



(51) International Patent Classification:

A61P 25/00 (2006.01) C07D 401/14 (2006.01)
 A61P 29/00 (2006.01) C07D 471/10 (2006.01)
 A61P 35/00 (2006.01) C07D 491/107 (2006.01)
 A61P 37/02 (2006.01) C07D 513/10 (2006.01)
 C07D 401/12 (2006.01)

(21) International Application Number:

PCT/IB2024/055815

(22) International Filing Date:

14 June 2024 (14.06.2024)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

202321040658 14 June 2023 (14.06.2023) IN

(71) Applicant: **ALEMBIC PHARMACEUTICALS LIMITED** [IN/IN]; Alembic City, Alembic Road, Vadodara, Gujarat 390003 (IN).

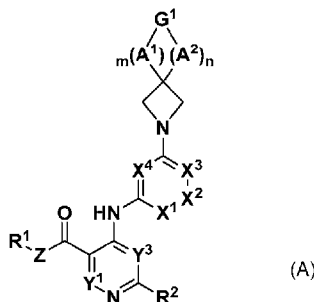
(72) Inventors: **KURHADE, Suresh**; c/o Alembic Pharmaceuticals Limited, 2nd Floor, Building 2700, MN Takshila Park, Genome Valley, Hyderabad, Telangana 500078 (IN). **PRIYADARSHANI, Garima**; c/o Alembic Pharmaceuticals Limited, 2nd Floor, Building 2700, MN Takshila Park, Genome Valley, Hyderabad, Telangana 500078 (IN). **SISODIYA, Shailendra**; c/o Alembic Pharmaceuticals Limited, 2nd Floor, Building 2700, MN Takshila Park, Genome Valley, Hyderabad, Telangana 500078 (IN). **HALLE, Mahesh**; c/o Alembic Pharmaceuticals Limited, 2nd Floor, Building 2700, MN Takshila Park, Genome Valley, Hyderabad, Telangana 500078 (IN). **KAPURE, Jeevak Sopanrao**; c/o Alembic Pharmaceuticals Limited, 2nd Floor, Building 2700, MN Takshila Park, Genome Valley, Hyderabad, Telangana 500078 (IN). **KURIAPPAN, Jissy Akkarapattikal**; c/o Alembic Pharmaceuticals Limited, 2nd Floor, Building 2700, MN Takshila Park, Genome Val-

ley, Hyderabad, Telangana 500078 (IN). **MALLIK, Sanchari Basu**; c/o Alembic Pharmaceuticals Limited, 2nd Floor, Building 2700, MN Takshila Park, Genome Valley, Hyderabad, Telangana 500078 (IN). **TANDON, Amol**; c/o Alembic Pharmaceuticals Limited, 2nd Floor, Building 2700, MN Takshila Park, Genome Valley, Hyderabad, Telangana 500078 (IN). **SUBRAMANIAM, Ganesan**; c/o Alembic Research Centre, Alembic Pharmaceuticals Limited, Alembic Road, Vadodara, Gujarat 390003 (IN). **IYER, Abishek Venkatasubramanian**; c/o Alembic Pharmaceuticals Limited, 2nd Floor, Building 2700, MN Takshila Park, Genome Valley, Hyderabad, Telangana 500078 (IN).

(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, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, 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, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, 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, ME, 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: TYK2 PSEUDOKINASE LIGANDS AND USES THEREOF



(57) Abstract: Described herein are compounds that are useful in the modulation of inflammation and treating associated disorders by acting on TYK2 to cause TYK2-mediated signal transduction inhibition. In some embodiments, the TYK2-mediated disorder is an autoimmune disorder, an inflammatory disorder, an endocrine disorder, a neurological disorder, a proliferative disorder, or a disorder associated with transplantation. Formula (A)

Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

TYK2 PSEUDOKINASE LIGANDS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit under 35 U.S.C. § 119(e) to Indian Application No. 202321040658, filed June 14, 2023, the entirety of which is incorporated herein by reference.

FIELD

[0002] The present invention relates to compounds and methods of making such compounds useful for inhibiting non-receptor tyrosine-protein kinase 2, also known as Tyrosine kinase 2 (TYK2). The invention also relates to pharmacologically acceptable compositions and medicaments comprising such compounds and methods of using said compounds and compositions in the treatment of various disorders.

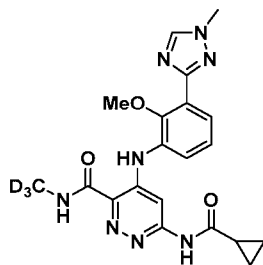
BACKGROUND

[0003] Cytokines play an important role in the regulation of immunity and inflammation. Janus kinase (JAK) is an intracellular non-receptor tyrosine kinase that mediates the process of transmitting various cytokine signals from the extracellular to the nucleus. The JAK kinase family is divided into four subtypes, JAK1, JAK2, JAK3 and TYK2, each of which mediates different types of cytokine signaling pathways.

[0004] JAK family members are composed of four JAK homology regions (JH), including a catalytically active kinase domain (JH1), a catalytically inactive kinase-like domain (JH2), and a SH2-like domain (JH3) and four FERM domains (JH4-7). Among them, the JH2 domain is the most special structure, which has a high degree of similarity with the amino acid sequence of the JH1 domain, but due to the lack of several key amino acids, it does not have phosphatase activity, so it cannot exert catalytic activity, and therefore is known as the kinase-like domain, and functions to regulate catalytic activity.

[0005] TYK2 has been shown to be critical in regulating the signal transduction cascade downstream of receptors for IL-12, IL-23 and type I interferons.

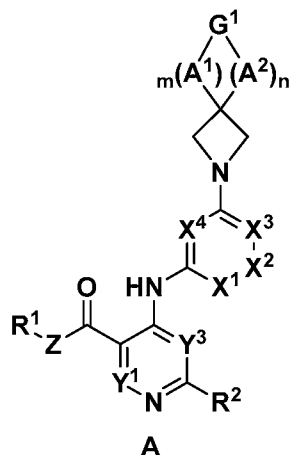
[0006] Due to high sequence similarity of the kinase domain JH2 among the JAK family (JAK1, JAK2, JAK3, and TYK2), it is challenging to develop a selective inhibitor towards TYK2's JH2 without inhibiting the JH1 of JAK1, JAK2, JAK3 or TYK2. Most JAK inhibitors that bind to the kinase domain of JAKs, including tofacitinib, ruxolitinib, baricitinib, upadacitinib, etc., are not very selective among the JAK family members and exhibit dose-dependent side effects clinically such as anemia. The development of highly selective TYK2 inhibitors remains attractive among pharmaceutical companies. Based on the structural differences between the ATP binding pockets in TYK2's JH1 and JH2, Bristol-Myers Squibb Company has developed a highly selective JH2 binder, Deucravacitinib, which only inhibits the physiological functions mediated by TYK2 without binding to the kinase domains (JH1) of JAKs. The structure of BMS-986165 is shown below (WO2014074661)



[0007] WO2015069310, WO2019183186, WO2020086616, WO2020092196, WO2020159904, WO2021222153, WO2022105771, and WO2022193499 disclose different compounds as TYK2 inhibitors, however, there remains a need to develop new compounds that selectively binds to the JH2 pseudokinase domain of TYK2, with minimal binding toward kinase domains of the JAK families.

SUMMARY

[0008] In embodiments, the present disclosure provides a compound of Formula (A):



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

Y^1 , Y^3 are independently selected from N or CH;

X^1 , X^2 , X^3 , X^4 are independently selected from N or CR^3 ;

Z is selected from NR^4 , $CR^4R^{4'}$, O, S or a bond;

A^1 and A^2 are independently selected from $CR^4R^{4'}$ or O;

G^1 is selected from O, S, $S(O)_2$, $C(=O)$, NR^5 , $NC(=O)OR^6$ or $CR^4R^{4'}$;

m and n are independently selected from 0, 1, 2, 3 or 4;

R^1 is selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

R^2 is selected from hydrogen, halogen, -CN, $-OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)_2R^6$, $-NO_2$, $-NR^5R^{5'}$, $-NR^6S(=O)_2R^6$, $-S(=O)_2NR^5R^{5'}$, $-C(=O)R^6$, $-OC(=O)R^6$, $-C(=O)OR^6$, $-OC(=O)OR^6$, $-C(=O)NR^5R^{5'}$, $-OC(=O)NR^5R^{5'}$, $-NR^6C(=O)NR^5R^{5'}$, $-NR^6C(=O)R^6$, $-NR^6C(=S)R^6$, $-NR^6C(=O)OR^6$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently

optionally substituted with one or more oxo, deuterium, halogen, -CN, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^cR^d, C₁-C₆alkyl, or C₁-C₆haloalkyl;

R³ is selected from hydrogen, deuterium, halogen, -CN, -OR^a, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -NO₂, -NR^cR^d, -NR^aS(=O)₂R^b, -S(=O)₂NR^cR^d, -C(=O)R^a, -OC(=O)R^a, -C(=O)OR^a, -OC(=O)OR^a, -C(=O)NR^cR^d, -OC(=O)NR^cR^d, -NR^aC(=O)NR^cR^d, -NR^aC(=O)R^b, -NR^aC(=O)OR^b, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^cR^d, C₁-C₆alkyl, or C₁-C₆haloalkyl, C₁-C₆deuteroalkyl; with a proviso that when each of X¹, X², X³, and X⁴ represents CR³, X⁴ represents CR³, R³ not being hydrogen.

R⁴ and R^{4'} are independently selected from hydrogen, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^a, -NR^aC(=O)R^b, -NR^aC(=O)OR^b; or alternatively R⁴ and R^{4'} together represents an oxo group; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OR^a, -NR^cR^d, -NR^aC(=O)OR^b, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^cR^d, aryl, C₁-C₆alkyl, or C₁-C₆haloalkyl;

R⁵ and R^{5'} are independently selected from hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆alkoxy, C₂-C₆alkenyl, C₂-C₆alkynyl, NC(=O)R^a, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C₁-C₆alkyl, C₁-C₆alkoxy, aryl or C₁-C₆haloalkyl; or R⁵ and R^{5'} are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo, deuterium, halogen,

-CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C₁-C₆alkyl, or C₁-C₆haloalkyl;

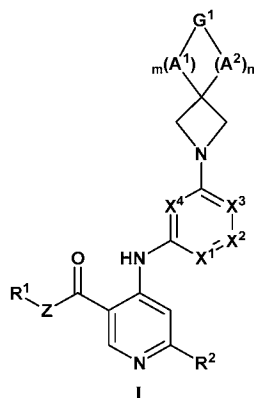
R⁶ and R^{6'} are independently selected from hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, aryl, C₁-C₆alkyl, or C₁-C₆haloalkyl;

each R^a and R^b is independently selected from hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, -C(=O)NHMe, C₁-C₆alkyl, cycloalkyl, aryl, heteroaryl or C₁-C₆haloalkyl; and

each R^c and R^d is independently selected from hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C₁-C₆alkyl, or C₁-C₆haloalkyl; or R^c and R^d are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C₁-C₆alkyl, or C₁-C₆haloalkyl.

[0009] In an embodiment, the compound of Formula (A) is a compound of Formula (I), Formula (II) or Formula (III).

[00010] Disclosed herein is a compound of Formula (I), or a pharmaceutically acceptable salt or stereoisomer thereof:



wherein:

X^1 , X^2 , X^3 , X^4 are independently selected from N or CR^3 ;

Z is selected from NR^4 , $CR^4R^{4'}$, O, S or a bond;

A^1 and A^2 are independently selected from $CR^4R^{4'}$ or O;

G^1 is selected from O, S, $S(O)_2$, $C(=O)$, NR^5 , $NC(=O)OR^6$ or $CR^4R^{4'}$;

m and n are independently selected from 0, 1, 2, 3 or 4;

[00011] R^1 is selected from hydrogen, alkyl, haloalkyl, deuterioalkyl, hydroxyalkyl, aminoalkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^cR^d$, alkyl, or haloalkyl;

[00012] R^2 is selected from hydrogen, halogen, -CN, $-OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)_2R^6$, $-NO_2$, $-NR^5R^{5'}$, $-NR^6S(=O)_2R^{6'}$, $-S(=O)_2NR^5R^{5'}$, $-C(=O)R^6$, $-OC(=O)R^6$, $-C(=O)OR^6$, $-OC(=O)OR^6$, $-C(=O)NR^5R^{5'}$, $-OC(=O)NR^5R^{5'}$, $-NR^6C(=O)NR^5R^{5'}$, $-NR^6C(=O)R^{6'}$, $-NR^6C(=S)R^{6'}$, $-NR^6C(=O)OR^{6'}$, alkyl, haloalkyl, deuterioalkyl, hydroxyalkyl, aminoalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^cR^d$, alkyl, or haloalkyl;

[00013] R^3 is selected from hydrogen, deuterium, halogen, -CN, $-OR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-NO_2$, $-NR^cR^d$, $-NR^aS(=O)_2R^b$, $-S(=O)_2NR^cR^d$, $-C(=O)R^a$, -

OC(=O)R^a, -C(=O)OR^a, -OC(=O)OR^a, -C(=O)NR^cR^d, - OC(=O)NR^cR^d, - NR^aC(=O)NR^cR^d, -NR^aC(=O)R^b, -NR^aC(=O)OR^b, alkyl, haloalkyl, deuterioalkyl, hydroxyalkyl, aminoalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^cR^d, alkyl, or haloalkyl, deuterioalkyl; with a proviso that when each of X¹, X², X³, and X⁴ represents CR³, X⁴ represents CR³, R³ not being hydrogen.

[00014] R⁴ and R^{4'} are independently selected from hydrogen, halogen, alkyl, haloalkyl, deuterioalkyl, hydroxyalkyl, aminoalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^a, -NR^aC(=O)R^b, -NR^aC(=O)OR^b; alternatively R⁴ and R^{4'} together represents an oxo group; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OR^a, -NR^cR^d, -NR^aC(=O)OR^b, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^cR^d, aryl, alkyl, or haloalkyl;

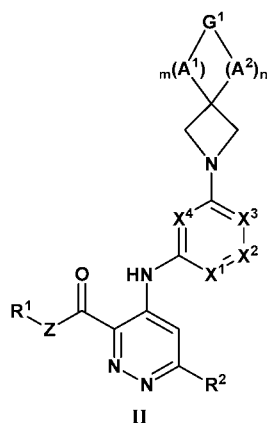
[00015] R⁵ and R^{5'} are independently selected from hydrogen, alkyl, haloalkyl, deuterioalkyl, hydroxyalkyl, aminoalkyl, alkoxy, alkenyl, alkynyl, NC(=O)R^a, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, alkyl, alkoxy, aryl or haloalkyl; or R⁵ and R^{5'} are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, alkyl, or haloalkyl;

[00016] R⁶ and R^{6'} are independently selected from hydrogen, alkyl, haloalkyl, deuterioalkyl, hydroxyalkyl, aminoalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, aryl, alkyl, or haloalkyl;

[00017] each R^a and R^b is independently selected from hydrogen, alkyl, haloalkyl, deutoalkyl, hydroxyalkyl, aminoalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, -C(=O)NHMe, alkyl, cycloalkyl, aryl, heteroaryl or haloalkyl; and

[00018] each R^c and R^d is independently selected from hydrogen, alkyl, haloalkyl, deutoalkyl, hydroxyalkyl, aminoalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, alkyl, or haloalkyl; or R^c and R^d are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, alkyl, or haloalkyl.

[00019] In another embodiment disclosed herein is a compound of Formula (II), or a pharmaceutically acceptable salt, or stereoisomer thereof:

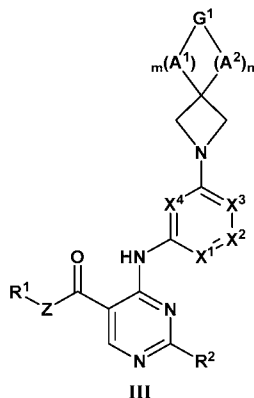


wherein:

R^2 is a heteroaryl wherein the carbon atom of heteraryl group is attached with the pyridazine ring; and

R^1 , Z, X^1 , X^2 , X^3 , X^4 , G^1 , A^1 , A^2 , m and n are as defined herein above for Formula (I).

[00020] In another embodiment disclosed herein is a compound of Formula (III), or a pharmaceutically acceptable salt, or stereoisomer thereof:



wherein R^1 , R^2 , Z , X^1 , X^2 , X^3 , X^4 , G^1 , A^1 , A^2 , m and n are as defined herein above for Formula (I).

[00021] Also disclosed herein is a pharmaceutical composition comprising a therapeutically effective amount of the compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer thereof, and a pharmaceutically acceptable excipient.

[00022] Also disclosed herein is a method of inhibiting a TYK2 enzyme in a patient or biological sample comprising contacting said patient or biological sample with a compound disclosed herein, or a pharmaceutically acceptable salt, or stereoisomer thereof.

[00023] Also disclosed herein is a method of treating a TYK2-mediated disorder comprising administering to a patient in need thereof a compound disclosed herein, or a pharmaceutically acceptable salt, or stereoisomer thereof. In some embodiments, the TYK2-mediated disorder is an autoimmune disorder, an inflammatory disorder, a proliferative disorder, an endocrine disorder, a neurological disorder, or a disorder associated with transplantation. In some embodiments, the disorder is associated with type I interferon, IL-10, IL-12, or IL-23 signaling.

INCORPORATION BY REFERENCE

[00024] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference for the specific purposes identified herein.

DETAILED DESCRIPTION

Definitions

[00025] In the context of this disclosure, a number of terms shall be utilized.

[00026] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood to which the claimed subject matter belongs. In the event that there is a plurality of definitions for terms herein, those in this section prevail. All patents, patent applications, publications and published nucleotide and amino acid sequences (e.g., sequences available in GenBank or other databases) referred to herein are incorporated by reference. Where reference is made to a URL or other such identifier or address, it is understood that such identifiers can change and particular information on the internet can come and go, but equivalent information can be found by searching the internet. Reference thereto evidences the availability and public dissemination of such information.

[00027] Unless specific definitions are provided, the nomenclature employed in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those recognized in the field. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients. Standard techniques can be used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (e.g., electroporation, lipofection). Reactions and purification techniques can be performed, e.g., using kits of manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures can be generally performed of conventional

methods and as described in various general and more specific references that are cited and discussed throughout the present specification.

[00028] It is to be understood that the methods and compositions described herein are not limited to the particular methodology, protocols, cell lines, constructs, and reagents described herein and as such may vary. It is also to be understood that the terminology used herein is for describing particular embodiments only, and is not intended to limit the scope of the methods, compounds, compositions described herein.

[00029] As used herein and in the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “an agent” includes a plurality of such agents, and reference to “the cell” includes reference to one or more cells (or to a plurality of cells) and equivalents thereof known to those skilled in the art, and so forth. When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and sub-combinations of ranges and specific embodiments therein are intended to be included. The term “about” when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range, in some instances, will vary between 1% and 15% of the stated number or numerical range. The term “comprising” (and related terms such as “comprise” or “comprises” or “having” or “including”) is not intended to exclude that in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, “consist of” or “consist essentially of” the described features.

[00030] Compounds of this invention may have one or more asymmetric centers. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms of compounds of the present invention are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. Cis- and trans-geometric isomers of the

compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. The present compounds can be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. All chiral, (enantiomeric and diastereomeric) and racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

[00031] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

[00032] “Aliphatic chain” refers to a linear chemical moiety that is composed of only carbons and hydrogens. In some embodiments, the aliphatic chain is saturated. In some embodiments, the aliphatic chain is unsaturated. In some embodiments, the unsaturated aliphatic chain contains one unsaturation. In some embodiments, the unsaturated aliphatic chain contains more than one unsaturation. In some embodiments, the unsaturated aliphatic chain contains two unsaturations. In some embodiments, the unsaturated aliphatic chain contains one double bond. In some embodiments, the unsaturated aliphatic chain contains two double bonds.

[00033] “Alkyl” refers to an optionally substituted straight-chain, or optionally substituted branched-chain saturated hydrocarbon monoradical having from one to about twenty carbon atoms, or from one to ten carbon atoms or from one to six carbon atoms, containing the indicated number of carbon atoms, for example, a C₁-C₆ alkyl group may have from 1 to 6 (inclusive) carbon atoms in it. Examples include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, tert-amyl and hexyl, and longer alkyl groups, such as heptyl, octyl, and the like. Whenever it appears herein, a numerical range such as “C₁-C₆ alkyl” means that the alkyl group consists of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms,

although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated. In some embodiments, the alkyl is a C₁-C₁₀ alkyl, a C₁-C₉ alkyl, a C₁-C₈ alkyl, a C₁-C₇ alkyl, a C₁-C₆ alkyl, a C₁-C₅ alkyl, a C₁-C₄ alkyl, a C₁-C₃ alkyl, a C₁-C₂ alkyl, or a C₁ alkyl. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkyl is optionally substituted with oxo, halogen, -CN, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkyl is optionally substituted with oxo, halogen, -CN, -CF₃, -OH, or -OMe.

[00034] “Alkenyl” refers to an optionally substituted straight-chain, or optionally substituted branched-chain hydrocarbon monoradical having one or more carbon-carbon double-bonds and having from two to about ten carbon atoms, more preferably two to about six carbon atoms. The group may be in either the cis or trans conformation about the double bond(s), and should be understood to include both isomers. Examples include, but are not limited to, ethenyl (-CH=CH₂), 1-propenyl (-CH₂CH=CH₂), isopropenyl [-C(CH₃)=CH₂], butenyl, 1,3-butadienyl and the like. Whenever it appears herein, a numerical range such as “C₂-C₆ alkenyl” means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkenyl” where no numerical range is designated. In some embodiments, the alkenyl is a C₂-C₁₀ alkenyl, a C₂-C₉ alkenyl, a C₂-C₈ alkenyl, a C₂-C₇ alkenyl, a C₂-C₆ alkenyl, a C₂-C₅ alkenyl, a C₂-C₄ alkenyl, a C₂-C₃ alkenyl, or a C₂ alkenyl. Unless stated otherwise specifically in the specification, an alkenyl group is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, an alkenyl is optionally substituted with oxo, halogen, -CN, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, an alkenyl is optionally substituted with oxo, halogen, -CN, -CF₃, -OH, or -OMe. In some embodiments, the alkenyl is optionally substituted with halogen.

[00035] “Alkynyl” refers to an optionally substituted straight-chain or optionally substituted branched-chain hydrocarbon monoradical having one or more carbon-carbon triple-bonds and having from two to about ten carbon atoms, more preferably from two to about six carbon atoms. Examples include, but are not limited to, ethynyl, 2-propynyl, 2-butylnyl, 1,3-butadiynyl and the like. Whenever it appears herein, a numerical range such as “C₂-C₆ alkynyl” means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkynyl” where no numerical range is designated. In some embodiments, the alkynyl is a C₂-C₁₀ alkynyl, a C₂-C₉ alkynyl, a C₂-C₈ alkynyl, a C₂-C₇ alkynyl, a C₂-C₆ alkynyl, a C₂-C₅ alkynyl, a C₂-C₄ alkynyl, a C₂-C₃ alkynyl, or a C₂ alkynyl. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, an alkynyl is optionally substituted with oxo, halogen, -CN, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, an alkynyl is optionally substituted with oxo, halogen, -CN, -CF₃, -OH, or -OMe. In some embodiments, the alkynyl is optionally substituted with halogen.

[00036] “Alkylene” refers to a straight or branched divalent hydrocarbon chain. Unless stated otherwise specifically in the specification, an alkylene group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, an alkylene is optionally substituted with oxo, halogen, -CN, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, an alkylene is optionally substituted with oxo, halogen, -CN, -CF₃, -OH, or -OMe. In some embodiments, the alkylene is optionally substituted with halogen.

[00037] “Alkoxy” refers to a radical of the formula -OR^a where R^a is an alkyl radical as defined. Unless stated otherwise specifically in the specification, an alkoxy group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, an alkoxy is optionally substituted

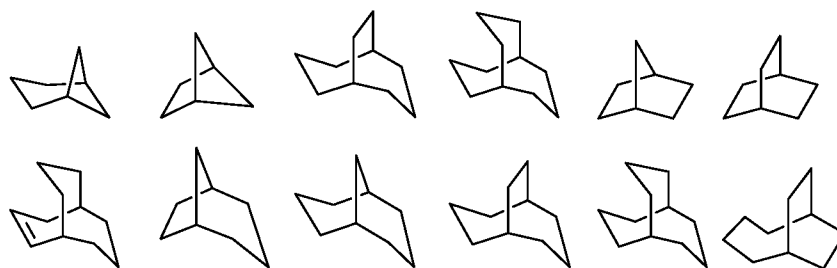
with oxo, halogen, -CN, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, an alkoxy is optionally substituted with oxo, halogen, -CN, -CF₃, -OH, or -OMe. In some embodiments, the alkoxy is optionally substituted with halogen.

[00038] “Aminoalkyl” refers to an alkyl radical, as defined above that is substituted by one or more amines. In some embodiments, the alkyl is substituted with one amine. In some embodiments, the alkyl is substituted with one, two, or three amines. Hydroxyalkyl include, for example, aminomethyl, aminoethyl, aminopropyl, aminobutyl, or aminopentyl. In some embodiments, the hydroxyalkyl is aminomethyl.

[00039] “Aryl” refers to a radical derived from a hydrocarbon ring system comprising hydrogen, 6 to 30 carbon atoms and at least one aromatic ring. The aryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the aryl is bonded through an aromatic ring atom) or bridged ring systems. In some embodiments, the aryl is a 6- to 10-membered aryl. In some embodiments, the aryl is a 6-membered aryl. Aryl radicals include, but are not limited to, aryl radicals derived from the hydrocarbon ring systems of anthrylene, naphthylene, phenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, as-indacene, s-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. In some embodiments, the aryl is phenyl. Unless stated otherwise specifically in the specification, an aryl may be optionally substituted, for example, with halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, an aryl is optionally substituted with halogen, methyl, ethyl, -CN, -CF₃, -OH, -OMe, -SMe, -NH₂, or -NO₂. In some embodiments, an aryl is optionally substituted with halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the aryl is optionally substituted with halogen.

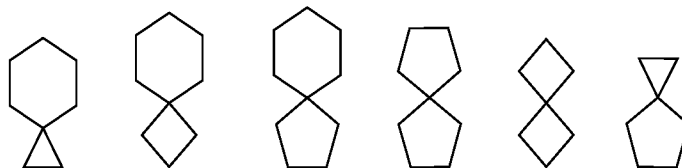
[00040] “Cycloalkyl” refers to a saturated or partially unsaturated monocyclic or polycyclic cyclic hydrocarbon ring system. The cycloalkyl ring contains 3 to 20 carbon atoms, preferably 3 to 12 carbon atoms, more preferably 3 to 8 carbon atoms, most preferably 3 to 6 carbon atoms. Monocyclic cycloalkyls

include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyl groups include spiro, fused, and bridged cycloalkyl groups. Polycyclic cycloalkyls or carbocycles include, for example, adamantyl, norbornyl, decalyl, bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, cis-decalin, trans-decalin, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, and bicyclo[3.3.2]decane, and 7,7-dimethyl-bicyclo[2.2.1]heptanyl. Partially saturated cycloalkyls include, for example cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Unless stated otherwise specifically in the specification, a cycloalkyl is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, a cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the cycloalkyl is optionally substituted with halogen. In some embodiments, cycloalkyl is bridged cycloalkyl. In some embodiments of a compound of Formula (I), bridged cycloalkyl is but not limited to



[00041] The term “spirocycloalkyl” refers to a polycyclic group that shares one carbon atom (called a spiro atom) between 5- to 20-membered monocyclic rings, which may contain one or more double bonds, but none of the rings have complete conjugate π electronic system. It is preferably 6 to 14 membered, more preferably 7 to 10 membered. According to the number of shared spiro atoms between the ring and the ring, the spirocycloalkyl group is classified into a single spirocycloalkyl group, a bispirocycloalkyl group or a polyspirocycloalkyl group, preferably a single spirocycloalkyl group and a bispirocycloalkyl group. More

preferably, it is a 4-membered/4-membered, 4-membered/5-membered, 4-membered/6-membered, 5-membered/5-membered, or 5-membered/6-membered monospirocycloalkyl. In some embodiments, spirocycloalkyl is but not limited to



[00042] “Deuteroalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more deuterium atoms. In some embodiments, the alkyl is substituted with one deuterium atom. In some embodiments, the alkyl is substituted with one, two, or three deuterium atoms. In some embodiments, the alkyl is substituted with one, two, three, four, five, or six deuterium atoms. Deuteroalkyl includes, for example, CD_3 , CH_2D , CHD_2 , CH_2CD_3 , CD_2CD_3 , CHDCD_3 , $\text{CH}_2\text{CH}_2\text{D}$, or CH_2CHD_2 . In some embodiments, the deuteroalkyl is CD_3 .

[00043] “Haloalkyl” refers to an alkyl radical, as defined above that is substituted by one or more halogen atoms. In some embodiments, the alkyl is substituted with one, two, or three halogen atoms. In some embodiments, the alkyl is substituted with one, two, three, four, five, or six halogen atoms. Haloalkyl includes, for example, trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like. In some embodiments, the haloalkyl is trifluoromethyl. “Halo” or “halogen” refers to bromo, chloro, fluoro or iodo. In some embodiments, halogen is fluoro or chloro. In some embodiments, halogen is fluoro.

[00044] “Heteroalkyl” refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, e.g., oxygen, nitrogen (e.g., $-\text{NH}-$, $-\text{N}(\text{alkyl})-$), sulfur, or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a C_1 - C_6 heteroalkyl wherein the heteroalkyl is comprised of 1 to 6 carbon atoms and one or more atoms other than carbon, e.g., oxygen, nitrogen (e.g., $-\text{NH}-$, $-\text{N}(\text{alkyl})-$), sulfur, or combinations thereof wherein the heteroalkyl is

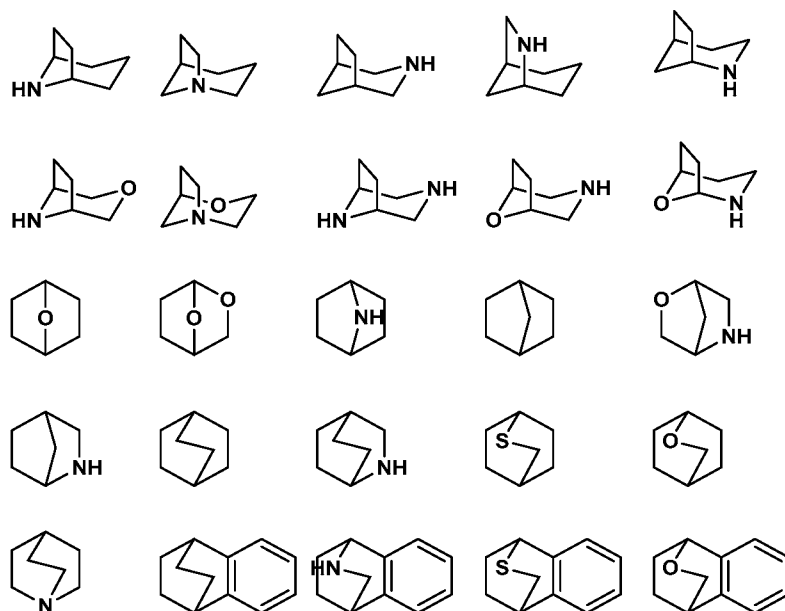
attached to the rest of the molecule at a carbon atom of the heteroalkyl. Examples of such heteroalkyl are, for example, $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$, or $-\text{CH}(\text{CH}_3)\text{OCH}_3$. Unless stated otherwise specifically in the specification, a heteroalkyl is optionally substituted for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, $-\text{CN}$, $-\text{CF}_3$, $-\text{OH}$, $-\text{OMe}$, $-\text{NH}_2$, or $-\text{NO}_2$. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, $-\text{CN}$, $-\text{CF}_3$, $-\text{OH}$, or $-\text{OMe}$. In some embodiments, the heteroalkyl is optionally substituted with halogen.

[00045] “Hydroxyalkyl” refers to an alkyl radical, as defined above that is substituted by one or more hydroxyls. In some embodiments, the alkyl is substituted with one hydroxyl. In some embodiments, the alkyl is substituted with one, two, or three hydroxyls. Hydroxyalkyl include, for example, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, or hydroxypentyl. In some embodiments, the hydroxyalkyl is hydroxymethyl.

[00046] The terms “heterocycle”, “heterocycloalkyl”, “heterocyclo”, “heterocyclic”, or “heterocyclyl” may be used interchangeably and refer to a saturated or partially unsaturated monocyclic or polycyclic cyclic hydrocarbon ring system which contains 3 to 20 ring atoms, one or more of which is selected from nitrogen, oxygen or $\text{S}(\text{O})_m$ (where m is an integer of 0 to 2) heteroatoms, but does not include the ring part of $-\text{OO}-$, $-\text{OS}-$ or $-\text{SS}-$, and the remaining ring atoms are carbon. It preferably contains 3 to 12 ring atoms, of which 1 to 4 are heteroatoms; more preferably contains 3 to 8 ring atoms; most preferably contains 3 to 8 ring atoms. Examples of heterocycloalkyl include, but are not limited to, aziridinyl, azetidiny, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazoliny, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-

thiomorpholinyl, 1,3-dihydroisobenzofuran-1-yl, 3-oxo-1,3-dihydroisobenzofuran-1-yl, methyl-2-oxo-1,3-dioxol-4-yl, and 2-oxo-1,3-dioxol-4-yl. Polycyclic heterocyclic groups include spiro, condensed and bridged heterocyclic groups; the spiro, condensed and bridged heterocyclic groups involved are optionally connected to other groups through a single bond, or through a ring any two or more of the above atoms are further connected to other cycloalkyl groups, heterocyclic groups, aryl groups and heteroaryl groups.

[00047] In some embodiments, bridged heterocycloalkyl is but not limited to

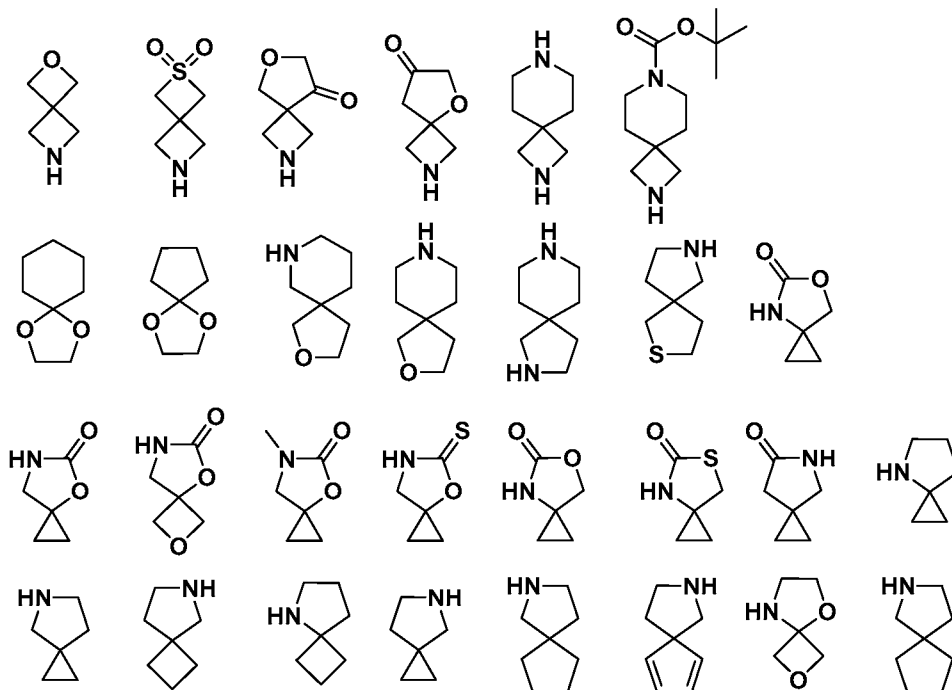


[00048] The term “heterocycloalkyl” also includes all ring forms of the carbohydrates, including but not limited to, the monosaccharides, the disaccharides and the oligosaccharides. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (i.e. skeletal atoms of the heterocycloalkyl ring). Unless stated otherwise specifically in the specification, a heterocycloalkyl is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heterocycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, -OMe,

-NH₂, or -NO₂. In some embodiments, a heterocycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heterocycloalkyl is optionally substituted with halogen.

[00049] The term “spiroheterocyclic group” refers to a polycyclic heterocyclic group sharing one atom (called a spiro atom) between 3 to 20 membered monocyclic rings, wherein one or more ring atoms are selected from nitrogen, oxygen or S(O)_m (where m is an integer of 0 to 2) heteroatoms, and the remaining ring atoms are carbon. It can contain one or more double bonds, but none of the rings have a fully conjugated π -electron system. It is preferably 6 to 14 membered, more preferably 7 to 10 membered. According to the number of spiro atoms shared between the ring and the ring, the spiro heterocyclic group is classified into a single spiro heterocyclic group, a dispiro heterocyclic group or a polyspiro heterocyclic group, preferably a single spiro heterocyclic group and a dispiro heterocyclic group. More preferably, it is a 3-membered/5-membered, 4-membered/5-membered, 4-membered/6-membered, 5-membered/5-membered or 5-membered/6-membered monospiro heterocyclic group.

[00050] In some embodiments, spiroheterocycloalkyl is but not limited to



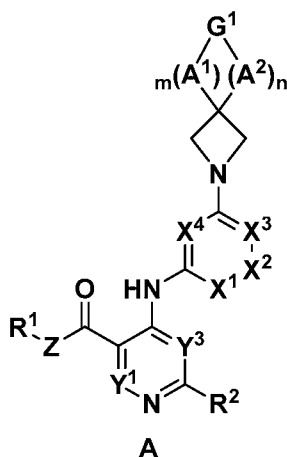
[00051] “Heteroalkyl” refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, e.g., oxygen, nitrogen (e.g. -NH-, -N(alkyl)-), sulfur, or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a C₁-C₆ heteroalkyl. Unless stated otherwise specifically in the specification, a heteroalkyl is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heteroalkyl is optionally substituted with halogen.

[00052] “Heteroaryl” refers to a 5- to 14-membered ring system radical comprising hydrogen atoms, one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous and sulfur, and at least one aromatic ring. The heteroaryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the heteroaryl is bonded through an aromatic ring atom) or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. In some embodiments, the heteroaryl is a 5- to 10-membered heteroaryl. In some embodiments, the heteroaryl is a 5- to 6-membered heteroaryl. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothieryl, benzothiophenyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl,

oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e., thienyl). Unless stated otherwise specifically in the specification, a heteroaryl is optionally substituted, for example, with halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heteroaryl is optionally substituted with halogen, methyl, ethyl, -CN, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, a heteroaryl is optionally substituted with halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heteroaryl is optionally substituted with halogen.

Compounds

[00053] In embodiments, the present disclosure provides a compound of Formula (A):



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

Y¹, Y³ are independently selected from N or CH;

X¹, X², X³, X⁴ are independently selected from N or CR³;

Z is selected from NR⁴, CR⁴R^{4'}, O, S or a bond;

A¹ and A² are independently selected from CR⁴R^{4'} or O;

G¹ is selected from O, S, S(O)₂, C(=O), NR⁵, NC(=O)OR⁶ or CR⁴R^{4'};

m and n are independently selected from 0, 1, 2, 3 or 4;

R^1 is selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

R^2 is selected from hydrogen, halogen, -CN, $-OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)_2R^6$, $-NO_2$, $-NR^5R^{5'}$, $-NR^6S(=O)_2R^{6'}$, $-S(=O)_2NR^5R^{5'}$, $-C(=O)R^6$, $-OC(=O)R^6$, $-C(=O)OR^6$, $-OC(=O)OR^6$, $-C(=O)NR^5R^{5'}$, $-OC(=O)NR^5R^{5'}$, $-NR^6C(=O)NR^5R^{5'}$, $-NR^6C(=O)R^{6'}$, $-NR^6C(=S)R^{6'}$, $-NR^6C(=O)OR^{6'}$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

R^3 is selected from hydrogen, deuterium, halogen, -CN, $-OR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-NO_2$, $-NR^cR^d$, $-NR^aS(=O)_2R^b$, $-S(=O)_2NR^cR^d$, $-C(=O)R^a$, $-OC(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)OR^a$, $-C(=O)NR^cR^d$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)NR^cR^d$, $-NR^aC(=O)R^b$, $-NR^aC(=O)OR^b$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl; with a proviso that when each of X^1 , X^2 , X^3 , and X^4 represents CR^3 , X^4 represents CR^3 , R^3 not being hydrogen.

R^4 and $R^{4'}$ are independently selected from hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-OR^a$, -

$\text{NR}^{\text{c}}\text{R}^{\text{d}}$, $-\text{C}(=\text{O})\text{R}^{\text{a}}$, $-\text{C}(=\text{O})\text{OR}^{\text{a}}$, $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{R}^{\text{b}}$, $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{OR}^{\text{b}}$; alternatively R^4 and $\text{R}^{4'}$ together represents an oxo group; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, $-\text{CN}$, $-\text{OR}^{\text{a}}$, $-\text{NR}^{\text{c}}\text{R}^{\text{d}}$, $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{OR}^{\text{b}}$, $-\text{C}(=\text{O})\text{R}^{\text{a}}$, $-\text{C}(=\text{O})\text{OR}^{\text{a}}$, $-\text{C}(=\text{O})\text{NR}^{\text{c}}\text{R}^{\text{d}}$, aryl, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

R^5 and $\text{R}^{5'}$ are independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 alkoxy, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, $\text{NC}(=\text{O})\text{R}^{\text{a}}$, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, $-\text{CN}$, $-\text{OH}$, $-\text{OMe}$, $-\text{NH}_2$, $-\text{C}(=\text{O})\text{Me}$, $-\text{C}(=\text{O})\text{OH}$, $-\text{C}(=\text{O})\text{OMe}$, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, aryl or C_1 - C_6 haloalkyl; or R^5 and $\text{R}^{5'}$ are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo, deuterium, halogen, $-\text{CN}$, $-\text{OH}$, $-\text{OMe}$, $-\text{NH}_2$, $-\text{C}(=\text{O})\text{Me}$, $-\text{C}(=\text{O})\text{OH}$, $-\text{C}(=\text{O})\text{OMe}$, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

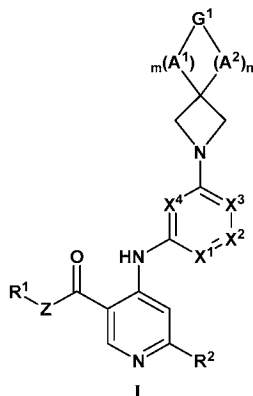
R^6 and $\text{R}^{6'}$ are independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, $-\text{CN}$, $-\text{OH}$, $-\text{OMe}$, $-\text{NH}_2$, $-\text{C}(=\text{O})\text{Me}$, $-\text{C}(=\text{O})\text{OH}$, $-\text{C}(=\text{O})\text{OMe}$, aryl, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

each R^{a} and R^{b} is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, $-\text{CN}$, $-\text{OH}$, $-\text{OMe}$, $-\text{NH}_2$, $-\text{C}(=\text{O})\text{Me}$, $-\text{C}(=\text{O})\text{OH}$, $-\text{C}(=\text{O})\text{OMe}$, $-\text{C}(=\text{O})\text{NHMe}$, C_1 - C_6 alkyl, cycloalkyl, aryl, heteroaryl or C_1 - C_6 haloalkyl; and

each R^c and R^d is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl; or R^c and R^d are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl.

[00054] In an embodiment, the compound of Formula (A) is a compound of Formula (I), Formula (II) or Formula (III).

[00055] Disclosed herein is a compound of Formula (I), or a pharmaceutically acceptable salt, or stereoisomer thereof:



wherein:

X^1 , X^2 , X^3 , X^4 are independently selected from N or CR^3 ;

Z is selected from NR^4 , $CR^4R^{4'}$, O, S or a bond;

A^1 and A^2 are independently selected from $CR^4R^{4'}$ or O;

G^1 is selected from O, S, $S(O)_2$, $C(=O)$, NR^5 , $NC(=O)OR^6$ or $CR^4R^{4'}$;

m and n are independently selected from 0, 1, 2, 3 or 4;

[00056] R^1 is selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each

alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^cR^d, C₁-C₆alkyl, or C₁-C₆haloalkyl;

[00057] R² is selected from hydrogen, halogen, -CN, -OR⁶, -SR⁶, -S(=O)R⁶, -S(=O)₂R⁶, -NO₂, -NR⁵R^{5'}, -NR⁶S(=O)₂R^{6'}, -S(=O)₂NR⁵R^{5'}, -C(=O)R⁶, -OC(=O)R⁶, -C(=O)OR⁶, -OC(=O)OR⁶, -C(=O)NR⁵R^{5'}, -OC(=O)NR⁵R^{5'}, -NR⁶C(=O)NR⁵R^{5'}, -NR⁶C(=O)R^{6'}, -NR⁶C(=S)R^{6'}, -NR⁶C(=O)OR^{6'}, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^cR^d, C₁-C₆alkyl, or C₁-C₆haloalkyl;

[00058] R³ is selected from hydrogen, deuterium, halogen, -CN, -OR^a, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -NO₂, -NR^cR^d, -NR^aS(=O)₂R^b, -S(=O)₂NR^cR^d, -C(=O)R^a, -OC(=O)R^a, -C(=O)OR^a, -OC(=O)OR^a, -C(=O)NR^cR^d, -OC(=O)NR^cR^d, -NR^aC(=O)NR^cR^d, -NR^aC(=O)R^b, -NR^aC(=O)OR^b, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^cR^d, C₁-C₆alkyl, or C₁-C₆haloalkyl, C₁-C₆deuteroalkyl; with a proviso that when each of X¹, X², X³, and X⁴ represents CR³, X⁴ represents CR³, R³ not being hydrogen.

[00059] R⁴ and R^{4'} are independently selected from hydrogen, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^a, -NR^aC(=O)R^b, -NR^aC(=O)OR^b, alternatively R⁴ and R^{4'} together represents an oxo group; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally

substituted with one or more oxo, deuterium, halogen, -CN, -OR^a, -NR^cR^d, -NR^aC(=O)OR^b, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^cR^d, aryl, C₁-C₆alkyl, or C₁-C₆haloalkyl;

[00060] R⁵ and R^{5'} are independently selected from hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆alkoxy, C₂-C₆alkenyl, C₂-C₆alkynyl, NC(=O)R^a, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C₁-C₆alkyl, C₁-C₆alkoxy, aryl or C₁-C₆haloalkyl; or R⁵ and R^{5'} are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C₁-C₆alkyl, or C₁-C₆haloalkyl;

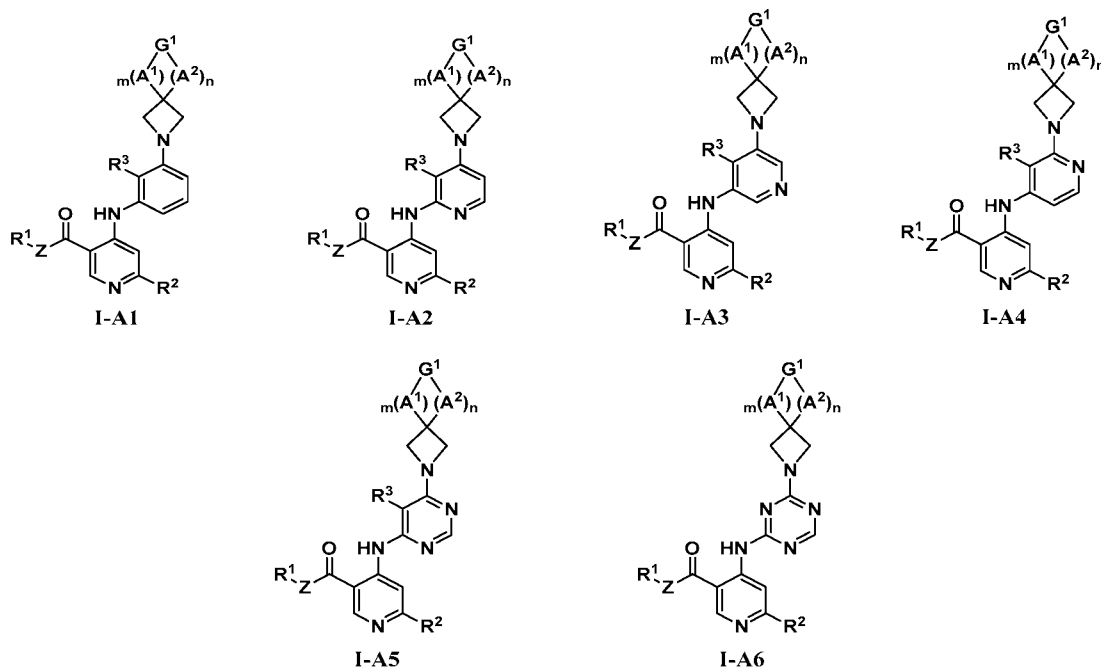
[00061] R⁶ and R^{6'} are independently selected from hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, aryl, C₁-C₆alkyl, or C₁-C₆haloalkyl;

[00062] each R^a and R^b is independently selected from hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, -C(=O)NHMe, C₁-C₆alkyl, cycloalkyl, aryl, heteroaryl or C₁-C₆haloalkyl; and

[00063] each R^c and R^d is independently selected from hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein

each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C₁-C₆alkyl, or C₁-C₆haloalkyl; or R^c and R^d are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C₁-C₆alkyl, or C₁-C₆haloalkyl.

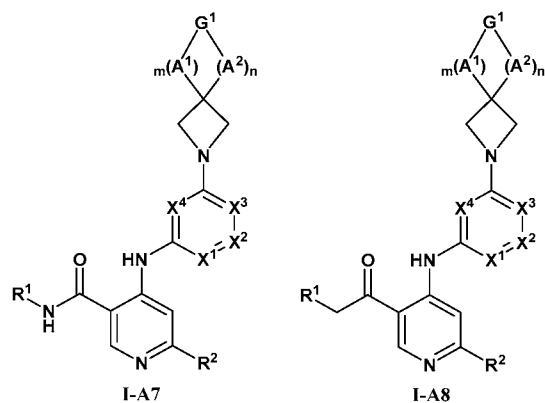
[00064] In some embodiments, the compound of Formula (I) is selected from a compound having Formula I-A1, I-A2, I-A3, I-A4, I-A5 or I-A6



wherein:

R¹, R², R³, Z, G¹, A¹, A², m and n are as defined hereinabove for Formula (I).

[00065] In some embodiments, the compound of Formula (I) is selected from a compound having Formula I-A7 or I-A8



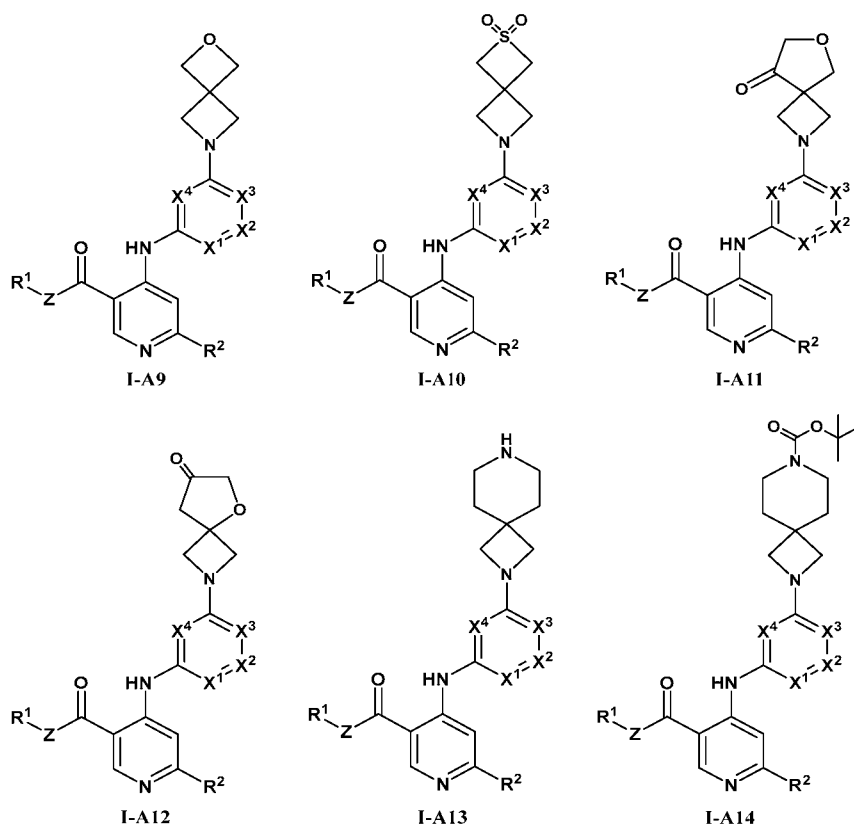
wherein:

R^1 is selected from alkyl and deutoalkyl;

G^1 is selected from O, $S(O)_2$, NR^5 or $NC(=O)OR^6$; and

R^2 , X^1 , X^2 , X^3 , X^4 , A^1 , A^2 , m and n are as defined hereinabove for Formula (I).

[00066] In some embodiments, the compound of Formula (I) is selected from a compound having Formula I-A9, I-A10, I-A11, I-A12, I-A13 or I-A14



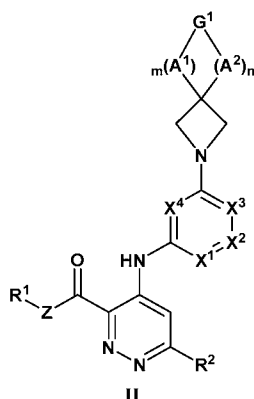
wherein:

R^1 is selected from alkyl or deutoalkyl;

Z is selected from NH or CH₂; and

R², X¹, X², X³, X⁴, A¹, A², m and n are as defined hereinabove for Formula (I).

[00067] In another embodiment, disclosed herein is a compound of Formula (II), or a pharmaceutically acceptable salt, or stereoisomer thereof:

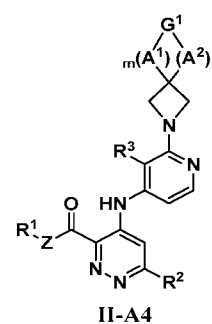
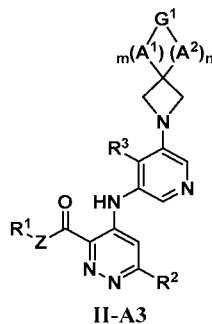
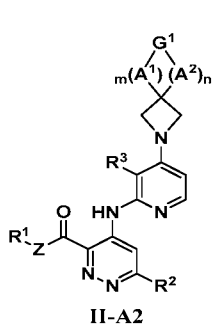
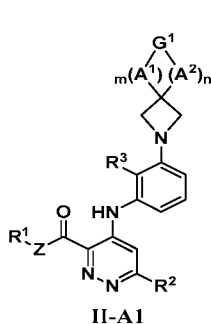


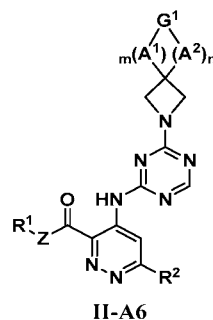
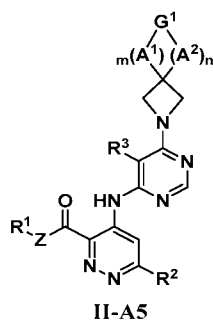
wherein:

R² is a heteroaryl wherein the carbon atom of heteraryl group is attached with the pyridazine ring; and

R¹, Z, X¹, X², X³, X⁴, G¹, A¹, A², m and n is as defined herein above for Formula (I).

[00068] In some embodiments, the compound of Formula (II) is selected from a compound having Formula II-A1, II-A2, II-A3, II-A4, II-A5, or II-A6



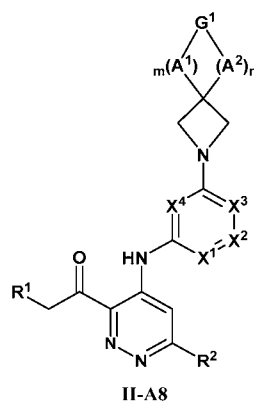
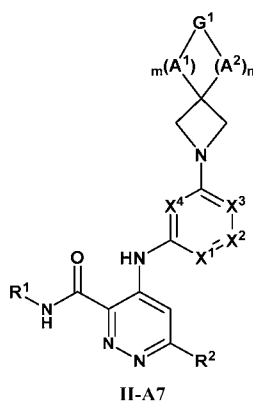


wherein:

R^2 is as defined hereinabove for Formula (II); and

R^1 , R^3 , Z , G^1 , A^1 , A^2 , m and n are as defined hereinabove for Formula (I).

[00069] In some embodiments, the compound of Formula (II) is selected from a compound having Formula II-A7, or II-A8



wherein:

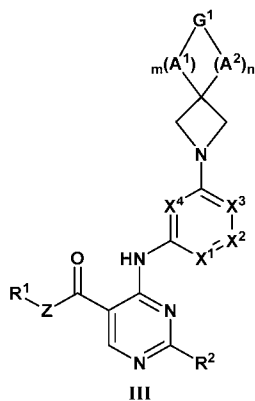
R^1 is selected from alkyl or deuterioalkyl;

R^2 is as defined hereinabove for Formula (II);

G^1 is selected from O, $S(O)_2$, NR^5 or $NC(=O)OR^6$; and

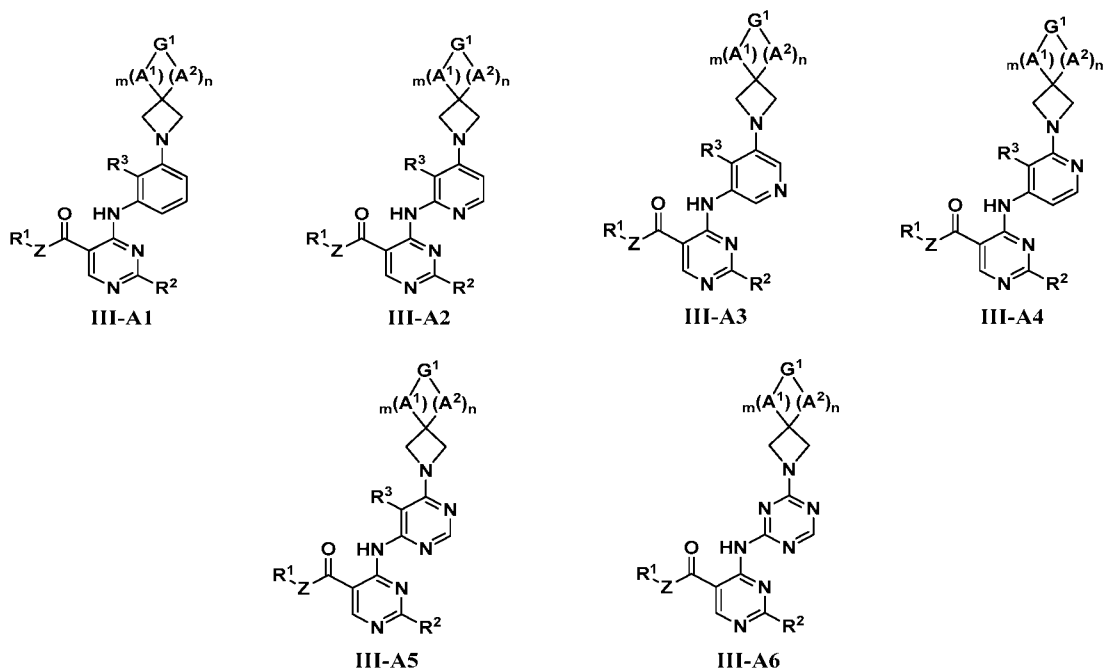
X^1 , X^2 , X^3 , X^4 , A^1 , A^2 , m and n are as defined hereinabove for Formula (I).

[00070] In another embodiment, disclosed herein is a compound of Formula (III), or a pharmaceutically acceptable salt, or stereoisomer thereof:



wherein R^1 , R^2 , Z , X^1 , X^2 , X^3 , X^4 , G^1 , A^1 , A^2 , m and n is as defined herein above for Formula (I).

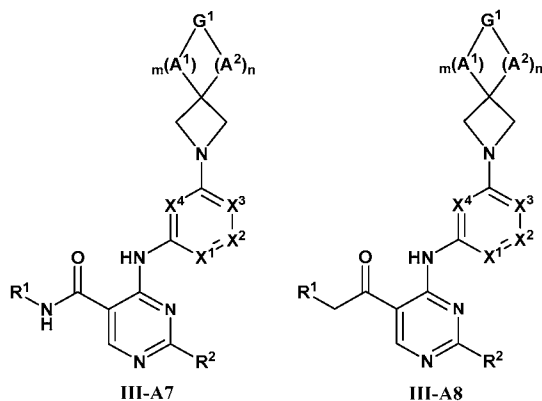
[00071] In some embodiments, the compound of Formula (III) is selected from a compound having Formula III-A1, III-A2, III-A3, III-A4, III-A5, or III-A6



wherein:

R^1 , R^2 , R^3 , Z , G^1 , A^1 , A^2 , m and n is as defined hereinabove for Formula (I).

[00072] In some embodiments, the compound of Formula (III) is selected from a compound having Formula III-A7, or III-A8



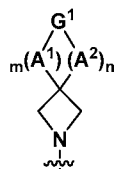
wherein:

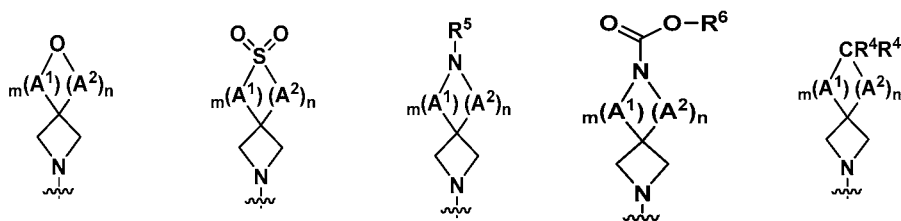
R^1 is selected from alkyl or deutoalkyl;

G^1 is selected from O, $S(O)_2$, NR^5 or $NC(=O)OR^6$; and

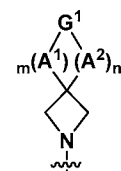
R^2 , X^1 , X^2 , X^3 , X^4 , A^1 , A^2 , m and n are as defined hereinabove for Formula (I).

[00073] In some embodiments, the group R^3 as defined in compound of Formula I-A1, II-A1 and III-A1, is selected from deuterium, halogen, $-CN$, $-OR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-NO_2$, $-NR^cR^d$, $-NR^aS(=O)_2R^b$, $-S(=O)_2NR^cR^d$, $-C(=O)R^a$, $-OC(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)OR^a$, $-C(=O)NR^cR^d$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)NR^cR^d$, $-NR^aC(=O)R^b$, $-NR^aC(=O)OR^b$, alkyl, haloalkyl, deutoalkyl, hydroxyalkyl, aminoalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, $-CN$, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^cR^d$, alkyl, or haloalkyl, deutoalkyl.

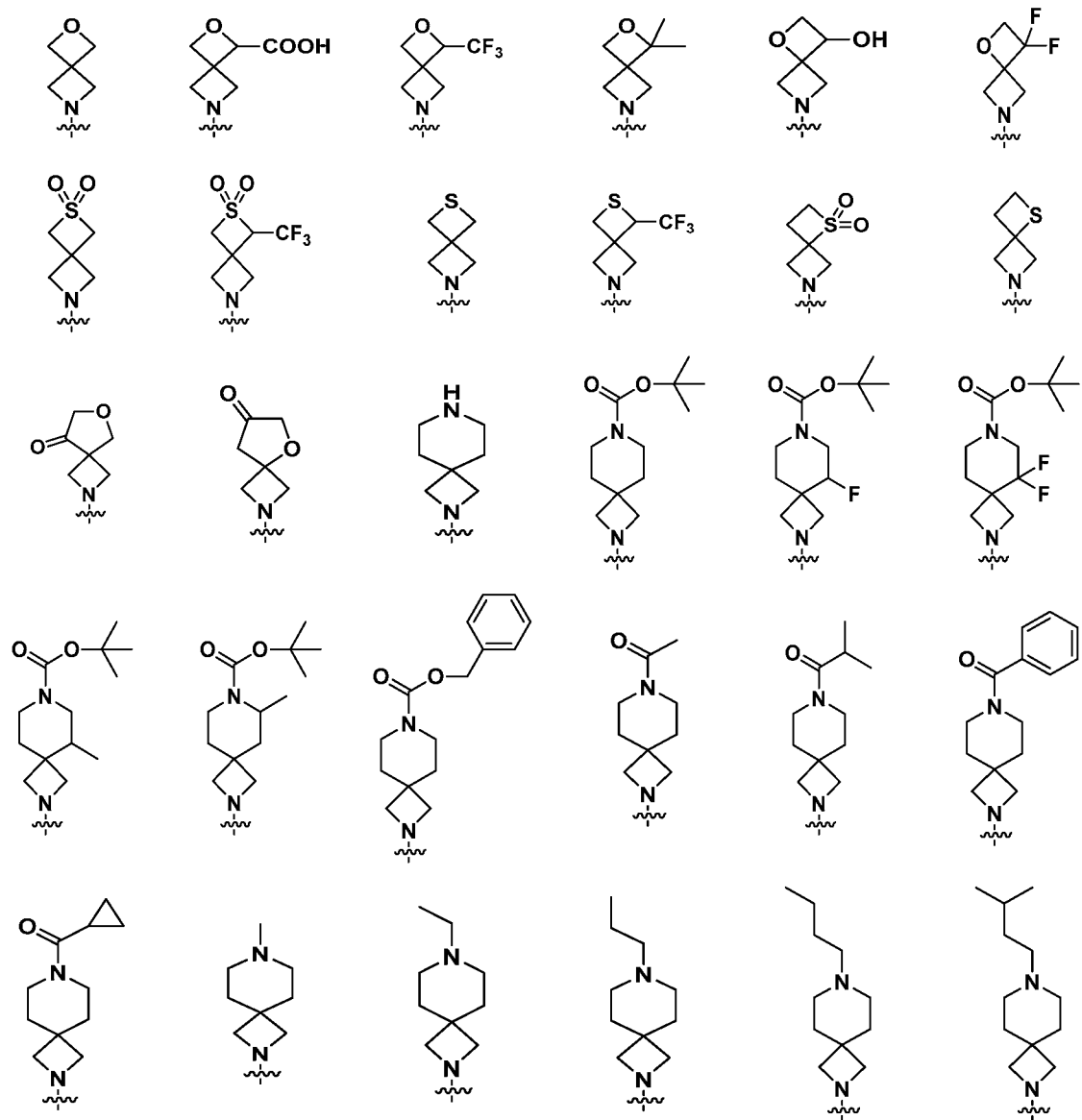
[00074] In some embodiments of present invention, the group  as defined in Formula (I), (II) and (III) herein above is selected from the following,

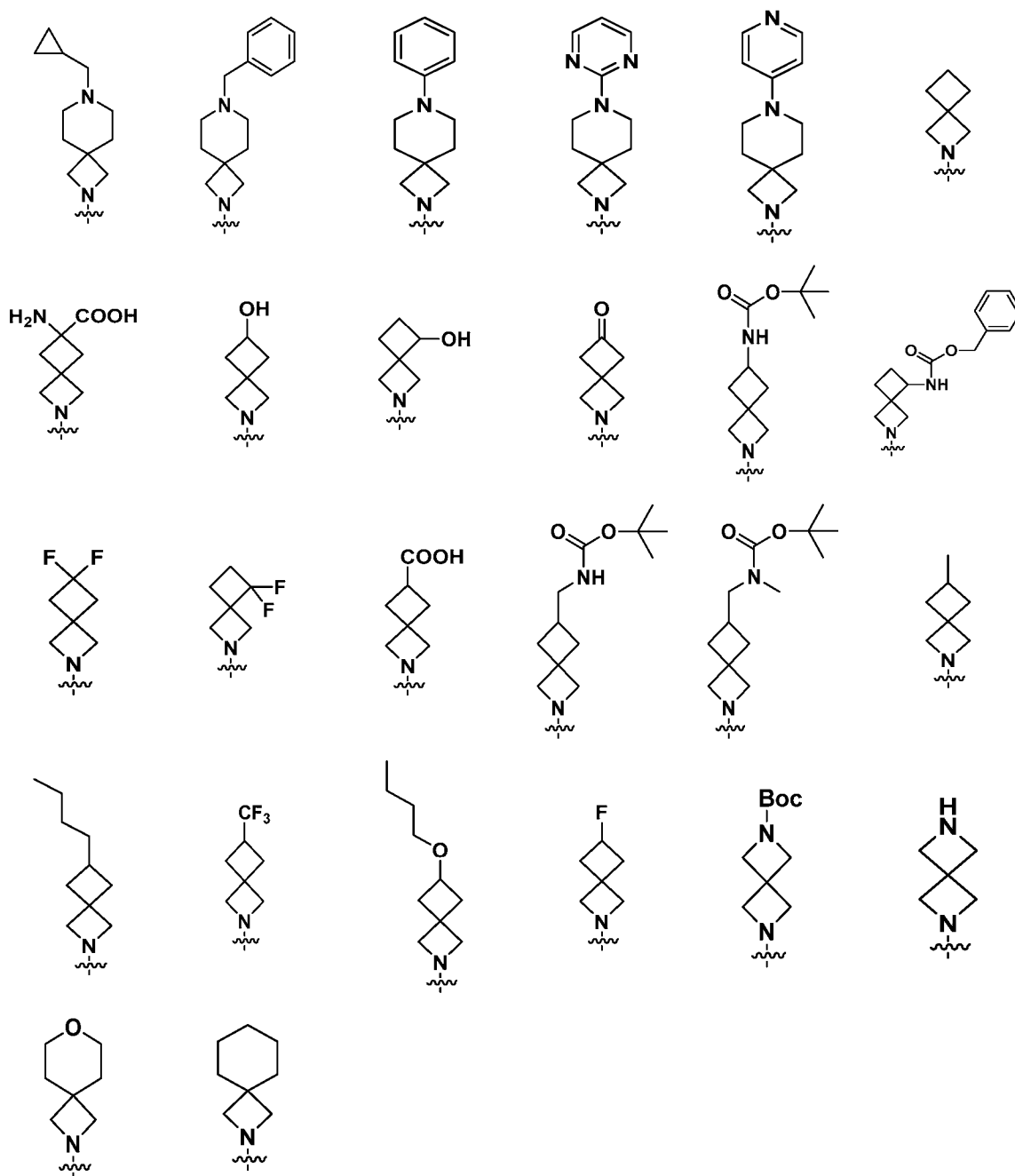


wherein G^1 , A^1 , A^2 , R^6 , m and n are as defined herein above for Formula (I).



[00075] In some embodiments of present invention, the group as defined in Formula (I), (II) and (III) herein above is selected from following,





[00076] In some embodiments of the compound of Formula (I), the compound, or a pharmaceutically acceptable salt, or stereoisomer thereof, is selected from the group consisting of:

Compound	Name
1	6-(cyclopropanecarboxamido)-4-((2-methoxy-3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl)amino)-N-(methyl-d3)nicotinamide
2	6-(cyclopropanecarboxamido)-4-((3-methoxy-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-2-yl)amino)-N-(methyl-d3)nicotinamide
3	6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide
4	6-(cyclopropanecarboxamido)-4-((3-methoxy-2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-4-yl)amino)-N-(methyl-d3)nicotinamide
5	6-(cyclopropanecarboxamido)-4-((3-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-2-methoxyphenyl)amino)-N-(methyl-d3)nicotinamide
6	6-(cyclopropanecarboxamido)-4-((4-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-3-methoxypyridin-2-yl)amino)-N-(methyl-d3)nicotinamide
7	6-(cyclopropanecarboxamido)-4-((5-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-4-methoxypyridin-3-yl)amino)-N-(methyl-d3)nicotinamide
8	6-(cyclopropanecarboxamido)-4-((2-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-3-methoxypyridin-4-yl)amino)-N-(methyl-d3)nicotinamide
9	6-(cyclopropanecarboxamido)-4-((2-methoxy-3-(8-oxo-6-oxa-2-azaspiro[3.4]octan-2-yl)phenyl)amino)-N-(methyl-d3)nicotinamide
10	6-(cyclopropanecarboxamido)-4-((3-methoxy-4-(8-oxo-6-oxa-2-azaspiro[3.4]octan-2-yl)pyridin-2-yl)amino)-N-(methyl-d3)nicotinamide
11	6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(8-oxo-6-oxa-2-azaspiro[3.4]octan-2-yl)pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide
12	6-(cyclopropanecarboxamido)-4-((3-methoxy-2-(8-oxo-6-oxa-2-azaspiro[3.4]octan-2-yl)pyridin-4-yl)amino)-N-(methyl-d3)nicotinamide

13	6-(cyclopropanecarboxamido)-4-((2-methoxy-3-(7-oxo-5-oxa-2-azaspiro[3.4]octan-2-yl)phenyl)amino)-N-(methyl-d3)nicotinamide
14	6-(cyclopropanecarboxamido)-4-((3-methoxy-4-(7-oxo-5-oxa-2-azaspiro[3.4]octan-2-yl)pyridin-2-yl)amino)-N-(methyl-d3)nicotinamide
15	6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(7-oxo-5-oxa-2-azaspiro[3.4]octan-2-yl)pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide
16	6-(cyclopropanecarboxamido)-4-((3-methoxy-2-(7-oxo-5-oxa-2-azaspiro[3.4]octan-2-yl)pyridin-4-yl)amino)-N-(methyl-d3)nicotinamide
17	tert-butyl 2-(3-((2-(cyclopropanecarboxamido)-5-((methyl-d3)carbamoyl)pyridin-4-yl)amino)-2-methoxyphenyl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
18	tert-butyl 2-(2-((2-(cyclopropanecarboxamido)-5-((methyl-d3)carbamoyl)pyridin-4-yl)amino)-3-methoxypyridin-4-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
19	tert-butyl 2-(5-((2-(cyclopropanecarboxamido)-5-((methyl-d3)carbamoyl)pyridin-4-yl)amino)-4-methoxypyridin-3-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
20	tert-butyl 2-(4-((2-(cyclopropanecarboxamido)-5-((methyl-d3)carbamoyl)pyridin-4-yl)amino)-3-methoxypyridin-2-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
21	6-(cyclopropanecarboxamido)-4-((2-methoxy-3-(2,7-diazaspiro[3.5]nonan-2-yl)phenyl)amino)-N-(methyl-d3)nicotinamide
22	6-(cyclopropanecarboxamido)-4-((3-methoxy-4-(2,7-diazaspiro[3.5]nonan-2-yl)pyridin-2-yl)amino)-N-(methyl-d3)nicotinamide
23	6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(2,7-diazaspiro[3.5]nonan-2-yl)pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide
24	6-(cyclopropanecarboxamido)-4-((3-methoxy-2-(2,7-diazaspiro[3.5]nonan-2-yl)pyridin-4-yl)amino)-N-(methyl-d3)nicotinamide
25	4-((2-methoxy-3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl)amino)-N-(methyl-d3)-6-(1H-pyrrol-2-yl)nicotinamide

26	4-((3-methoxy-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-2-yl)amino)-N-(methyl-d ₃)-6-(1H-pyrrol-2-yl)nicotinamide
27	4-((4-methoxy-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-3-yl)amino)-N-(methyl-d ₃)-6-(1H-pyrrol-2-yl)nicotinamide
28	4-((3-methoxy-2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-4-yl)amino)-N-(methyl-d ₃)-6-(1H-pyrrol-2-yl)nicotinamide
29	1-(4-((2-methoxy-3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl)amino)-6-(1H-pyrrol-2-yl)pyridin-3-yl)propan-1-one-3,3,3-d ₃
30	1-(4-((3-methoxy-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-2-yl)amino)-6-(1H-pyrrol-2-yl)pyridin-3-yl)propan-1-one-3,3,3-d ₃
31	1-(4-((4-methoxy-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-3-yl)amino)-6-(1H-pyrrol-2-yl)pyridin-3-yl)propan-1-one-3,3,3-d ₃
32	1-(4-((3-methoxy-2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-4-yl)amino)-6-(1H-pyrrol-2-yl)pyridin-3-yl)propan-1-one-3,3,3-d ₃
33	N-(4-((2-methoxy-3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl)amino)-5-(propanoyl-3,3,3-d ₃)pyridin-2-yl)cyclopropanecarboxamide
34	N-(4-((3-methoxy-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-2-yl)amino)-5-(propanoyl-3,3,3-d ₃)pyridin-2-yl)cyclopropanecarboxamide
35	N-(4-((4-methoxy-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-3-yl)amino)-5-(propanoyl-3,3,3-d ₃)pyridin-2-yl)cyclopropanecarboxamide
36	N-(4-((3-methoxy-2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-4-yl)amino)-5-(propanoyl-3,3,3-d ₃)pyridin-2-yl)cyclopropanecarboxamide
37	tert-butyl 2-(2-methoxy-3-((5-((methyl-d ₃)carbamoyl)-2-(1H-pyrrol-2-yl)pyridin-4-yl)amino)phenyl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
38	tert-butyl 2-(3-methoxy-2-((5-((methyl-d ₃)carbamoyl)-2-(1H-pyrrol-2-yl)pyridin-4-yl)amino)pyridin-4-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
39	tert-butyl 2-(4-methoxy-5-((5-((methyl-d ₃)carbamoyl)-2-(1H-pyrrol-2-yl)pyridin-4-yl)amino)pyridin-3-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
40	tert-butyl 2-(3-methoxy-4-((5-((methyl-d ₃)carbamoyl)-2-(1H-pyrrol-2-yl)pyridin-4-yl)amino)pyridin-2-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate

41	2-(cyclopropanecarboxamido)-4-((2-methoxy-3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl)amino)-N-(methyl-d3)pyrimidine-5-carboxamide
42	2-(cyclopropanecarboxamido)-4-((3-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-2-methoxyphenyl)amino)-N-(methyl-d3)pyrimidine-5-carboxamide
43	tert-butyl 2-(3-((2-(cyclopropanecarboxamido)-5-((methyl-d3)carbamoyl)pyrimidin-4-yl)amino)-2-methoxyphenyl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
44	2-(cyclopropanecarboxamido)-4-((2-methoxy-3-(8-oxo-6-oxa-2-azaspiro[3.4]octan-2-yl)phenyl)amino)-N-(methyl-d3)pyrimidine-5-carboxamide
45	6-(cyclopropanecarboxamido)-4-((6-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-5-methoxypyrimidin-4-yl)amino)-N-(methyl-d3)nicotinamide
46	6-(cyclopropanecarboxamido)-4-((6-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-5-methoxypyrimidin-4-yl)amino)-N-methylnicotinamide
47	6-(cyclopropanecarboxamido)-4-((4-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-1,3,5-triazin-2-yl)amino)-N-(methyl-d3)nicotinamide
48	6-(cyclopropanecarboxamido)-4-((4-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-1,3,5-triazin-2-yl)amino)-N-methylnicotinamide
49	6-(cyclopropanecarboxamido)-4-((2-methoxy-3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl)amino)-N-methylnicotinamide
50	6-(cyclopropanecarboxamido)-4-((3-methoxy-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-2-yl)amino)-N-methylnicotinamide
51	6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-3-yl)amino)-N-methylnicotinamide
52	6-(cyclopropanecarboxamido)-4-((3-methoxy-2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-4-yl)amino)-N-methylnicotinamide

53	6-(cyclopropanecarboxamido)-4-((3-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-2-methoxyphenyl)amino)-N-methylnicotinamide
54	6-(cyclopropanecarboxamido)-4-((4-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-3-methoxypyridin-2-yl)amino)-N-methylnicotinamide
55	6-(cyclopropanecarboxamido)-4-((5-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-4-methoxypyridin-3-yl)amino)-N-methylnicotinamide
56	6-(cyclopropanecarboxamido)-4-((2-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-3-methoxypyridin-4-yl)amino)-N-methylnicotinamide
57	6-(cyclopropanecarboxamido)-4-((2-methoxy-3-(8-oxo-6-oxa-2-azaspiro[3.4]octan-2-yl)phenyl)amino)-N-methylnicotinamide
58	6-(cyclopropanecarboxamido)-4-((3-methoxy-4-(8-oxo-6-oxa-2-azaspiro[3.4]octan-2-yl)pyridin-2-yl)amino)-N-methylnicotinamide
59	6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(8-oxo-6-oxa-2-azaspiro[3.4]octan-2-yl)pyridin-3-yl)amino)-N-methylnicotinamide
60	6-(cyclopropanecarboxamido)-4-((3-methoxy-2-(8-oxo-6-oxa-2-azaspiro[3.4]octan-2-yl)pyridin-4-yl)amino)-N-methylnicotinamide
61	6-(cyclopropanecarboxamido)-4-((2-methoxy-3-(7-oxo-5-oxa-2-azaspiro[3.4]octan-2-yl)phenyl)amino)-N-methylnicotinamide
62	6-(cyclopropanecarboxamido)-4-((3-methoxy-4-(7-oxo-5-oxa-2-azaspiro[3.4]octan-2-yl)pyridin-2-yl)amino)-N-methylnicotinamide
63	6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(7-oxo-5-oxa-2-azaspiro[3.4]octan-2-yl)pyridin-3-yl)amino)-N-methylnicotinamide
64	6-(cyclopropanecarboxamido)-4-((3-methoxy-2-(7-oxo-5-oxa-2-azaspiro[3.4]octan-2-yl)pyridin-4-yl)amino)-N-methylnicotinamide
65	tert-butyl 2-(3-((2-(cyclopropanecarboxamido)-5-(methylcarbamoyl)pyridin-4-yl)amino)-2-methoxyphenyl)-2,7-diazaspiro[3.5]nonane-7-carboxylate

66	tert-butyl 2-(2-((2-(cyclopropanecarboxamido)-5-(methylcarbamoyl)pyridin-4-yl)amino)-3-methoxypyridin-4-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
67	tert-butyl 2-(5-((2-(cyclopropanecarboxamido)-5-(methylcarbamoyl)pyridin-4-yl)amino)-4-methoxypyridin-3-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
68	tert-butyl 2-(4-((2-(cyclopropanecarboxamido)-5-(methylcarbamoyl)pyridin-4-yl)amino)-3-methoxypyridin-2-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
69	6-(cyclopropanecarboxamido)-4-((2-methoxy-3-(2,7-diazaspiro[3.5]nonan-2-yl)phenyl)amino)-N-methylnicotinamide
70	6-(cyclopropanecarboxamido)-4-((3-methoxy-4-(2,7-diazaspiro[3.5]nonan-2-yl)pyridin-2-yl)amino)-N-methylnicotinamide
71	6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(2,7-diazaspiro[3.5]nonan-2-yl)pyridin-3-yl)amino)-N-methylnicotinamide
72	6-(cyclopropanecarboxamido)-4-((3-methoxy-2-(2,7-diazaspiro[3.5]nonan-2-yl)pyridin-4-yl)amino)-N-methylnicotinamide
73	4-((2-methoxy-3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl)amino)-N-methyl-6-(1H-pyrrol-2-yl)nicotinamide
74	4-((3-methoxy-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-2-yl)amino)-N-methyl-6-(1H-pyrrol-2-yl)nicotinamide
75	4-((4-methoxy-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-3-yl)amino)-N-methyl-6-(1H-pyrrol-2-yl)nicotinamide
76	4-((3-methoxy-2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-4-yl)amino)-N-methyl-6-(1H-pyrrol-2-yl)nicotinamide
77	1-(4-((2-methoxy-3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl)amino)-6-(1H-pyrrol-2-yl)pyridin-3-yl)propan-1-one
78	1-(4-((3-methoxy-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-2-yl)amino)-6-(1H-pyrrol-2-yl)pyridin-3-yl)propan-1-one
79	1-(4-((4-methoxy-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-3-yl)amino)-6-(1H-pyrrol-2-yl)pyridin-3-yl)propan-1-one
80	1-(4-((3-methoxy-2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-4-yl)amino)-6-(1H-pyrrol-2-yl)pyridin-3-yl)propan-1-one

81	N-(4-((2-methoxy-3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl)amino)-5-propionylpyridin-2-yl)cyclopropanecarboxamide
82	N-(4-((3-methoxy-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-2-yl)amino)-5-propionylpyridin-2-yl)cyclopropanecarboxamide
83	N-(4-((4-methoxy-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-3-yl)amino)-5-propionylpyridin-2-yl)cyclopropanecarboxamide
84	N-(4-((3-methoxy-2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-4-yl)amino)-5-propionylpyridin-2-yl)cyclopropanecarboxamide
85	tert-butyl 2-(2-methoxy-3-((5-(methylcarbamoyl)-2-(1H-pyrrol-2-yl)pyridin-4-yl)amino)phenyl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
86	tert-butyl 2-(3-methoxy-2-((5-(methylcarbamoyl)-2-(1H-pyrrol-2-yl)pyridin-4-yl)amino)pyridin-4-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
87	tert-butyl 2-(4-methoxy-5-((5-(methylcarbamoyl)-2-(1H-pyrrol-2-yl)pyridin-4-yl)amino)pyridin-3-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
88	tert-butyl 2-(3-methoxy-4-((5-(methylcarbamoyl)-2-(1H-pyrrol-2-yl)pyridin-4-yl)amino)pyridin-2-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
89	2-(cyclopropanecarboxamido)-4-((2-methoxy-3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl)amino)-N-methylpyrimidine-5-carboxamide
90	2-(cyclopropanecarboxamido)-4-((3-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-2-methoxyphenyl)amino)-N-methylpyrimidine-5-carboxamide
91	tert-butyl 2-(3-((2-(cyclopropanecarboxamido)-5-(methylcarbamoyl)pyrimidin-4-yl)amino)-2-methoxyphenyl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
92	2-(cyclopropanecarboxamido)-4-((2-methoxy-3-(8-oxo-6-oxa-2-azaspiro[3.4]octan-2-yl)phenyl)amino)-N-methylpyrimidine-5-carboxamide
93	4-((4-(2,7-diazaspiro[3.5]nonan-2-yl)-1,3,5-triazin-2-yl)amino)-2-(cyclopropanecarboxamido)-N-(methyl-d3)pyrimidine-5-carboxamide
94	4-((4-(2,7-diazaspiro[3.5]nonan-2-yl)-1,3,5-triazin-2-yl)amino)-2-(cyclopropanecarboxamido)-N-methylpyrimidine-5-carboxamide

95	6-(cyclopropanecarboxamido)-4-((5-methoxy-6-(7-oxo-5-oxa-2-azaspiro[3.4]octan-2-yl)pyrimidin-4-yl)amino)-N-(methyl-d3)nicotinamide
96	6-(cyclopropanecarboxamido)-4-((5-methoxy-6-(7-oxo-5-oxa-2-azaspiro[3.4]octan-2-yl)pyrimidin-4-yl)amino)-N-methylnicotinamide
97	6-(cyclopropanecarboxamido)-4-((5-methoxy-6-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrimidin-4-yl)amino)-N-(methyl-d3)nicotinamide
98	6-(cyclopropanecarboxamido)-4-((5-methoxy-6-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrimidin-4-yl)amino)-N-methylnicotinamide
99	tert-butyl 2-(6-((2-(cyclopropanecarboxamido)-5-((methyl-d3)carbamoyl)pyridin-4-yl)amino)-5-methoxypyrimidin-4-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
100	4-((4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-1,3,5-triazin-2-yl)amino)-6-(cyclopropanecarboxamido)-N-(methyl-d3)nicotinamide
101	4-((4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-1,3,5-triazin-2-yl)amino)-6-(cyclopropanecarboxamido)-N-methylnicotinamide
102	tert-butyl 2-(6-((2-(cyclopropanecarboxamido)-5-(methylcarbamoyl)pyridin-4-yl)amino)-5-methoxypyrimidin-4-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
103	tert-butyl 2-(4-((2-(cyclopropanecarboxamido)-5-((methyl-d3)carbamoyl)pyridin-4-yl)amino)-1,3,5-triazin-2-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
104	4-((4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-1,3,5-triazin-2-yl)amino)-2-(cyclopropanecarboxamido)-N-(methyl-d3)pyrimidine-5-carboxamide
105	4-((4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-1,3,5-triazin-2-yl)amino)-2-(cyclopropanecarboxamido)-N-methylpyrimidine-5-carboxamide
106	tert-butyl 2-(4-((2-(cyclopropanecarboxamido)-5-(methylcarbamoyl)pyridin-4-yl)amino)-1,3,5-triazin-2-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
107	2-(cyclopropanecarboxamido)-4-((4-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-1,3,5-triazin-2-yl)amino)-N-(methyl-d3)pyrimidine-5-carboxamide

108	2-(cyclopropanecarboxamido)-4-((4-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-1,3,5-triazin-2-yl)amino)-N-methylpyrimidine-5-carboxamide
109	tert-butyl 2-(4-((2-(cyclopropanecarboxamido)-5-((methyl-d3)carbamoyl)pyrimidin-4-yl)amino)-1,3,5-triazin-2-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
110	tert-butyl 2-(4-((2-(cyclopropanecarboxamido)-5-(methylcarbamoyl)pyrimidin-4-yl)amino)-1,3,5-triazin-2-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
111	6-(cyclopropanecarboxamido)-4-((5-methoxy-6-(8-oxo-6-oxa-2-azaspiro[3.4]octan-2-yl)pyrimidin-4-yl)amino)-N-(methyl-d3)nicotinamide
112	6-(cyclopropanecarboxamido)-4-((5-methoxy-6-(8-oxo-6-oxa-2-azaspiro[3.4]octan-2-yl)pyrimidin-4-yl)amino)-N-methylnicotinamide
113	6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((4-(8-oxo-6-oxa-2-azaspiro[3.4]octan-2-yl)-1,3,5-triazin-2-yl)amino)nicotinamide
114	6-(cyclopropanecarboxamido)-N-methyl-4-((4-(8-oxo-6-oxa-2-azaspiro[3.4]octan-2-yl)-1,3,5-triazin-2-yl)amino)nicotinamide
115	6-(cyclopropanecarboxamido)-4-((5-methoxy-6-(2,7-diazaspiro[3.5]nonan-2-yl)pyrimidin-4-yl)amino)-N-(methyl-d3)nicotinamide
116	6-(cyclopropanecarboxamido)-4-((5-methoxy-6-(2,7-diazaspiro[3.5]nonan-2-yl)pyrimidin-4-yl)amino)-N-methylnicotinamide
117	4-((4-(2,7-diazaspiro[3.5]nonan-2-yl)-1,3,5-triazin-2-yl)amino)-6-(cyclopropanecarboxamido)-N-(methyl-d3)nicotinamide
118	4-((4-(2,7-diazaspiro[3.5]nonan-2-yl)-1,3,5-triazin-2-yl)amino)-6-(cyclopropanecarboxamido)-N-methylnicotinamide
119	2-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((4-(8-oxo-6-oxa-2-azaspiro[3.4]octan-2-yl)-1,3,5-triazin-2-yl)amino)pyrimidine-5-carboxamide
120	2-(cyclopropanecarboxamido)-N-methyl-4-((4-(8-oxo-6-oxa-2-azaspiro[3.4]octan-2-yl)-1,3,5-triazin-2-yl)amino)pyrimidine-5-carboxamide

121	N-(4-((3-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-2-methoxyphenyl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide
122	N-(4-((4-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-3-methoxypyridin-2-yl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide
123	N-(4-((5-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-4-methoxypyridin-3-yl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide
124	N-(4-((2-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-3-methoxypyridin-4-yl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide
125	N-(4-((2-methoxy-3-(8-oxo-6-oxa-2-azaspiro[3.4]octan-2-yl)phenyl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide
126	N-(4-((3-methoxy-4-(8-oxo-6-oxa-2-azaspiro[3.4]octan-2-yl)pyridin-2-yl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide
127	N-(4-((4-methoxy-5-(8-oxo-6-oxa-2-azaspiro[3.4]octan-2-yl)pyridin-3-yl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide
128	N-(4-((3-methoxy-2-(8-oxo-6-oxa-2-azaspiro[3.4]octan-2-yl)pyridin-4-yl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide
129	N-(4-((2-methoxy-3-(7-oxo-5-oxa-2-azaspiro[3.4]octan-2-yl)phenyl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide
130	N-(4-((3-methoxy-4-(7-oxo-5-oxa-2-azaspiro[3.4]octan-2-yl)pyridin-2-yl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide
131	N-(4-((4-methoxy-5-(7-oxo-5-oxa-2-azaspiro[3.4]octan-2-yl)pyridin-3-yl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide
132	N-(4-((3-methoxy-2-(7-oxo-5-oxa-2-azaspiro[3.4]octan-2-yl)pyridin-4-yl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide
133	tert-butyl 2-(3-((2-(cyclopropanecarboxamido)-5-(propanoyl-3,3,3-d3)pyridin-4-yl)amino)-2-methoxyphenyl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
134	tert-butyl 2-(2-((2-(cyclopropanecarboxamido)-5-(propanoyl-3,3,3-d3)pyridin-4-yl)amino)-3-methoxypyridin-4-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate

135	tert-butyl 2-(5-((2-(cyclopropanecarboxamido)-5-(propanoyl-3,3,3-d3)pyridin-4-yl)amino)-4-methoxypyridin-3-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
136	tert-butyl 2-(4-((2-(cyclopropanecarboxamido)-5-(propanoyl-3,3,3-d3)pyridin-4-yl)amino)-3-methoxypyridin-2-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
137	N-(4-((2-methoxy-3-(2,7-diazaspiro[3.5]nonan-2-yl)phenyl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide
138	N-(4-((3-methoxy-4-(2,7-diazaspiro[3.5]nonan-2-yl)pyridin-2-yl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide
139	N-(4-((4-methoxy-5-(2,7-diazaspiro[3.5]nonan-2-yl)pyridin-3-yl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide
140	N-(4-((3-methoxy-2-(2,7-diazaspiro[3.5]nonan-2-yl)pyridin-4-yl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide
141	N-(4-((6-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-5-methoxypyrimidin-4-yl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide
142	N-(4-((5-methoxy-6-(8-oxo-6-oxa-2-azaspiro[3.4]octan-2-yl)pyrimidin-4-yl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide
143	N-(4-((5-methoxy-6-(7-oxo-5-oxa-2-azaspiro[3.4]octan-2-yl)pyrimidin-4-yl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide
144	tert-butyl 2-(6-((2-(cyclopropanecarboxamido)-5-(propanoyl-3,3,3-d3)pyridin-4-yl)amino)-5-methoxypyrimidin-4-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
145	N-(4-((5-methoxy-6-(2,7-diazaspiro[3.5]nonan-2-yl)pyrimidin-4-yl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide
146	N-(4-((5-methoxy-6-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrimidin-4-yl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide
147	N-(4-((4-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-1,3,5-triazin-2-yl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide
148	N-(4-((4-(8-oxo-6-oxa-2-azaspiro[3.4]octan-2-yl)-1,3,5-triazin-2-yl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide

149	N-(4-((4-(7-oxo-5-oxa-2-azaspiro[3.4]octan-2-yl)-1,3,5-triazin-2-yl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide
150	tert-butyl 2-(4-((2-(cyclopropanecarboxamido)-5-(propanoyl-3,3,3-d3)pyridin-4-yl)amino)-1,3,5-triazin-2-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
151	N-(4-((4-(2,7-diazaspiro[3.5]nonan-2-yl)-1,3,5-triazin-2-yl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide
152	N-(4-((4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-1,3,5-triazin-2-yl)amino)-5-(propanoyl-3,3,3-d3)pyridin-2-yl)cyclopropanecarboxamide
153	6-amino-4-((2-methoxy-3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl)amino)-N-(methyl-d3)nicotinamide
154	6-amino-4-((4-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-3-methoxypyridin-2-yl)amino)-N-(methyl-d3)nicotinamide
155	6-amino-4-((4-methoxy-5-(7-oxo-5-oxa-2-azaspiro[3.4]octan-2-yl)pyridin-3-yl)amino)-N-(methyl-d3)pyridazine-3-carboxamide
156	2-amino-4-((3-methoxy-2-(8-oxo-6-oxa-2-azaspiro[3.4]octan-2-yl)pyridin-4-yl)amino)-N-(methyl-d3)pyrimidine-5-carboxamide
157	6-amino-4-((5-methoxy-6-(2,7-diazaspiro[3.5]nonan-2-yl)pyrimidin-4-yl)amino)-N-(methyl-d3)nicotinamide
158	tert-butyl 2-(4-((2-amino-5-((methyl-d3)carbamoyl)pyridin-4-yl)amino)-1,3,5-triazin-2-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate
159	1-(6-amino-4-((2-methoxy-3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl)amino)pyridin-3-yl)propan-1-one-3,3,3-d3
160	6-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((4-(7-oxo-5-oxa-2-azaspiro[3.4]octan-2-yl)-1,3,5-triazin-2-yl)amino)nicotinamide
161	6-(cyclopropanecarboxamido)-N-methyl-4-((4-(7-oxo-5-oxa-2-azaspiro[3.4]octan-2-yl)-1,3,5-triazin-2-yl)amino)nicotinamide
162	2-(cyclopropanecarboxamido)-N-(methyl-d3)-4-((4-(7-oxo-5-oxa-2-azaspiro[3.4]octan-2-yl)-1,3,5-triazin-2-yl)amino)pyrimidine-5-carboxamide
163	2-(cyclopropanecarboxamido)-N-methyl-4-((4-(7-oxo-5-oxa-2-azaspiro[3.4]octan-2-yl)-1,3,5-triazin-2-yl)amino)pyrimidine-5-carboxamide

164	4-((2-methoxy-3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl)amino)-N-(methyl-d3)-6-(1H-pyrrol-2-yl)pyridazine-3-carboxamide
165	4-((3-methoxy-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-2-yl)amino)-N-(methyl-d3)-6-(1H-pyrrol-2-yl)pyridazine-3-carboxamide
166	1-(4-((2-methoxy-3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl)amino)-6-(1H-pyrrol-2-yl)pyridazin-3-yl)propan-1-one-3,3,3-d3
167	1-(4-((3-methoxy-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-2-yl)amino)-6-(1H-pyrrol-2-yl)pyridazin-3-yl)propan-1-one-3,3,3-d3
168	6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(2-azaspiro[3.3]heptan-2-yl)pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide
169	6-(cyclopropanecarboxamido)-4-((4-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-3-methoxypyridin-2-yl)amino)-N-(methyl-d3)pyridazine-3-carboxamide
170	6-(cyclopropanecarboxamido)-4-((3-methoxy-2-(7-oxa-2-azaspiro[3.5]nonan-2-yl)pyridin-4-yl)amino)-N-(methyl-d3)nicotinamide
171	6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(7-oxa-2-azaspiro[3.5]nonan-2-yl)pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide
172	6-(cyclopropanecarboxamido)-4-((2-methoxy-3-(7-oxa-2-azaspiro[3.5]nonan-2-yl)phenyl)amino)-N-(methyl-d3)nicotinamide
173	tert-butyl 6-(3-((2-(cyclopropanecarboxamido)-5-((methyl-d3)carbamoyl)pyridin-4-yl)amino)-2-methoxyphenyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate
174	tert-butyl 6-(2-((2-(cyclopropanecarboxamido)-5-((methyl-d3)carbamoyl)pyridin-4-yl)amino)-3-methoxypyridin-4-yl)-2,6-diazaspiro[3.3]heptane-2-carboxylate
175	tert-butyl 6-(5-((2-(cyclopropanecarboxamido)-5-((methyl-d3)carbamoyl)pyridin-4-yl)amino)-4-methoxypyridin-3-yl)-2,6-diazaspiro[3.3]heptane-2-carboxylate

176	tert-butyl 6-(4-((2-(cyclopropanecarboxamido)-5-((methyl-d3)carbamoyl)pyridin-4-yl)amino)-3-methoxypyridin-2-yl)-2,6-diazaspiro[3.3]heptane-2-carboxylate
177	6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(2,6-diazaspiro[3.3]heptan-2-yl)pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide
178	6-(cyclopropanecarboxamido)-4-((3-methoxy-2-(2,6-diazaspiro[3.3]heptan-2-yl)pyridin-4-yl)amino)-N-(methyl-d3)nicotinamide
179	6-(cyclopropanecarboxamido)-4-((5-methoxy-6-(7-oxa-2-azaspiro[3.5]nonan-2-yl)pyrimidin-4-yl)amino)-N-(methyl-d3)nicotinamide
180	6-(cyclopropanecarboxamido)-4-((3-methoxy-4-(2-azaspiro[3.3]heptan-2-yl)pyridin-2-yl)amino)-N-(methyl-d3)nicotinamide
181	6-(cyclopropanecarboxamido)-4-((3-methoxy-2-(2-azaspiro[3.3]heptan-2-yl)pyridin-4-yl)amino)-N-(methyl-d3)nicotinamide
182	6-(cyclopropanecarboxamido)-4-((2-(6,6-difluoro-2-azaspiro[3.3]heptan-2-yl)-3-methoxypyridin-4-yl)amino)-N-(methyl-d3)nicotinamide
183	6-(cyclopropanecarboxamido)-4-((3-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-2-methoxyphenyl)amino)-N-(methyl-d3)pyridazine-3-carboxamide
184	6-(cyclopropanecarboxamido)-4-((3-methoxy-2-(2-azaspiro[3.5]nonan-2-yl)pyridin-4-yl)amino)-N-(methyl-d3)nicotinamide
185	2-(cyclopropanecarboxamido)-4-((4-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-3-methoxypyridin-2-yl)amino)-N-(methyl-d3)pyrimidine-5-carboxamide
186	2-(cyclopropanecarboxamido)-4-((2-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-3-methoxypyridin-4-yl)amino)-N-(methyl-d3)pyrimidine-5-carboxamide
187	6-(cyclopropanecarboxamido)-4-((2-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-3-methoxypyridin-4-yl)amino)-N-(methyl-d3)pyridazine-3-carboxamide

188	6-(cyclopropanecarboxamido)-4-((3-methoxy-4-(7-oxa-2-azaspiro[3.5]nonan-2-yl)pyridin-2-yl)amino)-N-(methyl-d3)nicotinamide
189	6-(cyclopropanecarboxamido)-4-((2-methoxy-3-(2-azaspiro[3.3]heptan-2-yl)phenyl)amino)-N-(methyl-d3)nicotinamide
190	6-(cyclopropanecarboxamido)-4-((3-(6,6-difluoro-2-azaspiro[3.3]heptan-2-yl)-2-methoxyphenyl)amino)-N-(methyl-d3)nicotinamide
191	6-(cyclopropanecarboxamido)-4-((5-(6,6-difluoro-2-azaspiro[3.3]heptan-2-yl)-4-methoxypyridin-3-yl)amino)-N-(methyl-d3)nicotinamide

[00077] The IUPAC names for compounds provided herein were obtained using ChemDraw[®] Professional, version: 19.1.1.21.

Further Forms of Compounds Disclosed Herein

Isomers/Stereoisomers

[00078] In some embodiments, the compounds described herein exist as geometric isomers. In some embodiments, the compounds described herein possess one or more double bonds. The compounds presented herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the corresponding mixtures thereof. In some situations, the compounds described herein possess one or more chiral centers and each center exists in the R configuration or S configuration. The compounds described herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are useful for the applications described herein. In some embodiments, the compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers, and recovering the optically pure enantiomers. In some embodiments, dissociable complexes are preferred. In some embodiments, the diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these

dissimilarities. In some embodiments, the diastereomers are separated by chiral chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In some embodiments, the optically pure enantiomer is then recovered, along with the resolving agent. Labeled compounds

[00079] In some embodiments, the compounds described herein exist in their isotopically-labeled forms. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds as pharmaceutical compositions. Thus, in some embodiments, the compounds disclosed herein include isotopically-labeled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds described herein, or stereoisomer thereof, include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, and chloride, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Compounds described herein, and the pharmaceutically acceptable salts, or stereoisomers thereof which contain the aforementioned isotopes and/or other isotopes of other atoms, are within the scope of this disclosure. Certain isotopically-labeled compounds, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavy isotopes such as deuterium, i.e., ^2H , produces certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements. In some embodiments, the isotopically labelled compound or a pharmaceutically acceptable salt, or stereoisomer thereof is prepared by any suitable method.

[00080] In some embodiments, the compounds described herein are labelled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

Pharmaceutically acceptable salts

[00081] In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

[00082] In some embodiments, the compounds described herein possess acidic or basic groups and therefor react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. In some embodiments, these salts are prepared in situ during the final isolation and purification of the compounds disclosed herein, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

[00083] Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds described herein with a mineral, organic acid, or inorganic base, such salts including acetate, acrylate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, bisulfite, bromide, butyrate, butyn-1,4-dioate, camphorate, camphorsulfonate, caproate, caprylate, chlorobenzoate, chloride, citrate, cyclopentanepropionate, decanoate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hexyne-1,6-dioate, hydroxybenzoate, g-hydroxybutyrate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isobutyrate, lactate, maleate, malonate, methanesulfonate, mandelate, metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, 1-naphthalenesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate,

picrate, pivalate, propionate, pyrosulfate, pyrophosphate, propiolate, phthalate, phenylacetate, phenylbutyrate, propanesulfonate, salicylate, succinate, sulfate, sulfite, succinate, suberate, sebacate, sulfonate, tartrate, thiocyanate, tosylate, undecionate, and xylenesulfonate.

[00084] Further, the compounds described herein can be prepared as pharmaceutically acceptable salts formed by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, including, but not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, metaphosphoric acid, and the like; and organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, p-toluenesulfonic acid, tartaric acid, trifluoroacetic acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, arylsulfonic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, and muconic acid.

[00085] In some embodiments, those compounds described herein which comprise a free acid group react with a suitable base, such as the hydroxide, carbonate, bicarbonate, or sulfate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, tertiary, or quaternary amine. Representative salts include the alkali or alkaline earth salts, like lithium, sodium, potassium, calcium, and magnesium, and aluminum salts and the like. Illustrative examples of bases include sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, $N^+(C_{1-4} \text{ alkyl})_4$, and the like.

[00086] Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine,

diethanolamine, piperazine, and the like. It should be understood that the compounds described herein also include the quaternization of any basic nitrogen-containing groups they contain. In some embodiments, water or oil-soluble or dispersible products are obtained by such quaternization.

Tautomers

[00087] In some situations, compounds exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein. Tautomers are compounds that are interconvertible by migration of a hydrogen atom, accompanied by a switch of a single bond and adjacent double bond. In bonding arrangements where tautomerization is possible, a chemical equilibrium of the tautomers will exist. All tautomeric forms of the compounds disclosed herein are contemplated. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH.

Preparation of the Compounds

[00088] The compounds used in the reactions described herein are made according to organic synthesis techniques known to those skilled in this art, starting from commercially available chemicals and/or from compounds described in the chemical literature. "Commercially available chemicals" are obtained from standard commercial sources including Acros Organics (Pittsburgh, PA), Aldrich Chemical (Milwaukee, WI, including Sigma Chemical and Fluka), Apin Chemicals Ltd. (Milton Park, UK), Avocado Research (Lancashire, U.K.), BDH, Inc. (Toronto, Canada), Bionet (Cornwall, U.K.), Chem Service Inc. (West Chester, PA), Crescent Chemical Co. (Hauppauge, NY), Eastman Organic Chemicals, Eastman Kodak Company (Rochester, NY), Fisher Scientific Co. (Pittsburgh, PA), Fisons Chemicals (Leicestershire, UK), Frontier Scientific (Logan, UT), ICN Biomedicals, Inc. (Costa Mesa, CA), Key Organics (Cornwall, U.K.), Lancaster Synthesis (Windham, NH), Maybridge Chemical Co. Ltd. (Cornwall, U.K.), Parish Chemical Co. (Orem, UT), Pfaltz & Bauer, Inc. (Waterbury, CN), Polyorganix (Houston, TX), Pierce Chemical Co. (Rockford, IL), Riedel de Haen AG (Hanover, Germany), Spectrum Quality Product, Inc. (New Brunswick, NJ), TCI America (Portland, OR), Trans World Chemicals, Inc. (Rockville, MD), Wako Chemicals

USA, Inc. (Richmond, VA), BLDpharm (Shanghai, China), Avra Labs (Telangana, India), and TCI Chemicals (Tokyo, Japan).

[00089] Suitable reference books and treatises that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, “Synthetic Organic Chemistry”, John Wiley & Sons, Inc., New York; S. R. Sandler et al., “Organic Functional Group Preparations,” 2nd Ed., Academic Press, New York, 1983; H. O. House, “Modern Synthetic Reactions”, 2nd Ed., W. A. Benjamin, Inc. Menlo Park, Calif. 1972; T. L. Gilchrist, “Heterocyclic Chemistry”, 2nd Ed., John Wiley & Sons, New York, 1992; J. March, “Advanced Organic Chemistry: Reactions, Mechanisms and Structure”, 4th Ed., Wiley-Interscience, New York, 1992. Additional suitable reference books and treatises that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, Fuhrhop, J. and Penzlin G. “Organic Synthesis: Concepts, Methods, Starting Materials”, Second, Revised and Enlarged Edition (1994) John Wiley & Sons ISBN: 3-527-29074-5; Hoffman, R.V. “Organic Chemistry, An Intermediate Text” (1996) Oxford University Press, ISBN 0-19-509618-5; Larock, R. C. “Comprehensive Organic Transformations: A Guide to Functional Group Preparations” 2nd Edition (1999) Wiley-VCH, ISBN: 0-471-19031-4; March, J. “Advanced Organic Chemistry: Reactions, Mechanisms, and Structure” 4th Edition (1992) John Wiley & Sons, ISBN: 0-471-60180-2; Otera, J. (editor) “Modern Carbonyl Chemistry” (2000) Wiley-VCH, ISBN: 3-527-29871-1; Patai, S. “Patai's 1992 Guide to the Chemistry of Functional Groups” (1992) Interscience ISBN: 0-471-93022-9; Solomons, T. W. G. “Organic Chemistry” 7th Edition (2000) John Wiley & Sons, ISBN: 0-471-19095-0; Stowell, J.C., “Intermediate Organic Chemistry” 2nd Edition (1993) Wiley-Interscience, ISBN: 0-471-57456-2; “Industrial Organic Chemicals: Starting Materials and Intermediates: An Ullmann's Encyclopedia” (1999) John Wiley & Sons, ISBN: 3-527-29645-X, in 8 volumes; “Organic Reactions” (1942-2000) John Wiley & Sons, in over 55 volumes; and “Chemistry of Functional Groups” John Wiley & Sons, in 73 volumes.

[00090] Specific and analogous reactants are optionally identified through the indices of known chemicals prepared by the Chemical Abstract Service of the American Chemical Society, which are available in most public and university libraries, as well as through on-line. Chemicals that are known but not commercially available in catalogs are optionally prepared by custom chemical synthesis houses, where many of the standard chemical supply houses (e.g., those listed above) provide custom synthesis services. A reference for the preparation and selection of pharmaceutical salts of the compounds described herein is P. H. Stahl & C. G. Wermuth “Handbook of Pharmaceutical Salts”, Verlag Helvetica Chimica Acta, Zurich, 2002.

Uses, Formulation and Administration

Pharmaceutically acceptable compositions

[00091] According to another embodiment, the invention provides a composition comprising a compound of this invention or a pharmaceutically acceptable derivative (e.g., pharmaceutically acceptable salt) thereof and a pharmaceutically acceptable carrier, adjuvant, or vehicle. The amount of compound in compositions of this invention is such that is effective to measurably inhibit a TYK2 protein kinase, or a mutant thereof, in a biological sample or in a patient. In certain embodiments, a composition of this invention is formulated for administration to a patient in need of such composition. In some embodiments, a composition of this invention is formulated for oral administration to a patient.

[00092] The term “patient,” as used herein, means an animal, preferably a mammal, and most preferably a human.

[00093] The term “pharmaceutically acceptable carrier, adjuvant, or vehicle” refers to a nontoxic carrier, adjuvant, or vehicle that does not substantially perturb the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or

electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[00094] A “pharmaceutically acceptable derivative” means any non-toxic salt, ester, salt of an ester or other derivative of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof.

[00095] As used herein, the term “inhibitorily active metabolite or residue thereof” means that a metabolite or residue thereof is also an inhibitor of a TYK2 protein kinase, or a mutant thereof.

[00096] Compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term “parenteral” as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension.

Uses of Compounds and Pharmaceutically Acceptable Compositions

[00097] Compounds and compositions described herein are generally useful for the inhibition of kinase activity and or kinase mediated signal transduction of one or more enzymes. In some embodiments, the kinase and or kinase mediated signal transduction inhibited by the compounds and methods of the invention is TYK2.

[00098] The activity of a compound utilized in this invention as an inhibitor of TYK2, or a mutant thereof, may be assayed in vitro, in vivo or in a cell line. In vitro assays include assays that determine inhibition of either the phosphorylation activity and/or the subsequent functional consequences, or ATPase activity of

activated TYK2, or a mutant thereof. Alternate in vitro assays quantitate the ability of the inhibitor to bind to TYK2. Inhibitor binding may be measured by radiolabeling the inhibitor prior to binding, isolating the inhibitor/TYK2 complex and determining the amount of radiolabel bound. Alternatively, inhibitor binding may be determined by running a competition experiment where new inhibitors are incubated with TYK2 bound to known radioligands. Representative in vitro and in vivo assays useful in assaying a TYK2 inhibitor include those described and disclosed in, e.g., each of which is herein incorporated by reference in its entirety. Detailed conditions for assaying a compound utilized in this invention as an inhibitor of TYK2, or a mutant thereof, are set forth in the Examples below.

[00099] As used herein, the terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, as described herein. In some embodiments, treatment may be administered after one or more symptoms have developed. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example to prevent or delay their recurrence.

[000100] Provided compounds are inhibitors of TYK2 and are therefore useful for treating one or more disorders associated with activity of TYK2 or mutants thereof. Thus, in certain embodiments, the present invention provides a method for treating a TYK2-mediated disorder comprising the step of administering to a patient in need thereof a compound of the present invention, or pharmaceutically acceptable composition thereof.

[000101] As used herein, the term “TYK2-mediated” disorders, diseases, and/or conditions as used herein means any disease or other deleterious condition in which TYK2 or a mutant thereof is known to play a role. Accordingly, another embodiment of the present invention relates to treating or lessening the severity of one or more diseases in which TYK2, or a mutant thereof, is known to play a role. Such TYK2-mediated disorders include but are not limited to autoimmune

disorders, inflammatory disorders, proliferative disorders, endocrine disorders, neurological disorders and disorders associated with transplantation.

[000102] In some embodiments, the present invention provides a method for treating one or more disorders, wherein the disorders are selected from autoimmune disorders, inflammatory disorders, proliferative disorders, endocrine disorders, neurological disorders, and disorders associated with transplantation, said method comprising administering to a patient in need thereof, a pharmaceutical composition comprising an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof.

[000103] In some embodiments, the disorder is an autoimmune disorder. In some embodiments the autoimmune disorder is selected from type 1 diabetes, systemic lupus erythematosus, multiple sclerosis, psoriasis, Behcet's disease, POEMS syndrome, Crohn's disease, ulcerative colitis, and inflammatory bowel disease.

[000104] In some embodiments, the disorder is an inflammatory disorder. In some embodiments, the inflammatory disorder is rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, psoriasis, hepatomegaly, Crohn's disease, ulcerative colitis, inflammatory bowel disease.

[000105] In some embodiments, the disorder is a proliferative disorder. In some embodiments, the proliferative disorder is a hematological cancer. In some embodiments, the proliferative disorder is a leukemia. In some embodiments, the leukemia is a T-cell leukemia. In some embodiments the T-cell leukemia is T-cell acute lymphoblastic leukemia (T-ALL). In some embodiments the proliferative disorder is polycythemia vera, myelofibrosis, essential or thrombocytosis.

[000106] In some embodiments, the disorder is an endocrine disorder. In some embodiments, the endocrine disorder is polycystic ovary syndrome, Crouzon's syndrome, or type 1 diabetes.

[000107] In some embodiments, the disorder is a neurological disorder. In some embodiments, the neurological disorder is Alzheimer's disease.

[000108] In some embodiments, the proliferative disorder is associated with one or more activating mutations in TYK2. In some embodiments, the activating

mutation in TYK2 is a mutation to the FERM domain, the JH2 domain, or the kinase domain. In some embodiments the activating mutation in TYK2 is selected from G36D, S47N, R425H, V73 II, E957D, and R1027H.

[000109] In some embodiments, the disorder is associated with transplantation. In some embodiments the disorder associated with transplantation is transplant rejection, or graft versus host disease.

[000110] In some embodiments the disorder is associated with type I interferon, IL-10, IL-12, or IL-23 signaling.

[000111] Compounds of the invention are also useful in the treatment of inflammatory or allergic conditions of the skin, for example psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, systemic lupus erythematosus, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, acne vulgaris, and other inflammatory or allergic conditions of the skin.

[000112] Compounds of the invention may also be used for the treatment of other diseases or conditions, such as diseases or conditions having an inflammatory component, for example, treatment of diseases and conditions of the eye such as ocular allergy, conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis, diseases affecting the nose including allergic rhinitis, and inflammatory disease in which autoimmune reactions are implicated or having an autoimmune component or etiology, such as systemic lupus erythematosus, multiple sclerosis, psoriasis, Behcet's disease, POEMS syndrome, rheumatoid arthritis, chronic obstructive pulmonary disease, hepatomegaly, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria bullous pemphigoid, lupus erythematosus, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, acne vulgaris, other inflammatory or allergic conditions of the skin, solid tumors (e.g., prostate cancer, renal cancer, hepatic cancer, pancreatic cancer, gastric cancer, breast cancer, lung cancer, cancers of the head and neck, thyroid cancer, glioblastoma, Kaposi's sarcoma, Castleman's

disease, melanoma etc), hematological cancers (e.g., lymphoma, leukemia such as acute lymphoblastic leukemia, T-cell leukemia, T-cell acute lymphoblastic leukemia (T-ALL), acute myelogenous leukemia (AML), or multiple myeloma), and skin cancer such as cutaneous T-cell lymphoma (CTCL) (such as Sezary syndrome and mycosis fungoides), cutaneous B-cell lymphoma, myeloproliferative disorders (MPDs) such as polycythemia vera (PV), essential thrombocythemia (ET), myeloid metaplasia with myelofibrosis (MMM), chronic myelogenous leukemia (CML), chronic myelomonocytic leukemia (CMML), hypereosinophilic syndrome (HES), systemic mast cell disease (SMCD), systemic inflammatory response syndrome (SIRS) and septic shock, Takayasu and Giant Cell arteritis, sarcoidosis, polymyositis, pityriasis rubra pilaris, granuloma annulare, morphea, lichen sclerosis, celiac disease, familial adenomatous polyposis, axial Spondylo Arthritis (SpA), thrombocytosis, polycystic ovary syndrome, Crouzon's syndrome, Alzheimer's disease, ocular allergy, conjunctivitis, keratoconjunctivitis sicca, vernal conjunctivitis, allergic rhinitis, hemolytic anemia, aplastic anemia, pure red cell anemia and idiopathic thrombocytopenia, polychondritis, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, irritable bowel syndrome, periodontitis, hyaline membrane disease, kidney disease, glomerular disease, alcoholic liver disease, endocrine ophthalmopathy, Grave's disease, alveolitis, chronic hypersensitivity pneumonitis, primary biliary cirrhosis, uveitis (anterior and posterior), Sjogren's syndrome, interstitial lung fibrosis, psoriatic arthritis, systemic juvenile idiopathic arthritis, nephritis, vasculitis, diverticulitis, interstitial cystitis, glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy), chronic granulomatous disease, endometriosis, leptospirosis renal disease, glaucoma, retinal disease, ageing, headache, pain, complex regional pain syndrome, cardiac hypertrophy, muscle wasting, catabolic disorders, obesity, fetal growth retardation, hypercholesterolemia, heart disease, chronic heart failure, mesothelioma, anhidrotic ectodermal dysplasia, incontinentia pigmenti, Paget's disease, pancreatitis, hereditary periodic fever syndrome, asthma (allergic and non-allergic,

mild, moderate, severe, bronchitic, and exercise-induced), acute lung injury, acute respiratory distress syndrome, eosinophilia, hypersensitivities, anaphylaxis, nasal sinusitis, silica induced diseases, pulmonary disease, cystic fibrosis, acid-induced lung injury, pulmonary hypertension, polyneuropathy, cataracts, muscle inflammation in conjunction with systemic sclerosis, inclusion body myositis, thyroiditis, Addison's disease, lichen planus, Type 1 diabetes, or Type 2 diabetes, appendicitis, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic graft rejection, colitis, Crohn's disease, cystitis, dacryoadenitis, dermatitis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, Henoch-Schonlein purpura, hepatitis, hidradenitis suppurativa, immunoglobulin A nephropathy, interstitial lung disease, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, polymyositis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, ulcerative colitis, vaginitis, vasculitis, or vulvitis, acute and chronic gout, chronic gouty arthritis, , Juvenile rheumatoid arthritis, Cryopyrin Associated Periodic Syndrome (CAPS), and osteoarthritis.

[000113] In some embodiments the inflammatory disease which can be treated according to the methods of this invention is selected from acute and chronic gout, chronic gouty arthritis, psoriasis, psoriatic arthritis, rheumatoid arthritis, Juvenile rheumatoid arthritis, Systemic juvenile idiopathic arthritis (SJIA), Cryopyrin Associated Periodic Syndrome (CAPS), and osteoarthritis.

[000114] In some embodiments the inflammatory disease which can be treated according to the methods of this invention is a Th1- or Th17-mediated disease. In some embodiments the Th1-mediated disease is selected from Systemic lupus erythematosus, Multiple sclerosis, and inflammatory bowel disease (including Crohn's disease or ulcerative colitis).

[000115] In some embodiments the inflammatory disease which can be treated according to the methods of this invention is selected from Sjogren's

syndrome, allergic disorders, osteoarthritis, conditions of the eye such as ocular allergy, conjunctivitis, keratoconjunctivitis sicca and vernal conjunctivitis, and diseases affecting the nose such as allergic rhinitis.

[000116] Furthermore, the invention provides the use of a compound according to the definitions herein, or a pharmaceutically acceptable salt, thereof for the preparation of a medicament for the treatment of an autoimmune disorder, an inflammatory disorder, or a proliferative disorder, or a disorder commonly occurring in connection with transplantation.

[000117] According to one embodiment, the invention relates to a method of inhibiting protein kinase activity in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound.

[000118] According to another embodiment, the invention relates to a method of inhibiting activity of TYK2, or a mutant thereof, in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or with a composition comprising said compound. In certain embodiments, the invention relates to a method of irreversibly inhibiting activity of TYK2, or a mutant thereof, in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or with a composition comprising said compound.

[000119] In another embodiment, the invention provides a method of selectively inhibiting TYK2 over one or more of JAK1, JAK2, and JAK3. In some embodiments, a compound of the present invention is more than 2-fold selective over JAK1 or JAK2 or JAK3. In some embodiments, a compound of the present invention is more than 5-fold selective over JAK1 or JAK2 or JAK3. In some embodiments, a compound of the present invention is more than 10-fold selective over JAK1 or JAK2 or JAK3. In some embodiments, a compound of the present invention is more than 50-fold selective over JAK 1/ JAK 2/ JAK 3. In some embodiments, a compound of the present invention is more than 100-fold selective over JAK1 or JAK2 or JAK3.

[000120] The term “biological sample”, as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[000121] Inhibition of activity of TYK2 (or a mutant thereof) in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, biological specimen storage, and biological assays.

[000122] Another embodiment of the present invention relates to a method of inhibiting protein kinase activity in a patient comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound.

[000123] According to another embodiment, the invention relates to a method of inhibiting activity of TYK2, or a mutant thereof, in a patient comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound.

[000124] According to certain embodiments, the invention relates to a method of reversibly or irreversibly inhibiting activity of one or more of TYK2, or a mutant thereof, in a patient comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound. In other embodiments, the present invention provides a method for treating a disorder mediated by TYK2, or a mutant thereof, in a patient in need thereof, comprising the step of administering to said patient a compound according to the present invention or pharmaceutically acceptable composition thereof. Such disorders are described in detail herein.

EXAMPLES AND METHODS OF PREPARATION

Synthetic scheme and procedure

[000125] The compounds of the present invention may be synthesised by many methods available to those skilled in the art of organic chemistry. General synthetic schemes for preparing compounds of the present invention are described

below. These schemes are illustrative and are not meant to limit the possible techniques one skilled in the art may use to prepare the compounds disclosed herein. Different methods to prepare the compounds of the present invention will be evident to those skilled in the art. Additionally, the various steps in the synthesis may be performed in an alternate sequence in order to give the desired compound or compounds. Example of compounds of the present invention prepared by methods described in the general schemes is given in the preparations and example section set out hereinafter.

[000126] The reactions and techniques described in this section are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and work up procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents that are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used. This will sometime require a judgement to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention. It will also be recognised that another major consideration in the planning of any synthetic route in this field is the judicious choice of protecting groups present in the compounds described in this invention.

[000127] In the reactions described, it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, in order to avoid their unwanted participation in reactions. Protecting groups are used to block some or all of the reactive moieties and prevent such groups from participating in chemical reactions until the protective group is removed. It is preferred that each protective group be

removable by a different means. Protective groups that are cleaved under totally disparate reaction conditions fulfill the requirement of differential removal.

[000128] Protective groups can be removed by acid, base, reducing conditions (such as, for example, hydrogenolysis), and/or oxidative conditions. Groups such as trityl, dimethoxytrityl, acetal and t-butyl dimethylsilyl are acid labile and may be used to protect carboxy and hydroxy reactive moieties in the presence of amino groups protected with Cbz groups, which are removable by hydrogenolysis, and Fmoc groups, which are base labile. Carboxylic acid and hydroxy reactive moieties may be blocked with base labile groups such as, but not limited to, methyl, ethyl, and acetyl in the presence of amines blocked with acid labile groups such as t-butyl carbamate or with carbamates that are both acid and base stable but hydrolytically removable.

[000129] Carboxylic acid and hydroxy reactive moieties may also be blocked with hydrolytically removable protective groups such as the benzyl group, while amine groups capable of hydrogen bonding with acids may be blocked with base labile groups such as Fmoc. Carboxylic acid reactive moieties may be protected by conversion to simple ester compounds as exemplified herein, which include conversion to alkyl esters, or they may be blocked with oxidatively-removable protective groups such as 2,4-dimethoxybenzyl, while co-existing amino groups may be blocked with fluoride labile silyl carbamates.

[000130] Allyl blocking groups are useful in the presence of acid- and base-protecting groups since the former are stable and can be subsequently removed by metal or pi-acid catalysts. For example, an allyl-blocked carboxylic acid can be deprotected with a Pd-catalyzed reaction in the presence of acid labile t-butyl carbamate or base-labile acetate amine protecting groups. Yet another form of protecting group is a resin to which a compound or intermediate may be attached. As long as the residue is attached to the resin, that functional group is blocked and cannot react. Once released from the resin, the functional group is available to react. Abbreviations and acronyms used herein are as follows:

Cs ₂ CO ₃	cesium carbonate
DCM	dichloromethane

DIPEA	N,N-diisopropylethylamine
DMAc	dimethylacetamide
DMF	dimethylformamide
DMF-DMA	N,N-dimethylformamide dimethyl acetal
DMSO	dimethyl sulfoxide
EtOAc	ethylacetate
Et ₃ N	triethylamine
H ₂ O	water
HBr	hydrogen bromide
HCl	hydrochloric acid
KHMDS	potassium hexamethyldisilazide
LiHMDS	lithium hexamethyldisilazide
MeOH	methanol
N,N'-CDI	N,N'-carbonyldiimidazole
Na ₂ SO ₄	sodium sulfate
NaHCO ₃	sodium bicarbonate
NaHMDS	sodium hexamethyldisilazide
NaOH	sodium hydroxide
NBS	N-bromosuccinamide
NH ₄ Cl	ammonium chloride
NH ₄ OH	ammonium hydroxide
NMP	N-Methyl-2-pyrrolidone
Pd(OAc) ₂	palladium acetate
Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium(0)
POCl ₃	phosphorus oxychloride
TFA	trifluoroacetic acid
THF	tetrahydrofuran

General methods of preparation:

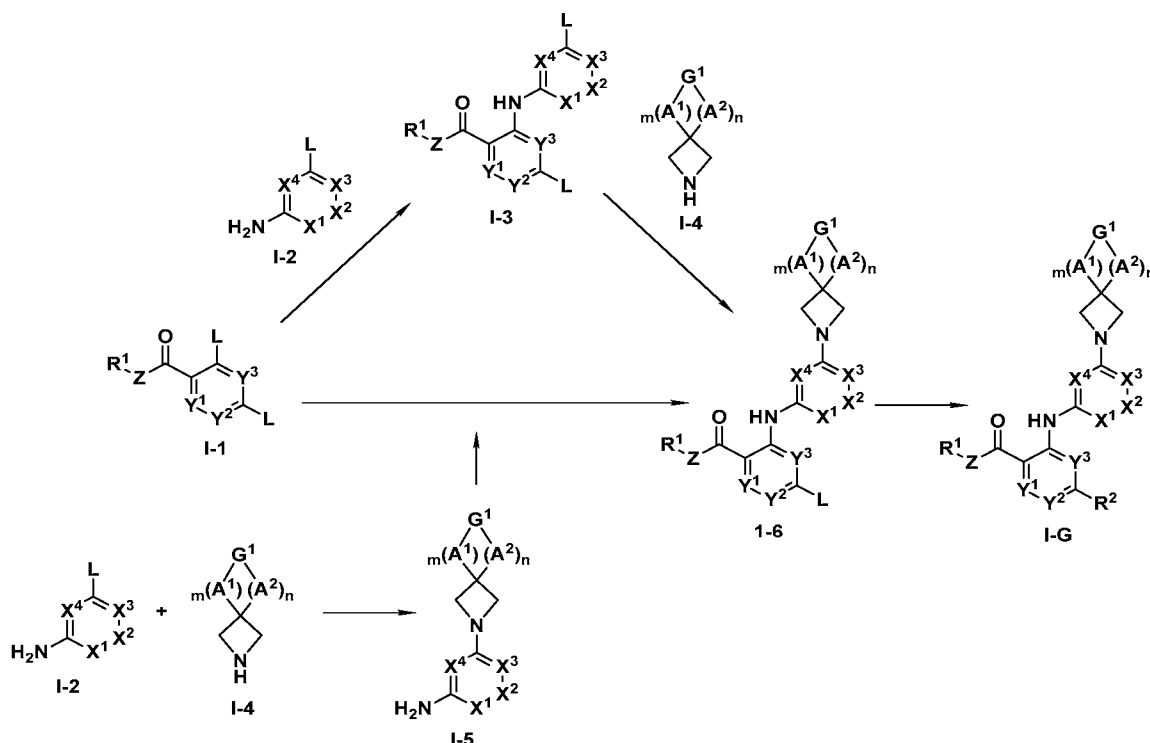
[000131] All of the derivatives of Formula (I), Formula (II), and Formula (III) may be prepared by the procedures described in the general methods presented

below or by routine modifications thereof for compounds of Formula (A). The present invention also encompasses any one or more of these processes for preparing the derivatives of Formula (A), in addition to any novel intermediates used therein. The person skilled in the art will appreciate that the following reactions may be heated thermally or under microwave irradiation. The course of reaction is monitored through an analytical technique known to the person such as for example using TLC, HPLC, NMR and the like. General processes for preparing compounds of Formula (A) of present invention are depicted below in general schemes 1-6.

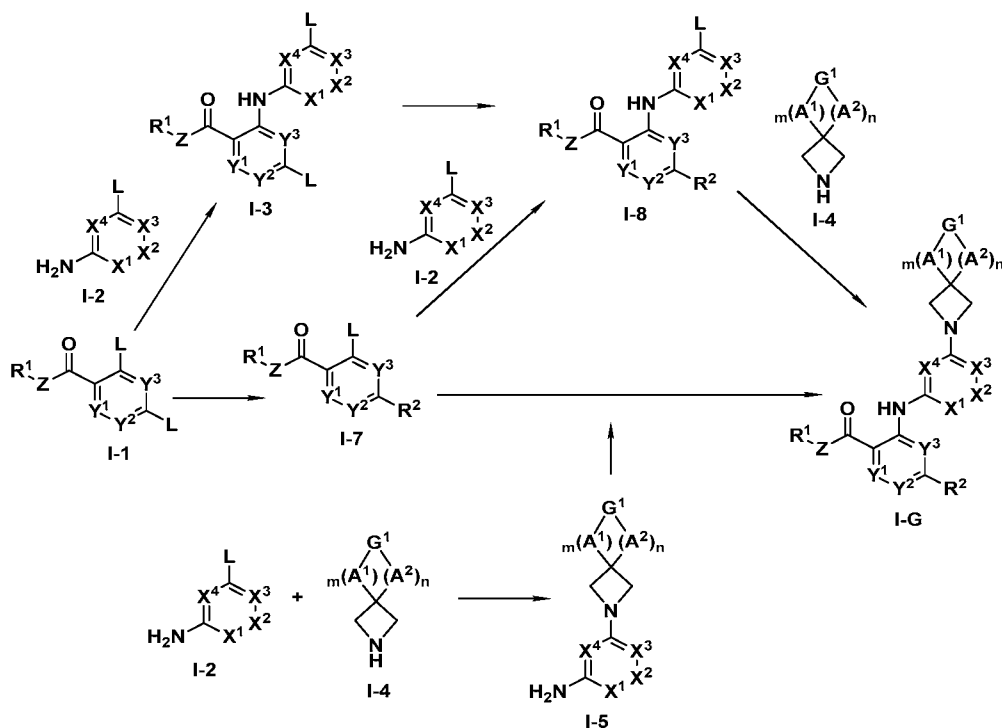
[000132] The generic compounds of Formula (A) as described in general procedure encompasses the compounds of Formula (I), Formula (II) and Formula (III); wherein Y^1 , Y^2 and Y^3 of formula (A) is N or CR^3 .

[000133] Unless specified the definitions of R^1 , R^2 , Z, X^1 , X^2 , X^3 , X^4 , Y^1 , Y^2 , Y^3 , G^1 , A^1 , A^2 , m and n in following general schemes are same as provided herein for Formula I, II, and III.

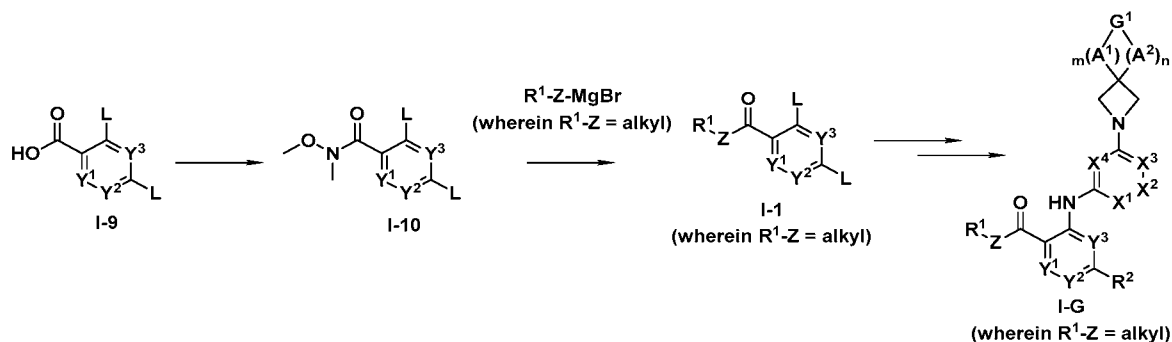
General scheme 1:



[000134] In general scheme 1, compound I-1 (wherein L represents leaving group such as halogen) is reacted with compound I-2 or its protected derivative to give a compound I-3, either in a base promoted reaction using suitable base such as but not limited to LiHMDS, NaHMDS, KHMDS, DIPEA or sodium hydride or in a acid catalysed reaction using suitable acid such as conc. HCl, in presence of suitable solvent such as but not limited to DMF, DMAc, THF, 2-Methyl-THF, NMP, MeOH or EtOH at suitable temperature, such as but not limited to, from room temperature to reflux temperature until desired conversion is achieved. The compound of the Formula I-3 is further reacted with compound of formula I-4 in palladium mediated reaction optionally in presence of ligands PPh₃, SPhos, Ruphos, XPhos, SPhos and BrettPhos and in presence of suitable base, such as but not limited to, NaOtBu, KOtBu, CS₂CO₃, triethylamine, and a suitable solvent, such as but not limited to toluene, dioxane, acetonitrile to give compound I-6. Reaction of compound 1-3 with compound 1-4 is also optionally performed without palladium catalyst and ligand. Alternatively, compound 1-6 is also prepared by reacting compound I-1 with compound 1-5 under similar conditions as used for preparing compound 1-3. Compound I-6 is further converted to compound A by various methods, including but not limited to, 1) palladium-mediated Buchwald coupling I-6 with substituted amino-heterocycles or substituted primary amides optionally in the presence of ligands PPh₃, SPhos, Ruphos, XPhos, SPhos and BrettPhos; and 2) suzuki coupling chemistry and the like. Wherever applicable the protective group is used during the course of the reaction and the said protective group is removed by a conventional methods known in the art, Compound I-5 was prepared by reacting compound I-2 with compound I-4 using conventional methods known in the art. Compounds I-2 and I-4 are commercially available.

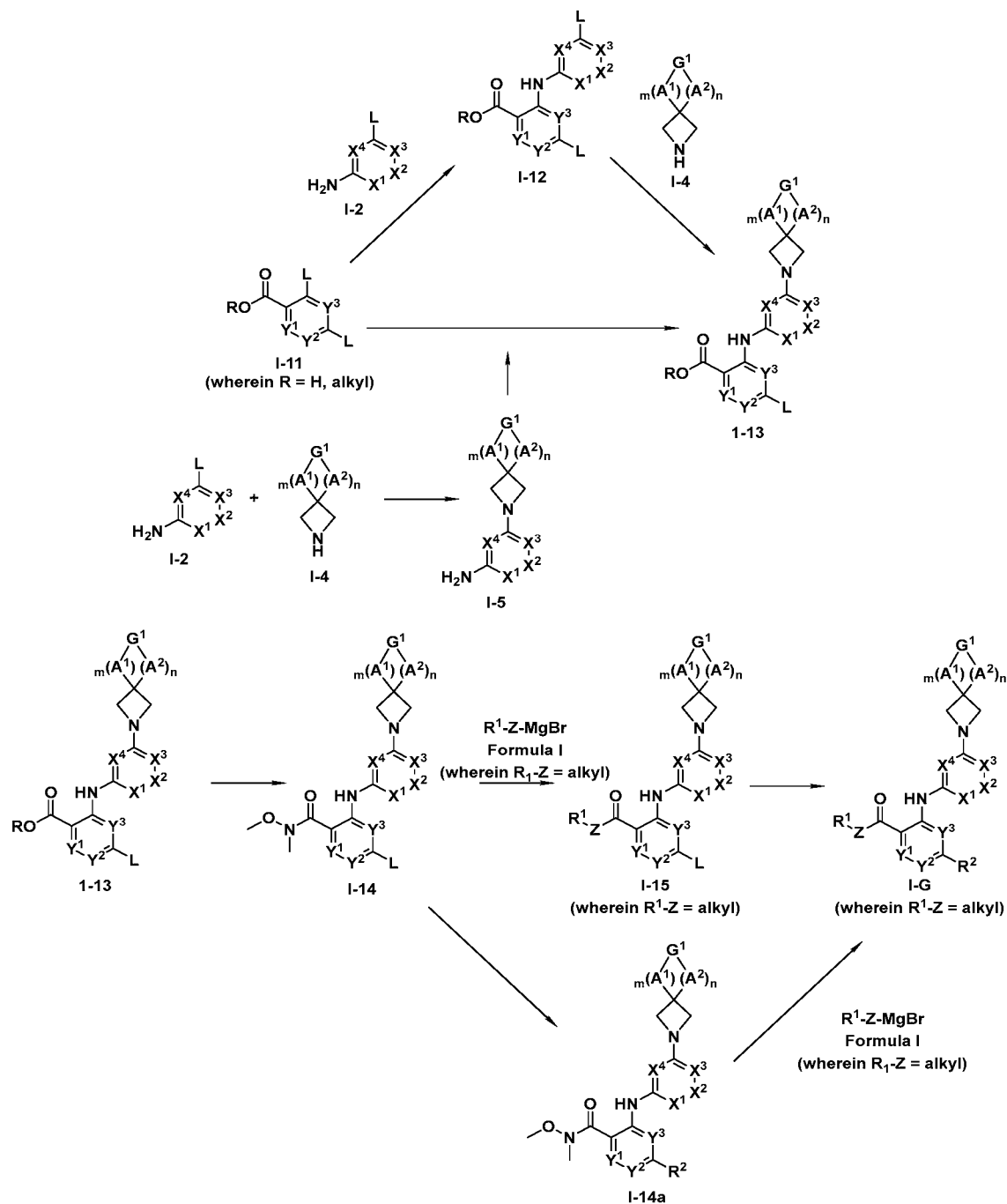
General scheme 2:

[000135] In general scheme 2, compound I-1 is converted to compound I-7 by following similar procedure as described in scheme 1 for preparing compound A from compound 1-6. The compound of the Formula I-7 is further reacted with compound of formula I-2 to give compound I-8 by following similar procedure as described in scheme 1 for preparing compound I-3 from compound I-1. Alternatively compound of formula I-3 is converted in to compound of formula I-8 by following similar procedure as described in scheme 1 for preparing compound A from compound 1-6. Compound I-8 is further converted to compound A by following similar procedure as described in scheme 1 for preparing compound I-6 from compound I-3. Alternatively, compound A is also be prepared by reacting compound I-7 with compound 1-5 by following similar procedure as described in scheme 1 for preparing compound I-6 from compound I-1 and compound 1-5.

General scheme 3:

[000136] In general scheme 3, compound I-9 is converted to compound I-10 (wherein L represents leaving group such as halogen) by treating with oxalyl chloride or phosphorous oxychloride in suitable solvent, such as but not limited to DCM or by treating with N,N'-CDI in suitable solvent, such as but not limited to THF, at suitable temperature such as but not limited to, from room temperature to reflux temperature until desired conversion is achieved followed by reacting with N,O -Dimethylhydroxylamine hydrochloride in presence of suitable base, such as but not limited to DIPEA and a suitable solvent, such as but not limited to THF. Compound I-10 is converted to compound I-1 by reacting with grignard or organolithium reagent of formula $\text{R}^1\text{-Z-MgBr}$ in presence of suitable base, such as but not limited to, triethylamine and a suitable solvent, such as but not limited to THF. Further, compound I-1 is converted to compound A by following similar procedure as described in general schemes provided herein. Compounds of Formula I-9 are commercially available.

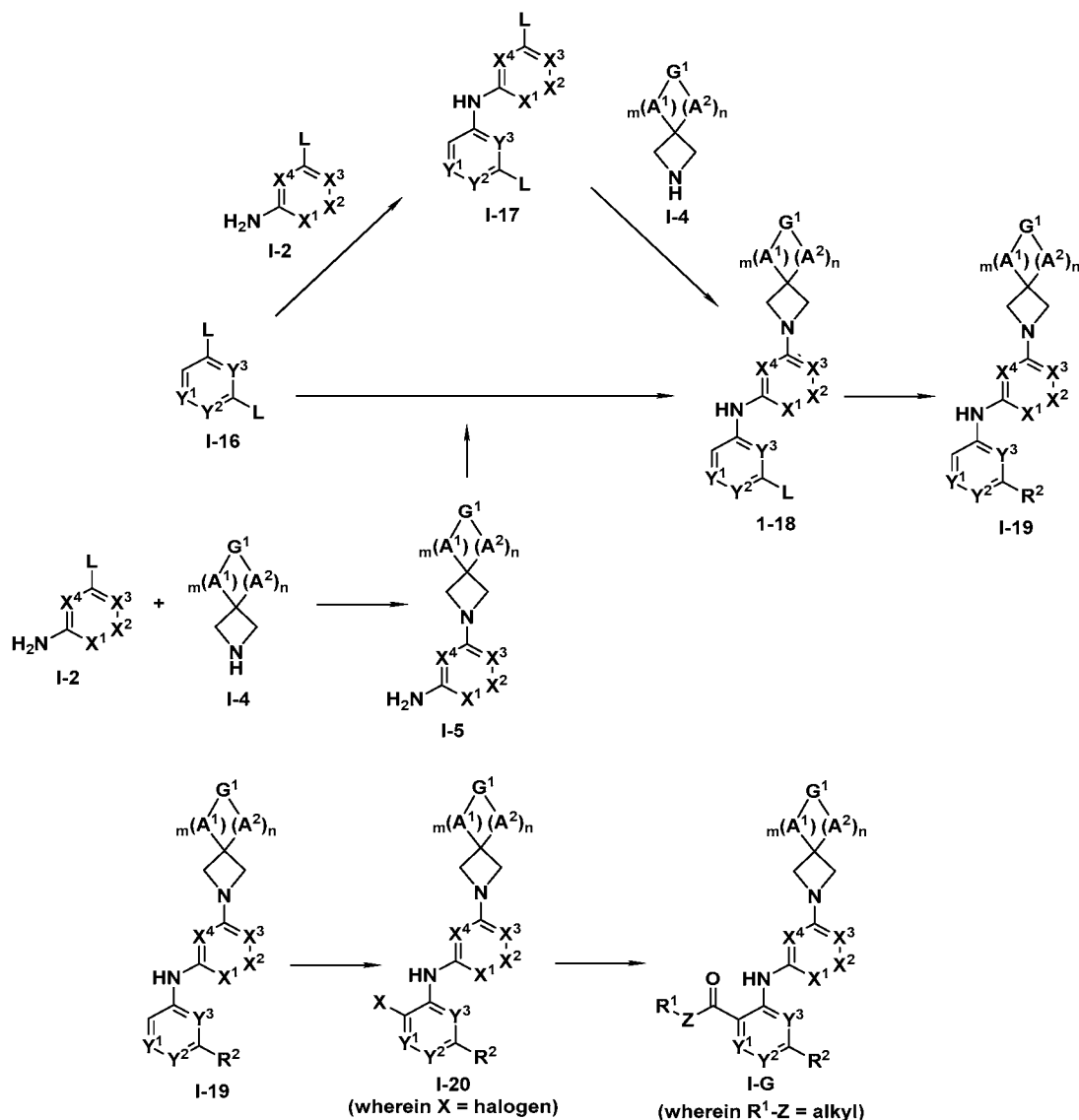
General scheme 4:



[000137] In general scheme 4, compound I-11 (wherein L represents leaving group such as halogen) is converted to compound I-12 by following similar procedure as described in scheme 1 for preparing compound I-3 from compound I-1. The compound of the Formula I-12 is further reacted with compound of formula I-4 to give compound I-13 by following similar procedure as described in scheme

1 for preparing compound I-6 from compound I-3. Alternatively, compound I-13 is also be prepared by reacting compound I-11 with compound 1-5 by following similar procedure as described in scheme 1 for preparing compound I-6 from compound I-1 and compound 1-5. Compound I-13 is converted to compound 1-14 by treating with oxalyl chloride in suitable solvent, such as but not limited to DCM or by treating with N,N'-CDI in suitable solvent, such as but not limited to THF, at suitable temperature such as but not limited to, from room temperature to reflux temperature until desired conversion is achieved followed by reacting with N,O - Dimethylhydroxylamine hydrochloride in presence of suitable base, such as but not limited to DIPEA and a suitable solvent, such as but not limited to THF. Compound I-14 is converted to compound 1-15 by reacting with grignard or organolithium reagent of formula $R^1-Z-MgBr$ in presence of suitable base, such as but not limited to, triethylamine and a suitable solvent, such as but not limited to THF. Compound I-15 is further converted to compound A by following similar procedure as described in scheme 1 for preparing compound A from compound I-6. Alternatively compound of formula I-14 is converted into compound of formula I-14a by following similar procedure as described for preparing compound A from compound I-16, which is further converted into compound of formula A by following similar procedure as described for preparing compound I-15 from compound I-14.

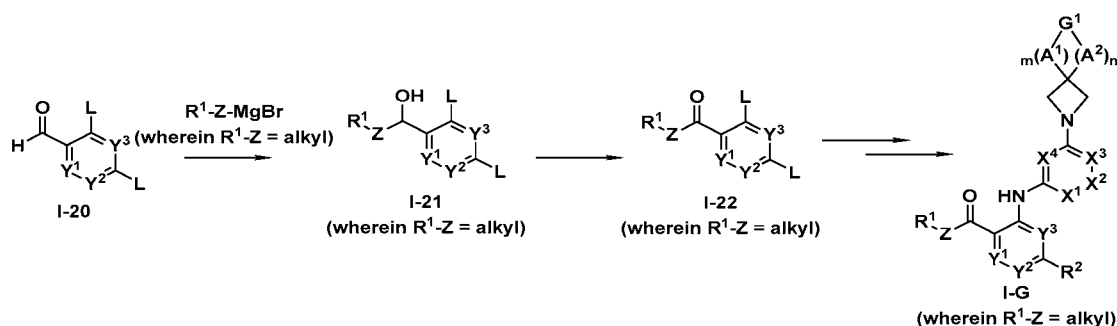
General scheme 5:



[000138] In general scheme 5, the compound of the Formula I-16 (wherein L represents leaving group such as halogen) is reacted with compound of formula I-2 to give compound I-17 by following similar procedure as described in scheme 1 for preparing compound I-3 from compound I-1. Compound I-17 is further converted to compound I-18 by following similar procedure as described in scheme 1 for preparing compound I-6 from compound I-3. Alternatively, compound I-18 is also be prepared by reacting compound I-16 with compound 1-5 by following similar procedure as described in scheme 1 for preparing compound I-6 from compound I-1 and compound 1-5. Further, compound I-18 is converted to

compound I-19 by following similar procedure as described in scheme 1 for preparing compound A from compound I-6. Compound I-19 is further converted to compound I-20 by treating with halogenating reagent such as N-bromosuccinimide or N-chlorosuccinimide in suitable solvent such as but not limited to DCM, THF, EtOAc, DMF. A palladium-mediated Heck reaction of compound I-20 with an alkyl substituted vinyl ether, followed by acid hydrolysis affords compound A.

General scheme 6:



[000139] In general scheme 6, compound I-20 (wherein L represents leaving group such as halogen) is converted to compound I-21 by reacting with Grignard or organolithium reagent of formula $R^1-Z-MgBr$ in presence of suitable base, such as but not limited to, triethylamine and a suitable solvent, such as but not limited to THF, at suitable temperature such as but not limited to, from room temperature to reflux temperature until desired conversion is achieved. Compound I-21 is converted to compound I-22 by reacting with suitable oxidizing agent such as but not limited to Dess–Martin periodinane, manganese dioxide in suitable solvent, such as but not limited to DCM. Further, compound I-22 is converted to compound A by following similar procedure as described in general scheme 1.

[000140] The routes described herein, including those mentioned in the Examples and Preparations, illustrate methods of synthesizing compounds of Formula (A). The skilled person will appreciate that the compounds of the invention, and intermediates thereto, could be made by methods other than those specifically described herein, for example by adaptation of the methods described herein, for example by methods known in the art such as use of protection-deprotection chemistry.

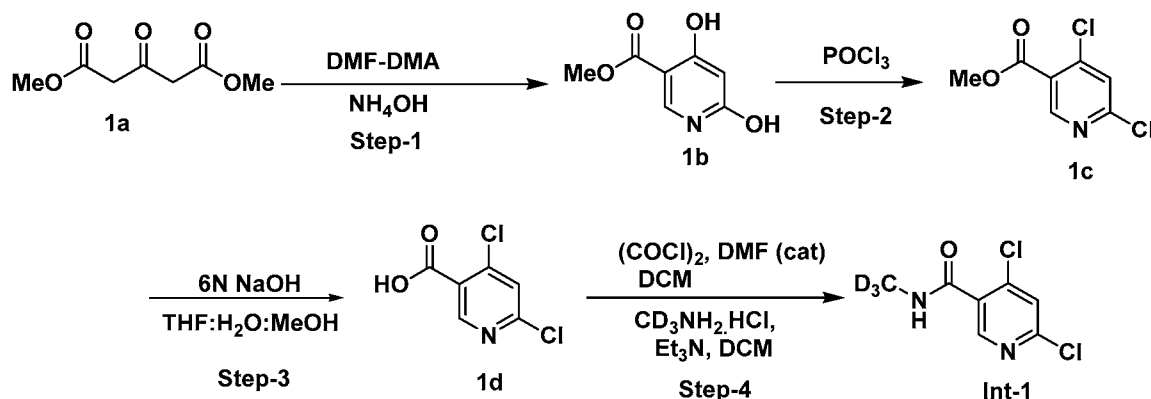
[000141] In the general synthetic methods described herein, unless otherwise specified, the substituents are as defined above with reference to the compounds of Formula (I) above.

[000142] The suitable solvent used for the above schemes may be selected from the one which does not affect the course of the reaction, that includes but not limited to DMSO, DMAc, NMP, DMF, sulfolane, diglyme, ketone, alcohol, halogenated hydrocarbon, ether, ester and the like or mixtures thereof.

[000143] The suitable base used for the above schemes may be selected from inorganic base or organic base such as but not limited to alkali metal hydroxides such as sodium or potassium hydroxide or alkali metal carbonates such as sodium or potassium carbonate or caesium carbonate or sodium or potassium methoxide or sodium or potassium ethoxide or potassium tert-butoxide or amides such as sodium amide, lithium bis (trimethylsilyl) amide or lithium diisopropylamide or amines such as triethylamine, diisopropylethylamine, diisopropylamine, 4-N, N-dimethylaminopyridine or pyridine.

[000144] It will be further appreciated that it may be necessary or desirable to carry out the transformations in a different order from that described in the schemes, or to modify one or more of the transformations, to provide the desired compound of the invention. The schemes are representative of methods useful in synthesizing the compounds of the present invention. They are not to constrain the scope of the invention in any way.

[000145] The following non-limiting Preparations and Examples illustrate the preparation of compounds of the present invention. The corresponding non-deuteriated intermediates may be prepared by using methyl amine instead of CD_3NH_2 .

Examples:**Preparation 1: Synthesis of Int-1 (Intermediate 1)****Step 1: synthesis of 1b**

[000146] Dimethyl 3-oxopentanedioate **1a** (184 g, 1.05 mol) was added to DMF-DMA (170 mL, 1.3 mol) at 25-30°C, the reaction mixture was heated to 90°C and stirred until completion of reaction under removal of MeOH formed during the reaction by distillation (boiling point = ~ 62 - 64 °C). After completion of reaction, the reaction mixture was cooled to 0°C, treated with a 28% aq. NH₄OH solution (440 mL) and stirred for 15 min at the same temperature. The pH was adjusted from 10 to 1 by addition of 6N HCl (500 mL) at 0°C. The resulting precipitate was collected by filtration, washed with H₂O, and dried to give **1b** (125 g, 70%) as a light yellow solid.

Step 2- synthesis of 1c:

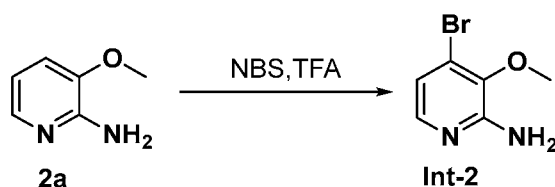
[000147] A suspension of **1b** (22.9 g, 0.135 mol) in POCl₃ (230 mL) was heated to 90 °C and stirred until completion of reaction. After completion of reaction, the reaction mixture was concentrated under reduced pressure. The residue was cooled to 0 °C, treated with crushed ice to quench the excess of POCl₃ and treated with additional H₂O (200 mL). After extraction of the reaction mixture with ethyl acetate, the ethyl acetate layer was washed with 2N NaOH followed by brine, dried over anhydrous Na₂SO₄, and concentrated to give **1c** (20.1 g, 72%) as a brown crystalline solid.

Step 3- synthesis of 1d:

[000148] To a solution of chloropyridine **1c** (28 g, 0.135 mol) in a mixture of THF (480 mL), MeOH (110 mL), and H₂O (110 mL); 5N NaOH (50 mL) was added at 25-30°C and the reaction mixture was stirred until completion of reaction. After completion of reaction, the pH of reaction mixture was adjusted from 10 to 2 by addition of 12N HCl (50 mL) and extracted with a 1:1 mixture of ethyl acetate and diethylether. The organic layer was washed with H₂O followed by brine, dried over anhydrous Na₂SO₄, and concentrated to give **1d** (25 g,) as a white crystalline solid.

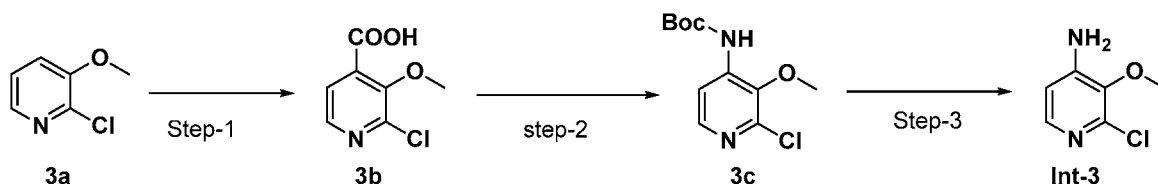
Step 4- synthesis of Int-1:

[000149] To a slurry of **1d** (5 g, 20.05 mmol, and 1.0 eq.) in DCM (80 mL), Oxalyl chloride (2.96 mL, 33.85 mmol, 1.7 eq.) was added at 25-30°C followed by 10-15 drops of DMF. The reaction mixture was stirred at 25-30°C for 1.5 h to form a nearly clear solution. The reaction mixture was concentrated under nitrogen, the residue was dissolved in DCM (30 mL) and re-concentrated and the process was repeated to ensure complete removal of the excess oxalyl chloride. The resulting crude acid chloride was dissolved in DCM (100 mL) and methyl-d₃-ammonium chloride (2.39 g, 33.85 mmol, 1.7 eq.) was added, the reaction mixture was cooled in an ice bath and diisopropylethylamine (13.65 mL, 78.17 mmol, 2.3 eq.) was added dropwise. After the addition was complete, the ice bath was removed and the resulting mixture was stirred at 25-30°C until completion of reaction. After completion of reaction, the reaction mixture was extracted with DCM, the DCM layer was washed with 1 N aq. HCl followed by brine, dried over anhydrous Na₂SO₄, and concentrated to give **Int-1** (2.7 g) as an off-white solid which was purified by silica gel flash column chromatography to give 4,6-dichloro-N-(methyl-d₃)nicotinamide as white solid.

Preparation 2: Synthesis of Int-2 (Intermediate 2)

[000150] To a stirred solution of **2a** (10 g, 80.64 mmol) in trifluoroacetic acid (200 mL), N-bromosuccinamide (15.7g, 88.70 mmol) was added at 0°C, and the reaction mixture was stirred at 25-30°C until completion of reaction.. After completion of reaction, the reaction mixture was concentrated under vacuum at low bath temperature, diluted with water and extracted with ethyl acetate. The ethyl acetate layer was washed with brine solution, dried over anhydrous Na₂SO₄, and concentrated under vacuum. The crude compound was purified by silica gel flash column chromatography to afford 7.5g of compound Int-2 as an off-white solid.

Preparation 3: Synthesis of Int-3 (Intermediate-3)



Step-1: synthesis of 3b

[000151] To a stirred solution of **3a** (10g, 69.47 mmol) in dry THF (300 mL), lithium diisopropylamide (2M in THF 52.3 mL, 104.62 mmol) was added at -78°C and the reaction mixture was stirred at 78°C for 90 min, then dry ice powder was added in to the reaction mixture at -78°C for portion wise, and reaction mixture was stirred at 25-30°C until completion of reaction. After completion of reaction, the reaction mixture was poured in to cold diluted HCl and white precipitate was observed, which was filtered to afford 6.9g of **3b** as white solid.

Step-2: synthesis of 3c

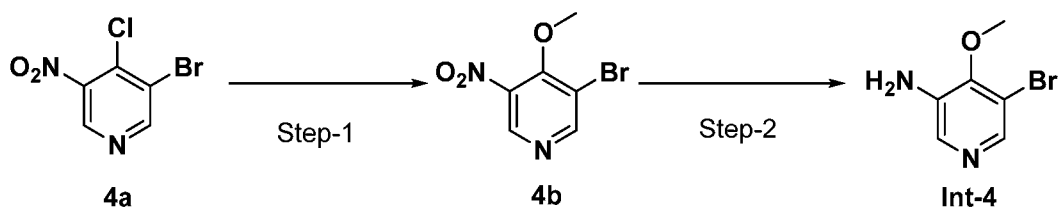
[000152] To a stirred solution of **3b** (6 g, 32.08 mmol) in t-butanol (200 mL), triethylamine (13.5 mL, 96.25 mmol) was added, then diphenylphosphoryl azide (10.3 mL, 48.12 mmol) was added subsequently at 25-30°, and reaction mixture was stirred at 80°C until completion of reaction. After completion of reaction, the reaction mixture was cooled to 25-30°C, concentrated under reduced pressure, diluted with water and extracted with ethyl acetate. The ethyl acetate was washed with brine solution, dried over anhydrous Na₂SO₄, and concentrated to give crude

compound which was purified by silica gel flash column chromatography to afford 8.75g of **3c** as colourless liquid.

Step-3: synthesis of Int-3.

[000153] To a stirred solution of **3c** (8.75 g, 33.91mmol) in dioxane (70mL), HCl in dioxane (20 mL) was added at 0°C and stirred at 25-30°C until completion of reaction.. After completion of reaction, the reaction mixture was concentrated under reduced pressure, basified with saturated NaHCO₃ solution, extracted with ethyl acetate. The ethyl acetate layer was washed with brine solution and dried over anhydrous Na₂SO₄, concentrated under vacuum to afford semi-pure compound, which was washed with 20% ethyl acetate in pet ether and dried under vacuum to afford 4.9 g of **Int-3** as white solid.

Preparation 4: Synthesis of Int-4 (Intermediate 4)



Step-1: synthesis of 4b

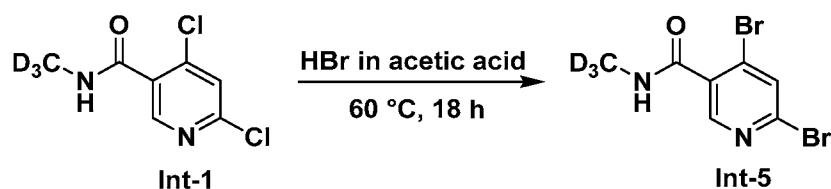
[000154] To a stirred solution **4a** (40 g, 168.46 mmol) in MeOH (400 mL), NaOMe (13.65 g, 252.69 mmol) was added sub-sequentially at 0°C, and stirred to room temperature till completion of reaction. The reaction mixture was diluted with water and extracted with MTBE, the organic layer was washed with cold brine solution, dried over anhydrous Na₂SO₄, and evaporated under reduced pressure. The crude compound **4b** (off white solid, 35 g, 89.17%) was used for next step without further purification.

Step-2: synthesis of 4

[000155] To a stirred solution compound **4b** (35 g, 150.21 mmol) in a mixture solution of EtOH and water (7:3) (350 mL), ammonium chloride (79.61 g, 1502.10 mmol) and iron powder (42.06 g, 751.05 mmol) were added sub-sequentially at room temperature stirred at 70 °C till completion of reaction. The reaction mixture was cooled to room temperature, excess iron powder was removed under celite

filtration and the organic layer was dried over anhydrous Na_2SO_4 , and evaporated under vacuum. The crude compound was purified by column chromatography over silica gel (100-200 mesh) by using gradient mixture of 50 to 70 % ethyl acetate/pet ether eluent to afford 21 g (68.88%, yield) of compound Int-4 as an off-white solid.

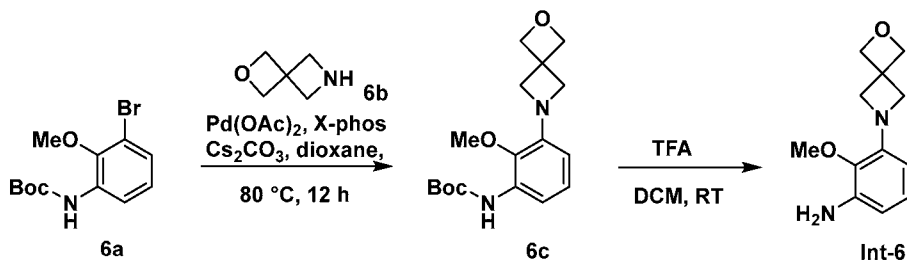
Preparation 5: Synthesis of Int-5 (intermediate 5)



Synthesis of Int-5

[000156] **Int-1** (5.0 g, 24.15 mmol) was suspended in hydrogen bromide (33% in Acetic Acid, 24 mL). The reaction vessel was sealed and heated to 60° C, until completion of reaction. After completion of reaction, the reaction mixture was cooled to 25-30°C and diluted with H_2O . The resulting solids were filtered and washed with H_2O . The solids were then suspended in H_2O , basified with aqueous sodium hydroxide, and extracted with ethylacetate. The ethylacetate layer was, dried over anhydrous Na_2SO_4 , and concentrated to provide **Int-5** (5 g, 71%) as an off white solid.

Preparation 6: Synthesis of Int-6 (Intermediate 6)



Step-1: synthesis of 6c

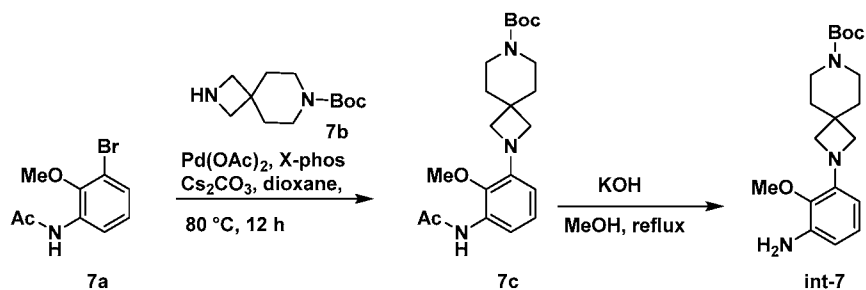
[000157] To the solution of 6a (1.0 g, 1.0 mmol) and 6b (0.328 mg, 1.0 mmol) in dioxane (5 mL) was added $\text{Pd}(\text{OAc})_2$ (0.089 mg, 10 mol%), X-Phos (190 mg, 10 mol%) and Cs_2CO_3 (3.20 g, 3.0 mmol) and the resulting solution was heated at 120°C until completion of reaction. After completion of reaction, the reaction

mixture was filtered through celite. The filtrate was concentrated and purified by silica gel flash column chromatography to give **6c** (0.900 g).

Step-2: synthesis of Int-6

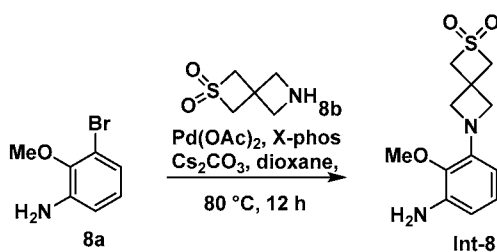
[000158] To a solution of **6c** (0.900, 2.81 mmol) in DCM (5 mL) was added TFA (excess) at 0°C. The reaction mass was stirred at 25-30°C until completion of reaction. After completion of reaction, the reaction mixture was concentrated and purified with silica gel flash column chromatography to give Int-6 (500 mg, 80%) as yellow solid.

Preparation 7: Synthesis of Int-7 (Intermediate 7)

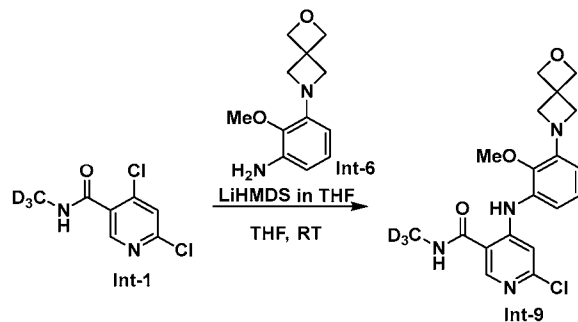


[000159] Int-7 was prepared from **7a** using procedure described for the synthesis of compound **Int-6** (300 mg, 59%).

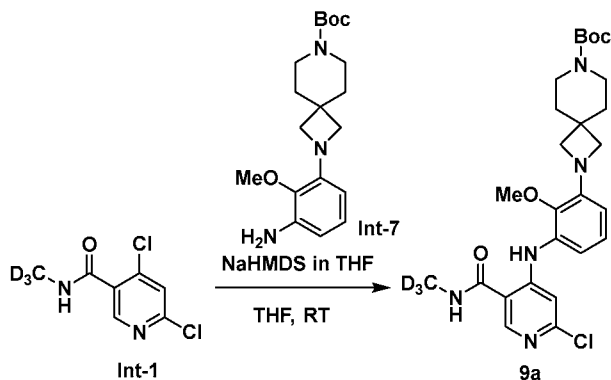
Preparation 8: Synthesis of Int-8 (Intermediate 8)



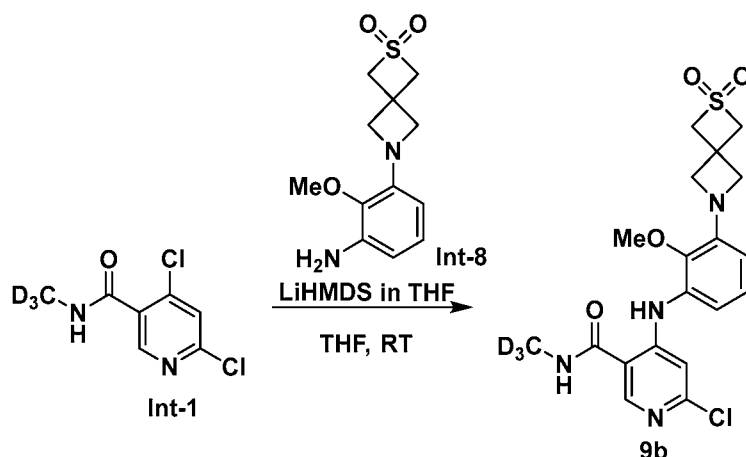
[000160] Int-8 was prepared from **8a** using procedure described for the synthesis of compound **6c** (200 mg, 39%).

Preparation 9: Synthesis of Int-9 (Intermediate 9)

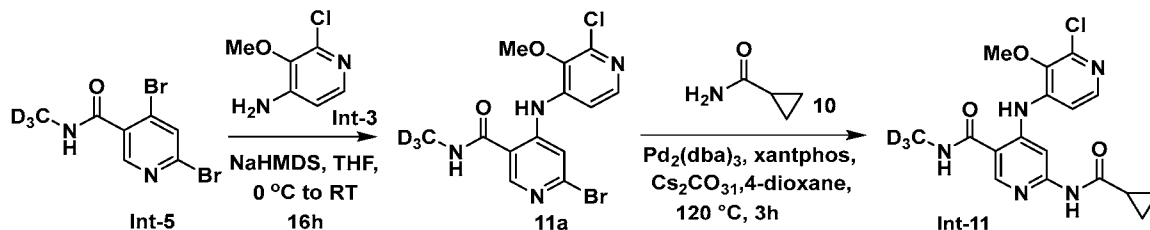
[000161] To a solution of Int-1 (0.584, 2.81mmol) and Int-6 (0.938, 2.81 mmol) in dry THF, LiHMDS (8.5 mL, 8.43 mmol) solution was added and the mixture was stirred at 25-30°C until completion of reaction. After completion of reaction, the reaction mixture was transferred into water and extracted with ethyl acetate. Aqueous layer was acidified with 1.0 N HCl and extracted with ethyl acetate. Ethyl acetate layer was, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography to afford Int- 9 (0.190 g, 30%) as a yellow solid.

Preparation 10: Synthesis of Int-9a (Intermediate 9a)

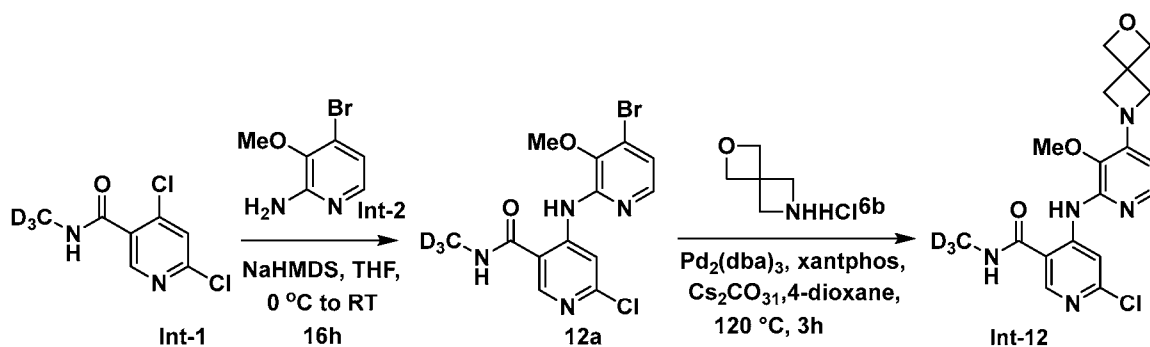
[000162] **Int 9a** was prepared from compound Int-1 and Int-7 using procedure described for synthesis of **Int-9**.

Preparation 11: Synthesis of Int-9b (Intermediate 9b)

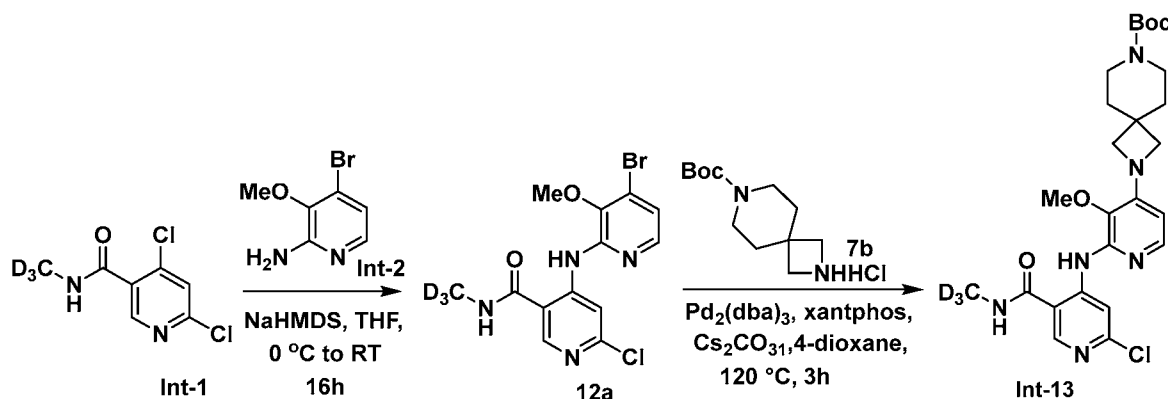
[000163] Int 9b was prepared from compound Int-1 and Int-8 using procedure described for synthesis of Int-9.

Preparation 12: Synthesis of Int-11 (Intermediate 11)

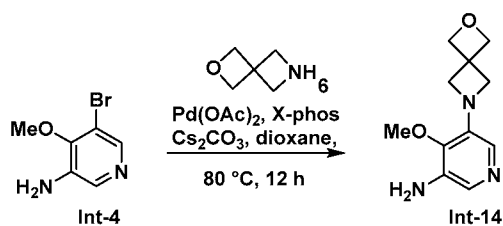
[000164] Int-11 (0.800 g, 80 %) as off-white solid was prepared from compound Int-5 and Int-3 using procedure described for synthesis of compound 1

Preparation 13: Synthesis of Int-12 (Intermediate 12)

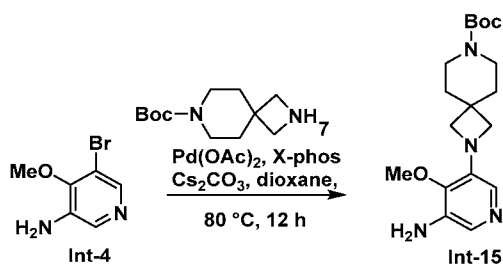
[000165] Int-12a was prepared from Int-1 and Int-2, which was converted to Int-12 (0.1 g, 38 %) using procedure described for synthesis of 6c as yellow solid.

Preparation 14: Synthesis of Int-13 (Intermediate 13)

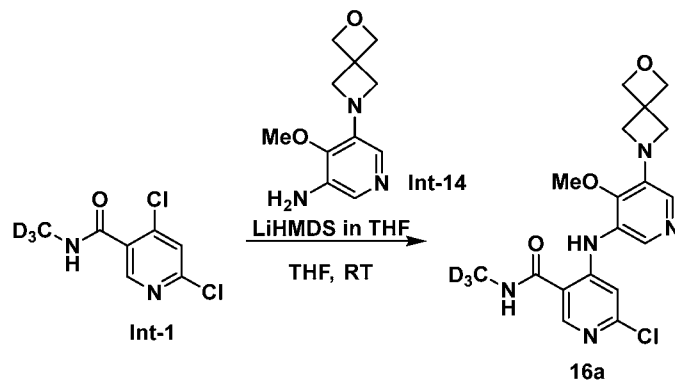
[000166] Int-13a was prepared from Int-1 and Int-2 which was converted to Int-13 (0.03 g, 27 %) as yellow solid using procedure described for synthesis of 7c.

Preparation 15: Synthesis of Int-14 (Intermediate 14)

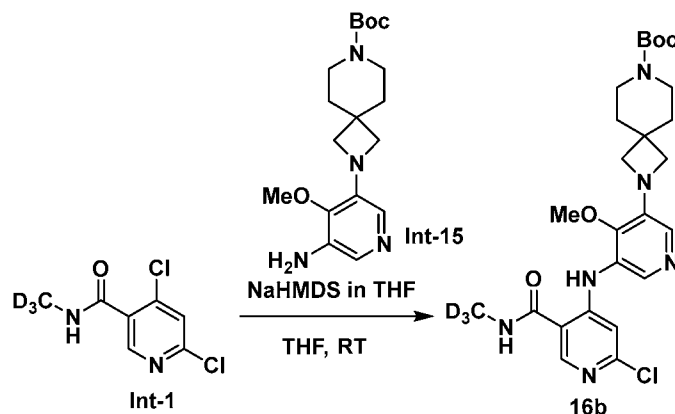
[000167] Int-14 (300 mg, 39%) was prepared from Int-4 and 6a using procedure described for the synthesis of compound 6c.

Preparation 16: Synthesis of Int-15 (Intermediate 15)

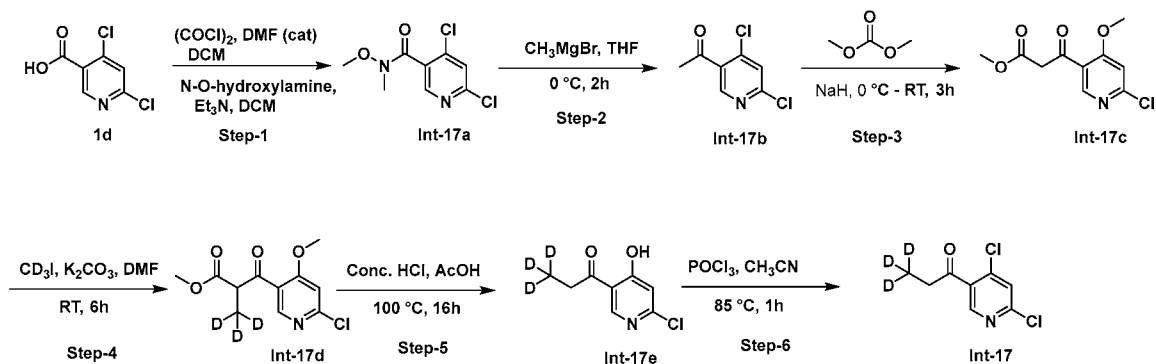
[000168] Int-15 (0.5g, 37%) as brown solid was prepared from int-4 and 7 using procedure described for the synthesis of 6c or 7c.

Preparation 17: Synthesis of Int-16a (Intermediate 16a)

[000169] Int 16a was prepared from compound Int-1 and Int-14 using procedure described for synthesis of Int-9.

Preparation 18: Synthesis of Int-16b (Intermediate 16b)

[000170] Int 16b was prepared from compound Int-1 and Int-15 using procedure described for synthesis of Int-9.

Preparation 19: Synthesis of Int-17 (Intermediate 17)

Step 1: synthesis of 17a

[000171] To a slurry of **1d** (12 g, 15.6 mmol, 1.0 eq.) in dichloromethane (120 mL) at room temperature was added oxalyl chloride (6 mL, 47.5 mmol, 3 eq.) followed by 10-15 drops of DMF causing some effervescence. The mixture was stirred at room temperature to form a nearly clear solution. The reaction was concentrated under nitrogen and the residue was dissolved in dichloroethane (50 mL) and re-concentrated and the process was repeated to ensure complete removal of the excess oxalyl chloride. The resulting crude acid chloride was dissolved in dichloromethane (100 mL) and N,O-Dimethylhydroxylamine hydrochloride (3 g, 31.6 mmol, 2 eq.) was added and the mixture was cooled in an ice bath, triethylamine (13.65 mL, 78.17 mmol, 2.3 eq.) was added dropwise via syringe. After the addition was complete, the ice bath was removed and the resulting mixture was allowed to warm to room temperature and stirred till completion of reaction. The mixture was extracted with dichloromethane, the organic layer was washed with 1 N aq. HCl, brine, dried over anhydrous Na₂SO₄, and concentrated under vacuum. to give off-white solid which was purified by silica gel flash column chromatography to give **17a** (12.2 g, 82%) as brown liquid

Step 2- synthesis of 17b:

[000172] Methylmagnesium chloride (3 M in THF), 37 mL, 113 mmol) was added portion wise to a stirred solution of **17a** (12 g, 51.5 mmol) in THF (100 mL) at 0 °C under nitrogen. The resulting suspension was stirred at 0 °C till completion of reaction. The reaction mixture was quenched with saturated aqueous NH₄Cl and extracted with EtOAc, the organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated to give **17b** (9.5 g, 98%) as white solid

Step 3- synthesis of 17c:

[000173] To a solution of **17b** (10.3 g, 54.8 mmol) in dimethyl carbonate (100 mL) was added NaH (3.9 g, 60% in mineral oil, 164.4 mmol) in portions at 0°C. The reaction mixture was stirred at room temperature till completion of reaction. The reaction mixture was quenched with 2 N aqueous HCl, extracted with EtOAc, the organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The

crude product was purified by silica gel flash column chromatography to give **17c** (7 g, 53%) as a white solid.

Step 4- synthesis of 17d:

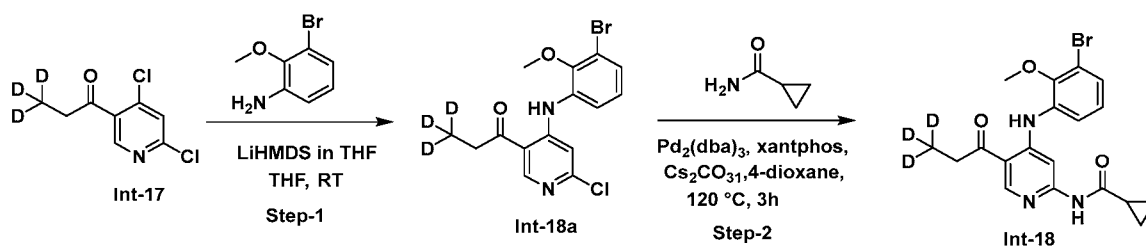
[000174] To a solution of **17c** (3 g, 12.34 mmol, 1.0 eq) and K_2CO_3 (1.5 g, 11.11 mmol) in DMF (50 mL) was added CD_3I (1.6 g, 11.11 mmol) at 0 °C. The reaction mixture was stirred at room temperature till completion of reaction. The mixture was extracted with EtOAc, the organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel flash column chromatography to give **17d** (2.7 g, 84%) as colorless oil.

Step 5- synthesis of 17e:

[000175] To a solution of **17d** (2.7 g, 10.38 mmol) in AcOH (20 mL) was added cone. HCl (40 mL). The reaction solution was heated at 100 °C till completion of the reaction. The reaction mixture was cooled to 25-30°C, concentrated, diluted with H_2O (20 mL) and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel flash column chromatography to give **17e** (1.1 g, 55%) as a white solid.

Step 6- synthesis of Int-17:

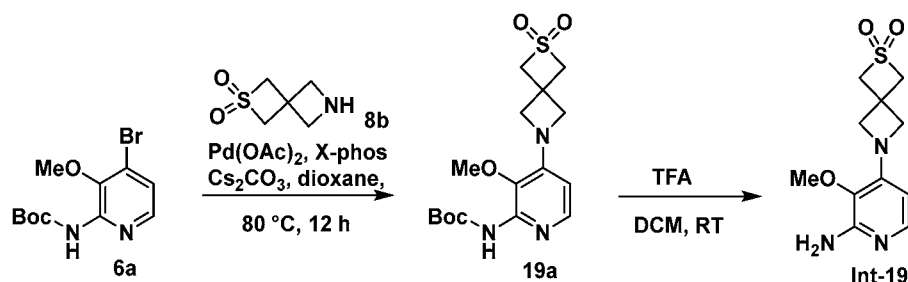
[000176] To a solution of **17e** (1.1 g, 5.85 mmol) in CH_3CN (15 mL) was added $POCl_3$ (2 mL). The reaction solution was heated at 85°C till the completion of reaction. The reaction mixture was cooled to 25-30°C, concentrated and diluted with EtOAc. The solution was added to a mixed solution of EtOAc and saturated aqueous $NaHCO_3$. After separation, the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel flash column chromatography to give **Int-17** (0.96 g, 80%) as a white solid.

Preparation 20: Synthesis of Int-18 (Intermediate 18)**Step 1: synthesis of 18a**

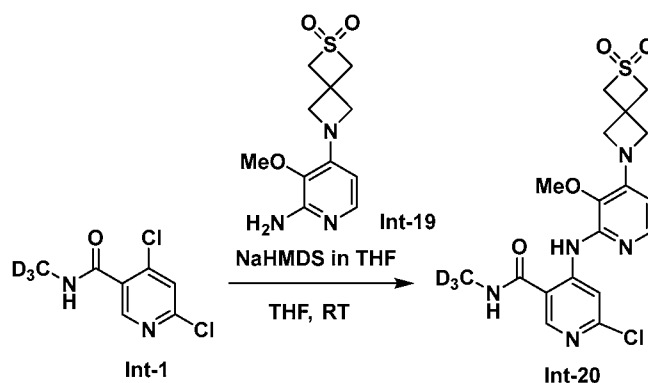
[000177] To a solution of **Int-17** (0.4 g, 1.94 mmol) and 3-bromo-2-methoxyaniline (0.47 g, 2.33 mmol) in dry THF. LiHMDS (0.97 g, 5.83 mmol) solution was added and the mixture was stirred at $25\text{--}30^\circ\text{C}$ till completion of reaction. After completion of reaction, the reaction mixture was transferred into water and extracted with ethyl acetate. Aqueous layer was acidified with 1.0 N HCl and extracted with ethyl acetate. EtOAc layer was, washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography to afford **Int 18a** (0.57 g, 79%) as a yellow solid.

Step 2- synthesis of Int-18

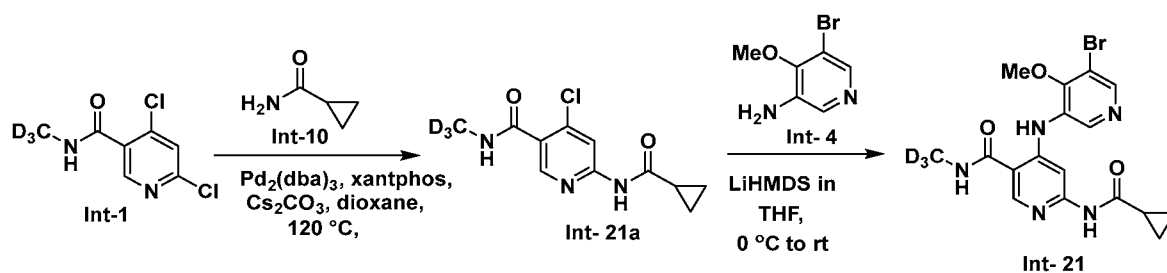
[000178] To a solution of **8** (0.25 g, 0.67 mmol) and cyclopropanecarboxamide (0.06 g, 0.67 mmol) in 1,4-dioxane (3 ml) was added 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos, 0.06 g, 0.100 mmol), cesium carbonate (0.55 g, 1.68 mmol) and tris(dibenzylideneacetone)dipalladium(0) (Pd_2dba_3 , 0.093 g, 0.100 mmol). The reaction mixture was degassed by nitrogen for three times and then heated to 120°C till completion of reaction. After completion of reaction the reaction mixture was, filtered and filtrate was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography providing **Int 18** (0.09 g, 32 %) as yellow solid.

Preparation 21: Synthesis of Int-19 (Intermediate 19)**Step 1: synthesis of 19a**

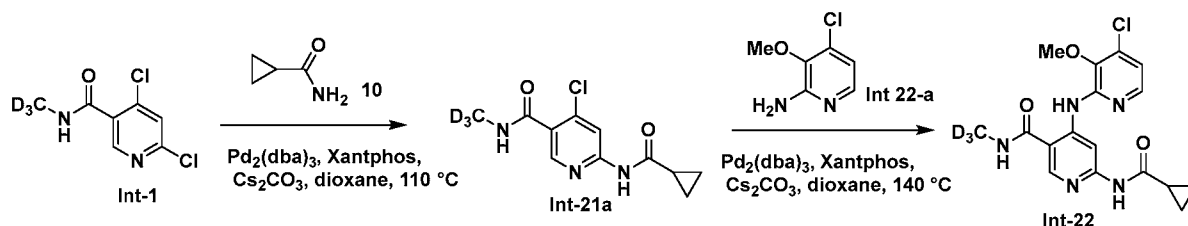
[000179] Int-19 was prepared from **6a** using procedure described for the synthesis of compound Int-6.

Preparation 22: Synthesis of Int-20 (Intermediate 20)

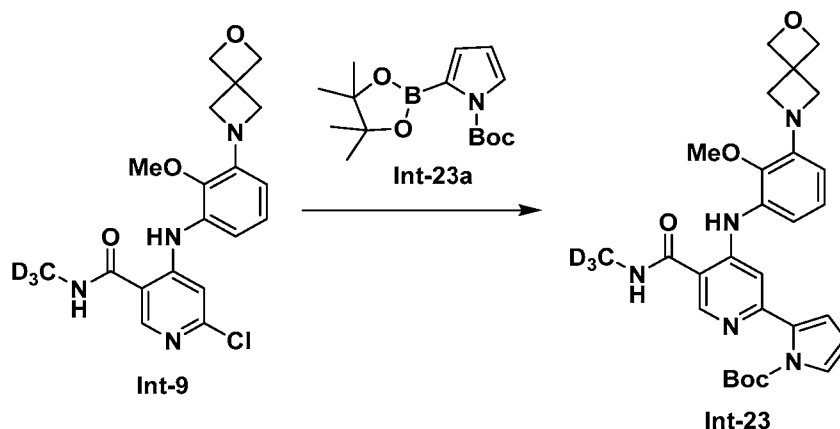
[000180] Int 20 was prepared from compound Int-1 and Int-19 using procedure described for synthesis of Int-9

Preparation 23: Synthesis of Int-21 (Intermediate 21)

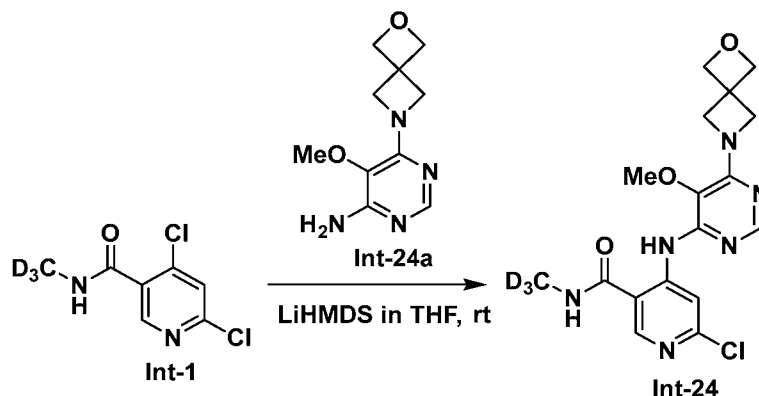
[000181] Int 21a was prepared from Int-1 and Int-10, using procedure described for synthesis of compound 1 which was converted to Int-21 using procedure described for synthesis of Int-9 (0.9 g, 54.55 %) as pink solid.

Preparation 24: Synthesis of Int-22 (Intermediate 22)

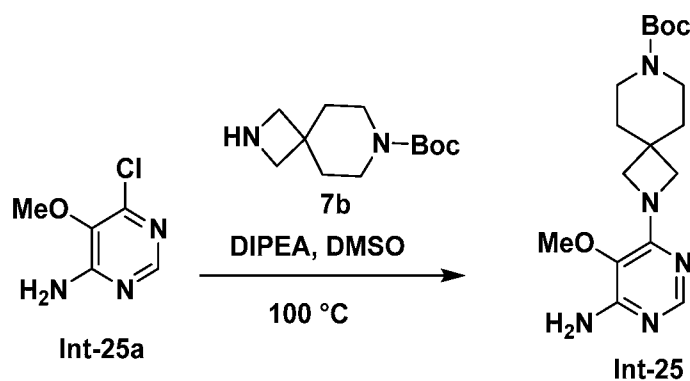
[000182] **Int 21a** was prepared from **Int-1** and **Int-10**, which was converted to **Int-22** using procedure, described for synthesis of compound 1 as pale-yellow solid (1.9 g, 38.99%).

Preparation 25: Synthesis of Int-23 (Intermediate 23)

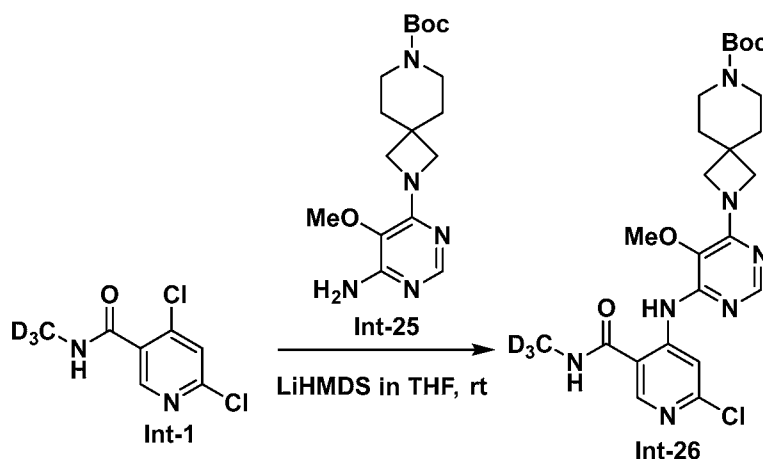
[000183] To a solution of **Int-9** (0.35 g, 0.89 mmol) and Pyrrole boronic acid **Int-23a** (0.76 g, 1.78 mmol) in mixture of 1,4-dioxane (6 ml) and water (0.22 ml) was added K_2CO_3 (0.36 g, 2.67 mmol). The mixture was degassed by Nitrogen and then charged $Pd(dppf)Cl_2 \cdot DCM$ (0.20 g, 0.2 mmol). The reaction mixture was heated to 110°C till completion of reaction. After completion of reaction, the insoluble materials were removed by filtration through celite and the solvent of the filtrate was evaporated under reduced pressure and crude purified using silica gel column chromatography, providing **Int-23**.

Preparation 26: Synthesis of Int-24 (Intermediate 24)

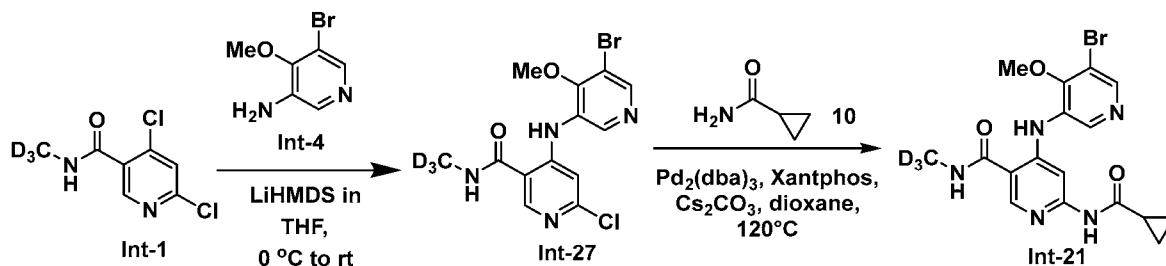
[000184] Int 24 was prepared from Int-1 and Int-24a using procedure described for synthesis of Int-9 (0.40 g, 35.1 %).

Preparation 27: Synthesis of Int-25 (Intermediate 25)

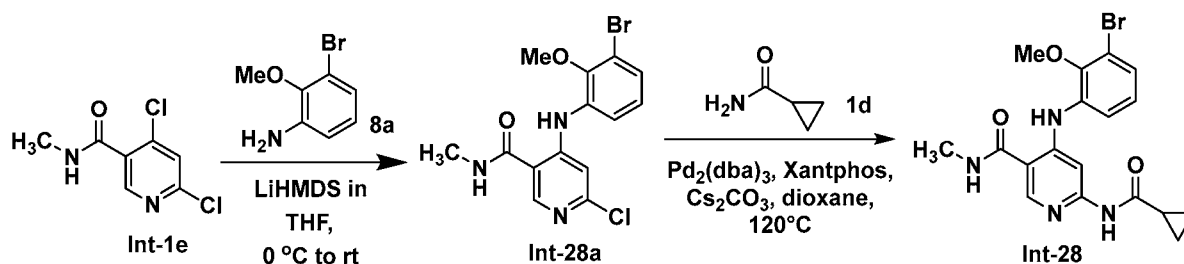
[000185] To the solution of Int-25a (0.30 g, 1.88 mmol) in DMSO (5 mL) was added DIPEA (2 mL) at rt. 7b (0.59 g, 2.2 mmol) was added after 15 min and the resulting solution was heated at 100 °C for 12 hr. After completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The filtrate was concentrated and purified by silica gel flash column chromatography to give Int-25 (0.29 g, 44%).

Preparation 28: Synthesis of Int-26 (Intermediate 26)

[000186] Int-27 was prepared from compound Int-1 and Int-25 using procedure described for synthesis of Int-9 (0.6 g, 29.5%).

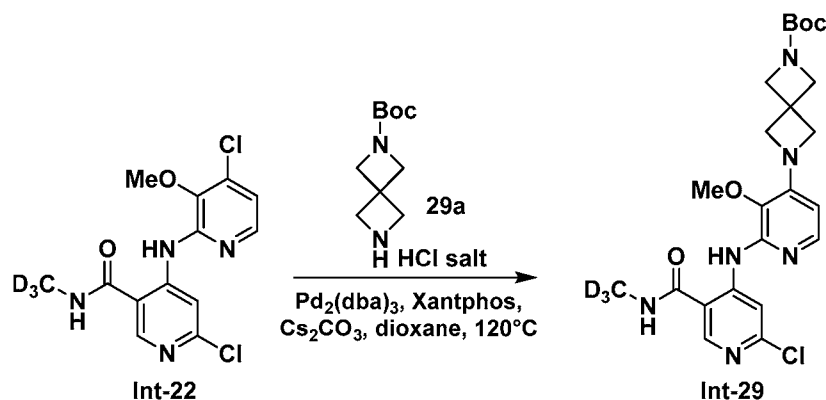
Preparation 29: Synthesis of Int-21 (Intermediate 21) using Int-27 (Intermediate 27)

[000187] Int-27 was prepared from Int-1 and Int-4 using procedure described for synthesis of compound 1, which was converted to Int-21 using procedure described for synthesis of Int-21a (0.04 g, 10.25 %) as light yellow solid.

Preparation 30: Synthesis of Int-28 (Intermediate 28)

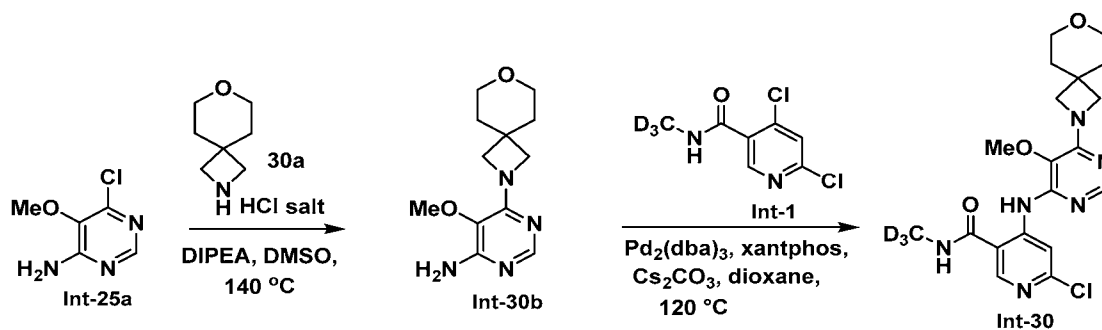
[000188] **Int-28a** was prepared from **Int-1e** and **8a**, which was converted to **Int-28** using procedure described for synthesis of **compound 1** (0.8 g, 36.4 %) as off-white solid.

Preparation 31: Synthesis of Int-29 (Intermediate 29)

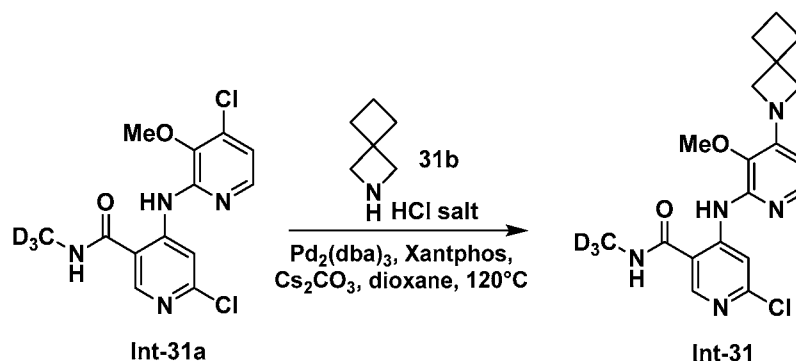


[000189] **Int-29** was prepared from **Int-22** and **29a** using procedure described for synthesis of **compound 1** (0.180 g, 45.80%) as yellow solid.

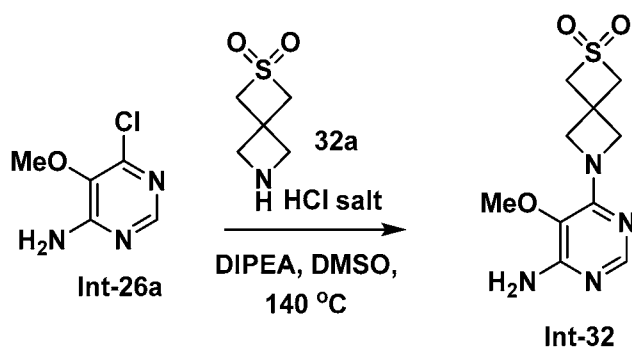
Preparation 32: Synthesis of Int-30 (Intermediate 30)



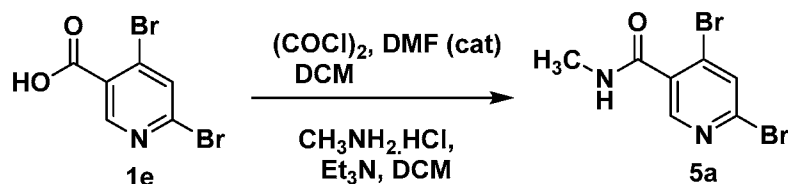
[000190] **Int-30b** was prepared from **Int-25a** and **30a**, which was converted to **Int-30** using procedure described for synthesis of **compound 1** (0.130 g, 21.4 %) as yellow liquid.

Preparation 33: Synthesis of Int-31 (Intermediate 31)

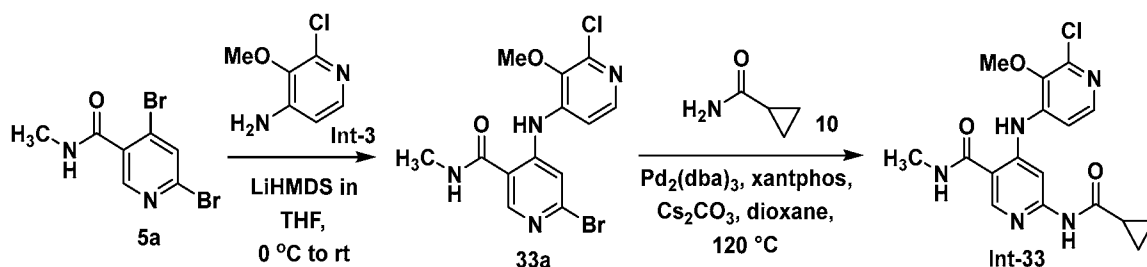
[000191] Int-31 was prepared from Int-31a and 31b using procedure described for synthesis of compound 1 (0.08 g, 25.64%) as yellow solid.

Preparation 34: Synthesis of Int-32 (Intermediate 32)

[000192] Int-32 was prepared from Int-26a and 32a using procedure described for synthesis of compound 1.

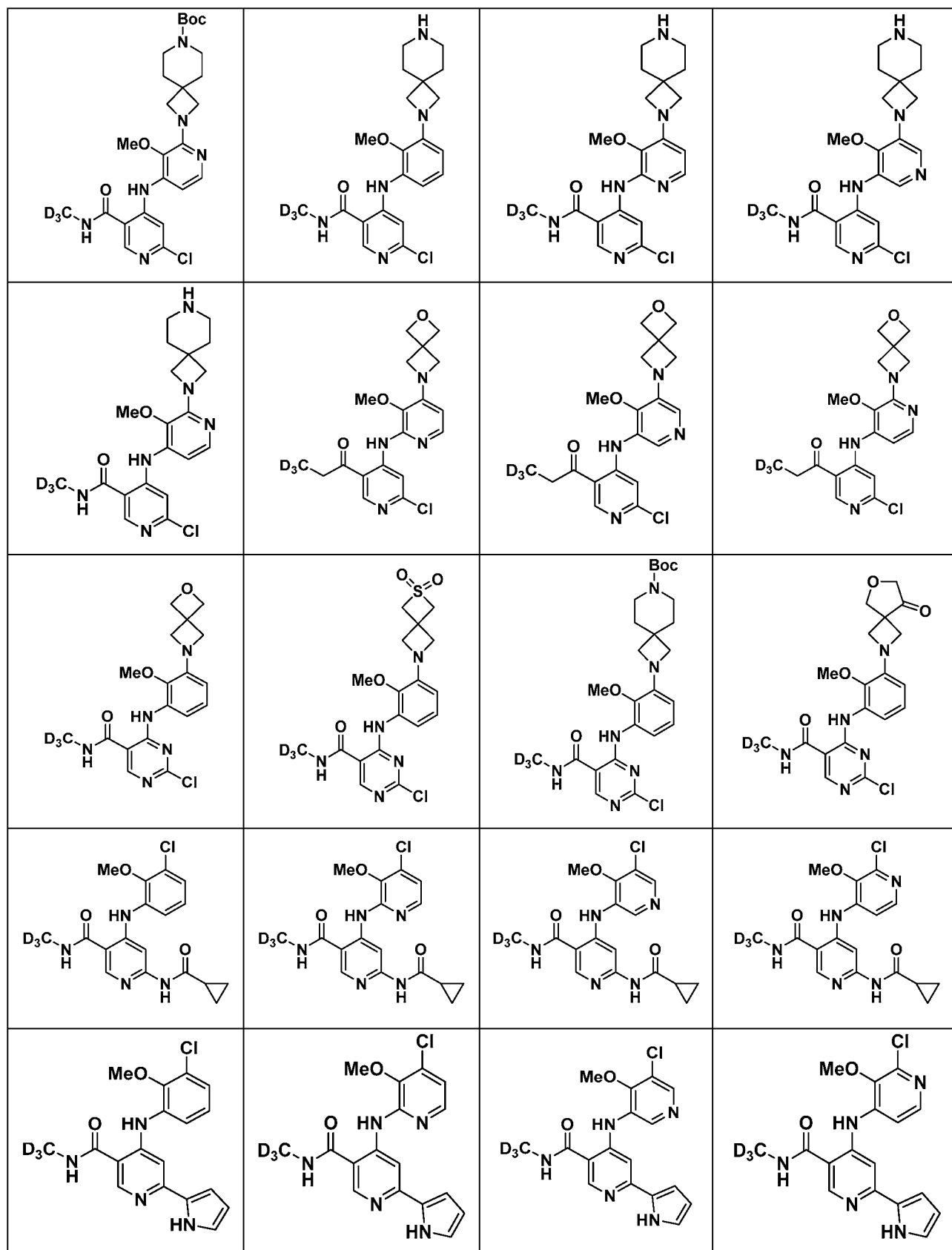
Preparation 35: Synthesis of Int-5a (Intermediate 5a)

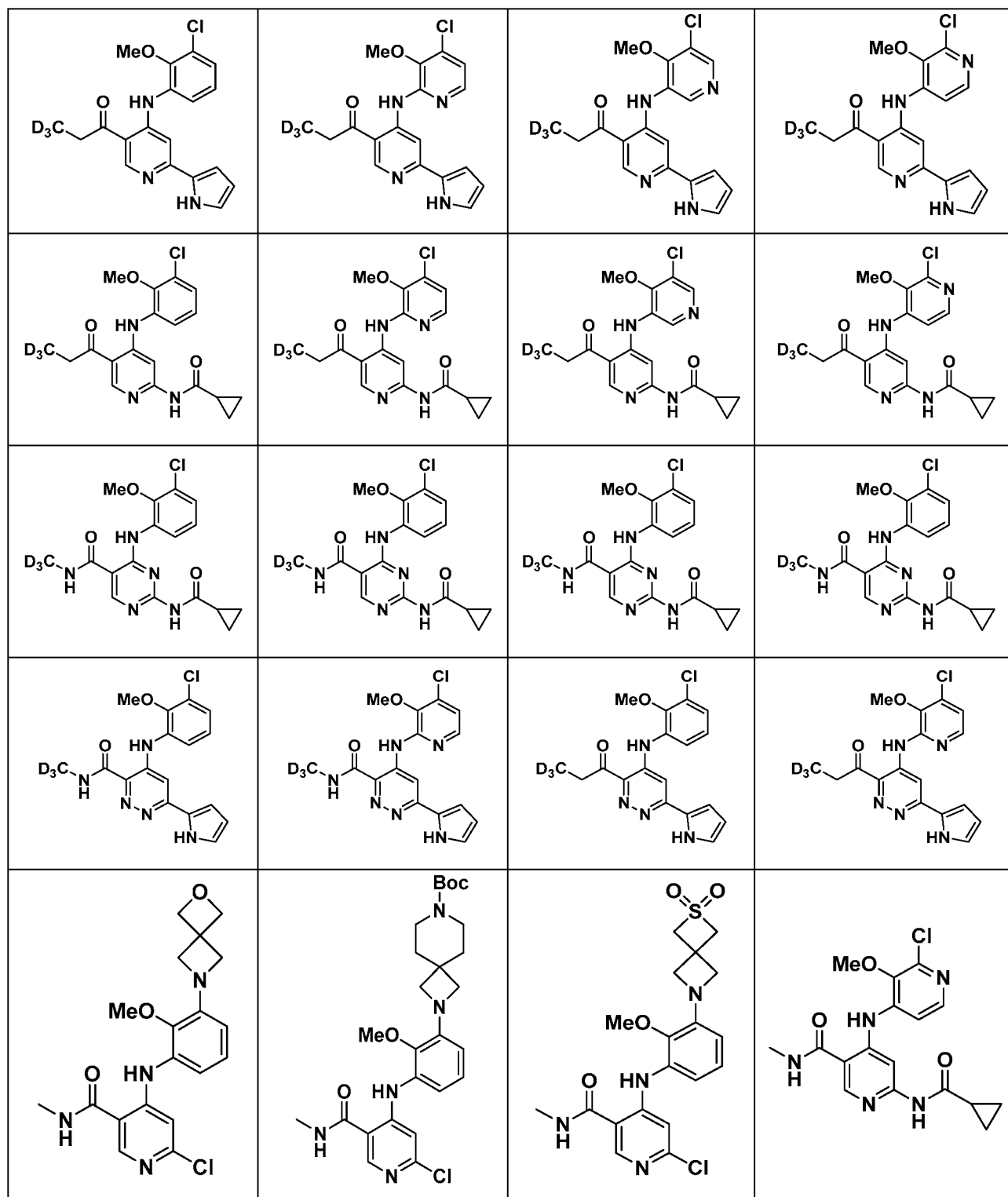
[000193] Int-32 was 5a was prepared from 1e using procedure described for synthesis of Int-1 (2.9g, 67.88%) off-white solid.

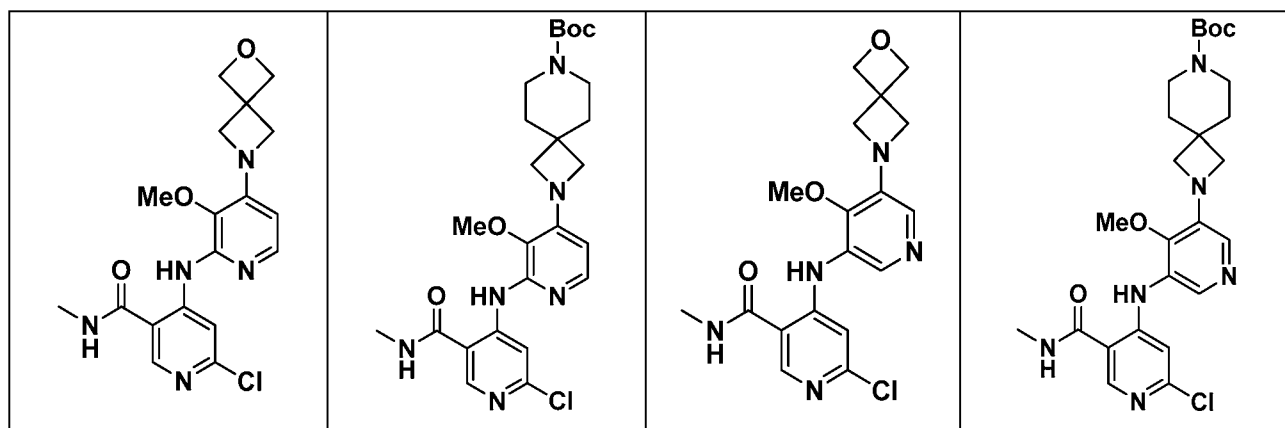
Preparation 36: Synthesis of Int-33 (Intermediate 33)

[000194] **Int-33a** was prepared from **5a** and **Int-3** using procedure described for **Int-9**, which was converted to **Int-33** using procedure described for synthesis of **compound 1** (6.0 g, 59.4 %) as light yellow solid.

[000195] The following intermediates may be prepared according to methods described herein using appropriate starting materials:

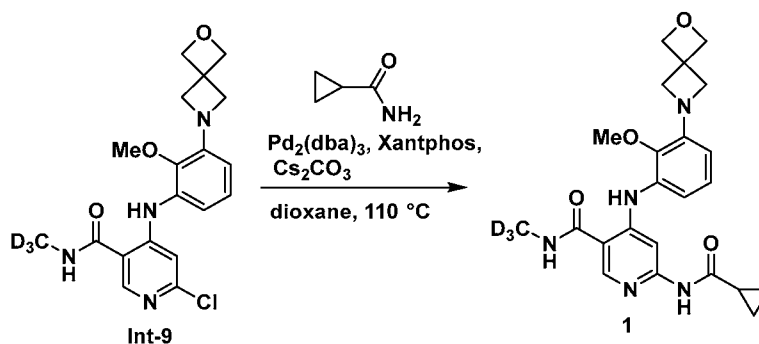






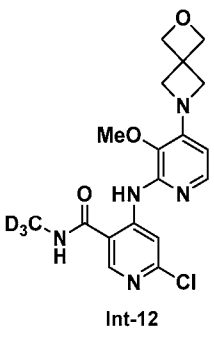
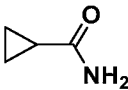
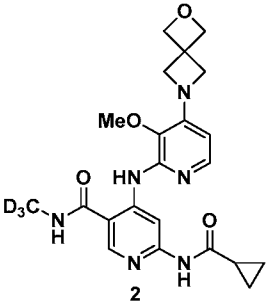
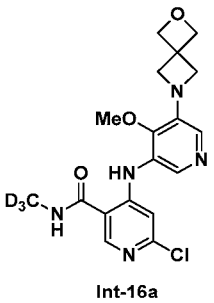
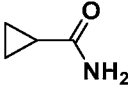
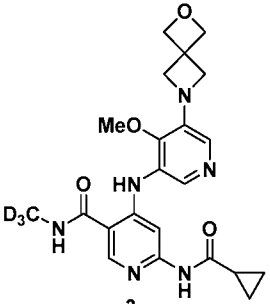
[000196] The corresponding non-deutriated intermediates may be prepared by using methyl amine instead of CD_3NH_2 .

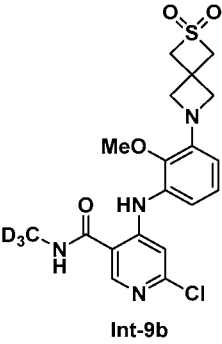
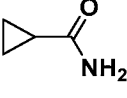
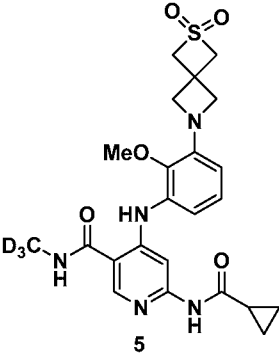
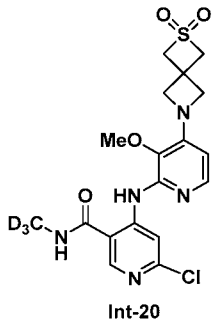
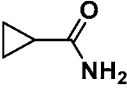
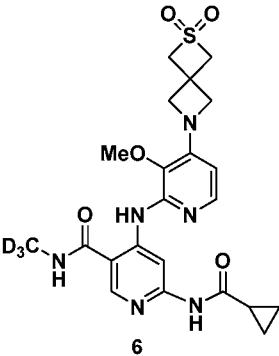
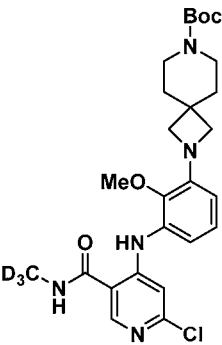
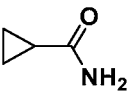
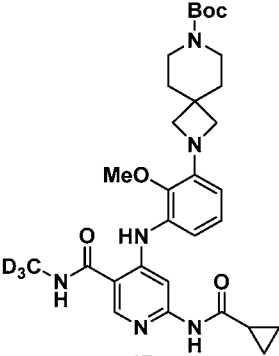
Example 1: Synthesis of compound 1

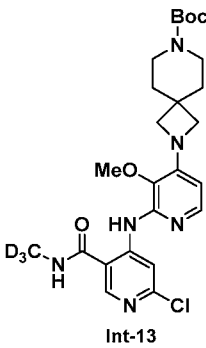
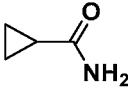
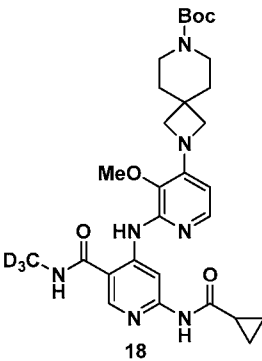
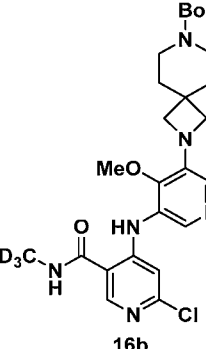
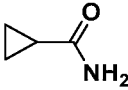
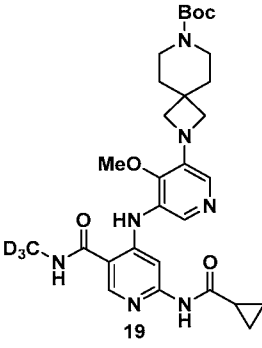
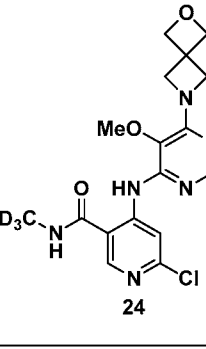
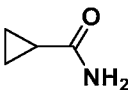
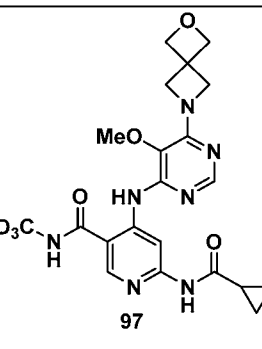


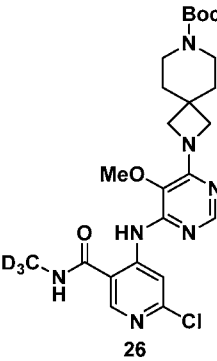
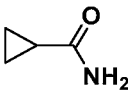
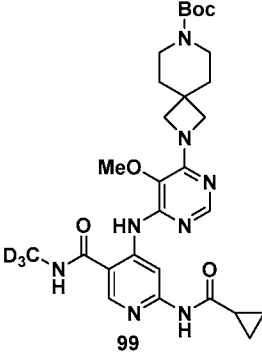
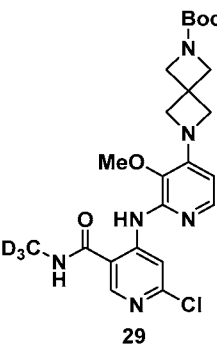
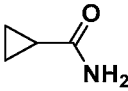
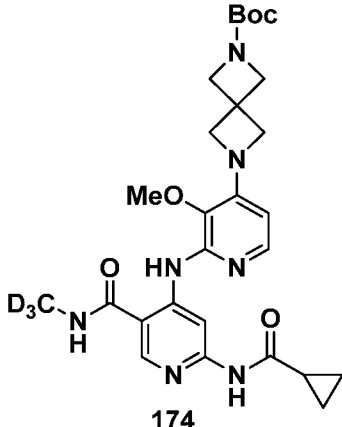
[000197] To a solution of **Int-9** (0.53 mmol) and cyclopropanecarboxamide (1.05 mmol) in 1,4-dioxane (3 ml) was added 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos, 0.105 mmol), cesium carbonate (1.59 mmol) and tris(dibenzylideneacetone)dipalladium(0) (Pd_2dba_3 , 0.048 g, 0.053 mmol). The reaction mixture was degassed by nitrogen for three times and then heated to 120°C until completion of reaction. After completion of reaction the reaction mixture was, filtered and filtrate was concentrated under reduced pressure and purified using preparative HPLC providing **compound 1** (0.120 g, 56 % yield) as yellow solid. ^1H NMR (400 MHz, DMSO-d_6): δ 11.23 (br-s, 1H), 10.72 (s, 1H), 8.77 (s, 2H), 8.43 (d, $J = 4.4$ Hz, 1H), 7.43 (br-s, 1H), 6.98-7.03 (m, 1H), 6.78-6.79 (m, 1H), 6.35 (d, $J = 8.0$ Hz, 1H), 4.73 (s, 3H), 4.06 (s, 3H), 3.55 (s, 3H), 1.88-1.91 (m, 1H), 0.85-0.88 (m, 4H) ppm. LCMS: m/z 441.34 ($\text{M}+\text{H}^+$); HPLC: 99.9%.

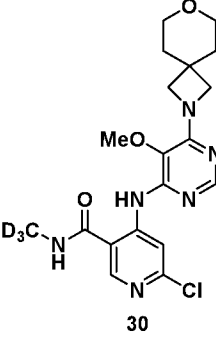
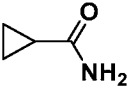
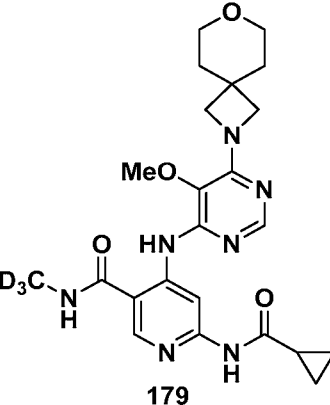
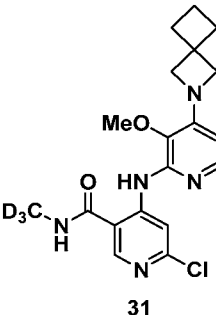
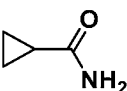
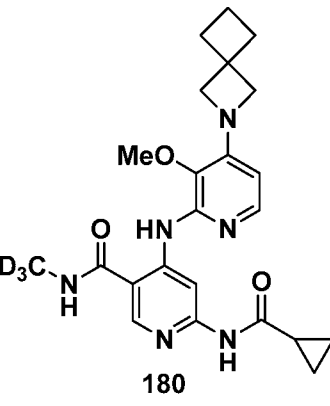
[000198] Following compounds were prepared analogously according to procedure described in Example 1 by using corresponding intermediate and starting material as provided in following table (the corresponding non-deutriated intermediates may be prepared by using methyl amine instead of CD₃NH₂):

Compound number	Intermediate	Starting material	Structure	Characterisation data
2	 Int-12		 Isolated yield: 0.05 g	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.28 (s, 1H), 10.61 (s, 1H), 9.19 (s, 1H), 8.50 (s, 1H), 8.47 (s, 1H), 7.09 (d, <i>J</i> = 2.4 Hz, 1H), 6.58 (d, <i>J</i> = 2 Hz, 1H), 4.72 (s, 4H), 4.01 (s, 4H), 3.86 (s, 3H), 1.99 (m, 1H), 0.79 (m, 4H) ppm. LCMS: <i>m/z</i> 442.30 (M+H ⁺); HPLC: 96 %.
3	 Int-16a		 Isolated yield: 0.080 g	¹ H NMR (400 MHz, DMSO-d ₆): δ 10.77 (s, 1H), 10.48 (s, 1H), 8.63 (s, 1H), 8.53 (s, 1H), 8.03 (s, 1H), 7.85 (s, 1H), 7.61 (s, 1H), 4.72 (s, 4H), 4.13 (s, 4H), 3.63 (s, 3H), 1.95-1.98 (m, 1H), 0.76-0.85 (m, 4H) ppm. LCMS: <i>m/z</i> 442.30 (M+H ⁺); HPLC: 96 %.

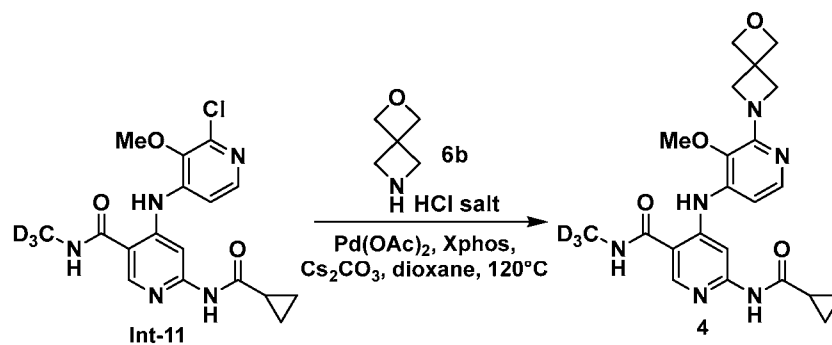
5	 Int-9b		 5 Isolated yield: 0.5 g	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 10.72 (s, 1H), 10.52 (s, 1H), 8.55 (s, 1H), 8.48 (s, 1H), 8.01 (s, 1H), 6.97 (t, <i>J</i> = 8.0 Hz, 1H), 6.82 (d, <i>J</i> = 8.0 Hz, 1H), 6.27 (d, <i>J</i> = 8.0 Hz, 1H), 4.48 (s, 4H), 4.09 (s, 3H), 3.56 (s, 3H), 1.94-1.99 (m, 1H), 0.75-0.77 (m, 4H) ppm. LCMS: <i>m/z</i> 489.37 (M+H ⁺); HPLC: 95.53 %.
6	 Int-20		 6 Isolated yield: 0.005 g	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): 11.25 (s, 1H), 10.60 (s, 1H), 9.21 (s, 1H), 8.49 (m, 2H), 7.13 (s, H), 6.64 (s, 1H), 4.48 (s, 4H), 4.07 (s, 4H), 3.87 (s, 3H), 1.98-1.99 (m, 1H), 0.77-0.79 (m, 4H) ppm. LCMS: <i>m/z</i> 490.24 (M+H) ⁺ ; HPLC: 94%.
17	 Int-9a		 17 Isolated yield: 0.120 g	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 10.71 (s, 1H), 10.49 (s, 1H), 8.53 (s, 2H), 8.46 (s, 1H), 7.99 (br-s, 1H), 6.94 (t, <i>J</i> = 8.0 Hz, 1H), 6.74 (d, <i>J</i> = 8.0 Hz, 1H), 6.22 (d, <i>J</i> = 8.0 Hz, 1H), 3.64 (s, 4H), 3.53 (s, 3H), 3.29-3.30 (m, 4H), 1.93-1.99 (m, 1H), 1.66-1.69 (m, 4H), 1.39 (s, 9H), 0.75-

				0.76 (m, 4H) ppm. LCMS: m/z 568.48 ($M+H^+$); HPLC: 96 %.
18	 Int-13		 18 Isolated yield: 0.02 g	^1H NMR (400 MHz, DMSO- d_6): δ 11.18 (s, 1H), 10.60 (s, 1H), 9.15 (s, 1H), 8.50 (s, 1H), 8.47 (s, 1H), 7.08 (d, J = 2 Hz, 1H), 6.56 (d, J = 2 Hz, 1H), 3.86 (s, 3H), 3.62 (s, 4H), 3.33 (s, 4H), 1.99 (m, 1H), 1.70 (m, 4H), 1.40 (s, 9H), 0.79 (m, 4H) ppm. LCMS: m/z 569.46 ($M+H^+$); HPLC: 99 %.
19	 16b		 19 Isolated yield: 0.020 g	^1H NMR (400 MHz, DMSO- d_6): δ 10.76 (s, 1H), 10.46 (s, 1H), 8.60 (s, 1H), 8.51 (s, 1H), 8.00 (s, 1H), 7.85 (s, 1H), 7.59 (s, 1H), 3.72 (s, 4H), 3.62 (s, 3H), 3.30 (br-s, 4H), 1.93-1.98 (m, 1H), 1.69-1.72 (m, 4H), 1.40 (s, 9H), 0.76-0.85 (m, 4H) ppm. LCMS: m/z 569.40 ($M+H^+$)
97	 24		 97	^1H NMR (400 MHz, DMSO- d_6): δ 11.80 (m, 1H), 10.77 (s, 1H), 9.46 (s, 1H), 8.68 (s, 1H), 8.57 (s, 1H), 8.05 (s, 1H), 4.72 (s, 4H), 4.31 (s, 4H), 3.65 (s, 3H), 2.03-1.98

			Isolated yield: 0.08 g	(m, 1H), 0.85-0.79 (m, 4H) ppm. LCMS: m/z 443.35 (M+H) ⁺ ; HPLC: 97 %.
99	 26		 99	¹ H NMR (400 MHz, DMSO-d ₆): 11.77 (s, 1H), 10.76 (s, 1H), 9.45 (s, 1H), 8.67 (s, 1H), 8.57 (s, 1H), 8.04 (s, 1H), 3.88 (m, 4H), 3.65 (s, 3H), 3.30 (s, 4H), 1.98-2.04 (m, 1H), 1.68-1.71 (m, 4H), 1.39 (m, 9H), 0.79-0.83 (m, 4H) ppm. LCMS: m/z 570.43 (M+H) ⁺ ; HPLC: 99.9%.
174	 29		 174	¹ H NMR (400 MHz, DMSO-d ₆): 11.22 (s, 1H), 10.60 (s, 1H), 9.19 (s, 1H), 8.50 (d, J=12.8Hz, 2H), 7.08 (d, J=2.4Hz, 1H), 6.57 (d, J=2 Hz, 1H), 4.024 (s, 4H), 3.96 (s, 4H), 3.86 (s, 3H), 1.99 (m, 1H), 1.38 (s, 9H), 0.80-0.77 (m, 4H) ppm. LCMS: m/z 541.35 (M+H) ⁺ ; HPLC: 97.99%.

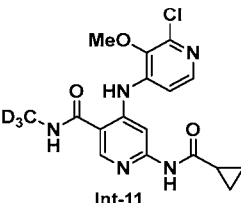
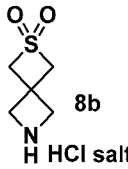
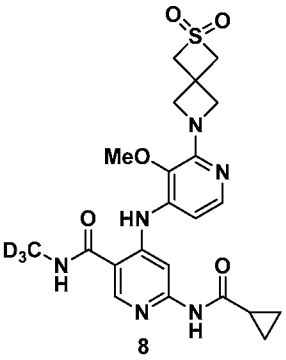
179	 30		 179 Isolated yield: 0.004 g	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.77 (s, 1H), 10.76 (s, 1H), 9.45 (s, 1H), 8.67 (s, 1H), 8.57 (s, 1H), 8.04 (s, 1H), 3.90 (s, 4H), 3.66 (s, 3H), 3.56-3.53 (m, 4H), 2.03-1.98 (m, 1H), 1.76-1.73 (m, 4H), 0.86-0.79 (m, 4H) ppm. LCMS: m/z 471.21 (M+H) ⁺ , HPLC: 94.54 %.
180	 31		 180 Isolated yield: 0.016 g	¹ H NMR (400 MHz, DMSO-d ₆): 11.19 (s, 1H), 10.59 (s, 1H), 9.17 (s, 1H), 8.49 (d, J=11.6Hz, 2H), 7.06 (d, J=2.4 Hz, 1H), 6.54 (d, J=2 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 4H), 2.18-2.15 (t, 4H), 1.96 (s, 2H), 1.85-1.78 (m, 1H), 0.79-0.77 (m, 4H) ppm. LCMS: m/z 440.14 (M+H) ⁺ , HPLC: 96.21%.

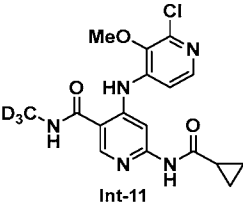
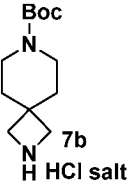
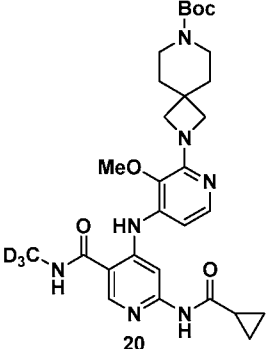
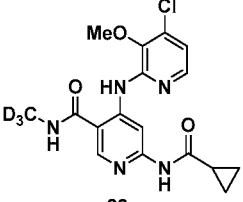
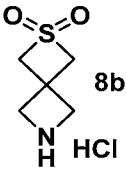
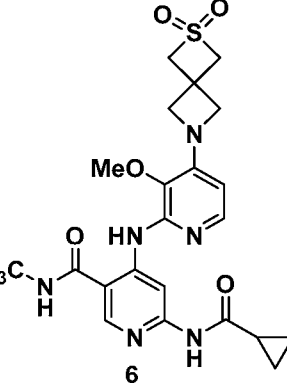
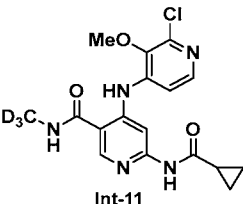
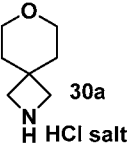
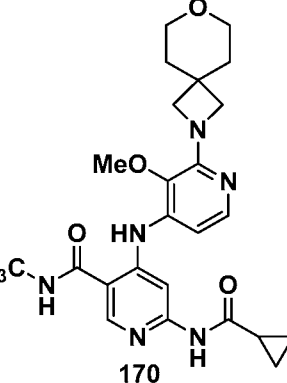
Example 2: Synthesis of compound 4

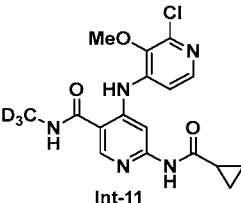
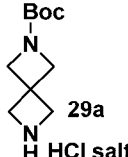
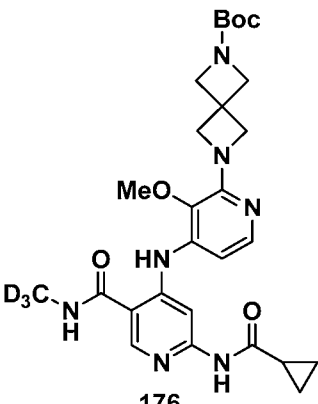
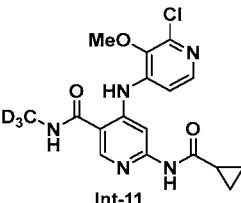
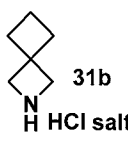
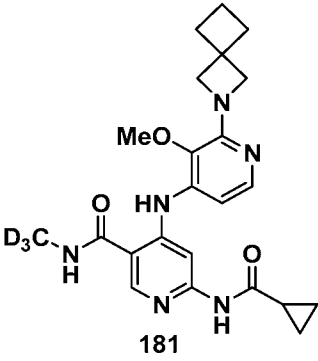


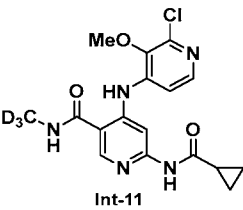
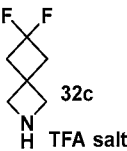
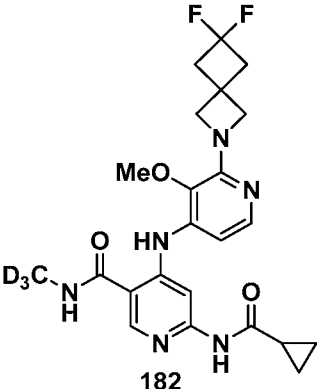
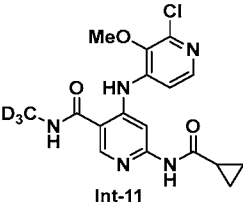
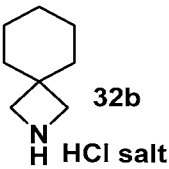
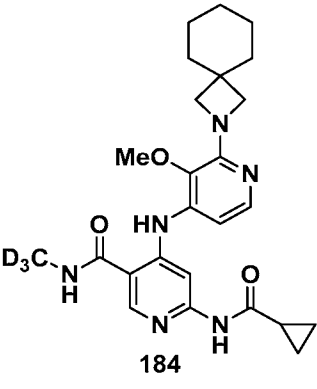
[000199] To the solution of **Int-11** (1.0 mmol) and **6b** (1.5 mmol) in dioxane (5 mL), was added Pd(OAc)₂ (10 mol%), X-Phos (20 mol%) and Cs₂CO₃ (3.0 mmol) and the resulting solution was heated at 120°C until completion of reaction. After completion of reaction the reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure and purified using flash column chromatography to give **compound 4** (0.054g, 18 %) as white solid. ¹H NMR (400 MHz, DMSO-d₆): d 10.91 (s, 2H), 8.65 (s, 1H), 8.54 (s, 1H), 8.20 (s, 1H), 7.77 (d, J = 5.6 Hz, 1H), 6.83 (d, J = 5.6 Hz, 1H), 4.71 (s, 4H), 4.17 (s, 4H), 3.60 (s, 3H), 1.96-2.00 (m, 1H), 0.79-0.81 (m, 4H) ppm. LCMS: m/z 442.10 (M+H⁺); HPLC: 99.00%.

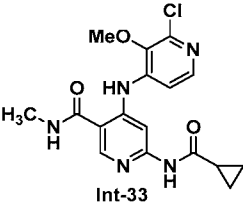
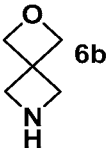
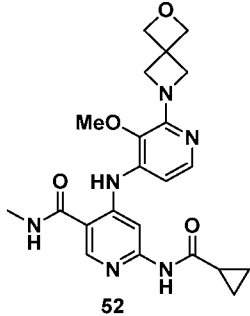
[000200] Following compounds were prepared analogously according to procedure described in Example 2 by using corresponding intermediate and starting material as provided in following table (the corresponding non-deutriated intermediates may be prepared by using methyl amine instead of CD₃NH₂):

Compound number	Intermediate	Starting material	Structure	Charecterisation data
8	 Int-11	 8b HCl salt	 Isolated yield: 0.050 g	¹ H NMR (400 MHz, DMSO-d ₆): d 10.92 (br-s, 2H), 8.66 (s, 1H), 8.55 (s, 1H), 8.21 (s, 1H), 7.81 (d, J = 5.2 Hz, 1H), 6.88 (d, J = 5.6 Hz, 1H), 4.48 (s, 4H), 4.22 (s, 4H), 3.62 (s, 3H), 1.98-2.02 (m, 1H), 1.79-1.81 ppm. LCMS: m/z 490.25 (M+H ⁺), HPLC: 98.13%.

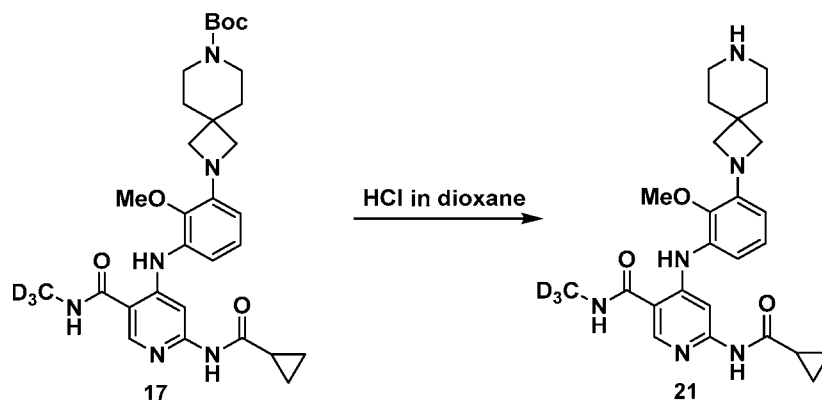
20	 Int-11	 7b HCl salt	 20 Isolated yield: 0.042 g	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 10.88 (s, 2H), 8.64 (s, 1H), 8.54 (s, 1H), 8.20 (s, 1H), 7.77 (d, <i>J</i> = 5.6 Hz, 1H), 6.81 (d, <i>J</i> = 5.6 Hz, 1H), 3.76 (s, 4H), 3.60 (s, 3H), 3.30 (br-s, 4H), 1.96-2.01 (m, 1H), 1.66-1.69 (m, 4H), 1.39 (s, 9H), 0.79-0.81 (m, 4H) ppm. LCMS: <i>m/z</i> 569.37 (M+H ⁺)
6	 22	 8b HCl	 6 Isolated yield: 0.43 g	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.53 (s, 1H), 10.67 (s, 1H), 9.42 (s, 1H), 8.60 (s, 1H), 8.52 (s, 1H), 7.73 (d, <i>J</i> =5.6Hz, 1H), 6.16 (d, <i>J</i> =5.6Hz, 1H), 4.50 (s, 4H), 4.25 (s, 4H), 3.62 (s, 3H), LCMS: <i>m/z</i> 490.52 (M+H ⁺) LCMS Purity: 97.62%
170	 Int-11	 30a HCl salt	 170 Isolated yield: 0.022 g	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 10.88 (s, 2H), 8.64 (s, 1H), 8.54 (s, 1H), 8.20 (s, 1H), 7.77 (d, <i>J</i> = 5.6 Hz, 1H), 6.81 (d, <i>J</i> = 5.6 Hz, 1H), 3.78 (s, 4H), 3.60 (s, 3H), 3.56-3.53 (m, 4H), 2.01-1.98

				(m, 1H), 1.75-1.72 (m, 4H), 0.81-0.79 (m, 4H) ppm. LCMS: m/z 470.65 (M+H) ⁺ , LCMS purity: 97.42 %.
176	 Int-11	 29a HCl salt	 176 Isolated yield: 0.09 g	¹ H NMR (400 MHz, DMSO-d ₆): 10.90-10.89 (d, J=3.2 Hz, 2H), 8.65 (s, 1H), 8.54 (s, 1H), 8.21 (s, 1H), 7.79-7.77 (d, J=5.6 Hz, 1H), 6.84-6.83 (d, J=5.6 Hz, 1H), 4.13 (s, 4H), 4.02 (s, 4H), 3.60 (s, 3H), 1.97-2.03 (m, 1H), 1.38 (s, 9H), 0.81-0.79 (d, 4H) ppm. LCMS: m/z 541.22 (M+H) ⁺ ; HPLC: 96.57%.
181	 Int-11	 31b HCl salt	 181 Isolated yield: 0.030 g	¹ H NMR (400 MHz, DMSO-d ₆): δ 10.88 (d, J = 3.6 Hz, 2H), 8.64 (s, 1H), 8.54 (s, 1H), 8.20 (s, 1H), 7.77 (d, J = 5.6 Hz, 1H), 6.81 (d, J = 5.6 Hz, 1H), 3.96 (s, 4H), 3.59 (s, 3H), 2.18 (t, 4H), 2.01-1.96 (m, 1H), 1.84-1.77 (m, 2H), 0.81-0.79 (m, 4H) ppm. LCMS: m/z 440.33

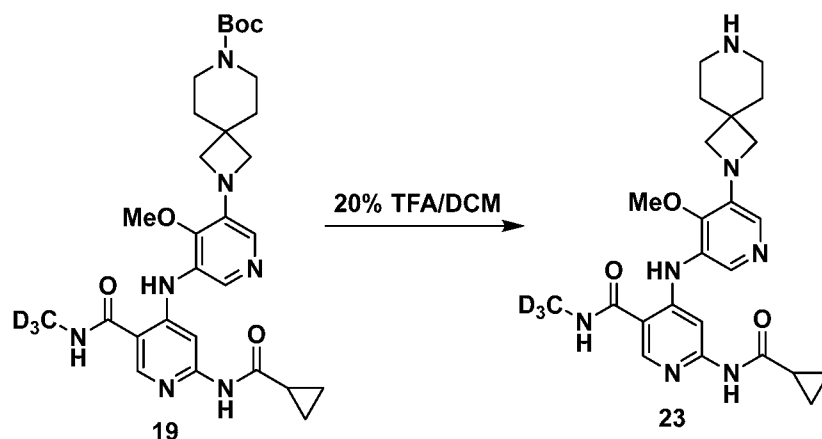
				(M+H ⁺), HPLC purity: 99.34 %.
182	 Int-11	 32c TFA salt	 182 Isolated yield: 0.014 g	¹ H NMR (400 MHz, DMSO-d ₆): δ 10.89 (s, 2H), 8.65 (s, 1H), 8.54 (s, 1H), 8.21 (s, 1H), 7.79 (d, J = 5.6 Hz, 1H), 6.85 (d, J = 5.6 Hz, 1H), 4.09 (s, 4H), 3.60 (s, 3H), 2.88 (t, 4H), 2.01-1.97 (m, 1H), 0.81-0.79 (m, 4H) ppm. LCMS: m/z 476.32 (M+H ⁺), HPLC purity: 98.83 %.
184	 Int-11	 32b HCl salt	 184 Isolated yield: 0.003 g Isolated yield:	¹ H NMR (400 MHz, DMSO-d ₆): δ 10.88 (d, J = 5.6 Hz, 2H), 8.64 (s, 1H), 8.54 (s, 1H), 8.20 (s, 1H), 7.76 (d, J = 5.6 Hz, 1H), 6.79 (d, J = 5.6 Hz, 1H), 3.69 (s, 4H), 3.59 (s, 3H), 1.63 (s, 4H), 1.43 (s, 4H), 1.36 (s, 3H), 0.86-0.79 (m, 4H) ppm. LCMS: m/z 468.38 (M+H ⁺), HPLC purity: 94.48 %.

52	 Int-33	 6b	 52 Isolated yield: 0.040 g	¹ H NMR (400 MHz, DMSO-d ₆): 10.90 (d, 2H, J=3.2Hz), 8.65 (s, 1H), 8.54 (s, 1H), 8.21 (s, 1H), 7.79 (d, J=5.6 Hz, 1H), 6.84 (d, J=5.6 Hz, 1H), 4.72 (s, 4H), 4.17 (s, 4H), 3.60 (s, 3H), 2.01-1.98 (m, 1H), 0.81-0.79 (m, 4H) ppm. LCMS: m/z 442.42 (M+H) ⁺ ; HPLC: 99.41%.
----	---	---	---	---

Example 3: Synthesis of compound 21

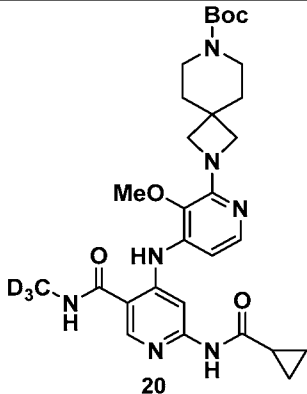
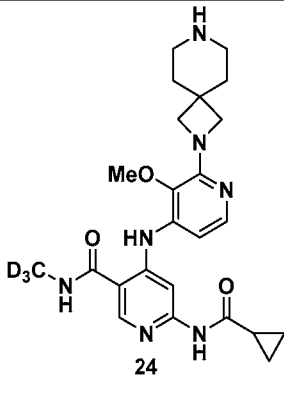
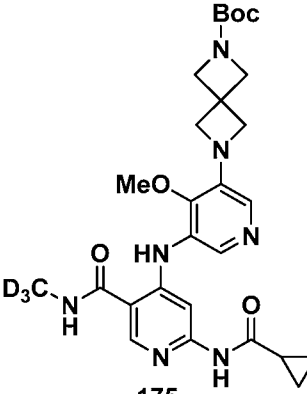
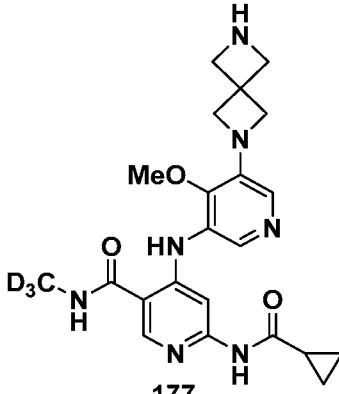
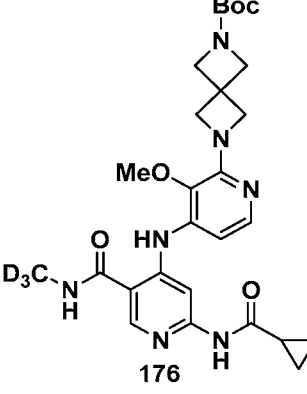
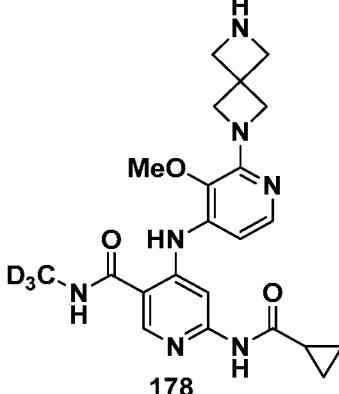


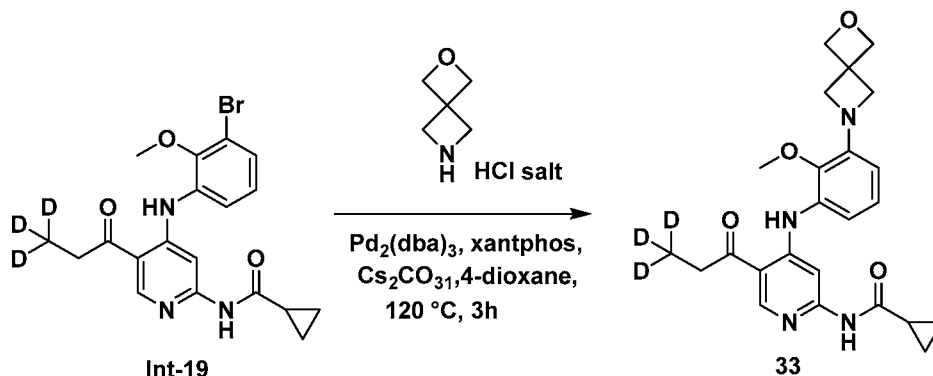
[000201] To a solution of **17** (0.10 g, 0.17 mmol) in dioxane, 4M HCl in dioxane solution (3 ml) was added at 0 °C and the mixture was stirred at 25-30°C until completion of reaction. After completion of reaction the reaction mixture was concentrated under vacuum and resulting residue was purified using preparative HPLC providing **compound 21** (0.015 g, 18 % yield) as yellow solid. ¹H NMR (400 MHz, DMSO-d₆): d 10.71 (s, 1H), 10.49 (s, 1H), 8.54 (s, 2H), 8.47 (s, 1H), 8.40 (s, 1H), 6.94 (t, J = 8.0 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.22 (d, J = 8.0 Hz, 1H), 3.62 (s, 4H), 3.53 (s, 3H), 2.77 (br-s, 4H), 1.89-1.99 (m, 1H), 1.73 (br-s, 4H), 0.75-0.76 (m, 4H) ppm. LCMS: m/z 468.48 (M+H)⁺; HPLC: 95.60%.

Example 3a: Synthesis of compound 23

[000202] To a solution of 19 (0.09 g, 0.157 mmol) in DCM, 20% TFA/DCM solution (15 mL) was added at 0 °C and the mixture was stirred at 25-30°C till completion of reaction. After completion of reaction the reaction mixture was concentrated under vacuum and resulting residue was purified using preparative HPLC providing compound **23** (0.038 g, 51.35% yield) as white solid. ¹H NMR (400 MHz, DMSO-*d*₆): 10.78 (s, 1H), 10.47 (s, 1H), 8.61 (s, 1H), 8.51 (s, 1H), 8.38 (s, 1H), 8.02 (s, 1H), 7.85 (s, 1H), 7.62 (s, 1H), 3.77 (s, 4H), 3.64 (s, 3H), 3.07 (s, 4H), 1.94 (s, 5H), 0.77-0.75 (m, 4H) ppm. LCMS: *m/z* 469.38 (M+H)⁺; LCMS purity: 97.58 %.

[000203] Following compound was prepared analogously according to procedure described in Example 3 or 3a by using corresponding intermediate and starting material as provided in following table (the corresponding non-deutriated intermediate may be prepared by using methyl amine instead of CD₃NH₂):

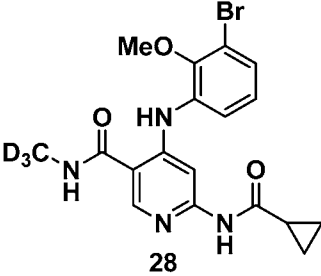
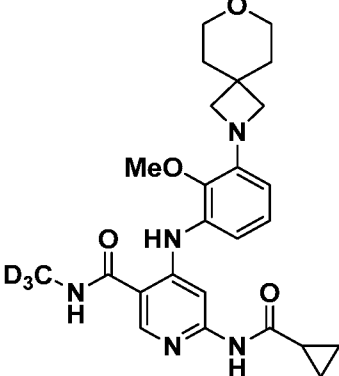
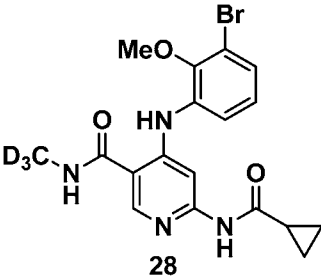
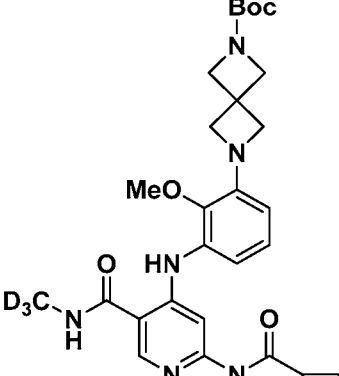
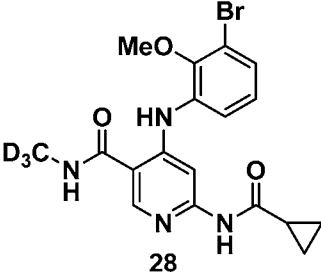
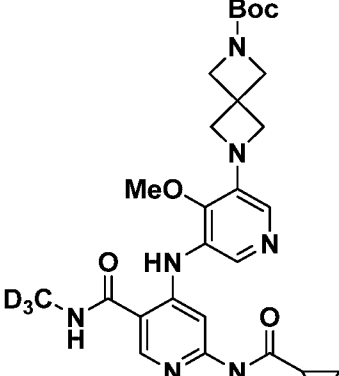
Compound number	Intermediate	Structure	Characterisation data
24	 20	 24 Isolated yield: 0.035 g	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 10.88 (s, 2H), 8.67 (s, 1H), 8.54 (s, 1H), 8.36 (s, 1H), 8.20 (s, 1H), 7.77 (d, <i>J</i> = 5.6 Hz, 1H), 6.81 (d, <i>J</i> = 5.6 Hz, 1H), 4.10 (s, 4H), 3.89 (s, 3H), 2.89 (br-s, 4H), 1.97-2.02 (m, 1H), 1.82 (br-s, 4H), 0.79-0.84 (m, 4H) ppm. LCMS: <i>m/z</i> 469.38 (M+H ⁺); HPLC: 97%.
177	 175	 177 Isolated yield: 0.012 g	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): 10.77 (s, 1H), 10.47 (s, 1H), 8.62 (s, 1H), 8.51 (s, 1H), 8.36 (s, 1H), 8.03 (s, 1H), 7.85 (s, 1H), 7.61 (s, 1H), 4.09 (s, 4H), 4.01 (s, 3H), 3.63 (s, 3H), 1.99-1.93 (m, 1H), 1.23 (s, 1H), 0.77-0.75 (m, 4H) ppm. LCMS: <i>m/z</i> 441.15 (M+H ⁺); HPLC: 97.19%.
178	 176	 178 Isolated yield: 0.016 g	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): 10.89 (s, 2H), 8.66 (s, 1H), 8.54 (s, 1H), 8.39 (s, 1H), 8.21 (s, 1H), 7.79 (d, <i>J</i> = 5.6 Hz, 1H), 6.84 (d, <i>J</i> = 5.6 Hz, 1H), 4.11 (s, 4H), 3.81 (s, 3H), 3.60 (s, 3H), 1.23 (s, 1H), 2.01-1.98 (m, 1H), 0.81-0.80 (m, 4H) ppm. LCMS: <i>m/z</i> 440.27 (M+H ⁺); HPLC: 94.40%.

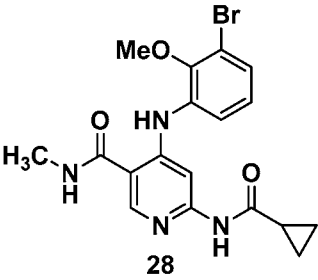
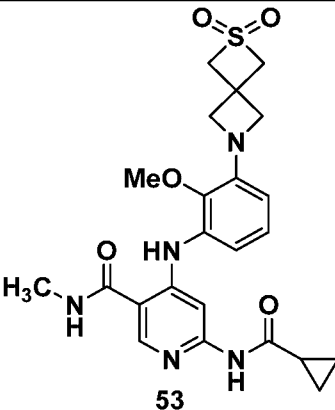
Example 4: Synthesis of compound 33

[000204] To a solution of **Int-19** (0.140 g, 0.33 mmol) and 2-Oxa-6-azaspiro[3.3]heptane hydrochloride (0.043 g, 1.3 mmol) in 1,4-dioxane (3 ml) was added 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) (0.03 g, 0.05 mmol), cesium carbonate (0.27 g, 0.82 mmol) and tris(dibenzylideneacetone)dipalladium(0) ($\text{Pd}_2(\text{dba})_3$, 0.045 g, 0.05 mmol). The reaction mixture was degassed by nitrogen for three times and then heated to 120°C till completion of reaction. After completion of reaction the reaction mixture was filtered and filtrate was concentrated under reduced pressure and purified using preparative HPLC providing **compound 33** (0.03 g, 34%) as yellow solid. ^1H NMR (400 MHz, DMSO- d_6): 10.86-10.91 (m, 2H), 8.39 (s, 1H), 7.99 (s, H), 6.96-7.00 (m, 1H), 6.80 (d, $J = 8$ Hz, 1H), 6.30 (d, $J = 8$ Hz, 1H), 5.76 (s, 1H), 4.71 (s, 4H), 4.05 (s, 4H), 3.53 (s, 3H), 3.08 (s, 2H), 1.98-2.03 (m, 1H), 0.76-0.77 (m, 4H) ppm. LCMS: m/z 440.20 ($\text{M}+\text{H}$) $^+$; HPLC: 97%.

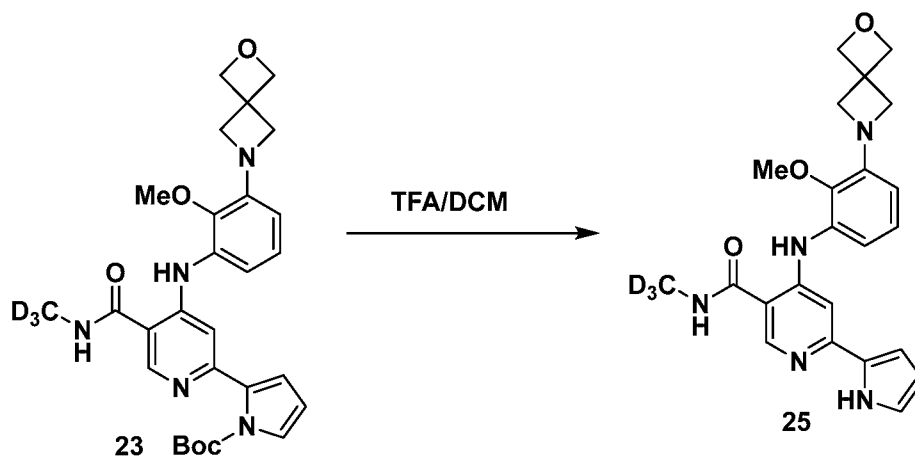
[000205] Following compounds were prepared analogously according to procedure described in Example 4 by using corresponding intermediate and starting material as provided in following table (the corresponding non-deutriated intermediate may be prepared by using methyl amine instead of CD_3NH_2):

Compound number	Intermediate	Structure	Characterisation data
7		 Isolated yield: 0.240 g	^1H NMR (400 MHz, DMSO- d_6): 10.77 (s, 1H), 10.47 (s, 1H), 8.60 (s, 1H), 8.51 (s, 1H), 8.05 (s, 1H), 7.85 (s, 1H), 7.63 (s, 1H), 4.47 (s, 4H), 4.17 (s, 4H), 3.64 (s, 3H), 1.93-1.93 (m, 1H), 0.77-0.75 (d, 4H) ppm. LCMS: m/z 490.24 ($M+H$) $^+$; HPLC: 95.44%.
168		 Isolated yield: 0.010 g	^1H NMR (400 MHz, DMSO- d_6): δ 10.75 (s, 1H), 10.44 (s, 1H), 8.59 (s, 1H), 8.507 (s, 1H), 7.99 (s, 1H), 7.85 (s, 1H), 7.56 (s, 1H), 3.907 (s, 4H), 3.61 (s, 3H), 2.18-2.14 (t, 4H), 1.99-1.93 (m, 1H), 1.84-1.77 (m, 2H), 0.77-0.75 (d, 4H) ppm. LCMS: m/z 440.27 ($M+H$) $^+$. HPLC Purity: 98.17 %.
171		 Isolated yield: 0.022 g	^1H NMR (400 MHz, DMSO- d_6): 10.75 (s, 1H), 10.45 (s, 1H), 8.59 (s, 1H), 8.50 (s, 1H), 7.99 (s, 1H), 7.85 (s, 1H), 7.60 (s, 1H), 3.74 (s, 4H), 3.62 (s, 3H), 3.56-3.53 (m, 4H), 1.99-1.93 (m, 1H), 1.76-1.74 (m, 4H), 0.77-0.75 (m, 4H), ppm. LCMS: m/z 470.14 ($M+H$) $^+$; HPLC: 95.65%.

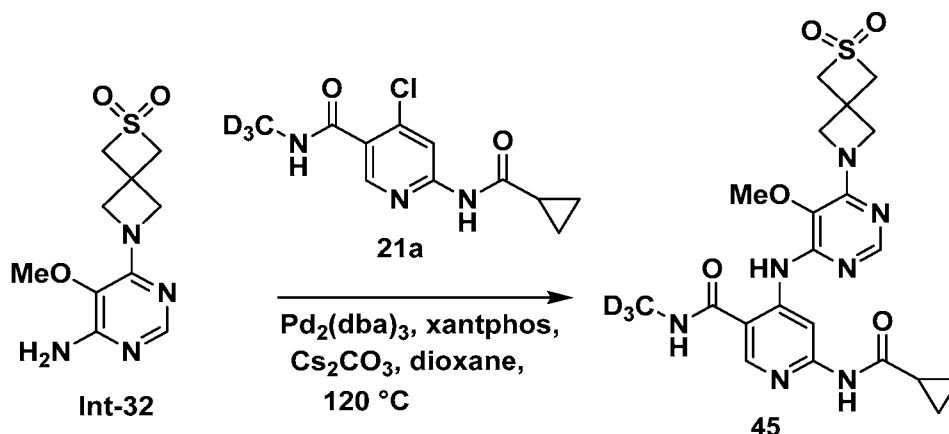
172	 28	 172 Isolated yield: 0.013 g	¹ H NMR (400 MHz, DMSO-d ₆): δ 10.71 (s, 1H), 10.49 (s, 1H), 8.5-8.46 (m, 2H), 7.98 (s, 1H), 6.94 (s, 1H), 6.75 (d, J = 6.8 Hz, 1H), 6.24 (d, J = 7.8 Hz, 1H), 3.66 (s, 3H), 3.54 (s, 8H), 1.74 (s, 5H), 0.75 (s, 4H) ppm. LCMS: m/z 469.3 (M+H) ⁺ , HPLC purity: 97.85 %.
173	 28	 173 Isolated yield: 0.24 g	¹ H NMR (400 MHz, DMSO-d ₆): 10.71 (s, 1H), 10.50 (s, 1H), 8.54 (s, 1H), 8.47 (s, 1H), 8.00 (s, 1H), 6.94 (t, J = 20 Hz, 1H), 6.78 (d, J = 20Hz 1H), 6.21 (d, J = 20Hz, 1H), 4.00 (d, 8H), 3.53 (s, 3H), 1.98-1.90 (m, 1H), 1.38 (s, 9H), 0.76 (d, 4H) ppm. LCMS: m/z 540.40 (M+H) ⁺ , HPLC: 98.73%.
175	 28	 175 Isolated yield: 0.120 g	¹ H NMR (400 MHz, DMSO-d ₆): 10.76 (s, 1H), 10.46 (s, 1H), 8.59 (s, 1H), 8.51 (s, 1H), 8.02 (s, 1H), 7.85 (s, 1H), 7.58 (s, 1H), 4.07 (s, 4H), 4.02 (s, 4H), 3.62 (s, 3H), 1.93-1.99 (m, 1H), 1.37 (s, 9H), 1.22-1.23 (d, 1H, J=4Hz), 0.75- 0.76 (d, 4H, J=5.2Hz) ppm. LCMS: m/z 541.41 (M+H) ⁺ ; HPLC: 96.26%.

53	 28	 53 Isolated yield: 0.040 g	¹ H NMR (400 MHz, DMSO-d ₆): δ 10.74-10.72 (m, 1H), 10.51 (s, 1H), 8.58 (d, J = 4.0 Hz, 1H), 8.51-8.48 (m, 1H), 8.01-7.97 (m, 1H), 6.99 (t, J = 8.4 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.28 (d, J = 8.0 Hz, 1H), 4.48 (s, 4H), 4.10 (s, 4H), 3.56 (s, 3H), 2.79 (d, 3H), 1.99-1.94 (m, 1H), 0.81-0.76 (m, 4H) ppm. LCMS: m/z 486.15 (M+H) ⁺ . HPLC Purity: 99.02%.
----	---	--	--

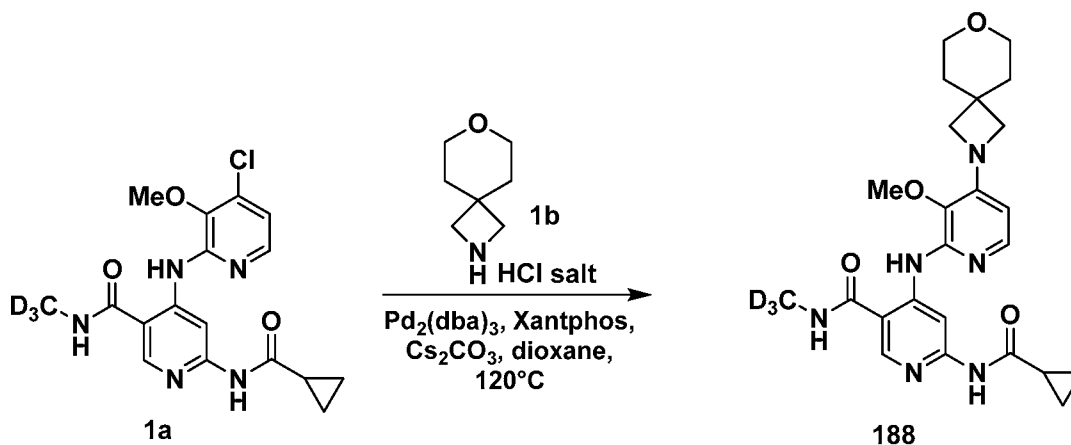
Example 5: Synthesis of compound 25



[000206] To a solution of **23** (0.40 g) in DCM (5 ml) was added TFA (1 ml) dropwise at 0°C and stirred for 6 hours at rt. After completion of reaction the reaction mixture was concentrated under reduced pressure and purified using flash column chromatography to give compound **25** (0.046 g, 14.2 %) as off-white solid. ¹H NMR (300 MHz, DMSO-d₆): 11.49 (m, 1H), 10.40 (m, 1H), 8.61 (s, 2H), 7.27 (s, 1H), 6.99 (t, J = 8 Hz, 1H), 6.85-6.84 (m, 2H), 6.56 (m, 1H), 6.26 (d, J = 7.2 Hz, 1H), 6.12-6.10 (m, 1H), 4.72 (s, 4H), 4.05 (s, 4H), 3.56 (s, 3H), ppm. MS: m/z 423 (M+H)⁺; HPLC: 98.81%

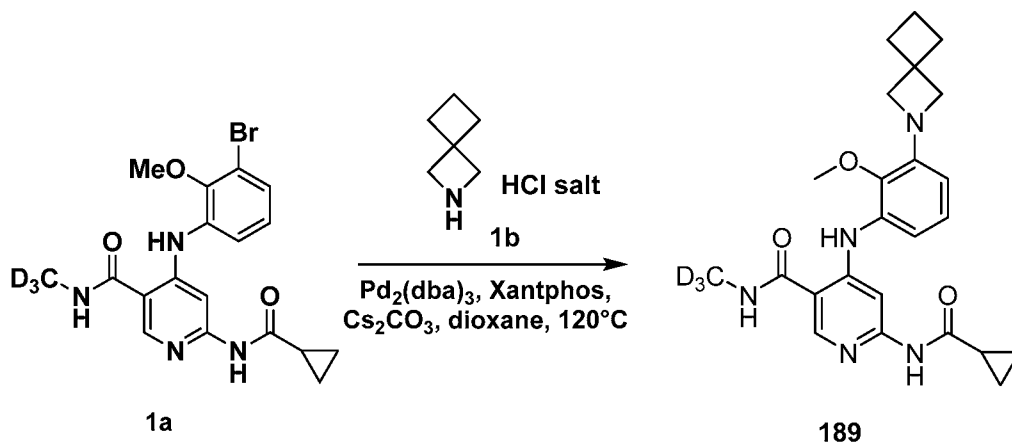
Example 6: Synthesis of compound 45

[000207] **Compound 45** was prepared from **Int-32** using procedure described for synthesis of **compound 1** (0.056 g, 19.54%) as white solid. ^1H NMR (400 MHz, DMSO- d_6): 11.85 (s, 1H), 10.79 (s, 1H), 9.47 (s, 1H), 8.70 (s, 1H), 8.59 (s, 1H), 8.09 (s, 1H), 4.52 (s, 4H), 4.38 (s, 4H), 3.67 (s, 3H), 2.05-1.99 (m, 1H), 0.85-0.78 (m, 4H) ppm. LCMS: m/z 491.06 ($\text{M}+\text{H}^+$); HPLC: 98.12%.

Example 7: Synthesis of compound 188

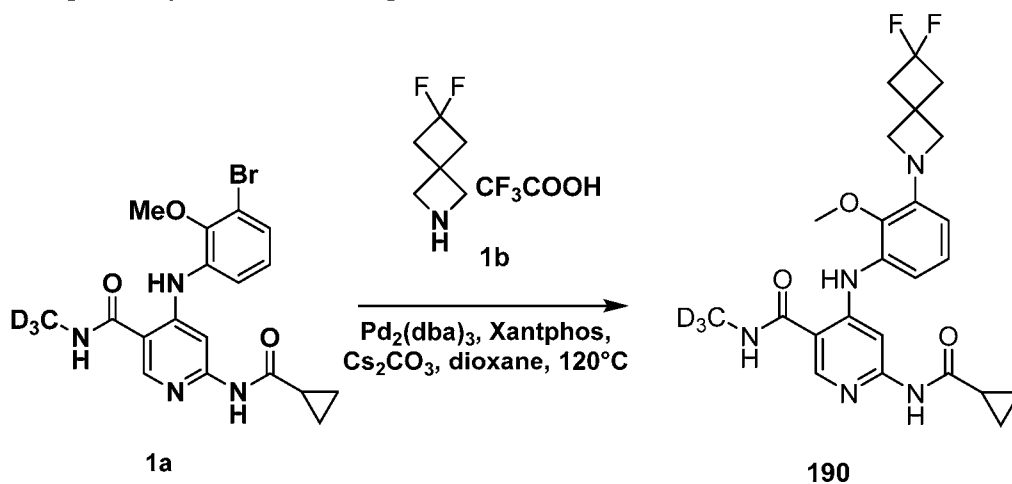
[000208] **Compound 188** was prepared from **1a** and **1b** using procedure described for synthesis of **compound 4** as pale-yellow solid (0.15 g, 25.48%).

[000209] ^1H NMR (400 MHz, DMSO- d_6): δ 11.47 (s, 1H), 10.64 (s, 1H), 9.40 (s, 1H), 8.57 (s, 1H), 8.50 (s, 1H), 7.70-7.69 (d, $J = 5.6$ Hz, 1H), 6.12-6.11 (d, $J = 5.6$ Hz, 1H), 3.79 (s, 4H), 3.61 (s, 3H), 3.55 (s, 4H), 1.96-1.99 (m, 1H), 1.74-1.75 (m, 4H), 0.77-0.80 (m, 4H) ppm. LCMS: m/z 470.33 ($\text{M}+\text{H}^+$), HPLC: 98.29 %.

Example 8: Synthesis of Compound 189

[000210] **Compound 189** was prepared from **1a** and **1b** using procedure described for synthesis of **compound 4** (0.02 g, 8.25%) as white solid.

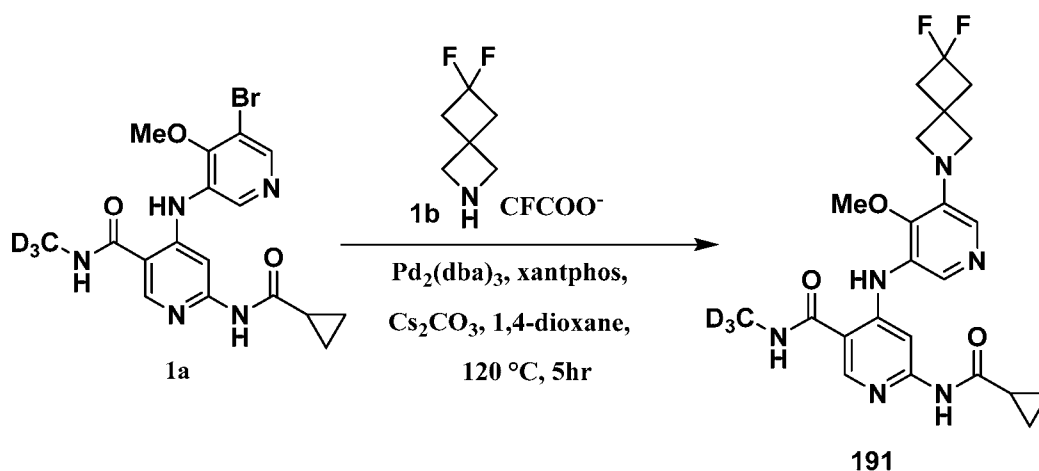
[000211] ^1H NMR (400 MHz, DMSO- d_6): 10.70 (s, 1H), 10.48 (s, 1H), 8.54 (s, 1H), 8.46 (s, 1H), 7.99 (s, 1H), 6.92 (t, $J = 8$ Hz, 1H), 6.74 (d, $J = 8$ Hz, 1H), 6.19 (d, $J = 8$ Hz, 1H), 3.82 (s, 4H), 3.53 (s, 3H), 2.15 (t, 4H), 1.99-1.93 (m, 1H), 1.81 (s, 2H), 0.76 (d, 4H) ppm. LCMS: m/z 540.25 ($\text{M}+\text{H}^+$); HPLC: 97.33%.

Example 9: Synthesis of Compound 190

[000212] **Compound 190** was prepared from **1a** and **1b** using procedure described for synthesis of **compound 4** (0.04 g, 7.74%) as white solid.

[000213] ^1H NMR (400 MHz, DMSO- d_6): 10.70 (s, 1H), 10.59 (s, 1H), 8.54 (s, 1H), 8.47 (s, 1H), 8.00 (s, 1H), 6.95 (t, $J = 8$ Hz, 1H), 6.78 (d, $J = 7.6$ Hz, 1H), 6.21 (d, $J = 8$ Hz, 1H), 3.96 (d, 4H), 3.54 (s, 3H), 2.84 (t, 4H), 1.99-1.93 (m, 1H), 0.76 (d, 4H) ppm. LCMS: m/z 475.23 ($M+H$) $^+$; HPLC: 95.92%.

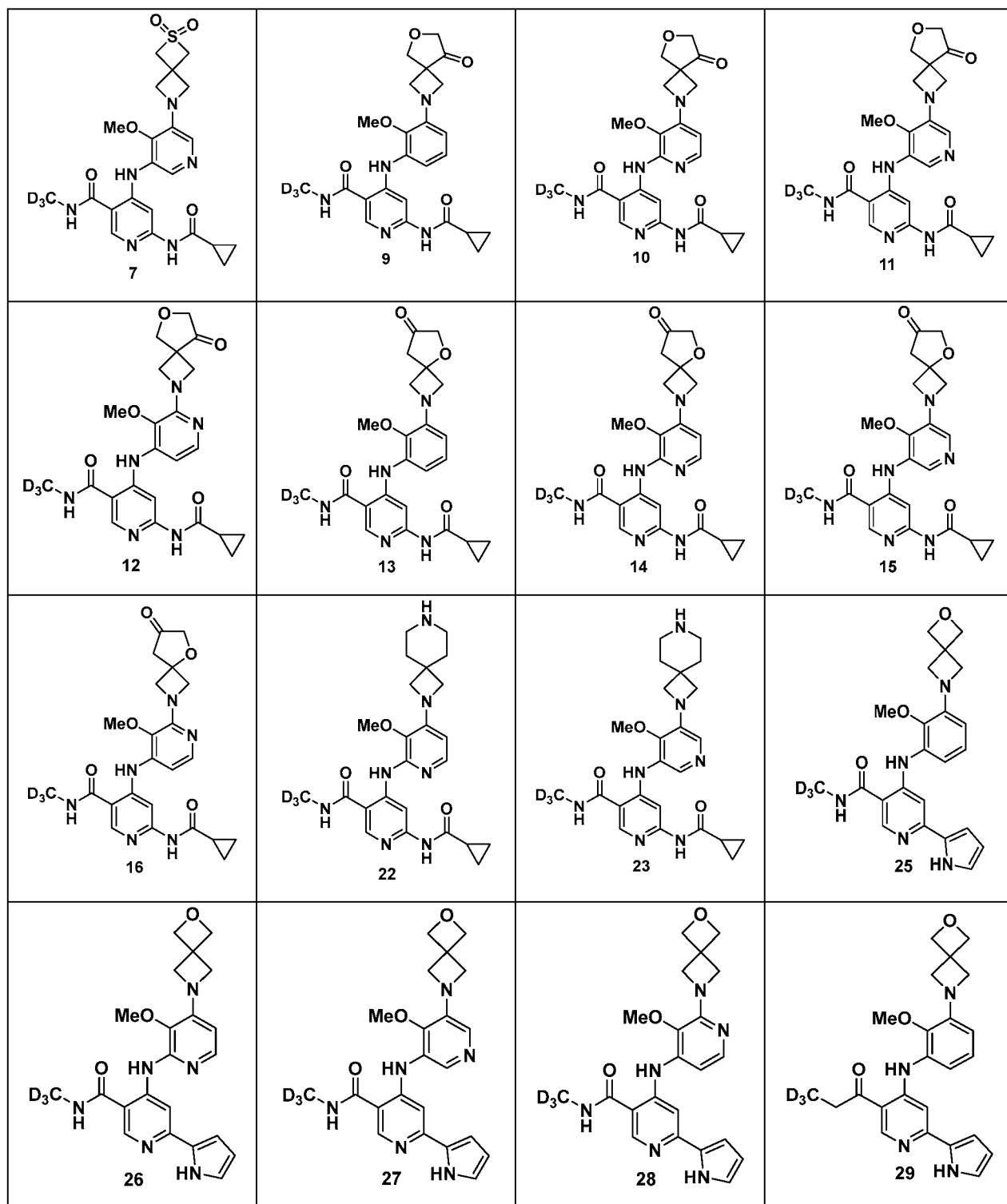
Example 10: Synthesis of Compound 191

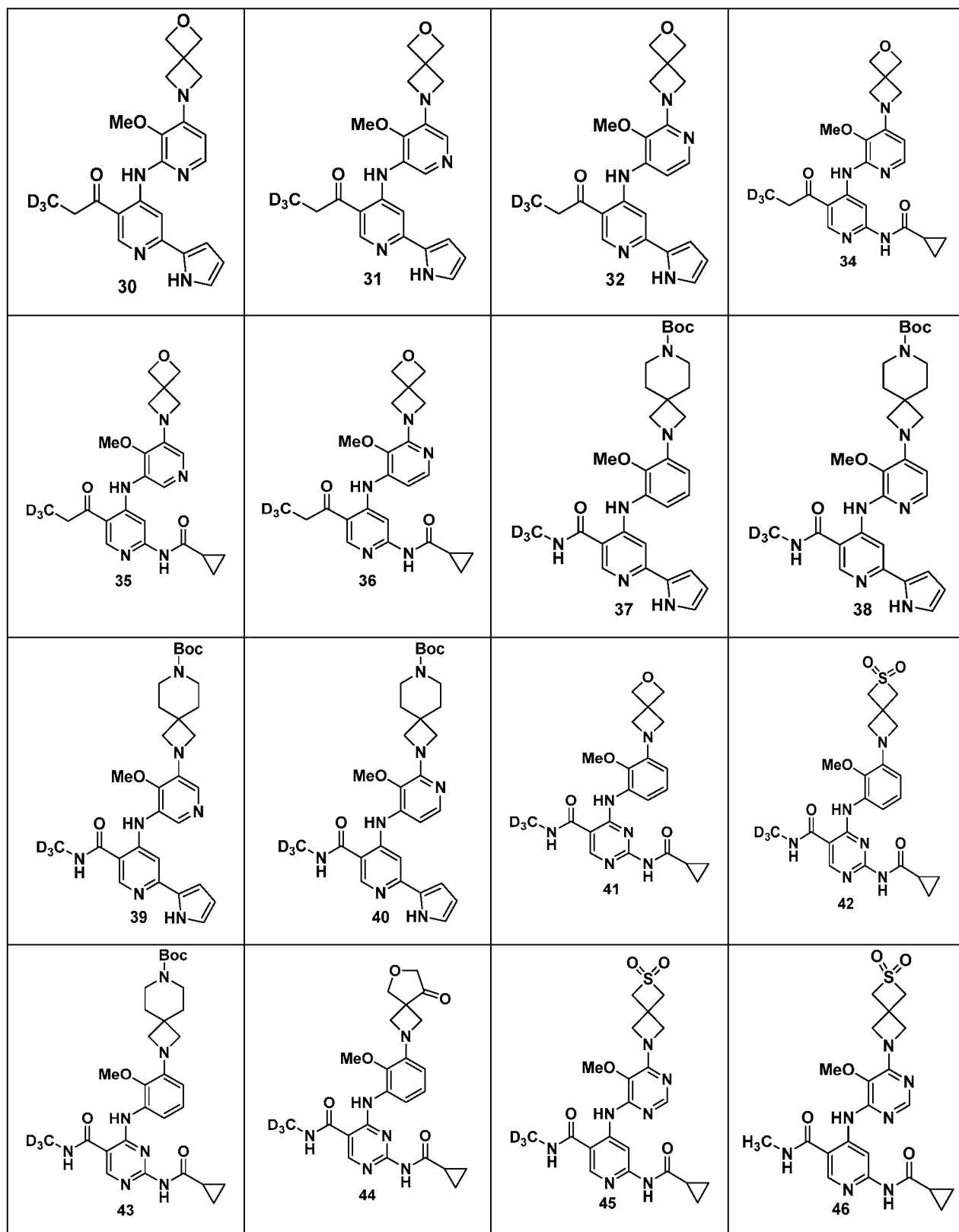


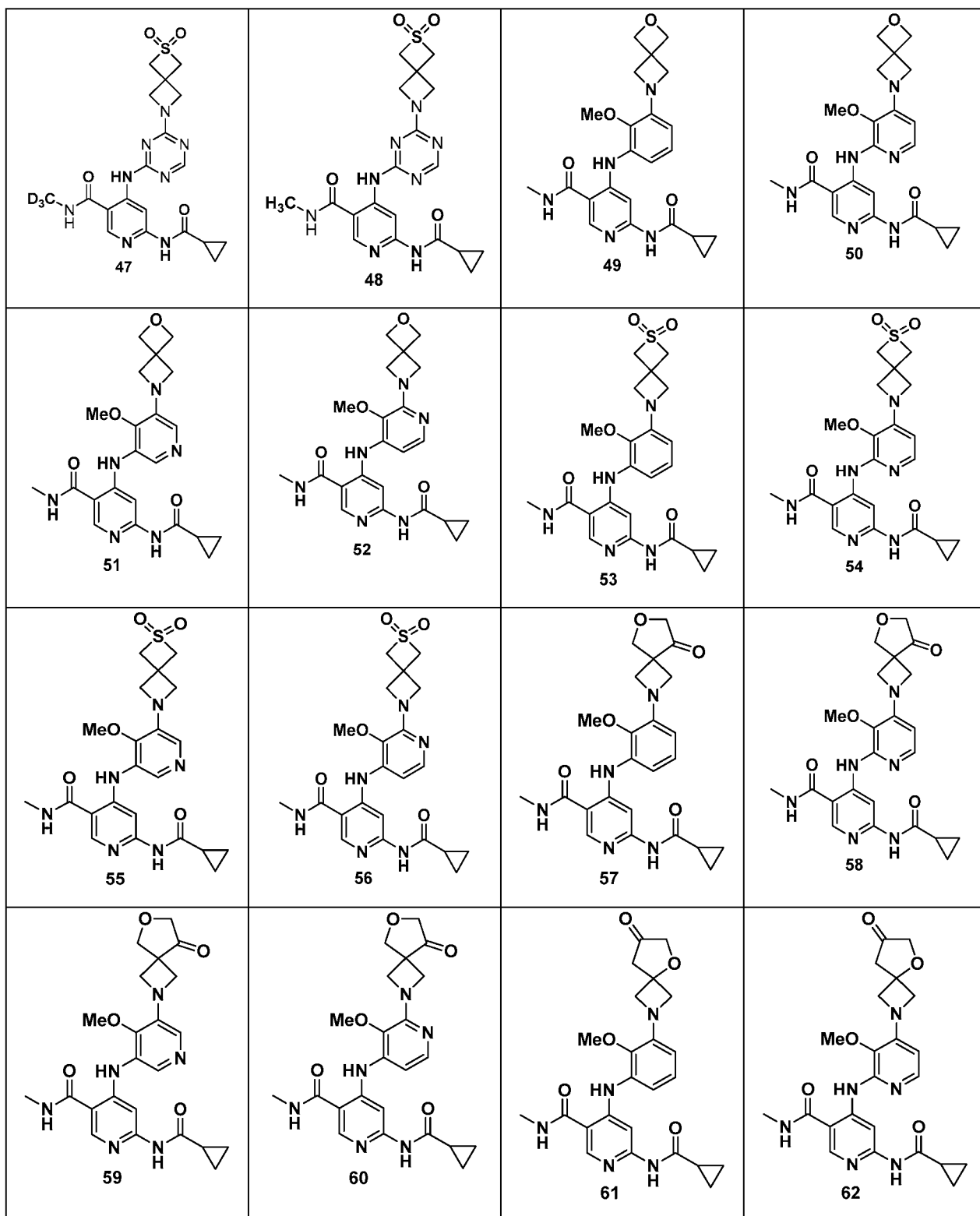
[000214] **Compound 191** was prepared from **1a** and **1b** using procedure described for synthesis of **compound 4** (0.058 g, 26.36 %) as white solid.

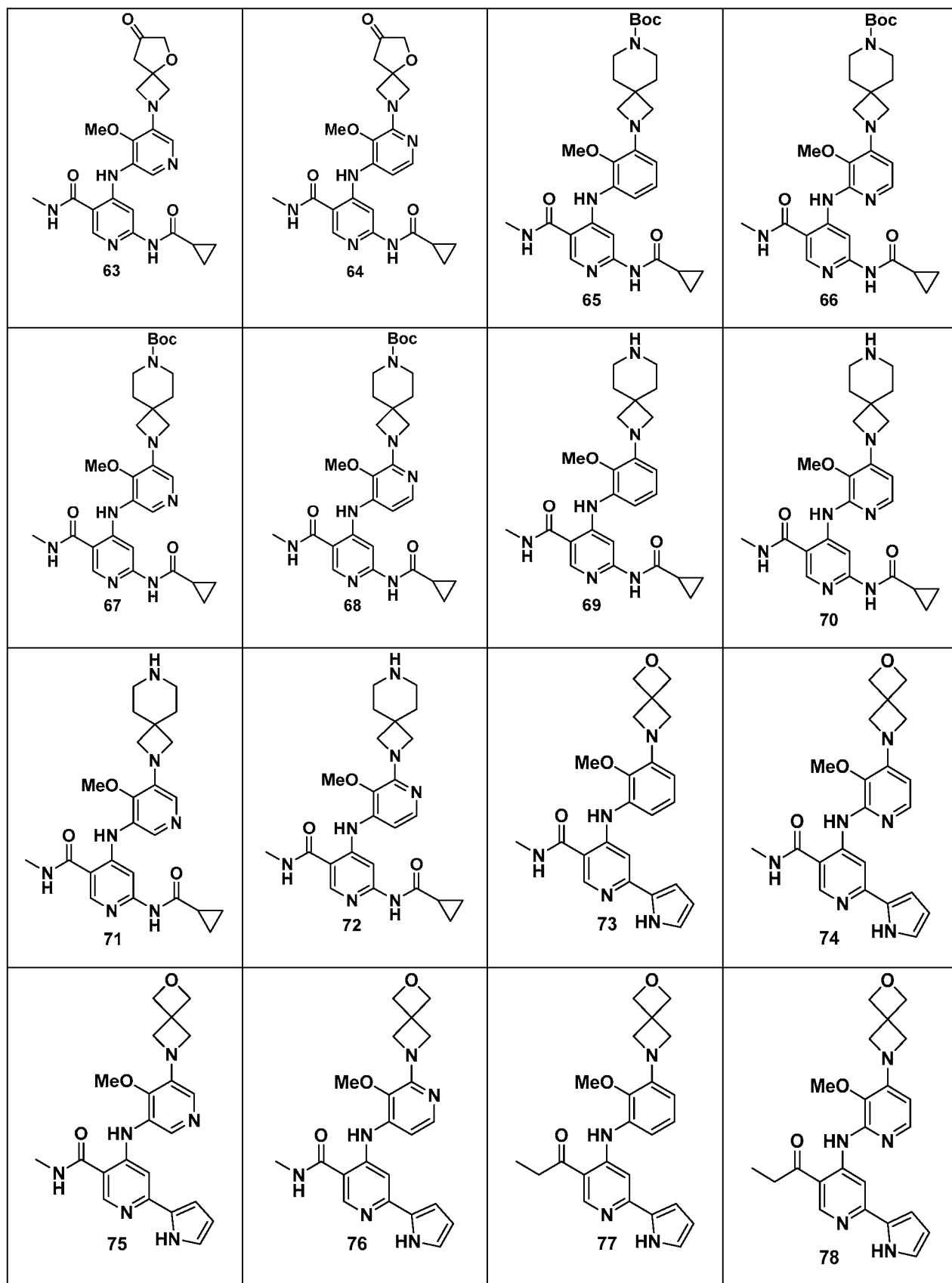
[000215] ^1H NMR (400 MHz, DMSO- d_6): δ 10.76 (s, 1H), 10.46 (s, 1H), 8.59 (s, 1H), 8.51 (s, 1H), 8.02 (s, 1H), 7.85 (s, 1H), 7.60 (s, 1H), 4.04 (s, 4H), 3.62 (s, 3H), 2.88 (t, 4H), 1.99-1.93 (m, 1H), 0.76-0.75 (m, 4H) ppm. LCMS: m/z 440.27 ($M+H$) $^+$; HPLC: 96.2%.

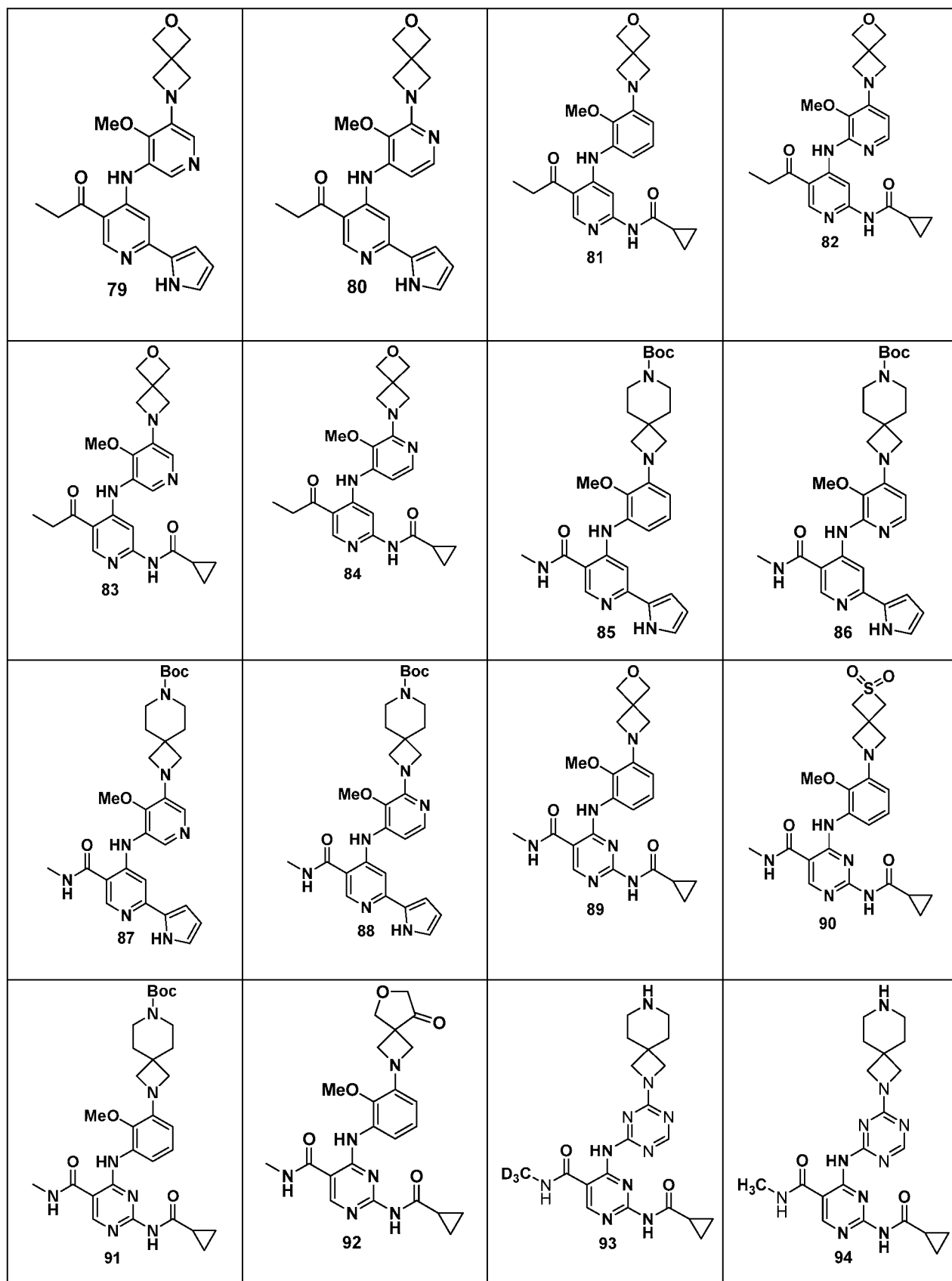
[000216] The following compounds may be prepared according to methods described herein by using appropriate intermediates (the corresponding non-deuteriated compounds may be prepared from the corresponding non-deuteriated intermediates prepared by using methyl amine instead of CD_3NH_2):

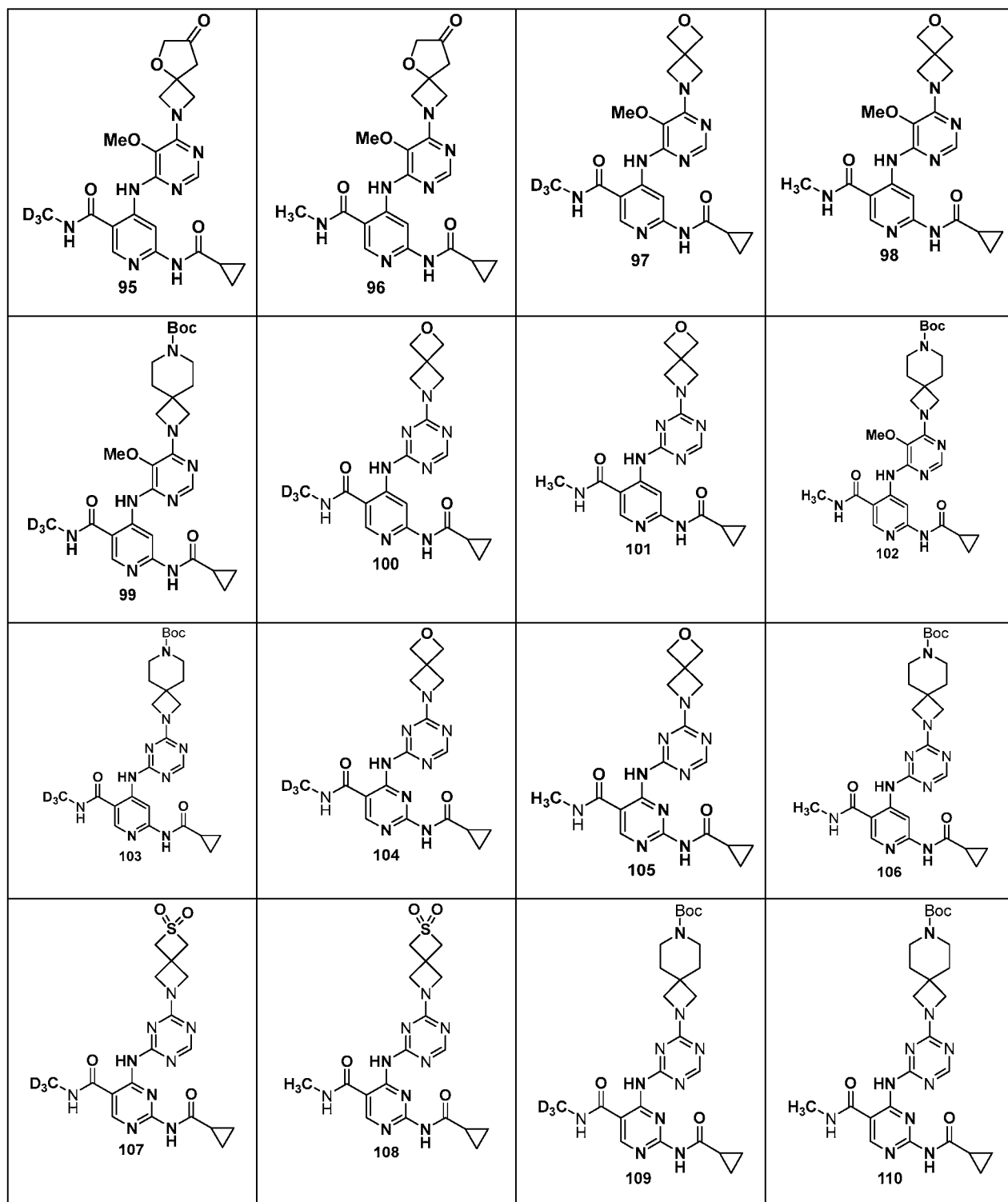


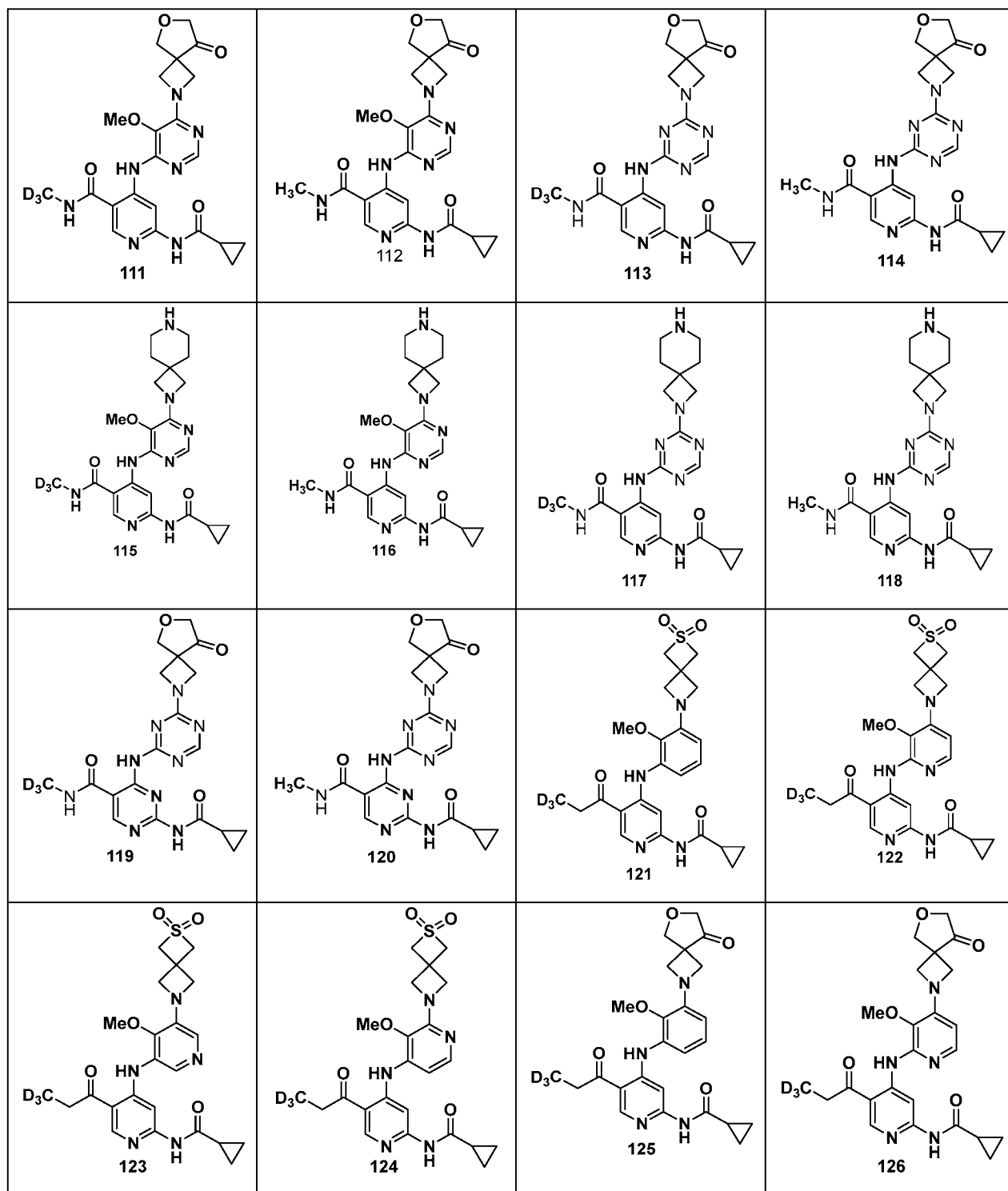


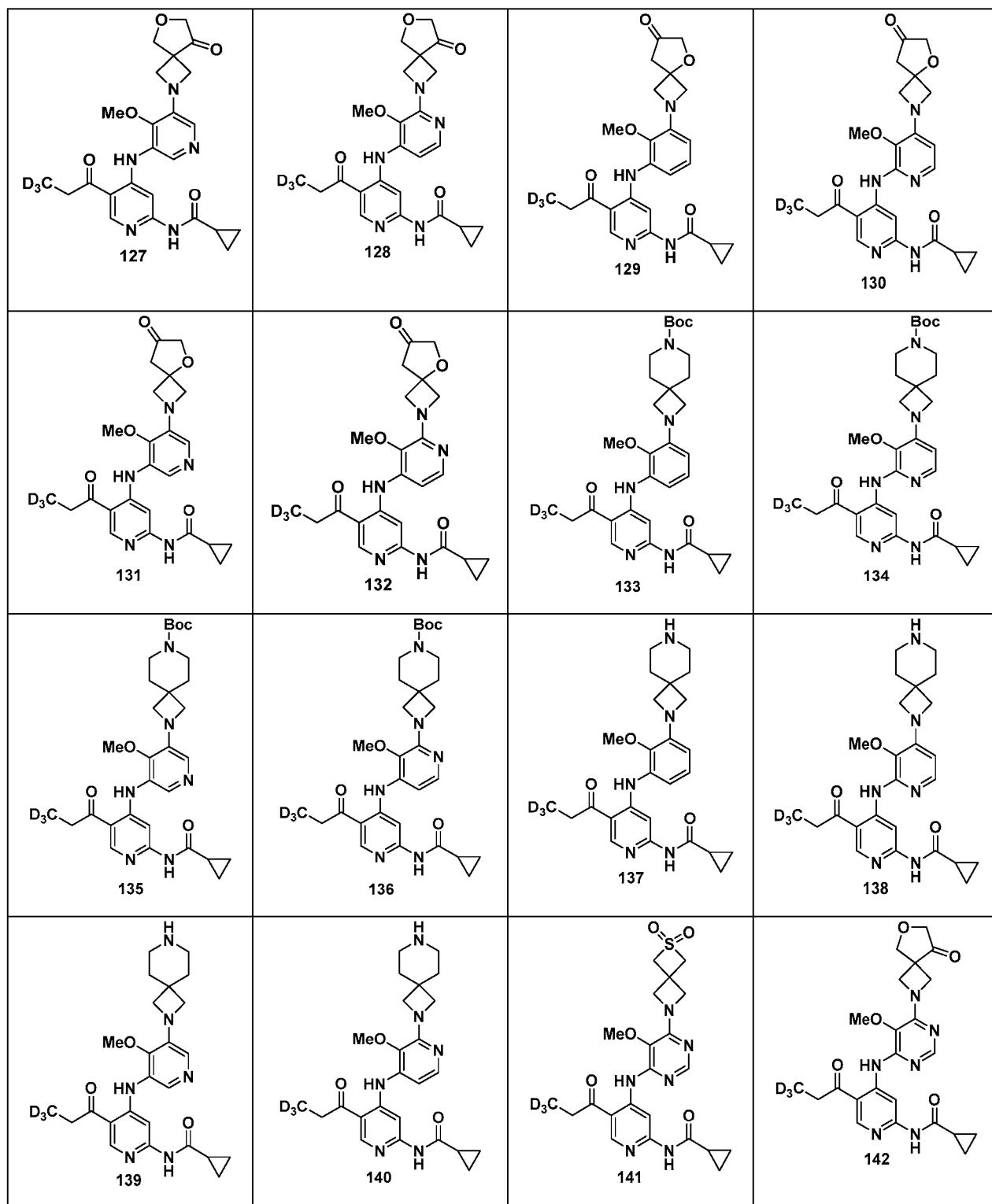


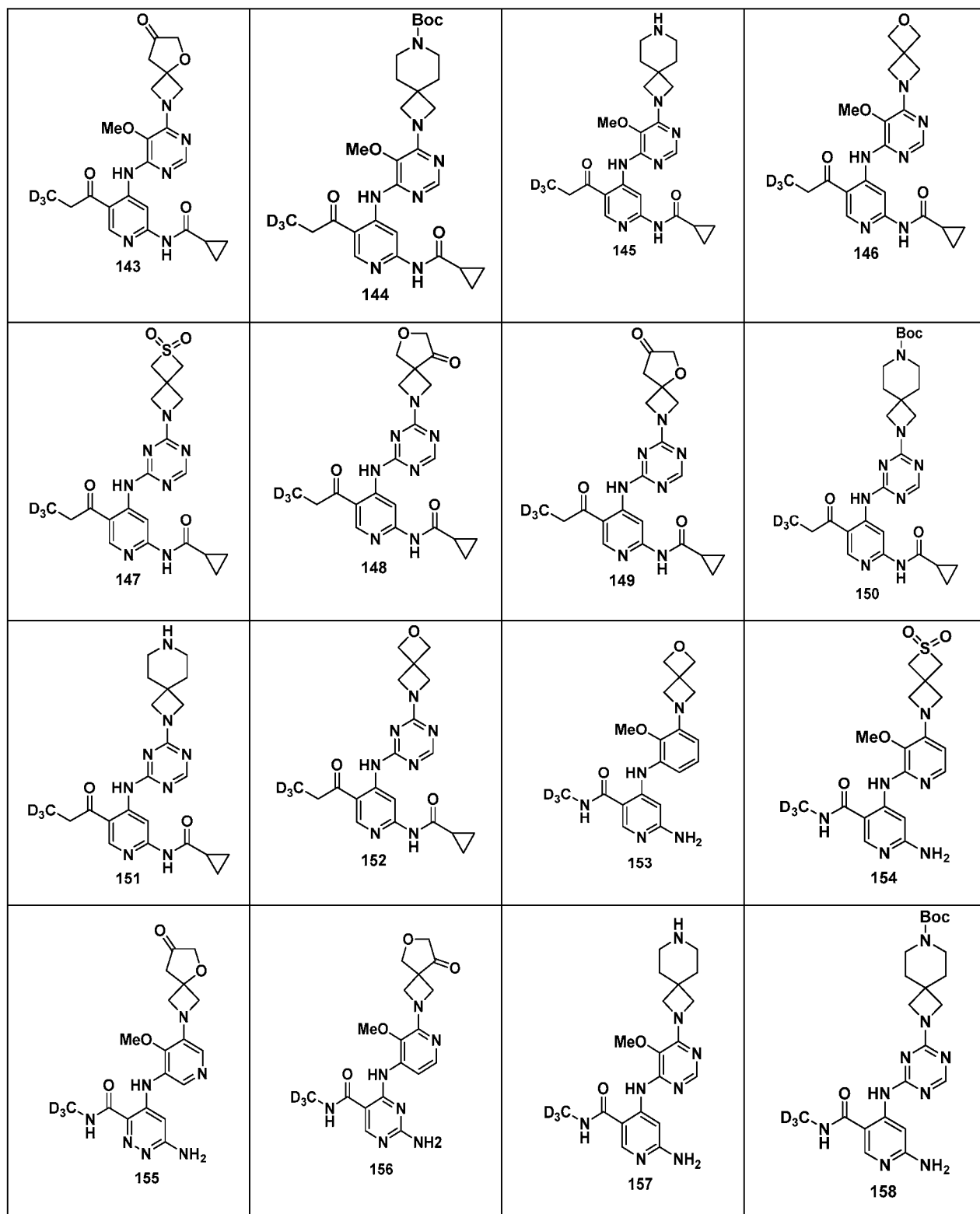


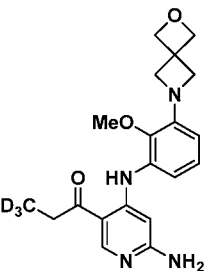
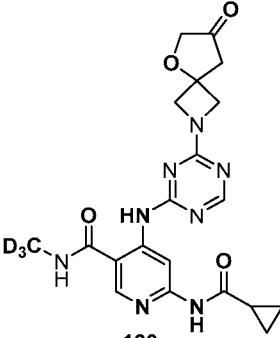
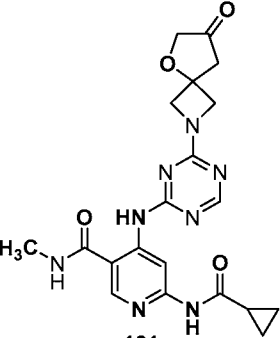
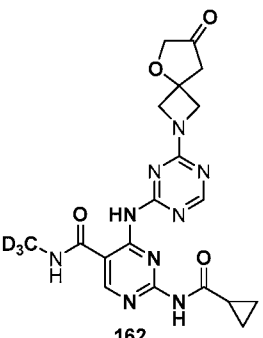
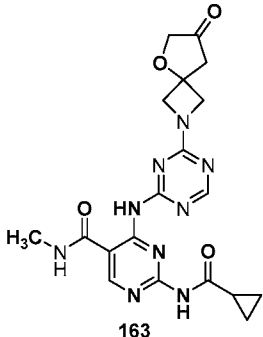
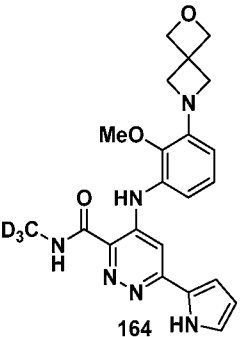
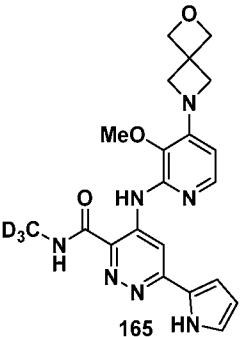
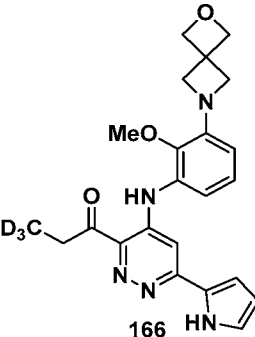
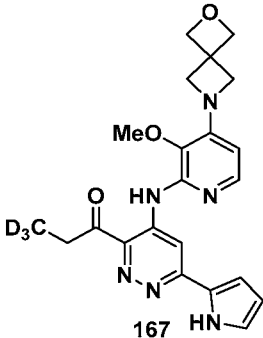
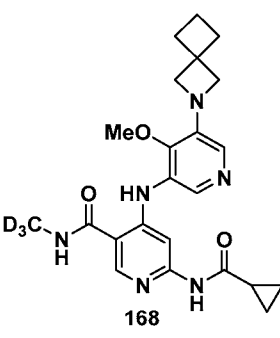
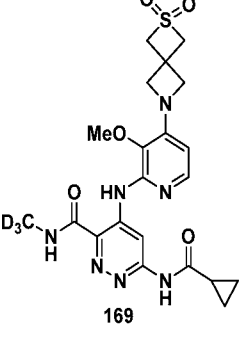
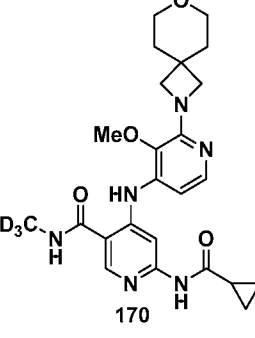
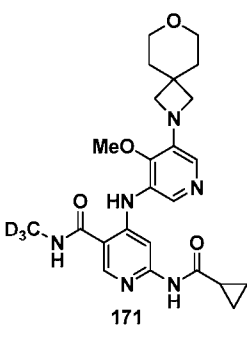
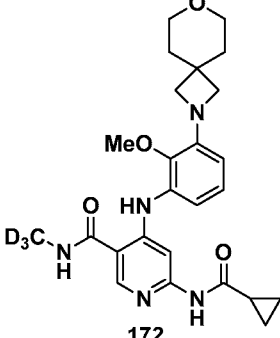
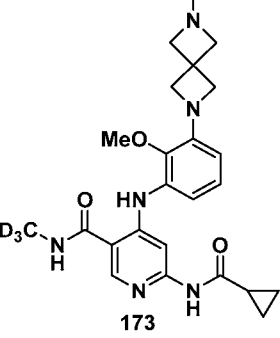
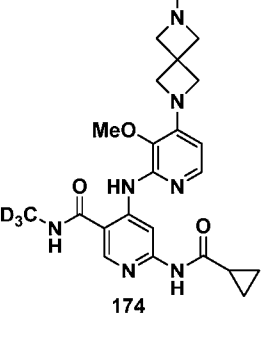


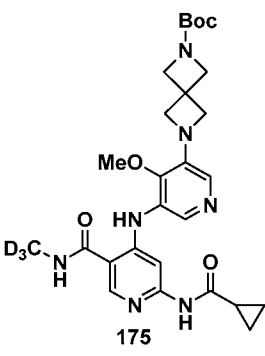
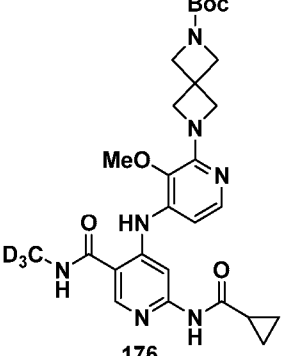
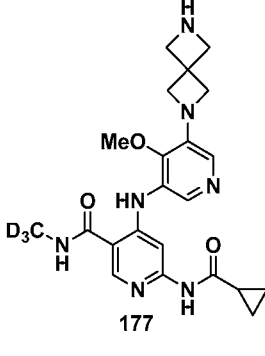
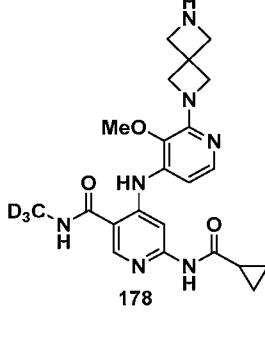
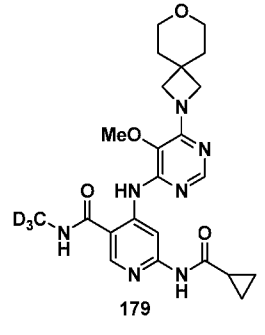
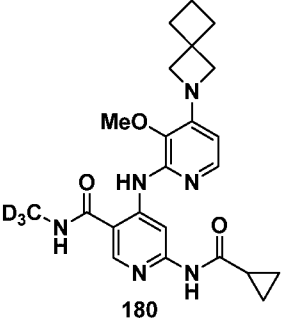
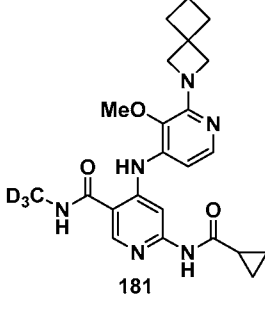
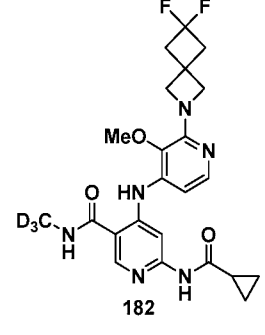
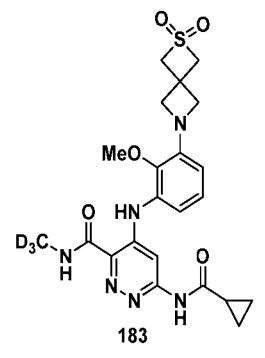
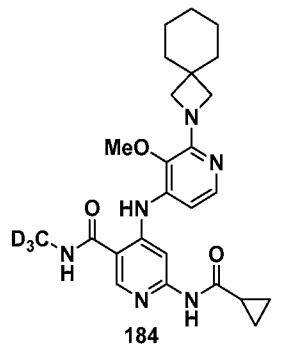
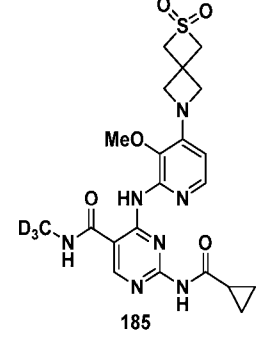
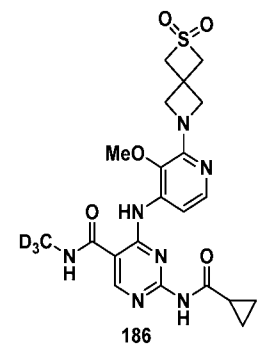
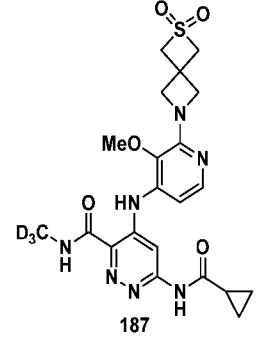








 159	 160	 161	 162
 163	 164	 165	 166
 167	 168	 169	 170
 171	 172	 173	 174

 175	 176	 177	 178
 179	 180	 181	 182
 183	 184	 185	 186
 187			

[000217] In an embodiment compounds having lower pyrimidine ring such as 41, 42, 43, 44, 89, 90, 91, 92, 93, 94, 104, 105, 107, 108, 109, 110, 119, 120, 156,

162, 163, 185, 186 may be prepared from appropriate starting materials obtained according to procedure as reported in WO2014074670.

[000218] In an embodiment compounds having lower pyridazine ring such as 155, 164, 165, 166, 167, 169, 183, 187 having may be prepared from appropriate starting materials obtained according to procedure as reported in WO2014074661.

BIOLOGICAL ASSAYS

TYK2 JH2 Binding Assay

Assay Procedure

[000219] Binding to TYK2 JH2 domain for test compounds was determined using the KINOMEScan™ platform by DiscoverX, which is a comprehensive high-throughput system for screening compounds against large numbers of human kinases. KINOMEScan™ is based on a competition binding assay that quantitatively measures the ability of a compound to compete with an immobilized, active-site directed ligand. The assay is performed by combining three components: DNA-tagged kinase; immobilized ligand; and a test compound. The ability of the test compound to compete with the immobilized ligand is measured via quantitative PCR of the DNA tag.

[000220] A fusion protein of a partial length construct of human TYK2 (JH2domain-pseudokinase) (amino acids G556 to D888 based on reference sequence NP 003322.3) and the DNA binding domain of NFkB was expressed in transiently transfected HEK293 cells. From these HEK 293 cells, extracts were prepared in M-PER extraction buffer (Pierce) in the presence of Protease Inhibitor Cocktail Complete (Roche) and Phosphatase Inhibitor Cocktail Set II (Merck) per manufacturers' instructions. The TYK2(JH2domain-pseudokinase) fusion protein was labelled with a chimeric double-stranded DNA tag containing the NFkB binding site (5'-GGGAATTCCC-3') fused to an amplicon for qPCR readout, which was added directly to the expression extract (the final concentration of DNA-tag in the binding reaction is 0.1 nM). Streptavidin-coated magnetic beads (DynaM280) were treated with a biotinylated small molecule ligand for 30 minutes at room

temperature to generate affinity resins the binding assays. The liganded beads were blocked with excess biotin and washed with blocking buffer (SeaBlock (Pierce), 1% BSA, 0.05% Tween 20, 1 mM DTT) to remove unbound ligand and to reduce nonspecific binding.

[000221] The binding reaction was assembled by combining 15.75 μ L of DNA-tagged kinase extract, 3.75 μ L liganded affinity beads, and 0.18 μ L test compound (PBS/0.05% Tween 20/10 mM DTT/0.1% BSA/2 pg/ml sonicated salmon sperm DNA)]. Extracts were used directly in binding assays without any enzyme purification steps at a >10,000-fold overall stock dilution (final DNA tagged enzyme concentration <0.1 nM). Extracts were loaded with DNA-tag and diluted into the binding reaction in a two-step process. First extracts were diluted 1:100 in 1x binding buffer (PBS/0.05% Tween 20/10 mM DTT/0.1% BSA/2 pg/ml sonicated salmon sperm DNA) containing 10 nM DNA-tag. This dilution was allowed to equilibrate at room temperature for 15 minutes and then subsequently diluted 1:100 in 1x binding buffer. Test compounds were prepared as 111x stocks in 100% DMSO. Kds were determined using an 11-point 3-fold compound dilution series with three DMSO control points.

[000222] All compounds for Kd measurements are distributed by acoustic transfer in the assays such that the final concentration of DMSO was 0.9%. All reactions were performed in polypropylene 384-well plates in a final volume of 0.02 mL. Assays were incubated with shaking for 1 hour at room temperature, then the beads were pelleted and washed with wash buffer (1x PBS, 0.05% Tween 20) to remove displaced kinase and test compound.

[000223] The washed beads were re-suspended in elution buffer (1x PBS, 0.05% Tween 20, 0.5 μ M non-biotinylated affinity ligand) and incubated at room temperature with shaking for 30 minutes. The kinase concentration in the eluates was measured by qPCR. qPCR reactions were assembled by adding 2.5 μ L of kinase eluate to 7.5 μ L of qPCR master mix containing 0.15 μ M amplicon primers and 0.15 μ M amplicon probe. The qPCR protocol consisted of a 10-minute hot start at 95 °C, followed by 35 cycles of 95 °C for 15 seconds, 60 °C for 1 minute. Test

compounds were prepared as 111X stocks in 100% DMSO. Kds were determined using an 11-point 3-fold compound dilution series with three DMSO control points. Binding constants (Kds) were calculated with a standard dose-response curve using the Hill equation:

$$\text{Response} = \text{Background} + \frac{\text{Signal} - \text{Background}}{1 + (\text{KdHill Slope} / \text{DoseHill Slope})}$$

The Hill Slope was set to -1. Curves were fitted using a non-linear least square fit with the Levenberg-Marquardt algorithm.

The Kd values for example compounds are reported in Table 1.

Table 1: TYK2 JH2 Binding Assay (Kd; nM)

Kd: A = <100nM, B = >100 and <1000nM, C = >1000 and <3000nM, D = >3000nM.

Compound No. / Example	TYK2 (JH2 domain) binding Kd (nM)
BMS986165	A
1	A
2	A
3	A
4	A
5	A
6	A
7	A
8	A
17	A
18	A
19	A

20	A
21	A
23	B
24	A
25	A
33	A
45	A
52	A
53	A
97	A
99	A
168	A
170	A
171	A
172	A
173	A
174	A
175	A
176	A
177	A
178	A
179	A

180	A
181	A
182	A
184	A
188	A
189	A
190	A
191	A

JAK1 JH2, JAK2 JH2, JAK1 JH1, JAK2 JH1, JAK3 JH1, TYK2 JH1

Binding Assays

Assay Procedure

[000224] Binding assays for JAK1 JH2, JAK2 JH2, JAK1 JH1, JAK2 JH1, JAK3 JH1, TYK2 JH1 for test compounds was determined using the KINOMEScan™ platform by DiscoverX. Assay protocol followed was similar to that of TYK2 JH2. The K_d values for example compounds are reported in Table 2.

Table 2: JAK1 JH2, JAK2 JH2, JAK1 JH1, JAK2 JH1, JAK3 JH1, TYK2 JH1 Binding Assay (K_d; nM)

K_d: A = <100nM, B = >100 and <1000nM, C = >1000 and <3000nM, D = >3000nM and <10000nM, E = >10000 and <30000nM, F = >30000nM.

Compound No. / Example	JAK1 (JH2 domain) binding K_d (nM)	JAK2 (JH2 domain) binding K_d (nM)	JAK1 (JH1 domain) binding K_d (nM)	JAK2 (JH1 domain) binding K_d (nM)	JAK3 (JH1 domain) binding K_d (nM)	TYK2 (JH1 domain) binding K_d (nM)
BMS986165	A	A	F	D	C	F

1	A	B	D	D	B	F
2	B	D	F	E	E	D
3	C	E	F	F	E	F
4	A	B	F	C	B	E
5	A	A	F	D	C	E
6	B	D	F	D	F	D
7	B	D	F	F	F	F
8	A	A	E	D	C	F
17	A	B	F	F	F	F
18	C	F	F	F	F	F
19	A	C	F	D	C	C
20	A	B	F	F	E	F
21	A	*	*	*	*	*
23	C	*	*	*	*	*
24	A	*	*	*	*	*
25	C	F	F	F	F	F
33	A	C	D	C	B	D
45	B	C	E	D	B	F

52	A	B	D	D	C	F
53	A	A	E	F	B	F
97	B	F	F	C	C	F
99	A	*	*	*	*	*
168	B	*	*	*	*	*
170	A	B	C	C	B	F
171	B	C	F	E	E	D
172	A	B	D	C	C	E
173	A	B	F	E	F	F
174	C	E	C	D	F	E
175	B	*	*	*	*	*
176	A	B	B	E	F	F
177	C	*	*	*	*	*
178	A	C	D	C	C	F
179	B	*	*	*	*	*
180	B	E	F	F	E	E
181	A	B	B	C	C	F
182	A	B	D	D	C	F

184	B	*	*	*	*	*
188	B	*	*	*	*	*
189	A	*	*	*	*	*
190	A	*	*	*	*	*
191	B	*	*	*	*	*

* indicates not performed

JAK1 JH1, JAK2 JH1, JAK3 JH1, TYK2 JH1 Kinase activity assays

Assay Procedure

[000225] Kinase activity assays were performed using the LANCE™ Ultra Kinase Activity Assay platform (Perkin Elmer). LANCE Ultra time-resolved fluorescence resonance energy transfer (TR-FRET) assays use a proprietary europium chelate donor dye, W1024 (Eu), together with ULight™, a small molecular weight acceptor dye with a red-shifted fluorescent emission. The binding of the Eu-labelled anti-phospho tyrosine PT66 antibody to the JAK-1 peptide substrate phosphorylated at Tyr1023 brings the Eu donor and ULight acceptor dye molecules into close proximity. Upon irradiation at 320 or 340 nm, the energy from the Eu donor is transferred to the ULight acceptor dye which, in turn, generates light at 665 nm. The intensity of the light emission is proportional to the level of ULight substrate phosphorylation.

[000226] Enzymes were diluted in kinase buffer containing 50mM HEPES pH 7.5, 1 mM EGTA, 10 mM MgCl₂, 2 mM DTT and 0.01% Tween-20. Test compounds were prepared as 10mM stock in 100% DMSO and further diluted to 0.4 mM in kinase buffer. A 3.33-fold series dilution was performed to generate 11 concentrations of each test compound. Kinase enzymes, ATP and substrate (ULight™ JAK-1) were added as per in-house standardized protocol (details provided in Table 3). The assay was carried out in a 384 well plate, where 2.5µL of 4X kinase enzyme and 2.5µL of 4X test compound were added. Further, 5µL of 2X ATP-

substrate mixture was added to initiate the reaction and incubated for respective durations at room temperature. 10 μ L of a 4X STOP solution and detection mixture containing 40mM EDTA (for terminating kinase reactions) and 8nM Eu-anti-phospho-tyrosine antibody (PT66) was added to all wells and further incubated at room temperature for 1 hour. At the end of the incubation period, the plate was read to determine TR-FRET signal at excitation wavelength at 320 nm and emission at 625 nm and 665 nm on a plate reader with TR-FRET capabilities. The TR-FRET signal observed was normalized to that of blank wells and percent inhibition was calculated by comparison to a control without inhibitor. Data was fitted to non-linear regression fit with variable slope (four parameters) for IC₅₀ calculations. The IC₅₀ values for example compounds are reported in Table 4.

Table 3: Enzyme, substrate concentrations and incubation times

Assays	Enzyme Concentration (nM)	ATP concentration (μ M)	U-light™ JAK1 peptide (nM)	Incubation time
JAK1 JH1	10	25	50	120 minutes
JAK2 JH1	0.25	10	50	30 minutes
JAK3 JH1	0.25	10	50	30 minutes
TYK2 JH1	20	10	50	120 minutes

Table 4: JAK1 JH1, JAK2 JH1, JAK3 JH1, TYK2 JH1 Activity Assay (IC₅₀; nM)

Cell free kinase activity assays

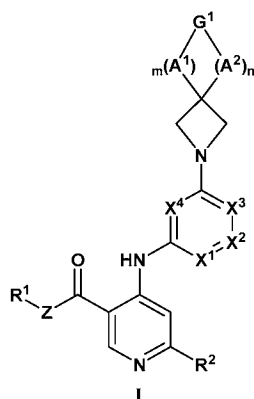
IC₅₀: A = <100nM, B = >100 and <1000nM, C = >1000 and <3000nM, D = >3000nM and <10000nM, E = >10000 and <30000nM, F = >30000 and <100000nM, G = >100000nM.

Compound No. / Example	JAK1 (JH1 domain) Activity IC₅₀ (nM)	JAK2 (JH1 domain) Activity IC₅₀ (nM)	JAK3 (JH1 domain) Activity IC₅₀ (nM)	TYK2 (JH1 domain) Activity IC₅₀ (nM)
BMS986165	D	C	C	G
1	C	D	D	F
2	F	E	F	G
3	F	F	F	G
4	C	D	D	G
5	D	D	C	G
6	F	F	G	G
7	G	G	G	G
8	D	D	D	G
17	G	G	G	G
18	G	F	G	G
19	G	E	E	F
20	G	G	G	G
97	G	G	G	G

[000227] In addition to the various embodiments described herein, the present disclosure includes the following embodiments numbered E1 through E60. This list

of embodiments is presented as an exemplary list and the application is not limited to these embodiments.

E1. A compound having the following formula (I):



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

X^1 , X^2 , X^3 , X^4 are independently selected from N or CR^3 ;

Z is selected from NR^4 , $CR^4R^{4'}$, O, S or a bond;

A^1 and A^2 are independently selected from $CR^4R^{4'}$ or O;

G^1 is selected from O, S, $S(O)_2$, $C(=O)$, NR^5 , $NC(=O)OR^6$ or $CR^4R^{4'}$;

m and n are independently selected from 0, 1, 2, 3 or 4;

R^1 is selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

R^2 is selected from hydrogen, halogen, -CN, $-OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)_2R^6$, $-NO_2$, $-NR^5R^{5'}$, $-NR^6S(=O)_2R^6$, $-S(=O)_2NR^5R^{5'}$, $-C(=O)R^6$, $-OC(=O)R^6$, $-C(=O)OR^6$, $-OC(=O)OR^6$, $-C(=O)NR^5R^{5'}$, $-OC(=O)NR^5R^{5'}$, $-NR^6C(=O)NR^5R^{5'}$, $-NR^6C(=O)R^6$, $-NR^6C(=S)R^6$, $-NR^6C(=O)OR^6$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_2 - C_6 alkenyl, C_2 -

C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^cR^d, C₁-C₆alkyl, or C₁-C₆haloalkyl;

R³ is selected from hydrogen, deuterium, halogen, -CN, -OR^a, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -NO₂, -NR^cR^d, -NR^aS(=O)₂R^b, -S(=O)₂NR^cR^d, -C(=O)R^a, -OC(=O)R^a, -C(=O)OR^a, -OC(=O)OR^a, -C(=O)NR^cR^d, -OC(=O)NR^cR^d, -NR^aC(=O)NR^cR^d, -NR^aC(=O)R^b, -NR^aC(=O)OR^b, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^cR^d, C₁-C₆alkyl, or C₁-C₆haloalkyl, C₁-C₆deuteroalkyl; with a proviso that when each of X¹, X², X³, and X⁴ represents CR³, X⁴ represents CR³, R³ not being hydrogen.

R⁴ and R^{4'} are independently selected from hydrogen, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^a, -NR^aC(=O)R^b, -NR^aC(=O)OR^b; alternatively R⁴ and R^{4'} together represents an oxo group; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OR^a, -NR^cR^d, -NR^aC(=O)OR^b, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^cR^d, aryl, C₁-C₆alkyl, or C₁-C₆haloalkyl;

R⁵ and R^{5'} are independently selected from hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆alkoxy, C₂-C₆alkenyl, C₂-C₆alkynyl, NC(=O)R^a, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl,

and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C₁-C₆alkyl, C₁-C₆alkoxy, aryl or C₁-C₆haloalkyl; or R⁵ and R^{5'} are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C₁-C₆alkyl, or C₁-C₆haloalkyl;

R⁶ and R^{6'} are independently selected from hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, aryl, C₁-C₆alkyl, or C₁-C₆haloalkyl;

each R^a and R^b is independently selected from hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, -C(=O)NHMe, C₁-C₆alkyl, cycloalkyl, aryl, heteroaryl or C₁-C₆haloalkyl; and

each R^c and R^d is independently selected from hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C₁-C₆alkyl, or C₁-C₆haloalkyl; or R^c and R^d are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo,

deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C₁-C₆alkyl, or C₁-C₆haloalkyl.

E2. A compound according to E1, wherein Z is NR⁴ or CR⁴R^{4'}.

E3. A compound according to E1 or E2, wherein A¹ and A² are independently selected from CR⁴R^{4'}.

E4. A compound according to E1- E3, wherein G¹ is selected from O, S(O)₂, NR⁵, NC(=O)OR⁶ or CR⁴R^{4'}.

E5. A compound according to E1-E4, wherein R¹ is selected from C₁-C₆alkyl or C₁-C₆deuteroalkyl.

E6. A compound according to E1-E5, wherein R² is selected from NR⁶C(=O)R^{6'} or heteroaryl.

E7. A compound according to E1-E6, wherein R³ is selected from hydrogen or -OR^a; with a proviso that when each of X¹, X², X³, and X⁴ represents CR³, X⁴ represents CR³, R³ not being hydrogen.

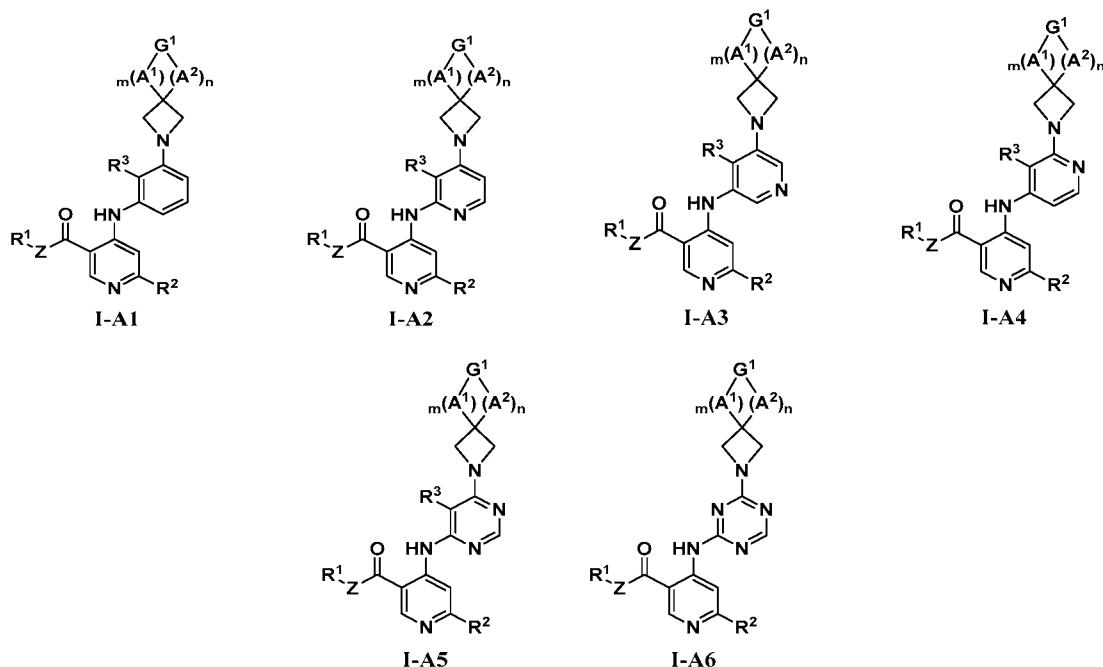
E8. A compound according to E1-E7, wherein R⁴ and R^{4'} are independently selected from hydrogen or halogen.

E9. A compound according to E1-E8, wherein R⁵ is hydrogen.

E10. A compound according to E1-E9, wherein R⁶ is selected from hydrogen, C₁-C₆alkyl or cycloalkyl.

E11. A compound according to E1-E10, wherein R^a is, C₁-C₆alkyl

E12. A compound according to E1 having the following formulae:



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^1 , R^2 , R^3 , Z , A^1 , A^2 , G^1 , m and n are as defined in E1.

E13. A compound according to E12, wherein Z is NR^4 or $CR^4R^{4'}$.

E14. A compound according to E12 or E13, wherein A^1 and A^2 are independently selected from $CR^4R^{4'}$.

E15. A compound according to E12-E14, wherein G^1 is selected from O , $S(O)_2$, NR^5 , $NC(=O)OR^6$ or $CR^4R^{4'}$.

E16. A compound according to E12-E15, wherein R^1 is selected from C_1 - C_6 alkyl or C_1 - C_6 deuteroalkyl.

E17. A compound according to E12-E16, wherein R^2 is selected from $NR^6C(=O)R^6$ or heteroaryl.

E18. A compound according to E12-E17, wherein R^3 is selected from hydrogen or $-OR^a$; with a proviso that when each of X^1 , X^2 , X^3 , and X^4 represents CR^3 , X^4 represents CR^3 , R^3 not being hydrogen.

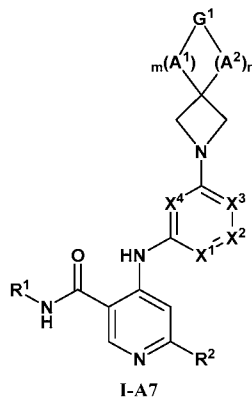
E19. A compound according to E12-E18, wherein R^4 and $R^{4'}$ are independently selected from hydrogen or halogen.

E20. A compound according to E12-E19, wherein R^5 is hydrogen.

E21. A compound according to E12-E20, wherein R^6 and $R^{6'}$ is selected from hydrogen, C_1 - C_6 alkyl or cycloalkyl.

E22. A compound according to E12-21, wherein R^a is, C_1 - C_6 alkyl

E23. A compound according to E1 having the following formula:



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein X^1 , X^2 , X^3 , X^4 , A^1 , A^2 , G^1 , R^1 , R^2 , m and n are as defined in E1.

E24. A compound according to E23, wherein X^1 , X^2 , X^3 , X^4 are independently selected from N or CR^3

E25. A compound according to E23 or E24, wherein A^1 and A^2 are independently selected from $CR^4R^{4'}$.

E26. A compound according to E23-E25, wherein G^1 is selected from O, $S(O)_2$, NR^5 , $NC(=O)OR^6$ or $CR^4R^{4'}$.

E27. A compound according to E23-E26, wherein R^1 is selected from C_1 - C_6 alkyl or C_1 - C_6 deuteroalkyl.

E28. A compound according to E23-E27, wherein R^2 is selected from $NR^6C(=O)R^{6'}$ or heteroaryl.

E29. A compound according to E23-E28, wherein R^3 is selected from hydrogen or $-OR^a$; with a proviso that when each of X^1 , X^2 , X^3 , and X^4 represents CR^3 , X^4 represents CR^3 , R^3 not being hydrogen.

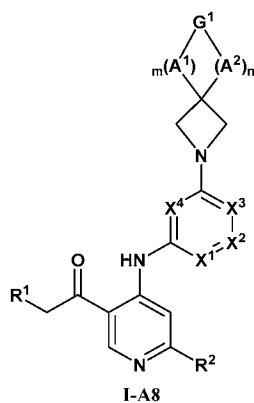
E30. A compound according to E23-E29, wherein R^4 and $R^{4'}$ are independently selected from hydrogen or halogen.

E31. A compound according to E23-30, wherein R^5 is hydrogen.

E32. A compound according to E23-31, wherein R^6 and $R^{6'}$ is selected from hydrogen, C_1 - C_6 alkyl or cycloalkyl.

E33. A compound according to E23-E32, wherein R^a is, C_1 - C_6 alkyl

E34. A compound according to E1 having the following formula:



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein X^1 , X^2 , X^3 , X^4 , A^1 , A^2 , G^1 , R^1 , R^2 , m and n are as defined in E1.

E35. A compound according to E34, wherein X^1 , X^2 , X^3 , X^4 are independently selected from N or CR^3

E36. A compound according to E34 or E35, wherein A^1 and A^2 are independently selected from $CR^4R^{4'}$.

E37. A compound according to E34-E36, wherein G^1 is selected from O, $S(O)_2$, NR^5 , $NC(=O)OR^6$ or $CR^4R^{4'}$.

E38. A compound according to E34-E37, wherein R^1 is selected from C_1 - C_6 alkyl or C_1 - C_6 deuteroalkyl.

E39. A compound according to E34-E38, wherein R^2 is selected from $NR^6C(=O)R^{6'}$ or heteroaryl.

E40. A compound according to E34-E39, wherein R^3 is selected from hydrogen or $-OR^a$; with a proviso that when each of X^1 , X^2 , X^3 , and X^4 represents CR^3 , X^4 represents CR^3 , R^3 not being hydrogen.

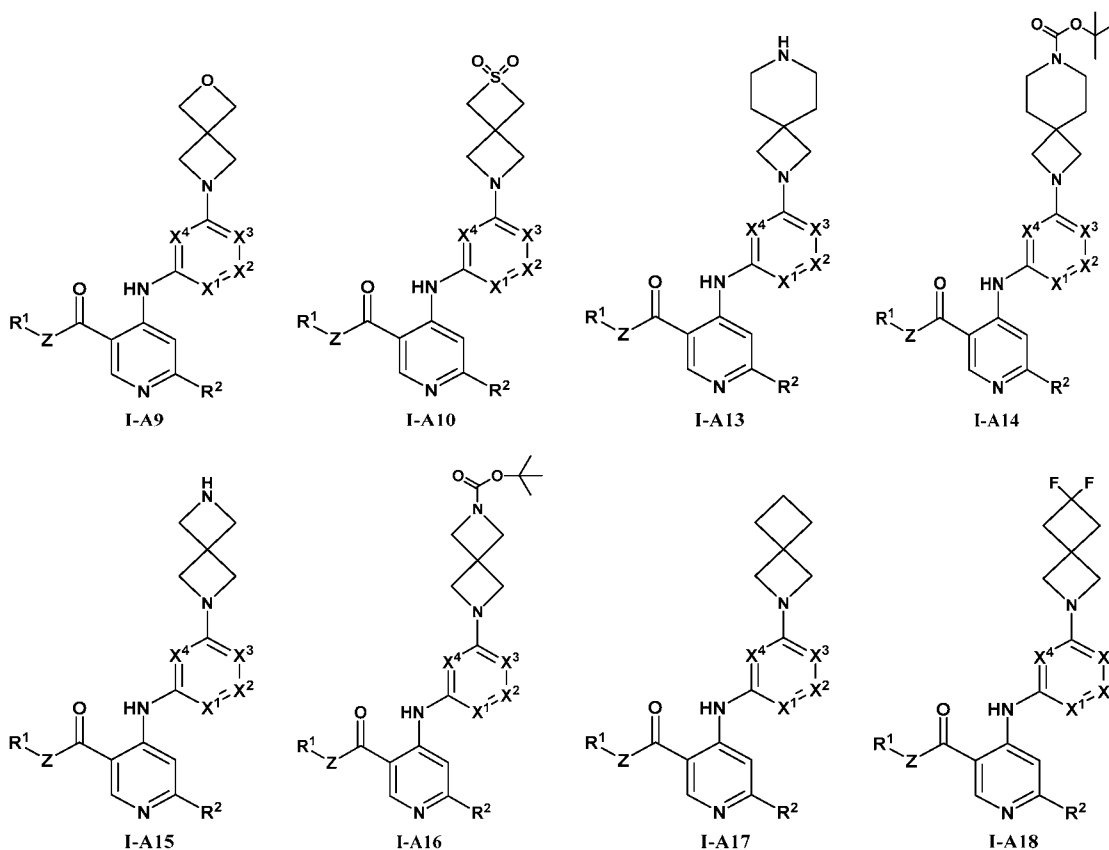
E41. A compound according to E34-E40, wherein R^4 and $R^{4'}$ are independently selected from hydrogen or halogen.

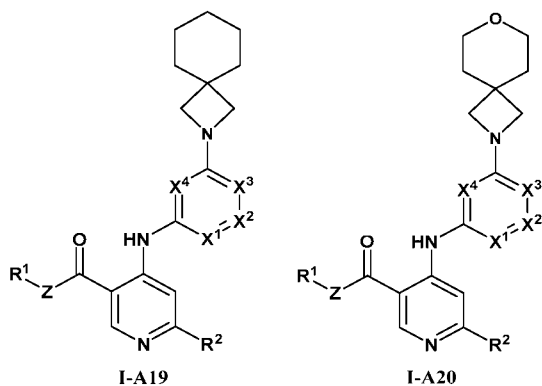
E42. A compound according to E34-E41, wherein R^5 is hydrogen.

E43. A compound according to E34-E42, wherein R^6 and $R^{6'}$ is selected from hydrogen, C_1 - C_6 alkyl or cycloalkyl.

E44. A compound according to E34-E43, wherein R^a is, C_1 - C_6 alkyl

E45. A compound according to E1 having the following formulae:





or a pharmaceutically acceptable salt or stereoisomer thereof, wherein X^1 , X^2 , X^3 , X^4 , Z , R^1 , R^2 are as defined in E1.

E46. A compound according to E45, wherein X^1 , X^2 , X^3 , X^4 are independently selected from N or CR^3

E47. A compound according to E45 or E46, wherein Z is NR^4 or $CR^4R^{4'}$.

E48. A compound according to E45-E47, wherein R^1 is selected from C_1 - C_6 alkyl or C_1 - C_6 deuteroalkyl.

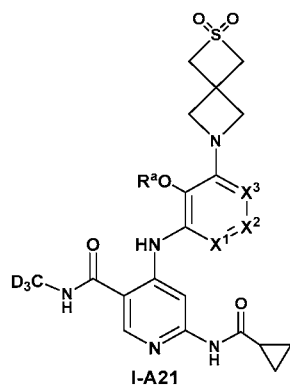
E49. A compound according to E45-E48, wherein R^2 is selected from $NR^6C(=O)R^{6'}$ or heteroaryl.

E50. A compound according to E45-E49, wherein R^3 is selected from hydrogen or $-OR^a$; with a proviso that when each of X^1 , X^2 , X^3 , and X^4 represents CR^3 , X^4 represents CR^3 , R^3 not being hydrogen.

E51. A compound according to E45-E50, wherein R^6 and $R^{6'}$ is selected from hydrogen, C_1 - C_6 alkyl or cycloalkyl.

E52. A compound according to E45-E51, wherein R^a is, C_1 - C_6 alkyl

E53. A compound according to E1 having the following formulae:

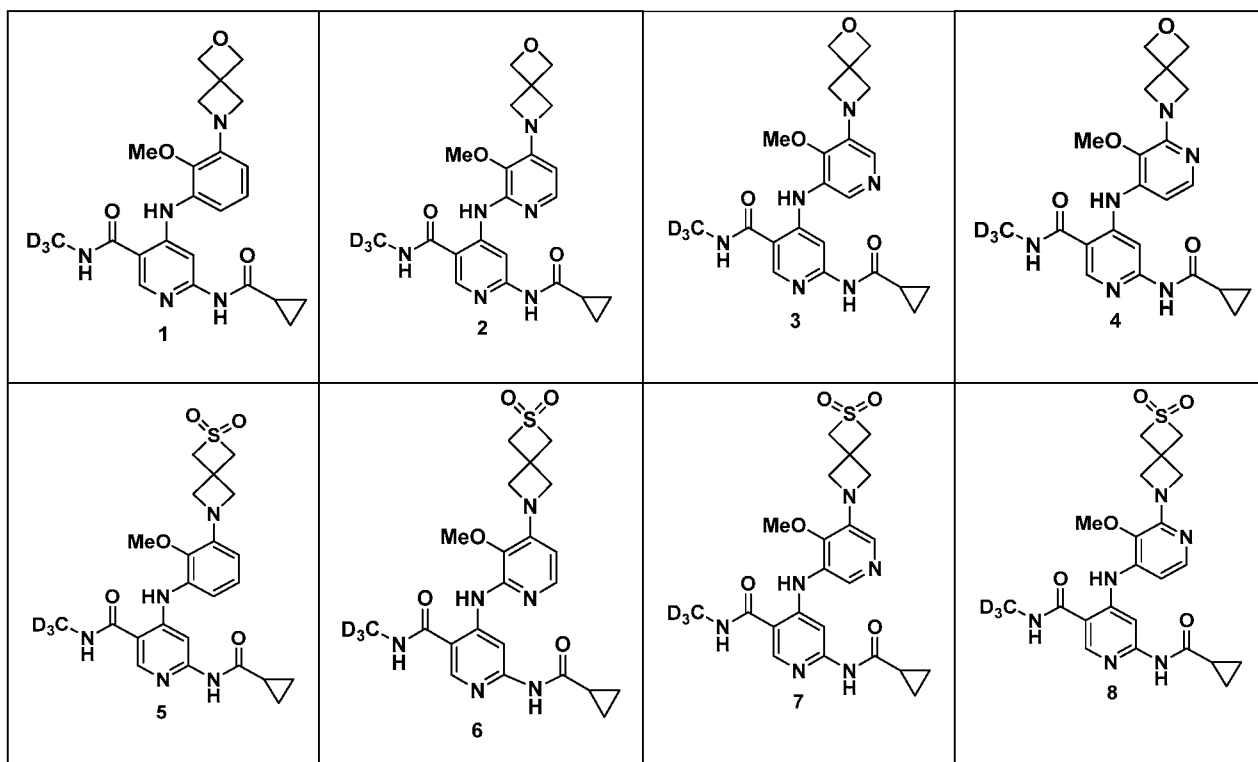


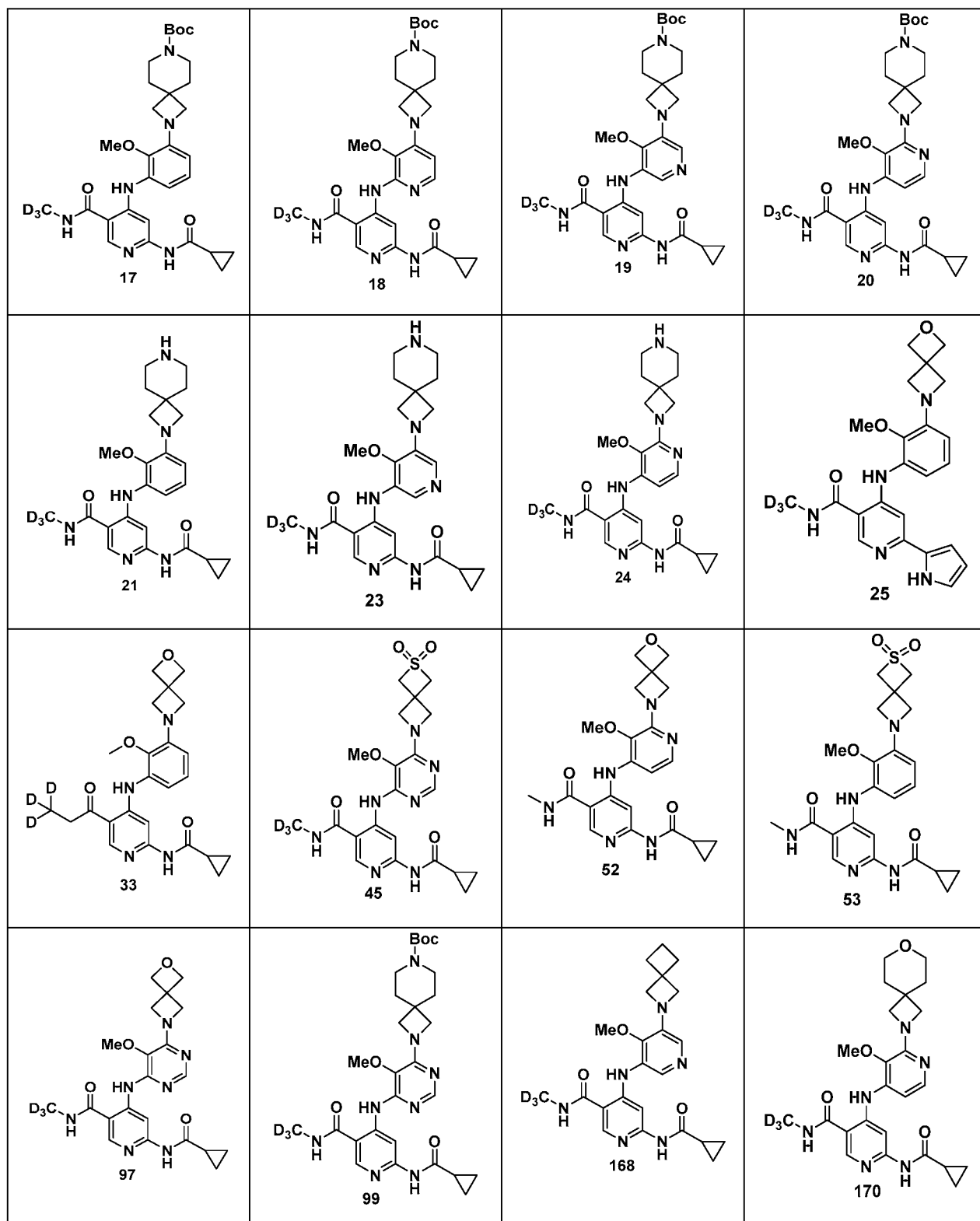
or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

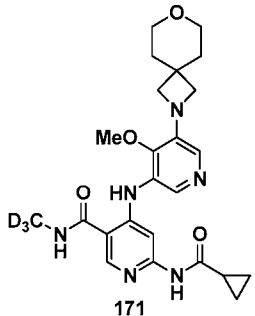
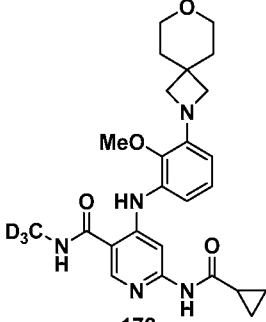
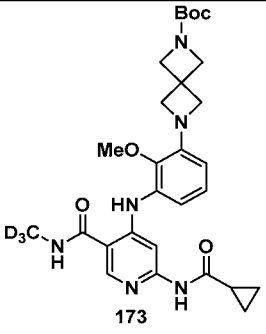
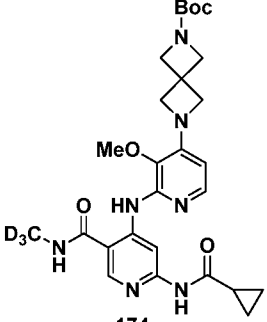
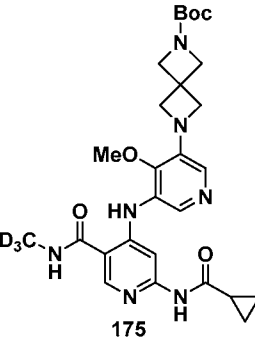
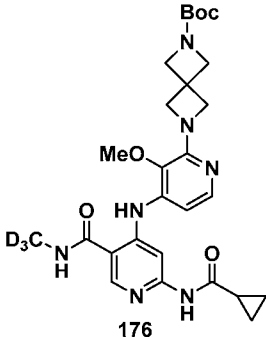
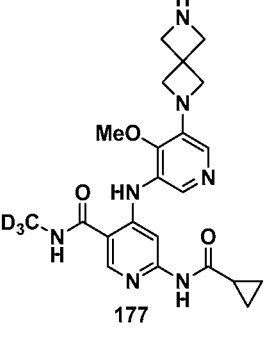
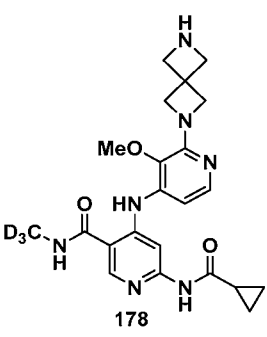
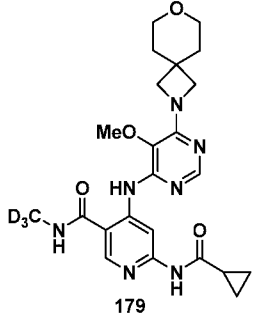
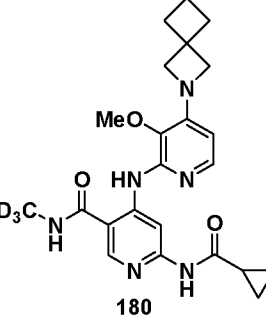
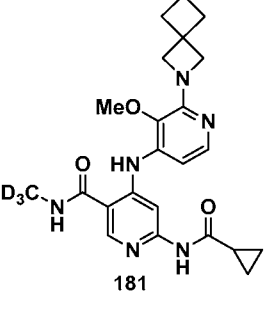
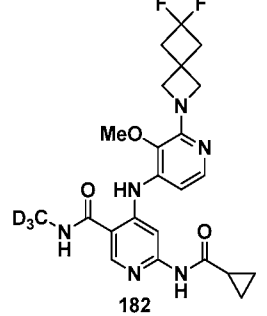
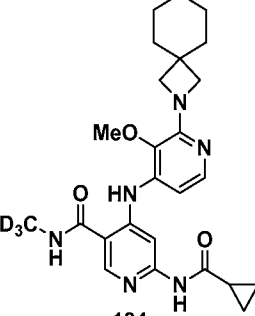
X^1 , X^2 , X^3 , X^4 are independently selected from N or CH

R^a is C_1 - C_6 alkyl

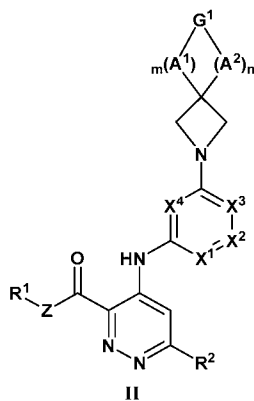
E54. A compound selected from the group consisting of:





 171	 172	 173	 174
 175	 176	 177	 178
 179	 180	 181	 182
 184			

E55. A compound having the following formula (II):

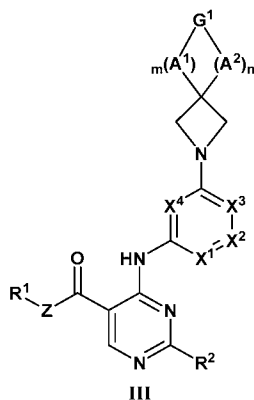


or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

R² is a heteroaryl wherein the carbon atom of heteraryl group is attached with the pyridazine ring; and

R¹, Z, X¹, X², X³, X⁴, G¹, A¹, A², m and n are as defined in E1.

E56. A compound having the following formula (III):

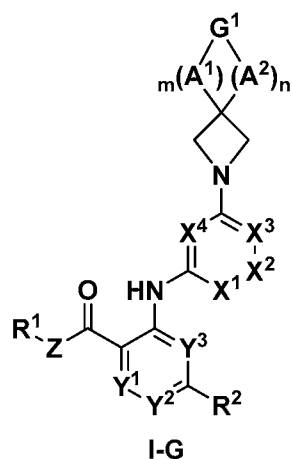


or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R¹, R², Z, X¹, X², X³, X⁴, G¹, A¹, A², m and n are as defined in E1.

E57. A pharmaceutical composition comprising one or more compounds according to E1-E54, and a pharmaceutically acceptable carrier or diluent.

E58. A method of treating a TYK2-mediated disorder comprising administering to a patient in need thereof, a compound of any one of E1-E55, or a pharmaceutically acceptable salt or stereoisomer thereof.

E59. A compound having the following formula (A):



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

Y^1 , Y^3 are independently selected from N or CH;

Y^2 is N;

X^1 , X^2 , X^3 , X^4 are independently selected from N or CR^3 ;

Z is selected from NR^4 , $CR^4R^{4'}$, O, S or a bond;

A^1 and A^2 are independently selected from $CR^4R^{4'}$ or O;

G^1 is selected from O, S, $S(O)_2$, $C(=O)$, NR^5 , $NC(=O)OR^6$ or $CR^4R^{4'}$;

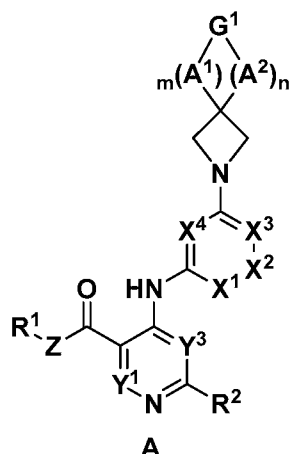
m and n are independently selected from 0, 1, 2, 3 or 4;

R^1 , R^2 , R^3 , R^4 , $R^{4'}$, R^5 , R^6 are as defined in E1.

E60. In an embodiment compound of Formula (A) as described in E59 encompasses the compounds of Formula (I), Formula (II) and Formula (III).

We Claim:

1. A compound of Formula (A):



or a pharmaceutically acceptable salt or stereoisomer thereof,
wherein:

Y^1 and Y^3 are independently selected from N or CH;

X^1 , X^2 , X^3 , and X^4 are independently selected from N or CR^3 ;

Z is selected from NR^4 , $CR^4R^{4'}$, O, S or a bond;

A^1 and A^2 are independently selected from $CR^4R^{4'}$ or O;

G^1 is selected from O, S, $S(O)_2$, $C(=O)$, NR^5 , $NC(=O)OR^6$ or $CR^4R^{4'}$;

m and n are independently selected from 0, 1, 2, 3 or 4;

R^1 is selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

R^2 is selected from hydrogen, halogen, -CN, $-OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)_2R^6$, $-NO_2$, $-NR^5R^{5'}$, $-NR^6S(=O)_2R^6$, $-S(=O)_2NR^5R^{5'}$, $-C(=O)R^6$, $-OC(=O)R^6$, $-C(=O)OR^6$, $-OC(=O)OR^6$, $-C(=O)NR^5R^{5'}$, $-OC(=O)NR^5R^{5'}$, $-NR^6C(=O)NR^5R^{5'}$, $-NR^6C(=O)R^6$, $-NR^6C(=S)R^6$, $-NR^6C(=O)OR^6$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 -

C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^cR^d, C₁-C₆alkyl, or C₁-C₆haloalkyl;

R³ is selected from hydrogen, deuterium, halogen, -CN, -OR^a, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -NO₂, -NR^cR^d, -NR^aS(=O)₂R^b, -S(=O)₂NR^cR^d, -C(=O)R^a, -OC(=O)R^a, -C(=O)OR^a, -OC(=O)OR^a, -C(=O)NR^cR^d, -OC(=O)NR^cR^d, -NR^aC(=O)NR^cR^d, -NR^aC(=O)R^b, -NR^aC(=O)OR^b, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^cR^d, C₁-C₆alkyl, or C₁-C₆haloalkyl, C₁-C₆deuteroalkyl; with a proviso that when each of X¹, X², X³, and X⁴ represents CR³, X⁴ represents CR³, R³ not being hydrogen.

R⁴ and R^{4'} are independently selected from hydrogen, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^a, -NR^aC(=O)R^b, -NR^aC(=O)OR^b; or alternatively R⁴ and R^{4'} together represents an oxo group; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OR^a, -NR^cR^d, -NR^aC(=O)OR^b, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^cR^d, aryl, C₁-C₆alkyl, or C₁-C₆haloalkyl;

R⁵ and R^{5'} are independently selected from hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆alkoxy, C₂-C₆alkenyl, C₂-C₆alkynyl, NC(=O)R^a, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -

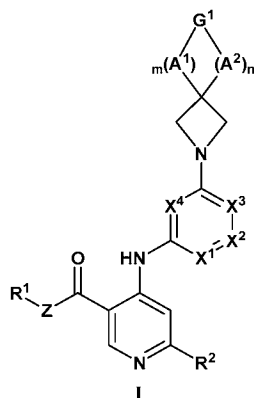
C(=O)OH, -C(=O)OMe, C₁-C₆alkyl, C₁-C₆alkoxy, aryl or C₁-C₆haloalkyl; or R⁵ and R^{5'} are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C₁-C₆alkyl, or C₁-C₆haloalkyl;

R⁶ and R^{6'} are independently selected from hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, aryl, C₁-C₆alkyl, or C₁-C₆haloalkyl;

each R^a and R^b is independently selected from hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, -C(=O)NHMe, C₁-C₆alkyl, cycloalkyl, aryl, heteroaryl or C₁-C₆haloalkyl; and

each R^c and R^d is independently selected from hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C₁-C₆alkyl, or C₁-C₆haloalkyl; or R^c and R^d are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C₁-C₆alkyl, or C₁-C₆haloalkyl.

2. The compound of claim 1, wherein the compound is of formula (I):



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

X^1 , X^2 , X^3 , and X^4 are independently selected from N or CR^3 ;

Z is selected from NR^4 , CR^4R^4 , O, S or a bond;

A^1 and A^2 are independently selected from CR^4R^4 or O;

G^1 is selected from O, S, $S(O)_2$, $C(=O)$, NR^5 , $NC(=O)OR^6$ or CR^4R^4 ;

m and n are independently selected from 0, 1, 2, 3 or 4;

R^1 is selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

R^2 is selected from hydrogen, halogen, -CN, $-OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)_2R^6$, $-NO_2$, $-NR^5R^{5'}$, $-NR^6S(=O)_2R^{6'}$, $-S(=O)_2NR^5R^{5'}$, $-C(=O)R^6$, $-OC(=O)R^6$, $-C(=O)OR^6$, $-OC(=O)OR^6$, $-C(=O)NR^5R^{5'}$, $-OC(=O)NR^5R^{5'}$, $-NR^6C(=O)NR^5R^{5'}$, $-NR^6C(=O)R^6$, $-NR^6C(=S)R^{6'}$, $-NR^6C(=O)OR^6$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

R^3 is selected from hydrogen, deuterium, halogen, $-CN$, $-OR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-NO_2$, $-NR^cR^d$, $-NR^aS(=O)_2R^b$, $-S(=O)_2NR^cR^d$, $-C(=O)R^a$, $-OC(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)OR^a$, $-C(=O)NR^cR^d$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)NR^cR^d$, $-NR^aC(=O)R^b$, $-NR^aC(=O)OR^b$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, $-CN$, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl; with a proviso that when each of X^1 , X^2 , X^3 , and X^4 represents CR^3 , X^4 represents CR^3 , R^3 not being hydrogen.

R^4 and $R^{4'}$ are independently selected from hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-NR^aC(=O)R^b$, $-NR^aC(=O)OR^b$; or alternatively R^4 and $R^{4'}$ together represents an oxo group; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, $-CN$, $-OR^a$, $-NR^cR^d$, $-NR^aC(=O)OR^b$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^cR^d$, aryl, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

R^5 and $R^{5'}$ are independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 alkoxy, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, $NC(=O)R^a$, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, $-CN$, $-OH$, $-OMe$, $-NH_2$, $-C(=O)Me$, $-C(=O)OH$, $-C(=O)OMe$, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, aryl or C_1 - C_6 haloalkyl; or R^5 and $R^{5'}$ are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo, deuterium, halogen, $-CN$, $-OH$, $-OMe$, $-NH_2$, $-C(=O)Me$, $-C(=O)OH$, $-C(=O)OMe$, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

R^6 and $R^{6'}$ are independently selected from hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, aryl, C₁-C₆alkyl, or C₁-C₆haloalkyl;

each R^a and R^b is independently selected from hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, -C(=O)NHMe, C₁-C₆alkyl, cycloalkyl, aryl, heteroaryl or C₁-C₆haloalkyl; and

each R^c and R^d is independently selected from hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C₁-C₆alkyl, or C₁-C₆haloalkyl; or R^c and R^d are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OMe, -NH₂, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C₁-C₆alkyl, or C₁-C₆haloalkyl.

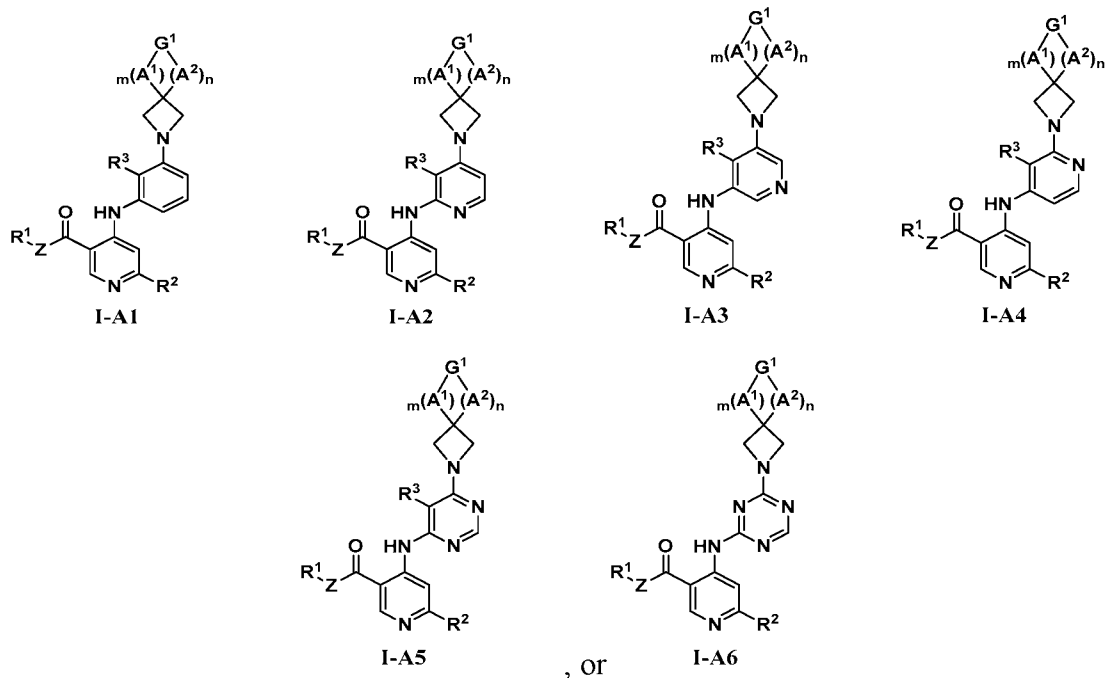
3. The compound according to claim 1 or 2, wherein Z is NR^4 or $CR^4R^{4'}$.

4. The compound according to any one of claims 1-3, wherein A^1 and A^2 are independently selected from $CR^4R^{4'}$.

5. The compound according to any one of claims 1-4, wherein G^1 is selected from O, $S(O)_2$, NR^5 , $NC(=O)OR^6$ or $CR^4R^{4'}$.
6. The compound according to claim 5, wherein G^1 is O or $S(O)_2$.
7. The compound according to any one of claims 1-6, wherein R^1 is selected from C_1 - C_6 alkyl or C_1 - C_6 deuteroalkyl.
8. The compound according to claim 7, wherein R^1 is $-CH_3$, $-CD_3$, or $-CH_2CD_3$.
9. The compound according to claim 1-8, wherein R^2 is selected from $NR^6C(=O)R^{6'}$ or heteroaryl.
10. The compound according to any one of claims 1-9, wherein R^6 is selected from hydrogen, C_1 - C_6 alkyl or cycloalkyl.
11. The compound according to any one of claims 1-10, wherein R^2 is $NHC(=O)$ -cycloalkyl.
12. The compound according to claim 11, wherein R^2 is $NHC(=O)$ -cyclopropyl.
13. The compound according to any one of claims 1-12, wherein R^3 is selected from hydrogen or $-OR^a$; with a proviso that when each of X^1 , X^2 , X^3 , and X^4 represents CR^3 , X^4 represents CR^3 , R^3 not being hydrogen.
14. The compound according to any one of claims 1-13, wherein R^4 and $R^{4'}$ are independently selected from hydrogen or halogen.
15. The compound according to any one of claims 1-14, wherein R^5 is hydrogen.
16. The compound according to any one of claims 1-15, wherein R^a is C_1 - C_6 alkyl.

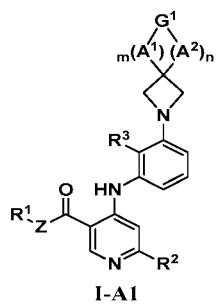
17. The compound according to claim 16, wherein R^a is methyl.

18. The compound according to claim 1, wherein the compound is of Formula I-A1, I-A2, I-A3, I-A4, I-A5 or I-A6:



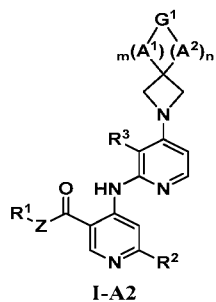
or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^1 , R^2 , R^3 , Z , A^1 , A^2 , G^1 , m and n are as defined in claim 1.

19. The compound according to claim 18, wherein the compound is of Formula I-A1



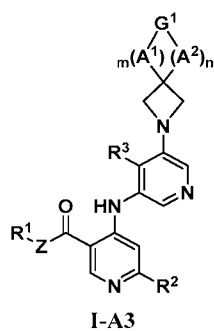
, or a pharmaceutically acceptable salt thereof.

20. The compound according to claim 18, wherein the compound is of Formula I-A2:



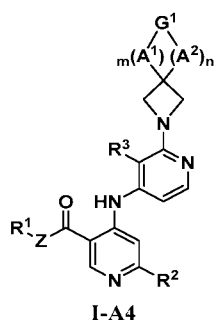
, or a pharmaceutically acceptable salt thereof.

21. The compound according to claim 18, wherein the compound is of Formula I-A3:



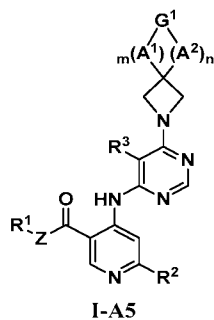
, or a pharmaceutically acceptable salt thereof.

22. The compound according to claim 18, wherein the compound is of Formula I-A4:



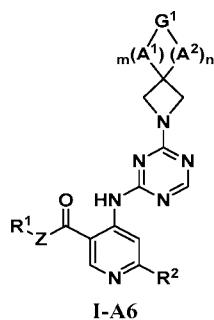
. or a pharmaceutically acceptable salt thereof.

23. The compound according to claim 18, wherein the compound is of Formula I-A5:



, or a pharmaceutically acceptable salt thereof.

24. The compound according to claim 18, wherein the compound is of Formula I-A6:



, or a pharmaceutically acceptable salt thereof.

25. The compound according to any one of claims 18-24, wherein Z is NR^4 or $\text{CR}^4\text{R}^{4'}$.

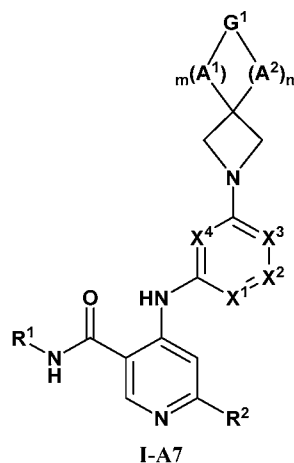
26. The compound according to any one of claims 18-25, wherein A^1 and A^2 are independently selected from $\text{CR}^4\text{R}^{4'}$.

27. The compound according to any one of claims 18-26, wherein G^1 is selected from O, $\text{S}(\text{O})_2$, NR^5 , $\text{NC}(=\text{O})\text{OR}^6$ or $\text{CR}^4\text{R}^{4'}$.

28. The compound according to any one of claims 18-27, wherein G^1 is O or $\text{S}(\text{O})_2$.

29. The compound according to any one of claims 18-28, wherein R^1 is selected from C_1 - C_6 alkyl or C_1 - C_6 deuteroalkyl.

30. The compound according to claim 29, wherein R^1 is $-CH_3$, $-CD_3$, or $-CH_2CD_3$.
31. The compound according to any one of claims 18-30, wherein R^2 is selected from $NR^6C(=O)R^{6'}$ or heteroaryl.
32. The compound according to any one of claims 18-31, wherein R^3 is selected from hydrogen or $-OR^a$, with a proviso that when each of X^1 , X^2 , X^3 , and X^4 represents CR^3 , X^4 represents CR^3 , R^3 not being hydrogen.
33. The compound according to any one of claims 18-32, wherein R^4 and $R^{4'}$ are independently selected from hydrogen or halogen.
34. The compound according to any one of claims 18-33, wherein R^5 is hydrogen.
35. The compound according to any one of claims 18-34, wherein R^6 and $R^{6'}$ is selected from hydrogen, C_1 - C_6 alkyl or cycloalkyl.
36. The compound according to any one of claims 18-35, wherein R^2 is $NHC(=O)$ -cycloalkyl.
37. The compound according to claim 36, wherein R^2 is $NHC(=O)$ -cyclopropyl.
38. The compound according to any one of claims 18-37, wherein R^a is, C_1 - C_6 alkyl.
39. The compound according to claim 38, wherein R^a is methyl.
40. The compound according to claim 1 having the following formula:



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein X^1 , X^2 , X^3 , X^4 , A^1 , A^2 , G^1 , R^1 , R^2 , m and n are as defined in claim 1.

41. The compound according to claim 40, wherein X^1 , X^2 , X^3 , and X^4 are independently selected from N or CR^3 .

42. The compound according to claim 40 or 41, wherein A^1 and A^2 are independently selected from $CR^4R^{4'}$.

43. The compound according to any one of claims 40-42, wherein G^1 is selected from O, $S(O)_2$, NR^5 , $NC(=O)OR^6$ or $CR^4R^{4'}$.

44. The compound according to claim 43, wherein G^1 is O or $S(O)_2$.

45. The compound according to any one of claims 40-44, wherein R^1 is selected from C_1 - C_6 alkyl or C_1 - C_6 deuteroalkyl.

46. The compound according to claim 45, wherein R^1 is $-CH_3$, $-CD_3$, or $-CH_2CD_3$.

47. The compound according to any one of claims 40-46, wherein R^2 is selected from $NR^6C(=O)R^{6'}$ or heteroaryl.

48. The compound according to any one of claims 40-47, wherein R^6 and $R^{6'}$ is selected from hydrogen, C_1 - C_6 alkyl or cycloalkyl.

49. The compound according to any one of claims 40-48, wherein R^2 is $NHC(=O)$ -cycloalkyl.

50. The compound according to claim 49, wherein R^2 is $NHC(=O)$ -cyclopropyl.

51. The compound according to any one of claims 40-50, wherein R^3 is selected from hydrogen or $-OR^a$, with a proviso that when each of X^1 , X^2 , X^3 , and X^4 represents CR^3 , X^4 represents CR^3 , R^3 not being hydrogen.

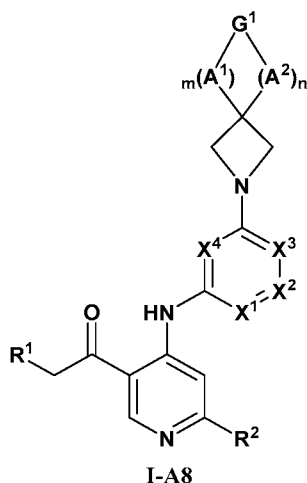
52. The compound according to any one of claims 40-51, wherein R^4 and $R^{4'}$ are independently selected from hydrogen or halogen.

53. The compound according to any one of claims 40-52, wherein R^5 is hydrogen.

54. The compound according to any one of claims 40-52, wherein R^a is, C_1 - C_6 alkyl.

55. The compound according to any one of claims 40-54, wherein R^a is methyl.

56. A compound according to claim 1 having the following formula:



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein X^1 , X^2 , X^3 , X^4 , A^1 , A^2 , G^1 , R^1 , R^2 , m and n are as defined in claim 1.

57. The compound according to claim 56, wherein X^1 , X^2 , X^3 , and X^4 are independently selected from N or CR^3 .

58. The compound according to any one of claims 56 or 57, wherein A^1 and A^2 are independently selected from $CR^4R^{4'}$.

59. The compound according to any one of claims 56-58, wherein G^1 is selected from O, $S(O)_2$, NR^5 , $NC(=O)OR^6$ or $CR^4R^{4'}$.

60. The compound according to any one of claims 56-59, wherein R^1 is selected from C_1 - C_6 alkyl or C_1 - C_6 deuteroalkyl.

61. The compound according to any one of claims 56-60, wherein R^2 is selected from $NR^6C(=O)R^{6'}$ or heteroaryl.

62. The compound according to any one of claims 56-61, wherein R^3 is selected from hydrogen or $-OR^a$, with a proviso that when each of X^1 , X^2 , X^3 , and X^4 represents CR^3 , X^4 represents CR^3 , R^3 not being hydrogen.

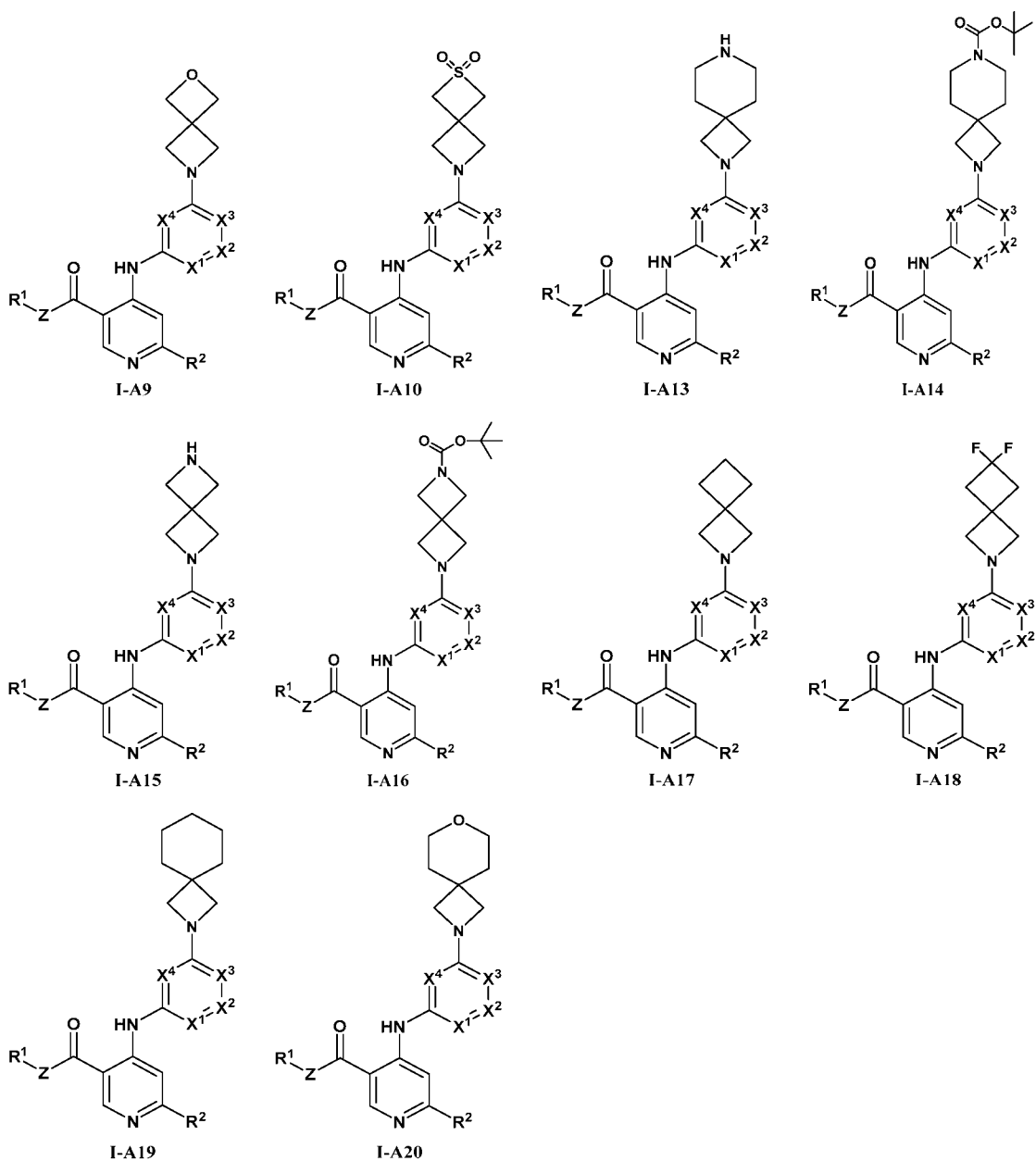
63. The compound according to any one of claims 56-62, wherein R^4 and $R^{4'}$ are independently selected from hydrogen or halogen.

64. The compound according to any one of claims 56-63, wherein R^5 is hydrogen.

65. The compound according to any one of claims 56-64, wherein R^6 and $R^{6'}$ is selected from hydrogen, C_1 - C_6 alkyl or cycloalkyl.

66. The compound according to any one of claims 56-65, wherein R^a is, C_1 - C_6 alkyl.

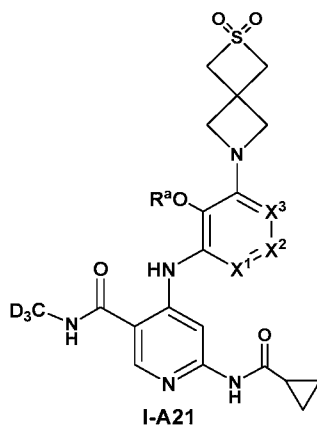
67. The compound according to claim 1, wherein the compound is of Formula I-A9, I-A10, I-A13, I-A14, I-A15, I-A16, I-A17, I-A18, I-A19, or I-A20:



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein X^1 , X^2 , X^3 , X^4 , Z , R^1 , R^2 are as defined in claim 1.

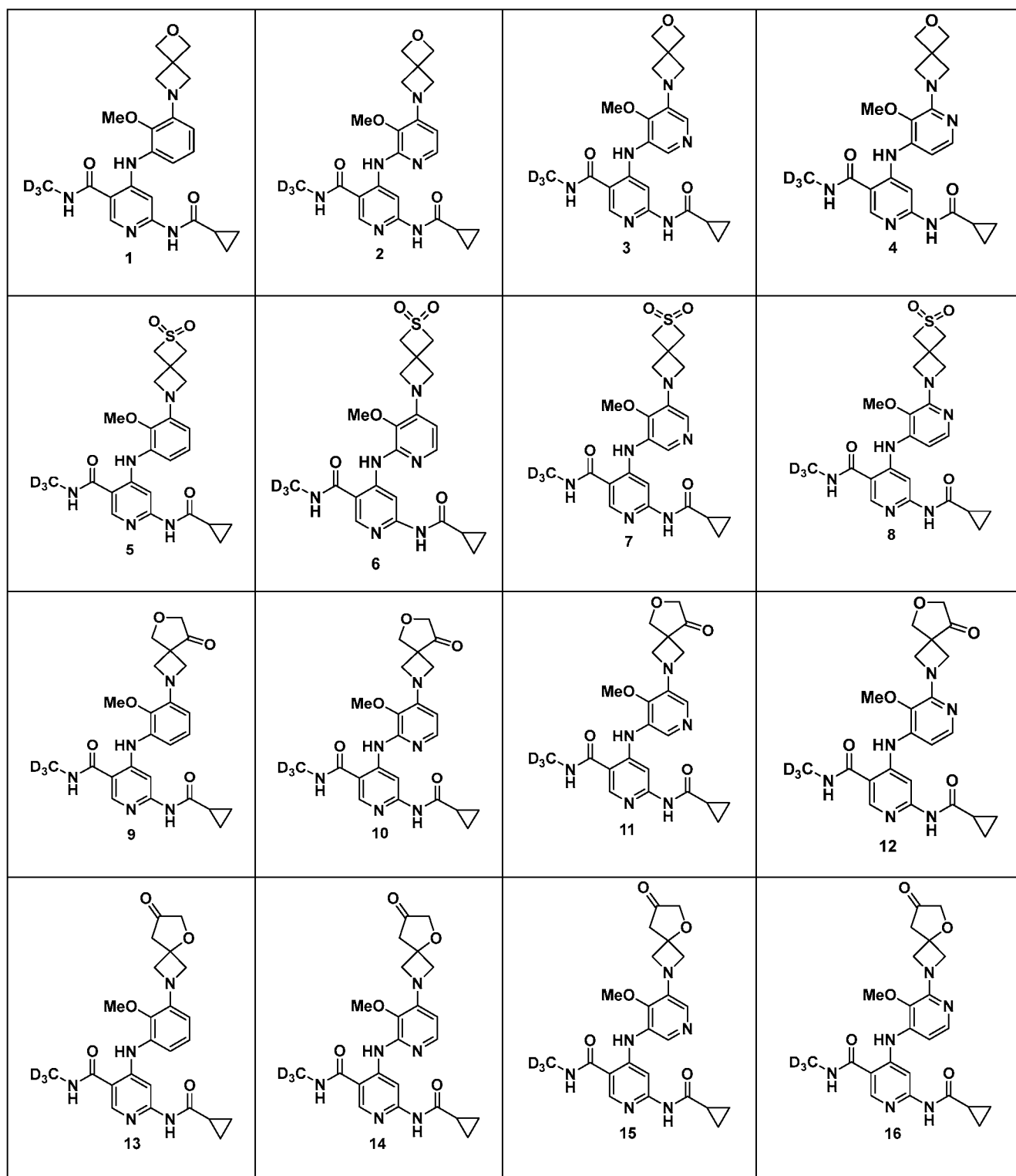
68. The compound according to claim 67, wherein X^1 , X^2 , X^3 , and X^4 are independently selected from N or CR^3 .

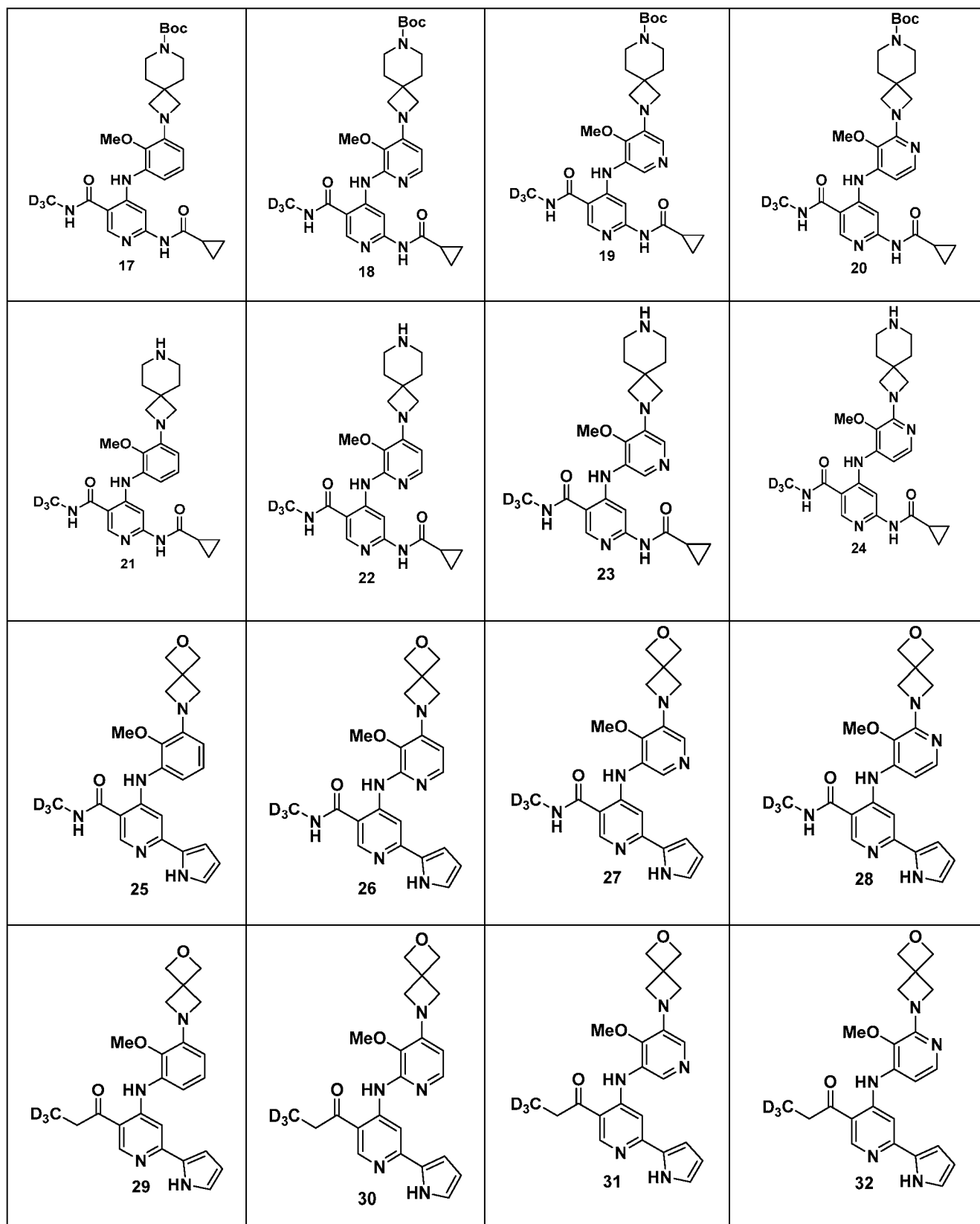
69. The compound according to claim 67 or 68 wherein Z is NR^4 or $\text{CR}^4\text{R}^{4'}$.
70. The compound according to any one of claims 67-69, wherein R^1 is selected from C_1 - C_6 alkyl or C_1 - C_6 deuteroalkyl.
71. The compound according to any one of claims 67-70, wherein R^2 is selected from $\text{NR}^6\text{C}(=\text{O})\text{R}^{6'}$ or heteroaryl.
72. The compound according to any one of claims 67-71, wherein R^3 is selected from hydrogen or $-\text{OR}^a$, with a proviso that when each of X^1 , X^2 , X^3 , and X^4 represents CR^3 , X^4 represents CR^3 , R^3 not being hydrogen.
73. The compound according to any one of claims 67-72, wherein R^6 and $\text{R}^{6'}$ is selected from hydrogen, C_1 - C_6 alkyl or cycloalkyl.
74. The compound according to any one of claims 67-73, wherein R^a is, C_1 - C_6 alkyl.
75. The compound according to claim 1 having the following formulae:

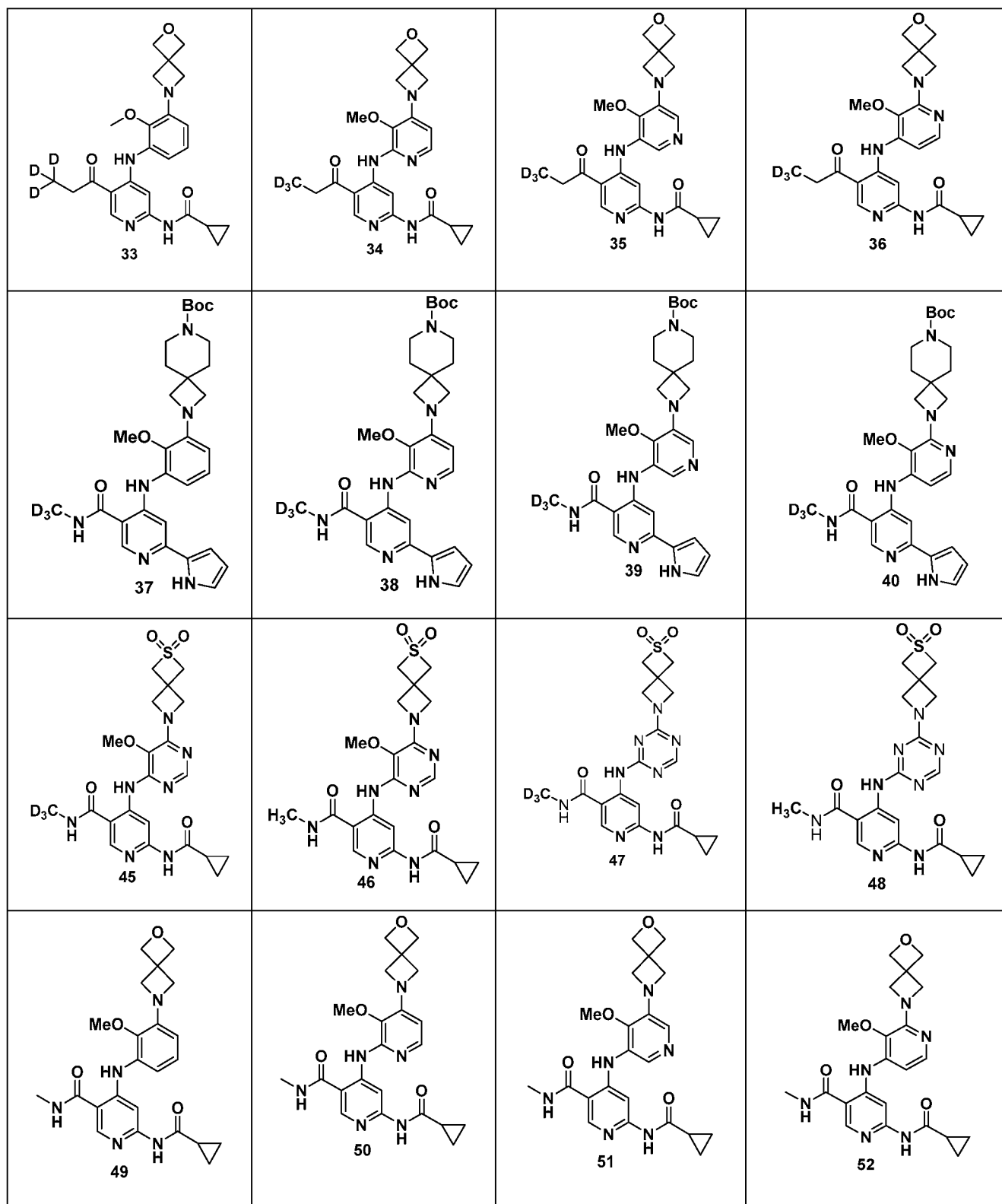


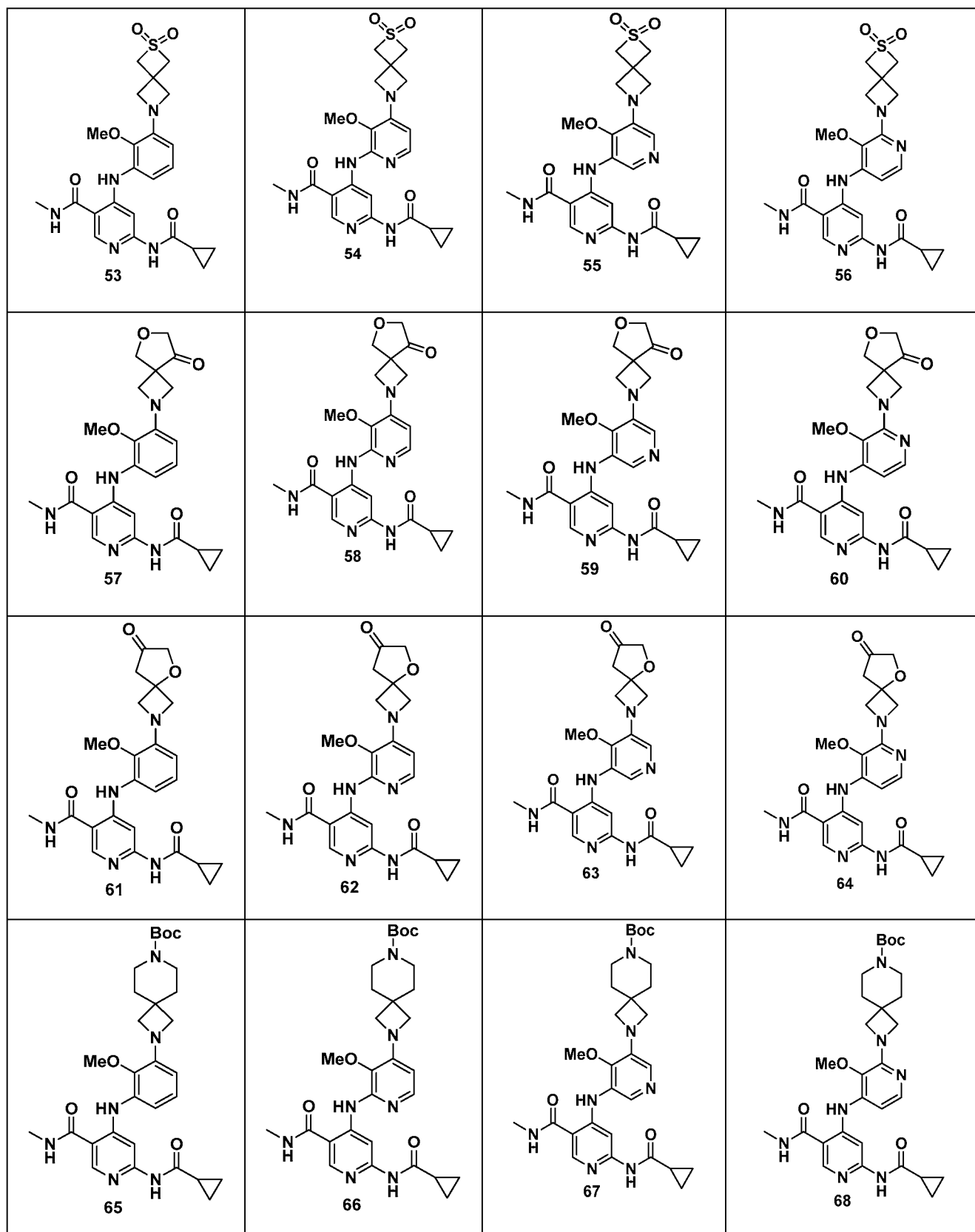
or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:
 X^1 , X^2 , X^3 , and X^4 are independently selected from N or CH; and
 R^a is C_1 - C_6 alkyl.

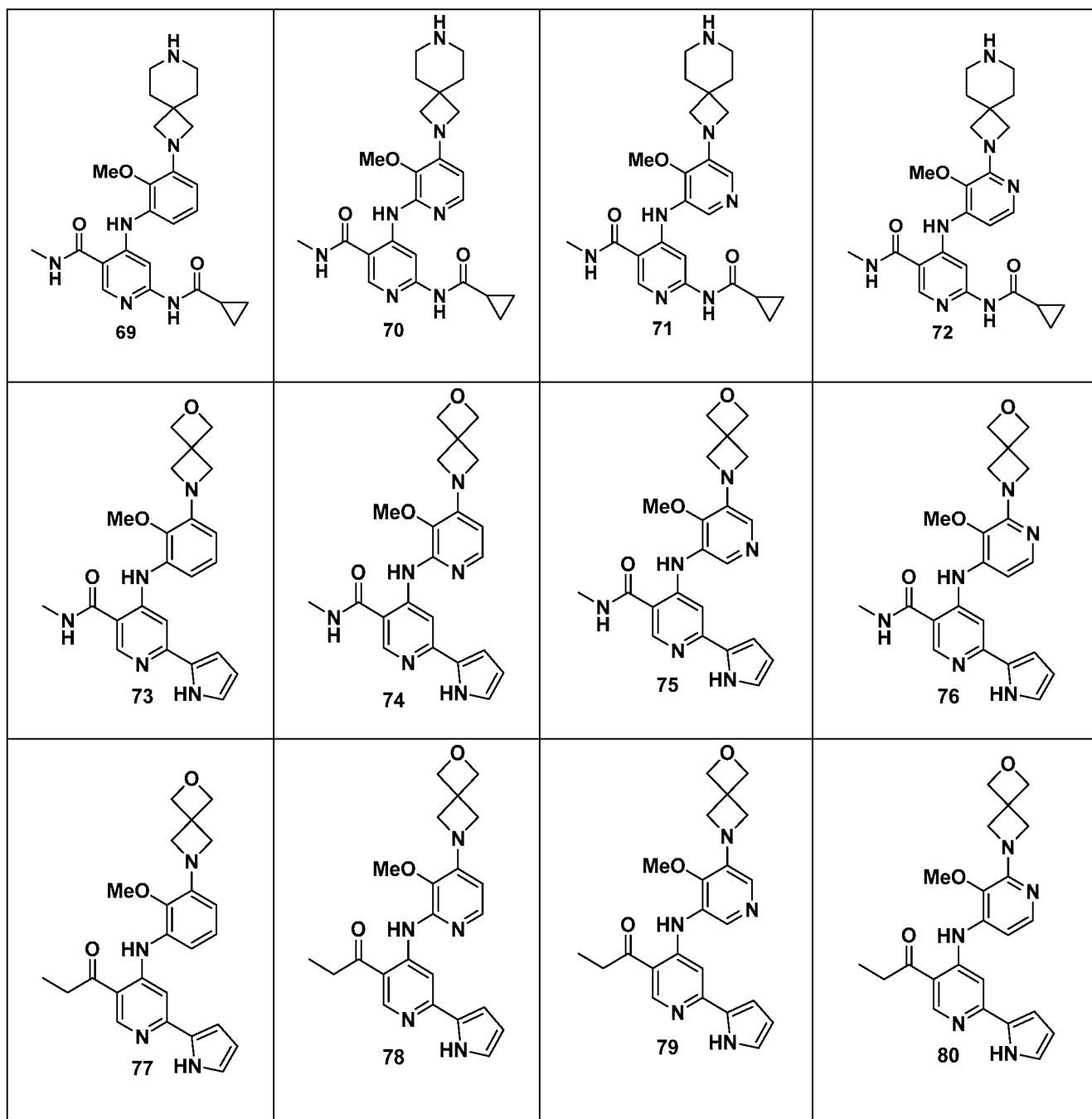
76. A compound selected from the group consisting of:

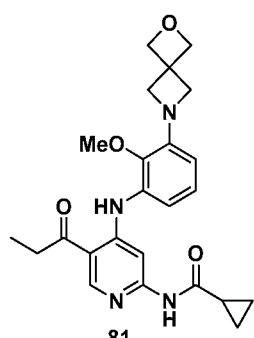
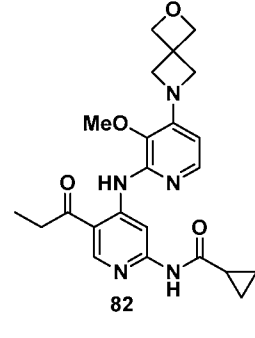
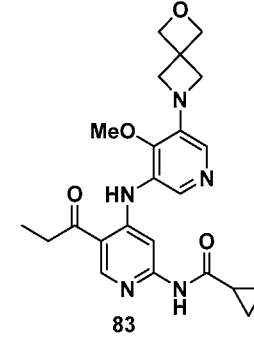
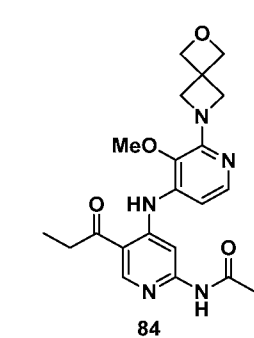
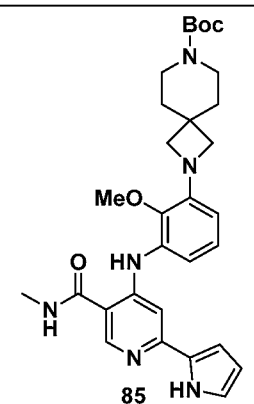
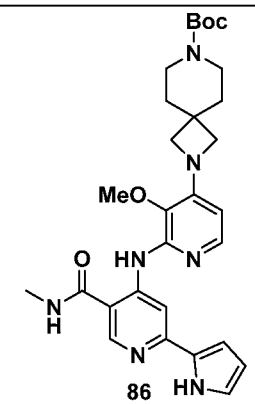
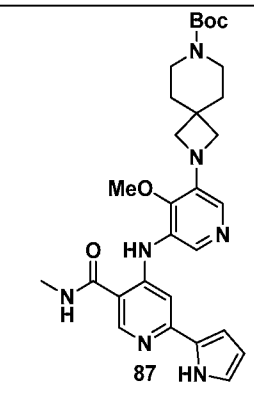
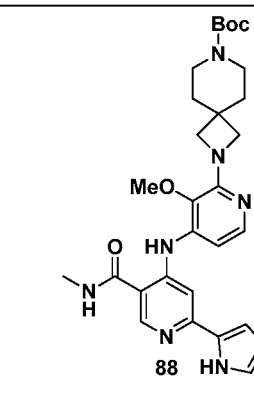
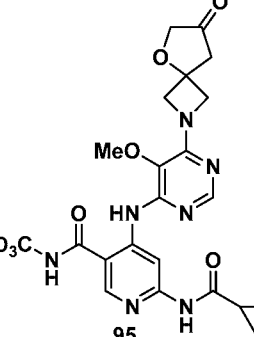
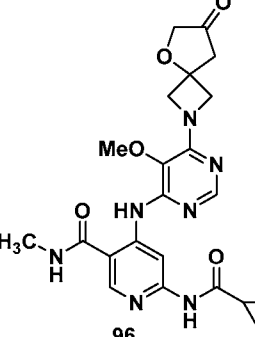
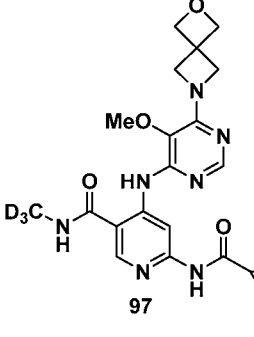
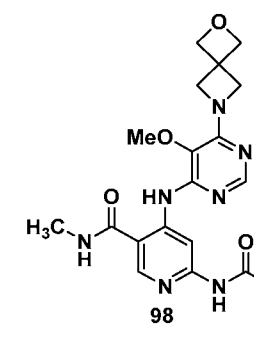
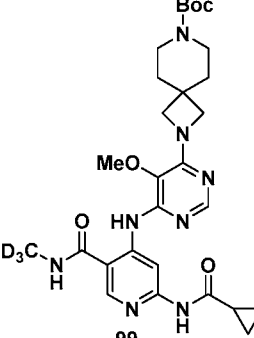
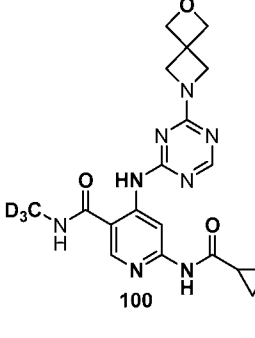
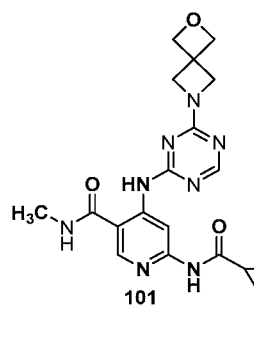
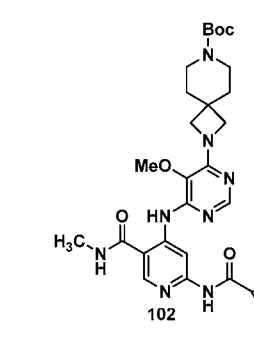


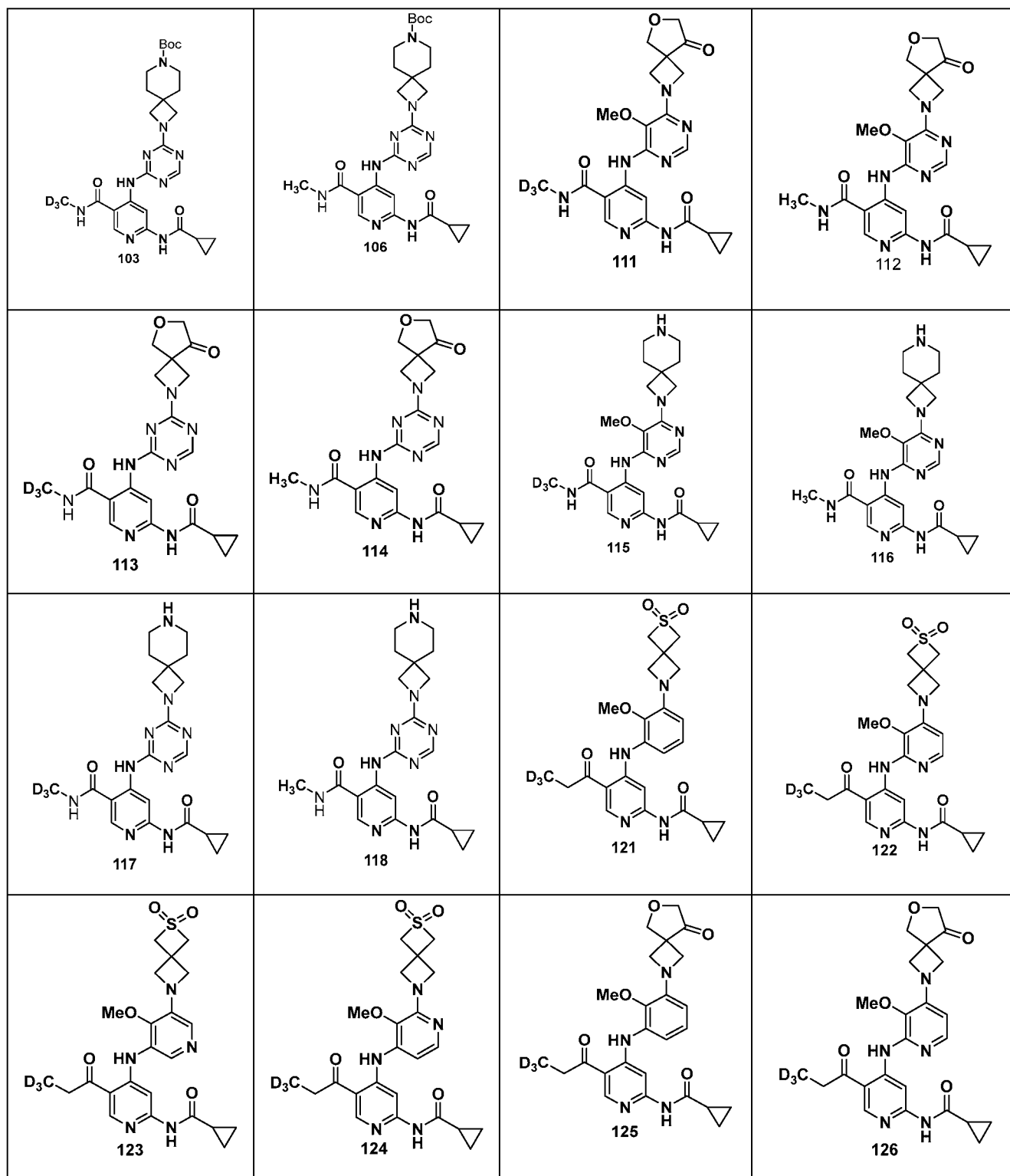


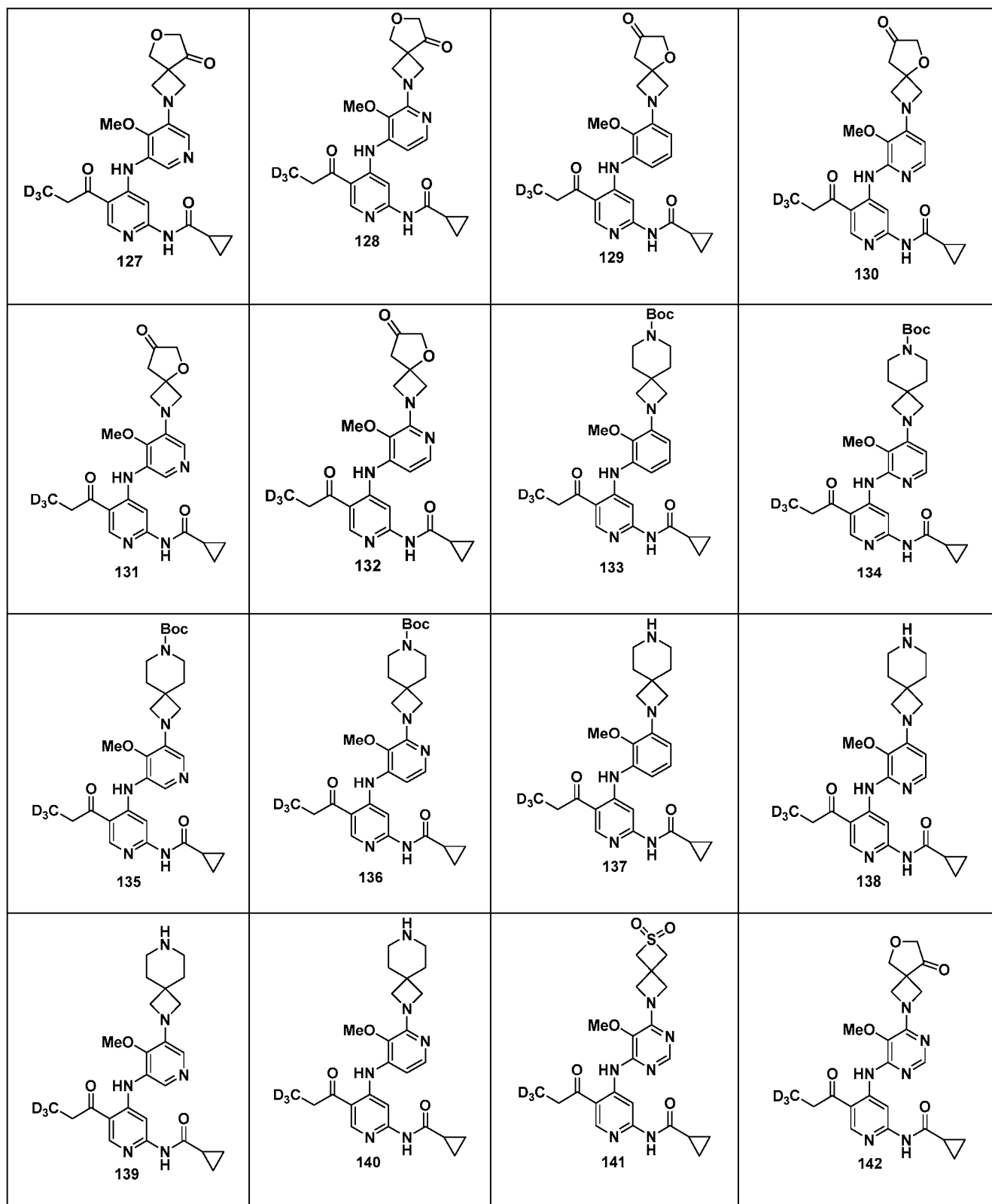


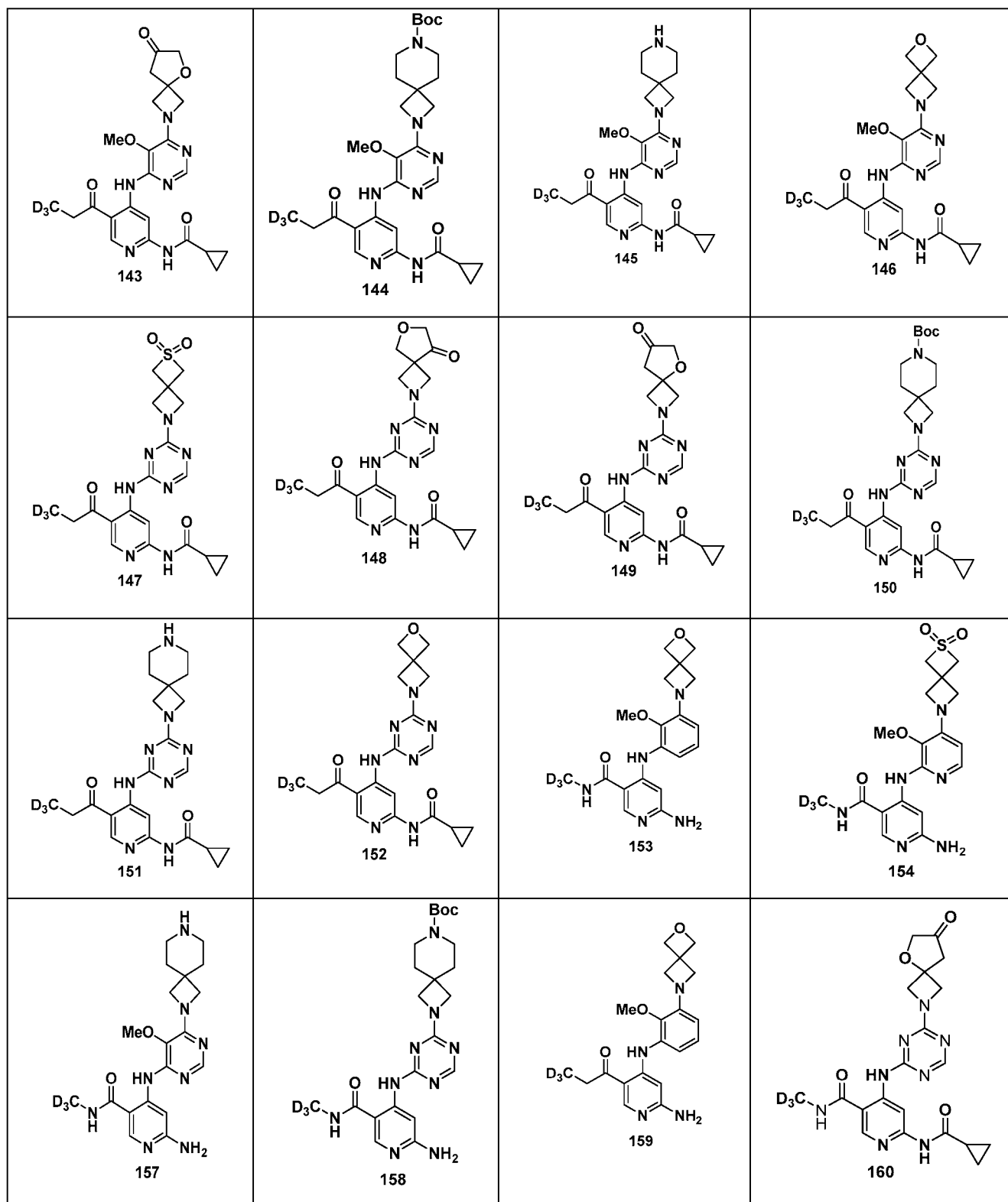


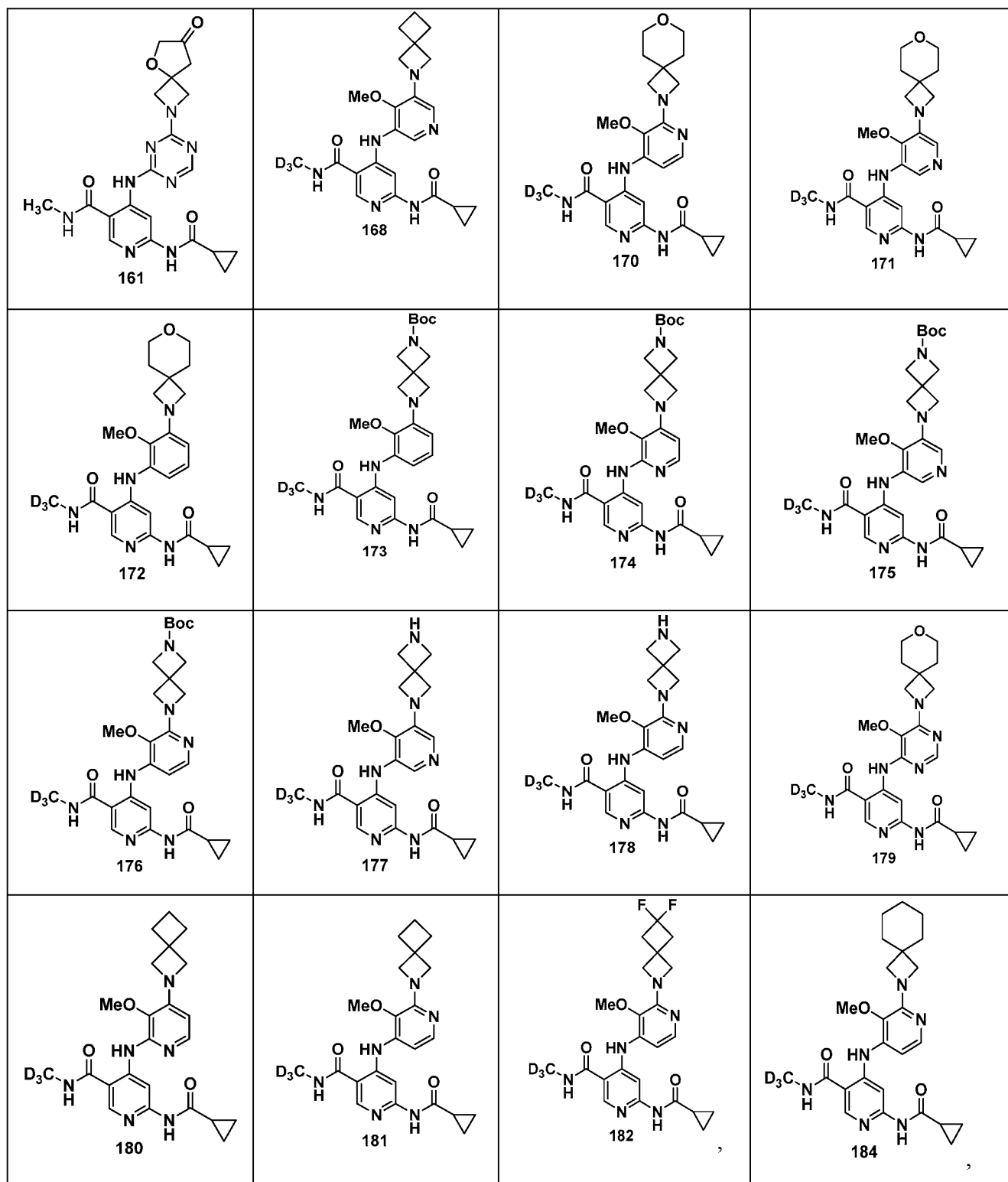


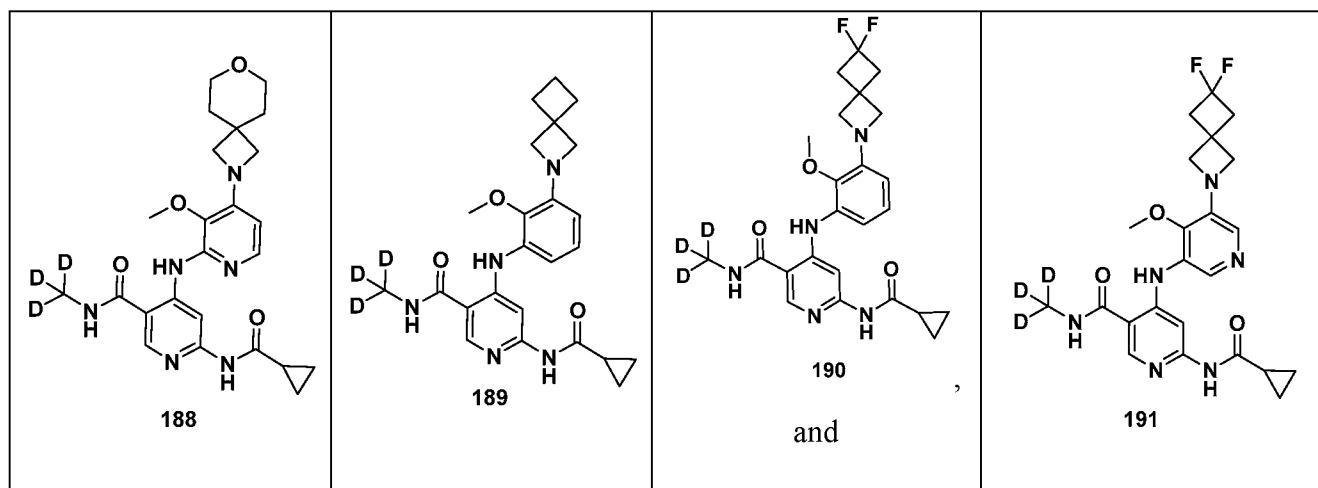
 81	 82	 83	 84
 85	 86	 87	 88
 95	 96	 97	 98
 99	 100	 101	 102





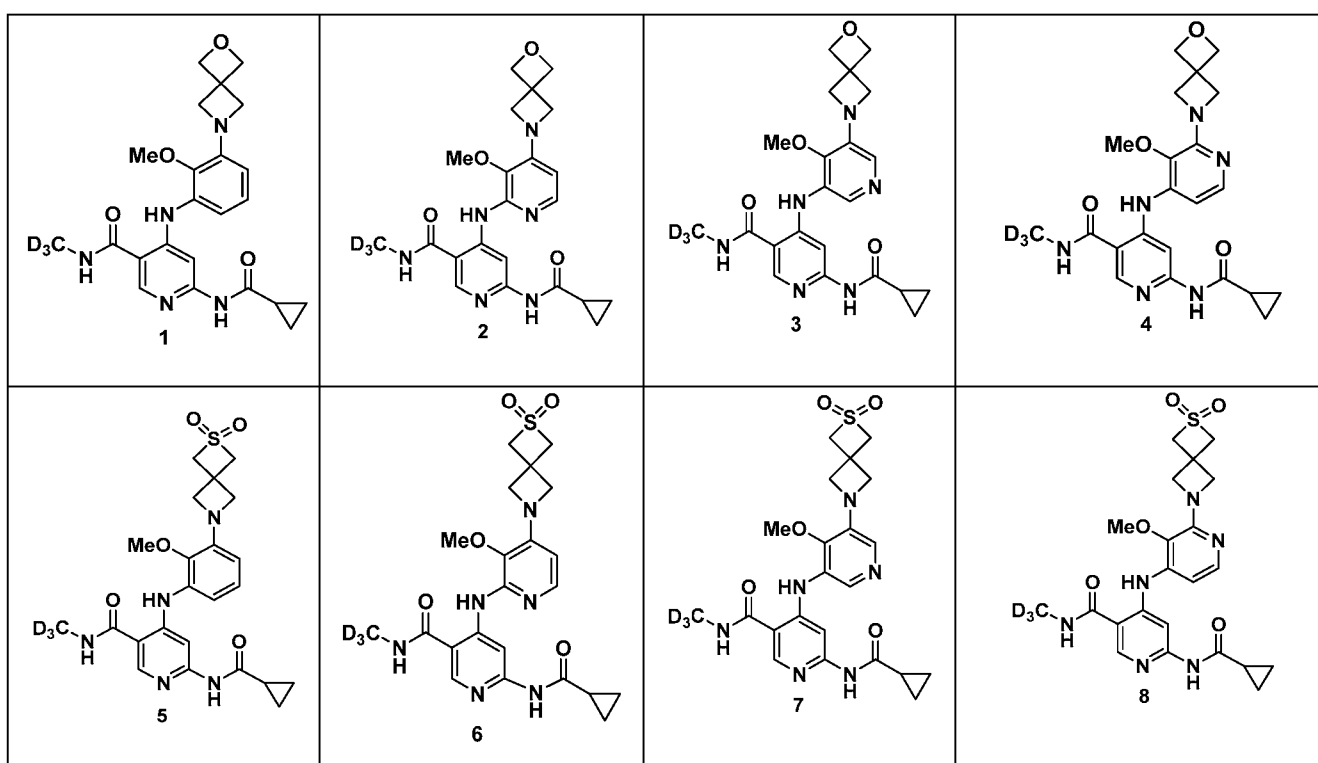


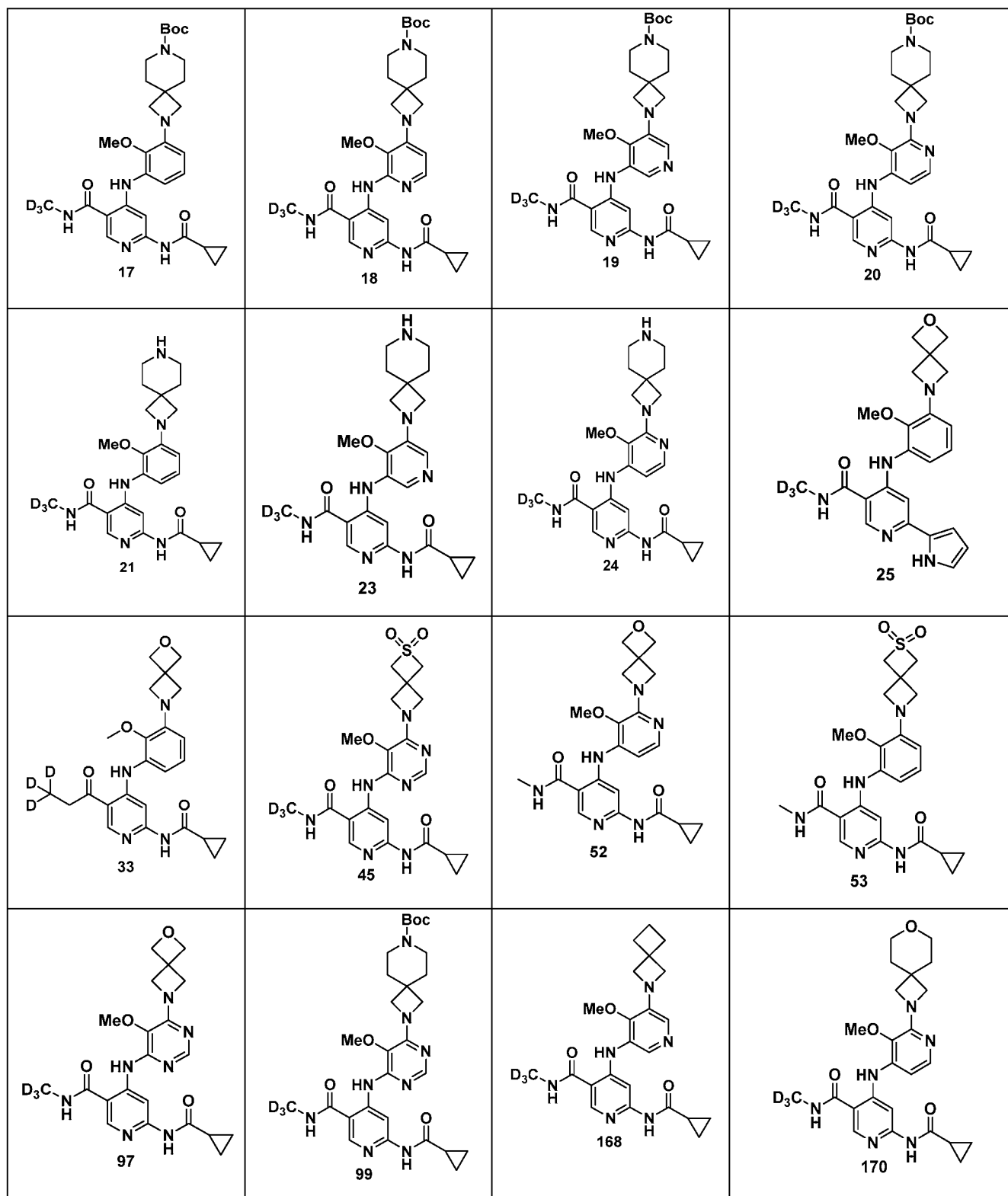


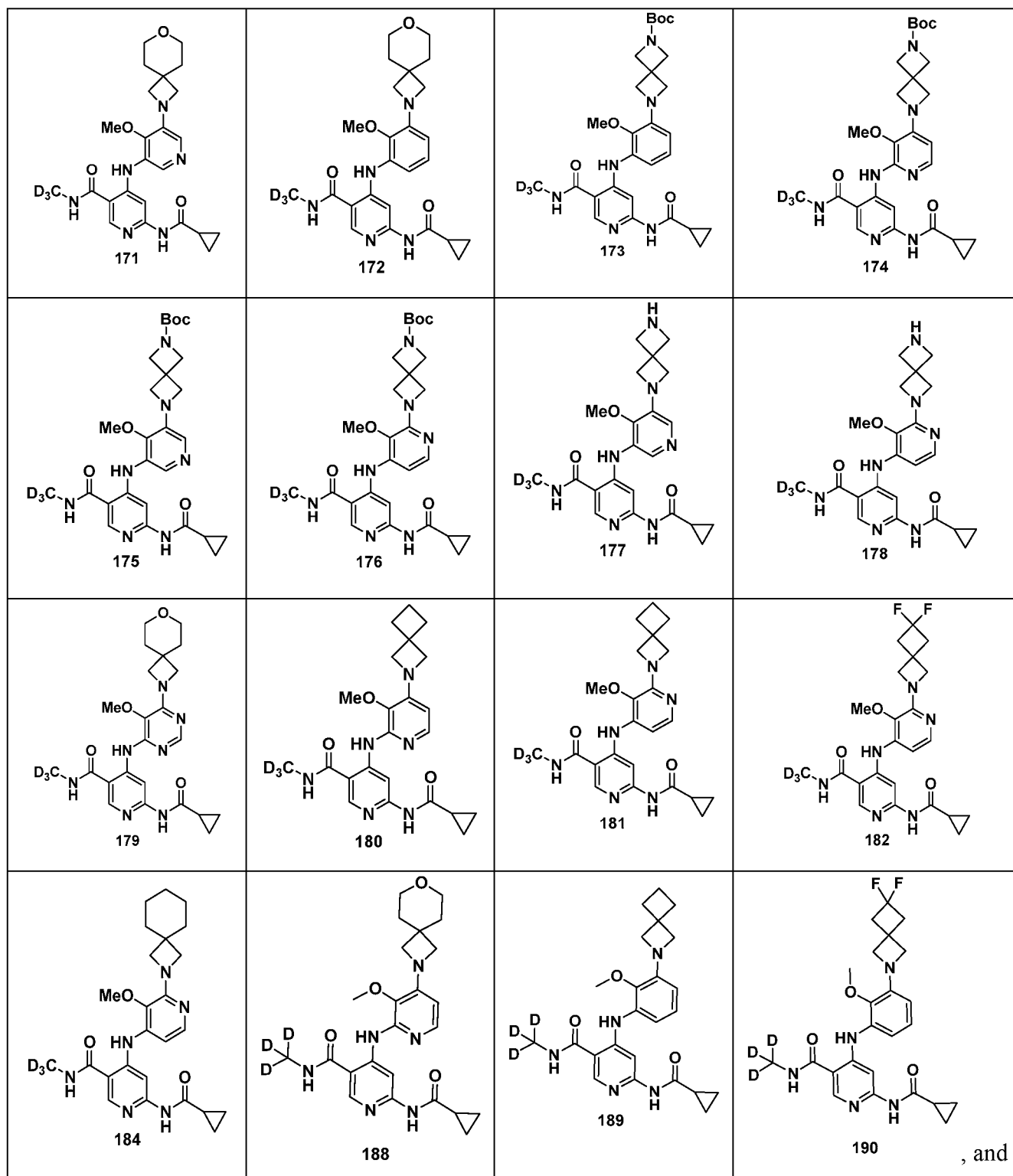


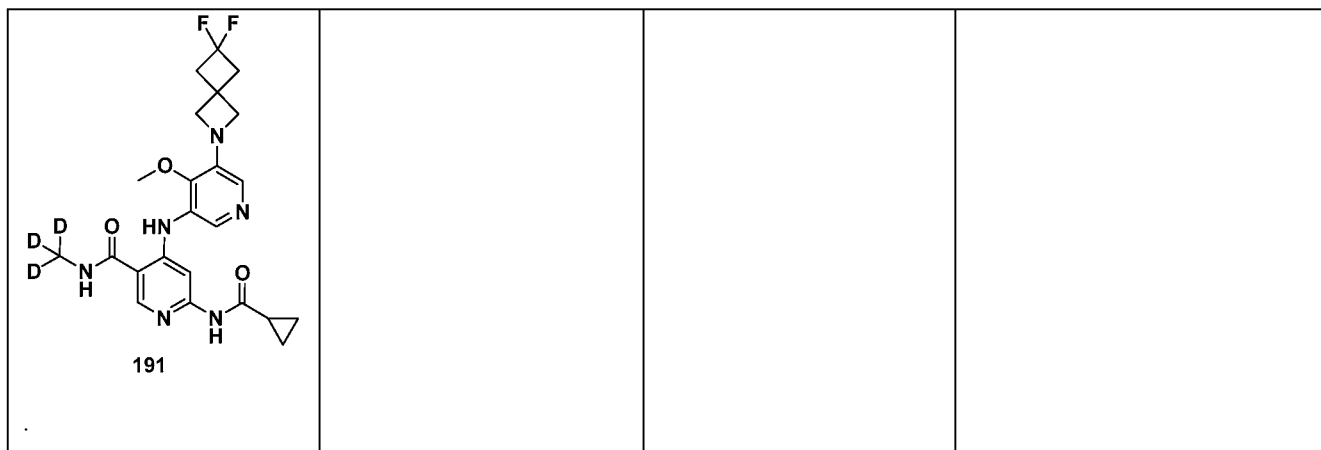
, or a pharmaceutically acceptable salt thereof.

77. A compound selected from the group consisting of:



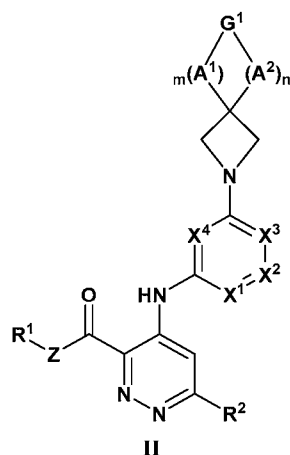






or a pharmaceutically acceptable salt thereof.

78. The compound of claim 1, wherein the compound is of formula (II):



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

R^2 is $-NH_2$, $-NR^6C(=O)R^6$, or a heteroaryl wherein the carbon atom of heteraryl group is attached with the pyridazine ring; and

R^1 , Z , X^1 , X^2 , X^3 , X^4 , G^1 , A^1 , A^2 , m and n are as defined in claim 1.

79. The compound according to claim 78, wherein Z is NR^4 or $CR^4R^{4'}$.

80. The compound according to claim 78 or 79, wherein A^1 and A^2 are independently selected from $CR^4R^{4'}$ or O .

81. The compound according to any one of claims 78-80, wherein G^1 is selected from O, $S(O)_2$, $C(=O)$, or $CR^4R^{4'}$.

82. The compound according to any one of claims 78-81, wherein R^1 is selected from C_1 - C_6 alkyl or C_1 - C_6 deuteroalkyl.

83. The compound according to claim 82, wherein R^1 is $-CH_3$ or $-CD_3$.

84. The compound according to any one of claims 78-83, wherein R^4 and $R^{4'}$ are hydrogen.

85. The compound according to any one of claims 78-84, wherein R^3 is selected from hydrogen or $-OR^a$, with a proviso that when each of X^1 , X^2 , X^3 , and X^4 represents CR^3 , X^4 represents CR^3 , R^3 not being hydrogen.

86. The compound according to any one of claims 78-85, wherein R^a is, C_1 - C_6 alkyl.

87. The compound according to any one of claims 78-86, wherein R^2 is $-NR^6C(=O)R^6$ or a heteroaryl wherein the carbon atom of heteraryl group is attached with the pyridazine ring.

88. The compound according to any one of claims 78-87, wherein R^2 is a heteroaryl wherein the carbon atom of heteraryl group is attached with the pyridazine ring.

89. The compound according to claim 87 or 88, wherein R^2 is a 5-membered heteroaryl.

90. The compound according to claim 89, wherein R^2 is a pyrrole.

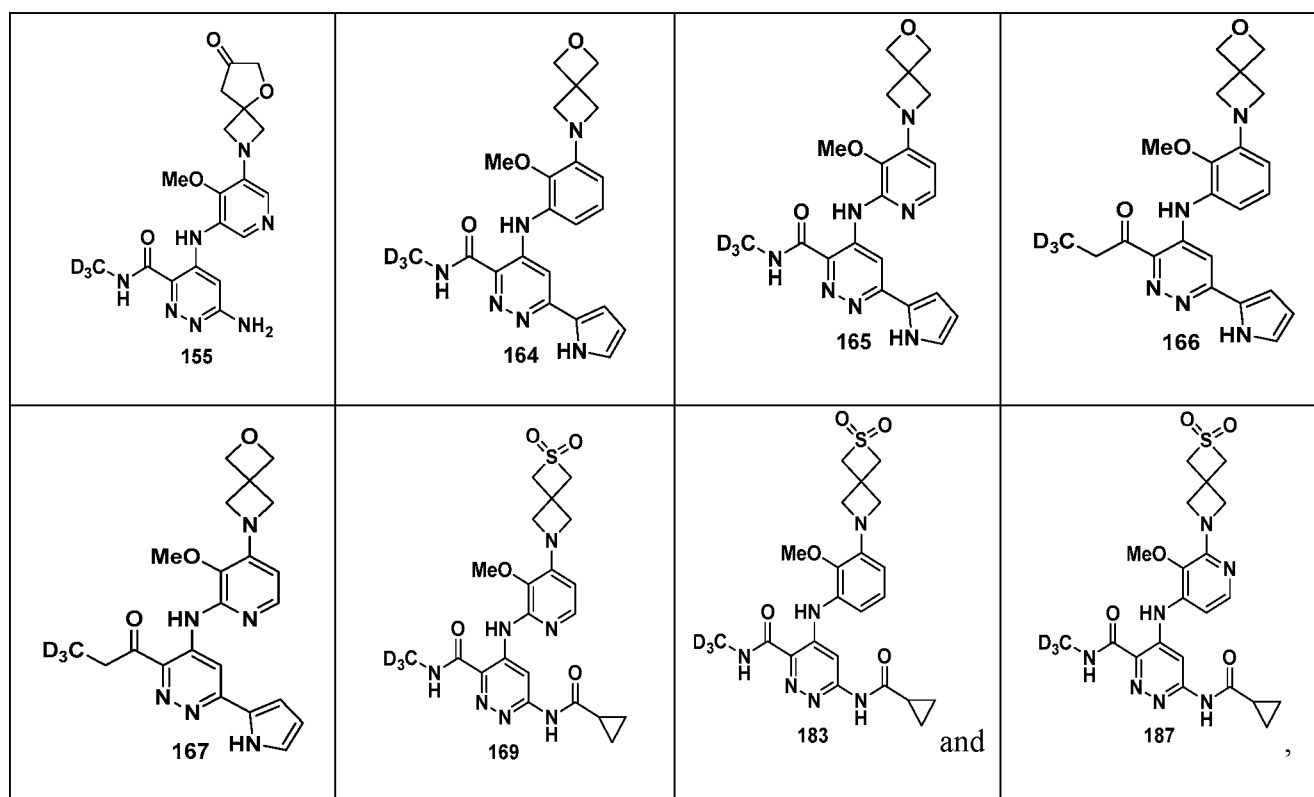
91. The compound according to any one of claims 78-87, wherein R^2 is a is $NHC(=O)$ -cycloalkyl.

92. The compound according to claim 91, wherein R^2 is $\text{NHC}(=\text{O})$ -cyclopropyl.

93. A compound according to any one of claims 78-92, wherein:

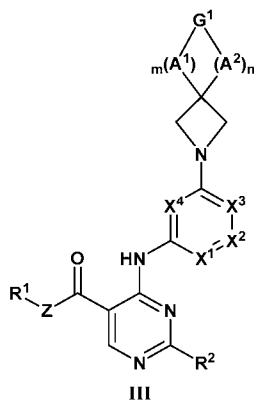
- (i) X^1 is N and X^2, X^3, X^4 are CR^3 ; or
- (ii) X^2 is N and X^1, X^3, X^4 are CR^3 ; or
- (iii) X^3 is N and X^1, X^2, X^4 are CR^3 ; or
- (iv) X^1, X^2, X^3 , and X^4 are CR^3 .

94. A compound selected from the group consisting of:



or a pharmaceutically acceptable salt thereof.

95. The compound of claim 1, wherein the compound is of formula (III):



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^1 , R^2 , Z , X^1 , X^2 , X^3 , X^4 , G^1 , A^1 , A^2 , m and n are as defined in claim 1.

96. The compound according to claim 95, wherein Z is NR^4 or $CR^4R^{4'}$.

97. The compound according to claim 95 or 96, wherein A^1 and A^2 are independently selected from $CR^4R^{4'}$ or O .

98. The compound according to any one of claims 95-97, wherein G^1 is selected from O , $S(O)_2$, $C(=O)$, or $CR^4R^{4'}$.

99. The compound according to any one of claims 95-98, wherein R^1 is selected from C_1 - C_6 alkyl or C_1 - C_6 deuteroalkyl.

100. The compound according to any one of claims 95-99, wherein R^4 and $R^{4'}$ are hydrogen.

101. The compound according to any one of claims 95-100 wherein R^3 is selected from hydrogen or $-OR^a$, with a proviso that when each of X^1 , X^2 , X^3 , and X^4 represents CR^3 , X^4 represents CR^3 , R^3 not being hydrogen.

102. The compound according to any one of claims 95-101, wherein R^a is, C_1 - C_6 alkyl

103. The compound according to any one of claims 95-102, wherein R^2 is $NR^6C(=O)R^6$.

104. The compound according to any one of claims 95-103, wherein R^6 is selected from hydrogen, C_1 - C_6 alkyl or cycloalkyl.

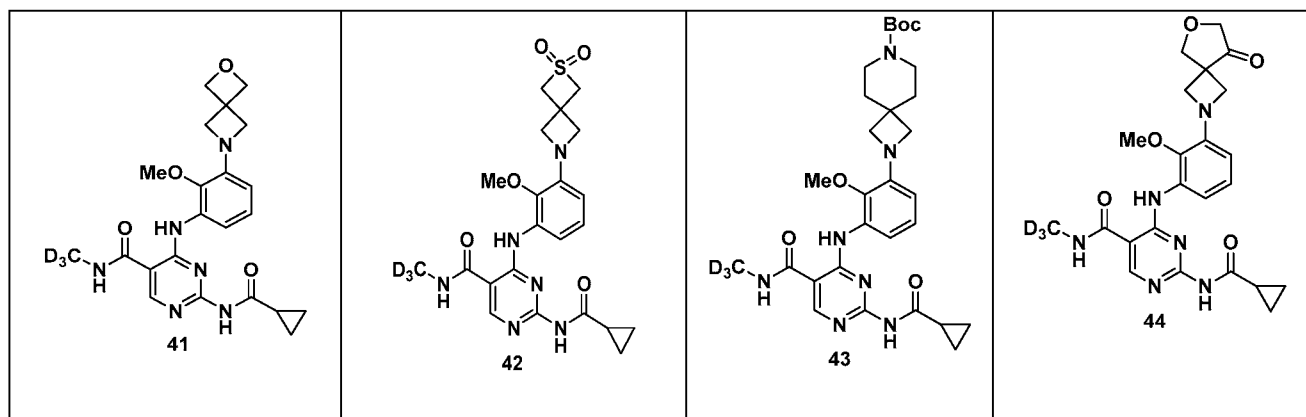
105. The compound according to any one of claims 95-104, wherein R^2 is $NHC(=O)$ -cycloalkyl.

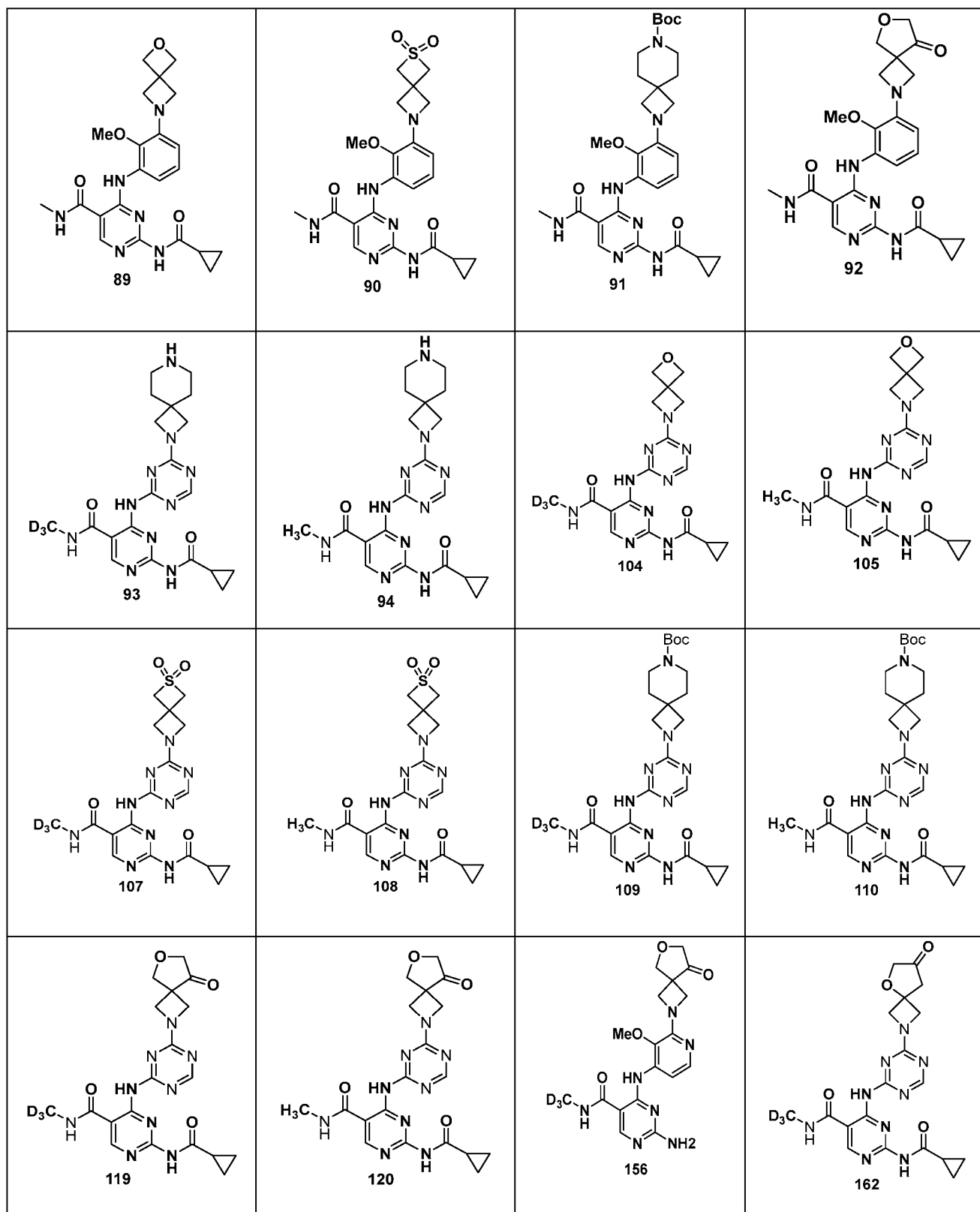
106. The compound according to claim 105, wherein R^2 is $NHC(=O)$ -cyclopropyl.

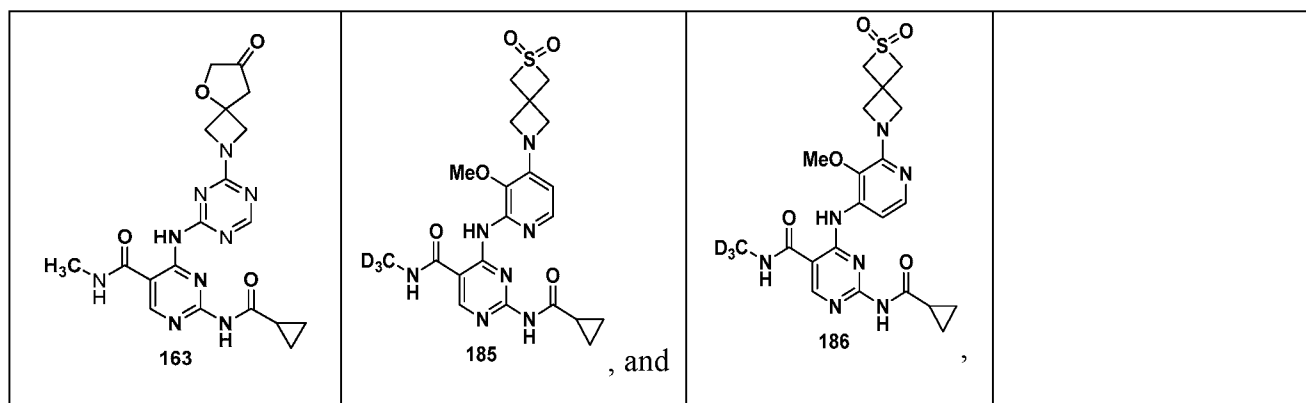
107. The compound according to any one of claims 95-106, wherein:

- (i) X^1 is N and X^2, X^3, X^4 are CR^3 ; or
- (ii) X^3 is N and X^1, X^2, X^4 are CR^3 ; or
- (iii) each of X^1, X^2, X^3 , and X^4 represents CR^3 ; or
- (iv) X^1, X^3 , and X^4 are N and X^2 is CR^3 ; or
- (v) X^2 is N and X^1, X^3, X^4 are CR^3 .

108. A compound selected from the group consisting of:







or a pharmaceutically acceptable salt thereof.

109. A pharmaceutical composition comprising one or more compounds according to claims 1-108, and a pharmaceutically acceptable carrier or diluent.

110. A method of treating a TYK2-mediated disorder comprising administering to a patient in need thereof, a compound of any one of claims 1-108, or a pharmaceutically acceptable salt or stereoisomer thereof or a pharmaceutical composition of claim 109.

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2024/055815

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61P25/00 A61P29/00 A61P35/00 A61P37/02 C07D401/12
C07D401/14 C07D471/10 C07D491/107 C07D513/10

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	CN 116 262 739 A (SHANGHAI HANSON BIOMEDICAL CO LTD ET AL.) 16 June 2023 (2023-06-16)	1-19, 25-74, 76-87, 91-93, 109,110
Y,P	the whole document; in particular claims 4-7 and 10-13; example 24; pages 27-28	20-24, 75, 88-90, 94-108
Y	----- WO 2020/086616 A1 (FRONTHERA U S PHARMACEUTICALS LLC [US]) 30 April 2020 (2020-04-30) cited in the application the whole document; in particular the claims; the examples, e.g. examples 1 and 24; example A and table 1; paragraphs [0038] and [0308] ----- - / - -	1-110

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

14 October 2024

Date of mailing of the international search report

30/10/2024

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Hanisch, Inken

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2024/055815

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2022/105771 A1 (JIANGSU HENGRUI MEDICINE CO [CN] ET AL.) 27 May 2022 (2022-05-27) cited in the application the whole document; in particular the claims; page 42; table 1 -----	1-110

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2024/055815

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CN 116262739 A	16-06-2023	NONE	

WO 2020086616 A1	30-04-2020	AU 2019364336 A1	27-05-2021
		BR 112021007679 A2	27-07-2021
		CA 3117200 A1	30-04-2020
		CL 2021000989 A1	29-10-2021
		CN 113490664 A	08-10-2021
		EP 3870579 A1	01-09-2021
		IL 282487 A	30-06-2021
		JP 2022505987 A	14-01-2022
		KR 20210095634 A	02-08-2021
		SG 11202104017V A	28-05-2021
		US 2020354338 A1	12-11-2020
		US 2022235035 A1	28-07-2022
		US 2023021554 A1	26-01-2023
		US 2023023761 A1	26-01-2023
		US 2023391751 A1	07-12-2023
		WO 2020086616 A1	30-04-2020

WO 2022105771 A1	27-05-2022	TW 202227430 A	16-07-2022
		WO 2022105771 A1	27-05-2022
