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Inventor(s)	ADEVA BARTOLOME; Marta et al.

FGFR2 INHIBITOR COMPOUNDS

Abstract

The present invention provides compounds of the formula (I):
##STR00001##
or a pharmaceutically acceptable salt thereof, wherein A, X.sub.1, X.sub.2, X.sub.3, Y, Z, Z.sub.1, Z.sub.2, R.sup.2 and R.sup.6 are as defined herein, for use in the treatment of cancer and a method of treating cancer.

Inventors: **ADEVA BARTOLOME; Marta (Alcobendas, ES), FERNANDEZ FIGUEROA; Maria Carmen (San Sebastián de los Reyes, ES), DEL PRADO CATALINA; Miriam Filadelfa (Alcobendas, ES), GARCIA-CERRADA; Susana Maria (San Sebastian de los Reyes, ES), GARCIA LOSADA; Pablo (Boadilla del Monte, ES), GARZÓN SANZ; Miguel (Madrid, ES), GUTIERREZ SANFELICIANO; Sonia Maria (San Sebastian de los Reyes, ES), MARTINEZ PEREZ; Jose Antonio (Alcobendas, ES), METCALF; Andrew Terrance (Erie, CO), PEIRÓ CADAHIA; Jorge (Navalafuente, ES), VALERO DE LA CRUZ; Alberto (Alcobendas, ES), PRIETO VALLEJO; Maria Lourdes (Alcobendas, ES)**

Applicant: **ELI LILLY AND COMPANY** (Indianapolis, IN)

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Background/Summary

BACKGROUND

[0001] Fibroblast growth factor (FGF) has been recognized as an important mediator of many physiological processes, such as morphogenesis during development, fibrosis, and angiogenesis. The fibroblast growth factor receptor (FGFR) family consists of five members four of which (FGFR 1-4) are glycoproteins composed of extracellular immunoglobulin (Ig)-like domains, a hydrophobic transmembrane region and a cytoplasmic part containing a tyrosine kinase domain. FGF binding leads to FGFR dimerization, followed by receptor autophosphorylation and activation of downstream signaling pathways. Receptor activation is sufficient for the recruitment and activation of specific downstream signaling partners that participate in the regulation of diverse processes such as cell growth, cell metabolism and cell survival. Thus, the FGF/FGFR signaling pathway has pleiotropic effects on many biological processes critical to tumor cell proliferation, migration, invasion, and angiogenesis.

SUMMARY

[0002] Provided herein are compounds of the formula:

##STR00002##

or a pharmaceutically acceptable salt thereof, wherein A, X.sub.1, X.sub.2, X.sub.3, Y, Z, Z.sub.1, Z.sub.2, R.sup.2 and R.sup.6 are as defined herein.

[0003] Provided herein are compounds of the formula:

##STR00003##

or a pharmaceutically acceptable salt thereof, wherein A, X.sub.1, X.sub.2, X.sub.3, Y, Z′, Z.sub.2, R.sup.2 and R.sup.6 are as defined herein.

[0004] Provided herein are compounds of the formula:

##STR00004##

or a pharmaceutically acceptable salt thereof, wherein A, X.sub.1, X.sub.2, X.sub.3, Y, Z.sub.2, R.sup.2 and R.sup.6 are as defined herein.

[0005] Provided herein are compounds of the formula:

##STR00005##

or a pharmaceutically acceptable salt thereof, wherein A, X.sub.1, X.sub.2, X.sub.3, X.sub.4, Y, Y.sub.1, Y.sub.2, Y.sub.3, Y.sub.4, Y.sub.5, Y.sub.6, Z, Z.sub.1, R.sup.2 and R.sup.6 are as defined herein.

[0006] Provided herein are compounds of the formula:

##STR00006##

or a pharmaceutically acceptable salt thereof, wherein A, X.sub.1, X.sub.2, X.sub.3, X.sub.4, Y, Y.sub.1, Y.sub.2, Y.sub.3, Y.sub.4, Y.sub.5, Y.sub.6, Z′, R.sup.2 and R.sup.6 are as defined herein.

[0007] Provided herein are compounds of the formula:

##STR00007##

or a pharmaceutically acceptable salt thereof, wherein A, X.sub.1, X.sub.2, X.sub.3, Y, Y.sub.1,

Y.sub.2, Y.sub.3, Y.sub.4, Y.sub.5, Y.sub.6, R.sup.2 and R.sup.6 are as defined herein.
[0008] Provided herein are pharmaceutical compositions comprising a compound of formula (I), (II), (III), (IA), (IIA) or (IIIA), or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically acceptable carriers, diluents, or excipients.
[0009] Provided herein are methods of using the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), or a pharmaceutically acceptable salt thereof, and pharmaceutical compositions thereof, to treat proliferative disorders such as cancer, particularly to treat FGFR2-associated cancer. The methods include administering an effective amount of a compound of formula (I), (II), (III), (IA), (IIA) or (IIIA), or a pharmaceutically acceptable salt thereof, to a patient in need.
[0010] Provided herein, are compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), or a pharmaceutically acceptable salt thereof, for use in therapy. Further provided herein, are the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, particularly for use in the treatment of FGFR2-associated cancer. The use of compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer, particularly for use in the treatment of FGFR2-associated cancer, is also provided.

Description

DESCRIPTION
[0011] Provided herein are compounds believed to have clinical use for the treatment of cancer and particularly for the treatment of FGFR2-associated cancer.
[0012] Certain compounds provided herein have superior FGFR2 potency compared to certain previously known FGFR inhibitors. Certain compounds provided herein have superior selectivity for FGFR2 over FGFR1 compared to certain previously known FGFR inhibitors, reducing potential dose limiting toxicity caused by inhibition of FGFR1 (e.g. hyperphosphatemia).
[0013] The compounds provided herein are of formula (I):
##STR00008##
[0014] wherein [0015] Z.sub.2 is
##STR00009## [0016] A is pyrazole, triazole, thiadiazole or oxadiazole, substituted with R.sup.1 and R.sup.1A; [0017] R.sup.1 is hydrogen or C.sub.1-C.sub.3 alkyl; [0018] R.sup.1A is hydrogen, halo, CN or C.sub.1-C.sub.3 alkyl optionally substituted with one or more substituents independently selected from halo, OH, and OCH.sub.3; [0019] X.sub.1 and X.sub.2 are independently selected from N and C, wherein when one of X.sub.1 or [0020] X.sub.2 is N the other is C; [0021] X.sub.3 is N or CH; [0022] X.sub.4 is N or C—R.sup.9; [0023] Y is NH, O, S or a bond; [0024] Y.sub.1 is a bond, CHR.sup.7, CH.sub.2—CHR.sup.7, CHR.sup.7—CH.sub.2, CF.sub.2, CH.sub.2—CF.sub.2 or CF.sub.2—CH.sub.2; [0025] Y.sub.2 is a bond, CHR.sup.3, CH.sub.2—CHR.sup.3, CHR.sup.3—CH.sub.2, CF.sub.2, CH.sub.2—CF.sub.2 or CF.sub.2—CH.sub.2; [0026] Y.sub.3 is CR.sup.4R.sup.5 or CF.sub.2; [0027] Y.sub.4 is CR.sup.3R.sup.4 or CF.sub.2; [0028] Y.sub.5 is CR.sup.13R.sup.14, CR.sup.13R.sup.14CH.sub.2 or CH.sub.2CR.sup.13R.sup.14; [0029] Y.sub.6 is CR.sup.13R.sup.14, CR.sup.13R.sup.14CH.sub.2 or CH.sub.2CR.sup.13R.sup.14; [0030] Z is a bond, CHR.sup.9A, CR.sup.4R.sup.4A, CR.sup.4R.sup.4A—CH.sub.2, CH.sub.2—CR.sup.4R.sup.4A, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo(1.1.1)pentane, bicyclo(2.1.1)hexane, azetidine, pyrrolidine or piperidine; [0031] Z.sub.1 is a bond when Z is a bond, CR.sup.4R.sup.4A, CR.sup.4R.sup.4A—CH.sub.2, CH.sub.2—CR.sup.4R.sup.4A, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo(1.1.1)pentane, bicyclo(2.1.1)hexane, azetidine, pyrrolidine or piperidine, or Z.sub.1 is CH.sub.2 or CH.sub.2—CH.sub.2 when Z is CHR.sup.9A; [0032] Z.sub.3 is a bond, C(O), SO.sub.2 or —NR.sup.4C(O); [0033] Z.sub.4 is a bond, C(O), SO.sub.2 or —NR.sup.4C(O); [0034] R.sup.2 is C.sub.1-C.sub.5

alkyl or R.sup.8, wherein C.sub.1-C.sub.5 alkyl is optionally substituted with one or more substituents independently selected from halo, OH, CN, oxo, —OC.sub.1-C.sub.4 alkyl, —OC.sub.3-C.sub.5 cycloalkyl, —Z.sub.3—R.sup.11 and R.sup.10, wherein C.sub.1-C.sub.4 alky and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN;
[0035] R.sup.3 is hydrogen, F, OH, OCH.sub.3, C.sub.1-C.sub.3 alkyl, cyclopropyl, or one R.sup.3 is fused with [0036] R.sup.5 or R.sup.7 to form CH.sub.2, CH.sub.2—CH.sub.2 or CH.sub.2OCH.sub.2; [0037] R.sup.4 is hydrogen or C.sub.1-C.sub.3 alkyl; [0038] R.sup.4A is hydrogen, halo, OH or C.sub.1-C.sub.3 alkyl; [0039] R.sup.5 is hydrogen, F, OH, OCH.sub.3, C.sub.1-C.sub.3 alkyl, cyclopropyl or is fused with one R.sup.3 to form CH.sub.2, CH.sub.2—CH.sub.2 or CH.sub.2OCH.sub.2; [0040] R.sup.6 is hydrogen, halo, C.sub.1-C.sub.5 alkyl, CN, 3-6 membered cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered aryl or 5-6 membered heteroaryl, wherein 3-6 membered cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered aryl and 5-6 membered heteroaryl are optionally substituted with one or more substituents independently selected from halo, methyl, halomethyl, OH or OCH.sub.3 and wherein C.sub.1-C.sub.5 alkyl is optionally substituted with one or more substituents independently selected from halo, OH and OCH.sub.3; [0041] R.sup.7 is hydrogen, F, OH, OCH.sub.3, C.sub.1-C.sub.3 alkyl or is fused with one R.sup.3 to form CH.sub.2, CH.sub.2—CH.sub.2 or CH.sub.2OCH.sub.2; [0042] R.sup.8 is 3-6 membered cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered aryl or 5-6 membered heteroaryl, optionally fused or substituted with R.sup.8A; [0043] R.sup.8A is 3-6 membered cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered aryl or 5-6 membered heteroaryl; [0044] R.sup.9 is hydrogen, C.sub.1-C.sub.3 alkyl, or is fused with R.sup.9A to form CH.sub.2 or CH.sub.2—CH.sub.2; [0045] R.sup.10 is 3-6 membered cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered aryl or 5-6 membered heteroaryl, optionally fused or substituted with R.sup.8A; [0046] R.sub.11 is C.sub.1-C.sub.4 alkyl, NH.sub.2, NHC.sub.1-C.sub.3 alkyl, NHC.sub.3-C.sub.5 cycloalkyl or N(C.sub.1-C.sub.3 alkyl).sub.2, wherein C.sub.1-C.sub.4 alkyl, C.sub.1-C.sub.3 alkyl and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN; [0047] R.sup.12 is C.sub.1-C.sub.4 alkyl, C.sub.3-C.sub.5 cycloalkyl, NH.sub.2, NHC.sub.1-C.sub.3 alkyl, NHC.sub.3-C.sub.5 cycloalkyl or N(C.sub.1-C.sub.3 alkyl).sub.2, wherein C.sub.1-C.sub.4 alky, C.sub.1-C.sub.3 alkyl and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN; [0048] R.sup.13 is hydrogen, halo or C.sub.1-C.sub.3 alkyl; [0049] R.sup.14 is hydrogen, halo or C.sub.1-C.sub.3 alkyl; and [0050] R.sup.8, R.sup.10 and R.sup.8A are optionally substituted with one or more substituents independently selected from halo, OH, CN, —OC.sub.1-C.sub.4 alkyl, —OC.sub.3-C.sub.5 cycloalkyl and —Z.sub.4—R.sup.12 wherein C.sub.1-C.sub.4 alky and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN; [0051] or a pharmaceutically acceptable salt thereof.

[0052] In formula (II) and (IIA), A, X.sub.1, X.sub.2, X.sub.3, Y, Y.sub.1, Y.sub.2, Y.sub.3, Y.sub.4, Y.sub.5, Y.sub.6, R.sup.2 and R.sup.6 are as defined above for formula (I); and [0053] X.sub.4 is N or C—R.sup.9, wherein R.sup.9 is hydrogen or C.sub.1-C.sub.3 alkyl; [0054] Z′ is a bond, CR.sup.4R.sup.4A, CR.sup.4R.sup.4A—CH.sub.2, CH.sub.2—CR.sup.4R.sup.4A, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo(1.1.1)pentane, bicyclo(2.1.1)hexane, azetidine, pyrrolidine or piperidine.

[0055] In formula (III), [0056] A, X.sub.1, X.sub.2, X.sub.3, Y, Y.sub.1, Y.sub.2, Y.sub.3, Y.sub.4, Y.sub.5, Y.sub.6, Z.sub.2, R.sup.2 and R.sup.6 are as defined above for formula (I); and [0057] X.sub.4 is N or C—R.sup.9, wherein R.sup.9 is hydrogen or C.sub.1-C.sub.3 alkyl.

[0058] In formula (IIIA), A, X.sub.1, X.sub.2, X.sub.3, Y, Y.sub.1, Y.sub.2, Y.sub.3, Y.sub.4, Y.sub.5, Y.sub.6, R.sup.2 and R.sup.6 are as defined above for formula (I).

[0059] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), X.sub.1 can be C, and X.sub.2 can be N; or X.sub.1 can be N, and X.sub.2 can be C.
[0060] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), X.sub.1 can be C, and X.sub.2 can be N, forming:
##STR00010##
wherein * indicates the connection point to A in formula (I), (II), (III), (IA), (IIA) or (IIIA).
[0061] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), X.sub.1 can be N, and X.sub.2 can be C, forming:
##STR00011##
wherein * indicates the connection point to A in formula (I), (II), (III), (IA), (IIA) or (IIIA).
[0062] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), X.sub.1 can be C, X.sub.2 can be N, and X.sub.3 can be CH, forming:
##STR00012##
wherein * indicates the connection point to A in formula (I), (II), (III), (IA), (IIA) or (IIIA).
[0063] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), X.sub.1 can be N, X.sub.2 can be C, and X.sub.3 can be CH, forming:
##STR00013##
wherein * indicates the connection point to A in formula (I), (II), (III), (IA), (IIA) or (IIIA).
[0064] The specific chemical naming conventions used herein are intended to be familiar to one of skill in the chemical arts. Some terms are defined specifically for additional clarity.
[0065] As used herein, the term “alkyl” refers to a hydrocarbon chain that may be a straight chain or branched chain, containing the indicated number of carbon atoms. For example, the term “C.sub.1-C.sub.5 alkyl” as used herein refers to saturated linear or branched-chain monovalent hydrocarbon radicals of one, two, three, four or five carbon atoms. Examples of C.sub.1-C.sub.5 alkyl include, but are not limited to, methyl, ethyl, 1-propyl, isopropyl, 1-butyl, isobutyl, sec-butyl, tert-butyl, 2-methyl-2-propyl, pentyl and neopentyl. Examples of C.sub.1-C.sub.4 alkyl include, but are not limited to, methyl, ethyl, 1-propyl, isopropyl, 1-butyl, isobutyl, sec-butyl, tert-butyl and 2-methyl-2-propyl. Examples of C.sub.1-C.sub.3 alkyl include, but are not limited to, methyl, ethyl, 1-propyl or isopropyl.
[0066] As used herein, the term “cycloalkyl” means a saturated cyclic hydrocarbon group containing the indicated number of carbon atoms. For example, the term “3-6 membered cycloalkyl” as used herein refers to a saturated cyclic hydrocarbon group having three, four, five or six carbon atoms. Examples of 3-6 membered cycloalkyl include, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Examples of 3-5 membered cycloalkyl include, cyclopropyl, cyclobutyl and cyclopentyl.
[0067] As used herein, the term “heterocycloalkyl” means a saturated cyclic group containing the indicated number of atoms selected from C(O).sub.0-1, N, O and S(O).sub.0-2. For example, the term “5-6 membered heterocycloalkyl” as used herein refers to a saturated cyclic ring system having five or six ring atoms, one, two or three of which are selected from N, O and S(O).sub.0-2, the remainder being C(O).sub.0-1. Examples of 4-6 membered heterocycloalkyl groups include, but are not limited to, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, pyrrolidinyl, pyrrolidin-2-onyl, dioxanyl, morpholinyl, oxetanyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydropyranyl, oxazolidinyl, isothiazolidinyl oxozolid-2-onyl and isothiazolid-2-onyl. Examples of 5-6 membered heterocycloalkyl groups include, but are not limited to, piperidinyl, piperazinyl, pyrrolidinyl, pyrrolidin-2-onyl, dioxanyl, morpholinyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydropyranyl, oxazolidinyl, isothiazolidinyl oxozolid-2-onyl and isothiazolid-2-onyl.
[0068] As used herein, the term “aryl” refers to an aromatic cyclic hydrocarbon group having the indicated number of carbon atoms. For example, the term “5-6 membered aryl” as used herein refers to an aromatic cyclic hydrocarbon group having five or six carbon atoms. Examples of 5-6 membered aryls include cyclopentadienyl and phenyl.

[0069] As used herein, the term “heteroaryl” refers to an aromatic cyclic group having the indicated number of atoms selected from C, N, O and S. For example, the term “5-6 membered heteroaryl” as used herein refers to an aromatic cyclic group having five or six ring atoms, one, two or three of which are selected from N, O and S, the remainder being C. Examples of 5-6 membered heteroaryls include, but are not limited to, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, pyrrolyl, thiophenyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl and thiadiazolyl. Examples of 6 membered heteroaryls include, but are not limited to, pyridinyl, pyrazinyl, pyrimidinyl and pyridazinyl.
[0070] As used herein the term “halogen” or “halo” refers to F (fluoro), Cl (chloro), Br (bromo) and I (iodo).
[0071] As used herein the term “halomethyl” refers to —CH.sub.3, in which one or more hydrogen atoms is/are replaced with an independently selected halo.
[0072] As used herein the term “oxo” refers to the substitution of CH.sub.2 with O to form C(O).
[0073] As used herein the term “N(C.sub.1-C.sub.3 alkyl).sub.2” allows the independent selection of each C.sub.1-C.sub.3 alkyl substituent, for example, N may be substituted by methyl and ethyl.
[0074] As used herein the substituent —NR.sup.4C(O) is connected to R.sup.2 through N.
[0075] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), A can be pyrazole, 1,2,3 triazole, 1,2,4 triazole, 1,2,3 thiadiazole, 1,2,4 thiadiazole, 1,2,5 thiadiazole, 1,3,4 thiadiazole, 1,2,3 oxadiazole, 1,2,4 oxadiazole, 1,2,5 oxadiazole or 1,3,4 oxadiazole, substituted with R.sup.1 and R.sup.1A.
[0076] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), A can be pyrazole, 1,2,3 triazole or 1,2,4 triazole, substituted with R.sup.1 and R.sup.1A.
[0077] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), A can be pyrazole, 1,2,3 triazole or 1,2,4 triazole, substituted with R.sup.1 and R.sup.1A, wherein R.sup.1A is hydrogen and R.sup.1 is C.sub.1-C.sub.3 alkyl.
[0078] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), A can be pyrazole, 1,2,3 triazole or 1,2,4 triazole, substituted with R.sup.1 and R.sup.1A, wherein R.sup.1A is hydrogen and R.sup.1 is CH.sub.3.
[0079] In the compounds of formula (I), (II), (III), (IA) or (IIA), A can be:
##STR00014##
wherein * indicates the connection point to Z, Z′ or Z.sub.2 and ** indicates the other connection point from A in formula (I), (II), (III), (IA) or (IIA); and R.sup.1 can be C.sub.1-C.sub.3 alkyl;
[0080] In the compounds of formula (IIIA), A can be:
##STR00015##
wherein * indicates the connection point to the substituent comprising Y.sub.1 and ** indicates the other connection point from A in formula (IIIA); and R.sup.1 can be C.sub.1-C.sub.3 alkyl; In the compounds of formula (I), Z can be CR.sup.9A, cyclobutyl, azetidine, pyrrolidine or piperidine.
[0081] In the compounds of formula (I) or (IA), Z can be a bond,
##STR00016##
wherein * indicates the connection point to Z.sub.1 and ** indicates the connection point to A in formula (I) or (IA).
[0082] In the compounds of formula (I) or (IA), Z can be a bond,
##STR00017##
wherein * indicates the connection point to Z.sub.1 and ** indicates the connection point to A in formula (I) or (IA).
[0083] In the compounds of formula (I) or (IA), Z can be CHR.sup.9A, Z.sub.1 can be selected from CH.sub.2 or CH.sub.2—CH.sub.2, and R.sup.9 can be fused with R.sup.9A to form CH.sub.2 or CH.sub.2—CH.sub.2.
[0084] In the compounds of formula (I) or (IA), Z can be CHR.sup.9A, Z.sub.1 can be CH.sub.2, and R.sup.9 can be fused with R.sup.9A to form CH.sub.2 or CH.sub.2—CH.sub.2.

[0085] In the compounds of formula (I) or (IA), Z can be CHR.sup.9A, Z.sub.1 can be CH.sub.2—CH.sub.2, and R.sup.9 can be fused with R.sup.9A to form CH.sub.2 or CH.sub.2—CH.sub.2.
[0086] In the compounds of formula (I) or (IA), Z can be CHR.sup.9A, Z.sub.1 can be selected from CH.sub.2 or CH.sub.2—CH.sub.2, and R.sup.9 can be fused with R.sup.9A to form CH.sub.2.
[0087] In the compounds of formula (I) or (IA), Z can be CHR.sup.9A, Z.sub.1 can be selected from CH.sub.2 or CH.sub.2—CH.sub.2, and R.sup.9 can be fused with R.sup.9A to form CH.sub.2—CH.sub.2.
[0088] In the compounds of formula (I) or (IA), Z can be CHR.sup.9A, Z.sub.1 can be CH.sub.2, and R.sup.9 can be fused with R.sup.9A to form CH.sub.2.
[0089] In the compounds of formula (I) or (IA), Z can be CHR.sup.9A, Z.sub.1 can be CH.sub.2—CH.sub.2, and R.sup.9 can be fused with R.sup.9A to form CH.sub.2—CH.sub.2.
[0090] In the compounds of formula (II) or (IIA), Z′ can be:
##STR00018##
wherein ** indicates the connection point to A and * indicates the other connection point from Z′ in formula (II) or (IIA).
[0091] In the compounds of formula (II) or (IIA), Z′ can be:
##STR00019##
wherein ** indicates the connection point to A and * indicates the other connection point from Z′ in formula (II) or (IIA).
[0092] In the compounds of formula (I) or (IA), Z can be a bond.
[0093] In the compounds of formula (II) or (IIA), Z′ can be a bond.
[0094] In the compounds of formula (I), (II), (IA) or (IIA), Z.sub.1 can be a bond.
[0095] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), Y can be NH or O.
[0096] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), Y can be O.
[0097] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), Y.sub.1 can be a bond, CHR.sup.7, CH.sub.2—CHR.sup.7 or CHR.sup.7—CH.sub.2, wherein R.sup.7 is selected from hydrogen, F, OH and CH.sub.3; and Y.sub.2 can a bond, CHR.sup.3, CH.sub.2—CHR.sup.3 or CHR.sup.3—CH.sub.2, wherein R.sup.3 is selected from hydrogen, F, OH and CH.sub.3.
[0098] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), Y.sub.1 can be a bond or CHR.sup.7, wherein R.sup.7 is hydrogen, F, OH or CH.sub.3; and Y.sub.2 can a bond or CHR.sup.3, wherein R.sup.3 is hydrogen, F, OH or CH.sub.3.
[0099] In the compounds of formula (I), (II), (III), (IA) or (IIA), Y.sub.1 can be a bond, CHR.sup.7, CH.sub.2—CHR.sup.7 or CHR.sup.7—CH.sub.2, wherein R.sup.7 is hydrogen, F, OH or CH.sub.3; and Y.sub.2 can a bond, CHR.sup.3, CH.sub.2—CHR.sup.3 or CHR.sup.3—CH.sub.2, wherein R.sup.3 is hydrogen, F, OH or CH.sub.3, forming.
##STR00020##
wherein * indicates the connection point to Z.sub.1, in formula (I) or (IA); Z′ in formula (II) or (IIA); or A in formula (III).
[0100] In the compounds of formula (I), (II), (III), (IA) or (IIA), Y.sub.1 can be a bond or CHR.sup.7, wherein R.sup.7 is hydrogen, F, OH or CH.sub.3; and Y.sub.2 can a bond or CHR.sup.3, wherein R.sup.3 is hydrogen, F, OH or CH.sub.3, forming:
##STR00021##
wherein * indicates the connection point to Z.sub.1 in formula (I) or (IA); Z′ in formula (II) or (IIA); or A in formula (III).
[0101] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), Y.sub.1 can be a bond, CHR.sup.7, CH.sub.2—CHR.sup.7 or CHR.sup.7—CH.sub.2, wherein R.sup.7 is hydrogen, F, OH or CH.sub.3; and Y.sub.2 can a bond, CHR.sup.3, CH.sub.2—CHR.sup.3 or CHR.sup.3—CH.sub.2, wherein R.sup.3 is hydrogen, F, OH or CH.sub.3, forming:
##STR00022##
wherein * indicates the connection point to A in formula (I), (II), (III), (IA), (IIA) or (IIIA).

[0102] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), Y.sub.1 can be a bond or CHR.sup.7, wherein R.sup.7 is hydrogen, F, OH or CH.sub.3; and Y.sub.2 can a bond or CHR.sup.3, wherein R.sup.3 is hydrogen, F, OH or CH.sub.3, forming:
##STR00023##
wherein * indicates the connection point to A in formula (I), (II), (III), (IA), (IIA) or (IIIA), or wherein * indicates the connection point to Z.sub.1 in formula (I) or (IA); Z′ in formula (II) or (IIA); or A in formula (III) or (IIIA).
[0103] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.1A can be hydrogen or C.sub.1-C.sub.3 alkyl optionally substituted with one or more substituents independently selected from halo, OH and OCH.sub.3.
[0104] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.1A can be hydrogen or CH.sub.3.
[0105] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.1A can be hydrogen.
[0106] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.1 can be methyl, ethyl or propyl.
[0107] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.1 can be methyl.
[0108] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.2 can be C.sub.1-C.sub.3 alkyl optionally substituted with one, two, three or four substituents independently selected from halo, OH, CN, oxo, —OC.sub.1-C.sub.4 alkyl, —OC.sub.3-C.sub.5 cycloalkyl, —Z.sub.3—R.sup.11 and R.sup.10, wherein C.sub.1-C.sub.4 alkyl and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN.
[0109] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.2 can be C.sub.1-C.sub.3 alkyl optionally substituted with one or more substituents independently selected from F, OH, CN, oxo, —OCH.sub.3, —OC.sub.3 cycloalkyl and R.sup.10.
[0110] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.2 can be:
##STR00024##
optionally substituted with one, two, three or four substituents independently selected from halo, OH, CN, oxo, —OC.sub.1-C.sub.4 alkyl, —OC.sub.3-C.sub.5 cycloalkyl, —Z.sub.3—R.sup.11 and R.sup.10, wherein C.sub.1-C.sub.4 alkyl and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN, wherein * indicates the connection point to Y in formula (I), (II), (III), (IA), (IIA) or (IIIA).
[0111] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.2 can be:
##STR00025##
[0112] optionally substituted with one, two, three or four substituents independently selected from halo, OH, CN, oxo, —OC.sub.1-C.sub.4 alkyl, —OC.sub.3-C.sub.5 cycloalkyl, —Z.sub.3—R.sup.11 and R.sup.10, wherein C.sub.1-C.sub.4 alkyl and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN, wherein * indicates the connection point to Y in formula (I), (II), (III), (IA), (IIA) or (IIIA).
[0113] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.2 can be:
##STR00026##
[0114] optionally substituted with one, two, three or four substituents independently selected from F, OH, CN, oxo, —OCH.sub.3, —OC.sub.3 cycloalkyl and R.sup.10, wherein * indicates the connection point to Y in formula (I), (II), (III), (IA), (IIA) or (IIIA).
[0115] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.2 can be:
##STR00027##
optionally substituted with one, two, three or four substituents independently selected from F, OH, CN, oxo, —OCH.sub.3 and —OC.sub.3 cycloalkyl and R.sup.10, wherein * indicates the

connection point to Y in formula (I), (II), (III), (IA), (IIA) or (IIIA).
[0116] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), Y.sub.1 can be a bond, CHR.sup.7, CH.sub.2—CHR.sup.7 or CHR.sup.7—CH.sub.2, wherein R.sup.7 can be selected from hydrogen, F, OH and CH.sub.3.
[0117] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), Y.sub.2 can be a bond, CHR.sup.3, CH.sub.2—CHR.sup.3 or CHR.sup.3—CH.sub.2, wherein R.sup.3 can be selected from hydrogen, F, OH and CH.sub.3.
[0118] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), Y.sub.3 can be CR.sup.4R.sup.5 or CF.sub.2, wherein R.sup.4 is hydrogen or CH.sub.3 and R.sup.5 is hydrogen, F, OH or CH.sub.3; and Y.sub.4 is CR.sup.3R.sup.4 or CF.sub.2 wherein R.sup.4 is hydrogen or CH.sub.3, and R.sup.3 is hydrogen, F, OH or CH.sub.3. In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), Y.sub.3 can be CR.sup.4R.sup.5, wherein R.sup.4 is hydrogen and R.sup.5 is fused with one R.sup.3 to form CH.sub.2, CH.sub.2—CH.sub.2 or CH.sub.2OCH.sub.2; and Y.sub.4 is CR.sup.3R.sup.4 wherein R.sup.4 is hydrogen, and R.sup.3 is fused with R.sup.5 to form CH.sub.2, CH.sub.2—CH.sub.2 or CH.sub.2OCH.sub.2.
[0119] In the compounds of formula (I), (II), (III), (IA) or (IIA), Y.sub.3 can be CR.sup.4R.sup.5, wherein R.sup.4 is hydrogen and R.sup.5 is fused with one R.sup.3 to form CH.sub.2, CH.sub.2—CH.sub.2 or CH.sub.2OCH.sub.2; and Y.sub.4 is CR.sup.3R.sup.4 wherein R.sup.4 is hydrogen, and R.sup.3 is fused with R.sup.5 to form CH.sub.2, CH.sub.2—CH.sub.2 or CH.sub.2OCH.sub.2, forming:
##STR00028##
wherein indicates the connection point to Z.sub.1 in formula or in formula or (IIA); or A in formula (III).
[0120] In the compounds of formula (IIIA), Y.sub.3 can be CR.sup.4R.sup.5, wherein R.sup.4 is hydrogen and R.sup.5 is fused with one R.sup.3 to form CH.sub.2, CH.sub.2—CH.sub.2 or CH.sub.2OCH.sub.2; and Y.sub.4 is CR.sup.3R.sup.4 wherein R.sup.4 is hydrogen, and R.sup.3 is fused with R.sup.5 to form CH.sub.2, CH.sub.2—CH.sub.2 or CH.sub.2OCH.sub.2, forming:
##STR00029##
wherein * indicates the connection point A in formula (IIIA), or, or wherein * indicates the connection point to Z.sub.1 in formula (I) or (IA); Z′ in formula (II) or (IIA); or A in formula (III) or (IIIA).
[0121] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), Y.sub.5 can be CR.sup.13R.sup.14, CR.sup.13R.sup.14—CH.sub.2 or CH.sub.2—CR.sup.13R.sup.14, wherein R.sup.13 and R.sup.14 are independently selected from H and CH.sub.3; and Y.sub.6 can be CR.sup.13R.sup.14, CR.sup.13R.sup.14—CH.sub.2 or CH.sub.2—CR.sup.13R.sup.14, wherein R.sup.13 and R.sup.14 are independently selected from H and CH.sub.3.
[0122] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), Y.sub.5 can be CH.sub.2 or CH.sub.2—CH.sub.2 and Y.sub.6 can be CH.sub.2 or CH.sub.2—CH.sub.2.
[0123] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), Y.sub.5 and Y.sub.6 can be CH.sub.2.
[0124] In the compounds of formula (I), (II), (III), (IA) or (IIA), X.sub.4 can be N or C—R.sup.9 wherein R.sup.9 is hydrogen or CH.sub.3.
[0125] In the compounds of formula (I) or (IA), X.sub.4 can be C—R.sup.9 wherein R.sup.9 is fused with R.sup.9A to form CH.sub.2 or CH.sub.2—CH.sub.2; and Z.sub.1 is CH.sub.2 or CH.sub.2—CH.sub.2.
[0126] In the compounds of formula (I), (II), (III), (IA) or (IIA), X.sub.4 can be N or CH.
[0127] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.6 can be CN, F, Cl, CH.sub.3, CF.sub.3 or cyclopropyl.
[0128] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.6 can be CN, F or Cl.
[0129] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.6 can be CN or Cl.

[0130] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.6 can be CN.
[0131] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.6 can be Cl.
[0132] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.8 can be 5-6 membered cycloalkyl, 5-6 membered heterocycloalkyl, 5-6 membered aryl or 5-6 membered heteroaryl, optionally fused or substituted with R.sup.8A.
[0133] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.8 can be 5-6 membered cycloalkyl or 5-6 membered heterocycloalkyl, optionally fused with R.sup.8A.
[0134] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.8 can be cyclopentyl, cyclohexyl, piperidinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, phenyl or pyridinyl, optionally fused with R.sup.8A.
[0135] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.8 can be cyclopentyl, cyclohexyl, piperidinyl, pyrrolidinyl, tetrahydrofuranyl or tetrahydropyranyl, fused with R.sup.8A.
[0136] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.8 can be cyclopentyl, cyclohexyl, piperidinyl, pyrrolidinyl, tetrahydrofuranyl or tetrahydropyranyl, fused with R.sup.8A, wherein R.sup.8A can be phenyl or 6 membered heteroaryl.
[0137] In the compounds of formula (I), (II), (III), (IA) or (IIA), R.sup.9 can be hydrogen.
[0138] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.10 can be 3-6 membered cycloalkyl, 5-6 membered heterocycloalkyl, 5-6 membered aryl or 5-6 membered heteroaryl, optionally fused with R.sup.8A.
[0139] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.10 can be 3-6 membered cycloalkyl, 5-6 membered heterocycloalkyl, phenyl or 5-6 membered heteroaryl, optionally fused or substituted with R.sup.8A.
[0140] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.10 can be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, piperidinyl, piperazinyl, pyrrolidinyl, pyrrolidin-2-onyl, dioxanyl, morpholinyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydropyranyl, oxazolidinyl, isothiazolidinyl, oxozolid-2-onyl, isothiazolid-2-onyl, phenyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, pyrrolyl, thiophenyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl or thiadiazolyl, optionally fused or substituted with R.sup.8A.
[0141] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.10 can be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl, phenyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl or thiadiazolyl, optionally fused or substituted with R.sup.8A.
[0142] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.10 can be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl, phenyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl or thiadiazolyl, optionally fused or substituted with R.sup.8A.
[0143] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.10 can be cyclopropyl, cyclobutyl, phenyl, pyridinyl, oxazolyl, isoxazolyl, thiazolyl or isothiazolyl, optionally fused or substituted with R.sup.8A.
[0144] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.10 can be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, piperidinyl, piperazinyl, pyrrolidinyl, pyrrolidin-2-onyl, dioxanyl, morpholinyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydropyranyl, oxazolidinyl, isothiazolidinyl, oxozolid-2-onyl, isothiazolid-2-onyl, phenyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, pyrrolyl, thiophenyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl or thiadiazolyl.
[0145] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.10 can be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl, phenyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl or thiadiazolyl.

[0146] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.10 can be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl, phenyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl or thiadiazolyl.
[0147] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.10 can be cyclopropyl, cyclobutyl, phenyl, pyridinyl, oxazolyl, isoxazolyl, thiazolyl or isothiazolyl.
[0148] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.10 can be cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl, phenyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl or thiadiazolyl, fused or substituted with R.sup.8A.
[0149] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.10 can be cyclopentyl, cyclohexyl, piperidinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, phenyl or pyridinyl, fused or substituted with R.sup.8A.
[0150] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.10 can be cyclopentyl, cyclohexyl, piperidinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, phenyl or pyridinyl, fused or substituted with R.sup.8A.
[0151] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.10 can be cyclopentyl, cyclohexyl, piperidinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, phenyl or pyridinyl, fused or substituted with R.sup.8A.
[0152] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.10 can be cyclopentyl, cyclohexyl, phenyl or pyridinyl, fused or substituted with R.sup.8A.
[0153] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.10 can be phenyl or pyridinyl, fused with R.sup.8A wherein R.sup.8A can be 5-6 membered heterocycloalkyl or 5-6 membered heteroaryl.
[0154] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.10 can be phenyl or pyridinyl, fused with R.sup.8A wherein R.sup.8A can be pyrrolidinyl, pyrrolidin-2-onyl, dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydropyranyl, oxazolidinyl, isothiazolidinyl, oxozolid-2-onyl, isothiazolid-2-onyl furanyl, pyrrolyl, thiophenyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl or thiadiazolyl.
[0155] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.10 can be phenyl or pyridinyl, fused with R.sup.8A wherein R.sup.8A can be tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydropyranyl, oxazolidinyl, isothiazolidinyl, oxozolid-2-onyl, isothiazolid-2-onyl, furanyl, pyrrolyl, thiophenyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl or thiadiazolyl.
[0156] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.10 can be phenyl or pyridinyl, fused with R.sup.8A wherein R.sup.8A can be tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydropyranyl, oxazolidinyl, isothiazolidinyl, oxozolid-2-only or isothiazolid-2-onyl.
[0157] In the compounds of formula (I) or (IA), where both Z and Z.sub.1 are a bond, together they form a single bond.
[0158] In the compounds of formula (I) or (IA), Z can be CHR.sup.9A, Z.sub.1 can be CH.sub.2, X.sub.4 can be C—R.sup.9, and R.sup.9 can be fused with R.sup.9A to form CH.sub.2, forming:
##STR00030##
[0159] wherein * indicates the connection point to A.
[0160] In the compounds of formula (I), (II), (III), (IA) or (IIA), R.sup.5 can be fused with one R.sup.3 to form CH.sub.2—CH.sub.2, for example forming:
##STR00031##
[0161] wherein * indicates the connection point to Z.sub.1 in formula (I) or (IA); or Z′ in formula (II) or (IIA); or A in formula (III).
[0162] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.5 can be fused with one R.sup.3 to form CH.sub.2—CH.sub.2, for example forming:

##STR00032##
wherein * indicates the connection point to Z.sub.1 in formula (I) or (IA); or Z′ in formula (II) or (IIA); or A in formula (III) or (IIIA).
[0163] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), R.sup.8 can be cyclopentyl, fused with R.sup.8A, wherein R.sup.8A can be pyridinyl, for example forming:
##STR00033##
wherein * indicates the connection point to Y.
[0164] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), A can be pyrazole, 1,2,3 triazole or 1,2,4 triazole, substituted with R.sup.1 and R.sup.1A; and Y can be NH or O.
[0165] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), A can be pyrazole, 1,2,3 triazole or 1,2,4 triazole, substituted with R.sup.1 and R.sup.1A, wherein R.sup.1A is hydrogen and R.sup.1 is C.sub.1-C.sub.3 alkyl; and Y can be NH or O.
[0166] In the compounds of formula (I), (II), (III), (IA) or (IIA), A can be:
##STR00034##
[0167] wherein * indicates the connection point to Z, Z′ or Z.sub.2 and ** indicates the other connection point from A in formula (I), (II), (III), (IA) or (IIA); R.sup.1 can be C.sub.1-C.sub.3 alkyl; and Y can be NH or O.
[0168] In the compounds of formula (IIIA), A can be:
##STR00035##
[0169] wherein * indicates the connection point to the substituent comprising Y.sub.1 and ** indicates the other connection point from A in formula (IIIA); R.sup.1 can be C.sub.1-C.sub.3 alkyl; and Y can be NH or O.
[0170] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), A can be pyrazole, 1,2,3 triazole or 1,2,4 triazole, substituted with R.sup.1 and R.sup.1A; and Y can be O.
[0171] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), A can be pyrazole, 1,2,3 triazole or 1,2,4 triazole, substituted with R.sup.1 and R.sup.1A, wherein R.sup.1A is hydrogen and R.sup.1 is C.sub.1-C.sub.3 alkyl; and Y can be O.
[0172] In the compounds of formula (I), (II), (III), (IA) or (IIA), A can be:
##STR00036##
[0173] wherein * indicates the connection point to Z, Z′ or Z.sub.2 and ** indicates the other connection point from A in formula (I), (II), (III), (IA) or (IIA); R.sup.1 can be C.sub.1-C.sub.3 alkyl; and Y can be O.
[0174] In the compounds of formula (IIIA), A can be:
##STR00037##
[0175] wherein * indicates the connection point to the substituent comprising Y.sub.1 and ** indicates the other connection point from A in formula (IIIA); R.sup.1 can be C.sub.1-C.sub.3 alkyl; and Y can be O.
[0176] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), A can be pyrazole, 1,2,3 triazole or 1,2,4 triazole, substituted with R.sup.1 and R.sup.1A; and R.sup.6 can be CN, F, Cl, CH.sub.3, CF.sub.3 or cyclopropyl.
[0177] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), A can be pyrazole, 1,2,3 triazole or 1,2,4 triazole, substituted with R.sup.1 and R.sup.1A, wherein R.sup.1A is hydrogen and R.sup.1 is C.sub.1-C.sub.3 alkyl; and R.sup.6 can be CN, F, Cl or CF.sub.3.
[0178] In the compounds of formula (I), (II), (III), (IA) or (IIA), A can be:
##STR00038##
[0179] wherein * indicates the connection point to Z, Z′ or Z.sub.2 and ** indicates the other connection point from A in formula (I), (II), (III), (IA) or (IIA); and R.sup.6 can be CN, F, Cl, CH.sub.3, CF.sub.3 or cyclopropyl.
[0180] In the compounds of formula (IIIA), A can be:
##STR00039##

[0181] wherein * indicates the connection point to the substituent comprising Y.sub.1 and ** indicates the other connection point from A in formula (IIIA) and R.sup.6 can be CN, F, Cl, CH.sub.3, CF.sub.3 or cyclopropyl.
[0182] In the compounds of formula (I), (II), (III), (IA) or (IIA), A can be:
##STR00040##
[0183] wherein * indicates the connection point to Z, Z′ or Z.sub.2 and ** indicates the other connection point from A in formula (I), (II), (III), (IA) or (IIA); and R.sup.6 can be CN, F, Cl or CF.sub.3.
[0184] In the compounds of formula (IIIA), A can be:
##STR00041##
[0185] wherein * indicates the connection point to the substituent comprising Y.sub.1 and ** indicates the other connection point from A in formula (IIIA) and R.sup.6 can be CN, F, Cl, CH.sub.3 or CF.sub.3.
[0186] In the compounds of formula (I), (II), (III), (IA) or (IIA), A can be:
##STR00042##
[0187] wherein * indicates the connection point to Z, Z′ or Z.sub.2 and ** indicates the other connection point from A in formula (I), (II), (III), (IA) or (IIA); R.sup.1 can be C.sub.1-C.sub.3 alkyl; and R.sup.6 can be CN or Cl.
[0188] In the compounds of formula (IIIA), A can be:
##STR00043##
[0189] wherein * indicates the connection point to the substituent comprising Y.sub.1 and ** indicates the other connection point from A in formula (IIIA); R.sup.1 can be C.sub.1-C.sub.3 alkyl; and R.sup.6 can be CN or Cl.
[0190] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), A can be pyrazole, 1,2,3 triazole or 1,2,4 triazole, substituted with R.sup.1 and R.sup.1A; R.sup.6 can be CN, F, Cl, CH.sub.3, CF.sub.3 or cyclopropyl; and Y can be NH or O.
[0191] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), A can be pyrazole, 1,2,3 triazole or 1,2,4 triazole, substituted with R.sup.1 and R.sup.1A, wherein R.sup.1A is hydrogen and R.sup.1 is C.sub.1-C.sub.3 alkyl; R.sup.6 can be CN, F, Cl or CF.sub.3; and Y can be NH or O.
[0192] In the compounds of formula (I), (II), (III), (IA) or (IIA), A can be:
##STR00044##
[0193] wherein * indicates the connection point to Z, Z′ or Z.sub.2 and ** indicates the other connection point from A in formula (I), (II), (III), (IA) or (IIA); R.sup.6 can be CN, F, Cl, CH.sub.3, CF.sub.3 or cyclopropyl; and Y can be NH or O.
[0194] In the compounds of formula (IIIA), A can be:
##STR00045##
[0195] wherein * indicates the connection point to the substituent comprising Y.sub.1 and ** indicates the other connection point from A in formula (IIIA); R.sup.6 can be CN, F, Cl, CH.sub.3, CF.sub.3 or cyclopropyl; and Y can be NH or O.
[0196] In the compounds of formula (I), (II), (III), (IA) or (IIA), A can be:
##STR00046##
[0197] wherein * indicates the connection point to Z, Z′ or Z.sub.2 and ** indicates the other connection point from A in formula (I), (II), (III), (IA) or (IIA); R.sup.6 can be CN, F, Cl or CF.sub.3; and Y can be NH or O.
[0198] In the compounds of formula (IIIA), A can be:
##STR00047##
[0199] wherein * indicates the connection point to the substituent comprising Y.sub.1 and ** indicates the other connection point from A in formula (IIIA); R.sup.6 can be CN, F, Cl or CF.sub.3; and Y can be NH or O.
[0200] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), A can be pyrazole, 1,2,3

triazole or 1,2,4 triazole, substituted with R.sup.1 and R.sup.1A; R.sup.6 can be CN, F, Cl, CH.sub.3, CF.sub.3 or cyclopropyl; and Y can be O.
[0201] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), A can be pyrazole, 1,2,3 triazole or 1,2,4 triazole, substituted with R.sup.1 and R.sup.1A, wherein R.sup.1A is hydrogen and R.sup.1 is C.sub.1-C.sub.3 alkyl; R.sup.6 can be CN, F, Cl or CF.sub.3; and Y can be O.
[0202] In the compounds of formula (I), (II), (III), (IA) or (IIA), A can be:
##STR00048##
[0203] wherein * indicates the connection point to Z, Z′ or Z.sub.2 and ** indicates the other connection point from A in formula (I), (II), (III), (IA) or (IIA); R.sup.6 can be CN, F, Cl, CH.sub.3, CF.sub.3 or cyclopropyl; and Y can be O.
[0204] In the compounds of formula (IIIA), A can be:
##STR00049##
[0205] wherein * indicates the connection point to the substituent comprising Y.sub.1 and ** indicates the other connection point from A in formula (IIIA); R.sup.6 can be CN, F, Cl, CH.sub.3, CF.sub.3 or cyclopropyl; and Y can be O.
[0206] In the compounds of formula (I), (II), (III), (IA) or (IIA), A can be:
##STR00050##
[0207] wherein * indicates the connection point to Z, Z′ or Z.sub.2 and ** indicates the other connection point from A in formula (I), (II), (III), (IA) or (IIA); R.sup.6 can be CN, F, Cl or CF.sub.3; and Y can be O.
[0208] In the compounds of formula (IIIA), A can be:
##STR00051##
[0209] wherein * indicates the connection point to the substituent comprising Y.sub.1 and ** indicates the other connection point from A in formula (IIIA); R.sup.6 can be CN, F, Cl or CF.sub.3; and Y can be O.
[0210] In the compounds of formula (I), (II), (III), (IA) or (IIA), A can be:
##STR00052##
[0211] wherein * indicates the connection point to Z, Z′ or Z.sub.2 and ** indicates the other connection point from A in formula (I), (II), (III), (IA) or (IIA); R.sup.1 can be C.sub.1-C.sub.3 alkyl; R.sup.6 can be CN or Cl; and Y can be O.
[0212] In the compounds of formula (IIIA), A can be:
##STR00053##
[0213] wherein * indicates the connection point to the substituent comprising Y.sub.1 and ** indicates the other connection point from A in formula (IIIA); R.sup.6 can be CN, F, Cl or CF.sub.3; and Y can be O.
[0214] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), A can be pyrazole, 1,2,3 triazole or 1,2,4 triazole, substituted with R.sup.1 and R.sup.1A; R.sup.6 can be CN, F, Cl, CH.sub.3, CF.sub.3 or cyclopropyl; Y can be NH or O; and R.sup.2 can be C.sub.1-C.sub.3 alkyl optionally substituted with one, two, three or four substituents independently selected from halo, OH, CN, oxo, —OC.sub.1-C.sub.4 alkyl, —OC.sub.3-C.sub.5 cycloalkyl, —Z.sub.3—R.sup.11 and R.sup.10, wherein C.sub.1-C.sub.4 alkyl and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN.
[0215] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), A can be pyrazole, 1,2,3 triazole or 1,2,4 triazole, substituted with R.sup.1 and R.sup.1A; R.sup.6 can be CN, F, Cl, CH.sub.3, CF.sub.3 or cyclopropyl; Y can be NH or O; and R.sup.2 can be C.sub.1-C.sub.4 alkyl optionally substituted with one or more substituents independently selected from F, OH, CN, oxo, —OCH.sub.3, —OC.sub.3 cycloalkyl and R.sup.10.
[0216] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), A can be pyrazole, 1,2,3 triazole or 1,2,4 triazole, substituted with R.sup.1 and R.sup.1A; R.sup.6 can be CN, F, Cl or

CF.sub.3; Y can be NH or O and R.sup.2 can be:
##STR00054##
[0217] optionally substituted with one, two, three or four substituents independently selected from halo, OH, CN, oxo, —OC.sub.1-C.sub.4 alkyl, —OC.sub.3-C.sub.5 cycloalkyl, —Z.sub.3—R.sup.11 and R.sup.10, wherein C.sub.1-C.sub.4 alkyl and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN, wherein * indicates the connection point to Y in formula (I), (II), (III), (IA), (IIA) or (IIIA).
[0218] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), A can be pyrazole, 1,2,3 triazole or 1,2,4 triazole, substituted with R.sup.1 and R.sup.1A; R.sup.6 can CN, F, Cl or CF.sub.3; Y can be NH or O; and R.sup.2 can be:
##STR00055##
[0219] optionally substituted with one, two, three or four substituents independently selected from F, OH, CN, oxo, —OCH.sub.3, —OC.sub.3 cycloalkyl and R.sup.10, wherein * indicates the connection point to Y in formula (I), (II), (III), (IA), (IIA) or (IIIA).
[0220] In the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), A can be pyrazole, 1,2,3 triazole or 1,2,4 triazole, substituted with R.sup.1 and R.sup.1A; R.sup.6 can be CN, F, Cl or CF.sub.3; Y can be NH or O; and R.sup.2 can be:
##STR00056##
[0221] optionally substituted with one, two, three or four substituents independently selected from halo, OH, CN, oxo, —OC.sub.1-C.sub.4 alkyl, —OC.sub.3-C.sub.5 cycloalkyl, —Z.sub.3—R.sup.11 and R.sup.10, wherein C.sub.1-C.sub.4 alkyl and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN, wherein * indicates the connection point to Y in formula (I), (II), (III), (IA), (IIA) or (IIIA).
[0222] In the compounds of formula (I), A can be pyrazole, 1,2,3 triazole or 1,2,4 triazole, substituted with R.sup.1 and R.sup.1A; R.sup.6 can CN, F, Cl or CF.sub.3; Y can be NH or O; and R.sup.2 can be:
##STR00057##
[0223] optionally substituted with one, two, three or four substituents independently selected from F, OH, CN, oxo, —OCH.sub.3, —OC.sub.3 cycloalkyl and R.sup.10, wherein * indicates the connection point to Y in formula (I), (II), (III), (IA), (IIA) or (IIIA).
[0224] In the compounds of formula (I), (II), (III), (IA) or (IIA), A can be:
##STR00058##
[0225] wherein * indicates the connection point to Z, Z′ or Z.sub.2 and ** indicates the other connection point from A in formula (I), (II), (III), (IA) or (IIA); R.sup.6 can be CN, F, Cl, CH.sub.3, CF.sub.3 or cyclopropyl; Y can be NH or O; and R.sup.2 can be C.sub.1-C.sub.3 alkyl optionally substituted with one, two, three or four substituents independently selected from halo, OH, CN, oxo, —OC.sub.1-C.sub.4 alkyl, —OC.sub.3-C.sub.5 cycloalkyl, —Z.sub.3—R.sup.11 and R.sup.10, wherein C.sub.1-C.sub.4 alkyl and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN.
[0226] In the compounds of formula (I), (II), (III), (IA) or (IIA), A can be:
##STR00059##
[0227] wherein * indicates the connection point to Z, Z′ or Z.sub.2 and ** indicates the other connection point from A in formula (I), (II), (III), (IA) or (IIA); R.sup.6 can be CN, F, Cl, CH.sub.3, CF.sub.3 or cyclopropyl; Y can be NH or O; and R.sup.2 can be C.sub.1-C.sub.4 alkyl optionally substituted with one or more substituents independently selected from F, OH, CN, oxo, —OCH.sub.3, —OC.sub.3 cycloalkyl and R.sup.10.
[0228] In the compounds of formula (I), (II), (III), (IA) or (IIA), A can be:

##STR00060##
[0229] wherein * indicates the connection point to Z, Z′ or Z.sub.2 and ** indicates the other connection point from A in formula (I), (II), (III), (IA) or (IIA); R.sup.6 can be CN, F, Cl or CF.sub.3; Y can be NH or O; and R.sup.2 can be:
##STR00061##
[0230] optionally substituted with one, two, three or four substituents independently selected from halo, OH, CN, oxo, —OC.sub.1-C.sub.4 alkyl, —OC.sub.3-C.sub.5 cycloalkyl, —Z.sub.3—R.sup.11 and R.sup.10, wherein C.sub.1-C.sub.4 alkyl and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN, wherein * indicates the connection point to Y in formula (I), (II), (III), (IA) or (IIA).
[0231] In the compounds of formula (I), (II), (III), (IA) or (IIA), A can be:
##STR00062##
[0232] wherein * indicates the connection point to Z, Z′ or Z.sub.2 and ** indicates the other connection point from A in formula (I), (II), (III), (IA) or (IIA); R.sup.6 can CN, F, Cl or CF.sub.3; Y can be NH or O; and R.sup.2 can be:
##STR00063##
[0233] optionally substituted with one, two, three or four substituents independently selected from F, OH, CN, oxo, —OCH.sub.3, —OC.sub.3 cycloalkyl and R.sup.10, wherein * indicates the connection point to Y in formula (I), (II), (III), (IA) or (IIA).
[0234] In the compounds of formula (I), (II), (III), (IA) or (IIA), A can be:
##STR00064##
wherein * indicates the connection point to Z, Z′ or Z.sub.2 and ** indicates the other connection point from A in formula (I), (II), (III), (IA) or (IIA); R.sup.6 can be CN, F, Cl or CF.sub.3; Y can be NH or O; and R.sup.2 can be:
##STR00065##
[0235] optionally substituted with one, two, three or four substituents independently selected from halo, OH, CN, oxo, —OC.sub.1-C.sub.4 alkyl, —OC.sub.3-C.sub.5 cycloalkyl, —Z.sub.3—R.sup.11 and R.sup.10, wherein C.sub.1-C.sub.4 alkyl and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN, wherein * indicates the connection point to Y in formula (I), (II), (III), (IA) or (IIA).
In the compounds of formula (I), (II), (III), (IA) or (IIA), A can be:
##STR00066##
wherein * indicates the connection point to Z, Z′ or Z.sub.2 and ** indicates the other connection point from A in formula (I), (II), (III), (IA) or (IIA); R.sup.6 can CN, F, Cl or CF.sub.3; Y can be NH or O; and R.sup.2 can be:
##STR00067##
[0236] optionally substituted with one, two, three or four substituents independently selected from F, OH, CN, oxo, —OCH.sub.3, —OC.sub.3 cycloalkyl and R.sup.10, wherein * indicates the connection point to Y in formula (I), (II), (III), (IA) or (IIA).
[0237] In the compounds of formula (IIIA), A can be:
##STR00068##
[0238] wherein * indicates the connection point to the substituent comprising Y.sub.1 and ** indicates the other connection point from A in formula (IIIA); R.sup.6 can CN, F, Cl or CF.sub.3; Y can be NH or O; and R.sup.2 can be:
##STR00069##
[0239] optionally substituted with one, two, three or four substituents independently selected from F, OH, CN, oxo, —OCH.sub.3, —OC.sub.3 cycloalkyl and R.sup.10, wherein * indicates the connection point to Y in formula (IIIA).

[0240] In the compounds of formula (IIIA), A can be:
##STR00070##
wherein * indicates the connection point to the substituent comprising Y.sub.1 and ** indicates the other connection point from A in formula (IIIA); R.sup.6 can be CN, F, Cl or CF.sub.3; Y can be NH or O; and R.sup.2 can be:
##STR00071##
optionally substituted with one, two, three or four substituents independently selected from halo, OH, CN, oxo, —OC.sub.1-C.sub.4 alkyl, —OC.sub.3-C.sub.5 cycloalkyl, —Z.sub.3—R.sup.11 and R.sup.10, wherein C.sub.1-C.sub.4 alkyl and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN, wherein * indicates the connection point to Y in formula (IIIA).
[0241] In the compounds of formula (IIIA), A can be:
##STR00072##
wherein * indicates the connection point to the substituent comprising Y.sub.1 and ** indicates the other connection point from A in formula (IIIA); R.sup.6 can CN, F, Cl or CF.sub.3; Y can be NH or O; and R.sup.2 can be:
##STR00073##
[0242] optionally substituted with one, two, three or four substituents independently selected from F, OH, CN, oxo, —OCH.sub.3, —OC.sub.3 cycloalkyl and R.sup.10, wherein * indicates the connection point to Y in formula (IIIA).
[0243] In the compounds of formula (I), (II), (III), (IA) or (IIA), A can be:
##STR00074##
[0244] wherein * indicates the connection point to Z, Z′ or Z.sub.2 and ** indicates the other connection point from A in formula (I), (II), (III), (IA) or (IIA); R.sup.6 can be CN, F, Cl, CH.sub.3, CF.sub.3 or cyclopropyl; Y can be NH or O; and R.sup.2 can be C.sub.1-C.sub.3 alkyl optionally substituted with one, two, three or four substituents independently selected from halo, OH, CN, oxo, —OC.sub.1-C.sub.4 alkyl, —OC.sub.3-C.sub.5 cycloalkyl, —Z.sub.3—R.sup.11 and R.sup.10, wherein C.sub.1-C.sub.4 alkyl and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN; Y.sub.5 is CR.sup.13R.sup.14, CR.sup.13R.sup.14—CH.sub.2 or CH.sub.2—CR.sup.13R.sup.14, wherein R.sup.13 and R.sup.14 are independently selected from H and CH.sub.3; and Y.sub.6 is CR.sup.13R.sup.14, CR.sup.13R.sup.14—CH.sub.2 or CH.sub.2—CR.sup.13R.sup.14, wherein R.sup.13 and R.sup.14 are independently selected from H and CH.sub.3.
[0245] In the compounds of formula (I), (II), (III), (IA) or (IIA), A can be:
##STR00075##
[0246] wherein * indicates the connection point to Z, Z′ or Z.sub.2 and ** indicates the other connection point from A in formula (I), (II), (III), (IA) or (IIA); R.sup.6 can be CN, F, Cl, CH.sub.3, CF.sub.3 or cyclopropyl; Y can be NH or O; and R.sup.2 can be C.sub.1-C.sub.4 alkyl optionally substituted with one or more substituents independently selected from F, OH, CN, oxo, —OCH.sub.3, —OC.sub.3 cycloalkyl and R.sup.10; Y.sub.5 is CR.sup.13R.sup.14, CR.sup.13R.sup.14—CH.sub.2 or CH.sub.2—CR.sup.13R.sup.14, wherein R.sup.13 and R.sup.14 are independently selected from H and CH.sub.3; and Y.sub.6 is CR.sup.13R.sup.14, CR.sup.13R.sup.14—CH.sub.2 or CH.sub.2—CR.sup.13R.sup.14, wherein R.sup.13 and R.sup.14 are independently selected from H and CH.sub.3.
[0247] In the compounds of formula (I), (II), (III), (IA) or (IIA), A can be:
##STR00076##
[0248] wherein * indicates the connection point to Z, Z′ or Z.sub.2 and ** indicates the other connection point from A in formula (I), (II), (III), (IA) or (IIA); R.sup.6 can be CN, F, Cl or

CF.sub.3; Y can be NH or O; and R.sup.2 can be:
##STR00077##
[0249] optionally substituted with one, two, three or four substituents independently selected from halo, OH, CN, oxo, —OC.sub.1-C.sub.4 alkyl, —OC.sub.3-C.sub.5 cycloalkyl, —Z.sub.3—R.sup.11 and R.sup.10, wherein C.sub.1-C.sub.4 alkyl and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN, wherein * indicates the connection point to Y in formula (I), (II), (III), (IA) or (IIA); Y.sub.5 is CR.sup.13R.sup.14, CR.sup.13R.sup.14—CH.sub.2 or CH.sub.2—CR.sup.13R.sup.14, wherein R.sup.13 and R.sup.14 are independently selected from H and CH.sub.3; and Y.sub.6 is CR.sup.13R.sup.14, CR.sup.13R.sup.14—CH.sub.2 or CH.sub.2—CR.sup.13R.sup.14, wherein R.sup.13 and R.sup.14 are independently selected from H and CH.sub.3.
[0250] In the compounds of formula (I), (II), (III), (IA) or (IIA), A can be:
##STR00078##
[0251] wherein * indicates the connection point to Z, Z′ or Z.sub.2 and ** indicates the other connection point from A in formula (I), (II), (III), (IA) or (IIA); R.sup.6 can CN, F, Cl or CF.sub.3; Y can be NH or O; and R.sup.2 can be:
##STR00079##
[0252] optionally substituted with one, two, three or four substituents independently selected from F, OH, CN, oxo, —OCH.sub.3, —OC.sub.3 cycloalkyl and R.sup.10, wherein * indicates the connection point to Y in formula (I), (II), (III), (IA) or (IIA); Y.sub.5 is CR.sup.13R.sup.14, CR.sup.13R.sup.14—CH.sub.2 or CH.sub.2—CR.sup.13R.sup.14, wherein R.sup.13 and R.sup.14 are independently selected from H and CH.sub.3; and Y.sub.6 is CR.sup.13R.sup.14, CR.sup.13R.sup.14—CH.sub.2 or CH.sub.2—CR.sup.13R.sup.14, wherein R.sup.13 and R.sup.14 are independently selected from H and CH.sub.3.
[0253] In the compounds of formula (I), (II), (III), (IA) or (IIA), A can be:
##STR00080##
wherein * indicates the connection point to Z, Z′ or Z.sub.2 and ** indicates the other connection point from A in formula (I), (II), (III), (IA) or (IIA); R.sup.6 can be CN, F, Cl or CF.sub.3; Y can be NH or O; and R.sup.2 can be:
##STR00081##
[0254] optionally substituted with one, two, three or four substituents independently selected from halo, OH, CN, oxo, —OC.sub.1-C.sub.4 alkyl, —OC.sub.3-C.sub.5 cycloalkyl, —Z.sub.3—R.sup.11 and R.sup.10, wherein C.sub.1-C.sub.4 alkyl and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN, wherein * indicates the connection point to Y in formula (I), (II), (III, (IA) or (IIA); Y.sub.5 is CR.sup.13R.sup.14. CR.sup.13R.sup.14—CH.sub.2 or CH.sub.2—CR.sup.13R.sup.14, wherein R.sup.3 and R.sup.14 are independently selected from H and CH.sub.3; and Y.sub.6 is CR.sup.13R.sup.14, CR.sup.13R.sup.14—CH.sub.2 or CH.sub.2—CR.sup.13R.sup.14, wherein R.sup.13 and R.sup.14 are independently selected from H and CH.sub.3.
[0255] In the compounds of formula (I), (II), (III), (IA) or (IIA), A can be:
##STR00082##
wherein * indicates the connection point to Z, Z′ or Z.sub.2 and ** indicates the other connection point from A in formula (I), (II), (III), (IA) or (IIA); R.sup.6 can CN, F, Cl or CF.sub.3; Y can be NH or O; and R.sup.2 can be:
##STR00083##
optionally substituted with one, two, three or four substituents independently selected from F, OH, CN, oxo, —OCH.sub.3, —OC.sub.3 cycloalkyl and R.sup.10, wherein * indicates the connection point to Y in formula (I), (II), (III), (IA) or (IIA); Y.sub.5 is CR.sup.13R.sup.14,

CR.sup.13R.sup.14—CH.sub.2 or CH.sub.2—CR.sup.13R.sup.14, wherein R.sup.13 and R.sup.14 are independently selected from H and CH.sub.3; and Y.sub.6 is CR.sup.13R.sup.14, CR.sup.13R.sup.14—CH.sub.2 or CH.sub.2—CR.sup.13R.sup.14, wherein R.sup.13 and R.sup.14 are independently selected from H and CH.sub.3.

[0256] In the compounds of formula (IIIA), A can be:

##STR00084##

[0257] wherein * indicates the connection point to the substituent comprising Y and ** indicates the other connection point from A in formula (IIIA); R.sup.6 can CN, F, Cl or CF.sub.3; Y can be NH or O; and R.sup.2 can be:

##STR00085##

[0258] optionally substituted with one, two, three or four substituents independently selected from F, OH, CN, oxo, —OCH.sub.3, —OC.sub.3 cycloalkyl and R.sup.10, wherein * indicates the connection point to Y in formula (IIIA); Y.sub.5 is CR.sup.13R.sup.14, CR.sup.13R.sup.14—CH.sub.2 or CH.sub.2—CR.sup.13R.sup.14, wherein R.sup.13 and R.sup.14 are independently selected from H and CH.sub.3; and Y.sub.6 is CR.sup.13R.sup.14, CR.sup.13R.sup.14—CH.sub.2 or CH.sub.2—CR.sup.13R.sup.14, wherein R.sup.13 and R.sup.14 are independently selected from H and CH.sub.3.

[0259] In the compounds of formula (IIIA), A can be:

##STR00086##

wherein * indicates the connection point to the substituent comprising Y.sub.1 and ** indicates the other connection point from A in formula (IIIA); R.sup.6 can be CN, F, Cl or CF.sub.3; Y can be NH or O; and R.sup.2 can be:

##STR00087##

[0260] optionally substituted with one, two, three or four substituents independently selected from halo, OH, CN, oxo, —OC.sub.1-C.sub.4 alkyl, —OC.sub.3-C.sub.5 cycloalkyl, —Z.sub.3—R.sup.11 and R.sup.10, wherein C.sub.1-C.sub.4 alkyl and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN, wherein * indicates the connection point to Y in formula (IIIA); Y.sub.5 is CR.sup.13R.sup.14. CR.sup.13R.sup.14—CH.sub.2 or CH.sub.2—CR.sup.13R.sup.14, wherein R.sup.13 and R.sup.14 are independently selected from H and CH.sub.3; and Y.sub.6 is CR.sup.13R.sup.14, CR.sup.13R.sup.14—CH.sub.2 or CH.sub.2—CR.sup.13R.sup.14, wherein R.sup.13 and R.sup.14 are independently selected from H and CH.sub.3.

[0261] In the compounds of formula (IIIA), A can be:

##STR00088##

wherein * indicates the connection point to the substituent comprising Y.sub.1 and ** indicates the other connection point from A in formula (IIIA); R.sup.6 can CN, F, Cl or CF.sub.3; Y can be NH or O; and R.sup.2 can be:

##STR00089##

[0262] optionally substituted with one, two, three or four substituents independently selected from F, OH, CN, oxo, —OCH.sub.3, —OC.sub.3 cycloalkyl and R.sup.10, wherein * indicates the connection point to Y in formula (IIIA); Y.sub.5 is CR.sup.13R.sup.14, CR.sup.13R.sup.14—CH.sub.2 or CH.sub.2—CR.sup.13R.sup.14, wherein R.sup.13 and R.sup.14 are independently selected from H and CH.sub.3; and Y.sub.6 is CR.sup.13R.sup.14, CR.sup.13R.sup.14—CH.sub.2 or CH.sub.2—CR.sup.13R.sup.14, wherein R.sup.13 and R.sup.14 are independently selected from H and CH.sub.3.

[0263] In one embodiment, the compounds of Formula (I) are selected from the group consisting of:

##STR00090## ##STR00091## ##STR00092##

or a pharmaceutically acceptable salt thereof,

wherein the bond at the * position is as represented,
##STR00093##
[0264] For example, for the compound of formula:
##STR00094##
where the bond at the * position is as represented,
##STR00095##
forms the compounds:
##STR00096##
[0265] In a further embodiment, the compounds of Formula (I) are selected from the group consisting of:
##STR00097## ##STR00098##
or a pharmaceutically acceptable salt thereof, where the bond at the * position is as represented,
##STR00099##
[0266] In a further embodiment, the compounds of Formula (I) are selected from the group consisting of:
##STR00100## ##STR00101## ##STR00102##
or a pharmaceutically acceptable salt thereof, where the bond at the * position is as represented,
##STR00103##
[0267] In a further embodiment, the compounds of Formula (I) are selected from the group consisting of:
##STR00104## ##STR00105##
or a pharmaceutically acceptable salt thereof, where the bond at the * position is as represented,
##STR00106##
[0268] In a further embodiment, the compounds of Formula (I) are selected from the group consisting of:
##STR00107## ##STR00108##
or a pharmaceutically acceptable salt thereof, where the bond at the * position is as represented,
##STR00109##
[0269] In a further embodiment, the compounds of Formula (I) are selected from the group consisting of:
##STR00110##
or a pharmaceutically acceptable salt thereof.
[0270] In a further embodiment, the compounds of Formula (I) are selected from the group consisting of:
##STR00111## ##STR00112## ##STR00113##
or a pharmaceutically acceptable salt thereof.
[0271] In a further embodiment, the compounds of Formula (I) are selected from the group consisting of:
##STR00114## ##STR00115##
or a pharmaceutically acceptable salt thereof.
[0272] In a further embodiment, the compounds of Formula (I) are selected from the group consisting of:
##STR00116## ##STR00117## ##STR00118## ##STR00119## ##STR00120## ##STR00121## ##STR00122## ##STR00123##
or a pharmaceutically acceptable salt thereof.
[0273] In a further embodiment, the compounds of Formula (I) are selected from the group consisting of:
##STR00124## ##STR00125## ##STR00126## ##STR00127## ##STR00128## ##STR00129## ##STR00130## ##STR00131## ##STR00132## ##STR00133## ##STR00134## ##STR00135## ##STR00136##

##STR00137##
or a pharmaceutically acceptable salt thereof.
[0274] The compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), provided herein, or a pharmaceutically acceptable salt thereof, any or all hydrogens present in the compound, or in a particular group or moiety within the compound, may be replaced by a deuterium or a tritium. Thus, a recitation of alkyl includes deuterated alkyl, where from one to the maximum number of hydrogens present may be replaced by deuterium. For example, ethyl refers to both C.sub.2H.sub.5 or C.sub.2H.sub.5 where from 1 to 5 hydrogens are replaced by deuterium, such as in C.sub.2D.sub.xH.sub.5-x.
[0275] The compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA) provided herein may form pharmaceutically acceptable salts. The Examples provided herein may form pharmaceutically acceptable salts. Such pharmaceutically acceptable salts are intended to be included. Pharmaceutically acceptable salts and common methodology for preparing them are well known in the art (see, e.g., P. Stahl, et al. *Handbook of Pharmaceutical Salts: Properties, Selection and Use,* 2.sup.nd Revised Edition (Wiley-VCH, 2011); S. M. Berge, et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Sciences*, Vol. 66, No. 1, January 1977).
[0276] The compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA) provided herein, or a pharmaceutically acceptable salt thereof, can be mixed with one or more pharmaceutically acceptable carriers, diluents, or excipients. More particularly, the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA) provided herein, or a pharmaceutically acceptable salt thereof, can be formulated as pharmaceutical compositions. Such pharmaceutical compositions and processes for preparing the same are well known in the art (see, e.g., *Remington: The Science and Practice of Pharmacy* (A. Gennaro, et al., eds., 21st ed., Mack Publishing Co., 2005)).
[0277] The compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA) provided herein, or a pharmaceutically acceptable salt thereof, and their pharmaceutical compositions can be administered by a variety of routes. Such routes of administration include oral and intravenous.
[0278] The compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA) provided herein, or a pharmaceutically acceptable salt thereof, can be combined with one or more other therapeutic agents.
[0279] The compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA) provided herein, or a pharmaceutically acceptable salt thereof, can be a component in a pharmaceutical composition for the treatment of cancer with one or more pharmaceutically acceptable carriers, diluents, or excipients, and optionally with one or more additional therapeutic agents.
[0280] The compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA) provided herein, or a pharmaceutically acceptable salt thereof, can be a component in a pharmaceutical composition for the treatment of cancer with one or more pharmaceutically acceptable carriers, diluents, or excipients, and optionally with one or more additional therapeutic agents.
[0281] The compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA) provided herein, or a pharmaceutically acceptable salt thereof, can be combined with one or more other therapeutic agents for simultaneous, separate or sequential administration.
[0282] The compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA) provided herein, or a pharmaceutically acceptable salt thereof, and their pharmaceutical compositions can be used in the methods described herein.
[0283] The compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA) provided herein, or a pharmaceutically acceptable salt thereof, are generally effective over a wide dosage range. For example, dosages per day normally fall within the range of about 0.5 to about 100 mg/kg of body weight. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, and therefore the above dosage range is not intended to limit the scope of the invention in any way. It will be understood that the amount of the compound actually administered will be

determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound or compounds administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms.
[0284] Certain compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), or a pharmaceutically acceptable salt thereof, selectively target FGFR2. For example, certain compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), or a pharmaceutically acceptable salt thereof, selectively target FGFR2 over another FGFR. For example, certain compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), or a pharmaceutically acceptable salt thereof, selectively target FGFR2 over FGFR1. For example, certain compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), or a pharmaceutically acceptable salt thereof, are at least about 3 fold (e.g. at least about 4-, 5-, 6-, 7-, 8-, 9-, 10-15-, 20-, 30-, 40-, 50-fold, or more) more selective for FGFR2 than for FGFR1.
[0285] As used herein, the term “selectivity” of a compound refers to the compound having more potent activity at the first target than the second target. A fold selectivity can be calculated by any method known in the art. For example, a fold selectivity can be calculated by dividing the IC.sub.50 value of a compound for the second target (e.g., FGFR1) by the IC.sub.50 value of the same compound for the first target (e.g., FGFR2). An IC.sub.50 value can be determined by any method known in the art. For example, an IC.sub.50 value can be determined as described in the assays below.
[0286] As used herein, the term “cancer” refers to or describes the physiological condition in patients that is typically characterized by unregulated cell proliferation. Included in this definition are benign and malignant cancers, primary and metastatic cancers.
[0287] As used herein, the term “FGFR2-associated cancer” refers to cancers associated with or having a dysregulation of the FGFR2 gene, the FGFR2 kinase protein, or expression or activity, or level of any of the same. Non-limiting examples of FGFR2-associated cancer are described herein. As used herein an “FGFR2-associated cancer” includes but is not limited to stomach cancer, hepatobiliary cancer, cancer of unknown primary, gallbladder cancer (e.g. gallbladder adenocarcinoma), bile duct cancer (e.g. intrahepatic bile duct cancer, extrahepatic bile duct cancer), sarcoma, esophagogastric cancer (e.g. gastroesophageal junction adenocarcinoma, gastric remnant adenocarcinoma), esophageal cancer (e.g. esophageal squamous cell cancer, esophageal adenocarcinoma), glioma (e.g. astrocytoma, oligodendroglioma, ependymoma), Non-Hodgkin Lymphoma (e.g. B-cell Non-Hodgkin Lymphoma), gastrointestinal stromal tumor, breast cancer (e.g. invasive ductal cancer, invasive lobular cancer), lung cancer (e.g. non-small-cell lung cancer, lung adenocarcinoma, squamous cell lung cancer and small-cell lung cancer), urothelial cancer, bladder cancer (e.g. urothelial bladder cancer, non-muscle invasive bladder cancer, muscle invasive bladder cancer), gastric cancer (e.g. gastric adenocarcinoma), pancreatic cancer (e.g. pancreatic adenocarcinoma), prostate cancer (e.g. prostate adenocarcinoma), colorectal cancer (e.g. colorectal adenocarcinoma, colon adenocarcinoma), multiple myeloma, liver cancer (e.g. hepatocellular cancer, fibrolamellar hepatocellular cancer), skin cancer (e.g. squamous cell skin cancer), melanoma (e.g. cutaneous melanoma), head and neck cancer (e.g. head and neck squamous cell cancer, hypopharyngeal cancer, laryngeal cancer, lip and oral cavity cancer, salivary gland cancer), glioblastoma, endometrial cancer (e.g. endometrial endometrioid adenocarcinoma), cervical cancer and ovarian cancer (e.g. epithelial ovarian cancer).
[0288] As used herein, the term “treating” (or “treatment”) refers to restraining, slowing, stopping, or reversing the progression or severity of an existing symptom, condition or disorder.
[0289] As used herein, the term “patient” refers to a mammal, particularly a human.
[0290] Provided herein, are compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), or a pharmaceutically acceptable salt thereof, for use in therapy.
[0291] Provided herein, are compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer.
[0292] Provided herein, are the use of compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), or

a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer.
[0293] Provided herein are methods of treating cancer, comprising administering to a patient in need of such treatment an effective amount of the compounds of formula (I), (II), (III), (IA), (IIA) or (IIIA), or a pharmaceutically acceptable salt thereof.
[0294] Provided in the methods and uses herein, the cancer is selected from the group consisting of stomach cancer, hepatobiliary cancer, cancer of unknown primary, gallbladder cancer (e.g. gallbladder adenocarcinoma), bile duct cancer (e.g. intrahepatic bile duct cancer, extrahepatic bile duct cancer), sarcoma, esophagogastric cancer (e.g. gastroesophageal junction adenocarcinoma, gastric remnant adenocarcinoma), esophageal cancer (e.g. esophageal squamous cell cancer, esophageal adenocarcinoma), glioma (e.g. astrocytoma, oligodendroglioma, ependymoma), Non-Hodgkin Lymphoma (e.g. B-cell Non-Hodgkin Lymphoma), gastrointestinal stromal tumor, breast cancer (e.g. invasive ductal cancer, invasive lobular cancer), lung cancer (e.g. non-small-cell lung cancer, lung adenocarcinoma, squamous cell lung cancer and small-cell lung cancer), urothelial cancer, bladder cancer (e.g. urothelial bladder cancer, non-muscle invasive bladder cancer, muscle invasive bladder cancer), gastric cancer (e.g. gastric adenocarcinoma), pancreatic cancer (e.g. pancreatic adenocarcinoma), prostate cancer (e.g. prostate adenocarcinoma), colorectal cancer (e.g. colorectal adenocarcinoma, colon adenocarcinoma), multiple myeloma, liver cancer (e.g. hepatocellular cancer, fibrolamellar hepatocellular cancer), skin cancer (e.g. squamous cell skin cancer), melanoma (e.g. cutaneous melanoma), head and neck cancer (e.g. head and neck squamous cell cancer, hypopharyngeal cancer, laryngeal cancer, lip and oral cavity cancer, salivary gland cancer), glioblastoma, endometrial cancer (e.g. endometrial endometrioid adenocarcinoma), cervical cancer and ovarian cancer (e.g. epithelial ovarian cancer). Particularly, the cancer is selected from the group consisting of stomach cancer, hepatobiliary cancer, cancer of unknown primary, gallbladder cancer (e.g. gallbladder adenocarcinoma), bile duct cancer (e.g. intrahepatic bile duct cancer, extrahepatic bile duct cancer), esophagogastric cancer (e.g. gastroesophageal junction adenocarcinoma, gastric remnant adenocarcinoma), esophageal cancer (e.g. esophageal squamous cell cancer, esophageal adenocarcinoma), glioma (e.g. astrocytoma, oligodendroglioma, ependymoma), breast cancer (e.g. invasive ductal cancer, invasive lobular cancer), lung cancer (e.g. non-small-cell lung cancer, lung adenocarcinoma, squamous cell lung cancer and small-cell lung cancer), gastric cancer (e.g. gastric adenocarcinoma), pancreatic cancer (e.g. pancreatic adenocarcinoma), colorectal cancer (e.g. colorectal adenocarcinoma, colon adenocarcinoma), liver cancer (e.g. hepatocellular cancer, fibrolamellar hepatocellular cancer), skin cancer (e.g. squamous cell skin cancer), melanoma (e.g. cutaneous melanoma), head and neck cancer (e.g. head and neck squamous cell cancer, hypopharyngeal cancer, laryngeal cancer, lip and oral cavity cancer, salivary gland cancer), glioblastoma, endometrial cancer (e.g. endometrial endometrioid adenocarcinoma) and ovarian cancer (e.g. epithelial ovarian cancer). More particularly, the cancer is selected from the group consisting of hepatobiliary cancer, cancer of unknown primary, gallbladder cancer (e.g. gallbladder adenocarcinoma), bile duct cancer (e.g. intrahepatic bile duct cancer, extrahepatic bile duct cancer), breast cancer (e.g. invasive ductal cancer, invasive lobular cancer), liver cancer (e.g. hepatocellular cancer, fibrolamellar hepatocellular cancer), skin cancer (e.g. squamous cell skin cancer), melanoma (e.g. cutaneous melanoma) and endometrial cancer (e.g. endometrial endometrioid adenocarcinoma). Most particularly, the cancer is selected from the group consisting of hepatobiliary cancer, gallbladder cancer (e.g. gallbladder adenocarcinoma), bile duct cancer (e.g. intrahepatic bile duct cancer, extrahepatic bile duct cancer), breast cancer (e.g. invasive ductal cancer, invasive lobular cancer), liver cancer (e.g. hepatocellular cancer, fibrolamellar hepatocellular cancer and endometrial cancer (e.g. endometrial endometrioid adenocarcinoma).
[0295] The compounds provided herein can be prepared as illustrated in the preparations and examples below.
##STR00138##
[0296] Scheme A depicts the preparation of compound (A8), where R.sub.1′ is defined as C.sub.1-

C.sub.3 alkyl, through multiple synthetic routes that lead to compound (A11) and will be further elaborated to Formula 1. Alcohol (A1) may react with mesyl chloride or tosyl chloride to afford compound (A2a) or (A2b), that may be further reacted with (A3a) to provide (A4). Treatment of compound (A4) with LDA and an appropriate alkylating agent may afford compound (A8). Alternatively, compound A8 may be directly synthesized by alkylating compound A3b with mesylate A2a or tosylate A2b to afford compound A8.

[0297] Compound (A8) may also be synthesized through an alternative route as depicted in Scheme 1. Alcohol (A1) may react under Mitsunobu conditions to provide azide (A5). Azide (A5) may be condensed with a beta-keto ester to afford triazole ester (A6) that can undergo saponification to provide carboxylic acid (7). Treatment of carboxylic acid (A7) with bromine in the presence of base affords compounds of (A8).

[0298] Scheme 1 further depicts the preparation of compounds of (A11). Compounds of (A8) may be deprotected to give (A9). Reacting compound (A9) with an appropriate ketone (A10) under reductive amination conditions affords compounds of (A11). R.sub.1′ is defined as C.sub.1-C.sub.3 alkyl.

##STR00139##

[0299] Scheme A1 depicts an alternative route to obtain compounds of (A8). Reaction of (A5) in the presence of trimethyl(prop-1-yn-1-yl)silane under microwave conditions may afford trimethylsilyl analogs of (A5a). Treatment of (A5a) with NBS in the presence of SiO.sub.2 may afford compounds of (A8).

##STR00140##

[0300] Scheme A2 depicts the preparation of compound (A2i′), where R.sub.1′ is defined as C.sub.1-C.sub.3 alkyl, that will be further elaborated to Formula 1. O-protected cyclobutan-1-one (A2a′) may be reacted in the presence of NaBH.sub.4 to afford alcohol (A2b′). Formation of the azide (A2c′) may be accomplished by reacting the alcohol (A2b′) with PPh.sub.3 and DIAD followed by DPPA. Reaction of azide (A2c′) with ethyl acetoacetate may yield ester (A2d′). Hydrolysis of (A2d′) under basic conditions may afford acid (A2e′) which then may be subjected to bromination under basic conditions to provide bromide (A2f′). Removal of the protecting group from (A2f′) may afford alcohol (A2g′). Oxidation of alcohol (A2g′) may afford ketone (A2h′) which may then be reacted under reductive amination conditions to afford (A2i′).

##STR00141##

[0301] Scheme A3 depicts the preparation of compound (A3h′) that will be further elaborated to Formula 1. A solution of (A3a′) may be reacted with N-diazo-1,1,1-trifluoro-methanesulfonamide in the presence of copper sulfate and NaHCO.sub.3 to afford azide (A3b′). Treatment of the azide in the presence of trimethyl(prop-1-yn-1-yl)silane under microwave conditions may provide (A3c′). Formation of bromide (A3d′) may be accomplished by treatment of (A3c′) with NBS in the presence of SiO.sub.2. Subjecting (A3d′) to Mitsunobu conditions with p-nitrobenzoic acid may yield ester (A3f′). Hydrolysis of the ester (A3e′) under basic conditions may provide alcohol (A3f′). Formation of triflate (A3g′) may result when the alcohol (A3f′) is treated with (trifluoromethane)sulfonyl trifluoromethanesulfonate in the presence of a base. Displacement of triflate (A3g′) with an appropriate amine may afford (A3h′)

##STR00142##

[0302] Scheme B depicts the preparation of compounds B6, B8, B9 and B10 that will be further elaborated to Formula 1. Compounds of (B10) and (B10a) may be further elaborated to Formula 2, Formula 3, Formula 4 or Formula 4a.

[0303] Compound (B2) may be synthesized starting from either halide (B1a) or (B1b) and reacting either one of these halides with tributyl(1-ethoxyethenyl)stannane under palladium catalyzed conditions. Hydrolysis of ethoxyvinly (B2) may afford ketone (B5). Ketone (B5) may be reduced to afford alcohol (B6) which is then reacted with MsCl to afford mesylate (B8) or chloride (B9).

[0304] Alternatively, compounds of (B6) may be synthesized by reacting aldehyde (B7) with the

appropriate Grignard reagent to provide alcohol (B6). A third alternative route to compounds of (B6) may be accomplished by treatment of halide (Bib) with lithium dibutyl(methyl) magnesite followed by the addition of acetaldehyde to afford alcohol (B6).
[0305] Treatment of ketone (B5) with phenyltrimethylammonium bromide may provide the alpha-bromo ketone (B10). Alternatively, the alpha-bromo ketone (B10) may be formed by the reaction of ethoxyvinyl (B2) in the presence of NBS in aq THF.
##STR00143##
[0306] Scheme B1 depicts an alternative route to alpha-halo ketones of (B10a) that will be further elaborated to Formula 1. Treatment of (Bib) with i-PrMgCl followed by the addition of chloro-N-methoxy-N-methylacetamide may afford (B10a) which may be further elaborated to compounds of Formula (I).
##STR00144##
[0307] Scheme C depicts the preparation of compounds (C5) that will be further elaborated to Formula 1. Treatment of compound (C1) with i-PrMgCl followed by the addition of aldehyde (C2) may provide alcohol (C3). Reaction of alcohol (C3) by the addition of potassium t-butoxide in the presence of methyl iodide may afford compound (C4) which is then deprotected to provide alcohol (C5).
##STR00145##
[0308] Scheme depicts the preparation of compounds (C1e) that will be further elaborated to Formula 1. Reaction of ethenyl (C1a) in the presence of K.sub.2OsO.sub.4 and NMO may afford the bis alcohol (C1b). The primary alcohol of (C1a) may be protected by treatment with SEM-Cl in the presence of a base which may provide (C1b). The secondary alcohol of (C1b) may be alkylated with methyl iodide under silver catalyzed conditions which may afford the ether (C1d). Removal of the protecting group of (C1d) under acidic conditions may provide the primary alcohol (C1e).
##STR00146##
[0309] Scheme D depicts the preparation of compound (D7) that will be further elaborated to Formula 1. Treatment of methyl 3,3-difluorocyclobutane-1-carboxylate with KHMDS in the presence of fluoro (D1), where X═Br, may provide ester (D2). The reduction of ester (D2) to alcohol (D4) is accomplished by treatment with LiBH.sub.4. Protection of alcohol (D4) with DHP and a catalytic amount of TsOH may afford the tetrahydropyran (D5). Reaction of tetrahydropyran (D5) with n-BuLi followed by addition of NFSI may afford (D6). Removal of the protecting group under acidic conditions may afford alcohol (D7).
##STR00147##
[0310] Scheme E depicts the preparation of compounds (E1) and (E6) that will be further elaborated to Formula 1. Compounds of (E6) may be synthesized by reaction of (E2) with POCl.sub.3 to provide halogenated (E3). Treatment of (E3) with tributyl(1-ethoxyethenyl)stannane under palladium catalyzed conditions may afford ethoxyvinyl (E4). Reaction of benzylamine with (E4) may provide N-benzyl protected (E5). Deprotection of (E5) may provide amine (F6).
[0311] Compounds of (E1) may be synthesized by treatment of (B5) with NH.sub.4OAc.
##STR00148##
[0312] Scheme F depicts the preparation of compound (F5) that will be further elaborated to Formula 1. Reaction of (F1) with methyl 2,2-difluoro-2-(fluorosulfonyl)acetate in the presence of CuI may provide (F2). Treatment of (F2) with bis(pinacolato)diboron under palladium catalyzed conditions may afford boronate ester (F3). Palladium catalyzed coupling with the appropriate bromide with boronate ester (F3) may provide (F4) which is then demethylated with NDM to afford (F5).
##STR00149##
[0313] Scheme G depicts the preparation of compound (G5) that will be further elaborated to Formula 1. Reaction of (G1) with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) may provide (G2), wherein R.sup.6 is defined as R.sup.6═F. Treatment of

(G2) with bis(pinacolato)diboron under palladium catalyzed conditions may afford boronate ester (F3). The coupling of boronate ester (F3) with the appropriate bromide in the presence of a palladium catalyst may provide (G4). Demethylation of (G4) with NDM may afford (G5).
##STR00150##
[0314] Scheme H depicts multiple methods for the preparation of the compounds (H4) and (H6), that will be further elaborated to Formula 1. Compound (G1), where Hal is defined as Hal=halogen, may be reacted with bis(pinacolato)diboron under palladium catalyzed conditions to provide boronate ester (H1). The boronate ester (H1) is coupled with the appropriate bromide in the presence of a palladium catalyst to provide (H2). Chlorination of (H2) with NSC may provide (H3), where R.sub.6 is defined as R.sub.6=Cl, which is then demethylated with NDM to afford (H4). Deprotection of (H4) under acidic conditions may yield (H5), which may then be subjected to reductive amination conditions with the appropriate ketone to provide (H6). Alternatively, boronate ester (H1), where R.sub.6 is defined as R.sub.6=H, may be coupled with the appropriate bromide to provide (H7). Chlorination of (H7) may be accomplished by treatment with NCS to afford (H8), where R.sub.6 is defined as R.sub.6=Cl. Demethylation of (H8) with NDM may afford (H6). Scheme H also depicts multiple methods for the preparation of the compounds (H4) and (H6), where R.sub.6 is defined as R.sub.6=CN, and Hal is defined as Hal=Br, that will be further elaborated to Formula (I). Compound (G1) may be reacted with bis(pinacolato)diboron under palladium catalyzed conditions to provide boronate ester (H1). The boronate ester (H1) is coupled with the appropriate bromide in the presence of a palladium catalyst to provide (H2). Subjecting (H2) with NDM may afford demethylated (H4). Deprotection of (H4) under acidic conditions may yield (H5), which may then be subjected to reductive amination conditions with the appropriate ketone to provide (H6). Alternatively, boronate ester (H1) may be coupled with the appropriate bromide to provide (H7). Demethylation of (H7) with NDM may afford (H6).
##STR00151##
[0315] Scheme J depicts the preparation of compounds of Formula 1. (J1) may be alkylated with halogens of (B8), (B10), (B10a) or with mesylates of (B9) to afford (K2). Alternatively, reaction of alcohols of (C1e), (C5) or (D7) under Mitsunobu conditions may also provide (J2). Deprotection of (J2) under acidic conditions may yield (J3) which is then subjected to reductive amination conditions with the appropriate ketone to afford compounds of Formula 1. Alternatively, compounds of Formula 1 may be synthesized by alkylation of (J4) with halogens of (B8), (B10), (B10a) or with mesylates of (B9) or alternatively, with reaction of alcohols of (C1e), (C5) or (D7) under Mitsunobu conditions. One skilled in the art may recognize that compound (J1) may be interchanged with compounds of (G5) or (H4). Additionally, one skilled in the art may recognize that compound (J4) may be interchanged with compounds of (F5) or (H6).
##STR00152##
[0316] Scheme K depicts the preparation of compounds of Formula 1. Reaction of (K1) and Hal is defined as Hal=Br, may be alkylated with halides of (B8), (B10), (B10a) or mesylates of (B9) to provide (L2). Treatment of (K2) with bis(pinacolato)diboron under palladium catalyzed conditions may afford boronate ester (K3). Palladium catalyzed coupling of (K3) with the appropriate bromide, (A2i′) or (A3h′) may provide compounds of Formula (I). Alternatively, compounds of Formula (I) may be synthesized by the palladium catalyzed coupling of (K3) with the appropriate bromide to yield (K4). Deprotection of (K4) under acidic conditions may afford (K5) which may be subjected to reductive amination conditions with the appropriate ketone to provide compounds of Formula 1.
##STR00153##
[0317] Scheme K1 depicts an alternative preparation of compound (K3) that may be taken on to Formula 1. Reaction of (K1) under Mitsunobu conditions may afford ketone (K1a). Reduction of the ketone (K1a) may afford alcohol (K1b) which may be alkylated with the appropriate alkylating agent to afford ether (K1c). Treatment of (K1b) or (K1c) with bis(pinacolato)diboron under

palladium catalyzed conditions may afford (K3). Alternatively, (K1a) may be reacted with the appropriate Grignard reagent to provide (K1d). Treatment of (Kid) with bis(pinacolato)diboron under palladium catalyzed conditions may afford (K3).

##STR00154##

[0318] Scheme L depicts two methods for the preparation of compounds of Formula 1. In the first method, treatment of (L1) with NIS may afford (L2) which is then reacted with CuCN to provide (L3). Reaction of (L3) with amine (F4) in the presence of an organic base may yield (L4). Treatment of (L4) with bis(pinacolato)diboron under palladium catalyzed conditions may afford boronate ester (L5). Palladium catalyzed coupling of (L5) with the appropriate bromide may provide compounds of Formula 1. Alternatively, in the second method, compounds of Formula 1 may be synthesized by the palladium catalyzed coupling of (L5) with the appropriate bromide to yield (L7). Deprotection of (L7) under acidic conditions may afford (L8) which may be subjected to reductive amination conditions with the appropriate ketone to provide compounds of Formula 1. For compounds of Formula 1 the enantiomers may be separated by chiral chromatography.

[0319] Scheme L also depicts the preparation of compounds of Formula 1. Treatment of (L3) with amine (F4) or (F5) under palladium catalyzed conditions may yield (L4). Reaction of (L4) with bis(pinacolato)diboron under palladium catalyzed conditions may afford boronate ester (L5). Palladium catalyzed coupling of (L5) with the appropriate bromide may provide compounds of Formula 1. For compounds of Formula 1 the enantiomers may be separated by chiral chromatography.

##STR00155##

[0320] Scheme M depicts the preparation of compounds of Formula 1 where R.sub.6 is defined as R.sub.6=Cl and X.sub.1, X.sub.2 and X.sub.3 are defined as X.sub.2=N, X.sub.1 and X.sub.3=C. Treatment of (M1), where Hal is defined as Cl and Y is defined 0, with chloroacetaldehyde in the presence of a base may result in (M2). Reaction of (M2) with bis(pinacolato)diboron under palladium catalyzed conditions may afford the boronic acid (M3). Palladium catalyzed coupling of (M3) with the appropriate bromide may yield (M4). Demethylation of (M4) with NDM may afford (M5) which may then be reacted with alcohols of (C1e) or (C5) under Mitsunobu conditions to provide (M6). Deprotection of (M6) under acidic conditions may afford (M7) which is then subjected to reductive amination conditions with the appropriate ketone to provide compounds of Formula 1. For compounds of Formula 1 the enantiomers may be separated by chiral chromatography.

##STR00156##

[0321] Scheme N depicts two methods for the preparation of compounds of Formula 2. In the first method (N1) may be alkylated with alpha-bromo ketone (B10) or (B10a) to afford (N2). Subsequent deprotection of (N2) under acidic conditions may yield (N3) which then may be reacted with an appropriate ketone to provide compounds of Formula 2. In the second method (N6) may be alkylated with alpha-bromo ketone (B10) or (B10a). For compounds of Formula 2 the enantiomers may be separated by chiral chromatography.

[0322] Compounds of Formula 3 may be synthesized by the treatment of compounds of Formula 2 with the appropriate Grignard reagent to provide compounds of Formula 3. For compounds of Formula 3 the enantiomers may be separated by chiral chromatography.

[0323] Compounds of Formula 4 may be synthesized by two routes. In the first route, reduction of the ketone for compounds of Formula 2 may be accomplished by treatment with NaBH.sub.4 to provide compounds of Formula 4. In the second route, the ketone (N2) may be reduced with NaBH.sub.4 to provide (N4) which may be deprotected under acidic conditions to afford (N5). Treatment of (N5) with the appropriate ketone under reductive amination conditions may yield compounds of Formula 4. For compounds of Formula 4 the enantiomers may be separated by chiral chromatography.

[0324] One skilled in the art may recognize that compounds of (N1) may be interchanged with

compounds of (G5) or (H4). Additionally, one skilled in the art may also recognize that compounds of (N6) may be interchanged with compounds of (F5).
[0325] Compounds of Formula (4a) may be synthesized by reacting trimethylsulfoxonium iodide in the presence of a base followed by the addition of compounds of Formula 4.
##STR00157##
[0326] Scheme N1 depicts the asymmetric synthesis of compounds of Formula 4b and 4c. The asymmetric reduction of ketone (N2) may be accomplished by treatment with chloro(n-[(1R,2R)-2-[(S)-[2-[[1,2,3,4,5,6-η)-4-methylphenyl]methoxy]ethyl]amino]-1,2-diphenyl ethylmethanesulfonamidato) ruthenium(II) to afford alcohol (N4a). Deprotection of (N4a) under acidic conditions may yield the amine (N5a). Reductive amination of (N5a) with the appropriate ketone may afford compounds of Formula 4b.
[0327] Alkylation of alcohol (N4a) with the appropriate alkylating agent may provide alkyl ether (N4b). Subsequent deprotection of (N4b) under acidic conditions may yield amine (N4c). Reductive amination of (N4c) with the appropriate ketone may provide compounds of Formula 4c.
##STR00158##
[0328] Scheme N2 depicts an alternative preparation for compounds of Formula 3. Ketone (N.sub.2) may be reacted with a Grignard reagent to afford the tertiary alcohol (N2a). Removal of the protecting group of (N2a) under acidic conditions may afford the amine (N2b). Subjecting (N2b) under reductive amination conditions with an appropriate ketone may afford compounds of Formula 3.
[0329] In cases where R.sub.6=H for (N2a), treatment with NCS may provide compounds where R.sub.6=Cl for (N2b′). Subsequent treatment of (N2b′) under acidic conditions may afford the amine (N2b).
##STR00159##
[0330] Scheme depicts an alternative route or the synthesis of compounds of Formula 4c. Alkylation of the alcohol (N4) with an appropriate alkylating agent may afford the alkyl ether (N4a′). Deprotection of (N4a′) under acidic conditions may provide the amine (N4b′) which is then reacted with the appropriate ketone under reductive amination conditions to afford compounds of Formula 4c.
##STR00160##
[0331] Scheme P depicts the preparation of compounds of Formula 6 or Formula 7. For the preparation of compounds of Formula 6, compounds of Formula 4 may be reacted with NaH followed by treatment with the appropriate alkylating agent to afford compounds of Formula 6. For the preparation of compounds of Formula 6, compounds of Formula 4 may be reacted with MsCl to provide (P1). Subsequent treatment of (P1) with an appropriate amine provides compounds of Formula 7.
##STR00161##
[0332] Scheme P1 depicts an alternative preparation for compounds of Formula 7. The mesylate (P1a) may be prepared by the reaction of (N4) with methane sulfonyl chloride. Displacement of the mesylate (P1a) with an amine may afford the alkyl amino (P1b). Deprotection of (P1b) under acidic conditions may lead to the amine (P1c) which is the reacted with the appropriate ketone under reductive amination conditions to afford compounds of Formula 7.
[0333] Certain stereochemical centers have been left unspecified and certain substituents have been eliminated in the following schemes for the sake of clarity and are not intended to limit the teaching of the schemes in any way. Furthermore, individual isomers, enantiomers, and diastereomers may be separated or resolved by one of ordinary skill in the art at any convenient point in the synthesis of compounds of the invention, by methods such as selective crystallization techniques or chiral chromatography (See for example, J. Jacques, et al., “*Enantiomers, Racemates, and Resolutions*”, John Wiley and Sons, Inc., 1981, and E. L. Eliel and S. H. Wilen, “*Stereochemistry of Organic Compounds*”, Wiley-Interscience. 1994). The designations “isomer 1”

and “isomer 2” refer to the compounds that elute from chiral chromatography first and second, respectively, under the conditions described herein and if chiral chromatography is initiated early in the synthesis, the same designation is applied to subsequent intermediates and examples. Additionally, the intermediates described in the following schemes may contain a number of nitrogen or oxygen protecting groups. The variable protecting group may be the same or different in each occurrence depending on the particular reaction conditions and the particular transformations to be performed. The protection and deprotection conditions are well known to the skilled artisan and are described in the literature (See for example “*Greene's Protective Groups in Organic Synthesis*”, Fourth Edition, by Peter G. M. Wuts and Theodora W. Greene, John Wiley and Sons, Inc. 2007).

[0334] The designation “isomer 1” was also used where ketones had been subjected to asymmetric reduction using ruthenium catalysts which are described herein. The same designation was applied to subsequent intermediates and examples unless the examples had been subjected to chiral chromatography. The asymmetric reduction of ketones to secondary alcohols using ruthenium catalysts is known in the literature (See for example “J. Am. Chem. Soc. 2011, 133, 14960-14963).

[0335] “AcOH” refers to acetic acid; “AcCN” refers to acetonitrile; “NH.sub.4OAc” refers to ammonium acetate; “NH.sub.4OH” refers to ammonium hydroxide; “aq” refers to aqueous; “BPR” refers to back pressure regulator; “NBS” refers to N-bromosuccinimide; “nBuOH” refers to 1-butanol; “n-BuLi” refers to n-butyl lithium; “DCDMH” refers to 1,3-dichloro-5,5-dimethyl-2,4-imidazolidinedione; “NCS” refers to N-chloro succinimide; “conc” refers to concentrated; “cHex” refers to cyclohexane; “DE” refers to diatomaceous earth; “DHP” refers to 3,4-dihydropyran; “DIAD” refers to diisopropyl azodicarboxylate; “DDQ” refers to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; “DCE” refers to 1,2-dichloroethane; “DCM” refers to dichloromethane; “DEA” refers to diethylamine; “Et.sub.2O” refers to diethyl ether; “DIPEA” refers to diisopropylethylamine; “DIEA” refers to diisopropylethylamine; “ex” refers to example; “DMA” refers to dimethylacetamide; “DME” refers to 1,2-dimethoxyethane; “HATU” refers to N-[(dimethylamino)-1H-1,2,3-triazolo-[4,5-b]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide; “NDM” refers to 1-dodecanethiol; “DMEA” refers to dimethylethyl amine: “NMO” refers to N-methylmorpholine N-oxide; “Et.sub.2O” refers to diethyl ether; “DMF” refers to N,N-dimethylformamide; “DMSO” refers to dimethyl sulfoxide; “dppf” refers to 1′-bis(diphenylphosphino)ferrocene; “DPPA” refers to diphenylphosphoryl azide; “EtOH” refers to ethanol; “EA” refers to ethyl acetate; “EtMgBr” refers to ethylmagnesium bromide; “NFSI” refers to N-fluorobenzene sulfonimide; “FA” refers to formic acid; “h” refers to hour(s); “hal” refers to halogen; “NIS” refers to N-iodo succinimide; “IPA” refers to isopropyl alcohol; “IPAm” refers to isopropylamine; “i-PrMgCl” refers to isopropyl magnesium chloride; “L” refers to liter(s); “LDA” refers to lithium diisopropylamide; “MsCl” refers to methanesulfonyl chloride; “MeMgBr” refers to methylmagnesium bromide; “MTBE” refers to methyl tert-butyl ether; “MeTHF” refers to 2-methyltetrahydrofuran; “ml” refers to milliliter; “min” refers to minute(s); ‘M’ refers to molar; “PdCl.sub.2(DtBPF)” refers to [1,1′-bis(di-tert-butyl phosphino)ferrocene]dichloropalladium(II); “KHMDS” refers to potassium bis(trimethylsilyl)amide; “Pd(PPh.sub.3).sub.4” refers tetetrakis(triphenylphosphine) palladium (0); “Pd(dppf)Cl2” refers to (1,1′-bis(diphenylphosphino)ferrocene) palladium(II) dichloride; “Pd.sub.2(dba).sub.3” refers to tris (dibenzylidene acetone)dipalladium (0): “PE” refers to petroleum ether; “POCl.sub.3” refers to phosphorus oxychloride; “KOAc” refers to potassium acetate; “t-BuOK” refers to potassium t-butoxide; “RT” refers to room temperature; “t.sub.R” refers to retention time; “sat” refers to saturated; “NaOMe” refers to sodium methoxide; “Na(OAc).sub.3BH” sodium triacetoxyborohydride; “sat.” refers to saturated; “soln” refers to solution; “SFC” refers to supercritical fluid chromatography; “THF” refers to tetrahydrofuran; “SOCl.sub.2” refers to thionyl chloride; “TsOH” refers to p-toluenesulfonic acid; “NEt.sub.3” and “Et.sub.3N” refers to triethylamine; “Et.sub.3Si” refers to triethylsilane; “TFA” refers to trifluoroacetic acid; “SEM-Cl”

refers to 2-(trimethylsilyl)ethoxymethyl chloride; “PPh.sub.3” refers to triphenylphosphine; “Dess-Martin” refers to 1,1,1-Tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one; “Xphos Palladacycle Gen 4” refers to chloro(2-dicyclohexyl phosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl) [2-(2-aminoethyl)phenyl)]palladium(II); “XPhos Pd G4” refers to dicyclohexyl-[2-[2,4,6-tri(propan-2-yl)phenyl]phenyl]phosphonium; methanesulfonic acid; N-methyl-2-phenylaniline; palladium; “ACN” refers to acetonitrile; “CAN” refers to acetonitrile; “NSC” refers to N-chloro succinimide.

TABLE-US-00001 TABLE A Analytical chiral chromatography methods. Analytical Method Column Dimensions Elution Conditions A Chiralpak AD 3 × 100 mm, 3 μm 40% IPA (0.2% IPAm) in CO.sub.2 B Chiralpak IA 3 × 100 mm, 3 μm 25% to 50% EtOH (0.2% IPAm) in CO.sub.2 for 2.5 min then 50% EtOH (0.2% IPAm) in CO.sub.2 C Chiralpak AD 3 × 100 mm, 3 μm 10% to 50% EtOH (0.2% IPAm) in CO.sub.2 for 0.40 min then 50% EtOH (0.2% IPAm) in CO.sub.2 D Chiralcel OJ 3 × 100 mm, 3 μm 10% to 50% MeOH (0.2% IPAm) in CO.sub.2 for 2.50 min then 50% EtOH (0.2% IPAm) in CO.sub.2 E Chiralcel OJ 4.6 × 150 mm, 5 μm MeOH (0.2% DMEA) F Chiralcel OJ 3 × 100 mm, 3 μm 10% to 50% MeOH (0.2% IPAm) in CO.sub.2 for 0.40 min then 50% MeOH (0.2% IPAm) in CO.sub.2 G Chiralpak IA 3 × 100 mm, 3 μm 40% IPA (0.2% IPAm) in CO.sub.2 H Chiralpak AD 3 × 100 mm, 3 μm 10% to 50% IPA (0.2% IPAm) in CO.sub.2 for 0.40 min then 50% IPA (0.2% IPAm) in CO.sub.2 I Chiralpak AD 3 × 100 mm, 3 μm 45% EtOH (0.2% IPAm) in CO.sub.2 J Chiralpak AD 3 × 100 mm, 3 μm 10% to 50% EtOH (0.2% IPAm) in CO.sub.2 for 2.50 min then 50% EtOH (0.2% IPAm) in CO.sub.2 K Chiralpak IH 3 × 100 mm, 3 μm 10% to 50% EtOH (0.2% IPAm) in CO.sub.2 for 2.50 min then 50% EtOH (0.2% IPAm) in CO.sub.2 L Chiralpak AD 3 × 100 mm, 3 μm 45% IPA (0.2% IPAm) in CO.sub.2 M Chiralcel OD 3 × 100 mm, 3 μm 10% to 50% IPA (0.2% IPAm) in CO.sub.2 for 2.5 min then 50% IPA (0.2% IPAm) in CO.sub.2 N Chiralpak IH 3 × 100 mm, 3 μm 10% to 50% MeOH (0.2% IPAm) in CO.sub.2 for 2.5 min then 50% MeOH (0.2% IPAm) in CO.sub.2 P Chiralpak IA 3 × 100 mm, 3 μm 25% to 50% IPA (0.2% IPAm) in CO.sub.2 for 2.5 min then 50% IPA (0.2% IPAm) in CO.sub.2 Q Chiralpak AD 3 × 100 mm, 3 μm 40% MeOH (0.2% IPAm) in CO.sub.2 R Chiralcel OD 3 × 100 mm, 3 μm 45% MeOH (0.2% IPAm) in CO.sub.2 S Chiralpak AD 3 × 100 mm, 3 μm 10% to 50% IPA (0.2% IPAm) in CO.sub.2 for 2.5 min then 50% IPA (0.2% IPAm) in CO.sub.2

Preparation 1

tert-Butyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate

##STR00162##

[0336] A MeOH soln (50 ml) of tert-butyl 6-oxo-2-azaspiro[3.3]heptane-2-carboxylate (3.6 g, 17 mmol) was cooled to 0° C. and treated in portions with NaBH.sub.4 (1.0 g, 26 mmol). Allowed the reaction to stir overnight slowly warming to RT. The reaction was diluted with EA (100 ml), washed with saturated aq NaHCO.sub.3 (2×100 ml), and brine (100 ml). The organic layer was collected, dried over MgSO.sub.4, filtered, and concentrated to obtain the title compound (3.1 g, 85%) as a white solid. MS ES+ m/z 158 [MH-.sup.tBu].sup.+.

[0337] The following compounds were prepared in a manner essentially analogous to the method of Preparation 1 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00002 TABLE 1 Prep .sup.1H NMR # Chemical Name Structure (400 MHz, CDCl.sub.3) δ 2 Tert-Butyl 4- hydroxyazepane-1- carboxylate [00163]  3.90 (brs, 1H), 3.56- 3.17 (m, 4H), 2.06- 1.81 (m, 3H), 1.80- 1.61 (m, 3H), 1.48 (s, 9H), 1.40-1.35 (m, 1H). 3 tert-Butyl (1R,5S)-3- hydroxy-8- azabicyclo[3.2.1]octane- 8-carboxylate [00164] 4.36-4.01 (m, 3H), 2.25-1.85 (m, 5H), 1.72 (d, J = 14.7 Hz, 1H), 1.67-1.58 (m, 2H), 1.48 (d, J = 5.2 Hz, 9H), 1.46-1.36 (m, 1H)

Preparation 4

tert-Butyl 6-methylsulfonyloxy-2-azaspiro[3.3]heptane-2-carboxylate

##STR00165##

[0338] A soln of tert-butyl 6-hydroxy-2-azaspiro[3.3]heptane-2-caroxyate (3.1 g, 15 mmol) in DCM (35 ml) cooled to 0° C. was treated with Et.sub.3N (3.6 ml, 26 mmol) followed by the dropwise addition of methanesulfonyl chloride (1.5 ml, 19 mmol). The reaction was allowed to stir at 0° C. and slowly warm to RT. After stirring for 1 h, the reaction was diluted with EA (75 ml), washed with 50% brine (100 mL), collected, dried over MgSO.sub.4, filtered, and concentrated to obtain the title compound (4.3 g, 87%) as a white solid which was used without purification. MS ES+ m/z 236 [MH-.sup.tBu].sup.+.

[0339] The following compounds were prepared in a manner essentially analogous to the method of Preparation 4 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00003 TABLE 2 Prep MS ES+ # Chemical Name Structure m/z 5 tert-Butyl 2-methylsulfonyloxy-7- azaspiro[3.5]nonane-7- carboxylate [00166]embedded image 6 tert-Butyl 4- methylsulfonyloxyazepane- 1-carboxylate [00167]embedded image 238 [M + H − tBu].sup.+ 7 [(1S)-1-[5- (Trifluoromethyl)-3- pyridyl]ethyl] methanesulfonate [00168]embedded image 270 [M + H].sup.+

Preparation 8

Benzyloxycyclobutanol

##STR00169##

[0340] A mixture of 3-(benzyloxy)cyclobutan-1-one (20 g, 113.5 mmol) and NaBH.sub.4 (4.29 g, 113.5 mmol) in MeOH (50 ml) was stirred for 2 h at RT under N.sub.2. The reaction was quenched with H.sub.2O at 0° C., extracted with EA (3×100 ml), washed with brine (2×100 ml), dried over Na.sub.2SO.sub.4, and filtered. The filtrate was concentrated under reduced pressure to afford the title compound (20 g, 99%) as a light-yellow oil. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ 7.42-7.21 (m, 5H), 4.45 (s, 2H), 3.93-3.85 (m, 1H), 3.71-3.62 (m, 1H), 2.82-2.63 (m, 2H), 1.97-1.92 (m, 2H).

Preparation 9

tert-Butyl (1R,5S)-3-azido-8-azabicyclo[3.2.1]octane-8-carboxylate

##STR00170##

[0341] A mixture of tert-butyl (1R,5S)-3-(p-tolylsulfonyloxy)-8-azabicyclo[3.2.1]octane-8-carboxylate (4.5 g, 12 mmol) in DMSO (79 ml) was sonicated to help solubilize the solid and then treated with NaN.sub.3 (4 M in H.sub.2O, 4.1 ml, 17 mmol). 80 mL of this soln was then passed through a Uniqsis Flowsyn system which consisted of a 14 ml Teflon reactor (1/16″) with a residence time of 40 min, a temperature of 135° C., and a BPR of 10 bar. The reaction was diluted with H.sub.2O (200 mL) and extracted with EA (2×100 ml). The combined organics were dried over MgSO.sub.4, filtered, and concentrated to obtain the title compound as a soln in DMSO which was used in the next synthetic step without purification and assuming 100% conversion.

Preparation 10

tert-Butyl (4R)-4-azido-3,3-difluoro-piperidine-1-carboxylate

##STR00171##

[0342] A solution of tert-butyl (4R)-4-amino-3,3-difluoro-piperidine-1-carboxylate (2 g, 8.47 mmol) and K.sub.2CO.sub.3 (1.99 g, 14.39 mmol) in MeOH (20 ml) was treated with CuSO.sub.4.Math.5H.sub.2O (0.21 g, 0.85 mmol) and 1H-imidazole-1-sulfonyl azide hydrochloride (2.13 g, 10.16 mmol) at RT under N.sub.2 and stirred overnight. The reaction was diluted with H.sub.2O (50 ml) and extracted with EA (2×100 ml). The combined organic layers were washed with brine (2×50 ml), dried over Na.sub.2SO.sub.4, filtered, and concentrated to afford the title compound as a yellow oil (3.4 g, crude). .sup.1H NMR (300 MHz, CDCl.sub.3) δ (ppm): 4.25-4.14 (m, 1H), 4.08-3.90 (m, 1H), 3.76-3.71 (m, 1H), 3.59-3.37 (m, 1H), 3.20 (d, 1H), 2.04-1.91 (m, 1H), 1.69-1.54 (m, 1H), 1.41 (s, 9H).

[0343] The following compounds were prepared in a manner essentially analogous to the method of Preparation 10 using the appropriate reagents, adjusting reaction time to determine completion

of the reaction, and adjusting the purification system as appropriate.
TABLE-US-00004 TABLE 3 Prep .sup.1H NMR # Chemical Name Structure (300 MHz, CDCl.sub.3), δ 11 tert-Butyl 4-azido- 4-methyl- piperidine-1- carboxylate [00172] 3.89-3.77 (m, 2H), 3.18-3.02 (m, 2H), 1.72-1.61 (m, 2H), 1.59-1.50 (m, 2H), 1.47 (s, 9H), 1.37 (s, 3H).
Preparation 12
N-Diazo-1,1,1-trifluoro-methanesulfonamide
##STR00173##
[0344] To a solution of NaN.sub.3 (9.22 g, 142 mmol) and hydrogen tetra(but-1-yl)ammonium sulfate (0.48 g, 1.42 mmol) in distilled H.sub.2O (30 mL) cooled to 0° C. was added slowly a solution of (CF.sub.3SO.sub.2).sub.2O (8.00 g, 28.4 mmol) in heptane (25 mL). The reaction was stirred 1-2 hr at 0° C. Heptane (25 ml) was added to the reaction and the layers were separated. The aqueous layer was extracted with heptane (3×10 ml). The combined organic layers were dried over NaOH pellets. The organic layer was decanted, and the solution was used immediately in the subsequent reaction.
Preparation 13
(1r,3r)-3-Azidocyclobutanol
##STR00174##
[0345] A solution of (1r,3r)-3-aminocyclobutan-1-ol (1.23 g, 14.2 mmol), NaHCO.sub.3 (4.05 g, 48.2 mmol), and CuSO.sub.4.Math.5H.sub.2O (1.77 g, 7.08 mmol) in MeOH (15 mL) and H.sub.2O (15 mL) (v/v) was treated with a freshly prepared stock solution of N-diazo-1,1,1-trifluoro-methanesulfonamide in heptane (4.96 g, 28.3 mmol). Additional MeOH was added to the reaction in 5 mL increments until a homogeneous mixture resulted (20 mL total added). The reaction was stirred overnight at RT. EA was added and the layers were separated. The aqueous layer was extracted with EA (3×). The combined organic layers were concentrated in vacuo to afford a dark green solution (1.60 g, 100%, assumed quantitative yield). .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ 2.05-2.31 (m, 4H) 4.07-4.18 (m, 1H) 4.29 (br s, 1H) 5.14-5.32 (m, 1H).
Preparation 14
tert-Butyl (3R,4R)-4-azido-3-fluoro-piperidine-1-carboxylate
##STR00175##
[0346] To tert-butyl (3R,4S)-3-fluoro-4-hydroxypiperidine-1-carboxylate (4 g, 18.24 mmol) and PPh.sub.3 (6.22 g, 23.72 mmol) in THE (40 ml) was added DIAD (5.53 g, 27.37 mmol) dropwise at 0° C. under N.sub.2 followed by the dropwise addition of DPPA (5.52 g, 20.07 mmol). The reaction was stirred for 3 h at RT then concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with PE/EA (10:1) to afford the title compound (1.7 g, 38%) as a light-yellow solid. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 4.63-4.24 (m, 1H), 4.09-3.83 (m, 2H), 3.80-3.55 (m, 1H), 3.20-2.84 (m, 2H), 2.06-1.78 (m, 1H), 1.42-1.36 (m, 10H).
[0347] The following compounds were prepared in a manner essentially analogous to the method of Preparation 14 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as
TABLE-US-00005 TABLE 4 .sup.1H NMR Prep (400 MHz, No. Chemical Name Structure CDCl.sub.3), δ 15.sup.1,2 tert-Butyl (3R,4S)-4- azido-3-fluoro-piperidine- 1-carboxylate [00176] 4.89-4.82 (m, 1H), 4.09- 4.01(m, 1H), 3.95-3.60 (m, 2H), 3.15 (dd, 2H), 1.90-1.64 (m,2H), 1.40 (s, 9H) 16.sup.2,3 tert-Butyl (3S,4S)-4-azido- 3-fluoro-piperidine-1- carboxylate [00177] 4.41-4.36 (m, 1H), 4.06- 3.85 (m, 2H), 3.68-3.57 (m, 1H), 3.06- 2.97 (m, 2H), 1.93-1.83 (m, 1H), 1.40 (s, 10H) 17.sup.4,5 tert-Butyl (3S,4R)-4- azido-3-fluoro-piperidine- 1-carboxylate [00178] 4.98-4.76 (m, 1H), 4.12- 3.96 (m, 1H), 3.97-3.64 (m, 2H), 3.26- 2.82 (m, 2H), 1.85-1.63 (m, 2H), 1.39 (s, 9 18 3- (Azidocyclobutoxy)methyl benzene [00179] 2.44-2.27 (m, 4H), 4.16- 4.08(m, 1H), 4.28-4.21(m, 1H), 4.41 (s, 2H), 7.39- 7.28 (m, 5H) .sup.1Purified by reverse phase chromatography; C18 column; eluting

with 40% to 50% ACN in H.sub.2O. .sup.21H NMR (300 MHz, DMSOd.sub.6). .sup.3 Purified by silica gel chromatography, eluting with PE / EA (20:1). .sup.4 Purified by silica gel chromatography, eluting with PE / EA (15:1). .sup.51H NMR (400 MHz, DMSOd.sub.6).

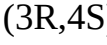
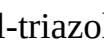
Preparation 19

tert-Butyl 4-methyl-4-(5-methyl-4-trimethylsilyl-triazol-1-yl)piperidine-1-carboxylate

##STR00180##

[0348] A mixture of tert-butyl 4-azido-4-methyl-piperidine-1-carboxylate (4 g, crude) and trimethyl(prop-1-yn-1-yl)silane (5.61 g, 49.94 mmol) was irradiated with microwave radiation for 1 h at 150° C. Once cooled to RT, the resulting mixture was concentrated in vacuo to afford the title compound as a yellow solid (4.1 g, crude). MS ES+ m/z 353 [M+H].sup.+.

[0349] The following compounds were prepared in a manner essentially analogous to the method of Preparation 19 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00006 TABLE 5 Prep MS ES+ # Chemical Name Structure m/z 20.sup.1,2 tert-Butyl (4R)-3,3- difluoro-4-(5-methyl-4- trimethylsilyl-triazol-1- yl)piperidine-1- carboxylate [00181]  375 [M + H].sup.+ 21 tert-Butyl (3R,4R)-3- fluoro-4-(5-methyl-4-trimethylsilyl-triazol-1- yl)piperidine-1- carboxylate [00182]  357 [M + H].sup.+ 22 tert-Butyl (3R,4S)-3- fluoro-4-(5-methyl-4- trimethylsilyl-triazol-1- yl)piperidine-1- carboxylate [00183]  357 [M + H].sup.+ 23 tert-Butyl (3S,4S)-3- fluoro-4-(5-methyl-4-trimethylsilyl-triazol-1- yl)piperidine-1- carboxylate [00184]  357 [M + H].sup.+ 24 tert-Butyl (3S,4R)-3- fluoro-4-(5-methyl-4- trimethylsilyl-triazol-1- yl)piperidine-1- carboxylate [00185]  357 [M + H].sup.+ 25.sup.3,4 (1r,3r)-3-(5-Methyl-4-(trimethylsilyl)-1H-1,2,3- triazol-1-yl)cyclobutan-1- ol [00186] a .sup.1Toluene used as solvent for this transformation. .sup.2Purified by silica gel chromatography eluting with PE / EA (5:1-3:1). .sup.3Purified by silica gel chromatography eluting with 0% to 100% EA in heptane. .sup.4Reaction was run in toluene. .sup.a1H NMR (400 MHz, DMSO-d.sub.6) δ 0.26 (s, 9 H) 2.24 (s, 3 H) 2.36-2.47 (m, 2 H) 2.65-2.75 (m, 2 H) 4.42-4.59 (m, 1 H) 4.97 (ttd, J = 8.38, 8.38, 5.14, 5.14, 0.73 Hz, 1 H) 5.31 (d, J = 4.89 Hz, 1 H).

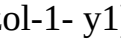
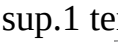
Preparation 26

tert-Butyl 4-(4-bromo-5-methyl-triazol-1-yl)-4-methyl-piperidine-1-carboxylate

##STR00187##

[0350] A mixture of tert-butyl 4-methyl-4-(5-methyl-4-trimethylsilyl-triazol-1-yl)piperidine-1-carboxylate (2.3 g, crude) and SiO.sub.2 (0.78 g, 13.05 mmol) in ACN (15 ml) was treated with NBS (1.74 g, 9.79 mmol) at RT under N.sub.2. The resulting mixture was stirred for 2 h at 80° C. under N.sub.2. Once cooled to RT, the reaction was quenched with H.sub.2O and extracted with EA (2×200 ml). The combined organic layers were washed with brine (2×100 ml), dried over Na.sub.2SO.sub.4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with PE/EA (4:1) to afford title compound as a yellow solid (2 g, 85%). MS ES+ m/z (.sup.79Br/.sup.81Br) 359/361 [M+H].sup.+.

[0351] The following compounds were prepared in a manner essentially analogous to the method of Preparation 26 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00007 TABLE 6 Prep MS ES+ m/z # Chemical Name Structure (.sup.79Br/.sup.81Br) 27.sup.1 tert-Butyl (4R)-4-(4- bromo-5-methyl-triazol-1- yl)-3,3-difluoro- piperidine-1-carboxylate [00188]  381/383 [M + H].sup.+ 28.sup.2 tert-Butyl (3R,4R)-4-(4- bromo-5-methyl-triazol-1- y1)-3-fluoro-piperidine-1- carboxylate [00189]  363/365 [M + H].sup.+ 29.sup.1 tert-Butyl (3R,4S)-4-(4- bromo-5-methyl-triazol-1- y1)-3-fluoro-piperidine-1-carboxylate [00190]  363/365 [M + H].sup.+ 30.sup.2 tert-Butyl (3S,4S)-4-(4-bromo-5-methyl-triazol-1- y1)-3-fluoro-piperidine-1- carboxylate [00191]  363/365 [M + H].sup.+ 31.sup.1 tert-Butyl (3S,4R)-4-(4- bromo-5-methyl-triazol-1- y1)-3-fluoro-

piperidine-1- carboxylate [00192]  embedded image 404.0/406.0 [M + H + ACN].sup.+ 32.sup.3 (1r,3r)-3-(4,5-Dimethyl- 1H-1,2,3-triazol-1- yl)cyclobutan-1-ol [00193]embedded image a .sup.1Purified by silica gel chromatography eluting with PE / EA (3:1). .sup.2Purified by silica gel chromatography, eluting with PE / EA (4:1). .sup.3Purified by silica gel chromatography eluting with 0% to 100% EA in heptane. .sup.a1H NMR (400 MHz, DMSO-d.sub.6) δ 2.20 (s, 3 H) 2.37-2.47 (m, 2 H) 2.69-2.77 (m, 2 H) 4.41-4.49 (m, 1 H) 4.99-5.09 (m, 1 H) 5.09-5.67 (m, 1 H).

Preparation 33

tert-Butyl 4-(4-ethoxycarbonyl-5-methyl-triazol-1-yl) azepane-1-carboxylate

##STR00194##

[0352] A solution of tert-butyl 4-(p-tolylsulfonyloxy) azepane-1-carboxylate (15 g, 38.57 mmol) in DMSO (120 ml) was stirred under N.sub.2. A solution of NaN.sub.3 (2.8 g, 42 mmol) in H.sub.2O (16.8 ml) was added. After stirring 30 min at RT a solution had resulted. The solution was subjected to the following flow chemistry conditions: Reactor size 20 ml (Teflon type mas T: 150° C.); flow rate: 0.666 ml/mi; BPR 1.2 bar, temperature: 100° C.; residence time: 30 min. The intermediate azide was isolated as a solution in DMSO/H.sub.2O (8:1)(0.28 M, 130 ml total). The soln of the azide intermediate was used in the next step.

[0353] To the above soln of the azide intermediate was added ethyl acetoacetate (5 ml, 39.30 mmol) and K.sub.2CO.sub.3 (12 g, 86.83 mmol). The reaction was stirred 15 min at RT then heated at 80° C. overnight. The reaction was cooled to RT then diluted with H.sub.2O (100 ml). After 15 min of stirring all the solids had dissolved. MTBE was added (100 ml) and mixture was stirred 15 min at RT. The organic layer was separated and the aq layer was extracted twice with MTBE (2×50 ml). The organic layers were combined, dried over Na.sub.2SO.sub.4, filtered and the filtrate was concentrated to afford the title compound (3.9 g, 25%, 75% purity). MS ES+ m/z 353 [M+H].sup.+.

Preparation 34

tert-Butyl (1R,5S)-3-(4-ethoxycarbonyl-5-methyl-triazol-1-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

##STR00195##

[0354] To a stirred solution of tert-butyl(3-endo)-3-azido-8-azabicyclo[3.2.1]octane-8-carboxylate (3.63 g, 14.4 mmol) and ethyl 3-oxobutanoate (2.25 g, 17.3 mmol) in DMSO (29 ml) was added K.sub.2CO.sub.3 (5.97 g, 43.2 mmol) at RT under N.sub.2. The reaction was stirred at 85° C. for 6 h. Upon cooling to RT the reaction was poured into ice/H.sub.2O (200 ml) with stirring. The resultant cream colored precipitate was collected by filtration, washed with H.sub.2O (100 ml) and dried at 40° C. overnight to afford the title compound (3.10 g, 59%). MS ES+ m/z 365 [MH-.sup.tBu].sup.+.

Preparation 35

Ethyl 1-(3-benzyloxycyclobutyl)-5-methyl-triazole-4-carboxylate

##STR00196##

[0355] To a stirred mixture of 3-(azidocyclobutoxy)methylbenzene (21 g, 103.32 mmol) and ethyl acetoacetate (14.79 g, 113.66 mmol) in DMF (100 ml) was added K.sub.2CO.sub.3 (42.84 g, 309.97 mmol) at RT under N.sub.2. The resulting mixture was stirred for 2 h at 80° C. under N.sub.2. Upon cooling to RT the reaction was concentrated in vacuo. The mixture was diluted with H.sub.2O (300 ml) and extracted with EA (3×200 ml). The combined organic layers were washed with brine (3×200 ml), dried over Na.sub.2SO.sub.4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography and eluted with 50% EA in PE, to afford the title compound (29 g, 93%) as a brownish yellow oil. ES+ m/z 316 [M+H].sup.+.

Preparation 36

1-[(1R,5S)-8-tert-Butoxycarbonyl-8-azabicyclo[3.2.1]octan-3-yl]-5-methyl-triazole-4-carboxylic acid

##STR00197##

[0356] A soln of tert-butyl (1R,5S)-3-(4-ethoxycarbonyl-5-methyl-triazol-1-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.5 g, 4.1 mmol) in H.sub.2O (8 ml) was treated with KOH (0.28 g, 5 mmol) and stirred at RT for 1 h, then stirred at 55° C. for 2 h, and then at 40° C. overnight. The reaction was allowed to cool to RT, quenched with 2 M aq HCl until the pH was ˜2, and extracted with EA (2×30 ml). The combined organic layers were dried over Na.sub.2SO.sub.4, filtered, and concentrated to obtain the title compound (1.16 g, 84%) which was used in the next synthetic step without purification or analysis.

[0357] The following compounds were prepared in a manner essentially analogous to the method of Preparation 36 using the appropriate reagents and adjusting the reaction times to determine completion of the reactions. MeOH can be used as a cosolvent.

TABLE-US-00008 TABLE 7 ES/MS Prep m/z # Chemical Name Structure [M + H].sup.+ 37 1-(3-Benzyloxycyclobutyl)-5- methyl-triazole-4- carboxylic acid [00198]  288

Preparation 38a

tert-Butyl 6-(4-bromo-5-methyl-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate

##STR00199##

and

Preparation 38b

tert-Butyl 6-(4-bromo-3-methyl-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate

##STR00200##

[0358] A DMSO suspension (10 ml) of tert-butyl 6-methylsulfonyloxy-2-azaspiro[3.3]heptane-2-carboxylate (2.5 g, 8.6 mmol) and 4-bromo-5-methyl-1H-pyrazole (1.2 g, 7.5 mmol) was treated with Cs.sub.2CO.sub.3 (5.7 g, 17 mmol) and the reaction stirred at 50° C. for 12 h and then placed into a refrigerator. After 4 days, the reaction was poured into ice and H.sub.2O which resulted in the formation of a precipitate. The insoluble material was removed by filtration and washed with H.sub.2O to obtain the title compounds (2.7 g, 44%) as a mixture. MS ES+ m/z 300/302 [M+H-tBu].sup.+.

Preparation 39a

tert-Butyl 2-(4-bromo-5-methyl-pyrazol-1-yl)-7-azaspiro[3.5]nonane-7-carboxylate

##STR00201##

and

Preparation 39b

tert-Butyl 2-(4-bromo-3-methyl-pyrazol-1-yl)-7-azaspiro[3.5]nonane-7-carboxylate

##STR00202##

[0359] tert-Butyl 2-methylsulfonyloxy-7-azaspiro[3.5]nonane-7-carboxylate (1.41 g, 4.41 mmol) and 4-bromo-5-methyl-1H-pyrazole (0.67 g, 4.14 mmol) in DMF (10 ml) was treated with Cs.sub.2CO.sub.3 (2.02 g, 6.2 mmol) at RT. After stirring at 90° C. for 3.5 h, the reaction was allowed to stir over the weekend at RT. Another portion of 4-bromo-5-methyl-1H-pyrazole (0.67 g, 4.14 mmol) and Cs.sub.2CO.sub.3 (2.02 g, 6.2 mmol) was added, and the reaction stirred at 90° C. for 2 h. Another portion of 4-bromo-5-methyl-1H-pyrazole (0.67 g, 4.14 mmol) was added and stirred at 90° C. for 1 h. After cooling to RT, the reaction was diluted with H.sub.2O (50 ml) and extracted with EA (2×). The organic layers were combined, dried over MgSO.sub.4, filtered, and concentrated. The resulting oil was purified by silica gel chromatography eluting with 33% EA in hexanes to obtain the title compound (1.68 g) as a mixture. MS ES+ m/z 328/330 [M+H-tBu].sup.+.

[0360] The following compounds were prepared in a manner essentially analogous to the method of Preparation 39a and 39b using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as

TABLE-US-00009 TABLE 8 Prep MS ES+ # Chemical Name Structure m/z 40a tert-Butyl 4-(4-bromo-5- methyl-pyrazol-1- yl)azepane-1-carboxylate [00203]  (.sup.79Br/.sup.81Br) 302/304 [M + H − tBu].sup.+ 40b tert-Butyl 4-(4-bromo-3- methyl-pyrazol-

1- yl)azepane-1-carboxylate [00204]  embedded image (.sup.79Br/.sup.81Br) 302/304 [M + H −
.sup.tBu].sup.+ 41 tert-Butyl 4-(4-bromo-3,5- dimethyl-pyrazol-1- y1)piperidine-1-carboxylate
[00205]embedded image (.sup.19Br/.sup.81Br) 358/360 [M + H].sup.+

Preparation 42

1-(1-tert-Butoxycarbonylazetidin-3-yl)-5-methyl-triazole-4-carboxylic acid

##STR00206##

[0361] To a soln of ethyl 1-(1-tert-butoxycarbonylazetidin-3-yl)-5-methyl-triazole-4-carboxylate (12.15 g, 39.14 mmol) in THE (75 ml) was added aq LiOH (75 ml, 75 mmol, 1M) and the reaction was stirred overnight at RT. After stirring 18 h, aq HCl (1N) was added until pH was between 5 and 6. The mixture was extracted with EA and DCM/MeOH (9:1) (5×). The combined organic layers were dried on MgSO.sub.4, filtered and the filtrate was concentrated to afford the title compound (10.3 g, 93%) of a pale brown solid. MS ES+ m/z 283 [M+H].sup.+.

Preparation 43

1-(1-tert-Butoxycarbonylazepan-4-yl)-5-methyl-triazole-4-carboxylic acid

##STR00207##

[0362] To a stirred solution of tert-butyl 4-(4-ethoxycarbonyl-5-methyl-triazol-1-yl)azepane-1-carboxylate (3.1 g, 8.8 mmol) in THE (15 ml) was added aq LiOH (15 ml, 15 mmol, 1M) and the reaction was stirred at RT for 210 minutes. Aq HCl (1N) was added until pH was approximately 5-6. The reaction was extracted twice with EA and twice with 10% MeOH in DCM. The organic layers were combined, dried on MgSO.sub.4, filtered and the filtrate was concentrated in vacuo to afford the title compound (2.89 g, 96%, 95 mass %). MS ES+ m/z 296 [M+H].sup.+.

Preparation 44

tert-Butyl (3S)-3-(4-bromo-5-methyl-pyrazol-1-yl)piperidine-1-carboxylate

##STR00208##

[0363] To tert-butyl (3S)-3-(4-bromopyrazol-1-yl)piperidine-1-carboxylate (500 mg, 1.51 mmol) in THE (5 ml) was added LDA in hexanes (2.3 ml, 4.6 mmol, 2 M) at −70° C. and stirred for 0.5 h. Next, CH.sub.3I (0.19 mL, 3.1 mmol) was added, and the stirring continued for 30 min. The reaction was quenched with sat. aq NH.sub.4Cl (50 ml) and concentrated. The mixture was extracted with EA (3×20 ml). The combined organic layers were wash with brine (3×20 ml), dried over Na.sub.2SO.sub.4, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with petroleum ether/EA (1:0 to 10:1) to afford the title compound (0.4 g, 70% Yield) as a yellow oil. MS ES+ m/z (.sup.79Br/.sup.81Br) 344/346 [M+H].sup.+.

[0364] The following compounds were prepared in a manner essentially analogous to the method of Preparation 44 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00010 TABLE 9 Prep MS ES+ # Chemical Name Structure m/z 45 tert-Butyl (3R)-3-(4-bromo-5- methyl-pyrazol-1- y1)piperidine-1-carboxylate [00209]  embedded image (.sup.79Br/.sup.81Br) 344/346 [M + H].sup.+

Preparation 46

tert-Butyl 4-(4-bromo-5-methyl-triazol-1-yl)piperidine-1-carboxylate

##STR00210##

[0365] A soln of 1-(1-tert-butoxycarbonyl-4-piperidyl)-5-methyl-triazole-4-carboxylic acid (17 g, 55 mmol) and KOH (3.7 g, 66 mmol) in H.sub.2O (60 ml) was treated in portions with Br.sub.2 (10.4 g, 66 mmol) at RT. After stirring at RT for 3 h at RT, the reaction was extracted with EA (3×30 ml). The combined organic layers were washed with brine (2×150 mL), dried over anhydrous Na.sub.2SO.sub.4, filtered, and concentrated to obtain the title compound (13 g, 68%) as a yellow solid. MS ES+ m/z 345 [M+H].sup.+.

[0366] The following compounds were prepared in a manner essentially analogous to the method of Preparation 46 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00011 TABLE 10 MS ES+ Prep # Chemical Name Structure m/z 47 tert-Butyl 3-(4-bromo-5- methyl-triazol-1- yl)azetidine-1-carboxylate [00211] (.sup.79Br/.sup.81Br) 317/319 [M + H].sup.+ 48 tert-Butyl (1R,5S)-3-(4- bromo-5-methyl-triazol-1- y1)-8-azabicyclo [3.2.1]octane-8- carboxylate [00212] (.sup.19Br/.sup.81Br) 371/373 [M + H].sup.+ 49.sup.1 tert-Butyl 4-(4-bromo-5- methyl-triazol-1- yl)azepane-1-carboxylate [00213] (.sup.79Br/.sup.81Br) 359/361 [M + H].sup.+ 50 1-(3-Benzyloxycyclobutyl)-4- bromo-5-methyl-triazole [00214] a .sup.1Prior to workup reaction was diluted with aq NaOH (2N). .sup.a1H NMR (400 MHz, DMSO-d.sub.6) δ 7.40-7.34 (m, 4H), 7.33-7.27 (m, 1H), 5.14-5.06 (m, 1H), 4.45 (s, 2H), 4.42-4.34 (m, 1H), 2.81-2.72 (m, 2H), 2.66-2.56 (m, 2H), 2.22 (s, 3H).

Preparation 51

(1s,3s)-[3-(4-Bromo-5-methyl-triazol-1-yl)cyclobutyl]4-nitrobenzoate

##STR00215##

[0367] To a solution of DIAD (4.18 g, 20.68 mmol) in THE (40 ml) was added PPh.sub.3 (5.88 g, 22.41 mmol) dropwise at 0° C. under N.sub.2. The reaction was stirred for 30 min at 0° C. Next, (1r,3r)-3-(4,5-dimethyl-1H-1,2,3-triazol-1-yl)cyclobutan-1-ol (4.0 g, 17.24 mmol) and p-nitrobenzoic acid (3.46 g, 20.68 mmol) were added in portions at RT under N.sub.2. The mixture was stirred for 2 h at RT then concentrated in vacuo. The residue was purified by silica gel column chromatography, eluted with PE/EA (5:1) to afford the title compound (8 g, crude) as a white solid. MS ES+ m/z (.sup.79Br/.sup.81Br) 381/383 [M+H].sup.+.

Preparation 52

(1s,3s)-3-(4-Bromo-5-methyl-1H-1,2,3-triazol-1-yl)cyclobutan-1-ol

##STR00216##

[0368] To a stirred solution of (1s,3s)-[3-(4-bromo-5-methyl-triazol-1-yl)cyclobutyl]4-nitrobenzoate (8.0 g, crude) in THE (50 ml) was added LiOH.Math.H.sub.2O (0.79 g, 18.89 mmol) in portions at RT under N.sub.2. The reaction was stirred for 2 h at RT then concentrated in vacuo. The residue was purified by reversed flash chromatography with the following conditions: column, C18; mobile phase, 10% to 50% ACN in H.sub.2O (0.1% FA), to afford the title compound (2.5 g, 51%) as a yellow oil. MS ES+ m/z (.sup.79Br/.sup.81Br) 232/234 [M+H].sup.+. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 5.46-5.28 (m, 1H), 4.55-4.40 (m, 1H), 4.14-3.90 (m, 1H), 2.87-2.76 (m, 2H), 2.49-2.41 (m, 2H), 2.25-2.19 (m, 3H).

Preparation 53

3-(4-Bromo-5-methyl-triazol-1-yl)cyclobutanol

##STR00217##

[0369] A mixture of 1-(3-benzyloxycyclobutyl)-4-bromo-5-methyl-triazole (8.5 g, 26.4 mmol) and FeCl.sub.3 (8.56 g, 52.8 mmol) in DCM (100 ml) was stirred for 2 h at 50° C. under N.sub.2. Upon cooling to RT the mixture was diluted with H.sub.2O (50 ml) and extracted with EA (3×100 ml). The combined organic layers were washed with brine (2×100 ml), dried over Na.sub.2SO.sub.4, filtered and the filtrate was concentrated in vacuo to afford the title compound (8 g, crude) as a brown solid. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ 5.09-4.99 (m, 1H), 4.55-4.42 (m, 1H), 2.80-2.71 (m, 2H), 2.48-2.37 (m, 2H), 2.21 (s, 3H).

Preparation 54

4-(4-Bromo-5-methyl-triazol-1-yl)piperidine hydrochloride

##STR00218##

[0370] A soln of tert-butyl 4-(4-bromo-5-methyl-triazol-1-yl)piperidine-1-carboxylate (58 g, 159.6 mmol) in 2-propanol (60 ml) was treated with HCl in 2-propanol (250 ml; 1250 mmol; 4.99 M) and allowed to stir overnight. The reaction was diluted with MTBE (250 ml) and the resulting suspension was stirred at RT for 1 h. The suspension was filtered to afford the title compound (41.5 g, 91%) as a white solid. MS ES+ m/z (.sup.79Br/.sup.81Br) 245/247 [M+H].sup.+.

Preparation 55

4-(4-Bromo-3,5-dimethyl-pyrazol-1-yl)piperidine
##STR00219##
[0371] A DCM soln (15 ml) of tert-butyl 4-(4-bromo-3,5-dimethyl-pyrazol-1-yl)piperidine-1-carboxylate (0.97 g, 2.70 mmol) was treated with TFA (4 ml) and the reaction stirred at RT. After stirring for 45 min, the reaction was loaded onto an SCX column pretreated with MeOH. The column was washed with MeOH. The title compound was eluted with 2 M NH.sub.3 in MeOH and concentrated to obtain the title compound (557 mg, 80%) as a colorless oil. MS ES+ m/z (.sup.79Br/.sup.81Br) 258/260 [M+H].sup.+.
[0372] The following compounds were prepared in a manner essentially analogous to the method of Preparation 55 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.
TABLE-US-00012 TABLE 11 MS ES+ Prep # Chemical Name Structure m/z 561 4-(4-Bromo-5-methyl-triazol- 1-yl)azepane [00220]  embedded image (.sup.79Br/.sup.81Br) 259/261 [M + H].sup.+ .sup.1Crude material loaded onto an SCX cartridge. Non-basic impurities were washed off the cartridge with MeOH then the title compound was eluted with methanolic ammonia (2N).
Preparation 57
3-(4-Bromo-5-methyl-triazol-yl)cyclobutanone
##STR00221##
[0373] A mixture of 3-(4-bromo-5-methyl-triazol-1-yl)cyclobutanol (4.00 g, 17.23 mmol) and Dess-Martin (10.97 g, 25.85 mmol) in DCM (40 mL) was stirred for 2 h at RT under N.sub.2. The mixture was diluted with H.sub.2O (100 mL), extracted with EA (3×100 mL), washed with brine (2×100 mL), dried over Na.sub.2SO.sub.4, and filtered. The filtrate was concentrated in vacuo. The residue was purified by reversed phase chromatography with the following conditions: column, C18; mobile phase, 20% to 40% ACN in H.sub.2O (0.1% FA) to afford the title compound (2.10 g, 52.96%) as a white solid. ES/MS m/z (.sup.79Br/.sup.81Br) 230/232 [M+H].sup.+.
Preparation 58
(1s,3s)-[3-(4-Bromo-5-methyl-triazol-1-yl)cyclobutyl]trifluoromethanesulfonate
##STR00222##
[0374] To (1s,3s)-3-(4-bromo-5-methyl-1H-1,2,3-triazol-1-yl)cyclobutan-1-ol (1.1 g, 4.74 mmol) and DIEA (3.06 g, 23.70 mmol) in DCM (10 ml) was added (trifluoromethane)sulfonyl trifluoromethanesulfonate (2.01 g, 7.11 mmol) dropwise at −70° C. under N.sub.2. The reaction was stirred for 1 h at −70° C. The mixture was used in the next step without further purification and assuming 100% conversion. ES/MS m/z (.sup.79Br/.sup.81Br) 364/366 [M+H].sup.+.
Preparation 59
tert-Butyl 4-((1r,3r)-3-(4-bromo-5-methyl-1H-1,2,3-triazol-1-yl)cyclobutyl)piperazine-1-carboxylate
##STR00223##
[0375] To (1s,3s)-[3-(4-Bromo-5-methyl-triazol-1-yl)cyclobutyl]trifluoromethanesulfonate (1.7 g, 4.67 mmol) and DIEA (1.81 g, 14.01 mmol) in DCM (10 ml) was added tert-butyl piperazine-1-carboxylate (1.74 g, 9.34 mmol) in portions at −70° C. under N.sub.2. The reaction was stirred for overnight at RT then concentrated in vacuo. The residue was purified by silica gel column chromatography, eluted with PE/EA (10:1) to afford the title compound (1.1 g, 59%) as a white solid. ES/MS m/z (.sup.79Br/.sup.81Br) 400/402 [M+H].sup.+. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 5.02-4.90 (m, 1H), 3.38-3.35 (m, 4H), 3.08-2.96 (m, 1H), 2.65-2.52 (m, 4H), 2.32-2.23 (m, 4H), 2.23-2.20 (m, 3H), 1.40 (s, 9H).
Preparation 60
tert-Butyl 4-[3-(4-bromo-5-methyl-triazol-1-yl)cyclobutyl]piperazine-1-carboxylate
##STR00224##
[0376] To 3-(4-bromo-5-methyl-triazol-1-yl)cyclobutanone (1.67 g, 7.25 mmol) and tert-butyl piperazine-1-carboxylate (0.90 g, 4.83 mmol) in MeOH (5 ml) was added CH.sub.3CO.sub.2H

(0.29 g, 4.83 mmol) in portions at RT. The resulting mixture was stirred for 30 min at 50° C. under N.sub.2. Next, NaBH.sub.3CN (0.61 g, 9.66 mmol) was added in portions at RT under N.sub.2. The reaction was stirred at 50° C. for 2 h. Upon cooling to RT, the reaction was quenched with H.sub.2O (100 ml) and pH adjusted to approximately 7 with saturated aq NaHCO.sub.3. The mixture was extracted with EA (3×100 ml). The organic layers were combined, washed with brine (2×100 ml), dried over Na.sub.2SO.sub.4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography, eluted with 1% to 50% EA in PE to afford the title compound (1.4 g, 72%) as an oil. ES/MS m/z (.sup.79Br/.sup.81Br) 400/402 [M+H].sup.+.

Preparation 61

4-(4-Bromo-5-methyl-triazol-1-yl)-1-(oxetan-3-yl)piperidine

##STR00225##

[0377] A soln (700 ml) of 4-(4-bromo-5-methyl-triazol-1-yl)piperidine hydrochloride 41 g, 142.69 mmol) in MeOH (700 ml) was treated with oxetan-3-one (35 g, 485.7 mmol) under N.sub.2 and allowed to stir at RT for 5 min. The reaction was treated with AcOH (11.53 g, 192 mmol), allowed to stir for 5 min, then treated in portions with NaBH.sub.3CN (35 g, 556.95 mmol) over 1 h. The reaction was stirred at RT for 30 min then stirred at 30° C. overnight. After cooling to RT, the reaction was quenched with H.sub.2O (50 ml) and the pH was adjusted to 9 with 2M aq K.sub.3PO.sub.4 (75 ml). The organic solvent removed in vacuo. The resulting suspension was diluted with H.sub.2O (30 ml), stirred for 30 min, and filtered to obtain the title compound (30 g, 62%) as a pale white solid. MS ES+ m/z 301/303 [M+H].sup.+.

Preparation 62

4-(4-Bromo-3,5-dimethyl-pyrazol-1-yl)-1-(oxetan-3-yl)piperidine

##STR00226##

[0378] NaBH.sub.3CN (0.51 g) was added to a soln of 4-(4-bromo-3,5-dimethyl-pyrazol-1-yl)piperidine (0.56 g, 2.18 mmol), oxetan-3-one (292 mg, 4.05 mmol) and AcOH (0.15 ml, 2.62 mmol) in MeOH (10 ml). The resulting mixture was stirred at RT for 15 min then at 50° C. for 18 h. Upon cooling to RT, the reaction was concentrated in vacuo. The residue was suspended in DCM and washed with a sat. soln of NaHCO.sub.3. The organic phase was separated, and the aq. phase was extracted with DCM (2×). The combined organic layers were dried over MgSO.sub.4, filtered and concentrated. The residue was purified by silica gel chromatography eluting with a gradient of 0% to 100% EA in cHex followed by 0% to 20% MeOH in DCM to afford the title compound (510 mg, 60%) as a white solid. MS ES+ m/z (.sup.79Br/.sup.81Br) 314/316 [M+H].sup.+.

[0379] The following compounds were prepared in a manner essentially analogous to the method of Preparation 62 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00013 TABLE 12 Prep MS ES+ # Chemical Name Structure m/z 63.sup.1 4-(4-Bromo-5-methyl-triazol- 1-y1)-1-(oxetan-3-yl)azepane [00227]  embedded image (.sup.79Br/.sup.81Br) 315/317 [M + H].sup.+ .sup.1Purified by silica gel chromatography eluting with 0% to 10% MeOH in DCM.

Preparation 64

(1R,5S)-3-(4-Bromo-5-methyl-triazol-1-yl)-8-(oxetan-3-yl)-8-azabicyclo[3.2.1]octane

##STR00228##

[0380] To a solution of tert-butyl (1R,5S)-3-(4-bromo-5-methyl-triazol-1-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.03 g, 2.77 mmol) in 1,4-dioxane (5 ml, 58.57 mmol) was added HCl in 1,4-dioxane (3 ml, 12 mmol, 4 mol/L) and the mixture was stirred for 1 h at RT, then heated at 50° C. for 1 h and stirred overnight at RT. The reaction was concentrated in vacuo to afford the intermediate (1R,5S)-3-(4-bromo-5-methyl-triazol-1-yl)-8-azoniabicyclo[3.2.1]octane hydrochloride as a solid. This material was used in the next step without further purification or characterization.

[0381] To a solution of (1R,5S)-3-(4-bromo-5-methyl-triazol-1-yl)-8-azoniabicyclo[3.2.1]octane

hydrochloride (0.75 g, 2.44 mmol) in MeOH (10 ml) was added 3-oxetanone (0.7 mL, 10 mmol). The mixture was stirred at RT for 5 min then NaBH.sub.3CN (0.7 g, 10 mmol) was added. The reaction was stirred overnight at RT. The reaction was heated at 50° C. for 9 h. Additional 3-oxetanone (170 μl, 2.79 mmol) and NaBH.sub.3CN (170 mg, 2.70 mmol) were added, and the reaction was stirred overnight at 50° C. The reaction was quenched with H.sub.2O and extracted with EA (3×25 ml). The combined organic layers were dried over Na.sub.2SO.sub.4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with 0% to 20% EA in DCM followed by 0% to 5% MeOH in DCM. To afford the title compound (630 mg, 69%) as an orange solid. ES+ m/z (.sup.79Br/.sup.81Br) 327/329[M+H].sup.+.

Preparation 65

2-Chloro-4-cyclopropyl-5-fluoropyridine

##STR00229##

[0382] A soln of 2-chloro-5-fluoro-4-iodopyridine (1.50 g, 5.827 mmol) and Pd(PPh.sub.3).sub.4 (674 mg, 0.583 mmol) in THE (5 ml) was degassed by three freeze-pump-thaw cycle. A soln of cyclopropylzinc bromide (30 ml, 15.150 mmol, 0.5M in THF) was added dropwise at 0° C. The reaction was stirred overnight allowing it to slowly warm to RT. The reaction was quenched with H.sub.2O and extracted with EA. The combined organic layers were washed with brine, dried over MgSO.sub.4, filtered, concentrated under in vacuo. The residue was purified by silica gel chromatography eluting with EA in heptane to afford the title compound as a colorless oil (758 mg, 76%). ES+ m/z 172.1 [M+H].sup.+.

Preparation 66

3-Chloro-5-(trifluoromethyl)pyridazine

##STR00230##

[0383] A soln of 4-(trifluoromethyl)-1H-pyridazin-6-one (10 g, 60.94 mmol) and POCl.sub.3 (46.72 g, 304.72 mmol) in ACN (80 ml) was stirred overnight at 80° C. under N.sub.2. The mixture was allowed to cool to RT, poured into H.sub.2O/ice (300 ml), and basified to pH 8 with NaHCO.sub.3. The resulting mixture was extracted with EA (3×100 ml). The combined organic layers were washed with brine (1×100 ml), dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was purified by silica gel chromatography eluting with PE/EA (40:1 to 10:1) to obtain the title compound (5 g, 45%) as a yellow oil. MS ES+ m/z 183 [M+H].sup.+.

Preparation 67

5-Fluoro-2-[1-(trifluoromethyl)vinyl]pyridine

##STR00231##

[0384] A soln of 2-bromo-5-fluoropyridine (8 g, 45.46 mmol) and 4,4,6-trimethyl-2-[1-(trifluoromethyl)vinyl]-1,3,2-dioxaborinane (11.10 g, 50.00 mmol) in DME (40 ml) and H.sub.2O (10 ml) was treated with K.sub.2CO.sub.3 (18.85 g, 136.37 mmol) and Pd(PPh.sub.3).sub.4 (1.05 g, 0.91 mmol) under N.sub.2. After stirring for 2 h at 100° C., the mixture was diluted with H.sub.2O (100 ml) and extracted with EA (3×100 ml). The combined organic layers were washed with brine (3×100 ml), dried over anhydrous Na.sub.2SO.sub.4, filtered, and concentrated. The residue was purified by silica gel chromatography, eluting with PE/EA (20 to 10:1) to obtain the title compound (3.4 g, 39%) as an off-white oil. MS ES+ m/z 192 [M+H].sup.+.

Preparation 68

3-(1-Ethoxyvinyl)-5-(trifluoromethyl)pyridazine

##STR00232##

[0385] To a mixture of tributyl(1-ethoxyethenyl)stannane (11.87 g, 32.87 mmol) and 3-chloro-5-(trifluoromethyl)pyridazine (5.00 g, 27.39 mmol) in 1,4-dioxane (40 ml) was added Pd(PPh.sub.3).sub.4 (0.95 g, 0.82 mmol) at RT under a N.sub.2. The reaction was stirred for 2 h at 100° C. After cooling to RT, the mixture was concentrated and purified by silica gel chromatography eluting with PE/EA (30:1 to 12:1) to afford the title compound (4.6 g, 77%) as a yellow oil. MS ES+ m/z 219 [M+H].sup.+.

[0386] The following compounds were prepared in a manner essentially analogous to the method of Preparation 68 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00014 TABLE 13 MS ES+ Prep # Chemical Name Structure m/z 69.sup.1 3-(1-Ethoxyvinyl)-2,5-dimethyl- pyrazine [00233]  embedded image 179 [M + H].sup.+ 70.sup.2,3 3-Chloro-2-(1-ethoxyvinyl)-5- fluoro-pyridine [00234]embedded image 202 [M + H].sup.+ 71.sup.3 4-Chloro-2-(1-ethoxyvinyl)-5- fluoropyridine [00235]  embedded image 201.9 [M].sup.+ .sup.1Purified by silica gel chromatography eluting with PE / EA 10:1 to 5:1. .sup.2Reaction quenched with sat. aq KF. .sup.3Purified by silica gel chromatography eluting with EA in heptane

Preparation 72

N-Methoxy-N-methyl-1-(trifluoromethyl)pyrazole-3-carboxamide

##STR00236##

[0387] 1-(Trifluoromethyl)-1H-pyrazole-3-carboxylic acid (780 mg, 4.33 mmol) was dissolved in SOCl.sub.2 (10 ml) and stirred at reflux for 2 h. The reaction was concentrated in vacuo then re-dissolved in DCM (8.5 ml) at 0° C. and DIPEA (2.2 ml, 12.84 mmol) was added followed by N,O-dimethylhydroxylamine hydrochloride (840 mg, 8.56 mmol). The reaction was allowed to warm to RT then stirred 1 h. The mixture was diluted with DCM and washed with sat. aq NaHCO.sub.3 soln, the combined organic phases were dried over MgSO.sub.4, filtered, and the filtrate was concentrated in vacuo to afford the title compound as a pale-yellow oil (809 mg, 85%). MS ES+ m/z 224.1 [M+H].sup.+.

Preparation 73

N-Methoxy-N-methyl-5-(trifluoromethyl)pyridine-3-carboxamide

##STR00237##

[0388] A DCM suspension (60 ml) of 5-(trifluoromethyl)pyridine-3-carboxylic acid (4 g, 20.93 mmol) was treated with 1,1′-carbonyldiimidazole (3.73 g, 23 mmol) and Et.sub.3N (5.8 mL, 42 mmol). The reaction was stirred at RT for 3 h, diluted with H.sub.2O, the organic phase collected, and the aq phase re-extracted with DCM. The combined organic layers were washed with sat. aq NaHCO.sub.3, collected, dried over MgSO.sub.4, filtered, and concentrated to obtain the title compound (3.75 g) as a yellow oil that was used without purification. MS ES+ m/z 235 [M+H].sup.+.

Preparation 74

N-Methoxy-N,2,5-trimethyl-thiazole-4-carboxamide

##STR00238##

[0389] To an ice-cold soln of 2,5-dimethylthiazole-4-carboxylic acid (1.25 g, 7.95 mmol) and methoxy(methyl)ammonium chloride (1.95 g, 20.0 mmol) in DMF (10 ml) was added NEt.sub.3 (2.85 g, 28 mmol). The mixture was stirred for 5 min then HATU (3.6 g, 9.3 mmol) was added. The reaction was stirred at RT for 16 h. The reaction was poured into H.sub.2O, the aq soln was extracted with DCM (2×) and the combined organic layers were washed with 10% aq. LiCl, dried over MgSO.sub.4, filtered and concentrated. The residue was purified by silica gel chromatography eluting with 0% to 30% EA in cHex to afford the title compound. The title compound was taken on to the next step.

Preparation 75

1-[5-(Trifluoromethyl)pyridazin-3-yl]ethanone

##STR00239##

[0390] A soln of 3-(1-ethoxyethenyl)-5-(trifluoromethyl)pyridazine (1.0 g, 4.58 mmol) and conc HCl (2.26 g, 22.92 mmol) in THE (10 ml) was stirred for 1 h at RT under a N.sub.2. The resulting mixture was diluted with H.sub.2O (10 ml), basified to pH 8 with NaHCO.sub.3, and extracted with MTBE (3×20 ml). The combined organic layers were washed with brine (1×10 ml), dried over anhydrous Na.sub.2SO.sub.4, collected, and filtered. The filtrate was concentrated to obtain the title compound (810 mg, 93%) as a yellow solid. MS ES+ m/z 191 [M+H].sup.+.

[0391] The following compounds were prepared in a manner essentially analogous to the method of Preparation 75 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00015 TABLE 14 MS ES+ Prep # Chemical Name Structure m/z 76 1-(3,6-Dimethylpyrazin-2- yl)ethanone [00240]embedded image 192 [M + H].sup.+

Preparation 77

1-(4-Cyclopropyl-5-fluoro-2-pyridyl)ethanone

##STR00241##

[0392] A soln of 2-chloro-4-cyclopropyl-5-fluoropyridine (617 mg, 3.60 mmol) and Pd(PPh.sub.3).sub.4 (416 mg, 0.36 mmol) in toluene (10 ml) was degassed by vacuum/N.sub.2 cycle (3×). Tributyl(1-ethoxyvinyl)tin (1.56 mL, 4.32 mmol) was added and the mixture was stirred at 100° C. under N.sub.2 for 6 h. The reaction was treated with sat. aq KF (2.5 mL), filtered through a pad of DE, and the cake was washed with EA (30 ml). The phases from the filtrate were separated. The organic phase was washed with sat. aq NaHCO.sub.3 (3×20 ml) and brine (20 ml), dried over MgSO.sub.4, filtered, and concentrated in vacuo to afford the intermediate vinyl ether as a brown oil.

[0393] The intermediate vinyl ether was dissolved in THE (10 ml) then aq HCl (2M, 5 mL) was added, and the reaction was stirred 12 h at RT. The reaction was treated with sat. aq NaHCO.sub.3 (30 ml), and the mixture was stirred vigorously for 10 min. The aq phase was extracted with EA (3×25 ml) and the combined organic layers were washed with brine (25 ml), dried over MgSO.sub.4, filtered, concentrated in vacuo. The residue was purified by silica gel chromatography eluting with EA in heptane to afford the title compound as a colorless oil (226 mg, 35%). ES+ m/z 180.1 [M+H].sup.+.

[0394] The following compounds were prepared in a manner essentially analogous to the method of Preparation 77 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00016 TABLE 15 MS ES+ Prep # Chemical Name Structure m/z 78 1-(7-Fluoro-4-isoquinolyl)ethanone [00242]embedded image 190.1 [M + H].sup.+

Preparation 79

1-[5-(Trifluoromethyl)-3-pyridyl]ethanone

##STR00243##

[0395] A soln of N-methoxy-N-methyl-5-(trifluoromethyl)pyridine-3-carboxamide (2 g, 6.41 mmol, 75 mass %) in THE (30 ml) at 0° C. was treated dropwise with MeMgBr (10 mL, 14 mmol, 1.4 M in toluene/THE [3:1]) and stirred for 1 h. The reaction was quenched with saturated aq NH.sub.4Cl at 0° C., diluted with H.sub.2O, and extracted with EA (2×). The organic layers were combined, dried over MgSO.sub.4, filtered, and concentrated. The resulting oil was purified by silica gel chromatography eluting with a gradient of 0% to 80% EA in cHex to obtain the title compound (1.0 g, 83%) as a white solid. .sup.1H NMR (400 MHz, CDCl.sub.3): δ 9.35 (d, J=1.9 Hz, 1H), 9.07 (d, J=1.5 Hz, 1H), 8.48-8.47 (m, 1H), 2.72 (s, 3H).

[0396] The following compounds were prepared in a manner essentially analogous to the method of Preparation 79 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00017 TABLE 16 .sup.1H NMR Prep # Chemical Name Structure (400 MHz, CDCl.sub.3) δ 80 1-(2,5-Dimethylthiazol- 4-y1)ethanone [00244]  embedded image a 81.sup.1 Cyclopropyl-(5-fluoro-2- pyridyl)methanone [00245]embedded image 8.57 (d, J = 2.8 Hz, 1H), 8.12 (ddd, J = 8.7, 4.7, 0.6 Hz, 1H), 7.54 (ddd, J = 8.7, 8.0, 2.8 Hz, 1H), 3.48 (tt, J = 7.9, 4.7 Hz, 1H), 1.29-1.23 (m, 2H), 1.16-1.07 (m, 2H). 82.sup.1 Cyclobutyl-(5-fluoro-2- pyridyl)methanone [00246]  embedded image a .sup.aMaterial used in subsequent step without further characterization. .sup.1Purified by silica gel chromatography eluting with 0% to 30% EA in cHex.

Preparation 83

Methyl 1-(5-bromo-2-pyridyl)-3,3-difluoro-cyclobutanecarboxylate
##STR00247##
[0397] A toluene (50 mL) soln of 5-bromo-2-fluoropyridine (7.0 g, 39.78 mmol) and methyl 3,3-difluorocyclobutane-1-carboxylate (6.57 g, 43.75 mmol) was treated dropwise with KHMDS (51.7 ml, 51.71 mmol, 1.0 M in THF) at −70° C. under a nitrogen atmosphere. After stirring for 30 min at −70° C., the reaction was quenched with saturated, aq NH.sub.4Cl at RT, acidified to pH 1-2 with aq HCl (1.2 M) and extracted with EA (3×100 ml). The combined organic layers were washed with brine (2×100 ml), dried over anhydrous Na.sub.2SO.sub.4, filtered, and concentrated to obtain the title compound (11 g, crude) as a yellow solid. The crude product was used directly without purification. MS ES+ m/z (.sup.79Br/.sup.81Br) 306/308 [M+H].sup.+.
Preparation 84
1-Methyl-2-(2-pyridyl)pyrrolidin-3-ol
##STR00248##
[0398] To a soln of 2-(2-pyridyl)pyrrolidin-3-ol (450 mg, 2.74 mmol) in DCM (40 ml) was added H2CO (13.31 mol/L) in H.sub.2O (0.65 ml). After stirring 10 minutes, Na(OAc).sub.3BH (0.9 g, 4 mmol) was added. The mixture was stirred overnight at RT. The reaction was quenched with saturated aq NaHCO.sub.3. The aq phase was acidified with HCl until pH 2 then directly loaded onto a SCX column. The title compound was eluted with 2N NH.sub.3 in MeOH to afford the title compound (200 mg, 9%), MS ES+ m/z 179 [M+H].sup.+.
Preparation 85
1-[1-(Trifluoromethyl)pyrazol-3-yl]ethanol
##STR00249##
[0399] MeMgBr (0.21 ml, 1.80 mmol, 3M) was added to a soln of N-methoxy-N-methyl-1-(trifluoromethyl)pyrazole-3-carboxamide (329 mg, 2.00 mmol) in THE (2.7 ml) under N.sub.2 at 0° C. After stirring 1 h at 0° C. the reaction was carefully quenched with AcOH (0.13 ml, 2.25 mmol) and diluted with MeOH (2 ml). Next, NaBH.sub.4 (102 mg, 2.70 mmol) was added in one portion, and the reaction was stirred for 40 min at 0° C. The reaction was diluted with saturated aq NH.sub.4Cl (4 ml), extracted with Et.sub.20 (2×5 ml) and DCM (2×5 ml) and the combined organic phases were dried over MgSO.sub.4, filtered, and the solvent was concentrated in vacuo to afford the title compound as a pale-yellow oil (174 mg, quantitative). ES+ m/z 180.9 [M+H].sup.+.
Preparation 86
1-(1-Methylpyrrolo[2,3-c]pyridin-4-yl)ethanol
##STR00250##
[0400] A 0.5 M soln of lithium dibutyl(methyl)magnesate was prepared by adding MeMgBr (5 ml, 15 mmol) and n-BuLi (18.75 mL, 30 mmol) to THE (6.25 ml) in a round-bottom flask at 0° C.
[0401] The stock soln of lithium dibutyl(methyl)magnesate (10 ml, 5 mmol) was added dropwise to a soln of 4-bromo-1-methyl-1H-pyrrolo[2,3-c]pyridine (979 mg, 4.64 mmol) in THE (25 ml) at −40° C. After 1 h acetaldehyde (2.6 ml, 46.40 mmol) was added at −40° C. The reaction was stirred for 1 h, allowing the temperature to reach −20° C. The reaction was quenched with saturated NH.sub.4Cl then extracted with EA. The combined organic layers were dried on MgSO.sub.4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with MeOH in DCM to give the title compound as beige solid (548 mg, 67%). MS ES+ m/z 177.1 [M+H].sup.+.
Preparation 87
1-(1-Methylpyrazolo[3,4-c]pyridin-4-yl)ethanol
##STR00251##
[0402] To a soln of MeMgBr (1.67 ml, 3.0 M soln, 5.0 mmol) in THE (10 ml) was added n-BuLi (6.25 ml, 1.6 M soln in hexane, 10.0 mmol) at 0° C. under N.sub.2. The reaction was stirred for 30 min. then cooled to −40° C. Next, 4-bromo-1-methyl-1H-pyrazolo[3,4-c]pyridine (1.01 g, 4.76 mmol) was added to the reaction. The resultant suspension was briefly (approx. 2 min) stirred at 0°

C. to reach complete dissolution of the solids. The soln was re-cooled to −40° C. and stirred for 1 h. Next, acetaldehyde (2.65 ml, 8.9 mmol) was added dropwise. The soln was stirred at −40° C. for 90 min. then the reaction was treated with saturated aq. NH.sub.4Cl soln and diluted with EA. The layers were separated, and the aq layer was extracted with EA (4×). The combined organic layers were dried on MgSO.sub.4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with MeOH in DCM to provide the title compound as beige solid (372 mg, 44%). MS ES+ m/z 178.2 [M+H].sup.+.

Preparation 88

1-(1-Isopropyltriazol-4-yl)ethanol

##STR00252##

[0403] MeMgBr in Et.sub.2O (2.5 M in Et.sub.2O, 2.2 ml, 5.47 mmol) was added dropwise to a soln of 1-isopropyl-1H-1,2,3-triazole-4-carbaldehyde (508 mg, 3.65 mmol) in THE (5 ml) at 0° C. under N.sub.2 and the reaction was allowed to stir at RT for 3 h. After that time, the soln was cooled to 0° C. and quenched with saturated NH.sub.4Cl (aq., 25 ml) and extracted with DCM (3×25 ml). The combined organic layers were dried over MgSO.sub.4, filtered, and concentrated in vacuo to give the title compound as a pale-yellow oil (558 mg, 99%). MS ES+ m/z 156.2 [M+H].sup.+.

[0404] The following compounds were prepared in a manner essentially analogous to the method of Preparation 88 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00018 TABLE 17 MS ES+ Prep # Chemical Name Structure m/z 89 1-(2-Cyclopropyl thiazol-4-yl)ethanol [00253]  embedded image 170 [M + H].sup.+ 90 1-(2-Methylthiazol- 4-yl)propan-1-ol [00254]  embedded image 158 [M + H].sup.+ 91 1-(2-Bromothiazol- 4-yl)ethanol [00255]  embedded image (.sup.79Br/.sup.81Br) 208/210 [M + H].sup.+

Preparation 92

1-(2-Isopropyltriazol-4-yl)ethanol

##STR00256##

[0405] 4-Bromo-2-isopropyl-2H-1,2,3-triazole (1.00 g, 5.26 mmol) was dissolved in 10 ml of THF under N.sub.2 and cooled to −78° C. A soln of n-BuLi (3.62 ml, 5.79 mmol, 1.6 M in hexane) was added dropwise. The soln was stirred at −78° C. for 45 min, then acetaldehyde (1.63 ml, 26.31 mmol) was added, and the reaction was slowly allowed to warm to RT then stirred for 18 h. The reaction was quenched with H.sub.2O (30 mL), extracted with EA (3×15 ml) and the combined organic layers were dried over MgSO.sub.4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography eluting with MeOH in DCM to afford the title compound as a pale-yellow oil (299 mg, 37%). .sup.1H NMR (400 MHz, CDCl.sub.3) δ (ppm): 7.51 (s, 1H), 5.04 (q, J=6.5 Hz, 1H), 4.79 (hept, J=6.7 Hz, 1H), 1.57 (t, J=6.5 Hz, 3H), 1.56 (d, J=6.7 Hz, 6H).

[0406] The following compounds were prepared in a manner essentially analogous to the method of Preparation 92 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00019 TABLE 18 MS ES+ Prep # Chemical Name Structure m/z 93.sup.1 1-(6-Bromopyrazin- 2-yl)ethanol [00257]  embedded image (.sup.79Br/.sup.81Br) 203/205 [M + H].sup.+ .sup.1Purified by silica gel chromatography eluting with 10% to 50% EA in cHex.

Preparation 94

1-[5-(Difluoromethyl)-3-pyridyl]ethanol

##STR00258##

[0407] In a separate flask, a degassed (by ultrasound) soln of 1-[5-(difluoromethyl)-3-pyridyl]ethanone (856 mg, 5.00 mmol) in aq FA (2.1 g, 1.7 ml, 45 mmol) and NEt.sub.3 (6.0 g, 60 mmol) was added [[(1S,2S)-2-amino-1,2-diphenyl-ethyl]-(p-tolylsulfonyl)amino]-chloro-ruthenium; 1-isopropyl-4-methyl-benzene (29 mg, 0.05 mmol) at RT. The mixture was stirred at RT

under N.sub.2 overnight. H.sub.2O and EtOH were added to the mixture and partially evaporated. Saturated aq NaHCO.sub.3 was added to ensure high pH and mixture was extracted with EA (4×). Combined organic layers were dried over Na.sub.2SO.sub.4 and filtered. DE was added, and the suspension was evaporated. The residue was purified by silica gel chromatography eluting with 30% to 90% EA in cHex to afford the title compound (815 mg, 94%) as a green oil. MS ES+ m/z 174 [M+H].sup.+.

[0408] The following compounds were prepared in a manner essentially analogous to the method of Preparation 94 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00020 TABLE 19 MS ES+ Prep # Chemical Name Structure m/z 95.sup.1 1-[6-(Trifluoromethyl)pyrazin- 2-yl]ethanol [00259]  embedded image 193 [M + H].sup.+ 96.sup.2 1-(2,5-Dimethylthiazol-4- yl)ethanol [00260]  embedded image 158 [M + H].sup.+ .sup.1Purified by silica gel chromatography eluting with 5% EA in cHex (2 CV), 5% to 50% EA in cHex (15 CV), 50% to 100% EA in cHex (5 CV). .sup.2Purified by silica gel chromatography eluting with 0% to 50% EA in cHex.

Preparation 97

1-(2-Methoxythiazol-4-yl)ethanol

##STR00261##

[0409] In a glass pressure flask 1-(2-bromothiazol-4-yl)ethanol (2.14 g, 9.25 mmol) in MeOH (23 ml) was added a soln of NaOMe (30 mass %) in MeOH (23 ml). The headspace was purged with N.sub.2, and the flask was sealed. The reaction was stirred at 50° C. After 6 h, the reaction was stirred overnight at RT. The next day heating was resumed for 4 h. Upon cooling to RT, the reaction was poured over aq saturated NH.sub.4Cl soln (150 ml), and DCM (30 ml) was added. The organic layer was separated and the aq layer was extracted with DCM (3×20 ml). The combined organic layers were dried over Na.sub.2SO.sub.4, filtered, and concentrated. The residue was dissolved in DCM, dry-loaded onto DE and purified by silica gel column chromatography eluting with the following conditions: 100% cHex (1 CV), 0% to 35% EA in cHex (16 CV), 35% to 50% EA in cHex (14 CV). .sup.1H NMR (400.21 MHz, CDCl.sub.3): δ 6.50 (d, J=1.0 Hz, 1H), 4.82-4.77 (m, 1H), 4.08 (s, 3H), 2.37 (d, J=4.4 Hz, 1H, OH), 1.53 (d, J=6.4 Hz, 3H).

Preparation 98

1-[5-(Trifluoromethyl)pyridazin-3-yl]ethanol

##STR00262##

[0410] To a stirred soln of 1-[5-(trifluoromethyl)pyridazin-3-yl]ethanone (810 mg, 4.26 mmol) in MeOH (10 ml) was added NaBH.sub.4 (48.35 mg, 1.28 mmol) at 0° C. under a N.sub.2. The resulting mixture was stirred for 30 min at RT. The reaction was quenched with H.sub.2O (10 ml) at 0° C. The mixture was extracted with EA (3×20 ml). The combined organic layers were washed with brine (2×10 ml), dried over anhydrous Na.sub.2SO.sub.4, filtered, and concentrated to obtain the title compound (800 mg, 98%). .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ 9.61 (d, 1H), 8.10 (d, 1H), 5.88 (d, 1H), 5.14-5.08 (m, 1H), 1.50 (d, 3H).

[0411] The following compounds were prepared in a manner essentially analogous to the method of Preparation 98 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00021 TABLE 20 MS Prep ES+ # Chemical Name Structure m/z 99 1-(3,6-Dimethylpyrazin- 2-yl)ethanol [00263]  embedded image 153 [M + H].sup.+ 100 1-(4-Cyclopropyl-5- fluoro-2-pyri- dyl)ethanol [00264]  embedded image 182.1 [M + H].sup.+ 101 1-(7-Fluoro-4- isoquinolyl)ethanol [00265]  embedded image 192.2 [M + H]+ 102 Cyclopropyl-(5-fluoro- 2-pyridyl)methanol [00266]  embedded image a 103 Cyclobutyl-(5-fluoro- 2-pyridyl)methanol [00267]  embedded image a .sup.aMaterial used in subsequent step without further characterization.

Preparation 104

[1-(5-Bromo-2-pyridyl)-3,3-difluoro-cyclobutyl]methanol
##STR00268##
[0412] To a soln of methyl 1-(5-bromo-2-pyridyl)-3,3-difluoro-cyclobutanecarboxylate (11.0 g, crude) in THE (100 ml) was treated with LiBH.sub.4 (0.78 g, 35.94 mmol) in portions at RT under N.sub.2. After stirring at RT for 3 h, the reaction was quenched with sat. NH.sub.4Cl and concentrated. The residue was purified by silica gel chromatography eluting with PE/EA (5:1) to afford the title compound (1.8 g, 16% over 2 steps) as a yellow solid. MS ES+ m/z 278/280 [M+H].sup.+.
Preparation 105
2-Benzyloxy-1-(3,5-difluoro-2-pyridyl)ethanol
##STR00269##
[0413] To 2-bromo-3,5-difluoropyridine (5 g, 25.78 mmol) in toluene (50 ml) was treated with i-PrMgCl (19.33 ml, 38.66 mmol, 2M in THF) at 0° C. under N.sub.2. After stirring for 3 h at RT, the reaction was cooled to 0° C. and treated with 2-(benzyloxy)acetaldehyde (3.10 g, 20.62 mmol). The reaction was stirred for 2 h at RT then quenched with saturated aq NH.sub.4Cl (200 mL). The reaction was extracted with EA (3×300 ml). The combined organic layers were washed with brine (2×200 ml), dried over Na.sub.2SO.sub.4, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with PE/EA (4:1) to obtain the title compound (1.6 g, 23%) as a light-yellow oil. MS ES+ m/z 266 [M+H].sup.+.
Preparation 106
1-(5-Fluoropyrimidin-2-yl)ethane-1,2-diol
##STR00270##
[0414] To a mixture of 2-ethenyl-5-fluoropyrimidine (15.0 g, crude) and K.sub.2OsO.sub.4.Math.2H.sub.2O (1.38 g, 3.75 mmol) in ACN:H.sub.2O (6:1, 140 ml) was added NMO (17.56 g, 149.86 mmol) at 0° C. under N.sub.2. The resulting mixture was stirred for 2 h at RT under N.sub.2. The reaction was diluted with H.sub.2O (20 ml), extracted with MTBE (3×200 ml). The aq layer was extracted with CHCl.sub.3:IPA (3:1) (3×250 ml). The combined organic layers were washed with brine (3×50 ml), dried over Na.sub.2SO.sub.4, filtered and concentrated to afford the title compound (6.0 g, 51%) as a black oil. MS ES+ m/z 159 [M+H].sup.+.
Preparation 107
1-(5-Fluoropyrimidin-2-yl)-2-(2-trimethylsilylethoxymethoxy)ethanol
##STR00271##
[0415] To a mixture of 1-(5-fluoropyrimidin-2-yl)ethane-1,2-diol (6.0 g, 37.94 mmol) and DIEA (14.71 g, 113.83 mmol) in DCM (60 ml) was added SEM-Cl (4.43 g, 26.56 mmol) dropwise at 0° C. under N.sub.2. The mixture was stirred for 1 h at RT. The reaction was quenched by the addition of MeOH (20 ml) at RT. The mixture was stirred for 30 min then concentrated in vacuo. The residue was purified by silica gel chromatography eluting with PE/EA (6:1 to 4:1) to afford the title compound (3.0 g, 27%) as a yellow oil. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 8.93 (d, 2H), 4.93-4.86 (m, 1H), 4.78-4.71 (m, 2H), 4.66-4.60 (m, 1H), 3.83-3.74 (m, 2H), 3.59-3.41 (m, 2H), 0.84-0.59 (m, 2H), 0.03-0.03 (s, 9H). MS ES+ m/z 289 [M+H].sup.+.
[0416] 2-(5-Fluoropyrimidin-2-yl)-2-(2-trimethylsilylethoxymethoxy)ethanol was also isolated after chromatography (600 mg, 5%). .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 8.91 (d, 2H), 5.56 (d, 1H), 4.89-4.75 (m, 1H), 4.61-4.53 (m, 2H), 3.98-3.71 (m, 2H), 3.47-3.38 (m, 2H), 0.88-0.78 (m, 2H), 0.03-0.03 (s, 9H). MS ES+ m/z 289 [M+H].sup.+.
Preparation 108
2-[tert-Butyl(dimethyl)silyl]oxy-1-(5-fluoro-2-pyridyl)ethanol
##STR00272##
[0417] A toluene soln (10 ml) of 2-bromo-5-fluoropyridine (1.2 g, 6.82 mmol) at 0° C. was treated dropwise with i-PrMgCl (5.11 ml, 10.23 mmol, 2M in THF) under N.sub.2. The resulting mixture was stirred for 30 min at 0° C. and treated with 2-[tert-butyl(dimethyl) silyl]oxyacetaldehyde (1.78

g, 10.23 mmol) dropwise over 10 min. The resulting mixture was stirred for 2 h at 0° C., quenched with H.sub.2O, and extracted with EA (3×20 mL). The combined organic layers were washed with brine (2×10 ml), dried over anhydrous Na.sub.2SO.sub.4, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with PE/EA (10:1 to 5:1) to obtain the title compound (420 mg, 23%) as a colorless oil. MS ES+ m/z 272 [M+H].sup.+.

Preparation 109

2-(2-Benzyloxy-1-methoxy-ethyl)-3,5-difluoro-pyridine

##STR00273##

[0418] A soln of 2-benzyloxy-1-(3,5-difluoro-2-pyridyl)ethanol (1.5 g, 5.66 mmol) and CH.sub.3I (1.20 g, 8.48 mmol) in THE (20 ml) was treated with t-BuOK (6.79 ml, 6.79 mmol, 1M in THF) at 0° C. under a N.sub.2. The resulting mixture was stirred for 1 h at RT, quenched with saturated aq NH.sub.4Cl (100 ml), and extracted with EA (3×200 ml). The combined organic layers were washed with brine (2×200 ml), dried over Na.sub.2SO.sub.4, filtered, and concentrated to obtain the title compound (1.52 g, 96%) as a light-yellow oil. MS ES+ m/z 280 [M+H].sup.+.

Preparation 110

tert-Butyl-[2-(5-fluoro-2-pyridyl)-2-methoxy-ethoxy]-dimethyl-silane

##STR00274##

[0419] A soln (30 ml) of 2-[tert-butyl(dimethyl)silyl]oxy-1-(5-fluoro-2-pyridyl)ethanol (3.0 g, 11.05 mmol) and CH.sub.3I (7.84 g, 55.27 mmol) in THE (30 ml) at 0° C. was treated in portions with NaH (0.53 g, 22.11 mmol, 60% wt) under N.sub.2. After stirring at RT for 2 h, the reaction was quenched with H.sub.2O (50 ml) and extracted with EA (2×50 ml). The combined organic layers were washed with brine (2×80 ml), dried over anhydrous Na.sub.2SO.sub.4, filtered, and concentrated to obtain the title compound (2.9 g, 92%) as a yellow solid. MS ES+ m/z 286 [M+H].sup.+.

Preparation 111

2-[[2-(5-Fluoropyrimidin-2-yl)-2-methoxy-ethoxy]methoxy]ethyl-trimethyl-silane

##STR00275##

[0420] To a stirred mixture of 1-(5-fluoropyrimidin-2-yl)-2-(2-trimethylsilylethoxy methoxy)ethanol (1.01 g, 3.50 mmol) in THE (10 ml) was added CH.sub.3I (746 mg, 5.25 mmol) and Ag.sub.2O (2.43 g, 10.51 mmol) in portions at RT under N.sub.2. The reaction was stirred for 4 h at 60° C. under N.sub.2. Upon cooling to RT the reaction was concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with DCM/EA (2:1 to 3:1) to afford the title compound (948 mg, 90%) as a yellow oil. MS ES+ m/z 303 [M+H].sup.+.

Preparation 112

5-Bromo-2-[3,3-difluoro-1-(tetrahydropyran-2-yloxymethyl)cyclobutyl]pyridine

##STR00276##

[0421] A soln of [1-(5-bromo-2-pyridyl)-3,3-difluoro-cyclobutyl]methanol (1.7 g, 6.113 mmol) and DHP (2.57 g, 30.565 mmol) in DCM (10 ml) was treated with TsOH (10.5 mg, 0.06 mmol) under N.sub.2. After stirring at 50° C. for 2 h, the reaction was allowed to cool to RT and concentrated. The residue was purified by silica gel chromatography eluting with PE/EA (20:1) to afford the title compound (2.1 g, 94.8%) as a yellow oil. MS ES+ m/z 362/364 [M+H].sup.+.

Preparation 113

2-[3,3-Difluoro-1-(tetrahydropyran-2-yloxymethyl)cyclobutyl]-5-fluoro-pyridine

##STR00277##

[0422] A soln of 5-bromo-2-[3,3-difluoro-1-(tetrahydropyran-2-yloxymethyl) cyclobutyl]pyridine (2.0 g, 5.5 mmol) in THE (20 ml) was treated dropwise with n-BuLi (2.87 ml, 7.18 mmol, 2.5 M in hexane) at −70° C. under N.sub.2. The reaction was stirred for 15 min at −70° C. and then treated with NFSI (3.48 g, 11.04 mmol). The reaction was stirred for an additional hour at −70° C. then quenched with H.sub.2O at RT. The resulting mixture was extracted with EA (3×100 ml), combined organic layers were washed with brine (2×100 ml), dried over Na.sub.2SO.sub.4,

filtered, and concentrated. The residue was purified by silica gel chromatography, eluting with PE/EA (20:1). To afford the title compound (930 mg, crude) as a yellow oil. MS ES+ m/z 302 [M+H].sup.+.

Preparation 114

[3,3-Difluoro-1-(5-fluoro-2-pyridyl)cyclobutyl]methanol

##STR00278##

[0423] A soln of 2-[3,3-difluoro-1-(tetrahydropyran-2-yloxymethyl)cyclobutyl]-5-fluoro-pyridine (900 mg, crude) in THE (10 mL) was treated with aq HCl (2.5 ml, 12M) at RT under N.sub.2. After stirring at RT for 3 h, the reaction was diluted with H.sub.2O (50 ml), basified to pH 7-8 with aq NaHCO.sub.3, and extracted with EA (3×50 ml). The combined organic layers were washed with brine (2×50 ml), dried over Na.sub.2SO.sub.4, filtered, and concentrated. The residue was purified by Prep-TLC:PE/EA (5:1) to afford the title compound (450 mg, 69%) as a light-yellow oil. MS ES+ m/z 218 [M+H].sup.+.

Preparation 115

2-(3,5-Difluoro-2-pyridyl)-2-methoxy-ethanol

##STR00279##

[0424] A soln of 2-benzyloxy-1-(3,5-difluoro-2-pyridyl)ethanol (1.5 g, 5.37 mmol) in TFA (15 ml) was stirred for 4 h at 80° C. under N.sub.2. The reaction was allowed to cool to RT, diluted with H.sub.2O (50 ml), basified to pH 9 with K.sub.2CO.sub.3, and extracted with EA (3×100 ml). The combined organic layers were washed with brine (2×100 ml), dried over Na.sub.2SO.sub.4, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with PE/EA (5:1 to 4:1) to afford the title compound (545 mg, 54%) as a light-yellow oil. MS ES+ m/z 190 [M+H].sup.+.

Preparation 116

2-(5-Fluoro-2-pyridyl)-2-methoxy-ethanol

##STR00280##

[0425] A soln of tert-butyl-[2-(5-fluoro-2-pyridyl)-2-methoxy-ethoxy]-dimethyl-silane (2.9 g, 10.16 mmol) in DCM (5 ml) was treated dropwise with 4M HCl in 1,4-dioxane (30 ml) at RT under N.sub.2. When complete, the reaction was concentrated and the residue dissolved in 50 ml of H.sub.2O, basified to pH 9 with saturated aq Na.sub.2CO.sub.3, and extracted with EA (2×60 ml). The combined organic layers were washed with brine (2×40 ml), dried over Na.sub.2SO.sub.4, and concentrated to obtain the title compound (1.6 g, crude) as a yellow oil. MS ES+ m/z 172 [M+H].sup.+.

Preparation 117

2-(5-Fluoropyrimidin-2-yl)-2-methoxy-ethanol

##STR00281##

[0426] To 2-[[2-(5-fluoropyrimidin-2-yl)-2-methoxy-ethoxy]methoxy]ethyl-trimethyl-silane (925 mg, 3.06 mmol) in MeOH (9 ml) was added conc. HCl (3 ml) dropwise at RT under N.sub.2. The reaction was stirred for 2 h at RT then quenched with H.sub.2O (100 ml). The mixture was basified to pH 8 with NaHCO.sub.3. The aqueous layer was extracted with EA (3×100 ml). The combined organic layers were concentrated in vacuo to afford the title compound as a white solid (450 mg, 85%). MS ES+ m/z 173 [M+H].sup.+.

Preparation 118

1-[5-(Trifluoromethyl)-3-pyridyl]ethanamine

##STR00282##

[0427] A soln of 1-[5-(trifluoromethyl)-3-pyridyl]ethanone (0.77 g, 4.06 mmol) in EtOH (30 ml) was treated with NH.sub.4OAc (4.7 g, 61 mmol) and stirred at RT for 20 min. The reaction was treated with NaBH.sub.3CN (0.54 g, 8.12 mmol) and stirred at RT for 1 h and then at 85° C. for 1.25 h. The reaction was allowed to cool to RT and concentrated. The resulting oil was loaded onto an SCX cartridge. Non-basic impurities were washed off the cartridge with MeOH then the title

compound was eluted with methanolic ammonia (2M). The resulting oil was purified by reversed phase (Claricep C) chromatography eluting with 20% to 50% aq NH.sub.4CO.sub.3 in ACN to obtain the title compound (1.9 g, 77%) as a yellow oil. MS ES+ m/z 191 [M+H].sup.+.

Preparation 119

N-Benzyl-3,3,3-trifluoro-2-(5-fluoro-2-pyridyl)propan-1-amine

##STR00283##

[0428] A THE soln (30 ml) of 5-Fluoro-2-[1-(trifluoromethyl)vinyl]pyridine (3.4 g, 17.79 mmol) was treated with benzylamine (3.81 g, 35.58 mmol) under N.sub.2. After stirring at 50° C. for 2 h, the reaction was cooled to RT, diluted with H.sub.2O (100 ml) and extracted with EA (3×100 ml). The combined organic layers were washed with brine (100 ml), dried over Na.sub.2SO.sub.4, filtered, and concentrated. The residue was purified by silica gel chromatography, eluting with PE/EA (20:1 to 10:1), to afford the title compound (4.0 g, 75%) as a colorless oil. MS ES+ m/z 299 [M+H].sup.+.

Preparation 120

3,3,3-Trifluoro-2-(5-fluoro-2-pyridyl)propan-1-amine

##STR00284##

[0429] To a soln of N-benzyl-3,3,3-trifluoro-2-(5-fluoro-2-pyridyl)propan-1-amine (3.50 g, 11.73 mmol) in IPA (50 ml) was added Pd/C (2.50 g, 23.47 mmol) and Pd(OH).sub.2/C (2.82 g, 20.11 mmol) under N.sub.2. The resulting mixture was stirred for 2 h at RT under H.sub.2. The mixture was filtered and washed with MeOH (3×10 ml). The filtrate was concentrated to afford the title compound (2.0 g, crude). MS ES+ m/z 209 [M+H].sup.+.

Preparation 121

3-(1-Chloroethyl)-5-(trifluoromethyl)pyridine

##STR00285##

[0430] To a stirred mixture of 1-[5-(trifluoromethyl)pyridin-3-yl]ethanol (36.00 g, 188 mmol) in DCM (400 ml) was add SOCl.sub.2 (44.81 g, 376 mmol) at RT under N.sub.2. The resulting mixture was stirred for 2 h at RT. The reaction was quenched with H.sub.2O (500 ml). The mixture was extracted with DCM (3×500 ml). The combined organic layers were washed with brine (1×500 ml), dried over anhydrous Na.sub.2SO.sub.4. After filtration, the filtrate was concentrated under reduced pressure to afford the title compound (40 g, crude) as a yellow oil. ES+ m/z 210 [M+H].sup.+.

Preparation 122

4-(1-Chloroethyl)-2-isopropyl-triazole

##STR00286##

[0431] 1-(2-Isopropyltriazol-4-yl)ethanol (344 mg, 2.22 mmol) was dissolved in SOCl.sub.2 (3 mL) and toluene (3 ml), then refluxed for 1 h. The reaction was concentrated in vacuo to obtain the title compound as a brown oil (365 mg, quantitative). The material was immediately used in the next step.

[0432] The following compounds were prepared in a manner essentially analogous to the method of Preparation 122 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00022 TABLE 21 .sup.1H NMR Prep # Chemical Name Structure (400 MHz, DMSO-d.sub.6) δ 123.sup.1 4-(1-Chloroethyl)-1- isopropyl-triazole [00287]embedded image 8.29 (s, 1H), 5.44 (q, J = 6.8 Hz, 1H), 4.80 (hept, J = 6.7 Hz, 1H), 1.84 (d, J = 6.8 Hz, 3H), 1.48 (d, J = 6.7 Hz, 5H) 124.sup.2,3 4-(1-Chloroethyl)-1- methyl- pyrazolo[3,4- c]pyridine hydrochloride [00288] embedded image 9.47 (s, 1H), 8.62 (s, 1H), 8.45 (s, 1H), 5.83 (q, J = 6.8 Hz, 1H), 4.27 (s, 3H), 2.00 (d, J = 6.9 Hz, 3H) HCl 125.sup.3,4 4-(1-Chloroethyl)-1- methyl-pyrrolo[2,3- c]pyridine hydrochloride [00289]embedded image 9.39 (s, 1H), 8.46 (s, 1H), 8.34 (d, J = 2.9 Hz, 1H), 7.14 (dd, J = 2.9, 0.6 Hz, 1H), 5.88 (q, J = 6.9 Hz, 1H), 4.09 (s, 3H), 1.99 (d, J = 6.9 Hz, 3H) HCl 126.sup.2,3 4-(1-Chloroethyl)-7- fluoroisoquinoline hydrochloride [00290]embedded image 9.39

(s, 1H), 8.74 (s, 1H), 8.45 (dd, J = 9.3, 5.2 Hz, 1H), 8.08 (dd, J = 9.1, 2.7 Hz, 1H), 7.90 (td, J = 9.0, 2.7 Hz, 1H), 6.17 (q, J = 6.9 Hz, 1H), 2.05 (d, J = 6.8 Hz, 3H) HCl .sup.1Reaction refluxed in a 1:1 mixture SOCl.sub.2:toluene. .sup.2Reaction run in a 1:1 mixture SOCl.sub.2:DCM at RT. .sup.3Reaction was evaporated and co-evaporated with toluene. .sup.4Reaction run in a 1:5 mixture SOCl.sub.2:DCM at RT.

Preparation 127

4-[1-Chloroethyl]-2-cyclopropyl-thiazole

##STR00291##

[0433] MsCl (0.16 ml, 2.1 mmol) was added dropwise to a soln of 1-(2-cyclopropylthiazol-4-yl)ethanol (320.5 mg, 1.76 mmol) and NEt.sub.3 (0.49 ml, 3.5 mmol) in DCM (7 ml) cooled to 0° C. under N.sub.2. The reaction was stirred at 0° C. for 1 h then the cooling bath was removed. After 3.5 h the reaction was re-cooled to 0° C. and quenched by slow addition of H.sub.2O (5 ml). The layers were separated, and the aq layer was extracted with DCM (3 ml). The combined organics layers were washed with brine (5 ml), dried over Na.sub.2SO.sub.4, filtered, and concentrated to afford the title compound (316 mg, 95%) as a brown oil. .sup.1HNMR (400 MHz, CDCl.sub.3): δ 7.03 (s, 1H), 5.18 (qd, J=6.8, 0.6 Hz, 1H), 2.38-2.33 (m, 1H), 1.90 (d, J=6.8 Hz, 3H), 1.18-1.15 (m, 4H).

[0434] The following compounds were prepared in a manner essentially analogous to the method of Preparation 127 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00023 TABLE 22 .sup.1H NMR Prep # Chemical Name Structure (400 MHz, CDCl.sub.3) δ 128 4-(1-Chloropropyl)- 2-methyl-thiazole [00292]  7.11 (d, J = 0.6 Hz, 1H), 4.96 (dd, J = 6.0, 7.9 Hz, 1H), 2.73 (3, 3H), 2.32-2.24 (m, 2H), 1.05 (t, J = 7.3 Hz, 3H) 129 4-(1-Chloroethyl)-2- methoxy-thiazole [00293]  6.65 (d, J = 0.7 Hz, 1H), 5.04 (qd, J = 6.8, 0.6 Hz, 1H), 4.10 (s, 3H), 1.86 (d, J = 6.8 Hz, 3H)

Preparation 130

1-(3,6-Dimethylpyrazin-2-yl)ethyl methanesulfonate

##STR00294##

[0435] MsCl (903.09 mg, 7.88 mmol) was added dropwise at 0° C. to a stirred mixture of 1-(3,6-dimethylpyrazin-2-yl)ethanol (1 g, 6.57 mmol) and DIEA (127.38 mg, 0.99 mmol) in DCM (10 ml) under N.sub.2 and stirred for 2 h. The reaction was removed from the cooling bath, quenched with H.sub.2O (10 ml), and extracted with DCM (3×10 ml). The combined organic layers were washed with brine (3×10 ml), dried over Na.sub.2SO.sub.4, filtered, and concentrated to obtain the title compound (1.1 g, 73%) as a brown oil. MS ES+ m/z 231 [M+H].sup.+.

[0436] The following compounds were prepared in a manner essentially analogous to the method of Preparation 130 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as

TABLE-US-00024 TABLE 23 MS ES+ Prep # Chemical Name Structure m/z 131 [(1S)-1-(2-Pyridyl)ethyl] methanesulfonate [00295]  202 [M + H].sup.+ 132 1-[1-(Trifluoromethyl) pyrazol-3-yl]ethyl methanesulfonate [00296]  a 133 1-(4-Cyclopropyl-5-fluoro- 2-pyridyl)ethyl methanesulfonate [00297]  a 134 1-[5-(Difluoromethyl)-3- pyridyl]ethyl methanesulfonate [00298]  252 [M + H].sup.+ 135 [Cyclopropyl-(5-fluoro-2- pyridyl)methyl] methanesulfonate [00299] a 136 1-(6-Bromopyrazin-2- yl)ethyl methanesulfonate [00300]  (.sup.79Br/.sup.81Br) 281/283 [M + H].sup.+ 137 [Cyclobutyl-(5-fluoro-2- pyridyl)methyl] methanesulfonate [00301]  a 138 1-(2,5-Dimethylthiazol-4- yl)ethyl methanesulfonate [00302] a 139 1-[6- (Trifluoromethyl)pyrazin-2- yl]ethyl methanesulfonate [00303]  271 [M + H].sup.+ 140 [2-Methyl-2-(2- pyridyl)propyl] methanesulfonate [00304]  a .sup.aMaterial used in subsequent step without further characterization.

Preparation 141
2-Bromo-1-(5-fluoro-2-pyridyl)pyridine
##STR00305##
[0437] NBS (1.14 g, 6.38 mmol) was added in small portions over a 5-10 min period to a soln of 3-chloro-2-(1-ethoxyvinyl)-5-fluoro-pyridine (1.22 g, 6.06 mmol) in a mixture of THE (12 ml) and H.sub.2O (3 ml) at 0° C. The reaction was stirred at 0° C. for 1 hr then diluted with EA (50 ml), washed with H.sub.2O (50 ml) and brine (50 ml), dried over MgSO.sub.4, filtered, concentrated in vacuo. The residue was purified by silica gel chromatography eluting with EA in heptane to afford the title compound as a pale yellow oil (1.394 g, 91%). .sup.1H NMR (400 MHz, CDCl.sub.3) δ (ppm): 8.44 (d, J=2.3 Hz, 1H), 7.61 (dd, J=7.9, 2.4 Hz, 1H), 4.69 (s, 2H).
[0438] The following compounds were prepared in a manner essentially analogous to the method of Preparation 141 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.
TABLE-US-00025 TABLE 24 MS ES+ Prep # Chemical Name Structure m/z 142.sup.1 2-Bromo-1-(4-chloro-5-fluoro- 2-pyridyl)ethanone [00306]  embedded image (.sup.79Br/.sup.18Br) 251.8/253.9 [M + H].sup.+ .sup.1Purified by silica gel chromatography eluting with EA in heptane.
Preparation 143
2-Bromo-1-(3,5-difluoro-2-pyridyl)ethanone
##STR00307##
[0439] A soln of phenyltrimethylammonium bromide (51.36 g, 133 mmol) in THE (423 ml) was treated with a THE soln (181 mL) of 1-(3,5-difluoro-2-pyridyl)ethanone (20 g, 120.93 mmol) at RT under N.sub.2. After stirring at 60° C. for 1.5 h, the mixture was cooled to RT and stirred for 1 h. The resulting suspension was filtered, and the solids were washed with THE (2×100 ml). The combined filtrates were concentrated to obtain a brown oil which was purified by silica gel chromatography eluting with a gradient of 10% to 50% DCM in cHex to obtain the title compound (15 g, 42%) as a yellow oil. MS ES+ m/z (.sup.79Br/.sup.81Br) 237 [M+H].sup.+.
[0440] The following compounds were prepared in a manner essentially analogous to the method of Preparation 143 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.
TABLE-US-00026 TABLE 25 Prep MS ES+ # Chemical Name Structure m/z 144.sup.1 2-Bromo-1-(3- chloro-5-fluoro- 2-pyridyl)ethanone [00308]  embedded image 252/254 (.sup.79Br/.sup.81Br) [M + H].sup.+ .sup.1Purified by silica gel chromatography eluting with a gradient of 5% to 30% DCM in cHex.
Preparation 145
2-Chloro-1-(5-fluoropyrimidin-2-yl)ethanone
##STR00309##
[0441] To a stirred solution of 2-bromo-5-fluoropyrimidine (3.0 g, 16.95) in toluene (30 ml) was added dropwise i-PrMgCl (1 M in THF)(10.17 mL, 20.340 mmol) at 0° C. under N.sub.2. The reaction was stirred for 2 h at RT. To the above mixture was added 2-chloro-N-methoxy-N-methylacetamide (2.33 g, 16.95 mmol) dropwise over a 20 min period at 0° C. under N.sub.2. The reaction was stirred for 1 h at RT then quenched with saturated aq NH.sub.4Cl (200 ml). The mixture was extracted with EA (2×300 ml). The combined organic layers were washed with brine (2×300 ml), dried over Na.sub.2SO.sub.4, filtered and concentrated in vacuo to afford the title compound (2.3 g, 78%) as a yellow oil. MS ES+ m/z 175 [M+H].sup.+.
Preparation 146
6-Bromo-3-iodo-4-methoxy-pyrazolo[1,5-a]pyridine
##STR00310##
[0442] 6-Bromo-4-methoxypyrazolo[1,5-a]pyridine (0.41 g, 1.81 mmol) and NIS (609 mg, 2.71 mmol) were dissolved in ACN (8 mL) and stirred at RT for 1 hr. The suspension was filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography

eluting with a linear gradient of 0% to 100% EA in heptane. The fractions containing the title compound was concentrated in vacuo and combined with the filtered solid to afford the title compound (0.60 g, 94.1%). ES/MS m/z (.sup.79Br/.sup.81Br) 352.6/354.6 [M+H].sup.+.

Preparation 147

6-Bromo-4-methoxy-3-(trifluoromethyl)pyrazolo[1,5-a]pyridine

##STR00311##

[0443] 6-Bromo-3-iodo-4-methoxy-pyrazolo[1,5-a]pyridine (2 g, 5.67 mmol) was dissolved in DMF (28 ml) and treated with CuI (3.8 g, 20 mmol). N.sub.2 was bubbled through the mixture for 5 min, then methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (3.9 g, 20 mmol) was added, and the reaction was stirred at 80° C. for 2 h. Upon cooling to RT, the reaction was diluted with EA, filtered, and solids were washed with EA. The filtrate was diluted with H.sub.2O and the layers were separated. The organic layer was dried over MgSO.sub.4, filtered, and concentrated to obtain the title compound (582 mg, 29%) as a yellow solid. MS ES+ m/z 295/297 [M+H].sup.+.

Preparation 148

6-Bromo-3-fluoro-4-methoxy-pyrazolo[1,5-a]pyridine

##STR00312##

[0444] A soln of 6-bromo-4-methoxypyrazolo[1,5-a]pyridine (5 g, 22.021 mmol) and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (7.04 g, 22.02 mmol) in ACN (50 ml) was stirred overnight at RT under N.sub.2. The resulting mixture was diluted with H.sub.2O (50 ml) and extracted with EA (3×100 ml). The combined organic layers were washed with brine (2×100 ml), dried over anhydrous Na.sub.2SO.sub.4, filtered, and concentrated. The residue was purified by reversed phase C18 flash chromatography with the following conditions: Column, C18; mobile phase, eluting with a gradient of 30% to 40% ACN in H.sub.2O (0.1% FA); 254 nm to obtain the title compound (810 mg, 15%) as a yellow solid. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 8.56 (t, 1H), 8.04 (d, 1H), 6.77 (d, 1H), 3.97 (s, 3H).

Preparation 149

6-Bromo-4-methoxy-3-methyl-pyrazolo[1,5-a]pyridine

##STR00313##

[0445] Et.sub.3Si (8.0 ml, 50.20 mmol) was added dropwise to a solution of (6-bromo-4-methoxypyrazolo[1,5-a]pyridin-3-yl)methanol (6.45 ml, 25.10 mmol) in TFA (50 ml) at 0° C. The reaction was allowed to warm to RT and stirred overnight. The reaction was concentrated in vacuo and the residue was dissolved in DCM, washed with saturated aq Na.sub.2CO.sub.3 (2×), dried over MgSO.sub.4, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with EA in heptane to afford the title compound as a white solid (3.81 g, 63%). MS ES+ m/z (.sup.35Cl/.sup.37Cl) 241/243 [M+H].sup.+.

Preparation 150

7-Chloro-5-methoxy-imidazo[1,2-a]pyridine

##STR00314##

[0446] A soln of 4-chloro-6-methoxypyridin-2-amine (7.00 g, 44.14 mmol), chloroacetaldehyde (8.32 g, 52.99 mmol, 50%) and NaHCO.sub.3 (11.12 g, 132.42 mmol) in n-BuOH (140 ml) was divided into fourteen batches and stirred overnight at 65° C. in sealed tubes. The soln was cooled to RT, diluted with H.sub.2O (200 ml) and extracted with EA (3×200 mL). The organic layers were combined, dried over Na.sub.2SO.sub.4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 50% EA in PE to give the title compound as a light-brown solid (6.1 g, 76%). ES/MS m/z 183 [M+H]+.

Preparation 151

6-Bromo-4-hydroxy-pyrazolo[1,5-a]pyridine-3-carbonitrile

##STR00315##

[0447] A suspension of 6-bromo-4-methoxy-pyrazolo[1,5-a]pyridine-3-carbonitrile (100 g, 396.72 mmol) in 1 L of DMA was treated with a soln of NaOH (31.7 g, 793 mmol) in H.sub.2O (100 ml)

in one portion at 40° C. followed by treatment with NDM (161 g, 793 mmol). After stirring at 50° C. for 1 h, the reaction was cooled to 0° C., quenched with 37% aq HCl (100 ml) to give a final pH of 5. The reaction was diluted with H.sub.2O (4 L) and the resulting solids were collected by filtration, washed with H.sub.2O (1 L) and heptane (500 ml) to obtain the title compound (85.5 g, 82%) as a beige solid. MS ES+ m/z 238 [M+H].sup.+.

Preparation 152

5,7-Dichloro-3-iodo-imidazo[1,2-a]pyridine

##STR00316##

[0448] A soln of 5,7-dichloroimidazo[1,2-a]pyridine (5.00 g, 26.74 mmol) in DCM (50 ml) was treated in portions with NIS (12.03 g, 53.47 mmol) at RT under N.sub.2. After stirring for 2 h at RT, the reaction was diluted with H.sub.2O (100 ml) and extracted with DCM (3×50 ml). The combined organic layers were washed with brine (3×50 ml), dried over Na.sub.2SO.sub.4, filtered, and concentrated to obtain the title compound (12.0 g, crude) as a dark yellow solid. MS ES+ m/z 313 [M+H].sup.+.

Preparation 153

5,7-Dichloroimidazo[1,2-a]pyridine-3-carbonitrile

##STR00317##

[0449] A DMF soln of 5,7-dichloro-3-iodo-imidazo[1,2-a]pyridine (11.00 g, 35.15 mmol) was treated in portions with CuCN (6.30 g, 70.31 mmol) at RT under N.sub.2. After stirring at 100° C. for 2 h, the reaction was allowed to cool to RT, treated dropwise with NH.sub.4OH (100 ml) over 5 min, diluted with H.sub.2O (300 ml), and stirred at RT for 2 h. The reaction was extracted with DCM (3×400 mL), and the combined organic layers were washed with brine (3×300 mL), dried over Na.sub.2SO.sub.4, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with PE/EA (5:1 to 1:2) to obtain the title compound (3.5 g, 47%) as a yellow solid. MS ES+ m/z (.sup.35Cl/.sup.37Cl) 212/214 [M+H].sup.+.

Preparation 154

7-Chloro-5-[2-(3,5-difluoro-2-pyridyl)-2-methoxy-ethoxy]imidazo[1,2-a]pyridine

##STR00318##

[0450] A stirred mixture of 2-(3,5-difluoro-2-pyridyl)-2-methoxy-ethanol (6.57 g, 34.76 mmol) and 5,7-dichloroimidazo[1,2-a]pyridine (6.5 g, 34.76 mmol) in THE (120 ml) was treated with t-BuOK (48.66 ml, 48.66 mmol, 1M in THF) dropwise at 0° C. under N.sub.2. After stirring at RT for 2 h, the reaction was quenched with saturated aq NH.sub.4Cl, extracted with EA (2×500 ml), washed with brine (2×200 ml), dried over Na.sub.2SO.sub.4, filtered, and concentrated. The residue was purified by reversed phase C18 flash chromatography eluting with a gradient of 40% to 50% ACN in H.sub.2O to afford the title compound as a light-yellow solid (1.75 g, 15%). MS ES+ m/z 340 [M+H].sup.+.

Preparation 155

6-bromo-4-[1-[5-(trifluoromethyl)-3-pyridyl]ethoxy]pyrazolo[1,5-a]pyridine-3-carbonitrile, Isomer 2

##STR00319##

[0451] To 6-bromo-4-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile (45.43 g, 190.84 mmol) in DMF (350 ml) were added K.sub.2CO.sub.3 (79.13 g, 572.52 mmol) and 3-(1-chloroethyl)-5-(trifluoromethyl)pyridine (40 g, crude) in portions over 2 min at 80° C. The reaction was stirred for 2 h at RT under N.sub.2. The resulting mixture was diluted with H.sub.2O (1 L), extracted with EA (3×1.5 L). The combined organic layers were washed with brine (5×1 L), dried over Na.sub.2SO.sub.4, and filtered. The filtrate was concentrated. The residue was purified by silica gel column chromatography, eluting with PE/EA (10:1 to 2:1) to afford the racemate of the title compound (32 g, 40.78%) as a yellow solid. MS ES+ m/z (.sup.79Br/.sup.81Br) 411/413 [M+H].sup.+.

[0452] The racemate of the title compound (32 g) was subjected to the following chromatography

conditions: SFC, Column: NB_CHIRAL ART Cellulose-SB; 5×25 cm, m, eluting with 15% IPA (0.2% DEA) in CO.sub.2 to afford the title compound, Isomer 2 (13.5 g, 42.19%), t.sub.R is 6.58 min with 99% ee. MS ES+ m/z (.sup.79Br/.sup.81Br) 411/413 [M+H].sup.+.

Preparation 156

6-Bromo-4-[(1R)-1-(2-pyridyl)ethoxy]pyrazolo[1,5-a]pyridine-3-carbonitrile tosylate

##STR00320##

[0453] A THE soln (300 ml) of PPh.sub.3 (34.1 g, 130 mmol) was treated dropwise over 4 min with DIAD (23.2 g, 115 mmol) at RT. After stirring at RT for 30 min, a THE soln (100 ml) of 6-bromo-4-hydroxy-pyrazolo[1,5-a]pyridine-3-carbonitrile (20 g, 76.5 mmol) and (1S)-1-(2-pyridyl)ethanol (11.3 g, 91.8 mmol) was added dropwise over 6 min. After stirring at RT for 45 min, the reaction was concentrated in vacuo. The residue was slurried in hexane/MTBE (4:1; 250 ml) and allowed to sit overnight at RT. The resulting solid was collected by filtration, washed with hexanes (2×100 ml) and purified by silica gel chromatography eluting with a gradient of 0% to 15% acetone in hexanes. The resulting solid was dissolved in MTBE (100 mL) and treated with 4-methylbenzenesulfonic acid hydrate (8.85 g, 46.5 mmol). The resulting suspension was stirred overnight at RT. The solid was collected by filtration and washed with MTBE (3×50 mL) to obtain the title compound (43.4 g, 87%) as a white solid. MS ES+(.sup.79Br/.sup.81Br) m/z 343/345 [M+H].sup.+.

Preparation 157

6-Bromo-3-chloro-4-[2-(5-fluoropyrimidin-2-yl)-2-methoxy-ethoxy]pyrazolo[1,5-a]pyridine

##STR00321##

[0454] To PPh.sub.3 (3.50 g, 13.34 mmol) in THE (10 ml) was added dropwise DIAD (2.52 g, 12.45 mmol) at 0° C. under N.sub.2. The reaction was stirred for 0.5 h at 0° C. Next, 6-bromo-3-chloropyrazolo[1,5-a]pyridin-4-ol (1.1 g, 4.45 mmol) and 2-(5-fluoropyrimidin-2-yl)-2-methoxy-ethanol (918.26 mg, 5.334 mmol, 1.2 equiv) in THE (10 mL) were added at RT. The reaction was stirred at RT for 2 h before being concentrated in vacuo. The residue was purified by reverse flash chromatography eluting with the following conditions: column, C18; mobile phase, 50% to 55% ACN in H.sub.2O to afford the title compound (700 mg, 39%) as a yellow solid. MS ES+ m/z 402/403 [M+H].sup.+.

Preparation 158

6-Bromo-4-[2-(5-fluoro-2-pyridyl)-2-oxo-ethoxy]pyrazolo[1,5-a]pyridine-3-carbonitrile

##STR00322##

[0455] A mixture of 6-bromo-4-hydroxy-pyrazolo[1,5-a]pyridine-3-carbonitrile (4 g, 16.80 mmol) and Cs.sub.2CO.sub.3 (8.21 g, 25.2 mmol) in ACN (20 ml) was stirred at RT under N.sub.2 for 0.5 h. A soln of 2-bromo-1-(5-fluoro-2-pyridyl)ethanone (4.6 g, 20 mmol) in ACN (20 ml) was added and the reaction was allowed to stir at RT for 1 h. The reaction was diluted with H.sub.2O (100 ml) that resulted in a suspension. The solid was collected by filtration and washed with H.sub.2O to obtain the title compound (5.86 g, 93%) as a white solid. MS ES+ m/z 375/377 [M+H].sup.+.

[0456] The following compounds were prepared in a manner essentially analogous to the method of Preparation 158 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as

TABLE-US-00027 TABLE 26 MS ES+ Prep # Chemical Name Structure m/z 159.sup.1,2 2-(6-Bromopyrazolo[1,5- a]pyridin-4-yl)oxy-1-(5- fluoro-2-pyridyl)ethanone [00323] (.sup.79Br/.sup.81Br) 350/352 [M + H].sup.+ 160.sup.1,3,4 2-(6-Bromo-3-chloro- pyrazolo[1,5-a]pyridin-4- yl)oxy-1-(5-fluoro-2- pyridyl)ethanone [00324] (.sup.79Br/.sup.81Br) 384/386 [M + H].sup.+ 161.sup.1,5,6 2-(6-Bromo-3-chloro- pyrazolo[1,5-a]pyridin-4- yl)oxy-1-(5-fluoropyrimidin- 2-yl)ethanone [00325] (.sup.79Br/.sup.81Br) 385/387 [M + H].sup.+ .sup.1DIPEA used as base for this transformation. .sup.2Workup: Reaction was concentrated in vacuo. Residue dissolved into MeOH and triturated with H.sub.2O. Precipitated product was collected by filtration.

.sup.3Reaction was heated at 80° C. .sup.4Workup: Reaction was concentrated in vacuo. Residue triturated in H.sub.2O. Precipitated product was collected by filtration. .sup.5Workup: Reaction was diluted with H.sub.2O, extracted with EA, dried over Na.sub.2SO.sub.4, filtered and concentrated in vacuo. .sup.6Purified by silica gel chromatography eluting with EA in DCM (1:30 to 1:15).

Preparation 162

1-(6-Bromopyrazolo[1,5-a]pyridin-4-yl)oxy-2-(5-fluoro-2-pyridyl)propan-2-ol

##STR00326##

[0457] A soln of 2-(6-bromopyrazolo[1,5-a]pyridin-4-yl)oxy-1-(5-fluoro-2-pyridyl)ethenone (3 g, 8.57 mmol) in THE (10 ml) was added to a stirred soln of MeMgBr (3M in Et.sub.2O, 14.3 ml, 42.84 mmol) in THE (30 ml) at RT under N.sub.2 and the reaction was allowed to stir for 2 h. The soln was quenched with H.sub.2O (50 ml) and extracted with EA (3×50 ml). The combined organic layers were washed with brine (3×50 ml), dried over Na.sub.2SO.sub.4, filtered, and concentrated in vacuo to obtain the title compound (3 g, crude) as a brown oil. MS ES+ m/z (.sup.79Br/.sup.81Br) 366/368 [M+H].sup.+.

[0458] The following compounds were prepared in a manner essentially analogous to the method of Preparation 162 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00028 TABLE 27 Prep MS ES+ # Chemical Name Structure m/z 163.sup.1,2 1-(6-Bromo-3-chloro- pyrazolo[1,5-a]pyridin-4- yl)oxy-2-(5-fluoro-2- pyridyl)propan-2-ol [00327] (.sup.79Br/.sup.81Br) 400/402 [M + H].sup.+ 164.sup.3 1-(6-Bromo-3-chloro-pyrazolo[1,5-a]pyridin-4- yl)oxy-2-(5-fluoropyrimidin-2- yl)propan-2-ol [00328] (.sup.79Br/.sup.81Br) 401/403 [M + H].sup.+ .sup.1Reaction quenched with sat. aq NH4Cl (30 ml) at 0° C. .sup.2Purified by silica gel chromatography eluting with DCM/PE (1:2-2:1). .sup.3Purified by Prep-TLC PE/EA (8:1).

Preparation 165

6-Bromo-4-[2-(5-fluoro-2-pyridyl)-2-hydroxy-ethoxy]pyrazolo[1,5-a]pyridine-3-carbonitrile

##STR00329##

[0459] A suspension of 6-bromo-4-[2-(5-fluoro-2-pyridyl)-2-oxo-ethoxy]pyrazolo[1,5-a]pyridine-3-carbonitrile (2.18 g, 5.82 mmol) in MeOH (50 ml) was cooled in an ice bath and then treated with NaBH.sub.4 (0.85 g, 22.47 mmol) in one portion. The reaction was allowed to stir at 0° C. for 5 min and then stirred at RT for 1 h. The reaction was concentrated, and the residue taken up in DCM and washed with H.sub.2O and brine. The organic layer was collected, dried over MgSO.sub.4, filtered, and concentrated to obtain the title compound (1.98 g, 83%) as a beige solid. MS ES+ m/z 377/379 [M+H].sup.+.

[0460] The following compounds were prepared in a manner essentially analogous to the method of Preparation 165 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00029 TABLE 28 Prep MS ES+ # Chemical Name Structure m/z 166.sup.1 2-(6-Bromo-3-chloro- pyrazolo[1,5-a]pyridin-4- yl)oxy-1-(5-fluoro-2- pyridyl)ethanol [00330] (.sup.79Br/.sup.81Br) 385/387 [M + H].sup.+ 167 2-(6-Bromo-3-chloro-pyrazolo[1,5-a]pyridin-4- yl)oxy-1-(5-fluoropyrimidin-2- yl)ethanol [00331] (.sup.79Br/.sup.81Br) 387/389 [M + H].sup.+ .sup.1Workup: Reaction was concentrated in vacuo. Residue triturated in H.sub.2O and the precipitate was collected by filtration.

Preparation 168

6-Bromo-3-chloro-4-[2-(5-fluoro-2-pyridyl)-2-methoxy-ethoxy]pyrazolo[1,5-a]pyridine

##STR00332##

[0461] To 2-(6-bromo-3-chloro-pyrazolo[1,5-a]pyridin-4-yl)oxy-1-(5-fluoro-2-pyridyl)ethanol (1.62 g, 4.19 mmol) in THE (10 ml) was added NaH (335 mg, 8.38 mmol, 60%) in portions at 0° C. under N.sub.2. To the mixture was added CH.sub.3I (2.97 g, 20.95 mmol) dropwise at 0° C. The

reaction was stirred for 2 h at RT then quenched with H.sub.2O (50 ml). The mixture was extracted with EA (3×100 ml), organic layers were combined, washed with brine (3×50 ml), dried over Na.sub.2SO.sub.4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography, eluting with PE/EA (10:1 to 5:1 to afford the title compound (1.01 g, 60%) as a light yellow solid. MS ES+ m/z 402 [M+H].sup.+.

Preparation 169

6-Bromo-4-[2-(5-fluoro-2-pyridyl)-2-methoxy-ethoxy]pyrazolo[1,5-a]pyridine-3-carbonitrile

##STR00333##

[0462] To a stirred solution of 6-bromo-4-[2-(5-fluoro-2-pyridyl)-2-hydroxy-ethoxy]pyrazolo[1,5-a]pyridine-3-carbonitrile (3 g, 7.95 mmol) and CH.sub.3I (2.26 g, 15.91 mmol) in THE (30 mL) was added NaH (60%) (636 mg, 15.91 mmol) in portions at 0° C. under N.sub.2. The mixture was stirred for 2 hr at RT then quenched with H.sub.2O (20 mL). The mixture was extracted with EA (3×40 mL). The combined organic layers were washed with brine (2×20 mL), dried over Na.sub.2SO.sub.4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography, eluted with PE/EA (4:1 to 1:1) to afford the title compound (2.9 g, 93%) as a yellow solid. MS ES+ m/z (.sup.79Br/.sup.81Br) 391.0/393.0 [M+H].sup.+.

Preparation 170

7-Chloro-5-[[3,3,3-trifluoro-2-(5-fluoro-2-pyridyl)propyl]amino]imidazo[1,2-a]pyridine-3-carbonitrile

##STR00334##

[0463] A stirred soln of 3,3,3-Trifluoro-2-(5-fluoro-2-pyridyl)propan-1-amine (2.0 g, 9.6 mmol) and 5,7-dichloroimidazo[1,2-a]pyridine-3-carbonitrile (2.64 g, 12.5 mmol) in DMF (5 ml) was treated with DIEA (3.72 g, 28.8 mmol) under N.sub.2. After stirring at 100° C. for 24 h, the reaction was purified by reversed flash C18 chromatography with the following conditions: Column, C18; eluting with a gradient of 50% to 70% ACN in H.sub.2O to afford the title compound (1.2 g, 34%). MS ES+ m/z 384 [M+H].sup.+.

Preparation 171

6-Bromo-4-[1-[5-(trifluoromethyl)-3-pyridyl]ethylamino]pyrazolo[1,5-a]pyridine-3-carbonitrile

##STR00335##

[0464] A pressure flask was charged with Pd.sub.2(dba).sub.3 (0.05 g, 0.05 mmol), dppf (0.06 g, 0.1 mmol), K.sub.3PO.sub.4 (1.3 g, 6 mmol), and DME (5 ml). The suspension was degassed by bubbling N.sub.2 through the mixture for several min then 1-[5-(trifluoromethyl)-3-pyridyl]ethanamine (0.40 g, 1.89 mmol) and 4,6-dibromopyrazolo[1,5-a]pyridine-3-carbonitrile (0.52 g, 1.7 mmol) were added and N.sub.2 was bubbled through the mixture for another couple of min. The tube was capped, and the reaction heated at 207° C. for 15 min. After stirring overnight at RT, the reaction was recharged with DME (5 mL), Pd.sub.2(dba).sub.3 (0.05 g, 0.05 mmol), and dppf (0.06 g, 0.1 mmol). After degassing the mixture, the reaction was capped and heated at 100° C. for 8 h. The reaction was cooled to RT, diluted with H.sub.2O, and extracted with EA (3×). The combined organic layers were dried over MgSO.sub.4, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with a gradient of 0% to 50% EA in cHex to obtain the title compound (393 mg) which was used in the next synthetic reaction without further purification. MS ES+ m/z 410/412 [M+H].sup.+.

[0465] The following compounds were prepared in a manner essentially analogous to the method of Preparation 171 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00030 TABLE 29 MS ES+ Prep # Chemical Name Structure m/z 172.sup.1 6-Bromo-4-[[2-(5-fluoro-2- pyridyl)-2-methoxy- ethyl]amino]pyrazolo[1,5- a]pyridine-3-carbonitrile [00336]embedded image (.sup.79Br/.sup.81Br) 390/392 [M + H].sup.+ 173.sup.2 6-Bromo-4-[3-hydroxy-3- (2-pyridyl)pyrrolidin-1- yl]pyrazolo[1,5-a]pyridine- 3-carbonitrile [00337] embedded image (.sup.79Br/.sup.81Br) 384/386 [M + H].sup.+ 1Purified by silica gel

chromatography eluted with 0% to 100% EA in cHex. .sup.2Purified by silica gel chromatography eluting with 0% to 50% EA in cHex.
Preparation 174
6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-4-[1-[5-(trifluoromethyl)-3-pyridyl]ethylamino]pyrazolo[1,5-a]pyridine-3-carbonitrile
##STR00338##
[0466] A high-pressure flask was charged with 6-bromo-4-[[2-(5-fluoro-2-pyridyl)-2-methoxy-ethyl]amino]pyrazolo[1,5-a]pyridine-3-carbonitrile (0.39 g, 0.55 mmol), bis(pinacolato)diboron (0.21 g, 0.82 mmol), KOAc (0.21 g, 2.18 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.01 g, 0.01 mmol), and 1,4-dioxane (4 ml). N.sub.2 was bubbled through the mixture for a few minutes, the flask was then closed, and the reaction was heated at 90° C. for 5.5 h. After cooling to RT, the reaction was diluted with H.sub.2O and extracted with EA (3×). The combined organic layers were dried over MgSO.sub.4, filtered, concentrated, and the residue purified by silica gel chromatography eluting with 0% to 80% EA in cHex to obtain the title compound (0.39 g, 82%) as a thick brown oil. MS ES+ m/z 376 [M+H].sup.+ as the boronic acid.
[0467] The following compounds were prepared in a manner essentially analogous to the method of Preparation 174 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.
TABLE-US-00031 TABLE 30 MS ES+ Prep # Chemical Name Structure m/z 175 4-[[2-(5-Fluoro-2- pyridyl)-2-methoxy- ethyl]amino]-6-(4,4,5,5- tetramethyl-1,3,2- dioxaborolan-2-yl) pyrazolo[1,5-a]pyridine- 3-carbonitrile [00339]  embedded image 438 [M + H].sup.+ 176 4-[3-Hydroxy-3-(2- pyridyl)pyrrolidin-1-yl]- 6-(4,4,5,5-tetramethyl- 1,3,2-dioxaborolan-2-yl)pyrazolo[1,5- a]pyridine-3-carbonitrile [00340]  embedded image 432 [M + H].sup.+
Preparation 177
4-Methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine
##STR00341##
[0468] A soln of 6-bromo-4-methoxy-pyrazolo[1,5-a]pyridine (50.0 g, 220.2 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (61.0 g, 240.3 mmol) in 1,4-dioxane (500 ml) was degassed with N.sub.2 at RT for 15 min. KOAc (64.0 g, 652.1 mmol) was added followed by the addition of Pd(dppf)Cl.sub.2 (6.0 g, 8.2 mmol) in portions at 25° C. under N.sub.2. Mixture was degassed with N.sub.2 for 15 min. The reaction was stirred at 80° C. for 12 h under N.sub.2. The reaction was cooled to 25° C. and filtered through DE. Filter cake was washed with 1,4-dioxane (3×100 ml). The filtrate was concentrated in vacuo at 45° C. to afford an oily black residue. The residue was purified by silica gel plug filtration (300 g, 12 cm column diameter). The plug was eluted with 20:1 to 3:1 c-Hex:EA to afford the title compound (62.7 g, 206 mmol) as a pale-yellow solid. MS ES+ m/z 275 [M+H].sup.+.
Preparation 178
4-Methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile
##STR00342##
[0469] A stirred 1,4-dioxane soln (200 ml) of 6-bromo-4-methoxy-pyrazolo[1,5-a]pyridine-3-carbonitrile (20.0 g, 79.34 mmol) was treated with bis(pinacolato)diboron (30.22 g, 119.01 mmol), KOAc (23.36 g, 238.03 mmol), and Pd(dppf)Cl.sub.2 (2.90 g, 3.97 mmol) at RT under N.sub.2. After stirring the reaction at 80° C. for 1 h, the crude reaction was taken on to the next synthetic step without purification. MS ES+ m/z 300 [M+H].sup.+.
[0470] The following compounds were prepared in a manner essentially analogous to the method of Preparation 178 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as
TABLE-US-00032 TABLE 31 MS ES+ Prep # Chemical Name Structure m/z 179 3-Fluoro-4-methoxy- (4,4,5,5-tetramethyl-1,3,2- dioxaborolan-2- yl)pyrazolo[1,5-a]pyridine [00343]

embedded image 293 [M + H].sup.+ 180.sup.a (5-Methoxyimidazo[1,2-a] pyridine-7-yl)boronic acid [00344]embedded image 193 [M + H].sup.+ 181.sup.3 4-[(1R)-1-(2- Pyridyl)ethoxy]-6-(4,4,5,5- tetramethyl-1,3,2- dioxaborolan-2-yl)pyrazolo [1,5-a]pyridine-3- carbonitrile [00345] embedded image 391 [M + H].sup.+ 182.sup.1,2 6-(4,4,5,5-Tetramethyl- 1,3,2-dioxaborolan-2-yl)-4- [1-[5-(trifluoromethyl)-3- pyridyl]ethoxy]pyrazolo[1,5- a]pyridine-3-carbonitrile, Isomer 2 [00346]embedded image 459 [M + H].sup.+ 183.sup.4 4-Methoxy-6-(4,4,5,5- tetramethyl-1,3,2-dioxaborolan-2-yl)-3- (trifluoromethyl)pyrazolo [1,5-a]pyridine [00347]embedded image 261 [M + H].sup.+ 184 4-[2-(5-Fluoro-2-pyridyl)-2- hydroxy-ethoxy]-6-(4,4,5,5- tetramethyl-1,3,2-dioxaborolan-2- yl)pyrazolo[1,5-a]pyridine- 3-carbonitrile [00348]embedded image a 185 2-(5-Fluoro-2-pyridyl)-1-[6- (4,4,5,5-tetramethyl-1,3,2- dioxaborolan-2- yl)pyrazolo[1,5-a]pyridin-4-yl]oxy-propan-2-ol [00349]embedded image a 186.sup.5 [5-[2-(3,5-Difluoro-2- pyridyl)-2-methoxy- ethoxy]imidazo[1,2- a]pyridin-7-yl]boronic acid [00350]embedded image 350 [M + H].sup.+ 187.sup.6,7 1-[3-Chloro-6-(4,4,5,5- tetramethyl-1,3,2- dioxaborolan-2- yl)pyrazolo[1,5-a]pyridin-4- yl]oxy-2-(5-fluoro-2- pyridyl)propan-2-ol [00351]embedded image 448 [M + H].sup.+ 188.sup.8 4-Methoxy-3-methyl-6- (4,4,5,5-tetramethyl-1,3,2- dioxaborolan-2-yl)ppyrazolo[1,5-a]pyridine [00352]embedded image 289 [M + H].sup.+ 1Purified by silica gel chromatography eluting with 0% to 50% EA in cHex. .sup.2Purified by silica gel chromatography eluting with 0% to 80% EA in cHex. .sup.3Compound degrades on MS. MS data indicates mixture of boronate ester and boronic acid. .sup.4Compound degrades on MS. MS data consistent for boronic acid. .sup.5Xphos Palladacycle Gen 4 used as catalyst for this transformation. .sup.6Pd(dppf)Cl.sub.2•CH.sub.2Cl.sub.2 used as catalyst for this transformation. .sup.7Reaction was heated at 100° C. .sup.aMaterial used in subsequent step without further characterization. .sup.8Purified by silica gel chromatography eluting with EA in heptane.

Preparation 189

tert-Butyl (3S,4R)-4-[4-[3-chloro-4-[2-(5-fluoropyrimidin-2-yl)-2-methoxy-ethoxy]pyrazolo[1,5-a]pyridin-6-yl]-5-methyl-triazol-1-yl]-3-fluoro-piperidine-1-carboxylate

##STR00353##

[0471] To 6-bromo-3-chloro-4-[2-(5-fluoropyrimidin-2-yl)-2-methoxy-ethoxy]pyrazolo[1,5-a]pyridine (626 mg, 1.56 mmol) and bis(pinacolato)diboron (475 mg, 1.87 mmol) in dioxane (7 ml) were added Pd(dppf)Cl.sub.2.Math.CH.sub.2Cl.sub.2 (64 mg, 0.08 mmol) and KOAc (459 mg, 4.68 mmol) in portions at RT under N.sub.2. The reaction was stirred for 2 h at 100° C. under N.sub.2 then allowed to cool down to RT. Next, tert-butyl (3S,4R)-4-(4-bromo-5-methyl-triazol-1-yl)-3-fluoro-piperidine-1-carboxylate (534 mg, 1.47 mmol), K.sub.2CO.sub.3 (554 mg, 4.01 mmol), PdCl.sub.2(DtBPF) (44 mg, 0.07 mmol) and H.sub.2O (2 ml) were added at RT under N.sub.2. The mixture was stirred overnight at 100° C. Upon cooling to RT, the reaction was quenched by the addition of H.sub.2O (100 ml). The mixture was extracted with EA (3×100 ml), organic layers were combined, dried over Na.sub.2SO.sub.4, filtered and the filtrate concentrated in vacuo. The residue was purified by silica gel chromatography, eluting with PE/EA (10:1 to 100% EA). To afford the title compound (585 mg, 72%) as a brown solid. MS ES+ m/z 605 [M+H].sup.+.

[0472] The following compounds were prepared in a manner essentially analogous to the method of Preparation 189 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00033 TABLE 32 Prep MS ES+ # Chemical Name Structure m/z 190.sup.1 tert-Butyl (3S,4R)-4- [4-[3-chloro-4-[2-(5- fluoropyrimidin-2- yl)-2-hydroxy- propoxy]pyrazolo[1, 5-a]pyridin-6-yl]-5- methyl-triazol-1-yl]- 3-fluoro-piperidine- 1-carboxylate [00354] embedded image 605 [M + H].sup.+ 191.sup.2 tert-Butyl (3S,4R)-4- [4-[3-chloro-4-[2-(5-fluoro-2-pyridyl)-2- methoxy- ethoxy]pyrazolo[1,5- a]pyridin-6-yl]-5- ethyl-triazol-1-yl]- 3-fluoro-piperidine- 1-carboxylate [00355]embedded image 604 [M + H].sup.+ 192.sup.3 tert-Butyl (3S,4R)-4- [4-[3-chloro-4-[2-(5- fluoropyrimidin-2- yl)-2-hydroxy- ethoxy]pyrazolo[1,5- a]pyridin-6-yl]-5- methyl-triazol-1-yl]- 3-fluoro-piperidine- 1-carboxylate [00356]embedded image 591

[M + H].sup.+ 193.sup.4 tert-Butyl (3S,4R)-4- [4-[3-cyano-4-[2-(5- fluoro-2-pyridyl)-2- methoxy-ethoxy]pyrazolo[1,5- a]pyridin-6-yl]-5- methyl-triazol-1-yl]- 3-fluoro-piperidine- 1-carboxylate
[00357]embedded image 595 .sup.1Purified by silica gel chromatography, eluted with PE/EA (2:3 to 1:4). .sup.2Purified by silica gel chromatography, eluted with PE/EA (1:3 to 1:4). .sup.3Purified by silica gel chromatography, eluted with PE/EA (1:2 to 1:3). .sup.4Purified by silica gel chromatography, eluted with PE/EA (1:2 to 1:3).
Preparation 194
tert-Butyl 4-[4-(3-cyano-4-methoxy-pyrazolo[1,5-a]pyridine-6-yl)-5-methyl-triazol-1-yl]piperidine-1-carboxylate
##STR00358##
[0473] The mixture obtained from the synthesis of 4-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (20.0 g, 79.34 mmol) was treated with tert-butyl 4-(4-bromo-5-methyl-triazol-1-yl)piperidine-1-carboxylate (27.70 g, 80.23 mmol), K.sub.2CO.sub.3 (27.72 g, 200.57 mmol), PdCl.sub.2(DtBPF) (2.18 g, 3.34 mmol), and H.sub.2O (50 mL) at RT under N.sub.2. The reaction was stirred at 80° C. for 1 h and allowed to cool to RT. The reaction was diluted with H.sub.2O (300 ml) and extracted with EA (3×300 ml). The combined organic layers were washed with brine (3×300 ml), dried over anhydrous Na.sub.2SO.sub.4, filtered, and concentrated to obtain the title compound (15.31 g, 44% two step yield) as a yellow solid. MS ES+ m/z 438 [M+H].sup.+.
Preparation 195
tert-Butyl 4-[4-(4-methoxypyrazolo[1,5-a]pyridine-6-yl)-5-methyl-triazol-1-yl]piperidine-1-carboxylate
##STR00359##
[0474] To 4-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine (5.160 g, 18.83 mmol) and K.sub.2CO.sub.3 (5.0 g, 36.18 mmol) was added a soln of tert-butyl 4-(4-bromo-5-methyl-triazol-1-yl)piperidine-1-carboxylate (7.0 g, 20.28 mmol) in toluene (50 ml) followed by the addition of H.sub.2O (12.5 ml). The mixture was degassed with N.sub.2 for 10 min then PdCl.sub.2(DtBPF) (1.0 g, 1.54 mmol) was added. Degassing with N.sub.2 continued for an additional 5 min. The reaction was heated at 90° C. for 18 h. Upon cooling to RT, the reaction was concentrated in vacuo to remove bulk of toluene. The residue was diluted with H.sub.2O to afford a brown solid. The solid was decanted from the H.sub.2O. EA (50 ml) was added to the solid then evaporated. This process was repeated three times. EA was added (25 ml) and mixture was heated to 50° C. then cooled to RT. A yellow solid was collected by filtration to afford the title compound (4.6 g, 53%). MS ES+ m/z 413.2 [M+H].sup.+. The filtrate was concentrated, and the residue was purified by silica gel chromatography eluting with 10% to 100% EA in c-Hex to afford the title compound (2.0 g, 24%) as an oily yellow solid. MS ES+ m/z 413.2 [M+H].sup.+.
Preparation 196
tert-Butyl 4-[4-[3-cyano-4-[(1R)-1-(2-pyridyl)ethoxy]pyrazolo[1,5-a]pyridine-6-yl]-5-methyl-pyrazol-1-yl]piperidine-1-carboxylate
##STR00360##
[0475] A mixture of 4-[(1R)-1-(2-Pyridyl)ethoxy]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (5.0 g, 12.81 mmol), tert-butyl 4-(4-bromo-5-methyl-pyrazol-1-yl)piperidine-1-carboxylate (5.0 g, 14.53 mmol) in toluene (50 ml) was degassed with bubbling N.sub.2 for 5 min. Next, a soln of K.sub.3CO.sub.2 (4.0 g, 28.94 mmol) in H.sub.2O (12.5 ml) was added, and the mixture was degassed for an additional 5 min. PdCl.sub.2(DtBPF) (500 mg, 0.77 mmol) was added and the mixture was degassed with N.sub.2 while the reaction was heated to 60° C. At this point N.sub.2 bubbling was stopped. Then reaction was heated to 100° C. under N.sub.2.
[0476] After 2 h the reaction was cooled to RT and DE was added (6 g) with stirring. 30 min later the mixture was filtered over a DE plug, and solids were washed with H.sub.2O (50 ml) and

toluene (150 ml). The layers from the filtrate were separated and the organic layer dried over MgSO.sub.4, filtered, and concentrated to afford the title compound (7.0 g, 98%) as oily brown material. MS ES+ m/z 528 [M+H].sup.+.

[0477] The following compounds were prepared in a manner essentially analogous to the method of Preparation 196 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate. K.sub.3PO.sub.4 can be used in place of K.sub.3CO.sub.2.

TABLE-US-00034 TABLE 33 Prep MS ES+ # Chemical Name Structure m/z 197.sup.1 tert-Butyl 4-[4-(3-fluoro- 4-methoxy-pyrazolo[1,5- a]pyridine-6-yl)-5- methyl-triazol-1- yl]piperidine-1-carboxylate [00361]embedded image 431 [M + H].sup.+ 198.sup.2,6 tert-Butyl 4-[4-(5-methoxyimidazo[1,2- a]pyridine-7-yl)-5- methyl-triazol-1- yl]piperidine-1- carboxylate [00362] embedded image 413 [M + H].sup.+ 199.sup.3 tert-Butyl 3-[4-(4- methoxypyrazolo[1,5-a]pyridine-6-yl)-5- methyl-triazol-1- yl]azetidine-1- carboxylate [00363]embedded image 385 [M + H].sup.+ 200 tert-Butyl (3R)-3-[4-[3- cyano-4-[(1R)-1-(2- pyridyl)ethoxy]pyrazolo [1,5-a]pyridin-6-yl]-5- methyl-pyrazol-1- yl]piperidine-1- carboxylate [00364]embedded image 528 [M + H].sup.+ 201 tert-Butyl (3S)-3-[4-[3- cyano-4-[(1R)-1-(2- pyridyl)ethoxy]pyrazolo [1,5-a]pyridin-6-yl]-5- methyl-pyrazol-1- yl]piperidine-1- carboxylate [00365]embedded image 528 [M + H].sup.+ 202.sup.4 tert-Butyl 6-[4-[3-cyano- 4-[(1R)-1-(2- pyridyl)ethoxy]pyrazolo [1,5-a]pyridin-6-yl]-5- methyl-pyrazol-1-yl]-2- azaspiro[3.3]heptane-2- carboxylate [00366] embedded image 540 [M + H].sup.+ 203.sup.5 tert-Butyl 3-[4-[3-cyano- 4-[1-[5-(trifluoromethyl)- 3-pyri- dyl]ethoxy]pyrazolo[1,5- a]pyridin-6-yl]-5- methyl-triazol-1-yl]azetidine-1- carboxylate, Isomer 2 [00367]embedded image 513 [M + H − tBu].sup.+ 204.sup.7,8,9,10 tert-Butyl (3S,4R)-3- fluoro-4-[4-[4-[2-(5- fluoro-2-pyridyl)-2- hydroxy-propoxy]pyrazolo[1,5- a]pyridin-6-yl]-5-methyl- triazol-1-yl]piperidine-1- carboxylate [00368] embedded image 570 [M + H].sup.+ 205.sup.7,9,11 tert-Butyl (3S,4S)-3- fluoro-4-[4-[4-[2-(5-fluoro-2-pyridyl)-2- hydroxy- propoxy]pyrazolo[1,5- a]pyridin-6-yl]-5-methyl- triazol-1-yl]piperidine-1- carboxylate [00369]embedded image 570 [M + H].sup.+ 206.sup.12 3-Fluoro-4-methoxy-6- [5-methyl-1-[1-(oxetan- 3-yl)-4-piperidyl]triazol- 4-yl]pyrazolo[1,5- a]pyridine [00370]embedded image 387 [M + H].sup.+ 207.sup.7,9,13 tert-Butyl 4-[4-[5-[2- (3,5-difluoro-2-pyridyl)- 2-methoxy- ethoxy]imidazo[1,2- a]pyridin-7-yl]-5-methyl- triazol-1-yl]-4-methyl-piperidine-1-carboxylate [00371]embedded image 584 [M + H].sup.+ 208.sup.7,14,15 tert-Butyl (4R)-3,3- difluoro-4-[4-[4-[2-(5- fluoro-2-pyridyl)-2- hydroxy- propoxy]pyrazolo[1,5- a]pyridin-6-yl]-5-methyl- triazol-1-yl]piperidine-1- carboxylate [00372]embedded image 588 [M + H].sup.+ 209.sup.7,16,17 tert-Butyl (3R,4S)-4-[4- [3-chloro-4-[2-(5-fluoro- 2-pyridyl)-2-hydroxy-propoxy]pyrazolo[1,5- a]pyridin-6-yl]-5-methyl- triazol-1-yl]-3-fluoro- piperidine-1-carboxylate [00373]embedded image 604 [M + H].sup.+ 210.sup.7,16,18 tert-Butyl (3R,4R)-3- fluoro-4-[4-[4-[2-(5- fluoro-2-pyridyl)-2- hydroxy- propoxy]pyrazolo[1,5- a]pyridin-6-yl]-5-methyl- triazol-1-yl]piperidine-1- carboxylate [00374]embedded image 570 [M + H].sup.+ 211.sup.19,20 tert-Butyl 4-[4-(4- methoxy-3-methyl- pyrazolo[1,5-a]pyridin-6- yl)-5-methyl-triazol-1- yl]piperidine-1- carboxylate [00375]embedded image 427 [M + H].sup.+ 212.sup.21 tert-Butyl 4-[3-[4-[5-[2-(3,5-difluoro-2-pyridyl)- 2-methoxy- ethoxy]imidazo[1,2- a]pyridin-7-yl]-5-methyl- triazol-1-yl]cyclobutyl]piperazine- 1-carboxylate [00376]embedded image 625 [M + H].sup.+ 213.sup.22 tert-Butyl 4-((1r,3R)-3-(4- (5-(2-(3,5- difluoropyridin-2-yl)-2- methoxyethoxy) imidazo[1,2-a]pyridin-7- yl)-5-methyl-1H-1,2,3- triazol-1-yl)cyclobutyl) piperazine-1-carboxylate [00377] embedded image 625 [M + H].sup.+ .sup.1Silica gel column chromatography, eluting with PE/EA (2:1 to 1:1). .sup.2Pd(PPh.sub.3).sub.4 used as catalyst for this transformation .sup.3Purified by silica gel chromatography eluting with 10% to 100% EA in cHex. .sup.4Purified by silica gel chromatography eluting with 0% to 100% EA in hex followed by 0% to 20% MeOH in EA. .sup.5Purified by silica gel chromatography eluting with 0% to 100% EA in cHex. .sup.6Purified by silica gel chromatography, eluting with EA/EtOH (30:1). .sup.7Dioxane used as

solvent. .sup.8Reaction was heated at 80° C. .sup.9Workup: Reaction extracted with EA. Combined organic layers washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. .sup.10Purified by silica gel column chromatography, eluting with PE/EA (10:1 to 3:1). .sup.11Purified by silica gel column chromatography, eluting with 50% EA in PE. .sup.12Workup: Reaction concentrated. Resude was slurried in H2O and the resultant insoluble material was collected by filtration. .sup.13Purifed by reversed phase C18 chromatography eluting with 40% to 60% ACN in H.sub.2O. .sup.14Workup: Reaction diluted with H.sub.2O and extracted with EA. Combined organic layers washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. .sup.15Purified by silic gel chromatography, eluting with 20% EA in PE. .sup.16Workup: Reaction concentrated. .sup.17Purified by silica gel column chromatography, eluting with 50% to 75% EA in PE. .sup.18Purified by silica gel column chromatography, eluting with 10% MeOH in DCM. .sup.19Pd(dppf)Cl.sub.2 was used as catalyst for this transformation. Reaction was heated at 90° C. .sup.20Purified by silica gel chromatography eluting with MeOH in DCM. .sup.21Purified by silica gel column chromatography, eluting with DCM/MeOH (15:1 to 10:1). .sup.22Purified by silica gel column chromatography, eluting with DCM/MeOH (10:1)

Preparation 214a

tert-Butyl 2-[4-[3-cyano-4-[(1R)-1-(2-pyridyl)ethoxy]pyrazolo[1,5-a]pyridin-6-yl]-5-methyl-pyrazol-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate

##STR00378##

Preparation 214b

tert-Butyl 2-[4-[3-cyano-4-[(1R)-1-(2-pyridyl)ethoxy]pyrazolo[1,5-a]pyridin-6-yl]-3-methyl-pyrazol-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate

##STR00379##

[0478] A mixture of tert-butyl 2-(4-bromo-5-methyl-pyrazol-1-yl)-7-azaspiro[3.5]nonane-7-carboxylate, tert-butyl 2-(4-bromo-3-methyl-pyrazol-1-yl)-7-azaspiro[3.5]nonane-7-carboxylate (1.68 g, 3.11 mmol), and 4-[(1R)-1-(2-pyridyl)ethoxy]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (1.33 g, 3.41 mmol) in toluene (40 ml) and H.sub.2O (4 ml) and treated with K.sub.2CO.sub.3 (1.14 g, 8.25 mmol). N.sub.2 was bubbled through the reaction for 2 min before adding PdCl.sub.2(DtBPF) (135 mg, 0.21 mmol) and the tube was sealed. After stirring at 90° C. for 20 h, the reaction was allowed to cool and diluted with EA (50 ml) and H.sub.2O (20 ml). The layers were separated, and the aq layer was extracted with EA. The combined organic layers were concentrated. The residue was purified by silica gel chromatography eluting with a gradient of 0% to 10% acetone in DCM to obtain a mixture of the title compounds (621 mg, 74%) as a thick yellow oil. MS ES+ m/z 568 [M+H].sup.+.

[0479] The following compounds were prepared in a manner essentially analogous to the method of Preparation for 214a and 214b using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00035 TABLE 34 Prep MS ES+ # Chemical Name Structure m/z 215a tert-Butyl 4-[4-[3-cyano-4- [(1R)-1-(2- pyridyl)ethoxy]pyrazolo[1,5- a]pyridin-6-yl]-5-methyl- pyrazol-1-yl]azepane-1- carboxylate [00380]  embedded image 542 [M + H].sup.+ 215b tert-Butyl 4-[4-[3-cyano-4- [(1R)-1-(2- pyridyl)ethoxy]pyrazolo[1,5- a]pyridin-6-yl]-3-methyl- pyrazol-1-yl]azepane-1- carboxylate [00381]  embedded image 542 [M + H].sup.+

Preparation 216

4-Methoxy-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile

##STR00382##

[0480] N.sub.2 was bubbled through a mixture of 4-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (39 g, 117 mmol 90 mass %), K.sub.2CO.sub.3 (40 g, 289 mmol), and 4-(4-bromo-5-methyl-triazol-1-yl)-1-(oxetan-3-yl)piperidine (42.6 g, 135 mmol) in toluene (390 ml) and H.sub.2O (116 mL). After 10 min,

PdCl.sub.2(DtBPF) (0.68 g, 1.04 mmol) was added and N.sub.2 was bubbled through the reaction for an additional 5 min. The reaction was stirred at 90° C. for 8 h then stirred at RT for approximately 60 h. The reaction was diluted with H.sub.2O (100 ml) and the mixture was concentrated to remove toluene. The resulting suspension was stirred at RT for 15 min, filtered, and the solids were washed with H.sub.2O (2×30 mL) to obtain the title compound (42.6 g, 83%). MS ES+ m/z 394 [M+H].sup.+.

[0481] The following compounds were prepared in a manner essentially analogous to the method of Preparation 216 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as

TABLE-US-00036 TABLE 35 Prep MS ES+ # Chemical Name Structure m/z 217 4-Methoxy-6-[5-methyl-1-[1- (oxetan-3-yl)-4-piperidyl] triazol-4-yl]pyrazolo[1,5- a]pyridine [00383]  369 [M + H].sup.+ 218.sup.1 4-Methoxy-6-[5-methyl-1-[1- (oxetan-3-yl)-4-piperidyl] triazol-4-yl]-3-(trifluoro- methyl)pyrazolo[1,5- a]pyridine [00384] 437 [M + H].sup.+ .sup.1Purified by silica gel chromatography eluting with 0% to 100% EA in cHex followed by 0% to 10% MeOH in DCM.

Preparation 219

tert-Butyl 4-[4-(3-chloro-4-methoxy-pyrazolo[1,5-a]pyridin-6-yl)-5-methyl-triazol-1-yl]piperidine-1-carboxylate

##STR00385##

[0482] A soln of tert-butyl 4-[4-(4-methoxypyrazolo[1,5-a]pyridin-6-yl)-5-methyl-triazol-1-yl]piperidine-1-carboxylate (4 g, 9.12 mmol) in DCM (50 ml) was treated with NCS (700 mg, 5.24 mmol). After stirring at RT for 24 h, another portion of NSC (700 mg, 5.24 mmol) was added and stirring continued for another 24 h. The reaction was treated with H.sub.2O (100 ml) and the layers were separated. The organic layer was dried over MgSO.sub.4, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with a gradient of 0% and 100% EA in cHex to obtain the title compound as a white solid (3.4 g, 82%). MS ES+ m/z 447/449 [M+H].sup.+.

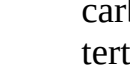
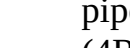
Preparation 220

3-Chloro-4-methoxy-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine

##STR00386##

[0483] 4-Methoxy-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine (34 g, 83.06 mmol) was dissolved in DCM (500 ml) and treated with NCS (12 g, 89.86 mmol) under N.sub.2. After stirring at RT for 18 h, added more NCS (6.5 g, 49 mmol) and allowed to stir overnight. Diluted with H.sub.2O (200 ml) and separated layers, dried organic layer over Na.sub.2SO.sub.4, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with a gradient of 0% to 10% MeOH in DCM to obtain the title compound (16 g, 45%) as an amber oil. MS ES+ m/z 403/405 [M+H].sup.+.

[0484] The following compounds were prepared in a manner essentially analogous to the method of Preparation 220 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00037 TABLE 36 MS ES+ Prep # Chemical Name Structure m/z 221.sup.1 tert-Butyl 3-[4-(3- chloro-4-methoxy- pyrazolo[1,5- a]pyridin-6-yl)-5- methyl-triazol-1- yl]azetidine-1-carboxylate [00387]  (.sup.35Cl/.sup.37Cl) 419/421 [M + H].sup.+ 222.sup.2,3 tert-Butyl (3S,4R)-4- [4-[3-chloro-4-[2-(5- fluoro-2-pyridyl)-2- hydroxy- propoxy]pyrazolo [1,5-a]pyridin-6-yl]-5- methyl-triazol-1-yl]- 3-fluoro-piperidine-1- carboxylate [00388]  604 [M + H].sup.+ 223.sup.5 tert-Butyl (3S,4S)-4- [4-[3-chloro-4-[2-(5- fluoro-2-pyridyl)-2- hydroxy- propoxy]pyrazolo [1,5-a]pyridin-6-yl]-5- methyl-triazol-1-yl]- 3-fluoro-piperidine-1- carboxylate [00389]  604 [M + H].sup.+ 224.sup.2,4 tert-Butyl (4R)-4-[4- [3-chloro-4-[2-(5- fluoro-2-pyridyl)-2- hydroxy- propoxy]pyrazolo [1,5-a]pyridin-6-

yl]-5- methyl-triazol-1-yl]- 3,3-difluoro- piperidine-1- carboxylate [00390]embedded image 622 [M + H].sup.+ 225.sup.3,6 tert-Butyl (3R,4R)-4- [4-[3-chloro-4-[2-(5- fluoro-2-pyridyl)-2-hydroxy- propoxy]pyrazolo [1,5-a]pyridin-6-yl]-5- methyl-triazol-1-yl]- 3-fluoro-piperidine-1-carboxylate [00391]embedded image 604 [M + H].sup.+ 226.sup.7,10 tert-Butyl 4-[4-(3- bromo-4-methoxy- pyrazolo[1,5- a]pyridin-6-yl)-5- methyl-triazol-1- yl]piperidine-1- carboxylate [00392] embedded image (.sup.19Br/.sup.81Br) 491/493 [M + H].sup.+ 227.sup.4,11 tert-Butyl 4-[3-[4-[3- chloro-5-[2-(3,5- difluoro-2-pyridyl)-2- methoxy- ethoxy]imidazo[1,2- a]pyridin-7-yl]-5-methyl-triazol-1- yl]cyclobutyl] piperazine- 1-carboxylate [00393]embedded image 659 [M + H].sup.+ 228.sup.8,9 tert-Butyl 4-((1r,3r)- 3-(4-(3-chloro-5-(2- (3,5-difluoropyridin- 2-yl)-2-methoxy ethoxy)imidazo[1,2- a]pyridin-7-yl)-5- methyl-1H-1,2,3- triazol-1-yl) cyclobutyl) piperazine-1- carboxylate [00394]embedded image 659 [M + H].sup.+ .sup.1Purified by silica gel chromatography eluting with 0% to 100% EA in cHex. .sup.2Reaction was heated at 50° C. .sup.3Purified by Prep TLC: PE/EA (1:1) .sup.4Purified by Prep TLC: DCM/MeOH (20:1) .sup.5Residue taken on to next step without purification. .sup.6Workup: Reaction concentrated. .sup.7Workup: Reaction quenched with 40% aq NaHSO.sub.3, layers separated, organic layer dried over MgSO.sub.4, filtered and concentrated. .sup.8Purified by reversed flash, eluted with 40% to 50% MeOH in H.sub.2O. .sup.9Column: XB-Phenyl, 50 x 250 mm, 10 μm; eluting with 60 to 70% ACN in H.sub.2O (10 mM NH3—H2O). .sup.10NBS used in place of NCS. .sup.11Purified by reversed flash, eluted with 45% to 55% ACN in H.sub.2O.

Preparation 229

4-Hydroxy-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile

##STR00395##

[0485] A mixture of 4-Methoxy-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile (20 g, 45.75 mmol) in DMA (250 ml) was added NDM (21.9 ml, 91.51 mmol) and aq NaOH (7.25 ml, 137.3 mmol, 18.94 mol/L) under N.sub.2. The reaction was degassed with N.sub.2 for 15 min then heated at 50° C. for 2 h. Upon cooling to RT, H.sub.2O (2 L) was added. After stirring 15 min the pH was adjusted to 6.9 by the addition of aq HCL (10% w/w) then K.sub.2HPO.sub.4. The reaction was stirred 15 min. The insoluble material was collected by filtration, washed with H.sub.2O (2×25 ml) to afford the title compound as pale grey solid (11.0 g, 62% Yield). MS ES+ m/z 380 [M+H].sup.+.

Preparation 230

tert-Butyl 4-[4-(3-chloro-4-hydroxy-pyrazolo[1,5-a]pyridine-6-yl)-5-methyl-triazol-1-yl]piperidine-1-carboxylate

##STR00396##

[0486] To tert-butyl 4-[4-(3-chloro-4-methoxy-pyrazolo[1,5-a]pyridin-6-yl)-5-methyl-triazol-1-yl]piperidine-1-carboxylate (3.4 g, 7.5 mmol) in DMA (20 ml) under N.sub.2 atmosphere was added NDM (5.5 ml, 23 mmol) and NaOH (18.94 mol/L) in H.sub.2O (1.4 ml). The reaction was heated overnight at 60° C. Upon cooling to RT, the mixture was diluted with H.sub.2O (100 ml) and the pH was adjusted to pH=5 with aq HCl A cream colored solid resulted. After stirring for 15 minutes the insoluble material was collected by filtration and the solids were rinsed with H.sub.2O to afford the title compound (1.4 g, 43%). MS ES+ m/z 433 [M+H].sup.+.

Preparation 231

tert-Butyl 4-[4-(3-cyano-4-hydroxy-pyrazolo[1,5-a]pyridine-6-yl)-5-methyl-triazol-1-yl]piperidine-1-carboxylate

##STR00397##

[0487] NaOH (50% aq.) (36.57 g, 457.14 mmol) was added dropwise to a stirred mixture of tert-butyl 4-(4-[3-cyano-4-methoxypyrazolo[1,5-a]pyridin-6-yl]-5-methyl-1,2,3-triazol-1-yl)piperidine-1-carboxylate (40.00 g, 91.43 mmol) and NDM (55.51 g, 274.28 mmol) in DMA (400 ml) at 0° C. The mixture is stirred for 8 h at 50° C. The mixture was diluted with H.sub.2O (400 ml), acidified

to pH 6 with FA, filtered, and the filter cake was washed with H.sub.2O, and dried under vacuum. The solid was triturated in hexanes (200 ml) and Et.sub.20 (200 ml), filtered, then stirred in MeOH (400 ml) for 2 h at 60° C. The mixture was filtered, and the filter cake was concentrated under vacuum to give the title compound as a light-yellow solid (32 g, 82.6%). ES/MS m/z 424.3 [M+H].sup.+.

[0488] The following compounds were prepared in a manner essentially analogous to the method of Preparation 231 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00038 TABLE 37 Prep # Chemical Name Structure MS ES+ m/z 232 tert-Butyl 4-[4-(3-fluoro-4- hydroxy-pyrazolo[1,5- a]pyridine-6-yl)-5-methyl- triazol-1-yl]piperidine-1-carboxylate [00398]embedded image 417 [M + H].sup.+ 233 tert-Butyl 4-[4-(5-hydroxyimidazo[1,2- a]pyridine-7-yl)-5-methyl- triazol-1-yl]piperidine-1- carboxylate [00399]embedded image 399 [M + H].sup.+ 234 3-Chloro-6-[5-methyl-1-[1- (oxetan-3-yl)-4-piperidyl]triazol-4- yl]pyrazolo[1,5-a]pyridine- 4-ol [00400]embedded image 389 [M + H].sup.+ 235 tert-Butyl 3-[4-(3-chloro-4- hydroxy-pyrazolo[1,5- a]pyridin-6-yl)-5-methyl- triazol-1-yl]azetidine-1- carboxylate [00401]embedded image 405/407 [M + H].sup.+ 236 6-[5-Methyl-1-[1-(oxetan- 3-yl)-4-piperidyl]triazol-4- yl]-3-(trifluoro- methyl)pyrazolo[1,5- a]pyridin-4-ol [00402]embedded image 423 [M + H].sup.+ 237.sup.1 3-Fluoro-6-[5-methyl-1-[1- (oxetan-3-yl)-4-piperidyl] triazol-4-yl]pyrazolo [1,5-a]pyridin-4-ol [00403]embedded image 373 [M + H].sup.+ 238.sup.2 tert-Butyl 4-[4-(4-hydroxy- 3-methyl-pyrazolo[1,5- a]pyridin-6-yl)-5-methyl-triazol-1-yl]piperidine-1- carboxylate [00404]embedded image 413 [M + H].sup.+ 239.sup.3,4 tert-Butyl 4-[4-(3-bromo-4- hydroxy-pyrazolo[1,5- a]pyridin-6-yl)-5-methyl- triazol-1-yl]piperidine-1- carboxylate [00405]embedded image (.sup.79Br/.sup.81Br) 477/479 [M + H].sup.+ .sup.1Workup: Reaction cooled to RT then aq citrus acid (3%) was added until pH approx 5. Resultant insoluble material was isolated by filtration, triterated in cHex, filtered and rinsed with cHEx followed by MTBE. .sup.2Workup: Reaction was neutralized with NH.sub.4Cl solution to pH 7-8 and concentrated in vacuo. The residue was treated with DCM and H.sub.2O, layers were separated, organic layer dried over MgSO.sub.4, filtered, and concentrated. Residue was triturated in heptane, filtered and washed with heptane. .sup.3Workup: Reaction cooled to RT then aq citrus acid (3%) was added. Resultant precipitate was isolated by filtration, washed with H.sub.2O then cHex. The solids were dissolved into DCM then cHex was added. The soln was sonicated until a precipitate had formed. The precipitate was collected by filtration. .sup.4Purified by silica gel chromatography eluting with 0% to 50% acetone in DCM.

Preparation 240

4-Hydroxy-6-[5-methyl-1-(4-piperidyl)triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile hydrochloride

##STR00406##

[0489] A soln of tert-butyl 4-[4-(3-cyano-4-hydroxy-pyrazolo[1,5-a]pyridin-6-yl)-5-methyl-triazol-1-yl]piperidine-1-carboxylate (50 g, 118.07 mmol) in MeOH (100 ml) was treated with 4M HCl in MeOH (300 ml) at RT under N.sub.2. The reaction was concentrated to obtain the title compound (40 g, HCl salt, crude) as a white solid. MS ES+ m/z 417 [M+H].sup.+.

[0490] The following compounds were prepared in a manner essentially analogous to the method of Preparation 240 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00039 TABLE 38 MS ES+ Prep # Chemical Name Structure m/z 241.sup.a 6-[1-(Azetidin-3-yl)-5-methyl- triazol-4-yl]-3-chloro- pyrazolo[1,5-a]pyridin-4-ol hydrochloride [00407]embedded image 305/307 [M + H].sup.+ .sup.aHCl in 2-propanol was used in this transformation.

Preparation 242

4-Hydroxy-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine-3-

carbonitrile
##STR00408##
[0491] A soln of 4-hydroxy-6-[5-methyl-1-(4-piperidyl)triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile hydrochloride (40 g, HCl salt, crude) in MeOH (300 ml) was basified to pH 12 with NaOH (5 g), then acidified to pH 5-6 with AcOH (10 g), then treated with 3-oxetanone (53.49 g, 742.21 mmol) at RT under N.sub.2. After stirring at 50° C. for 2 h, treated the reaction with NaBH.sub.3CN (23.32 g, 371.10 mmol) at RT and then stirred at 50° C. for 2 h. After cooling to RT, the reaction was concentrated, and the residue was suspended in H.sub.2O (500 ml) and basified to pH 8 with solid NaHCO.sub.3. The suspension was filtered, the solids washed with MTBE (3×100 ml), and the solids lyophilized to obtain the title compound (30 g, 64%) as a white solid. MS ES+ m/z 380 [M+H].sup.+.
[0492] The following compound was prepared in a manner essentially analogous to the method of Preparation 242 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.
TABLE-US-00040 TABLE 39 MS ES+ Prep # Chemical Name Structure m/z 243 3-Chloro-6-[5-methyl-1-[1- (oxetan-3-yl)azetidin-3- yl]triazol-4-yl]pyrazolo[1,5- a]pyridin-4-ol [00409]  embedded image 361/363 [M + H].sup.+
Preparation 244
4-[2-(5-fluoro-2-pyridyl)-2-oxo-ethoxy]-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile
##STR00410##
[0493] To a suspension of 4-hydroxy-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile (1 g, 2.64 mmol) in ACN (10 ml) was added Cs.sub.2CO.sub.3 (1.12 g, 3.43 mmol). The suspension was stirred at RT for 30 minutes. Next a solution of 2-bromo-1-(5-fluoro-2-pyridyl)ethanone (0.747 g, 3.43 mmol) in ACN (3 ml) was added dropwise at RT over a 30-minute period. The reaction was stirred vigorously stirred at RT for approximately 8 h. H.sub.2O was added and the suspension was stirred for 10 min then was left standing overnight. Suspension was further diluted with H.sub.2O then filtered. The solids were rinsed with EA followed by c-Hex then dried in vacuo to obtain the title compound (1.2 g, 83%). MS ES+ m/z 517 [M+H].sup.+.
Preparation 245
tert-Butyl 4-[4-[3-chloro-4-[2-(5-fluoro-2-pyridyl)-2-oxo-ethoxy]pyrazolo[1,5-a]pyridine-6-yl]-5-methyl-triazol-1-yl]piperidine-1-carboxylate
##STR00411##
[0494] A soln of tert-butyl 4-[4-(3-chloro-4-hydroxy-pyrazolo[1,5-a]pyridine-6-yl)-5-methyl-triazol-1-yl]piperidine-1-carboxylate (1.5 g, 3.47 mmol) and 2-bromo-1-(5-fluoro-2-pyridyl)pyridine (1.51 g, 6.93 mmol) in ACN (30 ml) was treated with DIPEA (1.34 g, 10.40 mmol) at RT under N.sub.2. After stirring at 50° C. for 1 h, the reaction was allowed to cool to RT, concentrated, and the residue purified by silica gel column chromatography eluting with PE/EA (1:1 to 1:2) to obtain the title compound (1.1 g, 56%) as a brown solid. MS ES+ m/z 570 [M+H].sup.+.
[0495] The following compounds were prepared in a manner essentially analogous to the method of Preparation 245 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate. Cs.sub.2CO.sub.3 can be used in place of DIPEA
TABLE-US-00041 TABLE 40 MS ES+ Prep # Chemical Name Structure m/z 246.sup.1 tert-Butyl 4-[4-[3- cyano-4-[2-(2,4- difluorophenyl)-2-oxo- ethoxy]pyrazolo[1,5-a] pyridine-6-yl]-5- methyl-triazol-1- yl]piperidine-1- carboxylate [00412]  embedded image 522 [M + H].sup.+ 247.sup.2 tert-Butyl 4-[4-[3- fluoro-4-[2-(5-fluoro-2- pyridyl)-2-oxo- ethoxy]pyrazolo[1,5-a] pyridine-6-yl]-5- methyl-triazol-1- yl]piperidine-1- carboxylate [00413]  embedded image 554 [M + H].sup.+

248.sup.3 tert-Butyl 4-[4-[3- cyano-4-[2-(5-fluoro-2- pyridyl)-2-oxo- ethoxy]pyrazolo[1,5-a]pyridin-6-yl]-5- methyl-triazol-1- yl]piperidine-1- carboxylate [00414]  embedded image 561 [M + H].sup.+ 249.sup.4,9 tert-Butyl 4-[4-[3- chloro-4-[2-(3,5- difluoro-2-pyridyl)-2- oxo-ethoxy]pyrazolo[1,5- a]pyridin-6-yl]-5- methyl-triazol-1- yl]piperidine-1- carboxylate [00415] embedded image (.sup.35Cl/.sup.37Cl) 588/590 [M + H].sup.+ 250.sup.4,5 tert-Butyl 4-[4-[4-[2-(3- chloro-5-fluoro-2- pyridyl)-2-oxo-ethoxy]- 3-cyano-pyrazolo[1,5- a]pyridin-6-yl]-5- methyl-triazol-1- yl]piperidine-1- carboxylate [00416]embedded image (.sup.35Cl/.sup.37Cl) 595/597 [M + H].sup.+ 251.sup.4,5 tert-Butyl 4-[4-[4-[2-(4- chloro-5-fluoro-2- pyridyl)-2-oxo-ethoxy]- 3-cyano-pyrazolo[1,5- a]pyridin-6-yl]-5- methyl-triazol-1- yl]piperidine-1- carboxylate [00417] embedded image (.sup.35Cl/.sup.37Cl) 595/597 [M + H].sup.+ 252.sup.6 tert-Butyl 4-[4-[3-cyano-4-[[1-(5-fluoro- 2-pyridyl)cyclopropyl] methoxy]pyrazolo[1,5- a]pyridin-6-yl]-5- methyl-triazol-1- yl]piperidine-1- carboxylate [00418]  embedded image 573 [M + H].sup.+ 253.sup.7 2-[3-Chloro-6-[5- methyl-1-[1-(oxetan-3- yl)azetidin-3-yl]triazol- 4-yl]pyrazolo[1,5- a]pyridin-4-yl]oxy-1- (5-fluoro-2- pyridyl)ethanone [00419]  embedded image (.sup.35Cl/.sup.37Cl) 498/500 [M + H].sup.+ 254.sup.7 2-[3-Chloro-6-[5- methyl-1-[1-(oxetan-3- yl)azetidin-3-yl]triazol- 4-yl]pyrazolo[1,5- a]pyridin-4-yl]oxy-1- (3,5-difluoro-2- pyridyl)ethanone [00420] embedded image (.sup.35Cl/.sup.37Cl) 516/518 [M + H].sup.+ 255.sup.8 4-(2-Cyclopentyl-2-oxo-ethoxy)-6-[5- methyl-1-[1-(oxetan-3- yl)-4-piperidyl]triazol- 4-yl]pyrazolo[1,5- a]pyridine-3-carbonitrile [00421]  embedded image 490 [M + H].sup.+ 256.sup.7 1-(5-Fluoro-2- pyridyl)-2-[6-[5- methyl-1-[1-(oxetan- 3-yl)-4- piperidyl]triazol-4- yl]-3- (trifluoromethyl)pyra- zolo[1,5-a]pyridin-4- ylloxy-ethanone [00422]  embedded image 560 [M + H].sup.+ 257.sup.4,5 tert-Butyl 4-[4-[3- chloro-4-(2- isothiazol-3-yl-2-oxo- ethoxy)pyrazolo[1,5- a]pyridin-6-yl]-5- methyl-triazol-1- yl]piperidine-1- carboxylate [00423]  embedded image 558 [M + H].sup.+ 258.sup.4,10 4-[2-(3,5-Difluoro-2- pyridyl)-2-oxo- ethoxy]-6-[5-methyl- 1-[1-(oxetan-3-yl)-4- piperidyl]triazol-4-yl]pyrazolo[1,5- a]pyridine-3- carbonitrile [00424]  embedded image 535 [M + H].sup.+ 259.sup.4,11 tert-Butyl 4-[4-[3- cyano-4-[2-(3,5- difluoro-2-pyridyl)-2- oxo-ethoxy]pyrazolo [1,5-a]pyridin-6-yl]- 5-methyl-triazol-1- yl]piperidine-1- carboxylate [00425]  embedded image 579 [M + H].sup.+ 260.sup.4,12 tert-Butyl 4-[4-[4-[2- (3,5-difluoro-2- pyridyl)-2-oxo- ethoxy]-3-fluoro- pyrazolo[1,5- a]pyridin-6-yl]-5- methyl-triazol-1-yl] piperidine-1- carboxylate [00426] embedded image 572 [M + H].sup.+ 261.sup.13 2-[3-Chloro-6-[5- methyl-1-[1-(oxetan- 3-yl)-4-piperidyl]triazol-4- yl]pyrazolo[1,5- a]pyridin-4-yl]oxy-1- (3,5-difluoro-2- pyridyl)ethanone [00427]  embedded image 544/546 [M + H].sup.+ 262.sup.4,14 1-(3-Chloro-5-fluoro- 2-pyridyl)-2-[3- fluoro-6-[5-methyl-1- [1-(oxetan-3-yl)-4- piperidyl]triazol-4- yl]pyrazolo[1,5-a]pyridin-4-yl]oxy- ethanone [00428]  embedded image 544 [M + H].sup.+ 263.sup.4,15 2-[3-Fluoro-6-[5- methyl-1-[1-(oxetan- 3-yl)-4- piperidyl]triazol-4- yl]pyrazolo[1,5- a]pyridin-4-yl]oxy-1- (5-fluoro-2- pyridyl)ethanone [00429]  embedded image 510 [M + H].sup.+ 264.sup.4,5 tert-Butyl 4-[4-[4-[2- (5-fluoro-2-pyridyl)- 2-oxo-ethoxy]-3- methyl-pyrazolo[1,5- a]pyridin-6-yl]-5-methyl-triazol-1-yl] piperidine-1- carboxylate [00430]  embedded image 550 [M + H].sup.+ 265.sup.4,5 tert-Butyl 4-[4-[4-[2- (3-chloro-2-pyridyl)- 2-oxo-ethoxy]-3- cyano-pyrazolo[1,5-a]pyridin-6-yl]-5- methyl-triazol-1-yl] piperidine-1- carboxylate [00431]  embedded image 577 [M + H].sup.+ 266.sup.4,14,16 tert-Butyl 4-[4-[3- cyano-4-[2-(3- methyl-2-pyridyl)-2- oxo-ethoxy]pyrazolo[1,5- a]pyridin-6-yl]-5- methyl-triazol-1- yl]piperidine-1- carboxylate [00432] embedded image 557 [M + H].sup.+ 267.sup.4,7,17 2-[3-Chloro-6-[5- methyl-1-[1-(oxetan- 3-yl)-4- piperidyl]triazol-4- yl]pyrazolo[1,5- a]pyridin-4-yl]oxy-1- (5-fluoro-2- pyridyl)ethanone [00433]  embedded image 526 [M + H].sup.+ 268.sup.4,18 tert-Butyl 4-[4-[3- bromo-4-[2-(5-fluoro-2-pyridyl)-2- oxo- ethoxy]pyrazolo[1,5- a]pyridin-6-yl]-5- methyl-triazol-1- yl]piperidine-1-carboxylate [00434]embedded image (.sup.79Br/.sup.81Br) 614/616 [M + H].sup.+ .sup.1Purified by reversed phase flash C18 chromatography with the following conditions: column, C18; eluting with 75% to 80% CAN in H.sub.2O. .sup.2Purified by reversed phase C18 chromatography eluting with 50% to 60% CAN in H2O (0.1% FA) .sup.3Workup: Reaction was

concentrated, diluted with H.sub.2O and insoluble material was collected by filtration. .sup.4Cs.sub.2CO.sub.3 used as base in this synthesis. .sup.5Purified by silica gel chromatography eluting with MeOH in DCM. .sup.6Purified by silica gel chromatography eluting with 5% (EA/EtOH 3:1) in cHex (2 CV), 5% to 50% (EA/EtOH 3:1) in cHex (20 CV) then 100% EA/EtOH (3:1). .sup.7Workup: Reaction was concentrated, diluted with H.sub.2O and insoluble material was collected by filtration. .sup.8Workup: EA and H.sub.2O were added, layers separated, organic layer washed with IN NaOH and brine. Organic layer was dried over MgSO.sub.4, filtered and concentrated. .sup.9Workup: Reaction concentrated in vacuo. Residue was dissolved into H.sub.2O and acetone. Solution concentrated until solid precipitated. Suspension was stirred overnight then solids collected by filtration. .sup.10Purified by silica gel chromatography eluting with DCM (5 CV), 2% MeOH in DCM (15 CV), 5% MeOH in DCM (10 CV) and MeOH (5 CV). .sup.11Workup: H.sub.2O added to reaction then concentrated. The residue was triturated in H.sub.2O and the insoluble material was collected by filtration. .sup.12Workup: Reaction diluted with H.sub.2O and triturated for 30 min. Insoluble material was collected by filtration, washed with H.sub.2O, MTBE and cHex. .sup.13Purified by silica gel chromatography eluting with acetone in 0% to 50% acetone in DCM (25 CV), 50% to 100% acetone in DCM (5 CV) then 100% acetone. .sup.14Workup: H.sub.2O was added to the recation then concentrated. The resultant suspension diluted with H.sub.2O then extracted with DCM. Organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concetrated. .sup.15Workup: H.sub.2O was added to the recation then concentrated. The resultant suspension diluted with H.sub.2O, triterated and the insoluble material was collected by filtration. .sup.16Purified by silica gel chromatography eluting with 5% MeOH in DCM. .sup.17Isolated material was sonicated in aqueous 2M Na.sub.2CO.sub.3 for 10 min then filtered and washed with water. .sup.18Workup: H.sub.2O was added and the resultant precipitate was collected by filtration.

Preparation 269

tert-Butyl 4-[4-[3-cyano-4-[1-(1-isopropyltriazol-4-yl)ethoxy]pyrazolo[1,5-a]pyridin-6-yl]-5-methyl-triazol-1-yl]piperidine-1-carboxylate

##STR00435##

[0496] Cs.sub.2CO.sub.3 (1.41 g, 4.31 mmol) was added to a degassed soln of tert-butyl 4-(4-(3-cyano-4-hydroxypyrazolo[1,5-a]pyridin-6-yl)-5-methyl-1H-1,2,3-triazol-1-yl)piperidine-1-carboxylate (665 mg, 1.57 mmol) and 4-(1-chloroethyl)-1-isopropyl-1H-1,2,3-triazole (495 mg, 2.35 mmol) in DMF (5 ml) and the mixture was stirred at 65° C. for 2 h. The reaction was diluted with EA (25 ml) and washed with H.sub.2O (25 ml) and brine (25 ml). The organic layer was dried over MgSO.sub.4, filtered, concentrated in vacuo. The residue was purified by silica gel chromatography eluting with MeOH in DCM to give the title compound as pale-yellow oil (601 mg, 68%). MS ES+ m/z 561.5 [M+H].sup.+.

[0497] The following compounds were prepared in a manner essentially analogous to the method of Preparation 269 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as

TABLE-US-00042 TABLE 41 Prep MS ES+ # Chemical Name Structure m/z 270.sup.1 tert-Butyl 4-[4-[3- cyano-4-[1-(2- isopropyltriazol-4- yl)ethoxy] pyrazolo[1,5- a]pyridin-6-yl]-5- methyl-triazol-1- yl]piperidine-1- carboxylate [00436]  505.4 [M − tbutyl + H].sup.+ 271.sup.1 tert-Butyl 4-[4-[3- cyano-4-[1-(1- methylpyrazolo[3,4- c]pyridin-4-yl)ethoxy] pyrazolo[1,5- a]pyridin-6-yl]-5- methyl-triazol-1-yl] piperidine-1- carboxylate [00437] 583.5 [M + H].sup.+ 272.sup.1 tert-Butyl 4-[4-[3- cyano-4-[1-(1-methylpyrrolo[2,3- c]pyridin-4-yl) ethoxy]pyrazolo[1,5- a]pyridin-6-yl]-5- methyl-triazol-1-yl] piperidine-1- carboxylate [00438]  582.5 [M + H].sup.+ 273.sup.1 tert-Butyl 4-[4-[3- cyano-4-[1-[1- (trifluoromethyl) pyrazol-3-yl]ethoxy] pyrazolo[1,5- a]pyridin-6-yl]-5-methyl-triazol-1-yl] piperidine-1- carboxylate [00439]  586.4 [M + H].sup.+ 274.sup.1 tert-Butyl 4-[4-[3- cyano-4-[1-(4- cyclopropyl-5-fluoro- 2-pyridyl)ethoxy] pyrazolo[1,5-

a]pyridin-6-yl]-5- methyl-triazol-1-yl] piperidine-1- carboxylate [00440]  embedded image 587.5 [M + H].sup.+ 275.sup.1 tert-Butyl 4-[4-[3- cyano-4-[1-(7-fluoro- 4-isoquinolyl) ethoxy]pyrazolo[1,5- a]pyridin-6-yl]-5- methyl-triazol-1- yl]piperidine-1- carboxylate [00441]  embedded image 597.5 [M + H].sup.+ 276.sup.2 4-[1-(6- Bromopyrazin-2- yl)ethoxy]-6-[5- methyl-1-[1-(oxetan- 3-yl)-4- piperidyl]triazol-4- yl]pyrazolo[1,5- a]pyridine-3- carbonitrile [00442]  embedded image (.sup.79Br/.sup.81Br) 564/566 [M + H].sup.+ 277.sup.3 tert-Butyl 4-[4-[3- cyano-4-[1-(2- cyclopropylthiazol-4- yl)ethoxy]pyrazolo [1,5-a]pyridin-6-yl]-5- methyl-triazol-1- yl]piperidine-1- carboxylate [00443]  embedded image 575 [M + H].sup.+ 278.sup.4 tert-Butyl 4-[4-[3- cyano-4-[2-methyl-2- (2-pyridyl) propoxy]pyrazolo [1,5-a]pyridin-6- yl]-5-methyl-triazol-1- yl]piperidine-1- carboxylate [00444]embedded image a 279.sup.5 tert-Butyl 4-[4-[3- cyano-4-[1-(2- methoxythiazol-4- yl)ethoxy]pyrazolo [1,5-a]pyridin-6-yl]-5- methyl-triazol-1-yl]piperidine-1- carboxylate [00445]  embedded image 565 [M + H].sup.+ 280.sup.6 tert-Butyl 4-[4-[3- cyano-4-[(1R)-1-[5- (trifluoromethyl)-3- pyridyl]ethoxy] pyrazolo [1,5-a]pyridin-6-yl]- 5-methyl-triazol-1- yl]piperidine-1- carboxylate [00446]  embedded image 597 [M + H].sup.+ .sup.1Purified by silica gel chromatography eluting with MeOH in DCM. .sup.2Purified by silica gel chromatography eluting with 20% to 100% EA in cHex. .sup.3Purified by silica gel chromatography eluting with 20% to 40% (3:1 EA:EtOH) in cHex. .sup.4Purified by silica gel chromatography eluting with 5% EA in cHex (2CV) at 5%; 5% to 50% EA in cHex (20 CV), 50% to 100% EA in cHex (10CV), then 100% EA. .sup.5Purified by silica gel chromatography eluting with 10% 3:1 EA/EtOH in cHex (3 CV), 10% to 20% gradient 3:1 EA/EtOH in cHex (12 CV), 20% 3:1 EA/EtOH in cHex (2 CV), 20% to 50% gradient 3:1 EA/EtOH in cHex (18 CV). .sup.6Upon cooling to RT the reaction was treated with H.sub.2O. Insoluble material was collected by filtration to afford title compound. .sup.aMaterial used in subsequent step without further characterization.

Preparation 281

tert-Butyl 4-[4-[4-[2-(3,5-difluoro-2-pyridyl)-2-methoxy-ethoxy]-3-fluoro-pyrazolo[1,5-a]pyridine-6-yl]-5-methyl-triazol-1-yl]piperidine-1-carboxylate

##STR00447##

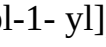
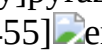
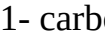
[0498] A soln of PPh.sub.3 (1.04 g, 3.96 mmol) in THE (10 ml) at 0° C. was treated dropwise with DIAD (0.77 g, 3.83 mmol) under N.sub.2. The reaction was stirred for 0.5 h at 0° C. before adding to a mixture of 2-(3,5-difluoro-2-pyridyl)-2-methoxy-ethanol (0.30 g, 1.59 mmol) and tert-butyl 4-[4-(3-fluoro-4-hydroxy-pyrazolo[1,5-a]pyridine-6-yl)-5-methyl-triazol-1-yl]piperidine-1-carboxylate (0.55 g, 1.32 mmol) in THE (10 ml). The resulting mixture was stirred for 2 h at RT then concentrated. The residue was purified by reversed phase flash C18 chromatography with the following conditions: column, C18; eluting with a gradient of 45% to 55% CAN in H.sub.2O (0.1% FA) to afford the title compound (480 mg, 62%) as a yellow solid. MS ES+ m/z 588 [M+H].sup.+.

[0499] The following compounds were prepared in a manner essentially analogous to the method of Preparation 281 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00043 TABLE 42 Prep MS ES+ # Chemical Name Structure m/z 282.sup.1 tert-Butyl 4-[4-[5-[2-(5- fluoro-2-pyridyl)-2- methoxy- ethoxy]imidazo[1,2- a]pyridine-7-yl]-5- methyl-triazol-1- yl]piperidine-1- carboxylate [00448]  embedded image 552 [M + H].sup.+ 283.sup.2 tert-Butyl 4-[4-[5-[2- (3,5-difluoro-2-pyridyl)- 2-methoxy- ethoxy]imidazo[1,2- a]pyridin-7-yl]-5- methyl-triazol-1- yl]piperidine-1- carboxylate [00449]  embedded image 570 [M + H].sup.+ .sup.1Purified by flash reversed phase C18 chromatography eluting with 30% to 50% CAN in H.sub.2O (0.1% NH.sub.4HCO.sub.3). .sup.2Purified by flash reversed phase C18 chromatography eluting with 60% to 70% CAN in H.sub.2O.

Preparation 284

tert-Butyl 4-[4-[3-chloro-5-[2-(5-fluoro-2-pyridyl)-2-methoxy-ethoxy]imidazo[1,2-a]pyridin-7-

yl]-5-methyl-triazol-1-yl]piperidine-1-carboxylate
##STR00450##
[0500] A soln of tert-butyl 4-[4-[5-[2-(5-fluoro-2-pyridyl)-2-methoxy-ethoxy]imidazo[1,2-a]pyridin-7-yl]-5-methyl-triazol-1-yl]piperidine-1-carboxylate (1.4 g, 2.54 mmol) in DMF (15 ml) at 0° C. was treated with DCDMH (400 mg, 2.03 mmol). After stirring at 0° C. for 0.5 h, the residue was purified by reversed phase flash C18 chromatography with the following conditions: column, C18; eluting with a gradient of 60% to 70% CAN in H.sub.2O to afford the title compound (700 mg, 47%) as a yellow solid. MS ES+ m/z 586 [M+H].sup.+.
[0501] The following compounds were prepared in a manner essentially analogous to the method of Preparation 284 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.
TABLE-US-00044 TABLE 43 MS Prep ES+ # Chemical Name Structure m/z 285 tert-Butyl 4-[4-[3- chloro-5-[2-(3,5- difluoro-2-pyridyl)- 2-methoxy- ethoxy]imidazo[1,2- a]pyridin-7-yl]-5-methyl-triazol-1- yl]piperidine-1- carboxylate [00451]  embedded image 604 [M + H].sup.+ 286.sup.1,2 tert-Butyl 4-[4-[3- chloro-5-[2-(3,5- difluoro-2-pyridyl)- 2-methoxy-ethoxy]imidazo[1,2- a]pyridin-7-yl]-5- methyl-triazol-1- yl]-4-methyl- piperidine-1- carboxylate [00452]  embedded image 618 [M + H].sup.+ .sup.1Purified by reversed phase C18 chromatography eluting with 45% to 50% AcCN in H.sub.2O. .sup.2Purified by Prep-TLC (PE/EA 1:3)
Preparation 287
tert-Butyl 4-[4-[3-cyano-4-[2-(3,5-difluoro-2-pyridyl)-2-hydroxy-ethoxy]pyrazolo[1,5-a]pyridin-6-yl]-5-methyl-triazol-1-yl]piperidine-1-carboxylate, Isomer 1
##STR00453##
[0502] In a sealed tube, chloro(N-[(1R,2R)-2-[(S)-[2-[[1,2,3,4,5,6-η)-4-methylphenyl]methoxy]ethyl]amino]-1,2-diphenylethylmethanesulfonamidato) ruthenium(II) (25 mg, 0.04 mmol, 98 mass %) was added to a stirred mixture of tert-butyl 4-[4-[3-cyano-4-[2-(3,5-difluoro-2-pyridyl)-2-oxo-ethoxy]pyrazolo[1,5-a]pyridin-6-yl]-5-methyl-triazol-1-yl]piperidine-1-carboxylate (3.5 g, 4.2 mmol) in FA NEt.sub.3 complex (5:2 ratio) (18 ml, 42.21 mmol) and DCM (14 ml, 218 mmol). The reaction was heated at 45° C. under N.sub.2 for 75 minutes. Upon cooling to RT, the reaction was diluted with DCM, washed with H.sub.2O, saturated aq NaHCO.sub.3, H.sub.2O and brine. The organic layer was dried over MgSO.sub.4, filtered and concentrated. The residue was purified by silica gel chromatography eluting with 20% acetone in DCM to afford the title compound as an orange colored solid (3.23 g, 99%). MS ES+ m/z 581 [M+H].sup.+.
[0503] The following compounds were prepared in a manner essentially analogous to the method of Preparation 287 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as
TABLE-US-00045 TABLE 44 Prep MS ES+ # Chemical Name Structure m/z 288.sup.1 tert-Butyl 4-[4-[4-[2-(3- chloro-2-pyridyl)-2- hydroxy-ethoxy]-3- cyano-pyrazolo[1,5- a]pyridin-6-yl]-5-methyl-triazol-1- yl]piperidine-1- carboxylate, Isomer 1 [00454]  embedded image 579 [M + H].sup.+ 289.sup.2 tert-Butyl 4-[4-[3- cyano-4-[2-hydroxy-2- (3-methyl-2-pyridyl)ethoxy]pyrazolo [1,5-a]pyridin-6-yl]-5- methyl-triazol-1- yl]piperidine-1- carboxylate, Isomer 1 [00455]  embedded image 559 [M + H].sup.+ 290.sup.2 tert-Butyl 4-[4-[3- bromo-4-[2-(5-fluoro-2- pyridyl)-2-hydroxy- ethoxy]pyrazolo[1,5- a]pyridin-6-yl]-5- methyl-triazol-1-yl]piperidine-1- carboxylate, Isomer 1 [00456]  embedded image (.sup.79Br/.sup.81Br) 616/618 [M + H].sup.+ .sup.1Purified by silica gel chromatography eluting with MeOH in DCM. .sup.2Crude taken on to next step after aq workup.
Preparation 291
4-[2-(5-Fluoro-2-pyridyl)-2-hydroxy-ethoxy]-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile
##STR00457##

[0504] To a suspension of 4-[2-(5-fluoro-2-pyridyl)-2-oxo-ethoxy]-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile (4.01 g, 6.58 mmol) in MeOH (65 ml) was added in one portion NaBH.sub.4 (1.0 g, 26.43 mmol) at 0° C. The mixture was stirred at 0° C. for 5 min and then at RT for 1 h. The reaction was diluted with H.sub.2O (100 ml). The resultant precipitate was collected by filtration and washed with H.sub.2O/MeOH (4:1) (20 ml). The resulting solid was dried at 40° C. under vacuum to afford the title compound (3.40 g, 91%). MS ES+ m/z 519 [M+H].sup.+.

Preparation 292

tert-Butyl 4-[4-[3-chloro-4-[2-(5-fluoro-2-pyridyl)-2-hydroxy-ethoxy]pyrazolo[1,5-a]pyridine-6-yl]-5-methyl-triazol-1-yl]piperidine-1-carboxylate

##STR00458##

[0505] A soln of tert-butyl 4-[4-[3-chloro-4-[2-(5-fluoro-2-pyridyl)-2-oxo-ethoxy]pyrazolo[1,5-a]pyridine-6-yl]-5-methyl-triazol-1-yl]piperidine-1-carboxylate (1 g, 1.75 mmol) in MeOH (20 ml) was treated with NaBH.sub.4 (66.37 mg, 1.75 mmol) at RT under N.sub.2. After stirring at RT for 1 h, the reaction was quenched with H.sub.2O (50 ml) and extracted with EA (3×100 ml). The combined organic layers were washed with brine (2×50 ml), dried over anhydrous Na.sub.2SO.sub.4, filtered, and concentrated to obtain the title compound (1.0 g, 100) as a brown solid. MS ES+ m/z 572 [M+H].sup.+.

[0506] The following compounds were prepared in a manner essentially analogous to the method of Preparation 292 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate. DCM can be used as a cosolvent.

TABLE-US-00046 TABLE 45 Prep MS ES+ # Chemical Name Structure m/z 293 tert-Butyl 4-[4-[3-cyano-4- [2-(2,4-difluorophenyl)-2- hydroxy-ethoxy] pyrazolo[1,5-a]pyridine-6- yl]-5-methyl-triazol-1- yl]piperidine-1- carboxylate [00459] 524 [M + H].sup.+ 294 tert-Butyl 4-[4-[3-cyano-4- [2-(5-fluoro-2-pyridyl)-2- hydroxy-ethoxy] pyrazolo[1,5-a]pyridin-6- yl]-5-methyl-triazol-1- yl]piperidine-1- carboxylate [00460] 563 [M + H].sup.+ 295 tert-Butyl 4-[4-[3-fluoro- 4-[2-(5-fluoro-2-pyridyl)- 2-hydroxy-ethoxy] pyrazolo[1,5-a]pyridin-6-yl]-5-methyl-triazol-1- yl]piperidine-1- carboxylate [00461] 556 [M + H].sup.+ 296 tert-Butyl 4-[4-[3-chloro- 4-[2-(3,5-difluoro-2- pyridyl)-2-hydroxy- ethoxy]pyrazolo[1,5-a]pyridin-6-yl]-5-methyl- triazol-1-yl]piperidine-1- carboxylate [00462] (.sup.35Cl/.sup.37Cl) 590/592 [M + H].sup.+ 297 2-[3-Chloro-6-[5-methyl- 1-[1-(oxetan-3-yl)azetidin- 3-yl]triazol-4- yl]pyrazolo[1,5-a]pyridin- 4-yl]oxy-1-(5-fluoro-2- pyridyl)ethanol [00463] (.sup.35Cl/.sup.37Cl) 500/502 [M + H].sup.+ 298 2-[3-Chloro-6-[5-methyl- 1-[1-(oxetan-3-yl)azetidin- 3-yl]triazol-4- yl]pyrazolo[1,5-a]pyridin- 4-yl]oxy-1-(3,5-difluoro- 2-pyridyl)ethanol [00464] (.sup.35Cl/.sup.37Cl) 518/520 [M + H].sup.+ 299 tert-Butyl 4-[4-[4-[2-(3- chloro-5-fluoro-2- pyridyl)-2-hydroxy- ethoxy]-3-cyano-pyrazolo[1,5-a]pyridin-6- yl]-5-methyl-triazol-1- yl]piperidine-1- carboxylate [00465] (.sup.35Cl/.sup.37Cl) 597/599 [M + H].sup.+ 300 tert-Butyl 4-[4-[4-[2-(4-chloro-5-fluoro-2- pyridyl)-2-hydroxy- ethoxy]-3-cyano- pyrazolo[1,5-a]pyridin- 6-yl]-5-methyl-triazol-1- yl]piperidine-1- carboxylate [00466] (.sup.35Cl/.sup.37Cl) 597/599 [M + H].sup.+ 301.sup.1 1-(5-Fluoro-2-pyridyl)- 2-[6-[5-methyl-1-[1- (oxetan-3-yl)-4-piperidyl]triazol-4-yl]-3- (trifluoromethyl)pyrazolo [1,5-a]pyridin-4- yl]oxy-ethanol [00467] 562 [M + H].sup.+ 302 4-(2-Cyclopentyl-2- hydroxy-ethoxy)-6-[5- methyl-1-[1-(oxetan-3- yl)-4-piperidyl]triazol-4- yl]pyrazolo[1,5- a]pyridine-3-carbonitrile [00468] 492 [M + H].sup.+ 303 tert-Butyl 4-[4-[3- chloro-4-(2-hydroxy-2- isothiazol-3-yl- ethoxy)pyrazolo[1,5- a]pyridin-6-yl]-5- methyl-triazol-1- yl]piperidine-1- carboxylate [00469] 560 [M + H].sup.+ 304.sup.2 4-[2-(3,5-Difluoro-2- pyridyl)-2-hydroxy-ethoxy]-6-[5-methyl-1- [1-(oxetan-3-yl)-4- piperidyl]triazol-4- yl]pyrazolo[1,5- a]pyridine-3-carbonitrile [00470] 537 [M + H].sup.+ 305.sup.3 1-(3-Chloro-5-fluoro-2-

pyridyl)-2-[3-fluoro-6- [5-methyl-1-[1-(oxetan- 3-yl)-4-piperidyl]triazol- 4-yl]pyrazolo[1,5-a]pyridin-4-yl]oxy- ethanol [00471]embedded image 546 [M + H].sup.+ 306.sup.4 2-[3-Fluoro-6-[5- methyl-1-[1-(oxetan-3- yl)-4-piperidyl]triazol-4- yl]pyrazolo[1,5- a]pyridin-4-yl]oxy-1-(5-fluoro-2-pyridyl)ethanol [00472]embedded image 512 [M + H].sup.+ .sup.1Purified by silica gel chromatography eluting with 0% to 10% MeOH in DCM. .sup.2Purified by silica gel chromatography eluting with DCM (5 CV), 2% MeOH in DCM (10 CV), 5% MeOH in DCM (10 CV). .sup.3Purified by silica gel chromatography eluting with 0% to 40% (10% MeOH in DCM) in DCM. .sup.4Purified by silica gel chromatography eluting with 0% to 40% (10% MeOH in DCM) in DCM.

Preparation 307

tert-Butyl 4-[4-[4-[2-(3,5-difluoro-2-pyridyl)-2-hydroxy-propoxy]-3-fluoro-pyrazolo[1,5-a]pyridin-6-yl]-5-methyl-triazol-1-yl]piperidine-1-carboxylate

##STR00473##

[0507] A soln of tert-butyl 4-[4-[4-[2-(3,5-difluoro-2-pyridyl)-2-oxo-ethoxy]-3-fluoro-pyrazolo[1,5-a]pyridin-6-yl]-5-methyl-triazol-1-yl]piperidine-1-carboxylate (0.61 g, 1.07 mmol) in DCM (10 ml) was slowly added to a solution of MeMgBr in THE (3 mL, 4.2 mmol, 1.4 mol/L) that was precooled cooled to 0° C. under N.sub.2. Additional DCM (2 ml) was added, and the reaction was stirred overnight. The reaction was quenched with aq. NH.sub.4Cl, extracted with DCM, and washed with H.sub.2O and brine. The organic phase was concentrated to afford a residue. The residue was purified by silica gel chromatography eluting with 0% to 20% acetone in DCM to afford the title compound (175 mg, 0.25 mmol, 24%, 85 mass %) as a yellow oil. MS ES+ m/z 588 [M+H].sup.+.

[0508] The following compounds were prepared in a manner essentially analogous to the method of Preparation 307 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate. DCM can be used as a cosolvent.

TABLE-US-00047 TABLE 46 MS ES+ Prep # Chemical Name Structure m/z 308.sup.1 tert-Butyl 4-[4-[4-[2- (5-fluoro-2-pyridyl)-2- hydroxy-propoxy]-3- methyl-pyrazolo[1,5- a]pyridin-6-yl]-5-methyl-triazol-1- yl]piperidine-1- carboxylate [00474]embedded image 566 [M + H].sup.+ .sup.1Purified by silica gel chromatography eluting with 30% (10% MeOH in DCM) in DCM.

Preparation 309

tert-Butyl 4-[4-[3-chloro-4-[2-(3,5-difluoro-2-pyridyl)-2-methylsulfonyloxy-ethoxy]pyrazolo[1,5-a]pyridin-6-yl]-5-methyl-triazol-1-yl]piperidine-1-carboxylate

##STR00475##

[0509] A solution of tert-butyl 4-[4-[3-chloro-4-[2-(3,5-difluoro-2-pyridyl)-2-hydroxy-ethoxy]pyrazolo[1,5-a]pyridin-6-yl]-5-methyl-triazol-1-yl]piperidine-1-carboxylate (0.60 g, 0.74 mmol) in DCM (6 ml) was successively treated at 0° C. with NEt.sub.3 (0.152 g, 1.51 mmol) and MsCl (0.13 g, 1.2 mmol). After 15 min, the cooling bath was removed, and the mixture was allowed to warm to RT. After 1 h the mixture was washed with H.sub.2O (1.5 ml), dried over MgSO.sub.4, and concentrated in vacuo to afford the title compound as a green solid. The product was used in the next step without further purification. MS ES+ m/z (.sup.35Cl/.sup.37Cl) 668/670 [M+H].sup.+.

Preparation 310

tert-Butyl 4-[4-[3-cyano-4-[2-(3,5-difluoro-2-pyridyl)-2-isopropoxy-ethoxy]pyrazolo[1,5-a]pyridin-6-yl]-5-methyl-triazol-1-yl]piperidine-1-carboxylate, Isomer 1

##STR00476##

[0510] To a mixture of tert-butyl 4-[4-[3-cyano-4-[(2S)-2-(3,5-difluoro-2-pyridyl)-2-hydroxy-ethoxy]pyrazolo[1,5-a]pyridin-6-yl]-5-methyl-triazol-1-yl]piperidine-1-carboxylate (1.0 g, 1.3 mmol, 75 mass %), Ag.sub.2O (600 mg, 2.59 mmol) and 2-iodopropane (2.6 ml, 26 mmol) in DMF (10 ml) at RT under N.sub.2 was added NaH in mineral oil (62 mg, 1.55 mmol, 60 mass %). The

reaction was stirred at RT for 10 min then additional NaH in mineral oil (62 mg, 1.55 mmol, 60 mass %) was added. Portions of NaH in mineral oil (62 mg, 1.55 mmol, 60 mass %), were added approximately every 10-20 min. After 90 minutes and 7 additions of NaH, H.sub.2O was added to the mixture. The mixture was extracted with EA, organic phase washed with brine (3×), dried over MgSO.sub.4, filtered and concentrated. The residue was purified by silica gel chromatography eluting with 20% to 50% EA in cHex. The isolated material was repurified by silica gel chromatography eluting with 20% EA in MTBE. An impurity had co-eluted with the title compound (720 mg, 56%, 63% purity). MS ES+ m/z 523 [M+H].sup.+.

Preparation 311

tert-Butyl 4-[4-[3-chloro-4-[2-(3,5-difluoro-2-pyridyl)-2-methoxy-ethoxy]pyrazolo[1,5-a]pyridin-6-yl]-5-methyl-triazol-1-yl]piperidine-1-carboxylate

##STR00477##

[0511] A soln of tert-butyl 4-[4-[3-chloro-4-[2-(3,5-difluoro-2-pyridyl)-2-hydroxy-ethoxy]pyrazolo[1,5-a]pyridin-6-yl]-5-methyl-triazol-1-yl]piperidine-1-carboxylate (0.63 g, 0.78 mmol) in N,N-dimethylacetamide (6 ml) was treated with NaH (65 mg, 1.63 mmol, 60% wt) followed by CH.sub.3I (0.08 ml, 1.28 mmol) at RT. After stirring at RT for 90 min, the reaction was quenched with MeOH (0.5 ml) and purified by reversed phase C18 chromatography eluting with a gradient of 30% to 90% ACN in H.sub.2O (NH.sub.4HCO.sub.3 buffer pH 9) to afford the title compound (192 mg, 38%) as an orange solid. MS ES+ m/z 604/606 [M+H].sup.+.

[0512] The following compounds were prepared in a manner essentially analogous to the method of Preparation 311 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00048 TABLE 47 MS ES+ Prep # Chemical Name Structure m/z 312.sup.1 3-Chloro-4-[2-(5-fluoro-2- pyridyl)-2-methoxy- ethoxy]-6-[5-methyl-1-[1- (oxetan-3-yl)azetidin-3-yl]triazol-4- yl]pyrazolo[1,5-a]pyridine [00478]  embedded image (.sup.35Cl/.sup.37Cl) 514/516 [M + H].sup.+ 313.sup.2,3 tert-Butyl 4-[4-[3-cyano- 4-[2-(5-fluoro-2-pyridyl)- 2-isopropoxy-ethoxy]pyrazolo [1,5- alpyridin-6-yl]-5-methyl- triazol-1-yl]piperidine-1- carboxylate [00479]embedded image 605 [M + H].sup.+ 314.sup.4 4-[2-(3-Chloro-5-fluoro- 2-pyridyl)-2-methoxy-ethoxy]-3-fluoro-6-[5- methyl-1-[1-(oxetan-3- yl)-4-piperidyl]triazol-4- yl]pyrazolo[1,5- alpyridine [00480]embedded image 560 [M + H].sup.+ 315.sup.5,6 tert-Butyl 4-[4-[3-chloro- 4-[2-(5-fluoro-2-pyridyl)- 2-methoxy- ethoxy]pyrazolo [1,5- alpyridin-6-yl]-5-methyl- triazol-1-yl] piperidine-1- carboxylate [00481]embedded image 587 [M + H].sup.+ 316.sup.5,7 tert-Butyl 4-[4-[4-[2-(3- chloro-2-pyridyl)-2- methoxy-ethoxy]-3- cyano-pyrazolo[1,5- alpyridin-6-yl]-5-methyl-triazol-1- yl]piperidine-1- carboxylate, Isomer 1 [00482]embedded image 594 [M + H].sup.+ 317.sup.5,6 tert-Butyl 4-[4-[3- cyano-4-[2-methoxy-2- (3-methyl-2-pyridyl) ethoxy]pyrazolo[1,5- a]pyridin-6-yl]-5- methyl-triazol-1- yl]piperidine-1- carboxylate, Isomer 1 [00483]embedded image 573 [M + H].sup.+ .sup.1Purified by reversed phase C18 chromatography eluting with aq NH.sub.4HCO.sub.3 pH 9 (5 CV), then 30% to 60% ACN in aq NH.sub.4HCO.sub.3 pH 9. .sup.2Ag.sub.2O (3.95 eq) was added to reaction. .sup.3Purification by silica gel chromatography eluting with 0% to 50% [DCM:MeOH (9:1)] in DCM. .sup.4Purified by SCX chromatography. Non-basic impurities were washed off with DCM, 5% MeOH in DCM. The title compound was eluted with methanolic ammonia (2M). .sup.5THF was used as the solvent. .sup.6Workup: Reaction was extracted with DCM, washed with H2O (3x), brine, dried over MgSO4, filtered and concentrated. .sup.7Workup: Reaction was diluted with H2O, extracted with DCM, washed with brine, dried over MgSO4, filtered and concentrated.

Preparation 318

tert-Butyl 4-[4-[3-chloro-4-[2-(3,5-difluoro-2-pyridyl)-2-(dimethylamino)ethoxy]pyrazolo[1,5-a]pyridin-6-yl]-5-methyl-triazol-1-yl]piperidine-1-carboxylate

##STR00484##

[0513] A mixture of tert-butyl 4-[4-[3-chloro-4-[2-(3,5-difluoro-2-pyridyl)-2-methylsulfonyloxy-

ethoxy]pyrazolo[1,5-a]pyridin-6-yl]-5-methyl-triazol-1-yl]piperidine-1-carboxylate (0.50 g, 0.74 mmol) and dimethylamine in THE (2M soln, 2 ml) was stirred at RT for 48 h. The crude mixture was purified by silica gel chromatography eluting with a gradient of 0% to 100% acetone in DCM to afford the title compound as a yellow solid (0.15 g, 27.8%, purity >85%). MS ES+ m/z (.sup.35Cl/.sup.37Cl) 617/619 [M+H].sup.+.

Preparation 319

4-[1-(1-Isopropyltriazol-4-yl)ethoxy]-6-[5-methyl-1-(4-piperidyl)triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile hydrochloride

##STR00485##

[0514] HCl in dioxane (4M, 2.0 ml, 5.98 mmol) was added to a soln of tert-butyl 4-(4-(3-cyano-4-(1-(1-isopropyl-1H-1,2,3-triazol-4-yl)ethoxy)pyrazolo[1,5-a]pyridine-6-yl)-5-methyl-1H-1,2,3-triazol-1-yl)piperidine-1-carboxylate (600 mg, 1.07 mmol) in DCM (10 ml) and the mixture was stirred at RT for 2 h. The reaction was concentrated in vacuo to afford the title compound as a hygroscopic beige solid (689 mg, quantitative). MS ES+ m/z 461.4 [M+H].sup.+.

[0515] The following compounds were prepared in a manner essentially analogous to the method of Preparation 319 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate. For compounds where the amine salt was isolated, the formation of the mono-, di-, or trivalent salt is dependent on the pKa of the amine and the acid used to form the salt. The exact mono-, di-, or trivalent salt form for each example was not identified.

TABLE-US-00049 TABLE 48 MS ES+ Prep # Chemical Name Structure m/z 320 4-[1-(2-Isopropyltriazol-4- yl)ethoxy]-6-[5-methyl-1- (4-piperidyl)triazol-4- yl]pyrazolo[1,5- a]pyridine-3-carbonitrile hydrochloride [00486]  embedded image 461 [M + H].sup.+ 321 6-[5-Methyl-1-(4-piperidyl)triazol-4-yl]-4- [1-(1-methylpyrazolo[3,4- c]pyridine-4- yl)ethoxy]pyrazolo [1,5-a]pyridine-3-carbonitrile hydrochloride [00487]  embedded image 483 [M + H].sup.+ 322 6-[5-Methyl-1-(4- piperidyl)triazol-4-yl]-4- [1-(1-methylpyrrolo[2,3- c]pyridine-4-yl)ethoxy] pyrazolo[1,5-a]pyridine-3- carbonitrile hydrochloride [00488]  embedded image 482 [M + H].sup.+ 323 2-[3-Fluoro-6-[5-methyl- 1-(4-piperidyl)triazol-4- yl]pyrazolo[1,5- a]pyridine-4-yl]oxy-1-(5- fluoro-2-pyridyl)ethanol hydrochloride [00489]  embedded image 456 [M + H].sup.+ 324 3-Chloro-4-[2-(3,5- difluoro-2-pyridyl)-2- methoxy-ethoxy]-6-[5- methyl-1-(4-piperidyl)triazol-4- yl]pyrazolo[1,5-a]pyridine hydrochloride [00490]  embedded image (.sup.35Cl/.sup.37Cl) 504/506 [M + H].sup.+ 325 6-[5-Methyl-1-(4- piperidyl)triazol-4-yl]-4- [1-[1- (trifluoromethyl)pyrazol- 3-yl]ethoxy]pyrazolo[1,5- a]pyridine-3-carbonitrile hydrochloride [00491]  embedded image 586 [M + H].sup.+ 326 4-[1-(4-Cyclopropyl-5- fluoro-2-pyridyl)ethoxy]- 6-[5-methyl-1-(4- piperidyl)triazol-4- yl]pyrazolo[1,5- a]pyridine-3-carbonitrile hydrochloride [00492]  embedded image 487 [M + H].sup.+ 327 4-[1-(7-Fluoro-4-isoquinolyl)ethoxy]-6-[5- methyl-1-(4- piperidyl)triazol-4- yl]pyrazolo[1,5- a]pyridine-3-carbonitrile hydrochloride [00493]  embedded image 497 [M + H].sup.+ 328 4-[2-(3-Chloro-5-fluoro-2- pyridyl)-2-hydroxy- ethoxy]-6-[5-methyl-1-(4- piperidyl)triazol-4- yl]pyrazolo[1,5-a]pyridine-3-carbonitrile hydrochloride [00494]  embedded image 497 [M + H].sup.+ 329 4-[2-(4-Chloro-5-fluoro-2- pyridyl)-2-hydroxy- ethoxy]-6-[5-methyl-1-(4- piperidyl)triazol-4-yl]pyrazolo[1,5- a]pyridine-3-carbonitrile hydrochloride [00495]  embedded image (.sup.35Cl/.sup.37Cl) 497/499 [M + H].sup.+ 330 2-[3-Chloro-6-[5-methyl- 1-(4-piperidyl)triazol-4- yl]pyrazolo[1,5-a]pyridin- 4-yl]oxy-1-isothiazol-3- yl-ethanol hydrochloride [00496]

embedded image 460 [M + H].sup.+ 331.sup.1 2-[3-Chloro-6-[5-methyl- 1-(4-piperidyl)triazol-4- yl]pyrazolo[1,5-a]pyridin- 4-yl]oxy-1-(3,5-difluoro- 2-pyridyl)-N,N-dimethyl- ethanamine hydrochloride [00497]embedded image (.sup.35Cl/.sup.37Cl) 517/519 [M + H].sup.+ 332 6-[5-Methyl-1-(4- piperidyl)triazol-4-yl]-4- [(1R)-1-[5- (trifluoromethyl)-3- pyridyl]ethoxy]pyrazolo [1,5-a]pyridine-3- carbonitrile hydrochloride [00498]embedded image 497 [M + H].sup.+ 333 1-[3-Chloro-6-[1- [(3S,4R)-3-fluoro-4- piperidyl]-5-methyl- triazol-4-yl]pyrazolo[1,5- a]pyridin-4-

yl]oxy-2-(5- fluoro-2-pyridyl)propan- 2-ol hydrochloride [00499]  embedded image 504 [M + H].sup.+ 334 2-(5-Fluoro-2-pyridyl)-1- [3-methyl-6-[5-methyl-1- (4-piperidyl)triazol-4-yl]pyrazolo[1,5-a]pyridin- 4-yl]oxy-propan-2-ol hydrochloride [00500]embedded image 466 [M + H].sup.+ 335 4-[2-(3-Chloro-2-pyridyl)- 2-methoxy-ethoxy]-6-[5- methyl-1-(4- piperidyl)triazol-4- yl]pyrazolo[1,5- a]pyridine-3-carbonitrile hydrochloride, Isomer 1 [00501]  embedded image 493 [M + H].sup.+ 336 4-[2-Methoxy-2-(3- methyl-2-pyridyl)ethoxy]- 6-[5-methyl-1-(4-piperidyl)triazol-4- yl]pyrazolo[1,5- a]pyridine-3-carbonitrile hydrochloride, Isomer 1 [00502]  embedded image 473 [M + H].sup.+ 337.sup.2 (1S)-2-[3-Bromo-6-[5- methyl-1-(4-piperidyl)triazol-4- yl]pyrazolo[1,5-a]pyridin- 4-yl]oxy-1-(5-fluoro-2- pyridyl)ethanol hydrochloride, Isomer 1 [00503]  embedded image (.sup.79Br/.sup.81Br) 516/518 [M + H].sup.+ 338 3-Chloro-5-(2-(3,5- difluoropyridin-2-yl)-2- methoxyethoxy)-7-(5- methyl-1-((1r,3r)-3-(piperazin-1- yl)cyclobutyl)-1H-1,2,3- triazol-4-yl)imidazo[1,2- a]pyridine, hydrochloride [00504]  embedded image 559 [M + H].sup.+ 339 6-[1-[(3S,4R)-3-Fluoro-4- piperidyl]-5-methyl- triazol-4-yl]-4-[2-(5- fluoro-2-pyridyl)-2- methoxy- ethoxy]pyrazolo[1,5- a]pyridine-3-carbonitrile; hydrochloride [00505]embedded image 495 .sup.1Reaction was run in MeOH. Upon workup residue was triturated in EA, filtered, collected by filtration to afford title compound. .sup.2Reaction concentrated in vacuo. The residue was diluted with EA, slurried for 1 h. The precipitate was collected by filtration.

Preparation 340

2-[3-Chloro-6-[5-methyl-1-(4-piperidyl)triazol-4-yl]pyrazolo[1,5-a]pyridine-4-yl]oxy-1-(5-fluoro-2-pyridyl)ethanol, 2,2,2-trifluoroacetic acid

##STR00506##

[0516] A soln of tert-butyl 4-[4-[3-chloro-4-[2-(5-fluoro-2-pyridyl)-2-hydroxy-ethoxy]pyrazolo[1,5-a]pyridine-6-yl]-5-methyl-triazol-1-yl]piperidine-1-carboxylate (1.0 g, 1.75 mmol) in DCM (10 ml) was treated with TFA (10 ml) and allowed to stir at RT for 1 h. The reaction was concentrated, and the crude product used in the next synthetic step without purification. MS ES+ m/z 472 [M+H].sup.+.

[0517] The following compounds were prepared in a manner essentially analogous to the method of Preparation 340 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate. For compounds where the amine salt was isolated, the formation of the mono-, di-, or trivalent salt is dependent on the pKa of the amine and the acid used to form the salt. The exact mono-, di-, or trivalent salt form for each example was not identified.

TABLE-US-00050 TABLE 49 MS ES+ Prep # Chemical Name Structure m/z 341 3-Chloro-5-[2-(5-fluoro-2- pyridyl)-2-methoxy-ethoxy]- 7-[5-methyl-1-(4- piperidyl)triazol-4- yl]imidazo[1,2-a]pyridine, 2,2,2-trifluoroacetic acid [00507]embedded image 486 [M + H].sup.+ 342 3-Chloro-5-[2-(3,5-difluoro- 2-pyridyl)-2-methoxy- ethoxy]-7-[5-methyl-1-(4- piperidyl)triazol-4-yl]imidazo[1,2-a]pyridine, 2,2,2-trifluoroacetic acid [00508]  embedded image 504 [M + H].sup.+ 343 6-[1-(2-Azaspiro[3.3]heptan- 6-yl)-5-methyl-pyrazol-4-yl]- 4-[(1R)-1-(2-pyridyl)ethoxy]pyrazolo[1,5- a]pyridine-3-carbonitrile, 2,2,2-trifluoroacetic acid [00509]  embedded image 440 [M + H].sup.+ 344a 6-[1-(Azepan-4-yl)-5-methyl- pyrazol-4-yl]-4-[(1R)-1-(2- pyridyl)ethoxy]pyrazolo[1,5- a]pyridine-3-carbonitrile, 2,2,2-trifluoroacetic acid [00510] embedded image a 344b 6-[1-(Azepan-4-yl)-3-methyl- pyrazol-4-yl]-4-[(1R)-1-(2-pyridyl)ethoxy]pyrazolo[1,5- a]pyridine-3-carbonitrile, 2,2,2-trifluoroacetic acid [00511]  embedded image a 345 4-[[1-(5-Fluoro-2- pyridyl)cyclopropyl]methoxy]- 6-[5-methyl-1-(4-piperidyl)triazol-4- yl]pyrazolo[1,5-a]pyridine-3- carbonitrile, 2,2,2- trifluoroacetic acid [00512]  embedded image 473 [M + H].sup.+ 346 4-[1-(2-Cyclopropylthiazol-4- yl)ethoxy]-6-[5-methyl-1-(4- piperidyl)triazol-4- yl]pyrazolo[1,5-a]pyridine-3- carbonitrile, 2,2,2- trifluoroacetic acid [00513]embedded image 475 [M + H].sup.+ 347 4-[1-(2-Methoxythiazol-4- yl)ethoxy]-6-[5-methyl-1-(4- piperidyl)triazol-4- yl]pyrazolo[1,5-a]pyridine-3- carbonitrile, 2,2,2- trifluoroacetic

acid [00514]embedded image 465 [M + H].sup.+ 348 1-[3-Chloro-6-[1-[(3S,4S)-3- fluoro-4-piperidyl]-5-methyl- triazol-4-yl]pyrazolo[1,5- a]pyridin-4-yl]oxy-2-(5- fluoro-2-pyridyl)propan-2-ol, 2,2,2-trifluoroacetic acid [00515]embedded image 504 [M + H].sup.+ 349 3-Chloro-5-[2-(3,5-difluoro- 2-pyridyl)-2-methoxy- ethoxy]-7-[5-methyl-1-(4- methyl-4-piperidyl)triazol-4-yl]imidazo[1,2-a]pyridine, 2,2,2-trifluoroacetic acid [00516]embedded image 518 [M + H].sup.+ 350 1-[3-Chloro-6-[1-[(4R)-3,3- difluoro-4-piperidyl]-5- methyl-triazol-4- yl]pyrazolo[1,5-a]pyridin-4- yl]oxy-2-(5-fluoro-2- pyridyl)propan-2-ol, 2,2,2- trifluoroacetic acid [00517] embedded image 522 [M + H].sup.+ 351 1-[3-Chloro-6-[1-[(3R,4S)-3- fluoro-4-piperidyl]-5-methyl- triazol-4-yl]pyrazolo[1,5- a]pyridin-4-yl]oxy-2-(5- fluoro-2-pyridyl)propan-2-ol, 2,2,2-trifluoroacetic acid [00518]embedded image 504 [M + H].sup.+ 352 1-[3-Chloro-6-[1-[(3R,4R)-3- fluoro-4-piperidyl]-5-methyl- triazol-4-yl]pyrazolo[1,5- a]pyridin-4-yl]oxy-2-(5-fluoro-2-pyridyl)propan-2-ol, 2,2,2-trifluoroacetic acid [00519]embedded image 504 [M + H].sup.+ 353 3-Chloro-6-[1-[(3S,4R)-3- fluoro-4-piperidyl]-5-methyl- triazol-4-yl]-4-[2-(5-fluoro-2- pyridyl)-2-methoxy- ethoxy]pyrazolo[1,5- a]pyridine, 2,2,2- trifluoroacetic acid [00520] embedded image 504 [M + H].sup.+ 354 3-Chloro-5-[2-(3,5-difluoro- 2-pyridyl)-2-methoxy-ethoxy]-7-[5-methyl-1-(3- piperazin-1- ylcyclobutyl)triazol-4- yl]imidazo[1,2-a]pyridine, 2,2,2-trifluoroacetic acid [00521]embedded image 559 [M + H].sup.+ .sup.aMaterial used in subsequent step without further characterization.

Preparation 355

4-[2-(2,4-Difluorophenyl)-2-hydroxy-ethoxy]-6-[5-methyl-1-(4-piperidyl)triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile

##STR00522##

[0518] tert-Butyl 4-[4-[3-cyano-4-[2-(2,4-difluorophenyl)-2-hydroxy-ethoxy]pyrazolo[1,5-a]pyridine-6-yl]-5-methyl-triazol-1-yl]piperidine-1-carboxylate (1.0 g, 1.73 mmol) was suspended in 4M HCl in 1,4-dioxane (20 ml) and the reaction stirred at RT for 2 h. The reaction was concentrated, and the residue basified to pH 9 with saturated aq Na.sub.2CO.sub.3 (10 ml). The resulting solid was collected by filtration and washed with H.sub.2O (3×50 ml) to obtain the title compound (0.80 g, crude) as a brown solid. MS ES+ m/z 480 [M+H].sup.+.

[0519] The following compounds were prepared in a manner essentially analogous to the method of Preparation 355 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00051 TABLE 50 Prep MS ES+ # Chemical Name Structure m/z 356 4-[2-(3,5-Difluoro-2- pyridyl)-2-methoxy-ethoxy]- 3-fluoro-6-[5-methyl-1-(4- piperidyl)triazol-4-yl]pyrazolo[1,5-a]pyridine [00523]embedded image 488 [M + H].sup.+ 357 6-[5-Methyl-1-(4-piperidyl)pyrazol-4-yl]-4- [(1R)-1-(2-pyridyl)ethoxy] pyrazolo[1,5-a]pyridine-3- carbonitrile [00524]embedded image 428 [M + H].sup.+ 358.sup.1 6-[5-Methyl-1-(4- piperidyl)triazol-4-yl]-4-[2- methyl-2-(2- pyridyl)propoxy] pyrazolo[1,5-a]pyridine-3- carbonitrile [00525] embedded image 457 [M + H].sup.+ 359.sup.2 6-[1-(Azetidin-3-yl)-5- methyl-triazol-4-yl]-4-[1-[5- (trifluoromethyl)-3- pyridyl]ethoxy]pyrazolo[1,5- a]pyridine-3-carbonitrile, Isomer 2 [00526] embedded image 469 [M + H].sup.+ 360.sup.2 6-[5-Methyl-1-[(3R)-3- piperidyl]pyrazol-4-yl]-4-[(1R)-1-(2-pyridyl)ethoxy] pyrazolo[1,5-a]pyridine-3- carbonitrile [00527]embedded image 428 [M + H].sup.+ 361.sup.2 6-[5-Methyl-1-[(3S)-3- piperidyl]pyrazol-4-yl]-4- [(1R)-1-(2-pyridyl)ethoxy] pyrazolo[1,5-a]pyridine-3- carbonitrile [00528]embedded image 428 [M + H].sup.+ 362.sup.1 4-[2-(5-Fluoro-2-pyridyl)-2- isopropoxy-ethoxy]-6-[5- methyl-1-(4-piperidyl) triazol-4-yl]pyrazolo[1,5- a]pyridine-3-carbonitrile [00529]embedded image 505 [M + H].sup.+ 363.sup.3,4 4-[2-(3,5-Difluoro-2- pyridyl)-2-isopropoxy- ethoxy]-6-[5-methyl-1-(4-piperidyl)triazol-4-yl] pyrazolo[1,5-a]pyridine-3- carbonitrile, Isomer 1 [00530]embedded image 523 [M + H].sup.+ 364.sup.1 2-(3,5-Difluoro-2-pyridyl)-1- [3-fluoro-6-[5-methyl-1-(4-piperidyl)triazol-4-yl] pyrazolo[1,5-a]pyridin-4- yl]oxy-propan-2-ol [00531]embedded image 488 [M + H].sup.+ 365.sup.5 3-Chloro-4-[2-(5-fluoro-2- pyridyl)-2-methoxy-ethoxy]- 6-[5-methyl-

1-(4-piperidyl) triazol-4-yl]pyrazolo[1,5- a]pyridine [00532]embedded image 486 [M + H].sup.+ 366.sup.5 3-Chloro-6-[1-[(3S,4R)-3- fluoro-4-piperidyl]-5-methyl- triazol-4-yl]-4-[2-(5-fluoropyrimidin-2-yl)-2- methoxy-ethoxy]pyrazolo [1,5-a]pyridine [00533]embedded image 505 [M + H].sup.+ 367.sup.6 1-[3-Chloro-6-[1-[(3S,4R)-3- fluoro-4-piperidyl]-5-methyl- triazol-4-yl]pyrazolo[1,5- a]pyridin-4-yl]oxy-2-(5- fluoropyrimidin-2-yl)propan- 2-ol [00534]
embedded image 505 [M + H].sup.+ 368 2-[3-Chloro-6-[1-[(3S,4R)-3- fluoro-4-piperidyl]-5-methyl- triazol-4-yl]pyrazolo[1,5- a]pyridin-4-yl]oxy-1-(5- fluoropyrimidin-2-yl)ethanol [00535]
embedded image 491 [M + H].sup.+ .sup.1Workup: Reaction concentrated. Residue was dissolved in MeOH and applied directly onto a SCX cartridge, previously conditioned with MeOH. Non-basic impurities were washed off with MeOH then the title compound was eluted with methanolic ammonia (2M). .sup.2Workup: Reaction concentrated. Residue was suspended in DCM and washed with aq 2M NaOH then brine. Organic layer dried over MgSO.sub.4, filtered and concentrated. .sup.3Workup: Reaction concentrated. Residue was suspended in DCM and washed with aq NaOH (1M). Phases were spearated and the organic layer dried over MgSO.sub.4, filtered and concentrated. .sup.4Product contained impurty that was carried on from previous step. .sup.5Workup: Reaction concentrated. Residue dissolved into DCM and washed with sat. aq NaHCO.sub.3 soln, dried over MgSO.sub.4, filtered and concentrated. .sup.6Workup: Reaction concentrated. Reside was dissolved into MeOH then treated with NaHCO.sub.3 to pH 8. Mixture was concentrated in vacuo.

Preparation 369a

6-[1-(7-Azaspiro[3.5]nonan-2-yl)-5-methyl-pyrazol-4-yl]-4-[(1R)-1-(2-pyridyl)ethoxy]pyrazolo[1,5-a]pyridine-3-carbonitrile

##STR00536##

and

Preparation 369b

6-[1-(7-Azaspiro[3.5]nonan-2-yl)-3-methyl-pyrazol-4-yl]-4-[(1R)-1-(2-pyridyl)ethoxy]pyrazolo[1,5-a]pyridine-3-carbonitrile

##STR00537##

[0520] A soln of tert-butyl 2-[4-[3-cyano-4-[(1R)-1-(2-pyridyl)ethoxy]pyrazolo[1,5-a]pyridin-6-yl]-5-methyl-pyrazol-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate and tert-butyl 2-[4-[3-cyano-4-[(1R)-1-(2-pyridyl)ethoxy]pyrazolo[1,5-a]pyridin-6-yl]-3-methyl-pyrazol-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate (621 mg, 0.77 mmol, 70%) in DCM (6 ml) was treated with TFA (1.2 ml). After stirring at RT for 3 days, the reaction was concentrated and loaded onto a SCX column pretreated with MeOH. After washing with MeOH, the title compounds were eluted with 2 M NH.sub.3 in MeOH to obtain a mixture of the title compounds (398 mg, 96%) as a pale-yellow solid. MS ES+ m/z 468 [M+H].sup.+.

Preparation 370

[2-[3-Cyano-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridin-4-yl]oxy-1-(5-fluoro-2-pyridyl)ethyl]methanesulfonate

##STR00538##

[0521] A soln of 4-[2-(5-fluoro-2-pyridyl)-2-hydroxy-ethoxy]-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile (1.39 g, 2.69 mmol) and NEt.sub.3 (0.80 ml, 5.7 mmol) in DCM (14 ml) was cooled to 0° C. and purged with N.sub.2. The reaction was treated dropwise with MsCl (0.26 mL, 3.4 mmol). The reaction was allowed to slowly warm to RT. After 75 min, the reaction was re-cooled to 0° C., quenched with H.sub.2O (15 ml) and the organic layer was removed. The aq layer was extracted with DCM (2×5 mL). The combined organic layers were dried over Na.sub.2SO.sub.4, filtered, and concentrated to afford the title compound as a light brown foamy solid (1.80 g, 100% yield, 90% purity) which was used without purification. MS ES+ m/z 597 [M+H].sup.+.

[0522] The following compounds were prepared in a manner essentially analogous to the method

of Preparation 370 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.
TABLE-US-00052 TABLE 51 Prep MS ES+ # Chemical Name Structure m/z 371 [2-[3-Cyano-6-[5-methyl- 1-[1-(oxetan-3-yl)-4- piperidyl]triazol-4- yl]pyrazolo[1,5-a]pyridin- 4-yl]oxy-1-(3,5-difluoro-2- pyridyl)ethyl] methanesulfonate [00539]  embedded image 615 [M + H].sup.+ 372 [2-[3-Fluoro-6-[5-methyl- 1-[1-(oxetan-3-yl)-4- piperidyl]triazol-4- yl]pyrazolo[1,5-a]pyridin- 4-yl]oxy-1-(5-fluoro-2- pyridyl)ethyl] methanesulfonate [00540]  embedded image 590 [M + H].sup.+
Preparation 373
7-[5-Methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]-5-[[3,3,3-trifluoro-2-(5-fluoro-2-pyridyl)propyl]amino]imidazo[1,2-a]pyridine-3-carbonitrile
##STR00541##
[0523] A mixture of 7-chloro-5-[[3,3,3-trifluoro-2-(5-fluoro-2-pyridyl)propyl]amino]imidazo[1,2-a]pyridine-3-carbonitrile (1.2 g, 3.28 mmol), bis(pinacolato)diboron (1.19 g, 4.69 mmol), and KOAc (0.92 g, 9.38 mmol) in dioxane (20 ml) was treated with Xphos Palladacycle Gen 4 (56.06 mg, 0.07 mmol) at 80° C. under N.sub.2. The resulting mixture was stirred for 2 h at 80° C. The reaction was taken on to the next step without workup or purification.
[0524] The above reaction was allowed to cool and treated with KF (0.53 g, 9.38 mmol), 4-(4-bromo-5-methyl-1,2,3-triazol-1-yl)-1-(oxetan-3-yl)piperidine (1.20 g, 3.97 mmol), H.sub.2O (4 ml) and PdCl.sub.2(DtBPF) (0.10 g, 0.15 mmol) under N.sub.2. After stirring at 100° C. for 2 h, the reaction was cooled to RT, quenched with H.sub.2O (100 ml), and extracted with EA (2×100 ml). The combined organic layers were washed with brine (150 ml), dried over anhydrous Na.sub.2SO.sub.4, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with DCM/MeOH (100 to 20:1) to afford the title compound (315 mg, 18%) as a white solid. MS ES+ m/z 570 [M+H].sup.+.
Preparation 374
(1S)-2-[3-Bromo-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridin-4-yl]oxy-1-(5-fluoro-2-pyridyl)ethanol, Isomer 1
##STR00542##
[0525] A solution of (1S)-2-[3-bromo-6-[5-methyl-1-(4-piperidyl)triazol-4-yl]pyrazolo[1,5-a]pyridin-4-yl]oxy-1-(5-fluoro-2-pyridyl)ethanol hydrochloride (7.57 g, 11.0 mmol) in MeOH (76 ml) at RT was treated with oxetan-3-one (1.97 g, 27.3 mmol), AcOH (1.60 mL, 27.9 mmol), and NaCNBH.sub.3 (2.80 g, 44.6 mmol). After 48 h, the reaction was quenched with aq. 1 N K.sub.2CO.sub.3 (150 ml), and extracted with DCM (300 ml). The organic phase was dried MgSO.sub.4, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with 0% to 100% acetone in DCM to afford the title compound as a white solid (0.352 g, 6%).
Example 1
4-[[2-(5-Fluoro-2-pyridyl)-2-methoxy-ethyl]amino]-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile
##STR00543##
[0526] To a vial was added 4-[[2-(5-fluoro-2-pyridyl)-2-methoxy-ethyl]amino]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (0.51 mmol, 224 mg), 4-(4-bromo-5-methyl-triazol-1-yl)-1-(oxetan-3-yl)piperidine (278 mg, 0.92 mmol), K.sub.2CO.sub.3 (142 mg, 1.03 mmol), toluene (2 mL), and H.sub.2O (200 ul). The vial was flushed with N.sub.2 then PdCl.sub.2(DtBPF) (51 mg, 0.08 mmol) was added. The reaction was heated at 100° C. for 3 h. The mixture was filtered through DE, the filtrate was loaded onto an SCX column pretreated with MeOH. The column was washed with MeOH. The product was eluted with 2 M NH.sub.3 in MeOH and concentrated. The residue was purified by silica gel chromatography eluting with 0% to 100% (25% EtOH in EA) in cHex to afford the title compound (0.40 g, 16%).

MS ES+ m/z 532 [M+H].sup.+.
Example 2
4-[1-(7-Fluoro-4-isoquinolyl)ethoxy]-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile
##STR00544##
[0527] 4-[1-(7-fluoro-4-isoquinolyl)ethoxy]-6-[5-methyl-1-(4-piperidyl)triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile hydrochloride (305 mg, 0.54 mmol) and DIPEA (0.28 ml, 1.61 mmol) were dissolved in MeOH (5 ml) and activated 4 A molecular sieves was added. To that soln, 3-oxetanone (0.17 ml, 2.70 mmol), NaBH.sub.3CN (172 mg, 2.74 mmol) and AcOH (0.37 ml, 6.43 mmol) were sequentially added, and the reaction was stirred at 70° C. for 2 h. Upon completion, the reaction was cooled to RT and diluted with EA. The mixture was washed with H.sub.2O (25 ml) and brine (25 ml), dried over MgSO.sub.4, filtered, concentrated in vacuo. The residue was purified by silica gel chromatography eluting with MeOH in DCM to afford the title compound as an off-white solid (35 mg, 15%). MS ES+ m/z 553.3 [M+H].sup.+.
[0528] The following compounds were prepared in a manner essentially analogous to the method of Example 2 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.
TABLE-US-00053 TABLE 52 MS ES+ Ex # Chemical Name Structure m/z 3.sup.1,2 6-[5-Methyl-1-(1- tetrahydropyran-4- ylazetidin-3-yl)triazol- 4-yl]-4-[1-[5- (trifluoromethyl)-3-pyridyl]ethoxy]pyrazolo [1,5-a]pyridine-3- carbonitrile, Isomer 2 [00545] 553 [M + H].sup.+ 4.sup.1,4 4-[[1-(5-Fluoro-2- pyridyl)cyclopropyl] methoxy]-6-[5-methyl- 1-[1-(oxetan-3-yl)-4- piperidyl]triazol-4- yl]pyrazolo[1,5- a]pyridine-3- carbonitrile [00546] 529 [M + H].sup.+ 5.sup.1,3 6-[5-Methyl-1-[1- (oxetan-3-yl)-4-piperidyl]triazol-4-yl]- 4-[2-methyl-2-(2- pyridyl)propoxy] pyrazolo[1,5-a] pyridine-3- carbonitrile [00547] 513 [M + H].sup.+ 6.sup.1,2 6-[5-Methyl-1-[1- (oxetan-3-yl)azetidin-3-yl]triazol-4-yl]-4-[1- [5-(trifluoromethyl)-3- pyridyl]ethoxy]pyrazolo [1,5-a]pyridine-3-carbonitrile, Isomer 2 [00548] 525 [M + H].sup.+ 7.sup.5 6-[5-Methyl-1-[(3R)-1-(oxetan-3-yl)-3- piperidyl]pyrazol-4- yl]-4-[(1R)-1-(2- pyridyl)ethoxy] pyrazolo[1,5-a] pyridine-3- carbonitrile [00549] 484 [M + H].sup.+ 8.sup.5 6-[5-Methyl-1-[(3S)- 1-(oxetan-3-yl)-3- piperidyl]pyrazol-4- yl]-4-[(1R)-1-(2- pyridyl)ethoxy]pyrazolo [1,5-a]pyridine-3-carbonitrile [00550] 484 [M + H].sup.+ 9.sup.6,7 4-[2-(3,5-Difluoro-2-pyridyl)-2-isopropoxy- ethoxy]-6-[5-methyl- 1-[1-(oxetan-3-yl)-4- piperidyl]triazol-4-yl]pyrazolo[1,5- a]pyridine-3- carbonitrile, Isomer 2 [00551] 579 [M + H].sup.+ 10.sup.8 4-[2-Methoxy-2-(3- methyl-2- pyridyl)ethoxy]-6-[5- methyl-1-[1-(oxetan- 3-yl)-4-piperidyl]triazol-4- yl]pyrazolo[1,5- a]pyridine-3- carbonitrile, Isomer 1 [00552] 529 [M + H].sup.+ 11.sup.9, 10 4-[2-(3-Chloro-2- pyridyl)-2-methoxy-ethoxy]-6-[5-methyl- 1-[1-(oxetan-3-yl)-4- piperidyl]triazol-4- yl]pyrazolo[1,5- a]pyridine-3-carbonitrile, Isomer 1 [00553] 550 [M + H].sup.+ .sup.14A molecular sieves and DIPEA were excluded in the reaction. .sup.2Purified by silica gel chromatography eluting with 0% to 10% MeOH in DCM. .sup.3Purified by silica gel chromatography eluting with 5% EA in cHex (2 CV), 5% to 50% EA in cHex (20 CV), 50% to 100% EA in cHex (5 CV), 100% EA (10 CV). .sup.4Purified by C18 reversed phase C18 chromatography: Column: XBridge C18, 19 × 150 mm, 5 μm, eluting with 45% to 65% ACN in H.sub.2O (10 mM NH.sub.4HCO.sub.3 buffer, pH 9). .sup.5Column: Luna Hilic, 30 × 150 mm, 5 μm, eluting with 10% to 20%: MeOH (10 mM NH.sub.4HCO.sub.3 pH 8). .sup.6Purified by silica gel chromatography eluting with 10% to 50% acetone in DCM. .sup.7Column: Luna Omega Polar, 21 × 150 mm, 5 μm; eluting with 25% to 55% ACN (0.1% FA) in H.sub.2O (0.1% FA). .sup.8Purified by silica gel chromatography eluting with 0% to 10% MeOH in DCM. .sup.9Purified by silica gel chromatography eluting with 50% (10% MeOH in DCM) in DCM. .sup.10Chiral method: LUX-2PROP-AMY-CELL-1Amy2-iAmy1.
Example 12

4-[2-(5-Fluoro-2-pyridyl)-2-oxo-ethoxy]-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile
##STR00554##
[0529] A suspension of 4-hydroxy-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile (0.162 g, 0.43 mmol) in ACN (1.8 ml) was treated with K.sub.2CO.sub.3 (53 mg, 0.53 mmol) and 2-bromo-1-(5-fluoropyridin-2-yl)ethanone (100 mg, 0.44 mmol). The suspension was stirred at 80° C. during 16 h. Upon cooling to RT, EA and H.sub.2O were added and the mixture was filtered. The layers from the filtrate were separated and washed with 2N NaOH, H.sub.2O and brine, dried MgSO.sub.4, filtered and concentrated. The residue was purified by silica gel chromatography eluting with 0% to 10% EtOH in EA to afford the title compound (91 mg, 47%). MS ES+ m/z 517 [M+H].sup.+.
Example 13
4-[2-(5-Fluoro-2-pyridyl)-2-hydroxy-ethoxy]-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile, Isomer 1
##STR00555##
and
Example 14
4-[2-(5-Fluoro-2-pyridyl)-2-hydroxy-ethoxy]-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile, Isomer 2
##STR00556##
[0530] NaBH.sub.4 (3.0 mg, 0.08 mmol) was added in one portion to a soln of 4-[2-(5-fluoro-2-pyridyl)-2-oxo-ethoxy]-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile (28.3 mg, 0.05 mmol) in EtOH (0.78 mL) and DCM (0.55 ml) at RT for 3 h. Reaction was quenched with saturated NH.sub.4Cl. The layers were separated, organic layer was washed with brine, dried over MgSO.sub.4, filtered through DE. The filtrate was concentrated to afford 16 mg. Combined aq layers were extracted with DCM and the organic layer was concentrated to afford 5 mg. Both lots were combined to afford 21 mg. This material was subjected to the following chiral chromatography conditions: Column: Chiralpak AD, 30×250 mm, 5 m; eluting with 35% IPA (0.5% DMEA) in CO.sub.2 to afford the title compound, Isomer 1 (9.0 mg, 32%), t.sub.R is 1.28 min with 98% ee. MS ES+ m/z 519 [M+H].sup.+ and title compound, Isomer 2, (9.2 mg, 32%), t.sub.R is 1.60 min with 85% ee. MS ES+ m/z 519 [M+H].sup.+. The retention times were obtained using analytical method A. (Refer to Table A for specific analytical conditions).
Example 15
4-[[2-(5-Fluoro-2-pyridyl)oxetan-2-yl]methoxy]-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile, Isomer 2
##STR00557##
[0531] t-BuOK (260 mg, 2.29 mmol) was added to a suspension of trimethylsulfoxonium iodide (545 mg, 2.40 mmol) in 2-methyl-2-butanol (0.1 M) at RT. The sealed vial was stirred at 50° C. for 90 min under N.sub.2. The suspension was cooled to RT and 4-[2-(5-fluoro-2-pyridyl)-2-oxo-ethoxy]-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile (400 mg, 0.77 mmol) was added in one portion. The resulting mixture was vigorously stirred at RT overnight in a sealed tube under N.sub.2. Next, the suspension was heated at 50° C. for 3 days then stirred at RT for 3 days.
[0532] In a separate tube, t-BuOK (260 mg, 2.29 mmol) was added to a suspension of trimethylsulfoxonium iodide (545 mg, 2.40 mmol) in 2-methyl-2-butanol (0.1 M) at RT. The sealed vial was stirred at 50° C. for 90 min under N.sub.2. The above reaction was added in one portion to this suspension and the resulting mixture was stirred at 50° C. in a sealed tube under N.sub.2 overnight. The reaction was poured into sat. aq NH.sub.4Cl, extracted with DCM and the aq layer extracted with DCM. The combined organic layers were washed with 1N NaOH (2×), then with

H.sub.2O, followed by brine and dried over MgSO.sub.4. The resultant residue was purified by reversed phase chromatography: Column; Claricep C-series eluted with 30% ACN in H.sub.2O (NH.sub.4HCO.sub.3 pH 9)(2 CV); then a linear gradient from 30% to 60% ACN in H.sub.2O (NH.sub.4HCO.sub.3 pH 9)(8 CV) and 60% ACN in H.sub.2O (NH.sub.4HCO.sub.3 pH 9). Fractions containing the title compound were partially evaporated, DCM was added, and the two-layer mixture was passed through a hydrophobic filter. Filtrate was dried over MgSO.sub.4, filtered, and evaporated.

[0533] The isolated material after reversed phase chromatography was subjected to the following chiral chromatography conditions: Column: Chiralpak IA, 20×250 mm, 5 μm; eluting with 40% IPA (0.5% DMEA) in CO.sub.2 to afford the title compound (29 mg, 7%), t.sub.R is 2.82 (Method P), ee >98% ee; MS ES+ m/z 545 [M+H].sup.+. The retention time was obtained using analytical method P.

Example 16

6-[5-Methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]-4-[1-[5-(trifluoromethyl)pyridazin-3-yl]ethoxy]pyrazolo[1,5-a]pyridine-3-carbonitrile, Isomer 2

##STR00558##

[0534] DIAD (384 mg, 1.90 mmol) was added dropwise to a soln of PPh.sub.3 (539 mg, 2.06 mmol) in THE (10 ml) at 0° C. under N.sub.2. The resulting mixture was stirred for 0.5 h at 0° C. and then added to 4-hydroxy-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile (600 mg, 1.58 mmol) and 1-[5-(trifluoromethyl)pyridazin-3-yl]ethanol (456 mg, 2.37 mmol) in THE (10 ml) and allowed to stir overnight. The reaction was acidified to pH 5 with conc HCl, diluted with H.sub.2O (80 ml), and extracted with EA (3×50 ml). The aq phase was basified to pH 8 with saturated aq NaHCO.sub.3, extracted with CHCl.sub.3:IPA (3:1) (3×100 mL), dried over anhydrous Na.sub.2SO.sub.4, filtered, and concentrated. The residue was purified by reversed phase chromatography using the following conditions: Column: XB—C18, 50×250 mm, 10 m; eluting with a gradient of 35% to 55% ACN in H.sub.2O (10 mM FA) to afford the racemate of the title compound (345 mg, 39%) as a green solid. MS ES+ m/z 554 [M+H].sup.+. The racemate (345 mg) was subjected to chiral chromatography using the following conditions: Column: CHIRALPAK IC, 2×25 cm, 5 m; eluting with 50% MeOH in MTBE (10 mM NH.sub.3-MeOH), 248/208 nm; to afford the title compound (117 mg, 34%), t.sub.R is 9.82 min with 100% ee. MS ES+ m/z 554 [M+H].sup.+.

[0535] The following compound was prepared in a manner essentially analogous to the method of Example 16 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate and separation of enantiomers where applicable.

[0536] If the retention time was obtained from an analytical column the method will be listed in the final column. Refer to Table A for specific analytical conditions for each method.

TABLE-US-00054 TABLE 53 MS ES+ t.sub.R Ex # Chemical Name Structure m/z (min)

17.sup.1,2 4-[[3,3-Difluoro-1- (5-fluoro-2-pyridyl) cyclobutyl]methoxy]- 6-[5-methyl-1-[1-(oxetan-3-yl)-4- piperidyl]triazol-4- yl]pyrazolo[1,5- a]pyridine-3- carbonitrile [00559] embedded image 579 [M + H].sup.+ — 18.sup.3,4 6-[5-Methyl-1-[1- (oxetan-3-yl)-4-piperidyl]triazol-4- yl]-4-[1-methyl-2- (2-pyridyl) pyrrolidin-3- yl]oxy-pyrazolo [1,5-a]pyridine-3-carbonitrile, Isomer 1 [00560]embedded image [M + H].sup.+ 2.0 B .sup.1Purified by silica gel chromatography eluting with DCM:MeOH (20 to 1) .sup.2Purified by reversed chromatography: Column: welch-XB C18, 50 × 250 mm, 10 μm; eluting with 28% to 35% ACN in H.sub.2O (0.1% NH.sub.4HCO.sub.3). .sup.3Residue was dissolved in MeOH and treated with TFA then applied directly onto a SCX cartridge, previously conditioned with MeOH. Non-basic impurities were washed off with MeOH then the title compound was eluted with methanolic ammonia (2M). .sup.4Column: Chiralpak IA, 20 × 250 mm, 5 μm; eluting with 35% EtOH (0.5% DMEA) in CO.sub.2.

Example 19

4-[1-(3,6-Dimethylpyrazin-2-yl)ethoxy]-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile, Isomer 1

##STR00561##

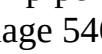
[0537] A mixture of 1-(3,6-dimethylpyrazin-2-yl)ethyl methanesulfonate (395 mg, 1.71 mmol), K.sub.2CO.sub.3 (546 mg, 3.95 mmol) and 4-hydroxy-6-{5-methyl-1-[1-(oxetan-3-yl)piperidin-4-yl]-1,2,3-triazol-4-yl}pyrazolo[1,5-a]pyridine-3-carbonitrile (500 mg, 1.32 mmol) in ACN (10 ml) was stirred for 2 h at 80° C. under N.sub.2. The resultant mixture was filtered, and the filter cake was washed with DCM (3×10 mL). The filtrate was concentrated in vacuo. The residue was purified by reversed flash C18 chromatography eluting with 20% to 40% ACN in H.sub.2O to afford the title compound (450 mg, 66%) as a brown solid.

[0538] The brown solid was subjected to chiral chromatography using the following conditions: Column: CHIRALPAK AD-H, 3×25 cm, 5 am; eluting with 4000 MeOH in CO.sub.2; to afford the title compound (163 mg, 360%), t.sub.R is 5.77 min with 10000 ee.

[0539] The following compounds were prepared in a manner essentially analogous to the method of Example 19 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate. Cs.sub.2CO.sub.3 and DMF can be used.

[0540] If the retention time was obtained from an analytical column the method will be listed in the final column. Refer to Table A for specific analytical conditions for each method.

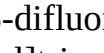
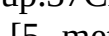
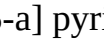
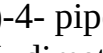
TABLE-US-00055 TABLE 54 t.sub.R (min) MS ES+ and Ex # Chemical Name Structure m/z method 20.sup.1,2 3-Chloro-4-[1-[5- (difluoromethyl)- 3-pyridyl]ethoxy]- 6-[5-methyl-1-[1-(oxetan-3-yl)-4- piperidyl]triazol-4- yl]pyrazolo[1,5- a]pyridine, Isomer 2 [00562]  544 [M + H].sup.+ 2.11 B 21.sup.3,4 4-[Cyclopropyl-(5- fluoro-2-pyridyl)methoxy]- 6-[5-methyl-1-[1- (oxetan-3-yl)-4- piperidyl]triazol-4- yl]pyrazolo[1,5-a]pyridine-3- carbonitrile, Isomer 1 [00563]  527 [M + H].sup.+ 2.61 C 22.sup.3,5 4-[Cyclobutyl-(5- fluoro-2- pyridyl)methoxy]- 6-[5-methyl-1-[1- (oxetan-3-yl)-4-piperidyl]triazol-4- yl]pyrazolo[1,5- a]pyridine-3- carbonitrile, Isomer 1 [00564]  541 [M + H].sup.+ 1.57 D 23.sup.6,7 4-[1-(2,5- Dimethylthiazol-4-yl)ethoxy]-6-[5- methyl-1-[1- (oxetan-3-yl)-4- piperidyl]triazol-4- yl]pyrazolo[1,5- a]pyridine-3-carbonitrile, Isomer 1 [00565]  519.2 [M + H].sup.+ 2.70 E 24.sup.8,9 6-[5-Methyl-1-[1- (oxetan-3-yl)-4- piperidyl]triazol-4- yl]-4-[1-[6- (trifluoromethyl) pyrazin-2-yl]ethoxy] pyrazolo[1,5- a]pyridine-3- carbonitrile, Isomer 1 [00566]  554 [M + H].sup.+ 1.45 F 25.sup.10,11 6-[5-Methyl-1-[1- (oxetan-3-yl)-4- piperidyl]triazol-4- yl]-4-[1-(2-methylthiazol-4- yl)propoxy]pyrazolo [1,5-a]pyridine- 3-carbonitrile, Isomer 1 [00567]  519 [M + H].sup.+ 2.47 C .sup.1Purified by silica gel chromatography eluting with 0% to 50% EA (25% EtOH) in cHex. .sup.2Column: Chiralpak IA, 20 × 250 mm, 5 μm; eluting with 35% IPA (0.5% DMEA) in CO2. .sup.3Purified by flash reversed phase C18 chromatography eluting with 40% to 70% ACN in H.sub.2O (NH.sub.5CO.sub.3 pH 9 buffer). .sup.4Chiralpak AD, 20 × 250 mm, 5 μm; eluting with 35% IPA (0.5% DMEA) in CO.sub.2. .sup.5Chiralcel OJ, 20 × 250 mm, 5 μm; eluting with 20% MeOH (0.5% DMEA) in CO.sub.2. .sup.6Purified by flash reversed phase C18 chromatography eluting with 30% to 60% ACN in H.sub.2O (NH.sub.5CO.sub.3 pH 9 buffer). .sup.7Column: Chiralcel OJ, 20 × 150 mm, 5 μm; eluting with MeOH (0.5% DMEA) in CO.sub.2. .sup.8Purified by silica gel chromatography eluting with 20% to 60% EA in cHex. .sup.9Column: Chiralcel OJ, 20 × 250 mm, 5 μm; eluting with 30% MeOH (0.5% DMEA) in CO.sub.2, flow rate: 80 (ml/min). .sup.10Purified by silica gel chromatography eluting with 20% 3:1 EA/EtOH in cHex (2 CV), 20% to 65% gradient 3:1 EA/EtOH in cHex (25 CV), 65% 3:1 EA/EtOH in cHex (10 CV), 65% to 100% gradient 3:1 EA/EtOH in cHex (15 CV), 100% 3:1 EA/EtOH in cHex (10 CV). .sup.11Chiralpak AD, 20 × 250 mm, 5 μm; eluting with 35% EtOH (0.5% DMEA) in CO.sub.2.

Example 26
4-[2-(5-Fluoro-2-pyridyl)-2-pyrrolidin-1-yl-ethoxy]-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile, Isomer 1
##STR00568##
and
Example 27 4-[2-(5-Fluoro-2-pyridyl)-2-pyrrolidin-1-yl-ethoxy]-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile, Isomer 2
##STR00569##
[0541] [2-[3-Cyano-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridin-4-yl]oxy-1-(5-fluoro-2-pyridyl)ethyl]methanesulfonate (155 mg, 0.26 mmol) was placed in a screw-cap vial and dissolved in ACN (0.65 ml) under N.sub.2. Pyrrolidine (183 mg, 0.002 mmol) was added. The reaction mixture was heated at 50° C. for 46 h. The reaction was concentrated, and the residue was treated with DCM (4 ml) and brine (2 ml). The organic layer was separated, washed with brine (2×2 ml), dried over Na.sub.2SO.sub.4, and filtered. The filtrate was concentrated to a brown oil (160 mg).
[0542] The brown oil was subjected to the following chiral chromatography conditions: Column: Amylose-1, 30×250 mm, 5 m; eluting with 40% IPA (0.5% DMEA) in CO.sub.2 to afford the title compound, Isomer 1 (59 mg, 37%), t.sub.R is 1.83, ee >98% ee; 572 [M+H].sup.+ and title compound, Isomer 2 (47 mg, 29%), t.sub.R is 2.58, ee >98% ee. MS ES+ m/z 572 [M+H].sup.+. The retention times were obtained using analytical method G (Refer to Table A for specific analytical conditions).
[0543] The following compound was prepared in a manner essentially analogous to the method of Examples 26 and 27 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.
[0544] If the retention time was obtained from an analytical column the method will be listed in the final column. Refer to Table A for specific analytical conditions for each method.
TABLE-US-00056 TABLE 55 t.sub.R (min) Ex # Chemical Name Structure MS ES+ m/z and method 28.sup.1,2 4-[2-(Dimethyl amino)-2-(5-fluoro-2- pyridyl)ethoxy]-6-[5- methyl-1-[1-(oxetan- 3-yl)-4- piperidyl]triazol-4- yl]pyrazolo[1,5- a]pyridine-3- carbonitrile, Isomer 2 [00570]  546 [M + H].sup.+ 2.76 H 29.sup.3,4,5 4-[2-(3,3- Difluoroazetidin-1-yl)- 2-(3,5-difluoro-2- pyridyl)ethoxy]-6-[5- methyl-1-[1-(oxetan- 3-yl)-4-piperidyl] triazol-4-yl]pyrazolo [1,5-a]pyridine-3- carbonitrile, Isomer 1 [00571]  612 [M + H].sup.+ 2.43 J 30.sup.6,7,8 2-[3-Fluoro-6-[5- methyl-1-[1-(oxetan- 3-yl)-4-piperidyl] triazol-4-yl] pyrazolo[1,5-a] pyridin-4-yl]oxy-1-(5- fluoro-2-pyridyl)-N,N- dimethyl-ethanamine, Isomer 2 [00572]  539 [M + H].sup.+ 2.82 P .sup.1Reaction run in dimethylamine (2M) in THF at RT. .sup.2Column: Chiralpak AD, 20 × 250 mm, 5 μm; eluting with 35% IPA (0.5% DMEA) in CO.sub.2. .sup.3Cs.sub.2CO.sub.3 used as base .sup.4Column: XBridge C18, 19 × 150 mm, 5 μm; eluting with 45% to 75% ACN in H.sub.2O (NH.sub.4HCO.sub.3 10 mM pH 9). .sup.5Column: Chiralpak AD, 20 × 250 mm, 5 μm; eluting with 45% EtOH (0.5% DMEA) in CO.sub.2. .sup.6Refluxed for 5 h then stirred at RT for 10 days. .sup.7Purified by reversed phase chromatography eluting with 0% to 50% (10% MeOH in DCM) in DCM (20 CV) then 50% (10% MeOH in DCM) in DCM (20 CV). .sup.8Column: Chiral Art Amylose C, 30 × 250 mm, 5 μm; eluting with 40% IPA (0.5% DMEA) in CO.sub.2.
Example 31
4-[4-[4-[3-Chloro-4-[2-(5-fluoro-2-pyridyl)-2-methoxy-ethoxy]pyrazolo[1,5-a]pyridin-6-yl]-5-methyl-triazol-1-yl]-1-piperidyl]tetrahydrofuran-3-ol, Isomer 1
##STR00573##
and
Example 32
4-[4-[4-[3-Chloro-4-[2-(5-fluoro-2-pyridyl)-2-methoxy-ethoxy]pyrazolo[1,5-a]pyridin-6-yl]-5-

methyl-triazol-1-yl]-1-piperidyl]tetrahydrofuran-3-ol, Isomer 2
##STR00574##
[0545] 3,6-dioxabicyclo[3.1.0]hexane (157 mg, 1.73 mmol) was added to a soln of 3-chloro-4-[2-(5-fluoro-2-pyridyl)-2-methoxy-ethoxy]-6-[5-methyl-1-(4-piperidyl)triazol-4-yl]pyrazolo[1,5-a]pyridine (350 mg, 0.72 mmol) in EtOH (3 ml) and it was stirred overnight at 80° C. Additional 3,6-dioxabicyclo[3.1.0]hexane (157 mg, 1.73 mmol) was added, and the reaction was stirred overnight. The reaction was diluted with DCM (50 ml), washed with H.sub.2O (2×20 ml) and brine (20 ml). The crude material was purified by silica gel chromatography eluting with MeOH in DCM to afford a brown colored oil. The oil was subjected to SFC eluting with 55% (50% 2-propanol in ACN) in CO.sub.2 (0.1% DEA). After the chiral separation both diastereomeric pairs were individually purified by flash chromatography and eluted with a gradient of MeOH in DCM. The isolated material from each purification was triturated in pentane, washed with pentane followed by Et.sub.2O to afford title compound, Isomer 1, (36 mg, 8%), t.sub.R is 6.46 min with 96% EE, MS ES+ m/z 572 [M+H].sup.+ and title compound, Isomer 2, (45 mg, 11%), t.sub.R is 6.86 min with 96% EE, MS ES+ m/z 572 [M+H].sup.+.
Example 33
2-[3-Chloro-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridin-4-yl]oxy-1-(5-fluoro-2-pyridyl)ethanol, Isomer 2
##STR00575##
[0546] To a stirred mixture of 2-[3-Chloro-6-[5-methyl-1-(4-piperidyl)triazol-4-yl]pyrazolo[1,5-a]pyridine-4-yl]oxy-1-(5-fluoro-2-pyridyl)ethanol 2,2,2 trifluoroacetic acid (800 mg, 1.37 mmol) in MeOH (20 ml) was added 3-oxetanone (611 mg, 8.48 mmol) at RT. The resulting mixture was stirred for 1 h at 50° C. under N.sub.2. To the above mixture was added NaBH.sub.3CN (426 mg, 6.78 mmol) in portions at RT. The resulting mixture was stirred for additional 2 h at 50° C. under N.sub.2. Upon cooling to RT the reaction was diluted with H.sub.2O (50 ml) and the mixture was basified to pH 9 with saturated aq Na.sub.2CO.sub.3. The mixture was extracted with EA (3×150 ml). The combined organic layers were washed with brine (2×50 ml), dried over anhydrous Na.sub.2SO.sub.4, filtered, and the filtrate was concentrated in vacuo. The residue was purified by reversed flash chromatography with the following conditions: column, C18; eluting with 30% to 35% ACN in H.sub.2O (0.1% NH.sub.3—H.sub.2O) to afford the racemate of the title compound (420 mg, 58%) as a yellow solid. MS ES+ m/z 528 [M+H].sup.+.
[0547] The yellow solid was subjected to chiral chromatography using the following conditions:
[0548] CHIRAL ART Amylose-SA, 2×25 cm, 5 m; Eluting with 50% MeOH in MtBE (10 mM NH.sup.3-MeOH); flow rate: 20 mL/min; 214/244 nm; to afford the title compound (140 mg, 19%) t.sub.R=10.92, ee=100%. MS ES+ m/z 528 [M+H].sup.+.
Example 34
4-[1-(1-Isopropyltriazol-4-yl)ethoxy]-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile, Isomer 1
##STR00576##
[0549] 4-[1-(1-Isopropyltriazol-4-yl)ethoxy]-6-[5-methyl-1-(4-piperidyl)triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile hydrochloride (689 mg, 1.29 mmol) and DIPEA (0.67 ml, 3.87 mmol) were dissolved in MeOH (10 ml) and activated 4 A molecular sieves was added. 3-oxetanone (0.46 ml, 6.46 mmol), NaBH.sub.3CN (406 mg, 6.46 mmol) and AcOH (0.89 ml, 15.50 mol) were added sequentially, and the reaction was stirred at 70° C. for 90 min. Upon cooling to RT, the reaction was diluted with EA. The mixture was washed with H.sub.2O (1×25 ml) and brine (1×25 ml), dried over MgSO.sub.4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with MeOH in DCM to afford an off-white solid (490 mg, 73%). The off-white solid was subjected to SFC, eluting with 50% EtOH (0.1% DEA) in CO.sub.2 to afford the title compound (140 mg, 21%). RT is 6.93 min. MS ES+ m/z 517.3 [M+H].sup.+.
[0550] The following compounds were prepared in a manner essentially analogous to the method

of Example 34 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

[0551] If the retention time was obtained from an analytical column the method will be listed in the final column. Refer to Table A for specific analytical conditions for each method.

TABLE-US-00057 TABLE 56 t.sub.R (min) MS ES+ and Ex # Chemical Name Structure m/z method 35.sup.1,2 4-[1-(2- Isopropyltriazol- 4-yl)ethoxy]-6- [5-methyl-1-[1- (oxetan-3-yl)-4-piperidyl]triazol- 4-yl]pyrazolo [1,5-a]pyridine- 3-carbonitrile, Isomer 1 [00577]  517.3 [M + H].sup.+ 6.61 36.sup.1,2 6-[5-Methyl-1- [1-(oxetan-3-yl)- 4-piperidyl] triazol-4-yl]-4- [1-(1-methyl- pyrazolo[3,4- c]pyridin-4- yl)ethoxy] pyrazolo[1,5-a]pyridine-3- carbonitrile, Isomer 2 [00578]  539.3 [M + H].sup.+ 9.46 37.sup.1,3 6-[5-Methyl-1- [1-(oxetan-3-yl)- 4-piperidyl] triazol-4-yl]-4- [1-(1-methyl pyrrolo[2,3-c]pyridin-4-yl) ethoxy]pyrazolo [1,5-a]pyridine- 3-carbonitrile, Isomer 2 [00579]  538.3 [M + H].sup.+ 10.2 38.sup.1,3 6-[5-Methyl-1- [1-(oxetan-3-yl)- 4-piperidyl] triazol-4-yl]-4- [1-[1-(trifluoro methyl)pyrazol- 3-yl]ethoxy] pyrazolo[1,5- a]pyridine-3-carbonitrile, Isomer 1 [00580]  542.2 [M + H].sup.+ 6.90 39.sup.1,3 4-[1-(4-Cyclopropyl-5- fluoro-2-pyridyl) ethoxy]-6-[5- methyl-1-[1- (oxetan-3-yl)-4- piperidyl]triazol- 4-yl]pyrazolo [1,5-a]pyridine- 3-carbonitrile, Isomer 2 [00581]  543.3 [M + H].sup.+ 8.97 40.sup.4 4-[2-(3,5- Difluoro-2- pyridyl)-2- methoxy- ethoxy]-3-fluoro- 6-[5-methyl-1- [1-(oxetan-3-yl)- 4-piperidyl] triazol-4- yl]pyrazolo[1,5- a]pyridine, Isomer 2 [00582]  544 [M + H].sup.+ 22.0 41.sup.5,6 3-Chloro-5-[2- (5-fluoro-2- pyridyl)-2-methoxy- ethoxy]-7-[5- methyl-1-[1- (oxetan-3-yl)-4- piperidyl]triazol- 4-yl]imidazo [1,2-a]pyridine, Isomer 2 [00583]  542 [M + H].sup.+ 20.2 42.sup.7,8 3-Chloro-5-[2- (3,5-difluoro-2- pyridyl)-2- methoxy- ethoxy]-7-[5- methyl-1-[1- (oxetan-3-yl)-4-piperidyl]triazol- 4-yl]imidazo [1,2-a]pyridine, Isomer 1 [00584]  560 [M + H].sup.+ 4.45 43.sup.9,10 3-Chloro-4-[2- (3,5-difluoro-2- pyridyl)-2- methoxy- ethoxy]-6-[5-methyl-1-[1- (oxetan-3-yl)-4- piperidyl]triazol- 4-yl]pyrazolo [1,5-a]pyridine, Isomer 1 [00585]  (.sup.35Cl/.sup.37Cl) 560/562 [M + H].sup.+ 2.51 H 44.sup.9,10 3-Chloro-4-[2- (3,5-difluoro-2- pyridyl)-2- methoxy- ethoxy]-6-[5- methyl-1-[1- (oxetan-3-yl)-4-piperidyl]triazol- 4-yl]pyrazolo [1,5-a]pyridine, Isomer 2 [00586]  (.sup.35Cl/.sup.37Cl) 560/562 [M + H].sup.+ 2.62 H 45.sup.11,12 4-[1-(2- Cyclopropyl thiazol-4-yl)ethoxy]-6-[5- methyl-1-[1- (oxetan-3-yl)-4- piperidyl]triazol- 4-yl]pyrazolo [1,5-a]pyridine- 3-carbonitrile, Isomer 1 [00587]  531 [M + H].sup.+ 1.12 I 46.sup.13,14 4-[1-(2-methoxy thiazol-4- yl)ethoxy]-6-[5- methyl-1-[1- (oxetan-3-yl)-4- piperidyl]triazol- 4-yl]pyrazolo [1,5-a]pyridine- 3-carbonitrile, Isomer 1 [00588]  521 [M + H].sup.+ 2.63 J 47.sup.15 4-[2-(5-Fluoro-2- pyridyl)-2- isopropoxy- ethoxy]-6-[5- methyl-1-[1-(oxetan-3-yl)-4- piperidyl]triazol- 4-yl]pyrazolo [1,5-a]pyridine- 3-carbonitrile, Isomer 2 [00589]  561 [M + H].sup.+ 1.68 H 48.sup.16,17 4-[2-(2,4- Difluorophenyl)- 2-hydroxy- ethoxy]-6-[5- methyl-1-[1- (oxetan-3-yl)-4- piperidyl]triazol- 4-yl]pyrazolo [1,5-a]pyridine- 3-carbonitrile [00590]  536 [M + H].sup.+ 1.47 49.sup.18 2-[3-Fluoro-6-[5- methyl-1-[1- (oxetan-3-yl)-4- piperidyl]triazol- 4-yl]pyrazolo [1,5-a]pyridin-4-yl]oxy-1-(5- fluoro-2-pyridyl) ethanol, Isomer 2 [00591]  512 [M + H].sup.+ 9.67 50.sup.1,19 2-[3-Chloro-6- [5-methyl-1-[1- (oxetan-3-yl)-4- piperidyl] triazol-4-yl] pyrazolo[1,5-a] pyridin-4-yl]oxy- 1-isothiazol-3-yl- ethanol, Isomer 2 [00592]  (.sup.35Cl/.sup.37Cl) 516/518 [M + H].sup.+ 7.99 51.sup.9,20 2-[3-Chloro-6- [5-methyl-1-[1-(oxetan-3-yl)-4- piperidyl]triazol- 4-yl]pyrazolo [1,5-a]pyridin-4- yl]oxy-1-(3,5- difluoro-2-pyridyl)-N,N- dimethyl- ethanamine, Isomer 2 [00593]  (.sup.35Cl/.sup.37Cl) 573/575 [M + H].sup.+ 1.06 J 52.sup.21,22,23 1-[3-Chloro-6- [1-[(3S,4R)-3- fluoro-1-(oxetan- 3-yl)-4- piperidyl]-5- methyl-thiazol-4- yl]pyrazolo[1,5-a] pyridin-4-yl]oxy- 2-(5- fluoro-2-pyridyl) propan-2-ol, Isomer 1 [00594]  560 [M + H].sup.+ 7.00 53.sup.21,24,25 1-[3-Chloro-6- [1-[(3S,4S)-3- fluoro-1-(oxetan- 3-yl)-4- piperidyl]-5- methyl-triazol-4- yl]pyrazolo[1,5-

a]pyridin-4- yl]oxy-2-(5- fluoro-2-pyridyl) propan-2-ol, Isomer 1 [00595]embedded image 560 [M + H].sup.+ 5.43 54.sup.26,27,28 2-(3,5-Difluoro- 2-pyridyl)-1-[3- fluoro-6-[5- methyl-1-[1-(oxetan-3-yl)-4- piperidyl]triazol- 4-yl]pyrazolo [1,5-a]pyridin-4- yl]oxy-propan-2- ol, Isomer 1 [00596]embedded image 544 [M + H].sup.+ 2.28 S 55.sup.21,29,30,31,32 3-Chloro-5-[2-(3,5-difluoro-2- pyridyl)-2- methoxy- ethoxy]-7-[5- methyl-1-[4- methyl-1- (oxetan-3-yl)-4-piperidyl]triazol- 4-yl]imidazo [1,2-a]pyridine, Isomer 2 [00597]embedded image 574 [M + H].sup.+ 9.70 56.sup.29,31,33,34,35 1-[3-Chloro-6- [1-[(4R)-3,3- difluoro-1- (oxetan-3-yl)-4-piperidyl]-5- methyl-triazol-4- yl]pyrazolo[1,5- a]pyridin-4- yl]oxy-2-(5- fluoro-2- pyridyl)propan-2-ol, Isomer 1 [00598]embedded image 578 [M + H].sup.+ 5.31 57.sup.29,34,36,37 1-[3-Chloro-6- [1-[(3R,4S)-3- fluoro-1-(oxetan- 3-yl)-4- piperidyl]-5- methyl-triazol-4- yl]pyrazolo[1,5-a]pyridin-4- yl]oxy-2-(5- fluoro-2- pyridyl)propan- 2-ol, Isomer 1 [00599]embedded image 560 [M + H].sup.+ 4.49 58.sup.21,29,37,38,39 1-[3-Chloro-6- [1-[(3R,4R)-3- fluoro-1-(oxetan- 3-yl)-4- piperidyl]-5- methyl-triazol-4- yl]pyrazolo[1,5- a]pyridin-4- yl]oxy-2-(5- fluoro-2-pyridyl)propan- 2-ol, Isomer 1 [00600]embedded image 560 [M + H].sup.+ 5.20 59.sup.40,41 2-(5-Fluoro-2- pyridyl)-1-[3- methyl-6-[5- methyl-1-[1- (oxetan-3-yl)-4- piperidyl]triazol- 4-yl]pyrazolo [1,5-a]pyridin-4- yl]oxy-propan-2- ol, Isomer 2 [00601]embedded image 522 [M + H].sup.+ 8.30 60.sup.21,43,44 3-Chloro-6-[1- [(3S,4R)-3- fluoro-1-(oxetan- 3-yl)-4- piperidyl]-5-methyl-triazol-4- yl]-4-[2-(5- fluoropyrimidin- 2-yl)-2-methoxy- ethoxy]pyrazolo [1,5-a]pyridine, Isomer 2 [00602]embedded image 561 [M + H].sup.+ 19.87 61.sup.5,45 1-[3-Chloro-6- [1-[(3S,4R)-3- fluoro-1-(oxetan- 3-yl)-4- piperidyl]-5- methyl-triazol-4- yl]pyrazolo[1,5- a]pyridin-4-yl]oxy-2-(5- fluoropyrimidin- 2-yl)propan-2-ol, Isomer 1 [00603]embedded image 561 [M + H].sup.+ 13.5 62.sup.46,47 3-Chloro-6-[1- [(3S,4R)-3- fluoro-1-(oxetan- 3-yl)-4- piperidyl]-5-methyl-thiazol-4- yl]-4-[2-(5- fluoro-2- pyridyl)-2- methoxy- ethoxy]pyrazolo [1,5-a]pyridine, Isomer 2 [00604]embedded image 560 [M + H].sup.+ 6.3 63.sup.54,48 2-[3-Chloro-6- [1-[(3S,4R)-3- fluoro-1-(oxetan- 3-yl)-4- piperidyl]-5- methyl-triazol-4- yl]pyrazolo[1,5- a]pyridin-4-yl]oxy-1-(5- fluoropyrimidin- 2-yl)ethanol, Isomer 2 [00605]embedded image 547 [M + H].sup.+ 19.0 64.sup.49,50,51 3-Chloro-5-[2- (3,5-difluoro-2- pyridyl)-2- methoxy- ethoxy]-7-[5-methyl-cis-1-[3- [4-(oxetan-3- yl)piperazin-1- yl]cyclobutyl] triazol-4-yl] imidazo[1,2- a]pyridine, Isomer 1 [00606]embedded image 615 [M + H].sup.+ 9.2 65.sup.21,42,52,53 3-Chloro-5-(2-(3,5-difluoro- pyridin-2-yl)-2- methoxyethoxy)- 7-(5-methyl-1- ((1r,3r)-3-(4- (oxetan-3-yl)piperazin-1- yl)cyclobutyl)- 1H-1,2,3-triazol- 4-yl)imidazo[1,2-a] pyridine, Isomer 2 [00607] embedded image 615 [M + H].sup.+ 15.7 .sup.1Purified by silica gel chromatography eluting with MeOH in DCM. .sup.2SFC, eluting with 60% MeOH (0.1% DEA) in CO.sub.2. .sup.3SFC, eluting with 50% EtOH (0.1% DEA) in CO.sub.2. .sup.4Column: Chiralpak IG, 3 × 25 cm column, 5 μm; eluting with 60% ACN in H.sub.2O (0.5% DEA). .sup.5Purified by Prep-TLC (DCM/MeOH 20:1) .sup.6Column: Chiralpak IA, 2 × 25 cm column, 5 μm; eluting with 20% MeOH in 1:1 hexane/MTBE (0.5% 2M NH.sub.3 in MeOH). .sup.7Purified by reversed phase chromatography: Column: AQ-C18, 250 × 50 mm, 10 μm; eluting with 20% to 35% ACN in aq FA. .sup.8Column: Chiralpak IG, 2 × 25 cm column, 5 μm; eluting with 25% MeOH in MTBE (10 mM NH.sub.3—MeOH). .sup.9Purified by silica gel chromatography, eluting with 0% to 100% acetone in DCM. .sup.10Column: Amylose-C, 20 × 250 mm column, 5 μm; eluting with 45% EtOH (0.5% DMEA) in CO.sub.2. .sup.11Purified by reversed phase C18 chromatography eluting with 30% to 60% ACN in H.sub.2O (NH.sub.4CO.sub.3 pH 9 buffer). .sup.12Column: Chiralpak AD, 20 × 250 mm, 5 μm; eluting with 45% EtOH (0.5% DMEA) in CO.sub.2. .sup.13Purified by silica gel chromatography eluting with 100% DCM (2 CV), 0% to 2% gradient MeOH in DCM (13 CV), 2% MeOH in DCM (10 CV), 2% to 5% gradient MeOH in DCM (10 CV), 5% to 10% gradient MeOH in DCM (2 CV), 10% MeOH in DCM (15 CV). .sup.14Column: Chiralart Amylose C, 30 × 250 mm, 5 μm; eluting with 40% EtOH (0.5% DMEA) in CO.sub.2. .sup.15Column: Chiralpak AD, 30 × 250 mm, 5 μm; eluting with 40% IPA (0.5% DMEA) in CO.sub.2. .sup.16Purified by silica gel chromatography eluting with DCM/MeOH (10:1). .sup.17Column: CHIRALPAK IE-3, 4.6 × 50

cm, 3 μm; eluting with 50% EtOH in MTBE (0.1% DEA). .sup.18Column: Chiralpak IA, 2 × 25 cm column, 5 μm; eluting with 50% EtOH in MTBE (10 mM NH.sub.3—MeOH). .sup.19SFC, eluting with 50% IPA (0.1% DEA) in CO.sub.2. .sup.20Column: Chiralpak AD, 20 × 250 mm, 5 μm; eluting with 35% EtOH in CO.sub.2. .sup.214A molecular sieves, DIPEA, and AcOH were excluded in the reaction. .sup.22Purified by Prep-TLC (PE/EA 1:1) .sup.23Column: CHIRALPAK IE, 3 × 25 cm, 5 μm; eluting with 50% MeOH in MTBE (0.5% 2M NH.sub.3—MeOH). .sup.24Purified by reversed phase C18 chromatography eluting with 50% to 60% ACN in H.sub.2O .sup.25Column: CHIRALPAK ID, 2 × 25 cm, 5 μm; eluting with 30% MeOH in MTBE (10 mM NH.sub.3—MeOH). .sup.26Workup: Reaction concentrated. Residue was dissolved into DCM and aq Na.sub.2CO.sub.3 then filtered through a phase separator. Organic phase dried over MgSO.sub.4, filtered and concentrated. .sup.27Purified by reversed phase flash chromatography eluting with 30% ACN in aq NH.sub.4HCO.sub.3 pH 9 (2 CV), 30% to 60% ACN in aq NH.sub.4HCO.sub.3 pH 9 (8 CV), 60% ACN in aq NH.sub.4HCO.sub.3 pH (2 CV) then 100% ACN. .sup.28Chiralpak AD, 20 × 250 mm, 5 μm; eluting with 45% IPA (0.5% DMEA) in CO.sub.2. .sup.29Reaction conducted at 50° C. .sup.30Workup: Reaction quenched at RT with H.sub.2O, pH adjusted to 8 with aq NaHCO.sub.3, extracted with EA (3 × 30 ml), washed with brine (2 × 20 ml), dried over Na.sub.2SO.sub.4, filtered, and concentrated. .sup.31Purified by Prep-TLC (5% MeOH in DCM). .sup.32Column: CHIRALPAK ID, 3 × 25 cm, 5 μm; eluting with 30% EtOH in 2:1 DCM/MeOH (0.1% 2M NH.sub.3—MeOH). .sup.334A molecular sieves and DIPEA were excluded in the reaction. .sup.34Workup: Reaction diluted at RT with saturated K.sub.2CO.sub.3 (30 ml), extracted with EA (3 × 50 ml), washed with brine (3 × 50 ml), dried over Na.sub.2SO.sub.4, filtered, and concentrated. .sup.35Column: CHIRALPAK IE, 2 × 25 cm, 5 μm; eluting with 50% MeOH in MTBE (0.5% 2M NH.sub.3—MeOH). .sup.36Workup: Reaction quenched at RT with saturated NaHCO.sub.3 (20 ml), extracted with 25% i-PrOH in CHCl.sub.3 (3 × 30 ml), washed with brine (2 × 20 ml), dried over Na.sub.2SO.sub.4, filtered, and concentrated. .sup.37Column: CHIRALPAK IE, 2 × 25 cm, 5 μm; eluting with 50% MeOH in MTBE (10 mM NH.sub.3—MeOH). .sup.38Workup: Reaction was concentrated and diluted with H.sub.2O (10 ml), extracted with 20% i-PrOH on CHCl.sub.3 (3 × 30 ml), dried over Na.sub.2SO.sub.4, filtered, and concentrated. .sup.39Purified by Prep-TLC EA 100%. .sup.40Purified by silica gel chromatography eluting with 40% (10% MeOH in DCM) in DCM. .sup.41SFC chromatography eluting with 40% EtOH (1% DEA) in 60% CO.sub.2. .sup.42Workup: Reaction quenched at RT with H.sub.2O, pH adjusted to 8 with aq NaHCO.sub.3, extracted with CHCl.sub.3:IPA, dried over Na.sub.2SO.sub.4, filtered, and concentrated. .sup.43Purified by silica gel chromatography eluting with MeOH in EA (1:30 to 1:20). .sup.44Column: CHIRALPAK IE, 2 × 25 cm, 5 μm; eluting with 30% to 50% MeOH in MTBE (0.5% 2M NH.sub.3—MeOH). .sup.45Column: Chiralpak IA, 2 × 25 cm column, 5 μm; eluting with 15% ACN:EtOH (2:1) in MTBE (10 mM NH.sub.3 in MeOH). .sup.46Purified by reversed phase C18 chromatography: Column: Ultimate XB-C18, 50 × 250 mm, 10 μm; eluting with 20% to 50% ACN in H.sub.2O (0.5% NH.sub.3H.sub.2O). .sup.47Column: CHIRALPAK ID, 2 × 25 cm, 5 μm; eluting with 50% [MeOH in DCM (1:1) (2M NH.sub.3—MeOH)] in MeOH. .sup.48Column: CHIRALPAK ID, 2 × 25 cm, 5 μm; eluting with 50% [MeOH in DCM (1:1) (0.1% 2M NH.sub.3—MeOH)] in MeOH. .sup.49Workup: Reaction quenched at RT with H.sub.2O, pH adjusted between 8 and 9 with aq Na.sub.2CO.sub.3, extracted with i-PrOH in CHCl.sub.3, washed with brine, dried over Na.sub.2SO.sub.4, filtered, and concentrated. .sup.50Purified by Prep-TLC MeOH in DCM (1 to 15). .sup.51Column: CHIRAL ART Cellulose-SC, 2 × 25 cm, 5 μm; eluting with 50% MeOH in MTBE (10 mM NH3—MeOH). .sup.52Purified by Prep-TLC (DCM/MeOH 10:1). .sup.53Column: Chiralpak IA, 2 × 25 cm column, 5 μm; eluting with 50% MeOH in MTBE (10 mM NH.sub.3—MeOH). .sup.5Purified by reversed phase C18 chromatography eluting with 10% to 40% ACN in H.sub.2O (10 mmol/L NH.sub.3H.sub.2O).

Example 66

6-[3,5-Dimethyl-1-[1-(oxetan-3-yl)-4-piperidyl]pyrazol-4-yl]-4-[1-[5-(trifluoromethyl)-3-

pyridyl]ethoxy]pyrazolo[1,5-a]pyridine-3-carbonitrile, Isomer 2
##STR00608##
[0552] A mixture of 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-[1-[5-(trifluoromethyl)-3-pyridyl]ethoxy]pyrazolo[1,5-a]pyridine-3-carbonitrile (95 mg, 0.21 mmol), 4-(4-bromo-3,5-dimethyl-pyrazol-1-yl)-1-(oxetan-3-yl)piperidine (73 mg, 0.23 mmol), and K.sub.2CO.sub.3 (78 mg, 0.56 mmol) in toluene (0.85 ml) and H.sub.2O (0.21 ml) was degassed with sonication under N.sub.2. PdCl.sub.2(DtBPF) (9 mg, 0.14 mmol) was added, the vessel was sealed, and stirred at 80° C. overnight. The reaction was diluted with EA and H.sub.2O, the layers were separated, the organic layer was dried over MgSO.sub.4, filtered, and concentrated. The resulting residue was purified by silica gel chromatography eluting with 0% to 60% EtOH in EA (1:3) in EA to obtain the title compound (91 mg, 76%) as a green solid. MS ES+ m/z 566 [M+H].sup.+.
[0553] The following compound was prepared in a manner essentially analogous to the method of Example 66 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.
TABLE-US-00058 TABLE 57 Ex MS ES+ # Chemical Name Structure m/z 67.sup.1 6-[5-Methyl-1-[1-(oxetan-3- yl)-4-piperidyl]triazol-4-yl]-4- [1-[5-(trifluoromethyl)-3-pyridyl]ethoxy]pyrazolo[1,5- a]pyridine-3-carbonitrile, Isomer 2 [00609]  embedded image 553 [M + H].sup.+ .sup.1Work up: Reaction concentrated. Residue diluted with H.sub.2O and 35% aq HCl was added to adjust pH to 1. i-PrOH was gradually added until soln resulted. Charcoal added and reaction was stirred 1 h. DE was added and stirred 30 min. Suspension filtered and solidswere washed with i-PrOH:H.sub.2O (1:2). pH of filtrate adjusted to 10 with aq NaOH (10M). Resultant insoluble material was collected by filtration to afford title compound.
Example 68
6-[5-Methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]-4-[1-[5-(trifluoromethyl)-3-pyridyl]ethylamino]pyrazolo[1,5-a]pyridine-3-carbonitrile, Isomer 1
##STR00610##
[0554] A pressure tube was charged with 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-[1-[5-(trifluoromethyl)-3-pyridyl]ethylamino]pyrazolo[1,5-a]pyridine-3-carbonitrile (0.39 g, 0.45 mmol), 4-(4-bromo-5-methyl-triazol-1-yl)-1-(oxetan-3-yl)piperidine (0.17 g, 0.55 mmol), K.sub.2CO.sub.3 (0.16 g, 1.12 mmol), toluene (8 ml) and H.sub.2O (1 ml) was degassed by bubbling N.sub.2 through the mixture for several min and then added PdCl.sub.2(DtBPF) (0.02 g, 0.03 mmol) and degassed for another 2 min. The tube was capped, and the reaction was heated to 95° C. for 6 h. The reaction was cooled to RT, diluted with H.sub.2O, and extracted with EA (3×). The combined organic layers were dried over MgSO.sub.4, filtered, and concentrated. The residue was purified by silica gel chromatography and was eluted with 0% to 100% EA in cHex and then 0% to 5% MeOH in DCM to afford a brown foam (184 mg, 65%). MS ES+ m/z 552 [M+H].sup.+.
[0555] The brown foam was subjected to chiral chromatography using the following conditions: Column: Chiralpak IH, 3×100 mm, 3 m; eluting with 10% to 50% EtOH (0.2% IPAm) in CO.sub.2 to afford the title compound (69 mg, 24%), t.sub.R is 1.70, ee >98%. MS ES+ m/z 552 [M+H].sup.+. The retention time was obtained using analytical method K. (Refer to Table A for specific analytical conditions).
[0556] The following compounds were prepared in a manner essentially analogous to the method of Example 68 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate. K.sub.3PO.sub.4 and IPA may also be used.
[0557] If the retention time was obtained from an analytical column the method will be listed in the final column. Refer to Table A for specific analytical conditions for each method.
TABLE-US-00059 TABLE 58 t.sub.R (min) MS ES+ and Ex # Chemical Name Structure m/z method 69.sup.1,2 6-[5-Methyl-1-[1- (oxetan-3-yl)azepan-4- yl]triazol-4-yl]-4-[1- [5-(trifluoromethyl)-3- pyridyl]ethoxy]pyrazolo [1,5-a]pyridine-3- carbonitrile, Isomer 1 [00611]

embedded image 567 [M + H].sup.+ 1.09 Q 70.sup.1,2 6-[5-Methyl-1-[1- (oxetan-3-yl)azepan-4-yl]triazol-4-yl]-4-[1- [5-(trifluoromethyl)-3- pyridyl]ethoxy] pyrazolo[1,5-a]pyridine- 3-carbonitrile, Isomer 2 [00612]embedded image 567 [M + H].sup.+ 2.32 Q 71.sup.3,4 4-[2-(5-Fluoro-2- pyridyl)-2-hydroxy- ethoxy]-6-[5-methyl- 1-[(1S,5R)-8-(oxetan- 3-yl)-8-azabicyclo [3.2.1]octan-3- yl]triazol-4- yl]triazolo[1,5- a]pyridine-3- carbonitrile [00613]embedded image 545 [M + H].sup.+ 72.sup.5,6 4-[3-Hydroxy-3-(2- pyridyl)pyrrolidin-1- yl]-6-[2-methyl-3-[1-(oxetan-3-yl)-4- piperidyl]cyclopenta- 1,4-dien-1- yl]pyrazolo[1,5- a]pyridine-3- carbonitrile, Isomer 2 [00614]embedded image 526 [M + H].sup.+ 1.24 R .sup.1Purified by silica gel chromatography eluted with 0% to 100% (25% EtOH:EA) in cHex. .sup.2Column: Chiralpak AD, 20 × 250 mm, 5 μm; eluting with 45% MeOH (0.2% DMEA) in CO.sub.2. .sup.3Column: Chiralpak IH, 3 × 100 mm, 3 μm; eluting with 10% to 50% EtOH (0.2% IPAm) in CO.sub.2. .sup.4Column: Chiralpak IA, 3 × 100 mm, 3 μm; eluting with 25% to 50% EtOH (0.2% IPAm) in CO.sub.2. .sup.5Purified by reversed phase flash C18 chromatography with following conditions: column, C18; eluting with 20% to 60% ACN in H2O (NH.sub.5CO.sub.3 pH 9). .sup.6Column: Chiralcel OD, 20 × 250 mm, 5 μm; eluting with 45% MeOH (0.5% DMEA) in CO.sub.2.

Example 73

6-[5-Methyl-1-[1-(2,2,6,6-tetramethyltetrahydropyran-4-yl)-4-piperidyl]pyrazol-4-yl]-4-[(1R)-1-(2-pyridyl)ethoxy]pyrazolo[1,5-a]pyridine-3-carbonitrile

##STR00615##

[0558] A soln of 6-[5-methyl-1-(4-piperidyl)pyrazol-4-yl]-4-[(1R)-1-(2-pyridyl)ethoxy]pyrazolo[1,5-a]pyridine-3-carbonitrile (55 mg, 0.13 mmol) and 2,2,6,6-tetramethyltetrahydropyran-4-one (36 mg, 0.23 mmol) in MeOH (3 ml) was treated with NEt.sub.3 (90 μl, 0.65 mmol) and ZnCl.sub.2 (10 ml, 0.02 mmol, 1.9 M in MeTHF) and the reaction stirred at 50° C. After stirring overnight, the reaction was allowed to cool to RT and treated with NaBH.sub.3CN (33 mg, 0.53 mmol). After stirring at 50° C. for 3 days, the reaction was quenched with H.sub.2O and EA. The phases were separated, and the aq phase was extracted with EA. The organic layers were combined, dried over MgSO.sub.4, filtered, and concentrated. The resulting residue was purified by silica gel chromatography eluting with 5% MeOH in DCM to obtain the title compound (50 mg, 66%) as an amber oil. MS ES+ m/z 568 [M+H].sup.+.

Example 74

6-[5-Methyl-1-[2-(oxetan-3-yl)-2-azaspiro[3.3]heptan-6-yl]pyrazol-4-yl]-4-[(1R)-1-(2-pyridyl)ethoxy]pyrazolo[1,5-a]pyridine-3-carbonitrile

##STR00616##

[0559] 6-[1-(2-Azaspiro[3.3]heptan-6-yl)-5-methyl-pyrazol-4-yl]-4-[(1R)-1-(2-pyridyl)ethoxy]pyrazolo[1,5-a]pyridine-3-carbonitrile, 2,2,2-trifluoroacetic acid (106 mg, 0.16 mmol) was dissolved into DCE (3 ml) and treated with NEt.sub.3 (100 μl, 0.72 mmol), 3-oxetanone (25 μL, 0.43 mmol), and Na(OAc).sub.3BH (89 mg, 0.42 mmol) and allowed the reaction to stir for 16 h at RT. An additional aliquot of 3-oxetanone (25 μl, 0.43 mmol) was added and stirred the reaction at 50° C. for 4 h. The reaction was diluted with EA (25 ml) and the organic layer was washed with saturated aq NaHCO.sub.3 (50 ml) and brine (50 ml). The organic layer was collected, dried over MgSO.sub.4, filtered, and concentrated. The resulting residue was purified by silica gel chromatography eluting with a gradient of 0% to 15% MeOH in DCM to obtain the title compound (26 mg, 31%) as an off-white solid. MS ES+ m/z 496 [M+H].sup.+.

Example 75

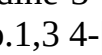
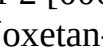
2-[3-Chloro-6-[5-methyl-1-[1-(oxetan-3-yl)azetidin-3-yl]triazol-4-yl]pyrazolo[1,5-a]pyridin-4-yl]oxy-1-(3,5-difluoro-2-pyridyl)ethanol, Isomer 2

##STR00617##

[0560] 2-[3-Chloro-6-[5-methyl-1-[1-(oxetan-3-yl)azetidin-3-yl]triazol-4-yl]pyrazolo[1,5-a]pyridin-4-yl]oxy-1-(3,5-difluoro-2-pyridyl)ethanol (126 mg) was subjected to the following chiral chromatography conditions: Column: Amylose-C, 30×250 mm column, 5 μm; eluting with

40% in IPA in CO.sub.2 to afford the title compound (32 mg, 25), t.sub.R is 2.51 with 90 ee, MS ES+ m/z 518.2 [M+H].sup.+. The retention time was obtained using analytical method H. (Refer to Table A for specific analytical conditions).

[0561] The following compounds were prepared in a manner essentially analogous to the method of Example 75 using the appropriate reagents, adjusting reaction time to determine completion of the reaction and adjusting the purification system as appropriate.

TABLE-US-00060 TABLE 59 t.sub.R (min) MS ES+ and Ex # Chemical Name Structure m/z method 76.sup.1,2 4-[2-(3-chloro-5- fluoro-2-pyridyl)- 2-hydroxy- ethoxy]-6-[5- methyl-1-[1-(oxetan-3-yl)-4- piperidyl]triazol- 4-yl]pyrazolo[1,5- a]pyridine-3- carbonitrile, Isomer 1 [00618]  553.2 [M + H].sup.+ 3.85 77.sup.1,2 4-[2-(3-Chloro-5- fluoro-2-pyridyl)- 2-hydroxy- ethoxy]-6-[5- methyl-1-[1- (oxetan-3-yl)-4- piperidyl]triazol- 4-yl]pyrazolo[1,5-a]pyridine-3- carbonitrile, Isomer 2 [00619]  553.2 [M + H].sup.+ 4.85 78.sup.1,3 4-[2-(4-Chloro-5- fluoro-2-pyridyl)- 2-hydroxy- ethoxy]-6-[5- methyl-1-[1- (oxetan-3-yl)-4- piperidyl]triazol-4- yl]pyrazolo[1,5- a]pyridine-3- carbonitrile, Isomer 1 [00620]  553.2 [M + H].sup.+ 4.42 79.sup.4 4-[2-(2,4- Difluorophenyl)-2- hydroxy-ethoxy]- 6-[5-methyl-1-[1- (oxetan-3-yl)-4- piperidyl]triazol- 4-yl]pyrazolo[1,5- a]pyridine-3-carbonitrile, Isomer 2 [00621]  536 [M + H].sup.+ 2.22 80.sup.5 7-[5-Methyl-1-[1- (oxetan-3-yl)-4- piperidyl]triazol-4- yl]-5-[[3,3,3- trifluoro-2-(5- fluoro-2-pyridyl) propyl]amino] imidazo[1,2- a]pyridine-3- carbonitrile, Isomer 1 [00622]  570 [M + H].sup.+ 10.92 81.sup.6,7 1-(5-Fluoro-2- pyridyl)-2-[6-[5- methyl-1-[1- (oxetan-3-yl)-4-piperidyl]triazol-4- yl]-3- (trifluoromethyl) pyrazolo[1,5- a]pyridin-4- yl]oxy-ethanol, Isomer 2 [00623]  562 [M + H].sup.+ 1.83 I 82.sup.7 3-Chloro-4-[2-(5- fluoro-2-pyridyl)-2-methoxy- ethoxy]-6-[5- methyl-1-[1- (oxetan-3- yl)azetidin-3- yl]triazol-4- yl]pyrazolo[1,5-a]pyridine, Isomer 2 [00624]  (.sup.35Cl/.sup.37Cl) 514/516 [M + H].sup.+ 2.68 P 83.sup.8 4-(2-Cyclopentyl- 2-hydroxy- ethoxy)-6-[5- methyl-1-[1- (oxetan-3-yl)-4-piperidyl]triazol- 4-yl]pyrazolo[1,5- a]pyridine-3- carbonitrile, Isomer 1 [00625]  492 [M + H].sup.+ 1.08 L 84.sup.8 4-(2-Cyclopentyl- 2-hydroxy- ethoxy)-6-[5-methyl-1-[1- (oxetan-3-yl)-4- piperidyl]triazol- 4-yl]pyrazolo[1,5- a]pyridine-3- carbonitrile, Isomer 2 [00626]  492 [M + H].sup.+ 1.68 L 85.sup.9 2-[3-Chloro-6-[5- methyl-1-[1- (oxetan-3- yl)azetidin-3- yl]triazol-4- yl]pyrazolo[1,5- a]pyridin-4- yl]oxy-1-(5-fluoro- 2-pyridyl)ethanol, Isomer 1 [00627]  (.sup.35Cl/.sup.37Cl) 500/502 [M + H].sup.+ 1.25 A 86.sup.9 2-[3-Chloro-6-[5- methyl-1-[1- (oxetan-3- yl)azetidin-3- yl]triazol-4-yl]pyrazolo[1,5- a]pyridin-4- yl]oxy-1-(5-fluoro- 2-pyridyl)ethanol, Isomer 2 [00628]  (.sup.35Cl/.sup.37Cl) 500/502 [M + H].sup.+ 1.54 A 87.sup.10 1-(3-Chloro-5-fluoro-2-pyridyl)- 2-[3-fluoro-6-[5- methyl-1-[1- (oxetan-3-yl)-4- piperidyl]triazol-4-yl]pyrazolo[1,5- a]pyridin-4- yl]oxy-ethanol, Isomer 2 [00629]  560 [M + H].sup.+ 2.8 S .sup.1Purified by silica gel chromatography eluting with MeOH in DCM. .sup.2SFC chromatography eluting with 60% 2-propanol (0.1% DEA) in 40% CO.sub.2. .sup.3SFC chromatography eluting with 60% MeOH (0.1% DEA) in 40% CO.sub.2. .sup.4Column: Chiralpak IE-3; 4.6 × 50 cm column, 3 μm; eluting with 50% EtOH in MTBE (0.1% DEA). .sup.5Column: Chiral ART Cellulose-SB, 2 × 25 cm column, 5 μm; eluting with 10% EtOH in MTBE (10 mM NH.sub.3—MeOH). .sup.6Column: Chiral Art AmylC, 30 × 250 mm, 5 μm; eluting with 45% EtOH (0.5% DMEA) in CO.sub.2. .sup.7Column: Amylose-C, 30 × 250 mm column, 5 μm; eluting with 45% EtOH (0.5% DMEA) in CO.sub.2. .sup.8Column: Chiralpak AD, 30 × 250 mm column, 5 μm; eluting with 55% IPA (0.5% DMEA) in CO.sub.2. .sup.9Column: Chiral Art AmylC, 20 × 250 mm, 5 μm; eluting with 60% IPA (0.5% DMEA) in CO.sub.2. .sup.10Column: Chiral Art Amylose C, 30 × 250 mm, 5 μm; eluting with 40% IPA (0.5% DMEA) in CO.sub.2.

Example 88

1-[3-Chloro-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridin-4-yl]oxy-2-(3,5-difluoro-2-pyridyl)propan-2-ol, Isomer 1

##STR00630##
[0562] To an ice-cooled soln of 2-[3-chloro-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridin-4-yl]oxy-1-(3,5-difluoro-2-pyridyl)ethanone (190 mg, 0.19 mmol, 55 mass %) in DCM (4 ml) under N.sub.2, was added dropwise a soln of MeMgBr (0.26 ml, 0.78 mmol, 3 M) over 5 minutes. The resulting mixture was stirred for 3 h then diluted with DCM and slowly quenched with MeOH (2 mL). NaBH.sub.4 (5 mg, 0.132161 mmol) was added, and the mixture stirred for 20 min. The reaction was purified by silica gel chromatography eluting with 0% to 50% (10% MeOH in DCM) in DCM. Material crashed out inside the column, 50% MeOH in DCM was used to dissolve and elute the title compound along with impurities. The residue was further purified by reversed phase chromatography, column: XBridge C18, 19×150 mm, 5 μm; eluting with 45% to 75% ACN in H.sub.2O (10 mM NH.sub.4HCO.sub.3, pH 9).
[0563] The isolated material after reversed phase chromatography was subjected to the following chiral chromatography conditions: Chiral Art Amylose C, 30×250 mm, 5 m; eluting with 40% IPA (0.5% DMEA) in CO.sub.2 to afford the title compound, Isomer 1 (7.5 mg, 7%), t.sub.R is 2.36, ee >98% ee; MS ES+ m/z 560/562 [M+H].sup.+.
Example 89
1-[3-Chloro-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridin-4-yl]oxy-2-(5-fluoro-2-pyridyl)butan-2-ol, Isomer 2
##STR00631##
[0564] EtMgBr (0.25 ml, 0.75 mmol, 3 M in Et.sub.2O) was treated with ZnCl.sub.2 (0.09 ml, 0.2 mmol, 1.9M in MeTHF) at 0° C. under N.sub.2. After stirring at 0° C. for 1 h, the reaction was treated dropwise with a soln of 2-[3-chloro-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridin-4-yl]oxy-1-(5-fluoro-2-pyridyl)ethanone (304 mg, 0.58 mmol) in DCM (1 ml) and allowed to stir at 0° C. for 2 h. The reaction was diluted with DCM and slowly quenched with aq NH.sub.4Cl. The reaction was passed through a phase separator and washed with DCM. The eluent was concentrated, and the residue dissolved in MeOH (5 ml), treated with NaBH.sub.4 (15 mg, 0.40 mmol), and stirred at RT for 1 h. The reaction was quenched with H.sub.2O, the MeOH was removed in vacuo, extracted with DCM, washed with brine, dried over MgSO.sub.4, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with a gradient of 0% to 5% MeOH in DCM to afford a colorless oil (125.6 mg, 35%). The colorless oil was subjected to the following chiral chromatography conditions: Column: Cellulose-1, 30×250 mm column, 5 μm; eluting with 35% IPA (0.5% DMEA) in CO.sub.2 to afford the title compound (18 mg, 6 #), t.sub.R is 2.64 with 980 ee. MS ES+ m/z (.sup.35Cl/.sup.37Cl) 556/558 [M+H].sup.+. The retention time was obtained using analytical method M.
[0565] The following compounds were prepared in a manner essentially analogous to the method of Example 89 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.
[0566] If the retention time was obtained from an analytical column the method will be listed in the final column. Refer to Table A for specific analytical conditions for each method.
TABLE-US-00061 TABLE 60 t.sub.R (min) MS ES+ and Ex # Chemical Name Structure m/z method 90.sup.1,2 2-[3-Chloro-6-[5- methyl-1-[1-(oxetan- 3-yl)-4- piperidyl]triazol-4-yl]pyrazolo[1,5-a] pyridine-4-yl]oxy-1- cyclopropyl-1-(5- fluoro-2- pyridyl)ethanol, Isomer 1 [00632]embedded image (.sup.35Cl/.sup.37Cl) 568/570 [M + H].sup.+ 2.29 N 91.sup.1,2 2-[3-Chloro-6-[5- methyl-1-[1-(oxetan- 3-yl)-4- piperidyl]triazol-4- yl]pyrazolo[1,5-a] pyridine-4-yl]oxy-1- cyclopropyl-1-(5- fluoro-2- pyridyl)ethanol, Isomer 2 [00633]embedded image (.sup.35Cl/.sup.37Cl) 568/570 [M + H].sup.+ 2.40 N .sup.1Purified by silica gel chromatography eluting with 0% to 40% (9:1 DCM in MeOH) in DCM .sup.2Column: Chiralpak IH, 20 × 250 mm column (5 μm) eluting with 35% MeOH (0.5% DMEA) in CO.sub.2.
Example 92
4-[1-(6-Cyclopropylpyrazin-2-yl)ethoxy]-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-

yl]pyrazolo[1,5-a]pyridine-3-carbonitrile, Isomer 2
##STR00634##
[0567] 4-[1-(6-Bromopyrazin-2-yl)ethoxy]-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridine-3-carbonitrile (182.2 mg, 0.32 mmol), cyclopropylboronic acid (48 mg, 0.56 mmol) were dissolved in 1,4-dioxane (3 ml) and CsF (197 mg, 1.30 mmol) was added. The mixture was degassed then PdCl.sub.2(DtBPF) (21 mg, 0.03 mmol) was added, and the mixture was stirred at 90° C. overnight. Upon cooling to RT, EA was added to the reaction. The mixture was washed with sat. aq NaHCO.sub.3 and brine. The organic phase was dried over MgSO.sub.4, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with 20% to 100% EA in cHex to afford a pale-yellow solid (120 mg, 67%). The yellow solid was subjected to chiral chromatography using the following conditions: Column: Chiralpak IH, 20×250 mm, 5 m; eluting with 25% MeOH (0.5% DMEA) in CO.sub.2 to afford the title compound (47 mg, 28%), t.sub.R is 2.32 min with 97% ee. MS ES+ m/z 526 [M+H].sup.+. The retention time was obtained using analytical method N.
Example 93
6-[5-Methyl-1-[7-(oxetan-3-yl)-7-azaspiro[3.5]nonan-2-yl]pyrazol-4-yl]-4-[(1R)-1-(2-pyridyl)ethoxy]pyrazolo[1,5-a]pyridine-3-carbonitrile
##STR00635##
and
Example 94
6-[3-Methyl-1-[7-(oxetan-3-yl)-7-azaspiro[3.5]nonan-2-yl]pyrazol-4-yl]-4-[(1R)-1-(2-pyridyl)ethoxy]pyrazolo[1,5-a]pyridine-3-carbonitrile
##STR00636##
[0568] A soln of 6-[1-(7-azaspiro[3.5]nonan-2-yl)-5-methyl-pyrazol-4-yl]-4-[(1R)-1-(2-pyridyl)ethoxy]pyrazolo[1,5-a]pyridine-3-carbonitrile, 6-[1-(7-azaspiro[3.5]nonan-2-yl)-3-methyl-pyrazol-4-yl]-4-[(1R)-1-(2-pyridyl)ethoxy]pyrazolo[1,5-a]pyridine-3-carbonitrile (101 mg, 0.19 mmol), and oxetan-3-one (20 mg, 0.28 mmol) in MeOH (5 ml) was treated with AcOH (21 μl, 0.37 mmol) and NaBH.sub.3CN (35 mg, 0.56 mmol) and stirred at RT for 2 h and then at 50° C. for 18 h. The reaction was allowed to cool then concentrated. The residue was suspended in saturated aq NaHCO.sub.3 and extracted with DCM (2×). The combined organic layers were dried over MgSO.sub.4, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with a gradient of 0% to 10% acetone in DCM to obtain a pale-yellow solid containing the two compounds. The compounds were separated using the following conditions: Column, Chiralpak IH, 20×250 mm, 5 μm; column eluting with 20% MeOH in CO.sub.2 to obtain 6-[3-methyl-1-[7-(oxetan-3-yl)-7-azaspiro[3.5]nonan-2-yl]pyrazol-4-yl]-4-[(1R)-1-(2-pyridyl)ethoxy]pyrazolo[1,5-a]pyridine-3-carbonitrile (27 mg; 27%). MS ES+ m/z 524 [M+H].sup.+, t.sub.R=1.80 min (analytical chiral chromatography method N, Table A), .sup.1H NMR (400 MHz, DMSO-d.sub.6): 8.60-8.58 (m, 3H), 7.85 (td, J=7.8, 1.8 Hz, 1H), 7.69-7.62 (m, 2H), 7.34 (ddd, J=7.5, 4.9, 1.1 Hz, 1H), 6.92 (s, 1H), 5.87 (q, J=6.4 Hz, 1H), 4.89 (quintet, J=8.2 Hz, 1H), 4.51 (t, J=6.5 Hz, 2H), 4.41 (t, J=6.1 Hz, 2H), 2.29-2.18 (m, 11H), 1.71 (d, J=6.4 Hz, 5H), 1.60 (t, J=5.4 Hz, 2H) and 6-[5-methyl-1-[7-(oxetan-3-yl)-7-azaspiro[3.5]nonan-2-yl]pyrazol-4-yl]-4-[(1R)-1-(2-pyridyl)ethoxy]pyrazolo[1,5-a]pyridine-3-carbonitrile (14 mg, 14%) MS ES+ m/z 524 [M+H].sup.+, t.sub.R=1.69 min (analytical chiral chromatography method N, Table A), .sup.1H NMR (400 MHz, DMSO-d.sub.6): 8.60-8.52 (m, 3H), 8.13 (s, 1H), 7.85 (td, J=7.7, 1.7 Hz, 1H), 7.65 (d, J=7.8 Hz, 1H), 7.35 (ddd, J=7.5, 4.8, 1.2 Hz, 1H), 7.03 (s, 1H), 5.89 (q, J=6.4 Hz, 1H), 4.78 (quintet, J=8.4 Hz, 1H), 4.51 (t, J=6.5 Hz, 2H), 4.41 (t, J=6.1 Hz, 2H), 2.33-2.18 (m, 11H), 1.72-1.61 (m, 7H) as thick colorless oils.
[0569] The following compounds were prepared in a manner essentially analogous to the method of Example 94 using the appropriate reagents, adjusting reaction time to determine completion of the reaction, and adjusting the purification system as appropriate.

TABLE-US-00062 TABLE 61 MS ES+ t.sub.R Ex # Chemical Name Structure m/z min 95.sup.1,a 6-[5-Methyl-1-[1- (oxetan-3-yl)azepan- 4-yl]pyrazol-4-yl]-4- [(1R)-1-(2- pyridyl)ethoxy] pyrazolo[1,5-a] pyridine-3- carbonitrile [00637]  embedded image 498 [M + H].sup.+ 2.71 96.sup.1,c 6-[5-Methyl-1-[1- (oxetan-3-yl)azepan- 4-yl]pyrazol-4-yl]-4- [(1R)-1-(2- pyridyl)ethoxy] pyrazolo[1,5-a] pyridine-3- carbonitrile, Isomer 1 [00638]  embedded image 498 [M + H].sup.+ 2.65 97.sup.1,b 6-[3-Methyl-1-[1- (oxetan-3-yl)azepan- 4-yl]pyrazol-4-yl]-4- [(1R)-1-(2- pyridyl)ethoxy] pyrazolo[1,5-a] pyridine-3- carbonitrile [00639]  embedded image 498 [M + H].sup.+ 2.49 .sup.1Column: Chiralpak AD, 20 × 250 mm column, 5 μm; eluting with 35% EtOH (0.5% DMEA) in CO.sub.2. .sup.a 1H NMR (400 MHz, DMSO-d.sub.6): 8.60-8.58 (m, 2H), 8.50 (d, J = 1.0 Hz, 1H), 8.14 (s, 1H), 7.85 (td, J = 7.7, 1.9 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.35 (ddd, J = 7.6, 4.9, 1.2 Hz, 1H), 7.07 (s, 1H), 5.91 (q, J = 6.4 Hz, 1H), 4.54 (td, J = 6.5, 2.4 Hz, 2H), 4.42- 4.35 (m, 3H), 3.66 (quintet, J = 6.4 Hz, 1H), 2.45-2.41 (m, 4H), 2.19 (s, 7H), 1.88-1.79 (m, 1H), 1.71 (d, J = 6.4 Hz, 4H). .sup.b 1H NMR (400 MHz, DMSO-d.sub.6): 8.60-8.58 (m, 2H), 8.50 (d, J = 1.0 Hz, 1H), 8.14 (s, 1H), 7.85 (td, J = 7.7, 1.9 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.35 (ddd, J = 7.6, 4.9, 1.2 Hz, 1H), 7.07 (s, 1H), 5.91 (q, J = 6.4 Hz, 1H), 4.54 (td, J = 6.5, 2.4 Hz, 2H), 4.42-4.35 (m, 3H), 3.66 (quintet, J = 6.4 Hz, 1H), 2.45-2.41 (m, 4H), 2.19 (s, 7H), 1.88-1.79 (m, 1H), 1.71 (d, J = 6.4 Hz, 4H). .sup.c 1H NMR (400 MHz, DMSO): 8.68-8.56 (m, 2H), 8.50 (d, J = 1.0 Hz, 1H), 8.14 (s, 1H), 7.85 (td, J = 7.7, 1.8 Hz, 1H), 7.66 (dt, J = 7.9, 1.1 Hz, 1H), 7.37-7.34 (dd, J = 7.5, 1.2 Hz, 1H), 7.36-7.32 (dd, J = 7.5, 1.2 Hz, 1H), 7.07 (d, J = 1.1 Hz, 1H), 5.91 (q, J = 6.4 Hz, 1H), 4.55 (td, J = 6.2, 2.5 Hz, 2H), 4.44-4.32 (m, 2H), 3.66 (p, J = 6.4 Hz, 1H), 2.50-2.38 (m, 4H), 2.19 (s, 3H), 2.15-1.95 (m, 4H), 1.88-1.77 (m, 1H), 1.71 (d, J = 6.4 Hz, 3H), 1.69-1.58 (m, 2H).

Example 98

1-(5-Fluoro-2-pyridyl)-2-[6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]-3-(1-methylpyrazol-4-yl)pyrazolo[1,5-a]pyridin-4-yl]oxy-ethanol, Isomer 1

##STR00640##

[0570] (1S)-2-[3-Bromo-6-[5-methyl-1-[1-(oxetan-3-yl)-4-piperidyl]triazol-4-yl]pyrazolo[1,5-a]pyridin-4-yl]oxy-1-(5-fluoro-2-pyridyl)ethanol (0.066 g, 0.10 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.115 g, 0.54 mmol), and XPhos Pd G4 (0.02 g, 0.02 mmol) in toluene (1.3 ml) was treated at RT with aq K.sub.2CO.sub.3 (1M, 0.55 mL, 0.55 mmol), and then heated to 90° C. After 5 h additional 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1h-pyrazole (0.35 g, 1.62 mmol), XPhos Pd G4 (0.02 g, 0.02 mmol), and H.sub.2O (0.65 ml) were added. After 7 h the reaction cooled to RT and EA (10 ml) was added. The phases were separated, and the organic phase was dried, filtered, and concentrated. The residue was purified by reversed phase chromatography eluting with 20% to 60% ACN in aq. NH.sub.4CO.sub.3 (pH=9) to afford the title compound as a white solid (0.017 mg, 28%). MS ES+ m/z 574 [M+H].sup.+.

Example 99

6-[1-[(3S,4R)-3-Fluoro-1-(oxetan-3-yl)-4-piperidyl]-5-methyl-triazol-4-yl]-4-[2-(5-fluoro-2-pyridyl)-2-methoxy-ethoxy]pyrazolo[1,5-a]pyridine-3-carbonitrile

##STR00641##

[0571] To a mixture of 6-[1-[(3S,4R)-3-Fluoro-4-piperidyl]-5-methyl-triazol-4-yl]-4-[2-(5-fluoro-2-pyridyl)-2-methoxy-ethoxy]pyrazolo[1,5-a]pyridine-3-carbonitrile; hydrochloride (2 g, crude) in MeOH (20 mL) was added 3-oxetanone (1.49 g, 20.63) at RT under N.sub.2. The resulting mixture was stirred for 60 min at 50° C. Next, NaBH.sub.3CN (432 mg, 6.88 mmol) was added at RT. The mixture was stirred for 2 hr at 50° C. Upon cooling to RT, the reaction was quenched with H.sub.2O (30 mL) and the mixture was basified to pH 9 with saturated aq Na.sub.2CO.sub.3. The mixture was extracted with EA (2×80 mL). The combined organic layers were washed with brine (2×20 mL), dried over Na.sub.2SO.sub.4, filtered and concentrated in vacuo. The residue was purified by C18 reversed flash chromatography, eluted with 30% to 50% ACN in H.sub.2O (0.1% NH.sub.3.Math.H.sub.2O) to afford the title compound (1.4 g, 73.97%) as a white solid. MS ES+

m/z 551 [M+H].sup.+.
Biological Assays
[0572] The following assays demonstrate that compounds provided herein are FGFR2 inhibitors. The following assays demonstrate that certain compounds provided herein selectively target FGFR2 over FGFR1.
FGFR2 and FGFR1 Enzyme Assay
[0573] FGFR1 and FGFR2 proteins were purchased from ThermoFisher Scientific (Cat. No. PR4660A and PR5332A, respectively). Enzyme activity was monitored using the KinEASETM-TK Assay Kit (CisBio, Cat. No. 62TKOPEC) according to the manufacturer's instructions. All assays were performed at the respective KmATP for each kinase in KinEASETM Kinase Buffer. Reactions were performed in a white, small volume polystyrene 384 well plate.
[0574] An incubation was conducted with each of the proteins, 50 nM TK-Biotin Substrate (CisBio), 6.25 nM Streptavidin-XL665 (CisBio), 0.25× Anti-Phosphorylate TK-Biotin-Cryptate (CisBio). Final enzyme concentrations were 0.08 nM for FGFR1, and 0.04 nM for FGFR2, in 10 μL reactions. Titration of compounds was performed using 1:3 serial dilutions in 100% dimethyl sulfoxide (DMSO) starting at 2.5 μM. Prior to the initiation of the reaction by adenosine triphosphate (ATP), each protein and compounds were pre-incubated for 15 minutes at room temperature. Reactions proceeded for 30 min at 30° C. Plates were quenched by the addition of the Anti-TK cryptate antibody/Streptavidin-XL665 mixture. After 1 hour in the stopping solution, the plates were read on the Envision plate reader ((PerkinElmer) (Ex. Filter. 320 nm and Em1 665 nm/Em2 615 nm)).
[0575] Ratios were converted to a percent of control (POC) using a ratiometric emission factor. One hundred POC was determined using no test compound (DMSO alone), and 0 POC was determined in the presence of 2.5 μM of an appropriate control inhibitor. A 4-parameter logistic curve was fit to the POC values as a function of the concentration of compound, and the IC50 value was the point where the best fit curve crossed 50 POC.
FGFR2 and FGFR1 Cell-Based Assay
[0576] HEK293 cells transfected with doxycycline (dox)-inducible human wild type FGFR1, and human wild type FGFR2, were plated at 10,000 cells/well in poly-D-lysine coated 384 well plates (Becton Dickinson, Cat. No. 356663) in Dulbecco's Modified Eagle Medium (Sigma, Cat. No. D5796) containing 10% FBS (Sigma, Cat. No. F2442), 1% Penicillin-Streptomycin (Gibco, Cat. No. 15140) and 1 μg/ml doxycycline, and allowed to attach for 24 hours at 37° C., 5% CO.sub.2. NCI-H716 cells (ATCC, Cat. No. CCL-251) were plated at 5,000 cells/well in poly-D-lysine coated 384 well plates (Becton Dickinson, Cat. No. 356663) in RPMI 1640 medium (Gibco, Cat. No. A10491) containing 10% FBS and 1% Penicillin-Streptomycin, and allowed to attach for 24 hours at 37° C., 5% CO.sub.2. Cells were treated with compounds using 1:3 serial dilutions with a maximum final concentration of 3 μM. Compounds were incubated on cells for 1 hour at 37° C., 5% CO.sub.2.
[0577] Cells were fixed with formaldehyde for 20 minutes at room temperature and permeabilized with 0.3% Triton-X 100 for 15 minutes at room temperature. Then cells were blocked with 1% bovine serum albumin in 0.05% Tween for 1 hour at room temperature, and they were incubated overnight at 4° C. with anti-phospho-FGFR primary antibody (Cell Signaling, Cat. No. 52928 for HEK293 FGFR1; Millipore, Cat. No. 06-1433 for the rest of the cell lines), in blocking solution. The next day, cells were incubated with goat anti-rabbit IgG Alexa 488 labeled secondary antibody (Invitrogen, Cat. No. A11008) for 1 hour at room temperature, and a solution containing 0.4 ug/ml DAPI (Sigma, Cat. No. D9564) and 50 μg/mL Ribonuclease A (Sigma, Cat. No. R-6513) was added to stain nuclei. Fluorescence plates were scanned with the Acumen Explorer laser-scanning fluorescence microplate cytometer (SPT Labtech) to quantify the number of cells and the phosphorylation of FGFR to calculate a percentage of phospho-FGFR positive cells.
[0578] One hundred POC was determined using no test compound (DMSO alone), and 0 POC was

determined in the presence of 3 μM of an appropriate control inhibitor. A 4-parameter logistic curve was fit to the POC values as a function of the concentration of compound, and the IC.sub.50 value was the point where the best fit curve crossed 50 POC.

Biological Assay Results

[0579] In the above enzyme assays the compounds of Examples 1-33, 35-60, 62-99 all exhibited IC.sub.50 values of less than 200 nM for FGFR2.

[0580] In the above enzyme assays the compounds of Examples 1, 2, 4, 7, 9-11, 13-16, 18-24, 26-28, 31-35, 38, 40, 42-59, 61-67, 69, 71-73, 75-77, 79-85, 87-93, 95-97 and 99 all exhibited IC.sub.50 values of less than 100 nM for FGFR2 and are at least 3 fold more selective for FGFR2 than for FGFR1.

[0581] In the above enzyme assays the compounds of Examples 1, 2, 7, 9-11, 15-16, 18, 20-22, 27-28, 31, 33-34, 40, 42, 44, 47-53, 55-57, 61-67, 69, 71, 73, 79, 81-82, 87-89, 91, 92, 96 and 99 all exhibited IC.sub.50 values of less than 50 nM for FGFR2 and are at least 8 fold more selective for FGFR2 than for FGFR1.

[0582] In the above cell-based assays the compounds of Examples 1-99 all exhibited IC.sub.50 values of less than 60 nM for FGFR2.

[0583] In the above cell-based assays the compounds of Examples 1-14, 16-29, 31-40, 42, 44, 45, 47-71, 73-75, 77, 79, 81-82, 84 and 86-99 all exhibited IC.sub.50 values of less than 30 nM for FGFR2 and are at least 5 fold more selective for FGFR2 than for FGFR1.

[0584] In the above cell-based assays the compounds of Examples 3-5, 7-9, 14, 16, 18-23, 28, 33, 42, 44, 51-53, 56, 60-63, 66-67, 69, 74-75, 77, 81, 88-89, 91, 95-97 and 99 all exhibited IC.sub.50 values of less than 10 nM for FGFR2 and are at least 10 fold more selective for FGFR2 than for FGFR1.

Claims

1. A compound of the formula: ##STR00642## wherein Z.sub.2 is ##STR00643## A is pyrazole, triazole, thiadiazole or oxadiazole, substituted with R.sup.1 and R.sup.1A; R.sup.1 is hydrogen or C.sub.1-C.sub.3 alkyl; R.sup.1A is hydrogen, halo, CN or C.sub.1-C.sub.3 alkyl optionally substituted with one or more substituents independently selected from halo, OH and OCH.sub.3; X.sub.1 and X.sub.2 are independently selected from N and C, wherein when one of X.sub.1 or X.sub.2 is N the other is C; X.sub.3 is N or CH; X.sub.4 is N or C—R.sup.9; Y is NH, O, S or a bond; Y.sub.1 is a bond, CHR.sup.7, CH.sub.2—CHR.sup.7, CHR.sup.7—CH.sub.2, CF.sub.2, CH.sub.2—CF.sub.2 or CF.sub.2—CH.sub.2; Y.sub.2 is a bond, CHR.sup.3, CH.sub.2—CHR.sup.3, CHR.sup.3—CH.sub.2, CF.sub.2, CH.sub.2—CF.sub.2 or CF.sub.2—CH.sub.2; Y.sub.3 is CR.sup.4R.sup.5 or CF.sub.2; Y.sub.4 is CR.sup.3R.sup.4 or CF.sub.2; Y.sub.5 is CR.sup.13R.sup.14, CR.sup.13R.sup.14—CH.sub.2 or CH.sub.2CR.sup.13R.sup.14; Y.sub.6 is CR.sup.13R.sup.14, CR.sup.13R.sup.14—CH.sub.2 or CH.sub.2CR.sup.13R.sup.14; Z is a bond, CHR.sup.9A, CR.sup.4R.sup.4A, CR.sup.4R.sup.4A—CH.sub.2, CH.sub.2—CR.sup.4R.sup.4A, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo(1.1.1)pentane, bicyclo(2.1.1)hexane, azetidine, pyrrolidine or piperidine; Z.sub.1 is a bond when Z is a bond, CR.sup.4R.sup.4A, CR.sup.4R.sup.4A—CH.sub.2, CH.sub.2—CR.sup.4R.sup.4A, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo(1.1.1)pentane, bicyclo(2.1.1)hexane, azetidine, pyrrolidine or piperidine, or Z.sub.1 is CH.sub.2 or CH.sub.2—CH.sub.2 when Z is CHR.sup.9A; Z.sub.3 is a bond, C(O), SO.sub.2 or —NR.sup.4C(O); Z.sub.4 is a bond, C(O), SO.sub.2 or —NR.sup.4C(O); R.sup.2 is C.sub.1-C.sub.5 alkyl or R.sup.8, wherein C.sub.1-C.sub.5 alkyl is optionally substituted with one or more substituents independently selected from halo, OH, CN, oxo, —OC.sub.1-C.sub.4 alkyl, —OC.sub.3-C.sub.5 cycloalkyl, —Z.sub.3—R.sup.11 and R.sup.10, wherein C.sub.1-C.sub.4 alky and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN;

R.sup.3 is hydrogen, F, OH, OCH.sub.3, C.sub.1-C.sub.3 alkyl, cyclopropyl, or one R.sup.3 is fused with R.sup.5 or R.sup.7 to form CH.sub.2, CH.sub.2—CH.sub.2 or CH.sub.2OCH.sub.2; R.sup.4 is hydrogen or C.sub.1-C.sub.3 alkyl; R.sup.4A is hydrogen, halo, OH or C.sub.1-C.sub.3 alkyl; R.sup.5 is hydrogen, F, OH, OCH.sub.3, C.sub.1-C.sub.3 alkyl, cyclopropyl or is fused with one R.sup.3 to form CH.sub.2, CH.sub.2—CH.sub.2 or CH.sub.2OCH.sub.2; R.sup.6 is hydrogen, halo, C.sub.1-C.sub.5 alkyl, CN, 3-6 membered cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered aryl or 5-6 membered heteroaryl, wherein 3-6 membered cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered aryl and 5-6 membered heteroaryl are optionally substituted with one or more substituents independently selected from halo, methyl, halomethyl, OH or OCH.sub.3 and wherein C.sub.1-C.sub.5 alkyl is optionally substituted with one or more substituents independently selected from halo, OH and OCH.sub.3; R.sup.7 is hydrogen, F, OH, OCH.sub.3, C.sub.1-C.sub.3 alkyl or is fused with one R.sup.3 to form CH.sub.2, CH.sub.2—CH.sub.2 or CH.sub.2OCH.sub.2; R.sup.8 is 3-6 membered cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered aryl or 5-6 membered heteroaryl, optionally fused or substituted with R.sup.8A; R.sup.8A is 3-6 membered cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered aryl or 5-6 membered heteroaryl; R.sup.9 is hydrogen, C.sub.1-C.sub.3 alkyl, or is fused with R.sup.9 to form CH.sub.2 or CH.sub.2—CH.sub.2; R.sup.10 is 3-6 membered cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered aryl or 5-6 membered heteroaryl, optionally fused or substituted with R.sup.8A; R.sup.11 is C.sub.1-C.sub.4 alkyl, NH.sub.2, NHC.sub.1-C.sub.3 alkyl, NHC.sub.3-C.sub.5 cycloalkyl or N(C.sub.1-C.sub.3 alkyl).sub.2, wherein C.sub.1-C.sub.4 alkyl, C.sub.1-C.sub.3 alkyl and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN; R.sup.12 is C.sub.1-C.sub.4 alkyl, C.sub.3-C.sub.5 cycloalkyl, NH.sub.2, NHC.sub.1-C.sub.3 alkyl, NHC.sub.3-C.sub.5 cycloalkyl or N(C.sub.1-C.sub.3 alkyl).sub.2, wherein C.sub.1-C.sub.4 alky, C.sub.1-C.sub.3 alkyl and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN; R.sup.13 is hydrogen, halo or C.sub.1-C.sub.3 alkyl; R.sup.14 is hydrogen, halo or C.sub.1-C.sub.3 alkyl; and R.sup.8, R.sup.10 and R.sup.8A are optionally substituted with one or more substituents independently selected from halo, OH, CN, —OC.sub.1-C.sub.4 alkyl, —OC.sub.3-C.sub.5 cycloalkyl and —Z.sub.4—R.sup.12 wherein C.sub.1-C.sub.4 alky and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN; or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 wherein X.sub.1 is C, and X.sub.2 is N; or X.sub.1 is N, and X.sub.2 is C, or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 1 wherein X.sub.1 is N, and X.sub.2 is C, or a pharmaceutically acceptable salt thereof.

4. The compound according to claim 1 wherein X.sub.1 is C, and X.sub.2 is N, or a pharmaceutically acceptable salt thereof.

5. The compound according to claim 1, wherein X.sub.3 is CH, or a pharmaceutically acceptable salt thereof.

6. The compound according to claim 1, wherein A is pyrazole or triazole, substituted with R.sup.1 and R.sup.1A, or a pharmaceutically acceptable salt thereof.

7. The compound according to claim 6, wherein A is triazole, substituted with R.sup.1 and R.sup.1A, or a pharmaceutically acceptable salt thereof.

8. The compound according to claim 1, wherein RA is hydrogen or C.sub.1-C.sub.3 alkyl optionally substituted with one or more substituents independently selected from halo, OH and OCH.sub.3, or a pharmaceutically acceptable salt thereof.

9. The compound according to claim 8, wherein R.sup.1A is hydrogen or CH.sub.3, or a pharmaceutically acceptable salt thereof.

10. The compound according to claim 9, wherein R.sup.1A is hydrogen, or a pharmaceutically acceptable salt thereof.
11. The compound according to claim 1, wherein R.sup.1 is CH.sub.3, or a pharmaceutically acceptable salt thereof.
12. The compound according to claim 1, wherein Y is NH or O, or a pharmaceutically acceptable salt thereof.
13. The compound according to claim 12, wherein Y is O, or a pharmaceutically acceptable salt thereof.
14. The compound according to claim 1, wherein R.sup.6 is CN, F, Cl, CH.sub.3, CF.sub.3 or cyclopropyl, or a pharmaceutically acceptable salt thereof.
15. The compound according to claim 14, wherein R.sup.6 is CN, F or Cl, or a pharmaceutically acceptable salt thereof.
16. The compound according to claim 15, wherein R.sup.6 is CN, or a pharmaceutically acceptable salt thereof.
17. The compound according to claim 16, wherein R.sup.6 is Cl, or a pharmaceutically acceptable salt thereof.
18. The compound according to claim 1, wherein Z is a bond, cyclobutyl, azetidine or piperidine, or a pharmaceutically acceptable salt thereof.
19. The compound according to claim 18, wherein Z is a bond, azetidine or piperidine, or a pharmaceutically acceptable salt thereof.
20. The compound according to claim 19, wherein Z is a bond, or a pharmaceutically acceptable salt thereof.
21. The compound according to claim 1, wherein Z is CHR.sup.9A, Z.sub.1 is CH.sub.2 and R.sup.9 is fused with R.sup.9A to form CH.sub.2, or a pharmaceutically acceptable salt thereof.
22. The compound according to claim 1, wherein Z.sub.1 is a bond, or a pharmaceutically acceptable salt thereof.
23. The compound according to claim 1, wherein X.sub.4 is N, or a pharmaceutically acceptable salt thereof.
24. The compound according to claim 1, wherein X.sub.4 is C—R.sup.9, wherein R.sup.9 is hydrogen or CH.sub.3, or a pharmaceutically acceptable salt thereof.
25. The compound according to claim 1, wherein Y.sub.1 is a bond, CHR.sup.7, CH.sub.2—CHR.sup.7 or CHR.sup.7—CH.sub.2, wherein R.sup.7 is selected from hydrogen, F, OH and CH.sub.3, or a pharmaceutically acceptable salt thereof.
26. The compound according to claim 1, wherein Y.sub.2 is a bond, CHR.sup.3, CH.sub.2—CHR.sup.3 or CHR.sup.3—CH.sub.2, wherein R.sup.3 is selected from hydrogen, F, OH and CH.sub.3, or a pharmaceutically acceptable salt thereof.
27. The compound according to claim 1, wherein Y.sub.3 is CR.sup.4R.sup.5 or CF.sub.2, wherein R.sup.4 is hydrogen or CH.sub.3 and R.sup.5 is hydrogen, F, OH or CH.sub.3, or a pharmaceutically acceptable salt thereof.
28. The compound according to claim 1, wherein Y.sub.3 is CR.sup.4R.sup.5 wherein R.sup.4 is hydrogen and R.sup.5 is fused with one R.sup.3 to form CH.sub.2, CH.sub.2—CH.sub.2 or CH.sub.2OCH.sub.2, or a pharmaceutically acceptable salt thereof.
29. The compound according to claim 28, wherein Y.sub.4 is CR.sup.3R.sup.4 wherein R.sup.4 is hydrogen or CH.sub.3 and R.sup.3 is fused with R.sup.5 to form CH.sub.2, CH.sub.2—CH.sub.2 or CH.sub.2OCH.sub.2, or a pharmaceutically acceptable salt thereof.
30. The compound according to claim 1, wherein Y.sub.4 is CR.sup.3R.sup.4 or CF.sub.2 wherein R.sup.4 is hydrogen or CH.sub.3 and R.sup.3 is hydrogen, F, OH or CH.sub.3, or a pharmaceutically acceptable salt thereof.
31. The compound according to claim 1, wherein Y.sub.3 is CR.sup.4R.sup.5, wherein R.sup.4 is hydrogen or CH.sub.3 and R.sup.5 is hydrogen or CH.sub.3, or a pharmaceutically acceptable salt

thereof.
32. The compound according to claim 1, wherein Y.sub.5 is CR.sup.13R.sup.14, CR.sup.13R.sup.14—CH.sub.2 or CH.sub.2—CR.sup.13R.sup.14, wherein R.sup.13 and R.sup.14 are independently selected from H and CH.sub.3; and Y.sub.6 is CR.sup.13R.sup.14, CR.sup.13R.sup.14—CH.sub.2 or CH.sub.2—CR.sup.13R.sup.14, wherein R.sup.13 and R.sup.4 are independently selected from H and CH.sub.3; or a pharmaceutically acceptable salt thereof.
33. The compound according to claim 32, wherein Y.sub.5 is CH.sub.2 or CH.sub.2—CH.sub.2 and Y.sub.6 is CH.sub.2 or CH.sub.2—CH.sub.2, or a pharmaceutically acceptable salt thereof.
34. The compound according to claim 32, wherein Y.sub.5 and Y.sub.6 are CH.sub.2, or a pharmaceutically acceptable salt thereof.
35. The compound according to claim 1, wherein R.sup.2 is C.sub.1-C.sub.3 alkyl optionally substituted with one, two, three or four substituents independently selected from halo, OH, CN, oxo, —OC.sub.1-C.sub.4 alkyl, —OC.sub.3-C.sub.5 cycloalkyl, —Z.sub.3—R.sup.11 and R.sup.10, wherein C.sub.1-C.sub.4 alkyl and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN, or a pharmaceutically acceptable salt thereof.
36. The compound according to claim 1, wherein R.sup.2 is selected from: ##STR00644## optionally substituted with one, two, three or four substituents independently selected from halo, OH, CN, oxo, —OC.sub.1-C.sub.4 alkyl, —OC.sub.3-C.sub.5 cycloalkyl, —Z.sub.3—R.sup.11 and R.sup.10, wherein C.sub.1-C.sub.4 alkyl and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN, wherein * indicates the connection point to Y, or a pharmaceutically acceptable salt thereof.
37. The compound according to claim 36, wherein R.sup.2 is selected from: ##STR00645## optionally substituted with one, two, three or four substituents independently selected from halo, OH, CN, oxo, —OC.sub.1-C.sub.4 alkyl, —OC.sub.3-C.sub.5 cycloalkyl, —Z.sub.3—R.sup.11 and R.sup.10, wherein C.sub.1-C.sub.4 alkyl and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN, wherein * indicates the connection point to Y, or a pharmaceutically acceptable salt thereof.
38. The compound according to claim 1, wherein R.sup.10 is 4-6 membered heterocycloalkyl or 5-6 membered heteroaryl, optionally substituted or fused with R.sup.8A, or a pharmaceutically acceptable salt thereof.
39. The compound according to claim 38, wherein R.sup.10 is 5-6 membered heteroaryl, optionally substituted or fused with R.sup.8A, or a pharmaceutically acceptable salt thereof.
40. The compound according to claim 1, wherein R.sup.10 is independently selected from cyclopropane, cyclobutane, cyclopropane, pyrrolidine, thiazole, pyrazole, triazole, phenyl, pyridine, pyrazine and pyridazine, optionally substituted or fused with R.sup.8A, or a pharmaceutically acceptable salt thereof.
41. The compound according to claim 1, wherein R.sup.10 and R.sup.8A are optionally substituted with one, two or three substituents independently selected from halo, OH, CN, —OC.sub.1-C.sub.4 alkyl, —OC.sub.3-C.sub.5 cycloalkyl and —Z.sub.4—R.sup.12 wherein C.sub.1-C.sub.4 alkyl and C.sub.3-C.sub.5 cycloalkyl are optionally substituted with one, two or three substituents independently selected from halo, OH, OCH.sub.3, methylamine, N,N-dimethylamine and CN, or a pharmaceutically acceptable salt thereof.
42. The compound according to claim 41, wherein R.sup.10 and R.sup.8A are optionally substituted with one or two substituents independently selected from F, Cl, CN, C.sub.1-C.sub.3 alkyl, CH.sub.2F, CHF.sub.2, CF.sub.3, —OCH.sub.3, —C(O)NH.sub.2 and —S(O).sub.2CH.sub.3, or a pharmaceutically acceptable salt thereof.
43. The compound according to claim 42, wherein R.sup.10 and R.sup.8A are optionally

substituted with one or two substituents independently selected from F, Cl, C.sub.1-C.sub.3 alkyl, CH.sub.2F, CHF.sub.2, CF.sub.3 and —OCH.sub.3, or a pharmaceutically acceptable salt thereof.

44. The compound according to claim 1, selected from: ##STR00646## ##STR00647## ##STR00648## ##STR00649## ##STR00650## ##STR00651## ##STR00652## ##STR00653## ##STR00654## ##STR00655## ##STR00656## ##STR00657## ##STR00658## ##STR00659## ##STR00660## ##STR00661## or a pharmaceutically acceptable salt thereof.

45. A pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt thereof, according to claim 1, and a pharmaceutically acceptable carrier, diluent or excipient.

46. A method of treating cancer, comprising administering to a patient in need of such treatment an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof.

47. The method of claim 46, wherein the cancer is selected from the group consisting of stomach cancer, hepatobiliary cancer, cancer of unknown primary, gallbladder cancer, gallbladder adenocarcinoma, bile duct cancer, intrahepatic bile duct cancer, extrahepatic bile duct cancer, sarcoma, esophagogastric cancer, gastroesophageal junction adenocarcinoma, gastric remnant adenocarcinoma, esophageal cancer, esophageal squamous cell cancer, esophageal adenocarcinoma, glioma, astrocytoma, oligodendroglioma, ependymoma, Non-Hodgkin Lymphoma, B-cell Non-Hodgkin Lymphoma, gastrointestinal stromal tumor, breast cancer, invasive ductal cancer, invasive lobular cancer, lung cancer, non-small-cell lung cancer, lung adenocarcinoma, squamous cell lung cancer and small-cell lung cancer, urothelial cancer, bladder cancer, urothelial bladder cancer, non-muscle invasive bladder cancer, muscle invasive bladder cancer, gastric cancer, gastric adenocarcinoma, pancreatic cancer, pancreatic adenocarcinoma, prostate cancer, prostate adenocarcinoma, colorectal cancer, colorectal adenocarcinoma, colon adenocarcinoma, multiple myeloma, liver cancer, hepatocellular cancer, fibrolamellar hepatocellular cancer, skin cancer, squamous cell skin cancer, melanoma, cutaneous melanoma, head and neck cancer, head and neck squamous cell cancer, hypopharyngeal cancer, laryngeal cancer, lip and oral cavity cancer, salivary gland cancer, glioblastoma, endometrial cancer, endometrial endometrioid adenocarcinoma, cervical cancer, ovarian cancer and epithelial ovarian cancer.

48. The method of claim 46, wherein the cancer is selected from the group consisting of hepatobiliary cancer, cancer of unknown primary, gallbladder cancer, gallbladder adenocarcinoma, bile duct cancer, intrahepatic bile duct cancer, extrahepatic bile duct cancer, breast cancer, invasive ductal cancer, invasive lobular cancer, liver cancer, hepatocellular cancer, fibrolamellar hepatocellular cancer, skin cancer, squamous cell skin cancer, melanoma, cutaneous melanoma, endometrial cancer and endometrial endometrioid adenocarcinoma.

49. The method of claim 46, wherein the cancer is selected from the group consisting of hepatobiliary cancer, gallbladder cancer, gallbladder adenocarcinoma, bile duct cancer, intrahepatic bile duct cancer, extrahepatic bile duct cancer, breast cancer, invasive ductal cancer, invasive lobular cancer, liver cancer, hepatocellular cancer, fibrolamellar hepatocellular cancer, endometrial cancer and endometrial endometrioid adenocarcinoma.

50. The method according to claim 46, wherein the cancer is FGFR2-associated cancer.

51. (canceled)

52. (canceled)

53. (canceled)

54. (canceled)

55. (canceled)

56. (canceled)

57. (canceled)