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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
02 January 2020 (02.01.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/001152 A1

(51) International Patent Classification:
C07D 471/14 (2006.01) *A61P 35/00* (2006.01)
A61K 31/437 (2006.01)

(21) International Application Number:
PCT/CN2019/084601

(22) International Filing Date:
26 April 2019 (26.04.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/CN2018/092542
25 June 2018 (25.06.2018) CN

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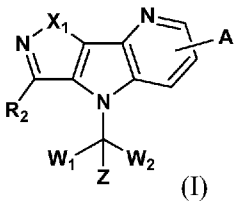
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS,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

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

Published:
— *with international search report (Art. 21(3))*

(54) Title: TRICYCLIC COMPOUNDS

(57) Abstract: Disclosed are tricyclic compounds as bromodomain and extra-terminal (BET) inhibitors which are shown as formula I, their synthesis and their use for treating diseases. More particularly, disclosed are fused heterocyclic derivatives useful as inhibitors of BET, methods for producing such compounds and methods for treating diseases and conditions wherein inhibition of one or more BET bromodomains provides a benefit.



(I)

WO 2020/001152 A1

NOVEL TRICYCLIC COMPOUNDS

Technical Field

This invention relates to certain novel tricyclic compounds (Formula I) as bromodomain and extra-terminal (BET) inhibitors which are shown as Formula I, their synthesis and their use for treating diseases. More particularly, this invention is directed to fused heterocyclic derivatives useful as inhibitors of BET, methods for producing such compounds and methods for treating diseases and conditions wherein inhibition of one or more BET bromodomains provides a benefit.

Background Art

Several physiological processes might contribute to epigenetic regulation, including DNA methylation, non-coding RNA-mediated scaffolding and complex formation, and histone modification. Histone modification is a process related to the post-translational covalent modification of histone proteins that markedly influences the ability of associated DNA to be transcribed. Lysine acetylation is a post-translational modification with broad relevance to cellular signaling and disease biology. Enzymes that regulate lysine acetylation in histones are termed as 'writers' or histone acetyltransferaes (HATs), and that regulate lysine deacetylation in histone as 'erasers' or histone deacetylases (HDACs). Bromodomains (BRDs), 'readers' of epigenetic marks, specifically recognize ε-N-acetyl lysine (Kac) residues on histones tails.

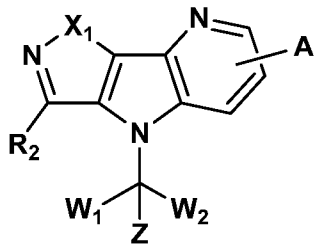
BRD is a conserved 110 amino acid structure motif composed of four α-helices (αZ, αA, αB, and αC) that comprise a left-handed bundle (S. Mujtaba, L. Zeng, M.M. Zhou, *Oncogene*, 2007 (26), 5521-5527). The α-helices are connected together by two loop regions (ZA and BC) and form a surface that interacts with acetylated lysines in nucleosomal histones (C. Dhalluin, J.E. Carlson, L. Zeng et al, *Nature*, 1999(399), 491-496). There are 46 known bromodomain containing proteins from humans which across eight families based on structure/sequence similarity. Among them, bromodomain and extra-terminal domain (BET) recognize acetylated lysine residues in histones H3 and H4. BET family, containing BRD2, BRD3, BRD4 and BRDT four members, share two N-terminal bromodomains and extra C-terminal domain (ET) exhibiting high levels of sequence conservation. As reported, BRD2 and BRD3 associate with histones along actively transcribed genes and maybe involved in facilitating transcriptional elongation (Leroy et al., *Mol. Cell* 2008 30(1), 51-60). BRD4 appears to be involved in the recruitment of the positive transcriptional elongation factor complex (pTEF-I3), which plays an essential role in the regulation of transcription by RNA polymerase and increased transcriptional output (Hargreaves et al., Cell, 2009 138(1):1294145). Unlike the other three BET proteins expressed ubiquitiously, BRDT expression is normally testis-specific (M.H. Jones et al, *Genomics*, 1997 (45), 529-534) and BRDT is essential for spermatogenesis (E. Shang et al, *Development*, 2007 (134), 3507-3515). Binding of BET proteins to acetylated histones leads to recruiting BET proteins to the

enhancer and promoter regions of genes for active transcription. By that, they interact with coactivators, repressors, transcription factors and transcriptional machinery to form protein complexs and influence target gene transcription (A. Dey et al, *Proc. Natl. Acad. Sci*, U.S.A. 2003 (100), 8758-8763). BET proteins, although having a similar structure and usually enhancing transcription, regulate different processes based on their binding partners, which are often tissue-specific.

It is thought that BET proteins primarily mediate their effects in disease pathogenesis and progression mainly by localizing to super-enhancers (SEs) at pathology-associated genes and driving their expression (M.A. Dawson et al, *Nature,* 2011 (478)，529-533; B. Chapuy et al, *Cancer Cell*, 2013(24), 777-790). In cancer, SEs are enriched at oncogenes like MYC, RUNX1, FOSL2, CCND1, MCL1, and BCL2L1 (B. Chapuy et al, *Cancer Cell*, 2013(24), 777-790; J. Loven, *Cell*, 2013(153), 320-334; W.A. Whyte et al, *Cell*, 2013 (153), 307-319; D.Hnisz et al *Cell*, 2013(155), 934-947). Inhibition of BET proteins has become a promising target for human diseases including virology, hart failure, inflammation, central nervous system (CNS) disorders and variety cancers (J.M. Sahni et al， Pharmacol Res, 2017, 1-21; P. Anand et al, *Cell*, 2013 (154), 569-582; C.-Y. Wang et al, *Trends Biochem. Sci*, 2015 (40), 468-479; A. Stathis et al, *Cancer Discovery*, 2017, 8(1), 1-13). Small molecule BET inhibitors that are reported in clinical development include RVX-208, GSK-525762A, GSK2820151, OTX-015, CPI-0610, TEN-010/RO6870810, ABBV-075/ABBV-744, BI 894999, BMS-986158, INCB054329/INCB057643, ZEN-3694 GS-5829, AZD5153 as well as an inhibitor from Celgene. There exists a need for generating further BET inhibitors that have improved properties over existing BET inhibitors, for example, improved potency, safety, tolerability, pharmacokinetics and/or pharmocodynamics.

Summary of Invention

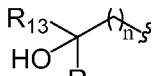
In one aspect, there is provided a compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof:



I

Wherein,

X_1 is selected from O, S, SO, SO_2 or NR_1;

R_1 is selected from hydrogen; deuterium; -CN; $-SOR_{11}$; $-SO_2R_{11}$; $-SO_2NR_{11}R_{12}$; $-C_{1-6}$alkyl; 

; $-C_{2-6}$alkenyl; $-C_{2-6}$alkynyl; carboxyl; $-NO_2$; $-COOR_{11}$; $-COR_{11}$; $-CONR_{11}R_{12}$; $-POR_{11}R_{12}$; $-C_{5-6}$aryl; $-C_{5-6}$heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2;

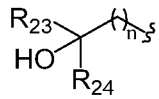
-C_{3-8}heterocyclic containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; or -C_{3-8}carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, oxo, -CN, -C_{1-6}alkyl, -C_{1-6}alkoxy, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, carboxyl or -C_{3-8}carbocyclic;

Each of R_{11} and R_{12} at each occurrence is independently selected from hydrogen; deuterium; -OH; -NH_2; -CN; -C_{1-6}alkyl; -C_{1-6}alkoxy; -C_{5-6}aryl; -C_{5-6}heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; -C_{1-6}alkylene-C_{3-8}carbocyclic; or -C_{3-8}carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, -CN, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -C_{1-6}alkyl, -C_{1-6}alkoxy, carboxyl, -SO_2(C_{1-6}alkyl) or -C_{3-8}carbocyclic; or

R_{11} and R_{12} together with the nitrogen atom to which they are both attached form 4-8 membered heterocyclic ring, and each of the heterocyclic ring at each occurrence can further contains 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2, and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium; halogen; -OH; oxo; -CN; -C_{1-6}alkyl; -C_{1-6}alkoxy; -SO_2(C_{1-6}alkyl); -CON(C_{1-6}alkyl)$_2$; -SO_2N(C_{1-6}alkyl)$_2$; -NH_2; -NH(C_{1-6}alkyl); -N(C_{1-6}alkyl)$_2$; -C_{3-6}heterocyclic containing 1 or 2 heteroatoms selected from N, O or S; or -C_{1-6}alkyl substituted with deuterium;

Each of R_{13} and R_{14} at each occurrence is independently selected from hydrogen, deuterium, halogen, -NH_2, -C_{1-6}alkoxy or -C_{1-6}alkyl; or

R_{13} and R_{14} together with the carbon atom to which they are both attached form 3-6 membered carbocyclic ring, and each of the carbocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, -NH_2, -CN, -C_{1-6}alkyl or -C_{1-6}alkoxy;

R_2 is selected from hydrogen; deuterium; halogen; -OR_{21}; -$NR_{21}R_{22}$; -CN; -SR_{21}; -SOR_{21}; -SO_2R_{21}; -$SO_2NR_{21}R_{22}$; -C_{1-6}alkyl; 

; -C_{2-6}alkenyl; -C_{2-6}alkynyl; carboxyl; -NO_2; -$COOR_{21}$; -COR_{21}; -$CONR_{21}R_{22}$; -$NR_{21}COR_{22}$; -$NR_{21}CONR_{21}R_{22}$; -$NR_{21}SO_2R_{22}$; -$NR_{21}SO_2NR_{21}R_{22}$; -$OCONR_{21}R_{22}$; -$POR_{21}R_{22}$; -C_{5-6}aryl; -C_{5-6}heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; -C_{3-8}heterocyclic containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; or -C_{3-8}carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, oxo, -CN, -NH_2, -C_{1-6}alkyl, -C_{1-6}alkoxy, carboxyl or -C_{3-8}carbocyclic;

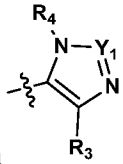
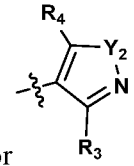
Each of R_{21} and R_{22} at each occurrence is independently selected from hydrogen; deuterium;

-OH; NH_2; -CN; -C_{1-6}alkyl; -C_{1-6}alkoxy; -C_{5-6}aryl; -C_{5-6}heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; -C_{1-6}alkylene-C_{3-8}carbocyclic; or -C_{3-8}carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, -CN, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -C_{1-6}alkyl, -C_{1-6}alkoxy, carboxyl, -SO_2(C_{1-6}alkyl) or -C_{3-8}carbocyclic; or

R_{21} and R_{22} together with the nitrogen atom to which they are both attached form 4-8 membered heterocyclic ring, and each of the heterocyclic ring at each occurrence can further contains 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2, and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium; halogen; -OH; oxo; -CN; -C_{1-6}alkyl; -C_{1-6}alkoxy; -SO_2(C_{1-6}alkyl); -CON(C_{1-6}alkyl)$_2$; -SO_2N(C_{1-6}alkyl)$_2$; -NH_2; -NH(C_{1-6}alkyl); -N(C_{1-6}alkyl)$_2$; -C_{3-6}heterocyclic containing 1 or 2 heteroatoms selected from N, O or S; or -C_{1-6}alkyl substituted with deuterium;

Each of R_{23} and R_{24} at each occurrence is independently selected from hydrogen, deuterium, halogen, -NH_2, -C_{1-6}alkoxy or -C_{1-6}alkyl; or

R_{23} and R_{24} together with the carbon atom to which they are both attached form 3-6 membered carbocyclic ring, and each of the carbocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, -NH_2, -CN, -C_{1-6}alkyl or -C_{1-6}alkoxy;

A is selected from  or  ;

Y_1 is selected from N or CR_{Y1};

Y_2 is selected from O, S, $CR_{Y1}R_{Y2}$ or NR_{Y2};

Each of R_{Y1} and R_{Y2} at each occurrence is independently selected from hydrogen, deuterium, halogen, -OH, NH_2, -CN, -C_{1-6}alkyl or -C_{1-6}alkoxy;

Each of R_3 and R_4 at each occurrence is independently selected from hydrogen, deuterium, halogen, -CN, -SOR_5, -SO_2R_5, -$SO_2NR_5R_6$, -C_{1-6}alkyl, -C_{1-6}alkoxy, -COR_5, -$CONR_5R_6$ or -POR_5R_6; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, -NH_2, -CN, -C_{1-6}alkyl or -C_{1-6}alkoxy;

Each of R_5 and R_6 at each occurrence is independently selected from hydrogen; deuterium; -OH; -NH_2; -CN; -C_{1-6}alkyl; -C_{1-6}alkoxy; -C_{5-6}aryl; -C_{5-6}heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; -C_{1-6}alkylene-C_{3-8}carbocyclic; or -C_{3-8}carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6

substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, -CN, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, $-C_{1-6}alkyl$, $-C_{1-6}alkoxy$, carboxyl, $-SO_2(C_{1-6}alkyl)$ or $-C_{3-8}carbocyclic$; or

R_5 and R_6 together with the nitrogen atom to which they are both attached form 4-8 membered heterocyclic ring, and each of the heterocyclic ring at each occurrence can further contains 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2, and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium; halogen; -OH; oxo; -CN; $-C_{1-6}alkyl$; $-C_{1-6}alkoxy$; $-SO_2(C_{1-6}alkyl)$; $-CON(C_{1-6}alkyl)_2$; $-SO_2N(C_{1-6}alkyl)_2$; $-NH_2$; $-NH(C_{1-6}alkyl)$; $-N(C_{1-6}alkyl)_2$; $-C_{3-6}$heterocyclic containing 1 or 2 heteroatoms selected from N, O or S; or $-C_{1-6}alkyl$ substituted with deuterium;

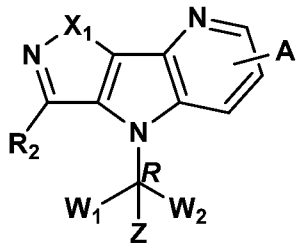
n is selected from 0, 1, 2, 3, 4, 5 or 6;

W_1 is selected from hydrogen; deuterium; halogen; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1-6}alkyl$; $-C_{1-6}alkoxy$; $-C_{1-6}alkylene-C_{1-6}alkoxy$; $-C_{5-10}aryl$; $-C_{5-10}$heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; $-C_{3-8}$heterocyclic containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; or $-C_{3-8}carbocyclic$; and each of which at each occurrence is independently optionally substituted;

W_2 is selected from hydrogen; deuterium; halogen; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1-6}alkyl$; $-C_{1-6}alkoxy$; $-C_{5-10}$ aryl; $-C_{5-10}$heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; $-C_{3-8}$heterocyclic containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; or $-C_{3-8}carbocyclic$; and each of which at each occurrence is independently optionally substituted;

Z is selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, carboxyl, $-C_{1-6}alkyl$ or $-C_{1-6}alkoxy$.

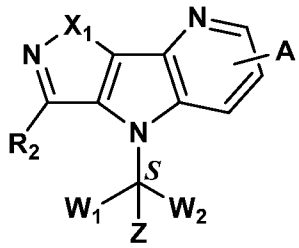
In some embodiments, wherein the compound is of formula I-1:



I-1

"*R*" in the formula I-1 indicates that the absolute configuration of the carbon that contacts with the W_1, W_2 and Z is *R* configuration when the carbon is chiral carbon.

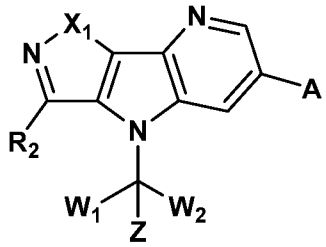
In some embodiments, wherein the compound is of formula I-2:



I-2

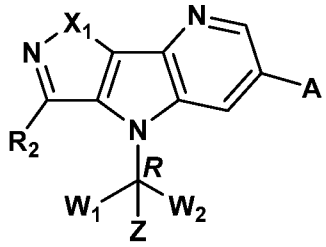
"*S*" in the formula I-2 indicates that the absolute configuration of the carbon that contacts with the W_1, W_2 and Z is *S* configuration when the carbon is chiral carbon.

In some embodiments, wherein the compound is of formula II:



II.

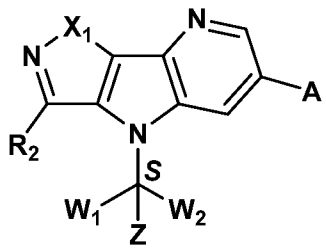
In some embodiments, wherein the compound is of formula II-1:



II-1

"*R*" in the formula II-1 indicates that the absolute configuration of the carbon that contacts with the W_1, W_2 and Z is *R* configuration when the carbon is chiral carbon.

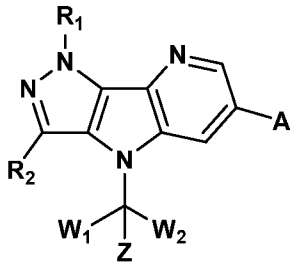
In some embodiments, wherein the compound is of formula II-2:



II-2

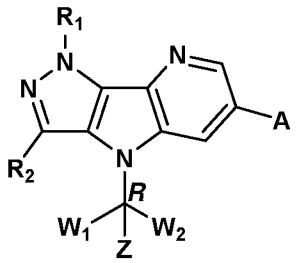
"*S*" in the formula II-2 indicates that the absolute configuration of the carbon that contacts with the W_1, W_2 and Z is *S* configuration when the carbon is chiral carbon.

In some embodiments, wherein the compound is of formula III:



III.

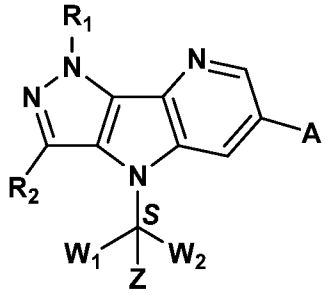
In some embodiments, wherein the compound is of formula III-1:



III-1

"*R*" in the formula III-1 indicates that the absolute configuration of the carbon that contacts with the W_1, W_2 and Z is *R* configuration when the carbon is chiral carbon.

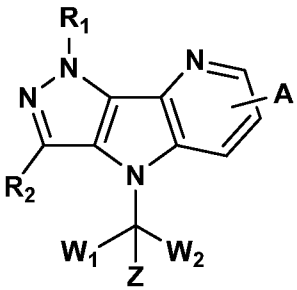
In some embodiments, wherein the compound is of formula III-2:



III-2

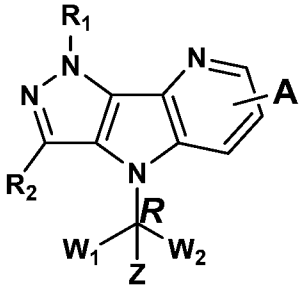
"*S*" in the formula III-2 indicates that the absolute configuration of the carbon that contacts with the W_1, W_2 and Z is *S* configuration when the carbon is chiral carbon.

In some embodiments, the compound is of formula IV:



IV.

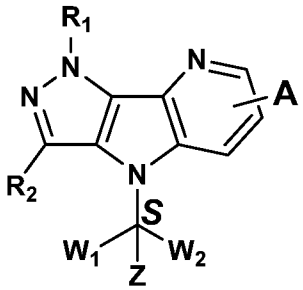
In some embodiments, the compound is of formula IV-1:



IV-1

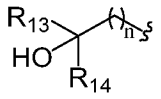
"*R*" in the formula IV-1 indicates that the absolute configuration of the carbon that contacts with the W_1, W_2 and Z is *R* configuration when the carbon is chiral carbon.

In some embodiments, the compound is of formula IV-2:



IV-2

"*S*" in the formula IV-2 indicates that the absolute configuration of the carbon that contacts with the W_1, W_2 and Z is *S* configuration when the carbon is chiral carbon.

In some embodiments, wherein R_1 is selected from hydrogen; deuterium; -SOR_{11}; -SO_2R_{11}; -$SO_2NR_{11}R_{12}$; -C_{1-6}alkyl;  ; -$COOR_{11}$; -COR_{11}; -$CONR_{11}R_{12}$; -$POR_{11}R_{12}$; -C_{5-6}heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S or SO_2; -C_{3-8}heterocyclic containing 1, 2, 3 or 4 heteroatoms selected from N, O, S or SO_2; or -C_{3-8}carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, -C_{1-6}alkyl, -C_{1-6}alkoxy, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$ or -C_{3-8}carbocyclic;

Each of R_{11} and R_{12} at each occurrence is independently selected from hydrogen, deuterium, -C_{1-6}alkyl, -C_{1-6}alkylene-C_{3-8}carbocyclic or -C_{3-8}carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, -CN, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -C_{1-6}alkyl, -C_{1-6}alkoxy, -SO_2(C_{1-6}alkyl) or -C_{3-8}carbocyclic; or

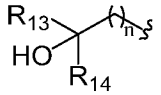
R_{11} and R_{12} together with the nitrogen atom to which they are both attached form 4-6 membered heterocyclic ring, and each of the heterocyclic ring at each occurrence can further contains 1, 2 or 3 heteroatoms selected from N, O, S or SO_2, and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium; halogen; -OH; oxo; -CN; -C_{1-6}alkyl;

-C_{1-6}alkoxy; -SO_2(C_{1-6}alkyl); -CON(C_{1-6}alkyl)$_2$; -SO_2N(C_{1-6}alkyl)$_2$; -NH_2; -NH(C_{1-6}alkyl); -N(C_{1-6}alkyl)$_2$; -C_{3-6}heterocyclic containing 1 or 2 heteroatoms selected from N, O or S; or -C_{1-6}alkyl substituted with deuterium;

Each of R_{13} and R_{14} at each occurrence is independently selected from hydrogen, deuterium or -C_{1-6}alkyl; or

R_{13} and R_{14} together with the carbon atom to which they are both attached form 3-6 membered carbocyclic ring, and each of the carbocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3 or 4 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, -NH_2, -CN, -C_{1-6}alkyl or -C_{1-6}alkoxy;

n is selected from 0, 1, 2 or 3.

In some embodiments, wherein R_1 is selected from hydrogen; deuterium; -SOR_{11}; -SO_2R_{11}; -$SO_2NR_{11}R_{12}$; -C_{1-3}alkyl;  ; -$COOR_{11}$; -COR_{11}; -$CONR_{11}R_{12}$; -$POR_{11}R_{12}$; -C_{5-6}heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S or SO_2; -C_{3-6}heterocyclic containing 1, 2, 3 or 4 heteroatoms selected from N, O, S or SO_2; or -C_{3-6}carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, -C_{1-3}alkyl, -C_{1-3}alkoxy, -NH_2, -NH(C_{1-3}alkyl), -N(C_{1-3}alkyl)$_2$ or -C_{3-6}carbocyclic;

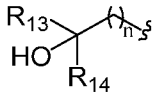
Each of R_{11} and R_{12} at each occurrence is independently selected from hydrogen, deuterium, -C_{1-3}alkyl, -C_{1-3}alkylene-C_{3-6}carbocyclic or -C_{3-6}carbocyclic, and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, -CN, -NH_2, -NH(C_{1-3}alkyl), -N(C_{1-3}alkyl)$_2$, -C_{1-3}alkyl, -C_{1-3}alkoxy, -SO_2(C_{1-3}alkyl) or -C_{3-6}carbocyclic; or

R_{11} and R_{12} together with the nitrogen atom to which they are both attached form 4-6 membered heterocyclic ring, and each of the heterocyclic ring at each occurrence can further contains 1, 2 or 3 heteroatoms selected from N, O or SO_2, and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium; -F; -Cl; -Br; -OH; oxo; -CN; -C_{1-3}alkyl; -C_{1-3}alkoxy; -SO_2(C_{1-3}alkyl); -CON(C_{1-3}alkyl)$_2$; -SO_2N(C_{1-3}alkyl)$_2$; -NH_2; -NH(C_{1-3}alkyl); -N(C_{1-3}alkyl)$_2$; -C_{4-6}heterocyclic containing 1 heteroatoms selected from N or O; or -C_{1-3}alkyl substituted with deuterium;

Each of R_{13} and R_{14} at each occurrence is independently selected from hydrogen, deuterium or -C_{1-3}alkyl; or

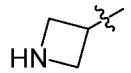
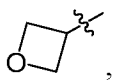
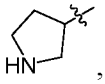
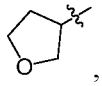
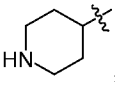
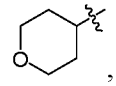
R_{13} and R_{14} together with the carbon atom to which they are both attached form 3-6 membered carbocyclic ring, and each of the carbocyclic ring is independently optionally substituted with 1, 2, 3 or 4 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, -NH_2, -CN, -C_{1-3}alkyl or -C_{1-3}alkoxy;

n is selected from 0, 1, 2 or 3.

In some embodiments, wherein R_1 is selected from hydrogen; deuterium; -SOR_{11}; -SO_2R_{11}; -$SO_2NR_{11}R_{12}$; methyl; ethyl; propyl; isopropyl;  ; -$COOR_{11}$; -COR_{11}; -$CONR_{11}R_{12}$; -$POR_{11}R_{12}$; 5-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 6-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 3-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 4-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 5-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 6-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 3-membered carbocyclic; 4-membered carbocyclic; 5-membered carbocyclic; or 6-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -NH_2, -$NH(CH_3)$, -$NH(CH_2CH_3)$, -$NH(CH_2CH_2CH_3)$, -$NH(CH(CH_3)_2)$, -$N(CH_3)_2$, -$N(CH_2CH_3)_2$, -$N(CH_3)(CH_2CH_3)$, -$N(CH_3)(CH_2CH_2CH_3)$, 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic or 6-membered carbocyclic;

Each of R_{11} and R_{12} at each occurrence is independently selected from hydrogen, deuterium, methyl, ethyl, propyl, isopropyl, -methylene-3-membered carbocyclic, -methylene-4-membered carbocyclic, -methylene-5-membered carbocyclic, -methylene-6-membered carbocyclic, -ethylene-3-membered carbocyclic, -ethylene-4-membered carbocyclic, -ethylene-5-membered carbocyclic, -ethylene-6-membered carbocyclic, 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic or 6-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, -CN, -NH_2, -$NH(CH_3)$, -$NH(CH_2CH_3)$, -$NH(CH_2CH_2CH_3)$, -$NH(CH(CH_3)_2)$, -$N(CH_3)_2$, -$N(CH_2CH_3)_2$, -$N(CH_3)(CH_2CH_3)$, -$N(CH_3)(CH_2CH_2CH_3)$, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -SO_2CH_3, -$SO_2CH_2CH_3$, -$SO_2CH_2CH_2CH_3$, -$SO_2CH(CH_3)_2$, 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic or 6-membered carbocyclic; or

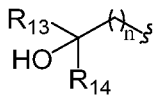
R_{11} and R_{12} together with the nitrogen atom to which they are both attached form 4 membered heterocyclic ring, 5 membered heterocyclic ring or 6 membered heterocyclic ring, and each of the heterocyclic ring at each occurrence can further contains 1 or 2 heteroatoms selected from N, O or SO_2, and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, oxo, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -SO_2CH_3, -$SO_2CH_2CH_3$, -$SO_2CH_2CH_2CH_3$, -$SO_2CH(CH_3)_2$, -$CON(CH_3)_2$, -$CON(CH_2CH_3)_2$, -$CON(CH_2CH_2CH_3)_2$, -$CON(CH(CH_3)_2)_2$, -$SO_2N(CH_3)_2$, -$SO_2N(CH_2CH_3)_2$, -$SO_2N(CH_2CH_2CH_3)_2$, -$SO_2N(CH(CH_3)_2)_2$, -NH_2, -$NH(CH_3)$, -$NH(CH_2CH_3)$, -$NH(CH_2CH_2CH_3)$,

-NH(CH(CH$_3$)$_2$), -N(CH$_3$)$_2$, -N(CH$_2$CH$_3$)$_2$, -N(CH$_3$)(CH$_2$CH$_3$), -N(CH$_3$)(CH$_2$CH$_2$CH$_3$),  ,  ,  ,  ,  ,  , methyl substituted with deuterium, ethyl substituted with deuterium, propyl substituted with deuterium or isopropyl substituted with deuterium;

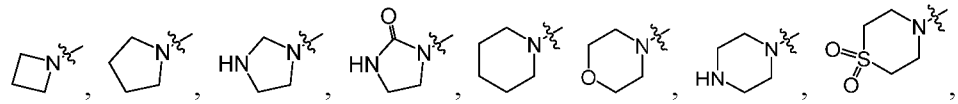
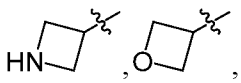
Each of R_{13} and R_{14} at each occurrence is independently selected from hydrogen, deuterium, methyl, ethyl, propyl or isopropyl; or

R_{13} and R_{14} together with the carbon atom to which they are both attached form 3 membered carbocyclic ring, 4 membered carbocyclic ring, 5 membered carbocyclic ring or 6 membered carbocyclic ring, and each of carbocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3 or 4 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, -NH$_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy;

n is selected from 0, 1, 2 or 3.

In some embodiments, wherein R_1 is selected from hydrogen; deuterium; -SOR$_{11}$; -SO$_2$R$_{11}$; -SO$_2$NR$_{11}$R$_{12}$; methyl; ethyl; propyl; isopropyl;  ; -COOR$_{11}$; -COR$_{11}$; -CONR$_{11}$R$_{12}$; -POR$_{11}$R$_{12}$; 5-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O, S or SO$_2$; 6-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O, S or SO$_2$; or 3-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -NH$_2$, -NH(CH$_3$), -NH(CH$_2$CH$_3$), -N(CH$_3$)$_2$, -N(CH$_3$)(CH$_2$CH$_3$) or 3-membered carbocyclic;

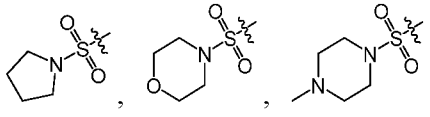
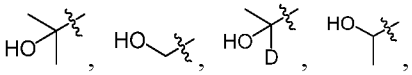
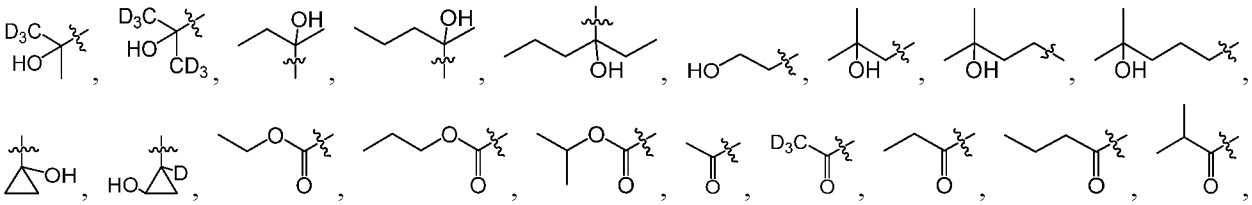
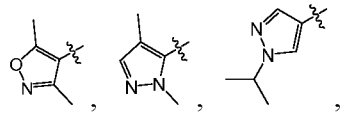
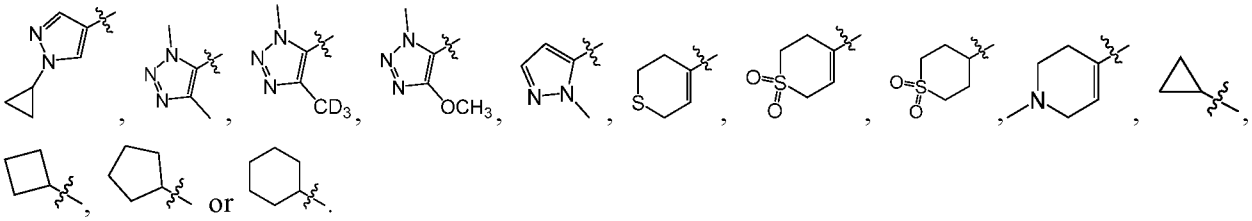
Each of R_{11} or R_{12} at each occurrence is independently selected from hydrogen, deuterium, methyl, ethyl, propyl, isopropyl, -methylene-3-membered carbocyclic or 3-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, -NH$_2$, -NH(CH$_3$), -N(CH$_3$)$_2$, methyl, methoxy, -SO$_2$CH$_3$ or 3-membered carbocyclic; or

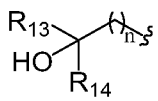
R_{11} and R_{12} together with the nitrogen atom to which they are both attached form the heterocyclic selected from  , and the heterocyclic ring is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, oxo, -CN, methyl, methoxy, -SO$_2$CH$_3$, -CON(CH$_3$)$_2$, -SO$_2$N(CH$_3$)$_2$, -NH$_2$, -NH(CH$_3$), -N(CH$_3$)$_2$,  , -CH$_2$D, -CHD$_2$ or -CD$_3$;

Each of R_{13} and R_{14} at each occurrence is independently selected from hydrogen, deuterium, methyl, ethyl, propyl or isopropyl; or

R_{13} and R_{14} together with the carbon atom to which they are both attached form 3 membered carbocyclic ring, and the carbocyclic ring is independently optionally substituted with 1, 2, 3 or 4 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -OH, methyl, ethyl, propyl or isopropyl;

n is selected from 0 or 1.

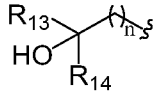
In some embodiments, wherein R_1 is selected from hydrogen, deuterium, $-SOCH_3$, $-SOCH_2CH_3$, $-SOCH_2CH_2CH_3$, $-SOCH(CH_3)_2$, $-SO_2CH_3$, $-SO_2CD_3$, $-SO_2CH_2CH_3$, $-SO_2CH_2CH_2CH_3$, $-SO_2CH(CH_3)_2$, $-SO_2CH(CD_3)_2$, $-SO_2NH_2$, $-SO_2NH(CH_3)$, $-SO_2N(CH_3)_2$, $-SO_2NH(CD_3)$, $-SO_2N(CD_3)_2$, $-SO_2NH(CH_2CH_3)$, $-SO_2N(CH_2CH_3)_2$, $-SO_2NH(CH_2CH_2CH_3)$, $-SO_2N(CH_2CH_2CH_3)_2$,  , $-CH_3$, $-CH_2D$, $-CHF_2$, $-CH_2F$, $-CD_2H$, $-CD_3$, $-CF_3$, $-CH_2CH_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHCH_3$, $-CH_2CH_2N(CH_3)_2$, $-CH_2CD_3$, $-CH_2CF_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CD_3$, $-CH_2CH_2CF_3$, $-CH(CH_3)_2$, $-CH(CH_3)(CD_3)$, $-CH(CF_3)_2$, $-CH(CD_3)_2$,  ,  , , $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, $-CONH(CD_3)$, $-CON(CD_3)_2$, $-CONH(CH_2CH_3)$, $-CON(CH_2CH_3)_2$, $-CONH(CH_2CH_2CH_3)$, $-CON(CH_2CH_2CH_3)_2$, $-P(O)H_2$, $-P(O)H(CH_3)$, $-PO(CH_3)_2$, $-P(O)H(CD_3)$, $-P(O)(CD_3)_2$, $-P(O)(CH_2CH_3)_2$, $-P(O)(CH_2CH_2CH_3)_2$, $-P(O)(CH(CH_3)_2)_2$,  ,  , , or .

In some embodiments, wherein R_1 is selected from $-SO_2R_{11}$, $-C_{1-6}$alkyl,  or $-C_{3-8}$carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-NH_2$, $-NH(C_{1-6}$alkyl),or $-N(C_{1-6}$alkyl$)_2$;

R_{11} is selected from hydrogen, deuterium or $-C_{1-6}$alkyl;

Each of R_{13} and R_{14} at each occurrence is independently selected from hydrogen, deuterium or $-C_{1-6}$alkyl;

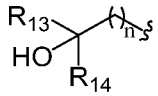
n is selected from 0, 1, 2, 3, 4, 5 or 6.

In some embodiments, wherein R_1 is selected from $-SO_2R_{11}$, $-C_{1-3}$alkyl,  or $-C_{3-6}$carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, $-C_{1-3}$alkyl, $-C_{1-3}$alkoxy, $-NH_2$, $-NH(C_{1-3}$alkyl) or $-N(C_{1-3}$alkyl)$_2$;

R_{11} is selected from hydrogen, deuterium or $-C_{1-3}$alkyl;

Each of R_{13} and R_{14} at each occurrence is independently selected from hydrogen, deuterium or $-C_{1-3}$alkyl;

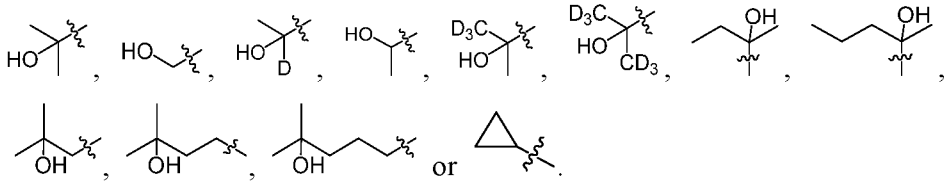
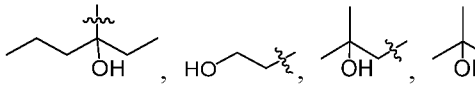
n is selected from 0, 1, 2 or 3.

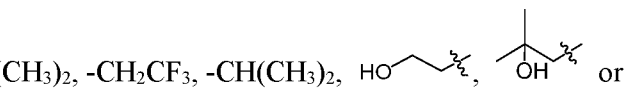
In some embodiments, wherein R_1 is selected from $-SO_2R_{11}$, methyl, ethyl, propyl, isopropyl,  , 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic or 6-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, $-NH_2$, $-NH(CH_3)$, $-NH(CH_2CH_3)$, $-NH(CH_2CH_2CH_3)$, $-NH(CH(CH_3)_2)$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_3)(CH_2CH_3)$ or $-N(CH_3)(CH_2CH_2CH_3)$;

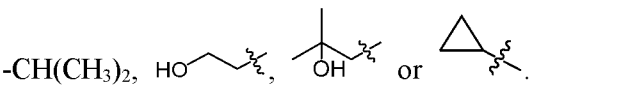
R_{11} is selected from hydrogen, deuterium, methyl, ethyl, propyl or isopropyl;

Each of R_{13} and R_{14} at each occurrence is independently selected from hydrogen, deuterium, methyl, ethyl, propyl or isopropyl;

n is selected from 0, 1, 2 or 3.

In some embodiments, wherein R_1 is selected from $-SO_2CH_3$, $-SO_2CD_3$, $-SO_2CH_2CH_3$, $-SO_2CH_2CH_2CH_3$, $-SO_2CH(CH_3)_2$, $-SO_2CH(CD_3)_2$, $-CH_3$, $-CH_2D$, $-CHF_2$, $-CH_2F$, $-CD_2H$, $-CD_3$, $-CF_3$, $-CH_2CH_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHCH_3$, $-CH_2CH_2N(CH_3)_2$, $-CH_2CD_3$, $-CH_2CF_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CD_3$, $-CH_2CH_2CF_3$, $-CH(CH_3)_2$, $-CH(CH_3)(CD_3)$, $-CH(CF_3)_2$, $-CH(CD_3)_2$,  or  .

In some embodiments, wherein R_1 is selected from hydrogen, deuterium, $-SO_2CH_3$, $-CH_3$, $-CHF_2$, $-CD_3$, $-CH_2CH_3$, $-CH_2CHF_2$, $-CH_2CH_2N(CH_3)_2$, $-CH_2CF_3$, $-CH(CH_3)_2$,  .

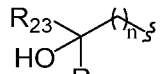
In some embodiments, wherein R_1 is selected from $-SO_2CH_3$, $-CH_3$, $-CHF_2$, $-CD_3$, $-CH_2CH_3$, $-CH_2CHF_2$, $-CH_2CH_2N(CH_3)_2$, $-CH_2CF_3$, $-CH(CH_3)_2$,  .

In some embodiments, wherein R_1 is $-C_{1-6}$alkyl.

In some embodiments, wherein R_1 is $-C_{1-3}$alkyl.

In some embodiments, wherein R_1 is selected from methyl, ethyl, propyl or isopropyl.

In some embodiments, wherein R_1 is methyl.

In some embodiments, wherein R_2 is selected from hydrogen; deuterium; halogen; $-OR_{21}$; $-NR_{21}R_{22}$; -CN; $-SR_{21}$; $-SOR_{21}$; $-SO_2R_{21}$; $-SO_2NR_{21}R_{22}$; $-C_{1-6}$alkyl;  ; $-C_{2-6}$alkenyl; $-COOR_{21}$; $-COR_{21}$; $-CONR_{21}R_{22}$; $-NR_{21}COR_{22}$; $-NR_{21}SO_2R_{22}$; $-POR_{21}R_{22}$; $-C_{5-6}$heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S or SO_2; $-C_{3-8}$heterocyclic containing 1, 2, 3 or 4 heteroatoms selected from N, O, S or SO_2; or $-C_{3-8}$carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each substituents at each occurrence is independently selected from deuterium, halogen, -OH, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy or $-C_{3-8}$carbocyclic;

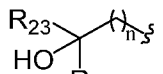
Each of R_{21} and R_{22} at each occurrence is independently selected from hydrogen, deuterium, $-C_{1-6}$alkyl, $-C_{1-6}$alkylene-C_{3-8}carbocyclic or $-C_{3-8}$carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, -CN, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-SO_2(C_{1-6}alkyl)$ or $-C_{3-8}$carbocyclic; or

R_{21} and R_{22} together with the nitrogen atom to which they are both attached form 4-6 membered heterocyclic ring, each of the heterocyclic ring at each occurrence can further contains 1, 2 or 3 heteroatoms selected from N, O, S or SO_2, and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium; halogen; -OH; oxo; -CN; $-C_{1-6}$alkyl; $-C_{1-6}$alkoxy; $-SO_2(C_{1-6}alkyl)$; $-CON(C_{1-6}alkyl)_2$; $-SO_2N(C_{1-6}alkyl)_2$; $-NH_2$; $-NH(C_{1-6}alkyl)$; $-N(C_{1-6}alkyl)_2$; $-C_{3-6}$heterocyclic containing 1 or 2 heteroatoms selected from N, O or S; or $-C_{1-6}$alkyl substituted with deuterium;

Each of R_{23} and R_{24} at each occurrence is independently selected from hydrogen, deuterium or $-C_{1-6}$alkyl; or

R_{23} and R_{24} together with the carbon atom to which they are both attached form 3-6 membered carbocyclic ring, and each of the carbocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3 or 4 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, $-NH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy;

n is selected from 0, 1, 2, 3, 4, 5 or 6.

In some embodiments, wherein R_2 is selected from hydrogen; deuterium; -F; -Cl; -Br; $-OR_{21}$; $-NR_{21}R_{22}$; -CN; $-SR_{21}$; $-SOR_{21}$; $-SO_2R_{21}$; $-SO_2NR_{21}R_{22}$; $-C_{1-3}$alkyl;  ; $-C_{2-3}$alkenyl; $-COOR_{21}$; $-COR_{21}$; $-CONR_{21}R_{22}$; $-NR_{21}COR_{22}$; $-NR_{21}SO_2R_{22}$; $-POR_{21}R_{22}$; $-C_{5-6}$heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S or SO_2; $-C_{3-6}$heterocyclic containing 1, 2, 3 or 4 heteroatoms selected from N, O, S or SO_2; or $-C_{3-6}$carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each substituents at each occurrence

is independently selected from deuterium, -F, -Cl, -Br, -OH, -C_{1-3}alkyl, -C_{1-3}alkoxy or -C_{3-6}carbocyclic;

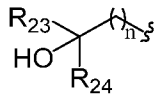
Each of R_{21} or R_{22} at each occurrence is independently selected from hydrogen, deuterium, -C_{1-3}alkyl, -C_{1-3}alkylene-C_{3-6}carbocyclic or -C_{3-6}carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, -CN, -NH_2, -NH(C_{1-3}alkyl), -N(C_{1-3}alkyl)$_2$, -C_{1-3}alkyl, -C_{1-3}alkoxy, -SO_2(C_{1-3}alkyl) or -C_{3-6}carbocyclic; or

R_{21} and R_{22} together with the nitrogen atom to which they are both attached form 4-6 membered heterocyclic ring, each of the heterocyclic ring at each occurrence can further contains 1, 2 or 3 heteroatoms selected from N, O or SO_2, and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium; -F; -Cl; -Br; -OH; oxo; -CN; -C_{1-3}alkyl; -C_{1-3}alkoxy; -SO_2(C_{1-3}alkyl); -CON(C_{1-3}alkyl)$_2$; -SO_2N(C_{1-3}alkyl)$_2$; -NH_2; -NH(C_{1-3}alkyl); -N(C_{1-3}alkyl)$_2$; -C_{4-6}heterocyclic containing 1 heteroatoms selected from N or O; or -C_{1-3}alkyl substituted with deuterium;

Each of R_{23} and R_{24} at each occurrence is independently selected from hydrogen, deuterium or -C_{1-3}alkyl; or

R_{23} and R_{24} together with the carbon atom to which they are both attached form 3-6 membered carbocyclic ring, and each of the carbocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3 or 4 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, -NH_2, -CN, -C_{1-3}alkyl or -C_{1-6}alkoxy;

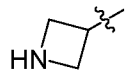
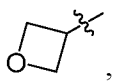
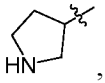
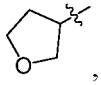
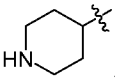
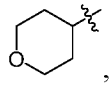
n is selected from 0, 1, 2 or 3.

In some embodiments, wherein R_2 is selected from hydrogen; deuterium; -F; -Cl; -Br; -OR_{21}; -$NR_{21}R_{22}$; -CN; -SR_{21}; -SOR_{21}; -SO_2R_{21}; -$SO_2NR_{21}R_{22}$; methyl; ethyl; propyl; isopropyl; 

; ethenyl; propenyl; -$COOR_{21}$; -COR_{21}; -$CONR_{21}R_{22}$; -$NR_{21}COR_{22}$; -$NR_{21}SO_2R_{22}$; -$POR_{21}R_{22}$; 5-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 6-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 3-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 4-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 5-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 6-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 3-membered carbocyclic; 4-membered carbocyclic; 5-membered carbocyclic; or 6-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic or 6-membered carbocyclic;

Each of R_{21} or R_{22} at each occurrence is independently selected from hydrogen, deuterium, methyl, ethyl, propyl, isopropyl, -methylene-3-membered carbocyclic, -methylene-4-membered carbocyclic,

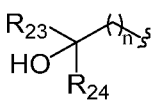
-methylene-5-membered carbocyclic, -methylene-6-membered carbocyclic, -ethylene-3-membered carbocyclic, -ethylene-4-membered carbocyclic, -ethylene-5-membered carbocyclic, -ethylene-6-membered carbocyclic, 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic or 6-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, -CN, $-NH_2$, $-NH(CH_3)$, $-NH(CH_2CH_3)$, $-NH(CH_2CH_2CH_3)$, $-NH(CH(CH_3)_2)$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_3)(CH_2CH_3)$, $-N(CH_3)(CH_2CH_2CH_3)$, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, $-SO_2CH_3$, $-SO_2CH_2CH_3$, $-SO_2CH_2CH_2CH_3$, $-SO_2CH(CH_3)_2$, 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic or 6-membered carbocyclic; or

R_{21} and R_{22} together with the nitrogen atom to which they are both attached form 4 membered heterocyclic ring, 5 membered heterocyclic ring, 6 membered heterocyclic ring, each of the heterocyclic ring at each occurrence can further contains 1 or 2 heteroatoms selected from N, O or SO_2, and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, oxo, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, $-SO_2CH_3$, $-SO_2CH_2CH_3$, $-SO_2CH_2CH_2CH_3$, $-SO_2CH(CH_3)_2$, $-CON(CH_3)_2$, $-CON(CH_2CH_3)_2$, $-CON(CH_2CH_2CH_3)_2$, $-CON(CH(CH_3)_2)_2$, $-SO_2N(CH_3)_2$, $-SO_2N(CH_2CH_3)_2$, $-SO_2N(CH_2CH_2CH_3)_2$, $-SO_2N(CH(CH_3)_2)_2$, $-NH_2$, $-NH(CH_3)$, $-NH(CH_2CH_3)$, $-NH(CH_2CH_2CH_3)$, $-NH(CH(CH_3)_2)$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_3)(CH_2CH_3)$, $-N(CH_3)(CH_2CH_2CH_3)$,  ,  ,  ,  ,  ,  , methyl substituted with deuterium, ethyl substituted with deuterium, propyl substituted with deuterium or isopropyl substituted with deuterium;

Each of R_{23} and R_{24} at each occurrence is independently selected from hydrogen, deuterium, methyl, ethyl, propyl or isopropyl; or

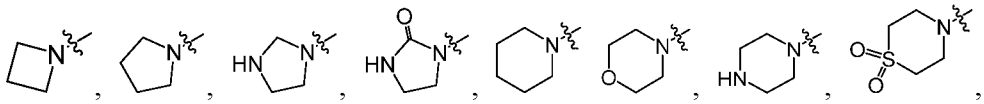
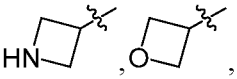
R_{23} and R_{24} together with the carbon atom to which they are both attached form 3-membered carbocyclic ring, 4-membered carbocyclic ring, 5-membered carbocyclic ring or 6 membered carbocyclic ring, and each of the carbocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3 or 4 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl methoxy, ethoxy, propoxy or isopropoxy;

n is selected from 0, 1, 2 or 3.

In some embodiments, wherein R_2 is independently selected from hydrogen; deuterium; -F; -Cl; -Br; $-OR_{21}$; $-NR_{21}R_{22}$; -CN; $-SR_{21}$; $-SOR_{21}$; $-SO_2R_{21}$; $-SO_2NR_{21}R_{22}$; methyl; ethyl; propyl; isopropyl;  ; ethenyl; $-COOR_{21}$; $-COR_{21}$; $-CONR_{21}R_{22}$; $-NR_{21}COR_{22}$; $-NR_{21}SO_2R_{22}$; $-POR_{21}R_{22}$; 5-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 6-membered

heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; or 3-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy or 3-membered carbocyclic;

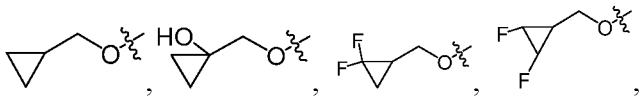
Each of R_{21} and R_{22} at each occurrence is independently selected from hydrogen, deuterium, methyl, ethyl, propyl, isopropyl, -methylene-3-membered carbocyclic or 3-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, methyl, methoxy, $-SO_2CH_3$ or 3-membered carbocyclic; or

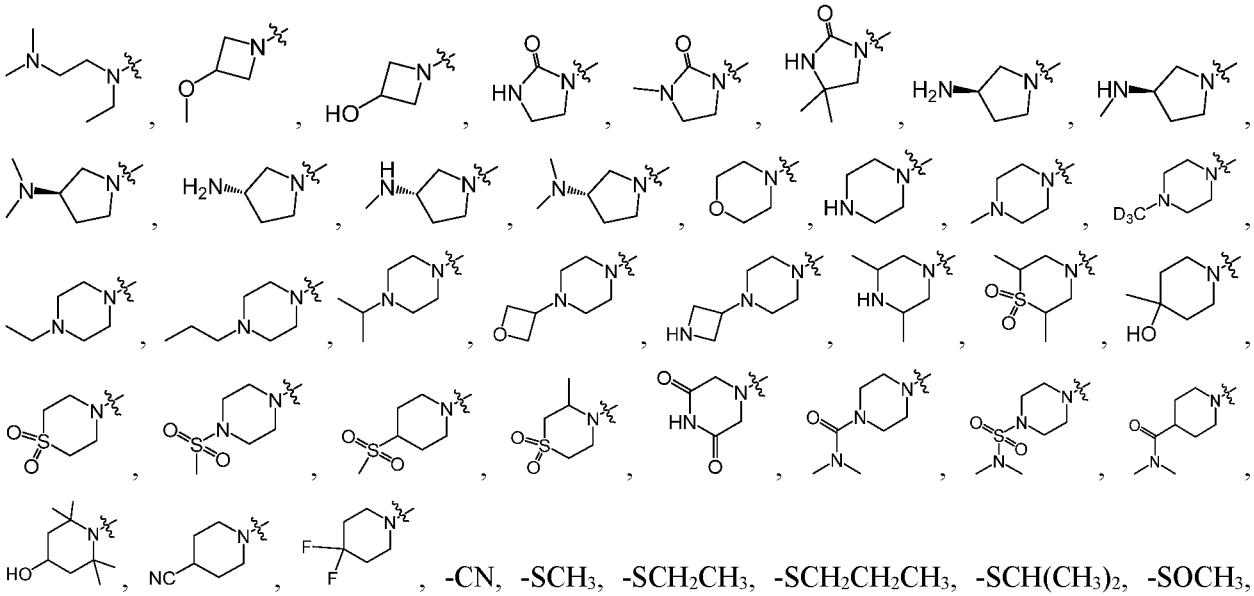
R_{21} and R_{22} together with the nitrogen atom to which they are both attached form the heterocyclic selected from  , and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, oxo, -CN, methyl, ethyl, propyl, isopropyl, methoxy, $-SO_2CH_3$, $-CON(CH_3)_2$, $-SO_2N(CH_3)_2$, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$,  , $-CH_2D$, $-CHD_2$ or $-CD_3$;

Each of R_{23} and R_{24} at each occurrence is independently selected from hydrogen, deuterium, methyl, ethyl, propyl or isopropyl; or

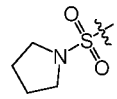
R_{23} and R_{24} together with the carbon atom to which they are both attached form 3-membered carbocyclic ring, and the carbocyclic ring is independently optionally substituted with 1, 2, 3 or 4 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy;

n is selected from 0 or 1.

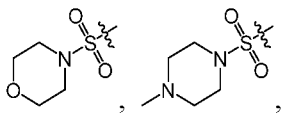
In some embodiments, wherein R_2 is selected from hydrogen, deuterium, -F, -Cl, -Br, -OH, $-OCH_3$, $-OCD_3$, $-OCH_2CH_3$, $-OCH_2CH_2CH_3$, $-OCH(CH_3)_2$, $-OCH_2CF_3$, $-OCH_2CHF_2$, $-OCF_2CH_3$, $-OCH_2OH$, $-OCH_2CH_2OH$, $-OCH_2CH_2CH_2OH$, $-OCH_2CH_2NH_2$, $-OCH_2N(CH_3)_2$, $-OCH_2CH_2N(CH_3)_2$, $-OCH_2CH_2CH_2N(CH_3)_2$, $-OCH_2CH_2NHCH_3$,  , $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCD_3$, $-N(CD_3)_2$, $-NHCH_2CH_3$, $-N(CH_3CH_2)_2$, $-N(CH_3)(CH_3CH_2)$, $-NHCH_2CH_2CH_3$, $-N(CH_2CH_2CH_3)_2$, $-NHCH(CH_3)_2$, $-N(CH_3)(CH(CH_3)_2)$, $-N(CH(CH_3)_2)_2$, $-NHCH_2CF_3$,  ,



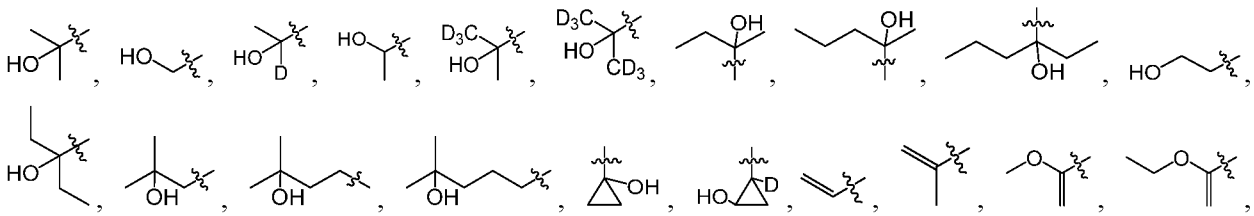
-CN, -SCH_3, -SCH_2CH_3, -$SCH_2CH_2CH_3$, -$SCH(CH_3)_2$, -$SOCH_3$, -$SOCH_2CH_3$, -$SOCH_2CH_2CH_3$, -$SOCH(CH_3)_2$, -SO_2CH_3, -SO_2CD_3, -$SO_2CH_2CH_3$, -$SO_2CH_2CH_2CH_3$, -$SO_2CH(CH_3)_2$, -$SO_2CH(CD_3)_2$, -SO_2NH_2, -$SO_2NH(CH_3)$, -$SO_2N(CH_3)_2$, -$SO_2NH(CD_3)$, -$SO_2N(CD_3)_2$,



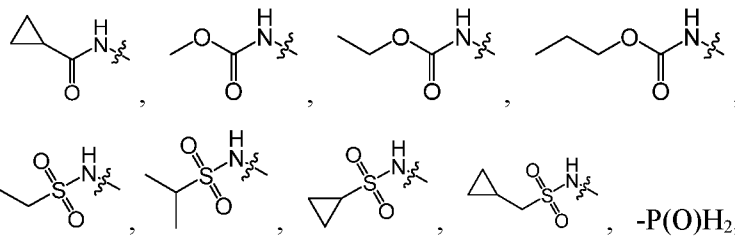
-$SO_2NH(CH_2CH_3)$, -$SO_2N(CH_2CH_3)_2$, -$SO_2NH(CH_2CH_3CH_2)$, -$SO_2N(CH_2CH_2CH_3)_2$,



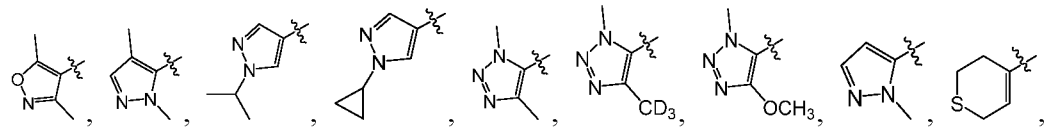
-CH_3, -CH_2D, -CD_2H, -CD_3, -CF_3, -CH_2CH_3, -CH_2CD_3, -CH_2CF_3, -$CH_2CH_2CH_3$, -$CH_2CH_2CH_2F$, -$CH_2CH_2CD_3$, -$CH_2CH_2CF_3$, -$CH(CH_3)_2$, -$CH(CH_3)(CD_3)$, -$CH(CF_3)_2$, -$CH(CD_3)_2$,

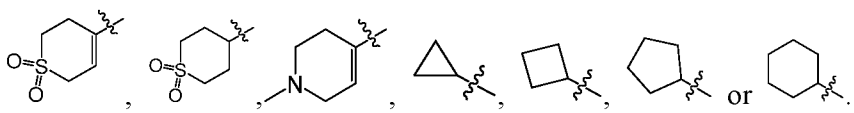


-$CONH_2$, -$CONH(CH_3)$, -$CON(CH_3)_2$, -$CONH(CD_3)$, -$CON(CD_3)_2$, -$CONH(CH_2CH_3)$, -$CON(CH_2CH_3)_2$, -$CONH(CH_2CH_2CH_3)$, -$CON(CH_2CH_2CH_3)_2$, -$NHCOCH_3$, -$NHCOCH_2CH_3$, -$NHCOCH_2CH_2CH_3$, -$NHCOCH(CH_3)_2$,

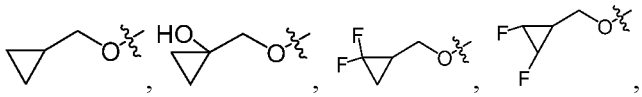


-$P(O)H_2$, -$P(O)H(CH_3)$, -$PO(CH_3)_2$, -$P(O)H(CD_3)$, -$PO(CD_3)_2$, -$PO(CH_2CH_3)_2$, -$PO(CH_2CH_2CH_3)_2$, -$PO(CH(CH_3)_2)_2$,

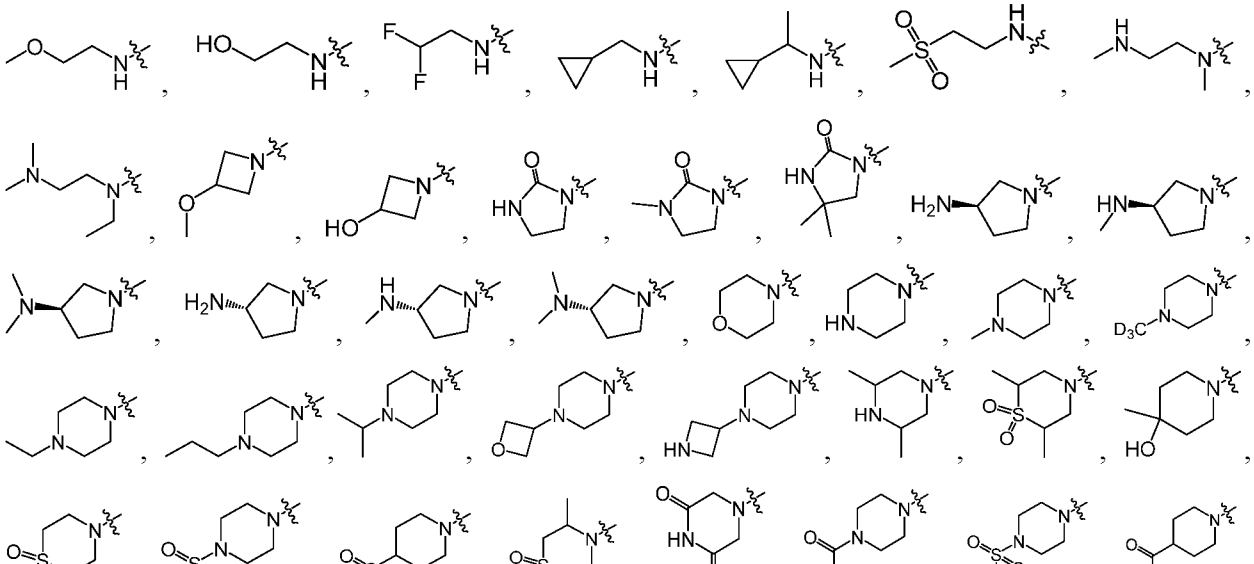




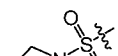
In some embodiments, wherein R_2 is selected from hydrogen, deuterium, -F, -Cl, -Br, -OH, $-OCH_3$, $-OCD_3$, $-OCH_2CH_3$, $-OCH_2CH_2CH_3$, $-OCH(CH_3)_2$, $-OCH_2CF_3$, $-OCH_2CHF_2$, $-OCF_2CH_3$, $-OCH_2OH$, $-OCH_2CH_2OH$, $-OCH_2CH_2CH_2OH$, $-OCH_2CH_2NH_2$, $-OCH_2N(CH_3)_2$, $-OCH_2CH_2N(CH_3)_2$, $-OCH_2CH_2CH_2N(CH_3)_2$, $-OCH_2CH_2NHCH_3$,



, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCD_3$, $-N(CD_3)_2$, $-NHCH_2CH_3$, $-N(CH_3CH_2)_2$, $-N(CH_3)(CH_3CH_2)$, $-NHCH_2CH_2CH_3$, $-N(CH_2CH_2CH_3)_2$, $-NHCH(CH_3)_2$, $-N(CH_3)(CH(CH_3)_2)$, $-N(CH(CH_3)_2)_2$, $-NHCH_2CF_3$,



, $-CN$, $-SCH_3$, $-SCH_2CH_3$, $-SCH_2CH_2CH_3$, $-SCH(CH_3)_2$, $-SOCH_3$, $-SOCH_2CH_3$, $-SOCH_2CH_2CH_3$, $-SOCH(CH_3)_2$, $-SO_2CH_3$, $-SO_2CD_3$, $-SO_2CH_2CH_3$, $-SO_2CH_2CH_2CH_3$, $-SO_2CH(CH_3)_2$, $-SO_2CH(CD_3)_2$, $-SO_2NH_2$, $-SO_2NH(CH_3)$, $-SO_2N(CH_3)_2$, $-SO_2NH(CD_3)$, $-SO_2N(CD_3)_2$, $-SO_2NH(CH_2CH_3)$, $-SO_2N(CH_2CH_3)_2$, $-SO_2NH(CH_2CH_3CH_2)$, $-SO_2N(CH_2CH_2CH_3)_2$,



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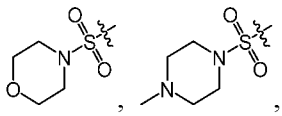
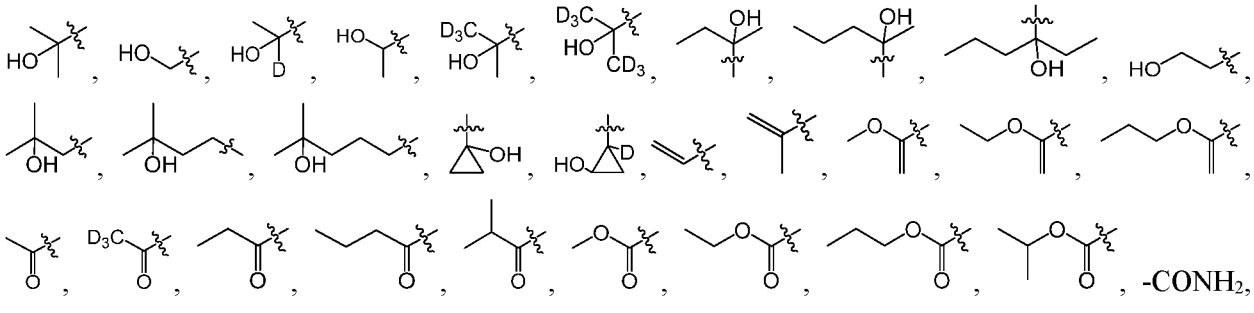
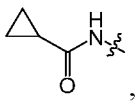
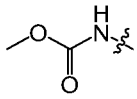
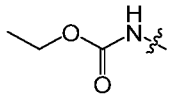
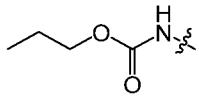
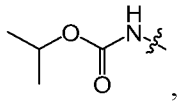
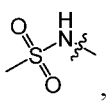
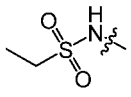
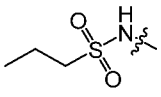
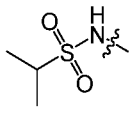
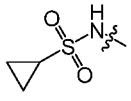
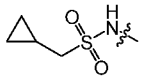
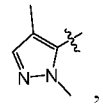
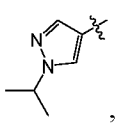
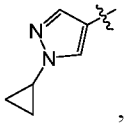
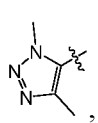
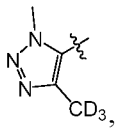
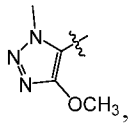
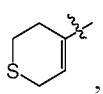
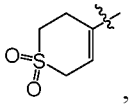
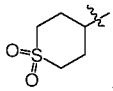
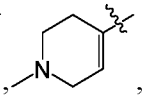
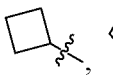
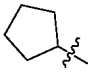


, $-CH_3$, $-CH_2D$, $-CD_2H$, $-CD_3$, $-CF_3$, $-CH_2CH_3$, $-CH_2CD_3$, $-CH_2CF_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CD_3$, $-CH_2CH_2CF_3$, $-CH(CH_3)_2$, $-CH(CH_3)(CD_3)$, $-CH(CF_3)_2$, $-CH(CD_3)_2$,



, $-CONH_2$,

-CONH(CH_3), -CON(CH_3)$_2$, -CONH(CD_3), -CON(CD_3)$_2$, -CONH(CH_2CH_3), -CON(CH_2CH_3)$_2$, -CONH($CH_2CH_2CH_3$), -CON($CH_2CH_2CH_3$)$_2$, -NHCOCH$_3$, -NHCOCH$_2$CH$_3$, -NHCOCH$_2$CH$_2$CH$_3$, -NHCOCH(CH_3)$_2$,            , -P(O)H$_2$, -P(O)H(CH_3), -PO(CH_3)$_2$, -P(O)H(CD_3), -PO(CD_3)$_2$, -PO(CH_2CH_3)$_2$, -PO($CH_2CH_2CH_3$)$_2$, -PO(CH(CH_3)$_2$)$_2$,                or  .

In some embodiments, wherein R_2 is selected from hydrogen, deuterium, halogen, -NR$_{21}$R$_{22}$, -SO$_2$R$_{21}$, -SO$_2$NR$_{21}$R$_{22}$, -C$_{1-6}$alkyl,  , -COOR$_{21}$, -COR$_{21}$, -CONR$_{21}$R$_{22}$, -NR$_{21}$COR$_{22}$, -NR$_{21}$SO$_2$R$_{22}$, -POR$_{21}$R$_{22}$ or -C$_{3-8}$carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, -C$_{1-6}$alkyl or -C$_{1-6}$alkoxy;

Each of R_{21} or R_{22} at each occurrence is independently selected from hydrogen, deuterium or -C$_{1-6}$alkyl; or

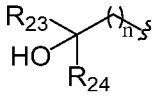
R_{21} and R_{22} together with the nitrogen atom to which they are both attached form 4-6 membered heterocyclic ring, each of the heterocyclic ring at each occurrence can further contains 1, 2 or 3 heteroatoms selected from N, O, S or SO_2, and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium; oxo; -C$_{1-6}$alkyl; -NH(C$_{1-6}$alkyl); or -C$_{3-6}$heterocyclic containing 1 or 2 heteroatoms selected from N or O;

Each of R_{23} and R_{24} at each occurrence is independently selected from hydrogen, deuterium or -C$_{1-6}$alkyl; or

R_{23} and R_{24} together with the carbon atom to which they are both attached form 3-6 membered carbocyclic ring, and each of the carbocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -OH or -C$_{1-6}$alkyl;

n is selected from 0, 1, 2, 3, 4, 5 or 6.

In some embodiments, wherein R_2 is selected from hydrogen, deuterium, halogen, -NR$_{21}$R$_{22}$, -SO$_2$R$_{21}$,



$-SO_2NR_{21}R_{22}$, $-C_{1-3}$alkyl, , $-COOR_{21}$, $-COR_{21}$, $-CONR_{21}R_{22}$, $-NR_{21}COR_{22}$, $-NR_{21}SO_2R_{22}$, $-POR_{21}R_{22}$ or $-C_{3-6}$carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy;

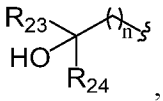
Each of R_{21} or R_{22} at each occurrence is independently selected from hydrogen, deuterium or $-C_{1-3}$alkyl; or

R_{21} and R_{22} together with the nitrogen atom to which they are both attached form 4-membered heterocyclic ring, 5-membered heterocyclic ring, 6-membered heterocyclic ring, each of the heterocyclic ring at each occurrence can further contains 1 or 2 heteroatoms selected from N or O, and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, oxo, $-C_{1-3}$alkyl, $-NH(C_{1-3}$alkyl) or $-C_{4-6}$heterocyclic containing 1 heteroatoms selected from N or O;

Each of R_{23} and R_{24} at each occurrence is independently selected from hydrogen, deuterium or $-C_{1-3}$alkyl; or

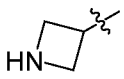
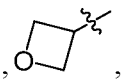
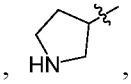
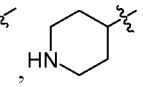
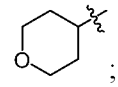
R_{23} and R_{24} together with the carbon atom to which they are both attached form 3-6 membered carbocyclic ring, and each of the carbocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -OH or $-C_{1-3}$alkyl;

n is selected from 0, 1, 2 or 3.

In some embodiments, wherein R_2 is selected from hydrogen, deuterium, -F, -Cl, -Br, $-NR_{21}R_{22}$, $-SO_2R_{21}$, $-SO_2NR_{21}R_{22}$, methyl, ethyl, propyl, isopropyl,  , $-COOR_{21}$, $-COR_{21}$, $-CONR_{21}R_{22}$, $-NR_{21}COR_{22}$, $-NR_{21}SO_2R_{22}$, $-POR_{21}R_{22}$, 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic or 6-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy;

Each of R_{21} or R_{22} at each occurrence is independently selected from hydrogen, deuterium, methyl, ethyl, propyl or isopropyl; or

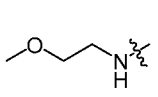
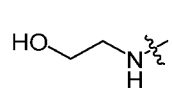
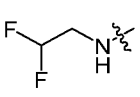
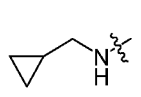
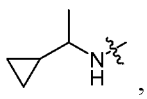
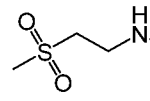
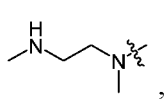
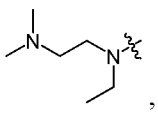
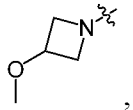
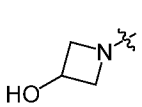
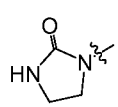
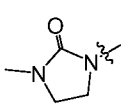
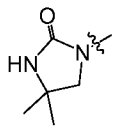
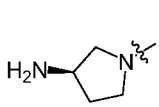
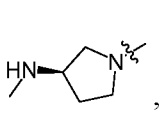
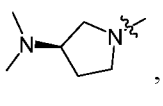
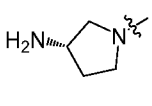
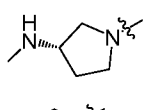
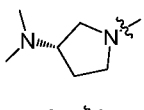
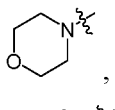
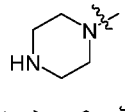
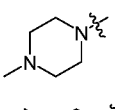
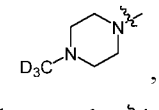
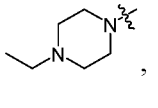
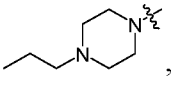
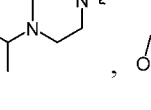
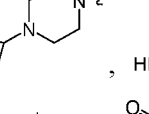
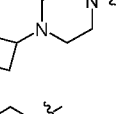
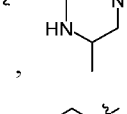
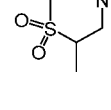
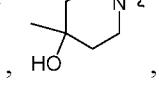
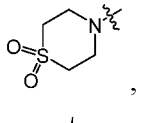
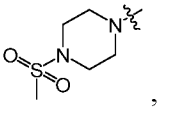
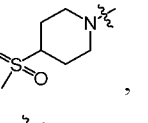
R_{21} and R_{22} together with the nitrogen atom to which they are both attached form 5-membered heterocyclic ring, 6-membered heterocyclic ring, each of the heterocyclic ring at each occurrence ring can further contains 1 heteroatoms selected from N or O, and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, oxo, methyl, ethyl, propyl,

isopropyl, -NHCH$_3$, -NHCH$_2$CH$_3$, -NHCH$_2$CH$_2$CH$_3$, -NHCH(CH$_3$)$_2$,  ,  ,  ,  ,  or  ;

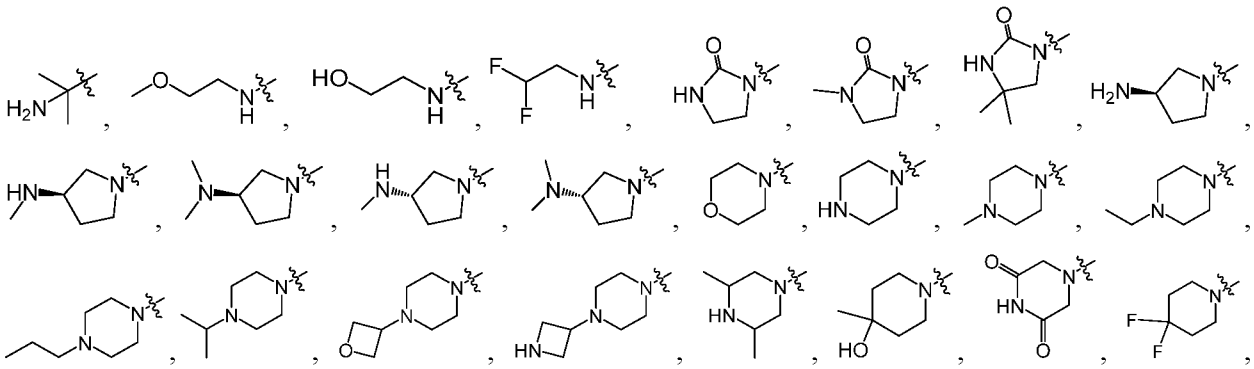
Each of R_{23} and R_{24} at each occurrence is independently selected from hydrogen, deuterium, methyl, ethyl, propyl or isopropyl; or

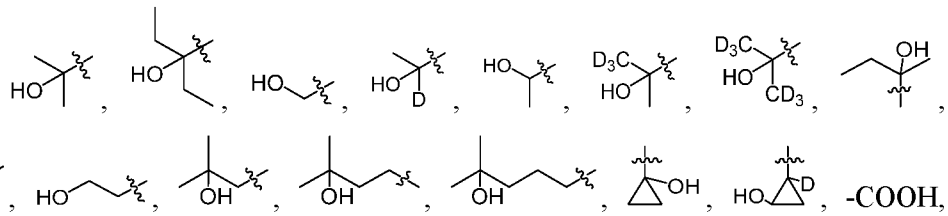
R_{23} and R_{24} together with the carbon atom to which they are both attached form 3-membered carbocyclic ring, 4-membered carbocyclic ring, 5-membered carbocyclic ring, 6-membered carbocyclic ring, and each of the carbocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -OH, methyl, ethyl, propyl or isopropyl;

n is selected from 0, 1, 2 or 3.

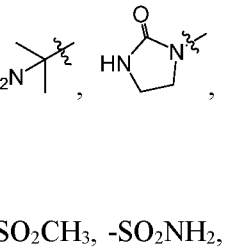
In some embodiments, wherein R_2 is selected from hydrogen, deuterium, -F, -Cl, -Br, -NH$_2$, -NHCH$_3$, -N(CH$_3$)$_2$, -NHCD$_3$, -N(CD$_3$)$_2$, -NHCH$_2$CH$_3$, -N(CH$_3$CH$_2$)$_2$, -N(CH$_3$)(CH$_3$CH$_2$), -NHCH$_2$CH$_2$CH$_3$, -N(CH$_2$CH$_2$CH$_3$)$_2$, -NHCH(CH$_3$)$_2$, -N(CH$_3$)(CH(CH$_3$)$_2$), -N(CH(CH$_3$)$_2$)$_2$, -NHCH$_2$CF$_3$,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , -SO$_2$CH$_3$, -SO$_2$CD$_3$, -SO$_2$CH$_2$CH$_3$, -SO$_2$CH$_2$CH$_2$CH$_3$, -SO$_2$CH(CH$_3$)$_2$, -SO$_2$CH(CD$_3$)$_2$, -SO$_2$NH$_2$, -SO$_2$NH(CH$_3$), -SO$_2$N(CH$_3$)$_2$, -SO$_2$NH(CD$_3$), -SO$_2$N(CD$_3$)$_2$, -SO$_2$NH(CH$_2$CH$_3$), -SO$_2$N(CH$_2$CH$_3$)$_2$, -SO$_2$NH(CH$_2$CH$_2$CH$_3$), -SO$_2$N(CH$_2$CH$_2$CH$_3$)$_2$, -CH$_3$, -CH$_2$D, -CD$_2$H, -CD$_3$, -CF$_3$, -CH$_2$CH$_3$, -CH$_2$CD$_3$, -CH$_2$CF$_3$, -CH$_2$CH$_2$CH$_3$, -CH$_2$CH$_2$CH$_2$F, -CH$_2$CH$_2$CD$_3$, -CH$_2$CH$_2$CF$_3$, -CH(CH$_3$)$_2$, -CH(CH$_3$)(CD$_3$), -CH(CF$_3$)$_2$, -CH(CD$_3$)$_2$, , , , , , , , , , , , , , , , -COOCH$_3$, -COOCH$_2$CH$_3$, -COOCH$_2$CH$_2$CH$_3$, -COOCH(CH$_3$)$_2$, -CONH$_2$, -CONH(CH$_3$), -CON(CH$_3$)$_2$, -CONH(CD$_3$), -CON(CD$_3$)$_2$, -CONH(CH$_2$CH$_3$), -CON(CH$_2$CH$_3$)$_2$, -CONH(CH$_2$CH$_2$CH$_3$),

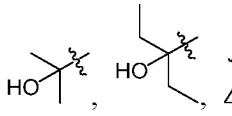
-$CON(CH_2CH_2CH_3)_2$, -$NHCOCH_3$, -$NHCOCH_2CH_3$, -$NHCOCH_2CH_2CH_3$, -$NHCOCH(CH_3)_2$, -$NHSO_2CH_3$, -$NHSO_2CD_3$, -$NHSO_2CH_2CH_3$, -$NHSO_2CH_2CH_3$, -$NHSO_2CH_2CH_2CH_3$, -$NHSO_2CH(CH_3)_2$, -$P(O)H_2$, -$P(O)H(CH_3)$, -$P(O)(CH_3)_2$, -$P(O)H(CD_3)$, -$PO(CD_3)_2$, -$PO(CH_2CH_3)_2$, -$PO(CH_2CH_2\ CH_3)_2$, -$PO(CH(CH_3)_2)_2$ or  .

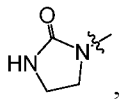
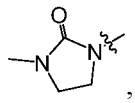
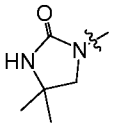
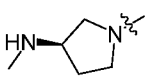
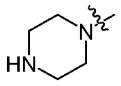
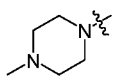
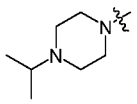
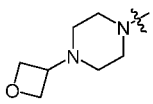
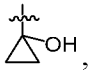
In some embodiments, wherein R_2 is selected from hydrogen, deuterium, -F, -Cl, -Br, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$NHCD_3$, -$N(CD_3)_2$, -$NHCH_2CH_3$, -$N(CH_3CH_2)_2$, -$N(CH_3)(CH_3CH_2)$, -$NHCH_2CH_2CH_3$, -$N(CH_2CH_2CH_3)_2$, -$NHCH(CH_3)_2$, -$N(CH_3)(CH(CH_3)_2)$, -$N(CH(CH_3)_2)_2$, -$NHCH_2CF_3$, 

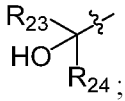
-SO_2CH_3, -SO_2CD_3, -$SO_2CH_2CH_3$, -$SO_2CH_2CH_2CH_3$, -$SO_2CH(CH_3)_2$, -$SO_2CH(CD_3)_2$, -SO_2NH_2, -$SO_2NH(CH_3)$, -$SO_2N(CH_3)_2$, -$SO_2NH(CD_3)$, -$SO_2N(CD_3)_2$, -$SO_2NH(CH_2CH_3)$, -$SO_2N(CH_2CH_3)_2$, -$SO_2NH(CH_2CH_2CH_3)$, -$SO_2N(CH_2CH_2CH_3)_2$, -CH_3, -CH_2D, -CD_2H, -CD_3, -CF_3, -CH_2CH_3, -CH_2CD_3, -CH_2CF_3, -$CH_2CH_2CH_3$, -$CH_2CH_2CH_2F$, -$CH_2CH_2CD_3$, -$CH_2CH_2CF_3$, -$CH(CH_3)_2$, -$CH(CH_3)(CD_3)$, -$CH(CF_3)_2$, -$CH(CD_3)_2$, 

-$COOCH_3$, -$COOCH_2CH_3$, -$COOCH_2CH_2CH_3$, -$COOCH(CH_3)_2$, -$CONH_2$, -$CONH(CH_3)$, -$CON(CH_3)_2$, -$CONH(CD_3)$, -$CON(CD_3)_2$, -$CONH(CH_2CH_3)$, -$CON(CH_2CH_3)_2$, -$CONH(CH_2CH_2CH_3)$, -$CON(CH_2CH_2CH_3)_2$, -$NHCOCH_3$, -$NHCOCH_2CH_3$, -$NHCOCH_2CH_2CH_3$, -$NHCOCH(CH_3)_2$, -$NHSO_2CH_3$, -$NHSO_2CD_3$, -$NHSO_2CH_2CH_3$, -$NHSO_2CH_2CH_3$, -$NHSO_2CH_2CH_2CH_3$, -$NHSO_2CH(CH_3)_2$, -$P(O)H_2$, -$P(O)H(CH_3)$, -$P(O)(CH_3)_2$, -$P(O)H(CD_3)$, -$PO(CD_3)_2$, -$PO(CH_2CH_3)_2$, -$PO(CH_2CH_2\ CH_3)_2$, -$PO(CH(CH_3)_2)_2$ or .

In some embodiments, wherein R_2 is selected from hydrogen, -Cl, -Br, -NH_2, 

-SO_2CH_3, -SO_2NH_2, -SO_2NHCH_3, -$SO_2N(CH_3)_2$, -CH_3,  , -COOH, -$COOCH_3$, -$CONH_2$, -$CONHCH_3$, -$CON(CH_3)_2$, -$NHCOCH_3$, -$NHSO_2CH_3$, -$PO(CH_3)_2$ or  .

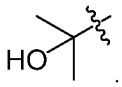
In some embodiments, wherein R_2 is selected from hydrogen, -Cl, -Br, -NH_2,  ,  ,  ,  ,  ,  ,  ,  , -SO_2CH_3, -SO_2NH_2, -SO_2NHCH_3, -$SO_2N(CH_3)_2$, -CH_3,  ,  , -$COOCH_3$, -$CONH_2$, -$CONHCH_3$, -$CON(CH_3)_2$, -$NHCOCH_3$, -$NHSO_2CH_3$, -$PO(CH_3)_2$ or  .

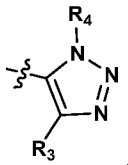
In some embodiments, wherein R_2 is  ;

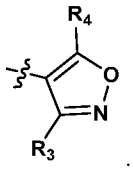
Each of R_{23} and R_{24} at each occurrence is -C_{1-6}alkyl.

In some embodiments, wherein each of R_{23} and R_{24} at each occurrence is -C_{1-3}alkyl.

In some embodiments, wherein each of R_{23} and R_{24} at each occurrence is selected from methyl, ethyl, propyl or isopropyl.

In some embodiments, wherein R_2 is  .

In some embodiments, wherein the A is  .

In some embodiments, wherein the A is  .

In some embodiments, wherein each of R_3 and R_4 at each occurrence is independently selected from hydrogen, deuterium, halogen, -CN, -SOR_5, -SO_2R_5, -SO_2NH_2, -SO_2NHR_5, -$SO_2NR_5R_6$, -C_{1-3}alkyl, -C_{1-3}alkoxy, -COR_5, -$CONH_2$, -$CONHR_5$, -$CONR_5R_6$, -$P(O)H_2$, -$P(O)HR_5$ or -POR_5R_6; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen or -OH;

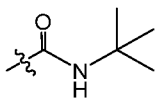
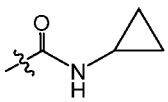
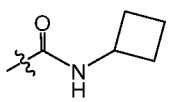
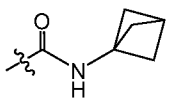
Each of R_5 and R_6 at each occurrence is independently selected from deuterium; -C_{1-3}alkyl; -C_{5-6}aryl; -C_{5-6}heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; or -C_{3-6}carbocyclic, and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -C_{1-3}alkyl or -C_{1-3}alkoxy.

In some embodiments, wherein each of R_3 and R_4 at each occurrence is independently selected from hydrogen, deuterium, -F, -Cl, -Br, -CN, -SOR_5, -SO_2R_5, -SO_2NH_2, -SO_2NHR_5, -$SO_2NR_5R_6$, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropyl, -$CONH_2$, -$CONHR_5$, -$CONR_5R_6$, -$P(O)H_2$, -$P(O)HR_5$ or -POR_5R_6; and each of which at each occurrence is independently optionally substituted with

1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br or -OH;

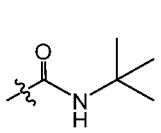
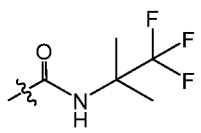
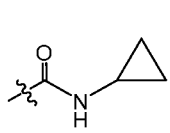
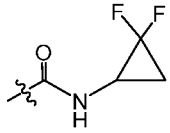
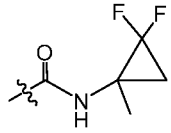
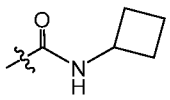
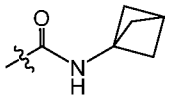
Each of R_5 and R_6 at each occurrence is independently selected from deuterium; methyl; ethyl; propyl; isopropyl; phenyl; 5-membered heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; 6-membered heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; 3-membered carbocyclic; 4-membered carbocyclic; 5-membered carbocyclic; or 6-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropyl.

In some embodiments, wherein each of R_3 and R_4 at each occurrence is independently selected from hydrogen, deuterium, -F, -Cl, -Br, -CN, $-SOCH_3$, $-SOCH_2CH_3$, $-SOCH_2CH_2CH_3$, $-SOCH(CH_3)_2$, $-SO_2CH_3$, $-SO_2CH_2CH_3$, $-SO_2CH_2CH_2CH_3$, $-SO_2CH(CH_3)_2$, $-SO_2NH_2$, $-SO_2NHCH_3$, $-SO_2NHCH_2CH_3$, $-SO_2NHCH_2CH_2CH_3$, $-SO_2NHCH(CH_3)_2$, $-SO_2N(CH_3)_2$, $-SO_2N(CH_2CH_3)_2$, $-SO_2N(CH_3)(CH_2CH_3)$, $-SO_2N(CH_2CH_2CH_3)_2$, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2CH_3$, $-OCH(CH_3)_2$, $-CONH_2$, $-CONHCH_3$, $-CONHCH_2CH_3$, $-CONHCH_2CH_2CH_3$, $-CONHCH(CH_3)_2$,

, $-CON(CH_3)_2$, $-CON(CH_2CH_3)_2$, $-CON(CH_3)(CH_2CH_3)$, $-CON(CH_2CH_2CH_3)_2$, $-P(O)H_2$, $-P(O)HCH_3$, $-P(O)HCH_2CH_3$, $-P(O)HCH_2CH_2CH_3$, $-P(O)HCH(CH_3)_2$, $-PO(CH_3)_2$, $-PO(CH_2CH_3)_2$, $-PO(CH_3)(CH_2CH_3)$ or $-PO(CH_2CH_2CH_3)_2$; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F or methyl.

In some embodiments, wherein each of R_3 and R_4 at each occurrence is independently selected from hydrogen, deuterium, -F, -Cl, -Br, -CN, $-SOCH_3$, $-SOCD_3$, $-SOCH_2CH_3$, $-SOCH_2CH_2CH_3$, $-SOCH(CH_3)_2$, $-SO_2CH_3$, $-SO_2CD_3$, $-SO_2CH_2CH_3$, $-SO_2CH_2CH_2CH_3$, $-SO_2CH(CH_3)_2$, $-SO_2NH_2$, $-SO_2NHCH_3$, $-SO_2NHCD_3$, $-SO_2NHCH_2CH_3$, $-SO_2NHCH_2CH_2CH_3$, $-SO_2NHCH(CH_3)_2$, $-SO_2N(CH_3)_2$, $-SO_2N(CD_3)_2$, $-SO_2N(CH_2CH_3)_2$, $-SO_2N(CH_3)(CH_2CH_3)$, $-SO_2N(CH_2CH_2CH_3)_2$, $-CH_3$, $-CD_3$, $-CH_2CH_3$, $-CD_2CD_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CD_3$, $-CH(CH_3)_2$, $-CH(CD_3)_2$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2CH_3$, $-OCH(CH_3)_2$, $-CONH_2$, $-CONHCH_3$, $-CONHCD_3$, $-CONHCH_2CH_3$, $-CONHCD_2CD_3$, $-CONHCH_2CH_2CH_3$, $-CONHCH(CH_3)_2$,

, $-CON(CH_3)_2$, $-CON(CH_2CH_3)_2$, $-CON(CH_3)(CH_2CH_3)$, $-CON(CH_2CH_2CH_3)_2$, $-P(O)H_2$, $-P(O)HCH_3$, $-P(O)HCH_2CH_3$, $-P(O)HCH_2CH_2CH_3$, $-P(O)HCH(CH_3)_2$, $-PO(CH_3)_2$, $-PO(CH_2CH_3)_2$, $-PO(CH_3)(CH_2CH_3)$ or $-PO(CH_2CH_2CH_3)_2$.

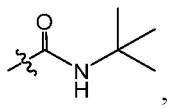
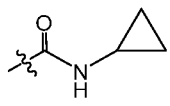
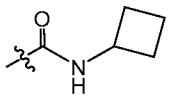
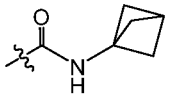
In some embodiments, wherein each of R_3 and R_4 at each occurrence is independently selected from $-C_{1-3}$alkyl, $-CONH_2$, $-CONHR_5$ or $-CONR_5R_6$; and each of which at each occurrence is independently

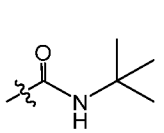
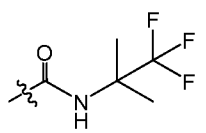
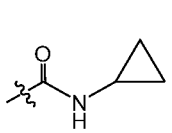
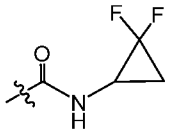
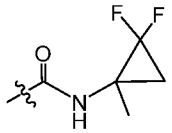
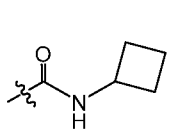
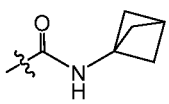
optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium or halogen;

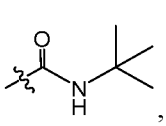
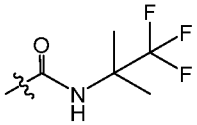
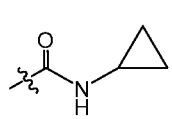
Each of R_5 and R_6 at each occurrence is independently selected from -C_{1-3}alkyl or -C_{3-6}carbocyclic, and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen or -C_{1-3}alkyl.

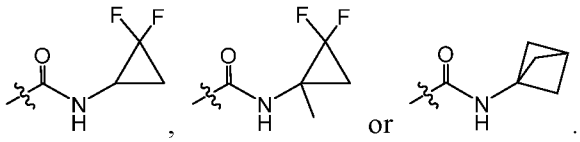
In some embodiments, wherein each of R_3 and R_4 at each occurrence is independently selected from methyl, ethyl, propyl, isopropyl, -$CONH_2$, -$CONHR_5$ or -$CONR_5R_6$; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl or -Br;

Each of R_5 and R_6 at each occurrence is independently selected from methyl, ethyl, propyl, isopropyl, 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic or 6-membered carbocyclic, and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, methyl, ethyl, propyl or isopropyl.

In some embodiments, wherein each of R_3 or R_4 at each occurrence is independently selected from -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -$CH(CH_3)_2$, -OCH_3, -OCH_2CH_3, -$OCH_2CH_2CH_3$, -$OCH(CH_3)_2$, -$CONH_2$, -$CONHCH_3$, -$CONHCH_2CH_3$, -$CONHCH_2CH_2CH_3$, -$CONHCH(CH_3)_2$,  ,  ,  ,  , -$CON(CH_3)_2$, -$CON(CH_2CH_3)_2$, -$CON(CH_3)(CH_2CH_3)$ or -$CON(CH_2CH_2CH_3)_2$; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F or methyl.

In some embodiments, wherein each of R_3 or R_4 at each occurrence is independently selected from -CH_3, -CD_3, -CH_2CH_3, -CD_2CD_3, -$CH_2CH_2CH_3$, -$CH_2CH_2CD_3$, -$CH(CH_3)_2$, -$CH(CD_3)_2$, -$CONH_2$, -$CONHCH_3$, -$CONHCD_3$, -$CONHCH_2CH_3$, -$CONHCD_2CD_3$, -$CONHCH_2CH_2CH_3$, -$CONHCH(CH_3)_2$,  ,  ,  ,  ,  ,  ,  , -$CON(CH_3)_2$, -$CON(CH_2CH_3)_2$, -$CON(CH_3)(CH_2CH_3)$ or -$CON(CH_2CH_2CH_3)_2$.

In some embodiments, wherein each of R_3 or R_4 at each occurrence is independently selected from -CH_3, -CD_3, -$CONH_2$, -$CONHCH_3$, -$CONHCH_2CH_3$,  ,  ,  ,



In some embodiments, wherein each of R_3 and R_4 at each occurrence is independently selected from -C_{1-3}alkyl, and the -C_{1-3}alkyl is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl or -Br.

In some embodiments, wherein each of R_3 and R_4 at each occurrence is independently selected from methyl, ethyl, propyl or isopropyl; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl or -Br.

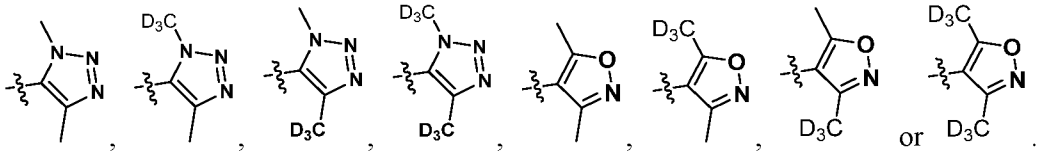
In some embodiments, wherein each of R_3 and R_4 at each occurrence is independently selected from methyl, ethyl, propyl or isopropyl; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium or -F.

In some embodiments, wherein each of R_3 and R_4 at each occurrence is independently selected from -CH_3, -CH_2D, -CD_2H, -CD_3, -CF_3, -CH_2CH_3, -CH_2CD_3, -CH_2CF_3, -$CH_2CH_2CH_3$, -$CH_2CH_2CH_2F$, -$CH_2CH_2CD_3$, -$CH_2CH_2CF_3$, -$CH(CH_3)_2$, -$CH(CH_3)(CD_3)$, -$CH(CF_3)_2$ or -$CH(CD_3)_2$.

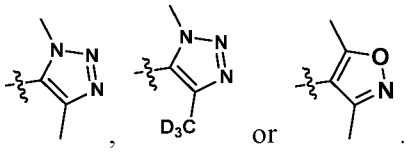
In some embodiments, wherein each of R_3 and R_4 at each occurrence is selected from -C_{1-3}alkyl or the -C_{1-3}alkyl substituted with 1, 2, 3, 4, 5 or 6 deuterium.

In some embodiments, wherein each of R_3 and R_4 at each occurrence is selected from methyl, ethyl, propyl, isopropyl, methyl substituted with deuterium, ethyl substituted with deuterium, propyl substituted with deuterium or isopropyl substituted with deuterium.

In some embodiments, wherein the A is selected from:

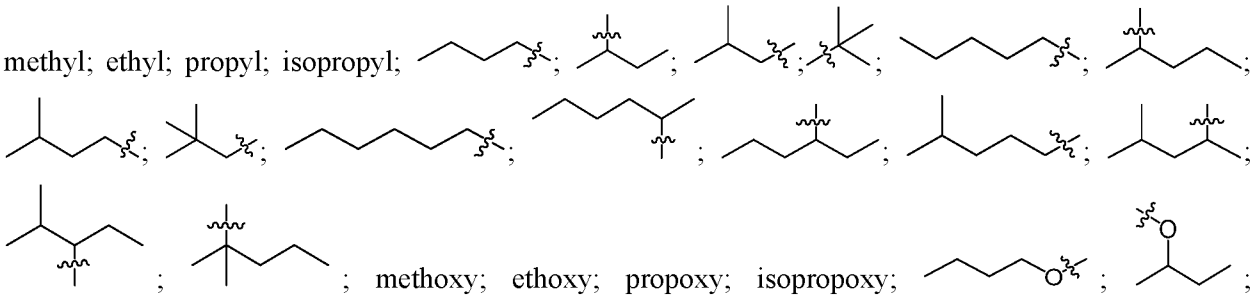
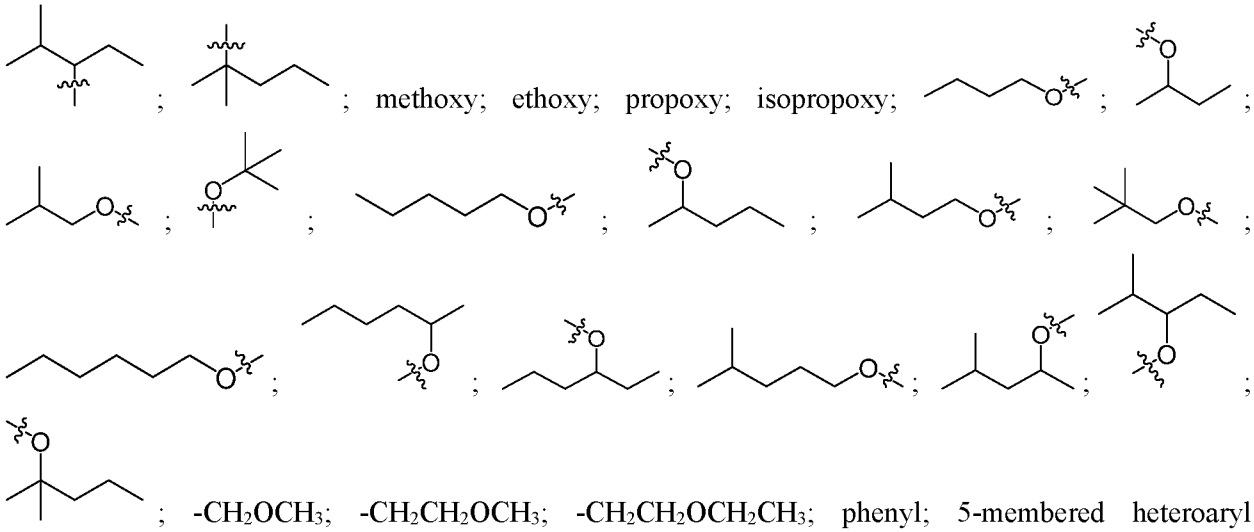


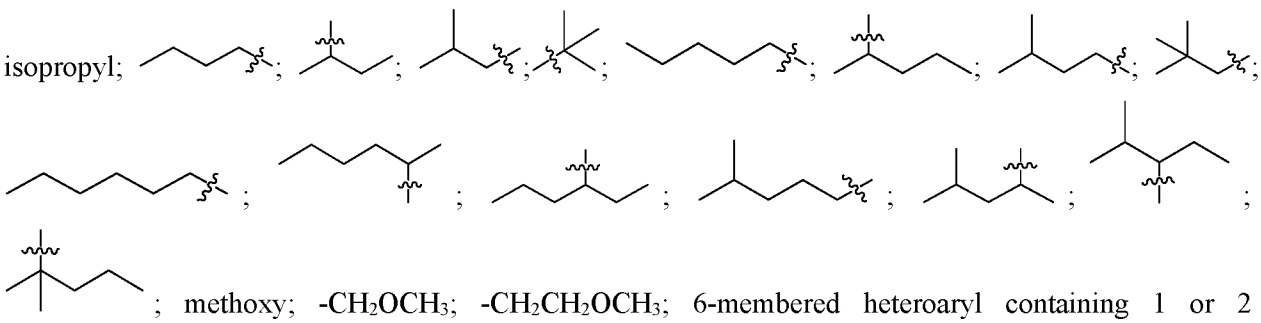
In some embodiments, wherein the A is independently selected from:

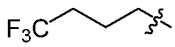
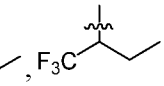
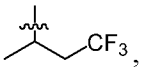
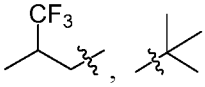
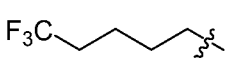
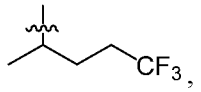
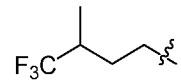
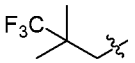
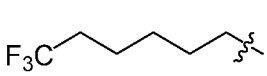
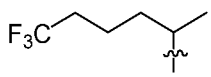
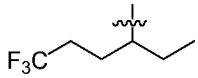
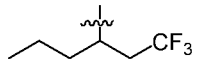
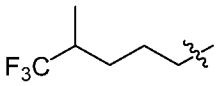
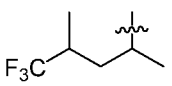
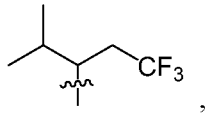
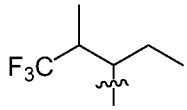
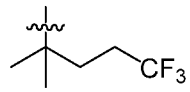
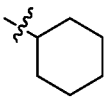
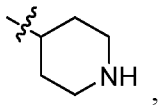
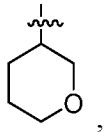
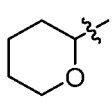
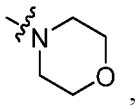
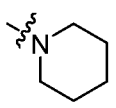
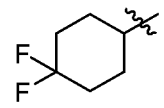
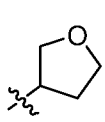
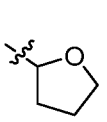
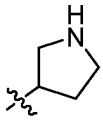
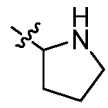
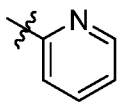
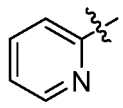
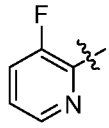
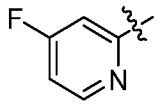
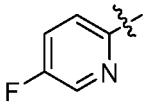


In some embodiments, wherein W_1 is selected from hydrogen; deuterium; -F; -Cl; -NH_2; -CN; -OH; carboxyl; -C_{1-6}alkyl; -C_{1-6}alkoxy; -C_{1-3}alkylene-C_{1-3}alkoxy; phenyl; 5-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O; 6-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O; 3-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O; 4-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O; 5-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O; 6-membered heterocyclic containing 1, 2 or 3 heteroatoms

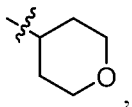
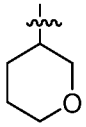
selected from N, O; 3-membered carbocyclic; 4-membered carbocyclic; 5-membered carbocyclic; or 6-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl,or $-C_{1-3}$alkoxy.

In some embodiments, wherein W_1 is selected from hydrogen; deuterium; -F; -Cl; $-NH_2$; -CN; -OH; methyl; ethyl; propyl; isopropyl;  ; methoxy; ethoxy; propoxy; isopropoxy;  ; $-CH_2OCH_3$; $-CH_2CH_2OCH_3$; $-CH_2CH_2OCH_2CH_3$; phenyl; 5-membered heteroaryl containing 1 or 2 heteroatoms selected from N or O; 6-membered heteroaryl containing 1 or 2 heteroatoms selected from N or O; 5-membered heterocyclic containing 1 or 2 heteroatoms selected from N or O; 6-membered heterocyclic containing 1 or 2 heteroatoms selected from N or O; 5-membered carbocyclic; or 6-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is selected from deuterium, -F, -Cl, $-NH_2$, -CN, -OH, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy,or isopropoxy.

In some embodiments, wherein W_1 is selected from hydrogen; deuterium; -F; methyl; ethyl; propyl; isopropyl;  ; methoxy; $-CH_2OCH_3$; $-CH_2CH_2OCH_3$; 6-membered heteroaryl containing 1 or 2 heteroatoms selected from N or O; 5-membered heterocyclic containing 1 or 2 heteroatoms selected from N or O; 6-membered heterocyclic containing 1 or 2 heteroatoms selected from N or O; 5-membered carbocyclic; or 6-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with deuterium or -F.

In some embodiments, wherein W_1 is selected from hydrogen, deuterium, -F, $-CH_3$, $-CD_3$, $-CH_2F$, $-CF_2H$, $-CF_3$, $-CH_2CH_3$, $-CH_2CD_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CD_3$, $-CH(CH_3)_2$, $-CH(CF_3)_2$, $-CH(CD_3)_2$, ,  ,  ,  ,  , ,  , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , methoxy, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  or  .

In some embodiments, wherein W_1 is selected from -C_{1-6}alkyl substituted with F or 6-membered heterocyclic containing 1 heteroatoms selected from O.

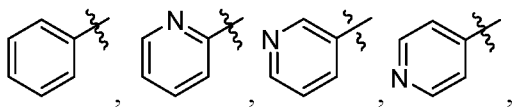
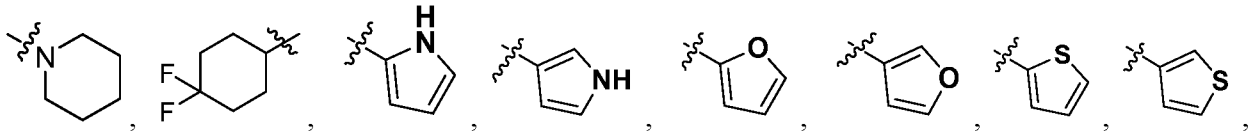
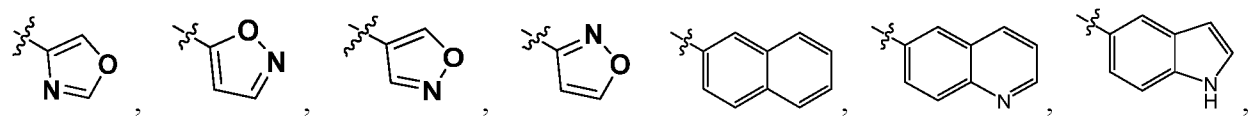
In some embodiments, wherein W_1 is selected from -C_{1-6}alkyl substituted with F,  ,  or .

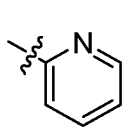
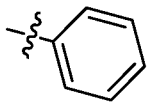
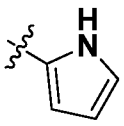
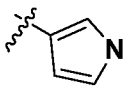
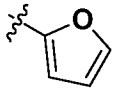
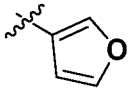
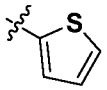
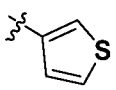
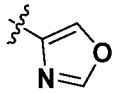
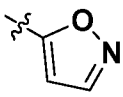
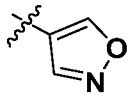
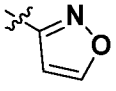
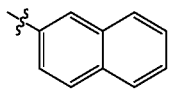
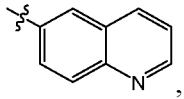
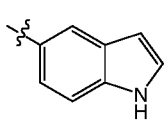
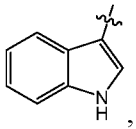
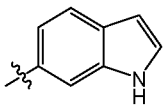
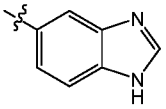
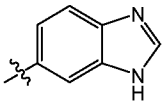
In some embodiments, wherein W_1 is selected from $-CH_2CH_2CF_3$ or .

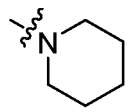
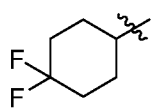
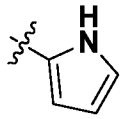
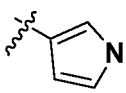
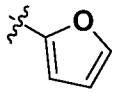
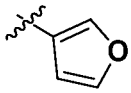
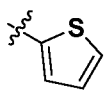
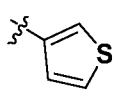
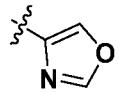
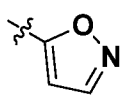
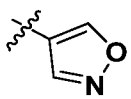
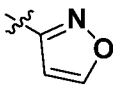
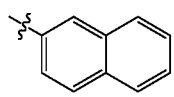
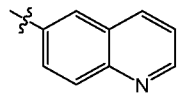
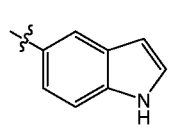
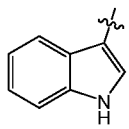
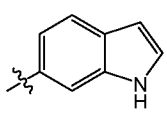
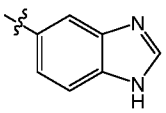
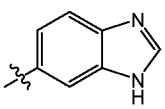
In some embodiments, wherein W_2 is selected from hydrogen; deuterium; -F; -Cl; $-NH_2$; -CN; -OH; carboxyl; -C_{1-3}alkyl; -C_{1-3}alkoxy; phenyl; naphthyl; 5-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O or S; 6-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O,or S; 7-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O or S; 8-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O or S; 9-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O or S; 10-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O,or S; 3-membered heterocyclic containing 1, 2 or 3 heteroatoms selected

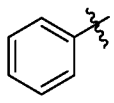
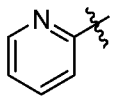
from N, O or S; 4-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O or S; 5-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O or S; 6-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O or S; 3-membered carbocyclic; 4-membered carbocyclic; 5-membered carbocyclic; or 6-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4 or 5 substituents, and the said each of substituents at each occurrence is selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments wherein W_2 is selected from hydrogen; deuterium; phenyl; 5-membered heteroaryl containing 1 or 2 heteroatoms selected from N, O or S; or 6-membered heteroaryl containing 1 or 2 heteroatoms selected from N, O or S; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4 or 5 substituents, and the said each of substituents at each occurrence is selected from deuterium, -F, -Cl, -Br, $-NH_2$, -CN, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.In some embodiments, wherein W_2 is selected from phenyl; 5-membered heteroaryl containing 1 or 2 heteroatoms selected from N, O,or S; or 6-membered heteroaryl containing 1 or 2 heteroatoms selected from N, O or S; and each of which at each occurrence is independently optionally substituted with 1, 2 or 3 substituents, and the said each of substituents at each occurrence is selected from -F, -Cl, -Br, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments, wherein W_2 is selected from  ,  ,  ; and each of which at each occurrence is independently optionally substituted with 1, 2 or 3 substituents, and the said each of substituents at each occurrence is selected from -F, -Cl, methyl or methoxy.

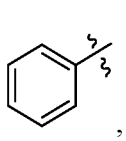
In some embodiments, wherein W_2 is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  ; and each of which at each occurrence is independently optionally substituted with 1, 2 or 3 substituents, and the said each of substituents at each occurrence is selected from -F, -Cl, methyl or methoxy.

In some embodiments, wherein W_2 is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  ; and each of which at each occurrence is independently optionally substituted with 1, 2 or 3 substituents, and the said each of substituents at each occurrence is selected from -F, -Cl, methyl or methoxy.

In some embodiments, wherein W_2 is selected from  ,  , , , , , , , , , , , , ; and each of which at each occurrence is independently optionally substituted

with 1, 2 or 3 substituents, and the said each of substituents at each occurrence is selected from -F, -Cl, methyl or methoxy.

In some embodiments, wherein W_2 is independently selected from: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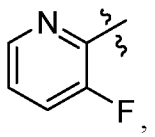
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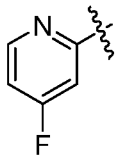
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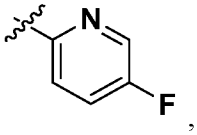
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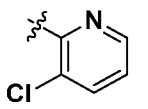
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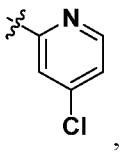
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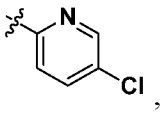
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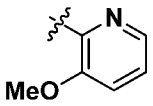
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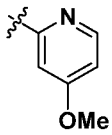
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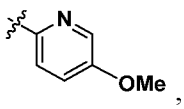
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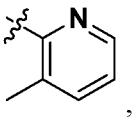
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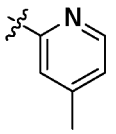
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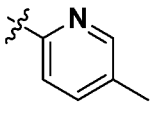
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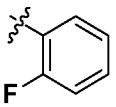
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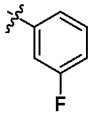
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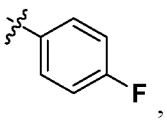
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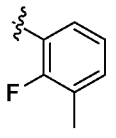
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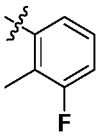
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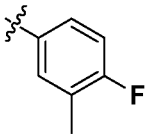
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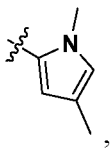
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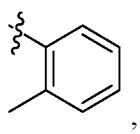
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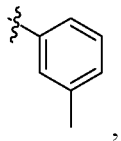
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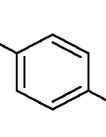
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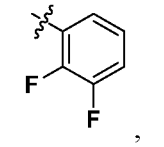
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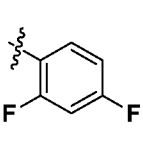
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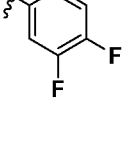
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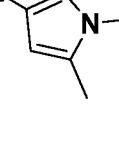
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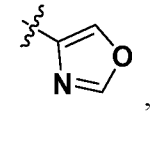
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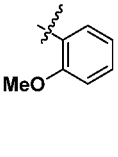
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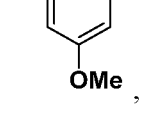
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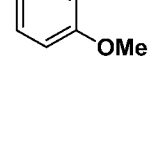
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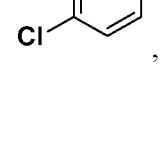
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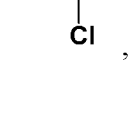
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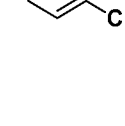
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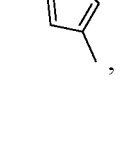
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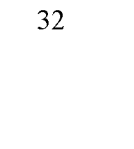
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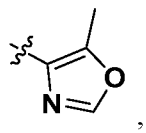
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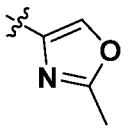
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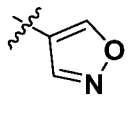
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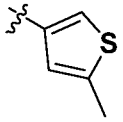
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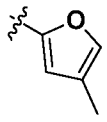
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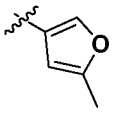
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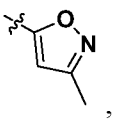
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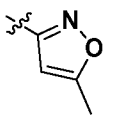
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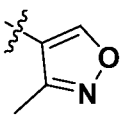
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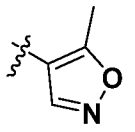
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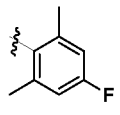
or 
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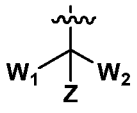
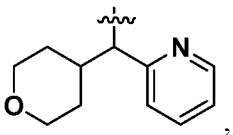
In some embodiments, wherein Z is selected from hydrogen, deuterium, -F, -Cl, -OH, -C_{1-3}alkyl or -C_{1-3}alkoxy.

In some embodiments, wherein Z is selected from hydrogen, deuterium, -F, -Cl, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments, wherein Z is selected from hydrogen or deuterium.

In some embodiments, wherein Z is hydrogen.

In some embodiments, wherein,  is selected from: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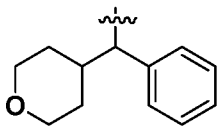
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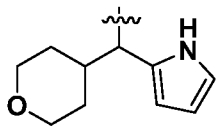
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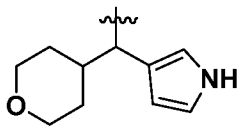
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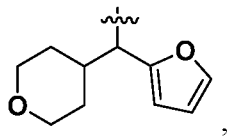
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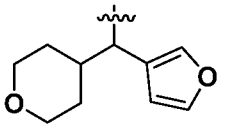
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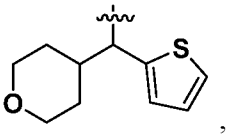
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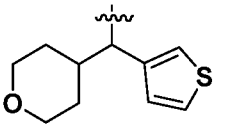
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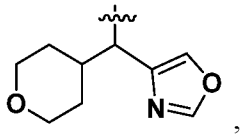
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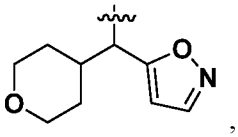
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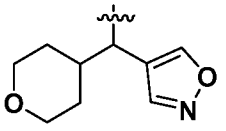
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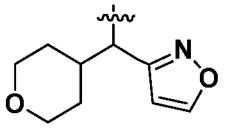
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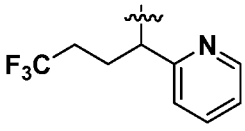
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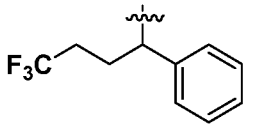
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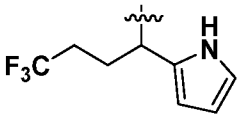
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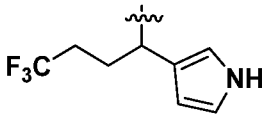
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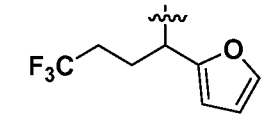
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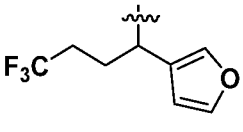
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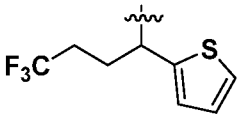
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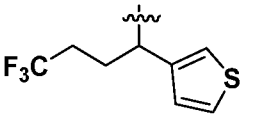
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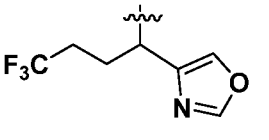
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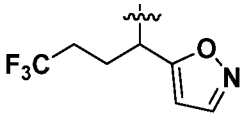
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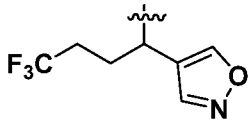
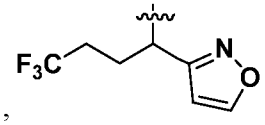
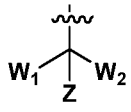
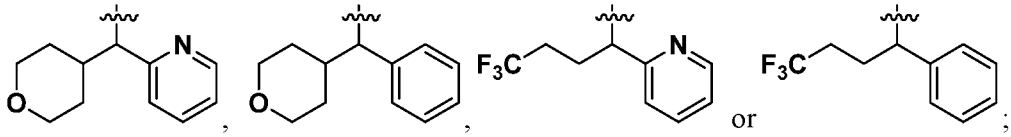


; and each of which at each occurrence is independently optionally substituted with 1, 2 or 3 substituents, and the said each of substituents at each occurrence is selected from -F, -Cl, -Br, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments, wherein, the  is selected from: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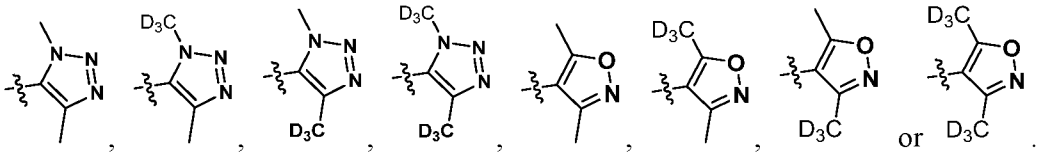
and each of which at each occurrence is independently optionally substituted with 1, 2 or 3 substituents, and the said each of substituents at each occurrence is selected from -F, -Cl, methyl or methoxy.

In some embodiments, wherein the A is independently selected from: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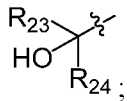
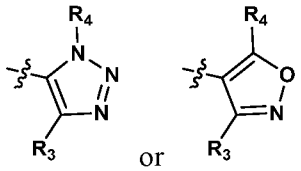
In some embodiments, wherein,

R_1 is -C_{1-6}alkyl;

R_2 is  ;

Each of R_{23} and R_{24} at each occurrence is -C_{1-6}alkyl;

the A is  ;

Each of R_3 and R_4 at each occurrence is selected from -C_{1-6}alkyl or -C_{1-6}alkyl substituted with 1, 2, 3, 4, 5 or 6 deuterium;

W_1 is selected from -C_{1-6}alkyl substituted with -F or 6-membered heterocyclic containing 1 heteroatoms selected from O;

W_2 is selected from phenyl; 5-membered heteroaryl containing 1 or 2 heteroatoms selected from N, O or S; or 6-membered heteroaryl containing 1 or 2 heteroatoms selected from N, O,or S; and each of which at each occurrence is independently optionally substituted with 1, 2 or 3 substituents, and the said each of substituents at each occurrence is selected from -F, -Cl, -Br, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy;

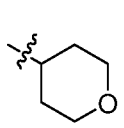
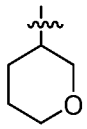
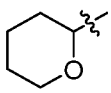
Z is selected from hydrogen or deuterium.

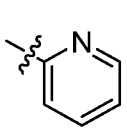
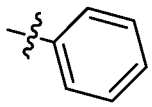
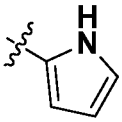
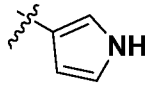
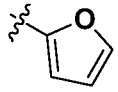
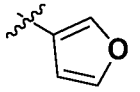
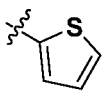
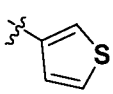
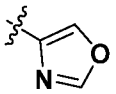
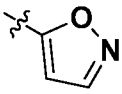
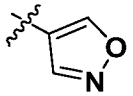
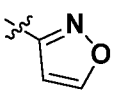
In some embodiments, wherein,

R_1 is -C_{1-3}alkyl;

Each of R_{23} and R_{24} at each occurrence is -C_{1-3}alkyl;

Each of R_3 and R_4 at each occurrence is selected from -C_{1-3}alkyl or -C_{1-3}alkyl substituted with 1, 2, 3, 4, 5 or 6 deuterium;

W_1 is selected from -C_{1-6}alkyl substituted with -F,  ,  or  ;

W_2 is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  or  ; and each of which at each occurrence is independently optionally substituted with 1, 2 or 3 substituents, and the said each of substituents at each occurrence is selected from -F, -Cl, -Br, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy;

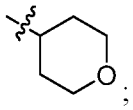
Z is selected from hydrogen.

In some embodiments, wherein,

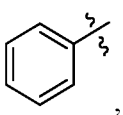
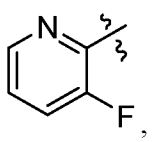
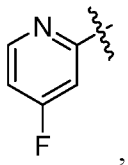
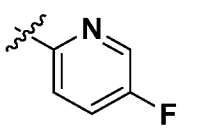
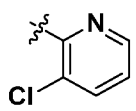
R_1 is selected from methyl, ethyl, propyl or isopropyl;

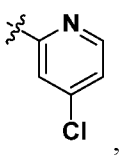
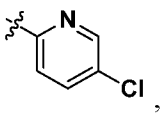
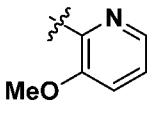
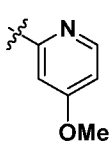
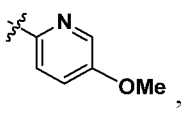
Each of R_{23} or R_{24} at each occurrence is selected from methyl, ethyl, propyl or isopropyl;

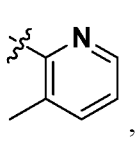
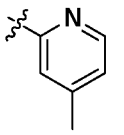
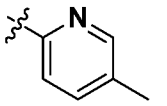
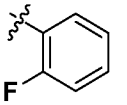
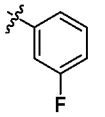
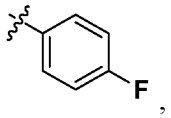
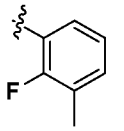
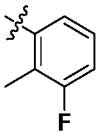
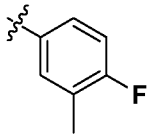
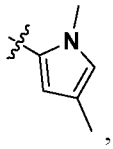
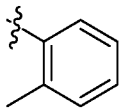
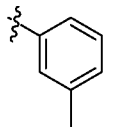
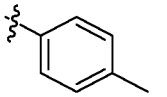
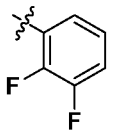
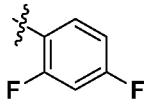
Each of R_3 and R_4 at each occurrence is selected from methyl, ethyl, propyl, isopropyl, methyl substituted with deuterium, ethyl substituted with deuterium, propyl substituted with deuterium or isopropyl substituted with deuterium;

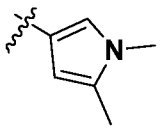
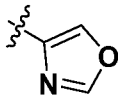
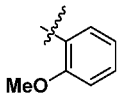
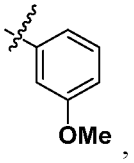
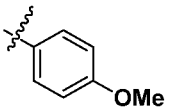
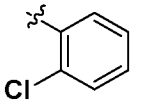
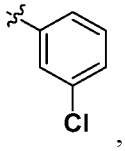
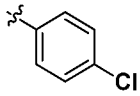
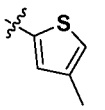
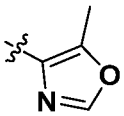
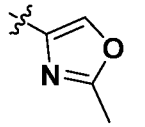
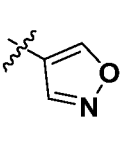
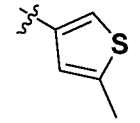
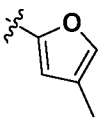
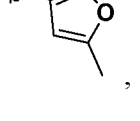
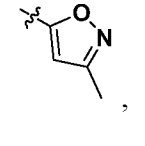
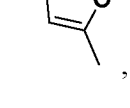
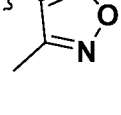
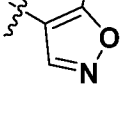
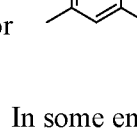
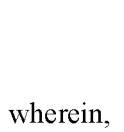
W_1 is selected from -$CH_2CH_2CF_3$ or  ;

W_2 is selected from:

 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

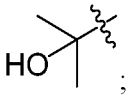
















or .

In some embodiments, wherein,

R_1 is methyl;

R_2 is  ;

Each of R_3 and R_4 at each occurrence is independently selected from $-CH_3$ or $-CD_3$.

In some embodiments, the compound is:

1	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
2	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
3	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
4	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
5	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((2-fluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
6	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((2-methoxyphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
7	2-(4-((3-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
8	2-(4-((2-chlorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
9	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
10	2-(4-((4-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
11	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methoxyphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
12	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
13	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((5-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
14	2-(4-((5-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
15	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
16	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((5-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
17	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
18	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
19	2-(4-((3-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
20	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((4-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
21	2-(4-((4-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
22	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((5-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
23	2-(4-((5-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
24	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((4-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;

25	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((5-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
26	2-(6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
27	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((tetrahydro-2H-pyran-4-yl)(o-tolyl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
28	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
29	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((5-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
30	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
31	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((4-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
32	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((5-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
33	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-fluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
34	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((tetrahydro-2H-pyran-4-yl)(m-tolyl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
35	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((tetrahydro-2H-pyran-4-yl)(p-tolyl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
36	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methoxyphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
37	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((2-fluoro-3-methylphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
38	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoro-2-methylphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
39	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-fluoro-3-methylphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
40	2-(4-((2,3-difluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
41	2-(4-((2,4-difluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
42	2-(4-((3,4-difluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
43	2-(4-((3-chlorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
44	2-(4-((4-chlorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
45	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-phenylbutyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
46	2-(6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-phenylbutyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
47	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(3-fluoropyridin-2-yl)butyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
48	2-(6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(3-methylpyridin-2-yl)butyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
49	1-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)cyclopropan-1-ol;
50	1-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)cyclopropan-1-ol;
51	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(oxazol-4-yl)butyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;

52	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(5-methyloxazol-4-yl)butyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
53	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(2-methyloxazol-4-yl)butyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
54	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(isoxazol-4-yl)butyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
55	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(5-methylisoxazol-4-yl)butyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
56	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(3-methylisoxazol-4-yl)butyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
57	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((2-methyloxazol-4-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
58	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((5-methylisoxazol-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
59	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methylisoxazol-5-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
60	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((5-methylfuran-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
61	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methylfuran-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
62	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
63	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
64	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
65	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((2-fluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
66	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((2-methoxyphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
67	2-(4-((3-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
68	2-(4-((2-chlorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
69	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
70	2-(4-((4-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
71	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methoxyphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
72	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((4-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
73	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((5-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
74	2-(4-((5-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
75	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
76	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((5-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
77	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
78	2-(4-((3-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;

79	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((4-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
80	2-(4-((4-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
81	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((5-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
82	2-(4-((5-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
83	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((4-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
84	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((5-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
85	2-(1-methyl-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
86	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((tetrahydro-2H-pyran-4-yl)(o-tolyl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol
87	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
88	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((5-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
89	2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
90	2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-((4-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
91	2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-((5-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
92	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-fluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
93	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((tetrahydro-2H-pyran-4-yl)(m-tolyl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
94	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((tetrahydro-2H-pyran-4-yl)(p-tolyl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
95	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methoxyphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
96	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((2-fluoro-3-methylphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
97	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoro-2-methylphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
98	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-fluoro-3-methylphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
99	2-(4-((2,3-difluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
100	2-(4-((2,4-difluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
101	2-(4-((3,4-difluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
102	2-(4-((3-chlorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
103	2-(4-((4-chlorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
104	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-phenylbutyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
105	2-(1-methyl-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-phenylbutyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;

106	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(3-fluoropyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
107	2-(1-methyl-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(3-methylpyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
108	2-(1-methyl-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(oxazol-4-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol
109	1-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)cyclopropan-1-ol;
110	1-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)cyclopropan-1-ol;
111	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(oxazol-4-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
112	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(5-methyloxazol-4-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
113	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(2-methyloxazol-4-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
114	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(isoxazol-4-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
115	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(5-methylisoxazol-4-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
116	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(3-methylisoxazol-4-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
117	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((2-methyloxazol-4-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
118	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((5-methylisoxazol-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
119	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((3-methylisoxazol-5-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
120	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((5-methylfuran-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
121	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((4-methylfuran-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
122	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((4-methylthiophen-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
123	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((5-methylthiophen-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
124	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((1,4-dimethyl-1H-pyrrol-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
125	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((1,5-dimethyl-1H-pyrrol-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
126	(S)-2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
127	2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-((tetrahydro-2H-pyran-4-yl)(o-tolyl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
128	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-3-(methylsulfonyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine;
129	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-sulfonamide;
130	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-N,1-dimethyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-sulfonamide;
131	(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)dimethylphosphine oxide;
132	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxamide;

133	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-N,1-dimethyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxamide;
134	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-N,N,1-trimethyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxamide;
135	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-N,N,1-trimethyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-sulfonamide;
136	1-(3-chloro-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)pyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-1(4H)-yl)-2-methylpropan-2-ol;
137	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-amine;
138	N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)acetamide;
139	N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)methanesulfonamide;
140	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-ethyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
141	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-isopropyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
142	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1-(2,2,2-trifluoroethyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
143	3-chloro-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-(methylsulfonyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine;
144	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-3-methyl-1-(methylsulfonyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine;
145	2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-(4,4,4-trifluoro-1-(3-methylpyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
146	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
147	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
148	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
149	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
150	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((2-fluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
151	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((2-methoxyphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
152	2-(4-((3-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
153	2-(4-((2-chlorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
154	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
155	2-(4-((4-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
156	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methoxyphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
157	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
158	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((5-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
159	2-(4-((5-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;

160	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl) methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
161	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((5-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl) methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
162	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H -isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
163	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
164	2-(4-((3-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-4H -isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
165	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((4-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H -isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
166	2-(4-((4-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-4H -isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
167	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((5-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H -isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
168	2-(4-((5-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-4H -isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
169	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((4-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
170	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((5-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
171	2-(6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
172	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((tetrahydro-2H-pyran-4-yl)(o-tolyl)methyl)-4H-isox azolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
173	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
174	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((5-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)m ethyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
175	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4 H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
176	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((4-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4 H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
177	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((5-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4 H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
178	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-fluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
179	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((tetrahydro-2H-pyran-4-yl)(m-tolyl)methyl)-4H-iso xazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
180	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((tetrahydro-2H-pyran-4-yl)(p-tolyl)methyl)-4H-isox azolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
181	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methoxyphenyl)(tetrahydro-2H-pyran-4-yl)meth yl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
182	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((2-fluoro-3-methylphenyl)(tetrahydro-2H-pyran-4-y l)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
183	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoro-2-methylphenyl)(tetrahydro-2H-pyran-4-y l)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
184	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-fluoro-3-methylphenyl)(tetrahydro-2H-pyran-4-y l)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
185	2-(4-((2,3-difluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5 -yl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
186	2-(4-((2,4-difluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5 -yl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;

187	2-(4-((3,4-difluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
188	2-(4-((3-chlorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
189	2-(4-((4-chlorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
190	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-phenylbutyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
191	2-(6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-phenylbutyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
192	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(3-fluoropyridin-2-yl)butyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
193	2-(6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(3-methylpyridin-2-yl)butyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
194	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(oxazol-4-yl)butyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
195	2-(6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(oxazol-4-yl)butyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
196	1-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)cyclopropan-1-ol;
197	1-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)cyclopropan-1-ol;
198	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(5-methyloxazol-4-yl)butyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
199	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(2-methyloxazol-4-yl)butyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
200	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(isoxazol-4-yl)butyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
201	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(5-methylisoxazol-4-yl)butyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
202	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(3-methylisoxazol-4-yl)butyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
203	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((2-methyloxazol-4-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
204	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((5-methylisoxazol-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
205	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methylisoxazol-5-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
206	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((5-methylfuran-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
207	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methylfuran-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
208	(S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
209	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(3-methylpyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
210	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-yl)propan-2-ol;
211	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
212	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine;
213	3-bromo-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine;

214	1-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)-4,4-dimethylimidazolidin-2-one;
215	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-3-(piperazin-1-yl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine
216	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-3-(4-methylpiperazin-1-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine;
217	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-3-(4-(oxetan-3-yl)piperazin-1-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine;
218	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-3-(4-isopropylpiperazin-1-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine;
219	(3R)-1-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)-N-methylpyrrolidin-3-amine;
220	1-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)imidazolidin-2-one;
221	1-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)-3-methylimidazolidin-2-one;
222	methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate;
223	2-(1-cyclopropyl-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
224	2-(1-(difluoromethyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
225	2-(1-(2,2-difluoroethyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
226	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1-(2,2,2-trifluoroethyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
227	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-(methyl-d3)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
228	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-(2-hydroxyethyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
229	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-ethyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
230	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-(2-(dimethylamino)ethyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol; or
231	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-(methylsulfonyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol.

In some embodiments, the compounds further is:

232	2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
233	2-(4-((3-Fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-(methyl-d3)-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
234	2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-amine;
235	3-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)pentan-3-ol;
236	6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylicacid;
237	6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxamide;
238	2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methylpyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;

239	2-(4-((3-Fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
240	2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-4-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
241	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methoxypyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
242	2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-(1-(4-fluoro-2,6-dimethylphenyl)ethyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
243	(S)-N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)methanesulfonamide;
244	(S)-N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)acetamide;
245	Methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate;
246	2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
247	(S)-2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
248	(S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-phenylbutyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
249	(S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(3-fluoropyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
250	(S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
251	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
252	(S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
253	(S)-2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
254	(S)-2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-((tetrahydro-2H-pyran-4-yl)(o-tolyl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
255	(S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(oxazol-4-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
256	(S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(3-methylpyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
257	(S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((2-methyloxazol-4-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
258	(S)-2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
259	(S)-2-(4-((3-Fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-(methyl-d3)-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
260	(S)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-N,N,1-trimethyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3’,4’:4,5]pyrrolo[3,2-b]pyridine-3-carboxamide;
261	(S)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3’,4’:4,5]pyrrolo[3,2-b]pyridine-3-carboxamide;
262	(S)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-N,1-dimethyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxamide;
263	(S)-2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-amine;
264	(S)-3-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)pentan-3-ol;

265	(S)-6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylic acid;
266	(S)-6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxamide;
267	(S)-2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methylpyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
268	(S)-2-(4-((3-Fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
269	(S)-2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-4-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
270	(S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methoxypyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
271	(S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
272	(S)-2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-(1-(4-fluoro-2,6-dimethylphenyl)ethyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
273	(S)-N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)methanesulfonamide;
274	N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)acetamide; or
275	(S)-Methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate.

In some embodiments, the compounds further is:

276	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-3-((4-methylpiperazin-1-yl)methyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine;
277	(S)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-3-((4-methylpiperazin-1-yl)methyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine;
278	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-3-((methylsulfonyl)methyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine;
279	(S)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-3-((methylsulfonyl)methyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine;
280	4-((6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)methyl)morpholine;
281	(S)-4-((6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)methyl)morpholine;
282	N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)-N-(methylsulfonyl)acetamide;
283	(S)-N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)-N-(methylsulfonyl)acetamide;
284	(R)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol; or
285	(R)-2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol.

In another aspect, there is provided a pharmaceutical composition comprising at least one compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof of the present invention, and at least one pharmaceutically acceptable excipient. In some embodiments, wherein the said

compound in a weight ratio to the said excipient within the range from about 0.0001 to about 10. In some embodiments, wherein the said compound in a weight ratio to the said excipient within the range from about 0.0005 to about 0.25.

In another aspect, there is provided a method of treating a patient having a diseases or conditions related to bromodomain proteins, said method comprising administering to the patient a therapeutically effective amount of at least one compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof; or the pharmaceutical composition. In some embodiments, wherein the diseases or conditions related to bromodomain proteins is solid tumor and/or blood tumor. In some embodiments, wherein the solid tumor is selected from lung cancer, gastrointestinal cancer, colon cancer, rectal cancer, colorectal cancer and/or ovarian cancer; the blood tumor is selected from myeloma and/or leukemia. In some embodiments, the lung cancer contains non-small cell lung cancer and/or small cell lung cancer; the gastrointestinal cancer contains esophageal cancer; the leukemia contains acute myeloid leukemia (AML)) and/or acute lymphocytic leukemia(ALL); the myeloma contains multiple myeloma.

In another aspect, there is provided the compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof; or the pharmaceutical composition for use in the treatment of diseases or conditions related to bromodomain protein. In some embodiments, wherein the diseases or conditions related to bromodomain proteins is solid tumor and/or blood tumor. In some embodiments, wherein the solid tumor is selected from lung cancer, gastrointestinal cancer, colon cancer, rectal cancer, colorectal cancer and/or ovarian cancer; the blood tumor is selected from myeloma and/or leukemia. In some embodiments, the lung cancer contains non-small cell lung cancer and/or small cell lung cancer; the gastrointestinal cancer contains esophageal cancer; the leukemia contains acute myeloid leukemia (AML)) and/or acute lymphocytic leukemia(ALL); the myeloma contains multiple myeloma.

In another aspect, there is provided use of the compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof; or the pharmaceutical composition for the manufacture of a medicament for the treatment of diseases or conditions related to bromodomain protein. In some embodiments, wherein the diseases or conditions related to bromodomain proteins is solid tumor and/or blood tumor. In some embodiments, wherein the solid tumor is selected from lung cancer, gastrointestinal cancer, colon cancer, rectal cancer, colorectal cancer and/or ovarian cancer; the blood tumor is selected from myeloma and/or leukemia. In some embodiments, wherein the lung cancer contains non-small cell lung cancer and/or small cell lung cancer; the gastrointestinal cancer contains esophageal cancer; the leukemia contains acute myeloid leukemia (AML)) and/or acute lymphocytic leukemia(ALL); the myeloma contains multiple myeloma.

Definition

The term “halogen”, as used herein, unless otherwise indicated, means fluoro, chloro, bromo or iodo. The preferred halogen groups include F, Cl and Br.

The term “alkyl”, as used herein, unless otherwise indicated, alkyl includes saturated monovalent hydrocarbon radicals having straight or branched. For example, alkyl radicals include methyl, ethyl, propyl, isopropyl, cyclcopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, cyclcobutyl, n-pentyl, 3- (2-methyl) butyl, 2-pentyl, 2-methylbutyl, neopentyl, cyclcopentyl, n-hexyl, 2-hexyl, 2-methylpentyl and cyclohexyl. Similary, C_{1-6}, as in C_{1-6}alkyl is defined to identify the group as having 1, 2, 3, 4, 5 or 6 carbon atoms in a linear or branched arrangement.

The term “alkylene” means a difunctional group obtained by removal of a hydrogen atom from an alkyl group that is defined above. For example, methylene (i.e., $-CH_2-$), ethylene (i.e., $-CH_2-CH_2-$ or $-CH(CH_3)-$) and propylene (i.e., $-CH_2-CH_2-CH_2-$, $-CH(-CH_2-CH_3)-$ or $-CH_2-CH(CH_3)-$).

The term “alkenyl” means a straight or branch-chained hydrocarbon radical containing one or more double bonds and typically from 2 to 20 carbon atoms in length. For example, “C_{2-6}alkenyl” contains from 2 to 6 carbon atoms. Alkenyl group include, but are not limited to, for example, ethenyl, propenyl, butenyl, 2-methyl-2-buten-1-yl, hepetenyl, octenyl and the like.

The term “alkynyl” contains a straight- or branch-chained hydrocarbon radical containing one or more triple bonds and typically from 2 to 20 carbon atoms in length. For example, “C_{2-6}alkynyl” contains from 2 to 6 carbon atoms. Representative alkynyl groups include, but are not limited to, for example, ethynyl, 1-propynyl, 1-butynyl, heptynyl, octynyl and the like.

The term “alkoxy” radicals are oxygen ethers formed from the previously described alkyl groups.

The term"aryl", as used herein, unless otherwise indicated, refers to an unsubstituted or substituted mono- or polycyclic aromatic ring system containing carbon ring atoms. The preferred aryls are mono cyclic or bicyclic 6-10 membered aromatic ring systems. Phenyl and naphthyl are preferred aryls. The most preferred aryl is phenyl.

The term“heterocyclic”, as used herein, unless otherwise indicated, refers to unsubstituted and substituted mono- or polycyclic non-aromatic ring system containing one or more heteroatoms. Preferred heteroatoms include N, O, and S, including N-oxides, sulfur oxides, and dioxides. Preferably the ring is three to eight membered and is either fully saturated or has one or more degrees of unsaturation. Multiple degrees of substitution, preferably one, two or three, are included within the present definition.

Examples of such heterocyclic groups include, but are not limited to azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, oxopiperazinyl, oxopiperidinyl, oxoazepinyl, azepinyl, tetrahydrofuranyl,

dioxolanyl, tetrahydroimidazolyl, tetrahydrothiazolyl, tetrahydrooxazolyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone and oxadiazolyl.

The term “heteroaryl”, as used herein, unless otherwise indicated, represents an aromatic ring system containing carbon(s) and at least one heteroatom. Heteroaryl may be monocyclic or polycyclic, substituted or unsubstituted. A monocyclic heteroaryl group may have 1 to 4 heteroatoms in the ring, while a polycyclic heteroaryl may contain 1 to 10 hetero atoms. A polycyclic heteroaryl ring may contain fused, spiro or bridged ring junction, for example, bycyclic heteroaryl is a polycyclic heteroaryl. Bicyclic heteroaryl rings may contain from 8 to 12 member atoms. Monocyclic heteroaryl rings may contain from 5 to 8 member atoms (cabons and heteroatoms). Examples of heteroaryl groups include, but are not limited to thienyl, furanyl, imidazolyl, isoxazolyl, oxazolyl, pyrazolyl, pyrrolyl, thiazolyl, thiadiazolyl, triazolyl, pyridyl, pyridazinyl, indolyl, azaindolyl, indazolyl, benzimidazolyl, benzofuranyl, benzothienyl, benzisoxazolyl, benzoxazolyl, benzopyrazolyl, benzothiazolyl, benzothiadiazolyl, benzotriazolyl adeninyl, quinolinyl or isoquinolinyl.

The term "carbocyclic" refers to a substituted or unsubstituted monocyclic, bicyclic or polycyclic non-aromatic saturated ring, which optionally includes an alkylene linker through which the cycloalkyl may be attached. Examplary "cycloalkyl" groups includes but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and so on.

The term “oxo” refers to oxygen atom together with the attached carbon atom.forms the group  .

The term “carboxyl” refers to the group C(O)OH.

The term"composition", as used herein, is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts. Accordingly, pharmaceutical compositions containing the compounds of the present invention as the active ingredient as well as methods of preparing the instant compounds are also part of the present invention. Furthermore, some of the crystalline forms for the compounds may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds may form solvates with water (i.e., hydrates) or common organic solvents and such solvates are also intended to be encompassed within the scope of this invention.

The compounds of the present invention may also be present in the form of pharmaceutically acceptable salts. For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts". The pharmaceutically acceptable salt forms include pharmaceutically acceptable acidic/anionic or basic/cationic salts. The pharmaceutically acceptable acidic/anionic salt generally takes a form in which the basic nitrogen is protonated with an inorganic or organic acid. Representative organic or inorganic acids include hydrochloric, hydrobromic, hydriodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, mandelic, methanesulfonic, hydroxyethanesulfonic, benzenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicylic, saccharinic or trifluoroacetic. Pharmaceutically acceptable basic/cationic salts include, and are not limited to aluminum, calcium, chloroprocaine, choline, diethanolamine, ethylenediamine, lithium, magnesium, potassium, sodium and zinc.

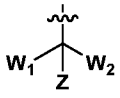
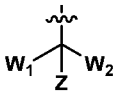
The present invention includes within its scope the prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds that are readily converted in vivo into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various disorders described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the subject. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

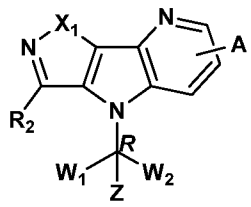
It is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. It is understood that substituents and substitution patterns on the compounds of this invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques know in the art as well as those methods set forth herein.

The present invention includes compounds described can contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof.

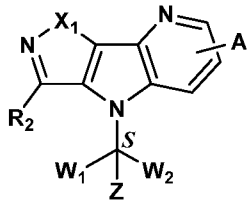
The present invention includes all stereoisomers of the compound and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also

included. During the course of the synthetic procedures used to prepare such compounds or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

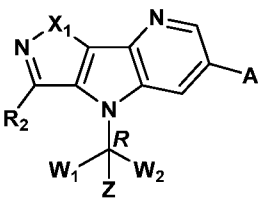
The term "stereoisomer" as used in the present invention refers to an isomer in which atoms or groups of atoms in the molecule are connected to each other in the same order but differ in spatial arrangement, including conformational isomers and conformational isomers. The configuration isomers include geometric isomers and optical isomers, and optical isomers mainly include enantiomers and diastereomers. The invention includes all possible stereoisomers of the compound, in particular, when the carbon atom directly attached to W_1, W_2, Z in formula (I) is a chiral carbon, the present invention includes stereoisomers in which the  in the formula (I) is "*R*" configuration, and stereoisomers in which the  in the formula (I) is "*S*" configuration. By way of general example and without limitation, the stereoisomers encompassed by the present invention. include:



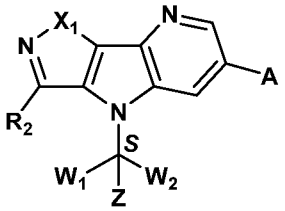
I-1



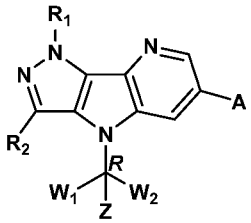
I-2



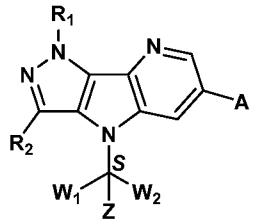
II-1



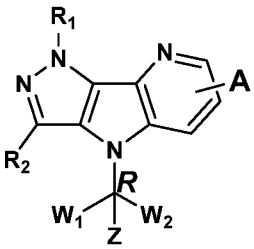
II-2



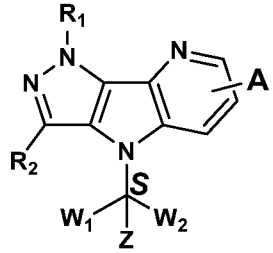
III-1



III-2



IV-1



IV-2

"*R*" in the formulae I-1, II-1, III-1, IV-1 indicates that when the carbon atom bonded to W_1, W_2 and Z is a chiral carbon, the absolute configuration of the chiral carbon is the *R* configuration. .

"*S*" in the formulae I-2, II-2, III-2, IV-2 indicates that when the carbon atom bonded to W_1, W_2 and Z is a chiral carbon, the absolute configuration of the chiral carbon is the *S* configuration.

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. The isotopes of hydrogen can be denoted as ^{1}H(hydrogen), ^{2}H(deuterium) and ^{3}H(tritium). They are also commonly denoted as D for deuterium and T for tritium. In the application, CD_3 denotes a methyl group wherein all of the hydrogen atom are deuterium. Isotopes of carbon include ^{13}C and ^{14}C.Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by prcesses analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent.

When a tautomer of the compound of Formula (I) exists, the present invention includes any possible tautomers and pharmaceutically acceptable salts thereof, and mixtures thereof, except where specifically stated otherwise.

When the compound of Formula (I) and pharmaceutically acceptable salts thereof exist in the form of solvates or polymorphic forms, the present invention includes any possible solvates and polymorphic forms. A type of a solvent that forms the solvate is not particularly limited so long as the solvent is pharmacologically acceptable. For example, water, ethanol, propanol, acetone or the like can be used.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Since the compounds of Formula (I) are intended for pharmaceutical use they are preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure, especially at least 98% pure (% are on a weight for weight basis).

The pharmaceutical compositions of the present invention comprise a compound represented by Formula I (or a pharmaceutically acceptable salt thereof) as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being

administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

In practice, the compounds represented by Formula I or a prodrug or a metabolite or pharmaceutically acceptable salts thereof, of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g. oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in- oil liquid emulsion. In addition to the common dosage forms set out above, the compound represented by Formula I or a pharmaceutically acceptable salt thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt, of Formula I. The compounds of Formula I or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen. In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used

to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques.

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.05mg to about 5g of the active ingredient and each cachet or capsule preferably containing from about 0.05mg to about 5g of the active ingredient. For example, a formulation intended for the oral administration to humans may contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 0.05 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 0.0lmg to about 2g of the active ingredient, typically 0.01mg, 0.02mg, 1mg, 2mg, 3mg, 4mg, 5mg, 6mg, 7mg, 8mg, 9mg, 10mg, 25mg, 50mg, l00mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg or l000mg.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound represented by Formula I of this invention or a pharmaceutically acceptable salt thereof, via conventional processing methods. As an example, a cream or ointment is prepared by admixing hydrophilic material and water, together with about 0.05wt% to about 10wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including antioxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound described by Formula I or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

Generally, dosage levels on the order of from about 0.001mg/kg to about 150mg/kg of body weight per day are useful in the treatment of the above-indicated conditions or alternatively about 0.05mg to about 7g per patient per day. For example, inflammation, cancer, psoriasis, allergy/asthma, disease and conditions of the immune system, disease and conditions of the central nervous system (CNS), may be effectively treated by the administration of from about 0.001 to 50mg of the compound per kilogram of body weight per day or alternatively about 0.05mg to about 3.5g per patient per day.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

These and other aspects will become apparent from the following written description of the invention.

METHODS OF PREPRATION

The compounds in the present invention can be synthesized in a number of ways well to one skilled in the art of organic synthesis described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods are not limited as those described below. The references cited here are incorporated by reference in their entirety.

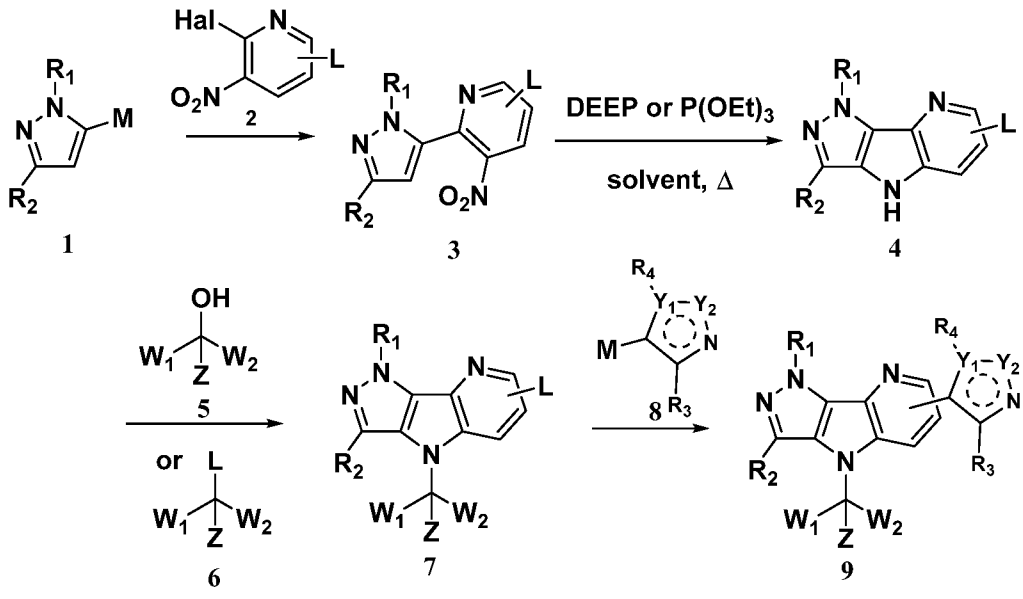
The methods of synthesis described hereinafter are intended as an illustration of the invention, without restricting its subject matter and the scope of the compounds claimed to these examples. Where the preparation of starting compounds is not described, they are commercially obtainable or may be prepared analogously to known compounds or methods described herein. Substances described in the literature are prepared according to the published methods of synthesis. Compounds of formula **(I)** may be synthesized by reference to methods illustrated in the following schemes. As shown herein, the end compound is a product having the same structural formula depicted as formula **(I)**. It will be understood that any compound of formula **(I)** may be prepared by the selection of reagents with appropriate substitution. Solvents, temperature, pressures, and other reaction conditions may be readily selected by one of ordinary skill in the art. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Green and P.G. M. Wuts (1999) Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons). These groups are removed at certain stage of the compound synthesis using the methods that are apparent to those skilled in the art.

General synthetic routes to compounds illustrated in the invention is described in Schemes 1-3, where the R_1, R_2, R_3, Y_1, Y_2, W_1, W_2 and Z substituents are defined previously in the text or a functional group that can be converted to the desired final substituent. The substituent Hal is a halide, and L is a leaving group such as a halide or OH that can easily converted to a leaving group such as triflate or tosylate. M is a suitable coupling partner, such as boronic acid, bonic ester or stannane

As depicted in Scheme 1, Suzuki coupling of pyrazole **1** with the aromatic heterocycle **2,** such as 2,5-dibromo-3-nitropyridine using a suitable coupling catalyst, such as $Pd(dppf)Cl_2$ at the present of a base, like K_3PO_4 in THF/H_2O (5:1 volume ratio) can give the **3**. Cadogan reductive cyclization of **3** at the present of a phosphine reagent, such as 1,2-bis(diphenylphosphino)ethane (DPPE) or triethyl phosphate $P(OEt)_3$ and solvent, such as 1,2-dichlorobenze or 1,2-dimethyl-benzene with heating can give the tricycle **4**. Mitsunobu reaction of **4** with an alkylating agent **5** using triphenophosphine and diisopropyl azodicarboxylate (DIAD) to provide **7**. Alternatively, the **7** can be generated from a reaction between **4** and an alkylating agent **6,** where L is a leaving group such as a halide, mesylate or triflate, in the presence of a base, such as potassium carbonate. A coupling of **7** with **8** (where M is a suitable coupling partner, such as boronic acid, boronic ester or stannane) by a Suzuki or Stille reaction can generate **9**. In cases where **9** is a racemate, chiral separation can provide enantiomerically pure products. Further derivatization of R_1 and R_2 can provide additional compounds of the invention. For example, when R_1 is a protecting group, it can be further functionalized after de-protecting; when R_2 is an ester, addition of a Grignard reagent or alky lithium can generate tertiary alcohols. The ester could instead be hydrolyzed using, for example, potassium hydroxide to give a carboxylic acid, which could be further functionalized

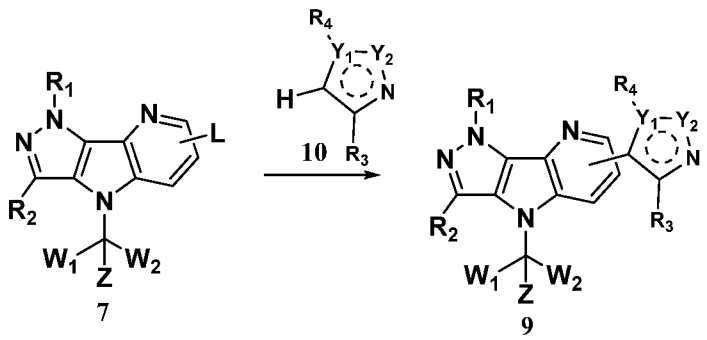
using alky amines; when R_2 is a -H, it can be replaced by a halogen, for example -Br, through a halogenation reaction using a reagent like NBS and can be further functionalized through a reaction, such as Buchwall, Mitszunobu or Stille reaction.

Scheme 1



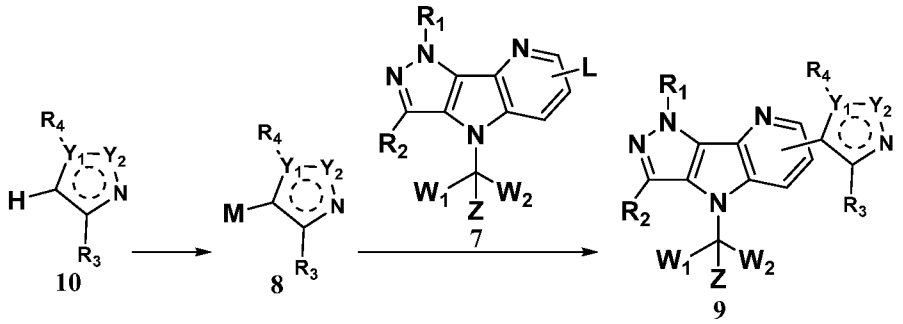
As illustrated in **Scheme 2**, a heterocyclic aromatic **10**, can be directly coupled to **7** (prepared as in Scheme 1) via palladium-mediated C-H activation to afford compound **9.**

Scheme 2



Alternatively, heterocyclic aromatic **10** can be deprotonated with a strong base such as n-BuLi and transmetallated to zinc or tin reagent to afford compound **8** which can be coupled by a Negishi or Stille reaction to **7** (prepared as in **Scheme 1**) at the present of a suitable palladium catalyst to afford compounds **9.** This is illustrated in **Scheme 3**.

Scheme 3



EXAMPLES

The invention is further defined using the following Examples and it should be understood that these examples are used by way of illustration only. One skilled in the art can determine with certainty the essential feature of the invention, and without departure from the spirit and scope thereof, can make versatile modifications to accommodate the invention to various uses and conditions. Hence, the invention is not restricted by the exemplifying examples set forth herein below, but rather is specified by the claims appended hereto.

Table 1 shows the part abbreviations of the present invention:

Table 1

aq	aqueous	KOtBu	potassium tert-butoxide
Bn	benzyl	LC-MS	Liquid Chromatography-Mass Spectroscopy
Boc	tert-butoxycarbonyl	LDA	lithium diisopropylamide
Boc_2O	di-tert-butyl dicarbonate	LiHMDS	lithium bis(trimethylsily)amide
CuI	copper iodide	Me	methane
DCM	dichloromethane	MeI	methyl iodide
DIAD	diisopropyl azodicarboxylate	MeCN	Acetonitrile
DIEA	diisopropylethylamine	MeOH	methanol
DMAP	4-dimethylaminopyridine	min	minute(s)
DMF	dimethylformamide	mL	milliliter(s)
DMSO	dimethyl sulfoxide	mmol	millimolar
DPPE	1,2-bis(diphenylphosphino)ethane	MTBE	methyl t-butyl ether
dtbpy	iodo(4,4 -di-tert-butyl-2,2 -bipyridine)methylpalladium(II)	$NaHCO_3$	sodium hydrogen carbonate
equiv.	equivalent(s)	NaHMDS	sodium bis(trimethylsilyl)amide
Et_3N	triethylamine	n-BuLi	n-butyl lithium
Et_2O	diethyl ether	NH_4OAc	amonium acetate
EtOAc	ethyl acetate	$Pd(OAc)_2$	polladium acetate
EtOH	ethanol	$Pd(dppf)Cl_2$	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
g	gram(s)	Prep-TLC	prep thin layer chromatography
h or hr	hour(s)	r.t.	room temperature
HBPin	Pinacolborane	TEA	triethylamine
HPLC	high pressure liquid chromatography	THF	Tetrahydrofuran

iPrOH	isopropyl alcohol	sat.	saturated
RT	retention time	SEMCl	2-(trimethylsilyl)ethoxymethyl chloride
DTAD	Ditert-butyl azodicarboxylate	$TMSN_3$	Trimethylsilyl azide
HATU	1-[Bis(dimethylamino)methylene]-1 H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate	DEA	diethylamine

Intermediate Preparation

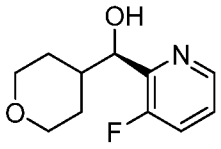
Unless otherwise stated, starting materials for the preparation of intermediates and Examples are commercially available.

Enantiomer a1 and Enantiomer b1

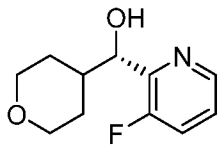
((R)-(3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methanol) ("Enantiomer a1")

And

((S)-(3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methanol) ("Enantiomer b1")



Enantiomer a1



Enantiomer b1

To a suspension of magnesium (24.3 g, 1.00 mol) in THF (500 mL) was added three crystals of iodine followed by dropwise addition of neat 4-bromotetrahydro-2H-pyran (100g, 607 mmoL) through an additional funnel under N_2, during which the inner temperature was controled under 45 °C. The reaction mixture was continued stirring for 2 h at ambient temperature. The reaction mixture was cooled to -30 °C followed by dropwise addition of 3-fluoropicolinaldehyde (50.3 g, 402 mmoL) in THF (300 mL) through an additional funnel, during which the inner temperature was kept between -20 °C to -30 °C. After 1 h, the reaction mixture was filtered through a thin pad of celite. To the filtrate was added sat. aq. NH_4Cl (100 mL) and the two layers were seperated. The organic phase was dried over anhydrous Na_2SO_4 and collected by filtration and washing with EtOAc (200ml). The filtrate was concentrated on a rotary evaporator. The crude compound was purified using a reverse phase chromatography eluting with 40~50 % MeCN in H_2O to afford the racemic compound (52 g, 61 % yield), which was separated by chiral prep SFC to give Enantiomer a1, (R)-(3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methanol (25.1 g, 29.6 % yield) and Enantiomer b1, (S)-(3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methanol (25.3 g, 29.7 %).

Enantiomer a1: LC-MS $[M+H]^+$ = 212. Chiral Chromatography Report: RT = 12.25 min (Column: Chiralpak AY-H(ADH0CE-VC001) 0.46×25 cm; Mobile Phase: 90/10/0.1 Hexane/EtOH/DEA; Flow: 1.0 mL/min). Chiral Chromatography Report: RT = 14.023 min (Column: YMC，Chiral ART-amylose-C Neo(5μm, 250×4.6mm; Mobile Phase: 90/10/0.1 Hexane/EtOH/TFA; Flow: 1.0 mL/min). ^1H NMR (400

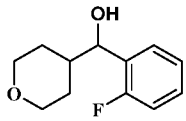
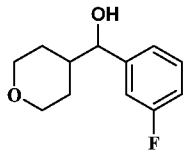
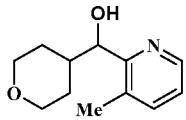
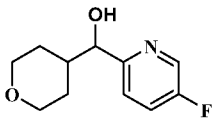
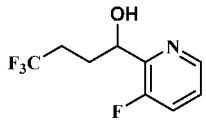
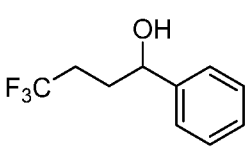
MHz, DMSO-d_6) δ 8.42 (dd, J = 3.20, 1.32 Hz, 1H), 7.66 (ddd, J = 9.8, 8.36, 1.12 Hz, 1H), 7.35 – 7.42 (m, 1H), 5.23 (d, J = 6.52 Hz, 1 H), 4.52 (dd, J = 7.32, 7.28 Hz, 1H), 3.88 (dd, J = 11.4, 2.92 Hz, 1H), 3.75 (dd, J = 11.2, 3.02 Hz, 1H), 3.26 (dt, J = 12.0, 2.04 Hz, 1H), 3.17 (dt, J = 11.8, 2.24 Hz, 1H), 2.01 -2.12 (m, 1H), 1.82 (dd, J = 13.3, 1.52 Hz, 1H), 1.24 -1.38 (m,1H), 1.12 - 1.24 (m, 1H), 1.00 (dd, J = 12.9, 1.34, 1H).

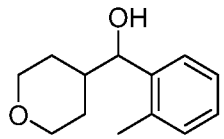
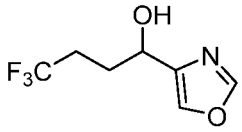
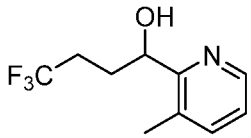
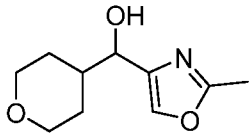
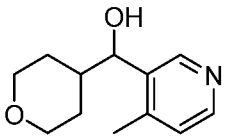
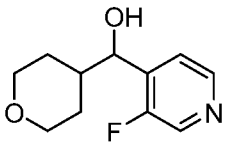
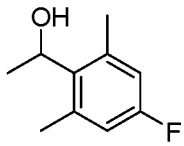
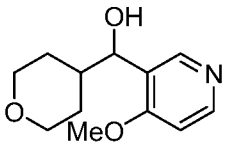
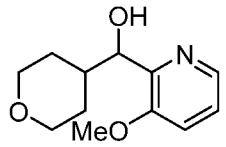
Enantiomer b1: LC-MS $[M+H]^+$ = 212. Chiral Chromatography Report: RT = 13.57 min (Column: Chiralpak AY-H(ADH0CE-VC001) 0.46×25 cm; Mobile Phase: 90/10/0.1 Hexane/EtOH/DEA; Flow: 1.0 mL/min). Chiral Chromatography Report: RT = 12.760 min (Column: YMC，Chiral ART-amylose-C Neo(5μm, 250×4.6mm; Mobile Phase: 90/10/0.1 Hexane/EtOH/TFA; Flow: 1.0 mL/min).^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (dd, J = 3.2, 1.35 Hz, 1H), 7.66 (ddd, J = 1.12, 8.4, 9.8 Hz, 1H), 7.35 – 7.42 (m, 1H), 5.23 (d, J = 6.48 Hz, 1 H), 4.52 (dd, J = 7.32, 7.24 Hz, 1H), 3.88 (dd, J = 11.3, 2.96, 1H), 3.75 (dd, J = 2.96, 11.2 Hz, 1H), 3.26 (dt, J = 12.0, 2.0 Hz, 1H), 3.17 (dt, J = 11.8, 2.24 Hz, 1H), 2.01 -2.12 (m, 1H), 1.82 (dd, J = 13.3, 1.52 Hz, 1H), 1.24 -1.38 (m, 1H), 1.12 – 1.24 (m, 1H), 1.00 (dd, J = 12.9, 1.34, 1H).

Intermediate 3-17

The intermediates in Table 2 were prepared using the same method described for the racemate of Enantiomer a1 and Enantiomer b1:

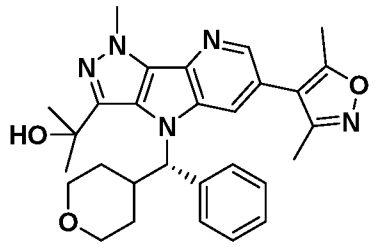
Table 2

Intermediate	Structure	LCMS (M + H)
3		**211**
4		**211**
5		**208**
6		**212**
7		**224**
8		**205**

9		**207**
10		**196**
11		**220**
12		**198**
13		**208**
14		**212**
15		**169**
16		**224**
17		**224**

Example 1

(S)-2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol("Compound 1")



Step 1: Methyl 5-(5-bromo-3-nitropyridin-2-yl)-1-methyl-1H-pyrazole-3-carboxylate

To a solution of HBPin (26.4 g, 0.21 mmol) , dtbpy (1.06 g, 3.95 mmol) and (1,5-cyclooctadiene)-(methoxy)iridium(I)dimer (1.02 g, 1.54 mmol) in THF (125 mL) was added methyl 1-methyl-1H-pyrazole-3-carboxylate (20.2 g, 0.14 mol) at room temperature under N_2. The resulting solution was vacuumed, backfilled with N_2, and this sequence was repeated three times, then the reaction mixture was refluxed for 12 h under N_2. Then the reaction mixture was concentrated under reduced pressure to afford a red substance. To the resulting crude substance in a 1L round bottom flask was added THF (500 mL), water (100mL), K_3PO_4 (65.13 g, 0.31 mol) and 2,5-dibromo-3-nitropyridine (47.1 g, 0.17 mol) . The flask was vacuumed, filled with N_2, and this process was repeated three times, followed by addition of $Pd(dppf)Cl_2$ (11.3 g, 0.014 mmol) under N_2. The mixture was refluxed for 3 h under N_2. After cooling to room temperature, the reaction mixture was extracted with EtOAc (500 mL). The extract was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography using 0-30% EtOAC in hexane to afford methyl 5-(5-bromo-3-nitropyridin-2-yl)-1-methyl-1H-pyrazole-3-carboxylate (27.6 g, 0.081 mol, 57% yield), LC-MS $[M+H]^+ = 341$.

Step 2: Methyl 6-bromo-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

A mixture of methyl 5-(5-bromo-3-nitropyridin-2-yl)-1-methyl-1H-pyrazole-3-carboxylate (22.1 g, 0.065 mol), DPPE (38.8 g, 0.088 mol) in 1,2-dichlorobenzene (250 mL) was heated to 150 °C and stirred for 4 h under N_2. The reaction was then cooled slowly to room temperature. The solvent was concentrated under reduced pressure. The crude product was purified by silica gel chromatography using 30-50% EtOAC in hexane to afford Methyl 6-bromo-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b] pyridine-3-carboxylate (3.98 g, 0.013 mol, 20% yield), LC-MS $[M+H]^+ = 309$.

Step 3: Methyl (S)-6-bromo-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

A solution of methyl 6-bromo-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (207 mg, 0.67 mmol), (R)-phenyl(tetrahydro-2H- pyran-4-yl)methanol (169 mg, 0.88 mmol) and triphenylphosphane (446 mg, 1.70 mmol) in dry THF (10 mL) was vacuumed，backfilled with nitrogen gas，and this sequence was repeated three times. Diisopropyl azodicarboxylate (321 mg, 1.59 mmol) was added dropwise at room temperature and the resulting solution was stirred for 2 h. Then the reaction was extracted with EtOAc (50 mL), washed with brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel

chromatography with 0-30% EtOAc in hexane to afford Methyl (S)-6-bromo-1-methyl-4-(phenyl (tetrahydro-2H-pyran-4-yl)methyl) -1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (315 mg, 97% yield), LC-MS $[M+H]^+$ = 483,485.

Step 4: Methyl (S)-6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl) methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

To a solution of methyl (S)-6-bromo-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (315 mg, 0.65 mmol) in 1,4-dioxane (20 mL) and water (5 mL) was added 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) isoxazole (208 mg, 0.93 mmol), $Pd(dppf)Cl_2$ (74 mg, 0.091 mmol) and K_3PO_4 (402 mg, 1.89 mmol). The mixture was vacuumed，backfilled with nitrogen gas，and this sequence was repeated. The resulting mixture was stirred at 80 °C for 2 h. The reaction mixture was cooled to r.t., diluted with water (50 mL) and extracted with EtOAc (3×50 mL). After separation, the organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel chromatography using 0-50% EtOAc in hexane to afford Methyl (S)-6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-(phenyl (tetrahydro-2H- pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (272 mg, 84% yield), LC-MS $[M+H]^+$ = 500.

Step 5: (S)-2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl) methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol

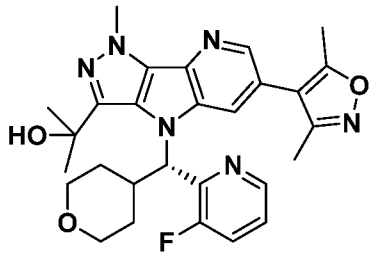
MeMgBr (1M in THF, 5.0 mL,5.03 mmol) was slowly added to a solution of methyl (S)-6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (272 mg, 0.54 mmol) in dry THF(10 ml) at -30 °C under N_2 over 1 min. After addition, the reaction was warmed to r.t. and stirred for 2 hr. The reaction was quenched with sat. NH_4Cl, and extracted with EtOAc (30 mL). The collected organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel chromatography using 0-4% MeOH in DCM to afford (S)-2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol (Compound 1, 121 mg, 44% yield), LC-MS $[M+H]^+$ = 500.

^1H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, J = 1.5 Hz, 1H), 7.75 (d, J = 1.3 Hz, 1H), 7.70 (d, J = 7.6 Hz, 2H), 7.31 (t, J = 7.5 Hz, 2H), 7.22 (t, J = 7.3 Hz, 1H), 6.44 (d, J = 11.2 Hz, 1H), 5.77 (s, 1H), 4.13 (s, 3H), 3.85 (d, J = 8.8 Hz, 1H), 3.74 (d, J = 8.7 Hz, 1H), 3.47 (t, J = 11.2 Hz, 1H), 3.25 (dd, J = 22.1, 11.0 Hz, 2H), 2.34 (s, 3H), 2.15 (s, 3H), 1.79 (d, J = 12.8 Hz, 1H), 1.70 (s, 3H), 1.71(s, 3H), 1.54 (qd, J = 12.5, 4.2 Hz, 1H), 1.37 (ddd, J = 15.6, 12.6, 4.1 Hz, 1H), 0.78 (d, J = 12.6 Hz, 1H).

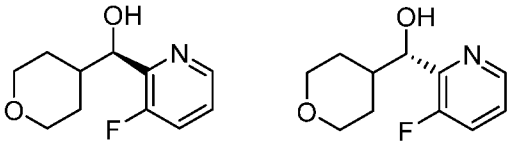
Example 2

(S)-2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl

)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol ("Compound 2")



Step 1: (R)-(3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methanol("Enantiomer a1") and (S)-(3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methanol("Enantiomer b1")



Enantiomer a1 Enantiomer b1

To a suspension of magnesium (24.3 g, 1.00 mol) in THF (500 mL) was added three crystals of iodine followed by dropwise addition of neat 4-bromotetrahydro-2H-pyran (100g, 607 mmoL) under N_2, during which the inner temperature was controled under 45 °C. The reaction mixture was continued stirring for 2 h at ambient temperature. The reaction mixture was cooled to –30 °C followed by addition of 3-fluoropicolinaldehyde (50.3 g, 402 mmoL) in THF (300 mL), during which the inner temperature was kept between -20 °C to -30 °C. After 1 h, the reaction mixture was filtered through a thin pad of celite. To the filtrate was added sat. aq. NH_4Cl (100 mL) and the two layers were seperated. The organic phase was dried over anhydrous Na_2SO_4 and collected by filtration. The filtrate was concentrated on a rotary evaporator. The crude compound was purified using a reverse phase chromatography eluting with 40~50 % MeCN in H_2O to afford the racemic compound (52 g, 61 % yield), which was separated by chiral prep SFC to give Enantiomer a1 of (R)-(3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methanol (25.1 g, 29.6 % yield) and Enantiomer b1 of (S)-(3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methanol (25.3 g, 29.7 %).

Enantiomer a1: LC-MS $[M+H]^+$ = 212. Chiral Chromatography Report: RT = 12.25 min (Column: Chiralpak AY-H(ADH0CE-VC001) 0.46×25 cm; Mobile Phase: 90/10/0.1 Hexane/EtOH/DEA; Flow: 1.0 mL/min). Chiral Chromatography Report: RT = 14.023 min (Column: YMC，Chiral ART-amylose-C Neo(5μm, 250×4.6mm; Mobile Phase: 90/10/0.1 Hexane/EtOH/TFA; Flow: 1.0 mL/min). ^1H NMR (400 MHz, DMSO-d_6) δ 8.42 (dd, J = 3.20, 1.32 Hz, 1H), 7.66 (ddd, J = 9.8, 8.36, 1.12 Hz, 1H), 7.35 – 7.42 (m, 1H), 5.23 (d, J = 6.52 Hz, 1 H), 4.52 (dd, J = 7.32, 7.28 Hz, 1H), 3.88 (dd, J = 11.4, 2.92 Hz, 1H), 3.75 (dd, J = 11.2, 3.02 Hz, 1H), 3.26 (dt, J = 12.0, 2.04 Hz, 1H), 3.17 (dt, J = 11.8, 2.24 Hz, 1H), 2.01 -2.12 (m, 1H), 1.82 (dd, J = 13.3, 1.52 Hz, 1H), 1.24 -1.38 (m,1H), 1.12 – 1.24 (m, 1H), 1.00 (dd, J = 12.9, 1.34, 1H).

Enantiomer b1: LC-MS $[M+H]^+$ = 212. Chiral Chromatography Report: RT = 13.57 min (Column: Chiralpak AY-H(ADH0CE-VC001) 0.46×25 cm; Mobile Phase: 90/10/0.1 Hexane/EtOH/DEA; Flow: 1.0 mL/min). Chiral Chromatography Report: RT = 12.760 min (Column: YMC，Chiral ART-amylose-C

Neo(5μm, 250×4.6mm; Mobile Phase: 90/10/0.1 Hexane/EtOH/TFA; Flow: 1.0 mL/min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (dd, J = 3.2, 1.35 Hz, 1H), 7.66 (ddd, J = 1.12, 8.4, 9.8 Hz, 1H), 7.35 – 7.42 (m, 1H), 5.23 (d, J = 6.48 Hz, 1 H), 4.52 (dd, J = 7.32, 7.24 Hz, 1H), 3.88 (dd, J = 11.3, 2.96, 1H), 3.75 (dd, J = 2.96, 11.2 Hz, 1H), 3.26 (dt, J = 12.0, 2.0 Hz, 1H), 3.17 (dt, J = 11.8, 2.24 Hz, 1H), 2.01 -2.12 (m, 1H), 1.82 (dd, J = 13.3, 1.52 Hz, 1H), 1.24 -1.38 (m, 1H), 1.12 – 1.24 (m, 1H), 1.00 (dd, J = 12.9, 1.34, 1H).

Step 2: (S)-Methyl 6-bromo-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl) methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

A solution of methyl 6-bromo-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (obtained from Example 1, step 2, 202 mg, 0.65 mmol), (R)-(3-fluoropyridin-2-yl)(tetrahydro -2H-pyran-4-yl)methanol (Enantiomer a1, from Step 1, 185 mg, 0.88 mmol) and triphenylphosphane (438 mg, 1.67 mmol) in dry THF (10 mL) was vacuumed， backfilled with nitrogen gas，and this sequence was repeated three times. Diisopropyl azodicarboxylate (336 mg, 1.66 mmol) in THF (2 mL) was added dropwise at room temperature and the resulting solution was stirred for 2 h. Then the reaction was extracted with EtOAc (50 mL) and the extract was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography with 0-35% EtOAc in hexane to afford (S)-methyl 6-bromo-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo [3,2-b]pyridine-3-carboxylate (317 mg, 92% yield), LC-MS $[M+H]^+$ = 502.

Step 3: (S)-Methyl 6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

To a solution of (S)-methyl 6-bromo-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl) -1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (from **Step 2**, 317 mg, 0.63 mmol) in 1,4-dioxane (20 mL) and water (5 mL) was added 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (207 mg, 0.93 mmol), and K_3PO_4 (386 mg, 1.82 mmol). The mixture was vacuumed， backfilled with nitrogen gas，and this sequence was repeated three times, followed by addition of $Pd(dppf)Cl_2$ (82 mg, 0.10 mmol) in one portion and the resulting mixture was stirred at 80 °C for 2 h under N_2. The reaction mixture was cooled to r.t., diluted with water (50 mL) and extracted with EtOAc (3×50 mL). After separation, the organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel chromatography using 0-5% EtOAc in MeOH to afford (S)-methyl 6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (254 mg, 78% yield), LC-MS $[M+H]^+$ = 519.

Step 4: (S)-2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl) methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol

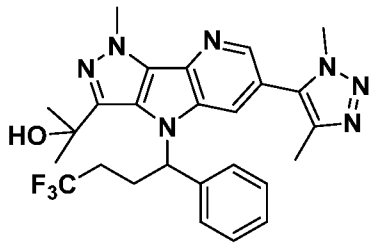
MeMgBr (1M in THF, 4.8 mL,4.77 mmol) was slowly added to a solution of (S)-methyl 6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (from **Step 3**, 254 mg, 0.49 mmol) in dry

THF (10 ml) at -30 °C under N_2 over 1 min. After addition, the reaction was warmed to r.t. and stirred for 2 hr. The reaction was quenched with sat. NH_4Cl, and extracted with EtOAc (30 mL). The organic layer was washed with sat. aqueous NaCl, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel chromatography using 0-4% MeOH in DCM to afford (S)-2-(6-(3,5-dimethyl isoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo [3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol (Compound 2, 93 mg, 37% yield), LC-MS $[M+H]^+$ = 519.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, J = 4.6 Hz, 1H), 8.32 (d, J = 1.6 Hz, 1H), 8.10 (d, J = 1.6 Hz, 1H), 7.72 (t, J = 8.9 Hz, 1H), 7.47 (dt, J = 8.5, 4.3 Hz, 1H), 6.98 (d, J = 10.7 Hz, 1H), 5.68 (s, 1H), 4.13 (s, 3H), 3.80 (d, J = 8.9 Hz, 1H), 3.68 (d, J = 8.6 Hz, 1H), 3.28 (d, J = 11.6 Hz, 1H), 3.23 – 3.06 (m, 2H), 2.41 (s, 3H), 2.23 (s, 3H), 1.73 (s, 3H), 1.66 – 1.60 (m, 1H), 1.57 (s, 3H), 1.51 (d, J = 12.4 Hz, 1H), 1.40 (ddd, J = 24.2, 12.2, 4.2 Hz, 1H), 0.50 (d, J = 12.2 Hz, 1H).

Example 3

2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-phenylbutyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol("Compound 3")



Step 1: Methyl 6-bromo-1-methyl-4-(4,4,4-trifluoro-1-phenylbutyl)-1,4-dihydropyrazolo [3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

To a solution of methyl 6-bromo-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (from Example 1 step 2, 213 mg, 0.69 mmol), 4,4,4-trifluoro-1-phenylbutan-1-ol (Intermediate 8, 179 mg, 0.88 mmol) and triphenylphosphane (449 mg, 1.71 mmol) in dry THF (10 mL) was dropwise added diisopropyl azodicarboxylate (350 mg, 1.73 mmol) in THF (2 mL) at room temperature and the resulting solution was stirred for 2 h. Then the reaction was extracted with EtOAc (50 mL). The extract was washed with brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography with 0-35% EtOAc in hexane to afford methyl 6-bromo-1-methyl-4-(4,4,4-trifluoro-1-phenylbutyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (314 mg, 92% yield), LC-MS $[M+H]^+$ = 495,497.

Step 2: Methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-phenylbutyl) -1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

To a solution of methyl 6-bromo-1-methyl-4-(4,4,4-trifluoro-1-phenylbutyl)-1,4-dihydropyrazolo

[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (314 mg, 0.63 mmol) in DMF (10 mL) was added 1,4-dimethyl-5-(tributylstannyl)-1H-1,2,3-triazole (521 mg, 1.35 mmol), tetrakis(triphenylphosphine) palladium (102 mg, 0.088 mmol), CuI (30 mg, 0.16 mmol) and TEA (221 mg, 2.00 mmol). The mixture was degassed under vacuum, backfilled with nitrogen gas, and this sequence was repeated three times. The resulting mixture was stirred at 110 °C for 2 h. The reaction mixture was cooled to r.t., diluted with water (50 mL) and extracted with EtOAc (3×50 mL). After separation, the organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel chromatography using 0-5% MeOH in DCM to afford methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-phenylbutyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxyl ate (176 mg, 55% yield), LC-MS $[M+H]^+ = 512$.

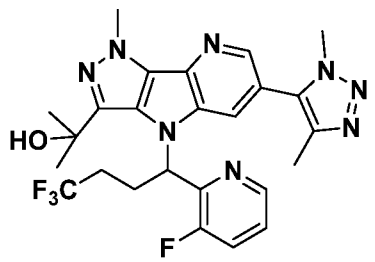
Step 3:2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-phenylbutyl)-1,4 -dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol

MeMgBr (1M in THF, 3.2 mL,3.20 mmol) was slowly added to a solution of methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-phenylbutyl)-1,4-dihydropyrazolo[3',4':4,5] pyrrolo[3,2-b]pyridine-3-carboxylate (176 mg, 0.34 mmol) in dry THF(10 ml) at -30 °C under N_2 over 1 min. After addition, the reaction was warmed to r.t. and stirred for 2 hr. The reaction was quenched with sat. NH_4Cl, and extracted with EtOAc (30 mL). The organic layer was washed with sat. aqueous NaCl, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel chromatography using 0-6% MeOH in DCM to afford 2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl -4-(4,4,4-trifluoro-1-phenylbutyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol (Compound 3, 94 mg, 53% yield), LC-MS $[M+H]^+ = 512$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (d, J = 1.2 Hz, 1H), 7.61 (s, 1H), 7.32 (d, J = 4.2 Hz, 4H), 7.25 (dd, J = 8.3, 4.0 Hz, 1H), 6.77 (t, J = 8.0 Hz, 1H), 5.77 (s, 1H), 4.19 (s, 3H), 3.73 (s, 3H), 2.80 (dd, J = 16.2, 8.0 Hz, 2H), 2.70 – 2.55 (m, 1H), 2.07 (s, 3H), 1.88 – 1.74 (m, 1H), 1.69 (s, 3H), 1.52 (s, 3H).

Example 4

2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(3-fluoropyridin-2-yl)bu tyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol, ("Compound 4")



Step 1: Methyl 6-bromo-1-methyl-4-(4,4,4-trifluoro-1-(3-fluoropyridin-2-yl)butyl)-1,4-dihydro pyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

To a solution of methyl 6-bromo-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (from Example 1 step 2, 221 mg, 0.71 mmol), 4,4,4-trifluoro-1-(3-fluoropyridin-2-yl)butan-1-ol (Intermediate 7, 215 mg, 0.97 mmol) and triphenylphosphane (471 mg, 1.80 mmol) in dry THF (10 mL) was vacuumed and backfilled with nitrogen, and this sequence was repeated three times. Diisopropyl azodicarboxylate (353 mg, 1.75 mmol) in THF (3 mL) was added dropwise at room temperature and the resulting solution was stirred for 2 h. Then the reaction was extracted EtOAc (50 mL).The extract was washed with brine, dried over anhydrous sodium sulfate and filtered.The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography with 0-40% EtOAc in hexane to afford methyl 6-bromo-1-methyl-4-(4,4,4-trifluoro-1-(3-fluoropyridin-2-yl)butyl)-1,4-dihydropyrazolo [3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (339 mg, 93% yield), LC-MS $[M+H]^+$ = 514,516.

Step 2: Methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(3-fluoropyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

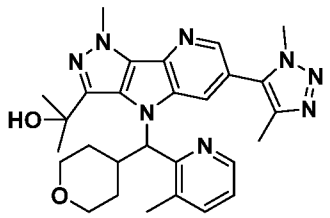
To a solution of methyl 6-bromo-1-methyl-4-(4,4,4-trifluoro-1-(3-fluoropyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (339 mg, 0.66 mmol) in DMF (10 mL) was added 1,4-dimethyl-5-(tributylstannyl)-1H-1,2,3-triazole (568 mg, 1.47mmol), tetrakis(triphenylphosphine)palladium (130 mg, 0.11 mmol), CuI (26 mg, 0.14 mmol) and TEA (243 mg, 2.20 mmol). The mixture was vacuumed and backfilled with nitrogen, and this sequence was repeated three times. The resulting mixture was stirred at 110 °C for 2 h. The reaction mixture was cooled to r.t., diluted with water (50 mL) and extracted with EtOAc (3×50 mL). After separation, the organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel chromatography using 0-6% MeOH in DCM to afford methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(3-fluoropyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (194 mg, 55% yield), LC-MS $[M+H]^+$ = 531.

Step 3:2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(3-fluoropyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol

MeMgBr (1M in THF, 3.7 mL,3.72 mmol) was slowly added to a solution of methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(3-fluoropyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (194 mg, 0.37 mmol) in dry THF (10 ml) at -30 °C under N_2 over 1 min. After addition, the reaction was warmed to r.t. and stirred for 2 hr. The reaction was quenched with sat. NH_4Cl, and extracted with EtOAc (30 mL). The organic layer was washed with sat. aqueous NaCl, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel chromatography using 0-6% MeOH in DCM to afford 2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(3-fluoropyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol (Compound 4, 101 mg, 53% yield), LC-MS $[M+H]^+$ = 531. ^1H NMR (400 MHz, DMSO-d_6) δ 8.55 (d, J = 4.6 Hz, 1H), 8.40 (d, J = 1.6 Hz, 1H), 7.76 – 7.66 (m, 1H), 7.58 – 7.47 (m, 2H), 7.09 (t, J = 7.0 Hz, 1H), 5.78 (s, 1H), 4.17 (s, 3H), 3.82 (s, 3H), 2.88 – 2.76 (m, 1H), 2.69 – 2.53 (m, 2H), 2.07 (s, 3H), 2.02 – 1.89 (m, 1H), 1.72 (s, 3H), 1.62 – 1.51 (m, 3H).

Example 5

2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol("Compound 5")



Step 1: Methyl 6-bromo-1-methyl-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

Following the procedure analogous to that described for the synthesis of methyl 6-bromo-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate, methyl 6-bromo-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (from Example 1 step2, 237 mg, 0.77 mmol), (3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methanol (Intermediate 5, 249 mg, 1.20 mmol) were converted to methyl 6-bromo-1-methyl-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (331 mg, 86% yield), LC-MS $[M+H]^+$= 498, 500.

Step 2: Methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

Following the procedure analogous to that described for the synthesis of methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-phenylbutyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate, methyl 6-bromo-1-methyl-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (331 mg, 0.66 mmol) and 1,4-dimethyl-5-(tributylstannyl)-1H-1,2,3 -triazole (528 mg, 1.37 mmol) were converted to methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (217 mg, 64% yield), LC-MS $[M+H]^+$ = 515.

Step 3:2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol

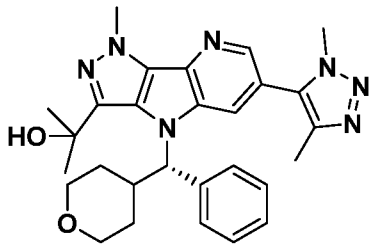
Following the procedure analogous to that described for the synthesis of 2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl) (tetrahydro -2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol, methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (217 mg, 0.42 mmol) was converted to 2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[

3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol (Compound 5, 115 mg, 53% yield), LC-MS $[M+H]^+$ = 515.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, J = 3.9 Hz, 1H), 8.36 (d, J = 1.2 Hz, 1H), 7.89 (s, 1H), 7.57 (d, J = 7.3 Hz, 1H), 7.26 (dd, J = 7.5, 4.8 Hz, 1H), 6.92 (d, J = 10.4 Hz, 1H), 5.97 (s, 1H), 4.16 (s, 3H), 3.85 (s, 3H), 3.80 (d, J = 8.5 Hz, 1H), 3.69 (d, J = 9.2 Hz, 1H), 3.33 (s, 1H), 3.28 (s, 1H), 3.12 (t, J = 11.5 Hz, 1H), 2.25 (d, J = 18.8 Hz, 3H), 2.11 (s, 3H), 1.72 (s, 3H), 1.67 (s, 1H), 1.66-1.60 (m, 1H), 1.57 (s, 3H), 1.44 – 1.31 (m, 1H), 0.46 (d, J = 12.3 Hz, 1H).

Example 6

(S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol("Compound 6")



Step 1: 5-bromo-2-(1-methyl-1H-pyrazol-5-yl)-3-nitropyridine

To a solution of 2,5-dibromo-3-nitropyridine (34.4 g,122 mmol) in THF (500 mL) and water (150 mL) was added (1-methyl-1H-pyrazol-5-yl)boronic acid (12.6 g, 99.7 mmol), Pd(dppf)Cl_2 (8.38 g, 10.3 mmol), and K_3PO_4 (42.3 g, 199.1mmol) under N_2. The mixture was vacuumed, backfilled with N_2 and this process was repeated three times. The resulting mixture was heated to reflux and stirred for 5 h under N_2. After cooling to r.t., the reaction mixture was poured into water and extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography using 10-30% EtOAc in hexane to afford 5-bromo-2-(1-methyl-1H-pyrazol-5-yl)-3-nitropyridine (9.47 g, 33.5 mmol, 34% yield), LC-MS $[M+H]^+$ = 283.

Step 2: 6-bromo-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine

A mixture of 5-bromo-2-(1-methyl-1H-pyrazol-5-yl)-3-nitropyridine (9.47 g, 33.5 mmol) and DPPE (22.8 g, 57.3 mmol) in 1,2-dichlorobenzene (100 mL) was heated to 180 °C and stirred for 4 h under N_2. The reaction was then cooled slowly to room temperature. The reaction mixture was concentrated under a reduced pressure. The crude product was purified by silica gel chromatography using 30-50% EtOAc in hexane to afford 6-bromo-1-methyl-1,4- dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine (4.12 g, 16.4 mmol, 49% yield), LC-MS $[M+H]^+$ = 251.

Step 3: (S)-6-bromo-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydro pyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine

To a solution of 6-bromo-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine (1.24 g, 4.96 mmol), (R)-phenyl(tetrahydro-2*H*-pyran-4-yl)methanol (2.52 g,13.1 mmol) and triphenylphosphane

(4.71 g, 18.0 mmol) in dry THF (30 mL) was added diisopropyl azodicarboxylate (4.02 g, 19.9 mmol) at r.t. under N_2. The resulting solution was refluxed for 2 h under N_2. After cooling to r.t., the reaction mixture was extracted with EtOAc (50 mL). The resulting organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography using 30-50% EtOAc in hexane to afford (S)-6-bromo-1-methyl-4-(phenyl (tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine (0.95 g, 2.23 mmol, 45%), LC-MS $[M+H]^+ = 425$.

Step 4: (S)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine

To a solution of (S)-6-bromo-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydro pyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine (0.95 g, 2.23mmol) in DMF (40 mL) was added 1,4-dimethyl-5-(tributylstannyl)-1*H*-1,2,3-triazole (2.51 g, 6.50 mmol), tetrakis(triphenylphosphine)palladium (0.54 g, 0.47 mmol), CuI (0.18 g, 0.95 mmol) and TEA (1.02 g, 9.26 mmol) under N_2. The mixture was vacuumed, backfilled with N_2 and this process was repeated three times. The resulting mixture was stirred at 85 °C for 3 h and then cooled to room temperature. The reaction mixture was poured into water and extracted with EtOAc (100 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel chromatography using 0-5% MeOH in DCM to afford (S)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine (0.63 g, 1.43 mmol, 64% yield), LC-MS $[M+H]^+ =$ 442.

Step 5: (S)-3-bromo-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine

N-bromosuccinimide (0.62 g, 3.48 mmol) was added in small batches to a solution of (S)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine (0.63 g, 1.43 mmol) in THF (20 mL) and water (10 mL) at room temperature over 10 min. After addition, the reaction was stirred at room temperature for 2 h. The reaction was quenched with sat. $NaHCO_3$ and extracted with EtOAc (100 mL). The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel chromatography using 0-3% MeOH in DCM to afford the expected (S)-3-bromo-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine (0.71 g, 1.36 mmol, 95%), LC-MS $[M+H]^+ = 520$.

Step 6:(S)-1-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)ethan-1-one

To a solution of (S)-3-bromo-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine (0.71 g, 1.36 mmol) in 1,4-dioxane (20 mL) was added tributyl(1-ethoxyvinyl)-stannane (1.08 g, 2.99 mmol), tetrakis(triphenylphosphine)palladium (0.27 g, 0.23mmol), cesium fluoride (0.71 g, 4.67 mmol) under N_2. The mixture was vacuumed, backfilled with N_2 and this process was repeated three times. The

resulting mixture was refluxed for 20 h. Then the solvent was taken off under a reduced pressure to afford a light yellow substance.

To this substance was added THF (10 mL) and followed by 2N HCl (2 mL) at room temperature , and stirred for 2 h. Then the reaction was quenched with sat. $NaHCO_3$ and extracted with EtOAc (100 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel chromatography using 0-5% MeOH in DCM to afford the expected (S)-1-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)ethan-1-one (390 mg, 0.81 mmol, 60% yield), LC-MS $[M+H]^+ = 484$.

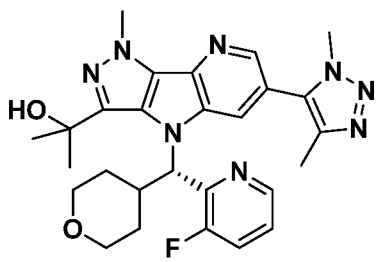
Step 6:(S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol

MeMgBr (1M in THF, 10.0 mL, 10.0 mmol) was dropwise added to a solution of (S)-1-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)ethan-1-one (390 mg, 0.81 mmol) in THF (30 ml) at -30 °C over 10 min under N_2. After addition, the reaction was stirred at room temperature for 2 h. The reaction was quenched with sat. NH_4Cl, and extracted with EtOAc (100 mL). The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel chromatography using 0-6% MeOH in DCM to afford the expected (S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol (Compound 6, 84 mg, 0.17 mmol, 44% yield), LC-MS $[M+H]^+ = 500$.

^1H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, J = 1.2 Hz, 1H), 7.94 (s, 1H), 7.71 (d, J = 7.6 Hz, 2H), 7.26 (m, 3H), 6.46 (d, J = 11.2 Hz, 1H), 5.81 (s, 1H), 4.15 (s, 3H), 3.85 (s, 3H), 3.52 – 3.39 (m, 2H), 3.29 – 3.19 (m, 2H), 2.17 (s, 3H), 2.00 (m, 1H), 1.71 (d, J = 13.2 Hz, 4H), 1.23 (s, 6H).

Example 7

(S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol("Compound 7")



Step 1: (S)-methyl 6-bromo-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

To a solution of methyl 6-bromo-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-

carboxylate (from Example 1 step 2, 409 mg, 1.32 mmol), (R)-(3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methanol (Enantiomer a1 from Example 2, 352 mg,1.67 mmol) and triphenylphosphane (0.52 g, 1.98 mol) in dry THF (30 mL) was added diisopropyl azodicarboxylate (0.49 g, 2.42 mmol) at r.t. under N_2. The resulting solution was refluxed for 2 hr under N_2. After cooling to r.t., the reaction mixture was extracted with EtOAc (50 mL). The resulting organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography using 30-50% EtOAc in hexane to afford (S)-methyl 6-bromo-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (442 mg, 0.88 mmol, 67% yield), LC-MS $[M+H]^+$ = 502.

Step 2: (S)-Methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate("Compound 7-2")

To a solution of (S)-methyl 6-bromo-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (442 mg, 0.88 mmol) in DMF (30 mL) was added 1,4-dimethyl-5-(tributylstannyl)-1*H*-1,2,3-triazole (680mg, 1.76mmol), tetrakis(triphenylphosphine)palladium (168 mg, 0.15 mmol), CuI (65 mg, 0.34 mmol) and TEA (0.92 g, 8.35 mmol) under N_2. The mixture was vacuumed, backfilled with N_2 and this process was repeated three times. The resulting mixture was stirred at 85 °C for 3 h and then cooled to room temperature. The reaction mixture was poured into water and extracted with EtOAc (50 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel chromatography using 0-5% MeOH in DCM to afford (S)-methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (Compound 7-2, 201 mg, 0.38 mmol, 43% yield), LC-MS $[M+H]^+$ = 519.

Step 3:(S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol

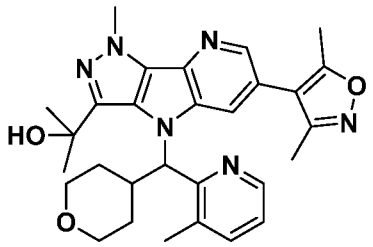
Following the procedure analogous to that described for the synthesis of 2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol, (S)-methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (0.20 g, 0.38 mmol) was converted to (S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol (Compound 7, 38 mg, 0.073 mmol, 19% yield), LC-MS[M+H]+ = 519.

^{1}H NMR (600 MHz, DMSO-d_6) δ 8.50 (d, J = 4.6 Hz, 1H), 8.40 (d, J = 1.6 Hz, 1H), 8.27 (d, J = 1.6 Hz, 1H), 7.71 (t, J = 9.3 Hz, 1H), 7.45 (dt, J = 8.5, 4.3 Hz, 1H), 6.99 (d, J = 10.9 Hz, 1H), 5.70 (s, 1H), 4.12 (s, 3H), 3.94 (s, 3H), 3.81 – 3.74 (m, 1H), 3.65 (dd, J = 11.3, 2.9 Hz, 1H), 3.26 (dd, J = 11.7, 9.9 Hz, 1H), 3.22 – 3.15 (m, 1H), 3.09 (t, J = 11.2 Hz, 1H), 2.21 (s, 3H), 1.70 (s, 3H), 1.59 (ddd, J = 25.2, 12.7,

4.6 Hz, 1H), 1.53 (s, 3H), 1.44 (d, J = 12.0 Hz, 1H), 1.41 – 1.32 (m, 1H), 0.52 (d, J = 12.5 Hz, 1H).

Example 8

2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl) methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol("Compound 8")



Step 1: Methyl 6-bromo-1-methyl-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl) methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

Following the procedure analogous to that described for the synthesis of methyl 6-bromo-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate, methyl 6-bromo-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b] pyridine-3-carboxylate (from Example 1 step 2, 200 mg, 0.65mmol) and (3-methylpyridin-2-yl) (tetrahydro-2H-pyran-4-yl)methanol (Intermediate 5, 184 mg, 0.89 mmol) were converted to methyl 6-bromo-1-methyl-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (210 mg, 0.42 mmol, 65%), LC-MS $[M+H]^+$ = 497.

Step 2: Methyl 6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

To a solution of methyl 6-bromo-1-methyl-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl) methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate(210 mg,0.42 mmol) in THF (20 mL) and water (5 mL), was added 3,5-dimethyl-4-(4,4,5,5- tetramethyl-1,3,2-dioxaborolan-2-yl) isoxazole (210 mg, 0.90 mmol), $Pd(dppf)Cl_2$ (112 mg, 0.14 mmol), and K_3PO_4 (428 mg, 2.02 mmol) under N_2. The mixture was vacuumed, backfilled with N_2 and this process was repeated three times. The resulting mixture was heated to reflux and stirred for 5 h under N_2. After cooling to r.t., the reaction mixture was poured into water and extracted with EtOAc (50 mL). The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography using 30-50% EtOAc in hexane to afford 6-(3,5-dimethylisoxazol -4-yl)-1-methyl-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (160 mg, 0.31 mmol, 73% yield), LC-MS $[M+H]^+$ = 515.

Step 3: 2-(6-(3,5-Dimethylisoxazol-4-yl)-1-methyl-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol

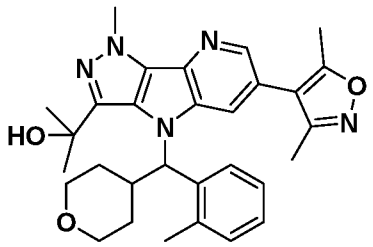
Following the procedure analogous to that described for the synthesis of 2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol, methyl 6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-((3-methyl pyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-c

arboxylate (160 mg, 0.31 mmol) was converted to 2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol (Compound 8, 33 mg, 0.064 mmol, 21% yield), LC-MS $[M+H]^+$ = 515.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (d, J = 4.4 Hz,1H), 8.27 (s, 1H), 7.71 (s, 1H), 7.56 (d, J = 7.2 Hz, 1H), 7.25 (m, 1H), 6.90 (d, J = 10.0 Hz, 1H), 5.96 (s, 1H), 4.15 (s, 1H), 4.11 (d, J = 6.0Hz, 3H), 3.80 (d, J = 10.8 Hz, 1H), 3.69 (d, J = 12.8 Hz, 1H), 3.36 (s, 2H), 3.27 – 3.20 (m, 1H), 3.13 (m, 3H), 2.64 (t, J = 1.6, 1.6 Hz, 3H), 2.31 (t, J = 1.6, 1.6 Hz, 3H), 2.19 (s, 2H), 2.12 (s, 1H), 1.74 – 1.62 (m, 6H).

Example 9

2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-((tetrahydro-2H-pyran-4-yl)(o-tolyl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol("Compound 9")



Step 1: Methyl 6-bromo-1-methyl-4-((tetrahydro-2H-pyran-4-yl)(o-tolyl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

Following the procedure analogous to that described for the synthesis of methyl 6-bromo-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate, methyl 6-bromo-1- methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b] pyridine-3-carboxylate (from Example 1 step 2, 200 mg, 0.65 mmol) and (tetrahydro-2H-pyran-4-yl) (o-tolyl) methanol (Intermediate 9, 191 mg,0.93 mmol) were converted to methyl 6-bromo-1-methyl-4-((tetrahydro-2H-pyran-4-yl)(o-tolyl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (280 mg, 0.56 mmol, 86%), LC-MS $[M+H]^+$ = 497.

Step 2: Methyl 6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-((tetrahydro-2H-pyran-4-yl)(o-tolyl) methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

To a solution of methyl 6-bromo-1-methyl-4-((tetrahydro-2H-pyran-4-yl)(o-tolyl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (280 mg, 0.56 mmol) in THF (20 mL) and water (5 mL) was added 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2 -dioxaborolan-2-yl)isoxazole (210mg, 0.90mmol), Pd(dppf)Cl_2 (102 mg, 0.12 mmol), and K_3PO_4 (389 mg, 1.83 mmol) under N_2. The mixture was vacuumed, backfilled with N_2 and this process was repeated three times. The resulting mixture was heated to reflux and stirred for 5 h under N_2. After cooling to r.t., the reaction mixture was poured into water and extracted with EtOAc (100 mL). The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography using 0-5% MeOH in DCM to afford methyl 6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-((tetrahydro-2H-pyran-4-yl)(o-tolyl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin

e-3-carboxylate (218 mg, 0.42 mmol, 75% yield), LC-MS $[M+H]^+ = 514$.

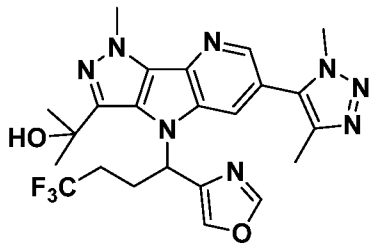
Step 3: 2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-((tetrahydro-2H-pyran-4-yl)(o-tolyl) methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol

Following the procedure analogous to that described for the synthesis of 2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5] pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol, methyl 6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-((tetrahydro-2H-pyran-4-yl)(o-tolyl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (218 mg, 0.42 mmol) was converted to 2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-((tetrahydro-2H-pyran-4-yl)(o-tolyl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol (Compound 9, 59mg, 0.11 mmol, 26% yield), LC-MS $[M+H]^+ = 514$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (d, J = 1.6Hz, 1H), 7.98 (d, J = 7.6 Hz, 1H), 7.48 (s, 1H), 7.32 (t, J = 7.2, 7.6 Hz, 1H), 7.18 (t, J = 7.6, 7.2Hz, 1H), 7.10 (d, J = 15.2 Hz, 1H), 6.79 (d, J = 10.8 Hz, 1H), 5.92 (s, 1H), 4.15 (s, 3H), 3.83 (d, J = 11.6 Hz, 1H), 3.72 (d, J = 10.8 Hz 1H), 3.45 (t, J = 11.6 Hz, 10.8 Hz, 1H), 3.17 (t, J = 11.2, 11.6 Hz, 2H), 2.23 (s, 3H), 2.04 (d, J = 2.8 Hz, 6H), 1.89 – 1.72 (m, 2H), 1.69 (d, J = 9.2 Hz, 6H), 1.51 – 1.31 (m, 2H).

Example 10

2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(oxazol-4-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol("Compound 10")



Step 1: Methyl 6-bromo-1-methyl-4-(4,4,4-trifluoro-1-(oxazol-4-yl)butyl)-1,4-dihydro pyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

Following the procedure analogous to that described for the synthesis of methyl 6-bromo-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate, methyl 6-bromo-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b] pyridine-3-carboxylate (from Example 1 step 2, 200 mg, 0.65 mmol) and 4,4,4-trifluoro-1-(oxazol-4-yl)butan-1-ol (Intermediate 10, 280 mg,1.43 mmol) were converted to methyl 6-bromo-1-methyl-4-(4,4,4-trifluoro-1-(oxazol-4-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (277 mg, 0.57 mmol, 87%), LC-MS $[M+H]^+ = 486$.

Step 2: Methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(oxazol-4-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

Following the procedure analogous to that described for the synthesis of methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-phenylbutyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate, methyl 6-bromo-1-methyl-4-(4,4,4-trifluoro-1-(oxazol-4-yl)butyl)-1,4-

dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (277mg, 0.57mmol) and 1,4-dimethyl-5-(tributylstannyl)-1*H*-1,2,3-triazole (485 mg, 1.26 mmol) were converted to methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(oxazol-4-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (211 mg, 0.42 mmol, 73% yield), LC-MS $[M+H]^+$ = 442.

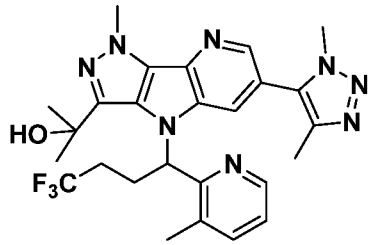
Step 3: 2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(oxazol-4-yl) butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol

Following the procedure analogous to that described for the synthesis of 2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol, methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(oxazol-4-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (211 mg, 0.42 mmol) was converted to 2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(oxazol-4-yl)butyl)- 1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol (Compound 10, 94 mg, 0.19 mmol, 45% yield), LC-MS $[M+H]^+$ = 503.

^{1}H NMR(400 MHz, DMSO-d_6) δ 8.38 (d, J = 42.4 Hz, 2H), 7.98 (s, 1H), 6.72 (s, 1H), 5.74 (s, 1H), 4.16 (s, 2H), 3.89 (s, 2H), 3.31 (s, 6H), 2.74 (s, 1H), 2.26 (s, 3H), 1.65 (s, 6H).

Example 11

2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(3-methylpyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol("Compound 11")



Step 1: Methyl 6-bromo-1-methyl-4-(4,4,4-trifluoro-1-(3-methylpyridin-2-yl)butyl)-1,4-dihydro pyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

Following the procedure analogous to that described for the synthesis of methyl 6-bromo-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate, methyl 6-bromo-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (from Example 6 step 2, 200 mg, 0.65 mmol) and 4,4,4-trifluoro-1-(3-methylpyridin-2-yl)butan-1-ol (Intermediate 11, 202 mg, 1.48mmol) and triphenylphosphane (387 mg, 1.48 mmol) were converted to methyl 6-bromo-1-methyl-4-(4,4,4-trifluoro-1-(3-methylpyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (257 mg, 0.50 mmol, 77%), LC-MS $[M+H]^+$ = 510.

Step 2: Methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(3-methylpyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

Following the procedure analogous to that described for the synthesis of methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-phenylbutyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate, methyl 6-bromo-1-methyl-4-(4,4,4-trifluoro-1-(3-methylpyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (257 mg, 0.50 mmol) and 1,4-dimethyl-5-(tributylstannyl)-1*H*-1,2,3-triazole (788 mg, 2.04 mmol) were converted to methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(3-methylpyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (200 mg, 0.38 mmol, 76% yield), LC-MS $[M+H]^+ = 527$.

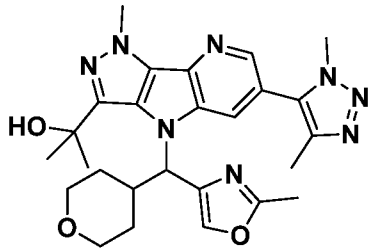
Step 3: 2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(3-methylpyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol

Following the procedure analogous to that described for the synthesis of 2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol, methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(3-methylpyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (200 mg, 0.38 mmol) was converted to 2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(3-methylpyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol (Compound 11, 89 mg, 0.17 mmol, 45% yield), LC-MS $[M+H]^+ = 527$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (d, J = 4.2 Hz, 1H), 8.27 (s, 1H), 7.69 (s, 1H), 7.56 (d, J = 7.6 Hz,1H), 7.25 (m, 1H), 6.95 (d, J = 9.8 Hz, 1H), 5.93 (s, 1H), 4.13 (s, 3H), 3.21 (s, 6H), 2.86 (s, 2H) 2.72 (s, 2H), 2.23 (s, 3H), 1.62 (d, J = 9.4 Hz, 6H).

Example 12

2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((2-methyloxazol-4-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol("Compound 12")



Step 1: (2-methyloxazol-4-yl)(tetrahydro-2H-pyran-4-yl)methanol

4-bromooxane (2.24 g, 13.6 mmol) was added dropwise to a stirred suspension of magnesium (683 mg, 29.1 mmol) and one crystal of iodine in THF (25 mL) at ambient temperature. The reaction mixture was stirred for 1h before it was cooled in an ice-water bath. 2-methyloxazole-4-carbaldehyde (1.00 g, 9.00 mmol) was added dropwise. The reaction mixture was then stirred overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride (40 mL) and diluted with ethyl acetate (100

mL). The product was extracted into the organic phase before the layers were separated. The aqueous layer was extracted with a second portion of ethyl acetate (50 mL), and the combined organics were dried over sodium sulfate. The volatiles were removed under reduced pressure. The crude reaction material was purified on silica gel column to afford (2-methyloxazol-4-yl)(tetrahydro-2H-pyran-4-yl)methanol (330 mg, 1.67 mmol, 19% yield) , LC-MS $[M+H]^+$ = 198.

Step 2: Methyl 6-bromo-1-methyl-4-((2-methyloxazol-4-yl)(tetrahydro-2H-pyran-4-yl) methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

To a solution of methyl 6-bromo-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (200 mg, 0.65 mmol), (2-methyloxazol-4-yl)(tetrahydro-2H-pyran-4-yl) methanol (Intermediate 12, 195 mg, 0.99 mmol) and triphenylphosphane (384 mg, 1.33 mmol) in dry THF (20 mL) was added DIAD (289 mg, 1.43 mmol) at 0 °C under N_2. After addition, the reaction was heated to 28 °C for 16 h. The reaction mixture was poured into water, and extracted with EtOAc (100 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography using 0~50% EtOAc in hexane to afford methyl 6-bromo-1-methyl-4- ((2-methyloxazol-4-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydro pyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (404 mg, crude), LC-MS$[M+H]^+$ = 489.

Step 3: Methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((2-methyloxazol-4-yl) (tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

To a solution of methyl 6-bromo-1-methyl-4-((2-methyloxazol-4-yl)(tetrahydro-2H-pyran-4-yl) methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (300 mg, 0.614 mmol) in DMF (10 mL) was added 1-methyl-4-(methyl)-5-(tributylstannyl)-1*H*-1,2,3-triazole (498 mg, 1.29 mmol), tetrakis(triphenylphosphine)palladium (92 mg, 0.08 mmol), CuI (29 mg, 0.15 mmol) and TEA (203 mg, 1.842 mmol). The mixture was degassed and flushed with nitrogen for three times and stirred at 110 °C for 16 h. The mixture was cooled to room temperature, diluted with water (50 mL) and extracted with EtOAc (3×50 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and the filtrated was concentrated under reduced pressure. The residue was purified by Prep-TLC with 5% MeOH in DCM to afford methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((2-methyloxazol-4-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (85 mg, 27% yield), LC-MS $[M+H]^+$ = 505.

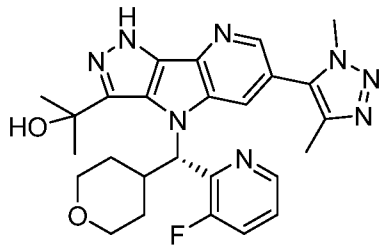
Step 4: 2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((2-methyloxazol-4-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol

Following the procedure analogous to that described for the synthesis of 2-(6-(3,5-dimethyl isoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydro pyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol, the methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((2-methyloxazol-4-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (85 mg, 0.17 mmol) was converted to 2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((2-methyloxazol-4-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3

',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol (Compound 12, 15mg, 18% yield), LC-MS [M+H$^+$] = 505. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (d, J = 3.2 Hz, 2H), 8.09 (s, 1H), 6.36 (d, J = 11.2 Hz, 1H), 5.67 (s, 1H), 4.14 (s, 3H), 4.02 (s, 3H), 3.82 (d, J = 8.1 Hz, 1H), 3.66 (d, J = 8.5 Hz, 1H), 3.17 – 3.04 (m, 1H), 2.97 (d, J = 11.2 Hz, 1H), 2.33 (s, 3H), 2.31 (s, 3H), 1.70 (s, 3H), 1.66 (s, 3H), 1.61 (s, 1H), 1.40 (dd, J = 12.3, 3.8 Hz, 1H), 1.26 (dd, J = 15.1, 6.4 Hz, 1H), 1.10 (s, 1H), 0.66 (d, J = 12.5 Hz, 1H).

Example 13

(S)-2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol("Compound 13")



Step 1: Methyl 1-(2-trimethylsilylethoxymethyl)pyrazole-3-carboxylate

To a solution of methyl 1H-pyrazole-3-carboxylate (20.1 g, 159 mmol) in THF (400 mL) in a three-neck round bottom flask was added NaH (8.20 g, 342 mmol) at r.t. The resulting mixture was stirred for 10 min under a N_2 atmosphere. The reaction mixture was cooled to 0 °C in an ice-water bath and followed by dropwise addition of SEMCl (29.1 g, 175 mmol) under N_2 atmosphere. Then the reaction mixture was slowly warmed to room temperature and continued stirring for 2 h. The reaction was quenched with sat. aq. NH_4Cl and extracted with EtOAc (100 mL). After separation, the organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel chromatography using 0~10% EtOAc in Hexane to afford methyl 1-(2-trimethylsilylethoxymethyl)pyrazole-3-carboxylate (29.3 g, 114 mmol, 71.7% yield) . LC/MS [M+H]$^+$ = 257.

Step 2: [5-Methoxycarbonyl-2-(2-trimethylsilylethoxymethyl)pyrazol-3-yl]boronic acid

To a solution of methyl 1-(2-trimethylsilylethoxymethyl)pyrazole-3-carboxylate, (29.10 g , 113.51 mmol) in THF (10mL) in a three-neck round bottom flask were added Dtbpy (113.51 mmol) and (1,5-cyclooctadiene)-(methoxy)iridium(I)dimer (2.71 g , 4.07 mmol) at r.t. The mixture was vacuumed and backfilled with N_2, and this sequence was repeated three times. The resulting mixture was added HBin (38.10 g, 289.32 mmol). Then the reaction mixture was slowly warmed to 55 °C and continued stirring for 1 h, then quenched with water (80 mL). The resulting mixture was concentrated under reduced pressure to give [5-methoxycarbonyl-2-(2-trimethylsilylethoxymethyl)pyrazol-3-yl]boronic acid (33.6 g, 98.6% yield) as a black substance, which was directly used in the next step without further purification. LC/MS [M+H]$^+$= 301.

Step 3: Methyl 5-(5-bromo-3-nitro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)pyrazole-3-carboxylate

To a three-neck bottom flask were added [5-methoxycarbonyl-2-(2-trimethylsilylethoxy methyl)pyrazol-3-yl]boronic acid (37.51 g, 124.92 mmol), 2,5-dibromo-3-nitro- pyridine (38.7 g, 137 m

mol), $Pd(dppf)Cl_2$, (4.63 g, 6.24 mmol), K_3PO_4 (57.5 g, 216 mmol) and THF (400 mL) under N_2. The mixture was purged with a N_2 stream for 3 min , attached with a condenser, then warmed to 38 °C and stirred for 3 h under a N_2 atmosphere. The reaction mixture was cooled to room temperature, poured into water (300 mL) and extracted with EtOAc (3×200 mL). The collected organic phases were washed with brine, dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator. The resulting residue was purified by a silica gel chromatography eluting with 0-40% EtOAC in hexane to afford methyl 5-(5-bromo-3-nitro-2-pyridyl)-1-(2-trimethylsilyle thoxymethyl)pyrazole-3-carboxylate (17.5 g, 30.6% yield). LC/MS $[M+H]^+$ = 458.

Step 4: Methyl 6-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

To a three-neck round bottom flask was added methyl 5-(5-bromo-3-nitro-2-pyridyl)-1-(2-trimethyl silylethoxymethyl)pyrazole-3-carboxylate (15.0 g, 32.8 mmol), Triethyl phosphite (10.5 g, 63.4 mmol) and 1,2-Dichlorobenzene(160 mL) under N_2. The mixture was purged with a N_2 stream for 3 min, attached with a condenser, then warmed to 140 °C and stirred for 2 h under a N_2 atmosphere. The reaction mixture was cooled to room temperature, then poured into water (200 mL) and extracted with EtOAc (3×150 mL). The collected organic phases were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography eluting with 0-10% EtOAc in hexane to afford methyl 6-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (3.40 g, 24.3% yield). LC/MS $[M+H]^+$ = 426.

Step 5: (S)-Methyl 6-bromo-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

To a three-neck round bottom flask were added methyl 6-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (2.01 g, 4.73 mmol), (R)-(3-fluoro-2-pyridyl)-tetrahydropyran-4-yl-methanol (Enantiomer a1, 1.40 g, 6.63 mmol), 2-(diphenylphosphanyl)pyridine (3.47 g,13.19 mmol) and THF (30 mL) under N_2. The mixture was purged with a N_2 stream for 3 min, followed by dropwise addition of DTAD (3.04 g, 13.19 mmol) under N_2 atmosphere. Then the reaction mixture was slowly warmed to 32 °C and continued stirring for 2 h. The reaction mixture was cooled to room temperature, poured into 4N HCl (30 mL) and extracted with EtOAC (2×60 mL). The collected organic phases were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography eluting with 0-20% EtOAc in hexane to afford (S)-methyl 6-bromo-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (3.02 g, 74% yield). LC/MS $[M+H]^+$ = 619.

Step 6: (S)-Methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

To a three-neck bottle was added 1,4-dimethyltriazole (312 mg , 3.21 mmol), (S)-Methyl 6-bromo-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (1.51 g , 2.38 mmol), Bis(triphenylphosphine) palladium(II) chloride (167 mg, 238 umol), tetramethylammonium acetate (634 mg, 4.76 mmol) and DMF (15 mL) under N_2. The mixture was purged with a N_2 stream for 3 min, attached with a condenser, then warmed to 110 °C and stirred for 16 h under a N_2 atmosphere. The reaction mixture was cooled to room temperature, poured into water (30 mL) and extracted with EtOAC (3×20mL). The collected organic phases were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography eluting with 0-75% EtOAc in hexane to afford (S)-methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (700 mg, 48% yield) as a brown substance. LC/MS $[M+H]^+$ = 635.

Step 7: (S)-Methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

To a vial were added (S)-methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (98 mg, 154 umol), 0.8 mL HCl (12N) and 0.8 mL EtOH. The mixture was warmed to 75 °C and stirred for 5 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was purified by a thin layer chromatography with 5% MeOH in DCM as a developing solvent to afford (S)-methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (62 mg, 80% yield). LC/MS $[M+H]^+$ = 505.

Step 8: (S)-2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol

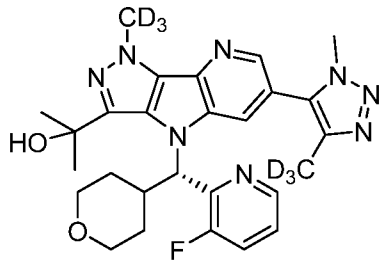
To a vial was added (S)-methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (62 mg, 0.123 mmol), The reaction mixture was cooled to 0 °C in an ice-water bath, followed by dropwise addition of 1 mL MeMgBr in Et_2O (3M) under N_2 atmosphere. Then the reaction mixture was slowly warmed to room temperature and continued stirring for 1 h. The reaction was quenched with sat. NH_4Cl. The reaction mixture was concentrated under reduced pressure. The resulting residue was purified by a thin layer chromatography with 5% MeOH in DCM as a developing solvent to afford (S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol (Compound 13, 34 mg , 54.8% yield). LC/MS $[M+H]^+$ = 505.

^1H NMR (400 MHz, MeOD) δ 8.50 (s, 1H), 8.49 (s, 1H), 8.35 (s, 1H), 7.56 (t, J = 9.1 Hz, 1H), 7.40 (dt, J = 8.4, 4.3 Hz, 1H), 7.15 (d, J = 10.1 Hz, 1H), 4.02 (s, 3H), 3.91 (d, J = 11.2 Hz, 1H), 3.79 (d, J = 8.1 Hz, 1H), 3.45 (d, J = 22.8 Hz, 1H), 3.25 (d, J = 12.5 Hz, 2H),

3.13 (s, 1H), 2.32 (s, 3H), 1.82 (d, J = 17.7 Hz, 3H), 1.76 (dd, J = 12.9, 4.1 Hz, 1H), 1.70 (s, 3H), 1.60 (s, 2H), 0.71 (d, J = 11.0 Hz, 1H).

Example 14

(S)-2-(4-((3-Fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-(methyl-d3)-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol("Compound 14")



Step 1: (S)-Methyl 4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

To a three-neck round bottom flask were added 1-methyl-4-(methyl-d3)-1H-1,2,3-triazole (622 mg, 6.22 mmol), (S)-methyl 6-bromo-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (from Example 13 step 5, 1.42 g, 2.24 mmol), Bis(triphenylphosphine) palladium(II) chloride (345 mg, 492 umol), tetramethylammonium acetate (820 mg, 6.16 mmol) and DMF (15 mL) under N_2. The mixture was purged with a N_2 stream for 3 min, attached with a condenser, then warmed to 110 °C and stirred for 16 h under a N_2 atmosphere. The reaction mixture was cooled to room temperature, poured into water (30 mL) and extracted with EtOAc (3x20 mL). The collected organic phases were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography eluting with 0-75% EtOAc in hexane to afford (S)-methyl 4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (750 mg, 54 % yield), LC-MS $[M+H]^+$ = 638.

Step 2: (S)-Methyl 4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

To a vial was added (S)-methyl 4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (750 mg, 1.18 mol), 7 mL HCl (12 N) and 7 mL EtOH. The mixture warmed to 75 °C and stirred for 5 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was purified by Prep-TLC with 5% MeOH in DCM as a developing solvent to afford (S)-methyl 4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]

pyridine-3-carboxylate (450 mg, 75% yield), LC-MS $[M+H]^+$ = 508.

Step 3: (S)-Methyl 4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-(methyl-d3)-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

To a solution of (S)-methyl 4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (601 mg , 1.18 mmol) in DMF (6 mL) were added Cs_2CO_3 (1.16 g, 3.56 mmol) in a vial at r.t., followed by dropwise addition of CD_3I (215 mg, 1.48 mmol) under N_2 atmosphere. Then the reaction mixture was slowly warmed to 60 °C and continued to stir for 2 h. The reaction was quenched with 10 mL HCl (1N) and extracted with EtOAc (10 mL). After separation, the organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by Prep-TLC using 10% MeOH in DCM as a developing solvent to afford (S)-methyl 4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl) methyl)-1-(methyl-d3)-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (150 mg, 24% yield) . LC/MS $[M+H]^+$ = 525.

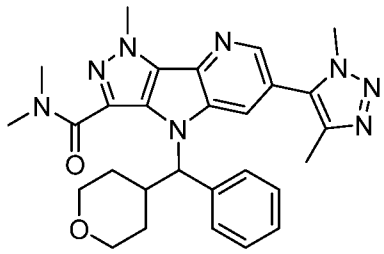
Step 4: (S)-2-(4-((3-Fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-(methyl-d3)-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol

To a vial was added (S)-methyl 4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-(methyl-d3)-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (148 mg, 0.282 mmol) and THF (10ml). The reaction mixture was cooled to 0 °C in an ice-water bath, followed by dropwise addition of 1.5 mL MeMgBr (3M in THF, 4.5 mmol) under N_2 atmosphere. Then the reaction mixture was slowly warmed to room temperature and continued stirring for 1 h. The reaction was quenched with sat. NH_4Cl. The reaction mixture was concentrated under reduced pressure. The resulting residue was purified by a reverse phase flash chromatography to afford (S)-2-(4-((3-Fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-(methyl-d3)-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol (Compound 14, 93 mg , 63% yield). LC/MS $[M+H]^+$ = 525.

^1H NMR (400 MHz, DMSO-d_6) δ 8.52 (d, J = 4.6 Hz, 1H), 8.41 (d, J = 1.7 Hz, 1H), 8.29 (d, J = 1.6 Hz, 1H), 7.78 – 7.66 (m, 1H), 7.47 (dt, J = 8.5, 4.3 Hz, 1H), 7.01 (d, J = 10.8 Hz, 1H), 5.69 (s, 1H), 3.96 (s, 3H), 3.80 (d, J = 9.6 Hz, 1H), 3.67 (dd, J = 11.0, 2.5 Hz, 1H), 3.33 – 3.24 (m, 1H), 3.20 (d, J = 11.1 Hz, 1H), 3.12 (t, J = 11.3 Hz, 1H), 1.73 (s, 3H), 1.68 – 1.59 (m, 1H), 1.56 (s, 3H), 1.47 (d, J = 12.5 Hz, 1H), 1.43 – 1.34 (m, 1H), 0.55 (d, J = 12.5 Hz, 1H).

Example 15

6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-N,N,1-trimethyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxamide("Compound 15")



Step1: Methyl 6-bromo-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydro pyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

To a solution of methyl 6-bromo-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (from **Example 1 step 2**, 1.00 g , 3.23 mmol) , phenyl(tetrahydro-2H-pyran-4-yl)methanol (933 mg , 4.85 mmol) and Triphenyl phosphine (1.29 g , 6.82 mmol) in dry THF (60 mL) was added DIAD (600 mg , 2.97 mmol) at r.t. under N_2. The reaction system was stirred for 3 hours. The reaction mixture was poured into water and extracted with EtOAc (400 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography using 5-30% EtOAc in hexane to afford of methyl 6-bromo-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine -3-carboxylate (1.31 g , 83% yield). LC/MS $[M+H]^+$ = 483,485.

Step 2: Methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

Following the procedure analogous to that described in **Step 4** for the synthesis of **Example 6,** methyl 6-bromo-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5] pyrrolo[3,2-b]pyridine-3-carboxylate (1.95 g, 4.04mmol) and 1,4-dimethyl-5-(tributylstannyl)-1*H*-1,2,3-triazole (2.81 g, 7.27 mmol) were converted to methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carb oxylate (1.29 g, 2.59 mmol, 64% yield), LC-MS $[M+H]^+$ = 500.

Step 3: 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl) methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylic acid

To a solution of methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (148 mg, 0.30 mmol) in methanol (5 mL) and H_2O (2 mL), was added LiOH (74 mg, 3.09 mmol). The reaction mixture was stirred at ambient temperature for 16 h. The mixture was poured into water (10 mL), adjusted pH=7 with 4N HCl aqueous and extracted with EtOAc (2×50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to afford the crude 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylic acid (143 mg, crude), LC-MS $[M+H]^+$ = 486.

Step 4: 6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carbonyl chloride

To a solution of crude 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylic acid (143 mg, 0.30 mmol) in DCM (5 mL) was added $SOCl_2$ (2 mL). The reaction mixture was stirred at ambient temperature for 4 h. The mixture was concentrated under reduced pressure to afford the crude 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carbonyl chloride (163 mg, crude).

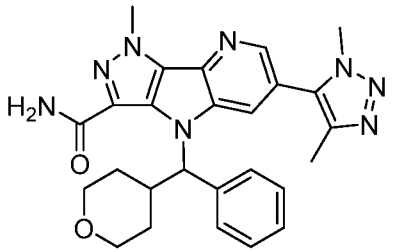
Step 5: 6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-N,N,1-trimethyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxamide

To a solution of crude 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carbonyl chloride (54 mg, 0.10 mmol) in THF (3 mL), dimethylamine (126 mg, 2.53 mmol) was added and then stirred at ambient temperature for 1 hour. The mixture was concentrated under vacuum and the residue was purified by Prep-HPLC to afford 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-N,N,1-trimethyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxamide (Compound 15, 15 mg, 29% yield for three steps), LC-MS $[M+H]^+ = 513$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H), 8.33 (s, 1H), 7.66 (s, 1H), 7.65 (s, 1H), 7.31-7.28 (m, 2H), 7.24-7.20 (m, 1H), 5.92 (d, J = 10.8 Hz, 1H), 4.25 (s, 3H), 3.96 (s, 3H), 3.86-3.78 (m, 2H), 3.37-3.20 (m, 3H), 3.14 (s, 6H), 2.25 (s, 3H), 1.51-1.48 (m, 1H), 1.41-1.18 (m, 3H).

Example 16

6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxamide("Compound 16")



Step1: 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxamide

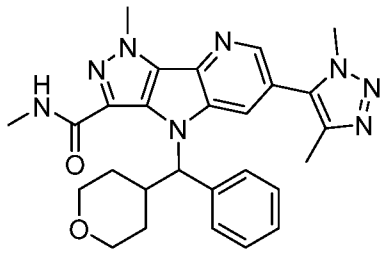
To a solution of ammonia (25% in 1,4-dioxane, 5 mL) was added a solution of crude 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carbonyl chloride (from **Example 15 step 4**, 52 mg, 0.10 mmol) in THF (3 mL). The mixture was stirred at ambient temperature for 1 hour. The mixture was concentrated under vacuum and the residue was purified by Prep-HPLC to afford 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxamide (16 mg , 33% yield), LC-MS $[M+H]^+ = 485$.

^{1}HNMR (400 MHz, DMSO-d_6) δ 8.44 (s, 1H), 8.19 (s, 1H), 7.80 (s, 1H), 7.67 (d, J = 7.6 Hz, 2H), 7.53 (s, 1H), 7.31 (t, J = 7.6 Hz, 2H), 7.22-7.20 (m, 1H), 6.92 (d, J = 11.2 Hz, 1H), 4.28 (s, 3H), 3.91 (s,

3H), 3.86 (d, J = 11.2 Hz, 1H), 3.75 (d, J = 10.8 Hz, 1H), 3.46-3.38 (m, 2H), 3.29-3.22 (m, 1H), 2.22 (s, 3H), 1.69 (d, J = 12.4 Hz, 1H), 1.40-1.23 (m, 2H), 1.03 (d, J = 12.4 Hz, 1H).

Example 17

6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-N,1-dimethyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxamide("Compound 17")



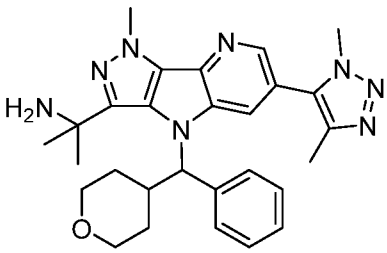
Step1: 6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-N,1-dimethyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxamide

To a solution of crude 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carbonyl chloride (from **Example 15 step 4**, 55 mg, 0.10 mmol) in THF (3 mL), was added a solution of methylamine in THF (3M, 3mL). The mixture was stirred at ambient temperature for 1 hour. The mixture was concentrated under vacuum and the residue was purified by Prep-HPLC to afford 12 mg of 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-N,1-dimethyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxamide (Compound 17, 11 mg， 24% yield of three steps), LC-MS $[M+H]^+$ = 499.

^{1}HNMR (400 MHz, DMSO-d_6) δ 8.44-8.41 (m, 2H), 8.21 (d, J = 1.2 Hz, 1H), 7.67 (d, J = 7.2 Hz, 2H), , 7.31 (t, J = 7.6 Hz, 2H), 7.22 (d, J = 7.6 Hz, 1H), 6.92 (d, J = 11.2 Hz, 1H), 4.28 (s, 3H), 3.91 (s, 3H), 3.86 (d, J = 11.2 Hz, 1H), 3.75 (d, J = 10.8 Hz, 1H), 3.46-3.38 (m, J = 8.2 Hz， 2H), 3.29-3.22 (m, 1H), 2.89 (d, J = 4.8 Hz, 3H), 2.22 (s, 3H), 1.69 (d, J = 12.4 Hz, 1H), 1.40-1.23 (m, 2H), 1.03 (d, J = 12.8 Hz, 1H).

Example 18

2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-amine("Compound 18")



Step1: 2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol

Following the procedure analogous to that described in **Step 5** for the synthesis of **Example 1,** methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-

1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (from **Example 15 step 2**, 125 mg, 0.250 mmol) was converted to 2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol (94 mg, 75% yield), LC-MS $[M+H]^+ = 499$.

Step 2: 3-(2-Azidopropan-2-yl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl (tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine

To a solution of 2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol (94 mg, 0.19 mmol) in DCM (3 mL) was added $TMSN_3$ (62 mg, 0.54 mmol) at 0 °C under N_2. The mixture was stirred at 0 °C for 10 min and $BF_3.OEt_2$ (118 mg, 0.83 mmol) was added. The mixture was stirred at ambient temperature for 2 days. The mixture was added to sat. aqueous $NaHCO_3$ (5 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under a rotary vacuum to afford 3-(2-Azidopropan-2-yl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl (tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine (110 mg, crude).

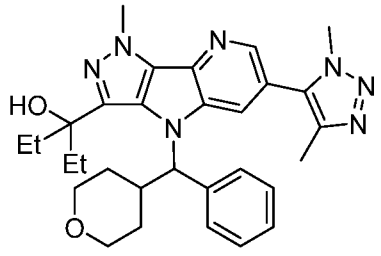
Step 3: 2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-amine

To a solution of the crude 3-(2-azidopropan-2-yl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine (110 mg, 0.19 mmol) in methanol (3 mL) was added wet Pd/C (20 mg , 18% w/w). The mixture was vacuumed, back filled with H_2, and this sequence was repeated three times. The resulting mixture was stirred at ambient temperature for 3h. The mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by Prep-HPLC to afford 2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propa n-2-amine (Compound 18, 20 mg, 21% yield for two steps), LC-MS $[M+H]^+ = 499$.

^{1}HNMR (400 MHz, DMSO-d_6) δ 9.08-8.48 (br, J = 10.2 Hz,2H), 8.39 (s, 1H), 7.86 (s, 1H), 7.62-7.60 (m, 2H), 7.34-7.30 (m, J = 6.5 Hz,2H), 7.26-7.22 (m, J = 9.3 Hz, 1H), 6.92 (d, J = 11.2 Hz, 1H), 4.19 (s, 3H), 3.88-3.85 (m, J = 8.45Hz, 1H), 3.82 (s, 3H), 3.74-3.71 (m, 1H), 3.50-3.44 (m, 1H), 3.34-3.20 (m, J = 7.5 Hz,2H), 2.14 (s, 3H), 1.90-1.80 (m, J = 7.3 Hz,1H), 1.71 (s, 6H), 1.60-1.43 (m, 2H), 0.80-0.78 (m, 1H).

Example 19

3-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)pentan-3-ol("Compound 19")

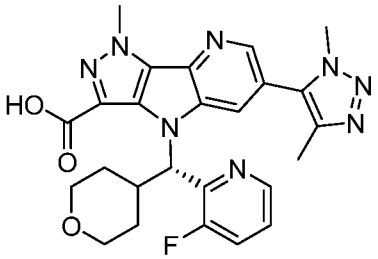


To a solution of methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (from **Example 15 step 2**, 103 mg, 0.21 mmol) in THF (3 mL) was added EtMgBr (1 M in THF, 0.2 mL), The mixture was stirred at ambient temperature for 1h. The mixture was poured into water (20 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were dried over Na_2SO_4, and concentrated on a rotary vacuum evaporator. The residue was purified by Prep-HPLC to afford 3-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)pentan-3-ol (Compound 19, 38 mg, 34% yield), LC-MS $[M+H]^+ = 528$.

^{1}HNMR (400 MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.23 (s, 1H), 7.66 (d, J = 7.2 Hz, 2H), 7.33 (t, J = 7.2 Hz, 2H), 7.26-7.22 (m,1H), 6.53 (d, J = 11.6 Hz, 1H), 5.40-5.31 (m, 1H), 4.31 (s, 3H), 3.91 (s, 3H), 3.90-3.85 (m, 1H), 3.77-3.74 (m,1H), 3.48-3.37 (m, 2H), 3.29-3.23 (m, 1H), 2.51 (m, 4H), 2.21 (s, 3H), 1.76-1.73 (m, 1H), 1.41 (t, J = 6.8 Hz, 6H), 1.37-1.25 (m, 2H), 1.07-1.04 (m, 1H).

Example 20

(S)-6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylic acid("Compound 20")



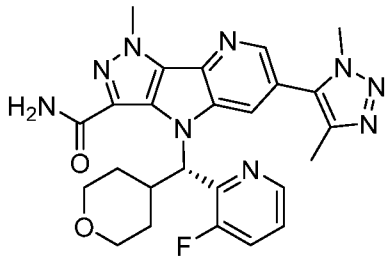
To a solution of (S)-methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (from **Example 7 step 2**, 36 mg, 0.069 mmol) in MeOH (5 ml) and H_2O (10 ml) was added LiOH (28 mg , 1.17 mmol). The resulting mixture was stirred at 25 °C for 1 hr. The reaction mixture was adjusted pH to 1 with CH_3COOH and extracted with EtOAc (10 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel chromatography using 0-5% MeOH in DCM to afford (S)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylic acid (Compound 20, 8 mg, 0.016 mmol, 23% yield), LC-MS $[M+H]^+ = 505$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (d, J = 4.5 Hz, 1H), 8.48 (d, J = 1.0 Hz, 1H), 8.15 (s, 1H), 7.67 (t, J = 9.0 Hz, 1H), 7.47 (dt, J = 8.3, 4.3 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 4.31 (d, J = 14.4 Hz, 3H), 3.92 (s, 3H), 3.82 (d, J = 9.6 Hz, 1H), 3.72 (d, J = 9.9 Hz, 1H), 3.37 (d, J = 10.5 Hz, 2H), 3.22 (t, J = 11.3 Hz, 1H), 2.18 (s, 3H), 1.63 (d, J = 11.9 Hz, 1H), 1.53 – 1.40 (m, 2H), 1.37 – 1.24 (m, 1H), 0.83 (d, J = 12.1 Hz, 1H).

Example 21

6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)met

hyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxamide("Compound 21")

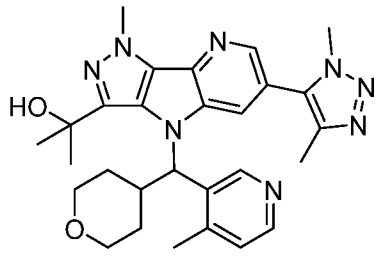


To a solution of (S)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylic acid (from **Example 20**, 100 mg, 0.20 mmol) in DMF (15 mL) was added HATU (68 mg, 0.18 mmol), NH_4Cl (48 mg, 0.90 mmol) and DIEA (72 mg, 0.56 mmol) under N_2. The mixture was vacuumed, backfilled with N_2, and this sequence was repeated three times. The resulting mixture was stirred at 25 °C for 1.5 hr. The reaction mixture was poured into water and extracted with EtOAc (100 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel chromatography using 0-5% MeOH in DCM to afford (S)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxamide (Compound 21, 10 mg, 0.020 mmol, 10% yield), LC-MS $[M+H]^+$= 504.

^1H NMR (400 MHz, DMSO-d_6) δ 8.57 (d, J = 4.6 Hz, 1H), 8.47 (d, J = 1.6 Hz, 1H), 8.09 (d, J = 1.6 Hz, 1H), 7.75 (s, 1H), 7.66 (t, J = 8.8 Hz, 1H), 7.49 (s, 1H), 7.46 (dd, J = 8.5, 4.3 Hz, 1H), 7.37 (d, J = 10.8 Hz, 1H), 4.28 (s, 3H), 3.91 (s, 3H), 3.83 (d, J = 9.6 Hz, 1H), 3.72 (d, J = 11.6 Hz, 1H), 3.38 (s, 2H), 3.21 (t, J = 11.1 Hz, 1H), 2.17 (s, 3H), 1.64 (d, J = 12.3 Hz, 1H), 1.49 (qd, J = 12.4, 4.3 Hz, 1H), 1.33 (ddd, J = 15.9, 12.3, 4.2 Hz, 1H), 0.78 (d, J = 12.2 Hz, 1H).

Example 22

2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methylpyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol("Compound 22")



Step1: Methyl 6-bromo-1-methyl-4-((4-methylpyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

To a solution of methyl 6-bromo-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (from **Example 1 Step 2**, 400 mg , 1.29 mmol) , (4-methylpyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methanol (**Intermediate 13**, 600 mg , 2.89 mmol) and Triphenyl phosphine (850 mg , 3.24

mmol) in dry THF (30 mL) was added DIAD(600 mg , 2.97 mmol) at r.t. under N_2 . The mixture was stirred for 18 hours. The reaction mixture was poured into water and extracted with EtOAc (200 mL). The resulting organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography using 5-50% EtOAc in hexane to afford methyl 6-bromo-1-methyl-4-((4-methylpyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methyl) -1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (170 mg , 26.35% yield), LC-MS $[M+H]^+$ = 498,500.

Step2: Methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((4-methylpyridin-3-yl) (tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxy late

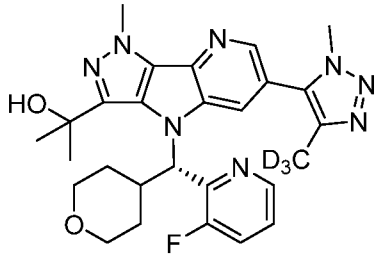
Following the procedure analogous to that described in **Step 2** for the synthesis of **Example 3,** methyl 6-bromo-1-methyl-4-((4-methylpyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydro pyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate(170 mg , 0.34 mmol) in DMF (5 mL) and 1,4-dimethyl-5-(tributylstannyl)-1H-1,2,3-triazole (274 mg, 0.71 mmol) were converted to methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((4-methylpyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (80 mg , 47.00% yield). LC/MS $[M+H]^+$ = 514.

Step3: 2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methylpyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol

Following the procedure analogous to that described in **Step 3** for the synthesis of **Example 3,** methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((4-methylpyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (130 mg, 0.26 mmol) was converted to 2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methylpyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol (Compound 22, 20 mg). LC/MS $[M+H]^+$ = 514.

Example 23

2-(4-((3-Fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol("Compound 23")



Step 1: (S)-Methyl 4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

To a solution of (S)-methyl 6-bromo-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (from **Example 7 Step 1**, 200 mg, 0.40 mmol) in DMF (30 mL) was added 1-methyl-4-(methyl-d3)-5-(tributylstannyl)-1H-1,2,3-triazole (378 mg, 0.97 mmol), tetrakis(triphenylphosphine)palladium (148 mg , 0.13 mmol), CuI (40 mg , 0.21 mmol) and TEA (415 mg, 3.77 mmol) under N_2. The mixture was vacuumed, backfilled with N_2 and this process was repeated three times. The resulting mixture was stirred at 85 °C for 3 hr and then cooled to room temperature. The reaction mixture was poured into water and extracted with EtOAc (100 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel chromatography using 0-5% MeOH in DCM to afford (S)-methyl 4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (132 mg, 0.25 mmol, 63% yield), LC-MS $[M+H]^+ = 522$.

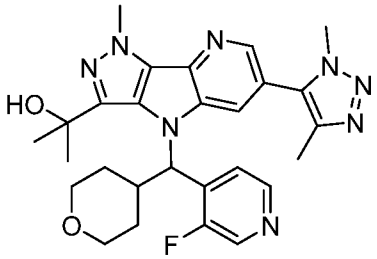
Step 2: (S)-2-(4-((3-Fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol

Following the procedure analogous to that described in **Step 3** for the synthesis of **Example 3,** (S)-methyl 4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (132 mg , 0.25 mmol) was converted to (S)-2-(4-((3-Fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol (Compound 23, 51 mg, 0.098 mmol, 39% yield), LC-MS $[M+H]^+ = 522$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (t, J = 5.5 Hz, 1H), 8.41 (d, J = 1.4 Hz, 1H), 8.29 (d, J = 1.2 Hz, 1H), 7.72 (t, J = 9.2 Hz, 1H), 7.47 (dt, J = 8.4, 4.3 Hz, 1H), 7.01 (d, J = 10.8 Hz, 1H), 5.70 (s, 1H), 4.14 (s, 3H), 3.96 (s, 3H), 3.80 (d, J = 9.4 Hz, 1H), 3.67 (d, J = 8.7 Hz, 1H), 3.24 (dd, J = 27.1, 11.1 Hz, 2H), 3.12 (t, J = 11.5 Hz, 1H), 1.73 (s, 3H), 1.62 (dd, J = 12.5, 3.9 Hz, 1H), 1.56 (s, 3H), 1.43 (m, 2H), 0.55 (d, J = 12.4 Hz, 1H).

Example 24

2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-4-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol("Compound 24")



Step 1: Methyl 6-bromo-4-((3-fluoropyridin-4-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

Following the procedure analogous to that described in **Step 1** for the synthesis of **Example 3,** methyl 6-bromo-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (from **Example 1 Step2**, 202 mg, 0.65 mmol) and (3-fluoropyridin-4-yl)(tetrahydro-2H-pyran -4-yl)methanol (**Intermediate 14**, 184 mg, 0.87 mmol) were converted to methyl 6-bromo-4-((3-fluoropyridin-4-yl) (tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carb oxylate (259 mg, 0.52 mmol, 80% yield), LC-MS $[M+H]^+ = 502$.

Step 2: Methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-4-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

Following the procedure analogous to that described in **Step 2** for the synthesis of **Example 3,** methyl 6-bromo-4-((3-fluoropyridin-4-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydro pyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (259 mg, 0.52 mmol) in DMF (30 mL) and 1,4-dimethyl-5-(tributylstannyl)-1H-1,2,3-triazole (383 mg, 0.98 mmol) were converted to methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-4-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-met hyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (178 mg, 0.34 mmol, 65% yield), LC-MS $[M+H]^+ = 519$.

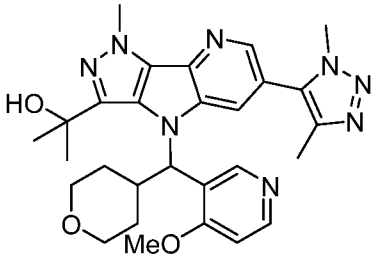
Step 3:2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-4-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol

Following the procedure analogous to that described in **Step 3** for the synthesis of **Example 3,** methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-4-yl)(tetrahydro-2H-pyran-4-yl) methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (178 mg , 0.34 mmol) was converted to 2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-4-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol (Compound 24, 63 mg, 0.13 mmol, 38% yield), LC-MS $[M+H]^+ = 519$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, J = 4.7 Hz, 2H), 8.41 (d, J = 1.4 Hz, 1H), 8.02 (t, J = 5.8 Hz, 1H), 7.92 (s, 1H), 6.89 (d, J = 11.1 Hz, 1H), 5.77 (s, 1H), 4.15 (s, 3H), 3.86 (s, 3H), 3.74 (d, J = 8.5 Hz, 1H), 3.41 (t, J = 11.1 Hz, 1H), 3.22 (m, 2H), 2.16 (s, 3H), 1.70 (s, 3H), 1.66 (d, J = 13.6 Hz, 2H), 1.58 (s, 3H), 1.46 (dd, J = 20.5, 8.9 Hz, 2H), 0.75 (d, J = 12.8 Hz, 1H).

Example 25

2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methoxypyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol("Compound 25")



Step 1: Methyl 6-bromo-4-((4-methoxypyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-

methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

To a solution of methyl 6-bromo-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (from **Example 1 Step 2**, 142 mg, 0.46 mmol), (4-methoxypyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methanol (**Intermediate 16**, 135 mg , 0.60 mmol) and triphenylphosphane (284 mg, 1.08 mmol) in dry THF (30 mL) was added diisopropyl azodicarboxylate (243 mg, 1.20 mmol) at r.t. under N_2. The resulting solution was refluxed for 2 hr under N_2. After cooling to r.t., the reaction mixture was poured into EtOAc (50 mL) and washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography using 30-50% EtOAc in hexane to afford methyl 6-bromo-4-((4-methoxypyridin-3-yl)(tetrahydro-2H-pyran-4-yl) methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (200 mg, 0.39 mmol, 85% yield), LC-MS $[M+H]^+$ = 514.

Step 2: Methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methoxypyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylat e

Following the procedure analogous to that described in **Step 2** for the synthesis of **Example 3,** methyl 6-bromo-4-((4-methoxypyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydro pyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (169 mg, 0.33 mmol) and 1,4-dimethyl-5-(tributylstannyl)-1H-1,2,3-triazole (318 mg, 0.82 mmol) were converted to methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methoxypyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydr opyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (109 mg, 0.21 mmol, 64% yield), LC-MS $[M+H]^+$ = 531.

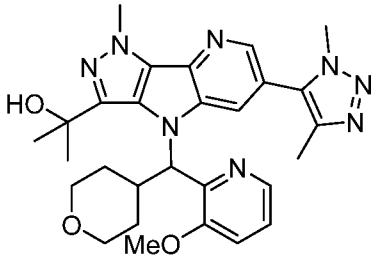
Step 3:2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methoxypyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol

Following the procedure analogous to that described in **Step 3** for the synthesis of **Example 3,** methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methoxypyridin-3-yl)(tetrahydro-2H-pyran-4-yl) methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (109 mg, 0.21 mmol) was converted to 2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methoxypyridin-3-yl) (tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)pro pan-2-ol (Compound 25, 9 mg, 0.017 mmol, 8% yield), LC-MS $[M+H]^+$ = 531.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.36 (m, 2H), 7.85 (s, 1H), 6.96 (d, J = 5.5 Hz, 1H), 6.66 (d, J = 10.9 Hz, 1H), 5.58 (s, 1H), 4.14 (s, 3H), 3.84 (s, 1H), 3.79 (s, 3H), 3.72 (d, J = 9.8 Hz, 1H), 3.56 (s, 3H), 3.43 (t, J = 11.4 Hz, 1H), 3.17 (t, J = 11.6 Hz, 1H), 2.13 (s, 3H), 1.72 (s, 2H), 1.66 (s, 3H), 1.44 (dd, J = 27.0, 8.9 Hz, 2H), 0.63 (d, J = 12.3 Hz, 1H).

Example 26

2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol("Compoun d 26")



Step 1: Methyl 6-bromo-4-((3-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

To a solution of methyl 6-bromo-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (from **Example 1 Step 2**, 290 mg, 0.94 mmol), (3-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methanol (**Intermediate 17**, 320 mg ,1.44 mmol) and triphenylphosphane (504 mg , 1.92 mmol) in dry THF (20 mL) was added DIAD (417 mg, 2.06 mmol) at 25 °C under N_2. After addition, the reaction was heated to 40 °C for 2 h. The reaction was then cooled slowly to room temperature and the reaction mixture was poured into water, and extracted with EtOAc (100 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by C-18 chromatography using 60-70% Acetonitrile in water to afford methyl 6-bromo-4-((3-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (400 mg, 0.78 mmol, 83% yield), LC-MS $[M+H]^+$ = 515.

Step 2: Methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methoxypyridin-2-yl) (tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

Following the procedure analogous to that described in **Step 2** for the synthesis of **Example 3,** methyl 6-bromo-4-((3-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (125 mg, 0.24 mmol) and 1-methyl-4-(methyl)-5-(tributylstannyl)-1H-1,2,3-triazole (197 mg, 0.51 mmol) were converted to methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (120 mg, 93% yield), LC-MS $[M+H]^+$ = 531.

Step3: 2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol

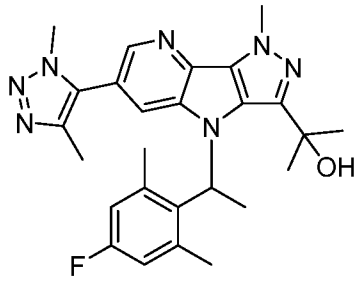
Following the procedure analogous to that described in **Step 3** for the synthesis of **Example 3,** methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (120 mg, 0.23 mmol) was converted to 2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol (Compound 26, 56 mg, 47% yield), LC-MS $[M+H]^+$ = 531.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, J = 1.4 Hz, 1H), 8.25 (d, J = 3.9 Hz, 1H), 8.14 (d, J = 1.3 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.35 (dd, J = 8.3, 4.6 Hz, 1H), 6.86 (d, J = 10.7 Hz, 1H), 5.49 (s, 1H),

4.14 (s, 3H), 3.91 (s, 3H), 3.77 (d, J = 10.7 Hz, 1H), 3.66 (s, 1H), 3.65 (s, 3H), 3.25 (dd, J = 10.8, 3.3 Hz, 1H), 3.09 (t, J = 11.4 Hz, 1H), 2.18 (s, 3H), 1.83 – 1.76 (m, 1H), 1.75 (s, 3H), 1.65 (s, 3H), 1.49 – 1.39 (m, 1H), 1.24 (s, 1H), 0.85 (t, J = 6.8 Hz, 1H), 0.41 (d, J = 12.3 Hz, 1H).

Example 27

2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-(1-(4-fluoro-2,6-dimethylphenyl)ethyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol("Compound 27")



Step 1: Methyl 6-bromo-4-(1-(4-fluoro-2,6-dimethylphenyl)ethyl)-1-methyl-1,4-dihydro pyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

Following the procedure analogous to that described in **Step 1** for the synthesis of **Example 26,** methyl 6-bromo-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3- carboxylate (from **Example 1 Step 2**, 200 mg, 0.65 mmol) and 1-(4-fluoro-2,6-dimethylphenyl)ethan-1-ol (**Intermediate 15**, 170 mg,1.02 mmol) were converted to methyl 6-bromo-4-(1-(4-fluoro-2,6-dimethylphenyl)ethyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (288 mg, 0.62 mmol, 96% yield), LC-MS$[M+H]^+$ = 460.

Step 2: Methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(1-(4-fluoro-2,6-dimethylphenyl)ethyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

Following the procedure analogous to that described in **Step 2** for the synthesis of **Example 3,** methyl 6-bromo-4-(1-(4-fluoro-2,6-dimethylphenyl)ethyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5] pyrrolo[3,2-b]pyridine-3-carboxylate (288 mg, 0.62 mmol) in DMF (10 mL) and 1-methyl-4-(methyl)-5-(tributylstannyl)-1H-1,2,3-triazole (509 mg, 1.32 mmol) were converted to methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(1-(4-fluoro-2,6-dimethylphenyl)ethyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (100 mg, 34% yield), LC-MS $[M+H]^+$ = 476.

Step 3: 2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-(1-(4-fluoro-2,6-dimethylphenyl)ethyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol

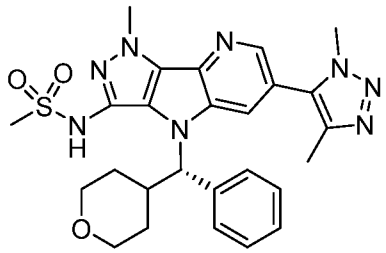
Following the procedure analogous to that described in **Step 3** for the synthesis of **Example 3,** methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(1-(4-fluoro-2,6-dimethylphenyl)ethyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (100 mg, 0.21 mmol) was converted to 2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(1-(4-fluoro-2,6-dimethylphenyl)ethyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol (Compound 27, 27 mg, 27% yield), LC-MS $[M+H]^+$ = 476.

^{1}HNMR(400MHz,DMSO-d_6) δ 8.40 (s, 1H), 7.48 (s, 1H), 6.88 (s, 2H), 6.84 (s, 1H), 5.61 (s, 1H), 4.18 (s, 3H), 3.87 (s, 3H), 3.33-3.28 (s, 6H), 2.11 (s, 3H), 2.03 (d, J=6.5Hz, 3H), 1.64 (s, 3H), 1.31 (s,

3H).

Example 28

(S)-N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)methanesulfonamide("Compound 28")



Step1: (S)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-amine

To a solution of ammonia (25%, 6 mL) in DMSO (3 mL) were added (S)-3-bromo-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine (from **Example 6 Step 5**, 201 mg, 0.39 mmol), CuI (43 mg, 0.23 mmol) L-proline (35 mg, 0.30 mmol) and Cs_2CO_3 (593 mg, 1.82 mmol). The mixture was stirred 110 °C for 3 days. The mixture was poured into water (50 mL) and extracted with EtOAc (150 mL). The collected organic layer was washed with brine (50 mL), dried by Na_2SO_4, and concentrated on a rotary vacuum evaporator. The residue was purified by column chromatography on silica gel with DCM/MeOH (0 %-5 %) to afford (S)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-amine (70 mg, 39% yield). LC-MS $[M+H]^+ = 457$.

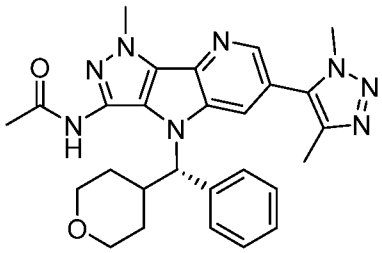
Step2: (S)-N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)methanesulfonamide

To a solution of (S)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-amine (20 mg, 0.044 mmol) and DMAP (4 mg, 0.033 mmol) in Pyridine (1 mL) was added a solution of MsCl (17 mg, 0.15 mmol) in DCM (1 mL), The mixture was stirred at ambient temperature for 16h. The mixture was poured into water (20 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by Prep-HPLC to afford the expected (S)-N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)methanesulfonamide (Compound 28, 2 mg, 8% yield), LC-MS $[M+H]^+ = 535$.

^{1}HNMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.59 (s, 1H), 7.53-7.48 (m, J = 6.9Hz,2H), 7.33-7.29 (m, 3H), 6.38 (s, 1H), 5.49 (d, J = 10.4, 1H), 4.31 (s, 3H), 4.02-3.89 (m, J = 9.8 Hz,2H), 3.88 (s, 3H), 2.55-2.44 (m, J = 11.3 Hz,2H), 3.33 (s, 3H), 3.15-3.09 (m, J = 8.6 Hz,1H), 2.31 (s, 3H), 1.81-1.78 (m, J = 7.9 Hz,1H), 1.57-1.50 (m, 1H), 1.39-1.25 (m, 2H).

Example 29

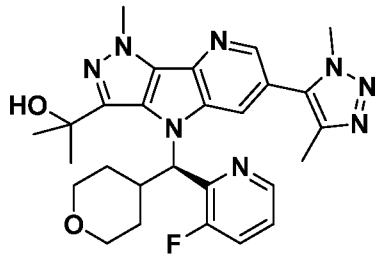
(S)-N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)acetamide("Compound 29")



To a solution of (S)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-amine (from **Example 28 Step 1**, 21 mg, 0.046 mmol) and DMAP (4 mg, 0.033 mmol) in Pyridine (1 mL) was added a solution of acetic anhydride (15 mg, 0.15 mmol) in DCM (1 mL), The mixture was stirred at ambient temperature for 16h. The mixture was poured into water (20 mL) and extracted with EtOAc (60 mL). The combined organic layer was dried over Na_2SO_4, and concentrated under vacuum. The residue was added to methanol (2 mL) and K_2CO_3 (97 mg) and stirred at ambient temperature for 16 h. The mixture was added to EtOAc (20 mL) and filtered. The filtrate was concentrated under vacuum and the residue was purified by Prep-HPLC to afford (S)-N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)acetamide (Compound 29, 7 mg, 30% yield), LC-MS $[M+H]^+ = 499$.

Example 30

(R)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol("Compound 30")



Step 1: (R)-Methyl 6-bromo-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

To a solution of methyl 6-bromo-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (from Example 1 step 2, 212 mg, 0.69 mmol), (S)-(3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methanol (Enantiomer b1 from Example 2, , 176 mg, 0.83 mmol) and triphenylphosphane (381 mg, 1.45 mmol) in dry THF (20 mL) was added diisopropyl azodicarboxylate (297 mg, 1.47 mmol) at r.t. under N_2. The resulting solution was refluxed for 2 hr under N_2. After cooling to r.t., the reaction mixture was extracted with EtOAc (30 mL). The resulting organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by

silica gel chromatography using 30-50% EtOAc in hexane to afford (R)-methyl 6-bromo-4-((3-fluoropyridin-2-yl) (tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo [3,2-b] pyridine-3-carboxylate (287mg, 0.57mmol, 83%), LC-MS $[M+H]^+$ = 502.

Step 2: (R)-Methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

To a solution of (R)-methyl 6-bromo-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (271 mg, 0.54 mmol) in DMF (20 mL) was added 1,4-dimethyl-5-(tributylstannyl)-1*H*-1,2,3-triazole (417 mg, 1.08mmol), tetrakis(triphenylphosphine)palladium (103 mg, 0.092 mmol), CuI (40 mg, 0.21 mmol) and TEA (0.56 g, 5.12 mmol) under N_2. The mixture was vacuumed, backfilled with N_2 and this process was repeated three times. The resulting mixture was stirred at 85 °C for 3 h and then cooled to room temperature. The reaction mixture was poured into water and extracted with EtOAc (30 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel chromatography using 0-5% MeOH in DCM to afford (R)-methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (126 mg, 0.24 mmol, 45% yield), LC-MS $[M+H]^+$ = 519.

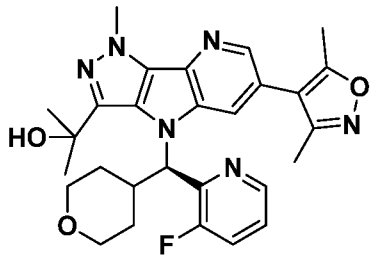
Step 3:(R)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol

Following the procedure analogous to that described for the synthesis of 2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5] pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol, (R)-methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (118 mg, 0.23mmol) was converted to (R)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5] pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol (Compound 30, 37 mg, 0.071 mmol, 31% yield), LC-MS[M+H]+ = 519.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 – 8.48 (m, 1H), 8.42 (d, J = 1.8 Hz, 1H), 8.29 (d, J = 1.8 Hz, 1H), 7.73 (dd, J = 10.0, 8.4, 1.2 Hz, 1H), 7.47 (dt, J = 8.5, 4.3 Hz, 1H), 7.02 (d, J = 10.9 Hz, 1H), 5.71 (s, 1H), 4.15 (s, 3H), 3.97 (s, 3H), 3.80 (d, J = 9.0 Hz, 1H), 3.68 (dd, J = 11.4, 2.8 Hz, 1H), 3.28 (dd, J = 11.4, 2.4 Hz, 1H), 3.21 (d, J = 11.2 Hz, 1H), 3.13 (t, J = 11.1 Hz, 1H), 2.24 (s, 3H), 1.74 (s, 3H), 1.69 – 1.60 (m, 1H), 1.57 (s, 3H), 1.48 (d, J = 12.9 Hz, 1H), 1.44 – 1.35 (m, 1H), 0.55 (d, J = 12.1 Hz, 1H).

Example 31

(R)-2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol(“Compound 31”)



Step 1: (R)-Methyl 6-bromo-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

Following the same procedure as depicted in the step 2 of Example 2, methyl 6-bromo-1-methyl-1,4- dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (obtained from Example 1, step 2, 195 mg, 0.627 mmol) and (S)-(3-fluoropyridin-2-yl)(tetrahydro-2H- pyran-4-yl) methanol (Enantiomer b1 from Example 2, 180 mg, 0.856 mmol) were converted to (R)-methyl 6-bromo-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (298 mg, 95 % yield), LC-MS $[M+H]^+$ = 502.

Step 2: (R)-Methyl 6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

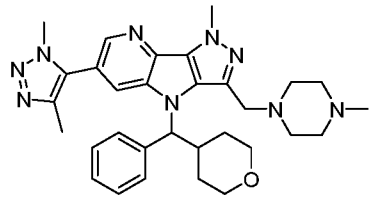
Following the same procedure as depicted in the step 3 of Example 2, (R)-methyl 6-bromo-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (298 mg, 0.59 mmol) and 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (198 mg, 0.890 mmol) were converted to (R)-methyl 6-(3,5-dimethyl isoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo [3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (206 mg, 67% yield), LC-MS $[M+H]^+$ = 519.

Step 3:(R)-2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl) methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol

Following the same procedure as depicted in the step 4 of Example 2, (R)-methyl 6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydro pyrazolo [3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (206 mg, 0.397 mmoL) was converted to (R)-2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol (Compound 31, 85 mg, 41% yield), LC-MS $[M+H]^+$ = 519. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, J = 4.6 Hz, 1H), 8.32 (d, J = 1.6 Hz, 1H), 8.10 (d, J = 1.5 Hz, 1H), 7.72 (t, J = 8.9 Hz, 1H), 7.47 (dt, J = 8.5, 4.3 Hz, 1H), 6.98 (d, J = 10.7 Hz, 1H), 5.67 (s, 1H), 4.13 (s, 3H), 3.80 (d, J = 9.1 Hz, 1H), 3.68 (d, J = 8.9 Hz, 1H), 3.30 – 3.17 (m, 2H), 3.11 (t, J = 11.4 Hz, 1H), 2.41 (s, 3H), 2.23 (s, 3H), 1.73 (s, 3H), 1.69 – 1.60 (m, 1H), 1.57 (s, 3H), 1.51 (d, J = 11.9 Hz, 1H), 1.40 (dd, J = 19.9, 11.5 Hz, 1H), 0.51 (d, J = 12.9 Hz, 1H).

Example 32

6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-3-((4-methylpiperazin-1-yl)methyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine("Compound 32")



Step1: methyl 6-bromo-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydro pyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate

To a solution of methyl 6-bromo-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (from Example 1 step 2, 1.00 g , 3.23 mmol), phenyl(tetrahydro-2H-pyran-4-yl)methanol (933 mg, 4.85 mmol) and Triphenyl phosphine (1.29 g , 6.82 mmol) in dry THF (60 mL) was added DIAD(600 mg, 2.97 mmol) at r.t. under N_2. The reaction system was stirred for 3 hours. The reaction mixture was poured into water and extracted with EtOAc (400 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography using 5-30% EtOAc in hexane to afford of methyl 6-bromo-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine -3-carboxylate (1.31 g , 83.28%yield), LC-MS $[M+H]^+$=483,485.

Step2:(6-bromo-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3' ,4':4,5]pyrrolo[3,2-b]pyridin-3-yl)methanol

To a solution of EtOH (20mL) with Methyl 6-bromo-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl) methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate (1.30 g , 2.69 mmol) was added $NaBH_4$ (540 mg ,14.27 mmol) and $CaCl_2$(374 mg, 3.36 mmol) at room temperature. The reaction system was stirred for 3 hours. The reaction mixture was poured into water and extracted with EtOAc (200 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford of (6-bromo-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)methanol(1.05 g , 86.24% yield), LC-MS $[M+H]^+$=455,457.

Step3:6-bromo-3-(bromomethyl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-di hydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine

To a solution of (6-bromo-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydro pyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)methanol (1.05 g , 2.32 mmol) in dry DCM (40 mL) was added phosphorus tribromide (600 mg, 2.97 mmol) at room temperature. The reaction system was stirred for 1 hours. The reaction mixture was poured into $NaHCO_3$(aq) and extracted with DCM(400 mL). The resulting organic phase was washed with brine , dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford of 6-bromo-3-(bromomethyl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine(1.12 g , 93.0% yield), LC-MS $[M+H]^+$=517,519.

Step4:6-bromo-1-methyl-3-((4-methylpiperazin-1-yl)methyl)-4-(phenyl(tetrahydro-2H-pyran-4 -yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine

6-bromo-3-(bromomethyl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyraz

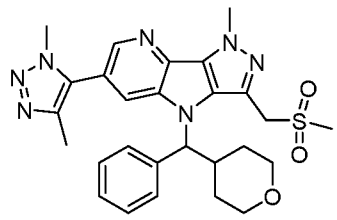
olo[3',4':4,5]pyrrolo[3,2-b]pyridine (160 mg, 0.31 mmol), N-methyl piperazine (141mg,1.41mmol) and K_2CO_3(140mg,1.01mmol) were mixtured in DMF(10mL) at room temperature. The reaction system was stirred for 2 hours. The reaction system was filtered and the organic phase was concentration under reduced pressure. The residue was purified by silica gel chromatography using 2-10% MeOH in DCM to afford of 6-bromo-1-methyl-3-((4-methylpiperazin-1-yl)methyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl) methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine(160 mg,96.0% yield), LC-MS $[M+H]^+$=538,540.

Step5:6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-3-((4-methylpiperazin-1-yl)methyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine

To a solution of 6-bromo-1-methyl-3-((4-methylpiperazin-1-yl)methyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine (160 mg , 0.30 mmol) in DMF (10 mL) was added 1,4-dimethyl-5-(tributylstannyl)-1H-1,2,3-triazole (290 mg, 0.75 mmol), CuI (40 mg,0.21 mmol) , $Pd(PPh_3)_4$(30 mg ,0.026 mmol) and TEA (120 mg , 1.09 mmol) under N_2 . The mixture was purged with N_2 for 2min, and stirred at 110°C for 16 hr . The reaction mixture was cooled to r.t , poured into water and extracted with EtOAc (100 mL). After separation, the organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel chromatography using 10-60% EtOAc in hexane to afford of 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-3-((4-methylpiperazin-1-yl)methyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1 ,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine(Compound 32, 20 mg), LC-MS $[M+H]^+$=554.

Example 33

6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-3-((methylsulfonyl)methyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine("Compound 33")



Step1:6-bromo-1-methyl-3-((methylsulfonyl)methyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine

6-bromo-3-(bromomethyl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine (from Example 32 step 3, 300 mg , 0.58 mmol) and Sodium methanesulphinate(100 mg , 0.98 mmol) were stirred in DMF(10 mL) solution at 60°C. The mixture was stirred for 2 hours . The mixture was cooled to r.t . poured into water and extracted with EtOAc (100 mL). After separation, the organic layer was washed with brine , dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel chromatography using 2-5% MeOH in DCM to afford of 6-bromo-1-methyl-3-((methylsulfonyl)methyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine(90 mg , 29.30% yield), LC-MS$[M+H]^+$=517,519.

Step2:6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-3-((methylsulfonyl)methyl)-4-(phenyl(tet

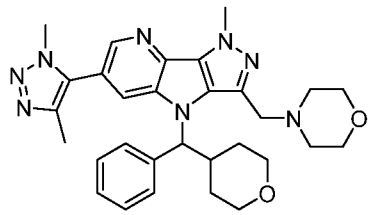
rahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine

To a solution of 6-bromo-1-methyl-3-((methylsulfonyl)methyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl) methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine (90 mg , 0.17 mmol) in Dioxane (6 mL) was added 1,4-dimethyl-5-(tributylstannyl)-1H-1,2,3-triazole (190 mg, 0.49 mmol),$PdCl_2(PPh_3)_2$(20 mg , 0.028 mmol) and DIEA (100 mg,0.77 mmol) under N_2 . The mixture was purged with N_2 for 2min, stirred at 110 °C for 20 hr . The reaction mixture was cooled to r.t , poured into water and extracted with EtOAc (100 mL). After separation, the organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel chromatography using 20-60% EtOAc in hexane to afford of 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-3-((methylsulfonyl)methyl)-4-(phenyl (tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine(Compound 33, 45mg,49.57% yield), LC-MS $[M+H]^+$=534.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (d, J = 1.2 Hz, 1H), 8.18 (s, 1H), 7.63 (d, J = 7.4 Hz, 2H), 7.32 (t, J = 7.4 Hz, 2H), 7.26 (t, J = 7.2 Hz, 1H), 5.48 (d, J = 10.9 Hz, 1H), 4.85 (dd, J = 31.6, 14.2 Hz, 2H), 4.23 (s, 3H), 3.92 (s, 3H), 3.85 (d, J = 9.1 Hz, 1H), 3.73 (d, J = 8.5 Hz, 1H), 3.43 (t, J = 11.0 Hz, 1H), 3.26 (d, J = 11.6 Hz, 2H), 3.17 (s, 3H), 2.24 (d, J = 12.7 Hz, 3H), 1.64 (d, J = 12.1 Hz, 1H), 1.59 – 1.45 (m, 2H), 1.00 (d, J = 12.2 Hz, 1H).

Example 34

4-((6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)methyl)morpholine(“Compound 34”)



Step1:4-((6-bromo-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo [3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)methyl)morpholine

6-bromo-3-(bromomethyl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyraz olo[3',4':4,5]pyrrolo[3,2-b]pyridine (from Example 32 step 3, 300 mg , 0.59 mmol), morpholine (100 mg , 1.15 mmol) and K_2CO_3(300 mg,2.17 mmol) were mixed in DMF(10 mL) at room temperature. The reaction system was stirred for 2 hours. The reaction system is filtered and decompressed for concentration. The residue was purified by silica gel chromatography using 2-10% MeOH in DCM to afford of 4-((6-bromo-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo [3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)methyl)morpholine(120 mg , 39.00% yield), LC-MS $[M+H]^+$=524,526.

Step2:4-((6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl) methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)methyl)morpholine

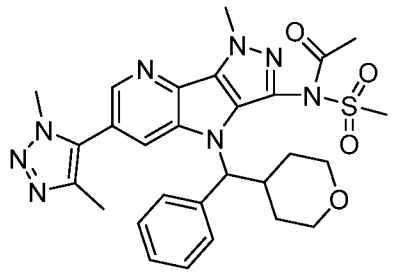
To a solution of 4-((6-bromo-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)methyl)morpholine (120 mg , 0.23 mmol) in

Dioxane (6 mL) was added 1,4-dimethyl-5-(tributylstannyl)-1H-1,2,3-triazole (185 mg, 0.48 mmol), $PdCl_2(PPh_3)_2$(30 mg , 0.043 mmol) and DIEA (100 mg,0.77 mmol) under N_2. The mixture was purged with N_2 for 2 min, stirred at 110 °C for 20 hr . The reaction mixture was cooled to r.t. , poured into water and extracted with EtOAc (100 mL). After separation, the organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel chromatography using 20-60% EtOAc in hexane to afford of 4-((6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)methyl)morpholine(Compound 34, 84 mg , 67.50% yield), LC-MS $[M+H]^+$=541.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (d, J = 1.5 Hz, 1H), 8.19 (s, 1H), 7.70 (d, J = 7.4 Hz, 2H), 7.32 (t, J = 7.4 Hz, 2H), 7.24 (t, J = 7.3 Hz, 1H), 5.68 (d, J = 11.3 Hz, 1H), 4.15 (s, 3H), 3.92 (s, 3H), 3.90 (s, 1H), 3.86 (d, J = 3.9 Hz, 1H), 3.82 (d, J = 7.6 Hz, 1H), 3.79 (s, 1H), 3.71 (d, J = 13.2 Hz, 1H), 3.64 (s, 4H), 3.47 – 3.33 (m, 4H), 2.22 (s, 3H), 1.63 (d, J = 12.3 Hz, 1H), 1.51 (d, J = 11.8 Hz, 1H), 1.42 – 1.33 (m, 1H), 1.14 (d, J = 13.5 Hz, 1H).

Example 35

N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)-N-(methylsulfonyl)acetamide("Compound 35")



Step1: N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)-N-(methylsulfonyl)acetamide

When the compound N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)methanesulfonamide(from Example 28 step 2), was purified by Prep-HPLC, also afford 3 mg of N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)-N-(methylsulfonyl)acetamide (Compound 35, 12% yield), LC-MS $[M+H]^+$=577.

^{1}HNMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.53 (s, 1H), 7.53-7.47 (m, J = 6.8 Hz, 2H), 7.33-7.28 (m, 3H), 5.47 (d, J = 10.4 Hz, 1H), 4.30 (s, 3H), 4.02-3.89 (m, J = 9.4 Hz, 2H), 3.87 (s, 3H), 2.55-2.44 (m, J = 11.0Hz, 2H), 3.33 (s, 3H), 3.15-3.09 (m, J = 10.3 Hz, 1H), 2.43 (s, 3H), 2.16 (s, 3H),1.83-1.79 (m, J = 7.1Hz, 1H), 1.55-1.50 (m, 1H), 1.35-1.22 (m, 2H).

PHARMACOLOGICAL TESTING

1. BRD4(BD1) binding assays

The BRD4(BD1) biochemical binding assay was performed by Sundia MediTech Co.Ltd. in

384-well white plate (OptiPlate-384, PerkinElmer) using HTRF technology.

Briefly, 20 nL of compounds were transferred to the 384-well plate by Echo® 550 liquid handler (Labcyte, USA), then 5 μL of BRD4(BD1) (Reaction Biology Company, RD-11-157) solution or the assay buffer was added to each well. After incubating at RT for 15 min, 5 μL of the biotinylated H4 derived acetylated peptide (synthesized by GL Biochem (Shanghai) Ltd) and 10 μL of the detection solution (Cisbio Assay) were added to each well. After incubating for 1h at RT, the HTRF signal was measure at 615nm and 665 nm using the EnVision Multilabel Plate Reader (PerkinElmer, USA). Results were analyzed with a two-wavelength signal ratio: intensity (665 nm)/intensity (615 nm). The inhibition percentage in the presence of the compound was calculated according to the equation, Percent inhibition = (Max-Signal) / (Max-Min)*100%. Fit the data in GrphaPad Prism V5.0 software (San Diego, CA) to obtain IC_{50} values with nonlinear regression analysis using equation, Y=Bottom+(Top–Bottom)/(1+10^((LogIC_{50}–X)×HillSlope), where Y stands for inhibition percentage and X stands for compound concentration.

Results:

The results of BRD4(BD1) binding assay are in the following Table 3.

Table 3. The results of BRD4(BD1) binding assay

Compound	BRD4(BD1) IC_{50}/nM	Compound	BRD4(BD1) IC_{50}/nM
Compound 1	0.48	Compound 16	0.3
Compound 2	0.35	Compound 17	0.55
Compound 3	0.66	Compound 18	1.1
Compound 4	0.57	Compound 19	0.79
Compound 5	0.59	Compound 23	0.54
Compound 6	0.49	Compound 24	0.88
Compound 7	0.97	Compound 26	0.68
Compound 8	12.0	Compound 27	17
Compound 9	0.99	Compound 29	1.9
Compound 10	2.2	Compound 30	3.0
Compound 11	1.3	Compound 31	4.6
Compound 12	1.6	Compound 33	4.67
Compound 13	0.4	Compound 34	0.34
Compound 15	0.61		

Table 3 shows that the compound of the present invention has a very strong affinity with BRD4 (BD1).

2. Cell Proliferation Assay

MTS assay protocol:

MV-4-11 cell proliferation analysis was conducted by the MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt)assay. Briefly, MV-4-11 cells will be cultured in IMDM(Iscove's Modified Dubecco's Medium) medium supplemented with 10% (v/v) FBS(fetal bovine serum), under the temperature of 37 °C, 5% CO_2 and 95% humidity. The cells will be harvested respectively during the logarithmic growth period and counted with hemocytometer. The cell viability is over 90% by trypan blue exclusion. Adjust MV-4-11 cells concentrations to 1.2×10^5 cells/mL with complete medium. Add 100 μL cell suspensions to 96-well plates (triplicates for each cell concentration), the final cell densities are 1.2×10^4 cells/well. The next day, dissolve the test compound with DMSO as stock solution. Dispense 5μL of the stock solution in 1 mL culture media and add 25μL drug media into 96-well plates. After serially diluting with culture media, the final concentration of the compound will be 0, 0.03, 0.1, 0.3, 1, 3, 10, 30, 100 nM. The plates will be cultured for 3 days, then measured by means of MTS assay. Add PMS(phenazinium methosulfate) solution to MTS solution (1:20) immediately before addition to the culture plate containing cells. Pipet 20 μL of the combined MTS/PMS solution into each well of the 96 well assay plate containing 100 μL of cells in culture medium. Incubate the plate for 1-4 hours at 37 °C in a humidified, 5% CO_2 atmosphere. Record the absorbance at 490 nm using an microplate spectrophotometer (Envision^R, PeikinElmer). Fit the data using GraphPad 5.0 and obtain IC_{50} values.

Results:

The results of the cellular proliferation activity are in the following Table 4:

Table 4. The results of the cellular proliferation activity

Compounds	MV-4-11 IC_{50}/nM	Compounds	MV-4-11 IC_{50}/nM
Compound 1	0.89	Compound 15	25.12
Compound 2	0.72	Compound 16	3.60
Compound 3	6.06	Compound 17	12.69
Compound 4	3.13	Compound 18	3.93
Compound 5	1.24	Compound 19	7.17
Compound 6	1.10	Compound 21	0.77
Compound 7	0.70	Compound 23	0.83
Compound 7-2	1.11	Compound 24	5.00
Compound 8	31.59	Compound 25	8.25
Compound 9	5.01	Compound 26	0.91
Compound 10	33.99	Compound 28	10.48
Compound 11	7.66	Compound 29	24.68
Compound 12	10.50	Compound 34	2.16
Compound 13	1.15	Compound 35	15.49

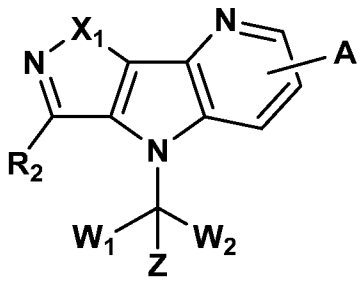
Table 4 shows that the compound of the present invention has an excellent inhibitory effect on

leukemia cell MV-4-11.

Furthermore, the compound of the present invention has a very excellent inhibitory effect on various cancer cells such as lung cancer cells, other leukemia cancer cells, myeloma cancer cells, esophageal cancer cells, and ovarian cancer cells, wherein the lung cancer cells include but are not limited to NCI-H526 lung cancer cells, NCI-H146 lung cancer cells, NCI-H820 lung cancer cells, DMS53 lung cancer cells, NCI-H446 lung cancer cells and the like; the leukemia cancer cells include but are not limited to NB4 leukemia cancer cells, JJN-3 leukemia cancer cells, Kasumi-1 leukemia cancer cells, OCI-AML3 leukemia cancer cells, THP-1 leukemia cancer cells and the like; the myeloma cancer cells include but are not limited to NCI-H929 myeloma cancer cells, KMS-11 myeloma cancer cells and the like; the esophageal cancer cells include but are not limited to COLO-680N esophageal cancer cells, KYSE-150 esophageal cancer cells, KYSE-270 esophageal cancer cells, KYSE-410 esophageal cancer cells, KYSE-70 esophageal cancer cells, OE19 esophageal cancer cells, T.Tn esophageal cancer cells, TE-1 esophageal cancer cells and the like; the ovarian cancer cells include but are not limited to RMG-I ovarian cancer cells, OVCAR-4 ovarian cancer cells and the like.

What is claimed is:

1. A compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof:

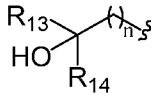


I

Wherein,

X_1 is selected from O, S, SO, SO_2 or NR_1;

R_1 is selected from hydrogen; deuterium; -CN; $-SOR_{11}$; $-SO_2R_{11}$; $-SO_2NR_{11}R_{12}$; $-C_{1-6}$alkyl;



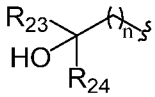
; $-C_{2-6}$alkenyl; $-C_{2-6}$alkynyl; carboxyl; $-NO_2$; $-COOR_{11}$; $-COR_{11}$; $-CONR_{11}R_{12}$; $-POR_{11}R_{12}$; $-C_{5-6}$aryl; $-C_{5-6}$heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; $-C_{3-8}$heterocyclic containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; or $-C_{3-8}$carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, oxo, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, carboxyl or $-C_{3-8}$carbocyclic;

Each of R_{11} and R_{12} at each occurrence is independently selected from hydrogen; deuterium; -OH; $-NH_2$; -CN; $-C_{1-6}$alkyl; $-C_{1-6}$alkoxy; $-C_{5-6}$aryl; $-C_{5-6}$heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; $-C_{1-6}$alkylene-C_{3-8}carbocyclic; or $-C_{3-8}$carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, -CN, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, carboxyl, $-SO_2(C_{1-6}alkyl)$ or $-C_{3-8}$carbocyclic; or

R_{11} and R_{12} together with the nitrogen atom to which they are both attached form 4-8 membered heterocyclic ring, and each of the heterocyclic ring at each occurrence can further contains 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2, and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium; halogen; -OH; oxo; -CN; $-C_{1-6}$alkyl; $-C_{1-6}$alkoxy; $-SO_2(C_{1-6}alkyl)$; $-CON(C_{1-6}alkyl)_2$; $-SO_2N(C_{1-6}alkyl)_2$; $-NH_2$; $-NH(C_{1-6}alkyl)$; $-N(C_{1-6}alkyl)_2$; $-C_{3-6}$heterocyclic containing 1 or 2 heteroatoms selected from N, O or S; or $-C_{1-6}$alkyl substituted with deuterium;

Each of R_{13} and R_{14} at each occurrence is independently selected from hydrogen, deuterium, halogen, $-NH_2$, $-C_{1-6}$alkoxy or $-C_{1-6}$alkyl; or

R_{13} and R_{14} together with the carbon atom to which they are both attached form 3-6 membered carbocyclic ring, and each of the carbocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, $-NH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy;

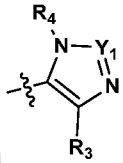
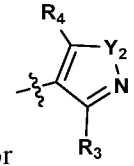
R_2 is selected from hydrogen; deuterium; halogen; $-OR_{21}$; $-NR_{21}R_{22}$; -CN; $-SR_{21}$; $-SOR_{21}$; $-SO_2R_{21}$; $-SO_2NR_{21}R_{22}$; $-C_{1-6}$alkyl;  ; $-C_{2-6}$alkenyl; $-C_{2-6}$alkynyl; carboxyl; $-NO_2$; $-COOR_{21}$; $-COR_{21}$; $-CONR_{21}R_{22}$; $-NR_{21}COR_{22}$; $-NR_{21}CONR_{21}R_{22}$; $-NR_{21}SO_2R_{22}$; $-NR_{21}SO_2NR_{21}R_{22}$; $-OCONR_{21}R_{22}$; $-POR_{21}R_{22}$; $-C_{5-6}$aryl; $-C_{5-6}$heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; $-C_{3-8}$heterocyclic containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; or $-C_{3-8}$carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, oxo, -CN, $-NH_2$, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, carboxyl or $-C_{3-8}$carbocyclic;

Each of R_{21} and R_{22} at each occurrence is independently selected from hydrogen; deuterium; -OH; NH_2; -CN; $-C_{1-6}$alkyl; $-C_{1-6}$alkoxy; $-C_{5-6}$aryl; $-C_{5-6}$heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; $-C_{1-6}$alkylene-C_{3-8}carbocyclic; or $-C_{3-8}$carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, -CN, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, carboxyl, $-SO_2(C_{1-6}alkyl)$ or $-C_{3-8}$carbocyclic; or

R_{21} and R_{22} together with the nitrogen atom to which they are both attached form 4-8 membered heterocyclic ring, and each of the heterocyclic ring at each occurrence can further contains 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2, and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium; halogen; -OH; oxo; -CN; $-C_{1-6}$alkyl; $-C_{1-6}$alkoxy; $-SO_2(C_{1-6}alkyl)$; $-CON(C_{1-6}alkyl)_2$; $-SO_2N(C_{1-6}alkyl)_2$; $-NH_2$; $-NH(C_{1-6}alkyl)$; $-N(C_{1-6}alkyl)_2$; $-C_{3-6}$heterocyclic containing 1 or 2 heteroatoms selected from N, O or S; or $-C_{1-6}$alkyl substituted with deuterium;

Each of R_{23} and R_{24} at each occurrence is independently selected from hydrogen, deuterium, halogen, $-NH_2$, $-C_{1-6}$alkoxy or $-C_{1-6}$alkyl; or

R_{23} and R_{24} together with the carbon atom to which they are both attached form 3-6 membered carbocyclic ring, and each of the carbocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, $-NH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy;

A is selected from  or  ;

Y_1 is selected from N or CR_{Y1};

Y_2 is selected from O, S, $CR_{Y1}R_{Y2}$ or NR_{Y2};

Each of R_{Y1} and R_{Y2} at each occurrence is independently selected from hydrogen, deuterium, halogen, -OH, NH_2, -CN, -C_{1-6}alkyl or -C_{1-6}alkoxy;

Each of R_3 and R_4 at each occurrence is independently selected from hydrogen, deuterium, halogen, -CN, -SOR_5, -SO_2R_5, -$SO_2NR_5R_6$, -C_{1-6}alkyl, -C_{1-6}alkoxy, -COR_5, -$CONR_5R_6$ or -POR_5R_6; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, -NH_2, -CN, -C_{1-6}alkyl or -C_{1-6}alkoxy;

Each of R_5 and R_6 at each occurrence is independently selected from hydrogen; deuterium; -OH; -NH_2; -CN; -C_{1-6}alkyl; -C_{1-6}alkoxy; -C_{5-6}aryl; -C_{5-6}heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; -C_{1-6}alkylene-C_{3-8}carbocyclic; or -C_{3-8}carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, -CN, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -C_{1-6}alkyl, -C_{1-6}alkoxy, carboxyl, -SO_2(C_{1-6}alkyl) or -C_{3-8}carbocyclic; or

R_5 and R_6 together with the nitrogen atom to which they are both attached form 4-8 membered heterocyclic ring, and each of the heterocyclic ring at each occurrence can further contains 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2, and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium; halogen; -OH; oxo; -CN; -C_{1-6}alkyl; -C_{1-6}alkoxy; -SO_2(C_{1-6}alkyl); -CON(C_{1-6}alkyl)$_2$; -SO_2N(C_{1-6}alkyl)$_2$; -NH_2; -NH(C_{1-6}alkyl); -N(C_{1-6}alkyl)$_2$; -C_{3-6}heterocyclic containing 1 or 2 heteroatoms selected from N, O or S; or -C_{1-6}alkyl substituted with deuterium;

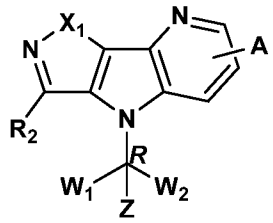
n is selected from 0, 1, 2, 3, 4, 5 or 6;

W_1 is selected from hydrogen; deuterium; halogen; -NH_2; -CN; -OH; -NO_2; carboxyl; -C_{1-6}alkyl; -C_{1-6}alkoxy; -C_{1-6}alkylene-C_{1-6}alkoxy; -C_{5-10}aryl; -C_{5-10}heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; -C_{3-8}heterocyclic containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; or -C_{3-8}carbocyclic; and each of which at each occurrence is independently optionally substituted;

W_2 is selected from hydrogen; deuterium; halogen; -NH_2; -CN; -OH; -NO_2; carboxyl; -C_{1-6}alkyl; -C_{1-6}alkoxy; -C_{5-10} aryl; -C_{5-10}heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; -C_{3-8}heterocyclic containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; or -C_{3-8}carbocyclic; and each of which at each occurrence is independently optionally substituted;

Z is selected from hydrogen, deuterium, halogen, -NH_2, -CN, -OH, carboxyl, -C_{1-6}alkyl or -C_{1-6}alkoxy.

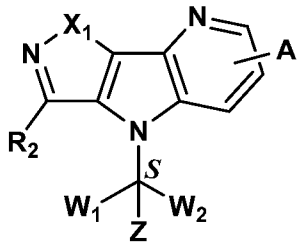
2. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to claim 1, wherein the compound is of formula I-1:



I-1

"*R*" in the formula I-1 indicates that the absolute configuration of the carbon that contacts with the W_1, W_2 and Z is *R* configuration when the carbon is chiral carbon.

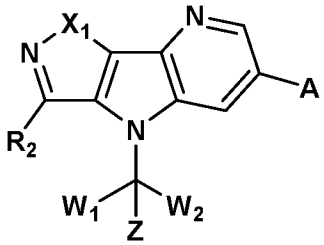
3. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to claim 1, wherein the compound is of formula I-2:



I-2

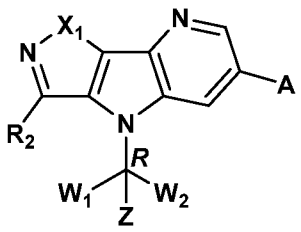
"*S*" in the formula I-2 indicates that the absolute configuration of the carbon that contacts with the W_1, W_2 and Z is *S* configuration when the carbon is chiral carbon.

4. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to claim 1 , wherein the compound is of formula II:



II.

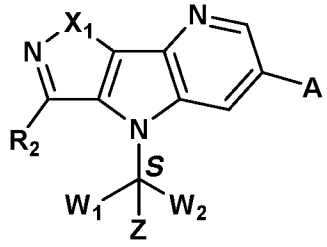
5. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to claim 1 or 4, wherein the compound is of formula II-1:



II-1

"*R*" in the formula II-1 indicates that the absolute configuration of the carbon that contacts with the W_1, W_2 and Z is *R* configuration when the carbon is chiral carbon.

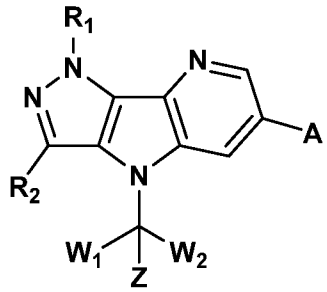
6. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to claim 1 or 4, wherein the compound is of formula II-2:



II-2

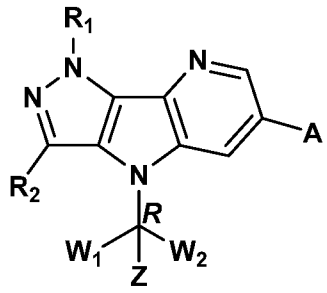
"*S*" in the formula II-2 indicates that the absolute configuration of the carbon that contacts with the W_1, W_2 and Z is *S* configuration when the carbon is chiral carbon.

7. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to claim 1 or 4, wherein the compound is of formula III:



III.

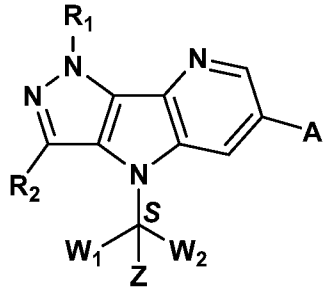
8. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to claim 1, 4 or 7, wherein the compound is of formula III-1:



III-1

"*R*" in the formula III-1 indicates that the absolute configuration of the carbon that contacts with the W_1, W_2 and Z is *R* configuration when the carbon is chiral carbon.

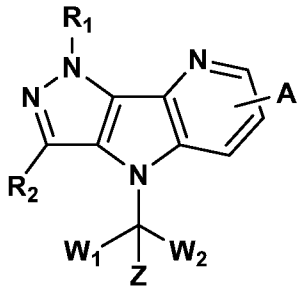
9. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to claim 1, 4 or 7, wherein the compound is of formula III-2:



III-2

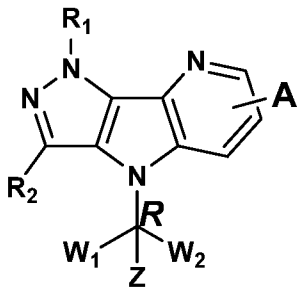
"*S*" in the formula III-2 indicates that the absolute configuration of the carbon that contacts with the W_1, W_2 and Z is *S* configuration when the carbon is chiral carbon.

10. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to claim 1, the compound is of formula IV:



IV.

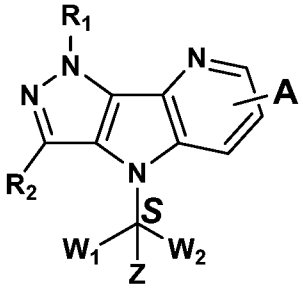
11. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to claim 1 or 10, the compound is of formula IV-1:



IV-1

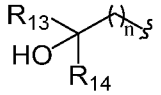
"*R*" in the formula IV-1 indicates that the absolute configuration of the carbon that contacts with the W_1, W_2 and Z is *R* configuration when the carbon is chiral carbon.

12. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to claim 1 or 10, the compound is of formula IV-2:



IV-2

"*S*" in the formula IV-2 indicates that the absolute configuration of the carbon that contacts with the W_1, W_2 and Z is *S* configuration when the carbon is chiral carbon.

13. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-12, wherein R_1 is selected from hydrogen; deuterium; $-SOR_{11}$; $-SO_2R_{11}$; $-SO_2NR_{11}R_{12}$; $-C_{1-6}$alkyl;  ; $-COOR_{11}$; $-COR_{11}$; $-CONR_{11}R_{12}$; $-POR_{11}R_{12}$; $-C_{5-6}$heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S or SO_2; $-C_{3-8}$heterocyclic containing 1, 2, 3 or 4 heteroatoms selected from N, O, S or SO_2; or $-C_{3-8}$carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-NH_2$, $-NH(C_{1-6}$alkyl), $-N(C_{1-6}$alkyl)$_2$ or $-C_{3-8}$carbocyclic;

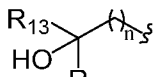
Each of R_{11} and R_{12} at each occurrence is independently selected from hydrogen, deuterium, $-C_{1-6}$alkyl, $-C_{1-6}$alkylene-C_{3-8}carbocyclic or $-C_{3-8}$carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, -CN, $-NH_2$, $-NH(C_{1-6}$alkyl), $-N(C_{1-6}$alkyl)$_2$, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-SO_2(C_{1-6}$alkyl) or $-C_{3-8}$carbocyclic; or

R_{11} and R_{12} together with the nitrogen atom to which they are both attached form 4-6 membered heterocyclic ring, and each of the heterocyclic ring at each occurrence can further contains 1, 2 or 3 heteroatoms selected from N, O, S or SO_2, and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium; halogen; -OH; oxo; -CN; $-C_{1-6}$alkyl; $-C_{1-6}$alkoxy; $-SO_2(C_{1-6}$alkyl); $-CON(C_{1-6}$alkyl)$_2$; $-SO_2N(C_{1-6}$alkyl)$_2$; $-NH_2$; $-NH(C_{1-6}$alkyl); $-N(C_{1-6}$alkyl)$_2$; $-C_{3-6}$heterocyclic containing 1 or 2 heteroatoms selected from N, O or S; or $-C_{1-6}$alkyl substituted with deuterium;

Each of R_{13} and R_{14} at each occurrence is independently selected from hydrogen, deuterium or $-C_{1-6}$alkyl; or

R_{13} and R_{14} together with the carbon atom to which they are both attached form 3-6 membered carbocyclic ring, and each of the carbocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3 or 4 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, $-NH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy;

n is selected from 0, 1, 2 or 3.

14. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-13, wherein R_1 is selected from hydrogen; deuterium; $-SOR_{11}$; $-SO_2R_{11}$; $-SO_2NR_{11}R_{12}$; $-C_{1-3}$alkyl;  ; $-COOR_{11}$; $-COR_{11}$; $-CONR_{11}R_{12}$; $-POR_{11}R_{12}$; $-C_{5-6}$heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S or SO_2; $-C_{3-6}$heterocyclic containing 1, 2, 3 or 4

heteroatoms selected from N, O, S or SO_2; or -C_{3-6}carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, -C_{1-3}alkyl, -C_{1-3}alkoxy, -NH_2, -NH(C_{1-3}alkyl), -N(C_{1-3}alkyl)$_2$ or -C_{3-6}carbocyclic;

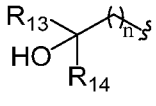
Each of R_{11} and R_{12} at each occurrence is independently selected from hydrogen, deuterium, -C_{1-3}alkyl, -C_{1-3}alkylene-C_{3-6}carbocyclic or -C_{3-6}carbocyclic, and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, -CN, -NH_2, -NH(C_{1-3}alkyl), -N(C_{1-3}alkyl)$_2$, -C_{1-3}alkyl, -C_{1-3}alkoxy, -SO_2(C_{1-3}alkyl) or -C_{3-6}carbocyclic; or

R_{11} and R_{12} together with the nitrogen atom to which they are both attached form 4-6 membered heterocyclic ring, and each of the heterocyclic ring at each occurrence can further contains 1, 2 or 3 heteroatoms selected from N, O or SO_2, and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium; -F; -Cl; -Br; -OH; oxo; -CN; -C_{1-3}alkyl; -C_{1-3}alkoxy; -SO_2(C_{1-3}alkyl); -CON(C_{1-3}alkyl)$_2$; -SO_2N(C_{1-3}alkyl)$_2$; -NH_2; -NH(C_{1-3}alkyl); -N(C_{1-3}alkyl)$_2$; -C_{4-6}heterocyclic containing 1 heteroatoms selected from N or O; or -C_{1-3}alkyl substituted with deuterium;

Each of R_{13} and R_{14} at each occurrence is independently selected from hydrogen, deuterium or -C_{1-3}alkyl; or

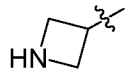
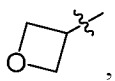
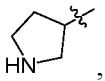
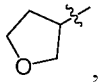
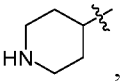
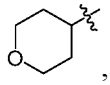
R_{13} and R_{14} together with the carbon atom to which they are both attached form 3-6 membered carbocyclic ring, and each of the carbocyclic ring is independently optionally substituted with 1, 2, 3 or 4 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, -NH_2, -CN, -C_{1-3}alkyl or -C_{1-3}alkoxy;

n is selected from 0, 1, 2 or 3.

15. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-14, wherein R_1 is selected from hydrogen; deuterium; -SOR_{11}; -SO_2R_{11}; -$SO_2NR_{11}R_{12}$; methyl; ethyl; propyl; isopropyl;  ; -$COOR_{11}$; -COR_{11}; -$CONR_{11}R_{12}$; -$POR_{11}R_{12}$; 5-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 6-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 3-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 4-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 5-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 6-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 3-membered carbocyclic; 4-membered carbocyclic; 5-membered carbocyclic; or 6-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, methyl, ethyl, propyl, isopropyl,

methoxy, ethoxy, propoxy, isopropoxy, $-NH_2$, $-NH(CH_3)$, $-NH(CH_2CH_3)$, $-NH(CH_2CH_2CH_3)$, $-NH(CH(CH_3)_2)$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_3)(CH_2CH_3)$, $-N(CH_3)(CH_2CH_2CH_3)$, 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic or 6-membered carbocyclic;

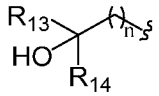
Each of R_{11} and R_{12} at each occurrence is independently selected from hydrogen, deuterium, methyl, ethyl, propyl, isopropyl, -methylene-3-membered carbocyclic, -methylene-4-membered carbocyclic, -methylene-5-membered carbocyclic, -methylene-6-membered carbocyclic, -ethylene-3-membered carbocyclic, -ethylene-4-membered carbocyclic, -ethylene-5-membered carbocyclic, -ethylene-6-membered carbocyclic, 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic or 6-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, -CN, $-NH_2$, $-NH(CH_3)$, $-NH(CH_2CH_3)$, $-NH(CH_2CH_2CH_3)$, $-NH(CH(CH_3)_2)$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_3)(CH_2CH_3)$, $-N(CH_3)(CH_2CH_2CH_3)$, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, $-SO_2CH_3$, $-SO_2CH_2CH_3$, $-SO_2CH_2CH_2CH_3$, $-SO_2CH(CH_3)_2$, 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic or 6-membered carbocyclic; or

R_{11} and R_{12} together with the nitrogen atom to which they are both attached form 4 membered heterocyclic ring, 5 membered heterocyclic ring or 6 membered heterocyclic ring, and each of the heterocyclic ring at each occurrence can further contains 1 or 2 heteroatoms selected from N, O or SO_2, and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, oxo, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, $-SO_2CH_3$, $-SO_2CH_2CH_3$, $-SO_2CH_2CH_2CH_3$, $-SO_2CH(CH_3)_2$, $-CON(CH_3)_2$, $-CON(CH_2CH_3)_2$, $-CON(CH_2CH_2CH_3)_2$, $-CON(CH(CH_3)_2)_2$, $-SO_2N(CH_3)_2$, $-SO_2N(CH_2CH_3)_2$, $-SO_2N(CH_2CH_2CH_3)_2$, $-SO_2N(CH(CH_3)_2)_2$, $-NH_2$, $-NH(CH_3)$, $-NH(CH_2CH_3)$, $-NH(CH_2CH_2CH_3)$, $-NH(CH(CH_3)_2)$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_3)(CH_2CH_3)$, $-N(CH_3)(CH_2CH_2CH_3)$,  ,  ,  ,  ,  ,  , methyl substituted with deuterium, ethyl substituted with deuterium, propyl substituted with deuterium or isopropyl substituted with deuterium;

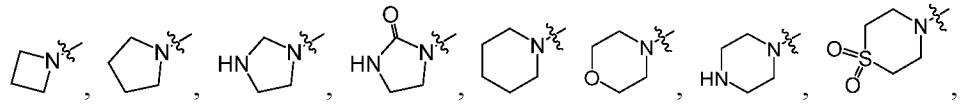
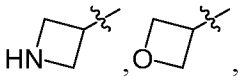
Each of R_{13} and R_{14} at each occurrence is independently selected from hydrogen, deuterium, methyl, ethyl, propyl or isopropyl; or

R_{13} and R_{14} together with the carbon atom to which they are both attached form 3 membered carbocyclic ring, 4 membered carbocyclic ring, 5 membered carbocyclic ring or 6 membered carbocyclic ring, and each of carbocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3 or 4 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy;

n is selected from 0, 1, 2 or 3.

16. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-15, wherein R_1 is selected from hydrogen; deuterium; $-SOR_{11}$; $-SO_2R_{11}$; $-SO_2NR_{11}R_{12}$; methyl; ethyl; propyl; isopropyl;  ; $-COOR_{11}$; $-COR_{11}$; $-CONR_{11}R_{12}$; $-POR_{11}R_{12}$; 5-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 6-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; or 3-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, $-NH_2$, $-NH(CH_3)$, $-NH(CH_2CH_3)$, $-N(CH_3)_2$, $-N(CH_3)(CH_2CH_3)$ or 3-membered carbocyclic;

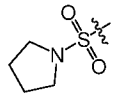
Each of R_{11} or R_{12} at each occurrence is independently selected from hydrogen, deuterium, methyl, ethyl, propyl, isopropyl, -methylene-3-membered carbocyclic or 3-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, methyl, methoxy, $-SO_2CH_3$ or 3-membered carbocyclic; or

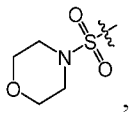
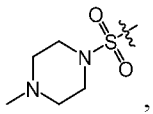
R_{11} and R_{12} together with the nitrogen atom to which they are both attached form the heterocyclic selected from  , and the heterocyclic ring is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, oxo, -CN, methyl, methoxy, $-SO_2CH_3$, $-CON(CH_3)_2$, $-SO_2N(CH_3)_2$, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$,  , $-CH_2D$, $-CHD_2$ or $-CD_3$;

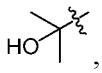
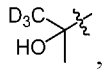
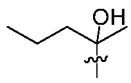
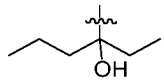
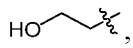
Each of R_{13} and R_{14} at each occurrence is independently selected from hydrogen, deuterium, methyl, ethyl, propyl or isopropyl; or

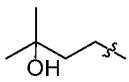
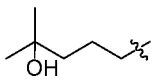
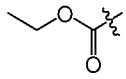
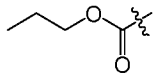
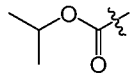
R_{13} and R_{14} together with the carbon atom to which they are both attached form 3 membered carbocyclic ring, and the carbocyclic ring is independently optionally substituted with 1, 2, 3 or 4 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -OH, methyl, ethyl, propyl or isopropyl;

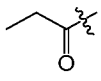
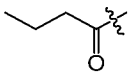
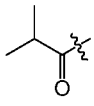
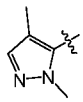
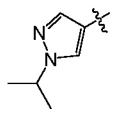
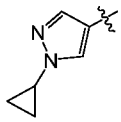
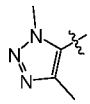
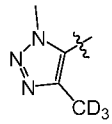
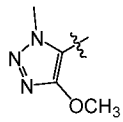
n is selected from 0 or 1.

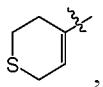
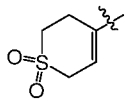
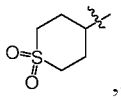
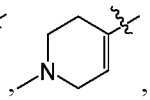
17. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-16, wherein R_1 is selected from hydrogen, deuterium, $-SOCH_3$, $-SOCH_2CH_3$, $-SOCH_2CH_2CH_3$, $-SOCH(CH_3)_2$, $-SO_2CH_3$, $-SO_2CD_3$, $-SO_2CH_2CH_3$, $-SO_2CH_2CH_2CH_3$, $-SO_2CH(CH_3)_2$, $-SO_2CH(CD_3)_2$, $-SO_2NH_2$, $-SO_2NH(CH_3)$, $-SO_2N(CH_3)_2$, $-SO_2NH(CD_3)$, $-SO_2N(CD_3)_2$, $-SO_2NH(CH_2CH_3)$, $-SO_2N(CH_2CH_3)_2$, $-SO_2NH(CH_2CH_2CH_3)$, $-SO_2N(CH_2CH_2CH_3)_2$,  ,

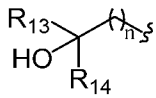
 ,  , $-CH_3$, $-CH_2D$, $-CHF_2$, $-CH_2F$, $-CD_2H$, $-CD_3$, $-CF_3$, $-CH_2CH_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHCH_3$, $-CH_2CH_2N(CH_3)_2$, $-CH_2CD_3$, $-CH_2CF_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CD_3$, $-CH_2CH_2CF_3$, $-CH(CH_3)_2$, $-CH(CH_3)(CD_3)$, $-CH(CF_3)_2$, $-CH(CD_3)_2$,

 ,  ,  ,  ,  ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,  ,  ,  ,

 ,  ,  ,  , $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, $-CONH(CD_3)$, $-CON(CD_3)_2$, $-CONH(CH_2CH_3)$, $-CON(CH_2CH_3)_2$, $-CONH(CH_2CH_2CH_3)$, $-CON(CH_2CH_2CH_3)_2$, $-P(O)H_2$, $-P(O)H(CH_3)$, $-PO(CH_3)_2$, $-P(O)H(CD_3)$, $-P(O)(CD_3)_2$, $-P(O)(CH_2CH_3)_2$, $-P(O)(CH_2CH_2CH_3)_2$, $-P(O)(CH(CH_3)_2)_2$,  ,  ,  ,  ,  ,  ,  ,  ,

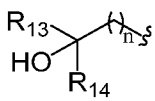
 ,  ,  ,  ,  ,  ,  , or  .

18. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-13, wherein R_1 is selected from $-SO_2R_{11}$, $-C_{1-6}$alkyl,  or $-C_{3-8}$carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-NH_2$, $-NH(C_{1-6}alkyl)$,or $-N(C_{1-6}alkyl)_2$;

R_{11} is selected from hydrogen, deuterium or $-C_{1-6}$alkyl;

Each of R_{13} and R_{14} at each occurrence is independently selected from hydrogen, deuterium or $-C_{1-6}$alkyl;

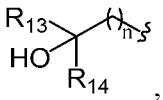
n is selected from 0, 1, 2, 3, 4, 5 or 6.

19. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-13 or 18, wherein R_1 is selected from $-SO_2R_{11}$, $-C_{1-3}$alkyl,  or $-C_{3-6}$carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, $-C_{1-3}$alkyl, $-C_{1-3}$alkoxy, $-NH_2$, $-NH(C_{1-3}alkyl)$ or $-N(C_{1-3}alkyl)_2$;

R_{11} is selected from hydrogen, deuterium or $-C_{1-3}$alkyl;

Each of R_{13} and R_{14} at each occurrence is independently selected from hydrogen, deuterium or $-C_{1-3}$alkyl;

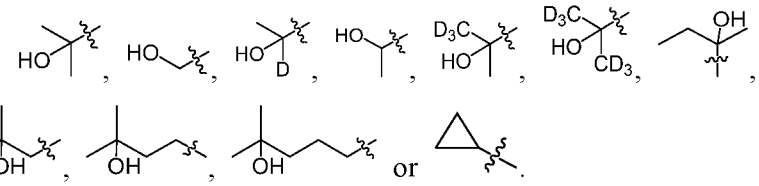
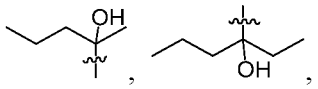
n is selected from 0, 1, 2 or 3.

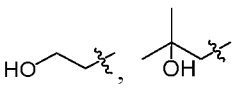
20. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-13, 18 or 19, wherein R_1 is selected from $-SO_2R_{11}$, methyl, ethyl, propyl, isopropyl,  , 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic or 6-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, $-NH_2$, $-NH(CH_3)$, $-NH(CH_2CH_3)$, $-NH(CH_2CH_2CH_3)$, $-NH(CH(CH_3)_2)$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_3)(CH_2CH_3)$ or $-N(CH_3)(CH_2CH_2CH_3)$;

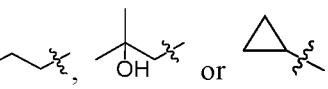
R_{11} is selected from hydrogen, deuterium, methyl, ethyl, propyl or isopropyl;

Each of R_{13} and R_{14} at each occurrence is independently selected from hydrogen, deuterium, methyl, ethyl, propyl or isopropyl;

n is selected from 0, 1, 2 or 3.

21. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-13 or 18-20, wherein R_1 is selected from $-SO_2CH_3$, $-SO_2CD_3$, $-SO_2CH_2CH_3$, $-SO_2CH_2CH_2CH_3$, $-SO_2CH(CH_3)_2$, $-SO_2CH(CD_3)_2$, $-CH_3$, $-CH_2D$, $-CHF_2$, $-CH_2F$, $-CD_2H$, $-CD_3$, $-CF_3$, $-CH_2CH_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHCH_3$, $-CH_2CH_2N(CH_3)_2$, $-CH_2CD_3$, $-CH_2CF_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CD_3$, $-CH_2CH_2CF_3$, $-CH(CH_3)_2$, $-CH(CH_3)(CD_3)$, $-CH(CF_3)_2$, $-CH(CD_3)_2$,  ,  , , , or .

22. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-13, wherein R_1 is selected from hydrogen, deuterium, $-SO_2CH_3$, $-CH_3$, $-CHF_2$, $-CD_3$, $-CH_2CH_3$, $-CH_2CHF_2$, $-CH_2CH_2N(CH_3)_2$, $-CH_2CF_3$, $-CH(CH_3)_2$,  or  .

23. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 18-21, wherein R_1 is selected from $-SO_2CH_3$, $-CH_3$, $-CHF_2$, $-CD_3$, $-CH_2CH_3$, $-CH_2CHF_2$, $-CH_2CH_2N(CH_3)_2$, $-CH_2CF_3$, $-CH(CH_3)_2$,  or .

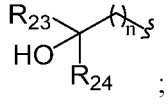
24. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-13 or 18, wherein R_1 is $-C_{1-6}$alkyl.

25. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any of any one of claims 1-13, 18 or 24, wherein R_1 is $-C_{1-3}$alkyl.

26. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof

according to any one of claims 1-13, 18, 24 or 25, wherein R_1 is selected from methyl, ethyl, propyl or isopropyl.

27. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-13, 18 or 24-26, wherein R_1 is methyl.

28. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-27, wherein R_2 is selected from hydrogen; deuterium; halogen; $-OR_{21}$; $-NR_{21}R_{22}$; -CN; $-SR_{21}$; $-SOR_{21}$; $-SO_2R_{21}$; $-SO_2NR_{21}R_{22}$; $-C_{1-6}$alkyl;  ; $-C_{2-6}$alkenyl; $-COOR_{21}$; $-COR_{21}$; $-CONR_{21}R_{22}$; $-NR_{21}COR_{22}$; $-NR_{21}SO_2R_{22}$; $-POR_{21}R_{22}$; $-C_{5-6}$heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S or SO_2; $-C_{3-8}$heterocyclic containing 1, 2, 3 or 4 heteroatoms selected from N, O, S or SO_2; or $-C_{3-8}$carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each substituents at each occurrence is independently selected from deuterium, halogen, -OH, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy or $-C_{3-8}$carbocyclic;

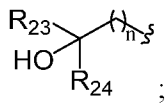
Each of R_{21} and R_{22} at each occurrence is independently selected from hydrogen, deuterium, $-C_{1-6}$alkyl, $-C_{1-6}$alkylene-C_{3-8}carbocyclic or $-C_{3-8}$carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, -CN, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-SO_2(C_{1-6}alkyl)$ or $-C_{3-8}$carbocyclic; or

R_{21} and R_{22} together with the nitrogen atom to which they are both attached form 4-6 membered heterocyclic ring, each of the heterocyclic ring at each occurrence can further contains 1, 2 or 3 heteroatoms selected from N, O, S or SO_2, and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium; halogen; -OH; oxo; -CN; $-C_{1-6}$alkyl; $-C_{1-6}$alkoxy; $-SO_2(C_{1-6}alkyl)$; $-CON(C_{1-6}alkyl)_2$; $-SO_2N(C_{1-6}alkyl)_2$; $-NH_2$; $-NH(C_{1-6}alkyl)$; $-N(C_{1-6}alkyl)_2$; $-C_{3-6}$heterocyclic containing 1 or 2 heteroatoms selected from N, O or S; or $-C_{1-6}$alkyl substituted with deuterium;

Each of R_{23} and R_{24} at each occurrence is independently selected from hydrogen, deuterium or $-C_{1-6}$alkyl; or

R_{23} and R_{24} together with the carbon atom to which they are both attached form 3-6 membered carbocyclic ring, and each of the carbocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3 or 4 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, $-NH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy;

n is selected from 0, 1, 2, 3, 4, 5 or 6.

29. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-28, wherein R_2 is selected from hydrogen; deuterium; -F; -Cl; -Br; $-OR_{21}$; $-NR_{21}R_{22}$; -CN; $-SR_{21}$; $-SOR_{21}$; $-SO_2R_{21}$; $-SO_2NR_{21}R_{22}$; $-C_{1-3}$alkyl;  ; $-C_{2-3}$alkenyl; $-COOR_{21}$;

$-COR_{21}$; $-CONR_{21}R_{22}$; $-NR_{21}COR_{22}$; $-NR_{21}SO_2R_{22}$; $-POR_{21}R_{22}$; $-C_{5-6}$heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S or SO_2; $-C_{3-6}$heterocyclic containing 1, 2, 3 or 4 heteroatoms selected from N, O, S or SO_2; or $-C_{3-6}$carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, $-C_{1-3}$alkyl, $-C_{1-3}$alkoxy or $-C_{3-6}$carbocyclic;

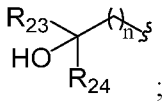
Each of R_{21} or R_{22} at each occurrence is independently selected from hydrogen, deuterium, $-C_{1-3}$alkyl, $-C_{1-3}$alkylene-C_{3-6}carbocyclic or $-C_{3-6}$carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, -CN, $-NH_2$, $-NH(C_{1-3}alkyl)$, $-N(C_{1-3}alkyl)_2$, $-C_{1-3}$alkyl, $-C_{1-3}$alkoxy, $-SO_2(C_{1-3}alkyl)$ or $-C_{3-6}$carbocyclic; or

R_{21} and R_{22} together with the nitrogen atom to which they are both attached form 4-6 membered heterocyclic ring, each of the heterocyclic ring at each occurrence can further contains 1, 2 or 3 heteroatoms selected from N, O or SO_2, and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium; -F; -Cl; -Br; -OH; oxo; -CN; $-C_{1-3}$alkyl; $-C_{1-3}$alkoxy; $-SO_2(C_{1-3}alkyl)$; $-CON(C_{1-3}alkyl)_2$; $-SO_2N(C_{1-3}alkyl)_2$; $-NH_2$; $-NH(C_{1-3}alkyl)$; $-N(C_{1-3}alkyl)_2$; $-C_{4-6}$heterocyclic containing 1 heteroatoms selected from N or O; or $-C_{1-3}$alkyl substituted with deuterium;

Each of R_{23} and R_{24} at each occurrence is independently selected from hydrogen, deuterium or $-C_{1-3}$alkyl; or

R_{23} and R_{24} together with the carbon atom to which they are both attached form 3-6 membered carbocyclic ring, and each of the carbocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3 or 4 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, $-NH_2$, -CN, $-C_{1-3}$alkyl or $-C_{1-6}$alkoxy;

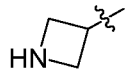
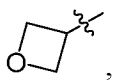
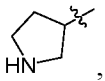
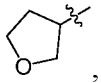
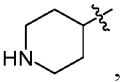
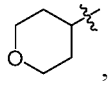
n is selected from 0, 1, 2 or 3.

30. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-29, wherein R_2 is selected from hydrogen; deuterium; -F; -Cl; -Br; $-OR_{21}$; $-NR_{21}R_{22}$; -CN; $-SR_{21}$; $-SOR_{21}$; $-SO_2R_{21}$; $-SO_2NR_{21}R_{22}$; methyl; ethyl; propyl; isopropyl; 

; ethenyl; propenyl; $-COOR_{21}$; $-COR_{21}$; $-CONR_{21}R_{22}$; $-NR_{21}COR_{22}$; $-NR_{21}SO_2R_{22}$; $-POR_{21}R_{22}$; 5-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 6-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 3-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 4-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 5-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 6-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 3-membered carbocyclic; 4-membered carbocyclic; 5-membered carbocyclic; or 6-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6

substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic or 6-membered carbocyclic;

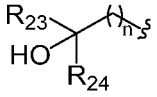
Each of R_{21} or R_{22} at each occurrence is independently selected from hydrogen, deuterium, methyl, ethyl, propyl, isopropyl, -methylene-3-membered carbocyclic, -methylene-4-membered carbocyclic, -methylene-5-membered carbocyclic, -methylene-6-membered carbocyclic, -ethylene-3-membered carbocyclic, -ethylene-4-membered carbocyclic, -ethylene-5-membered carbocyclic, -ethylene-6-membered carbocyclic, 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic or 6-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, -CN, $-NH_2$, $-NH(CH_3)$, $-NH(CH_2CH_3)$, $-NH(CH_2CH_2CH_3)$, $-NH(CH(CH_3)_2)$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_3)(CH_2CH_3)$, $-N(CH_3)(CH_2CH_2CH_3)$, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, $-SO_2CH_3$, $-SO_2CH_2CH_3$, $-SO_2CH_2CH_2CH_3$, $-SO_2CH(CH_3)_2$, 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic or 6-membered carbocyclic; or

R_{21} and R_{22} together with the nitrogen atom to which they are both attached form 4 membered heterocyclic ring, 5 membered heterocyclic ring, 6 membered heterocyclic ring, each of the heterocyclic ring at each occurrence can further contains 1 or 2 heteroatoms selected from N, O or SO_2, and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, oxo, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, $-SO_2CH_3$, $-SO_2CH_2CH_3$, $-SO_2CH_2CH_2CH_3$, $-SO_2CH(CH_3)_2$, $-CON(CH_3)_2$, $-CON(CH_2CH_3)_2$, $-CON(CH_2CH_2CH_3)_2$, $-CON(CH(CH_3)_2)_2$, $-SO_2N(CH_3)_2$, $-SO_2N(CH_2CH_3)_2$, $-SO_2N(CH_2CH_2CH_3)_2$, $-SO_2N(CH(CH_3)_2)_2$, $-NH_2$, $-NH(CH_3)$, $-NH(CH_2CH_3)$, $-NH(CH_2CH_2CH_3)$, $-NH(CH(CH_3)_2)$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_3)(CH_2CH_3)$, $-N(CH_3)(CH_2CH_2CH_3)$,  ,  ,  ,  ,  ,  , methyl substituted with deuterium, ethyl substituted with deuterium, propyl substituted with deuterium or isopropyl substituted with deuterium;

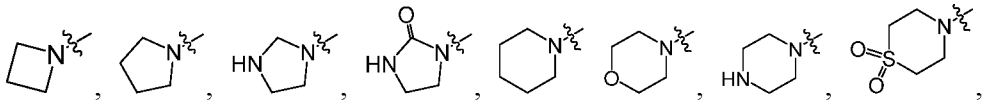
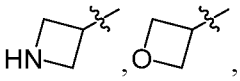
Each of R_{23} and R_{24} at each occurrence is independently selected from hydrogen, deuterium, methyl, ethyl, propyl or isopropyl; or

R_{23} and R_{24} together with the carbon atom to which they are both attached form 3-membered carbocyclic ring, 4-membered carbocyclic ring, 5-membered carbocyclic ring or 6 membered carbocyclic ring, and each of the carbocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3 or 4 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl methoxy, ethoxy, propoxy or isopropoxy;

n is selected from 0, 1, 2 or 3.

31. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-30, wherein R_2 is independently selected from hydrogen; deuterium; -F; -Cl; -Br; $-OR_{21}$; $-NR_{21}R_{22}$; -CN; $-SR_{21}$; $-SOR_{21}$; $-SO_2R_{21}$; $-SO_2NR_{21}R_{22}$; methyl; ethyl; propyl; isopropyl;  ; ethenyl; $-COOR_{21}$; $-COR_{21}$; $-CONR_{21}R_{22}$; $-NR_{21}COR_{22}$; $-NR_{21}SO_2R_{22}$; $-POR_{21}R_{22}$; 5-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; 6-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O, S or SO_2; or 3-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy or 3-membered carbocyclic;

Each of R_{21} and R_{22} at each occurrence is independently selected from hydrogen, deuterium, methyl, ethyl, propyl, isopropyl, -methylene-3-membered carbocyclic or 3-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, methyl, methoxy, $-SO_2CH_3$ or 3-membered carbocyclic; or

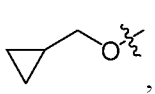
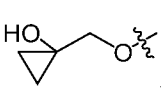
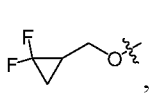
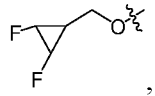
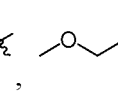
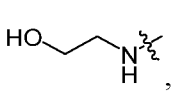
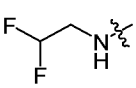
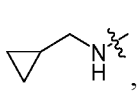
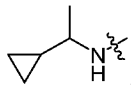
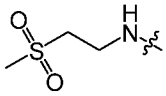
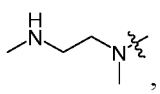
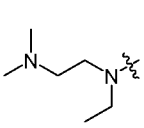
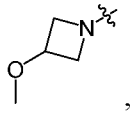
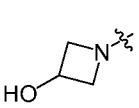
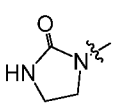
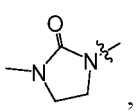
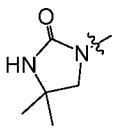
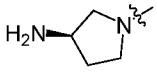
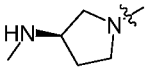
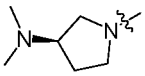
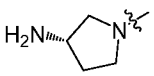
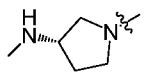
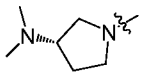
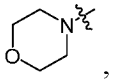
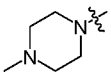
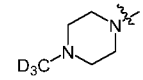
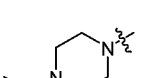
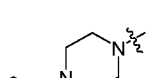
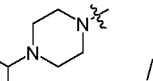
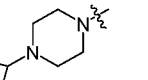
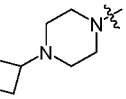
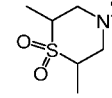
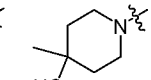
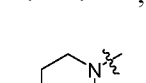
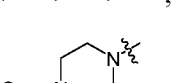
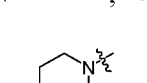
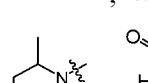
R_{21} and R_{22} together with the nitrogen atom to which they are both attached form the heterocyclic selected from  , and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, oxo, -CN, methyl, ethyl, propyl, isopropyl, methoxy, $-SO_2CH_3$, $-CON(CH_3)_2$, $-SO_2N(CH_3)_2$, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$,  , $-CH_2D$, $-CHD_2$ or $-CD_3$;

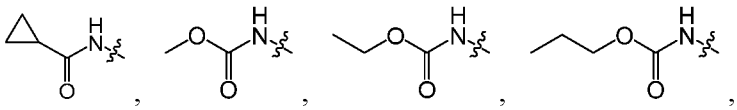
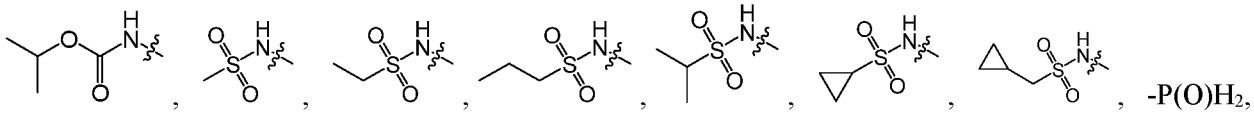
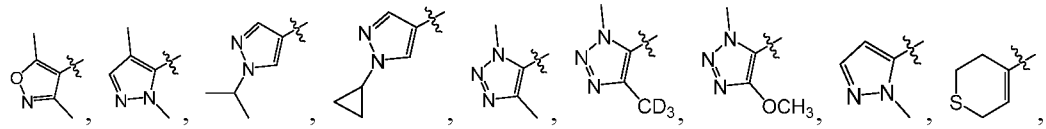
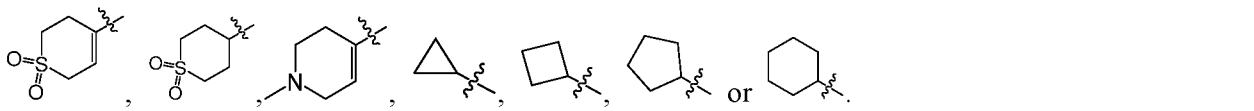
Each of R_{23} and R_{24} at each occurrence is independently selected from hydrogen, deuterium, methyl, ethyl, propyl or isopropyl; or

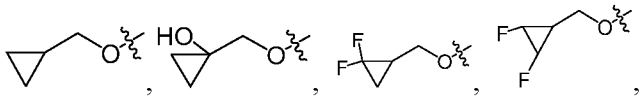
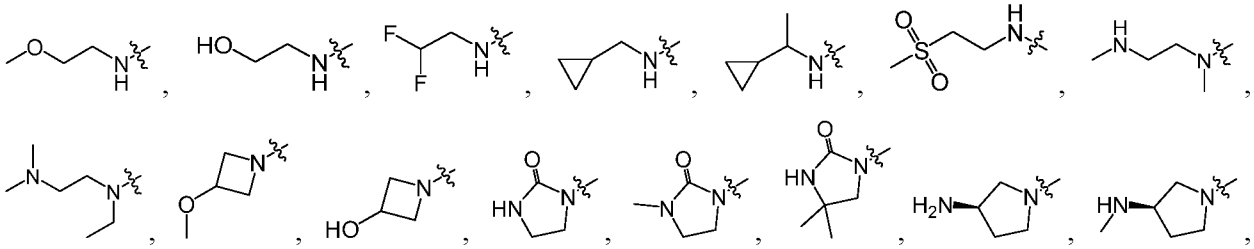
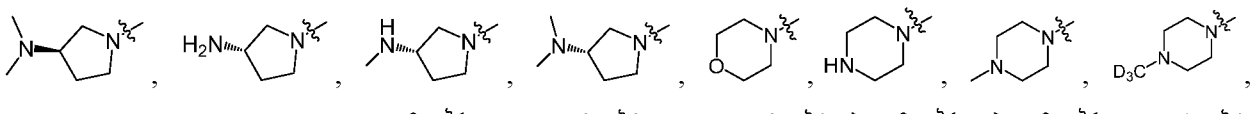
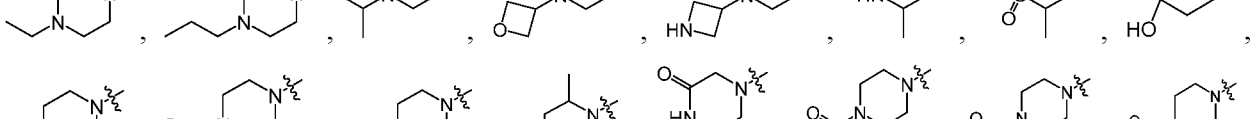
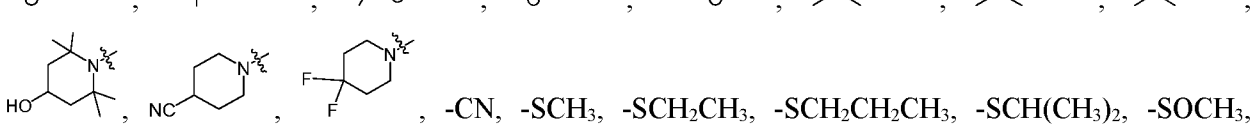
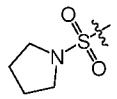
R_{23} and R_{24} together with the carbon atom to which they are both attached form 3-membered carbocyclic ring, and the carbocyclic ring is independently optionally substituted with 1, 2, 3 or 4 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy;

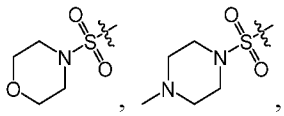
n is selected from 0 or 1.

32. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-26, wherein R_2 is selected from hydrogen, deuterium, -F, -Cl, -Br, -OH, $-OCH_3$, $-OCD_3$, $-OCH_2CH_3$, $-OCH_2CH_2CH_3$, $-OCH(CH_3)_2$, $-OCH_2CF_3$, $-OCH_2CHF_2$, $-OCF_2CH_3$, $-OCH_2OH$, $-OCH_2CH_2OH$, $-OCH_2CH_2CH_2OH$, $-OCH_2CH_2NH_2$, $-OCH_2N(CH_3)_2$, $-OCH_2CH_2N(CH_3)_2$,

-$OCH_2CH_2CH_2N(CH_3)_2$, -$OCH_2CH_2NHCH_3$,  ,  ,  ,  , -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$NHCD_3$, -$N(CD_3)_2$, -$NHCH_2CH_3$, -$N(CH_3CH_2)_2$, -$N(CH_3)(CH_3CH_2)$, -$NHCH_2CH_2CH_3$, -$N(CH_2CH_2CH_3)_2$, -$NHCH(CH_3)_2$, -$N(CH_3)(CH(CH_3)_2)$, -$N(CH(CH_3)_2)_2$, -$NHCH_2CF_3$,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , -$CONH_2$, -$CONH(CH_3)$, -$CON(CH_3)_2$, -$CONH(CD_3)$, -$CON(CD_3)_2$, -$CONH(CH_2CH_3)$, -$CON(CH_2CH_3)_2$, -$CONH(CH_2CH_2CH_3)$, -$CON(CH_2CH_2CH_3)_2$, -$NHCOCH_3$, -$NHCOCH_2CH_3$,

-NHCOCH$_2$CH$_2$CH$_3$, -NHCOCH(CH$_3$)$_2$,  ,  , -P(O)H$_2$, -P(O)H(CH$_3$), -PO(CH$_3$)$_2$, -P(O)H(CD$_3$), -PO(CD$_3$)$_2$, -PO(CH$_2$CH$_3$)$_2$, -PO(CH$_2$CH$_2$CH$_3$)$_2$, -PO(CH(CH$_3$)$_2$)$_2$,  ,  , or .

33. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-32, wherein R_2 is selected from hydrogen, deuterium, -F, -Cl, -Br, -OH, -OCH$_3$, -OCD$_3$, -OCH$_2$CH$_3$, -OCH$_2$CH$_2$CH$_3$, -OCH(CH$_3$)$_2$, -OCH$_2$CF$_3$, -OCH$_2$CHF$_2$, -OCF$_2$CH$_3$, -OCH$_2$OH, -OCH$_2$CH$_2$OH, -OCH$_2$CH$_2$CH$_2$OH, -OCH$_2$CH$_2$NH$_2$, -OCH$_2$N(CH$_3$)$_2$, -OCH$_2$CH$_2$N(CH$_3$)$_2$, -OCH$_2$CH$_2$CH$_2$N(CH$_3$)$_2$, -OCH$_2$CH$_2$NHCH$_3$,  , -NH$_2$, -NHCH$_3$, -N(CH$_3$)$_2$, -NHCD$_3$, -N(CD$_3$)$_2$, -NHCH$_2$CH$_3$, -N(CH$_3$CH$_2$)$_2$, -N(CH$_3$)(CH$_3$CH$_2$), -NHCH$_2$CH$_2$CH$_3$, -N(CH$_2$CH$_2$CH$_3$)$_2$, -NHCH(CH$_3$)$_2$, -N(CH$_3$)(CH(CH$_3$)$_2$), -N(CH(CH$_3$)$_2$)$_2$, -NHCH$_2$CF$_3$,  ,  ,  ,  , -CN, -SCH$_3$, -SCH$_2$CH$_3$, -SCH$_2$CH$_2$CH$_3$, -SCH(CH$_3$)$_2$, -SOCH$_3$, -SOCH$_2$CH$_3$, -SOCH$_2$CH$_2$CH$_3$, -SOCH(CH$_3$)$_2$, -SO$_2$CH$_3$, -SO$_2$CD$_3$, -SO$_2$CH$_2$CH$_3$, -SO$_2$CH$_2$CH$_2$CH$_3$, -SO$_2$CH(CH$_3$)$_2$, -SO$_2$CH(CD$_3$)$_2$, -SO$_2$NH$_2$, -SO$_2$NH(CH$_3$), -SO$_2$N(CH$_3$)$_2$, -SO$_2$NH(CD$_3$), -SO$_2$N(CD$_3$)$_2$, -SO$_2$NH(CH$_2$CH$_3$), -SO$_2$N(CH$_2$CH$_3$)$_2$, -SO$_2$NH(CH$_2$CH$_3$CH$_2$), -SO$_2$N(CH$_2$CH$_2$CH$_3$)$_2$,  ,



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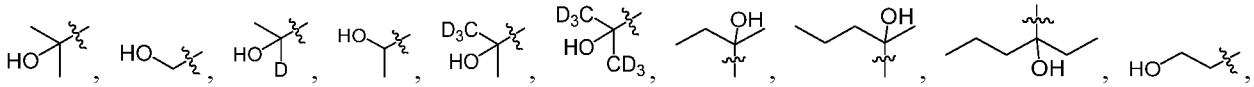
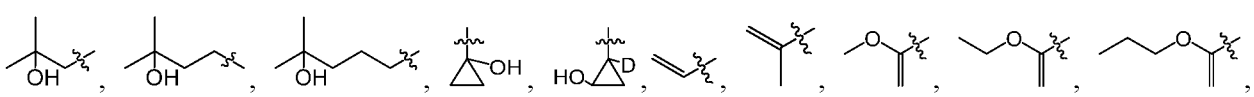
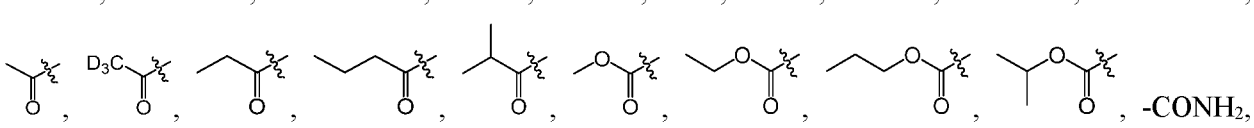
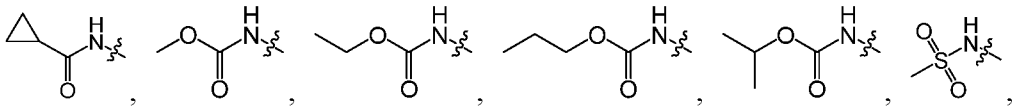
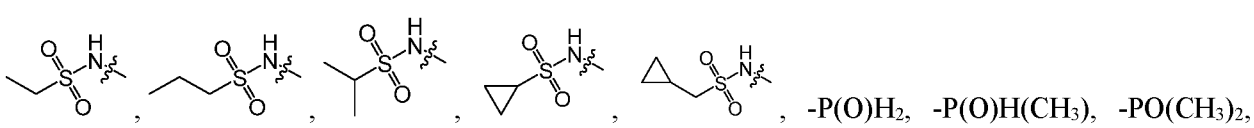




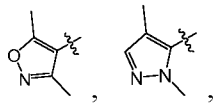


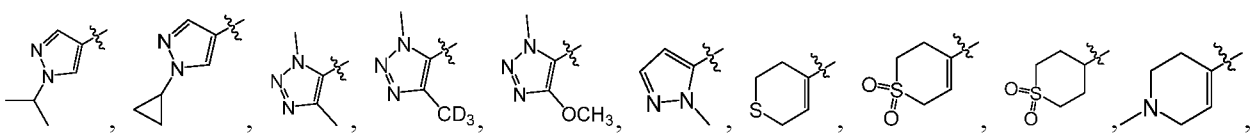
-$CONH_2$, -$CONH(CH_3)$, -$CON(CH_3)_2$, -$CONH(CD_3)$, -$CON(CD_3)_2$, -$CONH(CH_2CH_3)$, -$CON(CH_2CH_3)_2$, -$CONH(CH_2CH_2CH_3)$, -$CON(CH_2CH_2CH_3)_2$, -$NHCOCH_3$, -$NHCOCH_2CH_3$, -$NHCOCH_2CH_2CH_3$, -$NHCOCH(CH_3)_2$,

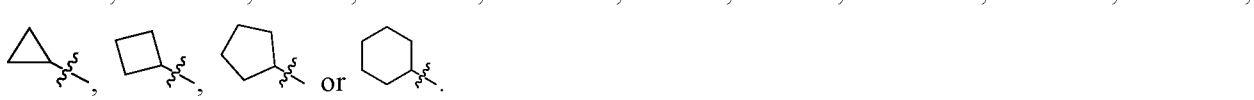


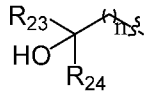


-$P(O)H_2$, -$P(O)H(CH_3)$, -$PO(CH_3)_2$, -$P(O)H(CD_3)$, -$PO(CD_3)_2$, -$PO(CH_2CH_3)_2$, -$PO(CH_2CH_2CH_3)_2$, -$PO(CH(CH_3)_2)_2$,






or

34. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-28, wherein R_2 is selected from hydrogen, deuterium, halogen, -$NR_{21}R_{22}$, -SO_2R_{21}, -$SO_2NR_{21}R_{22}$, -C_{1-6}alkyl,  , -$COOR_{21}$, -COR_{21}, -$CONR_{21}R_{22}$, -$NR_{21}COR_{22}$, -$NR_{21}SO_2R_{22}$, -$POR_{21}R_{22}$ or -C_{3-8}carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, -C_{1-6}alkyl or -C_{1-6}alkoxy;

Each of R_{21} or R_{22} at each occurrence is independently selected from hydrogen, deuterium or -C_{1-6}alkyl; or

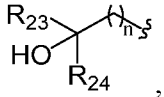
R_{21} and R_{22} together with the nitrogen atom to which they are both attached form 4-6 membered heterocyclic ring, each of the heterocyclic ring at each occurrence can further contains 1, 2 or 3 heteroatoms selected from N, O, S or SO_2, and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium; oxo; -C_{1-6}alkyl; -$NH(C_{1-6}$alkyl); or

-C_{3-6}heterocyclic containing 1 or 2 heteroatoms selected from N or O;

Each of R_{23} and R_{24} at each occurrence is independently selected from hydrogen, deuterium or -C_{1-6}alkyl; or

R_{23} and R_{24} together with the carbon atom to which they are both attached form 3-6 membered carbocyclic ring, and each of the carbocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -OH or -C_{1-6}alkyl;

n is selected from 0, 1, 2, 3, 4, 5 or 6.

35. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-28 or 34, wherein R_2 is selected from hydrogen, deuterium, halogen, -$NR_{21}R_{22}$, -SO_2R_{21}, -$SO_2NR_{21}R_{22}$, -C_{1-3}alkyl,  , -$COOR_{21}$, -COR_{21}, -$CONR_{21}R_{22}$, -$NR_{21}COR_{22}$, -$NR_{21}SO_2R_{22}$, -$POR_{21}R_{22}$ or -C_{3-6}carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -OH, -C_{1-3}alkyl or -C_{1-3}alkoxy;

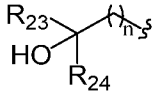
Each of R_{21} or R_{22} at each occurrence is independently selected from hydrogen, deuterium or -C_{1-3}alkyl; or

R_{21} and R_{22} together with the nitrogen atom to which they are both attached form 4-membered heterocyclic ring, 5-membered heterocyclic ring, 6-membered heterocyclic ring, each of the heterocyclic ring at each occurrence can further contains 1 or 2 heteroatoms selected from N or O, and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, oxo, -C_{1-3}alkyl, -NH(C_{1-3}alkyl) or -C_{4-6}heterocyclic containing 1 heteroatoms selected from N or O;

Each of R_{23} and R_{24} at each occurrence is independently selected from hydrogen, deuterium or -C_{1-3}alkyl; or

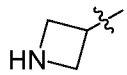
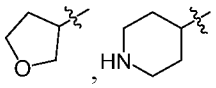
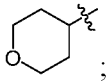
R_{23} and R_{24} together with the carbon atom to which they are both attached form 3-6 membered carbocyclic ring, and each of the carbocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -OH or -C_{1-3}alkyl;

n is selected from 0, 1, 2 or 3.

36. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any of claims 1-28, 34 or 35, wherein R_2 is selected from hydrogen, deuterium, -F, -Cl, -Br, -$NR_{21}R_{22}$, -SO_2R_{21}, -$SO_2NR_{21}R_{22}$, methyl, ethyl, propyl, isopropyl,  , -$COOR_{21}$, -COR_{21}, -$CONR_{21}R_{22}$, -$NR_{21}COR_{22}$, -$NR_{21}SO_2R_{22}$, -$POR_{21}R_{22}$, 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic or 6-membered carbocyclic; and each of which at each occurrence is

independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy;

Each of R_{21} or R_{22} at each occurrence is independently selected from hydrogen, deuterium, methyl, ethyl, propyl or isopropyl; or

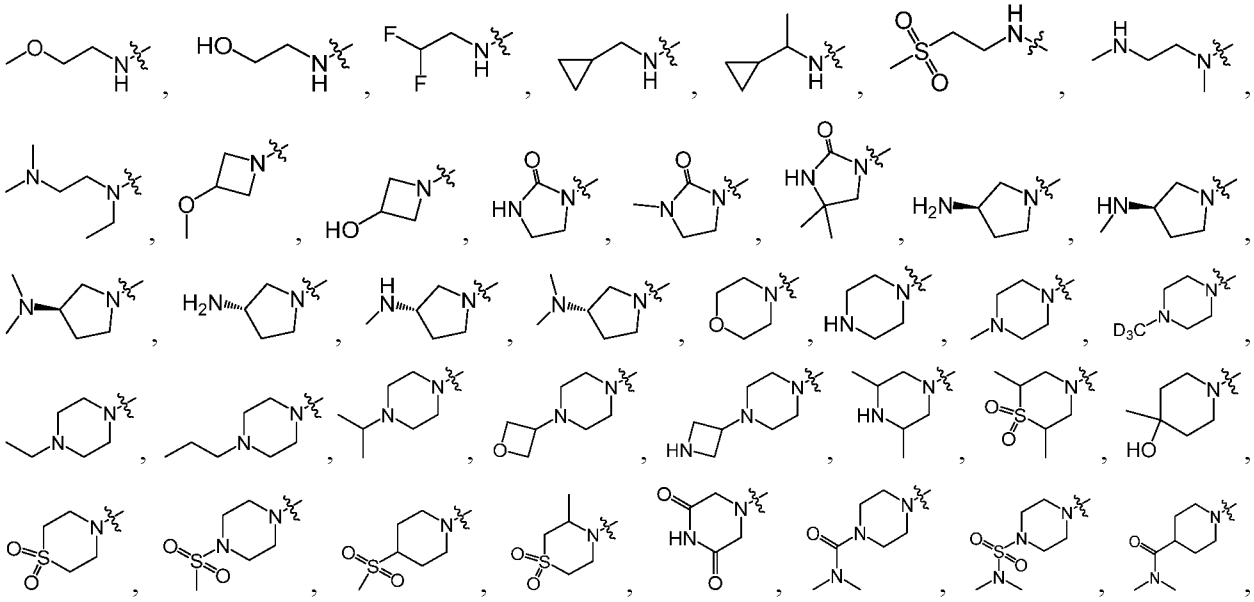
R_{21} and R_{22} together with the nitrogen atom to which they are both attached form 5-membered heterocyclic ring, 6-membered heterocyclic ring, each of the heterocyclic ring at each occurrence ring can further contains 1 heteroatoms selected from N or O, and each of the heterocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, oxo, methyl, ethyl, propyl, isopropyl, $-NHCH_3$, $-NHCH_2CH_3$, $-NHCH_2CH_2CH_3$, $-NHCH(CH_3)_2$,  ,  or  ;

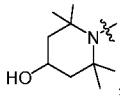
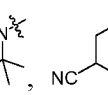
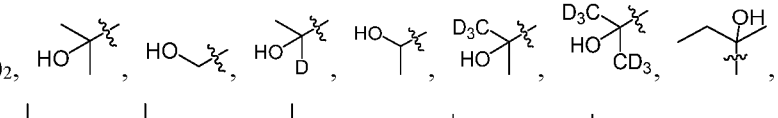
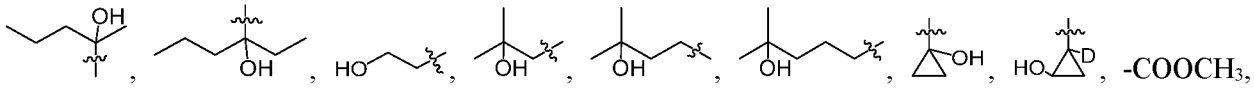
Each of R_{23} and R_{24} at each occurrence is independently selected from hydrogen, deuterium, methyl, ethyl, propyl or isopropyl; or

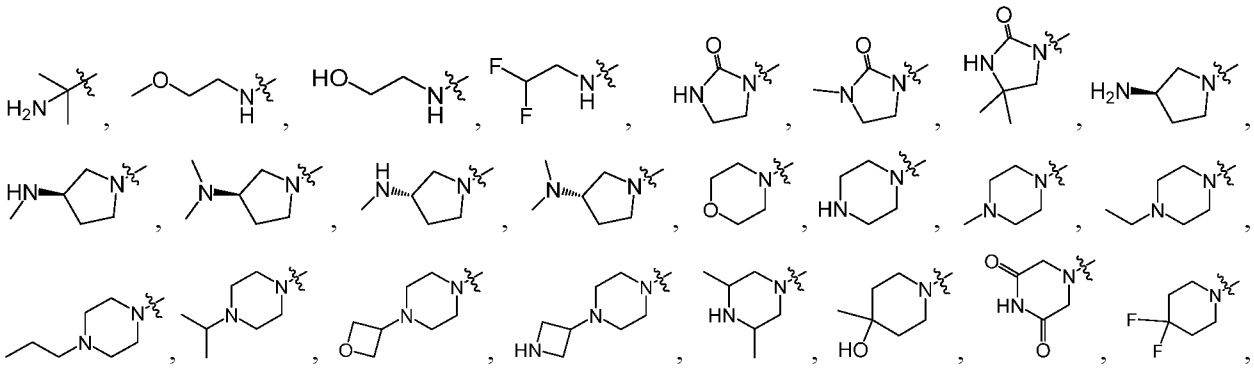
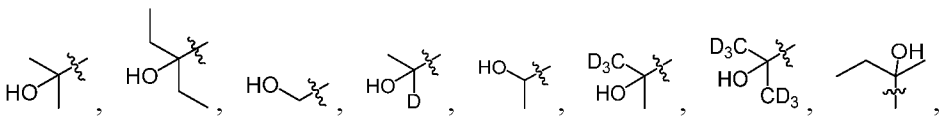
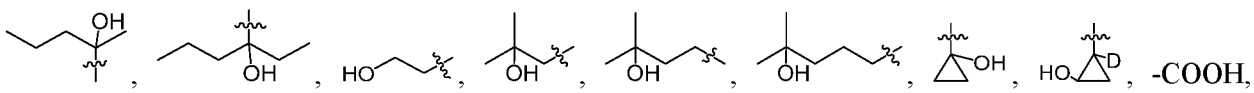
R_{23} and R_{24} together with the carbon atom to which they are both attached form 3-membered carbocyclic ring, 4-membered carbocyclic ring, 5-membered carbocyclic ring, 6-membered carbocyclic ring, and each of the carbocyclic ring at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -OH, methyl, ethyl, propyl or isopropyl;

n is selected from 0, 1, 2 or 3.

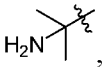
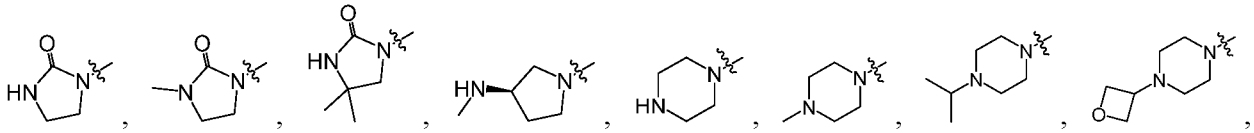
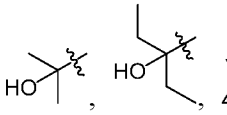
37. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-28, , wherein R_2 is selected from hydrogen, deuterium, -F, -Cl, -Br, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCD_3$, $-N(CD_3)_2$, $-NHCH_2CH_3$, $-N(CH_3CH_2)_2$, $-N(CH_3)(CH_3CH_2)$, $-NHCH_2CH_2CH_3$, $-N(CH_2CH_2CH_3)_2$, $-NHCH(CH_3)_2$, $-N(CH_3)(CH(CH_3)_2)$, $-N(CH(CH_3)_2)_2$, $-NHCH_2CF_3$,

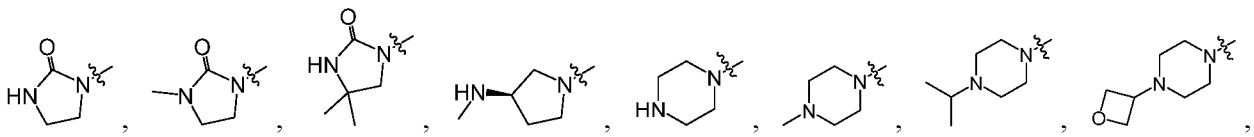
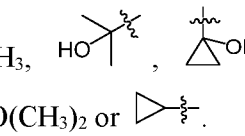


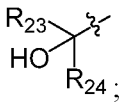
 , ,  , $-SO_2CH_3$, $-SO_2CD_3$, $-SO_2CH_2CH_3$, $-SO_2CH_2CH_2CH_3$, $-SO_2CH(CH_3)_2$, $-SO_2CH(CD_3)_2$, $-SO_2NH_2$, $-SO_2NH(CH_3)$, $-SO_2N(CH_3)_2$, $-SO_2NH(CD_3)$, $-SO_2N(CD_3)_2$, $-SO_2NH(CH_2CH_3)$, $-SO_2N(CH_2CH_3)_2$, $-SO_2NH(CH_2CH_2CH_3)$, $-SO_2N(CH_2CH_2CH_3)_2$, $-CH_3$, $-CH_2D$, $-CD_2H$, $-CD_3$, $-CF_3$, $-CH_2CH_3$, $-CH_2CD_3$, $-CH_2CF_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CD_3$, $-CH_2CH_2CF_3$, $-CH(CH_3)_2$, $-CH(CH_3)(CD_3)$, $-CH(CF_3)_2$, $-CH(CD_3)_2$,  ,  , $-COOCH_3$, $-COOCH_2CH_3$, $-COOCH_2CH_2CH_3$, $-COOCH(CH_3)_2$, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, $-CONH(CD_3)$, $-CON(CD_3)_2$, $-CONH(CH_2CH_3)$, $-CON(CH_2CH_3)_2$, $-CONH(CH_2CH_2CH_3)$, $-CON(CH_2CH_2CH_3)_2$, $-NHCOCH_3$, $-NHCOCH_2CH_3$, $-NHCOCH_2CH_2CH_3$, $-NHCOCH(CH_3)_2$, $-NHSO_2CH_3$, $-NHSO_2CD_3$, $-NHSO_2CH_2CH_3$, $-NHSO_2CH_2CH_3$, $-NHSO_2CH_2CH_2CH_3$, $-NHSO_2CH(CH_3)_2$, $-P(O)H_2$, $-P(O)H(CH_3)$, $-P(O)(CH_3)_2$, $-P(O)H(CD_3)$, $-PO(CD_3)_2$, $-PO(CH_2CH_3)_2$, $-PO(CH_2CH_2\ CH_3)_2$, $-PO(CH(CH_3)_2)_2$ or  .

38. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-28, wherein R_2 is selected from hydrogen, deuterium, -F, -Cl, -Br, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCD_3$, $-N(CD_3)_2$, $-NHCH_2CH_3$, $-N(CH_3CH_2)_2$, $-N(CH_3)(CH_3CH_2)$, $-NHCH_2CH_2CH_3$, $-N(CH_2CH_2CH_3)_2$, $-NHCH(CH_3)_2$, $-N(CH_3)(CH(CH_3)_2)$, $-N(CH(CH_3)_2)_2$, $-NHCH_2CF_3$,  , $-SO_2CH_3$, $-SO_2CD_3$, $-SO_2CH_2CH_3$, $-SO_2CH_2CH_2CH_3$, $-SO_2CH(CH_3)_2$, $-SO_2CH(CD_3)_2$, $-SO_2NH_2$, $-SO_2NH(CH_3)$, $-SO_2N(CH_3)_2$, $-SO_2NH(CD_3)$, $-SO_2N(CD_3)_2$, $-SO_2NH(CH_2CH_3)$, $-SO_2N(CH_2CH_3)_2$, $-SO_2NH(CH_2CH_2CH_3)$, $-SO_2N(CH_2CH_2CH_3)_2$, $-CH_3$, $-CH_2D$, $-CD_2H$, $-CD_3$, $-CF_3$, $-CH_2CH_3$, $-CH_2CD_3$, $-CH_2CF_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CD_3$, $-CH_2CH_2CF_3$, $-CH(CH_3)_2$, $-CH(CH_3)(CD_3)$, $-CH(CF_3)_2$, $-CH(CD_3)_2$,  ,  , $-COOH$, $-COOCH_3$, $-COOCH_2CH_3$, $-COOCH_2CH_2CH_3$, $-COOCH(CH_3)_2$, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, $-CONH(CD_3)$, $-CON(CD_3)_2$, $-CONH(CH_2CH_3)$, $-CON(CH_2CH_3)_2$, $-CONH(CH_2CH_2CH_3)$, $-CON(CH_2CH_2CH_3)_2$, $-NHCOCH_3$, $-NHCOCH_2CH_3$, $-NHCOCH_2CH_2CH_3$, $-NHCOCH(CH_3)_2$,

$-NHSO_2CH_3$, $-NHSO_2CD_3$, $-NHSO_2CH_2CH_3$, $-NHSO_2CH_2CH_3$, $-NHSO_2CH_2CH_2CH_3$, $-NHSO_2CH(CH_3)_2$, $-P(O)H_2$, $-P(O)H(CH_3)$, $-P(O)(CH_3)_2$, $-P(O)H(CD_3)$, $-PO(CD_3)_2$, $-PO(CH_2CH_3)_2$, $-PO(CH_2CH_2\ CH_3)_2$, $-PO(CH(CH_3)_2)_2$ or  .

39. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-28 or 38, wherein R_2 is selected from hydrogen, -Cl, -Br, $-NH_2$,  ,  , $-SO_2CH_3$, $-SO_2NH_2$, $-SO_2NHCH_3$, $-SO_2N(CH_3)_2$, $-CH_3$,  , $-COOH$, $-COOCH_3$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-NHCOCH_3$, $-NHSO_2CH_3$, $-PO(CH_3)_2$ or  .

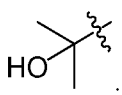
40. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-28 or 34-37, wherein R_2 is selected from hydrogen, -Cl, -Br, $-NH_2$,  , $-SO_2CH_3$, $-SO_2NH_2$, $-SO_2NHCH_3$, $-SO_2N(CH_3)_2$, $-CH_3$,  , $-COOCH_3$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-NHCOCH_3$, $-NHSO_2CH_3$, $-PO(CH_3)_2$ or  .

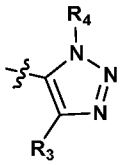
41. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-28 or 34, wherein R_2 is  ;

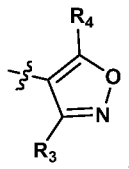
Each of R_{23} and R_{24} at each occurrence is $-C_{1-6}$alkyl.

42. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-28, 34 or 41, wherein each of R_{23} and R_{24} at each occurrence is $-C_{1-3}$alkyl.

43. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-28, 34, 41 or 42, wherein each of R_{23} and R_{24} at each occurrence is selected from methyl, ethyl, propyl or isopropyl.

44. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-28, 34 or 41-43, wherein R_2 is  .

45. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-44, wherein the A is  .

46. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-44, wherein the A is  .

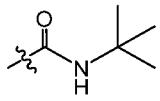
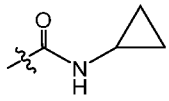
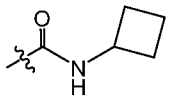
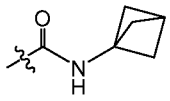
47. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-46, wherein each of R_3 and R_4 at each occurrence is independently selected from hydrogen, deuterium, halogen, -CN, -SOR_5, -SO_2R_5, -SO_2NH_2, -SO_2NHR_5, -$SO_2NR_5R_6$, -C_{1-3}alkyl, -C_{1-3}alkoxy, -COR_5, -$CONH_2$, -$CONHR_5$, -$CONR_5R_6$, -$P(O)H_2$, -$P(O)HR_5$ or -POR_5R_6; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen or -OH;

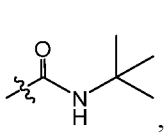
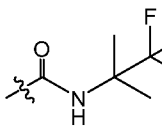
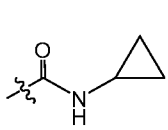
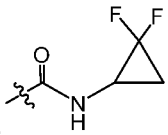
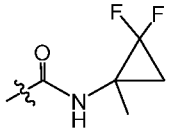
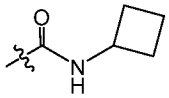
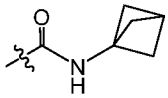
Each of R_5 and R_6 at each occurrence is independently selected from deuterium; -C_{1-3}alkyl; -C_{5-6}aryl; -C_{5-6}heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; or -C_{3-6}carbocyclic, and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen, -C_{1-3}alkyl or -C_{1-3}alkoxy.

48. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-47, wherein each of R_3 and R_4 at each occurrence is independently selected from hydrogen, deuterium, -F, -Cl, -Br, -CN, -SOR_5, -SO_2R_5, -SO_2NH_2, -SO_2NHR_5, -$SO_2NR_5R_6$, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropyl, -$CONH_2$, -$CONHR_5$, -$CONR_5R_6$, -$P(O)H_2$, -$P(O)HR_5$ or -POR_5R_6; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br or -OH;

Each of R_5 and R_6 at each occurrence is independently selected from deuterium; methyl; ethyl; propyl; isopropyl; phenyl; 5-membered heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; 6-membered heteroaryl containing 1, 2, 3 or 4 heteroatoms selected from N, O, S, SO or SO_2; 3-membered carbocyclic; 4-membered carbocyclic; 5-membered carbocyclic; or 6-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropyl.

49. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-48, wherein each of R_3 and R_4 at each occurrence is independently selected from hydrogen, deuterium, -F, -Cl, -Br, -CN, -$SOCH_3$, -$SOCH_2CH_3$, -$SOCH_2CH_2CH_3$, -$SOCH(CH_3)_2$, -SO_2CH_3, -$SO_2CH_2CH_3$, -$SO_2CH_2CH_2CH_3$, -$SO_2CH(CH_3)_2$, -SO_2NH_2, -SO_2NHCH_3, -$SO_2NHCH_2CH_3$, -$SO_2NHCH_2CH_2CH_3$, -$SO_2NHCH(CH_3)_2$, -$SO_2N(CH_3)_2$, -$SO_2N(CH_2CH_3)_2$, -$SO_2N(CH_3)(CH_2CH_3)$, -$SO_2N(CH_2CH_2CH_3)_2$, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -$CH(CH_3)_2$, -OCH_3, -OCH_2CH_3, -$OCH_2CH_2CH_3$, -$OCH(CH_3)_2$, -$CONH_2$, -$CONHCH_3$, -$CONHCH_2CH_3$, -$CONHCH_2CH_2CH_3$,

-$CONHCH(CH_3)_2$,  ,  ,  ,  , -$CON(CH_3)_2$, -$CON(CH_2CH_3)_2$, -$CON(CH_3)(CH_2CH_3)$, -$CON(CH_2CH_2CH_3)_2$, -$P(O)H_2$, -$P(O)HCH_3$, -$P(O)HCH_2CH_3$, -$P(O)HCH_2CH_2CH_3$, -$P(O)HCH(CH_3)_2$, -$PO(CH_3)_2$, -$PO(CH_2CH_3)_2$, -$PO(CH_3)(CH_2CH_3)$ or -$PO(CH_2CH_2CH_3)_2$; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F or methyl.

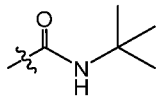
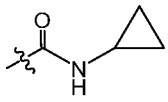
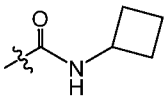
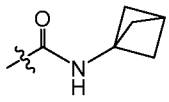
50. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-49, wherein each of R_3 and R_4 at each occurrence is independently selected from hydrogen, deuterium, -F, -Cl, -Br, -CN, -$SOCH_3$, -$SOCD_3$, -$SOCH_2CH_3$, -$SOCH_2CH_2CH_3$, -$SOCH(CH_3)_2$, -SO_2CH_3, -SO_2CD_3, -$SO_2CH_2CH_3$, -$SO_2CH_2CH_2CH_3$, -$SO_2CH(CH_3)_2$, -SO_2NH_2, -SO_2NHCH_3, -SO_2NHCD_3, -$SO_2NHCH_2CH_3$, -$SO_2NHCH_2CH_2CH_3$, -$SO_2NHCH(CH_3)_2$, -$SO_2N(CH_3)_2$, -$SO_2N(CD_3)_2$, -$SO_2N(CH_2CH_3)_2$, -$SO_2N(CH_3)(CH_2CH_3)$, -$SO_2N(CH_2CH_2CH_3)_2$, -CH_3, -CD_3, -CH_2CH_3, -CD_2CD_3, -$CH_2CH_2CH_3$, -$CH_2CH_2CD_3$, -$CH(CH_3)_2$, -$CH(CD_3)_2$, -OCH_3, -OCH_2CH_3, -$OCH_2CH_2CH_3$, -$OCH(CH_3)_2$, -$CONH_2$, -$CONHCH_3$, -$CONHCD_3$, -$CONHCH_2CH_3$, -$CONHCD_2CD_3$, -$CONHCH_2CH_2CH_3$, -$CONHCH(CH_3)_2$,  ,  ,  ,  ,  ,  ,  , -$CON(CH_3)_2$, -$CON(CH_2CH_3)_2$, -$CON(CH_3)(CH_2CH_3)$, -$CON(CH_2CH_2CH_3)_2$, -$P(O)H_2$, -$P(O)HCH_3$, -$P(O)HCH_2CH_3$, -$P(O)HCH_2CH_2CH_3$, -$P(O)HCH(CH_3)_2$, -$PO(CH_3)_2$, -$PO(CH_2CH_3)_2$, -$PO(CH_3)(CH_2CH_3)$ or -$PO(CH_2CH_2CH_3)_2$.

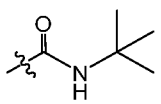
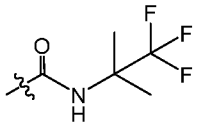
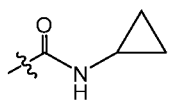
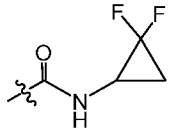
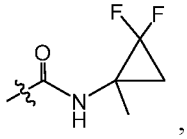
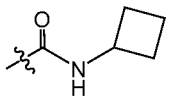
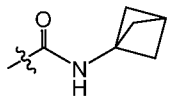
51. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-47, wherein each of R_3 and R_4 at each occurrence is independently selected from -C_{1-3}alkyl, -$CONH_2$, -$CONHR_5$ or -$CONR_5R_6$; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium or halogen;

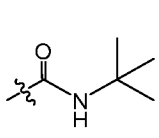
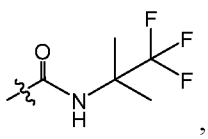
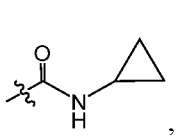
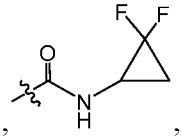
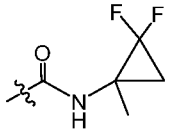
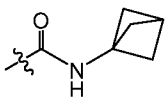
Each of R_5 and R_6 at each occurrence is independently selected from -C_{1-3}alkyl or -C_{3-6}carbocyclic, and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, halogen or -C_{1-3}alkyl.

52. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-47 or 51, wherein each of R_3 and R_4 at each occurrence is independently selected from methyl, ethyl, propyl, isopropyl, -$CONH_2$, -$CONHR_5$ or -$CONR_5R_6$; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl or -Br;

Each of R_5 and R_6 at each occurrence is independently selected from methyl, ethyl, propyl, isopropyl, 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic or 6-membered carbocyclic, and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl, -Br, methyl, ethyl, propyl or isopropyl.

53. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-47, 51 or 52, wherein each of R_3 or R_4 at each occurrence is independently selected from $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2CH_3$, $-OCH(CH_3)_2$, $-CONH_2$, $-CONHCH_3$, $-CONHCH_2CH_3$, $-CONHCH_2CH_2CH_3$, $-CONHCH(CH_3)_2$,     , $-CON(CH_3)_2$, $-CON(CH_2CH_3)_2$, $-CON(CH_3)(CH_2CH_3)$ or $-CON(CH_2CH_2CH_3)_2$; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F or methyl.

54. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-47 or 51-53, wherein each of R_3 or R_4 at each occurrence is independently selected from $-CH_3$, $-CD_3$, $-CH_2CH_3$, $-CD_2CD_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CD_3$, $-CH(CH_3)_2$, $-CH(CD_3)_2$, $-CONH_2$, $-CONHCH_3$, $-CONHCD_3$, $-CONHCH_2CH_3$, $-CONHCD_2CD_3$, $-CONHCH_2CH_2CH_3$, $-CONHCH(CH_3)_2$,      ,   , $-CON(CH_3)_2$, $-CON(CH_2CH_3)_2$, $-CON(CH_3)(CH_2CH_3)$ or $-CON(CH_2CH_2CH_3)_2$.

55. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any of claims 1-47 or 51-54, wherein each of R_3 or R_4 at each occurrence is independently selected from $-CH_3$, $-CD_3$, $-CONH_2$, $-CONHCH_3$, $-CONHCH_2CH_3$,   ,    or  .

56. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-47 or 51, wherein each of R_3 and R_4 at each occurrence is independently selected from $-C_{1-3}$alkyl, and the $-C_{1-3}$alkyl is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl or -Br.

57. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-47, 51 or 56, wherein each of R_3 and R_4 at each occurrence is independently selected from, methyl, ethyl, propyl or isopropyl; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium, -F, -Cl or -Br.

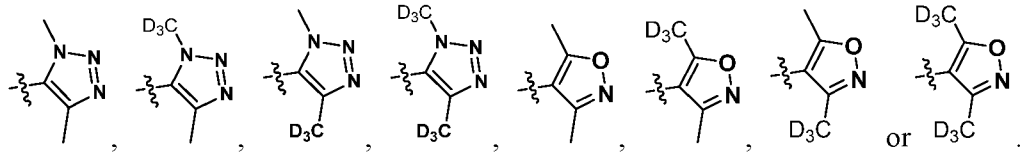
58. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-47, 51, 56 or 57, wherein each of R_3 and R_4 at each occurrence is independently selected from methyl, ethyl, propyl or isopropyl; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is independently selected from deuterium or -F.

59. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-47, 51 or 56-58, wherein each of R_3 and R_4 at each occurrence is independently selected from $-CH_3$, $-CH_2D$, $-CD_2H$, $-CD_3$, $-CF_3$, $-CH_2CH_3$, $-CH_2CD_3$, $-CH_2CF_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CD_3$, $-CH_2CH_2CF_3$, $-CH(CH_3)_2$, $-CH(CH_3)(CD_3)$, $-CH(CF_3)_2$ or $-CH(CD_3)_2$.

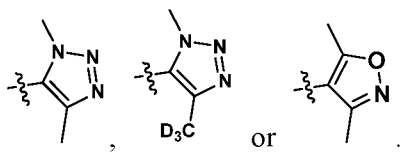
60. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-47, 51 or 56, wherein each of R_3 and R_4 at each occurrence is selected from $-C_{1-3}$alkyl or the $-C_{1-3}$alkyl substituted with 1, 2, 3, 4, 5 or 6 deuterium.

61. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-47, 51, 56 or 60, wherein each of R_3 and R_4 at each occurrence is selected from methyl, ethyl, propyl, isopropyl, methyl substituted with deuterium, ethyl substituted with deuterium, propyl substituted with deuterium or isopropyl substituted with deuterium.

62. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-47, 51, 56, 60 or 61, wherein the A is selected from:

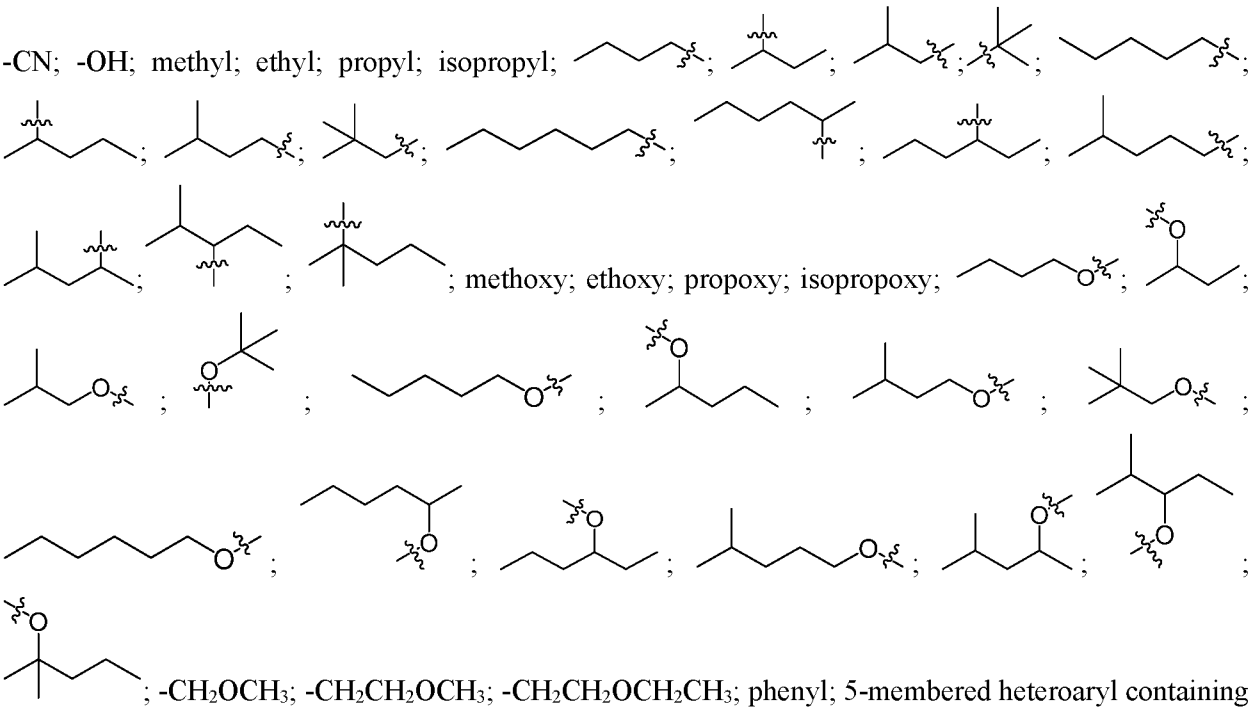


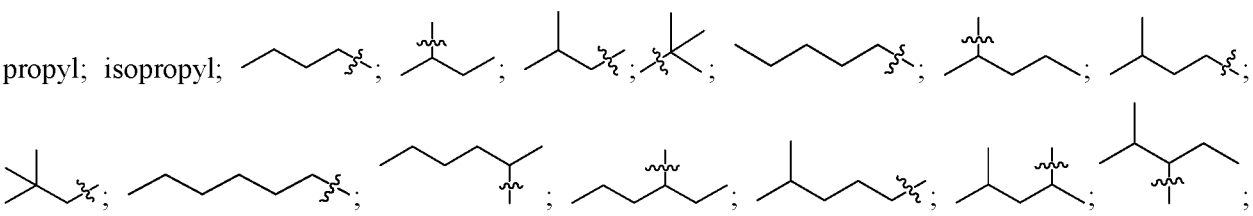
63. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-47, 51, 56 or 60-62, wherein the A is independently selected from:

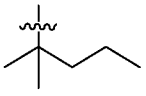


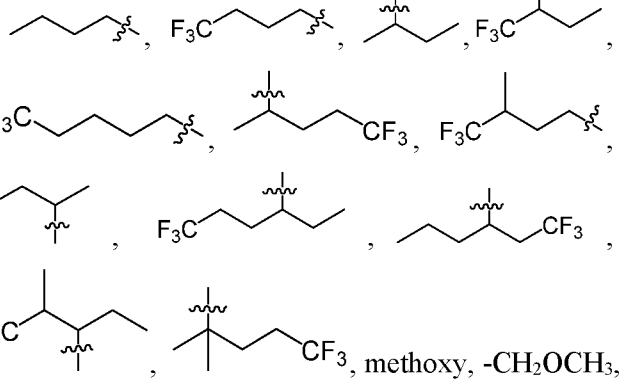
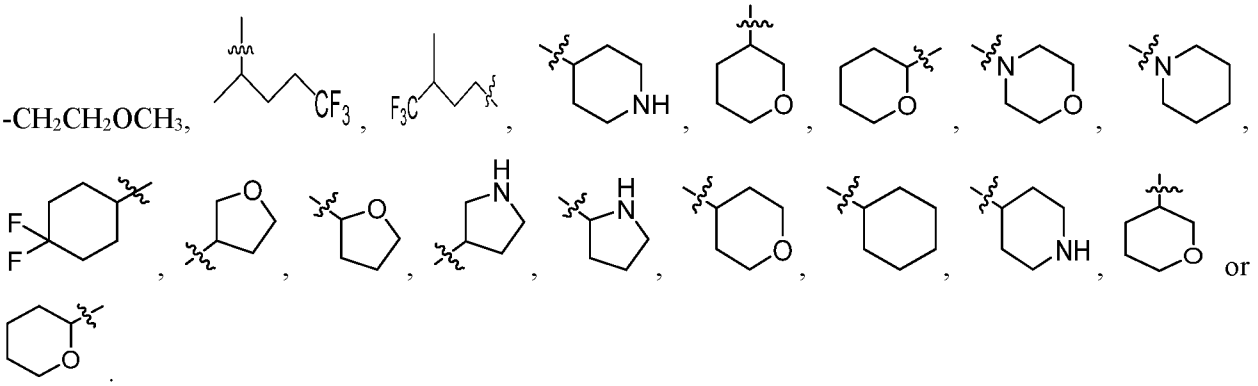
64. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-63, wherein W_1 is selected from hydrogen; deuterium; -F; -Cl; $-NH_2$; -CN; -OH; carboxyl; $-C_{1-6}$alkyl; $-C_{1-6}$alkoxy; $-C_{1-3}$alkylene-C_{1-3}alkoxy; phenyl; 5-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O; 6-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O; 3-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from

N, O; 4-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O; 5-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O; 6-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O; 3-membered carbocyclic; 4-membered carbocyclic; 5-membered carbocyclic; or 6-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl,or $-C_{1-3}$alkoxy.

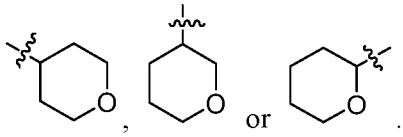
65. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-64, wherein W_1 is selected from hydrogen; deuterium; -F; -Cl; $-NH_2$; -CN; -OH; methyl; ethyl; propyl; isopropyl;  ; $-CH_2OCH_3$; $-CH_2CH_2OCH_3$; $-CH_2CH_2OCH_2CH_3$; phenyl; 5-membered heteroaryl containing 1 or 2 heteroatoms selected from N or O; 6-membered heteroaryl containing 1 or 2 heteroatoms selected from N or O; 5-membered heterocyclic containing 1 or 2 heteroatoms selected from N or O; 6-membered heterocyclic containing 1 or 2 heteroatoms selected from N or O; 5-membered carbocyclic; or 6-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4, 5 or 6 substituents, and the said each of substituents at each occurrence is selected from deuterium, -F, -Cl, $-NH_2$, -CN, -OH, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy,or isopropoxy.

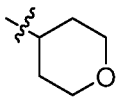
66. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-65, wherein W_1 is selected from hydrogen; deuterium; -F; methyl; ethyl; propyl; isopropyl; 

 ; methoxy; $-CH_2OCH_3$; $-CH_2CH_2OCH_3$; 6-membered heteroaryl containing 1 or 2 heteroatoms selected from N or O; 5-membered heterocyclic containing 1 or 2 heteroatoms selected from N or O; 6-membered heterocyclic containing 1 or 2 heteroatoms selected from N or O; 5-membered carbocyclic; or 6-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with deuterium or -F.

67. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-66, wherein W_1 is selected from hydrogen, deuterium, -F, $-CH_3$, $-CD_3$, $-CH_2F$, $-CF_2H$, $-CF_3$, $-CH_2CH_3$, $-CH_2CD_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CD_3$, $-CH(CH_3)_2$, $-CH(CF_3)_2$, $-CH(CD_3)_2$,  , methoxy, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$,  .

68. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-64, wherein W_1 is selected from $-C_{1-6}$alkyl substituted with F or 6-membered heterocyclic containing 1 heteroatoms selected from O.

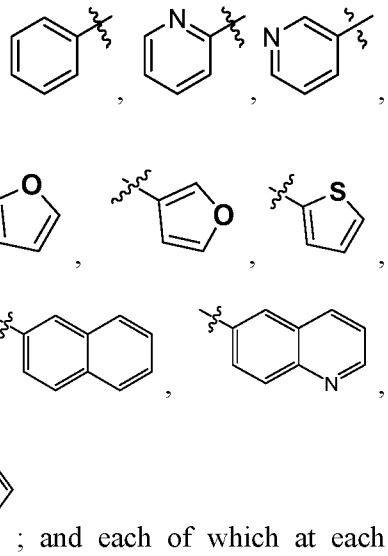
69. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-64 or 68, wherein W_1 is selected from $-C_{1-6}$alkyl substituted with F,  .

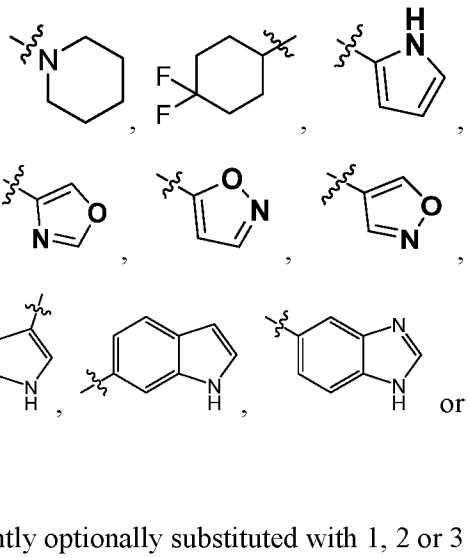
70. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-64, 68 or 69, wherein W_1 is selected from $-CH_2CH_2CF_3$ or  .

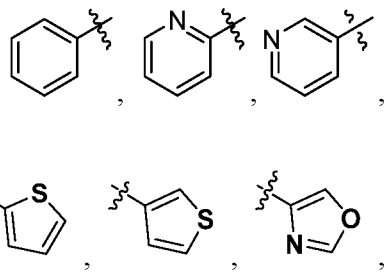
71. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-70, wherein W_2 is selected from hydrogen; deuterium; -F; -Cl; -NH_2; -CN; -OH; carboxyl; -C_{1-3}alkyl; -C_{1-3}alkoxy; phenyl; naphthyl; 5-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O or S; 6-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O,or S; 7-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O or S; 8-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O or S; 9-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O or S; 10-membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O,or S; 3-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O or S; 4-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O or S; 5-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O or S; 6-membered heterocyclic containing 1, 2 or 3 heteroatoms selected from N, O or S; 3-membered carbocyclic; 4-membered carbocyclic; 5-membered carbocyclic; or 6-membered carbocyclic; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4 or 5 substituents, and the said each of substituents at each occurrence is selected from deuterium, halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

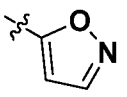
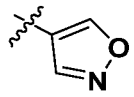
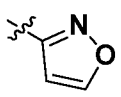
72. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-71, wherein W_2 is selected from hydrogen; deuterium; phenyl; 5-membered heteroaryl containing 1 or 2 heteroatoms selected from N, O or S; or 6-membered heteroaryl containing 1 or 2 heteroatoms selected from N, O or S; and each of which at each occurrence is independently optionally substituted with 1, 2, 3, 4 or 5 substituents, and the said each of substituents at each occurrence is selected from deuterium, -F, -Cl, -Br, -NH_2, -CN, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

73. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-72, wherein W_2 is selected from phenyl; 5-membered heteroaryl containing 1 or 2 heteroatoms selected from N, O,or S; or 6-membered heteroaryl containing 1 or 2 heteroatoms selected from N, O or S; and each of which at each occurrence is independently optionally substituted with 1, 2 or 3 substituents, and the said each of substituents at each occurrence is selected from -F, -Cl, -Br, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

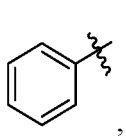
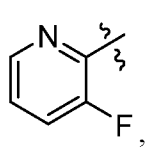
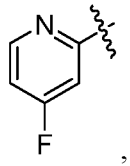
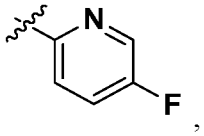
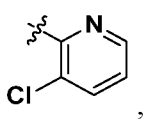
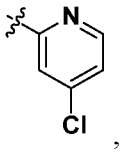
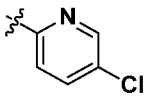
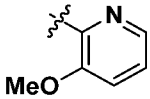
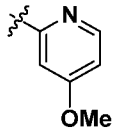
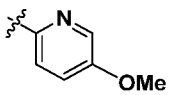
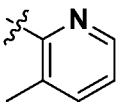
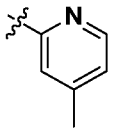
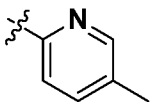
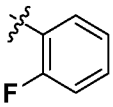
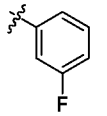
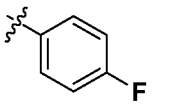
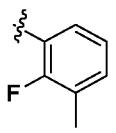
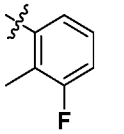
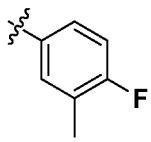
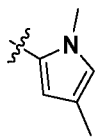
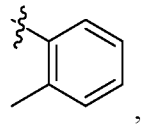
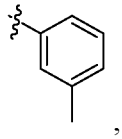
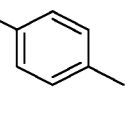
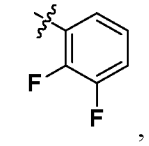
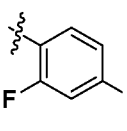
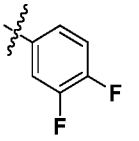
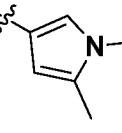
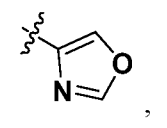
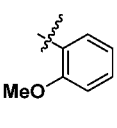
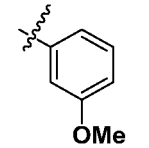
74. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-71, wherein W_2 is selected from  ; and each of which at each occurrence is independently optionally substituted with 1, 2 or 3 substituents, and the said each of substituents at each occurrence is selected from -F, -Cl, methyl or methoxy.

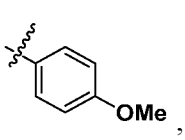
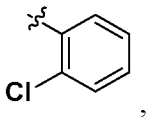
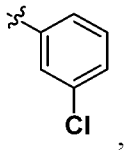
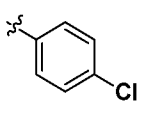
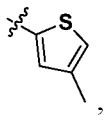
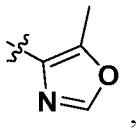
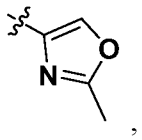
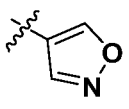
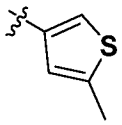
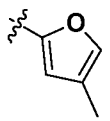
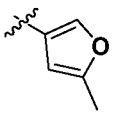
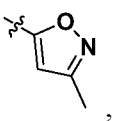
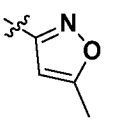
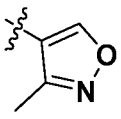
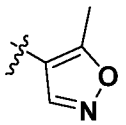
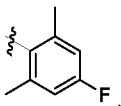
75. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-71, wherein W_2 is selected from  ; and each of which at each occurrence is independently optionally substituted with 1, 2 or 3 substituents, and the said each of substituents at each occurrence is selected from -F, -Cl, methyl or methoxy.

76. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-75, wherein W_2 is selected from 




; and each of which at each occurrence is independently optionally substituted with 1, 2 or 3 substituents, and the said each of substituents at each occurrence is selected from -F, -Cl, methyl or methoxy.

77. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-76, wherein W_2 is independently selected from:

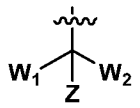
or .

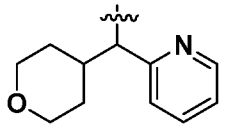
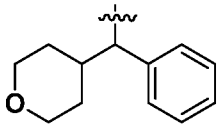
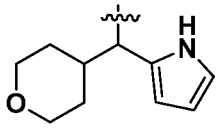
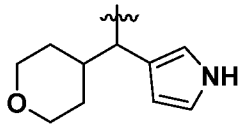
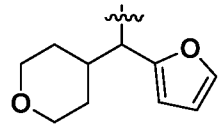
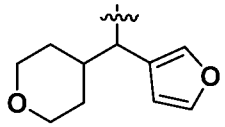
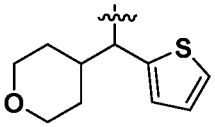
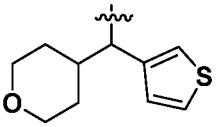
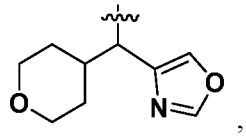
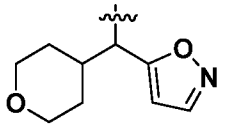
78. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-77, wherein Z is selected from hydrogen, deuterium, -F, -Cl, -OH, -C_{1-3}alkyl or -C_{1-3}alkoxy.

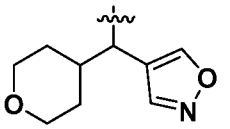
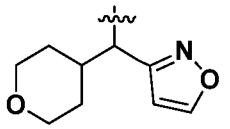
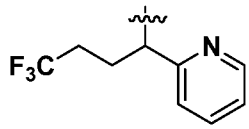
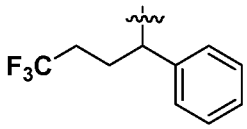
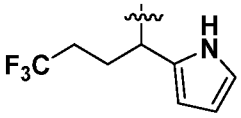
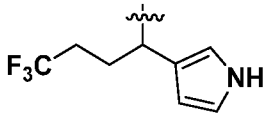
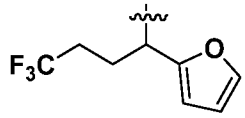
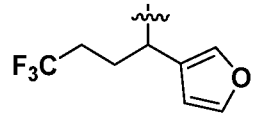
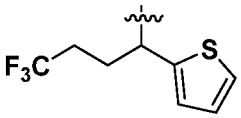
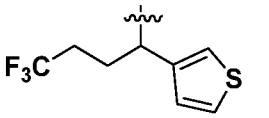
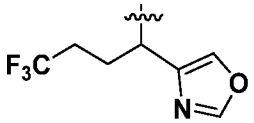
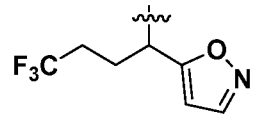
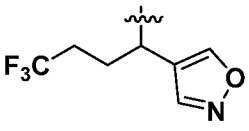
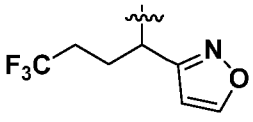
79. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-78, wherein Z is selected from hydrogen, deuterium, -F, -Cl, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

80. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-79, wherein Z is selected from hydrogen or deuterium.

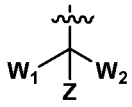
81. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-80, wherein Z is hydrogen.

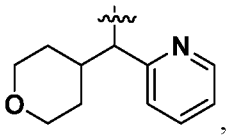
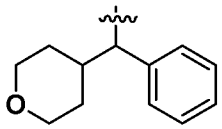
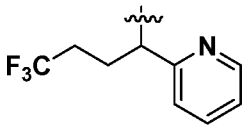
82. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-81, wherein,  is selected from:

; and each of which at each occurrence is independently optionally substituted with 1, 2 or 3 substituents, and the said each of substituents at each occurrence is selected from -F, -Cl, -Br, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

83. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-82, wherein, the  is selected from: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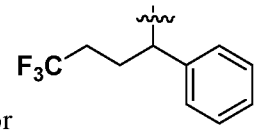
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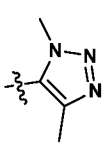
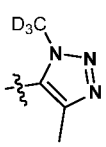
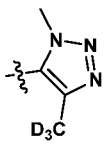
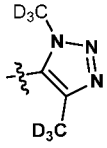
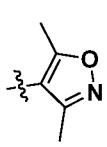
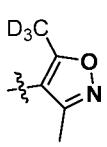
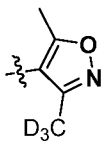
and each of which at each occurrence is independently optionally substituted with 1, 2 or 3 substituents, and the said each of substituents at each occurrence is selected from -F, -Cl, methyl or methoxy.

84. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-83, wherein the A is independently selected from: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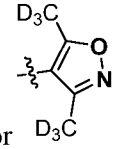
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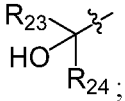
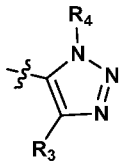
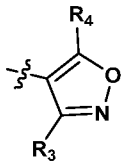
85. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-84, wherein,

R_1 is -C_{1-6}alkyl;

R_2 is  ;

Each of R_{23} and R_{24} at each occurrence is -C_{1-6}alkyl;

the A is  or  ;

Each of R_3 and R_4 at each occurrence is selected from -C_{1-6}alkyl or -C_{1-6}alkyl substituted with 1, 2, 3, 4, 5 or 6 deuterium;

W_1 is selected from -C_{1-6}alkyl substituted with -F or 6-membered heterocyclic containing 1 heteroatoms selected from O;

W_2 is selected from phenyl; 5-membered heteroaryl containing 1 or 2 heteroatoms selected from N, O or S; or 6-membered heteroaryl containing 1 or 2 heteroatoms selected from N, O,or S; and each of which at each occurrence is independently optionally substituted with 1, 2 or 3 substituents, and the said each of substituents at each occurrence is selected from -F, -Cl, -Br, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy;

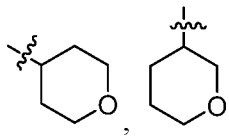
Z is selected from hydrogen or deuterium.

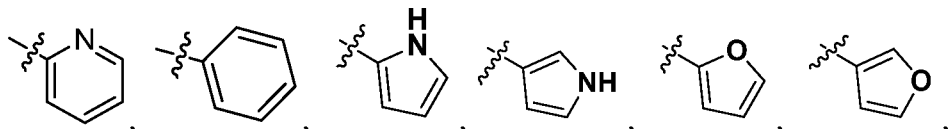
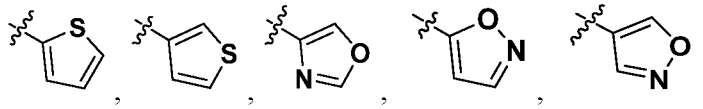
86. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-85, wherein,

R_1 is -C_{1-3}alkyl;

Each of R_{23} and R_{24} at each occurrence is -C_{1-3}alkyl;

Each of R_3 and R_4 at each occurrence is selected from -C_{1-3}alkyl or -C_{1-3}alkyl substituted with 1, 2, 3, 4, 5 or 6 deuterium;

W_1 is selected from -C_{1-6}alkyl substituted with -F,  ;

W_2 is selected from   ; and each of which at each occurrence is independently optionally substituted with 1, 2 or 3 substituents, and the said each of substituents at each occurrence is selected from -F, -Cl, -Br, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy;

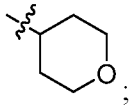
Z is selected from hydrogen.

87. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-86, wherein,

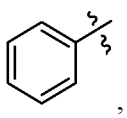
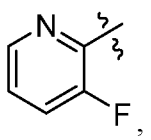
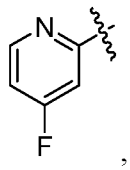
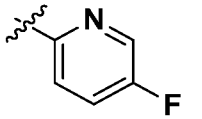
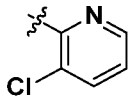
R_1 is selected from methyl, ethyl, propyl or isopropyl;

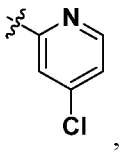
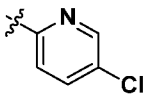
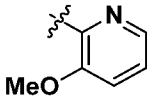
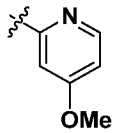
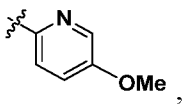
Each of R_{23} or R_{24} at each occurrence is selected from methyl, ethyl, propyl or isopropyl;

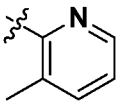
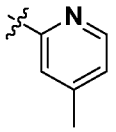
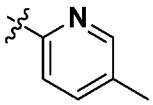
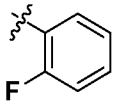
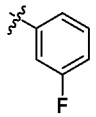
Each of R_3 and R_4 at each occurrence is selected from methyl, ethyl, propyl, isopropyl, methyl substituted with deuterium, ethyl substituted with deuterium, propyl substituted with deuterium or isopropyl substituted with deuterium;

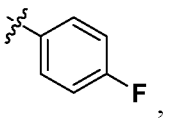
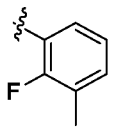
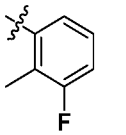
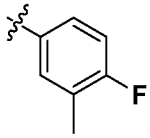
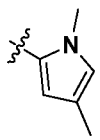
W_1 is selected from $-CH_2CH_2CF_3$ or  ;

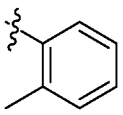
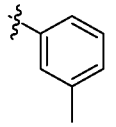
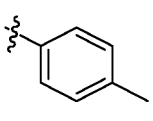
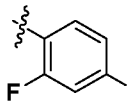
W_2 is selected from:

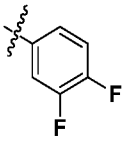
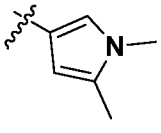
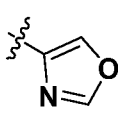
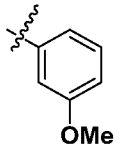
 ,  ,  ,  ,  ,

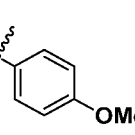
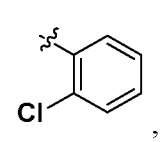
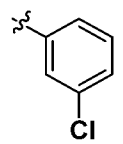
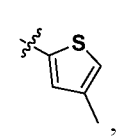
 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

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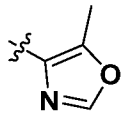
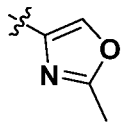
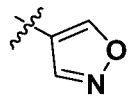
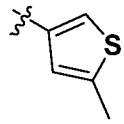
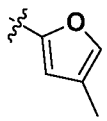
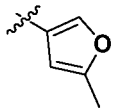
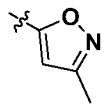
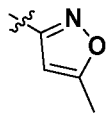
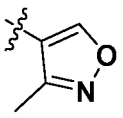
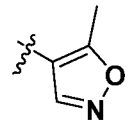
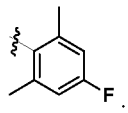
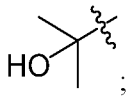
 ,  ,  ,  , 

 ,  ,  ,  ,  ,

or  .

88. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-87, wherein,

R_1 is methyl;

R_2 is  ;

Each of R_3 and R_4 at each occurrence is independently selected from $-CH_3$ or $-CD_3$.

89. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-88, the compound is:

1	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
2	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
3	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
4	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
5	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((2-fluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
6	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((2-methoxyphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
7	2-(4-((3-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
8	2-(4-((2-chlorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
9	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
10	2-(4-((4-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
11	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methoxyphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;

12	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
13	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((5-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
14	2-(4-((5-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
15	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
16	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((5-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
17	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
18	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
19	2-(4-((3-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
20	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((4-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
21	2-(4-((4-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
22	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((5-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
23	2-(4-((5-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
24	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((4-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
25	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((5-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
26	2-(6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
27	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((tetrahydro-2H-pyran-4-yl)(o-tolyl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
28	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
29	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((5-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
30	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
31	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((4-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
32	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((5-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
33	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-fluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
34	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((tetrahydro-2H-pyran-4-yl)(m-tolyl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
35	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((tetrahydro-2H-pyran-4-yl)(p-tolyl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
36	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methoxyphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
37	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((2-fluoro-3-methylphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
38	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoro-2-methylphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;

39	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-fluoro-3-methylphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
40	2-(4-((2,3-difluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
41	2-(4-((2,4-difluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
42	2-(4-((3,4-difluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
43	2-(4-((3-chlorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
44	2-(4-((4-chlorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
45	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-phenylbutyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
46	2-(6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-phenylbutyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
47	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(3-fluoropyridin-2-yl)butyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
48	2-(6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(3-methylpyridin-2-yl)butyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
49	1-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)cyclopropan-1-ol;
50	1-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)cyclopropan-1-ol;
51	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(oxazol-4-yl)butyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
52	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(5-methyloxazol-4-yl)butyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
53	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(2-methyloxazol-4-yl)butyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
54	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(isoxazol-4-yl)butyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
55	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(5-methylisoxazol-4-yl)butyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
56	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(3-methylisoxazol-4-yl)butyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
57	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((2-methyloxazol-4-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
58	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((5-methylisoxazol-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
59	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methylisoxazol-5-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
60	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((5-methylfuran-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
61	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methylfuran-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isothiazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
62	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
63	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
64	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
65	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((2-fluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;

66	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((2-methoxyphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
67	2-(4-((3-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
68	2-(4-((2-chlorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
69	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
70	2-(4-((4-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
71	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methoxyphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
72	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((4-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
73	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((5-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
74	2-(4-((5-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
75	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
76	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((5-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
77	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
78	2-(4-((3-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
79	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((4-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
80	2-(4-((4-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
81	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((5-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
82	2-(4-((5-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
83	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((4-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
84	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((5-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
85	2-(1-methyl-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
86	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((tetrahydro-2H-pyran-4-yl)(o-tolyl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol
87	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
88	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((5-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
89	2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
90	2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-((4-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
91	2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-((5-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
92	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-fluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;

93	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((tetrahydro-2H-pyran-4-yl)(m-tolyl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
94	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((tetrahydro-2H-pyran-4-yl)(p-tolyl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
95	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methoxyphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
96	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((2-fluoro-3-methylphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
97	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoro-2-methylphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
98	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-fluoro-3-methylphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
99	2-(4-((2,3-difluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
100	2-(4-((2,4-difluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
101	2-(4-((3,4-difluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
102	2-(4-((3-chlorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
103	2-(4-((4-chlorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
104	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-phenylbutyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
105	2-(1-methyl-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-phenylbutyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
106	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(3-fluoropyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
107	2-(1-methyl-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(3-methylpyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
108	2-(1-methyl-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(oxazol-4-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol
109	1-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)cyclopropan-1-ol;
110	1-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)cyclopropan-1-ol;
111	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(oxazol-4-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
112	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(5-methyloxazol-4-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
113	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(2-methyloxazol-4-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
114	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(isoxazol-4-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
115	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(5-methylisoxazol-4-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
116	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(3-methylisoxazol-4-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
117	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((2-methyloxazol-4-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
118	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((5-methylisoxazol-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
119	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((3-methylisoxazol-5-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;

120	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((5-methylfuran-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
121	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((4-methylfuran-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
122	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((4-methylthiophen-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
123	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((5-methylthiophen-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
124	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((1,4-dimethyl-1H-pyrrol-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
125	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((1,5-dimethyl-1H-pyrrol-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
126	(S)-2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
127	2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-((tetrahydro-2H-pyran-4-yl)(o-tolyl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
128	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-3-(methylsulfonyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine;
129	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-sulfonamide;
130	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-N,1-dimethyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-sulfonamide;
131	(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)dimethylphosphine oxide;
132	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxamide;
133	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-N,1-dimethyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxamide;
134	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-N,N,1-trimethyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxamide;
135	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-N,N,1-trimethyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-sulfonamide;
136	1-(3-chloro-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)pyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-1(4H)-yl)-2-methylpropan-2-ol;
137	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-amine;
138	N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)acetamide;
139	N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)methanesulfonamide;
140	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-ethyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
141	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-isopropyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
142	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1-(2,2,2-trifluoroethyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
143	3-chloro-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-(methylsulfonyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine;
144	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-3-methyl-1-(methylsulfonyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine;
145	2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-(4,4,4-trifluoro-1-(3-methylpyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
146	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;

147	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
148	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
149	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
150	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((2-fluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
151	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((2-methoxyphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
152	2-(4-((3-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
153	2-(4-((2-chlorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
154	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
155	2-(4-((4-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
156	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methoxyphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
157	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
158	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((5-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
159	2-(4-((5-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
160	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
161	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((5-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
162	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
163	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
164	2-(4-((3-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
165	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((4-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
166	2-(4-((4-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
167	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((5-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
168	2-(4-((5-chloropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
169	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((4-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
170	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((5-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
171	2-(6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
172	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((tetrahydro-2H-pyran-4-yl)(o-tolyl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
173	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;

174	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((5-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
175	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
176	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((4-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
177	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((5-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
178	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-fluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
179	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((tetrahydro-2H-pyran-4-yl)(m-tolyl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
180	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((tetrahydro-2H-pyran-4-yl)(p-tolyl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
181	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methoxyphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
182	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((2-fluoro-3-methylphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
183	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoro-2-methylphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
184	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-fluoro-3-methylphenyl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
185	2-(4-((2,3-difluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
186	2-(4-((2,4-difluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
187	2-(4-((3,4-difluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
188	2-(4-((3-chlorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
189	2-(4-((4-chlorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
190	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-phenylbutyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
191	2-(6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-phenylbutyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
192	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(3-fluoropyridin-2-yl)butyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
193	2-(6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(3-methylpyridin-2-yl)butyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
194	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(oxazol-4-yl)butyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
195	2-(6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(oxazol-4-yl)butyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
196	1-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)cyclopropan-1-ol;
197	1-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)cyclopropan-1-ol;
198	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(5-methyloxazol-4-yl)butyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
199	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(2-methyloxazol-4-yl)butyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
200	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(isoxazol-4-yl)butyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;

201	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(5-methylisoxazol-4-yl)butyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
202	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(4,4,4-trifluoro-1-(3-methylisoxazol-4-yl)butyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
203	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((2-methyloxazol-4-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
204	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((5-methylisoxazol-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
205	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methylisoxazol-5-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
206	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((5-methylfuran-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
207	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methylfuran-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-4H-isoxazolo[5',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
208	(S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
209	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(3-methylpyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
210	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-yl)propan-2-ol;
211	2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
212	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine;
213	3-bromo-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine;
214	1-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)-4,4-dimethylimidazolidin-2-one;
215	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-3-(piperazin-1-yl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine
216	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-3-(4-methylpiperazin-1-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine;
217	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-3-(4-(oxetan-3-yl)piperazin-1-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine;
218	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-3-(4-isopropylpiperazin-1-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine;
219	(3R)-1-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)-N-methylpyrrolidin-3-amine;
220	1-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)imidazolidin-2-one;
221	1-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)-3-methylimidazolidin-2-one;
222	methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate;
223	2-(1-cyclopropyl-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
224	2-(1-(difluoromethyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
225	2-(1-(2,2-difluoroethyl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
226	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1-(2,2,2-trifluoroethyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
227	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-(methyl-d3)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;

228	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-(2-hydroxyethyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
229	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-ethyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
230	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-(2-(dimethylamino)ethyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol; or
231	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-(methylsulfonyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol.

90. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-89, the compound further is:

232	2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
233	2-(4-((3-Fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-(methyl-d3)-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
234	2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-amine;
235	3-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)pentan-3-ol;
236	6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylic acid;
237	6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxamide;
238	2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methylpyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
239	2-(4-((3-Fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
240	2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-4-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
241	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methoxypyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
242	2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-(1-(4-fluoro-2,6-dimethylphenyl)ethyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
243	(S)-N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)methanesulfonamide;
244	(S)-N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)acetamide;
245	Methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate;
246	2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
247	(S)-2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
248	(S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-phenylbutyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
249	(S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(3-fluoropyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
250	(S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
251	2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;

252	(S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
253	(S)-2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-((3-methylpyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
254	(S)-2-(6-(3,5-dimethylisoxazol-4-yl)-1-methyl-4-((tetrahydro-2H-pyran-4-yl)(o-tolyl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
255	(S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(oxazol-4-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
256	(S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(4,4,4-trifluoro-1-(3-methylpyridin-2-yl)butyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
257	(S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-((2-methyloxazol-4-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
258	(S)-2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
259	(S)-2-(4-((3-Fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-(methyl-d3)-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
260	(S)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-N,N,1-trimethyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxamide;
261	(S)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxamide;
262	(S)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-N,1-dimethyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxamide;
263	(S)-2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-amine;
264	(S)-3-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)pentan-3-ol;
265	(S)-6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylic acid;
266	(S)-6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxamide;
267	(S)-2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methylpyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
268	(S)-2-(4-((3-Fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-6-(1-methyl-4-(methyl-d3)-1H-1,2,3-triazol-5-yl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
269	(S)-2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-4-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
270	(S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((4-methoxypyridin-3-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
271	(S)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-methoxypyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
272	(S)-2-(6-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-4-(1-(4-fluoro-2,6-dimethylphenyl)ethyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol;
273	(S)-N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)methanesulfonamide;
274	N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)acetamide; or
275	(S)-Methyl 6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine-3-carboxylate.

91. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-90, the compound further is:

276	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-3-((4-methylpiperazin-1-yl)methyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine;
277	(S)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-3-((4-methylpiperazin-1-yl)methyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine;
278	6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-3-((methylsulfonyl)methyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine;
279	(S)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-3-((methylsulfonyl)methyl)-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridine;
280	4-((6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)methyl)morpholine;
281	(S)-4-((6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)methyl)morpholine;
282	N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)-N-(methylsulfonyl)acetamide;
283	(S)-N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1-methyl-4-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)-N-(methylsulfonyl)acetamide;
284	(R)-2-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol; or
285	(R)-2-(6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoropyridin-2-yl)(tetrahydro-2H-pyran-4-yl)methyl)-1-methyl-1,4-dihydropyrazolo[3',4':4,5]pyrrolo[3,2-b]pyridin-3-yl)propan-2-ol.

92. A pharmaceutical composition comprising at least one compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-91, and at least one pharmaceutically acceptable excipient.

93. The pharmaceutical composition according to claim 92, wherein the said compound in a weight ratio to the said excipient within the range from about 0.0001 to about 10.

94. The pharmaceutical composition according to claim 92 or 93, wherein the said compound in a weight ratio to the said excipient within the range from about 0.0005 to about 0.25.

95. A method of treating a patient having a diseases or conditions related to bromodomain proteins, said method comprising administering to the patient a therapeutically effective amount of at least one compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-91; or the pharmaceutical composition according to any one of claims 92-94.

96. The method according to claim 95, wherein the diseases or conditions related to bromodomain proteins is solid tumor and/or blood tumor.

97. The method according to claim 96, wherein the solid tumor is selected from lung cancer, gastrointestinal cancer, colon cancer, rectal cancer, colorectal cancer and/or ovarian cancer; the blood tumor is selected from myeloma and/or leukemia.

98. The method according to claim 97, wherein the lung cancer contains non-small cell lung cancer and/or small cell lung cancer; the gastrointestinal cancer contains esophageal cancer; the leukemia contains acute myeloid leukemia (AML)） and/or acute lymphocytic leukemia(ALL); the myeloma contains multiple myeloma.

99. A compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof; or the pharmaceutical composition for use in the treatment of diseases or conditions related to bromodomain protein.

100. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof; or the pharmaceutical composition for use in the treatment of diseases or conditions related to bromodomain protein according to claim 99, wherein the diseases or conditions related to bromodomain proteins is solid tumor and/or blood tumor.

101. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof; or the pharmaceutical composition for use in the treatment of diseases or conditions related to bromodomain protein according to claim 100, wherein the solid tumor is selected from lung cancer, gastrointestinal cancer, colon cancer, rectal cancer, colorectal cancer and/or ovarian cancer; the blood tumor is selected from myeloma and/or leukemia.

102. The compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof; or the pharmaceutical composition for use in the treatment of diseases or conditions related to bromodomain protein according to claim 101, the lung cancer contains non-small cell lung cancer and/or small cell lung cancer; the gastrointestinal cancer contains esophageal cancer; the leukemia contains acute myeloid leukemia (AML)） and/or acute lymphocytic leukemia(ALL); the myeloma contains multiple myeloma.

103. Use of the compound of formula I, a pharmaceutically acceptable salt thereof or stereoisomer thereof according to any one of claims 1-91; or the pharmaceutical composition according to any one of claims 92-94 for the manufacture of a medicament for the treatment of diseases or conditions related to bromodomain protein.

104. The use according to claim 103, wherein the diseases or conditions related to bromodomain proteins is solid tumor and/or blood tumor.

105. The use according to claim 104, wherein the solid tumor is selected from lung cancer, gastrointestinal cancer, colon cancer, rectal cancer, colorectal cancer and/or ovarian cancer; the blood tumor is selected from myeloma and/or leukemia.

106. The use according to claim 105, wherein the lung cancer contains non-small cell lung cancer and/or small cell lung cancer; the gastrointestinal cancer contains esophageal cancer; the leukemia contains acute myeloid leukemia (AML)） and/or acute lymphocytic leukemia(ALL); the myeloma contains multiple myeloma.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2019/084601

A. CLASSIFICATION OF SUBJECT MATTER

C07D 471/14(2006.01)i; A61K 31/437(2006.01)i; A61P 35/00(2006.01)i

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 471/-, A61K 31/-, A61P 35/-

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)

CNABS, CNKI, EPODOC, WPI, REGISTRY(STN), CAPLUS(STN): bromodomain, extra-terminal, BET, inhibitor, cancer, tumor, tumour

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017124936 A1 (NINGBO WENDA PHARMA TECHNOLOY LTD.) 27 July 2017 (2017-07-27) abstract, claims 1, 10-13	1-106
A	WO 2014164596 A1 (THE REGENTS OF THE UNIVERSITY OF MICHIGAN) 09 October 2014 (2014-10-09) the whole document	1-106
A	WO 2016183118 A1 (BRISTOL-MYERS SQUIBB COMPANY) 17 November 2016 (2016-11-17) the whole document	1-106

☐ 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	Date of mailing of the international search report
08 July 2019	**29 July 2019**

Name and mailing address of the ISA/CN	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2019/084601

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **95-98**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 95-98 are directed to the methods for the treatment of human or animal body by therapy. But the search has been carried out and based on the following subject matter: the use of a compound according to any one of claims in the manufacture of medicaments for the treatment of diseases.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2019/084601

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
WO	2017124936	A1	27 July 2017	US	2019031660	A1	31 January 2019
				EP	3406612	A1	28 November 2018
				JP	2019504120	A	14 February 2019
				KR	20180108675	A	04 October 2018
				CN	108137589	A	08 June 2018
WO	2014164596	A1	09 October 2014	AU	2014249192	A1	10 September 2015
				EP	2970312	A1	20 January 2016
				JP	6401773	B2	10 October 2018
				US	2017281773	A1	05 October 2017
				EP	2970312	A4	10 August 2016
				US	2014256706	A1	11 September 2014
				US	9675697	B2	13 June 2017
				AU	2014249192	B2	21 December 2017
				EP	2970312	B1	15 November 2017
				CN	105377851	A	02 March 2016
				CA	2903463	A1	09 October 2014
				CN	105377851	B	20 July 2018
				JP	2016514134	A	19 May 2016
WO	2016183118	A1	17 November 2016	JP	2018515525	A	14 June 2018
				US	9725449	B2	08 August 2017
				TW	201713657	A	16 April 2017
				UY	36677	A	30 November 2016
				EP	3294739	A1	21 March 2018
				US	2016333013	A1	17 November 2016
				CN	107709322	A	16 February 2018