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

(19) World Intellectual Property
Organization
International Bureau

(43) International Publication Date
25 June 2015 (25.06.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/091584 A1

(51) International Patent Classification:
C07D 513/04 (2006.01) *A61P 29/00* (2006.01)
A61K 31/429 (2006.01) *A61P 37/00* (2006.01)

(21) International Application Number:
PCT/EP2014/078108

(22) International Filing Date:
17 December 2014 (17.12.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/917,531 18 December 2013 (18.12.2013) US

(71) Applicant *(for all designated States except US)*: **F. HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, CH-4070 Basel (CH).

(71) Applicant *(for US only)*: **GENENTECH, INC.** [US/US]; 1 DNA Way, South San Francisco, CA 94080 (US).

(72) Inventors: **GANCIA, Emanuela**; c/o Argenta Discovery 2009 Limited, 8/9 Spire Green Centre, Flex Meadow, Harlow Essex CM19 5TR (GB). **LAI, Yingjie**; c/o Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080 (US). **LIANG, Jun**; c/o Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080 (US). **MACLEOD, Calum**; c/o Argenta Discovery 2009 Limited, 8/9 Spire Green Centre, Flex Meadow, Harlow Essex CM19 5TR (GB). **MAGNUSON, Steven, R.**; c/o Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080 (US). **SAJAD, Mohammed**; c/o Argenta Discovery 2009 Limited, 8/9 Spire Green Centre, Flex Meadow, Harlow Essex CM19 5TR (GB). **TSUI, Vickie, H.**; c/o Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080 (US). **WILLIAMS, Karen**; c/o Argenta Discovery 2009 Limited, 8/9 Spire Green Centre, Flex Meadow, Harlow Essex CM19 5TR (GB). **ZHANG, Birong**; c/o Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080 (US).

(74) Agent: **SCHIRLIN, Julien**; Grenzacherstrasse 124, CH-4070 Basel (CH).

(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, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, 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).

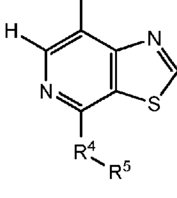
Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

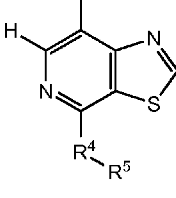
Published:

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

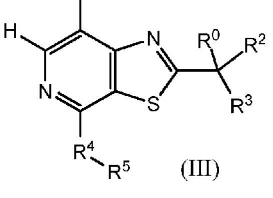
(54) **Title**: THIAZOLOPYRIDINE COMPOUNDS, COMPOSITIONS AND THEIR USE AS TYK2 KINASE INHIBITORS



(I)



(II)



(III)

(57) **Abstract**: Provided are thiazolopyridine compounds that are inhibitors of TYK2 kinase, compositions containing these compounds and methods for treating diseases mediated by TYK2 kinase. In particular, provided are compounds of Formula (I), (II) or (III), stereoisomers, tautomers, solvates, prodrugs or pharmaceutically acceptable salts thereof, where X, R^0, R^1, R^2, R^3, R^4 and R^5 are defined herein, pharmaceutical compositions comprising the compound and a pharmaceutically acceptable carrier, adjuvant or vehicle, methods of using the compound or composition in therapy, for example, for treating a disease or condition mediated by TYK2 kinase in a patient.

WO 2015/091584 A1

THIAZOLOPYRIDINE COMPOUNDS, COMPOSITIONS AND THEIR USE AS TYK2 KINASE INHIBITORS

FIELD OF THE INVENTION

The present invention relates to organic compounds useful for therapy and/or prophylaxis in a patient, and in particular to inhibitors of TYK2 kinase useful for treating diseases mediated by TYK2 kinase.

BACKGROUND OF THE INVENTION

Cytokine pathways mediate a broad range of biological functions, including many aspects of inflammation and immunity. Janus kinases (JAK), including JAK1, JAK2, JAK3 and TYK2, are cytoplasmic protein kinases that associate with type I and type II cytokine receptors and regulate cytokine signal transduction. Cytokine engagement with cognate receptors triggers activation of receptor associated JAKs and this leads to JAK-mediated tyrosine phosphorylation of signal transducer and activator of transcription (STAT) proteins and ultimately transcriptional activation of specific gene sets. JAK1, JAK2 and TYK2 exhibit broad patterns of gene expression, while JAK3 expression is limited to leukocytes. Cytokine receptors are typically functional as heterodimers, and as a result, more than one type of JAK kinase is usually associated with cytokine receptor complexes. The specific JAKs associated with different cytokine receptor complexes have been determined in many cases through genetic studies and corroborated by other experimental evidence.

JAK1 is functionally and physically associated with the type I interferon (e.g., IFNalpha), type II interferon (e.g., IFNgamma), IL-2 and IL-6 cytokine receptor complexes. JAK1 knockout mice die perinatally due to defects in LIF receptor signaling. Characterization of tissues derived from JAK1 knockout mice demonstrated critical roles for this kinase in the IFN, IL-10, IL-2/IL-4, and IL-6 pathways. A humanized monoclonal antibody targeting the IL-6 pathway (Tocilizumab) was recently approved by the European Commission for the treatment of moderate-to-severe rheumatoid arthritis.

Biochemical and genetic studies have shown an association between JAK2 and single-chain (e.g., EPO), IL-3 and interferon gamma cytokine receptor families. Consistent with this, JAK2 knockout mice die of anemia. Kinase activating mutations in JAK2 (e.g., JAK2 V617F) are associated with myeloproliferative disorders (MPDs) in humans.

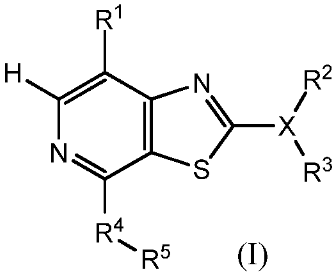
JAK3 associates exclusively with the gamma common cytokine receptor chain, which is present in the IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 cytokine receptor complexes. JAK3 is critical for lymphoid cell development and proliferation and mutations in JAK3 result in severe combined immunodeficiency (SCID). Based on its role in regulating lymphocytes, JAK3 and JAK3-mediated pathways have been targeted for immunosuppressive indications (e.g., transplantation rejection and rheumatoid arthritis).

TYK2 associates with the type I interferon (e.g., IFNalpha), IL-6, IL-10, IL-12 and IL-23 cytokine receptor complexes. Consistent with this, primary cells derived from a TYK2 deficient human are defective in type I interferon, IL-6, IL-10, IL-12 and IL-23 signaling. A fully human monoclonal antibody targeting the shared p40 subunit of the IL-12 and Il-23 cytokines (Ustekinumab) was recently approved by the European Commission for the treatment of moderate-to-severe plaque psoriasis. In addition, an antibody targeting the IL-12 and IL-23 pathways underwent clinical trials for treating Crohn's Disease.

BRIEF SUMMARY OF THE INVENTION

Disclosed are thiazolopyridine compounds that are inhibitors of TYK2 kinase, compositions containing these compounds and methods for treating diseases mediated by TYK2 kinase.

In one aspect, provided are compounds of Formula I:



(I)

or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein:

X is N or CR^0;

R^0 is hydrogen, hydroxyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, C_6-C_{14} aryl, or 5-10-membered heteroaryl, wherein R^0 maybe optionally substituted by R^{10};

R^1 is hydrogen, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, –CN, $–OR^8$, $–SR^8$, $–NR^8R^9$,

$–CF_3$, $–NO_2$, $–C(O)R^8$, $–C(O)OR^8$, $–C(O)NR^8R^9$, $–NR^8C(O)R^9$, $–S(O)R^8$, $–S(O)_2R^8$, $–NR^8S(O)R^9$,

$–NR^8S(O)_2R^9$, $–S(O)NR^8R^9$, $–S(O)_2NR^8R^9$, C_3-C_6 cycloalkyl, 3-6-membered heterocyclyl, 5-6-membered heteroaryl, C_6-C_{14} aryl, $–(C_1$-C_3 alkylene)CN, $–(C_1$-C_3 alkylene)OR^8, $–(C_1$-C_3 alkylene)SR^8,

–(C_1-C_3 alkylene)NR^8R^9, –(C_1-C_3 alkylene)CF_3, –(C_1-C_3 alkylene)NO_2, –(C_1-C_3 alkylene)C(O)R^8,

–(C_1-C_3 alkylene)C(O)OR^8, –(C_1-C_3 alkylene)C(O)NR^8R^9, –(C_1-C_3 alkylene)NR^8C(O)R^9,

–(C_1-C_3 alkylene)S(O)R^8, –(C_1-C_3 alkylene)S$(O)_2R^8$, –(C_1-C_3 alkylene)NR^8S(O)R^9, –(C_1-C_3 alkylene)NR^8S$(O)_2R^9$, –(C_1-C_3 alkylene)S(O)NR^8R^9, –(C_1-C_3 alkylene)S$(O)_2NR^8R^9$,

–(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), –(C_1-C_3 alkylene)(3-6-membered heterocyclyl), –(C_1-C_3 alkylene)(5-6-membered heteroaryl) or –(C_1-C_3 alkylene)(C_6-C_{14} aryl), wherein R^1 is optionally substituted by R^{10};

each R^2 and R^3 is independently hydrogen, hydroxyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, C_6-C_{14} aryl, or 5-10-membered heteroaryl, wherein R^2 and R^3 are each independently optionally substituted by R^{10}; or

> R^2 and R^3 are taken together with the atom to which they are attached to form a ring selected from C_3-C_{10} cycloalkyl and 3-10-membered heterocyclyl, wherein the ring may be optionally substituted by R^{10};

R^4 is hydrogen, –NR^6–, –NR^6R^7, –NR^6C(O)–, –NR^6C(O)O–, –NR^6C(O)NR^7–, –NR^6S(O)–,

–NR^6S$(O)_2$–, –NR^6S(O)NR^7– or –NR^6S$(O)_2NR^7$–;

R^5 is absent, hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, 3-10-membered heterocyclyl or 5-10-membered heteroaryl, wherein R^5 is optionally substituted by R^{10};

R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_6 cycloalkyl, wherein the alkyl, alkenyl, alkynyl and cycloalkyl are independently optionally substituted by halogen, C_1-C_6 alkyl, oxo, –CN, –OR^{11} or –$NR^{11}R^{12}$; or

> R^6 and R^7 are independently taken together with the atom to which they are attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, –OR^{11}, –$NR^{11}R^{12}$ or C_1-C_6 alkyl optionally substituted by halogen;

R^8 and R^9 are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo;

each R^{10} is independently hydrogen, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen,

–CN, –OR^{11}, –SR^{11}, –$NR^{11}R^{12}$, –NO_2, –C=NH(OR^{11}), –C(O)R^{11}, –C(O)OR^{11}, –C(O)$NR^{11}R^{12}$,

–NR^{11}C(O)R^{12}, –S(O)R^{11}, –S$(O)_2R^{11}$, –NR^{11}S(O)R^{12}, –NR^{11}S$(O)_2R^{12}$, –S(O)$NR^{11}R^{12}$, –

$S(O)_2NR^{11}R^{12}$,

C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, 5-10-membered heteroaryl, C_6-C_{14} aryl, –(C_1-C_3 alkylene)CN, –(C_1-C_3 alkylene)OR^{11}, –(C_1-C_3 alkylene)SR^{11}, –(C_1-C_3 alkylene)$NR^{11}R^{12}$,

–(C_1-C_3 alkylene)CF_3, –(C_1-C_3 alkylene)NO_2, –C=NH(OR^{11}), –(C_1-C_3 alkylene)C(O)R^{11}, –(C_1-C_3 alkylene)C(O)OR^{11}, –(C_1-C_3 alkylene)C(O)N$R^{11}R^{12}$, –(C_1-C_3 alkylene)NR^{11}C(O)R^{12},

–(C_1-C_3 alkylene)S(O)R^{11}, –(C_1-C_3 alkylene)$S(O)_2R^{11}$, –(C_1-C_3 alkylene)NR^{11}S(O)R^{12}, –(C_1-C_3 alkylene)N$R^{11}S(O)_2R^{12}$, –(C_1-C_3 alkylene)S(O)N$R^{11}R^{12}$, –(C_1-C_3 alkylene)$S(O)_2NR^{11}R^{12}$,

–(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), –(C_1-C_3 alkylene)(3-10-membered heterocyclyl), –(C_1-C_3 alkylene)(5-10-membered heteroaryl) or –(C_1-C_3 alkylene)(C_6-C_{14} aryl), wherein each R^{10} is independently optionally substituted by halogen, oxo, –OR^{13}, –$NR^{13}R^{14}$, –C(O)R^{13}, –S(O)R^{13}, –$S(O)_2R^{13}$, –(C_1-C_3 alkylene)OR^{13}, –(C_1-C_3 alkylene)$NR^{13}R^{14}$, –(C_1-C_3 alkylene)C(O)R^{13}, –(C_1-C_3 alkylene)S(O)R^{13}, –(C_1-C_3 alkylene)$S(O)_2R^{13}$ or C_1-C_6 alkyl optionally substituted by oxo, –CN or halogen;

R^{11} and R^{12} are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6 membered heteroaryl or 3-6 membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are independently optionally substituted by halogen, oxo, –CN, –OR^{16}, –$NR^{16}R^{17}$ or C_1-C_6 alkyl optionally substituted by halogen, –CN or oxo; or

> R^{11} and R^{12} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, –OR^{16}, –$NR^{16}R^{17}$ or C_1-C_6 alkyl optionally substituted by halogen, oxo or OH;

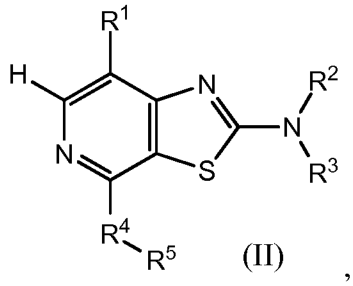
R^{13} and R^{14} are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo; or

> R^{13} and R^{14} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by halogen or oxo; and

R^{16} and R^{17} are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo; or

> R^{16} and R^{17} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by oxo or halogen.

In some embodiments, provided are compounds of Formula II:



(II) ,

or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein:

R^1 is hydrogen, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, –CN, or C_3-C_6 cycloalkyl, wherein R^1 is optionally substituted by R^{10};

R^2 is hydrogen or C_1-C_6 alkyl optionally substituted by R^{10}, or is taken together with R^3 and the nitrogen to which they are attached to form a 3-10-membered heterocyclyl optionally substituted by R^{10};

R^3 is hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, C_6-C_{14} aryl, or 5-10-membered heteroaryl, wherein R^3 may be optionally substituted by R^{10}; or is taken together with R^2 and the nitrogen to which they are attached to form a 3-10-membered heterocyclyl optionally substituted by R^{10};

R^4 is $–NR^6–$, $–NR^6C(O)–$, $–NR^6C(O)O–$ or $–NR^6C(O)NR^7–$;

R^5 is hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 5-10-membered heteroaryl, wherein R^5 is optionally substituted by R^{10};

R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_6 cycloalkyl, wherein the alkyl, alkenyl, alkynyl and cycloalkyl are independently optionally substituted by halogen, C_1-C_6 alkyl, oxo, –CN, $–OR^{11}$ or $–NR^{11}R^{12}$;

each R^{10} is independently hydrogen, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen,

–CN, $–OR^{11}$, $–SR^{11}$, $–NR^{11}R^{12}$, $–NO_2$, $–C{=}NH(OR^{11})$, $–C(O)R^{11}$, $–C(O)OR^{11}$, $–C(O)NR^{11}R^{12}$,

$–NR^{11}C(O)R^{12}$, $–S(O)R^{11}$, $–S(O)_2R^{11}$, $–NR^{11}S(O)R^{12}$, $–NR^{11}S(O)_2R^{12}$, $–S(O)NR^{11}R^{12}$, $–S(O)_2NR^{11}R^{12}$,

C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, 5-10-membered heteroaryl, C_6-C_{14} aryl, –(C_1-C_3 alkylene)CN, –(C_1-C_3 alkylene)OR^{11}, –(C_1-C_3 alkylene)SR^{11}, –(C_1-C_3 alkylene)$NR^{11}R^{12}$,

–(C_1-C_3 alkylene)CF_3, –(C_1-C_3 alkylene)NO_2, $–C{=}NH(OR^{11})$, –(C_1-C_3 alkylene)$C(O)R^{11}$, –(C_1-C_3 alkylene)$C(O)OR^{11}$, –(C_1-C_3 alkylene)$C(O)NR^{11}R^{12}$, –(C_1-C_3 alkylene)$NR^{11}C(O)R^{12}$,

–(C_1-C_3 alkylene)$S(O)R^{11}$, –(C_1-C_3 alkylene)$S(O)_2R^{11}$, –(C_1-C_3 alkylene)$NR^{11}S(O)R^{12}$, –(C_1-C_3 alkylene)$NR^{11}S(O)_2R^{12}$, –(C_1-C_3 alkylene)$S(O)NR^{11}R^{12}$, –(C_1-

C_3 alkylene)S(O)$_2$NR^{11}R^{12}, –(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), –(C_1-C_3 alkylene)(3-10-membered heterocyclyl), –(C_1-C_3 alkylene)(5-10-membered heteroaryl) or –(C_1-C_3 alkylene)(C_6-C_{14} aryl), wherein each R^{10} is independently optionally substituted by halogen, oxo, –OR^{13}, –NR^{13}R^{14}, –C(O)R^{13}, –S(O)R^{13}, –S(O)$_2$R^{13}, –(C_1-C_3 alkylene)OR^{13}, –(C_1-C_3 alkylene)NR^{13}R^{14}, –(C_1-C_3 alkylene)C(O)R^{13}, –(C_1-C_3 alkylene)S(O)R^{13}, –(C_1-C_3 alkylene)S(O)$_2$R^{13} or C_1-C_6 alkyl optionally substituted by oxo, –CN or halogen;

R^{11} and R^{12} are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6 membered heteroaryl or 3-6 membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are independently optionally substituted by halogen, oxo, –CN, –OR^{16}, –NR^{16}R^{17} or C_1-C_6 alkyl optionally substituted by halogen, –CN or oxo; or

R^{11} and R^{12} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, –OR^{16}, –NR^{16}R^{17} or C_1-C_6 alkyl optionally substituted by halogen, oxo or OH;

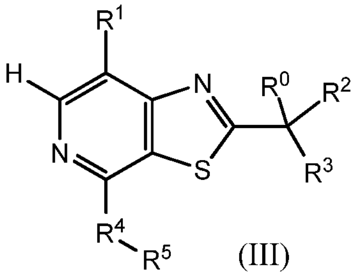
R^{13} and R^{14} are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo; or

R^{13} and R^{14} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by halogen or oxo; and

R^{16} and R^{17} are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo; or

R^{16} and R^{17} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by oxo or halogen.

In some embodiments, provided are compounds of Formula III:



(III) ,

or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein:

R^0 is hydrogen, hydroxyl, or C_1-C_6 alkyl optionally substituted by R^{10};

R^1 is hydrogen, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, –CN, or C_3-C_6 cycloalkyl, wherein R^1 is optionally substituted by R^{10};

R^2 is hydrogen or C_1-C_6 alkyl optionally substituted by R^{10}, or is taken together with R^3 and the carbon to which they are attached to form a ring selected from C_3-C_{10} cycloalkyl and 3-10-membered heterocyclyl, wherein the ring is optionally substituted by R^{10};

R^3 is hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, C_6-C_{14} aryl, or 5-10-membered heteroaryl, wherein R^3 may be optionally substituted by R^{10}; or is taken together with R^2 and the carbon to which they are attached to form a ring selected from C_3-C_{10} cycloalkyl and 3-10-membered heterocyclyl, wherein the ring is optionally substituted by R^{10};

R^4 is $–NR^6–$, $–NR^6C(O)–$, $–NR^6C(O)O–$ or $–NR^6C(O)NR^7–$;

R^5 is hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 5-10-membered heteroaryl, wherein R^5 is optionally substituted by R^{10};

R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_6 cycloalkyl, wherein the alkyl, alkenyl, alkynyl and cycloalkyl are independently optionally substituted by halogen, C_1-C_6 alkyl, oxo, –CN, $–OR^{11}$ or $–NR^{11}R^{12}$;

each R^{10} is independently hydrogen, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen,

–CN, $–OR^{11}$, $–SR^{11}$, $–NR^{11}R^{12}$, $–NO_2$, $–C{=}NH(OR^{11})$, $–C(O)R^{11}$, $–C(O)OR^{11}$, $–C(O)NR^{11}R^{12}$,

$–NR^{11}C(O)R^{12}$, $–S(O)R^{11}$, $–S(O)_2R^{11}$, $–NR^{11}S(O)R^{12}$, $–NR^{11}S(O)_2R^{12}$, $–S(O)NR^{11}R^{12}$, $–S(O)_2NR^{11}R^{12}$,

C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, 5-10-membered heteroaryl, C_6-C_{14} aryl, $–(C_1$-C_3 alkylene)CN, $–(C_1$-C_3 alkylene)OR^{11}, $–(C_1$-C_3 alkylene)SR^{11}, $–(C_1$-C_3 alkylene)$NR^{11}R^{12}$,

$–(C_1$-C_3 alkylene)CF_3, $–(C_1$-C_3 alkylene)NO_2, $–C{=}NH(OR^{11})$, $–(C_1$-C_3 alkylene)$C(O)R^{11}$, $–(C_1$-C_3 alkylene)$C(O)OR^{11}$, $–(C_1$-C_3 alkylene)$C(O)NR^{11}R^{12}$, $–(C_1$-C_3 alkylene)$NR^{11}C(O)R^{12}$,

$–(C_1$-C_3 alkylene)$S(O)R^{11}$, $–(C_1$-C_3 alkylene)$S(O)_2R^{11}$, $–(C_1$-C_3 alkylene)$NR^{11}S(O)R^{12}$, $–(C_1$-C_3 alkylene)$NR^{11}S(O)_2R^{12}$, $–(C_1$-C_3 alkylene)$S(O)NR^{11}R^{12}$, $–(C_1$-C_3 alkylene)$S(O)_2NR^{11}R^{12}$,

$–(C_1$-C_3 alkylene)(C_3-C_6 cycloalkyl), $–(C_1$-C_3 alkylene)(3-10-membered heterocyclyl), $–(C_1$-C_3 alkylene)(5-10-membered heteroaryl) or $–(C_1$-C_3 alkylene)(C_6-C_{14} aryl), wherein each R^{10} is independently optionally substituted by halogen, oxo, $–OR^{13}$, $–NR^{13}R^{14}$, $–C(O)R^{13}$, $–S(O)R^{13}$, $–S(O)_2R^{13}$, $–(C_1$-C_3 alkylene)OR^{13}, $–(C_1$-C_3 alkylene)$NR^{13}R^{14}$, $–(C_1$-C_3 alkylene)$C(O)R^{13}$, $–(C_1$-C_3 alkylene)$S(O)R^{13}$, $–(C_1$-C_3 alkylene)$S(O)_2R^{13}$ or C_1-C_6 alkyl optionally substituted by oxo, –CN or halogen;

R^{11} and R^{12} are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6 membered heteroaryl or 3-6 membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are independently optionally substituted by halogen, oxo, –CN, –OR^{16}, –$NR^{16}R^{17}$ or C_1-C_6 alkyl optionally substituted by halogen, –CN or oxo; or

R^{11} and R^{12} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, –OR^{16}, –$NR^{16}R^{17}$ or C_1-C_6 alkyl optionally substituted by halogen, oxo or OH;

R^{13} and R^{14} are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo; or

R^{13} and R^{14} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by halogen or oxo; and

R^{16} and R^{17} are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo; or

R^{16} and R^{17} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by oxo or halogen.

Further provided is a pharmaceutical composition comprising a compound of Formula I, II, III or any variations described herein (e.g., a compound of Examples 1-236 of Table 1), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof; and optionally further comprising a pharmaceutically acceptable carrier, adjuvant, and/or vehicle.

In another aspect, provided is a method of inhibiting TYK2 kinase activity in a cell, comprising introducing into said cell an amount effective to inhibit said kinase of a compound of Formula I, II, III, or any variations described herein (e.g., a compound of Examples 1-236 of Table 1), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof.

Further provided is a method of treating a disease responsive to the inhibition of TYK2 kinase activity in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula I, II, III, or any variations described herein (e.g., a compound of Examples 1-236 of Table 1), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof. In some embodiments, the disease is an immunological or inflammatory disease, such as asthma, inflammatory bowel disease, Crohn’s disease, ulcerative colitis, rheumatoid arthritis, psoriasis, allergic rhinitis, atopic dermatitis, contact dermatitis, delayed hypersensitivity reactions, lupus and multiple sclerosis.

In another aspect, provided is the use of a compound of Formula I, II, III, or any variations described herein (e.g., a compound of Examples 1-236 of Table 1), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof, in therapy.

In one embodiment, provided is the use of a compound of Formula I, II, III, or any variations described herein (e.g., a compound of Examples 1-236 of Table 1), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof, in the treatment of an immunological or inflammatory disease.

Further provided is the use of a compound of Formula I, II, III, or any variations described herein (e.g., a compound of Examples 1-236 of Table 1), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof, in the manufacturing of a medicament for the treatment of a disease responsive to the inhibition of TYK2 kinase activity in a patient, such as an immunological or inflammatory disease.

Also provided is a kit for treating a disease or disorder responsive to the inhibition of TYK2 kinase, comprising a compound of Formula I, II, III, or any variations described herein (e.g., a compound of Examples 1-236 of Table 1), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides, *inter alia*, thiazolopyridine compounds, and stereoisomers, tautomers, salts (e.g., pharmaceutically acceptable salts), solvates and prodrugs thereof. Compositions (e.g., pharmaceutical compositions) comprising the thiazolopyridine compounds, and pharmaceutical formulations thereof, are useful in inhibiting TYK2 kinase activity in a cell, and in the treatment of diseases, conditions and/or disorders responsive to the inhibition of TYK2 kinase activity in a patient.

Definition

The term “a” or “an” as used herein, unless clearly indicated otherwise, refers to one or more. Reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to “about X” includes description of “X”.

“Alkyl” as used herein refers to and includes, unless otherwise stated, a saturated linear (i.e., unbranched) or branched-chain monovalent hydrocarbon radical, wherein the alkyl radical may be optionally substituted independently with one or more substituents described herein. In one example, the alkyl radical has one to eighteen carbon atoms (“C_1-C_{18} alkyl”). In other examples, the alkyl radical is C_1-C_{12}, C_1-C_{10}, C_1-C_8, C_1-C_6, C_1-C_5, C_1-C_4, or C_1-C_3 alkyl. Examples of alkyl groups include, but are not limited to, groups such as methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-

propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $-C(CH_3)_3$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$, 1-heptyl and 1-octyl.

“Alkenyl” as used herein refers to a linear or branched-chain monovalent hydrocarbon radical with at least one site of unsaturation, i.e., a carbon-carbon double bond, wherein the alkenyl radical may be optionally substituted independently with one or more substituents described herein, and includes radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. In one example, the alkenyl radical has two to eighteen carbon atoms (“C_2-C_{18} alkenyl”). In other examples, the alkenyl radical is C_2-C_{12}, C_2-$C_{10,}$ C_2-C_8, C_2-C_6 or C_2-C_3 alkenyl. Examples of alkenyl groups include, but are not limited to, groups such as ethenyl or vinyl ($-CH=CH_2$), prop-1-enyl ($-CH=CHCH_3$), prop-2-enyl ($-CH_2CH=CH_2$), 2-methylprop-1-enyl, but-1-enyl, but-2-enyl, but-3-enyl, buta-1,3-dienyl, 2-methylbuta-1,3-diene, hex-1-enyl, hex-2-enyl, hex-3-enyl, hex-4-enyl and hexa-1,3-dienyl.

“Alkynyl” as used herein refers to a linear or branched monovalent hydrocarbon radical with at least one site of unsaturation, i.e., a carbon-carbon, triple bond, wherein the alkynyl radical may be optionally substituted independently with one or more substituents described herein. In one example, the alkynyl radical has two to eighteen carbon atoms (“C_2-C_{18} alkynyl”). In other examples, the alkynyl radical is C_2-C_{12}, C_2-$C_{10,}$ C_2-C_8, C_2-C_6 or C_2-C_3 alkynyl. Examples of alkynyl groups include, but are not limited to, groups such as ethynyl ($-C\equiv CH$), prop-1-ynyl ($-C\equiv CCH_3$), prop-2-ynyl (propargyl, $-CH_2C\equiv CH$), but-1-ynyl, but-2-ynyl and but-3-ynyl.

“Alkylene” as used herein refers to a saturated, branched or straight chain hydrocarbon group having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. In one example, the divalent alkylene group has one to eighteen carbon atoms (“C_1-C_{18} alkylene”). In other examples, the divalent alkylene group is C_1-C_{12}, C_1-$C_{10,}$ C_1-C_8, C_1-C_6, C_1-C_5, C_1-C_4, or C_1-C_3 alkylene. Examples of alkylene groups include, but are not limited to, groups such as methylene ($-CH_2-$), 1,1-ethylene ($-CH(CH_3)-$), 1,2-ethylene ($-CH_2CH_2-$), 1,1-propylene ($-CH(CH_2CH_3)-$), 2,2-propylene

($-C(CH_3)_2-$), 1,2-propylene ($-CH(CH_3)CH_2-$), 1,3-propylene ($-CH_2CH_2CH_2-$), 1,1-dimethyl-1,2-ethylene ($-C(CH_3)_2CH_2-$), 1,4-butylene ($-CH_2CH_2CH_2CH_2-$), and the like.

"Cycloalkyl" as used herein refers to a non-aromatic, saturated or partially unsaturated hydrocarbon ring group wherein the cycloalkyl group may be optionally substituted independently with one or more substituents described herein. In one example, the cycloalkyl group has 3 to 12 carbon atoms ("C_3-C_{12} cycloalkyl"). In other examples, cycloalkyl is C_3-C_8, C_3-C_{10} or C_5-C_{10} cycloalkyl. In other examples, the cycloalkyl group, as a monocycle, is C_3-C_4, C_3-C_6 or C_5-C_6 cycloalkyl. In another example, the cycloalkyl group, as a bicycle, is C_7-C_{12} cycloalkyl. Examples of monocyclic cycloalkyl groups include, but are not limited to, groups such as cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl and cyclododecyl. Exemplary arrangements of bicyclic cycloalkyl groups having 7 to 12 ring atoms include, but are not limited to, [4,4], [4,5], [5,5], [5,6] or [6,6] ring systems. Exemplary bridged bicyclic cycloalkanes include, but are not limited to, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane and bicyclo[3.2.2]nonane. In another example, the cycloalkyl group is a spiro cycloalkyl group, e.g., a C_5-C_{12} spiro cycloalkyl. Examples of spiro cycloalkanes include, but are not limited to, spiro[2.2]pentane, spiro[2.3]hexane, spiro[2.4]heptane, spiro[2.5]octane, spiro[3.3]heptane, spiro[3.4]octane, spiro[3.5]nonane, spiro[4.4]nonane and spiro[4.5]decane.

"Aryl" or "Ar" as used herein refers to a cyclic aromatic hydrocarbon group optionally substituted independently with one or more substituents described herein. In one example, the aryl group has 6 to 20 annular carbon atoms ("C_6-C_{20} aryl"). In another example, the aryl group has 6 to 14 annular carbon atoms ("C_6-C_{14} aryl"). In another example, the aryl group has 6 to 10 annular carbon atoms ("C_6-C_{10} aryl"). In another example, the aryl group is a C_6 aryl group. Aryl includes bicyclic groups comprising an aromatic ring with a fused non-aromatic or partially saturated ring. Examples of aryl groups include, but are not limited to, phenyl, naphthalenyl, anthracenyl, indenyl, indanyl, 1,2-dihydronapthalenyl and 1,2,3,4-tetrahydronapthyl. In one example, aryl includes phenyl. Substituted phenyl or substituted aryl means a phenyl group or aryl group substituted with one, two, three, four or five, for example 1-2, 1-3 or 1-4 substituents chosen from groups specified herein. In one example, optional substituents on aryl are selected from halogen (F, Cl, Br, I), hydroxy, protected hydroxy, cyano, nitro, alkyl (for example C_1-C_6 alkyl), alkoxy (for example C_1-C_6 alkoxy), benzyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, aminomethyl, protected aminomethyl, trifluoromethyl, alkylsulfonylamino, alkylsulfonylaminoalkyl, arylsulfonylamino, arylsulfonylaminoalkyl, heterocyclylsulfonylamino, heterocyclylsulfonylaminoalkyl, heterocyclyl, aryl, or other groups specified. One or more methine (CH) and/or methylene (CH_2) groups in these substituents may in turn be substituted with a similar group as those denoted above. Examples of the term "substituted phenyl" include a mono- or di(halo)phenyl group such as 2-chlorophenyl, 2-bromophenyl, 4-chlorophenyl, 2,6-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 3-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 3,4-dibromophenyl, 3-chloro-4-fluorophenyl, 2-fluorophenyl and the like; a mono- or di(hydroxy)phenyl group such as 4-hydroxyphenyl, 3-hydroxyphenyl, 2,4-dihydroxyphenyl, the protected-hydroxy derivatives thereof and the like; a nitrophenyl group such as 3- or 4-nitrophenyl; a cyanophenyl group, for example, 4-cyanophenyl; a mono- or di(lower alkyl)phenyl group such as 4-methylphenyl, 2,4-dimethylphenyl, 2-methylphenyl, 4-(isopropyl)phenyl, 4-ethylphenyl, 3-(n-propyl)phenyl and the like; a mono or di(alkoxy)phenyl group, for example, 3,4-dimethoxyphenyl, 3-methoxy-4-benzyloxyphenyl, 3-ethoxyphenyl, 4-(isopropoxy)phenyl, 4-(t-butoxy)phenyl, 3-ethoxy-4-methoxyphenyl and the like; 3- or 4-trifluoromethylphenyl; a mono- or dicarboxyphenyl or (protected carboxy)phenyl group such 4-carboxyphenyl, a mono- or di(hydroxymethyl)phenyl or (protected hydroxymethyl)phenyl such as 3-(protected hydroxymethyl)phenyl or 3,4-di(hydroxymethyl)phenyl; a mono- or di(aminomethyl)phenyl or (protected aminomethyl)phenyl such as 2-(aminomethyl)phenyl or 2,4-(protected aminomethyl)phenyl; or a mono- or di(N-(methylsulfonylamino))phenyl such as 3-(N-methylsulfonylamino))phenyl. Also, the term "substituted phenyl" represents disubstituted phenyl groups where the substituents are different, for example, 3-methyl-4-hydroxyphenyl, 3-chloro-4-hydroxyphenyl, 2-methoxy-4-bromophenyl, 4-ethyl-2-hydroxyphenyl, 3-hydroxy-4-nitrophenyl, 2-hydroxy-4-chlorophenyl, and the like, as well as trisubstituted phenyl groups where the substituents are different, for example 3-methoxy-4-benzyloxy-6-methyl sulfonylamino, 3-methoxy-4-benzyloxy-6-phenyl sulfonylamino, and tetrasubstituted phenyl groups where the substituents are different such as 3-methoxy-4-benzyloxy-5-methyl-6-phenyl sulfonylamino. Particular substituted phenyl groups include the 2-chlorophenyl, 2-aminophenyl, 2-bromophenyl, 3-methoxyphenyl, 3-ethoxy-phenyl, 4-benzyloxyphenyl, 4-methoxyphenyl, 3-ethoxy-4-benzyloxyphenyl, 3,4-diethoxyphenyl, 3-methoxy-4-benzyloxyphenyl, 3-methoxy-4-(1-chloromethyl)benzyloxy -6- methyl sulfonyl aminophenyl groups. Fused aryl rings may also be substituted with any, for example 1, 2 or 3, of the substituents specified herein in the same manner as substituted alkyl groups.

"Heterocycle", "heterocyclic", or "heterocyclyl" as used herein refers to a saturated or partially unsaturated cyclic group (i.e., having one or more double and/or triple bonds within the ring), having at least one annular heteroatom independently selected from nitrogen, oxygen, phosphorus and sulfur, the remaining annular atoms being carbon. The heterocyclyl group may be optionally substituted with one or more substituents described below. In one embodiment, heterocyclyl includes monocycles or bicycles having 1 to 9 annular carbon atoms (C_1-C_9) with the remaining ring atoms being heteroatoms selected from N, O, S and P. In other examples, heterocyclyl includes monocycles or bicycles having 1 to 5 annular carbon atoms (C_1-C_5), 3 to 5 annular carbon atoms (C_3-C_5), or 4 to 5 annular carbon atoms (C_4-C_5), with the remaining ring atoms being heteroatoms selected from N, O, S and P. In another embodiment, heterocyclyl includes 3-10 membered rings, 3-7-membered rings or 3-6 membered rings, containing one or more heteroatoms independently selected from N, O, S and P. In other examples, heterocyclyl includes monocyclic 3-, 4-, 5-, 6- or 7-membered rings, containing one or more heteroatoms independently selected from N, O, S and P. In another embodiment, heterocyclyl includes bi- or polycyclic, spiro or bridged 4-, 5-, 6-, 7-, 8- and 9- membered ring systems, containing one or more heteroatoms independently selected from N, O, S and P. Examples of bicycle systems include, but are not limited to, [3,5], [4,5], [5,5], [3,6], [4,6], [5,6], or [6,6] systems. Examples of bridged ring systems include, but are not limited to [2.2.1], [2.2.2], [3.2.2] and [4.1.0] arrangements, and having 1 to 3 heteroatoms selected from N, O, S and P. In another embodiment, heterocyclyl includes spiro cyclic groups having 1 to 4 heteroatoms selected from N, O, S and P. The heterocyclyl group may be a carbon-linked group or heteroatom-linked group. "Heterocyclyl" includes a heterocyclyl group fused to a cycloalkyl group.

Exemplary heterocyclyl groups include, but are not limited to, groups such as oxiranyl, aziridinyl, thiiranyl, azetidinyl, oxetanyl, thietanyl, 1,2-dithietanyl, 1,3-dithietanyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, homopiperazinyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, oxazepanyl, diazepanyl, 1,4-diazepanyl, diazepinyl, thiazepinyl, thiazepanyl, dihydrothienyl, dihydropyranyl, dihydrofuranyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, pyrazolidinyl, dithianyl, dithiolanyl, pyrazolidinylimidazolinyl, imidazolidinyl, 3-azabicyco[3.1.0]hexanyl, 3,6-diazabicyclo[3.1.1]heptanyl, 6-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[4.1.0]heptanyl and azabicyclo[2.2.2]hexanyl. Examples of a heterocyclyl group wherein a ring atom is substituted with oxo (=O) are pyrimidinonyl and 1,1-dioxo-thiomorpholinyl. The heterocyclyl groups herein are optionally substituted independently with one or more substituents described herein. Heterocycles are described in Paquette, Leo A.; "Principles of Modern Heterocyclic Chemistry" (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A Series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* (1960) 82:5566.

“Heteroaryl” or “HetAr” as used herein refers to an aromatic cyclic radical in which at least one ring atom is a heteroatom independently selected from nitrogen, oxygen and sulfur, the remaining ring atoms being carbon. Heteroaryl groups may be optionally substituted with one or more substituents described herein. In one example, the heteroaryl group contains 1 to 9 annular carbon atoms (C_1-C_9). In other examples, the heteroaryl group contains 1 to 5 annular carbon atoms (C_1-C_5), 3 to 5 annular carbon atoms (C_3-C_5), or 4 to 5 annular carbon atoms (C_4-C_5). In one embodiment, exemplary heteroaryl groups include 5 to 6-membered rings, or monocyclic aromatic 5-, 6- and 7-membered rings containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur. In another embodiment, exemplary heteroaryl groups include fused ring systems of up to 9 carbon atoms wherein at least one aromatic ring contains one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur. "Heteroaryl" includes heteroaryl groups fused with an aryl, cycloalkyl or heterocyclyl group. Examples of heteroaryl groups include, but are not limited to, groups such as pyridinyl, imidazolyl, imidazopyridinyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, triazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, thiazolopyridinyl, and furopyridinyl.

In certain embodiments, the heterocyclyl or heteroaryl group is C-attached. By way of example and not limitation, carbon bonded heterocyclyl groups include bonding arrangements at position 2, 3, 4, 5, or 6 of a piperidine (e.g., piperidin-2-yl, piperidin-3-yl or piperidin-4-yl), position 2, 3, 5, or 6 of a piperazine (e.g., piperizin-2-yl or piperizin-3-yl), position 2, 3, 4, or 5 of a tetrahydrofuran, tetrahydrothiophene, pyrroline or pyrrolidine, position 2, 3, or 4 of an azetidine, position 2 or 3 of an aziridine, and the like. Non-limiting examples of carbon bonded heteroaryl groups include bonding arrangements at position 2, 3, 4, 5, or 6 of a pyridine (2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl), position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, thiophene or pyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2, 3, 4, 5, 6, 7, or 8 of a quinolone, position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline, and the like.

In certain embodiments, the heterocyclyl or heteroaryl group contains at least one annular nitrogen atom with is attached to the parent structure (i.e. N-attached). By way of example and not limitation, the nitrogen bonded heterocyclyl groups include bonding arrangements at position 1 of an aziridine, azetidine, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazolidine, 2-imidazoline, 3-

imidazoline, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine or indoline, position 2 of an isoindoline, position 4 of a morpholine, and the like. Non-limiting examples of N-attached heteroaryl group include bonding arrangements at position 1 of a pyrrole, imidazole, pyrazole, indole or 1H-indazole, position 2 of a isoindole, position 9 of a carbazole or β-carboline, and the like.

"Halo" or "halogen" refers to fluoro (F), chloro (Cl), bromo (Br) and iodo (I). Where a residue is substituted with more than one halogen, it may be referred to by using a prefix corresponding to the number of halogen moieties attached, e.g., dihaloaryl, dihaloalkyl, trihaloaryl etc. refer to aryl and alkyl substituted with two ("di") or three ("tri") halo groups, which may be but are not necessarily the same halogen; thus 4-chloro-3-fluorophenyl is within the scope of dihaloaryl. An alkyl group in which each hydrogen is replaced with a halo group is referred to as a "perhaloalkyl." A preferred perhaloalkyl group is trifluoroalkyl ($-CF_3$). Similarly, "perhaloalkoxy" refers to an alkoxy group in which a halogen takes the place of each H in the hydrocarbon making up the alkyl moiety of the alkoxy group. An example of a perhaloalkoxy group is trifluoromethoxy ($-OCF_3$).

"Optionally substituted" unless otherwise specified means that a group may be unsubstituted or substituted by one or more (e.g., 1, 2, 3 or 4) of the substituents listed for that group in which said substituents may be the same or different. In an embodiment an optionally substituted group has 1 substituent. In another embodiment an optionally substituted group has 2 substituents. In another embodiment an optionally substituted group has 3 substituents.

The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space. Stereoisomers include diastereomers, enantiomers, conformers and the like.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g., melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., *McGraw-Hill Dictionary of Chemical Terms* (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., New York, 1994. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or *R* and *S*, are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms “racemic mixture” and “racemate” refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

The term “tautomer” or “tautomeric form” refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

A “solvate” refers to an association or complex of one or more solvent molecules and a compound provided herein. Examples of solvents that form solvates include, but are not limited to, water, isopropanol, ethanol, methanol, dimethyl sulfoxide (DMSO), ethyl acetate, acetic acid, and ethanolamine. The term "hydrate" refers to the complex where the solvent molecule is water.

The term “prodrug” as used in this application refers to a precursor or derivative form of a pharmaceutically active substance that is less efficacious to the patient or cytotoxic to tumor cells compared to the parent drug and is capable of being enzymatically or hydrolytically activated or converted into the more active parent form. See, *e.g.,* Wilman, “Prodrugs in Cancer Chemotherapy” Biochemical Society Transactions, 14, pp. 375-382, 615th Meeting Belfast (1986) and Stella et al., “Prodrugs: A Chemical Approach to Targeted Drug Delivery,” *Directed Drug Delivery*, Borchardt et al., (ed.), pp. 247-267, Humana Press (1985). Examples of prodrugs include, but are not limited to, phosphate-containing prodrugs, thiophosphate-containing prodrugs, sulfate-containing prodrugs, peptide-containing prodrugs, D-amino acid-modified prodrugs, glycosylated prodrugs, β-lactam-containing prodrugs, optionally substituted phenoxyacetamide-containing prodrugs or optionally substituted phenylacetamide-containing prodrugs.

“Leaving group” refers to a portion of a first reactant in a chemical reaction that is displaced from the first reactant in the chemical reaction. Examples of leaving groups include, but are not limited to, halogen atoms, hydroxyl, alkoxy (for example -OR, wherein R is independently alkyl, alkenyl, alkynyl, cycloalkyl, phenyl or heterocyclyl and R is independently optionally substituted) and sulfonyloxy (for example $-OS(O)_{1-2}R$, wherein R is independently alkyl, alkenyl, alkynyl, cycloalkyl, phenyl or heterocyclyl and R is independently optionally substituted) groups. Exemplary sulfonyloxy groups include, but are not limited to, alkylsulfonyloxy groups (for example methyl sulfonyloxy (mesylate group) and trifluoromethylsulfonyloxy (triflate group)) and arylsulfonyloxy groups (for example *p*-toluenesulfonyloxy (tosylate group) and *p*-nitrosulfonyloxy (nosylate group)).

The term "protecting group" or "Pg" refers to a substituent that is commonly employed to block or protect a particular functionality while reacting other functional groups on the compound. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include acetyl, trifluoroacetyl, phthalimido, t-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz) and 9-fluorenylmethylenoxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable hydroxy-protecting groups include acetyl, trialkylsilyl, dialkylphenylsilyl, benzoyl, benzyl, benzyloxymethyl, methyl, methoxymethyl, triarylmethyl, and tetrahydropyranyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Common carboxy-protecting groups include $-CH_2CH_2SO_2Ph$, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxymethyl, 2-(p-toluenesulfonyl)ethyl, 2-(p-nitrophenylsulfenyl)ethyl, 2-(diphenylphosphino)-ethyl, nitroethyl and the like. For a general description of protecting groups and their use, see T. W. Greene and P. Wuts, Protective Groups in Organic Synthesis, Third Ed., John Wiley & Sons, New York, 1999; and P. Kocienski, Protecting Groups, Third Ed., Verlag, 2003.

The term "patient" includes human patients and animal patients. The term "animal" includes companion animals (e.g., dogs, cats and horses), food-source animals, zoo animals, marine animals, birds and other similar animal species. In one example, patient is a human.

“Treat” and “treatment” includes therapeutic treatment, wherein the object is to slow down (lessen) an undesired physiological change or disorder. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (*i.e.,* not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, remission (whether partial or total), whether detectable or undetectable, sustaining remission and suppressing reoccurrence. “Treatment” can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder, (for example, through a genetic mutation) or those in which the condition or disorder is to be prevented. In some embodiments, a method may comprise prophylactic and/or preventative treatment.

The phrase "therapeutically effective amount" means an amount of a compound of the present invention that (i) treats or prevents the particular disease, condition or disorder, (ii) attenuates, ameliorates or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition or disorder described herein. In the case of immunological disorders, the therapeutic effective amount is an amount sufficient to decrease or alleviate an allergic disorder, the symptoms of an autoimmune disease (e.g., lupus) and/or an inflammatory disease, or the symptoms of an acute inflammatory reaction (e.g., asthma). In some embodiments, a therapeutically effective amount is an amount of a chemical entity described herein sufficient to significantly decrease the activity or number of B-cells.

The phrase "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

The phrase “pharmaceutically acceptable salt,” as used herein, refers to pharmaceutically acceptable organic or inorganic salts of a compound provided herein. “Pharmaceutically acceptable salts” include both acid and base addition salts. Exemplary salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and pamoate (i.e., 1,1’-methylene-bis-(2-hydroxy-3-naphthoate)) salts. A pharmaceutically acceptable salt may involve the inclusion of another molecule such as an acetate ion, a succinate ion or other counter ion. The counter ion may be any organic or inorganic moiety that stabilizes the charge on the parent compound. Furthermore, a pharmaceutically acceptable salt may have more than one charged atom in its structure. Instances where multiple charged atoms are part of the pharmaceutically acceptable salt can have multiple counter ions. Hence, a pharmaceutically acceptable salt can have one or more charged atoms and/or one or more counter ion, for example a dihydrochloride or diformate salt.

“Pharmaceutically acceptable acid addition salt” refers to those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid and the like, and organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, maleic acid, maloneic acid, succinic acid, fumaric acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid, anthranilic acid, benzoic acid, cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, salicyclic acid and the like.

“Pharmaceutically acceptable base addition salts” include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly base addition salts are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases includes salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, tromethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly organic non-toxic bases are isopropylamine, diethylamine, ethanolamine, tromethamine, dicyclohexylamine, choline, and caffeine.

The term "NSAID" is an acronym for "non-steroidal anti-inflammatory drug" and is a therapeutic agent with analgesic, antipyretic (lowering an elevated body temperature and relieving pain without impairing consciousness) and, in higher doses, with anti-inflammatory effects (reducing inflammation). The term "non-steroidal" is used to distinguish these drugs from steroids, which (among a broad range of other effects) have a similar eicosanoid-depressing, anti-inflammatory action. As analgesics, NSAIDs are unusual in that they are non-narcotic. NSAIDs include aspirin, ibuprofen, and naproxen. NSAIDs are usually indicated for the treatment of acute or chronic conditions where pain and inflammation are present. NSAIDs are generally indicated for the symptomatic relief of the following conditions: rheumatoid arthritis, osteoarthritis, inflammatory arthropathies (e.g., ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, acute gout, dysmenorrhoea, metastatic bone pain, headache and migraine, postoperative pain, mild-to-moderate pain due to inflammation and tissue injury, pyrexia, ileus, and renal colic. Most NSAIDs act as non-selective inhibitors of the enzyme cyclooxygenase, inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. Cyclooxygenase catalyzes the formation of prostaglandins and thromboxane from arachidonic acid (itself derived from the cellular phospholipid bilayer by phospholipase A_2). Prostaglandins act (among other things) as messenger molecules in the process of inflammation. COX-2 inhibitors include celecoxib, etoricoxib, lumiracoxib, parecoxib, rofecoxib, rofecoxib, and valdecoxib.

"Combination therapy" as used herein means a therapy that includes two or more different compounds. Thus, in one aspect, a combination therapy comprising a compound detailed herein and another compound is provided. In some variations, the combination therapy optionally includes one or more pharmaceutically acceptable carriers or excipients, non-pharmaceutically active compounds, and/or inert substances.

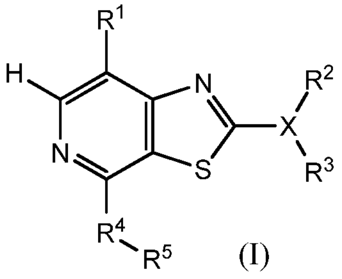
The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products.

The terms "compound of this invention," and "compounds of the present invention", unless otherwise indicated, include compounds of Formulae I, II, III, any variations thereof described herein, stereoisomers, tautomers, solvates, prodrugs and salts (e.g., pharmaceutically acceptable salts) thereof. Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds of Formulae I, II, III, and variations described herein, wherein one or more hydrogen atoms are replaced deuterium or tritium, or one or more carbon atoms are replaced by a ^{13}C or ^{14}C carbon atom, or one or more nitrogen atoms are replaced by a ^{15}N nitrogen atom, or one or more sulfur atoms are replaced by a ^{33}S, ^{34}S or ^{36}S sulfur atom, or one or more oxygen atoms are replaced by a ^{17}O or ^{18}O oxygen atom are within the scope of this invention. Other isotopes are described herein.

TYK2 Inhibitor Compounds

Compounds according to the invention are detailed herein, including in the Brief Summary of the Invention and the appended claims. The invention includes the use of all of the compounds described herein, including any and all stereoisomers, including geometric isomers (cis/trans), salts (including pharmaceutically acceptable salts) and solvates of the compounds described herein, as well as methods of making such compounds.

In one aspect, provided is a compound of Formula I:



(I)

or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein:

X is N or CR^0;

R^0 is hydrogen, hydroxyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, C_6-C_{14} aryl, or 5-10-membered heteroaryl, wherein R^0 maybe optionally substituted by R^{10};

R^1 is hydrogen, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, –CN, $–OR^8$, $–SR^8$, $–NR^8R^9$,

$–CF_3$, $–NO_2$, $–C(O)R^8$, $–C(O)OR^8$, $–C(O)NR^8R^9$, $–NR^8C(O)R^9$, $–S(O)R^8$, $–S(O)_2R^8$, $–NR^8S(O)R^9$,

$–NR^8S(O)_2R^9$, $–S(O)NR^8R^9$, $–S(O)_2NR^8R^9$, C_3-C_6 cycloalkyl, 3-6-membered heterocyclyl, 5-6-membered heteroaryl, C_6-C_{14} aryl, $–(C_1$-C_3 alkylene)CN, $–(C_1$-C_3 alkylene)OR^8, $–(C_1$-C_3 alkylene)SR^8,

$–(C_1$-C_3 alkylene)NR^8R^9, $–(C_1$-C_3 alkylene)CF_3, $–(C_1$-C_3 alkylene)NO_2, $–(C_1$-C_3 alkylene)$C(O)R^8$,

$–(C_1$-C_3 alkylene)$C(O)OR^8$, $–(C_1$-C_3 alkylene)$C(O)NR^8R^9$, $–(C_1$-C_3 alkylene)$NR^8C(O)R^9$,

$–(C_1$-C_3 alkylene)$S(O)R^8$, $–(C_1$-C_3 alkylene)$S(O)_2R^8$, $–(C_1$-C_3 alkylene)$NR^8S(O)R^9$, $–(C_1$-C_3 alkylene)$NR^8S(O)_2R^9$, $–(C_1$-C_3 alkylene)$S(O)NR^8R^9$, $–(C_1$-C_3 alkylene)$S(O)_2NR^8R^9$,

$–(C_1$-C_3 alkylene)(C_3-C_6 cycloalkyl), $–(C_1$-C_3 alkylene)(3-6-membered heterocyclyl), $–(C_1$-C_3 alkylene)(5-6-membered heteroaryl) or $–(C_1$-C_3 alkylene)(C_6-C_{14} aryl) , wherein R^1 is optionally substituted by R^{10};

each R^2 and R^3 is independently hydrogen, hydroxyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, C_6-C_{14} aryl, or 5-10-membered heteroaryl, wherein R^2 and R^3 are each independently optionally substituted by R^{10}; or

> R^2 and R^3 are taken together with the atom to which they are attached to form a ring selected from C_3-C_{10} cycloalkyl and 3-10-membered heterocyclyl, wherein the ring may be optionally substituted by R^{10};

R^4 is hydrogen, $–NR^6–$, $–NR^6R^7$, $–NR^6C(O)–$, $–NR^6C(O)O–$, $–NR^6C(O)NR^7–$, $–NR^6S(O)–$,

$–NR^6S(O)_2–$, $–NR^6S(O)NR^7–$ or $–NR^6S(O)_2NR^7–$;

R^5 is absent, hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, 3-10-membered heterocyclyl or 5-10-membered heteroaryl, wherein R^5 is optionally substituted by R^{10};

R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_6 cycloalkyl, wherein the alkyl, alkenyl, alkynyl and cycloalkyl are independently optionally substituted by halogen, C_1-C_6 alkyl, oxo, –CN, –OR^{11} or –$NR^{11}R^{12}$; or

R^6 and R^7 are independently taken together with the atom to which they are attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, –OR^{11}, –$NR^{11}R^{12}$ or C_1-C_6 alkyl optionally substituted by halogen;

R^8 and R^9 are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo;

each R^{10} is independently hydrogen, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen,

–CN, –OR^{11}, –SR^{11}, –$NR^{11}R^{12}$, –NO_2, –C=NH(OR^{11}), –C(O)R^{11}, –C(O)OR^{11}, –C(O)$NR^{11}R^{12}$,

–NR^{11}C(O)R^{12}, –S(O)R^{11}, –$S(O)_2R^{11}$, –NR^{11}S(O)R^{12}, –$NR^{11}S(O)_2R^{12}$, –S(O)$NR^{11}R^{12}$, –$S(O)_2NR^{11}R^{12}$,

C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, 5-10-membered heteroaryl, C_6-C_{14} aryl, –(C_1-C_3 alkylene)CN, –(C_1-C_3 alkylene)OR^{11}, –(C_1-C_3 alkylene)SR^{11}, –(C_1-C_3 alkylene)$NR^{11}R^{12}$,

–(C_1-C_3 alkylene)CF_3, –(C_1-C_3 alkylene)NO_2, –C=NH(OR^{11}), –(C_1-C_3 alkylene)C(O)R^{11}, –(C_1-C_3 alkylene)C(O)OR^{11}, –(C_1-C_3 alkylene)C(O)$NR^{11}R^{12}$, –(C_1-C_3 alkylene)NR^{11}C(O)R^{12},

–(C_1-C_3 alkylene)S(O)R^{11}, –(C_1-C_3 alkylene)$S(O)_2R^{11}$, –(C_1-C_3 alkylene)NR^{11}S(O)R^{12}, –(C_1-C_3 alkylene)$NR^{11}S(O)_2R^{12}$, –(C_1-C_3 alkylene)S(O)$NR^{11}R^{12}$, –(C_1-C_3 alkylene)$S(O)_2NR^{11}R^{12}$,

–(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), –(C_1-C_3 alkylene)(3-10-membered heterocyclyl), –(C_1-C_3 alkylene)(5-10-membered heteroaryl) or –(C_1-C_3 alkylene)(C_6-C_{14} aryl), wherein each R^{10} is independently optionally substituted by halogen, oxo, –OR^{13}, –$NR^{13}R^{14}$, –C(O)R^{13}, –S(O)R^{13}, –$S(O)_2R^{13}$, –(C_1-C_3 alkylene)OR^{13}, –(C_1-C_3 alkylene)$NR^{13}R^{14}$, –(C_1-C_3 alkylene)C(O)R^{13}, –(C_1-C_3 alkylene)S(O)R^{13}, –(C_1-C_3 alkylene)$S(O)_2R^{13}$ or C_1-C_6 alkyl optionally substituted by oxo, –CN or halogen;

R^{11} and R^{12} are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6 membered heteroaryl or 3-6 membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are independently optionally substituted by halogen, oxo, –CN, –OR^{16}, –$NR^{16}R^{17}$ or C_1-C_6 alkyl optionally substituted by halogen, –CN or oxo; or

R^{11} and R^{12} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, $–OR^{16}$, $–NR^{16}R^{17}$ or C_1-C_6 alkyl optionally substituted by halogen, oxo or OH;

R^{13} and R^{14} are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo; or

R^{13} and R^{14} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by halogen or oxo; and

R^{16} and R^{17} are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo; or

R^{16} and R^{17} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by oxo or halogen.

In some embodiments, the compound is of Formula I, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein:

X is N;

R^1 is hydrogen, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, –CN, $–CF_3$, C_3-C_6 cycloalkyl, –(C_1-C_3 alkylene)CN, –(C_1-C_3 alkylene)OR^8, –(C_1-C_3 alkylene)SR^8, –(C_1-C_3 alkylene)NR^8R^9, –(C_1-C_3 alkylene)CF_3, –(C_1-C_3 alkylene)NO_2, –(C_1-C_3 alkylene)C(O)R^8, –(C_1-C_3 alkylene)C(O)OR^8, –(C_1-C_3 alkylene)C(O)NR^8R^9, –(C_1-C_3 alkylene)$NR^8C(O)R^9$, –(C_1-C_3 alkylene)S(O)R^8, –(C_1-C_3 alkylene)$S(O)_2R^8$, –(C_1-C_3 alkylene)$NR^8S(O)R^9$, –(C_1-C_3 alkylene)$NR^8S(O)_2R^9$, –(C_1-C_3 alkylene)$S(O)NR^8R^9$,
–(C_1-C_3 alkylene)$S(O)_2NR^8R^9$, –(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), –(C_1-C_3 alkylene)(3-6-membered heterocyclyl), –(C_1-C_3 alkylene)(5-6-membered heteroaryl) or –(C_1-C_3 alkylene)(C_6-C_{14} aryl);

R^2 is hydrogen or C_1-C_6 alkyl optionally substituted by R^{10}, or is taken together with R^3 and the nitrogen to which they are attached to form a 3-10-membered heterocyclyl optionally substituted by R^{10};

R^3 is hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, C_6-C_{14} aryl, or 5-10-membered heteroaryl, wherein R^3 may be optionally substituted by R^{10}; or is taken together with R^2 and the nitrogen to which they are attached to form a 3-10-membered heterocyclyl optionally substituted by R^{10};

R^4 is $–NR^6–$, $–NR^6C(O)–$, $–NR^6C(O)O–$ or $–NR^6C(O)NR^7–$;

R^5 is hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 5-10-membered heteroaryl, wherein R^5 is optionally substituted by R^{10};

R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_6 cycloalkyl, wherein the alkyl, alkenyl, alkynyl and cycloalkyl are independently optionally substituted by halogen, C_1-C_6 alkyl, oxo, –CN, $–OR^{11}$ or $–NR^{11}R^{12}$;

R^8 and R^9 are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo;

each R^{10} is independently hydrogen, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen,

–CN, $–OR^{11}$, $–SR^{11}$, $–NR^{11}R^{12}$, $–NO_2$, $–C{=}NH(OR^{11})$, $–C(O)R^{11}$, $–C(O)OR^{11}$, $–C(O)NR^{11}R^{12}$,

$–NR^{11}C(O)R^{12}$, $–S(O)R^{11}$, $–S(O)_2R^{11}$, $–NR^{11}S(O)R^{12}$, $–NR^{11}S(O)_2R^{12}$, $–S(O)NR^{11}R^{12}$, $–S(O)_2NR^{11}R^{12}$,

C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, 5-10-membered heteroaryl, C_6-C_{14} aryl, –(C_1-C_3 alkylene)CN, –(C_1-C_3 alkylene)OR^{11}, –(C_1-C_3 alkylene)SR^{11}, –(C_1-C_3 alkylene)$NR^{11}R^{12}$,

–(C_1-C_3 alkylene)CF_3, –(C_1-C_3 alkylene)NO_2, $–C{=}NH(OR^{11})$, –(C_1-C_3 alkylene)$C(O)R^{11}$, –(C_1-C_3 alkylene)$C(O)OR^{11}$, –(C_1-C_3 alkylene)$C(O)NR^{11}R^{12}$, –(C_1-C_3 alkylene)$NR^{11}C(O)R^{12}$,

–(C_1-C_3 alkylene)$S(O)R^{11}$, –(C_1-C_3 alkylene)$S(O)_2R^{11}$, –(C_1-C_3 alkylene)$NR^{11}S(O)R^{12}$, –(C_1-C_3 alkylene)$NR^{11}S(O)_2R^{12}$, –(C_1-C_3 alkylene)$S(O)NR^{11}R^{12}$, –(C_1-C_3 alkylene)$S(O)_2NR^{11}R^{12}$,

–(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), –(C_1-C_3 alkylene)(3-10-membered heterocyclyl), –(C_1-C_3 alkylene)(5-10-membered heteroaryl) or –(C_1-C_3 alkylene)(C_6-C_{14} aryl), wherein each R^{10} is independently optionally substituted by halogen, oxo, $–OR^{13}$, $–NR^{13}R^{14}$, $–C(O)R^{13}$, $–S(O)R^{13}$, $–S(O)_2R^{13}$, –(C_1-C_3 alkylene)OR^{13}, –(C_1-C_3 alkylene)$NR^{13}R^{14}$, –(C_1-C_3 alkylene)$C(O)R^{13}$, –(C_1-C_3 alkylene)$S(O)R^{13}$, –(C_1-C_3 alkylene)$S(O)_2R^{13}$ or C_1-C_6 alkyl optionally substituted by oxo, –CN or halogen;

R^{11} and R^{12} are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6 membered heteroaryl or 3-6 membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are independently optionally substituted by halogen, oxo, –CN, $–OR^{16}$, $–NR^{16}R^{17}$ or C_1-C_6 alkyl optionally substituted by halogen, –CN or oxo; or

R^{11} and R^{12} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, –OR^{16}, –$NR^{16}R^{17}$ or C_1-C_6 alkyl optionally substituted by halogen, oxo or OH;

R^{13} and R^{14} are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo; or

R^{13} and R^{14} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by halogen or oxo; and

R^{16} and R^{17} are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo; or

R^{16} and R^{17} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by oxo or halogen.

In some embodiments, the compound is of Formula I, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein:

X is CR^0;

R^0 is hydrogen, hydroxyl, or C_1-C_6 alkyl optionally substituted by R^{10};

R^1 is hydrogen, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, –CN, –CF_3, C_3-C_6 cycloalkyl, –(C_1-C_3 alkylene)CN, –(C_1-C_3 alkylene)OR^8, –(C_1-C_3 alkylene)SR^8, –(C_1-C_3 alkylene)NR^8R^9, –(C_1-C_3 alkylene)CF_3, –(C_1-C_3 alkylene)NO_2, –(C_1-C_3 alkylene)C(O)R^8, –(C_1-C_3 alkylene)C(O)OR^8, –(C_1-C_3 alkylene)C(O)NR^8R^9, –(C_1-C_3 alkylene)NR^8C(O)R^9, –(C_1-C_3 alkylene)S(O)R^8, –(C_1-C_3 alkylene)$S(O)_2R^8$, –(C_1-C_3 alkylene)NR^8S(O)R^9, –(C_1-C_3 alkylene)$NR^8S(O)_2R^9$, –(C_1-C_3 alkylene)S(O)NR^8R^9,
–(C_1-C_3 alkylene)$S(O)_2NR^8R^9$, –(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), –(C_1-C_3 alkylene)(3-6-membered heterocyclyl), –(C_1-C_3 alkylene)(5-6-membered heteroaryl) or –(C_1-C_3 alkylene)(C_6-C_{14} aryl);

R^2 is hydrogen or C_1-C_6 alkyl optionally substituted by R^{10}, or is taken together with R^3 and the carbon to which they are attached to form a ring selected from C_3-C_{10} cycloalkyl and 3-10-membered heterocyclyl, wherein the ring is optionally substituted by R^{10};

R^3 is hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, C_6-C_{14} aryl, or 5-10-membered heteroaryl, wherein R^3 may be optionally substituted by R^{10}; or is taken together with R^2 and the carbon to which they are attached to form a ring selected from C_3-C_{10} cycloalkyl and 3-10-membered heterocyclyl, wherein the ring is optionally substituted by R^{10};

R^4 is $–NR^6–$, $–NR^6C(O)–$, $–NR^6C(O)O–$ or $–NR^6C(O)NR^7–$;

R^5 is hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 5-10-membered heteroaryl, wherein R^5 is optionally substituted by R^{10};

R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_6 cycloalkyl, wherein the alkyl, alkenyl, alkynyl and cycloalkyl are independently optionally substituted by halogen, C_1-C_6 alkyl, oxo, –CN, $–OR^{11}$ or $–NR^{11}R^{12}$;

R^8 and R^9 are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo;

each R^{10} is independently hydrogen, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen,

–CN, $–OR^{11}$, $–SR^{11}$, $–NR^{11}R^{12}$, $–NO_2$, $–C{=}NH(OR^{11})$, $–C(O)R^{11}$, $–C(O)OR^{11}$, $–C(O)NR^{11}R^{12}$,

$–NR^{11}C(O)R^{12}$, $–S(O)R^{11}$, $–S(O)_2R^{11}$, $–NR^{11}S(O)R^{12}$, $–NR^{11}S(O)_2R^{12}$, $–S(O)NR^{11}R^{12}$, $–S(O)_2NR^{11}R^{12}$,

C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, 5-10-membered heteroaryl, C_6-C_{14} aryl, $–(C_1$-C_3 alkylene)CN, $–(C_1$-C_3 alkylene)OR^{11}, $–(C_1$-C_3 alkylene)SR^{11}, $–(C_1$-C_3 alkylene)$NR^{11}R^{12}$,

$–(C_1$-C_3 alkylene)CF_3, $–(C_1$-C_3 alkylene)NO_2, $–C{=}NH(OR^{11})$, $–(C_1$-C_3 alkylene)$C(O)R^{11}$, $–(C_1$-C_3 alkylene)$C(O)OR^{11}$, $–(C_1$-C_3 alkylene)$C(O)NR^{11}R^{12}$, $–(C_1$-C_3 alkylene)$NR^{11}C(O)R^{12}$,

$–(C_1$-C_3 alkylene)$S(O)R^{11}$, $–(C_1$-C_3 alkylene)$S(O)_2R^{11}$, $–(C_1$-C_3 alkylene)$NR^{11}S(O)R^{12}$, $–(C_1$-C_3 alkylene)$NR^{11}S(O)_2R^{12}$, $–(C_1$-C_3 alkylene)$S(O)NR^{11}R^{12}$, $–(C_1$-C_3 alkylene)$S(O)_2NR^{11}R^{12}$,

$–(C_1$-C_3 alkylene)(C_3-C_6 cycloalkyl), $–(C_1$-C_3 alkylene)(3-10-membered heterocyclyl), $–(C_1$-C_3 alkylene)(5-10-membered heteroaryl) or $–(C_1$-C_3 alkylene)(C_6-C_{14} aryl), wherein each R^{10} is independently optionally substituted by halogen, oxo, $–OR^{13}$, $–NR^{13}R^{14}$, $–C(O)R^{13}$, $–S(O)R^{13}$, $–S(O)_2R^{13}$, $–(C_1$-C_3 alkylene)OR^{13}, $–(C_1$-C_3 alkylene)$NR^{13}R^{14}$, $–(C_1$-C_3 alkylene)$C(O)R^{13}$, $–(C_1$-C_3 alkylene)$S(O)R^{13}$, $–(C_1$-C_3 alkylene)$S(O)_2R^{13}$ or C_1-C_6 alkyl optionally substituted by oxo, –CN or halogen;

R^{11} and R^{12} are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6 membered heteroaryl or 3-6 membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are independently optionally substituted by halogen, oxo, –CN, $–OR^{16}$, $–NR^{16}R^{17}$ or C_1-C_6 alkyl optionally substituted by halogen, –CN or oxo; or

R^{11} and R^{12} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, $–OR^{16}$, $–NR^{16}R^{17}$ or C_1-C_6 alkyl optionally substituted by halogen, oxo or OH;

R^{13} and R^{14} are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo; or

R^{13} and R^{14} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by halogen or oxo; and

R^{16} and R^{17} are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo; or

R^{16} and R^{17} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by oxo or halogen.

In some embodiments, the compound is of Formula I, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^1 is hydrogen, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, –CN, $–OR^8$, $–SR^8$, $–NR^8R^9$, $–CF_3$, $–NO_2$, $–C(O)R^8$, $–C(O)OR^8$, $–C(O)NR^8R^9$, $–NR^8C(O)R^9$, $–S(O)R^8$, $–S(O)_2R^8$, $–NR^8S(O)R^9$, $–NR^8S(O)_2R^9$, $–S(O)NR^8R^9$, $–S(O)_2NR^8R^9$, C_3-C_6 cycloalkyl, 3-6-membered heterocyclyl, 5-6-membered heteroaryl, C_6-C_{14} aryl, –(C_1-C_3 alkylene)CN, –(C_1-C_3 alkylene)OR^8, –(C_1-C_3 alkylene)SR^8, –(C_1-C_3 alkylene)NR^8R^9, –(C_1-C_3 alkylene)CF_3, –(C_1-C_3 alkylene)NO_2, –(C_1-C_3 alkylene)$C(O)R^8$, –(C_1-C_3 alkylene)$C(O)OR^8$, –(C_1-C_3 alkylene)$C(O)NR^8R^9$, –(C_1-C_3 alkylene)$NR^8C(O)R^9$, –(C_1-C_3 alkylene)$S(O)R^8$, –(C_1-C_3 alkylene)$S(O)_2R^8$, –(C_1-C_3 alkylene)$NR^8S(O)R^9$, –(C_1-C_3 alkylene)$NR^8S(O)_2R^9$, –(C_1-C_3 alkylene)$S(O)NR^8R^9$, –(C_1-C_3 alkylene)$S(O)_2NR^8R^9$, –(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), –(C_1-C_3 alkylene)(3-6-membered heterocyclyl), –(C_1-C_3 alkylene)(5-6-membered heteroaryl) or –(C_1-C_3 alkylene)(C_6-C_{14} aryl).

In some embodiments, the compound is of Formula I, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^1 is hydrogen, halogen, C_1-C_6 alkyl or –CN. In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is hydrogen or halogen (e.g., F, Cl, or Br). In some embodiments, R^1 is fluoro, chloro, bromo or cyano. In some embodiments, R^1 is C_1-C_6 alkyl (e.g., CH_3). In some embodiments, R^1 is halogen, –CN, $–CF_3$ or $–NO_2$. In some embodiments, R^1 is C_2-C_6 alkenyl, C_2-C_6 alkynyl, $–OR^8$, $–SR^8$, $–NR^8R^9$, $–C(O)R^8$, $–C(O)OR^8$, $–C(O)NR^8R^9$, $–NR^8C(O)R^9$, $–S(O)R^8$, $–S(O)_2R^8$, $–NR^8S(O)R^9$, $–NR^8S(O)_2R^9$, $–S(O)NR^8R^9$ or $–S(O)_2NR^8R^9$. In some embodiments, R^1 is C_3-C_6 cycloalkyl, 3-6-membered heterocyclyl, 5-6-membered heteroaryl or C_6-C_{14} aryl. In some embodiments, R^1 is –(C_1-C_3 alkylene)CN, –(C_1-C_3 alkylene)OR^8, –(C_1-C_3 alkylene)SR^8, –(C_1-C_3 alkylene)NR^8R^9, –(C_1-C_3 alkylene)CF_3, –(C_1-

C_3 alkylene)NO_2, –(C_1-C_3 alkylene)C(O)R^8, –(C_1-C_3 alkylene)C(O)OR^8, –(C_1-C_3 alkylene)C(O)NR^8R^9, –(C_1-C_3 alkylene)NR^8C(O)R^9, –(C_1-C_3 alkylene)S(O)R^8, –(C_1-C_3 alkylene)$S(O)_2R^8$, –(C_1-C_3 alkylene)NR^8S(O)R^9, –(C_1-C_3 alkylene)N$R^8S(O)_2R^9$, –(C_1-C_3 alkylene)S(O)NR^8R^9, –(C_1-C_3 alkylene)$S(O)_2NR^8R^9$, –(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), –(C_1-C_3 alkylene)(3-6-membered heterocyclyl), –(C_1-C_3 alkylene)(5-6-membered heteroaryl) or –(C_1-C_3 alkylene)(C_6-C_{14} aryl). In some variations, R^8 is hydrogen or C_1-C_6 alkyl. In some variations, R^8 is hydrogen. In some variations, R^8 is C_1-C_6 alkyl optionally substituted by halogen or oxo. In some variations, R^8 and R^9 are each independently hydrogen or C_1-C_6 alkyl. In some variations, R^8 is hydrogen and R^9 is hydrogen or C_1-C_6 alkyl.

In certain embodiments, R^1 is hydrogen, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, –CN, –OR^8, –SR^8, –NR^8R^9, –CF_3, –OCF_3, –NO_2, –C(O)R^8, –C(O)OR^8, –C(O)NR^8R^9, –NR^8C(O)R^9, –S(O)R^8, –$S(O)_2R^8$, –NR^8S(O)R^9, –N$R^8S(O)_2R^9$, –S(O)NR^8R^9, –$S(O)_2NR^8R^9$, –(C_3-C_6 cycloalkyl), –(3-6-membered heterocyclyl), –(5-6-membered heteroaryl) or –phenyl. In certain embodiments, R^1 is hydrogen, halogen, –CF_3 or C_1-C_3 alkyl. In certain embodiments, R^1 is methyl. In certain embodiments, R^1 is halogen. In certain embodiments, R^{15} is F.

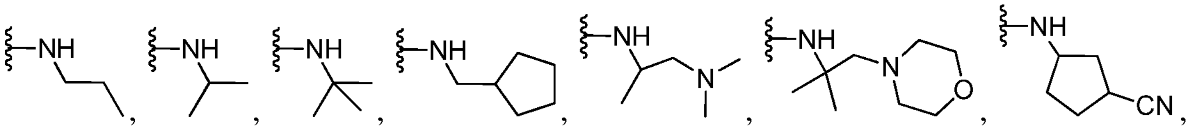
In certain embodiments, R^1 is –(C_1-C_3 alkylene)OR^8. In certain embodiments, R^1 is –CH_2OR^8. In certain embodiments, R^1 is –CH_2OH. In certain embodiments, R^1 is hydrogen, halogen, –CN, –CH_2OH, –CF_3 or C_1-C_3 alkyl. In certain embodiments, R^1 is methyl. In certain embodiments, R^1 is halogen. In certain embodiments, R^1 is F or Br. In certain embodiments, R^1 is F, Br, CN or CH_2OH.

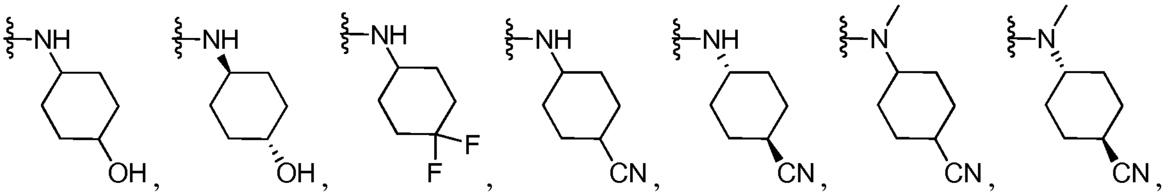
In some embodiments, the compound is of Formula I, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein X is N. In some embodiments, X is CR^0. In one variation, R^0 is hydrogen, hydroxyl, or C_1-C_6 alkyl optionally substituted by R^{10}. In one variation, R^0 is hydrogen, hydroxyl or unsubstituted C_1-C_6 alkyl. In one variation, R^0 is hydrogen or hydroxyl. In another variation, R^0 is hydrogen. In one variation, R^0 is hydroxyl. In another variation, R^0 is unsubstituted C_1-C_6 alkyl. In another variation, R^0 is C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, C_6-C_{14} aryl, or 5-10-membered heteroaryl.

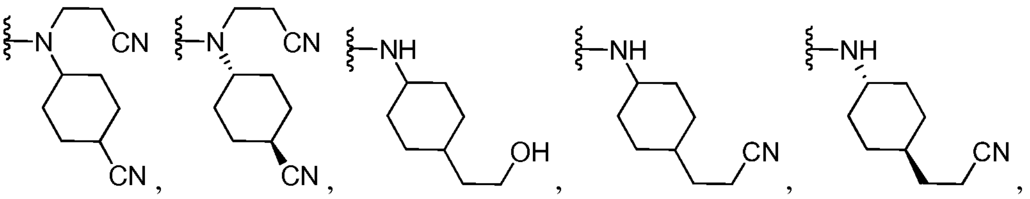
In some embodiments, the compound is of Formula I, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein each R^2 and R^3 is independently hydrogen, hydroxyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, C_6-C_{14} aryl, or 5-10-membered heteroaryl, wherein R^2 and R^3 are each independently optionally substituted by R^{10}. In some embodiments, each R^2 and R^3 is independently hydrogen, C_1-C_6 alkyl optionally substituted by R^{10}, C_3-C_6 cycloalkyl optionally substituted by R^{10}, or 3-10-membered heterocyclyl optionally substituted by R^{10}. In some embodiments, R^2 is hydrogen or C_1-C_6 alkyl optionally substituted by R^{10} and R^3 is C_1-C_6 alkyl optionally substituted by R^{10}, C_3-C_6

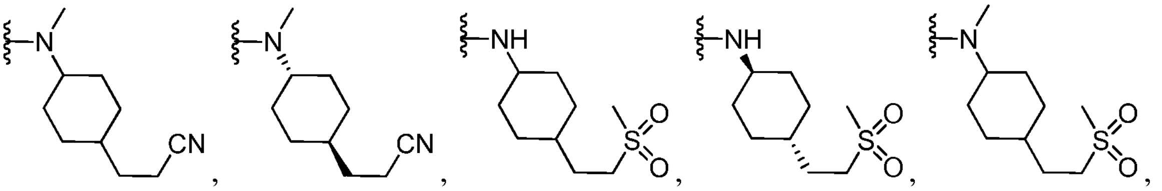
cycloalkyl optionally substituted by R^{10}, or 3-10-membered heterocyclyl optionally substituted by R^{10}. In some embodiments, R^2 is hydrogen and R^3 is C_1-C_6 alkyl optionally substituted by R^{10}, C_3-C_6 cycloalkyl optionally substituted by R^{10}, or 3-10-membered heterocyclyl optionally substituted by R^{10}. In some embodiments, R^2 is hydrogen and R^3 is C_1-C_6 alkyl optionally substituted by C_3-C_6 cycloalkyl (e.g., cyclopentyl), $–NR^{11}R^{12}$ (e.g., $–N(CH_3)_2$) or 3-10-membered heterocyclyl (e.g., morpholin4-yl). In some embodiments, R^2 is hydrogen and R^3 is C_3-C_6 cycloalkyl (e.g., cyclopentyl or cyclohexyl) optionally substituted by hydroxyl, cyano, halo (e.g., fluoro), C_1-C_6 alkyl or C_1-C_6 alkyl substituted by hydroxyl, cyano or sulfonyl (e.g., CH_2CH_2OH, CH_2CH_2CN, or $CH_2CH_2SO_2CH_3$). In some embodiments, R^2 is hydrogen and R^3 is 3-10-membered heterocyclyl optionally substituted by C_1-C_6 alkyl or C_1-C_6 alkyl substituted by hydroxyl, cyano or sulfonyl (e.g., CH_2CH_2OH, CH_2CH_2CN, or $CH_2CH_2SO_2CH_3$). In some embodiments, R^2 is C_1-C_6 alkyl optionally substituted by R^{10} and R^3 is C_1-C_6 alkyl optionally substituted by R^{10}, C_3-C_6 cycloalkyl optionally substituted by R^{10}, or 3-10-membered heterocyclyl optionally substituted by R^{10}.

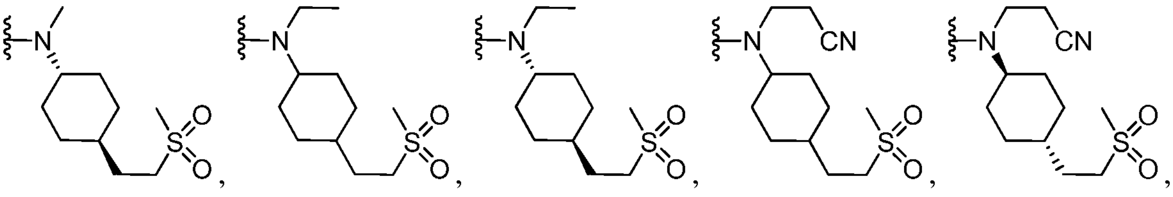
In some embodiments, X is N and the $–X(R^2)(R^3)$ moiety is selected from the group consisting of:

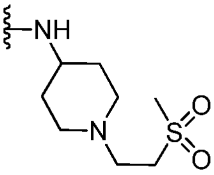
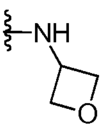
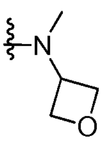
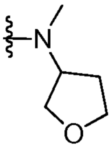
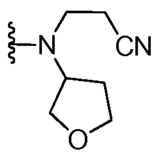
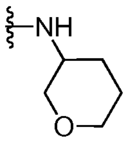
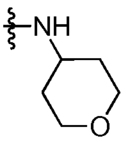




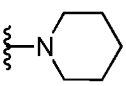
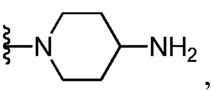
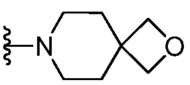
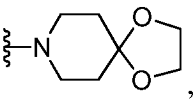
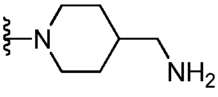
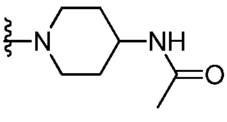
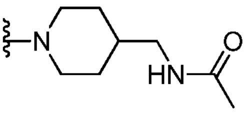
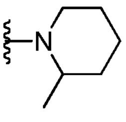
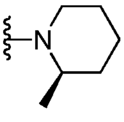
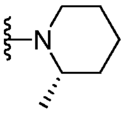
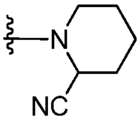
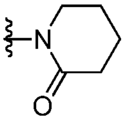
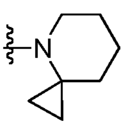
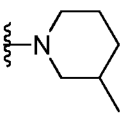
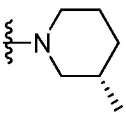
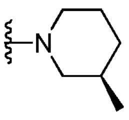
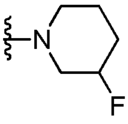
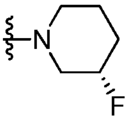
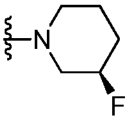
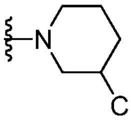


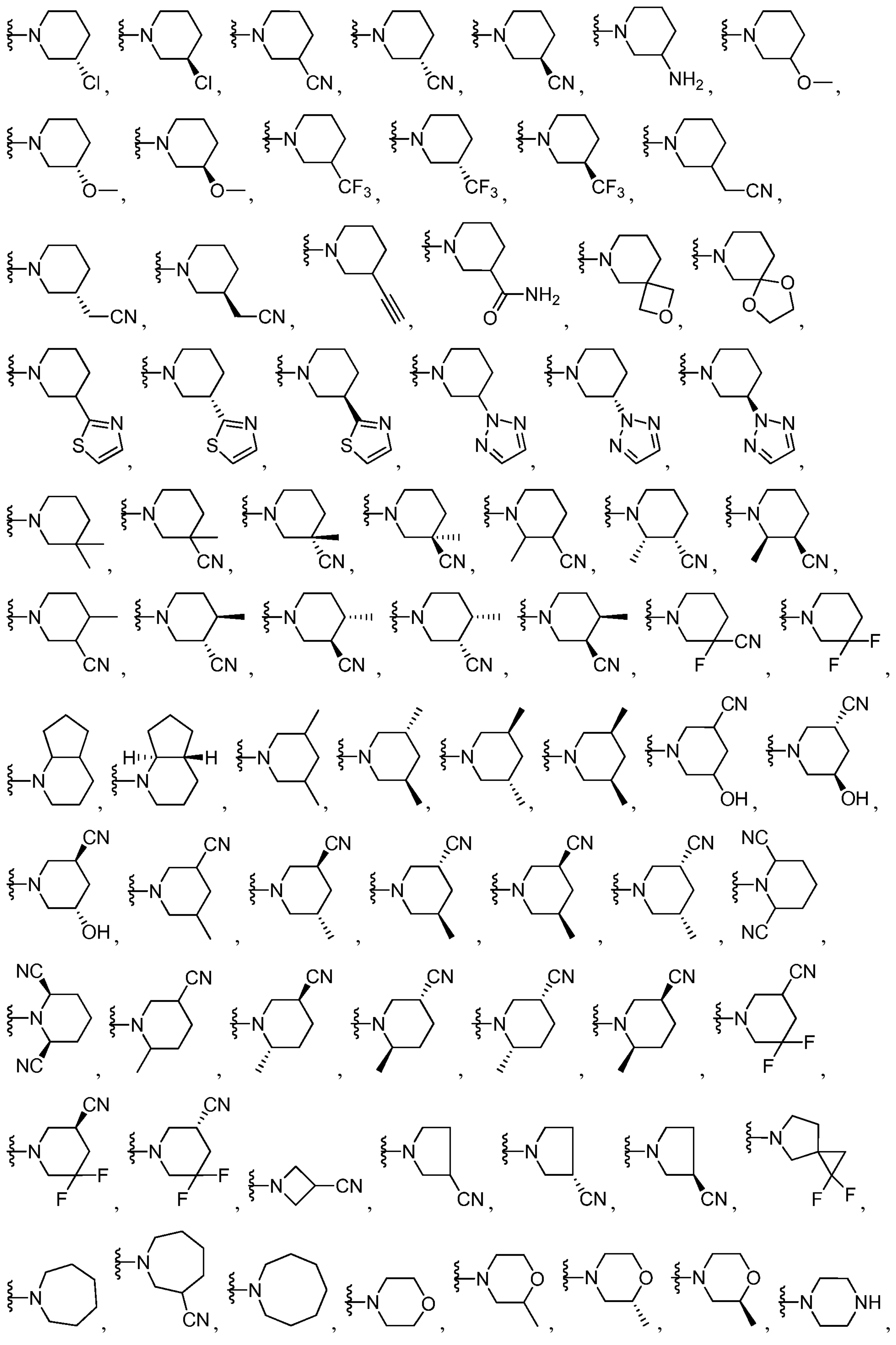


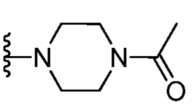
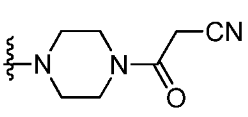
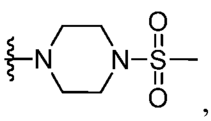
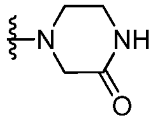
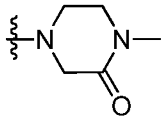
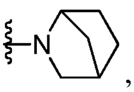


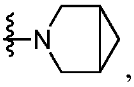
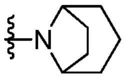
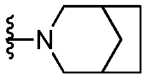

,

,

,

,

,

and

; wherein the wavy line represents the point of attachment in Formula I.

In some embodiments, R^2 and R^3 are taken together with the atom to which they are attached to form a ring selected from C_3-C_{10} cycloalkyl and 3-10-membered heterocyclyl, wherein the ring may be optionally substituted by R^{10}. In some embodiments, X is N and R^2 and R^3 are taken together with the atom to which they are attached to form a 3-10-membered heterocyclyl optionally substituted by R^{10}. In some embodiments, X is N and R^2 and R^3 are taken together with the atom to which they are attached to form a 4-9-membered heterocyclyl optionally substituted by R^{10}. In some embodiments, X is N and R^2 and R^3 are taken together with the atom to which they are attached to form a 4, 5, 6, 7, 8, or 9-membered heterocyclyl optionally substituted by R^{10}. In some embodiments, X is N and R^2 and R^3 are taken together with the atom to which they are attached to form a 5 or 6-membered heterocyclyl optionally substituted by R^{10}. In some embodiments, X is N and R^2 and R^3 are taken together with the atom to which they are attached to form a 4-membered heterocyclyl (e.g., azetidinyl) optionally substituted by R^{10}. In some embodiments, X is N and R^2 and R^3 are taken together with the atom to which they are attached to form a 5-membered heterocyclyl (e.g., pyrrolidinyl) optionally substituted by R^{10}. In some embodiments, X is N and R^2 and R^3 are taken together with the atom to which they are attached to form a 6-membered heterocyclyl (e.g., piperidinyl, piperazinyl or morpholinyl) optionally substituted by R^{10}. In some embodiments, X is N and R^2 and R^3 are taken together with the atom to which they are attached to form a 7-membered heterocyclyl (e.g., azepanyl) optionally substituted by R^{10}. In some embodiments, X is N and R^2 and R^3 are taken together with the atom to which they are attached to form an 8-membered heterocyclyl (e.g., azocanyl) optionally substituted by R^{10}.

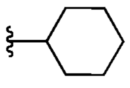
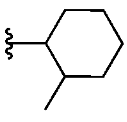
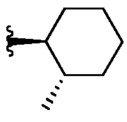
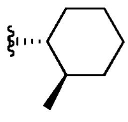
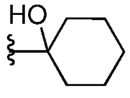
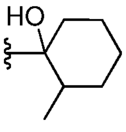
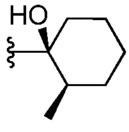
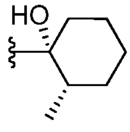
In some embodiments, X is N and the $-X(R^2)(R^3)$ moiety is selected from the group consisting of:

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

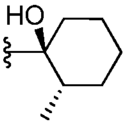
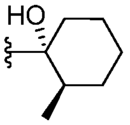


, , , , , ,

,  and ; wherein the wavy line represents the point of attachment in Formula I.

In some embodiments, X is CR^0 and R^2 and R^3 are taken together with the atom to which they are attached to form a ring selected from C_3-C_{10} cycloalkyl optionally substituted by R^{10}. In some embodiments, X is CR^0 where R^0 is hydrogen or hydroxyl and R^2 and R^3 are taken together with the atom to which they are attached to form a cyclohexyl group optionally substituted by C_1-C_6 alkyl (e.g., methyl). In some embodiments, X is CR^0 and R^2 and R^3 are taken together with the atom to which they are attached to form a 3-10-membered heterocyclyl optionally substituted by R^{10}.

In some embodiments, X is CR^0 and the $-X(R^2)(R^3)$ moiety is selected from the group consisting of: , , , , , , , ,

 and ; wherein the wavy line represents the point of attachment in Formula I.

It is intended and understood that each and every variation of X, R^2 and R^3 described for Formula I may be combined with each and every variation of R^1 described for Formula I as if each and every combination is individually described. For example, in some embodiments, R^1 is hydrogen, halogen, C_1-C_6 alkyl or –CN, X is N, R^2 is hydrogen or C_1-C_6 alkyl optionally substituted by R^{10} and R^3 is C_1-C_6 alkyl optionally substituted by R^{10}, C_3-C_6 cycloalkyl optionally substituted by R^{10}, or 3-10-membered heterocyclyl optionally substituted by R^{10}. In some embodiments, R^1 is hydrogen, halogen, X is N and R^2 and R^3 are taken together with the atom to which they are attached to form a 4, 5, 6, 7, 8, or 9-membered heterocyclyl optionally substituted by R^{10}. In some embodiments, R^1 is hydrogen, X is CR^0 where R^0 is hydrogen or hydroxyl and R^2 and R^3 are taken together with the atom to which they are attached to form a cyclohexyl group optionally substituted by C_1-C_6 alkyl.

In some embodiments, the compound is of Formula I, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^4 is $-NR^6-$, $-NR^6C(O)-$, $-NR^6C(O)O-$, $-NR^6C(O)NR^7-$, $-NR^6S(O)-$, $-NR^6S(O)_2-$, $-NR^6S(O)NR^7-$ or $-NR^6S(O)_2NR^7-$; R^5 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, 3-10-membered heterocyclyl or 5-10-membered heteroaryl, wherein R^5 is optionally substituted by R^{10}; and R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_6 cycloalkyl, wherein the alkyl, alkenyl, alkynyl and cycloalkyl are independently optionally substituted by halogen, C_1-C_6 alkyl, oxo, –CN, –OR^{11} or –$NR^{11}R^{12}$. In some embodiments, R^4 is hydrogen and R^5 is absent. In some embodiments, R^4 is –NR^6R^7, R^5 is absent, and R^6 and R^7 are taken together with the atom to which they are attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, –OR^{11},–$NR^{11}R^{12}$ or C_1-C_6 alkyl optionally substituted by halogen.

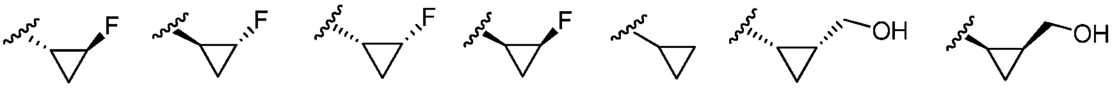
In certain embodiments, R^4 is –NR^6R^7; R^5 is absent; and R^6 and R^7 are independently hydrogen, C_1-C_3 alkyl or C_3-C_4 cycloalkyl, wherein said alkyl and cycloalkyl are independently optionally substituted by halogen, oxo, –OR^{11} or –$NR^{11}R^{12}$.

In certain embodiments, R^4 is –NR^6–. In certain embodiments, R^4 is –$NR^6C(O)$–. In certain embodiments, R^4 is –$NR^6C(O)O$–. In certain embodiments, R^4 is –$NR^6C(O)NR^7$–. In certain embodiments, R^4 is –NH–. In certain embodiments, R^4 is –NHC(O)–. In certain embodiments, R^4 is –NHC(O)O–. In certain embodiments, R^4 is –NHC(O)NH–.

In certain embodiments, R^4 is –NR^6–, –$NR^6C(O)$–, –$NR^6C(O)O$– or –$NR^6C(O)NR^7$–. In certain embodiments, R^4 is –NH–, –NHC(O)– or –NHC(O)NH–.

In certain embodiments, R^5 is hydrogen. In certain embodiments, R^5 is C_1-C_6 alkyl optionally substituted by halogen, oxo, –OR^{11}, –SR^{11}, –CN, C_3-C_{10} cycloalkyl, –$C(O)R^{11}$ or –$NR^{11}R^{12}$. In certain embodiments, R^5 is C_1-C_6 alkyl optionally substituted by halogen, oxo, –OR^{11}, –SR^{11}, –$C(O)R^{11}$ or –$NR^{11}R^{12}$. In certain embodiments, R^5 is methyl, ethyl, isopropyl, tert-butyl, –CH_2OH, –CH_2NH_2, –$CH_2N(CH_3)_2$ or –$CH_2CH_2NH_2$. In certain embodiments, R^5 is methyl, ethyl, isopropyl, tert-butyl, –CH_2OH, –CH_2CH_2OH, –CH_2CN, –CH_2NH_2, –$CH_2N(CH_3)_2$ or –$CH_2CH_2NH_2$.

In certain embodiments, R^5 is C_3-C_{10} cycloalkyl optionally substituted by R^{10}. In certain embodiments, R^5 is C_3-C_6 cycloalkyl optionally substituted by halogen. In certain embodiments, R^5 is cyclopropyl optionally substituted by halogen. In certain embodiments, R^5 is cyclopropyl. In certain embodiments, R^5 is cyclopropyl. In certain embodiments, R^5 is selected from:



wherein the wavy line represents the point of attachment in Formula I.

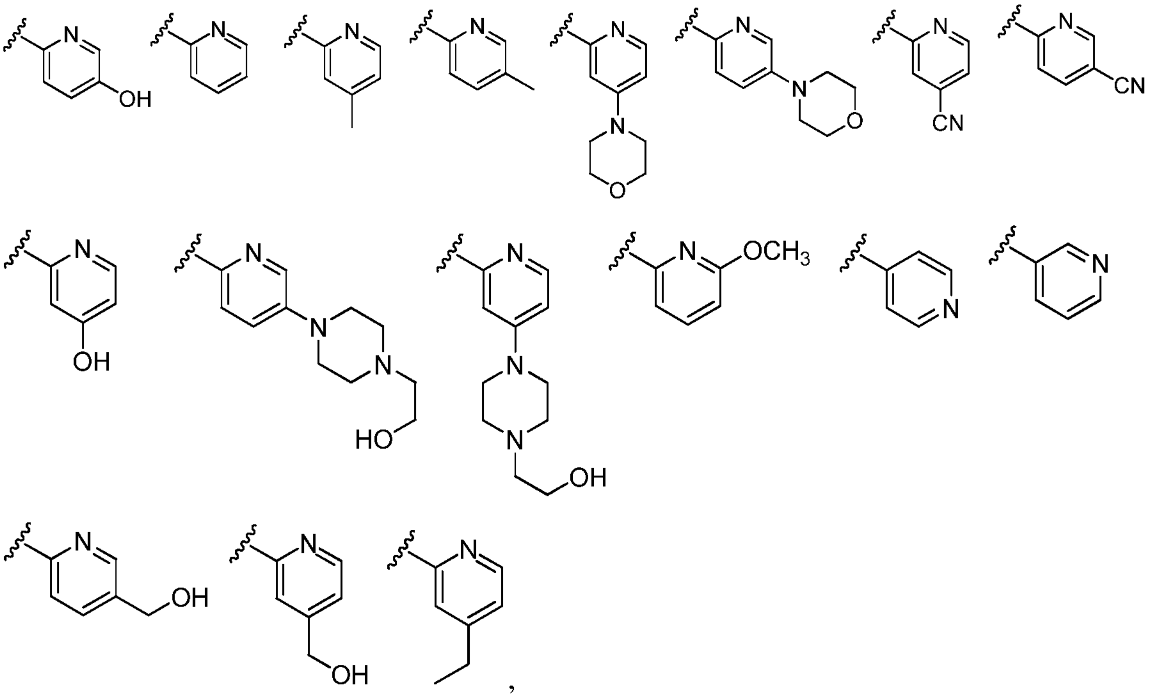
In certain embodiments, R^5 is C_6-C_{10} aryl optionally substituted by R^{10}. In certain embodiments, R^5 is selected from phenyl, naphthalenyl, dihyrdoindenyl and tetrahydronaphthalenyl, wherein R^5 is optionally substituted by R^{10}. In certain embodiments, R^5 is phenyl optionally substituted by R^{10}. In certain embodiments, R^5 is phenyl. In certain embodiments, R^5 is phenyl optionally substituted by –$O(CH_2)_2$pyrrolidinyl.

In certain embodiments, R^5 is 3-10-membered heterocyclyl optionally substituted by R^{10}. In certain embodiments, R^5 is 3-7-membered heterocyclyl optionally substituted by R^{10}. In certain embodiments, R^5 is 5-10-membered heteroaryl optionally substituted by R^{10}. In certain embodiments, R^5 is pyridinyl, pyrimidinyl, pyrazolyl, thiazolyl, pyrazinyl, pyridazinyl, oxazolyl or isoxazolyl, wherein said R^5 is optionally substituted by R^{10}. In certain embodiments, R^5 is pyridinyl, pyrimidinyl, pyrazolyl, thiazolyl, pyrazinyl, pyridazinyl, oxazolyl or isoxazolyl optionally substituted by C_1-C_6 alkyl, halogen, –CN, –O(C_0-C_3 alkyl), –CF_3, –$NR^{11}R^{12}$, –C=NH(OR^{11}), –C(O)OR^{11}, 3-6-membered heterocyclyl, wherein said alkyl is optionally substituted by halogen or OR^{11} and said heterocyclyl is optionally substituted by oxo, halogen or C_1-C_3 alkyl optionally substituted by halogen or OR^{11}. In certain embodiments, R^5 is pyridinyl, pyrimidinyl, pyrazolyl, thiazolyl, pyrazinyl, pyridazinyl, oxazolyl or isoxazolyl optionally substituted by C_1-C_6 alkyl, halogen, –CN, –O(C_1-C_3 alkyl), –CF_3, –$NR^{11}R^{12}$, –C=NH(OR^{11}), –C(O)OR^{11}, 3-6-membered heterocyclyl, wherein said alkyl is optionally substituted by halogen or OR^{13} and said heterocyclyl is optionally substituted by oxo, halogen or C_1-C_3 alkyl optionally substituted by halogen or OR^{13}.

In certain embodiments, R^5 is 5-6-membered heteroaryl, wherein R^5 is optionally substituted by R^{10}, wherein R^{10} is C_1-C_6 alkyl, halogen, –CN, –OR^{11}, –SR^{11}, –$NR^{11}R^{12}$, –CF_3, –C(O)R^{11}, –C(O)OR^{11}, –C(O)$NR^{11}R^{12}$, –NR^{11}C(O)R^{12}, –S(O)$_{1-2}R^{11}$, –NR^{11}S(O)$_{1-2}R^{12}$, –S(O)$_{1-2}NR^{11}R^{12}$, C_3-C_6 cycloalkyl, 3-6-membered heterocyclyl, –C(O)(3-6-membered heterocyclyl), 5-6-membered heteroaryl or phenyl, wherein R^{10} is independently optionally substituted by halogen, C_1-C_3 alkyl, oxo, –CF_3, –OR^{13}, –$NR^{13}R^{14}$, –C(O)R^{13} or –S(O)$_{1-2}R^{13}$. In an example, R^5 is pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, thienyl, pyrazolyl, pyranyl, triazolyl, isoxazolyl, oxazolyl, imidazolyl, thiazolyl or thiadiazolyl, wherein R^5 is optionally substituted by 1, 2 or 3 R^{10}.

In certain embodiments, R^5 is pyridinyl optionally substituted by C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, –(C_0-C_3 alkylene)CN, –(C_0-C_3 alkylene)OR^{11}, –(C_0-C_3 alkylene)SR^{11}, –(C_0-C_3 alkylene)$NR^{11}R^{12}$, –(C_0-C_3 alkylene)CF_3, –(C_0-C_3 alkylene)NO_2, –C=NH(OR^{11}),–(C_0-C_3 alkylene)C(O)R^{11}, –(C_0-C_3 alkylene)C(O)OR^{11}, –(C_0-C_3 alkylene)C(O)$NR^{11}R^{12}$, –(C_0-C_3 alkylene)NR^{11}C(O)R^{12}, –(C_0-C_3 alkylene)S(O)$_{1-2}R^{11}$, –(C_0-C_3 alkylene)NR^{11}S(O)$_{1-2}R^{12}$, –(C_0-C_3 alkylene)S(O)$_{1-2}NR^{11}R^{12}$,–(C_0-C_3 alkylene)(C_3-C_6 cycloalkyl), –(C_0-C_3 alkylene)(3-6-membered heterocyclyl), –(C_0-C_3 alkylene)C(O)(3-6-membered heterocyclyl), –(C_0-C_3 alkylene)(5-6-membered heteroaryl) or –(C_0-C_3 alkylene)phenyl, wherein R^{10} is independently optionally substituted by halogen, C_1-C_3 alkyl, oxo, –CF_3, –(C_0-C_3 alkylene)OR^{13}, –(C_0-C_3 alkylene)$NR^{13}R^{14}$, –(C_0-C_3 alkylene)C(O)R^{13} or –(C_0-C_3 alkylene)S(O)$_{1-2}R^{13}$.

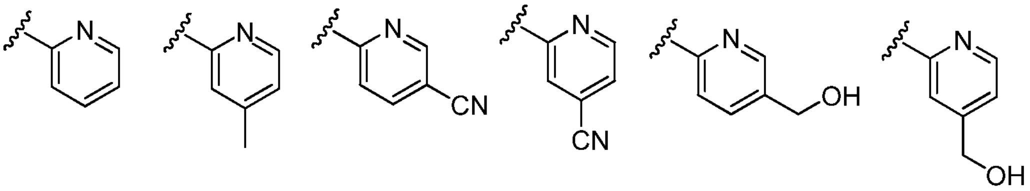
In certain embodiments, R^5 is selected from:



,

wherein the wavy lines represent the point of attachment in Formula I.

In certain embodiments, R^5 is selected from:

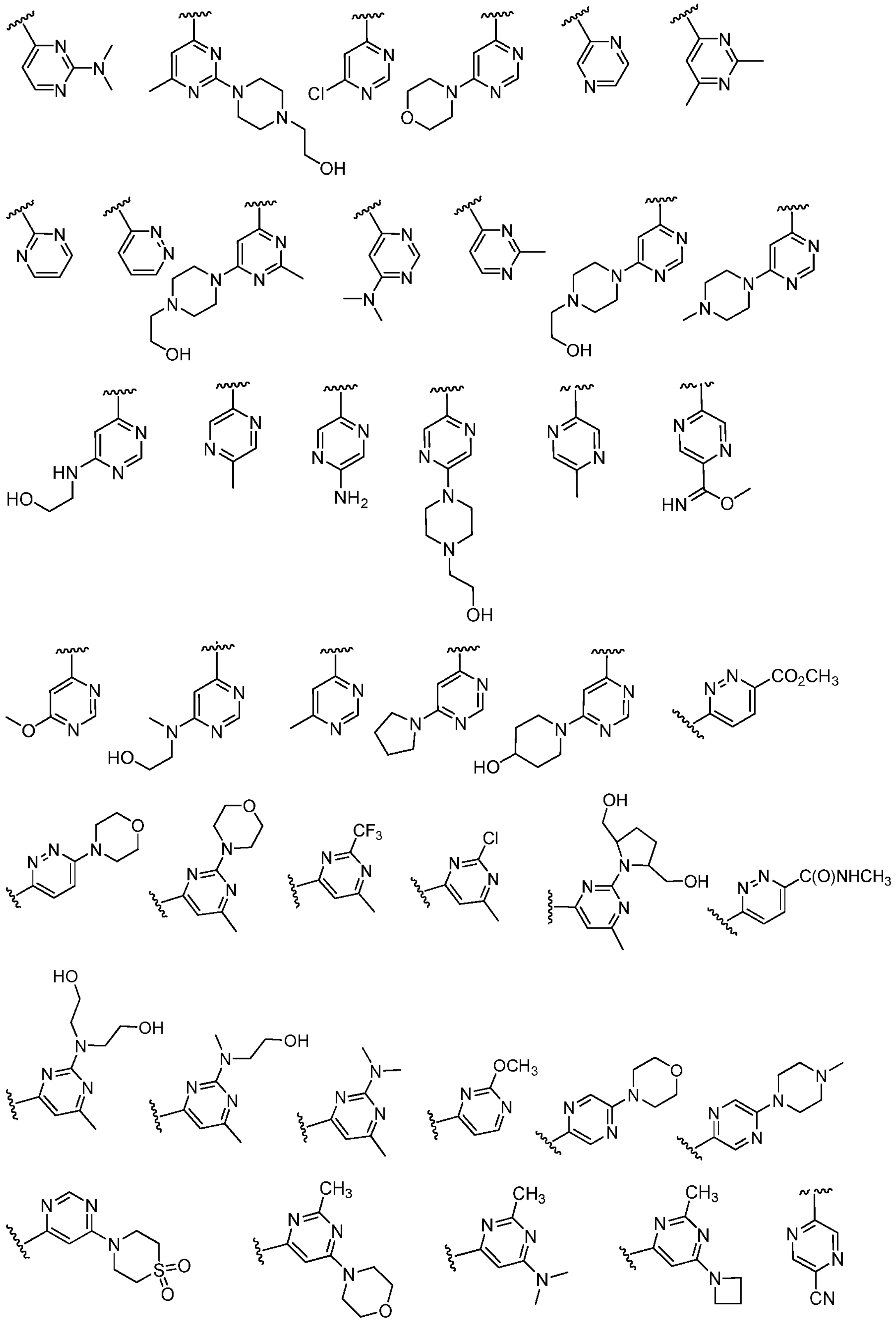


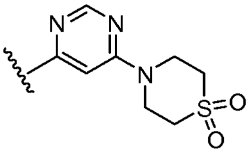
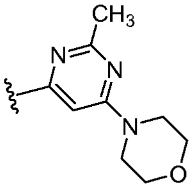
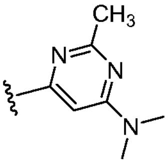
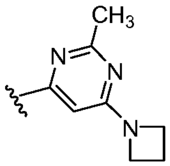
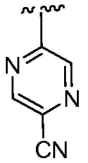
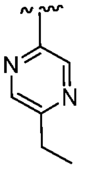
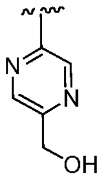
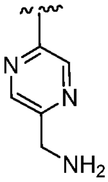
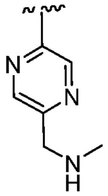
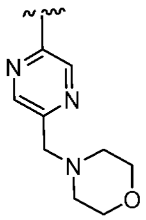
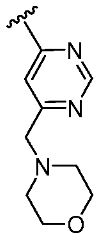
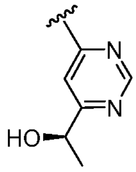
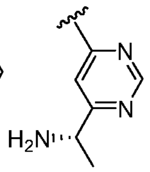
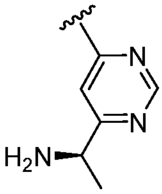
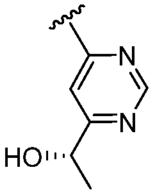
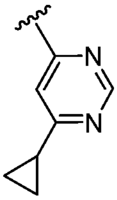
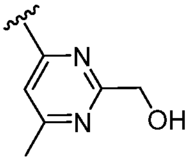
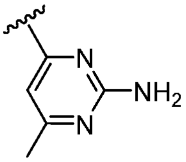
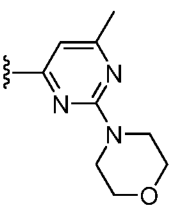
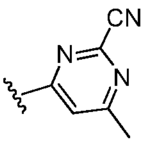
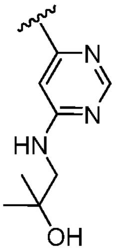
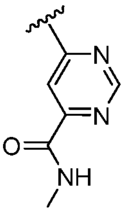
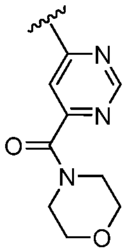
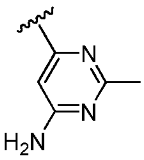
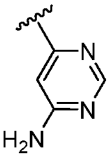
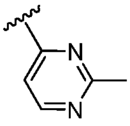
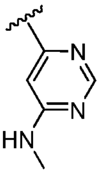
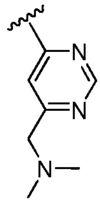
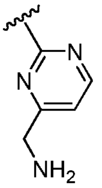
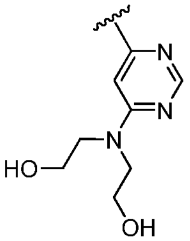
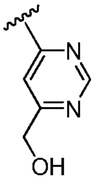
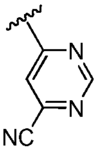
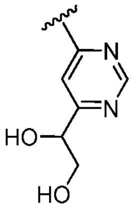
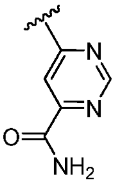
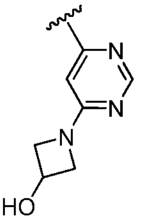
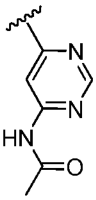
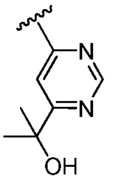
,

wherein the wavy lines represent the point of attachment in Formula I.

In certain embodiments, R^5 is pyrimidinyl, pyridazinyl, or pyrazinyl, optionally substituted by C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, –(C_0-C_3 alkylene)CN, –(C_0-C_3 alkylene)OR^{11}, –(C_0-C_3 alkylene)SR^{11}, –(C_0-C_3 alkylene)$NR^{11}R^{12}$, –(C_0-C_3 alkylene)CF_3, –(C_0-C_3 alkylene)NO_2, –C=NH(OR^{11}),–(C_0-C_3 alkylene)C(O)R^{11}, –(C_0-C_3 alkylene)C(O)OR^{11}, –(C_0-C_3 alkylene)C(O)$NR^{11}R^{12}$, –(C_0-C_3 alkylene)$NR^{11}C(O)R^{12}$, –(C_0-C_3 alkylene)$S(O)_{1\text{-}2}R^{11}$, –(C_0-C_3 alkylene)$NR^{11}S(O)_{1\text{-}2}R^{12}$, –($C_0$-$C_3$ alkylene)$S(O)_{1\text{-}2}NR^{11}R^{12}$, –($C_0$-$C_3$ alkylene)(C_3-C_6 cycloalkyl), –(C_0-C_3 alkylene)(3-6-membered heterocyclyl), –(C_0-C_3 alkylene)C(O)(3-6-membered heterocyclyl), –(C_0-C_3 alkylene)(5-6-membered heteroaryl) or –(C_0-C_3 alkylene)phenyl, wherein R^{10} is independently optionally substituted by halogen, C_1-C_3 alkyl, oxo, –CF_3, –(C_0-C_3 alkylene)OR^{13}, –(C_0-C_3 alkylene)$NR^{13}R^{14}$, –(C_0-C_3 alkylene)C(O)R^{13} or –(C_0-C_3 alkylene)$S(O)_{1\text{-}2}R^{13}$.

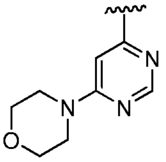
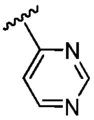
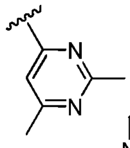
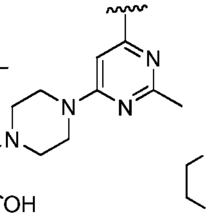
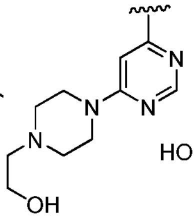
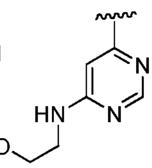
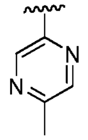
In certain embodiments, R^5 is selected from:

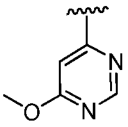
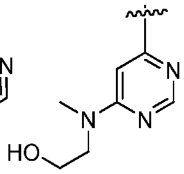
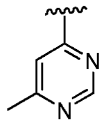
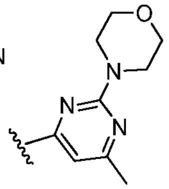
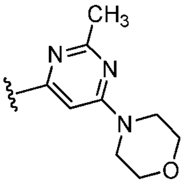
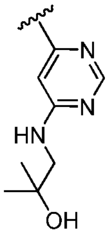
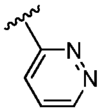
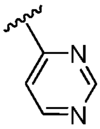
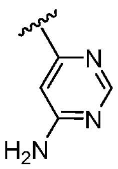
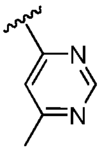
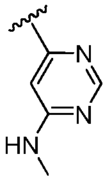
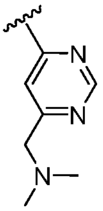
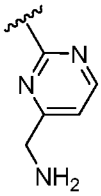
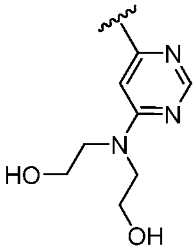
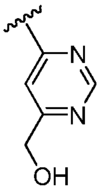
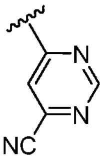
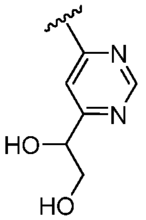
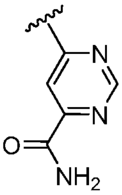
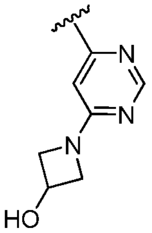
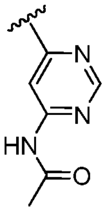
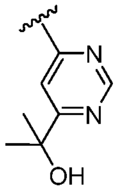
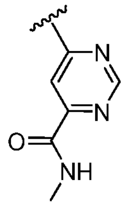
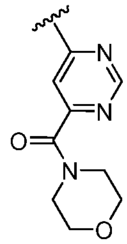







































,

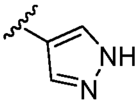
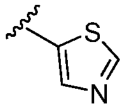
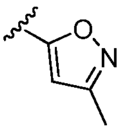
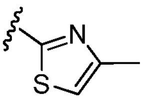
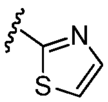
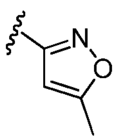
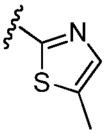
wherein the wavy lines represent the point of attachment in Formula I.

In certain embodiments, R^5 is selected from:

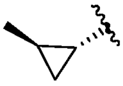
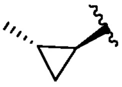
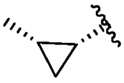
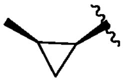
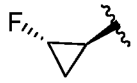







.

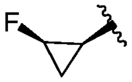
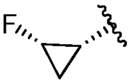
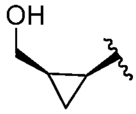
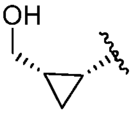
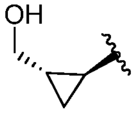
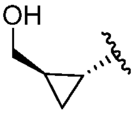
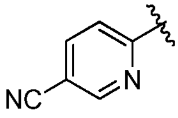























, wherein the wavy lines represent the point of attachment in Formula I.

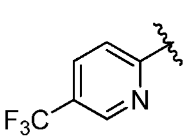
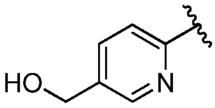
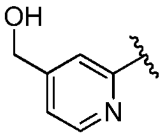
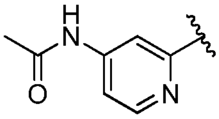
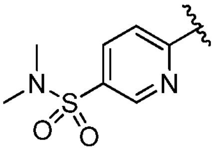
In certain embodiments, R^5 is pyrimidinyl optionally substituted by C_1-C_3 alkyl and $-NR^{11}R^{12}$. In certain embodiments, R^5 is pyrimidinyl optionally substituted by methyl and $-NH_2$. In certain embodiments, R^5 is pyrazolyl, isoxazolyl, oxazolyl, imidazolyl, thiazolyl or thiadiazolyl, wherein R^5 is optionally substituted by R^{10}, wherein R^{10} is C_1-C_6 alkyl, halogen, $-CN$, $-OR^{11}$, $-SR^{11}$, $-NR^{11}R^{12}$, $-CF_3$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-C(O)NR^{11}R^{12}$, $-NR^{11}C(O)R^{12}$, $-S(O)_{1\text{-}2}R^{11}$, $-NR^{11}S(O)_{1\text{-}2}R^{12}$, $-S(O)_{1\text{-}2}NR^{11}R^{12}$, C_3-C_6 cycloalkyl, 3-6-membered heterocyclyl, $-C(O)$(3-6-membered heterocyclyl), 5-6-membered heteroaryl or phenyl, wherein R^{10} is independently optionally substituted by halogen, C_1-C_3 alkyl, oxo, $-CF_3$, $-OR^{13}$, $-NR^{13}R^{14}$, $-C(O)R^{13}$ or $-S(O)_{1\text{-}2}R^{13}$. In certain embodiments, R^5 is pyrazolyl optionally substituted by R^{10}. In certain embodiments, R^5 is selected from:

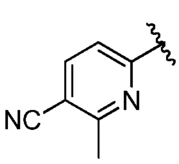
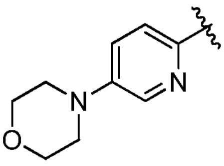
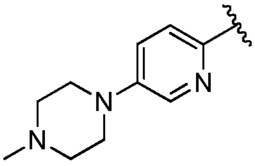
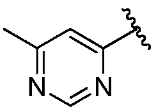
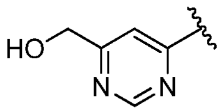







,

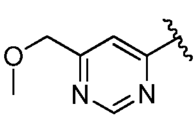
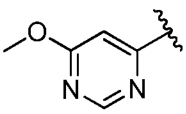
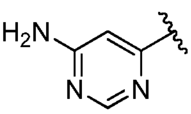
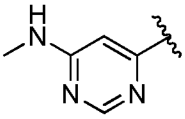
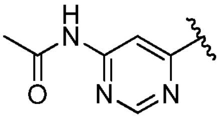
wherein the wavy lines represent the point of attachment in Formula I.

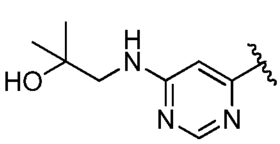
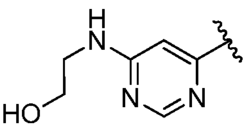
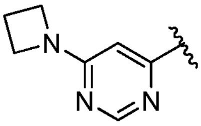
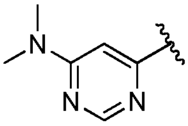
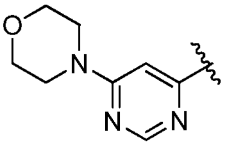
In some embodiments, R^5 is selected from the group consisting of methyl, ethyl, 2-propyl, cyclopropyl, 2-methylcyclopropyl, 2-fluorocyclopropyl, 2-(hydroxymethyl)cyclopropyl, cyclopropylmethyl, , , , , , ,

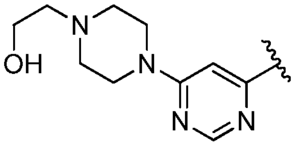
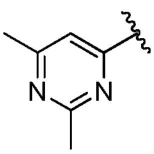
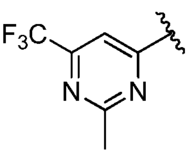
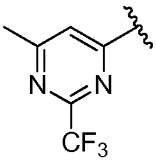
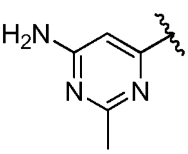
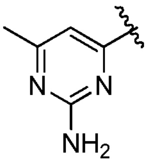
, , , , , , ,

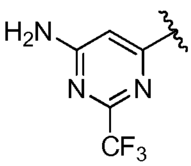
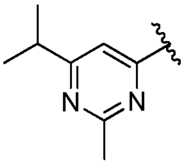
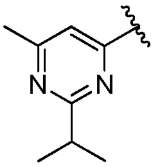
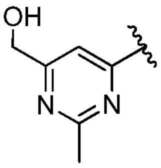
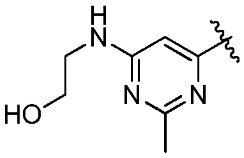
, , , , ,

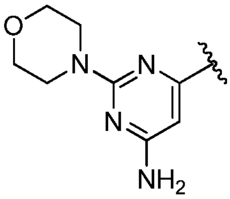
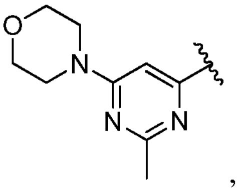
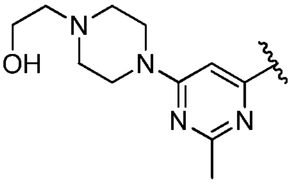
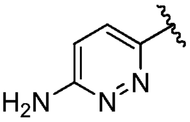
, , , , ,

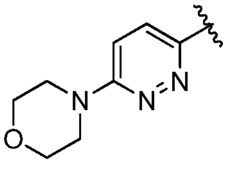
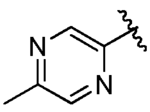
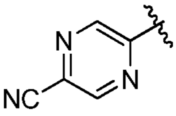
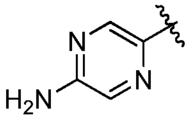
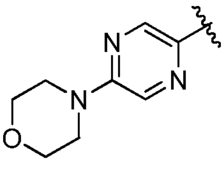
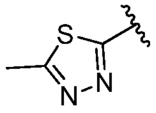
, , , , ,

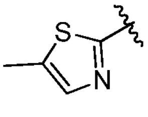
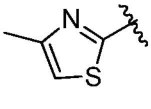
, , , , ,

, , , , , ,

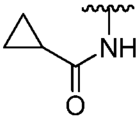
, , , , ,

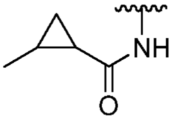
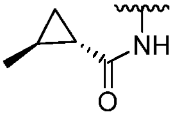
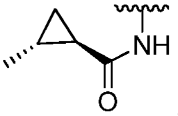
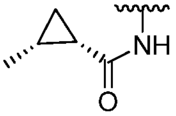
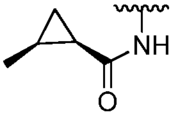
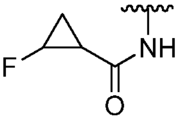
, , , ,

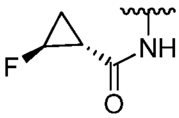
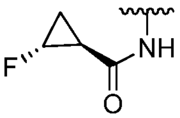
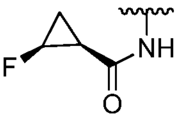
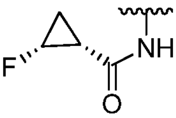
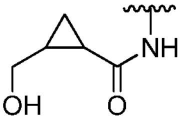
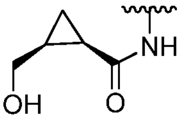
, , , , , ,

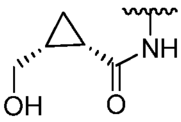
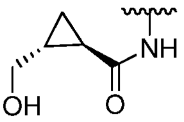
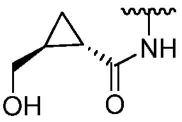
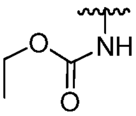
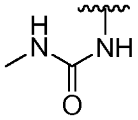
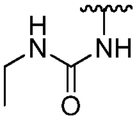
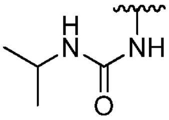
 and ; wherein the wavy line represents the point of attachment in Formula I.

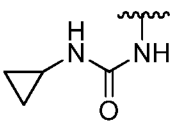
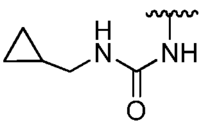
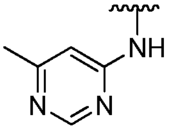
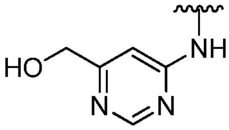
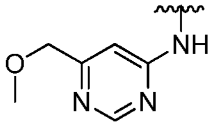
In certain embodiments, the group –R^4-R^5 is –NHR^5, –$NHC(O)R^5$, –$NHC(O)OR^5$ or –$NHC(O)NHR^5$. In certain embodiments, the group –R^4-R^5 is –NHR^5, –$NHC(O)R^5$, –$NHC(O)OR^5$ or –$NHC(O)NHR^5$, wherein R^5 is other than hydrogen. In certain embodiments, –R^4-R^5 is –NH_2.

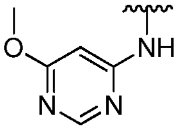
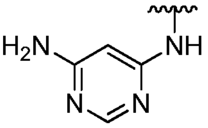
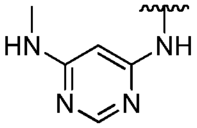
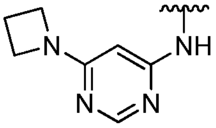
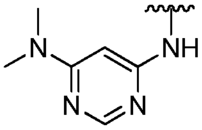
In some embodiments, the –R^4-R^5 moiety is selected form the group consisting of: ,

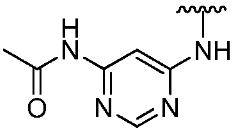
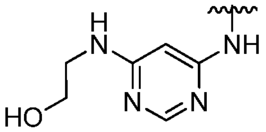
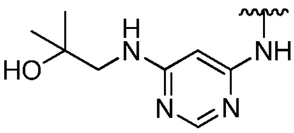
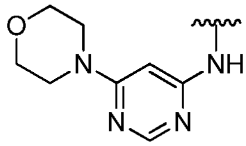
, , , , , ,

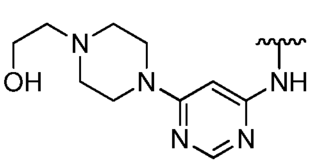
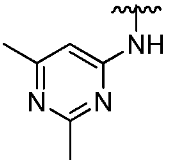
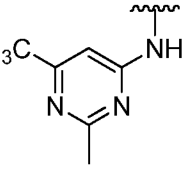
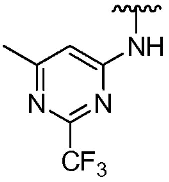
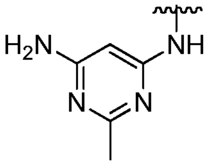
, , , , , ,

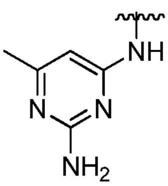
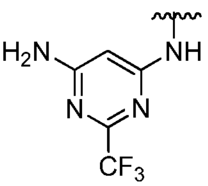
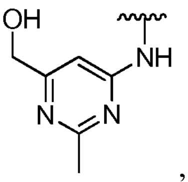
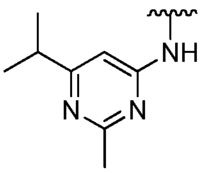
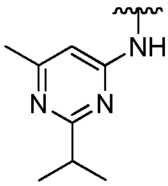
, , , , , , ,

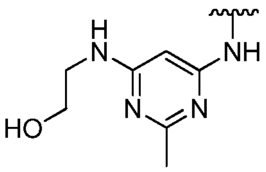
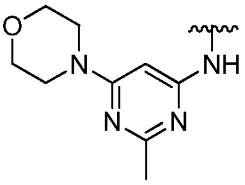
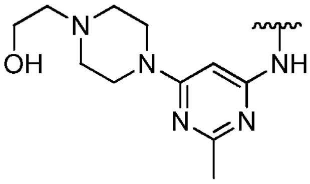
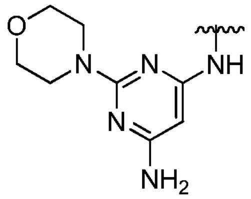
, , , , ,

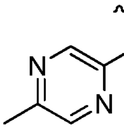
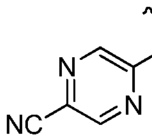
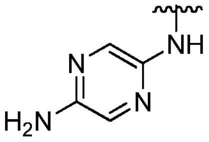
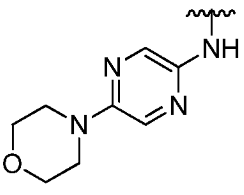
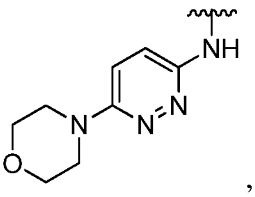
, , , , ,

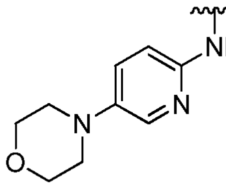
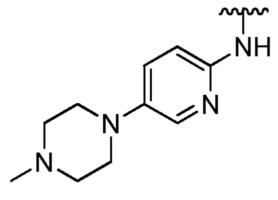
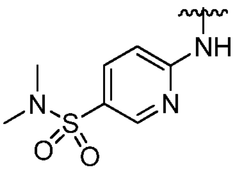
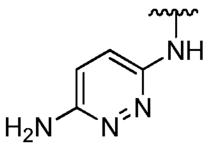
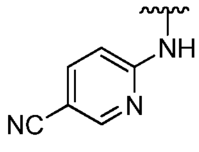
, , , ,

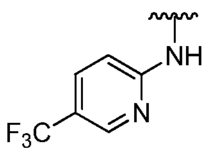
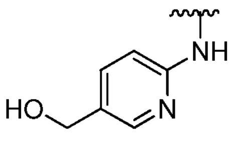
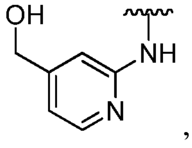
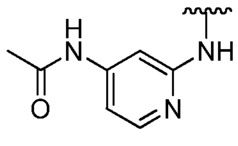
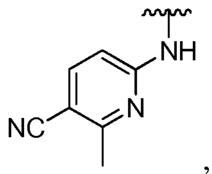
, , , , ,

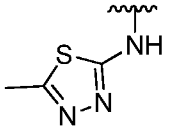
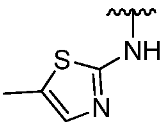
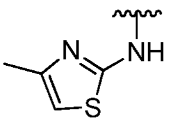
, , , , ,

, , , ,

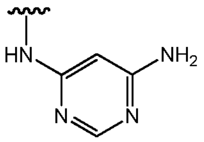
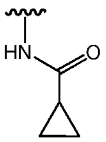
 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,  and  ; wherein the wavy line represents the point of attachment in Formula I.

In some embodiments, the –R^4-R^5 moiety is selected from the group consisting of:

 and  ,

wherein the wavy line represents the point of attachment in Formula I.

It is intended and understood that each and every variation of R^4 and R^5 described for Formula I may be combined with each and every variation of R^1 described for Formula I, and/or each and every variation of X, R^2 and R^3 described for Formula I as if each and every combination is individually described. For example, in some embodiments, R^1 is hydrogen or halogen, X is N, R^2 is hydrogen or optionally substituted C_1-C_6 alkyl, R^3 is optionally substituted C_1-C_6 alkyl, R^4 is –NR^6–, –$NR^6C(O)$– or –$NR^6C(O)NR^7$– and R^5 is optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 3-10-membered heterocyclyl or optionally substituted 5-10-membered heteroaryl. In some embodiments, R^1 is hydrogen, fluoro, chloro or bromo, X is N, R^2 and R^3 are taken together with the atom to which they are attached to form an optionally substituted piperidinyl (e.g., 3-cyanopiperidin-1-yl), and the –R^4-R^5 moiety is –NH–(optionally substituted pyrimidinyl) (e.g., (6-aminopyrimidin-4-yl)amino), –NHC(O)–(optionally substituted cyclopropyl) (e.g., cyclopropanecarbonylamino), or –NHC(O)NH–(optionally substituted C_1-C_6 alkyl) (e.g., isopropylurido). In some embodiments, R^1 is hydrogen, X is CR^0 where R^0 is hydrogen or hydroxy, R^2 and R^3 are taken together with the carbon to which they are attached to form an optionally substituted cycloalkyl and the $–R^4$-R^5 moiety is (6-aminopyrimidin-4-yl)amino or cyclopropanecarbonylamino.

In certain embodiments, R^1 is hydrogen; and the group $–R^4$-R^5 is $–NHR^5$, $–NHC(O)R^5$, $–NHC(O)OR^5$ or $–NHC(O)NHR^5$, wherein R^5 is other than hydrogen. In certain embodiments, R^1 is hydrogen; and the group $–R^4$-R^5 is $–NHR^5$, $–NHC(O)R^5$, $–NHC(O)OR^5$ or $–NHC(O)NHR^5$, wherein R^5 is other than hydrogen. In certain embodiments, R^1 is hydrogen, halogen or –CN; and the group $–R^4$-R^5 is $–NHR^5$, $–NHC(O)R^5$, $–NHC(O)OR^5$ or $–NHC(O)NHR^5$, wherein R^5 is other than hydrogen. In certain embodiments, X is N; R^1 is hydrogen, halogen or –CN; and the group $–R^4$-R^5 is $–NHR^5$, $–NHC(O)R^5$, $–NHC(O)OR^5$ or $–NHC(O)NHR^5$, wherein R^5 is other than hydrogen. In certain embodiments, R^1 is hydrogen, halogen or –CN; X is CR^0; R^0 is hydrogen or hydroxyl; and the group $–R^4$-R^5 is $–NHR^5$, $–NHC(O)R^5$, $–NHC(O)OR^5$ or $–NHC(O)NHR^5$, wherein R^5 is other than hydrogen.

In some of these embodiments, each R^{10} is independently oxo, C_1-C_6 alkyl, halogen, –CN, –OH, $–SR^{11}$, $–NR^{11}R^{12}$, $–NO_2$, $–C{=}NH(OR^{11})$, $–C(O)R^{11}$, $–C(O)OR^{11}$, $–C(O)NR^{11}R^{12}$, $–NR^{11}C(O)R^{12}$, $–S(O)R^{11}$, $–S(O)_2R^{11}$, $–NR^{11}S(O)R^{12}$, $–NR^{11}S(O)_2R^{12}$, $–S(O)NR^{11}R^{12}$, $–S(O)_2NR^{11}R^{12}$, C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, 5-10-membered heteroaryl, C_6-C_{14} aryl, $–(C_1$-C_3 alkylene)CN, $–(C_1$-C_3 alkylene)OR^{11}, $–(C_1$-C_3 alkylene)SR^{11}, $–(C_1$-C_3 alkylene)$NR^{11}R^{12}$, $–(C_1$-C_3 alkylene)CF_3, $–(C_1$-C_3 alkylene)NO_2, $–C{=}NH(OR^{11})$, $–(C_1$-C_3 alkylene)$C(O)R^{11}$, $–(C_1$-C_3 alkylene)$C(O)OR^{11}$, $–(C_1$-C_3 alkylene)$C(O)NR^{11}R^{12}$, $–(C_1$-C_3 alkylene)$NR^{11}C(O)R^{12}$, $–(C_1$-C_3 alkylene)$S(O)R^{11}$, $–(C_1$-C_3 alkylene)$S(O)_2R^{11}$, $–(C_1$-C_3 alkylene)$NR^{11}S(O)R^{12}$, $–(C_1$-C_3 alkylene)$NR^{11}S(O)_2R^{12}$, $–(C_1$-C_3 alkylene)$S(O)NR^{11}R^{12}$, $–(C_1$-C_3 alkylene)$S(O)_2NR^{11}R^{12}$, $–(C_1$-C_3 alkylene)(C_3-C_6 cycloalkyl), $–(C_1$-C_3 alkylene)(3-10-membered heterocyclyl), $–(C_1$-C_3 alkylene)(5-10-membered heteroaryl) or $–(C_1$-C_3 alkylene)(C_6-C_{14} aryl), wherein each R^{10} is independently optionally substituted by halogen, oxo, $–OR^{13}$, $–NR^{13}R^{14}$, $–C(O)R^{13}$, $–S(O)R^{13}$, $–S(O)_2R^{13}$, $–(C_1$-C_3 alkylene)OR^{13}, $–(C_1$-C_3 alkylene)$NR^{13}R^{14}$, $–(C_1$-C_3 alkylene)$C(O)R^{13}$, $–(C_1$-C_3 alkylene)$S(O)R^{13}$, $–(C_1$-C_3 alkylene)$S(O)_2R^{13}$ or C_1-C_6 alkyl optionally substituted by oxo, –CN or halogen.

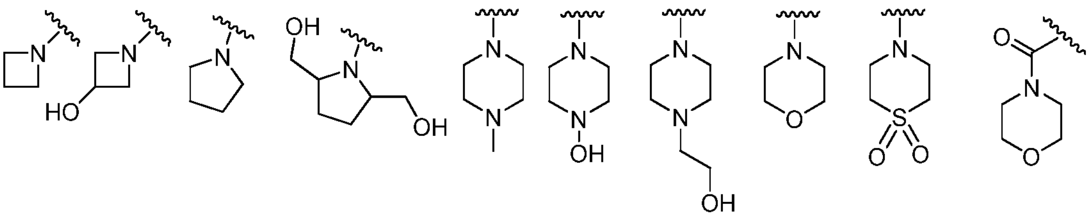
In certain embodiments, R^{10} is independently halogen. In certain embodiments, R^{10} is independently F. In certain embodiments, R^{10} is independently –CN.

In certain embodiments, R^{10} is independently C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein said alkyl, alkenyl and alkynyl are independently optionally substituted by halogen, oxo, $–OR^{13}$ or $–NR^{13}R^{14}$. In certain embodiments, R^{10} is methyl, ethyl, isopropyl, $–CH_2OH$, $–CH_2CH_2OH$, $–CH(OH)CH_2OH$, $–C(CH_3)_2OH$, $–CH_2NH_2$, $–CH_2NHCH_3$, $–CH_2N(CH_3)_2$, $–CF_3$, $–C(O)NH_2$, $–C(O)NHCH_3$, $–C(O)N(CH_3)_2$, $–CH_2$thiomorpholinyl dioxide, $–CH_2$morpholinyl, (*R*)-

$CH(OH)CH_3$, (*R*)-$CH(NH_2)CH_3$, (*S*)-$CH(OH)CH_3$, (*S*)-$CH(NH_2)CH_3$ or –C(O)morpholinyl. In certain embodiments, R^{10} is methyl.

In certain embodiments, R^{10} is independently C_3-C_6 cycloalkyl optionally substituted by halogen, oxo or C_1-C_3 alkyl. In certain embodiments, R^{10} is independently cyclopropyl. In certain embodiments, R^{10} is independently 3-6 membered heterocyclyl or –C(O)(3-6 membered heterocyclyl), wherein said heterocyclyl is independently optionally substituted by $–OR^{13}$, –(C_1-C_3 alkylene)OR^{13}, $–NR^{13}R^{14}$, –(C_1-C_3 alkylene)$NR^{13}R^{14}$, halogen, –CN, oxo or C_1-C_6 alkyl optionally substituted by oxo or halogen. In certain embodiments, said heterocyclyl is morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl or aziridinyl, wherein said heterocyclyl is independently optionally substituted by oxo, $–CH_2OH$, $–CH_2CH_2OH$, –OH, methyl or $–CF_3$.

In certain embodiments, R^{10} is independently selected from:



,

wherein the wavy line represents the point of attachment to the parent structure.

In certain embodiments, R^{10} is independently $–OR^{11}$, –(C_1-C_3 alkylene)OR^{11}, $–SR^{11}$ or –(C_1-C_3 alkylene)SR^{11}. In certain embodiments, R^{10} is –OH, $–OCH_3$, $–CH_2OH$, $–CH_2CH_2OH$, –$CH(OH)CH_2OH$ or $–C(CH_3)_2OH$. In certain embodiments, R^{10} is –OH or $–OCH_3$. In certain embodiments, R^{10} is –OH, $–OCH_3$, $–CH_2OH$, $–CH_2CH_2OH$, $–CH(OH)CH_2OH$, $–C(CH_3)_2OH$. (*R*)-$CH(OH)CH_3$ or (*S*)-$CH(OH)CH_3$.

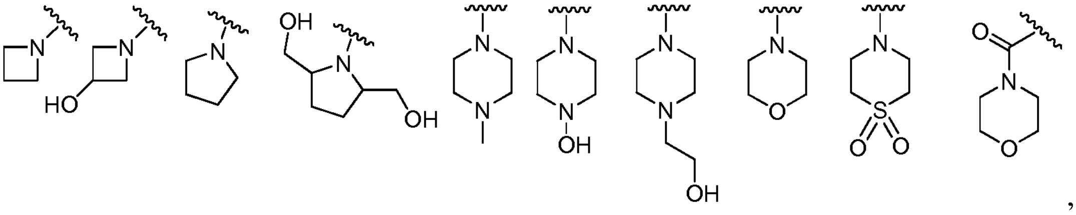
In certain embodiments, R^{10} is independently $–NR^{11}R^{12}$ or –(C_1-C_3 alkylene)$NR^{11}R^{12}$. In certain embodiments, R^{10} is $–NH_2$, $–NHCH_3$, $–NHC(O)CH_3$, $–N(CH_3)_2$¸ $–N(CH_2CH_2OH)_2$¸ –$NHCH_2CH_2OH$¸ $–N(CH_3)CH_2CH_2OH$¸ $–NHCH_2C(CH_3)_2OH$, $–N(CH_3)CH_2C(CH_3)_2OH$, 4-hydroxyaziridin-1-yl, morpholinyl, dioxothiomorpholinyl, piperidinyl, 4-hydroxypiperidinyl, 4-methylpiperazinyl, pyrrolidinyl or 4-(2-hydroxyethyl)piperazinyl. In certain embodiments, R^{10} is $–NH_2$, $–NHCH_3$, $–NHC(O)CH_3$, $–N(CH_3)_2$¸ $–N(CH_2CH_2OH)_2$¸ $–NHCH_2CH_2OH$¸ –$N(CH_3)CH_2CH_2OH$¸ $–NHCH_2C(CH_3)_2OH$, $–N(CH_3)CH_2C(CH_3)_2OH$, 4-hydroxyaziridin-1-yl, morpholinyl, dioxothiomorpholinyl, piperidinyl, 4-hydroxypiperidinyl, 4-methylpiperazinyl, pyrrolidinyl, $–CH_2$thiomorpholinyl dioxide, $–CH_2$morpholinyl, (*R*)-$CH(NH_2)CH_3$, (*S*)-$CH(NH_2)CH_3$ or 4-(2-hydroxyethyl)piperazinyl.

In certain embodiments, R^{10} is independently $–C(O)NR^{11}R^{12}$. In certain embodiments, R^{10} is –$C(O)NH_2$, $–C(O)NHCH_3$, $–C(O)N(CH_3)_2$ or –C(O)morpholinyl.

In certain embodiments, R^{10} is independently C_1-C_6 alkyl, halogen, –CN, $–OR^{11}$, $–SR^{11}$, –$NR^{11}R^{12}$, $–CF_3$, $–C{=}NH(OR^{11})$, $–C(O)OR^{11}$, C_3-C_6 cycloalkyl, 3-6-membered heterocyclyl, 5-6-

membered heteroaryl or phenyl, wherein R^{10} is independently optionally substituted by halogen, oxo, –CF_3, –OR^{13}, –$NR^{13}R^{14}$, –$C(O)R^{13}$, –$S(O)_{1\text{-}2}R^{13}$ or C_1-C_3 alkyl optionally substituted by oxo or halogen.

In certain embodiments, R^{10} is independently selected from F, –CN, methyl, ethyl, isopropyl, –CH_2OH, –CH_2CH_2OH, –$CH(OH)CH_2OH$, –$C(CH_3)_2OH$, –CH_2NH_2, –CH_2NHCH_3, –$CH_2N(CH_3)_2$, –CF_3, –OH, –OCH_3, –NH_2, –$NHCH_3$, –$NHC(O)CH_3$, –$N(CH_3)_2$, –$N(CH_2CH_2OH)_2$, –$NHCH_2CH_2OH$, –$N(CH_3)CH_2CH_2OH$, –$NHCH_2C(CH_3)_2OH$, –$N(CH_3)CH_2C(CH_3)_2OH$, –$C(O)NH_2$, –$C(O)NHCH_3$, –$C(O)N(CH_3)_2$, –CH_2thiomorpholinyl dioxide, –CH_2morpholinyl, –CH_2cyclopropyl, -$CH(OH)CH_3$, -$CH(NH_2)CH_3$, (*R*)-$CH(OH)CH_3$, (*R*)-$CH(NH_2)CH_3$, (*S*)-$CH(OH)CH_3$, (*S*)-$CH(NH_2)CH_3$,



,

wherein the wavy line represents the point of attachment to the parent structure.

In some embodiments, R^{11} and R^{12} are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6 membered heteroaryl or 3-6 membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are independently optionally substituted by halogen, oxo, –CN, –OR^{16}, –$NR^{16}R^{17}$ or C_1-C_6 alkyl optionally substituted by halogen, –CN or oxo. In some embodiments, R^{11} and R^{12} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, –OR^{16}, –$NR^{16}R^{17}$ or C_1-C_6 alkyl optionally substituted by halogen, oxo or OH.

In certain embodiments, R^{11} and R^{12} are independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen, oxo, –CN, –OR^{16} or –$NR^{16}R^{17}$, or are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, –OR^{16}, –$NR^{16}R^{17}$ or C_1-C_3 alkyl optionally substituted by halogen, oxo or OH.

In certain embodiments, R^{11} and R^{12} are independently hydrogen, methyl, –$C(O)CH_3$, 2-hydroxy-2-methylpropyl or 2-hydroxyethyl, or are taken together with the atom to which they attached to form a azetidinyl, pyrrolidinyl, morpholinyl, dioxothiomorpholinyl, piperazinyl or piperidinyl ring optionally substituted by halogen, oxo or C_1-C_3 alkyl optionally substituted by oxo, halogen or OH. In certain embodiments, R^{11} and R^{12} are independently hydrogen, methyl, –$C(O)CH_3$, 2-hydroxy-2-methylpropyl or 2-hydroxyethyl.

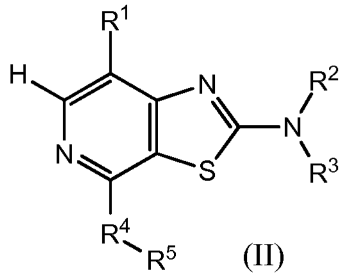
In some embodiments, R^{13} and R^{14} are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo. In some embodiments, R^{13} and R^{14} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by halogen or oxo.

In certain embodiments, R^{13} and R^{14} are independently hydrogen or C_1-C_3 alkyl. In certain embodiments, R^{13} and R^{14} are independently hydrogen or methyl.

In some embodiments, R^{16} and R^{17} are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo. In some embodiments, R^{16} and R^{17} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by oxo or halogen.

In certain embodiments, R^{16} and R^{17} are each independently hydrogen or C_1-C_3 alkyl. In certain embodiments, R^{16} and R^{17} are each independently hydrogen or methyl.

In some embodiments, provided are compounds of Formula II:



(II) ,

or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein:

R^1 is hydrogen, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, –CN, or C_3-C_6 cycloalkyl, wherein R^1 is optionally substituted by R^{10};

R^2 is hydrogen or C_1-C_6 alkyl optionally substituted by R^{10}, or is taken together with R^3 and the nitrogen to which they are attached to form a 3-10-membered heterocyclyl optionally substituted by R^{10};

R^3 is hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, C_6-C_{14} aryl, or 5-10-membered heteroaryl, wherein R^3 may be optionally substituted by R^{10}; or is taken together with R^2 and the nitrogen to which they are attached to form a 3-10-membered heterocyclyl optionally substituted by R^{10};

R^4 is $-NR^6-$, $-NR^6C(O)-$, $-NR^6C(O)O-$ or $-NR^6C(O)NR^7-$;

R^5 is hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 5-10-membered heteroaryl, wherein R^5 is optionally substituted by R^{10};

R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_6 cycloalkyl, wherein the alkyl, alkenyl, alkynyl and cycloalkyl are independently optionally substituted by halogen, C_1-C_6 alkyl, oxo, –CN, $-OR^{11}$ or $-NR^{11}R^{12}$;

each R^{10} is independently hydrogen, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen,

–CN, $-OR^{11}$, $-SR^{11}$, $-NR^{11}R^{12}$, $-NO_2$, $-C{=}NH(OR^{11})$, $-C(O)R^{11}$, $-C(O)OR^{11}$, –

C(O)NR^{11}R^{12},

–NR^{11}C(O)R^{12}, –S(O)R^{11}, –S(O)$_2$R^{11}, –NR^{11}S(O)R^{12}, –NR^{11}S(O)$_2$R^{12}, –S(O)NR^{11}R^{12}, –S(O)$_2$NR^{11}R^{12},

C$_3$-C$_6$ cycloalkyl, 3-10-membered heterocyclyl, 5-10-membered heteroaryl, C$_6$-C$_{14}$ aryl, –(C$_1$-C$_3$ alkylene)CN, –(C$_1$-C$_3$ alkylene)OR^{11}, –(C$_1$-C$_3$ alkylene)SR^{11}, –(C$_1$-C$_3$ alkylene)NR^{11}R^{12},

–(C$_1$-C$_3$ alkylene)CF$_3$, –(C$_1$-C$_3$ alkylene)NO$_2$, –C=NH(OR^{11}), –(C$_1$-C$_3$ alkylene)C(O)R^{11}, –(C$_1$-C$_3$ alkylene)C(O)OR^{11}, –(C$_1$-C$_3$ alkylene)C(O)NR^{11}R^{12}, –(C$_1$-C$_3$ alkylene)NR^{11}C(O)R^{12},

–(C$_1$-C$_3$ alkylene)S(O)R^{11}, –(C$_1$-C$_3$ alkylene)S(O)$_2$R^{11}, –(C$_1$-C$_3$ alkylene)NR^{11}S(O)R^{12}, –(C$_1$-C$_3$ alkylene)NR^{11}S(O)$_2$R^{12}, –(C$_1$-C$_3$ alkylene)S(O)NR^{11}R^{12}, –(C$_1$-C$_3$ alkylene)S(O)$_2$NR^{11}R^{12},

–(C$_1$-C$_3$ alkylene)(C$_3$-C$_6$ cycloalkyl), –(C$_1$-C$_3$ alkylene)(3-10-membered heterocyclyl), –(C$_1$-C$_3$ alkylene)(5-10-membered heteroaryl) or –(C$_1$-C$_3$ alkylene)(C$_6$-C$_{14}$ aryl), wherein each R^{10} is independently optionally substituted by halogen, oxo, –OR^{13}, –NR^{13}R^{14}, –C(O)R^{13}, –S(O)R^{13}, –S(O)$_2$R^{13}, –(C$_1$-C$_3$ alkylene)OR^{13}, –(C$_1$-C$_3$ alkylene)NR^{13}R^{14}, –(C$_1$-C$_3$ alkylene)C(O)R^{13}, –(C$_1$-C$_3$ alkylene)S(O)R^{13}, –(C$_1$-C$_3$ alkylene)S(O)$_2$R^{13} or C$_1$-C$_6$ alkyl optionally substituted by oxo, –CN or halogen;

R^{11} and R^{12} are each independently hydrogen, C$_1$-C$_6$ alkyl, C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkynyl, C$_3$-C$_6$ cycloalkyl, C$_6$-C$_{14}$ aryl, 5-6 membered heteroaryl or 3-6 membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are independently optionally substituted by halogen, oxo, –CN, –OR^{16}, –NR^{16}R^{17} or C$_1$-C$_6$ alkyl optionally substituted by halogen, –CN or oxo; or

R^{11} and R^{12} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, –OR^{16}, –NR^{16}R^{17} or C$_1$-C$_6$ alkyl optionally substituted by halogen, oxo or OH;

R^{13} and R^{14} are each independently hydrogen or C$_1$-C$_6$ alkyl optionally substituted by halogen or oxo; or

R^{13} and R^{14} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C$_1$-C$_6$ alkyl optionally substituted by halogen or oxo; and

R^{16} and R^{17} are each independently hydrogen or C$_1$-C$_6$ alkyl optionally substituted by halogen or oxo; or

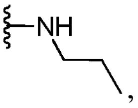
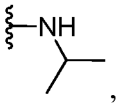
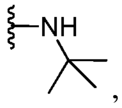
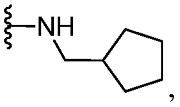
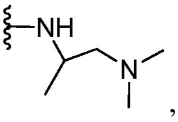
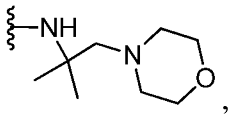
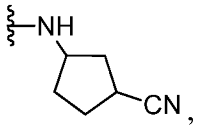
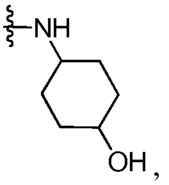
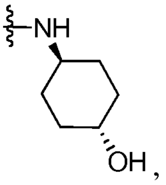
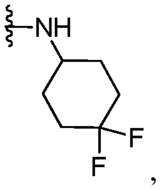
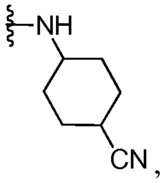
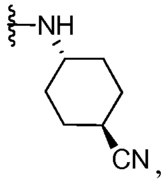
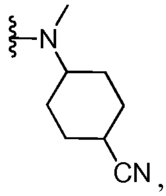
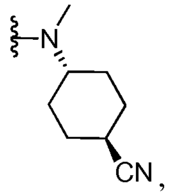
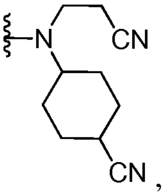
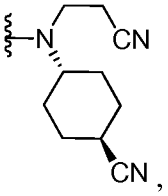
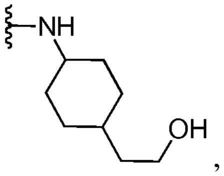
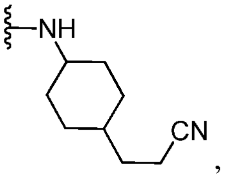
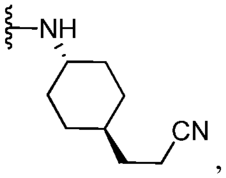
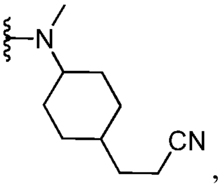
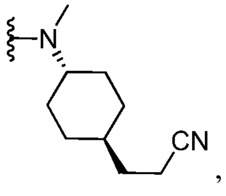
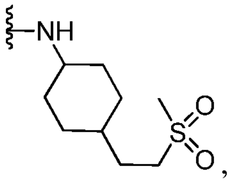
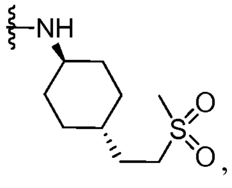
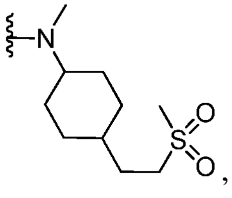
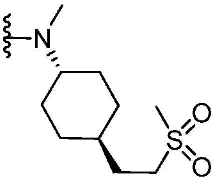
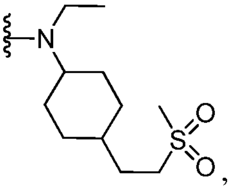
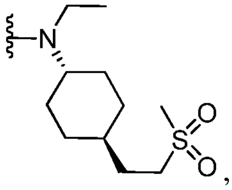
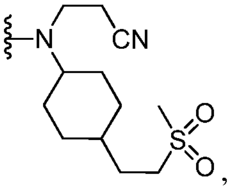
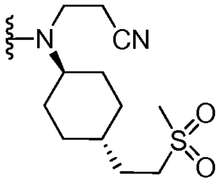
R^{16} and R^{17} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by oxo or halogen.

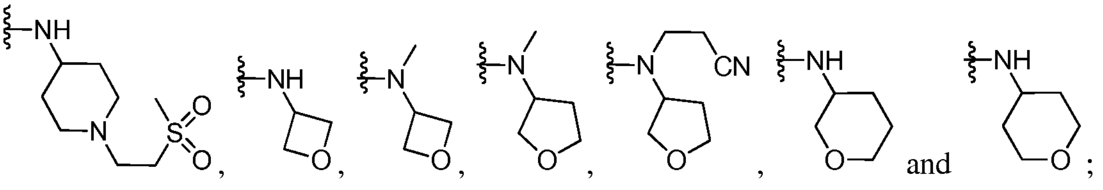
In some embodiments, the compound is of Formula II, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^1 is hydrogen, halogen, C_1-C_6 alkyl or –CN. In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is hydrogen or halogen (e.g., F, Cl, or Br). In some embodiments, R^1 is fluoro, chloro, bromo or cyano. In some embodiments, R^1 is C_1-C_6 alkyl (e.g., CH_3). In some embodiments, R^1 is C_1-C_6 alkyl optionally substituted by R^{10}. In some embodiments, R^1 is C_1-C_6 alkyl optionally substituted by halogen (e.g., $-CF_3$). In some embodiments, R^1 is C_2-C_6 alkenyl optionally substituted by R^{10} or C_2-C_6 alkynyl optionally substituted by R^{10}. In some embodiments, R^1 is C_3-C_6 cycloalkyl optionally substituted by R^{10}.

In some embodiments, the compound is of Formula II, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^2 is hydrogen or C_1-C_6 alkyl optionally substituted by R^{10} and R^3 is C_1-C_6 alkyl optionally substituted by R^{10}, C_3-C_6 cycloalkyl optionally substituted by R^{10}, or 3-10-membered heterocyclyl optionally substituted by R^{10}. In some embodiments, R^2 is hydrogen and R^3 is C_1-C_6 alkyl optionally substituted by R^{10}, C_3-C_6 cycloalkyl optionally substituted by R^{10}, or 3-10-membered heterocyclyl optionally substituted by R^{10}. In some embodiments, R^2 is hydrogen and R^3 is C_1-C_6 alkyl optionally substituted by C_3-C_6 cycloalkyl (e.g., cyclopentyl), $-NR^{11}R^{12}$ (e.g., $-N(CH_3)_2$) or 3-10-membered heterocyclyl (e.g., morpholin4-yl). In some embodiments, R^2 is hydrogen and R^3 is C_3-C_6 cycloalkyl (e.g., cyclopentyl or cyclohexyl) optionally substituted by hydroxyl, cyano, halo (e.g., fluoro), C_1-C_6 alkyl or C_1-C_6 alkyl substituted by hydroxyl, cyano or sulfonyl (e.g., CH_2CH_2OH, CH_2CH_2CN, or $CH_2CH_2SO_2CH_3$). In some embodiments, R^2 is hydrogen and R^3 is 3-10-membered heterocyclyl optionally substituted by C_1-C_6 alkyl or C_1-C_6 alkyl substituted by hydroxyl, cyano or sulfonyl (e.g., CH_2CH_2OH, CH_2CH_2CN, or $CH_2CH_2SO_2CH_3$). In some embodiments, R^2 is C_1-C_6 alkyl optionally substituted by R^{10} and R^3 is C_1-C_6 alkyl optionally substituted by R^{10}, C_3-C_6 cycloalkyl optionally substituted by R^{10}, or 3-10-membered heterocyclyl optionally substituted by R^{10}.

In some embodiments, R^2 and R^3 are taken together with the atom to which they are attached to form a ring selected from C_3-C_{10} cycloalkyl and 3-10-membered heterocyclyl, wherein the ring may be optionally substituted by R^{10}. In some embodiments, R^2 and R^3 are taken together with the atom to which they are attached to form a 3-10-membered heterocyclyl optionally substituted by R^{10}. In some embodiments, R^2 and R^3 are taken together with the atom to which they are attached to form a 4-9-membered heterocyclyl optionally substituted by R^{10}. In some embodiments, R^2 and R^3 are taken together with the atom to which they are attached to form a 4, 5, 6, 7, 8, or 9-membered heterocyclyl optionally substituted by R^{10}. In some embodiments, R^2 and R^3 are taken together with the atom to which they are attached to form a 5 or 6-membered heterocyclyl optionally substituted by R^{10}. In some embodiments, R^2 and R^3 are taken together with the atom to which they are attached to form a 4-membered heterocyclyl (e.g., azetidinyl) optionally substituted by R^{10}. In some embodiments, R^2 and R^3 are taken together with the atom to which they are attached to form a 5-membered heterocyclyl (e.g., pyrrolidinyl) optionally substituted by R^{10}. In some embodiments, R^2 and R^3 are taken together with the atom to which they are attached to form a 6-membered heterocyclyl (e.g., piperidinyl, piperazinyl or morpholinyl) optionally substituted by R^{10}. In some embodiments, R^2 and R^3 are taken together with the atom to which they are attached to form a 7-membered heterocyclyl (e.g., azepanyl) optionally substituted by R^{10}. In some embodiments, R^2 and R^3 are taken together with the atom to which they are attached to form an 8-membered heterocyclyl (e.g., azocanyl) optionally substituted by R^{10}.

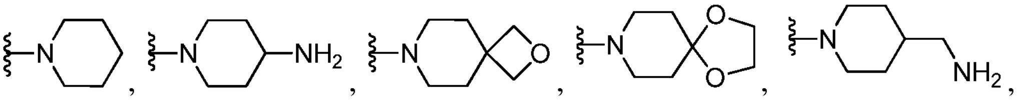
In some embodiments, the $-N(R^2)(R^3)$ moiety is selected from the group consisting of:

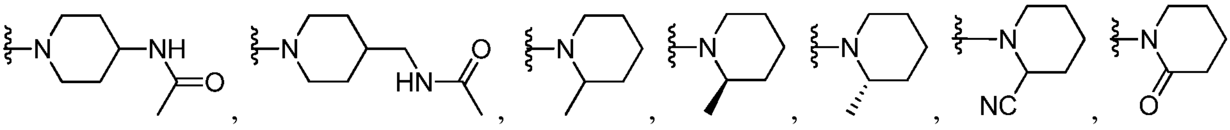






























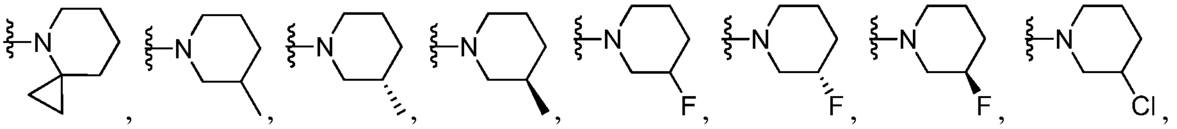


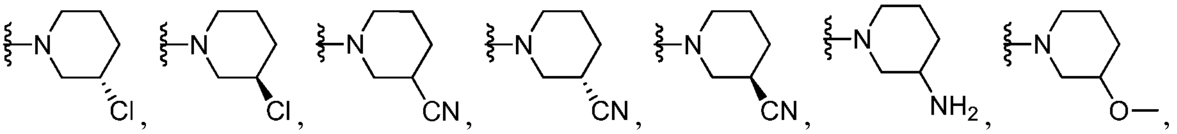
wherein the wavy line represents the point of attachment in Formula II.

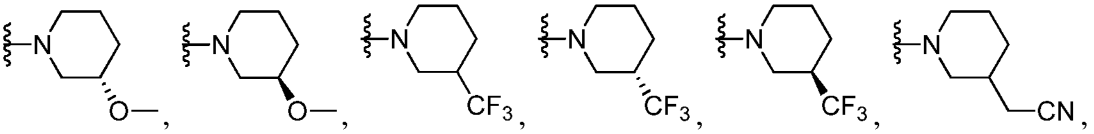
In some embodiments, the $-N(R^2)(R^3)$ moiety is selected from the group consisting of:

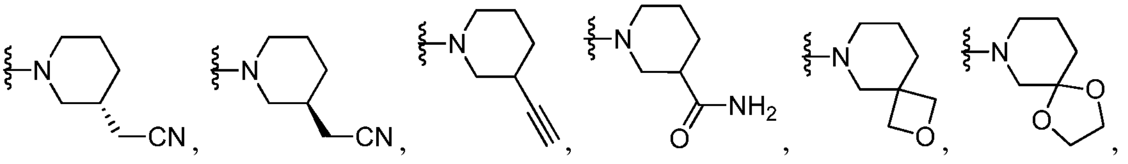


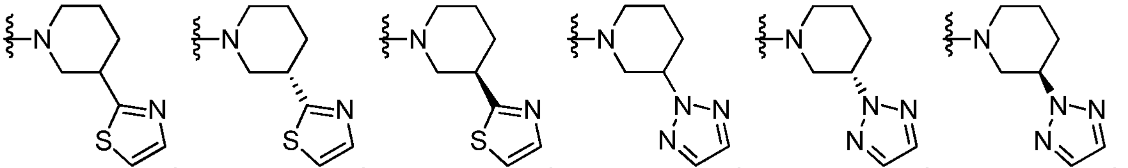


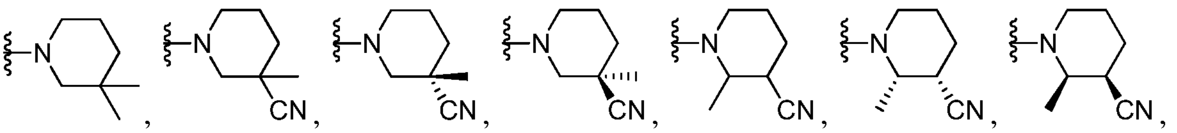


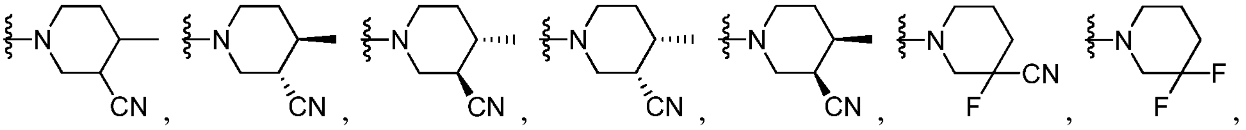


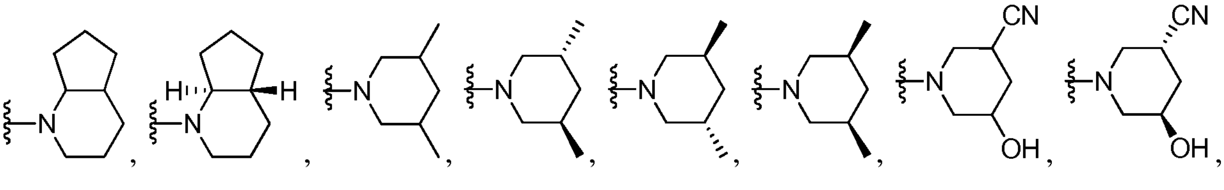


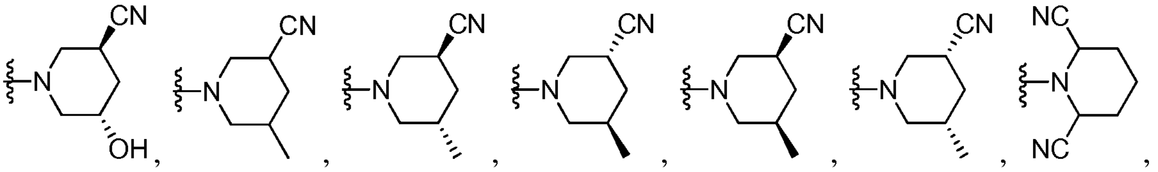


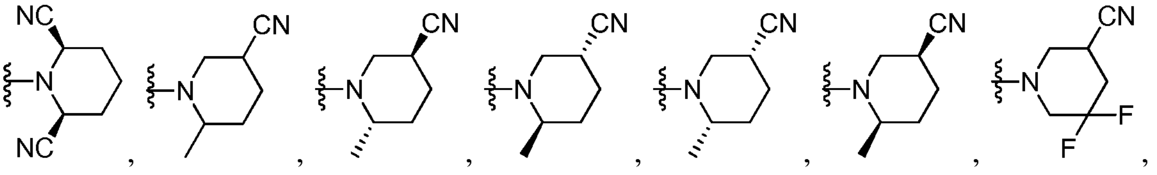


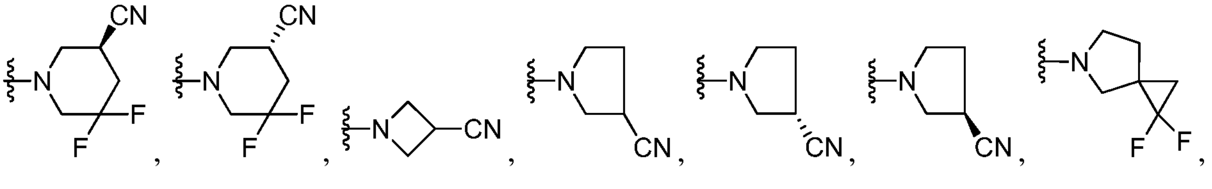


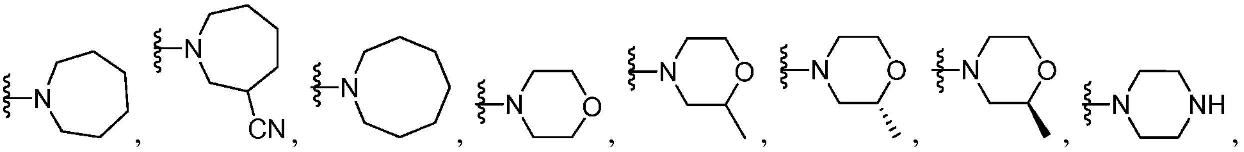


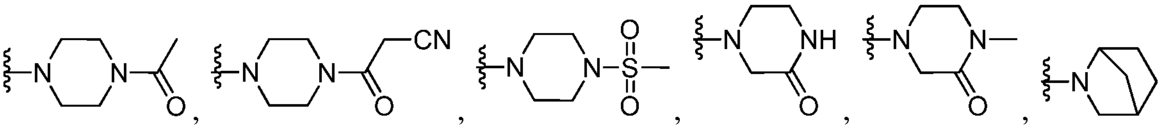


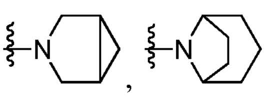
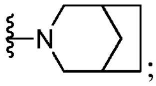










 and ; wherein the wavy line represents the point of attachment in Formula II.

It is intended and understood that each and every variation of R^2 and R^3 described for Formula II may be combined with each and every variation of R^1 described for Formula II as if each and every combination is individually described. For example, in some embodiments, R^1 is hydrogen, halogen, C_1-C_6 alkyl or –CN, R^2 is hydrogen or C_1-C_6 alkyl optionally substituted by R^{10} and R^3 is C_1-C_6 alkyl optionally substituted by R^{10}, C_3-C_6 cycloalkyl optionally substituted by R^{10}, or 3-10-membered heterocyclyl optionally substituted by R^{10}. In some embodiments, R^1 is hydrogen, halogen, and R^2 and R^3 are taken together with the atom to which they are attached to form a 4, 5, 6, 7, 8, or 9-membered heterocyclyl optionally substituted by R^{10}.

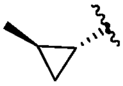
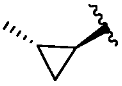
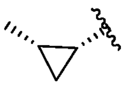
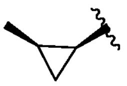
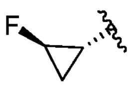
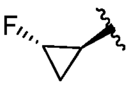
In some embodiments, the compound is of Formula II, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^4 is $-NR^6-$, $-NR^6C(O)-$ or $-NR^6C(O)NR^7-$. In some embodiments, R^4 is $-NR^6-$. In some embodiments, R^4 is $-NR^6C(O)-$. In some embodiments, R^4 is $-NR^6C(O)NR^7-$. In some embodiments, R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl optionally substituted by halogen, oxo, –CN, $-OR^{11}$ or $-NR^{11}R^{12}$, or C_3-C_6 cycloalkyl optionally substituted by halogen, C_1-C_6 alkyl, oxo, –CN, $-OR^{11}$ or $-NR^{11}R^{12}$. In some embodiments, R^6 is hydrogen or C_1-C_6 alkyl. In some embodiments, R^6 is hydrogen. In some embodiments, R^7 is hydrogen.

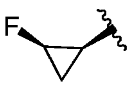
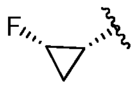
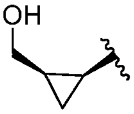
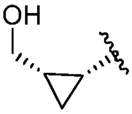
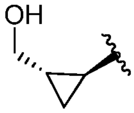
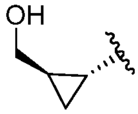
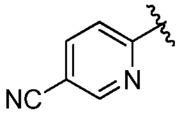
In some embodiments, R^4 is –NH–, –NHC(O)– or –NHC(O)NH–. In some embodiments, R^4 is –NH–. In some embodiments, R^4 is –NHC(O)–. In some embodiments, R^4 is –NHC(O)NH–. In some embodiments, R^4 is –NHC(O)O–.

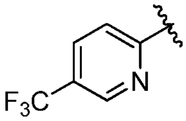
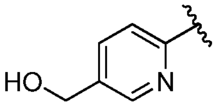
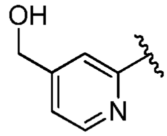
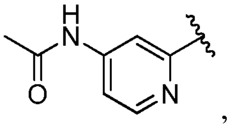
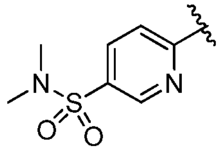
In some embodiments, the compound is of Formula II, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^5 is optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_{10} cycloalkyl or optionally substituted 5-10-membered heteroaryl. In some embodiments, R^5 is hydrogen. In some embodiments, R^5 is C_1-C_6 alkyl optionally substituted by R^{10}. In some embodiments, R^5 is C_1-C_6 alkyl (e.g., methyl, ethyl and 2-propyl). In some embodiments, R^5 is C_1-C_6 alkyl substituted by C_3-C_6 cycloalkyl (e.g., cyclopropylmethyl). In some embodiments, R^5 is C_3-C_{10} cycloalkyl optionally substituted by R^{10}. In some embodiments, R^5 is C_3-C_6 cycloalkyl optionally substituted by R^{10}. In some embodiments, R^5 is C_3-C_6 cycloalkyl (e.g., cyclopropyl). In some embodiments, R^5 is C_3-C_6 cycloalkyl substituted by halogen (e.g., 2-fluorocyclopropyl) or C_3-C_6 cycloalkyl substituted by C_1-C_6 alkyl which is optionally further substituted by halogen or hydroxyl (e.g., 2-methylcyclopropyl and 2-hydroxy methylcyclopropyl). In some embodiments, R^5 is C_3-C_6 cycloalkyl substituted with 1-3 substituents independently selected from fluoro, methyl and hydroxymethyl.

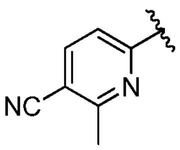
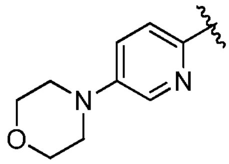
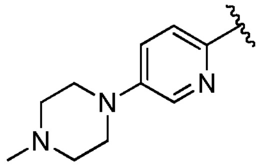
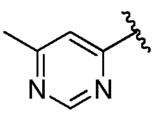
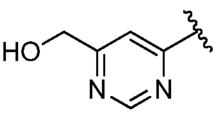
In some embodiments, R^5 is 5-10-membered heteroaryl optionally substituted by R^{10}. In some embodiments, R^5 is 5 or 6-membered heteroaryl optionally substituted by R^{10}. In some embodiments, R^5 is 5-membered heteroaryl optionally substituted by R^{10}. In some embodiments, R^5 is 5-membered heteroaryl (e.g., thiazolyl and thiadiazolyl). In some embodiments, R^5 is 5-membered heteroaryl substituted by C_1-C_6 alkyl (e.g., 4-methylthiazol-2-yl, 5-methylthiazol-2-yl and 5-methyl-1,3,4-thiadiazol-2-yl). In some embodiments, R^5 is 6-membered heteroaryl optionally substituted by R^{10}. In some embodiments, R^5 is 6-membered heteroaryl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimid-2-yl, pyrimid-4-yl, pyrimid-5-yl, pyrazin-2-yl and pyridazin-3-yl). In some embodiments, R^5 is 6-membered heteroaryl substituted by 1-4 substituents independently selected from C_1-C_6 alkyl, -CN, $-CF_3$, halogen,$-OR^{11}$, $-(C_1$-C_3 alkylene)OR^{11}, $-NR^{11}R^{12}$, $-NR^{11}C(O)R^{12}$, $-S(O)_2NR^{11}R^{12}$, and 3-10-membered heterocyclyl optionally substituted by C_1-C_6 alkyl or $-(C_1$-C_3 alkylene)OR^{13}. In some embodiments, R^5 is 6-membered heteroaryl substituted by 1-4 substituents independently selected from –CN, $-CF_3$, $-CH_3$, $-CH(CH_3)_2$, $-CH_2OH$,$-OCH_3$, $-CH_2OCH_3$, $-NH_2$, $-NHC(O)CH_3$, $-NHCH_2CH_2OH$, $-NHCH_2C(CH_3)_2OH$, $-NHCH_3$, $-N(CH_3)_2$, $-S(O)_2N(CH_3)_2$, azetidin-1-yl, morpholin-4-yl, 4-methylpiperzin-1-yl and 4-(2-hydroxyethyl)piperzin-1-yl. In some embodiments, R^5 is 2-pyridyl optionally substituted by 1-3 substituents independently selected from –CN, $-CF_3$, $-CH_3$, $-CH(CH_3)_2$, $-CH_2OH$,$-OCH_3$, $-CH_2OCH_3$, $-NH_2$, $-NHC(O)CH_3$, $-NHCH_2CH_2OH$, $-NHCH_2C(CH_3)_2OH$, $-NHCH_3$, $-N(CH_3)_2$, $-S(O)_2N(CH_3)_2$, azetidin-1-yl, morpholin-4-yl, 4-

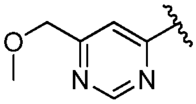
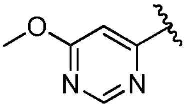
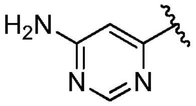
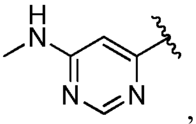
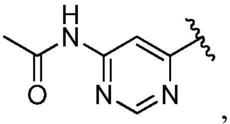
methylpiperzin-1-yl and 4-(2-hydroxyethyl)piperzin-1-yl. In some embodiments, R^5 is pyrimidin-4-yl optionally substituted by 1-2 substituents independently selected from $-CN$, $-CF_3$, $-CH_3$, $-CH(CH_3)_2$, $-CH_2OH$,$-OCH_3$, $-CH_2OCH_3$, $-NH_2$, $-NHC(O)CH_3$, $-NHCH_2CH_2OH$, $-NHCH_2C(CH_3)_2OH$, $-NHCH_3$, $-N(CH_3)_2$, $-S(O)_2N(CH_3)_2$, azetidin-1-yl, morpholin-4-yl, 4-methylpiperzin-1-yl and 4-(2-hydroxyethyl)piperzin-1-yl. In some embodiments, R^5 is pyridazin-3-yl optionally substituted by 1-2 substituents independently selected from $-CN$, $-CF_3$, $-CH_3$, $-CH(CH_3)_2$, $-CH_2OH$,$-OCH_3$, $-CH_2OCH_3$, $-NH_2$, $-NHC(O)CH_3$, $-NHCH_2CH_2OH$, $-NHCH_2C(CH_3)_2OH$, $-NHCH_3$, $-N(CH_3)_2$, $-S(O)_2N(CH_3)_2$, azetidin-1-yl, morpholin-4-yl, 4-methylpiperzin-1-yl and 4-(2-hydroxyethyl)piperzin-1-yl. In some embodiments, R^5 is pyrazin-2-yl optionally substituted by 1-2 substituents independently selected from $-CN$, $-CF_3$, $-CH_3$, $-CH(CH_3)_2$, $-CH_2OH$,$-OCH_3$, $-CH_2OCH_3$, $-NH_2$, $-NHC(O)CH_3$, $-NHCH_2CH_2OH$, $-NHCH_2C(CH_3)_2OH$, $-NHCH_3$, $-N(CH_3)_2$, $-S(O)_2N(CH_3)_2$, azetidin-1-yl, morpholin-4-yl, 4-methylpiperzin-1-yl and 4-(2-hydroxyethyl)piperzin-1-yl.

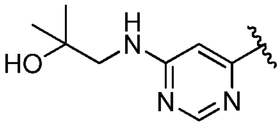
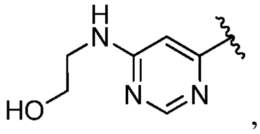
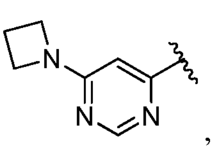
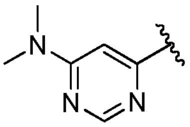
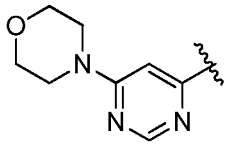
In some embodiments, R^5 is selected from the group consisting of methyl, ethyl, 2-propyl, cyclopropyl, 2-methylcyclopropyl, 2-fluorocyclopropyl, 2-(hydroxymethyl)cyclopropyl, cyclopropylmethyl, , , , , , ,

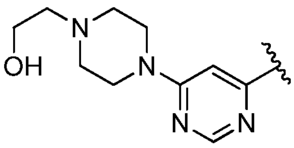
, , , , , , ,

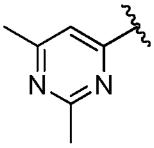
, , , , ,

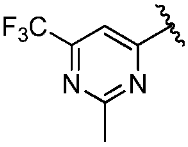
, , , , ,

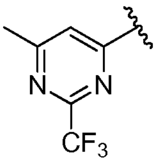
, , , , ,

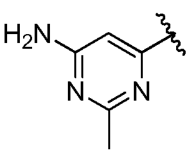
, , , , ,

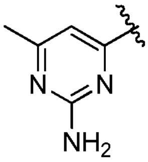


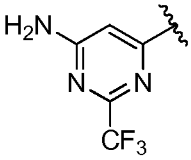
,


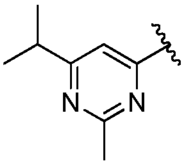
,


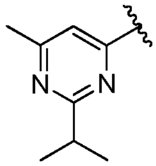
,


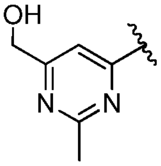
,


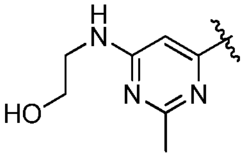
,


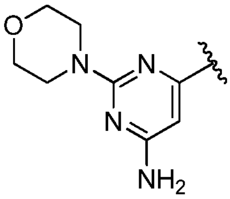
,


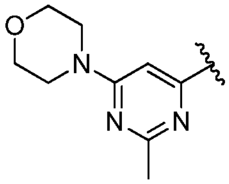
,


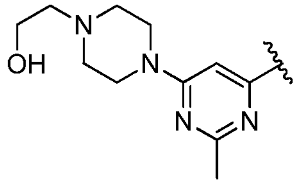
,


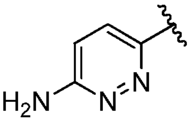
,


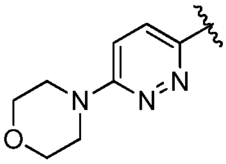
,


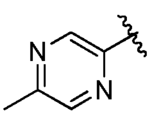
,


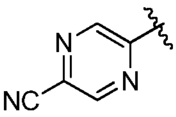
,


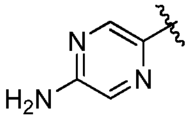
,


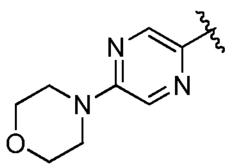
,


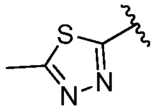
,


,


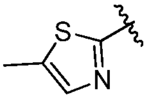
,


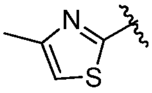
,


,


,


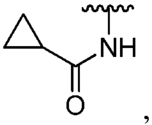
,

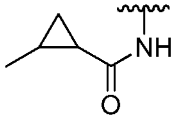


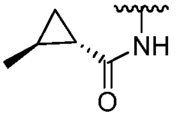
and


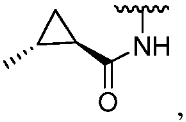
; wherein the wavy line represents the point of attachment in Formula II.

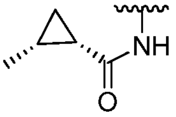
In some embodiments, the compound is of Formula II, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein the $-R^4$-R^5 moiety is $-NHR^5$, $-NHC(O)R^5$, $-NHC(O)OR^5$ or $-NHC(O)NHR^5$, wherein R^5 is other than hydrogen. In some embodiments, the $-R^4$-R^5 moiety is selected form the group consisting of:

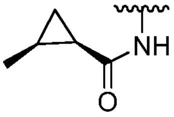


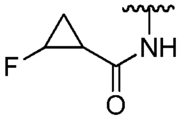
,


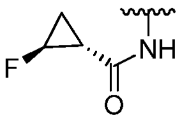
,


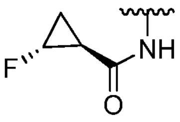
,


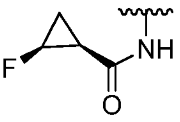
,


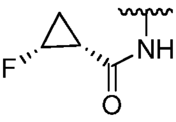
,


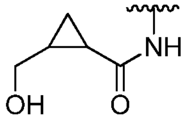
,


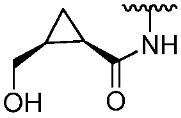
,


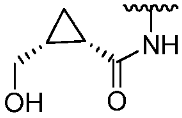
,


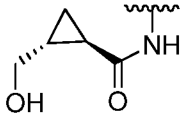
,


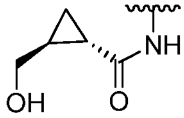
,


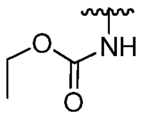
,


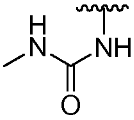
,


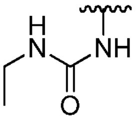
,


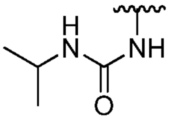
,


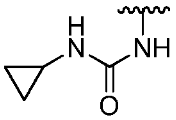
,


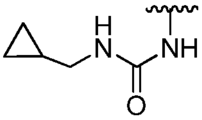
,


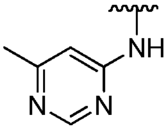
,


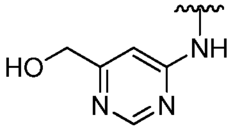
,


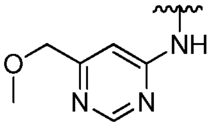
,


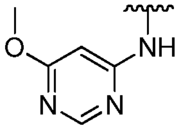
,


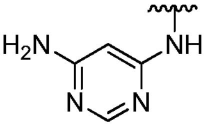
,


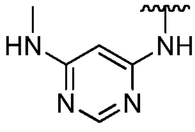
,


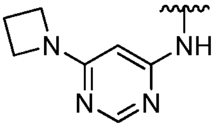
,


,


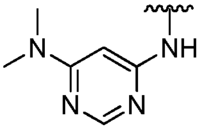
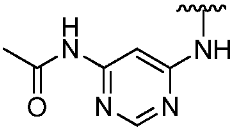
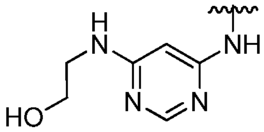
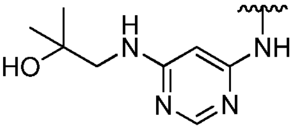
,


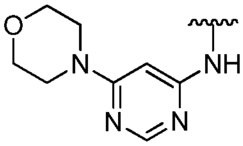
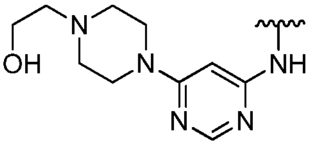
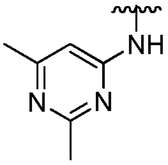
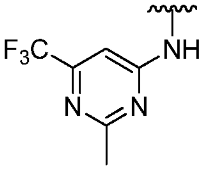
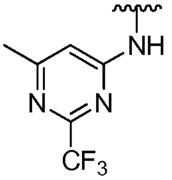
,


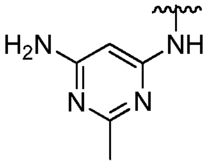
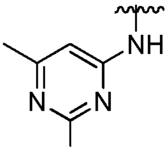
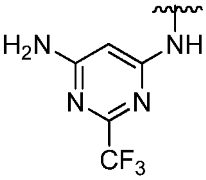
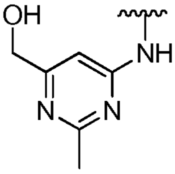
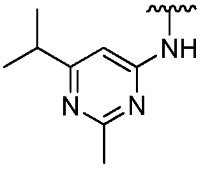
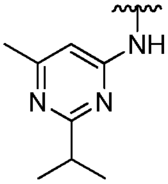
,


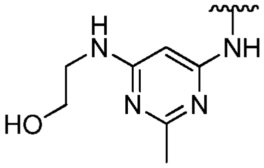
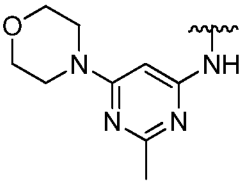
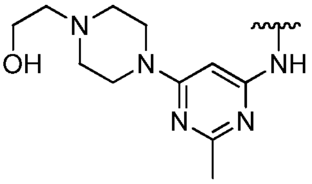
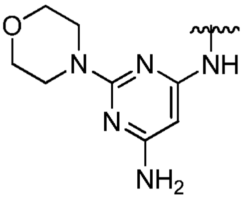
,


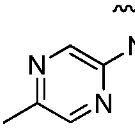
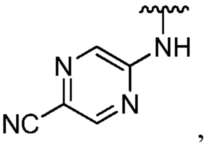
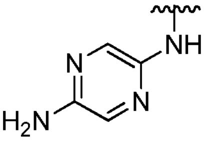
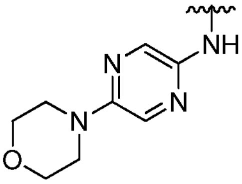
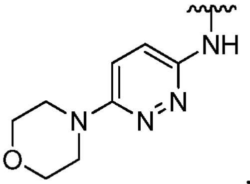
,

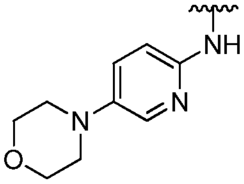
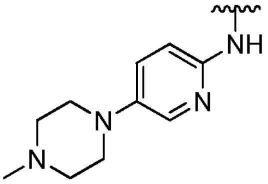
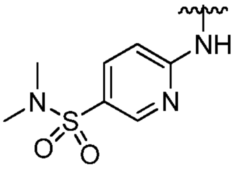
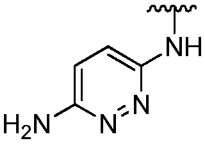
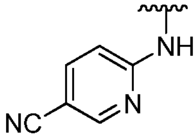
, , , ,

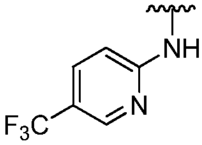
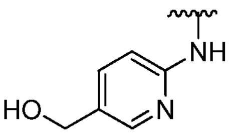
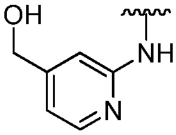
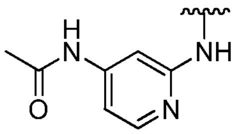
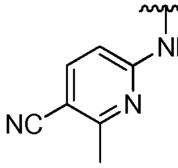
, , , , ,

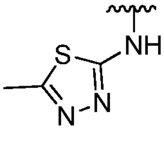
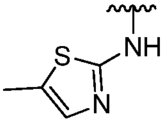
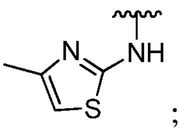
, , , , , ,

, , , ,

, , , , ,

, , , , ,

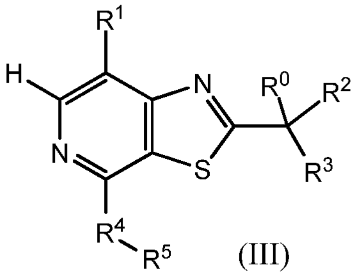
, , , , ,

,  and  ;

wherein the wavy line represents the point of attachment in Formula II.

It is intended and understood that each and every variation of R^4 and R^5 described for Formula II may be combined with each and every variation of R^1 described for Formula II, and/or each and every variation of R^2 and R^3 described for Formula II as if each and every combination is individually described. For example, in some embodiments, the compound is of Formula II where R^1 is hydrogen or halogen, R^2 is hydrogen or optionally substituted C_1-C_6 alkyl, R^3 is optionally substituted C_1-C_6 alkyl, R^4 is –NH–, –NHC(O)– or –NHC(O)NH– and R^5 is optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_6 cycloalkyl or optionally substituted 5 or 6-membered heteroaryl. In some embodiments, R^1 is hydrogen, fluoro, chloro or bromo, R^2 and R^3 are taken together with the atom to which they are attached to form an optionally substituted piperidinyl (e.g., 3-cyanopiperidin-1-yl), and the –R^4-R^5 moiety is –NH–(optionally substituted pyrimidinyl) (e.g., (6-aminopyrimidin-4-yl)amino), –NHC(O)–(optionally substituted cyclopropyl) (e.g., cyclopropanecarbonylamino), or –NHC(O)NH–(optionally substituted C_1-C_6 alkyl) (e.g., isopropylurido). It is further understood and intended that each and every variation of R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{16} and R^{17} described herein, where applicable, may be combined with each and every variation of R^1, R^2, R^3, R^4 and R^5 described for Formula II as if each and every combination is individually described.

In some embodiments, provided are compounds of Formula III:



(III) ,

or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein:

R^0 is hydrogen, hydroxyl, or C_1-C_6 alkyl optionally substituted by R^{10};

R^1 is hydrogen, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, –CN, or C_3-C_6 cycloalkyl, wherein R^1 is optionally substituted by R^{10};

R^2 is hydrogen or C_1-C_6 alkyl optionally substituted by R^{10}, or is taken together with R^3 and the carbon to which they are attached to form a ring selected from C_3-C_{10} cycloalkyl and 3-10-membered heterocyclyl, wherein the ring is optionally substituted by R^{10};

R^3 is hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, C_6-C_{14} aryl, or 5-10-membered heteroaryl, wherein R^3 may be optionally substituted by R^{10}; or is taken together with R^2 and the carbon to which they are attached to form a ring selected from C_3-C_{10} cycloalkyl and 3-10-membered heterocyclyl, wherein the ring is optionally substituted by R^{10};

R^4 is –NR^6–, –$NR^6C(O)$–, –$NR^6C(O)O$– or –$NR^6C(O)NR^7$–;

R^5 is hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 5-10-membered heteroaryl, wherein R^5 is optionally substituted by R^{10};

R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_6 cycloalkyl, wherein the alkyl, alkenyl, alkynyl and cycloalkyl are independently optionally substituted by halogen, C_1-C_6 alkyl, oxo, –CN, –OR^{11} or –$NR^{11}R^{12}$;

each R^{10} is independently hydrogen, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen,

–CN, –OR^{11}, –SR^{11}, –$NR^{11}R^{12}$, –NO_2, –C=NH(OR^{11}), –C(O)R^{11}, –C(O)OR^{11}, –C(O)$NR^{11}R^{12}$,

–NR^{11}C(O)R^{12}, –S(O)R^{11}, –S(O)$_2R^{11}$, –NR^{11}S(O)R^{12}, –NR^{11}S(O)$_2R^{12}$, –S(O)$NR^{11}R^{12}$, –S(O)$_2NR^{11}R^{12}$,

C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, 5-10-membered heteroaryl, C_6-C_{14} aryl, –(C_1-C_3 alkylene)CN, –(C_1-C_3 alkylene)OR^{11}, –(C_1-C_3 alkylene)SR^{11}, –(C_1-C_3 alkylene)$NR^{11}R^{12}$,

–(C_1-C_3 alkylene)CF_3, –(C_1-C_3 alkylene)NO_2, –C=NH(OR^{11}), –(C_1-C_3 alkylene)C(O)R^{11}, –(C_1-C_3 alkylene)C(O)OR^{11}, –(C_1-C_3 alkylene)C(O)$NR^{11}R^{12}$, –(C_1-C_3 alkylene)NR^{11}C(O)R^{12},

–(C_1-C_3 alkylene)S(O)R^{11}, –(C_1-C_3 alkylene)S(O)$_2R^{11}$, –(C_1-C_3 alkylene)NR^{11}S(O)R^{12}, –(C_1-C_3 alkylene)NR^{11}S(O)$_2R^{12}$, –(C_1-C_3 alkylene)S(O)$NR^{11}R^{12}$, –(C_1-C_3 alkylene)S(O)$_2NR^{11}R^{12}$,

–(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), –(C_1-C_3 alkylene)(3-10-membered heterocyclyl), –(C_1-C_3 alkylene)(5-10-membered heteroaryl) or –(C_1-C_3 alkylene)(C_6-C_{14} aryl), wherein each R^{10} is independently optionally substituted by halogen, oxo, –OR^{13}, –$NR^{13}R^{14}$, –C(O)R^{13}, –S(O)R^{13}, –S(O)$_2R^{13}$, –(C_1-C_3 alkylene)OR^{13}, –(C_1-C_3 alkylene)$NR^{13}R^{14}$, –(C_1-C_3 alkylene)C(O)R^{13}, –(C_1-C_3 alkylene)S(O)R^{13}, –(C_1-C_3 alkylene)S(O)$_2R^{13}$ or C_1-C_6 alkyl optionally substituted by oxo, –CN or halogen;

R^{11} and R^{12} are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6 membered heteroaryl or 3-6 membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are independently optionally substituted by halogen, oxo, –CN, –OR^{16}, –$NR^{16}R^{17}$ or C_1-C_6 alkyl optionally substituted by halogen, –CN or oxo; or

> R^{11} and R^{12} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, –OR^{16}, –$NR^{16}R^{17}$ or C_1-C_6 alkyl optionally substituted by halogen, oxo or OH;

R^{13} and R^{14} are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo; or

> R^{13} and R^{14} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by halogen or oxo; and

R^{16} and R^{17} are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo; or

R^{16} and R^{17} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by oxo or halogen.

In some embodiments, the compound is of Formula III, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^0 is hydrogen, hydroxyl or unsubstituted C_1-C_6 alkyl. In some embodiments, R^0 is hydrogen or hydroxyl. In some embodiments, R^0 is hydrogen. In some embodiments, R^0 is hydroxyl. In some embodiments, R^0 is C_1-C_6 alkyl optionally substituted by R^{10}.

In some embodiments, the compound is of Formula III, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^1 is hydrogen, halogen, C_1-C_6 alkyl or –CN. In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is hydrogen or halogen (e.g., F, Cl, or Br). In some embodiments, R^1 is fluoro, chloro, bromo or cyano. In some embodiments, R^1 is C_1-C_6 alkyl (e.g., CH_3). In some embodiments, R^1 is C_1-C_6 alkyl optionally substituted by R^{10}. In some embodiments, R^1 is C_1-C_6 alkyl optionally substituted by halogen (e.g., $-CF_3$). In some embodiments, R^1 is C_2-C_6 alkenyl optionally substituted by R^{10} or C_2-C_6 alkynyl optionally substituted by R^{10}. In some embodiments, R^1 is C_3-C_6 cycloalkyl optionally substituted by R^{10}.

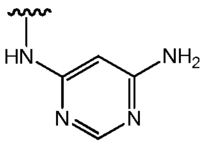
In some embodiments, the compound is of Formula III, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^2 is hydrogen or C_1-C_6 alkyl optionally substituted by R^{10} and R^3 is C_1-C_6 alkyl optionally substituted by R^{10}, C_3-C_6 cycloalkyl optionally substituted by R^{10}, or 3-10-membered heterocyclyl optionally substituted by R^{10}. In some embodiments, R^2 and R^3 are taken together with the atom to which they are attached to form a ring selected from C_3-C_{10} cycloalkyl optionally substituted by R^{10}. In some embodiments, R^0 is hydrogen or hydroxyl and R^2 and R^3 are taken together with the atom to which they are attached to form a cyclohexyl group optionally substituted by C_1-C_6 alkyl (e.g., methyl). In some embodiments, R^2 and R^3 are taken together with the atom to which they are attached to form a 3-10-membered heterocyclyl optionally substituted by R^{10}.

It is intended and understood that each and every variation of R^2 and R^3 described for Formula III may be combined with each and every variation of R^1, and/or each and every variation of R^0 described for Formula III as if each and every combination is individually described. In some embodiments, R^1 is hydrogen, R^0 is hydrogen or hydroxyl and R^2 and R^3 are taken together with the atom to which they are attached to form a cyclohexyl group optionally substituted by C_1-C_6 alkyl.

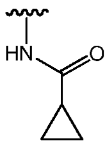
In some embodiments, the compound is of Formula III, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^4 is $–NR^6–$, $–NR^6C(O)–$ or $–NR^6C(O)NR^7–$ and R^5 is optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_{10} cycloalkyl or optionally substituted 5-10-membered heteroaryl. In some embodiments, R^4 is $–NR^6–$ or $–NR^6C(O)–$. In some embodiments, R^5 is C_3-C_{10} cycloalkyl optionally substituted by R^{10}. In some embodiments, R^5 is C_3-C_6 cycloalkyl optionally substituted by R^{10}. In some embodiments, R^5 is 5 or 6-membered heteroaryl optionally substituted by R^{10}. In some embodiments, R^6 is hydrogen. In some embodiments, R^6 and R^7 are hydrogen.

In some embodiments, R^4 is –NH– or –NHC(O)– and R^5 is optionally substituted C_3-C_{10} cycloalkyl or optionally substituted 5 or 6-membered heteroaryl. In some embodiments, R^4 is –NH– and R^5 is optionally substituted 6-membered heteroaryl (e.g., 6-aminopyrimid-4-yl). In some embodiments, R^4 is –NHC(O)– and R^5 is C_3-C_6 cycloalkyl (e.g., cyclopropyl).

In some embodiments, the $–R^4$-R^5 moiety is selected from the group consisting of:



and



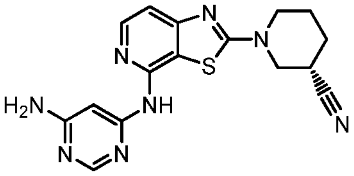
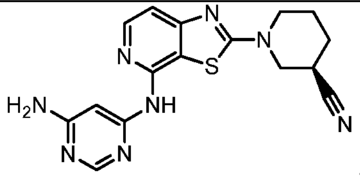
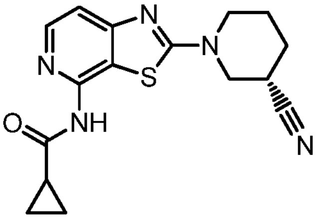
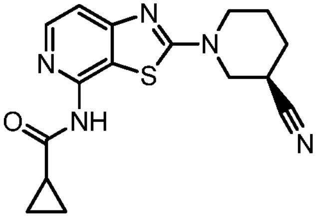
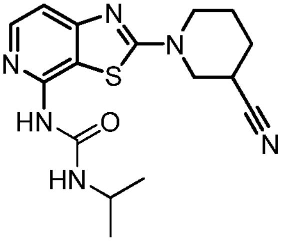
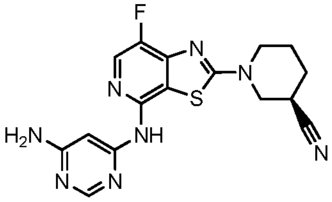
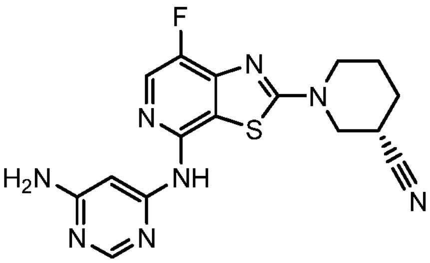
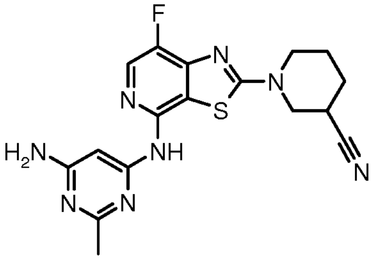
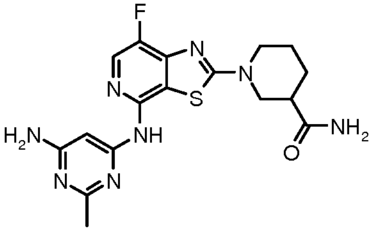
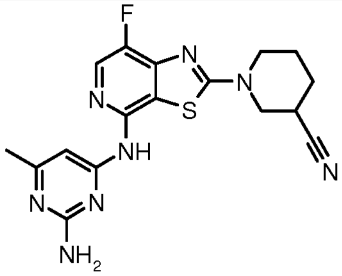
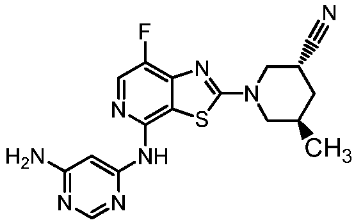
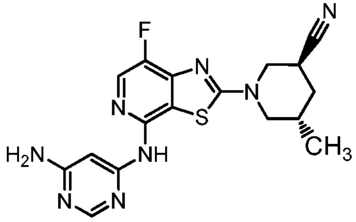
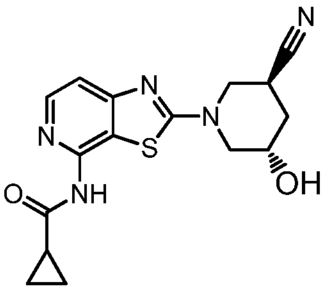
; wherein the wavy line represents the point of attachment in Formula III.

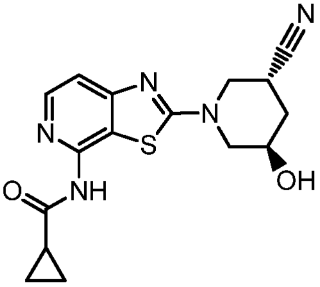
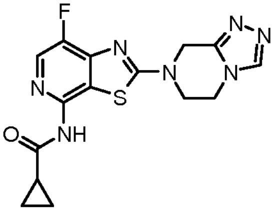
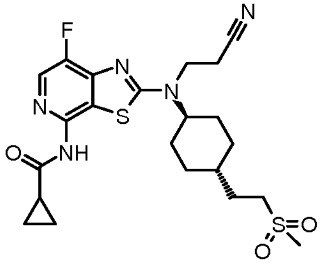
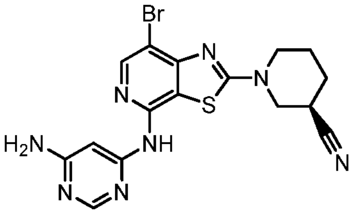
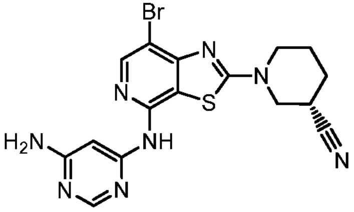
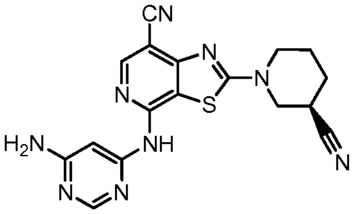
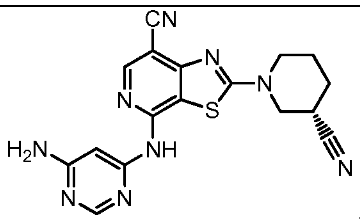
It is intended and understood that each and every variation of R^4 and R^5 described for Formula III may be combined with each and every variation of R^1 described for Formula III, and/or each and every variation of R^0, R^2 and R^3 described for Formula III as if each and every combination is individually described. For example, In some embodiments, R^1 is hydrogen, R^0 is hydrogen or hydroxy, R^2 and R^3 are taken together with the carbon to which they are attached to form an optionally substituted cycloalkyl and the $–R^4$-R^5 moiety is (6-aminopyrimidin-4-yl)amino or cyclopropanecarbonylamino. It is further understood and intended that each and every variation of R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{16} and R^{17} described herein, where applicable, may be combined with each and every variation of R^0, R^1, R^2, R^3, R^4 and R^5 described for Formula III as if each and every combination is individually described.

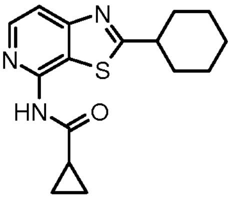
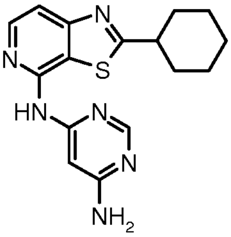
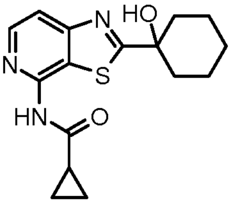
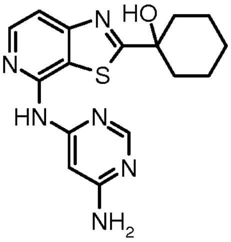
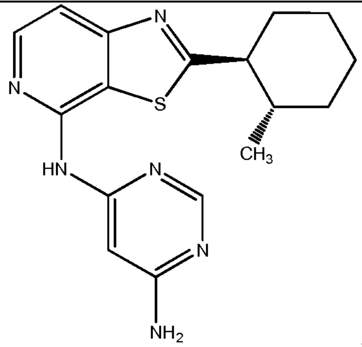
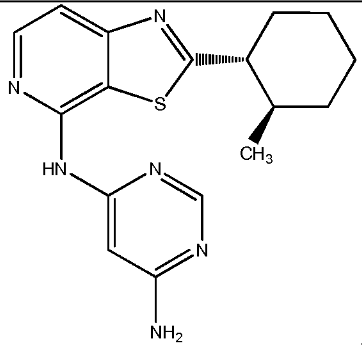
It is further intended and understood that each and every variation of R^1, R^2, R^3, R^4 and R^5 described for Formula I or variations thereof may be applicable to Formula II and/or Formula III as if each and every combination is individually described. Each and every variation of R^1, R^2, R^3, R^4 and R^5 described for Formula II or III or variations thereof may be applicable to Formula I as if each and every combination is individually described.

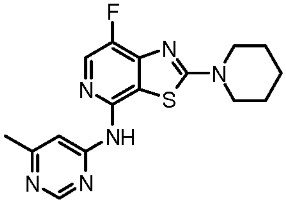
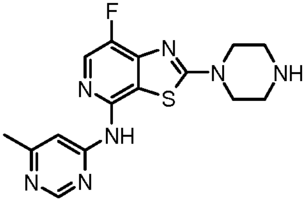
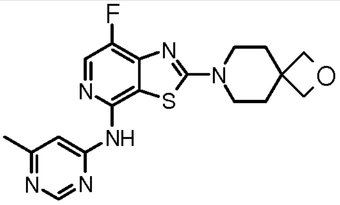
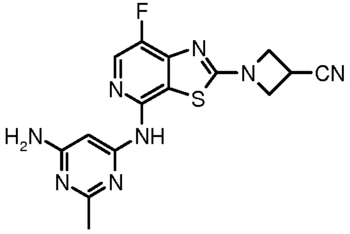
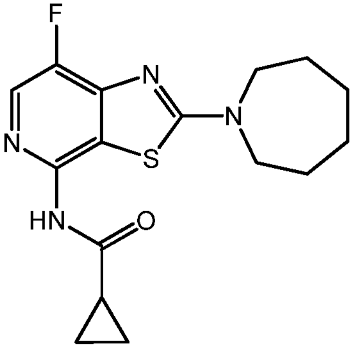
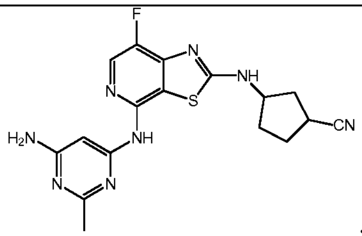
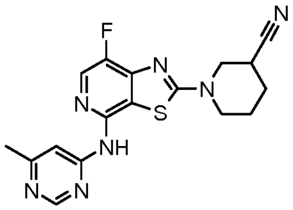
Representative compounds of the invention, and their stereoisomers, are listed in Table 1.

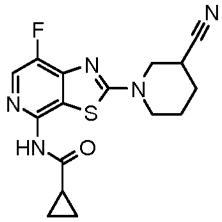
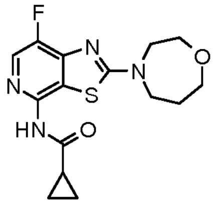
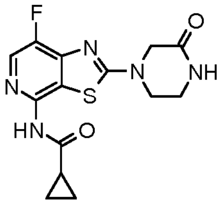
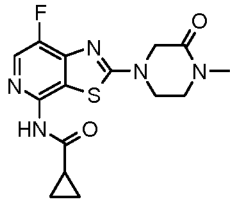
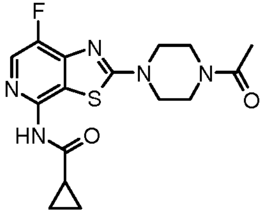
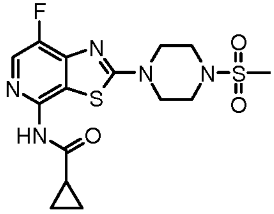
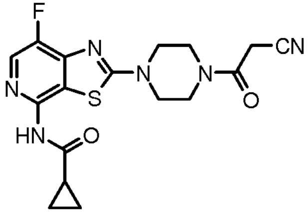
Table 1

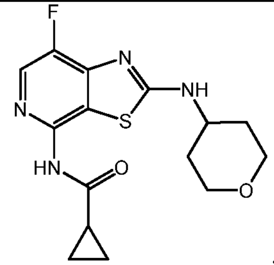
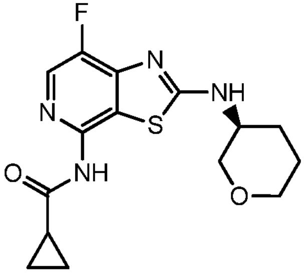
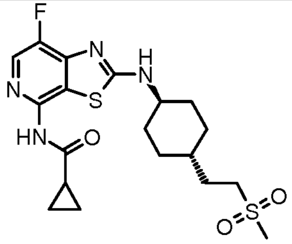
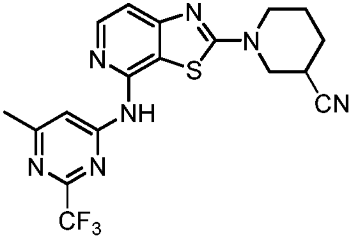
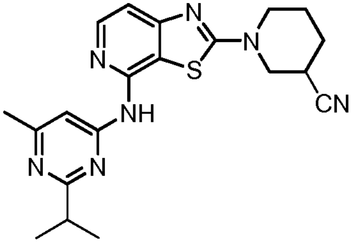
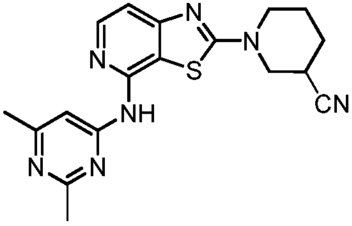
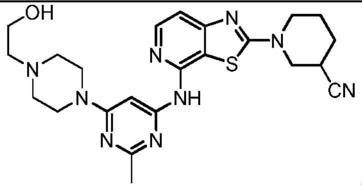
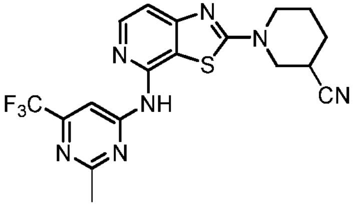
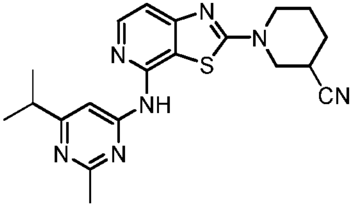
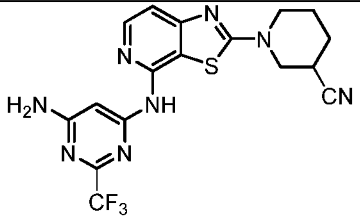
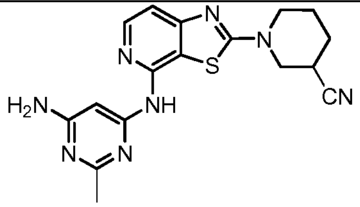
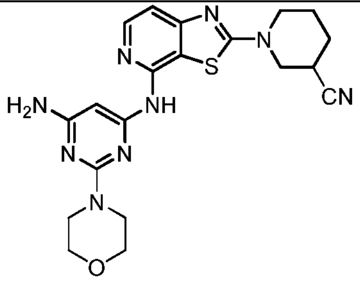
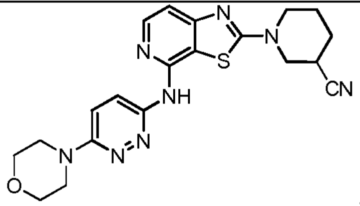
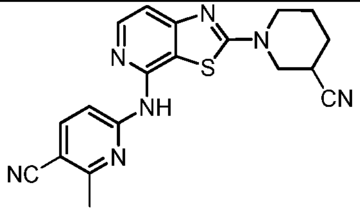
Example No.	Structure
1	 ,
2	 ,
3	 ,
4	 ,
5	 ,
6	 ,
7	 ,
8	 ,
9	 ,
10	 ,
11	 ,
12	 ,
13	 ,

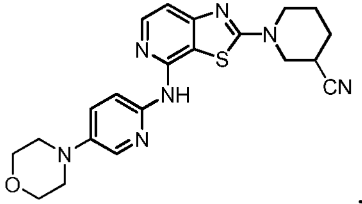
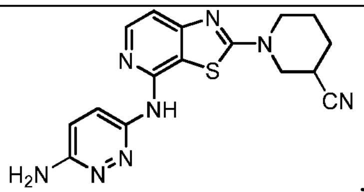
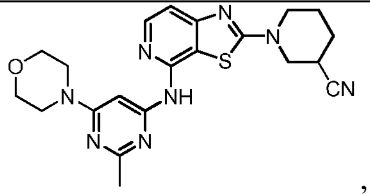
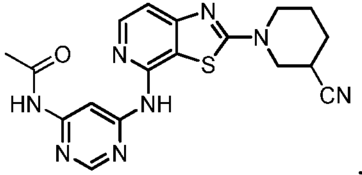
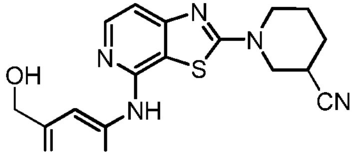
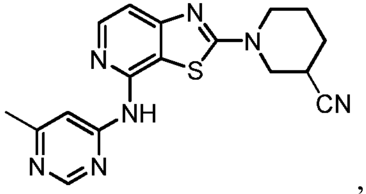
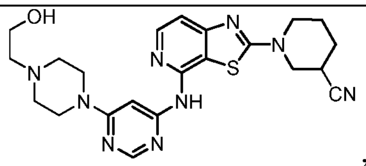
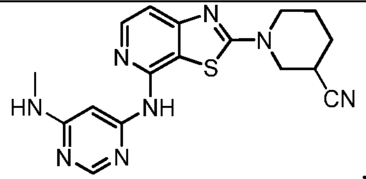
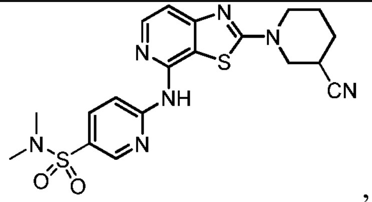
14	 ,
15	 ,
16	 ,
17	 ,
18	 ,
19	 ,
20	 ,

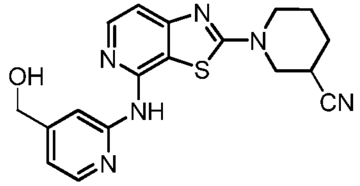
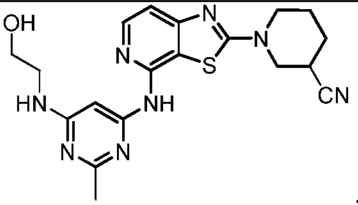
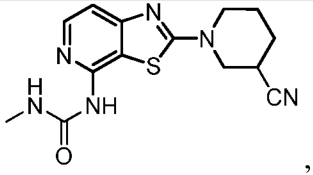
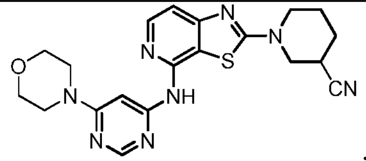
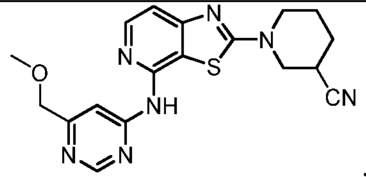
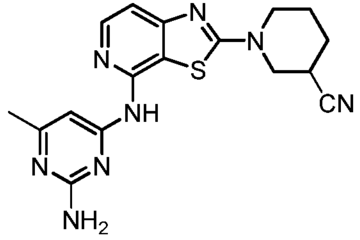
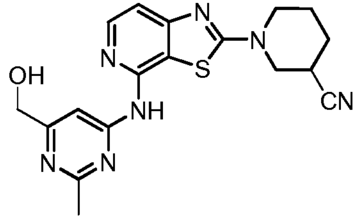
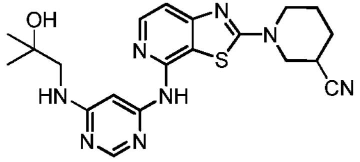
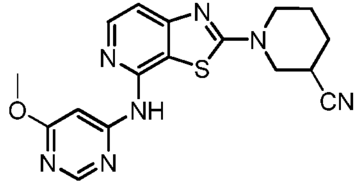
21	 ,
22	 ,
23	 ,
24	 ,
25	 ,
26	 ,

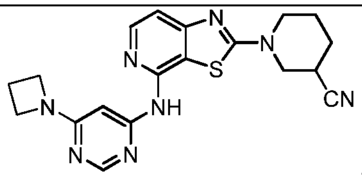
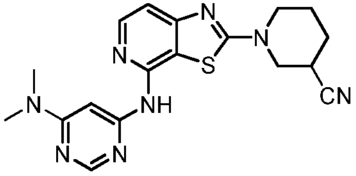
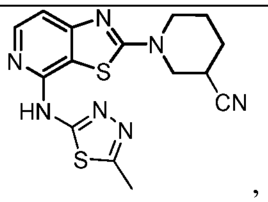
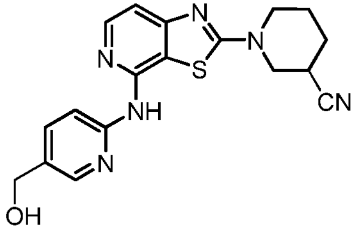
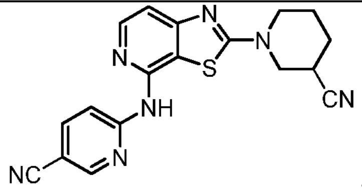
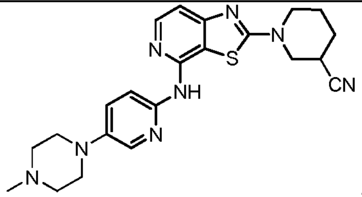
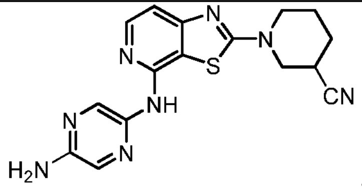
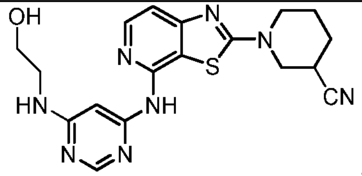
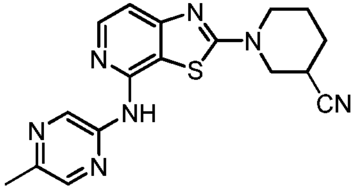
27	 ,
28	 ,
29	 ,
30	 ,
31	 ,
32	 ,
33	 ,

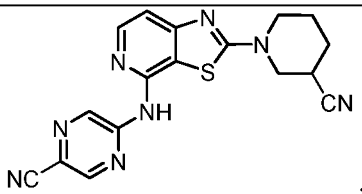
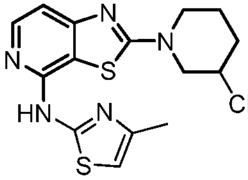
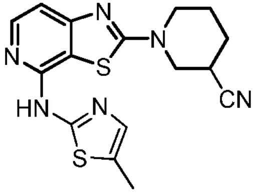
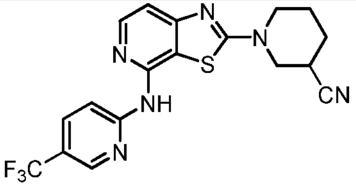
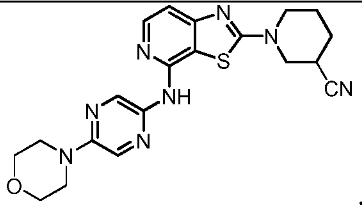
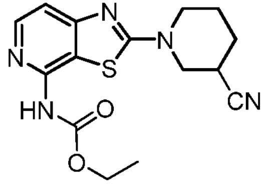
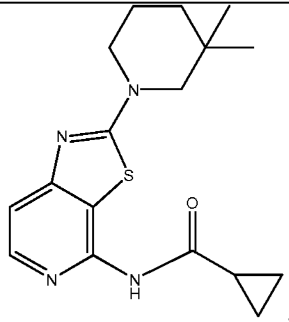
34	 ,
35	 ,
36	 ,
37	 ,
38	 ,
39	 ,
40	 ,

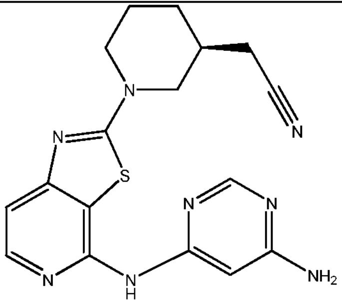
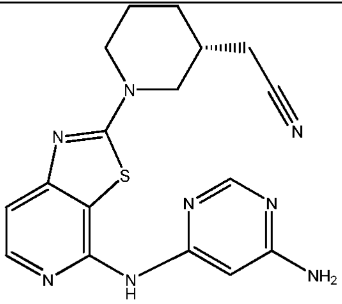
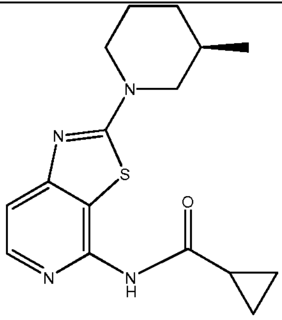
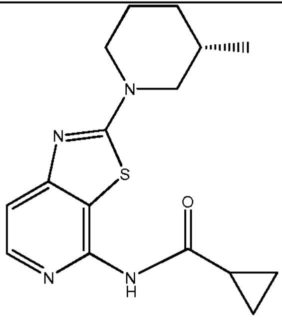
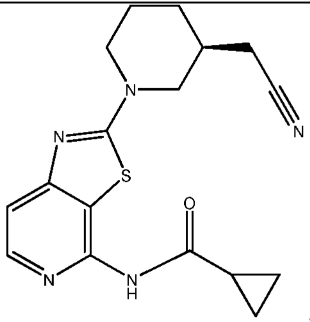
41	,
42	,
43	,
44	,
45	,
46	,
47	,
48	,
49	,
50	,
51	,
52	,
53	,
54	,

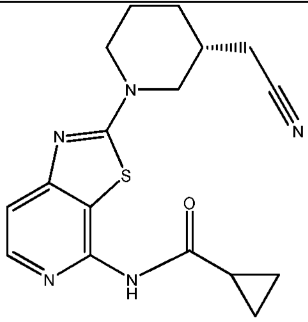
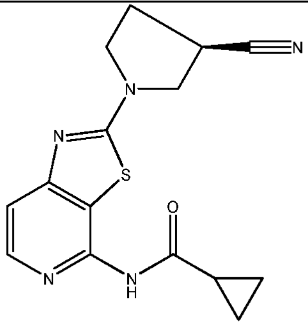
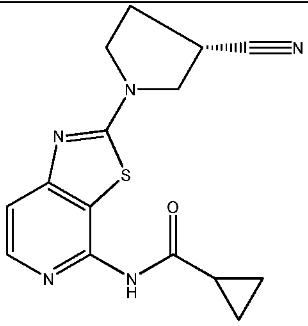
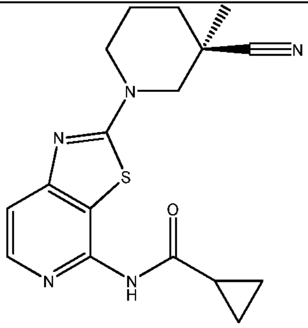
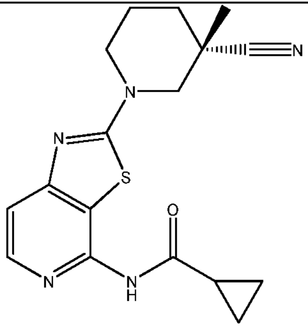
55	 ,
56	 ,
57	 ,
58	 ,
59	 ,
60	 ,
61	 ,
62	 ,
63	 ,

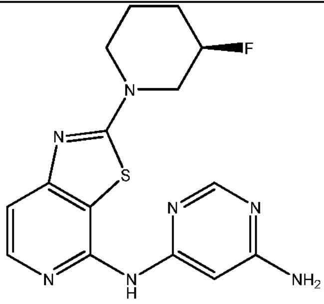
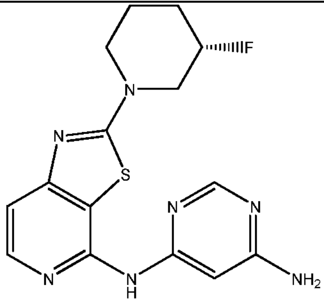
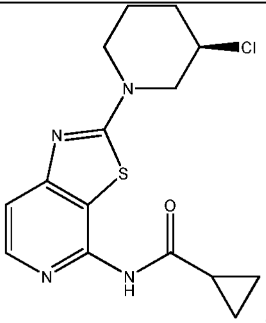
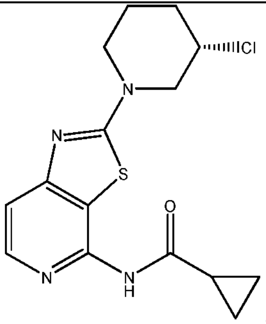
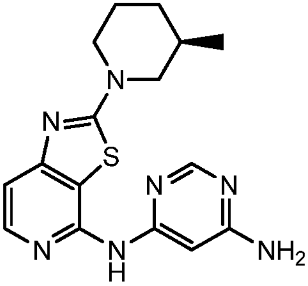
64	 ,
65	 ,
66	 ,
67	 ,
68	 ,
69	 ,
70	 ,
71	 ,
72	 ,

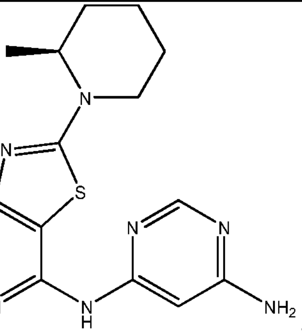
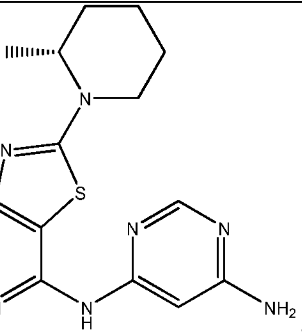
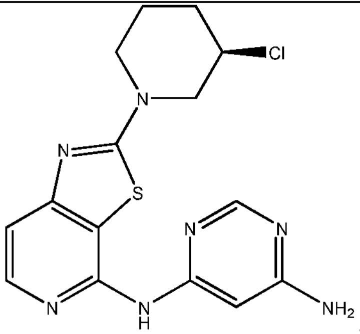
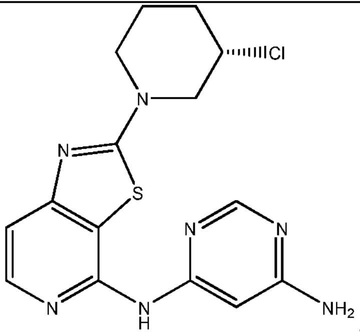
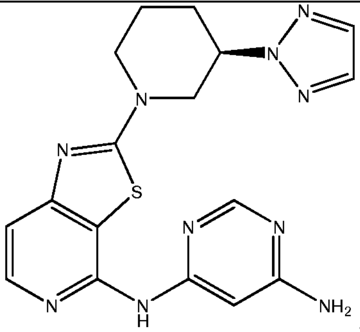
73	 ,
74	 ,
75	 ,
76	 ,
77	 ,
78	 ,
79	 ,
80	 ,
81	 ,

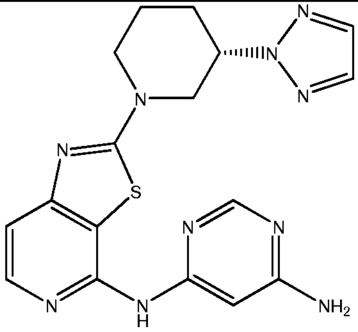
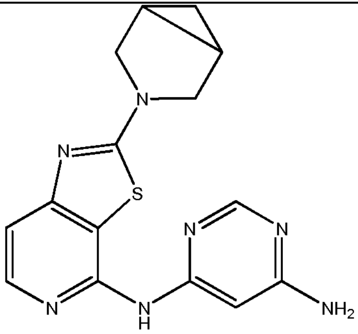
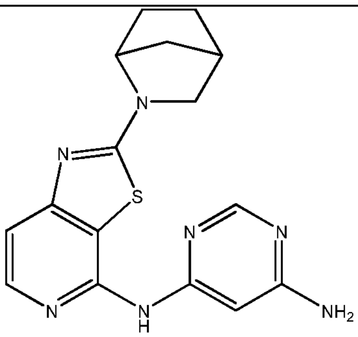
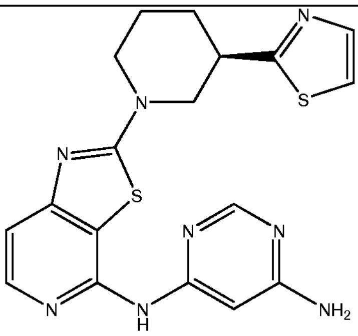
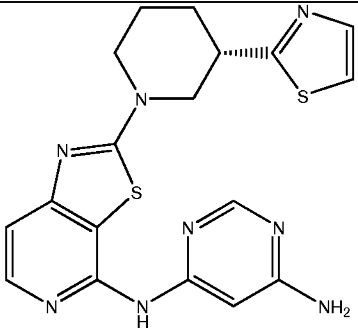
82	 ,
83	 ,
84	 ,
85	 ,
86	 ,
87	 ,
88	 ,

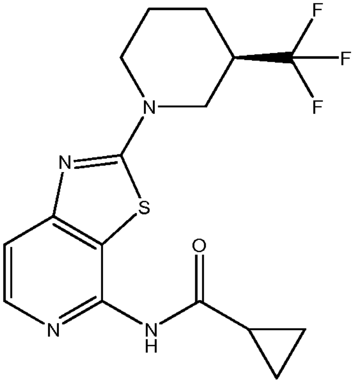
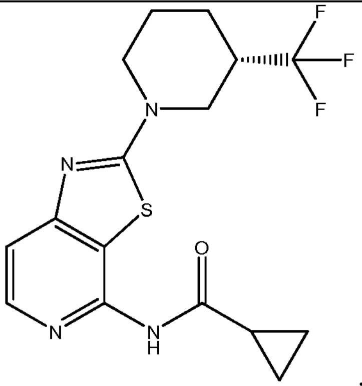
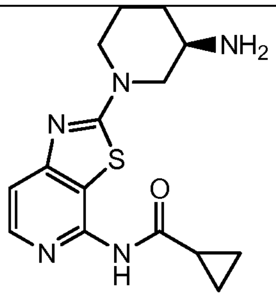
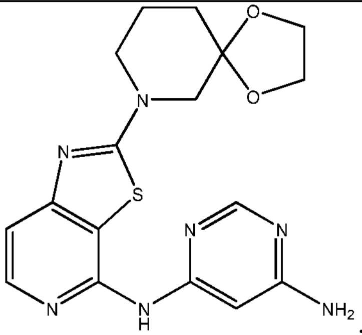
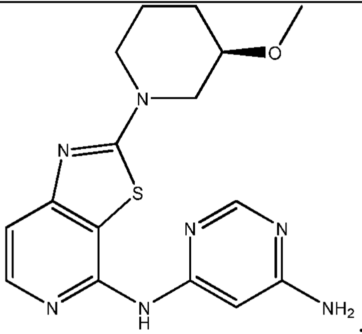
89	 ,
90	 ,
91	 ,
92	 ,
93	 ,

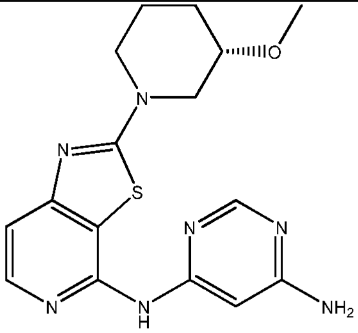
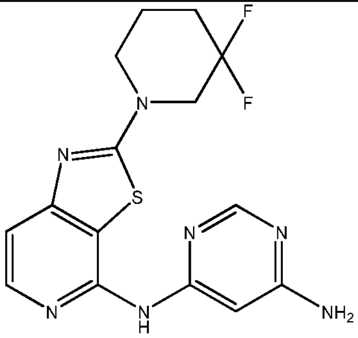
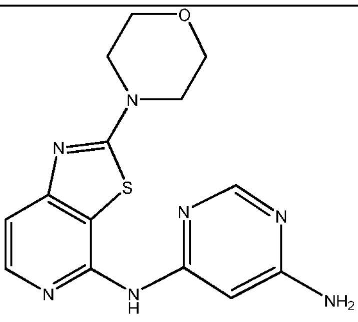
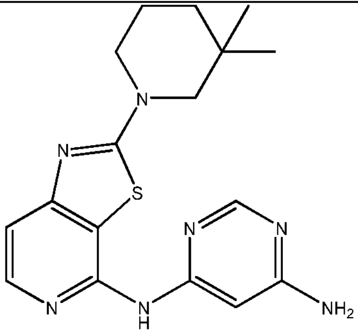
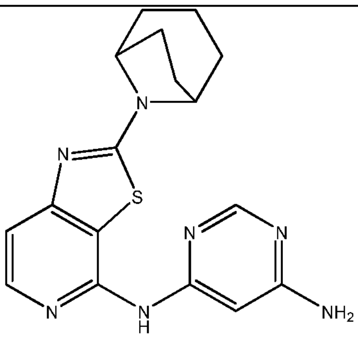
94	 ,
95	 ,
96	 ,
97	 ,
98	 ,

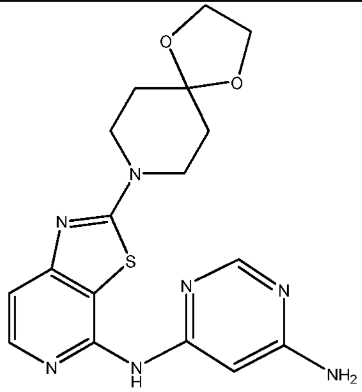
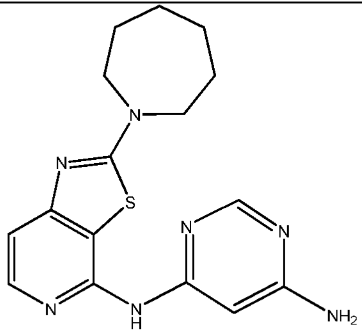
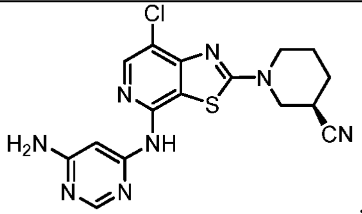
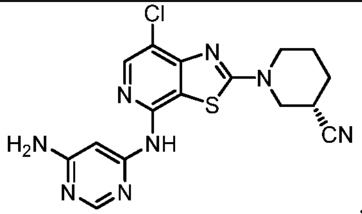
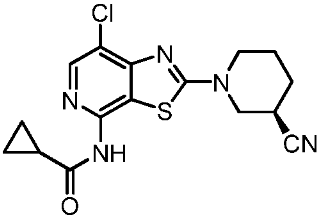
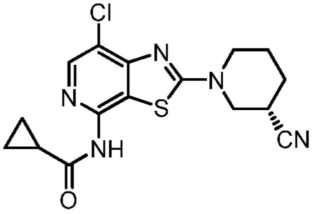
99	 ,
100	 ,
101	 ,
102	 ,
103	 ,

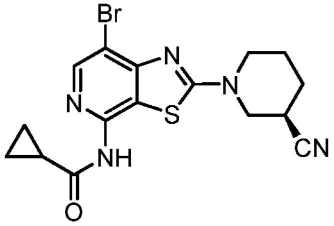
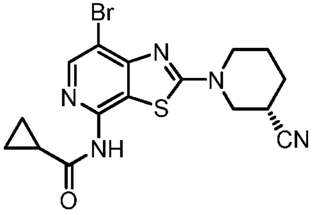
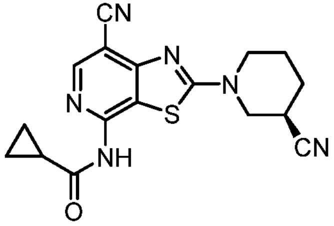
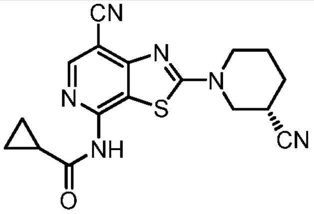
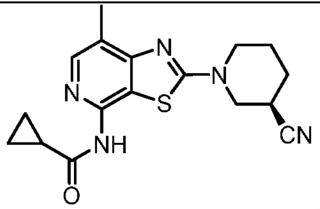
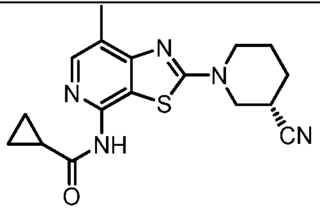
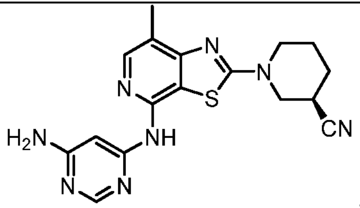
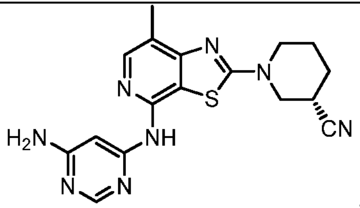
104	 ,
105	 ,
106	 ,
107	 ,
108	 ,

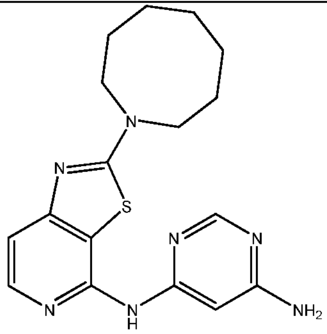
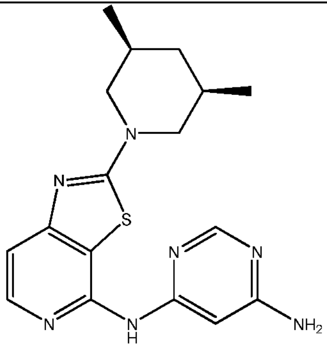
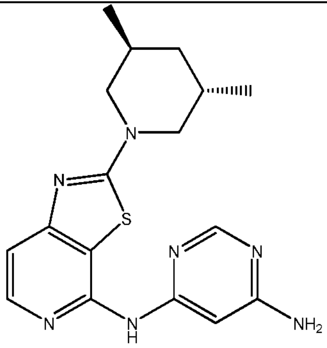
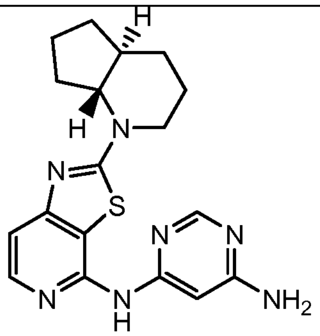
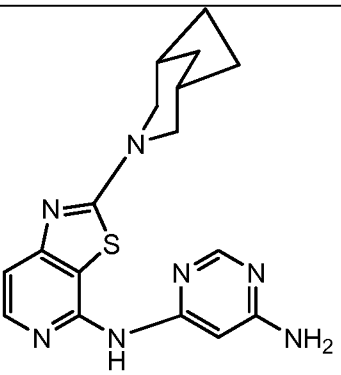
109	 ,
110	 ,
111	 ,
112	 ,
113	 ,

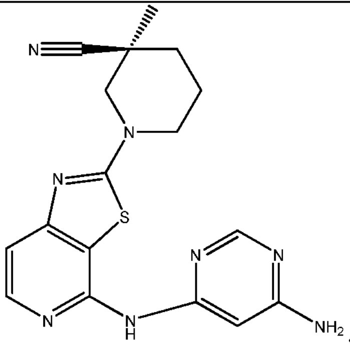
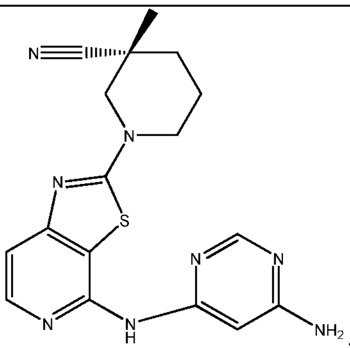
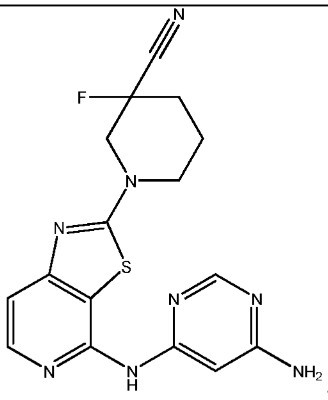
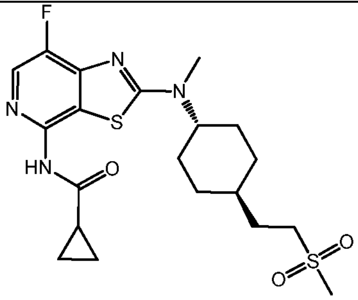
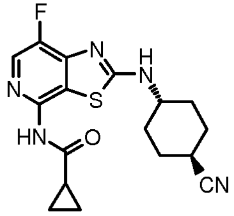
114	 ,
115	 ,
116	 ,
117	 ,
118	 ,

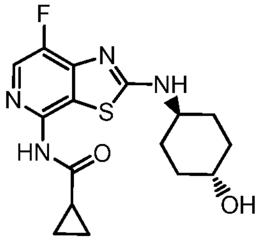
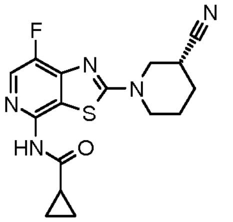
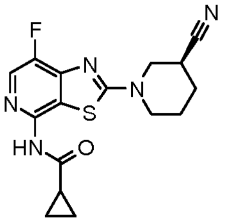
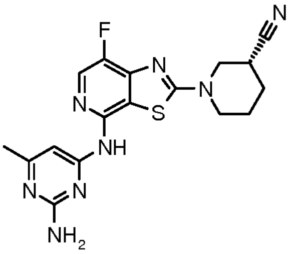
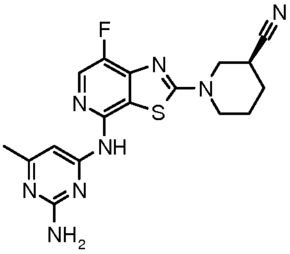
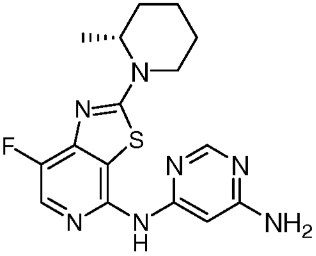
119	 ,
120	 ,
121	 ,
122	 ,
123	 ,

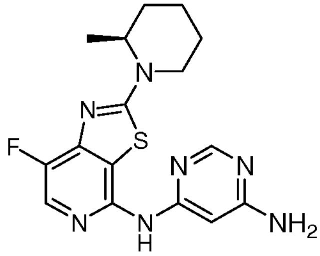
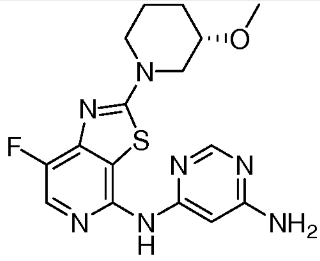
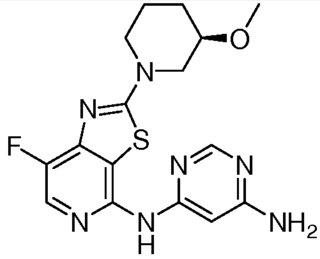
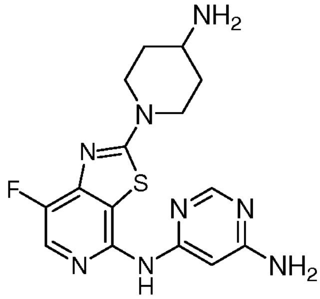
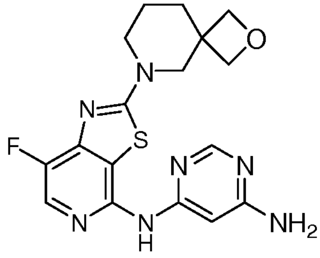
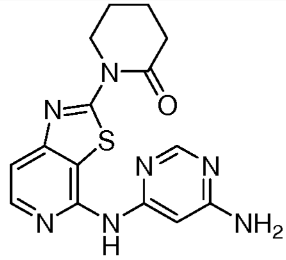
124	 ,
125	 ,
126	 ,
127	 ,
128	 ,
129	 ,

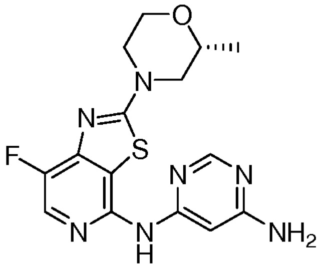
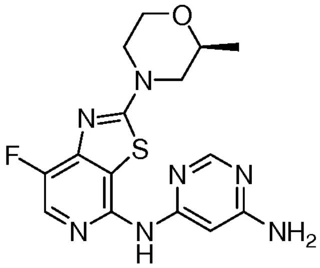
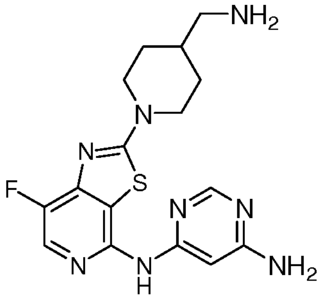
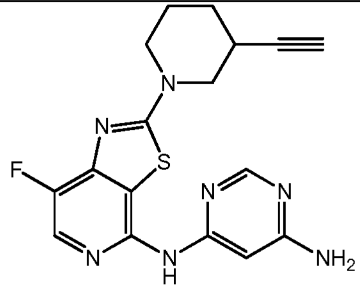
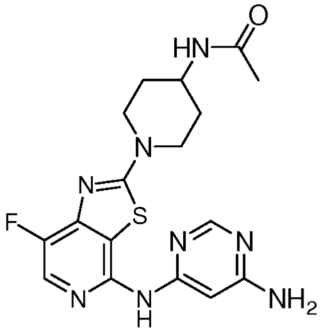
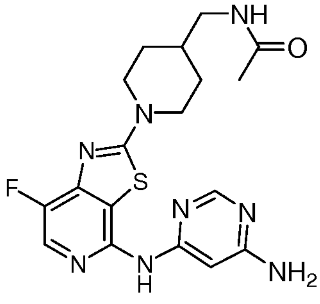
130	 ,
131	 ,
132	 ,
133	 ,
134	 ,
135	 ,
136	 ,
137	 ,

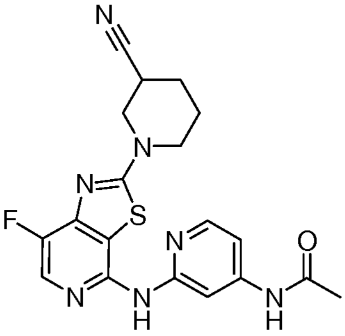
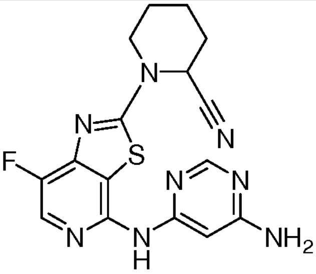
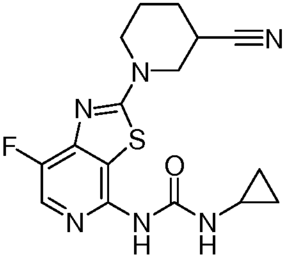
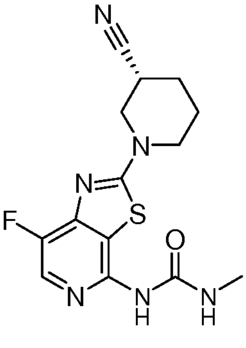
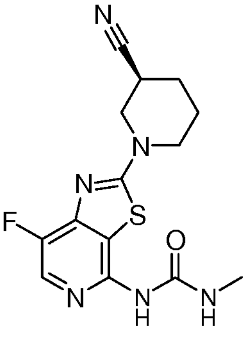
138	 ,
139	 ,
140	 ,
141	 ,
142	 ,

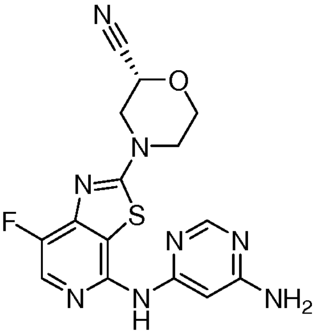
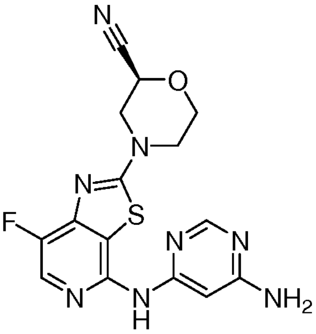
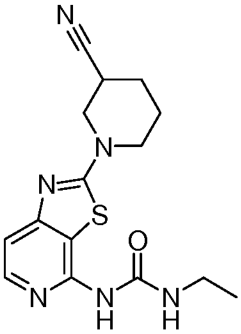
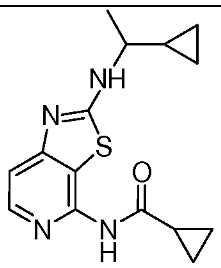
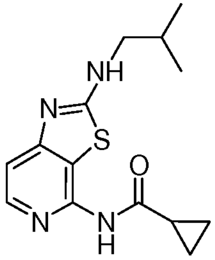
143	 ,
144	 ,
145	 ,
146	 ,
147	 ,

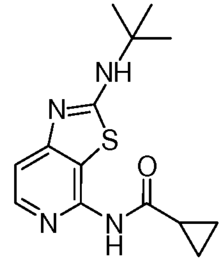
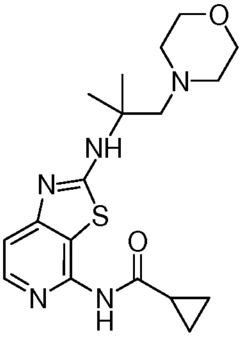
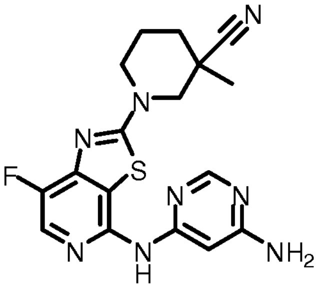
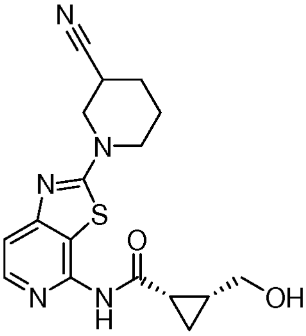
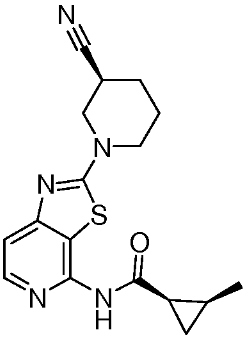
148	 ,
149	 ,
150	 ,
151	 ,
152	 ,
153	 ,

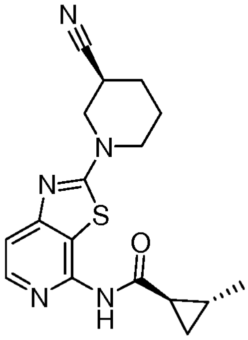
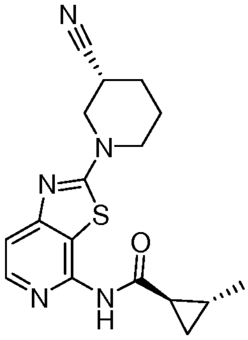
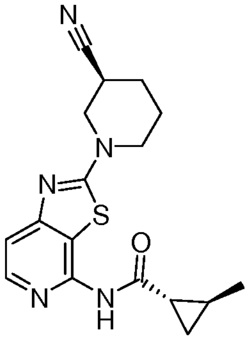
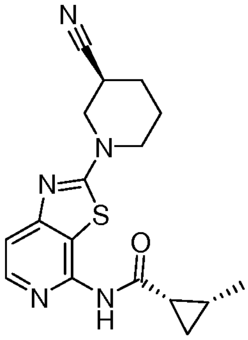
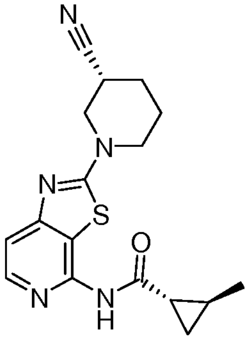
154	,
155	,
156	,
157	,
158	,
159	,

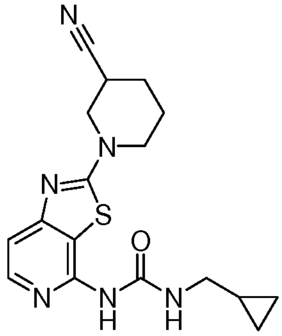
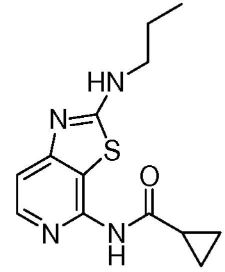
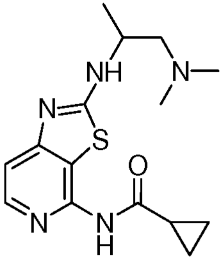
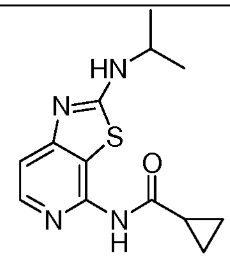
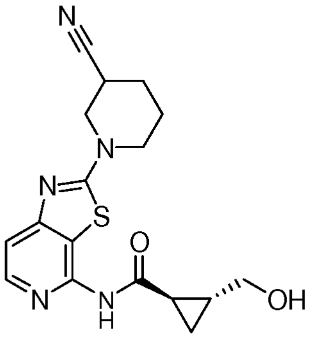
160	,
161	,
162	,
163	,
164	,
165	,

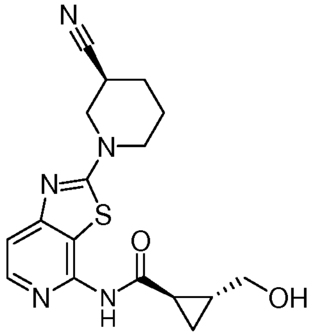
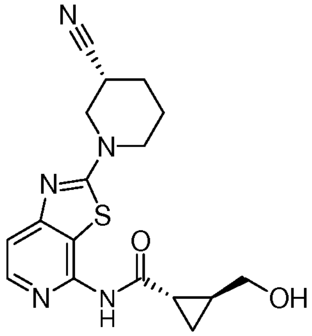
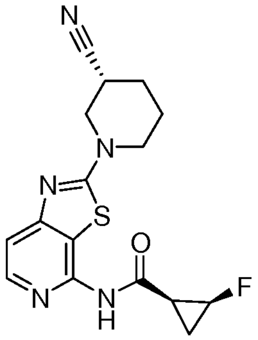
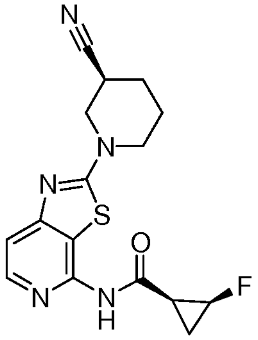
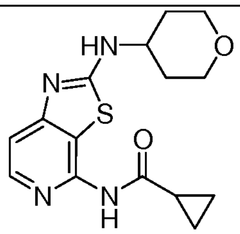
166	 ,
167	 ,
168	 ,
169	 ,
170	 ,

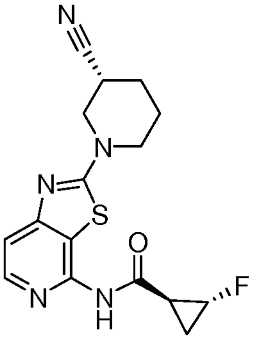
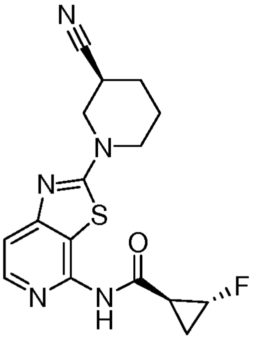
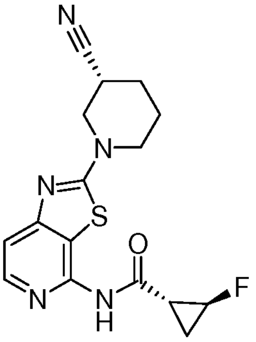
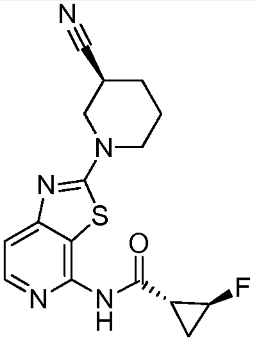
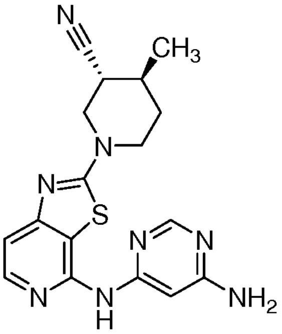
171	 ,
172	 ,
173	 ,
174	 ,
175	 ,

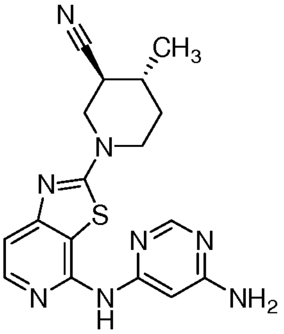
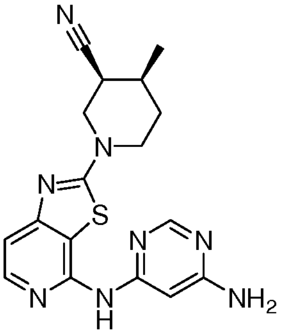
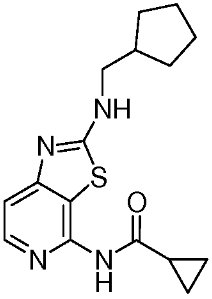
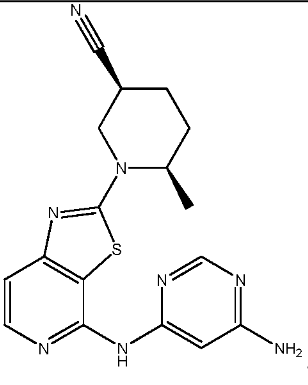
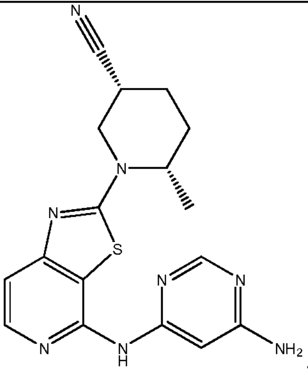
176	,
177	,
178	,
179	,
180	,

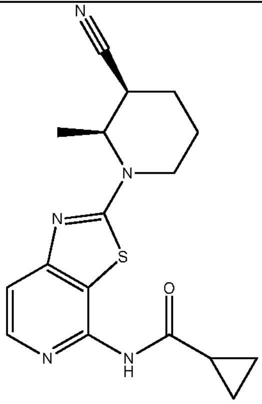
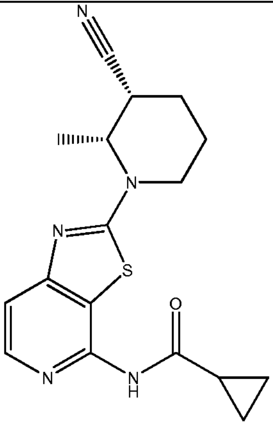
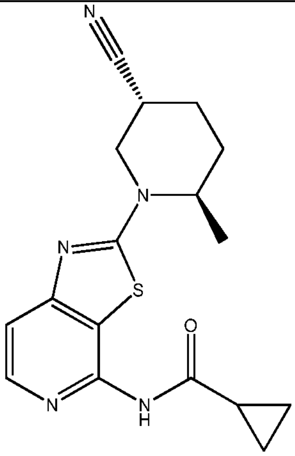
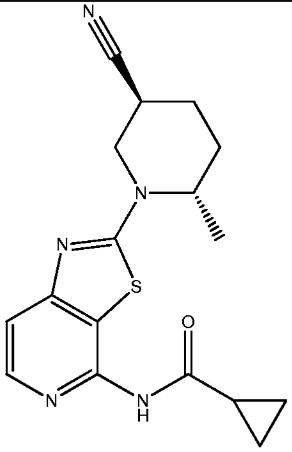
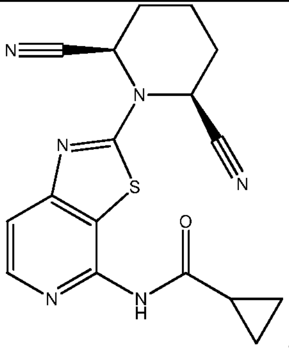
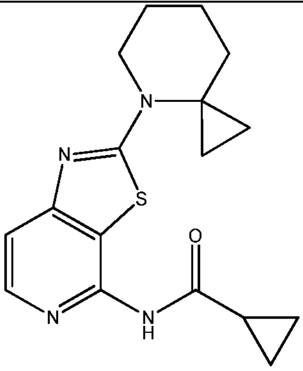
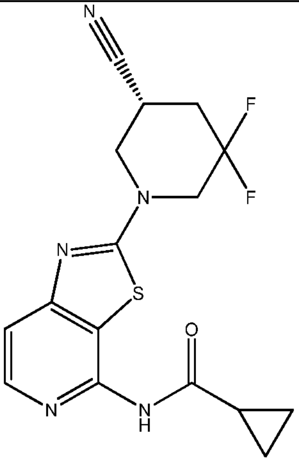
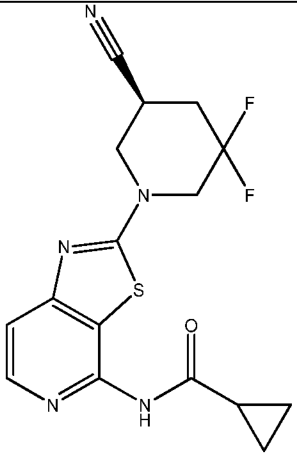
181	,
182	,
183	,
184	,
185	,

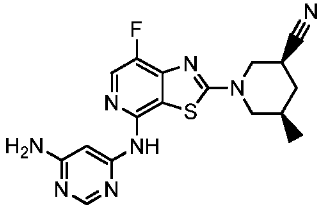
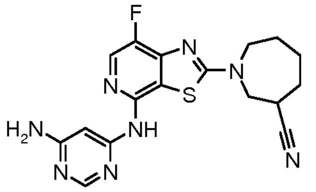
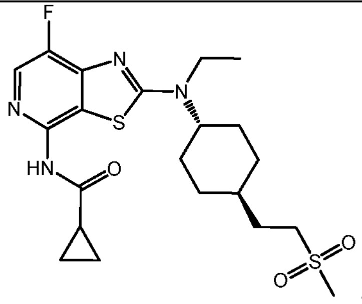
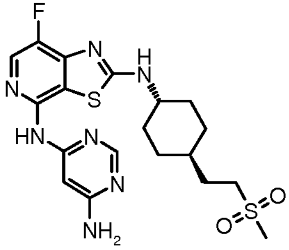
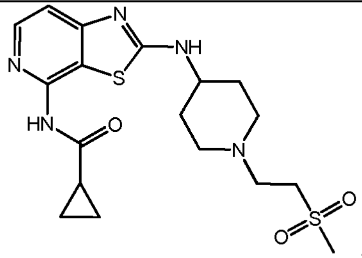
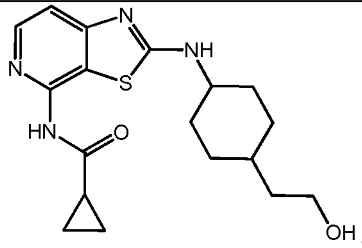
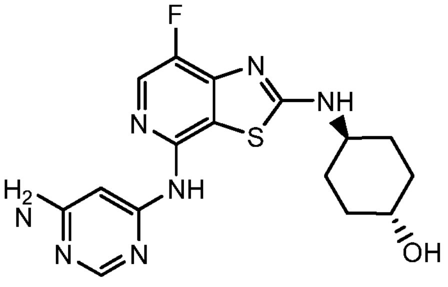
186	 ,
187	 ,
188	 ,
189	 ,
190	 ,

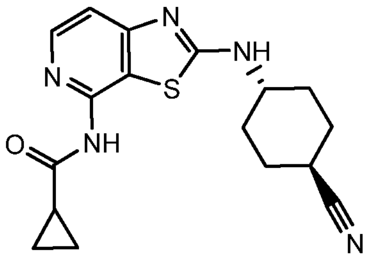
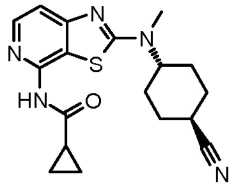
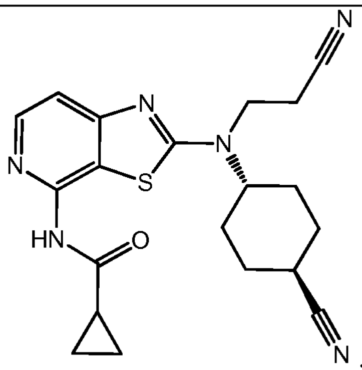
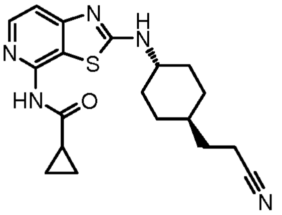
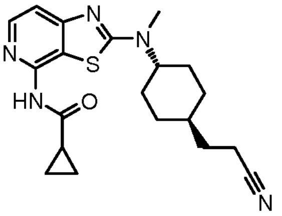
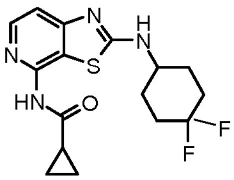
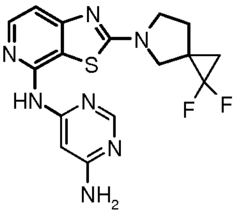
191	 ,
192	 ,
193	 ,
194	 ,
195	 ,

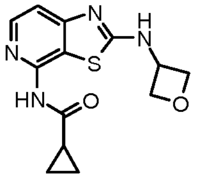
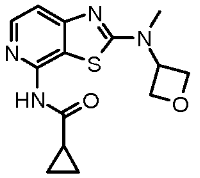
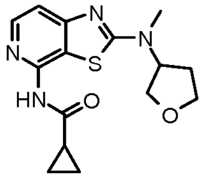
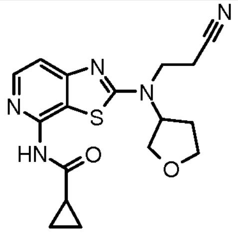
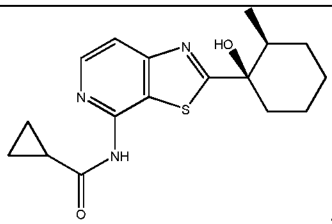
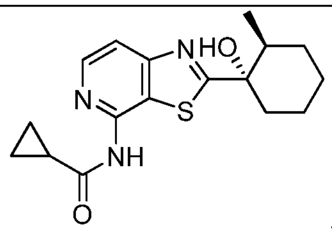
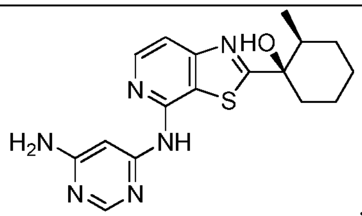
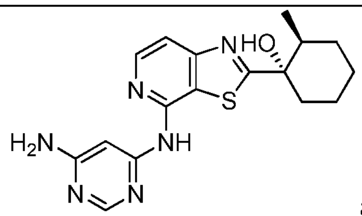
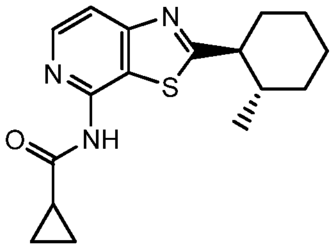
196	,
197	,
198	,
199	,
200	,

201	,
202	,
203	,
204	,
205	,

206	,
207	,
208	,
209	,
210	,
211	,
212	,
213	,

214	 ,
215	 ,
216	 ,
217	 ,
218	 ,
219	 ,
220	 ,

221	 ,
222	 ,
223	 ,
224	 ,
225	 ,
226	 ,
227	 ,

228	 ,
229	 ,
230	 ,
231	 ,
232	 ,
233	 ,
234	 ,
235	 and
236	 .

In some embodiments, the invention relates to one or more of the compounds depicted in Table 1 (e.g., compounds of Example Nos. 1-236 of Table 1), and uses thereof. In one embodiment, the invention relates to one or more of the compounds in Example Nos. 1, 2, 3, 4, 5, 6, 7, 8, 9, 16, 17, 18, 21, 22, 42, 43, 126 and 127, and uses thereof.

The compounds provided herein may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds provided herein, including but not limited to: diastereomers, enantiomers, and atropisomers as well as mixtures thereof such as racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers. For example, if a compound incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention. Both the single positional isomers and mixture of positional isomers, e.g., resulting from the N-oxidation of the pyrimidinyl and pyrazolyl rings, or the E and Z forms of the compound (for example oxime moieties), are also within the scope of the present invention.

In the structures shown herein, where the stereochemistry of any particular chiral atom is not specified, then all stereoisomers are contemplated and included as the compounds of the invention. Where stereochemistry is specified by a solid wedge or dashed line representing a particular configuration, then that stereoisomer is so specified and defined.

The compounds of the present invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention, as defined by the claims, embrace both solvated and unsolvated forms.

In an embodiment, compounds provided herein may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention, as defined by the claims. The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

The present invention also embraces isotopically-labeled compounds of Formulae I, II, III, and variations described herein, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. All isotopes of any particular atom or element as specified are contemplated within the scope of the invention. Exemplary isotopes that can be incorporated into compounds of Formula I include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C,

^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. Certain isotopically-labeled compounds of Formulae I, II, III, and variations described herein (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements). Positron emitting isotopes such as ^{15}O, ^{13}N, ^{11}C, and ^{18}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Isotopically labeled compounds provided herein can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples herein below, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

A compound as detailed herein may in one aspect be in a purified form and compositions comprising a compound in purified forms are detailed herein. Compositions comprising a compound as detailed herein or a salt thereof are provided, such as compositions of substantially pure compounds. In some embodiments, a composition containing a compound as detailed herein or a salt thereof is in substantially pure form. In some embodiments, substantially pure" intends a composition that contains no more than 35%, 30%, 25%, 20%, 15%, 10%, 5%, 2% or 1% impurity, wherein the impurity denotes a compound other than the compound comprising the majority of the composition or a salt thereof.

In one variation, the compounds herein are synthetic compounds prepared for administration to an individual. In another variation, compositions are provided containing a compound in substantially pure form. In another variation, the invention embraces pharmaceutical compositions comprising a compound detailed herein and a pharmaceutically acceptable carrier. In another variation, methods of administering a compound are provided. The purified forms, pharmaceutical compositions and methods of administering the compounds are suitable for any compound or form thereof detailed herein.

General Synthetic Methods

The invention includes methods of making the compounds (as well as compositions comprising the compounds) described herein. The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process descriptions, the symbols when used in the formulae depicted are to be understood to represent those groups described above in relation to the formulae herein.

Compounds described herein (e.g., Formulae I, II, III and variations thereof) may be synthesized by synthetic routes described herein. In certain embodiments, processes well-known in the chemical arts can be used, in addition to, or in light of, the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, Wis.) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, *Reagents for Organic Synthesis*, v. 1-19, Wiley, N.Y. (1967-1999 ed.), Beilsteins Handbuch der organischen Chemie, 4, Aufl. ed. Springer-Verlag, Berlin, including supplements (also available via the Beilstein online database)), or *Comprehensive Heterocyclic Chemistry*, Editors Katrizky and Rees, Pergamon Press, 1984.

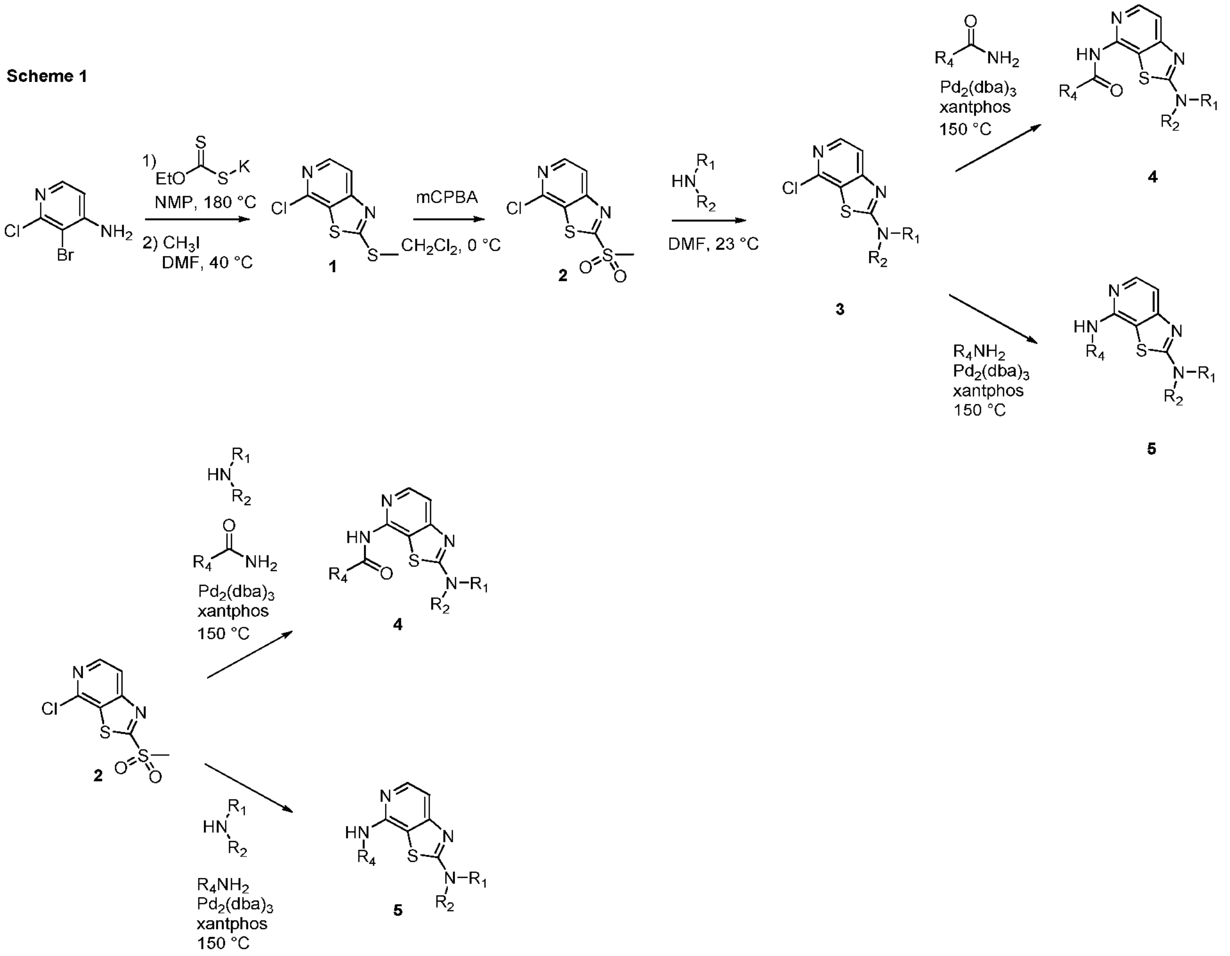
Compounds described herein (e.g., Formulae I, II, III and variations thereof) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, or 10 to 100 compounds described herein (e.g., Formulae I, II, III and variations thereof). Libraries of compounds described herein may be prepared by a combinatorial `split and mix` approach or by multiple parallel syntheses using either solution phase or solid phase chemistry, by procedures known to those skilled in the art. Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds described herein (e.g., Formulae I, II, III and variations thereof), enantiomers, diasteriomers or pharmaceutically acceptable salts thereof.

In the preparation of compounds of the present invention, protection of remote functionality (e.g., primary or secondary amine) of intermediates may be necessary. The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. Suitable amino-protecting groups (NH-Pg) include acetyl, trifluoroacetyl, t-butoxycarbonyl (Boc), benzyloxycarbonyl (CBz) and 9-fluorenylmethyleneoxycarbonyl (Fmoc). The need for such protection is readily determined by one skilled in the art. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

Compounds of the invention may be prepared from commercially available starting materials using the general methods illustrated herein.

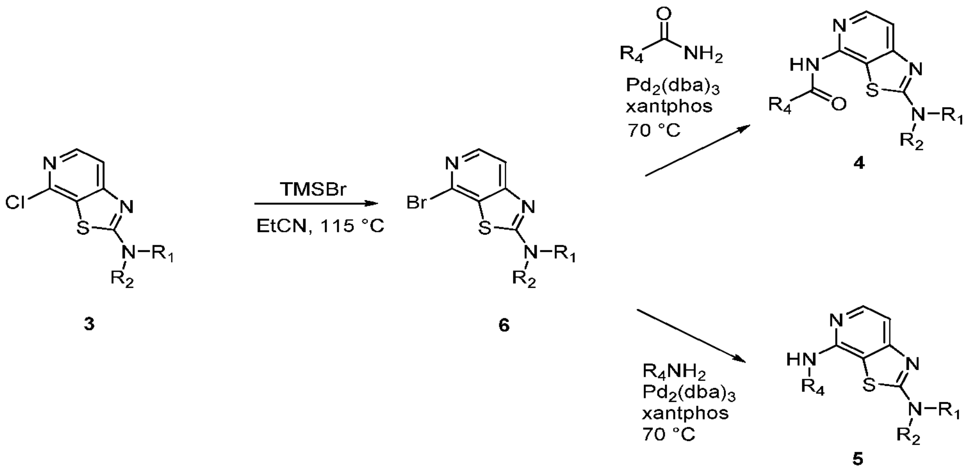
For illustrative purposes, reaction Schemes 1-5 depicted below provide routes for synthesizing the compounds of Formulae I, II, III and variations thereof, as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other synthetic routes may be available and used. Although specific starting materials and reagents are depicted in the Schemes and discussed below, other starting materials and reagents may be available for substitution to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

Scheme 1



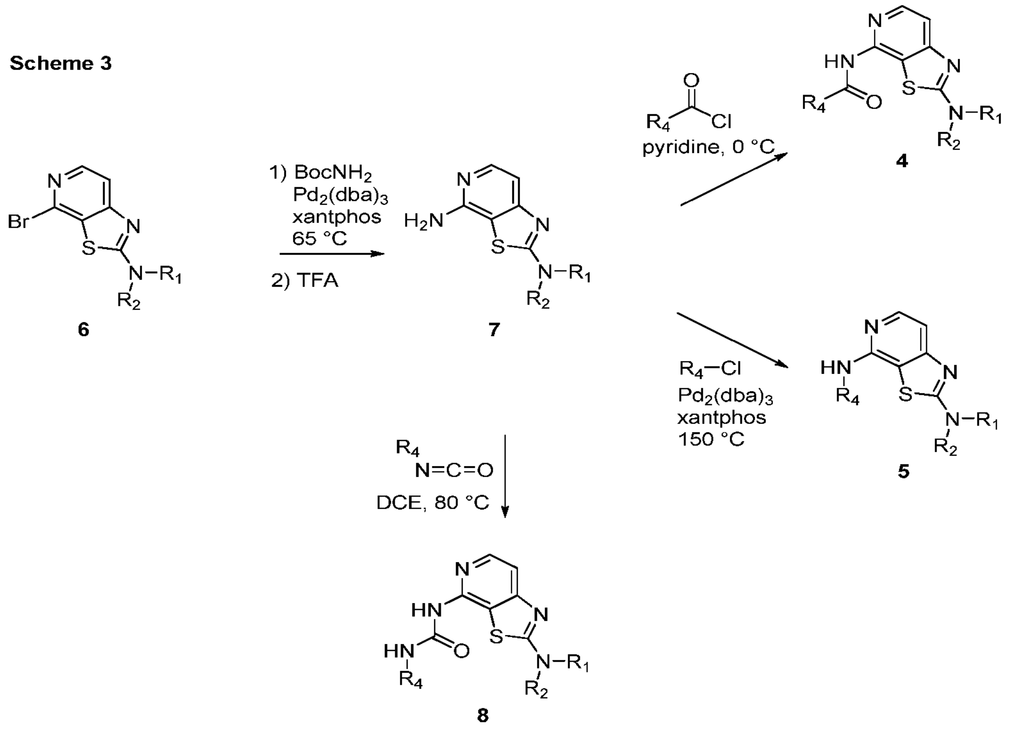
The general synthesis of targets **4** and **5** is outlined in Scheme 1. 3-Bromo-2-chloropyridin-4amine is treated with potassium ethyl xanthate, followed by methylation that provides compound **1**. Oxidation of methyl sulphide with mCPBA yields the corresponding methyl sulfone which could be displaced by an amine. The resulting chloride **2** can be coupled with an amide or an amine, under palladium-catalyzed conditions, to give the final targets. Alternatively, the amine displacement of methyl sulfone and the palladium-catalyzed coupling reaction can be carried out in one-pot, by mixing all the starting materials together and then heating the reaction mixture to 150 °C, typically done in a microwave irradiator.

Scheme 2



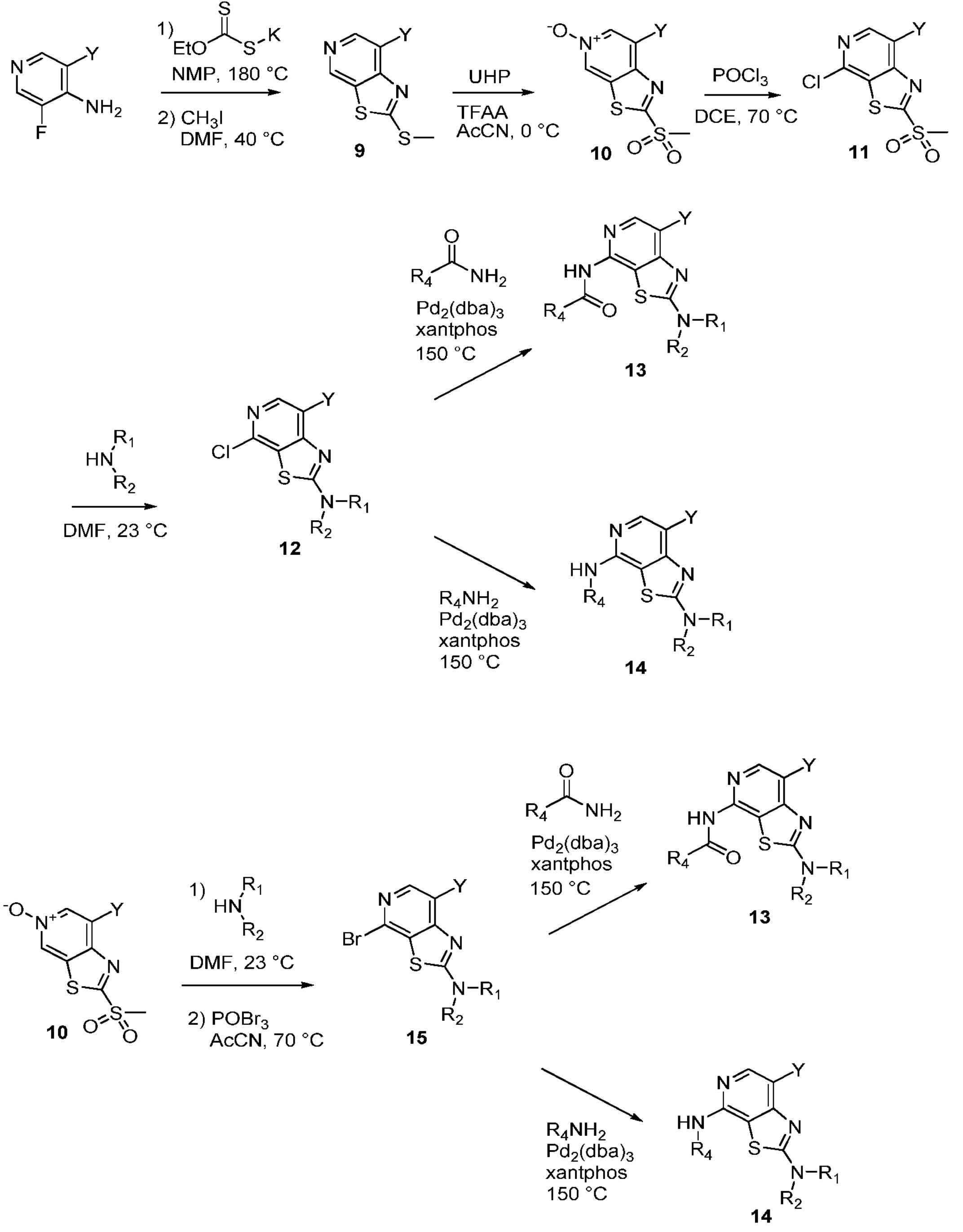
Treatment of chloride **3** in Scheme 1 with TMSBr in propionitrile leads to bromide **6**, which also undergoes palladium-catalyzed coupling reactions to give targets **4** and **5** (Scheme 2).

Scheme 3



Bromide **6** can be coupled with BocNH$_2$ in the presence of catalytic amount of Pd$_2$(dba)$_3$ and xantphos, followed by subsequent reaction with TFA which leads to amine **7** (Scheme 3). Compound **7** can react with an acid chloride to provide amide **4**. The amino group in **7** can also be coupled with an aryl chloride, under palladium-catalyzed conditions, to give **5**. In addition, when treated with an isocyanate, compound **7** is transformed to urea **8**.

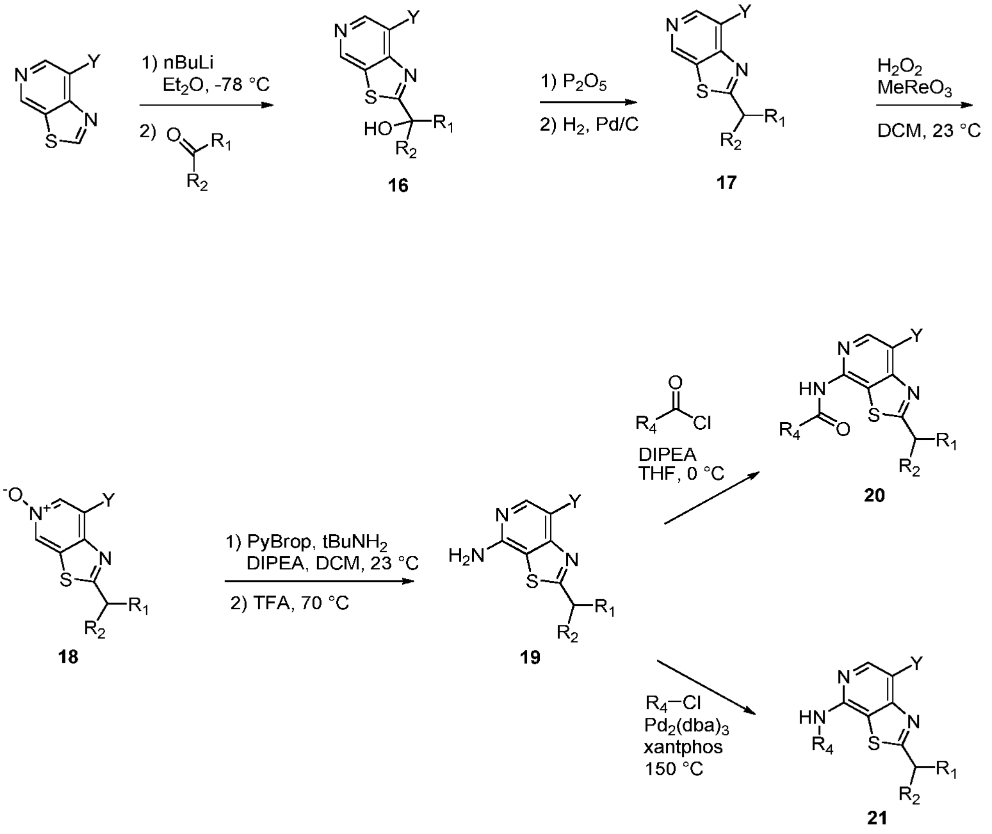
Scheme 4



Similarly, C5-substituted pyridine also undergoes reaction with potassium ethyl xanthate, followed by methylation to give methyl sulphide **9** (Scheme 4). Oxidation of methyl sulphide to methyl sulfone with urea hydrogen peroxide complex also leads to oxidation of pyridine to its corresponding N-oxide. When heated with $POCl_3$, pyridine N-oxide **10** is transformed to compound **11**. The methyl sulfone in compound **11** can be displaced with an amine to give compound **12**. Subsequently, chloride **12** undergoes palladium-catalyzed coupling reactions, with an amide or an amine, to give compounds **13** or **14**. Alternatively, methyl sulfone **10** can also react with an amine, followed by treatment with $POBr_3$ that leads to bromide **15**. Bromide

15 undergoes palladium-catalyzed coupling reactions with an amide or an amine to yield targets **13** or **14**.

Scheme 5



Scheme 5 outlines the preparation of compounds such as **20** and **21**. Benzothiazole is treated with *n*-butyllithium at -78 °C, followed by addition of a ketone to provide alcohol **16**. Alcohol is deoxygenated via a 2-step process. First, dehydration of **16** leads to an olefin which is hydrogenated to give **17**. Oxidation of **17** with hydrogen peroxide in the presence of $MeReO_3$ provides N-oxide **18**. When treated with PyBrop and *tert*-butylamine, N-oxide **18** undergoes rearrangement to give 2-*tert*-butylaminopyridine, which is deprotected with TFA to furnish amine **19**. Reaction of amine **19** with an acid chloride yields amide **20**. Alternatively, the amino group in **19** can be coupled with an aryl chloride, under palladium-catalyzed conditions, to provide compound **21**.

It will be appreciated that where appropriate functional groups exist, compounds of various formulae or any intermediates used in their preparation may be further derivatized by one or more standard synthetic methods employing condensation, substitution, oxidation, reduction, or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, sulfonylation, halogenation, nitration, formylation and coupling procedures.

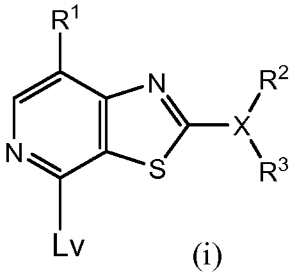
In each of the exemplary Schemes it may be advantageous to separate reaction products from one another and/or from starting materials. Diastereomeric mixtures can be separated into their individual diastereoisomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereoisomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Also, some of the compounds of the present invention may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of a chiral HPLC column.

A single stereoisomer, e.g., an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents (Eliel, E. and Wilen, S., *Stereochemistry of Organic Compounds*, John Wiley & Sons, Inc., New York, 1994; Lochmuller, C. H., *J. Chromatogr.*, 113(3):283-302 (1975)). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions. See: *Drug Stereochemistry, Analytical Methods and Pharmacology*, Irving W. Wainer, Ed., Marcel Dekker, Inc., New York (1993).

Diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, α-methyl-β-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts.

Alternatively, the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S., *Stereochemistry of Organic Compounds*, John Wiley & Sons, Inc., New York, 1994, p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the pure or enriched enantiomer. A method of determining optical purity involves making chiral esters, such as a menthyl ester, e.g., (-) menthyl chloroformate in the presence of base, or Mosher ester, α-methoxy-α-(trifluoromethyl)phenyl acetate (Jacob, *J. Org. Chem.* 47:4165 (1982)), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric enantiomers or diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (WO 96/15111). By method (3), a racemic mixture of two enantiomers can be separated by chromatography using a chiral stationary phase (*Chiral Liquid Chromatography* W. J. Lough, Ed., Chapman and Hall, New York, (1989); Okamoto, *J. of Chromatogr.* 513:375-378 (1990)). Enriched or purified enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

Another embodiment includes a method of manufacturing a compound of Formula I. The method includes: (a) reacting a compound of formula (i):



(i)

wherein Lv is a leaving group, for example a halogen, and X, R^1, R^2 and R^3 are as defined for Formula I, with a compound of the formula H-R^4-R^5 under conditions sufficient to form a compound of Formula I; and (b) optionally further functionalizing said above compound.

Certain embodiments include a compound of formula (i), stereoisomers or pharmaceutically acceptable salts thereof. Certain embodiments include a compound of formula (i), stereoisomers or pharmaceutically acceptable salts thereof, wherein X, R^1, R^2 and R^3 are as defined for Formula I and the group –Lv is a halogen, -OR or $-OS(O)_{1-2}R$, wherein R is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, phenyl or heterocyclyl and R is independently optionally substituted. In certain embodiments, the group –Lv is halogen. Certain embodiments include a compound of formula (i) wherein the group –Lv is –Br or –I.

In certain embodiments, the conditions for reacting a compound of formula (i) with a compound of the formula H-R^4-R^5 include transition metal catalyzed reaction conditions. In one embodiment, the transition metal catalyst is selected from a platinum, palladium or copper catalyst. In one embodiment, the catalyst is a Pd(0) catalyst. Pd(0) catalysts for use in the method include tetrakis(tri-optionally substituted phenyl)phosphine palladium(0) catalyst, wherein said optional substituents on phenyl are selected from –OMe, -CF_3, -OCF_3, -Me and –Et and dipalladium(0) catalysts, such as tris(dibenzylideneacetone)dipalladium(0). In certain embodiments, the conditions include heating the reactants under basic conditions, for example, in the presence of an inorganic base, for example, a cesium, potassium, ammonium, or sodium carbonate or bicarbonate base, for example Cs_2CO_3. In certain embodiments, the conditions further include ligands to the transition metal catalyst. In one embodiment, a bidentate ligand is included, for example, the bidentate ligand xantphos is added.

Pharmaceutical Compositions and Administration

Pharmaceutical compositions of any of the compounds detailed herein are embraced by this invention. Thus, the invention includes pharmaceutical compositions comprising a compound of the invention or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient. In one aspect, the pharmaceutically acceptable salt is an acid addition salt, such as a salt formed with an inorganic or organic acid. Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration or a form suitable for administration by inhalation.

Another embodiment provides pharmaceutical compositions or medicaments containing the compounds of the invention and a therapeutically inert carrier, diluent or excipient, as well as methods of using the compounds of the invention to prepare such compositions and medicaments. In one example, compounds of described herein (e.g., Formulae I, II, III and variations thereof) may be formulated by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed into a galenical administration form. The pH of the formulation depends on the particular use and the concentration of compound, and can range anywhere from about 3 to about 8. In one example, a compound described herein (e.g., Formulae I, II, III and variations thereof) is formulated in an acetate buffer, at pH 5. In another embodiment, the compounds described herein (e.g., Formulae I, II, III and variations thereof) are sterile. The compound may be stored, for example, as a solid or amorphous composition, as a lyophilized formulation or as an aqueous solution.

Compositions are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular patient being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The “effective amount” of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to inhibit TYK2 kinase activity. For example, such amount may be below the amount that is toxic to normal cells, or the patient as a whole.

The pharmaceutical composition (or formulation) for application may be packaged in a variety of ways depending upon the method used for administering the drug. Generally, an article for distribution includes a container having deposited therein the pharmaceutical formulation in an appropriate form. Suitable containers are well-known to those skilled in the art and include materials such as bottles (plastic and glass), sachets, ampoules, plastic bags, metal cylinders, and the like. The container may also include a tamper-proof assemblage to prevent indiscreet access to the contents of the package. In addition, the container has deposited thereon a label that describes the contents of the container. The label may also include appropriate warnings.

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing a compound described herein (e.g., Formulae I, II, III and variations thereof) , which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides, copolymers of L-glutamic acid and gamma-ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid.

In one example, the pharmaceutically effective amount of the compound of the invention administered parenterally per dose will be in the range of about 0.01-100 mg/kg, alternatively about 0.1 to 20 mg/kg of patient body weight per day, with the typical initial range of compound used being 0.3 to 15 mg/kg/day. In another embodiment, oral unit dosage forms, such as tablets and capsules, contain from about 5-100 mg of the compound of the invention.

The compounds of the present invention may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, aerosols, etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents.

A typical formulation is prepared by mixing a compound of the present invention and a carrier or excipient. Suitable carriers and excipients are well known to those skilled in the art and are described in detail in, e.g., Ansel, Howard C., et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lippincott, Williams & Wilkins, 2004; Gennaro, Alfonso R., et al. Remington: The Science and Practice of Pharmacy. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Raymond C. Handbook of Pharmaceutical Excipients. Chicago, Pharmaceutical Press, 2005. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

An example of a suitable oral dosage form is a tablet containing about 25 mg, 50 mg, 100 mg, 250 mg or 500 mg of the compound of the invention compounded with about 5-30 mg anhydrous lactose, about 5-40 mg sodium croscarmellose, about 5-30 mg polyvinylpyrrolidone (PVP) K30, and about 1-10 mg magnesium stearate. The powdered ingredients are first mixed together and then mixed with a solution of the PVP. The resulting composition can be dried, granulated, mixed with the magnesium stearate and compressed to tablet form using conventional equipment. An example of an aerosol formulation can be prepared by dissolving the compound, for example 5-400 mg, of the invention in a suitable buffer solution, e.g., a phosphate buffer, adding a tonicifier, e.g., a salt such sodium chloride, if desired. The solution may be filtered, e.g., using a 0.2 micron filter, to remove impurities and contaminants.

In one embodiment, the pharmaceutical composition also includes an additional therapeutic agent. In some embodiments, the additional therapeutic agent is selected from an anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory agent, a neurotropic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, or an agent for treating immunodeficiency disorders.

An embodiment, therefore, includes a pharmaceutical composition comprising a compound of Formulae I, II, III or variations thereof, or a stereoisomer or pharmaceutically acceptable salt thereof. In a further embodiment includes a pharmaceutical composition comprising a compound of Formulae I, II, III or variations thereof, or a stereoisomer or pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or excipient. Another embodiment includes a pharmaceutical composition comprising a compound of Formulae I, II, III or variations thereof, or a stereoisomer or pharmaceutically acceptable salt thereof, for use in the treatment of an immunological or inflammatory disease. Another embodiment includes a pharmaceutical composition comprising a compound of Formulae I, II, III or variations thereof, or a stereoisomer or pharmaceutically acceptable salt thereof for use in the treatment of psoriasis or inflammatory bowel disease.

Methods of Use

Compounds and compositions of the invention, such as a pharmaceutical composition containing a compound of any formula provided herein or a salt thereof and a pharmaceutically acceptable carrier or excipient, may be used in methods of administration and treatment as provided herein. The compounds described herein (e.g., Formulae I, II, III and variations thereof) inhibit TYK2 kinase activity. Accordingly, the compounds are useful for reducing inflammation in particular patient tissue and cells. Compounds described herein (e.g., Formulae I, II, III and variations thereof) are useful for inhibiting TYK2 kinase activity in cells that overexpress TYK2 kinase. Alternatively, compounds are useful for inhibiting TYK2 kinase activity in cells in which, for example, the type I interferon, IL-6, IL-10, IL-12 and IL-23 signaling pathway is disruptive or abnormal, for example by binding to TYK2 kinase and inhibiting its activity. Alternatively, the compounds described herein (e.g., Formulae I, II, III and variations thereof) can be used for the treatment of immunological or inflammatory disorders. Accordingly, the invention provides methods of treatment of a disease responsive to the inhibition of TYK2 kinase activity in a patient.

In some embodiments, provided is a method of treating a disease responsive to the inhibition of TYK2 kinase activity in a patient, comprising administering to the patient a therapeutically effective amount of a compound described herein (e.g., or a compound of Formulae I, II, III or variations thereof), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof. In one aspect, provided is a method of treating a disease responsive to the inhibition of TYK2 kinase activity in a patient, comprising administering to the patient a therapeutically effective amount of a pharmaceutical composition comprising a compound described herein (e.g., or a compound of Formulae I, II, III or variations thereof), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition further comprises a pharmaceutically acceptable carrier, adjuvant or vehicle.

In some embodiments, provided is a method of treating or lessening the severity of a disease or condition responsive to the inhibition of TYK2 kinase activity in a patient. The method includes the step of administering to a patient a therapeutically effective amount of a compound of Formula I, II, or III, or any variation thereof described herein, or stereoisomers, tautomers or salts thereof.

In one embodiment, a compound of Formula I, II, or III, or any variation thereof described herein, is administered to a patient in a therapeutically effective amount to treat or lessen the severity of a disease or condition responsive to the inhibition of TYK2 kinase activity, and the compound is at least 15 fold, alternatively 10 fold, alternatively 5 fold or more selective in inhibiting TYK2 kinase activity over inhibiting each of the other Janus kinase activities. In one embodiment, a compound of Formula I, II, or III, or any variation thereof described herein, is administered to a patient in a therapeutically effective amount to treat or lessen the severity of a disease or condition responsive to the inhibition of TYK2 kinase activity, and the compound is at least 15 fold, alternatively 10 fold, alternatively 5 fold or more selective in inhibiting TYK2 kinase activity over inhibiting JAK1. In one embodiment, a compound of Formula I, II, or III, or any variation thereof described herein, is administered to a patient in a therapeutically effective amount to treat or lessen the severity of a disease or condition responsive to the inhibition of TYK2 kinase activity, and the compound is at least 15 fold, alternatively 10 fold, alternatively 5 fold or more selective in inhibiting TYK2 kinase activity over inhibiting JAK2. In one embodiment, a compound of Formula I, II, or III, or any variation thereof described herein, is administered to a patient in a therapeutically effective amount to treat or lessen the severity of a disease or condition responsive to the inhibition of TYK2 kinase activity, and the compound is at least 15 fold, alternatively 10 fold, alternatively 5 fold or more selective in inhibiting TYK2 kinase activity over inhibiting JAK3.

In some embodiments, the disease responsive to the inhibition of TYK2 kinase activity is an inflammatory disease. In some embodiments, the disease responsive to the inhibition of TYK2 kinase activity is asthma, inflammatory bowel disease, Crohn’s disease, ulcerative colitis, rheumatoid arthritis, psoriasis, allergic rhinitis, atopic dermatitis, contact dermatitis, delayed hypersensitivity reactions, lupus or multiple sclerosis.

Another embodiment includes a compound of Formula I, II, or III, or any variation thereof described herein, or stereoisomers, tautomers or salts thereof for use in therapy.

Another embodiment includes a compound of Formula I, II, or III, or any variation thereof described herein, or stereoisomers, tautomers or salts thereof for use in treating an immunological or inflammatory disease.

Another embodiment includes a compound of Formula I, II, or III, or any variation thereof described herein, or stereoisomers, tautomers or salts thereof for use in treating psoriasis or inflammatory bowel disease.

Another embodiment includes the use of a compound of Formula I, II, or III, or any variation thereof described herein, or stereoisomers, tautomers or salts thereof for treating an immunological or inflammatory disease.

Another embodiment includes the use of a compound of Formula I, II, or III, or any variation thereof described herein, or stereoisomers, tautomers or salts thereof for treating psoriasis or inflammatory bowel disease.

Another embodiment includes the use of a compound of Formula I, II, or III, or any variation thereof described herein, or stereoisomers, tautomers or salts thereof in the preparation of a medicament for the treatment of an immunological or inflammatory disease.

Another embodiment includes the use of a compound of Formula I, II, or III, or any variation thereof described herein, or stereoisomers, tautomers or salts thereof in the preparation of a medicament for the treatment of psoriasis or inflammatory bowel disease.

In one embodiment, the disease or condition is stroke, diabetes, hepatomegaly, cardiovascular disease, multiple sclerosis, Alzheimer's disease, cystic fibrosis, viral disease, autoimmune diseases, immunological disease, atherosclerosis, restenosis, psoriasis, allergic disorders, inflammatory disease, neurological disorders, a hormone-related disease, conditions associated with organ transplantation, immunodeficiency disorders, destructive bone disorders, proliferative disorders, infectious diseases, conditions associated with cell death, thrombin-induced platelet aggregation, liver disease, pathologic immune conditions involving T cell activation, CNS disorders or a myeloproliferative disorder.

In one embodiment, the disease or condition is an immunological disorder.

In one embodiment, the disease is a myeloproliferative disorder.

In one embodiment, the myeloproliferative disorder is polycythemia vera, essential thrombocytosis, or myelofibrosis.

In one embodiment, the disease is asthma.

In one embodiment, the cardiovascular disease is restenosis, cardiomegaly, atherosclerosis, myocardial infarction or congestive heart failure.

In one embodiment, the neurodegenerative disease is Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, cerebral ischemia, neurodegenerative disease caused by traumatic injury, glutamate neurotoxicity or hypoxia.

In one embodiment, the inflammatory disease is inflammatory bowel disease, Crohn’s disease, ulcerative colitis, rheumatoid arthritis, psoriasis, contact dermatitis or delayed hypersensitivity reactions.

In one embodiment, the inflammatory disease is asthma, inflammatory bowel disease, Crohn’s disease, ulcerative colitis, rheumatoid arthritis, psoriasis, allergic rhinitis, atopic dermatitis, contact dermatitis or delayed hypersensitivity reactions.

In one embodiment, the autoimmune disease is lupus.

In one embodiment, the disease is asthma, inflammatory bowel disease, Crohn’s disease, pouchitis, microscopic colitis, ulcerative colitis, rheumatoid arthritis, psoriasis, allergic rhinitis, atopic dermatitis, contact dermatitis, delayed hypersensitivity reactions, lupus or multiple sclerosis.

Evaluation of drug-induced immunosuppression by the compounds of the invention may be performed using *in vivo* functional tests, such as rodent models of induced arthritis and therapeutic or prophylactic treatment to assess disease score, T cell-dependent antibody response (TDAR), and delayed-type hypersensitivity (DTH). Other *in vivo* systems including murine models of host defense against infections or tumor resistance (Burleson GR, Dean JH, and Munson AE. *Methods in Immunotoxicology, Vol. 1*. Wiley-Liss, New York, 1995) may be considered to elucidate the nature or mechanisms of observed immunosuppression. The *in vivo* test systems can be complemented by well-established *in vitro* or *ex vivo* functional assays for the assessment of immune competence. These assays may comprise B or T cell proliferation in response to mitogens or specific antigens, measurement of signaling through one or more of the Janus kinase pathways in B or T cells or immortalized B or T cell lines, measurement of cell surface markers in response to B or T cell signaling, natural killer (NK) cell activity, mast cell activity, mast cell degranulation, macrophage phagocytosis or kill activity, and neutrophil oxidative burst and/or chemotaxis. In each of these tests determination of cytokine production by particular effector cells (e.g., lymphocytes, NK, monocytes/macrophages, neutrophils) may be included. The *in vitro* and *ex vivo* assays can be applied in both preclinical and clinical testing using lymphoid tissues and/or peripheral blood (House RV. "Theory and practice of cytokine assessment in immunotoxicology" (1999) Methods 19:17-27; Hubbard AK. "Effects of xenobiotics on macrophage function: evaluation in vitro" (1999) Methods;19:8-16; Lebrec H, et al (2001) Toxicology 158:25-29).

Collagen-induced arthritis (CIA) is an animal model of human rheumatoid arthritis (RA). Joint inflammation, which develops in animals with CIA, strongly resembles inflammation observed in patients with rheumatoid arthritis (RA). Blocking tumor necrosis factor (TNF) is an efficacious treatment of CIA, just as it is a highly efficacious therapy in treatment of RA patients. CIA is mediated by both T-cells and antibodies (B-cells). Macrophages are believed to play an important role in mediating tissue damage during disease development. CIA is induced by immunizing animals with collagen emulsified in Complete Freund’s Adjuvant (CFA). It is most commonly induced in the DBA/1 mouse strain, but the disease can also be induced in Lewis rats.

The T-cell Dependent Antibody Response (TDAR) is An assay for immune function testing when potential immunotoxic effects of compounds need to be studied. The IgM-Plaque Forming Cell (PFC) assay, using Sheep Red Blood Cells (SRBC) as the antigen, is currently a widely accepted and validated standard test. TDAR is an assay for adult exposure immunotoxicity detection in mice based on the US National Toxicology Program (NTP) database (M.I. Luster et al (1992) Fundam. Appl. Toxicol. 18:200–210). The utility of this assay stems from the fact that it is a holistic measurement involving several important components of an immune response. A TDAR is dependent on functions of the following cellular compartments: (1) antigen-presenting cells, such as macrophages or dendritic cells; (2) T-helper cells, which are critical players in the genesis of the response, as well as in isotype switching; and (3) B-cells, which are the ultimate effector cells and are responsible for antibody production. Chemically-induced changes in any one compartment can cause significant changes in the overall TDAR (M.P. Holsapple In: G.R. Burleson, J.H. Dean and A.E. Munson, Editors, *Modern Methods in Immunotoxicology, Volume 1*, Wiley-Liss Publishers, New York, NY (1995), pp. 71–108). Usually, this assay is performed either as an ELISA for measurement of soluble antibody (R.J. Smialowizc et al (2001) Toxicol. Sci. 61:164–175) or as a plaque (or antibody) forming cell assay (L. Guo et al (2002) Toxicol. Appl. Pharmacol. 181:219–227) to detect plasma cells secreting antigen specific antibodies. The antigen of choice is either whole cells (e.g., sheep erythrocytes) or soluble protein antigens (T. Miller et al (1998) Toxicol. Sci. 42:129–135).

The compounds described herein (e.g., Formulae I, II, III and variations thereof) may be administered by any route appropriate to the disease or condition to be treated. Suitable routes include oral, parenteral (including subcutaneous, intramuscular, intravenous, intraarterial, intradermal, intrathecal and epidural), transdermal, rectal, nasal, topical (including buccal and sublingual), vaginal, intraperitoneal, intrapulmonary, inhaled, intralesional, and intranasal. For local immunosuppressive treatment, the compounds may be administered by intralesional administration, including perfusing or otherwise contacting the graft with the inhibitor before transplantation. It will be appreciated that the route may vary with, for example, the condition of the recipient. Where the compound is administered orally, it may be formulated as a pill, capsule, tablet, etc. with a pharmaceutically acceptable carrier or excipient. Where the compound is administered parenterally, it may be formulated with a pharmaceutically acceptable parenteral vehicle and in a unit dosage injectable form.

A dose to treat human patients may range from about 5 mg to about 1000 mg of a compound described herein (e.g., a compound of Formula I, II or III or any variation thereof). A typical dose may be about 5 mg to about 300 mg of a compound described herein (e.g., a compound of Formulae I, II, III and variations thereof). A dose may be administered once a day (QD), twice per day (BID), or more frequently, depending on the pharmacokinetic and pharmacodynamic properties, including absorption, distribution, metabolism, and excretion of the particular compound. In addition, toxicity factors may influence the dosage and administration regimen. When administered orally, the pill, capsule, or tablet may be ingested daily or less frequently for a specified period of time. The regimen may be repeated for a number of cycles of therapy.

Combination Therapy

The compounds described herein (e.g., Formulae I, II, III and variations thereof) may be employed alone or in combination with other therapeutic agents for the treatment of a disease or disorder described herein, such as an immunologic disorder (e.g., psoriasis or inflammation). In certain embodiments, the compound is combined in a pharmaceutical combination formulation, or dosing regimen as combination therapy, with a second therapeutic compound that has anti-inflammatory properties or that is useful for treating an inflammation or immune-response disorder. The second therapeutic agent may be a NSAID or other anti-inflammatory agent. The second therapeutic agent of the pharmaceutical combination formulation or dosing regimen can have complementary activities to the compound of Formula I, II or III or any variation thereof such that they do not adversely affect each other. Such compounds are suitably present in combination in amounts that are effective for the purpose intended. In one embodiment, a composition of this invention comprises a compound of Formula I, II or III or any variation thereof, or a stereoisomer, geometric isomer, tautomer, solvate, metabolite, or pharmaceutically acceptable salt or prodrug thereof, in combination with a therapeutic agent such as an NSAID. Another embodiment, therefore, includes a method of treating or lessening the severity of a disease or condition responsive to the inhibition of TYK2 kinase in a patient, comprising administering to said patient a therapeutically effective amount of a compound of Formula I, II or III or any variation thereof described herein, and further comprising, administering a second therapeutic agent.

The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations. The combined administration includes coadministration, using separate formulations or a single pharmaceutical formulation, and consecutive administration in either order, wherein there is a time period while both (or all) active agents simultaneously exert their biological activities. Suitable dosages for any of the above coadministered agents are those presently used and may be lowered due to the combined action (synergy) of the newly identified agent and other chemotherapeutic agents or treatments.

In a particular embodiment of therapy, a compound of Formula I, II or III or any variation thereof described herein, or a stereoisomer, geometric isomer, tautomer, solvate, metabolite, or pharmaceutically acceptable salt or prodrug thereof, may be combined with other therapeutic, hormonal or antibody agents such as those described herein, as well as combined with surgical therapy and radiotherapy. Combination therapies according to the present invention thus comprise the administration of at least one compound of Formula I, II or III or any variation thereof described herein, or a stereoisomer, geometric isomer, tautomer, solvate, metabolite, or pharmaceutically acceptable salt or prodrug thereof, and the use of at least one other immunological disorder method. The amounts of the compound(s) of Formula I, II or III or any variation thereof described herein and the other pharmaceutically active immunologic agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

In one embodiment, compounds of the present invention are coadministered with any of anti-IBD agents, including but not limited to anti-inflammatory drugs, such as sulfasalazine, mesalamine or corticosteroids, such as budesonide, prednisone, cortisone or hydrocortisone, immune suppressing agents, such as azathioprine, mercaptopurine, infliximab, adalimumab, certolizumab pegol, methotrexate, cyclosporine or natalizumab, antibiotics, such as metronidazole or ciprofloxacin, anti-diarrheals, such as psyllium powder, loperamide or methylcellulose, laxatives, pain relievers, such as NSAIDs or acetaminophen, iron supplements, vitamin B supplements, vitamin D supplements and any combination of the above. In another example, compounds of the present invention are administered with (e.g., before, during or after) other anti-IBD therapies, such as surgery.

In one embodiment, compounds of the present invention are coadministered with any of anti-psoriasis agents, including but not limited to topical corticosteroids, vitamin D analogues, such as calcipotriene or calcitriol, anthralin, topical retinoids, such as tazarotene, calcineurin inhibitors, such as tacrolimus or pimecrolimus, salicylic acid, coal tar, NSAIDs, moisturizing creams and ointments, oral or injectible retinoids, such as acitretin, methotrexate, cyclosporine, hydroxyurea. immunomodulator drugs, such as alefacept, etanercept, infliximab or ustekinumab, thioguanine, and any combinations of the above. In another example, compounds of the present invention are administered with (e.g., before, during or after) other anti-psoriasis therapies, such as light therapy, sunlight therapy, UVB therapy, narrow-band UVB therapy, Goeckerman therapy, photochemotherapy, such as psoralen plus ultraviolet A (PUVA), excimer and pulsed dye laser therapy, or in any combination of antipsoriasis agents and anti-psoriasis therapies.

In one embodiment, compounds of the present invention are coadministered with any of anti-asthmatic agents, including but not limited to beta2-adrenergic agonists, inhaled and oral corticosteroids, leukotriene receptor antagonist, and omalizumab. In another embodiment, compounds of the present invention are coadministered with an anti-asthmatic agent selected from a NSAID, combinations of fluticasone and salmeterol, combinations of budesonide and formoterol, omalizumab, lebrikizumab and corticosteroid selected from fluticasone, budesonide, mometasone, flunisolide and beclomethasone.

Kits

The invention further provides kits for carrying out the methods of the invention, which comprises one or more compounds described herein (e.g., Formulae I, II, III and variations thereof) or a pharmacological composition comprising a compound described herein. The kits may employ any of the compounds disclosed herein. In one variation, the kit employs a compound described herein (e.g., Formulae I, II, III and variations thereof) or a pharmaceutically acceptable salt thereof. The kits may be used for any one or more of the uses described herein, and, accordingly, may contain instructions for the treatment of diseases, conditions and/or disorders responsive to the inhibition of TYK2 kinase activity in a patient.

Kits generally comprise suitable packaging. The kits may comprise one or more containers comprising any compound described herein. Each component (if there is more than one component) can be packaged in separate containers or some components can be combined in one container where cross-reactivity and shelf life permit.

The kits may be in unit dosage forms, bulk packages (*e.g.*, multi-dose packages) or sub-unit doses. For example, kits may be provided that contain sufficient dosages of a compound as disclosed herein (e.g., Formulae I, II, III and variations thereof) and/or a second pharmaceutically active compound useful for a disease detailed herein to provide effective treatment of an individual for an extended period, such as any of a week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 7 months, 8 months, 9 months, or more. Kits may also include multiple unit doses of the compounds and instructions for use and be packaged in quantities sufficient for storage and use in pharmacies (e.g., hospital pharmacies and compounding pharmacies).

The kits may optionally include a set of instructions, generally written instructions, although electronic storage media (e.g., magnetic diskette or optical disk) containing instructions are also acceptable, relating to the use of component(s) of the methods of the present invention. The instructions included with the kit generally include information as to the components and their administration to an individual.

Another embodiment includes a kit for treating a disease or disorder responsive to the inhibition of aTYK2 kinase. The kit includes:

(a) a first pharmaceutical composition comprising a compound of Formula I, II or III or any variation thereof; and

(b) instructions for use.

In another embodiment, the kit further includes:

(c) a second pharmaceutical composition, which includes an immunologic agent.

In one embodiment, the instructions include instructions for the simultaneous, sequential or separate administration of said first and second pharmaceutical compositions to a patient in need thereof.

In one embodiment, the first and second compositions are contained in separate containers.

In one embodiment, the first and second compositions are contained in the same container.

Containers for use include, for example, bottles, vials, syringes, blister pack, etc. The containers may be formed from a variety of materials such as glass or plastic. The container includes a compound of Formula I or formulation thereof which is effective for treating the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The container includes a composition comprising at least one compound of Formula I. The label or package insert indicates that the composition is used for treating the condition of choice, such as lupus. In one embodiment, the label or package inserts indicates that the composition comprising the compound of Formula I can be used to treat a disorder. In addition, the label or package insert may indicate that the patient to be treated is one having a disorder characterized by overactive or irregular kinase activity. The label or package insert may also indicate that the composition can be used to treat other disorders.

Also provided are articles of manufacture comprising a compound of Formula I, II or III or any variation thereof described herein, or a salt thereof, composition, and unit dosages described herein in suitable packaging for use in the methods described herein. Suitable packaging is known in the art and includes, for example, vials, vessels, ampules, bottles, jars, flexible packaging and the like. An article of manufacture may further be sterilized and/or sealed.

The article of manufacture may comprise (a) a first container with a compound of Formula I, II or III, or any variation thereof described herein, contained therein; and (b) a second container with a second pharmaceutical formulation contained therein, wherein the second pharmaceutical formulation comprises an immunologic agent. The article of manufacture in this embodiment of the invention may further comprise a package insert indicating that the first and second compounds can be used to treat patients at risk of stroke, thrombus or thrombosis disorder. Alternatively, or additionally, the article of manufacture may further comprise a second (or third) container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

In order to illustrate the invention, the following examples are included. However, it is to be understood that these examples do not limit the invention and are only meant to suggest a method of practicing the invention. Persons skilled in the art will recognize that the chemical reactions described may be readily adapted to prepare other compounds of Formula I, II or III or any variation thereof described herein, and alternative methods for preparing the compounds are within the scope of this invention. For example, the synthesis of non-exemplified compounds according to the invention may be successfully performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting interfering groups, by utilizing other suitable reagents known in the art other than those described, and/or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds of the invention.

EXAMPLES

The following Examples are provided to illustrate but not to limit the invention.

Compounds detailed herein may be prepared by those of skill in the art by referral to the General Method. Particular examples of the General Method are provided in the Examples below.

Abbreviations

AIBN	Azobisisobutyronitrile
$CDCl_3$	Deuterochloroform
mCPBA	3-Chloroperbenzoic acid
CDI	1,1'-Carbonyl diimidazole
Cs_2CO_3	Cesium carbonate
DCM	Dichloromethane
DCE	1,2-Dichloroethane
DIPEA	Diisopropylethylamine
DMAP	N,N-Dimethyl-4-aminopyridine
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
DMSO-d_6	Deuterodimethylsulfoxide
Eaton's reagent	7.7 wt% phosphorus pentoxide in methanesulfonic acid
EtOAc	Ethyl acetate
HCl	Hydrochloric acid
HPLC	High Pressure Liquid Chromatography
IMS	Industrial Methylated Spirits
LCMS	Liquid Chromatography Mass Spectrometry
MeOH	Methanol
MeOH-d_4	Deuteromethanol
$MgSO_4$	Magnesium sulfate
NMP	N-Methyl-2-pyrrolidone

NMR	Nuclear Magnetic Resonance
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
Pet. Ether	Petroleum Ether
$POCl_3$	Phosphoryl chloride
PyBrop	Bromo-tris-pyrrolidino phosphoniumhexafluorophosphate
RT	Retention time
TFA	Trifluoroacetic acid
TMSBr	Trimethylsilyl bromide
UHP	Urea hydrogen peroxide complex
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
PE-AX	ISOLUTE® PE-AX Columns

General Experimental Conditions

Compounds of this invention may be prepared from commercially available starting materials using the general methods illustrated herein. Specifically, 3-bromo-5-fluoropyridin-4amine, piperidine 3-carbonitrile and 3,4-diamino-2-chloropyridine were purchased from Ark Pharm Inc. (Libertyville, IL). 4,6-diaminopyrimidine was purchased from Allichem (Baltimore, MD). 6-chloropyrimidin-4-ylamine was purchased from Toronto Research Chemicals (North York, Ontario). 4-amino-2,6-dimethylpyrimidine and cyclopropanecarboxamide were purchased from Alfa Aesar (Ward Hill, MA). 4-amino-3-bromo-2-chloropyridine was purchased from Matrix Scientific (Columbia, SC). All commercial chemicals, including reagents and solvents, were used as received.

High Pressure Liquid Chromatography - Mass Spectrometry (LCMS) experiments to determine retention times (RT) and associated mass ions were performed using one of the following methods, with UV detector monitoring at 220 nm and 254 nm, and mass spectrometry scanning 110-800 amu in ESI+ ionization mode.

LCMS Analytical Methods

Final compounds were analyzed using a couple of LC/MS conditions, with UV detector monitoring at 220 nm and 254 nm, and mass spectrometry scanning 110-800 amu in ESI+ ionization mode.

Method A: Experiments performed on a Waters Micromass ZQ2000 quadrupole mass spectrometer linked to a Waters Acquity UPLC system with a PDA UV detector. The spectrometer has an electrospray source operating in positive and negative ion mode. This system uses an Acquity BEH C18 1.7 μm 100 x 2.1mm column, maintained at 40°C or an Acquity BEH Shield RP18 1.7 μm 100 x 2.1mm column, maintained at 40°C and a 0.4 ml / minute flow rate. The initial solvent system was 95% water containing 0.1% formic acid (solvent

A) and 5% acetonitrile containing 0.1% formic acid (solvent B) for the first 0.4 minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 5.6 minutes. This was maintained for 0.8 minute before returning to 95% solvent A and 5% solvent B over the next 1.2 minutes. Total run time was 8 minutes.

<u>Method B</u>: Experiments performed on a Waters Platform LC quadrupole mass spectrometer linked to a Hewlett Packard HP1100 LC system with a diode array and a Sedex 85 evaporative light scattering detector. The spectrometer has an electrospray source operating in positive and negative ion mode. This system uses a Phenomenex Luna 3 micron C18(2) 30 x 4.6mm column and a 2 ml / minute flow rate. The initial solvent system was 95% water containing 0.1% formic acid (solvent A) and 5% acetonitrile containing 0.1% formic acid (solvent B) for the first 0.5 minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 4.0 minutes. This was maintained for 1 minute before returning to 95% solvent A and 5% solvent B over the next 0.5 minute. Total run time was 6 minutes.

<u>Method C</u>: Experiments performed on a VG Platform II quadrupole mass spectrometer linked to a Hewlett Packard HP1050 LC system with diode array detector and 100 position autosampler, using a Phenomenex Luna 3 µm C_{18}(2) 30 x 4.6mm and a 2 mL/minute flow rate. The mobile phase consisted of formic acid 0.1% in water (solvent A) and formic acid 0.1% in acetonitrile (solvent B). The initial solvent system was 95% solvent A and 5% solvent B for the first 0.3 minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 4 minutes. The final solvent system was held constant for a further 1 minute.

<u>Method D</u>: column: AgilentSD-C18, 2.1 X 30 mm, 1.8 um; mobile phase: A water with 0.5% TFA, B CH_3CN with 0.5% TFA in 8.5 min; flow rate 0.4 mL/min; oven temperature 40 °C.

<u>Method E</u>: column: XBridge C18, 4.6 X 50 mm, 3.5 um; mobile phase: A water (0.01% ammonia), B CH_3CN; gradient: 5%-95% B in 8.0 min; flow rate: 1.2 mL/min; oven temperature 40 °C.

<u>Method F</u>: column: XBridge C18, 4.6 X 50 mm, 3.5 um; mobile phase: A water (10 mM ammonium hydrogen carbonate), B CH_3CN; gradient: 5%-95% B in 8.0 min; flow rate: 1.2 mL/min; oven temperature 40 °C.

<u>Method G</u>: column: XBridge C18, 4.6 X 50 mm, 3.5 um; mobile phase: A water (0.05% TFA), B CH_3CN (0.05% TFA); gradient: 5%-100% B in 1.6 min and hold at 100% AcCN for 1.4 min; flow rate: 2 mL/min; oven temperature 40 °C.

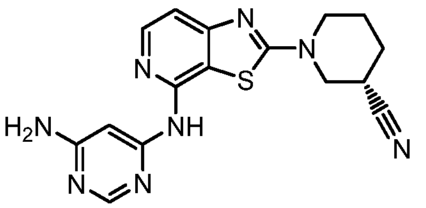
<u>Method H</u>: column: Phenomenex Onyx Monolithic C18, 4.6 X 50 mm, 3.5 um; mobile phase: A water (0.05% TFA), B CH_3CN (0.037% TFA); gradient: 2%-98% B in 3.2 min and hold at 98% AcCN for 0.4 min; flow rate: 2 mL/min; temperature 23 °C.

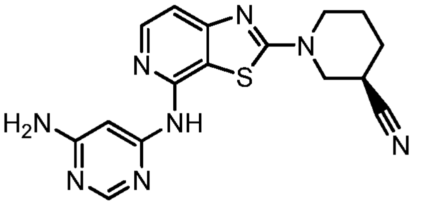
Retention time for each enantiomer was determined using either SFC or HPLC with a chiral column. The column and mobile phases used for each enantiomer are specified below in the Examples. Conditions are: column dimension: 4.6x50 mm, 3 um; flow rate: 5 mL/min; pressure: 120 bars; temperature: 40 °C.

^{1}H NMR spectra were recorded at ambient temperature using a Varian Unity Inova (400 MHz) spectrometer with a triple resonance 5 mm probe or a Bruker Avance DPX (300 MHz) spectrometer with a dual frequency 5 mm probe. Chemical shifts are expressed in ppm relative to tetramethylsilane. The following abbreviations have been used: br = broad signal, s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet.

Microwave experiments were carried out using a Biotage Initiator 60™ which uses a single-mode resonator and dynamic field tuning. Temperature from 40-250°C can be achieved, and pressures of up to 30 bar can be reached.

Example 1 and 2





(*S*)-and (*R*)-1-[4-(6-Aminopyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl]-piperidine-3-carbonitrile

Step 1. **4-chlorothiazolo[5,4-c]pyridine-2(1H)-thione** A mixture of 3-bromo-2-chloropyridin-4-amine (10 g, 48.2 mmol) and potassium ethyl xanthate (16.2 g, 101.2 mmol) in NMP (60 mL) was heated to 180 °C for 20 min when the reaction mixture turned dark red. The reaction mixture was cooled to 23 °C, poured into water and AcOH (10% v/v, 600 mL). The resulting precipitate was collected by filtration to give the desired product (8.37 g, 86 % yield) as grey solid. LCMS (Method G): RT = 1.36 min, m/z: 202 [M+H$^+$].

Step 2. **4-chloro-2-(methylthio)thiazolo[5,4-c]pyridine** To a solution of 4-chlorothiazolo[5,4-c]pyridine-2(1H)-thione (8.37 g, 41.4 mmol) in DMF (70 mL) was added K_2CO_3 (11.46 g, 82.9 mmol) at 23 °C. After the mixture was stirred for 10 min, methyl iodide (5.88 g, 41.1 mmol) was added dropwise. The resulting mixture was heated to 40 °C for 1 hour when monitoring the reaction by LCMS showed complete conversion. The mixture was poured into water and AcOH (10% v/v, 700 mL), and the resulting precipitate was collected by filtration. The filtrate was extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine (200 mL × 2), dried over Na_2SO_4, and concentrated via rotavap to give a grey residue. This residue was combined with the filter cake obtained above to give the desired product (6.6 g, 74% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28 (d, *J* = 9.0 Hz, 1H), 7.57 (d, *J* = 9.5 Hz, 1H), 2.75 (s, 3H). LCMS (Method G): RT = 1.59 min, m/z: 216 [M+H$^+$].

Step 3. **4-chloro-2-(methylsulfonyl)thiazolo[5,4-c]pyridine** To a solution of 4-chloro-2-(methylthio)thiazolo[5,4-c]pyridine (10 g, 46 ml) in DCM (300 ml) was added *m*CPBA (31 g, 138 mmol) at 0 °C. The mixture was stirred for 1 hour at 0 °C and then 3 hours at 23 °C to give a white suspension. The reaction mixture was filtered and the cake washed with DCM (30 mL× 3). The filtrate was washed with aq. $Na_2S_2O_3$ solution (10%, 200 mL), sat. $NaHCO_3$ solution (100 mL × 4) and brine (100 mL), respectively. The organic layer was dried over Na_2SO_4, and concentrated via rotavep. The crude product was recrystallized to give the desired product (6.8 g, 60% yield) as off-white solid. ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 8.79 (d, *J* = 10.0 Hz, 1H), 8.33 (d, *J* = 9.5 Hz, 1H), 3.68 (s, 3H). LCMS (Method G): RT = 1.49 min, m/z: 249 [M+H$^+$].

Step 4. (±)-**1-(4-chlorothiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile** A mixture of 4-chloro-2-methylsulfonyl-thiazolo[5,4-c]pyridine (4.97 g, 20.0 mmol), piperidine-3-carbonitrile (2.42 g, 22 mmol) and K_2CO_3 (5.53 g, 40.0 mmol) in DMF (5 mL) was stirred at room temperature for 2 hours when LCMS showed complete conversion. The reaction was quenched with dH_2O (100 mL), extracted with EtOAc (3x100 mL). The combined organics were dried (Na_2SO_4), filtered and concentrated via rotavap. The crude mixture was purified by silica gel column chromatography (0-8% MeOH/DCM) to give the title compound (5.28 g, 94.7% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 5.5 Hz, 1H), 7.31 (d, *J* = 5.5 Hz, 1H), 4.17 (dd, *J* = 13.4, 3.6 Hz, 1H), 3.82 (dd, *J* = 13.4, 7.9 Hz, 1H), 3.77 – 3.66 (m, 1H), 3.65 – 3.54 (m, 1H), 3.00 – 2.81 (m, 1H), 2.20 – 2.13 (m, 1H), 2.09 – 1.93 (m, 2H), 1.83 – 1.68 (m, 1H). LCMS m/z: 279.1 [M+H$^+$].

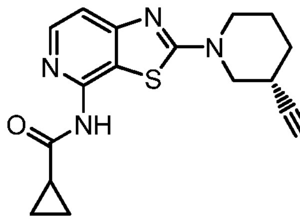
Step 5. **(*S*)-and (*R*)-1-[4-(6-Aminopyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl]-piperidine-3-carbonitrile** A mixture of (±)-1-(4-chlorothiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile (556 mg, 2.0 mmol), 6-amino-(pyrimidin-4-yl)-*bis*-carbamic acid *tert*-butyl ester (744 mg, 2.4 mmol), Cs_2CO_3 (1629 mg, 5.0 mmol), Xantphos (116 mg, 0.2 mmol), $Pd_2(dba)_3$ (92 mg, 0.1 mmol) in dioxane (15 mL) was degassed and re-filled with N_2. The mixture was sealed and irradiated in a microwave reactor at 140 ^{o}C for 1 hour. The reaction mixture was diluted with EtOAc (20 mL) and filtered. The filtrate was concentrated to give a yellow residue which was dissolved in DCM (50 mL). Conc. HCl (30 mL) was added dropwise and the mixture was stirred at 23 °C for 2 hours. The reaction mixture was diluted with *aq.* Na_2CO_3 solution (1M, 50 mL) and extracted with EtOAc (3x50 mL). Combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by chiral SFC (Phenomenex Lux-Cellulose-3 (21.2 x 150 mm, 5 um), 30% Methanol w/ 0.1% NH_4OH / 70% CO_2 (flow rate 70 mL/min, 100 Bars, column temperature 40 °C) to separate the two enantiomers.

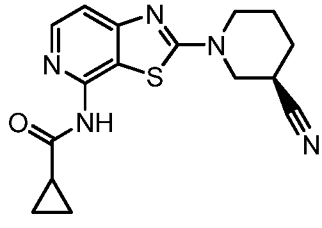
First eluting peak (69 mg, 10% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.37 (s, 1H), 8.09 (d, *J* = 5.5 Hz, 1H), 8.05 (s, 1H), 7.10 (d, *J* = 5.5 Hz, 1H), 6.53 (s, 1H), 6.47 (s, 2H), 4.01 (dd, *J* = 13.3, 5.9 Hz, 1H), 3.81 (dd, *J* = 13.3, 3.6 Hz, 1H), 3.78 – 3.69 (m, 1H), 3.54 – 3.45 (m, 1H), 3.26 – 3.20 (m, 1H), 1.99 – 1.90 (m, 2H), 1.82 – 1.64 (m, 2H). LCMS m/z: 353.1 [M+H$^+$] (RT = 0.55 min, Phenomenex Lux-Cellulose-3, 30% Methanol with 0.1% NH_4OH / 70% CO_2, flow rate 5 mL/min).

Second eluting peak (33 mg, 5% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.37 (s, 1H), 8.09 (d, *J* = 5.5 Hz, 1H), 8.06 (s, 1H), 7.10 (d, *J* = 5.5 Hz, 1H), 6.53 (s, 1H), 6.48 (s, 2H), 4.01 (dd, *J* = 13.3, 5.9 Hz, 1H), 3.81 (dd, *J* = 13.3, 3.5 Hz, 1H), 3.78 – 3.70 (m, 1H), 3.54 – 3.45 (m, 1H), 3.27 – 3.20 (m, 1H), 2.00 – 1.89 (m, 2H), 1.82 – 1.63 (m, 2H). LCMS m/z: 353.1 [M+H$^+$] (RT = 0.58 min, Phenomenex Lux-Cellulose-3, 30% Methanol with 0.1% NH_4OH / 70% CO_2, flow rate 5 mL/min).

Alternatively, (±)-**1-(4-chlorothiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile** could also be prepared by a one-pot procedure: A mixture of 4-chloro-2-methylsulfonyl-thiazolo[5,4-c]pyridine (100 mg, 0.4 mmol), piperidine-3-carbonitrile (49 mg, 0.4 mmol), potassium carbonate (117 mg, 0.8 mmol), Xantphos (6 mg, 0.01 mmol), Cs_2CO_3 (397 mg, 1.2 mmol), 4,6-diaminopyrimidine (133 mg, 1.2 mmol) and $Pd_2(dba)_3$ (12 mg, 0.01 mmol) in DMF (1 mL) and 1,4-dioxane (1 mL) was heated in a microwave reactor at 150 °C for 10 minutes. The resulting mixture was filtered and the filter cake washed with ethyl acetate. Combined filtrate was washed with saturated $NaHCO_3$ solution and brine. The aqueous layer was further extracted with DCM (x2) and the combined organic extracts were dried ($MgSO_4$), concentrated and purified by flash column chromatography (0-10% methanol in DCM) to yield a crude title compound. The crude material was further purified by prep-HPLC to yield the title compound (racemic mixture) as a pale yellow powder (58 mg, 41% yield).

Example 3 and 4





(S)-and (R)-N-(2-(3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridine-4-yl)cyclopropanecarboxamide

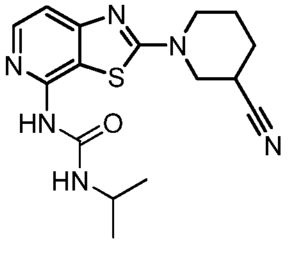
A mixture of 4-chloro-2-methanesulfonylthiazolo[5,4-c]pyridine (400 mg, 1.6 mmol), potassium carbonate (445 mg, 3.2 mmol), piperidine-3-carbonitrile (200 mg, 1.6 mmol), Xantphos (48 mg, 0.08 mmol), Cs_2CO_3 (1048 mg, 3.2 mmol), cyclopropanecarboxamide (410 mg, 4.8 mmol) and

$Pd_2(dba)_3$ (74 mg, 0.08 mmol) in DMF (1 mL) and 1,4-dioxane (1 mL) was heated in a microwave reactor at 150 °C for 10 minutes.. The resulting mixture was filtered and the filtrate cake was washed with ethyl acetate. Combined filtrate was washed with sat. $NaHCO_3$ solution and brine. The aqueous layer was further extracted with DCM (x2) and the combined organic extracts were dried ($MgSO_4$), concentrated and purified by flash column chromatography (0-10% methanol in DCM) to yield the title compound (302 mg, 57% yield) as a racemic mixture. The crude material was further purified by chiral SFC (Column: Chiralpak IB 21.2 x 150mm, 5 um, mobile Phase: 30% Methanol w/ 0.1% NH_4OH / 70% CO_2, flow rate 70 mL/min, pressure: 100 Bars, temp: 40 °C) to give pure enantiomers.

First eluting peak (113 mg, 21% yield): ^1H NMR (400 MHz, DMSO-d_6) δ 10.89 (s, 1H), 8.12 (d, J = 5.5 Hz, 1H), 7.21 (d, J = 5.5 Hz, 1H), 4.00 (dd, J = 13.3, 6.0 Hz, 1H), 3.80 (dd, J = 13.4, 3.6 Hz, 1H), 3.75 (d, J = 13.4 Hz, 1H), 3.56 – 3.45 (m, 1H), 3.25 – 3.18 (m, 1H), 2.05 – 1.87 (m, 3H), 1.74 (ddd, J = 12.9, 9.6, 4.9 Hz, 2H), 0.85 (d, J = 6.2 Hz, 3H). LCMS m/z: 327 [$M+H^+$] (RT = 0.69 min, Chiralpak IB 4.6 x 50mm, 5um, 25% Ethanol w/ 0.1% NH_4OH / 75% CO_2, Flow rate: 5 mL/min, Pressure: 120 Bars, Temp: 40 °C).

Second eluting peak (120 mg, 22% yield): ^1H NMR (400 MHz, DMSO-d_6) δ 10.89 (s, 1H), 8.12 (d, J = 5.5 Hz, 1H), 7.20 (d, J = 5.5 Hz, 1H), 4.00 (dd, J = 13.3, 5.9 Hz, 1H), 3.80 (dd, J = 13.4, 3.6 Hz, 1H), 3.77 – 3.69 (m, 1H), 3.49 (ddd, J = 18.5, 8.9, 4.9 Hz, 1H), 3.25 – 3.18 (m, 1H), 2.04 – 1.86 (m, 3H), 1.82 – 1.63 (m, 2H), 0.84 (d, J = 6.2 Hz, 4H). LCMS m/z: 327 [$M+H^+$] (RT = 0.74 min, Chiralpak IB 4.6 x 50 mm, 5 um, 25% Ethanol w/ 0.1% NH_4OH / 75% CO_2, Flow rate: 5 mL/min, Pressure: 120 Bars, Temp: 40 °C).

Example 5



(±)-1-(2-(3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)-3-isopropylurea

Step 1. **4-bromo-2-(methylthio)thiazolo[5,4-c]pyridine.** To a suspension of 4-chloro-2-methylsulfanyl-thiazolo[5,4-c]pyridine (5.0 g, 23.1 mmol) in propionitrile (70 mL) was added bromo(trimethyl)silane (17.7 g, 115 mmol). The reaction mixture was heated at 115 °C under N_2. After 25 hours, additional TMSBr (5.0 g, 32 mmol) was added and the mixture was heated at 115 °C for another 22 hours. The mixture was then cooled to room temperature and a suspension resulted. The solid was collected by filtration, washed with Et_2O to give the title compound (7.43

g, quantitative yield) as a yellow solid. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.39 (d, J = 5.8 Hz, 1H), 7.85 (d, J = 5.8 Hz, 1H), 2.88 (s, 3H). LCMS m/z: 262.0 [M+H$^+$].

Step 2. **4-bromo-2-methylsulfonyl-thiazolo[5,4-c]pyridine.** To a suspension of 4-bromo-2-methylsulfanyl-thiazolo[5,4-c]pyridine(7.16 g, 27.4 mmol) in dichloromethane (200 mL) was added *m*-CPBA (14.1 g, 63.0 mmol) portion-wise. The reaction mixture was stirred at room temperature for 18 hours. The mixture was then washed with aq. 10% $Na_2S_2O_3$ solution, sat. $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4), filtered and concentrated. The crude product was purified by silica flash chromatography (0-5% EtOAc/DCM) to give the title compound (14.0 g, 49.8% yield) as a white solid. LCMS m/z: 295.0 [M+H$^+$].

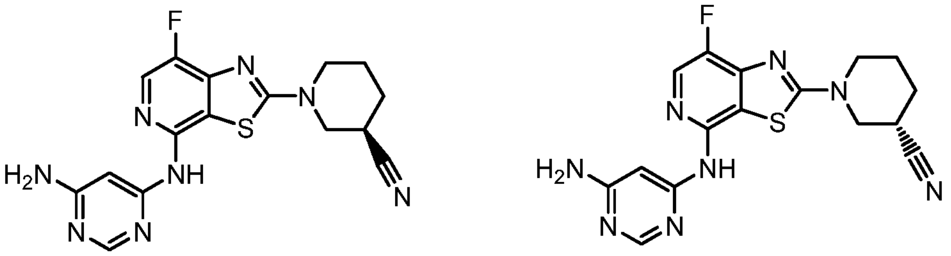
Step 3. (±)-**1-(4-bromothiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile.** A mixture of 4-bromo-2-methylsulfonyl-thiazolo[5,4-c]pyridine (1.35 g, 4.60 mmol), piperidine-3-carbonitril (558 mg, 5.06 mmol), K_2CO_3 (1.27 g, 9.21 mmol) and DMF (4 mL) was stirred at room temperature for 1.5 hours. The reaction mixture was quenched with water. The precipitated solid was collected by filtration, washed with water, dried in high vacuum to give the title compound (1.336 g, 89.8% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (d, J = 5.5 Hz, 1H), 7.42 (d, J = 5.5 Hz, 1H), 4.06 (dd, J = 13.3, 5.6 Hz, 1H), 3.85 (dd, J = 13.4, 3.5 Hz, 1H), 3.82 -3.76 (m, 1H), 3.61 – 3.51 (m, 1H), 3.28 - 3.24 (m, 1H), 2.02 – 1.92 (m, 2H), 1.82 – 1.67 (m, 2H). LCMS m/z: 325.1 [M+H$^+$].

Step 4. (±)-**1-(4-aminothiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile.** A mixture of 1-(4-bromothiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile (323 mg, 1.0 mmol), *tert*-butyl carbamate (702 mg, 6.0 mmol), $Pd_2(dba)_3$ (46 mg, 0.05 mmol), Xantphos (58 mg, 0.1 mmol) toluene (10 mL) and K_3PO_4 (1.27 M, 7.87 mL) was heated at 65 °C in an oil bath under N_2 for 3 hours. The reaction mixture was filtered through celite, washed with EtOAc, and then concentrated via rotavap. The crude mixture was purified by silica gel column chromatography (0-10% MeOH/DCM) to give *tert*-butyl N-[2-(3-cyano-1-piperidyl)thiazolo[5,4-c]pyridin-4-yl]carbamate (240 mg, 66.8% yield) as a yellow solid. LCMS m/z: 360.2 [M+H$^+$].

To the above yellow solid was added DCM (3 mL), followed by TFA (0.5 mL). The reaction mixture was stirred at room temperature for 1.5 hours. The mixture was then concentrated. The resultant residue was loaded onto an ISOLUTE SCX-2 column, washed with MeOH to elute non-basic impurities, and then washed with 7 N ammonia in MeOH to elute the desired product. The relevant fractions were combined and concentrated. The resultant solid was triturated with MeOH to give the title compound (150 mg, 57.8% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (d, J = 5.6 Hz, 1H), 6.70 (d, J = 5.6 Hz, 1H), 6.09 (s, 2H), 3.95 (dd, J = 13.2, 6.0 Hz, 1H), 3.79 (dd, J = 13.2, 3.6 Hz, 1H), 3.75 – 3.68 (m, 1H), 3.50 – 3.43 (m, 1H), 3.25 – 3.21 (m, 1H), 2.00 – 1.92 (m, 2H), 1.81 – 1.66 (m, 2H). LCMS m/z: 260.2 [M+H$^+$].

Step 5. (±)-**1-(2-(3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)-3-isopropylurea.** To a suspension of 1-(4-aminothiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile (50 mg, 0.19 mmol) in 1,2-dichloroethane (3 mL) was added 2-isocyanatopropane (100 mg, 1.16 mmol). The mixture was heated at 80 °C under N_2 for 18 hours. The mixture was then concentrated, and purified by reverse phase HPLC (5-50% gradient of CH_3CN in 0.1% NH_4OH/water over 10 min) to give the title compound (11.4 mg, 17.2% yield) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.00 (d, *J* = 5.6 Hz, 1H), 7.05 (d, *J* = 5.6 Hz, 1H), 6.73 (s, 1H), 3.99 (dd, *J* = 13.2, 5.9 Hz, 1H), 3.84 -3.72 (m, 3H), 3.53 – 3.44 (m, 1H), 3.24 - 3.22 (m 1H), 1.98 - 1.93 (m, 2H), 1.78 - 1.68 (m, 2H), 1.14 (d, *J* = 6.5 Hz, 6H). LCMS m/z: 345.1 [M+H^+].

Examples 6 and 7



(S)- and (R)-1-[4-(6-Aminopyrimidin-4-ylamino)-7-fluorothiazolo[5,4-c]pyridin-2-yl]-piperidine-3-carbonitrile

Step 1. **7-Fluoro-1H-thiazolo[5,4-c]pyridine-2-thione.** To a solution of 4-amino-3,5-difluoropyridine (4.87 g, 37.4 mmol) in NMP (30 mL) was added potassium ethyl xanthate (8.71 g, 54.0 mmol). The reaction mixture was heated in the microwave reactor at 200 °C for 20 minutes, then cooled to room temperature and poured into water. After stirring for 10 minutes, the product was collected by filtration and washed with water. The product was dried *in vacuo* to afford the title compound as a pale yellow powder (2.97 g, 43% yield). ^1H NMR (300 MHz, DMSO-d_6): δ 8.65 (d, *J* = 1.1 Hz, 1H), 8.51 (d, *J* = 3.0 Hz, 1H). LCMS (Method B): RT = 1.89 min, m/z: 187 [M+H^+].

Step 2. **7-Fluoro-2-methanesulfanylthiazolo[5,4-c]pyridine.** To a suspension of 7-fluoro-1H-thiazolo[5,4-c]pyridine-2-thione (2.58 g, 13.87 mmol) in DMF (20 mL) was added cesium carbonate (8.783 g, 26.7 mmol). The resultant mixture was stirred for 5 minutes before methyl iodide (0.9 mL, 17.7 mmol) was added dropwise over 30 minutes and the reaction mixture was stirred at 23 °C for 3 hours. The resultant mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (x2) and the combined organic extracts were washed with water, then brine, dried ($MgSO_4$) and concentrated under vacuum. The resultant solid was triturated with isopropanol, filtered and dried to afford the title compound as a pale yellow solid (2.04 g, 74% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.81 (d, *J* = 0.9 Hz, 1H), 8.44 (d, *J* = 2.2 Hz, 1H), 2.87 (s, 3H). LCMS (Method C): RT = 2.51 min, m/z: 201 [$M+H^+$].

Step 3. **7-Fluoro-2-methanesulfonylthiazolo[5,4-c]pyridine-5-oxide.** To a cooled (ice bath) suspension of urea-hydrogen peroxide (14.89 g, 158 mmol) in acetonitrile (200 mL) was slowly added trifluoroacetic anhydride (17.0 mL, 122 mmol). The resultant mixture was stirred for 30 minutes, then 7-fluoro-2-methanesulfanylthiazolo[5,4-c]pyridine (4.28 g, 21.3 mmol) was added and the reaction mixture was stirred for 1 hour and then slowly allowed to warm to room temperature. The resultant mixture was then partitioned between DCM and water. The aqueous layer was extracted with DCM (x2), and the combined organic extracts were dried ($MgSO_4$) and concentrated under vacuum. The resultant solid was triturated with isopropanol, filtered and dried to afford the title compound as a pale yellow powder (4.67 g, 88% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.71 (dd, *J* = 1.2, 1.4 Hz, 1H), 8.35 (dd, *J* = 1.7, 5.1 Hz, 1H), 3.48 (s, 3H). LCMS (Method B): RT = 1.70 min, m/z: 249 [$M+H^+$].

Step 4. **4-Chloro-7-fluoro-2-methanesulfonylthiazolo[5,4-c]pyridine.** To a suspension of 7-fluoro-2-methanesulfonylthiazolo[5,4-c]pyridine-5-oxide (4.10 g, 16.5 mmol) in dichloroethane (100 mL) was added phosphorus oxychloride (4.0 mL, 42 mmol) and the reaction mixture was heated at 70 °C for 2 hours. The resultant mixture was allowed to cool to room temperature, quenched with ice and was then extracted with DCM (x2). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (DCM) to yield the title compound as a white solid (2.19 g, 50% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.46 (d, *J* = 1.8 Hz, 1H), 3.49 (1H, s).

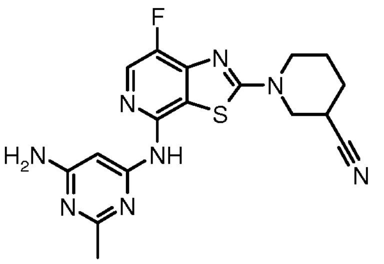
Step 5. **(±)-1-(4-Chloro-7-fluorothiazolo[5,4-c]pyridin-2-yl)-piperidine-3-carbonitrile**. To a solution of 4-chloro-7-fluoro-2-methanesulfonylthiazolo[5,4-c]pyridine (1.10 g, 4.1 mmol) in acetonitrile (5.0 mL) was added potassium carbonate (1.09 g, 7.9 mmol) and 3-cyanopiperidine (0.50 g, 4.6 mmol). The reaction mixture was stirred at room temperature for 1 hour before pouring into water. The resultant precipitate was collected by filtration and dried under vacuum to yield the title compound as a white powder (1.18 g, 96% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13 (d, *J* = 2.4 Hz, 1H), 4.16 (dd, *J* = 3.8, 13.4 Hz, 1H), 3.90 (dd, *J* = 7.6, 13.6 Hz, 1H), 3.78-3.61 (m, 2H), 2.98-2.88 (m, 1H), 2.22-1.96 (m, 3H), 1.86-1.71 (m, 1H). LCMS (Method C): RT = 3.13 min, m/z: 297 [$M+H^+$].

Step 6. (±)-**1-[4-(6-Aminopyrimidin-4-ylamino)-7-fluorothiazolo[5,4-c]pyridin-2-yl]-piperidine-3-carbonitrile.** A mixture of (±)-1-(4-chloro-7-fluorothiazolo[5,4-c]pyridin-2-yl)-piperidine-3-carbonitrile (0.332 g, 1.1 mmol), Xantphos (64 mg, 0.11 mmol), Cs_2CO_3 (0.796 g, 2.44 mmol) and 6-amino-(pyrimidin-4-yl)-*bis*-carbamic acid *tert*-butyl ester (0.341 g, 1.09 mmol) was purged with argon for two minutes. $Pd_2(dba)_3$ (48 mg, 0.052 mmol) was added, purged with argon for a further two minutes and the reaction mixture was then heated at 80 °C for 16 hours. Further Xantphos (64 mg, 0.11 mmol) and $Pd_2(dba)_3$ (0.132 g, 0.14 mmol) were added and the reaction mixture was heated at 80 °C for 24 hours. The resultant mixture was poured into ethyl acetate, dried ($MgSO_4$) and concentrated to yield a brown solid. To this crude residue was added DCM (5.0 mL) and TFA (5.0 mL). The resultant solution was stirred for 90 minutes, diluted with DCM (150 mL) and then carefully washed with saturated sodium hydrogen carbonate solution. The aqueous layer was further extracted with DCM (x2) and the combined organic extracts were dried ($MgSO_4$), concentrated and purified by flash column chromatography (0-10% methanol in DCM) to yield the title compound as a pale yellow powder. The crude product was purified by chiral SFC (Chiralpak OJ (21.2 x 250 mm, 5 um), 30% Methanol w/ 0.1% NH_4OH / 70% CO_2, flow rate 70 mL/min, 100 Bars, column temperature 40 °C) to give a pair of enantiomers.

First eluted peak (21 mg, 5% yield): ^1H NMR (400 MHz, DMSO-d_6) δ 9.45 (s, 1H), 8.10 (d, J = 2.3 Hz, 1H), 8.04 (s, 1H), 6.47 (s, 2H), 6.30 (s, 1H), 4.05 (dd, J = 13.5, 5.8 Hz, 1H), 3.82 (dd, J = 13.4, 3.5 Hz, 1H), 3.78 – 3.72 (m, 1H), 3.56 – 3.46 (m, 1H), 3.27 – 3.23 (m, 1H), 1.98 – 1.93 (m, 2H), 1.82 – 1.65 (m, 2H). LCMS m/z: 370.0 [$M+H^+$] (RT = 0.60 min, Chiralpak OJ, 25% Methanol w/ 0.1% NH_4OH / 75% CO_2, flow rate 5 mL/min).

Second elute peak (19 mg, 5% yield): ^1H NMR (400 MHz, DMSO-d_6) δ 9.45 (s, 1H), 8.10 (d, J = 2.3 Hz, 1H), 8.04 (s, 1H), 6.47 (s, 2H), 6.30 (s, 1H), 4.05 (dd, J = 13.4, 5.8 Hz, 1H), 3.82 (dd, J = 13.4, 3.5 Hz, 1H), 3.79 – 3.72 (m, 1H), 3.57 – 3.47 (m, 1H), 3.27 – 3.23 (m, 1H), 1.98 – 1.93 (m, 2H), 1.82 – 1.65 (m, 2H). LCMS m/z: 370.0 [M+H+] (RT = 0.66 min, Chiralpak OJ, 25% Methanol w/ 0.1% NH_4OH / 75% CO_2, 5 mL/min).

Example 8



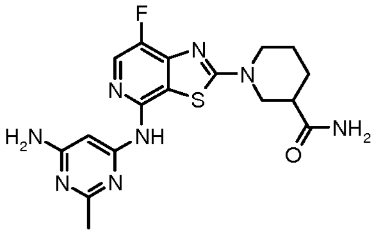
(±)-1-[4-(6-Amino-2-methylpyrimidin-4-ylamino)-7-fluorothiazolo[5,4-c]pyridin-2-yl]-piperidine-3-carbonitrile

Step 1. **(±)-1-[4-(6-Amino-2-methylpyrimidin-4-yl)-*bis*-carbamic acid *tert*-butyl ester-7-fluoro-thiazolo[5,4-c]pyridin-2-yl]-piperidine-3-carbonitrile**. A mixture of (±)-1-(4-chloro-7-fluorothiazolo[5,4-c]pyridin-2-yl)-piperidine-3-carbonitrile (78 mg, 0.26 mmol), (6-amino-2-methylpyrimidin-4-yl)-*bis*-carbamic acid *tert*-butyl ester (93.9 mg, 0.29 mmol), Xantphos (15.1

mg, 0.026 mmol) and Cs_2CO_3 (169.4 mg, 0.52 mmol) in 1,4-dioxane (2.5 mL) was de-gassed with a stream of argon for 10 minutes. $Pd_2(dba)_3$ (11.9 mg, 0.013 mmol), was added and the reaction mixture heated in a sealed vial at 90 °C overnight. The resultant mixture was allowed to cool, and further $Pd_2(dba)_3$ (11.9 mg, 0.013 mmol) and Xantphos (15.1 mg, 0.026 mmol) were added and the reaction mixture was heated at 90 °C overnight. After cooling to room temperature, the crude mixture was filtered through Celite®, washing with EtOAc, DCM and then DCM (1% MeOH) and the combined organic washings were concentrated to dryness under reduced pressure. The resultant residue was purified by column chromatography on silica gel (0-50% EtOAc/petroleum ether) to afford the title compound as an off-white solid (120 mg, 79% yield). LCMS (Method A): RT = 3.57 min, m/z: 586 [M+H$^+$].

Step 2. **(±)-1-[4-(6-Amino-2-methylpyrimidin-4-ylamino)-7-fluorothiazolo[5,4-c]pyridin-2-yl]-piperidine-3-carbonitrile.** A mixture of (±)-1-[4-(6-amino-2-methylpyrimidin-4-yl)-bis-carbamic acid *tert*-butyl ester-7-fluorothiazolo[5,4-c]pyridin-2-yl]-piperidine-3-carbonitrile (114 mg, 0.20 mmol) in HCl (4 N in 1,4-dioxane, 2.0 mL) was heated at 50 °C under a nitrogen atmosphere for 3 hours. After cooling to room temperature, the volatiles were removed under reduced pressure. The resultant residue was purified by column chromatography on silica gel (0-10% MeOH in DCM) to afford the title compound as an off-white solid (60 mg, 80% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.41 (s, 1H), 8.03 (d, J = 2.2 Hz, 1H), 6.34 (br s, 2H), 6.03 (s, 1H), 3.98 (dd, J = 5.6, 13.3 Hz, 1H), 3.81-3.68 (m, 2H), 3.49-3.41 (m, 1H), 3.24-3.16 (m, 1H), 2.19 (s, 3H), 1.95-1.87 (m, 2H), 1.79-1.60 (m, 2H). LCMS (Method A): RT = 2.63 min, m/z: 385 [M+H$^+$].

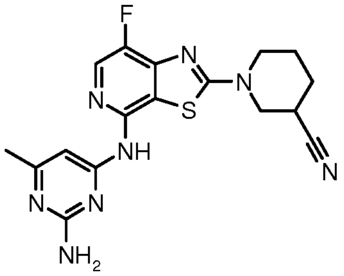
Example 9



(±)-1-[4-(6-Amino-2-methylpyrimidin-4-ylamino)-7-fluorothiazolo[5,4-c]pyridin-2-yl]-piperidine-3-carboxylic acid amide.

Also isolated during the purification of (±)-1-[4-(6-amino-2-methylpyrimidin-4-ylamino)-7-fluorothiazolo[5,4-c]pyridin-2-yl]-piperidine-3-carbonitrile (Example 8) was the title compound as an off-white solid (6.0 mg, 8% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.33 (s, 1H), 8.00 (d, J = 2.4 Hz, 1H), 7.39 (s, 1H), 6.91 (s, 1H), 6.33 (br s, 2H), 6.06 (s, 1H), 4.19-3.73 (m, 2H), 3.24-3.10 (m, 2H), 2.42-2.31 (m, 1H), 2.22 (s, 3H), 1.97-1.37 (m, 4H). LCMS (Method A): RT = 2.29 min, m/z: 403 [M+H$^+$].

Example 10



(±)-1-[4-(2-Amino-6-methylpyrimidin-4-ylamino)-7-fluorothiazolo[5,4-c]pyridin-2-yl]-piperidine-3-carbonitrile

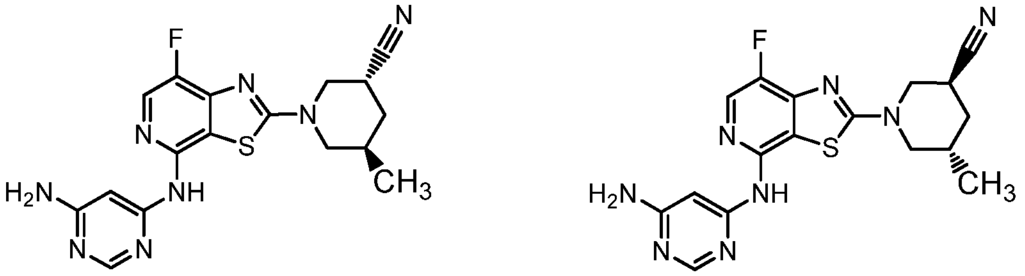
Step 1. **(±)-1-(7-Fluoro-5-oxythiazolo[5,4-c]pyridin-2-yl)-piperidine-3-carbonitrile.** To a solution of 3-cyanopiperidine (1.11 g, 10.1 mmol) in acetonitrile (20 mL) was added 7-fluoro-2-methanesulfonylthiazolo[5,4-c]pyridine-5-oxide (2.53 g, 10.2 mmol). The reaction mixture was stirred at room temperature for 3 hours and then partitioned between DCM and water. The aqueous layer was extracted with DCM (x2) and the combined organic extracts were dried ($MgSO_4$) and concentrated to dryness under reduced pressure. The resultant crude residue was re-crystallized from propan-2-ol to yield the title compound as a white powder (1.50 g, 53% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.68 (d, J = 1.7 Hz, 1H), 8.42 (dd, J = 6.4, 1.6 Hz, 1H), 4.02 (dd, J = 13.4, 5.5 Hz, 1H), 3.81 (dd, J = 13.4, 3.7 Hz, 1H), 3.81-3.71 (m, 1H), 3.52 (ddd, J = 12.7, 7.9, 4.4 Hz, 1H), 3.32-3.21 (m, 1H), 2.00-1.89 (m, 2H), 1.80-1.66 (m, 2H).

Step 2. **(±)-1-(4-Bromo-7-fluorothiazolo[5,4-c]pyridin-2-yl)-piperidine-3-carbonitrile.** To a suspension of (±)-1-(7-fluoro-5-oxythiazolo[5,4-c]pyridin-2-yl)-piperidine-3-carbonitrile (1.50 g, 5.4 mmol) in acetonitrile (60 mL) was added phosphorus oxybromide (4.14 g, 14.4 mmol) and the reaction mixture was heated at 80 °C for 1 hour. A second portion of phosphorus oxybromide was added (2.56 g, 9.0 mmol) and the reaction mixture heated at 80 °C for another 1 hour. A third portion of phosphorus oxybromide was then added (5.21 g, 18 mmol), and after heating at 80 °C for additional 1 hour, the reaction mixture was cooled to room temperature and then poured onto ice. The resultant mixture was extracted with ethyl acetate and the organic extracts were washed with water (x2), dried ($MgSO_4$) and concentrated to dryness under reduced pressure. The resultant crude residue was triturated with propan-2-ol and dried to yield the title compound as a white powder (1.01 g, 55% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.28 (d, J = 2.7 Hz, 1H), 4.10 (dd, J = 13.0, 4.4 Hz, 1H), 3.85 (dd, J = 13.5, 3.6 Hz, 2H), 3.66-3.51 (m, 1H), 3.34-3.22 (m, 1H), 2.05-1.90 (m, 2H), 1.84-1.68 (m, 2H).

Step 3. **(±)-1-[4-(2-Amino-6-methylpyrimidin-4-ylamino)-7-fluorothiazolo[5,4-c]pyridin-2-yl]-piperidine-3-carbonitrile.** To a mixture of 1-(4-bromo-7-fluorothiazolo[5,4-c]pyridin-2-yl)-piperidine-3-carbonitrile (0.187 g, 0.55 mmol), Xantphos (0.037 g, 0.064 mmol), $Pd_2(dba)_3$

(0.026 g, 0.028 mmol), Cs_2CO_3 (0.384 g, 1.17 mmol) and (4-amino-6-methylpyrimidin-2-yl)-*N*,*N*-*bis*-carbamic acid *tert*-butyl ester (0.217 g, 0.67 mmol), was added dioxane (5 mL). The reaction mixture was purged with argon for five minutes, and then heated at 80 °C for 20 hours. The resultant mixture was poured into ethyl acetate, dried ($MgSO_4$) and concentrated to dryness. The crude residue was dissolved in DCM (5 mL), TFA (5 mL) was added and the reaction mixture stirred at room temperature for 1h. The resultant mixture was diluted with DCM and washed with saturated sodium hydrogen carbonate solution. The aqueous layer was further extracted with DCM and the combined organic extracts were dried ($MgSO_4$) and concentrated to dryness. The resultant crude residue was purified by column chromatography on silica gel (4-10% MeOH in DCM) to afford the title compound as a pale yellow solid (0.048 g, 23% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.57 (br s, 1H), 8.06 (d, *J* = 2.2 Hz, 1H), 6.09 (br s, 1H), 6.08 (br s, 1H), 3.99 (dd, *J* = 13.0, 5.6 Hz, 1H), 3.77 (dd, *J* = 13.4, 4.4 Hz, 1H), 3.77-3.66 (m, 1H), 3.49 (ddd, *J* = 12.0, 7.7, 3.6 Hz, 1H), 3.24-3.17 (m, 1H), 2.06 (s, 3H), 1.98-1.85 (m, 2H), 1.80-1.62 (m, 2H). LCMS (Method A): RT = 2.46 min, m/z: 385 [M+H$^+$].

Example 11 and 12



(3R,5R/3S,5S)-1-[4-(6-Aminopyrimidin-4-ylamino)-7-fluorothiazolo[5,4-c]pyridin-2-yl]-5-methylpiperidine-3-carbonitrile

Step 1. **3-Carbamoyl-5-methylpiperidine-1-carboxylic acid *tert*-butyl ester (mixture of *cis* and *trans* isomers).** To a suspension of 5-methylnicotinamide (3.05 g, 22.4 mmol) in absolute ethanol (110 mL) was added platinum oxide (0.698 g, 3.07 mmol) and concentrated sulphuric acid (4 mL). The reaction mixture was stirred under an atmosphere of hydrogen (3.8 bar pressure) for 24 hours. The resultant mixture was then purged with nitrogen, filtered through a pad of Celite, washed with propan-2-ol (x2) and concentrated under reduced pressure. The residue obtained was suspended in THF (100 mL), then ~10% aqueous sodium carbonate (7.01 g Na_2CO_3 in 70 mL water, 66 mmol) and di-*tert*-butyl dicarbonate (10.27 g, 47.0 mmol) were added. The resultant mixture was stirred for 17 hours, then quenched by addition of *N*,*N*-dimethylethylenediamine (4.0 mL). After stirring for 30 minutes, this mixture was poured into DCM and washed with 0.2 N HCl (x2). The organic extracts were dried (Na_2SO_4), concentrated and the resultant residue obtained was triturated with a mixture of cyclohexane:DCM (4:1) to afford the title compounds (0.78 g, 14% yield) as a white solid. The trituration supernatant was concentrated and was then triturated with cyclohexane to yield a second crop of the title product as a white solid (0.91 g, 17% yield). LCMS (Method C): RT = 2.57 min, m/z: 243 [M+H$^+$].

Step 2. **3-Carbamoyl-5-methylpiperidine-1-carboxylic acid *tert*-butyl ester (mixture of *cis* and *trans* isomers).** To a solution of *cis* and *trans* 3-carbamoyl-5-methylpiperidine-1-carboxylic acid *tert*-butyl esters (1.69 g, 6.98 mmol) in DCM (20 mL) was added Burgess's reagent [methyl *N*-(triethylammoniumsulfonyl)carbamate] (2.06 g, 8.60 mmol) and the reaction mixture was stirred for 19 hours. The resultant mixture was poured into ethyl acetate. And was then washed with water (x2), brine, dried (Na_2SO_4) and then concentrated under reduced pressure to yield a mixture of the title compounds as a colorless oil (1.42 g, 91% yield). LCMS (Method C): RT = 3.21, 3.42 min, m/z: 225 [M+H$^+$].

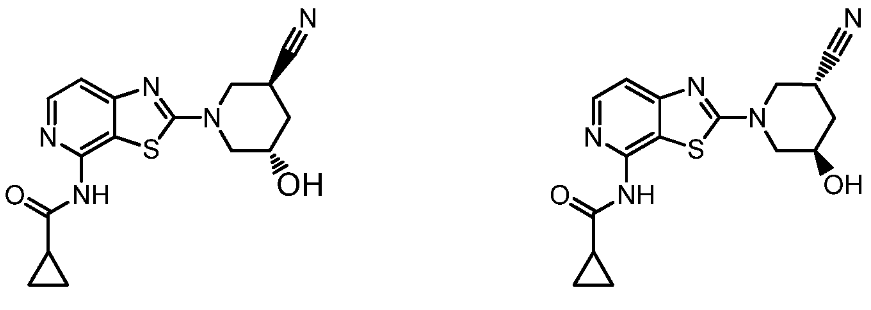
Step 3. **(3S,5R/3R,5S)-1-(4-Chloro-7-fluorothiazolo[5,4-c]pyridin-2-yl)-5-methylpiperidine-3-carbonitrile** (Isomer 1) and **(3R,5R/3S,5S)-1-(4-Chloro-7-fluorothiazolo[5,4-c]pyridin-2-yl)-5-methylpiperidine-3-carbonitrile** (Isomer 2). To a mixture of *cis* and *trans* carbamoyl-5-methyl-piperidine-1-carboxylic acid *tert*-butyl esters (0.48 g, 2.13 mmol) was added HCl solution (4N in dioxane, 20 mL, 80 mmol). The reaction mixture was stirred for 30 minutes, then concentrated under vacuum. The resultant residue was suspended in acetonitrile (20 mL), then potassium carbonate (2.85 g, 20.5 mmol) and 4-chloro-7-fluoro-2-methanesulfonylthiazolo[5,4-c]pyridine (0.63 g, 2.35 mmol) were added. The reaction mixture was stirred at room temperature for 3 hours and then quenched with water. The resultant mixture was extracted with DCM (x3), and the combined organic extracts were dried ($MgSO_4$) and then concentrated under reduced pressure. The resultant residue was purified by column chromatography on silica gel (0-50% ethyl acetate in cyclohexane) to afford (3S,5R/3R,5S)-1-(4-chloro-7-fluorothiazolo[5,4-c]pyridin-2-yl)-5-methylpiperidine-3-carbonitrile as a pale yellow solid: (0.167 g, 25%, first eluting, *cis* isomer): ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.30 (d, *J* = 2.7 Hz, 1H), 4.56-4.32 (m, 1H), 4.09-3.84 (m, 1H), 3.49 (t, *J* = 11.6 Hz, 1H), 3.24-3.10 (m, 1H), 3.02 (t, *J* = 12.5 Hz, 1H), 2.16 (d, *J* = 13.1 Hz, 1H), 1.86-1.68 (m, 1H), 1.55 (q, *J* = 12.2 Hz, 1H), 0.97 (d, *J* = 6.85, 3H), followed by (3R,5R/3S,5S)-1-(4-chloro-7-fluorothiazolo[5,4-c]pyridin-2-yl)-5-methylpiperidine-3-carbonitrile as a pale yellow solid (0.115 g, 17%, second eluting, *trans* isomer): ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.30 (d, *J* = 2.6 Hz, 1H), 4.52-4.30 (m, 1H), 4.16-3.95 (m, 1H), 3.58-3.47 (m, 1H), 3.45-3.37 (m, 1H), 3.02 (t, *J* = 14.1 Hz, 1H), 2.09-1.88 (m, 2H), 1.65-1.51 (m, 1H), 0.99 (d, *J* = 6.5 Hz, 3H).

Step 4. **(3R,5R/3S,5S)-1-[4-(6-Aminopyrimidin-4-ylamino)-7-fluorothiazolo[5,4-c]pyridin-2-yl]-5-methylpiperidine-3-carbonitrile.** A mixture of (3S,5S/3R,5R)-1-(4-chloro-7-fluorothiazolo[5,4-c]pyridin-2-yl)-5-methylpiperidine-3-carbonitrile (0.089 g, 0.29 mmol), Xantphos (0.069 g, 0.12 mmol), $Pd_2(dba)_3$ (0.072 g, 0.08 mmol), Cs_2CO_3 (0.264 g, 0.75 mmol), 6-amino-2-methylpyrimidin-4-yl)-*bis*-carbamic acid *tert*-butyl ester (0.115 g, 0.37 mmol) in dioxane (10 mL) was purged with argon for five minutes, then heated at 75 °C for 24 hours. The reaction mixture was poured into ethyl acetate, dried ($MgSO_4$) and concentrated under reduced pressure. The resultant residue was dissolved in DCM (5 mL) and TFA (5 mL) was then added. The resultant mixture was stirred for 3 hours and then quenched with saturated sodium bicarbonate solution, before extracting with ethyl acetate (x6). The combined organic extracts were dried ($MgSO_4$) and then concentrated under reduced pressure. The resultant residue was purified by column chromatography on silica gel (10% methanol in DCM) to afford the title compound as a pale tan powder which was purified by preparative chiral SFC (Chiralpak AD 21.2 x 150cm, 5um @ 40% methanol w/ 0.1% NH4OH/ 60% CO_2 at 70 ml/min, 100 Bars, 40 °C) to give a pair of enantiomers.

First eluted peak (7.1 mg, 6% yield): ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.49 (s, 1H), 8.11 (s, 1H), 8.04 (s, 1H), 6.51 (s, 2H), 6.28 (s, 1H), 4.46 – 4.25 (m, 1H), 4.10 – 3.90 (m, 1H), 3.50 – 3.36 (m, 2H), 2.94 (t, *J* = 11.8 Hz, 1H), 2.08 - 1.92 (m, 2H), 1.558 - 1.53(m, 1H), 0.98 (d, *J* = 6.5 Hz, 3H). LCMS m/z: 385.0 [M+H$^+$] (RT = 0.64 min, Chiralpak AD, 40% Methanol w/ 0.1% NH_4OH / 60% CO_2, flow rate 5 mL/min).

Second eluted peak (15.3 mg, 14% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.49 (s, 1H), 8.11 (s, 1H), 8.04 (s, 1H), 6.51 (s, 2H), 6.28 (s, 1H), 4.48 – 4.25 (m, 1H), 4.04 - 3.92 (m, 1H), 3.50 – 3.37 (m, 2H), 2.94 (t, *J* = 11.5 Hz, 1H), 2.11 – 1.85 (m, 2H), 1.58 - 1.53 (m, 1H), 0.98 (d, *J* = 6.4 Hz, 3H). LCMS m/z: 385.0 [M+H+] (RT = 0.66 min, Chiralpak AD, 40% Methanol w/ 0.1% NH_4OH / 60% CO_2, 5 mL/min).

Example 13 and 14



N-(2-((3R,5R/3S,5S)-3-cyano-5-hydroxypiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide

Step 1. **Methyl 1-(4-chlorothiazolo[5,4-c]pyridin-2-yl)-5-hydroxypiperidine-3-carboxylate (mixture of *cis* and *trans* isomers).** The mixture of 4-chloro-2-methylsulfonyl-thiazolo[5,4-c]pyridine (2.02 g, 8.1 mmol), methyl 5-hydroxypiperidine-3-carboxylate hydrochloride (1.9 g, 9.3 mmol) and K_2CO_3 (2.8 g, 20.3 mmol) in DMF (10 mL) was stirred at room temperature for

18 h. The mixture was diluted with water, extracted with EtOAc (2x), DCM (2x). The combined organics were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by silica flash chromatography (0-5% MeOH/DCM) to give the title compound (1.87 g, 70% yield) as a pale yellow solid. ^1H NMR (400 MHz, DMSO) δ 8.23 – 8.14 (m, 1H), 7.39 (d, J = 5.5 Hz, 0.4H), 7.36 (d, J = 5.5 Hz, 0.6H), 5.28 (d, J = 4.1 Hz, 0.4H), 5.11 (d, J = 3.6 Hz, 0.6H), 4.06 – 3.90 (m, 1H), 3.72 – 3.57 (m, 5H), 3.56 – 3.43 (m, 1H), 3.15 – 2.96 (m, 1H), 2.85 – 2.75 (m, 0.5H), 2.23 - 2.20 (m, 0.5H), 1.92 (m, 1H), 1.58 (dd, J = 22.8, 11.7 Hz, 0.5H), 1.18 (dd, J = 14.2, 7.1 Hz, 0.5H). LCMS m/z: 328 [M+H$^+$].

Step 2. **5-(Benzyloxy)-1-(4-chlorothiazolo[5,4-c]pyridin-2-yl)piperidine-3-carboxylic acid (mixture of *cis* and *trans* isomers).** To a solution of *cis*- and *trans*-methyl 1-(4-chlorothiazolo[5,4-c]pyridin-2-yl)-5-hydroxy-piperidine-3-carboxylate (1.8 g, 5.48 mmol) and benzyl bromide (3.75 g, 21.9 mmol) in THF (10 mL) at 0 °C was added NaH (60% in mineral oil, 0.88 g, 21.9 mmol) in one portion. The mixture was slowly warmed to room temperature and stirred for 20 h. More benzyl bromide (48 uL) and NaH (16 mg) were added at 0 °C. After 4 h, the reaction was quenched with ice water, extracted with EtOAc once. The organic layer was back extracted with 1 N LiOH once. The combined aqueous layers were acidified with 1 N HCl to pH=4, extracted with EtOAc (3x). The combined organics were dried (Na_2SO_4), filtered and concentrated to give the title compound (2.12 g, 96% yield) as a pale yellow solid. LCMS m/z: 404 [M+H$^+$].

Step 3. **5-(Benzyloxy)-1-(4-chlorothiazolo[5,4-c]pyridin-2-yl)piperidine-3-carboxamide (mixture of *cis* and *trans* isomers).** To a suspension of *cis*- and *trans*-5-benzyloxy-1-(4-chlorothiazolo[5,4-c]pyridin-2-yl)piperidine-3-carboxylic acid (2.2 g, 5.44 mmol) in acetone (15 mL) was added Et_3N (1.1 g, 10.9 mmol). The reaction mixture was cooled to 0 °C. Ethyl chloroformate (1.18 g, 10.89 mmol) was added dropwise. The reaction mixture was slowly warmed to room temperature and stirred for 1.5 h. The mix was then re-cooled to 0 °C. NH_4OH (28% in water, 4 mL) was added dropwise. The mixture was stirred at room temperature for 2 h. The mixture was then diluted with water. The precipitated solid was collected by filtration, washed with water, dried in high vacuum to give the title compound (0.97 g, 44% yield) as a pale yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.18 (dd, J = 12.6, 5.5 Hz, 1H), 7.54 (d, J = 36.6 Hz, 1H), 7.43 – 7.19 (m, 6H), 7.03 (d, J = 27.4 Hz, 1H), 4.66 – 4.49 (m, 2H), 4.13 -4.07 (m, 1H), 3.62 – 3.46 (m, 1H), 3.33 – 3.09 (m, 1H), 2.85 - 2.79 (m, 1H), 2.37 - 2.08 (m, 1H), 1.91 - 1.82 (m, 1H), 1.64 - 1.55 (m, 1H), 1.26 – 1.09 (m, 1H). LCMS m/z: 403 [M+H$^+$].

Step 4. **5-(Benzyloxy)-1-(4-chlorothiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile** (mixture of *cis* and *trans* isomers). To a suspension of *cis*- and *trans*-5-benzyloxy-1-(4-chlorothiazolo[5,4-c]pyridin-2-yl)piperidine-3-carboxamide (1.02 g, 2.53 mmol) in 1,4-dioxane was added Et_3N (0.769 g, 7.59 mmol), followed by TFAA (1.06 g, 5.06 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with sat. NH_4Cl, extracted with DCM (2x). The combined organics were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by silica flash chromatography (0-15% EtOAc/DCM) give the title compound (0.91 g, 93% yield) as a white solid. ^1H NMR (400 MHz, DMSO-*d*$_6$) δ 8.24 – 8.18 (m, 1H), 7.41 (t, *J* = 5.7 Hz, 1H), 7.34 (t, *J* = 7.3 Hz, 1H), 7.31 – 7.17 (m, 4H), 4.61 (d, *J* = 9.5 Hz, 2H), 4.11 - 3.97 (m, 1H), 3.94 – 3.68 (m, 4H), 2.28 – 2.06 (m, 2H), 1.24 – 1.13 (m, 1H). LCMS m/z: 385 [M+H$^+$].

Step 5. ***N*-(2-(3-(Benzyloxy)-5-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide (mixture of *cis* and *trans* isomers**). The mixture of *cis*- and *trans*-5-benzyloxy-1-(4-chlorothiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile (200 mg, 0.52 mmol), cyclopropanecarboxamide (88 mg, 1.039 mmol), Pd_2dba_3 (24 mg, 0.026 mmol), Xantphos (30 mg, 0.052 mmol) and Cs_2CO_3 (337 mg, 1.04 mmol) in 1,4-dioxane (5 mL) and 1,2-dimethoxyethane (5 mL) in a microwave tube was purged with N_2 for 5 min, then sealed and heated at 150 °C in a microwave for 25 min. The mixture was cooled to room temperature and filtered through celite, washed with EtOAc, concentrated. The crude product was purified by silica flash chromatography (0-6% MeOH/DCM) to give the title compound (210 mg, 93% yield) as a yellow solid. ^1H NMR (400 MHz, DMSO-*d*$_6$) δ 10.92 (s, 1H), 8.12 (d, *J* = 5.4 Hz, 1H), 7.37 – 7.19 (m, 7H), 4.59 (d, *J* = 7.8 Hz, 2H), 4.08 - 4.02 (m, 1H), 3.81 - 3.78 (m, 2H), 3.57 (s, 2H), 3.25 - 3.21 (m, 1H), 2.35 – 1.93 (m, 4H), 1.23 - 1.16 (m, 1H), 0.85 (d, *J* = 6.1 Hz, 4H). LCMS m/z: 434 [M+H$^+$].

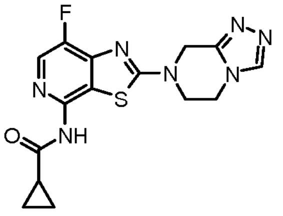
Step 6. ***N*-(2-((3*R*,5*R*/3*S*,5*S*)-3-Cyano-5-hydroxypiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide**. To a solution of *cis*- and *trans*-*N*-[2-(3-benzyloxy-5-cyano-1-piperidyl)thiazolo[5,4-c]pyridin-4-yl]cyclopropanecarboxamide (180 mg, 0.415 mmol) in DCM (5 mL) at 0 °C was added BBr_3 (1 M in DCM, 1.25 mL). The reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with ice/sat. $NaHCO_3$, extracted with DCM (3x). The combined organics were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by reverse phase HPLC (Gemini NX 3.0 x 10 cm, 10um @ 5-85% ACN in 10 min with 0.1% NH_4OH in water at 60 ml/min) followed by chiral SFC (Phenomenex Cellulose-4 21.2x150cm, 5u @ 30% methanol w/ 0.1% NH_4OH/ 70% CO_2 at 70 ml/min, 100 Bars, 40 °C) to give the two *trans*-enantiomers.

First eluted peak (6.4 mg, 4.5% yield): ^1H NMR (400 MHz, DMSO-*d*$_6$) δ 10.92 (s, 1H), 8.12 (d, *J* = 5.5 Hz, 1H), 7.20 (d, *J* = 5.5 Hz, 1H), 5.32 (d, *J* = 3.7 Hz, 1H), 4.02 – 3.73 (m, 4H), 3.33 - 3.29 (m, 1H), 2.16 – 2.06 (m, 1H), 1.99 (dt, *J* = 12.4, 6.3 Hz, 1H), 1.91 – 1.79 (m, 1H), 0.98 –

0.67 (m, 4H). LCMS (Phenomenex Cellulose-4 4.6x50cm, 3um @ 30% methanol w/ 0.1% NH_4OH/ 70% CO_2): RT = 0.65 min, m/z: 344 [$M+H^+$].

Second eluted peak (5.3 mg, 3.7% yield): ^1H NMR (400 MHz, DMSO-d_6) δ 10.92 (s, 1H), 8.12 (d, *J* = 5.4 Hz, 1H), 7.20 (d, *J* = 5.4 Hz, 1H), 5.32 (d, *J* = 3.6 Hz, 1H), 4.14 – 4.13 (m, 1H), 4.07 – 3.72 (m, 4H), 3.31 - 3.29 (m, 1H), 2.15 – 2.04 (m, 1H), 2.04 – 1.94 (m, 1H), 1.91 – 1.80 (m, 1H), 0.94 – 0.71 (m, 4H). LCMS (Phenomenex Cellulose-4 4.6x50cm, 3um @ 30% methanol w/ 0.1% NH_4OH/ 70% CO_2): RT = 0.84 min, m/z: 344 [$M+H^+$].

Example 15

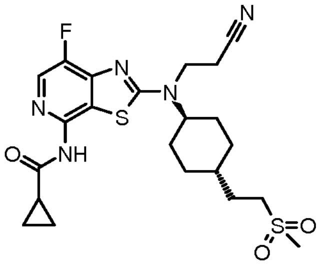


Cyclopropanecarboxylic acid [2-(5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-7-fluorothiazolo[5,4-c]pyridin-4-yl]-amide

Step 1. **7-(4-Chloro-7-fluorothiazolo[5,4-c]pyridin-2-yl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine.** To a mixture of 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine (0.583 g, 4.70 mmol) and potassium carbonate (1.31 g, 9.45 mmol) in acetonitrile (10 mL) was added 4-chloro-7-fluoro-2-methanesulfonylthiazolo[5,4-c]pyridine (1.10 g, 4.13 mmol). The reaction mixture was stirred at room temperature for 1 hour and then quenched with water (100 mL). The resultant mixture was extracted with DCM (x5), and the combined organic extracts were dried ($MgSO_4$) and then concentrated under reduced pressure. The resultant crude residue was purified by trituration with hot propan-2-ol to yield the title compound as a pale yellow powder (0.92 g, 72% yield). ^1H NMR (300 MHz, DMSO-d_6): δ 8.57 (s, 1H), 8.34 (d, *J* = 2.7 Hz, 1H), 5.09 (s, 2H), 4.33-4.26 (m, 2H), 4.22-4.14 (m, 2H).

Step 2. **Cyclopropanecarboxylic acid [2-(5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-7-fluorothiazolo[5,4-c]pyridin-4-yl]-amide**. A mixture of 7-(4-chloro-7-fluorothiazolo[5,4-c]pyridin-2-yl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine (0.261 g, 0.84 mmol), Xantphos (0.053 g, 0.09 mmol), $Pd_2(dba)_3$ (0.033 g, 0.04 mmol), Cs_2CO_3 (0.533 g, 1.64 mmol), cyclopropanecarboxamide (0.149 g, 1.75 mmol) in dioxane (10 mL) was purged with argon for five minutes, then heated at 75 °C for 24 hours. Additional Xantphos (0.055 g, 0.09 mmol) and $Pd_2(dba)_3$ (0.035 g, 0.04 mmol) were added and the reaction mixture was heated for a further 24 hours. The resultant mixture was poured into ethyl acetate (250 mL), dried ($MgSO_4$) and then concentrated under reduced pressure. The resultant residue was purified by column chromatography on silica gel (10% methanol in DCM) to afford the title compound as a pale tan powder (27.6 mg, 9% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.96 (br s, 1H), 8.50 (s, 1H), 8.14 (d, J = 2.2 Hz, 1H), 4.98 (s, 2H), 4.21 (t, J = 5.7 Hz, 2H), 4.06 (t, J = 5.7 Hz, 2H), 2.45 (qn, J = 2.1 Hz, 1H), 0.84-0.77 (m, 4H). LCMS (Method A): RT = 2.38 min, m/z: 360 [M+H$^+$].

Example 16



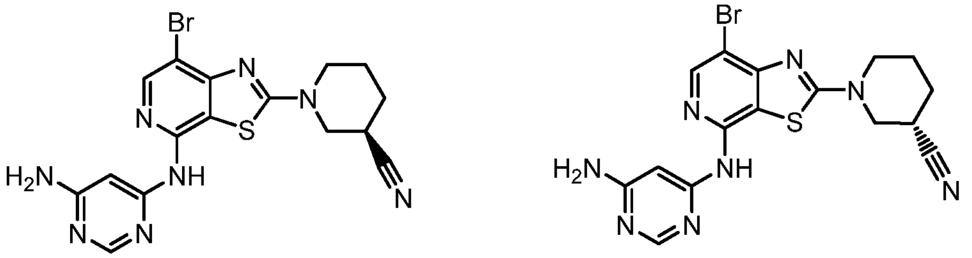
trans-Cyclopropanecarboxylic acid (2-{(2-cyanoethyl)-[4-(2-methanesulfonylethyl)-cyclohexyl]-amino}-7-fluorothiazolo[5,4-c]pyridin-4-yl)-amide

Step 1. ***trans*- (4-Chloro-7-fluorothiazolo[5,4-c]pyridin-2-yl)-[4-(2-methanesulfonylethyl)-cyclohexyl]-amine.** To a mixture of 4-(2-methanesulfonylethyl)-cyclohexylamine (295 mg, 1.44 mmol) and potassium carbonate (284 mg, 2.06 mmol) in acetonitrile (20 mL) was added 4-chloro-7-fluoro-2-methanesulfonylthiazolo[5,4-c]pyridine (366 mg, 1.37 mmol). The reaction mixture was stirred at room temperature for 18 hours and was then quenched by addition of water. This solution was concentrated to approximately half the volume and the resulting precipitate was filtered and dried under vacuum to yield the title compound as a white solid (369 mg, 69% yield). LCMS (Method B): RT = 3.28 min, m/z: 392 [M+H$^+$].

Step 2. ***trans*-3-{(4-Chloro-7-fluorothiazolo[5,4-c]pyridin-2-yl)-[4-(2-methanesulfonylethyl)-cyclohexyl]-amino}-propionitrile.** To a mixture of (4-chloro-7-fluorothiazolo[5,4-c]pyridin-2-yl)-[4-(2-methanesulfonylethyl)-cyclohexyl]-amine (186 mg, 0.47 mmol) and potassium carbonate (71.9 mg, 0.52 mmol) in acetonitrile (8 mL) was added acrylonitrile (0.31 mL, 4.75 mmol). The reaction mixture was heated at 80°C for 18 hours, allowed to cool and then partitioned between water and EtOAc. The aqueous layer was further washed with EtOAc (x2). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under vacuum to yield the title compound as a white solid (204 mg, 98% yield). LCMS (Method B): RT = 3.51 min, m/z: 445 [M+H$^+$].

Step 3. ***trans*-Cyclopropanecarboxylic acid (2-{(2-cyanoethyl)-[4-(2-methanesulfonylethyl)-cyclohexyl]-amino}-7-fluorothiazolo[5,4-c]pyridin-4-yl)-amide**. A mixture of 3-{(4-chloro-7-fluorothiazolo[5,4-c]pyridin-2-yl)-[4-(2-methanesulfonylethyl)-cyclohexyl]-amino}-propionitrile (201 mg, 0.45 mmol), Xantphos (26 mg, 0.045 mmol), $Pd_2(dba)_3$ (21 mg, 0.023 mmol), Cs_2CO_3 (295 mg, 0.91 mmol), cyclopropanecarboxamide (40 mg, 0.47 mmol) in dioxane (10 mL) was purged with argon for five minutes and then heated at 150°C under microwave irradiation for 30 minutes. Additional Xantphos (104 mg, 0.18 mmol) and $Pd_2(dba)_3$ (82.4 mg, 0.092 mmol) were added and the reaction mixture was de-gassed with argon for 5 minutes, before heating at 150°C under microwave irradiation for 1 hour. The resultant mixture was allowed to cool before filtering through Celite®, washing with EtOAc and then DCM (1% MeOH). The combined organic washings were concentrated under vacuum and the resultant crude residue was purified by column chromatography on silica gel (0-100% EtOAc in Pet. Ether), followed by HPLC [10%-80% MeCN (0.1% formic acid) in H_2O (0.1% formic acid)] to afford the title compound as a white solid (13.4 mg, 6% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.93 (s, 1H), 8.16 (d, J = 2.1 Hz, 1H), 3.84 (t, J = 7.1 Hz, 2H), 3.57 (br s, 1H), 3.18-3.10 (m, 2H), 3.00-2.93 (m, 5H), 2.00-1.92 (m, 1H), 1.90-1.81 (m, 4H), 1.79-1.58 (m, 4H), 1.48-1.35 (m, 1H), 1.24-1.09 (m, 2H), 0.89-0.81 (m, 4H). LCMS (Method A): RT = 3.63 min, m/z: 494 [M+H$^+$].

Example 17 and 18



(R)- and (S)-1-(4-(6-aminopyrimidin-4-ylamino)-7-bromothiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile

Step 1. **7-bromo-1H-thiazolo[5,4-c]pyridine-2-thione** A mixture of 4-bromo-2-fluoro-pyridin-3-amine (2.29 g, 12.0 mmol) and potassium ethoxymethanedithioate (3.85 g, 24.0 mmol) in NMP (12 mL) was heated in a microwave at 170 °C for 45 min when the reaction mixture turned dark red. The reaction mixture was cooled to 23 °C, poured into AcOH and water (10% v/v, 200 mL). The resulting precipitate was collected by filtration to give the title compound (2.94 g, 99% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (s, 1H), 8.60 (s, 1H). LCMS m/z: 249 [M+H$^+$].

Step 2. **7-bromo-2-methylsulfanyl-thiazolo[5,4-c]pyridine** To a solution of 7-bromo-1H-thiazolo[5,4-c]pyridine-2-thione (2.95 g, 12.0 mmol) in DMF (20 mL) was added K_2CO_3 (3.31 g, 24 mmol) at 23 °C. After the mixture was stirred for 10 min, methyl iodide (1.87 g, 413.2 mmol) was added dropwise. The resulting mixture was stirred at 23 °C for 1.5 hour when monitoring the reaction by LCMS showed complete conversion. The mixture was poured into AcOH and water (10% v/v, 200 mL), and the resulting precipitate was collected by filtration to give the desired product (2.73 g, 87% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.68 (s, 1H), 2.87 (s, 3H). LCMS m/z: 263 [M+H$^+$].

Step 3. **7-bromo-2-methylsulfonyl-5-oxido-thiazolo[5,4-c]pyridin-5-ium** To a cooled (ice bath) suspension of urea-hydrogen peroxide (9.41 g, 100 mmol) in acetonitrile (100 mL) was slowly added trifluoroacetic anhydride (10.4 mL, 75 mmol). The resultant mixture was stirred for 30 minutes, then 7-bromo-2-methylsulfanyl-thiazolo[5,4-c]pyridine (3.26 g, 12.5 mmol) was added and the reaction mixture was stirred for 1 hour and then slowly allowed to warm to room temperature. The resultant mixture was then partitioned between DCM and water. The aqueous layer was extracted with DCM (x2), and the combined organic extracts were dried ($MgSO_4$) and concentrated under vacuum. The resultant solid was triturated with isopropanol, filtered and dried to afford the title compound as a pale yellow powder (3.21 g, 83% yield). ^1H NMR (400 MHz, CDC13) δ 8.76 (d, $J = 1.3$ Hz, 1H), 8.54 (d, $J = 1.4$ Hz, 1H), 3.48 (s, 3H). LCMS m/z: 311 [M+H$^+$].

Step 4. **1-(7-bromo-5-oxido-thiazolo[5,4-c]pyridin-5-ium-2-yl)piperidine-3-carbonitrile** A mixture of 7-bromo-2-methylsulfonyl-5-oxido-thiazolo[5,4-c]pyridin-5-ium (3.21 g, 10.4 mmol), piperidine-3-carbonitrile (1.37 g, 12.5 mmol) and K_2CO_3 (2.87 g, 20.8 mmol) in DMF (20 mL) was stirred at room temperature for 1 hour when LCMS showed complete conversion. The reaction was quenched with dH_2O (100 mL). The resulting precipitate was collected by filtration. The filtrate was extracted with DCM (5x). The combined organics were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by silica flash chromatography (0-10% MeOH/DCM) and combined with the above solid to give the title compound (3.08 g, 88% yield) as yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, $J = 1.1$ Hz, 1H), 8.33 (d, $J = 1.1$ Hz, 1H), 4.12 (dd, $J = 13.4, 3.6$ Hz, 1H), 3.87 (dd, $J = 13.4, 7.5$ Hz, 1H), 3.66 (t, $J = 5.5$ Hz, 2H), 2.95 (m, 1H), 2.20 – 2.11 (m, 1H), 2.09 – 1.98 (m, 2H), 1.85 – 1.72 (m, 1H). LCMS m/z: 341.1 [M+H$^+$].

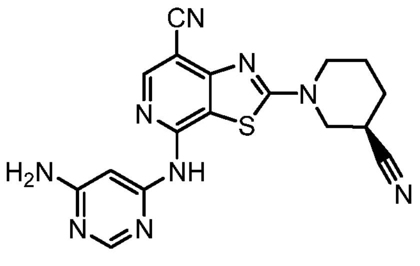
Step 5. **1-(4,7-dibromothiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile** To a suspension of 1-(7-bromo-5-oxido-thiazolo[5,4-c]pyridin-5-ium-2-yl)piperidine-3-carbonitrile (2.04 g, 6.00 mmol) in 1,2-dichloroethane (40 mL) was added $POBr_3$ (10.3 g, 36.0 mmol). The mix was heated at 85 °C for 1 hour, then at 75 °C for 16 hours. The reaction mixture was cooled to 23 °C, poured into sat. $NaHCO_3$ (100 mL), stirred for 10 min. The aqueous layer was extracted with DCM (4x). The combined organics were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by silica flash chromatography (0-5% EtOAc/DCM) to give the title compound (1.04 g, 43% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 4.23 – 4.16 (m, 1H), 3.85 (dd, $J = 13.4, 7.7$ Hz, 1H), 3.75 – 3.62 (m, 2H), 2.97 – 2.88 (m, 1H), 2.21 – 2.12 (m, 1H), 2.09 – 1.98 (m, 2H), 1.85 – 1.71 (m, 1H). LCMS m/z: 401.0 [M+H$^+$].

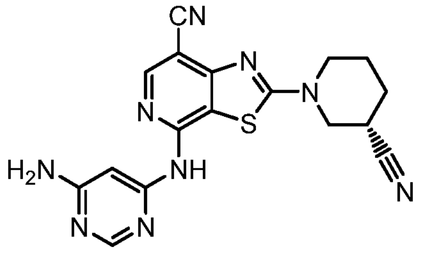
Step 6. **(*R*)- and (*S*)-1-(4-(6-aminopyrimidin-4-ylamino)-7-bromothiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile** A mixture of 1-(4,7-dibromothiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile (100 mg, 0.25 mmol), 6-amino-(pyrimidin-4-yl)-*bis*-carbamic acid *tert*-butyl ester (232 mg, 0.74 mmol), Cs_2CO_3 (243 mg, 0.75 mmol), Xantphos (14 mg, 0.025 mmol) and $Pd_2(dba)_3$ (11 mg, 0.012 mml) in 1,4-dioxane (2 mL) and 1,2-dimethoxyethane (2 mL) was degassed and re-filled with N_2. The mixture was sealed and irradiated in a microwave reactor at 100 °C for 40 min. The reaction mixture was diluted with EtOAc (20 mL) and filtered. The filtrate was concentrated to give a yellow residue which was dissolved in DCM (3 mL). TFA (1 mL) was added dropwise and the mixture was stirred at 23 °C for 16 hours. The reaction mixture was diluted with aq. Na_2CO_3 solution (1M, 10 mL) and extracted with EtOAc (3x10 mL). Combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by chiral SFC (Chiralpax OJ 21.2 x 250 mm, 5 um @ 30% methanol with 0.1% NH_4OH at 60 mL/min, 100 bars, 254 nm, 40 °C) to separate the two enantiomers.

First eluting peak (30 mg, 28% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 9.56 (s, 1H), 8.20 (s, 1H), 8.07 (s, 1H), 6.52 (s, 2H), 6.40 (s, 1H), 4.03 (dd, *J* = 13.2, 5.9 Hz, 1H), 3.83 (dd, *J* = 13.4, 3.4 Hz, 1H), 3.80 - 3.74 (m, 1H), 3.57 – 3.46 (m, 1H), 3.28 - 3.22 (m, 1H), 2.02 – 1.89 (m, 2H), 1.83 – 1.63 (m, 2H). LCMS m/z: 431.0 $[M+H^+]$ (RT = 0.59 min, chiralpak OJ 30% methanol with 0.1% NH_4OH / 70% CO_2).

Second eluting peak (28 mg, 25% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 9.56 (s, 1H), 8.20 (s, 1H), 8.07 (s, 1H), 6.52 (s, 2H), 6.40 (s, 1H), 4.03 (dd, *J* = 13.3, 5.3 Hz, 1H), 3.83 (dd, *J* = 13.4, 3.4 Hz, 1H), 3.80 – 3.72 (m, 1H), 3.56 – 3.47 (m, 1H), 3.29 – 3.24 (m, 1H), 2.01 – 1.89 (m, 2H), 1.83 – 1.65 (m, 2H). LCMS m/z: 431.0 $[M+H^+]$ (RT = 0.67 min, SFC, chiralpak OJ 30% methanol with 0.1% NH_4OH / 70% CO_2).

Example 19 and 20





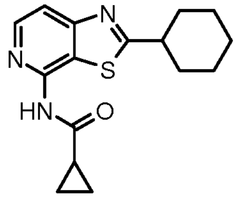
(R)- and (S)- 4-(6-aminopyrimidin-4-ylamino)-2-(3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridine-7-carbonitrile

A mixture of *tert*-butyl N-[6-[[7-bromo-2-(3-cyano-1-piperidyl)thiazolo[5,4-c]pyridin-4-yl]amino]pyrimidin-4-yl]-N-*tert*-butoxycarbonyl-carbamate (192 mg, 0.3 mmol), $Zn(CN)_2$ (35 mg, 0. 3 mmol), $Pd_2(dba)_3$ (28 mg, 0.03 mmol), DPPF (33 mg, 0.06 mmol) and TMEDA (7 mg, 0.06 mmol) in DMF (3 mL) in a microwave tube was purged with N_2. The tube was sealed and heated at 140 °C in a microwave for 40 min. The reaction mixture was cooled to room temperature, filtered through celite, washed with EtOAc, concentrated. The residue was dissolved in DCM (3 mL), TFA (0.6 mL) was added. The reaction mixture was stirred at 23 °C for 16 hours. The reaction mixture was diluted with aq. Na_2CO_3 solution (1M, 10 mL) and extracted with EtOAc (3x10 mL). Combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by chiral SFC (Chiralpax AD 21.2 x 250 mm, 5 um 45% methanol with 0.1% NH_4OH / 55% CO_2) to separate the two enantiomers.

First eluting peak (8.9 mg, 7.8% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 10.09 (s, 1H), 8.48 (s, 1H), 8.15 (s, 1H), 6.69 (s, 2H), 6.51 (s, 1H), 4.08 (dd, J = 13.3, 4.6 Hz, 1H), 3.85 (dd, J = 13.3, 3.4 Hz, 1H), 3.81 – 3.74 (m, 1H), 3.61 – 3.50 (m, 1H), 2.02 – 1.91 (m, 2H), 1.84 – 1.68 (m, 2H). LCMS m/z: 378 [M+H$^+$] (RT = 0.60 min, Chiralpak AD 4.6 x 50 mm, 5 um, 45% methanol with 1% NH_4OH / 55% CO_2).

Second eluting peak (12 mg, 11% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 10.09 (s, 1H), 8.48 (s, 1H), 8.15 (s, 1H), 6.69 (s, 2H), 6.51 (s, 1H), 4.08 (dd, J = 13.2, 4.9 Hz, 1H), 3.85 (dd, J = 13.3, 3.4 Hz, 1H), 3.79 - 3.75 (m, 1H), 3.60 – 3.50 (m, 1H), 2.03 – 1.91 (m, 2H), 1.85 – 1.66 (m, 2H). LCMS m/z: 378 [M+H$^+$] (RT = 0.66 min, Chiralpak AD 4.6 x 50mm,5 um, 45% methanol with 0.1% NH_4OH / 55% CO_2).

Example 21



Cyclopropanecarboxylic acid (2-cyclohexylthiazolo[5,4-c]pyridin-4-yl)-amide

Step 1. **1-Thiazolo[5,4-c]pyridin-2-yl-cyclohexanol.** To a suspension of thiazolo[5,4-c]pyridine (0.60 g, 4.41 mmol) in diethyl ether (50 mL) at -78 °C was added drop-wise *n*-butyllithium (2.5 N in hexanes, 1.9 mL, 4.63 mmol) and the reaction mixture was kept at -78 °C for 30 minutes. Then a solution of cyclohexanone (455 mg, 4.63 mmol) in diethyl ether (5.0 mL) was added drop-wise and the reaction mixture was stirred at -78 °C for another 30 minutes, before warming to room temperature over 40 minutes and then stirring at room temperature for a further 30 minutes. The resultant mixture was quenched with a saturated ammonium chloride solution and extracted with EtOAc (x2). The combined organic extracts were washed with water, then brine, dried (Na_2SO_4) and concentrated under vacuum. The crude residue was purified by flash column chromatography (0-5% MeOH in DCM) to afford the title compound as a white solid (428 mg, 41% yield). LCMS (Method B): RT = 1.69 min, m/z: 235 [M+H$^+$].

Step 2. **2-Cyclohex-1-enylthiazolo[5,4-c]pyridine.** A solution of 1-thiazolo[5,4-c]pyridin-2-yl-cyclohexexanol (428 mg, 1.84 mmol) in Eaton's reagent (7.0 mL) was heated at 80 °C for 16 hours. The reaction mixture was allowed to cool to room temperature and adjusted to pH 7 *via* careful addition of saturated sodium hydrogen carbonate solution. The resultant mixture was extracted with ethyl acetate (x2) and the combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum to afford the title compound as a pale yellow solid (400 mg, quantitative yield). LCMS (Method C): RT = 2.19 min, m/z: 217 [$M+H^+$].

Step 3. **2-Cyclohexylthiazolo[5,4-c]pyridine.** A suspension of 2-cyclohex-1-enylthiazolo[5,4-c]pyridine (400 mg, 1.84 mmol) in IMS (30 mL) was added Pd/C (10 %wt %, 492 mg, 0.46 mmol), under an atmosphere of hydrogen (atmospheric pressure) and the reaction mixture was stirred at room temperature for 3 days. The resultant mixture was filtered through Celite®, washing with EtOAc (x3). The combined organic washings were concentrated under vacuum to afford the title compound as a pale yellow solid (372 mg, 92% yield). LCMS (Method B): RT = 2.54 min, m/z: 219 [$M+H^+$].

Step 4. **2-Cyclohexylthiazolo[5,4-c]pyridine-5-oxide.** To a solution of 2-cyclohexylthiazolo[5,4-c]pyridine (372 mg, 1.59 mmol) in DCM (16 mL), under a nitrogen atmosphere, was added methyltrioxorhenium(VII) (40 mg, 0.16 mmol) followed by 27% aqueous hydrogen peroxide solution (0.41 mL, 3.18 mmol). The reaction mixture was stirred at room temperature for 18 hours. Further portions of methyltrioxorhenium(VII) (10 mg, 0.04 mmol) and 27% aqueous hydrogen peroxide (0.10 mL, 0.78 mmol) were added and the reaction mixture was stirred at room temperature for another 2 hours. The resultant mixture was partitioned between saturated sodium hydrogen carbonate and DCM. The aqueous layer was extracted with DCM (x2) and the combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure to afford the title compound as a pale yellow solid (336 mg, 90% yield). LCMS (Method B): RT = 2.63 min, m/z: 235 [$M+H^+$].

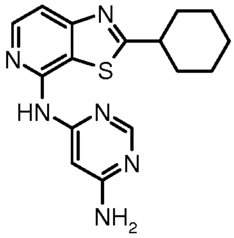
Step 5. ***tert*-Butyl-(2-cyclohexylthiazolo[5,4-c]pyridin-4-yl)-amine.** To a solution of 2-cyclohexylthiazolo[5,4-c]pyridine-5-oxide (47 mg, 0.2 mmol) in DCM (1.0 mL), tert-butylamine (19 mg, 0.26 mmol) and DIPEA (0.13 mL, 0.75 mmol), was added bromotripyrrolidinophosphonium hexafluorophosphate (121 mg, 0.26 mmol) and the reaction mixture was stirred at room temperature for 2 hours. The resultant mixture was partitioned between saturated sodium hydrogen carbonate and DCM. The aqueous layer was extracted with DCM (x2) and the combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (0-50% EtOAc in pentane) to afford the title compound as a white solid (35 mg, 60% yield). LCMS (Method B): RT = 2.86 min, m/z: 290 [$M+H^+$].

Step 6. **Cyclohexylthiazolo[5,4-c]pyridin-4-ylamine.** A solution of *tert*-butyl-(2-cyclohexylthiazolo[5,4-c]pyridin-4-yl)-amine (30 mg, 0.1 mmol) in TFA (2.0 mL) was stirred at

70 °C for 2 hours. The reaction mixture was allowed to cool to room temperature and adjusted to pH 8 *via* careful addition of saturated sodium hydrogen carbonate solution. The resultant mixture was extracted with DCM (x3) and the combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum to afford the title compound as a pale yellow solid (25 mg, quantitative yield). LCMS (Method C): RT = 1.92 min, m/z: 234 [M+H$^+$].

Step 7. **Cyclopropanecarboxylic acid (2-cyclohexylthiazolo[5,4-c]pyridin-4-yl)-amide.** To a solution of cyclohexylthiazolo[5,4-c]pyridin-4-ylamine (19 mg, 0.08 mmol) and DIPEA (21 μL, 0.16 mmol) in THF (1.0 mL), was added a solution of cyclopropanecarbonyl chloride (22 mg, 0.20 mmol) in THF (1.0 mL) and the reaction mixture was stirred at room temperature for 2 hours. After this time, HCl (12 N, 0.5 mL) was added and the reaction mixture was stirred at 50 °C for 1 hour. The resultant mixture was allowed to cool to room temperature and adjusted to pH 7 *via* careful addition of saturated sodium hydrogen carbonate and then extracted with DCM (x2) and EtOAc (x1). The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum. The resultant crude residue was purified by column chromatography on silica gel (0-60% EtOAc in pentane) to afford the title compound as a white solid (15 mg, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (br s, 1H), 8.25 (d, J = 5.7 Hz, 1H), 7.66 (d, J = 5.5 Hz, 1H), 3.10 (tt, J = 11.6, 3.6 Hz, 1H), 2.24-2.15 (m, 2H), 1.93-1.84 (m, 2H), 1.81-1.56 (m, 3H), 1.50.1.37 (m, 2H), 1.36-1.21 (m, 2H), 1.20-1.15 (m, 2H), 0.99-0.92 (m, 2H). LCMS (Method A): RT = 4.38 min, m/z: 302 [M+H$^+$].

Example 22

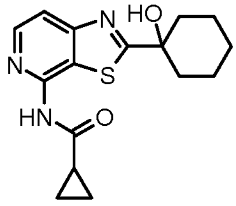


N-(2-Cyclohexylthiazolo[5,4-c]pyridin-4-yl)-pyrimidine-4,6-diamine

Step 1. **[6-(2-Cyclohexylthiazolo[5,4-c]pyridin-4-ylamino)-pyrimidin-4-yl]-*bis*-carbamic acid *tert*-butyl ester.** A mixture of cyclohexylthiazolo[5,4-c]pyridin-4-ylamine (40 mg, 0.17 mmol), Xantphos (20 mg, 0.034 mmol), Cs_2CO_3 (166 mg, 0.51 mmol) and 6-chloro-(pyrimidin-4-yl)-*bis*-carbamic acid *tert*-butyl ester (55 mg, 0.17 mmol) was purged with argon for five minutes. $Pd_2(dba)_3$ (16 mg, 0.017 mmol) was added, purged with argon for a further two minutes and the reaction mixture was then heated at 80 °C for 16 hours. The resultant mixture was allowed to cool and then filtered through Celite® washing with EtOAc (x3). The combined organic washings were concentrated under vacuum and the resultant crude residue was purified by column chromatography on silica gel (0-60% EtOAc in pentane) to afford the title compound as a yellow glass (73 mg, 22% yield). LCMS (Method C): RT = 4.19 min, m/z: 527 [M+H$^+$].

Step 2. ***N*-(2-Cyclohexylthiazolo[5,4-c]pyridin-4-yl)-pyrimidine-4,6-diamine.** To a solution of [6-(2-cyclohexylthiazolo[5,4-c]pyridin-4-ylamino)-pyrimidin-4-yl]-*bis*-carbamic acid *tert*-butyl ester (70 mg, 0.13 mmol) in DCM (2.0 mL), was added TFA (0.5 mL) and the reaction mixture was stirred at room temperature for 1 hour. The resulting mixture was partitioned between DCM and saturated sodium hydrogen carbonate solution. The aqueous layer was further extracted with DCM (x2) and the combined organic extracts were dried (Na_2SO_4), concentrated and the resultant residue was purified by column chromatography on silica gel [0-5% MeOH (2 N ammonia solution) in DCM] to afford the title compound as a white solid (35 mg, 81% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.71 (s, 1H), 8.26 (d, J = 5.5 Hz, 1H), 8.09 (s, 1H), 7.54 (d, J = 5.7 Hz, 1H), 6.85 (s, 1H), 6.57 (br s, 2H), 3.15 (tt, J = 11.4, 3.6 Hz, 1H), 2.17-2.07 (m, 2H), 1.86-1.20 (m, 8H). LCMS (Method A): RT = 3.13 min, m/z: 327 [M+H$^+$].

Example 23



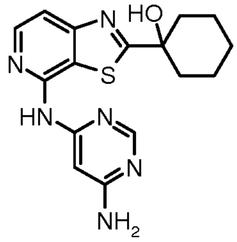
Cyclopropanecarboxylic acid [2-(1-hydroxycyclohexyl)-thiazolo[5,4-c]pyridin-4-yl]-amide

Step 1. **1-(5-Oxythiazolo[5,4-c]pyridin-2-yl)-cyclohexanol.** To a solution of 1-thiazolo[5,4-c]pyridin-2-yl-cyclohexanol (326 mg, 1.391 mmol) in DCM (12 mL), was added 3-chloroperoxybenzoic acid (658 mg, 2.782 mmol). The reaction mixture was stirred at room temperature for 90 minutes. Saturated potassium carbonate was then added until pH 8-9 was achieved. The reaction mixture was loaded onto a PE-AX column and the non-acidic eluting fractions were concentrated to dryness under reduced pressure. The crude residue was then dissolved with chloroform and the insoluble residues were removed by filtration. The filtrate was concentrated under reduced pressure to afford the title compound as a yellow solid (260 mg, 75% yield). LCMS (Method C): RT = 1.98 min, m/z: 251 [M+H$^+$].

Step 2. **1-(4-Aminothiazolo[5,4-c]pyridin-2-yl)-cyclohexanol.** To a solution of 1-(5-Oxythiazolo[5,4-c]pyridin-2-yl)-cyclohexanol (252 mg, 1.01 mmol) in DCM (15.0 mL) and ammonium hydroxide (33%, 1.0 mL), was added *p*-toluenesulfonyl chloride (194 mg, 1.02 mmol) and the reaction mixture was stirred at room temperature for 18 hours. Further 33% ammonium hydroxide (33%, 2.0 mL), and *p*-toluenesulfonyl chloride (100 mg) were added and the reaction mixture was stirred at room temperature for 2 hours The resultant mixture was concentrated to dryness under reduced pressure. The crude residue was purified by flash column chromatography (0-20% MeOH in DCM) to afford the title compound as a tan solid (118 mg, 47% yield). LCMS (Method B): RT = 1.86 min, m/z: 250 [M+H$^+$].

Step 3. **Cyclopropanecarboxylic acid [2-(1-hydroxycyclohexyl)-thiazolo[5,4-c]pyridin-4-yl]-amide.** To a solution of 1-(4-aminothiazolo[5,4-c]pyridin-2-yl)-cyclohexanol (38 mg, 0.15 mmol) and DIPEA (53 µL, 0.30 mmol) in THF (3.0 mL), was added a solution of cyclopropanecarbonyl chloride (14 µL, 0.15 mmol) in THF (1.0 mL) and the reaction mixture was stirred at room temperature for 2 hours. After this time, HCl (12 N, 1.0 mL) was added and the reaction mixture was stirred at 45 °C for 0.5 hour followed by room temperature for 16 hours. The resultant mixture was adjusted to pH 7 *via* careful addition of saturated sodium hydrogen carbonate and then extracted with DCM (x2) and EtOAc (x1). The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum. The resultant crude residue was purified by column chromatography on silica gel (0-60% EtOAc in cyclohexane), followed by HPLC [0%-50% MeCN (0.1% formic acid) in H_2O (0.1% formic acid)] to afford the title compound as a white solid (10 mg, 21% yield). ^1H NMR (400 MHz, DMSO-d_6): δ 11.06 (br s, 1H), 8.27 (d, J = 5.6 Hz, 1H), 7.66 (d, J = 5.3 Hz, 1H), 6.03 (s, 1H), 2.01-1.93 (m, 1H), 1.92-1.81 (m, 2H), 1.78-1.46 (m, 7H), 1.32-1.17 (m, 1H), 0.86-0.79 (m, 4H). LCMS (Method A): RT = 3.31 min, m/z: 318 [M+H$^+$].

Example 24

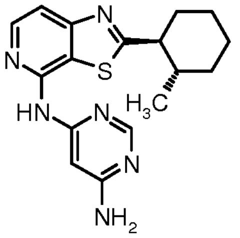


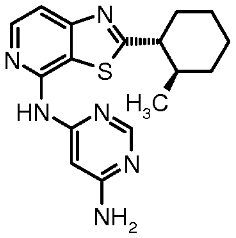
1-[4-(6-Aminopyrimidin-4-ylamino)-thiazolo[5,4-c]pyridin-2-yl]-cyclohexanol

Step 1. **{6-[2-(1-Hydroxycyclohexyl)-thiazolo[5,4-c]pyridin-4-ylamino]-pyrimidin-4-yl}-*bis*-carbamic acid *tert*-butyl ester.** A mixture of 1-(4-aminothiazolo[5,4-c]pyridin-2-yl)-cyclohexanol (40 mg, 0.16 mmol), Xantphos (19 mg, 0.032 mmol), Cs_2CO_3 (157 mg, 0.48 mmol) and 6-chloro-2-methylpyrimidin-4-yl)-*bis*-carbamic acid *tert*-butyl ester (53 mg, 0.16 mmol) was purged with argon for five minutes. $Pd_2(dba)_3$ (15 mg, 0.016 mmol) was added, purged with argon for a further two minutes and the reaction mixture was then heated at 80 °C for 16 hours. The resultant mixture was allowed to cool and then filtered through Celite® washing with EtOAc (x3). The combined organic washings were concentrated under vacuum and the resultant crude residue was purified by column chromatography on silica gel (0-60% EtOAc in cyclohexane) to afford the title compound as a cream solid (50 mg, 57% yield). LCMS (Method C): RT = 3.65 min, m/z: 543 [M+H$^+$].

Step 2. **1-[4-(6-Aminopyrimidin-4-ylamino)-thiazolo[5,4-c]pyridin-2-yl]-cyclohexanol.** To a solution of {6-[2-(1-hydroxycyclohexyl)-thiazolo[5,4-c]pyridin-4-ylamino]-pyrimidin-4-yl}-*bis*-carbamic acid *tert*-butyl ester (50 mg, 0.09 mmol) in DCM (3.0 mL), was added TFA (1.0 mL) and the reaction mixture was stirred at room temperature for 1 hour followed by warming at 45°C for 15 minutes. The resulting mixture was partitioned between DCM and saturated sodium hydrogen carbonate solution. The aqueous layer was further extracted with DCM (x2) and the combined organic extracts were dried (Na_2SO_4), concentrated and the resultant residue was purified by column chromatography on silica gel [0-10% MeOH (2 N ammonia solution) in DCM] to afford the title compound as a cream solid (9 mg, 29% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.62 (s, 1H), 8.20 (d, J = 5.7 Hz, 1H), 8.03 (s, 1H), 7.48 (d, J = 5.7 Hz, 1H), 6.87 (s, 1H), 6.52 (br s, 2H), 6.12 (s, 1H), 1.94-1.82 (m, 2H), 1.80-1.44 (m, 6H), 1.33-1.06 (m, 2H). LCMS (Method A): RT = 2.72 min, m/z: 343 [M+H$^+$].

Example 25 and 26





N-[2-((1R,2R/1S,2S)-2-Methylcyclohexyl)-thiazolo[5,4-c]pyridin-4-yl]-pyrimidine-4,6-diamine

Step 1. **(±)-*cis/trans*-2-Methyl-1-thiazolo[5,4-c]pyridin-2-yl-cyclohexanol.** To a suspension of thiazolo[5,4-c]pyridine (1.20 g, 8.82 mmol) in diethyl ether (100 mL) at -78 °C, was added drop-wise, *n*-butyllithium (2.5 N in hexanes, 4.24 mL, 10.6 mmol) and the reaction mixture was aged at -78°C for 30 minutes. A solution of 2-methylcyclohexanone (1.28 mL, 10.6 mmol) in diethyl ether (10.0 mL) was then added drop-wise and the reaction mixture was stirred at -78°C for a further 60 minutes, before warming to room temperature over 60 minutes. The resultant mixture was quenched with saturated ammonium chloride solution and extracted with EtOAc (x3). The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum. The crude residue was purified by flash column chromatography (0-5% MeOH in DCM) and then C18 reverse phase column chromatography [10-70% MeOH (0.1% NH_3) in H_2O (0.1% NH_3)] to afford a mixture of the title compounds as a white solid (0.82 g, 37% yield). LCMS (Method B): RT = 2.09, 2.19 min, m/z: 249 [M+H$^+$].

Step 2. (±)-**2-(6-Methylcyclohex-1-enyl)-thiazolo[5,4-c]pyridine**^{A} **and 2-(2-methylcyclohex-1-enyl)-thiazolo[5,4-c]pyridine**^{B}**.** To a solution of (±)-*cis/trans*-2-methyl-1-thiazolo[5,4-c]pyridin-2-yl-cyclohexanol (210 mg, 0.86 mmol) in DCM (5 mL), was added a solution of *bis*[α,α-bis(trifluoromethyl)benzyloxy]diphenylsulfur (810 mg, 1.20 mmol) in DCM (2.5 mL), the reaction mixture was stirred at room temperature for 7 hours and then evaporated to dryness. The reaction above was repeated on the same scale and the combined crude residues were purified by flash column chromatography (0-50% EtOAc in DCM) to afford a 5:1 (A:B) mixture of the title compounds as a pale yellow solid (370 mg, 94% yield). LCMS (Method B): RT = 2.64^{B}, 2.71^{A} min, m/z: 231 [M+H^{+}].

Step 3. **(±)-*cis/trans*-2-(2-Methylcyclohexyl)-thiazolo[5,4-c]pyridine.** A suspension of (±)-2-(6-methylcyclohex-1-enyl)-thiazolo[5,4-c]pyridine and 2-(2-methylcyclohex-1-enyl)-thiazolo[5,4-c]pyridine (370 mg, 1.61 mmol) in IMS (10 mL) was added Pd/C (10 %wt, 100 mg, 0.10 mmol), under an atmosphere of hydrogen (atmospheric pressure) and the reaction mixture was stirred at 48°C for 3 days. The resultant mixture was filtered through Celite®, washing with IMS and the combined washings were evaporated to dryness. The crude residue was dissolved in *n*-butanol (10 mL), Pd/C was added and the reaction mixture was stirred at 70°C for 2 days, under an atmosphere of hydrogen (atmospheric pressure). The resultant mixture was filtered through Celite®, washing with EtOAc (x3). The combined organic extracts were concentrated under vacuum to afford a mixture of the title compounds as a pale yellow solid (340 mg, 91% yield). LCMS (Method B): RT = 2.74 min, m/z: 233 [M+H^{+}].

Step 4. **(±)-*cis/trans*-2-(2-Methylcyclohexyl)-thiazolo[5,4-c]pyridine 5-oxide.** To a solution of (±)-*cis/trans*-2-(2-methylcyclohexyl)-thiazolo[5,4-c]pyridine (340 mg, 1.47 mmol) in DCM (10 mL), under a nitrogen atmosphere, was added methyltrioxorhenium(VII) (37 mg, 0.15 mmol) followed by 27% aqueous hydrogen peroxide solution (0.43 mL, 3.52 mmol). The reaction mixture was stirred at room temperature for 18 hours. Further portions of methyltrioxorhenium(VII) (20 mg, 0.08 mmol) and 27% aqueous hydrogen peroxide (0.20 mL, 1.56 mmol) were added and the reaction mixture was stirred at room temperature for another 1 hour. The resultant mixture was partitioned between saturated sodium hydrogen carbonate and DCM. The aqueous layer was extracted with DCM (x2) and the combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The resultant crude residue was purified by flash column chromatography (0-5% MeOH in DCM) to afford a mixture of the title compounds as a pale yellow solid (305 mg, 84% yield). LCMS (Method B): RT = 2.84 min, m/z: 249 [M+H^{+}].

Step 5. **(±)-*cis/trans*-*tert*-Butyl-[2-(2-methylcyclohexyl)-thiazolo[5,4-c]pyridin-4-yl]-amine.** To a solution of (±)-*cis/trans*-2-(2-methylcyclohexyl)-thiazolo[5,4-c]pyridine 5-oxide (100 mg, 0.40 mmol) in DCM (2.0 mL), *tert*-butylamine (52 μL, 0.50 mmol) and DIPEA (0.26 mL, 1.50 mmol), was added bromotripyrrolidinophosphonium hexafluorophosphate (242 mg, 0.52 mmol) and the reaction mixture was stirred at room temperature for 2.5 hours. The resultant mixture was partitioned between saturated sodium hydrogen carbonate and DCM. The aqueous layer was extracted with DCM (x2) and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The above reaction was repeated on twice this scale and the combined crude residues were purified by flash column chromatography (0-30% EtOAc in cyclohexane) to afford a mixture of the title compounds as a white solid (205 mg, 56% yield). LCMS (Method B): RT = 2.99 min, m/z: 304 [$M+H^+$].

Step 6. **2-((1R,2R/1S,2S)-2-Methylcyclohexyl)-thiazolo[5,4-c]pyridin-4-ylamine.** A solution of (±)-*cis/trans-tert*-butyl-[2-(2-methylcyclohexyl)-thiazolo[5,4-c]pyridin-4-yl]-amine (205 mg, 0.68 mmol) in TFA (5.0 mL) was stirred at 70°C for 2 hours. The reaction mixture was allowed to cool to room temperature and adjusted to pH 8 *via* careful addition of saturated sodium hydrogen carbonate solution. The resultant mixture was extracted with DCM (x4) and the combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum to afford the title compound as a pale yellow solid (185 mg, quantitative yield). LCMS (Method C): RT = 2.24 min, m/z: 248 [$M+H^+$].

Step 7. **{6-[2-((1R,2R/1S,2S)-2-Methylcyclohexyl)-thiazolo[5,4-c]pyridin-4-ylamino]-pyrimidin-4-yl}-*bis*-carbamic acid tert-butyl ester.** A mixture of 2-((1R,2R/1S,2S)-2-methylcyclohexyl)-thiazolo[5,4-c]pyridin-4-ylamine (90 mg, 0.328 mmol), Xantphos (39 mg, 0.066 mmol), Cs_2CO_3 (320 mg, 0.99 mmol) and 6-chloro-(pyrimidin-4-yl)-*bis*-carbamic acid *tert*-butyl ester (108 mg, 0.328 mmol) was purged with argon for five minutes. $Pd_2(dba)_3$ (31 mg, 0.033 mmol) was added, purged with argon for a further two minutes and the reaction mixture was then heated at 80°C for 16 hours. The resultant mixture was allowed to cool and then filtered through Celite®, washing with EtOAc (x3). The combined organic extracts were concentrated under vacuum and the resultant crude residue was purified by column chromatography on silica gel (0-40% EtOAc in pentane) and then (0-20% EtOAc in DCM) to afford the title compound as a yellow glass (103 mg, 58% yield). LCMS (Method B): RT = 4.51 min, m/z: 539 [$M+H^+$].

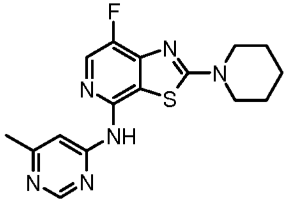
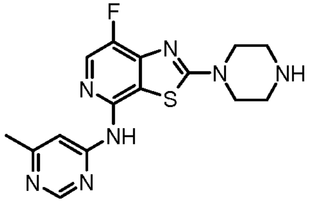
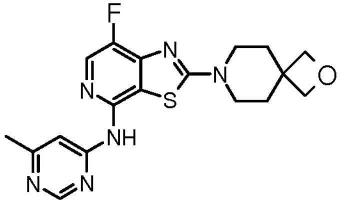
Step 8. ***N*-[2-((1R,2R/1S,2S)-2-Methylcyclohexyl)-thiazolo[5,4-c]pyridin-4-yl]-pyrimidine-4,6-diamine.** To a solution of {6-[2-((1R,2R/1S,2S)-2-methylcyclohexyl)-thiazolo[5,4-c]pyridin-4-ylamino]-pyrimidin-4-yl}-*bis*-carbamic acid *tert*-butyl ester (104 mg, 0.19 mmol) in DCM (2.0 mL), was added TFA (2.0 mL) and the reaction mixture was stirred at room temperature for 1.5 hours. The resulting mixture was evaporated to dryness and was then partitioned between DCM and saturated sodium hydrogen carbonate solution. The aqueous layer was further extracted with DCM (x2) and the combined organic extracts were dried (Na_2SO_4)

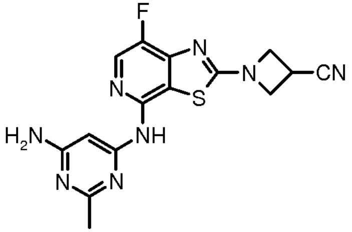
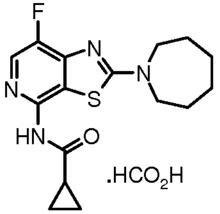
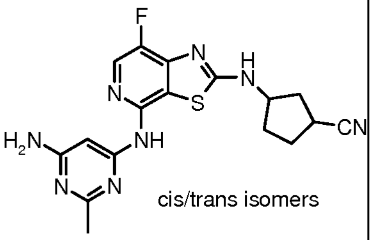
and concentrated under vacuum to afford the title compound as a white solid which was purified by chiral SFC (Chiralpak AD 21.2x150cm, 5um @ 35% methanol w/ 0.1% NH_4OH/ 65% CO_2 at 70 ml/min, 100 Bars, 40 °C) to give a pair of enantiomers.

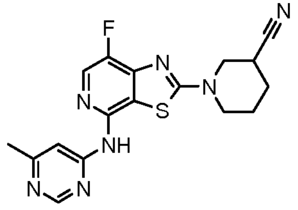
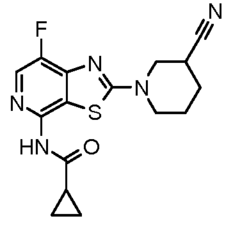
First eluted peak (12.9 mg, 20% yield): ^1H NMR (400 MHz, DMSO-d_6): δ 9.79 – 9.67 (s, 1H), 8.32 – 8.20 (d, J = 5.6 Hz, 1H), 8.15 – 8.05 (s, 1H), 7.61 – 7.49 (d, J = 5.6 Hz, 1H), 6.92 – 6.82 (s, 1H), 6.66 – 6.50 (s, 2H), 2.87 – 2.73 (td, J = 10.9, 3.3 Hz, 1H), 2.03 – 1.92 (d, J = 12.6 Hz, 1H), 1.87 – 1.70 (m, 4H), 1.64 – 1.52 (q, J = 12.9, 12.0 Hz, 1H), 1.44 – 1.30 (dd, J = 17.2, 9.8 Hz, 2H), 1.20 – 1.05 (q, J = 12.4, 12.0 Hz, 1H), 0.84 – 0.71 (d, J = 6.2 Hz, 3H). LCMS m/z: 341.0 [M+H$^+$] (RT = 0.68 min, Chiralpak AD, 35% Methanol w/ 0.1% NH_4OH / 65% CO_2, flow rate 5 mL/min).

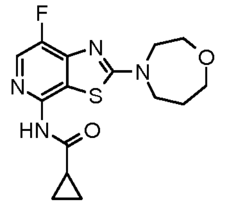
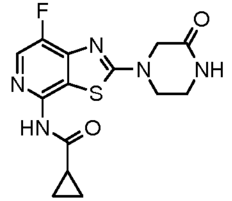
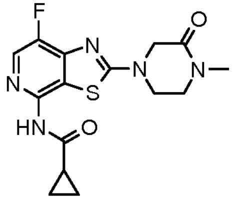
Second eluted peak (13.6 mg, 21% yield): ^1H NMR (400 MHz, DMSO-d_6): δ 9.78 – 9.65 (s, 1H), 8.32 – 8.21 (d, J = 5.5 Hz, 1H), 8.12 – 8.02 (s, 1H), 7.60 – 7.48 (d, J = 5.6 Hz, 1H), 6.91 – 6.80 (s, 1H), 6.66 – 6.50 (s, 2H), 2.87 – 2.73 (td, J = 12.3, 11.5, 3.3 Hz, 1H), 2.02 – 1.92 (d, J = 13.3 Hz, 1H), 1.85 – 1.68 (m, 4H), 1.64 – 1.51 (q, J = 12.3 Hz, 1H), 1.45 – 1.29 (m, 2H), 1.21 – 1.04 (q, J = 11.8 Hz, 1H), 0.83 – 0.67 (d, J = 6.1 Hz, 3H). LCMS m/z: 341.0 [M+H+] (RT = 0.86 min, Chiralpak AD, 35% Methanol w/ 0.1% NH_4OH / 65% CO_2, 5 mL/min).

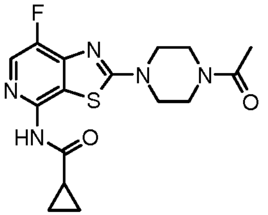
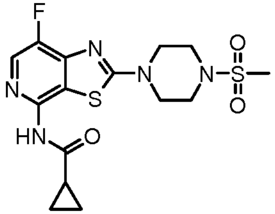
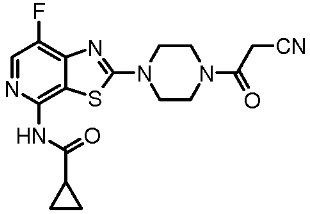
Examples 27-236

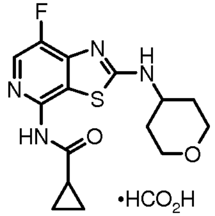
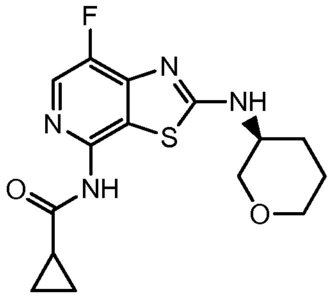
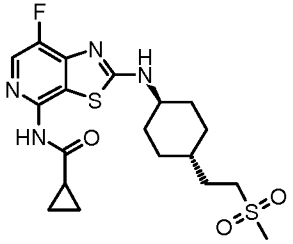
Example	Structure	Name	LCMS(ESI) *m/z* [M+H$^+$]	LCMS Method	R$_T$ (min)	NMR
27		(7-Fluoro-2-piperidin-1-yl-thiazolo[5,4-c]pyridin-4-yl)-(6-methylpyrimidin-4-yl)-amine	345	A	2.93	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.96 (br s, 1H), 8.46 (d, J = 1.0 Hz, 1H), 8.10 (d, J = 2.7 Hz, 1H), 7.05 (s, 1H), 3.64-3.56 (m, 4H), 2.27 (s, 3H), 1.64-1.54 (m, 6H)
28		(7-Fluoro-2-piperazin-1-yl-thiazolo[5,4-c]pyridin-4-yl)-(6-methylpyrimidin-4-yl)-amine	346	A	1.64	^{1}H NMR (400 MHz, D_2O): δ 8.57 (s, 1H), 8.13 (d, J = 2.7 Hz, 1H), 7.05 (s, 1H), 3.89 (t, J = 5.6 Hz, 4H), 3.35 (t, J = 5.6 Hz, 4H), 2.40 (s, 3H).
29		[7-Fluoro-2-(2-oxa-7-aza-spiro[3.5]non-7-yl)-thiazolo[5,4-c]pyridin-4-yl]-(6-methylpyrimidin-4-yl)-amine	387	A	2.43	^{1}H NMR (400 MHz, MeOD-d_4): δ 8.45 (d, J = 0.9 Hz, 1H), 8.03 (d, J = 2.6 Hz, 1H), 7.22 (s, 1H), 4.49 (s, 4H), 3.67 (dd, J = 5.7, 5.7 Hz, 4H), 2.36 (s, 3H), 2.03-1.97 (m, 4H).

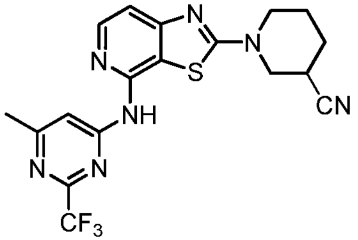
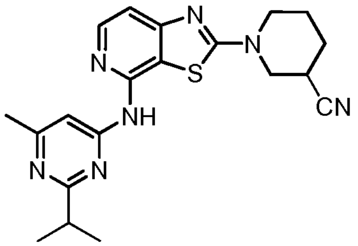
30		1-[4-(6-Amino-2-methylpyrimidin-4-ylamino)-7-fluorothiazolo[5,4-c]pyridin-2-yl]-azetidine-3-carbonitrile	357	A	2.24	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.46 (s, 1H), 8.03 (d, J = 2.3 Hz, 1H), 6.35 (br s, 2H), 6.05 (s, 1H), 4.45-4.33 (m, 4H), 4.05-3.96 (m, 1H), 2.19 (s, 3H).
31		Cyclopropanecarboxylic acid (2-azepan-1-yl-7-fluorothiazolo[5,4-c]pyridin-4-yl)-amide formate salt	335	A	4.15	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.87 (s, 1H), 8.42 (br s, 1H), 8.10 (d, J = 2.3 Hz, 1H), 3.97-3.44 (m, 4H), 1.99-1.91 (m, 1H), 1.86-1.74 (m, 4H), 1.59-1.50 (m, 4H), 0.86-0.81 (m, 4H).
32		Cis/trans mixture of (±)-3-[4-(6-Amino-2-methylpyrimidin-4-ylamino)-7-fluorothiazolo[5,4-c]pyridin-2-ylamino]-cyclopentanecarbo	385	A	2.59, 2.63	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.28 (br s, $1H^A + 1H^B$), 8.86 (d, J = 6.6 Hz, $1H^A$), 8.76 (d, J = 6.6 Hz, $1H^B$), 8.16 (s, $1H^A + 1H^B$), 8.05-8.02 (m, $1H^A + 1H^B$), 6.37 (br s, $2H^A + 2H^B$), 6.22 (s, $1H^A + 1H^B$), 4.36 (br s, $1H^B$), 4.26 (br s, $1H^A$), 3.23-3.03

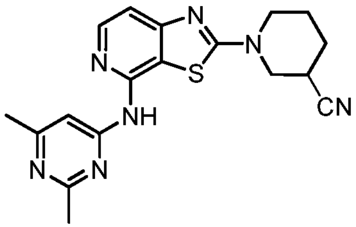
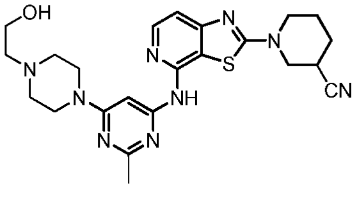
		nitrile				(m, $2H^A + 2H^B$), 2.26-1.61 (m, $7H^A + 7H^B$).
33		(±)1-[7-Fluoro-4-(6-methylpyrimidin-4-ylamino) thiazolo[5,4c]pyridin-2-yl]-piperidine-3-carbonitrile	370	A	2.49	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (d, *J* = 0.9 Hz, 1H), 8.07 (d, *J* = 2.5 Hz, 1H), 7.62 (s, 1H), 7.08 (br s, 1H), 4.13 (dd, *J* = 13.5, 3.5 Hz, 1H), 3.86 (dd, *J* = 13.2, 7.5 Hz, 1H), 3.68-3.62 (m, 2H), 2.95-2.86 (m, 1H), 2.46 (s, 3H), 2.17-2.07 (m, 1H), 2.06-1.95 (m, 2H), 1.81-1.70 (m, 1H).
34		(±)Cyclopropanecarboxylic acid [2-(3-cyanopiperidin-1-yl)-7-fluorothiazolo[5,4-c]pyridin-4-yl]-amide	346	A	3.33	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.90 (br s, 1H), 8.10 (d, *J* = 2.2 Hz, 1H), 4.00 (dd, *J* = 13.5, 5.7 Hz, 1H), 3.77 (dd, *J* = 13.3, 3.6 Hz, 1H), 3.77-3.68 (m, 1H), 3.46 (ddd, *J* = 12.5, 8.0, 3.71 Hz, 1H) 3.23-3.15 (m, 1H), 1.97-1.83 (m, 3H), 1.78-1.58 (m, 2H), 0.83-0.76 (m, 4H).

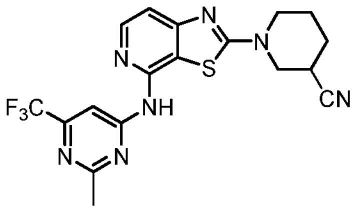
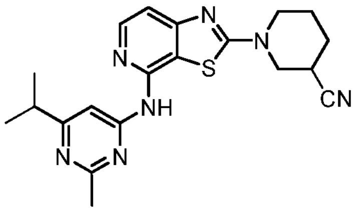
35		Cyclopropanecarboxylic acid (7-fluoro-2-[1,4]oxazepan-4-yl-thiazolo[5,4-c]pyridin-4-yl)-amide	337	A	3.06	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.85 (br s, 1H), 8.08 (d, *J* = 2.1 Hz, 1H), 3.88-3.68 (m, 6H), 3.64 (dd, *J* = 5.4, 5.4 Hz, 2H), 1.96-1.86 (m, 3H), 0.83-0.76 (m, 4H).
36		Cyclopropanecarboxylic acid [7-fluoro-2-(3-oxopiperazin-1-yl)-thiazolo[5,4c]pyridin-4-yl]-amide	336	A	2.38	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.91 (br s, 1H), 8.24 (br s, 1H), 8.11 (d, *J* = 2.4 Hz, 1H), 4.10 (s, 2H), 3.75 (t, *J* = 5.0 Hz, 2H), 3.35-3.29 (m, 2H), 1.96-1.88 (m, 1H), 0.84-0.77 (m, 4H).
37		Cyclopropanecarboxylic acid [7-fluoro-2-(4-methyl-3-oxopiperazin-1-yl)-thiazolo[5,4c]pyridin-4-yl]-amide	350	A	2.62	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.91 (br s, 1H), 8.12 (d, *J* = 2.2 Hz, 1H), 4.15 (s, 2H), 3.84 (t, *J* = 5.3 Hz, 2H), 3.46 (t, *J* = 5.3 Hz, 2H), 2.86 (s, 3H), 1.96-1.87 (m, 1H), 0.83-0.77 (m, 4H).

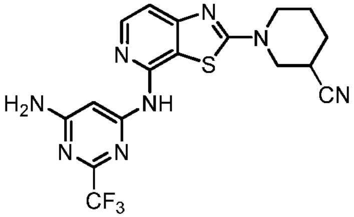
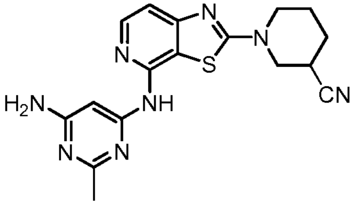
38		Cyclopropanecarboxylic acid [2-(4-acetylpiperazin-1-yl)-7-fluorothiazolo[5,4-c]pyridin-4-yl]-amide	364	A	2.72	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.88 (s, 1H), 8.11-8.09 (d, J = 2.5 Hz, 1H), 3.70-3.61 (m, 2H), 3.60-3.52 (m, 6H), 2.01 (s, 3H), 1.95-1.88 (m, 1H), 0.84-0.77 (m, 4H)
39		Cyclopropanecarboxylic acid [7-fluoro-2-(4-methanesulfonylpiperazin-1-yl)-thiazolo[5,4]pyridin-4-yl]-amide	340	A	3.13	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.91 (s, 1H), 8.12-8.10 (d, J = 2.2 Hz, 1H), 3.80-3.64 (m, 4H), 3.26-3.20 (m, 4H), 2.87 (s, 3H), 1.97-1.87 (m, 1H), 0.84-0.75 (m, 4H)
40		Cyclopropanecarboxylic acid {2-[4-(2-cyanoacetyl)-piperazin-1-yl]-7-fluorothiazolo[5,4-c]pyridin-4-yl}-amide	389	A	2.83	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.89 (s, 1H), 8.11-8.09 (d, J = 2.2 Hz, 1H), 4.07 (s, 2H), 3.72-3.55 (m, 6H), 3.52-3.45 (m, 2H), 1.96-1.87 (m, 1H), 0.85-0.75 (m, 4H)

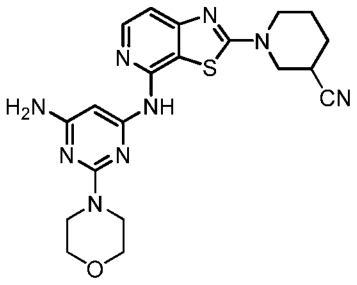
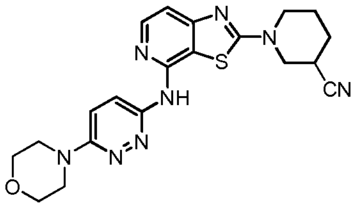
41		Cyclopropanecarboxylic acid [7-fluoro-2-(tetrahydro-pyran-4-ylamino)-thiazolo[5,4c]pyridin-4-yl]-amide formate salt	337	A	2.85	^{1}H NMR (400 MHz, DMSO-d$_6$): δ 10.77 (s, 1H), 8.69-8.56 (br s, 1H), 8.06-8.02 (d, J = 2.2 Hz, 1H), 4.01-3.85 (br s, 1H), 3.45-3.76 (m, 2H), 3.45-3.34 (m, 2H), 1.95-1.83 (m, 3H), 1.51-1.38 (m, 2H), 0.84-0.71 (m, 4H)
42		(*S*)-N-(7-fluoro-2-((tetrahydro-2H-pyran-3-yl)amino)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	337	A	3.03	^{1}H NMR (400 MHz, DMSO-d$_6$): δ 10.77 (s, 1H), 8.67-8.59 (br s, 1H), 8.06-8.02 (d, J = 2.6 Hz, 1H), 3.94-3.77 (m, 2H), 3.68-3.58 (m, 1H), 3.45-3.35 (m, 1H), 3.25-3.19 (m, 1H), 2.00-1.85 (m, 2H), 1.76-1.64 (m, 1H), 1.62-1.45 (m, 2H), 0.85-0.73 (m, 4H)
43		*trans*-Cyclopropanecarboxylic acid {7-fluoro-2-[4-(2-methanesulfonylethyl)-	441	A	3.20	^{1}H NMR (400 MHz, DMSO-d$_6$): δ 10.75 (s, 1H), 8.66-8.37 (br s, 1H), 8.04-8.02 (d, J = 2.6 Hz, 1H), 3.84-3.46 (br s, 1H), 3.13-3.02 (m, 2H), 2.95-2.85 (s, 3H), 2.06-1.95 (m,

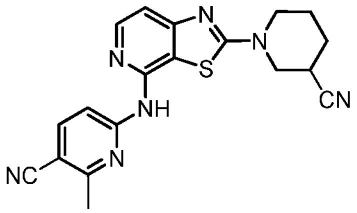
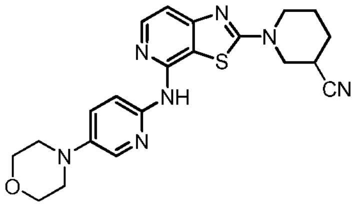
		cyclohexylamino]-thiazolo[5,4c]pyridin-4-yl}-amide				2H), 1.92-1.81 (m, 1H), 1.79-1.69 (m, 2H), 1.62-1.51 (m, 2H), 1.38-0.97 (m, 5H), 0.85-0.71 (m, 4H)
44		(±)-1-(4-(6-methyl-2-(trifluoromethyl)pyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	420	D	3.81	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.67 (s, 1H), 8.21 (d, J = 5.5 Hz, 1H), 7.53 (s, 1H), 7.25 (d, J = 5.5 Hz, 1H), 4.03 (dd, J = 13.2, 5.9 Hz, 1H), 3.83 (dd, J = 13.3, 3.5 Hz, 1H), 3.78 – 3.74 (m, 1H), 3.56 – 3.45 (m, 2H), 2.43 (s, 3H), 2.02 – 1.89 (m, 2H), 1.83 – 1.63 (m, 2H)
45		(±)-1-(4-(2-isopropyl-6-methylpyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	394	D	3.37	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.90 (s, 1H), 8.14 (d, J = 5.5 Hz, 1H), 7.17 (d, J = 5.5 Hz, 1H), 7.00 (s, 1H), 4.00 (dd, J = 13.3, 5.9 Hz, 1H), 3.87 – 3.70 (m, 2H), 3.55 – 3.43 (m, 1H), 3.28 – 3.19 (m, 1H), 2.94 (dt, J = 13.8, 6.9 Hz, 1H), 2.31 (s, 3H), 2.02 –

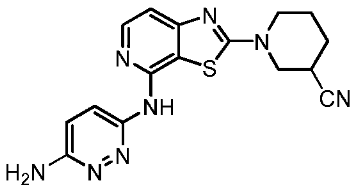
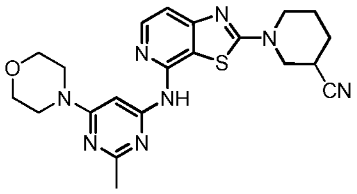
						1.89 (m, 2H), 1.74 (ddd, J = 16.3, 11.6, 4.9 Hz, 2H), 1.22 (d, J = 6.9 Hz, 6H)
46		(±)-1-(4-(2,6-dimethylpyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	366	D	2.98	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (s, 1H), 8.13 (d, J = 5.5 Hz, 1H), 7.16 (d, J = 5.5 Hz, 1H), 7.00 (s, 1H), 4.01 (dd, J = 13.3, 5.8 Hz, 1H), 3.87 – 3.70 (m, 2H), 3.53 – 3.41 (m, 1H), 3.27 – 3.19 (m, 1H), 2.43 (s, 3H), 2.29 (s, 3H), 2.00 – 1.90 (m, 2H), 1.81 – 1.66 (m, 2H)
47		(±)-1-(4-(6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	480	D	3.12	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (s, 1H), 8.08 (d, J = 5.5 Hz, 1H), 7.09 (d, J = 5.5 Hz, 1H), 6.45 (s, 1H), 4.40 (s, 1H), 3.99 (dd, J = 13.3, 5.8 Hz, 1H), 3.85 – 3.72 (m, 2H), 3.56 – 3.44 (m, 7H), 3.25 – 3.18 (m, 2H), 2.48 – 2.45 (m, 3H), 2.42 (t, J = 6.2 Hz, 2H), 2.31 (s, 3H), 2.00 – 1.91 (m,

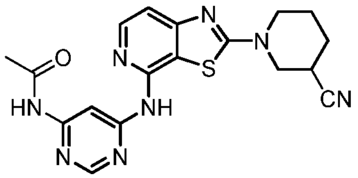
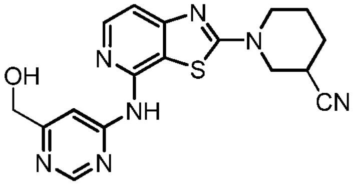
						2H), 1.74 (dt, J = 10.5, 6.9 Hz, 2H)
48		(±)-1-(4-(2-methyl-6-(trifluoromethyl)pyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	420	D	3.78	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.60 (d, J = 144.5 Hz, 1H), 8.17 (d, J = 5.5 Hz, 1H), 7.58 (s, 1H), 7.21 (d, J = 5.5 Hz, 1H), 4.03 (dd, J = 13.3, 5.6 Hz, 1H), 3.83 (dd, J = 13.3, 3.4 Hz, 2H), 3.57 – 3.43 (m, 1H), 3.24 (dd, J = 9.2, 4.8 Hz, 1H), 2.53 (s, 3H), 2.01 – 1.88 (m, 2H), 1.82 – 1.56 (m, 2H)
49		(±)-1-(4-(6-isopropyl-2-methylpyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	394	D	3.40	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (s, 1H), 8.12 (d, J = 5.5 Hz, 1H), 7.16 (d, J = 5.5 Hz, 1H), 6.98 (s, 1H), 4.01 (dd, J = 13.3, 5.7 Hz, 1H), 3.82 (dd, J = 13.3, 3.3 Hz, 2H), 3.57 – 3.43 (m, 1H), 3.27 – 3.19 (m, 1H), 2.79 (dt, J = 13.8, 6.9 Hz, 1H), 2.45 (s, 3H), 1.95 (d, J = 4.9 Hz, 2H),

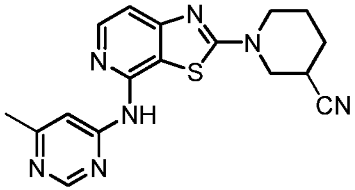
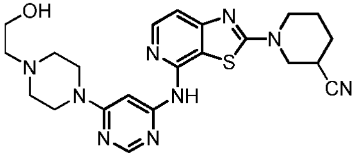
						1.84 – 1.63 (m, 2H), 1.19 (d, J = 6.9 Hz, 6H)
50		(±)-1-(4-(6-amino-2-(trifluoromethyl)pyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	421	D	3.74	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (s, 1H), 8.14 (d, J = 5.5 Hz, 1H), 7.17 (d, J = 5.5 Hz, 1H), 7.07 (s, 2H), 6.77 (s, 1H), 4.01 (dd, J = 13.3, 5.9 Hz, 1H), 3.82 (dd, J = 13.3, 3.5 Hz, 1H), 3.79 – 3.67 (m, 1H), 3.57 – 3.45 (m, 1H), 3.24 (dd, J = 9.3, 4.9 Hz, 1H), 2.02 – 1.88 (m, 2H), 1.83 – 1.64 (m, 2H)
51		(±)-1-(4-(6-amino-2-methylpyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	367	D	2.98	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.33 (s, 1H), 8.07 (d, J = 5.5 Hz, 1H), 7.08 (d, J = 5.5 Hz, 1H), 6.37 (s, 2H), 6.28 (s, 1H), 3.99 (dd, J = 13.2, 5.8 Hz, 1H), 3.87 – 3.68 (m, 2H), 3.53 – 3.44 (m, 1H), 3.26 – 3.22 (m, 1H), 2.25 (s, 3H), 1.98 – 1.93 (m, 2H), 1.84 – 1.59 (m, 2H)

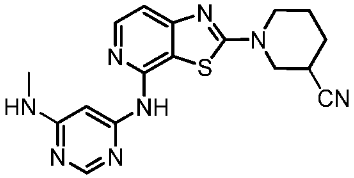
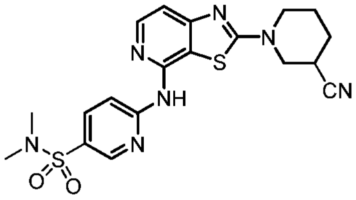
52		(±)-1-(4-(6-amino-2-morpholinopyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	438	D	3.36	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 (s, 1H), 8.06 (d, J = 5.5 Hz, 1H), 7.08 (d, J = 5.5 Hz, 1H), 6.08 (s, 2H), 5.67 (s, 1H), 4.02 (dd, J = 13.2, 5.7 Hz, 1H), 3.83 – 3.69 (m, 2H), 3.56 (s, 8H), 3.51 – 3.42 (m, 1H), 3.25 – 3.18 (m, 1H), 1.99 – 1.90 (m, 2H), 1.82 – 1.63 (m, 2H)
53		(±)-1-(4-(6-morpholinopyridazin-3-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	423	D	3.38	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.19 (s, 1H), 7.99 (d, J = 5.6 Hz, 1H), 7.32 (d, J = 9.4 Hz, 1H), 7.01 (d, J = 5.1 Hz, 1H), 4.00 (dd, J = 13.2, 5.9 Hz, 1H), 3.85 – 3.77 (m, 1H), 3.77 – 3.69 (m, 5H), 3.53 – 3.42 (m, 6H), 1.96 (dt, J = 10.8, 5.3 Hz, 2H), 1.84 – 1.63 (m, 2H)

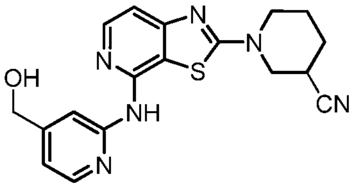
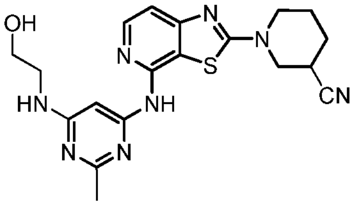
54		(±)-6-(2-(3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-ylamino)-2-methylnicotinonitrile	376	D	3.65	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H), 8.13 (d, J = 5.5 Hz, 1H), 7.93 (d, J = 8.7 Hz, 1H), 7.28 (d, J = 8.7 Hz, 1H), 7.18 (d, J = 5.5 Hz, 1H), 4.01 (dd, J = 13.3, 5.7 Hz, 1H), 3.82 (dd, J = 13.3, 3.3 Hz, 2H), 3.57 – 3.39 (m, 1H), 3.26 – 3.20 (m, 1H), 2.56 (s, 3H), 2.01 – 1.86 (m, 2H), 1.80 – 1.55 (m, 2H)
55		(±)-1-(4-(5-morpholinopyridin-2-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	422	D	3.65	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.16 (s, 1H), 7.99 (d, J = 5.5 Hz, 1H), 7.92 (d, J = 2.9 Hz, 1H), 7.50 (d, J = 9.0 Hz, 1H), 7.39 (dd, J = 9.0, 3.0 Hz, 1H), 3.99 (dd, J = 13.3, 5.9 Hz, 1H), 3.80 (dd, J = 13.3, 3.5 Hz, 1H), 3.77 – 3.73 (m, 4H), 3.71 (m, 1H), 3.53 – 3.42 (m, 1H), 3.26 – 3.19 (m, 1H), 3.11 – 3.02 (m, 4H), 2.02 – 1.88 (m, 2H), 1.84 –

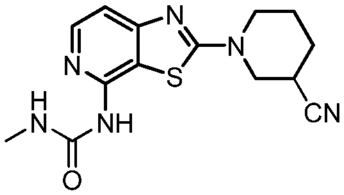
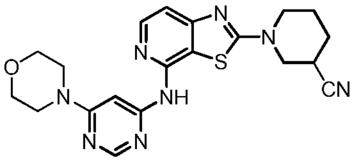
						1.59 (m, 2H)
56		(±)-1-(4-(6-aminopyridazin-3-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	353	D	2.70	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.29 (s, 1H), 7.95 (d, J = 5.5 Hz, 1H), 7.53 (d, J = 9.4 Hz, 1H), 6.98 (d, J = 5.5 Hz, 1H), 6.81 (d, J = 9.4 Hz, 1H), 5.95 (s, 2H), 3.98 (dd, J = 13.2, 6.0 Hz, 1H), 3.80 (dd, J = 13.2, 3.4 Hz, 1H), 3.76 – 3.67 (m, 1H), 3.54 – 3.42 (m, 1H), 3.27 – 3.18 (m, 1H), 1.99 – 1.90 (m, 2H), 1.82 – 1.62 (m, 2H)
57		(±)-1-(4-(2-methyl-6-morpholinopyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	437	D	3.83	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.53 (s, 1H), 8.09 (d, J = 5.5 Hz, 1H), 7.10 (d, J = 5.5 Hz, 1H), 6.47 (s, 1H), 3.99 (dd, J = 13.3, 5.8 Hz, 1H), 3.79 (td, J = 13.3, 3.9 Hz, 2H), 3.70 – 3.62 (m, 4H), 3.51 (m , 1H), 3.48 – 3.44 (m, 4H), 3.23 (m, 1H), 2.32 (s, 3H), 1.96 (m, 2H), 1.82 –

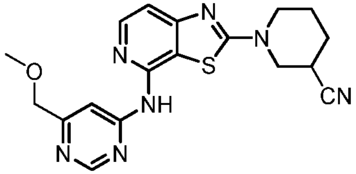
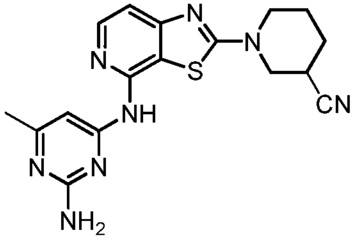
						1.65 (m, 2H)
58		(±)-N-(6-(2-(3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-ylamino)pyrimidin-4-yl)acetamide	395	D	3.24	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.52 (s, 1H), 10.04 (s, 1H), 8.39 (s, 1H), 8.13 (d, J = 5.5 Hz, 1H), 7.95 (s, 1H), 7.19 (d, J = 5.5 Hz, 1H), 4.01 (dd, J = 13.3, 5.9 Hz, 1H), 3.82 (dd, J = 13.3, 3.4 Hz, 1H), 3.78 – 3.68 (m, 1H), 3.58 – 3.48 (m, 1H), 3.24 – 3.21 (m , 1H), 3.48 – 3.44 (m, 4H), 2.09 (s, 3H), 2.09 - 1.93 (m, 2H), 1.83 – 1.61 (m, 2H)
59		(±)-1-(4-(6-(hydroxymethyl)pyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	368	D	2.95	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1H), 8.56 (s, 1H), 8.17 (d, J = 5.6 Hz, 1H), 7.45 (s, 1H), 7.21 (d, J = 5.6 Hz, 1H), 5.49 (s, 1H), 4.44 (s, 2H), 4.03 (dd, J = 13.3, 5.7 Hz, 1H), 3.82 (dd, J = 13.4, 3.5 Hz, 1H), 3.76 (dd, J = 11.6, 6.1 Hz, 1H), 3.58 – 3.46 (m, 1H), 3.24 (m, 1H), 1.97

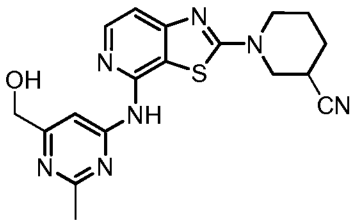
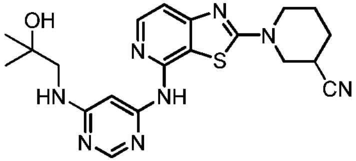
						(m, 2H), 1.83 – 1.64 (m, 2H)
60		(±)-1-(4-(6-methylpyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	352	D	3.05	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H), 8.54 (s, 1H), 8.15 (d, J = 5.5 Hz, 1H), 7.26 (s, 1H), 7.18 (d, J = 5.5 Hz, 1H), 4.02 (dd, J = 13.3, 5.9 Hz, 1H), 3.82 (dd, J = 13.3, 3.6 Hz, 1H), 3.79 – 3.70 (m, 1H), 3.55 – 3.46 (m, 1H), 3.23 (m, 1H), 2.34 (s, 3H), 2.00 – 1.90 (m, 2H), 1.73 (m 2H)
61		(±)-1-(4-(6-(4-(2-hydroxyethyl)piperazin-1-yl)pyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	466	D	2.99	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.50 (s, 1H), 8.19 (s, 1H), 8.11 (d, J = 5.5 Hz, 1H), 7.12 (d, J = 5.5 Hz, 1H), 6.72 (s, 1H), 4.38 (t, J = 5.2 Hz, 1H), 4.00 (dd, J = 13.2, 5.9 Hz, 1H), 3.81 (dd, J = 13.3, 3.5 Hz, 1H), 3.78 – 3.69 (m, 1H), 3.58 – 3.44 (m, 8H), 3.29 - 3.21 (m, 1H), 2.47 (t, J = 6.2 Hz, 2H), 2.43 (t, J = 6.2

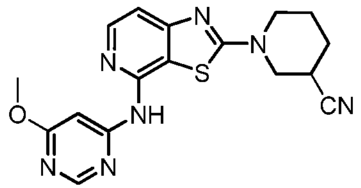
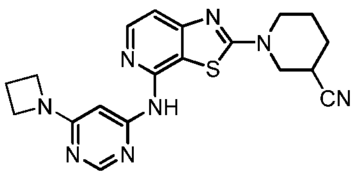
						Hz, 2H), 2.00 – 1.92 (m, 2H), 1.82 – 1.65 (m, 2H)
62		(±)-1-(4-(6-(methylamino)pyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	367	D	3.10	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.33 (s, 1H), 8.17 – 8.00 (m, 2H), 7.10 (d, J = 5.5 Hz, 1H), 6.94 (d, J = 3.8 Hz, 1H), 6.53 (s, 1H), 4.00 (dd, J = 13.3, 5.9 Hz, 1H), 3.81 (dd, J = 13.3, 3.5 Hz, 1H), 3.78 – 3.70 (m, 1H), 3.55 – 3.46 (m, 1H), 3.25 – 3.18 (m, 1H), 2.75 (d, J = 4.7 Hz, 3H), 2.00 – 1.92 (m, 2H), 1.82 – 1.64 (m, 2H)
63		(±)-6-(2-(3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-ylamino)-N,N-dimethylpyridine-3-sulfonamide	444	D	2.37	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H), 8.50 (d, J = 2.5 Hz, 1H), 8.14 (d, J = 5.5 Hz, 1H), 7.94 (dd, J = 8.9, 2.5 Hz, 1H), 7.59 (d, J = 8.9 Hz, 1H), 7.18 (d, J = 5.5 Hz, 1H), 4.03 (dd, J = 13.3, 5.8 Hz, 1H), 3.82 (dd, J = 13.4, 3.6 Hz, 1H), 3.76 (dd, J = 9.3,

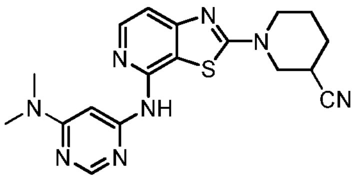
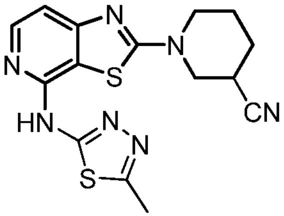
						3.6 Hz, 1H), 3.54 – 3.46 (m, 1H), 3.24 (m , 1H), 2.63 (s, 6H), 1.96 (m, 2H), 1.84 – 1.63 (m, 2H
64		(±)-1-(4-(4-(hydroxymethyl)pyridin-2-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	367	D	2.11	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (s, 1H), 8.08 (dd, J = 18.5, 5.3 Hz, 2H), 7.38 (s, 1H), 7.06 (d, J = 5.5 Hz, 1H), 6.82 (d, J = 5.0 Hz, 1H), 5.31 (t, J = 5.7 Hz, 1H), 4.48 (d, J = 5.7 Hz, 2H), 3.98 (dd, J = 13.3, 6.0 Hz, 1H), 3.80 (dd, J = 13.3, 3.6 Hz, 1H), 3.77 – 3.66 (m, 1H), 3.54 – 3.44 (m, 1H), 3.26 – 3.18 (m, 1H), 1.99 – 1.90 (m, 2H), 1.74 (m, 2H)
65		(±)-1-(4-(6-(2-hydroxyethylamino)-2-methylpyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-	411	D	2.02	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (s, 1H), 8.06 (d, J = 5.5 Hz, 1H), 7.08 (d, J = 5.5 Hz, 1H), 6.31 (s, 1H), 4.70 (t, J = 5.3 Hz, 1H), 3.99 (dd, J = 13.3, 5.9 Hz, 1H), 3.81 (dd, J

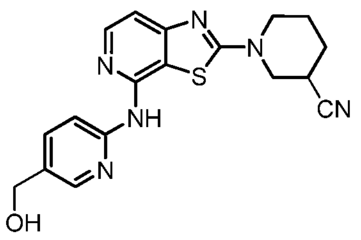
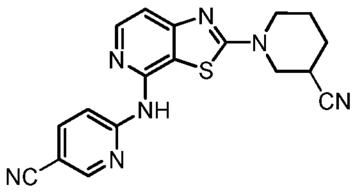
		yl)piperidine-3-carbonitrile				= 13.3, 3.5 Hz, 1H), 3.79 - 3.74 (m, 1H),3.52 - 3.48 m, 4H), 3.24 - 3.22 (m, 1H), 2.27 (s, 3H), 2.00 – 1.91 (m, 2H), 1.73 (m, 2H)
66		(±)-1-(2-(3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)-3-methylurea	317	D	2.90	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.18 (s, 1H), 8.01 (d, J = 5.6 Hz, 1H), 7.92 (s, 1H), 7.06 (d, J = 5.6 Hz, 1H), 3.99 (dd, J = 13.3, 5.9 Hz, 1H), 3.80 (dd, J = 13.3, 3.5 Hz, 1H), 3.77 – 3.69 (m, 1H), 3.54 – 3.45 (m, 1H), 3.27 – 3.20 (m, 1H), 2.73 (d, J = 4.6 Hz, 3H), 1.99 – 1.91 (m, 2H), 1.82 – 1.64 (m, 2H)
67		(±)-1-(4-(6-morpholinopyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	423	D	2.33	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.55 (s, 1H), 8.22 (s, 1H), 8.11 (d, J = 5.5 Hz, 1H), 7.12 (d, J = 5.5 Hz, 1H), 6.74 (s, 1H), 4.01 (dd, J = 13.3, 5.9 Hz, 1H), 3.81 (dd, J = 13.4, 3.6 Hz, 1H), 3.77 - 3.72

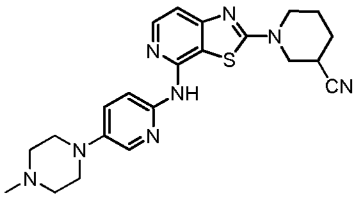
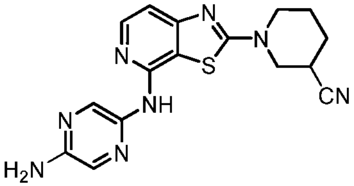
						(m, 1H), 3.70 – 3.63 (m, 4H), 3.53 - 3.52 (m 1H), 3.50 - 3.47 (m, 4H), 3.26 - 3.21 (m, 1H), 2.00 – 1.89 (m, 2H), 1.82 – 1.64 (m, 2H)
68		(±)-1-(4-(6-(methoxymethyl)pyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	382	D	2.04	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (s, 1H), 8.58 (s, 1H), 8.16 (d, J = 5.5 Hz, 1H), 7.38 (s, 1H), 7.20 (d, J = 5.5 Hz, 1H), 4.39 (s, 2H), 4.02 (dd, J = 13.4, 5.9 Hz, 1H), 3.82 (dd, J = 13.3, 3.6 Hz, 1H), 3.77 - 3.74 (m, 1H), 3.55 – 3.47 (m, 1H), 3.40 (s, 3H), 3.27 – 3.20 (m, 1H), 1.99 – 1.92 (m, 2H), 1.78 - 1.69 (m 2H)
69		(±)-1-(4-(2-amino-6-methylpyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-	367	D	2.77	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.55 (s, 1H), 8.09 (d, J = 5.5 Hz, 1H), 7.12 (d, J = 5.5 Hz, 1H), 6.25 (s, 1H), 6.10 (s, 2H), 4.00 (dd, J = 13.3, 6.0 Hz, 1H), 3.81 (dd, J = 13.3,

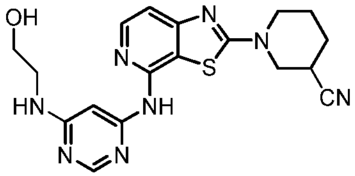
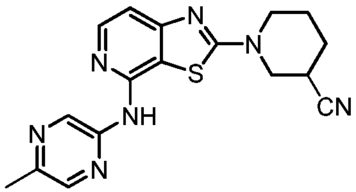
		carbonitrile				3.6 Hz, 1H), 3.77 – 3.69 (m, 1H), 3.56 – 3.46 (m, 1H), 3.26 – 3.19 (m, 1H), 2.12 (s, 3H), 2.00 – 1.89 (m, 2H), 1.81 – 1.63 (m, 2H)
70		(±)-1-(4-(6-(hydroxymethyl)-2-methylpyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	382	D	3.0	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 8.13 (d, J = 5.5 Hz, 1H), 7.21 (s, 1H), 7.17 (d, J = 5.5 Hz, 1H), 5.39 (s, 1H), 4.39 (s, 2H), 4.00 (dd, J = 13.3, 5.8 Hz, 1H), 3.84 - 3.80 (m, 2H), 3.55 – 3.44 (m, 1H), 3.25 - 3.22 (m, 1H), 2.43 (s, 3H), 1.99 – 1.92 (m, 2H), 1.79 - 1.69 (m, 2H)
71		(±)-1-(4-(6-(2-hydroxy-2-methylpropylamino)pyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	425	D	2.18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.33 (s, 1H), 8.10 (d, J = 5.5 Hz, 2H), 7.10 (d, J = 5.5 Hz, 1H), 6.87 (s, 1H), 6.66 (s, 1H), 4.55 (s, 1H), 4.00 (dd, J = 13.3, 5.9 Hz, 1H), 3.81 (dd, J = 13.3, 3.5 Hz, 1H), 3.75 - 3.72 (m, 1H), 3.54 – 3.46 (m,

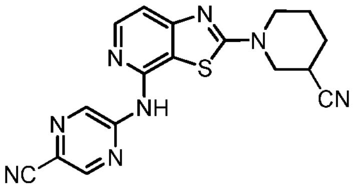
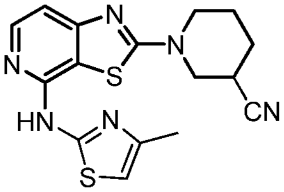
						1H), 3.24 - 3.21 (m 3H), 1.99 – 1.91 (m, 2H), 1.82 – 1.64 (m, 2H), 1.10 (s, 6H)
72		(±)-1-(4-(6-methoxypyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	368	D	3.38	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.40 (s, 1H), 8.14 (d, J = 5.5 Hz, 1H), 7.16 (d, J = 5.5 Hz, 1H), 6.97 (s, 1H), 4.01 (dd, J = 13.3, 5.9 Hz, 1H), 3.87 (s, 3H), 3.82 (dd, J = 13.3, 3.6 Hz, 1H), 3.79 – 3.71 (m, 1H), 3.55 – 3.47 (m, 2H), 1.99 – 1.92 (m, 2H), 1.749 - 1.69 (m, 2H)
73		(±)-1-(4-(6-(azetidin-1-yl)pyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	393	D	3.44	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (s, 1H), 8.15 (s, 1H), 8.10 (d, J = 5.5 Hz, 1H), 7.11 (d, J = 5.5 Hz, 1H), 6.32 (s, 1H), 4.04 – 3.99 (m, 1H), 3.96 (t, J = 7.5 Hz, 4H), 3.81 (dd, J = 13.3, 3.6 Hz, 1H), 3.78 - 3.73 (m, 1H), 3.53 – 3.46 (m, 1H), 33.25 - .23 (m,

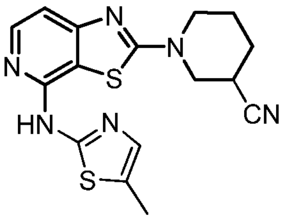
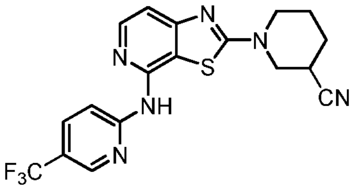
						1H), 2.38 – 2.29 (m, 2H), 1.98 - 1.93 (m, 2H), 1.82 – 1.65 (m, 2H)
74		(±)-1-(4-(6-(dimethylamino)pyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	381	D	3.53	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (s, 1H), 8.17 (s, 1H), 8.10 (d, J = 5.5 Hz, 1H), 7.11 (d, J = 5.5 Hz, 1H), 6.61 (s, 1H), 4.01 (dd, J = 13.3, 5.9 Hz, 1H), 3.81 (dd, J = 13.3, 3.6 Hz, 1H), 3.78 – 3.69 (m, 1H), 3.54 – 3.45 (m, 1H), 3.27 – 3.20 (m, 1H), 3.02 (s, 6H), 2.00 – 1.89 (m, 2H), 1.82 – 1.65 (m, 2H)
75		(±)-1-(4-(5-methyl-1,3,4-thiadiazol-2-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	358	D	3.45	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.01 (d, J = 5.6 Hz, 1H), 6.86 (d, J = 4.9 Hz, 1H), 3.97 (dd, J = 13.2, 6.0 Hz, 1H), 3.82 (dd, J = 13.2, 3.6 Hz, 1H), 3.77 – 3.68 (m, 1H), 3.54 – 3.46 (m, 1H), 3.24 - 3.21 (m, 1H), 2.48 (s, 3H), 1.99 – 1.92 (m, 2H),

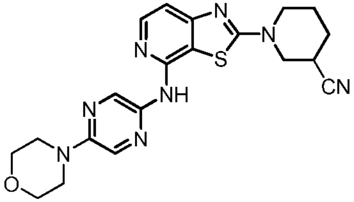
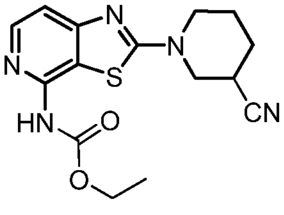
						1.83 – 1.66 (m, 2H)
76		(±)-1-(4-(5-(hydroxymethyl)pyridin-2-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	367	D	3.21	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.48 (s, 1H), 8.13 (d, J = 2.0 Hz, 1H), 8.05 (d, J = 5.5 Hz, 1H), 7.60 (dd, J = 8.5, 2.3 Hz, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.05 (d, J = 5.5 Hz, 1H), 5.12 (s, 1H), 4.43 (s, 2H), 3.99 (dd, J = 13.2, 5.9 Hz, 1H), 3.80 (dd, J = 13.3, 3.5 Hz, 1H), 3.76 – 3.68 (m, 1H), 3.53 – 3.44 (m, 1H), 3.26 – 3.18 (m, 1H), 2.00 – 1.89 (m, 2H), 1.79 - 1.68 (m, 2H)
77		(±)-6-(2-(3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-ylamino)nicotinonitrile	362	D	3.44	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.35 (s, 1H), 8.62 (d, J = 2.2 Hz, 1H), 8.14 (d, J = 5.5 Hz, 1H), 8.00 (dd, J = 8.9, 2.3 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.18 (d, J = 5.5 Hz, 1H), 4.03 (dd, J = 13.3, 5.9 Hz, 1H), 3.82 (dd, J = 13.4, 3.6 Hz, 1H), 3.79 - 3.75 (m,

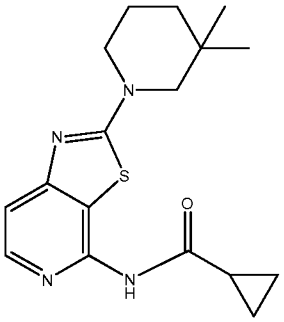
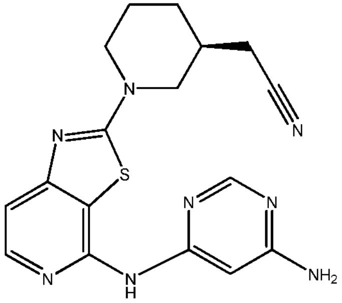
						1H), 3.56 – 3.45 (m, 1H), 3.27 – 3.19 (m, 1H), 2.00 – 1.91 (m, 2H), 1.80 – 1.66 (m, 2H)
78		(±)-1-(4-(5-(4-methylpiperazin-1-yl)pyridin-2-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	435	D	2.98	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.14 (s, 1H), 7.99 (d, J = 5.5 Hz, 1H), 7.91 (d, J = 2.9 Hz, 1H), 7.48 (d, J = 9.0 Hz, 1H), 7.38 (dd, J = 9.1, 3.0 Hz, 1H), 6.98 (d, J = 5.5 Hz, 1H), 3.98 (dd, J = 13.2, 6.0 Hz, 1H), 3.79 (dd, J = 13.3, 3.5 Hz, 1H), 3.76 – 3.68 (m, 1H), 3.52 – 3.43 (m, 1H), 3.26 – 3.19 (m, 1H), 3.12 – 3.04 (m, 4H), 2.48 – 2.43 (m, 4H), 2.22 (s, 3H), 1.98 – 1.91 (m, 2H), 1.78 - 1.68 (m, 2H)
79		(±)-1-(4-(5-aminopyrazin-2-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-	353	D	3.08	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.89 (s, 1H), 8.31 (d, J = 1.2 Hz, 1H), 7.95 (d, J = 5.6 Hz, 1H), 7.66 (d, J = 1.4 Hz, 1H), 6.93 (d, J = 5.5 Hz, 1H),

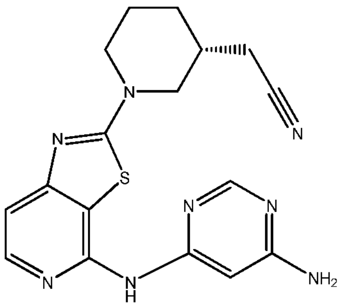
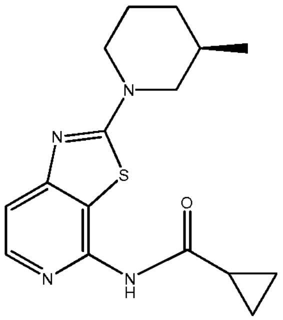
		carbonitrile				5.96 (s, 2H), 3.96 (dd, J = 13.3, 5.9 Hz, 1H), 3.79 (dd, J = 13.3, 3.5 Hz, 1H), 3.75 – 3.67 (m, 1H), 3.50 – 3.42 (m, 1H), 3.26 - 3.21 (m, 1H), 1.97 - 1.92 (m, 2H), 1.80 – 1.64 (m, 2H)
80		(±)-1-(4-(6-(2-hydroxyethylamino)pyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	397	D	3.12	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (s, 1H), 8.11 (s, 1H), 8.09 (d, J = 5.5 Hz, 1H), 7.10 (d, J = 5.5 Hz, 1H), 7.01 (s, 1H), 6.59 (s, 1H), 4.68 (t, J = 5.5 Hz, 1H), 4.00 (dd, J = 13.2, 5.9 Hz, 1H), 3.81 (dd, J = 13.3, 3.5 Hz, 1H), 3.78 – 3.69 (m, 1H), 3.57 – 3.43 (m, 4H), 3.25 - 3.23 (m, 1H), 2.00 – 1.91 (m, 2H), 1.82 – 1.63 (m, 2H)
81		(±)-1-(4-(5-methylpyrazin-2-ylamino)thiazolo[5,4-c]pyridin-2-	352	D	3.26	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (s, 1H), 8.82 (s, 1H), 8.13 (s, 1H), 8.07 (d, J = 5.5 Hz, 1H), 7.09 (d, J = 5.5

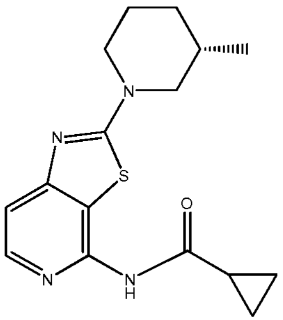
		yl)piperidine-3-carbonitrile				Hz, 1H), 4.01 (dd, J = 13.3, 5.9 Hz, 1H), 3.81 (dd, J = 13.3, 3.6 Hz, 1H), 3.77 - 3.73 (m, 1H), 3.54 – 3.46 (m, 1H), 3.26 – 3.21 (m, 1H), 2.40 (s, 3H), 1.98 – 1.92 (m, 2H), 1.82 – 1.64 (m, 2H)
82		(±)-5-(2-(3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-ylamino)pyrazine-2-carbonitrile	363	D	3.30	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (s, 1H), 8.71 (s, 1H), 8.16 (d, J = 5.7 Hz, 1H), 7.22 (d, J = 5.7 Hz, 1H), 4.05 (dd, J = 13.3, 5.9 Hz, 1H), 3.83 (dd, J = 13.4, 3.5 Hz, 1H), 3.80 – 3.73 (m, 1H), 3.57 – 3.47 (m, 1H), 3.26 - 3.23 (m, 1H), 1.99 - 1.94 (m, 2H), 1.82 – 1.66 (m, 2H)
83		(±)-1-(4-(4-methylthiazol-2-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	357	D	3.60	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 1H), 8.10 (d, J = 5.6 Hz, 1H), 7.01 (d, J = 5.6 Hz, 1H), 6.46 (s, 1H), 4.00 (dd, J = 13.2, 5.9 Hz, 1H), 3.82 (dd, J = 13.3, 3.5 Hz,

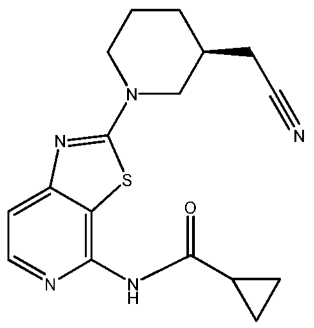
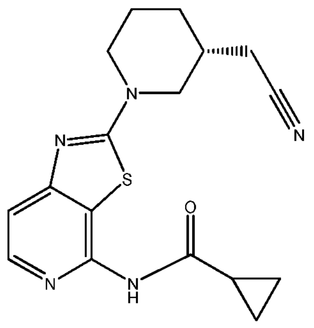
						1H), 3.79 – 3.70 (m, 1H), 3.55 – 3.47 (m, 1H), 3.28 – 3.24 (m, 1H), 2.22 (s, 3H), 1.99 – 1.93 (m, 2H), 1.83 – 1.66 (m, 2H)
84		(±)-1-(4-(5-methylthiazol-2-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	357	D	3.62	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.26 (s, 1H), 8.08 (d, J = 5.6 Hz, 1H), 7.00 (d, J = 4.1 Hz, 2H), 4.00 (dd, J = 13.3, 5.9 Hz, 1H), 3.82 (dd, J = 13.3, 3.5 Hz, 1H), 3.78 – 3.70 (m, 1H), 3.55 – 3.46 (m, 1H), 3.29 – 3.22 (m, 1H), 2.29 (s, 3H), 2.00 – 1.92 (m, 2H), 1.78 - 1.68 (m, 2H)
85		(±)-1-(4-(5-(trifluoromethyl)pyridin-2-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	405	D	3.98	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.54 (s, 1H), 8.13 (d, J = 5.5 Hz, 1H), 7.97 (dd, J = 8.9, 2.5 Hz, 1H), 7.57 (d, J = 8.9 Hz, 1H), 7.17 (d, J = 5.5 Hz, 1H), 4.03 (dd, J = 13.3, 5.8 Hz, 1H), 3.85 – 3.78 (m, 1H), 3.80 - 3.74 (m

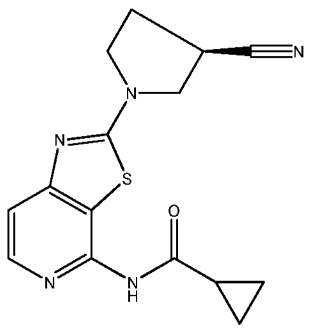
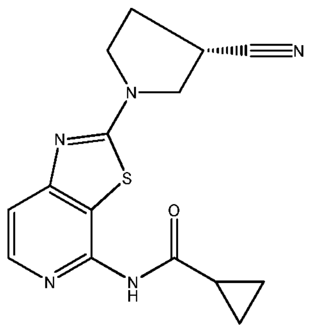
						1H), 3.55 – 3.46 (m, 1H), 3.28 – 3.19 (m, 1H), 2.01 – 1.90 (m, 2H), 1.81 – 1.63 (m, 2H)
86		(±)-1-(4-(5-morpholinopyrazin-2-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	423	D	3.60	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (s, 1H), 8.62 (d, J = 1.2 Hz, 1H), 8.02 (d, J = 1.2 Hz, 1H), 7.98 (d, J = 5.5 Hz, 1H), 6.98 (d, J = 5.5 Hz, 1H), 3.99 (dd, J = 13.3, 5.9 Hz, 1H), 3.80 (dd, J = 13.3, 3.5 Hz, 1H), 3.75 -5 3.72 (m, 5H), 3.53 – 3.45 (m, 1H), 3.43 – 3.37 (m, 4H), 3.27 – 3.21 (m, 1H), 1.98 - 1.93 (m, 2H), 1.82 – 1.64 (m, 2H)
87		(±)-ethyl 2-(3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-ylcarbamate	332	D	3.02	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 8.10 (d, J = 5.4 Hz, 1H), 7.21 (d, J = 5.5 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 4.02 (dd, J = 13.3, 5.9 Hz, 1H), 3.82 (dd, J = 13.3, 3.4 Hz, 1H), 3.78 -3.73

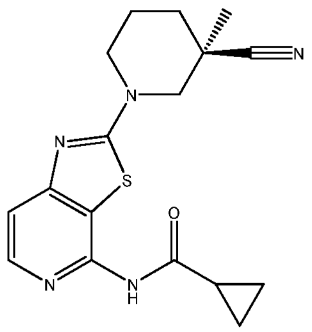
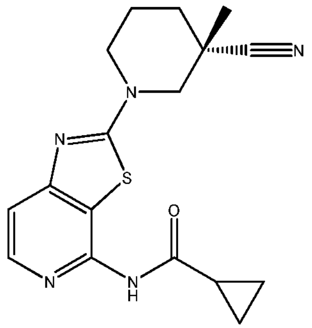
						(m, 1H), 3.57 – 3.47 (m, 1H), 3.27 – 3.18 (m, 1H), 2.01 – 1.88 (m, 2H), 1.83 – 1.62 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H)
88		N-(2-(3,3-dimethylpiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	331	D	3.96	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.79 (s, 1H), 8.07 (d, *J* = 5.5 Hz, 1H), 7.13 (d, *J* = 5.5 Hz, 1H), 3.58 (d, *J* = 5.3 Hz, 2H), 2.06 – 1.89 (m, 1H), 1.73 – 1.58 (m, 2H), 1.51 – 1.38 (m, 2H), 0.94 (s, 6H), 0.84 (t, *J* = 7.2 Hz, 4H).
89		(*S*)-2-(1-(4-(6-aminopyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidin-3-yl)acetonitrile	366	SFC:Chiralpak OJ @35% methanol w/ 0.1% NH_4OH	0.54	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (s, 1H), 8.07 (d, *J* = 5.5 Hz, 1H), 8.04 (s, 1H), 7.08 (d, *J* = 5.5 Hz, 1H), 6.53 (s, 1H), 6.46 (s, 2H), 4.13 (d, *J* = 11.5 Hz, 1H), 3.91 (d, *J* = 11.5 Hz, 1H), 3.23 – 3.17 (m, 1H), 3.04 (dd, *J* = 12.7, 10.6 Hz, 1H), 2.71 – 2.54 (m, 2H), 2.04 – 1.87 (m, 2H), 1.81 (d, *J* = 13.6 Hz, 1H), 1.58 (d, *J* =

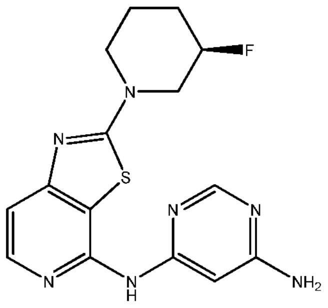
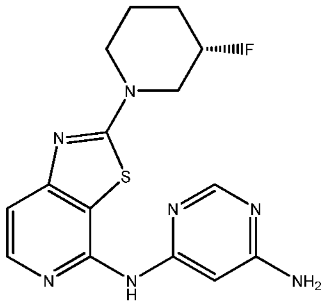
						12.3 Hz, 1H), 1.38 (dd, *J* = 21.4, 10.4 Hz, 1H).
90		(*R*)-2-(1-(4-(6-aminopyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidin-3-yl)acetonitrile	366	SFC: Chiralpak OJ @35% methanol w/ 0.1% NH_4OH	0.43	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.41 – 9.20 (m, 1H), 8.07 (d, *J* = 5.5 Hz, 1H), 8.05 (s, 1H), 7.08 (d, *J* = 5.5 Hz, 1H), 6.53 (s, 1H), 6.46 (s, 2H), 4.13 (d, *J* = 12.0 Hz, 1H), 3.91 (d, *J* = 12.4 Hz, 1H), 3.21 – 3.16 (m, 1H), 3.10 – 3.00 (m, 1H), 2.72 – 2.55 (m, 3H), 2.04 – 1.86 (m, 2H), 1.81 (d, *J* = 13.5 Hz, 1H), 1.58 (d, *J* = 12.8 Hz, 1H), 1.38 (dd, *J* = 20.5, 11.0 Hz, 1H).
91		(*R*)-N-(2-(3-methylpiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	316	SFC:Chiralpak AD (@35% methanol w/ 0.1% NH_4OH	0.60	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.80 (s, 1H), 8.08 (d, *J* = 5.5 Hz, 1H), 7.15 (d, *J* = 5.5 Hz, 1H), 3.97 (d, *J* = 9.8 Hz, 2H), 3.15 (dd, *J* = 18.0, 7.7 Hz, 1H), 2.92 – 2.79 (m, 1H), 1.98 (p, *J* = 6.2 Hz, 1H),

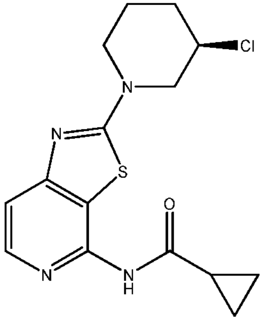
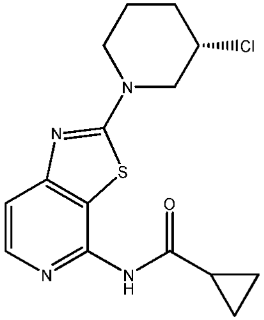
						1.86 – 1.61 (m, 3H), 1.59 – 1.42 (m, 1H), 1.21 (dt, *J* = 11.6, 6.2 Hz, 1H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 6.2 Hz, 4H).
92		(*S*)-N-(2-(3-methylpiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	316	SFC:Chiralpak AD (@35% methanol w/ 0.1% NH_4OH	0.96	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.80 (s, 1H), 8.08 (d, *J* = 5.5 Hz, 1H), 7.15 (d, *J* = 5.5 Hz, 1H), 3.97 (d, *J* = 9.8 Hz, 2H), 3.15 (dd, *J* = 18.0, 7.7 Hz, 1H), 2.92 – 2.79 (m, 1H), 1.98 (p, *J* = 6.2 Hz, 1H), 1.86 – 1.61 (m, 3H), 1.59 – 1.42 (m, 1H), 1.21 (dt, *J* = 11.6, 6.2 Hz, 1H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 6.2 Hz, 4H).

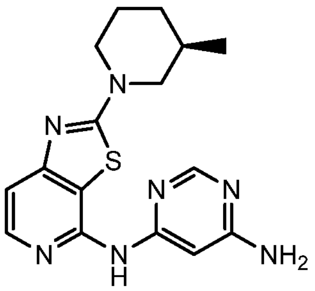
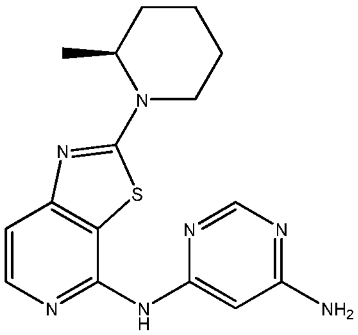
93		(*S*)-N-(2-(3-(cyanomethyl)piperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	341	SFC: Chiralpak AD @45% methanol w/ 0.1% NH_4OH	0.76	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 8.09 (t, *J* = 5.9 Hz, 1H), 7.16 (t, *J* = 8.5 Hz, 1H), 4.14 (d, *J* = 12.1 Hz, 1H), 3.94 (d, *J* = 11.2 Hz, 1H), 3.25 – 3.13 (m, 1H), 3.02 (dd, *J* = 12.6, 10.8 Hz, 1H), 2.63 (qd, *J* = 17.0, 6.5 Hz, 2H), 2.02 – 1.86 (m, 3H), 1.85 – 1.74 (m, 1H), 1.56 (dd, *J* = 24.7, 12.1 Hz, 1H), 1.37 (dd, *J* = 21.0, 10.9 Hz, 1H), 0.90 – 0.78 (m, 4H).
94		(*R*)-N-(2-(3-(cyanomethyl)piperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	341	SFC: Chiralpak AD @45% methanol w/ 0.1% NH_4OH	0.53	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 8.09 (t, *J* = 5.9 Hz, 1H), 7.16 (t, *J* = 8.5 Hz, 1H), 4.14 (d, *J* = 12.1 Hz, 1H), 3.94 (d, *J* = 11.2 Hz, 1H), 3.25 – 3.13 (m, 1H), 3.02 (dd, *J* = 12.6, 10.8 Hz, 1H), 2.63 (qd, *J* = 17.0, 6.5 Hz, 2H), 2.02 – 1.86 (m, 3H), 1.85 – 1.74 (m, 1H), 1.56 (dd,

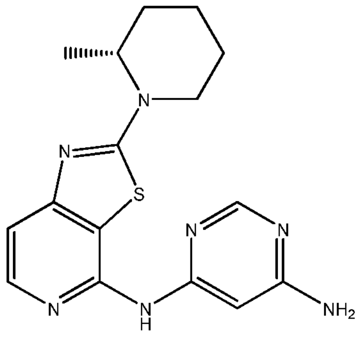
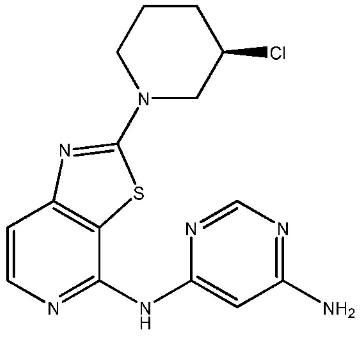
						J = 24.7, 12.1 Hz, 1H), 1.37 (dd, J = 21.0, 10.9 Hz, 1H), 0.90 – 0.78 (m, 4H).
95		(*R*)-N-(2-(3-cyanopyrrolidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	313	SFC:Chiralpak AD @ 50% Methanol w/ 0.1%NH_4OH	0.81	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.85 (s, 1H), 8.11 (d, J = 5.5 Hz, 1H), 7.23 (d, J = 5.5 Hz, 1H), 3.95 – 3.85 (m, 1H), 3.76 (dd, J = 10.4, 5.8 Hz, 1H), 3.71 – 3.52 (m, 2H), 2.48 – 2.39 (m, 1H), 2.33 (td, J = 13.6, 6.8 Hz, 1H), 2.05 – 1.93 (m, 1H), 0.85 (d, J = 6.2 Hz, 2H).
96		(*S*)-N-(2-(3-cyanopyrrolidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	313	SFC:Chiralpak AD @ 50% Methanol w/ 0.1%NH_4OH	0.62	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.85 (s, 1H), 8.11 (d, J = 5.5 Hz, 1H), 7.23 (d, J = 5.5 Hz, 1H), 3.95 – 3.85 (m, 1H), 3.76 (dd, J = 10.4, 5.8 Hz, 1H), 3.71 – 3.52 (m, 2H), 2.48 – 2.39 (m, 1H), 2.33 (td, J = 13.6, 6.8 Hz, 1H), 2.05 – 1.93 (m, 1H), 0.85 (d, J = 6.2 Hz, 2H).

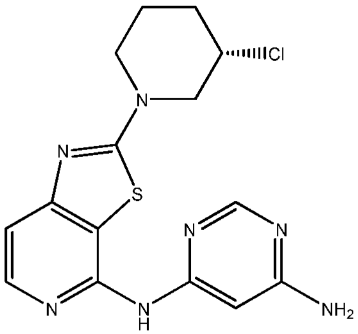
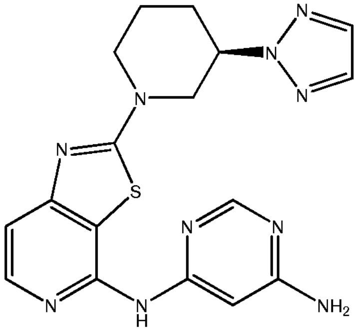
97		(*R*)-N-(2-(3-cyano-3-methylpiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	341	SFC:Chiralpak AD @ 30% Methanol w/ 0.1%NH_4OH	0.62	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.85 (s, 1H), 8.11 (d, *J* = 5.5 Hz, 1H), 7.20 (d, *J* = 5.5 Hz, 1H), 4.38 (d, *J* = 13.1 Hz, 1H), 4.05 (d, *J* = 13.3 Hz, 1H), 3.26 – 3.14 (m, 2H), 2.07 (t, *J* = 6.3 Hz, 1H), 1.99 (p, *J* = 6.2 Hz, 1H), 1.83 (ddd, *J* = 17.7, 8.8, 5.5 Hz, 1H), 1.75 (dd, *J* = 9.9, 6.3 Hz, 1H), 1.65 (td, *J* = 12.5, 3.6 Hz, 1H), 1.39 (s, 2H), 0.89 – 0.81 (m, 3H).
98		(*S*)-N-(2-(3-cyano-3-methylpiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	341	SFC:Chiralpak AD @ 30% Methanol w/ 0.1%NH_4OH	0.95	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.85 (s, 1H), 8.11 (d, *J* = 5.5 Hz, 1H), 7.20 (d, *J* = 5.5 Hz, 1H), 4.38 (d, *J* = 13.1 Hz, 1H), 4.05 (d, *J* = 13.3 Hz, 1H), 3.26 – 3.14 (m, 2H), 2.07 (t, *J* = 6.3 Hz, 1H), 1.99 (p, *J* = 6.2 Hz, 1H), 1.83 (ddd, *J* = 17.7, 8.8, 5.5 Hz, 1H), 1.75 (dd, *J* = 9.9, 6.3

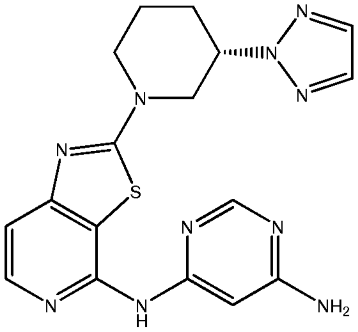
						Hz, 1H), 1.65 (td, J = 12.5, 3.6 Hz, 1H), 1.39 (s, 2H), 0.89 – 0.81 (m, 3H).
99		(*R*)-N4-(2-(3-fluoropiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	345	SFC:Chiralpak OJ @30% methanol w/ 0.1% NH_4OH	0.43	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.27 (s, 1H), 8.14 – 8.01 (m, 2H), 7.07 (d, J = 5.5 Hz, 1H), 6.54 (s, 1H), 6.44 (s, 2H), 4.96 (s, 1H), 4.84 (s, 1H), 4.11 – 3.96 (m, 1H), 3.86 (d, J = 13.0 Hz, 1H), 3.79 – 3.59 (m, 1H), 3.41 (dd, J = 16.3, 6.7 Hz, 1H), 2.03 – 1.90 (m, 2H), 1.85 (d, J = 10.1 Hz, 2H), 1.64 (dd, J = 8.9, 4.1 Hz, 1H).
100		(*S*)-N4-(2-(3-fluoropiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	345	SFC:Chiralpak OJ @30% methanol w/ 0.1% NH_4OH	0.58	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.27 (s, 1H), 8.14 – 8.01 (m, 2H), 7.07 (d, J = 5.5 Hz, 1H), 6.54 (s, 1H), 6.44 (s, 2H), 4.96 (s, 1H), 4.84 (s, 1H), 4.11 – 3.96 (m, 1H), 3.86 (d, J = 13.0 Hz, 1H), 3.79 – 3.59 (m, 1H), 3.41 (dd,

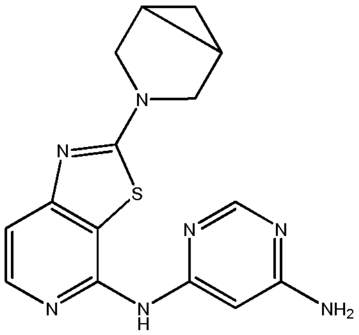
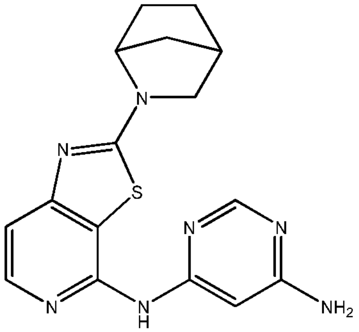
						J = 16.3, 6.7 Hz, 1H), 2.03 – 1.90 (m, 2H), 1.85 (d, J = 10.1 Hz, 2H), 1.64 (dd, J = 8.9, 4.1 Hz, 1H).
101		(*R*)-N-(2-(3-chloropiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	336	SFC:Chiralpak IC @40% methanol w/ 0.1% NH_4OH	0.81	^1H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 8.10 (d, J = 5.5 Hz, 1H), 7.18 (d, J = 5.5 Hz, 1H), 4.39 (td, J = 7.1, 3.5 Hz, 1H), 4.17 – 4.00 (m, 1H), 3.72 (dd, J = 13.5, 7.1 Hz, 1H), 3.68 – 3.54 (m, 2H), 2.18 (dd, J = 9.1, 4.1 Hz, 1H), 2.03 – 1.94 (m, 1H), 1.88 (ddd, J = 12.0, 9.2, 3.8 Hz, 2H), 1.72 – 1.58 (m, 1H), 0.84 (d, J = 6.2 Hz, 3H).
102		(*S*)-N-(2-(3-chloropiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	336	SFC:Chiralpak IC @40% methanol w/ 0.1% NH_4OH	0.65	^1H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 8.10 (d, J = 5.5 Hz, 1H), 7.18 (d, J = 5.5 Hz, 1H), 4.39 (td, J = 7.1, 3.5 Hz, 1H), 4.17 – 4.00 (m, 1H), 3.72 (dd, J = 13.5, 7.1 Hz, 1H), 3.68 – 3.54 (m, 2H),

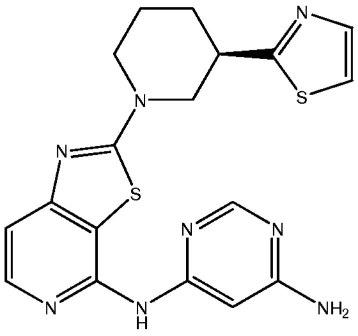
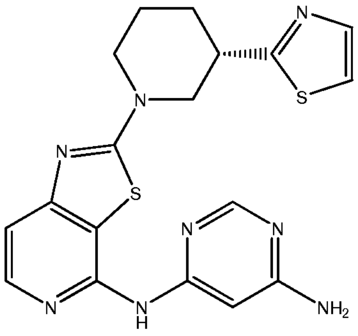
						2.18 (dd, *J* = 9.1, 4.1 Hz, 1H), 2.03 – 1.94 (m, 1H), 1.88 (ddd, *J* = 12.0, 9.2, 3.8 Hz, 2H), 1.72 – 1.58 (m, 1H), 0.84 (d, *J* = 6.2 Hz, 3H).
103		(*R*)-N4-(2-(3-methylpiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	342	D	2.38	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (s, 1H), 8.06 (d, *J* = 5.5 Hz, 1H), 8.04 (s, 1H), 7.05 (d, *J* = 5.5 Hz, 1H), 6.53 (s, 1H), 6.43 (s, 2H), 3.96 (s, 2H), 3.20 (dd, *J* = 17.4, 7.5 Hz, 2H), 2.87 (dd, *J* = 12.8, 10.7 Hz, 1H), 1.86 – 1.63 (m, 3H), 1.53 (dd, *J* = 15.3, 9.5 Hz, 1H), 1.30 – 1.15 (m, 2H), 0.93 (d, *J* = 6.6 Hz, 3H).
104		(*S*)-N4-(2-(2-methylpiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	342	SFC:Chiralpak OJ @25% methanol w/ 0.1% NH_4OH	3.48	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (s, 1H), 8.06 (d, *J* = 5.5 Hz, 1H), 8.04 (s, 1H), 7.05 (d, *J* = 5.5 Hz, 1H), 6.54 (s, 1H), 6.43 (s, 2H), 4.40 (s, 1H), 3.89 (d, *J* = 12.5 Hz, 1H), 1.73 (dd, *J* = 21.2, 12.8

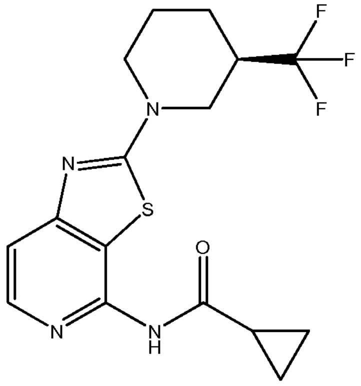
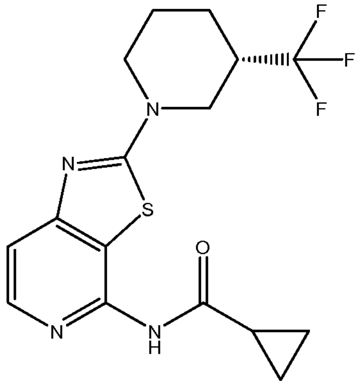
						Hz, 2H), 1.62 (d, J = 10.0 Hz, 2H), 1.49 (d, J = 13.1 Hz, 1H), 1.26 (d, J = 6.8 Hz, 2H).
105		(*R*)-N4-(2-(2-methylpiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	342	SFC:Chiralpak OJ @25% methanol w/ 0.1% NH_4OH	3.49	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (s, 1H), 8.06 (d, J = 5.5 Hz, 1H), 8.04 (s, 1H), 7.05 (d, J = 5.5 Hz, 1H), 6.54 (s, 1H), 6.43 (s, 2H), 4.40 (s, 1H), 3.89 (d, J = 12.5 Hz, 1H), 1.73 (dd, J = 21.2, 12.8 Hz, 2H), 1.62 (d, J = 10.0 Hz, 2H), 1.49 (d, J = 13.1 Hz, 1H), 1.26 (d, J = 6.8 Hz, 2H).
106		(*R*)-N4-(2-(3-chloropiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	361	SFC:Phenomenex Cellulose-3 @30% methanol w/ 0.1% NH_4OH	0.38	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 5H), 8.08 (d, J = 5.5 Hz, 1H), 8.05 (s, 1H), 7.45 – 7.30 (m, 1H), 7.08 (d, J = 5.5 Hz, 1H), 6.54 (s, 1H), 6.45 (s, 2H), 4.46 – 4.36 (m, 3H), 4.09 (dd, J = 13.5, 3.2 Hz, 2H), 3.73 (dd, J = 13.5, 7.1 Hz, 2H), 3.69 – 3.54 (m, 2H), 2.19 (d, J = 9.3 Hz, 1H),

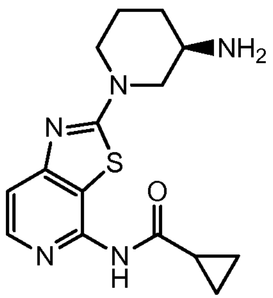
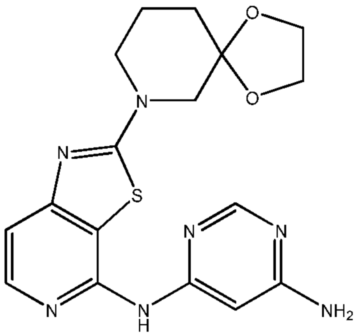
						1.97 – 1.82 (m, 2H), 1.67 (d, *J* = 16.2 Hz, 1H).
107		(*S*)-N4-(2-(3-chloropiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	361	SFC:Phenomenex Cellulose-3 @30% methanol w/ 0.1% NH_4OH	0.42	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 5H), 8.08 (d, *J* = 5.5 Hz, 1H), 8.05 (s, 1H), 7.45 – 7.30 (m, 1H), 7.08 (d, *J* = 5.5 Hz, 1H), 6.54 (s, 1H), 6.45 (s, 2H), 4.46 – 4.36 (m, 3H), 4.09 (dd, *J* = 13.5, 3.2 Hz, 2H), 3.73 (dd, *J* = 13.5, 7.1 Hz, 2H), 3.69 – 3.54 (m, 2H), 2.19 (d, *J* = 9.3 Hz, 1H), 1.97 – 1.82 (m, 2H), 1.67 (d, *J* = 16.2 Hz, 1H).
108		(*R*)-N4-(2-(3-(2H-1,2,3-triazol-2-yl)piperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	394	SFC:Phenomenex Cellulose-3 @30% methanol w/ 0.1% NH_4OH	0.56	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (s, 1H), 8.63 (s, 1H), 8.09 (d, *J* = 5.5 Hz, 1H), 8.04 (d, *J* = 11.0 Hz, 2H), 7.10 (d, *J* = 5.5 Hz, 1H), 6.54 (s, 1H), 6.48 (s, 2H), 4.59 (ddd, *J* = 14.0, 9.6, 4.1 Hz, 1H), 4.39 (d, *J* = 12.3 Hz, 1H), 3.90 (d, *J* = 13.3 Hz,

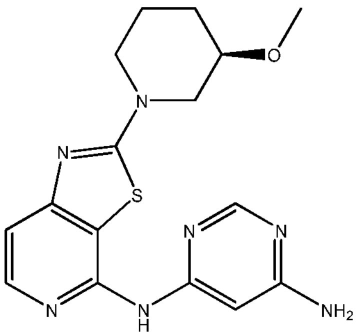
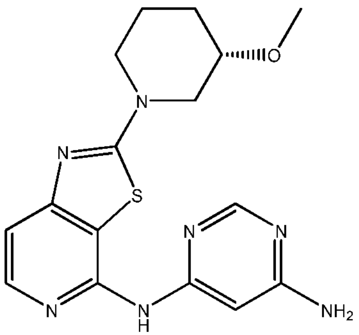
						1H), 3.65 (dd, J = 12.8, 9.7 Hz, 1H), 3.48 – 3.36 (m, 2H), 2.30 – 2.07 (m, 2H), 1.92 (dd, J = 10.5, 3.2 Hz, 1H), 1.74 (dd, J = 24.9, 11.1 Hz, 1H).
109		(*S*)-N4-(2-(3-(2H-1,2,3-triazol-2-yl)piperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	394	SFC:Phenomenex Cellulose-3 @30% methanol w/ 0.1% NH_4OH	0.67	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (s, 1H), 8.63 (s, 1H), 8.09 (d, J = 5.5 Hz, 1H), 8.04 (d, J = 11.0 Hz, 2H), 7.10 (d, J = 5.5 Hz, 1H), 6.54 (s, 1H), 6.48 (s, 2H), 4.59 (ddd, J = 14.0, 9.6, 4.1 Hz, 1H), 4.39 (d, J = 12.3 Hz, 1H), 3.90 (d, J = 13.3 Hz, 1H), 3.65 (dd, J = 12.8, 9.7 Hz, 1H), 3.48 – 3.36 (m, 2H), 2.30 – 2.07 (m, 2H), 1.92 (dd, J = 10.5, 3.2 Hz, 1H), 1.74 (dd, J = 24.9, 11.1 Hz, 1H).

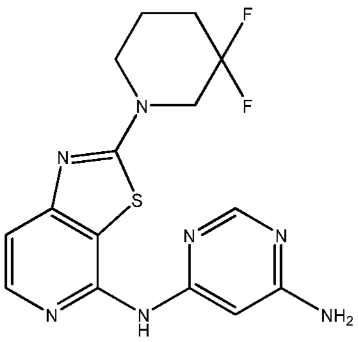
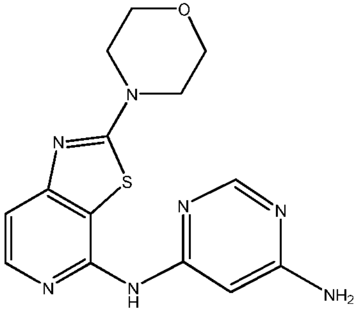
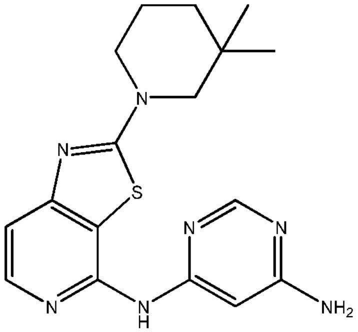
110		N4-(2-(3-azabicyclo[3.1.0]hexan-3-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	326	D	3.04	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.30 (s, 1H), 8.11 – 8.01 (m, 2H), 7.08 (d, J = 5.5 Hz, 1H), 6.57 (d, J = 4.6 Hz, 1H), 6.46 (s, 2H), 3.64 (s, 4H), 1.75 (s, 2H), 0.82 (td, J = 7.8, 5.0 Hz, 1H), 0.22 (q, J = 4.3 Hz, 1H).
111		N4-(2-(2-azabicyclo[2.2.1]heptan-2-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	340	D	3.16	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (s, 1H), 8.05 (d, J = 5.4 Hz, 2H), 7.05 (d, J = 5.5 Hz, 1H), 6.55 (s, 1H), 6.45 (s, 2H), 3.50 (d, J = 7.3 Hz, 1H), 3.14 (s, 1H), 2.70 (s, 1H), 1.86 – 1.62 (m, 4H), 1.56 (d, J = 9.7 Hz, 1H), 1.44 (d, J = 10.6 Hz, 1H).

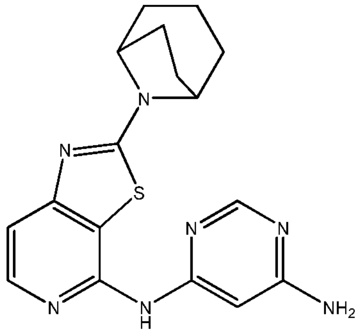
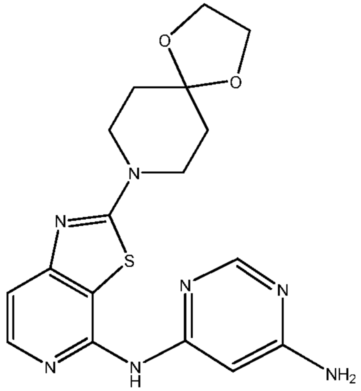
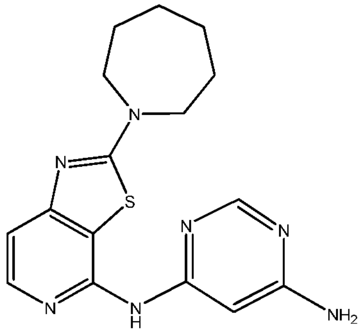
112		(R)-N4-(2-(3-(thiazol-2-yl)piperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	410	SFC:Chiralpak AD @50% methanol w/ 0.1% NH_4OH	0.85	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.32 (s, 1H), 8.08 (d, J = 5.5 Hz, 1H), 8.05 (s, 1H), 7.78 (d, J = 3.3 Hz, 1H), 7.67 (d, J = 3.3 Hz, 1H), 7.10 (d, J = 5.5 Hz, 1H), 6.57 (s, 1H), 6.47 (s, 2H), 4.39 (s, 1H), 3.93 (s, 1H), 3.56 – 3.45 (m, 1H), 3.39 (dd, J = 21.2, 10.9 Hz, 2H), 2.23 (d, J = 9.3 Hz, 1H), 1.89 (dd, J = 19.7, 10.0 Hz, 2H), 1.81 – 1.65 (m, 1H).
113		(S)-N4-(2-(3-(thiazol-2-yl)piperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	410	SFC:Chiralpak AD @50% methanol w/ 0.1% NH_4OH	0.94	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.32 (s, 1H), 8.08 (d, J = 5.5 Hz, 1H), 8.05 (s, 1H), 7.78 (d, J = 3.3 Hz, 1H), 7.67 (d, J = 3.3 Hz, 1H), 7.10 (d, J = 5.5 Hz, 1H), 6.57 (s, 1H), 6.47 (s, 2H), 4.39 (s, 1H), 3.93 (s, 1H), 3.56 – 3.45 (m, 1H), 3.39 (dd, J = 21.2, 10.9 Hz, 2H), 2.23 (d, J = 9.3 Hz, 1H), 1.89 (dd, J = 19.7, 10.0

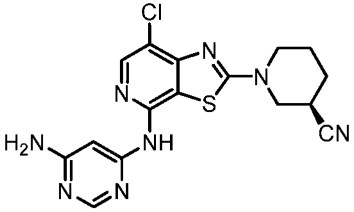
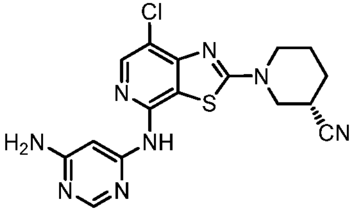
						Hz, 2H), 1.81 – 1.65 (m, 1H).
114		(*R*)-N-(2-(3-(trifluoromethyl)piperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	370	SFC:Phenomenex Cellulose-4 @25% methanol w/ 0.1% NH_4OH	0.54	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.87 (s, 1H), 8.11 (d, *J* = 5.5 Hz, 1H), 7.22 (d, *J* = 5.5 Hz, 1H), 4.34 (d, *J* = 11.2 Hz, 1H), 3.87 (d, *J* = 12.8 Hz, 1H), 2.69 (s, 1H), 2.09 – 1.92 (m, 2H), 1.83 (s, 1H), 1.62 (p, *J* = 11.8 Hz, 2H), 0.84 (d, *J* = 6.2 Hz, 3H).
115		(*S*)-N-(2-(3-(trifluoromethyl)piperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	370	SFC:Phenomenex Cellulose-4 @25% methanol w/ 0.1% NH_4OH	0.65	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.87 (s, 1H), 8.11 (d, *J* = 5.5 Hz, 1H), 7.22 (d, *J* = 5.5 Hz, 1H), 4.34 (d, *J* = 11.2 Hz, 1H), 3.87 (d, *J* = 12.8 Hz, 1H), 2.69 (s, 1H), 2.09 – 1.92 (m, 2H), 1.83 (s, 1H), 1.62 (p, *J* = 11.8 Hz, 2H), 0.84 (d, *J* = 6.2 Hz, 3H).

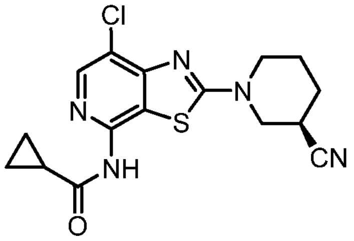
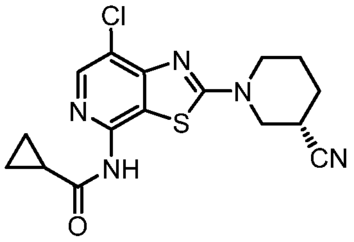
116		(*R*)-N-(2-(3-aminopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	318	D	2.46	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.84 (s, 1H), 8.26 (s, 1H), 8.09 (d, J = 5.5 Hz, 1H), 7.11 (dd, J = 31.7, 5.5 Hz, 1H), 3.20 (dd, J = 17.4, 6.8 Hz, 4H), 3.10 – 2.92 (m, 3H), 2.88 (d, J = 8.3 Hz, 2H), 1.97 (ddd, J = 28.9, 26.8, 17.7 Hz, 3H), 1.86 – 1.69 (m, 1H), 1.53 (dd, J = 24.8, 11.2 Hz, 1H), 1.44 – 1.21 (m, 1H), 0.99 – 0.75 (m, 4H).
117		N4-(2-(1,4-dioxa-7-azaspiro[4.5]decan-7-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	386	D	3.10	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.27 (s, 1H), 8.16 (s, 1H), 8.07 (d, J = 5.5 Hz, 1H), 8.04 (s, 1H), 7.06 (d, J = 5.5 Hz, 1H), 6.51 (s, 1H), 6.46 (s, 2H), 3.98 (dt, J = 6.2, 5.2 Hz, 2H), 3.92 (dt, J = 9.9, 5.2 Hz, 2H), 3.64 (s, 3H), 3.58 (s, 3H), 1.94 – 1.56 (m, 5H).

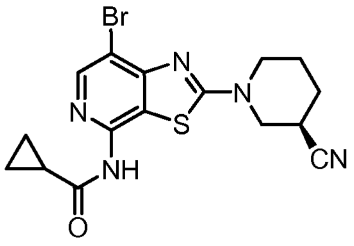
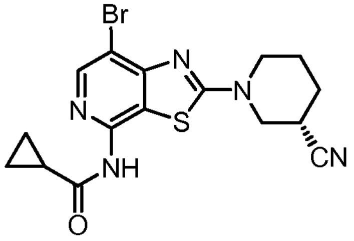
118		(*R*)-N4-(2-(3-methoxypiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	357	SFC:Phenomenex Cellulose-3 @20% methanol w/ 0.1% NH_4OH	0.50	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.27 (s, 1H), 8.13 – 7.94 (m, 2H), 7.06 (d, J = 5.5 Hz, 1H), 6.54 (s, 1H), 6.46 (s, 2H), 3.86 – 3.72 (m, 1H), 3.70 – 3.50 (m, 3H), 3.46 – 3.37 (m, 1H), 1.95 – 1.84 (m, 1H), 1.79 (ddd, J = 16.5, 8.5, 4.0 Hz, 1H), 1.72 – 1.59 (m, 1H), 1.61 – 1.44 (m, 1H).
119		(*S*)-N4-(2-(3-methoxypiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	357	SFC:Phenomenex Cellulose-3 @20% methanol w/ 0.1% NH_4OH	0.58	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.27 (s, 1H), 8.13 – 7.94 (m, 2H), 7.06 (d, J = 5.5 Hz, 1H), 6.54 (s, 1H), 6.46 (s, 2H), 3.86 – 3.72 (m, 1H), 3.70 – 3.50 (m, 3H), 3.46 – 3.37 (m, 1H), 1.95 – 1.84 (m, 1H), 1.79 (ddd, J = 16.5, 8.5, 4.0 Hz, 1H), 1.72 – 1.59 (m, 1H), 1.61 – 1.44 (m, 1H).

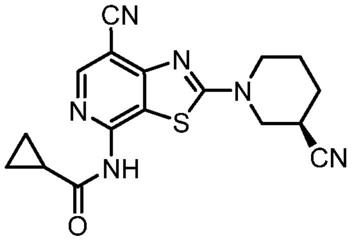
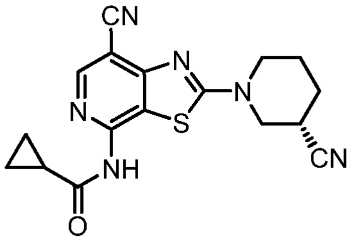
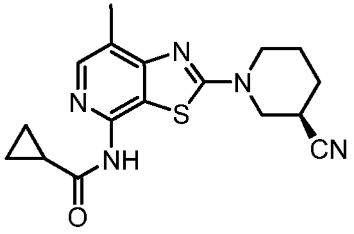
120		N4-(2-(3,3-difluoropiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	364	D	3.37	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (s, 1H), 8.16 – 8.00 (m, 2H), 7.11 (d, J = 5.5 Hz, 1H), 6.49 (d, J = 10.9 Hz, 3H), 4.03 (t, J = 11.8 Hz, 2H), 3.81 – 3.54 (m, 3H), 2.25 – 2.03 (m, 2H), 1.79 (d, J = 27.4 Hz, 2H).
121		N4-(2-morpholinothiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	330	D	2.86	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.40 (s, 1H), 8.09 (dd, J = 17.5, 11.9 Hz, 2H), 7.12 (dd, J = 11.2, 6.4 Hz, 1H), 6.61 – 6.42 (m, 3H), 3.85 – 3.67 (m, 4H), 3.67 – 3.50 (m, 4H).
122		N4-(2-(3,3-dimethylpiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	356	D	3.76	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.16 – 7.96 (m, 2H), 7.04 (d, J = 5.5 Hz, 1H), 6.48 (d, J = 25.5 Hz, 3H), 3.61 (dd, J = 16.4, 11.0 Hz, 2H), 3.34 (s, 1H), 1.66 (s, 2H), 1.51 – 1.41 (m, 2H), 0.94 (d, J = 6.4 Hz, 4H).

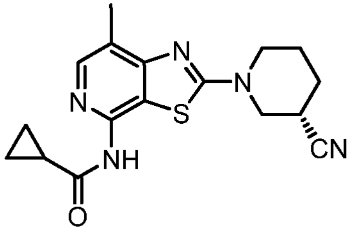
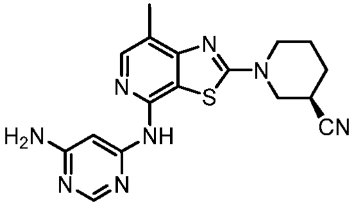
123		N4-(2-(8-azabicyclo[3.2.1]octan-8-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	354	D	3.34	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.16 – 7.96 (m, 2H), 7.08 (d, J = 5.5 Hz, 1H), 6.52 (t, J = 23.2 Hz, 3H), 4.33 (s, 2H), 2.18 – 1.97 (m, 2H), 1.93 – 1.71 (m, 4H), 1.63 – 1.42 (m, 3H).
124		N4-(2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	386	D	3.18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (s, 1H), 8.15 – 7.99 (m, 2H), 7.08 (d, J = 5.5 Hz, 1H), 6.53 (s, 1H), 6.47 (s, 1H), 3.91 (d, J = 24.7 Hz, 4H), 3.77 – 3.57 (m, 3H), 1.90 – 1.65 (m, 3H).
125		N4-(2-(azepan-1-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	342	D	3.47	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1H), 8.06 (dd, J = 13.3, 7.8 Hz, 2H), 7.07 (d, J = 5.5 Hz, 1H), 6.55 (s, 2H), 6.45 (s, 2H), 3.67 (s, 5H), 1.80 (s, 4H), 1.68 – 1.31 (m, 5H).

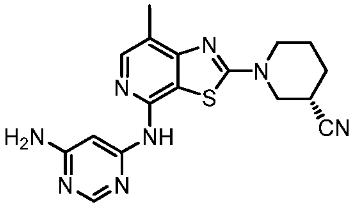
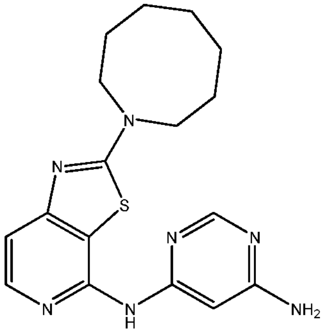
126		(R)-1-(4-(6-aminopyrimidin-4-ylamino)-7-chlorothiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	387	SFC:Phenomenex Cellulose-3 @ 30% ethanol w/ 0.1%NH_4OH	0.56	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.56 (s, 1H), 8.13 (s, 1H), 8.07 (s, 1H), 6.53 (s, 2H), 6.39 (s, 1H), 4.04 (dd, J = 13.2, 5.6 Hz, 1H), 3.83 (dd, J = 13.4, 3.5 Hz, 1H), 3.79 - 3.74 (m, 1H), 3.56 – 3.46 (m, 1H), 3.27 - 3.24 (m, 1H), 2.03 – 1.89 (m, 2H), 1.82 – 1.65 (m, 2H).
127		(S)-1-(4-(6-aminopyrimidin-4-ylamino)-7-chlorothiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	387	SFC:Phenomenex Cellulose-3 @ 30% ethanol w/ 0.1%NH_4OH	0.64	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.56 (s, 1H), 8.21 (s, 1H), 8.13 (s, 1H), 8.06 (s, 1H), 6.52 (s, 2H), 6.39 (s, 1H), 4.04 (dd, J = 13.4, 5.6 Hz, 1H), 3.83 (dd, J = 13.4, 3.4 Hz, 1H), 3.79 - 3.74 (m, 1H), 3.55 – 3.49 (m, 3H), 3.30 - 3.25 (m, 1H), 1.99 – 1.92 (m, 2H), 1.82 – 1.67 (m, 2H).

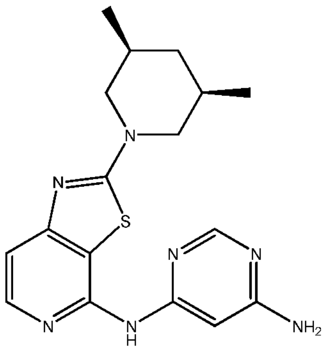
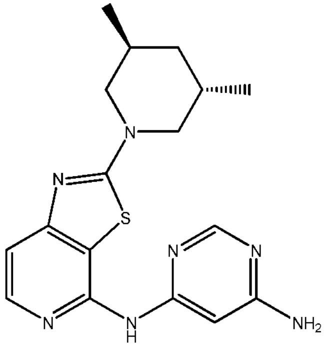
128		(R)-N-(7-chloro-2-(3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	362	SFC:Chiralpak IC @ 35% ethanol w/ 0.1%NH_4OH	0.51	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 8.19 (s, 1H), 4.04 (dd, J = 13.5, 5.2 Hz, 1H), 3.83 (dd, J = 13.3, 3.3 Hz, 1H), 3.79 - 3.75 (m, 1H), 3.57 – 3.47 (m, 1H), 3.27 - 3.24 (m, 1H), 2.03 – 1.90 (m, 3H), 1.83 – 1.64 (m, 2H), 0.90 – 0.79 (m, 4H).
129		(S)-N-(7-chloro-2-(3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	362	SFC:Chiralpak IC @ 35% ethanol w/ 0.1%NH_4OH	0.67	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 8.19 (s, 1H), 4.04 (dd, J = 13.6, 5.3 Hz, 1H), 3.83 (dd, J = 13.3, 3.3 Hz, 1H), 3.79 – 3.72 (m, 1H), 3.58 – 3.47 (m, 1H), 3.27 - 3.24 (m, 1H), 2.02 – 1.89 (m, 3H), 1.82 – 1.64 (m, 2H), 0.89 – 0.81 (m, 4H).

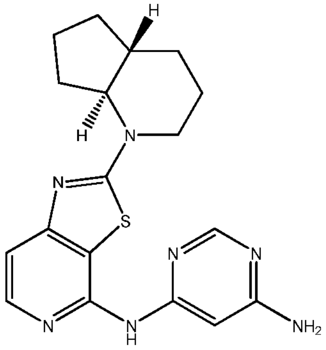
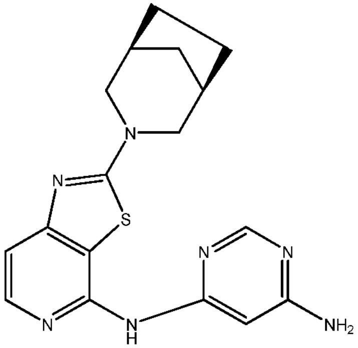
130		(R)-N-(7-bromo-2-(3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	406	SFC:Chiralpak IC @ 35% ethanol w/ 0.1% NH_4OH	0.51	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 8.27 (s, 1H), 4.03 (dd, J = 13.0, 5.8 Hz, 1H), 3.82 (dd, J = 13.3, 3.3 Hz, 1H), 3.79 - 3.74 (m 1H), 3.56 – 3.46 (m, 1H), 3.26 (dt, J = 9.9, 5.1 Hz, 1H), 2.03 – 1.89 (m, 3H), 1.82 – 1.64 (m, 2H), 0.90 – 0.78 (m, 4H).
131		(S)-N-(7-bromo-2-(3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	406	SFC:Chiralpak IC @ 35% ethanol w/ 0.1% NH_4OH	0.78	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 8.27 (s, 1H), 4.03 (dd, J = 13.3, 4.5 Hz, 1H), 3.82 (dd, J = 13.4, 3.4 Hz, 1H), 3.79 – 3.68 (m, 1H), 3.57 – 3.46 (m, 1H), 3.29 – 3.21 (m, 1H), 2.03 – 1.89 (m, 3H), 1.83 – 1.65 (m, 2H), 0.92 – 0.76 (m, 4H).

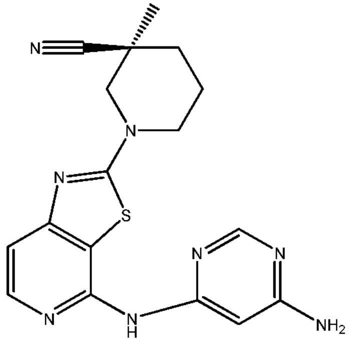
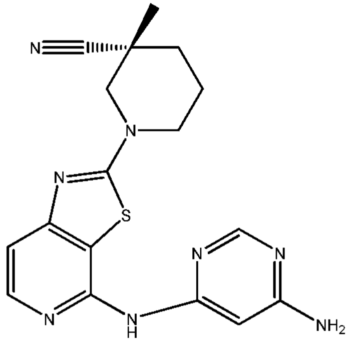
132		(R)-N-(7-cyano-2-(3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	353	SFC:Chiralpal IC @ 30% Ethanol w/ 0.1% NH_4OH	0.66	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.33 (s, 1H), 8.56 (s, 1H), 4.09 (dd, J = 8.7, 3.4 Hz, 1H), 3.84 (dd, J = 13.2, 2.6 Hz, 2H), 3.60 – 3.48 (m, 1H), 3.28 – 3.21 (m, 1H), 2.09 – 2.01 (m, 1H), 2.00 – 1.90 (m, 2H), 1.82 – 1.72 (m, 2H), 0.95 – 0.81 (m, 4H).
133		(S)-N-(7-cyano-2-(3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	353.0	SFC:Chiralpal IC @ 30% Ethanol w/ 0.1% NH_4OH	0.74	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.33 (s, 1H), 8.56 (s, 1H), 4.09 (dd, J = 8.7, 3.4 Hz, 1H), 3.84 (dd, J = 13.2, 2.6 Hz, 2H), 3.60 – 3.48 (m, 1H), 3.28 – 3.21 (m, 1H), 2.09 – 2.01 (m, 1H), 2.00 – 1.90 (m, 2H), 1.82 – 1.72 (m, 2H), 0.95 – 0.81 (m, 4H).
134		(R)-N-(2-(3-cyanopiperidin-1-yl)-7-methylthiazolo[5,4-c]pyridin-4-	342	SFC:Chiralpak AD @ 45% methanol w/ 0.1%NH_4OH	0.57	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75 (s, 1H), 7.97 (s, 1H), 4.00 (dd, J = 13.3, 5.9 Hz, 1H), 3.82 (dd, J = 13.3, 3.4 Hz, 1H), 3.78 – 3.71 (m,

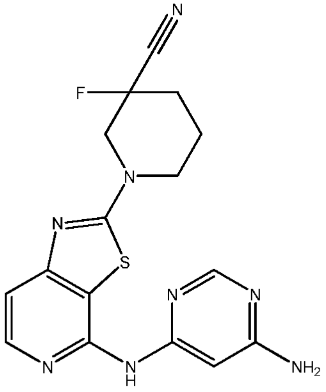
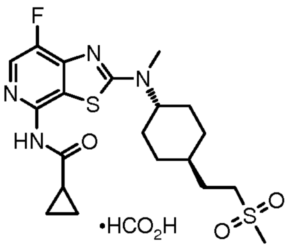
		yl)cyclopropanecarboxamide				1H), 3.55 – 3.45 (m, 1H), 3.27 – 3.18 (m, 1H), 2.37 (s, 3H), 2.01 – 1.88 (m, 3H), 1.82 – 1.62 (m, 2H), 0.83 (d, J = 6.2 Hz, 4H). LCMS (ESI) m/z 342.0 [M+H$^+$].
135		(S)-N-(2-(3-cyanopiperidin-1-yl)-7-methylthiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	342	SFC:Chiralpak AD @ 45% methanol w/ 0.1%NH4OH	0.67	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.75 (s, 1H), 7.97 (s, 1H), 4.00 (dd, J = 13.2, 5.8 Hz, 1H), 3.82 (dd, J = 13.3, 3.3 Hz, 1H), 3.78 – 3.71 (m, 1H), 3.55 – 3.45 (m, 1H), 3.25 - 3.19 m, 1H), 2.37 (s, 3H), 2.02 – 1.88 (m, 3H), 1.81 – 1.63 (m, 2H), 0.83 (d, J = 6.1 Hz, 4H). LCMS (ESI) m/z 342.0 [M+H$^+$].
136		(R)-1-(4-(6-aminopyrimidin-4-ylamino)-7-methylthiazolo[5,4-c]pyridin-2-yl)piperidine-3-	367	SFC:Regis Whelko-1 @ 40% Methanol w/ 0.1% NH_4OH	1.26	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.93 (s, 1H), 8.19 (s, 1H), 8.13 (s, 1H), 7.99 (s, 1H), 7.07 – 6.98 (s, 1H), 6.38 (s, 1H), 4.05 (dd, J = 13.2, 5.2 Hz, 1H), 3.86 - 3.82 (m,

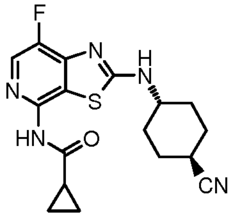
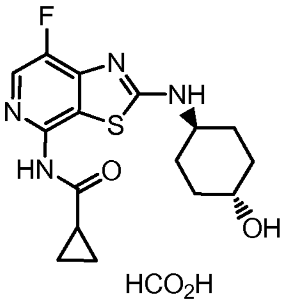
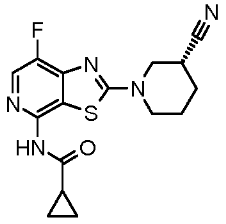
		carbonitrile				2H), 3.57 – 3.46 (m, 1H), 2.39 (s, 3H), 2.03 – 1.89 (m, 2H), 1.84 – 1.67 (m, 2H).
137		(S)-1-(4-(6-aminopyrimidin-4-ylamino)-7-methylthiazolo[5,4-c]pyridin-2-yl)piperidine-3-carbonitrile	367	SFC:Regis Whelko-1 @ 40% Methanol w/ 0.1% NH_4OH	1.40	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (s, 1H), 8.02 (s, 1H), 7.95 (s, 1H), 6.42 (s, 2H), 6.39 (s, 1H), 4.00 (dd, J = 13.2, 5.9 Hz, 1H), 3.82 (dd, J = 13.3, 3.5 Hz, 1H), 3.79 – 3.70 (m, 1H), 3.55 – 3.43 (m, 1H), 3.27 – 3.20 (m, 1H), 2.37 (s, 3H), 2.01 – 1.89 (m, 2H), 1.83 – 1.62 (m, 2H).
138		N4-(2-(azocan-1-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	356	D	3.63	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1H), 8.06 (dd, *J* = 13.3, 7.8 Hz, 2H), 7.07 (d, *J* = 5.5 Hz, 1H), 6.55 (s, 2H), 6.45 (s, 2H), 3.67 (s, 5H), 1.80 (s, 4H), 1.68 – 1.21 (m, 7H).

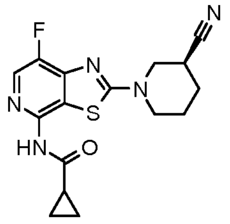
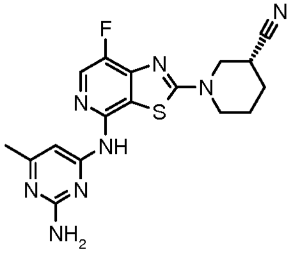
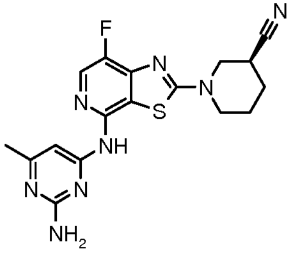
139		*cis*-N4-(2-Cis-3,5-dimethylpiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	356	D	3.77	^{1}H NMR (500 MHz, DMSO) δ 9.31 (s, 1H), 8.06 (dd, *J* = 8.6, 3.2 Hz, 2H), 7.07 (d, *J* = 5.5 Hz, 1H), 6.52 (d, *J* = 12.0 Hz, 3H), 4.06 (d, *J* = 58.8 Hz, 2H), 3.17 (s, 1H), 2.70 (t, *J* = 12.2 Hz, 2H), 1.79 (d, *J* = 12.9 Hz, 1H), 1.73 – 1.59 (m, 2H), 0.92 (s, 3H), 0.91 (s, 3H), 0.86 (dd, *J* = 24.4, 12.0 Hz, 1H).
140		*trans*-N4-(2-(trans-3,5-dimethylpiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	356	D	3.70	^{1}H NMR (500 MHz, DMSO) δ 8.38 (s, 5H), 8.06 (dd, *J* = 10.9, 5.3 Hz, 2H), 7.06 (dd, *J* = 14.1, 5.6 Hz, 1H), 6.59 – 6.41 (m, 3H), 3.72 (d, *J* = 11.4 Hz, 4H), 3.23 (dt, *J* = 35.5, 17.8 Hz, 3H), 2.00 (td, *J* = 12.4, 6.3 Hz, 2H), 1.49 (t, *J* = 5.8 Hz, 2H), 0.93 (t, *J* = 6.8 Hz, 6H).

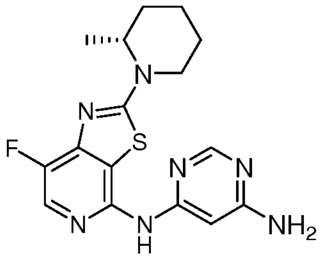
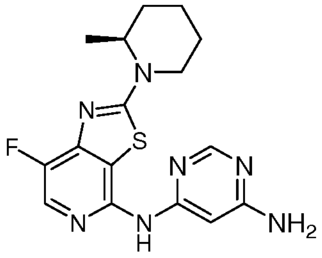
141		N4-(2-(trans-octahydro-1H-cyclopenta[b]pyridin-1-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	368	D	4.00	^{1}H NMR (400 MHz, DMSO) δ 9.28 (s, 1H), 8.15 – 7.99 (m, 2H), 7.09 (d, *J* = 5.5 Hz, 1H), 6.62 (s, 1H), 6.47 (s, 2H), 4.01 (dt, *J* = 12.7, 4.3 Hz, 1H), 3.26 – 3.14 (m, 1H), 2.96 (td, *J* = 10.8, 6.4 Hz, 1H), 2.72 (dt, *J* = 17.5, 8.4 Hz, 1H), 1.79 (dddd, *J* = 37.3, 28.8, 13.9, 7.7 Hz, 7H), 1.22 (dt, *J* = 15.8, 11.5 Hz, 2H).
142		N4-(2-(cis-3-azabicyclo[3.2.1]octan-3-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	354	D	3.57	^{1}H NMR (400 MHz, DMSO) δ 9.27 (s, 1H), 8.14 – 8.01 (m, 2H), 7.07 (d, *J* = 5.5 Hz, 1H), 6.55 (s, 1H), 6.46 (s, 2H), 3.27 (d, *J* = 11.7 Hz, 2H), 2.36 (s, 2H), 1.69 (d, *J* = 10.8 Hz, 3H), 1.64 – 1.53 (m, 1H), 1.49 (d, *J* = 7.5 Hz, 2H).

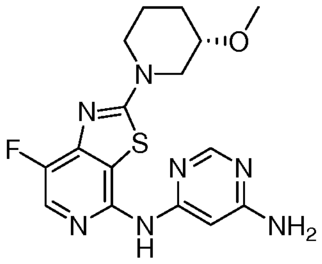
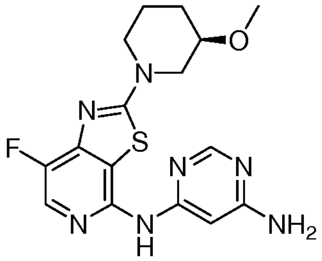
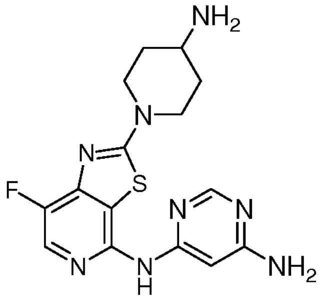
143		(S)-1-(4-(6-aminopyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)-3-methylpiperidine-3-carbonitrile	366	SFC:Phenomenex Cellulose-4 @40% methanol w/ 0.1% NH_4OH	0.69	^{1}H NMR (400 MHz, DMSO) δ 9.37 (s, 1H), 8.09 (d, *J* = 5.5 Hz, 1H), 8.06 (s, 1H), 7.10 (d, *J* = 5.5 Hz, 1H), 6.49 (d, *J* = 5.2 Hz, 3H), 4.40 (d, *J* = 13.2 Hz, 1H), 4.01 (d, *J* = 12.5 Hz, 1H), 3.23 (t, *J* = 10.6 Hz, 2H), 2.08 (d, *J* = 13.3 Hz, 1H), 1.90 – 1.60 (m, 3H), 1.39 (s, 3H).
144		(R)-1-(4-(6-aminopyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)-3-methylpiperidine-3-carbonitrile	366	SFC: Phenomenex Cellulose-4 @40% methanol w/ 0.1% NH_4OH	0.61	^{1}H NMR (400 MHz, DMSO) δ 9.37 (s, 1H), 8.09 (d, *J* = 5.5 Hz, 1H), 8.06 (s, 1H), 7.10 (d, *J* = 5.5 Hz, 1H), 6.49 (d, *J* = 5.2 Hz, 3H), 4.40 (d, *J* = 13.2 Hz, 1H), 4.01 (d, *J* = 12.5 Hz, 1H), 3.23 (t, *J* = 10.6 Hz, 2H), 2.08 (d, *J* = 13.3 Hz, 1H), 1.90 – 1.60 (m, 3H), 1.39 (s, 3H).

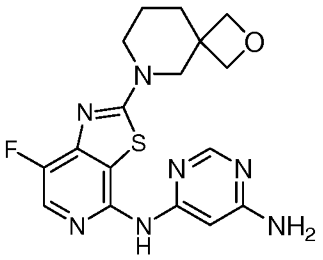
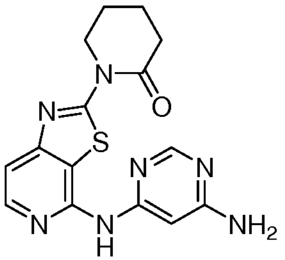
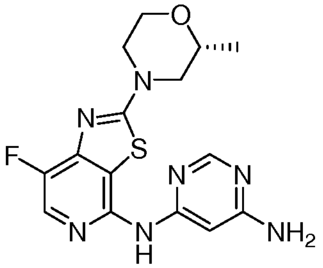
145		1-(4-(6-aminopyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)-3-fluoropiperidine-3-carbonitrile	371	D	3.28	^{1}H NMR (500 MHz, DMSO) δ 9.30 (s, 1H), 8.10 (t, *J* = 4.9 Hz, 1H), 8.08 – 8.04 (m, 1H), 7.12 (d, *J* = 5.5 Hz, 1H), 6.48 (d, *J* = 7.2 Hz, 1H), 6.39 (s, 2H), 4.30 (s, 1H), 4.27 (d, *J* = 5.3 Hz, 1H), 3.78 – 3.69 (m, 1H), 3.65 – 3.57 (m, 1H), 2.48 – 2.26 (m, 2H), 1.89 (ddd, *J* = 18.0, 9.0, 4.5 Hz, 1H), 1.83 – 1.72 (m, 1H).
146		*trans*-Cyclopropanecarboxylic acid (7-fluoro-2-{[4-(2-methanesulfonyl-ethyl)-cyclohexyl]-methylamino}-thiazolo[5,4-c]pyridin-4-yl)-amide formate salt	455	A	3.54	^{1}H NMR (400 MHz, DMSO-d$_6$): δ 10.82 (s, 1H), 8.06 (d, *J* = 2.0 Hz, 1H), 3.12-3.05 (m, 2H), 3.00 (br s, 3H), 2.91 (s, 3H), 1.95-1.85 (m, 1H), 1.84-1.48 (m, 9H), 1.41-1.25 (m , 1H), 1.20-1.01 (m, 2H), 0.83-0.71 (m, 4H).

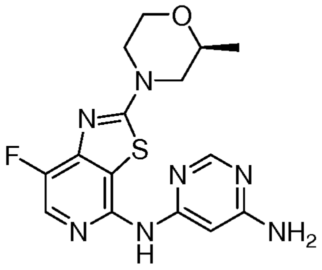
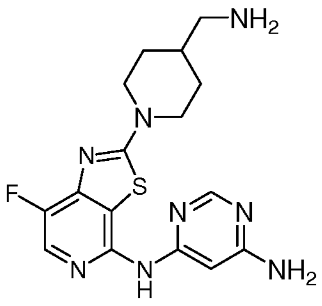
147		*trans*-Cyclopropanecarboxylic acid [2-(4-cyanocyclohexylamino)-7-fluorothiazolo[5,4-c]pyridin-4-yl]-amide	360	A	3.33	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.77 (s, 1H), 8.55 (br s, 1H), 8.03 (d, *J* = 2.1 Hz, 1H), 3.71 (br s, 1H), 2.77-2.65 (m, 1H), 2.05-1.93 (m, 4H), 1.92-1.84 (m, 1H), 1.69-1.54 (m, 2H), 1.38-1.22 (m, 2H), 0.84-0.70 (m, 4H).
148		*trans*-Cyclopropanecarboxylic acid [7-fluoro-2-(4-hydroxy-cyclohexylamino)-thiazolo[5,4-c]pyridin-4-yl]-amide formate salt	350	A	2.58	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.75 (s, 1H), 8.50 (br s, 1H), 8.03 (d, *J* = 2.6 Hz, 1H), 4.53 (d, *J* = 4.6 Hz, 1H), 3.60 (br s, 1H), 3.42-3.33 (m, 1H), 1.99-1.92 (m, 2H), 1.90-1.84 (m, 1H), 1.83-1.74 (m, 2H), 1.31-1.16 (m, 4H), 0.81-0.71 (m, 4H).
149		Cyclopropanecarboxylic acid [2-((R)-3-cyanopiperidin-1-yl)-7-fluorothiazolo[5,4-c]pyridin-4-yl]-	346	HPLC: ChiralPak IC @ 30% EtOAc/ 70%	2.14	^{1}H NMR (400 MHz, CD_3OD + d1-TFA): δ 8.15 (d, *J* = 4.6 Hz, 1H), 4.30 (br s, 1H), 4.00-3.85 (m, 2H), 3.74-3.64 (m, 1H), 3.24-3.18 (m, 1H), 2.11-1.91 (m, 4H), 1.90-1.80

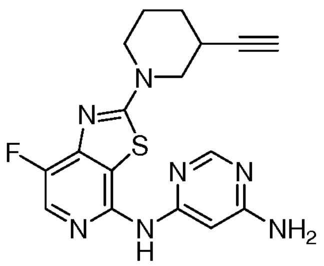
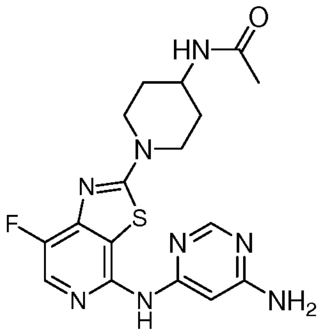
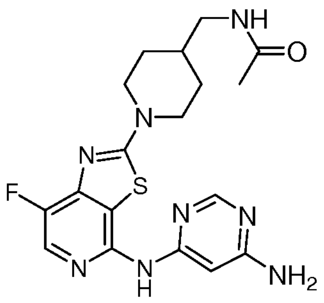
		amide		Heptane		(m, 1H), 1.17-1.03 (m, 4H).
150		Cyclopropanecarboxylic acid [2-((S)-3-cyanopiperidin-1-yl)-7-fluorothiazolo[5,4-c]pyridin-4-yl]-amide	346	HPLC: ChiralPak IC @ 30% EtOAc/ 70% Heptane	2.58	^{1}H NMR (400 MHz, CD_3OD + d1-TFA): δ 8.15 (d, *J* = 4.4 Hz, 1H), 4.30 (br s, 1H), 4.00-3.85 (m, 2H), 3.74-3.64 (m, 1H), 3.24-3.18 (m, 1H), 2.11-1.91 (m, 4H), 1.90-1.80 (m, 1H), 1.17-1.03 (m, 4H).
151		(R)-1-[4-(2-Amino-6-methylpyrimidin-4-ylamino)-7-fluorothiazolo[5,4-c]pyridin-2-yl]-piperidine-3-carbonitrile	385	HPLC: ChiralPak IA @ 80% TBME/ 20% EtOH	20.0	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.57 (s, 1H), 8.06 (d, *J* = 2.7 Hz, 1H), 6.07 (br s, 3H), 3.99 (dd, *J* = 5.8, 13.7 Hz, 1H), 3.81-3.65 (m, 2H), 3.54-3.43 (m, 1H), 3.24-3.16 (m, 1H), 2.06 (s, 3H), 1.95-1.87 (m, 2H), 1.79-1.60 (m, 2H).
152		(S)-1-[4-(2-Amino-6-methylpyrimidin-4-ylamino)-7-fluorothiazolo[5,4-c]pyridin-2-yl]-piperidine-3-	385	HPLC: ChiralPak IA @ 80% TBME/ 20%	7.50	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.57 (s, 1H), 8.06 (d, *J* = 2.7 Hz, 1H), 6.07 (br s, 3H), 3.99 (dd, *J* = 5.8, 13.7 Hz, 1H), 3.81-3.65 (m, 2H), 3.54-3.43 (m, 1H), 3.24-3.16

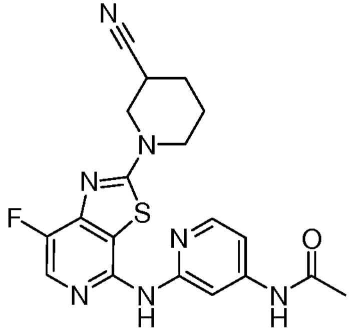
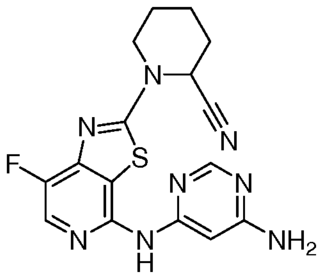
		carbonitrile		EtOH		(m, 1H), 2.06 (s, 3H), 1.95-1.87 (m, 2H), 1.79-1.60 (m, 2H).
153		(*R*)-N^4-(7-fluoro-2-(2-methylpiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	360	SFC: Chiralpak AD-H @ 30% MeOH	4.93	^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 9.38 (s, 1H), 8.07 (d, *J* = 2.0 Hz, 1H), 8.03 (s, 1H), 6.49 (br s, 2H), 6.31 (s, 1H), 4.41 (br s, 1H), 3.91 (br s, 1H), 3.32–3.27 (m, 1H), 1.77–1.68 (m, 5H), 1.50–1.47 (m, 1H), 1.26 (d, *J* = 7.0 Hz, 3H).
154		(*S*)-N^4-(7-fluoro-2-(2-methylpiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	360	SFC: Chiralpak AD-H @ 30% MeOH	5.79	^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 9.37 (s, 1H), 8.07 (d, *J* = 2.0 Hz, 1H), 8.03 (s, 1H), 6.47 (br s, 2H), 6.31 (s, 1H), 4.41 (br s, 1H), 3.91 (br s, 1H), 3.32–3.27 (m, 1H), 1.77–1.68 (m, 5H), 1.50–1.47 (m, 1H), 1.26 (d, *J* = 7.0 Hz, 3H).

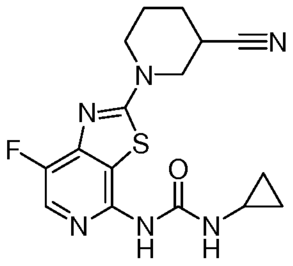
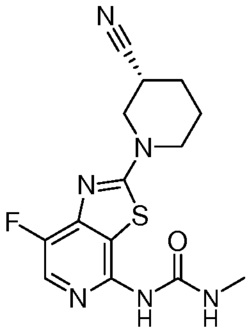
155		(*S*)-N^4-(7-fluoro-2-(3-methoxypiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	376	SFC: Chiralpak AD-H @ 30% MeOH	2.80	^{1}H NMR (500 MHz, DMSO-d_6): δ 9.41 (s, 1H), 8.07 (d, *J* = 2.5 Hz, 1H), 8.03 (s, 1H), 6.49 (br s, 2H), 6.31 (s, 1H), 3.76–3.43 (m, 5H), 3.30 (s, 3H), 1.87–1.52 (m, 4H).
156		(*R*)-N^4-(7-fluoro-2-(3-methoxypiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	376	SFC:Chiralpak AD-H @ 30% MeOH	3.47	^{1}H NMR (500 MHz, DMSO-d_6): δ 9.41 (s, 1H), 8.07 (d, *J* = 2.5 Hz, 1H), 8.03 (s, 1H), 6.49 (br s, 2H), 6.31 (s, 1H), 3.76–3.43 (m, 5H), 3.30 (s, 3H), 1.87–1.52 (m, 4H).
157		N^4-(2-(4-aminopiperidin-1-yl)-7-fluorothiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	361	F	2.75	^{1}H NMR (500 MHz, DMSO-d_6): δ 9.40 (br s, 1H), 8.08 (s, 1H), 8.03 (s, 1H), 6.48 (br s, 2H), 6.31 (s, 1H), 4.01 (br s, 2H), 3.33–3.28 (m, 4H), 2.93–2.91 (m, 1H), 1.90–1.84 (m, 2H), 1.46–1.30 (m, 2H).

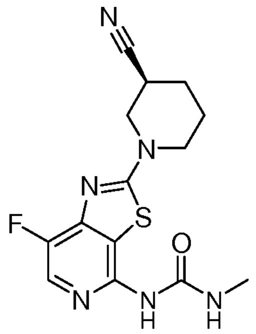
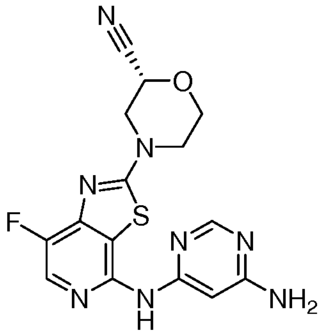
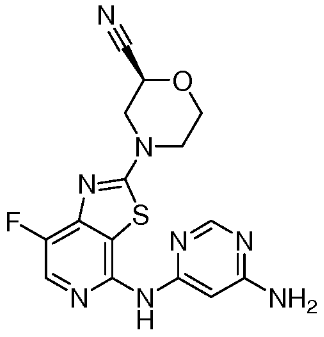
158		4-N-(7-fluoro-2-{2-oxa-6-azaspiro[3.5]nonan-6-yl}-[1,3]thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	388	F	3.80	^{1}H NMR (500 MHz, DMSO-d_6): δ 9.43 (s, 1H), 8.09 (d, J = 2.0 Hz, 1H), 8.04 (s, 1H), 6.47 (br s, 2H), 6.30 (s, 1H), 4.34–4.30 (m, 4H), 3.91 (br s, 2H), 3.54 (m, 2H), 1.92–1.89 (m, 2H), 1.60–1.59 (m, 2H).
159		1-(4-(6-aminopyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)piperidin-2-one	342	F	3.87	^{1}H NMR (500 MHz, DMSO-d_6): δ 9.66 (s, 1H), 8.24 (d, J = 5.5 Hz, 1H), 8.06 (d, J = 1.0 Hz, 1H), 7.43 (d, J = 5.5 Hz, 1H), 6.75 (s, 1H), 6.55 (br s, 2H), 4.20–4.16 (m, 2H), 2.69–2.66 (m, 2H), 1.98–1.84 (m, 4H).
160		(*R*)-N^4-(7-fluoro-2-(2-methylmorpholino)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	362	HPLC:Chiralpak IA @ 80% Hexane / 20% EtOH	26.97	^{1}H NMR (500 MHz, DMSO-d_6): δ 9.52 (s, 1H), 8.10 (d, J = 2.0 Hz, 1H), 8.05 (s, 1H), 6.52 (br s, 2H), 6.28 (s, 1H), 3.95–3.91 (m, 3H), 3.66–3.57 (m, 2H), 3.30–3.27 (m, 1H), 3.00–2.95 (m, 1H), 1.17 (d, J

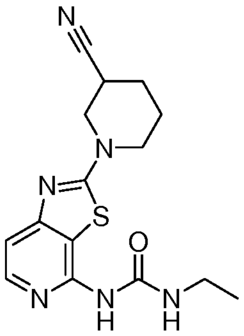
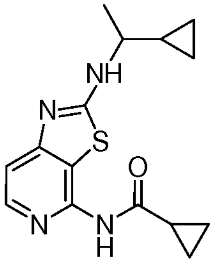
				(0.1% DEA)		= 6.0 Hz, 3H).
161		(*S*)-N^4-(7-fluoro-2-(2-methylmorpholino)thiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	362	HPLC: Chiralpak IA @ 80% Hexane / 20% EtOH (0.1% DEA)	22.75	^{1}H NMR (500 MHz, DMSO-d_6): δ 9.48 (s, 1H), 8.10 (d, J = 2.0 Hz, 1H), 8.04 (s, 1H), 6.50 (br s, 2H), 6.28 (s, 1H), 3.95–3.91 (m, 3H), 3.66–3.57 (m, 2H), 3.30–3.27 (m, 1H), 3.00–2.95 (m, 1H), 1.17 (d, J = 6.5 Hz, 3H).
162		N^4-(2-(4-(aminomethyl)piperidin-1-yl)-7-fluorothiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	376	F	2.75	^{1}H NMR (500 MHz, DMSO-d_6): δ 9.39 (br s, 1H), 8.07 (d, J = 2.5 Hz, 1H), 8.03 (s, 1H), 6.47 (br s, 2H), 6.31 (s, 1H), 4.10–4.06 (m, 2H), 3.23–3.18 (m, 4H), 2.89–2.86 (m, 1H), 2.47–2.45 (m, 2H), 1.85–1.76 (m, 2H), 1.23–1.17 (m, 2H).

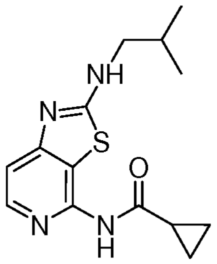
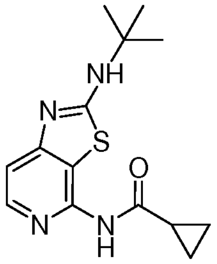
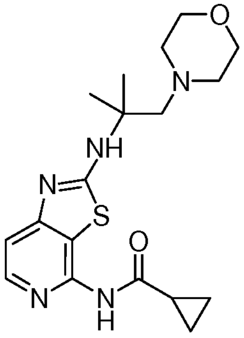
163		(±)N^4-(2-(3-ethynylpiperidin-1-yl)-7-fluorothiazolo[5,4-c]pyridin-4-yl)pyrimidine-4,6-diamine	370	F	4.76	^{1}H NMR (500 MHz, DMSO-d_6): δ 9.43 (s, 1H), 8.08 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 6.49 (br s, 2H), 6.33 (s, 1H), 3.66-3.48 (m, 4H), 3.05 (d, J = 2.5 Hz, 1H), 2.74–2.73 (m, 1H), 1.96–1.57 (m, 4H).
164		N-(1-(4-(6-aminopyrimidin-4-ylamino)-7-fluorothiazolo[5,4-c]pyridin-2-yl)piperidin-4-yl)acetamide	403	F	3.16	^{1}H NMR (500 MHz, DMSO-d_6): δ 9.43 (s, 1H), 8.08 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 6.49 (br s, 2H), 6.31 (s, 1H), 4.01–3.86 (m, 3H), 3.39–3.37 (m, 2H), 1.90–1.87 (m, 2H), 1.81 (s, 3H), 1.47–1.41 (m, 2H).
165		N-((1-(4-(6-aminopyrimidin-4-ylamino)-7-fluorothiazolo[5,4-c]pyridin-2-yl)piperidin-4-yl)methyl)acetamid	417	F	3.38	^{1}H NMR (500 MHz, DMSO-d_6): δ 9.40 (br s, 1H), 8.07 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.90 (t, J = 6.0 Hz, 1H), 6.48 (br s, 2H), 6.31 (s, 1H), 4.08 (br s, 2H), 3.23–3.18 (m,

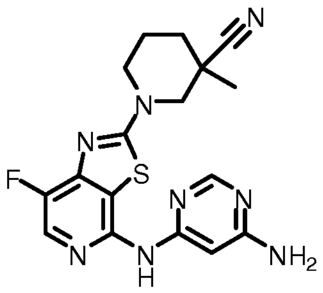
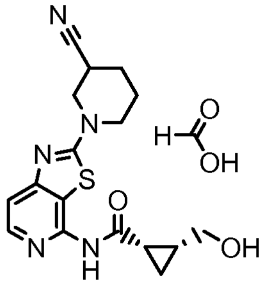
		e				2H), 2.99–2.96 (m, 2H), 1.81 (s, 3H), 1.78–1.70 (m, 3H), 1.25–1.17 (m, 2H).
166		(±)-N-(2-(2-(3-cyanopiperidin-1-yl)-7-fluorothiazolo[5,4-c]pyridin-4-ylamino)pyridin-4-yl)acetamide	412	F	4.18	^{1}H NMR (500 MHz, DMSO-d_6): δ 10.21 (s, 1H), 9.55 (s, 1H), 8.06 (d, J = 1.5 Hz, 1H), 8.01 (d, J = 5.5 Hz, 1H), 7.47 (s, 1H), 7.09 (d, J = 5.5 Hz, 1H), 4.04–4.01 (m, 1H), 3.82–3.74 (m, 2H), 3.52–3.49 (m, 1H), 3.31–3.24 (m, 1H), 2.07 (s, 3H), 1.96–1.94 (m, 2H), 1.76–1.70 (m, 2H).
167		(±)-1-(4-(6-aminopyrimidin-4-ylamino)-7-fluorothiazolo[5,4-c]pyridin-2-yl)piperidine-2-carbonitrile	371	F	4.44	^{1}H NMR (500 MHz, MeOH-d_4): δ 8.11 (s, 1H), 8.08 (s, 1H), 6.63 (d, J = 6.5 Hz, 1H), 5.82 (s, 1H), 3.92-3.89 (m, 1H), 3.48-3.43 (m, 1H), 2.16-1.72 (m, 6H).

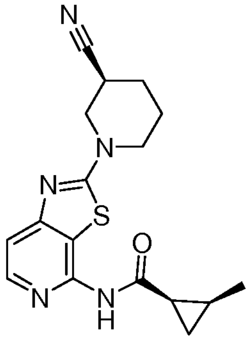
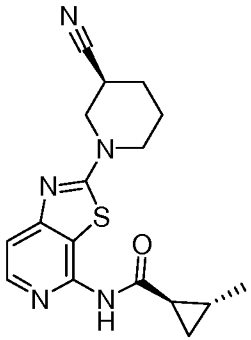
168		(±)-1-(2-(3-cyanopiperidin-1-yl)-7-fluorothiazolo[5,4-c]pyridin-4-yl)-3-cyclopropylurea	361	F	4.67	^{1}H NMR (500 MHz, DMSO-d_6): δ 9.06 (br s, 1H), 8.03 (s, 1H), 7.43 (br s, 1H), 4.06–4.03 (m, 1H), 3.83–3.80 (m, 2H), 3.53-3.49 (m, 1H), 3.31–3.25 (m, 1H), 2.57 (br s, 1H), 1.96–1.95 (m, 2H), 1.77–1.72 (m, 2H), 0.66 (m, 2H), 0.44 (m, 2H).
169		(*R*)-1-(2-(3-cyanopiperidin-1-yl)-7-fluorothiazolo[5,4-c]pyridin-4-yl)-3-methylurea	355	SFC: Chiralpak AD-H @ 30% MeOH	4.73	^{1}H NMR (500 MHz, DMSO-d_6): δ 9.22 (br s, 1H), 8.03 (d, J = 1.5 Hz, 1H), 7.25 (br s, 1H), 4.05–4.03 (m, 1H), 3.83–3.76 (m, 2H), 3.53–3.48 (m, 1H), 3.31–3.26 (m, 1H), 2.69 (d, J = 4.5 Hz, 3H), 1.96–1.72 (m, 4H).

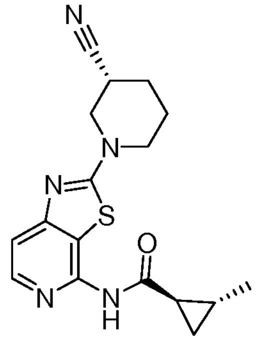
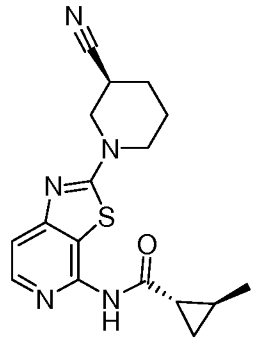
170		(*S*)-1-(2-(3-cyanopiperidin-1-yl)-7-fluorothiazolo[5,4-c]pyridin-4-yl)-3-methylurea	355	SFC: Chiralpak AD-H @ 30% MeOH	5.49	^{1}H NMR (500 MHz, DMSO-d_6): δ 9.21 (br s, 1H), 8.03 (d, *J* = 2.0 Hz, 1H), 7.24 (br s, 1H), 4.05–4.02 (m, 1H), 3.83–3.76 (m, 2H), 3.53–3.48 (m, 1H), 3.31–3.26 (m, 1H), 2.69 (d, *J* = 4.5 Hz, 3H), 1.97–1.72 (m, 4H).
171		(*R*)-4-(4-(6-aminopyrimidin-4-ylamino)-7-fluorothiazolo[5,4-c]pyridin-2-yl)morpholine-2-carbonitrile	373	F	3.77	^{1}H NMR (500 MHz, DMSO-d_6): δ 9.59 (s, 1H), 8.13 (d, *J* = 1.5 Hz, 1H), 8.05 (s, 1H), 6.52 (br s, 2H), 6.30 (s, 1H), 5.18-5.17 (m, 1H), 4.16-4.13 (m, 1H), 3.96-3.81 (m, 4H), 3.59-3.54 (m, 1H).
172		(*S*)-4-(4-(6-aminopyrimidin-4-ylamino)-7-fluorothiazolo[5,4-c]pyridin-2-yl)morpholine-2-carbonitrile	373	F	3.77	^{1}H NMR (500 MHz, DMSO-d_6): δ 9.59 (s, 1H), 8.13 (d, *J* = 1.5 Hz, 1H), 8.05 (s, 1H), 6.52 (br s, 2H), 6.30 (s, 1H), 5.18-5.17 (m, 1H), 4.16-4.13 (m, 1H), 3.96-3.81 (m, 4H), 3.59-3.54 (m, 1H).

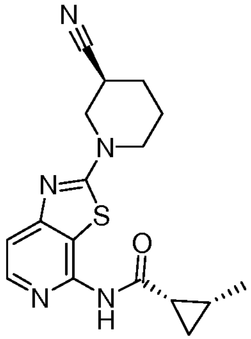
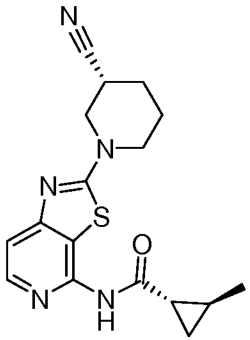
173		(±)-1-(2-(3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)-3-ethylurea	331	F	4.45	^{1}H NMR (500 MHz, DMSO-d_6): δ 9.12 (s, 1H), 8.01 (d, J = 5.5 Hz, 1H), 7.94 (br s, 1H), 7.06 (d, J = 5.5 Hz, 1H), 4.02-3.73 (m, 3H), 3.51-3.48 (m, 1H), 3.25-3.15 (m, 3H), 1.97-1.92 (m, 2H), 1.76-1.70 (m, 2H), 1.09 (t, J = 7.0 Hz, 3H).
174		(±)-*N*-(2-(1-cyclopropylethylamino)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	303	F	4.60	^{1}H NMR (500 MHz, DMSO-d_6): δ 10.76 (s, 1H), 8.39 (d, J = 6.0 Hz, 1H), 8.04 (d, J = 5.5 Hz, 1H), 7.09 (d, J = 5.0 Hz, 1H), 3.46 (br s, 1H), 1.97-1.94 (m, 1H), 1.24 (d, J = 6.5 Hz, 3H), 0.99-0.95 (m, 1H), 0.85-0.80 (m, 4H), 0.47-0.22 (m, 4H).

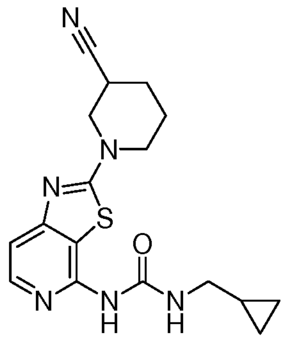
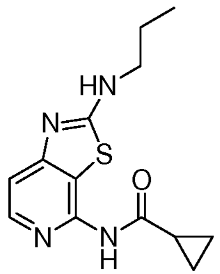
175		*N*-(2-(isobutylamino)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	291	F	4.52	^{1}H NMR (500 MHz, DMSO-d_6): δ 10.80 (s, 1H), 8.43 (br s, 1H), 8.05 (d, J = 6.0 Hz, 1H), 7.12 (d, J = 5.5 Hz, 1H), 3.19 (br s, 2H), 1.98-1.88 (m, 2H), 0.92 (d, J = 6.5 Hz, 6H), 0.85-0.79 (m, 4H).
176		*N*-(2-(tert-butylamino)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	291	F	4.80	^{1}H NMR (500 MHz, DMSO-d_6): δ 10.75 (s, 1H), 8.17 (s, 1H), 8.05 (d, J = 5.0 Hz, 1H), 7.15 (d, J = 5.5 Hz, 1H), 1.95 (m, 1H), 1.44 (s, 9H), 0.84-0.78 (m, 4H).
177		*N*-(2-(2-methyl-1-morpholinopropan-2-ylamino)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	376	F	4.75	^{1}H NMR (500 MHz, DMSO-d_6): δ 10.76 (s, 1H), 8.05 (m, 2H), 7.14 (d, J = 6.0 Hz, 1H), 3.53-3.51 (m, 4H), 2.69 (s, 2H), 2.44-2.42 (m, 4H), 1.96-1.93 (m, 1H), 1.37 (s, 6H), 0.85-0.78 (m, 4H).

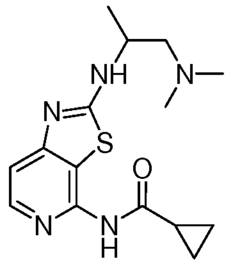
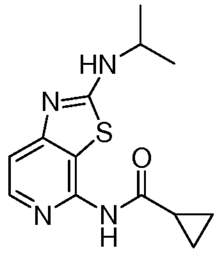
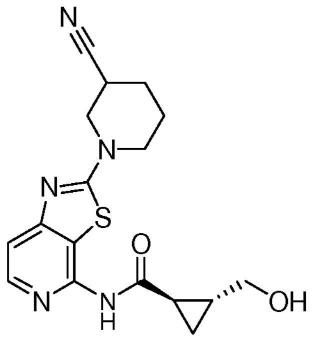
178		(±)-1-(4-(6-aminopyrimidin-4-ylamino)-7-fluorothiazolo[5,4-c]pyridin-2-yl)-3-methylpiperidine-3-carbonitrile	385	F	4.15	^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 9.51 (s, 1H), 8.11 (d, *J* = 2.0 Hz, 1H), 8.04 (s, 1H), 6.51 (br s, 1H), 6.26 (s, 1H), 4.40 (br s, 2H), 4.02 (br s, 2H), 3.25-3.22 (m, 2H), 2.10-2.06 (m, 1H), 1.87-1.63 (m, 2H), 1.40 (s, 3H).
179		(1*S*,2*R*) and (1*R*, 2*S*)-N-(2-(3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)-2-(hydroxymethyl)cyclopropanecarboxamide formate	358	F	3.49	^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 10.84 (s, 1H), 8.11 (d, *J* = 5 Hz, 1H), 7.20 (d, *J* = 5.5 Hz, 1H), 4.03-4.00 (m, 1H), 3.81-3.46 (m, 6H), 3.23 (br s, 1H), 2.09-2.05 (m, 1H), 1.97-1.91 (m, 2H), 1.79-1.70 (m, 2H), 1.51-1.46 (m, 1H), 1.04-0.92 (m, 2H).

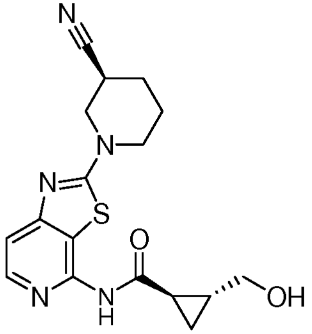
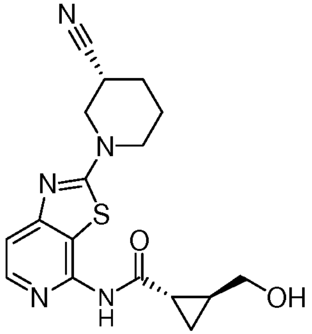
180		(1*R*,2*S*)-N-(2-((*S*)-3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)-2-methylcyclopropanecarboxamide	342	F	4.51	^{1}H NMR (500 MHz, DMSO-d_6): δ 10.83 (s, 1H), 8.12 (d, J = 5.5 Hz, 1H), 7.20 (d, J = 5.5 Hz, 1H), 4.04-4.00 (m, 1H), 3.81-3.73(m, 2H), 3.51-3.46(m, 1H), 3.25-3.21 (m, 1H), 2.03-1.94 (m, 3H), 1.77-1.68 (m, 2H), 1.34-1.28 (m, 1H), 1.14 (d, J = 6.5 Hz, 3H), 1.01-0.97 (m, 1H), 0.83-0.79 (m, 1H)
181		(1*R*,2*R*)-N-(2-((*S*)-3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)-2-methylcyclopropanecarboxamide	342	F	4.51	^{1}H NMR (500 MHz, DMSO-d_6): δ 10.84 (s, 1H), 8.11 (d, J = 5.5 Hz, 1H), 7.20 (d, J = 5.5 Hz, 1H), 4.03-4.00 (m, 1H), 3.81-3.73(m, 2H), 3.52-3.47(m, 1H), 3.24-3.20(m, 1H), 1.97-1.94 (m, 2H), 1.76-1.69 (m, 3H), 1.28-1.24 (m, 1H), 1.10 (d, J = 6.0 Hz, 3H), 1.05-1.02 (m, 1H), 0.72-0.68 (m, 1H)

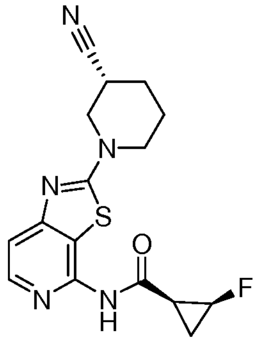
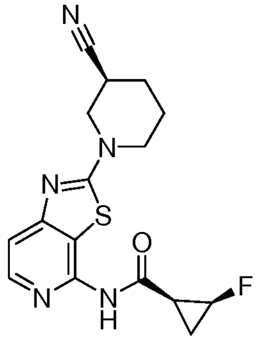
182		(1*R*,2*R*)-N-(2-((*R*)-3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)-2-methylcyclopropanecarboxamide	342	F	4.53	^{1}H NMR (500 MHz, DMSO-d_6): δ 10.84 (s, 1H), 8.11 (d, J = 5.5 Hz, 1H), 7.20 (d, J = 6.0 Hz, 1H), 4.02-4.00 (m, 1H), 3.81-3.74(m, 2H), 3.51-3.46(m, 1H), 3.24-3.20(m, 1H), 1.97-1.92 (m, 2H), 1.76-1.69 (m, 3H), 1.28-1.24 (m, 1H), 1.10 (d, J = 6.0 Hz, 3H), 1.05-1.02 (m, 1H), 0.72-0.68 (m, 1H)
183		(1*S*,2*S*)-N-(2-((S)-3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)-2-methylcyclopropanecarboxamide	342	F	4.84	^{1}H NMR (500 MHz, DMSO-d_6): δ 10.84 (s, 1H), 8.11 (d, J = 5.5 Hz, 1H), 7.20 (d, J = 5.5 Hz, 1H), 4.02-4.00 (m, 1H), 3.81-3.74(m, 2H), 3.51-3.46(m, 1H), 3.24-3.20(m, 1H), 1.97-1.92 (m, 2H), 1.76-1.67 (m, 3H), 1.28-1.24 (m, 1H), 1.10 (d, J = 6.0 Hz, 3H), 1.05-1.02 (m, 1H), 0.72-0.68 (m, 1H)

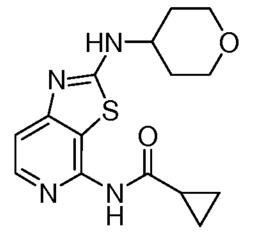
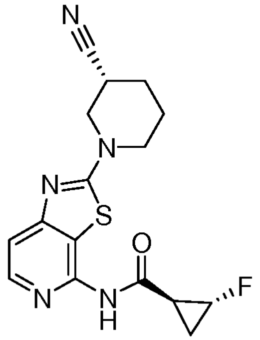
184		(1*S*,2*R*)-N-(2-((*S*)-3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)-2-methylcyclopropanecarboxamide	342	F	4.45	^{1}H NMR (500 MHz, DMSO-d_6): δ 10.84 (s, 1H), 8.12 (d, J = 5.5 Hz, 1H), 7.20 (d, J = 5.5 Hz, 1H), 4.04-4.00 (m, 1H), 3.81-3.73 (m, 2H), 3.51-3.46 (m, 1H), 3.25-3.21 (m, 1H), 2.03-1.94 (m, 3H), 1.76-1.68 (m, 2H), 1.34-1.28 (m, 1H), 1.14 (d, J = 6.0 Hz, 3H), 1.01-0.97 (m, 1H), 0.83-0.79 (m, 1H)
185		(1*S*,2*S*)-N-(2-((*R*)-3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)-2-methylcyclopropanecarboxamide	342	F	4.54	^{1}H NMR (500 MHz, DMSO-d_6): δ 10.84 (s, 1H), 8.11 (d, J = 5.5 Hz, 1H), 7.20 (d, J = 5.5 Hz, 1H), 4.03-4.00 (m, 1H), 3.81-3.73 (m, 2H), 3.52-3.47 (m, 1H), 3.24-3.20 (m, 1H), 1.97-1.92 (m, 2H), 1.76-1.67 (m, 3H), 1.29-1.23 (m, 1H), 1.10 (d, J = 6.0 Hz, 3H), 1.05-1.02 (m, 1H), 0.72-0.68 (m, 1H)

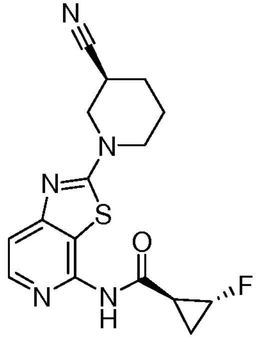
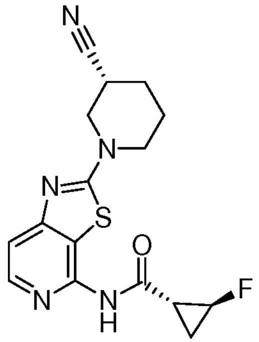
186		(±)-1-(2-(3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)-3-(cyclopropylmethyl)urea	357	F	5.04	^{1}H NMR (500 MHz, DMSO-d_6): δ 9.16 (s, 1H), 8.01 (d, J = 6.0Hz, 2H), 7.07 (d, J = 5.5 Hz, 1H), 4.02-4.00 (m, 1H), 3.82-3.73 (m, 2H), 3.51-3.46 (m, 1H), 3.26-3.23 (m, 1H), 3.06 (t, J = 6.25 Hz, 2H), 1.97-1.93 (m, 2H), 1.71-1.69 (m, 2H), 1.00-0.97 (m, 1H), 0.46-0.43 (m, 2H), 0.22-0.19 (m, 2H)
187		N-(2-(propylamino)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	277	F	4.06	^{1}H NMR (500 MHz, DMSO-d_6): δ 10.78 (s, 1H), 8.40 (br s, 1H), 8.05 (d, J = 5.5Hz, 1H), 7.13(d, J = 6.0 Hz, 1H), 3.33 (s, 2H), 1.98-1.94 (m, 1H), 1.63-1.55 (m, 2H), 0.92 (t, J = 7.5Hz, 3H), 0.85-0.79 (m, 4H)

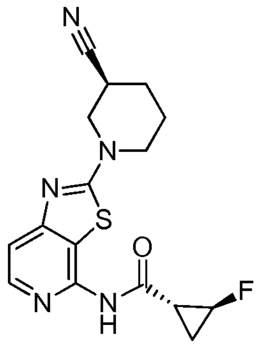
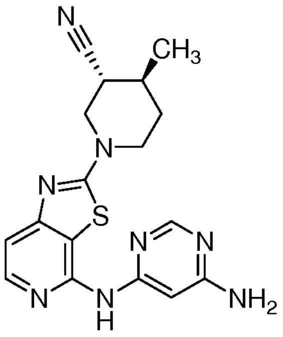
188		(±)-*N*-(2-(1-(dimethylamino)propan-2-ylamino)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	320	F	3.46	^{1}H NMR (500 MHz, DMSO-d_6): δ 10.78 (s, 1H), 8.27 (d, *J* = 6.5 Hz, 1H), 8.05 (d, *J* = 5.0 Hz, 1H), 7.12 (d, *J* = 5.5 Hz, 1H), 4.03 (br s, 1H), 2.41-2.37 (m, 1H), 2.23-2.19 (m, 1H), 2.17 (s, 6H), 1.96 (br s, 1H), 1.17 (d, *J* = 6.5 Hz, 3H), 0.84-0.81 (m, 4H),
189		*N*-(2-(isopropylamino)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	277	F	4.01	^{1}H NMR (500 MHz, DMSO-d_6): δ 10.78(s, 1H), 8.31(s, 1H), 8.05 (d, *J* = 5.5 Hz, 1H), 7.13 (d, *J* = 5.0 Hz, 1H), 4.00 (br s, 1H), 1.99-1.94(m, 1H), 1.21 (d, *J* = 6.5 Hz, 6H), 0.84-0.81 (m, 4H),
190		(1R,2R) and (1S,2S)-N-(2-(3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)-2-(hydroxymethyl)cyclopropanecarboxa	358	F	3.50	^{1}H NMR (500 MHz, DMSO-d_6): δ 10.85 (s, 1H), 8.12 (d, *J* = 5.0 Hz, 1H), 7.20 (d, *J* = 5.5 Hz, 1H), 4.73-4.71 (m, 1H), 4.03-3.99 (m, 1H), 3.81-3.74 (m, 2H), 3.52-3.45 (m, 2H), 3.32-3.27 (m, 1H), 3.25-

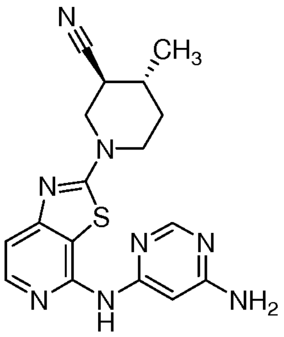
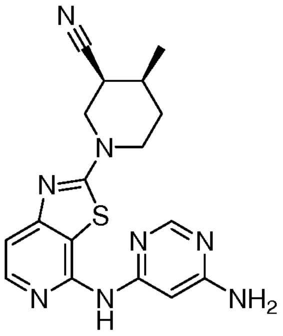
		mide				3.21 (m, 1H), 1.97-1.89 (m, 3H), 1.75-1.67 (m, 2H), 1.51-1.48 (m, 1H), 1.01-0.98 (m, 1H), 0.85-0.82 (m, 1H).
191		(1*R*,2*R*)-N-(2-((*S*)-3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)-2-(hydroxymethyl)cyclopropanecarboxamide	358	F	3.43	^{1}H NMR (500 MHz, DMSO-d_6): δ 10.85 (s, 1H), 8.12 (d, *J* = 5.0 Hz, 1H), 7.20 (d, *J* = 5.5 Hz, 1H), 4.73-4.71 (m, 1H), 4.03-3.99 (m, 1H), 3.81-3.74 (m, 2H), 3.52-3.45 (m, 2H), 3.32-3.27 (m, 1H), 3.25-3.21 (m, 1H), 1.97-1.89 (m, 3H), 1.75-1.68 (m, 2H), 1.51-1.48 (m, 1H), 1.01-0.98 (m, 1H), 0.85-0.82 (m, 1H).
192		(1*S*,2*S*)-N-(2-((*R*)-3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)-2-(hydroxymethyl)cyclopropanecarboxamide	358	F	3.51	^{1}H NMR (500 MHz, DMSO-d_6): δ 10.86 (s, 1H), 8.12 (d, *J* = 5.5 Hz, 1H), 7.20 (d, *J* = 5.5 Hz, 1H), 4.73 (br s, 1H), 4.03-3.99 (m, 1H), 3.82-3.74 (m, 2H), 3.51-3.45 (m, 2H), 3.31-3.28 (m, 1H), 3.25-3.21 (m, 1H), 1.97-1.89 (m, 3H),

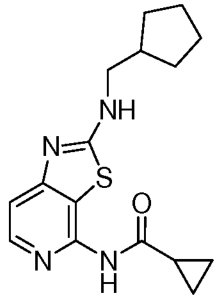
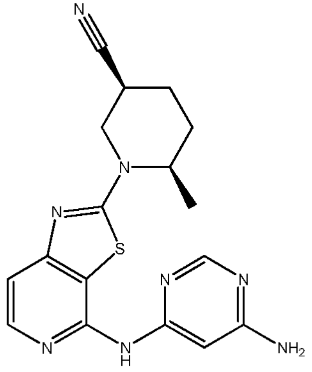
						1.78-1.67 (m, 2H), 1.51-1.48 (m, 1H), 1.01-0.97 (m, 1H), 0.85-0.82 (m, 1H).
193		(1S,2S)-N-(2-((R)-3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)-2-fluorocyclopropane carboxamide	346	F	3.87	^{1}H NMR (500 MHz, DMSO-d_6): δ 10.99 (s, 1H), 8.13 (d, J = 5.5 Hz, 1H), 7.23 (d, J = 5.0 Hz, 1H), 5.04-4.98 (m, 1H), 4.03-4.00 (m, 1H), 3.81-3.75 (m, 2H), 3.50-3.46 (m, 1H), 3.24-3.22 (m, 1H), 2.19-2.18 (m, 1H), 1.96-1.94 (m, 2H), 1.74-1.66 (m, 2H), 1.23-1.17 (m, 2H).
194		(1*S*,2*S*)-N-(2-((*S*)-3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)-2-fluorocyclopropane carboxamide	346	F	3.86	^{1}H NMR (500 MHz, DMSO-d_6): δ 10.99 (s, 1H), 8.13 (d, J = 5.5 Hz, 1H), 7.23 (d, J = 5.0 Hz, 1H), 5.04-4.98 (m, 1H), 4.03-4.00 (m, 1H), 3.81-3.75 (m, 2H), 3.50-3.46 (m, 1H), 3.24-3.22 (m, 1H), 2.19-2.18 (m, 1H), 1.96-1.94 (m, 2H), 1.74-1.66 (m, 2H), 1.23-1.17 (m, 2H).

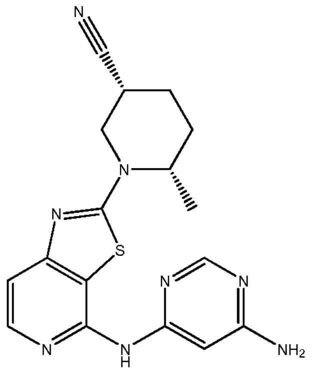
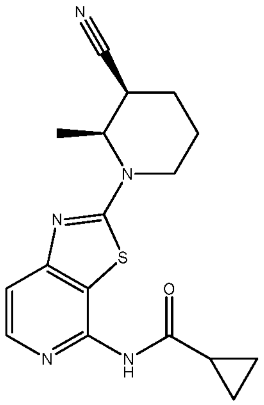
195		*N*-(2-(tetrahydro-2H-pyran-4-ylamino)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	319	F	3.50	^{1}H NMR (500 MHz, DMSO-d_6): δ 10.78 (s, J = 6.2 Hz, 1H), 8.43 (d, J = 7.0 Hz, 1H), 8.05 (t, 1H), 7.14 (d, J = 6.0 Hz, 1H), 3.94-3.82 (m, 3H), 3.44-3.40 (m, 2H), 1.98-1.92 (m, 3H), 1.52-1.45 (m, 2H), 0.85-0.79 (m, 4H).
196		(1*S*,2*R*)-N-(2-((*R*)-3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide	346	F	4.19	^{1}H NMR (500 MHz, DMSO-d_6): δ 11.11 (s, 1H), 8.18 (s, 1H), 7.25 (s, 1H), 4.98-4.84 (m, 1H), 4.02-3.98 (m, 1H), 3.81-3.73 (m, 2H), 3.52-3.47 (m, 1H), 3.24-3.20 (m, 1H), 1.98-1.91(m, 2H), 1.78-1.53 (m, 3H), 1.29-1.22 (m, 1H), 0.99-0.98 (m, 1H).

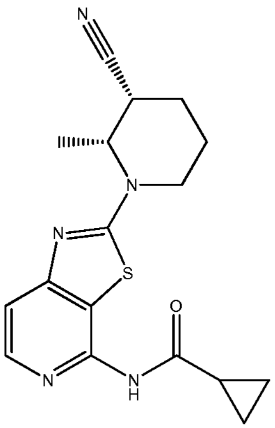
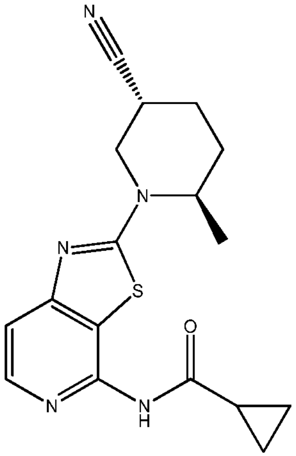
197		(1*S*,2*R*)-N-(2-((*S*)-3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)-2-fluorocyclopropane carboxamide	346	F	4.20	^{1}H NMR (500 MHz, DMSO-d_6): δ 11.11 (s, 1H), 8.18 (s, 1H), 7.25 (s, 1H), 4.98-4.84 (m, 1H), 4.02-3.98 (m, 1H), 3.81-3.73 (m, 2H), 3.52-3.47 (m, 1H), 3.24-3.20 (m, 1H), 1.98-1.91(m, 2H), 1.78-1.53 (m, 3H), 1.29-1.22 (m, 1H), 0.99-0.98 (m, 1H).
198		(1*R*,2*S*)-N-(2-((*R*)-3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)-2-fluorocyclopropane carboxamide	346	F	4.20	^{1}H NMR (500 MHz, DMSO-d_6): δ 11.11 (s, 1H), 8.18 (s, 1H), 7.25 (s, 1H), 4.98-4.84 (m, 1H), 4.02-3.98 (m, 1H), 3.81-3.73 (m, 2H), 3.52-3.47 (m, 1H), 3.24-3.20 (m, 1H), 1.98-1.91(m, 2H), 1.78-1.53 (m, 3H), 1.29-1.22 (m, 1H), 0.99-0.98 (m, 1H).

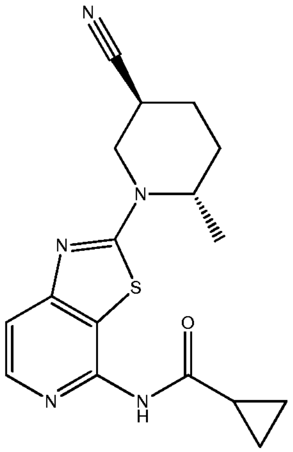
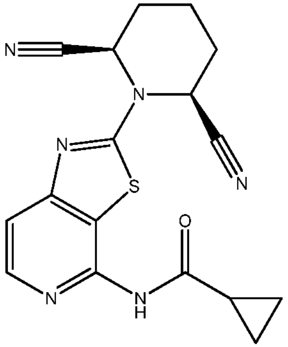
199		(1*R*,2*S*)-N-(2-((*S*)-3-cyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)-2-fluorocyclopropane carboxamide	346	F	4.20	^{1}H NMR (500 MHz, DMSO-d_6): δ 11.11 (s, 1H), 8.18 (s, 1H), 7.25 (s, 1H), 4.98-4.84 (m, 1H), 4.02-3.98 (m, 1H), 3.81-3.73 (m, 2H), 3.52-3.47 (m, 1H), 3.24-3.20 (m, 1H), 1.98-1.91(m, 2H), 1.78-1.53 (m, 3H), 1.29-1.22 (m, 1H), 0.99-0.98 (m, 1H).
200		(3*R*,4*S*)-1-(4-(6-aminopyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)-4-methylpiperidine-3-carbonitrile	367	F	4.12	^{1}H NMR (500 MHz, DMSO-d_6): δ 9.42 (s, 1H), 8.09 (d, *J* = 6.0 Hz, 1H), 8.06 (s, 1H), 7.12 (d, *J* = 6.0 Hz, 1H), 6.53 (s, 1H), 6.51 (br s, 2H), 4.42 (br s, 1H), 3.91 (br s, 1H), 3.48-3.35 (m, 1H), 2.81-2.76 (m, 1H), 2.81-2.77 (m, 1H), 1.97-1.93 (m, 1H), 1.34-1.23 (m, 2H), 1.10 (d, *J* = 6.5 Hz, 3H).

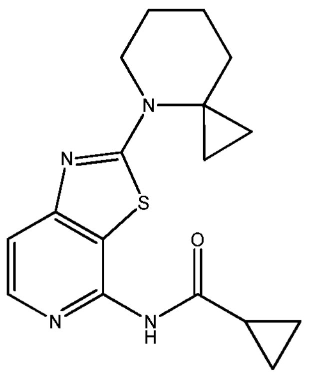
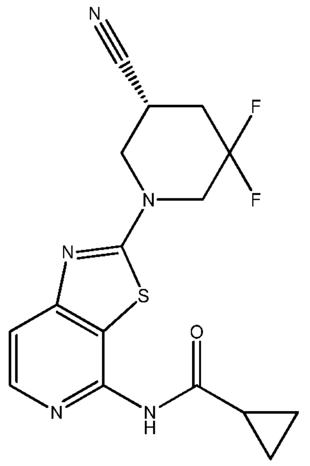
201		(3*S*,4*R*)-1-(4-(6-aminopyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)-4-methylpiperidine-3-carbonitrile	367	F	4.12	^{1}H NMR (500 MHz, DMSO-d_6): δ 9.42 (s, 1H), 8.09 (d, J = 6.0 Hz, 1H), 8.06 (s, 1H), 7.12 (d, J = 6.0 Hz, 1H), 6.53 (s, 1H), 6.51 (br s, 2H), 4.42 (br s, 1H), 3.91 (br s, 1H), 3.48-3.35 (m, 1H), 2.81-2.76 (m, 1H), 2.81-2.77 (m, 1H), 1.97-1.93 (m, 1H), 1.34-1.23 (m, 2H), 1.10 (d, J = 6.5 Hz, 3H).
202		(3*S*,4*S*) and (3*R*, 4*R*)-1-(4-(6-aminopyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl)-4-methylpiperidine-3-carbonitrile	367	F	4.12	^{1}H NMR (500 MHz, DMSO-d_6): δ9.45 (s, 1H), 8.09 (d, J = 6.0 Hz, 1H), 8.06 (s, 1H), 7.12 (d, J = 6.0 Hz, 1H), 6.53 (s, 1H), 6.51 (br s, 2H), 4.42 (br s, 1H), 3.91 (br s, 1H), 3.48-3.40 (m, 1H), 2.81-2.76 (m, 1H), 2.81-2.77 (m, 1H), 1.97-1.93 (m, 1H), 1.84-1.81 (m, 1H), 1.34-1.23 (m, 2H), 1.10 (d, J = 6.5 Hz, 3H).

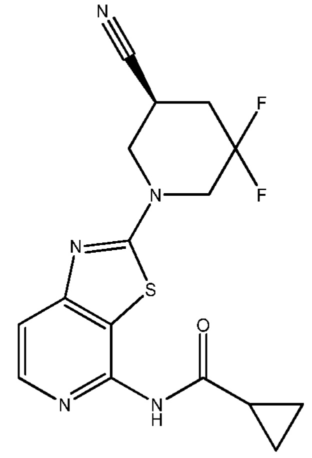
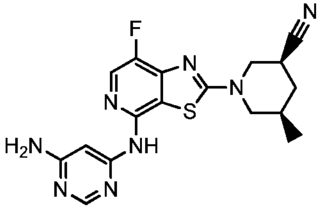
203		*N*-(2-(cyclopentylmethylamino)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	317	F	5.20	^{1}H NMR (500 MHz, DMSO-d_6): δ 10.81 (s, 1H), 8.45 (br s, 1H).8.05 (d, *J* = 5.5 Hz, 1H), 7.12 (d, *J* = 5.5 Hz, 1H), 3.35 (s, 2H), 2.20-2.14 (m, 1H), 1.98-1.94 (m, 1H), 1.75-1.69 (m, 2H), 1.63-1.47 (m, 4H), 1.27-1.20 (m, 2H), 0.86-0.79 (m, 4H)
204		(3*S*,6*R*)-1-(4-((6-aminopyrimidin-4-yl)amino)thiazolo[5,4-c]pyridin-2-yl)-6-methylpiperidine-3-carbonitrile	367	SFC:Phenomenex Cellulose-3 @Methanol w/ 0.1% NH4OH	3.29	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.37 (s, 1H), 8.09 (d, *J* = 5.5 Hz, 1H), 8.05 (s, 1H), 7.10 (d, *J* = 5.5 Hz, 1H), 6.53 (s, 1H), 6.47 (s, 2H), 4.35 (d, *J* = 52.8 Hz, 2H), 3.45 (t, *J* = 19.6 Hz, 1H), 2.18 – 1.91 (m, 3H), 1.85 (d, *J* = 13.4 Hz, 1H), 1.65 (d, *J* = 13.2 Hz, 1H), 1.24 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 7.1 Hz, 4H).

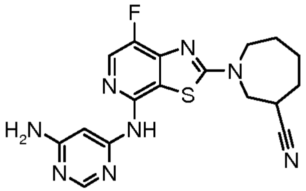
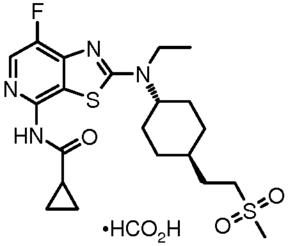
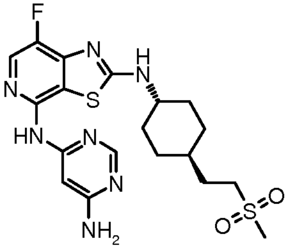
205		(3*R*,6*S*)-1-(4-((6-aminopyrimidin-4-yl)amino)thiazolo[5,4-c]pyridin-2-yl)-6-methylpiperidine-3-carbonitrile	367	SFC:Phenomenex Cellulose-3 @Methanol w/ 0.1% NH4OH	3.28	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.37 (s, 1H), 8.09 (d, J = 5.5 Hz, 1H), 8.05 (s, 1H), 7.10 (d, J = 5.5 Hz, 1H), 6.53 (s, 1H), 6.47 (s, 2H), 4.35 (d, J = 52.8 Hz, 2H), 3.45 (t, J = 19.6 Hz, 1H), 2.18 – 1.91 (m, 3H), 1.85 (d, J = 13.4 Hz, 1H), 1.65 (d, J = 13.2 Hz, 1H), 1.24 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 7.1 Hz, 4H).
206		N-(2-((2*S*,3*S*)-3-cyano-2-methylpiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	342	SFC:Phenomenex Cellulose-1 @Methanol w/ 0.1% NH4OH	0.64	^{1}H NMR (400 MHz, DMSO) δ 11.12 – 10.79 (s, 1H), 8.25 – 7.99 (d, J = 5.3 Hz, 1H), 7.28 – 7.10 (d, J = 5.5 Hz, 1H), 4.80 (s, 1H), 3.89 (d, J = 12.3 Hz, 1H), 3.38 (dd, J = 20.6, 10.2 Hz, 2H), 2.00 (dd, J = 9.3, 6.3 Hz, 2H), 1.81 (d, J = 13.8 Hz, 1H), 1.64 – 1.50 (m, 1H), 1.42 (d, J = 6.9 Hz, 3H).

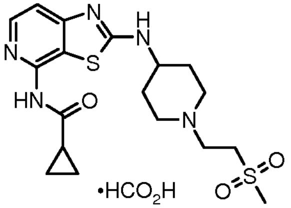
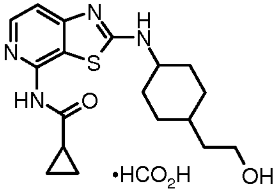
207		N-(2-((2*R*,3*R*)-3-cyano-2-methylpiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	342	SFC:Phenomenex Cellulose-1 @Methanol w/ 0.1% NH4OH	0.47	^{1}H NMR (400 MHz, DMSO) δ 11.12 – 10.79 (s, 1H), 8.25 – 7.99 (d, *J* = 5.3 Hz, 1H), 7.28 – 7.10 (d, *J* = 5.5 Hz, 1H), 4.80 (s, 1H), 3.89 (d, *J* = 12.3 Hz, 1H), 3.38 (dd, *J* = 20.6, 10.2 Hz, 2H), 2.00 (dd, *J* = 9.3, 6.3 Hz, 2H), 1.81 (d, *J* = 13.8 Hz, 1H), 1.64 – 1.50 (m, 1H), 1.42 (d, *J* = 6.9 Hz, 3H).
208		N-(2-((2*R*,5*R*)-5-cyano-2-methylpiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	342	SFC:Phenomenex Cellulose-3 @Methanol w/ 0.1% NH4OH	0.22	^{1}H NMR (400 MHz, DMSO) δ 11.12 – 10.79 (s, 1H), 8.25 – 7.99 (d, *J* = 5.3 Hz, 1H), 7.28 – 7.10 (d, *J* = 5.5 Hz, 1H), 4.52 – 4.17 (d, *J* = 47.7 Hz, 2H), 3.60 – 3.40 (d, *J* = 13.8 Hz, 1H), 2.18 – 1.91 (m, 3H), 1.90 – 1.80 (d, *J* = 13.1 Hz, 1H), 1.69 – 1.60 (d, *J* = 13.1 Hz, 1H), 1.28 – 1.20 (d, *J* = 6.5 Hz, 3H), 0.89 – 0.80 (m, 4H).

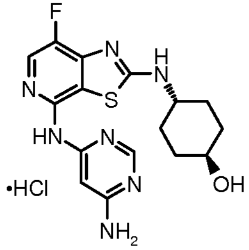
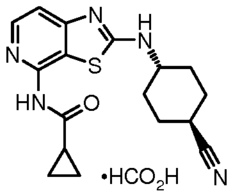
209		N-(2-((2*S*,5*S*)-5-cyano-2-methylpiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	342	SFC:Phenomenex Cellulose-3 @Methanol w/ 0.1% NH4OH	0.23	^{1}H NMR (400 MHz, DMSO) δ 11.12 – 10.79 (s, 1H), 8.25 – 7.99 (d, *J* = 5.3 Hz, 1H), 7.28 – 7.10 (d, *J* = 5.5 Hz, 1H), 4.52 – 4.17 (d, *J* = 47.7 Hz, 2H), 3.60 – 3.40 (d, *J* = 13.8 Hz, 1H), 2.18 – 1.91 (m, 3H), 1.90 – 1.80 (d, *J* = 13.1 Hz, 1H), 1.69 – 1.60 (d, *J* = 13.1 Hz, 1H), 1.28 – 1.20 (d, *J* = 6.5 Hz, 3H), 0.89 – 0.80 (m, 4H).
210		N-(2-((2*S*,6*R*)-2,6-dicyanopiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	352	D	3.35	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (s, 1H), 8.06 (d, *J* = 5.5 Hz, 1H), 8.04 (s, 1H), 7.05 (d, *J* = 5.5 Hz, 1H), 6.54 (s, 1H), 6.43 (s, 2H), 4.40 (s, 1H), 3.89 (d, *J* = 12.5 Hz, 1H), 1.73 (dd, *J* = 21.2, 12.8 Hz, 2H), 1.62 (d, *J* = 10.0 Hz, 2H), 1.49 (d, *J* = 13.1 Hz, 1H)

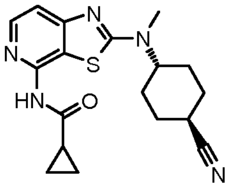
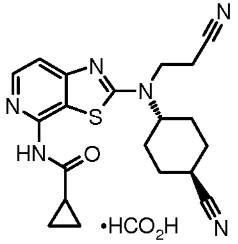
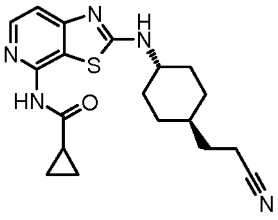
211		N-(2-(4-azaspiro[2.5]octan-4-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	329	D	3.77	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.79 (s, 1H), 8.07 (d, *J* = 5.5 Hz, 1H), 7.13 (d, *J* = 5.5 Hz, 1H), 3.58 (d, *J* = 5.3 Hz, 2H), 2.06 – 1.89 (m, 1H), 1.73 – 1.58 (m, 2H), 1.51 – 1.38 (m, 2H), 0.94 (s, 4H), 0.84 (t, *J* = 7.2 Hz, 4H).
212		(*R*)-N-(2-(5-cyano-3,3-difluoropiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	364	SFC:Chiralpak IC @Ethanol w/ 0.1%NH4OH	0.58	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.89 (s, 1H), 8.12 (d, *J* = 5.5 Hz, 1H), 7.21 (d, *J* = 5.5 Hz, 1H), 4.00 (dd, *J* = 13.3, 6.0 Hz, 1H), 3.80 (dd, *J* = 13.4, 3.6 Hz, 1H), 3.75 (d, *J* = 13.4 Hz, 1H), 3.56 – 3.45 (m, 1H), 3.25 – 3.18 (m, 1H), 2.05 – 1.87 (m, 3H), 0.85 (d, *J* = 6.2 Hz, 3H).

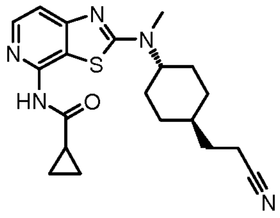
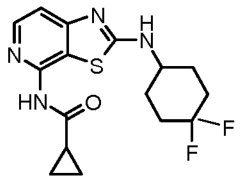
213		(*S*)-N-(2-(5-cyano-3,3-difluoropiperidin-1-yl)thiazolo[5,4-c]pyridin-4-yl)cyclopropanecarboxamide	364	SFC:Chiralpak IC @Ethanol w/ 0.1%NH4OH	0.93	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.89 (s, 1H), 8.12 (d, *J* = 5.5 Hz, 1H), 7.21 (d, *J* = 5.5 Hz, 1H), 4.00 (dd, *J* = 13.3, 6.0 Hz, 1H), 3.80 (dd, *J* = 13.4, 3.6 Hz, 1H), 3.75 (d, *J* = 13.4 Hz, 1H), 3.56 – 3.45 (m, 1H), 3.25 – 3.18 (m, 1H), 2.05 – 1.87 (m, 3H), 0.85 (d, *J* = 6.2 Hz, 3H).
214		*cis*-1-[4-(6-Aminopyrimidin-4-ylamino)-7-fluorothiazolo[5,4-c]pyridin-2-yl]-5-methylpiperidine-3-carbonitrile	385	A	2.86	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.46 (br s, 1H), 8.11 (d, *J* = 2.2 Hz, 1H), 8.04 (d, *J* = 0.8 Hz, 1H), 6.48 (br s, 2H), 6.27 (d, *J* = 0.8 Hz, 1H), 4.48-4.34 (m, 1H), 3.97-3.83 (m, 1H), 3.40 (t, *J* = 11.4 Hz, 1H), 3.13 (tt, *J* = 11.4, 4.0 Hz, 1H), 2.95 (t, *J* = 12.2 Hz, 1H), 2.18-2.11 (m, 1H), 1.82-1.68 (m, 1H), 1.52 (q, *J* = 12.4 Hz, 1H), 0.96 (d, *J* = 6.6 Hz, 3H).

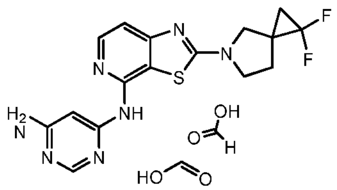
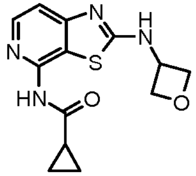
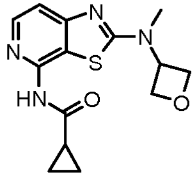
215		(±)-1-[4-(6-Amino-pyrimidin-4-ylamino)-7-fluoro-thiazolo[5,4c]pyridin-2-yl]-azepane-3-carbonitrile	385	A	2.68	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.47 (s, 1H), 8.10 (d, *J* = 2.4 Hz, 1H), 8.04 (s, 1H), 6.48 (s, 2H), 6.32 (s, 1H), 4.24-3.90 (m, 2H), 3.72-3.49 (m, 2H), 3.45-3.34 (m, 1H), 1.95-1.79 (m, 4H), 1.75-1.60 (m, 2H).
216		*trans*-Cyclopropanecarboxylic acid (2-{ethyl-[4-(2-methanesulfonylethyl)-cyclohexyl]-amino}-7-fluorothiazolo[5,4-c]pyridin-4-yl)-amide formate salt	469	A	3.85	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.85 (s, 1H), 8.11 (d, *J* = 2.3 Hz, 1H), 3.60-3.47 (m, 2H), 3.17-3.10 (m, 2H), 2.96 (s, 3H), 1.99-1.91 (m, 1H), 1.89-1.78 (m, 5H), 1.75-1.58 (m, 5H), 1.47-1.34 (m, 1H), 1.26-1.08 (m, 4H), 0.86-0.81 (m, 4H).
217		*trans*-*N**4*-(6-Aminopyrimidin-4-yl)-7-fluoro-N*2*-[4-(2-methanesulfonyl-	466	A	2.59	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.26 (s, 1H), 8.67-8.59 (m, 1H), 8.04 (d, *J* = 2.3 Hz, 1H), 8.02 (d, *J* = 0.8 Hz, 1H), 6.44 (br s, 2H), 6.38 (d, *J* =

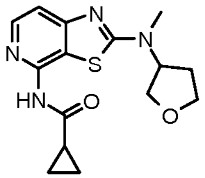
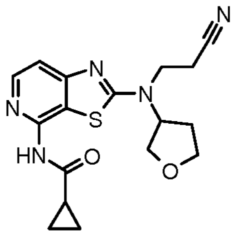
		ethyl)-cyclohexyl]-thiazolo[5,4c]pyridine-2,4-diamine				0.8 Hz, 1H), 3.71 (s, 1H), 3.17-3.08 (m, 2H), 2.95 (s, 3H), 2.10-2.02 (m, 2H), 1.84-1.75 (m, 2H), 1.65-1.57 (m, 2H), 1.43-1.18 (m, 3H), 1.16-1.02 (m, 2H).
218		Cyclopropanecarboxylic acid {2-[1-(2-methanesulfonyl-ethyl)-piperidin-4-ylamino]thiazolo[5,4-c]pyridin-4-yl}-amideformate salt	424	A	1.60	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.76 (s, 1H), 8.35 (d, *J* = 7.3 Hz, 1H), 8.05 (d, *J* = 5.7 Hz, 1H), 7.14 (d, *J* = 5.6 Hz, 1H), 3.72 (br s, 1H), 3.30-3.25 (m, 2H), 3.03 (s, 3H), 2.90-2.81 (m, 2H), 2.71 (t, *J* = 6.7 Hz, 2H), 2.71 (t, *J* = 10.5 Hz, 2H), 2.00-1.91 (m, 3H), 1.55-1.42 (m, 2H), 0.87-0.78 (m, 4H),
219		*cis/trans*-Cyclopropanecarboxylic acid {2-[4-(2-hydroxyethyl) cyclohexylamino]-thiazolo[5,4c]pyrid	361	A	2.52	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.76 (s, 1H), 8.36-8.27 (m, 1H), 8.04 (dd, *J* = 5.7, 09 Hz, 1H), 7.12 (d, *J* = 5.4 Hz, 1H), 4.31 (br s, 1H), 4.03-3.55 (m, 1H), 3.47-3.40 (m,

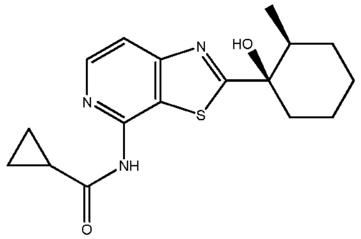
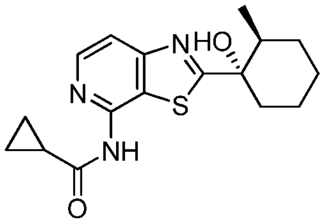
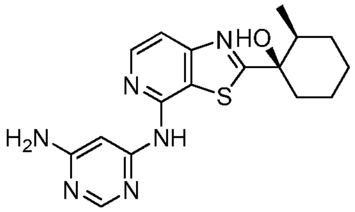
		in-4-yl}-amideformate salt				2H), 2.06-1.90 (m, 2H), 1.80-1.68 (m, 2H), 1.65-1.45 (m, 3H), 1.43-1.16 (m, 4H), 1.09-0.94 (m, 1H), 0.88-0.76 (m, 4H),
220		*trans*- 4-[4-(6-Aminopyrimidin-4-ylamino)-7-fluorothiazolo[5,4-c]pyridin-2-ylamino]cyclohexanol hydrochloride salt	376	A	2.12	^{1}H NMR (400 MHz, DMSO-d$_6$): δ 10.87 (s, 1H), 9.03 (br s, 1H), 8.45 (s, 1H), 8.34-7.97 (m, 3H), 6.62 (s, 1H), 3.65-3.34 (m, 2H), 2.07-1.96 (m, 2H), 1.90-1.81 (m, 2H), 1.41-1.21 (m, 4H).
221		*trans*-Cyclopropanecarboxylic acid [2-(4-cyanocyclohexylamino)-thiazolo[5,4-c]pyridin-4-yl]-amide formate salt	342	A	2.55	^{1}H NMR (400 MHz, DMSO-d$_6$): δ 10.76 (s, 1H), 8.34 (d, *J* = 7.6 Hz, 1H), 8.06 (d, *J* = 5.5 Hz, 1H), 7.14 (d, *J* = 5.8 Hz, 1H), 3.76 (br s, 1H), 2.81-2.70 (m, 1H), 2.09-1.90 (m, 5H), 1.72-1.58 (m, 2H), 1.41-1.22 (m, 2H), 0.88-0.77 (m, 4H).

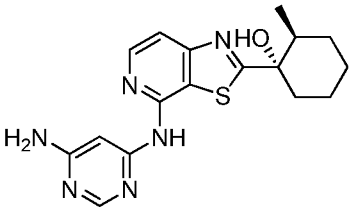
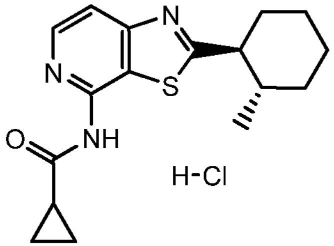
222		*trans*-Cyclopropanecarboxylic acid {2-[(4-cyanocyclohexyl)-methylamino]-thiazolo[5,4c]pyridin-4-yl}-amide	356	A	2.74	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.83 (s, 1H), 8.08 (d, *J* = 5.8 Hz, 1H), 7.18 (d, *J* = 5.6 Hz, 1H), 4.11 (br s, 1H), 3.00 (s, 3H), 2.76-2.63 (m, 1H), 2.17-2.06 (m, 2H), 2.02-1.93 (m, 1H), 1.80-1.63 (m, 6H), 0.84 (d, *J* = 6.2 Hz, 4H).
223		*trans*-Cyclopropanecarboxylic acid {2-[(4-cyanocyclohexyl)-(2-cyanoethyl)-amino]-thiazolo[5,4-c]pyridin-4-yl}-amide formate salt	395	A	2.84	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.89 (s, 1H), 8.12 (d, *J* = 5.6 Hz, 1H), 7.24 (d, *J* = 5.4 Hz, 1H), 3.84-3.63 (m, 3H), 2.95 (t, *J* = 6.9 Hz, 2H), 2.74-2.64 (m, 1H), 2.19-2.08 (m, 2H), 2.03-1.95 (m, 1H), 1.90-1.68 (m, 6H), 0.85 (d, *J* = 6.3 Hz, 4H).
224		*trans*-Cyclopropanecarboxylic acid {2-[4-(2-cyanoethyl)-cyclohexylamino]-thiazolo[5,4c]pyrid	370	A	2.90	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.75 (s, 1H), 8.31 (d, *J* = 7.5 Hz, 1H), 8.05 (d, *J* = 5.5 Hz, 1H), 7.12 (d, *J* = 5.6 Hz, 1H), 3.73-3.53 (m, 1H), 2.55-2.45 (m, 2H), 2.07-1.91

		in-4-yl}-amide				(m, 2H), 1.82-1.72 (m, 2H), 1.54-1.45 (m, 2H), 1.37-1.16 (m, 3H), 1.11-0.98 (m, 2H), 0.86-0.76 (m, 4H).
225		*trans*-Cyclopropanecarboxylic acid (2-{[4-(2-cyanoethyl)-cyclohexyl]methyl-amino}thiazolo[5,4-c]pyridin-4-yl)-amide	374	A	3.11	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.81 (s, 1H), 8.07 (d, *J* = 5.4 Hz, 1H), 7.17 (d, *J* = 5.5 Hz, 1H), 4.23-3.73 (m, 1H), 3.03 (s, 3H), 2.53-2.42 (m, 2H), 1.98 (qn, *J* = 6.2 Hz, 1H), 1.89-1.81 (m, 2H), 1.80-1.59 (m, 4H), 1.51 (q, *J* = 7.0 Hz, 2H), 1.42-1.29 (m, 1H), 1.19-1.05 (m, 2H), 0.84 (d, *J* = 6.2 Hz, 4H).
226		Cyclopropanecarboxylic acid [2-(4-fluorocyclohexylamino)-thiazolo[5,4-c]pyridin-4-yl]-amide	353	A	2.93	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (s, 1H), 8.10 (d, *J* = 5.4 Hz, 1H), 7.21 (d, *J* = 5.4 Hz, 1H), 5.64 (br s, 1H), 3.82 (br s, 1H), 2.24-2.08 (m, 4H), 2.02-1.84 (m, 2H), 1.75-1.55 (m, 3H), 1.17-1.11 (m, 2H), 0.96-0.89 (m, 2H).

227		*N*-[2-(1,1-Difluoro-5-azaspiro[2.4]hept-5-yl)-thiazolo[5,4c]pyridin-4-yl]-pyrimidine-4,6-diamineformate salt	376	A	2.67	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.79 (br s, 1H), 9.39 (br s, 1H), 8.08 (d, *J* = 5.4 Hz, 1H), 8.05 (d, *J* = 0.8 Hz, 1H), 7.12 (d, *J* = 5.5 Hz, 1H), 6.56 (d, *J* = 0.8 Hz, 1H), 6.49 (s, 2H), 3.81-3.61 (m, 4H), 2.35-2.15 (m, 2H), 1.84-1.65 (m, 2H).
228		Cyclopropanecarboxylic acid [2-(oxetan-3-ylamino)-thiazolo[5,4c]pyridin-4-yl]-amide	291	A	1.97	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.83 (s, 1H), 9.11 (d, *J* = 6.3 Hz, 1H), 8.08 (d, *J* = 5.4 Hz, 1H), 7.16 (d, *J* = 5.4 Hz, 1H), 5.01-4.91 (m, 1H), 4.85 (t, *J* = 6.6 Hz, 2H), 4.51 (t, *J* = 6.4 Hz, 2H), 2.02-1.93 (m,, 1H), 0.87-0.79 (m, 4H).
229		Cyclopropanecarboxylic acid [2-(methyloxetan-3-yl-amino)-thiazolo[5,4-c]pyridin-4-yl]-	305	A	2.15	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.88 (s, 1H), 8.11 (d, *J* = 5.2 Hz, 1H), 7.20 (d, *J* = 5.2 Hz, 1H), 5.36 (qn, *J* = 6.9 Hz, 1H), 4.85-4.76 (m, 4H), 3.28 (s, 3H), 1.99 (qn, *J* = 6.1

		amide				Hz, 1H), 0.85 (d, J = 6.1 Hz, 4H).
230		(±)-Cyclopropanecarboxylic acid {2-[methyl(tetrahydrofuran-3-yl)-amino]thiazolo[5,4c]pyridin-4-yl}-amide	319	A	2.31	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.85 (s, 1H), 8.10 (d, J = 5.5 Hz, 1H), 7.19 (d, J = 5.7 Hz, 1H), 4.97 (br s, 1H), 4.06-3.95 (m, 1H), 3.86 (dd, J = 10.0, 3.4 Hz, 1H), 3.76 (dd, J = 9.9, 3.1 Hz, 1H), 3.63 (q, J = 8.0 Hz, 1H), 3.06 (s, 3H), 2.37-2.26 (m, 1H), 2.03-1.92 (m, 2H), 0.84 (d, J = 6.2 Hz, 4H),
231		(±)-Cyclopropanecarboxylic acid {2-[(2-cyanoethyl)-(tetrahydrofuran-3-yl)-amino]-thiazolo[5,4c]pyridin-4-yl}-amide	358	A	2.42	^{1}H NMR (400 MHz, DMSO-d_6): δ 10.92 (s, 1H), 8.14 (d, J = 5.7 Hz, 1H), 7.26 (d, J = 5.7 Hz, 1H), 4.03 (dt, J = 4.8, 8.6 Hz, 1H), 3.92 (dd, J = 10.0, 3.6 Hz, 1H), 3.87-3.72 (m, 3H), 3.66 (q, J = 8.0 Hz, 1H), 3.02 (t, J = 7.0 Hz, 2H), 2.44-2.31 (m, 1H), 2.10-1.96 (m, 2H), 0.87-0.83 (m, 4H).

232		Cyclopropanecarboxylic acid [2-((1S,2R/1R,2S)-1-hydroxy-2-methylcyclohexyl)-thiazolo[5,4-c]pyridin-4-yl]-amide	332	A	3.68	^{1}H NMR (400 MHz, DMSO-d_6): δ 11.11 (s, 1H), 8.31 (d, J = 5.6 Hz, 1H), 7.70 (d, J = 5.6 Hz, 1H), 5.88 (s, 1H), 2.11-1.99 (m, 2H), 1.97-1.80 (m, 2H), 1.74-1.32 (m, 6H), 0.90-0.85 (m, 4H). 0.63 (d, J = 6.8 Hz, 3H).
233		Cyclopropanecarboxylic acid [2-((1R,2R/1S,2S)-1-hydroxy-2-methyl-cyclohexyl)-thiazolo[5,4-c]pyridin-4-yl]-amide	332	A	3.78	^{1}H NMR (400 MHz, DMSO-d_6): δ 11.09 (s, 1H), 8.31 (d, J = 5.5 Hz, 1H), 7.74 (d, J = 5.5 Hz, 1H), 6.03 (s, 1H), 2.11-1.90 (m, 3H), 1.88-1.78 (m, 2H), 1.74-1.56 (m, 4H), 1.42-1.29 (s, 1H), 0.90-0.84 (m, 4H). 0.73 (d, J = 6.3 Hz, 3H).
234		(1S,2R/1R,2S)-1-[4-(6-Amino-pyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl]-2-methyl-	357	A	2.95	^{1}H NMR (400 MHz, MeOH-d_4): δ 8.30 (d, J = 5.7 Hz, 1H), 8.26 (br s, 1H), 8.15 (s, 1H), 7.56 (d, J = 5.7 Hz, 1H), 7.08 (s, 1H), 2.25-2.15 (m, 1H), 2.12-2.02 (m, 1H), 1.98-

		cyclohexanol				1.91 (m, 1H), 1.84-1.43 (m, 6H), 0.75 (d, J = 6.8 Hz, 3H).
235		(1R,2R/1S,2S)-1-[4-(6-Amino-pyrimidin-4-ylamino)thiazolo[5,4-c]pyridin-2-yl]-2-methyl-cyclohexanol	357	A	3.09	^{1}H NMR (400 MHz, MeOH-d_4): δ 8.31 (s, 1H), 8.29 (d, J = 5.7 Hz, 1H), 8.15 (s, 1H), 7.60 (d, J = 5.7 Hz, 1H), 7.10 (s, 1H), 2.27-2.19 (m, 1H), 2.13-2.02 (m, 1H), 1.99-1.86 (m, 2H), 1.84-1.66 (m, 4H), 1.52-1.41 (m, 1H), 0.84 (d, J = 6.4 Hz, 3H).
236		Cyclopropanecarboxylic acid [2-((1R,2R/1S,1S)-2-methylcyclohexyl)-thiazolo[5,4c]pyridin-4-yl]-amide hydrochloride salt	316	A	4.73	^{1}H NMR (400 MHz, DMSO-d_6): δ 11.33 (br s, 1H), 8.33 (d, J = 5.7 Hz, 1H), 7.75 (d, J = 5.7 Hz, 1H), 2.84-2.75 (m, 1H), 2.13-2.02 (m, 1H), 2.00-1.91 (m, 1H), 1.85-1.70 (m, 4H), 1.64-1.52 (m, 1H), 1.46.1.28 (m, 2H), 1.19-1.07 (m, 1H), 0.92-0.86 (m, 3H), 0.77 (d, J = 6.2 Hz, 4H)

BIOLOGICAL EXAMPLES

Compounds of Formula I, II or III or any variation thereof described herein may be assayed for the ability to modulate the activity of protein kinases, tyrosine kinases, additional serine/threonine kinases, and/or dual specificity kinases *in vitro* and *in vivo*. *In vitro* assays include biochemical and cell-based assays that determine inhibition of the kinase activity. Alternate *in vitro* assays quantify the ability of a compound described herein to bind to kinases and may be measured either by radiolabelling the compound prior to binding, isolating the compound/kinase complex and determining the amount of radiolabel bound, or by running a competition experiment where a compound is incubated with known radiolabeled ligands. These and other useful *in vitro* assays are well known to those of skill in the art. For example, a TYK2 inhibition assay is presented below, and JAK1, JAK2 and JAK3 inhibition assays are described in, e.g., WO 2012/035039.

In an embodiment, the compounds described herein can be used to control, modulate or inhibit tyrosine kinase activity, for example TYK2 kinase activity, additional serine/threonine kinases, and/or dual specificity kinases. Thus, they are useful as pharmacological standards for use in the development of new biological tests, assays and in the search for new pharmacological agents.

TYK2 preparation: Sf9 cells were infected with baculovirus containing the kinase domain of TYK2 at a MOI of 2. Cells were harvested 72 hrs after infection and lysed with Lysis Buffer (20 mM Tris•Cl, pH 8, 200 mM NaCl, 20 mM imidazole, 1x Complete Protease Inhibitor Cocktail (Roche), 1 mM TCEP). The cell lysate was loaded on a Ni-NTA column (Qiagen), washed extensively with wash buffer (20 mM Tris•Cl, pH 8, 300 mM NaCl, 20 mM imidazole, 20% Glycerol, 0.5 mM TCEP), and the proteins were eluted with elution buffer (20 mM Tris•Cl, pH 8, 300 mM NaCl, 250 mM imidazole, 20% glycerol, 0.5 mM TCEP). The recovered proteins were then loaded on a Superdex® 200 (GE) column pre-equilibrated with gel filtration buffer (20 mM Tris•Cl, pH 8, 300 mM NaCl, 20% glycerol, 0.5mM TECP). The purity of purified TYK2 was greater than 95% as assessed by SDS-PAGE.

Example A

TYK2 Inhibition Assay Protocol

The activity of the isolated TYK2 kinase domain was measured by monitoring phosphorylation of a peptide derived from JAK3 (Val-Ala-Leu-Val-Asp-Gly-Tyr-Phe-Arg-Leu-Thr-Thr) fluorescently labeled on the N-terminus with 5-carboxyfluorescein using the Caliper LabChip technology (Caliper Life Sciences, Hopkinton, MA). To determine the inhibition constants (K_i) of Examples 1-236 of Table 1, compounds were diluted serially in DMSO and added to 50 μL kinase reactions containing 1 nM purified TYK2 enzyme, 100 mM Hepes pH7.2, 0.015% Brij-

35, 1.5 µM peptide substrate, 25 µM ATP, 10 mM $MgCl_2$, and 4 mM DTT at a final DMSO concentration of 2%. Reactions were incubated at 22 °C in 384-well polypropylene microtiter plates for 30 minutes and then stopped by addition of 25 µL of an EDTA containing solution (100 mM Hepes pH 7.2, 0.015% Brij-35, 150 mM EDTA), resulting in a final EDTA concentration of 50 mM. After termination of the kinase reaction, the proportion of phosphorylated product was determined as a fraction of total peptide substrate using the Caliper LabChip 3000 according to the manufacturer's specifications. K_i values were then determined using the Morrison tight binding model. Morrison, J.F., *Biochim. Biophys. Acta.* 185:269-296 (1969); William, J.W. and Morrison, J.F., *Meth. Enzymol.*, 63:437-467 (1979).

The K_i values for TYK2 inhibition (Example A) measured for compounds of Examples 1-236 of Table 1 are shown in Table 2.

Table 2

Example No.	TYK2 K_i (µM)
1	0.035
2	0.00161
3	0.0616
4	0.00251
5	0.167
6	0.000982
7	0.0131
8	0.0069
9	0.1
10	0.00214
11	0.000436
12	0.0103
13	0.19
14	0.00442
15	0.421
16	0.0154
17	0.000414
18	0.00461
19	0.00934
20	0.000215
21	0.0482
22	0.0104
23	0.0835
24	0.147
25	0.00837
26	0.00109
27	0.0477
28	0.474
29	0.546
30	0.456
31	0.0198
32	0.035
33	0.00844
34	0.00596
35	0.195
36	0.315
37	0.636
38	0.787
39	2.1

40	0.285
41	0.146
42	0.0758
43	0.0071
44	0.269
45	0.162
46	0.021
47	0.126
48	0.19
49	0.029
50	0.0561
51	0.00713
52	0.405
53	0.019
54	0.0759
55	0.00649
56	0.0525
57	0.119
58	0.0127
59	0.0145
60	0.00721
61	0.0389
62	0.00533
63	0.00583
64	0.0107
65	0.0211
66	0.00299
67	0.0339
68	0.00865
69	0.00221
70	0.0672
71	0.00318
72	0.0684
73	0.0814
74	0.133
75	3.2
76	0.0132
77	0.0203
78	0.0122
79	0.0763
80	0.00413
81	0.0537
82	0.131
83	2.6
84	0.408
85	0.0164
86	0.0312
87	0.0282
88	0.0071
89	0.0343
90	0.0158
91	0.0209
92	0.0363
93	0.0416
94	0.0507
95	0.506
96	0.629
97	0.13
98	0.00376
99	0.0103
100	0.0264
101	0.0031
102	0.0214
103	0.019
104	0.0125
105	0.0283

106	0.00168
107	0.0104
108	0.0453
109	0.218
110	0.0973
111	0.0285
112	0.205
113	0.0571
114	0.109
115	0.0674
116	1
117	0.807
118	0.0934
119	0.455
120	0.00901
121	0.551
122	0.0157
123	0.0166
124	0.842
125	0.0231
126	0.000395
127	0.0106
128	0.000751
129	0.0251
130	0.000664
131	0.0144
132	0.00139
133	0.0317
134	0.00206
135	0.0255
136	0.00264
137	0.0279
138	0.0153
139	0.0656
140	0.00319
141	0.0673
142	0.0407
143	0.0872
144	0.00256
145	0.00205
146	0.00356
147	0.0417
148	0.0639
149	0.00325
150	0.0913
151	0.00153
152	0.0191
153	0.0112
154	0.00516
155	0.0278
156	0.168
157	0.0846
158	0.0242
159	0.21
160	0.33
161	0.405
162	0.522
163	0.00567
164	0.0572
165	0.0559
166	0.00196
167	0.00543
168	0.0159
169	0.0445
170	0.00139
171	0.0895

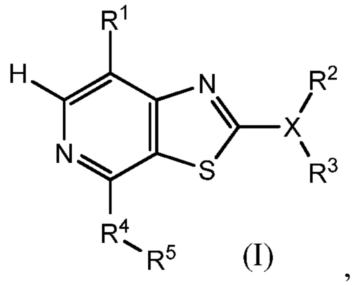
172	0.0114
173	0.011
174	0.0159
175	0.0703
176	0.0187
177	0.715
178	0.00427
179	0.186
180	0.263
181	0.0157
182	0.39
183	0.0258
184	2.1
185	1.2
186	0.0181
187	0.129
188	3
189	0.0452
190	0.0753
191	0.0259
192	1.5
193	0.214
194	0.00511
195	0.185
196	0.00708
197	0.349
198	0.0361
199	1.4
200	0.0283
201	0.22
202	0.0766
203	0.169
204	0.0177
205	0.0191
206	0.36
207	0.0221
208	0.00101
209	0.233
210	0.568
211	0.015
212	0.11
213	0.00436
214	0.0271
215	0.00473
216	0.00195
217	0.00755
218	0.137
219	0.0454
220	0.0807
221	0.0874
222	0.0794
223	0.139
224	0.0919
225	0.0365
226	0.147
227	0.21
228	0.417
229	0.654
230	0.234
231	0.0742
232	0.07
233	0.0243
234	0.0254
235	0.0615
236	0.00917

All references throughout, such as publications, patents, patent applications and published patent applications, are incorporated herein by reference in their entireties.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is apparent to those skilled in the art that certain minor changes and modifications will be practiced. Therefore, the description and examples should not be construed as limiting the scope of the invention.

CLAIMS

1. A compound of Formula I:



(I) ,

or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein:

X is N or CR^0;

R^0 is hydrogen, hydroxyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, C_6-C_{14} aryl, or 5-10-membered heteroaryl, wherein R^0 maybe optionally substituted by R^{10};

R^1 is hydrogen, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, –CN, –OR^8, –SR^8, –NR^{8}R^9, –CF$_3$, –NO$_2$, –C(O)R^8, –C(O)OR^8, –C(O)NR^{8}R^9, –NR^{8}C(O)R^9, –S(O)R^8, –S(O)$_2$R^8, –NR^{8}S(O)R^9, –NR^{8}S(O)$_2$R^9, –S(O)NR^{8}R^9, –S(O)$_2$NR^{8}R^9, C_3-C_6 cycloalkyl, 3-6-membered heterocyclyl, 5-6-membered heteroaryl, C_6-C_{14} aryl, –(C_1-C_3 alkylene)CN, –(C_1-C_3 alkylene)OR^8, –(C_1-C_3 alkylene)SR^8, –(C_1-C_3 alkylene)NR^{8}R^9, –(C_1-C_3 alkylene)CF$_3$, –(C_1-C_3 alkylene)NO$_2$,–(C_1-C_3 alkylene)C(O)R^8, –(C_1-C_3 alkylene)C(O)OR^8, –(C_1-C_3 alkylene)C(O)NR^{8}R^9, –(C_1-C_3 alkylene)NR^{8}C(O)R^9, –(C_1-C_3 alkylene)S(O)R^8, –(C_1-C_3 alkylene)S(O)$_2$R^8, –(C_1-C_3 alkylene)NR^{8}S(O)R^9, –(C_1-C_3 alkylene)NR^{8}S(O)$_2$R^9, –(C_1-C_3 alkylene)S(O)NR^{8}R^9, –(C_1-C_3 alkylene)S(O)$_2$NR^{8}R^9, –(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), –(C_1-C_3 alkylene)(3-6-membered heterocyclyl), –(C_1-C_3 alkylene)(5-6-membered heteroaryl) or –(C_1-C_3 alkylene)(C_6-C_{14} aryl) , wherein R^1 is optionally substituted by R^{10};

each R^2 and R^3 is independently hydrogen, hydroxyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, C_6-C_{14} aryl, or 5-10-membered heteroaryl, wherein R^2 and R^3 are each independently optionally substituted by R^{10}; or

R^2 and R^3 are taken together with the atom to which they are attached to form a ring selected from C_3-C_{10} cycloalkyl and 3-10-membered heterocyclyl, wherein the ring may be optionally substituted by R^{10};

R^4 is hydrogen, –NR^6–, –NR^{6}R^7, –NR^{6}C(O)–, –NR^{6}C(O)O–, –NR^{6}C(O)NR^7–, –NR^{6}S(O)–, –NR^{6}S(O)$_2$–, –NR^{6}S(O)NR^7– or –NR^{6}S(O)$_2$NR^7–;

R^5 is absent, hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, 3-10-membered heterocyclyl or 5-10-membered heteroaryl, wherein R^5 is optionally substituted by R^{10};

R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_6 cycloalkyl, wherein the alkyl, alkenyl, alkynyl and cycloalkyl are independently optionally substituted by halogen, C_1-C_6 alkyl, oxo, –CN, $–OR^{11}$ or $–NR^{11}R^{12}$; or

R^6 and R^7 are independently taken together with the atom to which they are attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, $–OR^{11}$, $–NR^{11}R^{12}$ or C_1-C_6 alkyl optionally substituted by halogen;

R^8 and R^9 are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo;

each R^{10} is independently hydrogen, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, –CN, $–OR^{11}$, $–SR^{11}$, $–NR^{11}R^{12}$, $–NO_2$, $–C{=}NH(OR^{11})$, $–C(O)R^{11}$, $–C(O)OR^{11}$, $–C(O)NR^{11}R^{12}$, $–NR^{11}C(O)R^{12}$, $–S(O)R^{11}$, $–S(O)_2R^{11}$, $–NR^{11}S(O)R^{12}$, $–NR^{11}S(O)_2R^{12}$, $–S(O)NR^{11}R^{12}$, $–S(O)_2NR^{11}R^{12}$, C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, 5-10-membered heteroaryl, C_6-C_{14} aryl, –(C_1-C_3 alkylene)CN, –(C_1-C_3 alkylene)OR^{11}, –(C_1-C_3 alkylene)SR^{11}, –(C_1-C_3 alkylene)$NR^{11}R^{12}$, –(C_1-C_3 alkylene)CF_3, –(C_1-C_3 alkylene)NO_2, $–C{=}NH(OR^{11})$, –(C_1-C_3 alkylene)$C(O)R^{11}$, –(C_1-C_3 alkylene)$C(O)OR^{11}$, –(C_1-C_3 alkylene)$C(O)NR^{11}R^{12}$, –(C_1-C_3 alkylene)$NR^{11}C(O)R^{12}$, –(C_1-C_3 alkylene)$S(O)R^{11}$, –(C_1-C_3 alkylene)$S(O)_2R^{11}$, –(C_1-C_3 alkylene)$NR^{11}S(O)R^{12}$, –(C_1-C_3 alkylene)$NR^{11}S(O)_2R^{12}$, –(C_1-C_3 alkylene)$S(O)NR^{11}R^{12}$, –(C_1-C_3 alkylene)$S(O)_2NR^{11}R^{12}$, –(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), –(C_1-C_3 alkylene)(3-10-membered heterocyclyl), –(C_1-C_3 alkylene)(5-10-membered heteroaryl) or –(C_1-C_3 alkylene)(C_6-C_{14} aryl), wherein each R^{10} is independently optionally substituted by halogen, oxo, $–OR^{13}$, $–NR^{13}R^{14}$, $–C(O)R^{13}$, $–S(O)R^{13}$, $–S(O)_2R^{13}$, –(C_1-C_3 alkylene)OR^{13}, –(C_1-C_3 alkylene)$NR^{13}R^{14}$, –(C_1-C_3 alkylene)$C(O)R^{13}$, –(C_1-C_3 alkylene)$S(O)R^{13}$, –(C_1-C_3 alkylene)$S(O)_2R^{13}$ or C_1-C_6 alkyl optionally substituted by oxo, –CN or halogen;

R^{11} and R^{12} are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6 membered heteroaryl or 3-6 membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are independently optionally substituted by halogen, oxo, –CN, $–OR^{16}$, $–NR^{16}R^{17}$ or C_1-C_6 alkyl optionally substituted by halogen, –CN or oxo; or

R^{11} and R^{12} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, –OR^{16}, –$NR^{16}R^{17}$ or C_1-C_6 alkyl optionally substituted by halogen, oxo or OH;

R^{13} and R^{14} are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo; or

R^{13} and R^{14} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by halogen or oxo; and

R^{16} and R^{17} are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo; or

R^{16} and R^{17} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by oxo or halogen.

2. The compound of claim 1, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein X is N.

3. The compound of claim 1 or 2, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^1 is hydrogen, halogen, –CN, optionally substituted C_1-C_6 alkyl or optionally substituted C_3-C_6 cycloalkyl.

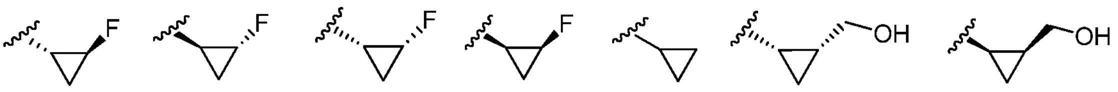
4. The compound of claim 1 or 3, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^2 is hydrogen or optionally substituted C_1-C_6 alkyl and R^3 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_6 cycloalkyl or optionally substituted 3-6-membered heterocyclyl.

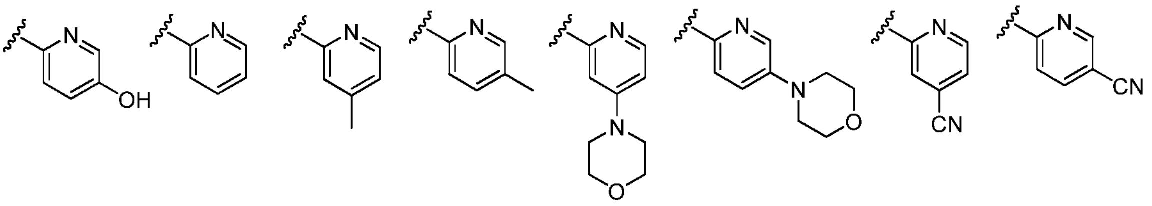
5. The compound of claim 1 or 3, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^2 and R^3 are taken together with the atom to which they are attached to form an optionally substituted cycloalkyl or an optionally substituted heterocyclyl.

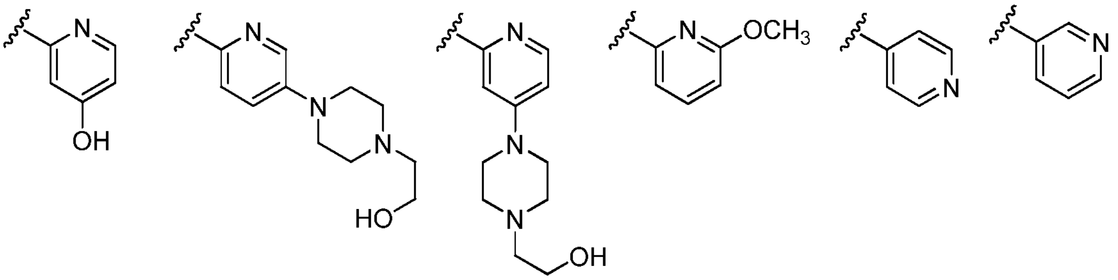
6. The compound of any one of claims 1 to 5, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^4 is –NR^6–, –$NR^6C(O)$–, –$NR^6C(O)O$– or –$NR^6C(O)NR^7$–.

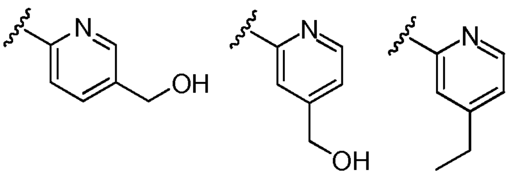
7. The compound of any one of claims 1 to 6, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^5 is C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, 3-10-membered heterocyclyl or 5-10-membered heteroaryl, wherein R^5 is optionally substituted by R^{10}.

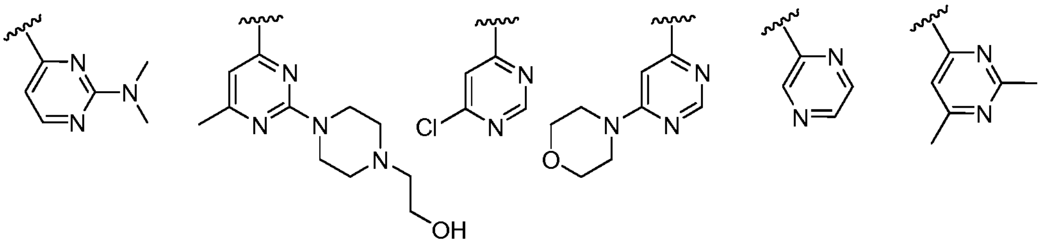
8. The compound of claim 7, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^5 is selected from methyl, ethyl, isopropyl, *tert*-butyl, $–CH_2OH$, $–CH_2CH_2OH$, $–CH_2CN$, $–CH_2NH_2$, $–CH_2N(CH_3)_2$ or $–CH_2CH_2NH_2$, phenyl,

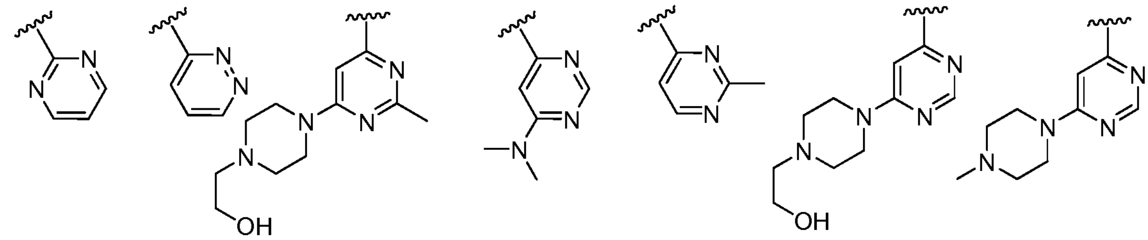


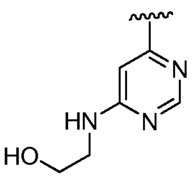
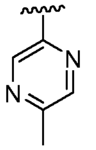
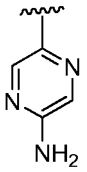
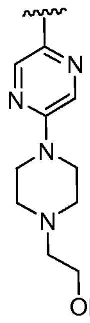
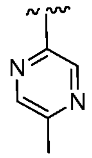
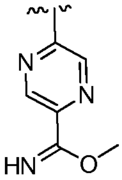
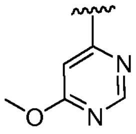
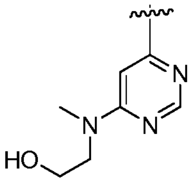
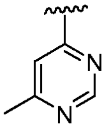
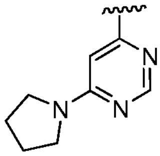
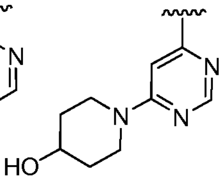
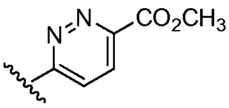
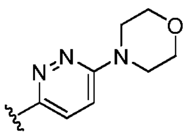
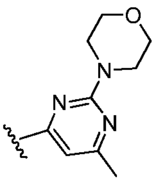
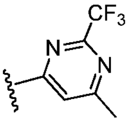
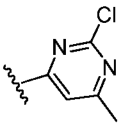
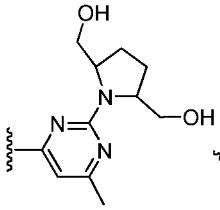
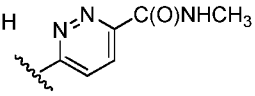
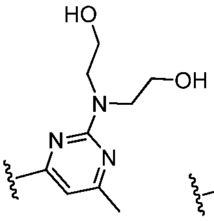
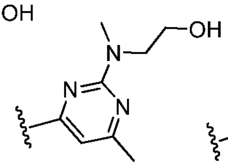
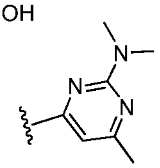
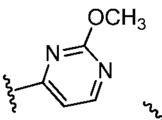
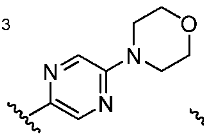
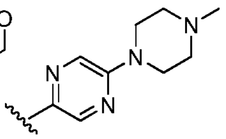
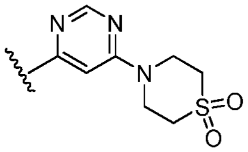
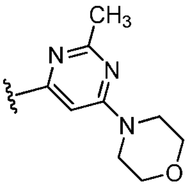
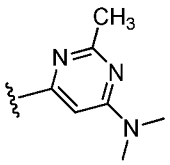
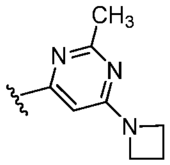
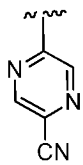


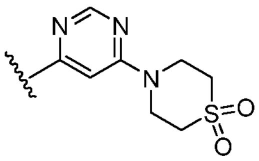
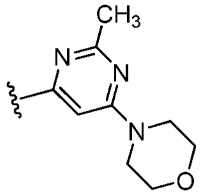
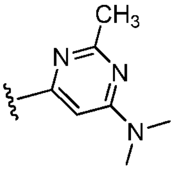
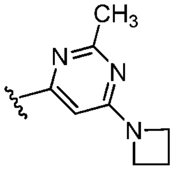
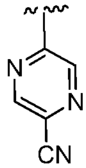
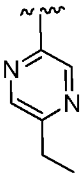
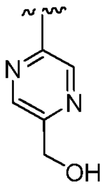
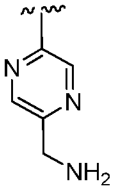
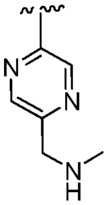
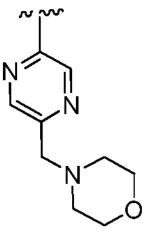
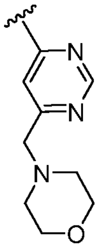
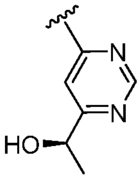
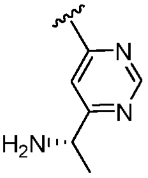
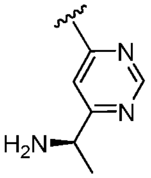
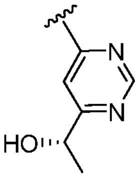
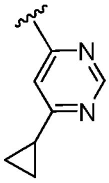
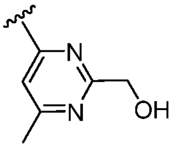
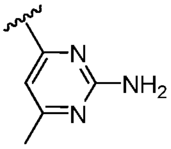
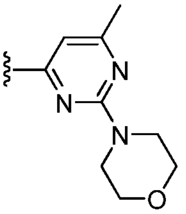
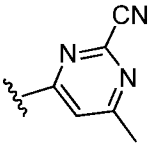
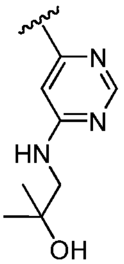
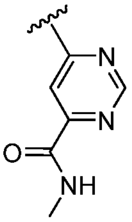
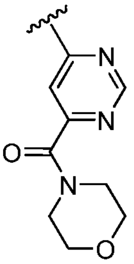
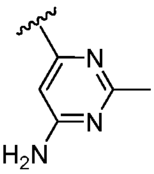
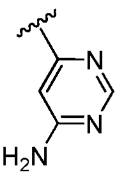
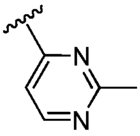
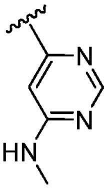
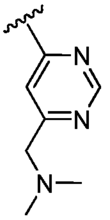
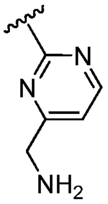
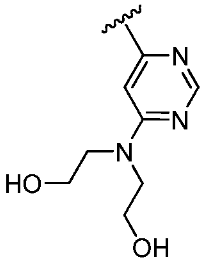
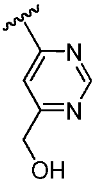
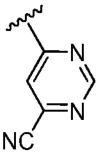
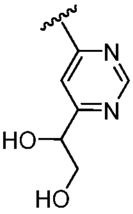
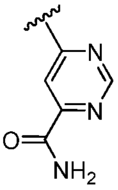
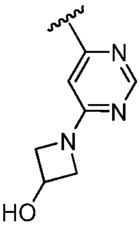
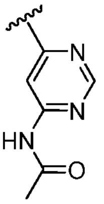
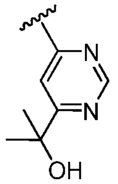
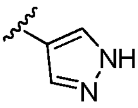
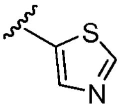
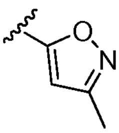
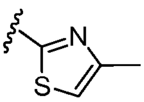
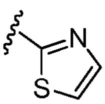
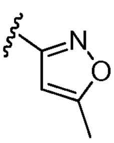
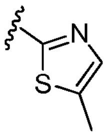








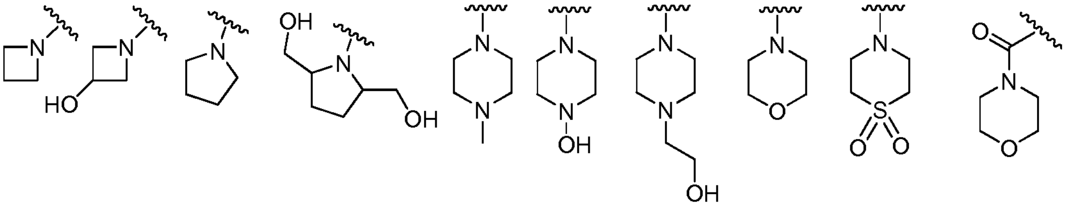










































































,

wherein the wavy line represents the point of attachment of R^5 in Formula I.

9. The compound of any one of claims 1 to 8, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^{10} is selected from F, –CN, methyl, ethyl, isopropyl, $–CH_2OH$,

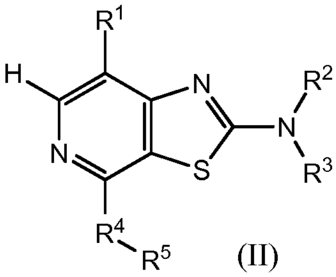
–CH_2CH_2OH, –$CH(OH)CH_2OH$, –$C(CH_3)_2OH$, –CH_2NH_2, –CH_2NHCH_3, –$CH_2N(CH_3)_2$, –CF_3, –OH, –OCH_3, –NH_2, –$NHCH_3$, –$NHC(O)CH_3$, –$N(CH_3)_2$, –$N(CH_2CH_2OH)_2$, –$NHCH_2CH_2OH$, –$N(CH_3)CH_2CH_2OH$, –$NHCH_2C(CH_3)_2OH$, –$N(CH_3)CH_2C(CH_3)_2OH$, –$C(O)NH_2$, –$C(O)NHCH_3$, –$C(O)N(CH_3)_2$, –CH_2thiomorpholinyl dioxide, –CH_2morpholinyl, –CH_2cyclopropyl, -$CH(OH)CH_3$, -$CH(NH_2)CH_3$, (*R*)-$CH(OH)CH_3$, (*R*)-$CH(NH_2)CH_3$, (*S*)-$CH(OH)CH_3$, (*S*)-$CH(NH_2)CH_3$,



,

wherein the wavy line represents the point of attachment in Formula I.

10. The compound of claim 1, further defined as a compound of Formula II:



(II) ,

or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein:

R^1 is hydrogen, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, –CN, or C_3-C_6 cycloalkyl, wherein R^1 is optionally substituted by R^{10};

R^2 is hydrogen or C_1-C_6 alkyl optionally substituted by R^{10}, or is taken together with R^3 and the nitrogen to which they are attached to form a 3-10-membered heterocyclyl optionally substituted by R^{10};

R^3 is hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, C_6-C_{14} aryl, or 5-10-membered heteroaryl, wherein R^3 may be optionally substituted by R^{10}; or is taken together with R^2 and the nitrogen to which they are attached to form a 3-10-membered heterocyclyl optionally substituted by R^{10};

R^4 is –NR^6–, –$NR^6C(O)$–, –$NR^6C(O)O$– or –$NR^6C(O)NR^7$–;

R^5 is hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 5-10-membered heteroaryl, wherein R^5 is optionally substituted by R^{10};

R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_6 cycloalkyl, wherein the alkyl, alkenyl, alkynyl and cycloalkyl are independently optionally substituted by halogen, C_1-C_6 alkyl, oxo, –CN, –OR^{11} or –$NR^{11}R^{12}$;

each R^{10} is independently hydrogen, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, –CN, $–OR^{11}$, $–SR^{11}$, $–NR^{11}R^{12}$, $–NO_2$, $–C{=}NH(OR^{11})$, $–C(O)R^{11}$, $–C(O)OR^{11}$, $–C(O)NR^{11}R^{12}$, $–NR^{11}C(O)R^{12}$, $–S(O)R^{11}$, $–S(O)_2R^{11}$, $–NR^{11}S(O)R^{12}$, $–NR^{11}S(O)_2R^{12}$, $–S(O)NR^{11}R^{12}$, $–S(O)_2NR^{11}R^{12}$, C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, 5-10-membered heteroaryl, C_6-C_{14} aryl, –(C_1-C_3 alkylene)CN, –(C_1-C_3 alkylene)OR^{11}, –(C_1-C_3 alkylene)SR^{11}, –(C_1-C_3 alkylene)$NR^{11}R^{12}$, –(C_1-C_3 alkylene)CF_3, –(C_1-C_3 alkylene)NO_2, $–C{=}NH(OR^{11})$, –(C_1-C_3 alkylene)$C(O)R^{11}$, –(C_1-C_3 alkylene)$C(O)OR^{11}$, –(C_1-C_3 alkylene)$C(O)NR^{11}R^{12}$, –(C_1-C_3 alkylene)$NR^{11}C(O)R^{12}$, –(C_1-C_3 alkylene)$S(O)R^{11}$, –(C_1-C_3 alkylene)$S(O)_2R^{11}$, –(C_1-C_3 alkylene)$NR^{11}S(O)R^{12}$, –(C_1-C_3 alkylene)$NR^{11}S(O)_2R^{12}$, –(C_1-C_3 alkylene)$S(O)NR^{11}R^{12}$, –(C_1-C_3 alkylene)$S(O)_2NR^{11}R^{12}$, –(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), –(C_1-C_3 alkylene)(3-10-membered heterocyclyl), –(C_1-C_3 alkylene)(5-10-membered heteroaryl) or –(C_1-C_3 alkylene)(C_6-C_{14} aryl), wherein each R^{10} is independently optionally substituted by halogen, oxo, $–OR^{13}$,
$–NR^{13}R^{14}$, $–C(O)R^{13}$, $–S(O)R^{13}$, $–S(O)_2R^{13}$, –(C_1-C_3 alkylene)OR^{13}, –(C_1-C_3 alkylene)$NR^{13}R^{14}$, –(C_1-C_3 alkylene)$C(O)R^{13}$, –(C_1-C_3 alkylene)$S(O)R^{13}$, –(C_1-C_3 alkylene)$S(O)_2R^{13}$ or C_1-C_6 alkyl optionally substituted by oxo, –CN or halogen;

R^{11} and R^{12} are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6 membered heteroaryl or 3-6 membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are independently optionally substituted by halogen, oxo, –CN, $–OR^{16}$, $–NR^{16}R^{17}$ or C_1-C_6 alkyl optionally substituted by halogen, –CN or oxo; or

R^{11} and R^{12} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, $–OR^{16}$, $–NR^{16}R^{17}$ or C_1-C_6 alkyl optionally substituted by halogen, oxo or OH;

R^{13} and R^{14} are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo; or

R^{13} and R^{14} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by halogen or oxo; and

R^{16} and R^{17} are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo; or

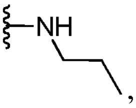
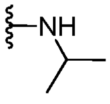
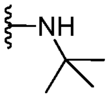
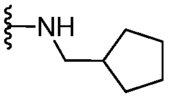
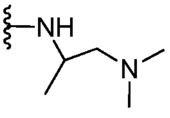
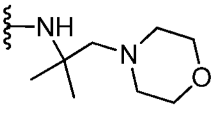
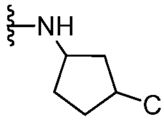
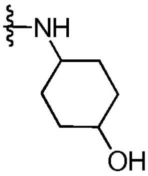
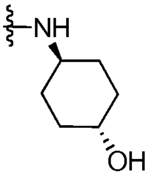
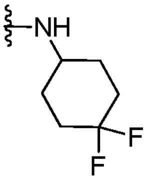
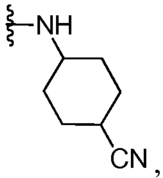
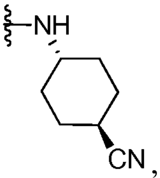
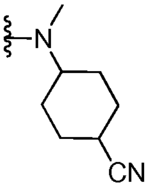
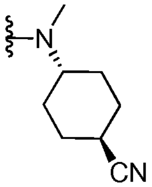
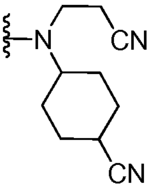
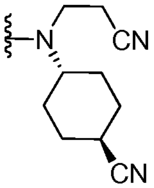
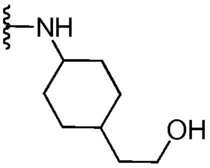
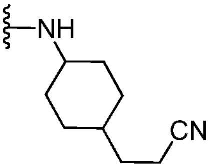
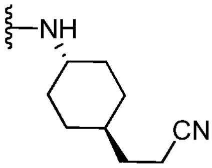
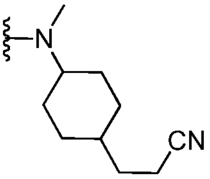
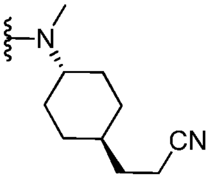
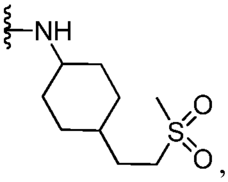
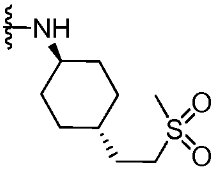
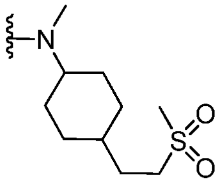
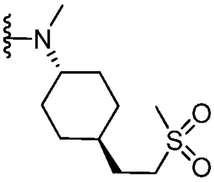
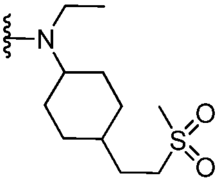
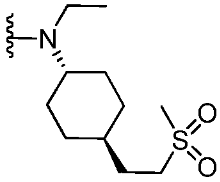
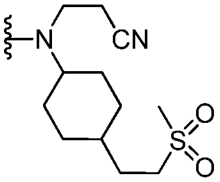
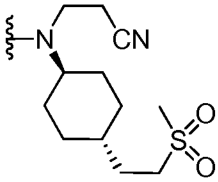
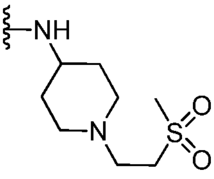
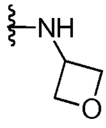
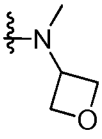
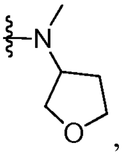
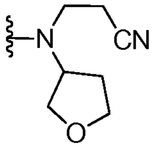
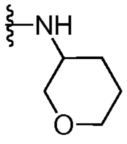
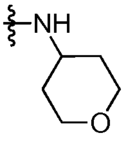
R^{16} and R^{17} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by oxo or halogen.

11. The compound of claim 10, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^1 is hydrogen, halogen, –CN or C_1-C_6 alkyl optionally substituted by R^{10}.

12. The compound of claim 11, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^1 is hydrogen, fluoro, chloro, bromo, –CN or C_1-C_6 alkyl.

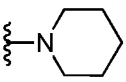
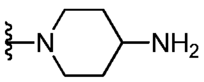
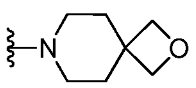
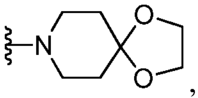
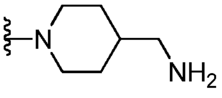
13. The compound of any one of claims 10 to 12, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^2 is hydrogen or optionally substituted C_1-C_6 alkyl and R^3 is optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_6 cycloalkyl or optionally substituted 3-6-membered heterocyclyl.

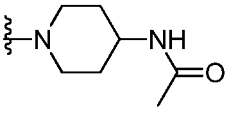
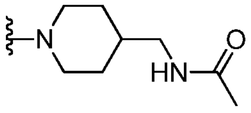
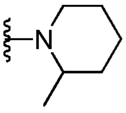
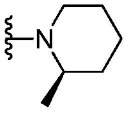
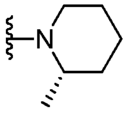
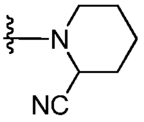
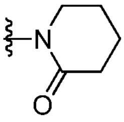
14. The compound of claim 13, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein the $-N(R^2)(R^3)$ moiety of Formula II is selected from the group consisting of:

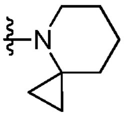
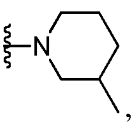
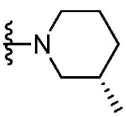
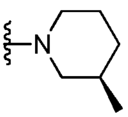
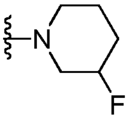
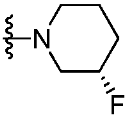
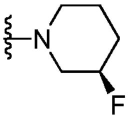
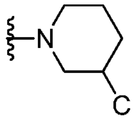
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
 and
 ; wherein the wavy line represents the point of attachment in Formula II.

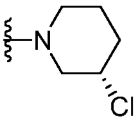
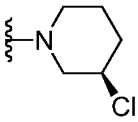
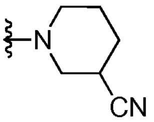
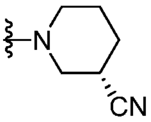
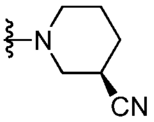
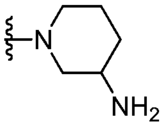
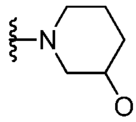
15. The compound of any one of claims 10 to 12, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^2 and R^3 are taken together with the atom to which they are attached to form an optionally substituted cycloalkyl or an optionally substituted heterocyclyl.

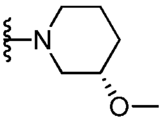
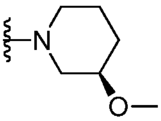
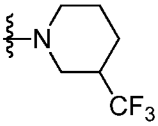
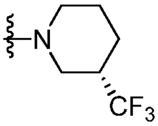
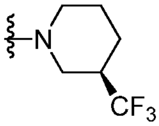
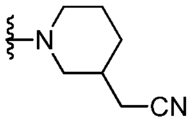
16. The compound of claim 15, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein the $-N(R^2)(R^3)$ moiety of Formula II is selected from the group consisting of:

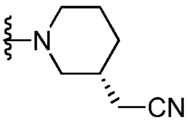
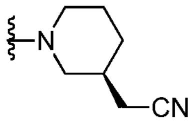
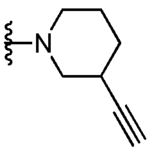
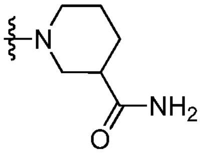
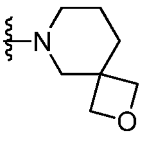
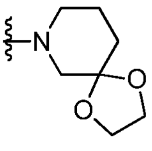
, , , , ,

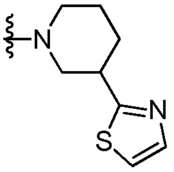
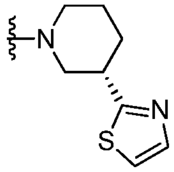
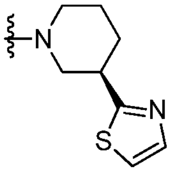
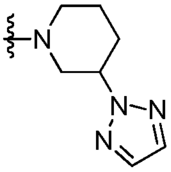
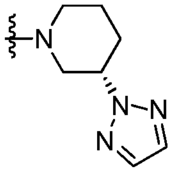
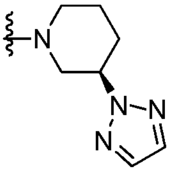
, , , , , , ,

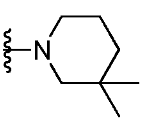
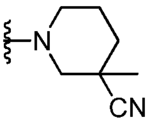
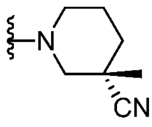
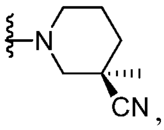
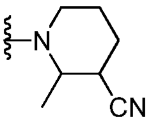
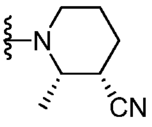
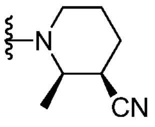
, , , , , , , ,

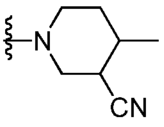
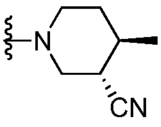
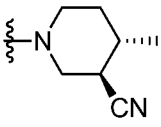
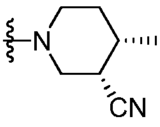
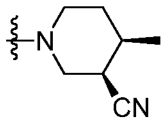
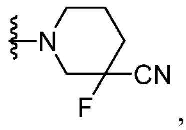
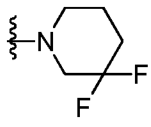
, , , , , , ,

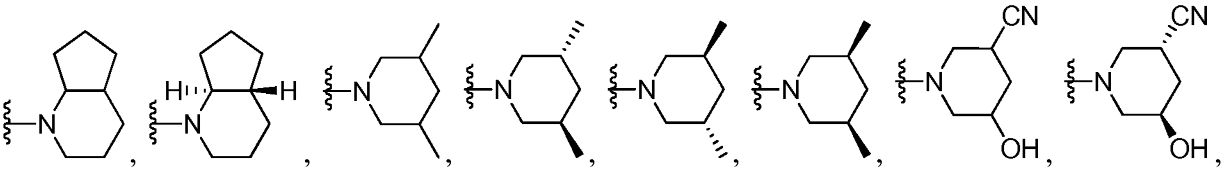
, , , , , ,

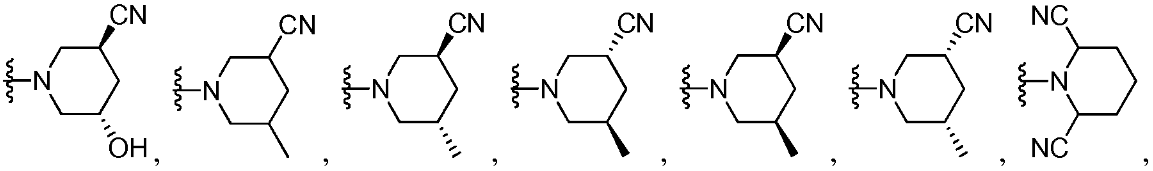
, , , , , ,

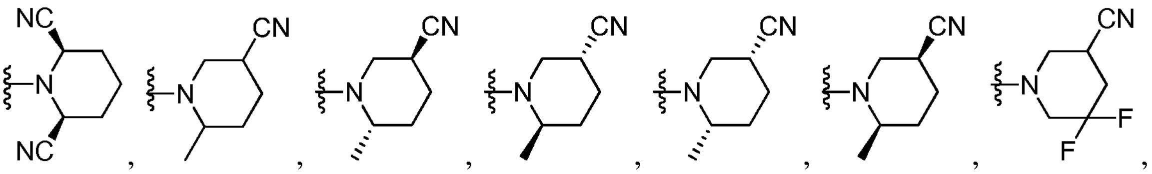
, , , , , ,

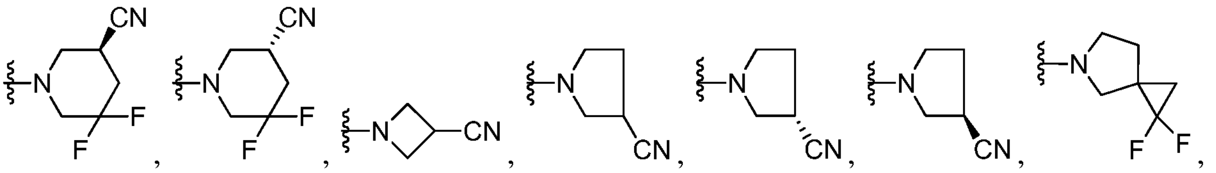
, , , , , , ,

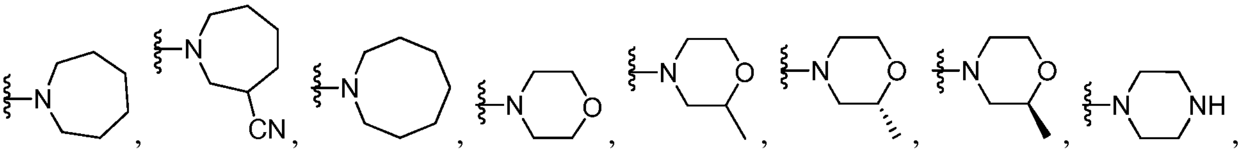
, , , , , , ,

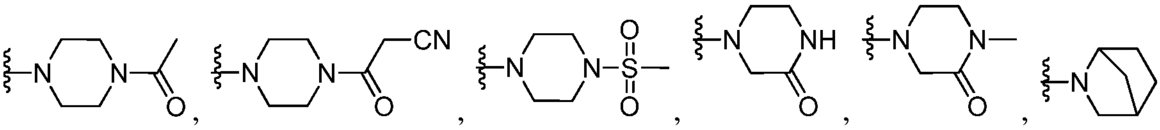










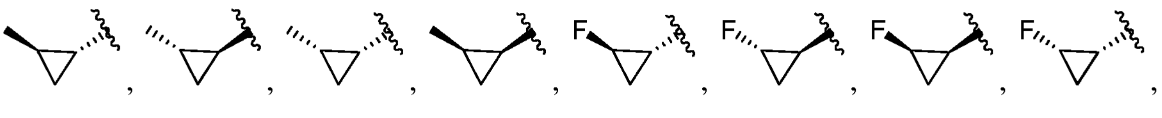


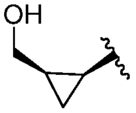
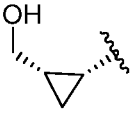
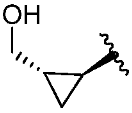
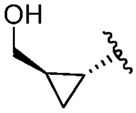
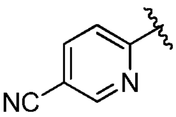
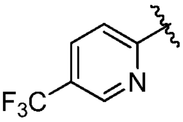
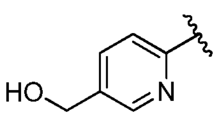
; wherein the wavy line represents the point of attachment in Formula II.

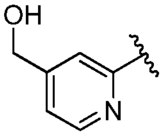
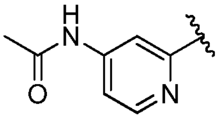
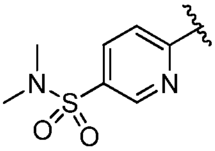
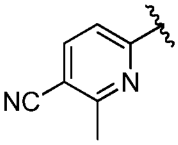
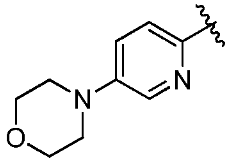
17. The compound of any one of claims 10 to 15, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^4 is $-NR^6-$, $-NR^6C(O)-$ or $-NR^6C(O)NR^7-$.

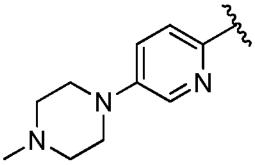
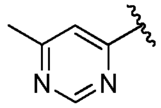
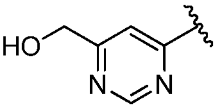
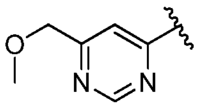
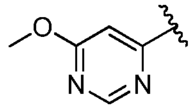
18. The compound of any one of claims 10 to 17, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^5 is optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_{10} cycloalkyl or optionally substituted 5-10-membered heteroaryl.

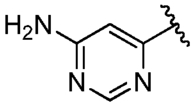
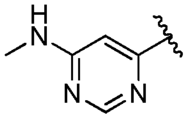
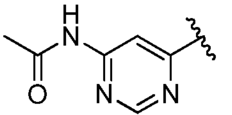
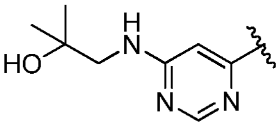
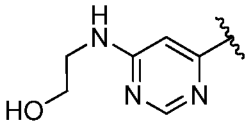
19. The compound of claim 18, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^5 is selected from the group consisting of methyl, ethyl, 2-propyl, cyclopropyl, 2-methylcyclopropyl, 2-fluorocyclopropyl, 2-(hydroxymethyl)cyclopropyl, cyclopropylmethyl,

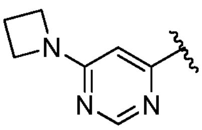
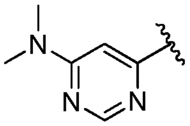
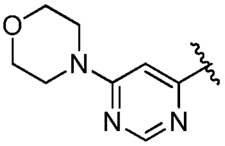
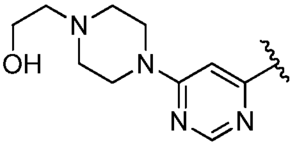
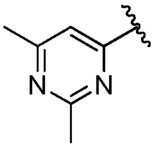


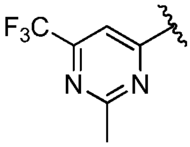
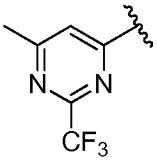
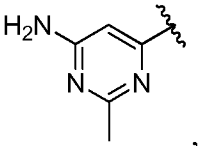
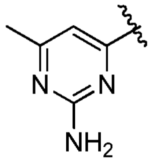
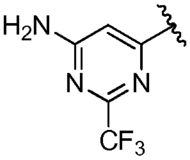
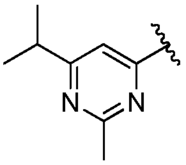
, , , , , , ,

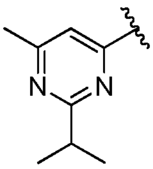
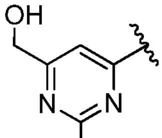
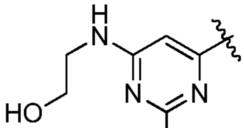
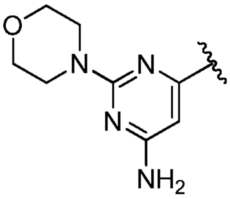
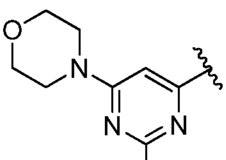
, , , , ,

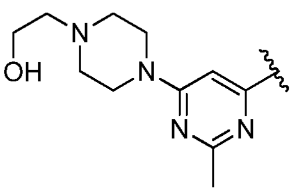
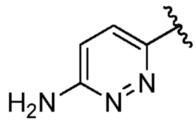
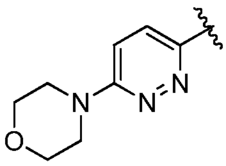
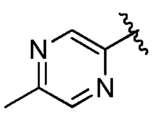
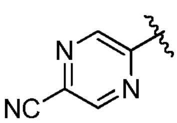
, , , , ,

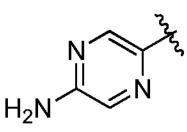
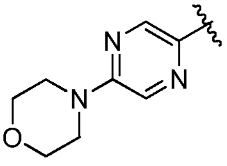
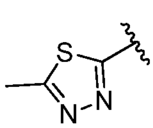
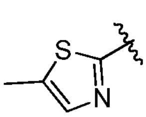
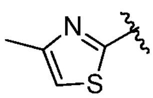
, , , , ,

, , , , ,

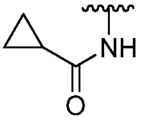
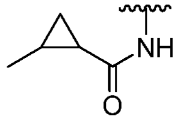
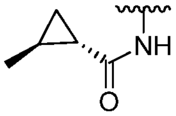
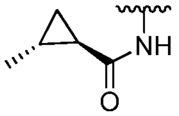
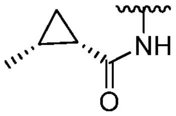
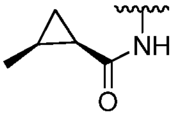
, , , , , ,

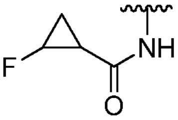
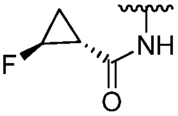
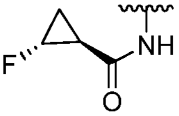
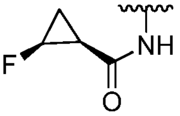
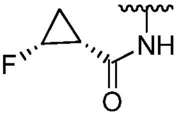
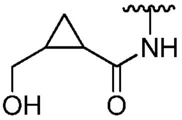
, , , , ,

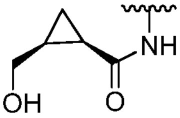
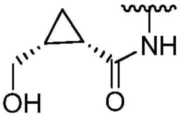
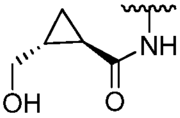
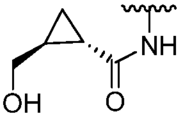
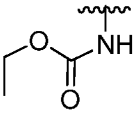
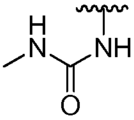
, , , , ,

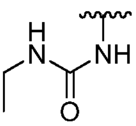
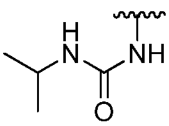
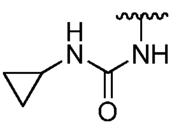
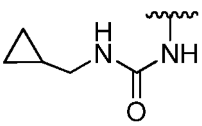
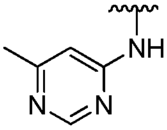
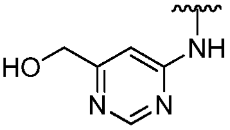
, , ,  and  ; wherein the wavy line represents the point of attachment in Formula II.

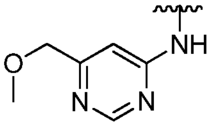
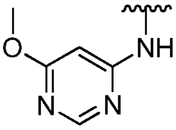
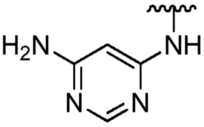
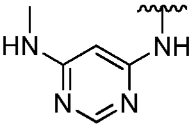
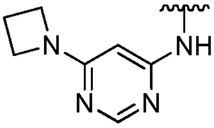
20. The compound of claim 18, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein the $-R^4$-R^5 moiety of Formula III is selected form the group consisting of:

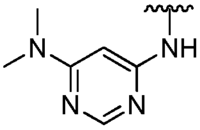
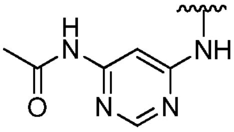
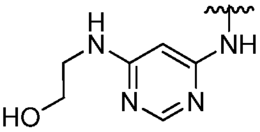
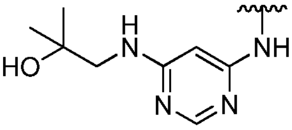
, , , , , ,

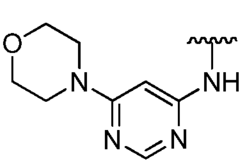
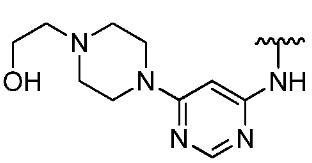
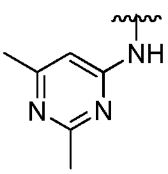
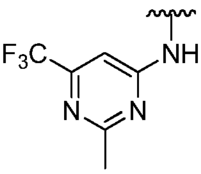
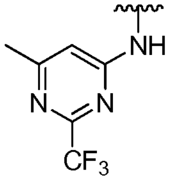
, , , , , ,

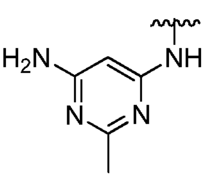
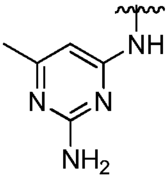
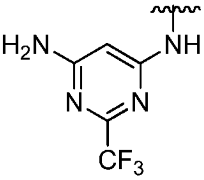
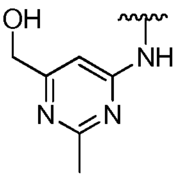
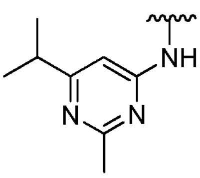
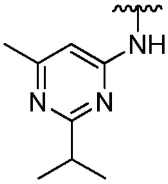
, , , , , ,

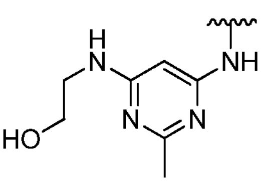
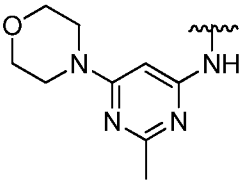
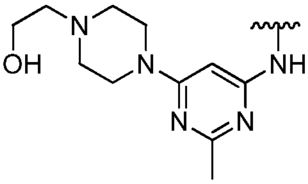
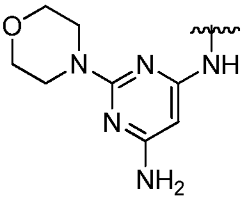
, , , , , ,

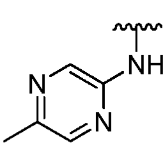
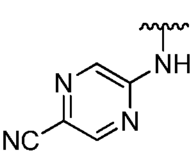
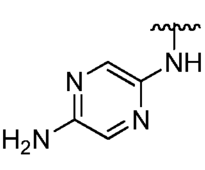
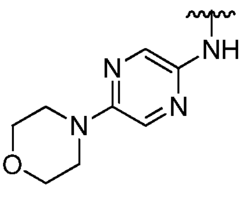
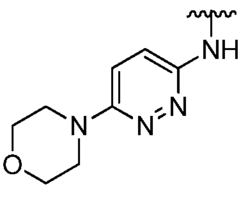
, , , , ,

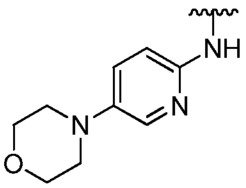
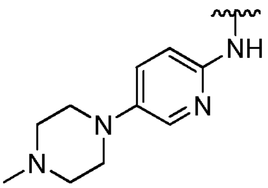
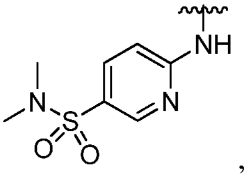
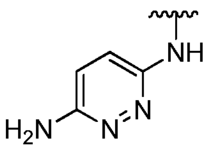
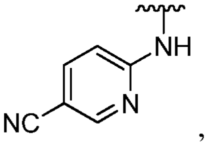
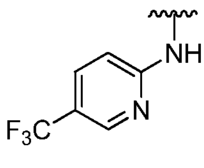
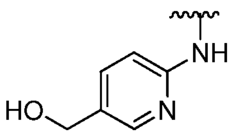
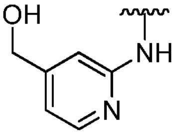
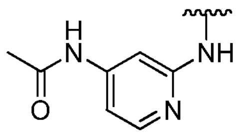
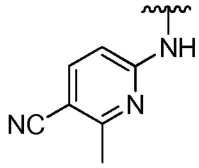
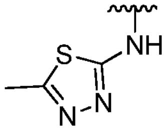
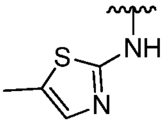
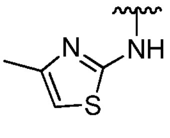
, , , ,

, , , , ,

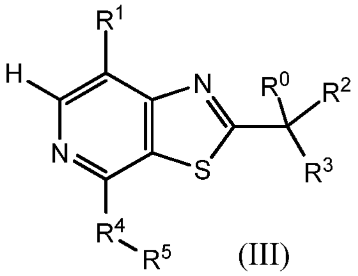
, , , , , ,

, , , ,

, , , , ,


, 
, 
, 
, 
, 
, 
, 
, 
, 
, 
, 
and 
; wherein the wavy line represents the point of attachment in Formula II.

21. The compound of claim 1, further defined as a compound of Formula III:


(III)
,

or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein:

R^0 is hydrogen, hydroxyl, or C_1-C_6 alkyl optionally substituted by R^{10};

R^1 is hydrogen, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, –CN, or C_3-C_6 cycloalkyl, wherein R^1 is optionally substituted by R^{10};

R^2 is hydrogen or C_1-C_6 alkyl optionally substituted by R^{10}, or is taken together with R^3 and the carbon to which they are attached to form a ring selected from C_3-C_{10} cycloalkyl and 3-10-membered heterocyclyl, wherein the ring is optionally substituted by R^{10};

R^3 is hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, C_6-C_{14} aryl, or 5-10-membered heteroaryl, wherein R^3 may be optionally substituted by R^{10}; or is taken together with R^2 and the carbon to which they are attached to form a ring selected from C_3-C_{10} cycloalkyl and 3-10-membered heterocyclyl, wherein the ring is optionally substituted by R^{10};

R^4 is $-NR^6-$, $-NR^6C(O)-$, $-NR^6C(O)O-$ or $-NR^6C(O)NR^7-$;

R^5 is hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, or 5-10-membered heteroaryl, wherein R^5 is optionally substituted by R^{10};

R^6 and R^7 are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_6 cycloalkyl, wherein the alkyl, alkenyl, alkynyl and cycloalkyl are independently optionally substituted by halogen, C_1-C_6 alkyl, oxo, –CN, $–OR^{11}$ or $–NR^{11}R^{12}$;

each R^{10} is independently hydrogen, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, –CN, $–OR^{11}$, $–SR^{11}$, $–NR^{11}R^{12}$, $–NO_2$, $–C{=}NH(OR^{11})$, $–C(O)R^{11}$, $–C(O)OR^{11}$, $–C(O)NR^{11}R^{12}$, $–NR^{11}C(O)R^{12}$, $–S(O)R^{11}$, $–S(O)_2R^{11}$, $–NR^{11}S(O)R^{12}$, $–NR^{11}S(O)_2R^{12}$, $–S(O)NR^{11}R^{12}$, $–S(O)_2NR^{11}R^{12}$, C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, 5-10-membered heteroaryl, C_6-C_{14} aryl, –(C_1-C_3 alkylene)CN, –(C_1-C_3 alkylene)OR^{11}, –(C_1-C_3 alkylene)SR^{11}, –(C_1-C_3 alkylene)$NR^{11}R^{12}$, –(C_1-C_3 alkylene)CF_3, –(C_1-C_3 alkylene)NO_2, $–C{=}NH(OR^{11})$, –(C_1-C_3 alkylene)$C(O)R^{11}$, –(C_1-C_3 alkylene)$C(O)OR^{11}$, –(C_1-C_3 alkylene)$C(O)NR^{11}R^{12}$, –(C_1-C_3 alkylene)$NR^{11}C(O)R^{12}$, –(C_1-C_3 alkylene)$S(O)R^{11}$, –(C_1-C_3 alkylene)$S(O)_2R^{11}$, –(C_1-C_3 alkylene)$NR^{11}S(O)R^{12}$, –(C_1-C_3 alkylene)$NR^{11}S(O)_2R^{12}$, –(C_1-C_3 alkylene)$S(O)NR^{11}R^{12}$, –(C_1-C_3 alkylene)$S(O)_2NR^{11}R^{12}$, –(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), –(C_1-C_3 alkylene)(3-10-membered heterocyclyl), –(C_1-C_3 alkylene)(5-10-membered heteroaryl) or –(C_1-C_3 alkylene)(C_6-C_{14} aryl), wherein each R^{10} is independently optionally substituted by halogen, oxo, $–OR^{13}$,
$–NR^{13}R^{14}$, $–C(O)R^{13}$, $–S(O)R^{13}$, $–S(O)_2R^{13}$, –(C_1-C_3 alkylene)OR^{13}, –(C_1-C_3 alkylene)$NR^{13}R^{14}$, –(C_1-C_3 alkylene)$C(O)R^{13}$, –(C_1-C_3 alkylene)$S(O)R^{13}$, –(C_1-C_3 alkylene)$S(O)_2R^{13}$ or C_1-C_6 alkyl optionally substituted by oxo, –CN or halogen;

R^{11} and R^{12} are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6 membered heteroaryl or 3-6 membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are independently optionally substituted by halogen, oxo, –CN, $–OR^{16}$, $–NR^{16}R^{17}$ or C_1-C_6 alkyl optionally substituted by halogen, –CN or oxo; or

R^{11} and R^{12} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, $–OR^{16}$, $–NR^{16}R^{17}$ or C_1-C_6 alkyl optionally substituted by halogen, oxo or OH;

R^{13} and R^{14} are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo; or

R^{13} and R^{14} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by halogen or oxo; and

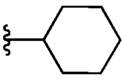
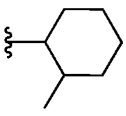
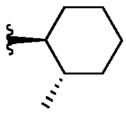
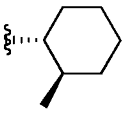
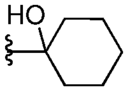
R^{16} and R^{17} are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo; or

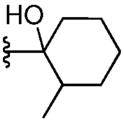
R^{16} and R^{17} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by oxo or halogen.

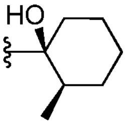
22. The compound of claim 21, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^0 is hydrogen or hydroxyl.

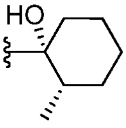
23. The compound of claim 21 or 22, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^2 and R^3 are taken together with the carbon to which they are attached to form an optionally substituted cycloalkyl.

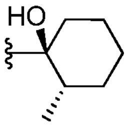
24. The compound of claim 23, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein the $-C(R^0)(R^2)(R^3)$ moiety of Formula III is selected from the group consisting of:

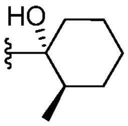

,

,

,

,


,


,


,


,


and


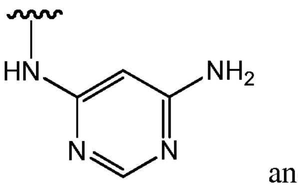
; wherein the wavy line represents the point of attachment in Formula III.

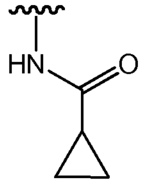
25. The compound of any one of claims 21 to 24, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^1 is hydrogen or halogen.

26. The compound of any one of claims 21 to 25, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^4 is $-NR^6-$ or $-NR^6C(O)-$.

27. The compound of claim 26, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^5 is optionally substituted C_3-C_{10} cycloalkyl or optionally substituted 5-10-membered heteroaryl.

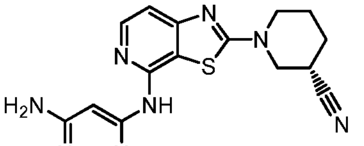
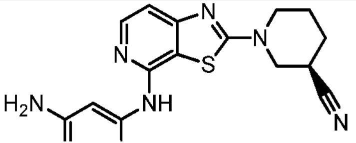
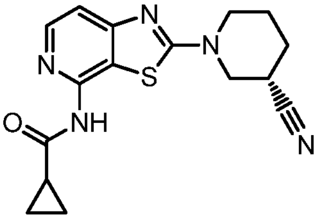
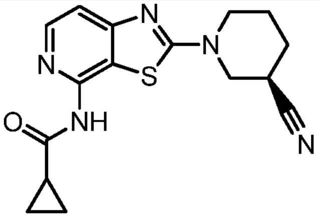
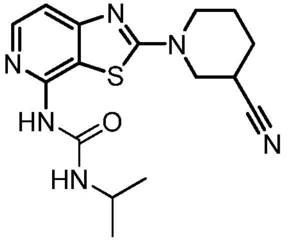
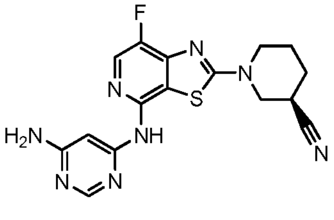
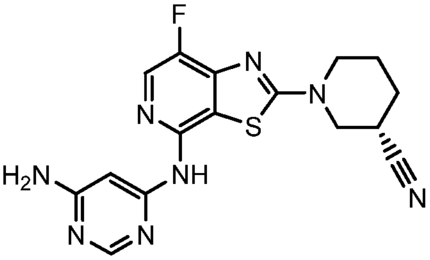
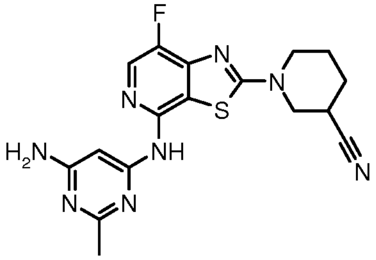
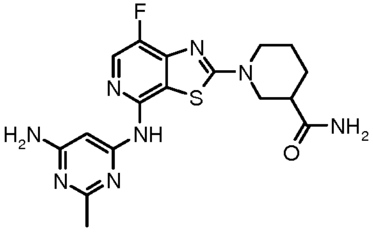
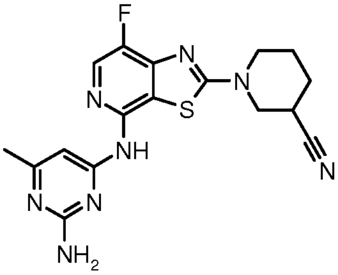
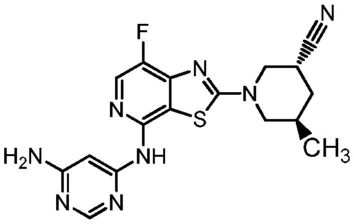
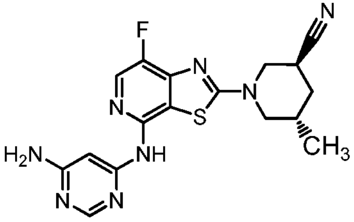
28. The compound of claim 18 or claim 27, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein the $-R^4$-R^5 moiety of Formula II or Formula III, respectively, is selected from the group consisting of:

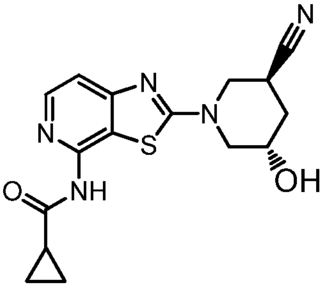
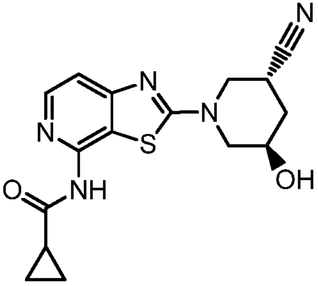
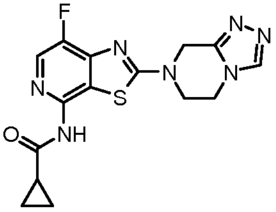
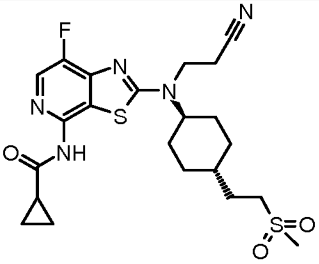
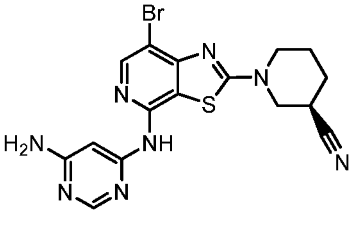
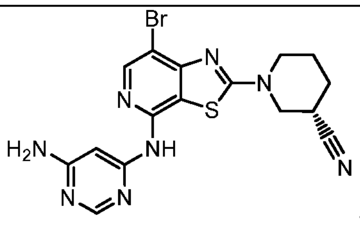


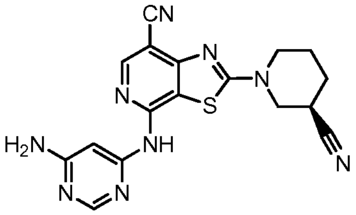
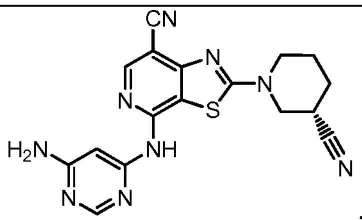
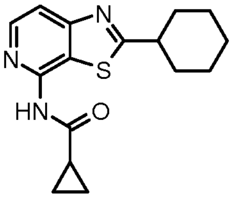
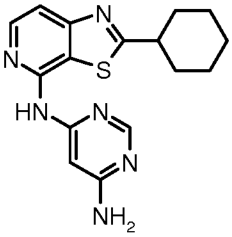
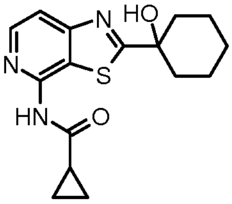
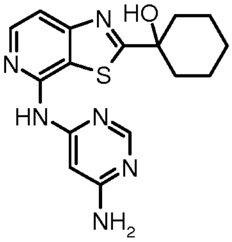
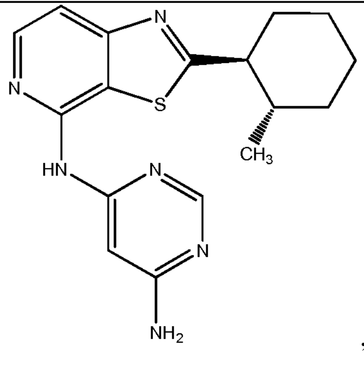
and


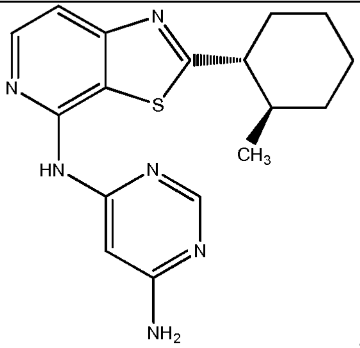
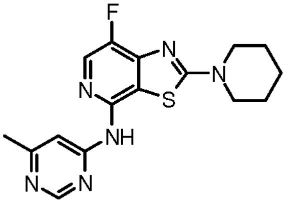
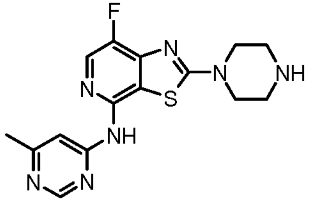
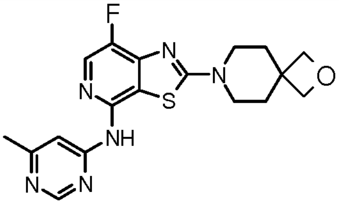
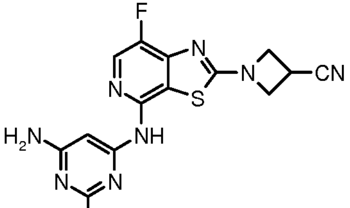
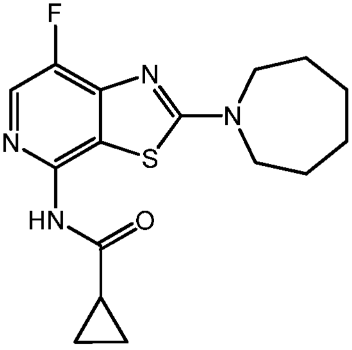
; wherein the wavy line represents the point of attachment in Formula II or Formula III.

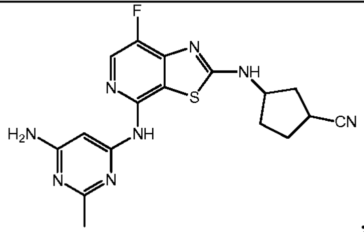
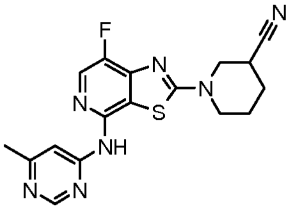
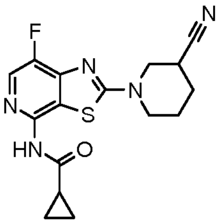
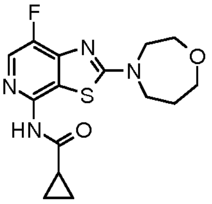
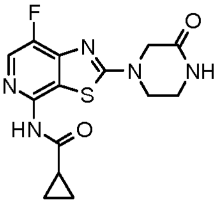
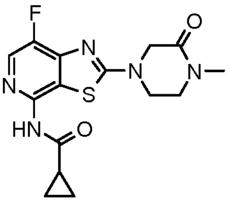
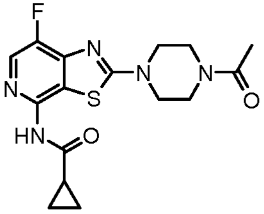
29. The compound of claim 1, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein the compound is selected from:

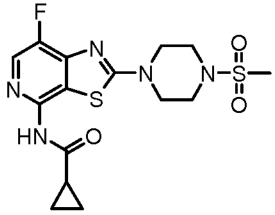
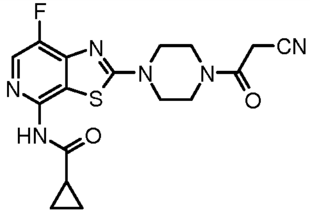
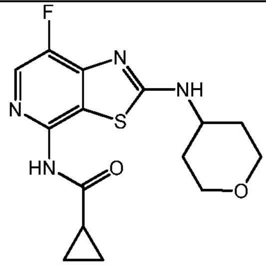
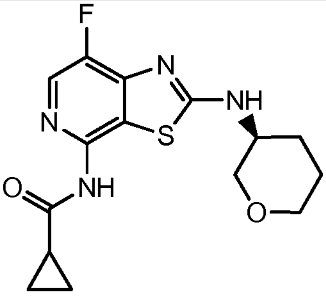
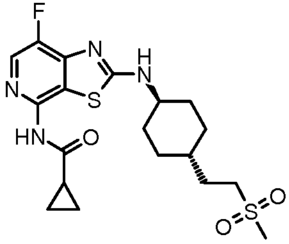
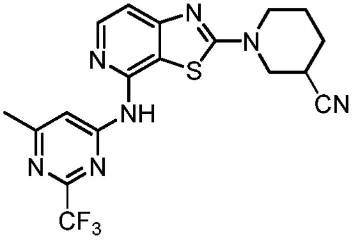
Example No.	**Structure**
1	 ,
2	 ,
3	 ,
4	 ,
5	 ,
6	 ,
7	 ,
8	 ,
9	 ,
10	 ,
11	 ,
12	 ,

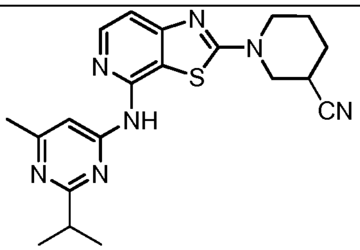
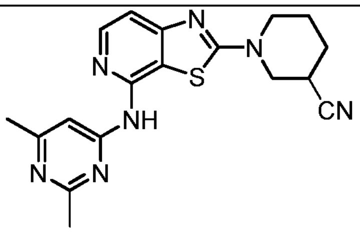
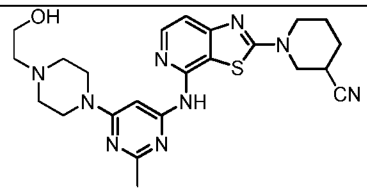
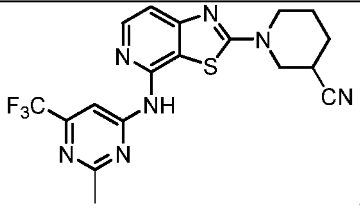
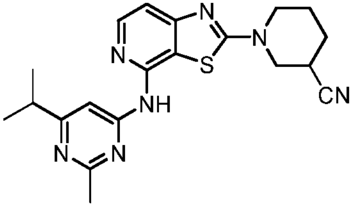
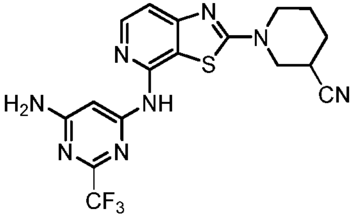
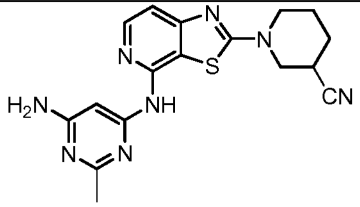
13	 ,
14	 ,
15	 ,
16	 ,
17	 ,
18	 ,

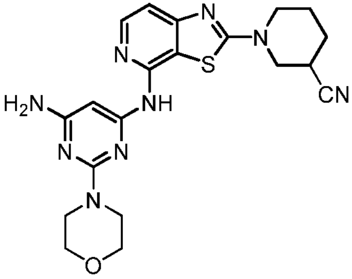
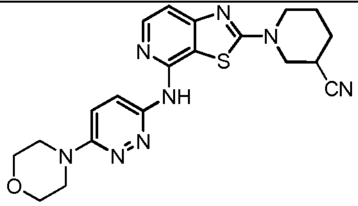
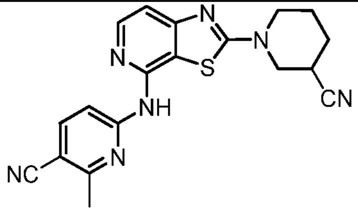
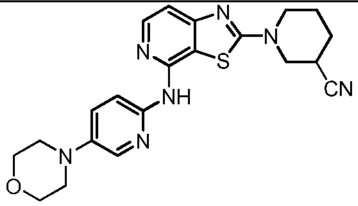
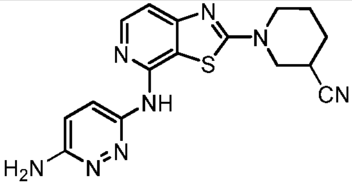
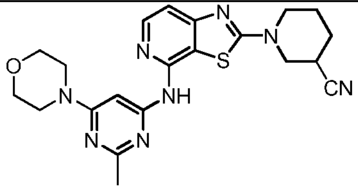
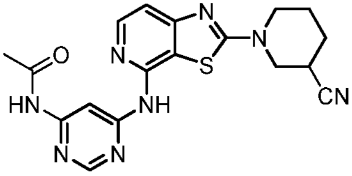
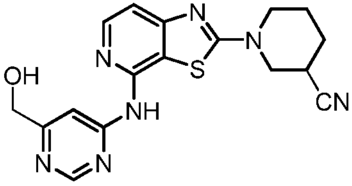
19	 ,
20	 ,
21	 ,
22	 ,
23	 ,
24	 ,
25	 ,

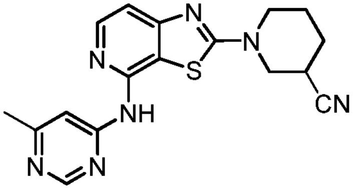
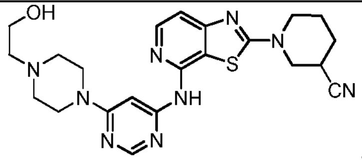
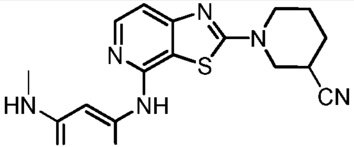
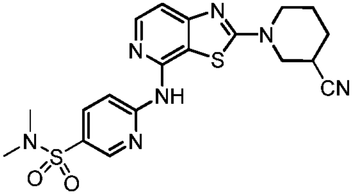
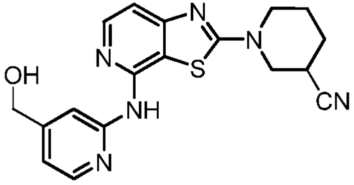
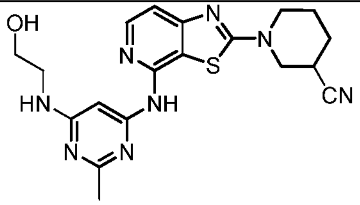
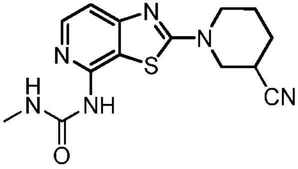
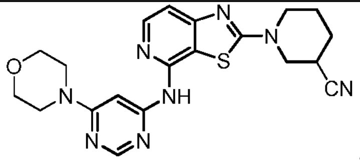
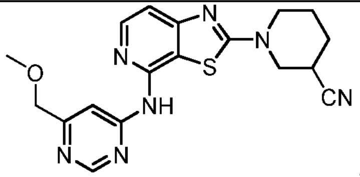
26	 ,
27	 ,
28	 ,
29	 ,
30	 ,
31	 ,

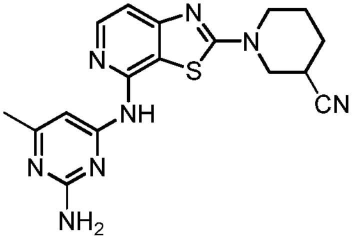
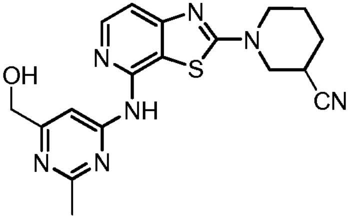
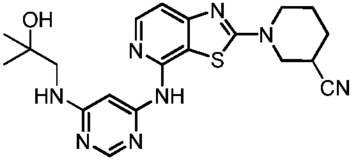
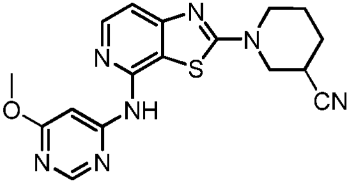
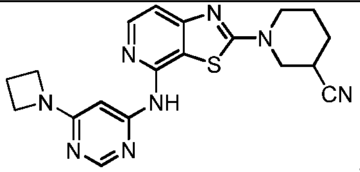
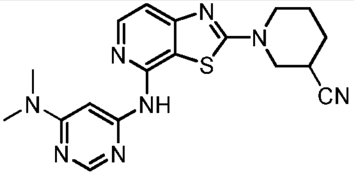
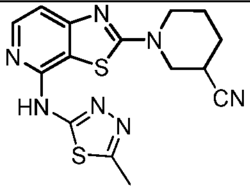
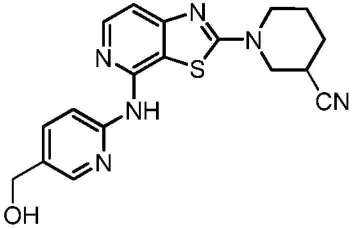
32	 ,
33	 ,
34	 ,
35	 ,
36	 ,
37	 ,
38	 ,

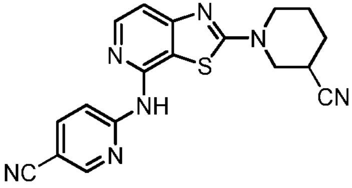
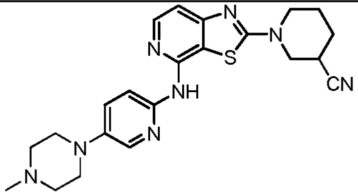
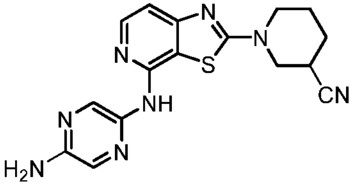
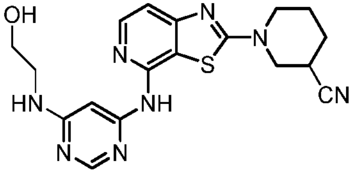
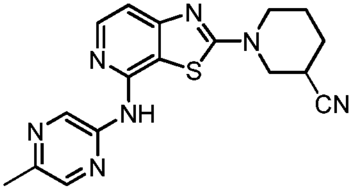
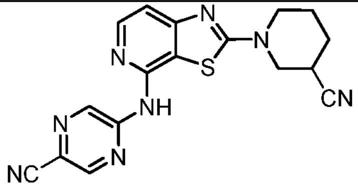
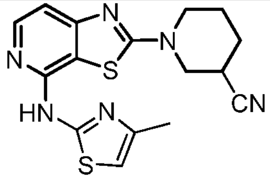
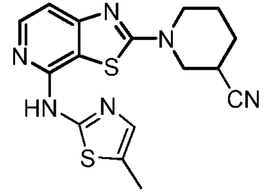
39	 ,
40	 ,
41	 ,
42	 ,
43	 ,
44	 ,

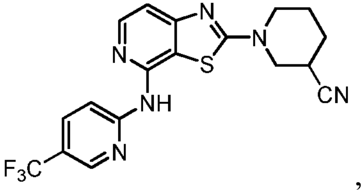
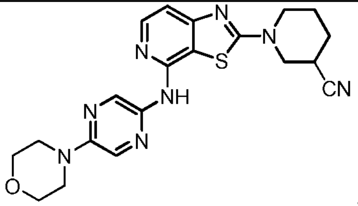
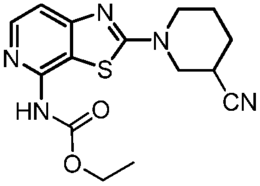
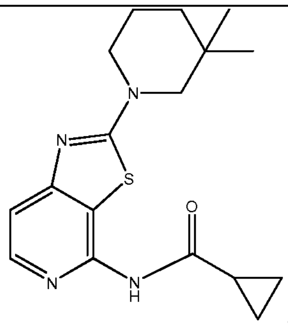
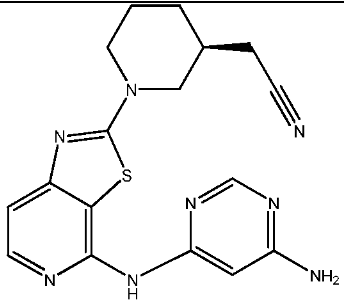
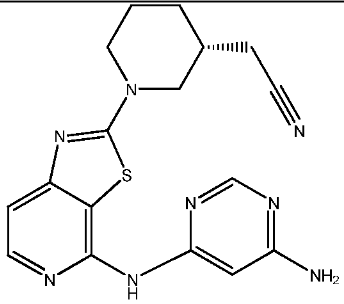
45	 ,
46	 ,
47	 ,
48	 ,
49	 ,
50	 ,
51	 ,

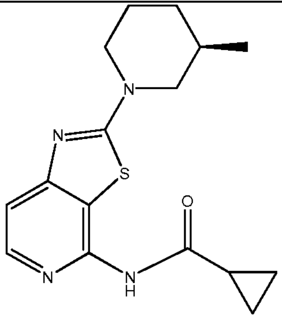
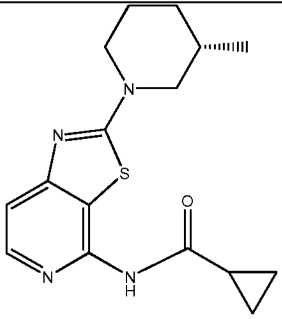
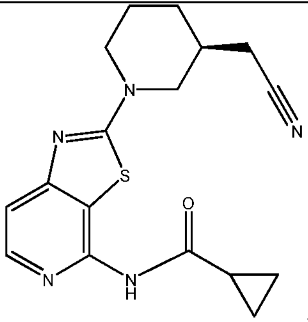
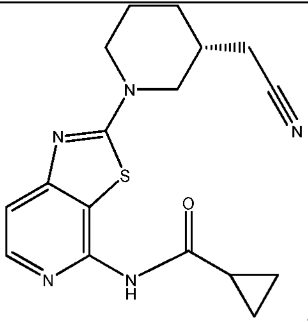
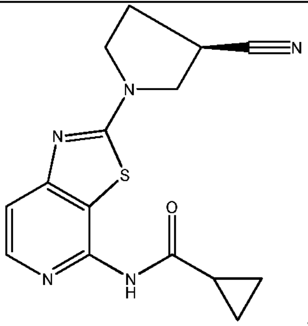
52	 ,
53	 ,
54	 ,
55	 ,
56	 ,
57	 ,
58	 ,
59	 ,

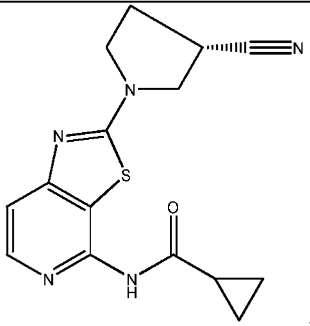
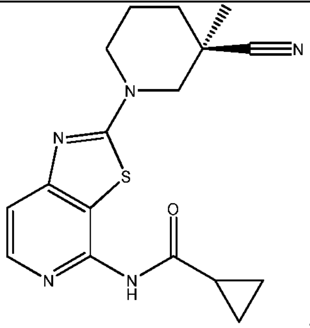
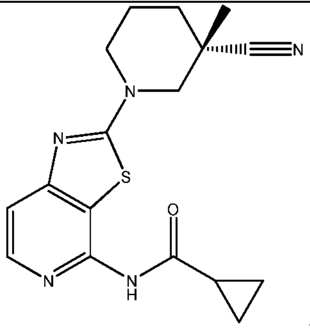
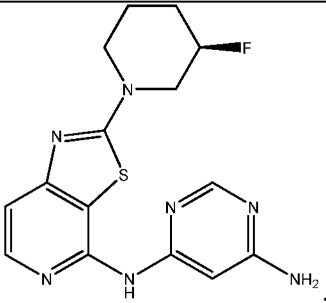
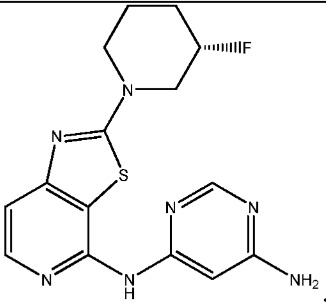
60	 ,
61	 ,
62	 ,
63	 ,
64	 ,
65	 ,
66	 ,
67	 ,
68	 ,

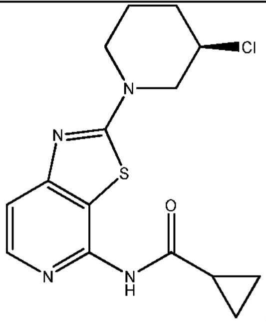
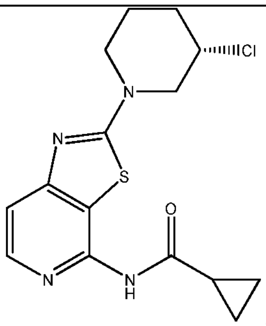
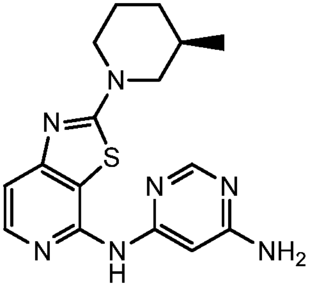
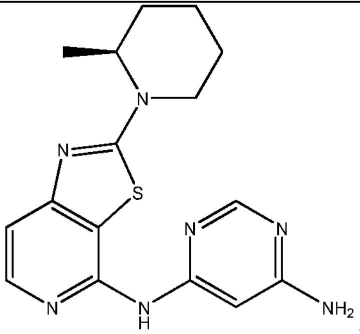
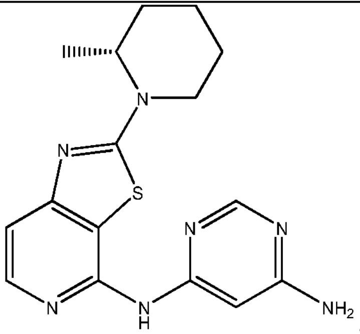
69	 ,
70	 ,
71	 ,
72	 ,
73	 ,
74	 ,
75	 ,
76	 ,

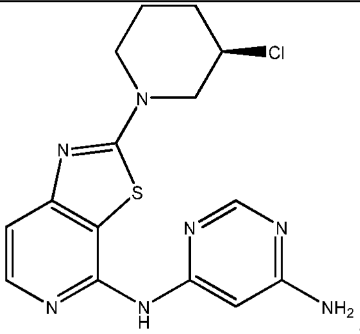
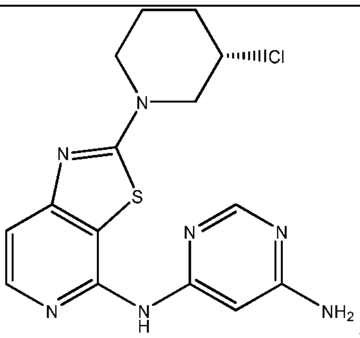
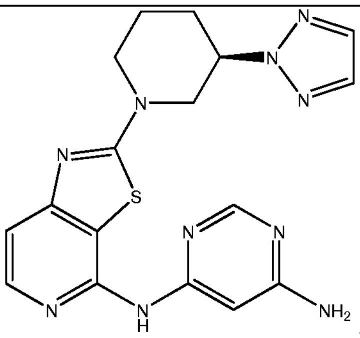
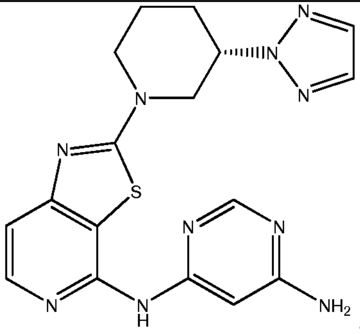
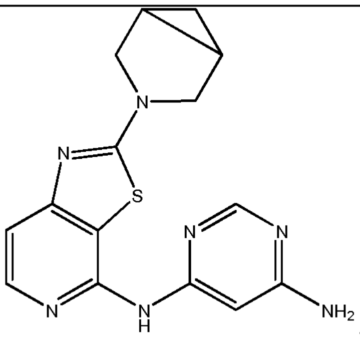
77	 ,
78	 ,
79	 ,
80	 ,
81	 ,
82	 ,
83	 ,
84	 ,

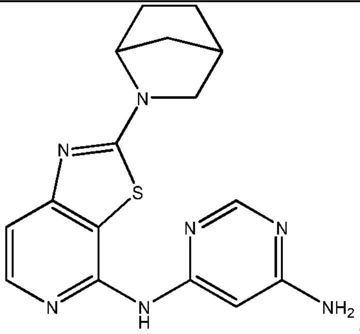
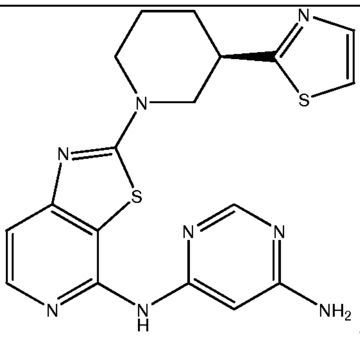
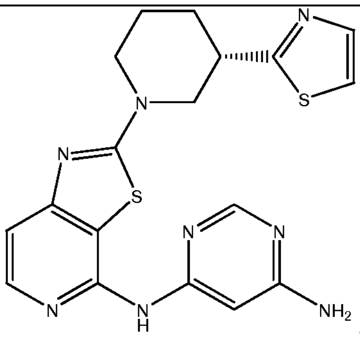
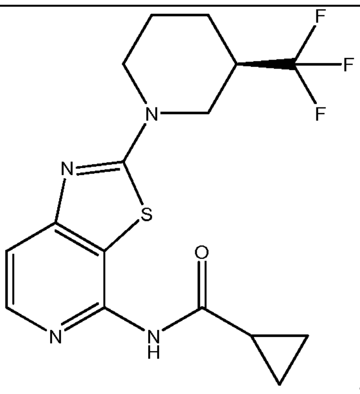
85	 ,
86	 ,
87	 ,
88	 ,
89	 ,
90	 ,

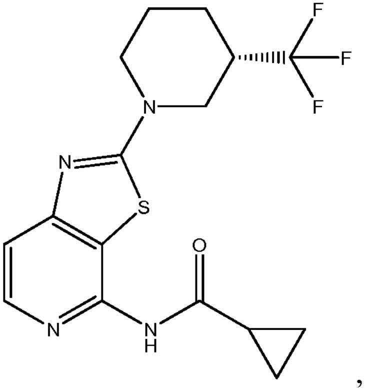
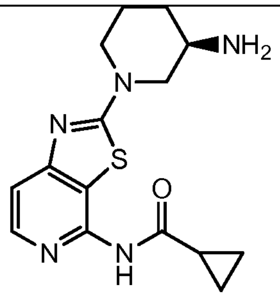
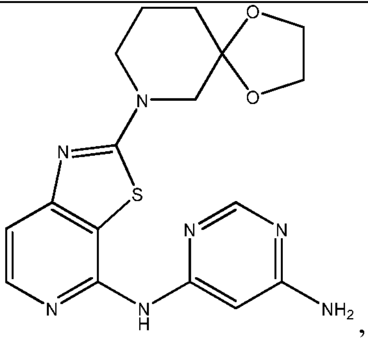
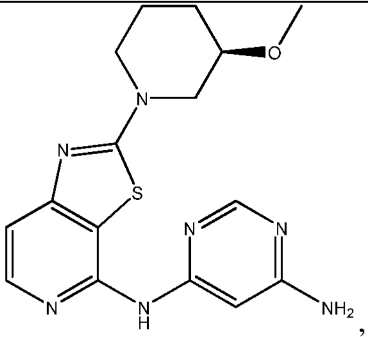
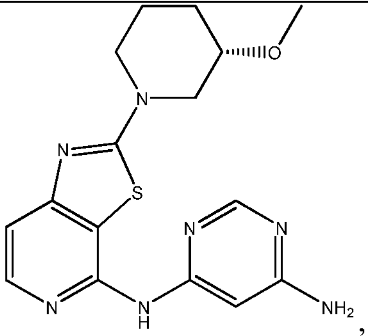
91	 ,
92	 ,
93	 ,
94	 ,
95	 ,

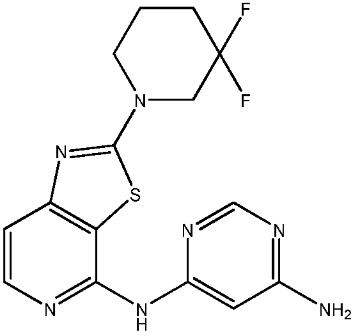
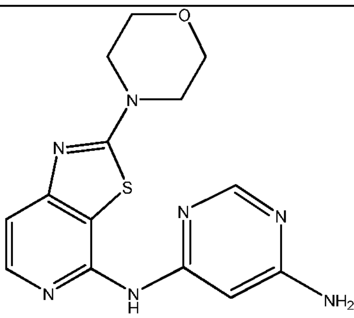
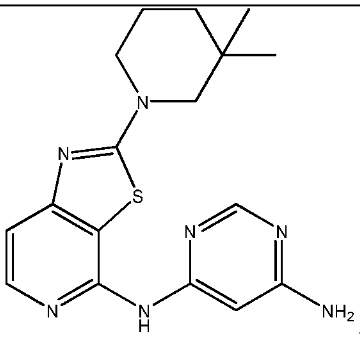
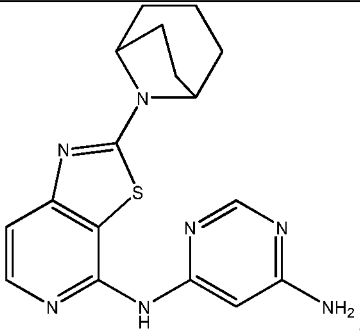
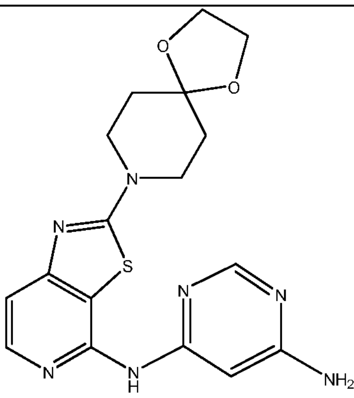
96	 ,
97	 ,
98	 ,
99	 ,
100	 ,

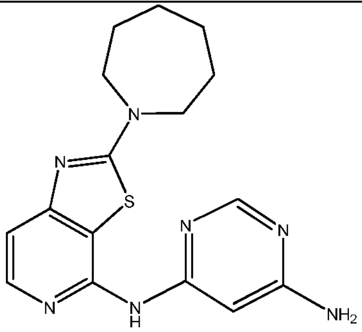
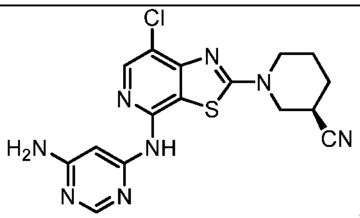
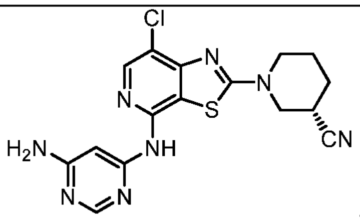
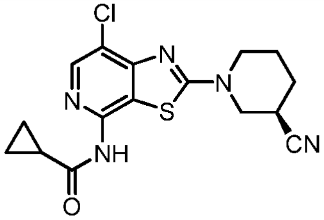
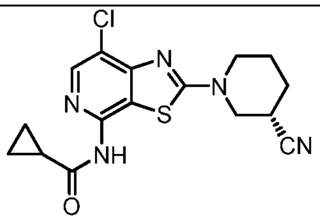
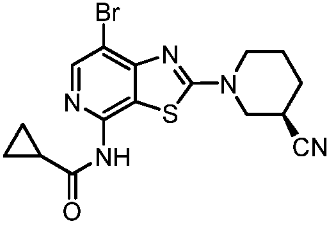
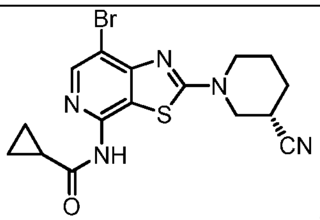
101	 ,
102	 ,
103	 ,
104	 ,
105	 ,

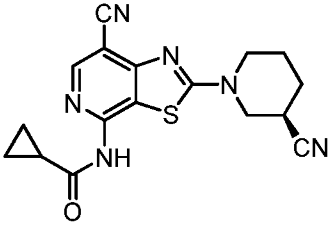
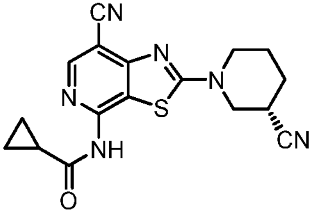
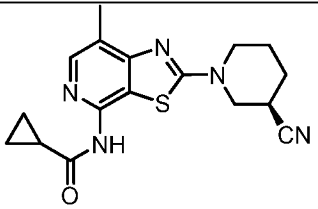
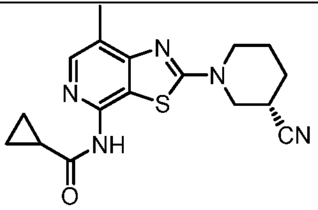
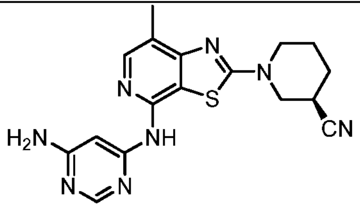
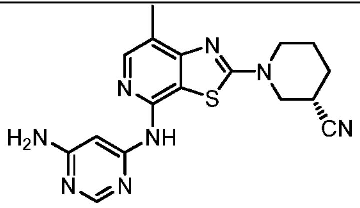
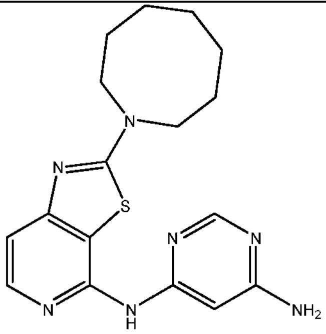
106	 ,
107	 ,
108	 ,
109	 ,
110	 ,

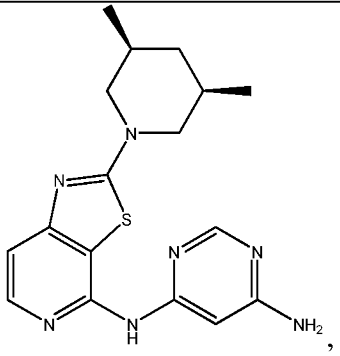
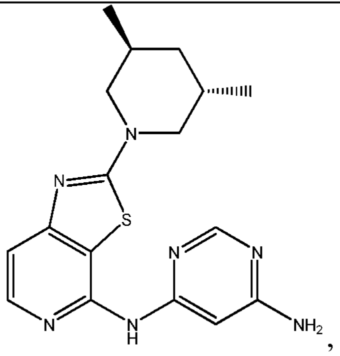
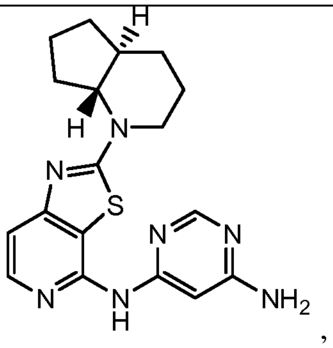
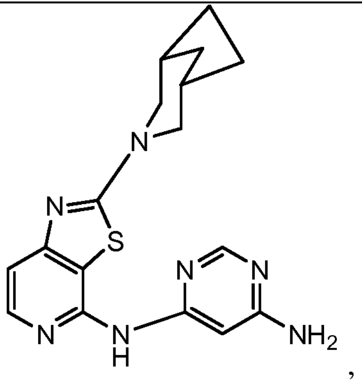
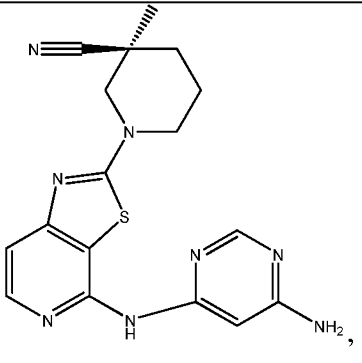
111	 ,
112	 ,
113	 ,
114	 ,

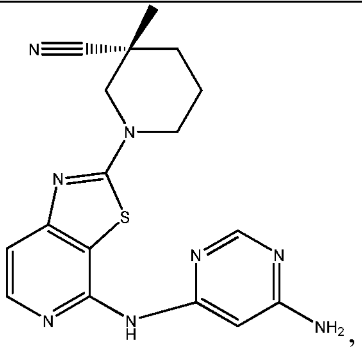
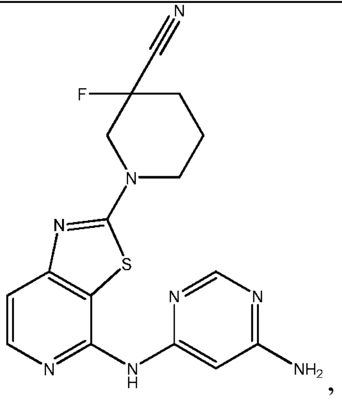
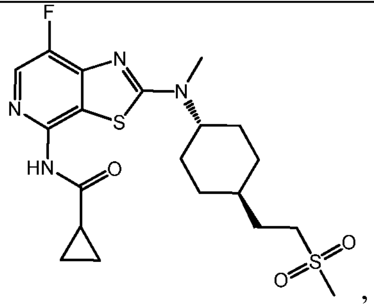
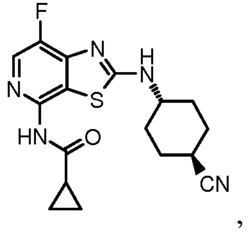
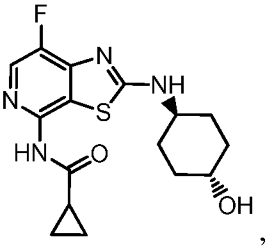
115	 ,
116	 ,
117	 ,
118	 ,
119	 ,

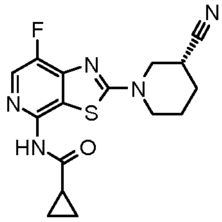
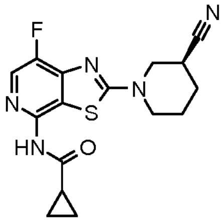
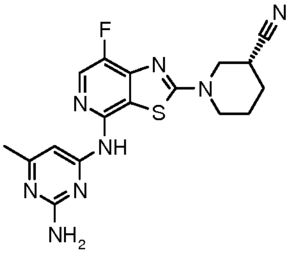
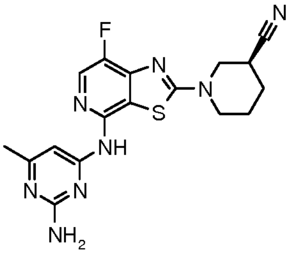
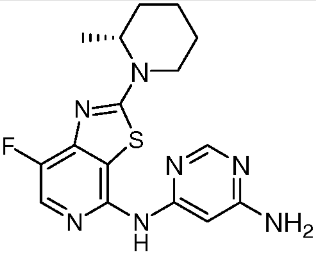
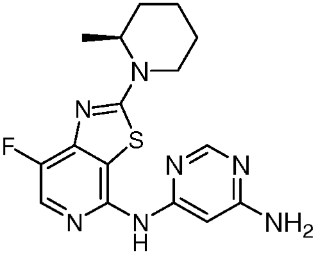
120	 ,
121	 ,
122	 ,
123	 ,
124	 ,

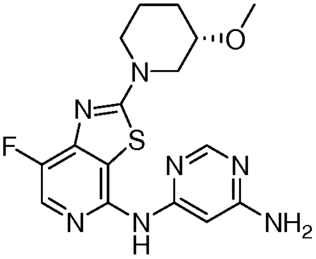
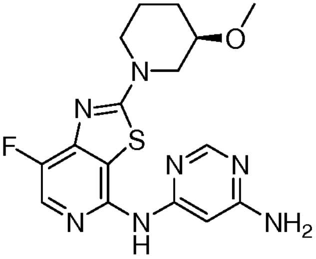
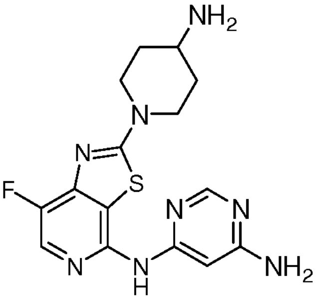
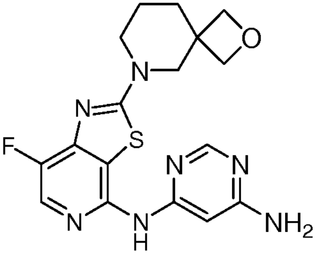
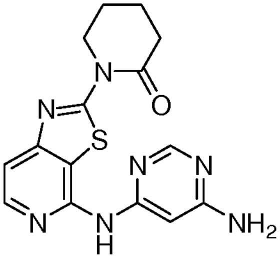
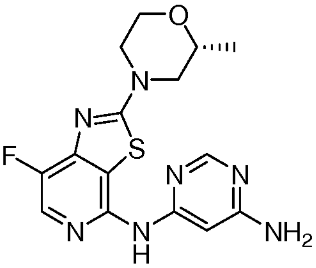
125	,
126	,
127	,
128	,
129	,
130	,
131	,

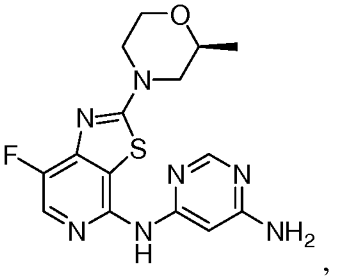
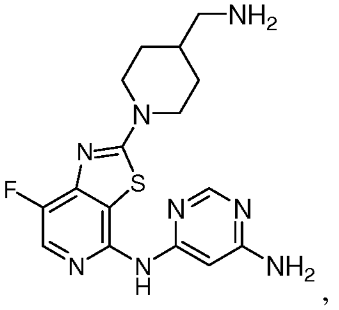
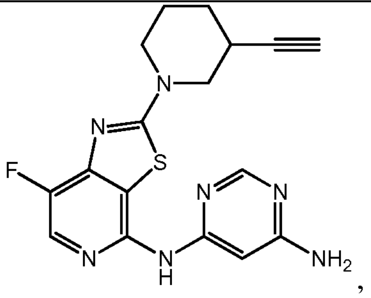
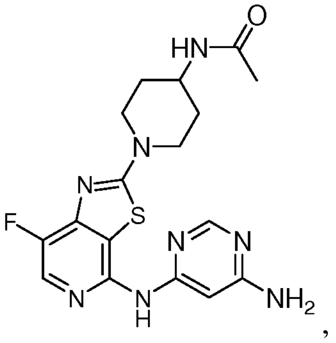
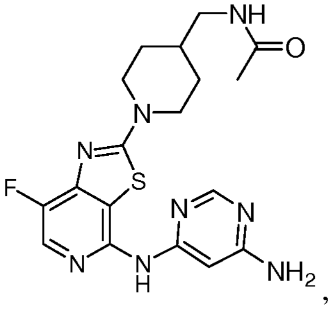
132	,
133	,
134	,
135	,
136	,
137	,
138	,

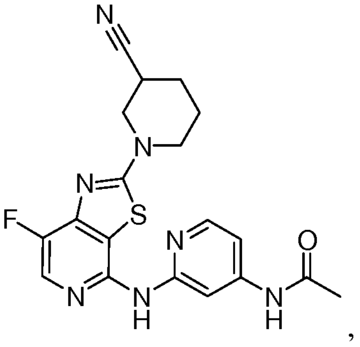
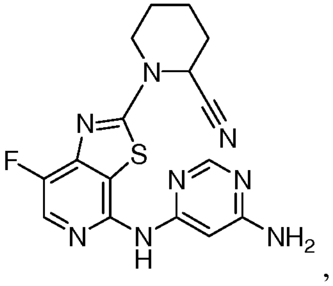
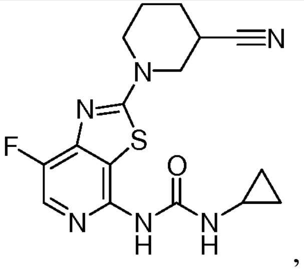
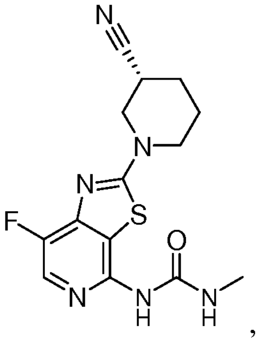
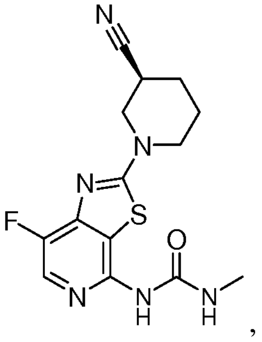
139	
140	
141	
142	
143	

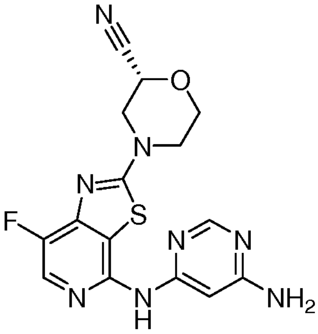
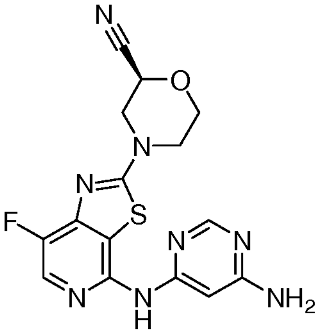
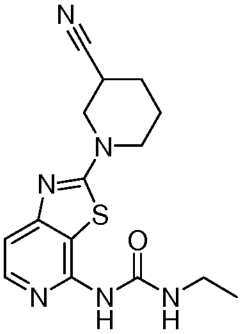
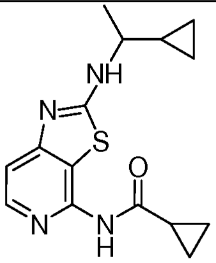
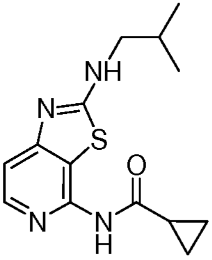
144	
145	
146	
147	
148	

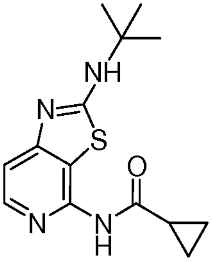
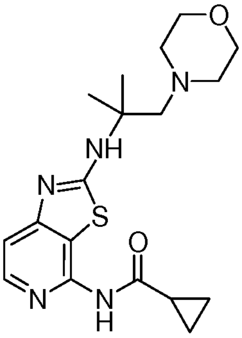
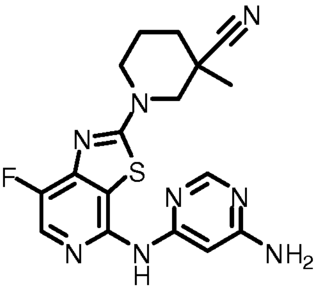
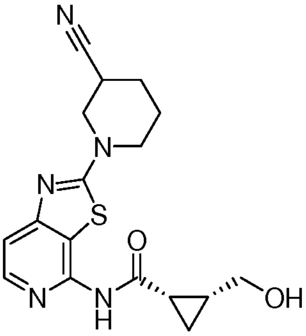
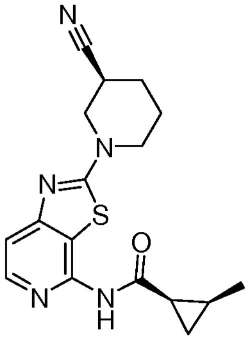
149	 ,
150	 ,
151	 ,
152	 ,
153	 ,
154	 ,

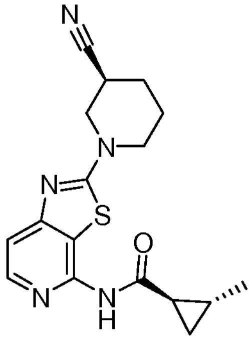
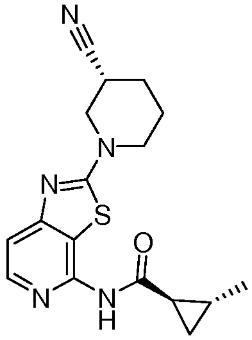
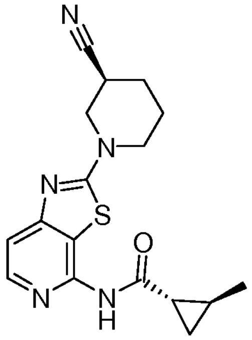
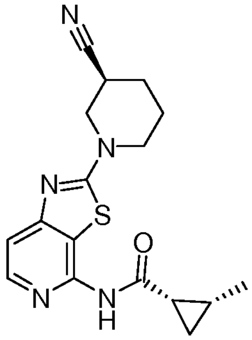
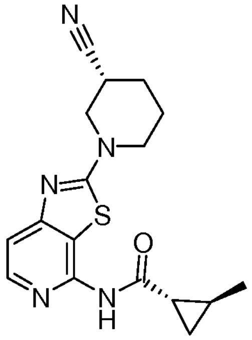
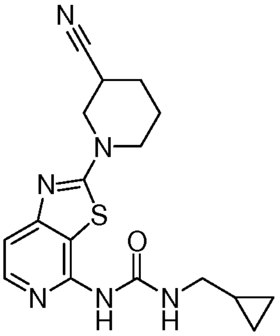
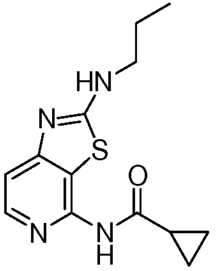
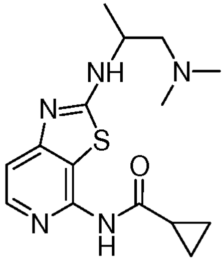
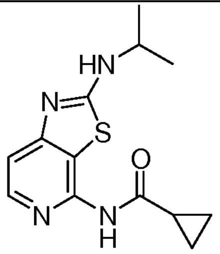
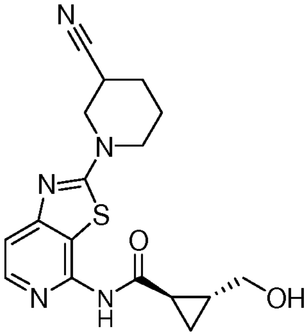
155	 ,
156	 ,
157	 ,
158	 ,
159	 ,
160	 ,

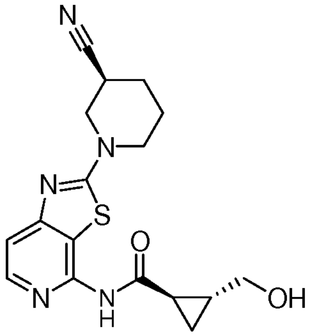
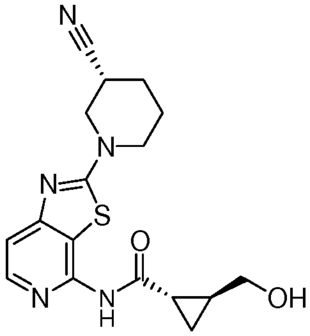
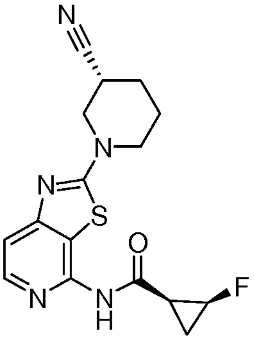
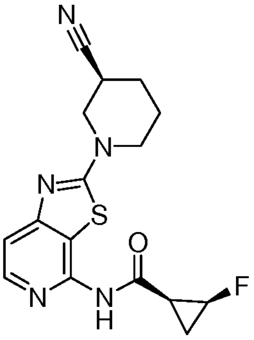
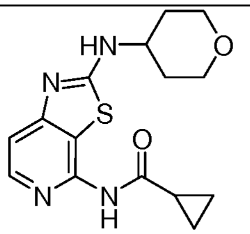
161	
162	
163	
164	
165	

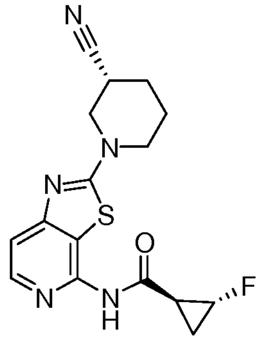
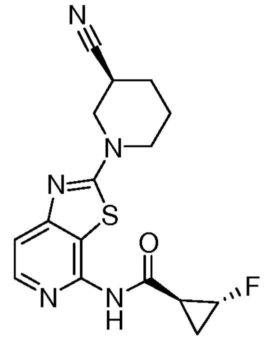
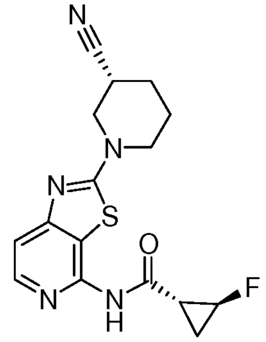
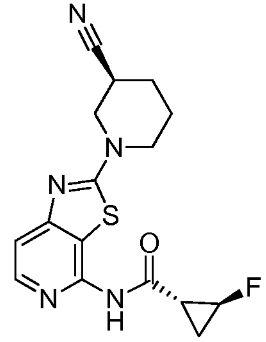
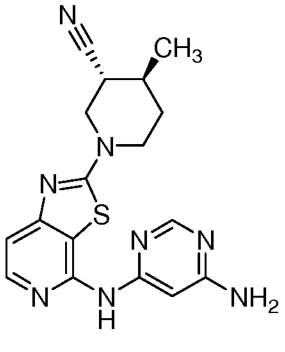
166	
167	
168	
169	
170	

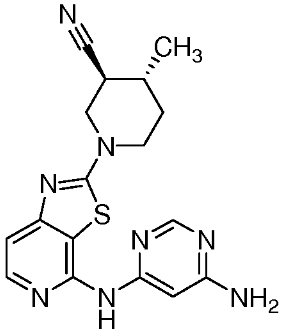
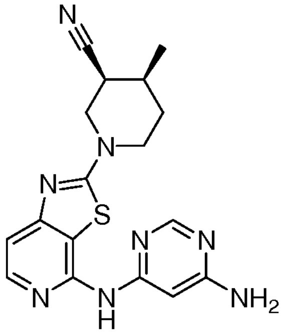
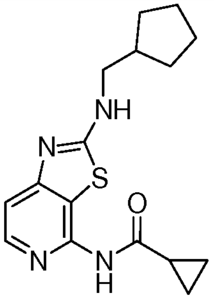
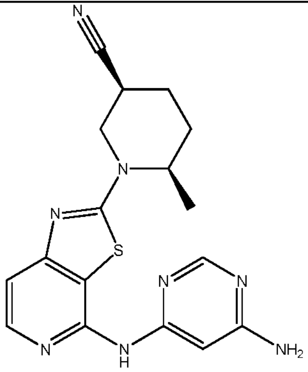
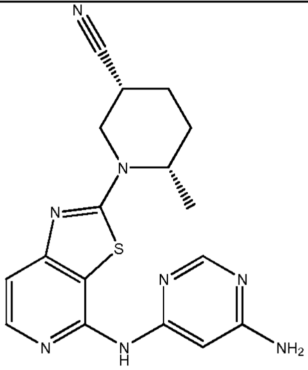
171	 ,
172	 ,
173	 ,
174	 ,
175	 ,

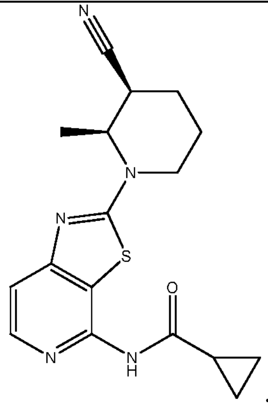
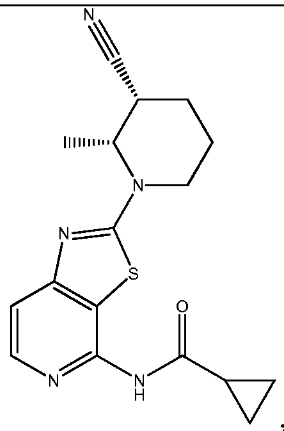
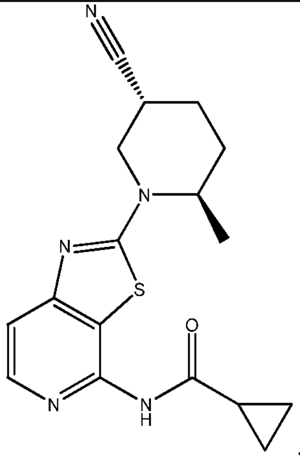
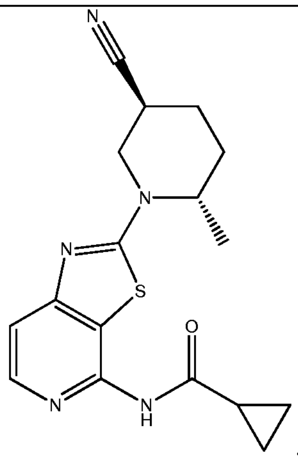
176	 ,
177	 ,
178	 ,
179	 ,
180	 ,

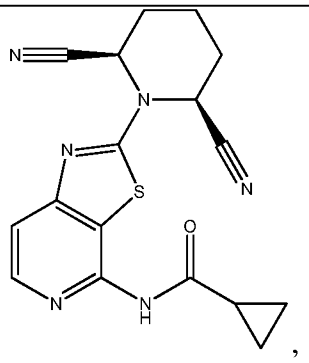
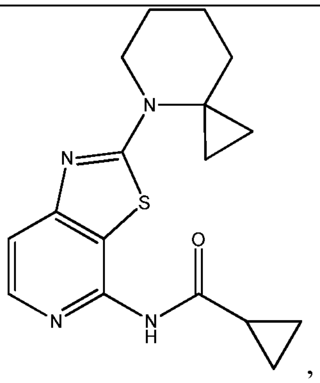
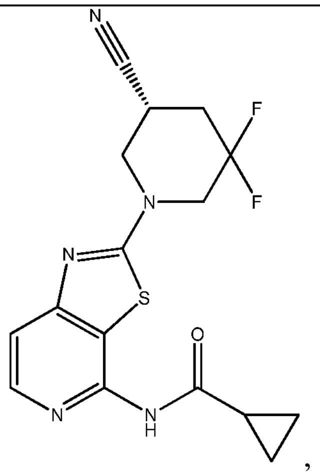
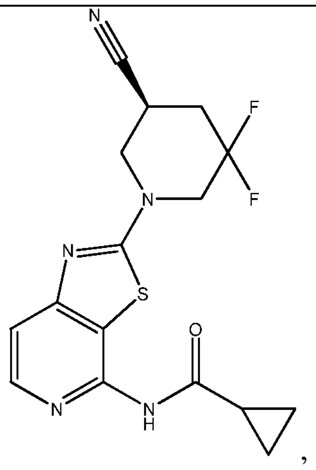
181	 ,
182	 ,
183	 ,
184	 ,
185	 ,
186	 ,
187	 ,
188	 ,
189	 ,
190	 ,

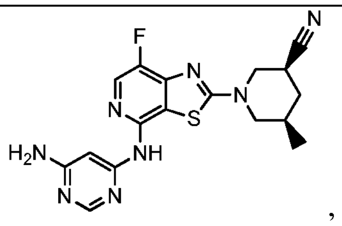
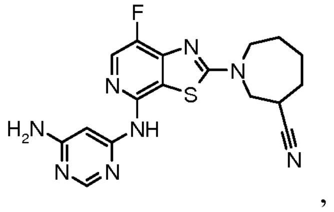
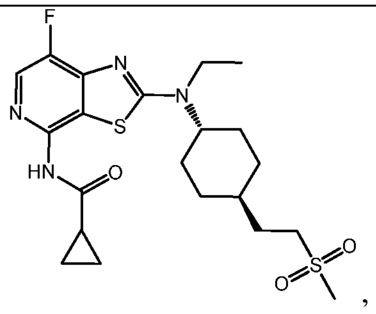
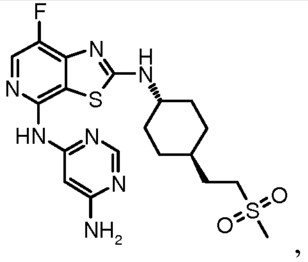
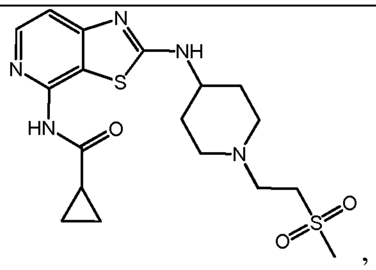
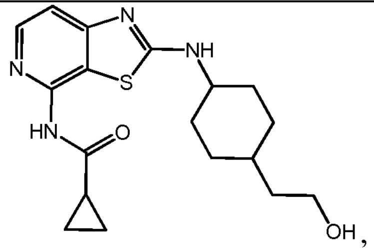
191	 ,
192	 ,
193	 ,
194	 ,
195	 ,

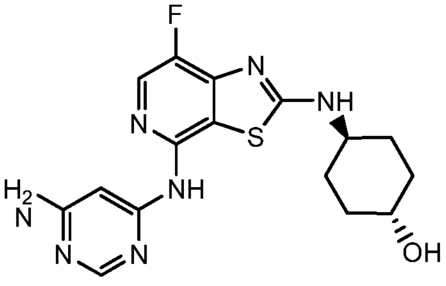
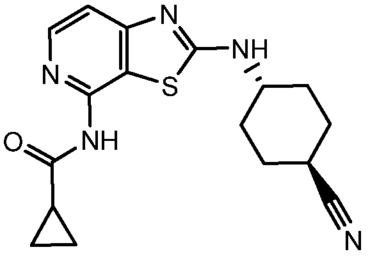
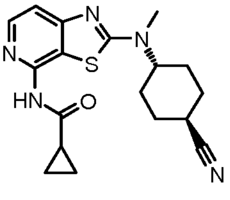
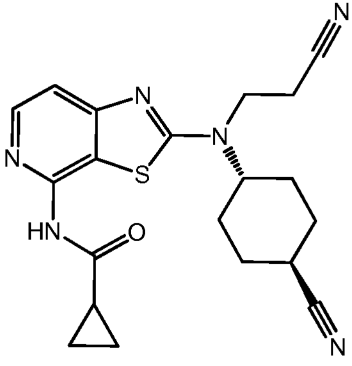
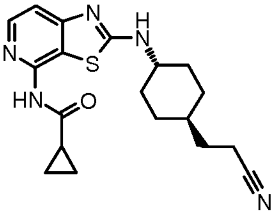
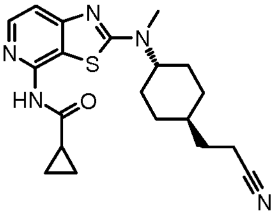
196	 ,
197	 ,
198	 ,
199	 ,
200	 ,

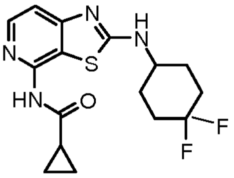
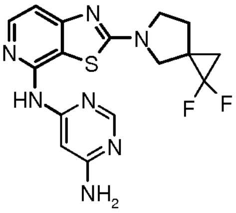
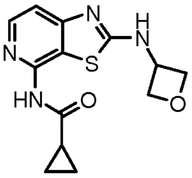
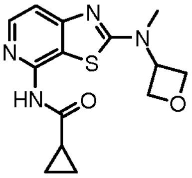
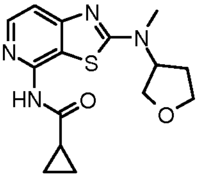
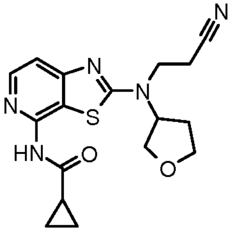
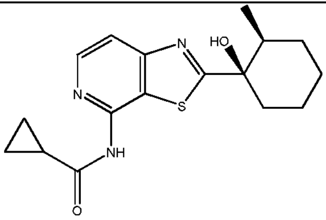
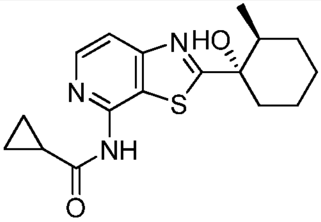
201	 ,
202	 ,
203	 ,
204	 ,
205	 ,

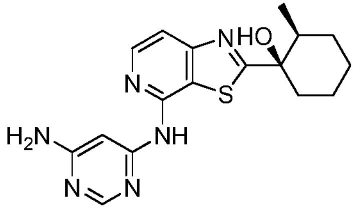
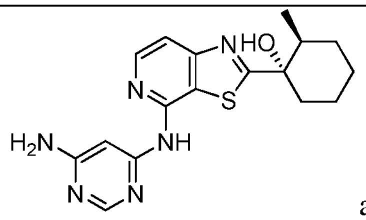
206	 ,
207	 ,
208	 ,
209	 ,

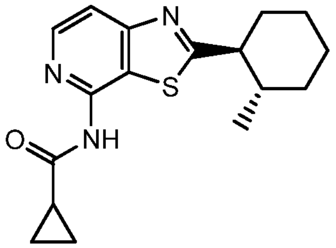
210	
211	
212	
213	

214	
215	
216	
217	
218	
219	

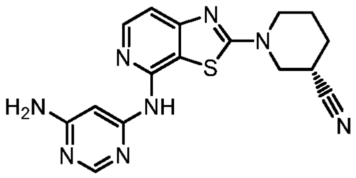
220	 ,
221	 ,
222	 ,
223	 ,
224	 ,
225	 ,

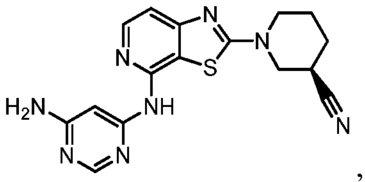
226	 ,
227	 ,
228	 ,
229	 ,
230	 ,
231	 ,
232	 ,
233	 ,

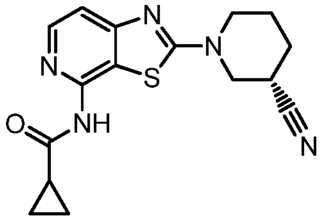
234	 ,
235	 and

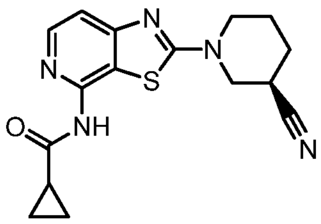
236	 .

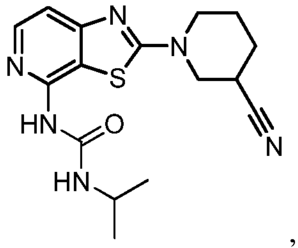
30. The compound of claim 1, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein the compound is selected from:

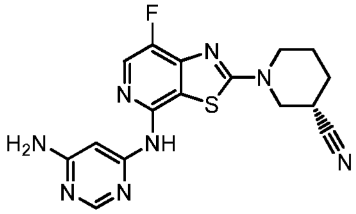

,

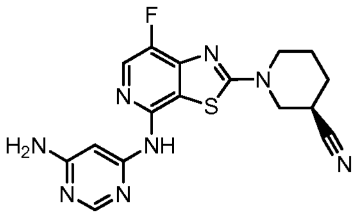

,

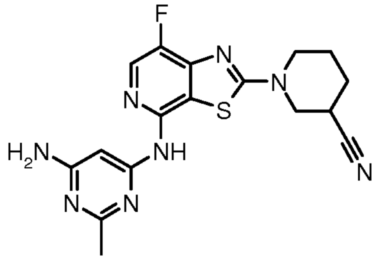

,

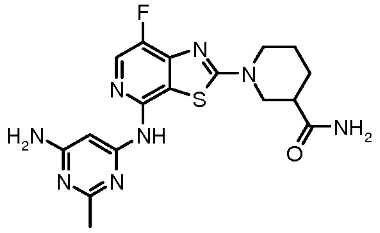

,

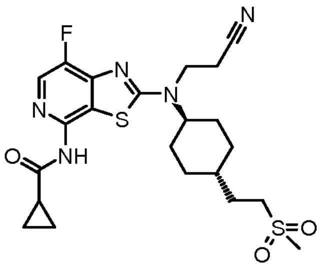

,

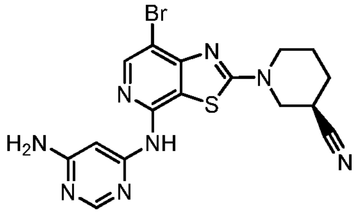

,

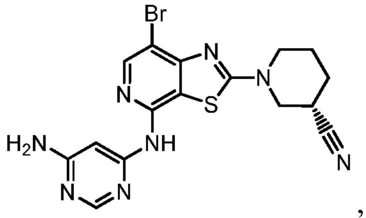

,

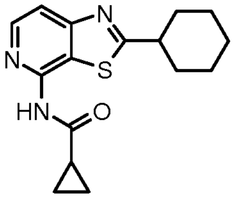

,


,

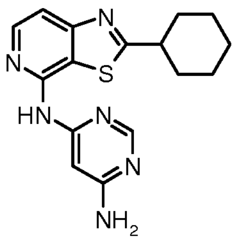

,


,

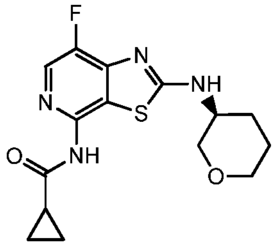

,



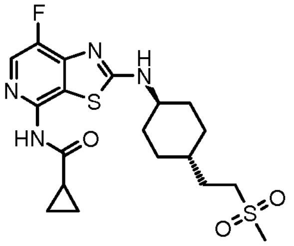
,



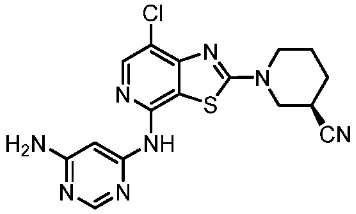
,



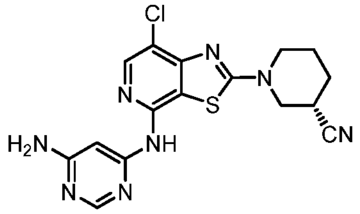
,



,



and



.

31. A pharmaceutical composition comprising a compound of any one of claims 1-1, or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof.

32. The composition of claim 31, further comprising a pharmaceutically acceptable carrier, adjuvant or vehicle.

33. A method of treating a disease responsive to the inhibition of TYK2 kinase activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition of claim 32.

34. The method of claim 33, wherein the disease is an inflammatory disease.

35. The method of claim 34, wherein the disease is asthma, inflammatory bowel disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriasis, allergic rhinitis, atopic dermatitis, contact dermatitis, delayed hypersensitivity reactions, lupus or multiple sclerosis.

36. The method of claim 33, further comprising administering a second therapeutic agent.

37. A kit comprising a pharmaceutical composition of claim 31 and instructions for use.

38. A compound according to any one of claims 1 to 30 for use in treating an inflammatory disease, in particular wherein the inflammatory disease is asthma, inflammatory bowel disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriasis, allergic rhinitis,

atopic dermatitis, contact dermatitis, delayed hypersensitivity reactions, lupus or multiple sclerosis.

39. The use of a compound according to any one of claims 1 to 30 in the manufacture of a medicament for the treatment of inflammatory diease, in particular wherein the inflammatory disease is asthma, inflammatory bowel disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriasis, allergic rhinitis, atopic dermatitis, contact dermatitis, delayed hypersensitivity reactions, lupus or multiple sclerosis.

40. The invention as hereinbefore described.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/078108

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D513/04 A61K31/429 A61P29/00 A61P37/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012/035039 A1 (HOFFMANN LA ROCHE [CH]; BLENCH TOBY [GB]; ELLWOOD CHARLES [GB]; GOODAC) 22 March 2012 (2012-03-22) claims -----	1-40
X	WO 01/46189 A1 (JANSSEN PHARMACEUTICA NV [BE]; JANSSENS FRANS EDUARD [BE]; GUILLEMONT) 28 June 2001 (2001-06-28) page 11 lines 1-8; page 38; compound 215 (B.18) -----	1-20,31, 32,38-40
X	WO 2010/010435 A2 (GLENMARK PHARMACEUTICAL S A [CH]; IRLAPATI NAGOSWARA RAO [IN]; THOMAS) 28 January 2010 (2010-01-28) page 29 lines 2-4; examples 44, 45 ----- -/--	1-20,31, 32,38-40

☒ 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 11 March 2015	Date of mailing of the international search report 26/03/2015
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Gregoire, Ariane

2

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/106192 A2 (GENENTECH INC [US]; KOEHLER MICHAEL F T [US]; GAZZARD LEWIS J [US]; TS) 20 September 2007 (2007-09-20) compound h and intermediate compound g in example 16 on page 59 -----	1-9, 21-28, 31,32
X	KEITH SMITH, CHARLES M. LINDSAY, IAN K. MORRIS, IAN MATTHEWS AND GARETH J. PRITCHARD: "The synthesis of 2-substituted thiazolo[5,4-c]pyridines via directed metalation", SULFUR LETTERS, vol. 17, no. 4, 09183099, 10 March 1994 (1994-03-10), XP002737080, Hardwood Academic Publishers GmbH USA table 2; compounds 29, 37-41 -----	1-9, 21-28
X	US 2005/065151 A1 (NORCROSS ROGER DAVID [CH]) 24 March 2005 (2005-03-24) intermediate example 1f on page 15 -----	1-20

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2014/078108

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012035039 A1	22-03-2012	AR 082974 A1	23-01-2013
		CA 2812087 A1	22-03-2012
		CN 103209695 A	17-07-2013
		EP 2616072 A1	24-07-2013
		JP 2013538223 A	10-10-2013
		KR 20130051507 A	20-05-2013
		TW 201217387 A	01-05-2012
		US 2012202788 A1	09-08-2012
		US 2014171408 A1	19-06-2014
		WO 2012035039 A1	22-03-2012
WO 0146189 A1	28-06-2001	AT 416174 T	15-12-2008
		AU 781144 B2	05-05-2005
		BG 65784 B1	30-11-2009
		BR 0016638 A	01-10-2002
		CA 2393158 A1	28-06-2001
		CN 1411460 A	16-04-2003
		CY 1108844 T1	02-07-2014
		CZ 20022055 A3	18-06-2003
		DK 1250337 T3	30-03-2009
		EE 200200326 A	15-10-2003
		EP 1250337 A1	23-10-2002
		ES 2317856 T3	01-05-2009
		HK 1053109 A1	01-08-2008
		HR P20020518 A2	31-08-2004
		HU 0203847 A2	28-03-2003
		IL 150310 A	08-07-2008
		JP 4852210 B2	11-01-2012
		JP 2003518118 A	03-06-2003
		MX PA02006346 A	13-12-2002
		MY 127758 A	29-12-2006
		NO 20022977 A	08-08-2002
		NZ 518816 A	31-01-2003
		PL 355442 A1	19-04-2004
		PT 1250337 E	05-03-2009
		SI 1250337 T1	30-04-2009
		SK 8542002 A3	01-07-2003
		TW I225488 B	21-12-2004
		UA 73963 C2	15-10-2002
		US 2003139393 A1	24-07-2003
		WO 0146189 A1	28-06-2001
		ZA 200204983 A	22-09-2003
WO 2010010435 A2	28-01-2010	NONE	
WO 2007106192 A2	20-09-2007	AU 2006340014 A1	20-09-2007
		CA 2632807 A1	20-09-2007
		CN 101374829 A	25-02-2009
		EP 1973899 A2	01-10-2008
		JP 5155184 B2	27-02-2013
		JP 2009520041 A	21-05-2009
		KR 20080080203 A	02-09-2008
		NZ 594746 A	28-03-2013
		US 2009221630 A1	03-09-2009
		US 2012270886 A1	25-10-2012
		WO 2007106192 A2	20-09-2007
		ZA 200805152 A	27-01-2010

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2014/078108

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2005065151 A1	24-03-2005	AR 045659 A1	02-11-2005
		AU 2004274154 A1	31-03-2005
		BR PI0414266 A	07-11-2006
		CA 2539314 A1	31-03-2005
		CN 1871244 A	29-11-2006
		EP 1670805 A1	21-06-2006
		JP 2007505851 A	15-03-2007
		KR 20060058132 A	29-05-2006
		MX PA06002943 A	31-05-2006
		TW I297339 B	01-06-2008
		US 2005065151 A1	24-03-2005
		WO 2005028484 A1	31-03-2005