₄) δ = 7.62 - 7.71 (m, 4 H), 7.36 - 7.48 (m, 6 H), 5.83 (ddd, *J* = 7.34, 10.30, 17.33 Hz, 1 H), 4.97 - 5.08 (m, 2 H), 4.22 (dd, *J* = 4.89, 7.09 Hz, 1 H), 3.82 (dd, *J* = 3.55, 10.27 Hz, 1 H), 3.60 (t, *J* = 9.90 Hz, 1 H), 3.13 - 3.20 (m, 1 H), 2.97 - 3.06 (m, 1 H), 2.60 (s, 3 H), 2.04 - 2.14 (m, 1 H), 1.07 (s, 9 H).

30 Intermediate 22: tert-butyl (8Z)-11-methyl-12-oxo-3,4,7,10-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazocine-2-carboxylate.



Step 1. 5-tert-butyl 3-ethyl 2-allyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-3,5-dicarboxylate.

To a solution of 5-tert-butylO3-ethyl 2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-3,5-dicarboxylate (20.00 g, 67.72 mmol, 1.00 *eq*) and 3-bromoprop-1-ene (12.29 g, 101.58 mmol, 1.50 *eq*) in DMF (200.00 mL) was added Cs₂CO₃ (55.16 g, 169.30 mmol, 2.50 *eq*). Then the mixture was stirred at 25 °C for 16 h. TLC (PE: EtOAc = 3:1) showed that reactant 5-tert-butylO3-ethyl 2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-3,5-dicarboxylate was consumed completely and two new spots formed. The mixture was diluted with 100 mL of water and extracted with EtOAc (100 mL*3). The organic phase was washed with brine (100 mL*1) and dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=50/1 to 3/1) to afford the title compound (13.50 g, 40.25 mmol, 59.44% yield) was obtained as white solid.

Step 2. 2-allyl-5-tert-butoxycarbonyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-3-carboxylic acid.

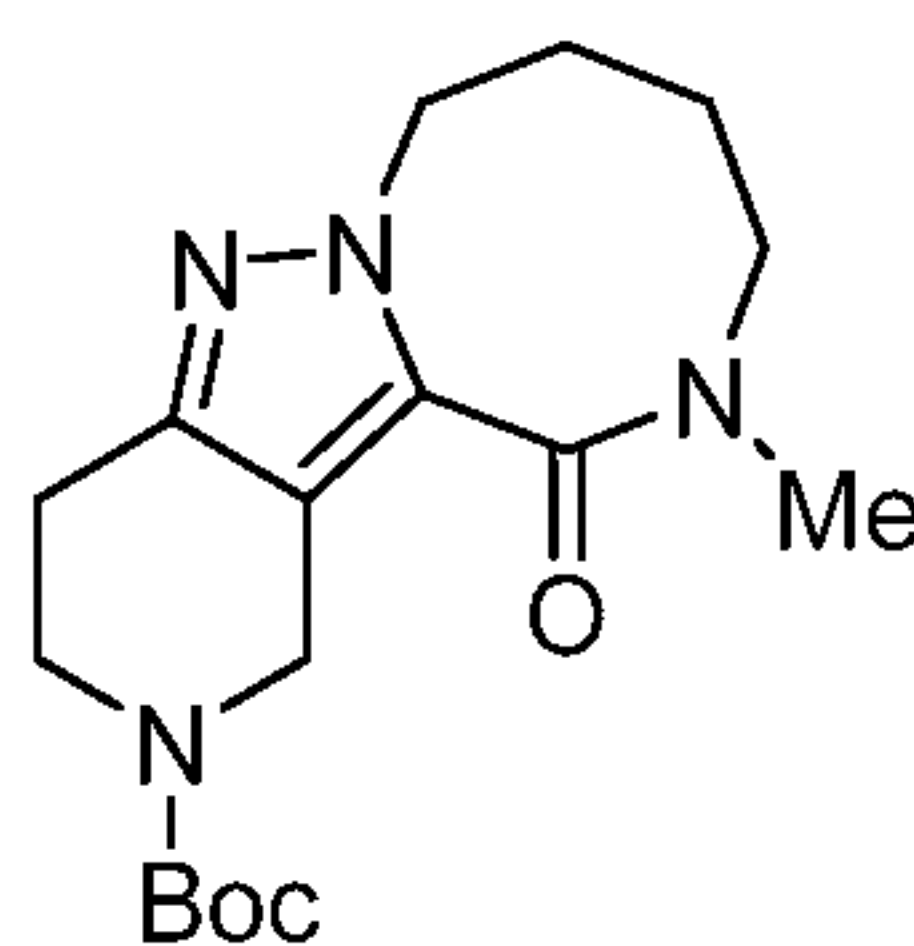
To a solution of 5-tert-butyl 3-ethyl 2-allyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-3,5-dicarboxylate (640.00 mg, 1.91 mmol, 1.00 *eq*) in THF (20.00 mL) and H₂O (4.00 mL) was added NaOH (152.65 mg, 3.82 mmol, 2.00 *eq*) at 25 °C. Then the mixture was heated to 50 °C for another 16 h. TLC (EtOAc:MeOH = 10:1) showed that reactant 5-tert-butyl 3-ethyl 2-allyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-3,5-dicarboxylate remained and one new spot formed. Then 2 mL of MeOH was added and the resulting mixture was still stirred at 50 °C for 3 h. TLC (EtOAc: MeOH=10:1) showed that reactant 5-tert-butyl 3-ethyl 2-allyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-3,5-dicarboxylate was consumed completely and one main new spot formed. The mixture was diluted with 30 mL of water and concentrated in vacuo to remove the organic solvent. Then the pH of the aqueous phase was adjusted to 5 by adding HCl (3N). The aqueous phase was extracted with EtOAc (30 mL*4), and the organic phase was washed with brine (30 mL*1), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The title compound (590.00 mg, crude) was obtained as white solid.

Step 3. tert-butyl 2-allyl-3-[allyl(methyl)carbamoyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate. To a solution of 2-allyl-5-tert-butoxycarbonyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-3-carboxylic acid (590.00 mg, 1.92 mmol, 1.00 *eq*) and N-methylprop-2-en-1-amine (204.79 mg, 2.88 mmol, 273.06 μ L, 1.50 *eq*) in DMF (10.00 mL) was added PYBOP (1.10 g, 2.11 mmol, 1.10 *eq*), HOBt (285.33 mg, 2.11 mmol, 1.10 *eq*) and DIPEA (1.49 g, 11.52 mmol, 2.01 mL, 6.00 *eq*) with stirring at 25 °C for 1 h. TLC (PE:EtOAc=1:1) showed that reactant 2-allyl-5-tert-butoxycarbonyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-3-carboxylic acid was consumed completely and one new spot formed. LCMS indicated that desired product was detected. The mixture was diluted with 30 mL of water and extracted with EtOAc (30 mL*4).

The organic phase was collected and washed with brine (20 mL*1), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=30/1 to 1/1) to afford the title compounds (650.00 mg, 1.80 mmol, 93.76% yield) as colorless oil.

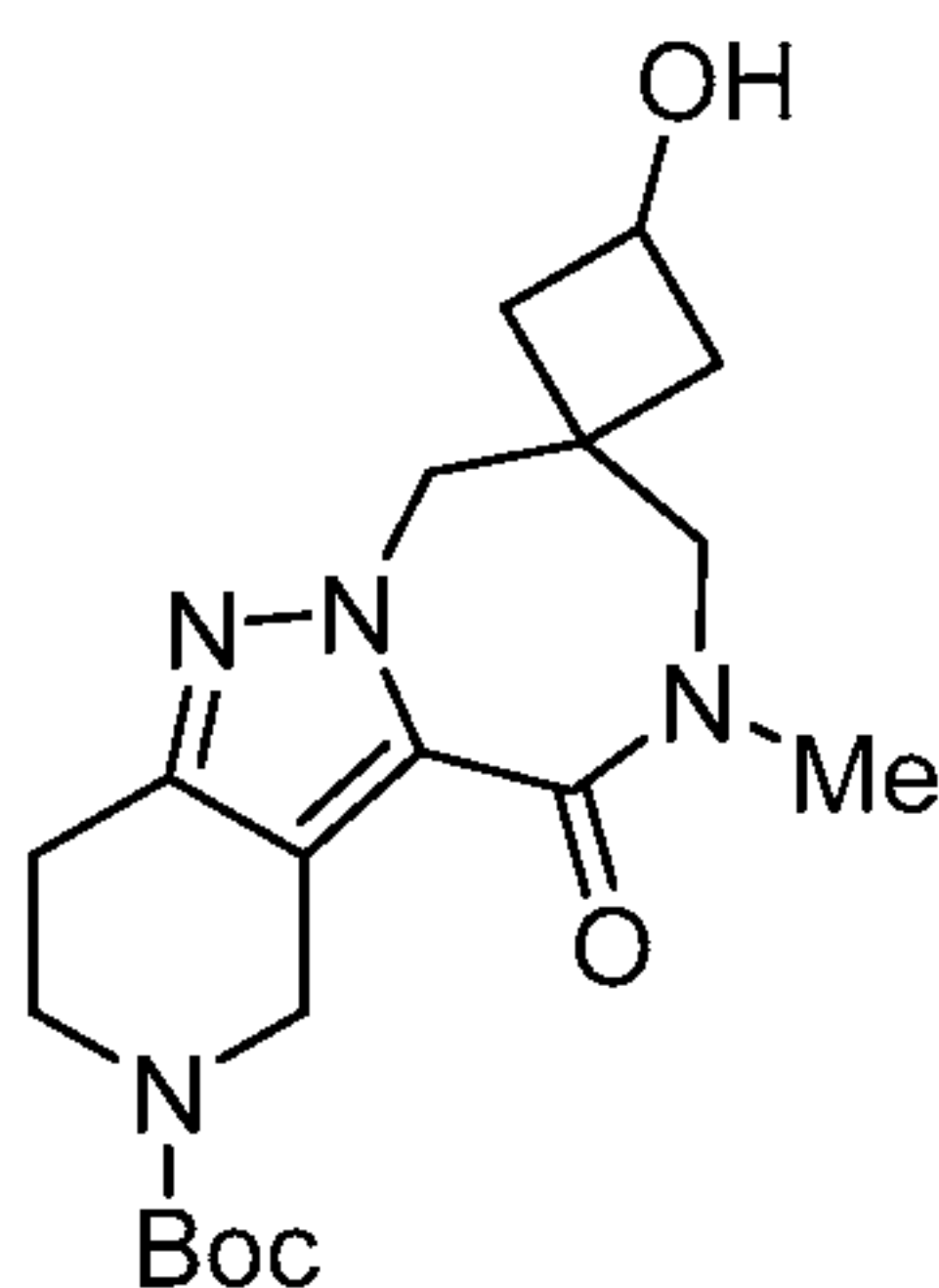
Step 4. tert-butyl (8Z)-11-methyl-12-oxo-3,4,7,10-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazocine-2-carboxylate. To a solution of tert-butyl 2-allyl-3-[allyl(methyl)carbamoyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (275.00 mg, 762.94 μ mol, 1.00 *eq*) in DCE (480.00 mL) was added [1,3-bis(2,4,6-trimethylphenyl)imidazolidin-2-ylidene]-dichloro-[(2-isopropoxyphenyl)methylene]ruthenium (95.61 mg, 152.59 μ mol, 0.20 *eq*) in one portion under N₂. Then the mixture was stirred at 85 °C for 16 h. TLC (PE:EtOAc = 1:3) showed that reactant **5** still remained and two new spots formed. The mixture was concentrated in vacuo. The 600 mg of the residue combined with two batches in parallel was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 50/1 to 1/3) to afford the title compound (180.00 mg, 541.52 μ mol, 35.49% yield) as yellow oil.

Intermediate 23: tert-butyl 11-methyl-12-oxo-3,4,7,8,9,10-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazocine-2-carboxylate.



To a solution of tert-butyl (8Z)-11-methyl-12-oxo-3,4,7,10-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazocine-2-carboxylate (Intermediate 22, 60.00 mg, 180.51 μ mol, 1.00 *eq*) in MeOH (5.00 mL) was added Pd/C (50.00 mg, 10.00 μ L, 10% purity) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 25 °C for 2 hours. TLC (PE: EtOAc = 1:3) showed that reactant 6 consumed completely and one main new spot formed. The mixture was diluted with 10 mL of MeOH, filtered and concentrated in vacuo to afford the title compound (61.00 mg, crude) as yellow oil, which was directly used without further purification.

Intermediate 24: tert-butyl 3'-hydroxy-10-methyl-11-oxo-spiro[3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-8,1'-cyclobutane]-2-carboxylate.



Step 1. [3-benzyloxy-1-(hydroxymethyl)cyclobutyl]methanol. To a suspension of LAH (1.55 g, 40.80 mmol, 2.50 *eq*) in THF (50.00 mL) was added a solution of diethyl 3-benzyloxycyclobutane-1,1-dicarboxylate (5.00 g, 16.32 mmol, 1.00 *eq*) in THF (20.00 mL) dropwise at -40 °C. The resulting suspension was stirred at 20 °C for 3 hr. TLC (PE:EtOAc = 0:1) showed the starting material consumed and one main spot formed. The mixture was diluted with THF (300 mL) and quenched by H₂O (1.5 mL), 15% NaOH (1.5 mL) and H₂O (4.5 mL), filtrated. The filtrate was concentrated in vacuum to afford the title compound (3.30 g, crude) as white solid.

Step 2. 2-(benzyloxy)-6,8-dioxo-7-thiaspiro[3.5]nonane 7-oxide. To a solution of [3-benzyloxy-1-(hydroxymethyl)cyclobutyl]methanol (3.30 g, 14.85 mmol, 1.00 *eq*) in DCM (90.00 mL) was added TEA (3.31 g, 32.67 mmol, 4.53 mL, 2.20 *eq*) followed by SOCl₂ (2.12 g, 17.82 mmol, 1.29 mL, 1.20 *eq*) at -10 °C. The mixture was stirred at 0 °C for 1 hr. TLC (PE:EtOAc = 1:1) showed the starting material consumed, TLC (PE:EtOAc = 10:1) showed one main spot appeared. The mixture was diluted with H₂O (50 mL) and extracted with DCM (100 mL*2). The combined organic layer was dried over Na₂SO₄, filtrated. The filtrate was concentrated in vacuum. The residue was purified by column chromatography (PE:EtOAc = 100:1) to afford the title compound (3.20 g, 11.93 mmol, 80.31% yield) as colorless oil.

Step 3. 2-benzyloxy-6,8-dioxo-7thiaspiro[3.5]nonane 7,7-dioxide. 2-benzyloxy-6,8-dioxo-7thiaspiro[3.5]nonane 7-oxide (2.50 g, 9.32 mmol, 1.00 *eq*) was dissolved in H₂O (7.50 mL), MeCN (5.00 mL) and CCl₄ (5.00 mL). RuCl₃·H₂O (210.04 mg, 931.69 μmol, 0.10 *eq*) was added to the mixture, followed by NaIO₄ (3.99 g, 18.63 mmol, 1.03 mL, 2.00 *eq*). The reaction mixture was then stirred at 20 °C for 1 hr. TLC (PE:EtOAc = 5:1) showed the starting material consumed and one main spot appeared. The mixture was diluted with saturated NaHCO₃ (80 mL) and extracted with EtOAc (200 mL*2). The combined organic layer was dried over Na₂SO₄, filtrated and concentrated in vacuum. The residue was purified by flash chromatography (PE:EtOAc = 10% ~ 30%) to afford the title compound (2.40 g, 8.44 mmol, 90.57% yield) as white solid.

Step 4. [3-benzyloxy-1-(methylaminomethyl)cyclobutyl]methyl hydrogen sulfate. To a solution of 2-benzyloxy-6,8-dioxo-7thiaspiro[3.5]nonane 7,7-dioxide (1.00 g, 3.52 mmol, 1.00 *eq*) in MeCN (2.00 mL) was added CH₃NH₂ (2 M in THF, 26.40 mL, 15.00 *eq*). The mixture was heated to 65 °C for 16 hr. Three peaks showed on LCMS and 40% desired product detected. The mixture was concentrated in vacuum and the residue was washed with methyl tert-butyl (50 mL) to afford the title compound (1.10 g, crude) as white solid.

Step 5. tert-butyl N-[[3-benzyloxy-1-(hydroxymethyl)cyclobutyl]methyl]-N-methyl-carbamate. To a solution of [3-benzyloxy-1-(methylaminomethyl)cyclobutyl]methyl hydrogen sulfate (1.10 g, 3.49 mmol, 1.00 *eq*) in THF (5.00 mL) was added H₂SO₄ (68.42 mg, 697.57 μmol, 37.18 μL, 0.20 *eq*). The mixture was heated to 50 °C for 6 hr. LCMS showed the starting material remained. The mixture was stirred at 70 °C for another 32 hr. LCMS showed a little starting material remained. The pH of the mixture was adjust to 11 with saturated NaHCO₃ and added

Boc₂O (761.22 mg, 3.49 mmol, 801.29 μ L, 1.00 *eq*). The mixture was stirred at 20 °C for 30 min. TLC (PE:EtOAc = 3:1) showed two main spots appeared. The mixture was diluted with H₂O (50 mL) and extracted with EtOAc (80 mL*2). The combined organic layer was dried over Na₂SO₄, filtrated and concentrated in vacuum. The residue was purified by flash chromatography (PE:EtOAc:0%~20%) to afford the title compound (519.00 mg, 1.38 mmol, 39.46% yield, 89% purity) as colorless oil.

Step 6. (3-(benzyloxy)-1-((methylamino)methyl)cyclobutyl)methanol. To a solution of tert-butyl N-[[3-benzyloxy-1-(hydroxymethyl)cyclobutyl] methyl]-N-methyl-carbamate (519.00 mg, 1.55 mmol, 1.00 *eq*) in DCM (5.00 mL) was added TFA (3.00 mL). The mixture was stirred at 20 °C for 0.5 hr. TLC (PE:EtOAc = 5:1) showed the starting material consumed. The mixture was concentrated in vacuum to afford the title compound (600.00 mg, crude, TFA) as brown oil.

Step 7. tert-butyl 3-[[3-benzyloxy-1-(hydroxy methyl cyclobutyl)methyl-methyl-carbamoyl]-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate. To a solution of 5-tert-butoxycarbonyl-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine -3-carboxylic acid (400.00 mg, 1.50 mmol, 1.00 *eq*) and [3-benzyloxy-1-(methyl aminomethyl)cyclobutyl]methanol (524.01 mg, 1.50 mmol, 1.00 *eq*, TFA) in DMF (5.00 mL) was added PYBOP (780.58 mg, 1.50 mmol, 1.00 *eq*), HOBt (202.68 mg, 1.50 mmol, 1.00 *eq*) followed by DIEA (969.30 mg, 7.50 mmol, 1.31 mL, 5.00 *eq*). The mixture was stirred at 20 °C for 1 hr. LCMS showed one main peak with desired Ms detected. The mixture was extracted with EtOAc (80 mL*3) and H₂O (50 mL). The combined organic layer was washed with H₂O (80 mL*2), 1N HCl (50 mL) and saturated NaHCO₃ (50 mL). The combined organic layer was dried over Na₂SO₄, filtrated and concentrated in vacuum. The residue was purified by column chromatography (PE:EtOAc = 30%~50%) to afford the title compound (300.00 mg, 433.36 μ mol, 28.89% yield, 70% purity) as colorless oil.

Step 8. tert-butyl-3-[[3-benzyloxy-1-(methylsulfonyloxy-methyl)cyclobutyl]methyl-methyl-carbamoyl]-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate. To a solution of tert-butyl 3-[[3-benzyloxy-1-(hydroxymethyl)cyclobutyl]methyl- methyl-carbamoyl]-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (200.00 mg, 288.90 μ mol, 1.00 *eq*) in DCM (1.00 mL) was added pyridine (114.26 mg, 1.44 mmol, 116.59 μ L, 5.00 *eq*) followed by MsCl (49.64 mg, 433.35 μ mol, 33.54 μ L, 1.50 *eq*). The mixture was stirred at 20 °C for 2 hr. TLC (PE:EtOAc = 1:1) showed the starting material remained and two new main spots appeared. Another batch of MsCl (49.64 mg, 433.35 μ mol, 33.54 μ L, 1.50 *eq*) was added and the mixture

was stirred at 20 °C for 1 hr. TLC (PE:EtOAc = 1:1) showed a little starting material remained and two new main spots appeared. The mixture was extracted with DCM (30 mL*2) and H₂O (20 mL). The combined organic layer was washed saturated Cu₂SO₄ (20 mL*2), dried over Na₂SO₄, filtrated and concentrated in vacuum. The residue was purified by prep-TLC (PE:EtOAc = 1:1) to afford the title compound (60.00 mg, 106.63 μmol, 36.91% yield) as colorless oil.

Step 9. tert-butyl 3'-benzyloxy-10-methyl-11-oxo-spiro[3,4,7,9-tetrahydro-1H-

pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-8,1'-cyclobutane]-2-carboxylate. To a solution of tert-butyl 3-[[3-benzyloxy-1-(methylsulfonyloxymethyl)cyclobutyl] methyl-methyl-carbamoyl]-

2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (60.00 mg, 106.63 μmol, 1.00 *eq*) in

THF (1.00 mL) was added NaH (8.53 mg, 213.27 μmol, 60% purity, 2.00 *eq*) at 0 °C. The mixture was stirred at 0 °C for 0.5 hr. LCMS showed 22% of starting material remained. The mixture was stirred at 20 °C for another 2 hr. LCMS showed one main peak with desired Ms detected.

The mixture was quenched by saturated NH₄Cl (10 mL) and extracted with EtOAc (10 mL*2). The combined organic layer was dried over Na₂SO₄, filtrated and concentrated in vacuum. The residue was purified by prep-TLC (PE:EtOAc = 1:1) to afford the title compound (27.00 mg, 57.87 μmol, 54.27% yield) as colorless oil.

Step 10. tert-butyl 3'-hydroxy-10-methyl-11-oxo-spiro[3,4,7,9-tetrahydro-1H-

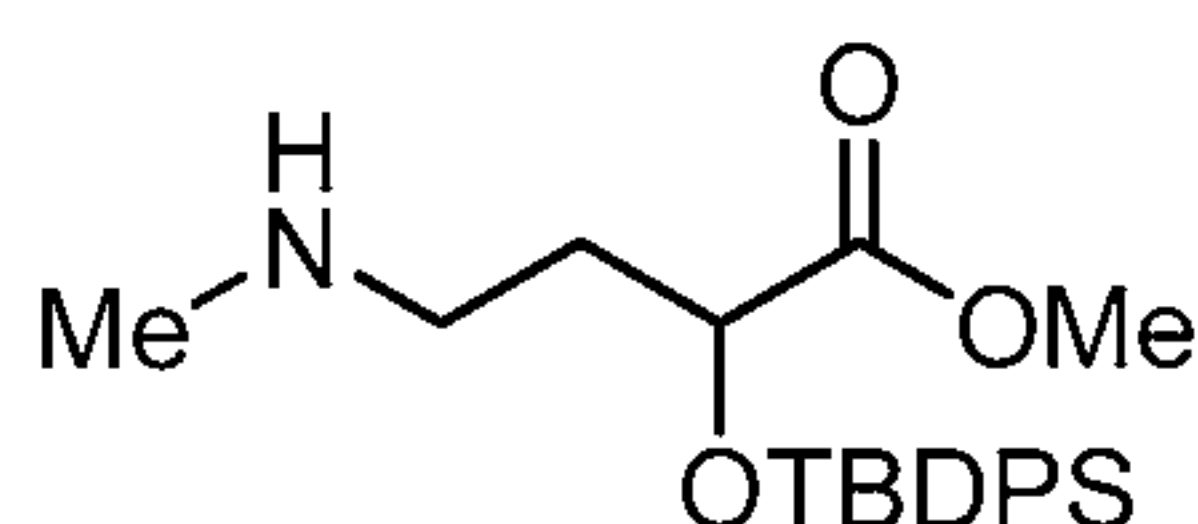
pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-8,1'-cyclobutane]-2-carboxylate. To a solution of tert-

butyl 3'-benzyloxy-10-methyl-11-oxo-spiro[3,4,7,9-tetrahydro -1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-8,1'-cyclobutane]-2-carboxylate (27.00 mg, 57.87 μmol, 1.00 *eq*) in MeOH

(10.00 mL) was added Pd-C (10%, 5mg) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (20 psi) at 40 °C for 16 hours. LCMS showed one main peak with desired MS detected. The mixture was dilute with

MeOH (30 mL), filtrated and concentrated in vacuum to afford the title compound (30.00 mg, crude) as brown oil.

Intermediate 25: methyl 2-[tert-butyl(diphenyl)silyl]oxy-4-(methylamino)butanoate.



Step 1. 4-(tert-butoxycarbonylamino)-2-hydroxy-butanoic acid. To a solution of 4-amino-2-hydroxy-butanoic acid (10.00 g, 83.95 mmol, 1.00 *eq*) in H₂O (75.00 mL) was added K₂CO₃ (11.60 g, 83.95 mmol, 1.00 *eq*) followed by a solution of Boc₂O (18.32 g, 83.95 mmol, 19.29 mL, 1.00 *eq*) in dioxane (50.00 mL) dropwise at 0 °C. The resulting solution was stirred at 20 °C for 16 hr. TLC (PE:EtOAc = 0:1) showed one main spot appeared. The mixture was diluted with H₂O (80 mL) and washed with 100 ml DCM to remove the remained Boc₂O. The pH of the aqueous layer was adjusted to 4-5 with 1N hydrochloric acid and the resulting solution was extracted with 4 x 100 mL of ethyl acetate. The organic layers were combined and concentrated under vacuum to afford the title compound (16.00 g, 72.98 mmol, 86.94% yield) as colorless oil.

Step 2. methyl 4-(tert-butoxycarbonylamino)-2-hydroxy-butanoate. To a solution of 4-(tert-butoxycarbonylamino)-2-hydroxy-butanoic acid (5.00 g, 22.81 mmol, 1.00 *eq*) in DMF (50.00 mL) was added Cs₂CO₃ (8.92 g, 27.37 mmol, 1.20 *eq*) and CH₃I (3.24 g, 22.81 mmol, 1.42 mL, 1.00 *eq*) dropwise at 0 °C. The mixture was stirred at 20 °C for 2 hr. TLC (PE:EtOAc = 1:1) showed the starting material consumed and one main spot appeared. The mixture was diluted with H₂O (100 mL) and extracted with EtOAc (200 mL*2). The combined organic layer was washed with H₂O (200 mL*2), dried over Na₂SO₄, filtrated and concentrated in vacuum. The residue was purified by column chromatography (PE:EtOAc = 30%~50%) to afford the title compound (5.50 g, crude) as colorless oil.

Step 3. methyl 4-(tert-butoxycarbonylamino)-2-[tert-butyl(diphenyl)silyl]oxy-butanoate. To a solution of methyl 4-(tert-butoxycarbonylamino)-2-hydroxy-butanoate (5.00 g, 21.44 mmol, 1.00 *eq*) in DCM (50.00 mL) was added imidazole (2.19 g, 32.16 mmol, 1.50 *eq*) followed by TBDPSCl (5.89 g, 21.44 mmol, 5.50 mL, 1.00 *eq*) and DMAP (261.88 mg, 2.14 mmol, 0.10 *eq*). The mixture was stirred at 20 °C for 16 hr. TLC (PE:EtOAc = 1:1) showed the starting material remained and TLC (PE:EtOAc = 10:1) showed two main spots appeared. The mixture was diluted with H₂O (50 mL) and extracted with DCM (80 mL*3). The combined organic layer was washed with H₂O (20 mL*3), dried over Na₂SO₄, filtrated and concentrated in vacuum. The residue was purified by flash chromatography (PE:EtOAc:0%~10%) to afford the title compound (6.50 g, 13.78 mmol, 64.28% yield) as colorless oil.

Step 4. methyl 4-[tert-butoxycarbonyl(methyl)amino]-2-[tert-butyl(diphenyl)silyl]oxy-butanoate.

To a solution of methyl 4-(tert-butoxycarbonylamino)-2-[tert-butyl(diphenyl)silyl]oxy-butanoate (4.40 g, 9.33 mmol, 1.00 *eq*) in DMF (50.00 mL) was added Ag₂O (10.81 g, 46.65 mmol, 5.00

eq) followed by CH₃I (6.62 g, 46.65 mmol, 2.90 mL, 5.00 *eq*). The mixture was stirred at 20 °C for 16 hr. TLC (PE:EtOAc = 10:1) showed the starting material remained, additional Ag₂O (2.0g) and CH₃I (3 mL) were added and the mixture was stirred at 20 °C for another 120 hr.

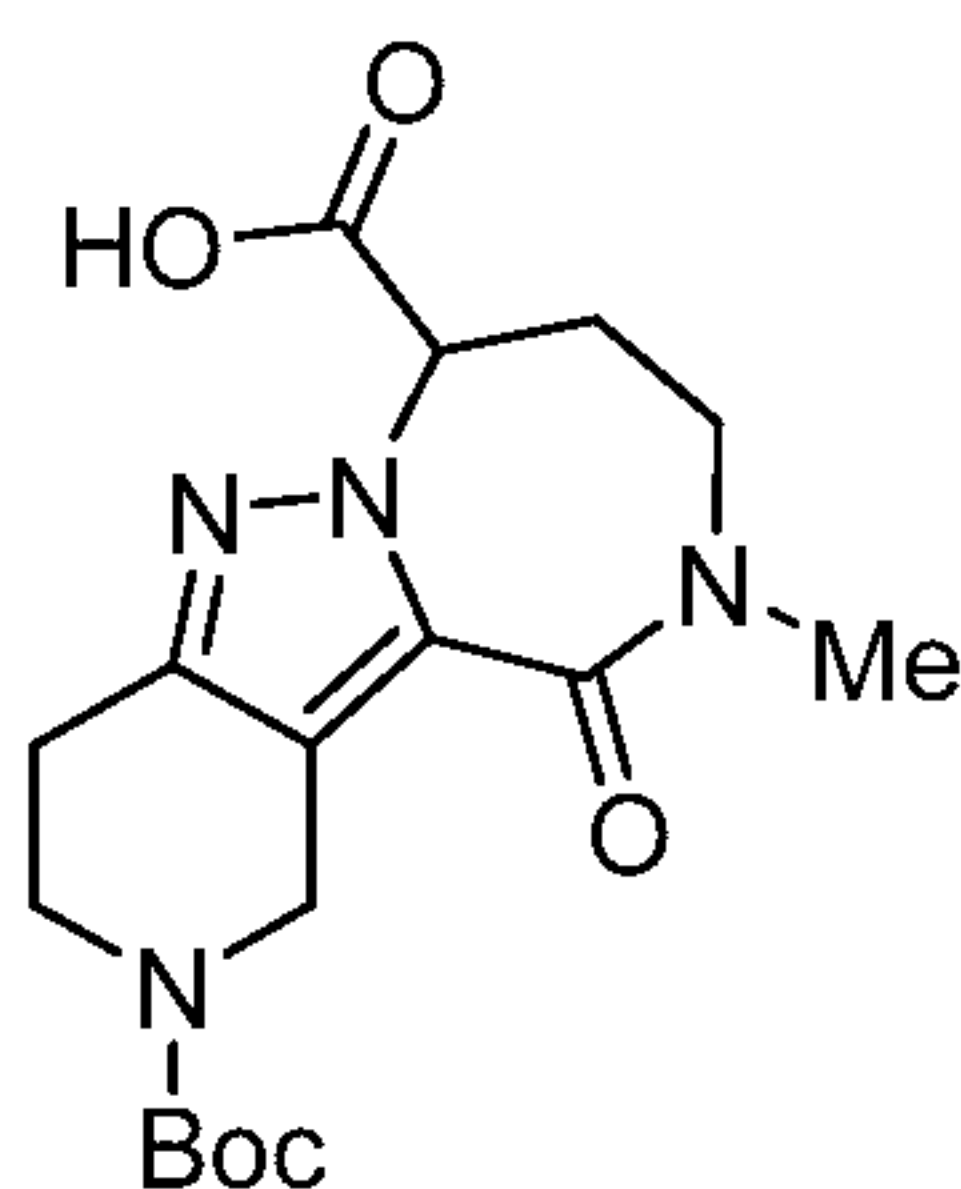
TLC (PE:EtOAc=10:1) showed a little starting material remained and two main spots appeared.

5 The mixture was diluted with EtOAc (200 mL) and filtrated. The filtrates was diluted with H₂O (100 mL) and seperated out the organic layer. The organic layer was wahsed with H₂O (200 mL*2), dried over Na₂SO₄, filtrated. The filtrate was concentrated in vacuum. The residue was purified by flash chromatography (PE:EtOAc: 0% ~ 10%) to afford the title compound (3.20 g, 6.59 mmol, 70.62% yield) as colorless oil.

10 Step 5. methyl 2-[tert-butyl(diphenyl)silyl]oxy-4-(methylamino)butanoate. To a solution of methyl 4-[tert-butoxycarbonyl(methyl)amino]-2-[tert-butyl(diphenyl) silyl]oxy-butanoate (1.30 g, 2.68 mmol, 1.00 *eq*) in DCM (10.00 mL) was added TFA (5.00 mL) at 0 °C. The mixture was stirred at 20 °C for 2 hr. TLC (PE:EtOAc = 10:1) showed the starting consumed. The mixture was concentrated in vacuum to afford the title compound (2.80 g, crude, TFA) as brown oil.

15

Intermediate 26: 2-(tert-butoxycarbonyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-7-carboxylic acid.



20 Step 1. tert-butyl 3-[[3-[tert-butyl(diphenyl)silyl]oxy-4-methoxy-4-oxo-butyl]-methyl-carbamoyl]-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate. To a solution of 5-tert-butoxycarbonyl-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-3-carboxylic acid (800.00 mg, 2.99 mmol, 1.00 *eq*) and methyl 2-[tert-butyl(diphenyl)silyl]oxy-4-(methylamino)butanoate (Intermediate 25, 2.99 g, 5.98 mmol, 2.00 *eq*, TFA) in DMF (10.00 mL) was added PYBOP (1.71 g, 3.29 mmol, 1.10 *eq*), HOBt (444.41 mg, 3.29 mmol, 1.10 *eq*), followed by DIEA (1.93 g, 14.95 mmol, 2.61 mL, 5.00 *eq*). The mixture was stirred at 20 °C for 2 hr. LCMS showed

25

one main peak with desired MS detected. The mixture was extracted with EtOAc (50 mL*3) and H₂O(50 mL). The combined organic layer was washed H₂O (50 mL*3), 1N HCl (50 mL) and saturated NaHCO₃ (50 mL), dried over Na₂SO₄, filtrated and concentrated in vacuum. The residue was re-purified by column chromatography (PE:EtOAc: 20% ~ 100%) to afford the title compound (1.60 g, 2.52 mmol, 84.29% yield) as white solid.

Step 2. tert-butyl 3-[(3-hydroxy-4-methoxy-4-oxo-butyl)-methyl-carbamoyl]-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate. To a solution of tert-butyl 3-[[3-[tert-butyl(diphenyl)silyl]oxy-4-methoxy-4-oxo-but-yl]-methyl-carbamoyl]-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (1.40 g, 2.21 mmol, 1.00 *eq*) in THF (14.00 mL) was added TBAF (2 M, 2.21 mL, 2.00 *eq*). The mixture was stirred at 20 °C for 1 hr. TLC (PE:EtOAc = 1:2) showed the starting material consumed and two main spots appeared. The mixture was extracted with DCM (50 mL*2) and H₂O (30 mL). The combined organic layer was washed with H₂O (30 mL*2), 1N HCl (30 mL) and saturated NaHCO₃ (30 mL), dried over Na₂SO₄, filtrated. The filtrate was concentrated in vacuum to afford the title compound (1.5 g crude) as white solid.

Step 3. tert-butyl3-[(4-methoxy-3-methylsulfonyloxy-4-oxo-butyl)-methyl-carbamoyl]- 2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate and tert-butyl 3-[(4-methoxy-3-methylsulfonyloxy-4- oxo-butyl)-methyl-carbamoyl]-2-methylsulfonyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate. To a solution of tert-butyl 3-[(3-hydroxy-4-methoxy-4-oxo-butyl)-methyl-carbamoyl] -2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (150.00 mg, 378.37 μmol, 1.00 *eq*) in DCM (5.00 mL) was added Py (29.93 mg, 378.37 μmol, 30.54 μL, 1.00 *eq*), followed by MsCl (43.34 mg, 378.37 μmol, 29.28 μL, 1.00 *eq*). The mixture was stirred at 20 °C for 2 hr. TLC (PE:EtOAc = 0:1) showed the starting material remained and two new spots appeared. Additional MsCl (43.34 mg, 378.37 μmol, 29.28 μL, 1.00 *eq*) was added and the mixture was stirred at 20 °C for 1hr. TLC (PE:EtOAc = 0:1) showed the starting material consumed and two new spots appeared. The mixture was extracted with DCM (20 mL*2) and H₂O (20 mL). The combined organic layer was washed saturated Cu₂SO₄ (10 mL*2), dried over Na₂SO₄, filtrated and concentrated in vacuum. The residue was purified by prep-TLC (PE:EtOAc=0:1) to afford tert-butyl3-[(4-methoxy-3-methylsulfonyloxy-4-oxo-butyl)-methyl-carbamoyl]- 2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (20.00 mg, 42.15 μmol, 11.14% yield) as white solid and tert-butyl 3-[(4-methoxy-3-methylsulfonyloxy-4- oxo-

butyl)-methyl-carbamoyl]-2-methylsulfonyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (150.00 mg, 271.43 μ mol, 71.74% yield) as white solid.

Step 4. 2-(tert-butoxycarbonyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-

pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-7-carboxylic acid. To a solution of tert-butyl 3-

[(4-methoxy-3-methylsulfonyloxy-4-oxo-butyl)-methyl -carbamoyl]-2-methylsulfonyl-6,7-

dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (150.00 mg, 271.43 μ mol, 1.00 *eq*) in THF

(3.00 mL) was added NaH (21.71 mg, 542.87 μ mol, 60% purity, 2.00 *eq*). The mixture was

stirred at 0 °C for 0.5 hr. LCMS showed the starting material and 2-(tert-butoxycarbonyl)-10-

methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-7-

carboxylic acid in one peak. The mixture was stirred at 20 °C for another 3 hr. LCMS showed a

little starting material remained. Additional NaH (21.71 mg, 542.87 μ mol, 60% purity, 2.00 *eq*)

was added and the mixture was stirred at 20 °C for 16 h. LCMS showed 57% of 2-(tert-

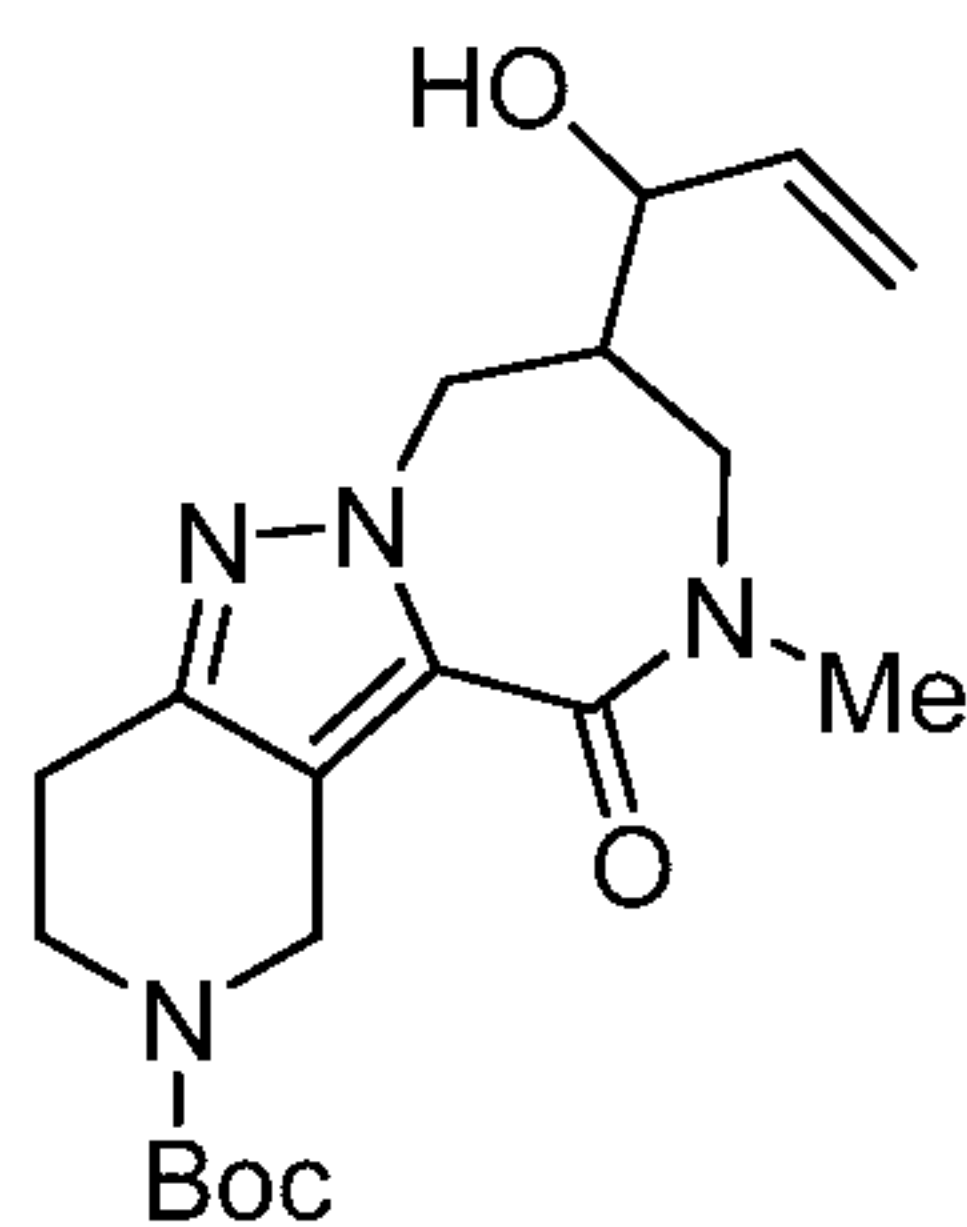
butoxycarbonyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-7-carboxylic acid and 22% of an unknown

compound. The mixture was diluted with H₂O (5 mL) and concentrated in vacuum to afford a

crude mixture of the title compound (116.00 mg, crude) as brown oil.

Intermediate 27: tert-butyl 8-(1-hydroxyallyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexa-

hydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate.



To a mixture of tert-butyl 10-methyl-11-oxo-8-prop-2-enoyl-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (3.70 g, 9.88 mmol, 1.00 *eq*)

in MeOH (100.00 mL) was added CeCl₃ (4.87 g, 19.76 mmol, 1.24 mL, 2.00 *eq*) in one portion

at 0 °C under N₂. The mixture was stirred at 0 °C for 15 min, then NaBH₄ (1.50 g, 39.52 mmol,

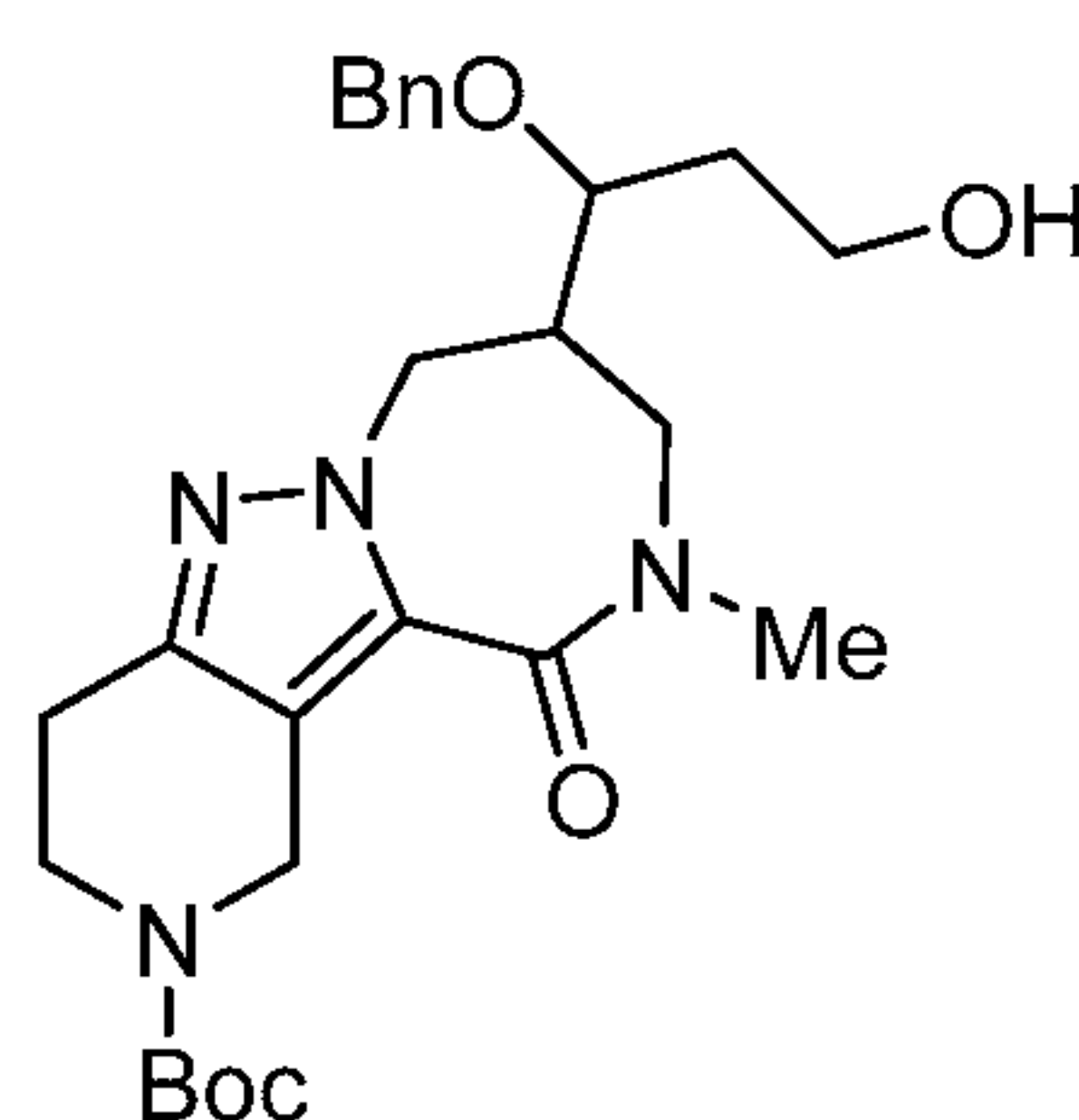
4.00 *eq*) was added to the mixture. The mixture was heated to 30 °C and stirred for 2 hours.

LCMS and TLC (Dichloromethane : Methanol=10:1) showed the reaction was completed. The

mixture was poured into water (20 mL) and concentrated in reduced pressure. The aqueous phase was extracted with ethyl acetate (50 mL*3). The combined organic phase was washed with brine (20 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Dichloromethane : Methanol=100/1~20:1) to afford the title compound (2.70 g, 6.74 mmol, 68.24% yield, 94% purity) as yellow solid, Which was separated by SFC (Analytical method: IC-3S_3_5_40_3ML Column: Chiralpak IC-3 100×4.6mm I.D., 3um Mobile phase: methanol (0.05% DEA) in CO₂ from 5% to 40% Flow rate: 3mL/min Wavelength: 220nm. Separation method: Instrument: SFC 80; Column: IC-10um; Mobile phase: A for CO₂ and B for MeOH(0.1% NH₃ H₂O); Gradient: B 35%; Flow rate: 60mL/min; Back pressure: 100bar; Column temperature: 35°C; Wavelength: 220 nm) to give four isomers: tert-butyl (S*)-8-((S*)-1-hydroxyallyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate: 650 mg, tert-butyl (R*)-8-((S*)-1-hydroxyallyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate: 640 mg, tert-butyl (S*)-8-((R*)-1-hydroxyallyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate: 650 mg and tert-butyl (R*)-8-((R*)-1-hydroxyallyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate: 650 mg.

* Pure but unknown stereoisomer.

Intermediate 28: tert-butyl 8-(1-benzyloxy-3-hydroxy-propyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate.



Step 1. tert-butyl 8-(1-benzyloxyallyl)-10-methyl-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of tert-butyl 8-(1-hydroxyallyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexa hydropyrido[2,3]pyrazolo[2,4-

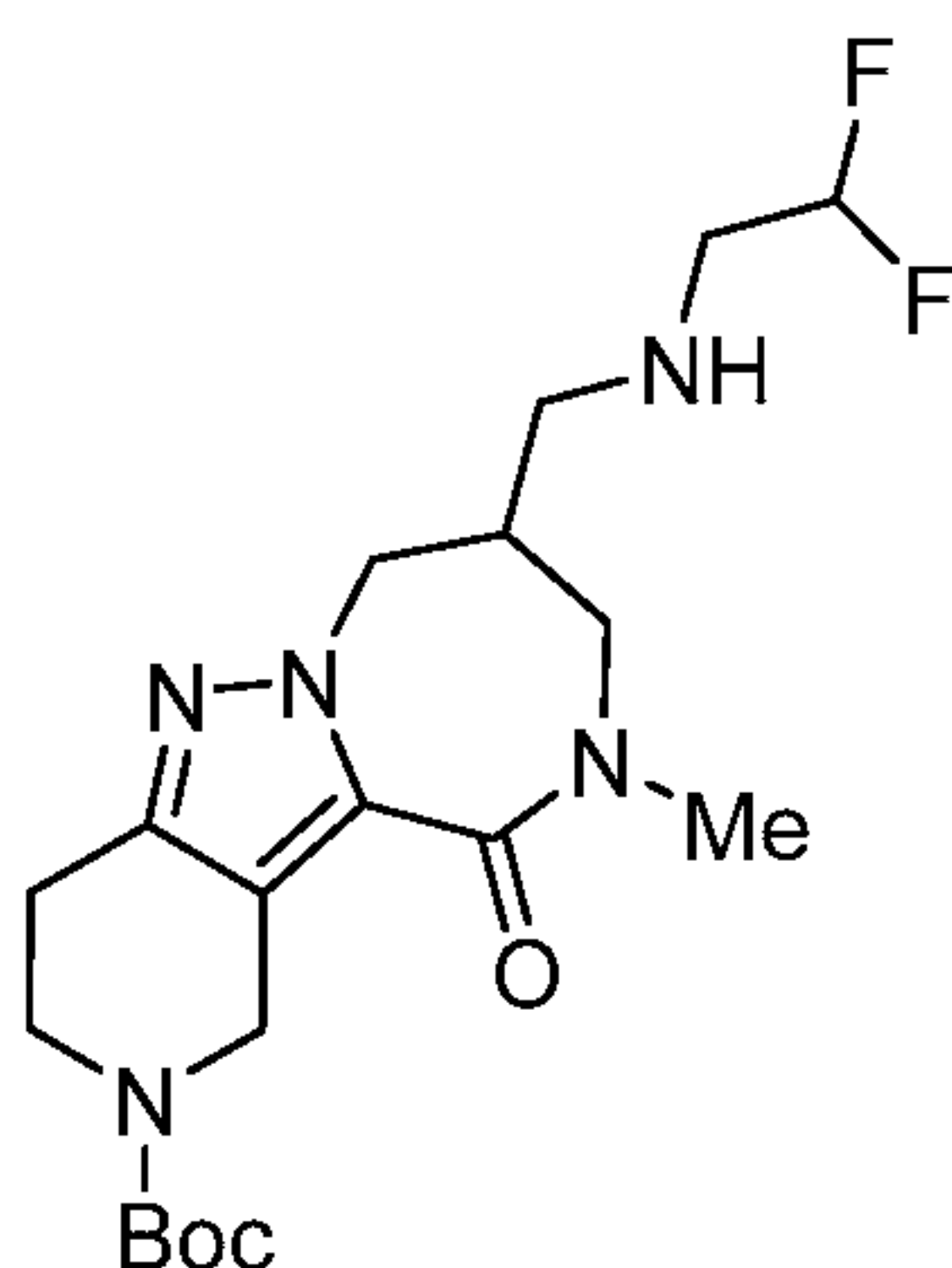
b][1,4]diazepine-2-carboxylate (Intermediate 27, 1.00 g, 2.66 mmol, 1.00 *eq*) in THF (15.00 mL) was added NaH (425.60 mg, 10.64 mmol, 60% purity, 4.00 *eq*). The mixture was stirred at 0 °C for 30 min, then BnBr (682.41 mg, 3.99 mmol, 473.90 μL, 1.50 *eq*) was added. The mixture was stirred at 40 °C for 2 hr. TLC (PE:EtOAc = 0:1) showed the starting material consumed and one new spot appeared. The mixture was quenched with H₂O (50 mL) and extracted with EtOAc (30 mL*3). The combined organic layer was dried over Na₂SO₄, filtrated and concentrated in vacuum. The residue was purified by column chromatography (PE:EtOAc = 2:1~1:1) to afford the title compound (700.00 mg, 1.47 mmol, 55.44% yield, 98.3% purity) as white solid.

Step 2. tert-butyl 8-(1-benzyloxy-3-hydroxy-propyl)-10-methyl-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of tert-butyl 8-(1-benzyloxyallyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexa hydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (350.00 mg, 750.16 μmol, 1.00 *eq*) and chlororhodium triphenylphosphane (69.41 mg, 75.02 μmol, 0.10 *eq*) in THF (8.00 mL) was added 1,3,2-benzodioxaborole (1 M, 3.75 mL, 5.00 *eq*) at 0 °C. The mixture was stirred at 10 °C for 3 hr. A solution of NaOH (210.04 mg, 5.25 mmol, 7.00 *eq*) in H₂O (4.00 mL) was added at -3°C dropwise. Then H₂O₂ (2.38 g, 20.97 mmol, 2.02 mL, 30% purity, 27.96 *eq*) was added slowly. The mixture was stirred at 25 °C for 2 hr. TLC (PE:EtOAc = 0:1) showed the starting material consumed and one main spot appeared. The mixture was extracted with DCM (90 mL*3) and H₂O (20 mL). The organic layer was washed with 20% NaOH (80 mL*2), dried over Na₂SO₄, filtrated and concentrated in vacuum. The residue was purified by column chromatography (PE:EtOAc:50%~100% then to EtOAc:MeOH:10%) to afford the title compound (272.00 mg, 516.40 μmol, 68.84% yield, 92% purity) as brown solid.

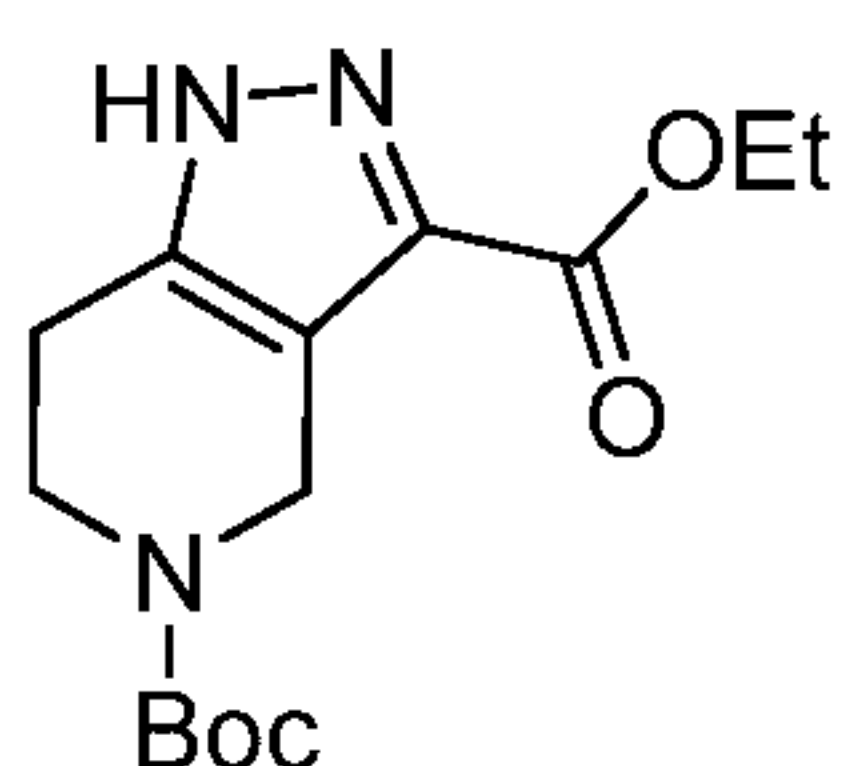
Intermediate 29: racemic tert-butyl 8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-

1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate.



A mixture of tert-butyl 11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (150.00 mg, 350.06 μ mol, 1.00 eq), 2,2-difluoroethanamine (567.51 mg, 7.00 mmol, 20.00 eq) in DMSO (5.00 mL) was
 5 degassed and purged with N₂ for 3 times, and then the mixture was stirred at 88 °C for 16 hour under N₂ atmosphere. LCMS showed the starting material was consumed completely, desired product was major. The mixture was poured into water (20 mL) and extracted with EtOAc (10 mL*2). The combined organic phase was washed with brine (20 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column
 10 chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 1:3) to afford the title compound (82.00 mg, 176.51 μ mol, 50.42% yield, 89% purity) as a yellow solid. LCMS: 414 [M+1].

Intermediate 30: 5-tert-butyl 3-ethyl 1,4,6,7-tetrahydropyrazolo [4,3-c]pyridine-3,5-dicarboxylate.

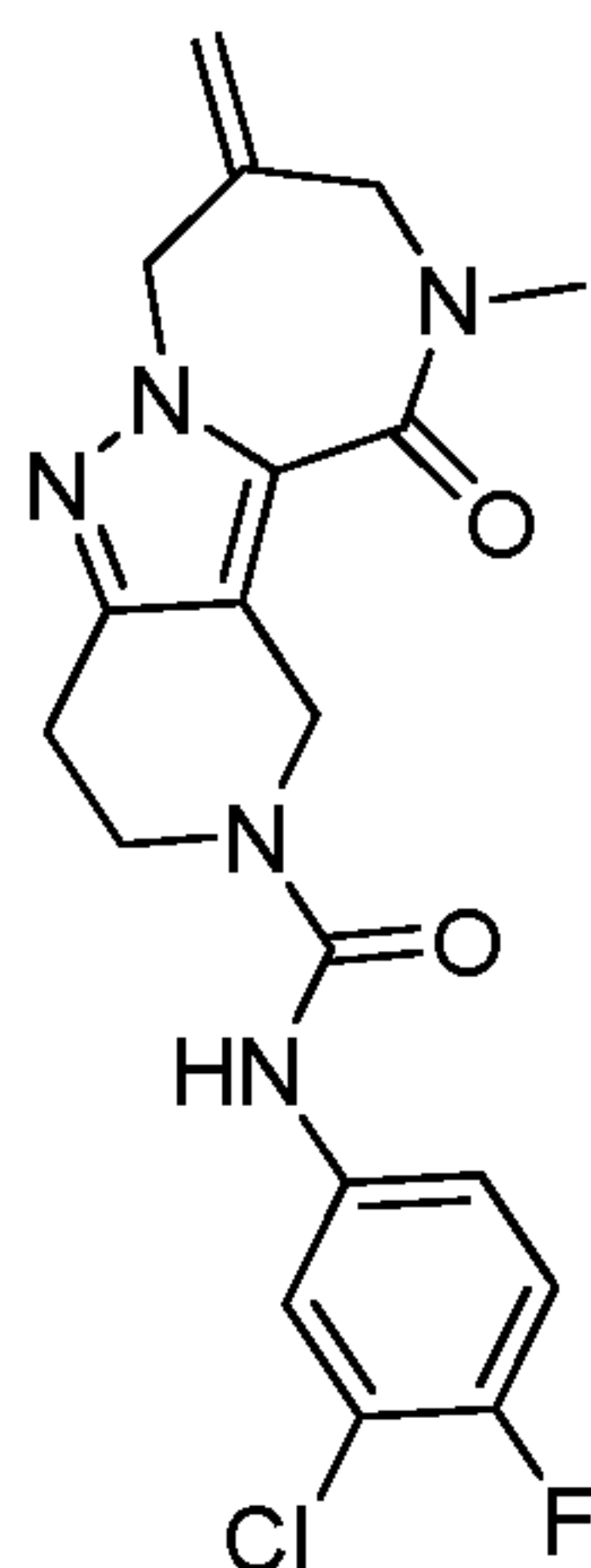


15 Step 1. tert-butyl 3-(2-ethoxy-2-oxo-acetyl)-4-oxo-piperidine-1-carboxylate. To LiHMDS (1 M, 652.44 mL, 1.30 eq) was added a solution of tert-butyl 4-oxopiperidine -1- carboxylate (100.00 g, 501.88 mmol, 1.00 eq) in THF (1.00 L) dropwise at -78 °C under N₂. The reaction mixture was stirred at -78 °C for 30 minutes under N₂. Then diethyl oxalate (95.35 g, 652.44 mmol, 1.30
 20 eq) was added dropwise. After addition, the reaction mixture was warmed to 15 °C over a period of 30 minutes and stirred at 15 °C for another 2 hours. TLC (PE/EA=3/1, R_f=0.2) showed the reaction was completed. The reaction was quenched with saturated aqueous solution of NH₄Cl

(1.5 L) and then neutralized with diluted hydrochloric acid, the aqueous layer was extracted with EtOAc (800 mL x 3). The combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to afford the title compound (165.00 g, crude) as yellow oil and used directly for next step.

- 5 Step 2. 5-tert-butyl-3-ethyl-1,4,6,7-tetrahydropyrazolo [4,3-c]pyridine-3,5-dicarboxylate. A mixture of tert-butyl 3-(2-ethoxy-2-oxo-acetyl)-4-oxo-piperidine-1-carboxylate (165.00 g, 551.25 mmol, 1.00 eq) and NH₂NH₂•H₂O (35.71 g, 606.37 mmol, 1.10 eq) in AcOH (1.00 L) was degassed and purged with N₂ for 3 times. Then the mixture was stirred at 80 °C for 1 hour under N₂ atmosphere. TLC (PE/EA=1/1, R_f=0.4) and LCMS showed the reaction was
- 10 completed. The mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (800 mL) and washed with Na₂CO₃ (1 N, 1.2 L). The aqueous phase was extracted with ethyl acetate (800 mL x 2). The combined organic phase was washed with brine (1 L x 2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to afford the title compound
- 15 (130.00 g, 440.19 mmol, 79.85% yield) as a yellow solid. LCMS: 296 [M+1]. ¹H NMR (400 MHz, METHANOL-d₄) δ = 4.57 - 4.65 (m, 2 H), 4.36 (d, *J* = 7.03 Hz, 2 H), 3.67 - 3.74 (m, 2 H), 2.75 (t, *J* = 5.65 Hz, 2 H), 1.49 (s, 9 H), 1.36 - 1.40 (m, 3 H).

Compound 001: N-(3-chloro-4-fluorophenyl)-10-methyl-8-methylene-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



20

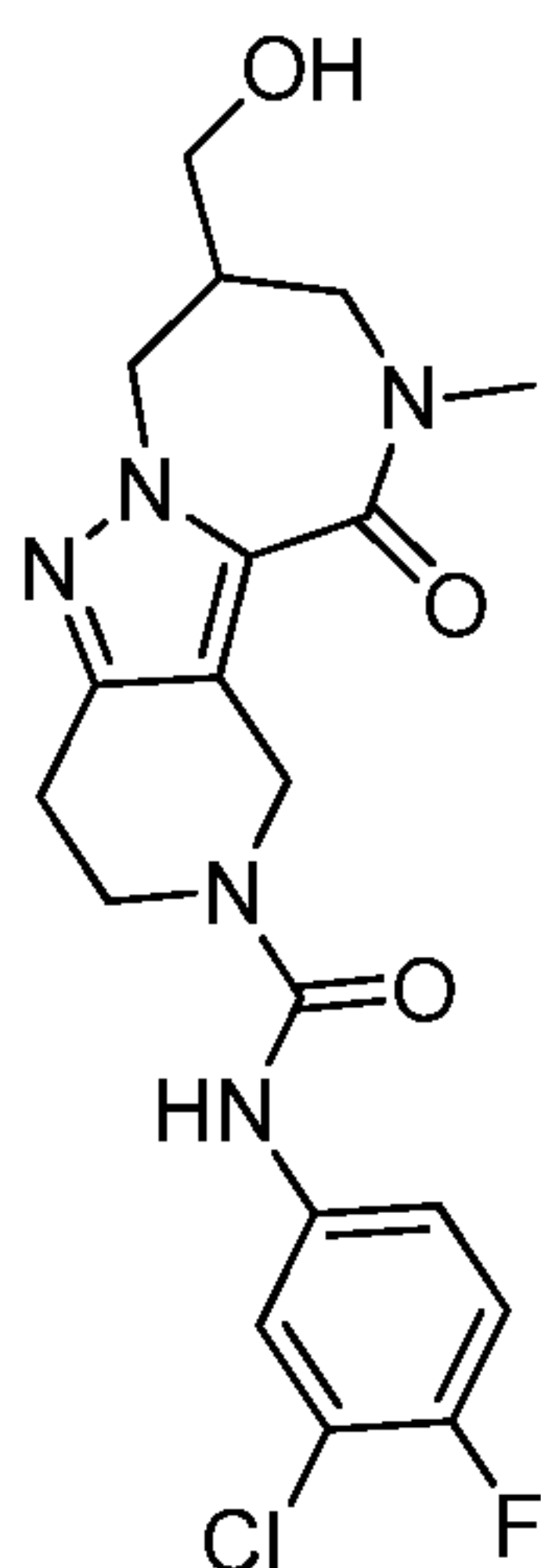
Step 1. 10-methyl-8-methylene-3,4,7,8,9,10-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11(2H)-one. To a solution of tert-butyl 10-methyl-8-methylene-11-oxo-3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (Intermediate 1, 340.00

mg, 1.02 mmol, 1.00 *eq*) in DCM (2.00 mL) was added TFA (3.08 g, 27.01 mmol, 2.00 mL, 26.48 *eq*) under N₂ and the mixture was stirred at 15 °C for 1 h. The mixture was concentrated in vacuo to afford the title compound as the TFA salt (446.00 mg, crude), which was used directly for the next step.

5 Step 2: N-(3-chloro-4-fluorophenyl)-10-methyl-8-methylene-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

A mixture of 10-methyl-8-methylene-1,2,3,4,7,9-hexahydropyrido[2,3]pyrazolo [2,4-b][1,4]diazepin-11-one (446.00 mg, 515.16 μmol, 1.00 *eq*, TFA), Et₃N (260.65 mg, 2.58 mmol, 357.05 μL, 5.00 *eq*) and phenyl N-(3-chloro-4-fluoro-phenyl) carbamate (136.86 mg, 515.16 μmol, 1.00 *eq*) in DCM (3.00 mL) was stirred at 10 °C for 16 h. The mixture was diluted with DCM (30 mL) and washed with HCl (1 M, 30 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo to give yellow oil. The oil was purified by silica gel column and prep-HPLC (FA) to afford the title compound (39.00 mg, 96.28 μmol, 18.69% yield, 99.7% purity) as a white solid. LCMS: 404/406 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 7.60 (dd, *J* = 2.69, 6.48 Hz, 1 H), 7.18 - 7.23 (m, 1 H), 7.03 - 7.11 (m, 1 H), 6.55 (s, 1 H), 5.18 (d, *J* = 10.39 Hz, 2 H), 5.02 (s, 2 H), 4.70 (s, 2 H), 3.98 (s, 2 H), 3.87 (t, *J* = 5.75 Hz, 2 H), 3.19 (s, 3 H), 2.86 (t, *J* = 5.81 Hz, 2 H).

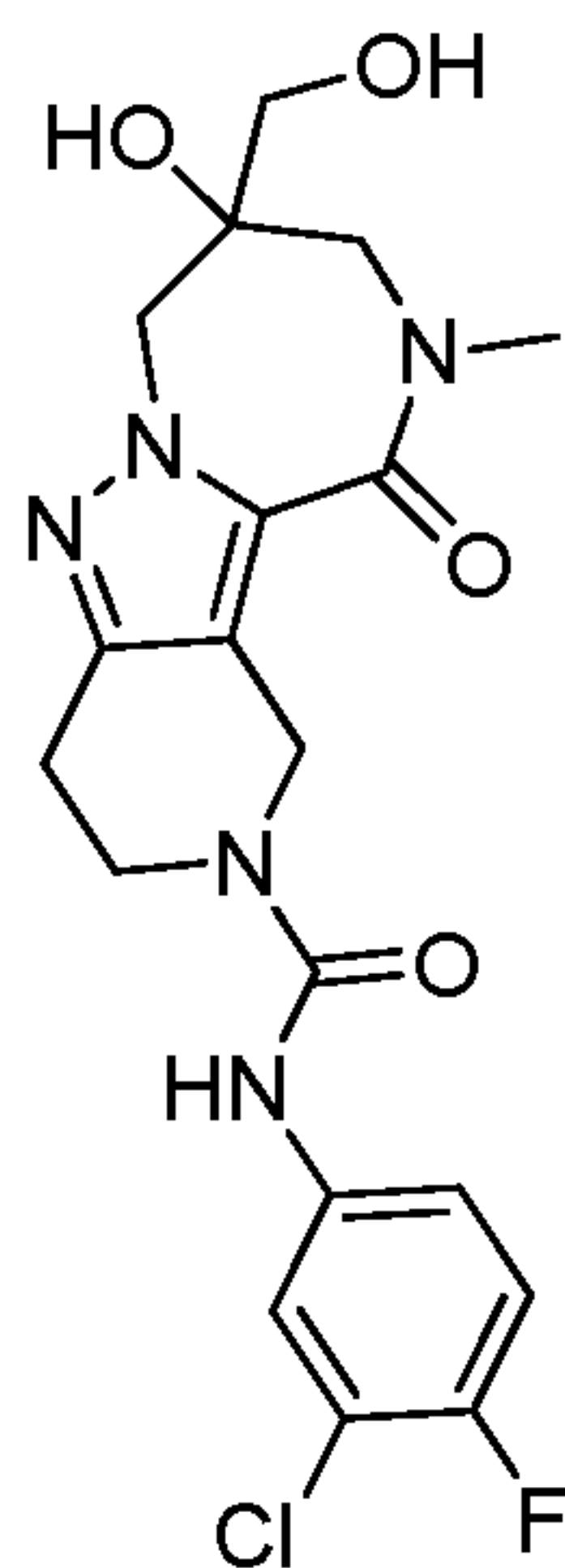
20 Compound 002: N-(3-chloro-4-fluorophenyl)-8-(hydroxymethyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



To a solution of N-(3-chloro-4-fluoro-phenyl)-10-methyl-8-methylene-11-oxo- 3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide (Compound 001; 50.00

mg, 123.81 μ mol, 1.00 *eq*) and chlororhodium triphenylphosphane (4.58 mg, 4.95 μ mol, 0.04 *eq*) in THF (3.00 mL) was added 1,3,2-benzodioxaborole (1 M, 371.43 μ L, 3.00 *eq*) at 0 °C under N₂. The mixture was stirred at 0 °C for 3 hr. TLC (DCM : MeOH = 15 : 1) showed the starting material was consumed completely nearly. A solution of NaOH (34.67 mg, 866.67 μ mol, 7.00 *eq*) in H₂O (1.50 mL) was added at -30 °C dropwise. Then H₂O₂ (393.01 mg, 3.47 mmol, 333.06 μ L, 30% purity, 28.00 *eq*) was added slowly. The mixture was stirred at 10 °C for 16 hr. LCMS showed the starting material/desire product=1/3. The mixture was quenched with saturated NaHSO₃ (50 mL) and extracted with EtOAc (50 mL). The organic phase was washed with NaOH (15 %, 30 mL *3) and brine (30 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to give brown oil. The oil was purified by prep-HPLC(FA) to afford the title compound (10.00 mg, 23.49 μ mol, 18.97% yield, 99.1% purity) as white solid. LCMS: 422/424 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 7.58 (dd, *J* = 2.63, 6.54 Hz, 1 H), 7.14 - 7.24 (m, 1 H), 7.00 - 7.11 (m, 1 H), 6.52 (s, 1 H), 4.67 (s, 2 H), 4.41 (dd, *J* = 7.09, 14.31 Hz, 1 H), 4.20 (dd, *J* = 5.56, 14.24 Hz, 1 H), 3.77 - 3.94 (m, 2 H), 3.62 - 3.77 (m, 2 H), 3.43 - 3.54 (m, 1 H), 3.32 - 3.43 (m, 1 H), 3.19 (s, 3 H), 2.84 (t, *J* = 5.75 Hz, 2 H), 2.61 - 2.77 (m, 1 H), 1.75 (br. s, 1 H).

Compound 003: N-(3-chloro-4-fluorophenyl)-8-hydroxy-8-(hydroxymethyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



20 Step 1. 10-methyl-8-methylene-3,4,7,8,9,10-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11(2H)-one To a solution of tert-butyl 10-methyl-8-methylene-11-oxo-3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (Intermediate 1, 312.00 mg, 938.63 μ mol, 1.00 *eq*) in DCM (3.00 mL) was added TFA (4.62 g, 40.52 mmol, 3.00 mL,

43.17 *eq*) under N₂ and the mixture was stirred at 15 °C for 1 h. The mixture was concentrated in vacuo to afford the title compound (325.00 mg, crude, TFA) as yellow oil, which was used directly for the next step.

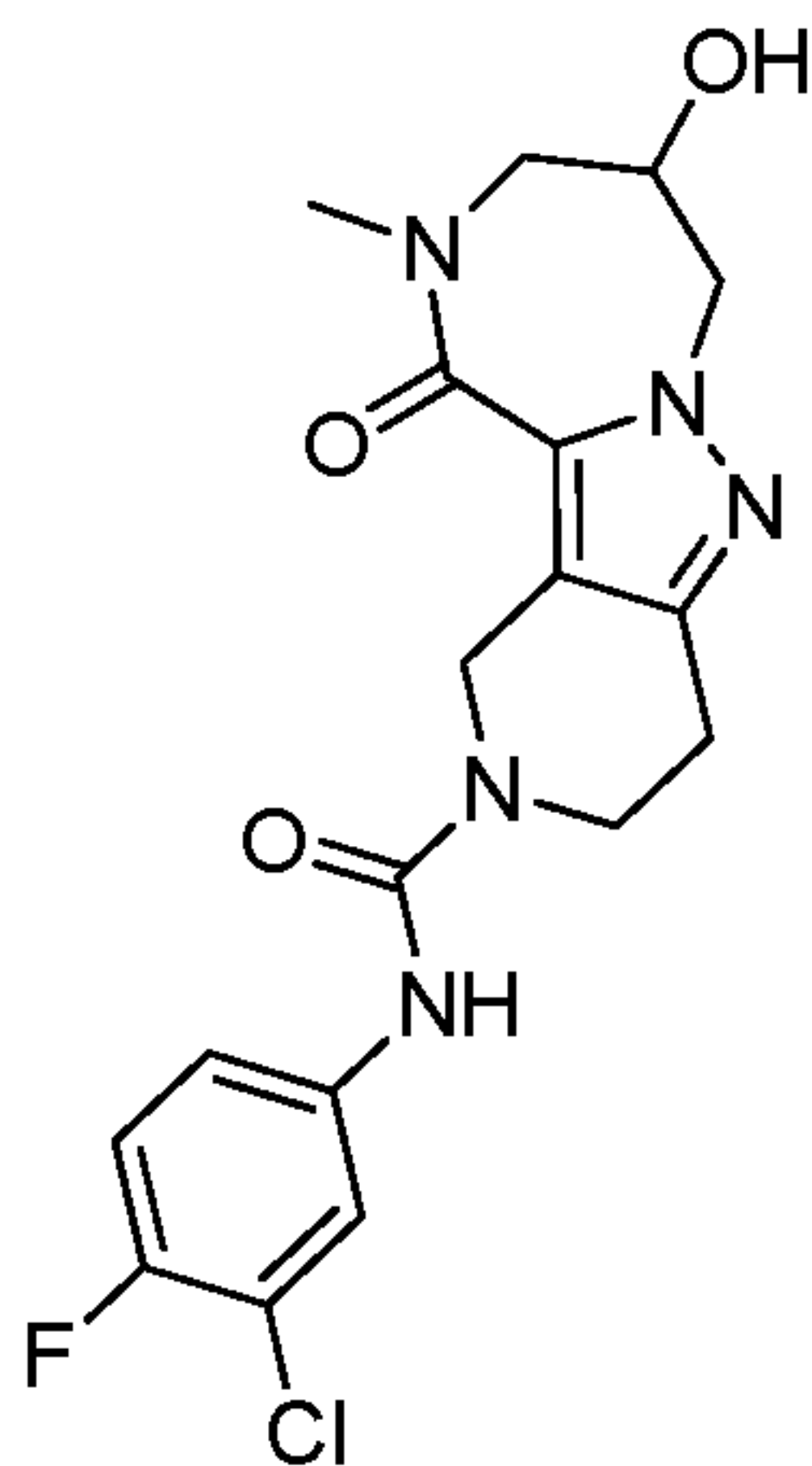
Step 2. N-(3-chloro-4-fluorophenyl)-10-methyl-8-methylene-11-oxo-3,4,8,9,10,11-hexahydro-

5 1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide A mixture of 10-methyl-8-methylene-1,2,3,4,7,9-hexahydropyrido[2,3]pyrazolo [2,4-b][1,4]diazepin-11-one (325.00 mg, 938.49 μmol, 1.00 *eq*, TFA), Et₃N (474.83 mg, 4.69 mmol, 650.45 μL, 5.00 *eq*) and phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (249.33 mg, 938.49 μmol, 1.00 *eq*) in DCM (5.00 mL) was stirred at 10 °C for 16 h. LCMS indicated the starting material/desired product = 10 2/1. The mixture was heated to 30 °C for another 16 h. LCMS indicated the starting material/desired product = 1/2. The mixture was heated to 40 °C for another 16 h. TLC (DCM/MeOH = 8/1) indicated the starting material was consumed completely. The mixture was diluted with DCM (60 mL) and washed with HCl (1 M, 60 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo to give yellow oil. The oil was purified by silica 15 gel column to afford the title compound (320.00 mg, 792.39 μmol, 84.43% yield) as yellow solid. LCMS: 404/406 [M+1].

Step 3. N-(3-chloro-4-fluorophenyl)-8-hydroxy-8-(hydroxymethyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

To a solution of N-(3-chloro-4-fluoro-phenyl)-10-methyl-8-methylene-11-oxo- 3,4,7,9- 20 tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide (50.00 mg, 123.81 μmol, 1.00 *eq*) in acetone (3.00 mL) and H₂O (1.50 mL) was added K₂OsO₄·2H₂O (2.28 mg, 6.19 μmol, 0.05 *eq*) and NMO (58.02 mg, 495.24 μmol, 52.27 μL, 4.00 *eq*) at 0 °C. The mixture was stirred at 10 °C for 16 h. The mixture was quenched with saturated NaHSO₃ (40 mL) and extracted with EtOAc (40 mL). The organic phase was dried over Na₂SO₄, filtered and 25 concentrated in vacuo to give black oil. The oil was purified by prep-HPLC(FA) to afford the title compound (26.00 mg, 59.38 μmol, 47.96% yield, 100% purity) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.57 (dd, *J* = 2.69, 6.48 Hz, 1 H), 7.14 - 7.22 (m, 1 H), 7.02 - 7.10 (m, 1 H), 6.56 (s, 1 H), 4.67 (d, *J* = 4.52 Hz, 2 H), 4.31 - 4.41 (m, 1 H), 4.18 - 4.29 (m, 1 H), 3.84 (d, *J* = 7.95 Hz, 2 H), 3.67 - 3.74 (m, 1 H), 3.58 - 3.66 (m, 1 H), 3.34 - 3.45 (m, 1 H), 3.26 - 3.34 (m, 30 1 H), 3.22 (s, 3 H), 3.02 (br. s., 1 H), 2.83 (t, *J* = 5.81 Hz, 2 H), 2.32 - 2.50 (m, 1 H). LCMS: 438/440 [M+1].

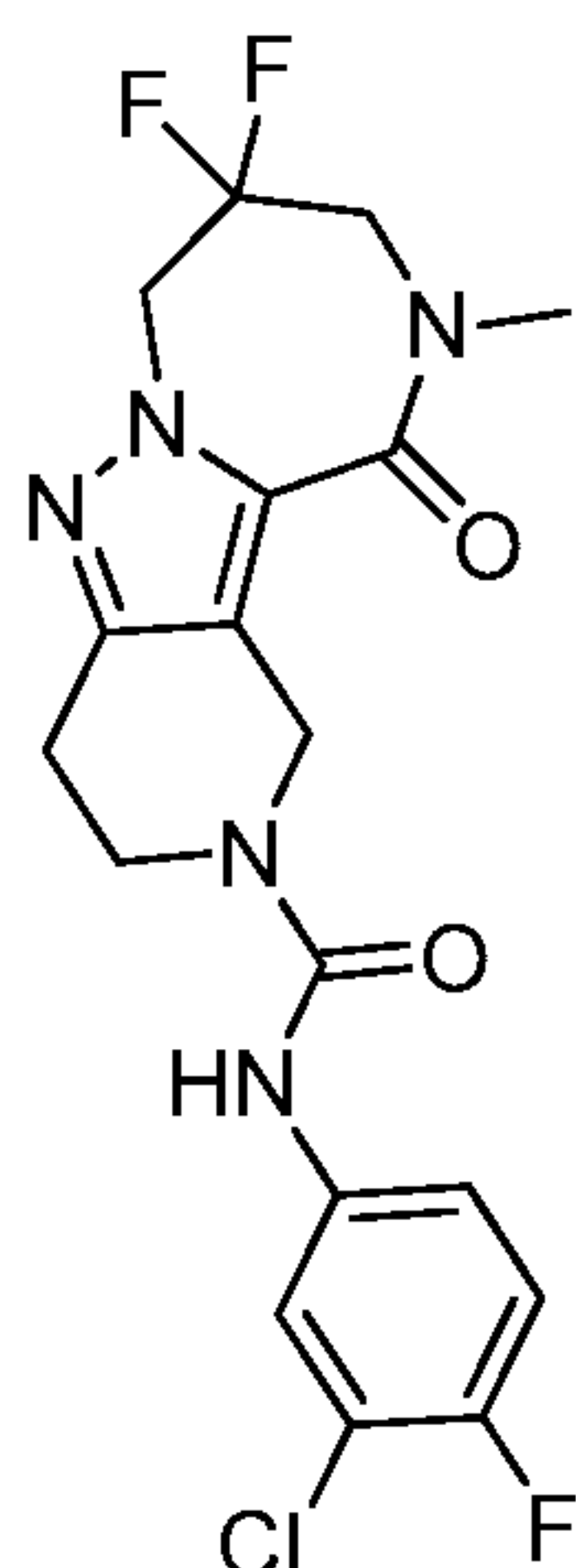
Compound 004: N-(3-chloro-4-fluorophenyl)-8-hydroxy-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



- 5 Step 1. 8-hydroxy-10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo [2,4-
b][1,4]diazepin-11-one. To a solution of tert-butyl 8-hydroxy-10-methyl-11-oxo-1,3,4,7,8,9-
hexahydropyrido [2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (Intermediate 3, 49.00 mg,
145.66 μmol , 1.00 *eq*) in DCM (2.00 mL) was added TFA (3.08 g, 27.01 mmol, 2.00 mL,
185.45 *eq*) and the mixture was stirred at 15 °C under N₂ for 1 h. LCMS indicated the starting
10 material was consumed completely. The mixture was concentrated in vacuo to afford desired
product (51.00 mg, 145.59 μmol , 99.95% yield, TFA) as yellow oil, which was used directly for
the next step.
- Step 2. N-(3-chloro-4-fluorophenyl)-8-hydroxy-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-
2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. A mixture of 8-hydroxy-10-
15 methyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo [2,4-b][1,4]diazepin-11-one (51.00 mg,
145.59 μmol , 1.00 *eq*, TFA), Et₃N (73.66 mg, 727.95 μmol , 100.90 μL , 5.00 *eq*) and phenyl
N-(3-chloro-4-fluoro-phenyl) carbamate (38.68 mg, 145.59 μmol , 1.00 *eq*) in DCM (4.00 mL)
was stirred at 10 °C for 16 h. The mixture was diluted with DCM (40 mL) and washed with HCl
(1M, 40 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo to
20 give yellow oil. The oil was purified by prep-HPLC (FA) to afford the title compound (35.00
mg, 84.10 μmol , 57.77% yield, 98% purity) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.58
(dd, *J* = 2.63, 6.54 Hz, 1 H), 7.15 - 7.22 (m, 1 H), 7.02 - 7.10 (m, 1 H), 6.51 (s, 1 H), 4.68 (d, *J* =
2.69 Hz, 2 H), 4.53 - 4.64 (m, 2 H), 4.26 (d, *J* = 9.17 Hz, 1 H), 3.85 (t, *J* = 5.81 Hz, 2 H), 3.59

(dd, $J = 4.10, 15.22$ Hz, 1 H), 3.35 (dd, $J = 5.44, 15.22$ Hz, 1 H), 3.22 (s, 3 H), 2.85 (t, $J = 5.75$ Hz, 2 H), 2.10 (br. s., 1 H). LCMS: 408/410 [M+1].

5 Compound 005: N-(3-chloro-4-fluorophenyl)-8,8-difluoro-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



10 Step 1. tert-butyl 8,8-difluoro-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxylate To a solution of tert-butyl 10-methyl-8,11-dioxo-3,4,7,9-tetrahydro-1H-pyrido [2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (Intermediate 2, 80.00 mg, 239.26 μ mol, 1.00 *eq*) in DCM (4.00 mL) was added DAST (115.70 mg, 717.78 μ mol, 94.84 μ L, 3.00 *eq*) at -30 °C. The mixture was stirred at 15 °C for 16 h. The mixture was diluted with brine (30 mL), extracted with DCM (30 mL *2). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo to give yellow oil. The oil was purified by prep-TLC to afford the title compound (60.00 mg, 153.21 μ mol, 64.04% yield, 91% purity) as yellow solid. LCMS: 379[M+23].

15 Step 2. 8,8-difluoro-10-methyl-3,4,7,8,9,10-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11(2H)-one. To a solution of tert-butyl 8,8-difluoro-10-methyl-11-oxo-3,4,7,9-tetrahydro-1H- pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (60.00 mg, 168.36 μ mol, 1.00 *eq*) in DCM (2.00 mL) was added TFA (3.08 g, 27.01 mmol, 2.00 mL, 160.45 *eq*) and the mixture was stirred at 15 °C under N₂ for 1 h. The mixture was concentrated in vacuo to afford the title compound (62.00 mg, 150.70 μ mol, 89.51% yield, 90% purity, TFA) as yellow oil, which was used directly for the next step. LCMS: 257 [M+1].

Step 3. N-(3-chloro-4-fluorophenyl)-8,8-difluoro-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide A mixture of 8,8-difluoro-10-methyl-1,2,3,4,7,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (62.00 mg, 167.45 μ mol, 1.00 *eq*, TFA), Et₃N (84.72 mg, 837.23 μ mol, 116.05 μ L, 5.00 *eq*) and phenyl N-(3-chloro-4-fluoro-phenyl) carbamate (44.49 mg, 167.45 μ mol, 1.00 *eq*) in DCM (4.00 mL) was stirred at 15 °C for 16 h. The mixture was diluted with DCM (40 mL) and washed with HCl (1 M, 40 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo to give yellow oil. The oil was purified by prep-HPLC (FA) to afford the title compound (37.00 mg, 86.31 μ mol, 51.55% yield, 99.8% purity) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.58 (dd, *J* = 2.57, 6.48 Hz, 1 H), 7.16 - 7.24 (m, 1 H), 7.03 - 7.12 (m, 1 H), 6.46 (s, 1 H), 4.60 - 4.80 (m, 4 H), 3.86 (t, *J* = 5.75 Hz, 2 H), 3.72 (t, *J* = 12.29 Hz, 2 H), 3.25 (s, 3 H), 2.88 (t, *J* = 5.81 Hz, 2 H). LCMS: 428/430[M+1].

Compound 006: N-(3-chloro-4-fluorophenyl)-8-fluoro-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

Step 1. tert-butyl 8-fluoro-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxylate. To a solution of tert-butyl 8-hydroxy-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (Intermediate 3, 80.00 mg, 237.82 μ mol, 1.00 *eq*) in DCM (4.00 mL) was added DAST (153.34 mg, 951.28 μ mol, 125.69 μ L, 4.00 *eq*) at - 30 °C. The mixture was stirred at 15 °C for 16 h. TLC indicated the starting material was consumed completely and one major new spot with lower polarity was detected. The mixture was diluted with brine (30 mL), extracted with DCM (30 mL *2). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo to give yellow oil. The oil was purified by prep-TLC to afford the title compound (56.00 mg, 162.18 μ mol, 68.20% yield, 98% purity) as yellow solid. LCMS: 361[M+23].

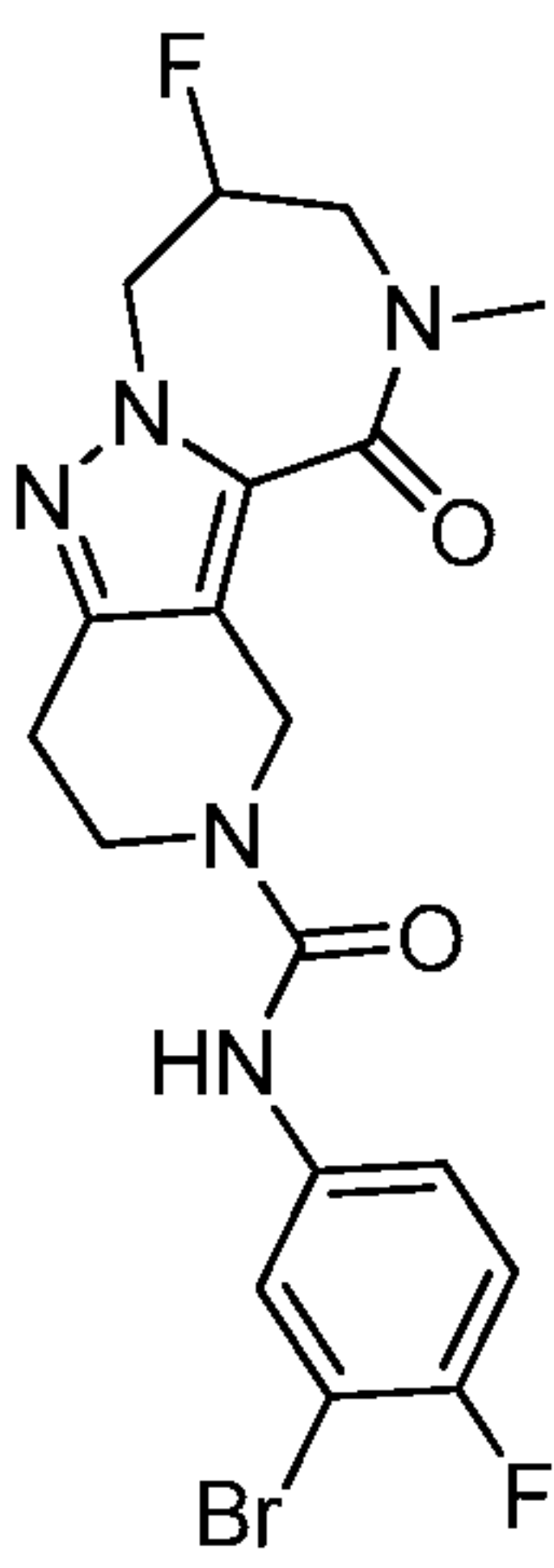
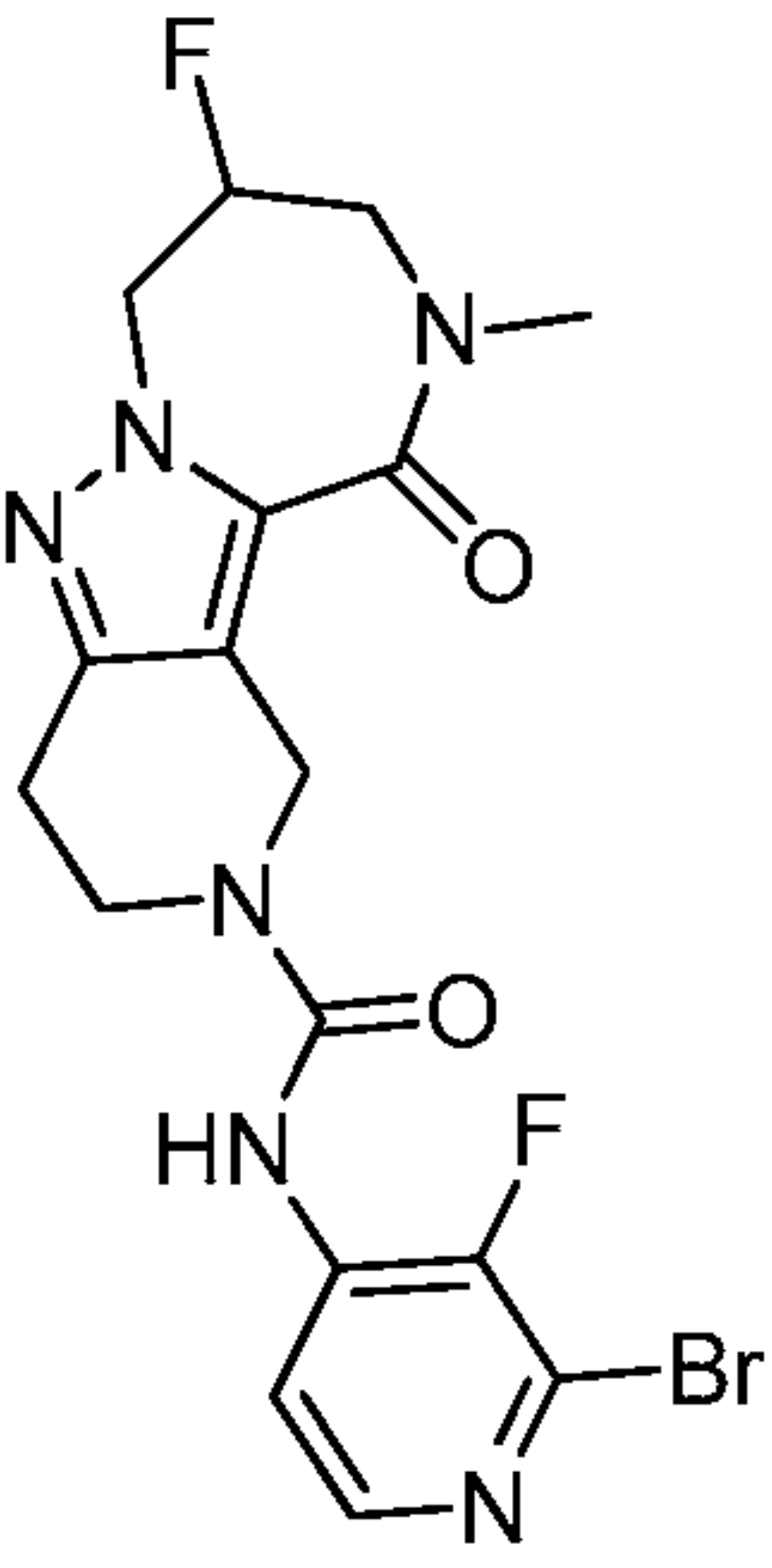
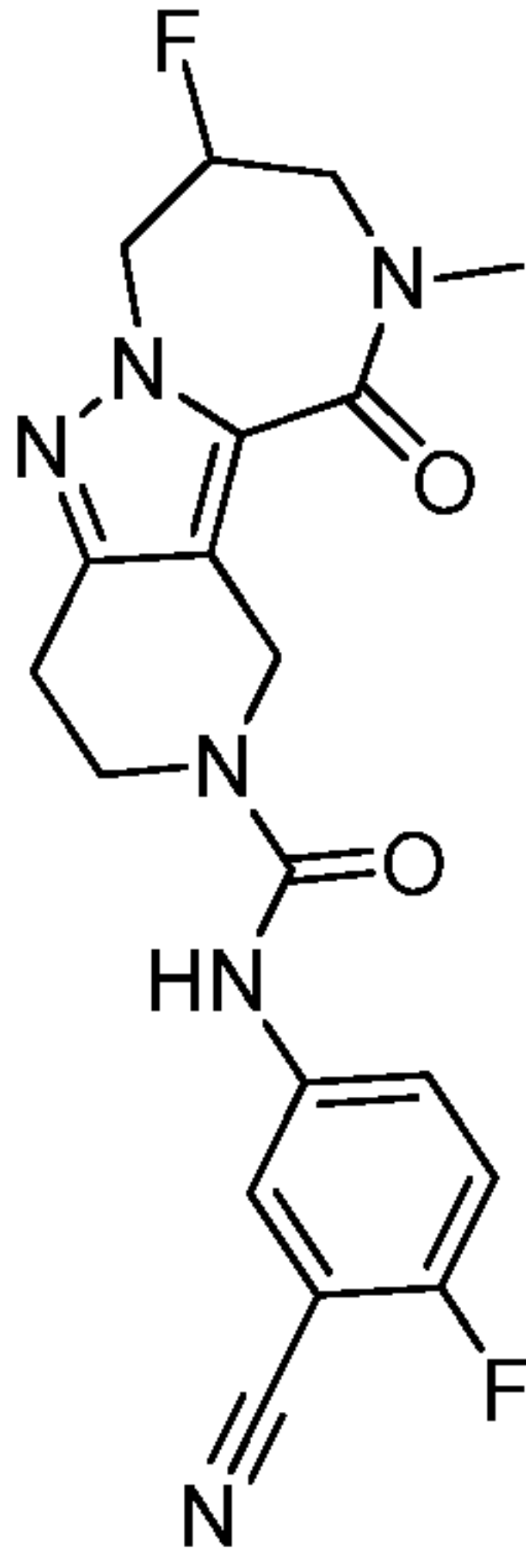
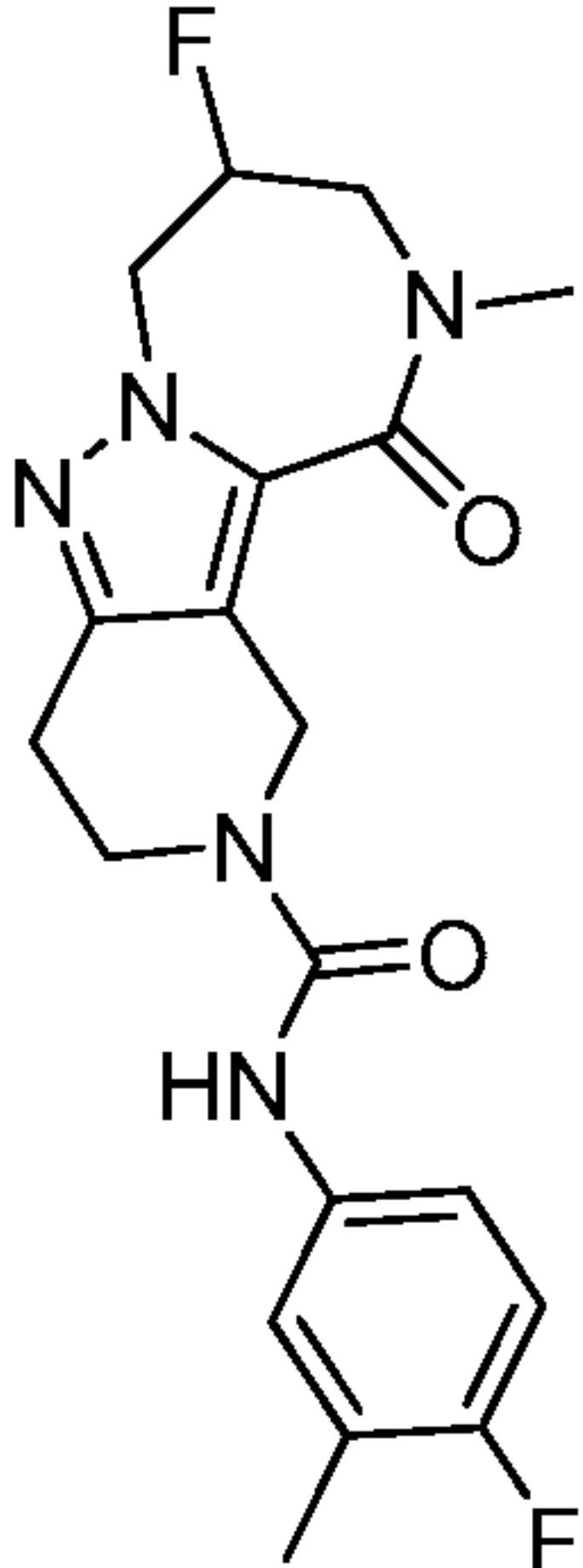
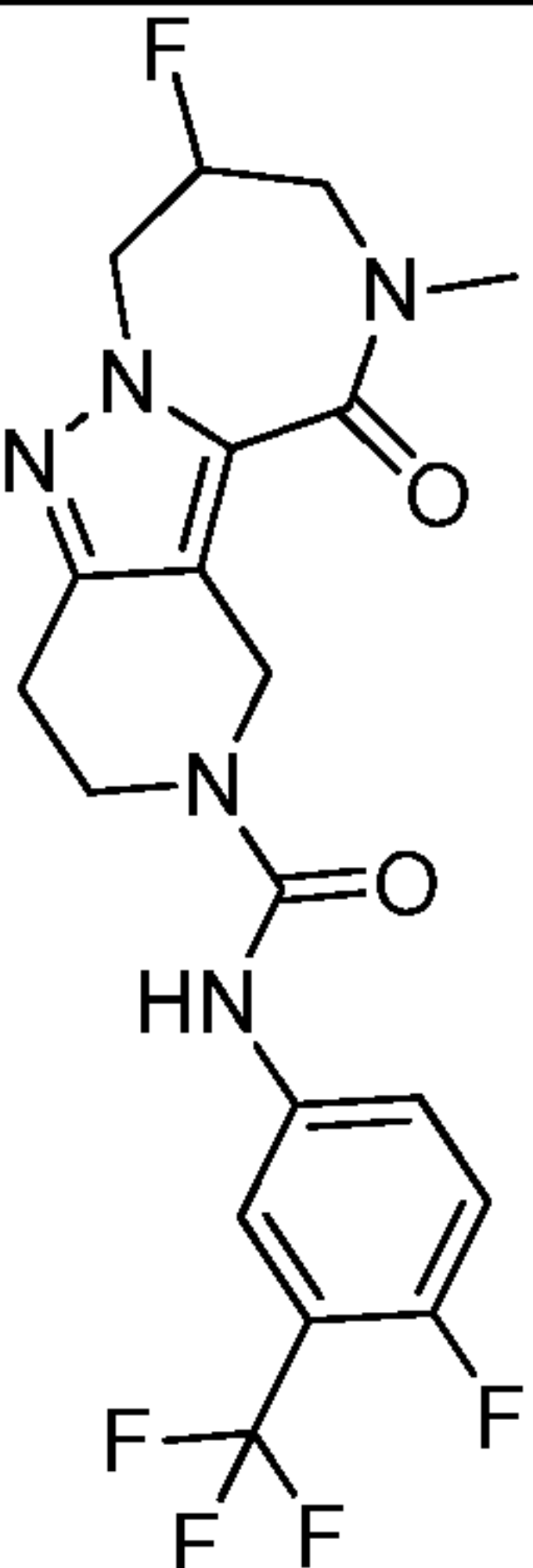
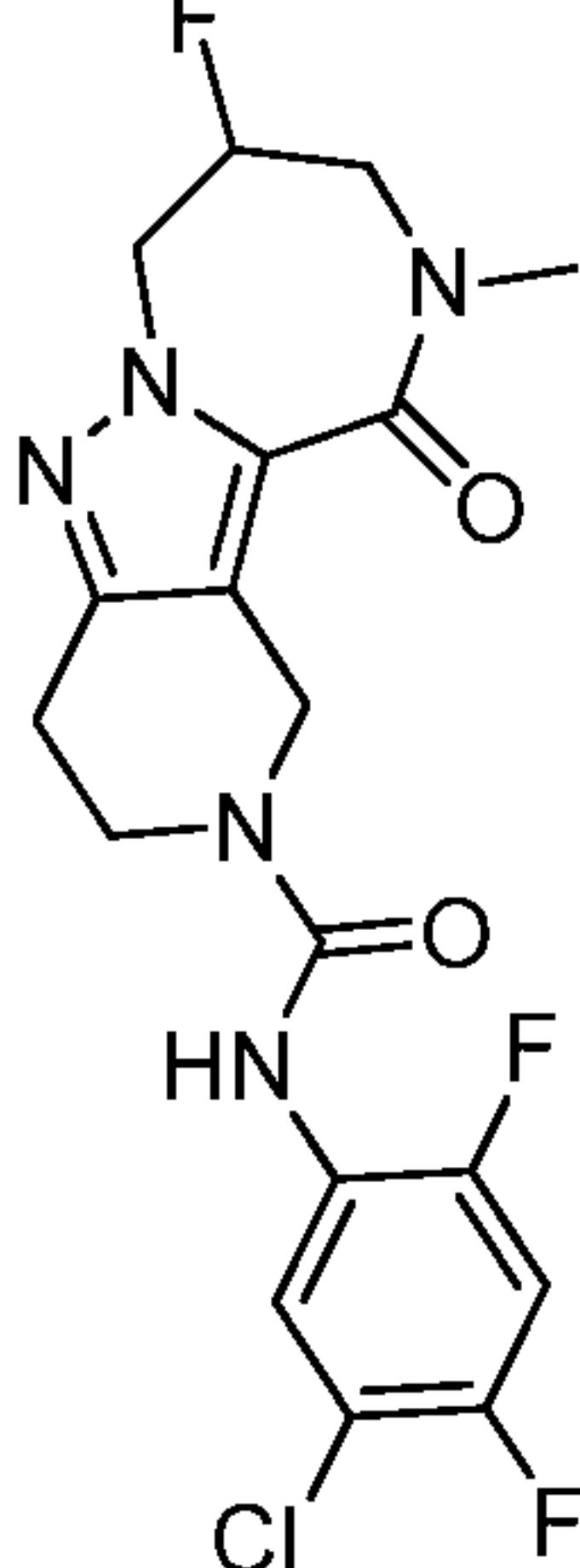
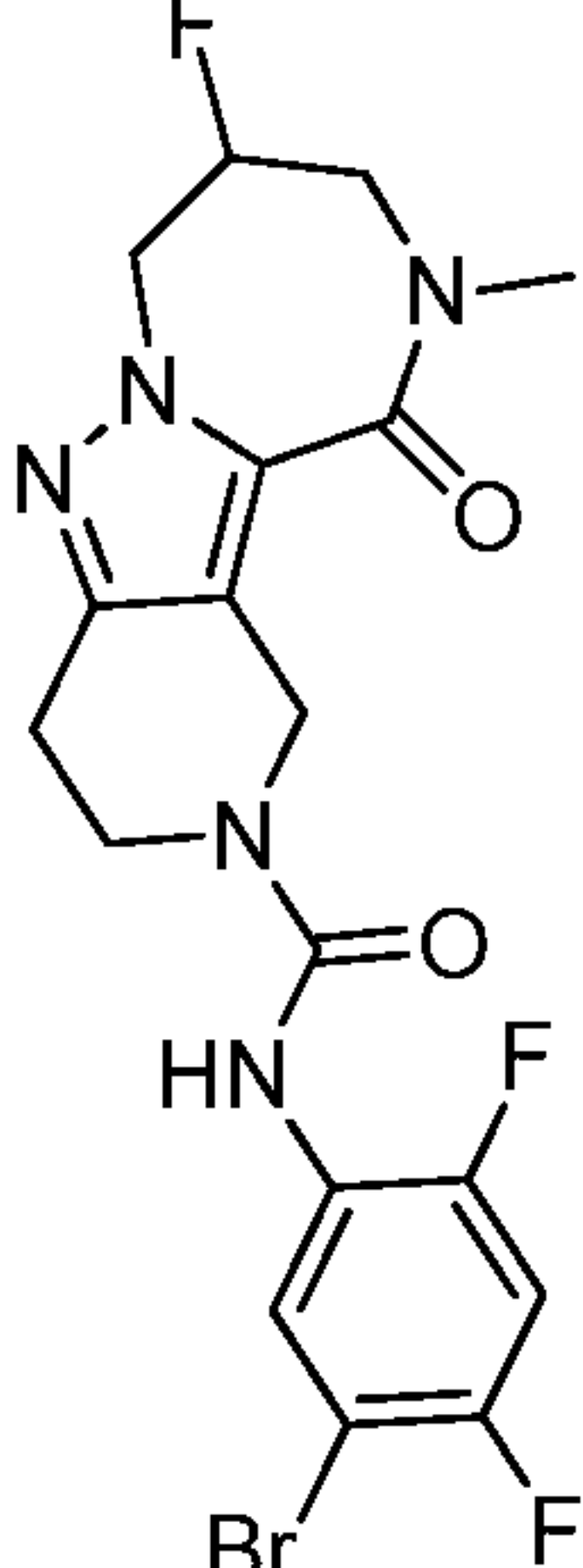
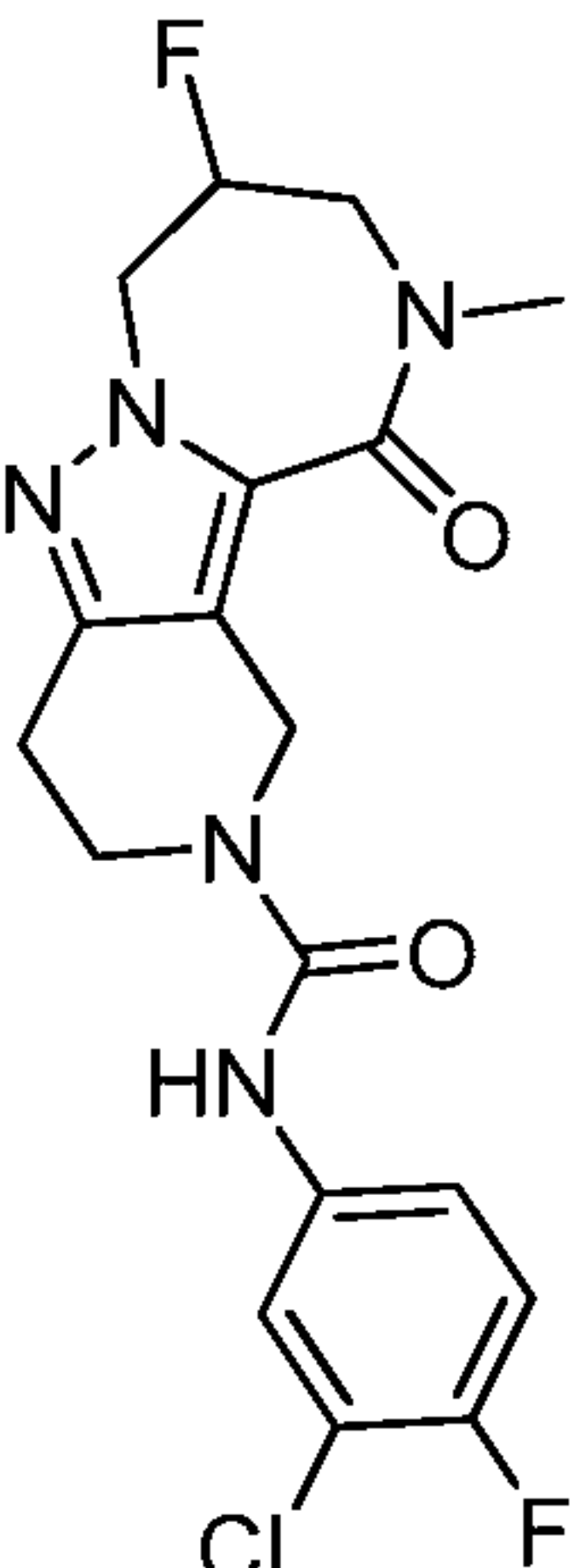
Step 2. 8-fluoro-10-methyl-3,4,7,8,9,10-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11(2H)-one. To a solution of tert-butyl 8-fluoro-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (56.00 mg, 165.49 μ mol,

1.00 *eq*) in DCM (1.00 mL) was added TFA (1.54 g, 13.51 mmol, 1.00 mL, 81.61 *eq*) and the mixture was stirred at 15 °C under N₂ for 1 h. TLC showed the reactant was consumed completely and one major new spot with larger polarity was detected. The mixture was concentrated in vacuo to afford 8-fluoro-10-methyl-2,3,4,7,8,9- hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (59.00 mg, 150.73 μmol, 91.08% yield, 90% purity, TFA) as yellow oil, which was used directly for the next step. LCMS: 239 [M+1].

Step 3. N-(3-chloro-4-fluorophenyl)-8-fluoro-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. A mixture of 8-fluoro-10-

methyl-2,3,4,7,8,9-hexahydro-1H-pyrido [2,3]pyrazolo [2,4-b][1,4]diazepin-11-one (59.00 mg, 167.48 μmol, 1.00 *eq*, TFA), Et₃N (84.74 mg, 837.40 μmol, 116.08 μL, 5.00 *eq*) and phenyl N-(3-chloro-4-fluoro-phenyl) carbamate (44.49 mg, 167.48 μmol, 1.00 *eq*) in DCM (4.00 mL) was stirred at 15 °C for 16 h. The mixture was diluted with DCM (30 mL) and washed with HCl (1M, 30 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo to give yellow oil, which was purified by prep-HPLC(FA) to afford the title compound (41.00 mg, 99.04 μmol, 59.14% yield, 99% purity) as white solid. LCMS [M+1]: 410. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (dd, *J* = 2.63, 6.54 Hz, 1H), 7.17 - 7.23 (m, 1H), 7.02 - 7.10 (m, 1H), 6.63 (s, 1H), 4.64 - 4.85 (m, 2H), 4.34 - 4.62 (m, 4H), 3.95 - 4.08 (m, 1H), 3.86 (q, *J* = 5.42 Hz, 2H), 3.22 (s, 3H), 2.87 (br t, *J* = 5.69 Hz, 2H).

Compounds 007, 008, 009, 010, 011, 012, and 013 were prepared in manner analogous to Compound 006.

 007	 008	 009
 010	 011	 012
 013	 006	

Compound 007: N-(3-bromo-4-fluorophenyl)-8-fluoro-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

LCMS [M+1]: 454. ¹H NMR (400 MHz, CDCl₃) δ = 7.71 -7.73 (m, 1 H) 7.27 - 7.29 (m, 1 H) 7.04 (t, *J* = 8.4 Hz, 1 H) 6.71 (s, 1 H) 4.66 - 4.81 (m, 2 H) 4.38 - 4.52 (m, 4 H) 3.87 - 3.89 (m, 1 H) 3.83 - 3.86 (m, 2 H) 3.21 (s, 3 H) 2.85 - 2.88 (m, 2 H)

Compound 008: N-(2-bromo-3-fluoropyridin-4-yl)-8-fluoro-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

LCMS [M+1]: 455. ¹H NMR (400 MHz, CDCl₃) δ = 8.15 (t, *J* = 5.4 Hz, 1 H) 8.06 (d, *J* = 5.6 Hz, 1 H) 7.06 - 7.07 (m, 1 H) 4.79 - 4.87 (m, 2 H) 4.37 - 4.51 (m, 4 H) 3.87 - 3.89 (m, 1 H) 3.84 - 3.86 (m, 2 H) 3.21 (s, 3 H) 2.90 (t, *J* = 5.6 Hz, 2H).

Compound 009: N-(3-cyano-4-fluorophenyl)-8-fluoro-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

LCMS [M+1]: 401. ¹H NMR (400 MHz, CDCl₃) δ = 7.77 - 7.80 (m, 1 H) 7.61 - 7.62 (m, 1 H) 7.13 (t, *J* = 8.6 Hz, 1 H) 6.99 (s, 1 H) 4.82 (d, *J* = 16 Hz, 1 H) 4.68 (d, *J* = 15.6 Hz, 1 H) 4.46 - 4.51 (m, 4 H) 3.81 - 3.90 (m, 2 H) 3.21 (s, 3 H) 2.85 - 2.88 (m, 2 H).

Compound 010: 8-fluoro-N-(4-fluoro-3-methylphenyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

LCMS [M+1]: 390. ¹H NMR (400 MHz, CDCl₃) δ = 7.24 - 7.25 (m, 1 H) 7.10 - 7.13 (m, 1 H) 6.92 (t, *J* = 9.0 Hz, 1 H) 4.67 - 4.80 (m, 2 H) 4.38 - 4.52 (m, 4 H) 3.86 - 3.87 (m, 1 H) 3.84 - 3.85 (m, 1 H) 3.21 (s, 3 H) 2.85 - 2.88 (m, 2 H) 2.25 (s, 3 H).

Compound 011: 8-fluoro-N-(4-fluoro-3-(trifluoromethyl)phenyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

LCMS [M+1]: 444. ¹H NMR (400 MHz, CDCl₃) δ = 7.68 - 7.70 (m, 1 H) 7.59 - 7.61 (m, 1 H) 7.13 (t, *J* = 9.4 Hz, 1 H) 6.8 (s, 1 H) 4.82 (d, *J* = 15.6 Hz, 1 H) 4.70 (d, *J* = 16 Hz, 1 H) 4.39 - 4.52 (m, 4 H) 3.90 - 3.92 (m, 1 H) 3.84 - 3.89 (m, 2 H) 3.22 (s, 3 H) 2.87 (t, *J* = 5.4 Hz, 2 H).

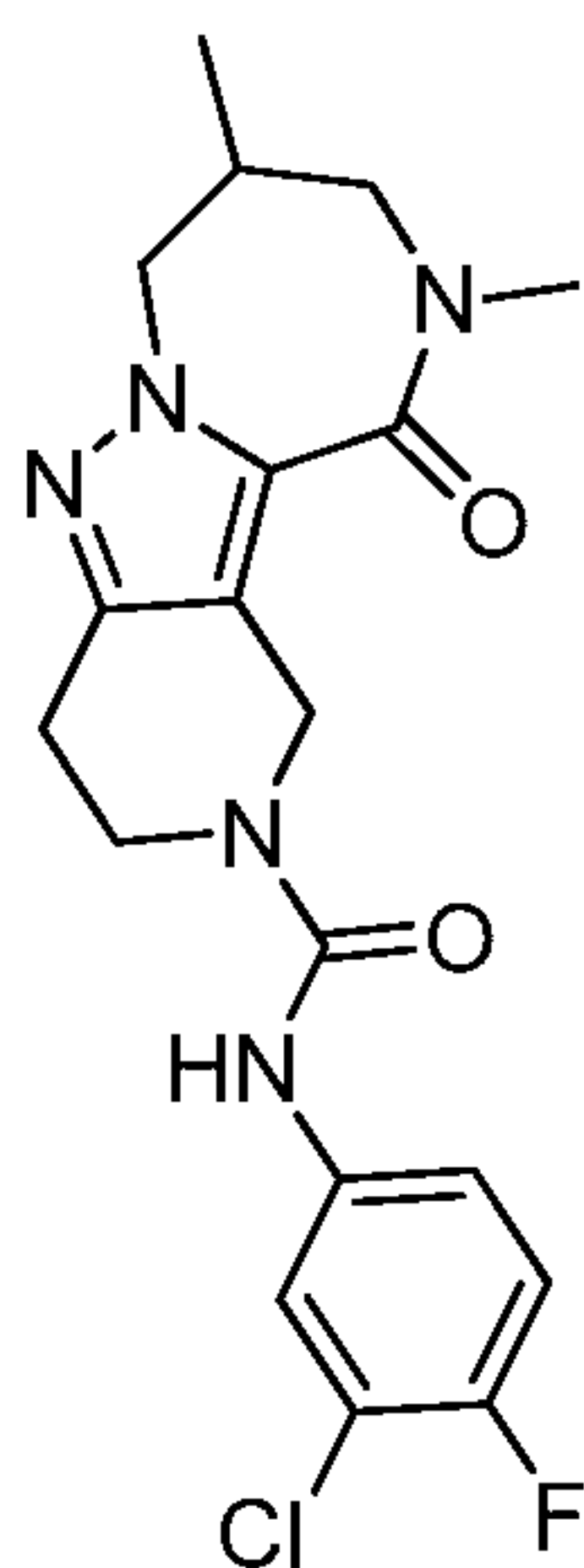
Compound 012: N-(5-chloro-2,4-difluorophenyl)-8-fluoro-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

LCMS [M+1]: 428. ¹H NMR (400 MHz, CDCl₃) δ = 8.17 (t, J = 8.0 Hz, 1 H) 6.95 (t, J = 5.6 Hz, 1 H) 6.6 (s, 1 H) 4.75 – 4.83 (m, 2 H) 4.46 – 4.50 (m, 4 H) 3.90 – 4.00 (m, 1 H) 3.83 – 3.89 (m, 2 H) 3.21 (s, 3 H) 2.87 – 2.90 (m, 2 H).

Compound 013: N-(5-bromo-2,4-difluorophenyl)-8-fluoro-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

LCMS [M+1]: 472. ¹H NMR (400 MHz, CDCl₃) δ = 8.31 (t, J = 7.8 Hz, 1 H) 6.91 – 6.96 (m, 1 H) 6.61 (s, 1 H) 4.71 – 4.83 (m, 2 H) 4.46 – 4.51 (m, 4 H) 3.87 – 3.88 (m, 1 H) 3.84 – 3.86 (m, 2 H) 3.21 (s, 3 H) 2.88 (t, J = 5.6 Hz, 2 H).

Compound 014: N-(3-chloro-4-fluoro-phenyl)-8,10-dimethyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide.



Step 1. tert-butyl 3-[methyl-[2-(methanesulfonyloxymethyl)allyl]carbamoyl]-2,4,6,7-

tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate. To a solution of tert-butyl 3-[2-

(hydroxymethyl)allyl-methyl-carbamoyl]-2,4,6,7- tetrahydropyrazolo[4,3-c]pyridine-5-

carboxylate (100.00 mg, 285.38 μ mol, 1.00 *eq*) and Et₃N (57.76 mg, 570.76 μ mol, 79.12 μ L,

2.00 *eq*) in DCM (3.00 mL) was added a solution of MsCl (49.04 mg, 428.07 μ mol, 33.14 μ L,

1.50 *eq*) in DCM (1.00 mL) at 0 °C under N₂ and the mixture was stirred for another 1 h. The

mixture was diluted with EtOAc (40 mL) and washed with brine (30 mL *2). The organic phase

was dried over Na₂SO₄, filtered and concentrated in vacuo to afford the title compound (120.00 mg, crude), which was used directly for the next step.

Step 2. tert-butyl 8,10-dimethyl-11-oxo-3,4,10,11-tetrahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(9H)-carboxylate and tert-butyl 8,10-dimethyl-11-oxo-3,4,10,11-tetrahydro-

5 1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxylate. To a solution of tert-butyl 3-[methyl-[2-(methylsulfonyloxymethyl)allyl]carbamoyl]-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (40.00 mg, 93.35 μ mol, 1.00 *eq*) in DMF (2.00 mL) was added t-BuOK (15.71 mg, 140.03 μ mol, 1.50 *eq*) and the mixture was stirred at 50 °C for 16 h. TLC showed the starting material was consumed completely and one major new spot with larger polarity was
10 detected. LCMS indicated two peaks with desired Ms. The mixture was diluted with EtOAc (30 mL) and washed with HCl (1 M, 30 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo to give oil. The oil was purified by prep-HPLC (FA) to afford tert-butyl 8,10-dimethyl-11-oxo-1,3,4,7-tetrahydropyrido [2,3]pyrazolo [2,4-b][1,4]diazepine-2-carboxylate (8.00 mg, 24.07 μ mol, 25.78% yield). ¹H NMR (400 MHz, CDCl₃) δ 5.89 (s, 1H),
15 4.63 - 4.65 (m, 4H), 3.70 (s, 2H), 3.22 (s, 3H), 2.73 (s, 2H), 1.94 (s, 3H), 1.48 (s, 9H) and tert-butyl 8,10- dimethyl-11-oxo-1,3,4,9-tetrahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (8.00 mg, 24.07 μ mol, 25.78% yield) (8.00 mg). ¹H NMR (400 MHz, CDCl₃) δ 5.91 (s, 1H), 4.64 - 4.66 (m, 4H), 3.72 (s, 2H), 3.24 (s, 3H), 2.75 (s, 2H), 1.96 (s, 3H), 1.49 (s, 9H).

Step 3. tert-butyl 8,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-

20 pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxylate. A mixture of tert-butyl 8,10-dimethyl-11-oxo-1,3,4,9-tetrahydropyrido[2,3] pyrazolo [2,4-b][1,4]diazepine-2-carboxylate (3.00 mg, 9.03 μ mol, 0.11 *eq*), tert-butyl 8,10-dimethyl-11-oxo-1,3,4,7-tetrahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (27.00 mg, 81.23 μ mol, 1.00 *eq*) in MeOH (5.00 mL) was Pd/C (10.00 mg, 4.51 μ mol, 0.10 *eq*) under N₂. The suspension
25 was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (50 psi) at 25 °C for 16 hr. LCMS showed the starting material was consumed completely, the desired product was major. The reaction mixture was diluted with DCM/MeOH = 1/1 (50 mL) and filtered. The filtrate was concentrated to give the title compound (15.00 mg, 44.86 μ mol, 99.40% yield) as a white solid, which was used directly for the next step. ¹H NMR (400
30 MHz, CDCl₃) δ 4.61 (br. s., 2H) 4.37 (dd, *J* = 14.05, 6.78 Hz, 1H) 3.95 (dd, *J* = 13.99, 5.58 Hz,

1H) 3.60 - 3.81 (m, 2H) 3.33 - 3.46 (m, 1H) 3.17 (s, 3H) 3.03 - 3.12 (m, 1H) 2.75 (br. s., 2H) 2.52 - 2.66 (m, 1H) 1.44 - 1.54 (m, 9H) 1.10 (d, $J = 6.78$ Hz, 3H). LCMS: 335 [M+1].

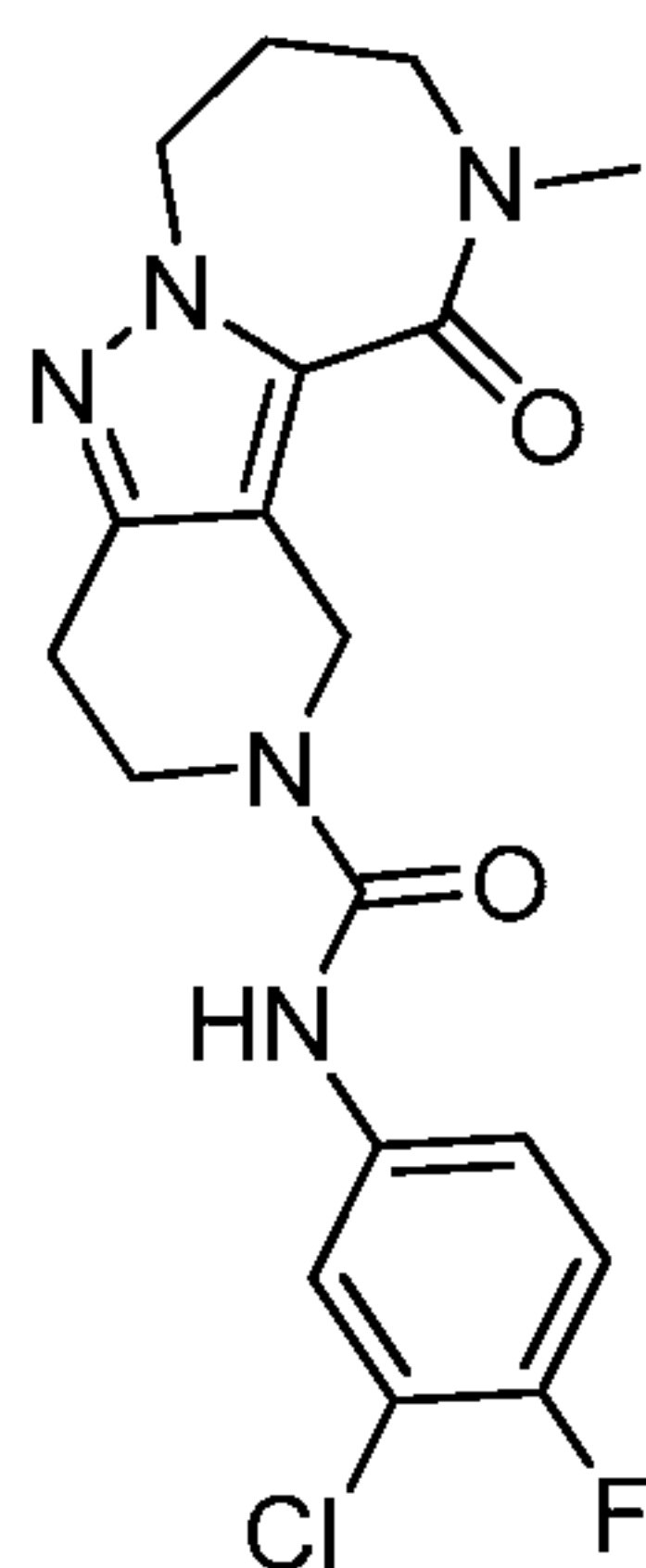
Step 4. 8,10-dimethyl-3,4,7,8,9,10-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11(2H)-one. A mixture of tert-butyl 8,10-dimethyl-11-oxo-1,3,4,7,8,9-hexahydropyrido

5 [2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (38.00 mg, 113.63 μ mol, 1.00 *eq*) in DCM (2.00 mL) was added TFA (1.54 g, 13.51 mmol, 1.00 mL, 118.86 *eq*), and then the mixture was stirred at 10 °C for 1 hour. TLC showed the starting material was consumed completely and a new spot appeared. The mixture was concentrated in vacuum to give the title compound as the TFA salt (39.58 mg, 113.63 μ mol, 100.00% yield) as a yellow oil, which was used directly for
10 the next step.

Step 5. N-(3-chloro-4-fluoro-phenyl)-8,10-dimethyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide. A mixture of 8,10-dimethyl-

2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (39.58 mg, 113.63 μ mol, 1.00 *eq*, TFA), phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (45.28 mg, 170.45 μ mol, 1.50 *eq*), TEA (23.00 mg, 227.26 μ mol, 31.51 μ L, 2.00 *eq*) in DCM (3.00 mL) was degassed
15 and purged with N₂ for 3 times, and then the mixture was stirred at 30 °C for 16 hour under N₂ atmosphere. LCMS showed the starting material was consumed completely and desired product was major. The mixture was poured into water (5 mL) and stirred at 5 min. The aqueous phase was extracted with DCM (3 mL *3). The combined organic phase was washed with brine (5
20 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-HPLC(FA) to give the title compound (15.00 mg, 36.59 μ mol, 32.20% yield, 99% purity) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.56 - 7.61 (m, 1H) 7.16 - 7.23 (m, 1H) 7.01 - 7.09 (m, 1H) 6.60 (s, 1H) 4.67 (s, 2H) 4.37 - 4.48 (m, 1H) 3.99 (dd, $J = 14.06, 5.87$ Hz, 1H) 3.79 - 3.92 (m, 2H) 3.39 - 3.47 (m, 1H) 3.19 (s, 3H) 3.13 (s, 1H) 2.84 (s, 2H) 2.57 - 2.69
25 (m, 1H) 1.13 (d, $J = 6.85$ Hz, 3H). LCMS: 406 [M+1].

Compound 015: N-(3-chloro-4-fluoro-phenyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide.



Step 1. 10-methyl -2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one.

Tert-butyl 10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4] diazepine-2-carboxylate (Intermediate 4, 40.00 mg, 124.85 μ mol, 1.00 *eq*) was dissolved in TFA (2.46 g, 21.61 mmol, 1.60 mL, 173.09 *eq*) and stirred at 10 °C for 1 hr. TLC (DCM:MeOH=10:1) showed the starting material consumed. The mixture was concentrated in vacuum. The residue was concentrated in vacuum to get 10-methyl -2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one as the TFA salt (42.00 mg, crude) as colorless oil.

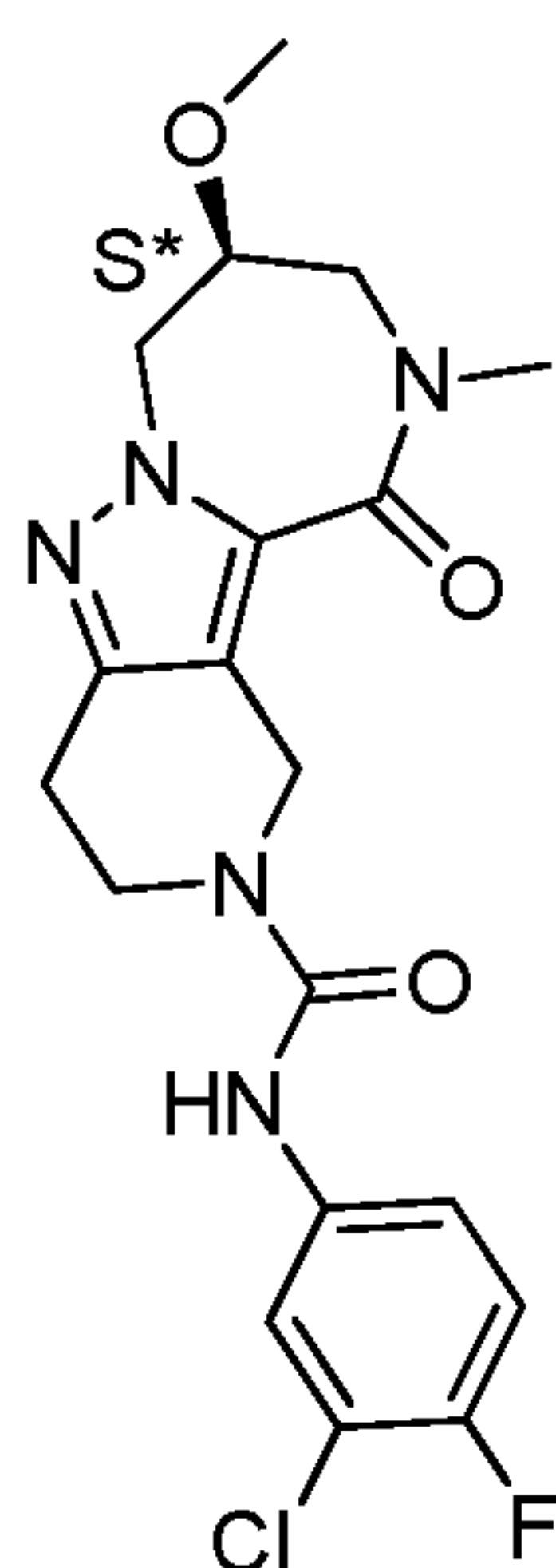
Step 2. N-(3-chloro-4-fluoro-phenyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido

[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide. To a solution of 10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4] diazepin-11-one (42.00 mg, 125.64 μ mol, 1.00 *eq*, TFA) in DCM (3.00 mL) was added phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (33.38 mg, 125.64 μ mol, 1.00 *eq*) followed by TEA (63.57 mg, 628.20 μ mol, 87.08 μ L, 5.00 *eq*). The mixture was stirred at 10 °C for 16 hr. LCMS showed one main peak with desired Ms. The mixture was concentrated in vacuum. The residue was purified by prep-HPLC (FA) to afford title compound (33.00 mg, 84.22 μ mol, 67.03% yield, 100% purity) as white solid. ^1H NMR (400MHz, METHANOL- d_4) δ = 7.60 (dd, J = 2.6, 6.7 Hz, 1 H), 7.31 (ddd, J = 2.6, 4.1, 9.0 Hz, 1 H), 7.11 - 7.19 (m, 1 H), 4.70 (s, 2 H), 4.37 (t, J = 7.0 Hz, 2 H), 3.83 (t, J = 5.8 Hz, 2 H), 3.45 - 3.53 (m, 2 H), 3.17 (s, 3 H), 2.82 (t, J = 5.8 Hz, 2 H), 2.28 - 2.38 (m, 2 H).

Compound 016A: (S*)-N-(3-chloro-4-fluorophenyl)-8-methoxy-10-methyl-11-oxo-

3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide.

* pure but unknown stereochemistry E1.



Step 1. tert-butyl 8-methoxy-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate.

To a solution of tert-butyl 8-hydroxy-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido [2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (Intermediate 3, 90.00 mg, 267.55 μ mol, 1.00 *eq*) in THF (4.00 mL) was added NaH (16.05 mg, 401.32 μ mol, 60% purity, 1.50 *eq*) at 0 °C, followed by MeI (75.95 mg, 535.09 μ mol, 33.31 μ L, 2.00 *eq*) after 0.5 h. The mixture was stirred at 15 °C for 1 h. The mixture was diluted with brine (30 mL), extracted with EtOAc (30 mL, *2). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo to give yellow oil, which was purified by prep-TLC to the title compound (70.00 mg, 184.78 μ mol, 69.07% yield, 92.5% purity) as yellow solid. LCMS: 373[M+23].

Step 2. 8-methoxy-10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido [2,3]pyrazolo [2,4-b][1,4]diazepin-11-one.

To a solution of tert-butyl 8-methoxy-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido [2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (70.00 mg, 199.77 μ mol, 1.00 *eq*) in DCM (2.00 mL) was added TFA (3.08 g, 27.01 mmol, 2.00 mL, 135.22 *eq*) and the mixture was stirred at 15 °C under N₂ for 1 h. The mixture was concentrated in vacuo to afford the title compound as the TFA salt (72.00 mg, 177.87 μ mol, 89.04% yield, 90% purity) as yellow oil, which was used directly for the next step. LCMS: 251[M+1].

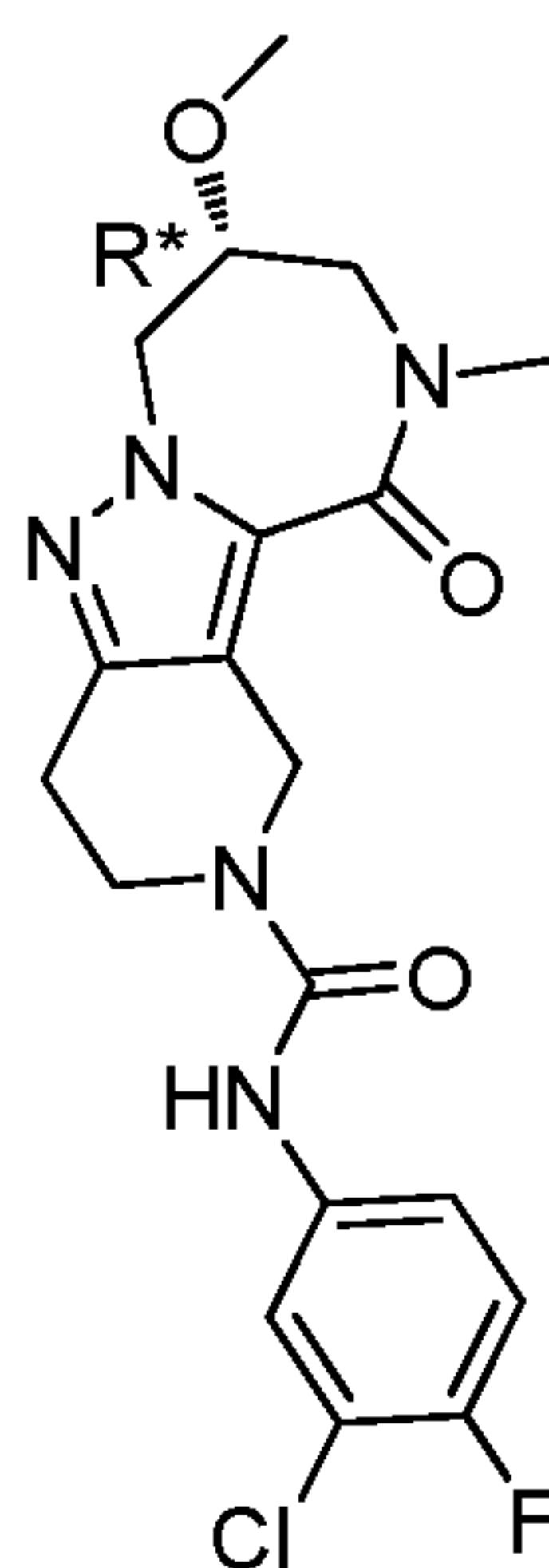
Step 3. (S*)-N-(3-chloro-4-fluorophenyl)-8-methoxy-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide.

A mixture of 8-methoxy-10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido [2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (77.00 mg, 211.35 μ mol, 1.00 *eq*, TFA), Et₃N (106.93 mg, 1.06 mmol, 146.48 μ L, 5.00 *eq*) and phenyl N- (3-chloro-4-fluoro-phenyl)carbamate (56.15 mg, 211.35 μ mol, 1.00 *eq*) in DCM (4.00 mL) was stirred at 15 °C for 16 h. The mixture was diluted with DCM (30 mL*2)

and washed with HCl (1 N, 30 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo to give yellow oil. The oil was purified by prep-HPLC (FA) to get 48 mg of desired product which was resolved via SFC (OD-3S_4_40_3ML Column: Chiralcel OD-3 100×4.6mm I.D., 3µm Mobile phase: 40% iso-propanol (0.05% DEA) in CO₂ Flow rate:

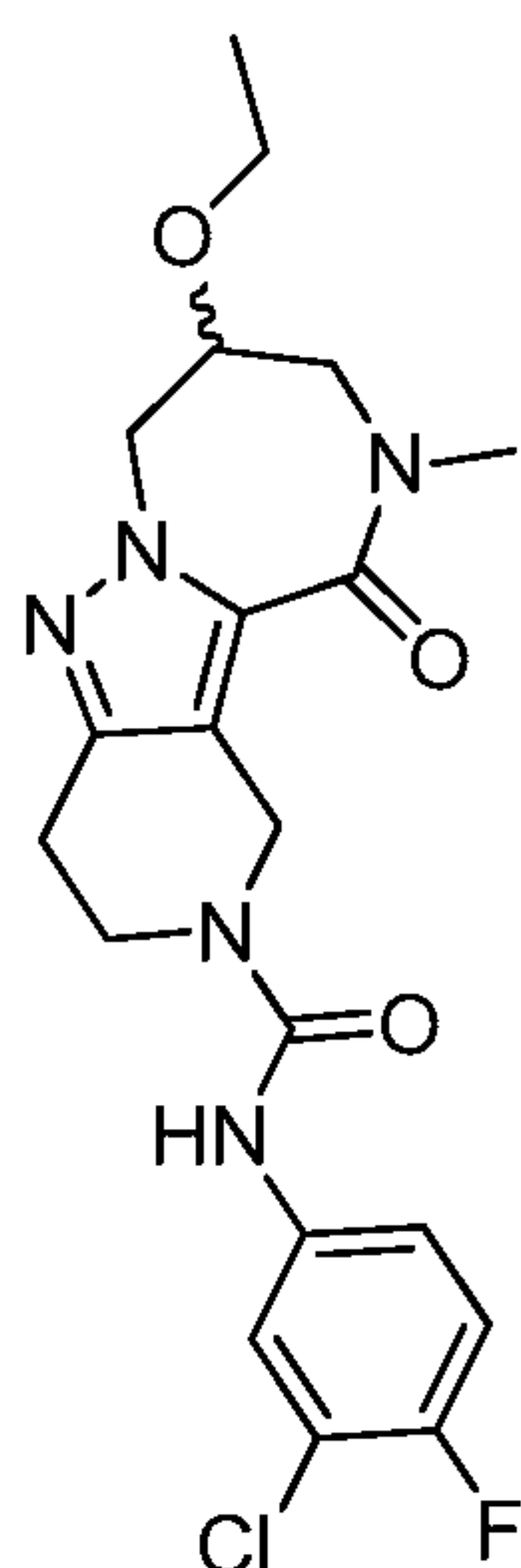
5 3mL/min Wavelength: 220 nm) and further purified by prep-HPLC(FA) to get both enantiomers Compound 016_E1 (17.9 mg) and Compound 016_E2 (15.4 mg). LCMS: 422/424 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (dd, *J* = 2.63, 6.54 Hz, 1H), 7.16 - 7.23 (m, 1H), 7.03 - 7.10 (m, 1H), 6.55 (s, 1H), 4.68 (d, *J* = 5.26 Hz, 2H), 4.57 (dd, *J* = 6.24, 14.43 Hz, 1H), 4.29 (dd, *J* = 5.93, 14.37 Hz, 1H), 4.08 (br t, *J* = 5.01 Hz, 1H), 3.86 (q, *J* = 5.75 Hz, 2H), 3.40 - 3.58 (m, 5H),
10 3.21 (s, 3H).

Compound 016B: (R*)-N-(3-chloro-4-fluorophenyl)-8-methoxy-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide.
* pure but unknown stereochemistry E2.



15 LCMS: 422/424 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (dd, *J* = 2.63, 6.54 Hz, 1H), 7.16 - 7.23 (m, 1H), 7.03 - 7.10 (m, 1H), 6.55 (s, 1H), 4.68 (d, *J* = 5.26 Hz, 2H), 4.57 (dd, *J* = 6.24, 14.43 Hz, 1H), 4.29 (dd, *J* = 5.93, 14.37 Hz, 1H), 4.08 (br t, *J* = 5.01 Hz, 1H), 3.86 (q, *J* = 5.75 Hz, 2H), 3.40 - 3.58 (m, 5H), 3.21 (s, 3H).

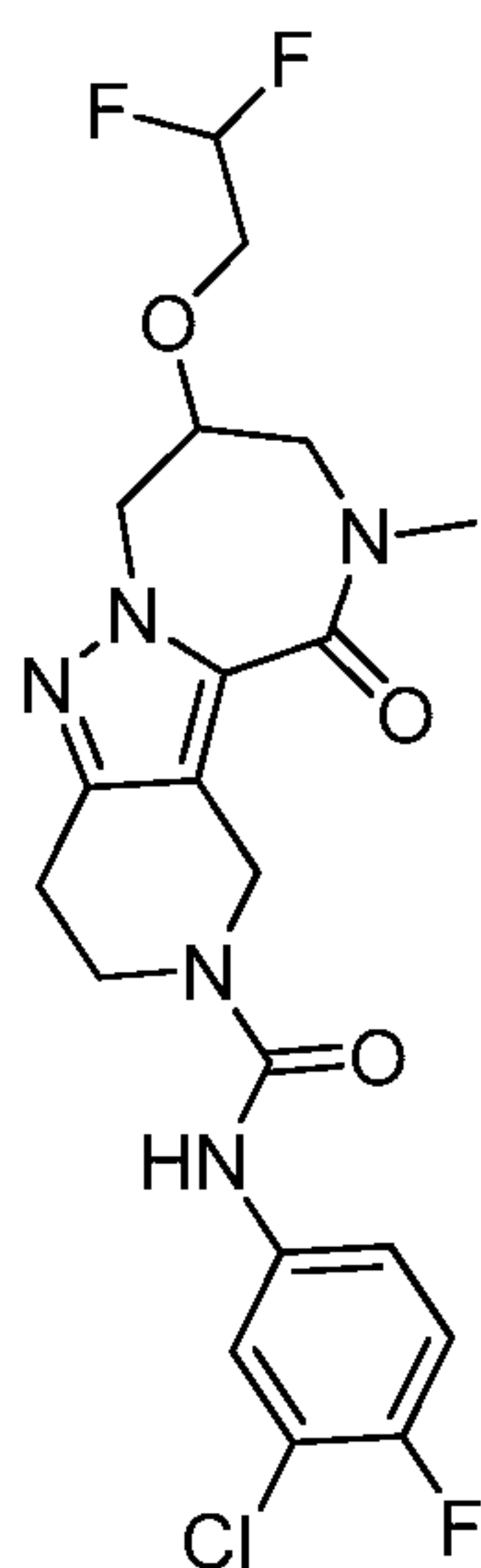
20 Compound 017: N-(3-chloro-4-fluorophenyl)-8-ethoxy-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



The title compound was prepared in a manner analogous to Compound 016, using EtI instead of MeI in Step 1; to give yellow oil, which was purified by prep-HPLC(FA) to afford the title compound (76.90 mg, 168.13 μ mol, 56.80% yield, 95.3% purity) as white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.59 (dd, J = 2.64, 6.52 Hz, 1 H), 7.20 (ddd, J = 2.70, 4.08, 8.91 Hz, 1 H), 7.02 - 7.10 (m, 1 H), 6.60 (s, 1 H), 4.62 - 4.76 (m, 2 H), 4.57 (dd, J = 6.34, 14.24 Hz, 1 H), 4.21 - 4.34 (m, 1 H), 4.12 - 4.21 (m, 1 H), 3.86 (t, J = 6.27 Hz, 2 H), 3.64 (ddt, J = 2.13, 7.00, 13.76 Hz, 2 H), 3.47 (dq, J = 4.58, 15.04 Hz, 2 H), 3.21 (s, 3 H), 2.85 (q, J = 5.48 Hz, 2 H), 1.27 (t, J = 6.96 Hz, 3 H). LCMS: 436/438 $[\text{M}+1]$.

10

Compound 018: N-(3-chloro-4-fluorophenyl)-8-(2,2-difluoroethoxy)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



The title compound was prepared in a manner analogous to Compound 016, using 2, 2-difluoroethyl trifluoromethanesulfonate instead of MeI in Step 1.

Step 1. tert-butyl-8-(2,2-difluoroethoxy)-10-methyl-11-oxo-1,3,4,7,8,9-

5 hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of tert-butyl 8-hydroxy-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido [2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (100.00 mg, 297.27 μmol , 1.00 *eq*) in THF (3.00 mL) was added NaH (35.67 mg, 891.82 μmol , 22.70 μL , 60% purity, 3.00 *eq*) with stirring at 0 °C for 0.5 h under N₂. Then 2, 2-difluoroethyl trifluoromethanesulfonate (2.97 mmol, 10.00 *eq*) in DCM (7.4 mL) was added.
10 The mixture was stirred at 15 °C for 2 h. TLC showed that the starting material was consumed completely and one main spot formed. The mixture was poured into 10 mL of ice water and extracted with EtOAc (10 mL*3). The organic layers was combined and dried over anhydrous Na₂SO₄, filtered and concentrated. The resulting residue combined with another batch reaction mixture (50 mg of starting material) was purified by prep-TLC (PE: EtOAc = 1:5) to afford the
15 title compound (140.00 mg, 349.63 μmol , 78.41% yield) as off-white oil.

Step 2. 8-(2,2-difluoroethoxy)-10-methyl-2,3,4,7,8,9 -hexahydro-1H-pyrido[2,3]pyrazolo[2,4-

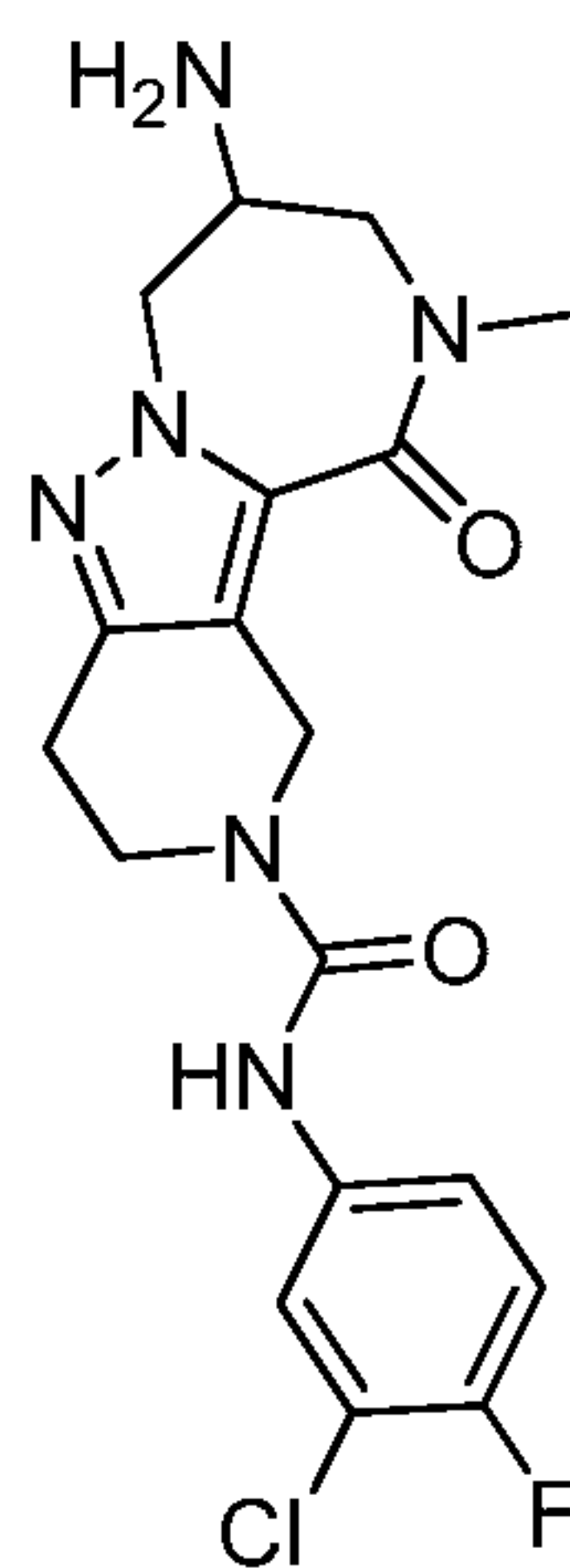
b][1,4]diazepin-11-one. To a solution of tert-butyl 8-(2,2-difluoroethoxy)-10-methyl-11-oxo-1,3,4,7,8,9- hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate(140.00 mg, 349.63 μmol , 1.00 *eq*) in DCM (2.00 mL) was added TFA (1.54 g, 13.51 mmol, 1.00 mL, 38.63
20 *eq*) with stirring at 15 °C for 1 h. TLC (PE: EtOAc=0:1) showed that the starting material was consumed completely and one major spot formed. The mixture was concentrated in vacuo to give the the title compound as the TFA salt (200.00 mg, crude) as yellow oil and directly used in the next step.

Step 3. N-(3-chloro-4-fluorophenyl)-8-(2,2-difluoroethoxy)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-

25 octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. To a solution of 8-(2,2-difluoroethoxy)-10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido [2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (144.86 mg, 349.62 μmol , 1.00 *eq*, TFA) and phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (102.17 mg, 384.59 μmol , 1.10 *eq*) in DCM (2.00 mL) was added TEA (283.03 mg, 2.80 mmol, 387.71 μL , 8.00 *eq*). The mixture was heated to 15 °C with stirring
30 for 16 h. LCMS indicated that reactant 8-(2,2-difluoroethoxy)-10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido [2,3]pyrazolo[2,4-b][1,4]diazepin-11-one was consumed completely and

the desired product was detected. The mixture was diluted with DCM (10 mL) and washed with HCl (1%, 10 mL*2) and brine (10 mL*1). The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated. The resulting residue was purified by prep-HPLC (FA) to give the title compound (93.60 mg, 189.64 μmol, 54.24% yield, 95.6% purity) as white solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.56 (br d, *J* = 5.75 Hz, 1 H), 7.14 - 7.21 (m, 1 H), 6.97 - 7.09 (m, 1 H), 6.66 (br s, 1 H), 5.73 - 6.06 (m, 1 H), 4.53 - 4.74 (m, 3 H), 4.22 - 4.32 (m, 2 H), 3.70 - 3.91 (m, 4 H), 3.39 - 3.58 (m, 2 H), 3.19 (s, 3 H), 2.75 - 2.89 (m, 2 H). LCMS [M+1]: 472.

Compound 019: 8-amino-N-(3-chloro-4-fluorophenyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. [2-[(3-chloro-4-fluoro-phenyl)carbamoyl]-10-methyl-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-8-yl]methanesulfonate. A mixture of N-(3-chloro-4-fluoro-phenyl)-8-hydroxy-10-methyl-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide (Compound 004, 200.00 mg, 490.40 μmol, 1.00 *eq*) and TEA (297.74 mg, 2.94 mmol, 407.87 μL, 6.00 *eq*) in DCM (5.00 mL) was added MsCl (224.70 mg, 1.96 mmol, 151.83 μL, 4.00 *eq*) at 0 °C under N₂, and then the mixture was stirred at 15 °C for 16 hours under N₂ atmosphere. The mixture was poured into water (5 mL) and stirred at 5 min. The aqueous phase was extracted with DCM (3 mL*2). The combined organic phase was washed with brine (5 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to afford the title compound (200.00 mg, 391.01 μmol, 79.73% yield, 95% purity) as a white solid, which was used directly for the next step. LCMS: 486/488 [M+1].

Step 2. 8-azido-N-(3-chloro-4-fluoro-phenyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydro

pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide. To a solution of [2-[(3-chloro-4-

fluoro-phenyl)carbamoyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydro-pyrido[2,3]pyrazolo[2,4-

b][1,4]diazepin-8-yl]methanesulfonate (120.00 mg, 246.95 μ mol, 1.00 *eq*) in DMF (2.00

5 mL) was added NaN₃ (32.11 mg, 493.91 μ mol, 17.36 μ L, 2.00 *eq*) and the resulting mixture

was heated to 65 °C for 32 h. The mixture was diluted with EtOAc (20 mL) and washed with

brine (20 mL *3). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo

to afford the title compound (106.00 mg, crude), which was used directly for the next step.

LCMS: 433/435 [M+1].

10 Step 3. 8-amino-N-(3-chloro-4-fluorophenyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-

2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. A mixture of 8-azido-N-(3-

chloro-4-fluoro-phenyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydro-pyrido[2,3]pyrazolo[2,4-

b][1,4]diazepine-2-carboxamide (120.00 mg, 277.24 μ mol, 1.00 *eq*), NH₄Cl (37.07 mg, 693.10

μ mol, 24.23 μ L, 2.50 *eq*) and Zn (27.19 mg, 415.86 μ mol, 1.50 *eq*) in H₂O (500.00 μ L)/EtOH

15 (5.00 mL) was stirred at 30 °C for 16 hours. The mixture was filtered and the filtrate was

concentrated in vacuo. The residue was purified by prep-HPLC(FA) to afford (59.40 mg, 144.54

μ mol, 52.14% yield, 99% purity) as yellow solid. LCMS: 407/409 [M+1]. ¹H NMR (400 MHz,

CDCl₃) δ 8.04 (s, 1 H), 7.61 (dd, *J* = 2.64, 6.53 Hz, 1 H), 7.18 - 7.24 (m, 1 H), 7.04 - 7.11 (m, 1

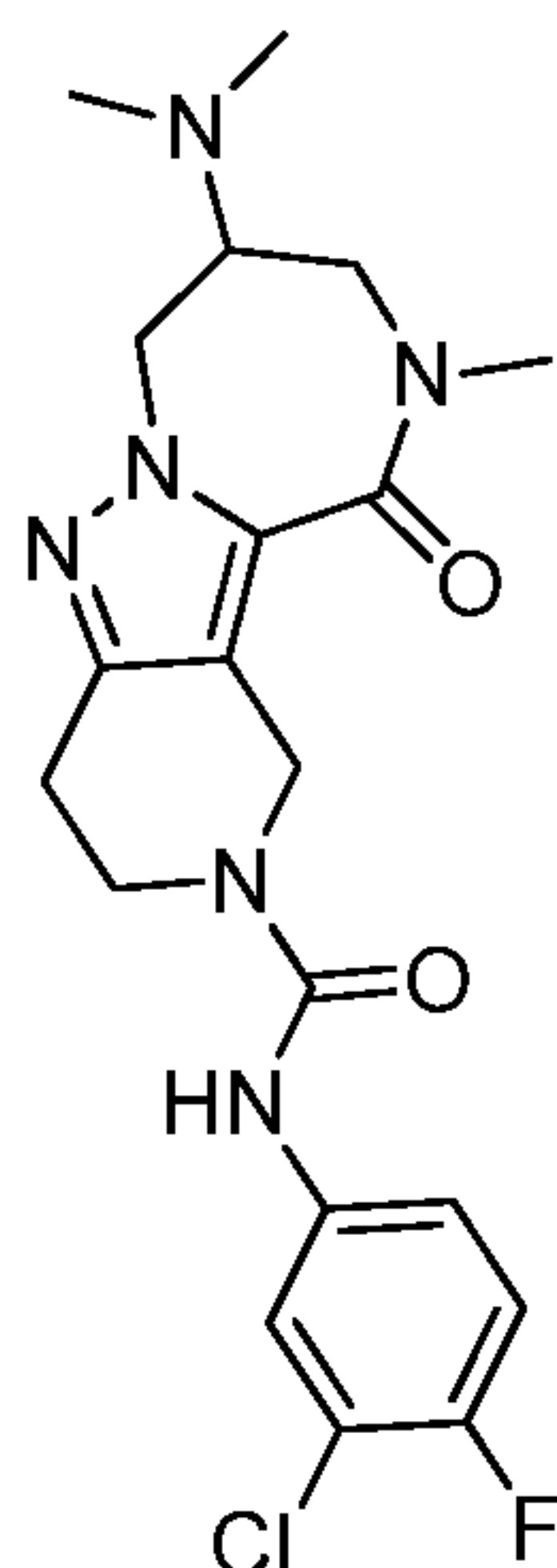
H), 6.62 (s, 1 H), 4.69 (d, *J* = 3.26 Hz, 2 H), 4.54 (dd, *J* = 6.02, 14.30 Hz, 1 H), 4.12 (dd, *J* =

20 4.83, 14.24 Hz, 1 H), 3.77 - 3.92 (m, 3 H), 3.54 (dd, *J* = 5.14, 14.81 Hz, 1 H), 3.11 - 3.27 (m, 4

H), 2.86 (t, *J* = 5.83 Hz, 2 H).

Compound 020: N-(3-chloro-4-fluorophenyl)-8-(dimethylamino)-10-methyl-11-oxo-

1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. tert-butyl 8-(dimethylamino)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido

[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To solution of N-methylmethanamine (87.79

mg, 1.08 mmol, 98.64 μ L, 3.00 *eq*, HCl) in THF (3.00 mL) was added AcONa (88.32 mg, 1.08

mmol, 3.00 *eq*), tert-butyl 10-methyl-8,11-dioxo-3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-

b][1,4]diazepine-2-carboxylate (Intermediate 2, 120.00 mg, 358.88 μ mol, 1.00 *eq*),

tetraethoxytitanium (245.59 mg, 1.08 mmol, 223.26 μ L, 3.00 *eq*) and CH₃COOH (adjusted pH

to 6), and the mixture was stirred at 75 °C for 16 h. NaBH₃CN (22.55 mg, 358.88 μ mol, 1.00 *eq*)

was added at 15 °C and the mixture was stirred for another 2 h. The mixture was diluted with

EtOAc (40 mL) and brine (20 mL) and filtered. The filtrate was washed with brine (40 mL).

The organic phase was dried over Na₂SO₄, filtrated and concentrated in vacuo, which was

purified by prep-TLC twice to afford the title compound (43.00 mg, 100.56 μ mol, 28.02% yield,

85% purity) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 4.50 - 4.60 (m, 2H), 4.46 - 4.48 (m,

1H), 4.25 - 4.30 (m, 1H), 3.78 - 3.82 (m, 1H), 3.52 - 3.56 (m, 2H), 3.17 - 3.35 (m, 5H), 2.70 -

2.80 (m, 2H), 2.35 (s, 6H), 1.49 (s, 9H). LCMS: 364[M+1].

Step 2. 8-(dimethylamino)-10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-

b][1,4]diazepin-11-one. To a solution of tert-butyl 8-(dimethylamino)-10-methyl-11-oxo-

1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (43.00 mg,

100.56 μ mol, 1.00 *eq*) in DCM (1.00 mL) was added TFA (1.54 g, 13.51 mmol, 1.00 mL, 134.31

eq) and the mixture was stirred at 15 °C under N₂ for 1 h. TLC showed the reactant was

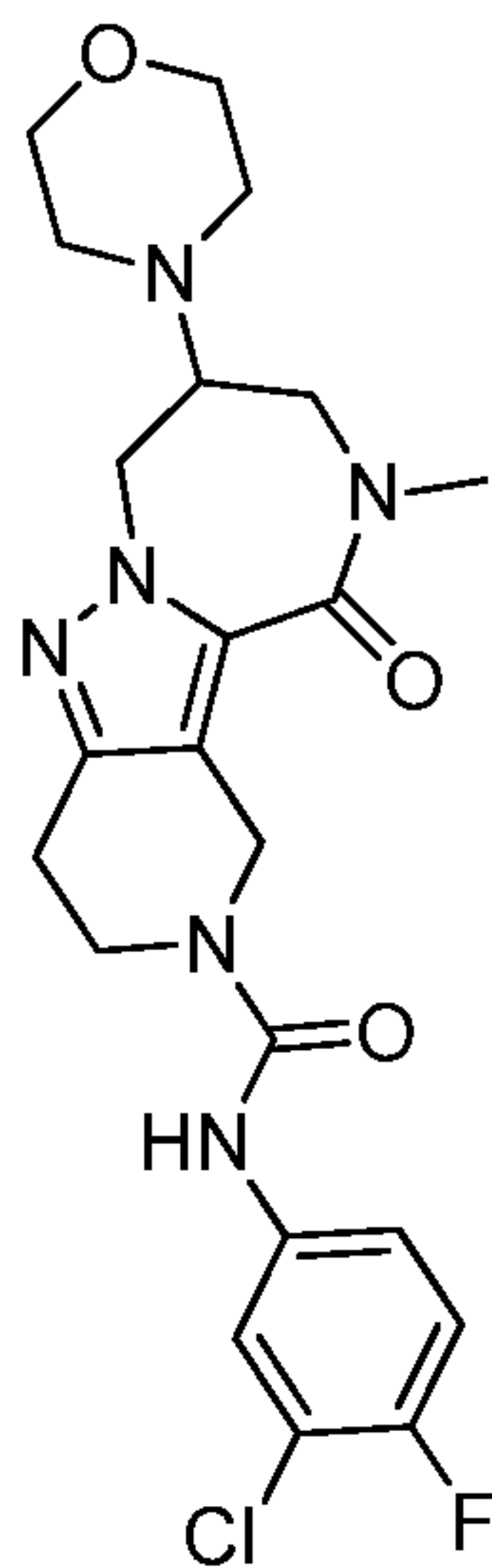
consumed completely and one major new spot with larger polarity was detected. The mixture

was concentrated in vacuo to afford the title compound (38.00 mg, crude, TFA) as yellow oil,

which was used directly for the next step. LCMS: 264 [M+1].

Step 3. N-(3-chloro-4-fluorophenyl)-8-(dimethylamino)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. A mixture of 8-(dimethylamino)-10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido [2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (38.00 mg, 100.70 μ mol, 1.00 *eq*, TFA), Et₃N (50.95 mg, 503.50 μ mol, 69.79 μ L, 5.00 *eq*) and phenyl N- (3-chloro-4-fluoro-phenyl)carbamate (26.75 mg, 100.70 μ mol, 1.00 *eq*) in DCM (4.00 mL) was stirred at 15 °C for 16 h. The mixture was diluted with DCM (30 mL) and washed with HCl (1M, 30 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo to give yellow oil. The oil was purified by prep-HPLC (FA) to afford the title compound (33.00 mg, 75.12 μ mol, 74.60% yield, 99% purity) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.10 (s, 1H), 7.60 (dd, *J* = 2.69, 6.48 Hz, 1H), 7.19 - 7.25 (m, 1H), 7.02 - 7.11 (m, 1H), 6.71 (s, 1H), 4.53 - 4.80 (m, 3H), 4.35 (dd, *J* = 6.30, 14.86 Hz, 1H), 3.80 - 3.93 (m, 2H), 3.54 - 3.65 (m, 1H), 3.38 - 3.50 (m, 2H), 3.20 (s, 3H), 2.85 (t, *J* = 5.75 Hz, 2H), 2.42 (s, 6H). LCMS: 435/437[M+1].

Compound 021: N-(3-chloro-4-fluorophenyl)-10-methyl-8-morpholino-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. tert-butyl 10-methyl-8-morpholino-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. A mixture of tert-butyl 10-methyl-8,11-dioxo-3,4,7,9-tetrahydro-1H-pyrido[2,3] pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (Intermediate 2, 150.00 mg, 448.60 μ mol, 1.00 *eq*), morpholine (78.16 mg, 897.20

μmol, 78.95 μL, 2.00 *eq*), CH₃COOH (26.94 mg, 448.60 μmol, 25.66 μL, 1.00 *eq*) and 4A molecular sieve (250.00 mg) in DCE (4.00 mL) was stirred at 20 °C for 3 h. NaBH₃CN (140.95 mg, 2.24 mmol, 5.00 *eq*) was added and the mixture was stirred at 20 °C for 16 h. The mixture was diluted with EtOAc (40 mL) and washed with brine (30 mL). The organic phase was dried over Na₂SO₄, filtrated and concentrated in vacuo to give oil, which was purified by prep-TLC to afford the title compound (72.00 mg, 174.01 μmol, 38.79% yield, 98% purity) as yellow oil.

LCMS: 406[M+1].

Step 2. 10-methyl-8-morpholino- 2,3,4,7,8,9-hexahydro-1H- pyrido[2,3]pyrazolo[2,4-

b][1,4]diazepin-11-one. To a solution of tert-butyl 10-methyl-8-morpholino-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (78.00 mg, 192.36 μmol, 1.00 *eq*) in DCM (2.00 mL) was added TFA (3.08 g, 27.01 mmol, 2.00 mL, 140.43 *eq*) and the mixture was stirred at 15 °C under N₂ for 1 h . The mixture was concentrated in vacuo to afford the title compound as the TFA salt (80.00 mg, 190.75 μmol, 99.16% yield) as yellow oil, which was used directly for the next step.

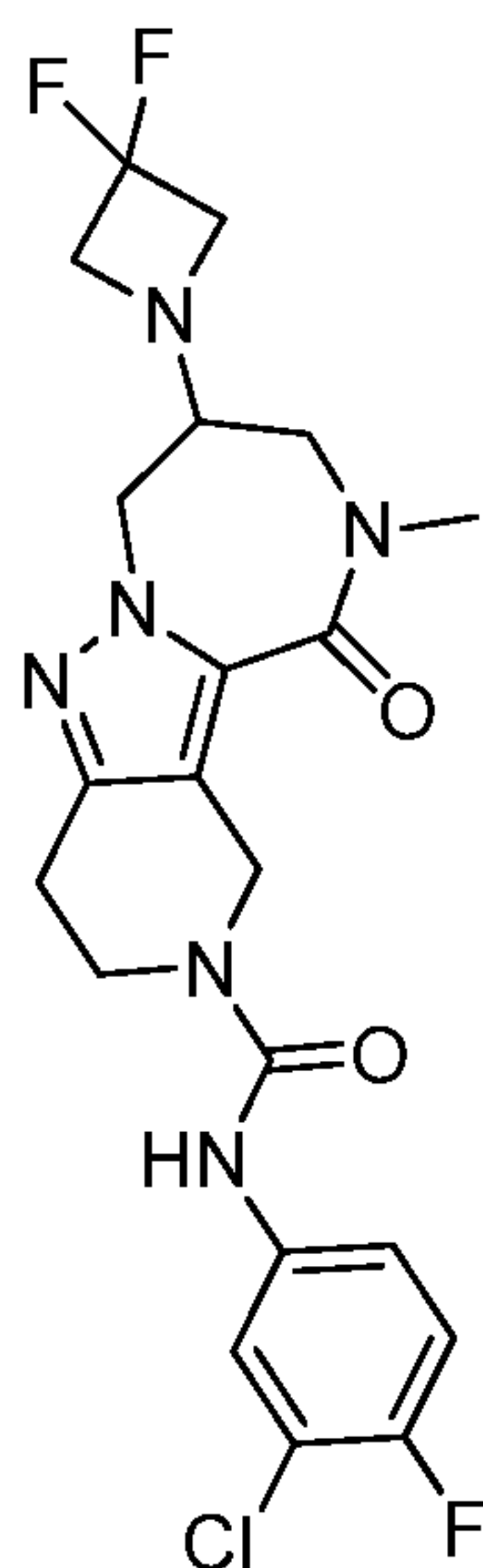
Step 3. N-(3-chloro-4-fluorophenyl)-10-methyl-8-morpholino-11-oxo-1,3,4,7,8,9,10,11-

octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. A mixture of 10-

methyl-8-morpholino-2,3,4,7,8,9-hexahydro-1H-pyrido [2,3]pyrazolo [2,4-b][1,4]diazepin-11-one (80.00 mg, 190.75 μmol, 1.00 *eq*, TFA), Et₃N (96.51 mg, 953.75 μmol, 132.21 μL, 5.00 *eq*) and phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (55.74 mg, 209.83 μmol, 1.10 *eq*) in

DCM (5.00 mL) was stirred at 25 °C for 16 h. The mixture was diluted with DCM (30 mL) and washed with HCl (1 M, 30 mL*2). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting residue was purified by prep-HPLC(FA) to afford the title compound (53.00 mg, 116.02 μmol, 57.68% yield, 99% purity) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.60 (dd, *J* = 2.63, 6.54 Hz, 1 H), 7.18 - 7.25 (m, 1 H), 7.03 - 7.11 (m, 1 H), 6.62 (s, 1 H), 4.69 (d, *J* = 12.23 Hz, 2 H), 4.58 (dd, *J* = 3.91, 14.67 Hz, 1 H), 4.36 (dd, *J* = 6.36, 14.67 Hz, 1 H), 3.78 - 3.96 (m, 2 H), 3.73 (br t, *J* = 4.10 Hz, 4 H), 3.55 - 3.65 (m, 1 H), 3.39 (br d, *J* = 10.88 Hz, 2 H), 3.20 (s, 3 H), 2.86 (t, *J* = 5.75 Hz, 2 H), 2.66 - 2.76 (m, 2 H), 2.52 - 2.63 (m, 2 H). LCMS: 477/479[M+1].

Compound 022: N-(3-chloro-4-fluorophenyl)-8-(3,3-difluoroazetidin-1-yl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. tert-butyl 8-(3,3- difluoroazetidin-1-yl)-10-methyl-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. A mixture of 3,3-

difluoroazetidine;hydrochloride (116.22 mg, 897.20 μ mol, 2.00 *eq*) and NaOAc (73.60 mg,

897.20 μ mol, 2.00 *eq*) in DCE (4.00 mL) was stirred at 25 °C for 0.5 h, tert-butyl 10-methyl-

8,11-dioxo-3,4,7,9-tetrahydro-1H-pyrido[2,3] pyrazolo[2,4-b] [1,4]diazepine-2-carboxylate

(Intermediate 2, 150.00 mg, 448.60 μ mol, 1.00 *eq*) and 4A molecular sieve (250.00 mg) was

added and the mixture was stirred for 3 h. NaBH₃CN (140.95 mg, 2.24 mmol, 5.00 *eq*) was

added and the mixture was stirred at 25 °C for 16 h. The mixture was diluted with EtOAc (40

mL) and washed with brine (30 mL). The organic phase was dried over Na₂SO₄, filtrated and

concentrated in vacuo to give oil, which was purified by prep-TLC to afford the title compound

(120.00 mg, 288.73 μ mol, 64.36% yield, 99% purity) as yellow oil. LCMS: 412[M+1].

Step 2. 8-(3,3-difluoroazetidin-1-yl)-10-methyl-2,3,4,7,8,9- hexahydro-1H-

pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one. To a solution of tert-butyl 8-(3,3-

difluoroazetidin-1-yl)-10-methyl-11-oxo-1,3,4,7,8,9 -hexahydropyrido[2,3]pyrazolo[2,4-

b][1,4]diazepine-2-carboxylate (80.00 mg, 194.43 μ mol, 1.00 *eq*) in DCM (2.00 mL) was added

TFA (3.08 g, 27.01 mmol, 2.00 mL, 138.93 *eq*) and the mixture was stirred at 15 °C under N₂ for

1 h. The mixture was concentrated in vacuo to afford the title compound (82.00 mg, 192.78

μ mol, 99.15% yield, TFA) as yellow oil, which was used directly for the next step.

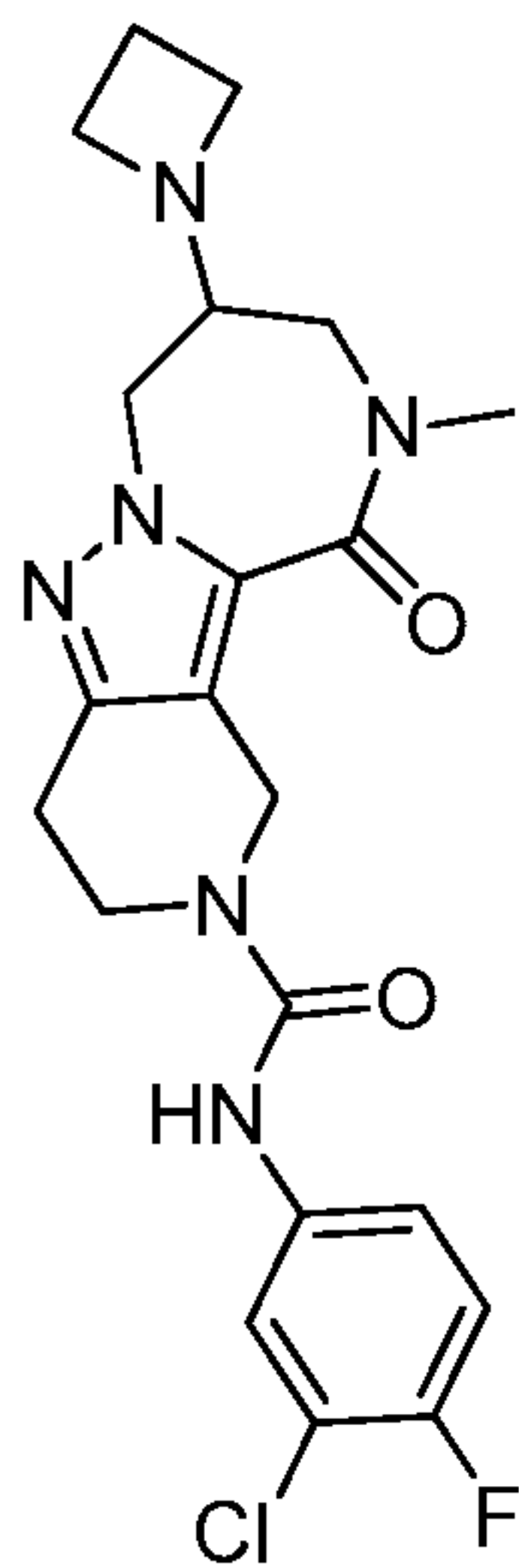
Step 3. N-(3-chloro-4-fluorophenyl)-8-(3,3-difluoroazetidin-1-yl)-10-methyl-11-oxo-

1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

A mixture of 8-(3,3-difluoroazetidin-1-yl)-10-methyl-2,3,4,7,8,9-hexahydro-1H-

pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (82.00 mg, 192.78 μ mol, 1.00 *eq*, TFA), Et₃N (97.54 mg, 963.91 μ mol, 133.61 μ L, 5.00 *eq*) and phenyl N-(3-chloro-4-fluorophenyl)carbamate (56.34 mg, 212.06 μ mol, 1.10 *eq*) in DCM (5.00 mL) was stirred at 22 °C for 16 h. The mixture was diluted with DCM (30 mL) and washed with HCl (1 M, 30 mL*2). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting residue was purified by prep-HPLC(FA) to afford the title compound (50.00 mg, 102.51 μ mol, 53.17% yield, 99% purity) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (dd, *J* = 2.64, 6.53 Hz, 1 H), 7.16 - 7.24 (m, 1 H), 7.02 - 7.11 (m, 1 H), 6.56 (s, 1 H), 4.68 (d, *J* = 1.76 Hz, 2 H), 4.40 (dd, *J* = 6.09, 14.12 Hz, 1 H), 4.13 (dd, *J* = 5.96, 14.12 Hz, 1 H), 3.82 - 3.93 (m, 2 H), 3.74 (br d, *J* = 4.89 Hz, 4 H), 3.36 - 3.47 (m, 1 H), 3.20 (s, 5 H), 2.86 (br d, *J* = 5.02 Hz, 2 H), 2.03 (s, 1 H). LCMS: 483/485 [M+1].

Compound 023: 8-(azetidin-1-yl)-N-(3-chloro-4-fluorophenyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



15

Step 1. tert-butyl 8-(azetidin-1-yl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. A mixture of azetidine (51.23 mg, 897.20 μ mol, 60.27 μ L, 2.00 *eq*) and NaOAc (73.60 mg, 897.20 μ mol, 2.00 *eq*) in DCE (4.00 mL) was stirred at 25 °C for 0.5 h, tert-butyl 10-methyl-8,11-dioxo-3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (Intermediate 2, 150.00 mg, 448.60 μ mol, 1.00 *eq*) and 4A molecular sieve (250.00 mg) was added and the mixture was stirred for 3 h. NaBH₃CN (140.95 mg, 2.24 mmol, 5.00 *eq*) was added and the mixture was stirred at 25 °C

20

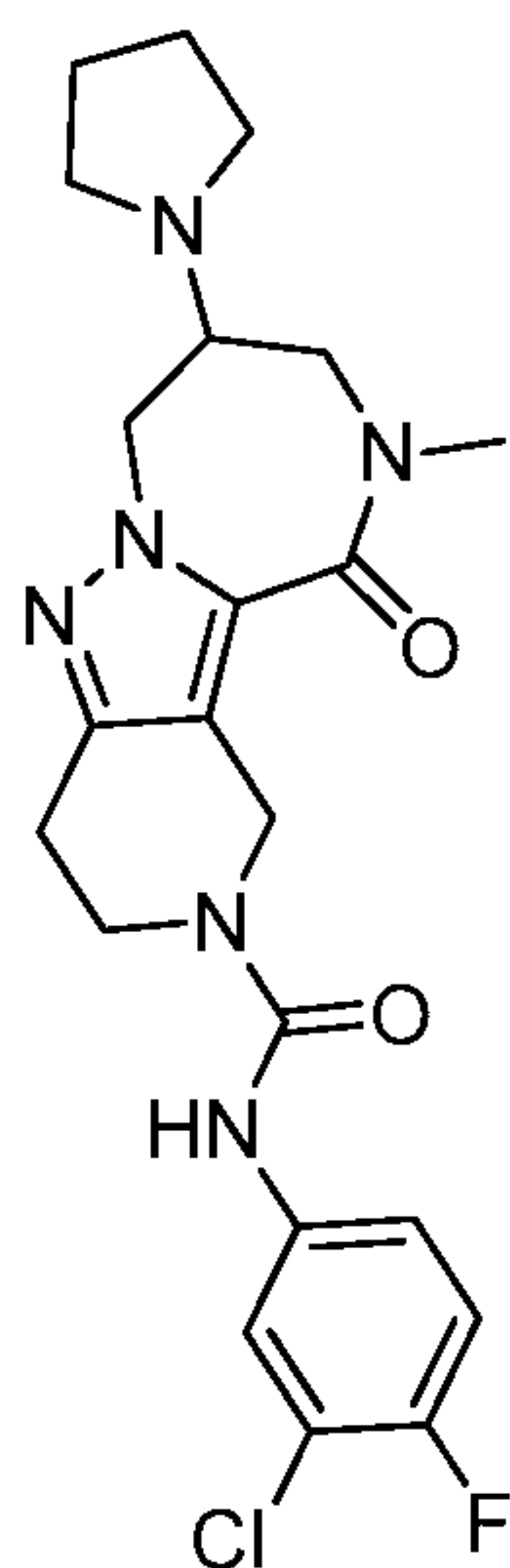
for 16 h. The mixture was diluted with EtOAc (40 mL) and brine (30 mL). The organic phase was dried over Na₂SO₄, filtrated and concentrated in vacuo. The resulting oil was purified by prep-TLC to afford the title compound (85.00 mg, 181.11 μmol, 40.37% yield, 80% purity) as yellow oil. LCMS: 398[M+23].

5 Step 2. 8-(azetidin-1-yl)-10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one. To a solution of tert-butyl 8-(azetidin-1-yl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (106.25 mg, 226.38 μmol, 1.00 *eq*) in DCM (2.00 mL) was added TFA (3.08 g, 27.01 mmol, 2.00 mL, 119.33 *eq*) and the mixture was stirred at 15 °C under N₂ for 1 h. The mixture was concentrated in
10 vacuo to afford the title compound (88.00 mg, 226.01 μmol, 99.83% yield, TFA) as yellow oil, which was used directly for the next step.

Step 3. 8-(azetidin-1-yl)-N-(3-chloro-4-fluorophenyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. A mixture of 8-(azetidin-1-yl)-10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-
15 11-one (88.00 mg, 226.01 μmol, 1.00 *eq*, TFA), Et₃N (114.35 mg, 1.13 mmol, 156.64 μL, 5.00 *eq*) and phenyl N-(3-chloro-4-fluoro-phenyl) carbamate (66.05 mg, 248.61 μmol, 1.10 *eq*) in DCM (5.00 mL) was stirred at 15 °C for 16 h. The mixture was diluted with DCM (30 mL) and washed with HCl (1 M, 30 mL*2). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo to give residue, which was purified by prep-HPLC(FA) to afford the title
20 compound (52.80 mg, 118.15 μmol, 52.28% yield) as yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.06 (s, 1H), 7.60 (dd, *J* = 2.69, 6.60 Hz, 1 H), 7.17 - 7.25 (m, 1 H), 7.03 - 7.11 (m, 1 H), 6.64 (s, 1 H), 4.68 (s, 2 H), 4.34 - 4.45 (m, 1 H), 4.20 - 4.33 (m, 1 H), 3.76 - 3.96 (m, 2 H), 3.53 (br s, 5 H), 3.29 (br s, 2 H), 3.19 (s, 3 H), 2.80 - 2.89 (m, 2 H), 2.26-2.30 (m, 2 H). LCMS: 447/449[M+1].

25

Compound 024: N-(3-chloro-4-fluorophenyl)-10-methyl-11-oxo-8-(pyrrolidin-1-yl)-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. tert-butyl 10-methyl-11-oxo-8-pyrrolidin-1-yl-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. A mixture of tert-butyl 10-

5 methyl-8,11-dioxo-3,4,7,9-tetrahydro-1H-pyrido[2,3] pyrazolo[2,4-b][1,4]diazepine-2-
carboxylate (Intermediate 2, 150.00 mg, 448.60 μmol , 1.00 *eq*), pyrrolidine (63.81 mg, 897.20
 μmol , 75.07 μL , 2.00 *eq*), CH_3COOH (26.94 mg, 448.60 μmol , 25.66 μL , 1.00 *eq*) and 4A
molecular sieve (250.00 mg, 448.60 μmol , 1.00 *eq*) in DCE (4.00 mL) was stirred at 20 °C for 3
h. NaBH_3CN (140.95 mg, 2.24 mmol, 5.00 *eq*) was added and the mixture was stirred at 20 °C
10 for 16 h. The mixture was diluted with EtOAc (40 mL) and washed with brine (60 mL). The
organic phase was dried over Na_2SO_4 , filtrated and concentrated in vacuo to give oil, which was
purified by prep-TLC to afford the title compound (138.00 mg, 350.77 μmol , 78.19% yield, 99%
purity) as yellow oil. LCMS: 390[M+1].

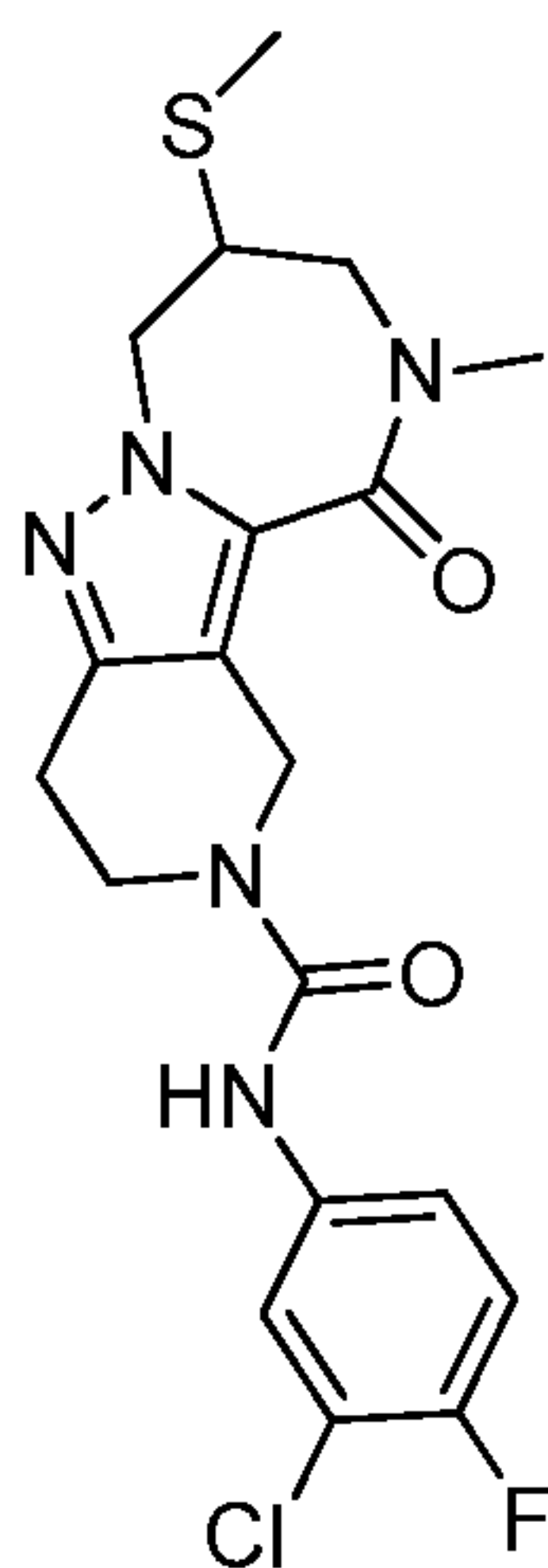
Step 2. 10-methyl-8-pyrrolidin-1-yl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-

b][1,4]diazepin-11-one. To a solution of tert-butyl 10-methyl-11-oxo-8-pyrrolidin-1-yl-
15 1,3,4,7,8,9- hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (80.00 mg,
205.40 μmol , 1.00 *eq*) in DCM (4.50 mL) was added TFA (6.93 g, 60.78 mmol, 4.50 mL, 295.90
eq) and the mixture was stirred at 20 °C under N_2 for 1 h. The mixture was concentrated in
vacuo to afford the title compound (82.86 mg, 205.40 μmol , 100.00% yield, TFA) as yellow oil,
which was used directly for the next step.

20 Step 3. N-(3-chloro-4-fluorophenyl)-10-methyl-11-oxo-8-(pyrrolidin-1-yl)-1,3,4,7,8,9,10,11-
octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. A mixture of 10-
methyl-8-pyrrolidin-1-yl-2,3,4,7,8,9-hexahydro-1H-pyrido [2,3] pyrazolo[2,4-b][1,4]diazepin-

11-one (82.86 mg, 205.40 μ mol, 1.00 *eq*, TFA), Et₃N (103.92 mg, 1.03 mmol, 142.36 μ L, 5.00 *eq*) and phenyl N- (3-chloro-4-fluoro-phenyl) carbamate (60.03 mg, 225.94 μ mol, 1.10 *eq*) in DCM (5.00 mL) was stirred at 22 °C for 16 h. The mixture was diluted with DCM (30 mL) and washed with HCl (1 M, 30 mL*2). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by prep-HPLC(FA) to afford the title compound (21.65 mg, 46.50 μ mol, 22.64% yield, 99% purity) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.56 – 7.58 (m, 1 H), 7.18 - 7.19 (m, 1 H), 7.02 – 7.06 (m, 1 H), 6.71 (s, 1 H), 4.66 – 4.72 (m, 2 H), 4.49-4.55 (m, 2 H), 3.83 – 3.88 (m, 2 H), 3.63 - 3.65 (m, 3 H), 3.18 (s, 3 H), 2.96 - 3.04 (m, 4 H), 2.82 – 2.85 (m, 2 H), 1.95-2.00 (m, 4 H). LCMS: 461/463 [M+1].

Compound 025: N-(3-chloro-4-fluorophenyl)-10-methyl-8-(methylthio)-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. [2-[(3-chloro-4-fluoro-phenyl)carb amoyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-8-yl] methanesulfonate. A mixture of N-(3-chloro-4-fluoro-phenyl)-8-hydroxy-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide (Compound 004, 100.00 mg, 245.20 μ mol, 1.00 *eq*), TEA (49.62 mg, 490.40 μ mol, 67.97 μ L, 2.00 *eq*) in DCM (5.00 mL) was added MsCl (42.13 mg, 367.80 μ mol, 28.47 μ L, 1.50 *eq*) at 0 °C under N₂, and then the mixture was stirred at 15 °C for 16 hr under N₂ atmosphere. TLC showed the starting material/desired product=1/3. Then MsCl (14 mg, 122.6 μ mol, 9.49 μ L, 0.50 *eq*) was added to the mixture, the mixture was stirred at 15 °C for 4 hr, TLC showed the starting material/desired

product=1/3. The mixture was stirred at 50 °C for 2 hr, TLC showed the starting material/
desired product=1/3. The mixture was poured into water (5 mL) and stirred at 5 min. The
aqueous phase was extracted with ethyl acetate (3 mL*2). The combined organic phase was
washed with brine (5 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum.

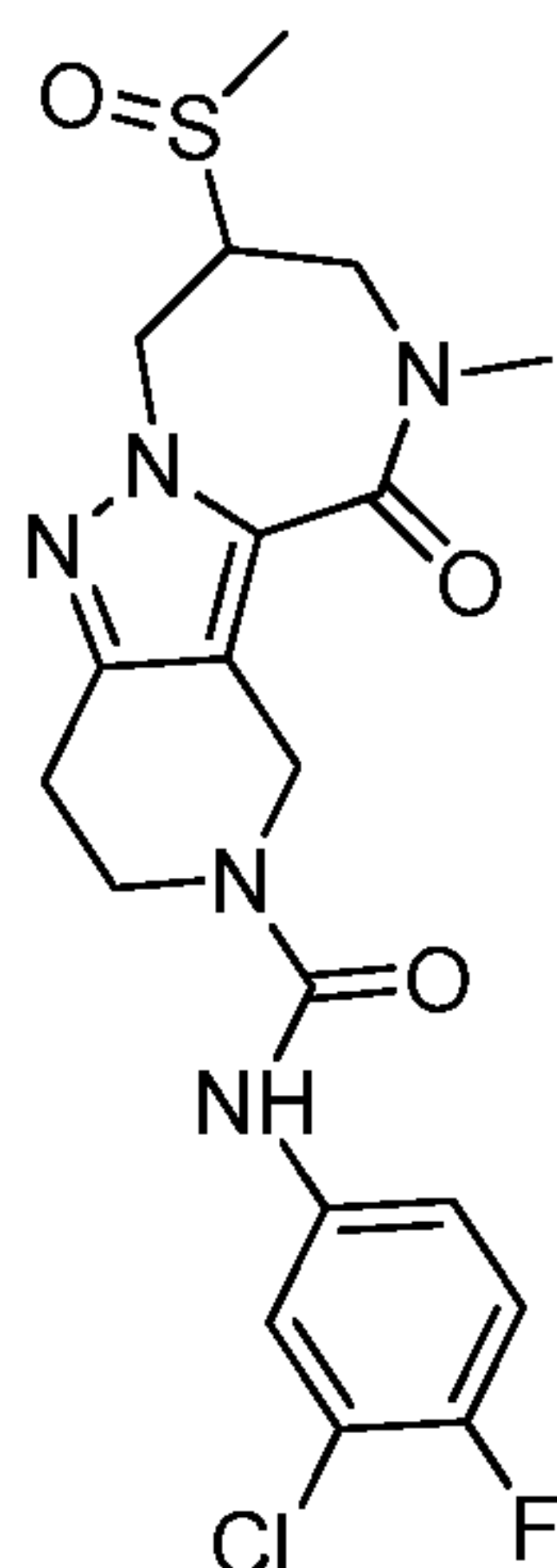
- 5 The residue was purified by prep-TLC to afford the title compound (82.00 mg, 162.00 μmol,
66.07% yield, 96% purity) as a white solid. LCMS: 486 [M+1]

Step 2: N-(3-chloro-4-fluorophenyl)-10-methyl-8-(methylthio)-11-oxo-1,3,4,7,8,9,10,11-
octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. A mixture of [2-
[(3-chloro-4-fluoro-phenyl)carbamoyl]-10-methyl-11-oxo- 1,3,4,7,8,9-

- 10 hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-8-yl]methanesulfonate (50.00 mg, 102.90
μmol, 1.00 *eq*) in DMF (2.00 mL) was added sodium;methanethiolate (50.48 mg, 720.30 μmol,
45.89 μL, 7.00 *eq*) at 0 °C under N₂, and then the mixture was stirred at 15 °C for 2 hour under
N₂ atmosphere. LCMS showed the starting material was consumed completely, desired
product/byproduct = 1/1. The mixture was poured into ice-water (10 mL) and stirred at 5 min.

- 15 The aqueous phase was extracted with ethyl acetate (5 mL*3). The combined organic phase was
washed with brine (10 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum.
The residue was purified by Prep-HPLC (FA) to afford the title compound (18.00 mg, 40.28
μmol, 39.15% yield, 98% purity) as a white solid. ¹H NMR (400MHz, CDCl₃) δ 7.58 (dd, *J* =
2.6, 6.5 Hz, 1 H), 7.18 (s, 1 H), 7.02 - 7.09 (m, 1 H), 6.55 (s, 1 H), 4.64 - 4.74 (m, 3 H), 4.22 -
20 4.33 (m, 1 H), 3.81 - 3.90 (m, 2 H), 3.69 (dd, *J* = 4.5, 14.8 Hz, 1 H), 3.36 - 3.54 (m, 2 H), 3.23
(s, 3 H), 2.85 (br d, *J* = 4.6 Hz, 2 H), 2.24 (s, 3 H). LCMS: 438/440 [M+1]; and N-(3-chloro-4-
fluorophenyl)-10-methyl-11-oxo-3,4,10,11-tetrahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-
a][1,4]diazepine-2(7H)-carboxamide as a by-product.

- 25 Compound 026A: N-(3-chloro-4-fluoro-phenyl)-10-methyl-8-methylsulfinyl-11-oxo-1,3,4,7,8,9-
hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide: pure but unknown
diastereomer D1:



Step 1. tert-butyl-10-methyl-8-methylsulfonyloxy-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate.

To a solution of tert-butyl 8-hydroxy-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido [2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (220.00 mg, 654.00 μ mol, 1.00 *eq*) in DCM (2.00 mL) was added methanesulfonyl chloride (89.90 mg, 784.80 μ mol, 60.74 μ L, 1.20 *eq*). The mixture was stirred at 10 °C for 4 hr. TLC (Dichloromethane: Methanol=10:1) showed the mixture was completed. The mixture was quenched with water(20 mL), extracted with ethyl acetate(10 mL*3), the organic layer was washed with brine(10 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo to afford the title compound (200.00 mg, 482.53 μ mol, 73.78% yield) as colorless oil.

Step 2. tert-butyl-8-acetylsulfanyl-10-methyl-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of tert-butyl 10-methyl-8-methylsulfonyloxy-11-oxo-1,3,4,7,8,9 -hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (220.00 mg, 530.79 μ mol, 1.00 *eq*) in DMF (2.00 mL) was added acetylsulfanylpotassium (181.86 mg, 1.59 mmol, 3.00 *eq*). The mixture was stirred at 80 °C for 16 hr. LCMS showed the reaction was complete. The mixture was quenched by addition water (10 mL), and extracted with ethyl acetate (10 mL*3). The organic layer was washed with water (10 mL) and brine (10 mL) and dried over anhydrous Na₂SO₄, concentrated in vacuum to give the residue which was purified by prep-TLC (Dichloromethane:Methanol=10:1) to afford the title compound (170.00 mg, 396.46 μ mol, 74.69% yield, 92% purity) as yellow oil.

Step 3. tert-butyl 10- methyl -8-methylsulfanyl- 11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of tert-butyl 8-acetylsulfanyl-10-methyl-11-oxo-1,3,4,7,8,9- hexahydropyrido[2,3]pyrazolo[2,4-

b][1,4]diazepine-2-carboxylate (150.00 mg, 380.24 μ mol, 1.00 *eq*) in MeOH (2.00 mL) was added K₂CO₃ (157.66 mg, 1.14 mmol, 3.00 *eq*). The mixture was stirred at 15 °C for 15 mins, while MeI (59.37 mg, 418.26 μ mol, 26.04 μ L, 1.10 *eq*) was added, the mixture was stirred at 15 °C for 15 mins. LCMS showed the reaction complete. The mixture was concentrated in vacuum to give the residue which was washed with DCM (30 mL) and filtered, the filtrate was concentrated in vacuum to afford the title compound (132.00 mg, 356.58 μ mol, 93.78% yield, 99% purity) as colorless oil.

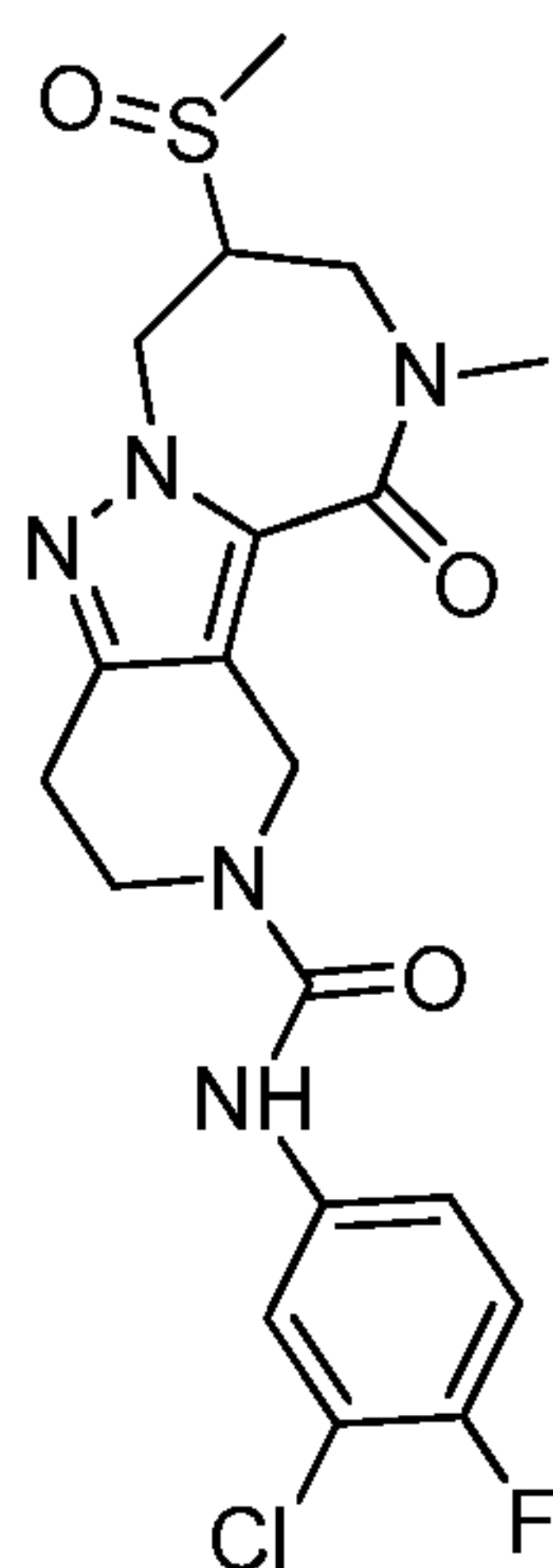
Step 4. 10-methyl-8-methylsulfanyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3] pyrazolo [2,4-b][1,4]diazepin-11-one. To a solution of tert-butyl 10-methyl-8-methylsulfanyl-11-oxo-1,3,4,7,8,9 -hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (150.00 mg, 409.30 μ mol, 1.00 *eq*) in DCM (2.00 mL) was added TFA (3.08 g, 27.01 mmol, 2.00 mL, 66.00 *eq*), the mixture was stirred at 15 °C for 30 min. TLC (Dichloromethane: Methanol=10:1) showed the reaction was completed. The mixture was concentrated to afford the title compound (140.00 mg, 368.05 μ mol, 89.92% yield, TFA) as white solid.

Step 5. N-(3-chloro-4-fluoro-phenyl)-10-methyl-8- methylsulfanyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide. To a solution of 10-methyl-8-methylsulfanyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3] pyrazolo[2,4-b][1,4]diazepin-11-one (140.00 mg, 368.05 μ mol, 1.00 *eq*, TFA) and phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (97.78 mg, 368.05 μ mol, 1.00 *eq*) in DCM (2.00 mL) was added TEA (93.11 mg, 920.13 μ mol, 127.55 μ L, 2.50 *eq*). The mixture was stirred at 15 °C for 16 hr. LCMS showed the reaction was completed. The mixture was quenched by water (10 mL) and extracted with ethyl acetate (30 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuum to afford the title compound (200.00 mg, 365.36 μ mol, 99.27% yield, 80% purity) as white solid.

Step 6. N-(3-chloro-4-fluoro-phenyl)-10-methyl-8-methylsulfinyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide To a solution of N-(3-chloro-4-fluoro-phenyl)-10-methyl-8-methylsulfanyl-11 -oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide (100.00 mg, 228.35 μ mol, 1.00 *eq*) and (Bu₃Sn)₂O (204.18 mg, 342.53 μ mol, 174.52 μ L, 1.50 *eq*) in DCM (3.00 mL) was added Br₂ (54.74 mg, 342.53 μ mol, 17.66 μ L, 1.50 *eq*) in DCM (500.00 μ L) for 30 min. The mixture was stirred at 15 °C for 2 hr. LCMS showed the reactant remained, then another batch

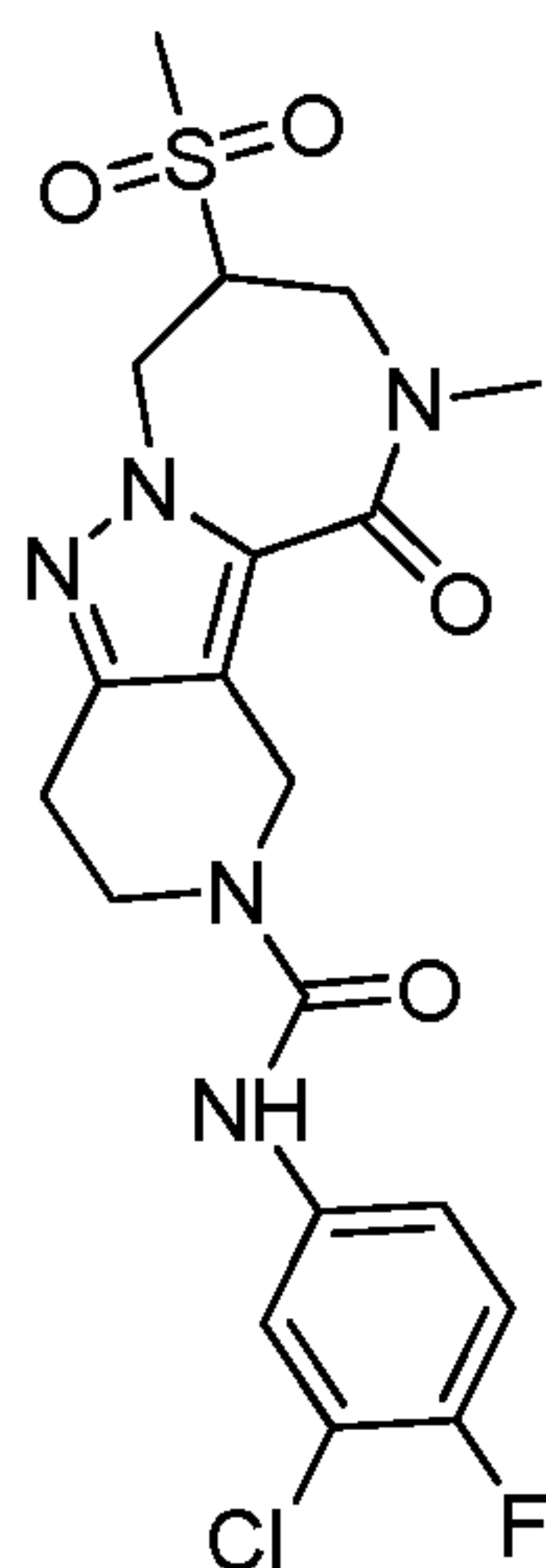
of (Bu₃Sn)₂O (272.24 mg, 456.70 μmol, 232.69 μL, 2.00 *eq*) and Br₂ (72.99 mg, 456.70 μmol, 23.54 μL, 2.00 *eq*) was added in turn. The mixture was stirred for another 2 hr. LCMS showed the reaction was completed. The mixture was washed with saturated KF (10 mL), the organic layer was concentrated in vacuum. The residue was purified by prep-HPLC to give N-(3-chloro-4-fluoro-phenyl)-10-methyl-8-methylsulfinyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide (50.00 mg, 106.85 μmol, 46.79% yield, 97% purity) as yellow oil, 35 mg of which was separated by SFC(column: AS(250mm*30mm, 10um); mobile phase: [Neu-ETOH]; Gradient Time (min): 5.5minuminute, 80minutes), followed by prep-HPLC to afford two isomers Compound 026, D1 (peak1, 14 mg), and Compound 026, D2 (peak 2, 18 mg). Compound 026, D1: ¹H NMR (400 MHz, CDCl₃) δ 7.58 (dd, *J* = 2.51, 6.42 Hz, 1 H), 7.15 - 7.24 (m, 1 H), 7.01 - 7.11 (m, 1 H), 6.64 (s, 1 H), 4.18 - 4.83 (m, 4 H), 3.64 - 4.05 (m, 4 H), 3.44 - 3.58 (m, 1 H), 3.23 (d, *J* = 13.94 Hz, 3 H), 2.84 (br d, *J* = 4.77 Hz, 2 H), 2.63 - 2.74 (m, 3 H).

15 Compound 026B: N-(3-chloro-4-fluoro-phenyl)-10-methyl-8-methylsulfinyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide: pure but unknown diastereomer D2:



20 Compound 026, D2: ¹H NMR (400 MHz, CDCl₃) δ 7.57 (dd, *J* = 2.63, 6.54 Hz, 1 H), 7.17 - 7.24 (m, 1 H), 7.01 - 7.10 (m, 1 H), 6.70 (s, 1 H), 4.18 - 4.87 (m, 4 H), 3.64 - 4.02 (m, 4 H), 3.42 - 3.60 (m, 1 H), 3.23 (d, *J* = 13.82 Hz, 3 H), 2.77 - 2.91 (m, 2 H), 2.62 - 2.74 (m, 3 H).

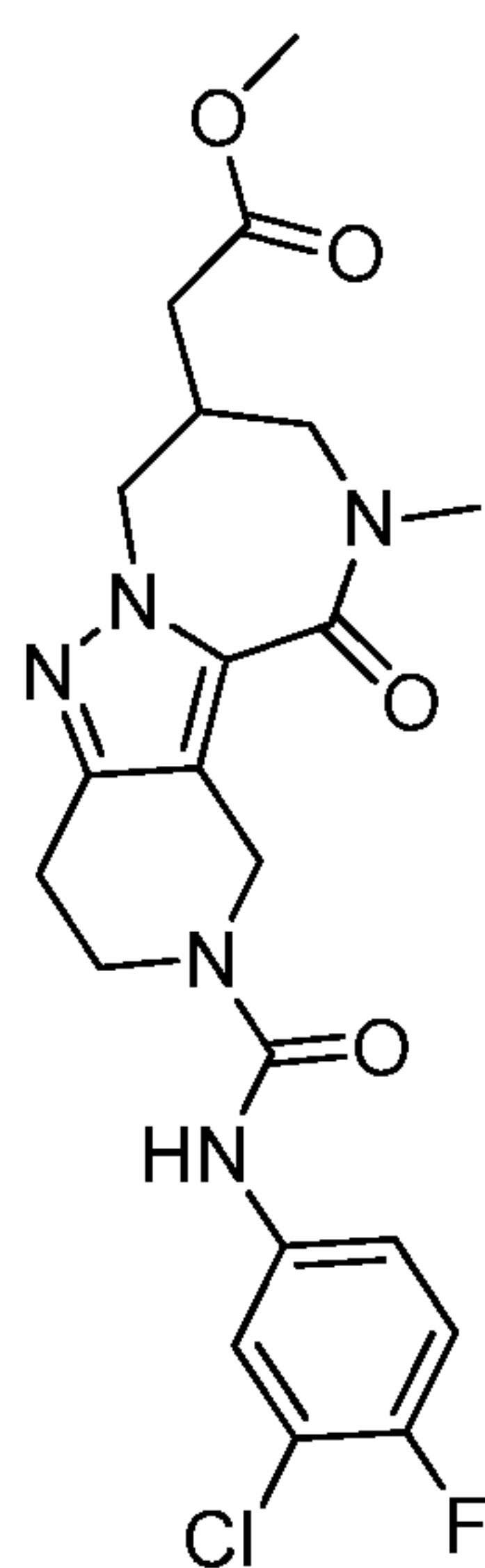
Compound 027: N-(3-chloro-4-fluoro-phenyl)-10-methyl-8-methylsulfonyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide.



To a solution of N-(3-chloro-4-fluoro-phenyl)-10-methyl-8-methylsulfonyl-11-oxo- 1,3,4,7,8,9-
 5 hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide (Compound 26, product
 from Step 5, 50.00 mg, 114.18 μmol , 1.00 *eq*) in DCM (2.00 mL) was added *m*-CPBA (123.15
 mg, 570.88 μmol , 80% purity, 5.00 *eq*). The resulting solution was stirred at 15 °C for 2 hr.
 LCMS showed the reaction was complete. The mixture was quenched with water (10 mL), the
 organic layer was washed with sat. NaHCO_3 (10 mL) and brine (10 mL), dried over anhydrous
 10 Na_2SO_4 and concentrated in vacuum. The mixture was purified by prep-HPLC to afford the title
 compound (17.00 mg, 35.81 μmol , 31.37% yield, 99% purity) as the white solid. ^1H NMR (400
 MHz, CDCl_3) δ 7.57 (dd, J = 2.70, 6.46 Hz, 1 H), 7.16 - 7.23 (m, 1 H), 7.02 - 7.10 (m, 1 H),
 6.66 (s, 1 H), 4.83 - 4.93 (m, 1 H), 4.58 - 4.79 (m, 3 H), 3.74 - 3.98 (m, 5 H), 3.22 (s, 3 H), 2.95
 (s, 3 H), 2.84 (t, J = 5.83 Hz, 2 H). LCMS: 470/472 $[\text{M}+1]$.

15

Compound 028: methyl 2-(2-((3-chloro-4-fluorophenyl)carbamoyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-8-yl)acetate.



Step 1. tert-butyl (8E)-8-(2-methoxy-2-oxo-ethylidene)-10-methyl -11-oxo-3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of methyl 2-

dimethoxyphosphorylacetate (162.85 mg, 894.22 μmol , 129.25 μL , 1.30 *eq*) in THF (10.00

5 mL) was added potassium 2-methylpropan-2-olate (115.78 mg, 1.03 mmol, 1.50 *eq*) at 0 °C for

10 min. Then the mixture was added tert-butyl 10-methyl-8,11-dioxo-3,4,7,9-tetrahydro-1H-

pyrido[2,3]pyrazolo [2,4-b] [1,4]diazepine-2-carboxylate (230.00 mg, 687.86 μmol , 1.00 *eq*) and

the mixture was stirred at 15 °C for 4 h. The reaction mixture was quenched with H₂O (10 mL),

diluted with brine (40 mL) and extracted with EtOAc (30 mL*2). The combined organic phase

10 was washed with brine (30 mL * 2), dried over Na₂SO₄, filtered and concentrated under reduced

pressure. The residue was purified by column chromatography to afford the title compound

(164.00 mg, 382.25 μmol , 55.57% yield, 91% purity) as a yellow oil. LCMS: 391 [M+1].

Step 2. tert-butyl 8-(2-methoxy-2-oxo-ethyl)-10-methyl-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of tert-butyl

15 (8E)-8-(2-methoxy-2-oxo-ethylidene)-10-methyl-11-oxo- 3,4,7,9-tetrahydro-1H-

pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (200 mg, 512.26 μmol , 1.00 *eq*) in

MeOH (10.00 mL) was added Pd/C (50.00 mg, 10% purity) and the mixture was stirred at 15 °C

under H₂ (15 psi) for 16 h. The reaction mixture was filtered and the filtrate was concentrated

in vacuo to afford the title compound (195.00 mg, 472.03 μmol , 92.15% yield, 95% purity) as a

20 oil, which was used directly for the next step. LCMS: 393 [M+1].

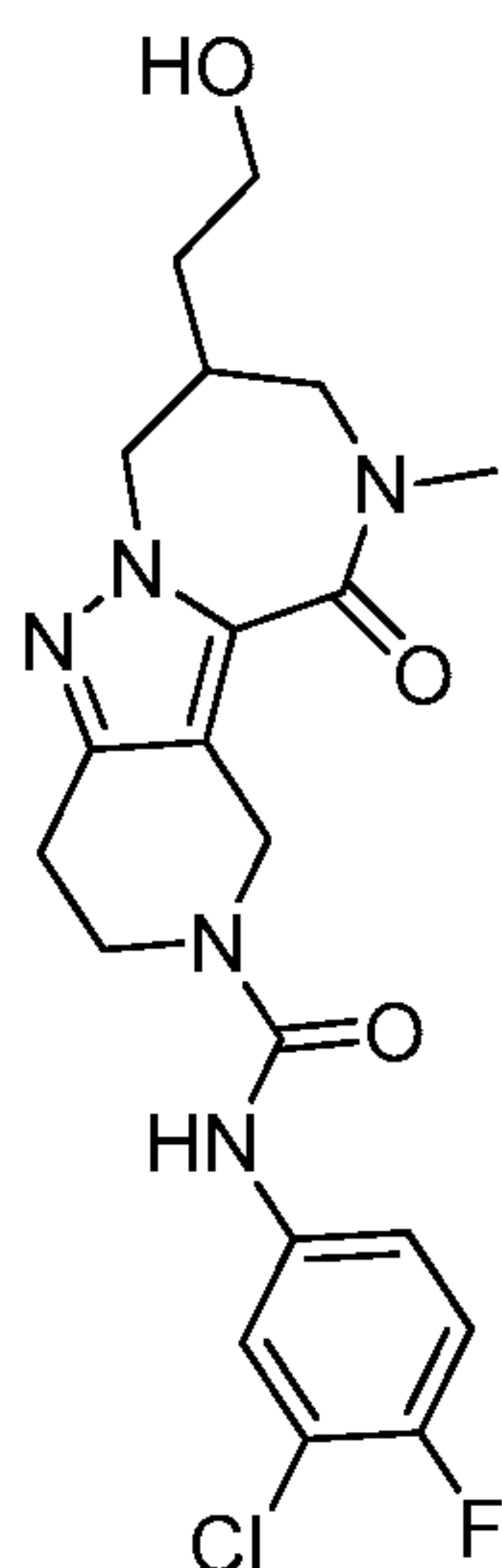
Step 3. methyl 2-(10-methyl-11-oxo -2,3,4,7,8,9-hexahydro -1H-pyrido[2,3]pyrazolo[2,4-

b][1,4]diazepin-8-yl)acetate. To a solution of tert-butyl 8-(2-methoxy-2-oxo-ethyl)-10-methyl-

11-oxo-1,3,4,7,8,9- hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (195.00 mg, 496.88 μ mol, 1.00 *eq*) in DCM (3.00 mL) was added TFA (4.62 g, 40.52 mmol, 3.00 mL, 81.55 *eq*) and the mixture was stirred at 15 °C for 1 h. The mixture was concentrated in vacuo to afford the title compound (190.00 mg, 448.86 μ mol, 90.34% yield, 96% purity, TFA), which was used directly for the next step.

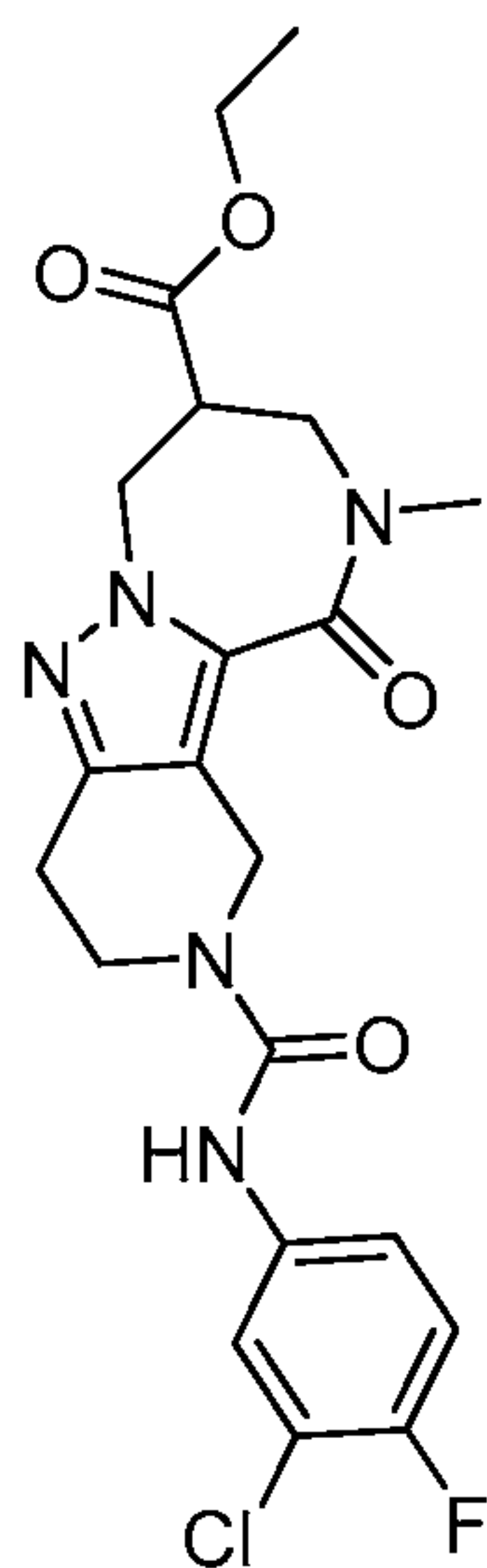
Step 4. methyl 2-(2-((3-chloro-4-fluorophenyl)carbamoyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-8-yl)acetate. A mixture of methyl 2-(10-methyl-11-oxo-2,3,4,7,8,9-hexahydro-1H- pyrido [2,3] pyrazolo[2,4-b][1,4]diazepin-8-yl)acetate (195.00 mg, 479.87 μ mol, 1.00 *eq*, TFA), Et₃N (242.79 mg, 2.40 mmol, 332.59 μ L, 5.00 *eq*) and phenyl N- (3-chloro-4-fluoro-phenyl)carbamate (127.49 mg, 479.87 μ mol, 1.00 *eq*) in DCM (5.00 mL) was stirred at 15 °C for 16 h. The mixture was diluted with DCM (30 mL) and washed with HCl (1 M, 30 mL*2). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography to afford desired product (180 mg, 97 % purity), 40 mg of which was further purified by prep-HPLC(FA) to afford the title compound (35.7 mg, 99 % purity) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.57 - 7.59 (m, 1 H), 7.16 - 7.27 (m, 1 H), 7.03 - 7.07 (t, *J* = 8.8 Hz, 1 H), 6.56 (s, 1 H), 4.66 - 4.67 (m, 2 H), 4.45 - 4.47 (m, 1 H), 4.12 - 4.15 (m, 1 H), 3.84 - 3.86 (m, 2 H), 3.74 (s, 3 H), 3.46 - 3.48 (m, 1 H), 3.18 - 3.26 (m, 4 H), 2.95 - 3.05 (m, 1 H), 2.82 - 2.85 (m, 2 H), 2.39 - 2.51 (m, 2 H). LCMS: 464/466 [M+1].

Compound 029: N-(3-chloro-4-fluorophenyl)-8-(2-hydroxyethyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



To a solution of methyl 2-[2-[(3-chloro-4-fluorophenyl)carbamoyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-8-yl]acetate (Compound 028, 40.00 mg, 86.23 μ mol, 1.00 *eq*) in THF (3.00 mL) was added LiBH₄ (5.63 mg, 258.69 μ mol, 3.00 *eq*) at 0 °C and the mixture was stirred at 15 °C for 4 h. The reaction mixture was quenched with H₂O (20 mL) at 0 °C and extracted with ethyl acetate (20 mL*2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC(FA) to afford the title compound (18.50 mg, 42.02 μ mol, 48.73% yield, 99% purity) as a white solid. ¹H NMR (400 MHz, CD₃CN) δ 7.64 - 7.66 (m, 1 H), 7.44 (s, 1 H), 7.31 - 7.32 (m, 1 H), 7.11 - 7.15 (t, *J* = 9.0 Hz, 1 H), 4.59 (s, 2 H), 4.34 - 4.36 (m, 1 H), 4.06 - 4.10 (m, 1 H), 3.73 - 3.75 (m, 2 H), 3.59 - 3.62 (m, 2 H), 3.36 - 3.39 (m, 1 H), 3.08 - 3.13 (m, 4 H), 2.73 - 2.76 (m, 2 H), 2.55 - 2.65 (m, 1 H), 1.52 - 1.55 (m, 2 H). LCMS: 436/438 [M+1].

15 Compound 030: ethyl 2-((3-chloro-4-fluorophenyl)carbamoyl)-10-methyl-11-oxo-2,3,4,7,8,9,10,11-octahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-8-carboxylate.



Step 1. ethyl 2-[[tert-butoxycarbonyl(methyl)amino]methyl]prop-2-enoate. A mixture of tert-butyl N-methylcarbamate (200.00 mg, 1.52 mmol, 1.00 *eq*) in THF (5.00 mL) was added NaH (91.20 mg, 2.28 mmol, 60% purity, 1.50 *eq*) at 0 °C for 0.5 hr under N₂, then ethyl 2-(bromomethyl)prop-2-enoate (352.10 mg, 1.82 mmol, 1.20 *eq*) was added to the mixture dropwise at 0 °C, and the mixture was stirred at 15 °C for 2 hr under N₂ atmosphere. TLC showed the starting material was consumed completely, two new spots appeared. The mixture was poured into ice-water (10 mL) and stirred at 5 min. The aqueous phase was extracted with ethyl acetate (5 mL*3). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 5/1) to afford the title compound (112.00 mg, 460.34 μmol, 30.29% yield) as a colorless oil. ¹H NMR (400MHz, CDCl₃) δ 6.28 (s, 1 H), 5.55 (s, 1 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 4.07 (br s, 2 H), 2.88 (br s, 3 H), 1.45 (br s, 9 H), 1.31 (br s, 3 H).

Step 2. ethyl2-(methylaminomethyl)prop -2-enoate. A mixture of ethyl 2-[[tert-butoxycarbonyl(methyl)amino]methyl]prop-2-enoate (112.00 mg, 460.34 μmol, 1.00 *eq*) in dioxane (1.00 mL) was added HCl/dioxane (4 M, 5.00 mL, 43.45 *eq*), and then the mixture was stirred at 15 °C for 0.5 hour. TLC showed the starting material was consumed completely, a new spot was major. The mixture was concentrated in vacuum to afford the title compound (82.50 mg, 459.25 μmol, 99.76% yield, HCl) as a white solid, which was used directly for next step.

Step 3. tert-butyl 3-[2-ethoxycarbonylallyl (methyl) carbamoyl]-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate. A mixture of 5-tert-butoxycarbonyl-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-3-carboxylic acid (80.00 mg, 299.31 μmol , 1.00 *eq*), ethyl 2-(methylaminomethyl) prop-2-enoate (59.14 mg, 329.24 μmol , 1.10 *eq*, HCl), T₃P (285.70 mg, 897.93 μmol , 267.01 μL , 3.00 *eq*), TEA (151.44 mg, 1.50 mmol, 207.45 μL , 5.00 *eq*) in THF (3.00 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 15 °C for 16 hour under N₂ atmosphere. TLC showed the starting material was consumed completely and a new spot appeared. The mixture was poured into water (10 mL) and stirred at 5 min. The aqueous phase was extracted with ethyl acetate (5 mL*3). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by Prep-TLC (DCM/MeOH=10/1) to afford the title compound (46.00 mg, 105.49 μmol , 35.24% yield, 90% purity) as a white solid. LCMS: 393 [M+1]. ¹H NMR (400MHz, CDCl₃) δ 6.35 (s, 1 H), 5.67 (br s, 1 H), 4.63 (s, 4 H), 4.18 - 4.30 (m, 2 H), 3.71 (br s, 2 H), 2.91 - 3.47 (m, 3 H), 2.74 (br t, *J* = 5.4 Hz, 2 H), 1.48 (s, 9 H), 1.31 (t, *J* = 7.2 Hz, 3 H).

Step 4. 2-tert-butyl 8-ethyl 10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2,8(7H)-dicarboxylate. A mixture of tert-butyl 3-[2-ethoxycarbonylallyl(methyl)carbamoyl]-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (36.00 mg, 91.73 μmol , 1.00 *eq*), DBU (6.98 mg, 45.87 μmol , 6.91 μL , 0.50 *eq*) in MeCN (1.00 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 50 °C for 2 hour under N₂ atmosphere. TLC showed the starting material was consumed completely and desired product was major. The mixture was poured into water (5 mL) and stirred at 5 min. The aqueous phase was extracted with ethyl acetate (3 mL*3). The combined organic phase was washed with brine (5 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by Prep-TLC (DCM/MeOH=20/1) to give the title compound (20.00 mg, 50.96 μmol , 55.56% yield) as a white solid. LCMS: 393 [M+1]

Step 5. ethyl 10-methyl-11-oxo-2,3,4,7,8,9,10,11-octahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-8-carboxylate. A mixture of 2-tert-butyl 8-ethyl 10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2,8(7H)-dicarboxylate (22.00 mg, 56.06 μmol , 1.00 *eq*) in DCM (1.00 mL) was added TFA (1.54 g, 13.51 mmol, 1.00 mL, 240.93 *eq*), and then the mixture was stirred at 15 °C for 1 hour. TLC showed the starting material was consumed completely, a new spot appeared. The mixture was

concentrated in vacuum to afford the title compound (22.70 mg, 55.86 μmol , 99.65% yield, TFA) as a yellow oil, which was used directly for next step.

Step 6. ethyl 2-((3-chloro-4-fluorophenyl)carbamoyl)-10-methyl-11-oxo-2,3,4,7,8,9,10,11-

octahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-8-carboxylate. A mixture of ethyl

10-methyl-11-oxo-2,3,4,7,8,9,10,11-octahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-

a][1,4]diazepine-8-carboxylate (22.00 mg, 54.14 μmol , 1.00 *eq*, TFA), phenyl N-(3-chloro-4-

fluoro-phenyl)carbamate (15.82 mg, 59.55 μmol , 1.10 *eq*) and TEA (10.96 mg, 108.28 μmol ,

15.01 μL , 2.00 *eq*) in DCM (3.00 mL) was degassed and purged with N_2 for 3 times, and then

the mixture was stirred at 15 $^\circ\text{C}$ for 16 hour under N_2 atmosphere. LCMS showed the starting

material was consumed completely, desired product was major. The mixture was poured into

water (5 mL) and stirred at 5 min. The aqueous phase was extracted with DCM (3 mL*3). The

combined organic phase was washed with brine (5 mL), dried with anhydrous Na_2SO_4 , filtered

and concentrated in vacuum. The residue was purified by Prep-HPLC (FA) to afford the title

compound (15.00 mg, 32.01 μmol , 59.13% yield, 99% purity) as a white solid. ^1H NMR

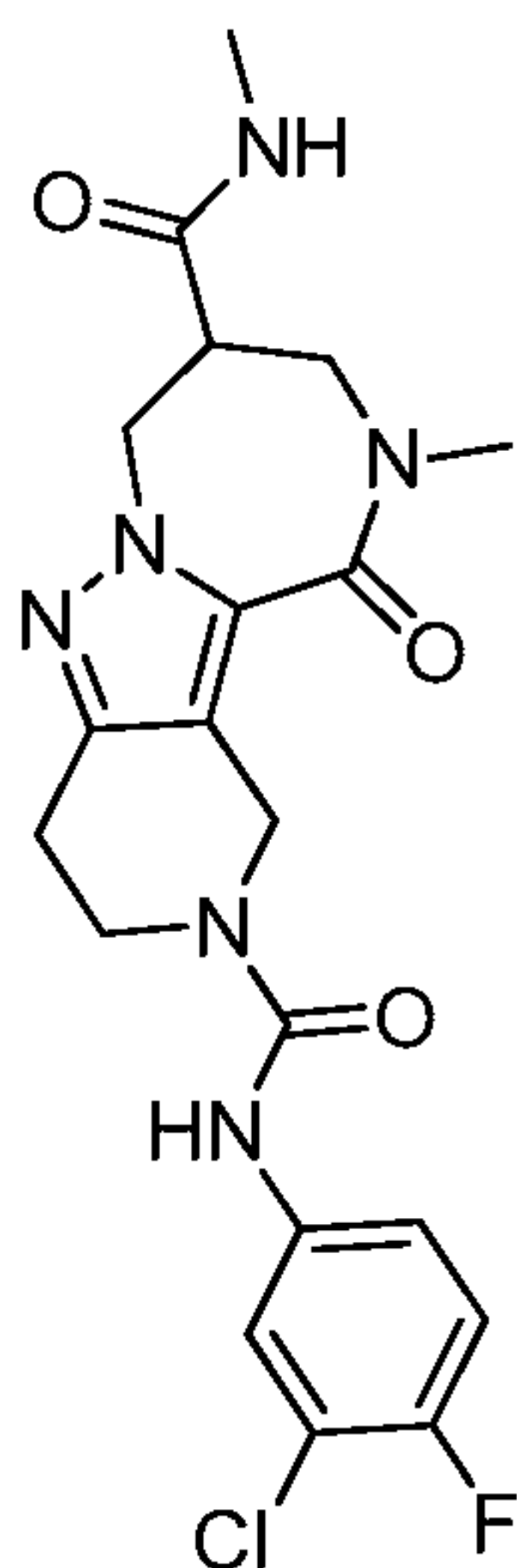
(400MHz, CDCl_3) δ 7.58 (dd, $J = 2.6, 6.5$ Hz, 1 H), 7.16 - 7.22 (m, 1 H), 7.02 - 7.09 (m, 1 H),

6.58 (s, 1 H), 4.50 - 4.76 (m, 4 H), 4.27 (d, $J = 7.1$ Hz, 2 H), 3.73 - 3.91 (m, 3 H), 3.58 - 3.70

(m, 1 H), 3.33 - 3.43 (m, 1 H), 3.19 (s, 3 H), 2.84 (br d, $J = 5.4$ Hz, 2 H), 1.33 (t, $J = 7.2$ Hz, 3

H). LCMS: 464/466 $[\text{M}+1]$.

Compound 031: N2-(3-chloro-4-fluorophenyl)-N8,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-
octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2,8-dicarboxamide.



Step 1. 2-((3-chloro-4-fluorophenyl)carbamoyl)-10-methyl-11-oxo-2,3,4,7,8,9,10,11-octahydro-

1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-8-carboxylic acid. To a mixture of ethyl 2-

((3-chloro-4-fluorophenyl)carbamoyl)-10-methyl-11-oxo-2,3,4,7,8,9,10,11-octahydro-1H-

5 pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-8-carboxylate (Compound 030, 80.00 mg, 172.45

μmol, 1.00 *eq*) in MeOH (5.00 mL) and H₂O (1.00 mL) was added NaOH (10.35 mg, 258.68

μmol, 1.50 *eq*) in one portion. The mixture was stirred at 30 °C for 12 hours. LCMS showed the

reaction was completed. The mixture was concentrated in vacuum and adjust to pH=7 with

HCl(1 N). The residue was purified by prep-HPLC(FA) to the title compound (28.00 mg, 63.73

10 μmol, 36.96% yield, 99.2% purity) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.53 - 7.59 (m,

1 H), 7.16 - 7.23 (m, 1 H), 7.00 - 7.10 (m, 1 H), 6.58 - 6.67 (m, 1 H), 4.54 - 4.79 (m, 4 H), 3.84

(br t, *J* = 5.81 Hz, 3 H), 3.58 - 3.68 (m, 1 H), 3.39 - 3.49 (m, 1 H), 3.20 (s, 3 H), 2.81 - 2.91 (m,

2 H). LCMS: 436/438 [M+1].

Step 2. N2-(3-chloro-4-fluorophenyl)-N8,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-

15 pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2,8-dicarboxamide. To a mixture 2-((3-chloro-4-

fluorophenyl)carbamoyl)-10-methyl-11-oxo-2,3,4,7,8,9,10,11-octahydro-1H-

pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-8-carboxylic acid (70.00 mg, 160.61 μmol, 1.00

eq) and methanamine (43.38 mg, 642.44 μmol, 4.00 *eq*, HCl) in DMF (5.00 mL) was added

HATU (91.60 mg, 240.92 μmol, 1.50 *eq*) and DIPEA (311.36 mg, 2.41 mmol, 420.76 μL,

20 15.00 *eq*) in one portion under N₂. The mixture was stirred at 30 °C for 12 hours. LCMS

showed the reaction was completed and the desired product was detected. The mixture was

poured into water (10 mL), and extracted with ethyl acetate (10 mL*2). The combined organic

phase was washed with brine (10 mL*2), dried with anhydrous Na₂SO₄, filtered and

concentrated in vacuum. The residue was purified by prep-HPLC(FA) to afford N2-(3-chloro-4-

25 fluoro-phenyl)-N8,10-dimethyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-

b][1,4]diazepine-2,8-dicarboxamide (25.00 mg, 53.02 μmol, 33.01% yield, 95.2% purity) as

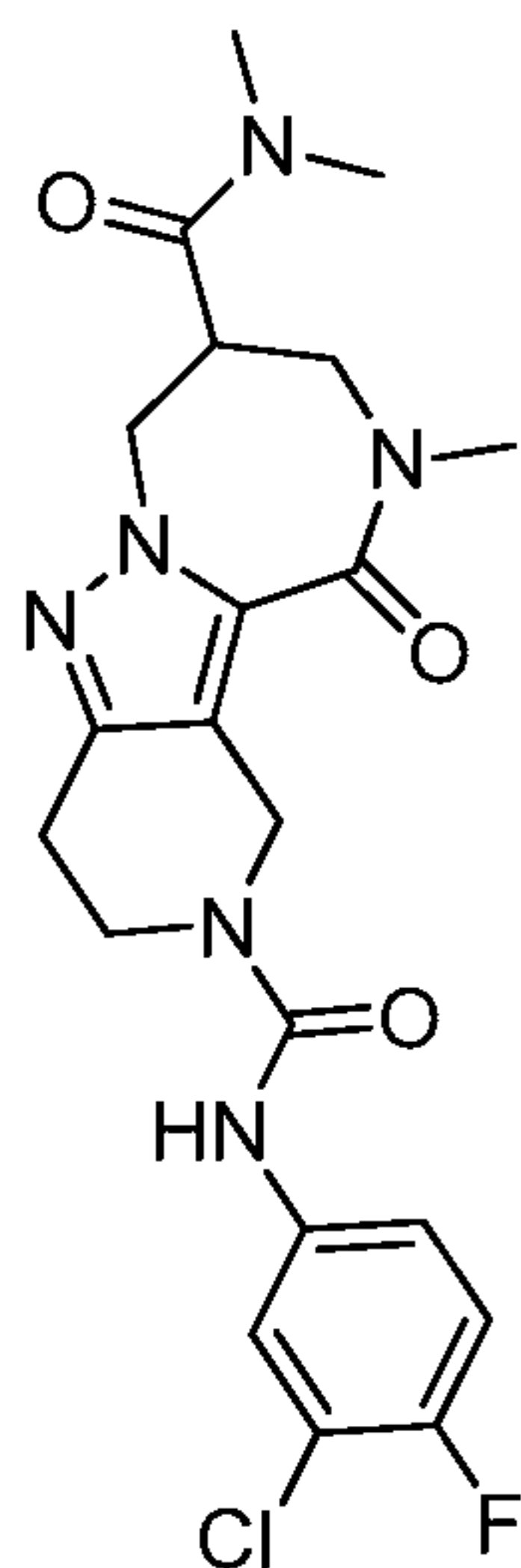
white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.54 - 7.63 (m, 1 H), 7.15 - 7.22 (m, 1 H), 7.02 - 7.10

(m, 1 H), 6.52 - 6.58 (m, 1 H), 5.82 - 5.91 (m, 1 H), 4.67 (s, 2 H), 4.46 - 4.64 (m, 2 H), 3.81 -

3.94 (m, 2 H), 3.48 - 3.67 (m, 2 H), 3.22 (s, 3 H), 2.87 (d, *J* = 4.77 Hz, 5 H). LCMS: 449/451

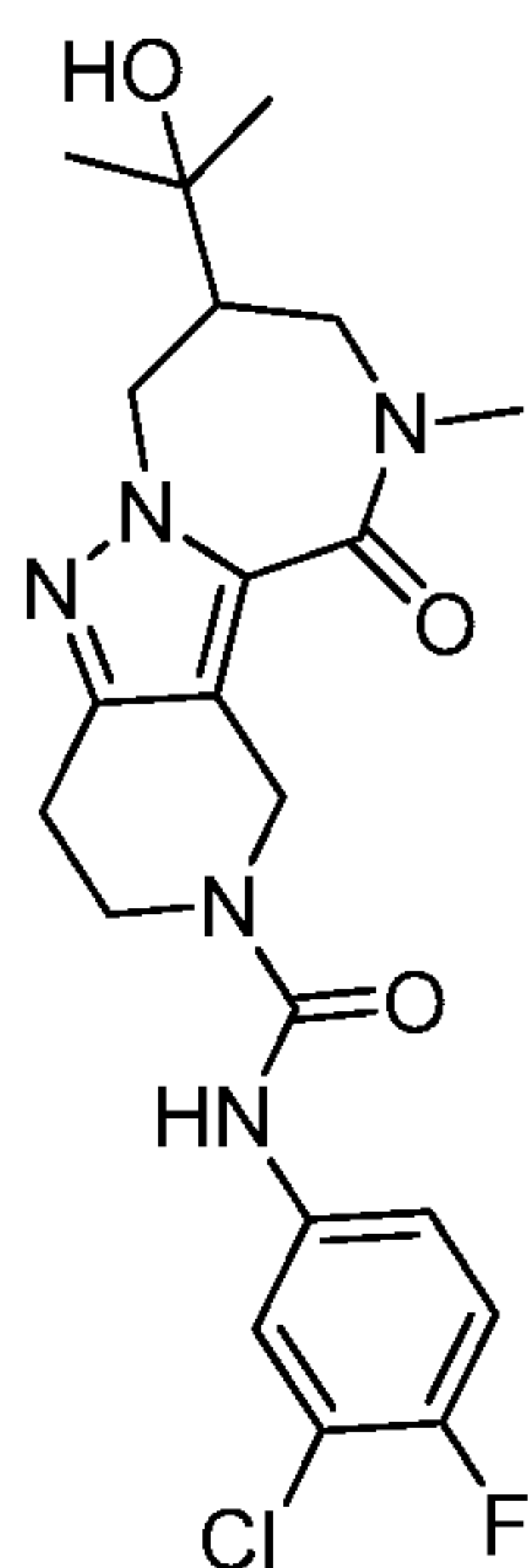
30 [M+1].

Compound 032: N2-(3-chloro-4-fluorophenyl)-N8,N8,10-trimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2,8-dicarboxamide.



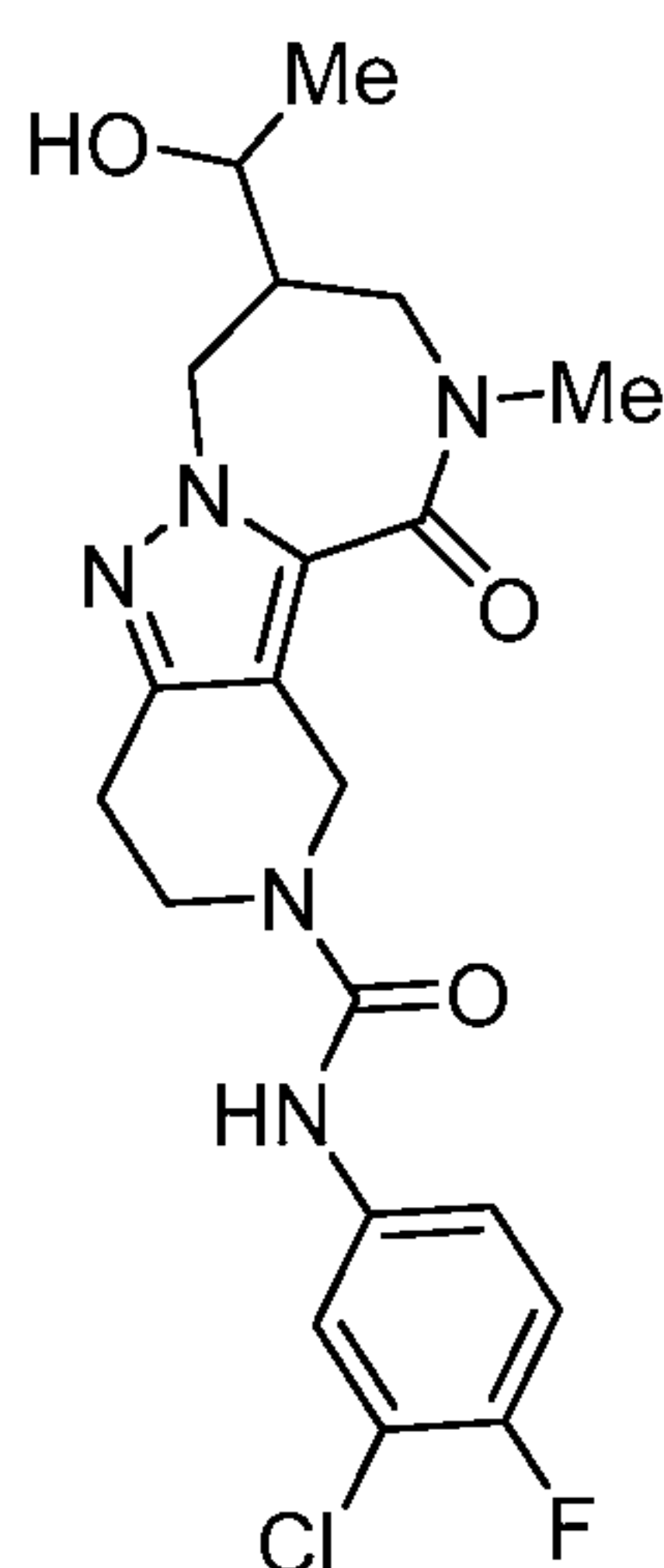
To a mixture of 2-((3-chloro-4-fluorophenyl)carbamoyl)-10-methyl-11-oxo-2,3,4,7,8,9,10,11-octahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-8-carboxylic acid (Compound 030, product from Step 1, 70.00 mg, 160.61 μ mol, 1.00 eq) and N-methylmethanamine (65.48 mg, 803.05 μ mol, 73.57 μ L, 5.00 eq, HCl) in DMF (5.00 mL) was added HATU (91.60 mg, 240.92 μ mol, 1.50 eq) and DIPEA (311.36 mg, 2.41 mmol, 420.76 μ L, 15.00 eq) in one portion under N₂. The mixture was stirred at 30 °C for 12 hours. LCMS showed the reaction was completed and the desired product was detected. The residue was poured into water (10 mL). The aqueous phase was extracted with ethyl acetate (10 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-HPLC(FA) to afford N2-(3-chloro-4-fluoro-phenyl)-N8,N8,10-trimethyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2,8-dicarboxamide (30.00 mg, 63.71 μ mol, 39.67% yield, 98.3% purity) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.56 - 7.63 (m, 1 H), 7.15 - 7.22 (m, 1 H), 7.02 - 7.10 (m, 1 H), 6.51 - 6.60 (m, 1 H), 4.40 - 4.80 (m, 4 H), 3.87 (s, 2 H), 3.52 - 3.70 (m, 3 H), 3.26 (s, 3 H), 3.15 (s, 3 H), 3.02 (s, 3 H), 2.78 - 2.91 (m, 2 H). LCMS: 463/465 [M+1].

Compound 033: N-(3-chloro-4-fluorophenyl)-8-(2-hydroxypropan-2-yl)-10-methyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide.



To a mixture of MeMgBr (3 M, 344.90 μ L, 6.00 *eq*) in THF (3.00 mL) was added ethyl 2-[(3-chloro-4-fluoro-phenyl)carbamoyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-8-carboxylate (Compound 030, 80.00 mg, 172.45 μ mol, 1.00 *eq*) in THF (3.00 mL) in one portion at -40 °C under N₂. The mixture was stirred at -40 °C for 30 min, then heated to 15 °C and stirred for 2 hours. LCMS showed the reaction was completed. The mixture was poured into sat. NH₄Cl (10 mL) and stirred for 1 min. The aqueous phase was extracted with ethyl acetate (10 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-HPLC(FA) to afford the title compound (45.00 mg, 98.91 μ mol, 57.36% yield, 98.89% purity) as white solid. LCMS:450/452 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (dd, J = 2.64, 6.53 Hz, 1 H), 7.17 - 7.22 (m, 1 H), 7.05 (t, J = 8.78 Hz, 1 H), 6.62 (s, 1 H), 4.69 - 4.75 (m, 1 H), 4.52 - 4.65 (m, 2 H), 4.33 (dd, J = 7.22, 14.62 Hz, 1 H), 3.86 (q, J = 5.86 Hz, 2 H), 3.43 - 3.58 (m, 2 H), 3.19 (s, 3 H), 2.83 (t, J = 5.77 Hz, 2 H), 2.36 - 2.53 (m, 1 H), 1.62 (s, 10 H), 1.54 (br s, 1 H), 1.31 (d, J = 8.66 Hz, 6 H).

Compound 034: N-(3-chloro-4-fluorophenyl)-8-(1-hydroxyethyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. N2-(3-chloro-4-fluoro-phenyl)-N8-methoxy-N8,10-dimethyl-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2,8-dicarboxamide. To a mixture of 2-[(3-chloro-4-fluoro-phenyl)carbamoyl]-10-methyl-11-oxo-1,3,4,7,8,9-

5 hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-8-carboxylic acid (Compound 030, product from Step 1, 300.00 mg, 688.33 μ mol, 1.00 *eq*) and N-methoxymethanamine;hydrochloride (268.56 mg, 2.75 mmol, 4.00 *eq*) in DMF (5.00 mL) was added HATU (392.58 mg, 1.03 mmol, 1.50 *eq*) and DIPEA (1.33 g, 10.32 mmol, 1.80 mL, 15.00 *eq*) in one portion under N₂. The mixture was stirred at 30 °C for 5 hours. TLC (Dichloromethane : Methanol=10:1) showed the
10 reaction was completed. The mixture was poured into water (15 mL) and extracted with ethyl acetate (20 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Dichloromethane : Methanol=50:1,20:1) to afford the title compound (310.00 mg, 586.47 μ mol, 85.20% yield, 90.6% purity) as white solid. LCMS: 479/481 [M+1].

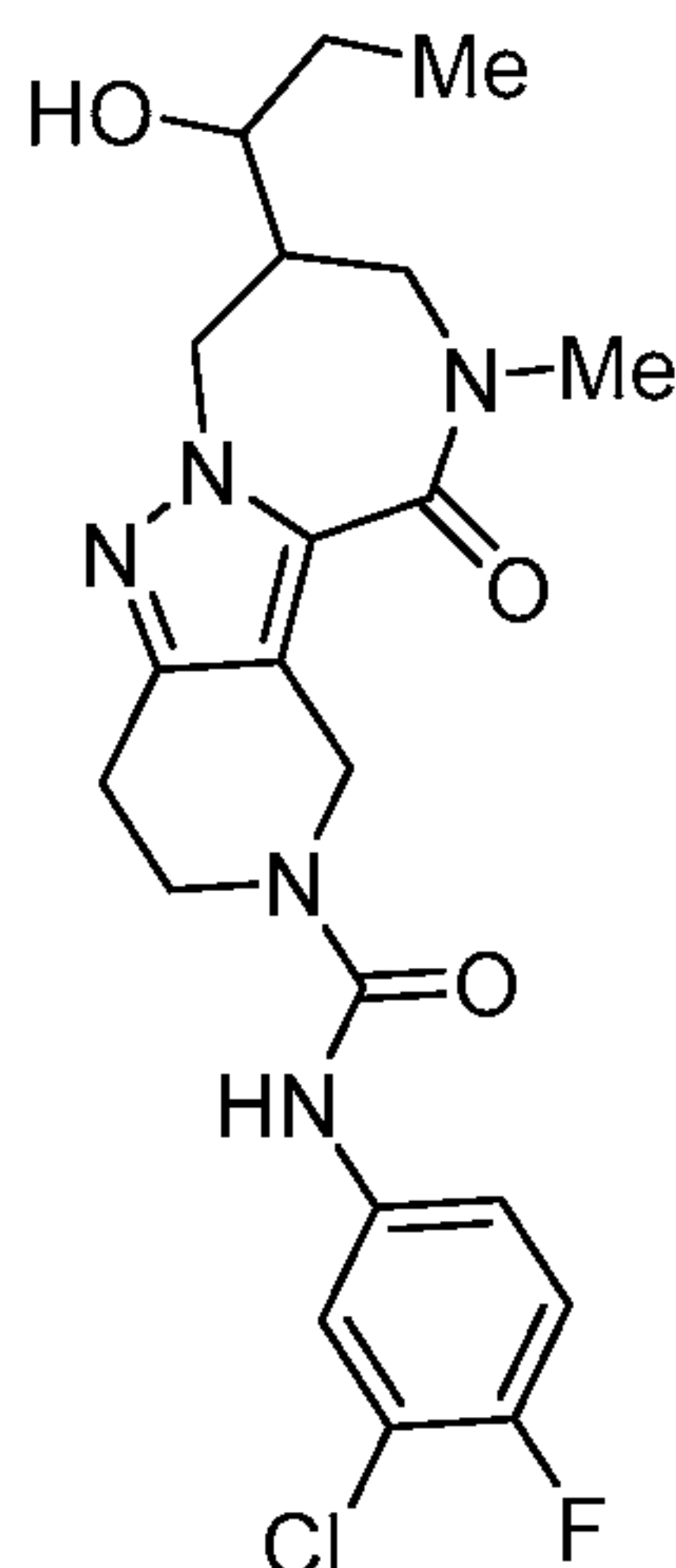
15 Step 2. 8-acetyl-N-(3-chloro-4-fluoro- phenyl)-10-methyl-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide. To a mixture of MeMgBr (3 M, 1.11 mL, 20.00 *eq*) in THF (3.00 mL) was added N2-(3-chloro-4-fluoro-phenyl)-N8-methoxy-N8,10-dimethyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2,8-dicarboxamide (80.00 mg, 167.05 μ mol, 1.00 *eq*) in THF (1.00 mL) drop-
20 wise at 0 °C under N₂. The mixture was heated to 30 °C and stirred for 14 hours. TLC (Ethyl acetate : Methanol=20:1) showed the reaction was completed. The mixture was poured into sat. NH₄Cl (20 mL) and extracted with ethyl acetate (15 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in

vacuum. The residue was purified by prep-TLC (Ethyl acetate : Methanol=20:1) to afford the title compound (25.00 mg, 54.16 μ mol, 32.42% yield, 94% purity) as yellow solid. LCMS: 434/436 [M+1].

5 Step 3. N-(3-chloro-4-fluorophenyl)-8-(1-hydroxyethyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. To a mixture of 8-acetyl-N-(3-chloro-4-fluoro-phenyl)-10-methyl-11-oxo- 1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide (25.00 mg, 57.62 μ mol, 1.00eq) in EtOH (3.00 mL) was added NaBH₄ (3.27 mg, 86.43 μ mol, 1.50 eq) in one portion at 0 °C under N₂. The mixture was stirred at 0 °C for 2 hours. LCMS showed the reaction was
10 completed. The residue was poured into water (10 mL) and extracted with ethyl acetate (10 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-HPLC(FA) to afford the title compound (15.00 mg, 34.31 μ mol, 59.55% yield, 99.7% purity) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (d, *J* = 6.43 Hz, 1 H), 7.17 - 7.25 (m, 1 H), 7.05 (t, *J* = 8.90 Hz, 1 H), 6.60 (br d, *J* = 4.03 Hz, 1 H), 4.56 - 4.73 (m, 2 H), 4.31 - 4.44 (m, 1 H), 4.10 (dd, *J* = 6.97, 14.31 Hz, 1 H), 3.88 - 3.92 (m, 1 H), 3.77 - 3.88 (m, 1H), 3.75 - 3.95 (m, 1 H), 3.63 (dd, *J* = 6.05, 14.73 Hz, 1 H), 3.48 (dd, *J* = 5.14, 14.92 Hz, 1 H), 3.31 - 3.38 (m, 1 H), 3.19 (d, *J* = 3.67 Hz, 3 H), 2.84 (t, *J* = 5.75 Hz, 2 H), 2.36 - 2.47 (m, 1 H), 1.61 (br s, 12 H), 1.31 (dd, *J* = 6.30, 11.80 Hz, 3 H). LCMS:436/438 [M+1].

20 Compound 035: N-(3-chloro-4-fluorophenyl)-8-(1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. N-(3-chloro-4-fluoro-phenyl)-10-methyl-11-oxo-8-propanoyl-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide. To a mixture of

bromo(ethyl)magnesium (3 M, 1.39 mL, 20.00 *eq*) in THF (3.00 mL) was added N2-(3-chloro-4-fluoro-phenyl)-N8-methoxy-N8,10-dimethyl-11-oxo- 1,3,4,7,8,9-

5 hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2,8-dicarboxamide (Compound 034, product from Step 1, 100.00 mg, 208.81 μ mol, 1.00 *eq*) in THF (2.00 mL) drop-wise at 0 °C under N₂.

The mixture was heated to 30 °C and stirred for 4 hours. LCMS and TLC (Ethyl acetate :

Methanol=20:1) showed the reaction was completed. The mixture was poured into water (10

mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (10 mL*2). The

10 combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na₂SO₄,

filtered and concentrated in vacuum. The residue was purified by prep-TLC (Ethyl acetate :

Methanol=20:1) to afford the title compound (30.00 mg, 66.98 μ mol, 32.08% yield, 100%

purity) as yellow solid. LCMS: 448/450 [M+1].

Step 2. N-(3-chloro-4-fluorophenyl)-8-(1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-

15 octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. To a mixture of N-(3-chloro-4-fluoro-phenyl)-10-methyl-11-oxo-8-propanoyl- 1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide (30.00 mg, 66.98 μ mol, 1.00

eq) in EtOH (3.00 mL) was added NaBH₄ (3.80 mg, 100.47 μ mol, 1.50 *eq*) in one portion at 0 °C

under N₂. The mixture was stirred at 20 °C for 2 hours. LCMS showed the reaction was

20 completed. The residue was poured into water (10 mL). The aqueous phase was extracted

with ethyl acetate (10 mL*2). The combined organic phase was washed with brine (10 mL*2),

dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified

by prep-HPLC(FA) to afford the title compound (25.00 mg, 52.90 μ mol, 78.98% yield, 95.2%

purity) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (dd, *J* = 1.96, 6.60 Hz, 1 H), 7.17 -

25 7.25 (m, 1 H), 7.05 (t, *J* = 8.80 Hz, 1 H), 6.62 (br d, *J* = 3.79 Hz, 1 H), 4.57 - 4.73 (m, 3 H),

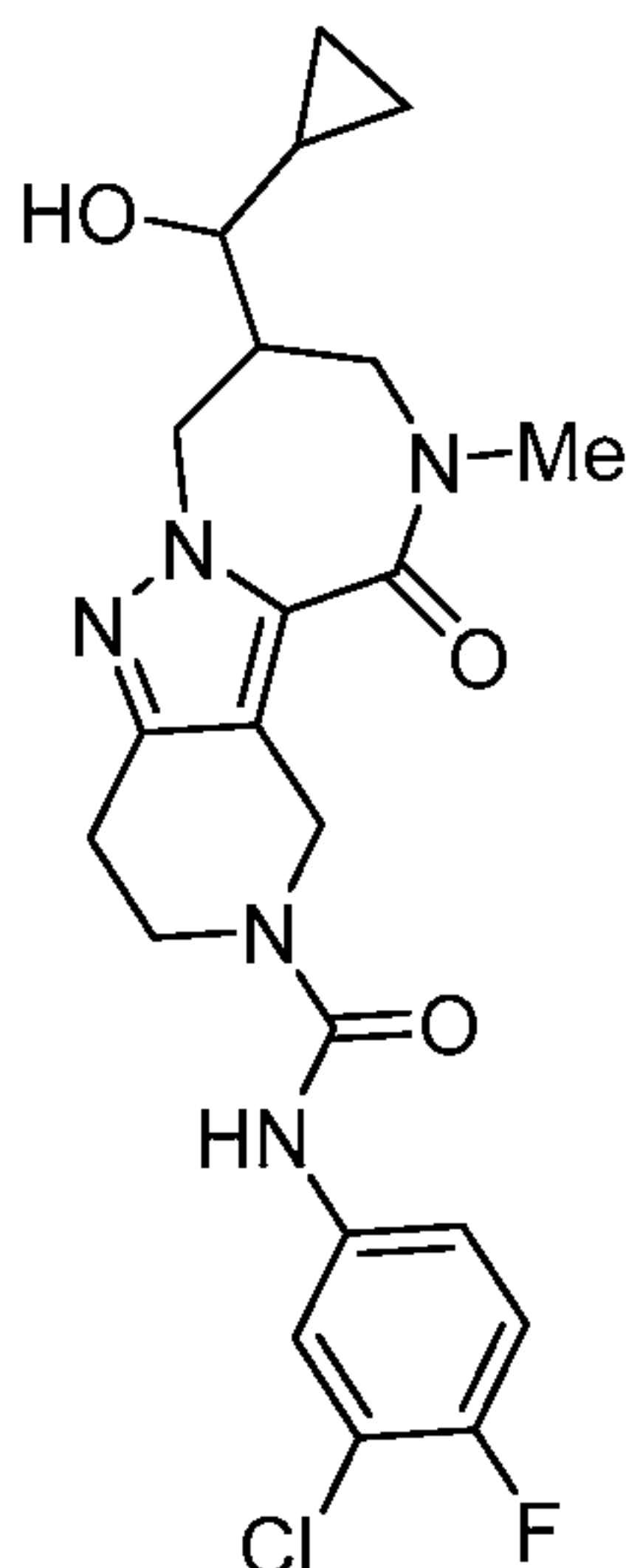
4.29 - 4.44 (m, 1 H), 4.15 (br d, *J* = 7.09 Hz, 1 H), 3.79 - 3.92 (m, 2 H), 3.64 (br dd, *J* = 5.87,

15.04 Hz, 1 H), 3.48 (br d, *J* = 5.14 Hz, 1 H), 3.37 (d, *J* = 7.46 Hz, 1 H), 3.19 (d, *J* = 2.08 Hz, 3

H), 2.84 (br t, *J* = 5.50 Hz, 2 H), 2.43 - 2.53 (m, 1 H), 1.85 - 1.99 (m, 1 H), 1.40 - 1.57 (m, 2 H),

0.99 - 1.07 (m, 3 H). LCMS: 450/452 [M+1].

Compound 036: N-(3-chloro-4-fluorophenyl)-8-(cyclopropyl(hydroxy)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



- 5 Step 1. N-(3-chloro-4-fluoro-phenyl)-8-(cyclopropanecarbonyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide. To a mixture of bromo(cyclopropyl)magnesium (0.5 M, 7.52 mL, 15.00 *eq*) in THF (3.00 mL) was added N2-(3-chloro-4-fluoro-phenyl)-N8-methoxy-N8,10-dimethyl- 11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2,8-dicarboxamide (Compound 034, product
- 10 from Step 1, 120.00 mg, 250.57 μ mol, 1.00 *eq*) in THF (2.00 mL) drop-wise at 0 °C under N₂. The mixture was heated to 15 °C and stirred for 14 hours. LCMS and TLC (Ethyl acetate : Methanol=20:1) showed the starting material :desired product=2:3. The mixture was poured into 1N HCl (10 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (10 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous
- 15 Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-TLC (Ethyl acetate : Methanol=20:1) to afford the title compound (50.00 mg, 101.11 μ mol, 40.35% yield, 93% purity) as yellow solid. LCMS: 460/462 [M+1].

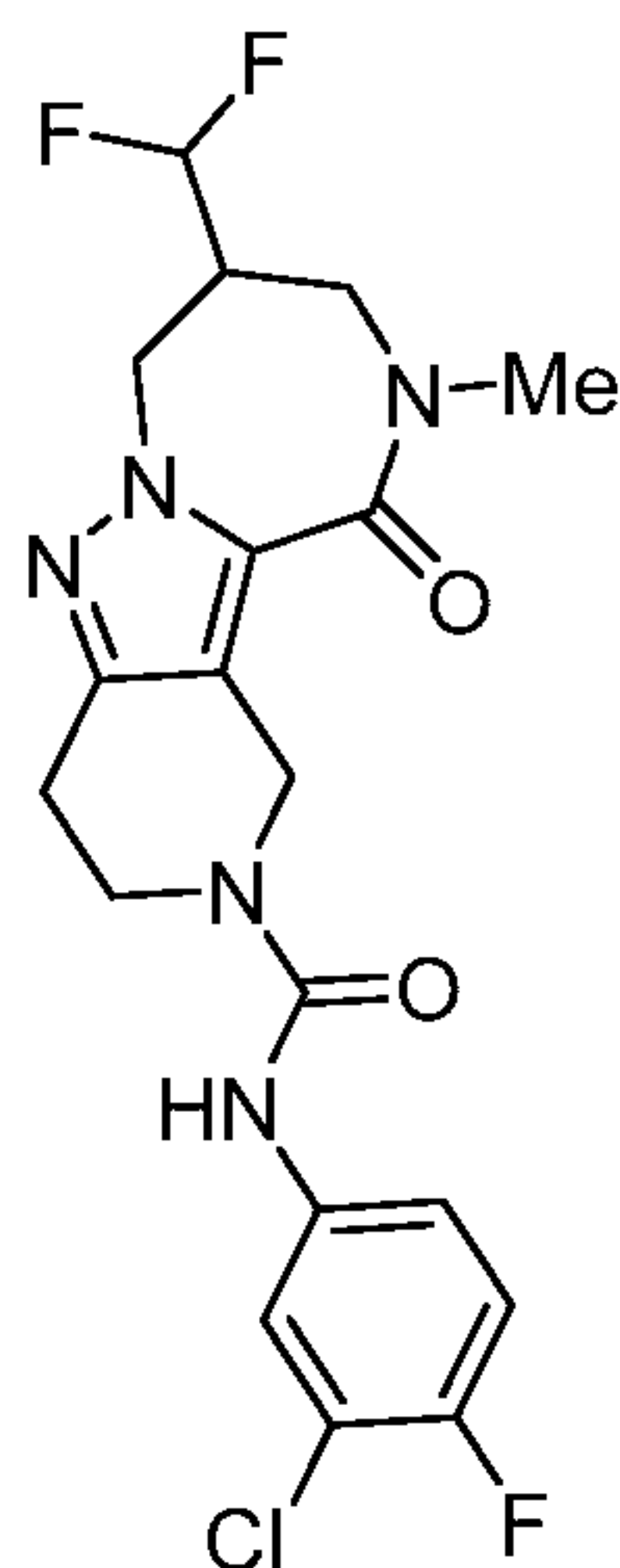
Step 2. N-(3-chloro-4-fluorophenyl)-8-(cyclopropyl(hydroxy)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

- 20 To a mixture of N-(3-chloro-4-fluoro-phenyl)-8-(cyclopropanecarbonyl)-10- methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide (50.00 mg, 108.72 μ mol, 1.00 *eq*) in EtOH (3.00 mL) was added NaBH₄ (6.17 mg, 163.08 μ mol, 1.50 *eq*) in

one portion at 0 °C under N₂. The mixture was stirred at 20 °C for 2 hours. LCMS showed the reaction was completed. The residue was poured into water (10 mL) and extracted with ethyl acetate (10 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-

5 HPLC(FA) to afford the title compound (46.00 mg, 98.29 μmol, 90.41% yield, 98.7% purity) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (dd, *J* = 2.32, 6.48 Hz, 1 bH), 7.15 - 7.23 (m, 1 H), 7.05 (t, *J* = 8.80 Hz, 1 H), 6.61 (br s, 1 H), 4.59 - 4.74 (m, 3 H), 4.44 - 4.54 (m, 1 H), 4.24 - 4.42 (m, 1 H), 3.78 - 3.92 (m, 2 H), 3.60 - 3.68 (m, 1 H), 3.45 - 3.58 (m, 1 H), 3.33 - 3.43 (m, 1 H), 3.19 (d, *J* = 5.50 Hz, 2 H), 3.13 - 3.25 (m, 1 H), 2.79 - 2.90 (m, 2 H), 2.79 - 2.91 (m, 1 H),
10 2.65 (br d, *J* = 6.97 Hz, 1 H), 1.74 - 1.98 (m, 1 H), 0.90 - 1.06 (m, 1 H), 0.57 - 0.78 (m, 2 H), 0.40 - 0.51 (m, 1 H), 0.32 (br dd, *J* = 3.55, 7.95 Hz, 2 H). LCMS: 462/464 [M+1].

Compound 037: N-(3-chloro-4-fluorophenyl)-8-(difluoromethyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



15

Step 1. N-(3-chloro-4-fluoro-phenyl)-8-(hydroxymethyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide. To a mixture of ethyl 2-[(3-chloro-4-fluoro-phenyl)carbamoyl]-10-methyl-11-oxo- 1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-8-carboxylate (Compound 030, 500.00 mg, 1.08 mmol, 1.00 *eq*) in THF (5.00 mL) was added LiAlH₄ (61.48 mg, 1.62 mmol, 1.50 *eq*) in one portion at -40 °C under N₂. The mixture was stirred at -40 °C for 30 min, then heated to 0 °C and stirred for 2 hours. TLC (Dichloromethane : Methanol=10:1) showed the reaction was

20

completed. The mixture was poured into HCl (1 N, 10 mL) and stirred for 1 min. The resulting was extracted with ethyl acetate (20 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Dichloromethane : Methanol=100:1~20:1) to afford the title compound (330.00 mg, 775.38 μmol, 71.79% yield, 99.12% purity) as yellow solid. LCMS: 422/424 [M+1].

Step 2. N-(3-chloro-4-fluoro-phenyl)-8-formyl- 10-methyl-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide. To a mixture of N-(3-chloro-4-fluoro-phenyl)-8-(hydroxymethyl)-10-methyl-11-oxo- 1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide (50.00 mg, 118.53 μmol, 1.00 *eq*) in DCM (3.00 mL) was added Dess-Martin (75.41 mg, 177.79 μmol, 55.04 μL, 1.50 *eq*) in one portion at 0°C under N₂. The mixture was stirred at 30 °C for 12 hours. LCMS showed the reaction was completed. The mixture was concentrated in vacuum. The residue was purified by silica gel chromatography (Ethyl acetate) to afford the title compound (40.00 mg, 43.83 μmol, 36.97% yield, 46% purity) as yellow solid.

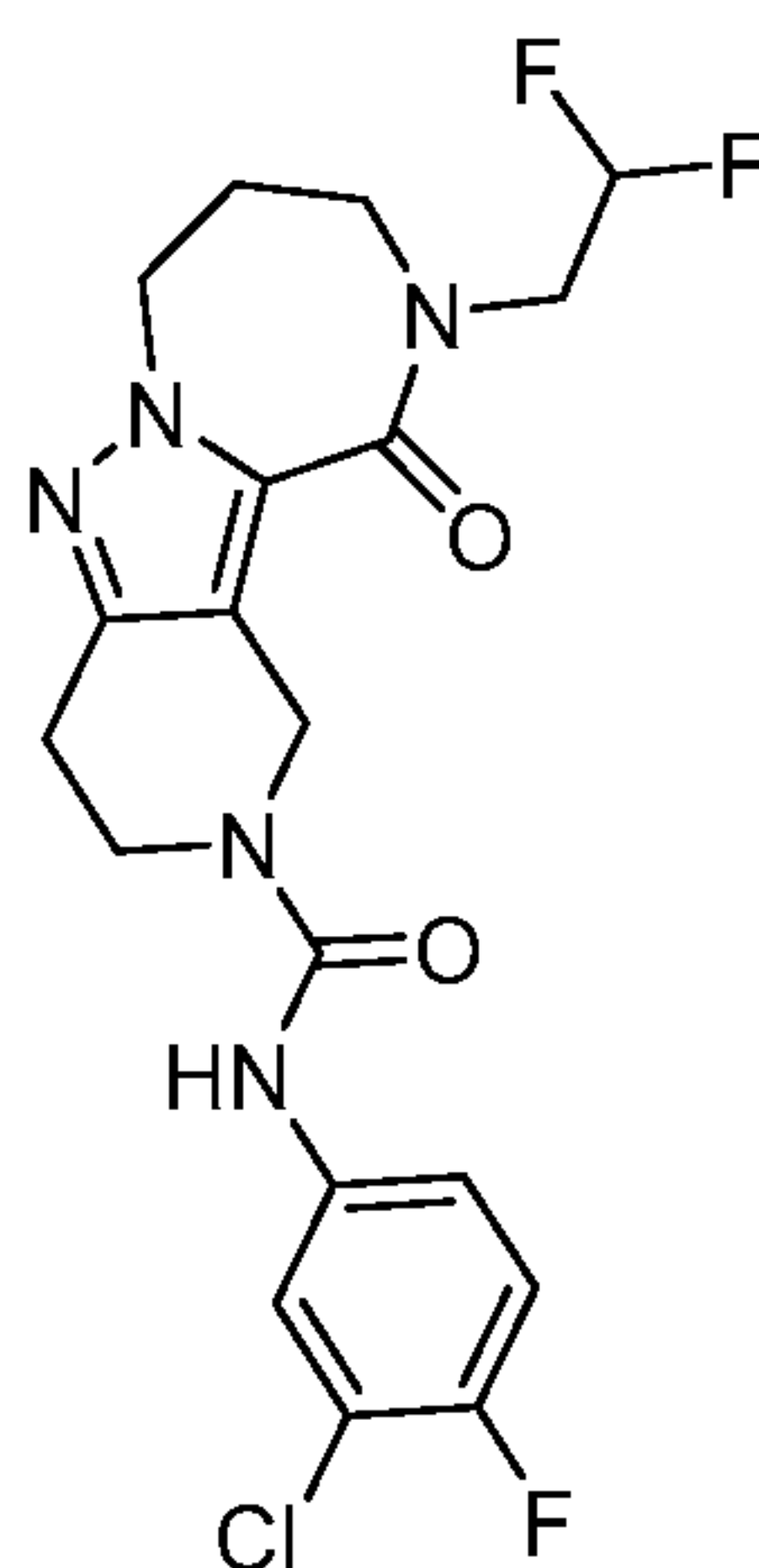
Step 3. N-(3-chloro-4-fluorophenyl)-8-(difluoromethyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-

octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. To a mixture of N-(3-chloro-4-fluoro-phenyl)-8-formyl-10-methyl-11-oxo- 1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide (40.00 mg, 95.27 μmol, 1.00*eq*) in DCM (4.00 mL) was added DAST (76.78 mg, 476.35 μmol, 62.93 μL, 5.00 *eq*) in one portion at -78 °C under N₂. The mixture was stirred at -78 °C for 2 hours, then heated to 20 °C and stirred for 12 hours. LCMS showed the reaction was completed. The mixture was poured into water (10 mL) and stirred for 2 min. The aqueous phase was extracted with DCM (10 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with

anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-HPLC(FA) to afford the title compound (15.00 mg, 33.58 μmol, 35.24% yield, 98.9% purity) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.58 (dd, *J* = 2.63, 6.54 Hz, 1 H), 7.17 - 7.26 (m, 1 H), 7.06 (t, *J* = 8.74 Hz, 1 H), 6.57 (br s, 1 H), 5.72 - 6.06 (m, 1 H), 4.63 - 4.72 (m, 2H), 4.52 (dd, *J* = 7.15, 14.49 Hz, 1 H), 4.40 (dd, *J* = 6.91, 14.61 Hz, 1 H), 3.85 (q, *J* = 5.42 Hz, 2 H), 3.55 (dq, *J* = 5.81, 15.39 Hz, 2 H), 3.19 (s, 3 H), 2.80 - 2.97 (m, 3 H), 1.60 (br s, 11 H). LCMS: 442/444 [M+1].

Compound 038: N-(3-chloro-4-fluorophenyl)-10-(2,2-difluoroethyl)-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



- 5 Step 1. tert-butyl 10-(2,2-difluoroethyl)-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of tert-butyl 11-oxo-3,4,7,8,9,10-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (Intermediate 5, 100.00 mg, 326.41 μ mol, 1.00 *eq*) in DMF (3.00 mL) was added NaH (19.58 mg, 489.61 μ mol, 60% purity, 1.50 *eq*) at 0 °C under N₂. After stirred at 0 °C for 30 minutes, 2,2-difluoroethyl
- 10 trifluoromethanesulfonate (349.44 mg, 1.63 mmol, 5.00 *eq*) was added. The reaction mixture was stirred at 15 °C for one hour. LCMS showed compound 5 was consumed completely and about 65% of desired compound was detected. The reaction was quenched with water (30 mL) and then extracted with EtOAc (50 mL*3). The combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel
- 15 chromatography to afford the title compound (64.00 mg, 172.79 μ mol, 52.94% yield) was obtained as yellow oil. LCMS: 371 [M+1].

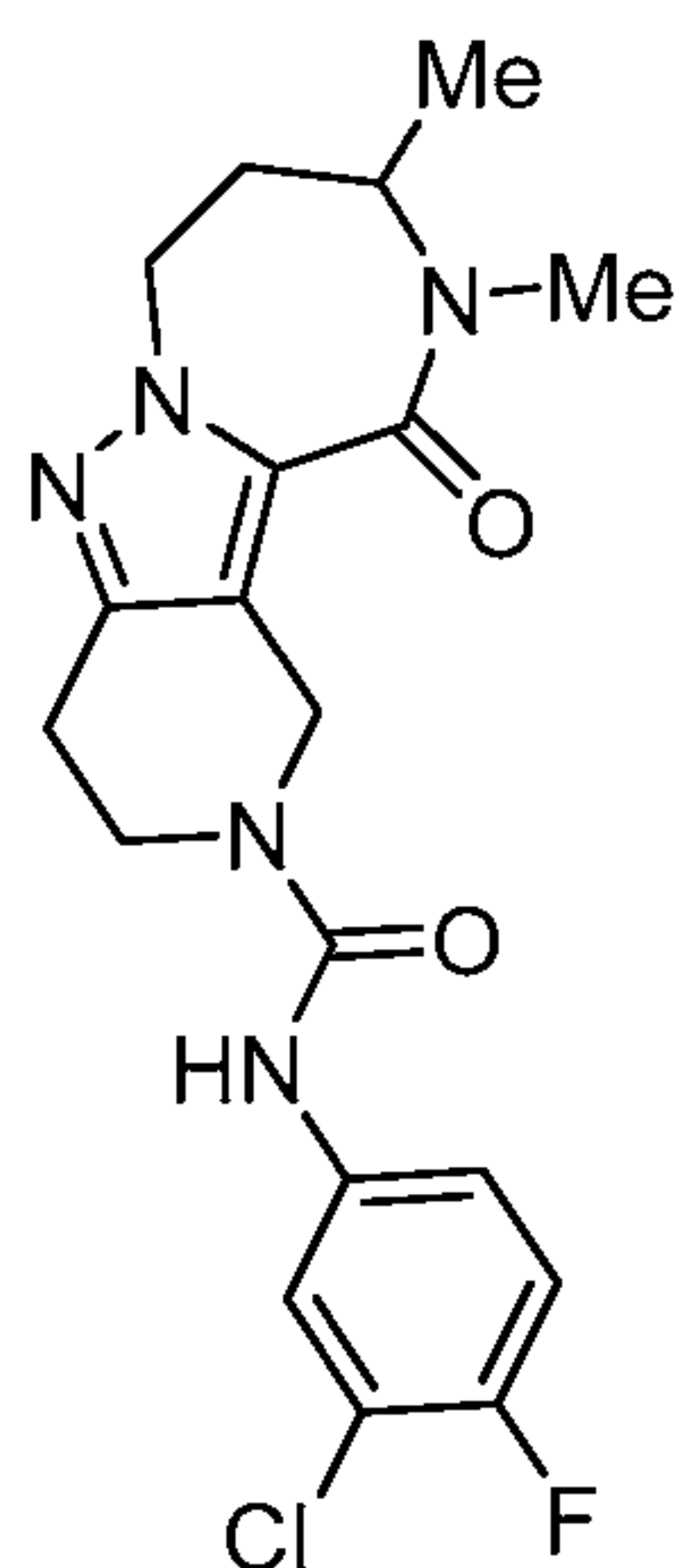
- Step 2. 10-(2,2-difluoroethyl)-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one. To a solution of tert-butyl 10-(2,2-difluoroethyl)-11-oxo-1,3,4,7,8,9-hexahydropyrido [2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (62.00 mg, 167.39 μ mol, 1.00 *eq*) in DCM (2.00 mL) was added TFA (1.54 g, 13.51 mmol, 1.00 mL, 80.69 *eq*), the
- 20 reaction mixture was stirred at 20 °C for one hour. TLC indicated compound 6 was consumed completely, and one major new spot with larger polarity was detected. The solvent was removed

on a rotary evaporator to afford the title compound (64.00 mg, crude, TFA) was obtained as yellow oil, which was used in next step directly without further purification.

Step 3. N-(3-chloro-4-fluorophenyl)-10-(2,2-difluoroethyl)-11-oxo-1,3,4,7,8,9,10,11-octahydro-

5 2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. To a mixture of 10-(2,2-difluoroethyl)-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo [2,4-b][1,4]diazepin-11-one (64.00 mg, 166.54 μ mol, 1.00 *eq*, TFA) in DCM (5.00 mL) was added TEA (67.41 mg, 666.15 μ mol, 92.34 μ L, 4.00 *eq*), followed by phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (44.24 mg, 166.54 μ mol, 1.00 *eq*), the reaction mixture was stirred at 20 °C for 16 hours. LCMS showed a main peak with desired MS was detected. The mixture was extracted with DCM (50 mL*2) and
10 water (30 mL), the organic phase was dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-HPLC(FA)to afford the title compound (72.00 mg, 161.20 μ mol, 96.79% yield, 98.92% purity) was obtained as white solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.55 - 7.57 (dd, *J* = 6.48, 2.69 Hz, 1 H) 7.18 - 7.20 (m, 1 H) 7.03 - 7.07 (m, 1 H) 6.54 (s, 1 H) 5.89 - 6.18 (m, 1 H) 4.67 (s, 2 H) 4.39 - 4.43 (t, *J* = 6.91 Hz, 2 H) 3.83 - 3.92 (m, 4
15 H) 3.57 - 3.61 (t, *J* = 6.24 Hz, 2 H) 2.83 - 2.86 (t, *J* = 5.75 Hz, 2 H) 2.32 - 2.38 (m, *J* = 6.57 Hz, 2 H). LCMS: 442/444 [M+1]

Compound 039: N-(3-chloro-4-fluorophenyl)-9,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

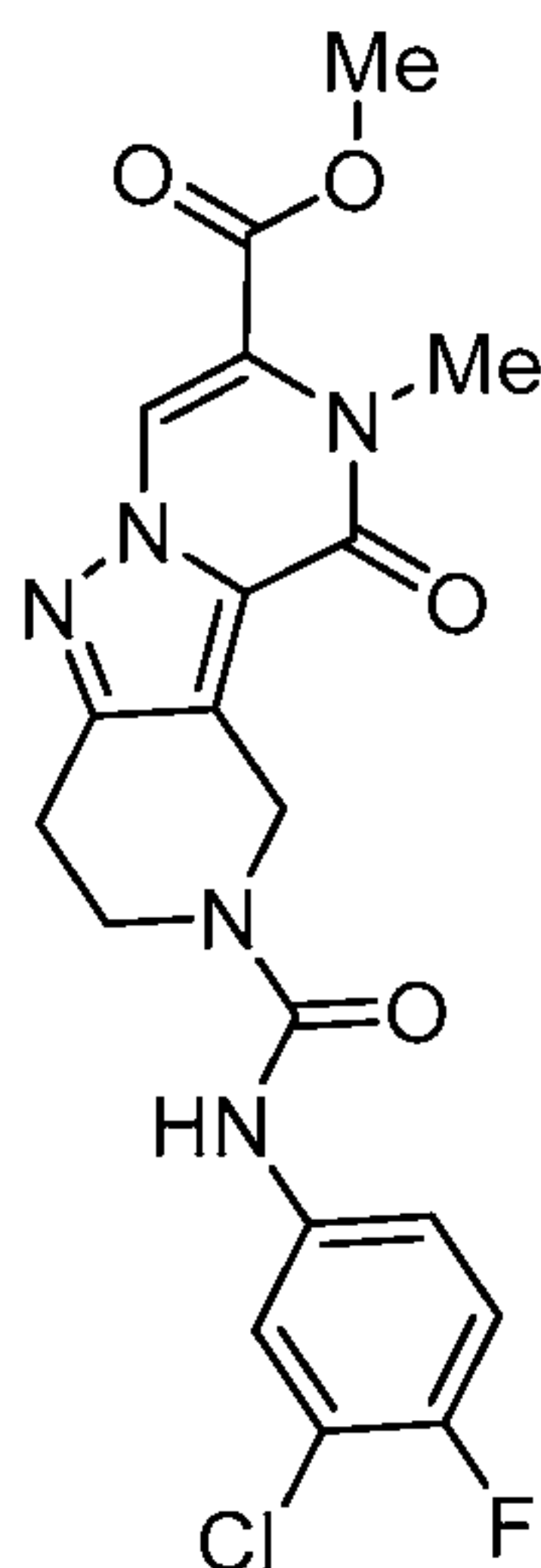


20 Step 1. 9,10-dimethyl-2,3,4,7,8,9-hexahydro -1H-pyrido[2,3]pyrazolo[2,4-c][1,4]diazepin-11-one. To a mixture of tert-butyl 9,10-dimethyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-2-carboxylate (Intermediate 8, 66.00 mg, 197.36 μ mol,

1.00 *eq*) in DCM (2.00 mL) was added TFA (1.54 g, 13.51 mmol, 1.00 mL, 68.44 *eq*) in one portion under N₂. The mixture was stirred at 15 °C for 2 hours. TLC (Dichloromethane : Methanol=10:1) showed the reaction was completed. The mixture was concentrated in vacuum to afford the title compound (68.74 mg, 197.35 μmol, 100.00% yield, TFA) as yellow oil.

- 5 Step 2. N-(3-chloro-4-fluorophenyl)-9,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. To a mixture of 9,10-dimethyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-c][1,4]diazepin-11-one (68.74 mg, 197.35 μmol, 1.00 *eq*, TFA) and phenyl N-(3-chloro -4-fluoro-phenyl)carbamate (52.43 mg, 197.35 μmol, 1.00 *eq*) in DCM (6.00 mL) was added TEA (199.70 mg, 1.97 mmol, 273.56 μL, 10.00 *eq*) under N₂. The mixture was stirred at 25 °C for 10 hours. LCMS showed the reaction was completed. The residue was poured into water (10 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (10 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-HPLC(FA) to afford the title compound (46.00 mg, 112.20 μmol, 15 56.85% yield, 98.99% purity) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.57 - 7.61 (m, 1 H), 7.16 - 7.22 (m, 1 H), 7.01 - 7.09 (m, 1 H), 6.52 - 6.59 (m, 1 H), 4.71 (s, 2 H), 4.44 - 4.54 (m, 1 H), 4.31 - 4.43 (m, 1 H), 3.84 (s, 3 H), 3.14 (s, 3 H), 2.79 - 2.89 (m, 2 H), 2.36 - 2.51 (m, 1 H), 2.11 - 2.27 (m, 1 H), 1.35 (d, *J* = 6.97 Hz, 3 H). LCMS: 406/408 [M+1].

- 20 Compound 040: methyl 2-((3-chloro-4-fluorophenyl)carbamoyl)-9-methyl-10-oxo-1,2,3,4,9,10-hexahydropyrido[4',3':3,4]pyrazolo[1,5-a]pyrazine-8-carboxylate.



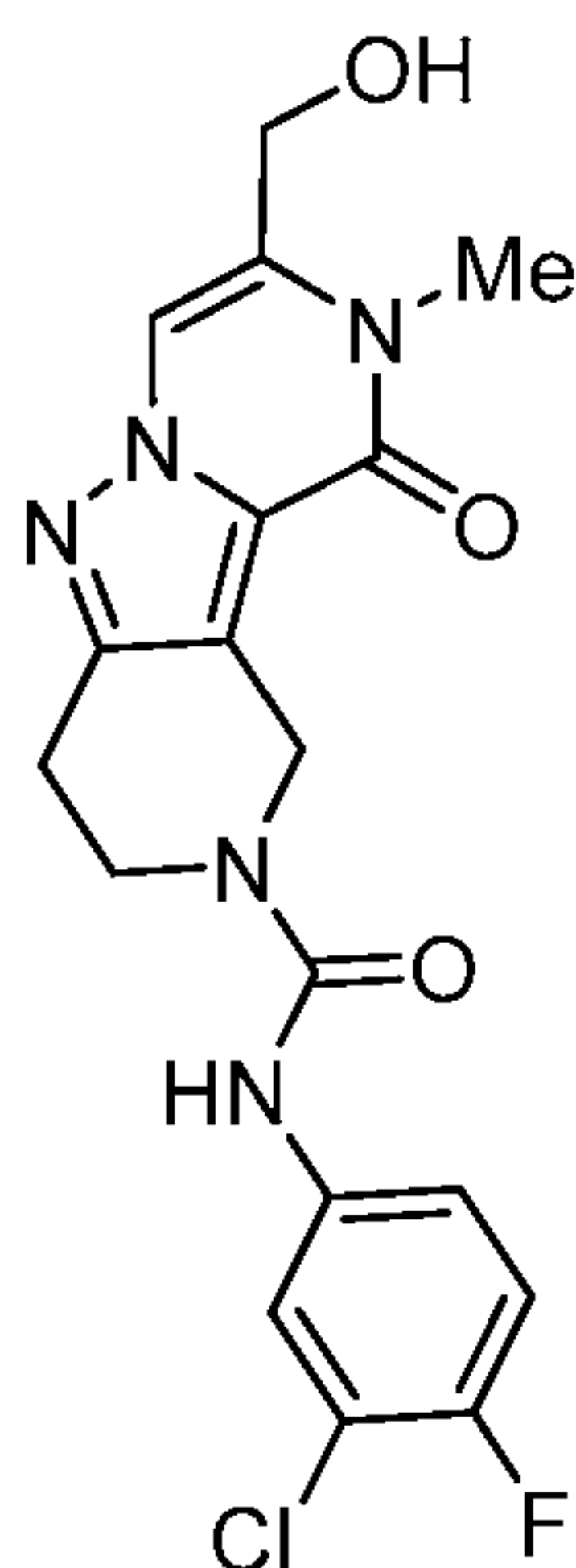
Step 1. methyl 9-methyl-10-oxo-1,2,3,4-tetrahydropyrido[2,3]pyrazolo [2,4-b]pyrazine-8-

carboxylate. A mixture of 2-tert-butyl-8-methyl-8-methoxy-9-methyl-10-oxo-1,3,4,7-tetrahydro
pyrido[2,3]pyrazolo[2,4-c]pyrazine-2,8-dicarboxylate (Intermediate 9, 20.00 mg, 50.71 μ mol,
1.00 *eq*) in HCl/dioxane (4 M, 20.00 mL, 1577.60 *eq*) was stirred at 20 °C for 2 hours. LCMS
5 showed the reaction was completed. The residue was concentrated in vacuum to afford the title
compound (15.15 mg, 50.71 μ mol, 100.00% yield, HCl) as yellow solid. LCMS: 263 [M+1].

Step 2. methyl 2-((3-chloro-4-fluorophenyl)carbamoyl)-9-methyl-10-oxo-1,2,3,4,9,10-

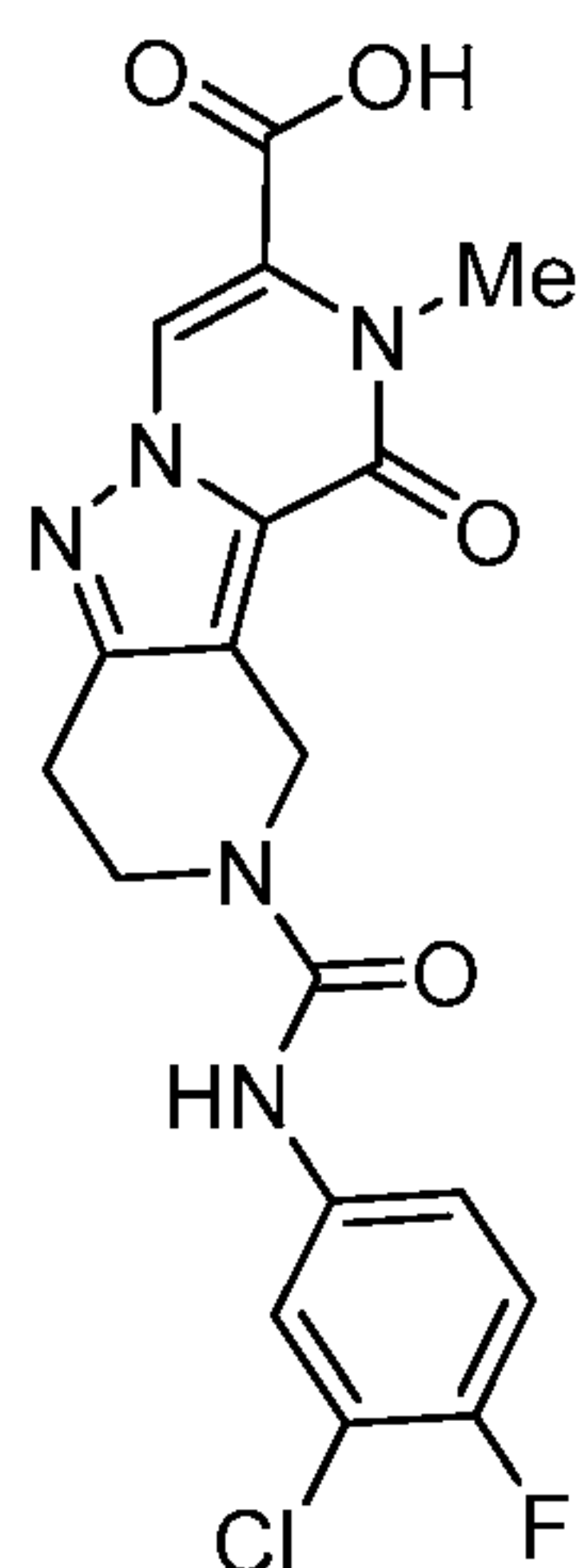
hexahydropyrido[4',3':3,4]pyrazolo[1,5-a]pyrazine-8-carboxylate. To a mixture of methyl 9-
methyl-10-oxo-1,2,3,4-tetrahydropyrido[2,3]pyrazolo [2,4-b]pyrazine-8-carboxylate (15.15 mg,
10 50.71 μ mol, 1.00 *eq*, HCl) and phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (13.47 mg, 50.71
 μ mol, 1.00 *eq*) in DCM (4.00 mL) was added TEA (51.32 mg, 507.15 μ mol, 70.30 μ L,
10.00 *eq*) under N₂. The mixture was stirred at 25 °C for 10 hours. LCMS showed the reaction
was completed. The residue was poured into water (10 mL) and stirred for 2 min. The aqueous
phase was extracted with ethyl acetate (10 mL*2). The combined organic phase was washed
15 with brine (10 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The
residue was purified by prep-HPLC (FA) to afford the title compound (15.00 mg, 32.43 μ mol,
63.96% yield, 93.8% purity) as white solid. ¹H NMR (400 MHz, CDCl₃) 8.20 (s, 1 H), 7.56 -
7.63 (m, 1 H), 7.14 - 7.24 (m, 1 H), 7.02 - 7.12 (m, 1 H), 6.55 (s, 1 H), 4.93 (s, 2 H), 3.95 (s, 3
H), 3.92 (s, 1 H), 3.75 (s, 3 H), 2.97-3.05 (m, 1 H). LCMS: 434 [M+1].

Compound 041: N-(3-chloro-4-fluorophenyl)-8-(hydroxymethyl)-9-methyl-10-oxo-3,4,9,10-
tetrahydropyrido[4',3':3,4]pyrazolo[1,5-a]pyrazine-2(1H)-carboxamide.



To a mixture of methyl 2-[(3-chloro-4-fluoro-phenyl)carbamoyl]-9-methyl-10-oxo- 3,4-dihydro-1H-pyrido[2,3]pyrazolo[2,4-b]pyrazine-8-carboxylate (Compound 040, 30.00 mg, 69.15 μ mol, 1.00 eq) in THF (2.00 mL) was added LiBH₄ (2.26 mg, 103.73 μ mol, 1.50 eq) in one portion at 0°C under N₂. The mixture was stirred at 0 °C for 1 hour, then heated to 20 °C and stirred
 5 for 2 hours. LCMS showed the reaction was completed. The reaction was quenched with NH₄Cl(5 mL). The aqueous phase was extracted with ethyl acetate (10 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-HPLC(FA) to afford the title compound (18.00 mg, 44.18 μ mol, 63.89% yield, 99.6% purity) as white solid. ¹H NMR
 10 (400 MHz, METHANOL-d₄) 7.60 (s, 2 H), 7.26 - 7.39 (m, 1 H), 7.06 - 7.20 (m, 1 H), 4.94 (s, 2 H), 4.56 (s, 2 H), 3.82 - 3.93 (m, 2 H), 3.59 (s, 3 H), 2.89 - 2.98 (m, 2 H). LCMS: 406 [M+1].

Compound 042: 2-((3-chloro-4-fluorophenyl)carbamoyl)-9-methyl-10-oxo-1,2,3,4,9,10-hexahydropyrido[4',3':3,4]pyrazolo[1,5-a]pyrazine-8-carboxylic acid.

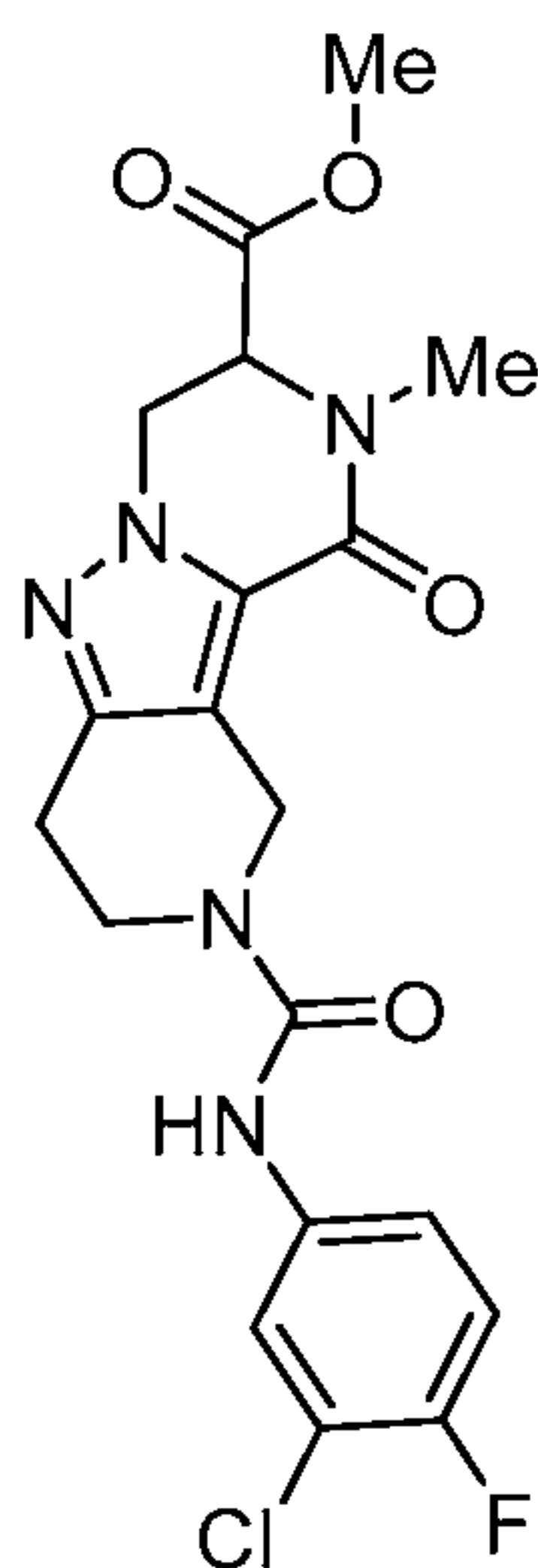


15

To a mixture of methyl 2-[(3-chloro-4-fluoro-phenyl)carbamoyl]-9-methyl-10-oxo- 3,4-dihydro-1H-pyrido[2,3]pyrazolo[2,4-b]pyrazine-8-carboxylate (Compound 040, 36.00 mg, 82.98 μ mol, 1.00 eq) in MeOH (4.00 mL) and H₂O (1.00 mL) was added NaOH (6.64 mg, 165.96 μ mol, 2.00 eq) in one portion under N₂. The mixture was stirred at 30 °C for 5 hours. LCMS showed
 20 the reaction was completed. The residue was adjust to pH=7 with 1N HCl and concentrated in vacuum. The residue was purified by prep-HPLC(HCl) to afford the title compound (8.00 mg, 18.77 μ mol, 22.62% yield, 98.5% purity) as white solid. ¹H NMR (400 MHz, METHANOL-d₄)

7.81 - 7.94 (m, 1 H), 7.51-7.72 (m, 1 H), 7.22 - 7.38 (m, 1 H), 7.04 - 7.19 (m, 1 H), 4.94 (s, 2 H), 3.82 - 3.91 (m, 2 H), 3.67 (s, 3 H), 2.89 - 3.01 (m, 2 H). LCMS: 420 [M+1].

Compound 043: methyl 2-((3-chloro-4-fluorophenyl)carbamoyl)-9-methyl-10-oxo-1,2,3,4,7,8,9,10-octahydropyrido[4',3':3,4]pyrazolo[1,5-a]pyrazine-8-carboxylate.



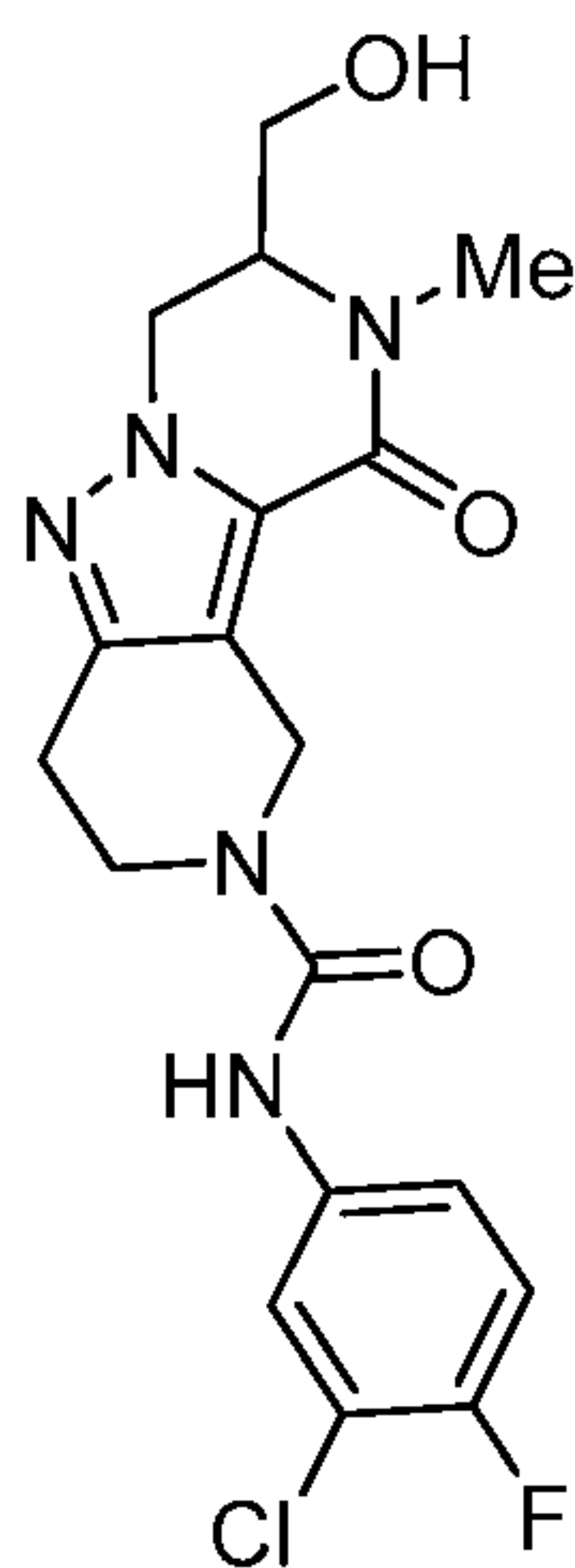
Step 1. methyl 9-methyl-10-oxo-1,2,3,4,7,8-hexahydropyrido[2,3]pyrazolo[2,4-c]pyrazine-8-carboxylate. To a solution of methyl 9-methyl-10-oxo-1,2,3,4-

10 tetrahydropyrido[2,3]pyrazolo[2,4-b]pyrazine-8-carboxylate (Intermediate 10, 10.00 mg, 33.48 μ mol, 1.00 *eq*, HCl) in AcOH (2.00 mL) was added Pd/C (4.00 mg, 33.48 μ mol, 1.00 *eq*) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (50 psi) at 40°C for 12 hours. LCMS showed little Desired product was detected. The reaction mixture was filtered and the filter was concentrated to afford the title
15 compound (10.86 mg, crude, HOAC) as yellow oil. LCMS: 265 [M+1].

Step 2. methyl 2-((3-chloro-4-fluorophenyl)carbamoyl)-9-methyl-10-oxo-1,2,3,4,7,8,9,10-octahydropyrido[4',3':3,4]pyrazolo[1,5-a]pyrazine-8-carboxylate. To a mixture of methyl 9-methyl-10-oxo-1,2,3,4,7,8-hexahydropyrido[2,3]pyrazolo[2,4-c]pyrazine-8-carboxylate (15.57 mg, 41.16 μ mol, 1.00 *eq*, TFA) and phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (10.93 mg, 41.16 μ mol, 1.00 *eq*) in DCM (4.00 mL) was added TEA (41.65 mg, 411.58 μ mol, 57.05 μ L, 10.00 *eq*) under N₂. The mixture was stirred at 25 °C for 10 hours. LCMS and TLC (Dichloromethane: Methanol=10:1) showed the reaction was completed. The residue was
20

poured into water (10 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (10 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-TLC (Dichloromethane:Methanol=10:1) to afford the title compound (16.00 mg, 35.76 μmol, 86.87% yield, 97.4% purity) as white solid. ¹H NMR (400 MHz, CDCl₃) 7.58 - 7.65 (m, 1 H), 7.17 - 7.24 (m, 1 H), 7.00 - 7.11 (m, 1 H), 6.64 - 6.72 (m, 1 H), 4.65 - 4.90 (m, 3 H), 4.50 - 4.61 (m, 1 H), 4.32 - 4.39 (m, 1 H), 3.83 - 3.91 (m, 2 H), 3.79 (s, 3 H), 3.17 (s, 3 H), 2.79 - 2.90 (m, 2 H). LCMS: 436 [M+1].

10 Compound 044: N-(3-chloro-4-fluorophenyl)-8-(hydroxymethyl)-9-methyl-10-oxo-3,4,7,8,9,10-hexahydropyrido[4',3':3,4]pyrazolo[1,5-a]pyrazine-2(1H)-carboxamide.

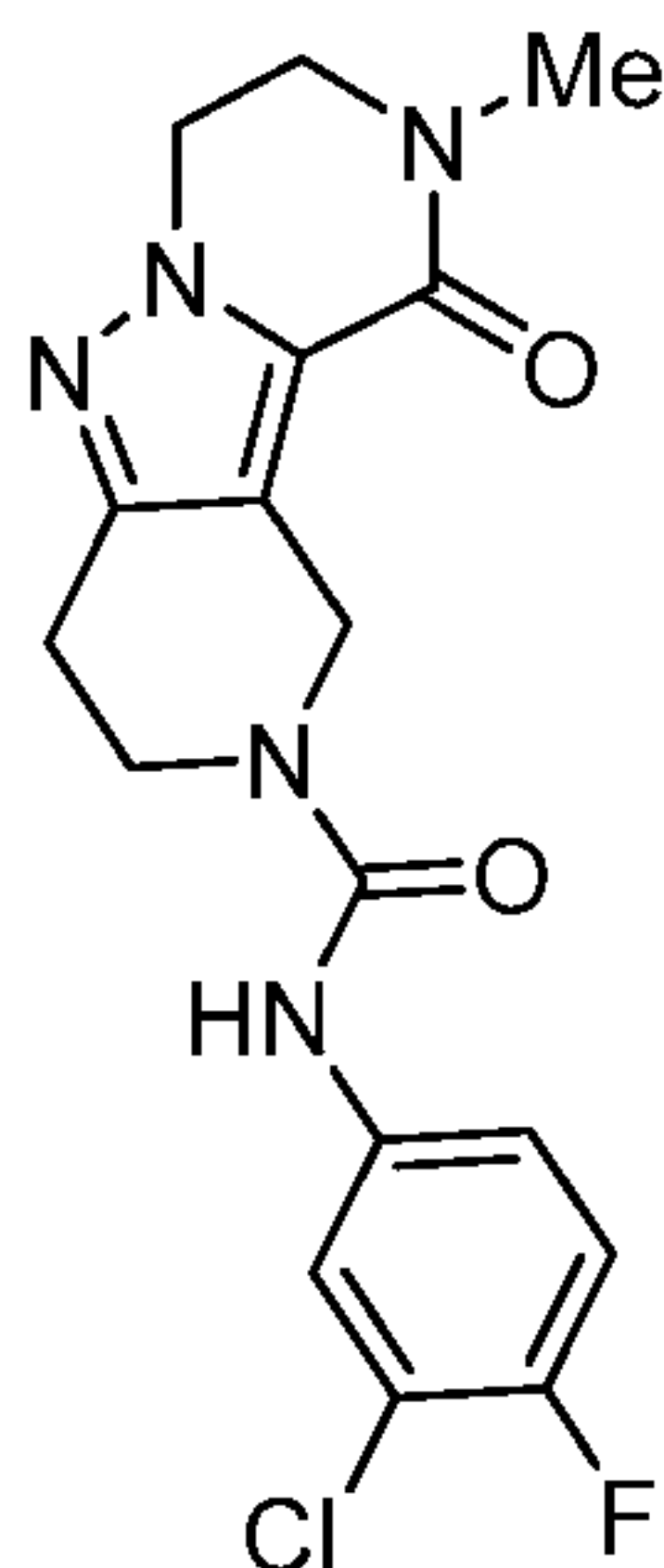


To a mixture of methyl 2-[(3-chloro-4-fluoro-phenyl)carbamoyl]-9-methyl-10-oxo- 3,4,7,8-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-c]pyrazine-8-carboxylate (Compound 043, 13.00 mg, 29.83 μmol, 1.00 *eq*) in THF (2.00 mL) was added LiBH₄ (3.25 mg, 149.14 μmol, 5.00 *eq*) in one portion at 0°C under N₂. The mixture was stirred at 0 °C for 1 hours, then heated to 20 °C and stirred for 2 hours. LCMS showed the reaction was completed. The reaction was quenched with NH₄Cl(5 mL), the aqueous phase was extracted with ethyl acetate (10 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-HPLC(FA) to afford the title compound (9.00 mg, 21.94 μmol, 73.54% yield, 99.4% purity) as white solid. ¹H NMR (400 MHz, METHANOL-d₄) 7.55 - 7.62 (m, 1 H), 7.26 - 7.33 (m, 1 H), 7.08 - 7.19 (m, 1 H),

4.75 (d, $J = 2.32$ Hz, 2 H), 4.35 - 4.56 (m, 2 H), 3.65 - 3.93 (m, 4 H), 3.43 - 3.53 (m, 1 H), 3.18 (s, 3 H), 2.82 (s, 2 H). LCMS: 408 [M+1].

Compound 045: N-(3-chloro-4-fluorophenyl)-9-methyl-10-oxo-3,4,7,8,9,10-

5 hexahydropyrido[4',3':3,4]pyrazolo[1,5-a]pyrazine-2(1H)-carboxamide.



Step 1. 9-methyl-1,2,3,4,7,8-hexahydropyrido[2,3]pyrazolo[2,4-b]pyrazin-10-one.

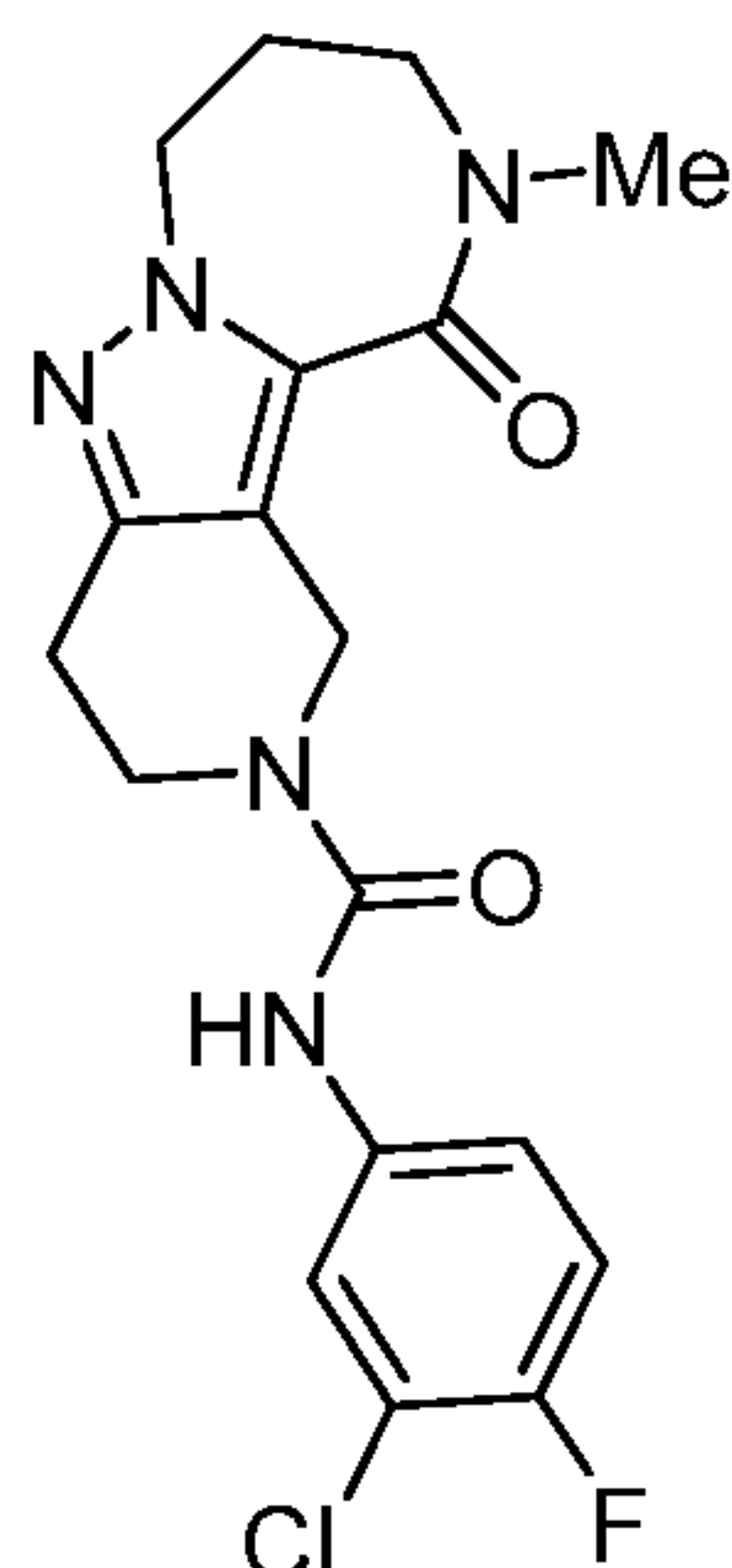
10 To a mixture of tert-butyl 9-methyl-10-oxo-3,4,7,8-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b]pyrazine-2-carboxylate (Intermediate 6, 70.00 mg, 228.49 μ mol, 1.00 *eq*) in DCM (1.00 mL) was added TFA (1.54 g, 13.51 mmol, 1.00 mL, 59.11 *eq*) in one portion under N₂. The mixture was stirred at 20 °C for 2 hours. TLC (Dichloromethane : Methanol=10:1) showed the reaction was completed. The mixture was concentrated in vacuum to afford the title compound (73.18 mg, 228.49 μ mol, 100.00% yield, TFA) as yellow oil.

Step 2. N-(3-chloro-4-fluorophenyl)-9-methyl-10-oxo-3,4,7,8,9,10-

15 hexahydropyrido[4',3':3,4]pyrazolo[1,5-a]pyrazine-2(1H)-carboxamide. To a mixture of 9-methyl-1,2,3,4,7,8-hexahydropyrido[2,3]pyrazolo[2,4-b]pyrazin-10-one (73.18 mg, 228.49 μ mol, 1.00 *eq*, TFA) and phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (60.70 mg, 228.49 μ mol, 1.00 *eq*) in DCM (6.00 mL) was added TEA (231.21 mg, 2.28 mmol, 316.73 μ L, 10.00 *eq*) under N₂. The mixture was stirred at 25 °C for 10 hours. LCMS showed the reaction
20 was completed. The residue was poured into water (10 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (10 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-HPLC(FA) to afford the title compound (47.00 mg, 124.16 μ mol, 54.34% yield, 99.8% purity) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.56 - 7.63 (m, 1 H),

7.14 - 7.24 (m, 1 H), 7.01 - 7.11 (m, 1 H), 6.61 (s, 1 H), 4.74 (s, 2 H), 4.32 - 4.44 (m, 2 H), 3.87 (t, $J = 5.75$ Hz, 2 H), 3.74 - 3.81 (m, 2 H), 3.14 (s, 3 H), 2.86 (t, $J = 5.75$ Hz, 2 H). LCMS: 378/380 [M+1].

- 5 Compound 046: N-(3-chloro-4-fluorophenyl)-10-methyl-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



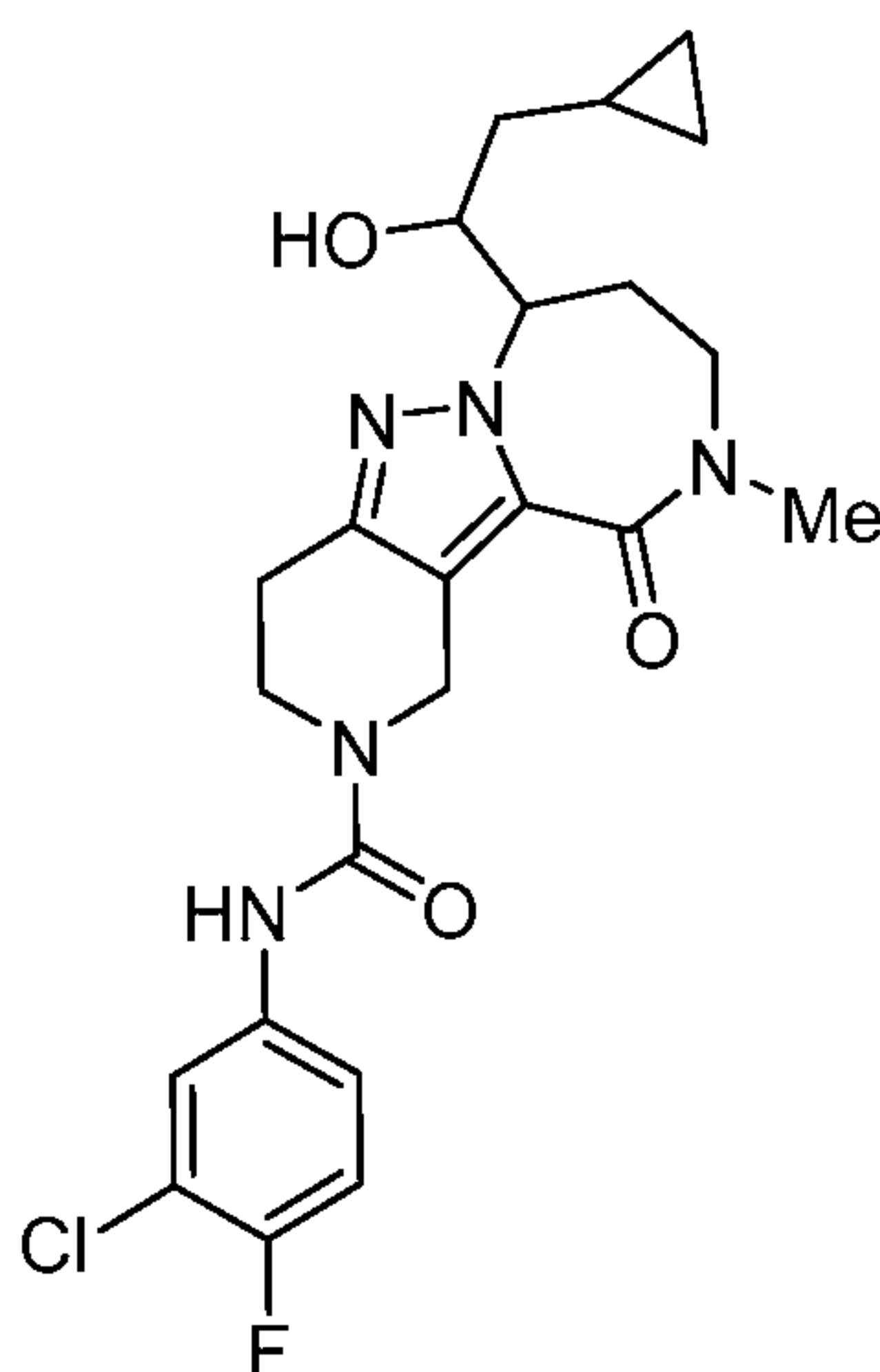
- 10 Step 1. tert-butyl 1,3,4,7,8,9,10,11-octahydropyrido[2,3]pyrazolo[2,4-a][1,4]diazepine-2-carboxylate. To a solution of tert-butyl 11-oxo-3,4,7,8,9,10-hexahydro-1H-pyrido[2,3]pyrazolo
- 15 [2,4-b][1,4]diazepine-2-carboxylate (Intermediate 5, 180.00 mg, 587.54 μ mol, 1.00 *eq*) in toluene (3.00 mL) was added Red-Al® (503.96 mg, 1.76 mmol, 503.96 μ L, 70% purity, 3.00 *eq*). The mixture was stirred at 0 °C for 30 min. Additional 0.05 mL of aliquots of the Red-Al® (sodium bis(2-methoxyethoxy)aluminum dihydride) solution was added every 30 minutes for four times. TLC (EA:MeOH=10:1) and LCMS showed tert-butyl 11-oxo-3,4,7,8,9,10-
- 20 Step 2. tert-butyl 10-methyl-3,4,7,8,9,11-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-a][1,4]diazepine-2-carboxylate. To a solution of tert-butyl 1,3,4,7,8,9,10,11-
- octahydropyrido[2,3]pyrazolo[2,4-a][1,4]diazepine-2-carboxylate (60.00 mg, 205.21 μ mol, 1.00 *eq*) and HCHO (166.55 mg, 2.05 mmol, 152.80 μ L, 37% purity, 10.00 *eq*) in MeOH (5.00 mL) was added HOAc (1.23 mg, 20.52 μ mol, 1.17 μ L, 0.10 *eq*). The mixture was stirred at 20 °C

for 0.5 hr. Then NaBH₃CN (51.58 mg, 820.85 μmol, 4.00 *eq*) was added. The mixture was stirred at 20 °C for 16 hr. TLC (EtOAc:MeOH = 10:1) showed one main spot appeared. The mixture was concentrated in vacuum. The residue was extracted with EtOAc (20 mL*2) and H₂O (10 mL). The combined organic layer was dried over Na₂SO₄, filtrated. The filtrate was concentrated in vacuum to afford the title compound (62.00 mg, crude) as brown oil.

Step 3. 10-methyl-1,2,3,4,7,8,9,11-octahydropyrido[2,3]pyrazolo[2,4-a][1,4]diazepine. To a solution of tert-butyl 10-methyl-3,4,7,8,9,11-hexahydro-1H-pyrido[2,3]pyrazolo [2,4-a][1,4]diazepine-2-carboxylate (80.00 mg, 261.10 μmol, 1.00 *eq*) in DCM (4.00 mL) was added TFA (6.16 g, 54.03 mmol, 4.00 mL, 206.92 *eq*). The mixture was stirred at 20 °C for 2 hr. TLC (EA:MeOH = 10:1) showed Compound 3 consumed. The mixture was concentrated in vacuum to afford the title compound (85.00 mg, crude, TFA) as brown oil.

Step 4. N-(3-chloro-4-fluorophenyl)-10-methyl-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. To a solution of 10-methyl-1,2,3,4,7,8,9,11-octahydropyrido[2,3]pyrazolo[2,4-a][1,4]diazepine (85.00 mg, 265.37 μmol, 1.00 *eq*, TFA) and phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (70.50 mg, 265.37 μmol, 1.00 *eq*) in DCM (3.00 mL) was added TEA (134.26 mg, 1.33 mmol, 183.92 μL, 5.00 *eq*). The mixture was heated to 20 °C for 16 hr. LCMS showed one main peak with desired Ms. The mixture was concentrated in vacuum. The residue was purified by prep-HPLC(FA), followed by prep-TLC (DCM:MeOH=10:1) and prep-HPLC(Base) to afford the title compound (15.00 mg, 39.58 μmol, 14.92% yield, 99.7% purity) as white solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.46 (dd, *J* = 2.69, 6.48 Hz, 1 H), 7.07 - 7.16 (m, 1 H), 6.90 - 7.02 (m, 1 H), 6.34 (s, 1 H), 4.41 (s, 2 H), 4.15 - 4.25 (m, 2 H), 3.67 (t, *J* = 5.81 Hz, 2 H), 3.57 (s, 2 H), 2.86 - 2.99 (m, 2 H), 2.74 (t, *J* = 5.75 Hz, 2 H), 2.30 (s, 3 H), 1.82 (br t, *J* = 4.95 Hz, 2 H). LCMS [M+1]: 378.

Compound 047: N-(3-chloro-4-fluoro-phenyl)-8-(2-cyclopropyl-1-hydroxy-ethyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide.



Step 1. 8-but-3-enoyl-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-

b][1,4]diazepine-2-carboxylate. To a solution of allyl(bromo)magnesium (1 M, 2.09 mL, 2.00 *eq*) in THF (10.00 mL) was added a solution of tert-butyl 8-[methoxy(methyl)carbamoyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (Intermediate 11, 500.00 mg, 1.04 mmol, 1.00 *eq*) in THF (10.00 mL) drop-wise at -30 °C over a period of 10 mins under N₂ and stirred for 1 hour. TLC indicated about 35% starting material remained, then another batch of allyl(bromo)magnesium (1 M, 2.09 mL, 2.00 *eq*) was added into the mixture drop-wise at -30 °C over a period of 10 mins and stirred for 1 hour.

TLC indicated the starting material was completely consumed, one new spot was detected. The reaction mixture was poured into 1N HCl (50 mL) at 0 °C and stirred for 10 min. The aqueous phase was extracted with ethyl acetate (10 mL * 2). The combined organic layers were washed with brine (10 mL * 1), dried over with Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound (170.00 mg, crude) as yellow solid, which was used into the next step without further purification.

Step 2. tert-butyl 8-(1-hydroxybut-3-enyl)-10-methyl-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a mixture of tert-butyl 8-but-3-enoyl-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (300.00 mg, 772.28 μmol, 1.00 *eq*) in MeOH (10.00 mL) was added NaBH₄ (58.43 mg, 1.54 mmol, 2.00 *eq*) in one portion at 0 °C. The mixture was stirred at 25 °C for 2 hours. TLC indicated the starting material was consumed completely and one new spot formed. The reaction mixture was filtered and concentrated in vacuum, then diluted with H₂O (20 mL) and extracted with EtOAc (10 * 3 mL). The combined organic layers were washed with

brine (15 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/1 to 0:1) to afford the title compound (182.00 mg, 466.09 μmol, 60.35% yield) as yellow oil.

Step 3. tert-butyl 8-(2-cyclopropyl-1-hydroxy-ethyl)-10-methyl-11-oxo-1,3,4,7,8,9-

5 hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a stirred suspension of ZnEt₂ (1 M, 1.23 mL, 12.00 eq) in toluene (8.00 mL) was added CH₂ICl (438.60 mg, 2.49 mmol, 24.27 eq) slowly drop-wise at -20 °C. The resulting mixture was stirred for 1 h and added a solution of tert-butyl 8-(1-hydroxybut-3-enyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (40.00 mg, 102.44 μmol, 1.00
10 eq) in toluene (2.00 mL) drop-wise at -20 °C. The resulting mixture was stirred at -20 °C for 12 h. TLC indicated one major new spot with larger polarity was detected. LC-MS showed the starting material was consumed completely and one main peak with desired MS was detected. The reaction was cooled to 0 °C and quenched with saturated solution of NH₄Cl (25 mL) and extracted with EtOAc (2* 20 mL), dried over sodium sulfate and evaporated under reduced
15 pressure. The residue was purified by prep-TLC (SiO₂, Petroleum ether : Ethyl acetate = 1:10) to afford the title compound (30.00 mg, 74.17 μmol, 72.40% yield) as white solid.

LCMS: 405[M+1].

Step 4. 8-(2-cyclopropyl-1-hydroxy-ethyl)-10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido

[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one. To a solution of tert-butyl 8-(2-cyclopropyl-1-
20 hydroxy-ethyl)-10-methyl-11-oxo- 1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (30.00 mg, 74.17 μmol, 1.00 eq) in DCM (8.00 mL) was added TFA (6.16 g, 54.03 mmol, 4.00 mL, 728.40 eq). The mixture was stirred at 30°C for 1h. TLC and LCMS indicated the starting material was consumed completely and one main peak with desired MS was detected. The mixture was concentrated under reduced pressure to afford the
25 title compound (50.00 mg, crude, TFA) as yellow oil. The residue was used into the next step without further purification.

LCMS: 305[M+1].

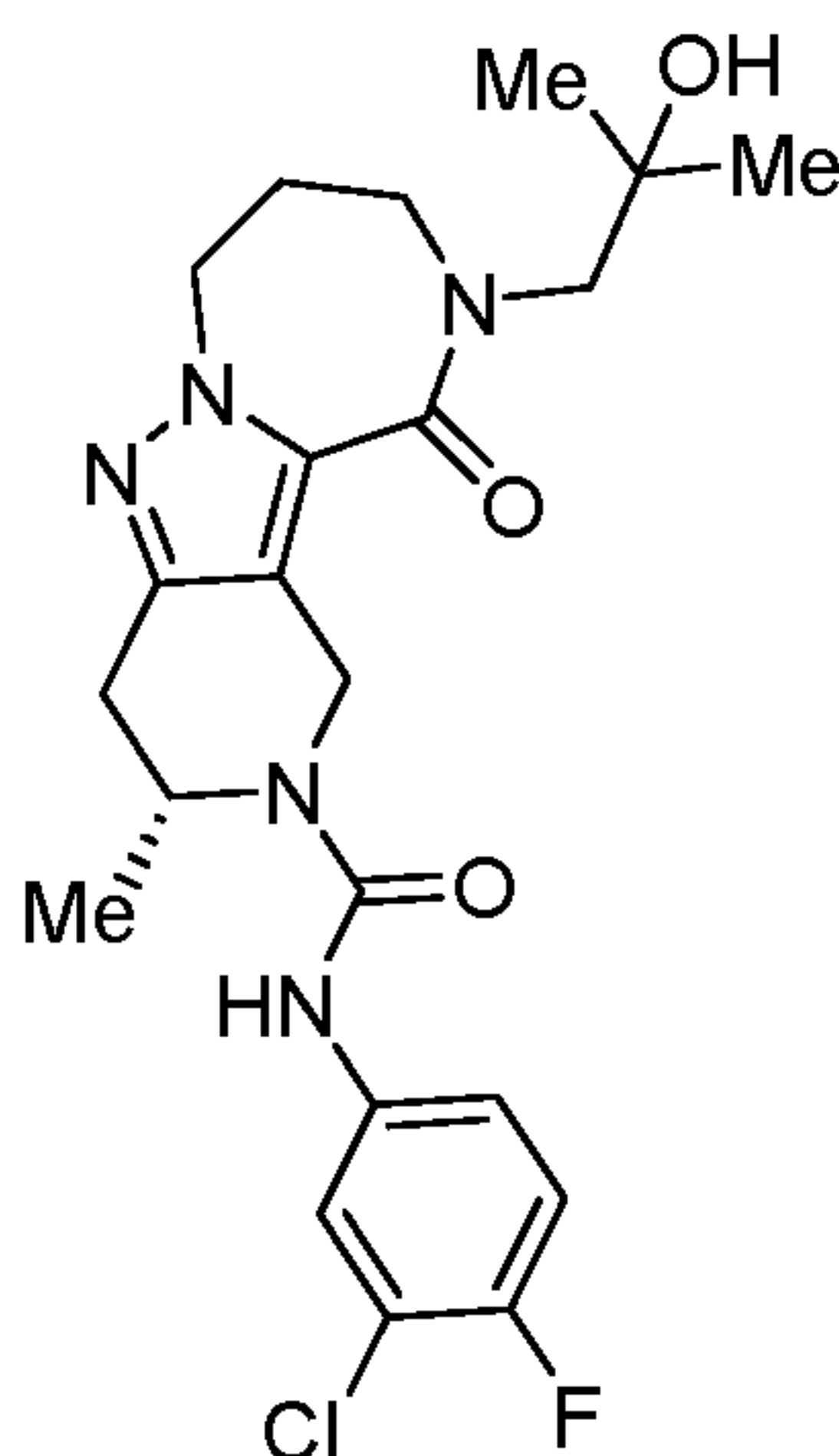
Step 5. N-(3-chloro-4-fluoro-phenyl)-8-(2-cyclopropyl-1-hydroxy-ethyl)-10-methyl-11-oxo- 1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide. To a solution of 8-(2-cyclopropyl-1-
30 hydroxy-ethyl)-10-methyl-2,3,4,7,8,9-hexahydro -1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (18.00 mg, 43.02 μmol, 1.00 eq, TFA) and TEA (21.77 mg, 215.10 μmol, 29.82 μL, 5.00

eq) in DCM (8.00 mL) was added phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (13.71 mg, 51.62 μ mol, 1.20 eq) with stirring at 30 °C for 1 h. LCMS indicated the desired MS. The mixture was directly evaporated in vacuo and purified by prep-HPLC(FA) to afford the title compound (2.49 mg, 5.23 μ mol, 12.16% yield) as white solid. LCMS: 476[M+1]. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (dd, *J*=2.57, 6.60 Hz, 1H), 7.15-7.25 (m, 1H), 7.00-7.11 (m, 1H), 6.60 (br d, *J*=4.40 Hz, 1H), 4.61-4.72 (m, 2.5 H), 4.38-4.39 (m, 1H), 4.10-4.16 (m, 0.5 H), 3.81-3.87 (m, 3H), 3.48-3.62 (m, 1H), 3.35-3.38 (m, 1H), 3.18 (s, 3H), 2.82-2.84 (m, 2H), 2.51-2.53 (m, 1H), 2.11-2.13 (m, 1H), 1.35-1.42 (m, 2H), 0.75-0.81 (m, 1H), 0.53-0.61 (m, 2H), 0.10-0.216 (m, 2H).

10

Compound 048: (3R)- N-(3-chloro-4-fluorophenyl)-10-(2-hydroxy-2-methylpropyl)-3-methyl-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



- 15 Step 1. tert-butyl (3R)-10-(2-methoxy-2-oxo-ethyl)-3-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of tert-butyl (3R)-3-methyl-11-oxo-3,4,7,8,9,10-hexahydro-1H-pyrido [2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (Intermediate 12, 100.00 mg, 312.12 μ mol, 1.00 eq) in THF (5.00 mL) was added NaH (24.97 mg, 624.24 μ mol, 60% purity, 2.00 eq) at 0 °C with stirring for 0.5 h under N₂.
- 20 Then followed by methyl 2-bromoacetate (62.07 mg, 405.76 μ mol, 38.32 μ L, 1.30 eq). The mixture was stirred at 20 °C for 2 h. TLC (PE: EtOAc = 1:3) showed that the tert-butyl (3R)-3-methyl-11-oxo-3,4,7,8,9,10-hexahydro-1H-pyrido [2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate was consumed completely and one main new spot formed. The mixture was

quenched with 10 mL of ice-water and extracted with EtOAc (20 mL*3). The organic phase was washed with brine (15 mL*1), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by prep-TLC (PE: EtOAc = 1:3) to obtain the title compound (116.00 mg, 280.29 μmol, 89.80% yield) as white solid.

5 Step 2. tert-butyl(3R)-10-(2-hydroxy-2-methyl-propyl)-3-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a mixture of MeMgBr (3 M, 1.02 mL, 10.00 eq) in THF (5.00 mL) was added a solution of tert-butyl (3R)-10-(2-methoxy-2-oxo-ethyl)-3-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (120.00 mg, 305.77 μmol, 1.00 eq) in THF (3.00 mL) in one portion at 0 °C under
10 N₂. TLC showed that the tert-butyl (3R)-10-(2-methoxy-2-oxo-ethyl)-3-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate was consumed completely and one new spot formed. The mixture was stirred at 0 °C for 0.5 h, then warmed to 20 °C and stirred for 2 h. The mixture was quenched with saturated NH₄Cl aqueous solution and extracted with EtOAc (20 mL*3). The organic phase was washed with brine (20 mL*1), dried
15 over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by prep-TLC and further purified by prep-HPLC (FA) to obtain the title compound (40 mg, 93% purity) as off-white oil. ¹H NMR (400 MHz, CDCl₃) δ = 4.76 - 5.07 (m, 2 H), 4.29 - 4.50 (m, 2 H), 4.07 - 4.21 (m, 1 H), 3.64 - 3.70 (m, 1 H), 3.47 - 3.62 (m, 3 H), 2.92 (br dd, *J* = 5.90, 15.81 Hz, 1 H), 2.56 (br d, *J* = 15.81 Hz, 2 H), 2.25 - 2.42 (m, 2 H), 2.15 - 2.23 (m, 1 H), 1.47 (s, 9 H), 1.28 (d, *J* = 4.64 Hz, 6 H), 1.12 (d, *J* = 6.90 Hz, 3 H).

Step 3. (3R)-10-(2-hydroxy-2-methyl-propyl)-3-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one. To a solution of tert-butyl (3R)-10-(2-hydroxy-2-methyl-propyl)-3-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (40.00 mg, 101.91 μmol, 1.00 eq) in DCM (5.00 mL) was added
25 TFA (770.00 mg, 6.75 mmol, 500.00 μL, 66.27 eq) with stirring at 25 °C for 1 h. LCMS indicated that the tert-butyl(3R)-10-(2-hydroxy-2-methyl-propyl)-3-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate was consumed completely and desired product was detected. The mixture was directly evaporated in vacuo. The residue was not purified and used in the next step. (45.00 mg, crude, TFA) was obtained as yellow oil
30 and used in the next step.

Step 4. (3R)- N-(3-chloro-4-fluorophenyl)-10-(2-hydroxy-2-methylpropyl)-3-methyl-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

To a solution of (3R)-10-(2-hydroxy-2-methyl-propyl)-3-methyl-2,3,4,7,8,9- hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (45.00 mg, 116.73 μ mol, 1.00 *eq*, TFA) and

TEA (67.23 mg, 664.38 μ mol, 92.10 μ L, 6.00 *eq*) in DCM (5.00 mL) was added phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (32.36 mg, 121.80 μ mol, 1.10 *eq*) with stirring at 25 °C for 16

h. LCMS indicated that the (3R)-10-(2-hydroxy-2-methyl-propyl)-3-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one was consumed completely and desired product was detected. The mixture was directly evaporated in vacuo. The residue was

purified by prep-HPLC (FA), following by by SFC (Instrument: SFC 80; Column: OD-10 μ m.

Mobile phase: A for CO₂ and B for MeOH(0.1%NH₃H₂O); Gradient: B 30% ; Flow rate: 60mL/min; Back pressure: 100bar; Column temperature: 35°C; Wavelength: 220nm.). The title

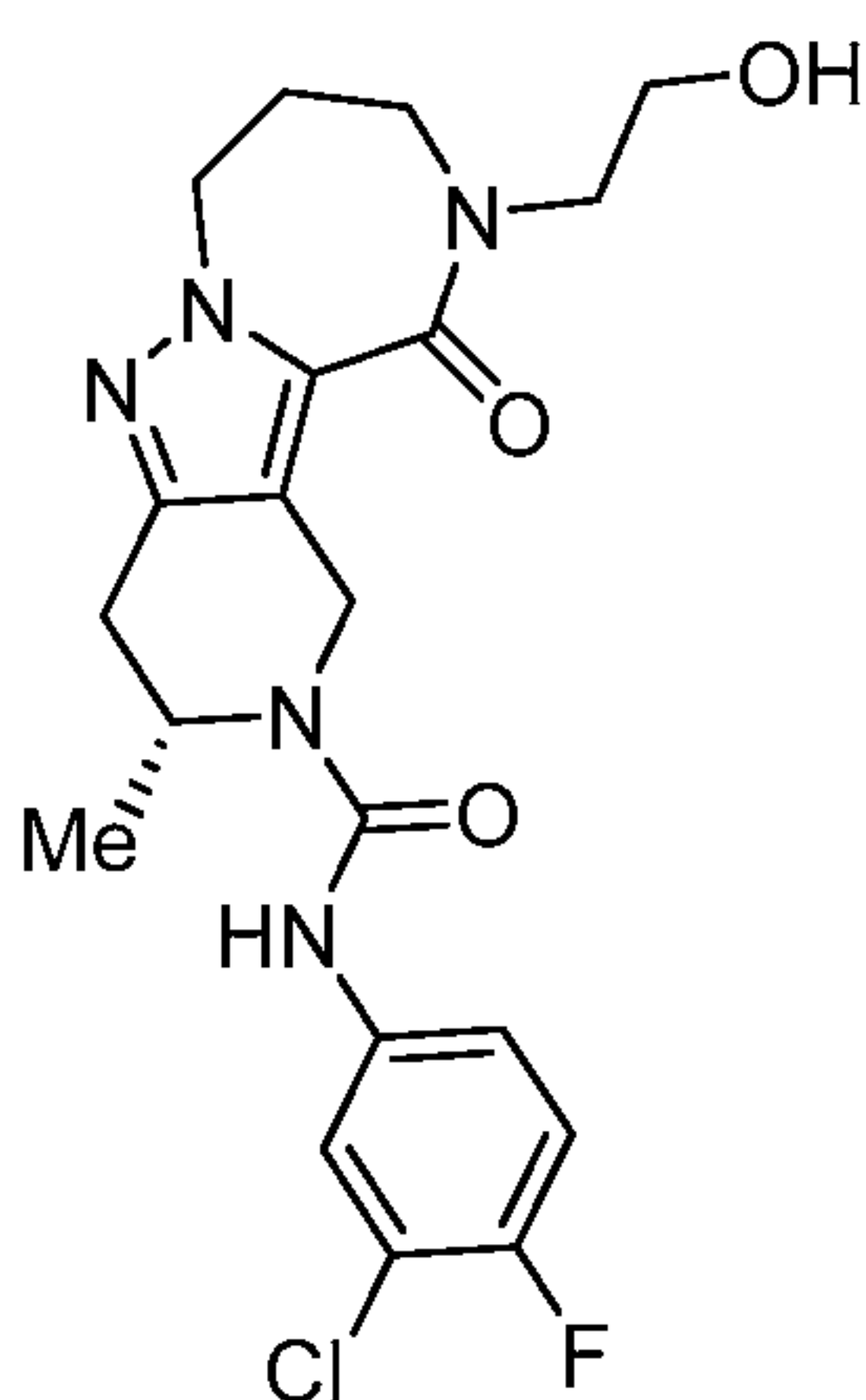
compound (19.00 mg, 40.54 μ mol, 36.62% yield, 99% purity) was obtained as white solid.

LCMS: 464[M+1]. ¹H NMR (400 MHz, CDCl₃) δ = 7.60 (dd, *J* = 2.63, 6.54 Hz, 1 H), 7.18 -

7.25 (m, 1 H), 7.00 - 7.09 (m, 1 H), 6.61 (s, 1 H), 5.14 (quin, *J* = 6.57 Hz, 1 H), 4.79 -4.81 (d, *J* = 15.53 Hz, 1 H), 4.37 - 4.48 (m, 3 H), 3.55 - 3.69 (m, 4 H), 3.00 – 3.03 (m, 1 H), 2.64-2.67 (d, *J* = 15.89 Hz, 1 H), 2.32 - 2.48 (m, 2 H), 1.32 (s, 6 H), 1.18 (d, *J* = 6.85 Hz, 3 H).

Compound 049: (3R)- N-(3-chloro-4-fluorophenyl)-10-(2-hydroxyethyl)-3-methyl-11-oxo-

1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. tert-butyl (3R)-10-(2-hydroxyethyl)-3-methyl -11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of tert-butyl

(3R)-10-(2-methoxy-2-oxo-ethyl)-3-methyl-11-oxo-1,3,4,7, 8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (Compound 048, product from Step 1, 50.00 mg, 127.40 μ mol, 1.00 *eq*) in THF (5.00 mL) was added LiAlH₄ (9.67 mg, 254.80 μ mol, 2.00 *eq*) at -78 °C with stirring under N₂. The mixture was warmed to 0 °C with stirring for 2 h. TLC (PE: EtOAc = 1:3) showed that the tert-butyl (3R)-10-(2-methoxy-2-oxo-ethyl)-3-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate consumed completely and one main new spot formed. LCMS indicated desired product was detected. The mixture was quenched with 20 mL of water and extracted with EtOAc (20 mL*3). The organic phase was washed with brine (20 mL*1), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by prep-TLC (PE: EtOAc = 1:3). The title compound (35.00 mg, 96.04 μ mol, 75.38% yield) was obtained as light-yellow oil.

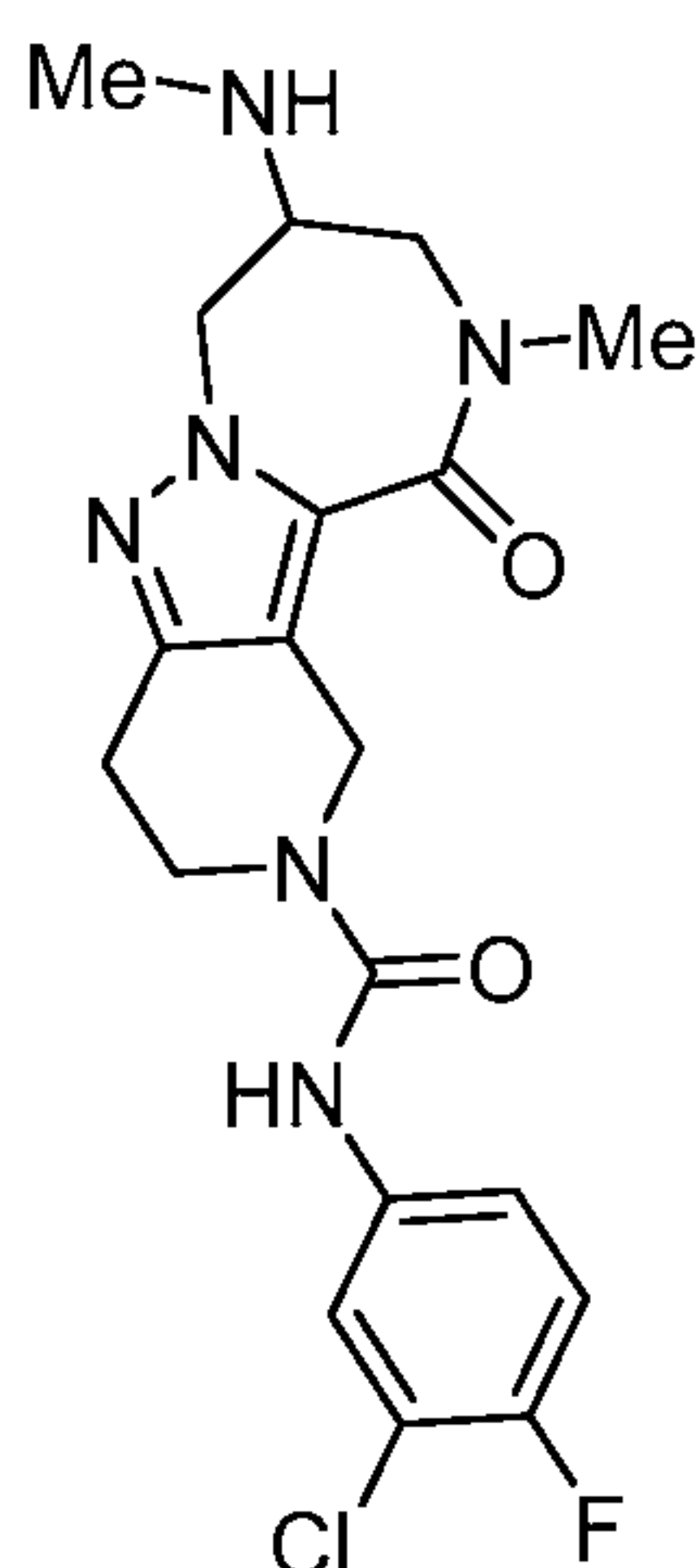
Step 2. (3R)-10-(2-hydroxyethyl)-3-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one. To a solution of tert-butyl (3R)-10-(2-hydroxyethyl)-3-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (35.00 mg, 96.04 μ mol, 1.00 *eq*) in DCM (3.00 mL) was added TFA (770.00 mg, 6.75 mmol, 500.00 μ L, 70.32 *eq*) at 20 °C with stirring for 1 h. TLC (PE: EtOAc = 1:1) showed that the tert-butyl (3R)-10-(2-hydroxyethyl)-3-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate consumed completely and one new spot formed. The mixture was concentrated in vacuo to afford the title compound (40.00 mg, crude, TFA) as yellow oil and directly used in the next step.

Step 3. (3R)-N-(3-chloro-4-fluorophenyl)-10-(2-hydroxyethyl)-3-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. To a solution of (3R)-10-(2-hydroxyethyl)-3-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (40.00 mg, 105.72 μ mol, 1.00 *eq*, TFA) and phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (30.90 mg, 116.29 μ mol, 1.10 *eq*) in DCM (3.00 mL) was added TEA (32.09 mg, 317.17 μ mol, 43.96 μ L, 3.00 *eq*) with stirring at 20 °C for 16 h. LCMS indicated that reactant was consumed completely and 55% of desired product. The mixture was concentrated in vacuo, and the residue was purified by prep-HPLC (FA). The title compound (17.50 mg, 38.14 μ mol, 36.08% yield, 95% purity) was obtained as white solid. LCMS: 436[M+1]. ¹H NMR (400 MHz, CDCl₃) δ = 7.60 (dd, *J* = 2.63, 6.54 Hz, 1 H), 7.18 - 7.25 (m, 1 H), 7.00 - 7.09 (m, 1 H), 6.61 (s, 1 H), 5.12 - 5.15 (m, 1 H), 4.09-4.85 (m, 1 H), 4.37 -

4.48 (m, 3 H), 3.89 - 3.92 (m, 2 H), 3.76 - 3.78 (m, 2 H), 3.54 - 3.56 (m., 2H), 3.00-3.04 (m, 1 H), 2.65-2.69 (m, 1 H), 2.34 - 2.37 (m, 2 H), 1.17 (d, $J = 6.85$ Hz, 3 H).

Compound 050: N-(3-chloro-4-fluorophenyl)-10-methyl-8-(methylamino)-11-oxo-

5 1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. tert-butyl 10-methyl-8-(methylamino)-11-oxo-1,3,4,7,8,9-hexahydropyrido [2,3]

pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. A mixture of tert-butyl 10-methyl-8,11-dioxo-

3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxylate

10 (Intermediate 2, 300.00 mg, 897.21 μmol , 1.00 *eq*), methylamine (7.5 M, 239.26 μL , 2.00 *eq*,

EtOH solution), CH_3COOH (53.88 mg, 897.21 μmol , 51.31 μL , 1.00 *eq*) and 4A molecular

sieve (400.00 mg) in DCE (8.00 mL) was stirred at 20 °C for 16 h. NaBH_3CN (281.90 mg, 4.49

mmol, 5.00 *eq*) was added and the mixture was stirred at 20 °C for 3 h. The mixture was diluted

with EtOAc (40 mL) and washed with brine (40 mL). The organic phase was dried over

15 Na_2SO_4 , filtered and concentrated in vacuo, which was purified by silica gel column to afford the

title compound (120.00 mg, 309.07 μmol , 34.45% yield, 90% purity) as yellow oil.

LCMS: 350 [M+1].

Step 2. tert-butyl 8-[allyloxycarbonyl(methyl)amino]-10- methyl-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of tert-butyl 10-

20 methyl-8-(methylamino)-11-oxo-1,3,4,7,8,9- hexahydropyrido[2,3]pyrazolo[2,4-

b][1,4]diazepine-2-carboxylate (116.00 mg, 314.80 μmol , 1.00 *eq*) and NaHCO_3 (79.34 mg,

944.40 μmol , 36.73 μL , 3.00 *eq*) in THF (4.00 mL) and H_2O (1.00 mL) was added allyl

carbonochloridate (49.33 mg, 409.24 μmol , 43.27 μL , 1.30 *eq*), and the mixture was stirred at

20 °C for 16 h. The mixture was diluted with EtOAc (40 mL) and washed with HCl (1 M, 40 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo, which was purified by prep-TLC to afford the title compound (99.00 mg, 228.37 μmol, 72.55% yield) as yellow oil.

5 Step 3. allyl N-methyl-N-(10-methyl-11-oxo- 2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-8-yl)carbamate. To a solution of tert-butyl 8-[allyloxycarbonyl(methyl)amino]-10-methyl-11-oxo- 1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (108.00 mg, 249.13 μmol, 1.00 *eq*) in DCM (2.00 mL) was added TFA (3.08 g, 27.01 mmol, 2.00 mL, 108.43 *eq*) and the
10 mixture was stirred at 25 °C under N₂ for 1 h. The mixture was concentrated in vacuo to afford the title compound (111.00 mg, 248.09 μmol, 99.58% yield, TFA) as yellow oil, which was used directly for the next step.

Step 4. allyl N-[2-[(3-chloro-4-fluoro-phenyl)carbamoyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-8-yl]-N-methyl-carbamate. A mixture of allyl
15 N-methyl-N-(10-methyl-11-oxo-2,3,4,7,8,9-hexahydro-1H-pyrido [2,3]pyrazolo[2,4-b][1,4]diazepin-8-yl)carbamate (111.00 mg, 248.09 μmol, 1.00 *eq*, TFA), Et₃N (125.52 mg, 1.24 mmol, 171.95 μL, 5.00 *eq*) and phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (72.50 mg, 272.90 μmol, 1.10 *eq*) in DCM (5.00 mL) was stirred at 25 °C for 16 h. The mixture was diluted with DCM (30 mL) and washed with HCl (1 M, 30 mL*2). The organic phase was dried over
20 Na₂SO₄, filtered and concentrated in vacuo, which was purified by prep-TLC to afford (108.00 mg, 213.89 μmol, 86.21% yield) as yellow solid.

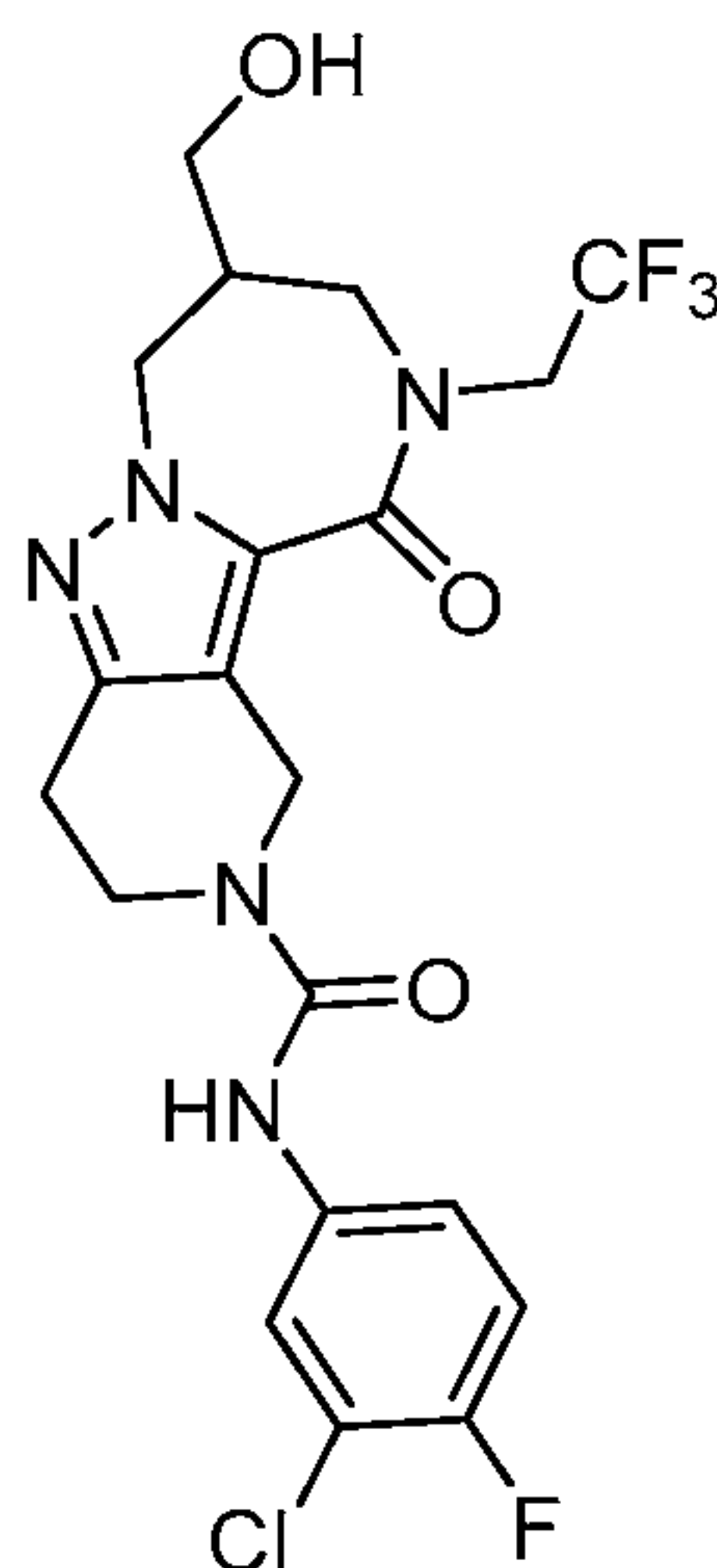
LCMS: 505/507 [M+1].

Step 5. N-(3-chloro-4-fluorophenyl)-10-methyl-8-(methylamino)-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. A mixture of allyl
25 N-[2-[(3-chloro-4-fluoro-phenyl)carbamoyl]-10-methyl-11-oxo- 1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-8-yl]-N-methyl-carbamate (98.00 mg, 194.08 μmol, 1.00 *eq*), 1,3-dimethylhexahydropyrimidine-2,4,6-trione (151.52 mg, 970.41 μmol, 5.00 *eq*) and Pd(PPh₃)₄ (22.43 mg, 19.41 μmol, 0.10 *eq*) in THF (3.00 mL) was stirred at 25 °C for 16 h. The mixture was diluted with EtOAc (30 mL) and washed with brine (30 mL). The organic
30 phase was dried over Na₂SO₄, filtered and concentrated in vacuo, which was purified by silica gel column and prep-HPLC(HCl) to afford the title compound (55.00 mg, 119.06 μmol, 61.35%

yield, 99% purity, HCl) as yellow solid. ^1H NMR (400 MHz, METHANOL- d_4) δ 7.60 (dd, J = 2.57, 6.72 Hz, 1 H), 7.24 - 7.37 (m, 1 H), 7.15 (t, J = 8.99 Hz, 1 H), 4.76 - 4.88 (m, 2 H), 4.55 (s, 2 H), 4.25 - 4.36 (m, 1 H), 3.86 - 3.97 (m, 1 H), 3.71 - 3.82 (m, 1 H), 3.23 (s, 5 H), 2.83 - 2.89 (m, 1 H), 2.82 - 2.83 (m, 1 H), 2.77 (s, 3 H). LCMS: 421/423 [M+1].

5

Compound 051: N-(3-chloro-4-fluorophenyl)-8-(hydroxymethyl)-11-oxo-10-(2,2,2-trifluoroethyl)-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



10 Step 1. 5-tert-butyl 3-ethyl 2-[2-[(2,2,2-trifluoroethylamino) methyl]allyl] -6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-3,5-dicarboxylate. A solution of 5-tert-butyl 3-ethyl 2-[2-(chloromethyl)allyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-3,5-dicarboxylate (500.00 mg, 1.30 mmol, 1.00 *eq*) and 2,2,2-trifluoroethanamine (3.86 g, 39.00 mmol, 3.06 mL, 30.00 *eq*) in EtOH (50.00 mL) was stirred at 90 °C for 32 h. The mixture was diluted with EtOAc (120mL)

15 and washed with saturated NaHCO_3 solution (120 mL). The organic phase was dried over Na_2SO_4 , filtered and concentrated in vacuo which was purified by silica gel column to afford the title compound (460.00 mg, 1.03 mmol, 79.26% yield) as yellow oil.

LCMS: 447 [M+1].

Step 2. tert-butyl 8-methylene-11-oxo-10-(2,2,2-trifluoroethyl)-3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of 5-tert-butyl 3-ethyl 2-[2-[(2,2,2-trifluoroethylamino)methyl]allyl]- 6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-3,5-dicarboxylate (460.00 mg, 1.03 mmol, 1.00 *eq*) in toluene (10.00 mL) was added $\text{Al}(\text{CH}_3)_3$ (2 M, 2.06 mL, 4.00 *eq*) at -30 °C and the mixture was stirred at 60 °C for 16 h. The mixture was

20

quenched with H₂O (10.00 mL). Na₂CO₃ (109.20 mg, 1.03 mmol, 1.00 *eq*) and Boc₂O (269.84 mg, 1.24 mmol, 284.04 μ L, 1.20 *eq*) was added and the mixture was stirred at 20 °C for 16 h. The mixture was diluted with EtOAc (50 mL) and washed with HCl (1M, 50 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo, which was purified by silica gel column to afford the title compound (390.00 mg, 974.05 μ mol, 94.57% yield) as yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 5.07 (br d, *J* = 4.16 Hz, 2 H), 4.91 (s, 2 H), 4.48 - 4.59 (m, 2 H), 4.08 - 4.20 (m, 2 H), 3.97 - 4.05 (m, 2 H), 3.56 - 3.73 (m, 2 H), 2.59 - 2.75 (m, 2 H), 1.44 - 1.50 (m, 5 H), 1.41 (s, 9 H). LCMS: 401 [M+1].

Step 3. tert-butyl 8-(hydroxymethyl)-11-oxo-10-(2,2,2-trifluoroethyl)-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of tert-butyl 8-methylene-11-oxo-10-(2,2,2-trifluoroethyl)-3,4,7,9- tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (150.00 mg, 374.63 μ mol, 1.00 *eq*) in THF (3.00 mL) was added BH₃•DMS (10 M, 149.85 μ L, 4.00 *eq*) at 0 °C and the mixture was stirred at 20 °C for 16 h. TLC indicated the starting material was consumed completely. H₂O₂ (297.30 mg, 2.62 mmol, 251.95 μ L, 30% purity, 7.00 *eq*) and a solution of NaOH (74.93 mg, 1.87 mmol, 5.00 *eq*) in H₂O (500.00 μ L) was added at -30 °C, and the mixture was stirred at 20 °C for 2 h. The mixture was diluted with EtOAc (40 mL) and washed with saturated Na₂SO₃ (30 mL), brine (30 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo, which was purified by prep-TLC to afford the title compound (86.00 mg, 199.37 μ mol, 53.22% yield, 97% purity) as yellow oil.

LCMS: 419 [M+1].

Step 4. 8-(hydroxymethyl)-10-(2,2,2- trifluoroethyl)-2,3,4,7,8,9-hexahydro-1H-

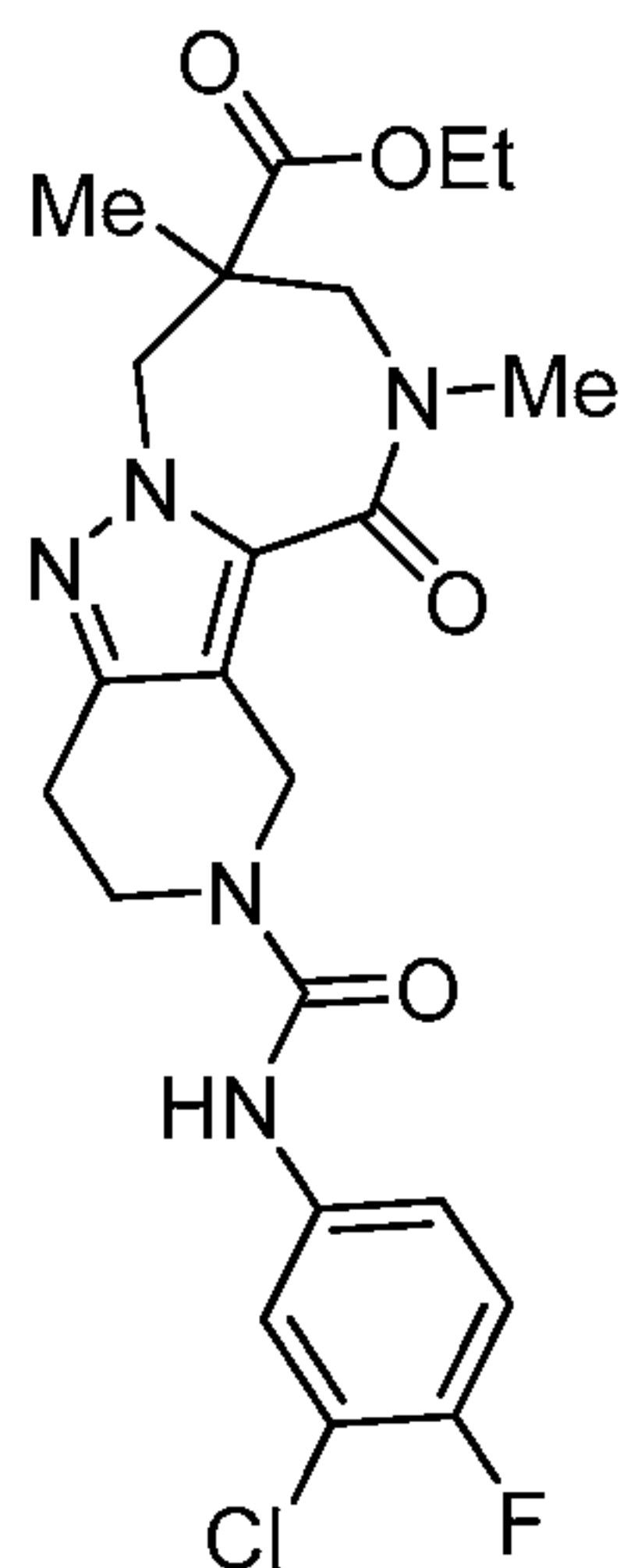
pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one. To a solution of tert-butyl 8-(hydroxymethyl)-11-oxo-10-(2,2,2-trifluoroethyl)- 1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (106.00 mg, 253.34 μ mol, 1.00 *eq*) in DCM (2.00 mL) was added TFA (3.08 g, 27.01 mmol, 2.00 mL, 106.63 *eq*) and the mixture was stirred at 25 °C under N₂ for 1 h. The mixture was concentrated in vacuo to afford the title compound (109.00 mg, 252.13 μ mol, 99.52% yield, TFA) as yellow oil, which was used directly for the next step.

Step 5. N-(3-chloro-4-fluorophenyl)-8-(hydroxymethyl)-11-oxo-10-(2,2,2-trifluoroethyl)-

1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. A mixture of 8-(hydroxymethyl)-10-(2,2,2-trifluoroethyl)-2,3,4,7,8,9 –hexahydro-1H -

pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (109.00 mg, 252.13 μmol , 1.00 *eq*, TFA), Et_3N (127.56 mg, 1.26 mmol, 174.74 μL , 5.00 *eq*) and phenyl N-(3-chloro-4-fluorophenyl)carbamate (73.68 mg, 277.34 μmol , 1.10 *eq*) in DCM (5.00 mL) was stirred at 25 °C for 16 h. The mixture was diluted with DCM (30 mL) and washed with HCl (1 M, 30 mL). The organic phase was dried over Na_2SO_4 , filtered and concentrated in vacuo, which was purified by prep-HPLC(FA) to afford the title compound (56.00 mg, 113.18 μmol , 44.89% yield, 99% purity) as yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 7.59 (dd, $J = 2.63, 6.54$ Hz, 1 H), 7.17 - 7.24 (m, 1 H), 7.03 - 7.12 (m, 1 H), 6.56 (s, 1 H), 4.76 - 4.92 (m, 1 H), 4.65-4.72 (m, 2 H), 4.30 - 4.49 (m, 2 H), 3.78 - 3.95 (m, 2 H), 3.63 - 3.76 (m, 3 H), 3.46 - 3.61 (m, 2 H), 2.82 - 2.92 (m, 2 H), 2.71 - 2.81 (m, 1 H). LCMS: 490/492 $[\text{M}+1]$.

Compound 052: ethyl 2-((3-chloro-4-fluorophenyl)carbamoyl)-8,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-8-carboxylate.



Step 1. 2-tert-butyl 8-ethyl 8,10-dimethyl-11-oxo-3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2,8-dicarboxylate. To a solution of 2-tert-butyl 8-ethyl 10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2,8-dicarboxylate (Intermediate 14, 200.00 mg, 509.62 μmol , 1.00 *eq*) in THF (6.00 mL) was added LDA (1 M, 1.53 mL, 3.00 *eq*) at -65 °C under N_2 , followed by MeI (217.01 mg, 1.53 mmol, 95.18 μL , 3.00 *eq*) after 0.5 h and the mixture was stirred at 25 °C for 2 h. The mixture was quenched with HCl (1M, 40 mL) and extracted with EtOAc (40 mL). The organic phase was dried over Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by prep-TLC to

afford the title compound (140.00 mg, 309.99 μ mol, 60.83% yield, 90% purity) as yellow oil.
LCMS: 407 [M+1].

Step 2. ethyl 8,10-dimethyl-11-oxo-1,2,3,4,7,9-hexahydropyrido [2,3] pyrazolo[2,4-

b][1,4]diazepine-8-carboxylate. To a solution of 2-tert-butyl 8-ethyl 8,10-dimethyl-11-oxo-
3,4,7,9-tetrahydro-1H- pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2,8-dicarboxylate (210.00 mg,
516.63 μ mol, 1.00 *eq*) in DCM (3.00 mL) was added TFA (4.62 g, 40.52 mmol, 3.00 mL, 78.43
eq) and the mixture was stirred at 25 °C under N₂ for 1 h. The mixture was concentrated in
vacuo to afford the title compound (217.00 mg, 516.20 μ mol, 99.92% yield, TFA) as yellow oil,
which was used directly for the next step.

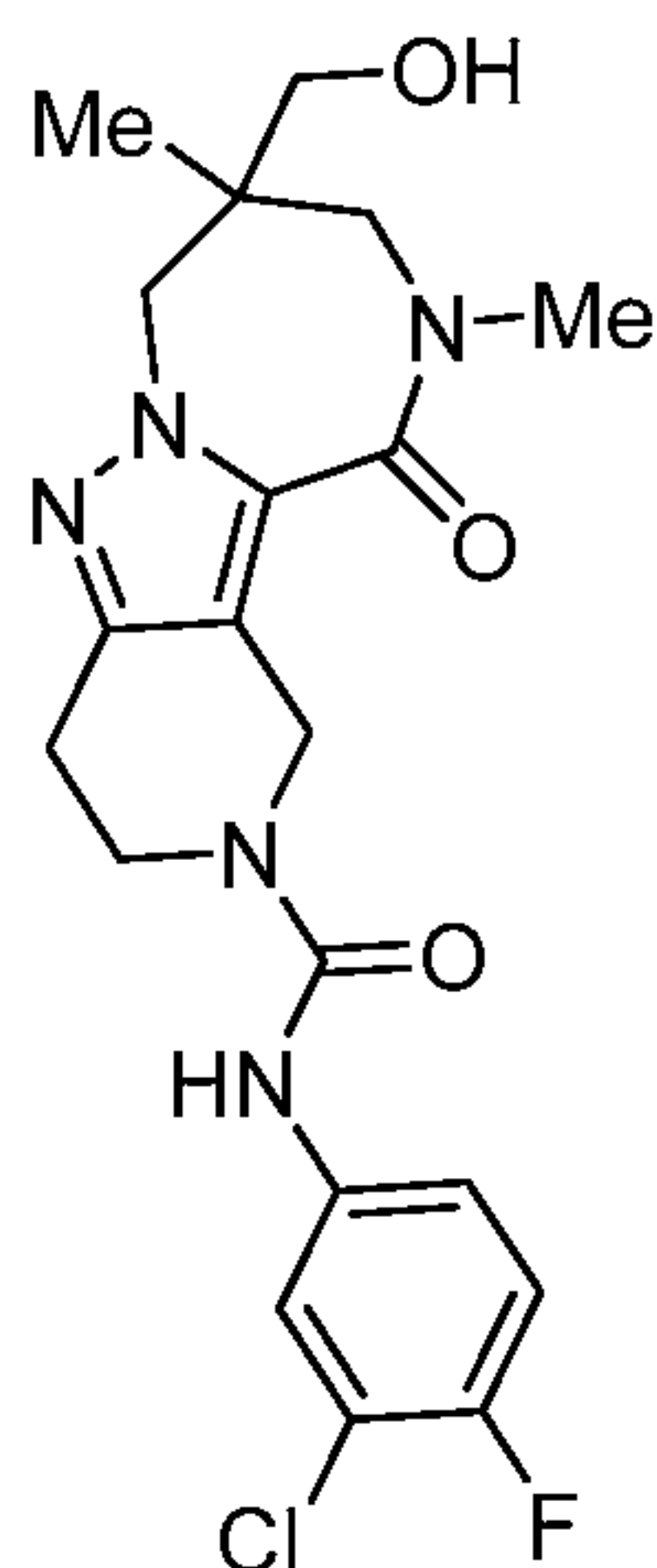
Step 3. ethyl 2-((3-chloro-4-fluorophenyl)carbamoyl)-8,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-

octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-8-carboxylate. A mixture of ethyl
8,10-dimethyl-11-oxo-1,2,3,4,7,9-hexahydropyrido[2,3]pyrazolo [2,4-b][1,4]diazepine-8-
carboxylate (217.00 mg, 516.20 μ mol, 1.00 *eq*, TFA), Et₃N (261.17 mg, 2.58 mmol, 357.77 μ L,
5.00 *eq*) and phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (150.85 mg, 567.82 μ mol, 1.10 *eq*)
in DCM (7.00 mL) was stirred at 25 °C for 16 h. The mixture was diluted with DCM (30 mL)
and washed with HCl (1 M, 30 mL). The organic phase was dried over Na₂SO₄, filtered and
concentrated in vacuo, which was purified by prep-HPLC(FA) to afford the title compound
(175.00 mg, 362.51 μ mol, 70.23% yield, 99% purity) as white solid.

¹H NMR (400 MHz, CDCl₃) δ 7.58 (dd, *J* = 2.69, 6.48 Hz, 1 H), 7.15 - 7.23 (m, 1 H), 7.01 -
7.09 (m, 1 H), 6.63 (s, 1 H), 4.70 (s, 1 H), 4.54 - 4.65 (m, 2 H), 4.21 - 4.32 (m, 3 H), 3.79 - 3.91
(m, 2 H), 3.70 - 3.78 (m, 1 H), 3.22 (d, *J*=15.04 Hz, 1 H), 3.17 (s, 3 H), 2.79-2.88 (m, 2 H), 1.31-
1.36 (m, 6 H). LCMS: 478/480 [M+1].

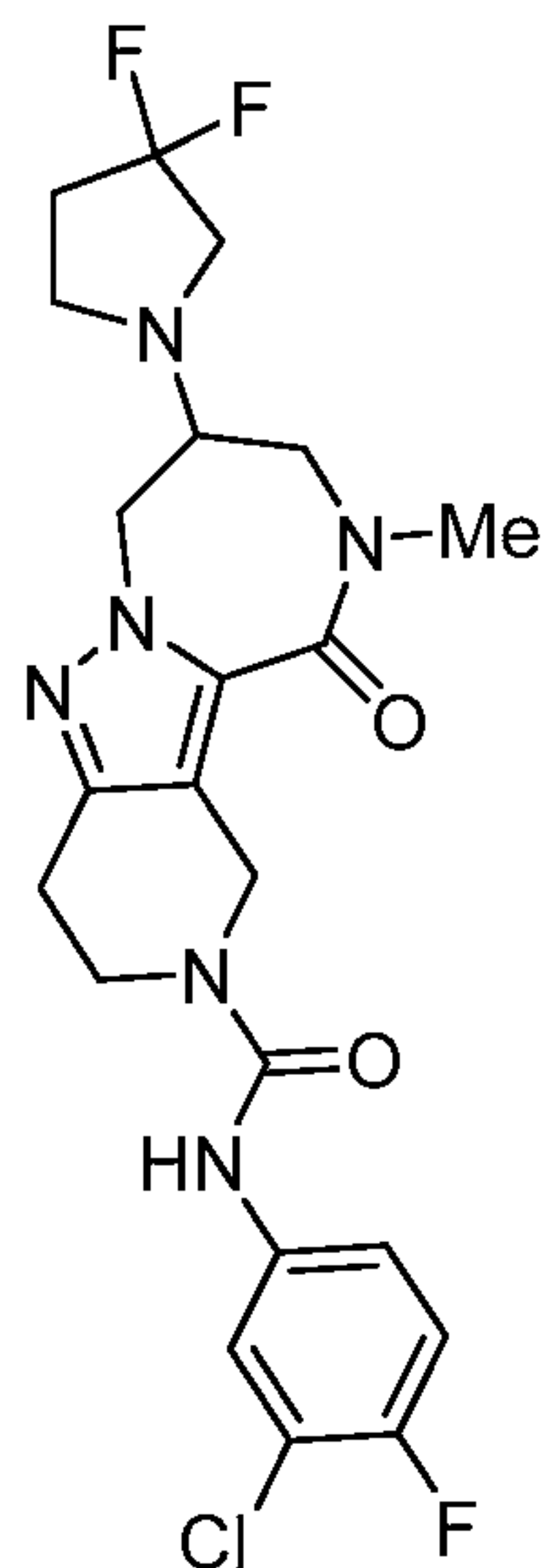
Compound 053: N-(3-chloro-4-fluorophenyl)-8-(hydroxymethyl)-8,10-dimethyl-11-oxo-

1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



To a solution of ethyl 2-[(3-chloro-4-fluorophenyl)carbamoyl]-8,10- dimethyl-11- oxo-3,4,7,9- tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-8-carboxylate (Compound 052, 60.00 mg, 125.54 μmol , 1.00 *eq*) in THF (5.00 mL) was added LiBH_4 (8.20 mg, 376.62 μmol , 3.00 *eq*) at 0 °C and the mixture was stirred at 25 °C for 2 h. The mixture was quenched with H_2O (30 mL) and extracted with EtOAc (30 mL). The organic phase was dried over Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by prep-HPLC(FA) to afford the title compound (34.00 mg, 77.22 μmol , 61.51% yield, 99% purity) as white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.60 (dd, $J = 2.63, 6.54$ Hz, 1 H), 7.20 (br d, $J = 1.34$ Hz, 1 H), 7.07 (s, 1 H), 6.62 (s, 1H), 4.64 - 4.74 (m, 2 H), 4.19 (s, 1 H), 4.01 (s, 1 H), 3.87 (s, 1 H), 3.50 - 3.66 (m, 2 H), 3.37 (d, $J = 14.79$ Hz, 1 H), 3.22 (s, 3 H), 3.03 - 3.11 (m, 1 H), 2.85 (s, 1 H), 1.88 - 1.97 (m, 1 H), 1.16 (s, 3 H). LCMS: 436/438 $[\text{M}+1]$.

Compound 054: N-(3-chloro-4-fluorophenyl)-8-(3,3-difluoropyrrolidin-1-yl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. tert-butyl 8-(3,3-difluoropyrrolidin-1-yl)-10-methyl-11-oxo-1,3,4,7,8,9-

5 hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of 3,3-difluoropyrrolidine (96.09 mg, 669.34 μ mol, 1.49 *eq*, HCl) in DCE (4.00 mL) was added NaOAc (73.60 mg, 897.20 μ mol, 2.00 *eq*). After stirring for 1 hr, tert-butyl 10-methyl-8,11-dioxo-3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo [2,4-b][1,4]diazepine-2-carboxylate (150.00 mg, 448.60 μ mol, 1.00 *eq*) and 4A MS (300.00 mg) was added. The mixture was stirred at 20 °C for 10 4 hr. NaBH₃CN (112.76 mg, 1.79 mmol, 4.00 *eq*) was added. Then the mixture was stirred at 20 °C for 12 hr. LCMS showed the reaction completed. The mixture was poured into saturated NH₄Cl (20mL), extracted with DCM (10 mL*2). The organic layer was washed with brine (20 mL*2), dried over anhydrous Na₂SO₄ and concentrated in vacuum to give the crude, which was purified by prep.TLC (100% Ethyl acetate) to afford the title compound (120.00 mg, 282.04 15 μ mol, 62.87% yield) as colorless oil.

LCMS: 426 [M+1].

Step 2. 8-(3,3-difluoropyrrolidin-1-yl) -10-methyl-2,3,4,7,8,9-hexahydro-1H-

pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one. To a solution tert-butyl 8-(3,3-difluoropyrrolidin-1-yl)-10-methyl-11 -oxo- 1,3,4,7,8,9 -hexahydropyrido[2,3]pyrazolo[2,4- 20 b][1,4]diazepine-2-carboxylate (90.00 mg, 211.53 μ mol, 1.00 *eq*) in DCM (2.00 mL) was added TFA (3.08 g, 27.01 mmol, 2.00 mL, 127.70 *eq*). The mixture was stirred at 20 °C for 1 hr. TLC

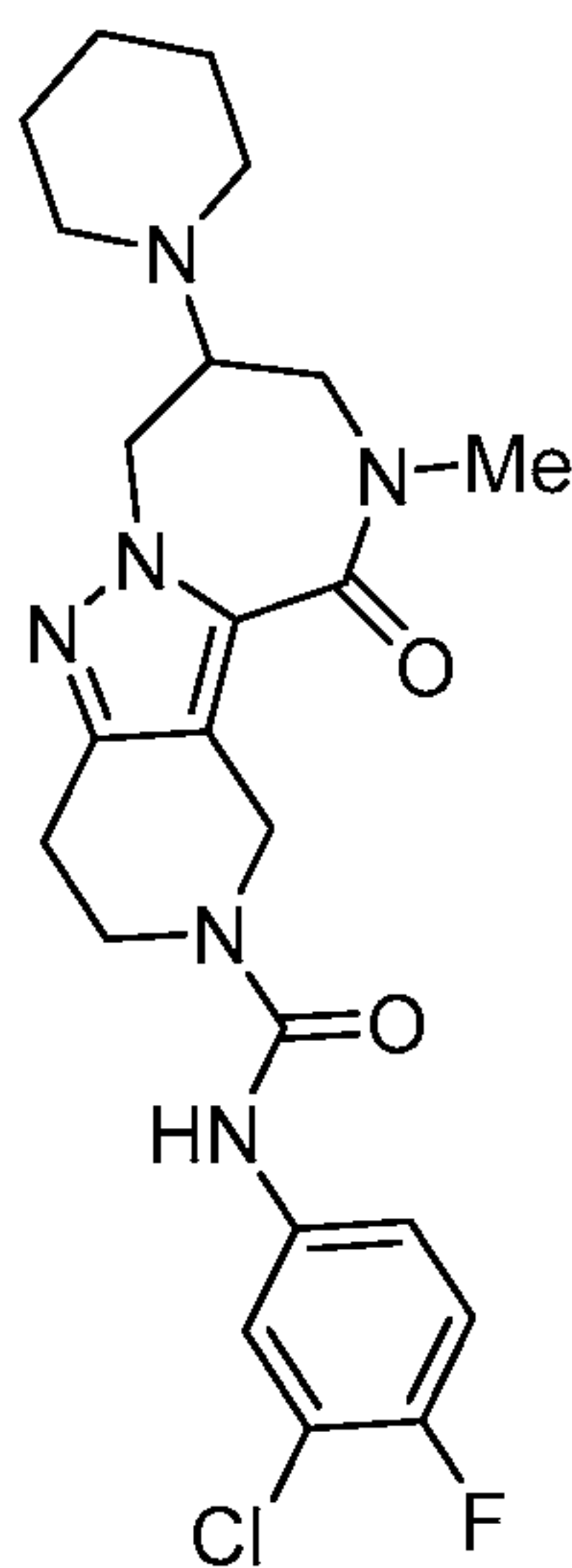
showed the reaction completed. The mixture was concentrated to afford the title compound (90.00 mg, 204.83 μ mol, 96.83% yield, TFA) as the colorless oil, which was used directly.

Step 3. N-(3-chloro-4-fluorophenyl)-8-(3,3-difluoropyrrolidin-1-yl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

5 To a solution of 8-(3,3-difluoropyrrolidin-1-yl)-10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (90.00 mg, 204.83 μ mol, 1.00 *eq*, TFA) and phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (55.52 mg, 209.00 μ mol, 1.00 *eq*) in DCM (2.00 mL) was added TEA (62.18 mg, 614.50 μ mol, 85.18 μ L, 3.00 *eq*). The mixture was stirred at 20 °C for 12 h. LCMS showed the reaction was completed. The mixture was concentrated in
10 vacuum to give the crude, which was purified by prep-HPLC to afford the title compound (57.00 mg, 113.56 μ mol, 55.44% yield, 99% purity) as white solid. LCMS: 497/499 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 7.58 (dd, *J* = 2.57, 6.48 Hz, 1 H), 7.15 - 7.22 (m, 1 H), 6.99 - 7.09 (m, 1 H), 6.58 (s, 1 H), 4.67 (s, 2 H), 4.31 - 4.46 (m, 2 H), 3.79 - 3.98 (m, 2 H), 3.44 (d, *J* = 5.38 Hz, 2 H), 3.29-3.31 (m, 1 H), 3.20 (s, 3 H), 2.81 - 3.12 (m, 6 H), 2.28-2.33 (m, 2 H).

15

Compound 055: N-(3-chloro-4-fluorophenyl)-10-methyl-11-oxo-8-(piperidin-1-yl)-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. tert-butyl 10-methyl-11-oxo-8-(1-piperidyl)-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of tert-butyl 10-methyl-8,11-dioxo-3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (120.00 mg, 358.88 μ mol, 1.00 *eq*) and piperidine (61.12 mg, 717.76 μ mol, 71.07

20

μL, 2.00 *eq*) in DCE (2.00 mL) was added HOAc (21.55 mg, 358.88 μmol, 20.52 μL, 1.00 *eq*), 4A MS (300.00 mg), the mixture was stirred at 20 °C for 3 hr. NaBH₃CN (112.76 mg, 1.79 mmol, 5.00 *eq*) was added and the mixture was stirred at 20 °C for 12 hr. TLC showed the reaction was completed. The mixture was poured into saturated NH₄Cl (20 mL), extracted with
5 Ethyl acetate (15 mL*2). The organic layer was washed with brine (20 mL*2), dried over anhydrous Na₂SO₄ and concentrated in vacuum. The crude was purified by prep.TLC to afford the title compound (50.00 mg, 111.52 μmol, 31.07% yield, 90% purity) as colorless oil.

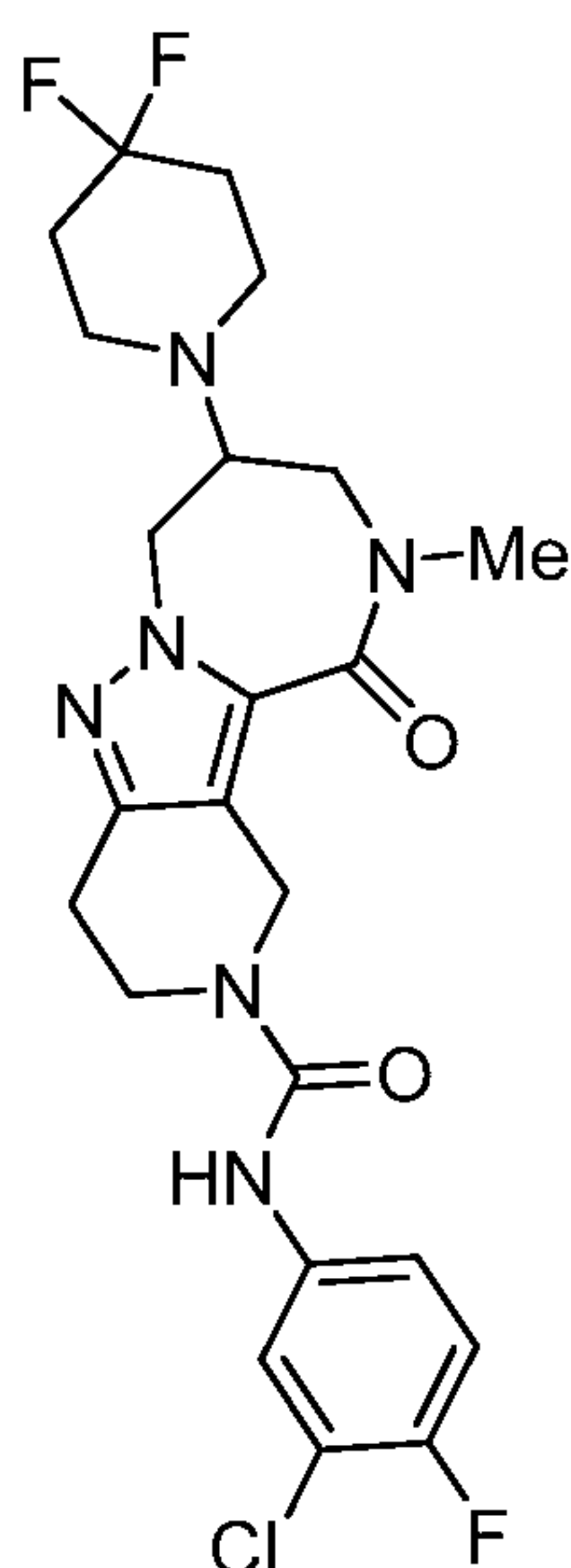
Step 2. 10-methyl- 8- (1-piperidyl)-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-

b][1,4]diazepin-11-one. To a solution of tert-butyl 10-methyl-11-oxo-8-(1-piperidyl)-1,3,4,7,8,9-
10 hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (50.00 mg, 123.91 μmol, 1.00 *eq*) in DCM (2.00 mL) was added TFA (14.13 mg, 123.91 μmol, 9.17 μL, 1.00 *eq*). The mixture was stirred at 20 °C for 1 hr. TLC showed the reaction was completed. The mixture was concentrated in vacuum to afford the title compound (50.00 mg, 119.78 μmol, 96.67% yield, TFA) as colorless oil, which was used for the next step without purification.

Step 3. N-(3-chloro-4-fluorophenyl)-10-methyl-11-oxo-8-(piperidin-1-yl)-1,3,4,7,8,9,10,11-
octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. To a solution of

10-methyl-8-(1-piperidyl)-2,3,4,7,8,9-hexahydro-1H-pyrido [2,3] pyrazolo[2,4-b][1,4]diazepin-
11-one (50.00 mg, 119.78 μmol, 1.00 *eq*, TFA) and phenyl N-(3-chloro-4-fluoro-
phenyl)carbamate (31.82 mg, 119.78 μmol, 1.00 *eq*) in DCM (2.00 mL) was added TEA (36.36
20 mg, 359.35 μmol, 49.81 μL, 3.00 *eq*). The mixture was stirred at 20 °C for 16 hr. LCMS showed the reaction was completed. The mixture was concentrated in vacuum to give the crude. The crude was purified by prep-HPLC to afford the title compound (22.00 mg, 45.86 μmol, 38.28% yield, 99% purity) as white solid. LCMS: 475/477 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 8.13 (s, 1 H), 7.58 (dd, *J* = 2.63, 6.54 Hz, 1 H), 7.17 - 7.24 (m, 1 H), 7.05 (t, *J* = 8.80 Hz, 1 H),
25 6.73 (s, 1 H), 4.67 - 4.76 (m, 2 H), 4.58 - 4.67 (m, 1 H), 4.35 (dd, *J* = 6.54, 15.34 Hz, 1 H), 3.87 - 3.95 (m, 1 H), 3.67 - 3.82 (m, 3 H), 3.54 - 3.59 (m, 1 H), 3.18 (s, 3 H), 2.79 - 2.93 (m, 4 H), 2.65 - 2.78 (m, 2 H), 1.66 - 1.80 (m, 4 H), 1.47 - 1.64 (m, 2 H).

Compound 056: N-(3-chloro-4-fluorophenyl)-8-(4,4-difluoropiperidin-1-yl)-10-methyl-11-oxo-
30 1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. tert-butyl 8-(4,4-difluoro-1-piperidyl)-10-methyl-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of tert-butyl

10-methyl-8,11-dioxo-3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-

5 carboxylate (150.00 mg, 448.60 μmol , 1.00 *eq*) and 4,4-difluoropiperidine (108.68 mg, 897.22 μmol , 2.00 *eq*) in DCE (2.00 mL) was added 4A MS (300.00 mg) and HOAc (26.94 mg, 448.60 μmol , 25.66 μL , 1.00 *eq*), the mixture was stirred at 20 °C for 16 hr. NaBH_3CN (140.95 mg, 2.24 mmol, 5.00 *eq*) was added. The mixture was stirred at 20 °C for 3 hr. TLC showed the reaction was completed. The mixture was poured into saturated NH_4Cl (20 mL), extracted with

10 Ethyl acetate (15 mL*2), the organic layer was washed with brine (20 mL*2), dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude was purified by prep-TLC to afford the title compound (53.00 mg, 114.56 μmol , 25.54% yield, 95% purity) as colorless oil.

Step 2. 8-(4,4-difluoro-1-piperidyl)-10-methyl-2,3,4,7,8,9-hexahydro-1H-

pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one. To a solution of tert-butyl 8-(4,4-difluoro-1-

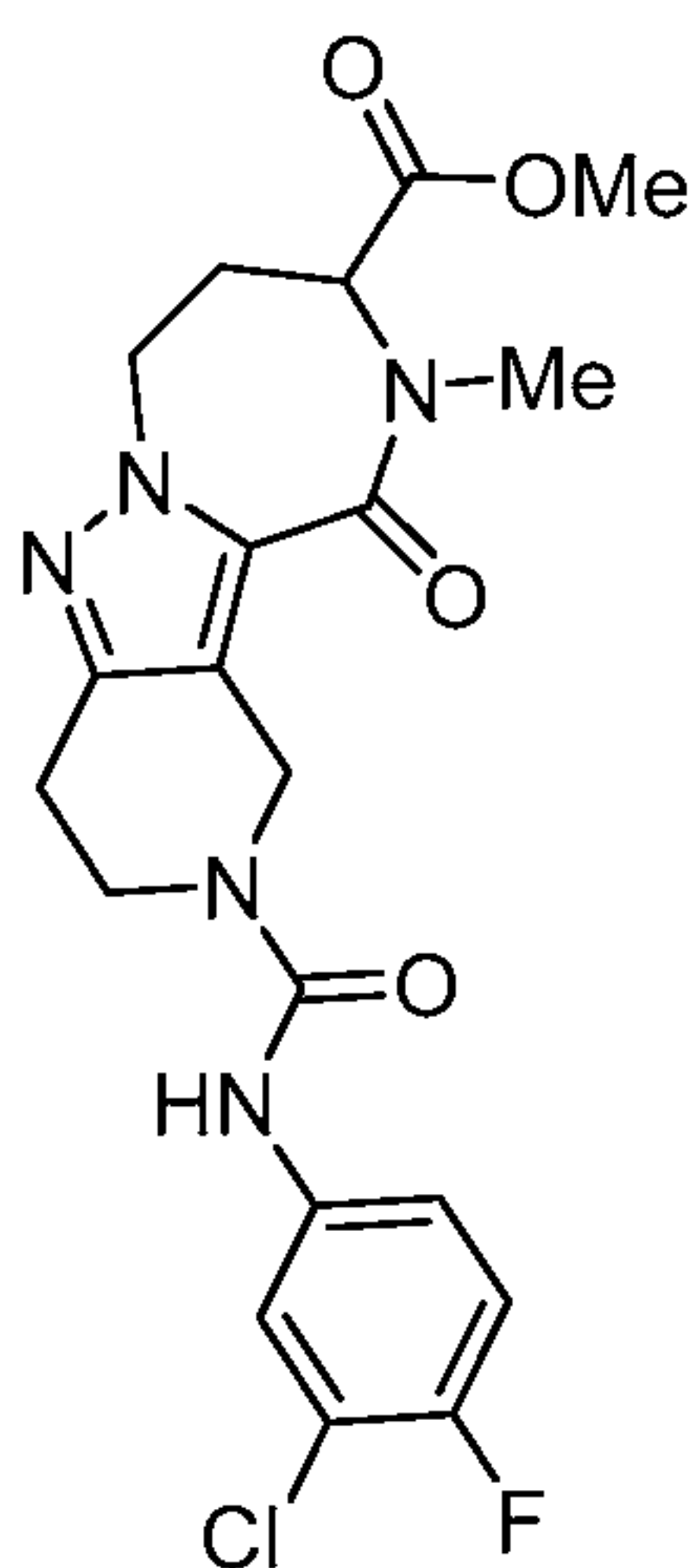
15 piperidyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (53.00 mg, 120.59 μmol , 1.00 *eq*) in DCM (2.00 mL) was added TFA (3.08 g, 27.01 mmol, 2.00 mL, 224.01 *eq*), the mixture was stirred at 20 °C for 1 hr. TLC showed the reaction complete. The mixture was concentrated in vacuum to afford the title compound (54.00 mg, 119.10 μmol , 98.76% yield, TFA) as colorless oil, which was used for the next step without

20 purification.

Step 3. N-(3-chloro-4-fluorophenyl)-8-(4,4-difluoropiperidin-1-yl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

To a solution of 8-(4,4-difluoro-1-piperidyl)-10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (54.00 mg, 119.10 μ mol, 1.00 *eq*, TFA) and
 5 phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (31.64 mg, 119.10 μ mol, 1.00 *eq*) in DCM (2.00 mL) was added TEA (36.15 mg, 357.29 μ mol, 49.53 μ L, 3.00 *eq*). The mixture was stirred at 20 °C for 16 hr. LCMS showed the reaction complete. The mixture was concentrated in vacuum. The crude was purified by prep-HPLC to afford the title compound (24.00 mg, 45.09 μ mol, 37.86% yield, 96% purity) as white solid. LCMS: 511/513 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 7.58 (dd, *J* = 2.64, 6.53 Hz, 1 H), 7.18-7.20 (m, 1 H), 7.02 - 7.08 (m, 1 H), 6.65 (s, 1 H), 4.51 - 4.80 (m, 3 H), 4.28 - 4.39 (m, 1 H), 3.76 - 3.93 (m, 2 H), 3.47 - 3.63 (m, 2 H), 3.28 - 3.40 (m, 1 H), 3.18 (s, 3 H), 2.74 - 2.89 (m, 4 H), 2.63 - 2.67 (m, 2 H), 1.92 - 2.10 (m, 4 H).

Compound 057: methyl 2-((3-chloro-4-fluorophenyl)carbamoyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-9-carboxylate.



Step 1. 2-tert-butyl 9-methyl 10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-2,9-dicarboxylate and 2-tert-butyl 9-methyl 9,10-dimethyl-11-oxo-3,4,7,8-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-2,9-dicarboxylate. To a solution of 2-tert-butyl 9-methyl 11-oxo-3,4,7,8,9,10-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-2,9-dicarboxylate (Intermediate 13, 1.10 g, 3.02 mmol, 1.00 *eq*) in DMF (20.00 mL) was added NaH (144.90 mg, 3.62 mmol, 60% purity, 1.20 *eq*) at -30 °C, stirring for 30 min MeI (557.01

mg, 3.93 mmol, 244.30 μ L, 1.30 *eq*) was added and the mixture was stirred at 20 °C for 2 hr. LCMS showed the reactant consumed and 70% of 2-tert-butyl 9-methyl 10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-2,9-dicarboxylate and 18 % of 2-tert-butyl 9-methyl 9,10-dimethyl-11-oxo-3,4,7,8-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-2,9-dicarboxylate were detected. The mixture was poured into water (100 mL), extracted with ethyl acetate (50 mL*3), the organic layer was washed with brine (50 mL*3), dried over anhydrous Na₂SO₄ and concentrated in vacuum. The crude was purified by prep-HPLC to afford 2-tert-butyl 9-methyl 10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-2,9-dicarboxylate (680.00 mg, 1.80 mmol, 59.60% yield) and 2-tert-butyl 9-methyl 9,10-dimethyl-11-oxo-3,4,7,8-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-2,9-dicarboxylate (120.00 mg, 305.77 μ mol, 10.12% yield) as colorless oil.

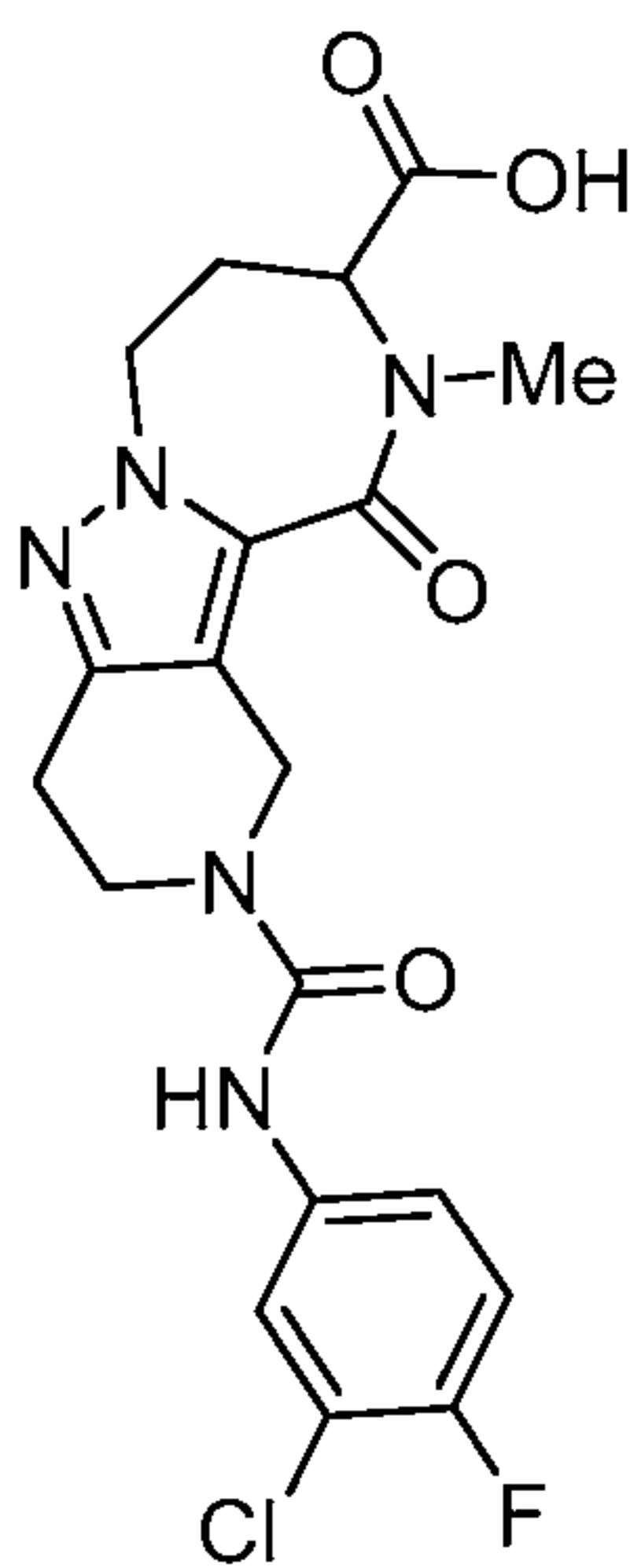
Step 2. methyl-10-methyl-11-oxo-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-9-carboxylate. To a solution of 2-tert-butyl 9-methyl 10-methyl-11-oxo-1,3,4,7,8,9 – hexahydropyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-2,9-dicarboxylate (200.00 mg, 528.51 μ mol, 1.00 *eq*) in DCM (3.00 mL) was added TFA (4.62 g, 40.52 mmol, 3.00 mL, 76.67 *eq*). The mixture was stirred at 20 °C for 1 hr. TLC (Petroleum ether: ethyl acetate = 1:1) showed the reaction was completed. The mixture was concentrated in vacuum to afford the title compound (200.00 mg, 509.77 μ mol, 96.46% yield, TFA) as colorless oil.

Step 3. methyl 2-((3-chloro-4-fluorophenyl)carbamoyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-9-carboxylate. To a solution of methyl 10-methyl-11-oxo-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-9-carboxylate (190.00 mg, 484.29 μ mol, 1.00 *eq*, TFA) and phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (128.66 mg, 484.29 μ mol, 1.00 *eq*) in DCM (3.00 mL) was added TEA (98.01 mg, 968.57 μ mol, 134.26 μ L, 2.00 *eq*). The mixture was stirred at 20 °C for 16 hr. LCMS showed the reaction was completed. The mixture was poured into water (20 mL), extracted with ethyl acetate (20 mL*2), the organic layer was washed with brine (20 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuum. The crude was purified by prep-HPLC to afford the title compound (150.00 mg, 323.43 μ mol, 66.79% yield, 97% purity) as white solid.

LCMS: 450/452 [M+1]. ^1H NMR (400 MHz, CDCl_3) δ 7.60 (dd, $J = 2.63, 6.54$ Hz, 1 H), 7.18 - 7.24 (m, 1 H), 7.00 - 7.09 (m, 1 H), 6.64 (s, 1 H), 4.59 - 4.80 (m, 2 H), 4.28 - 4.47 (m, 3 H), 3.74 - 3.95 (m, 2 H), 3.67 (s, 3 H), 3.20 (s, 3 H), 2.88 - 2.99 (m, 1 H), 2.81 (t, $J = 5.81$ Hz, 2 H), 2.49 - 2.65 (m, 1 H).

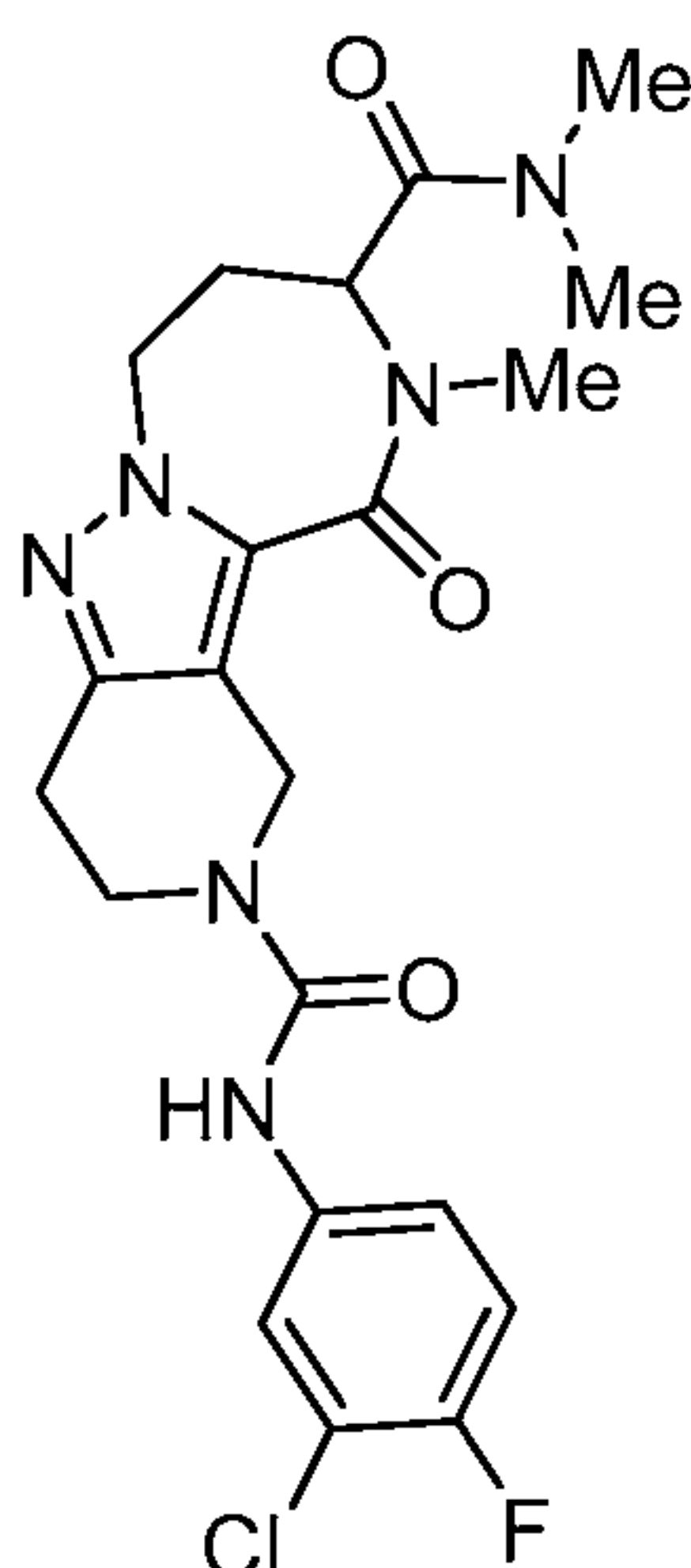
5

Compound 058: 2-((3-chloro-4-fluorophenyl)carbamoyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-9-carboxylic acid.



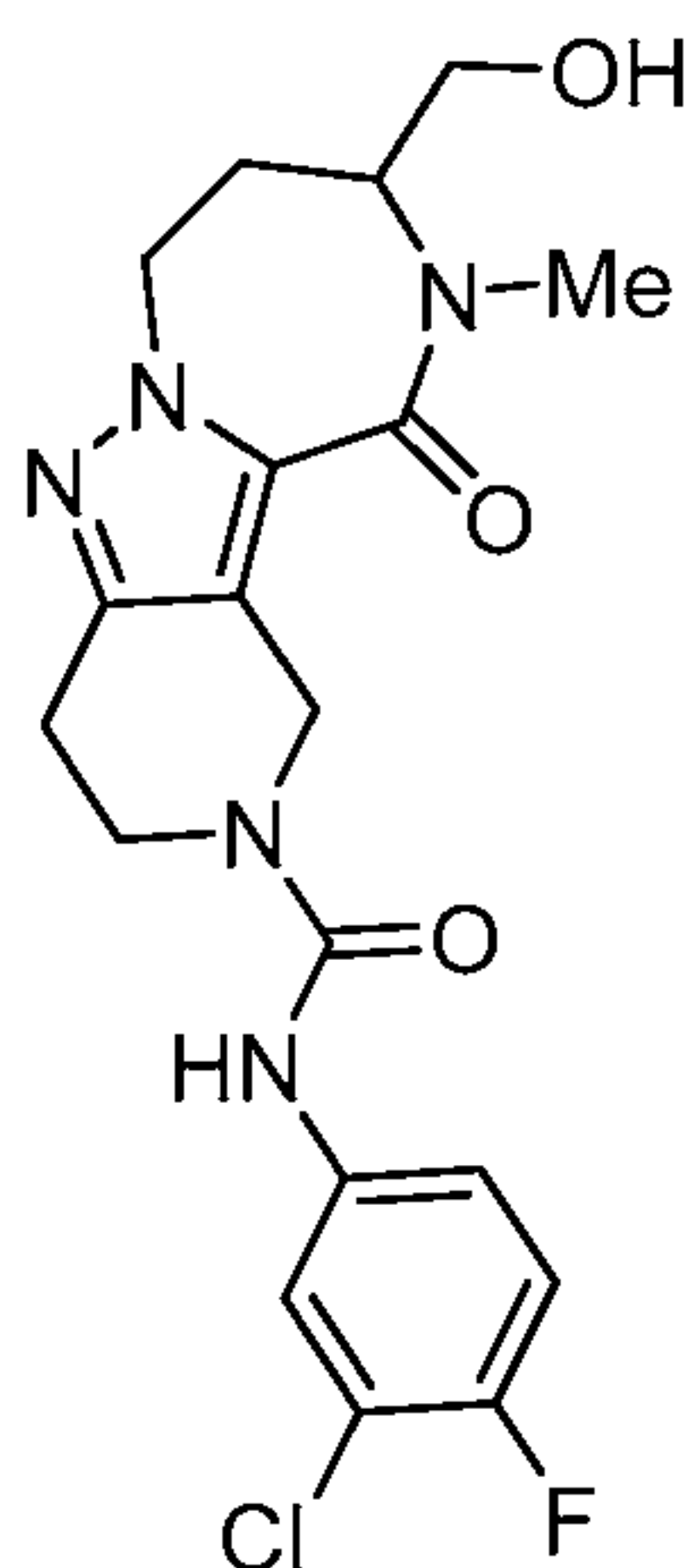
To a solution of methyl 2-[(3-chloro-4-fluoro-phenyl)carbamoyl]- 10- methyl -11 -oxo-
 10 1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-9-carboxylate (Compound 057,
 30.00 mg, 66.69 μmol , 1.00 *eq*) in MeOH (2.00 mL) and H_2O (2.00 mL) was added NaOH (8.00
 mg, 200.07 μmol , 3.00 *eq*), the mixture was stirred at 20 $^\circ\text{C}$ for 16 hr. LCMS showed the
 reaction was completed. The mixture was acidified by HCl (1N) to pH 4. The residue was
 purified by prep-HPLC to afford the title compound (24.00 mg, 54.52 μmol , 81.74% yield, 99%
 15 purity) as white solid LCMS: 436/438 [M+1]. ^1H NMR (400 MHz, METHANOL- d_4) δ 7.56 -
 7.64 (m, 1 H), 7.25 - 7.35 (m, 1 H), 7.13 (t, $J = 8.93$ Hz, 1 H), 4.60 (br s, 2 H), 4.37 (br d, $J =$
 5.01 Hz, 3 H), 3.84 - 3.99 (m, 1 H), 3.59 - 3.75 (m, 1 H), 3.17 (s, 3 H), 2.93 (br d, $J = 14.43$ Hz,
 1 H), 2.75 (br t, $J = 5.32$ Hz, 2 H), 2.53 (br dd, $J = 5.93, 14.61$ Hz, 1 H).

20 Compound 059: N2-(3-chloro-4-fluorophenyl)-N9,N9,10-trimethyl-11-oxo-1,3,4,7,8,9,10,11-
octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2,9-dicarboxamide.



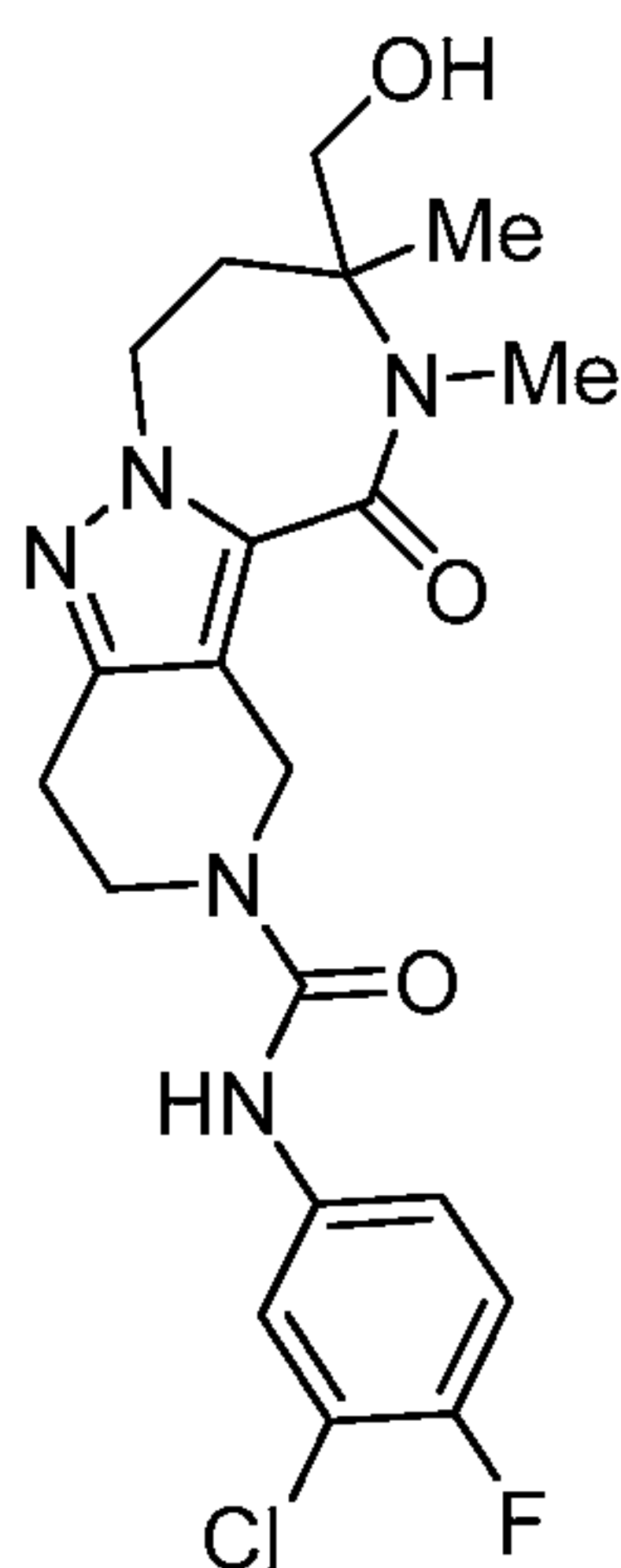
To a solution of 2-[(3-chloro-4-fluoro-phenyl)carbamoyl]-10-methyl-11-oxo - 1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-9-carboxylic acid (Compound 058, 100.00 mg, 229.44 μ mol, 1.00 *eq*) and Me₂NH (187.09 mg, 2.29 mmol, 210.21 μ L, 10.00 *eq*, HCl) in DMF (3.00 mL) was added DIPEA (593.06 mg, 4.59 mmol, 801.43 μ L, 20.00 *eq*) and HATU (104.69 mg, 275.33 μ mol, 1.20 *eq*). The mixture was stirred at 20 °C for 16 hr. LCMS showed the reaction was completed. The mixture was poured into water (20 mL), extracted with ethyl acetate (20 mL*2), the organic layer was washed with brine (20 mL *3), dried over anhydrous Na₂SO₄ and concentrated in vacuum. The residue was purified by prep-HPLC to afford the title compound (50.00 mg, 106.93 μ mol, 46.61% yield, 99% purity) as white solid. LCMS: 463/465 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 7.60 (dd, *J* = 2.63, 6.54 Hz, 1 H), 7.18 - 7.25 (m, 1 H), 7.04 (t, *J* = 8.80 Hz, 1 H), 6.77 (s, 1 H), 4.75 (q, *J* = 15.89 Hz, 2 H), 4.61 (dd, *J* = 4.52, 7.58 Hz, 1 H), 4.51 (td, *J* = 4.52, 14.31 Hz, 1 H), 4.18 (ddd, *J* = 4.71, 10.33, 14.55 Hz, 1 H), 3.76 - 3.94 (m, 2 H), 3.07 (s, 3 H), 3.03 (d, *J* = 8.31 Hz, 6 H), 2.75 - 2.84 (m, 2 H), 2.50 - 2.64 (m, 2 H).

Compound 060: N-(3-chloro-4-fluorophenyl)-9-(hydroxymethyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



To a solution of methyl 2-[(3-chloro-4-fluorophenyl)carbamoyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-9-carboxylate (Compound 057, 100.00 mg, 222.29 μ mol, 1.00 *eq*) in THF (3.00 mL) was added LiBH₄ (14.52 mg, 666.87 μ mol, 3.00 *eq*) at 10 °C. The mixture was stirred at 20 °C for 16 hr. LCMS showed the reaction was completed. The mixture was poured into aqueous HCl (0.5 M), extracted with DCM (20 mL*2), the organic layer was washed with brine (20 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuum. The crude was purified by prep-HPLC to afford the title compound (43.00 mg, 100.91 μ mol, 45.40% yield, 99% purity) as white solid. LCMS: 422/424 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 7.57 (dd, *J* = 2.63, 6.54 Hz, 1 H), 7.18 - 7.25 (m, 1 H), 7.04 (t, *J* = 8.80 Hz, 1 H), 6.90 (s, 1 H), 4.66 (s, 2 H), 4.32 - 4.52 (m, 2 H), 3.90 (td, *J* = 5.61, 13.36 Hz, 1 H), 3.69 - 3.83 (m, 4 H), 3.21 (s, 3 H), 2.80 (t, *J* = 5.75 Hz, 2 H), 2.21 - 2.57 (m, 3 H).

Compound 061: N-(3-chloro-4-fluorophenyl)-9-(hydroxymethyl)-9,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. 2-tert-butyl 9-methyl 9,10-dimethyl-11-oxo-3,4,7,8-tetrahydro-1H-

pyrido[2,3]pyrazolo[2,4-c] [1,4]diazepine-2,9-dicarboxylate. To a solution of methyl 2-[(3-

chloro-4-fluoro-phenyl)carbamoyl]-9,10-dimethyl-11 -oxo-3,4,7,8-tetrahydro-1H-

pyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-9-carboxylate (100.00 mg, 285.41 μ mol, 1.00 *eq*) in

5 DMF (3.00 mL) was added NaH (34.25 mg, 856.23 μ mol, 60% purity, 3.00 *eq*), stirring for 30 min, MeI (202.56 mg, 1.43 mmol, 88.84 μ L, 5.00 *eq*) was added and the mixture was stirred at 20°C for 2 hr. LCMS showed the reactant consumed and the major product was detected. The mixture was poured into water(10 mL), extracted with ethyl acetate(10 mL*2). The combined organic layer was washed with brine(10 mL*2), dried over anhydrous Na₂SO₄ and concentrated
10 in vacuum to afford the title compound (120.00 mg, crude) as the yellow oil.

Step 2. methyl 9,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-

pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-9-carboxylate. To a solution of 2-tert-butyl 9-

methyl 9,10-dimethyl-11-oxo- 3,4,7,8 –tetrahydro - 1H-pyrido[2,3]pyrazolo[2,4-

c][1,4]diazepine-2,9-dicarboxylate (120.00 mg, 305.77 μ mol, 1.00 *eq*) in DCM (3.00 mL) was

15 added TFA (4.62 g, 40.52 mmol, 3.00 mL, 132.52 *eq*). The mixture was stirred at 20 °C for 1 hr. TLC showed the reaction was completed. The mixture was concentrated in vacuum to give methyl9,10-dimethyl-11-oxo-1,2,3,4,7,8-hexahydropyrido[2,3]pyrazolo [2,4-c] [1,4] diazepine-9-carboxylate (120.00 mg, 295.30 μ mol, 96.58% yield, TFA) as the colorless oil, which was used for the next step without purification.

20 Step 3. methyl 2-((3-chloro-4-fluorophenyl)carbamoyl)-9,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-
octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-9-carboxylate. To a solution of

methyl 9,10-dimethyl-11-oxo-1,2,3,4,7,8-hexahydropyrido[2,3] pyrazolo[2,4-c][1,4]diazepine-9-

carboxylate (120.00 mg, 295.30 μ mol, 1.00 *eq*, TFA) and phenyl N-(3-chloro-4-fluoro-

25 phenyl)carbamate (78.45 mg, 295.30 μ mol, 1.00 *eq*) in DCM (3.00 mL) was added TEA (365.00

mg, 3.61 mmol, 500.00 μ L, 12.21 *eq*). The mixture was stirred at 20 °C for 16 hr. TLC

showed the reaction was completed. The reaction mixture was partitioned between ethyl acetate

(20 mL) and water (20 mL) and extracted with ethyl acetate (20 mL*2), the organic layer was

washed with brine (20 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuum. The

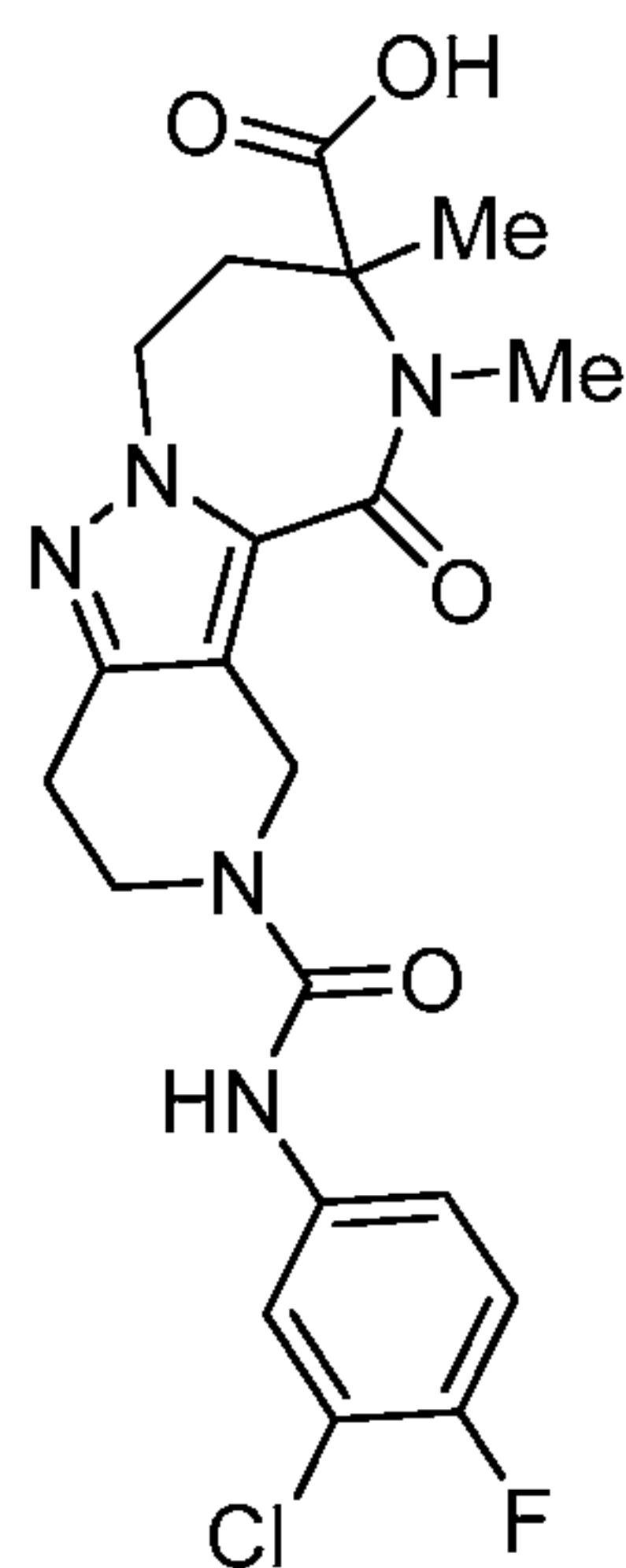
crude was purified by prep-TLC to afford the title compound (90.00 mg, 188.19 μ mol, 63.73%

30 yield, 97% purity) as white solid.

Step 4. N-(3-chloro-4-fluorophenyl)-9-(hydroxymethyl)-9,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. To a solution of methyl 2-[(3-chloro-4-fluoro-phenyl)carbamoyl]-9,10-dimethyl-11-oxo-3,4,7,8-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-9-carboxylate (45.00 mg, 97.01 μmol , 1.00 *eq*) in THF (2.00 mL) was added LiBH_4 (4.23 mg, 194.02 μmol , 2.00 *eq*) at 0 °C. The mixture was stirred at 20 °C for 16 hr. LCMS showed 15% reactant remained and LiBH_4 (4.23 mg, 194.02 μmol , 2.00 *eq*) was added, the mixture was stirred at 20 °C for 4 hr. LCMS showed the reaction was completed. The mixture was poured into aqueous HCl (0.5M), extracted with DCM (20 mL*2), the organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude was purified by prep-HPLC to afford the title compound (22.00 mg, 49.46 μmol , 50.99% yield, 98% purity) as white solid. LCMS: 436/438 [M+1].

^1H NMR (400 MHz, CDCl_3) δ 7.57 (dd, $J = 2.64, 6.53$ Hz, 1 H), 7.22 (ddd, $J = 2.76, 4.08, 8.97$ Hz, 1 H), 7.00 - 7.09 (m, 1 H), 6.79 (s, 1 H), 4.64 - 4.75 (m, 2 H), 4.51 - 4.59 (m, 1 H), 4.38 - 4.47 (m, 1 H), 3.77 - 3.92 (m, 3 H), 3.55 (d, $J = 11.29$ Hz, 1 H), 3.12 (s, 3 H), 2.80 (t, $J = 5.77$ Hz, 2 H), 2.49 - 2.63 (m, 1 H), 2.27 (ddd, $J = 2.38, 8.28, 15.56$ Hz, 2 H), 1.44 (s, 3 H).

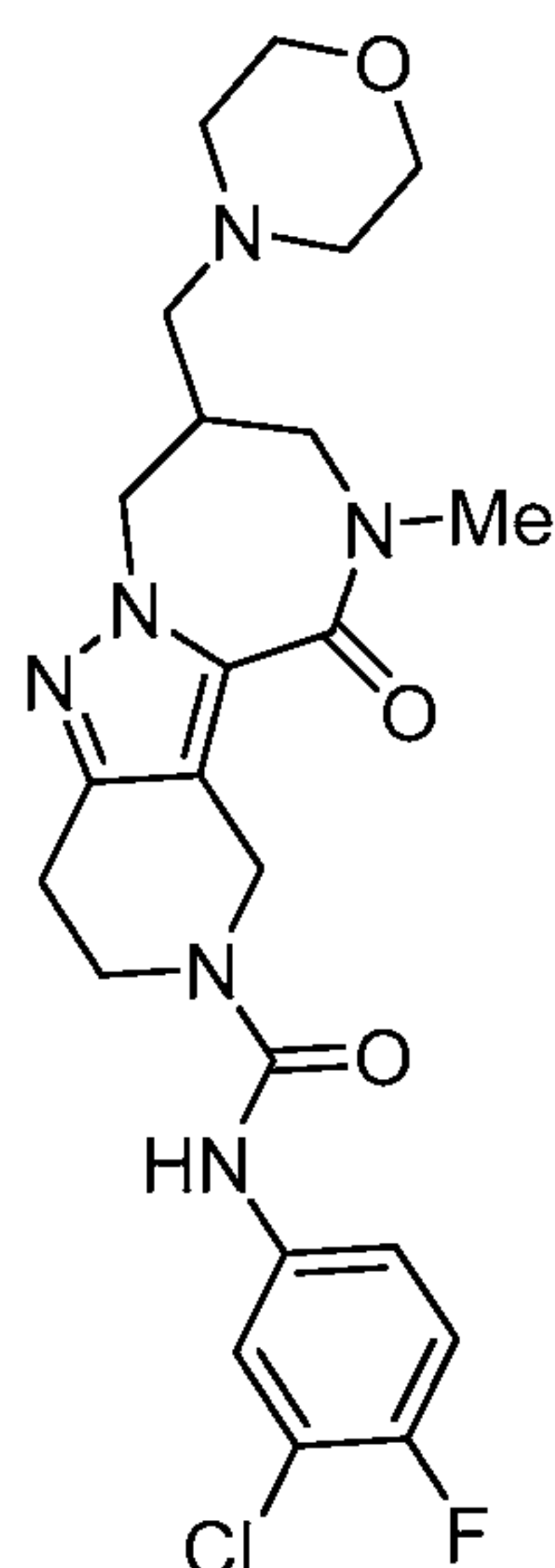
Compound 062: 2-((3-chloro-4-fluorophenyl)carbamoyl)-9,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-9-carboxylic acid.



To a solution of methyl 2-[(3-chloro-4-fluoro-phenyl)carbamoyl]-9,10-dimethyl-11-oxo-3,4,7,8-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-9-carboxylate (10.00 mg, 21.56 μmol , 1.00 *eq*) in MeOH (1.00 mL) and H_2O (1.00 mL) was added NaOH (1.29 mg, 32.34 μmol , 1.50 *eq*). The mixture was stirred at 20 °C for 16 hrs. LCMS showed 60% reactant remained, NaOH

(2.59 mg, 64.67 μ mol, 3.00 *eq*) was added. The mixture was heated to 40 °C and stirred at 40 °C for 16 hr. LCMS showed the reaction completed. The mixture was acidified to pH 3 by HCl (3 M). The resulting mixture was purified by prep-HPLC to afford the title compound (7.00 mg, 15.09 μ mol, 70.01% yield, 97% purity) as white solid. LCMS: 450/452 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 7.45 (dd, *J* = 2.51, 6.27 Hz, 1 H), 7.11 - 7.20 (m, 1 H), 7.01 - 7.08 (m, 1 H), 6.80 (br s, 1 H), 6.74 - 6.86 (m, 1 H), 4.70 - 4.75 (m, 1 H), 4.21 - 4.45 (m, 3 H), 3.93 - 3.96 (m, 1 H), 3.56 (br s, 1 H), 3.17 (s, 4 H), 2.70 - 2.92 (m, 2 H), 2.08 - 2.23 (m, 1 H), 1.66 (s, 3 H).

10 Compound 063: N-(3-chloro-4-fluorophenyl)-10-methyl-8-(morpholinomethyl)-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. tert-butyl 8-(hydroxymethyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. A mixture of 2-tert-butyl 8-ethyl 10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido [2,3]pyrazolo[2,4-b][1,4]diazepine-2,8-dicarboxylate (Intermediate 14, 500.00 mg, 1.27 mmol, 1.00 *eq*) in THF (10.00 mL) was added LiAlH₄ (96.39 mg, 2.54 mmol, 2.00 *eq*) at -40 °C under N₂, then the mixture was stirred at -40 °C for 2 hr under N₂ atmosphere. The mixture was poured into ice-water (20 mL) and stirred at 5 min. The aqueous phase was extracted with ethyl acetate (10 mL*3). The combined organic phase was washed with HCl (1N, 20 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, Petroleum

ether/Ethyl acetate=100/1 to 1:2) to afford the title compound (120.00 mg, 342.46 μ mol, 26.97% yield) as a white solid. LCMS: 351 [M+1].

Step 2. tert-butyl 10-methyl-8-(methylsulfonyloxymethyl)-11-oxo- 1,3,4,7,8,9 -

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. A mixture of tert-butyl 8-

5 (hydroxymethyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (100.00 mg, 285.38 μ mol, 1.00 *eq*), TEA (144.39 mg, 1.43 mmol, 197.79 μ L, 5.00 *eq*) in DCM (3.00 mL) was added MsCl (130.76 mg, 1.14 mmol, 88.35 μ L, 4.00 *eq*) at 0 °C under N₂, and then the mixture was stirred at 15 °C for 2 hour under N₂ atmosphere. LCMS and TLC showed the starting material was consumed completely, a new
10 spot appeared. The mixture was poured into ice-water (20 mL) and stirred at 5 min. The aqueous phase was extracted with DCM (10 mL*2). The combined organic phase was washed with brine (20 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to afford the title compound (102.00 mg, 238.04 μ mol, 83.41% yield) as a white solid, which was used directly for next step. LCMS 429 [M+1].

15 Step 3. tert-butyl 10-methyl-8-(morpholinomethyl)-11-oxo- 1,3,4,7,8,9-hexahydropyri

do[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. A mixture of tert-butyl 10-methyl-8-

(methylsulfonyloxymethyl)-11-oxo-1,3,4, 7,8,9 - hexahydropyrido[2,3]pyrazolo[2,4-

b][1,4]diazepine-2-carboxylate (100.00 mg, 233.37 μ mol, 1.00 *eq*), morpholine (203.31 mg, 2.33

mmol, 205.37 μ L, 10.00 *eq*) in DMSO (2.00 mL) was degassed and purged with N₂ for 3

20 times, and then the mixture was stirred at 88 °C for 16 hour under N₂ atmosphere. LCMS showed the starting material was consumed completely, desired product was major. The mixture was poured into water (10 mL) and extracted with EtOAc (5 mL*3). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by Prep-TLC (DCM/MeOH=20/1) to afford the title
25 compound (65.00 mg, 147.19 μ mol, 63.07% yield, 95% purity) as a white solid.

LCMS: 420 [M+1].

Step 4. 10-methyl-8-(morpholinomethyl)-2,3,4,7,8,9-hexahydro-1H-pyrido [2,3]pyrazolo[2,4-

b][1,4]diazepin-11-one. A mixture of tert-butyl 10-methyl-8-(morpholinomethyl)-11-oxo-

1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (65.00 mg,

30 154.94 μ mol, 1.00 *eq*), TFA (1.54 g, 13.51 mmol, 1.00 mL, 87.17 *eq*) in DCM (2.00 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 20 °C for 1

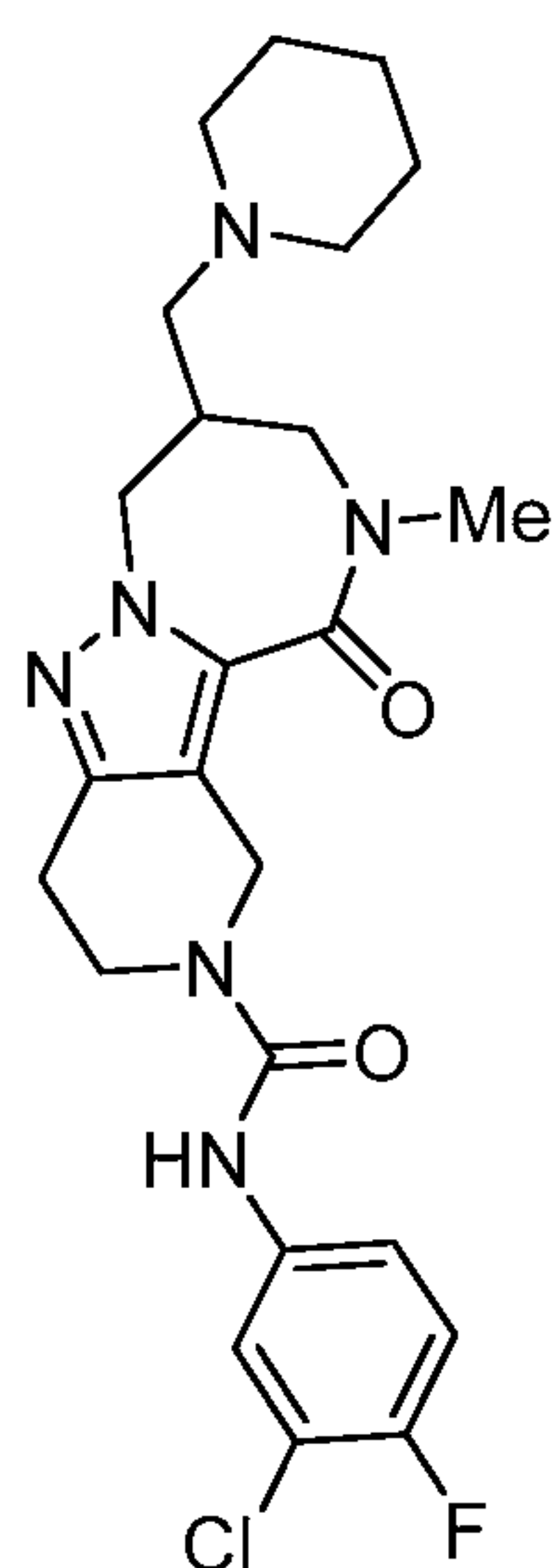
hour under N₂ atmosphere. TLC showed the starting material was consumed completely, a new spot appeared. The mixture was concentrated in vacuum to afford the title compound (67.00 mg, 154.58 μmol, 99.77% yield, TFA) as a yellow oil, which was used directly for next step.

Step 5. N-(3-chloro-4-fluorophenyl)-10-methyl-8-(morpholinomethyl)-11-oxo-1,3,4,7,8,9,10,11-

5 octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. A mixture of 10-methyl-8-(morpholinomethyl)-2,3,4,7,8,9-hexahydro-1H-pyrido [2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (67.00 mg, 209.77 μmol, 1.00 *eq*), phenyl N-(3-chloro-4-fluorophenyl)carbamate (66.88 mg, 251.72 μmol, 1.20 *eq*), TEA (42.45 mg, 419.54 μmol, 58.15 μL, 2.00 *eq*) in DCM (5.00 mL) was degassed and purged with N₂ for 3 times, and then the mixture
10 was stirred at 20 °C for 16 hour under N₂ atmosphere. LCMS showed the starting material was consumed completely, desired product was major. The mixture was poured into water (10 mL) and stirred at 5 min. The aqueous phase was extracted with DCM (5 mL*3). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by Prep-HPLC (FA) to afford the title
15 compound (60.00 mg, 120.99 μmol, 57.68% yield, 99% purity) as a white solid. LCMS: 491/493 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 7.58 (dd, *J* = 2.63, 6.54 Hz, 1 H), 7.18 - 7.24 (m, 1 H), 7.01 - 7.09 (m, 1 H), 6.72 (s, 1 H), 4.67 (s, 2 H), 4.38 - 4.47 (m, 1 H), 4.11 - 4.20 (m, 1 H), 3.74 - 3.92 (m, 6 H), 3.49 (m, 1 H), 3.28 (m, 1 H), 3.17 (s, 3 H), 2.75 - 2.91 (m, 4 H), 2.67 (m, 4 H), 2.48 - 2.56 (m, 1 H).

20

Compound 064: N-(3-chloro-4-fluorophenyl)-10-methyl-11-oxo-8-(piperidin-1-ylmethyl)-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. tert-butyl 8-(hydroxymethyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. A mixture of tert-butyl 10-methyl-8-methylene-11-oxo-3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate

- 5 (Intermediate 1, 800.00 mg, 2.41 mmol, 1.00 *eq*), chlororhodium;triphenylphosphane (89.19 mg, 96.40 μ mol, 0.04 *eq*) in THF (10.00 mL) was added 1,3,2-benzodioxaborole (1 M, 7.23 mL, 3.00 *eq*) at 0 °C under N₂, and then the mixture was stirred at 20 °C for 3 hr under N₂ atmosphere. TLC showed the starting material was consumed completely. A solution of sodium;hydroxide (482.00 mg, 12.05 mmol, 5.00 *eq*) in H₂O (5.00 mL) was added at -30 °C dropwise, then
- 10 hydrogen peroxide (1.91 g, 16.87 mmol, 1.62 mL, 30% purity, 7.00 *eq*) was added slowly. The mixture was stirred at 20 °C for 16 hr. TLC showed no starting material, desired product was major. The mixture was quenched with NaHSO₃ (saturated, 40 mL) and extracted with EtOAc (20 mL). The organic phase was washed with NaOH (15%, 40 mL*3) and brine, dried over Na₂SO₄, filtered and concentrated in vacuo to give brown oil. The residue was purified by
- 15 column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 1/4) to afford the title compound (522.00 mg, 1.42 mmol, 58.72% yield, 95% purity) as a white solid.

LCMS: 351 [M+1].

Step 2. tert-butyl 10-methyl-8-(methylsulfonyloxymethyl)-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. A mixture of tert-butyl 8-

- 20 (hydroxymethyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (500.00 mg, 1.43 mmol, 1.00 *eq*), TEA (723.51 mg, 7.15 mmol, 991.11 μ L, 5.00 *eq*) in DCM (10.00 mL) was added MsCl (655.23 mg, 5.72 mmol, 442.72 μ L,

4.00 *eq*) at 0 °C under N₂, and then the mixture was stirred at 20 °C for 2 hour under N₂ atmosphere. TLC showed the starting material was consumed completely, a new spot appeared. The mixture was poured into ice-water (20 mL) and stirred at 5 min. The aqueous phase was extracted with DCM (10 mL*2). The combined organic phase was washed with brine (20 mL),
 5 dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to afford the title compound (550.00 mg, 1.09 mmol, 76.29% yield, 85% purity) as a colorless oil.

LCMS: 429 [M+1].

Step 3. tert-butyl 10-methyl-11-oxo-8-(1-piperidylmethyl)-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. A mixture of tert-butyl 10-

10 methyl-8-(methylsulfonyloxymethyl)-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (120.00 mg, 280.05 μmol, 1.00 *eq*), piperidine (238.46 mg, 2.80 mmol, 277.28 μL, 10.00 *eq*) in DMSO (2.00 mL) was degassed and purged with N₂ for 3

times, and then the mixture was stirred at 88 °C for 16 hour under N₂ atmosphere. LCMS showed the starting material was consumed completely, desired product was major. The mixture

15 was poured into water (10 mL). The aqueous phase was extracted with ethyl acetate (5 mL*2).

The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by Prep-TLC

(DCM/MeOH=10/1) to afford the title compound (60.00 mg, 143.70 μmol, 51.31% yield) as a white solid. LCMS: 418 [M+1]

20 Step 4. 10-methyl-8-(1-piperidylmethyl)-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one. A mixture of tert-butyl 10-methyl-11-oxo-8-(1-piperidylmethyl)-

1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (54.00 mg, 129.33 μmol, 1.00 *eq*) in DCM (2.00 mL) was added TFA (1.54 g, 13.51 mmol, 1.00 mL, 104.43 *eq*), and then the mixture was stirred at 20 °C for 1 hour under N₂ atmosphere. TLC showed the

25 starting material was consumed completely, a new spot appeared. The mixture was concentrated in vacuum to afford the title compound (55.80 mg, 129.33 μmol, 100.00% yield, TFA) as a yellow oil, which was used directly for next step.

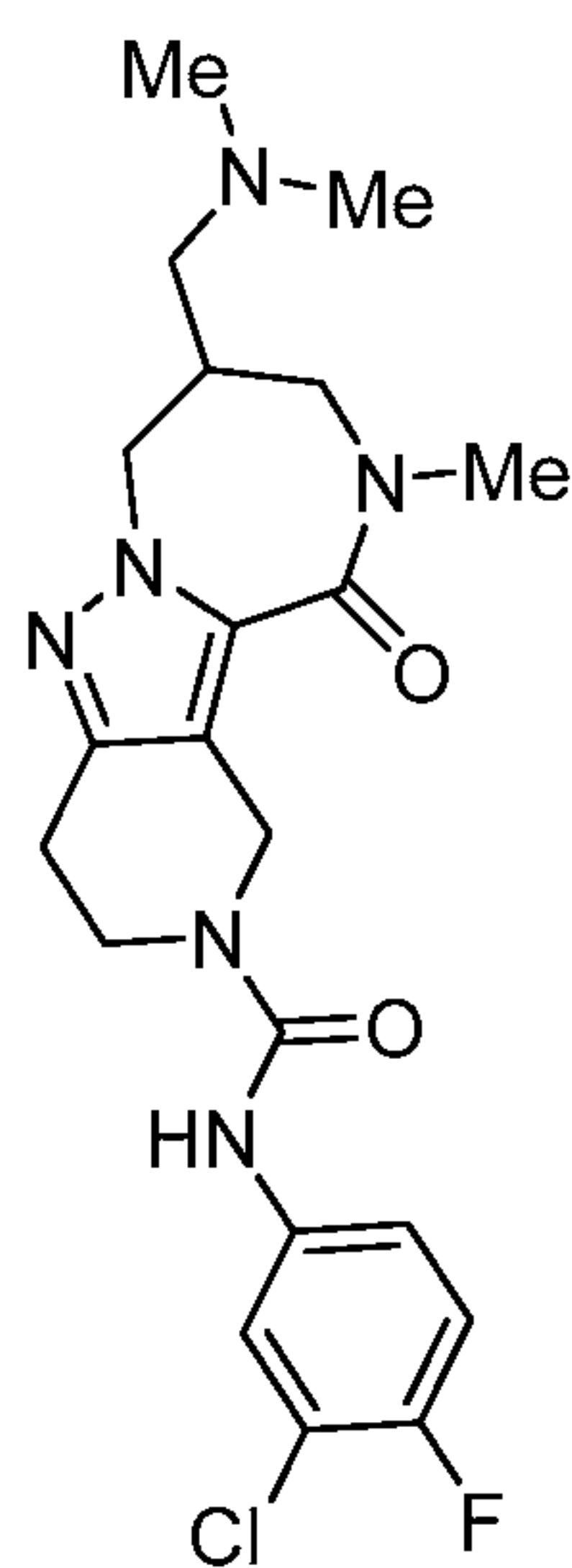
Step 5. N-(3-chloro-4-fluorophenyl)-10-methyl-11-oxo-8-(piperidin-1-ylmethyl)-

1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. A

30 mixture of 10-methyl-8-(1-piperidylmethyl)-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (55.80 mg, 129.33 μmol, 1.00 *eq*, TFA), phenyl N-(3-chloro-4-fluoro-

phenyl)carbamate (41.23 mg, 155.20 μ mol, 1.20 *eq*), TEA (26.17 mg, 258.66 μ mol, 35.85 μ L, 2.00 *eq*) in DCM (5.00 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 20 °C for 16 hour under N₂ atmosphere. LCMS showed the starting material was consumed completely, desired product was major. The mixture was poured into water (10 mL) and stirred at 5 min. The aqueous phase was extracted with DCM (5 mL*3). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by Prep-HPLC (HCl) to afford the title compound (40.00 mg, 80.98 μ mol, 62.62% yield, 99% purity) as a white solid. LCMS: 489/491 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 7.60 (m, 1 H), 7.18 (m, 1 H), 7.02 - 7.10 (m, 1 H), 6.60 (br s, 1 H), 4.57 - 4.77 (m, 2 H), 4.48 (m, 1 H), 4.35 (m, 1 H), 3.84 (m, 3 H), 3.68 (m, 1 H), 3.32 - 3.58 (m, 3 H), 3.24 (m, 3 H), 2.63 - 3.08 (m, 6 H), 2.37 (m, 2 H), 1.81 - 2.02 (m, 3 H), 1.48 (m, 1 H).

Compound 065: N-(3-chloro-4-fluorophenyl)-8-((dimethylamino)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. tert-butyl 8-[(dimethylamino)methyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate. A mixture of tert-butyl 10-methyl-8-

(methylsulfonyloxymethyl)-11-oxo-1,3,4,7,8,9-hexahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (Compound 064, product from Step 2, 120.00 mg, 280.05 μ mol, 1.00 *eq*), N-methylmethanamine (2 M, 1.40 mL, 10.00 *eq*) in DMSO (5.00 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 88 °C for 16 hour under N₂

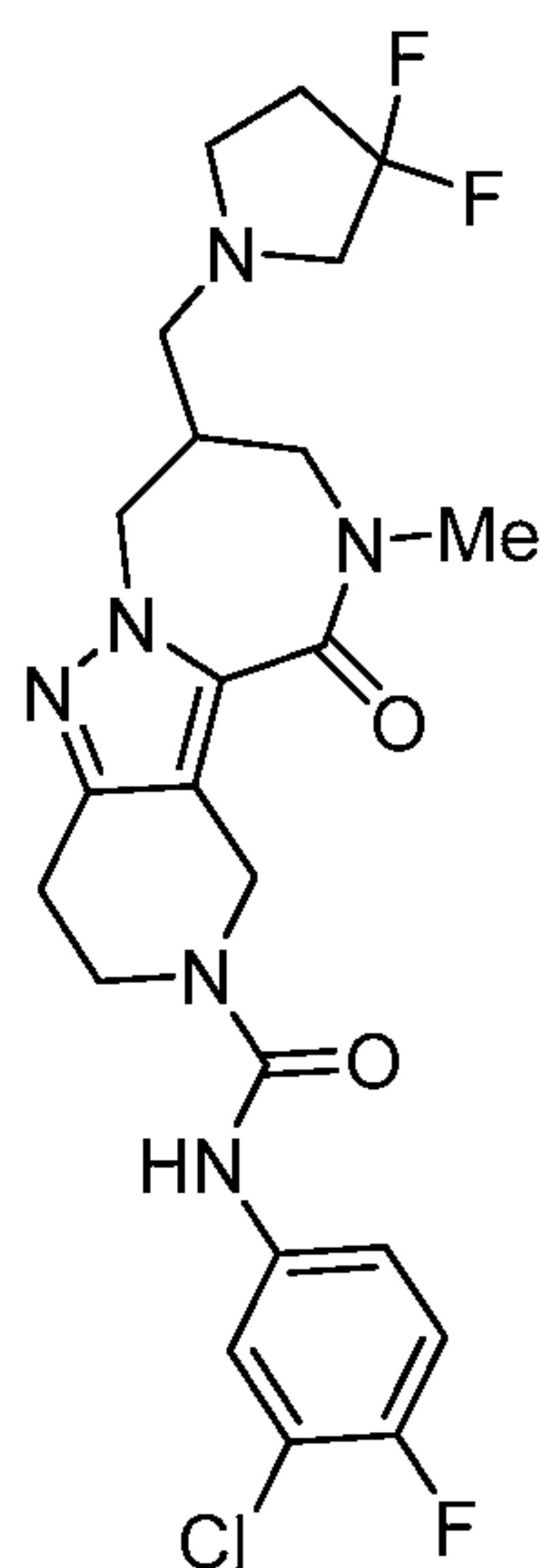
atmosphere. TLC showed the starting material was consumed completely, desired product was major. The mixture was poured into water (10 mL) and extracted with EtOAc (5 mL*3). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by Prep-TLC (DCM/MeOH=10/1) to afford the title compound (65.00 mg, 165.31 μmol, 59.03% yield, 96% purity) as a white solid. LCMS: 378 [M+1]

Step 2. 8-[(dimethylamino)methyl]-10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one. A mixture of tert-butyl 8-[(dimethylamino)methyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (55.00 mg, 145.70 μmol, 1.00 eq) in DCM (2.00 mL) was added

TFA (1.69 g, 14.86 mmol, 1.10 mL, 101.97 eq) and then the mixture was stirred at 20 °C for 1 hour under N₂ atmosphere. TLC showed the starting material was consumed completely, a new spot appeared. The mixture was concentrated in vacuum to afford the title compound (57.00 mg, 145.63 μmol, 99.96% yield, TFA) as yellow oil, which was used directly for next step.

Step 3. N-(3-chloro-4-fluorophenyl)-8-((dimethylamino)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. A mixture of 8-[(dimethylamino)methyl]-10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (57.00 mg, 145.63 μmol, 1.00 eq, TFA), phenyl N-(3-amino-4-fluoro-phenyl)carbamate (43.03 mg, 174.76 μmol, 1.20 eq), TEA (29.47 mg, 291.27 μmol, 40.37 μL, 2.00 eq) in DCM (5.00 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 20 °C for 16 hour under N₂ atmosphere. LCMS showed the starting material was consumed completely, desired product was major. The mixture was poured into water (10 mL) and stirred at 5 min. The aqueous phase was extracted with DCM (5 mL*2). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by Prep-HPLC (HCl) to afford the title compound (59.00 mg, 130.11 μmol, 89.34% yield, 99% purity) as a white solid. LCMS: 449/451 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 7.57 - 7.63 (m, 1 H), 7.15 - 7.22 (m, 1 H), 7.02 - 7.10 (m, 1 H), 6.51 - 6.57 (m, 1 H), 4.58 - 4.77 (m, 2 H), 4.46 - 4.56 (m, 1 H), 4.31 (s, 1 H), 3.84-3.89 (m, 3 H), 3.47 - 3.61 (m, 1 H), 3.25 (s, 3 H), 3.12 - 3.20 (m, 1 H), 3.04 (m, 2 H), 2.83-2.92 (m, 6 H), 2.80 - 2.86 (m, 2 H).

Compound 066: N-(3-chloro-4-fluorophenyl)-8-((3,3-difluoropyrrolidin-1-yl)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



- 5 Step 1. tert-butyl 8-[(3,3-difluoropyrrolidin-1-yl)methyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. A mixture of tert-butyl 10-methyl-8-(methylsulfonyloxymethyl)-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (Compound 064, product from Step 2, 20.00 mg, 46.67 μ mol, 1.00 *eq*), 3,3-difluoropyrrolidine (49.99 mg, 466.74 μ mol, 10.00 *eq*) in DMSO (1.00 mL) was
- 10 degassed and purged with N₂ for 3 times, and then the mixture was stirred at 88 °C for 16 hr under N₂ atmosphere. TLC showed the starting material/desired product/byproduct=3/2/1. Then 3,3-difluoropyrrolidine (49.99 mg, 466.74 μ mol, 10.00 *eq*) was added to the mixture, and the mixture was stirred at 90 °C for 16 hr. TLC showed the starting material was consumed completely, desired product/byproduct=3/1. The mixture was poured into water (10 mL) and
- 15 stirred at 5 min. The aqueous phase was extracted with ethyl acetate (5 mL*2). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by Prep-TLC (DCM/MeOH=10/1) to afford the title compound (8.00 mg, 16.20 μ mol, 34.71% yield, 89% purity) as a white solid. LCMS: 440 [M+1].
- 20 Step 2. 8-[(3,3-difluoropyrrolidin-1-yl)methyl]-10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one. A mixture of tert-butyl 8-[(3,3-difluoropyrrolidin-1-yl)methyl]-10-methyl-11-oxo-1,3,4,7,8,9-

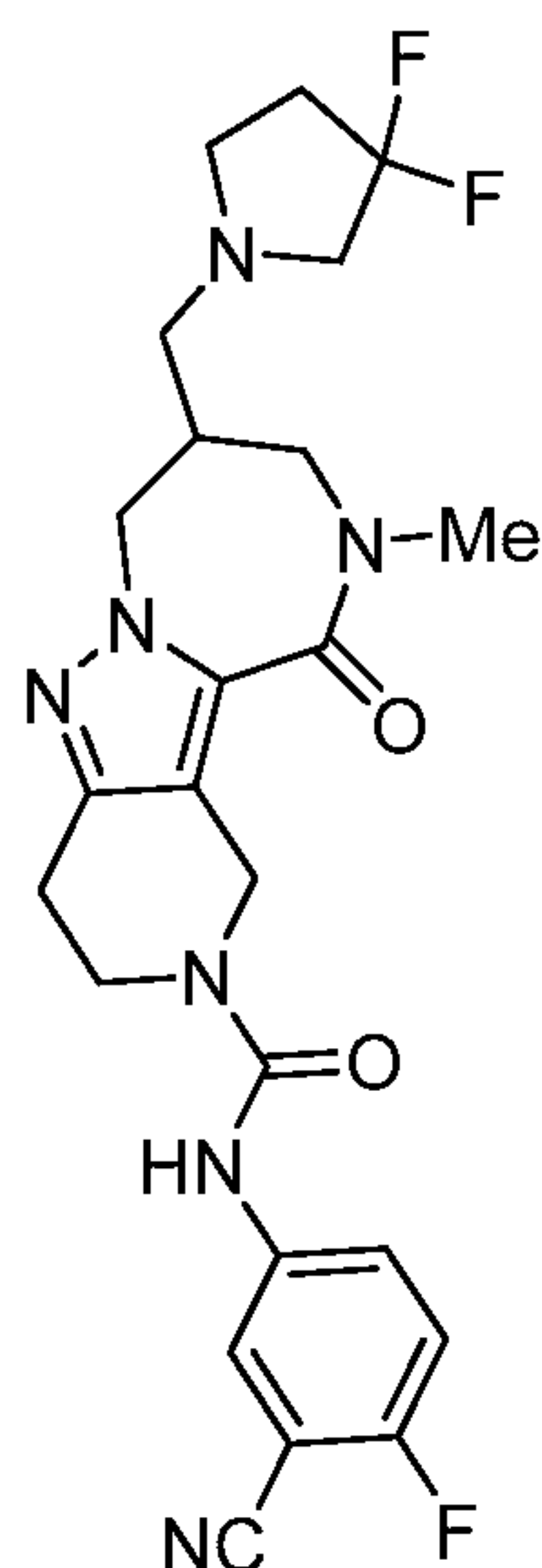
hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (8.00 mg, 18.20 μ mol, 1.00 *eq*) in DCM (2.00 mL) was added TFA (821.32 mg, 7.20 mmol, 533.32 μ L, 395.73 *eq*), and then the mixture was stirred at 20 °C for 1 hour. TLC showed the starting material was consumed completely, and a new spot formed. The mixture was concentrated in vacuum to afford the title compound (8.25 mg, 18.20 μ mol, 100.00% yield, TFA) as a yellow oil, which was used directly for next step.

Step 3. N-(3-chloro-4-fluorophenyl)-8-((3,3-difluoropyrrolidin-1-yl)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. A

mixture of 8-[(3,3-difluoropyrrolidin-1-yl)methyl]-10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (8.25 mg, 18.20 μ mol, 1.00 *eq*, TFA), phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (5.32 mg, 20.01 μ mol, 1.10 *eq*), TEA (3.68 mg, 36.39 μ mol, 5.04 μ L, 2.00 *eq*) in DCM (3.00 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 20 °C for 16 hours under N₂ atmosphere. LCMS showed the starting material was consumed completely, and the desired product was major. The mixture was poured into water (10 mL) and extracted with DCM (5 mL*2). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by Prep-HPLC (HCl) to afford the title compound (8.50 mg, 16.47 μ mol, 90.49% yield, 99% purity) as a light yellow solid. LCMS: 511/513 [M+1].

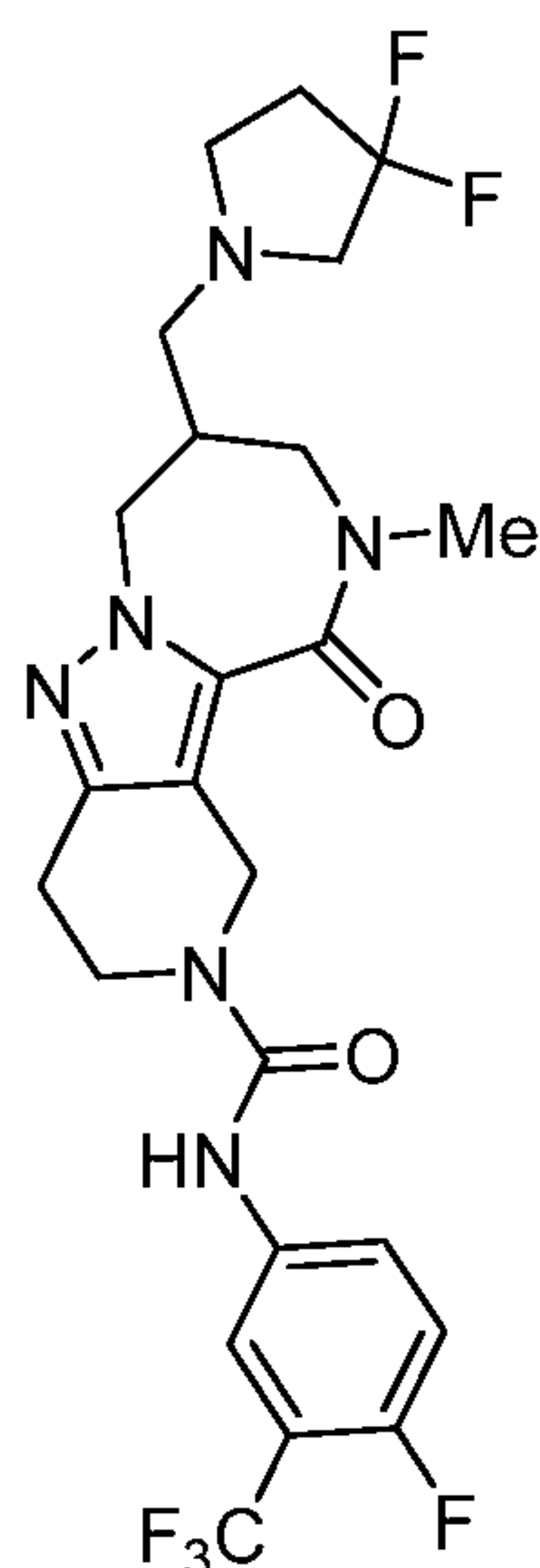
¹H NMR (400MHz, METHANOL-d₄) δ = 7.58 (dd, *J* = 2.6, 6.7 Hz, 1 H), 7.31 - 7.25 (m, 1 H), 7.14 (s, 1 H), 4.68 (d, *J* = 3.0 Hz, 2 H), 4.56 - 4.47 (m, 1 H), 4.36 - 4.27 (m, 1 H), 4.04 - 3.53 (m, 7 H), 3.35 (br s, 3 H), 3.19 (d, *J* = 1.6 Hz, 3 H), 3.09 - 2.97 (m, 1 H), 2.82 (s, 4 H).

Compound 067: N-(3-cyano-4-fluorophenyl)-8-((3,3-difluoropyrrolidin-1-yl)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



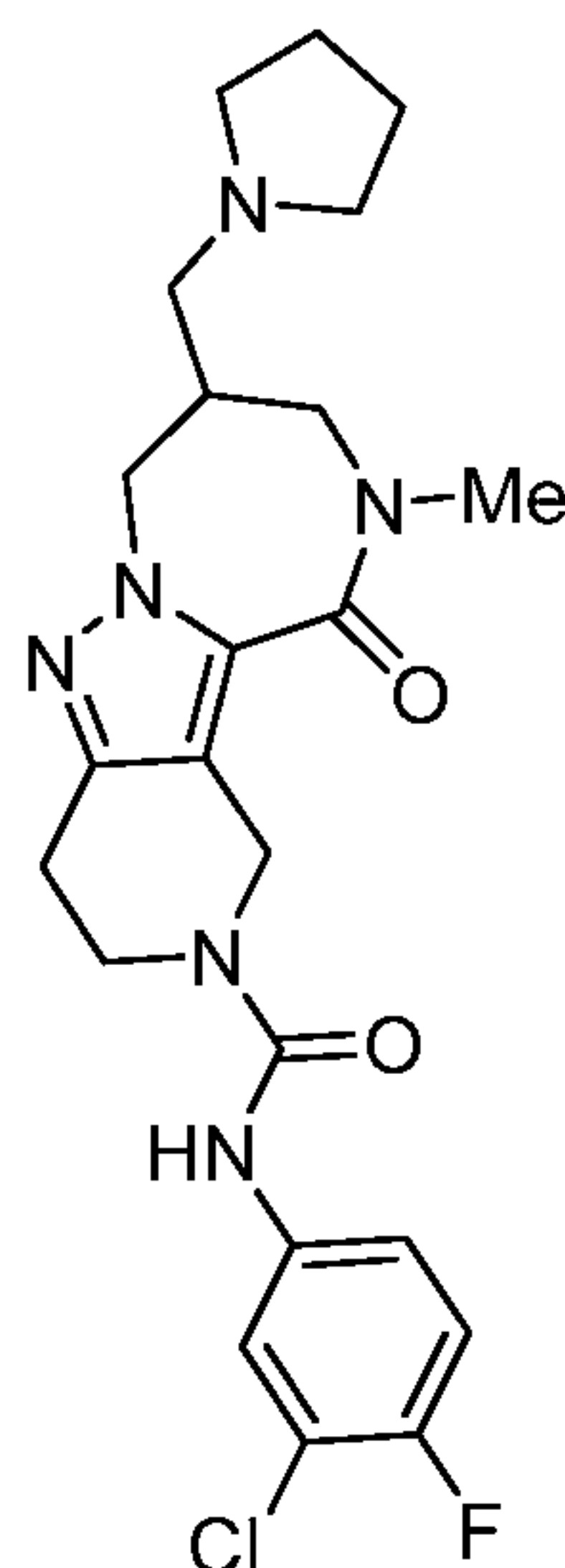
A mixture of 8-[(3,3-difluoropyrrolidin-1-yl)methyl]-10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (Compound 066, product from Step 2, 62.00 mg, 136.74 μmol , 1.00 *eq*, TFA), Et_3N (69.18 mg, 683.70 μmol , 94.77 μL , 5.00 *eq*) and phenyl N-(3-cyano-4-fluoro-phenyl)carbamate (42.04 mg, 164.09 μmol , 1.20 *eq*) in DCM (6.00 mL) was stirred at 30 $^\circ\text{C}$ for 2 h. LCMS indicated the starting material was consumed completely and major desired product. The mixture was concentrated in vacuo, which was purified by prep-HPLC (FA) to afford (43.00 mg, 81.46 μmol , 59.57% yield, 95% purity) as yellow solid. LCMS: 502[M+1]. ^1H NMR (400 MHz, CDCl_3) δ 7.78 (m, 1 H), 7.60 (m, 1 H), 7.13 (t, J = 8.74 Hz, 1 H), 6.93 (s, 1 H), 4.68 (s, 2 H), 4.41 (m, 1 H), 4.13 (d, J = 5.87 Hz, 1 H), 3.87 (m, 2 H), 3.46 (m, 1 H), 3.26 - 3.37 (m, 1 H), 3.18 (s, 3 H), 2.93 (m, 2 H), 2.73 - 2.87 (m, 4 H), 2.56 - 2.66 (m, 1 H), 2.47 - 2.55 (m, 2 H), 2.30 (m, 2 H).

Compound 068: 8-((3,3-difluoropyrrolidin-1-yl)methyl)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



A mixture of 8-[(3,3-difluoropyrrolidin-1-yl)methyl]-10-methyl-2,3,4,7,8,9- hexahydro-1H-
 pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (Compound 066, product from Step 2, 62.00
 mg, 136.74 μmol , 1.00 *eq*, TFA), Et_3N (69.18 mg, 683.70 μmol , 94.77 μL , 5.00 *eq*) and phenyl
 5 N-[4-fluoro-3-(trifluoromethyl)phenyl]carbamate (49.10 mg, 164.09 μmol , 1.20 *eq*) in DCM
 (6.00 mL) was stirred at 30 °C for 2 h. LCMS indicated the starting material was consumed
 completely and major desired product. The mixture was concentrated in vacuo, which was
 purified by prep-HPLC (FA) to afford the title compound (42.00 mg, 76.37 μmol , 55.85% yield,
 99% purity) as white solid. LCMS: 545 $[\text{M}+1]^+$ ^1H NMR (400 MHz, CDCl_3) δ 7.70 (m, 1 H), 7.57
 10 - 7.64 (m, 1 H), 7.11 – 7.16 (m, 1 H), 6.83 (s, 1 H), 4.71 (s, 2 H), 4.42 (m, 1H), 4.13 (m, 1 H),
 3.89 (m, 2 H), 3.42 - 3.54 (m, 1 H), 3.27 - 3.39 (m, 1 H), 3.19 (s, 3 H), 2.95 (m, 2 H), 2.86 (m, 4
 H), 2.58 - 2.69 (m, 1 H), 2.49 - 2.56 (m, 2 H), 2.32 (m, 2 H).

Compound 069: N-(3-chloro-4-fluorophenyl)-10-methyl-11-oxo-8-(pyrrolidin-1-ylmethyl)-
 15 1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of tert-butyl 10-methyl-8-(methylsulfonyloxymethyl)-11-oxo- 1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-

LCMS: 404 [M+1].

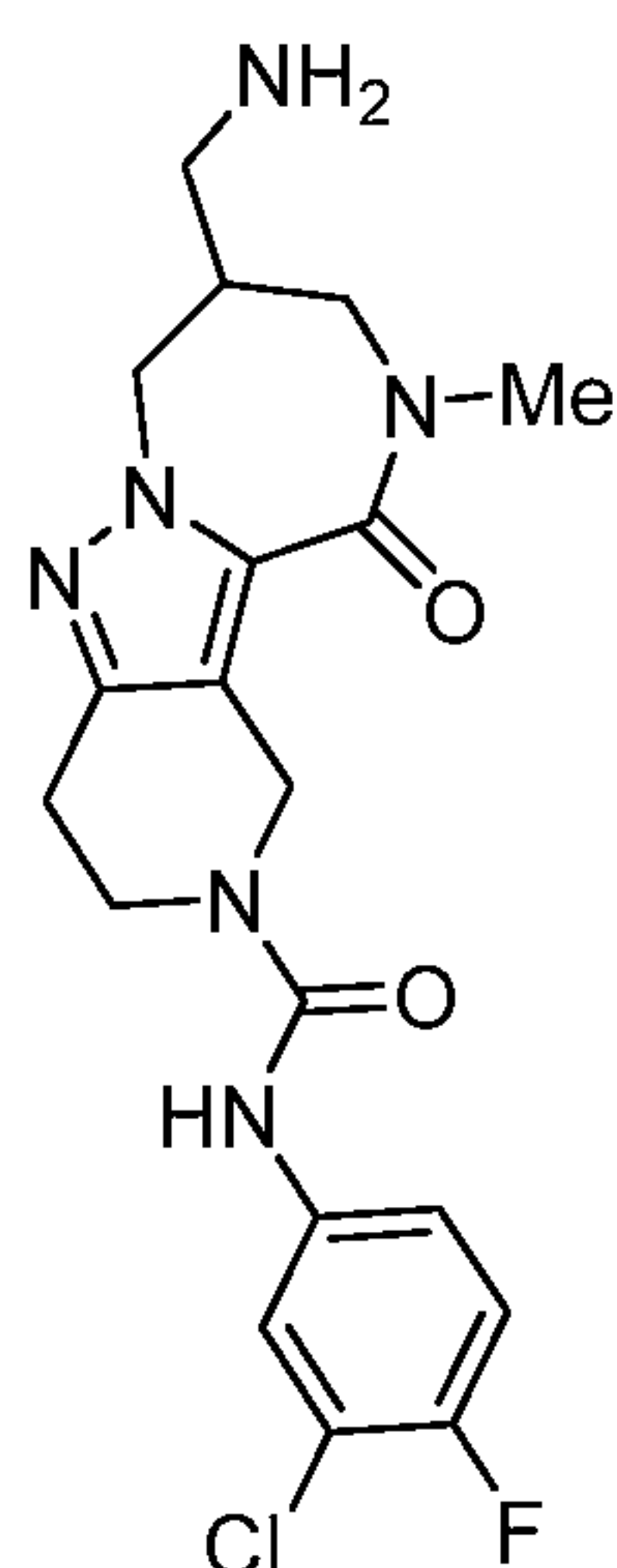
pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one. To a solution of tert-butyl 10-methyl-11-oxo-8-(pyrrolidin-1-ylmethyl) -1,3,4,7,8,9- hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-

LCMS: 304 [M+1].

1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

To a solution of 10-methyl-8-(pyrrolidin-1-ylmethyl)-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (94.14 mg, 225.53 μ mol, 1.00 *eq*, TFA) and Et₃N (114.11 mg, 1.13 mmol, 156.31 μ L, 5.00 *eq*) in DCM (3.00 mL) was added phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (59.92 mg, 225.53 μ mol, 1.00 *eq*), the mixture was stirred at 25 °C for 16 h. The mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC(Base) to afford the title compound (61.00 mg, 127.15 μ mol, 56.38% yield, 99% purity) as white solid. LCMS: 475/477 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 7.58 - 7.61 (m, 1 H), 7.17 - 7.19 (m, 1 H), 7.03 - 7.07 (m, 1 H), 6.61 (s, 1 H), 4.67 (s, 2 H), 4.39 - 4.44 (m, 1 H), 4.0 - 4.2 (m, 1 H), 3.84 - 3.87 (m, 2 H), 3.36 - 3.45 (m, 1 H), 3.34 - 3.35 (m, 1 H), 3.17 (s, 3 H), 2.82 - 2.85 (m, 2 H), 2.65 - 2.67 (m, 1 H), 2.48 - 2.55 (m, 6 H), 1.79 (m, 4 H).

Compound 070: 8-(aminomethyl)-N-(3-chloro-4-fluorophenyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. 8-(azidomethyl)-N-(3-chloro-4-fluoro-phenyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide. A mixture of [2-[(3-chloro-4-fluoro-phenyl)carbamoyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-8-yl]methanesulfonate (80.00 mg, 160.02 μ mol, 1.00 *eq*) in DMF (5.00 mL) was added NaN₃ (20.81 mg, 320.04 μ mol, 11.25 μ L, 2.00 *eq*) at 0 °C under N₂, and then the mixture was stirred at 50 °C for 16 hr under N₂ atmosphere. LCMS showed starting material/desired product=1/8. Then NaN₃ (20.81 mg, 320.04 μ mol, 11.25 μ L, 2.00 *eq*) was added to the mixture at 0 °C under N₂, and the mixture was stirred at 50 °C for another 16 hr.

The mixture was diluted with EtOAc(20 mL) and washed with brine(20 mL*3). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuum to afford the title compound (50.00 mg, 111.89 μmol, 69.92% yield) as a yellow oil, which was used directly for next step.

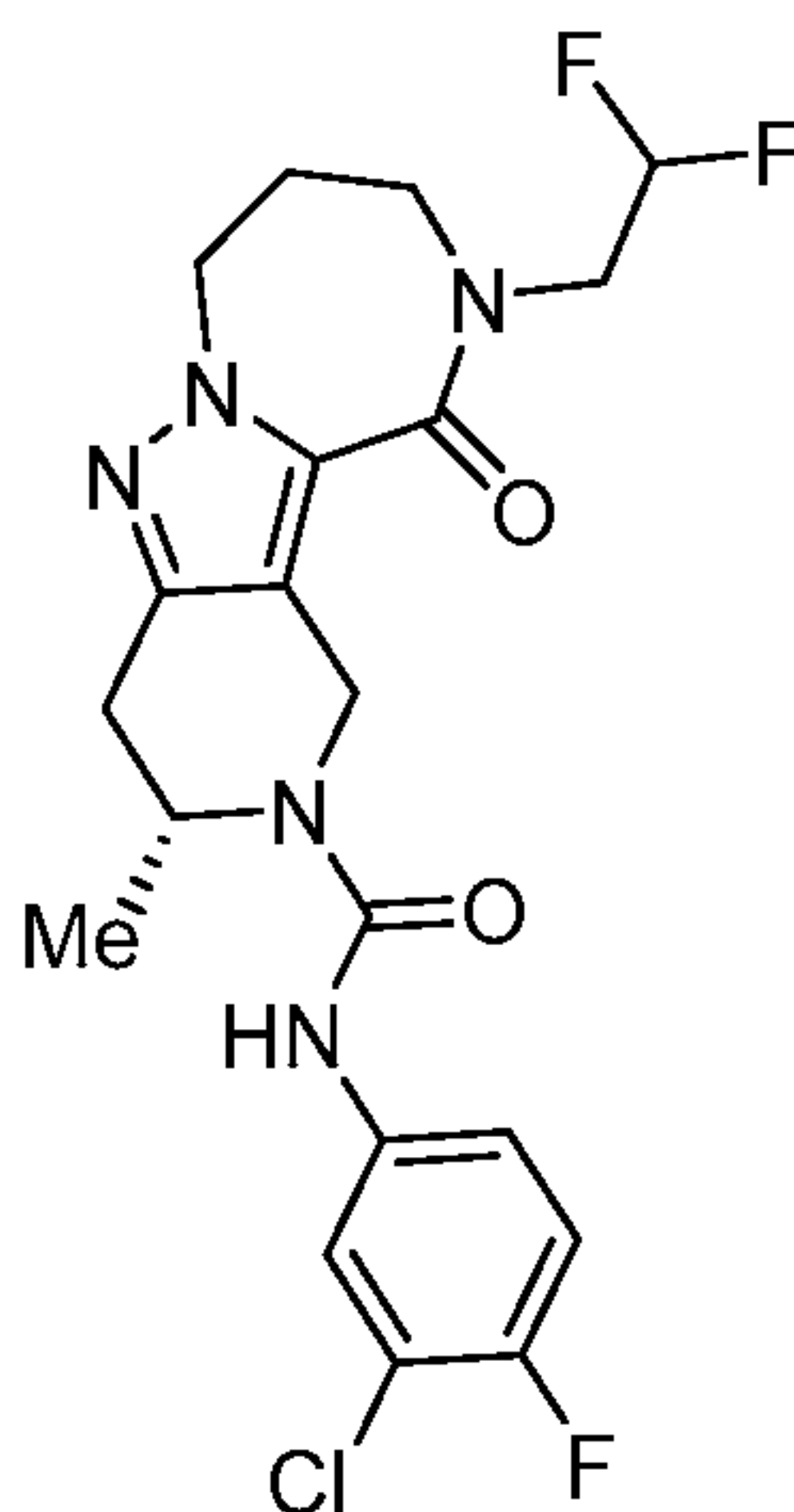
LCMS: 447 [M+1].

- 5 Step 3. 8-(aminomethyl)-N-(3-chloro-4-fluorophenyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. A mixture of 8-(azidomethyl)-N-(3-chloro-4-fluoro-phenyl)-10-methyl-11-oxo-1,3,4,7, 8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide (40.00 mg, 89.51 μmol, 1.00 *eq*), NH₄Cl (14.36 mg, 268.53 μmol, 9.39 μL, 3.00 *eq*) and Zn (11.71 mg, 179.02 μmol, 2.00 *eq*) in EtOH (5.00 mL) and H₂O (500.00 uL) was degassed and purged with N₂ for 3 times, and
10 then the mixture was stirred at 30 °C for 16 hour under N₂ atmosphere. LCMS showed the starting material was consumed completely, desired product was major. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by Prep-HPLC (FA) to afford the title compound (32.00 mg, 74.51 μmol, 83.24% yield, 98% purity) as a white solid.
15 LCMS: 421 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 7.57 - 7.62 (m, 1 H), 7.17 - 7.23 (m, 1 H), 7.05 (s, 1 H), 6.60 - 6.64 (m, 1 H), 4.67 (d, *J* = 2.51 Hz, 2 H), 4.37 - 4.47 (m, 1 H), 4.13 - 4.25 (m, 1 H), 3.86 (d, *J* = 6.90 Hz, 2 H), 3.44 (d, *J* = 5.40 Hz, 1 H), 3.38 (d, *J* = 7.53 Hz, 1 H), 3.19 (s, 3 H), 2.83 (d, *J* = 5.65 Hz, 4 H), 2.43 - 2.57 (m, 1 H).

- 20 Compound 071: (R)-N-(2-bromo-5-chloro-4-fluorophenyl)-10-(2,2-difluoroethyl)-3-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

- The title compound was prepared in a manner analogous to Compound 072, using phenyl (2-bromo-5-chloro-4-fluorophenyl)carbamate in Step 3. LCMS [M+1] : 534/536. ¹H NMR
25 (400MHz, CDCl₃) δ = 8.32 (d, *J* = 7.5 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 6.93 - 6.98 (m, 1 H), 5.88 - 6.24 (m, 1 H), 5.00 - 5.09 (m, 1 H), 4.91 (s, 1 H), 4.35 - 4.53 (m, 3 H), 3.79 - 4.07 (m, 2 H), 3.59 (s, 2 H), 3.00 - 3.09 (m, 1 H), 2.66 - 2.75 (m, 1 H), 2.36 (s, 2 H), 1.23 (d, *J* = 6.9 Hz, 3 H).

Compound 072: (3R)-N-(3-chloro-4-fluorophenyl)-10-(2,2-difluoroethyl)-3-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. tert-butyl (3R)-10-(2,2-difluoroethyl)-3-methyl-11-oxo-1,3,4,7,8,9-

5 hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of tert-butyl (3R)-3-methyl-11-oxo-3,4,7,8,9,10-hexahydro-1H-pyrido [2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (700.00 mg, 2.18 mmol, 1.00 *eq*) in DMF (7.00 mL) was added NaH (261.60 mg, 6.54 mmol, 60% purity, 3.00 *eq*) at -10 °C. The mixture was stirred at -10 °C for 30 min. Then a solution of 2,2-difluoroethyl trifluoromethanesulfonate (1.40 g, 6.54 mmol, 3.00 *eq*) in DMF
10 (800.00 uL) was added dropwise at -10 °C. The mixture was stirred at 0 °C for 1 hr. TLC (PE:EtOAc = 1:1) showed one main spot appeared. The mixture was added into ice-water (50 mL) and extracted with EtOAc (50 mL*3). The combined organic layer was washed with H₂O (50 mL*3), dried over Na₂SO₄, filtrated. The filtrate was concentrated in vacuum. The residue was purified by column chromatography (PE:EtOAc = 30% ~ 50%) to afford the title compound
15 (800.00 mg, 2.08 mmol, 95.41% yield) as colorless oil.

Step 2. (3R)-10-(2,2-difluoroethyl)-3-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]

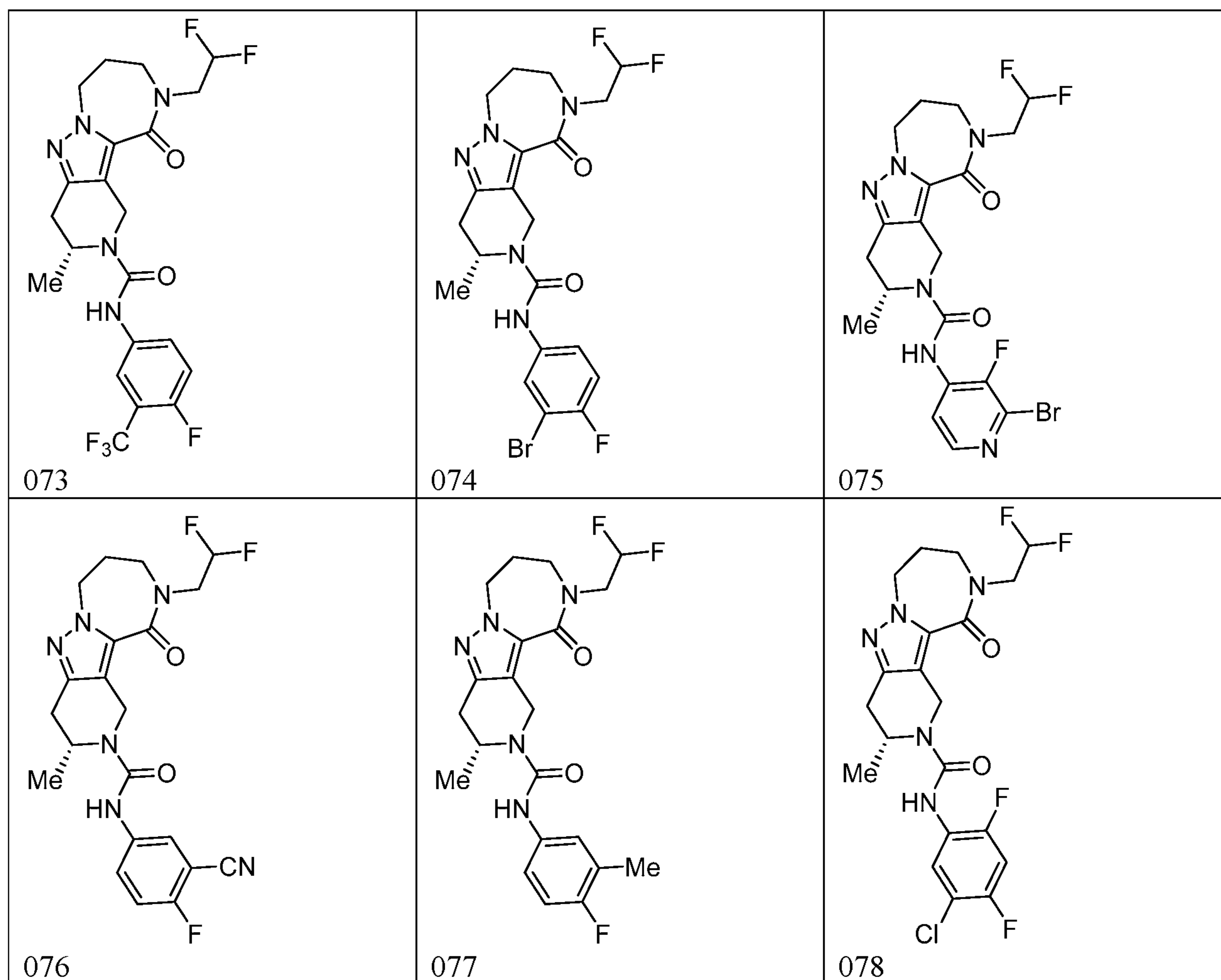
pyrazolo[2,4-b][1,4]diazepin-11-one. To a solution of tert-butyl (3R)-10-(2,2-difluoroethyl)-3-methyl-11-oxo-1,3,4,7,8,9- hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (350.00 mg, 910.46 μmol, 1.00 *eq*) in DCM (5.00 mL) was added TFA (7.70 g, 67.53 mmol, 5.00 mL, 74.17 *eq*). The mixture was stirred at 20 °C for 1 hr. TLC (PE:EtOAc = 1:1) showed the starting material consumed. The mixture was concentrated in vacuum to afford the title compound (380.00 mg, crude, TFA) as brown oil.

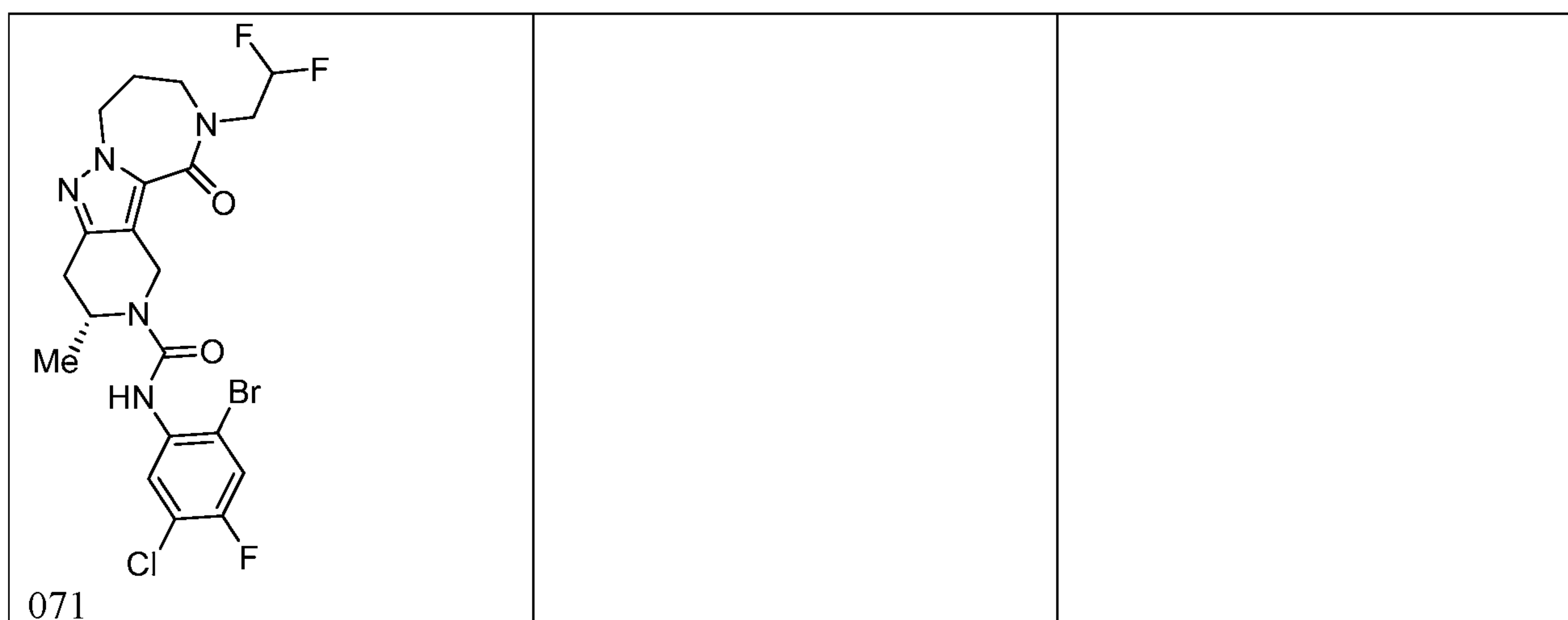
Step 3. (3R)-N-(3-chloro-4-fluorophenyl)-10-(2,2-difluoroethyl)-3-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

To a solution of (3R)-10-(2,2-difluoroethyl)-3-methyl-2,3,4,7,8,9-hexahydro -1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (55.00 mg, 138.08 μ mol, 1.00 *eq*, TFA) and
 5 Et₃N (69.86 mg, 690.40 μ mol, 95.70 μ L, 5.00 *eq*) in DCM (2.00 mL) was added phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (36.68 mg, 138.08 μ mol, 1.00 *eq*). The mixture was stirred at 25 °C for 16 h. The mixture was directly evaporated. The residue was purified by prep-HPLC (FA) to afford the title compound (31.70 mg, 69.33 μ mol, 50.21% yield, 99.7% purity) as white solid. LCMS [M+1] : 456

10

Compounds 073, 074, 075, 076, 077, 078, and 071 were prepared in a manner analogous to Compound 072.





Compound 073: (R)-10-(2,2-difluoroethyl)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-3-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

- 5 The title compound was prepared in a manner analogous to Compound 072, using phenyl (4-fluoro-3-(trifluoromethyl)phenyl)carbamate in Step 3. LCMS [M+1] :489. ¹H NMR (400MHz, CDCl₃) δ = 7.65 - 7.71 (m, 1 H), 7.56 - 7.63 (m, 1 H), 7.13 (s, 1 H), 6.61 (s, 1 H), 6.05 (s, 1 H), 5.13 (m, 1 H), 4.84 (m, 1 H), 4.38 - 4.51 (m, 3 H), 3.81 - 4.07 (m, 2 H), 3.55 - 3.68 (m, 2 H), 3.03 (m, 1 H), 2.68 (m, 1 H), 2.37 (m, 2 H), 1.19 (d, *J* = 6.8 Hz, 3 H).

10

Compound 074: (R)-N-(3-bromo-4-fluorophenyl)-10-(2,2-difluoroethyl)-3-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

The title compound was prepared in a manner analogous to Compound 072, using phenyl (3-bromo-4-fluorophenyl)carbamate in Step 3. LCMS [M+1] : 500/502. ¹H NMR (400MHz,

- 15 CDCl₃) δ = 7.69 - 7.74 (m, 1 H), 7.27 - 7.30 (m, 1 H), 7.04 (br d, *J* = 2.4 Hz, 1 H), 6.46 - 6.58 (m, 1 H), 5.86 - 6.24 (m, 1 H), 5.05 - 5.18 (m, 1 H), 4.82 (m, 1 H), 4.35 - 4.52 (m, 3 H), 3.77 - 4.08 (m, 2 H), 3.59 - 3.61 (m, 2 H), 2.93 - 3.09 (m, 1 H), 2.69 (s, 1 H), 2.36 (m, 2 H), 1.18 (dd, *J* = 2.2, 6.8 Hz, 3 H).

- 20 Compound 075: (R)-N-(2-bromo-3-fluoropyridin-4-yl)-10-(2,2-difluoroethyl)-3-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

The title compound was prepared in a manner analogous to Compound 072, using phenyl (2-bromo-3-fluoropyridin-4-yl)carbamate in Step 3. LCMS [M+1] : 501. ¹H NMR (400MHz, CDCl₃) δ = 8.14 - 8.18 (m, 1 H), 8.06 (d, *J* = 5.5 Hz, 1 H), 6.96 - 7.07 (m, 1 H), 5.87 - 6.23 (m, 1 H), 5.00 - 5.10 (m, 1 H), 4.85 - 4.96 (m, 1 H), 4.35 - 4.56 (m, 3 H), 3.77 - 4.09 (m, 2 H), 3.58 - 3.63 (m, 2 H), 2.99 - 3.10 (m, 1 H), 2.66 - 2.77 (m, 1 H), 2.31 - 2.44 (m, 2 H), 1.23 (d, *J* = 6.9 Hz, 3 H).

Compound 076: (R)-N-(3-cyano-4-fluorophenyl)-10-(2,2-difluoroethyl)-3-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

The title compound was prepared in a manner analogous to Compound 072, using phenyl (3-cyano-4-fluorophenyl)carbamate in Step 3. LCMS [M+1] : 446. ¹H NMR (400MHz, CDCl₃) δ = 7.78 (s, 1 H), 7.58 - 7.65 (m, 1 H), 7.13 (s, 1 H), 6.79 - 6.89 (m, 1 H), 5.87 - 6.24 (m, 1 H), 5.07 - 5.18 (m, 1 H), 4.84-4.92 (m, 1 H), 4.39 - 4.51 (m, 3 H), 3.93 (br s, 2 H), 3.57 - 3.68 (m, 2 H), 2.96 - 3.08 (m, 1 H), 2.66 - 2.77 (m, 1 H), 2.32 - 2.44 (m, 2 H), 1.19 (d, *J* = 6.9 Hz, 3 H).

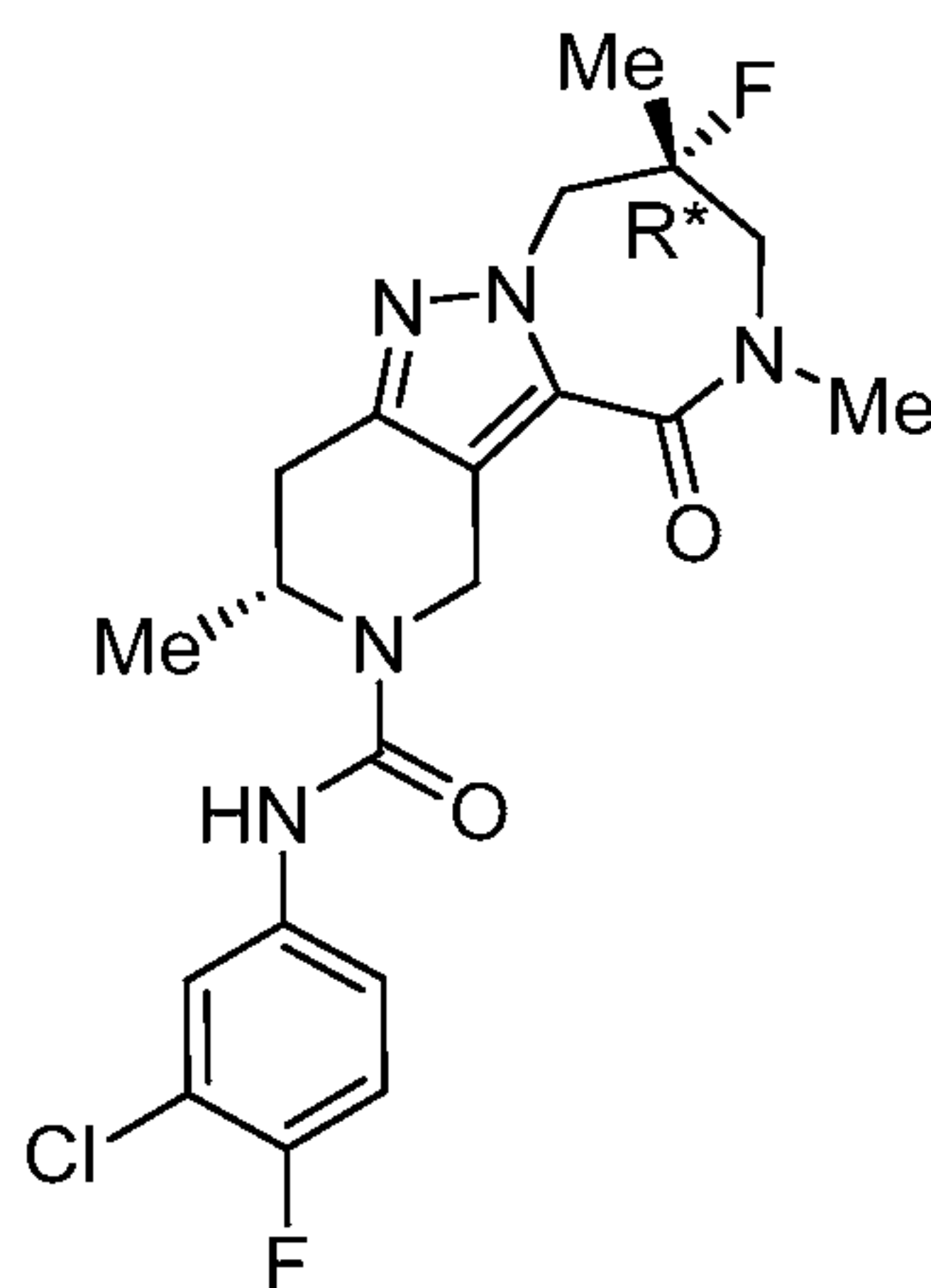
Compound 077: (R)-10-(2,2-difluoroethyl)-N-(4-fluoro-3-methylphenyl)-3-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

The title compound was prepared in a manner analogous to Compound 072, using phenyl (4-fluoro-3-methylphenyl)carbamate in Step 3. LCMS [M+1] : 435. ¹H NMR (400MHz, CDCl₃) δ = 7.24 - 7.27 (m, 1 H), 7.08 - 7.16 (m, 1 H), 6.88 - 6.97 (m, 1 H), 6.46 (s, 1 H), 6.05 (s, 1 H), 5.12 (s, 1 H), 4.83 - 4.89 (m, 1 H), 4.35 - 4.50 (m, 3 H), 3.80 - 4.05 (m, 2 H), 3.52 - 3.69 (m, 2 H), 2.98 - 3.07 (m, 1 H), 2.62 - 2.70 (m, 1 H), 2.36 (s, 2 H), 2.25 (d, *J* = 1.5 Hz, 3 H), 1.18 (d, *J* = 6.9 Hz, 3 H).

Compound 078: (R)-N-(5-chloro-2,4-difluorophenyl)-10-(2,2-difluoroethyl)-3-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

The title compound was prepared in a manner analogous to Compound 072, using phenyl (5-chloro-2,4-difluorophenyl)carbamate in Step 3. LCMS [M+1] : 474. ¹H NMR (400MHz, CDCl₃) δ = 8.19 (s, 1 H), 6.95 (dd, *J* = 8.5, 10.6 Hz, 1 H), 6.53 - 6.59 (m, 1 H), 6.05 (s, 1 H), 5.02 - 5.13 (m, 1 H), 4.80 - 4.91 (m, 1 H), 4.44 (s, 3 H), 3.78 - 4.08 (m, 2 H), 3.49 - 3.69 (m, 2 H), 2.99 - 3.09 (m, 1 H), 2.71 (s, 1 H), 2.36 (br s, 2 H), 1.21 (d, *J* = 6.8 Hz, 3 H).

Compound 079 D1: (3R,8R*)-N-(3-chloro-4-fluorophenyl)-8-fluoro-3,8,10-trimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



5 Step 1. tert-butyl (3R)-8-fluoro-3,8,10-trimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate. To a solution of tert-butyl (3R)-8-hydroxy-3,8,10-trimethyl-11-oxo-3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (Intermediate 18, 65.00 mg, 178.36 μ mol, 1.00 *eq*) in DCM (5.00 mL) was added BAST (236.76 mg, 1.07 mmol, 234.42 μ L, 6.00 *eq*) at -30 °C under N₂, and the
10 mixture was stirred at 20 °C for 2 hours. TLC (PE: EtOAc = 1:1) showed that starting material was consumed completely and two main new spots formed. The mixture was diluted with 10 mL and extracted with DCM (15 mL*3). The combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The combined residue of two batches of reaction was purified by prep-TLC (PE:EtOAc=1:1) to give two diastereomers of the title compound **D1**:
15 40.00 mg, 109.16 μ mol, 30.60% yield and **D2**: 35.00 mg, 95.52 μ mol, 26.78% yield as white solid.

Step 2. (3R)-8-fluoro-3,8,10-trimethyl-1,2,3,4,7,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one D1. To a solution of tert-butyl (3R)-8-fluoro-3,8,10-trimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate_D1
20 (40.00 mg, 109.16 μ mol, 1.00 *eq*) in DCM (3.00 mL) was added TFA (1.23 g, 10.80 mmol, 799.73 μ L, 98.95 *eq*) at 20 °C with stirring for 1 h. LC-MS showed that reactant starting material was consumed completely and desired product was detected. The mixture was directly evaporated in vacuo to afford the title compound (45.00 mg, crude, TFA) as yellow oil.

The other diastereomer was made by an analogous method.

*Pure but unknown diastereomer D1.

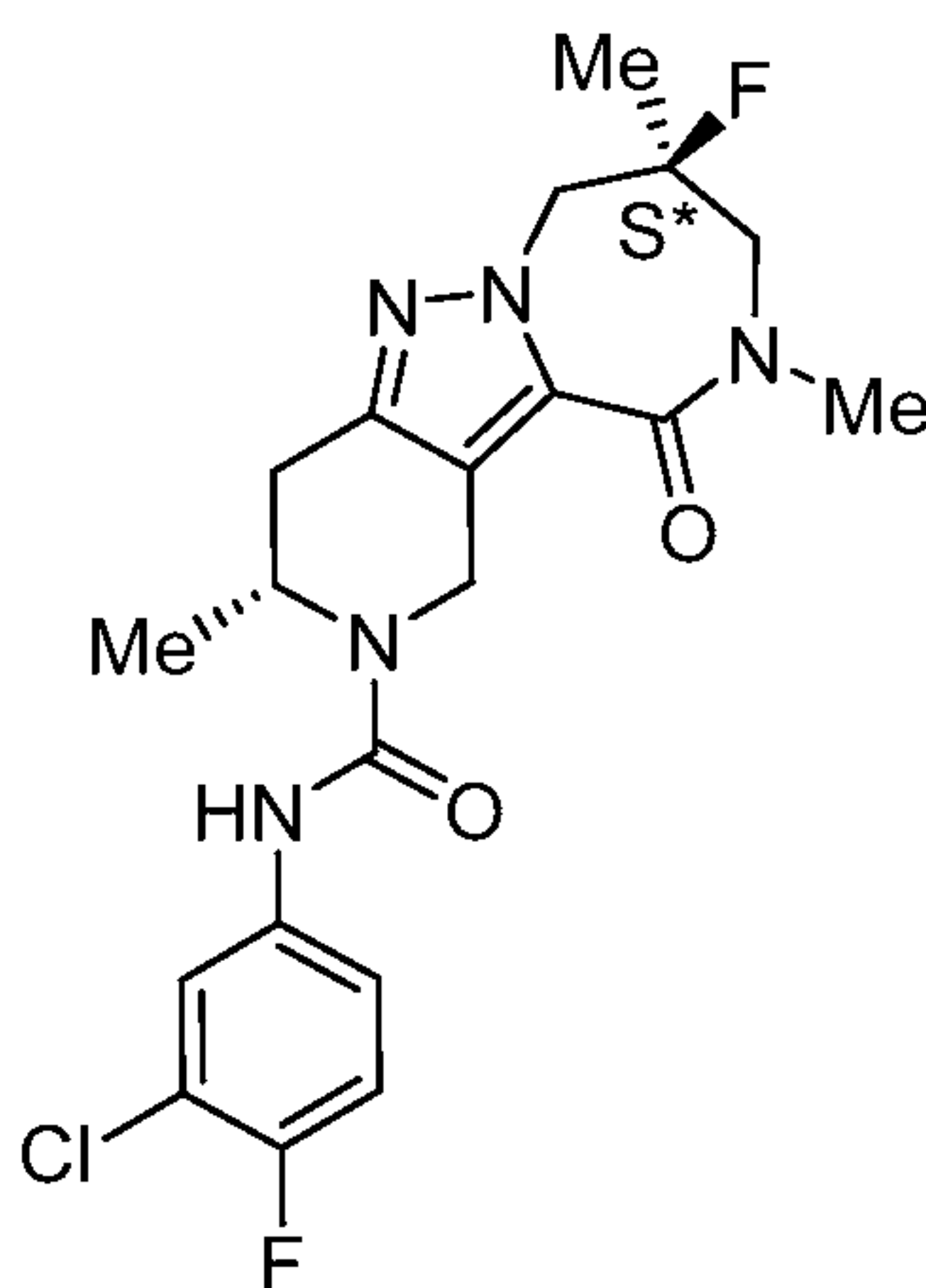
Step 3. (3R,8R*)-N-(3-chloro-4-fluorophenyl)-8-fluoro-3,8,10-trimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

5 To a solution of (3R)-8-fluoro-3,8,10-trimethyl-1,2,3,4,7,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one_D1 (50.00 mg, 131.46 μ mol, 1.00 *eq*, TFA) and phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (38.42 mg, 144.61 μ mol, 1.10 *eq*) in DCM (3.00 mL) was added TEA (106.42 mg, 1.05 mmol, 145.78 μ L, 8.00 *eq*) at 20 °C for 16 h. LC-MS indicated that reactant consumed completely and desired product was detected. The reaction mixture was concentrated
10 in vacuo. The resulting residue was purified by prep-HPLC (FA) to afford the title compound (33.00 mg, 75.36 μ mol, 57.33% yield, 100% purity) as white solid.

LCMS: 438 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ = 7.58 (dd, *J* = 2.69, 6.48 Hz, 1 H), 7.14 - 7.22 (m, 1 H), 7.00 - 7.10 (m, 1 H), 6.52 (s, 1 H), 5.10 (m, 1 H), 4.78 (d, *J* = 15.65 Hz, 1 H), 4.35 - 4.53 (m, 3 H), 3.48 (m, 1 H), 3.37 - 3.45 (m, 1 H), 3.18 - 3.26 (m, 3 H), 2.94 - 3.06 (m, 1
15 H), 2.68 (m, 1 H), 1.51 - 1.59 (m, 3 H), 1.19 (d, *J* = 6.85 Hz, 3 H).

079_D2 was prepared by an analogous method.

Compound 079_D2: (3R,8S*)-N-(3-chloro-4-fluorophenyl)-8-fluoro-3,8,10-trimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

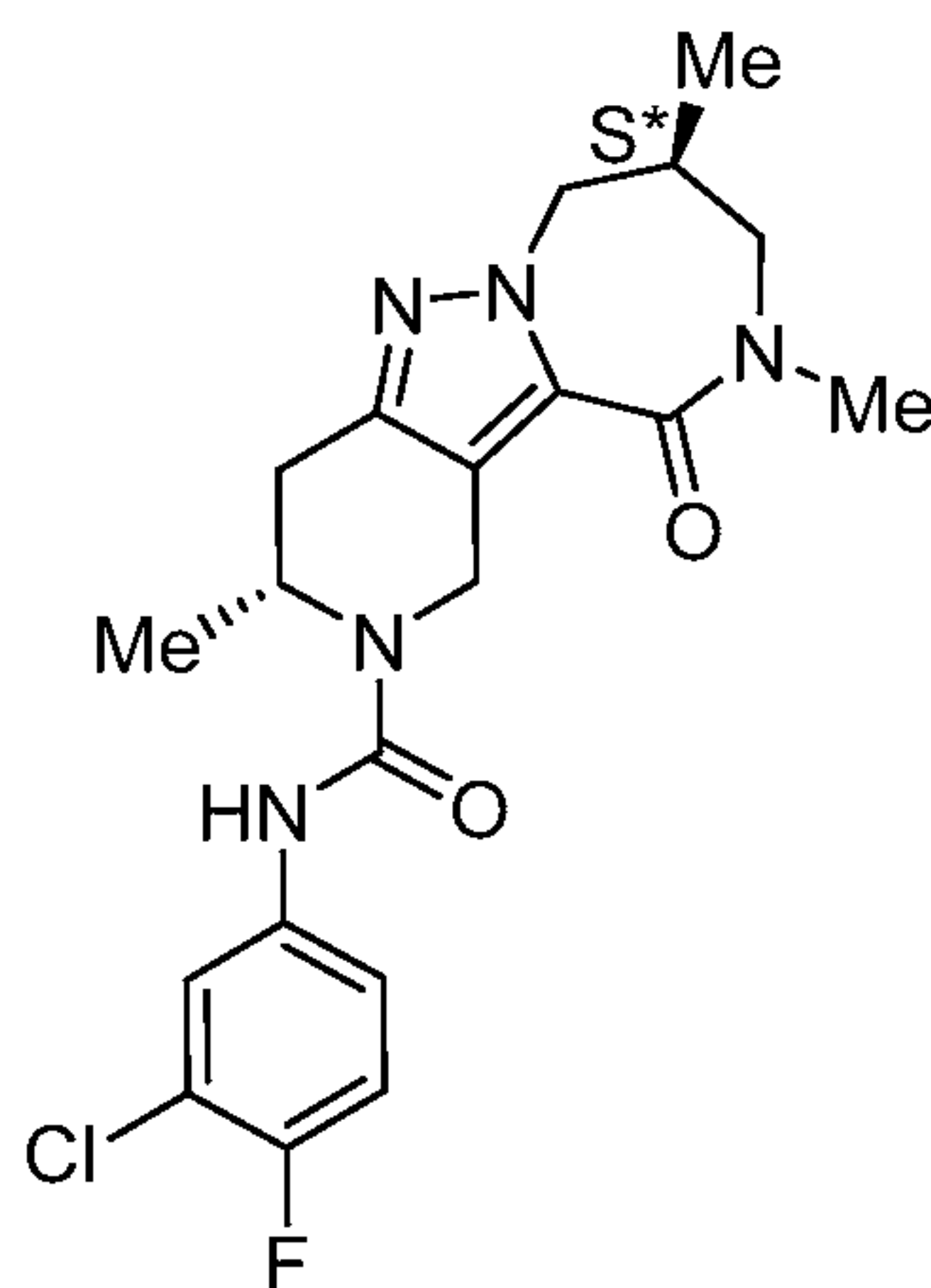


20

The title compound was prepared in a manner analogous to Compound 079 D1, *Pure but unknown diastereomer D2. LCMS: 438 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ = 7.60 (dd, *J* = 2.63, 6.54 Hz, 1 H), 7.17 - 7.23 (m, 1 H), 7.03 - 7.09 (m, 1 H), 6.60 (s, 1 H), 5.13 (m, 1 H), 4.88

(d, $J = 15.41$ Hz, 1 H), 4.34 - 4.54 (m, 3 H), 3.47 - 3.58 (m, 1 H), 3.35 - 3.46 (m, 1 H), 3.22 (s, 3 H), 3.03 (m, 1 H), 2.66 (m, 1 H), 1.55 - 1.62 (m, 3 H), 1.18 (d, $J = 6.85$ Hz, 3 H).

5 Compound 080_D1: (3R,8S*)-N-(3-chloro-4-fluorophenyl)-3,8,10-trimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide.



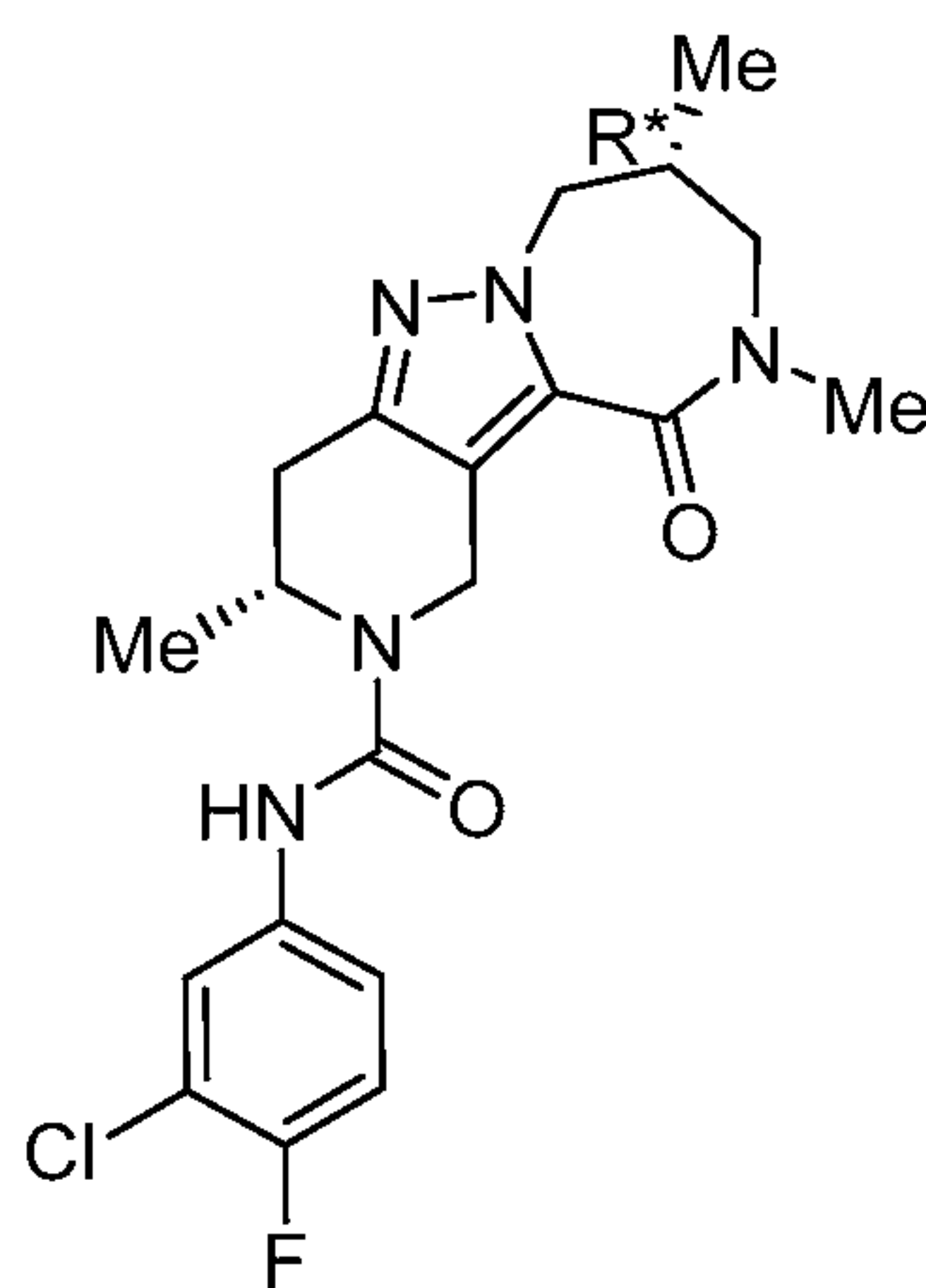
10 Step 1. (3R)-3,8,10-trimethyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one. To a solution of tert-butyl (3R)-3,8,10-trimethyl-11-oxo-1,3,4,7,8,9-hexahydro pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (Intermediate 17, 60.00 mg, 172.20 μ mol, 1.00 *eq*) in DCM (3.00 mL) was added TFA (770.00 mg, 6.75 mmol, 500.00 μ L, 39.22 *eq*) at 20 °C with stirring for 1 h. TLC (PE: EtOAc = 0:1) showed that starting material consumed completely and one main spot formed. The mixture was concentrated to afford the title compound (65.00 mg, crude, TFA) as yellow oil.

15 Step 2. (3R,8S*)-N-(3-chloro-4-fluorophenyl)-3,8,10-trimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide; *Pure but unknown diastereomer D1. To a solution of (3R)-3,8,10-trimethyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo [2,4-b][1,4]diazepin-11-one (65.00 mg, 179.38 μ mol, 1.00 *eq*, TFA) and phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (50.04 mg, 188.35 μ mol, 1.05 *eq*) in DCM (3.00 mL) was added TEA (145.22 mg, 1.44 mmol, 198.93 μ L, 8.00 *eq*) at 20 °C for 16 h. LCMS

20 indicated that reactant 7 was consumed completely and desired product was detected. The residue was directly evaporated. The residue was purified by prep-HPLC (FA), followed by SFC to give two diastereomers: **080_D1** (15.50 mg, 36.92 μ mol, 20.58% yield) as white solid and **080_D2** (17.24 mg, 40.24 μ mol, 22.43% yield, 98% purity) as white solid.

SFC separation condition: Instrument: SFC 80; Column: AD-10um; Mobile phase: A for CO₂ and B for EtOH (0.1%NH₃H₂O); Gradient: B 30%; Flow rate: 60mL /min; Back pressure: 100bar; Column temperature: 35 °C; Wavelength: 220nm. LCMS: 420 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ = 7.61 (dd, *J* = 2.63, 6.54 Hz, 1 H), 7.17 - 7.23 (m, 1 H), 7.02 - 7.08 (m, 1 H), 6.61 (s, 1 H), 5.14 (m, 1 H), 4.81 (d, *J* = 15.28 Hz, 1 H), 4.39 - 4.49 (m, 2 H), 3.98 - 4.03 (m, 1 H), 3.89 - 3.42 (m, 1 H), 3.19 (s, 3 H), 3.13 - 3.16 (m, 1 H), 3.02 - 3.08 (m, 1 H), 2.61 - 2.70 (m, 2 H), 1.17 (d, *J* = 6.85 Hz, 3H), 1.12 (d, *J* = 6.72 Hz, 3 H).

Compound 080_D2: (3R,8R*)-N-(3-chloro-4-fluorophenyl)-3,8,10-trimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide.



The title compound was prepared in a manner analogous to Compound 080D1, *Pure but unknown diastereomer D2. LCMS: 420 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ = 7.61 (dd, *J* = 2.69, 6.60 Hz, 1 H), 7.16 - 7.23 (m, 1 H), 7.01 - 7.08 (m, 1 H), 6.59 (s, 1 H), 5.14 (m, 1 H), 4.81 (d, *J* = 15.41 Hz, 1 H), 4.40 - 4.50 (m, 2 H), 3.98 (m, 1 H), 3.45 - 3.47 (m, 1 H), 3.20 (s, 3 H), 3.13 - 3.16 (m, 1 H), 3.01 - 3.08 (m, 1 H), 2.58 - 2.69 (m, 2 H), 1.17 (dd, *J* = 6.91, 12.78 Hz, 6 H).

Compound 081: (3R,8S*)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide.

Step 1. (3R,S*)-8-(hydroxymethyl)-3,10-dimethyl-1,2,3,4,7,8,9,10-octahydro-11H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11-one. To a solution of tert-butyl (3R)-8-

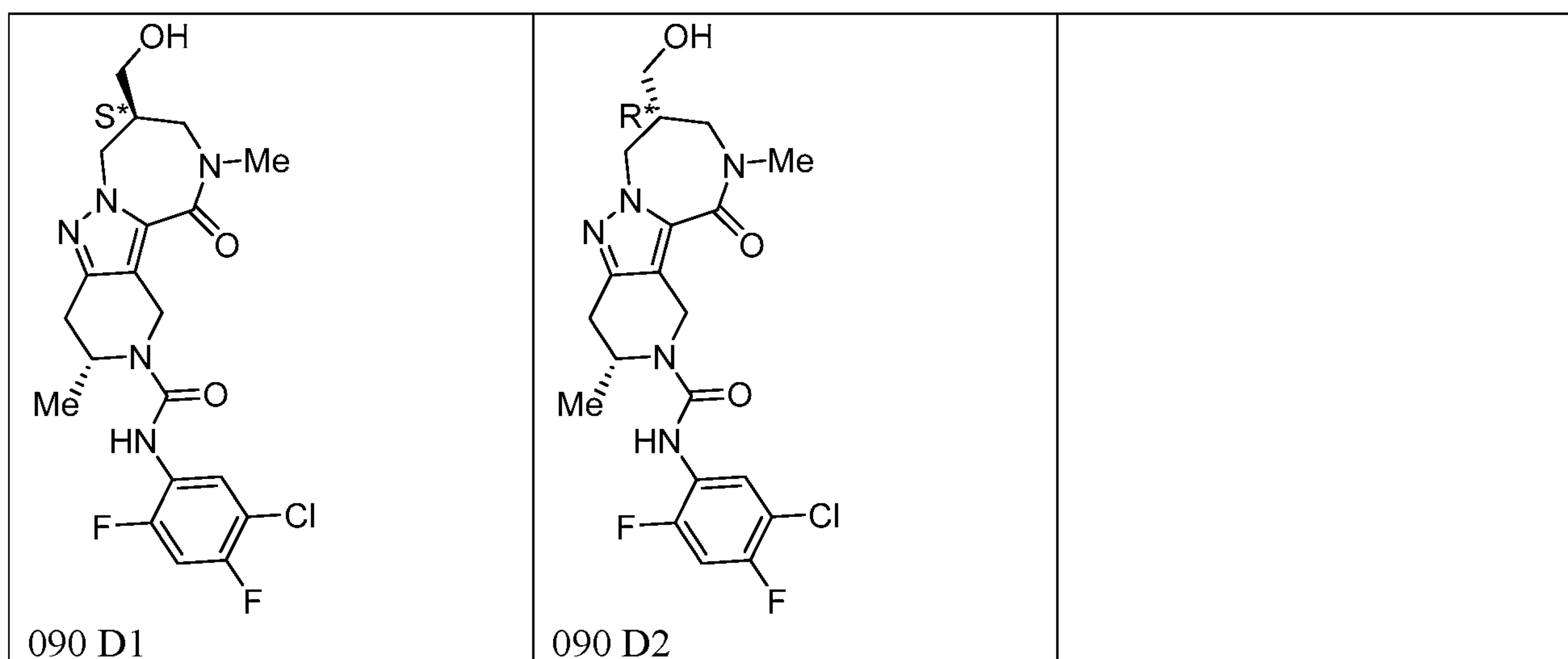
(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8, 9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (Intermediate 16, 2.00 g, 4.72 mmol, 1.00 *eq*) in MeOH (20.00 mL) was added HCl/MeOH (4 M, 10.00 mL, 8.47 *eq*) at 25 °C with stirring for 3 h. TLC (PE: EtOAc=0:1) showed that reactant tert-butyl (3R)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8, 9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate was consumed completely. The mixture was concentrated in vacuo. The residue with 92% purity was resolved by SFC (Analytic condition: AD-3S_4_5_40_3ML Column: Chiralpak AD-3 100×4.6mm I.D., 3µm Mobile phase: iso-propanol (0.05% DEA) in CO₂ from 5% to 40%. Flow rate: 3mL/min Wavelength: 220nm. Separation condition: Instrument: SFC 80; Column: AD-5µm.Mobile phase: A for CO₂ and B for IPA (0.1%NH₃H₂O); Gradient: B 25%; Flow rate: 55mL /min; Back pressure: 100bar; Column temperature: 35; Wavelength: 220nm) to give both diastereomers: (3R,8S*)-8-(hydroxymethyl)-3,10-dimethyl-1,2,3,4,7,8,9,10-octahydro-11H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11-one (520 mg) and (3R,8R*)-8-(hydroxymethyl)-3,10-dimethyl-1,2,3,4,7,8,9,10-octahydro-11H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11-one (670 mg) as white solid.

Step 2. (3R,8S*)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide. To a solution of (3R,8S*)-8-(hydroxymethyl)-3,10-dimethyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (40.00 mg, 151.33 µmol, 1.00 *eq*) in DCM (3.00 mL) was added phenyl N-[4-fluoro-3-(trifluoromethyl)phenyl] carbamate (54.34 mg, 181.60 µmol, 1.20 *eq*) and Et₃N (76.57 mg, 756.65 µmol, 104.89 µL, 5.00 *eq*). The mixture was stirred at 25 °C for 16 h. The mixture was concentrated under reduced pressure. The resulting residue was purified by prep-HPLC(FA) to afford (24.10 mg, 50.83 µmol, 33.59% yield, 99% purity) as white solid. *Pure but unknown diastereomer. LCMS: 470 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 7.70 (m, 1 H), 7.55 - 7.64 (m, 1 H), 7.12 (t, *J* = 9.35 Hz, 1 H), 6.82 (s, 1 H), 5.14 - 5.17 (m, 1 H), 4.84 - 4.88 (m, 1 H), 4.36 - 4.49 (m, 2 H), 4.19 - 4.23 (m, 1 H), 3.65 - 3.77 (m, 2 H), 3.32 - 3.54 (m, 2 H), 3.20 (s, 3 H), 3.01 - 3.05 (m, 1 H), 2.61 - 2.77 (m, 2 H), 1.18 (d, *J* = 6.90 Hz, 3 H).

Compounds 082, 083, 084, 085, 086, 087, 088, 089, and 090 were prepared in a manner analogous to compound 081 from the corresponding diastereomer.

 081	 081 D2	 082 D1
 082 D2	 083 D1	 083 D2
 084 D1	 084 D2	 085 D1

<p>085 D2</p>	<p>086 D1</p>	<p>086 D2</p>
<p>087 D1</p>	<p>087 D2</p>	<p>088 D1</p>
<p>088 D2</p>	<p>089 D1</p>	<p>089 D2</p>



Compound 081 D2: (3R,8R*)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-3,4,8,9,10,11-hexahydro-1H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2(7H)-carboxamide.

- 5 The title compound was prepared in a manner analogous to Compound 081, *Pure but unknown diastereomer. LCMS : 470 [M+1] ¹H NMR (400 MHz, CDCl₃) δ 7.69 - 7.10 (m, 1 H), 7.59 - 7.61 (m, 1 H), 7.12 (t, *J* = 9.41 Hz, 1 H), 6.77 (s, 1 H), 5.15 (t, *J* = 6.53 Hz, 1 H), 4.80 - 4.84 (m, 1 H), 4.36 - 4.52 (m, 2 H), 4.25 - 4.27 (m, 1 H), 3.64 - 3.76 (m, 2 H), 3.32 - 3.52 (m, 2 H), 3.20 (s, 3 H), 3.00 - 3.04 (m, 1 H), 2.61 - 2.78 (m, 2 H), 1.19 (d, *J* = 6.90 Hz, 3 H).

10

Compound 082 D1: (3R,8S*)-N-(2,4-difluoro-5-(trifluoromethyl)phenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

- 15 The title compound was prepared in a manner analogous to Compound 081, *Pure but unknown diastereomer. LCMS : 488 [M+1] ¹H NMR (400 MHz, CDCl₃) δ 8.38 (t, *J* = 7.97 Hz, 1 H), 6.99 (t, *J* = 10.04 Hz, 1 H), 6.66 (br d, *J* = 2.89 Hz, 1 H), 5.10 - 5.30 (m, 1 H), 4.84 - 4.88 (m, 1 H), 4.39 - 4.52 (m, 2 H), 4.16 - 4.20 (m, 1 H), 3.67 - 3.77 (m, 2 H), 3.33 - 3.55 (m, 2 H), 3.20 (s, 3 H), 3.00 - 3.04 (m, 1 H), 2.63 - 2.76 (m, 2 H), 1.20 (d, *J* = 6.90 Hz, 3 H).

- 20 Compound 082 D2: (3R,8R*)-N-(2,4-difluoro-5-(trifluoromethyl)phenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

The title compound was prepared in a manner analogous to Compound 081*Pure but unknown diastereomer. LCMS :488 [M+1] ¹H NMR (400 MHz, CDCl₃) δ 8.38 (t, *J* = 8.03 Hz, 1 H), 6.99 (t, *J* = 10.10 Hz, 1 H), 6.63 (s, 1 H), 5.08 - 5.12 (m, 1 H), 4.81 - 4.85 (m, 1 H), 4.52 (d, *J* = 15.56 Hz, 1 H), 4.22 - 4.45 (m, 2 H), 3.60 - 3.76 (m, 2 H), 3.30 - 3.50 (m, 2 H), 3.20 (s, 3 H), 3.00 - 3.05 (m, 1 H), 2.61 - 2.79 (m, 2 H), 1.21 (d, *J* = 6.90 Hz, 3 H).

Compound 083_D1: (3R,8S*)-N-(2,4-difluoro-3-(trifluoromethyl)phenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

The title compound was prepared in a manner analogous to Compound 081*Pure but unknown diastereomer. LCMS : 488 [M+1] ¹H NMR (400 MHz, CDCl₃) δ 8.17 – 8.23 (m, 1 H), 6.98 (t, *J* = 9.16 Hz, 1 H), 6.67 (s, 1 H), 5.08 - 5.10 (m, 1 H), 4.85 - 4.89 (m, 1 H), 4.39 - 4.53 (m, 2 H), 4.17 - 4.19 (m, 1 H), 3.66 - 3.78 (m, 2 H), 3.32 - 3.55 (m, 2 H), 3.20 (s, 3 H), 3.01 - 3.05 (m, 16.06 Hz, 1 H), 2.63 - 2.76 (m, 2 H), 1.20 (d, *J* = 6.90 Hz, 3 H).

Compound 083_D2: (3R,8R*)-N-(2,4-difluoro-3-(trifluoromethyl)phenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

The title compound was prepared in a manner analogous to Compound 081*Pure but unknown diastereomer. LCMS : 488 [M+1] ¹H NMR (400 MHz, CDCl₃) δ 8.19 - 8.25 (m, 1 H), 6.99 (t, *J* = 9.41 Hz, 1 H), 6.61 (s, 1 H), 5.06 - 5.09 (m, 1 H), 4.83 - 4.86 (m, 1H), 4.49 - 4.51 (m, 1H), 4.22 - 4.44 (m, 2 H), 3.62 - 3.74 (m, 2 H), 3.31 - 3.50 (m, 2 H), 3.20 (s, 3 H), 3.01 - 3.05 (m, 1 H), 2.64 - 2.77 (m, 2 H), 1.21 (d, *J* = 6.85 Hz, 3 H).

Compound 084_D1: (3R,8S*)-N-(3-bromo-2,4-difluorophenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

The title compound was prepared in a manner analogous to Compound 081*Pure but unknown diastereomer. LCMS : 498/500 [M+1] ¹H NMR (400 MHz, CDCl₃) δ 7.89 – 7.95 (m, 1 H), 6.94 (t, *J* = 7.6 Hz, 1 H), 6.58 (s, 1 H), 5.08 - 5.10 (m 1 H), 4.85 - 4.88 (m, 1 H), 4.38 - 4.53 (m, 2 H),

4.14 - 4.18 (m, 1 H), 3.66 - 3.79 (m, 2 H), 3.32 - 3.56 (m, 2 H), 3.20 (s, 3 H), 3.01 - 3.05 (m, 1 H), 2.61 - 2.76 (m, 2 H), 1.20 (d, $J = 6.90$ Hz, 3 H).

Compound 084_D2: (3R,8R*)-N-(3-bromo-2,4-difluorophenyl)-8-(hydroxymethyl)-3,10-

5 dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-
2-carboxamide.

The title compound was prepared in a manner analogous to Compound 081, *Pure but unknown diastereomer. LCMS : 498/500 [M+1] ^1H NMR (400 MHz, CDCl_3) δ 7.90 - 7.96 (m, 1 H), 6.91 - 6.96 (m, 1 H), 6.55 (s, 1 H), 5.02 - 5.13 (m, 1 H), 4.82-4.86 (m, 1 H), 4.49 - 4.53 (m, 1 H), 4.22
10 - 4.45 (m, 2 H), 3.62 - 3.74 (m, 2 H), 3.30 - 3.50 (m, 2 H), 3.20 (s, 3 H), 3.01 - 3.05 (m, 1 H), 2.63 - 2.77 (m, 2 H), 1.21 (d, $J = 6.90$ Hz, 3 H).

Compound 085_D1: (3R,8S*)-N-(5-bromo-2,4-difluorophenyl)-8-(hydroxymethyl)-3,10-

15 dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-
2-carboxamide.

The title compound was prepared in a manner analogous to Compound 081, *Pure but unknown diastereomer. LCMS : 498/500 [M+1] ^1H NMR (400 MHz, CDCl_3) δ 8.23 - 8.39 (m, 1 H), 6.93 (t, $J = 7.97$ Hz, 1 H), 6.57 (s, 1 H), 5.09 - 5.11 (m, 1 H), 4.82- 4.86 (m, 1 H), 4.37 - 4.52 (m, 2 H), 4.17 - 4.19 (m, 1 H), 3.64 - 3.80 (m, 2 H), 3.33 - 3.54 (m, 2 H), 3.20 (s, 3 H), 2.98 - 3.02 (m,
20 1 H), 2.63 - 2.77 (m, 2 H), 1.20 (d, $J = 6.78$ Hz, 3 H).

Compound 085_D2: (3R,8R*)-N-(5-bromo-2,4-difluorophenyl)-8-(hydroxymethyl)-3,10-

25 dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-
2-carboxamide.

The title compound was prepared in a manner analogous to Compound 081, *Pure but unknown diastereomer. LCMS : 498/500 [M+1] ^1H NMR (400 MHz, CDCl_3) δ 8.25 - 8.37 (m, 1 H), 6.91 - 6.95 (m, 1 H), 6.55 (s, 1 H), 5.09 - 5.11 (m, 1 H), 4.79 - 4.83 (m, 1 H), 4.48 - 4.52 (m, 1 H), 4.20 - 4.44 (m, 2 H), 3.63 - 3.73 (m, 2 H), 3.29 - 3.51 (m, 2 H), 3.20 (s, 3 H), 3.01 - 3.05 (m, 1 H), 2.62 - 2.77 (m, 2 H), 1.20 (d, $J = 6.90$ Hz, 3 H).

30

Compound 086_D1: (3R,8S*)-N-(3-bromo-4-fluorophenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

The title compound was prepared in a manner analogous to Compound 081, *Pure but unknown diastereomer. LCMS : 480/482 [M+1] ¹H NMR (400 MHz, CDCl₃) δ 7.73 – 7.75 (m, 1 H), 7.24 - 7.27 (m, 1 H), 6.95 - 7.09 (m, 1 H), 6.65 (s, 1 H), 5.06 - 5.20 (m, 1 H), 4.83 (d, *J* = 15.18 Hz, 1 H), 4.36 - 4.48 (m, 2 H), 4.20 - 4.22 (m, 1 H), 3.70 - 3.74 (m, 2 H), 3.33 - 3.54 (m, 2 H), 3.20 (s, 3 H), 3.00 - 3.05 (m, 1 H), 2.58 - 2.78 (m, 2 H), 1.18 (d, *J* = 6.90 Hz, 3 H).

Compound 086_D2: (3R,8R*)-N-(3-bromo-4-fluorophenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

The title compound was prepared in a manner analogous to Compound 081, *Pure but unknown diastereomer. LCMS : 480/482 [M+1] ¹H NMR (400 MHz, CDCl₃) δ 7.72 - 7.75 (m, 1 H), 7.25 - 7.26 (m, 1 H), 7.04 (t, *J* = 8.53 Hz, 1 H), 6.61 (s, 1 H), 5.13 - 5.15 (m, 1 H), 4.78 - 4.81 (m, 1 H), 4.37 - 4.51 (m, 2 H), 4.24 - 4.27 (m, 1 H), 3.62 - 3.75 (m, 2 H), 3.30 - 3.50 (m, 2 H), 3.20 (s, 3 H), 3.01 - 3.04 (m, 1 H), 2.59 - 2.79 (m, 2 H), 1.18 (d, *J* = 6.78 Hz, 3 H).

Compound 087_D1: (3R,8S*)-N-(3-cyano-4-fluorophenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

The title compound was prepared in a manner analogous to Compound 081, *Pure but unknown diastereomer. LCMS : 427 [M+1] ¹H NMR (400 MHz, CDCl₃) δ 7.79 - 7.81 (m, 1 H), 7.59 - 7.61 (m, 1 H), 7.07 - 7.17 (m, 1 H), 6.93 (s, 1 H), 5.07 - 5.19 (m, 1 H), 4.86 (d, *J* = 15.43 Hz, 1 H), 4.36 - 4.49 (m, 2 H), 4.19 - 4.24 (m, 1 H), 3.66 - 3.80 (m, 2 H), 3.30 - 3.55 (m, 2 H), 3.20 (s, 3 H), 3.01 - 3.05 (m, 1 H), 2.58 - 2.76 (m, 2 H), 1.18 (d, *J* = 6.90 Hz, 3 H).

Compound 087_D2: (3R,8R*)-N-(3-cyano-4-fluorophenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

The title compound was prepared in a manner analogous to Compound 081, *Pure but unknown diastereomer. LCMS : 427 [M+1] ¹H NMR (400 MHz, CDCl₃) δ 7.78 - 7.80 (m, 1 H), 7.59 - 7.62 (m, 1 H), 7.13 (t, *J* = 8.68 Hz, 1 H), 6.88 (s, 1 H), 5.13 - 5.15 (m, 1 H), 4.80 - 4.85 (m, 1 H), 4.37 - 4.53 (m, 2 H), 4.22 - 4.25 (m, 1 H), 3.62 - 3.76 (m, 2 H), 3.31 - 3.53 (m, 2 H), 3.20 (s, 3 H), 3.00 - 3.03 (m, 1 H), 2.62 - 2.76 (m, 2 H), 1.19 (d, *J* = 6.97 Hz, 3 H).

Compound 088_D1: (3R,8S*)-N-(3-cyano-2,4-difluorophenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

The title compound was prepared in a manner analogous to Compound 081, *Pure but unknown diastereomer. LCMS : 445 [M+1] ¹H NMR (400 MHz, CDCl₃) δ 8.23 - 8.29 (m, 1 H), 7.01 (t, *J* = 7.97 Hz, 1 H), 6.69 (s, 1 H), 5.08 (m, 1 H), 4.86 - 4.89 (m, 1 H), 4.38 - 4.54 (m, 2 H), 4.18 - 4.20 (m, 1 H), 3.65 - 3.78 (m, 2 H), 3.33 - 3.55 (m, 2 H), 3.20 (s, 3 H), 3.01 - 3.06 (m, 1 H), 2.62 - 2.78 (m, 2 H), 1.21 (d, *J* = 6.90 Hz, 3 H).

Compound 088_D2: (3R,8R*)-N-(3-cyano-2,4-difluorophenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

The title compound was prepared in a manner analogous to Compound 081, *Pure but unknown diastereomer. LCMS : 445 [M+1] ¹H NMR (400 MHz, CDCl₃) δ 8.24 - 8.30 (m, 1 H), 6.99 - 7.27 (m, 1 H), 6.63 (s, 1 H), 5.07 - 5.09 (m, 1 H), 4.82 - 4.86 (m, 1 H), 4.50 - 4.54 (m, 1 H), 4.20 - 4.45 (m, 2 H), 3.64 - 3.75 (m, 2 H), 3.31 - 3.52 (m, 2 H), 3.20 (s, 3 H), 3.01 - 3.05 (m, 1 H), 2.61 - 2.76 (m, 2 H), 1.21 (d, *J* = 6.90 Hz, 3 H).

Compound 089_D1: (3R,8S*)-N-(3-chloro-2,4-difluorophenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

The title compound was prepared in a manner analogous to Compound 081, *Pure but unknown diastereomer. LCMS : 454/456 [M+1] ¹H NMR (400 MHz, CDCl₃) δ 7.83 - 7.89 (m, 1 H), 6.92 - 6.97 (m, 9.25 Hz, 1 H), 6.58 (s, 1 H), 5.08 - 5.10 (m, 1 H), 4.85 - 4.89 (m, 1 H), 4.39 - 4.54 (m,

2 H), 4.17 - 4.19 (m, 1 H), 3.64 - 3.78 (m, 2 H), 3.33 - 3.56 (m, 2 H), 3.20 (s, 3 H), 3.01 - 3.05 (m, 1 H), 2.61 - 2.76 (m, 2 H), 1.20 (d, $J = 6.90$ Hz, 3 H).

5 Compound 089_D2: (3R,8R*)-N-(3-chloro-2,4-difluorophenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

The title compound was prepared in a manner analogous to Compound 081, *Pure but unknown diastereomer. LCMS : 454/456 [M+1] ^1H NMR (400 MHz, CDCl_3) δ 7.84 - 7.90 (m, 1 H), 6.92 - 6.97 (m, 1 H), 6.55 (s, 1 H), 5.01 - 5.14 (m, 1 H), 4.82 - 4.86 (m, 1 H), 4.49 - 4.53 (m, 1 H),
10 4.22 - 4.44 (m, 2 H), 3.67 - 3.69 (m, 2 H), 3.30 - 3.49 (m, 2 H), 3.20 (s, 3 H), 3.01 - 3.05 (m, 1 H), 2.62 - 2.76 (m, 2 H), 1.21 (d, $J = 6.85$ Hz, 3 H).

15 Compound 090_D1: (3R,8S*)-N-(5-chloro-2,4-difluorophenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

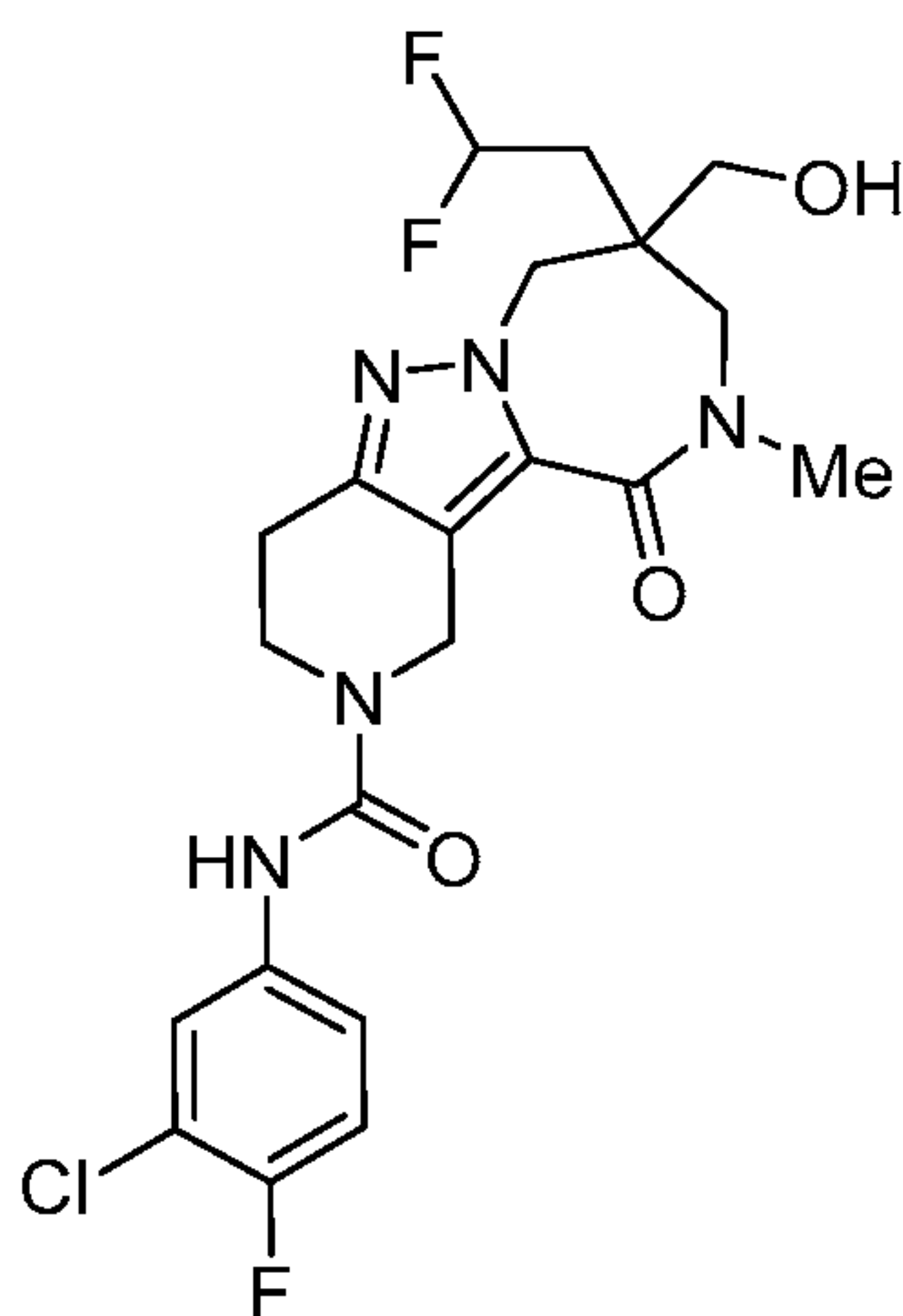
The title compound was prepared in a manner analogous to Compound 081, *Pure but unknown diastereomer. LCMS : 454/456 [M+1] ^1H NMR (400 MHz, CDCl_3) δ 8.18 (t, $J = 8.09$ Hz, 1 H), 6.92 - 6.97 (m, 1 H), 6.58 (s, 1 H), 5.08 - 5.10 (m, 1 H), 4.83 - 4.87 (m, 1 H), 4.38 - 4.54 (m, 2 H), 4.17 - 4.19 (m, 1 H), 3.65 - 3.79 (m, 2 H), 3.32 - 3.57 (m, 2 H), 3.20 (s, 3 H), 3.01 - 3.04 (m,
20 1 H), 2.61 - 2.74 (m, 2 H), 1.20 (d, $J = 6.78$ Hz, 3 H).

Compound 090_D2: (3R,8R*)-N-(5-chloro-2,4-difluorophenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

25 The title compound was prepared in a manner analogous to Compound 081, *Pure but unknown diastereomer. LCMS : 454/456 [M+1] ^1H NMR (400 MHz, CDCl_3) δ 8.16 - 8.20 (m, 1 H), 6.92 - 6.97 (m, 1 H), 6.55 (s, 1 H), 5.08 - 5.12 m, 1 H), 4.80 - 4.84 (m, 1 H), 4.48 - 4.52 (m, 1 H), 4.22 - 4.43 (m, 2 H), 3.60 - 3.75 (m, 2 H), 3.30 - 3.50 (m, 2 H), 3.20 (s, 3 H), 3.01 - 3.05 (m, 1 H), 2.62 - 2.77 (m, 2 H), 1.20 (d, $J = 6.90$ Hz, 3 H).

30

Compound 091: N-(3-chloro-4-fluorophenyl)-8-(2,2-difluoroethyl)-8-(hydroxymethyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



- 5 Step 1. 2-tert-butyl 8-ethyl 8-(2,2-difluoroethyl)-10-methyl-11-oxo-3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2,8-dicarboxylate. To a solution of 2-tert-butyl 8-ethyl 10-methyl-11-oxo-1,3,4,7,8,9- hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2,8-dicarboxylate (Intermediate 14, 400.00 mg, 1.02 mmol, 1.00 *eq*) in THF (8.00 mL) was added LDA (1 M, 3.06 mL, 3.00 *eq*) at -65 °C under N₂, followed by 2,2-difluoroethyl
- 10 trifluoromethanesulfonate (1.09 g, 5.10 mmol, 5.00 *eq*) after 0.5 h, and the mixture was stirred at 25 °C for another 5 h. LCMS indicated ~45% desired product and multiple peaks. The mixture combine with another batch and was diluted with EtOAc (60 mL) and washed with HCl (1 M, 60 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo, which was purified by prep-HPLC(FA) to afford the title compound (185.00 mg, 405.28 μmol, 39.73%
- 15 yield) as yellow solid. LCMS: 457 [M+1].

- Step 2. ethyl 8-(2,2-difluoroethyl)-10-methyl-11-oxo- 1,2,3,4,7,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-8-carboxylate. To a solution of 2-tert-butyl 8-ethyl 8-(2,2-difluoroethyl)-10-methyl-11-oxo- 3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2,8-dicarboxylate (215.00 mg, 471.00 μmol, 1.00 *eq*) in DCM (3.00 mL) was
- 20 added TFA (4.62 g, 40.52 mmol, 3.00 mL, 86.03 *eq*), and the mixture was stirred at 25 °C under N₂ for 1 h. TLC showed no starting material and one major new spot was detected. The mixture was concentrated in vacuo to afford the title compound (221.00 mg, 469.82 μmol, 99.75% yield, TFA) as yellow oil, which was used directly for the next step.

Step 3. ethyl 2-[(3-chloro-4-fluoro-phenyl)carbamoyl]-8-(2,2-difluoroethyl)-10-methyl-11-oxo-3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-8-carboxylate. A mixture of

ethyl 8-(2,2-difluoroethyl)-10-methyl-11-oxo-1,2,3,4,7,9-hexahydro pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-8-carboxylate (221.00 mg, 469.82 μ mol, 1.00 *eq*, TFA), Et₃N (237.71 mg, 2.35

5 mmol, 325.63 μ L, 5.00 *eq*) and phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (137.30 mg, 516.80 μ mol, 1.10 *eq*) in DCM (10.00 mL) was stirred at 25 °C for 16 h. LCMS indicated the

starting material was consumed completely and major desired product. The mixture was diluted with DCM (40 mL) and washed with HCl (1 M, 40 mL). The organic phase was dried over

Na₂SO₄, filtered and concentrated in vacuo, which was purified by silica gel column to afford the

10 title compound (195.00 mg, 361.99 μ mol, 77.05% yield, 98% purity) as yellow solid.
LCMS: 528 [M+1].

Step 4. N-(3-chloro-4-fluorophenyl)-8-(2,2-difluoroethyl)-8-(hydroxymethyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

To a solution of ethyl 2-[(3-chloro-4-fluoro-phenyl)carbamoyl]-8-(2,2-difluoroethyl)-10-methyl-

15 11-oxo-3,4,7,9-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-8-carboxylate (90.00 mg, 170.48 μ mol, 1.00 *eq*) in THF (5.00 mL) was added LiBH₄ (11.14 mg, 511.44 μ mol, 3.00

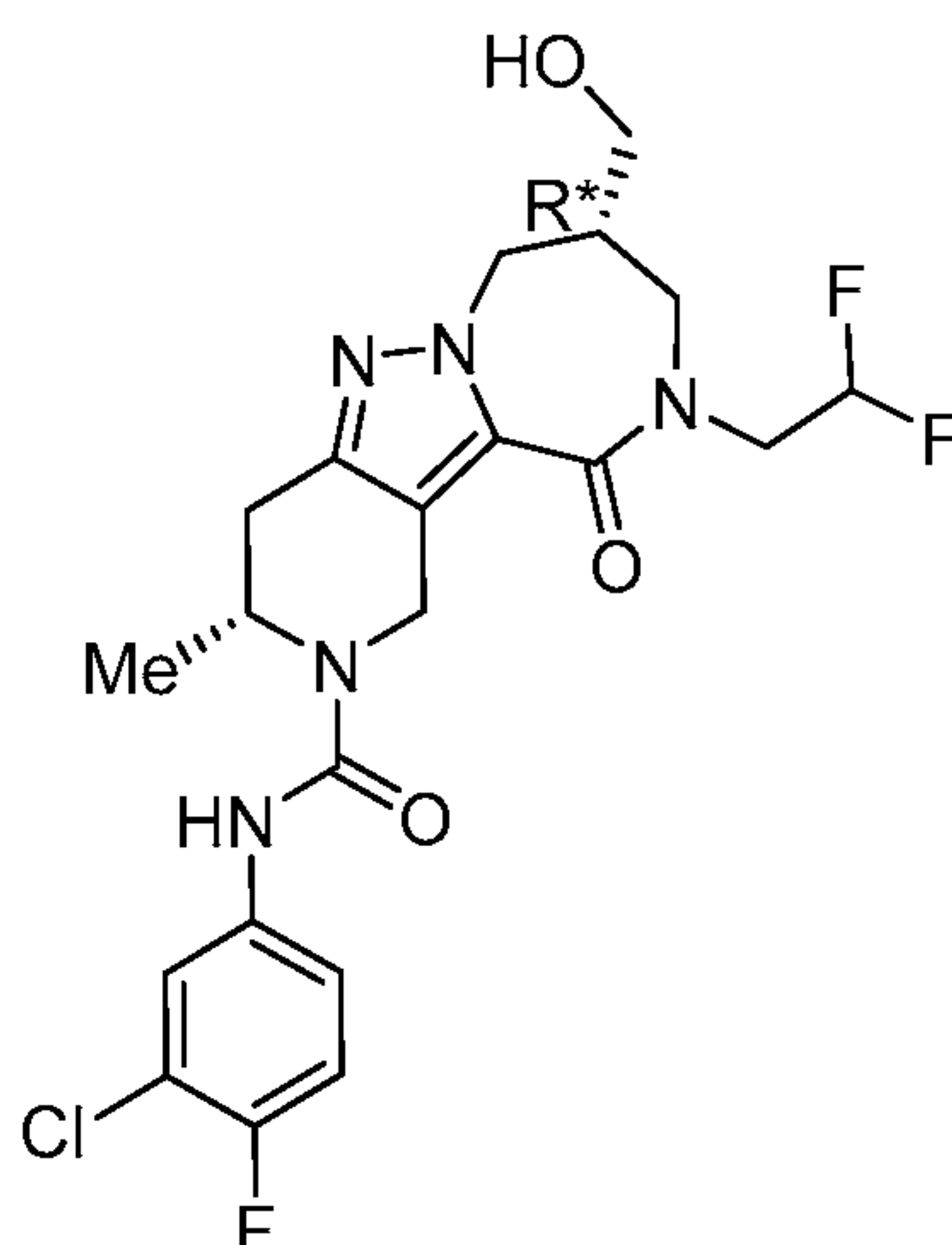
eq) at 0 °C and the mixture was stirred at 25 °C for 2 h. LCMS indicated starting material consumed and desired product was detected. The mixture was quenched with H₂O (30 mL) and extracted with EtOAc (30 mL). The organic phase was dried over Na₂SO₄, filtered and

20 concentrated in vacuo, which was purified by prep-HPLC(FA) to afford the title compound (50.00 mg, 101.87 μ mol, 59.76% yield, 99% purity) as white solid. LCMS: 486 [M+1]. ¹H NMR

(400 MHz, CDCl₃) δ 7.58 – 7.61 (m, 1 H), 7.21 - 7.28 (m, 1 H), 7.05 - 7.09 (t, *J* = 8.8 Hz, 1 H), 6.68 (s, 1 H), 6.06 - 6.34 (m, 1 H), 4.68 – 4.73 (m, 2 H), 4.24 – 4.28 (m, 1 H), 4.05 - 4.09 (m, 1

25 2.09 (m, 2 H).

Compound 092_D1: (3R,8R*)-N-(3-chloro-4-fluorophenyl)-10-(2,2-difluoroethyl)-8-(hydroxymethyl)-3-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. ethyl (3R)-10-(2,2-difluoroethyl)-3-methyl-11-oxo-2,3,4,7,8,9-hexahydro-1H-

pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-8-carboxylate. To a solution of 2-tert-butyl 8-ethyl

(3R)-10-(2,2-difluoroethyl)-3-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-

5 b][1,4]diazepine-2,8-dicarboxylate (Intermediate 20, 130.00 mg, 284.79 μmol , 1.00 *eq*) in DCM

(3.00 mL) was added TFA (4.62 g, 40.52 mmol, 3.00 mL, 142.28 *eq*), and the mixture was

stirred at 25 °C under N₂ for 1 h. TLC showed no starting material and one major new spot was

detected. The mixture was concentrated in vacuo to afford the title compound (133.00 mg,

282.74 μmol , 99.28% yield, TFA) as yellow oil, which was used directly for the next step.

10 Step 2. ethyl (16S)-12-chloro-26-(2,2-difluoroethyl)-11-fluoro-18,19-dioxo-22,23,24,25,26-

pentazapentacyclodocosa-1(11),2(12),9,13(22),14-pentaene-17-carboxylate. A mixture of ethyl

(3R)-10-(2,2-difluoroethyl)-3-methyl-11-oxo-2,3,4,7,8,9-hexahydro-1H-

pyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-8-carboxylate (133.00 mg, 282.74 μmol , 1.00 *eq*,

TFA), Et₃N (143.05 mg, 1.41 mmol, 195.96 μL , 5.00 *eq*) and phenyl N-(3-chloro-4-fluoro-

15 phenyl)carbamate (90.14 mg, 339.29 μmol , 1.20 *eq*) in DCM (10.00 mL) was stirred at 25 °C for

16 h. TLC indicated the starting material was consumed completely and major desired product.

The mixture was diluted with DCM (40 mL) and washed with HCl (1 M, 40 mL). The organic

phase was dried over Na₂SO₄, filtered and concentrated in vacuo, which was purified by silica

gel column to afford the title compound (120.00 mg, 229.74 μmol , 81.26% yield, 98% purity) as

20 yellow solid. LCMS: 528 [M+1].

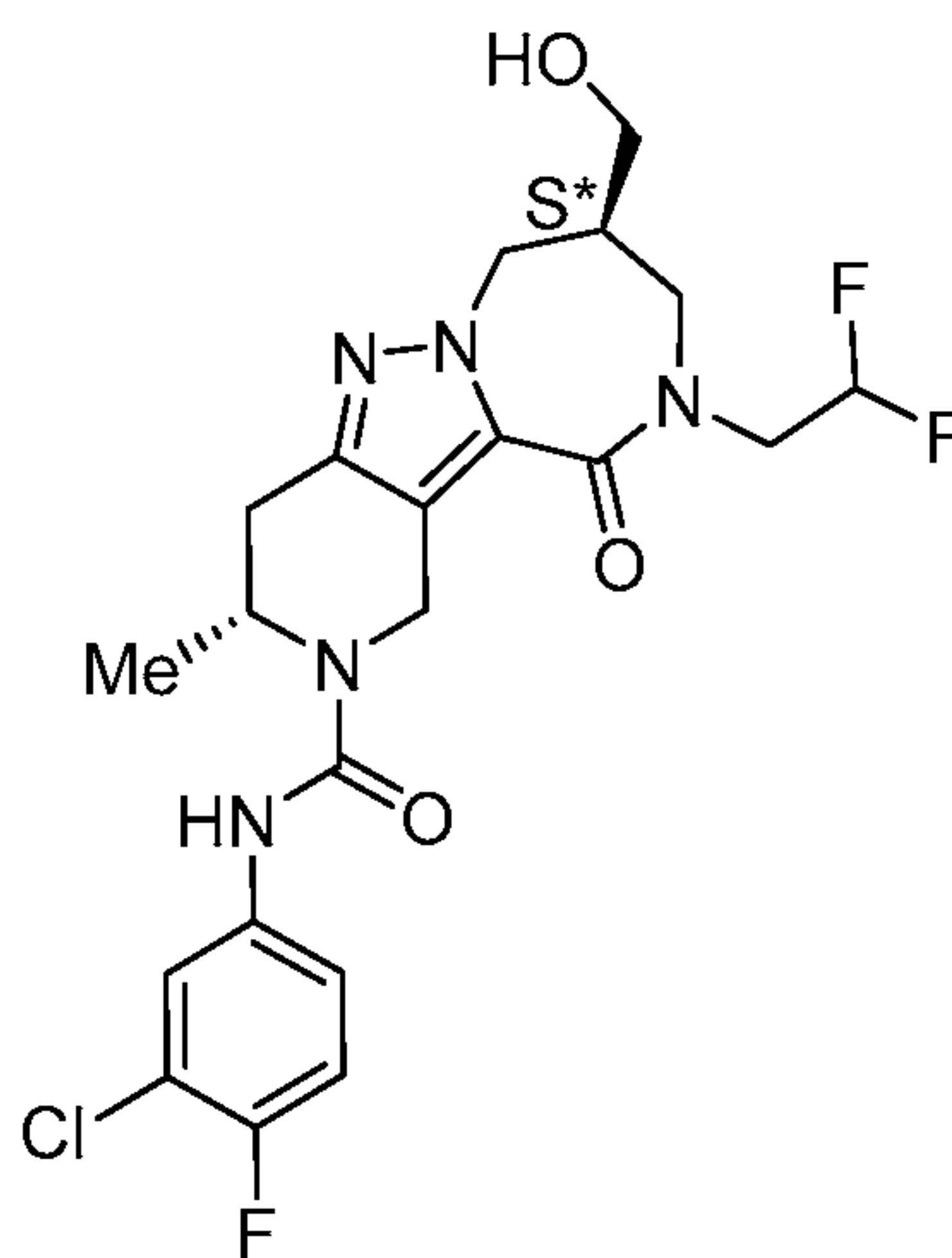
Step 3. (3R,8R*)-N-(3-chloro-4-fluorophenyl)-10-(2,2-difluoroethyl)-8-(hydroxymethyl)-3-

methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-

carboxamide; *Pure but unknown diastereomer D1. To a solution of ethyl (3R)-2-[(3-chloro-4-

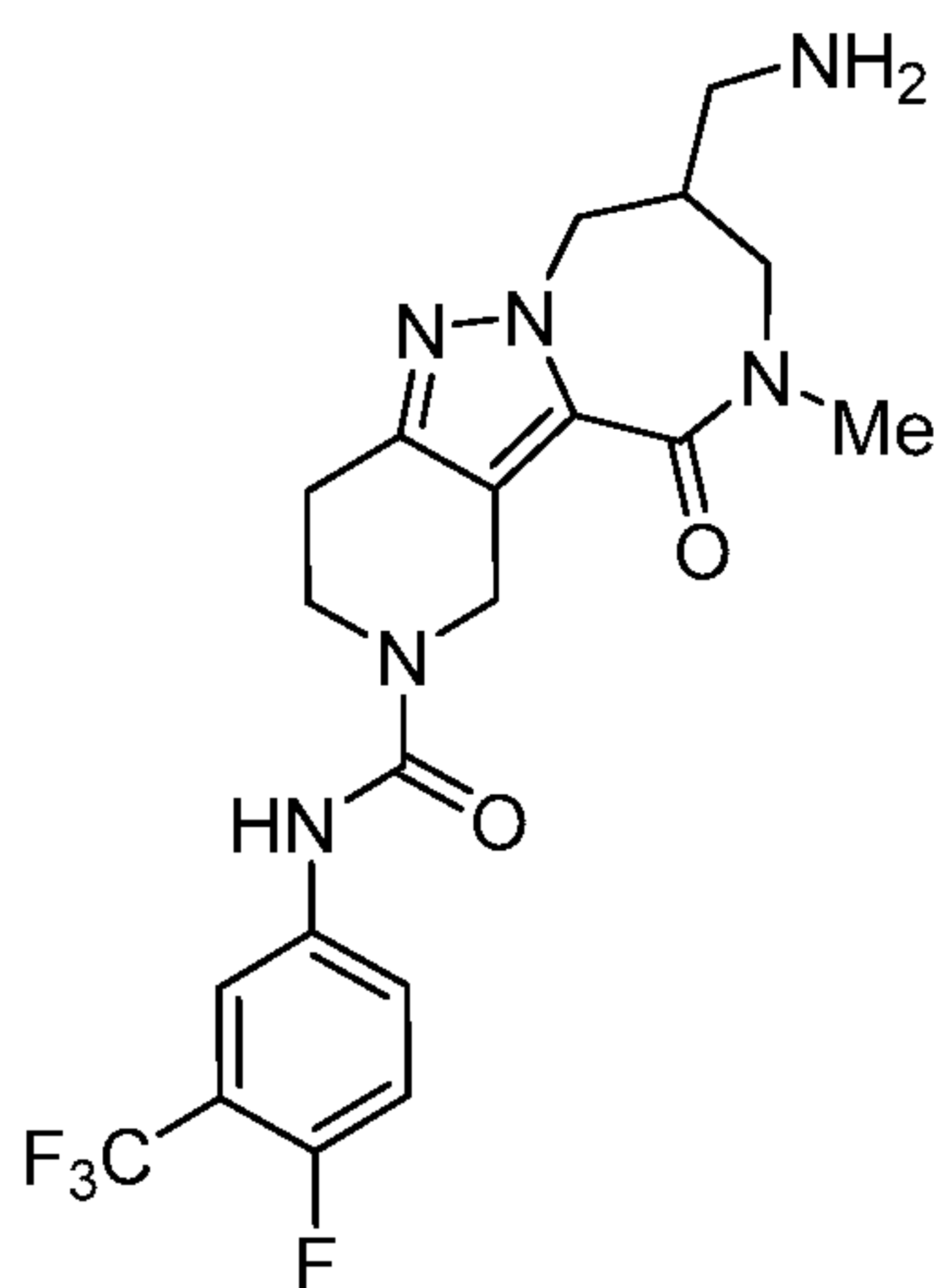
fluoro-phenyl)carbamoyl]-10-(2,2- difluoroethyl)-3-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-8-carboxylate (30.00 mg, 56.83 μ mol, 1.00 *eq*) in THF (2.00 mL) was added LiBH₄ (3.71 mg, 170.48 μ mol, 3.00 *eq*) at 0 °C and the mixture was stirred at 25 °C for 2 h. LCMS showed no starting material and major desired product. The mixture was quenched with H₂O (20 mL) and extracted with EtOAc (30 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo. The residue combined another batch (EW645-046) was purified by prep-TLC to give 10 mg of product, which was resolved by SFC ("AD-3S_3_5_40_3ML Column: Chiralpak AD-3 100×4.6mm I.D., 3 μ m Mobile phase: methanol (0.05% DEA) in CO₂ from 5% to 40% Flow rate: 3mL/min Wavelength: 220nm"), following by prep-HPLC (FA) to afford each 24 mg of the title compound. LCMS: 486/488 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 7.60 (m, 1 H), 7.18 - 7.25 (m, 1 H), 7.02 - 7.11 (m, 1 H), 6.59 (s, 1 H), 5.91 - 6.28 (m, 1 H), 5.13 (m, 1 H), 4.87 (m, 1 H), 4.12 - 4.48 (m, 3 H), 3.43 - 3.81 (m, 4 H), 3.03 (m, 1 H), 2.58 - 2.80 (m, 1 H), 1.18 (m, 3 H).

15 Compound 092_D2: (3R,8S*)-N-(3-chloro-4-fluorophenyl)-10-(2,2-difluoroethyl)-8-(hydroxymethyl)-3-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



The title compound was prepared in a manner analogous to Compound 092_D1 was synthesized by an analogous method. *Pure but unknown diastereomer D2. LCMS: 486/488 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (m, 1 H), 7.17 - 7.25 (m, 1 H), 7.04 - 7.12 (m, 1 H), 6.51 (s, 1 H), 5.90 - 6.29 (m, 1 H), 5.10 (s, 1 H), 4.79 (m, 1 H), 4.19 - 4.54 (m, 4 H), 3.42 - 3.76 (m, 5 H), 2.99 - 3.09 (m, 1 H), 2.71 (s, 2 H), 1.21 (m, 3 H).

Compound 93: 8-(aminomethyl)-N-[4-fluoro-3-(trifluoromethyl)phenyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide.



- 5 Step 1. 8-(hydroxymethyl)-10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one. To a solution of tert-butyl 8-(hydroxymethyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (Compound 064, product from Step 1, 200.00 mg, 570.76 μ mol, 1.00 eq) in DCM (2.00 mL) was added TFA (3.08 g, 27.01 mmol, 2.00 mL, 47.33 eq) at 0 °C. The mixture was stirred at 25 °C for 1 h. LCMS
- 10 showed that the reactant was consumed completely and the desired product was major. The mixture was concentrated under reduced pressure to afford the title compound (207.00 mg, 568.18 μ mol, 99.55% yield, TFA) as yellow oil which was used directly for the next step.
- Step 2. N-[4-fluoro-3-(trifluoromethyl)phenyl]-4-(hydroxymethyl)-2-methyl-1-oxo-5,8,9,11-tetrahydro-4H-pyrido[2,3]pyrazolo[2,4-d][1,2,5]oxadiazepine-10-carboxamide. To a solution of
- 15 4-(hydroxymethyl)-2-methyl-4,5,8,9,10,11-hexahydropyrido [2,3]pyrazolo[2,4-d][1,2,5]oxadiazepin-1-one (100.00 mg, 273.01 μ mol, 1.00 eq, TFA) in DCM (3.00 mL) was added phenyl N-[4-fluoro-3-(trifluoromethyl) phenyl]carbamate (98.03 mg, 327.61 μ mol, 1.20 eq) and Et₃N (138.13 mg, 1.37 mmol, 189.22 μ L, 5.00 eq). The mixture was stirred at 25 °C for 16 h. LCMS showed the reactant was consumed completely and the desired product was
- 20 major. The mixture was diluted with Ethyl acetate (30 mL) and extracted with brine (30 mL*3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure which was purified by prep-TLC to afford the title compound (120.00 mg, 259.74 μ mol, 95.14% yield, 99% purity) as white solid.

Step 3. [2-[[4-fluoro-3-(trifluoromethyl)phenyl]carbamoyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-8-yl]methyl methanesulfonate. To a solution of N-[4-fluoro-3-(trifluoromethyl)phenyl]-8-(hydroxymethyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide (120.00 mg, 263.50 μ mol, 1.00 *eq*) in DCM (2.00 mL) was added TEA (133.32 mg, 1.32 mmol, 182.63 μ L, 5.00 *eq*) and MsCl (90.55 mg, 790.50 μ mol, 61.18 μ L, 3.00 *eq*) at 0 °C. The mixture was stirred at 25 °C for 2 hr. TLC (Dichloromethane : Methanol= 10:1) showed the reaction was completed. The mixture was poured into water (20 mL), and extracted with ethyl acetate (20 mL *2). The organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuum to afford the title compound (140.00 mg, 262.42 μ mol, 99.59% yield) as colorless oil.

Step 4. 8-(azidomethyl)-N-[4-fluoro-3-(trifluoromethyl)phenyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide. To a solution of [2-[[4-fluoro-3-(trifluoromethyl)phenyl]carbamoyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-8-yl]methyl methanesulfonate (140.00 mg, 262.42 μ mol, 1.00 *eq*) in DMF (3.00 mL) was added NaN₃ (68.24 mg, 1.05 mmol, 4.00 *eq*) at 0 °C. The mixture was stirred at 50 °C for 16 hr. LCMS showed the reaction was completed. The reaction mixture was quenched by addition water (20 mL), and then extracted with ethyl acetate (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound (120.00 mg, 249.78 μ mol, 95.18% yield) as colorless oil.

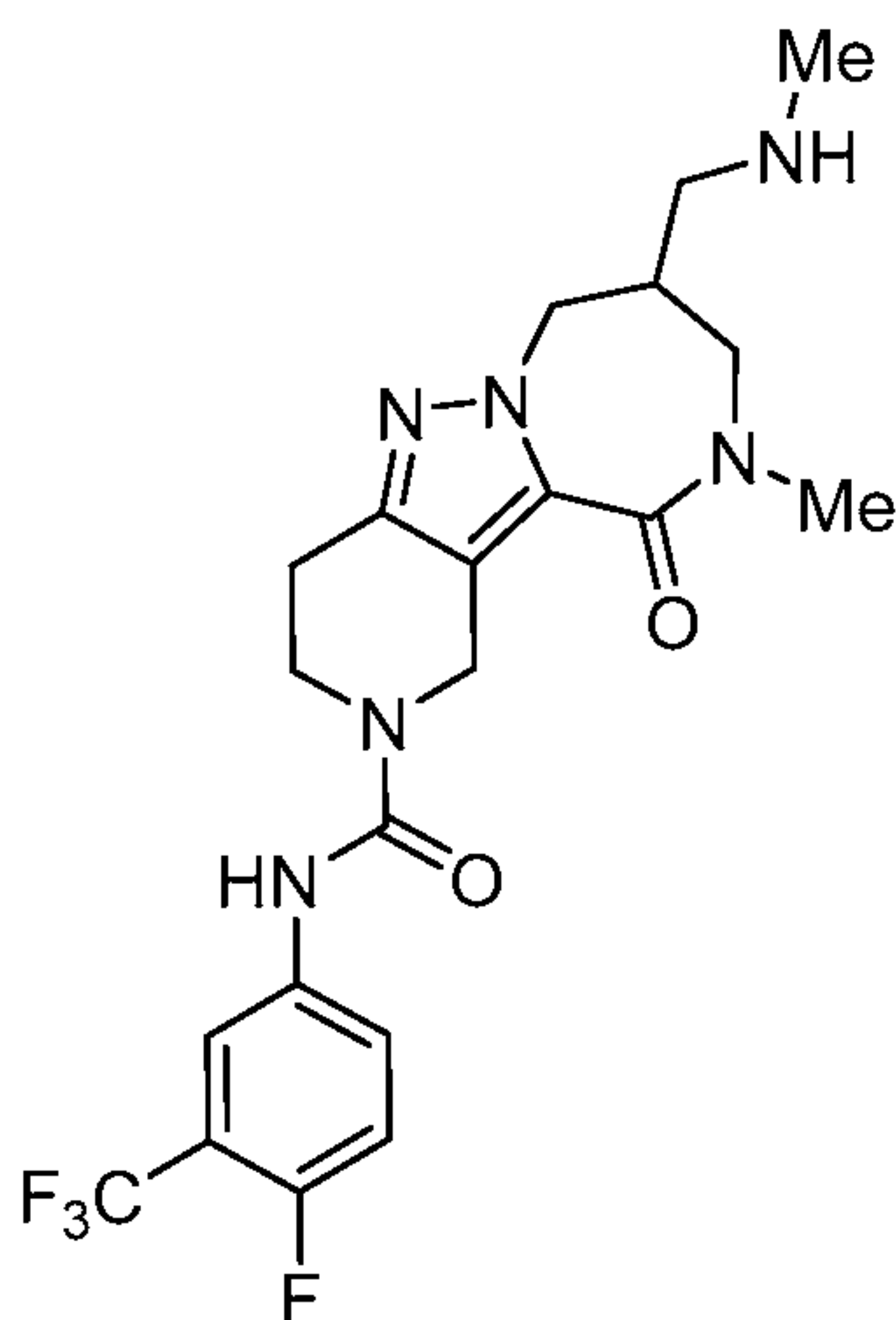
Step 5. 8-(aminomethyl)-N-[4-fluoro-3-(trifluoromethyl)phenyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide and N-[4-fluoro-3-(trifluoromethyl)phenyl]-10-methyl-8-(methylaminomethyl)-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide: To a solution of 8-(azidomethyl)-N-[4-fluoro-3-(trifluoromethyl)phenyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide (120.00 mg, 249.78 μ mol, 1.00 *eq*) in MeOH (5.00 mL) was added Pd/C (20.00 mg, 10% purity). The mixture was stirred under H₂ (15 PSi) at 25 °C for 3 hr. TLC showed the reactant consumed, LCMS showed 32 % Compound **093** and 39 % Compound **094** (N-[4-fluoro-3-(trifluoromethyl)phenyl]-10-methyl-8-(methylaminomethyl)-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide). The mixture was filtered and the filtrate was concentrated in vacuum which was

purified by prep-HPLC to afford Compound 93: 8-(aminomethyl)-N-[4-fluoro-3-(trifluoromethyl)phenyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide (20.00 mg, 41.81 μ mol, 16.74% yield, 95% purity) as white solid and Compound 94: N-[4-fluoro-3-(trifluoromethyl)phenyl]-10-methyl-8-

(methylaminomethyl)-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide (9.00 mg, 18.25 μ mol, 7.31% yield, 95% purity) was obtained as white solid.

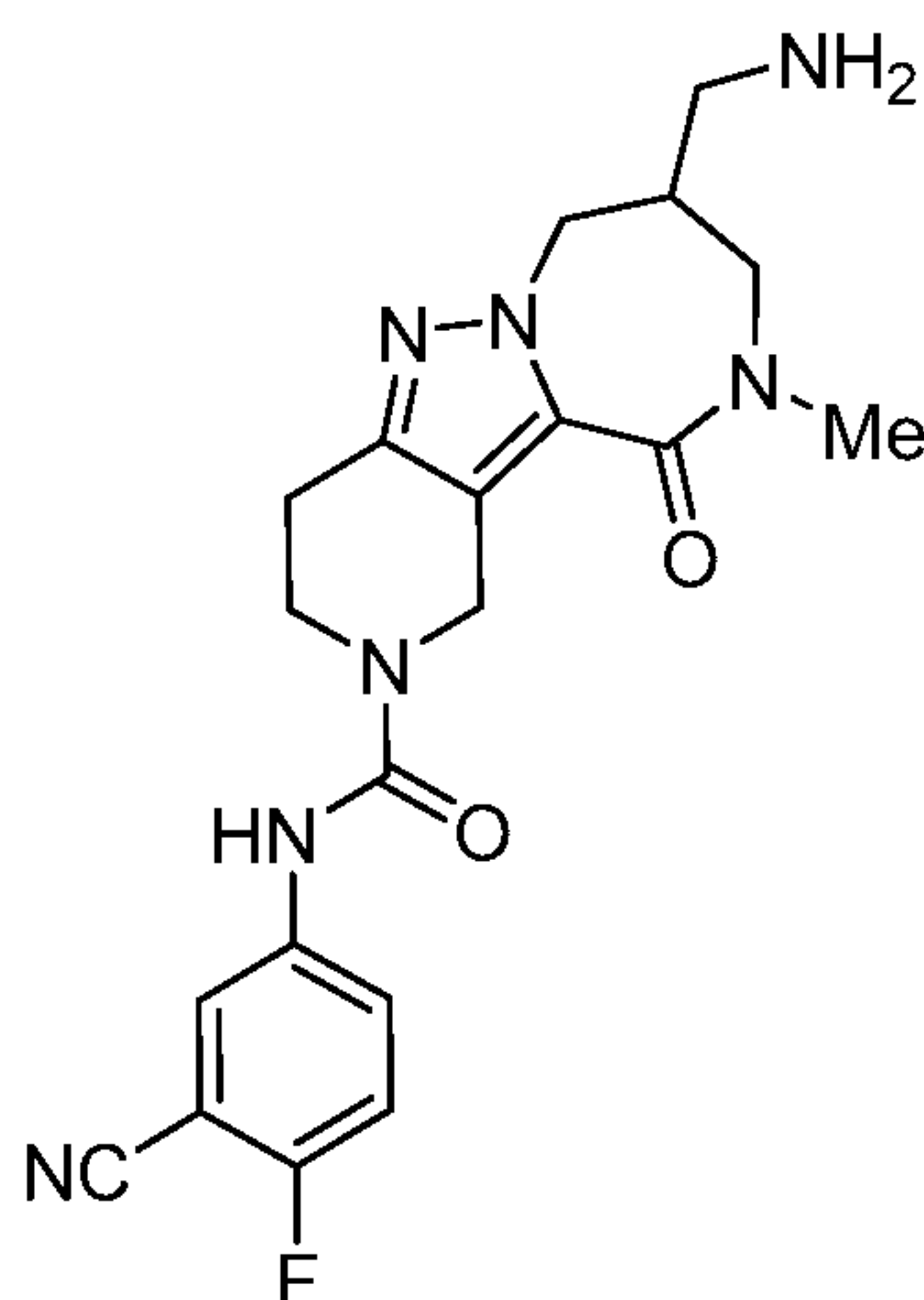
LCMS: 455 [M+1]. ^1H NMR (400 MHz, CDCl_3) δ 7.69 (dd, $J = 2.63, 6.05$ Hz, 1 H), 7.56 - 7.63 (m, 1 H), 7.12 (t, $J = 9.41$ Hz, 1 H), 6.86 (s, 1 H), 4.62 - 4.78 (m, 2 H), 4.40-4.44 (m, 1 H), 4.21-4.38 (m, 1 H), 3.78 - 3.96 (m, 2 H), 3.32 - 3.55 (m, 2 H), 3.19 (s, 3 H), 2.71 - 2.88 (m, 4 H), 2.38 - 2.59 (m, 1 H).

Compound 94: N-[4-fluoro-3-(trifluoromethyl)phenyl]-10-methyl-8-(methylaminomethyl)-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide.



LCMS: 469 [M+1]. ^1H NMR (400 MHz, CDCl_3) δ 7.69 (dd, $J = 2.70, 6.09$ Hz, 1 H), 7.56 - 7.64 (m, 1 H), 7.11 (t, $J = 9.35$ Hz, 1 H), 6.98 (s, 1 H), 4.57 - 4.75 (m, 2 H), 4.40-4.42 (m, 1 H), 4.13 - 4.15 (m, 1 H), 3.78 - 3.95 (m, 2 H), 3.30 - 3.53 (m, 2 H), 3.17 (s, 3 H), 2.84 (t, $J = 5.77$ Hz, 2 H), 2.53 - 2.75 (m, 3 H), 2.46 (s, 3 H).

Compound 095: 8-(aminomethyl)-N-(3-cyano-4-fluorophenyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. N-(3-cyano-4-fluoro-phenyl)-4-(hydroxymethyl)-2-methyl-1-oxo-5,8,9,11-tetrahydro-4H-pyrido[2,3]pyrazolo[2,4-d][1,2,5]oxadiazepine-10-carboxamide. To a solution of 4-

(hydroxymethyl)-2-methyl-4,5,8,9,10,11-hexahydropyrido [2,3]pyrazolo[2,4-

d][1,2,5]oxadiazepin-1-one (Compound 093, product from Step 1, 100.00 mg, 273.01 μ mol, 1.00

eq, TFA) in DCM (3.00 mL) was added phenyl N-(3-cyano-4-fluoro-phenyl)carbamate (83.94

mg, 327.61 μ mol, 1.20 eq) and Et₃N (138.13 mg, 1.37 mmol, 189.22 μ L, 5.00 eq). The

mixture was stirred at 25 °C for 16 h. LCMS showed that the reactant was consumed completely

and the desired product was major. The mixture was diluted with Ethyl acetate (30 mL) and

extracted with brine (30 mL*3). The combined organic layers were dried over Na₂SO₄, filtered

and concentrated under reduced pressure to give a residue which was purified by prep-TLC to

afford the title compound (80.00 mg, 189.19 μ mol, 69.30% yield, 98% purity) as white solid.

Step 2. [2-[(3-cyano-4-fluoro-phenyl)carbamoyl]-10-methyl-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-8-yl]methyl methanesulfonate. To a solution

of N-(3-cyano-4-fluoro-phenyl)-8-(hydroxymethyl)-10-methyl -11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide (80.00 mg, 193.98 μ mol,

1.00 eq) in DCM (3.00 mL) was added TEA (98.14 mg, 969.90 μ mol, 134.44 μ L, 5.00 eq) and

MsCl (66.66 mg, 581.94 μ mol, 45.04 μ L, 3.00 eq). The mixture was stirred at 20 °C for 4 hr.

TLC showed the reactant consumed and a new spot detected. The mixture was poured into

water(10 mL), extracted with ethyl acetate(10 mL*3), the organic layer was washed with

brine(10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to afford the

title compound (95.00 mg, 193.68 μ mol, 99.84% yield) as white solid.

Step 3. 8-(azidomethyl)-N-(3-cyano-4-fluoro-phenyl)-10-methyl-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide. To a solution of [2-[(3-

cyano-4-fluoro-phenyl)carbamoyl]-10- methyl-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-8-yl)methyl methanesulfonate (100.00 mg,

5 203.87 μ mol, 1.00 *eq*) in DMF (3.00 mL) was added NaN₃ (53.01 mg, 815.48 μ mol, 4.00 *eq*) at 0 °C. The mixture was stirred at 50 °C for 16 hr. LCMS showed the reaction was completed.

The reaction mixture was quenched by addition water (20 mL), and extracted with ethyl acetate (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over

anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound

10 (80.00 mg, 182.89 μ mol, 89.71% yield) as colorless oil.

Step 4. 8-(aminomethyl)-N-(3-cyano-4-fluorophenyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-

octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. To a mixture of 8-

(azidomethyl)-N-(3-cyano-4-fluoro-phenyl)-10 -methyl-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide (80.00 mg, 182.89 μ mol,

15 1.00 *eq*) in EtOH (5.00 mL) and H₂O (500.00 μ L) was added Zn (47.84 mg, 731.56 μ mol, 4.00 *eq*) and NH₄Cl (58.70 mg, 1.10 mmol, 38.37 μ L, 6.00 *eq*). The mixture was stirred at 25 °C

for 16 hr. LCMS showed the reactant consumed and the desired product detected. The mixture

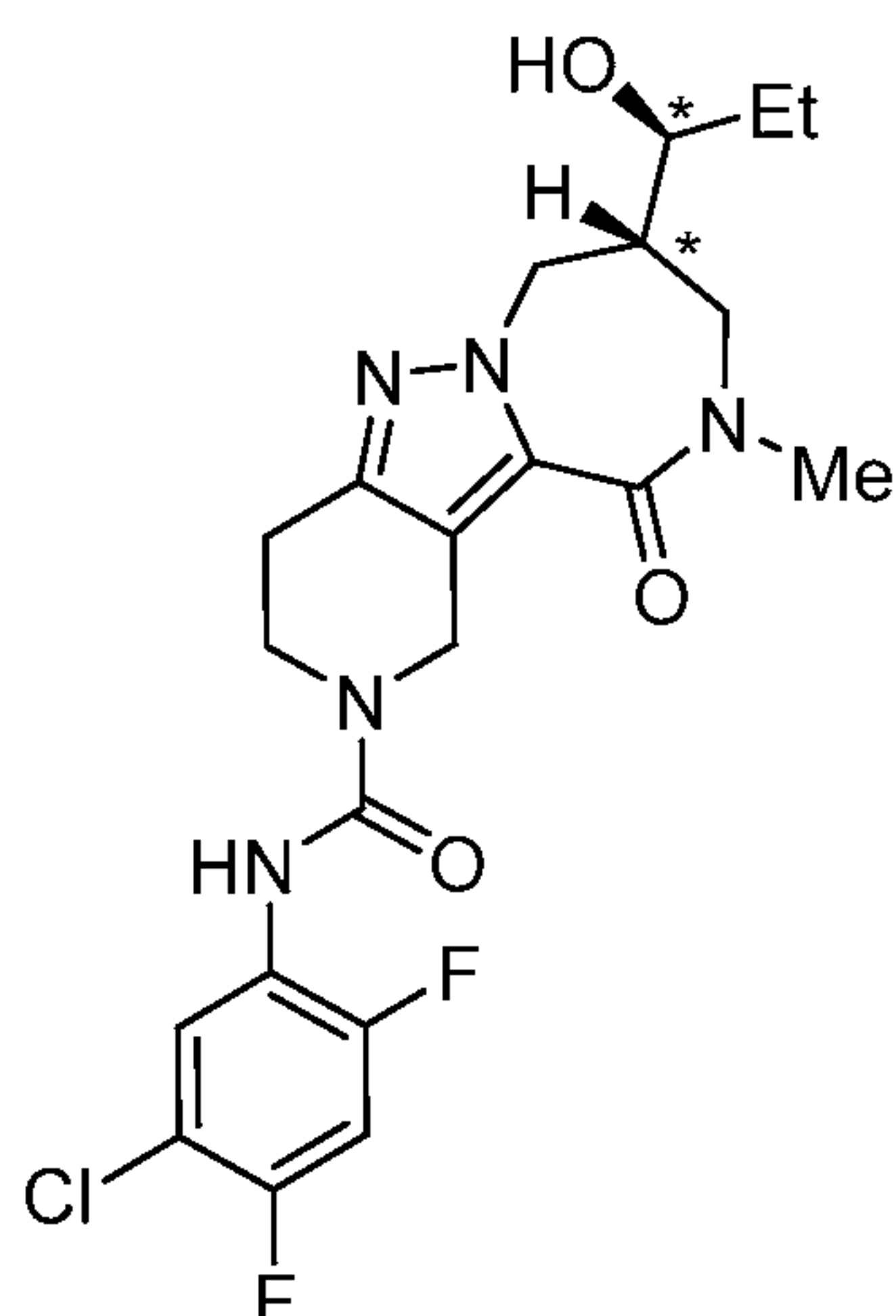
was filtered and the filtrate was purified by prep-HPLC to afford (30.00 mg, 69.27 μ mol, 37.88%

yield, 95% purity) as white solid. LCMS: 412 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 7.78 (dd, *J*

20 = 2.75, 5.44 Hz, 1 H), 7.60 (ddd, *J* = 2.87, 4.52, 9.11 Hz, 1 H), 7.13 (t, *J* = 8.74 Hz, 1 H), 6.93 (s, 1H), 4.58 - 4.75 (m, 2 H), 4.40 - 4.42 (m, 1 H), 4.18 - 4.20 (m, 1 H), 3.87 (t, *J* = 5.87 Hz, 2 H), 3.31 - 3.53 (m, 2 H), 3.13 - 3.26 (m, 3 H), 2.72 - 2.89 (m, 4 H), 2.39 - 2.57 (m, 1 H).

Compound 096 E1: (R*)-N-(5-chloro-2,4-difluorophenyl)-8-((S*)-1-hydroxypropyl)-10-methyl-

25 11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-
carboxamide.



Step 1. 2-tert-butoxycarbonyl-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-

b][1,4]diazepine-8-carboxylic acid. To a mixture of 2-tert-butyl 8-ethyl 10-methyl-11-oxo-

1,3,4,7,8,9- hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2,8-dicarboxylate (Intermediate

14, 4.80 g, 12.23 mmol, 1.00 *eq*) in MeOH (20.00 mL) and H₂O (4.00 mL) was added NaOH (978.47 mg, 24.46 mmol, 2.00 *eq*) in one portion. The mixture was stirred at 30 °C for 5 hours.

LCMS and TLC (Dichloromethane : Methanol=10:1) showed the reaction was completed. The mixture was concentrated in vacuum to remove MeOH. The residue poured into water (10 mL) and stirred for 1 min. The aqueous phase was extracted with DCM (30 mL*2). The aqueous

phase was adjust to pH=3 with 1N HCl and extracted with ethyl acetate(30 mL*2), The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to afford the title compound (4.40 g, 12.07 mmol, 98.73% yield, 100% purity) as white solid. LCMS[M+1]: 365

Step 2. tert-butyl 8-[methoxy(methyl) carbamoyl]-10-methyl-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a mixture of 2-tert-

butoxycarbonyl-10-methyl-11-oxo-1,3,4,7,8,9- hexahydropyrido[2,3]pyrazolo[2,4-

b][1,4]diazepine-8-carboxylic acid (500.00 mg, 1.37 mmol, 1.00 *eq*) and N-

methoxymethanamine hydrochloride (534.52 mg, 5.48 mmol, 4.00 *eq*) in THF (10.00 mL) was added T₃P (1.74 g, 2.74 mmol, 1.63 mL, 50% purity, 2.00 *eq*) and TEA (2.08 g, 20.55 mmol,

2.85 mL, 15.00 *eq*) in one portion under N₂. The mixture was stirred at 30 °C for 12 hours.

LCMS and TLC (Dichloromethane : Methanol=10:1) showed the reaction was completed. The mixture was poured into water (15 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (20 mL*2). The combined organic phase was washed with brine (10 mL*2),

dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Dichloromethane : Methanol=50:1~20:1) to afford the title compound (510.00 mg, 1.24 mmol, 90.45% yield, 99% purity) as white solid. LCMS[M+1]: 408.

Step 3. tert-butyl 10-methyl-11-oxo-8-prop-2-enoyl- 1,3,4,7,8,9-

5 hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a mixture of vinylmagnesium bromide (1 M, 4.91 mL, 5.00 *eq*) in THF (4.00 mL) was added tert-butyl 8-[methoxy(methyl)carbamoyl]-10-methyl-11-oxo-1,3,4, 7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (400.00 mg, 981.69 μmol, 1.00 *eq*) in THF (2.00 mL) drop-wise at -30 °C under N₂. The mixture was heated to 0 °C and
10 stirred for 1 hours. LCMS and TLC (Ethyl acetate) showed the reaction was completed and the desired product was detected. The mixture was poured into 1N HCl (30 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (10 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to afford the title compound (288.00 mg, 769.17 μmol, 78.35% yield) as
15 yellow solid. LCMS[M+1]: 375.

Step 4. tert-butyl 8-(1-hydroxyallyl)- 10-methyl-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate E1-E4. To a mixture of tert-butyl 10-methyl-11-oxo-8-prop-2-enoyl-1,3,4,7,8,9- hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (3.70 g, 9.88 mmol, 1.00 *eq*) in MeOH (100.00 mL) was added
20 CeCl₃ (4.87 g, 19.76 mmol, 1.24 mL, 2.00 *eq*) in one portion at 0°C under N₂. The mixture was stirred at 0 °C for 15 min, then NaBH₄ (1.50 g, 39.52 mmol, 4.00 *eq*) was added to the mixture. The mixture was heated to 30 °C and stirred for 2 hours. LCMS and TLC (Dichloromethane : Methanol=10:1) showed the reaction was completed. The mixture was poured into water (20 mL) and concentrated in reduced pressure. The aqueous phase was extracted with ethyl acetate
25 (50 mL*3). The combined organic phase was washed with brine (20 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Dichloromethane : Methanol=100/1~20:1) to afford racemic title compound (2.70 g, 6.74 mmol, 68.24% yield, 94% purity) as yellow solid, Which was separated by SFC (Analytical method: IC-3S_3_5_40_3ML Column: Chiralpak IC-3 100×4.6mm I.D., 3μm
30 Mobile phase: methanol (0.05% DEA) in CO₂ from 5% to 40% Flow rate: 3mL/min Wavelength: 220nm. Separation method: Instrument: SFC 80; Column: IC-10μm; Mobile phase:

A for CO₂ and B for MeOH(0.1% NH₃ H₂O); Gradient: B 35%; Flow rate: 60mL/min; Back pressure: 100bar; Column temperature: 35 °C; Wavelength: 220 nm) to give four isomers: **E1**: 650 mg, **E2**: 640 mg, **E3**: 650 mg and **E4**: 650 mg.

Step 5. tert-butyl 8-(1-hydroxypropyl)-10-methyl- 11-oxo-1,3,4,7,8,9-

5 hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate **E1**. To a solution of tert-butyl 8-(1-hydroxyallyl)-10-methyl-11-oxo-1,3,4,7,8,9- hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (550.00 mg, 1.46 mmol, 1.00 *eq*) in MeOH (20.00 mL) was added Pd/C (100.00 mg) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 30 °C for 5 hours LCMS showed
10 the starting material was consumed completely. The reaction mixture was filtered and the filtrate was concentrated to afford the title compound (520.00 mg, 1.37 mmol, 94.11% yield) as yellow solid. LCMS[M+1]: 379.

Step 6. 8-(1-hydroxypropyl)-10-methyl-2,3,4,7,8,9- hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one **E1**. To a mixture of tert-butyl 8-(1-hydroxypropyl)-10-methyl-11-oxo-

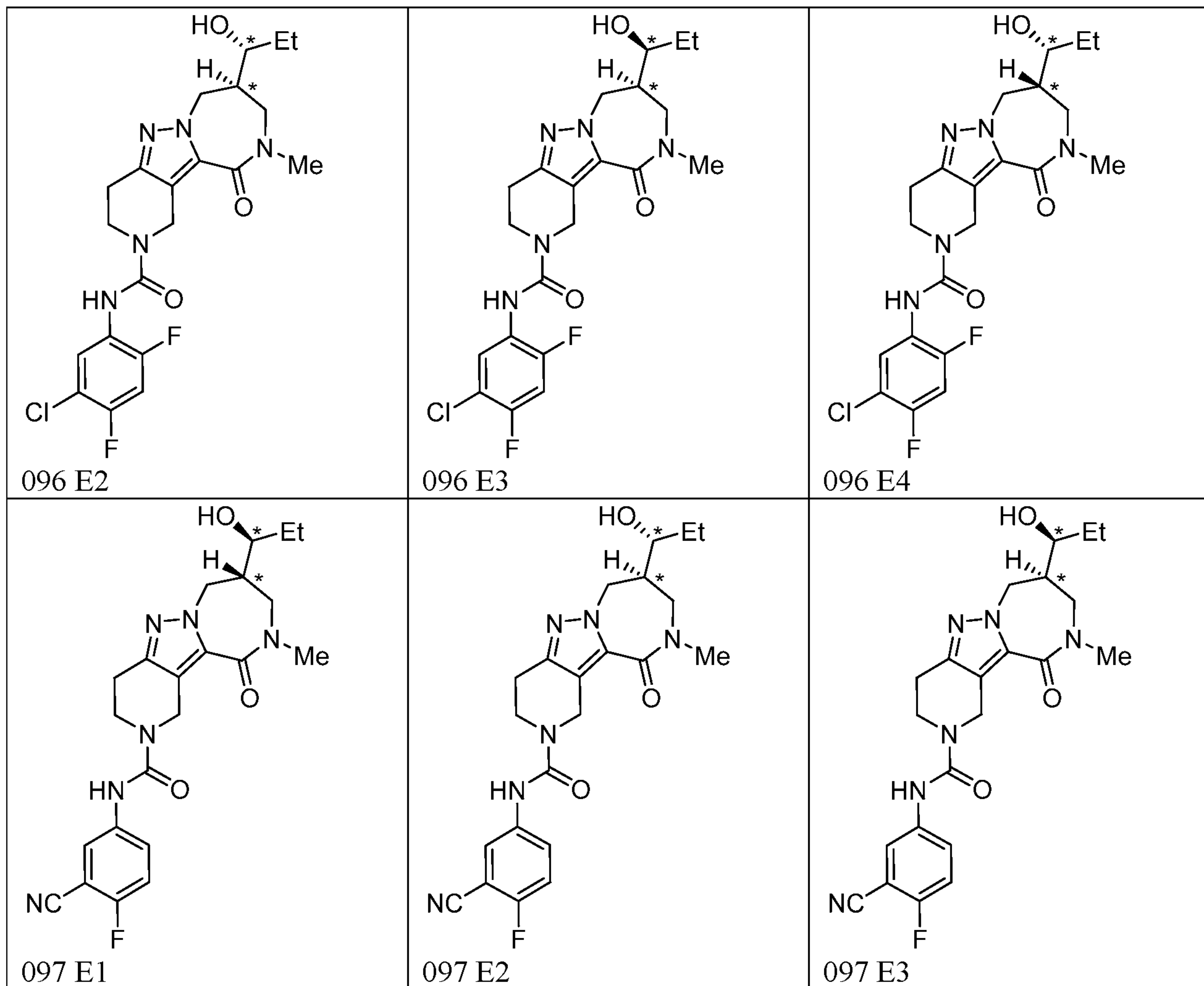
15 1,3,4,7,8,9- hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (200.00 mg, 528.46 μmol, 1.00*eq*) in DCM (2.00 mL) was added TFA (3.08 g, 27.01 mmol, 2.00 mL, 51.12 *eq*) in one portion at 30 °C under N₂. The mixture was stirred at 30 °C for 2 hours. LCMS showed the reaction was completed. The mixture was concentrated in vacuum to afford the title compound (207.00 mg, 527.56 μmol, 99.83% yield, TFA) as yellow oil.

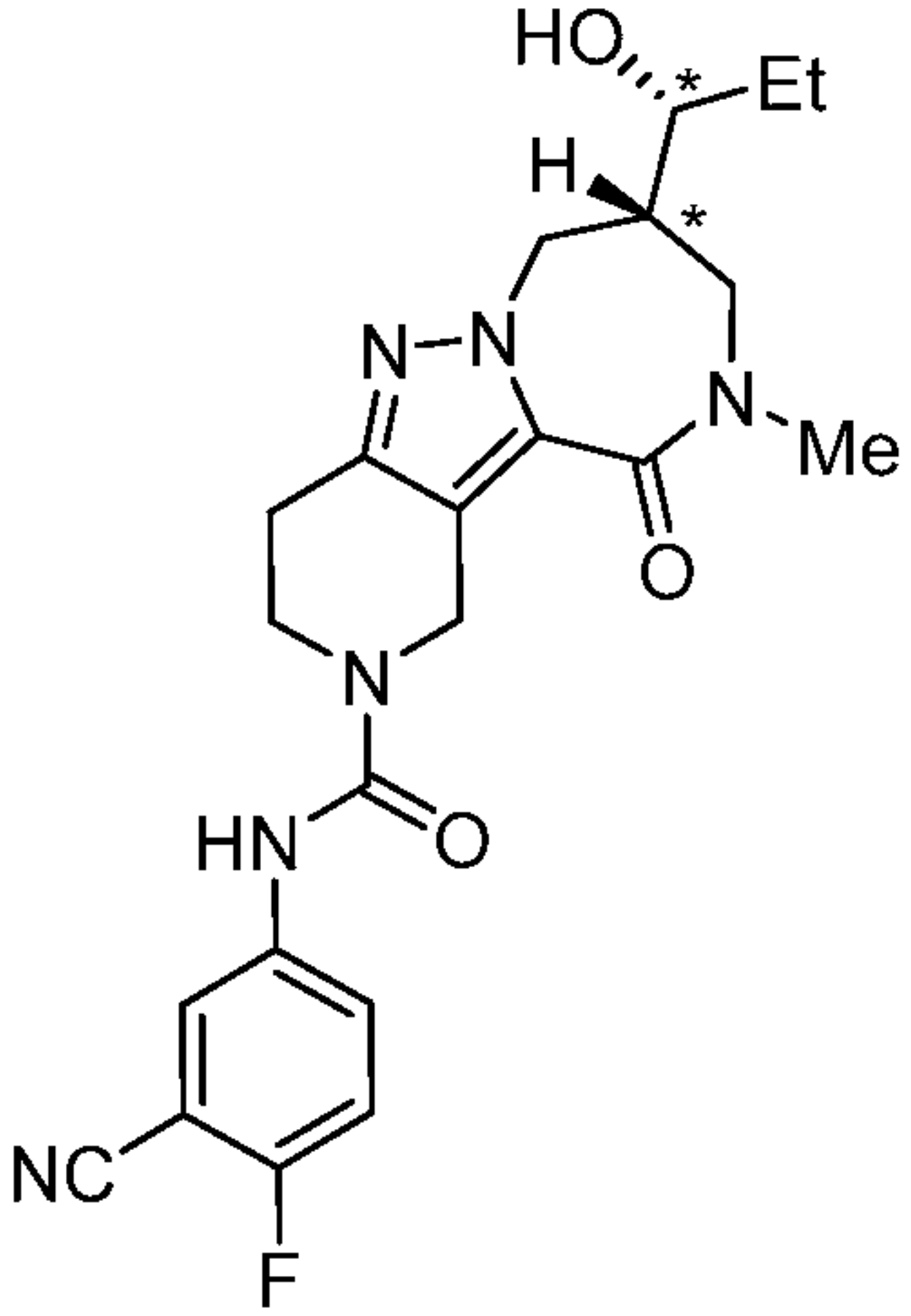
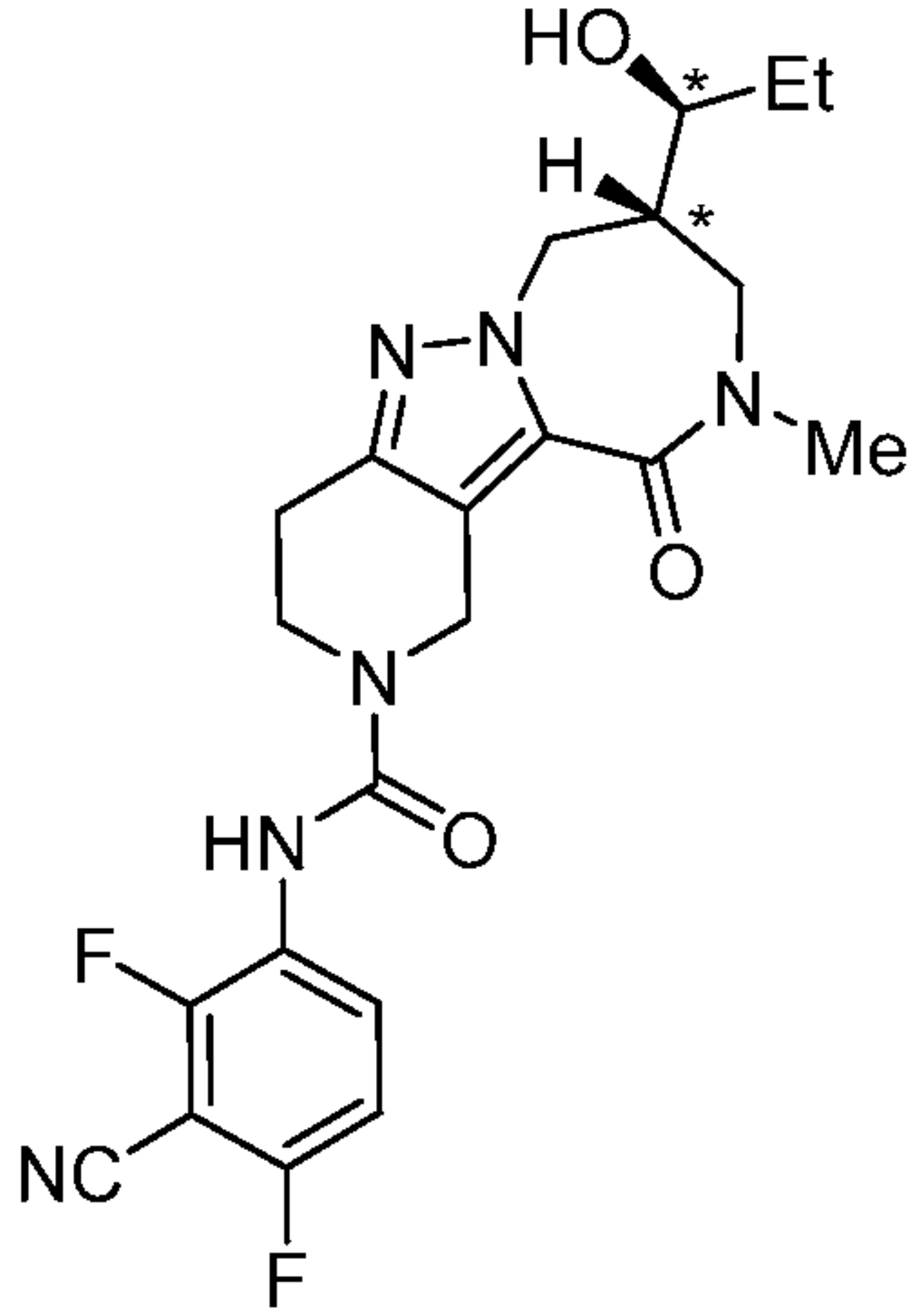
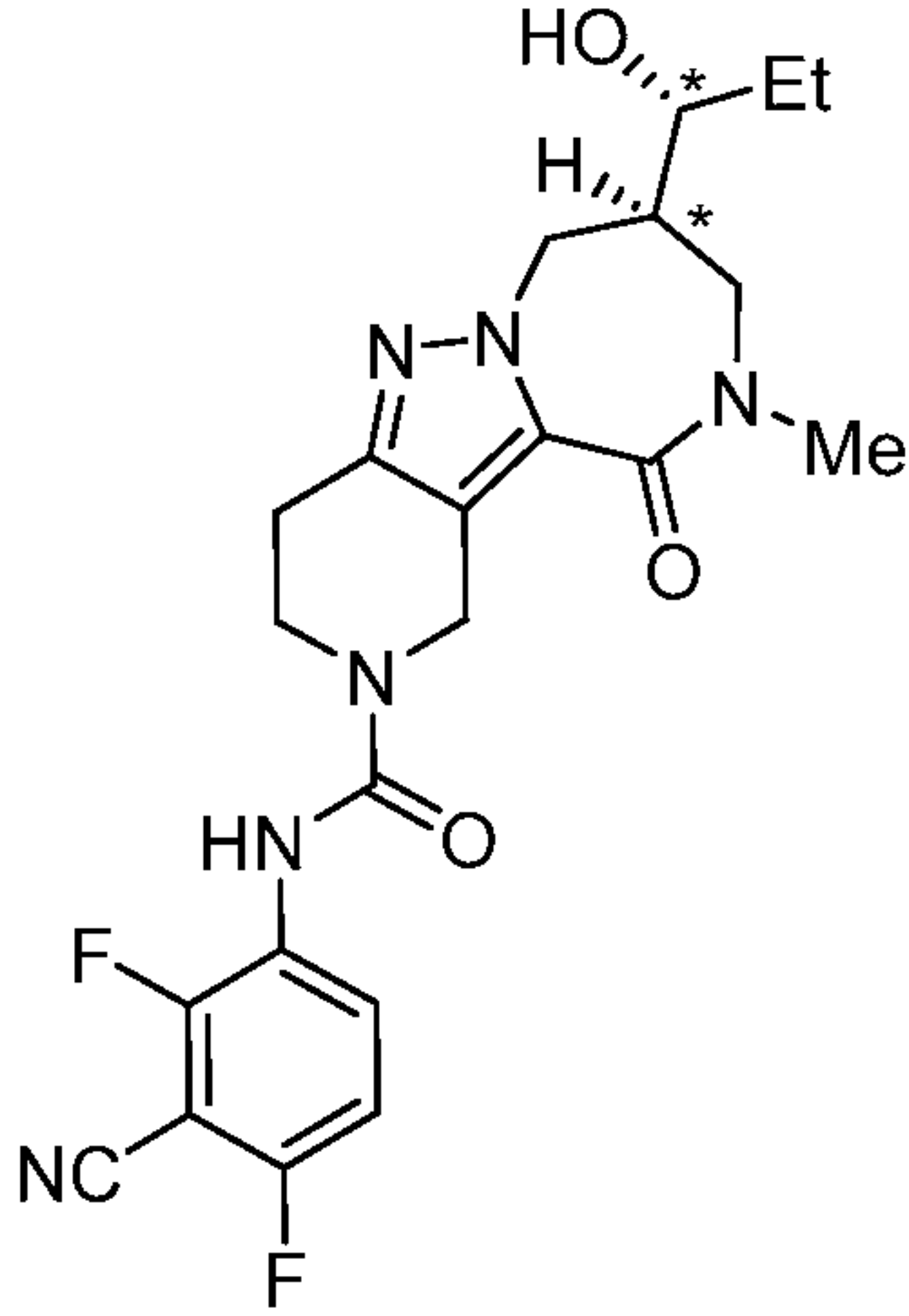
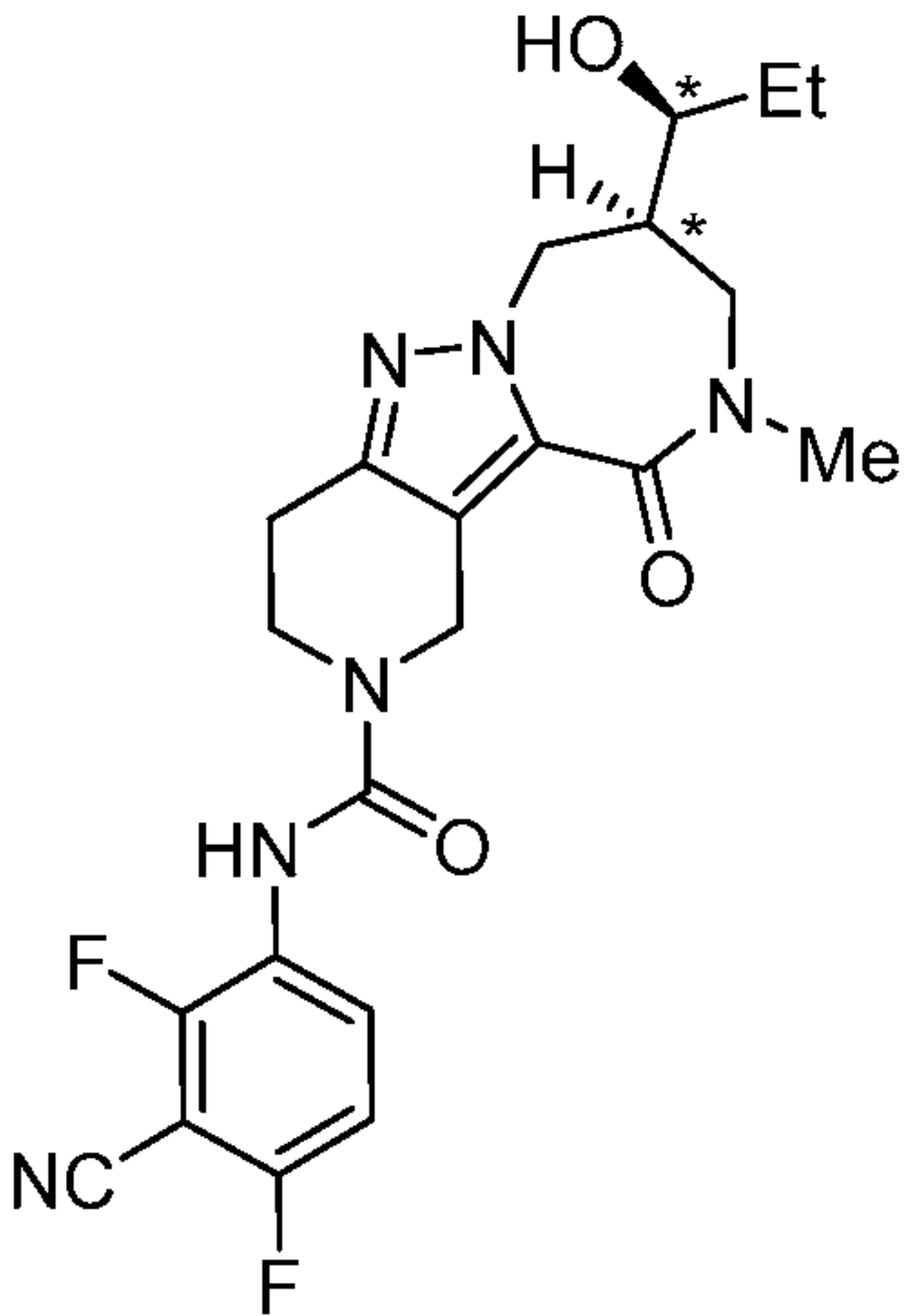
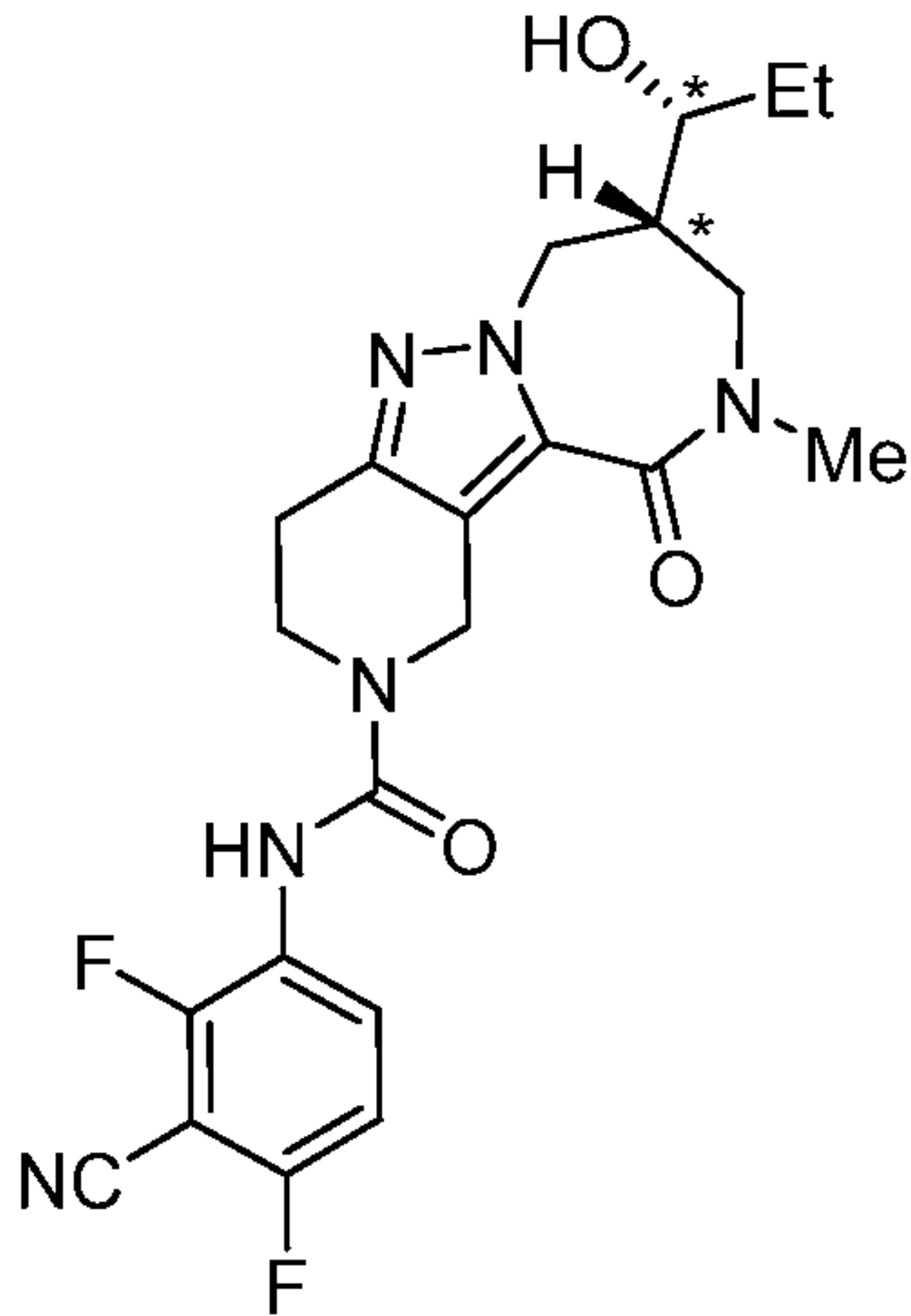
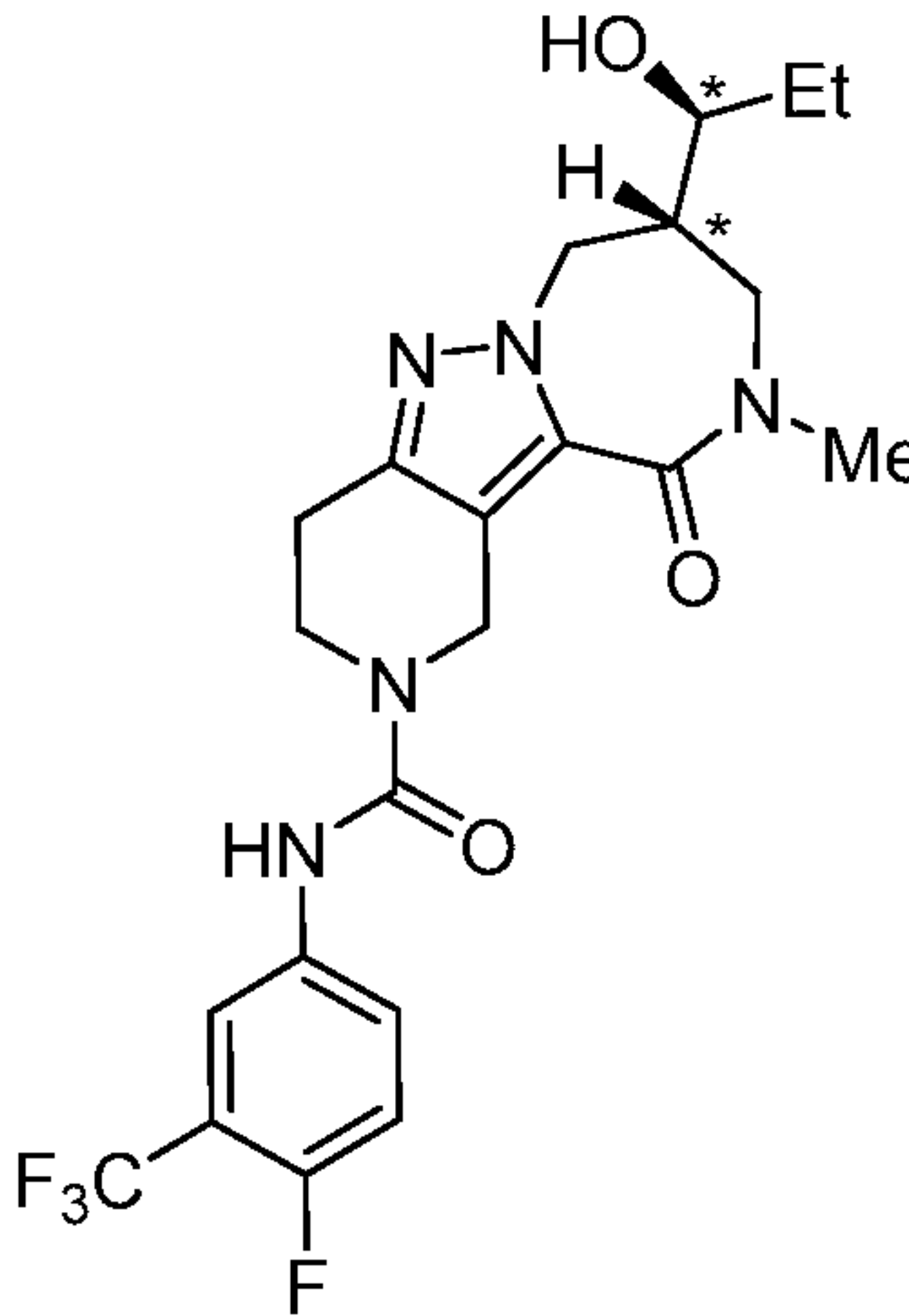
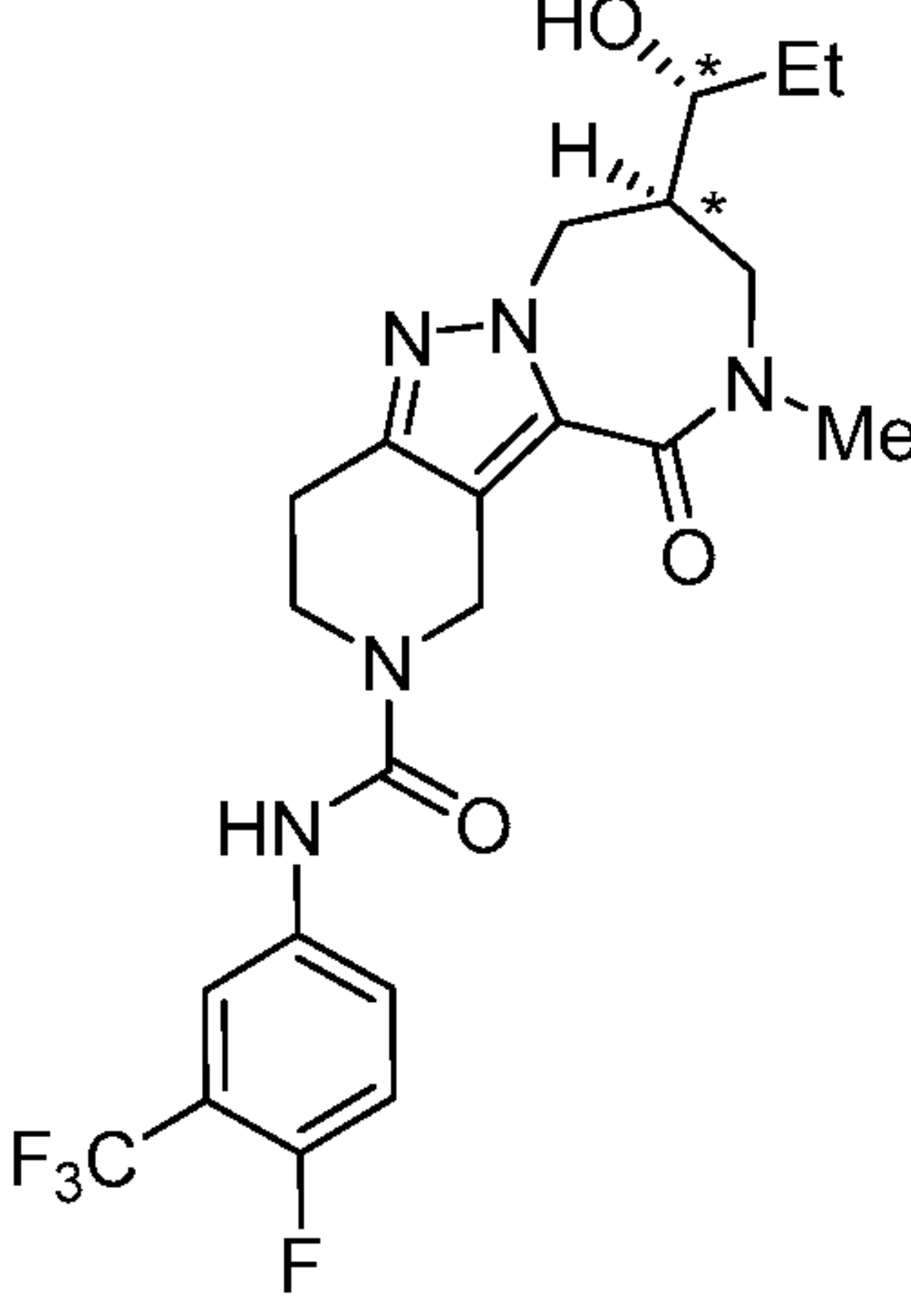
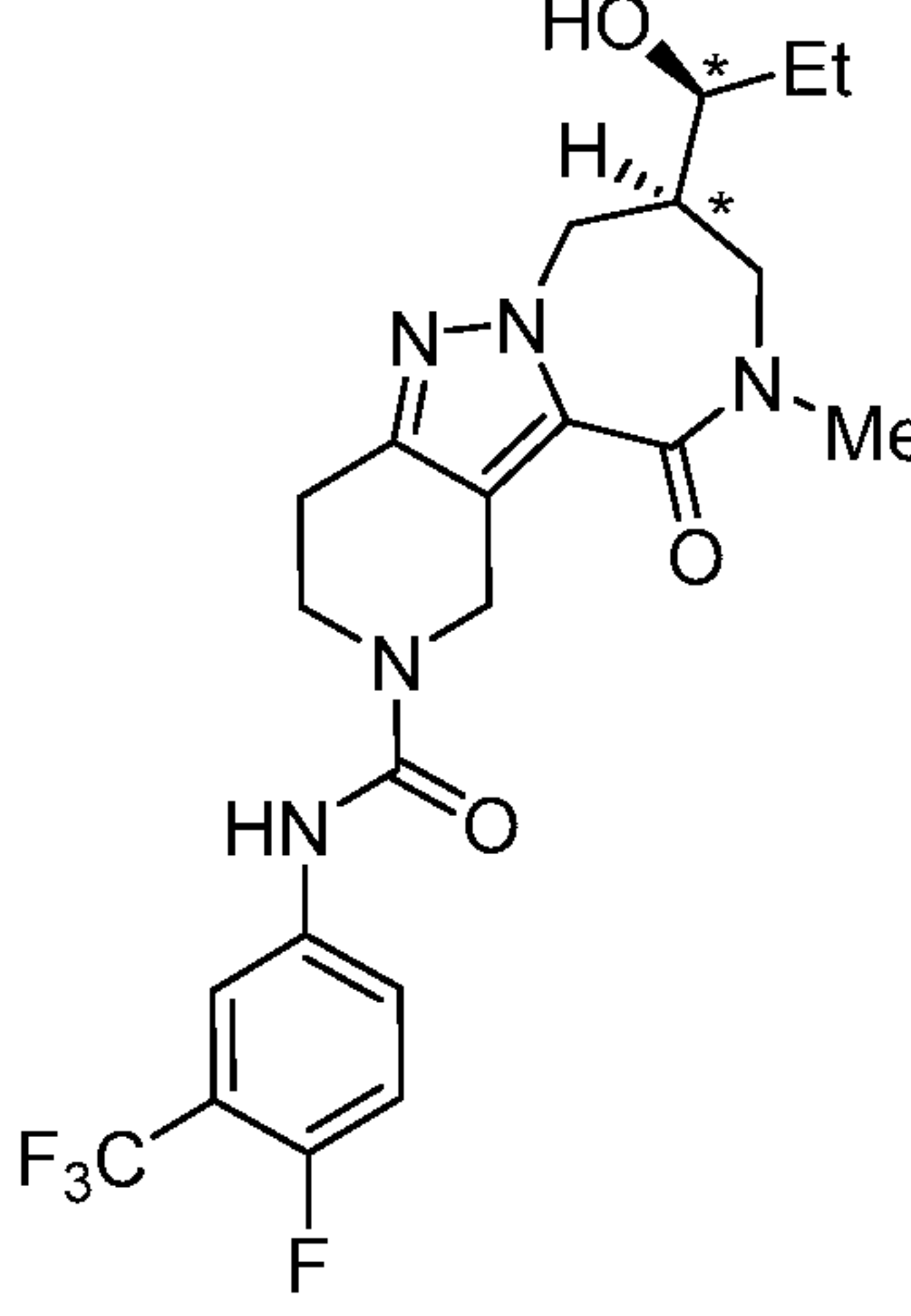
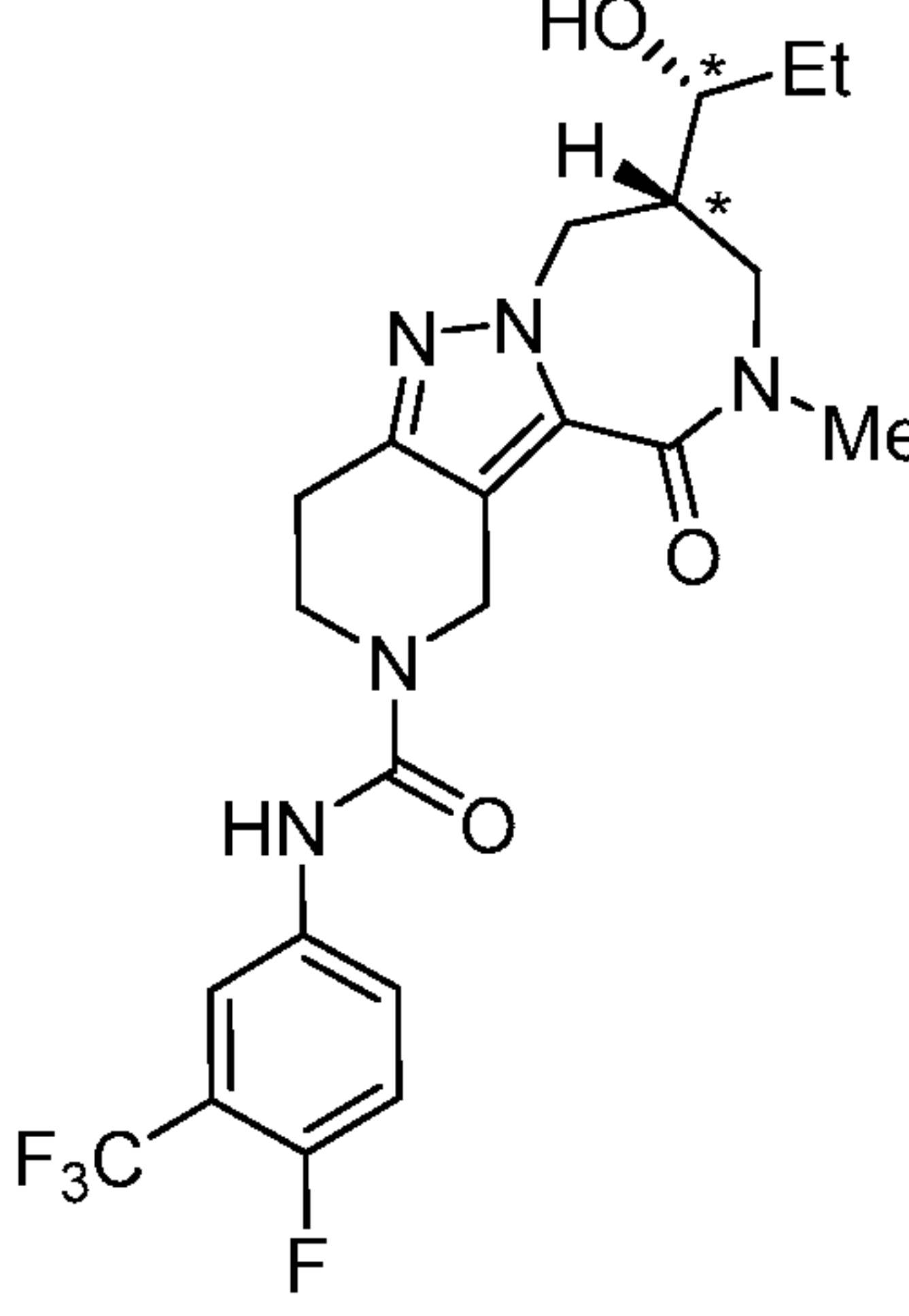
20 Step 7. (R*)-N-(5-chloro-2,4-difluorophenyl)-8-((S*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

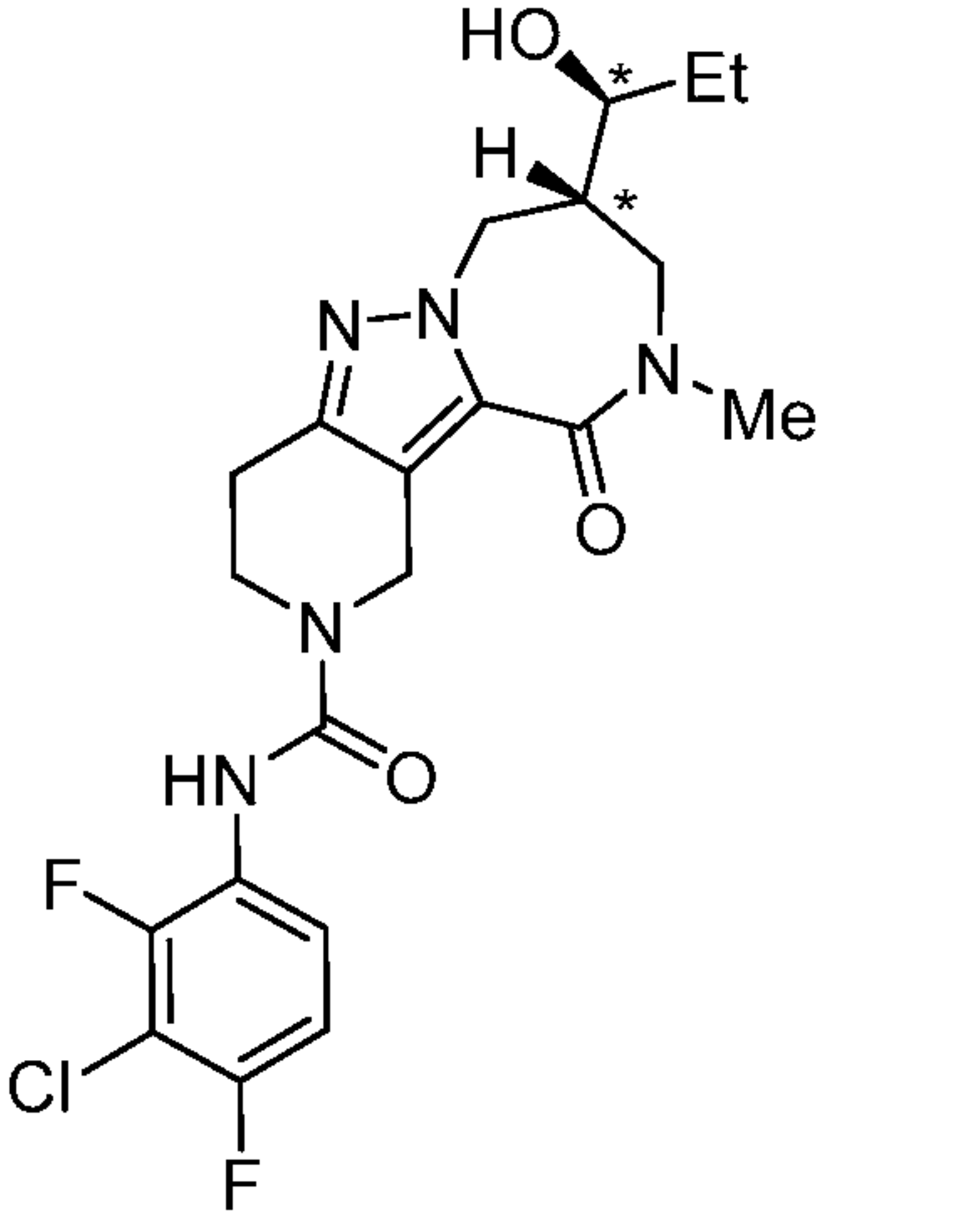
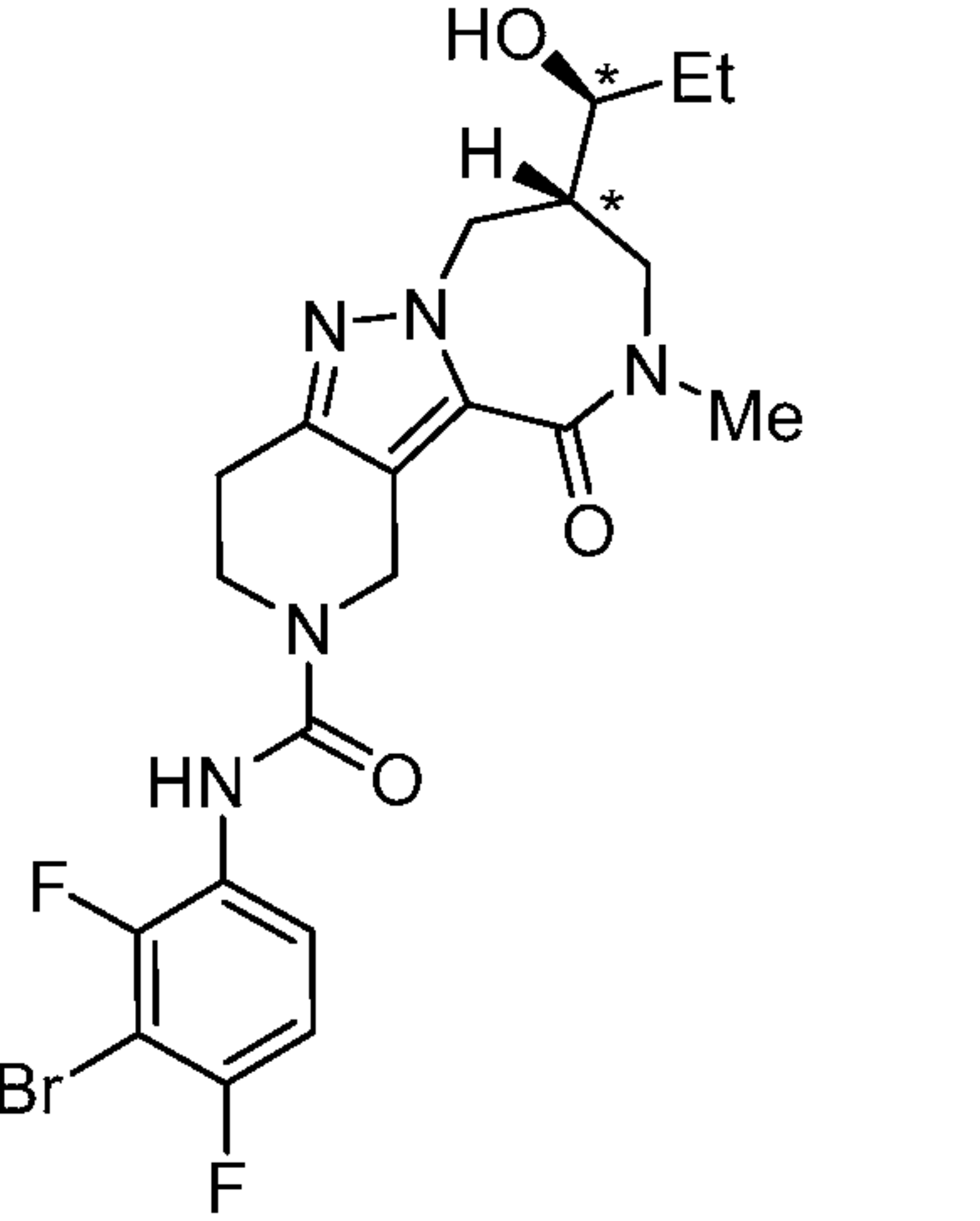
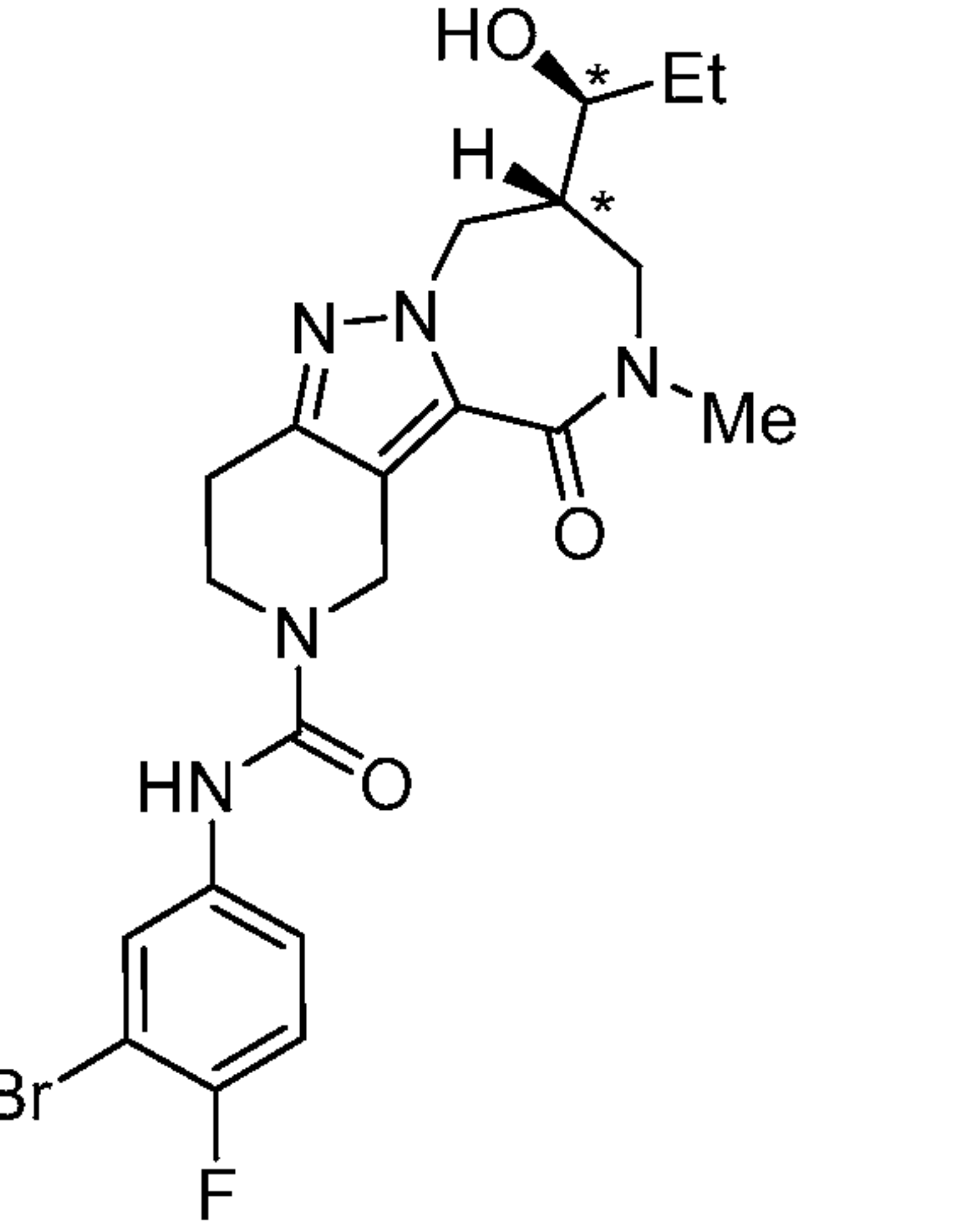
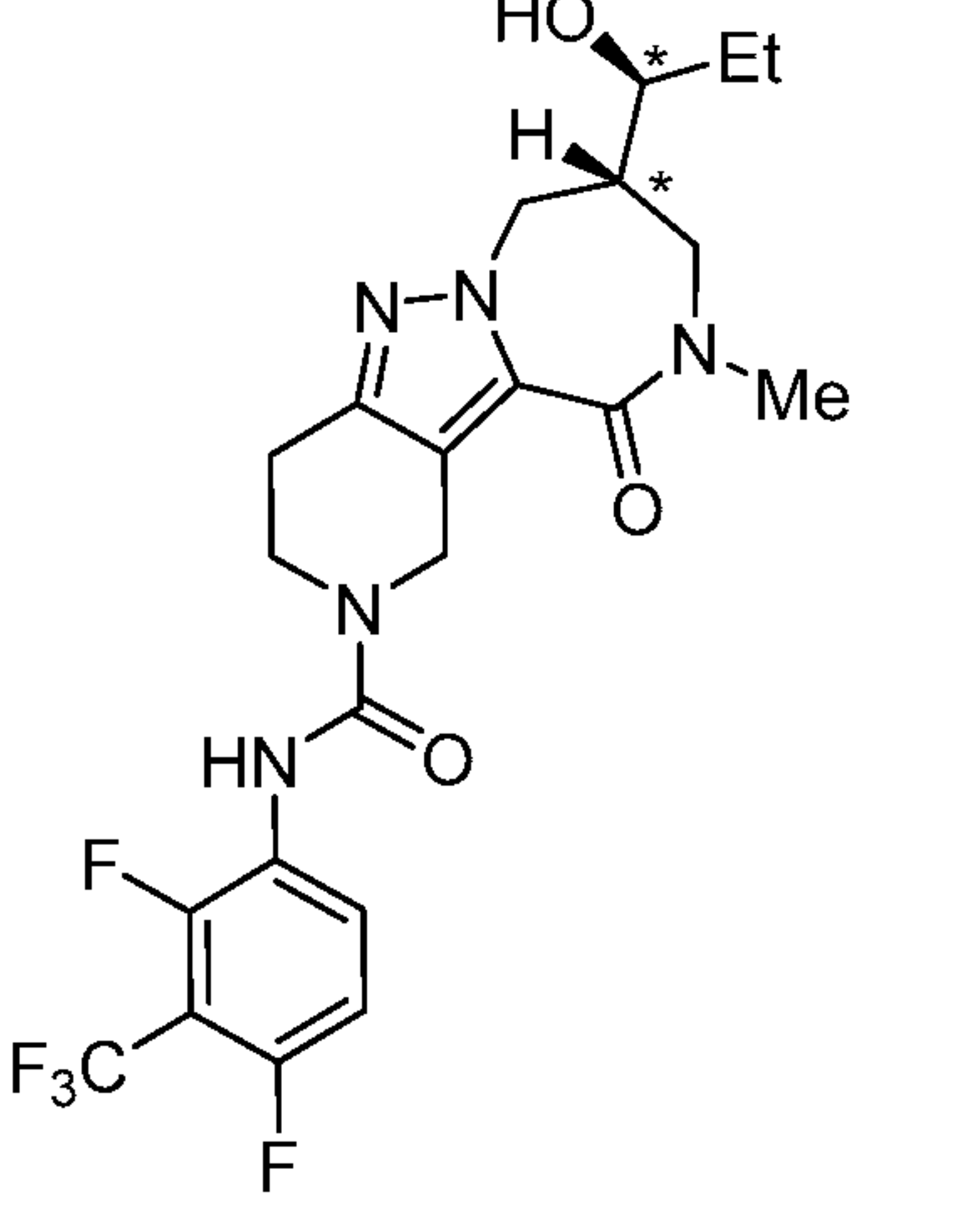
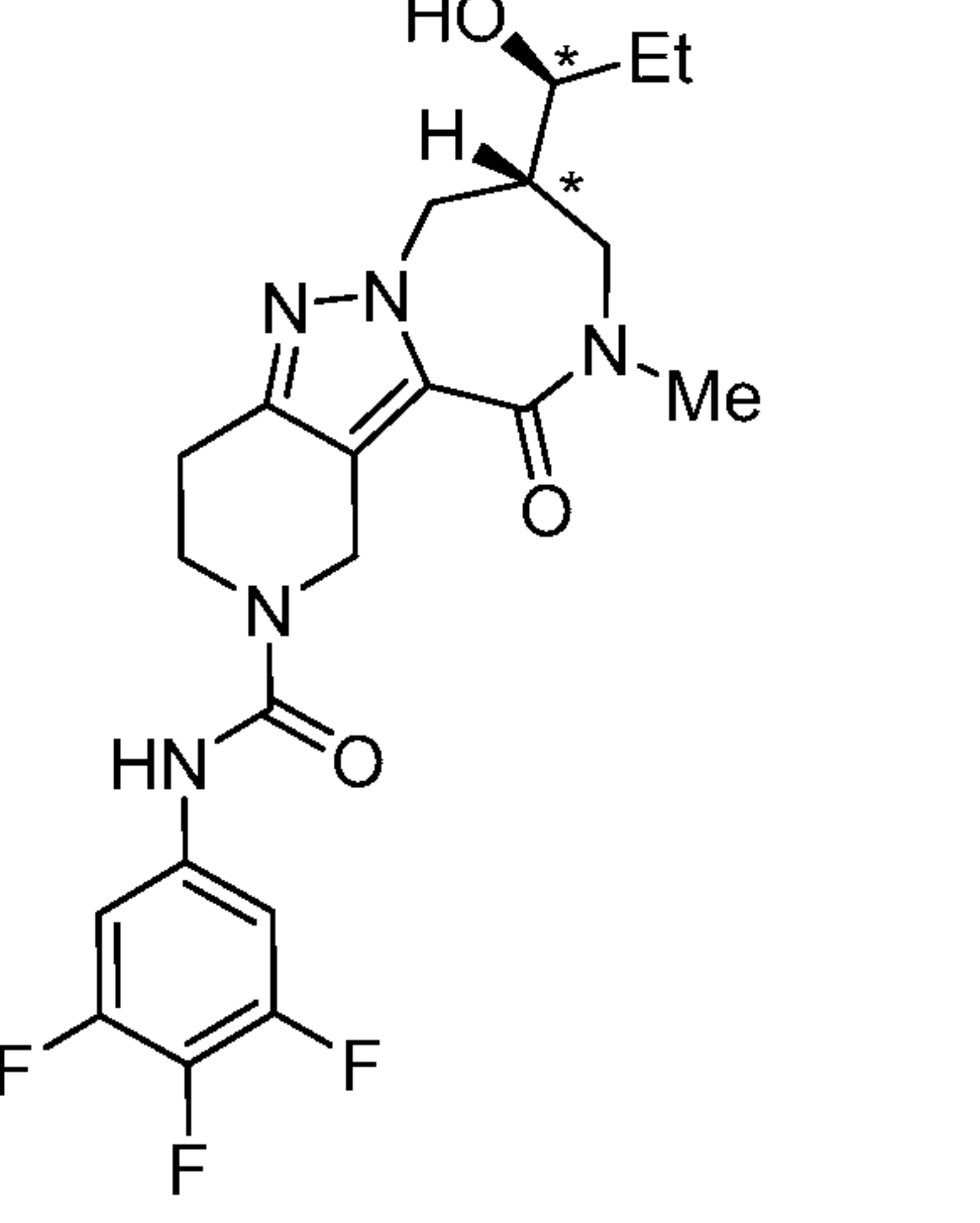
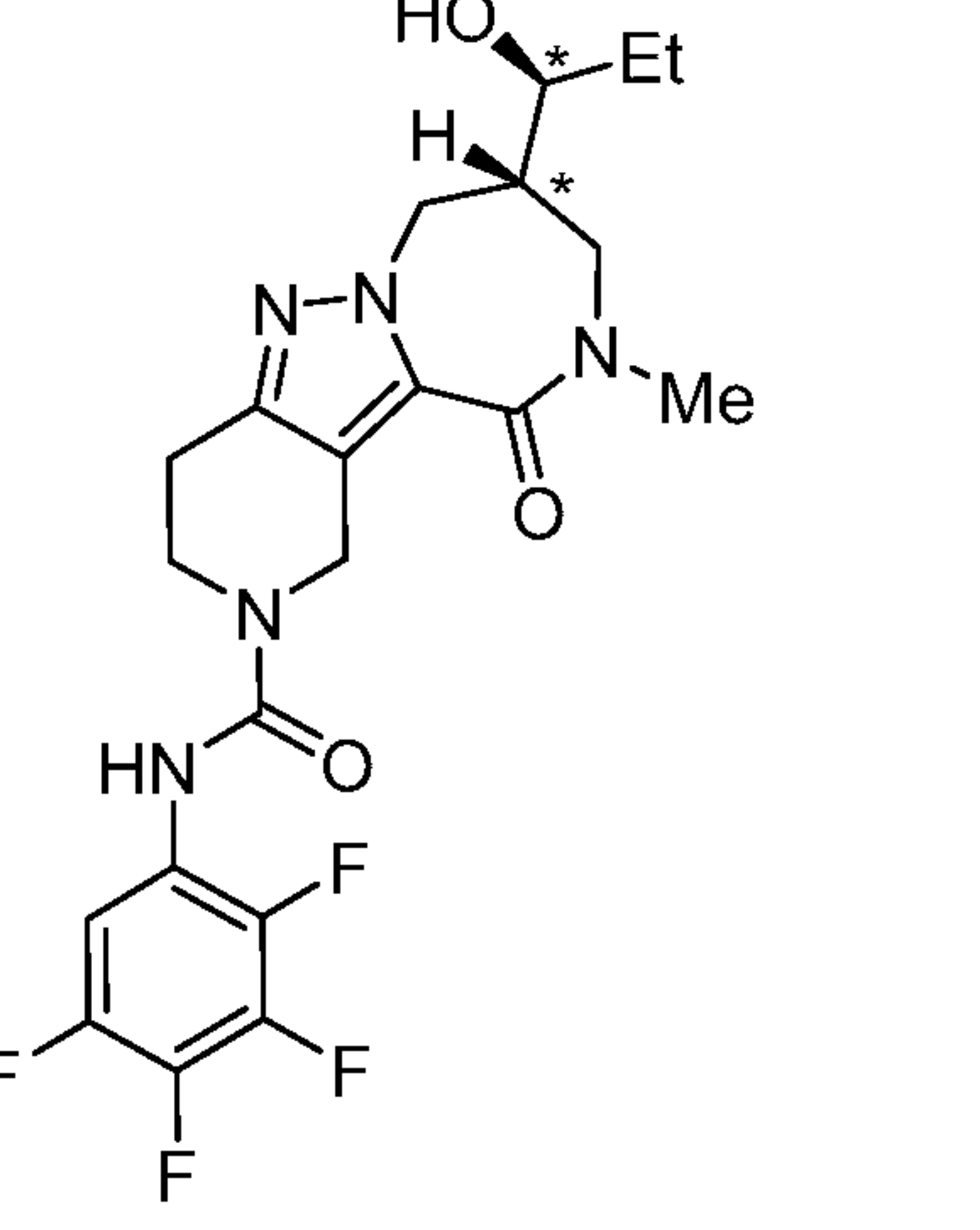
*Pure but unknown diastereomer E1. To a mixture of 8-(1-hydroxypropyl)-10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido [2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (50.00 mg, 127.43 μmol, 1.00 *eq*, TFA) and phenyl N-(5-chloro-2,4-difluoro-phenyl)carbamate (46.99 mg, 165.66 μmol, 1.30 *eq*) in DCM (6.00 mL) was added TEA (128.95 mg, 1.27 mmol, 176.64 μL, 10.00 *eq*) under N₂. The mixture was stirred at 25 °C for 10 hours. LCMS showed the reaction was completed. The residue was poured into water (10 mL). The aqueous phase was extracted with ethyl acetate (10 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-
25 HPLC(FA) to afforded the title compound (40.00 mg, 84.89 μmol, 66.62% yield, 99.3% purity)
30 as white solid. LCMS [M+1] : 468 ¹H NMR (400 MHz, CDCl₃) δ 8.17 (t, *J*=8.03 Hz, 1H), 6.94

(dd, $J=8.47, 10.60$ Hz, 1H), 6.59 (d, $J=2.89$ Hz, 1H), 4.70 (s, 2H), 4.40-4.42 (m, 1H), 4.13-4.16 (m, 1H), 3.82-3.89 (m, 2H), 3.64-3.66 (m, 2H), 3.46 - 3.48 (m, 1H), 3.19 (s, 3H), 2.85 (t, $J=5.77$ Hz, 2H), 2.46-2.47 (m, 1H), 1.70-1.77 (m, 1H), 1.44-1.55 (m, 2H), 1.04 (t, $J=7.40$ Hz, 3H).

- 5 Compounds 096,097,098,099,100,101,102,103,104, and 105 were prepared from the corresponding enantiomer separately through an analogous method.



 <p>097 E4</p>	 <p>098 E1</p>	 <p>098 E2</p>
 <p>098 E3</p>	 <p>098 E4</p>	 <p>099 E1</p>
 <p>099 E2</p>	 <p>099 E3</p>	 <p>099 E4</p>

 <p>100 E1</p>	 <p>101 E1</p>	 <p>102 E1</p>
 <p>103 E1</p>	 <p>104 E1</p>	 <p>105 E1</p>

Compound 096_E2: (S*)-N-(5-chloro-2,4-difluorophenyl)-8-((R*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

5 *Pure but unknown diastereomer E2.

LCMS [M+1] : 468 ¹H NMR (400 MHz, CDCl₃) δ 8.18 (t, *J*=8.03 Hz, 1H), 6.96 (dd, *J*=8.47, 10.60 Hz, 1H), 6.61 (s, 1H), 4.71 (s, 2H), 4.40 - 4.42 (m, 1H), 4.14 - 4.16 (m, 1H), 3.83-3.91 (m, 2H), 3.62-3.69 (m, 2H), 3.47-3.48 (m, 1H), 3.20 (s, 3H), 2.86 (t, *J*=5.71 Hz, 2H), 2.47-2.49 (m, 1H), 1.71-1.79 (m, 1H), 1.45-1.56 (m, 2H), 1.05 (t, *J*=7.34 Hz, 3H).

Compound 096_E3: (S*)-N-(5-chloro-2,4-difluorophenyl)-8-((S*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

5 *Pure but unknown diastereomer E3.

LCMS [M+1] : 468 ¹H NMR (400 MHz, CDCl₃) δ 8.18 (t, *J*=8.07 Hz, 1H), 6.96 (dd, *J*=8.50, 10.45 Hz, 1H), 6.63 (br d, *J*=2.69 Hz, 1H), 4.59-4.77 (m, 3H), 4.32 (m, 1H), 3.79-3.95 (m, 2H), 3.49-3.56 (m, 1H), 3.36-3.37 (m, 2H), 3.20 (s, 3H), 2.87 (t, *J*=5.81 Hz, 2H), 2.46-2.54 (m, 1H), 1.90-2.20 (m, 1H), 1.44-1.54 (m, 2H), 1.03 (t, *J*=7.40 Hz, 3H).

10

Compound 096_E4: (R*)-N-(5-chloro-2,4-difluorophenyl)-8-((R*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

15 *Pure but unknown diastereomer E4.

LCMS [M+1] : 468 ¹H NMR (400 MHz, CDCl₃) δ 8.18 (t, *J*=8.07 Hz, 1H), 6.96 (dd, *J*=8.50, 10.58 Hz, 1H), 6.63 (s, 1H), 4.59-4.77 (m, 3H), 4.32 (m, 1H), 3.79-3.95 (m, 2H), 3.50-3.56 (m, 1H), 3.36 (m, 2H), 3.20 (s, 3H), 2.87 (t, *J*=5.81 Hz, 2H), 2.46-2.54 (m, 1H), 2.03 (s, 1H), 1.75 (br s, 1H), 1.66 (m, 19H), 1.42-1.55 (m, 2H), 1.03 (t, *J*=7.34 Hz, 3H).

20

Compound 097_E1: (R*)-N-(3-cyano-4-fluorophenyl)-8-((S*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

25 *Pure but unknown diastereomer E1.

LCMS [M+1] : 441. ¹H NMR (400 MHz, CDCl₃) δ 7.80 (dd, *J*=2.76, 5.52 Hz, 1H), 7.60-7.63 (m, 1H), 7.14 (t, *J*=8.72 Hz, 1H), 6.99-7.04 (m, 1H), 4.64-4.75 (m, 2H), 4.43 (m, 1H), 4.15 (m, 1H), 3.81-3.95 (m, 2H), 3.66 (m, 2H), 3.48 (m, 1H), 3.21 (s, 3H), 2.85 (t, *J*=5.71 Hz, 2H), 2.45-2.53 (m, 1H), 1.79 (m, 1H), 1.44-1.59 (m, 2H), 1.05 (t, *J*=7.40 Hz, 3H).

30

Compound 097_E2: (S*)-N-(3-cyano-4-fluorophenyl)-8-((R*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

*Pure but unknown diastereomer E2.

- 5 LCMS [M+1] : 441. ¹H NMR (400 MHz, CDCl₃) δ 7.80 (dd, *J*=2.76, 5.40 Hz, 1H), 7.60-7.63 (m, 1H), 7.14 (t, *J*=8.72 Hz, 1H), 6.99 (br s, 1H), 4.64-4.75 (m, 2H), 4.43 (dd, *J*=7.28, 14.18 Hz, 1H), 4.15 (m, 1H), 3.81-3.95 (m, 2H), 3.66 (m, 2H), 3.48 (m, 14.87 Hz, 1H), 3.21 (s, 3H), 2.85 (t, *J*=5.83 Hz, 2H), 2.49 (m, 1H), 1.79 (br s, 1H), 1.60-1.71 (m, 18H), 1.52 (m, 2H), 1.05 (t, *J*=7.40 Hz, 3H).

10

Compound 097_E3: (S*)-N-(3-cyano-4-fluorophenyl)-8-((S*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

*Pure but unknown diastereomer E3.

- 15 LCMS [M+1] : 441. ¹H NMR (400 MHz, CDCl₃) δ 7.79 (dd, *J*=2.69, 5.38 Hz, 1H), 7.60-7.63 (m, 1H), 7.14 (t, *J*=8.68 Hz, 1H), 7.04 (s, 1H), 4.70-4.79 (m, 1H), 4.59-4.69 (m, 2H), 4.33 (m, 1H), 3.81-3.95 (m, 2H), 3.50-3.58 (m, 1H), 3.38 (m, 2H), 3.20 (s, 3H), 2.85 (t, *J*=5.81 Hz, 2H), 2.51 (m, 1H), 1.97-2.18 (m, 1H), 1.46-1.57 (m, 1H), 1.45-1.56 (m, 1H), 1.04 (t, *J*=7.40 Hz, 3H).

- 20 Compound 097_E4: (R*)-N-(3-cyano-4-fluorophenyl)-8-((R*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. *Pure but unknown diastereomer E4.

- LCMS [M+1] : 441. ¹H NMR (400 MHz, CDCl₃) δ 7.79 (dd, *J*=2.75, 5.44 Hz, 1H), 7.61-7.63 (m, 1H), 7.05-7.17 (m, 2H), 4.71-4.79 (m, 1H), 4.58-4.67 (m, 2H), 4.33 (m, 1H), 3.81-3.95 (m, 2H), 3.51-3.57 (m, 1H), 3.38 (d, *J*=7.46 Hz, 2H), 3.20 (s, 3H), 2.85 (t, *J*=5.81 Hz, 2H), 2.47-2.55 (m, 1H), 2.03 (s, 1H), 1.62-1.74 (m, 1H), 1.45-1.58 (m, 2H), 1.04 (t, *J*=7.40 Hz, 3H).

- 30 Compound 098_E1: (R*)-N-(3-cyano-2,4-difluorophenyl)-8-((S*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

*Pure but unknown diastereomer E1.

LCMS [M+1] : 459. ¹H NMR (400 MHz, CDCl₃) δ 8.25 (dt, *J*=5.84, 9.13 Hz, 1H), 7.01 (ddd, *J*=1.76, 7.97, 9.47 Hz, 1H), 6.73 (d, *J*=2.26 Hz, 1H), 4.72 (d, *J*=3.51 Hz, 2H), 4.41 (m, 1H), 4.14 (m, 1H), 3.78-3.95 (m, 2H), 3.59-3.71 (m, 2H), 3.46 (m, 1H), 3.19 (s, 3H), 2.85 (t, *J*=5.71 Hz, 2H), 2.40-2.54 (m, 1H), 1.43-1.59 (m, 2H), 1.03 (t, *J*=7.40 Hz, 3H).

5

Compound 098_E2: (S*)-N-(3-cyano-2,4-difluorophenyl)-8-((R*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

*Pure but unknown diastereomer E2.

10 LCMS [M+1] : 459 ¹H NMR (400 MHz, CDCl₃) δ 8.25 (dt, *J*=5.90, 9.10 Hz, 1H), 7.01 (ddd, *J*=1.69, 7.94, 9.44 Hz, 1H), 6.73 (d, *J*=2.01 Hz, 1H), 4.72 (d, *J*=3.64 Hz, 2H), 4.41 (m, 1H), 4.14 (m, 1H), 3.86 (m, 2H), 3.57-3.71 (m, 2H), 3.46 (m, 1H), 3.19 (s, 3H), 2.85 (t, *J*=5.71 Hz, 2H), 2.37-2.57 (m, 1H), 1.51 (dt, *J*=7.40, 14.93 Hz, 2H), 1.04 (t, *J*=7.40 Hz, 3H).

15 Compound 098_E3: (S*)-N-(3-cyano-2,4-difluorophenyl)-8-((S*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

*Pure but unknown diastereomer E3.

20 LCMS [M+1] : 459. ¹H NMR (400 MHz, CDCl₃) δ 8.26 (dt, *J*=5.83, 9.13 Hz, 1H), 7.01 (ddd, *J*=1.76, 7.97, 9.47 Hz, 1H), 6.72 (d, *J*=2.26 Hz, 1H), 4.53-4.85 (m, 3H), 4.31 (m, 1H), 3.77-3.95 (m, 2H), 3.52 (m, 1H), 3.36 (m, 2H), 3.19 (s, 3H), 2.86 (t, *J*=5.77 Hz, 2H), 2.42-2.56 (m, 1H), 1.44-1.58 (m, 2H), 1.02 (t, *J*=7.40 Hz, 3H).

25 Compound 098_E4: (R*)-N-(3-cyano-2,4-difluorophenyl)-8-((R*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

*Pure but unknown diastereomer E4.

30 LCMS [M+1] : 459. ¹H NMR (400 MHz, CDCl₃) δ 8.18-8.35 (m, 1H), 7.02 (ddd, *J*=1.76, 8.03, 9.54 Hz, 1H), 6.65-6.80 (m, 1H), 4.54-4.83 (m, 3H), 4.20-4.37 (m, 1H), 3.75-3.96 (m, 2H), 3.47-3.59 (m, 1H), 3.36 (m, 2H), 3.19 (s, 3H), 2.86 (s, 2H), 2.41-2.58 (m, 1H), 1.42-1.56 (m, 2H), 1.02 (t, *J*=7.40 Hz, 3H).

Compound 099_E1: (R*)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-((S*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

5 *Pure but unknown diastereomer E1.

LCMS [M+1] : 484. ¹H NMR (400 MHz, CDCl₃) δ 7.69 (dd, *J*=2.63, 6.05 Hz, 1H), 7.59 (td, *J*=3.38, 9.02 Hz, 1H), 7.12 (t, *J*=9.35 Hz, 1H), 6.87 (s, 1H), 4.60-4.77 (m, 2H), 4.41 (m, 1H), 4.13 (m, 1H), 3.78-3.96 (m, 2H), 3.64 (m, 2H), 3.47 (m, 1H), 3.19 (s, 3H), 2.84 (t, *J*=5.93 Hz, 2H), 2.40-2.53 (m, 1H), 1.72-1.82 (m, 1H), 1.46-1.57 (m, 2H), 1.04 (t, *J*=7.40 Hz, 3H).

10

Compound 099_E2: (S*)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-((R*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

*Pure but unknown diastereomer E2.

15 LCMS [M+1] : 484. ¹H NMR (400 MHz, CDCl₃) δ 7.69 (dd, *J*=2.75, 6.17 Hz, 1H), 7.56-7.63 (m, 1H), 7.12 (t, *J*=9.35 Hz, 1H), 6.87 (s, 1H), 4.61-4.78 (m, 2H), 4.41 (m, 1H), 4.13 (m, 1H), 3.79-3.96 (m, 2H), 3.59-3.71 (m, 2H), 3.47 (m, 1H), 3.19 (s, 3H), 2.84 (t, *J*=5.93 Hz, 2H), 2.38-2.54 (m, 1H), 1.74 (br dd, *J*=3.24, 7.27 Hz, 1H), 1.71-1.81 (m, 1H), 1.51 (dt, *J*=7.64, 14.95 Hz, 2H), 1.04 (t, *J*=7.34 Hz, 3H).

20

Compound 099_E3: (S*)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-((S*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

*Pure but unknown diastereomer E3.

25 LCMS [M+1] : 484. ¹H NMR (400 MHz, CDCl₃) δ 7.69 (dd, *J*=2.57, 5.87 Hz, 1H), 7.55-7.62 (m, 1H), 7.12 (t, *J*=9.41 Hz, 1H), 6.86 (s, 1H), 4.55-4.80 (m, 3H), 4.31 (m, 14.37 Hz, 1H), 3.82-3.93 (m, 2H), 3.48-3.57 (m, 1H), 3.36 (m, 2H), 3.19 (s, 3H), 2.84 (t, *J*=5.75 Hz, 2H), 2.39-2.54 (m, 1H), 1.95-2.10 (m, 1H), 1.45-1.55 (m, 2H), 1.02 (t, *J*=7.40 Hz, 3H).

Compound 099_E4: (R*)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-((R*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

*Pure but unknown diastereomer E4.

5 LCMS [M+1] : 484. ¹H NMR (400 MHz, CDCl₃) δ 7.66-7.72 (m, 1H), 7.55-7.63 (m, 1H), 7.12 (s, 1H), 6.86 (s, 1H), 4.55-4.79 (m, 3H), 4.24-4.37 (m, 1H), 3.87 (s, 2H), 3.47-3.59 (m, 1H), 3.36 (d, *J*=7.46 Hz, 2H), 3.19 (s, 3H), 2.80-2.89 (m, 2H), 2.44-2.55 (m, 1H), 1.99-2.13 (m, 1H), 1.44-1.55 (m, 2H), 1.02 (t, *J*=7.40 Hz, 3H).

10 Compound 100_E1: (R*)-N-(3-chloro-2,4-difluorophenyl)-8-((S*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

*Pure but unknown diastereomer E1.

15 LCMS [M+1] : 468 ¹H NMR (400 MHz, CDCl₃) δ 7.86 (dt, *J* = 5.56, 8.89 Hz, 1 H), 6.90 - 7.00 (m, 1 H), 6.60 (br s, 1 H), 4.71 (d, *J* = 1.34 Hz, 2 H), 4.41 (m, 1 H), 4.13 (m, 1 H), 3.80 - 3.92 (m, 2 H), 3.56 - 3.70 (m, 2 H), 3.46 (m, 1 H), 3.19 (s, 3 H), 2.85 (t, *J* = 5.62 Hz, 2H), 2.40 - 2.52 (m, 1 H), 1.44 - 1.57 (m, 2 H), 1.04 (t, *J* = 7.40 Hz, 3 H).

20 Compound 101_E1: (R*)-N-(3-bromo-2,4-difluorophenyl)-8-((S*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

*Pure but unknown diastereomer E1.

25 LCMS [M+1] : 512. ¹H NMR (400 MHz, CDCl₃) δ 7.92 (dt, *J* = 5.62, 8.93 Hz, 1 H), 6.93 (dt, *J* = 2.08, 8.62 Hz, 1 H), 6.61 (br s, 1 H), 4.67 - 4.76 (m, 2 H), 4.41 (m, 1 H), 4.13 (m, 1 H), 3.80 - 3.89 (m, 1 H), 3.58 - 3.70 (m, 2 H), 3.46 (m, 1 H), 3.19 (s, 3 H), 2.85 (t, *J* = 5.81 Hz, 2 H), 2.46 (m, 1H), 1.44 - 1.57 (m, 2 H), 1.03 (t, *J* = 7.40 Hz, 3 H).

30 Compound 102_E1: (R*)-N-(3-bromo-4-fluorophenyl)-8-((S*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

*Pure but unknown diastereomer E1.

LCMS [M+1] : 494. ¹H NMR (400 MHz, CDCl₃) δ 7.72 (dd, *J* = 2.69, 6.11 Hz, 1 H), 7.24 - 7.27 (m, 1 H), 7.03 (t, *J* = 8.56 Hz, 1 H), 6.68 (s, 1 H), 4.60 - 4.73 (m, 2 H), 4.41 (m, 1 H), 4.13 (m, 1 H), 3.76 - 3.93 (m, 2 H), 3.64 (m, 2 H), 3.46 (m, 1 H), 3.19 (s, 3 H), 2.83 (t, *J* = 5.75 Hz, 2 H), 2.41 - 2.52 (m, 1 H), 1.76 (m, 1 H), 1.43 - 1.57 (m, 2 H), 1.04 (t, *J* = 7.40 Hz, 3 H).

5

Compound 103_E1: (R*)-N-(2,4-difluoro-3-(trifluoromethyl)phenyl)-8-((S*)-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

*Pure but unknown diastereomer E1.

10 LCMS [M+1] : 502. ¹H NMR (400 MHz, CDCl₃) δ 8.13 - 8.28 (m, 1 H), 6.90 - 7.10 (m, 1 H), 6.69 (br s, 1 H), 4.63 - 4.80 (m, 2 H), 4.05 - 4.47 (m, 2 H), 3.86 (m, 2 H), 3.64 (m, 2 H), 3.39 - 3.50 (m, 1 H), 3.19 (s, 3 H), 2.85 (br t, *J* = 5.50 Hz, 2 H), 2.40 - 2.52 (m, 1 H), 1.44 - 1.55 (m, 2H), 1.04 (t, *J* = 7.40 Hz, 3 H).

15 Compound 104_E1: (R*)-8-((S*)-1-hydroxypropyl)-10-methyl-11-oxo-N-(3,4,5-trifluorophenyl)-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

*Pure but unknown diastereomer E1.

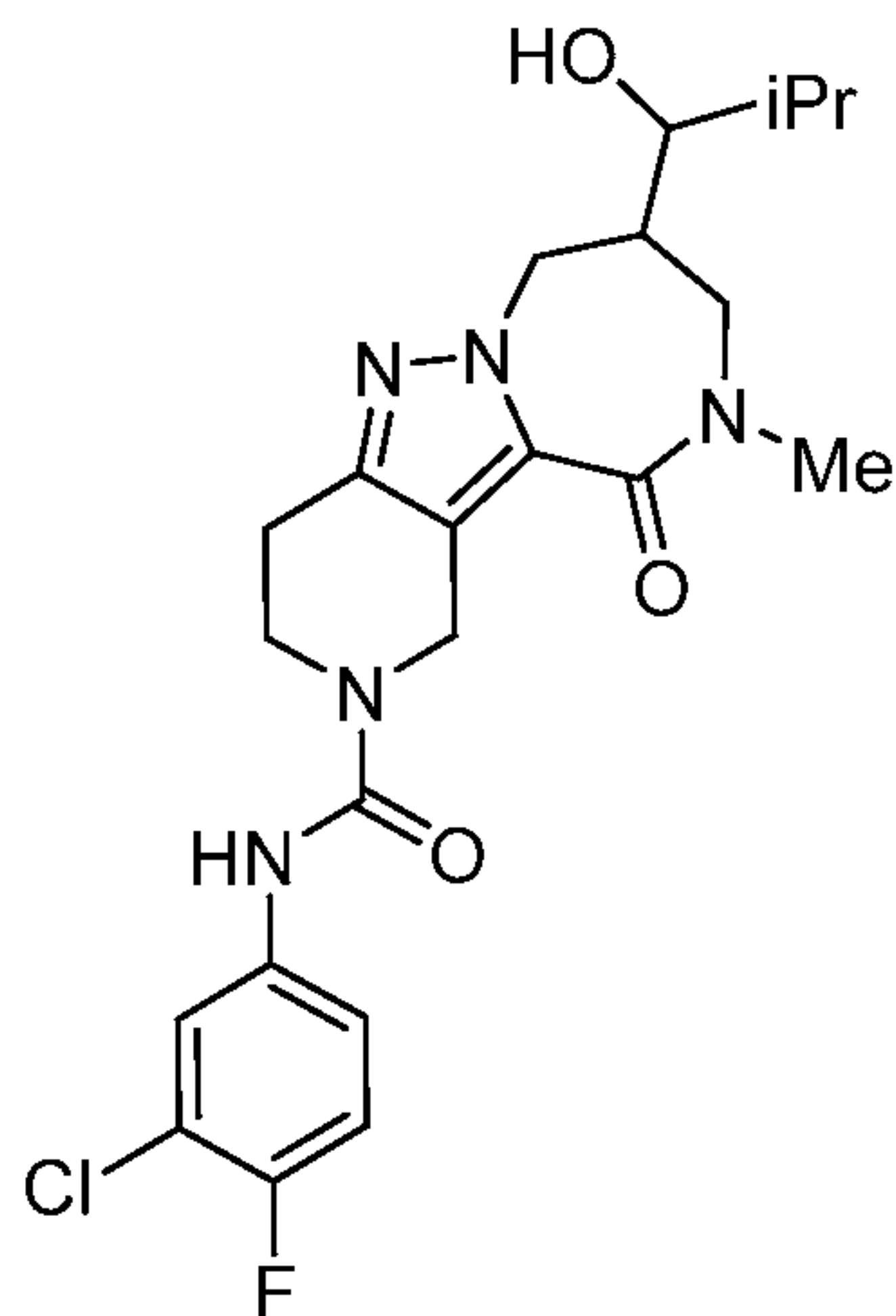
20 LCMS [M+1] : 452. ¹H NMR (400 MHz, CDCl₃) δ 7.14 (dd, *J* = 6.09, 9.60 Hz, 2 H), 6.74 - 6.86 (m, 1 H), 4.58 - 4.73 (m, 2H), 4.41 (m, 1 H), 4.13 (m, 1 H), 3.76 - 3.93 (m, 2 H), 3.64 (m, 2 H), 3.46 (m, 1 H), 3.19 (s, 3 H), 2.83 (br t, *J* = 5.65 Hz, 2 H), 2.40 - 2.53 (m, 1 H), 1.41 - 1.57 (m, 2 H), 1.04 (t, *J* = 7.40 Hz, 3 H).

25 Compound 105_E1: (R*)-8-((S*)-1-hydroxypropyl)-10-methyl-11-oxo-N-(2,3,4,5-tetrafluorophenyl)-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

*Pure but unknown diastereomer E1.

30 LCMS [M+1] : 470. ¹H NMR (400 MHz, CDCl₃) δ 7.82 (m, 1 H), 6.71 (br s, 1 H), 4.70 (d, *J* = 2.57 Hz, 2 H), 4.41 (m, 1 H), 4.13 (m, 1 H), 3.78 - 3.92 (m, 2 H), 3.60 - 3.67 (m, 2 H), 3.46 (m, 1 H), 3.19 (s, 3 H), 2.85 (t, *J* = 5.75 Hz, 2 H), 2.40 - 2.52 (m, 1 H), 1.42 - 1.57 (m, 2 H), 1.03 (t, *J* = 7.40 Hz, 3 H).

Compound 106: N-(3-chloro-4-fluoro-phenyl)-8-(1-hydroxybutyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide.



5 Step 1. tert-butyl 8-butanoyl-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a mixture of propylmagnesium bromide (2 M, 490.85 μ L, 2.00 *eq*) in THF (3.00 mL) was added tert-butyl 8-[methoxy(methyl)carbamoyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (Compound 096, Product from Step 2, 200.00 mg, 490.85 μ mol, 1.00 *eq*) in THF (3.00 mL) drop-wise at -10
10 $^{\circ}$ C under N_2 . The mixture was heated to 0 $^{\circ}$ C and stirred for 1 hours. LCMS showed the starting material/Desired product=1:2, then added bromo(propyl)magnesium (2 M, 1.23 mL, 5.00 *eq*) at 0 $^{\circ}$ C and stirred for 1 hours. TLC (Ethyl acetate) showed the reaction was completed and mainly the desired product was detected. The mixture was poured into 1N HCl (50 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (10 mL*2). The combined organic
15 phase was washed with brine (10 mL*2), dried with anhydrous Na_2SO_4 , filtered and concentrated in vacuum to afford the title compound (170.00 mg, 217.68 μ mol, 44.35% yield, 50% purity) as yellow solid. LCMS[M+1]: 391.

Step 2. tert-butyl 8-(1-hydroxybutyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a mixture of tert-butyl 8-butanoyl-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate
20 (170.00 mg, 435.36 μ mol, 1.00 *eq*) in MeOH (5.00 mL) was added $NaBH_4$ (32.94 mg, 870.72 μ mol, 2.00 *eq*) in one portion at -10 $^{\circ}$ C under N_2 . The mixture was stirred at -10 $^{\circ}$ C for 30 min, then heated to 25 $^{\circ}$ C and stirred for 1 hours. LCMS and TLC (Petroleum ether : Ethyl

acetate=0:1) showed the reaction was completed. The mixture was poured into water (10 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (10 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-TLC (ethyl acetate) to afford the title compound (75.00 mg, 185.36 μmol, 42.58% yield, 97% purity) as yellow solid. LCMS [M+1]: 393.

Step 3. 8-(1-hydroxybutyl)-10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one.

To a mixture of tert-butyl 8-(1-hydroxybutyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (75.00 mg, 191.09 μmol, 1.00 eq) in DCM (2.00 mL) was added TFA (1.54 g, 13.51 mmol, 1.00 mL, 70.68 eq) in one portion at 30°C under N₂. The mixture was stirred at 30 °C for 2 hours. TLC (Ethyl acetate) showed the reaction was completed. The mixture was concentrated in vacuum to afford the title compound (77.66 mg, 191.09 μmol, 100.00% yield, TFA) as yellow oil.

Step 4. N-(3-chloro-4-fluoro-phenyl)-8-(1-hydroxybutyl)-10-methyl-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide. To a mixture of 8-(1-hydroxybutyl)-10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido [2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (77.66 mg, 191.09 μmol, 1.00 eq, TFA) and phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (50.77 mg, 191.09 μmol, 1.00 eq) in DCM (6.00 mL) was added TEA (193.37 mg, 1.91 mmol, 264.89 μL, 10.00 eq) under N₂. The mixture was stirred at 25 °C for 10 hours. LCMS showed the reaction was completed. The residue was poured into water (10 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (10 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-HPLC(FA) to afford the title compound (49.00 mg, 105.62 μmol, 55.27% yield) as white solid.

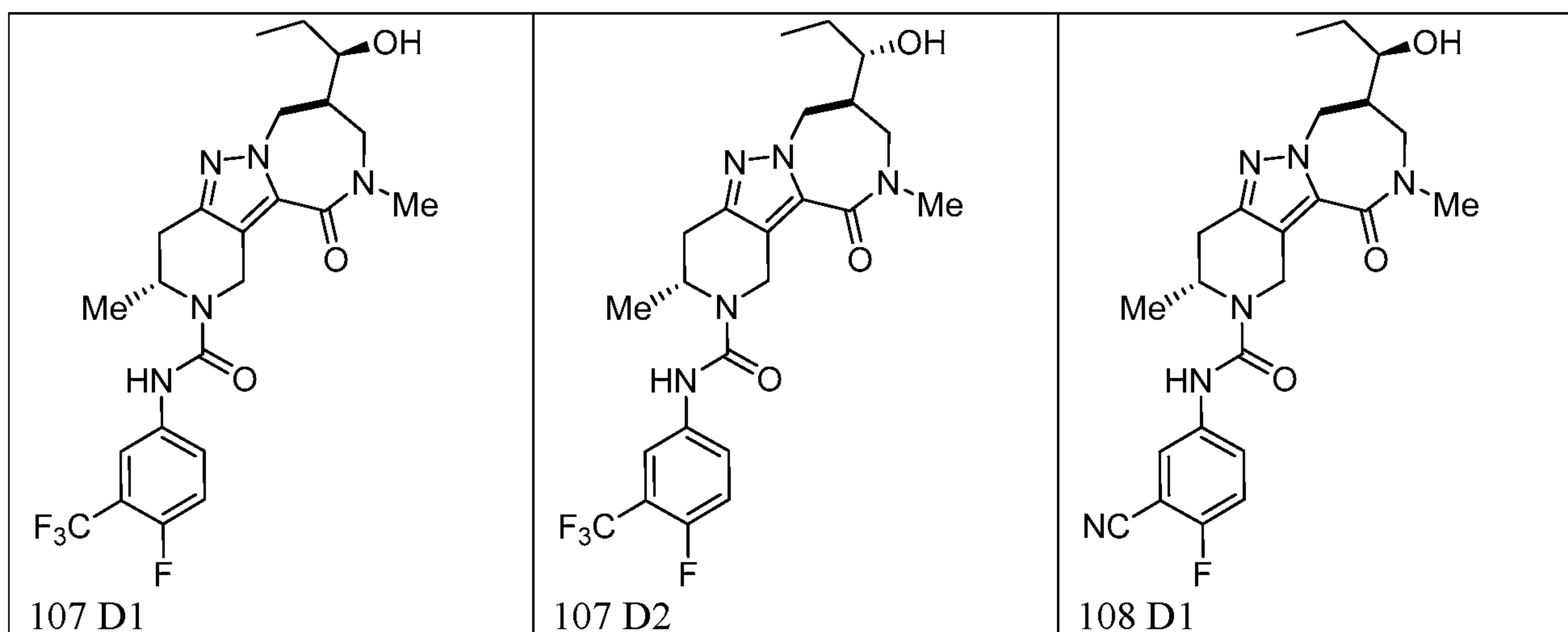
LCMS [M+1]: 464. ¹H NMR (400 MHz, CDCl₃) δ 7.60 (dd, *J*=2.32, 6.36 Hz, 1H), 7.22 (m, 1H), 7.01-7.11 (m, 1H), 6.73 (m, 1H), 4.54-4.78 (m, 3H), 4.27-4.48 (m, 1H), 4.26-4.50 (m, 1H), 4.09-4.22 (m, 1H), 3.81-3.95 (m, 2H), 3.58-3.79 (m, 2H), 3.43-3.51 (m, 1H), 3.35-3.42 (m, 1H), 3.20 (s, 3H), 2.85 (br t, *J*=5.01 Hz, 2H), 2.41-2.53 (m, 1H), 1.40-1.55 (m, 4H), 0.99 (q, *J*=7.05 Hz, 3H).

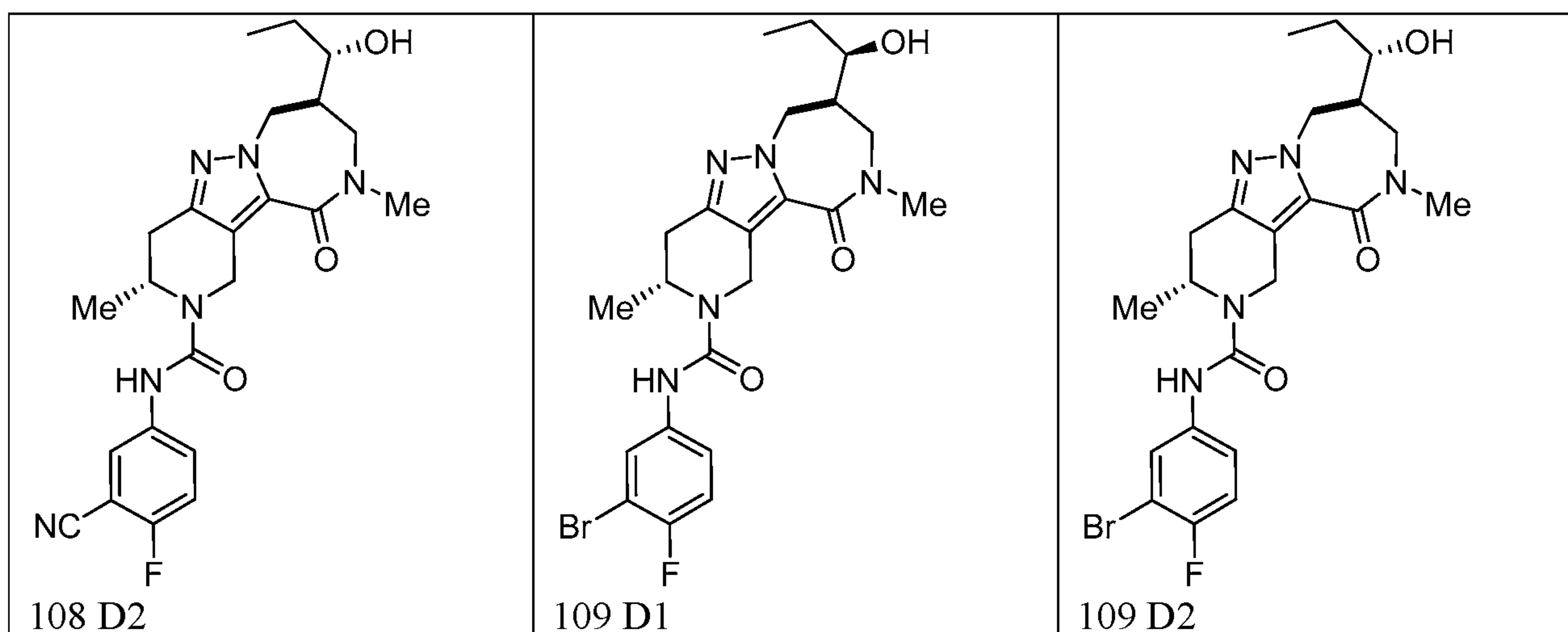
Compound 107_D1: (3R,8S*)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-((R)-1-hydroxypropyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

5 *Pure but unknown diastereomer D1.

To a solution of (3R,8S*)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-((R)-1-hydroxyallyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (Compound 122_D1, 45.00 mg, 90.82 μ mol, 1.00 *eq*) in MeOH (5.00 mL) was added Pd/C (5.00 mg, 10% purity) under N₂, the suspension was degassed under vacuum and purged with H₂ three times, the mixture was stirred under H₂ (15 psi) at 20 °C for 30 minutes. LCMS showed one main peak with desired MS was detected. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by prep-HPLC(FA) to afford the title compound (44.00 mg, 86.68 μ mol, 95.44% yield, 98% purity) as white solid. LCMS (M+1): 498. ¹H NMR (400 MHz, CDCl₃) δ = 7.69 (dd, *J* = 2.75, 6.05 Hz, 1 H), 7.55 - 7.62 (m, 1 H), 7.13 (t, *J* = 9.41 Hz, 1 H), 6.64 (s, 1 H), 5.15 (m, 1 H), 4.80 (m, 1 H), 4.39 - 4.54 (m, 2 H), 4.12 (m, 1 H), 3.62 - 3.71 (m, 2 H), 3.48 (m, 1 H), 3.20 (s, 3 H), 3.01 (m, 1 H), 2.67 (m, 1 H), 2.41 - 2.52 (m, 1 H), 1.45 - 1.57 (m, 2 H), 1.19 (d, *J* = 6.97 Hz, 3 H), 1.05 (t, *J* = 7.40 Hz, 3 H).

20 Compounds 107~109_D1&D2 were prepared in a manner analogous to Compound 107.





Compound 107_D2: (3R,8R*)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-((R)-1-hydroxypropyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

- 5 The title compound was prepared in a manner analogous to Compound 107_D1, using Compound 122_D2.

*Pure but unknown diastereomer D2.

LCMS (M+1): 498. ¹H NMR (400 MHz, CDCl₃) δ = 7.70 (dd, *J* = 2.75, 6.17 Hz, 1 H), 7.55 - 7.62 (m, 1 H), 7.13 (t, *J* = 9.35 Hz, 1 H), 6.66 (s, 1 H), 5.16 (br t, *J* = 6.36 Hz, 1 H), 4.84 (m, 1 H), 4.39 - 4.49 (m, 2 H), 4.16 (m, 1 H), 3.65 (m, 2 H), 3.48 (m, 1 H), 3.20 (s, 3 H), 3.03 (m, 1 H), 2.65 (m, 1 H), 2.45 - 2.55 (m, 1 H), 1.44 - 1.56 (m, 2 H), 1.18 (d, *J* = 6.85 Hz, 3 H), 1.04 (t, *J* = 7.40 Hz, 3 H).

15 Compound 108_D1: (3R,8S*)-N-(3-cyano-4-fluorophenyl)-8-((R)-1-hydroxypropyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

The title compound was prepared in a manner analogous to Compound 107_D1, using Compound 123_D1. *Pure but unknown diastereomer D1.

20 LCMS (M+1): 455. ¹H NMR (400 MHz, CDCl₃) δ = 7.79 (dd, *J* = 2.81, 5.38 Hz, 1 H), 7.59 (m, 1 H), 7.13 (t, *J* = 8.74 Hz, 1 H), 6.80 (s, 1 H), 5.14 (m, 1 H), 4.80 (m, 1 H), 4.39 - 4.52 (m, 2 H), 4.13 (m, 1 H), 3.61 - 3.70 (m, 2 H), 3.48 (m, 1 H), 3.20 (s, 3 H), 3.01 (dd, *J* = 5.81, 15.83 Hz, 1

H), 2.67 (m, 1 H), 2.43 - 2.53 (m, 1 H), 1.44 - 1.60 (m, 2 H), 1.19 (d, $J = 6.97$ Hz, 3 H), 1.04 (t, $J = 7.40$ Hz, 3 H).

5 Compound 108_D2: (3R,8R*)-N-(3-cyano-4-fluorophenyl)-8-((R)-1-hydroxypropyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

The title compound was prepared in a manner analogous to Compound 107_D1, using Compound 123_D2. *Pure but unknown diastereomer D2.

10 LCMS (M+1): 455. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.80$ (dd, $J = 2.81, 5.50$ Hz, 1 H), 7.59 (m, 1 H), 7.13 (t, $J = 8.74$ Hz, 1 H), 6.82 (s, 1 H), 5.09 - 5.20 (m, 1 H), 4.84 (m, 1 H), 4.39 - 4.48 (m, 2 H), 4.15 (m, 1 H), 3.65 (m, 2 H), 3.48 (m, 1 H), 3.20 (s, 3 H), 3.02 (m, 1 H), 2.65 (m, 1 H), 2.45 - 2.55 (m, 1 H), 1.43 - 1.60 (m, 2 H), 1.18 (d, $J = 6.85$ Hz, 3 H), 1.04 (t, $J = 7.40$ Hz, 3 H).

15 Compound 109_D1: (3R,8S*)-N-(3-bromo-4-fluorophenyl)-8-((R)-1-hydroxypropyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

The title compound was prepared in a manner analogous to Compound 107_D1, Compound 124_D1. *Pure but unknown diastereomer D1.

20 LCMS (M+1): 508/510. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.74$ (dd, $J = 2.70, 6.09$ Hz, 1 H), 7.22 - 7.27 (m, 1 H), 7.00 - 7.07 (m, 1 H), 6.55 (s, 1 H), 5.08 - 5.19 (m, 1 H), 4.78 (m, 1 H), 4.39 - 4.51 (m, 2 H), 4.11 (m, 1 H), 3.61 - 3.71 (m, 2 H), 3.48 (m, 1 H), 3.20 (s, 3 H), 3.01 (m, 1 H), 2.66 (m, 1 H), 2.41 - 2.52 (m, 1 H), 1.42 - 1.57 (m, 2 H), 1.18 (d, $J = 6.90$ Hz, 3 H), 1.05 (t, $J = 7.40$ Hz, 3 H).

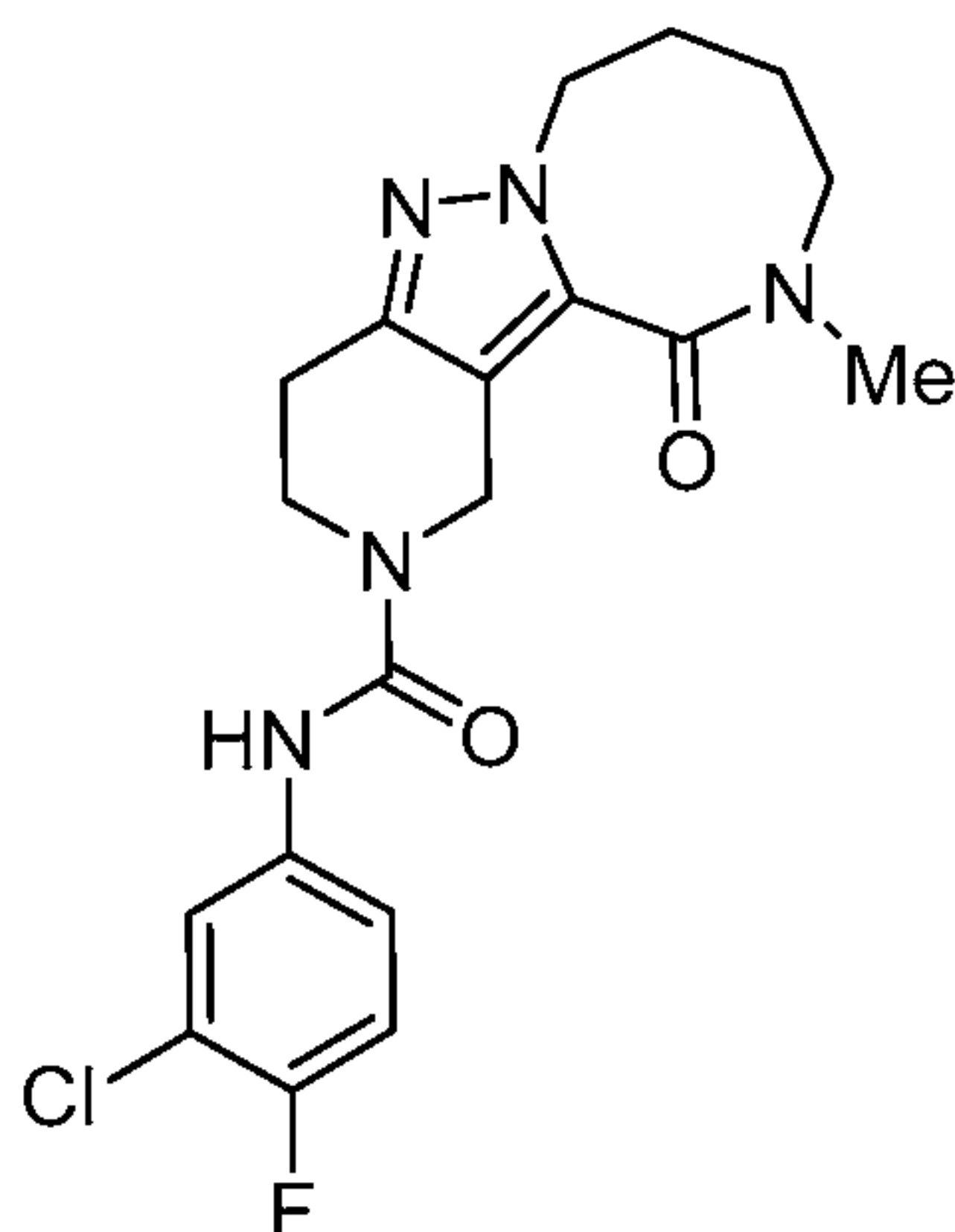
25 Compound 109_D2: (3R,8R*)-N-(3-bromo-4-fluorophenyl)-8-((R)-1-hydroxypropyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

The title compound was prepared in a manner analogous to Compound 107_D1, Compound 124_D2. *Pure but unknown diastereomer D2.

30 LCMS (M+1): 508/510. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.75$ (dd, $J = 2.70, 6.09$ Hz, 1 H), 7.25 (m, 1 H), 7.04 (t, $J = 8.53$ Hz, 1 H), 6.61 (s, 1 H), 5.15 (m, 1 H), 4.82 (d, $J = 15.43$ Hz, 1 H),

4.38 - 4.48 (m, 2 H), 4.15 (m, 1 H), 3.64 (m, 2 H), 3.47 (m, 1 H), 3.19 (s, 3 H), 3.02 (m, 1 H), 2.64 (m, 1 H), 2.45 - 2.55 (m, 1 H), 1.44 - 1.59 (m, 2 H), 1.17 (d, $J = 6.90$ Hz, 3 H), 1.04 (t, $J = 7.40$ Hz, 3 H).

- 5 Compound 110: N-(3-chloro-4-fluorophenyl)-11-methyl-12-oxo-3,4,7,8,9,10,11,12-octahydropyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazocine-2(1H)-carboxamide



Step 1. 11-methyl-1,2,3,4,7,8,9,10-octahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazocin- 12-one.

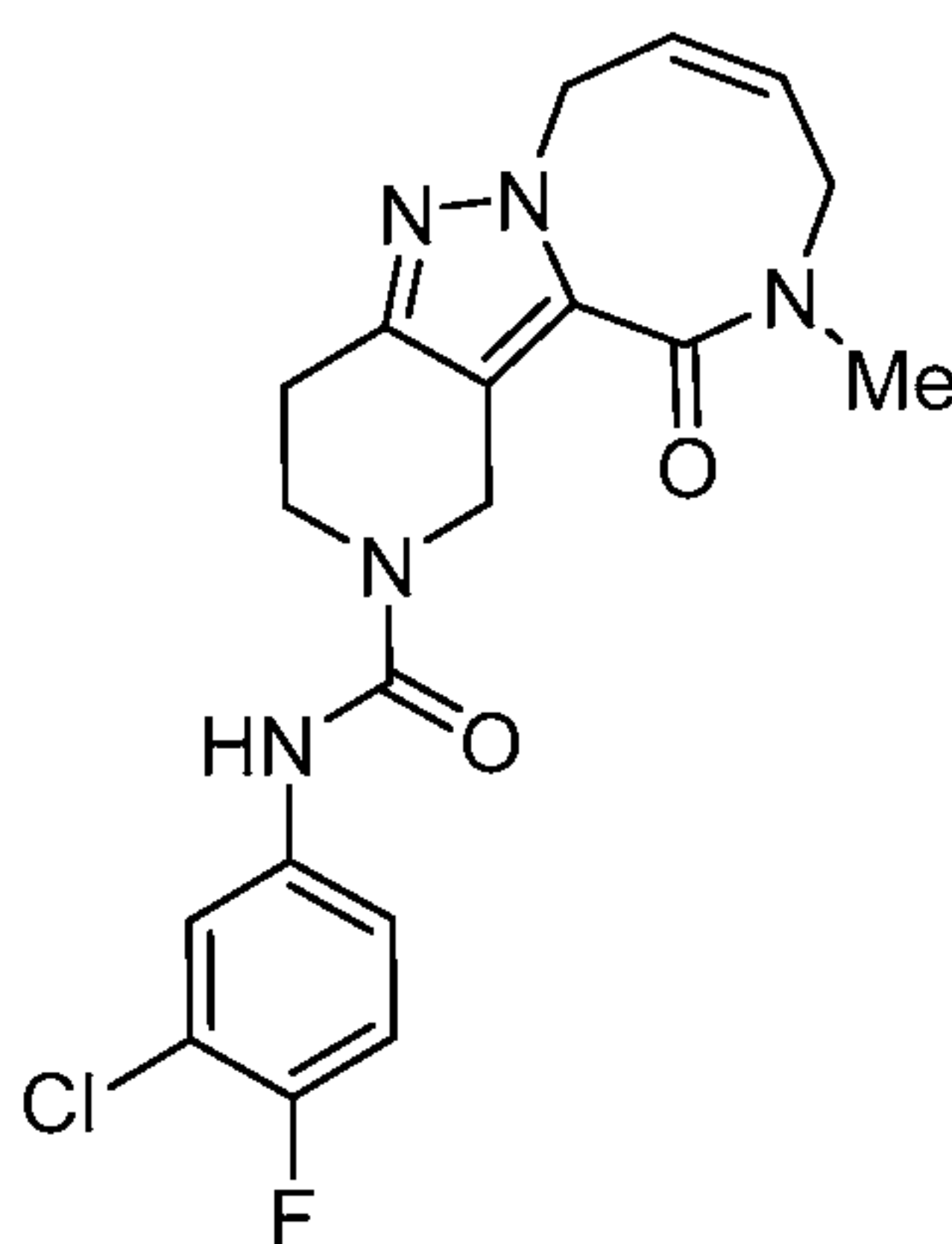
To a solution of tert-butyl 11-methyl-12-oxo-3,4,7,8,9,10-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazocine-2-carboxylate (Intermediate 23, 61.00 mg, 182.41 μ mol, 1.00 *eq*) in DCM (5.00 mL) was added TFA (308.00 mg, 2.70 mmol, 200.00 μ L, 14.81 *eq*), then the mixture was stirring at 25 °C for 1 h. TLC (PE: EtOAc = 1:3) showed that compound 7 consumed completely and one new spot formed. The mixture was concentrated in vacuo to afford the title compound (65.00 mg, crude, TFA) as yellow oil, without further purification and directly used in the next step.

Step 2. N-(3-chloro-4-fluorophenyl)-11-methyl-12-oxo-3,4,7,8,9,10,11,12-octahydropyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazocine-2(1H)-carboxamide. To a solution of 11-methyl-1,2,3,4,7,8,9,10-octahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazocin-12-one (65.00 mg, 186.61 μ mol, 1.00 *eq*, TFA) and phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (54.53 mg, 205.27 μ mol, 1.10 *eq*) in DCM (3.00 mL) was added TEA (151.06 mg, 1.49 mmol, 206.94 μ L, 8.00 *eq*), then the mixture was stirring at 25 °C for 16 h. LCMS indicated that 11-methyl-1,2,3,4,7,8,9,10-octahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazocin- 12-one was consumed completely and desired product was detected. The mixture was concentrated in vacuo. The residue was purified by prep-HPLC (FA) to afford the title compound (33.32 mg, 81.61 μ mol,

43.73% yield, 99.4% purity) as a yellow solid. LCMS: 406[M+1]. ¹H NMR (400 MHz, CDCl₃) δ = 7.58 (dd, J = 2.69, 6.60 Hz, 1 H), 7.16 - 7.22 (m, 1 H), 7.02 - 7.09 (m, 1 H), 6.55 (s, 1 H), 4.60 (s, 2 H), 4.29 (br s, 2 H), 3.85 (t, J = 5.75 Hz, 2 H), 3.31 (br d, J = 8.80 Hz, 2 H), 3.14 (s, 3 H), 2.84 (t, J = 5.81 Hz, 2 H), 1.97 (br s, 2 H), 1.86 (br s, 2 H).

5

Compound 111: (Z)-N-(3-chloro-4-fluorophenyl)-11-methyl-12-oxo-3,4,7,10,11,12-hexahydropyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazocine-2(1H)-carboxamide.



Step 1. (8Z)-11-methyl-1,2,3,4,7,10-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazocin-12-one.

10 To a solution of tert-butyl (8Z)-11-methyl-12-oxo-3,4,7,10-tetrahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazocine-2-carboxylate (Intermediate 22, 50.00 mg, 150.42 μ mol, 1.00 *eq*) in DCM (3.00 mL) was added TFA (329.99 mg, 2.89 mmol, 214.28 μ L, 19.24 *eq*), then the mixture was stirring at 25 °C for 1 h. TLC (PE: EtOAc = 1:3) showed that the reactant **6** consumed completely and one new spot formed. The mixture was concentrated in vacuum. The
15 title compound (55.00 mg, crude, TFA) was obtained as yellow oil.

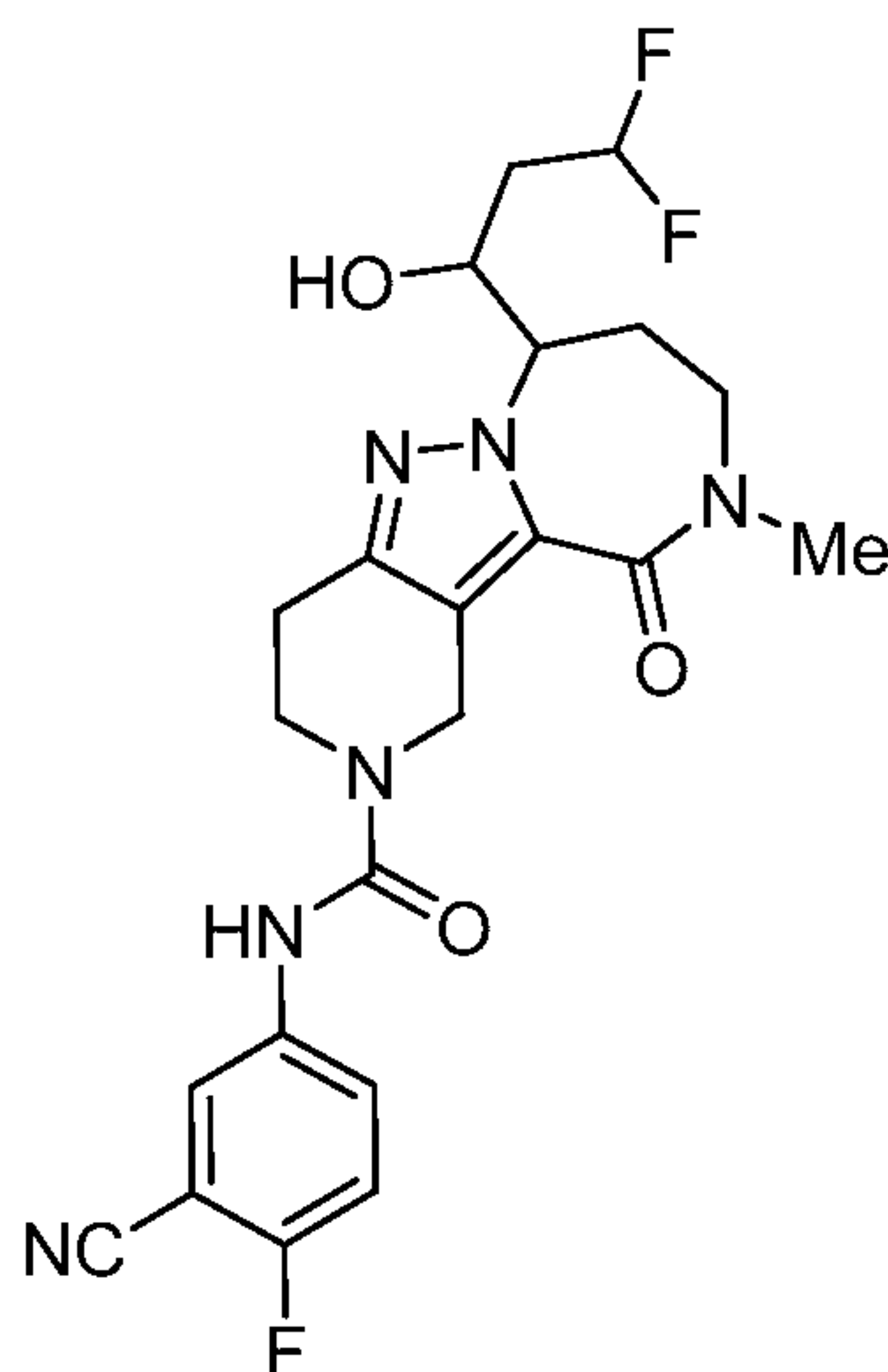
Step 2. (Z)-N-(3-chloro-4-fluorophenyl)-11-methyl-12-oxo-3,4,7,10,11,12-

hexahydropyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazocine-2(1H)-carboxamide. To a solution of (8Z)-11-methyl-1,2,3,4,7,10-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazocin-12-one (55.00 mg, 158.82 μ mol, 1.00 *eq*, TFA) and phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (46.41 mg, 174.70 μ mol, 1.10 *eq*) in DCM (3.00 mL) was added TEA (128.57 mg, 1.27 mmol, 176.12 μ L, 8.00 *eq*), then the mixture was stirring at 25 °C for 16 h. LCMS indicated that (8Z)-11-methyl-1,2,3,4,7,10-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazocin-12-one was consumed completely and desired product was detected. The mixture was concentrated in vacuo. The residue was purified by prep-HPLC(FA) to afford the title compound (25.57 mg, 62.68 μ mol,
20

39.47% yield, 99% purity) as yellow solid. LCMS: 404[M+1]. ^1H NMR (400 MHz, CDCl_3) δ = 7.57 (dd, J = 2.63, 6.54 Hz, 1 H), 7.16 - 7.21 (m, 1 H), 7.03 - 7.09 (m, 1 H), 6.54 (s, 1 H), 5.91 - 6.05 (m, 2 H), 4.89 (d, J = 3.79 Hz, 2 H), 4.61 (s, 2 H), 3.85 (t, J = 5.87 Hz, 2 H), 3.80 (br d, J = 5.38 Hz, 2 H), 3.12 (s, 3 H), 2.85 (t, J = 5.81 Hz, 2 H).

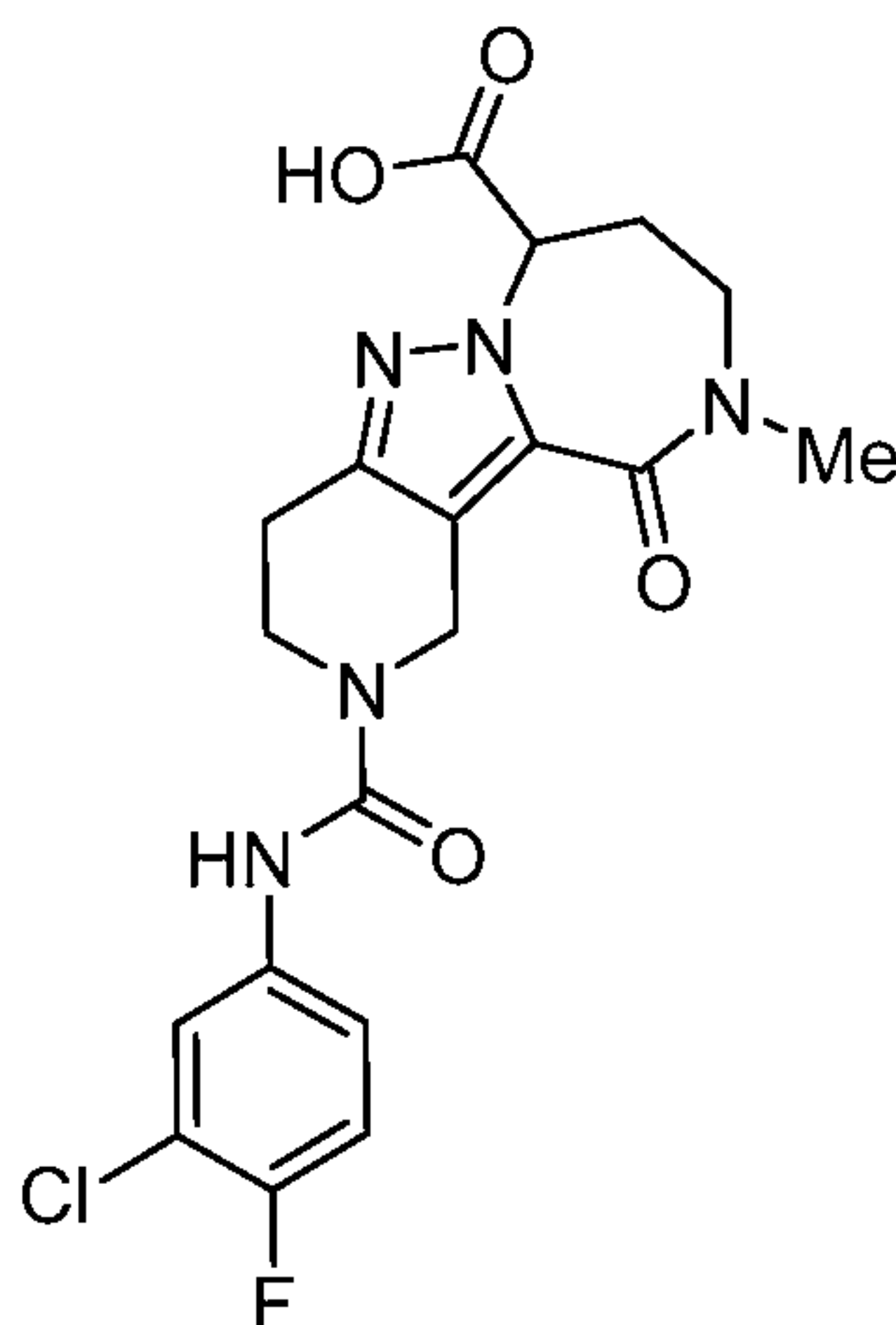
5

Compound 112: N-(3-cyano-4-fluorophenyl)-7-(3,3-difluoro-1-hydroxypropyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



- 10 The title compound was prepared in a manner analogous to Compound 116, using phenyl (3-cyano-4-fluorophenyl)carbamate in Step 5. LCMS: 477[M+1]. ^1H NMR (400MHz, CDCl_3) δ = 7.79 (dd, J = 2.7, 5.4 Hz, 1 H), 7.60 (br d, J = 9.8 Hz, 1 H), 7.15 (t, J = 8.6 Hz, 1 H), 6.79 (brs, 1 H), 5.92 - 6.28 (m, 1 H), 4.58 - 4.80 (m, 3 H), 4.22 - 4.49 (m, 2 H), 4.13 (brs, 1H), 3.84 - 3.95 (m, 3 H), 3.63 (m, 1 H), 3.29 - 3.50 (m, 2 H), 3.21 (d, J = 2.6 Hz, 3 H), 2.86 (br t, J = 5.5 Hz, 2
- 15 H), 2.70 (brs, 1 H), 2.56 (brd, J = 6.2 Hz, 1 H), 2.25 (brs, 1 H), 2.00 - 2.13 (m, 2 H).

Compound 113: 2-((3-chloro-4-fluorophenyl)carbamoyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-7-carboxylic acid.



Step 1. methyl 2-((3-chloro-4-fluorophenyl)carbamoyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-7-carboxylate and 2-((3-chloro-4-fluorophenyl)carbamoyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-

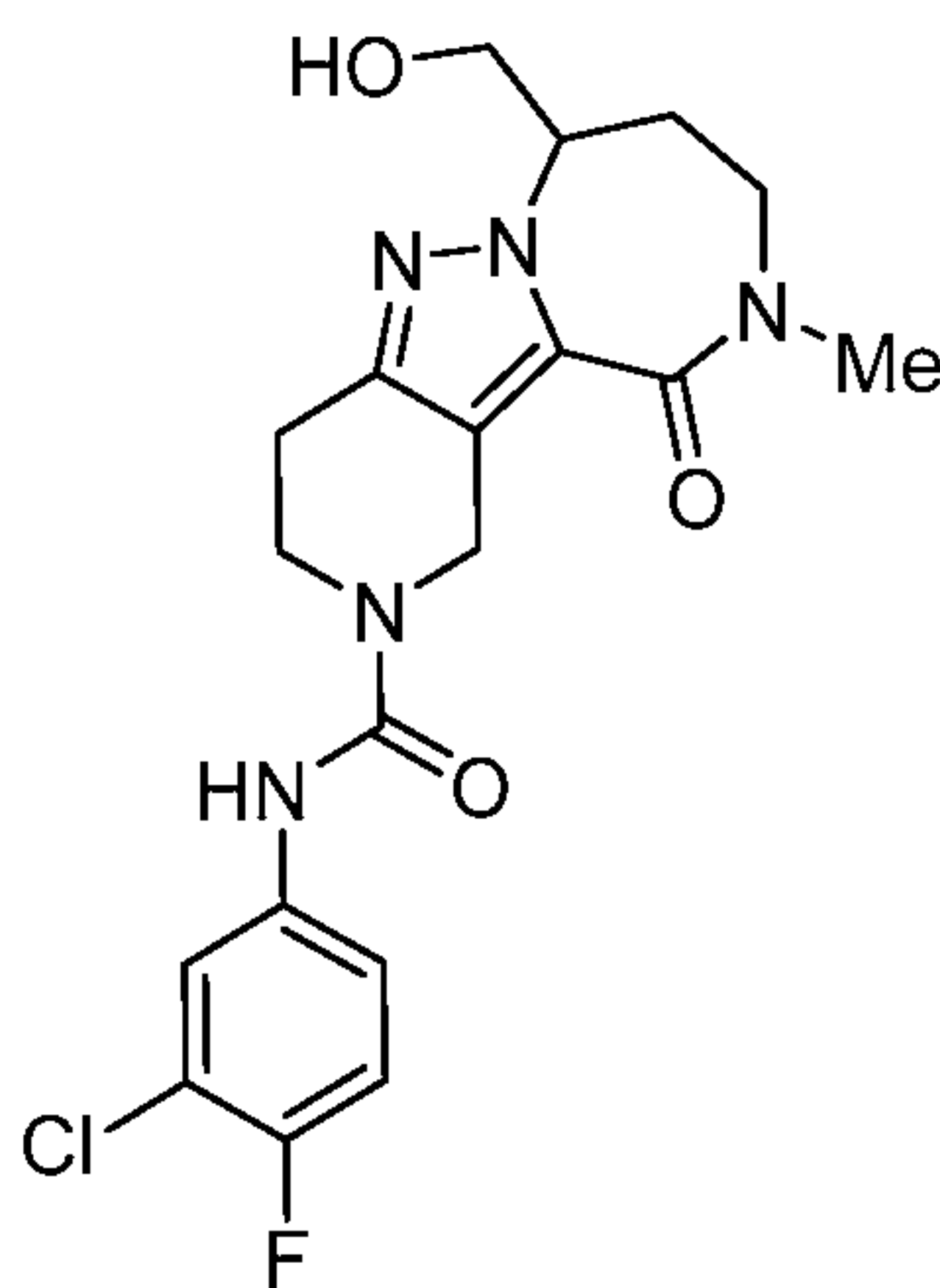
5 pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-7-carboxylic acid. To a solution of 2-(tert-butoxycarbonyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-7-carboxylic acid (Intermediate 26, 116.00 mg) in MeOH (2.00 mL) was added HCl/MeOH (4 M, 2.00 mL). The mixture was stirred at 20 °C for 2 hr. TLC (DCM:MeOH = 10:1) showed one main spot appeared. The mixture was concentrated
10 in vacuum a residue (96.00 mg, crude, HCl) as brown oil.

Step 2. 2-((3-chloro-4-fluorophenyl)carbamoyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-7-carboxylic acid. To a solution of methyl

above oil (95.00 mg, 301.81 µmol, 1.00 *eq*, HCl) and phenyl N-(3-chloro-4-fluorophenyl)carbamate (80.18 mg, 301.81 µmol, 1.00 *eq*) in DCM (3.00 mL) was added TEA (152.70
15 mg, 1.51 mmol, 209.18 µL, 5.00 *eq*). The mixture was stirred at 20 °C for 5 hr. Several peaks showed on LCMS, 24% 2-((3-chloro-4-fluorophenyl)carbamoyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-7-carboxylic acid and 22% methyl 2-((3-chloro-4-fluorophenyl)carbamoyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-7-carboxylate were detected. The
20 mixture was extracted with EtOAc (10 mL*2) and H₂O(10 mL). The combined organic layer was washed 1N HCl (10 mL), dried over Na₂SO₄, filtrated and concentrated in vacuum. The residue was purified by prep-TLC (PE:EtOAc = 0:1) and prep-HPLC(FA) to afford methyl 2-((3-chloro-4-fluorophenyl)carbamoyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-

pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-7-carboxylate (40.00 mg, 88.92 μ mol, 29.46% yield) as colorless oil and 2-((3-chloro-4-fluorophenyl)carbamoyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-7-carboxylic acid (9.00 mg, 19.25 μ mol, 6.38% yield, 93.2% purity) as white solid. LCMS: 436[M+1]. ^1H NMR (400 MHz, METHANOL- d_4) δ = 7.61 (dd, J = 2.63, 6.66 Hz, 1 H), 7.26 - 7.38 (m, 1 H), 7.06 - 7.20 (m, 1 H), 5.32 (br d, J = 9.54 Hz, 1 H), 4.65 - 4.73 (m, 1 H), 4.54 - 4.80 (m, 1 H), 4.69 (brs, 3 H), 3.71 - 3.97 (m, 2 H), 3.54 - 3.65 (m, 1 H), 3.52 - 3.65 (m, 1 H), 3.37 - 3.52 (m, 1 H), 3.36 - 3.52 (m, 1 H), 3.66 (s, 1 H), 3.36 - 3.53 (m, 1 H), 3.34 - 3.70 (m, 1 H), 3.15 (brs, 1 H), 3.08 (s, 2 H), 2.98 - 3.00 (m, 1 H), 2.90 - 2.99 (m, 1 H), 2.89 - 2.99 (m, 1 H), 2.89 - 2.99 (m, 1 H), 2.89 - 2.99 (m, 1 H), 2.88 - 3.00 (m, 1 H), 2.74 - 2.86 (m, 2 H), 2.41 - 2.60 (m, 1 H), 2.41 - 2.60 (m, 1 H).

Compound 114: N-(3-chloro-4-fluorophenyl)-7-(hydroxymethyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



15

Step 1. methyl 10-methyl-11-oxo-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-7-carboxylate. To a solution of 2-(tert-butoxycarbonyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-7-carboxylic acid (Intermediate 26, 370.00 mg, 1.02 mmol, 1.00 *eq*) in MeOH (10.00 mL) was added HCl/MeOH (4 M, 10.00 mL, 39.22 *eq*). The mixture was heated to 45 $^{\circ}\text{C}$ for 1 hr. TLC (DCM:MeOH = 10:1) showed the starting material consumed and one main spot appeared. The mixture was concentrated in vacuum to afford methyl 10-methyl-11-oxo-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-7-carboxylate (340.00 mg, crude, HCl) as brown solid.

20

Step 2. 2-tert-butyl 7-methyl 10-methyl-11-oxo-1,3,4,7,8,9-hexahydro pyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-2,7-dicarboxylate. To a solution of methyl 10-methyl-11-oxo-2,3,4,7,8,9-hexahydro-1H-pyrido [2,3]pyra-zolo[2,4-c][1,4]diazepine-7-carboxylate (240.00 mg, 762.46 μ mol, 1.00 *eq*, HCl) in DCM (10.00 mL) was added TEA (385.77 mg, 3.81 mmol, 528.45 μ L, 5.00 *eq*) followed by Boc₂O (332.81 mg, 1.52 mmol, 350.33 μ L, 2.00 *eq*). The mixture was heated to 20 °C for 16 hr. LCMS showed one main peak with desired Ms detected. The mixture was extracted with EtOAc (20 mL*3) and H₂O (10 mL). The combined organic layer was washed with 1N HCl (10 mL), dried over Na₂SO₄, filtrated and concentrated in vacuum. The residue was purified by column chromatography (PE:EtOAc = 70%~100%) to afford the title compound (160.00 mg, 422.81 μ mol, 55.45% yield) as colorless oil.

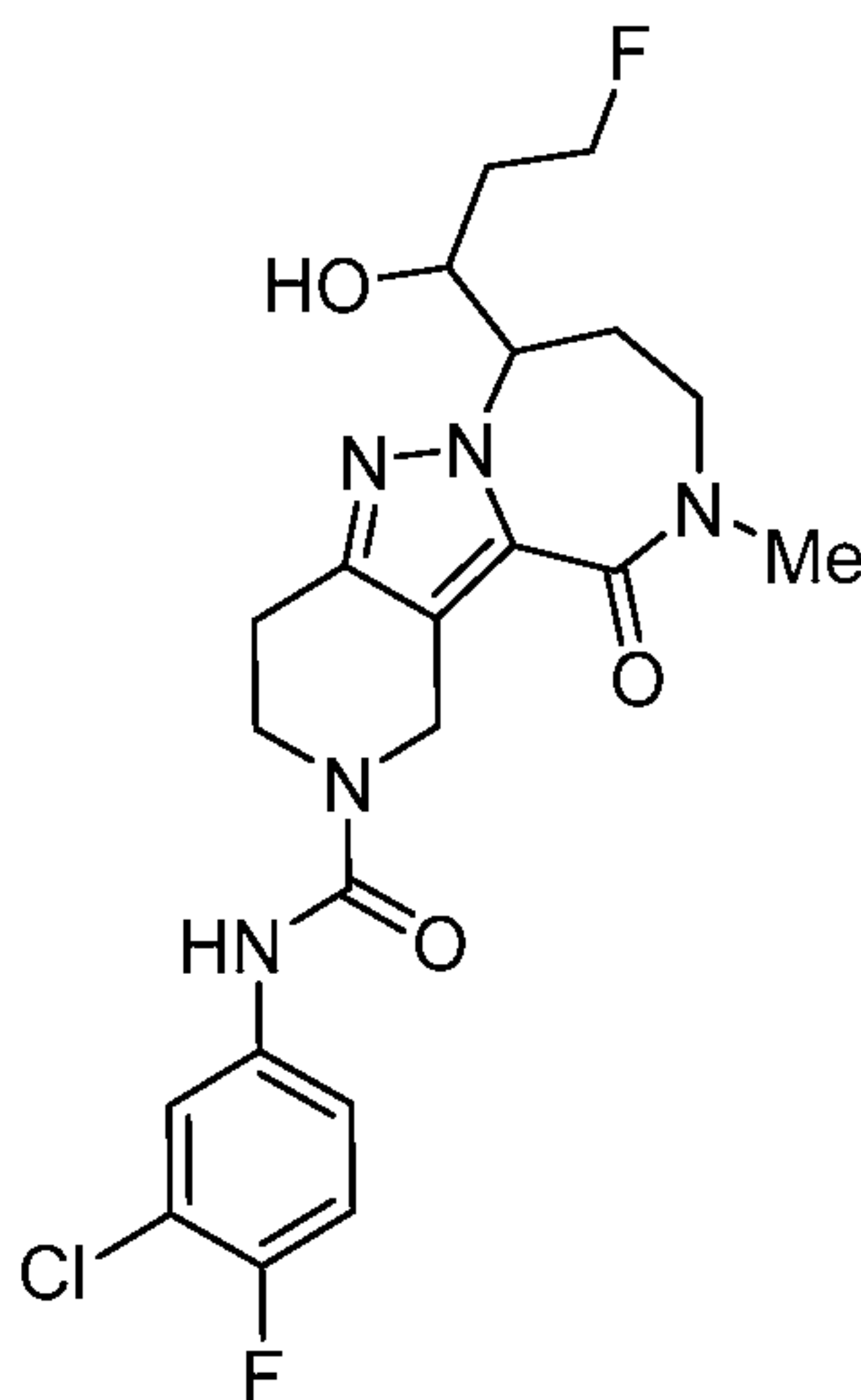
Step 3. tert-butyl 7-(hydroxymethyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-2-carboxylate. To a solution of 2-tert-butyl 7-methyl 10-methyl-11-oxo-1,3,4,7,8,9-hexahydro pyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-2,7-dicarboxylate (60.00 mg, 158.55 μ mol, 1.00 *eq*) in THF (3.00 mL) was added LiBH₄ (13.81 mg, 634.20 μ mol, 4.00 *eq*) at 0 °C. The mixture was stirred at 25 °C for 1 hr. TLC (PE:EtOAc = 0:1) showed the starting material consumed and three new spots formed. LCMS showed one main peak with desired Ms detected. The mixture was quenched with saturated NH₄Cl (20 mL) and extracted with EtOAc(20 mL*3). The combined organic layer was dried over Na₂SO₄, filtrated and concentrated in vacuum to afford the title compound (45.00 mg, crude) as colorless oil.

Step 5. N-(3-chloro-4-fluorophenyl)-7-(hydroxymethyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. To a solution of tert-butyl 7-(hydroxymethyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-c][1,4]diazepine-2-carboxylate (60.00 mg, 171.23 μ mol, 1.00 *eq*) in DCM (3.00 mL) was added TFA (4.62 g, 40.52 mmol, 3.00 mL, 236.64 *eq*). The mixture was stirred at 25 °C for 1 hr. TLC (PE:EtOAc = 0:1) showed the starting material consumed. The mixture was concentrated in vacuum to get 7-(hydroxymethyl)-10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-c][1,4]diazepin-11-one (63.00 mg, crude, TFA) as brown oil.

Step 6. N-(3-chloro-4-fluorophenyl)-7-(hydroxymethyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. To a solution of 7-(hydroxymethyl)-10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido [2,3]pyrazolo[2,4-c][1,4]diazepin-

11-one (62.00 mg, 170.18 μmol , 1.00 *eq*, TFA) and phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (45.21 mg, 170.18 μmol , 1.00 *eq*) in DCM (3.00 mL) was added TEA (86.10 mg, 850.90 μmol , 117.95 μL , 5.00 *eq*). The mixture was stirred at 20 °C for 5 hr. TLC (DCM:MeOH = 10:1) showed one main spot appeared. The mixture was extracted with EtOAc (10 mL*2) and H₂O (10 mL). The combined organic layer was washed 1N HCl (10 mL), dried over Na₂SO₄, filtrated and concentrated in vacuum. The residue was purified by prep-TLC (DCM:MeOH = 10:1) to get 40 mg product, which was combined with another batch (EW619-1536, 15 mg with 80% purity) to further purify by prep-HPLC(FA) to afford the title compound (40.00 mg, 65.51 μmol , 38.50% yield, 98.7% purity) as colorless oil. LCMS: 422[M+1]. ¹H NMR (400 MHz, METHANOL-d₄) δ = 7.60 (dd, *J* = 2.57, 6.60 Hz, 1H), 7.27 - 7.35 (m, 1 H), 7.11 - 7.19 (m, 1 H), 4.59 - 4.73 (m, 3 H), 3.84 - 3.94 (m, 1 H), 3.72 - 3.83 (m, 3 H), 3.53 - 3.63 (m, 1 H), 3.36 - 3.46 (m, 1 H), 3.15 (s, 3 H), 2.83 (t, *J* = 5.75 Hz, 2 H), 2.40 - 2.52 (m, 1 H), 2.23 - 2.35 (m, 1 H).

15 Compound 115: N-(3-chloro-4-fluoro-phenyl)-8-(3-fluoro-1-hydroxy-propyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide.



20 Step 1. tert-butyl 8-(1-benzyloxy-3-fluoro-propyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of tert-butyl 8-(1-benzyloxy-3-hydroxy-propyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (Intermediate 28, 90.00 mg,

185.72 μ mol, 1.00 *eq*) in THF (1.00 mL) was added DAST (119.75 mg, 742.88 μ mol, 98.16 μ L, 4.00 *eq*) at -40 °C. The mixture was stirred at -40 °C for 1 hr. TLC (PE:EtOAc = 1:2) showed the starting material consumed and one main spot appeared. The mixture was extracted with DCM (10 mL*2) and H₂O (10 mL). The combined organic layer was washed saturated NaHCO₃ (10 mL), dried over Na₂SO₄, filtrated and concentrated in vacuum. The residue was purified by prep-TLC (PE:EtOAc = 1:2) to afford the title compound (55.00 mg, 91.56 μ mol, 49.30% yield, 81% purity) as yellow oil.

Step 2. tert-butyl 8-(3-fluoro-1-hydroxy-propyl)-10-methyl-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of tert-butyl 8-

(1-benzyloxy-3-fluoro-propyl)-10-methyl-11-oxo- 1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (55.00 mg, 113.03 μ mol, 1.00 *eq*) in MeOH (10.00 mL) was added Pd/C (50.00 mg) under N₂. The suspension was degassed

under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (50 Psi) at 30 °C for 32 hours. LCMS indicated that 70% of the starting material still remained and 13% of

desired product was detected. Then the mixture was filtered and the filtrate was added Pd/C

(50.00 mg) under N₂. The suspension was degassed under vacuum and purged with H₂ several

times. The mixture was stirred under H₂ (50 Psi) at 30 °C for 48 hours. LCMS indicated that

8% of the starting material still remained and 70% of desired product was detected. The mixture was filtered and concentrated in vacuum. The title compound (45.00 mg, crude) was obtained as

colorless oil.

Step 3. 8-(3-fluoro-1-hydroxy-propyl)-10-methyl- 2,3,4,7,8,9-hexahydro-1H-

pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one. To a solution of tert-butyl 8-(3-fluoro-1-

hydroxy-propyl)-10-methyl-11-oxo-1,3,4, 7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-

b][1,4]diazepine-2-carboxylate (45.00 mg, 113.50 μ mol, 1.00 *eq*) in DCM (2.00 mL) was added

TFA (308.00 mg, 2.70 mmol, 200.00 μ L, 23.80 *eq*) with stirring at 20 °C for 1 h. TLC (PE:

EtOAc = 0:1) showed that the reactant **9** consumed completely and one main new spot formed.

The mixture was concentrated in vacuum. The title compound (47.00 mg, crude, TFA) was obtained as yellow oil and used in the next step.

Step 4. N-(3-chloro-4-fluoro-phenyl)-8-(3-fluoro-1-hydroxy-propyl)-10-methyl-11-oxo-

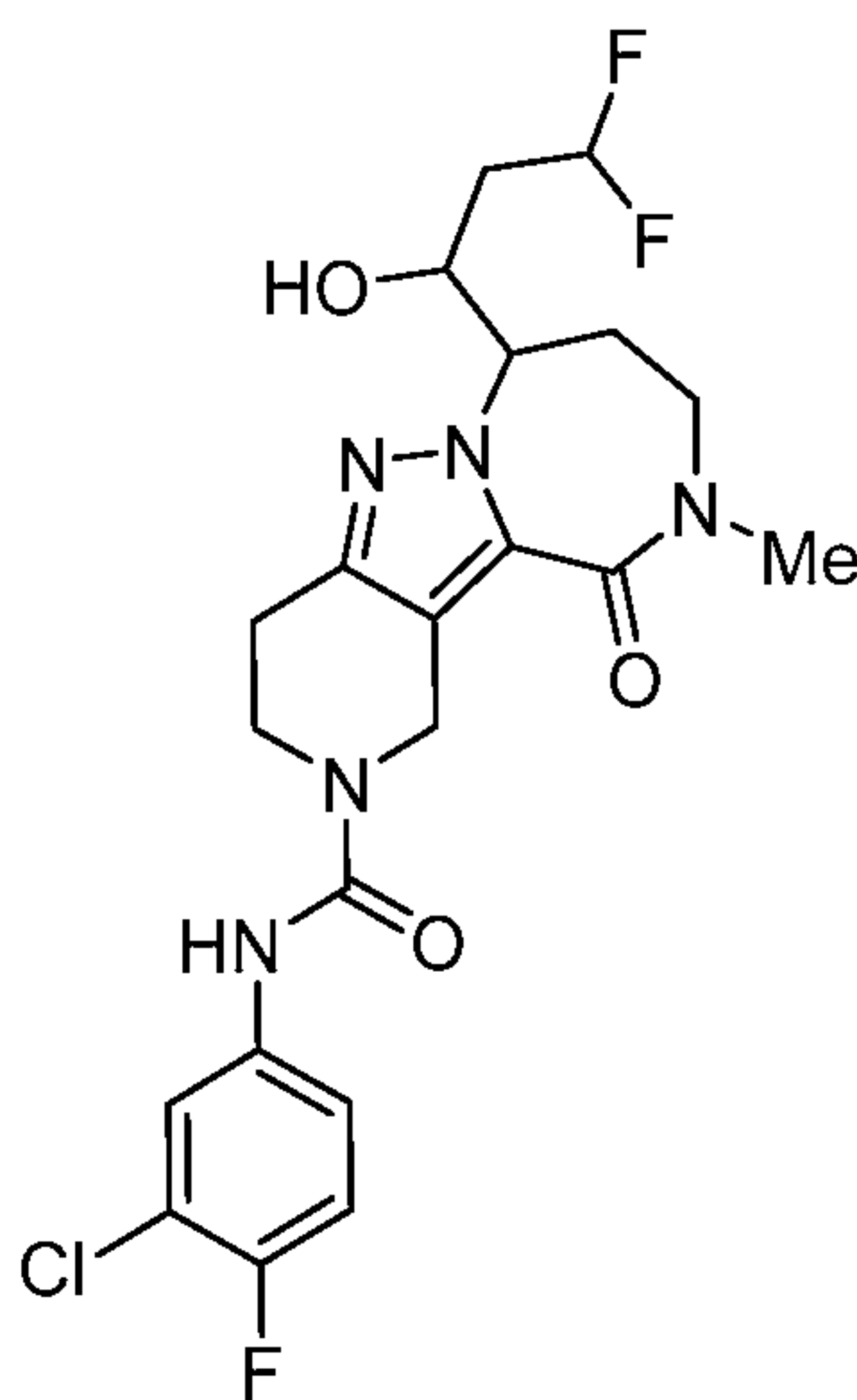
1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide. To a solution of

8-(3-fluoro-1-hydroxy-propyl)-10-methyl-2,3,4,7,8,9-hexahydro- 1H-pyrido[2,3]pyrazolo[2,4-

b][1,4]diazepin-11-one (47.00 mg, 114.53 μmol , 1.00 *eq*, TFA) and TEA (69.54 mg, 687.18 μmol , 95.26 μL , 6.00 *eq*) in DCM (2.00 mL) was added phenyl N-(3-chloro-4-fluorophenyl)carbamate (30.43 mg, 114.53 μmol , 1.00 *eq*) with stirring at 20 °C for 16 h. LCMS indicated that the starting material was consumed completely and desired product was detected.

5 The mixture was concentrated in vacuum. The resulting residue was purified by prep-HPLC (FA) to afford the title compound (10.00 mg, 21.16 μmol , 18.47% yield, 99% purity) as white solid. LCMS: 468[M+1]. ^1H NMR (400 MHz, CDCl_3) δ = 7.59 (dd, J = 2.64, 6.53 Hz, 1 H), 7.15 - 7.22 (m, 1 H), 7.03 - 7.09 (m, 1 H), 6.56 (s, 1 H), 4.71 - 4.84 (m, 1 H), 4.61 - 4.71 (m, 3 H), 4.39 - 4.61 (m, 1 H), 4.15 - 4.39 (m, 1 H), 3.99 (br s, 1 H), 3.79 - 4.03 (m, 3 H), 3.30 - 3.68
10 (m, 2 H), 3.19 (d, J = 4.02 Hz, 3 H), 2.84 (t, J = 5.65 Hz, 2 H), 2.50 - 2.61 (m, 1 H), 2.16 - 2.43 (m, 1 H), 1.78 - 2.00 (m, 2 H).

Compound 116: N-(3-chloro-4-fluorophenyl)-8-(3,3-difluoro-1-hydroxy-propyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide.



15

Step 1. tert-butyl 8-(1-benzyloxy-3-oxo-propyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of tert-butyl 8-(1-benzyloxy-3-hydroxy-propyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (Intermediate 28, 200.00 mg, 412.72 μmol , 1.00 *eq*) in DCM (4.00 mL) was added Dess-Martin (525.15 mg, 1.24 mmol, 383.32 μL , 3.00 *eq*) at 0 °C. The mixture was stirred at 25 °C for 1 hr. TLC (PE:EtOAc= 0:1) showed the starting material consumed and one main new spot formed. The reaction mixture

20

was diluted with DCM (50 mL) and filtrated. The filtrate was concentrated in vacuum. The residue was purified by prep-TLC (PE:EtOAc = 0:1) to afford the title compound (160.00 mg, 331.56 μ mol, 80.34% yield) as white solid.

Step 2. tert-butyl 8-(1-benzyloxy-3,3-difluoro-propyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexa

5 hydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of tert-butyl 8-(1-benzyloxy-3-oxo-propyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (116.00 mg, 227.95 μ mol, 1.00 *eq*) in DCM (1.00 mL) was added DAST (146.97 mg, 911.80 μ mol, 120.47 μ L, 4.00 *eq*) at -40 °C. The mixture was stirred at 20 °C for 1 hr. TLC (PE:EtOAc = 1:1) showed the starting material consumed and one main spot
10 formed. The mixture was extracted with DCM (10 mL*2) and H₂O(10 mL). The combined organic layer was dried over Na₂SO₄, filtrated and concentrated in vacuum. The residue was purified by prep-TLC (PE:EtOAc = 1:1) to get tert-butyl 8-(1-benzyloxy-3,3-difluoro-propyl)-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (75.00 mg, 123.37 μ mol, 54.12% yield, 83% purity) as yellow oil. The residue was purified by
15 prep-HPLC (FA) to afford the title compound (56.00 mg, 109.54 μ mol, 69.09% yield, 98.7% purity) as yellow oil.

Step 3. tert-butyl 8-(3,3-difluoro-1-hydroxy-propyl)-10-methyl-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. To a solution of tert-butyl 8-(1-benzyloxy-3,3-difluoro-propyl)-10-methyl-11-oxo-1,3,4,7,8,9-
20 hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (50.00 mg, 99.09 μ mol, 1.00 *eq*) in MeOH (15.00 mL) was added Pd/C (10.00 mg, 99.09 μ mol, 10% purity, 1.00 *eq*) and HOAc (595.06 μ g, 9.91 μ mol, 0.57 μ L, 0.10 *eq*) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 25 °C for 24 hours. TLC (PE:EtOAc = 0:1) showed the starting material remained, the mixture was
25 diluted with MeOH (20 mL), filtrated. The filtrate was added Pd/C (20 mg) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (40 psi) at 30 °C for 20 hours. LCMS showed the starting material remained and 60% desired product. The mixture was stirred under H₂ (45 psi) at 30 °C for another 16 hours. LCMS showed the starting material consumed completely. The mixture was diluted with
30 MeOH (30 mL) and filtrated. The filtrate was concentrated in vacuum to afford the title compound (60.00 mg, crude) as yellow oil.

Step 4. 8-(3,3-difluoro-1-hydroxy-propyl)-10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido

[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one. To a solution of tert-butyl 8-(3,3-difluoro-1-hydroxy-propyl)-10-methyl-11-oxo-1, 3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (60.00 mg, 144.77 μ mol, 1.00 *eq*) in DCM (5.00 mL) was added TFA (40.52 mmol, 3.00 mL, 279.89 *eq*). The mixture was stirred at 20 °C for 0.5 hr. TLC (PE:EtOAc = 0:1) showed the starting material consumed. The mixture was concentrated in vacuum to afford the title compound (64.00 mg, crude, TFA) as yellow oil.

Step 5. N-(3-chloro-4-fluoro-phenyl)-8-(3,3-difluoro-1-hydroxy-propyl)-10-methyl-11-oxo-

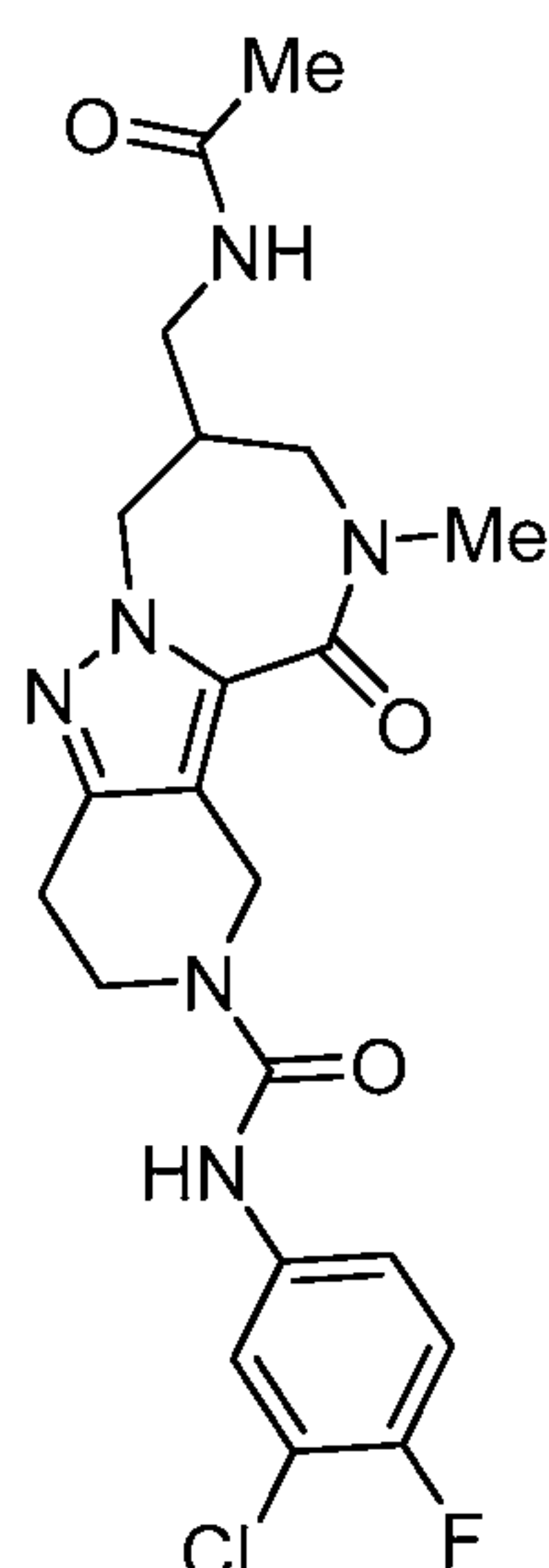
1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide. To a solution of

8-(3,3-difluoro-1-hydroxy-propyl)-10-methyl-2,3,4,7,8,9-hexahydro -1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (30.00 mg, 70.04 μ mol, 1.00 *eq*, TFA) and phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (18.61 mg, 70.04 μ mol, 1.00 *eq*) in DCM (5.00 mL) was added TEA (35.44 mg, 350.20 μ mol, 48.55 μ L, 5.00 *eq*). The mixture was stirred at 20 °C for 16 hr. LCMS showed one main peak (254 nm) with desired Ms detected. The mixture was concentrated in vacuum. The residue was purified by prep-HPLC (FA) to afford the title compound (14.00 mg, 28.32 μ mol, 40.44% yield, 98.3% purity) as white solid. LCMS:

486[M+1]. ^1H NMR (400MHz, CDCl_3) δ = 7.79 (dd, J = 2.7, 5.4 Hz, 1 H), 7.60 (br d, J = 9.8 Hz, 1 H), 7.15 (t, J = 8.6 Hz, 1 H), 6.79 (brs, 1 H), 5.92 - 6.28 (m, 1H), 4.58 - 4.80 (m, 3 H), 4.22 - 4.49 (m, 2 H), 4.13 (brs, 1 H), 3.84 - 3.95 (m, 3 H), 3.63 (m, 1 H), 3.29 - 3.50 (m, 2 H), 3.21 (d, J = 2.6 Hz, 3 H), 2.86 (br t, J = 5.5 Hz, 2 H), 2.70 (brs, 1 H), 2.56 (br d, J = 6.2 Hz, 1 H), 2.25 (brs, 1 H), 2.00 - 2.13 (m, 2 H).

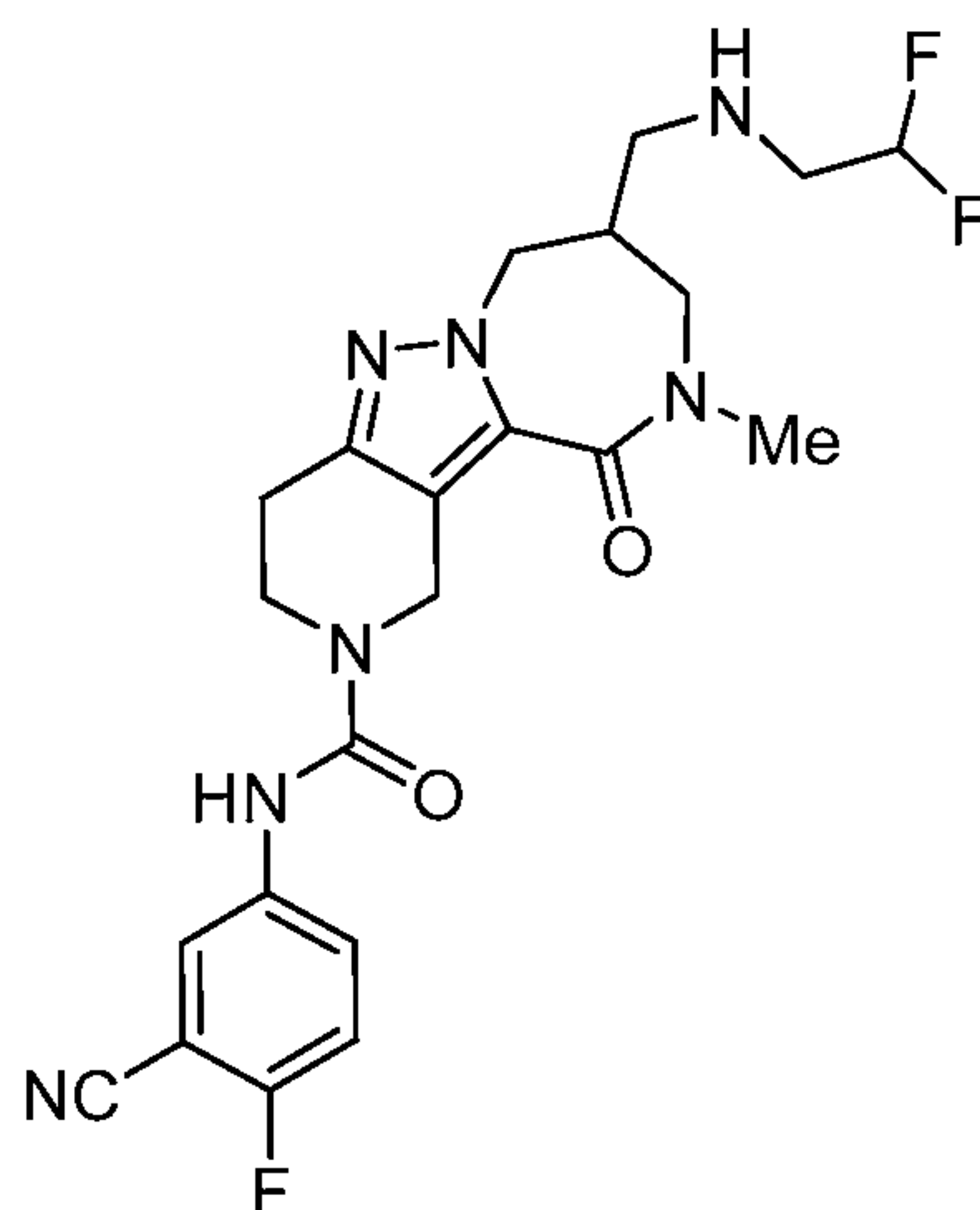
Compound 117: 8-(acetamidomethyl)-N-(3-chloro-4-fluorophenyl)-10-methyl-11-oxo-

1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



A mixture of 8-(aminomethyl)-N-(3-chloro-4-fluoro-phenyl)-10-methyl-11-oxo- 1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide (Compound 070, 30.00 mg, 71.28 μmol , 1.00 *eq*), TEA (10.82 mg, 106.92 μmol , 14.82 μL , 1.50 *eq*) and Ac_2O (8.73 mg, 85.54 μmol , 8.01 μL , 1.20 *eq*) in DCM (3.00 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 20 $^\circ\text{C}$ for 1 hour under N_2 atmosphere. LCMS showed the starting material was consumed completely, desired product was major. The mixture was poured into water (10 mL) and stirred at 5 min. The aqueous phase was extracted with DCM (5 mL*3). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by Prep-HPLC (HCl) to afford the title compound (25.00 mg, 53.47 μmol , 75.01% yield, 99% purity) as a white solid. LCMS: 463/465 $[\text{M}+1]$. ^1H NMR (400 MHz, CDCl_3) δ 7.55 - 7.61 (m, 1 H), 7.15 - 7.22 (m, 1 H), 7.04 - 7.10 (m, 1 H), 6.47 (s, 1 H), 6.12 - 6.20 (m, 1 H), 4.67 (m, 2 H), 4.29 - 4.45 (m, 2 H), 3.87 (m, 2 H), 3.41 (m, 2 H), 3.19 (s, 4 H), 3.01 - 3.13 (m, 1 H), 2.88 (m, 3 H), 2.00 (s, 3 H).

Compound 118: N-(3-cyano-4-fluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. 8-[(2,2-difluoroethylamino)methyl]-10-methyl-2,3,4,7,8,9-hexahydro-1H-

pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one. A solution of tert-butyl 8-[(2,2-

difluoroethylamino)methyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-

5 b][1,4]diazepine-2-carboxylate (Intermediate 29, 80.00 mg, 193.49 μ mol, 1.00 *eq*) in DCM (2.00

mL) was added TFA (6.16 g, 54.03 mmol, 4.00 mL, 279.23 *eq*), and then the mixture was stirred

at 20 °C for 1 hour. TLC showed the starting material was consumed completely and a new

spot formed. The mixture was concentrated in vacuum to afford the title compound (104.75 mg,

193.48 μ mol, 100.00% yield, 2TFA) as a yellow oil, which was used directly for next step.

10 Step 2. N-(3-cyano-4-fluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-

1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

A mixture of 8-[(2,2-difluoroethylamino)methyl]-10-methyl-2,3,4,7,8,9-hexahydro-1H-

pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (80.00 mg, 147.77 μ mol, 1.00 *eq*, 2TFA),

phenyl N-(3-cyano-4-fluoro-phenyl)carbamate (34.08 mg, 132.99 μ mol, 0.90 *eq*), TEA (29.91

15 mg, 295.54 μ mol, 40.97 μ L, 2.00 *eq*) in DCM (3.00 mL) was degassed and purged with N₂ for

3 times, and then the mixture was stirred at 30 °C for 16 hour under N₂ atmosphere. LCMS

showed the starting material was consumed completely, desired product was major. The

mixture was poured into water (10 mL) and extracted with DCM (5 mL). The combined organic

phase was washed with brine (10 mL), dried with anhydrous Na₂SO₄, filtered and concentrated

20 in vacuum. The residue was purified by Prep-HPLC (HCl), following by Prep-HPLC (BASE) to

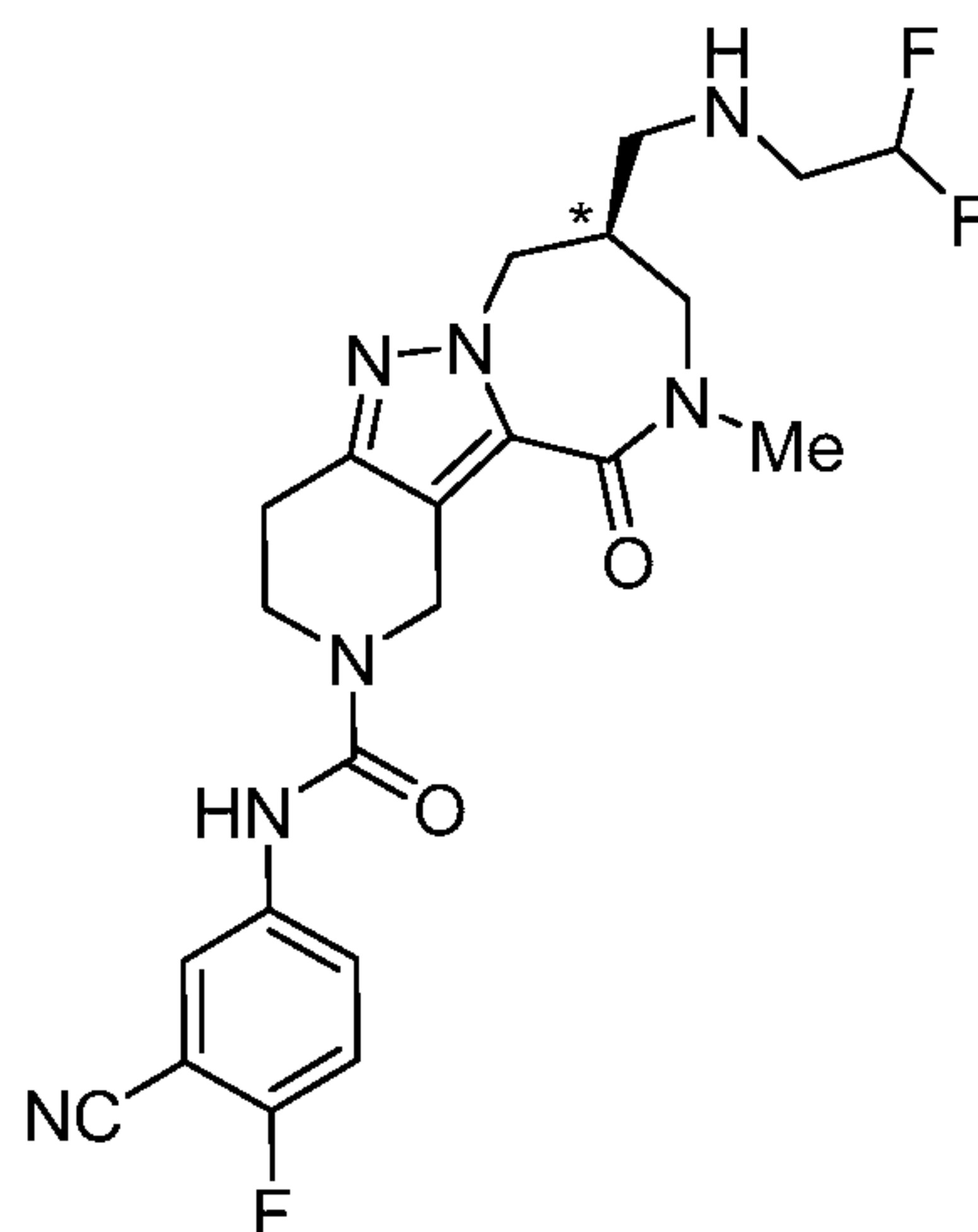
afford the title compound (51.00 mg, 106.19 μ mol, 71.86% yield, 99% purity) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 7.77 (dd, *J* = 2.75, 5.44 Hz, 1 H), 7.55 - 7.62 (m, 1 H), 7.09 -

7.16 (m, 1 H), 6.79 (s, 1 H), 5.70-5.98 (m, 1 H), 4.68 (s, 2 H), 4.36 - 4.47 (m, 1 H), 4.17 (dd, *J* =

5.62, 14.31 Hz, 1 H), 3.80 - 3.92 (m, 2 H), 3.42 - 3.50 (m, 1 H), 3.30 - 3.40 (m, 1 H), 3.18 (s, 3 H), 2.94 - 3.07 (m, 2 H), 2.69 - 2.87 (m, 4 H), 2.50 - 2.62 (m, 1 H), 1.14 - 1.31 (m, 1 H).

5 Compound 118_E1: (R*)-N-(3-cyano-4-fluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



*Pure but unknown diastereomer E1.

10 Step 1. tert-butyl 8-[[tert-butoxycarbonyl(2,2-difluoroethyl)amino]methyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. A mixture of racemic tert-butyl 8-[(2,2-difluoroethylamino)methyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (Intermediate 29, 1.60 g, 3.87 mmol, 1.00 *eq*), Boc₂O (2.53 g, 11.61 mmol, 2.67 mL, 3.00 *eq*), TEA (1.37 g, 13.54 mmol, 1.88 mL, 3.50 *eq*) in DCM (20.00 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 30 °C for 72 hour under N₂ atmosphere. TLC showed the starting material was consumed completely, and a new spot formed. The mixture was concentrated in vacuum.

15 The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 1:1) to afford the title compound (1.88 g, 3.51 mmol, 90.81% yield, 96% purity) as a yellow solid, which was separated by SFC (column: IC(250mm*30mm,10um);mobile phase: [0.1%NH₃H₂O IPA];B%: 40%-40%,4.7min;500minmin) to give each 930 mg of both enantiomers.

20

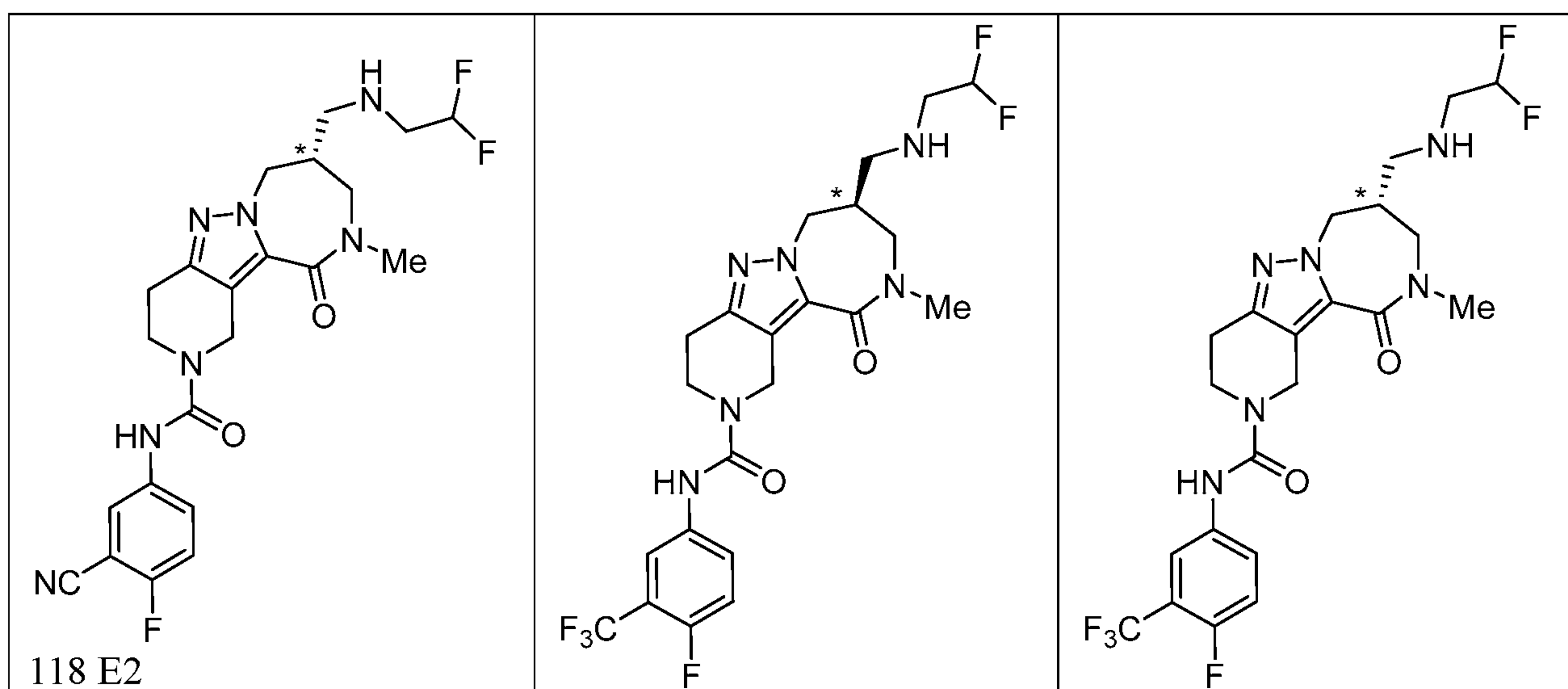
Step 2. 8-[(2,2-difluoroethylamino)methyl]-10-methyl-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one. To a solution of tert-butyl 8-[[tert-

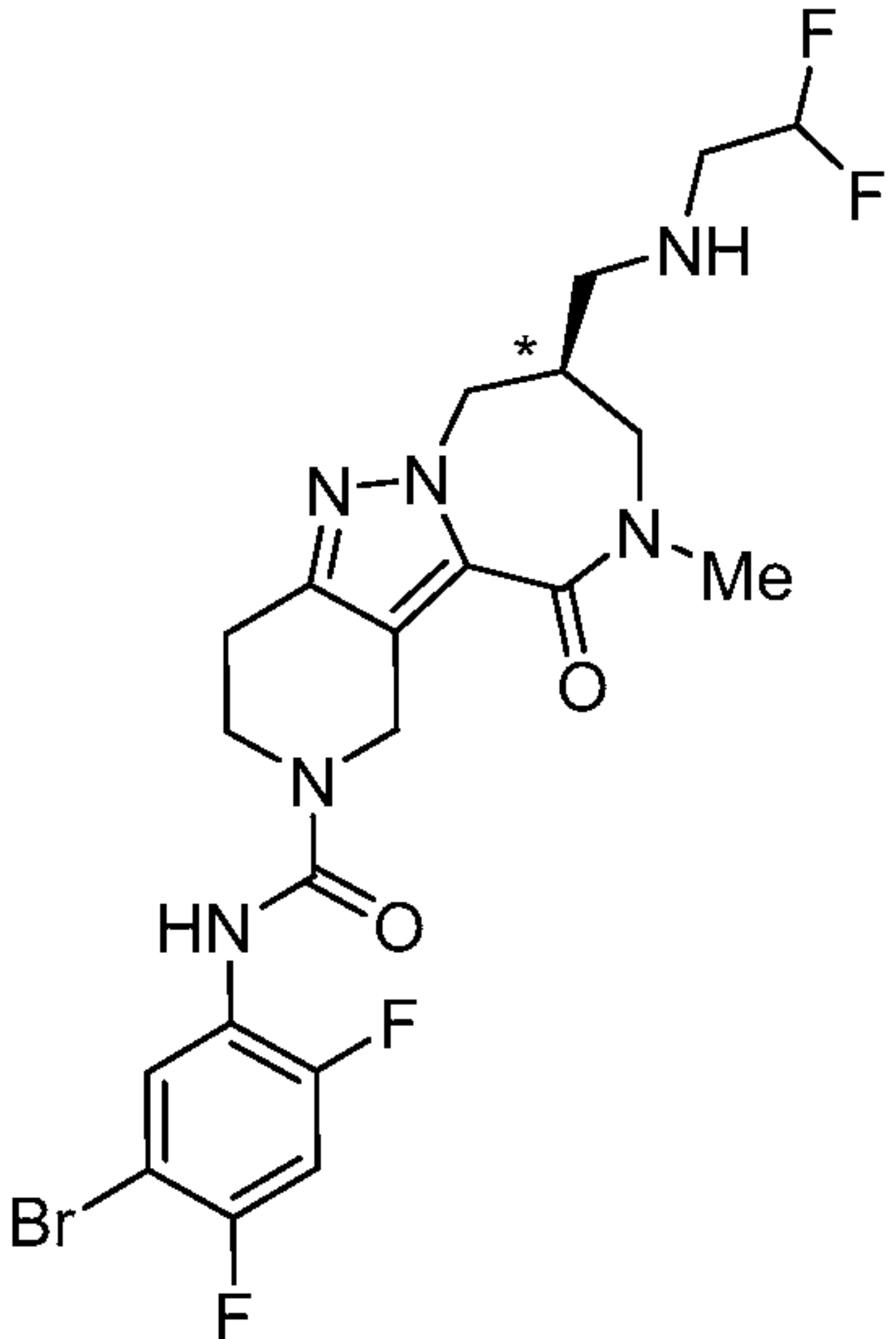
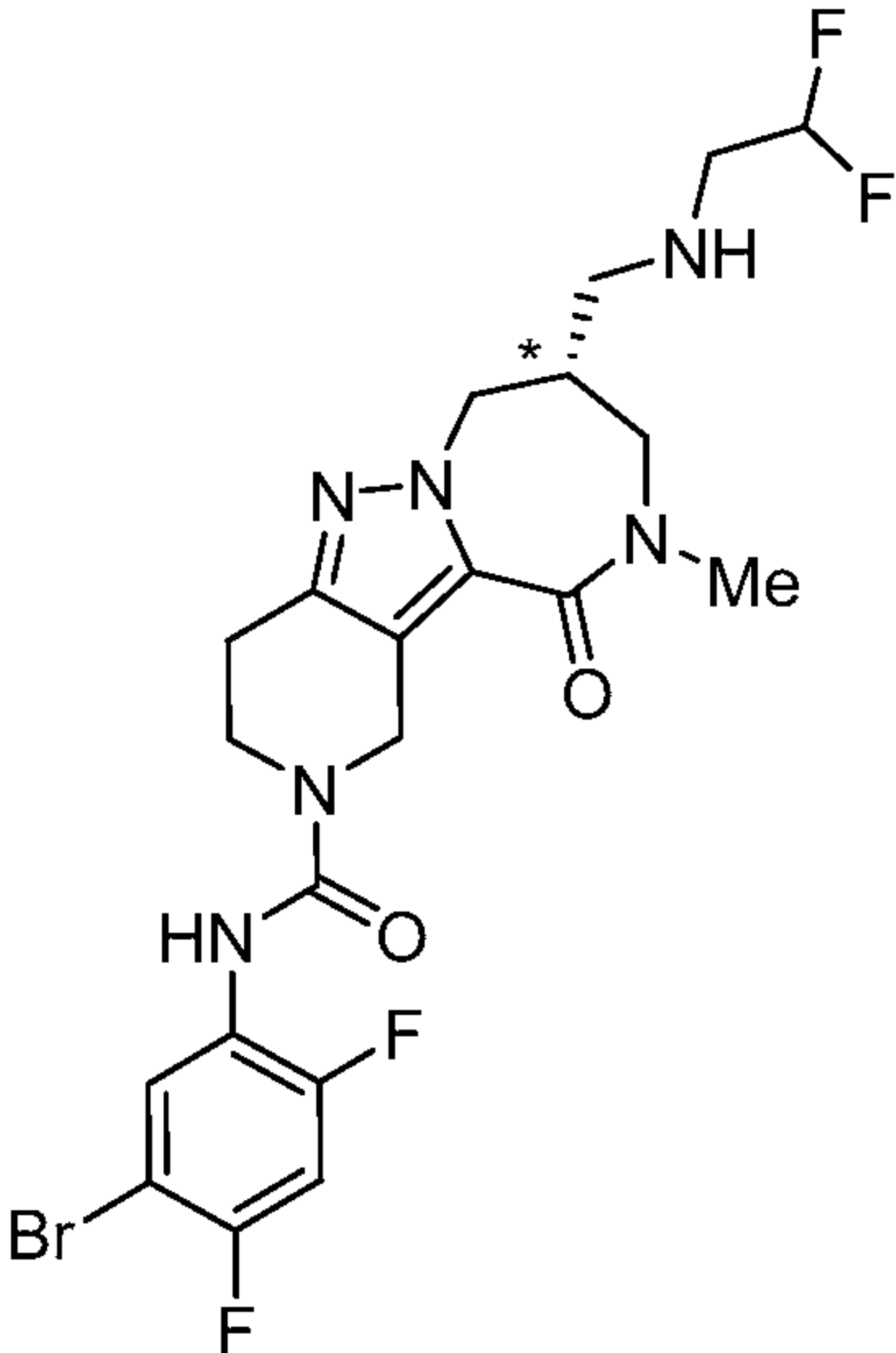
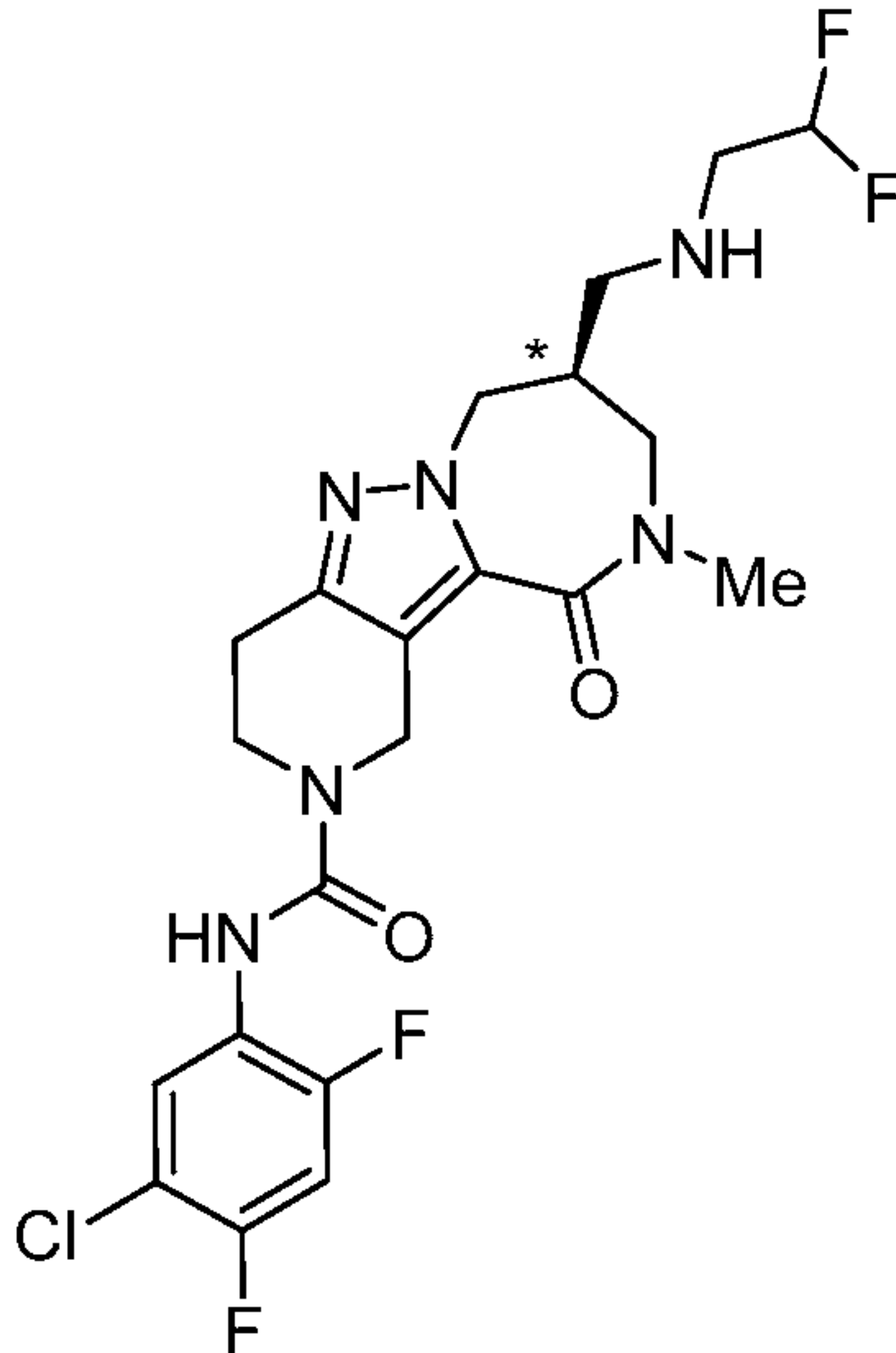
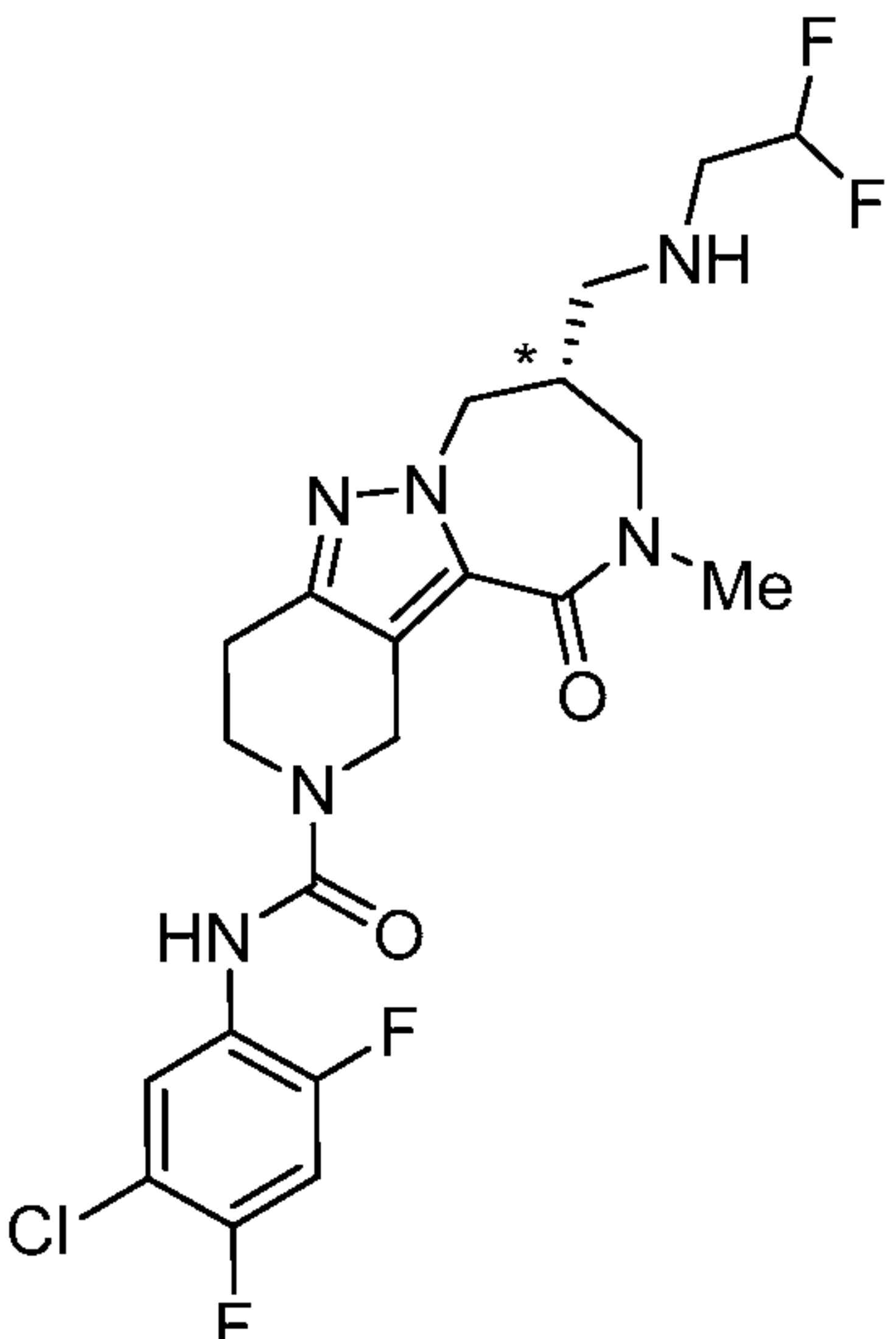
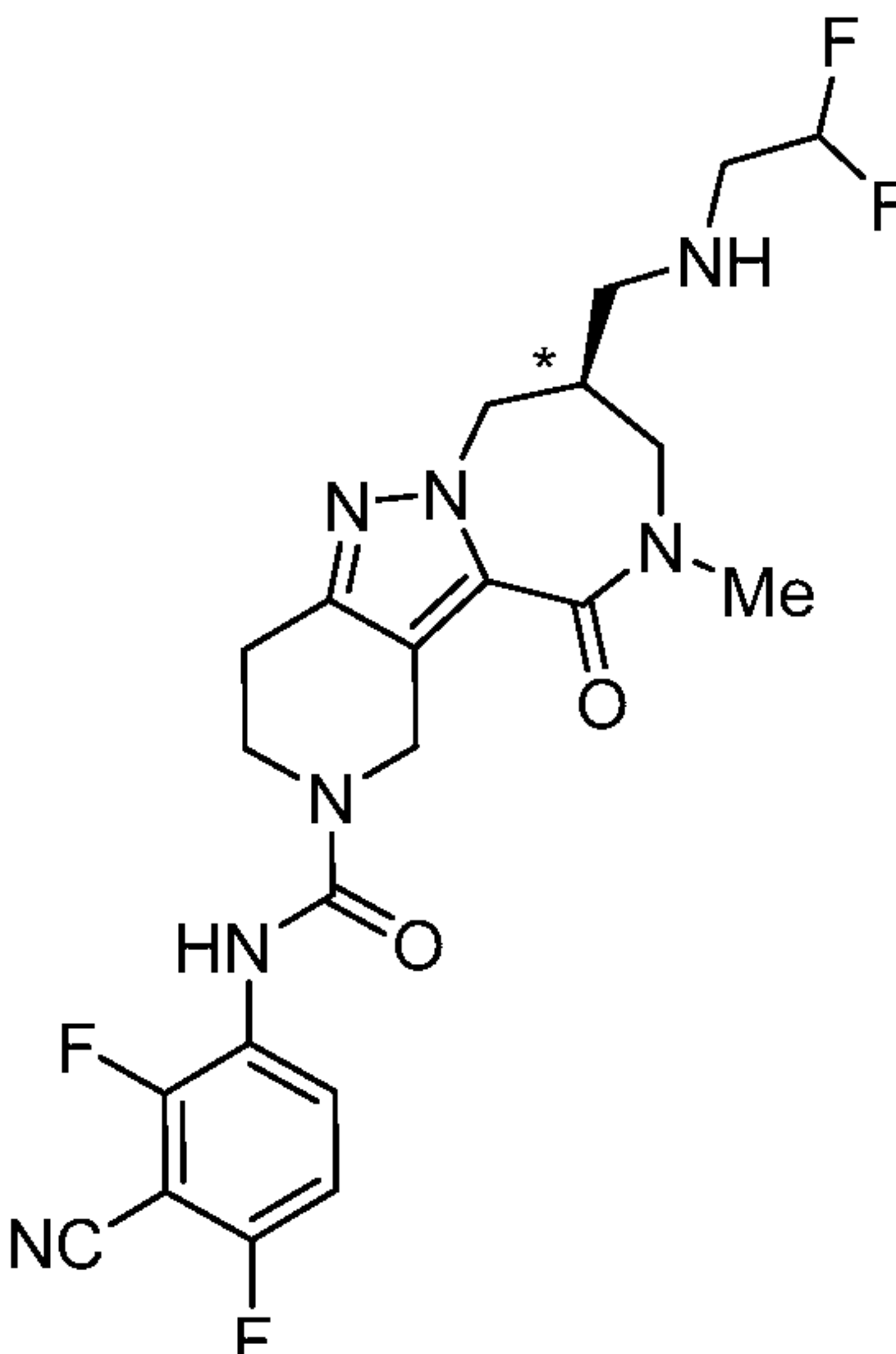
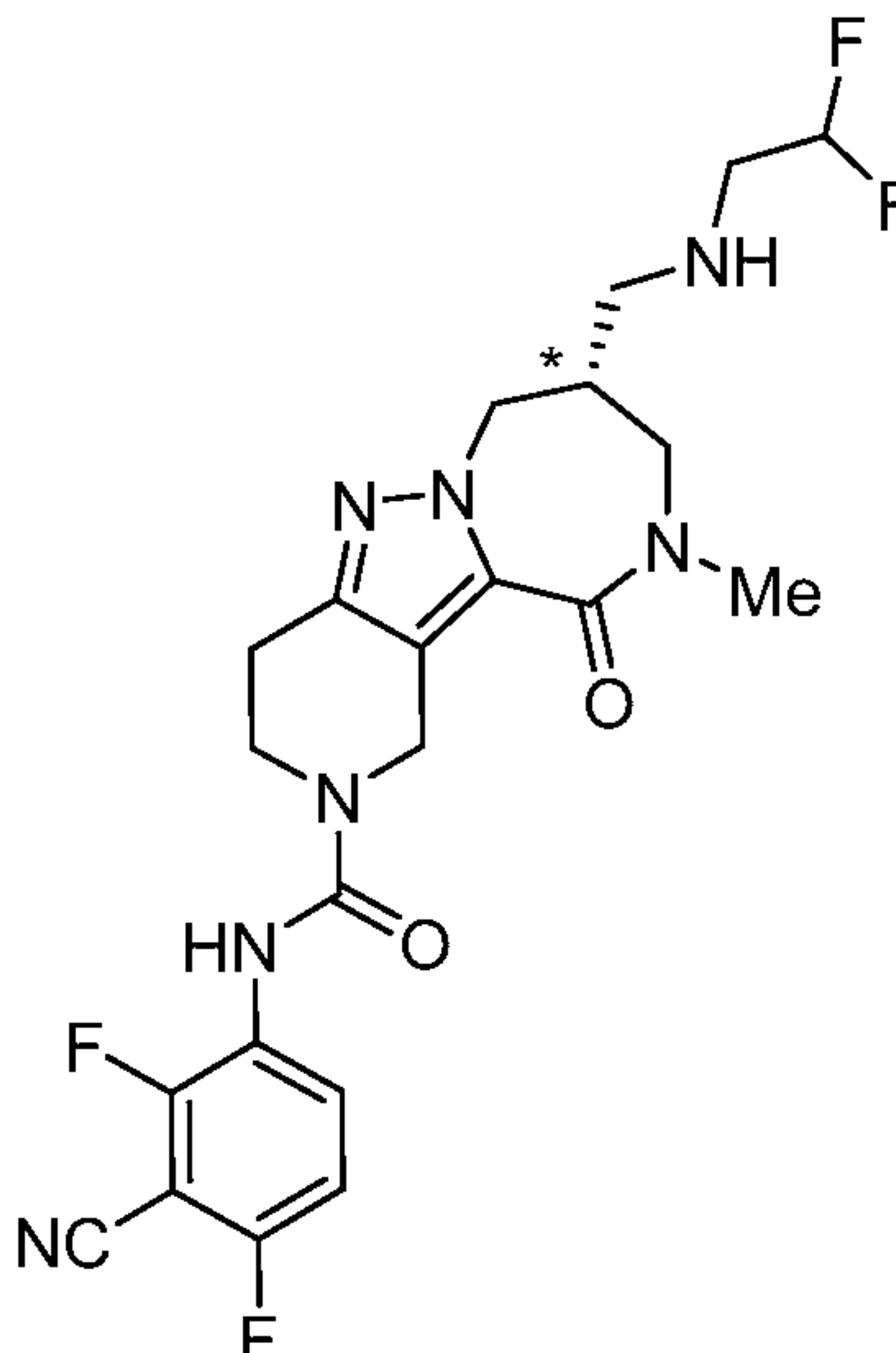
butoxycarbonyl(2,2-difluoroethyl)amino] methyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (630.00 mg, 1.23 mmol, 1.00 *eq*) in DCM (4.00 mL) was added TFA (3.08 g, 27.01 mmol, 2.00 mL, 21.96 *eq*) at 0 °C. The mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure to afford the title compound (665.00 mg, 1.17 mmol, 94.87% yield, 95% purity, 2TFA) as yellow oil, the crude product was used directly for the next step.

Step 3. (R*)-N-(3-cyano-4-fluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. To a solution of 8-[(2,2-difluoroethylamino)methyl]-10-methyl-2,3,4,7,8,9 -

hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (52.00 mg, 96.05 μmol, 1.00 *eq*, 2TFA) in DCM (3.00 mL) was added phenyl N-(3-cyano-4-fluoro-phenyl)carbamate (24.61 mg, 96.05 μmol, 1.00 *eq*) and Et₃N (48.60 mg, 480.25 μmol, 66.57 μL, 5.00 *eq*). The mixture was stirred at 25 °C for 16 h. The mixture was concentrated under reduced pressure. The residue combined with EW5335-130 was purified by prep-HPLC(HCl) to afford the title compound (37.50 mg, 71.05 μmol, 97% purity, HCl) as yellow solid. LCMS :476 [M+1]. ¹H NMR (400 MHz, METHANOL-d₄) δ 7.81 (dd, *J* = 2.81, 5.62 Hz, 1 H), 7.69 (m, 1 H), 7.27 (t, *J* = 8.99 Hz, 1 H), 6.21 - 6.52 (m, 1 H), 4.69 (s, 2 H), 4.52 (m, 1 H), 4.33 (m, 1 H), 3.73 - 3.94 (m, 2 H), 3.53 - 3.72 (m, 3 H), 3.09 - 3.26 (m, 5 H), 2.97 (br d, *J* = 6.48 Hz, 1 H), 2.77 - 2.88 (m, 2 H).

118/119/127-125_E1, 118/119/127-125_E2 were prepared through an analogous procedure to Compound 118.



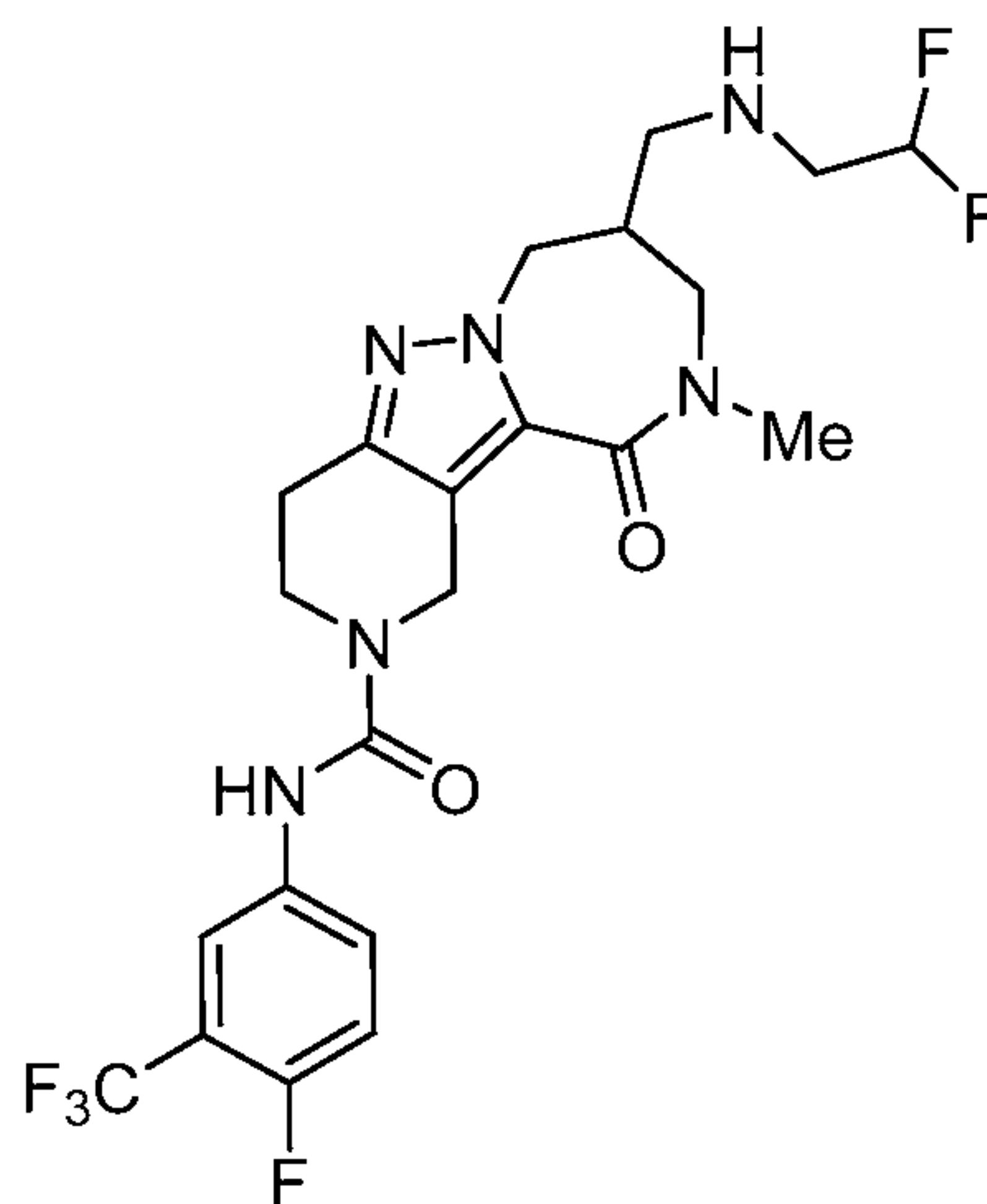
	119 E1	119 E2
 125 E1	 125 E2	 126 E1
 126 E2	 127 E1	 127 E2

Compound 118_E2: (S*)-N-(3-cyano-4-fluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

- 5 The title compound was prepared in a manner analogous to Compound 118_E1. *Pure but unknown diastereomer E2. LCMS :476 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 7.77 (dd, *J* = 2.76, 5.40 Hz, 1 H), 7.61 (m, 1 H), 7.12 (t, *J* = 8.72 Hz, 1 H), 7.06 (s, 1 H), 5.65 - 6.01 (m, 1 H), 4.61 - 4.74 (m, 2 H), 4.40 (m, 1 H), 4.17 (m, 1 H), 3.86 (t, *J* = 5.83 Hz, 2 H), 3.30 - 3.52 (m, 2

H), 3.17 (s, 3 H), 2.93 - 3.07 (m, 2 H), 2.84 (t, $J = 5.77$ Hz, 2 H), 2.67 - 2.79 (m, 2 H), 2.50 - 2.61 (m, 1 H).

Compound 119: 8-(((2,2-difluoroethyl)amino)methyl)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. tert-butyl 8-[[2,2-difluoroethyl-(2,2,2-trifluoroacetyl)amino]methyl]-10-methyl-1-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. A mixture of tert-

butyl 8-[(2,2-difluoroethylamino)methyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (Intermediate 29, 89.00 mg, 215.26 μ mol, 1.00 *eq*), TEA (43.56 mg, 430.52 μ mol, 59.67 μ L, 2.00 *eq*) in DCM (5.00 mL) was added (2,2,2-trifluoroacetyl) 2,2,2-trifluoroacetate (67.82 mg, 322.89 μ mol, 44.91 μ L, 1.50 *eq*) dropwise at 0 °C under N₂. Then the mixture was stirred at 30 °C for 1 hour under N₂ atmosphere. TLC showed the starting material was consumed completely, desired product was major. The mixture was poured into water (10 mL) and extracted with DCM (5 mL*3). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by Prep-TLC (DCM/MeOH=10/1) to afford the title compound (85.00 mg, 158.50 μ mol, 73.63% yield, 95% purity) as a white solid.

LCMS: 509 [M+1].

Step 2. N-(2,2-difluoroethyl)-2,2,2-trifluoro-N-[(10-methyl-11-oxo-2,3,4,7,8,9-hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-8-yl)methyl]acetamide. A solution of tert-butyl 8-[[2,2-difluoroethyl-(2,2,2-trifluoroacetyl)amino]methyl]-10-methyl-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate (85.00 mg, 166.84 μ mol, 1.00 *eq*) in DCM (2.00 mL) was added TFA (2.62 g, 22.96 mmol, 1.70 mL, 137.62 *eq*), and then the mixture was stirred at 30 °C for 1 hour. TLC showed the starting material was consumed completely, a new spot appeared. The mixture was concentrated in vacuum to afford the title compound (87.00 mg, 166.23 μ mol, 99.63% yield, TFA) as a yellow oil, which was used directly for next step.

Step 3. 8-[[2,2-difluoroethyl-(2,2,2-trifluoroacetyl)amino]methyl]-N-[4-fluoro-3-

(trifluoromethyl)phenyl]-10-methyl-11-oxo-1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide. A mixture of N-(2,2-difluoroethyl)-2,2,2-trifluoro-N-[(10-

methyl-11-oxo-2,3,4,7,8,9- hexahydro-1H-pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-8-

yl)methyl]acetamide (85.00 mg, 162.41 μ mol, 1.00 *eq*, TFA) , phenyl N-[4-fluoro-3-

(trifluoromethyl)phenyl] carbamate (58.31 mg, 194.89 μ mol, 1.20 *eq*), TEA (82.17 mg, 812.03

μ mol, 112.56 μ L, 5.00 *eq*) in DCM (5.00 mL) was degassed and purged with N₂ for 3 times,

and then the mixture was stirred at 30 °C for 16 hour under N₂ atmosphere. LCMS showed the

starting material was consumed completely, desired product was major. The mixture was poured into water (10 mL) and stirred at 5 min. The aqueous phase was extracted with DCM (5 mL*3).

The combined organic phase was washed with brine (10 mL), dried with anhydrous Na₂SO₄,

filtered and concentrated in vacuum. The residue was purified by Prep-TLC (PE/EtOAc=0/1) to

afford the title compound (74.00 mg, 115.61 μ mol, 71.19% yield, 96% purity) as a white solid.

LCMS: 614 [M+1].

Step 4. 8-(((2,2-difluoroethyl)amino)methyl)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-10-methyl-

11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-

carboxamide. A mixture of 8-[[2,2-difluoroethyl-(2,2,2-trifluoroacetyl)amino]methyl]-N-[4-

fluoro- 3-(trifluoromethyl)phenyl]-10-methyl-11-oxo-1,3,4,7,8,9-

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxamide (74.00 mg, 120.43 μ mol,

1.00 *eq*), K₂CO₃ (49.93 mg, 361.29 μ mol, 3.00 *eq*) in MeOH (5.00 mL) and H₂O (1.00 mL) was

degassed and purged with N₂ for 3 times, and then the mixture was stirred at 50 °C for 1

hour under N₂ atmosphere. LCMS showed the starting material was consumed completely, and

desired product was major. The mixture was poured into water (10 mL) and extracted with

DCM (5 mL*3). The combined organic phase was washed with brine (10 mL), dried with

anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by Prep-

HPLC (Base) to afford the title compound (32.00 mg, 59.25 μ mol, 49.20% yield, 96% purity) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.66 - 7.71 (m, 1 H), 7.56 - 7.62 (m, 1 H), 7.09 - 7.16 (m, 1 H), 6.75 - 6.80 (m, 1 H), 5.67 - 6.03 (m, 1 H), 4.69 (s, 2 H), 4.35 - 4.47 (m, 1 H), 4.12 - 4.23 (m, 1 H), 3.87 (m, 2 H), 3.42 - 3.50 (m, 1 H), 3.35 - 3.37 (d, J = 7.28 Hz, 1 H), 3.18 (s, 3 H), 2.95 - 3.06 (m, 2 H), 2.68 - 2.88 (m, 4 H), 2.50 - 2.62 (m, 1 H), 1.11 - 1.34 (m, 1 H).

Compound 119_E1: (R*)-8-(((2,2-difluoroethyl)amino)methyl)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

10 *Pure but unknown diastereomer E1.

LCMS : 519 [M+1]. ^1H NMR (400 MHz, CDCl_3) δ 7.68 (dd, J = 2.70, 6.09 Hz, 1 H), 7.55 - 7.63 (m, 1 H), 7.12 (t, J = 9.41 Hz, 1 H), 6.87 (s, 1 H), 5.67 - 6.01 (m, 1 H), 4.69 (d, J = 1.51 Hz, 2 H), 4.40 (dd, J = 6.78, 14.31 Hz, 1 H), 4.17 (m, 1 H), 3.81 - 3.92 (m, 2 H), 3.30 - 3.50 (m, 2 H), 3.12 - 3.22 (m, 3 H), 2.94 - 3.06 (m, 2 H), 2.84 (t, J = 5.77 Hz, 2 H), 2.67 - 2.80 (m, 2 H), 2.50 - 2.63 (m, 1 H).

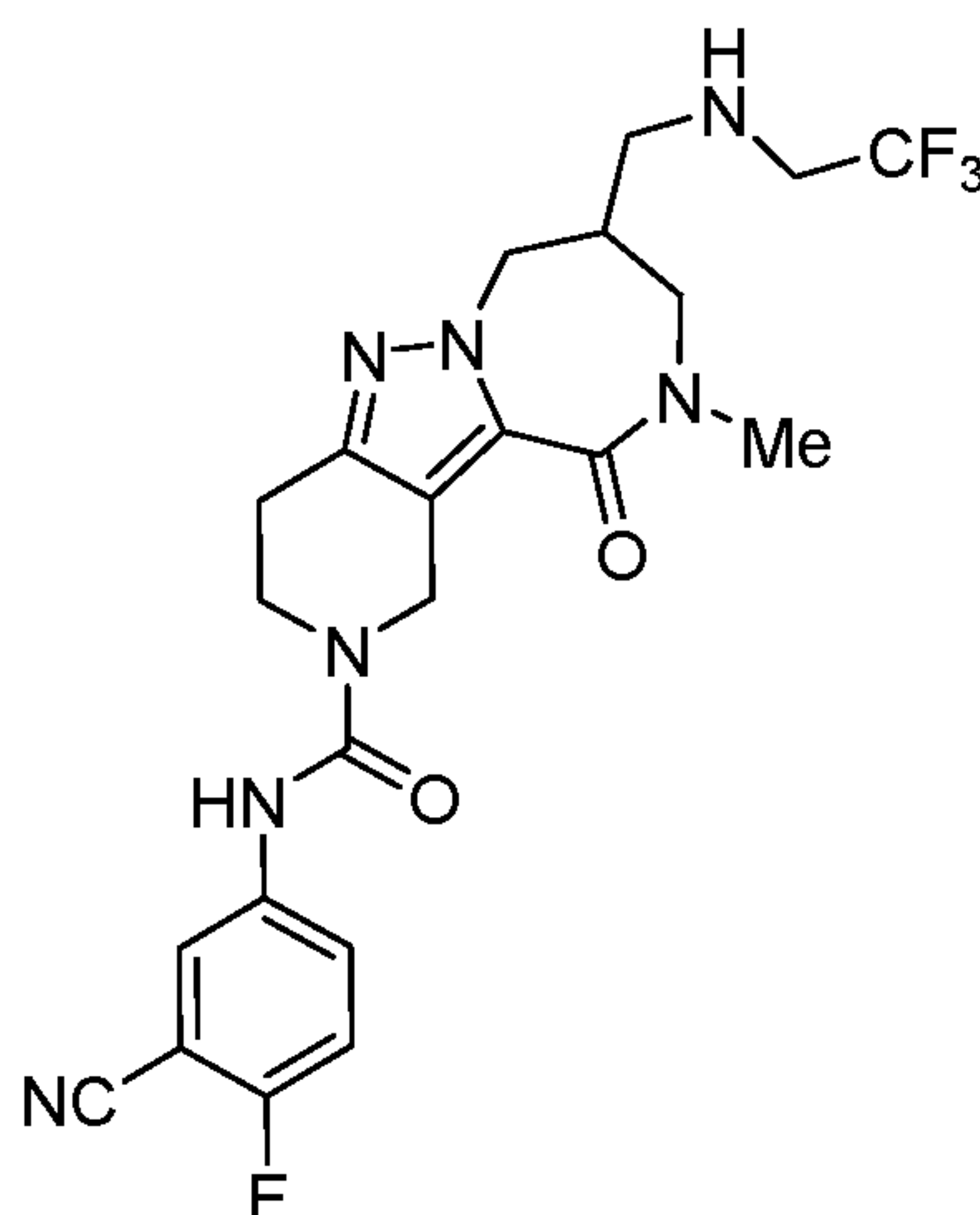
Compound 119_E2: (S*)-8-(((2,2-difluoroethyl)amino)methyl)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

20 *Pure but unknown diastereomer E2.

LCMS : 519 [M+1]. ^1H NMR (400 MHz, CDCl_3) δ 7.68 (dd, J = 2.70, 6.09 Hz, 1 H), 7.54 - 7.63 (m, 1 H), 7.12 (t, J = 9.35 Hz, 1 H), 6.78 (s, 1 H), 5.66 - 6.02 (m, 1 H), 4.64 - 4.75 (m, 2 H), 4.41 (m, 1 H), 4.17 (m, 1 H), 3.79 - 3.93 (m, 2 H), 3.29 - 3.50 (m, 2 H), 3.18 (s, 3 H), 3.01 (m, 2 H), 2.84 (t, J = 5.77 Hz, 2H), 2.68 - 2.80 (m, 2 H), 2.50 - 2.61 (m, 1 H).

25

Compound 120: N-(3-cyano-4-fluorophenyl)-10-methyl-11-oxo-8-(((2,2,2-trifluoroethyl)amino)methyl)-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. tert-butyl 10-methyl-11-oxo-8-[(2,2,2-trifluoroethylamino)methyl]-1,3,4,7,8,9 -

hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-2-carboxylate. A mixture of tert-butyl 10-

methyl-8-(methylsulfonyloxymethyl)-11-oxo-1,3,4,7,8,9- hexahydropyrido[2,3]pyrazolo[2,4-

b][1,4]diazepine-2-carboxylate (300.00 mg, 700.12 μmol , 1.00 *eq*) and 2,2,2-trifluoroethanamine

(1.39 g, 14.00 mmol, 1.10 mL, 20.00 *eq*) in DMSO (8.00 mL) was heated to 116 °C in sealed

tube for 16 h. LCMS showed starting material/desired product: ~1/2. another batch of 2,2,2-

trifluoroethanamine (1.39 g, 14.00 mmol, 1.10 mL, 20.00 *eq*) was added and the mixture was

heated to 116 °C in sealed tube for another 16 h. LCMS showed no starting material and major

desired product. The mixture was diluted with EtOAc (50 mL) and washed with brine (50 mL,

three times). The organic phase was dried over Na_2SO_4 , filtered and concentrated in vacuo,

which was purified by prep-TLC to afford the title compound (164.00 mg, 372.51 μmol , 53.21%

yield, 98% purity) as white solid. LCMS: 454 [M+23].

Step 2. 10-methyl-8-[(2,2,2-trifluoroethylamino)methyl]- 2,3,4,7,8,9-hexahydro-1H-

pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one. To a solution of tert-butyl 10-methyl-11-oxo-8-

[(2,2,2-trifluoroethylamino)methyl]- 1,3,4,7,8,9-hexahydropyrido[2,3]pyrazolo[2,4-

b][1,4]diazepine-2-carboxylate (174.00 mg, 403.29 μmol , 1.00 *eq*) in DCM (2.00 mL) was added

TFA (3.08 g, 27.01 mmol, 2.00 mL, 66.98 *eq*), and the mixture was stirred at 30 °C for 1 h. The

mixture was concentrated in vacuo to afford the title compound (228.00 mg, 407.59 μmol ,

101.07% yield, 2TFA) as yellow oil, which was used directly for the next step.

Step 3. N-(3-cyano-4-fluorophenyl)-10-methyl-11-oxo-8-(((2,2,2-trifluoroethyl)amino)methyl)-

1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. A

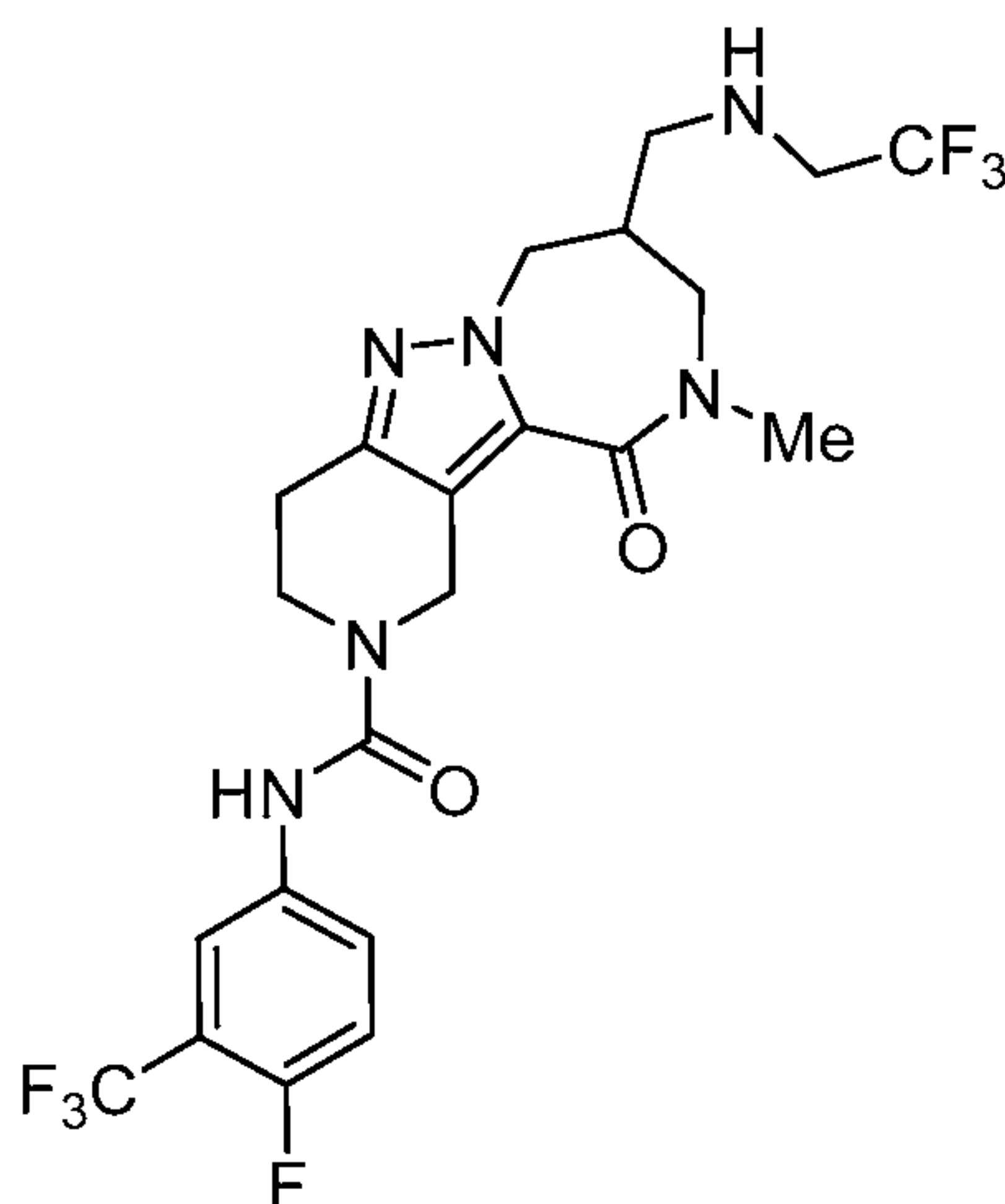
mixture of 10-methyl-8-[(2,2,2-trifluoroethylamino)methyl]-2,3,4,7,8,9-hexahydro -1H-

pyrido[2,3]pyrazolo[2,4-b][1,4]diazepin-11-one (114.00 mg, 203.80 μ mol, 1.00 *eq*, 2TFA), Et₃N (123.74 mg, 1.22 mmol, 169.51 μ L, 6.00 *eq*) and phenyl N-(3-cyano-4-fluorophenyl)carbamate (44.39 mg, 173.23 μ mol, 0.85 *eq*) in DCM (4.00 mL) was stirred at 30 °C for 2 h. LCMS indicated the starting material was consumed completely and major desired product.

The mixture was concentrated in vacuo, which was purified by prep-HPLC (base) two times to afford the title compound (36.00 mg, 72.95 μ mol, 35.80% yield) as yellow solid.

LCMS: 494 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 7.79 (m, 1 H), 7.60 (m, 1 H), 7.15 (t, *J* = 8.8 Hz, 1 H), 6.83 (s, 1 H), 4.70 (s, 2 H), 4.37 - 4.51 (m, 1 H), 4.10 - 4.25 (m, 1 H), 3.82 - 3.97 (m, 2 H), 3.31 - 3.54 (m, 2 H), 3.16 - 3.30 (m, 5 H), 2.86 (m, 4 H), 2.50 - 2.63 (m, 1 H), 1.32-1.42 (m, 1 H).

Compound 121: N-(4-fluoro-3-(trifluoromethyl)phenyl)-10-methyl-11-oxo-8-(((2,2,2-trifluoroethyl)amino)methyl)-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



The title compound was prepared in a manner analogous to Compound 120, using phenyl (4-fluoro-3-(trifluoromethyl)phenyl)carbamate in Step 3. LCMS: 537 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 7.70 (m, 1 H), 7.56 - 7.64 (m, 1 H), 7.14 (t, *J* = 9.4 Hz, 1H), 6.78 (s, 1 H), 4.70 (s, 2 H), 4.43 (m, 1 H), 4.17 (m, 1 H), 3.82 - 3.98 (m, 2 H), 3.43 - 3.55 (m, 1 H), 3.32 - 3.43 (m, 1 H), 3.19 (s, 5 H), 2.71 - 2.93 (m, 4 H), 2.48 - 2.64 (m, 1 H), 1.28-1.45 (m, 1 H).

Compound 122_D1: (3R,8S*)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-((R*)-1-hydroxyallyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

5 *Pure but unknown diastereomer D1.

Step 1. tert-butyl(6R)-3-[(2R,3S)-3-[tert-butyl(diphenyl)silyl]oxy-2-(hydroxymethyl)pent-4-enyl]-methyl-carbamoyl]-6-methyl-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate. To a mixture of (2S,3R)-3-[tert-butyl(diphenyl)silyl]oxy-2-(methylaminomethyl)pent-4-en-1-ol (Intermediate 21, 1.35 g, 2.71 mmol, 1.00 *eq*, TFA) and (6R)-5-tert-butoxycarbonyl-6-methyl-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-3-carboxylic acid (763.17 mg, 2.71 mmol, 1.00 *eq*) in DMF (8.00 mL) was added PYBOP (1.69 g, 3.26 mmol, 1.20 *eq*), HOBt (439.88 mg, 3.26 mmol, 1.20 *eq*) and DIPEA (1.40 g, 10.85 mmol, 1.90 mL, 4.00 *eq*), the reaction mixture was stirred at 25 °C for 2 hours. Several new peaks were shown on LCMS and about 30% of desired compound was detected. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (80 mL*2), the organic phase was dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to afford the title compound (1.00 g, 3.09 mmol, 57.04% yield) as white solid.

Step 2. tert-butyl (R)-3-(((2S,3R)-3-((tert-butyl)diphenylsilyl)oxy)-2-(((methylsulfonyl)oxy)methyl)pent-4-en-1-yl)(methyl)carbamoyl)-6-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate. To a mixture of tert-butyl (6R)-3-[(2R,3S)-3-[tert-butyl(diphenyl)silyl]oxy-2-(hydroxymethyl)pent-4-enyl]-methylcarbamoyl]-6-methyl-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (350.00 mg, 541.05 μmol, 1.00 *eq*) and TEA (164.25 mg, 1.62 mmol, 225.00 μL, 3.00 *eq*) in DCM (8.00 mL) was added MsCl (185.93 mg, 1.62 mmol, 125.63 μL, 3.00 *eq*) at 0 °C under N₂, the reaction mixture was stirred at 25 °C for 30 minutes. TLC indicated starting material was consumed completely, and two major new spots with lower polarity was detected. The reaction was quenched with water (20 mL) and then extracted with DCM (50 mL*2), the combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to afford the title compound (700.00 mg, crude) and as yellow oil, used in next step directly.

Step 3. tert-butyl (3R,8S)-8-((R)-1-((tert-butyl)diphenylsilyl)oxy)allyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate. To

a mixture of tert-butyl (6R)-3-[[[(2R,3S)-3-[tert-butyl(diphenyl)silyl]oxy-2-(methylsulfonyloxymethyl)pent-4-enyl]-methylcarbamoyl]-6-methyl-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (700.00 mg, 965.54 μ mol, 1.00 *eq*) and tert-butyl (6R)-3-[[[(2R,3S)-3-[tert-butyl(diphenyl)silyl]oxy-2-(methylsulfonyloxy methyl)pent-4-enyl]-methyl-carbamoyl]-6-methyl-2-methylsulfonyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (965.54 μ mol, 1.00 *eq*) in DMF (5.00 mL) was added Cs₂CO₃ (629.18 mg, 1.93 mmol, 2.00 *eq*) and TBAI (35.66 mg, 96.55 μ mol, 0.10 *eq*) under N₂, the reaction mixture was stirred at 25 °C for 16 hours. LCMS showed one main peak with desired MS was detected. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (50 mL*2), the organic phase was dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to afford the title compound (350.00 mg, 556.55 μ mol, 57.64% yield) as white solid.

Step 4. tert-butyl (3R,8S)-8-((R)-1-hydroxyallyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate. To a solution of tert-butyl (3R,8S)-8-((R)-1-((tert-butyldiphenylsilyl)oxy)allyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (700.00 mg, 1.11 mmol, 1.00 *eq*) in THF (10.00 mL) was added TBAF (1 M, 2.22 mL, 2.00 *eq*), the reaction mixture was stirred at 25 °C for one hour. TLC indicated starting material was consumed completely and one major new spot with larger polarity was detected. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (50 mL*2), the organic phase was dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to afford the title compound (375.00 mg, 931.55 μ mol, 83.92% yield, 97% purity) as white solid.

Step 5. tert-butyl (3R,8S)-8-((R)-1-((tert-butyldiphenylsilyl)oxy)allyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate

D1 and D2. Compound tert-butyl (3R,8S*)-8-((R*)-1-((tert-butyldiphenylsilyl)oxy)allyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (500.00 mg, 97% purity) was separated by SFC to get both diastereomers (**D1**: 190 mg and **D2**: 190 mg). SFC separation condition: Instrument: SFC 80; Column: AD-10um; Mobile phase: A for CO₂ and B for MeOH (0.1% NH₃H₂O); Gradient: B 30%; Flow rate: 60mL/min; Back pressure: 100 bar; Column temperature: 35 °C; Wavelength: 220 nm.

D1: ^1H NMR (400 MHz, CDCl_3) δ = 5.85 (ddd, J = 7.15, 10.16, 17.19 Hz, 1 H), 5.39 (d, J = 17.19 Hz, 1 H), 5.28 - 5.34 (m, 1 H), 4.78 - 5.08 (m, 2 H), 4.33 (dd, J = 7.47, 14.24 Hz, 1 H), 4.09 - 4.22 (m, 2 H), 4.02 (br dd, J = 8.66, 14.18 Hz, 1 H), 3.56 - 3.64 (m, 1 H), 3.46 - 3.55 (m, 1 H), 3.19 (s, 3 H), 2.91 (br dd, J = 5.77, 15.69 Hz, 1 H), 2.56 (d, J = 15.69 Hz, 1 H), 2.42 - 2.52 (m, 1 H), 1.48 (s, 9 H), 1.13 (d, J = 7.03 Hz, 3 H).

*Pure but unknown diastereomer D1.

D2: ^1H NMR (400 MHz, CDCl_3) δ = 5.87 (ddd, J = 7.09, 10.23, 17.19 Hz, 1 H), 5.41 (d, J = 17.19 Hz, 1 H), 5.32 (d, J = 10.29 Hz, 1 H), 4.79 - 5.08 (m, 2 H), 4.25 - 4.34 (m, 1 H), 4.10 - 4.25 (m, 3 H), 3.40 - 3.58 (m, 2 H), 3.18 (s, 3 H), 2.93 (dd, J = 5.83, 15.75 Hz, 1 H), 2.47 - 2.59 (m, 2 H), 1.48 (s, 9 H), 1.12 (d, J = 6.90 Hz, 3 H).

*Pure but unknown diastereomer D2.

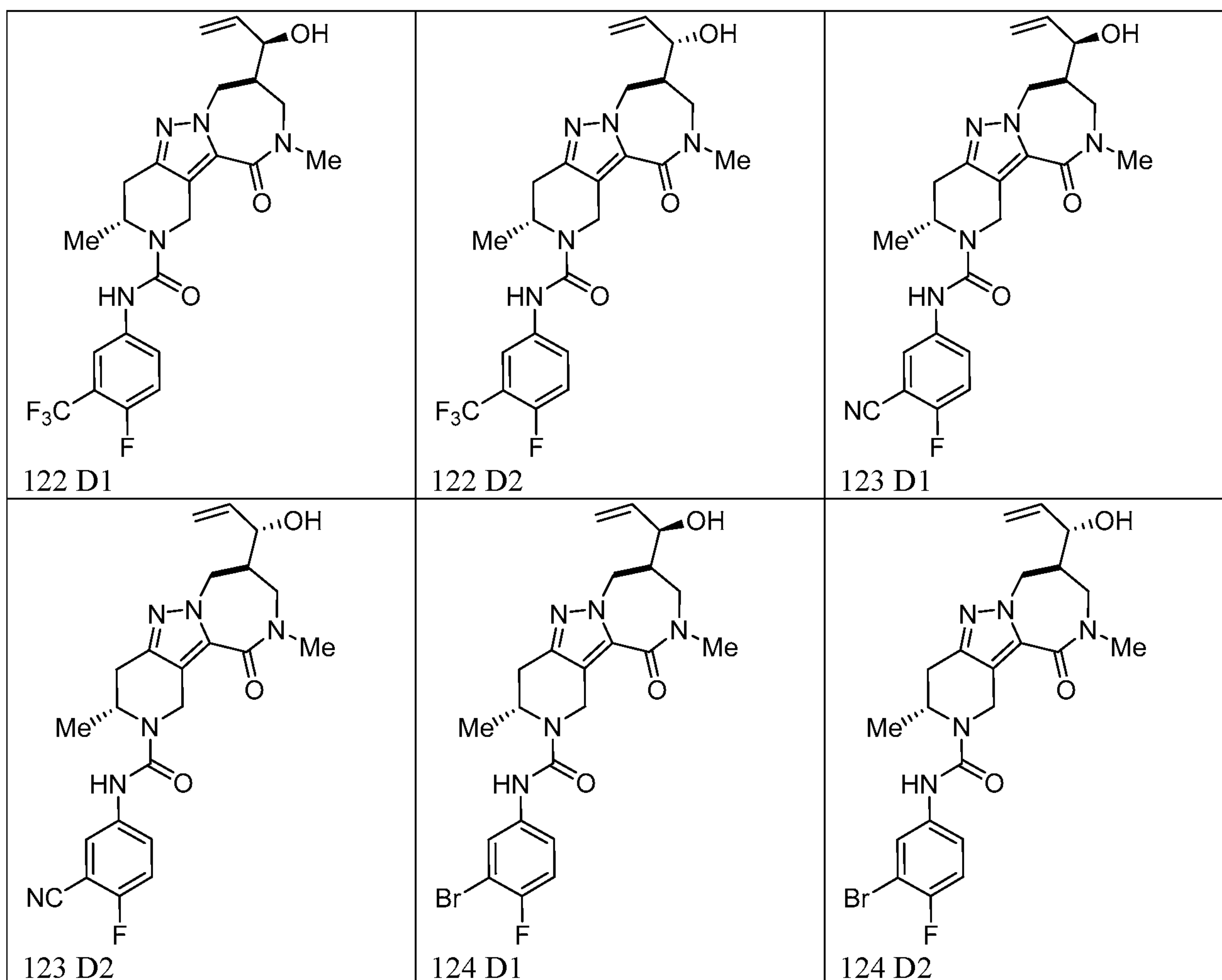
Step 6. (3R,8S*)-8-((R*)-1-hydroxyallyl)-3,10-dimethyl-1,2,3,4,7,8,9,10-octahydro-11H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11-one _D1. To a solution of tert-butyl (3R,8S*)-8-((R*)-1-((tert-butyldiphenylsilyl)oxy)allyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate _D1 (190.00 mg, 471.98 μmol , 1.00 *eq*) in DCM (5.00 mL) was added TFA (2.99 g, 26.20 mmol, 1.94 mL, 55.52 *eq*), the reaction mixture was stirred at 25 °C for one hour. TLC indicated starting material was consumed completely. The reaction mixture was concentrated on a rotary evaporator to afford the title compound (190.00 mg, crude, TFA) as yellow oil, used in next step directly.

*Pure but unknown diastereomer D1.

Step 7. D1: (3R,8S*)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-((R*)-1-hydroxyallyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. To a mixture of (3R,8S*)-8-((R*)-1-hydroxyallyl)-3,10-dimethyl-1,2,3,4,7,8,9,10-octahydro-11H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11-one _D1 (63.00 mg, 155.79 μmol , 1.00 *eq*, TFA) in DCM (2.00 mL) was added TEA (63.06 mg, 623.16 μmol , 86.38 μL , 4.00 *eq*), followed by phenyl N-[4-fluoro-3-(trifluoromethyl)phenyl] carbamate (46.62 mg, 155.79 μmol , 1.00 *eq*), the reaction mixture was stirred at 25 °C for 4 hours. LCMS showed one main peak with desired MS was detected. Removed the solvent on a rotary evaporator. The residue was purified by prep-HPLC(FA) to afford the title compound (56.00 mg, 111.89 μmol , 71.82% yield, 99% purity) as white solid. LCMS ($M+1$): 496. ^1H NMR (400 MHz, CDCl_3) δ = 7.69 (dd, J = 2.69, 6.11 Hz, 1 H), 7.56 - 7.61 (m, 1 H), 7.13 (t, J = 9.35 Hz, 1

H), 6.62 (s, 1 H), 5.88 (ddd, $J = 7.15, 10.24, 17.21$ Hz, 1 H), 5.42 (d, $J = 17.12$ Hz, 1 H), 5.34 (d, $J = 10.27$ Hz, 1 H), 5.15 (t, $J = 6.42$ Hz, 1 H), 4.80 (d, $J = 15.16$ Hz, 1 H), 4.50 (d, $J = 15.28$ Hz, 1 H), 4.36 (dd, $J = 7.46, 14.43$ Hz, 1 H), 4.10 - 4.18 (m, 2 H), 3.49 - 3.65 (m, 2 H), 3.20 (s, 3 H), 3.01 (dd, $J = 5.93, 15.71$ Hz, 1 H), 2.67 (d, $J = 16.14$ Hz, 1 H), 2.49 - 2.57 (m, 1 H), 1.79 (br s, 1 H), 1.19 (d, $J = 6.85$ Hz, 3 H).

122~124_D1 and D2 were prepared in a manner analogous to Compound 122.



Compound 122_D2: (3R,8S*)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-((S*)-1-hydroxyallyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

*Pure but unknown diastereomer D2.

LCMS (M+1): 496. ¹H NMR (400 MHz, CDCl₃) δ = 7.70 (dd, J = 2.69, 5.99 Hz, 1 H), 7.56 - 7.62 (m, 1 H), 7.13 (t, J = 9.41 Hz, 1 H), 6.68 (br s, 1 H), 5.88 (ddd, J = 7.09, 10.21, 17.18 Hz, 1 H), 5.42 (d, J = 17.12 Hz, 1 H), 5.34 (d, J = 10.27 Hz, 1 H), 5.16 (quin, J = 6.39 Hz, 1 H), 4.84 (d, J = 15.28 Hz, 1 H), 4.46 (d, J = 15.16 Hz, 1 H), 4.36 (dd, J = 7.27, 14.37 Hz, 1 H), 4.11 - 4.22 (m, 2 H), 3.47 - 3.63 (m, 2 H), 3.20 (s, 3 H), 3.03 (dd, J = 6.05, 15.96 Hz, 1 H), 2.66 (d, J = 15.77 Hz, 1 H), 2.51 - 2.61 (m, 1 H), 1.83 (br s, 1 H), 1.18 (d, J = 6.97 Hz, 3 H).

Compound 123_D1: (3R,8S*)-N-(3-cyano-4-fluorophenyl)-8-((R*)-1-hydroxyallyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

*Pure but unknown diastereomer D1.

LCMS (M+1): 453. ¹H NMR (400 MHz, CDCl₃) δ = 7.80 (dd, J = 2.75, 5.44 Hz, 1 H), 7.58 (ddd, J = 2.87, 4.49, 9.02 Hz, 1 H), 7.13 (t, J = 8.68 Hz, 1 H), 6.71 (s, 1 H), 5.88 (ddd, J = 7.15, 10.15, 17.18 Hz, 1 H), 5.42 (d, J = 17.12 Hz, 1 H), 5.35 (d, J = 10.27 Hz, 1 H), 5.14 (quin, J = 6.66 Hz, 1 H), 4.80 (d, J = 15.41 Hz, 1 H), 4.49 (d, J = 15.28 Hz, 1 H), 4.36 (dd, J = 7.40, 14.37 Hz, 1 H), 4.12 - 4.19 (m, 2 H), 3.49 - 3.65 (m, 2 H), 3.20 (s, 3 H), 3.01 (dd, J = 5.69, 15.96 Hz, 1 H), 2.67 (d, J = 15.77 Hz, 1 H), 2.49 - 2.57 (m, 1 H), 1.81 (br s, 1 H), 1.19 (d, J = 6.97 Hz, 3 H).

Compound 123_D2: (3R,8S*)-N-(3-cyano-4-fluorophenyl)-8-((S*)-1-hydroxyallyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

*Pure but unknown diastereomer D2.

LCMS (M+1): 453. ¹H NMR (400 MHz, CDCl₃) δ = 7.80 (dd, J = 2.81, 5.50 Hz, 1 H), 7.58 (ddd, J = 2.87, 4.55, 9.08 Hz, 1 H), 7.13 (t, J = 8.74 Hz, 1 H), 6.74 (s, 1 H), 5.88 (ddd, J = 7.03, 10.18, 17.15 Hz, 1 H), 5.42 (d, J = 17.12 Hz, 1 H), 5.34 (d, J = 10.27 Hz, 1 H), 5.14 (quin, J = 6.30 Hz, 1 H), 4.83 (d, J = 15.28 Hz, 1 H), 4.45 (d, J = 15.28 Hz, 1 H), 4.36 (dd, J = 7.27, 14.37 Hz, 1 H), 4.12 - 4.22 (m, 2 H), 3.48 - 3.63 (m, 2 H), 3.20 (s, 3 H), 3.02 (dd, J = 5.81,

15.71 Hz, 1 H), 2.66 (d, $J = 15.53$ Hz, 1 H), 2.52 - 2.60 (m, 1 H), 1.82 (br s, 1 H), 1.18 (d, $J = 6.97$ Hz, 3 H).

5 Compound 124_D1: (3R,8S*)-N-(3-bromo-4-fluorophenyl)-8-((R*)-1-hydroxyallyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

*Pure but unknown diastereomer D1.

10 LCMS (M+1): 506/508. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.74$ (dd, $J = 2.63, 6.05$ Hz, 1 H), 7.23 - 7.26 (m, 1 H), 7.04 (t, $J = 8.56$ Hz, 1 H), 6.52 (s, 1 H), 5.87 (ddd, $J = 7.15, 10.24, 17.21$ Hz, 1 H), 5.42 (d, $J = 17.24$ Hz, 1 H), 5.34 (d, $J = 10.39$ Hz, 1 H), 5.10 - 5.17 (m, 1 H), 4.78 (d, $J = 15.41$ Hz, 1 H), 4.48 (d, $J = 15.16$ Hz, 1 H), 4.36 (dd, $J = 7.46, 14.31$ Hz, 1 H), 4.09 - 4.18 (m, 2 H), 3.48 - 3.65 (m, 2 H), 3.20 (s, 3 H), 3.00 (dd, $J = 5.75, 15.53$ Hz, 1 H), 2.66 (d, $J = 16.02$ Hz, 1 H), 2.48 - 2.57 (m, 1 H), 1.79 (br s, 1 H), 1.18 (d, $J = 6.97$ Hz, 3 H).

15 Compound 124_D2: (3R,8S*)-N-(3-bromo-4-fluorophenyl)-8-((S*)-1-hydroxyallyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

*Pure but unknown diastereomer D2.

20 LCMS (M+1): 506/508. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.75$ (dd, $J = 2.69, 6.11$ Hz, 1 H), 7.23 - 7.27 (m, 1 H), 7.04 (t, $J = 8.50$ Hz, 1 H), 6.53 (s, 1 H), 5.88 (ddd, $J = 7.03, 10.15, 17.18$ Hz, 1 H), 5.42 (d, $J = 17.12$ Hz, 1 H), 5.34 (d, $J = 10.27$ Hz, 1 H), 5.11 - 5.18 (m, 1 H), 4.81 (d, $J = 15.28$ Hz, 1 H), 4.45 (d, $J = 15.16$ Hz, 1 H), 4.32 - 4.39 (m, 1 H), 4.12 - 4.23 (m, 2 H), 3.48 - 3.62 (m, 2 H), 3.20 (s, 3 H), 3.02 (dd, $J = 5.87, 15.89$ Hz, 1 H), 2.65 (d, $J = 15.53$ Hz, 1 H), 2.51 - 2.60 (m, 1 H), 1.81 (br s, 1 H), 1.17 (d, $J = 6.97$ Hz, 3 H).

25 Compound 125_E1: (R*)-N-(5-bromo-2,4-difluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

*Pure but unknown diastereomer E1.

30 LCMS : 547/549 [M+1]. ^1H NMR (400 MHz, CDCl_3) $\delta 8.31$ (t, $J = 7.95$ Hz, 1 H), 6.93 (m, 1 H), 6.58 (br d, $J = 2.81$ Hz, 1 H), 5.67 - 6.02 (m, 1 H), 4.70 (s, 2 H), 4.12 - 4.45 (m, 2 H), 3.74 -

3.94 (m, 2 H), 3.28 - 3.50 (m, 2 H), 3.18 (s, 3 H), 2.93 - 3.06 (m, 2 H), 2.85 (t, $J = 5.75$ Hz, 2 H), 2.67 - 2.80 (m, 2 H), 2.49 - 2.61 (m, 1 H).

Compound 125_E2: (S*)-N-(5-bromo-2,4-difluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

*Pure but unknown diastereomer E2.

LCMS : 547/549 [M+1]. ^1H NMR (400 MHz, CDCl_3) δ 8.32 (t, $J = 7.89$ Hz, 1 H), 6.93 (dd, $J = 7.95, 10.64$ Hz, 1 H), 6.57 (br d, $J = 2.93$ Hz, 1 H), 5.67 - 6.02 (m, 1 H), 4.70 (s, 2 H), 4.14 - 4.45 (m, 2 H), 3.76 - 3.93 (m, 2 H), 3.28 - 3.49 (m, 2 H), 3.18 (s, 3 H), 2.93 - 3.08 (m, 1 H), 2.91 - 3.00 (m, 1 H), 2.85 (t, $J = 5.81$ Hz, 2 H), 2.75 (m, 2 H), 2.46 - 2.60 (m, 1 H).

Compound 126_E1: (R*)-N-(5-chloro-2,4-difluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

*Pure but unknown diastereomer E1.

LCMS : 503/505 [M+1]. ^1H NMR (400 MHz, CDCl_3) δ 8.17 (t, $J = 8.03$ Hz, 1 H), 6.94 (m, 1 H), 6.59 (br d, $J = 3.01$ Hz, 1 H), 5.65 - 6.02 (m, 1 H), 4.70 (s, 2 H), 4.40 (m, 1 H), 4.17 (m, 1 H), 3.76 - 3.93 (m, 2 H), 3.28 - 3.50 (m, 2 H), 3.18 (s, 3 H), 2.93 - 3.08 (m, 2 H), 2.85 (t, $J = 5.77$ Hz, 2 H), 2.75 (dq, $J = 7.47, 11.94$ Hz, 2 H), 2.48 - 2.62 (m, 1 H).

Compound 126_E2: (S*)-N-(5-chloro-2,4-difluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

*Pure but unknown diastereomer E2.

LCMS : 503/505 [M+1]. ^1H NMR (400 MHz, CDCl_3) δ 8.16 (t, $J = 8.03$ Hz, 1 H), 6.94 (dd, $J = 8.41, 10.54$ Hz, 1 H), 6.61 (br d, $J = 2.89$ Hz, 1 H), 5.67-6.02 (m, 1 H), 4.70 (s, 2 H), 4.40 (m, 1 H), 4.17 (m, 1 H), 3.77 - 3.94 (m, 2 H), 3.28 - 3.50 (m, 2 H), 3.17 (s, 3 H), 2.92 - 3.06 (m, 2 H), 2.85 (t, $J = 5.77$ Hz, 2 H), 2.65 - 2.80 (m, 2 H), 2.48 - 2.62 (m, 1 H).

Compound 127_E1: (R*)-N-(3-cyano-2,4-difluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

*Pure but unknown diastereomer E1.

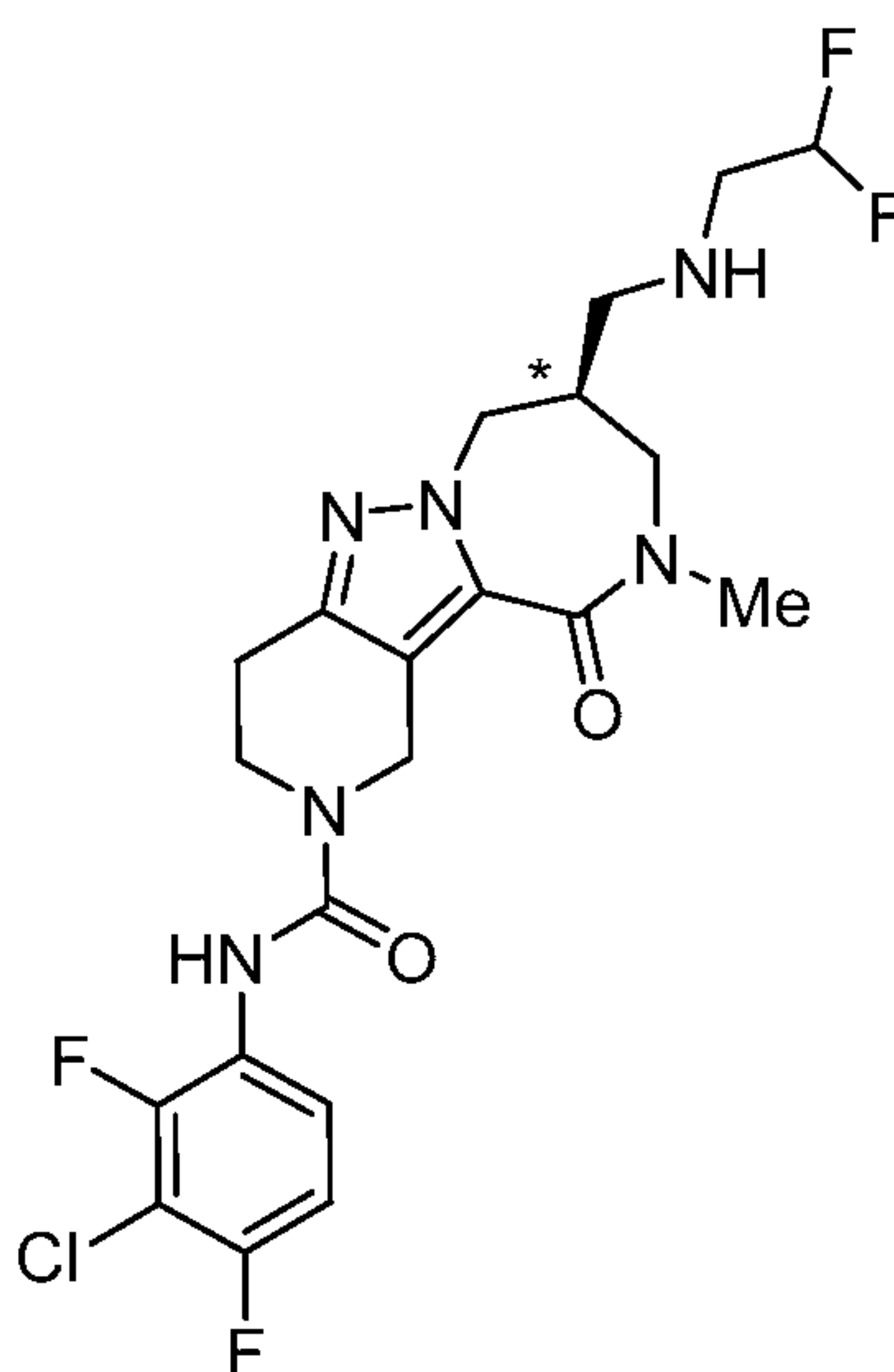
- 5 LCMS : 494 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 8.27 (dt, *J* = 5.77, 9.16 Hz, 1 H), 6.97 - 7.05 (m, 1 H), 6.66 (br d, *J* = 2.51 Hz, 1 H), 5.67 - 6.02 (m, 1 H), 4.72 (s, 2 H), 4.40 (m, 1 H), 4.17 (m, 1 H), 3.78 - 3.94 (m, 2 H), 3.29 - 3.50 (m, 2 H), 3.18 (s, 3 H), 2.92 - 3.07 (m, 2 H), 2.86 (t, *J* = 5.84 Hz, 2 H), 2.67 - 2.80 (m, 2 H), 2.50 - 2.62 (m, 1 H).

- 10 Compound 127_E2: (S*)-N-(3-cyano-2,4-difluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

*Pure but unknown diastereomer E2.

- 15 LCMS : 494 [M+1]. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 7.76 (dt, *J* = 5.99, 8.93 Hz, 1 H), 7.17 - 7.26 (m, 1 H), 6.21 - 6.57 (m, 1 H), 4.72 (s, 2 H), 4.54 (m, 1 H), 4.36 (m, 1 H), 3.76 - 3.97 (m, 2H), 3.54 - 3.74 (m, 3 H), 3.08 - 3.27 (m, 5 H), 3.00 (br s, 1 H), 2.86 (br t, *J* = 5.56 Hz, 2 H).

- 20 Compound 128_E1: (R*)-N-(3-chloro-2,4-difluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

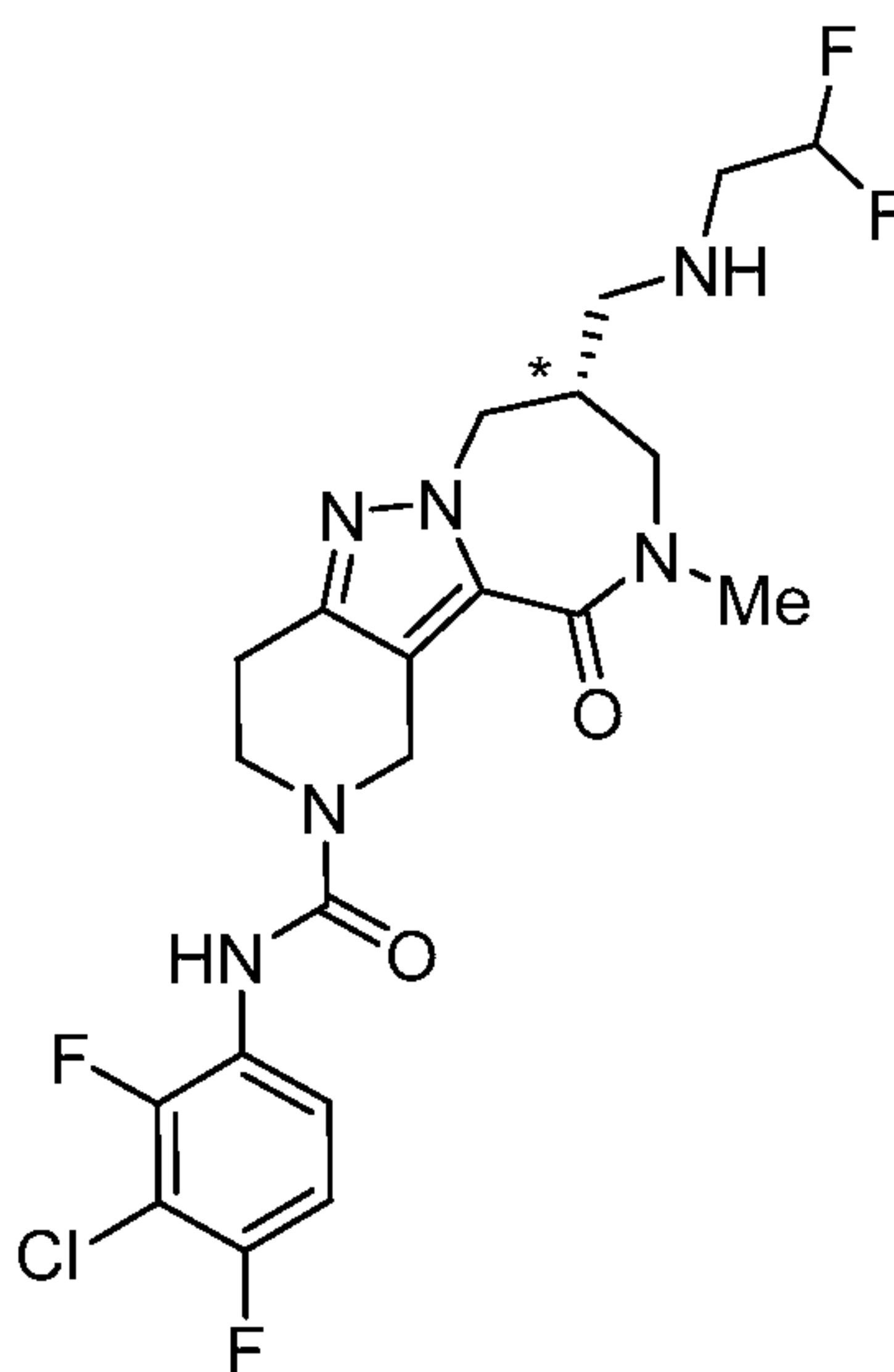


*Pure but unknown diastereomer E1.

LCMS : 503/505 [M+1]. ^1H NMR (400 MHz, METHANOL- d_4) δ 7.34 (dt, $J = 5.62, 8.74$ Hz, 1 H), 7.08 (dt, $J = 1.90, 8.83$ Hz, 1 H), 6.21 - 6.54 (m, 1 H), 4.63 - 4.77 (m, 2 H), 4.53 (m, 1 H), 4.34 (m, 1 H), 3.75 - 3.95 (m, 2 H), 3.53 - 3.72 (m, 3 H), 3.08 - 3.27 (m, 5 H), 2.98 (br s, 1 H), 2.84 (t, $J = 5.75$ Hz, 2 H).

5

Compound 128_E2: (S*)-N-(3-chloro-2,4-difluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

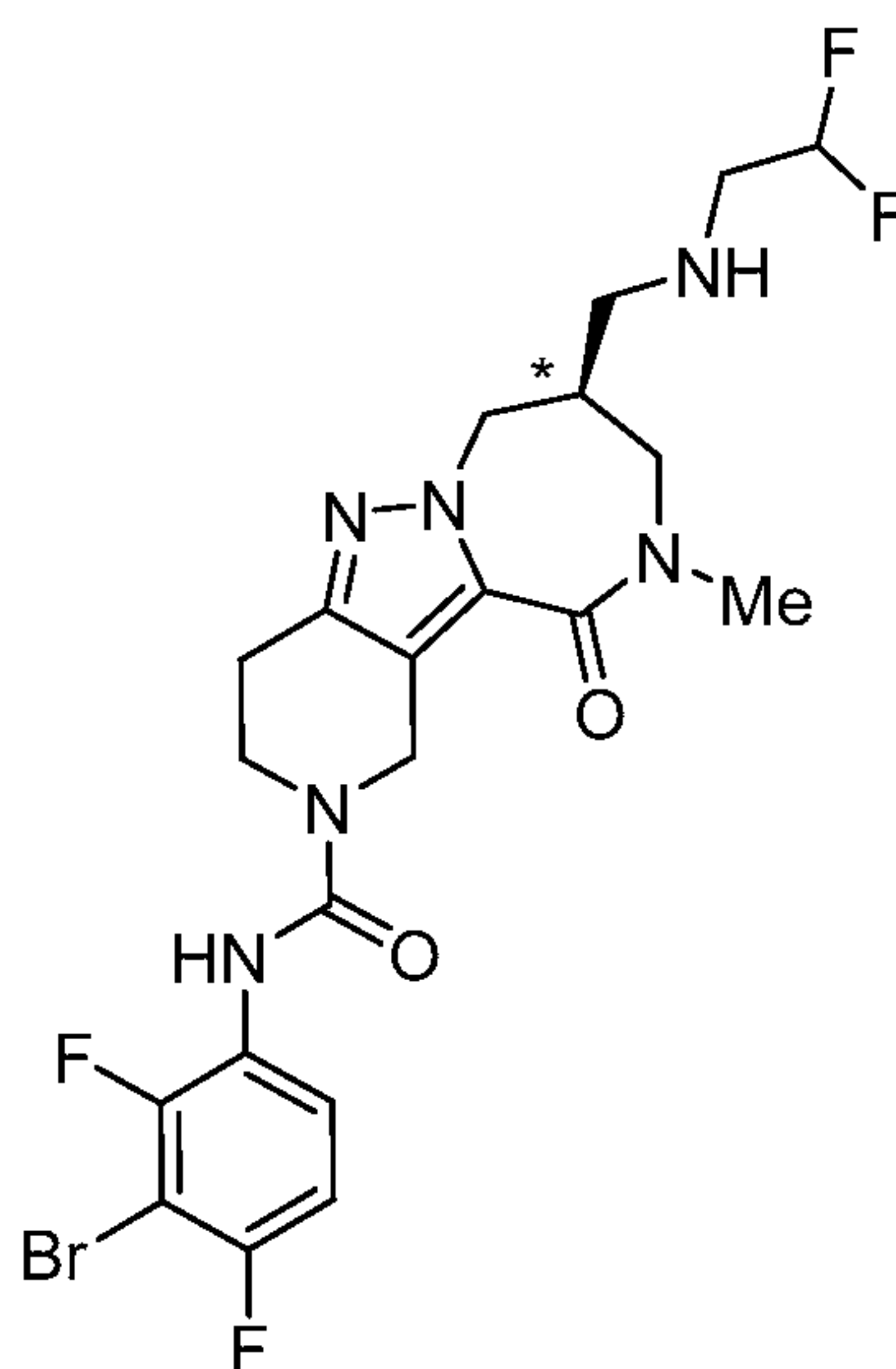


10 *Pure but unknown diastereomer E2.

LCMS : 503/505 [M+1]. ^1H NMR (400 MHz, CDCl_3) δ 7.86 (dt, $J = 5.50, 8.93$ Hz, 1 H), 6.90 - 7.00 (m, 1 H), 6.62 (br d, $J = 2.32$ Hz, 1 H), 5.66 - 6.01 (m, 1 H), 4.71 (s, 2 H), 4.40 (dd, $J = 6.85, 14.31$ Hz, 1 H), 4.17 (m, 1 H), 3.74 - 3.94 (m, 2 H), 3.26 - 3.49 (m, 2 H), 3.06 - 3.22 (m, 3 H), 2.91 - 3.05 (m, 2 H), 2.85 (t, $J = 5.75$ Hz, 2 H), 2.65 - 2.80 (m, 2 H), 2.49 - 2.59 (m, 1 H).

15

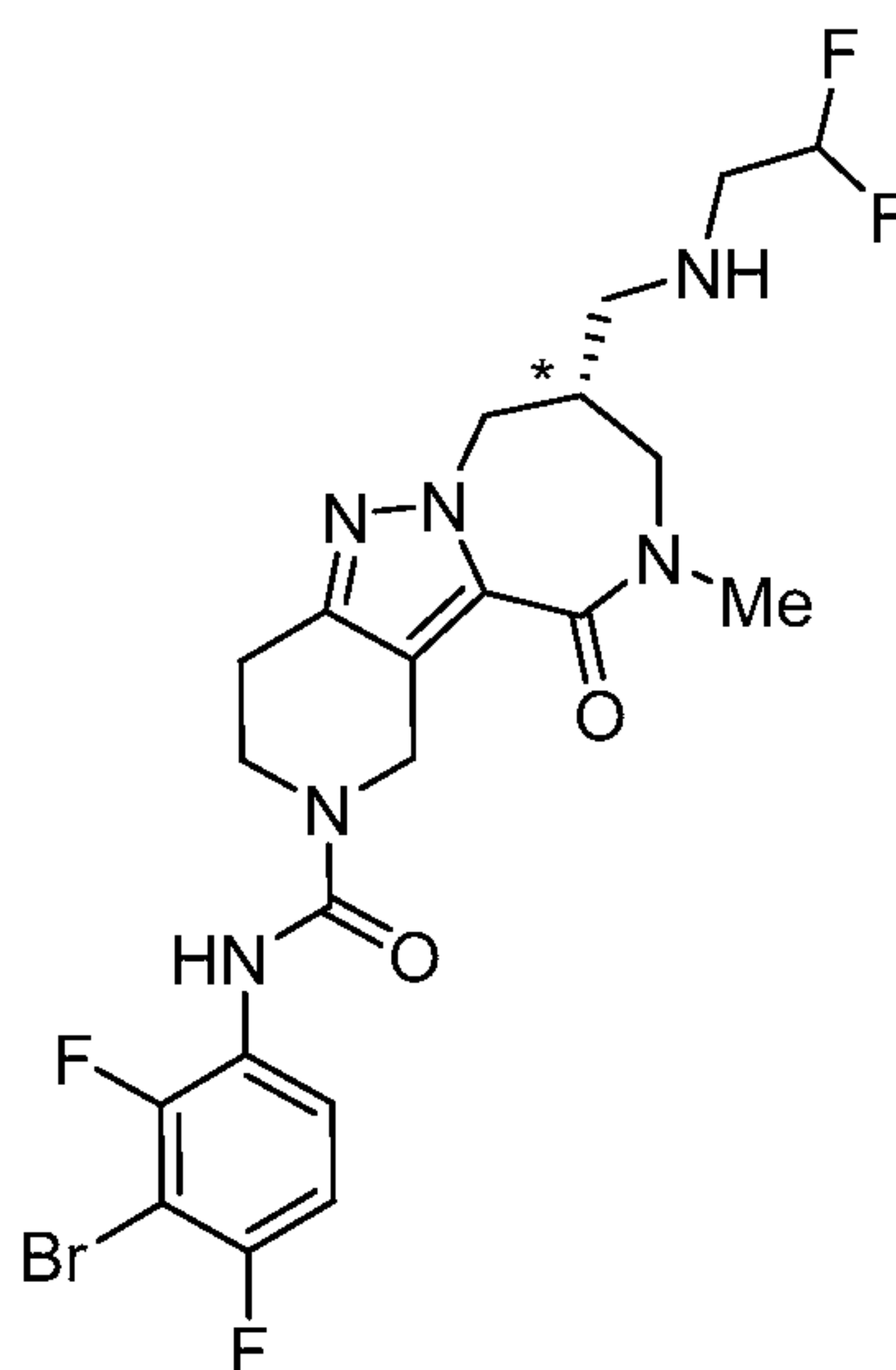
Compound 129_E1: (R*)-N-(3-bromo-2,4-difluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



*Pure but unknown diastereomer E1.

LCMS : 547/549 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 7.93 (dt, *J* = 5.58, 8.94 Hz, 1 H), 6.94 (m, 1 H), 6.59 (d, *J* = 2.76 Hz, 1 H), 5.66 - 6.03 (m, 1 H), 4.71 (s, 2 H), 4.40 (m, 1 H), 4.17 (m, 1 H), 3.77 - 3.93 (m, 2 H), 3.28 - 3.49 (m, 2 H), 3.18 (s, 3 H), 2.91 - 3.08 (m, 2 H), 2.85 (t, *J* = 5.77 Hz, 2 H), 2.75 (m, 2 H), 2.49 - 2.61 (m, 1 H).

Compound 129 E2: (S*)-N-(3-bromo-2,4-difluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

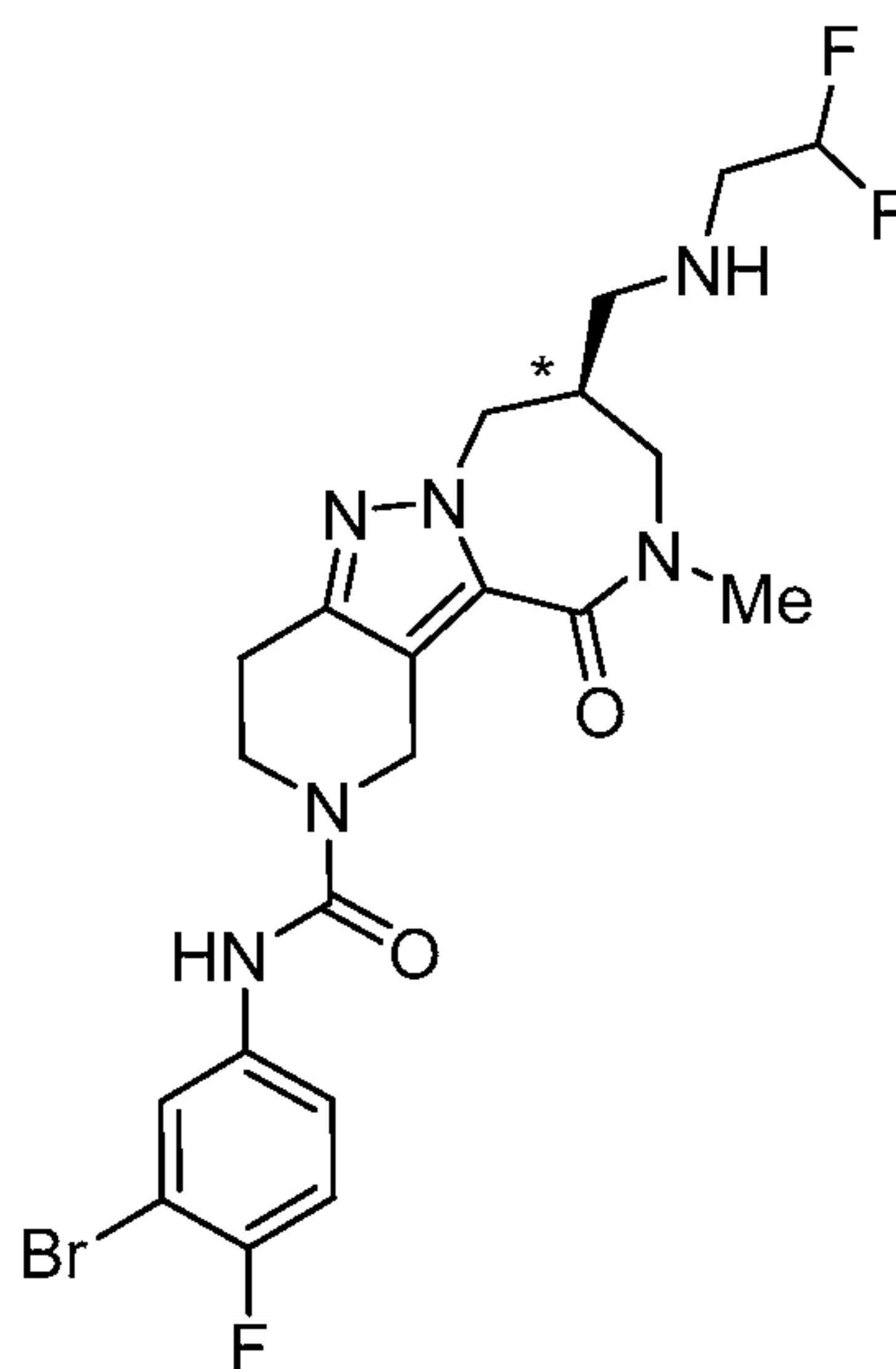


*Pure but unknown diastereomer E2.

LCMS : 547/549 [M+1]. ^1H NMR (400 MHz, CDCl_3) δ 8.00 (s, 1 H), 7.93 (dt, $J = 5.75, 8.86$ Hz, 1 H), 6.89 - 7.00 (m, 1 H), 6.58 (br s, 1 H), 5.68 - 6.02 (m, 1 H), 4.71 (s, 2 H), 4.12 - 4.44 (m, 2 H), 3.77 - 3.93 (m, 2 H), 3.28 - 3.50 (m, 2 H), 3.18 (s, 3 H), 2.95 - 3.08 (m, 2 H), 2.85 (t, $J = 5.81$ Hz, 2 H), 2.70 - 2.82 (m, 2 H), 2.51 - 2.63 (m, 1 H).

5

Compound 130_E1: (R*)-N-(3-bromo-4-fluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

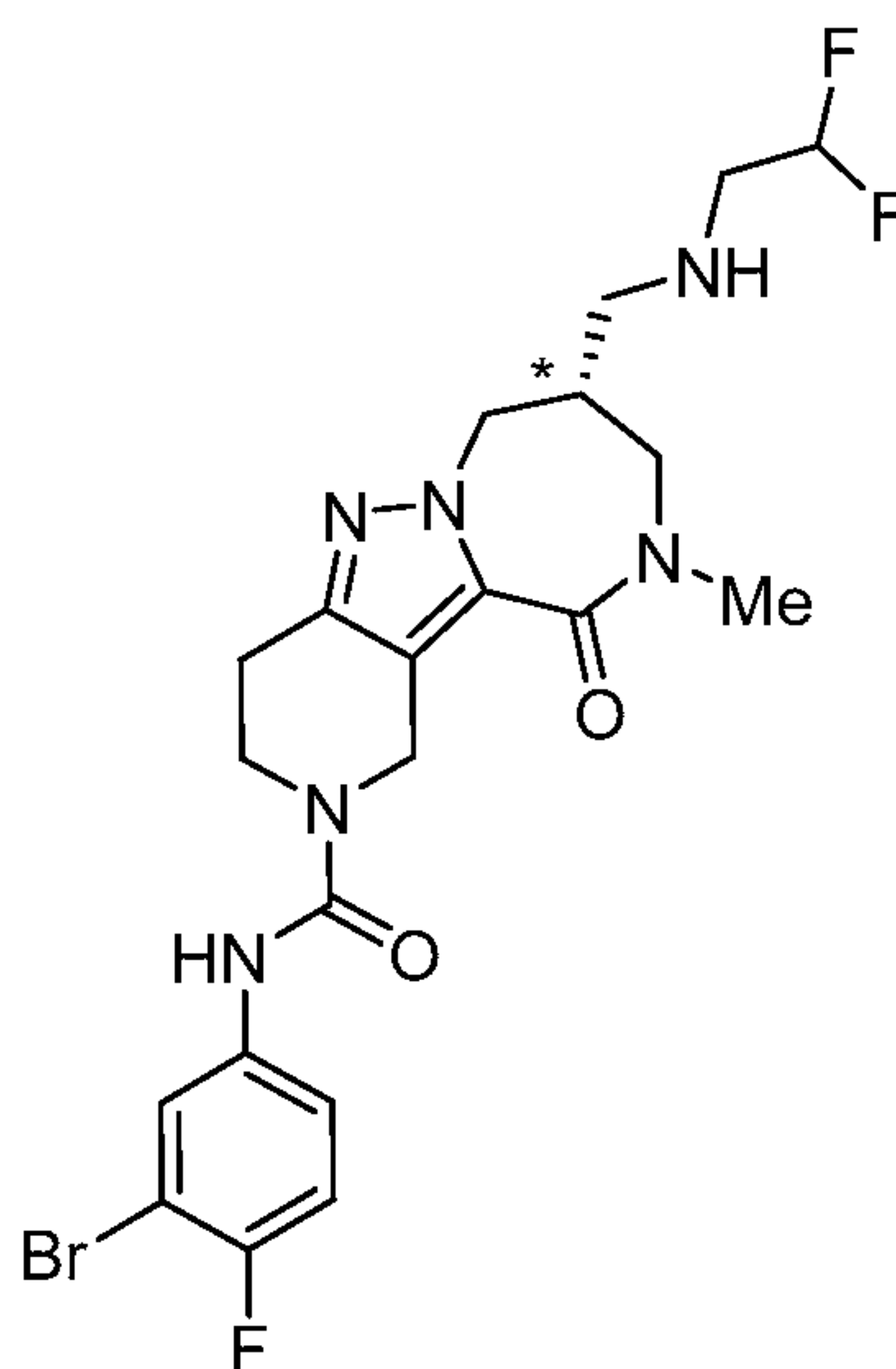


10 *Pure but unknown diastereomer E1.

LCMS : 529/531 [M+1]. ^1H NMR (400 MHz, METHANOL-d_4) δ 7.68 - 7.75 (m, 1 H), 7.33 (m, 1 H), 7.11 (t, $J = 8.74$ Hz, 1 H), 6.19 - 6.52 (m, 1 H), 4.67 (d, $J = 1.96$ Hz, 2 H), 4.51 (m, 1 H), 4.33 (mz, 1 H), 3.71 - 3.93 (m, 2 H), 3.51 - 3.70 (m, 3 H), 3.07 - 3.26 (m, 5 H), 2.90 - 3.03 (m, 1 H), 2.82 (br t, $J = 5.62$ Hz, 2 H).

15

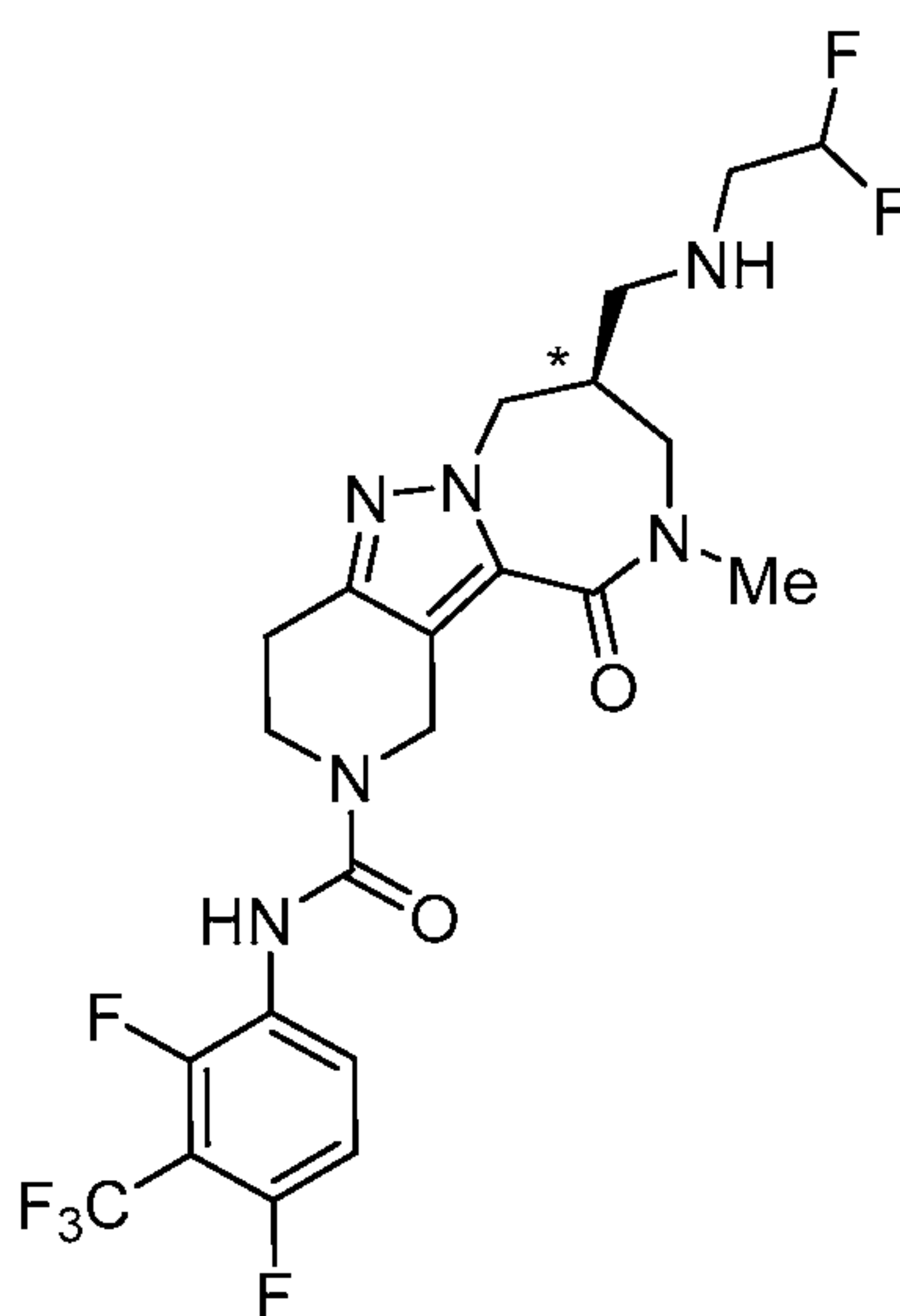
Compound 130_E2: (S*)-N-(3-bromo-4-fluorophenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



*Pure but unknown diastereomer E2.

LCMS : 529/531 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 8.01 (s, 1 H), 7.72 (dd, *J* = 2.64, 6.02 Hz, 1 H), 7.23 - 7.26 (m, 1 H), 7.00 - 7.07 (m, 1 H), 6.52 - 6.64 (m, 1 H), 6.58 (s, 1 H), 5.66 - 6.05 (m, 1 H), 4.67 (s, 2 H), 4.41 (m, 1 H), 4.18 (dd, *J* = 5.40, 14.56 Hz, 1 H), 3.77 - 3.93 (m, 2 H), 3.26 - 3.51 (m, 2 H), 3.18 (s, 3 H), 2.94 - 3.09 (m, 2 H), 2.84 (t, *J* = 5.71 Hz, 2H), 2.65 - 2.80 (m, 2 H), 2.52 - 2.63 (m, 1H).

10 Compound 131_E1: (R*)-N-(2,4-difluoro-3-(trifluoromethyl)phenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

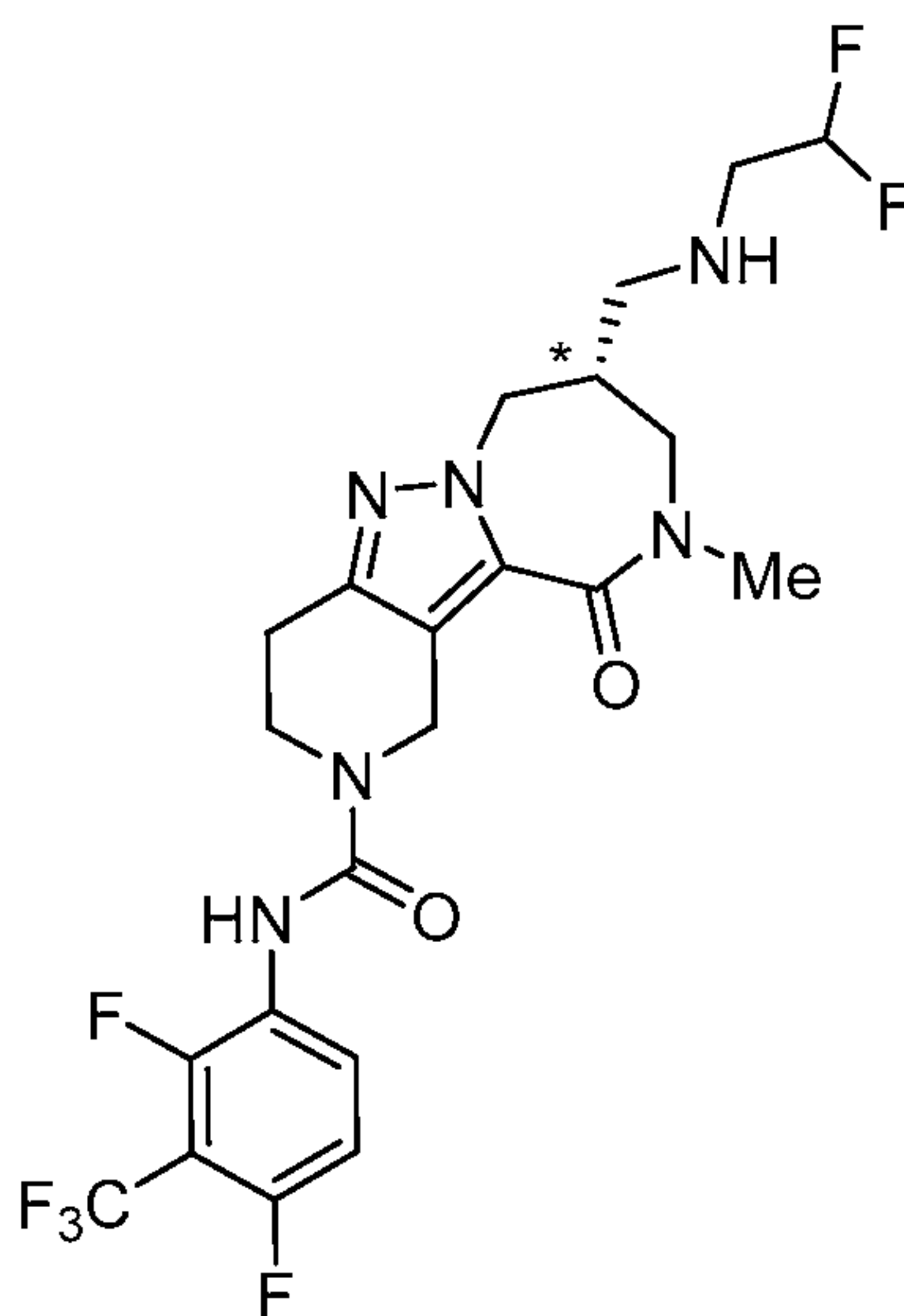


*Pure but unknown diastereomer E1.

LCMS : 537 [M+1]. ¹H NMR (400 MHz, METHANOL-d₄) δ 7.68 (dt, *J* = 5.62, 8.68 Hz, 1 H), 7.14 (t, *J* = 9.72 Hz, 1 H), 6.19 - 6.52 (m, 1 H), 4.70 (d, *J* = 2.32 Hz, 2 H), 4.51 (m, 1 H), 4.33 (m, 1 H), 3.73 - 3.95 (m, 2 H), 3.52 - 3.70 (m, 3 H), 3.09 - 3.27 (m, 5 H), 2.98 (br s, 1 H), 2.83 (br t, *J* = 5.75 Hz, 2 H).

5

Compound 131_E2: (S*)-N-(2,4-difluoro-3-(trifluoromethyl)phenyl)-8-(((2,2-difluoroethyl)amino)methyl)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

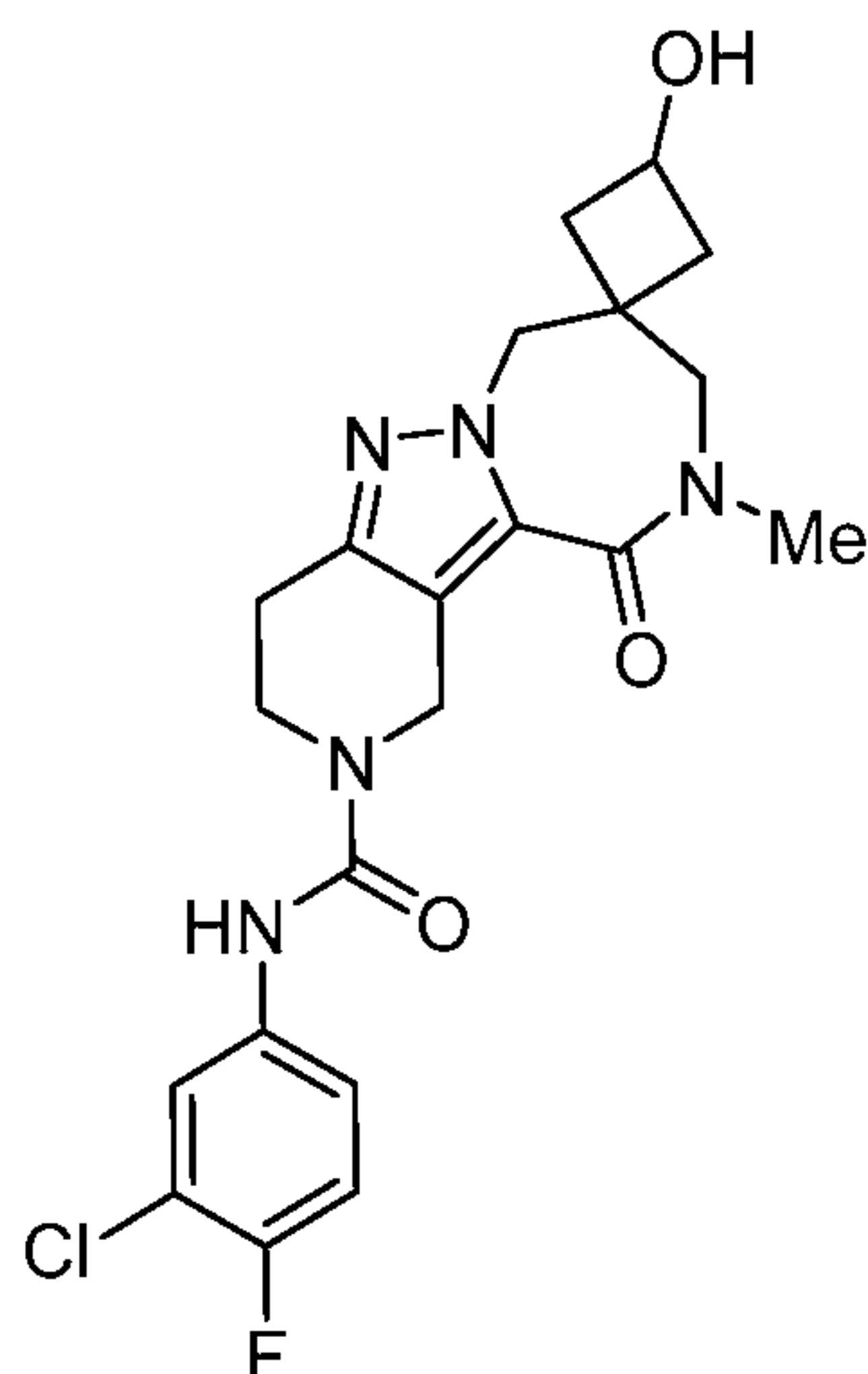


10 *Pure but unknown diastereomer E2.

LCMS : 537 [M+1]. ¹H NMR (400 MHz, CDCl₃) δ 8.21 (dt, *J* = 5.46, 8.94 Hz, 1 H), 6.98 (t, *J* = 8.85 Hz, 1 H), 6.65 (br d, *J* = 3.01 Hz, 1 H), 5.66 - 6.01 (m, 1 H), 4.72 (s, 2 H), 4.40 (m, 1 H), 4.17 (m, 1 H), 3.77 - 3.95 (m, 2 H), 3.29 - 3.49 (m, 2 H), 3.18 (s, 3 H), 3.00 (m, 2 H), 2.86 (t, *J* = 5.71 Hz, 2 H), 2.67 - 2.80 (m, 2 H), 2.50 - 2.60 (m, 1 H).

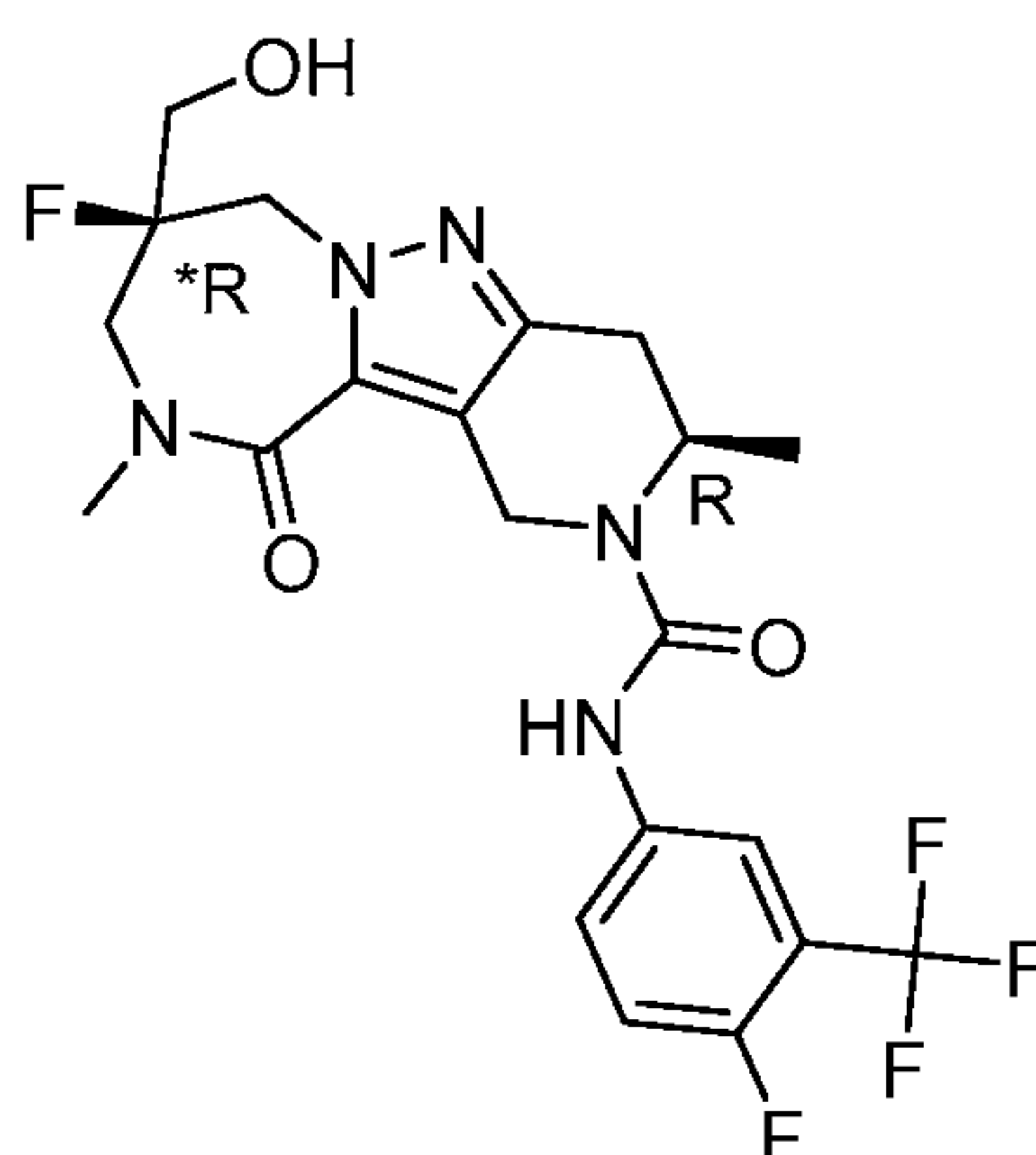
15

Compound 132: N-(3-chloro-4-fluorophenyl)-3-hydroxy-10'-methyl-11'-oxo-1',3',4',9',10',11'-hexahydro-2'H,7'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine]-2'-carboxamide.



To a solution of 3'-hydroxy-10-methyl-spiro[1,2,3,4,7,9-hexahydropyrido[2,3]pyrazolo[2,4-b][1,4]diazepine-8,1'-cyclobutane]-11-one (Intermediate 24, 30.00 mg, 76.85 μ mol, 1.00 *eq*, TFA) in DCM (4.00 mL) was added TEA (38.88 mg, 384.25 μ mol, 53.26 μ L, 5.00 *eq*), followed by phenyl N-(3-chloro-4-fluoro-phenyl)carbamate (20.42 mg, 76.85 μ mol, 1.00 *eq*). The mixture was stirred at 20 °C for 1 hr. LCMS showed one main peak with desired Ms detected. The mixture was concentrated in vacuum. The residue was purified by prep-HPLC (FA) to afford the title compound (24.00 mg, 53.58 μ mol, 69.73% yield) as white solid. LCMS: 448[M+1]. ^1H NMR (400 MHz, METHANOL- d_4) δ = 7.60 (dd, J = 2.63, 6.66 Hz, 1 H), 7.27 - 7.33 (m, 1 H), 7.09 - 7.18 (m, 1 H), 4.68 (s, 2 H), 4.34 - 4.42 (m, 1 H), 4.32 (s, 2 H), 3.83 (t, J = 5.81 Hz, 2 H), 3.41 (s, 2 H), 3.18 (s, 3 H), 2.82 (t, J = 5.81 Hz, 2 H), 2.38 - 2.49 (m, 2 H), 1.87 - 1.98 (m, 2 H).

Compound 133_D1: (3R,8R*)-8-fluoro-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide_D1.



Step 1. 2-(tert-butyl) 8-ethyl (3R)-8-fluoro-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2,8-dicarboxylate. To a solution of LDA (1 M, 959.45 μ L, 1.30 eq) in THF (2.00 mL) was added a solution of 2-(tert-butyl) 8-ethyl (3R)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2,8-dicarboxylate (300.00 mg, 738.04 μ mol, 1.00 eq) in THF (2.00 mL) at -78°C. The mixture was stirred at -78°C for 30 min. Then a solution of NFSI (279.28 mg, 885.65 μ mol, 1.20 eq) in THF (2.00 mL) was added at -78°C. Then the mixture was stirred at -78°C for 1 hr. The reaction mixture was quenched with saturated NH_4Cl (10 mL) and extracted with EtOAc (80 mL*2). The combined organic layers were dried over Na_2SO_4 , filtrated and concentrated in vacuum. The residue was purified column chromatography (PE:EA:30%~50%) to afford the title compound (250.00 mg, 512.40 μ mol, 69.43% yield, 87% purity) as a white solid. ^1H NMR (400MHz, CHLOROFORM-d) δ = 4.72 (dd, J = 15.1, 17.8 Hz, 1H), 4.59 - 4.42 (m, 3H), 4.33 - 4.21 (m, 2H), 3.86 - 3.73 (m, 1H), 3.70 - 3.49 (m, 3H), 3.11 (s, 3H), 2.69 (br s, 2H), 1.41 (s, 9H), 1.29 (t, J = 7.2 Hz, 3H).

Step 2. tert-Butyl (3R)-8-fluoro-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate D1 and tert-Butyl (3R)-8-fluoro-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate D2. To a solution of 2-(tert-butyl) 8-ethyl (3R)-8-fluoro-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2,8-dicarboxylate (230.00 mg, 541.85 μ mol, 1.00 eq) in THF (6.00 mL) was added LiBH_4 (35.40 mg, 1.63 mmol, 3.00 eq) with stirring at 0 °C for 1 h. The mixture was poured into the 20 mL of saturated NH_4Cl and extracted with EtOAc (20 mL*3), and then the combined organic phase was washed with brine (20 mL*1), dried over

anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was combined with a 30 mg (pilot reaction) and purified by prep-TLC (PE: EtOAc = 1:2) to obtain two diastereomers of the title compound: 45 mg tert-butyl (3R)-8-fluoro-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate as colorless oil and 120 mg of and tert-Butyl (3R)-8-fluoro-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate D2 as a white solid.

Step 3. (3R)-8-fluoro-8-(hydroxymethyl)-3,10-dimethyl-1,2,3,4,7,8,9,10-octahydro-11H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11-one D1 and (3R)-8-fluoro-8-(hydroxymethyl)-3,10-dimethyl-1,2,3,4,7,8,9,10-octahydro-11H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11-one D2

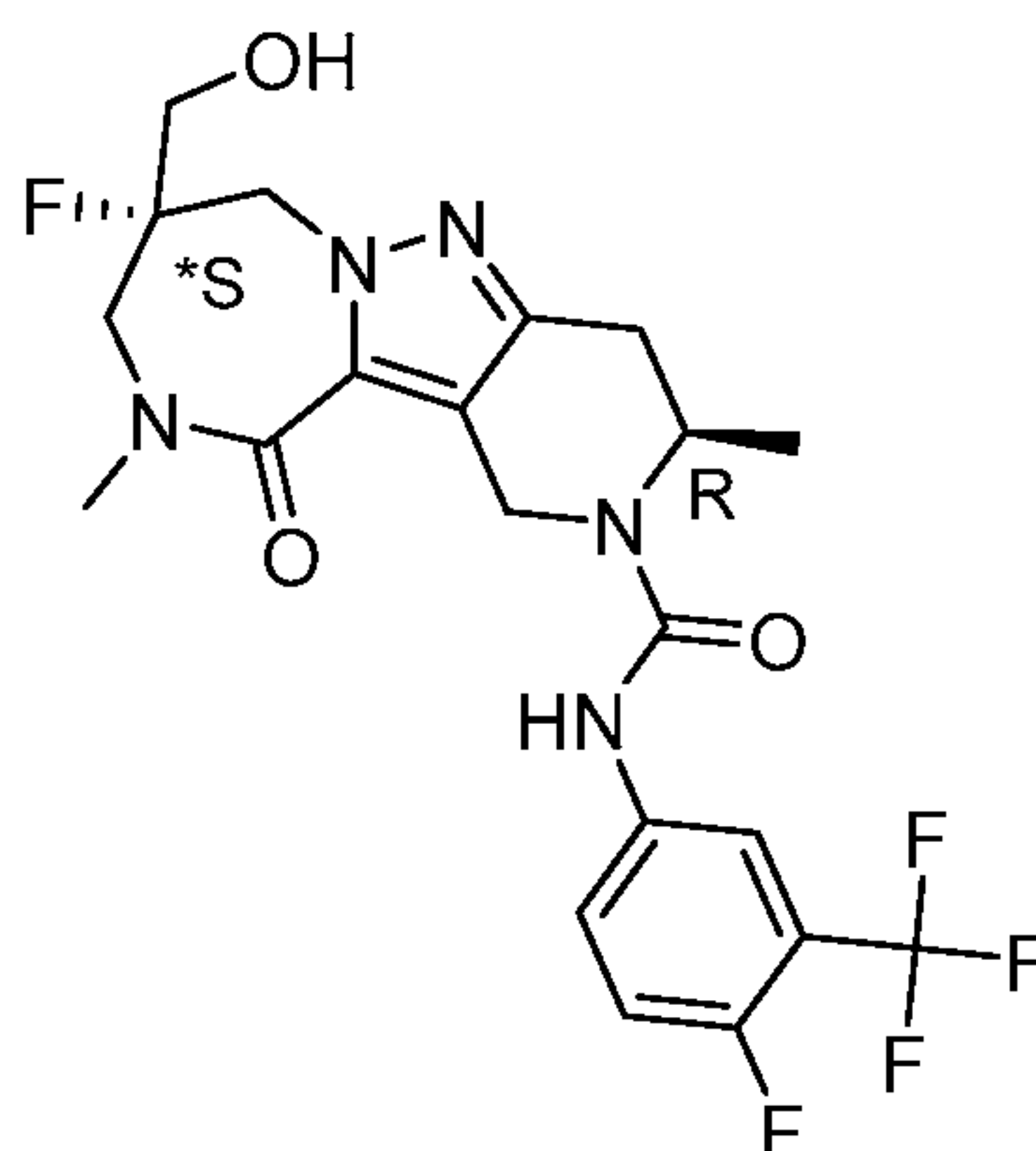
To a solution of tert-butyl (3R)-8-fluoro-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (45.00 mg, 117.67 μmol, 1.00 *eq*) in DCM (3.00 mL) was added TFA (462.00 mg, 4.05 mmol, 300.00 μL, 34.43 *eq*) at 15 °C with stirring for 1 h. The mixture was concentrated in vacuo.

The residue was not purified. The title compound (47.00 mg, crude, TFA) was obtained as yellow oil and directly used in the next step.

Step 4. (3R,8R*)-8-fluoro-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide D1.

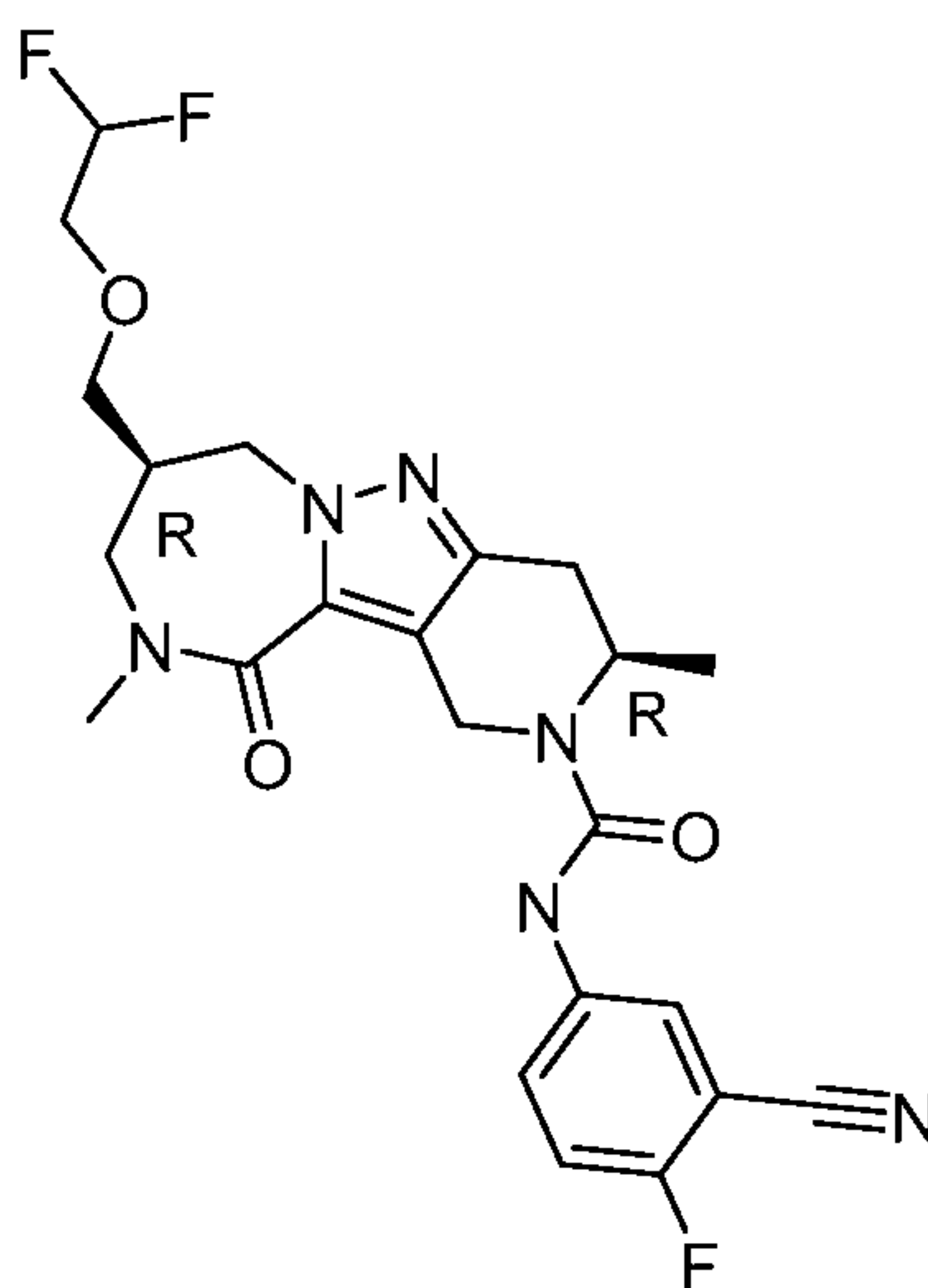
To a solution of (3R)-8-fluoro-8-(hydroxymethyl)-3,10-dimethyl-1,2,3,4,7,8,9,10-octahydro-11H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11-one D1 (47.00 mg, 118.59 μmol, 1.00 *eq*, TFA) and phenyl N-[4-fluoro-3-(trifluoromethyl)phenyl]carbamate (35.48 mg, 118.59 μmol, 1.00 *eq*) in DCM (5.00 mL) was added TEA (72.00 mg, 711.54 μmol, 98.63 μL, 6.00 *eq*) at 20 °C with stirring for 2 h. The mixture was concentrated in vacuo. The residue was purified by prep-HPLC(FA) to obtain the title compound (34.00 mg, 69.76 μmol, 58.82% yield) as white solid. LCMS: 488 [M+1]; ¹H NMR (400 MHz, CHLOROFORM-d) δ 7.67 (dd, *J* = 2.76, 6.15 Hz, 1 H), 7.54 - 7.62 (m, 1 H), 7.13 (t, *J* = 9.35 Hz, 1 H), 6.55 (s, 1 H), 5.07 - 5.17 (m, 1 H), 4.81 (d, *J* = 15.56 Hz, 1 H), 4.39 - 4.58 (m, 3 H), 3.75 - 3.97 (m, 2 H), 3.63 (d, *J* = 5.90 Hz, 1 H), 3.59 (s, 1 H), 3.23 (s, 3 H), 3.01 (dd, *J* = 5.83, 16.12 Hz, 1 H), 2.69 (d, *J* = 16.06 Hz, 1 H), 2.01 - 2.12 (m, 1 H), 1.20 (d, *J* = 6.90 Hz, 3 H).

Compound 133_D2: (3R,8S*)-8-fluoro-N-(4-fluoro-3-(trifluoromethyl)phenyl)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide_D2.



- 5 The title compound was prepared in a manner analogous to Compound 133_D1. LCMS: 488 [M+1]. ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.70 (dd, J = 2.70, 6.09 Hz, 1 H), 7.56 - 7.64 (m, 1 H), 7.27 (s, 3 H), 7.13 (t, J = 9.35 Hz, 1 H), 6.74 (br s, 1 H), 5.10 - 5.20 (m, 1 H), 4.89 (d, J = 15.56 Hz, 1 H), 4.40 - 4.52 (m, 3 H), 3.77 - 3.98 (m, 2 H), 3.64 (d, J = 2.89 Hz, 1 H), 3.60 (s, 1 H), 3.22 (s, 3 H), 3.03 (dd, J = 6.02, 15.94 Hz, 1 H), 2.67 (d, J = 16.19 Hz, 1 H), 2.20 (br s, 1 H), 1.18 (d, J = 6.90 Hz, 3 H).
- 10

Compound 134_D1: (3R,8R)-N-(3-Cyano-4-fluorophenyl)-8-((2,2-difluoroethoxy)methyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. tert-Butyl (3R,8R)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate. To a mixture of tert-butyl (3R,8R)-8-(methoxy(methyl)carbamoyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (400.00 mg, 901.56 μ mol, 1 *eq*) in THF (6 mL) and MeOH (6 mL) was added NaBH₄ (68.21 mg, 1.80 mmol, 2 *eq*) in one portion at 0 °C under N₂. The mixture was stirred at 0 °C for 3 hours. The mixture was poured into water (10 mL) and stirred for 1 min. The aqueous phase was extracted with DCM (20 mL*2). The combined organic layers were washed with brine (15 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, Dichloromethane : Methanol=100/1, 20/1) to afford the title compound (328 mg, 900.01 μ mol, 99.83% yield, 100% purity) as yellow solid. LCMS: 365 [M+1].

Step 2. tert-Butyl (3R,8R)-8-((2,2-difluoroethoxy)methyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate.

To a mixture of tert-butyl (3R,8R)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (100.00 mg, 274.39 μ mol, 1 *eq*) in THF (1 mL) was added NaH (21.95 mg, 548.79 μ mol, 60% purity, 2 *eq*) in one portion at -20 °C under N₂. The mixture was stirred at -20 °C for 30 min, then 2,2-difluoroethyl trifluoromethanesulfonate (176.25 mg, 823.18 μ mol, 3 *eq*) was added to the mixture. The mixture was stirred at -20 °C for 2 hours. The mixture was poured into water (15 mL) and stirred for 1 min. The aqueous phase was extracted with ethyl acetate (25 mL*2). The combined organic layers were washed with brine (10 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-TLC (Ethyl acetate : Petroleum ether=2/1) to afford the title compound (107 mg, 249.72 μ mol, 91.01% yield, 100% purity) as a yellow solid. LCMS: 429 [M+1].

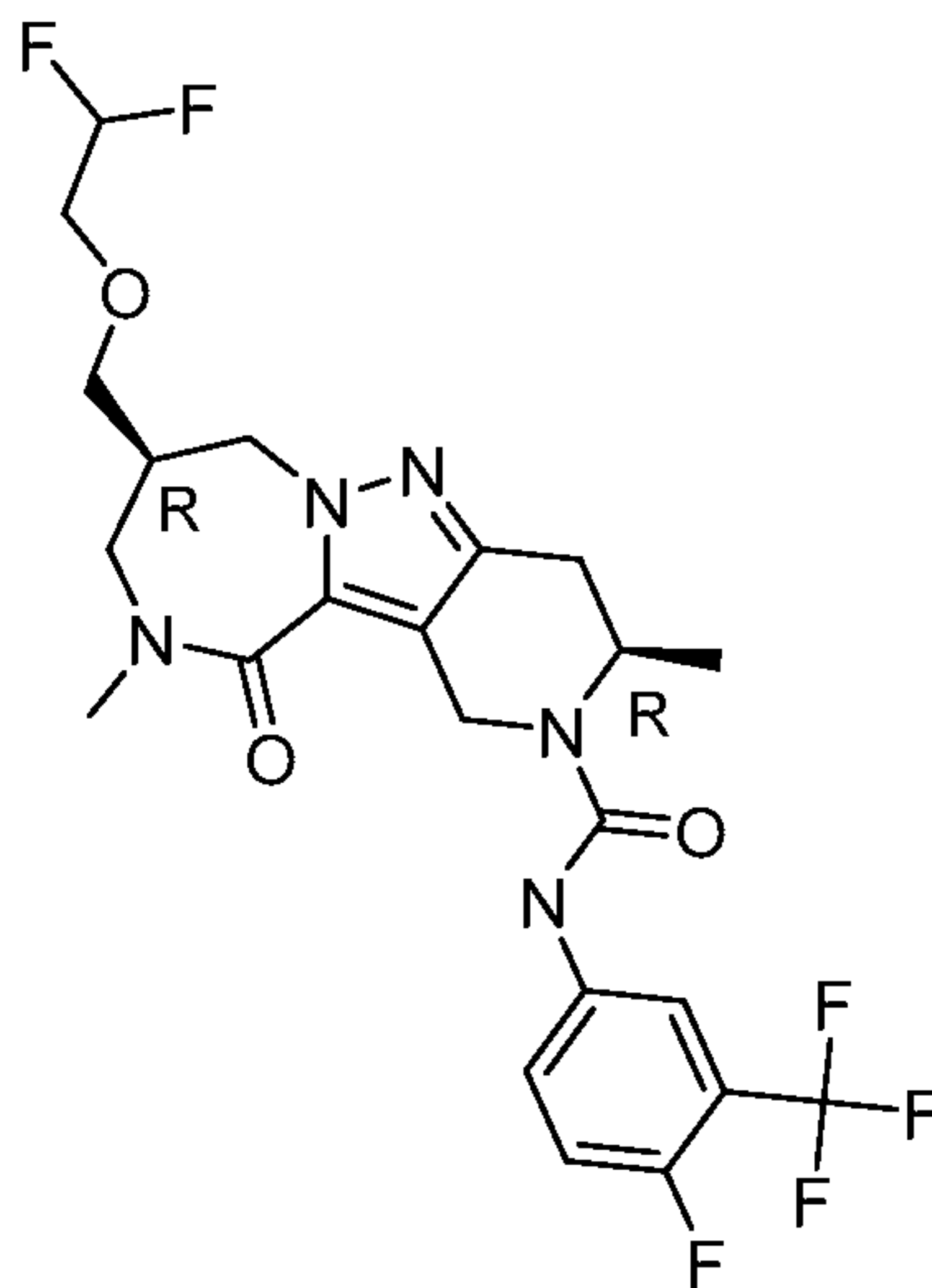
Step 3. (3R,8R)-8-((2,2-Difluoroethoxy)methyl)-3,10-dimethyl-1,2,3,4,7,8,9,10-octahydro-11H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11-one. To a solution of tert-butyl (3R,8R)-8-((2,2-difluoroethoxy)methyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (160.00 mg, 373.42 μ mol, 1.00 *eq*) in DCM (2 mL) was added TFA (4.39 g, 38.48 mmol, 2.85 mL, 103.04 *eq*) under N₂. The

mixture was stirred at 30 °C for 2 hours. The mixture was concentrated in vacuum to afford the title compound (166 mg, crude) as yellow oil.

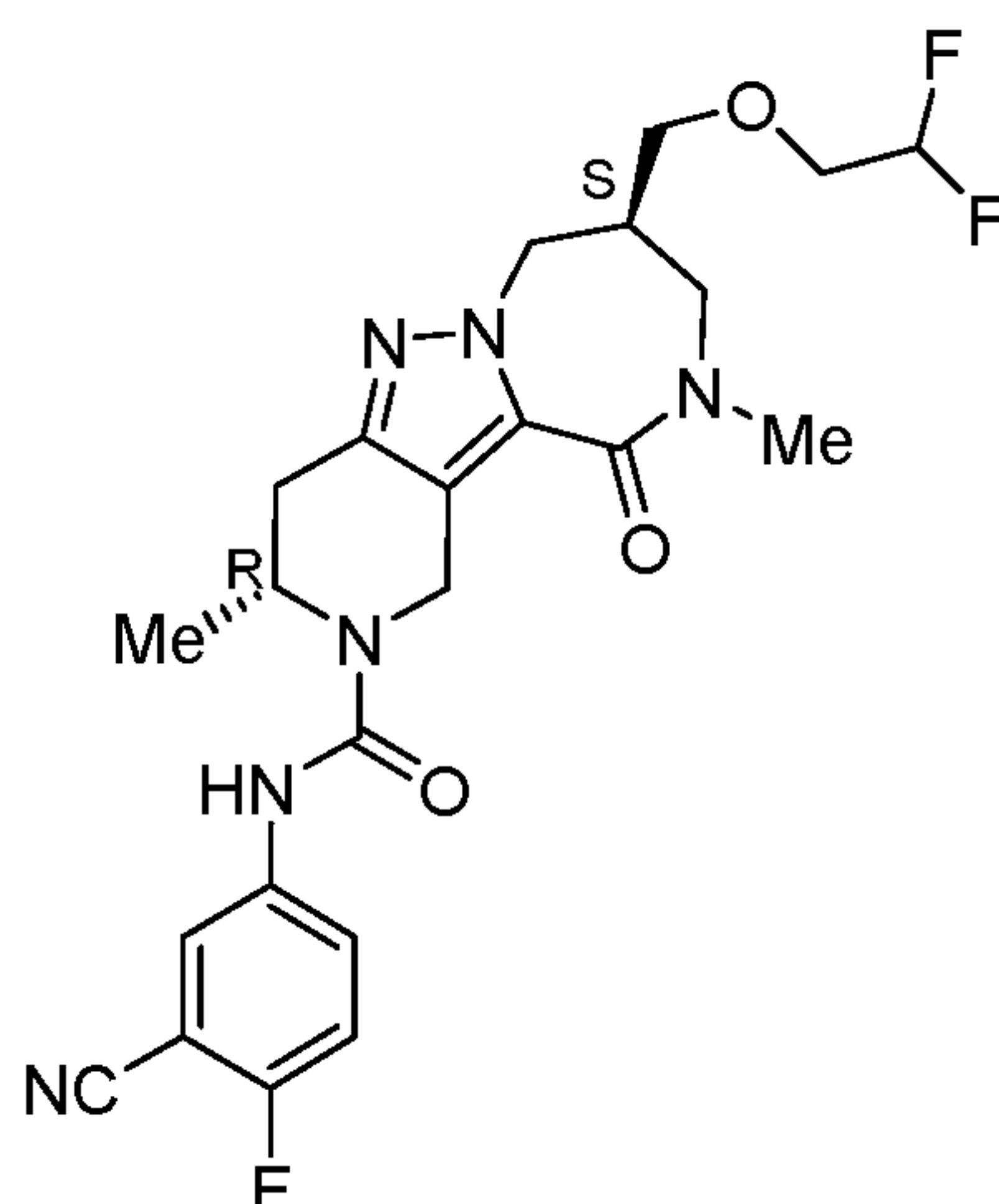
Step 4. (3R,8R)-N-(3-Cyano-4-fluorophenyl)-8-((2,2-difluoroethoxy)methyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-

5 carboxamide. To a mixture of (3R,8R)-8-((2,2-difluoroethoxy)methyl)-3,10-dimethyl-1,2,3,4,7,8,9,10-octahydro-11H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11-one (61.61 mg, 187.62 μmol, 1 *eq*, TFA) and phenyl N-(3-cyano-4-fluoro-phenyl)carbamate (53.42 mg, 187.62 μmol, 1 *eq*) in DCM (6.00 mL) was added TEA (189.85 mg, 1.88 mmol, 261.15 μL, 10.00 *eq*) under N₂. The mixture was stirred at 30 °C for 10 hours. The residue was poured into water (10
10 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (10 mL*2). The combined organic layers were washed with brine (5 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-HPLC(FA) to afford the title compound (76 mg, 152.63 μmol, 81.35% yield, 98.5% purity) as a white solid. LCMS: 491
15 [M+1]. ¹H NMR (400 MHz, CHLOROFORM-d) δ 7.79 (dd, *J* = 2.81, 5.50 Hz, 1 H), 7.51-7.60 (m, 1 H), 7.14 (t, *J* = 8.74 Hz, 1 H), 6.60 (s, 1 H), 5.72-6.08 (m, 1 H), 5.08-5.19 (m, 1 H), 4.80 (d, *J* = 15.41 Hz, 1 H), 4.38-4.53 (m, 2 H), 4.13 (dd, *J* = 6.97, 14.31 Hz, 1 H), 3.49-3.84 (m, 5 H), 3.37 (d, *J* = 6.24 Hz, 1 H), 3.18 (s, 3 H), 3.00 (d, *J* = 5.99 Hz, 1 H), 2.82 (br d, *J* = 6.36 Hz, 1 H), 2.68 (d, *J* = 16.26 Hz, 1 H), 1.19 (d, *J* = 6.97 Hz, 3 H).

20 Compound 135 D1: (3R,8R)-8-((2,2-difluoroethoxy)methyl)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Compound 134 D2: (3R,8S)-N-(3-cyano-4-fluorophenyl)-8-((2,2-difluoroethoxy)methyl)-3,10-
dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-
2-carboxamide.



Step 1. tert-Butyl (3R,8S)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-
octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate.

To a solution of tert-butyl (3R,8S)-8-(methoxy(methyl)carbamoyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-
 5 octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (300 mg, 711.76
 μmol , 1 eq) in THF (6 mL) and MeOH (6 mL) was added NaBH_4 (53.85 mg, 1.42 mmol, 2 eq) at
 0 °C. The solution was stirred at 25 °C for 16 hr. The solution was poured into water (30 mL).
 The mixture extracted with ethyl acetate (20 mL*2). The combined organic layers were washed
 with brine (20 mL), dried with anhydrous Na_2SO_4 , filtered and concentrated. The residue was
 10 purified by column chromatography. The title compound (230 mg, 602.71 μmol , 84.68% yield,
 95.5% purity) was obtained as yellow oil. LCMS: 365 [M+1].

Step 2. tert-Butyl (3R,8S)-8-((2,2-difluoroethoxy)methyl)-3,10-dimethyl-11-oxo-
1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate.

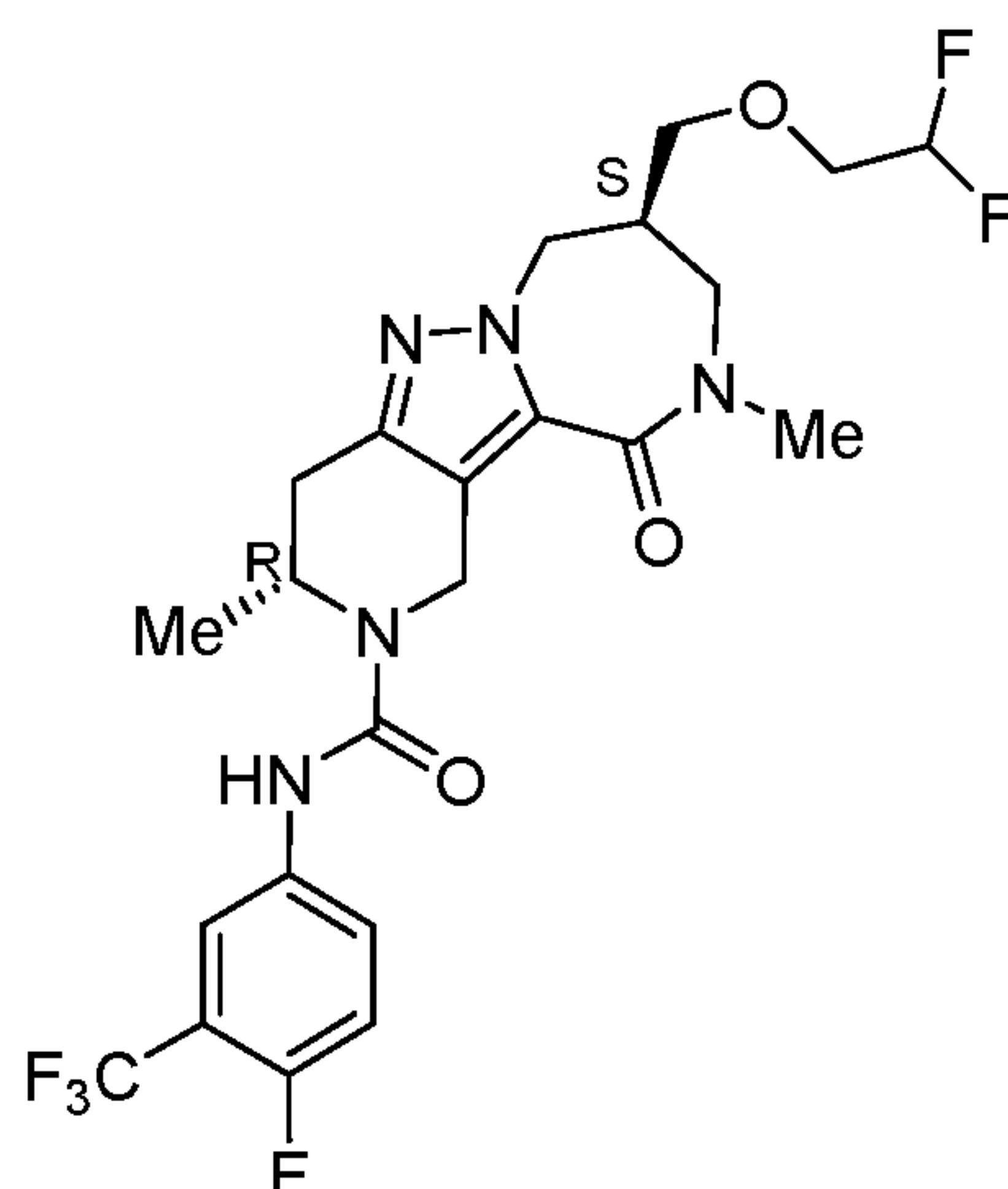
To a solution of tert-butyl (3R,8S)-8-(hydroxymethyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-
 15 octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (230 mg, 631.11
 μmol , 1 eq) in THF (10 mL) was added NaH (50.49 mg, 1.26 mmol, 60% purity, 2 eq) at -20 °C.
 The solution was stirred at -20 °C for 30 min. Then 2, 2,2-difluoroethyl
 trifluoromethanesulfonate (405.38 mg, 1.89 mmol, 3 eq) was added, the solution was stirred at -
 15 °C for 2 hr. The solution was poured into water (30 mL). The mixture extracted with ethyl
 20 acetate (20 mL*2). The combined organic layers were washed with brine (20 mL*3), dried with
 anhydrous Na_2SO_4 , filtered and concentrated. The residue was purified by prep-TLC. The title
 compound (190 mg, 443.44 μmol , 70.26% yield) was obtained as yellow oil.

Step 3. (3R,8S)-8-((2,2-Difluoroethoxy)methyl)-3,10-dimethyl-1,2,3,4,7,8,9,10-octahydro-11H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11-one. To a solution of tert-butyl (3R,8S)-8-((2,2-difluoroethoxy)methyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (190 mg, 443.44 μ mol, 1 eq) in DCM (5 mL) was added TFA (7.70 g, 67.53 mmol, 5.00 mL, 152.29 eq). The solution was stirred at 25 °C for 30 min. The solution was concentrated. The title compound (196 mg, crude, TFA) was obtained as yellow oil.

Step 4. (3R,8S)-N-(3-Cyano-4-fluorophenyl)-8-((2,2-difluoroethoxy)methyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-

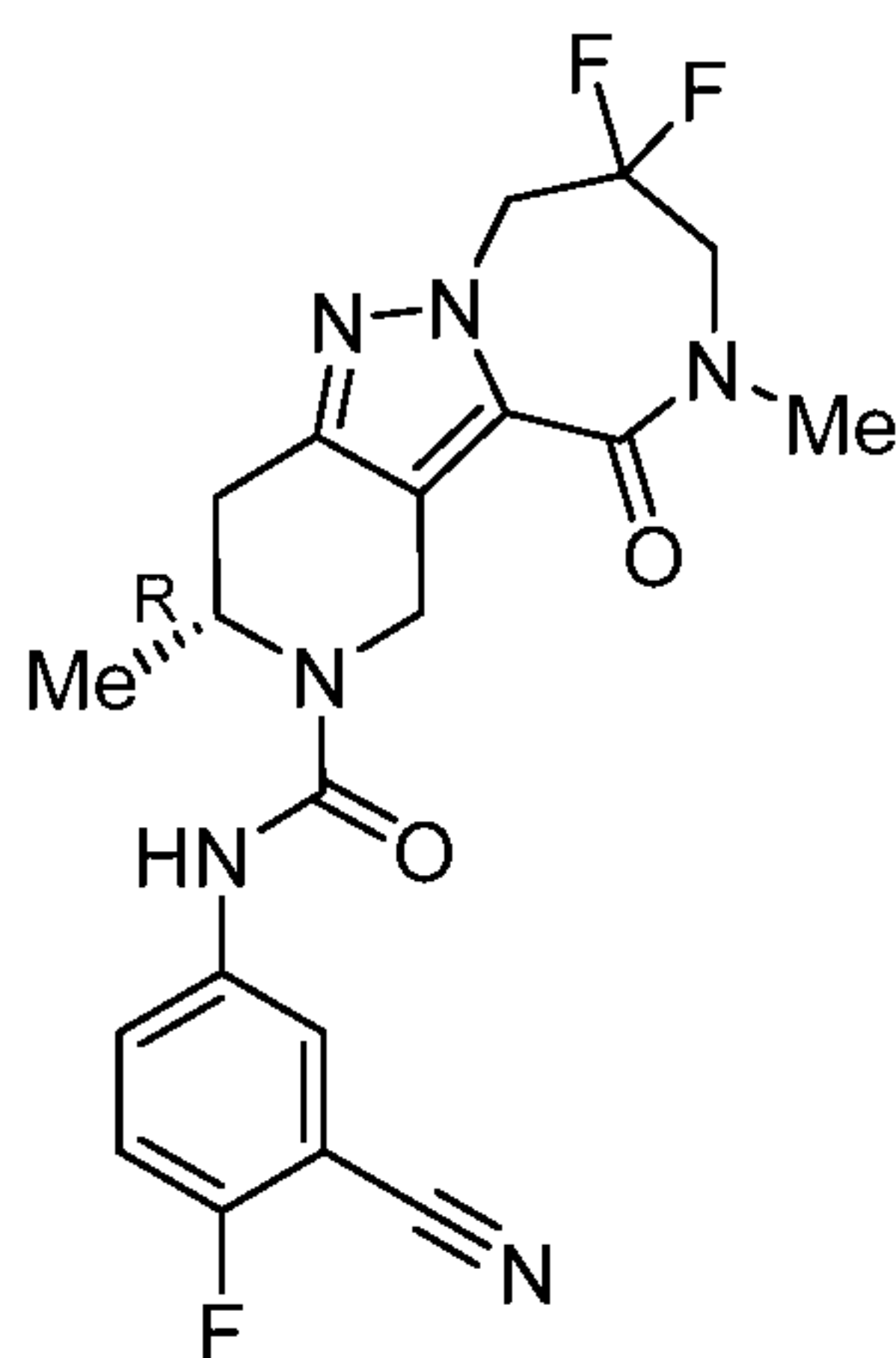
carboxamide. To a solution of (3R,8S)-8-((2,2-difluoroethoxy)methyl)-3,10-dimethyl-1,2,3,4,7,8,9,10-octahydro-11H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11-one (98 mg, 221.53 μ mol, 1 eq, TFA) in DCM (2 mL) was added TEA (67.25 mg, 664.59 μ mol, 92.50 μ L, 3 eq) and phenyl N-(3-cyano-4-fluoro-phenyl)carbamate (56.76 mg, 221.53 μ mol, 1 eq). The solution was stirred at 25 °C for 16 hr. TEA (67.25 mg, 664.59 μ mol, 92.50 μ L, 3 eq) was added. The solution was stirred at 25 °C for 16 hr. The solution was concentrated. The residue was purified by prep-HPLC (FA). The title compound (47.37 mg, 94.32 μ mol, 42.58% yield, 97.66% purity) was obtained as white solid. LCMS: 491 [M+1]; ^{1} H NMR (400 MHz, CHLOROFORM-d) δ 7.79 (dd, J=2.81, 5.38 Hz, 1H), 7.60 (ddd, J=2.87, 4.55, 9.08 Hz, 1H), 7.13 (t, J=8.68 Hz, 1H), 6.86 (s, 1H), 5.68-6.07 (m, 1H), 5.13 (quin, J=6.57 Hz, 1H), 4.84 (d, J=15.41 Hz, 1H), 4.36-4.52 (m, 2H), 4.15 (dd, J=5.93, 14.37 Hz, 1H), 3.48-3.83 (m, 5H), 3.33 (dd, J=7.09, 15.04 Hz, 1H), 3.18 (s, 3H), 3.01 (dd, J=5.75, 16.02 Hz, 1H), 2.82 (td, J=6.40, 12.75 Hz, 1H), 2.66 (d, J=15.89 Hz, 1H), 1.18 (d, J=6.85 Hz, 3H).

Compound 135_D2: (3R,8S)-8-((2,2-difluoroethoxy)methyl)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



To a solution of (3R,8S)-8-((2,2-difluoroethoxy)methyl)-3,10-dimethyl-1,2,3,4,7,8,9,10-octahydro-11H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11-one (98 mg, 221.53 μ mol, 1 eq, TFA) in DCM (2 mL) was added TEA (67.25 mg, 664.59 μ mol, 92.50 μ L, 3 eq) and phenyl N-[4-fluoro-3-(trifluoromethyl)phenyl]carbamate (66.29 mg, 221.53 μ mol, 1 eq). The solution was stirred at 25 °C for 16 hr. TEA (67.25 mg, 664.59 μ mol, 92.50 μ L, 3 eq) was added. The solution was stirred at 25 °C for 16 hr. The solution was concentrated. The residue was purified by prep-HPLC (FA). The title compound (68.35 mg, 122.53 μ mol, 55.31% yield, 95.63% purity) was obtained as a white solid. LCMS: 534 [M+1]; ^{1} H NMR (400 MHz, CHLOROFORM-d) δ 7.69 (dd, J =2.63, 6.05 Hz, 1H), 7.54-7.64 (m, 1H), 7.12 (t, J =9.41 Hz, 1H), 6.81 (s, 1H), 5.70-6.08 (m, 1H), 5.14 (quin, J =6.42 Hz, 1H), 4.84 (d, J =15.41 Hz, 1H), 4.33-4.53 (m, 2H), 4.16 (dd, J =5.75, 14.31 Hz, 1H), 3.43-3.88 (m, 5H), 3.32 (dd, J =7.27, 14.98 Hz, 1H), 3.17 (s, 3H), 3.02 (dd, J =5.81, 15.83 Hz, 1H), 2.74-2.89 (m, 1H), 2.66 (d, J =15.77 Hz, 1H), 1.17 (d, J =6.97 Hz, 3H).

Compound 136: (R)-N-(3-cyano-4-fluorophenyl)-8,8-difluoro-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. tert-Butyl (R)-3,10-dimethyl-8,11-dioxo-1,3,4,7,8,9,10,11-octahydro-2H-

pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate. To a solution of tert-butyl (R)-

3,10-dimethyl-8-methylene-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-

5 pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (370.00 mg, 1.07 mmol, 1.00 *eq*) in

THF (10.00 mL) and H₂O (5.00 mL) was added OsO₄ (27.20 mg, 107.00 μmol, 5.55 μL, 0.10

eq) and NaIO₄ (686.59 mg, 3.21 mmol, 177.87 μL, 3.00 *eq*) at 0 °C. The mixture was stirred at

15 °C for 16 hr. The mixture was diluted with EtOAc (60 mL) and washed with saturated

Na₂SO₃ (60 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo

10 to give brown oil. The resulting oil was purified via silica gel column (EA/PE=5/1) to afford the

title compound (200.00 mg, 539.61 μmol, 50.43% yield, 94% purity).

Step 2. tert-Butyl (R)-8,8-difluoro-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-

pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate. To a solution of tert-butyl (R)-

3,10-dimethyl-8,11-dioxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-

15 a][1,4]diazepine-2-carboxylate (80.00 mg, 229.62 μmol, 1.00 *eq*) in DCM (3.00 mL) was added

DAST (222.08 mg, 1.38 mmol, 182.03 μL, 6.00 *eq*) slowly with stirring at -30 °C under N₂. The

mixture was warmed to 15 °C with stirring for 16 h. The mixture was quenched with 10 mL of

water and extracted with DCM (15 mL*3). The combined organic layers were washed with

brine (15 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue

20 was purified by prep-TLC (DCM:MeOH=10:1) to afford the title compound (40.00 mg, 97.19

μmol, 42.33% yield, 90% purity) as colorless oil.

Step 3. (R)-8,8-Difluoro-3,10-dimethyl-1,2,3,4,7,8,9,10-octahydro-11H-

pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11-one. To a solution of tert-butyl (R)-8,8-

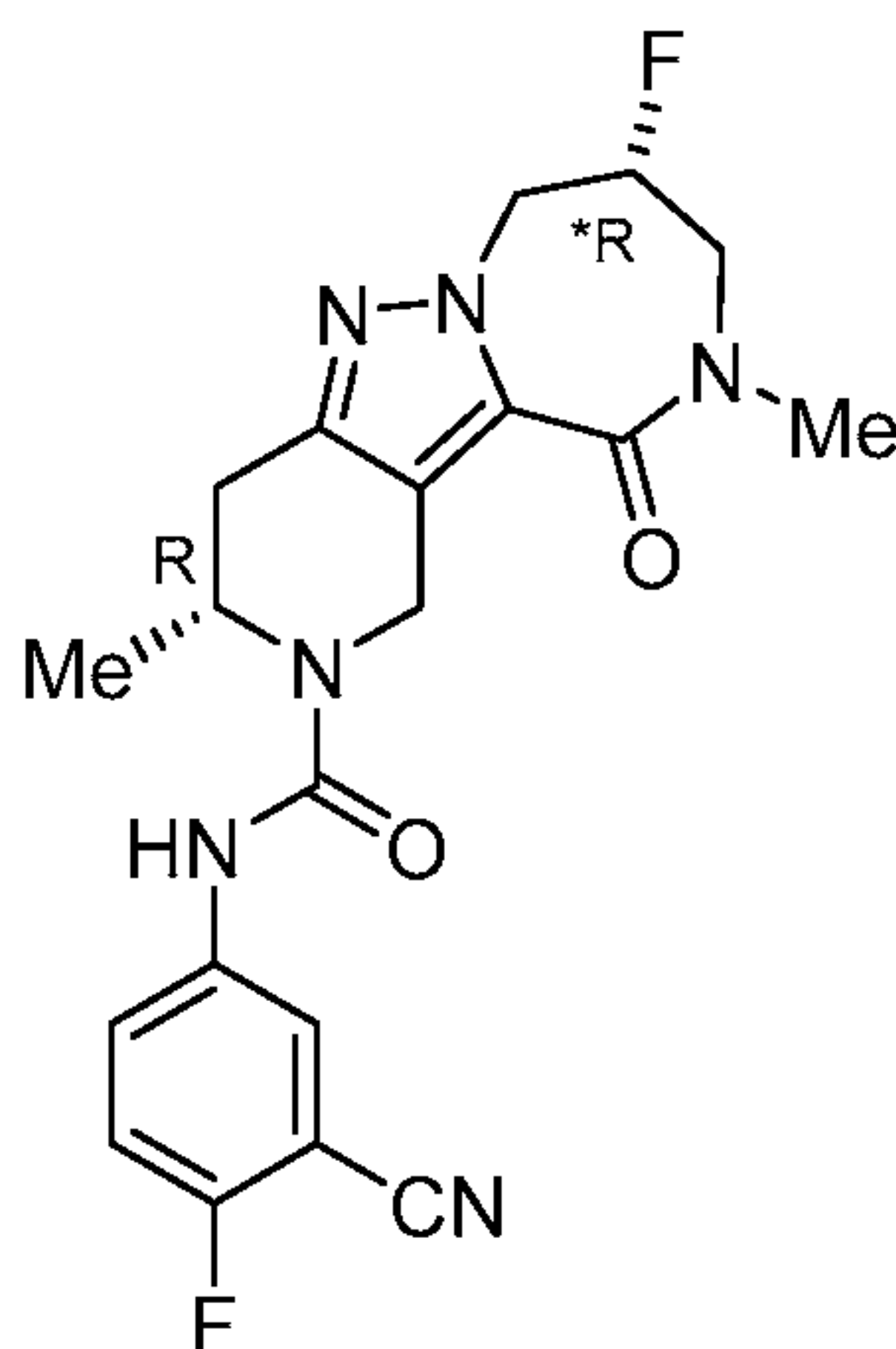
5 difluoro-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (40.00 mg, 97.19 μ mol, 1.00 *eq*) in DCM (3.00 mL) was added TFA (462.00 mg, 4.05 mmol, 300.00 μ L, 41.69 *eq*) at 15 °C, and the mixture was stirring for 2 h. The mixture was concentrated in vacuum to afford the title compound (40.00 mg, crude, TFA) was obtained as yellow oil, which was not purified and directly used in the next step.

Step 4. (R)-N-(3-Cyano-4-fluorophenyl)-8,8-difluoro-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-

octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. To a solution of (R)-8,8-difluoro-3,10-dimethyl-1,2,3,4,7,8,9,10-octahydro-11H-pyrido[4',3':3,4]pyrazolo[1,5-

10 TEA (63.20 mg, 624.54 μ mol, 86.58 μ L, 6.00 *eq*) and phenyl N-(3-cyano-4-fluoro-phenyl)carbamate (32.00 mg, 124.91 μ mol, 1.20 *eq*) at 15 °C, and then the mixture was stirring for 16 h. The mixture was concentrated in vacuum and purified by prep-HPLC (TFA) twice to give the title compound (18 mg, 39.96 μ mol, 38.39% yield, 96% purity) as a white solid. LCMS: 433 [M+1]; ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.76 (dd, *J* = 2.82, 5.33 Hz, 1 H), 7.60 (m, 1 H), 7.15 (t, *J* = 8.72 Hz, 1 H), 6.67 (s, 1 H), 5.07 - 5.16 (m, 1 H), 4.87 (d, *J* = 15.69 Hz, 1 H), 4.72 (t, *J* = 12.42 Hz, 2 H), 4.47 (d, *J* = 15.69 Hz, 1 H), 3.68 - 3.79 (m, 2 H), 3.25 (s, 3 H), 3.04 (dd, *J* = 5.58, 16.12 Hz, 1 H), 2.72 (d, *J* = 15.56 Hz, 1 H), 1.20 (d, *J* = 6.90 Hz, 3 H).

20 Compound 137_D1: (3R,8R*)-N-(3-cyano-4-fluorophenyl)-8-fluoro-3,10-dimethyl-11-oxo-
1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-
carboxamide_D1.



Step 1. tert-Butyl (3R)-8-hydroxy-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate. To a solution of tert-butyl (R)-3,10-dimethyl-8,11-dioxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (120.00 mg, 344.43 μmol , 1.00 *eq*) in MeOH (5.00 mL) was added NaBH₄ (39.09 mg, 1.03 mmol, 3.00 *eq*) at 0 °C, and then the mixture was warmed to 15 °C with stirring for 1 h under N₂ atmosphere. The mixture was poured into ice-water (20 mL) and stirred at 5 min. The aqueous phase was extracted with ethyl acetate (10 mL*3). The combined organic layers were washed with brine (20 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-TLC (DCM:MeOH=10:1) to give the title compound (78.00 mg, 222.60 μmol , 64.63% yield,) as colorless oil.

Step 2. tert-Butyl (3R)-8-fluoro-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate _D1 and tert-butyl (3R)-8-fluoro-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate _D2. To a solution of tert-butyl (3R)-8-hydroxy-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (60.00 mg, 171.23 μmol , 1.00 *eq*) in DCM (1.00 mL) was added DAST (82.80 mg, 513.68 μmol , 67.87 μL , 3.00 *eq*) drop wise at - 30 °C, and then the mixture was warmed to 15 °C with stirring for 1 h. The mixture was continued to stir at 15 °C for another 1 h. The mixture was quenched with 10 mL of water and extracted with DCM (15 mL*3). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue with was purified by prep-TLC (DCM:MeOH=10:1), following by SFC (SFC separation condition: column: IC(250mm*30mm,10um);mobile phase: [0.1%NH₃H₂O MEOH];B%: 25%-25%,4.35min;90 min) separation to give two diastereomers: 20 mg of tert-butyl (3R)-8-fluoro-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate _D1 and 18 mg of tert-butyl (3R)-8-fluoro-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate _D2 as colorless oil.

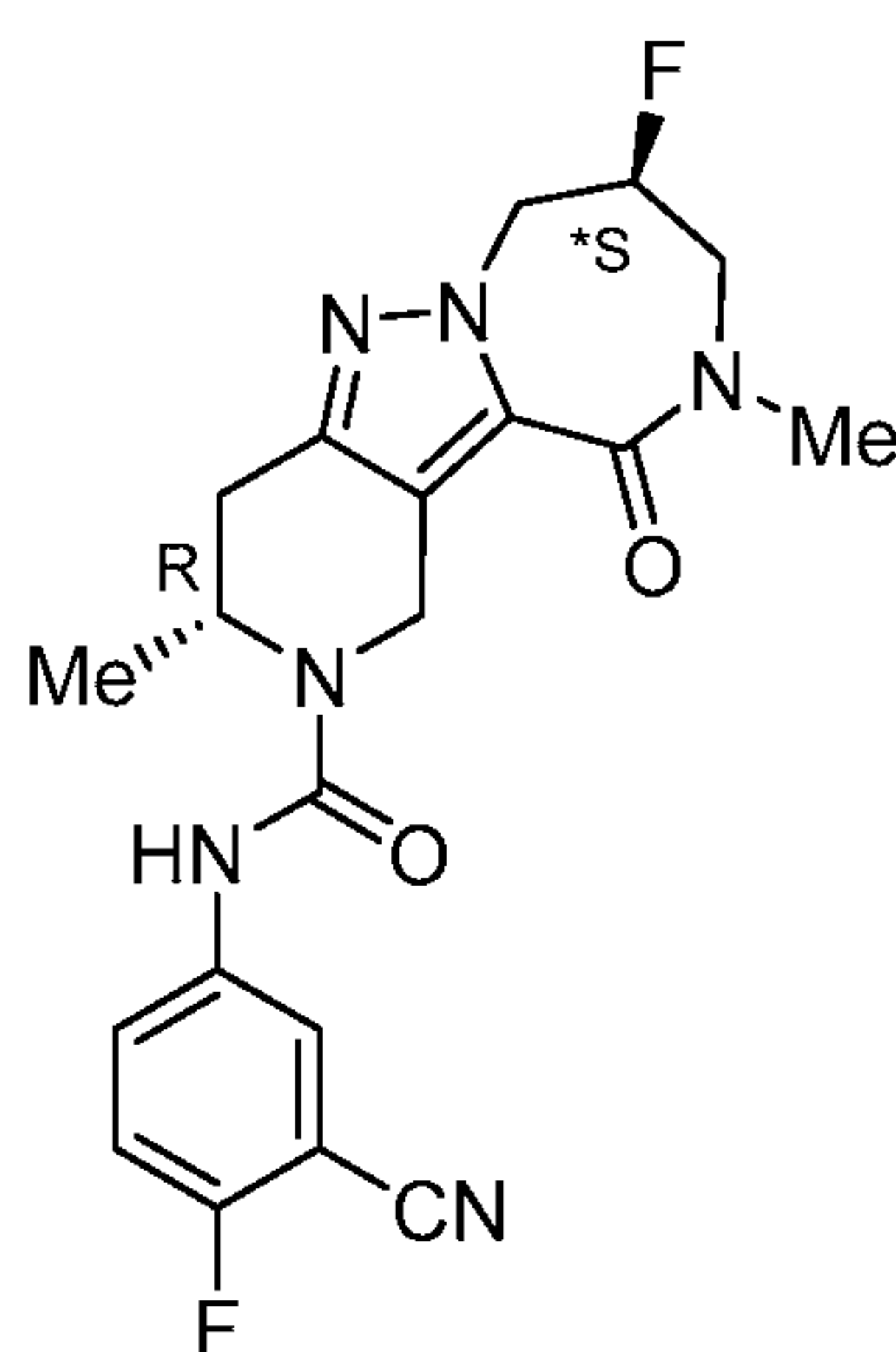
Step 3. (3R)-8-Fluoro-3,10-dimethyl-1,2,3,4,7,8,9,10-octahydro-11H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11-one _D1. To a solution of tert-butyl (3R)-8-fluoro-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate _D1 (20 mg, 56.75 μmol , 1 *eq*) in DCM (1 mL) was added TFA

(307.99 mg, 2.70 mmol, 199.99 μ L, 47.60 *eq*) dropwise at 15 °C, and the mixture was stirred for 1 h. The mixture was concentrated in vacuum to give the title compound (20.79 mg, crude, TFA) as yellow oil, which was not further purified and directly used in the next step.

Step 4. (3R,8R*)-N-(3-cyano-4-fluorophenyl)-8-fluoro-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-

5 octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide _D1. To a solution of (3R)-8-fluoro-3,10-dimethyl-1,2,3,4,7,8,9,10-octahydro-11H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11-one _D1 (20.79 mg, 56.75 μ mol, 1 *eq*, TFA) and TEA (34.46 mg, 340.52 μ mol, 47.40 μ L, 6 *eq*) in DCM (1 mL) was added phenyl N-(3-cyano-4-fluoro-phenyl)carbamate (18.91 mg, 73.78 μ mol, 1.3 *eq*), and stirred at 15 °C for 16 h. The mixture was concentrated in
10 vacuum, and was purified by prep-HPLC(FA) to give the title compound (7.5 mg, 18.03 μ mol, 31.76% yield, 99.6% purity) as a white solid. LCMS: 415 [M+1]. ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.80 (dd, *J* = 2.82, 5.46 Hz, 1 H), 7.56 (m, 1 H), 7.15 (t, *J* = 8.66 Hz, 1 H), 6.58 (s, 1 H), 5.11 - 5.19 (m, 1 H), 4.83 (d, *J* = 15.69 Hz, 1 H), 4.36 - 4.59 (m, 5 H), 3.97 - 4.07 (m, 1 H), 3.23 (s, 3 H), 3.04 (dd, *J* = 6.21, 16.00 Hz, 1 H), 2.72 (d, *J* = 16.19 Hz, 1 H), 1.19
15 (d, *J* = 6.90 Hz, 3 H).

Compound 137 _D2: (3R,8S*)-N-(3-Cyano-4-fluorophenyl)-8-fluoro-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide _D2.

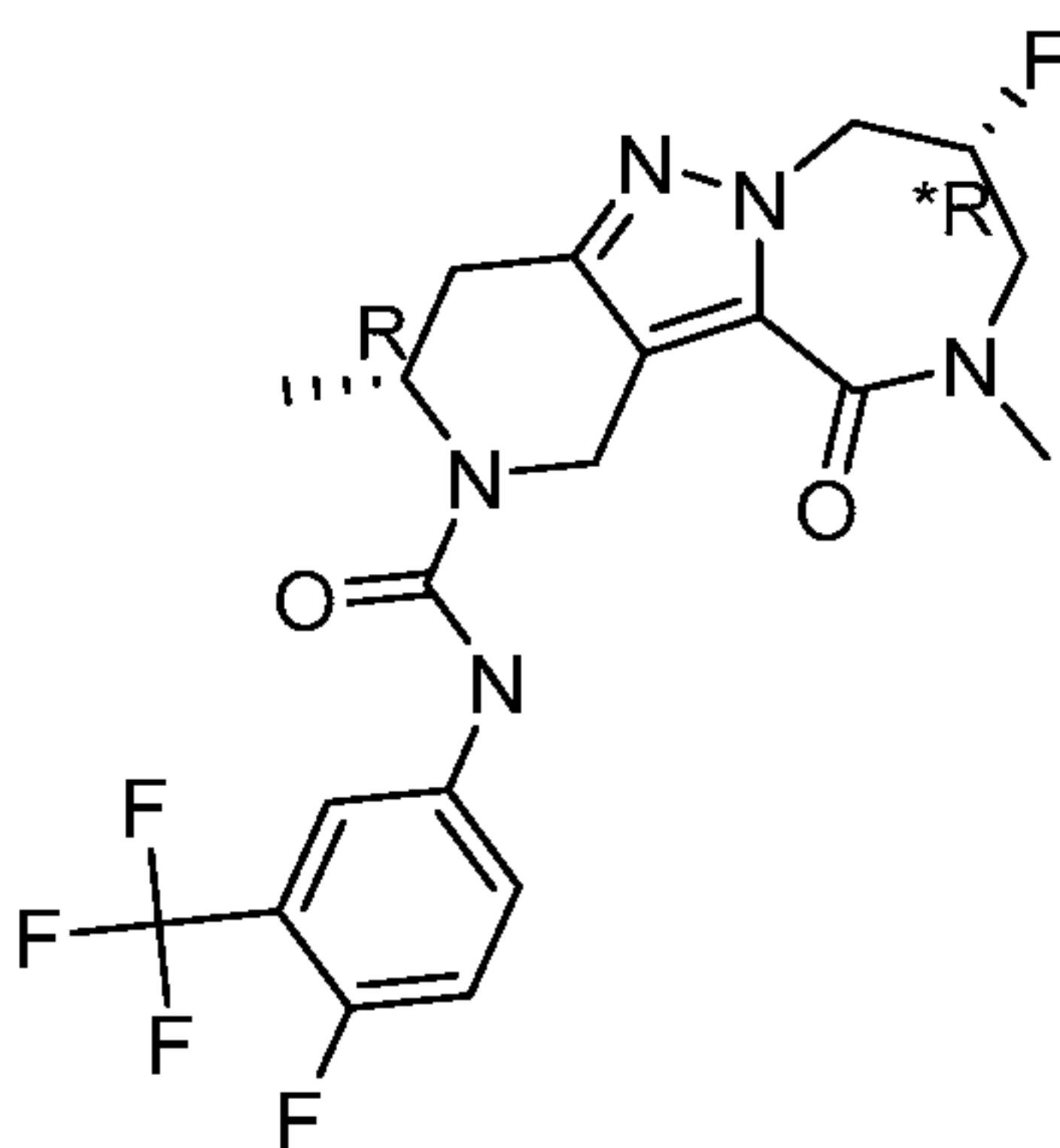


20

The title compound was prepared in a manner analogous to Compound 246 tert-butyl (3R)-8-fluoro-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-

a][1,4]diazepine-2-carboxylate _D2. LCMS: 415 [M+1]. ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.81 (dd, J = 2.76, 5.40 Hz, 1 H), 7.59 (m, 1H), 7.27 (s, 2 H), 7.15 (t, J = 8.72 Hz, 1 H), 6.67 (s, 1 H), 5.11 - 5.21 (m, 1 H), 4.93 (d, J = 15.56 Hz, 1 H), 4.36 - 4.64 (m, 5 H), 3.95 - 4.09 (m, 1 H), 3.23 (s, 3 H), 3.06 (dd, J = 5.58, 15.87 Hz, 1 H), 2.70 (d, J = 15.81 Hz, 1 H), 1.16 (d, J = 6.90 Hz, 3 H).

Compound 138: (3R,8R*)-8-fluoro-N-(4-fluoro-3-(trifluoromethyl)phenyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. tert-Butyl (3R,8R)-8-hydroxy-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate. Tert-butyl (5R)-11-hydroxy-5,13-dimethyl-14-oxo-4,8,9,13-tetrazatricyclo[7.5.0.0^{2,7}] tetradeca-1,7-diene-4-carboxylate (674 mg, 1.92 mmol, 1 *eq*) was separated via SFC to give both diastereomers: tert-butyl (3R,8R)-8-hydroxy-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate _D1 and (345 mg, 936.31 μ mol, 95.1% purity, t =1.66 min) and tert-butyl (3R,8R)-8-hydroxy-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate _D2 (310 mg, 874.94 μ mol, 45.49% yield, 98.9% purity, t =1.89 min) as white solid. SFC analysis condition: AD-3S_4_5_40_3ML. Column: Chiralpak AD-3 100 $\times$ 4.6mm I.D., 3 μ m; Mobile phase: iso-propanol (0.05% DEA) in CO₂ from 5% to 40%; Flow rate: 3mL/min Wavelength: 220 nm. SFC separation condition: Column: AD(250mm*30mm,10 μ m); Mobile phase: [0.1%NH₃H₂O IPA]; B%: 20%-20%, 2.3 min; 150 min.

Step 2. tert-Butyl (3R,8S)-8-fluoro-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate D1. To a solution of resulting tert-butyl (3R,8R)-8-hydroxy-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate D1 (150.00 mg, 428.07 μmol , 1 *eq*) in DCM (2 mL) was added DAST (207.00 mg, 1.28 mmol, 169.67 μL , 3 *eq*) at -30 °C. The mixture was stirred at -30 °C for 2 hr. The mixture was diluted with H₂O (20mL) and extracted with DCM (20 mL * 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, EA: MeOH = 10:1) to afford the title compound (89 mg, 250.78 μmol , 58.58% yield, 99.3% purity) as yellow oil and checked by HPLC. SFC (IC-3S_3_5_40_3ML Column: Chiralpak IC-3 100×4.6mm I.D., 3 μm Mobile phase: methanol (0.05% DEA) in CO₂ from 5% to 40% Flow rate: 3mL/min Wavelength: 220nm) indicated that the resulting product was corresponding to first diastereomer D1.

Step 3. (3R,8S)-8-Fluoro-3,10-dimethyl-1,2,3,4,7,8,9,10-octahydro-11H-

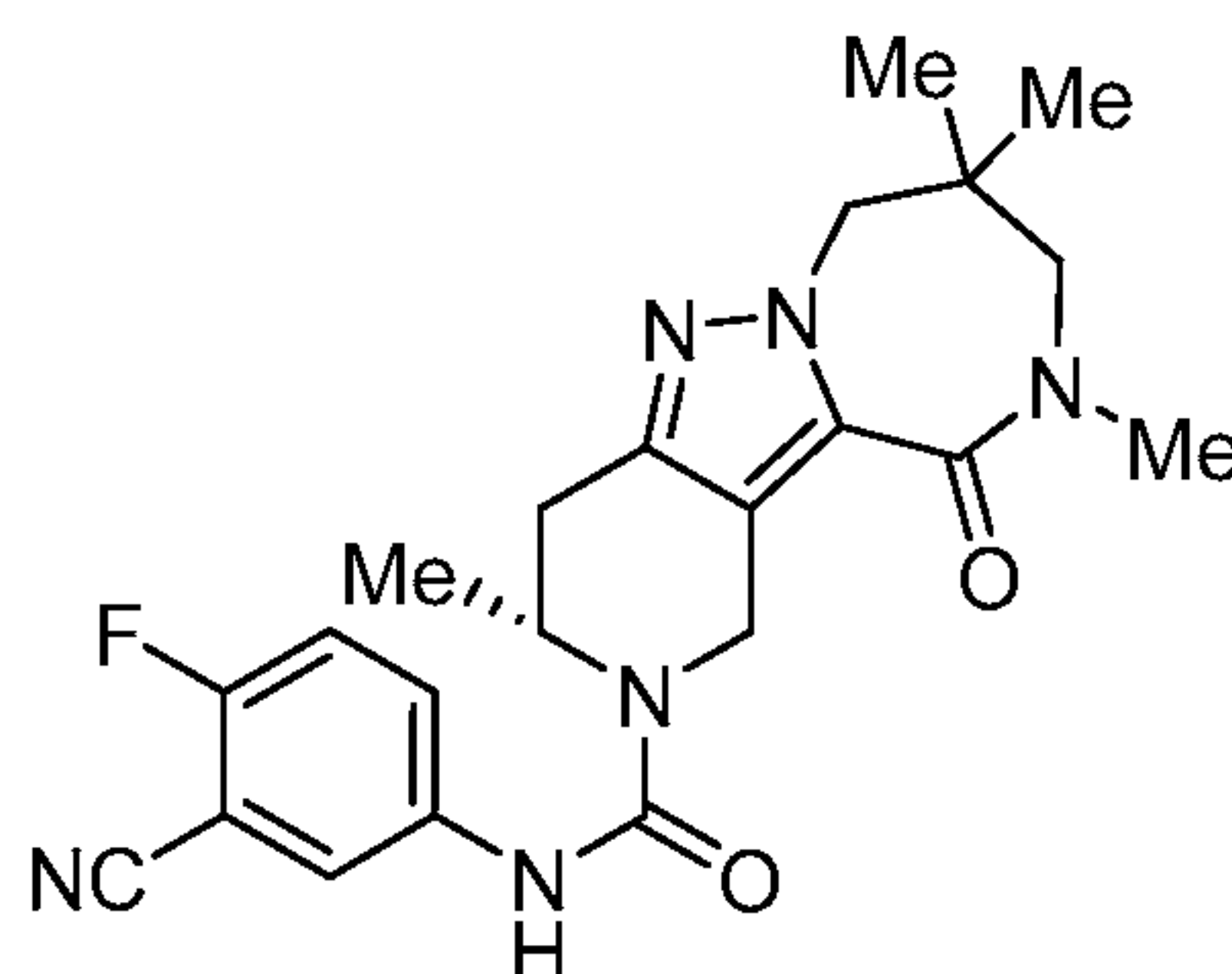
pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11-one D1. To a solution of tert-butyl (3R,8S)-8-fluoro-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate D1 (85.00 mg, 241.20 μmol , 1 *eq*) in DCM (5 mL) was added TFA (770.00 mg, 6.75 mmol, 500.00 μL , 28.00 *eq*). The mixture was stirred at 16 °C for 2 hr. The mixture was concentrated under reduced pressure to give the title compound (89 mg, crude, TFA) as yellow oil, which without further purified and directly used in the next step.

Step 4. (3R,8R*)-8-fluoro-N-(4-fluoro-3-(trifluoromethyl)phenyl)-3,10-dimethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

To a solution of (3R,8S)-8-fluoro-3,10-dimethyl-1,2,3,4,7,8,9,10-octahydro-11H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11-one D1 (70 mg, 277.46 μmol , 1 *eq*, TFA) in DCM (5 mL) were added TEA (140.38 mg, 1.39 mmol, 193.10 μL , 5 *eq*) and phenyl N-[4-fluoro-3-(trifluoromethyl)phenyl]carbamate (83.02 mg, 277.46 μmol , 1 *eq*). The mixture was stirred at 16 °C for 10 hr. The mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (FA) to give the title compound (54 mg, 118.06 μmol , 42.55% yield, 100% purity) as white solid. LCMS: 458 [M+1]. ¹H NMR (400 MHz, CHLOROFORM-d) δ 7.70 (dd, *J* = 2.64, 6.15 Hz, 1H), 7.55-7.62 (m, 1H), 7.14 (t, *J* = 9.35 Hz, 1H), 6.62 (s, 1H), 5.17

(quin, $J = 6.84$ Hz, 1H), 4.85 (d, $J = 15.69$ Hz, 1H), 4.31 - 4.63 (m, 5H), 3.93 - 4.10 (m, 1H), 3.23 (s, 3H), 3.05 (dd, $J = 6.02, 15.69$ Hz, 1H), 2.71 (d, $J = 16.19$ Hz, 1H), 1.19 (d, $J = 6.90$ Hz, 3H).

- 5 Compound 139: (R)-N-(3-cyano-4-fluorophenyl)-3,8,8,10-tetramethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



- 10 Step 1. N-(3-Hydroxy-2,2-dimethylpropyl)formamide. To a solution of 3-amino-2,2-dimethylpropan-1-ol (3.3 g, 31.99 mmol, 1 *eq*) in EtOH (60 mL) was added HCOOEt (4.73 g, 63.98 mmol, 2 *eq*). The mixture was stirred at 80 °C for 6 hr. The mixture was concentrated in vacuum to afford the title compound (4.1 g, crude) as colorless oil, used in the next step directly.

- 15 Step 2. 2,2-Dimethyl-3-(methylamino)propan-1-ol. To a solution of N-(3-hydroxy-2,2-dimethylpropyl)formamide (4 g, 30.49 mmol, 1 *eq*) in THF (50 mL) at -40 °C was added LAH (1.50 g, 39.64 mmol, 1.3 *eq*) portionwise. Then the mixture was heated to 20 °C for 16 hr. The mixture was quenched by H₂O (1.5 mL), 15% NaOH (1.5 mL) and H₂O (3 mL). The mixture was filtered and concentrated in vacuum to afford the title compound (3.5 g, crude) as a white solid, used in the next step directly.

- 20 Step 3. tert-Butyl (R)-3-((3-hydroxy-2,2-dimethylpropyl)(methyl)carbamoyl)-6-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate. To a solution of (R)-5-(tert-butoxycarbonyl)-6-methyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine-3-carboxylic acid (1.5 g, 5.33 mmol, 1 *eq*) and 2,2-dimethyl-3-(methylamino)propan-1-ol (812.34 mg, 6.93 mmol, 1.3 *eq*) in pyridine (15 mL) was added EDCI (1.23 g, 6.40 mmol, 1.2 *eq*). The mixture was heated to 40 °C for 16 hr. The mixture was extracted with EA (100 mL*3) and H₂O (100 mL). The combined organic layers were washed with 1N HCl (60mL*3), filtered, dried over Na₂SO₄,

concentrated in vacuum. The residue was purified by flash silica chromatography (PE:EA:50%~100%) to afford the title compound (1.0 g, 2.63 mmol, 49.29% yield) as a white solid.

5 Step 4. tert-Butyl (R)-3-((2,2-dimethyl-3-((methylsulfonyl)oxy)propyl)(methyl)carbamoyl)-6-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate. To a solution of tert-butyl (R)-3-((3-hydroxy-2,2-dimethylpropyl)(methyl)carbamoyl)-6-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (800 mg, 2.10 mmol, 1 *eq*) in DCM (8 mL) was added DIEA (815.24 mg, 6.31 mmol, 1.10 mL, 3 *eq*), followed by MsCl (289.03 mg, 2.52 mmol, 195.29 μ L, 1.2 *eq*) slowly at -10 °C. The mixture was stirred at 10 °C for 10 min. Additional
10 MsCl (240.85 mg, 2.10 mmol, 162.74 μ L, 1 *eq*) was added and the mixture was stirred at 10 °C for 10 min. The mixture was diluted with H₂O (20 mL) and extracted with DCM (20 mL). The organic layer was washed with 0.5N HCl (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum to give the title compound (1.0 g, crude) as a white solid used in the next step directly.

15 Step 5. tert-Butyl (R)-3,8,8,10-tetramethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate. To a solution of tert-butyl (R)-3-((2,2-dimethyl-3-((methylsulfonyl)oxy)propyl)(methyl)carbamoyl)-6-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (1.0 g, 1.86 mmol, 1 *eq*) in THF (10 mL) was added NaH (149.07 mg, 3.73 mmol, 60% purity, 2 *eq*) at 0 °C. The mixture was stirred at 40 °C for 16
20 hr. The mixture was heated to 40 °C for an additional 32 hr. Additional NaH (111.79 mg, 2.80 mmol, 60% purity, 1.5 *eq*) was added and the mixture was heated to 40 °C for 48 hr. The mixture was poured into water (10 mL) and extracted with EA (30 mL*3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography (PE:EA:30%~50%) to afford the title compound
25 (670 mg, 1.85 mmol, 99.20% yield) as a white solid.

Step 6. (R)-3,8,8,10-Tetramethyl-1,2,3,4,7,8,9,10-octahydro-11H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11-one. To a solution of tert-butyl (R)-3,8,8,10-tetramethyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (160 mg, 441.42 μ mol, 1 *eq*) in DCM (2 mL) was added TFA (3.08 g, 27.01 mmol, 2 mL, 61.19

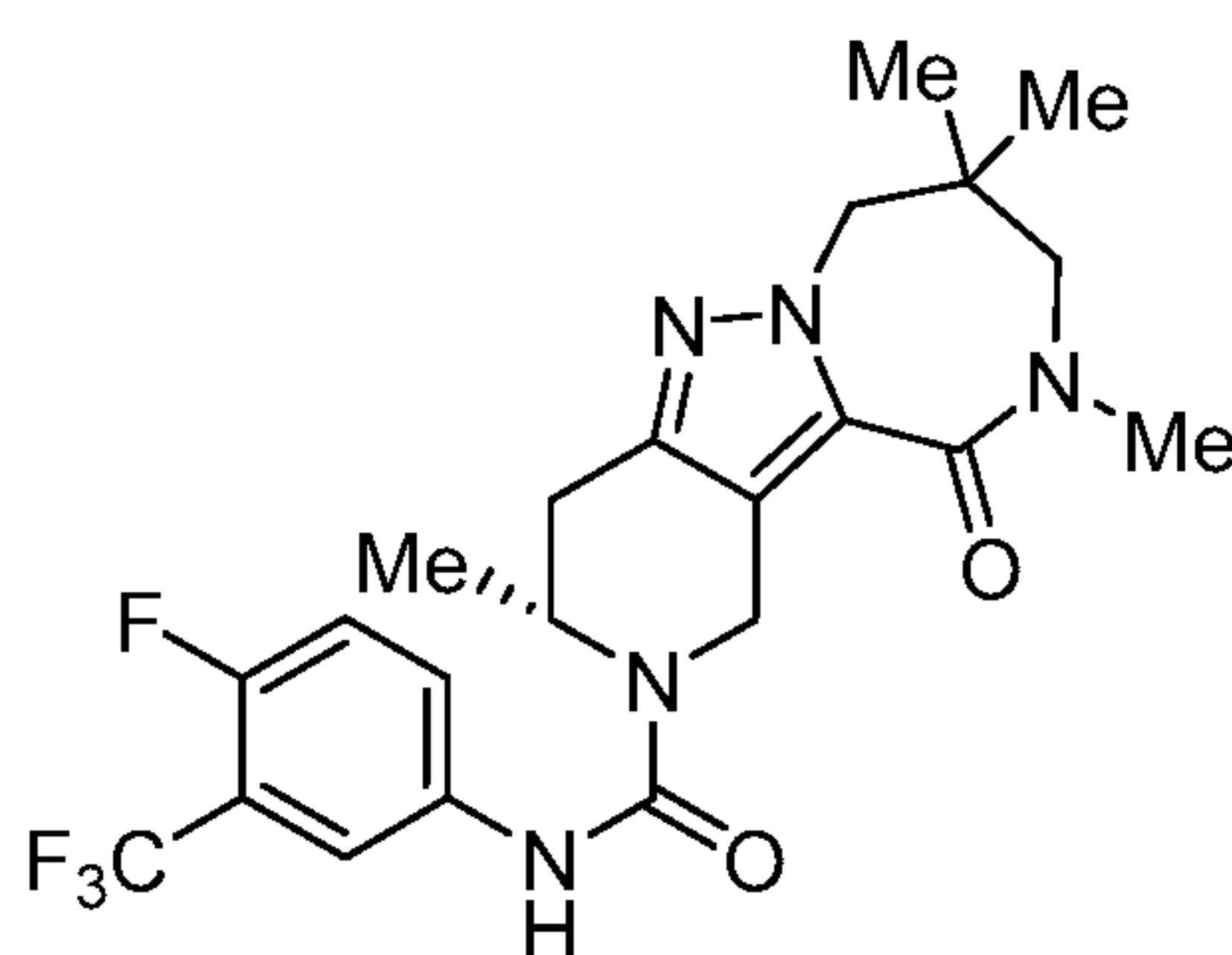
eq). The mixture was stirred at 15 °C for 1 hr. The mixture was concentrated in vacuum to afford the title compound (172 mg, crude, TFA) as brown oil, used in the next step directly.

Step 7. (R)-N-(3-Cyano-4-fluorophenyl)-3,8,8,10-tetramethyl-11-oxo-1,3,4,7,8,9,10,11-

octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. To a solution of
 5 (R)-3,8,8,10-tetramethyl-1,2,3,4,7,8,9,10-octahydro-11H-pyrido[4',3':3,4]pyrazolo[1,5-
 a][1,4]diazepin-11-one (85 mg, 225.84 μ mol, 1 *eq*, TFA) in DCM (2 mL) was added TEA
 (114.26 mg, 1.13 mmol, 157.17 μ L, 5 *eq*) and phenyl N-(3-cyano-4-fluoro-phenyl)carbamate
 (57.87 mg, 225.84 μ mol, 1 *eq*). The mixture was stirred at 15 °C for 16 hr. The mixture was
 concentrated in vacuum. The residue was purified by prep-HPLC (FA) to afford the title
 10 compound (51.44 mg, 118.04 μ mol, 52.27% yield, 97.4% purity) as a white solid.

LCMS: 425 [M+1]. ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.81 (dd, *J* = 2.76, 5.52 Hz, 1 H), 7.53 - 7.61 (m, 1 H), 7.15 (t, *J* = 8.72 Hz, 1 H), 6.57 (s, 1 H), 5.14 (br t, *J* = 6.90 Hz, 1 H), 4.81 (d, *J* = 15.43 Hz, 1 H), 4.51 (d, *J* = 15.31 Hz, 1 H), 4.04 (s, 2 H), 3.22 (s, 3 H), 3.00 - 3.17 (m, 3 H), 2.70 (d, *J* = 15.94 Hz, 1 H), 1.11 - 1.24 (m, 9 H).

Compound 140: (R)-N-(4-Fluoro-3-(trifluoromethyl)phenyl)-3,8,8,10-tetramethyl-11-oxo-
1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.

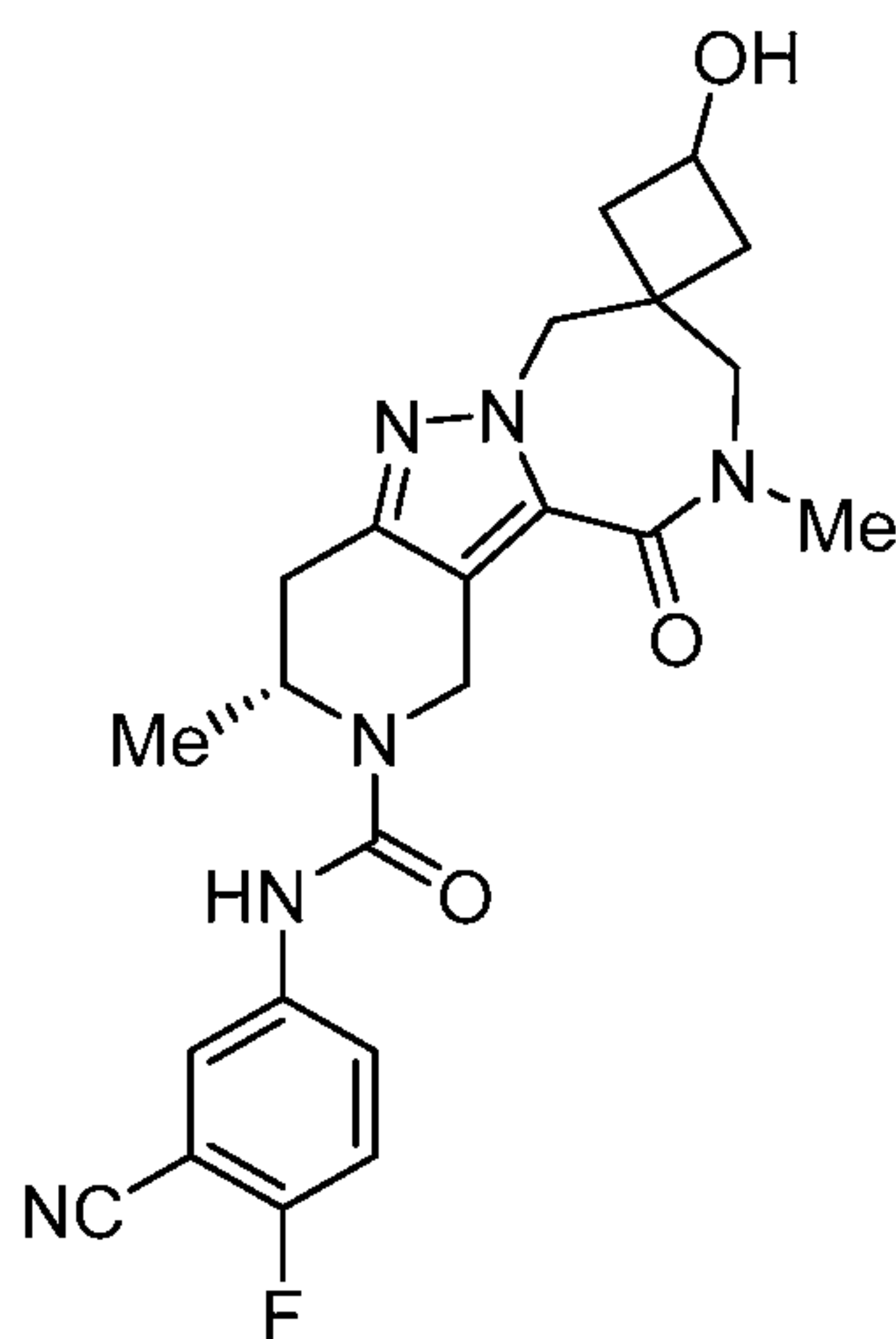


The title compound was prepared in a manner analogous to Compound 139, substituting phenyl
 20 (4-fluoro-3-(trifluoromethyl)phenyl)carbamate for phenyl N-(3-cyano-4-fluoro-
 phenyl)carbamate in Step 7. LCMS: 468 [M+1]. ¹H NMR (400 MHz, CHLOROFORM-d) δ =
 7.70 (dd, *J* = 2.57, 6.21 Hz, 1 H), 7.56 - 7.63 (m, 1 H), 7.15 (t, *J* = 9.35 Hz, 1 H), 6.54 (s, 1 H),
 5.08 - 5.21 (m, 1 H), 4.81 (d, *J* = 15.31 Hz, 1 H), 4.52 (d, *J* = 15.18 Hz, 1 H), 4.04 (s, 2 H), 3.22

(s, 3 H), 3.11 - 3.18 (m, 1 H), 2.99 - 3.09 (m, 2 H), 2.70 (d, $J = 16.19$ Hz, 1 H), 1.11 - 1.23 (m, 9 H).

Compound 141: (R)-N-(3-Cyano-4-fluorophenyl)-3-hydroxy-3',10'-dimethyl-11'-oxo-

5 1',3',4',9',10',11'-hexahydro-2'H,7'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine]-2'-carboxamide.



Step 1. tert-Butyl (R)-3-(((3-(benzyloxy)-1-

(hydroxymethyl)cyclobutyl)methyl)(methyl)carbamoyl)-6-methyl-2,4,6,7-tetrahydro-5H-

10 pyrazolo[4,3-c]pyridine-5-carboxylate. To a mixture of [3-benzyloxy-1-

(methylaminomethyl)cyclobutyl]methanol (1.6 g, 4.58 mmol, 1 *eq*, TFA) and (R)-5-(tert-

butoxycarbonyl)-6-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-3-carboxylic acid

(1.03 g, 3.66 mmol, 0.8 *eq*) in pyridine (10 mL) was added EDCI (1.05 g, 5.50 mmol, 1.2 *eq*),

15 the reaction mixture was stirred at 40 °C for 16 hours. The reaction mixture was diluted with

ethyl acetate (100 mL) and washed with diluted HCl (1N, 80 mL*3), the organic phase was dried

with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica

gel chromatography. The title compound (835 mg, 98% purity) was obtained as yellow solid.

Step 2. tert-Butyl (R)-3-(((3-(benzyloxy)-1-

(((methylsulfonyl)oxy)methyl)cyclobutyl)methyl)(methyl)carbamoyl)-6-methyl-2,4,6,7-

20 tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate and tert-butyl (R)-3-(((3-(benzyloxy)-1-

(((methylsulfonyl)oxy)methyl)cyclobutyl)methyl)(methyl)carbamoyl)-6-methyl-2-

(methylsulfonyl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate. To a solution of tert-butyl (R)-3-(((3-(benzyloxy)-1-(hydroxymethyl)cyclobutyl)methyl)(methyl)carbamoyl)-6-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (612.24 mg, 1.20 mmol, 1.00 *eq*) in DCM (6 mL) were added DIEA (466.56 mg, 3.61 mmol, 628.78 μ L, 3 *eq*) and MsCl

(206.76 mg, 1.81 mmol, 139.71 μ L, 1.5 *eq*). The mixture was stirred at 20 °C for 2 hr.

Additional MsCl (206.76 mg, 1.81 mmol, 139.71 μ L, 1.5 *eq*) was added and the mixture was stirred at 20 °C for 1 hr. The mixture was extracted with DCM (30 mL*2) and H₂O (20 mL).

The combined organic layers were washed 0.5 N HCl (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. To afford a mixture of the title compounds as brown oil., used in the

next step directly.

Step 3. tert-Butyl (R)-3-(benzyloxy)-3',10'-dimethyl-11'-oxo-1',3',4',9',10',11'-hexahydro-2'H,7'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine]-2'-carboxylate.

To a solution of tert-butyl (R)-3-(((3-(benzyloxy)-1-

(((methylsulfonyl)oxy)methyl)cyclobutyl)methyl)(methyl)carbamoyl)-6-methyl-2,4,6,7-

tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate and tert-butyl (R)-3-(((3-(benzyloxy)-1-

(((methylsulfonyl)oxy)methyl)cyclobutyl)methyl)(methyl)carbamoyl)-6-methyl-2-

(methylsulfonyl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (900 mg, 1.46

mmol, 1 *eq*) in THF (10 mL) was added NaH (234.15 mg, 5.85 mmol, 60% purity, 4 *eq*) and NaI

(43.87 mg, 292.68 μ mol, 0.2 *eq*) at 0 °C. The mixture was stirred at 40 °C for 16 hr. Additional

NaH (234.12 mg, 5.85 mmol, 60% purity, 4 *eq*) was added and the mixture was stirred at 40 °C

for 48 hr. The mixture was stirred at 40 °C for 16 hr. The mixture was combined with another

batch and was quenched with H₂O (40 mL) and extracted with EA(80 mL*3). The combined

organic layer was dried over Na₂SO₄, filtrated and concentrated in vacuum. The resulting

residue s combined with another batch of crude product and purified by column chromatography

(SiO₂, PE:EA=30%~60%) to give 350 mg desired product totally as colorless oil.

Step 4. tert-Butyl (R)-3-hydroxy-3',10'-dimethyl-11'-oxo-1',3',4',9',10',11'-hexahydro-2'H,7'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine]-2'-carboxylate. To a

solution of tert-butyl (R)-3-(benzyloxy)-3',10'-dimethyl-11'-oxo-1',3',4',9',10',11'-hexahydro-

2'H,7'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine]-2'-carboxylate

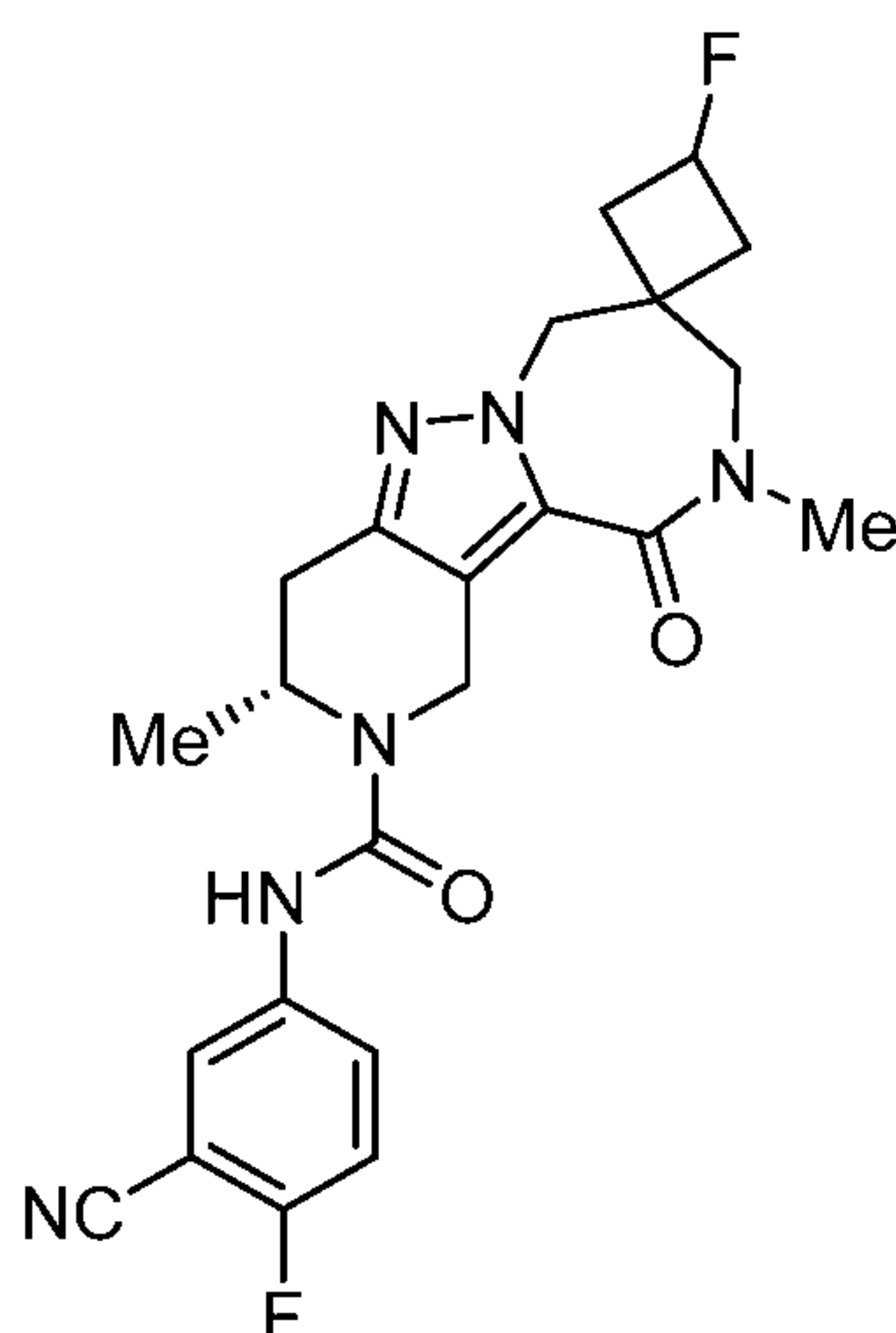
(350 mg, 728.26 μ mol, 1.00 *eq*) in MeOH (10.00 mL) was added Pd/C (50 mg, 728.26 μ mol,

10% purity, 1.00 *eq*) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (20psi) at 40 °C for 3 hours. The mixture was stirred under H₂ (20 psi) at 40 °C for 16 hours. The mixture was stirred under H₂ (50 psi) at 25 °C for 16 hours. The mixture was diluted with MeOH (80 mL), filtrated and concentrated in vacuum to give the title compound (290 mg, crude) as white solid, which was used in the next step directly.

Step 5. (R)-3-Hydroxy-3',10'-dimethyl-1',2',3',4',9',10'-hexahydro-7'H,11'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin]-11'-one. To a solution of tert-butyl (R)-3-hydroxy-3',10'-dimethyl-11'-oxo-1',3',4',9',10',11'-hexahydro-2'H,7'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine]-2'-carboxylate (55 mg, 140.85 μmol, 1 *eq*) in DCM (2 mL) was added TFA (2.82 g, 24.76 mmol, 1.83 mL, 175.79 *eq*). The mixture was stirred at 15 °C for 0.5 hr. The mixture was concentrated in vacuo. The title compound (60 mg, crude, TFA) was obtained as brown oil, which was used in the next step directly.

Step 6. (R)-N-(3-Cyano-4-fluorophenyl)-3-hydroxy-3',10'-dimethyl-11'-oxo-1',3',4',9',10',11'-hexahydro-2'H,7'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine]-2'-carboxamide. To a solution of (R)-3-hydroxy-3',10'-dimethyl-1',2',3',4',9',10'-hexahydro-7'H,11'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin]-11'-one (58 mg, 143.43 μmol, 1 *eq*, TFA) and phenyl N-(3-cyano-4-fluoro-phenyl)carbamate (36.75 mg, 143.43 μmol, 1 *eq*) in DCM (2 mL) was added TEA (72.57 mg, 717.14 μmol, 99.82 μL, 5 *eq*). The mixture was stirred at 15 °C for 30 min. The mixture was concentrated in vacuo. The residue was purified by prep-HPLC (FA). The title compound (25.02 mg, 54.65 μmol, 38.11% yield, 98.84% purity) was obtained as white solid. LCMS: 453 [M+1]. ¹H NMR (400 MHz, METHANOL-d₄) δ = 7.82 (dd, *J* = 2.76, 5.65 Hz, 1 H), 7.70 (ddd, *J* = 2.76, 4.74, 9.19 Hz, 1 H), 7.28 (t, *J* = 8.97 Hz, 1 H), 4.94 - 5.04 (m, 2 H), 4.31 - 4.41 (m, 4 H), 3.43 (s, 2 H), 3.19 (s, 3 H), 3.01 (dd, *J* = 5.90, 15.81 Hz, 1 H), 2.67 (d, *J* = 15.94 Hz, 1 H), 2.40 - 2.50 (m, 2 H), 1.98 (dd, *J* = 7.84, 12.11 Hz, 1 H), 1.89 (dd, *J* = 7.15, 12.67 Hz, 1 H), 1.22 (d, *J* = 6.90 Hz, 3 H).

Compound 142: (R)-N-(3-Cyano-4-fluorophenyl)-3-fluoro-3',10'-dimethyl-11'-oxo-1',3',4',9',10',11'-hexahydro-2'H,7'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine]-2'-carboxamide.



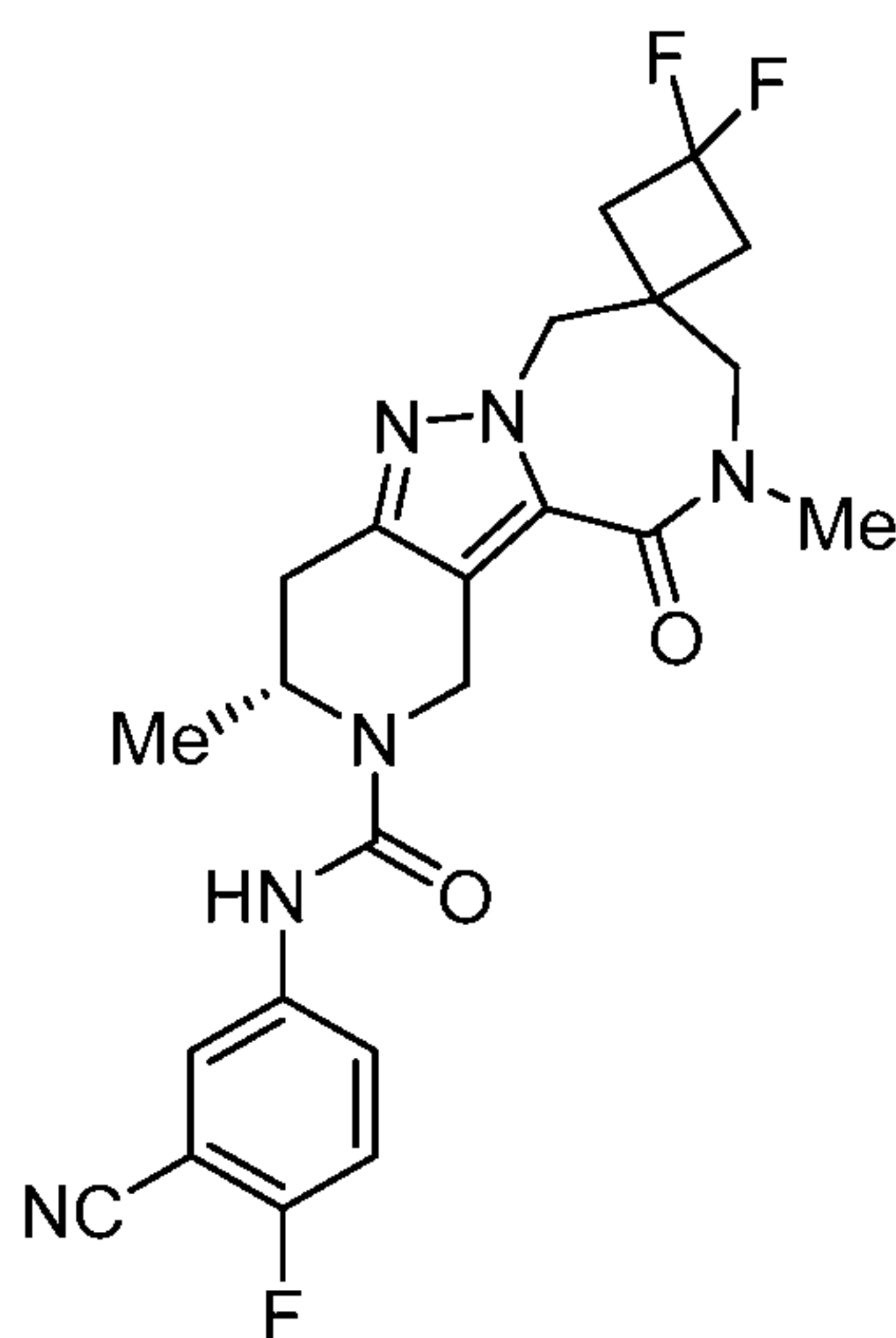
5 Step 1. tert-Butyl (R)-3-fluoro-3',10'-dimethyl-11'-oxo-1',3',4',9',10',11'-hexahydro-2'H,7'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine]-2'-carboxylate. To a solution of tert-butyl (R)-3-hydroxy-3',10'-dimethyl-11'-oxo-1',3',4',9',10',11'-hexahydro-2'H,7'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine]-2'-carboxylate (70 mg, 179.27 μ mol, 1 *eq*) in DCM (1.5 mL) was added DAST (86.69 mg, 537.81 μ mol, 71.06 μ L, 3
10 *eq*) at -40 °C. The mixture was stirred at 0 °C for 1 hr. The mixture was combined with another batch of the crude reaction. Diluted with H₂O (30 mL) and extracted with DCM (20 mL*2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo to afford 100 mg of the title compound was obtained as brown oil.

15 Step 2. (R)-3-Fluoro-3',10'-dimethyl-1',2',3',4',9',10'-hexahydro-7'H,11'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin]-11'-one. To a solution of tert-butyl (R)-3-fluoro-3',10'-dimethyl-11'-oxo-1',3',4',9',10',11'-hexahydro-2'H,7'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine]-2'-carboxylate (80 mg, 203.84 μ mol, 1 *eq*) in DCM (1.5 mL) was added TFA (3.50 g, 30.71 mmol, 2.27 mL, 150.68 *eq*). The mixture was stirred at 10 °C for 1 hr. The mixture was concentrated in vacuo. The title compound (85 mg, 20
crude, TFA) was obtained as brown oil.

Step 3. (R)-N-(3-Cyano-4-fluorophenyl)-3-fluoro-3',10'-dimethyl-11'-oxo-1',3',4',9',10',11'-hexahydro-2'H,7'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine]-2'-carboxamide. To a solution of (R)-3-fluoro-3',10'-dimethyl-1',2',3',4',9',10'-hexahydro-7'H,11'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin]-11'-one (80 mg, 196.86 μmol , 1 *eq*, TFA) and phenyl N-(3-cyano-4-fluoro-phenyl)carbamate (50.44 mg, 196.86 μmol , 1 *eq*) in DCM (2 mL) was added TEA (99.60 mg, 984.31 μmol , 137.01 μL , 5 *eq*). The mixture was stirred at 15 °C for 30 min. The mixture was concentrated in vacuo. The residue was purified by prep-TLC (PE:EA = 0:1), Further purification by prep-HPLC (FA). The title compound (16.53 mg, 35.97 μmol , 18.27% yield, 98.9% purity) was obtained as white solid.

LCMS: 455 [M+1]. ^1H NMR (400 MHz, METHANOL- d_4) δ = 7.82 (dd, J = 2.76, 5.65 Hz, 1H), 7.70 (ddd, J = 2.76, 4.71, 9.10 Hz, 1 H), 7.28 (t, J = 8.97 Hz, 1 H), 5.21 (quin, J = 6.21 Hz, 1 H), 5.05 - 5.24 (m, 1 H), 5.04 - 5.12 (m, 1 H), 4.93 - 5.04 (m, 2 H), 4.41 (d, J = 2.01 Hz, 2 H), 4.35 (d, J = 16.69 Hz, 1 H), 3.44 (s, 2 H), 3.21 (s, 3 H), 3.01 (dd, J = 5.83, 15.75 Hz, 1 H), 2.66 (d, J = 15.81 Hz, 1 H), 2.42 - 2.62 (m, 2 H), 2.22 - 2.36 (m, 2 H), 1.23 (d, J = 6.90 Hz, 3 H).

Compound 143: (R)-N-(3-Cyano-4-fluorophenyl)-3,3-difluoro-3',10'-dimethyl-11'-oxo-1',3',4',9',10',11'-hexahydro-2'H,7'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine]-2'-carboxamide.



Step 1. tert-Butyl (R)-3',10'-dimethyl-3,11'-dioxo-1',3',4',9',10',11'-hexahydro-2'H,7'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine]-2'-carboxylate. To a

solution of tert-butyl (R)-3-hydroxy-3',10'-dimethyl-11'-oxo-1',3',4',9',10',11'-hexahydro-2'H,7'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine]-2'-carboxylate (130 mg, 332.93 μ mol, 1 *eq*) in DCM (2 mL) was added DMP (282.42 mg, 665.86 μ mol, 206.14 μ L, 2 *eq*). The mixture was stirred at 15 °C for 1 hr. The mixture was combined with another batch to dilute with DCM (30 mL) and filtered, the filtrates was concentrated in vacuo. The residue was purified by column chromatography(SiO₂, PE:EA:2:1~1:2) to give 100 mg of desired product as white solid.

Step 2. tert-butyl (R)-3,3-difluoro-3',10'-dimethyl-11'-oxo-1',3',4',9',10',11'-hexahydro-2'H,7'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine]-2'-carboxylate. To a

solution of tert-butyl (R)-3',10'-dimethyl-3,11'-dioxo-1',3',4',9',10',11'-hexahydro-2'H,7'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine]-2'-carboxylate (90 mg, 231.68 μ mol, 1 *eq*) in DCM (2 mL) was added DAST (186.72 mg, 1.16 mmol, 153.05 μ L, 5 *eq*) at -40 °C. The mixture was stirred at 0 °C for 1 hr. The mixture was combined with another batch (EW619-1976) to dilute with H₂O (30 mL) and extracted with DCM (20 mL*2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. 100 mg crude product was obtained as brown oil, which was used in the next step directly.

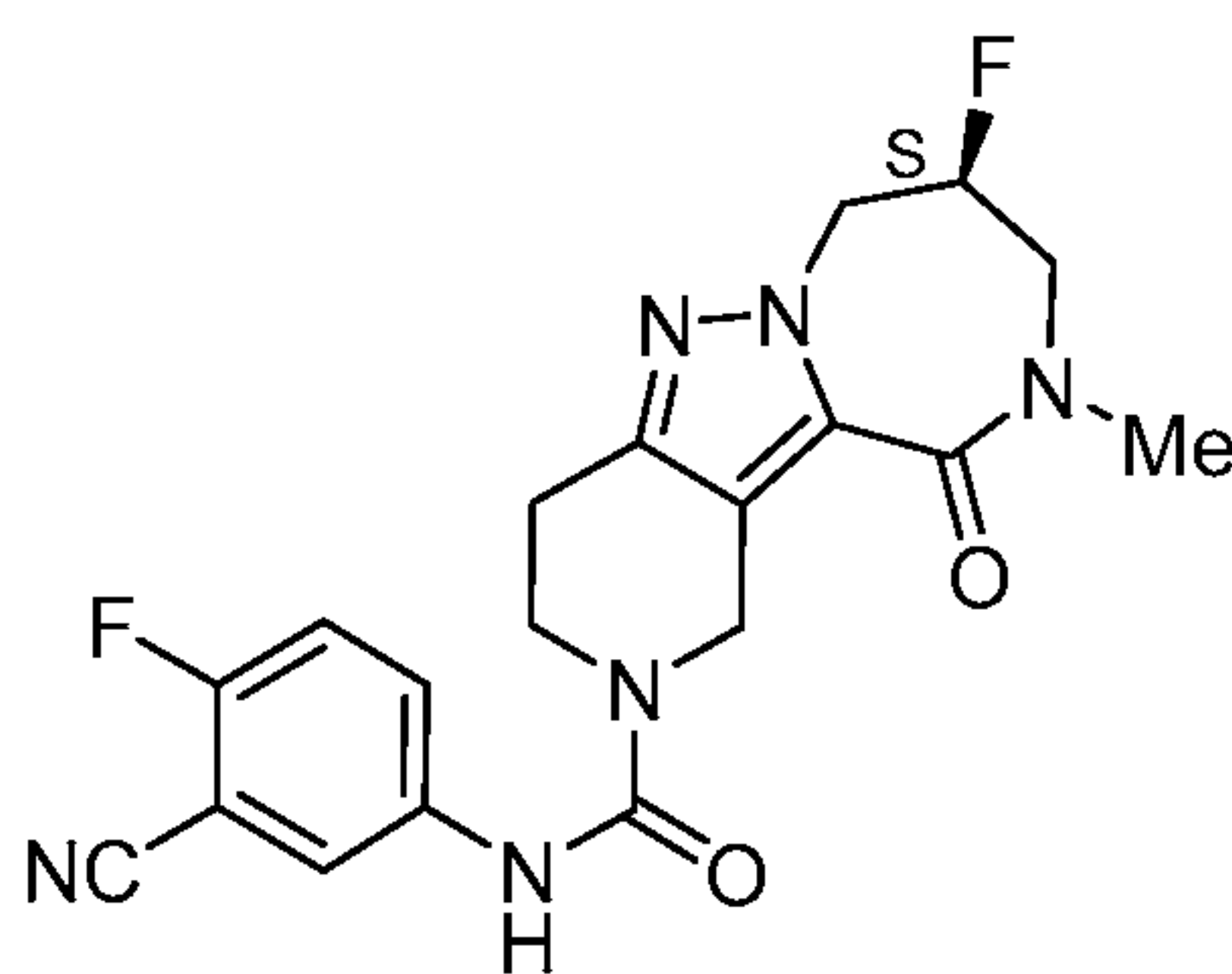
Step 3. (R)-3,3-Difluoro-3',10'-dimethyl-1',2',3',4',9',10'-hexahydro-7'H,11'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin]-11'-one. To a solution of tert-butyl (R)-3,3-difluoro-3',10'-dimethyl-11'-oxo-1',3',4',9',10',11'-hexahydro-2'H,7'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine]-2'-carboxylate (100 mg, 243.63 μ mol, 1 *eq*) in DCM (2 mL) was added TFA (3.08 g, 27.01 mmol, 2 mL, 110.87 *eq*). The mixture was stirred at 20 °C for 0.5 hr. The mixture was concentrated in vacuo to give the title compound (110 mg, crude, TFA) as brown oil.

Step 4. (R)-N-(3-Cyano-4-fluorophenyl)-3,3-difluoro-3',10'-dimethyl-11'-oxo-1',3',4',9',10',11'-hexahydro-2'H,7'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine]-2'-carboxamide. To a solution of (R)-3,3-Difluoro-3',10'-dimethyl-1',2',3',4',9',10'-hexahydro-7'H,11'H-spiro[cyclobutane-1,8'-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin]-11'-one (100 mg, 322.23 μ mol, 1 *eq*, TFA) and phenyl N-(3-cyano-4-fluoro-phenyl)carbamate (82.56 mg, 322.23 μ mol, 1 *eq*) in DCM (2 mL) was added TEA (163.03 mg, 1.61 mmol, 224.25 μ L, 5 *eq*). The

mixture was stirred at 15 °C for 30 min. The residue was purified by prep-HPLC (FA). The title compound (35.85 mg, 73.15 μmol, 22.70% yield, 96.4% purity) was obtained as white solid.

LCMS: 473 [M+1]. ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.79 (dd, *J* = 2.75, 5.44 Hz, 1 H), 7.59 (ddd, *J* = 2.87, 4.52, 9.11 Hz, 1 H), 7.15 (t, *J* = 8.74 Hz, 1 H), 6.69 (s, 1 H), 5.14 (quin, *J* = 6.51 Hz, 1 H), 4.84 (d, *J* = 15.53 Hz, 1 H), 4.41 - 4.52 (m, 3 H), 3.46 - 3.58 (m, 2 H), 3.24 (s, 3 H), 3.03 (dd, *J* = 5.87, 16.02 Hz, 1 H), 2.51 - 2.78 (m, 5 H), 1.20 (d, *J* = 6.97 Hz, 3 H).

Compound 144_E1: (S)-N-(3-Cyano-4-fluorophenyl)-8-fluoro-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide_E1.



Step 1. 5-(tert-Butyl) 3-ethyl 2-(2-(chloromethyl)allyl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-3,5-dicarboxylate. To a solution of 5-(tert-butyl) 3-ethyl 2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-3,5-dicarboxylate (10 g, 33.86 mmol, 1 eq) in DMF (130 mL) was added Cs₂CO₃ (16.55 g, 50.79 mmol, 1.5 eq) and 3-chloro-2-(chloromethyl)prop-1-ene (21.16 g, 169.30 mmol, 19.59 mL, 5 eq). The solution was stirred at 50 °C for 3 hr. The mixture was diluted with EtOAc (100 mL) and filtered. The filtrate was poured into 0.5 N HCl (300 mL). The solution was extracted with ethyl acetate (200 mL*2). The combined organic layers were washed with brine (200 mL*3), dried with anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography. The title compound (5.3 g, 13.53 mmol, 39.96% yield, 98% purity) was obtained as white solid. LCMS: 384 [M+1].

Step 2. tert-Butyl 10-methyl-8-methylene-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate. To a solution of 5-(tert-butyl) 3-ethyl 2-(2-(chloromethyl)allyl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-3,5-dicarboxylate (5.3 g, 13.81 mmol, 1 eq) in EtOH (21 mL) was added MeNH₂ (42.88 g, 414.20 mmol, 30 eq,

30% MeNH₂ in EtOH). The mixture was heated to 80 °C for 16 hr in a sealed tube. The solution was concentrated. The residue was purified by column chromatography. The title compound (2.6 g, 7.82 mmol, 56.65% yield) was obtained as white solid. LCMS: 333 [M+1].

Step 3. tert-Butyl 10-methyl-8,11-dioxo-1,3,4,7,8,9,10,11-octahydro-2H-

5 pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate. To a solution of tert-butyl 10-methyl-8-methylene-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (1.2 g, 3.61 mmol, 1 eq) in THF (30 mL) and H₂O (15 mL) was added OsO₄ (275.34 mg, 1.08 mmol, 56.19 µL, 0.3 eq) and NaIO₄ (2.32 g, 10.83 mmol, 600.14 µL, 3 eq) at 0 °C. The mixture was stirred at 10 °C for 7 hr. The solution was poured into ice
10 sat. NaHSO₃ (100mL). The mixture extracted with ethyl acetate (50 mL*2). The combined organic layers were washed with brine (50 mL), dried with anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography. The title compound (580 mg, 1.56 mmol, 43.21% yield, 90% purity) was obtained as white solid. LCMS: 353 [M+19].

Step 4. tert-Butyl 8-hydroxy-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-

15 pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate. To a solution of tert-butyl 10-methyl-8,11-dioxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (580 mg, 1.56 mmol, 1 eq) in MeOH (15 mL) was added NaBH₄ (107.62 mg, 2.84 mmol, 1.82 eq) at 0 °C. The solution was stirred at 0 °C for 1 hr. The solution was poured into water (30mL). The mixture extracted with ethyl acetate (20 mL*2). The
20 combined organic layers were washed with brine (20 mL), dried with anhydrous Na₂SO₄, filtered and concentrated. The title compound (550 mg, crude) was obtained as white solid. LCMS: 337 [M+1].

Step 5. tert-Butyl 8-hydroxy-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-

pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate_E1 and tert-butyl 8-hydroxy-10-
25 methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-
carboxylate_E2. Racemate of tert-butyl 8-hydroxy-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (580 mg, 1.53 mmol) was resolved via SFC to give both enantiomers : tert-Butyl 8-hydroxy-10-methyl-11-oxo-
1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate_E1
30 (200 mg, 558.29 µmol, 36.38% yield, 93.9% purity, t=3.176 min) and tert-Butyl 8-hydroxy-10-

methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate_E2 (250 mg, 684.48 μ mol, 44.60% yield, 92.1% purity, t_r =3.401 min) as white solid. SFC analytical method: IC-3S_4_5_40_3ML Column: Chiralpak IC-3 100 $\times$ 4.6mm I.D., 3 μ m Mobile phase: iso-propanol (0.05% DEA) in CO₂ from 5% to 40% Flow rate: 3mL/min

5 Wavelength: 254nm.

SFC separation method: column: IC(250mm*30mm,10 μ m); mobile phase: [0.1%NH₃H₂O IPA]; B%: 35%-35%, 4.35min; 100 min.

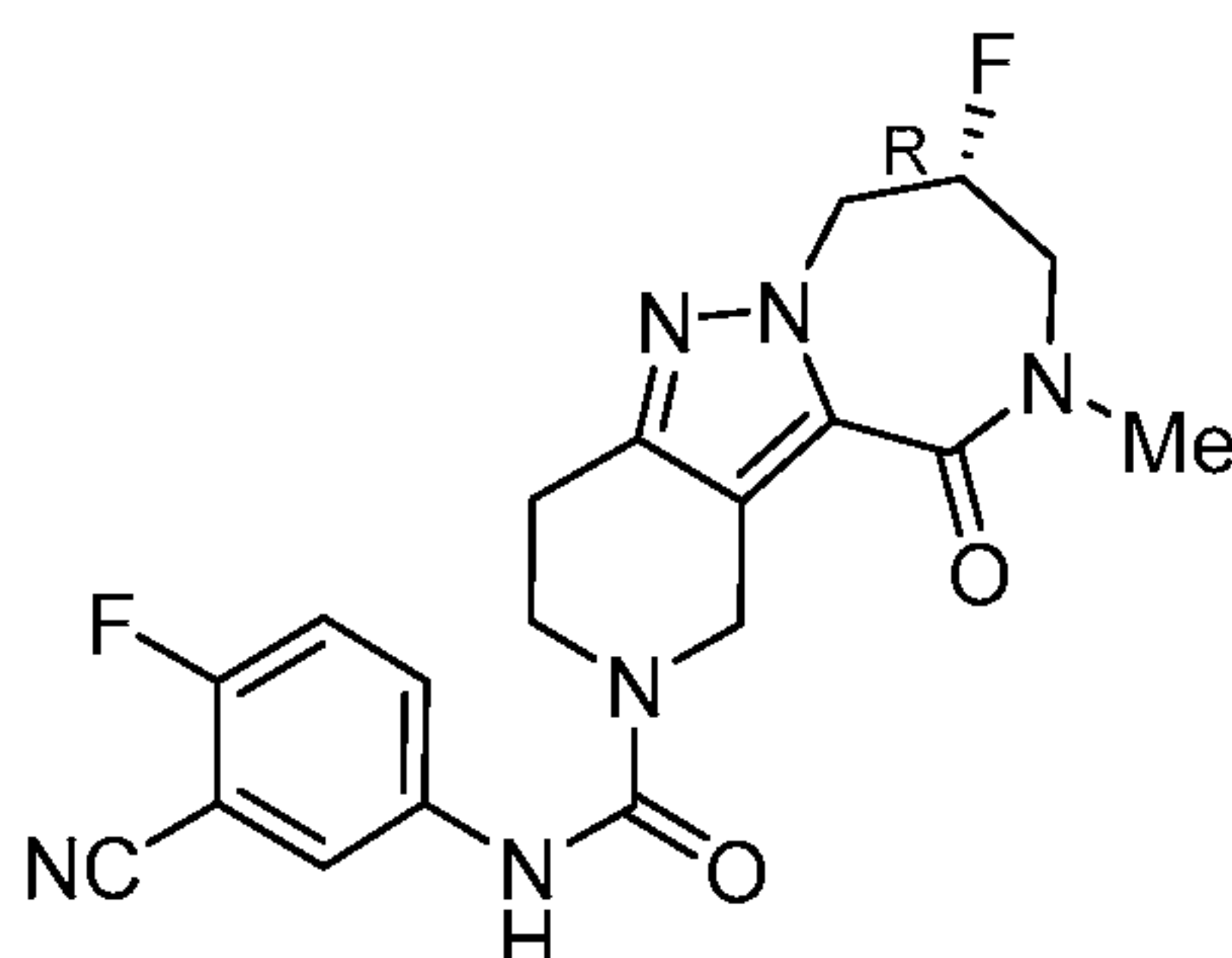
Step 6. tert-Butyl (S)-8-fluoro-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate_E1. To a solution of tert-Butyl 8-hydroxy-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate_E1 (140.00 mg, 390.80 μ mol, 1 eq) in DCM (2 mL) was added DAST (201.26 mg, 1.25 mmol, 164.97 μ L, 3.19 eq) at -20 °C. The solution was stirred at 0 °C for 0.5 hr. The solution was poured into ice sat.NaHCO₃ (30 mL). The mixture extracted with ethyl acetate (20 mL*2). The combined organic layers were washed with brine (20 mL), dried with anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by prep-TLC. The title compound (75 mg, 221.65 μ mol, 56.72% yield) was obtained as yellow oil.

Step 7. (S)-8-Fluoro-10-methyl-1,2,3,4,7,8,9,10-octahydro-11H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11-one_E1. To a solution of tert-butyl (S)-8-fluoro-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate_E1 (75.00 mg, 221.65 μ mol, 1 eq) in DCM (5 mL) was added TFA (7.70 g, 67.53 mmol, 5.00 mL, 304.68 eq). The solution was stirred at 25 °C for 0.5 hr. The solution was concentrated. The title compound (80 mg, crude, TFA) was obtained as yellow oil.

Step 8. (S)-N-(3-Cyano-4-fluorophenyl)-8-fluoro-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide E1. To a solution of (S)-8-fluoro-10-methyl-1,2,3,4,7,8,9,10-octahydro-11H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11-one_E1(78 mg, 1 eq, TFA) in DCM (5 mL) was added TEA (112.02 mg, 1.11 mmol, 154.09 μ L, 5 eq) and phenyl N-(3-cyano-4-fluoro-phenyl)carbamate (56.73 mg, 221.40 μ mol, 1 eq). The solution was stirred at 25 °C for 16 hr. The solution was concentrated. The residue was purified by prep-HPLC. The title compound (52.09 mg, 129.06 μ mol, 99.2% purity) was obtained as white solid. LCMS: 401 [M+1]. ¹H NMR (400 MHz, CHLOROFORM-

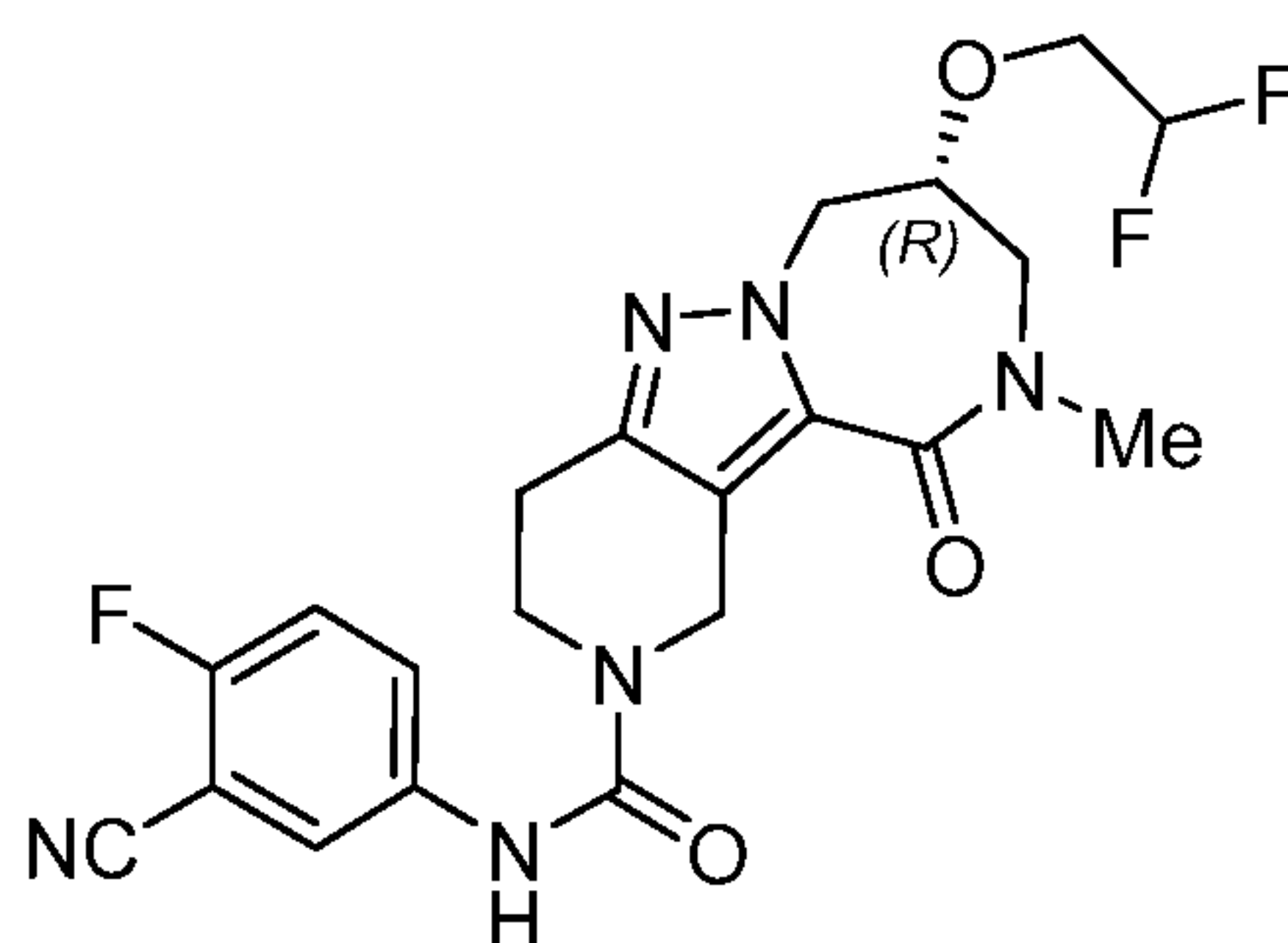
d) δ 7.79 (dd, $J=2.76, 5.52$ Hz, 1H), 7.59 (ddd, $J=2.76, 4.52, 9.03$ Hz, 1H), 7.14 (t, $J=8.66$ Hz, 1H), 6.78 (s, 1H), 4.65-4.86 (m, 2H), 4.35-4.63 (m, 1H), 3.97-4.07 (m, 1H), 3.79-3.95 (m, 2H), 3.22 (s, 3H), 2.88 (br t, $J=5.71$ Hz, 2H).

- 5 Compound 144_E2: (R)-N-(3-Cyano-4-fluorophenyl)-8-fluoro-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide E2.



- The title compound was prepared in a manner analogous to Compound 144_E1 substituting tert-Butyl 8-hydroxy-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate_E2 for tert-butyl 8-hydroxy-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate_E1. LCMS: 401 [M+1]. ^1H NMR (400 MHz, CHLOROFORM-d) δ 7.78 (dd, $J=2.76, 5.27$ Hz, 1H), 7.56-7.63 (m, 1H), 7.14 (t, $J=8.72$ Hz, 1H), 6.81 (s, 1H), 4.65-4.89 (m, 2H), 4.32-4.62 (m, 4H), 4.01 (br dd, $J=5.21, 10.85$ Hz, 1H), 3.77-3.95 (m, 2H), 3.22 (s, 3H), 2.82-2.94 (m, 2H).

Compound 145_D1: (R)-N-(3-Cyano-4-fluorophenyl)-8-(2,2-difluoroethoxy)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.



Step 1. tert-Butyl (R)-8-(2,2-difluoroethoxy)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate.

To a suspension of NaH (24.97 mg, 624.28 μ mol, 60% purity, 3 *eq*) in THF (0.6 mL) was added a solution of tert-butyl (R)-8-hydroxy-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate_E1 (70 mg, 208.09 μ mol, 1 *eq*) in THF (0.6 mL) at -40 °C, the mixture was stirred at -40 °C for 30min. Then a solution of 2,2-difluoroethyl trifluoromethanesulfonate (133.67 mg, 624.28 μ mol, 3 *eq*) in THF (0.4 mL) was added at -40 °C dropwise. The mixture was stirred at 5 °C for 1 hr. The mixture was quenched with H₂O (20 mL) at 0 °C and extracted with EA (30 mL*2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo to give the title compound (85 mg, crude) as yellow oil, which was used in the next step directly.

Step 2. (R)-8-(2,2-Difluoroethoxy)-10-methyl-1,2,3,4,7,8,9,10-octahydro-11H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11-one. To a solution of tert-butyl (R)-8-(2,2-difluoroethoxy)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (120 mg, 299.69 μ mol, 1 *eq*) in DCM (2 mL) was added TFA (3.08 g, 27.01 mmol, 2.00 mL, 90.13 *eq*). The mixture was stirred at 15 °C for 0.5 hr. The mixture was concentrated in vacuo to give the title compound (126 mg, crude, TFA) as yellow oil.

Step 3. (R)-N-(3-Cyano-4-fluorophenyl)-8-(2,2-difluoroethoxy)-10-methyl-11-oxo-1,3,4,7,8,9,10,11-octahydro-2H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepine-2-carboxamide. To a solution of (R)-8-(2,2-difluoroethoxy)-10-methyl-1,2,3,4,7,8,9,10-octahydro-11H-pyrido[4',3':3,4]pyrazolo[1,5-a][1,4]diazepin-11-one (125 mg, 301.69 μ mol, 1 *eq*, TFA) and phenyl N-(3-cyano-4-fluoro-phenyl)carbamate (77.30 mg, 301.69 μ mol, 1 *eq*) in DCM (5 mL)

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 353

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 353

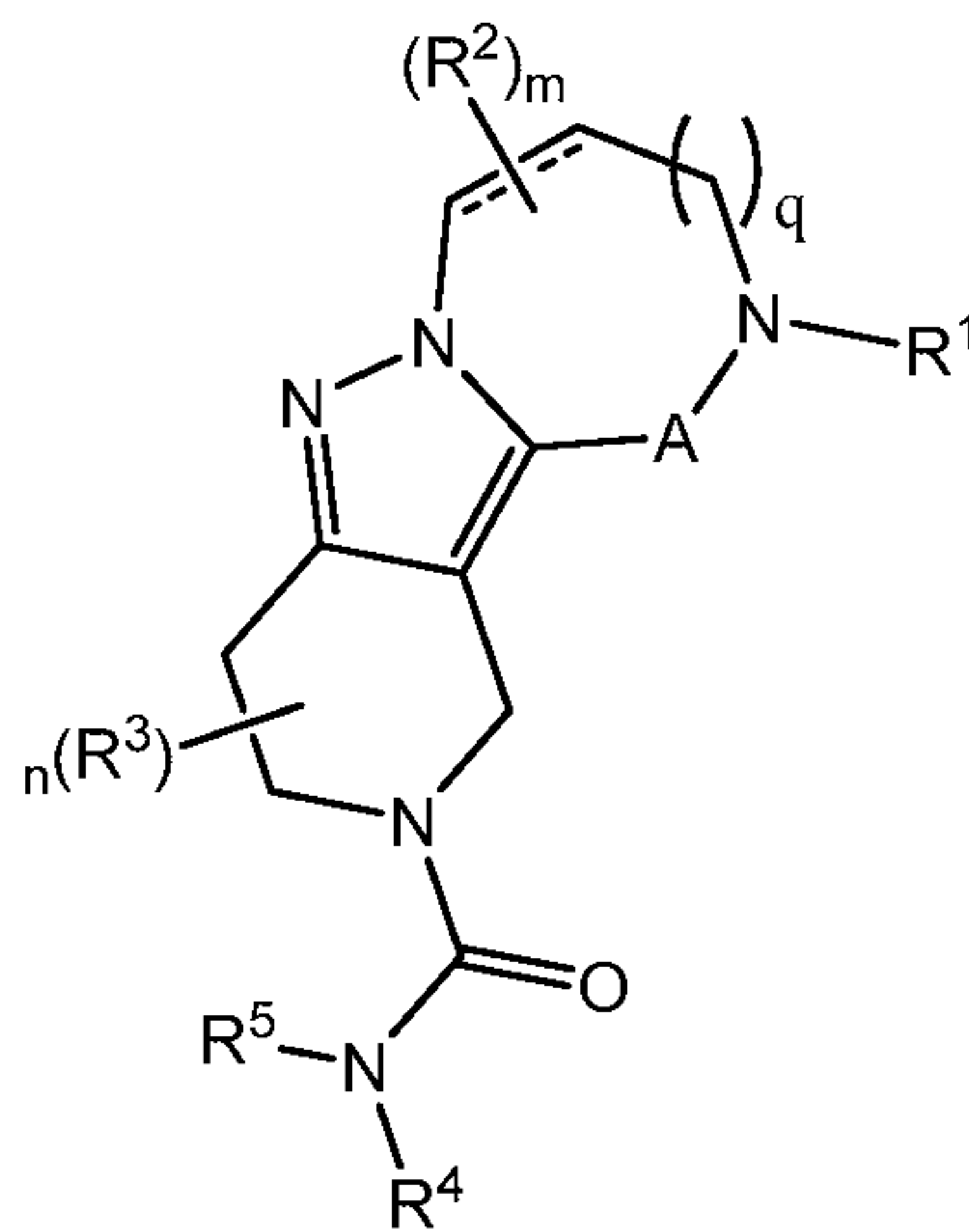
NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

CLAIMS

1. A compound of Formula IA:



I,

5 or a pharmaceutically acceptable salt thereof, wherein

A is CH₂ or C=O;

R¹ is H, C₁-C₆-alkyl, C₁-C₆-alkenyl, C₁-C₆-alkyl-OH, or C₁-C₆-haloalkyl;

R² is, at each occurrence, independently selected from -OH, halo, C₁-C₆-alkyl, C₁-C₆-alkylene, C₀-C₆-alkyl-C₃-C₆-cycloalkyl, C₀-C₆-alkyl-C₂-C₆-heterocycloalkyl,

10 C₀-C₆-alkyl-OR⁶, C₀-C₆-alkyl-N(R⁷)₂, C₀-C₆-alkyl-SR⁸, C₀-C₆-alkyl-S(O)R⁸, C₀-C₆-alkyl-S(O)₂R⁸, C₀-C₆-alkyl-C(O)OR⁹, C₀-C₆-alkyl-OC(O)R⁹, C₀-C₆-alkyl-OC(O)OR⁹, C₀-C₆-alkyl-OC(O)N(R⁷)₂, and C₀-C₆-alkyl-C(O)N(R⁷)₂, wherein alkyl, alkylene, cycloalkyl, and heterocycloalkyl are optionally substituted with 1, 2, or 3 groups, each independently selected from -OH and halo; or

15 two R² groups together form a C₃-C₆ spiro cycloalkyl, wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups, each individually selected from -OH and halo;

R³ is, at each occurrence, independently selected from -OH, halo, C₁-C₆-alkyl, C₁-C₆-haloalkyl, -O-C₁-C₆-alkyl, and C₁-C₆-alkyl-OH;

20 R⁴ is selected from (CR^aR^b)_p-C₁-C₉-heteroaryl, (CR^aR^b)_p-C₆-C₁₂-aryl, (CR^aR^b)_p-C₃-C₇-cycloalkyl, and (CR^aR^b)_p-C₂-C₆-heterocycloalkyl, wherein heteroaryl, aryl, cycloalkyl, and heterocycloalkyl are optionally substituted with 1, 2, 3, or 4 groups, each independently selected from -OH, halo, -CN, -SF₅, C₁-C₆-alkyl, C₁-C₆-haloalkyl, -O-C₁-C₆-alkyl, and C₁-C₆-alkyl-OH;

R⁵ is selected from H, C₁-C₆-alkyl, and C₁-C₆-alkyl-OH;

R^6 is selected from H, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkenyl, and C₀-C₆-alkyl-C₃-C₆-cycloalkyl;

R^7 is, at each occurrence, independently selected from H, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C(O) C₁-C₆-alkyl and C₁-C₆-alkyl-OH;

5 R^8 is selected from H and C₁-C₆-alkyl;

R^9 is selected from H and C₁-C₆-alkyl;

R^a is, at each occurrence, independently selected from H, -OH, halo, C₁-C₆-alkyl, C₁-C₆-haloalkyl, -O-C₁-C₆-alkyl, and C₁-C₆-alkyl-OH;

R^b is, at each occurrence, independently selected from H and C₁-C₆-alkyl;

10 m is 0, 1, 2, 3, or 4;

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

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

q is 0 or 1; and

a ---- line denotes an optionally double bond.

15

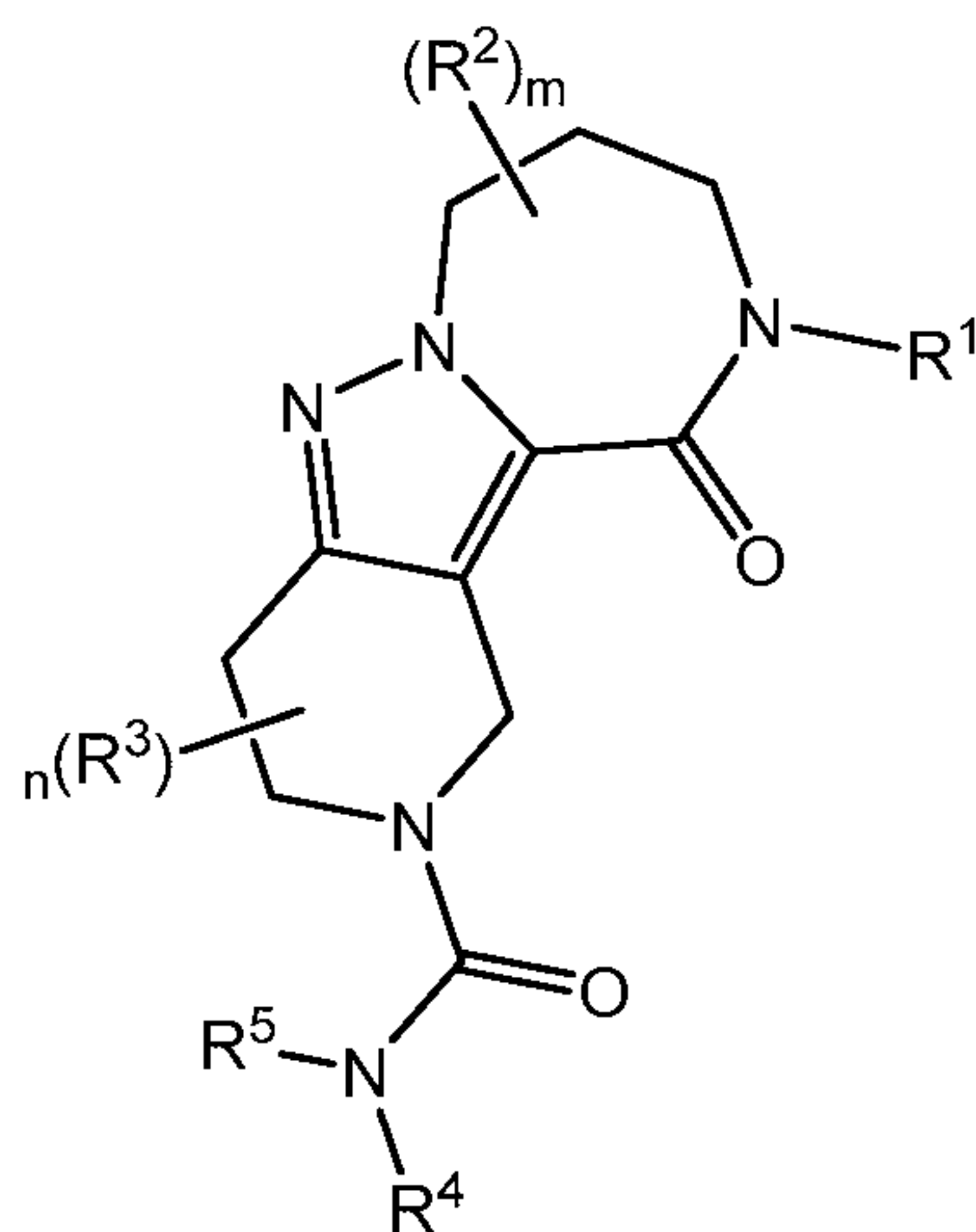
2. The compound of claim 1, wherein A is C=O.

3. The compound of claim 1 or 2, wherein q is 1.

20 4. The compound of any one of claims 1-3, wherein R^1 is H, C₁-C₆-alkyl, or C₁-C₆-haloalkyl.

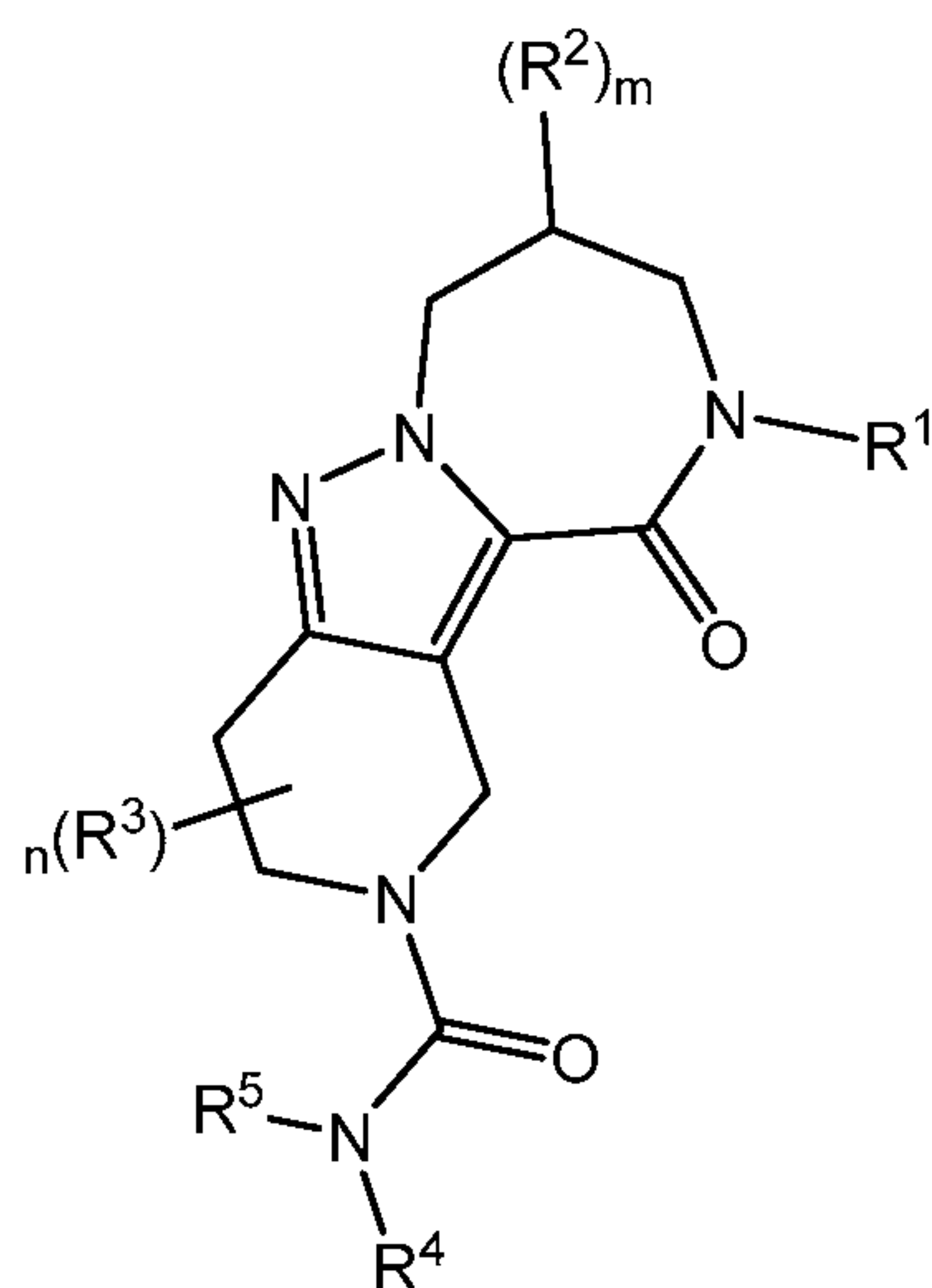
5. The compound of any one of claims 1-4, wherein R^1 is -CH₃, or -CH₂CHF₂.

25 6. The compound of any one of claims 1-5, having the structure of Formula II:

**II,**

or a pharmaceutically acceptable salt thereof.

- 5 7. The compound of any one of claims 1-6, having the structure of Formula III:

**III,**

or a pharmaceutically acceptable salt thereof,

wherein m is 0, 1, or 2.

10

8. The compound of any one of claims 1-7, wherein m is 0, 1, or 2; and

R^2 is, at each occurrence, independently selected from $-OH$, halo, C_1-C_6 -alkyl, C_1-C_6 -alkenyl, C_0-C_6 -alkyl- OR^6 , C_0-C_6 -alkyl- $N(R^7)_2$, C_0-C_6 -alkyl- C_3-C_6 -cycloalkyl, C_0-C_6 -alkyl- C_2-C_6 -heterocycloalkyl, C_0-C_6 -alkyl- SR^8 , C_0-C_6 -alkyl- $S(O)R^8$, C_0-C_6 -alkyl- $S(O)_2R^8$, C_0-C_6 -alkyl- $C(O)OR^9$, and C_0-C_6 -alkyl- $C(O)N(R^7)_2$, wherein alkyl, cycloalkyl, and heterocycloalkyl are

15

optionally substituted with 1 or 2 groups, each independently selected from -OH and halo.

9. The compound of any one of claims 1-8, wherein m is 1 or 2; and

R^2 , is at each occurrence, independently selected from =CH₂, -CH₂OH, -OH, -F, -CH₃,
 5 -CHF₂, -OCH₃, -OCH₂CH₃, -OCH₂CHF₂, -NH₂, -N(CH₃)₂, morpholinyl, azetidiny, pyrrolidinyl, -SCH₃, -S(O)CH₃, -S(O)₂CH₃, -CH₂C(O)OCH₃, -CH₂CH₂OH, -C(O)OH, -C(O)OCH₃, -C(O)OCH₂CH₃, -C(O)NHCH₃, -C(O)N(CH₃)₂, -C(OH)(CH₃)₂, -CH(OH)CH₃, -CH(OH)CH₂CH₃, and -CH(OH)-cyclopropyl, wherein morpholinyl, azetidiny, and pyrrolidinyl are optionally substituted with 1 or 2 groups, each independently selected from -OH and halo.

10. The compound of any one of claims 1-9, wherein n is 0, 1, or 2; and R^3 is, at each occurrence, selected from -OH, halo, and C₁-C₆-alkyl.

11. The compound of any one of claims 1-10, wherein R^4 is (CR^aR^b)_p-C₁-C₅-heteroaryl or
 15 (CR^aR^b)_p-C₆-aryl, wherein heteroaryl and aryl are optionally substituted with 1, 2, 3, or 4 groups, each independently selected from -OH, halo, -CN, -SF₅, C₁-C₆-alkyl, C₁-C₆-haloalkyl, -O-C₁-C₆-alkyl, and C₁-C₆-alkyl-OH;

R^a is H or C₁-C₆-alkyl;

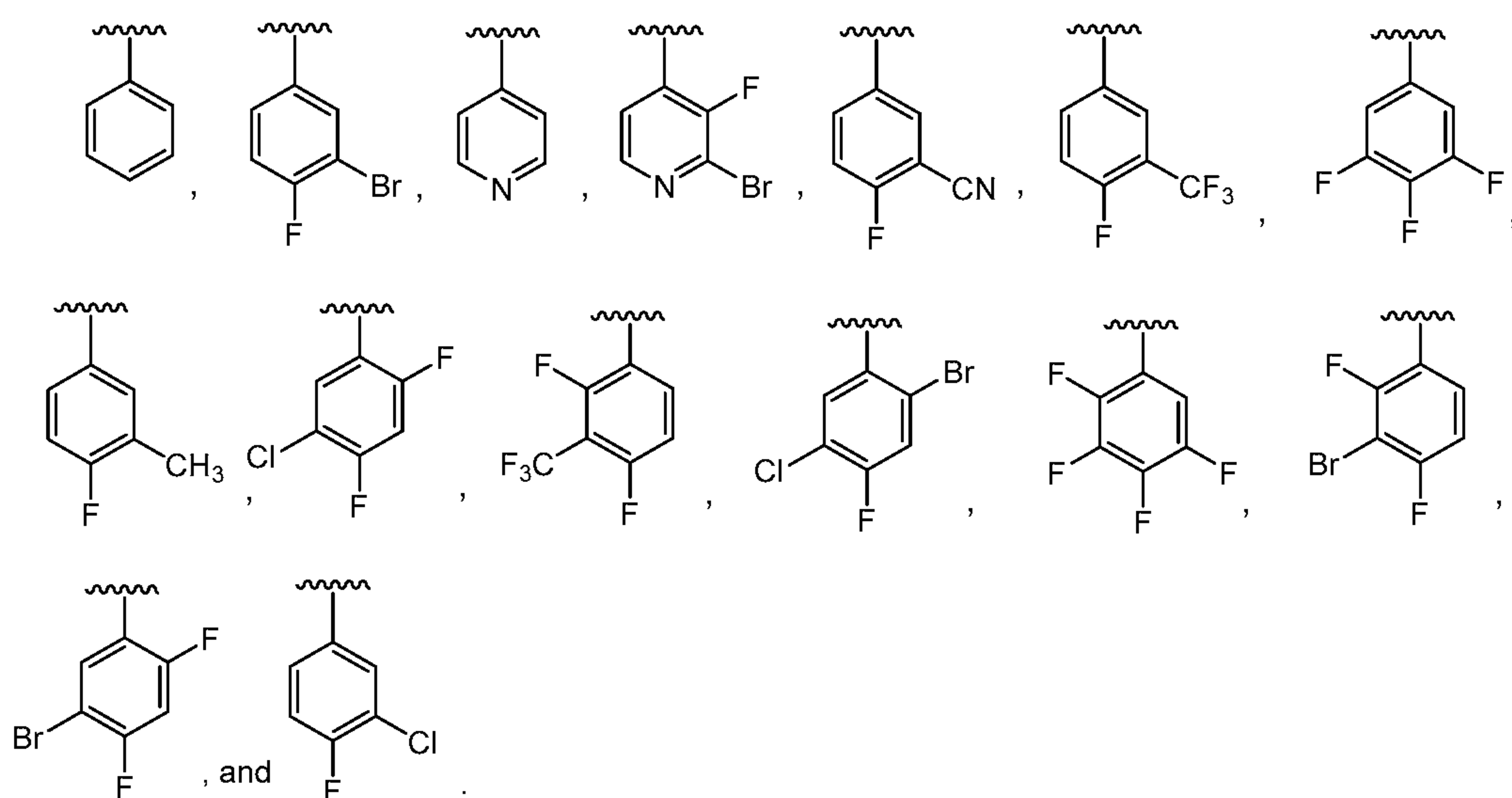
R^b is H or C₁-C₆-alkyl; and

20 p is 0 or 1.

12. The compound of any one of claims 1-11, wherein R^4 is C₁-C₅-heteroaryl or C₆-aryl, any of which is optionally substituted with 1, 2, 3, or 4 groups, each independently selected from halo, -CN, C₁-C₆-alkyl, and C₁-C₆-haloalkyl.

13. The compound of any one of claims 1-12, wherein R^4 is phenyl or pyridinyl, any of which is optionally substituted with 1, 2, 3, or 4 groups, each independently selected from halo, -CN, C₁-C₆-alkyl, and C₁-C₆-haloalkyl.

14. The compound of any one of claims 1-13, wherein R^4 is selected from the group consisting of:



15. The compound of any one of claims 1-14, wherein R^5 is H or C_1 - C_6 -alkyl.

5 16. The compound of any one of claims 1-15, wherein R^5 is H.

17. The compound of any one of claims 1-16, wherein

A is $C=O$;

R^1 is C_1 - C_6 -alkyl;

10 R^2 is, at each occurrence, independently selected from $-OH$, halo, C_1 - C_6 -alkyl, C_1 - C_6 -alkylene, C_0 - C_6 -alkyl- C_3 - C_6 -cycloalkyl, C_0 - C_6 -alkyl- C_2 - C_6 -heterocycloalkyl, C_0 - C_6 -alkyl- OR^6 , C_0 - C_6 -alkyl- $N(R^7)_2$, C_0 - C_6 -alkyl- SR^8 , C_0 - C_6 -alkyl- $S(O)R^8$, C_0 - C_6 -alkyl- $S(O)_2R^8$, C_0 - C_6 -alkyl- $C(O)OR^9$, and C_0 - C_6 -alkyl- $C(O)N(R^7)_2$, wherein alkyl, cycloalkyl, and heterocycloalkyl are optionally substituted with 1, 2, or 3 groups, each independently selected
15 from $-OH$ and halo;

R^4 is $(CR^aR^b)_p$ - C_6 - C_{12} -aryl, wherein aryl is optionally substituted with 1, 2, 3, or 4 groups, each independently selected from halo, $-CN$, and C_1 - C_6 -alkyl;

R^5 is H;

R^6 is selected from H, C_1 - C_6 -alkyl, and C_1 - C_6 -haloalkyl;

20 R^7 is, at each occurrence, independently selected from H, and C_1 - C_6 -alkyl;

R^8 is C_1 - C_6 -alkyl;

R^9 is selected from H and C_1 - C_6 -alkyl;

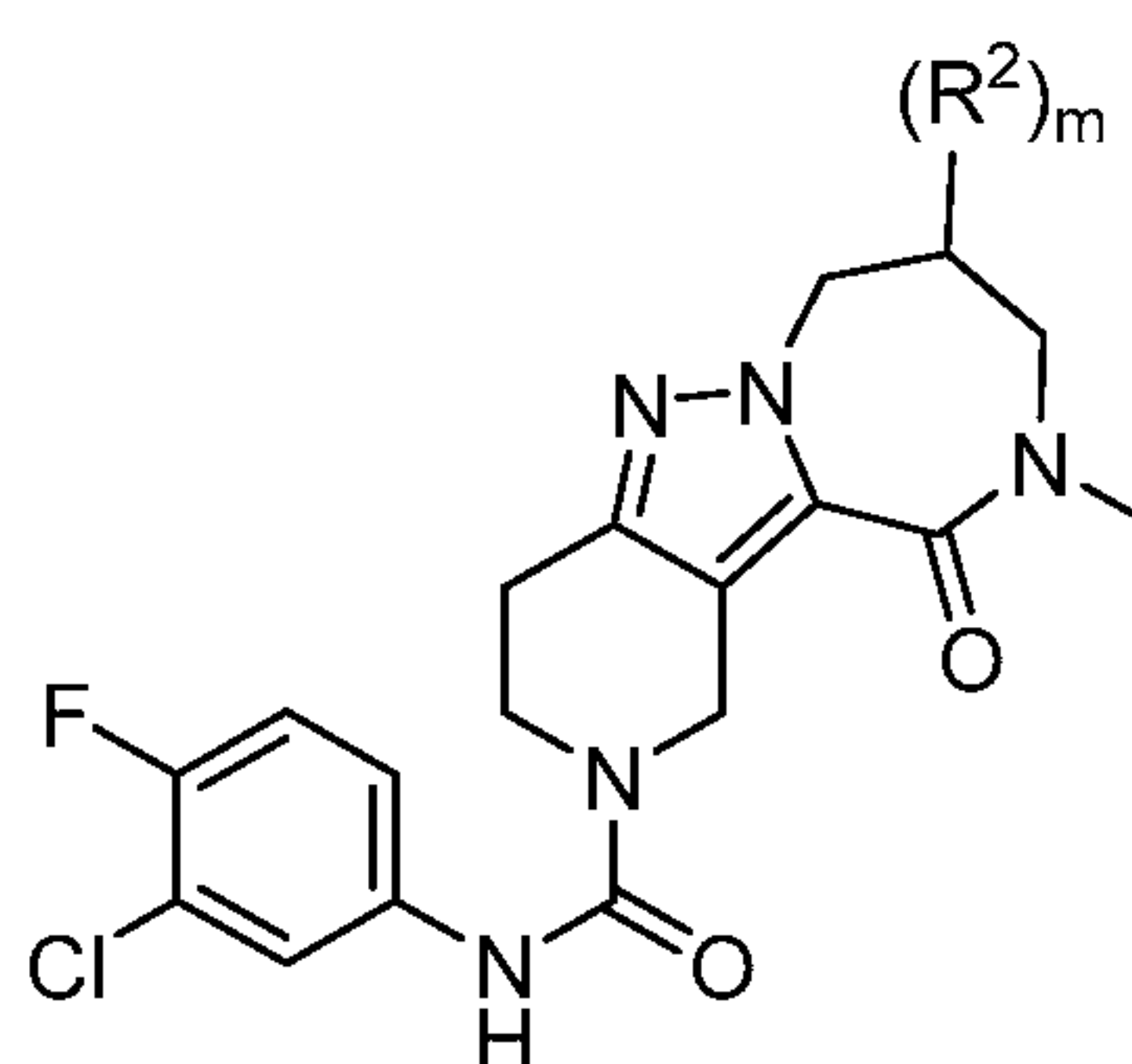
m is 0, 1 or 2;

n is 0;

5 p is 0; and

q is 1.

18. The compound of any one of claims 1-17, having the structure of Formula IV:



IV

wherein

m is 1 or 2; and

R^2 , is at each occurrence, independently selected from $=CH_2$, $-CH_2OH$, $-OH$, $-F$, $-CH_3$, $-CHF_2$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CHF_2$, $-NH_2$, $-N(CH_3)_2$, morpholinyl, azetidiny, pyrrolidinyl, $-SCH_3$, $-S(O)CH_3$, $-S(O)_2CH_3$, $-CH_2C(O)OCH_3$, $-CH_2CH_2OH$, $-C(O)OH$, $-C(O)OCH_3$, $-C(O)OCH_2CH_3$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-C(OH)(CH_3)_2$, $-CH(OH)CH_3$, $-CH(OH)CH_2CH_3$, $-CH(OH)$ -cyclopropyl, $-CH_2N(H)(C(O)-CH_3)$, $-CH_2N(H)CH_2CHF_2$, $-CH_2N(H)CH_2CF_3$, $-CH(OH)CH=CH_2$ and spiro-cyclobutyl, which is substituted with $-OH$, wherein morpholinyl, azetidiny, and pyrrolidinyl are optionally substituted with 1 or 2 groups, each independently selected from $-OH$ and halo.

19. The compound of claim 1, wherein m is 0, 1, or 2; and

R^2 is, at each occurrence, independently selected from $-OH$, halo, C_1 - C_6 -alkyl, C_1 - C_6 -alkylene, C_0 - C_6 -alkyl- C_3 - C_6 -cycloalkyl, C_0 - C_6 -alkyl- C_2 - C_6 -heterocycloalkyl, C_0 - C_6 -alkyl- OR^6 , C_0 - C_6 -alkyl- $N(R^7)_2$, C_0 - C_6 -alkyl- SR^8 , C_0 - C_6 -alkyl- $S(O)R^8$, C_0 - C_6 -alkyl-

$S(O)_2R^8$, C_0 - C_6 -alkyl- $C(O)OR^9$, C_0 - C_6 -alkyl- $OC(O)R^9$, C_0 - C_6 -alkyl- $OC(O)OR^9$, C_0 - C_6 -alkyl- $OC(O)N(R^7)_2$, and C_0 - C_6 -alkyl- $C(O)N(R^7)_2$, wherein alkyl, alkylene, cycloalkyl, and heterocycloalkyl are optionally substituted with 1, 2, or 3 groups, each independently selected from $-OH$ and halo; or

5 two R^2 groups together form a C_3 - C_6 spiro cycloalkyl, wherein the cyloalkyl is optionally substituted with 1, 2, or 3 groups, each individually selected from $-OH$ and halo.

20. The compound of claim 1 or claim 19, wherein m is 1 or 2; and

R^2 , is at each occurrence, independently selected from $-CH_2N(H)(C(O)-CH_3)$, -
10 $CH_2N(H)CH_2CHF_2$, $CH_2N(H)CH_2CF_3$, $CH(OH)CH=CH_2$ and spiro-cyclobutyl, which is substituted with $-OH$.

21. The compound of any one of claims 1 and 19-20, wherein

 A is $C=O$;

15 R^1 is C_1 - C_6 -alkyl;

R^2 is, at each occurrence, independently selected from $-OH$, halo, C_1 - C_6 -alkyl, C_1 - C_6 -alkylene, C_0 - C_6 -alkyl- C_3 - C_6 -cycloalkyl, C_0 - C_6 -alkyl- C_2 - C_6 -heterocycloalkyl, C_0 - C_6 -alkyl- OR^6 , C_0 - C_6 -alkyl- $N(R^7)_2$, C_0 - C_6 -alkyl- SR^8 , C_0 - C_6 -alkyl- $S(O)R^8$, C_0 - C_6 -alkyl- $S(O)_2R^8$, C_0 - C_6 -alkyl- $C(O)OR^9$, and C_0 - C_6 -alkyl- $C(O)N(R^7)_2$, wherein alkyl, alkylene, cycloalkyl, and heterocycloalkyl are optionally substituted with 1, 2, or 3 groups, each
20 independently selected from $-OH$ and halo; or

 two R^2 groups together form a C_3 - C_6 spiro cycloalkyl, wherein the cyloalkyl is optionally substituted with 1, 2, or 3 groups, each individually selected from $-OH$ and halo;

R^4 is $(CR^aR^b)_p$ - C_6 - C_{12} -aryl, wherein aryl is optionally substituted with 1, 2, 3, or 4
25 groups, each independently selected from halo, $-CN$, and C_1 - C_6 -alkyl;

R^5 is H;

R^6 is selected from H, C_1 - C_6 -alkyl, and C_1 - C_6 -haloalkyl;

R^7 is, at each occurrence, independently selected from H, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, $C(O)$ C_1 - C_6 -alkyl and C_1 - C_6 -alkyl- OH ;

30 R^8 is C_1 - C_6 -alkyl;

R^9 is selected from H and C_1 - C_6 -alkyl;

cycloalkyl, and $(CR^aR^b)_p$ -C₂-C₆-heterocycloalkyl, wherein heteroaryl, aryl, cycloalkyl, and heterocycloalkyl are optionally substituted with 1, 2, 3, or 4 groups, each independently selected from -OH, halo, -CN, -SF₅, C₁-C₆-alkyl, C₁-C₆-haloalkyl, -O-C₁-C₆-alkyl, and C₁-C₆-alkyl-OH;

R⁵ is selected from H, C₁-C₆-alkyl, and C₁-C₆-alkyl-OH;

5 R⁶ is selected from H, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkenyl, and C₀-C₆-alkyl-C₃-C₆-cycloalkyl;

R⁷ is, at each occurrence, independently selected from H, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C(O) C₁-C₆-alkyl and C₁-C₆-alkyl-OH;

R⁸ is selected from H and C₁-C₆-alkyl;

10 R⁹ is selected from H and C₁-C₆-alkyl;

R^a is, at each occurrence, independently selected from H, -OH, halo, C₁-C₆-alkyl, C₁-C₆-haloalkyl, -O-C₁-C₆-alkyl, and C₁-C₆-alkyl-OH;

R^b is, at each occurrence, independently selected from H and C₁-C₆-alkyl;

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

15 n is 0, 1, 2, 3, or 4;

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

a ---- line denotes an optionally double bond.

23. The compound of claim 22, wherein A is C=O.

20

24. The compound of claim 22 or 23, wherein R¹ is H or C₁-C₆-alkyl.

25. The compound of any one of claims 22-24, wherein m is 0.

25 26. The compound of any one of claims 22-25, wherein R⁴ is $(CR^aR^b)_p$ -C₁-C₅-heteroaryl or $(CR^aR^b)_p$ -C₆-aryl, wherein heteroaryl and aryl are optionally substituted with 1, 2, 3, or 4 groups, each independently selected from -OH, halo, -CN, -SF₅, C₁-C₆-alkyl, C₁-C₆-haloalkyl, -O-C₁-C₆-alkyl, and C₁-C₆-alkyl-OH;

R^a is H or C₁-C₆-alkyl;

30 R^b is H or C₁-C₆-alkyl; and

p is 0 or 1.

27. The compound of any one of claims 22-26, wherein

A is C=O;

R¹ is -CH₃;

5 R⁴ is (CR^aR^b)_p-C₆-C₁₂-aryl, wherein aryl is optionally substituted with 1, 2, 3, or 4 groups, each independently selected from halo, -CN, and C₁-C₆-alkyl;

R⁵ is H;

m is 0;

n is 0; and

10 p is 0.

28. A pharmaceutical composition comprising a compound of any one of claims 1-27, and a pharmaceutically acceptable carrier.

15 29. A method of treating an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound according to any one of claims 1-27.

20 30. A method of inhibiting or reducing the formation or presence of HBV DNA-containing particles or HBV RNA-containing particles in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound according to any one of claims 1-27.

25 31. The method of claim 29 or 30, further comprising administering to the individual at least one additional therapeutic agent selected from the group consisting of an HBV polymerase inhibitor, immunomodulatory agents, interferon, viral entry inhibitor, viral maturation inhibitor, capsid assembly modulator, reverse transcriptase inhibitor, cyclophilin/TNF inhibitor, TLR-agonist, HBV vaccine, and any combination thereof.

30 32. A method of preparing the compound of claim 1.

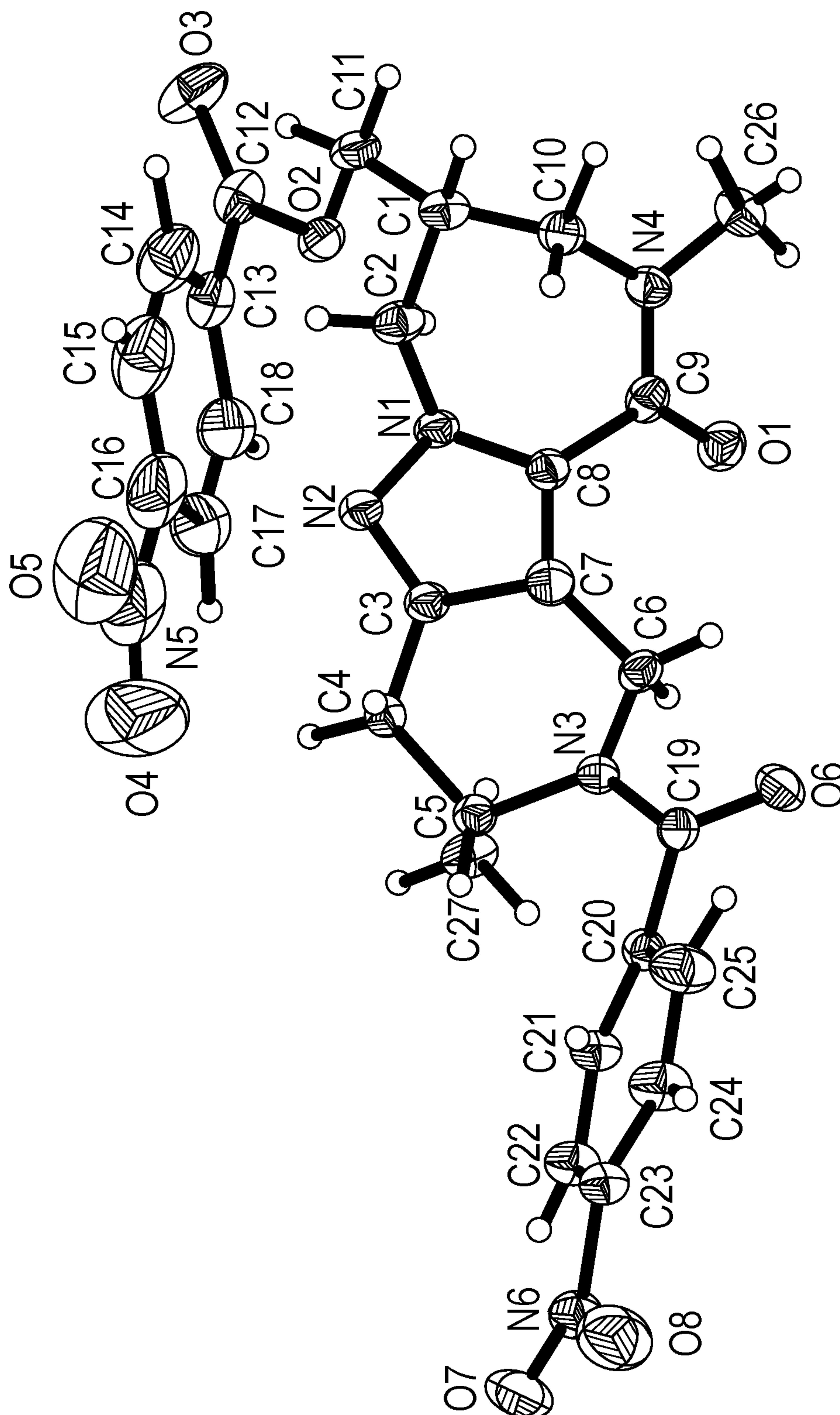
Fig. 1

Fig. 1

