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Compounds for treating Huntington's disease

Abstract

The present description relates to compounds, forms, and pharmaceutical compositions thereof and methods of using such compounds, forms, or compositions thereof for treating or ameliorating Huntington's disease. In particular, the present description relates to substituted bicyclic heteroaryl compounds of Formula (I), forms and pharmaceutical compositions thereof and methods of using such compounds, forms, or compositions thereof for treating or ameliorating Huntington's disease.

Inventors: **Woll; Matthew G. (Dunellen, NJ), Amedzo; Lukiana (Somerset, NJ), Babu; Suresh (Pennington, NJ), Barraza; Scott J. (Piscataway, NJ), Bhattacharyya; Anuradha (Edison, NJ), Karp; Gary Mitchell (Princeton Junction, NJ), Mazzotti; Anthony R. (Rahway, NJ), Narasimhan; Jana (Scotch Plains, NJ), Patel; Jigar (Edison, NJ), Turpoff; Anthony (Hillsborough, NJ), Xu; Zhenrong (Chalfont, PA)**

Applicant: **PTC Therapeutics, Inc.** (South Plainfield, NJ)

Family ID: **1000008748565**

Assignee: **PTC Therapeutics, Inc. (South Plainfield, NJ)**

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Primary Examiner: Lundgren; Jeffrey S

Assistant Examiner: Bori; Ibrahim D

Attorney, Agent or Firm: McCarter & English, LLP

Background/Summary

CROSS-REFERENCE TO RELATED APPLICATIONS (1) This application is a continuation of U.S. patent application Ser. No. 16/617,450, filed Nov. 26, 2019, which in turn is a U.S. National Stage filing under 35 U.S.C. § 371 of International Application No. PCT/US2018/035954, filed Jun. 5, 2018, which in turn claims priority to U.S. Provisional Application No. 62/514,999, filed Jun. 5, 2017, the entire contents of which are incorporated by reference herein.

(1) An aspect of the present description relates to compounds, forms, and pharmaceutical compositions thereof and methods of using such compounds, forms, or compositions thereof useful for treating or ameliorating Huntington's disease. In particular, another aspect of the present description relates to substituted bicyclic heteroaryl compounds, forms and pharmaceutical compositions thereof and methods of using such compounds, forms, or compositions thereof for treating or ameliorating Huntington's disease.

BACKGROUND

(2) Huntington's disease (HD) is a progressive, autosomal dominant neurodegenerative disorder of the brain, having symptoms characterized by involuntary movements, cognitive impairment, and mental deterioration. Death, typically caused by pneumonia or coronary artery disease, usually occurs 13 to 15 years after the onset of symptoms. The prevalence of HD is between three and seven individuals per 100,000 in populations of western European descent. In North America, an estimated 30,000 people have HD, while an additional 200,000 people are at risk of inheriting the disease from an affected parent. The disease is caused by an expansion of uninterrupted trinucleotide CAG repeats in the “mutant” huntingtin (Htt) gene, leading to production of HTT (Htt protein) with an expanded poly-glutamine (polyQ) stretch, also known as a “CAG repeat” sequence. There are no current small molecule therapies targeting the underlying cause of the disease, leaving a high unmet need for medications that can be used for treating or ameliorating HD. Consequently, there remains a need to identify and provide small molecule compounds for treating or ameliorating HD.

(3) All other documents referred to herein are incorporated by reference into the present application as though fully set forth herein.

SUMMARY

(4) An aspect of the present description includes compounds comprising, a compound of Formula (I):

(5) ##STR00001##

or a form thereof, wherein R.sub.1, R.sub.2, W.sub.1, W.sub.2, W.sub.3, W.sub.4, W.sub.5 and W.sub.6 are as defined herein.

(6) An aspect of the present description includes a method for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of a compound of Formula (I) or a form thereof.

(7) An aspect of the present description includes a method for use of a compound of Formula (I) or a form or composition thereof for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of the compound of Formula (I) or a form or composition thereof.

(8) An aspect of the present description includes a use for a compound of Formula (I) or a form thereof for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of the compound of Formula (I) or a form thereof.

(9) An aspect of the present description includes a use for a compound of Formula (I) or a form thereof in the manufacture of a medicament for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of the medicament.

(10) An aspect of the present description includes a use for a compound of Formula (I) or a form thereof in a combination product with one or more therapeutic agents for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of the compound of Formula (I) or a form thereof in combination with an effective amount of the one or more agents.

Description

DETAILED DESCRIPTION
(1) An aspect of the present description relates to compounds comprising, a compound of Formula (I):
(2) ##STR00002##
or a form thereof, wherein: W.sub.1, W.sub.2, W.sub.3, W.sub.4, W.sub.5 and W.sub.6 are independently C—R.sub.a, C—R.sub.b or N, wherein, when one, two or three of W.sub.1, W.sub.5 and W.sub.6 are N, then W.sub.2, W.sub.3 and W.sub.4 are C—R.sub.a or C—R.sub.b, and wherein, when one, two or three of W.sub.2, W.sub.3 and W.sub.4 are N, then W.sub.1, W.sub.5 and W.sub.6 are C—R.sub.a or C—R.sub.b; R.sub.1 is aryl, heterocyclyl, heterocyclyl-amino, (heterocyclyl)(C.sub.1-8alkyl)amino or heteroaryl, wherein, each instance of heterocyclyl is optionally substituted with one, two or three R.sub.3 substituents and optionally, with one additional R.sub.4 substituent, or, wherein, alternatively, each instance of heterocyclyl is optionally substituted with one, two, three or four R.sub.3 substituents; R.sub.2 is aryl, heteroaryl, heteroaryl-amino or (heteroaryl)(C.sub.1-8alkyl)amino, wherein, each instance of aryl and heteroaryl is optionally substituted with one, two or three R.sub.6 substituents and optionally, with one additional R.sub.7 substituent; R.sub.a is, in each instance, independently selected from hydrogen, halogen or C.sub.1-8alkyl; R.sub.b is, in each instance, independently selected from hydrogen, halogen or C.sub.1-8alkyl; R.sub.3 is, in each instance, independently selected from cyano, halogen, hydroxy, C.sub.1-8alkyl, halo-C.sub.1-8alkyl, C.sub.1-8alkyl-carbonyl, C.sub.1-8alkoxy, halo-C.sub.1-8alkoxy, C.sub.1-8alkoxy-C.sub.1-8alkyl, C.sub.1-8 alkoxy-carbonyl, amino, C.sub.1-8alkyl-amino, (C.sub.1-8 alkyl).sub.2-amino, amino-C.sub.1-8alkyl, C.sub.1-8alkyl-amino-C.sub.1-8alkyl, amino-C.sub.1-8alkyl-amino, C.sub.1-8alkyl-amino-C.sub.1-8alkyl-amino, (C.sub.1-8alkyl-amino-C.sub.1-8alkyl).sub.2-amino, (C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl-amino, [(C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl].sub.2-amino, (C.sub.1-8alkyl-amino-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino, [(C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl]C.sub.1-8alkyl)amino, C.sub.1-8alkoxy-C.sub.1-8alkyl-amino, (C.sub.1-8alkoxy-C.sub.1-8 alkyl).sub.2-amino, (C.sub.1-8 alkoxy-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino, C.sub.1-8alkyl-carbonyl-amino, C.sub.1-8alkoxy-carbonyl-amino, hydroxy-C.sub.1-8alkyl, hydroxy-C.sub.1-8alkoxy-C.sub.1-8alkyl, hydroxy-C.sub.1-8alkyl-amino, (hydroxy-C.sub.1-8alkyl).sub.2-amino or (hydroxy-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino; R.sub.4 is C.sub.3-14cycloalkyl, C.sub.3-14Cycloalkyl-C.sub.1-8alkyl, C.sub.3-14cycloalkyl-amino, aryl-C.sub.1-8alkyl, aryl-C.sub.1-8alkoxy-carbonyl, aryl-sulfonyloxy-C.sub.1-8alkyl, heterocyclyl, heterocyclyl-C.sub.1-8alkyl, heteroaryl or heteroaryl-C.sub.1-8alkyl; wherein, each instance of C.sub.3-14cycloalkyl, aryl, heterocyclyl and heteroaryl is optionally substituted with one, two or three R.sub.5 substituents; R.sub.5 is, in each instance, independently selected from halogen, hydroxy, cyano, nitro, C.sub.1-8alkyl, halo-C.sub.1-8alkyl, C.sub.1-8alkoxy, halo-C.sub.1-8alkoxy, amino, C.sub.1-8alkyl-amino, (C.sub.1-8alkyl).sub.2-amino or C.sub.1-8alkyl-thio; R.sub.6 is, in each instance, independently selected from halogen, hydroxy, cyano, nitro, C.sub.1-8alkyl, C.sub.2-8alkenyl, cyano-C.sub.1-8alkyl, halo-C.sub.1-8alkyl, hydroxy-C.sub.1-8alkyl, C.sub.1-8alkoxy, halo-C.sub.1-8alkoxy, C.sub.1-8alkoxy-C.sub.1-8alkyl, C.sub.1-8alkoxy-C.sub.1-8alkoxy, amino, C.sub.1-8alkyl-amino, (C.sub.1-8alkyl).sub.2-amino, C.sub.1-8alkoxy-C.sub.1-8alkyl-amino, (C.sub.1-8alkoxy-C.sub.1-8alkyl,

C.sub.1-8 alkyl)amino or C.sub.1-8alkyl-thio; and, R.sub.7 is C.sub.3-14cycloalkyl, C.sub.3-14cycloalkyl-oxy, aryl, heterocyclyl, heteroaryl or heteroaryl-C.sub.1-8alkoxy; wherein a form of the compound is selected from the group consisting of a prodrug, salt, hydrate, solvate, clathrate, isotopologue, racemate, enantiomer, diastereomer, stereoisomer, polymorph and tautomer form thereof.

ASPECTS OF THE DESCRIPTION

(3) Another aspect of the present description includes a compound of Formula (I) comprising, a compound of Formula (I.1):

(4) ##STR00003##

or a form thereof, wherein: W.sub.1, W.sub.2, W.sub.3, W.sub.4, W.sub.5 and W.sub.6 are independently C—R.sub.a, C—R.sub.b or N, wherein, when one, two or three of W.sub.1, W.sub.5 and W.sub.6 are N, then W.sub.2, W.sub.3 and W.sub.4 are C—R.sub.a or C—R.sub.b, and wherein, when one, two or three of W.sub.2, W.sub.3 and W.sub.4 are N, then W.sub.1, W.sub.5 and W.sub.6 are C—R.sub.a or C—R.sub.b; R.sub.1 is C.sub.1-8alkyl, amino, C.sub.1-8alkyl-amino, (C.sub.1-8alkyl).sub.2-amino, C.sub.1-8alkoxy-C.sub.1-8alkyl-amino, (C.sub.1-8alkoxy-C.sub.1-8 alkyl).sub.2-amino, (C.sub.1-8 alkoxy-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino, amino-C.sub.1-8 alkyl, C.sub.1-8alkyl-amino-C.sub.1-8alkyl, (C.sub.1-8alkoxy-C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl, C.sub.1-8 alkoxy-C.sub.1-8 alkyl-amino-C.sub.1-8alkyl, (C.sub.1-8alkoxy-C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl, (C.sub.1-8alkoxy-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino-C.sub.1-8alkyl, amino-C.sub.1-8alkyl-amino, (amino-C.sub.1-8alkyl).sub.2-amino, (amino-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino, C.sub.1-8alkyl-amino-C.sub.1-8alkyl-amino, (C.sub.1-8alkyl-amino-C.sub.1-8alkyl).sub.2-amino, (C.sub.1-8 alkyl-amino-C.sub.1-8alkyl) (C.sub.1-8 alkyl)amino, (C.sub.1-8 alkyl).sub.2-amino-C.sub.1-8alkyl-amino, [(C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl]C.sub.1-8alkyl)amino, amino-C.sub.1-8 alkoxy, C.sub.1-8alkyl-amino-C.sub.1-8alkoxy, (C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkoxy, C.sub.1-8alkoxy-C.sub.1-8alkyl-amino-C.sub.1-8alkoxy, C.sub.1-8alkoxy-C.sub.1-8alkyl-amino-C.sub.1-8alkoxy, (C.sub.1-8alkoxy-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino-C.sub.1-8alkoxy, amino-C.sub.2-8alkenyl, C.sub.1-8alkyl-amino-C.sub.2-8alkenyl, (C.sub.1-8alkyl).sub.2-amino-C.sub.2-8alkenyl, amino-C.sub.2-8alkynyl, C.sub.1-8alkyl-amino-C.sub.2-8alkynyl, (C.sub.1-8alkyl).sub.2-amino-C.sub.2-8alkynyl, halo-C.sub.1-8alkyl-amino, (halo-C.sub.1-8alkyl).sub.2-amino, (halo-C.sub.1-8alkyl) (C.sub.1-8alkyl)amino, hydroxy-C.sub.1-8alkyl, hydroxy-C.sub.1-8alkoxy-C.sub.1-8alkyl, hydroxy-C.sub.1-8alkyl-amino, (hydroxy-C.sub.1-8alkyl).sub.2-amino, (hydroxy-C.sub.1-8alkyl) (C.sub.1-8alkyl)amino, hydroxy-C.sub.1-8alkyl-amino-C.sub.1-8alkyl, (hydroxy-C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl, (hydroxy-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino-C.sub.1-8alkyl, hydroxy-C.sub.1-8alkyl-amino-C.sub.1-8alkoxy, (hydroxy-C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkoxy, (hydroxy-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino-C.sub.1-8alkoxy, hydroxy-C.sub.1-8alkyl-amino-C.sub.1-8 alkyl-amino, (hydroxy-C.sub.1-8alkyl-amino-C.sub.1-8alkyl).sub.2-amino, (hydroxy-C.sub.1-8alkyl)amino-C.sub.1-8 alkyl-amino, (hydroxy-C.sub.1-8alkyl-amino-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino, (hydroxy-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino-C.sub.1-8alkyl-amino, [(hydroxy-C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl] (C.sub.1-8 alkyl)amino, [(hydroxy-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino-C.sub.1-8alkyl](C.sub.1-8alkyl)amino, C.sub.3-14cycloalkyl, aryl, aryl-C.sub.1-8alkyl-amino, (aryl-C.sub.1-8alkyl).sub.2-amino, (aryl-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino, aryl-C.sub.1-8alkyl-amino-C.sub.1-8 alkyl, (aryl-C.sub.1-8alkyl).sub.2-amino-C.sub.1-8 alkyl, (aryl-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino-C.sub.1-8alkyl, heterocyclyl, heterocyclyl-C.sub.1-8alkyl, heterocyclyl-C.sub.1-8alkoxy, heterocyclyl-amino, (heterocyclyl)(C.sub.1-8alkyl)amino, heterocyclyl-amino-C.sub.1-8alkyl, heterocyclyl-C.sub.1-8alkyl-amino, (heterocyclyl-C.sub.1-8 alkyl).sub.2-amino, (heterocyclyl-C.sub.1-8alkyl)(C.sub.1-8 alkyl)amino, heterocyclyl-C.sub.1-8alkyl-amino-C.sub.1-8alkyl, (heterocyclyl-C.sub.1-8alkyl).sub.2-amino-C.sub.1-8 alkyl, (heterocyclyl-C.sub.1-8 alkyl)(C.sub.1-8 heterocyclyl-oxy, heterocyclyl-carbonyl, heterocyclyl-carbonyl-oxy, heteroaryl, heteroaryl-

C.sub.1-8alkyl, heteroaryl-C.sub.1-8alkoxy, heteroaryl-amino, heteroaryl-C.sub.1-8alkyl-amino, (heteroaryl-C.sub.1-8alkyl).sub.2-amino, (heteroaryl-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino, heteroaryl-C.sub.1-8alkyl-amino-C.sub.1-8alkyl, (heteroaryl-C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl or (heteroaryl-C.sub.1-8 alkyl)(C.sub.1-8alkyl)amino-C.sub.1-8 alkyl, wherein, each instance of C.sub.3-14cycloalkyl, aryl, heterocyclyl and heteroaryl is optionally substituted with one, two or three R.sub.3 substituents and optionally, with one additional R.sub.4 substituent, or, wherein, alternatively, each instance of C.sub.3-14cycloalkyl, aryl, heterocyclyl and heteroaryl is optionally substituted with one, two, three or four R.sub.3 substituents; R.sub.2 is aryl, heteroaryl, heteroaryl-amino or (heterocyclyl)(C.sub.1-8alkyl)amino, wherein, each instance of aryl and heteroaryl is optionally substituted with one, two or three R.sub.6 substituents and optionally, with one additional R.sub.7 substituent; R.sub.a is, in each instance, independently selected from hydrogen, or C.sub.1-8alkyl; R.sub.b is, in each instance, independently selected from hydrogen, or halogen; R.sub.3 is, in each instance, independently selected from cyano, halogen, hydroxy, halo-C.sub.1-8alkyl, C.sub.1-8alkyl-carbonyl, C.sub.1-8alkoxy, halo-C.sub.1-8alkoxy, C.sub.1-8 alkoxy-C.sub.1-8alkyl, C.sub.1-8 alkoxy-carbonyl, amino, C.sub.1-8 alkyl-amino, amino-C.sub.1-8 alkyl, C.sub.1-8 alkyl-amino-C.sub.1-8alkyl, amino-C.sub.1-8alkyl-amino, C.sub.1-8alkyl-amino-C.sub.1-8alkyl-amino, (C.sub.1-8alkyl-amino-C.sub.1-8alkyl).sub.2-amino, (C.sub.1-8alkyl-amino, [(C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl].sub.2-amino, (C.sub.1-8 alkyl-amino-C.sub.1-8alkyl)(C.sub.1-8 alkyl)amino, [(C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl](C.sub.1-8alkyl)amino, C.sub.1-8alkoxy-C.sub.1-8alkyl-amino, (C.sub.1-8 alkoxy-C.sub.1-8 alkyl).sub.2-amino, (C.sub.1-8 alkoxy-C.sub.1-8 alkyl)(C.sub.1-8 alkyl)amino, C.sub.1-8 alkyl-carbonyl-amino, C.sub.1-8alkoxy-carbonyl-amino, hydroxy-C.sub.1-8 alkyl, hydroxy-C.sub.1-8 alkoxy-C.sub.1-8alkyl, hydroxy-C.sub.1-8alkyl-amino, (hydroxy-C.sub.1-8alkyl).sub.2-amino or (hydroxy-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino; R.sub.4 is C.sub.3-14cycloalkyl, C.sub.3-14Cycloalkyl-C.sub.1-8alkyl, C.sub.3-14cycloalkyl-amino, aryl-C.sub.1-8alkyl, aryl-C.sub.1-8alkoxy-carbonyl, aryl-sulfonyloxy-C.sub.1-8alkyl, heterocyclyl, heterocyclyl-C.sub.1-8alkyl, heteroaryl or heteroaryl-C.sub.1-8 alkyl; wherein, each instance of C.sub.3-14cycloalkyl, aryl, heterocyclyl and heteroaryl is optionally substituted with one, two or three R.sub.5 substituents; R.sub.5 is, in each instance, independently selected from halogen, hydroxy, cyano, nitro, C.sub.1-8alkyl, halo-C.sub.1-8 alkyl, C.sub.1-8alkoxy, halo-C.sub.1-8 alkoxy, hydroxy-C.sub.1-8 alkyl, amino, C.sub.1-8 alkyl-amino, (C.sub.1-8alkyl).sub.2-amino, (C.sub.1-8 alkyl).sub.2-amino-C.sub.1-8alkyl, C.sub.1-8alkyl-thio or heteroaryl-C.sub.1-8alkyl; R.sub.6 is, in each instance, independently selected from halogen, hydroxy, cyano, nitro, C.sub.1-8alkyl, C.sub.2-8alkenyl, cyano-C.sub.1-8alkyl, halo-C.sub.1-8alkyl, hydroxy-C.sub.1-8alkyl, C.sub.1-8alkoxy, halo-C.sub.1-8alkoxy, C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkoxy, C.sub.1-8alkoxy-C.sub.1-8alkyl, C.sub.1-8alkoxy-C.sub.1-8alkoxy, amino, C.sub.1-8alkyl-amino, C.sub.1-8alkyl).sub.2-amino, C.sub.1-8alkoxy-C.sub.1-8alkyl-amino, (C.sub.1-8alkoxy-C.sub.1-8alkyl, C.sub.1-8alkyl)amino or C.sub.1-8alkyl-thio; and, R.sub.7 is C.sub.1-14cycloalkyl, C.sub.1-14cycloalkyl-oxy, aryl, heterocyclyl, heteroaryl or heteroaryl-C.sub.1-8alkoxy. One aspect includes a compound of Formula (I), wherein W.sub.1 is N. Another aspect includes a compound of Formula (I), wherein W.sub.1 is N, W.sub.4 is C—R.sub.b and W.sub.2, W.sub.3, W.sub.5 and W.sub.6 are C—R.sub.a. One aspect includes a compound of Formula (I), wherein W.sub.2 is N. Another aspect includes a compound of Formula (I), wherein W.sub.2 is N, W.sub.4 is C—R.sub.b and W.sub.1, W.sub.3, W.sub.5 and W.sub.6 are C—R.sub.a. One aspect includes a compound of Formula (I), wherein W.sub.3 is N. Another aspect includes a compound of Formula (I), wherein W.sub.3 is N, W.sub.4 is C—R.sub.b and W.sub.1, W.sub.2, W.sub.5 and W.sub.6 are C—R.sub.a. One aspect includes a compound of Formula (I), wherein W.sub.4 is N. Another aspect includes a compound of Formula (I), wherein W.sub.4 is N and W.sub.1, W.sub.2, W.sub.3, W.sub.5 and W.sub.6 are independently C—R.sub.a. One aspect includes a compound of Formula (I), wherein W.sub.5 is N. Another aspect includes a compound of Formula (I), wherein W.sub.5 is N, W.sub.4 is C—R.sub.b and W.sub.1, W.sub.2, W.sub.3 and

W.sub.6 are C—R.sub.a. One aspect includes a compound of Formula (I), wherein W.sub.6 is N. Another aspect includes a compound of Formula (I), wherein W.sub.6 is N, W.sub.4 is C—R.sub.b and W.sub.1, W.sub.2, W.sub.3 and W.sub.5 are C—R.sub.a. Another aspect includes a compound of Formula (I), wherein R.sub.1 is aryl, heterocyclyl, heterocyclyl-amino, (heterocyclyl)(C.sub.1-8alkyl)amino, or heteroaryl. Another aspect includes a compound of Formula (I), wherein R.sub.1 is aryl or heteroaryl. Another aspect includes a compound of Formula (I), wherein R.sub.1 is aryl. Another aspect includes a compound of Formula (I), wherein R.sub.1 is heteroaryl. Another aspect includes a compound of Formula (I), wherein R.sub.1 is heterocyclyl, heterocyclyl-amino or (heterocyclyl)(C.sub.1-8alkyl)amino. Another aspect includes a compound of Formula (I), wherein R.sub.1 is heterocyclyl. Another aspect includes a compound of Formula (I), wherein R.sub.1 is heterocyclyl-amino. Another aspect includes a compound of Formula (I), wherein R.sub.1 is (heterocyclyl)(C.sub.1-8alkyl)amino. Another aspect includes a compound of Formula (I), wherein R.sub.a is hydrogen or C.sub.1-8alkyl. Another aspect includes a compound of Formula (I), wherein R.sub.b is hydrogen or halogen. Another aspect includes a compound of Formula (I), wherein R.sub.4 is heterocyclyl-C.sub.1-8alkyl or heteroaryl-C.sub.1-8alkyl. Another aspect includes a compound of Formula (I), wherein R.sub.5 is hydroxy-C.sub.1-8alkyl, (C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl, or heteroaryl-C.sub.1-8alkyl. Another aspect includes a compound of Formula (I), wherein R.sub.6 is halogen, hydroxy, cyano, C.sub.1-8alkyl, cyano-C.sub.1-8alkyl, halo-C.sub.1-8alkyl, hydroxy-C.sub.1-8alkyl, C.sub.1-8alkoxy, (C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkoxy-C.sub.1-8alkoxy-C.sub.1-8alkoxy, or C.sub.1-8alkoxy-C.sub.1-8alkyl-amino. Another aspect includes a compound of Formula (I), wherein R.sub.7 is C.sub.3-14cycloalkyl, heterocyclyl, or heteroaryl-C.sub.1-8alkoxy. One aspect includes a compound of Formula (I), wherein W.sub.1 and W.sub.5 are N. Another aspect includes a compound of Formula (I), wherein W.sub.1 and W.sub.5 are N, W.sub.4 is C—R.sub.b and W.sub.2, W.sub.3 and W.sub.6 are C—R.sub.a. One aspect includes a compound of Formula (I), wherein W.sub.1 and W.sub.6 are N. Another aspect includes a compound of Formula (I), wherein W.sub.1 and W.sub.6 are N, W.sub.4 is C—R.sub.b and W.sub.2, W.sub.3 and W.sub.5 are C—R.sub.a. One aspect includes a compound of Formula (I), wherein W.sub.2 and W.sub.3 are N. Another aspect includes a compound of Formula (I), wherein W.sub.2 and W.sub.3 are N, W.sub.4 is C—R.sub.b and W.sub.1, W.sub.5 and W.sub.6 are C—R.sub.a. One aspect includes a compound of Formula (I), wherein W.sub.2 and W.sub.4 are N. Another aspect includes a compound of Formula (I), wherein W.sub.2 and W.sub.4 are N, and W.sub.1, W.sub.3, W.sub.5 and W.sub.6 are independently C—R.sub.a. One aspect includes a compound of Formula (I), wherein W.sub.3 and W.sub.4 are N. Another aspect includes a compound of Formula (I), wherein W.sub.3 and W.sub.4 are N, and W.sub.1, W.sub.2, W.sub.5 and W.sub.6 are independently C—R.sub.a. One aspect includes a compound of Formula (I), wherein W.sub.5 and W.sub.6 are N. Another aspect includes a compound of Formula (I), wherein W.sub.5 and W.sub.6 are N, W.sub.4 is C—R.sub.b and W.sub.1, W.sub.2 and W.sub.3 are C—R.sub.a. Another aspect includes a compound of Formula (I), wherein W.sub.5 and W.sub.6 are N, W.sub.2 is C—R.sub.b and W.sub.1, W.sub.3 and W.sub.4 are C—R.sub.a. Another aspect includes a compound of Formula (I), wherein W.sub.5 and W.sub.6 are N, W.sub.3 is C—R.sub.b and W.sub.1, W.sub.2 and W.sub.4 are C—R.sub.a. One aspect includes a compound of Formula (I), wherein W.sub.1, W.sub.5 and W.sub.6 are N. Another aspect includes a compound of Formula (I), wherein W.sub.1, W.sub.5 and W.sub.6 are N, W.sub.4 is C—R.sub.b and W.sub.2 and W.sub.3 are C—R.sub.a. One aspect includes a compound of Formula (I), wherein W.sub.2, W.sub.3 and W.sub.4 are N. Another aspect includes a compound of Formula (I), wherein W.sub.2, W.sub.3 and W.sub.4 are N, and W.sub.1, W.sub.5 and W.sub.6 are independently C—R.sub.a. One aspect includes a compound of Formula (I), wherein R.sub.1 is heterocyclyl selected from azetidinyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, azepanyl, 1,4-diazepanyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, (3aR,6aR)-

hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-(1H)-yl, (3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, (4aR,7aR)-octahydro-6H-pyrrolo[3,4-b]pyridinyl, (4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-c]pyrazin-(2H)-one, hexahydropyrrolo[1,2-c]pyrazin-(1H)-yl, (7R,8aS)-hexahydropyrrolo[1,2-c]pyrazin-(1H)-yl, (8aS)-hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aR)-hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1,2-c:1,4-c′]dipyrrol-(3H)-yl, (8aS)-octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aR)-octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, 3-azabicyclo[3.1.0]hexyl, (1R,5S)-3-azabicyclo[3.1.0]hexyl, 8-azabicyclo[3.2.1]octyl, (1R,5S)-8-azabicyclo[3.2.1]octyl, 8-azabicyclo[3.2.1]oct-2-enyl, (1R,5S)-8-azabicyclo[3.2.1]oct-2-enyl, 9-azabicyclo[3.3.1]nonyl, (1R,5S)-9-azabicyclo[3.3.1]nonyl, 2,5-diazabicyclo[2.2.1]heptyl, (1S,4S)-2,5-diazabicyclo[2.2.1]heptyl, 1,4-diazabicyclo[3.1.1]heptyl, 3,6-diazabicyclo[3.2.0]heptyl, 2,5-diazabicyclo[2.2.2]octyl, 1,4-diazabicyclo[3.2.1]octyl, 3,8-diazabicyclo[3.2.1]octyl, (1R,5S)-3,8-diazabicyclo[3.2.1]octyl, 1,4-diazabicyclo[3.2.2]nonyl, azaspiro[3.3]heptyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptyl, 2,6-diazaspiro[3.4]octanyl, 1,7-diazaspiro[4.4]nonyl, 2,6-diazaspiro[3.5]nonyl, 2,7-diazaspiro[3.5]nonyl, 5,8-diazaspiro[3.5]nonyl, 2,7-diazaspiro[4.4]nonyl, 2,7-diazaspiro[4.5]decanyl or 6,9-diazaspiro[4.5]decyl; wherein, each instance of heterocyclyl is optionally substituted with R.sub.3 and R.sub.4 substituents. Another aspect includes a compound of Formula (I), wherein R.sub.1 is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-4-yl, piperazin-1-yl, azepan-4-yl, 1,4-diazepan-1-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, (3aS,6aS)-hexahydropyrrolo[3,4-h]pyrrol-1 (2H)-yl, (3aS,6aS)-hexahydropyrrolo[3,4-h]pyrrol-5(1H)-yl, (3aR,6aR)-hexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, (3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, (4aR,7aR)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, (4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, (7R,8aS)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, (8aS)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, (8aR)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1,2-c:1,4-c′]dipyrrol-2(3H)-yl, (8aS)-octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, (8aR)-octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, (1R,5S)-8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, (1R,5S)-8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, (1R,5S)-9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, (1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]hepant-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]hepant-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, (1R,5S)-3,8-diazabicyclo[3.2.1]ocant-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, azaspiro[3.3]hepant-2-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptanan-2-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7-diazaspiro[4.4]nonan-1-yl, 1,7,-diazaspiro[4.4]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl or 6,9-diazaspiro[4.5]decan-9-yl; wherein, each instance of heterocyclyl is optionally substituted with R.sub.3 and R.sub.4 substituents. Another aspect includes a compound of Formula (I), wherein R.sub.1 is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, azepanyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, 3-azabicyclo[3.1.0]hexyl, 8-azabicyclo[3.2.1]octyl, 2,5-

diazabicyclo[2.2.1]heptyl, 2,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.5]nonyl, 2,7-diazaspiro[3.5]nonyl. Another aspect includes a compound of Formula (I), wherein R.sub.1 is heterocyclyl selected from pyrrolidin-3-yl, piperidin-4-yl, piperazin-1-yl, azepan-4-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-2-yl, and 2,7-diazaspiro[3.5]nonan-7-yl. Another aspect includes a compound of Formula (I), wherein R.sub.1 is substituted heterocyclyl selected from N,N-dimethylpyrrolidin-3-amine, N,N-dimethylpiperidin-4-amine, N,N-4-trimethylpiperidin-4-amine, 1-methylpiperidin-4-yl, 1-ethylpiperidin-4-yl, 1-(propan-2-yl)piperidin-4-yl, 2-hydroxyethylpiperidin-4-yl, 2-fluoroethylpiperidin-4-yl, 2,2-difluoroethylpiperidin-4-yl, N,N-dimethyl-2-(piperidin-1-yl)ethan-1-amine, N,N-dimethyl-2-(piperidin-1-yl)propan-1-amine, (2S,6S)-2,6-dimethylpiperidin-4-yl, (2R,6S)-2,6-dimethylpiperidin-4-yl, (2S,6S)-2,6-diethylpiperidin-4-yl, (2S,6S)-(2,6-diethyl-1-methyl)piperidin-4-yl, (2S,6S)-1,2,6-trimethylpiperidin-4-yl, (2R,6S)-1,2,6-trimethylpiperidin-4-yl, (2S,4R,6R)-1,2,6-trimethylpiperidin-4-yl, (2R,6R)-1-ethyl-2,6-dimethylpiperidin-4-yl, (2R,6S)-[1-(2-fluoroethyl)-2,6-dimethyl]piperidin-4-yl, (ethyl-1-ol)piperidin-1-yl, 2,6-dimethylpiperidin-1-yl-ethan-1-ol, 3-(1H-pyrazol-1-yl)propyl]piperidin-4-yl, 3-(1H-benzimidazol-1-yl)propyl]piperidin-4-yl, 2-(1H-benzimidazol-1-yl)ethyl]piperidin-4-yl, 1-ethyl-1,2,3,6-tetrahydropyridin-4-yl, 2,2,6,6-tetramethylpiperidin-4-yl, 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl, (3R,5S)-3,5-dimethylpiperazin-1-yl, 1-methylazepan-4-yl, 1-ethylazepan-4-yl, 2-fluoroethyl)azepan-4-yl, azepan-1-yl-ethan-1-ol, 4-methyl-1,4-diazepan-1-yl, (3aS,6aS)-1-methylhexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl, (3aS,6aS)-5-methylhexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, (3aR,6aR)-1-methylhexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl, (3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, (3aR,6aS)-5-(2-hydroxyethyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, (3aR,6aS)-5-(propan-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, (3aR,6aS)-5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, (4aR,7aR)-1-methyloctahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, (4aR,7aR)-1-ethyloctahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, (4aR,7aR)-1-(2-hydroxyethyfloctahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, (4aS,7aS)-1-methyloctahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, (4aS,7aS)-1-(2-hydroxyethyfloctahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, (7R,8aS)-7-hydroxyhexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, (8aS)-8a-methyloctahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, (8aR)-8a-methyloctahydropyrrolo[1,2-c]pyrazin-2(1H)-yl, (1R,5S,6s)-6-(dimethylamino)-3-azabicyclo[3.1.0]hex-3-yl, N,N-dimethyl-3-azabicyclo[3.1.0]hexan-6-amine, (1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl, 9-methyl-9-azabicyclo[3.3.1]non-3-yl, (3-exo)-9-methyl-9-azabicyclo[3.3.1]non-3-yl, (1R,5S)-9-methyl-9-azabicyclo[3.3.1]non-3-yl, 5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl, (1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl, (1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl or (1S,4S)-5-ethyl-2,5-diazabicyclo[2.2.1]hept-2-yl. Another aspect includes a compound of Formula (I), wherein R.sub.1 is substituted heterocyclyl selected from N,N-dimethylpyrrolidin-3-amine, N,N-dimethylpiperidin-4-amine, N,N-4-trimethylpiperidin-4-amine, 1-methylpiperidin-4-yl, 1-ethyl-piperidin-4-yl, 1-(propan-2-yl)piperidin-4-yl, 2-hydroxyethylpiperidin-4-yl, 2-fluoroethylpiperidin-4-yl, 2,2-difluoroethylpiperidin-4-yl, N,N-dimethyl-2-(piperidin-1-yl)ethan-1-amine, N,N-dimethyl-2-(piperidin-1-yl)propan-1-amine, (2S,6S)-2,6-dimethylpiperidin-4-yl, (2R,6S)-2,6-dimethylpiperidin-4-yl, (2S,6S)-2,6-diethylpiperidin-4-yl, (2S,6S)-2,6-diethyl-1-methylpiperidin-4-yl, (2S,6S)-1,2,6-trimethylpiperidin-4-yl, (2R,6S)-1,2,6-trimethylpiperidin-4-yl, (2S,4R,6R)-1,2,6-trimethylpiperidin-4-yl, (2R,6R)-1-ethyl-2,6-dimethylpiperidin-4-yl, (2R,6S)-1-(2-fluoroethyl)-2,6-dimethylpiperidin-4-yl, piperidin-1-yl-ethan-1-ol, 2,6-dimethylpiperidin-1-yl-ethan-1-ol, 3-(1H-pyrazol-1-yl)propyl]piperidin-4-yl, 3-(1H-benzimidazol-1-yl)propyl]piperidin-4-yl, 2-(1H-benzimidazol-1-yl)ethyl]piperidin-4-yl, 1-ethyl-1,2,3,6-tetrahydropyridin-4-yl, 2,2,6,6-tetramethylpiperidin-4-yl, 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl, (3R,5S)-3,5-dimethylpiperazin-1-yl, 1-methylazepan-4-yl, 1-ethylazepan-4-yl, 2-fluoroethylazepan-4-yl,

azepan-1-yl-ethan-1-ol, N,N-dimethyl-3-azabicyclo[3.1.0]hexan-6-amine, 5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl or (1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl. One aspect includes a compound of Formula (I), wherein R.sub.1 is heterocyclyl-amino, wherein heterocyclyl is selected from azetidinyl, pyrrolidinyl, piperidinyl, 9-azabicyclo[3.3.1]nonyl or (1R,5S)-9-azabicyclo[3.3.1]nonyl; and, wherein, each instance of heterocyclyl is optionally substituted with R.sub.3 and R.sub.4 substituents. Another aspect includes a compound of Formula (I), wherein R.sub.1 is heterocyclyl-amino selected from azetidin-3-yl-amino, pyrrolidin-3-yl-amino, piperidin-4-yl-amino, 9-azabicyclo[3.3.1]non-3-yl-amino, (1R,5S)-9-azabicyclo[3.3.1]non-3-yl-amino, 9-methyl-9-azabicyclo[3.3.1]non-3-yl-amino, (3-exo)-9-methyl-9-azabicyclo[3.3.1]non-3-yl-amino or (1R,5S)-9-methyl-9-azabicyclo[3.3.1]non-3-yl-amino; wherein, each instance of heterocyclyl is optionally substituted with R.sub.3 and R.sub.4 substituents. One aspect includes a compound of Formula (I), wherein R.sub.1 is (heterocyclyl)(C.sub.1-8alkyl)amino, wherein heterocyclyl is selected from pyrrolidinyl or piperidinyl; and, wherein, each instance of heterocyclyl is optionally substituted with R.sub.3 and R.sub.4 substituents. Another aspect includes a compound of Formula (I), wherein R.sub.1 is (heterocyclyl)(C.sub.1-8alkyl)amino wherein heterocyclyl is piperidinyl. Another aspect includes a compound of Formula (I), wherein R.sub.1 is (heterocyclyl)(C.sub.1-8alkyl)amino selected from (pyrrolidin-3-yl)(methyl)amino or (piperidin-4-yl)(methyl)amino; wherein, each instance of heterocyclyl is optionally substituted with R.sub.3 and R.sub.4 substituents. One aspect includes a compound of Formula (I), wherein R.sub.3 is selected from cyano, halogen, hydroxy, oxo, C.sub.1-8alkyl, halo-C.sub.1-8alkyl, C.sub.1-8alkyl-carbonyl, C.sub.1-8alkoxy, halo-C.sub.1-8alkoxy, C.sub.1-8alkoxy-C.sub.1-8alkyl, C.sub.1-8alkoxy-carbonyl, amino, C.sub.1-8 alkyl-amino, (C.sub.1-8alkyl).sub.2-amino, amino-C.sub.1-8 C.sub.1-8 alkyl-amino-C.sub.1-8 alkyl, (C.sub.1-8 alkyl).sub.2-amino-C.sub.1-8alkyl, amino-C.sub.1-8 C.sub.1-8alkyl-amino-C.sub.1-8 alkyl-amino, (C.sub.1-8alkyl).sub.2-amino-C.sub.1-8 alkyl-amino, C.sub.1-8alkoxy-C.sub.1-8 alkyl-amino, C.sub.1-8alkyl-carbonyl-amino, C.sub.1-8 alkoxy-carbonyl-amino, hydroxy-C.sub.1-8 alkyl, hydroxy-C.sub.1-8 alkoxy-C.sub.1-8alkyl, hydroxy-C.sub.1-8alkyl-amino, (hydroxy-C.sub.1-8alkyl).sub.2-amino or (hydroxy-C.sub.1-8alkyl)(C.sub.1-8 alkyl)amino. Another aspect includes a compound of Formula (I), wherein R.sub.3 is selected from cyano, halogen, hydroxy, oxo, C.sub.1-8 alkyl, halo-C.sub.1-8alkyl, C.sub.1-8alkoxy, C.sub.1-8 alkoxy-C.sub.1-8alkyl, C.sub.1-8 alkoxy-carbonyl, amino, C.sub.1-8 alkyl-amino, (C.sub.1-8alkyl).sub.2-amino, amino-C.sub.1-8alkyl, C.sub.1-8 alkyl-amino-C.sub.1-8 alkyl, (C.sub.1-8 alkyl).sub.2-amino-C.sub.1-8alkyl, C.sub.1-8alkyl-amino-C.sub.1-8 alkyl-amino, C.sub.1-8 alkoxy-C.sub.1-8alkyl-amino, C.sub.1-8alkoxy-carbonyl-amino, hydroxy-C.sub.1-8alkyl, hydroxy-C.sub.1-8alkoxy-C.sub.1-8alkyl, hydroxy-C.sub.1-8alkyl-amino, (hydroxy-C.sub.1-8alkyl).sub.2-amino or (hydroxy-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino. Another aspect includes a compound of Formula (I), wherein R.sub.3 is C.sub.1-8alkyl selected from methyl, ethyl, propyl, isopropyl or tert-butyl. Another aspect includes a compound of Formula (I), R.sub.3 is C.sub.1-8alkyl selected from methyl, ethyl, propyl, isopropyl or tert-butyl. Another aspect includes a compound of Formula (I), wherein R.sub.3 is halo-C.sub.1-8alkyl selected from trihalo-methyl, dihalo-methyl, halo-methyl, trihalo-ethyl, dihalo-ethyl, halo-ethyl, trihalo-propyl, dihalo-propyl or halo-propyl; wherein, halo is selected from fluoro, chloro, bromo or iodo. Another aspect includes a compound of Formula (I), wherein R.sub.3 is halo-C.sub.1-8alkyl selected from trihalo-methyl, dihalo-methyl, halo-methyl, trihalo-ethyl, dihalo-ethyl, trihalo-propyl or dihalo-propyl; wherein, halo is selected from fluoro, chloro, bromo or iodo. Another aspect includes a compound of Formula (I), wherein R.sub.3 is hydroxy-C.sub.1-8alkyl selected from hydroxy-methyl, hydroxy-ethyl, hydroxy-propyl, dihydroxy-propyl, hydroxy-butyl or dihydroxy-butyl. Another aspect includes a compound of Formula (I), wherein R.sub.3 is hydroxy-C.sub.1-8alkyl selected from hydroxy-methyl, hydroxy-ethyl, dihydroxy-propyl, hydroxy-butyl or dihydroxy-butyl. Another aspect includes a compound of Formula (I), wherein R.sub.3 is C.sub.1-8alkoxy selected from methoxy, ethoxy, propoxy or isopropoxy. Another aspect includes a compound of Formula (I),

wherein R.sub.3 is halo-C.sub.1-8alkoxy selected from trihalo-methoxy, dihalo-methoxy, halo-methoxy, trihalo-ethoxy, dihalo-ethoxy, halo-ethoxy, trihalo-propoxy, dihalo-propoxy or halo-propoxy; wherein, halo is selected from fluoro, chloro, bromo or iodo. Another aspect includes a compound of Formula (I), wherein R.sub.3 is C.sub.1-8alkoxy-carbonyl-amino selected from methoxy-carbonyl-amino, ethoxy-carbonyl-amino, propoxy-carbonyl-amino, isopropoxy-carbonyl-amino, tert-butoxy-carbonyl-amino. Another aspect includes a compound of Formula (I), wherein R.sub.4 is C.sub.3-14cycloalkyl, C.sub.3-14cycloalkyl-C.sub.1-8alkyl, C.sub.3-14cycloalkyl-amino, aryl-C.sub.1-8alkyl, aryl-C.sub.1-8 alkoxy-carbonyl, aryl-sulfonyloxy-C.sub.1-8 alkyl, heterocyclyl, heterocyclyl-C.sub.1-8alkyl or heteroaryl; wherein, each instance of C.sub.3-14cycloalkyl, aryl, heterocyclyl and heteroaryl is optionally substituted with one, two or three R.sub.5 substituents. Another aspect includes a compound of Formula (I), wherein R.sub.5 is, in each instance, independently selected from halogen, hydroxy, cyano, nitro, C.sub.1-8alkyl, halo-C.sub.1-8alkyl, C.sub.1-8 alkoxy, halo-C.sub.1-8 alkoxy, hydroxy-C.sub.1-8alkyl, amino, C.sub.1-8 alkyl-amino, (C.sub.1-8 alkyl).sub.2-amino, (C.sub.1-8 alkyl).sub.2-amino-C.sub.1-8alkyl, C.sub.1-8alkyl-thio or heteroaryl-C.sub.1-8 alkyl. One aspect includes a compound of Formula (I), wherein R.sub.2 is aryl, heteroaryl, heteroaryl-amino, (heteroaryl)(C.sub.1-8 alkyl)amino or (heterocyclyl)(C.sub.1-8 alkyl)amino. Another aspect includes a compound of Formula (I), wherein R.sub.2 is aryl, heteroaryl, heteroaryl-amino or (heteroaryl)(C.sub.1-8 alkyl)amino. Another aspect includes a compound of Formula (I), wherein R.sub.2 is aryl. Another aspect includes a compound of Formula (I), wherein R.sub.2 is heteroaryl. Another aspect includes a compound of Formula (I), wherein R.sub.2 is heteroaryl-amino. Another aspect includes a compound of Formula (I), wherein R.sub.2 is (heteroaryl)(C.sub.1-8alkyl)amino. Another aspect includes a compound of Formula (I), wherein R.sub.2 is (heterocyclyl)(C.sub.1-8alkyl)amino. One aspect includes a compound of Formula (I), wherein R.sub.2 is heteroaryl selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridinyl, pyrimidinyl, 1H-indolyl, 2H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzothiazolyl, 1,3-benzoxazolyl, 9H-purinyl, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, 1H-pyrrolo[2,3-b]pyridinyl, 1H-pyrrolo[2,3-c]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, 2H-pyrazolo[3,4-c]pyridinyl, 2H-pyrazolo[4,3-b]pyridinyl, 2H-pyrazolo[4,3-c]pyridinyl, pyrazolo[1,5-a]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-c]pyrimidinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrazinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,3]oxazolo[4,5-c]pyridinyl, [1,3]thiazolo[4,5-c]pyridinyl, [1,3]thiazolo[5,4-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl or quinoxalinyl; wherein, each instance of heteroaryl is optionally substituted with R.sub.6 and R.sub.7 substituents. Another aspect includes a compound of Formula (I), wherein R.sub.2 is heteroaryl selected from thien-2-yl, thien-3-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 1H-imidazol-1-yl, 1H-imidazol-4-yl, 1,3-thiazol-2-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-4-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-indol-5-yl, 1H-indol-6-yl, 1H-indazol-5-yl, 2H-indazol-5-yl, indolizin-2-yl, benzofuran-2-yl, benzofuran-5-yl, benzothien-2-yl, benzothien-3-yl, 1H-benzimidazol-2-yl, 1H-benzimidazol-6-yl, 1,3-benzoxazol-2-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzothiazol-2-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl, 9H-purin-8-yl, furo[3,2-b]pyridin-2-yl, furo[3,2-c]pyridin-2-yl, furo[2,3-c]pyridin-2-yl, thieno[3,2-c]pyridin-2-yl, thieno[2,3-d]pyrimidin-6-yl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1H-pyrrolo[2,3-c]pyridin-2-yl, 1H-pyrrolo[2,3-c]pyridin-4-yl, pyrrolo[1,2-a]pyrimidin-7-yl, pyrrolo[1,2-a]pyrazin-7-yl, pyrrolo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-5-yl, 2H-pyrazolo[3,4-c]pyridin-5-yl, 2H-pyrazolo[4,3-b]pyridin-5-yl, 2H-pyrazolo[4,3-c]pyridin-5-yl, pyrazolo[1,5-a]pyrazin-2-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-c]pyrimidin-2-yl, imidazo[1,2-b]pyridazin-2-yl,

imidazo[1,2-b]pyridazin-6-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-a]pyrazin-6-yl, 3H-imidazo[4,5-b]pyridin-5-yl, imidazo[2,1-b][1,3]thiazol-6-yl, imidazo[2,1-b][1,3,4]thiadiazol-6-yl, [1,3]oxazolo[4,5-b]pyridin-2-yl, [1,3]oxazolo[4,5-c]pyridin-2-yl, [1,3]thiazolo[5,4-b]pyridin-5-yl, [1,3]thiazolo[5,4-c]pyridin-2-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, or quinoxalin-2-yl; wherein, each instance of heteroaryl is optionally substituted with R.sub.6 and R.sub.7 substituents. One aspect includes a compound of Formula (I), wherein R.sub.6 is selected from halogen, hydroxy, cyano, nitro, C.sub.1-8alkyl, halo-C.sub.1-8alkyl, hydroxy-C.sub.1-8alkyl, C.sub.1-8alkoxy, halo-C.sub.1-8 alkoxy, C.sub.1-8alkoxy-C.sub.1-8alkyl, C.sub.1-8alkoxy-C.sub.1-8alkoxy, (C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkoxy, heteroaryl-C.sub.1-8 alkoxy, aryl-oxy, (C.sub.1-8alkyl).sub.2-amino, C.sub.1-8alkoxy-C.sub.1-8 alkyl-amino, C.sub.1-8alkyl-thio, C.sub.3-14cycloalkyl; wherein, halogen and halo is selected from fluoro, chloro, bromo or iodo. Another aspect includes a compound of Formula (I), wherein R.sub.6 is C.sub.1-8alkyl selected from methyl, ethyl, propyl, isopropyl or tert-butyl. Another aspect includes a compound of Formula (I), wherein R.sub.6 is C.sub.1-8alkyl selected from methyl, ethyl, propyl, isopropyl or tert-butyl. Another aspect includes a compound of Formula (I), wherein R.sub.6 is halo-C.sub.1-8alkyl selected from trihalo-methyl, dihalo-methyl, halo-methyl, trihalo-ethyl, dihalo-ethyl, halo-ethyl, trihalo-propyl, dihalo-propyl or halo-propyl; wherein, halo is selected from fluoro, chloro, bromo or iodo. Another aspect includes a compound of Formula (I), wherein R.sub.7 is C.sub.3-14cycloalkyl, C.sub.3-14cycloalkyl-oxy, aryl, heterocyclyl or heteroaryl. One aspect includes a compound of Formula (I), wherein R.sub.a is hydrogen or C.sub.1-8alkyl. One aspect includes a compound of Formula (I), wherein R.sub.b is hydrogen or C.sub.1-8alkyl. Another aspect includes a compound of Formula (I), wherein R.sub.h is halo. One aspect of the compound of Formula (I) includes a compound selected from Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (Ie), Formula (If), Formula (Ig), Formula (Ih), Formula (Ii), Formula (Ij), Formula (Ik), Formula (Il), Formula (Im) or Formula (In):

(5) ##STR00004## ##STR00005## or a form thereof. Another aspect of the compound of Formula (I) includes the compound selected from Formula (Ib), Formula (Ic), Formula (Ie), Formula (If), Formula (Ig), Formula (Ii), Formula (Ij), Formula (Ik) Formula (Im) or Formula (In):

(6) ##STR00006## ##STR00007## or a form thereof. Another aspect of the compound of Formula (I) includes the compound selected from of Formula (Ia1), Formula (Ib 1), Formula (Ic1), Formula (Id1), Formula (Ie1), Formula (If1), Formula (Ig1), Formula (Ih1), Formula (Ii1), Formula (Ij1), Formula (Ik1), Formula (Il1), Formula (Im1) or Formula (In1), respectively:

(7) ##STR00008## ##STR00009## ##STR00010## or a form thereof. Another aspect of the compound of Formula (I) includes the compound selected from Formula (Ib 1), Formula (Ic1), Formula (Ie1), Formula (If1), Formula (Ig1), Formula (Ii1), Formula (Ij1), Formula (Ik1), Formula (Il1), Formula (Im1) or Formula (In1), respectively:

(8) ##STR00011## ##STR00012## or a form thereof. Another aspect of the compound of Formula (I) includes the compound of Formula (Ia1):

(9) ##STR00013## or a form thereof. Another aspect of the compound of Formula (I) includes the compound of Formula (Ib 1):

(10) ##STR00014## or a form thereof. Another aspect of the compound of Formula (I) includes the compound of Formula (Ic1):

(11) ##STR00015##

(12) or a form thereof.

(13) Another aspect of the compound of Formula (I) includes the compound of Formula (Id1):

(14) ##STR00016## or a form thereof. Another aspect of the compound of Formula (I) includes the compound of Formula (Ie1):

(15) ##STR00017## or a form thereof. Another aspect of the compound of Formula (I) includes the compound of Formula (If1):

(16) ##STR00018## or a form thereof. Another aspect of the compound of Formula (I) includes the

compound of Formula (Ig1):
(17) ##STR00019## or a form thereof. Another aspect of the compound of Formula (I) includes the compound of Formula (Ih1):
(18) ##STR00020## or a form thereof. Another aspect of the compound of Formula (I) includes the compound of Formula (Ii1):
(19) ##STR00021## or a form thereof. Another aspect of the compound of Formula (I) includes the compound of Formula (Ij1):
(20) ##STR00022## or a form thereof. Another aspect of the compound of Formula (I) includes the compound of Formula (Ik1):
(21) ##STR00023## or a form thereof. Another aspect of the compound of Formula (I) includes the compound of Formula (Il1):
(22) ##STR00024## or a form thereof. Another aspect of the compound of Formula (I) includes the compound of Formula (Im1):
(23) ##STR00025## or a form thereof. Another aspect of the compound of Formula (I) includes the compound of Formula (In1):
(24) ##STR00026## or a form thereof. One aspect of the compound of Formula (I) or a form thereof includes a compound selected from the group consisting of:
(25) ##STR00027## ##STR00028## ##STR00029## ##STR00030## ##STR00031## ##STR00032## ##STR00033## ##STR00034## ##STR00035## ##STR00036## ##STR00037## ##STR00038## ##STR00039## ##STR00040## ##STR00041## ##STR00042## ##STR00043## ##STR00044## ##STR00045## ##STR00046## ##STR00047## ##STR00048## ##STR00049## ##STR00050## ##STR00051## ##STR00052## ##STR00053## ##STR00054## ##STR00055## ##STR00056## ##STR00057## ##STR00058## ##STR00059## ##STR00060## ##STR00061## ##STR00062## ##STR00063## ##STR00064## ##STR00065## ##STR00066##
(26) ##STR00067## ##STR00068## ##STR00069## ##STR00070## ##STR00071## ##STR00072## ##STR00073## ##STR00074## ##STR00075## ##STR00076## ##STR00077## ##STR00078## ##STR00079## ##STR00080## ##STR00081## ##STR00082## ##STR00083## ##STR00084## ##STR00085## ##STR00086## ##STR00087## ##STR00088## ##STR00089## ##STR00090## ##STR00091## ##STR00092## ##STR00093## ##STR00094## ##STR00095## ##STR00096## ##STR00097## ##STR00098## ##STR00099## ##STR00100## ##STR00101## ##STR00102## wherein the form of the compound is selected from the group consisting of a salt, prodrug, hydrate, solvate, clathrate, isotopologue, racemate, enantiomer, diastereomer, stereoisomer, polymorph and tautomer form thereof. An aspect the compound of Formula (I) or a form thereof (wherein compound number (#1) indicates that the salt form was isolated) includes a compound selected from the group consisting of:
(27) TABLE-US-00001 Cpd Name 1.sup.1 2-(2-methyl-2H-indazol-5-yl)-6-(piperidin-4-yl)quinoline 2.sup.1 6-(1-ethylpiperidin-4-yl)-2-(2-methyl-2H-indazol-5-yl)quinoline 3.sup.1 6-(2-methyl-2H-indazol-5-yl)-2-(piperidin-4-yl)quinolone 4.sup.1 3-(2-methyl-2H-indazol-5-yl)-7-(1,2,3,6-tetrahydropyridin-4-yl)cinnoline 5.sup.1 4-methyl-6-(2-methyl-2H-indazol-5-yl)-2-(piperidin-4-yl)quinoline 6.sup.1 6-(2-methyl-2H-indazo1-5-yl)-2-(1-methylpiperidin-4-yl)quinoline 7 2-(2-methyl-2H-indazol-5-yl)-6-(piperazin-1-yl)quinoline 9.sup.1 2-(1-ethylpiperidin-4-yl)-6-(2-methyl-2H-indazol-5-yl)quinoline 10.sup.1 2-(2-methyl-2H-indazol-5-yl)-6-(piperidin-4-yl)quinazoline 11 6-(2,7-dimethyl-2H-indazol-5-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin- 4-yl)quinolin-2-amine 12 N-methyl-6-(2-methyl-2H-indazol-5-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)quinolin- 2-amine 13 6-(2,7-dimethyl-2H-indazol-5-yl)-2-(2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin- 4-yl)quinoline 14 6-(2,7-dimethyl-2H-indazol-5-yl)-2-(2,2,6,6-tetramethylpiperidin-4-yl)quinoline 15 6-(2,7-dimethyl-2H-indazol-5-yl)-2-(piperidin-4-yl)quinoline 16 7-(2,7-dimethyl-2H-indazol-5-yl)-3-(piperidin-4-yl)-1,2,4-benzotriazine 17 3-(2,7-dimethyl-2H-indazol-5-yl)-7-(piperidin-4-yl)-1,2,4-benzotriazine 18 6-(2,8-dimethylimidazo[1,2-a]pyrazin-6-yl)-2-(piperidin-4-yl)quinoline 19 6-(2,8-

dimethylimidazo[1,2-b]pyridazin-6-yl)-2-(piperidin-4-yl)quinoline 20 6-(2,7-dimethyl-2H-indazol-5-yl)-8-fluoro-2-(piperidin-4-yl)quinoline 23 6-(2,7-dimethyl-2H-indazol-5-yl)-2-(piperidin-4-yl)quinazoline 24.sup.1 6-[2-methyl-7-(trifluoromethyl)-2H-indazol-5-yl]-2-(piperidin-4-yl)quinoxaline 25.sup.1 3-(7-fluoro-2-methyl-2H-indazol-5-yl)-7-(piperidin-4-yl)-1,2,4-benzotriazine 26 2-methyl-5-[7-(piperidin-4-yl)-1,2,4-benzotriazin-3-yl]-2H-indazole-7-carbonitrile 27 3-(2,8-dimethylimidazo[1,2-a]pyridin-6-yl)-7-(piperidin-4-yl)-1,2,4-benzotriazine 28 3-(1,3-dimethylpyrrolo[1,2-a]pyrazin-7-yl)-7-(piperidin-4-yl)-1,2,4-benzotriazine 29 3-(2,7-dimethyl-2H-indazol-5-yl)-7-(piperidin-4-yl)quinoline 30 7-(2,7-dimethyl-2H-indazol-5-yl)-3-(piperidin-4-yl)isoquinoline 31.sup.1 6-(2,7-dimethyl-2H-indazol-5-yl)-2-(piperidin-4-yl)quinoxaline 32 5-fluoro-7-(7-fluoro-2-methyl-2H-indazol-5-yl)-3-(piperidin-4-yl)-1,2,4-benzotriazine 33 7-(2,7-dimethyl-2H-indazol-5-yl)-5-fluoro-3-(piperidin-4-yl)-1,2,4-benzotriazine 34.sup.1 6-(2,7-dimethyl-2H-indazol-5-yl)-8-fluoro-2-(piperidin-4-yl)quinazoline 35.sup.1 5-[8-fluoro-2-(piperidin-4-yl)quinazolin-6-yl]-2-methyl-2H-indazole-7-carbonitrile 36.sup.1 8-fluoro-6-(7-fluoro-2-methyl-2H-indazol-5-yl)-2-(piperidin-4-yl)quinazoline 37.sup.1 6-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-8-fluoro-2-(piperidin-4-yl)quinazoline 38.sup.1 6-(2,7-dimethyl-2H-indazol-5-yl)-5-fluoro-2-(piperidin-4-yl)quinazoline 39.sup.1 6-(2,7-dimethyl-2H-indazol-5-yl)-7-fluoro-2-(piperidin-4-yl)quinazoline 40 3-(2,8-dimethylimidazo[1,2-a]pyridin-6-yl)-5-fluoro-7-(piperidin-4-yl)- 1,2,4-benzotriazine 41 5-fluoro-3-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-7-(piperidin-4-yl)- 1,2,4-benzotriazine 42 7-(2,7-dimethyl-2H-indazol-5-yl)-5-fluoro-N-methyl-N-(piperidin-4-yl)- 1,2,4-benzotriazin-3-amine 43 3-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-7-(piperidin-4-yl)-1,2,4-benzotriazine 44 3-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-(piperidin-4-yl)-1,2,4-benzotriazine 45.sup.1 6-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-8-fluoro-2-(piperidin-4-yl)quinoline 46 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(piperidin-4-yl)- 1,2,4-benzotriazine 47.sup.1 6-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-8-fluoro-2-(1-methylpiperidin- 4-yl)quinoline 48.sup.1 6-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-2-(1-ethylpiperidin-4-yl)- 8-fluoroquinoline 49.sup.1 8-fluoro-6-(7-methoxy-2-methyl-2H-indazol-5-yl)-2-(piperidin-4-yl)quinoline 50.sup.1 8-fluoro-6-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-(piperidin-4-yl)quinoline 51.sup.1 8-fluoro-6-(8-methoxy-2-methylimidazo[1,2-b]pyridazin-6-yl)-2-(piperidin- 4-yl)quinoline 52 3-(7-methoxy-2-methyl-2H-indazol-5-yl)-7-(piperidin-4-yl)-1,2,4-benzotriazine 53.sup.1 8-fluoro-6-[8-(2-methoxyethoxy)-2-methylimidazo[1,2-b]pyridazin-6-yl]-2-(piperidin- 4-yl)quinoline 54.sup.1 6-[8-fluoro-2-(piperidin-4-yl)quinolin-6-yl]-N-(2-methoxyethyl)- 2-methylimidazo[1,2-b]pyridazin-8-amine 55.sup.1 7-(2,7-dimethyl-2H-indazol-5-yl)-5-fluoro-3-(1,2,3,6-tetrahydropyridin-4-yl)cinnoline 56.sup.1 7-(8-azabicyclo[3.2.1]oct-3-yl)-3-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)- 1,2,4-benzotriazine 57.sup.1 3-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-7-(piperidin-4-yl)- 1,2,4-benzotriazine 58.sup.1 5-fluoro-7-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-3-(piperidin-4-yl)- 1,2,4-benzotriazine 59.sup.1 7-(8-ethoxy-2-methylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(piperidin-4-yl)- 1,2,4-benzotriazine 60.sup.1 7-(2,8-dimethylimidazo[1,2-a]pyridin-6-yl)-5-fluoro-3-(piperidin-4-yl)- 1,2,4-benzotriazine 61.sup.1 5-fluoro-7-[2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl]-3-(piperidin-4-yl)-1,2,4-benzotriazine 62.sup.1 7-(2,4-dimethyl-1,3-benzoxazol-6-yl)-5-fluoro-3-(piperidin-4-yl)-1,2,4-benzotriazine 63.sup.1 7-(2,4-dimethyl-1H-benzimidazol-6-yl)-5-fluoro-3-(piperidin-4-yl)-1,2,4-benzotriazine 64.sup.1 7-(1,3-dimethylpyrrolo[1,2-a]pyrazin-7-yl)-5-fluoro-3-(piperidin-4-yl)- 1,2,4-benzotriazine 65.sup.1 7-(2,7-dimethylpyrazolo[1,5-a]pyridin-5-yl)-5-fluoro-3-(piperidin-4-yl)- 1,2,4-benzotriazine 66.sup.1 7-(2,7-dimethyl-2H-pyrazolo[4,3-b]pyridin-5-yl)-5-fluoro-3-(piperidin-4-yl)- 1,2,4-benzotriazine 67.sup.1 7-(2,7-dimethyl-2H-pyrazolo[3,4-c]pyridin-5-yl)-5-fluoro-3-(piperidin-4-yl)- 1,2,4-benzotriazine 68 5-fluoro-7-(4-fluoro-2-methyl-1,3-benzoxazol-6-yl)-3-(piperidin-4-yl)- 1,2,4-benzotriazine 69.sup.1 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(1-methylpiperidin- 4-yl)-1,2,4-benzotriazine 70 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-3-(1-ethylpiperidin-4-yl)-5-fluoro- 1,2,4-benzotriazine

71.sup.1 7-(2,7-dimethyl-2H-indazol-5-yl)-5-fluoro-3-(piperidin-4-yl)isoquinoline 72.sup.1 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(piperidin-4-yl)isoquinoline 73.sup.1 7-(2,7-dimethyl-2H-indazol-5-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline 74.sup.1 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline 75 2-{4-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluorocinnolin-3-yl]piperidin- 1-yl}ethanol 76 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-3-(1-ethylpiperidin-4-yl)- 5-fluorocinnoline 77 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(l-propylpiperidin- 4-yl)cinnoline 78 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-[1-(propan-2-yl)piperidin- 4-yl]cinnoline 79 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(1-methylpiperidin- 4-yl)cinnoline 80.sup.1 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(piperazin-1-yl)cinnoline 81.sup.1 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-3-[(3R,5S)-3,5-dimethylpiperazin-1-yl]- 5-fluorocinnoline 82 6-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-8-fluoro-2-(piperidin-4-yl)quinoxaline 83.sup.1 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-[1-(2-fluoroethyl)piperidin- 4-yl]cinnoline 84.sup.1 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-3-(piperidin-4-yl)cinnoline 85 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-3-(1-ethylpiperidin-4-yl)cinnoline 86 1-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluorocinnolin-3-yl]-N,N-dimethylpyrrolidin-3-amine 87.sup.1 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-3-[(2S,6S)-2,6-dimethylpiperidin-4-yl]- 5-fluorocinnoline 88 1-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluorocinnolin-3-yl]- N,N-dimethylpiperidin-4-amine 89 (3R)-1-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluorocinnolin-3-yl]- N,N-dimethylpyrrolidin-3-amine 90 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-3-[(2R,4r,6S)-2,6-dimethylpiperidin- 4-yl]-5-fluorocinnoline 91.sup.1 5-fluoro-7-(2-methylimidazo[1,2-a]pyrimidin-6-yl)-3-(piperidin-4-yl)cinnoline 92.sup.1 5-fluoro-7-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-3-(piperidin-4-yl)cinnoline 93.sup.1 6-[5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl]-2-methylimidazo[1,2-a]pyridine- 8-carbonitrile 94.sup.1 5-fluoro-7-(2-methyl[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-(piperidin-4-yl)cinnoline 95.sup.1 5-fluoro-7-(2-methyl-2H-indazol-5-yl)-3-(piperidin-4-yl)cinnoline 96.sup.1 5-fluoro-7-(7-fluoro-2-methyl-2H-indazol-5-yl)-3-(piperidin-4-yl)cinnoline 97.sup.1 5-fluoro-7-(6-fluoro-2-methyl-2H-indazol-5-yl)-3-(piperidin-4-yl)cinnoline 98.sup.1 3-[1-(2,2-difluoroethyl)piperidin-4-yl]-7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)- 5-fluorocinnoline 99.sup.1 5-fluoro-7-(2-methylimidazo[1,2-b]pyridazin-6-yl)-3-(piperidin-4-yl)cinnoline 100.sup.1 3-(1-ethylpiperidin-4-yl)-5-fluoro-7-(2-methylimidazo[1,2-b]pyridazin-6-yl)cinnoline 101.sup.1 7-(1,3-dimethylpyrrolo[1,2-a]pyrazin-7-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline 102.sup.1 3-(1-ethylpiperidin-4-yl)-5-fluoro-7-(8-fluoro-2-methylimidazo[1,2-a]pyridin- 6-yl)cinnoline 103.sup.1 7-(2,8-dimethylimidazo[1,2-a]pyridin-6-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline 104.sup.1 5-[5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl]-2-methyl-2H-indazole-7-carbonitrile 105 7-(8-ethyl-2-methylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline 106 5-fluoro-7-(8-methoxy-2-methylimidazo[1,2-b]pyridazin-6-yl)-3-(piperidin- 4-yl)cinnoline 107 {6-[5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl]-2-methylimidazo[1,2-b]pyridazin- 8-yl}methanol 108 6-[5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl]-2-methylimidazo[1,2-b]pyridazine- 8-carbonitrile 109.sup.1 5-fluoro-7-(4-fluoro-2-methyl-2H-indazol-5-yl)-3-(piperidin-4-yl)cinnoline 110 6-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-2-(1-ethylpiperidin-4-yl)- 8-fluoroquinoxaline 111 3-(1-ethylpiperidin-4-yl)-5-fluoro-7-(8-methoxy-2-methylimidazo[1,2-b]pyridazin- 6-yl)cinnoline 112 7-(8-cyclopropyl-2-methylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(piperidin- 4-yl)cinnoline 113 {6-[3-(1-ethylpiperidin-4-yl)-5-fluorocinnolin-7-yl]- 2-methylimidazo[1,2-b]pyridazin-8-yl}methanol 114 6-[3-(1-ethylpiperidin-4-yl)-5-fluorocinnolin-7-yl]-2-methylimidazo[1,2-b]pyridazine- 8-carbonitrile 115.sup.1 7-(8-cyclopropyl-2-methylimidazo[1,2-b]pyridazin-6-yl)-3-(1-ethylpiperidin-4-yl)- 5-fluorocinnoline 116 7-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline 117.sup.1 5-fluoro-3-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-7-(1,2,3,6-tetrahydropyridin- 4-yl)cinnoline 118 7-(2,4-dimethyl-1,3-benzothiazol-6-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline 119 7-

(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-3-(1-ethylpiperidin-4-yl)-5-fluorocinnoline 120.sup.1 7-(2,4-dimethyl-1,3-benzothiazol-6-yl)-3-(1-ethylpiperidin-4-yl)-5-fluorocinnoline 121.sup.1 7-(8-ethyl-2-methylimidazo[1,2-b]pyridazin-6-yl)-3-(1-ethylpiperidin-4-yl)- 5-fluorocinnoline 122.sup.1 7-(8-ethyl-2-methylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(1-methylpiperidin- 4-yl)cinnoline 123.sup.1 2-{4-[7-(8-ethyl-2-methylimidazo[1,2-b]pyridazin-6-yl)-5-fluorocinnolin- 3-yl]piperidin-1-yl}ethan-1-ol 124 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro- 3-[(25,6S)-1,2,6-trimethylpiperidin-4-yl]cinnoline 125 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-3-[(2R,6R)-1-ethyl- 2,6-dimethylpiperidin-4-yl]-5-fluorocinnoline 126 7-(2,7-dimethyl-3H-imidazo[4,5-b]pyridin-5-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline 127.sup.1 2-{4-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluorocinnolin-3-yl]piperidin- 1-yl}-N,N-dimethylethan-1-amine 128.sup.1 5-fluoro-3-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-7-(piperidin-4-yl)cinnoline 129 3-(azepan-4-yl)-7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluorocinnoline 130 3-[(2S,6S)-2,6-diethylpiperidin-4-yl]-7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)- 5-fluorocinnoline 131 3-[(2S,6S)-2,6-diethyl-1-methylpiperidin-4-yl]-7-(2,8-dimethylimidazo[1,2-b]pyridazin- 6-yl)-5-fluorocinnoline 132 7-(2,7-dimethyl-3H-imidazo[4,5-b]pyridin-5-yl)-3-(1-ethylpiperidin-4-yl)- 5-fluorocinnoline 133.sup.1 7-(2,7-dimethyl[1,3]thiazolo[5,4-b]pyridin-5-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline 134.sup.1 5-fluoro-3-(7-fluoro-2-methyl-2H-indazol-5-yl)-7-(1,2,3,6-tetrahydropyridin- 4-yl)cinnoline 135.sup.1 7-(2,7-dimethyl[1,3]thiazolo[5,4-b]pyridin-5-yl)-3-(1-ethylpiperidin-4-yl)- 5-fluorocinnoline 136 7-(4,6-dimethyl[1,3]oxazolo[4,5-c]pyridin-2-yl)-3-(1-ethylpiperidin-4-yl)- 5-fluorocinnoline 137 7-(4,6-dimethyl[1,3]oxazolo[4,5-c]pyridin-2-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline 138.sup.1 2-({6-[5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl]-2-methylimidazo[1,2-b]pyridazin- 8-yl}oxy)-N,N-dimethylethan-1-amine 139.sup.1 3-({6-[5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl]-2-methylimidazo[1,2-b]pyridazin- 8-yl}oxy)-N,N-dimethylpropan-1-amine 140.sup.1 5-fluoro-7-{2-methyl-8-[2-(1H-pyrazol-1-yl)ethoxy]imidazo[1,2-b]pyridazin-6-yl}- 3-(piperidin-4-yl)cinnoline 141.sup.1 5-fluoro-7-{2-methyl-8-[3-(1H-pyrazol-1-yl)propoxy]imidazo[1,2-b]pyridazin-6-yl}- 3-(piperidin-4-yl)cinnoline 142.sup.1 5-fluoro-7-{8-[3-(1H-imidazol-1-yl)propoxy]-2-methylimidazo[1,2-b]pyridazin-6-yl}- 3-(piperidin-4-yl)cinnoline 143 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(pyrrolidin-3-yl)cinnoline 144 7-(1-ethylpiperidin-4-yl)-5-fluoro-3-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)cinnoline 145.sup.1 3-{1-[3-(1H-benzimidazol-1-yl)propyl]piperidin-4-yl}- 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluorocinnoline 146.sup.1 7-(5,7-dimethylfuro[2,3-c]pyridin-2-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline 147 7-(4,6-dimethyl[1,3]thiazolo[4,5-c]pyridin-2-yl)-3-(1-ethylpiperidin-4-yl)- 5-fluorocinnoline 148 7-(2,7-dimethyl[1,3]oxazolo[5,4-b]pyridin-5-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline 149 7-(4,6-dimethyl[1,3]thiazolo[4,5-c]pyridin-2-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline 150.sup.1 7-{8-[3-(1H-benzimidazol-1-yl)propoxy]-2-methylimidazo[1,2-b]pyridazin-6-yl}- 5-fluoro-3-(piperidin-4-yl)cinnoline 151.sup.1 5-fluoro-3-(7-fluoro-2-methyl-2H-indazol-5-yl)-7-(piperidin-4-yl)cinnoline 152 7-(2,7-dimethyl[1,3]oxazolo[5,4-b]pyridin-5-yl)-3-(1-ethylpiperidin-4-yl)- 5-fluorocinnoline 153.sup.1 7-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-5-fluoro-3-(7-fluoro-2-methyl-2H-indazol- 5-yl)cinnoline 154 7-(1-ethylpiperidin-4-yl)-5-fluoro-3-(7-fluoro-2-methyl-2H-indazol-5-yl)cinnoline 155 2-{(25,65)-4-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluorocinnolin-3-yl]- 2,6-dimethylpiperidin-1-yl}ethan-1-ol 156.sup.1 3-(2,8-dimethylimidazo[1,2-a]pyridin-6-yl)-5-fluoro-7-(1,2,3,6-tetrahydropyridin- 4-yl)cinnoline 157.sup.1 3-(2,7-dimethyl-2H-indazol-5-yl)-5-fluoro-7-(1,2,3,6-tetrahydropyridin-4-yl)cinnoline 158 3-{4-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluorocinnolin-3-yl]piperidin- 1-yl}-N,N-dimethylpropan-1-amine 159 3-{1-[2-(1H-benzimidazol-1-yl)ethyl]piperidin-4-yl}- 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluorocinnoline 160 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-{1-[3-(1H-pyrazol-1-yl)propyl]piperidin-4-yl}cinnoline 161 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-|(2R,6S)-1,2,6-trimethylpiperidin-4-yl]cinnoline 162 7-(2,7-dimethyl-2H-pyrazolo[4,3-b]pyridin-5-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline 163.sup.1 5-fluoro-7-(7-methoxy-2-methyl-2H-

pyrazolo[4,3-b]pyridin-5-yl)-3-(piperidin- 4-yl)cinnoline 164 7-(2,7-dimethyl-2H-pyrazolo[4,3-b]pyridin-5-yl)-3-(1-ethylpiperidin-4-yl)- 5-fluorocinnoline 165.sup.1 8-fluoro-2-(7-fluoro-2-methyl-2H-indazol-5-yl)-6-(1,2,3,6-tetrahydropyridin- 4-yl)quinazoline 166.sup.1 8-fluoro-2-(7-fluoro-2-methyl-2H-indazol-5-yl)-6-(1,2,3,6-tetrahydropyridin- 4-yl)quinoline 167.sup.1 3-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-7-(1,2,3,6-tetrahydropyridin- 4-yl)cinnoline 168 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-3-[(2R,6S)-1-ethyl-2,6-dimethylpiperidin- 4-yl]-5-fluorocinnoline 169 3-[(1R,3r,5S)-8-azabicyclo[3.2.1]octan-3-yl]-7-(2,8-dimethylimidazo[1,2-b]pyridazin- 6-yl)-5-fluorocinnoline 170 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-[(2R,6S)-1-(2-fluoroethyl)- 2,6-dimethylpiperidin-4-yl]cinnoline 171.sup.1 5-fluoro-3-(7-fluoro-2-methyl-2H-benzotriazol-5-yl)-7-(1,2,3,6-tetrahydropyridin- 4-yl)cinnoline 172 7-(7-ethyl-2-methyl-2H-pyrazolo[4,3-b]pyridin-5-yl)-5-fluoro-3-(piperidin- 4-yl)cinnoline 173.sup.1 3-(1-ethylpiperidin-4-yl)-5-fluoro-7-(7-methoxy-2-methyl-2H-pyrazolo[4,3-b]pyridin- 5-yl)cinnoline 174 7-(7-ethyl-2-methyl-2H-pyrazolo[4,3-b]pyridin-5-yl)-3-(1-ethylpiperidin-4-yl)- 5-fluorocinnoline 175.sup.1 5-[5-fluoro-7-(1,2,3,6-tetrahydropyridin-4-yl)cinnolin-3-yl]-2-methyl-2H-indazole- 7-carbonitrile 176.sup.1 6-[5-fluoro-3-(1-methylpiperidin-4-yl)cinnolin-7-yl]-2-methylimidazo[1,2-b]pyridazine- 8-carbonitrile 177.sup.1 3-(2,7-dimethyl-2H-indazol-5-yl)-5-fluoro-7-(piperidin-4-yl)cinnoline 178.sup.1 6-{5-fluoro-3-[1-(2-hydroxyethyl)piperidin-4-yl]cinnolin-7-yl}- 2-methylimidazo[1,2-b]pyridazine-8-carbonitrile 179.sup.1 6-{5-fluoro-3-[1-(2-fluoroethyl)piperidin-4-yl]cinnolin-7-yl}- 2-methylimidazo[1,2-b]pyridazine-8-carbonitrile 180 {6-[5-fluoro-3-(1-methylpiperidin-4-yl)cinnolin-7-yl]- 2-methylimidazo[1,2-b]pyridazin-8-yl}methanol 181.sup.1 2-(4-{5-fluoro-7-[8-(hydroxymethyl)-2-methylimidazo[1,2-b]pyridazin-6-yl]cinnolin- 3-yl}piperidin-1-yl)ethan-1-ol 182.sup.1 (6-{5-fluoro-3-[1-(2-fluoroethyl)piperidin-4-yl]cinnolin-7-yl}- 2-methylimidazo[1,2-b]pyridazin-8-yl)methanol 183 3-(2,7-dimethyl-2H-indazol-5-yl)-7-(1-ethylpiperidin-4-yl)-5-fluorocinnoline 184.sup.1 6-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-8-fluoro-2-(7-fluoro-2-methyl-2H-indazol- 5-yl)quinoline 185.sup.1 3-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-7-(piperidin-4-yl)cinnoline 186 3-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-(1-ethylpiperidin-4-yl)- 5-fluorocinnoline 187 {6-[5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl]-2-methylimidazo[1,2-b]pyridazin- 8-yl}acetonitrile 188 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(1-methylazepan- 4-yl)cinnoline 189 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-3-(1-ethylazepan-4-yl)-5-fluorocinnoline 190 2-{4-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluorocinnolin-3-yl]azepan- 1-yl}ethan-1-ol 191.sup.1 7-(5,7-dimethyl-1H-pyrrolo[2,3-c]pyridin-2-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline 192.sup.1 8-fluoro-2-(7-fluoro-2-methyl-2H-indazol-5-yl)-6-(piperidin-4-yl)quinoline 193.sup.1 6-(1-ethylpiperidin-4-yl)-8-fluoro-2-(7-fluoro-2-methyl-2H-indazol-5-yl)quinoline 194.sup.1 5-fluoro-7-[8-(1H-imidazol-1-yl)-2-methylimidazo[1,2-b]pyridazin-6-yl]-3-(piperidin- 4-yl)cinnoline 195.sup.1 5-fluoro-7-(2-methyl-8-phenoxyimidazo[1,2-b]pyridazin-6-yl)-3-(piperidin- 4-yl)cinnoline 196.sup.1 7-(4,6-dimethyl[1,3]thiazolo[5,4-c]pyridin-2-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline 197 7-(4,6-dimethyl[1,3]thiazolo[5,4-c]pyridin-2-yl)-3-(1-ethylpiperidin-4-yl)- 5-fluorocinnoline 198 3-(2,7-dimethyl-2H-indazol-5-yl)-5-fluoro-7-(2,3,6,7-tetrahydro-1H-azepin- 4-yl)cinnoline 199 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-[1-(2-fluoroethyl)azepan- 4-yl]cinnoline 200 3-(1-ethylpiperidin-4-yl)-5-fluoro-7-(2-methyl-8-phenoxyimidazo[1,2-b]pyridazin- 6-yl)cinnoline 201.sup.1 6-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-8-fluoro-2-(7-fluoro-2-methyl-2H-indazol- 5-yl)quinazoline 202.sup.1 6-(1-ethylpiperidin-4-yl)-8-fluoro-2-(7-fluoro-2-methyl-2H-indazol-5-yl)quinazoline 203 (3S,4S)-4-[3-(2,7-dimethyl-2H-indazol-5-yl)-5-fluorocinnolin-7-yl]piperidine-3,4-diol 204 5-fluoro-7-(2-methyl-8-propylimidazo[1,2-b]pyridazin-6-yl)-3-(piperidin-4-yl)cinnoline 205.sup.1 {6-[3-(1-ethylpiperidin-4-yl)-5-fluorocinnolin-7-yl]-2-methylimidazo[1,2-b]pyridazin- 8-yl}acetonitrile 206 2-{6-[3-(1-ethylpiperidin-4-yl)-5-fluorocinnolin-7-ylJ- 2-methylimidazo[1,2-b]pyridazin-8-yl}ethan-1-ol 207 2-{6-[5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl]-2-methylimidazo[1,2-b]pyridazin- 8-yl}ethan-1-ol 208 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(2,2,6,6-tetramethyl- 1,2,3,6-

tetrahydropyridin-4-yl)cinnoline 209 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(5-methyl- 2,5-diazabicyclo[2.2.1]heptan-2-yl)cinnoline 210.sup.1 5-fluoro-7-(2-methylimidazo[1,2-a]pyridin-6-yl)-3-(piperidin-4-yl)cinnoline 211 5-fluoro-7-[2-methyl-8-(propan-2-yl)imidazo[1,2-b]pyridazin-6-yl]-3-(piperidin- 4-yl)cinnoline 212 3-(1-ethylpiperidin-4-yl)-5-fluoro-7-(2-methyl-8-propylimidazo[1,2-b]pyridazin- 6-yl)cinnoline 213 2-{4-[7-(4,6-dimethyl[1,3]oxazolo[4,5-c]pyridin-2-yl)-5-fluorocinnolin-3-yl]piperidin- 1-yl}ethan-1-ol 214 7-(4,6-dimethyl[1,3]oxazolo[4,5-c]pyridin-2-yl)-5-fluoro-3-(1-methylpiperidin- 4-yl)cinnoline 215 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-[(1S,4S)-5-methyl- 2,5-diazabicyclo[2.2.1]heptan-2-yl]cinnoline 216.sup.1 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(piperidin-3-yl)cinnoline 217.sup.1 3-(2,6-diazaspiro[3.4]octan-2-yl)-7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)- 5-fluorocinnoline 218.sup.1 3-(2,6-diazaspiro[3.5]nonan-2-yl)-7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)- 5-fluorocinnoline 219.sup.1 3-(2,7-diazaspiro[3.5]nonan-7-yl)-7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)- 5-fluorocinnoline 220.sup.1 3-(2,6-diazaspiro[3.4]octan-6-yl)-7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)- 5-fluorocinnoline 221.sup.1 3-(2,7-diazaspiro[3.5]nonan-2-yl)-7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)- 5-fluorocinnoline 222 3-(1-ethylpiperidin-4-yl)-5-fluoro-7-[2-methyl-8-(propan-2-yl)imidazo[1,2-b]pyridazin- 6-yl]cinnoline 223 (1R,5S,6s)-3-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluorocinnolin-3-yl]- N,N-dimethyl-3-azabicyclo[3.1.0]hexan-6-amine 224 1-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluorocinnolin-3-yl]- N,N,4-trimethylpiperidin-4-amine 225.sup.1 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(1,2,3,6-tetrahydropyridin- 4-yl)cinnoline 226 5-(5-fluoro-3-((2S,4R,6R)-1,2,6-trimethylpiperidin-4-yl)cinnolin-7-yl)- 2,7-dimethyloxazolo[5,4-b]pyridine 227 7-(2,7-dimethyl-2H-pyrazolo[4,3-b]pyridin-5-yl)-5-fluoro- 3-((2S,4R,6R)-1,2,6-trimethylpiperidin-4-yl)cinnoline and 228 7-(4,6-dimethyloxazolo[4,5-c]pyridin-2-yl)-5-fluoro-3- ((2S,4R,6R)-1,2,6-trimethylpiperidin-4-yl)cinnoline; wherein the form of the compound is selected from the group consisting of a salt, prodrug, hydrate, solvate, clathrate, isotopologue, racemate, enantiomer, diastereomer, stereoisomer, polymorph and tautomer form thereof. Another aspect of the compound of Formula (I) or a form thereof is a compound salt selected from the group consisting of:

(28) TABLE-US-00002 Cpd Name 1 2-(2-methyl-2H-indazol-5-yl)-6-(piperidin-4-yl)quinoline hydrochloride 2 6-(1-ethylpiperidin-4-yl)-2-(2-methyl-2H-indazol-5-yl)quinoline hydrochloride 3 6-(2-methyl-2H-indazol-5-yl)-2-(piperidin-4-yl)quinoline hydrochloride 4 3-(2-methyl-2H-indazol-5-yl)-7-(1,2,3,6-tetrahydropyridin-4-yl)cinnoline hydrochloride 5 4-methyl-6-(2-methyl-2H-indazol-5-yl)-2-(piperidin-4-yl)quinoline hydrochloride 6 6-(2-methyl-2H-indazol-5-yl)-2-(1-methylpiperidin-4-yl)quinoline hydrochloride 9 2-(1-ethylpiperidin-4-yl)-6-(2-methyl-2H-indazol-5-yl)quinoline hydrochloride 10 2-(2-methyl-2H-indazol-5-yl)-6-(piperidin-4-yl)quinazoline hydrochloride 24 6-[2-methyl-7-(trifluoromethyl)-2H-indazol-5-yl]-2-(piperidin-4-yl)quinoxaline hydrochloride 25 3-(7-fluoro-2-methyl-2H-indazol-5-yl)-7-(piperidin-4-yl)-1,2,4-benzotriazine dihydrochloride 31 6-(2,7-dimethyl-2H-indazol-5-yl)-2-(piperidin-4-yl)quinoxaline hydrochloride 34 6-(2,7-dimethyl-2H-indazol-5-yl)-8-fluoro-2-(piperidin-4-yl)quinazoline dihydrochloride 35 5-[8-fluoro-2-(piperidin-4-yl)quinazolin-6-yl]-2-methyl-2H-indazole-7-carbonitrile dihydrochloride 36 8-fluoro-6-(7-fluoro-2-methyl-2H-indazol-5-yl)-2-(piperidin-4-yl)quinazoline dihydrochloride 37 6-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-8-fluoro-2-(piperidin-4-yl)quinazoline dihydrochloride 38 6-(2,7-dimethyl-2H-indazol-5-yl)-5-fluoro-2-(piperidin-4-yl)quinazoline dihydrochloride 39 6-(2,7-dimethyl-2H-indazol-5-yl)-7-fluoro-2-(piperidin-4-yl)quinazoline dihydrochloride 45 6-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-8-fluoro-2-(piperidin-4-yl)quinoline hydrochloride 47 6-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-8-fluoro-2-(1-methylpiperidin- 4-yl)quinoline hydrochloride 48 6-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-2-(1-ethylpiperidin-4-yl)- 8-fluoroquinoline hydrochloride 49 8-fluoro-6-(7-methoxy-2-methyl-2H-indazol-5-yl)-2-(piperidin-4-yl)quinoline hydrochloride 50 8-fluoro-6-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-(piperidin-4-yl)quinoline hydrochloride 51 8-

fluoro-6-(8-methoxy-2-methylimidazo[1,2-b]pyridazin-6-yl)-2-(piperidin- 4-yl)quinoline hydrochloride 53 8-fluoro-6-[8-(2-methoxyethoxy)-2-methylimidazo[1,2-b]pyridazin-6-yl]-2-(piperidin- 4-yl)quinoline hydrochloride 54 6-[8-fluoro-2-(piperidin-4-yl)quinolin-6-yl]-N-(2-methoxyethyl)- 2-methylimidazo[1,2-b]pyridazin-8-amine hydrochloride 55 7-(2,7-dimethyl-2H-indazol-5-yl)-5-fluoro-3-(1,2,3,6-tetrahydropyridin-4-yl)cinnoline hydrochloride 56 7-(8-azabicyclo[3.2.1]oct-3-yl)-3-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)- 1,2,4-benzotriazine hydrochloride 57 3-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-7-(piperidin-4-yl)- 1,2,4-benzotriazine hydrochloride 58 5-fluoro-7-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-3-(piperidin-4-yl)- 1,2,4-benzotriazine hydrochloride 59 7-(8-ethoxy-2-methylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(piperidin-4-yl)- 1,2,4-benzotriazine hydrochloride 60 7-(2,8-dimethylimidazo[1,2-a]pyridin-6-yl)-5-fluoro-3-(piperidin-4-yl)- 1,2,4-benzotriazine hydrochloride 61 5-fluoro-7-[2-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl]-3-(piperidin-4-yl)- 1,2,4-benzotriazine hydrochloride 62 7-(2,4-dimethyl-1,3-benzoxazol-6-yl)-5-fluoro-3-(piperidin-4-yl)-1,2,4-benzotriazine hydrochloride 63 7-(2,4-dimethyl-1H-benzimidazol-6-yl)-5-fluoro-3-(piperidin-4-yl)-1,2,4-benzotriazine hydrochloride 64 7-(1,3-dimethylpyrrolo[1,2-a]pyrazin-7-yl)-5-fluoro-3-(piperidin-4-yl)- 1,2,4-benzotriazine hydrochloride 65 7-(2,7-dimethylpyrazolo[1,5-a]pyridin-5-yl)-5-fluoro-3-(piperidin-4-yl)- 1,2,4-benzotriazine hydrochloride 66 7-(2,7-dimethyl-2H-pyrazolo[4,3-b]pyridin-5-yl)-5-fluoro-3-(piperidin-4-yl)-1,2,4-benzotriazine dihydrochloride 67 7-(2,7-dimethyl-2H-pyrazolo[3,4-c]pyridin-5-yl)-5-fluoro-3-(piperidin-4-yl)- 1,2,4-benzotriazine dihydrochloride 69 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(1-methylpiperidin-4-yl)- 1,2,4-benzotriazine dihydrochloride 71 7-(2,7-dimethyl-2H-indazol-5-yl)-5-fluoro-3-(piperidin-4-yl)isoquinoline hydrochloride 72 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(piperidin-4-yl)isoquinoline hydrochloride 73 7-(2,7-dimethyl-2H-indazol-5-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline hydrochloride 74 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline dihydrochloride 80 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(piperazin-1-yl)cinnoline dihydrochloride 81 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-3-[(3R,5S)-3,5-dimethylpiperazin-1-yl]- 5-fluorocinnoline dihydrochloride 83 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-[1-(2-fluoroethyl)piperidin- 4-yl]cinnoline dihydrochloride 84 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-3-(piperidin-4-yl)cinnoline dihydrochloride 87 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-3-[(2S,6S)-2,6-dimethylpiperidin-4-yl]- 5-fluorocinnoline hydrochloride 91 5-fluoro-7-(2-methylimidazo[1,2-a]pyrimidin-6-yl)-3-(piperidin-4-yl)cinnoline dihydrochloride 92 5-fluoro-7-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-3-(piperidin-4-yl)cinnoline dihydrochloride 93 6-[5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl]-2-methylimidazo[1,2-a]pyridine-8-carbonitrile dihydrochloride 94 5-fluoro-7-(2-methyl[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-(piperidin-4-yl)cinnoline dihydrochloride 95 5-fluoro-7-(2-methyl-2H-indazol-5-yl)-3-(piperidin-4-yl)cinnoline hydrochloride 96 5-fluoro-7-(7-fluoro-2-methyl-2H-indazol-5-yl)-3-(piperidin-4-yl)cinnoline hydrochloride 97 5-fluoro-7-(6-fluoro-2-methyl-2H-indazol-5-yl)-3-(piperidin-4-yl)cinnoline hydrochloride 98 3-[1-(2,2-difluoroethyl)piperidin-4-yl]-7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)- 5-fluorocinnoline dihydrochloride 99 5-fluoro-7-(2-methylimidazo[1,2-b]pyridazin-6-yl)-3-(piperidin-4-yl)cinnoline dihydrochloride 100 3-(1-ethylpiperidin-4-yl)-5-fluoro-7-(2-methylimidazo[1,2-b]pyridazin-6-yl)cinnoline dihydrochloride 101 7-(1,3-dimethylpyrrolo[1,2-a]pyrazin-7-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline dihydrochloride 102 3-(1-ethylpiperidin-4-yl)-5-fluoro-7-(8-fluoro-2-methylimidazo[1,2-a]pyridin- 6-yl)cinnoline dihydrochloride 103 7-(2,8-dimethylimidazo[1,2-a]pyridin-6-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline dihydrochloride 104 5-[5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl]-2-methyl-1H-indazole-7-carbonitrile hydrochloride 109 5-fluoro-7-(4-fluoro-2-methyl-2H-indazol-5-yl)-3-(piperidin-4-yl)cinnoline hydrochloride 115 7-(8-cyclopropyl-2-methylimidazo[1,2-b]pyridazin-6-yl)-3-(1-ethylpiperidin-4-yl)- 5-fluorocinnoline formate 117 5-fluoro-3-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-7-(1,2,3,6-tetrahydropyridin- 4-yl)cinnoline hydrochloride 120

7-(2,4-dimethyl-1,3-benzothiazol-6-yl)-3-(1-ethylpiperidin-4-yl)-5-fluorocinnoline formate 121 7-(8-ethyl-2-methylimidazo[1,2-b]pyridazin-6-yl)-3-(1-ethylpiperidin-4-yl)- 5-fluorocinnoline dihydrochloride 122 7-(8-ethyl-2-methylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(1-methylpiperidin- 4-yl)cinnoline dihydrochloride 123 2-{4-[7-(8-ethyl-2-methylimidazo[1,2-b]pyridazin-6-yl)-5-fluorocinnolin- 3-yl]piperidin-1-yl}ethan-1-ol dihydrochloride 127 2-{4-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluorocinnolin-3-yl]piperidin- 1-yl}-N,N-dimethylethan-1-amine trihydrochloride 128 5-fluoro-3-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-7-(piperidin-4-yl)cinnoline dihydrochloride 133 7-(2,7-dimethyl[1,3]thiazolo[5,4-b]pyridin-5-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline formate 134 5-fluoro-3-(7-fluoro-2-methyl-2H-indazol-5-yl)-7-(1,2,3,6-tetrahydropyridin- 4-yl)cinnoline hydrochloride 135 7-(2,7-dimethyl[1,3]thiazolo[5,4-b]pyridin-5-yl)-3-(1-ethylpiperidin-4-yl)- 5-fluorocinnoline formate 138 2-({6-[5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl]-2-methylimidazo[1,2-b]pyridazin- 8-yl}oxy)-N,N-dimethylethan-1-amine trihydrochloride 139 3-({6-[5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl]-2-methylimidazo[1,2-b]pyridazin- 8-yl}oxy)-N,N-dimethylpropan-1-amine trihydrochloride 140 5-fluoro-7-{2-methyl-8-[2-(1H-pyrazol-1-yl)ethoxy]imidazo[1,2-b]pyridazin-6-yl}- 3-(piperidin-4-yl)cinnoline dihydrochloride 141 5-fluoro-7-{2-methyl-8-[3-(1H-pyrazol-1-yl)propoxy]imidazo[1,2-b]pyridazin-6-yl}- 3-(piperidin-4-yl)cinnoline trihydrochloride 142 5-fluoro-7-{8-[3-(1H-imidazol-1-yl)propoxy]-2-methylimidazo[1,2-b]pyridazin-6-yl}- 3-(piperidin-4-yl)cinnoline trihydrochloride 145 3-{1-[3-(1H-benzimidazol-1-yl)propyl]piperidin-4-yl}- 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluorocinnoline trihydrochloride 146 7-(5,7-dimethylfuro[2,3-c]pyridin-2-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline hydrochloride 150 7-{8-[3-(1H-benzimidazol-1-yl)propoxy]-2-methylimidazo[1,2-b]pyridazin-6-yl}- 5-fluoro-3-(piperidin-4-yl)cinnoline trihydrochloride 151 5-fluoro-3-(7-fluoro-2-methyl-2H-indazol-5-yl)-7-(piperidin-4-yl)cinnoline hydrochloride 153 7-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-5-fluoro-3-(7-fluoro-2-methyl-2H-indazol- 5-yl)cinnoline hydrochloride 156 3-(2,8-dimethylimidazo[1,2-a]pyridin-6-yl)-5-fluoro-7-(1,2,3,6-tetrahydropyridin- 4-yl)cinnoline hydrochloride 157 3-(2,7-dimethyl-2H-indazol-5-yl)-5-fluoro-7-(1,2,3,6-tetrahydropyridin-4-yl)cinnoline hydrochloride 163 5-fluoro-7-(7-methoxy-2-methyl-2H-pyrazolo[4,3-b]pyridin-5-yl)-3-(piperidin- 4-yl)cinnoline formate 165 8-fluoro-2-(7-fluoro-2-methyl-2H-indazol-5-yl)-6-(1,2,3,6-tetrahydropyridin- 4-yl)quinazoline hydrochloride 166 8-fluoro-2-(7-fluoro-2-methyl-2H-indazol-5-yl)-6-(1,2,3,6-tetrahydropyridin- 4-yl)quinoline hydrochloride 167 3-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-7-(1,2,3,6-tetrahydropyridin- 4-yl)cinnoline hydrochloride 171 5-fluoro-3-(7-fluoro-2-methyl-2H-benzotriazol-5-yl)-7-(1,2,3,6-tetrahydropyridin- 4-yl)cinnoline hydrochloride 173 3-(1-ethylpiperidin-4-yl)-5-fluoro-7-(7-methoxy-2-methyl-2H-pyrazolo[4,3-b]pyridin- 5-yl)cinnoline formate 175 5-[5-fluoro-7-(1,2,3,6-tetrahydropyridin-4-yl)cinnolin-3-yl]-2-methyl-2H-indazole- 7-carbonitrile hydrochloride 176 6-[5-fluoro-3-(1-methylpiperidin-4-yl)cinnolin-7-yl]-2-methylimidazo[1,2-b]pyridazine- 8-carbonitrile trihydrochloride 177 3-(2,7-dimethyl-2H-indazol-5-yl)-5-fluoro-7-(piperidin-4-yl)cinnoline hydrochloride 178 6-{5-fluoro-3-[1-(2-hydroxyethyl)piperidin-4-yl]cinnolin-7-yl}- 2-methylimidazo[1,2-b]pyridazine-8-carbonitrile trihydrochloride 179 6-{5-fluoro-3-[1-(2-fluoroethyl)piperidin-4-yl]cinnolin-7-yl}- 2-methylimidazo[1,2-b]pyridazine-8-carbonitrile trihydrochloride 181 2-(4-{5-fluoro-7-[8-(hydroxymethyl)-2-methylimidazo[1,2-b]pyridazin-6-yl]cinnolin- 3-yl]piperidin-1-yl)ethan-1-ol trihydrochloride 182 (6-{5-fluoro-3-[1-(2-fluoroethyl)piperidin-4-yl]cinnolin-7-yl}- 2-methylimidazo[1,2-b]pyridazin-8-yl)methanol trihydrochloride 184 6-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-8-fluoro-2-(7-fluoro-2-methyl-2H-indazol- 5-yl)quinoline hydrochloride 185 3-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-7-(piperidin-4-yl)cinnoline hydrochloride 191 7-(5,7-dimethyl-1H-pyrrolo[2,3-c]pyridin-2-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline dihydrochloride 192 8-fluoro-2-(7-fluoro-2-methyl-2H-indazol-5-yl)-6-(piperidin-4-yl)quinoline hydrochloride 193 6-(1-ethylpiperidin-4-yl)-8-fluoro-2-(7-fluoro-2-methyl-2H-indazol-5-yl)quinoline hydrochloride 194 5-fluoro-7-[8-(1H-imidazol-1-yl)-2-methylimidazo[1,2-

b]pyridazin-6-yl]-3-(piperidin- 4-yl)cinnoline formate 195 5-fluoro-7-(2-methyl-8-phenoxyimidazo[1,2-b]pyridazin-6-yl)-3-(piperidin- 4-yl)cinnoline formate 196 7-(4,6-dimethyl[1,3]thiazolo[5,4-c]pyridin-2-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline formate 201 6-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-8-fluoro-2-(7-fluoro-2-methyl-2H-indazol- 5-yl)quinazoline hydrochloride 202 6-(1-ethylpiperidin-4-yl)-8-fluoro-2-(7-fluoro-2-methyl-2H-indazol-5-yl)quinazoline hydrochloride 205 {6-[3-(1-ethylpiperidin-4-yl)-5-fluorocinnolin-7-yl]-2-methylimidazo[1,2-b]pyridazin- 8-yl}acetonitrile formate 210 5-fluoro-7-(2-methylimidazo[1,2-a]pyridin-6-yl)-3-(piperidin-4-yl)cinnoline dihydrochloride 216 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(piperidin-3-yl)cinnoline dihydrochloride 217 3-(2,6-diazaspiro[3.4]octan-2-yl)-7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)- 5-fluorocinnoline trihydrochloride 218 3-(2,6-diazaspiro[3.5]nonan-2-yl)-7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)- 5-fluorocinnoline trihydrochloride 219 3-(2,7-diazaspiro[3.5]nonan-7-yl)-7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)- 5-fluorocinnoline ditrifluoroacetate 220 3-(2,6-diazaspiro[3.4]octan-6-yl)-7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)- 5-fluorocinnoline ditrifluoroacetate 221 3-(2,7-diazaspiro[3.5]nonan-2-yl)-7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)- 5-fluorocinnoline ditrifluoroacetate and 225 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(1,2,3,6-tetrahydropyridin- 4-yl)cinnoline dihydrochloride;
wherein the form of the compound salt is selected from the group consisting of a prodrug, hydrate, solvate, clathrate, isotopologue, racemate, enantiomer, diastereomer, stereoisomer, polymorph and tautomer form thereof.

(29) An aspect of the present description includes a method for preventing, treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of a compound of Formula (I) or a form thereof.

(30) An aspect of the present description includes a method for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of a compound of Formula (I) or a form thereof.

(31) Another aspect of the present description includes a method for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of a compound salt of Formula (I) or a form thereof.

(32) An aspect of the present description includes a method for use of a compound of Formula (I) or a form or composition thereof for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of the compound of Formula (I) or a form or composition thereof.

(33) Another aspect of the present description includes a method for use of a compound salt of Formula (I) or a form or composition thereof for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of the compound salt of Formula (I) or a form thereof.

(34) An aspect of the present description includes a use for a compound of Formula (I) or a form thereof for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of the compound of Formula (I) or a form thereof.

(35) Another aspect of the present description includes a use for a compound salt of Formula (I) or a form thereof for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of the compound salt of Formula (I) or a form thereof.

(36) An aspect of the present description includes a use for a compound of Formula (I) or a form thereof in the manufacture of a medicament for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of the medicament.

(37) Another aspect of the present description includes a use for a compound salt of Formula (I) or a form thereof in the manufacture of a medicament for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of the medicament.

(38) An aspect of the present description includes a use for a compound of Formula (I) or a form thereof in a combination product with one or more therapeutic agents for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of the compound of Formula (I) or a form thereof in combination with an effective amount of the one or more agents.
(39) Another aspect of the present description includes a use for a compound salt of Formula (I) or a form thereof in a combination product with one or more therapeutic agents for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of the compound salt of Formula (I) or a form thereof in combination with an effective amount of the one or more agents.
Chemical Definitions
(40) The chemical terms used above and throughout the description herein, unless specifically defined otherwise, shall be understood by one of ordinary skill in the art to have the following indicated meanings.
(41) As used herein, the term “C.sub.1-8alkyl” generally refers to saturated hydrocarbon radicals having from one to eight carbon atoms in a straight or branched chain configuration, including, but not limited to, methyl, ethyl, n-propyl (also referred to as propyl or propanyl), isopropyl, n-butyl (also referred to as butyl or butynyl), isobutyl, sec-butyl, tert-butyl, n-pentyl (also referred to as pentyl or pentanyl), n-hexyl (also referred to as hexyl or hexanyl), n-heptyl (also referred to as heptyl or heptanyl), n-octyl and the like. In certain aspects, C.sub.1-8alkyl includes, but is not limited to, C.sub.1-6alkyl, C.sub.1-4alkyl and the like. A C.sub.1-8alkyl radical is optionally substituted with substituent species as described herein where allowed by available valences.
(42) As used herein, the term “C.sub.2-8alkenyl” generally refers to partially unsaturated hydrocarbon radicals having from two to eight carbon atoms in a straight or branched chain configuration and one or more carbon-carbon double bonds therein, including, but not limited to, ethenyl (also referred to as vinyl), allyl, propenyl and the like. In certain aspects, C.sub.2-8alkenyl includes, but is not limited to, C.sub.2-6alkenyl, C.sub.2-4alkenyl and the like. A C.sub.2-8alkenyl radical is optionally substituted with substituent species as described herein where allowed by available valences.
(43) As used herein, the term “C.sub.2-8alkynyl” generally refers to partially unsaturated hydrocarbon radicals having from two to eight carbon atoms in a straight or branched chain configuration and one or more carbon-carbon triple bonds therein, including, but not limited to, ethynyl, propynyl, butynyl and the like. In certain aspects, C.sub.2-8alkynyl includes, but is not limited to, C.sub.2-6alkynyl, C.sub.2-4alkynyl and the like. A C.sub.2-8alkynyl radical is optionally substituted with substituent species as described herein where allowed by available valences.
(44) As used herein, the term “C.sub.1-8alkoxy” generally refers to saturated hydrocarbon radicals having from one to eight carbon atoms in a straight or branched chain configuration of the formula: —O—C.sub.1-8alkyl, including, but not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentoxy, n-hexoxy and the like. In certain aspects, C.sub.1-8alkoxy includes, but is not limited to, C.sub.1-6alkoxy, C.sub.1-4alkoxy and the like. A C.sub.1-8alkoxy radical is optionally substituted with substituent species as described herein where allowed by available valences.
(45) As used herein, the term “C.sub.3-14cycloalkyl” generally refers to a saturated or partially unsaturated monocyclic, bicyclic or polycyclic hydrocarbon radical, including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, 1H-indanyl, indenyl, tetrahydro-naphthalenyl and the like. In certain aspects, C.sub.3-14cycloalkyl includes, but is not limited to, C.sub.3-8cycloalkyl, C.sub.5-8cycloalkyl, C.sub.3-14cycloalkyl and the like. A C.sub.3-14cycloalkyl radical is optionally substituted with substituent species as described herein where allowed by available valences.

(46) As used herein, the term “aryl” generally refers to a monocyclic, bicyclic or polycyclic aromatic carbon atom ring structure radical, including, but not limited to, phenyl, naphthyl, anthracenyl, fluorenyl, azulenyl, phenanthrenyl and the like. An aryl radical is optionally substituted with substituent species as described herein where allowed by available valences.
(47) As used herein, the term “heteroaryl” generally refers to a monocyclic, bicyclic or polycyclic aromatic carbon atom ring structure radical in which one or more carbon atom ring members have been replaced, where allowed by structural stability, with one or more heteroatoms, such as an O, S or N atom, including, but not limited to, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, isothiazolyl, oxazolyl, 1,3-thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, indolyl, indazolyl, indolizinyl, isoindolyl, benzofuranyl, benzothienyl, benzoimidazolyl, 1,3-benzothiazolyl, 1,3-benzoxazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, 1,3-diazinyl, 1,2-diazinyl, 1,2-diazolyl, 1,4-diazanaphthalenyl, acridinyl, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, 6H-thieno[2,3-b]pyrrolyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, 1H-pyrrolo[2,3-b]pyridinyl, 1H-pyrrolo[2,3-c]pyridinyl, 1H-pyrrolo[3,2-b]pyridinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-a]pyrazinyl, imidazo[1,2-a]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-c]pyrimidinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrazinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,2,4]triazolo[1,5-a]pyridinyl, [1,2,4]triazolo[4,3-a]pyridinyl and the like. A heteroaryl radical is optionally substituted on a carbon or nitrogen atom ring member with substituent species as described herein where allowed by available valences.
(48) In certain aspects, the nomenclature for a heteroaryl radical may differ, such as in non-limiting examples where furanyl may also be referred to as furyl, thienyl may also be referred to as thiophenyl, pyridinyl may also be referred to as pyridyl, benzothienyl may also be referred to as benzothiophenyl and 1,3-benzoxazolyl may also be referred to as 1,3-benzooxazolyl.
(49) In certain other aspects, the term for a heteroaryl radical may also include other regioisomers, such as in non-limiting examples where the term pyrrolyl may also include 2H-pyrrolyl, 3H-pyrrolyl and the like, the term pyrazolyl may also include 1H-pyrazolyl and the like, the term imidazolyl may also include 1H-imidazolyl and the like, the term triazolyl may also include 1H-1,2,3-triazolyl and the like, the term oxadiazolyl may also include 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl and the like, the term tetrazolyl may also include 1H-tetrazolyl, 2H-tetrazolyl and the like, the term indolyl may also include 1H-indolyl and the like, the term indazolyl may also include 1H-indazolyl, 2H-indazolyl and the like, the term benzoimidazolyl may also include 1H-benzoimidazolyl and the term purinyl may also include 9H-purinyl and the like.
(50) As used herein, the term “heterocyclyl” generally refers to a saturated or partially unsaturated monocyclic, bicyclic or polycyclic carbon atom ring structure radical in which one or more carbon atom ring members have been replaced, where allowed by structural stability, with a heteroatom, such as an O, S or N atom, including, hut not limited to, oxiranyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrrolinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, isoxazolinyl, isoxazolidinyl, isothiazolinyl, isothiazolidinyl, oxazolinyl, oxazolidinyl, thiazolinyl, thiazolidinyl, triazolinyl, triazolidinyl, oxadiazolinyl, oxadiazolidinyl, thiadiazolinyl, thiadiazolidinyl, tetrazolinyl, tetrazolidinyl, pyranyl, dihydro-2H-pyranyl, thiopyranyl, 1,3-dioxanyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,4-diazepanyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl, 2,3-dihydro-1,4-benzodioxinyl, hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, (3aR,6aR)-hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, (3aR,6aR)-hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-(1H)-yl, (3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-(1H)-yl, (3aR,6aR)-hexahydropyrrolo[3,4-c]pyrrol-(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, (4aR,7aR)-

octahydro-6H-pyrrolo[3,4-b]pyridinyl, (4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (7R,8aS)-hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aS)-hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aR)-hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aS)-octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aR)-octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, octahydro-2H-pyrido[1,2-a]pyrazinyl, 3-azabicyclo[3.1.0]hexyl, (1R,5S)-3-azabicyclo[3.1.0]hexyl, 8-azabicyclo[3.2.1]octyl, (1R,5S)-8-azabicyclo[3.2.1]octyl, 8-azabicyclo[3.2.1]oct-2-enyl, (1R,5S)-8-azabicyclo[3.2.1]oct-2-enyl, 9-azabicyclo[3.3.1]nonyl, (1R,5S)-9-azabicyclo[3.3.1]nonyl, 2,5-diazabicyclo[2.2.1]heptyl, (1S,4S)-2,5-diazabicyclo[2.2.1]heptyl, 2,5-diazabicyclo[2.2.2]octyl, 3,8-diazabicyclo[3.2.1]octyl, (1R,5S)-3,8-diazabicyclo[3.2.1]octyl, 1,4-diazabicyclo[3.2.2]nonyl, azaspiro[3.3]heptyl, 2,6-diazaspiro[3.3]heptyl, 2,7-diazaspiro[3.5]nonyl, 5,8-diazaspiro[3.5]nonyl, 2,7-diazaspiro[4.4]nonyl, 6,9-diazaspiro[4.5]decyl and the like. A heterocyclyl radical is optionally substituted on a carbon or nitrogen atom ring member with substituent species as described herein where allowed by available valences.

(51) In certain aspects, the nomenclature for a heterocyclyl radical may differ, such as in non-limiting examples where 1,3-benzodioxolyl may also be referred to as benzo[d][1,3]dioxolyl and 2,3-dihydro-1,4-benzodioxinyl may also be referred to as 2,3-dihydrobenzo[b][1,4]dioxinyl.

(52) As used herein, the term “heteroaryl-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8alkyl-heteroaryl.

(53) As used herein, the term “C.sub.1-8alkoxy-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8alkyl-O—C.sub.1-8alkyl.

(54) As used herein, the term “C.sub.1-8alkoxy-C.sub.1-8alkyl-amino” refers to a radical of the formula: —NH—C.sub.1-8alkyl-O—C.sub.1-8alkyl.

(55) As used herein, the term “(C.sub.1-8alkoxy-C.sub.1-8alkyl).sub.2-amino” refers to a radical of the formula: —N(C.sub.1-8alkyl-O—C.sub.1-8 alkyl).sub.2.

(56) As used herein, the term “C.sub.1-8alkoxy-C.sub.1-8alkyl-amino-C.sub.1-8alkoxy” refers to a radical of the formula: —O—C.sub.1-8alkyl-NH—C.sub.1-8alkyl-O—C.sub.1-8alkyl.

(57) As used herein, the term “(C.sub.1-8alkoxy-C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkoxy” refers to a radical of the formula: —O—C.sub.1-8alkyl-N(C.sub.1-8alkyl-O—C.sub.1-8alkyl).sub.2.

(58) As used herein, the term “(C.sub.1-8alkoxy-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino-C.sub.1-8alkoxy” refers to a radical of the formula: —O—C.sub.1-8alkyl-N(C.sub.1-8alkyl)(C.sub.1-8alkyl-O—C.sub.1-8alkyl).

(59) As used herein, the term “C.sub.1-8alkoxy-C.sub.1-8alkyl-amino-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8alkyl-NH—C.sub.1-8alkyl-O—C.sub.1-8alkyl.

(60) As used herein, the term “(C.sub.1-8alkoxy-C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8alkyl-N(C.sub.1-8alkyl-O—C.sub.1-8alkyl).sub.2.

(61) As used herein, the term “(C.sub.1-8alkoxy-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8alkyl-N(C.sub.1-8alkyl)(C.sub.1-8alkyl-O—C.sub.1-8alkyl).

(62) As used herein, the term “C.sub.1-8alkoxy-carbonyl” refers to a radical of the formula: —C(O)—O—C.sub.1-8alkyl.

(63) As used herein, the term “C.sub.1-8alkoxy-carbonyl-C.sub.2-8alkenyl” refers to a radical of the formula: —C.sub.2-8alkenyl-C(O)—O—C.sub.1-8alkyl.

(64) As used herein, the term “C.sub.1-8alkoxy-carbonyl-amino” refers to a radical of the formula: —NH—C(O)—O—C.sub.1-8alkyl.

(65) As used herein, the term “heteroaryl-C.sub.1-8alkoxy” refers to a radical of the formula: —O—C.sub.1-8alkyl-heteraryl.

(66) As used herein, the term “C.sub.1-8alkyl-amino” refers to a radical of the formula: —NH—C.sub.1-8alkyl.

(67) As used herein, the term “(C.sub.1-8alkyl).sub.2-amino” refers to a radical of the formula: —N(C.sub.1-8alkyl).sub.2.
(68) As used herein, the term “C.sub.1-8alkyl-amino-C.sub.2-8alkenyl” refers to a radical of the formula: —C.sub.2-8alkenyl-NH—C.sub.1-8alkyl.
(69) As used herein, the term “(C.sub.1-8alkyl).sub.2-amino-C.sub.2-8alkenyl” refers to a radical of the formula: —C.sub.2-8alkenyl-N(C.sub.1-8alkyl).sub.2.
(70) As used herein, the term “C.sub.1-8alkyl-amino-C.sub.1-8alkoxy” refers to a radical of the formula: —O—C.sub.1-8alkyl-NH—C.sub.1-8alkyl.
(71) As used herein, the term “(C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkoxy” refers to a radical of the formula: —O—C.sub.1-8alkyl-N(C.sub.1-8alkyl).sub.2.
(72) As used herein, the term “C.sub.1-8alkyl-amino-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8alkyl-NH—C.sub.1-8alkyl.
(73) As used herein, the term “(C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8alkyl-N(C.sub.1-8 alkyl).sub.2.
(74) As used herein, the term “C.sub.1-8alkyl-amino-C.sub.1-8alkyl-amino” refers to a radical of the formula: —NH—C.sub.1-8alkyl-NH—C.sub.1-8alkyl.
(75) As used herein, the term “(C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl-amino” refers to a radical of the formula: —NH—C.sub.1-8alkyl-N(C.sub.1-8alkyl).sub.2.
(76) As used herein, the term “(C.sub.1-8alkyl-amino-C.sub.1-8alkyl).sub.2-amino” refers to a radical of the formula: —N(C.sub.1-8alkyl-NH—C.sub.1-8alkyl).sub.2.
(77) As used herein, the term “[(C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl].sub.2-amino” refers to a radical of the formula: —N[C.sub.1-8alkyl-N(C.sub.1-8alkyl).sub.2].sub.2.
(78) As used herein, the term “(C.sub.1-8alkyl-amino-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino” refers to a radical of the formula: —N(C.sub.1-8alkyl)(C.sub.1-8alkyl-NH—C.sub.1-8alkyl).
(79) As used herein, the term “[(C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl](C.sub.1-8alkyl)amino” refers to a radical of the formula: —N(C.sub.1-8alkyl)[C.sub.1-8alkyl-N(C.sub.1-8alkyl).sub.2].
(80) As used herein, the term “C.sub.1-8alkyl-amino-C.sub.2-8alkynyl” refers to a radical of the formula: —C.sub.2-8alkynyl-NH—C.sub.1-8 alkyl.
(81) As used herein, the term “(C.sub.1-8alkyl).sub.2-amino-C.sub.2-8alkynyl” refers to a radical of the formula: —C.sub.2-8alkynyl-N(C.sub.1-8alkyl).sub.2.
(82) As used herein, the term “C.sub.1-8alkyl-carbonyl” refers to a radical of the formula: —C(O)—C.sub.1-8alkyl.
(83) As used herein, the term “C.sub.1-8alkyl-carbonyl-amino” refers to a radical of the formula: —NH—C(O)—C.sub.1-8alkyl.
(84) As used herein, the term “C.sub.1-8alkyl-thio” refers to a radical of the formula: —S—C.sub.1-8alkyl.
(85) As used herein, the term “amino-C.sub.2-8alkenyl” refers to a radical of the formula: —C.sub.2-8alkenyl-NH.sub.2.
(86) As used herein, the term “amino-C.sub.1-8alkoxy” refers to a radical of the formula: —O—C.sub.1-8 alkyl-NH.sub.2.
(87) As used herein, the term “amino-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8alkyl-NH.sub.2.
(88) As used herein, the term “amino-C.sub.1-8alkyl-amino” refers to a radical of the formula: —NH—C.sub.1-8 alkyl-NH.sub.2.
(89) As used herein, the term “(amino-C.sub.1-8alkyl).sub.2-amino” refers to a radical of the formula: —N(C.sub.1-8alkyl-NH.sub.2.
(90) As used herein, the term “(amino-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino” refers to a radical of the formula: —N(C.sub.1-8alkyl)(C.sub.1-8alkyl-NH.sub.2).
(91) As used herein, the term “amino-C.sub.2-8alkynyl” refers to a radical of the formula: —

C.sub.2-8alkynyl-NH.sub.2.
(92) As used herein, the term “aryl-C.sub.1-8alkoxy-carbonyl” refers to a radical of the formula: —C(O)—O—C.sub.1-8 alkyl-aryl.
(93) As used herein, the term “aryl-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8alkyl-aryl.
(94) As used herein, the term “aryl-C.sub.1-8alkyl-amino” refers to a radical of the formula: —NH—C.sub.1-8alkyl-aryl.
(95) As used herein, the term “(aryl-C.sub.1-8alkyl).sub.2-amino” refers to a radical of the formula: —N(C.sub.1-8 alkyl-aryl).sub.2.
(96) As used herein, the term “(aryl-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino” refers to a radical of the formula: —N(C.sub.1-8alkyl)(C.sub.1-8alkyl-aryl).
(97) As used herein, the term “aryl-C.sub.1-8alkyl-amino-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8alkyl-NH—C.sub.1-8alkyl-aryl.
(98) As used herein, the term “(aryl-C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8 alkyl-N(C.sub.1-8 alkyl-aryl).sub.2.
(99) As used herein, the term “(aryl-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8alkyl-N(C.sub.1-8alkyl)(C.sub.1-8alkyl-aryl).
(100) As used herein, the term “aryl-amino” refers to a radical of the formula: —NH-aryl.
(101) As used herein, the term “aryl-amino-carbonyl” refers to a radical of the formula: —C(O)—NH-aryl.
(102) As used herein, the term “aryl-sulfonyloxy-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8alkyl-O—SO.sub.2-aryl.
(103) As used herein, the term “benzoxy-carbonyl” refers to a radical of the formula: —C(O)—O—CH.sub.2-phenyl.
(104) As used herein, the term “C.sub.3-14cycloalkyl-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8 alkyl-C.sub.3-14cycloalkyl.
(105) As used herein, the term “C.sub.3-14cycloalkyl-amino” refers to a radical of the formula: —NH—C.sub.3-14cycloalkyl.
(106) As used herein, the term “C.sub.3-14cycloalkyl-oxy” refers to a radical of the formula: —O—C.sub.3-14cycloalkyl.
(107) As used herein, the term “aryl-oxy” refers to a radical of the formula: —O-aryl.
(108) As used herein, the term “halo” or “halogen” generally refers to a halogen atom radical, including fluoro, chloro, bromo and iodo.
(109) As used herein, the term “halo-C.sub.1-8alkoxy” refers to a radical of the formula: —O—C.sub.1-8alkyl-halo, wherein C.sub.1-8alkyl is partially or completely substituted with one or more halogen atoms where allowed by available valences.
(110) As used herein, the term “halo-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8alkyl-halo, wherein C.sub.1-8alkyl is partially or completely substituted with one or more halogen atoms where allowed by available valences.
(111) As used herein, the term “halo-C.sub.1-8alkyl-amino” refers to a radical of the formula: —NH—C.sub.1-8alkyl-halo.
(112) As used herein, the term “(halo-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino” refers to a radical of the formula: —N(C.sub.1-8alkyl)(C.sub.1-8 alkyl-halo).
(113) As used herein, the term “(halo-C.sub.1-8alkyl).sub.2-amino” refers to a radical of the formula: —N(C.sub.1-8alkyl-halo).sub.2.
(114) As used herein, the term “heteroaryl-C.sub.1-8alkoxy” refers to a radical of the formula: —O—C.sub.1-8alkyl-heteroaryl.
(115) As used herein, the term “heteroaryl-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8 alkyl-heteroaryl.
(116) As used herein, the term “heteroaryl-C.sub.1-8alkyl-amino” refers to a radical of the formula:

—NH—C.sub.1-8alkyl-heteroaryl.
(117) As used herein, the term “(heteroaryl-C.sub.1-8alkyl).sub.2-amino” refers to a radical of the formula: —N(C.sub.1-8alkyl-heteroaryl).sub.2.
(118) As used herein, the term “(heteroaryl-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino” refers to a radical of the formula: —N(C.sub.1-8alkyl)(C.sub.1-8alkyl-heteroaryl).
(119) As used herein, the term “heteroaryl-C.sub.1-8alkyl-amino-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8 alkyl-NH—C.sub.1-8alkyl-heteroaryl.
(120) As used herein, the term “(heteroaryl-C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8alkyl-N(C.sub.1-8alkyl-heteroaryl).sub.2.
(121) As used herein, the term “(heteroaryl-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8alkyl-N(C.sub.1-8alkyl)(C.sub.1-8alkyl-heteroaryl).
(122) As used herein, the term “heteroaryl-amino” refers to a radical of the formula: —NH-heteroaryl.
(123) As used herein, the term “heterocyclyl-C.sub.1-8alkoxy” refers to a radical of the formula: —O—C.sub.1-8alkyl-heterocyclyl.
(124) As used herein, the term “heterocyclyl-C.sub.1-8alkyl” refers to a radical of the formula: —C alkyl-heterocyclyl.
(125) As used herein, the term “heterocyclyl-C.sub.1-8alkyl-amino” refers to a radical of the formula: —NH—C.sub.1-8alkyl-heterocyclyl.
(126) As used herein, the term “(heterocyclyl-C.sub.1-8alkyl).sub.2-amino” refers to a radical of the formula: —N(C.sub.1-8alkyl-heterocyclyl).sub.2.
(127) As used herein, the term “(heterocyclyl-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino” refers to a radical of the formula: —N(C.sub.1-8alkyl)(C.sub.1-8alkyl-heterocyclyl).
(128) As used herein, the term “heterocyclyl-C.sub.1-8alkyl-amino-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.8alkyl-NH—C.sub.1-8alkyl-heterocyclyl.
(129) As used herein, the term “(heterocyclyl-C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8alkyl-N(C.sub.1-8alkyl-heterocyclyl).sub.2.
(130) As used herein, the term “(heterocyclyl-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8alkyl-N(C.sub.1-8alkyl)(C.sub.1-8alkyl-heterocyclyl).
(131) As used herein, the term “heterocyclyl-amino” refers to a radical of the formula: —NH-heterocyclyl.
(132) As used herein, the term “(heterocyclyl)(C.sub.1-8alkyl)amino” refers to a radical of the formula: —N(C.sub.1-8alkyl)(heterocyclyl).
(133) As used herein, the term “heterocyclyl-amino-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8alkyl-NH-heterocyclyl.
(134) As used herein, the term “heterocyclyl-carbonyl” refers to a radical of the formula: —C(O)-heterocyclyl.
(135) As used herein, the term “heterocyclyl-carbonyl-oxy” refers to a radical of the formula: —O—C(O)-heterocyclyl.
(136) As used herein, the term “heterocyclyl-oxy” refers to a radical of the formula: —O-heterocyclyl.
(137) As used herein, the term “hydroxy” refers to a radical of the formula: —OH.
(138) As used herein, the term “hydroxy-C.sub.1-8alkoxy-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8 alkyl-O—C.sub.1-8 alkyl-OH.
(139) As used herein, the term “hydroxy-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8alkyl-OH, wherein C.sub.1-8alkyl is partially or completely substituted with one or more hydroxy radicals where allowed by available valences.
(140) As used herein, the term “hydroxy-C.sub.1-8alkyl-amino” refers to a radical of the formula: —NH—C.sub.1-8alkyl-OH.

(141) As used herein, the term “(hydroxy-C.sub.1-8alkyl).sub.2-amino” refers to a radical of the formula: —N(C.sub.1-8alkyl-OH).sub.2.
(142) As used herein, the term “(hydroxy-C.sub.1-8alkyl)(C.sub.1-8alkylamino” refers to a radical of the formula: —N(C.sub.1-8alkyl)(C.sub.1-8alkyl-OH).
(143) As used herein, the term “hydroxy-C.sub.1-8alkyl-amino-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8alkyl-NH—C.sub.1-8alkyl-OH.
(144) As used herein, the term “(hydroxy-C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8 alkyl-N(C.sub.1-8 alkyl-OH).sub.2.
(145) As used herein, the term “(hydroxy-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino-C.sub.1-8alkyl” refers to a radical of the formula: —C.sub.1-8alkyl-N(C.sub.1-8 alkyl)(C.sub.1-8 alkyl-OH).
(146) As used herein, the term “hydroxy-C.sub.1-8alkyl-amino-C.sub.1-8alkoxy” refers to a radical of the formula: —O—C.sub.1-8alkyl-NH—C.sub.1-8alkyl-OH.
(147) As used herein, the term “(hydroxy-C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkoxy” refers to a radical of the formula: —O—C.sub.1-8alkyl-N(C.sub.1-8alkyl-OH).sub.2.
(148) As used herein, the term “(hydroxy-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino-C.sub.1-8alkoxy” refers to a radical of the formula: —O—C.sub.1-8alkyl-N(C.sub.1-8alkyl)(C.sub.1-8 alkyl-OH).
(149) As used herein, the term “hydroxy-C.sub.1-8alkyl-amino-C.sub.1-8alkyl-amino” refers to a radical of the formula: —NH—C.sub.1-8alkyl-NH—C.sub.1-8alkyl-OH.
(150) As used herein, the term “(hydroxy-C.sub.1-8alkyl-amino-C.sub.1-8alkyl).sub.2-amino” refers to a radical of the formula: —N(C.sub.1-8 alkyl-NH—C.sub.1-8alkyl-OH).sub.2.
(151) As used herein, the term “(hydroxy-C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl-amino” refers to a radical of the formula: —NH—C.sub.1-8alkyl-N(C.sub.1-8alkyl-OH).sub.2.
(152) As used herein, the term “(hydroxy-C.sub.1-8alkyl-amino-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino” refers to a radical of the formula: —N(C.sub.1-8alkyl)(C.sub.1-8 alkyl-NH—C.sub.1-8alkyl-OH).
(153) As used herein, the term “[(hydroxy-C.sub.1-8alkyl).sub.2-amino-C.sub.1-8 alkyl](C.sub.1-8alkyl)amino” refers to a radical of the formula: —N(C.sub.1-8alkyl)[C.sub.1-8alkyl-N(C.sub.1-8alkyl-OH).sub.2].
(154) As used herein, the term “(hydroxy-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino-C.sub.1-8alkyl-amino” refers to a radical of the formula: —NH—C.sub.1-8alkyl-N(C.sub.1-8alkyl,C.sub.1-8alkyl-OH).
(155) As used herein, the term “[(hydroxy-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino-C.sub.1-8alkyl](C.sub.1-8alkyl)amino” refers to a radical of the formula: —N(C.sub.1-8alkyl) [C.sub.1-8 alkyl-N(C.sub.1-8 alkyl)(C.sub.1-8alkyl-OH)].
(156) As used herein, the term “substituent” means positional variables on the atoms of a core molecule that are substituted at a designated atom position, replacing one or more hydrogens on the designated atom, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. A person of ordinary skill in the art should note that any carbon as well as heteroatom with valences that appear to be unsatisfied as described or shown herein is assumed to have a sufficient number of hydrogen atom(s) to satisfy the valences described or shown. In certain instances one or more substituents having a double bond (e.g., “oxo” or “═O”) as the point of attachment may be described, shown or listed herein within a substituent group, wherein the structure may only show a single bond as the point of attachment to the core structure of Formula (I). A person of ordinary skill in the art would understand that, while only a single bond is shown, a double bond is intended for those substituents.
(157) As used herein, the term “and the like,” with reference to the definitions of chemical terms provided herein, means that variations in chemical structures that could be expected by one skilled in the art include, without limitation, isomers (including chain, branching or positional structural

isomers), hydration of ring systems (including saturation or partial unsaturation of monocyclic, bicyclic or polycyclic ring structures) and all other variations where allowed by available valences which result in a stable compound.
(158) For the purposes of this description, where one or more substituent variables for a compound of Formula (I) or a form thereof encompass functionalities incorporated into a compound of Formula (I), each functionality appearing at any location within the disclosed compound may be independently selected, and as appropriate, independently and/or optionally substituted.
(159) As used herein, the terms “independently selected,” or “each selected” refer to functional variables in a substituent list that may occur more than once on the structure of Formula (I), the pattern of substitution at each occurrence is independent of the pattern at any other occurrence. Further, the use of a generic substituent variable on any formula or structure for a compound described herein is understood to include the replacement of the generic substituent with species substituents that are included within the particular genus, e.g., aryl may be replaced with phenyl or naphthalenyl and the like, and that the resulting compound is to be included within the scope of the compounds described herein.
(160) As used herein, the terms “each instance of” or “in each instance, when present,” when used preceding a phrase such as “ . . . C.sub.1-14cycloalkyl, C.sub.1-14cycloalkyl-C.sub.1-4alkyl, aryl, aryl-C.sub.1-4alkyl, heteroaryl, heteroaryl-C.sub.1-4alkyl, heterocyclyl and heterocyclyl-C.sub.1-4alkyl,” are intended to refer to the C.sub.1-14cycloalkyl, aryl, heteroaryl and heterocyclyl ring systems when each are present either alone or as a substituent.
(161) As used herein, the term “optionally substituted” means optional substitution with the specified substituent variables, groups, radicals or moieties.
(162) Compound Forms
(163) As used herein, the term “form” means a compound of Formula (I) having a form selected from the group consisting of a free acid, free base, prodrug, salt, hydrate, solvate, clathrate, isotopologue, racemate, enantiomer, diastereomer, stereoisomer, polymorph and tautomer form thereof.
(164) In certain aspects described herein, the form of the compound of Formula (I) is a free acid, free base or salt thereof.
(165) In certain aspects described herein, the form of the compound of Formula (I) is a salt thereof.
(166) In certain aspects described herein, the form of the compound of Formula (I) is an isotopologue thereof.
(167) In certain aspects described herein, the form of the compound of Formula (I) is a stereoisomer, racemate, enantiomer or diastereomer thereof.
(168) In certain aspects described herein, the form of the compound of Formula (I) is a tautomer thereof.
(169) In certain aspects described herein, the form of the compound of Formula (I) is a pharmaceutically acceptable form.
(170) In certain aspects described herein, the compound of Formula (I) or a form thereof is isolated for use.
(171) As used herein, the term “isolated” means the physical state of a compound of Formula (I) or a form thereof after being isolated and/or purified from a synthetic process (e.g., from a reaction mixture) or natural source or combination thereof according to an isolation or purification process or processes described herein or which are well known to the skilled artisan (e.g., chromatography, recrystallization and the like) in sufficient purity to be characterized by standard analytical techniques described herein or well known to the skilled artisan.
(172) As used herein, the term “protected” means that a functional group in a compound of Formula (I) or a form thereof is in a form modified to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such

as, for example, T. W. Greene et al, Protective Groups in organic Synthesis (1991), Wiley, New York. Such functional groups include hydroxy, phenol, amino and carboxylic acid. Suitable protecting groups for hydroxy or phenol include trialkylsilyl or diarylalkylsilyl (e.g., t-butyldimethylsilyl, t-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl, benzyl, substituted benzyl, methyl, methoxymethanol, and the like. Suitable protecting groups for amino, amidino and guanidino include t-butoxycarbonyl, benzyloxycarbonyl, and the like. Suitable protecting groups for carboxylic acid include alkyl, aryl or arylalkyl esters. In certain instances, the protecting group may also be a polymer resin, such as a Wang resin or a 2-chlorotrityl-chloride resin. Protecting groups may be added or removed in accordance with standard techniques, which are well-known to those skilled in the art and as described herein. It will also be appreciated by those skilled in the art, although such protected derivatives of compounds described herein may not possess pharmacological activity as such, they may be administered to a subject and thereafter metabolized in the body to form compounds described herein which are pharmacologically active. Such derivatives may therefore be described as “prodrugs”. All prodrugs of compounds described herein are included within the scope of the use described herein.

(173) As used herein, the term “prodrug” means a form of an instant compound (e.g., a drug precursor) that is transformed in vivo to yield an active compound of Formula (I) or a form thereof. The transformation may occur by various mechanisms (e.g., by metabolic and/or non-metabolic chemical processes), such as, for example, by hydrolysis and/or metabolism in blood, liver and/or other organs and tissues. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, “Pro-drugs as Novel Delivery Systems,” Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

(174) In one example, when a compound of Formula (I) or a form thereof contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a functional group such as alkyl and the like. In another example, when a compound of Formula (I) or a form thereof contains a hydroxyl functional group, a prodrug form can be prepared by replacing the hydrogen atom of the hydroxyl with another functional group such as alkyl, alkylcarbonyl or a phosphonate ester and the like. In another example, when a compound of Formula (I) or a form thereof contains an amine functional group, a prodrug form can be prepared by replacing one or more amine hydrogen atoms with a functional group such as alkyl or substituted carbonyl. Pharmaceutically acceptable prodrugs of compounds of Formula (I) or a form thereof include those compounds substituted with one or more of the following groups: carboxylic acid esters, sulfonate esters, amino acid esters, phosphonate esters and mono-, di- or triphosphate esters or alkyl substituents, where appropriate. As described herein, it is understood by a person of ordinary skill in the art that one or more of such substituents may be used to provide a compound of Formula (I) or a form thereof as a prodrug.

(175) One or more compounds described herein may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and the description herein is intended to embrace both solvated and unsolvated forms.

(176) As used herein, the term “solvate” means a physical association of a compound described herein with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. As used herein, “solvate” encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like.

(177) As used herein, the term “hydrate” means a solvate wherein the solvent molecule is water.

(178) The compounds of Formula (I) can form salts, which are intended to be included within the scope of this description. Reference to a compound of Formula (I) or a form thereof herein is

understood to include reference to salt forms thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula (I) or a form thereof contains both a basic moiety, such as, without limitation an amine moiety, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein.

(179) The term "pharmaceutically acceptable salt(s)", as used herein, means those salts of compounds described herein that are safe and effective (i.e., non-toxic, physiologically acceptable) for use in mammals and that possess biological activity, although other salts are also useful. Salts of the compounds of the Formula (I) may be formed, for example, by reacting a compound of Formula (I) or a form thereof with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

(180) Pharmaceutically acceptable salts include one or more salts of acidic or basic groups present in compounds described herein. Particular aspects of acid addition salts include, and are not limited to, acetate, ascorbate, benzoate, benzenesulfonate, bisulfate, bitartrate, borate, bromide, butyrate, chloride, citrate, camphorate, camphorsulfonate, ethanesulfonate, formate, fumarate, gentisinate, gluconate, glucaronate, glutamate, iodide, isonicotinate, lactate, maleate, methanesulfonate, naphthalenesulfonate, nitrate, oxalate, pamoate, pantothenate, phosphate, propionate, saccharate, salicylate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate (also known as tosylate), trifluoroacetate salts and the like. Certain particular aspects of acid addition salts include chloride or dichloride.

(181) Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl et al, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use*. (2002) Zurich: Wiley-VCH; S. Berge et al, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33, 201-217; Anderson et al, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

(182) Suitable basic salts include, but are not limited to, aluminum, ammonium, calcium, lithium, magnesium, potassium, sodium and zinc salts.

(183) All such acid salts and base salts are intended to be included within the scope of pharmaceutically acceptable salts as described herein. In addition, all such acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of this description.

(184) Compounds of Formula (I) and forms thereof, may further exist in a tautomeric form. All such tautomeric forms are contemplated and intended to be included within the scope of the compounds of Formula (I) or a form thereof as described herein.

(185) The compounds of Formula (I) or a form thereof may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. The present description is intended to include all stereoisomeric forms of the compounds of Formula (I) as well as mixtures thereof, including racemic mixtures.

(186) The compounds described herein may include one or more chiral centers, and as such may exist as racemic mixtures (R/S) or as substantially pure enantiomers and diastereomers. The compounds may also exist as substantially pure (R) or (S) enantiomers (when one chiral center is present). In one particular aspect, the compounds described herein are (S) isomers and may exist as enantiomerically pure compositions substantially comprising only the (S) isomer. In another particular aspect, the compounds described herein are (R) isomers and may exist as enantiomerically pure compositions substantially comprising only the (R) isomer. As one of skill in

the art will recognize, when more than one chiral center is present, the compounds described herein may also exist as a (R,R), (R,S), (S,R) or (S,S) isomer, as defined by IUPAC Nomenclature Recommendations.

(187) As used herein, the term “substantially pure” refers to compounds consisting substantially of a single isomer in an amount greater than or equal to 90%, in an amount greater than or equal to 92%, in an amount greater than or equal to 95%, in an amount greater than or equal to 98%, in an amount greater than or equal to 99%, or in an amount equal to 100% of the single isomer.

(188) In one aspect of the description, a compound of Formula (I) or a form thereof is a substantially pure (S) enantiomer form present in an amount greater than or equal to 90%, in an amount greater than or equal to 92%, in an amount greater than or equal to 95%, in an amount greater than or equal to 98%, in an amount greater than or equal to 99%, or in an amount equal to 100%.

(189) In one aspect of the description, a compound of Formula (I) or a form thereof is a substantially pure (R) enantiomer form present in an amount greater than or equal to 90%, in an amount greater than or equal to 92%, in an amount greater than or equal to 95%, in an amount greater than or equal to 98%, in an amount greater than or equal to 99%, or in an amount equal to 100%.

(190) As used herein, a “racemate” is any mixture of isometric forms that are not “enantiomerically pure”, including mixtures such as, without limitation, in a ratio of about 50/50, about 60/40, about 70/30, or about 80/20.

(191) In addition, the present description embraces all geometric and positional isomers. For example, if a compound of Formula (I) or a form thereof incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the description. Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by use of chiral HPLC column or other chromatographic methods known to those skilled in the art. Enantiomers can also be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of Formula (I) may be atropisomers (e.g., substituted biaryls) and are considered as part of this description.

(192) All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this description, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). Individual stereoisomers of the compounds described herein may, for example, be substantially free of other isomers, or may be present in a racemic mixture, as described supra.

(193) The use of the terms “salt”, “solvate”, “ester”, “prodrug” and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or isotopologues of the instant compounds.

(194) The term “isotopologue” refers to isotopically-enriched compounds described herein which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds described herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as

.sup.2H, .sup.3H, .sup.13C, .sup.14C, .sup.15N, .sup.18O, .sup.17O, .sup.31P, .sup.32P, .sup.35S, .sup.18F, .sup.35C and .sup.36Cl, respectively, each of which are also within the scope of this description.

(195) Certain isotopically-enriched compounds described herein (e.g., those labeled with .sup.3H and .sup.14C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., .sup.3H) and carbon-14 (i.e., .sup.14C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., .sup.2H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances.

(196) Polymorphic crystalline and amorphous forms of the compounds of Formula (I) and of the salts, solvates, hydrates, esters and prodrugs of the compounds of Formula (I) are further intended to be included in the present description.

(197) Compound Uses

(198) In accordance with the intended scope of the present description, aspects of the present description include compounds that have been identified and have been demonstrated to be useful in selectively preventing, treating or ameliorating HD and have been provided for use for preventing, treating or ameliorating HD.

(199) An aspect of the present description includes a method for preventing, treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of a compound of Formula (I) or a form thereof.

(200) An aspect of the present description includes a method for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of a compound of Formula (I) or a form thereof.

(201) An aspect of the present description includes a method for preventing HD in a subject in need thereof comprising, administering to the subject an effective amount of a compound of Formula (I) or a form thereof.

(202) An aspect of the present description includes a method for treating HD in a subject in need thereof comprising, administering to the subject an effective amount of a compound of Formula (I) or a form thereof.

(203) An aspect of the present description includes a method for ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of a compound of Formula (I) or a form thereof.

(204) Another aspect of the present description includes a method for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of a compound salt of Formula (I) or a form thereof.

(205) An aspect of the present description includes a method for use of a compound of Formula (I) or a form or composition thereof for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of the compound of Formula (I) or a form or composition thereof.

(206) Another aspect of the present description includes a method for use of a compound salt of Formula (I) or a form or composition thereof for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of the compound salt of Formula (I) or a form thereof.

(207) An aspect of the present description includes a use for a compound of Formula (I) or a form thereof for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of the compound of Formula (I) or a form thereof.

(208) Another aspect of the present description includes a use for a compound salt of Formula (I) or a form thereof for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of the compound salt of Formula (I) or a form

thereof.
(209) An aspect of the present description includes a use for a compound of Formula (I) or a form thereof in the manufacture of a medicament for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of the medicament.
(210) Another aspect of the present description includes a use for a compound salt of Formula (I) or a form thereof in the manufacture of a medicament for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of the medicament.
(211) An aspect of the present description includes in vitro or in vivo use of the compound of Formula (I) or a form thereof having activity toward HD.
(212) An aspect of the present description includes a use of the compound of Formula (I) or a form thereof in a combination therapy to provide additive or synergistic activity, thus enabling the development of a combination product for treating or ameliorating HD.
(213) Another aspect of the present description includes a combination therapy comprising compounds described herein in combination with one or more known drugs or one or more known therapies may be used to treat HD regardless of whether HD is responsive to the known drug.
(214) An aspect of the present description includes a use for a compound of Formula (I) or a form thereof in a combination product with one or more therapeutic agents for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of the compound of Formula (I) or a form thereof in combination with an effective amount of the one or more agents.
(215) Another aspect of the present description includes a use for a compound salt of Formula (I) or a form thereof in a combination product with one or more therapeutic agents for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of the compound salt of Formula (I) or a form thereof in combination with an effective amount of the one or more agents.
(216) In an aspect of a use or method provided herein, compounds of Formula (I) or a form thereof used in combination with one or more additional agents can be administered to a subject or contacted with a subject or patient cell(s) prior to, concurrently with, or subsequent to administering to the subject or patient or contacting the cell with an additional agent(s). A compound(s) of Formula (I) or a form thereof and an additional agent(s) can be administered to a subject or contacted with a cell in single composition or different compositions. In a specific aspect, a compound(s) of Formula (I) or a form thereof is used in combination with gene therapy to inhibit HTT expression (using, e.g., viral delivery vectors) or the administration of another small molecule HTT inhibitor. In another specific aspect, a compound(s) of Formula (I) or a form thereof are used in combination with cell replacement using differentiated non-mutant HTT stem cells. In another specific aspect, a compound(s) of Formula (I) or a form thereof are used in combination with cell replacement using differentiated HTT stem cells.
(217) In one aspect, provided herein is the use of compounds of Formula (I) or a form thereof in combination with supportive standard of care therapies, including palliative care.
(218) An aspect of the present description includes a use for a compound of Formula (I) or a form thereof in the preparation of a kit for treating or ameliorating HD in a subject in need thereof comprising, the compound of Formula (I) or a form thereof and instructions for administering an effective amount of the compound of Formula (I) or a form thereof.
(219) An aspect of the present description includes a use for a compound of Formula (I) or a form thereof in the preparation of a kit for treating or ameliorating HD in a subject in need thereof comprising, the compound of Formula (I) or a form thereof and instructions for administering an effective amount of the compound of Formula (I) or a form thereof; and optionally, for administering to the subject an effective amount of the compound of Formula (I) or a form thereof in a combination product with an effective amount of one or more therapeutic agents.
(220) An aspect of the present description includes a use for a compound of Formula (I) or a form

thereof in the preparation of a kit for treating or ameliorating HD in a subject in need thereof comprising, the compound of Formula (I) or a form thereof and instructions for administering an effective amount of the compound of Formula (I) or a form thereof; and optionally, for administering to the subject an effective amount of the compound of Formula (I) or a form thereof in a combination product with an effective amount of the one or more therapeutic agents; and optionally, for administering to the subject an effective amount of the compound of Formula (I) or a form thereof in a combination product with an effective amount of the one or more therapeutic agents in a combination therapy with a standard of care supportive therapy, wherein the standard of care supportive therapy is palliative care.

(221) In one respect, for each of such aspects, the subject is treatment naive. In another respect, for each of such aspects, the subject is not treatment naive.

(222) As used herein, the term “preventing” refers to keeping a disease, disorder or condition from occurring in a subject that may be predisposed to the disease, disorder and/or condition but has not yet been diagnosed as having the disease, disorder and/or condition.

(223) As used herein, the term “treating” refers to inhibiting the progression of a disease, disorder or condition in a subject already exhibiting the symptoms of the disease, disorder and/or condition, i.e., arresting the development of a disease, disorder and/or condition that has already affected the subject.

(224) As used herein, the term “ameliorating” refers to relieving the symptoms of a disease, disorder or condition in a subject already exhibiting the symptoms of the disease, disorder and/or condition, i.e., causing regression of the disease, disorder and/or condition that has already affected the subject.

(225) As used herein, the term “subject” refers to an animal or any living organism having sensation and the power of voluntary movement, and which requires oxygen and organic food. Nonlimiting examples include members of the human, primate, equine, porcine, bovine, murine, rattus, canine and feline specie. In certain aspects, the subject is a mammal or a warm-blooded vertebrate animal. In other aspects, the subject is a human. As used herein, the term “patient” may be used interchangeably with “subject” and “human”.

(226) As used herein, the terms “effective amount” or “therapeutically effective amount” mean an amount of compound of Formula (I) or a form, composition or medicament thereof that achieves a target plasma concentration that is effective in treating or ameliorating HD as described herein and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect in a subject in need thereof. In one aspect, the effective amount may be the amount required to treat HD in a subject or patient, more specifically, in a human.

(227) In another aspect, the concentration-biological effect relationships observed with regard to a compound of Formula (I) or a form thereof indicate a target plasma concentration ranging from approximately 0.001 μg/mL to approximately 50 μg/mL, from approximately 0.01 μg/mL to approximately 20 μg/mL, from approximately 0.05 μg/mL to approximately 10 μg/mL, or from approximately 0.1 μg/mL to approximately 5 μg/mL. To achieve such plasma concentrations, the compounds described herein may be administered at doses that vary, such as, for example, without limitation, from 1.0 ng to 10,000 mg.

(228) In one aspect, the dose administered to achieve an effective target plasma concentration may be administered based upon subject or patient specific factors, wherein the doses administered on a weight basis may be in the range of from about 0.001 mg/kg/day to about 3500 mg/kg/day, or about 0.001 mg/kg/day to about 3000 mg/kg/day, or about 0.001 mg/kg/day to about 2500 mg/kg/day, or about 0.001 mg/kg/day to about 2000 mg/kg/day, or about 0.001 mg/kg/day to about 1500 mg/kg/day, or about 0.001 mg/kg/day to about 1000 mg/kg/day, or about 0.001 mg/kg/day to about 500 mg/kg/day, or about 0.001 mg/kg/day to about 250 mg/kg/day, or about 0.001 mg/kg/day to about 200 mg/kg/day, or about 0.001 mg/kg/day to about 150 mg/kg/day, or about 0.001 mg/kg/day to about 100 mg/kg/day, or about 0.001 mg/kg/day to about 75 mg/kg/day, or about 0.001

mg/kg/day to about 50 mg/kg/day, or about 0.001 mg/kg/day to about 25 mg/kg/day, or about 0.001 mg/kg/day to about 10 mg/kg/day, or about 0.001 mg/kg/day to about 5 mg/kg/day, or about 0.001 mg/kg/day to about 1 mg/kg/day, or about 0.001 mg/kg/day to about 0.5 mg/kg/day, or about 0.001 mg/kg/day to about 0.1 mg/kg/day, or from about 0.01 mg/kg/day to about 3500 mg/kg/day, or about 0.01 mg/kg/day to about 3000 mg/kg/day, or about 0.01 mg/kg/day to about 2500 mg/kg/day, or about 0.01 mg/kg/day to about 2000 mg/kg/day, or about 0.01 mg/kg/day to about 1500 mg/kg/day, or about 0.01 mg/kg/day to about 1000 mg/kg/day, or about 0.01 mg/kg/day to about 500 mg/kg/day, or about 0.01 mg/kg/day to about 250 mg/kg/day, or about 0.01 mg/kg/day to about 200 mg/kg/day, or about 0.01 mg/kg/day to about 150 mg/kg/day, or about 0.01 mg/kg/day to about 100 mg/kg/day, or about 0.01 mg/kg/day to about 75 mg/kg/day, or about 0.01 mg/kg/day to about 50 mg/kg/day, or about 0.01 mg/kg/day to about 25 mg/kg/day, or about 0.01 mg/kg/day to about 10 mg/kg/day, or about 0.01 mg/kg/day to about 5 mg/kg/day, or about 0.01 mg/kg/day to about 1 mg/kg/day, or about 0.01 mg/kg/day to about 0.5 mg/kg/day, or about 0.01 mg/kg/day to about 0.1 mg/kg/day, or from about 0.1 mg/kg/day to about 3500 mg/kg/day, or about 0.1 mg/kg/day to about 3000 mg/kg/day, or about 0.1 mg/kg/day to about 2500 mg/kg/day, or about 0.1 mg/kg/day to about 2000 mg/kg/day, or about 0.1 mg/kg/day to about 1500 mg/kg/day, or about 0.1 mg/kg/day to about 1000 mg/kg/day, or about 0.1 mg/kg/day to about 500 mg/kg/day, or about 0.1 mg/kg/day to about 250 mg/kg/day, or about 0.1 mg/kg/day to about 200 mg/kg/day, or about 0.1 mg/kg/day to about 150 mg/kg/day, or about 0.1 mg/kg/day to about 100 mg/kg/day, or about 0.1 mg/kg/day to about 75 mg/kg/day, or about 0.1 mg/kg/day to about 50 mg/kg/day, or about 0.1 mg/kg/day to about 25 mg/kg/day, or about 0.1 mg/kg/day to about 10 mg/kg/day, or about 0.1 mg/kg/day to about 5 mg/kg/day, or about 0.1 mg/kg/day to about 1 mg/kg/day, or about 0.1 mg/kg/day to about 0.5 mg/kg/day.

(229) Effective amounts for a given subject may be determined by routine experimentation that is within the skill and judgment of a clinician or a practitioner skilled in the art in light of factors related to the subject. Dosage and administration may be adjusted to provide sufficient levels of the active agent(s) or to maintain the desired effect. Factors which may be taken into account include genetic screening, severity of the disease state, status of disease progression, general health of the subject, ethnicity, age, weight, gender, diet, time of day and frequency of administration, drug combination(s), reaction sensitivities, experience with other therapies, and tolerance/response to therapy.

(230) The dose administered to achieve an effective target plasma concentration may be orally administered once (once in approximately a 24 hour period; i.e., “q.d.”), twice (once in approximately a 12 hour period; i.e., “b.i.d.” or “q.12h”), thrice (once in approximately an 8 hour period; i.e., “t.i.d.” or “q.8h”), or four times (once in approximately a 6 hour period; i.e., “q.d.s.”, or “q.6h”) daily.

(231) In certain aspects, the dose administered to achieve an effective target plasma concentration may also be administered in a single, divided, or continuous dose for a patient or subject having a weight in a range of between about 40 to about 200 kg (which dose may be adjusted for patients or subjects above or below this range, particularly children under 40 kg). The typical adult subject is expected to have a median weight in a range of about 70 kg. Long-acting pharmaceutical compositions may be administered every 2, 3 or 4 days, once every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

(232) The compounds and compositions described herein may be administered to the subject via any drug delivery route known in the art. Nonlimiting examples include oral, ocular, rectal, buccal, topical, nasal, sublingual, transdermal, subcutaneous, intramuscular, intraveneous (bolus and infusion), intracerebral, and pulmonary routes of administration.

(233) In another aspect, the dose administered may be adjusted based upon a dosage form described herein formulated for delivery at about 0.02, 0.025, 0.03, 0.05, 0.06, 0.075, 0.08, 0.09, 0.10, 0.20, 0.25, 0.30, 0.50, 0.60, 0.75, 0.80, 0.90, 1.0, 1.10, 1.20, 1.25, 1.50, 1.75, 2.0, 3.0, 5.0, 10,

20, 30, 40, 50, 100, 150, 200, 250, 300, 400, 500, 1000, 1500, 2000, 2500, 3000 or 4000 mg/day.
(234) For any compound, the effective amount can be estimated initially either in cell culture assays or in relevant animal models, such as a mouse, guinea pig, chimpanzee, marmoset or tamarin animal model. Relevant animal models may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., ED.sub.50 (the dose therapeutically effective in 50% of the population) and LD.sub.50 (the dose lethal to 50% of the population). The dose ratio between therapeutic and toxic effects is therapeutic index, and can be expressed as the ratio, LD.sub.50/ED.sub.50. In certain aspects, the effective amount is such that a large therapeutic index is achieved. In further particular aspects, the dosage is within a range of circulating concentrations that include an ED.sub.50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.
(235) In one aspect, provided herein are methods for modulating the amount of HTT (huntingtin protein), comprising contacting a human cell with a compound of Formula (I) or a form thereof. In a specific aspect, provided herein are methods for modulating the amount of HTT, comprising contacting a human cell with a compound of Formula (I) or a form thereof that modulates the expression of HTT. The human cell can be contacted with a compound of Formula (I) or a form thereof in vitro, or in vivo, e.g., in a non-human animal or in a human. In a specific aspect, the human cell is from or in a human. In another specific aspect, the human cell is from or in a human with HD. In another specific aspect, the human cell is from or in a human with HD, caused by a CAG repeat in the Htt gene, resulting in a loss of HTT expression and/or function. In another aspect, the human cell is from a human with HD. In another aspect, the human cell is in a human with HD. In one aspect, the compound is a form of the compound of Formula (I).
(236) In a specific aspect, provided herein is a method for enhancing the inhibition of mutant HTT transcribed from the Htt gene, comprising contacting a human cell with a compound of Formula (I) or a form thereof. The human cell can be contacted with a compound of Formula (I) or a form thereof in vitro, or in vivo, e.g., in a non-human animal or in a human. In a specific aspect, the human cell is from or in a human. In another specific aspect, the human cell is from or in a human with HD. In another specific aspect, the human cell is from or in a human with HD, caused by a CAG repeat in the Htt gene, resulting in a loss of wild-type “normal” HTT expression and/or function. In another aspect, the human cell is from a human with HD. In another aspect, the human cell is in a human with HD. In one aspect, the compound is a form of the compound of Formula (I).
(237) In another aspect, provided herein is a method for modulating the inhibition of mutant HTT transcribed from the Htt gene, comprising administering to a non-human animal model for HD a compound of Formula (I) or a form thereof. In a specific aspect, provided herein is a method for modulating the inhibition of mutant HTT transcribed from the Htt gene, comprising administering to a non-human animal model for HD a compound of Formula (I) or a form thereof. In a specific aspect, the compound is a form of the compound of Formula (I).
(238) In another aspect, provided herein is a method for decreasing the amount of mutant HTT, comprising contacting a human cell with a compound of Formula (I) or a form thereof. In a specific aspect, provided herein is a method for decreasing the amount of mutant HTT, comprising contacting a human cell with a compound of Formula (I) that inhibits the transcription of mutant HTT (huntingtin mRNA) from the Htt gene. In another specific aspect, provided herein is a method for decreasing the amount of HTT, comprising contacting a human cell with a compound of Formula (I) that inhibits the expression of mutant HTT transcribed from the Htt gene. The human cell can be contacted with a compound of Formula (I) or a form thereof in vitro, or in vivo, e.g., in a non-human animal or in a human. In a specific aspect, the human cell is from or in a human. In another specific aspect, the human cell is from or in a human with HD. In another specific aspect,

the human cell is from or in a human with HD, caused by a CAG repeat in the Htt gene, resulting in a loss of HTT expression and/or function. In another aspect, the human cell is from a human with HD. In another aspect, the human cell is in a human with HD. In one aspect, the compound is a form of the compound of Formula (I).

(239) In certain aspects, treating or ameliorating HD with a compound of Formula (I) or a form thereof (alone or in combination with an additional agent) has a therapeutic effect and/or beneficial effect. In a specific aspect, treating HD with a compound of Formula (I) or a form thereof (alone or in combination with an additional agent) results in one, two or more of the following effects: (i) reduces or ameliorates the severity of HD; (ii) delays onset of HD; (iii) inhibits the progression of HD; (iv) reduces hospitalization of a subject; (v) reduces hospitalization length for a subject; (vi) increases the survival of a subject; (vii) improves the quality of life for a subject; (viii) reduces the number of symptoms associated with HD; (ix) reduces or ameliorates the severity of a symptom(s) associated with HD; (x) reduces the duration of a symptom associated with HD; (xi) prevents the recurrence of a symptom associated with HD; (xii) inhibits the development or onset of a symptom of HD; and/or (xiii) inhibits of the progression of a symptom associated with HD.

(240) Metabolites

(241) Another aspect included within the scope of the present description are the use of in vivo metabolic products of the compounds described herein. Such products may result, for example, from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the description includes the use of compounds produced by a process comprising contacting a compound described herein with a mammalian tissue or a mammal for a period of time sufficient to yield a metabolic product thereof.

(242) Such products typically are identified by preparing a radio-labeled isotopologue (e.g., .sup.14C or .sup.3H) of a compound described herein, administering the radio-labeled compound in a detectable dose (e.g., greater than about 0.5 mg/kg) to a mammal such as a rat, mouse, guinea pig, dog, monkey or human, allowing sufficient time for metabolism to occur (typically about 30 seconds to about 30 hours), and identifying the metabolic conversion products from urine, bile, blood or other biological samples. The conversion products are easily isolated since they are "radiolabeled" by virtue of being isotopically-enriched (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g., by MS or NMR analysis. In general, analysis of metabolites may be done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found in vivo, are useful in diagnostic assays for therapeutic dosing of the compounds described herein even if they possess no biological activity of their own.

(243) Pharmaceutical Compositions

(244) In accordance with the intended scope of the present description, aspects of the present description include compounds that have been identified and have been demonstrated to be useful in selectively preventing, treating or ameliorating HD and have been provided for use as one or more pharmaceutical compositions for preventing, treating or ameliorating HD.

(245) An aspect of the present description includes a use for a compound of Formula (I) or a form thereof in the preparation of a pharmaceutical composition for treating or ameliorating HD in a subject in need thereof comprising, administering to the subject an effective amount of the compound of Formula (I) or a form thereof in admixture with one or more pharmaceutically acceptable excipients.

(246) An aspect of the present description includes a use for a pharmaceutical composition of the compound of Formula (I) or a form thereof in the preparation of a kit for treating or ameliorating HD in a subject in need thereof comprising, the pharmaceutical composition of the compound of Formula (I) or a form thereof and instructions for administering the pharmaceutical composition.

(247) As used herein, the term "composition" means a product comprising the specified ingredients

in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

(248) The pharmaceutical composition may be formulated to achieve a physiologically compatible pH, ranging from about pH 3 to about pH 11. In certain aspects, the pharmaceutical composition is formulated to achieve a pH of from about pH 3 to about pH 7. In other aspects, the pharmaceutical composition is formulated to achieve a pH of from about pH 5 to about pH 8.

(249) The term “pharmaceutically acceptable excipient” refers to an excipient for administration of a pharmaceutical agent, such as the compounds described herein. The term refers to any pharmaceutical excipient that may be administered without undue toxicity. Pharmaceutically acceptable excipients may be determined in part by the particular composition being administered, as well as by the particular mode of administration and/or dosage form. Nonlimiting examples of pharmaceutically acceptable excipients include carriers, solvents, stabilizers, adjuvants, diluents, etc. Accordingly, there exists a wide variety of suitable formulations of pharmaceutical compositions for the instant compounds described herein (see, e.g., Remington's Pharmaceutical Sciences).

(250) Suitable excipients may be carrier molecules that include large, slowly metabolized macromolecules such as proteins, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers, and inactive antibodies. Other exemplary excipients include antioxidants such as ascorbic acid; chelating agents such as EDTA; carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose (e.g., hydroxypropylmethylcellulose, also known as HPMC), stearic acid; liquids such as oils, water, saline, glycerol and ethanol; wetting or emulsifying agents; pH buffering substances; and the like. Liposomes are also included within the definition of pharmaceutically acceptable excipients.

(251) The pharmaceutical compositions described herein may be formulated in any form suitable for the intended use described herein. Suitable formulations for oral administration include solids, liquid solutions, emulsions and suspensions, while suitable inhalable formulations for pulmonary administration include liquids and powders. Alternative formulations include syrups, creams, ointments, tablets, and lyophilized solids which can be reconstituted with a physiologically compatible solvent prior to administration.

(252) When intended for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, non-aqueous solutions, dispersible powders or granules (including micronized particles or nanoparticles), emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents, and preserving agents, in order to provide a palatable preparation.

(253) Pharmaceutically acceptable excipients suitable for use in conjunction with tablets include, for example, inert diluents, such as celluloses, calcium or sodium carbonate, lactose, calcium or sodium phosphate; disintegrating agents, such as croscarmellose sodium, cross-linked povidone, maize starch, or alginic acid; binding agents, such as povidone, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid, or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

(254) Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example celluloses, lactose, calcium phosphate, or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with non-aqueous or oil medium, such as glycerin, propylene glycol, polyethylene glycol, peanut oil, liquid paraffin, or olive oil.

(255) In other aspects, pharmaceutical compositions described herein may be formulated as suspensions comprising a compound of Formula (I) or a form thereof in admixture with one or more pharmaceutically acceptable excipients suitable for the manufacture of a suspension. In yet other aspects, pharmaceutical compositions described herein may be formulated as dispersible powders and granules suitable for preparation of a suspension by the addition of one or more excipients.
(256) Excipients suitable for use in connection with suspensions include suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth, gum acacia, dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycethanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate); and thickening agents, such as carbomer, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives such as acetic acid, methyl and/or n-propyl p-hydroxy-benzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.
(257) The pharmaceutical compositions described herein may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth; naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids; hexitol anhydrides, such as sorbitan monooleate; and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.
(258) Additionally, the pharmaceutical compositions described herein may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous emulsion or oleaginous suspension. Such emulsion or suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,2-propanediol. The sterile injectable preparation may also be prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or di-glycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.
(259) The compounds described herein may be substantially insoluble in water and sparingly soluble in most pharmaceutically acceptable protic solvents and vegetable oils, but generally soluble in medium-chain fatty acids (e.g., caprylic and capric acids) or triglycerides and in propylene glycol esters of medium-chain fatty acids. Thus, contemplated in the description are compounds which have been modified by substitutions or additions of chemical or biochemical moieties which make them more suitable for delivery (e.g., increase solubility, bioactivity, palatability, decrease adverse reactions, etc.), for example by esterification, glycosylation, PEGylation, etc.
(260) In certain aspects, the compound described herein is formulated for oral administration in a lipid-based composition suitable for low solubility compounds. Lipid-based formulations can generally enhance the oral bioavailability of such compounds. As such, pharmaceutical

compositions described herein may comprise a effective amount of a compound of Formula (I) or a form thereof, together with at least one pharmaceutically acceptable excipient selected from medium chain fatty acids or propylene glycol esters thereof (e.g., propylene glycol esters of edible fatty acids such as caprylic and capric fatty acids) and pharmaceutically acceptable surfactants, such as polysorbate 20 or 80 (also referred to as Tween® 20 or Tween® 80, respectively) or polyoxyl 40 hydrogenated castor oil.
(261) In other aspects, the bioavailability of low solubility compounds may be enhanced using particle size optimization techniques including the preparation of nanoparticles or nanosuspensions using techniques known to those skilled in the art. The compound forms present in such preparations include amorphous, partially amorphous, partially crystalline or crystalline forms.
(262) In alternative aspects, the pharmaceutical composition may further comprise one or more aqueous solubility enhancer(s), such as a cyclodextrin. Nonlimiting examples of cyclodextrin include hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of α-, β-, and γ-cyclodextrin, and hydroxypropyl-β-cyclodextrin (HPBC). In certain aspects, the pharmaceutical composition further comprises HPBC in a range of from about 0.1% to about 20%, from about 1% to about 15%, or from about 2.5% to about 10%. The amount of solubility enhancer employed may depend on the amount of the compound in the composition.
(263) Preparation of Compounds
(264) General Synthetic Methods
(265) As disclosed herein, general methods for preparing the compounds of Formula (I) or a form thereof as described herein are available via standard, well-known synthetic methodology. Many of the starting materials are commercially available or, when not available, can be prepared using the routes described below using techniques known to those skilled in the art. The synthetic schemes provided herein comprise multiple reaction steps, each of which is intended to stand on its own and can be carried out with or without any preceding or succeeding step(s). In other words, each of the individual reaction steps of the synthetic schemes provided herein in isolation is contemplated.
(266) Compounds of Formula (I), wherein R.sub.1 and R.sub.2 are monocyclic or bicyclic heterocyclyl or heteroaryl ring systems, may be prepared as described in Scheme A below.
(267) ##STR00103##
(268) Compound A1 (where X.sub.1 and X.sub.2 are independently bromine, chlorine and the like) is converted to Compound A2 by a nucleophilic substitution with a primary or secondary amine in the presence of a suitable base (such as K.sub.2CO.sub.3 and the like) in a suitable solvent (such as DMF and the like). Alternatively, Compound A1 is converted to Compound A2 via cross coupling with a primary or secondary amine (i.e., an R.sub.1 substituent base) in the presence of a suitable catalyst (such as RuPhos Pd G2 and the like) and base (such as sodium tert-butoxide and the like) in an appropriate solvent (such as 1,4-dioxane and the like). Compound A2 is converted to Compound A3 by a Suzuki coupling with an aryl- or heteroaryl-boronic acid (or pinacol boronic ester) (i.e., an R.sub.2 substituted-boronic acid or ester) in the presence of a catalyst (such as Pd(dppf)Cl.sub.2 and the like) and base (such as aqueous K.sub.2CO.sub.3 and the like) in a suitable solvent (such as 1,4-dioxane and the like).
(269) Compounds of Formula (I), wherein R.sub.1 and R.sub.2 are monocyclic or bicyclic heterocyclyl or heteroaryl ring systems, may be prepared as described in Scheme B below.
(270) ##STR00104##
(271) Following conditions described in Scheme A, but switching the order of steps 1 and 2, compound B1 can be converted to compound A3.
(272) Compounds of Formula (I), wherein R.sub.1 and R.sub.2 are monocyclic or bicyclic heterocyclyl or heteroaryl ring systems, may be prepared as described in Scheme C below.
(273) ##STR00105##
(274) Compound B1 (where X.sub.1 is bromine, chlorine and the like) is converted to Compound C1 by a Suzuki coupling with an optionally substituted and appropriately protected amino-

containing cycloalkyl/cycloalkenyl pinacol boronic ester (where Y is hydrogen or an optionally substituted alkyl group and P is a protecting group such as Boc and the like) (i.e., an R.sub.1 substituted-boronic ester) in the presence of a catalyst (such as Pd(dppf)Cl.sub.2 and the like) and base (such as aqueous K.sub.2CO.sub.3 and the like) in a suitable solvent (such as 1,4-dioxane and the like). Alternatively, Compound B1 is converted to Compound C1 by a Negishi coupling with an optionally substituted and appropriately protected amino-containing cycloalkyl zinc halide (i.e., an R.sub.1 substituted-zinc halide) in the presence of a catalyst (such as Pd(dppf)Cl.sub.2 and the like) in a suitable solvent (such as 1,4-dioxane and the like). Upon treatment with a deprotecting agent appropriate for the protecting group (such as HCl in dioxane for a Boc protecting group), Compound C1 is converted to Compound C2. Compound C2 is converted to Compound C3 by reductive amination with a suitable aldehyde and reducing agent (such as NaBH(OAc).sub.3 and the like) in a suitable solvent (such as 1,2-dichloroethane and the like). Alternatively, Compound C2 is converted to Compound C3 by alkylation with an alkyl halide (such as 2-iodopropane and the like) in the presence of an appropriate base (such as K.sub.2CO.sub.3 and the like). In cases where unsaturation exists in the ring containing the basic amino group, the compound may be converted to the fully saturated analog under an atmosphere of H.sub.2 in a suitable solvent (such as methanol and the like) and in the presence of catalyst (such as 10% Pd/C and the like).

(275) Compounds of Formula (I), wherein R.sub.1 and R.sub.2 are monocyclic or bicyclic heterocyclyl or heteroaryl ring systems, may be prepared as described in Scheme D below.

(276) ##STR00106##

(277) Following the general conditions described in Scheme C, compound D1 can be converted to compound D5.

(278) Compounds of Formula (I), wherein R.sub.1 and R.sub.2 are monocyclic or bicyclic heterocyclyl or heteroaryl ring systems, may be prepared as described in Scheme E below.

(279) ##STR00107##

(280) Following the general conditions described in Scheme A and/or Scheme C, compound A1 can be converted to compound E1.

(281) Compounds of Formula (I), wherein R.sub.1 and R.sub.2 are monocyclic or bicyclic heterocyclyl or heteroaryl ring systems, may be prepared as described in Scheme F below.

(282) ##STR00108##

(283) Compound F1 (where X is bromine, chlorine and the like) is converted to Compound F2 through a condensation with an optionally substituted N-Boc-piperidine-4-aldehyde (where Y is hydrogen or an optionally substituted alkyl group and P is a protecting group such as Boc and the like) in a suitable solvent (such as EtOH and the like). Compound F2 is converted to Compound F3 by reducing the nitro group with H.sub.2 in the presence of a catalyst (such as PtO.sub.2 and the like) in an appropriate solvent (such as EtOH and the like). Compound F3 is converted to Compound F4 through a cyclization/oxidation reaction with an appropriate oxidant (such as DDQ and the like) in an appropriate solvent (such as CH.sub.3CN and the like). Compound F4 is converted to Compound F5 by a Suzuki coupling with an aryl- or heteroaryl-boronic acid (or pinacol boronic ester) (i.e., an R.sub.2 substituted-boronic acid or ester) in the presence of a catalyst (such as Pd(dppf)Cl.sub.2 and the like) and base (such as aqueous K.sub.2CO.sub.3 and the like) in a suitable solvent (such as 1,4-dioxane and the like). Alternatively, Compound F4 is converted to Compound F5 by treatment with pinacolatodiboron and a base (such as KOAc and the like) in the presence of a catalyst (such as Pd(dppf)Cl.sub.2 and the like) in an appropriate solvent (such as 1,4-dioxane and the like), followed by addition of an aryl- or heteroaryl-halide (i.e., an R.sub.2 substituted-halide). Compound F5 is converted to Compound F6 upon treatment with conditions appropriate to the removal of the protecting group (such as TFA or HCl in dioxane for a Boc protecting group). Additional modification to the basic amino group can be achieved according to methods described in Scheme C.

(284) Compounds of Formula (I), wherein R.sub.1 and R.sub.2 are monocyclic or bicyclic

heterocyclyl or heteroaryl ring systems, may be prepared as described in Scheme G below.
(285) ##STR00109##
(286) Compound G1 (where X is bromine, chlorine and the like; Y is hydrogen or optionally substituted alkyl; and P is an appropriate protecting group) is converted to Compound G2 through a condensation/cyclization sequence in the presence of catalyst (such as CuI and the like), ligand (such as 1,10-phenanthroline and the like) and base (such as NaOt-Bu and the like) in an appropriate solvent (such as DMF and the like). Compound G2 is converted to Compound G3 by treatment with strong acid (conc. HCl and the like) in the presence of oxygen. Compound G3 is converted to Compound G4 by a Suzuki coupling with an aryl- or heteroaryl-boronic acid (or pinacol boronic ester) (i.e., an R.sub.2 substituted-boronic acid or ester) in the presence of a catalyst (such as Pd(dppf)Cl.sub.2 and the like) and base (such as aqueous K.sub.2CO.sub.3 and the like) in a suitable solvent (such as 1,4-dioxane and the like). Alternatively, Compound G3 is converted to Compound G4 by treatment with pinacolatodiboron and a base (such as KOAc and the like) in the presence of a catalyst (such as Pd(dppf)Cl.sub.2 and the like) in an appropriate solvent (such as 1,4-dioxane and the like), followed by addition of an aryl- or heteroaryl-halide (i.e., an R.sub.2 substituted-halide). Compound G4 is converted to Compound G5 upon treatment with conditions appropriate to the removal of the protecting group (such as TFA or HCl in dioxane for a Boc protecting group). Additional modification to the basic amino group can be achieved according to methods described in Scheme C.
(287) Compounds of Formula (I), wherein R.sub.1 and R.sub.2 are monocyclic or bicyclic heterocyclyl or heteroaryl ring systems, may be prepared as described in Scheme H below.
(288) ##STR00110##
(289) Compound H1 (where X.sub.2 is bromine, chlorine and the like; and P is a protecting group such as tert-butyl and the like) is converted to Compound H2 by a Suzuki coupling with an aryl- or heteroaryl-boronic acid or ester (i.e., an R.sub.2 substituted-boronic acid or ester) in the presence of a catalyst (such as Pd(dppf)Cl.sub.2 and the like) and base (such as aqueous K.sub.2CO.sub.3 and the like) in a suitable solvent (such as 1,4-dioxane and the like). Upon treatment with acid (such as TFA or HCl in dioxane and the like) Compound H2 is converted to Compound H3. Compound H3 is converted to Compound B1 (where X.sub.1 is triflate and the like) by treatment with an activated triflate (such as Tf.sub.2O or Tf.sub.2NPh and the like) in the presence of base (such as K.sub.2CO.sub.3 or NaH and the like) in an appropriate solvent (such as THF or DMF and the like). Alternatively, Compound H3 can be converted to Compound B1 (where X.sub.1 is Cl and the like) by treatment with a dehydrative halogenating agent (such as POCl.sub.3 and the like). Additional modification to the basic amino group can be achieved according to methods described in Scheme C.
(290) Compounds of Formula (I), wherein R.sub.1 and R.sub.2 are monocyclic or bicyclic heterocyclyl or heteroaryl ring systems, may be prepared as described in Scheme I below.
(291) ##STR00111##
(292) Compound I1 (where X.sub.1 is bromine, chlorine and the like; and P is a protecting group such as methyl and the like) is converted to Compound I2 by a Suzuki coupling with an optionally substituted and appropriately protected amino-containing cycloalkyl/cycloalkenyl pinacol boronic ester (where Y is hydrogen or an optionally substituted alkyl group and P is a protecting group such as Boc and the like) (i.e., an R.sub.1 substituted-boronic ester) in the presence of a catalyst (such as Pd(dppf)Cl.sub.2 and the like) and base (such as aqueous K.sub.2CO.sub.3 and the like) in a suitable solvent (such as 1,4-dioxane and the like). Compound I2 is converted to Compound E2 (where X.sub.2 is triflate and the like) by treatment with an activated triflate (such as Tf.sub.2O or Tf.sub.2NPh and the like) in the presence of base (such as K.sub.2CO.sub.3 or NaH and the like) in an appropriate solvent (such as THF or DMF and the like). Additional modification to the basic amino group can be achieved according to methods described in Scheme C.
Specific Synthetic Examples

(293) To describe in more detail and assist in understanding, the following non-limiting examples are offered to more fully illustrate the scope of compounds described herein and are not to be construed as specifically limiting the scope thereof. Such variations of the compounds described herein that may be now known or later developed, which would be within the purview of one skilled in the art to ascertain, are considered to fall within the scope of the compounds as described herein and hereinafter claimed. These examples illustrate the preparation of certain compounds. Those of skill in the art will understand that the techniques described in these examples represent techniques, as described by those of ordinary skill in the art, that function well in synthetic practice, and as such constitute preferred modes for the practice thereof. However, it should be appreciated that those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific methods that are disclosed and still obtain a like or similar result without departing from the spirit and scope of the present description.
(294) Other than in the following examples of the embodied compounds, unless indicated to the contrary, all numbers expressing quantities of ingredients, reaction conditions, experimental data, and so forth used in the specification and claims are to be understood as being modified by the term “about”. Accordingly, all such numbers represent approximations that may vary depending upon the desired properties sought to be obtained by a reaction or as a result of variable experimental conditions. Therefore, within an expected range of experimental reproducibility, the term “about” in the context of the resulting data, refers to a range for data provided that may vary according to a standard deviation from the mean. As well, for experimental results provided, the resulting data may be rounded up or down to present data consistently, without loss of significant figures. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should be construed in light of the number of significant digits and rounding techniques used by those of skill in the art.
(295) While the numerical ranges and parameters setting forth the broad scope of the present description are approximations, the numerical values set forth in the examples set forth below are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements.
COMPOUND EXAMPLES
(296) As used above, and throughout the present description, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:
(297) TABLE-US-00003 Abbreviation Meaning Δ heating (chemistry) or deletion (biology) AcOH or HOAc acetic acid Ac.sub.2O acetic anhydride Ag.sub.2SO.sub.4 silver sulfate Ar argon ACN or CH.sub.3CN acetonitrile atm atmosphere(s) B.sub.2pin.sub.2 bis(pinacolato)diboron Boc tert-butoxy-carbonyl Boc.sub.2O di-tert-butyl dicarbonate Br.sub.2 bromine nBuLi n-butyl lithium iBuNO isobutyl nitrite BuOH n-butanol Bu.sub.3SnCl Tributylchlorostannane or tributyltin chloride ° C. degrees Centigrade Celite ® or Celite diatomaceous earth CO.sub.2Cl.sub.2 oxalyl chloride Cs.sub.2CO.sub.3 cesium carbonate CuI copper (I) iodide d/h/hr/hrs/min/s day(d)/hour(h, hr or hrs)/minute(min)/second(s) DCM or CH.sub.2Cl.sub.2 dichloromethane DDQ 2,3-dichloro-5,6-dicyano-p-benzoquinone DIEA or DIPEA N,N-diisopropylethylamine DMA dimethylacetamide DMAP 4-(dimethylamino)pyridine or N,N-dimethylpyridin-4- amine DMF dimethylformamide DMSO dimethylsulfoxide EtOAc ethyl acetate EtOH ethanol Et.sub.2O diethyl ether Fe(acac)3.sub.2 iron(III) acetylacetonate H.sub.2 hydrogen HCl hydrochloric acid HI hydriodic acid H.sub.2SO.sub.4 sulfuric acid K.sub.2CO.sub.3 potassium carbonate KOAc potassium acetate KOtBu Potassium t-butoxide KOH potassium hydroxide K.sub.2OsO.sub.4•2H.sub.20 potassium osmate(VI) dihydrate LAH or LiAlH.sub.4 lithium aluminum hydride Lawesson's reagent 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane- 2,4-disulfide LC/MS, LCMS or liquid chromatographic mass spectroscopy LC-MS LiOH lithium hydroxide MeOH methanol MeSO.sub.3H methanesulfonic acid MgSO.sub.4 magnesium sulfate MnO.sub.2 manganese dioxide MS mass spectroscopy MsCl methanesulfonyl chloride NBS N-

bromosuccinimide NEt.sub.3 triethylamine NH.sub.4Cl ammonium chloride NH.sub.4OAc ammonium acetate NaBH.sub.4 sodium borohydride NaBH(OAc).sub.3 sodium triacetoxyborohydride NaH sodium hydride NaHCO.sub.3 sodium bicarbonate NaHMDS sodium bis(trimethylsilyl)amide or sodium hexamethyldisilazide NaH sodium hydride NaOH sodium hydroxide NaOMe sodium methoxide NaNO.sub.2 sodium nitrite Na.sub.2SO.sub.4 sodium sulfate N.sub.2 nitrogen NH.sub.4Cl ammoniuim chloride NMO 4-methylmoropholine N-oxide NMP methylpyrrolidone NMR nuclear magnetic resonance NOBF.sub.4 nitrosonium tetrafluoroborate or nitrosyl tetrafluoroborate Pb(OAc).sub.4 lead(IV) acetate or lead tetracetate Pd palladium Pd/C palladium on carbon Pd(dppf)Cl.sub.2 or [1,1′- Pd(dppf)Cl.sub.2—CH.sub.2Cl.sub.2 bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane PHBU.sub.3BF.sub.4 or tBu.sub.3PHBF.sub.4 tri-tert-butylphosphonium tetrafluoroborate PhCH.sub.3 toluene PhI iodobenzene PhI(OTFA).sub.2 [bis(trifluoroacetoxy)iodo]benzene PhMe toluene Ph—N(Tf).sub.2 or PhN(Tf).sub.2 N-phenyl triflimide, also referred to as N-phenyl-bis(trifluoromethanesulfonimide) POBr.sub.3 phosphoryl bromide or phosphorous(V) oxybromide P.sub.2O.sub.5 phosphorous pentoxide or phosphorous(V) oxide POCl.sub.3 phosphoryl chloride or phosphorous(V) oxychloride PhMe toluene Psi pounds per square inch pressure Pt.sub.2O Platinum(IV) oxide Rt or rt room temperature SEMCl 2-(trimethylsilyl)ethoxymethyl chloride SnCl.sub.2 tin(II) chloride or stannous chloride SOCl.sub.2 thionly chloride S-Phos, SPhos or Sphos 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl SPhos Pd G2 chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′- biphenyl)(2′-amino-1,1′-biphenyl-2-yl) palladium(II) TBAF tetrabutylamonium fluoride TBSCl tert-butyldimetylsilyl chloride TEA, Et.sub.3N or NEt.sub.3 triethylamine TFA trifluoroacetic acid THF tetrahydrofuran TIPS tiisopropylsilane TLC thin layer chromatography TMEDA tetramethylethylenediamine TMS trimethylsilyl TMSCCH trimethylsilylacetylene t-Bu tert-butyl Zn(CN).sub.2 zinc cyanide ZnMe.sub.2 dimethyl zinc

Example 1

(298) Preparation of Compound 11

(299) ##STR00112##

(300) Step A: 6-Bromo-2-chloro-quinoline (121 mg, 0.5 mmol) was combined with N,2,2,6,6-pentamethylpiperidin-4-amine (170 mg, 0.95 mmol) and Cs.sub.2CO.sub.3 (325 mg, 1.0 mmol) in DMF (2 mL) and the mixture was stirred at 100° C. for 2 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Cs.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-5% MeOH in CH.sub.2Cl.sub.2 to yield 6-bromo-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)quinolin-2-amine (480 mg, 65%). MS m/z 375.9, 377.9 [M+H].sup.+.

(301) Step B: 6-Bromo-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)quinolin-2-amine (40 mg, 0.11 mmol), 2,7-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole (51 mg, 0.15 mmol), and [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium(II) complex with dichloromethane (8 mg, 0.01 mmol) were combined with aqueous 1 M K.sub.2CO.sub.3 (0.5 mL, 0.5 mmol) and 1,4-dioxane (1 mL). The mixture was stirred at 80° C. for 2 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-10% MeOH (2 N NH.sub.3) in CH.sub.2Cl.sub.2 to yield 6-(2,7-dimethyl-2H-indazol-5-yl)-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)quinolin-2-amine (40 mg, 85%) as an off white solid.

(302) MS m/z 442.1 [M+H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.35 (s, 1H), 8.11 (d, J=9.4 Hz, 1H), 8.01 (m, 1H), 7.89 (dd, J=9.0, 1.5 Hz, 1H), 7.83 (s, 1H), 7.58 (d, J=9.0 Hz, 1H), 7.46 (s, 1H), 7.13 (d, J=8.9 Hz, 1H), 5.24 (br, 1H), 4.20 (s, 3H), 2.99 (s, 3H), 2.59 (s, 3H), 1.69-1.01 (m, 16H).

(303) Using the procedure described for Example 1, above, additional compounds described herein were prepared by substituting the appropriate boronic acid in Step B, suitable reagents and reaction

conditions, obtaining compounds such as those selected from:
(304) TABLE-US-00004 Cpd Data 12 MS m/z 428.5 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.39 (s, 1H), 8.11 (d, J = 9.4 Hz, 1H), 8.00-8.05 (m, 2H), 7.91 (dd, J = 9.0, 1.5 Hz, 1H), 7.71-7.66 (m, 2H), 7.59 (d, J = 9.0 Hz, 1H), 7.13 (d, J = 8.9 Hz, 1H), 5.24 (br, 1H), 4.20 (s, 3H), 2.99 (s, 3H), 1.69- 1.01 (m, 16 H).
Example 2
(305) Preparation of Compound 15
(306) ##STR00113##
(307) Step A: 6-Bromo-2-chloro-quinoline (242 mg, 1.0 mmol) was combined with 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (45 mg, 0.05 mmol), 2,7-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole (350 mg, 1.0 mmol), 1,4-dioxane (5 mL) and aqueous 1 M K.sub.2CO.sub.3 (2.5 mL, 2.5 mmol). The mixture was stirred at 80° C. for 1 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 10-100% EtOAc in hexanes to yield 2-chloro-6-(2,7-dimethyl-2H-indazol-5-yl)quinoline (150 mg, 49%). MS m/z 308.0, 310.0 [M+H].sup.+.
(308) Step B: 2-Chloro-6-(2,7-dimethyl-2H-indazol-5-yl)quinoline (135 mg, 0.30 mmol) was combined with N-Boc-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester (193 mg, 0.61 mmol), 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (40 mg, 0.05 mmol), 1,4-dioxane (2.5 mL), and aqueous 1 M K.sub.2CO.sub.3 (1.2 mL, 1.2 mmol). The mixture was stirred at 90° C. for 2 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-10% MeOH in EtOAc to yield tert-butyl 4-[6-(2,7-dimethylindazol-5-yl)-2-quinolyl]-3,6-dihydro-2H-pyridine-1-carboxylate (135 mg, 61%). MS m/z 455.1 [M+H].sup.+.
(309) Step C: tert-Butyl 4-[6-(2,7-dimethylindazol-5-yl)-2-quinolyl]-3,6-dihydro-2H-pyridine-1-carboxylate (35 mg, 0.08 mmol) was combined with 10% Pd/C (10 mg) in MeOH (3 mL). The mixture was stirred under H.sub.2 (1 atm) for 18 h. The mixture was filtered over Celite®. The filtrate was concentrated to yield tert-butyl 4-[6-(2,7-dimethylindazol-5-yl)-2-quinolyl]piperidine-1-carboxylate (35 mg, 99%). MS m/z 457.2 [M+H].sup.+.
(310) Step D: tert-Butyl 4-[6-(2,7-dimethylindazol-5-yl)-2-quinolyl]piperidine-1-carboxylate from Step C (35 mg, 0.077 mmol) was combined with TFA (1 mL). The solution stood for 20 min before the volatiles were removed with a stream of N.sub.2. The residue was partitioned between EtOAc and aqueous 1 M aqueous K.sub.2CO.sub.3. The organic layer was collected and concentrated to yield 6-(2,7-dimethyl-2H-indazol-5-yl)-2-(piperidin-4-yl)quinoline (25 mg, 91%).
(311) MS m/z 357.1 [M+H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.40 (s, 1H), 8.33 (d, J=8.5 Hz, 1H), 8.23 (d, J=2.2 Hz, 1H), 8.09 (dd, J=8.8, 2.2 Hz, 1H), 7.99 (d, J=8.8 Hz, 1H), 7.93-7.97 (m, 1H), 7.50-7.57 (m, 1H), 7.48 (d, J=8.5 Hz, 1H), 4.21 (s, 3H), 3.05-3.11 (m, 2H), 2.92-2.99 (m, 1H), 2.61-2.68 (m, 2H), 2.61 (s, 3H), 1.81-1.88 (m, 2H), 1.69-1.79 (m, 2H), NH proton not observed.
(312) Using the procedure described for Example 2, above, additional compounds described herein were prepared by substituting the appropriate starting material, suitable reagents and reaction conditions, obtaining compounds such as those selected from:
(313) TABLE-US-00005 Cpd Data 3 MS m/z 343.2 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.29 (br s, 1H), 9.19 (br s, 1H), 8.81 (br s, 1H), 8.47-8.52 (m, 2H), 8.33-8.40 (m, 2H), 8.21 (m, 1H), 7.73-7.80 (m, 3H), 4.22 (s, 3H), 3.54 (br s, 1H), 3.41-3.48 (m, 2H), 3.02-3.12 (m, 2H), 2.14-2.25 (m, 4H).
Example 3
(314) Preparation of Compound 13

(315) ##STR00114##
(316) Step A: 2,2,6,6-Tetramethylpiperidin-4-one (3.1 g, 20 mmol) was dissolved in THF (100 mL) and cooled to −78° C. NaHMDS (21 mL, 21 mmol, 1.0 M in THF) was added to the solution. The mixture was stirred for 15 min at −78° C. N,N-bis(trifluoromethylsulfonyl)aniline (7.8 g, 22 mmol) was added to the mixture as a solid. The mixture was allowed to warm to room temperature before being quenched with aqueous saturated NaHCO.sub.3. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with aqueous 2 M KOH, dried over Na.sub.2SO.sub.4, filtered and concentrated to yield 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (6.0 g, 100%).
(317) .sup.1H NMR (acetone-d.sub.6) δ: 10.28 (br s, 1H), 6.13 (s, 1H), 2.85 (br s, 2H), 1.76 (s, 6H), 1.68 (s, 6H).
(318) Step B: (2,2,6,6-Tetramethyl-1,3-dihydropyridin-4-yl) trifluoromethanesulfonate (100 mg, 0.35 mmol) was combined with bis(pinacolato)diboron (125 mg, 0.50 mmol), potassium acetate (100 mg, 1.0 mmol), 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (12 mg, 0.015 mmol) and 1,4-dioxane (2.4 mL). The mixture was stirred at 90° C. for 2 h. The mixture was cooled to room temperature. To the mixture was added aqueous 1 M K.sub.2CO.sub.3 (1 mL, 1 mmol), 2-chloro-6-(2,7-dimethylindazol-5-yl)quinoline (100 mg, 0.30 mmol, prepared according to Example 2, Step A) and 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (12 mg, 0.015 mmol). The mixture was stirred at 80° C. for 1 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-10% MeOH (2 N NH.sub.3) in CH.sub.2Cl.sub.2 to yield 6-(2,7-dimethyl-2H-indazol-5-yl)-2-(2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl)quinoline (90 mg, 46%).
(319) MS m/z 411.5 [M+H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.41 (s, 1H), 8.34 (d, J=8.5 Hz, 1H), 8.24 (d, J=2.2 Hz, 1H), 8.10 (dd, J=8.8, 2.2 Hz, 1H), 8.02 (d, J=8.8 Hz, 1H), 7.93-7.97 (m, 1H), 7.88 (d, J=8.8 Hz, 1H), 7.54 (t, J=1.6 Hz, 1H), 6.78-6.82 (m, 1H), 4.21 (s, 3H), 2.61 (s, 3H), 2.50 (m, 2H), 1.49 (s, 1H), 1.26 (s, 6H), 1.17 (s, 6H).
Example 4
(320) Preparation of Compound 14
(321) ##STR00115##
(322) 6-(2,7-Dimethylindazol-5-yl)-2-(2,2,6,6-tetramethyl-1,3-dihydropyridin-4-yl)quinoline (20 mg, 0.05 mmol) was combined with 10% Pd/C (10 mg) in MeOH (2 mL). The mixture was stirred under H.sub.2 (1 atm) at room temperature for 6 h. The mixture was then filtered over Celite. The filtrate was concentrated to yield 6-(2,7-dimethyl-2H-indazol-5-yl)-2-(2,2,6,6-tetramethylpiperidin-4-yl)quinoline (20 mg, 99%).
(323) MS m/z 413.5 [M+H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.40 (s, 1H), 8.34 (d, J=8.5 Hz, 1H), 8.23 (d, J=2.2 Hz, 1H), 8.09 (dd, J=8.8, 2.2 Hz, 1H), 8.01 (d, J=8.8 Hz, 1H), 7.93-7.95 (m, 1H), 7.49-7.53 (m, 2H), 4.21 (s, 3H), 2.61 (s, 3H), 1.73-1.79 (m, 2H), 1.47-1.55 (m, 2H), 1.27 (s, 6H), 1.11 (s, 6H), NH proton not observed.
Example 5
(324) Preparation of Compound 20
(325) ##STR00116##
(326) Step A: 6-Bromo-2-chloro-8-fluoro-quinoline (52 mg, 0.2 mmol) was combined with 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (8 mg, 0.01 mmol), 2,7-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole (54 mg, 0.2 mmol), 1,4-dioxane (1 mL) and aqueous 1 M K.sub.2CO.sub.3 (0.5 mL, 0.5 mmol). The mixture was stirred at 80° C. for 1 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 10-100% EtOAc in hexanes to yield 2-chloro-6-

(2,7-dimethyl-2H-indazol-5-yl)-8-fluoroquinoline (25 mg, 38%). MS m/z 326.2, 328.2 [M+H].sup.+.
(327) Step B: Zinc powder (5 g, 76 mmol) was suspended in N,N-dimethylacetamide (10 mL) under argon. A mixture of 1,2-dibromoethane (520 μL, 6.02 mmol) and chlorotrimethylsilane (730 μL, 5.74 mmol) was added dropwise over 10 min. Over the course of the addition the internal temperature rose to 50° C. The reaction mixture was allowed to cool to room temperature. A solution of tert-butyl 4-iodopiperidine-1-carboxylate (16.5 g, 53.0 mmol) in N,N-dimethylacetamide (26 mL) was added dropwise over 20 min. The reaction mixture was filtered through Celite in a Schlenk filter to yield roughly 50 mL of ˜1M (1-tert-butoxycarbonyl-4-piperidyl)-iodo-zinc solution. 2-Chloro-6-(2,7-dimethyl-2H-indazol-5-yl)-8-fluoroquinoline (25 mg, 0.077 mmol) was combined with the 1-Cert-butoxycarbonylpiperidin-4-ylzinc iodide solution (0.25 mL, 0.25 mmol), chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)(2′-amino-1,1′-biphenyl-2-yl) palladium(II) (4 mg, 0.005 mmol) and 1,4-dioxane (1 mL). The mixture was stirred at 80° C. for 2 h. The mixture was cooled to room temperature. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-10% MeOH in EtOAc to yield tert-butyl 4-[6-(2,7-dimethylindazol-5-yl)-8-fluoro-2-quinolyl]piperidine-1-carboxylate (30 mg, 82%). MS m/z 475.4 [M+H].sup.+.
(328) Step C: tert-Butyl 4-[6-(2,7-dimethylindazol-5-yl)-8-fluoro-2-quinolyl]piperidine-1-carboxylate (30 mg, 0.06 mmol) was combined with TFA (1 mL). After 10 min, the volatiles were removed. The mixture was partitioned between CH.sub.2Cl.sub.2 and aqueous 1 M K.sub.2CO.sub.3. The organic layer was loaded onto silica gel, eluting with 0-10% MeOH (2 N NH.sub.3) in CH.sub.2Cl.sub.2 to yield 6-(2,7-dimethyl-2H-indazol-5-yl)-8-fluoro-2-(piperidin-4-yl)quinoline (20 mg, 85%).
(329) MS m/z 375.3 [M+H].sup.+; .sup.1H NMR (acetone-d.sub.6) δ: 8.22 (dd, J=8.7, 1.7 Hz, 1H), 8.14 (s, 1H), 7.88 (d, J=2.2 Hz, 1H), 7.79-7.81 (m, 1H), 7.70 (dd, J=12.5, 2.0 Hz, 1H), 7.42 (d, J=8.5 Hz, 1H), 7.36-7.40 (m, 1H), 4.12 (s, 3H), 2.99-3.06 (m, 2H), 2.87-2.93 (m, 1H), 2.58-2.65 (m, 2H), 2.52 (s, 3H), 1.67-1.81 (m, 4H), NH proton not observed.
(330) Using the procedure described for Example 5, above, additional compounds described herein were prepared by substituting the indicated starting material in Step A, suitable reagents and reaction conditions, obtaining compounds such as those selected from:
(331) TABLE-US-00006 Cpd Starting Material and Data 23 Starting material: 6-bromo-2-chloroquinazoline MS m/z 358.3 [M + H]+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.59 (s, 1H), 8.43 (s, 1H), 8.40 (s, 1H), 8.36 (dd, J = 8.5, 1.9 Hz, 1H), 7.98-8.02 (m, 2H), 7.54 (s, 1H), 4.22 (s, 3H), 3.29-3.35 (m, 2H), 2.86-2.94 (m, 1H), 3.01-3.09 (m, 2H), 2.61 (s, 3H), 1.90-1.96 (m, 2H), 1.75-1.84 (m, 2H), NH proton not observed. 30 Starting material: 7-bromo-3-chloroisoquinoline MS m/z 357.3 [M + H]+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.32 (s, 1H), 8.41 (s, 1H), 8.38 (s, 1H), 8.13 (dd, J = 8.5, 1.9 Hz, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.96-7.97 (m, 1H), 7.64 (s, 1H), 7.54 (t, J = 1.6 Hz, 1H), 4.21 (s, 3H), 3.09-3.15 (m, 2H), 2.86-2.94 (m, 1H), 2.66-2.74 (m, 2H), 2.61 (s, 3H), 1.87-1.93 (m, 2H), 1.69-1.78 (m, 2H), NH proton not observed.
Example 6
(332) Preparation of Compound 72
(333) ##STR00117## ##STR00118##
(334) Step A: Methyl cyanoacetate (5.71 g, 57.6 mmol) was added to a mixture of DMSO (30 mL) and NaH (60 mass %) in mineral oil (2.3 g, 57.6 mmol) at 0° C. The mixture was stirred at 0° C. for 15 min. 5-Chloro-2,3-difluoro-benzonitrile (5.0 g, 28.8 mmol) in DMSO (5 mL) was added to the mixture. The mixture was stirred at room temperature for 30 min and then heated to 90° C. for 4 h. The mixture was cooled to room temperature and diluted with H.sub.2O (200 mL), brine (100 mL) and
(335) EtOAc (200 mL). A precipitate formed and was collected by vacuum filtration. The solid was

washed with H.sub.2O and dried to yield methyl 2-(4-chloro-2-cyano-6-fluoro-phenyl)-2-cyano-acetate (6 g, 82%) as a tan powder. MS m/z 251.1, 253.1 [M−H].sup.−.
(336) Step B: Methyl 2-(4-chloro-2-cyano-6-fluoro-phenyl)-2-cyano-acetate (5.5 g, 22 mmol) was combined with aqueous concentrated HCl (40 mL) and 1,4-dioxane (20 mL). The mixture was heated at 80° C. for 4 h. The mixture was cooled to room temperature and filtered. The solid was washed with H.sub.2O and CH.sub.3CN, and then dried to yield 7-chloro-5-fluoro-4H-isoquinoline-1,3-dione (3.0 g, 65%) as an off white solid. MS m/z 214.1, 216.1 [M+H].sup.+.
(337) Step C: 7-Chloro-5-fluoro-4H-isoquinoline-1,3-dione (3.0 g, 14.0 mmol) was combined with POCl.sub.3 (20 mL, 212 mmol). The mixture was heated at 110° C. for 2 h and then 90° C. overnight. The mixture was cooled to room temperature and then poured onto ice with vigorous stirring. The solid material was collected by vacuum filtration, dried, and chromatographed on silica gel, eluting with CH.sub.2Cl.sub.2 to afford 1,3,7-trichloro-5-fluoro-isoquinoline (1.3 g, 37%) as a white powder. MS m/z 250.2, 252.2, 254.2 [M+H].sup.+.
(338) Step D: 1,3,7-Trichloro-5-fluoro-isoquinoline (1.3 g, 5.2 mmol) was combined with [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (210 mg, 0.26 mmol), TMEDA (0.77 mL, 5.2 mmol) and THF (20 mL). To the mixture was added sodium borohydride (378 mg, 10 mmol). The mixture was stirred at room temperature for 30 min, and then was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-10% EtOAc in CH.sub.2Cl.sub.2 to yield 3,7-dichloro-5-fluoro-isoquinoline (870 mg, 78%) as a white solid.
(339) MS m/z 216.2, 218.2, 220.2 [M+H].sup.+; .sup.1H NMR (acetone-d.sub.6) δ: 9.26 (m, 1H), 8.16 (m, 1H), 8.00 (s, 1H), 7.72 (dd, J=9.8, 1.9 Hz, 1H).
(340) Step E: 3,7-Dichloro-5-fluoro-isoquinoline (432 mg, 2.0 mmol) was combined with N-Boc-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester (610 mg, 2.4 mmol), 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (50 mg, 0.06 mmol), 1,4-dioxane (6 mL) and aqueous 1 M K.sub.2CO.sub.3 (4 mL, 4 mmol). The mixture was stirred at 80° C. for 1 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was concentrated. The residue was chromatographed on silica gel, eluting with 0-30% EtOAc in hexanes to yield tert-butyl 4-(7-chloro-5-fluoro-3-isoquinolyl)-3,6-dihydro-2H-pyridine-1-carboxylate (370 mg, 51%) as an off-white solid. MS m/z 362.2, 364.2 [M-F1-1].sup.+.
(341) Step F: 6-Chloro-2,8-dimethyl-imidazo[1,2-b]pyridazine hydrochloride (62 mg, 0.28 mmol, prepared according to the procedure in Example 11) was combined with KOAc (83 mg, 0.85 mmol), 1,1′-bis(diphenylphosphino) ferrocene-palladium(II)dichloride dichloromethane complex (23 mg, 0.03 mmol), bis(pinacolato)diboron (91 mg, 0.36 mmol) and 1,4-dioxane (1.5 mL). The mixture was stirred under N.sub.2 at 100° C. for 2 h. To the mixture was added 1 M K.sub.2CO.sub.3 (aq) (0.75 mL, 0.75 mmol), followed by 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (11 mg, 0.014 mmol) and tert-butyl 4-(7-chloro-5-fluoro-3-isoquinolyl)-3,6-dihydro-2H-pyridine-1-carboxylate (100 mg, 0.28 mmol). The mixture was stirred under N.sub.2 for 1 h at 80° C. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was concentrated. The residue was chromatographed on silica gel, eluting with 10-100% EtOAc in CH.sub.2Cl.sub.2 then 5% MeOH in EtOAc to yield tert-butyl 4-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-isoquinolyl]-3,6-dihydro-2H-pyridine-1-carboxylate (90 mg, 69%) as a white solid. MS m/z 474.5 [M+H].sup.+.
(342) Step G: tert-Butyl 4-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-isoquinolyl]-3,6-dihydro-2H-pyridine-1-carboxylate (90 mg, 0.19 mmol) was combined with 10% Pd/C (20 mg) in MeOH (3 mL). The mixture was stirred under H.sub.2 (1 atm) for 2 h at 40° C. The mixture was filtered through a syringe filter. The filtrate was concentrated. The residue was chromatographed on silica gel, eluting with 40-100% EtOAc in hexanes to yield tert-butyl 4-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-isoquinolyl]piperidine-1-carboxylate (52

mg, 57%) as an off-white solid. MS m/z 476.3 [M+H].sup.+.
(343) Step H: tert-Butyl 4-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-isoquinolyl]piperidine-1-carboxylate (52 mg, 0.11 mmol) was combined with 4 N HCl in 1,4-dioxane (2 mL, 8 mmol). The mixture was stirred and sonicated and room temperature. After 1 h, the volatiles were removed. The residue was suspended in CH.sub.3CN, sonicated and filtered. The solid was dried to give 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(4-piperidyl)isoquinoline hydrochloride (36 mg, 46%) as a yellow solid.
(344) MS m/z 376.5 [M+H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.58 (s, 1H), 9.14-9.22 (br, 1H), 8.96-9.05 (br, 1H), 8.89 (s, 1H), 8.48-8.53 (m, 2H), 8.34 (dd, J=11.6, 1.5 Hz, 1H), 7.84 (s, 1H), 3.39-3.45 (m, 2H), 3.25-3.31 (m, 1H), 3.02-3.12 (m, 2H), 2.79 (s, 3H), 2.60 (s, 3H), 2.07-2.17 (m, 4H).
(345) Using the procedure described for Example 6, above, additional compounds described herein were prepared by substituting the appropriate boronic acid in Step F, suitable reagents and reaction conditions, obtaining compounds such as those selected from:
(346) TABLE-US-00007 Cpd Data 71 MS m/z 375.4 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.56 (s, 1H), 9.12-9.20 (br, 1H), 8.89-8.98 (br, 1H), 8.89 (s, 1H), 8.43-8.48 (m, 2H), 8.34 (d, J = 12.2 Hz, 1H), 7.84 (s, 1H), 7.58 (s, 1H), 4.22 (s, 3H), 3.39-3.46 (m, 2H), 3.27-3.34 (m, 1H), 3.02-3.12 (m, 2H), 2.61 (s, 3H), 2.05-2.20 (m, 4H).
(347) Using the procedure described for Example 6, Steps E-H, above, additional compounds described herein were prepared by substituting the appropriate starting material in Step E, appropriate boronic acid in Step F, suitable reagents and reaction conditions, obtaining compounds such as those selected from:
(348) TABLE-US-00008 Cpd Starting Material and Data 1 Starting material: 6-bromo-2-chloroquinoline MS m/z 343.2 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.75-8.80 (br, 2H), 8.64 (s, 1H), 8.54 (s, 1H), 8.47-8.50 (m, 1H), 8.22-8.26 (m, 2H), 8.07-8.10 (m, 1H), 7.83 (s, 1H), 7.70-7.76 (m, 2H), 4.22 (s, 3H), 3.42-3.48 (m, 2H), 3.05-3.14 (m, 3H), 2.07- 2.12 (m, 2H), 1.87-1.95 (m, 2H). 10 Starting material: 6-bromo-2-chloroquinazoline MS m/z 344.1 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.67 (s, 1H), 9.03-9.12 (br s, 2H), 9.00 (s, 1H), 8.55 (s, 1H), 8.44-8.47 (m, 1H), 8.02-8.05 (m, 1H), 7.91-7.96 (m, 2H), 7.71-7.74 (m, 1H), 4.21 (s, 3H), 3.40-3.44 (m, 2H), 3.03-3.11 (m, 3H), 1.98- 2.09 (m, 4H).
Example 7
(349) Preparation of Compound 74
(350) ##STR00119## ##STR00120##
(351) Step A: 1,2-Difluoro-3-nitro-benzene (23 g, 145 mmol) was combined with Ag.sub.2SO.sub.4 (45.2 g, 145 mmol) in H.sub.2SO.sub.4 (150 mL). The mixture was stirred for 5 min at room temperature. To the mixture was added Br.sub.2 (11.2 mL, 217 mmol). The mixture was stirred at room temperature for 16 h, and then was poured into ice water (800 mL). The mixture was extracted with Et.sub.2O (3×500 mL). The combined organics were dried, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 10-30% CH.sub.2Cl.sub.2 in hexanes to yield 5-bromo-1,2-difluoro-3-nitro-benzene (18.8 g, 55%) as a white crystalline solid.
(352) .sup.1H NMR (acetone-d.sub.6) δ: 8.20 (ddd, J=5.8, 2.4, 2.2 Hz, 1H), 8.12 (ddd, J=9.2, 6.5, 2.2 Hz, 1H).
(353) Step B: 5-Bromo-1,2-difluoro-3-nitro-benzene (15 g, 63 mmol), dimethyl malonate (12.5 g, 95 mmol), Cs.sub.2CO.sub.3 (41.1 g, 126 mmol), and DMF (63 mL) were stirred at rt for 6 h. The reaction mixture was partitioned between aqueous 1 M HCl and EtOAc. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4 and concentrated. The residue was combined with AcOH (30 mL) and conc. HCl (30 mL) and heated at 110° C. for 16 h. The mixture was diluted with H.sub.2O to form a precipitate. The solid was collected by vacuum filtration, washed with H.sub.2O, washed with 1:1 hexane/ether and dried to afford 2-(4-bromo-2-fluoro-6-nitro-

phenyl)acetic acid (14.5 g, 83%) as a white solid.
(354) .sup.1H NMR (acetone-d.sub.6) δ: 11.28 (br s, 1H), 8.16 (t, J=1.5 Hz, 1H), 7.92 (dd, J=9.0, 1.5 Hz, 1H), 4.06 (s, 2H).
(355) Step C: 2-(4-Bromo-2-fluoro-6-nitro-phenyl)acetic acid (14.5 g, 52 mmol) was suspended in CH.sub.2Cl.sub.2 (250 mL). Oxalyl chloride (7 mL, 79 mmol) was added to the mixture followed by DMF (0.1 mL, 1 mmol). The mixture was stirred at room temperature for 1 h, and then added dropwise to MeOH at 0° C. The volatiles were removed under vacuum to yield methyl 2-(4-bromo-2-fluoro-6-nitro-phenyl)acetate (15 g, 98%) as an off-white solid.
(356) .sup.1H NMR (acetone-d.sub.6) δ: 8.16 (t, J=1.5 Hz, 1H), 7.93 (dd, J=9.0, 1.5 Hz, 1H), 4.05 (s, 2H), 3.71 (s, 3H).
(357) Step D: Methyl 2-(4-bromo-2-fluoro-6-nitro-phenyl)acetate (15 g, 51 mmol) was suspended in a mixture of MeOH (200 mL) and NH.sub.4Cl (55 g, 1.03 mol) at 0° C. Zinc powder (16.8 g, 257 mmol) was added in one portion. The mixture was stirred at room temperature for 4 h, and then was filtered through Celite. The filtrate was concentrated and then partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated to yield methyl 2-(2-amino-4-bromo-6-fluoro-phenyl)acetate (12.6 g, 94%) as a white solid. MS m/z 262.0, 264.0 [M+H].sup.+.
(358) Step E: Methyl 2-(2-amino-4-bromo-6-fluoro-phenyl)acetate (12.6 g, 48 mmol) was suspended in CH.sub.2Cl.sub.2 (150 mL) at 0° C. Nitrosonium tetrafluoroborate (8.4 g, 72 mmol) was added in one portion to the mixture. The mixture was stirred at 0° C. for 1 h. The mixture was added directly to a vigorously stirred mixture of SnCl.sub.2 dihydrate (43.8 g, 194 mmol) in conc. HCl (200 mL) at 0° C. The mixture was allowed to slowly warm to room temperature with stirring. After 24 h, the mixture was filtered. The solid was washed with H.sub.2O and ether, and then dried to yield 1-amino-6-bromo-4-fluoro-indolin-2-one (9.0 g, 76%) as a white solid. MS m/z 244.9, 246.9 [Mal].sup.+.
(359) Step F: 1-Amino-6-bromo-4-fluoro-indolin-2-one (9.0 g, 37 mmol) was suspended in CH.sub.2Cl.sub.2 (500 mL) at 0° C. Pb(OAc).sub.4 (22.8 g, 51.4 mmol) was added to the mixture in one portion. The mixture was stirred at room temperature for 16 h. MeOH (50 mL) was added to the mixture, and the mixture was eluted through a pad of silica gel. The filtrate was concentrated and chromatographed on silica gel, eluting with 0-100% EtOAc in CH.sub.2Cl.sub.2 to yield 7-bromo-5-fluoro-cinnolin-3-ol (3.5 g, 39%) as a yellow powder. MS m/z 241.1, 243.1 [M−H].sup.−.
(360) Step G: 7-Bromo-5-fluoro-cinnolin-3-ol (3.5 g, 14 mmol) was suspended in POCl.sub.3 (28 mL, 300 mmol). The mixture was stirred at 100° C. for 4 h in a sealed tube. The mixture was cooled to room temperature and quenched onto ice. The ice water was extracted with CH.sub.2Cl.sub.2 (2×). The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-10% EtOAc in CH.sub.2Cl.sub.2 to yield 7-bromo-3-chloro-5-fluorocinnoline (2.6 g, 69%) as an off white powder. MS m/z 261.1, 263.1, 265.1 [M+H].sup.+.
(361) Step H: 7-Bromo-3-chloro-5-fluoro-cinnoline (785 mg, 3.00 mmol) was combined with (2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)boronic acid (3.6 mmol, prepared according to the procedure in Example 11), chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)(2′-amino-1,1′-biphenyl-2-yl) palladium(II) (108 mg, 0.15 mmol), 1,4-dioxane and aqueous 1 M K.sub.2CO.sub.3 (10 mL, 10 mmol). The mixture was stirred at 50° C. for 2 h. The mixture was partitioned between EtOAc and H.sub.2O, then filtered through Celite. The organic layer was concentrated. The residue was chromatographed on silica gel, eluting with 40-100% EtOAc in hexanes followed by 5% MeOH in EtOAc to yield 3-chloro-7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-cinnoline (605 mg, 62%) as a tan solid. MS m/z 328.2, 330.2 [M+H].sup.+.
(362) Step I: 3-Chloro-7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-cinnoline (400 mg, 1.2 mmol) was combined with 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (50 mg, 0.06 mmol), N-Boc-1,2,5,6-tetrahydropyridine-4-boronic acid

pinacol ester (462 mg, 1.47 mmol), 1,4-dioxane (6 mL) and aqueous 1 M K.sub.2CO.sub.3 (3 mL, 3.0 mmol). The mixture was stirred at 80° C. for 1 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was concentrated. The residue was chromatographed on silica gel, eluting with 40-100% EtOAc in hexanes, then 5% MeOH in EtOAc to yield tert-butyl 4-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-cinnolin-3-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (430 mg, 74%) as a tan solid. MS m/z 475.5 [M+H].sup.+.

(363) Step J: tert-Butyl 4-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-cinnolin-3-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (430 mg, 0.91 mmol) was combined with 10% Pd/C (500 mg) in MeOH:EtOAc (1:1) (25 mL). The mixture was stirred under H.sub.2 (1 atm) for 3 h at 40° C. The mixture was filtered through a syringe filter and the filtrate was concentrated. The residue was dissolved in CH.sub.2Cl.sub.2 (2 mL). MnO.sub.2 (20 equiv.) was added to the solution. The mixture was stirred at room temperature for 30 min and then filtered through Celite. The filtrate was concentrated. The residue was chromatographed on silica gel, eluting with 40-100% EtOAc in hexanes to yield tert-butyl 4-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-cinnolin-3-yl]piperidine-1-carboxylate (200 mg, 46%) as an off-white solid. MS m/z 477.5 [M+H].sup.+.

(364) Step K: tert-Butyl 4-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-cinnolin-3-yl]piperidine-1-carboxylate (200 mg, 0.42 mmol) was combined with 4 N HCl in 1,4-dioxane (1 mL, 4 mmol). The mixture was stirred at room temperature for 1 h. The volatiles were removed with a stream of N.sub.2. The residue was suspended in CH.sub.3CN, sonicated and filtered. The solid was dried to give 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(4-piperidyl)cinnoline hydrochloride (190 mg, quant.) as an off white solid.

(365) MS m/z 377.3 [M+H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.13 (s, 1H), 8.84 (br, 1H), 8.58 (br, 1H), 8.32-8.41 (m, 3H), 8.20 (s, 1H), 3.55-3.62 (m, 1H), 3.47-3.53 (m, 2H), 3.11-3.20 (m, 2H), 2.71 (s, 3H), 2.52 (s, 3H), 2.16-2.30 (m, 4H).

(366) Using the procedure described for Example 7, above, additional compounds described herein were prepared by substituting the appropriate boronic acid or boronic acid equivalent in Step H or I, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

(367) TABLE-US-00009 Cpd Data 73 MS m/z 376.4 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.02-9.10 (br, 1H), 8.75-8.84 (br, 1H), 8.64 (s, 1H), 8.48 (s, 1H), 8.34 (dd, J = 11.4, 1.4 Hz, 1H), 8.16-8.19 (m, 1H), 8.10 (s, 1H), 7.68 (s, 1H), 4.23 (s, 3H), 3.51-3.59 (m, 1H), 3.43-3.50 (m, 2H), 3.08- 3.18 (m, 2H), 2.62 (s, 3H), 2.18-2.28 (m, 4H). 84 MS m/z 359.3 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.26 (s, 1H), 8.71 (dd, J = 8.5, 1.5 Hz, 1H), 8.58 (s, 1H), 8.44 (s, 1H), 8.40 (s, 1H), 8.32 (d, J = 8.5 Hz, 1H), 3.61-3.69 (m, 3H), 2.45-2.55 (m, 2H - overlaps with residual solvent peak), 2.88 (s, 3H), 2.72 (s, 3H), 2.30-2.50 (m, 4H). NH proton not observed. 87 MS m/z 405.3 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.13 (s, 1H), 8.59 (s, 1H), 8.40-8.45 (m, 2H), 8.32 (s, 1H), 4.04 (m, 1H), 3.91 (t, J = 12.5 Hz, 1H), 3.79 (br s, 1H), 2.87 (s, 3H), 2.70 (s, 3H), 2.38-2.50 (m, 2H), 2.24 (d, J = 14 Hz, 1H), 2.06 (q, J = 14 Hz, 1H), 1.65 (d, J = 7 Hz, 3H), 1.45 (d, J = 6 Hz, 3H). NH and HCl protons not observed. 90 MS m/z 405.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.88 (s, 1H), 8.28 (d, J = 10 Hz, 1H), 8.14 (s, 1H), 7.98 (s, 1H), 7.85 (s, 1H), 3.48 (tt, J = 10, 3 Hz, 1H), 2.98-3.04 (m, 2H), 2.71 (s, 3H), 2.51 (s, 3H), 2.13 (d, J = 15 Hz, 2H), 1.55 (q, J = 12 Hz, 2H), 1.26 (d, J = 7 Hz, 6H). NH proton not observed. 129 MS m/z 391.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.96 (s, 1H), 8.36 (dd, J = 11 Hz, 1H), 8.23 (s, 1H), 8.02 (s, 1H), 7.90 (s, 1H), 3.60-3.71 (m, 2H), 3.37-3.52 (m, 3H), 2.74 (s, 3H), 2.42-2.55 (m, 5H), 2.30-2.40 (m, 1H), 2.05-2.30 (m, 3H), NH proton not observed. 130 MS m/z 433.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.91 (s, 1H), 8.30 (dd, J = 11, 1.5 Hz, 1H), 8.18 (s, 1H), 8.00 (s, 1H), 7.88 (s, 1H), 3.62-3.71 (m, 1H), 3.16-3.20 (m, 1H), 2.95-3.02 (m, 1H), 2.73 (s, 3H), 2.51 (s, 3H), 2.21 (d, J = 12.5 Hz, 1H), 2.07- 2.16 (m, 2H), 1.89 (pentet, J = 7.5 Hz, 2H), 1.46-1.60 (m, 3H), 1.00-1.08 (m, 6H). NH proton not observed. 143 MS m/z 363.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.00 (s, 1H), 8.39 (d, J = 11 Hz, 1H), 8.34 (s, 1H),

8.03 (s, 1H), 7.92 (s, 1H), 4.24 (septet, J = 7.5 Hz, 1H), 3.91 (d, J = 7.5 Hz, 2H), 3.68-3.75 (m, 1H), 3.54-3.61 (m, 1H), 2.70-2.78 (m, 4H), 2.53 (s, 3H), 2.45-2.52 (m, 1H), NH proton not observed. 169 MS m/z 403.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.13 (s, 1H), 8.56 (s, 1H), 8.52 (s, 1H), 8.40 (m, 2H), 4.18 (br s, 2H), 3.87 (m, 1H), 3.12 (d, J = 15 Hz, 2H), 2.85 (s, 3H), 2.60-2.70 (m, 5H), 1.96 (m, 2H), 1.80-1.84 (m, 2H). 210 MS m/z 362.3 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.76 (s, 1H), 8.88 (s, 1H), 8.83- 8.86 (m, 1H), 8.30 (s, 1H), 8.14 (s, 1H), 8.07 (d, J = 9.5 Hz, 1H), 7.72 (d, J = 9.5 Hz, 1H), 3.61-3.64 (m, 2H), 3.23-3.31 (m, 3H), 2.63 (s, 3H), 2.28-2.35 (m, 2H), 2.07- 2.18 (m, 2H), NH and HCl protons not observed. 216 MS m/z 377.3 [M + H].sup.+; .sup.1H NMR (methanol-d) δ 9.15 (s, 1 H), 8.55 (s, 1 H), 8.44 (br d, J = 10.8 Hz, 1 H), 8.41 (s, 1 H), 8.39 (s, 1 H), 3.83-3.45 (m, 5 H), 2.86 (s, 3 H) 2.69 (s, 3 H) 2.33-2.42 (m, 1 H) 2.02-2.19 (m, 3 H), NH and HCl protons not observed.

(368) Boronic acid or bornic acid equivalents for use in Step H or I were prepared according to the following procedures:

Example 7-1

rac-(2R,6R)-1-Benzyl-2,6-dimethyl-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate and rac-(2S,6R)-1-benzyl-2,6-dimethyl-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate

(369) Step A: 3-Oxopentanedioic acid (20.5 g, 140 mmol) and acetaldehyde (15.7 mL, 279 mmol) were suspended in H.sub.2O (50 mL). The mixture was stirred with a strong stir bar at room temperature for 10 min. The mixture was then cooled in an ice bath. Benzylamine (15.3 mL, 140 mmol) was added dropwise. The mixture became thick. Stirring was continued at room temperature for 5 days. Aqueous 6N HCl was added. The mixture was stirred at room temperature for 1 h. The mixture was then made basic with aqueous K.sub.2CO.sub.3 and washed 3 times with CH.sub.2Cl.sub.2. The organic layer was dried over MgSO.sub.4, filtered, and concentrated under vacuum. Purification by silica gel chromatography (10-20% EtOAc in hexanes) yielded 6.6 g (17% total yield) of a mixture of rac-(2R,6R)-1-benzyl-2,6-dimethylpiperidin-4-one and (2S,6R)-1-benzyl-2,6-dimethylpiperidin-4-one. These two components readily interconvert one to the other.

(370) Step B: A roughly 2:3 ratio of rac-(2R,6R)-1-benzyl-2,6-dimethylpiperidin-4-one and (2S,6R)-1-benzyl-2,6-dimethylpiperidin-4-one (4.45 g, 18.4 mmol) was dissolved in THF (12.8 mL) at −78° C. NaHMDS (2M in THF, 13.1 mL, 26.2 mmol) was added dropwise. The mixture was stirred at −78° C. for 3 h. N,N-Bis(trifluoromethylsulfonyl)aniline (9.25 g, 25.9 mmol) was added to the mixture in one portion. The mixture was slowly warmed to room temperature over 15 h. THF was removed from the mixture under vacuum. The product mixture was diluted with CH.sub.2Cl.sub.2 and was filtered through a plug of silica to remove solid impurities. The filtrate was concentrated under vacuum. The residue was dissolved in EtOAc. This solution was washed with dilute aqueous NaOH (ca. 800 mL) and then with brine. The organic layer was dried over MgSO.sub.4, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (50-100% CH.sub.2Cl.sub.2 in hexanes) yielding trans-isomer rac-(2R,6R)-1-benzyl-2,6-dimethyl-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (1.5 g, 23%) as the higher Rf component. .sup.1H NMR (acetone-d.sub.4) δ: 7.37-7.40 (m, 2H), 7.30-7.35 (m, 2H), 7.22-7.27 (m, 1H), 5.87 (s, 1H), 3.76 (d, J=14.5 Hz, 1H), 3.58 (d, J=14.5 Hz, 1H), 3.30-3.42 (m, 2H), 2.41-2.50 (m, 1H), 2.24-2.30 (m, 1H), 1.20-1.25 (m, 6H). The cis-isomer rac-(2S,6R)-1-benzyl-2,6-dimethyl-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (2.1 g, 33%) was collected as the lower Rf component.

(371) .sup.1H NMR (acetone-d.sub.4) δ: 7.37-7.40 (m, 2H), 7.30-7.35 (m, 2H), 7.20-7.25 (m, 1H), 5.85 (s, 1H), 3.87 (d, J=16 Hz, 1H), 3.82 (d, J=16 Hz, 1H), 3.50-3.57 (m, 1H), 3.16-3.22 (m, 1H), 2.49-2.57 (m, 1H), 2.24-2.30 (m, 1H), 1.22 (d, J=7 Hz, 3H), 1.17 (d, J=6.5 Hz, 3H).

Example 7-2

(2R,6R)-1-Benzyl-2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine

(372) Potassium acetate (1.8 g, 18 mmol) was dried under Ar at 180° C. for 30 min and then cooled

to room temperature. To the solid was added rac-(2S,6R)-1-benzyl-2,6-dimethyl-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (1.5 g, 4.3 mmol, prepared according to Example 36), Pd(dppf)Cl.sub.2 (146 mg, 0.175 mmol), dppf (110 mg, 0.19 mmol), bis(pinacolato)diboron (1.2 g, 4.7 mmol), and 1,4-dioxane (14.5 mL). The mixture was heated at 80° C. for 15 h. The reaction mixture was then diluted in EtOAc and filtered through Celite. The filtrate was concentrated under vacuum. The residue was dissolved in EtOAc and washed with 800 mL of dilute aqueous NaHCO.sub.3 and brine. The organic layer was dried over MgSO.sub.4, filtered, and concentrated under vacuum. The residue was dissolved in ether and filtered through Celite to remove brown insoluble impurities. The filtrate was concentrated to afford (2S,6R)-1-benzyl-2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine (1.43 g, 80% pure, 81% yield) as a crude black oil.

(373) .sup.1H NMR (acetone-d.sub.4) δ: 7.40-7.45 (m, 2H), 7.25-7.32 (m, 2H), 7.16-7.21 (m, 1H), 6.31 (s, 1H), 3.80 (m, 2H), 3.20-3.28 (m, 1H), 2.73-2.79 (m, 1H), 2.12-2.19 (m, 1H), 1.90-1.98 (m, 1H), 1.35 (s, 12H), 1.22 (d, J=5.5 Hz, 3H), 1.00 (d, J=6.5 Hz, 3H).

Example 7-3

(2R,6R)-1-Benzyl-2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine was prepared from rac-(2R,6R)-1-benzyl-2,6-dimethyl-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate according to Example 7-2

(374) .sup.1H NMR (acetone-d.sub.4) δ: 7.40-7.45 (m, 2H), 7.25-7.32 (m, 2H), 7.16-7.21 (m, 1H), 6.38 (s, 1H), 3.62 (m, 2H), 3.12-3.21 (br s, 1H), 3.00-3.08 (m, 1H), 2.12-2.21 (m, 1H), 1.90-1.98 (m, 1H), 1.27 (s, 12H), 1.22 (m, 6H).

Example 7-4

(2R,6R)-1-Benzyl-2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine was prepared by substituting the appropriate acetaldehyde in Step A of Example 7-1

(375) .sup.1H NMR (acetone-d.sub.4) δ: 7.40-7.45 (m, 2H), 7.25-7.32 (m, 2H), 7.16-7.21 (m, 1H), 6.38 (s, 1H), 3.62 (m, 2H), 3.12-3.21 (br s, 1H), 3.00-3.08 (m, 1H), 2.12-2.21 (m, 1H), 1.90-1.98 (m, 1H), 1.27 (s, 12H), 1.22 (m, 6H).

Example 8

(376) Preparation of Compound 34

(377) ##STR00121##

(378) Step A: 2-Amino-5-bromo-3-fluoro-benzoic acid (1.0 g, 4.27 mmol) was dissolved in THF (20 mL). To the solution was added LAH (8.5 mL, 8.5 mmol, 1.0 M in THF) at 0° C. The mixture was warmed to room temperature. After 1 h, the mixture was quenched with aqueous 2 N NaOH at 0° C. After vigorous stirring for 30 min, the mixture was filtered over Celite. The filter cake was washed with THF and MeOH. The combined filtrate was concentrated to yield (2-amino-5-bromo-3-fluoro-phenyl)methanol (900 mg, 96%). MS m/z 220.2, 222.2 [M+H].sup.+.

(379) Step B: (2-Amino-5-bromo-3-fluoro-phenyl)methanol (900 mg, 4.09 mmol) was combined with MnO.sub.2 (6.9 g, 79 mmol) in CH.sub.2Cl.sub.2 (20 mL). The mixture was stirred at room temperature for 1 h. The mixture was filtered over Celite. The filtrate was concentrated to yield 2-amino-5-bromo-3-fluoro-benzaldehyde (650 mg, 73%). MS m/z 218.1, 220.1 [M+H].sup.+.

(380) Step C: 2-Amino-5-bromo-3-fluoro-benzaldehyde (650 mg, 3.0 mmol) was combined with urea (3.6 g, 60 mmol) and DMSO (3 mL). The mixture was stirred at 180° C. for 2 h. The mixture was cooled to room temperature, upon which H.sub.2O (10 mL) was added. The precipitate was collected, washed with H.sub.2O and dried to yield 6-bromo-8-fluoro-quinazolin-2-ol (615 mg, 85%). MS m/z 243.1, 245.1 [M+H].sup.+.

(381) Step D: 6-Bromo-8-fluoro-quinazolin-2-ol (615 mg, 2.53 mmol) was combined with POCl.sub.3 (5 mL, 53 mmol). The mixture was stirred at 110° C. for 2 h. The mixture was cooled to room temperature and poured over ice. After vigorously stirring for 15 min, the solid was collected, dried and chromatographed on silica gel, eluting with 0-20% EtOAc in CH.sub.2Cl.sub.2

to yield 6-bromo-2-chloro-8-fluoroquinazoline (345 mg, 52%). MS m/z 261.1, 263.1, 265.1 [M+H].sup.+.
(382) Steps E-G: Following a procedure similar to that found in Example 5 (Steps A-C), 6-bromo-2-chloro-8-fluoroquinazoline was converted to 6-(2,7-dimethyl-2H-indazol-5-yl)-8-fluoro-2-(piperidin-4-yl)quinazoline hydrochloride.
(383) MS m/z 376.3 [M+H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.70 (s, 1H), 8.86-8.93 (br, 1H), 8.54-8.63 (br, 1H), 8.46 (s, 1H), 8.34 (d, J=1.9 Hz, 1H), 8.32 (dd, J=12.10, 1.9 Hz, 1H), 8.07 (s, 1H), 7.57 (s, 1H), 4.22 (s, 3H), 3.36-3.44 (m, 3H), 3.08-3.16 (m, 2H), 2.61 (s, 3H), 2.22-2.28 (m, 2H), 2.08-2.15 (m, 2H).
(384) Using the procedure described for Example 8, above, additional compounds described herein were prepared by substituting the appropriate boronic acid in Step E, suitable reagents and reaction conditions, obtaining compounds such as those selected from:
(385) TABLE-US-00010 Cpd Data 35 MS m/z 387.3 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.69 (d, J = 1.6 Hz, 1H), 8.79-8.85 (br, 1H), 8.78 (s, 1H), 8.67 (d, J = 1.9 Hz, 1H), 8.49-8.55 (br, 1H), 8.48 (d, J = 1.7 Hz, 1H), 8.47 (d, J = 1.8 Hz, 1H), 8.43 (dd, J = 12.2, 1.8 Hz, 1H), 4.30 (s, 3H), 3.37- 3.46 (m, 3H), 3.07-3.17 (m, 2H), 2.22-2.28 (m, 2H), 2.07-2.16 (m, 2H). 36 MS m/z 380.3 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.69 (s, 1H), 8.73-8.79 (br, 1H), 8.63 (d, J = 1.9 Hz, 1H), 8.43-8.52 (br, 1H), 8.40 (d, J = 1.8 Hz, 1H), 8.37 (dd, J = 12.3, 1.8 Hz, 1H), 8.13 (d, J = 1.8 Hz, 1H), 7.65 (dd, J = 12.2, 1.9 Hz, 1H), 4.25 (s, 3H), 3.37-3.46 (m, 3H), 3.08-3.18 (m, 2H), 2.22-2.28 (m, 2H), 2.05-2.14 (m, 2H). 37 MS m/z 377.3 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.83 (s, 1H), 8.85-8.91 (br, 1H), 8.83 (d, J = 1.9 Hz, 1H), 8.59-8.64 (br, 1H), 8.56 (dd, J = 12.3, 1.8 Hz, 1H), 8.42 (s, 1H), 8.31 (s, 1H), 3.58 (s, 3H), 3.39-3.47 (m, 3H), 3.08-3.18 (m, 2H), 2.74 (s, 3H), 2.23-2.30 (m, 2H), 2.07-2.15 (m, 2H).
(386) Using the procedure described for Example 8, above, additional compounds described herein were prepared by substituting the indicated starting material, suitable reagents and reaction conditions, obtaining compounds such as those selected from:
(387) TABLE-US-00011 Cpd Starting Material and Data 38 Starting material: 6-amino-3-bromo-2-fluorobenzoic acid MS m/z 376.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.70 (s, 1H), 7.94 (s, 1H), 7.81- 7.86 (m, 1H), 7.58-7.61 (m, 1H), 7.47 (d, J = 8.5 Hz, 1H), 6.37 (s, 1H), 4.40 (s, 3H), 3.63-3.70 (m, 3H), 3.21-3.29 (m, 2H), 2.69 (s, 3H), 2.29-2.40 (m, 4H) NH proton not observed. 39 Starting material: 2-amino-5-bromo-4-fluorobenzoic acid MS m/z 376.3 [M + H]+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.77 (s, 1H), 7.98 (s, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.63-7.68 (m, 1H), 7.43 (d, J = 10.4 Hz, 1H), 6.27 (s, 1H), 4.42 (s, 3H), 3.63-3.70 (m, 3H), 3.24-3.31 (m, 2H), 2.69 (s, 3H), 2.28-2.45 (m, 4H), NH proton not observed.
Example 9
(388) Preparation of Compound 17
(389) ##STR00122##
(390) Step A: 4-Bromo-2-nitroaniline (3.7 g, 17 mmol), cyanamide (5.72 g, 135 mmol) and Et.sub.2O (3 mL) were combined in a 75 mL tube. The mixture was stirred at 100° C. for 30 min. The mixture was cooled to 50° C. To the mixture was slowly added aqueous concentrated HCl (7.2 mL). The resulting mixture was stirred for 1 h at 110° C. The reaction mixture was again cooled to 50° C., before adding aqueous 7.5 M NaOH (16 mL). The mixture was again heated to 110° C. for 1 h. After cooling to room temperature, 20 mL of H.sub.2O was added to the mixture. The solid material was collected, washed with H.sub.2O and dried to yield 7-bromo-1-oxido-1,2,4-benzotriazin-1-ium-3-amine (3.2 g, 79%). MS m/z 240.8, 242.8 [M+H].sup.+.
(391) Step B: To a solution of 7-bromo-1-oxido-1,2,4-benzotriazin-1-ium-3-amine (3.2 g, 13 mmol) and TFA (25 mL) was added NaNO.sub.2 (2.76 g, 40.0 mmol) in small portions at room temperature. The mixture stirred at room temperature for 30 min. To the mixture was added H.sub.2O (75 mL) to form a white precipitate. The solid was collected, washed with H.sub.2O and dried. The solid was combined with POCl.sub.3 (30 mL, 318.6 mmol). The mixture was stirred at

110° C. for 2 h. After cooling to room temperature, the mixture was poured onto ice with vigorous stirring. After stirring for 10 min, CH.sub.2Cl.sub.2 (400 mL) was added. The organic phase was collected and dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-10% EtOAc in CH.sub.2Cl.sub.2 to yield 7-bromo-3-chloro-1-oxido-1,2,4-benzotriazin-1-ium (2.37 g, 54%). MS m/z 259.9, 261.9, 264.0 [M+H].sup.+.
(392) Step C: 7-Bromo-3-chloro-1-oxido-1,2,4-benzotriazin-1-ium (520 mg, 2.0 mmol) was combined with N-Boc-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester (773 mg, 2.45 mmol), 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (80 mg, 0.10 mmol), 1,4-dioxane (10 mL), and aqueous 1 M K.sub.2CO.sub.3 (5 mL, 5.0 mmol). The mixture was stirred at 80° C. for 1 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 10-100% EtOAc in hexanes to yield tert-butyl 4-(3-chloro-1-oxido-1,2,4-benzotriazin-1-ium-7-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (540 mg, 75%). MS m/z 307.1, 309.1 [M+H-tBu].sup.+ (molecule ionizes as M+H minus tBu).
(393) Step D: tert-Butyl 4-(3-chloro-1-oxido-1,2,4-benzotriazin-1-ium-7-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (72 mg, 0.20 mmol) was combined with 2,7-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole (80 mg, 0.30 mmol), 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (8 mg, 0.01 mmol), 1,4-dioxane (1 mL), and aqueous 1 M K.sub.2CO.sub.3 (0.5 mL, 0.5 mmol). The mixture was stirred at 80° C. for 1 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 5% MeOH in EtOAc to yield tert-butyl 4-[3-(2,7-dimethylindazol-5-yl)-1-oxido-1,2,4-benzotriazin-1-ium-7-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (72 mg, 77%). MS m/z 473.4 [M+H].sup.+.
(394) Step E: tert-Butyl 4-[3-(2,7-dimethylindazol-5-yl)-1-oxido-1,2,4-benzotriazin-1-ium-7-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (60 mg, 0.13 mmol) was combined with 10% Pd/C (10 mg) and MeOH (3 mL). The mixture was stirred under H.sub.2 (1 atm) for 2 h at 30° C. The mixture was filtered through a 0.2 μm syringe filter to yield tert-butyl 4-[3-(2,7-dimethylindazol-5-yl)-1,2,4-benzotriazin-7-yl]piperidine-1-carboxylate (58 mg, 99%). MS m/z 459.4 [M+H].sup.+.
(395) Step F: tert-Butyl 4-[3-(2,7-dimethylindazol-5-yl)-1,2,4-benzotriazin-7-yl]piperidine-1-carboxylate (58 mg, 0.13 mmol) was dissolved in TFA (1 mL). After 20 min, the volatiles were removed from the mixture. The residue was partitioned between EtOAc and aqueous 1 M K.sub.2CO.sub.3. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-10% MeOH (2 N NH.sub.3) in CH.sub.2Cl.sub.2 to yield 3-(2,7-dimethyl-2H-indazol-5-yl)-7-(piperidin-4-yl)benzo[e][1,2,4]triazine (20 mg, 44%).
(396) MS m/z 359.3 [M+H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.01 (s, 1H), 8.59 (s, 1H), 8.31 (s, 1H), 8.26 (s, 1H), 8.06-8.12 (m, 2H), 4.24 (s, 3H), 3.11-3.19 (m, 2H), 2.94-3.01 (m, 1H), 2.68-2.76 (m, 2H), 2.64 (s, 3H), 1.88-1.94 (m, 2H), 1.66-1.76 (m, 2H), NH proton not observed.
(397) Using the procedure described for Example 9, above, additional compounds described herein were prepared by substituting the appropriate boronic acid in Steps B and/or C, suitable reagents and reaction conditions, obtaining compounds such as those selected from:
(398) TABLE-US-00012 Cpd Data 25 MS m/z 363.3 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.03 (s, 1H), 8.76 (d, J = 2.7 Hz, 1H), 8.31 (s, 1H), 8.16 (dd, J = 13.0, 1.2 Hz, 1H), 8.10-8.14 (m, 2H), 4.24 (s, 3H), 3.14- 3.20 (m, 2H), 2.97-3.05 (m, 1H), 2.71-2.79 (m, 2H), 1.90-1.97 (m, 2H), 1.69- 1.79 (m, 2H), NH proton not observed. 26 MS m/z 370.3 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.48 (d, J = 1.6 Hz, 1H), 9.05 (d, J = 1.6 Hz, 1H), 8.68 (s, 1H), 8.36 (s, 1H), 8.09-8.17 (m, 2H), 4.36 (s, 3H), 3.35-3.42 (m, 2H), 3.11-3.20 (m, 1H), 2.97-3.05 (m, 2H), 2.11-2.19 (m, 2H), 1.89-1.99 (m, 2H), NH proton not observed. 27 MS m/z 359.3 [M + H].sup.+;

.sup.1H NMR (methanol-d.sub.4) δ: 9.52 (s, 1H), 8.29 (s, 1H), 8.18 (s, 1H), 8.01-8.07 (m, 2H), 7.73 (s, 1H), 3.27-3.32 (m, 2H), 3.03-3.10 (m, 1H), 2.88- 2.94 (m, 2H), 2.63 (s, 3H), 2.45 (s, 3H), 2.04-2.09 (m, 2H), 1.81-1.91 (m, 2H), NH proton not observed. 43 MS m/z 363.3 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.78 (s, 1H), 8.36 (s, 1H), 8.10-8.17 (m, 3H), 8.04 (dd, J = 12.2, 1.3 Hz, 1H), 3.09-3.15 (m, 2H), 2.94-3.01 (m, 1H), 2.66-2.72 (m, 2H), 2.42 (s, 3H), 1.87-1.93 (m, 2H), 1.64-1.74 (m, 2H), NH proton not observed. 52 MS m/z 375.4 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.78 (s, 1H), 8.57 (s, 1H), 8.31 (s, 1H), 8.07-8.12 (m, 2H), 7.82 (s, 1H), 4.21 (s, 3H), 4.07 (s, 3H), 3.10-3.17 (m, 2H), 2.93-2.99 (m, 1H), 2.66-2.73 (m, 2H), 1.87-1.93 (m, 2H), 1.65-1.75 (m, 2H), NH proton not observed. 56 MS m/z 389.2 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 10.01 (s, 1H), 8.88-8.92 (m, 1H), 8.75 (s, 1H), 8.36 (dd, J = 9.0, 2.2 Hz, 1H), 8.30-8.33 (m, 1H), 8.24-8.27 (m, 1H), 4.18-4.28 (m, 2H), 3.61-3.69 (m, 1H), 2.58-2.74 (m, 5H), 2.20-2.33 (m, 4H), 2.08-2.13 (m, 2H), NH proton not observed.

Example 10

(399) Preparation of Compound 28

(400) ##STR00123##

(401) Step A: 1-(1H-Pyrrol-2-yl)ethanone (1.09 g, 10.0 mmol) was dissolved in 50 mL CH.sub.2Cl.sub.2 and cooled to −78° C. A solution of Br.sub.2 (620 μL, 12.1 mmol) in 12 mL of CH.sub.2Cl.sub.2 was added dropwise to the solution. The reaction mixture was poured onto ice. The organic layer was washed with aqueous 1M NaOH, dried over MgSO.sub.4, filtered and concentrated to yield 1-(4-bromo-1H-pyrrol-2-yl)ethanone (1.42 g, 76%).

(402) .sup.1H NMR (acetone-d.sub.6) δ: 11.08 (br s, 1H), 7.19 (m, 1H), 7.02 (m, 1H), 2.34 (s, 3H).

(403) Step B: 1-(4-Bromo-1H-pyrrol-2-yl)ethanone (1.36 g, 7.2 mmol) was dissolved in DMF (15 mL) and cooled to 0° C. To the solution was added NaH (60 mass % in mineral oil) (316 mg, 7.9 mmol). The mixture was warmed to room temperature for 30 min. Chloroacetone (0.6 mL, 7 mmol) was added dropwise. The mixture was stirred at room temperature for 16 h. The mixture was partitioned between H.sub.2O and EtOAc. The organic layer was dried over MgSO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 30% EtOAc in hexanes to yield 1-(2-acetyl-4-bromo-pyrrol-1-yl)propan-2-one (1.2 g, 68%) as a white solid.

(404) .sup.1H NMR (acetone-d.sub.6) δ: 7.13 (d, J=2 Hz, 1H), 7.10 (d, J=2 Hz, 1H), 5.17 (s, 2H), 2.36 (s, 3H), 2.18 (s, 3H).

(405) Step C: 1-(2-Acetyl-4-bromo-pyrrol-1-yl)propan-2-one (1.15 g, 4.7 mmol), acetic acid (40 mL) and ammonium acetate (7.2 g, 93 mmol) were heated at 120° C. for 16 h. The volatiles were removed under reduced pressure. The residue was partitioned between aqueous 1 M NaOH and EtOAc. The organic layer was dried over MgSO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 10-50% EtOAc in CH.sub.2Cl.sub.2 to yield 7-bromo-1,3-dimethyl-pyrrolo[1,2-a]pyrazine (975 mg, 92%).

(406) .sup.1H NMR (acetone-d.sub.6) δ: 7.86 (s, 1H), 7.63 (s, 1H), 6.84 (s, 1H), 2.56 (s, 3H), 2.31 (s, 3H).

(407) Step D: 7-Bromo-1,3-dimethylpyrrolo[1,2-a]pyrazine (2.0 g, 8.9 mmol) was dissolved in THF (90 mL). The solution was cooled to −78° C., upon which n-butyllithium was added (6.7 mL, 13.3 mmol, 2 M solution in cyclohexane). The mixture was stirred at −78° C. for 30 min. To the mixture was added tributylchlorostannane. The mixture was allowed to slowly warm to 0° C. The excess reagent was quenched with saturated aqueous NH.sub.4Cl. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-100% EtOAc in hexanes to yield tributyl-(1,3-dimethylpyrrolo[1,2-a]pyrazin-7-yl)stannane (1.3 g, 30%).

(408) .sup.1H NMR (chloroform-d) δ: 7.53 (s, 1H), 7.20 (s, 1H), 6.72 (s, 1H), 2.65 (s, 3H), 2.37 (s, 3H), 1.52-1.58 (m, 6H), 1.30-1.38 (m, 6H), 1.04-1.08 (m, 6H), 0.88-0.94 (m, 9H).

(409) Step E: tert-Butyl 4-(3-chloro-1-oxido-1,2,4-benzotriazin-4-ium-7-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (72 mg, 0.20 mmol, prepared according to the procedure in Example 9, Step

C) was combined with tributyl-(1,3-dimethylpyrrolo[1,2-a]pyrazin-7-yl)stannane (140 mg, 0.32 mmol), 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (12 mg, 0.015 mmol), 1,4-dioxane (1.5 mL) and aqueous 1 M K.sub.2CO.sub.3 (0.75 mL, 0.75 mmol). The mixture was stirred at 80° C. for 2 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 50-100% EtOAc in CH.sub.2Cl.sub.2, then EtOAc containing 5% MeOH to yield tert-butyl 4-[3-(1,3-dimethylpyrrolo[1,2-a]pyrazin-7-yl)-1-oxido-1,2,4-benzotriazin-1-ium-7-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (50 mg, 53%). MS m/z 473.5 [M+M].sup.+.

(410) Step F: tert-Butyl 4-[3-(1,3-dimethylpyrrolo[1,2-a]pyrazin-7-yl)-1-oxido-1,2,4-benzotriazin-1-ium-7-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (30 mg, 0.06 mmol) was combined with 10% Pd/C (10 mg) in EtOAc:MeOH (1:1, 2 mL). The mixture was stirred under H.sub.2 (1 atm) for 2 h at 40° C. The mixture was filtered through a 2 μm syringe filter. The filtrate was concentrated to yield tert-butyl 4-(3-(1,3-dimethylpyrrolo[1,2-a]pyrazin-7-yl)benzo[e][1,2,4]triazin-7-yl)-3,6-dihydropyridine-1(2H)-carboxylate (25 mg, 86%). MS m/z 457.5 [M+H].sup.+.

(411) Step G: tert-Butyl 4-[3-(1,3-dimethylpyrrolo[1,2-a]pyrazin-7-yl)-1,2,4-benzotriazin-7-yl]piperidine-1-carboxylate (25 mg, 0.05 mmol) was dissolved in TFA (1 mL). After 15 min, the volatiles were removed. The residue was partitioned between CH.sub.2Cl.sub.2 and aqueous 1 M K.sub.2CO.sub.3. The organic layer was loaded on silica gel, eluting with 0-10% MeOH (2 N NH.sub.3) in CH.sub.2Cl.sub.2 to yield 3-(1,3-dimethylpyrrolo[1,2-a]pyrazin-7-yl)-7-(1,2,3,6-tetrahydropyridin-4-yl)benzo[e][1,2,4]triazine (8 mg, 43%).

(412) .sup.1H NMR (DMSO-d.sub.6) δ: 8.34 (s, 1H), 8.25 (s, 1H), 8.23 (dd, T=9.0, 2.0 Hz, 1H), 7.90 (d, T=8.8 Hz, 1H), 7.86 (s, 1H), 7.57 (s, 1H), 6.62 (s, 1H), 3.58-3.62 (m, 2H), 3.15-3.19 (m, 2H), 2.64-2.70 (m, 5H), 2.35 (s, 3H), NH proton not observed.

Example 11

(413) Preparation of Compound 44

(414) ##STR00124##

(415) Step A: 4-Bromo-6-chloro-pyridazin-3-amine (5.2 g, 25 mmol) was combined with tetrakis(triphenylphosphine)palladium(0) (700 mg, 0.61 mmol) and DMF (50 mL). To the mixture was added dimethylzinc in heptane (50 mL, 50 mmol, 1.0 M) at room temperature. The mixture was heated at 50° C. for 2 h then 70° C. for 1 h. The mixture was cooled to 0° C. and excess reagent was quenched by the addition of H.sub.2O. The mixture was filtered over Celite and concentrated. The residue was chromatographed on silica gel, eluting with 0-10% MeOH in CH.sub.2Cl.sub.2. MS m/z 144.2, 146.2 [M+H].sup.+.

(416) Step B: 6-Chloro-4-methyl-pyridazin-3-amine (3.5 g, 24 mmol) was combined with ethanol (40 mL), triethylamine (8.7 mL, 62 mmol) and chloroacetone (4 mL, 49 mmol) in a 100 mL high pressure flask. The flask was sealed and heated behind a blast shield at 150° C. for 45 min. The mixture was concentrated and chromatographed on silica gel, eluting with 30-80% EtOAc in CH.sub.2Cl.sub.2 to yield 6-chloro-2,8-dimethylimidazo[1,2-b]pyridazine (2.2 g, 49%). MS m/z 182.3, 184.3 [M+H].sup.+.

(417) Step C: 6-Chloro-2,8-dimethyl-imidazo[1,2-b]pyridazine (54 mg, 0.30 mmol) was combined with potassium acetate (87 mg, 0.89 mmol), 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (12 mg, 0.015 mmol), and bis(pinacolato)diboron (94 mg, 0.37 mmol) in 1,4-dioxane (1 mL). The mixture was stirred under N.sub.2 at 95° C. for 2 h to yield (2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)boronic acid. MS m/z 192.4 [M+H].sup.+. The crude mixture was used directly in the next step.

(418) Step D: To the crude mixture from Step C was added aqueous 1 M K.sub.2CO.sub.3 (0.75 mL, 0.75 mmol), tert-butyl 4-(3-chloro-1-oxido-1,2,4-benzotriazin-1-ium-7-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (72 mg, 0.20 mmol, prepared according to the procedure in Example 9, Step C), and 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (8

mg, 0.01 mmol). The mixture was stirred at 80° C. for 1 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-80% EtOAc in CH.sub.2Cl.sub.2 to yield tert-butyl 4-[3-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-1-oxido-1,2,4-benzotriazin-1-ium-7-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (69 mg, 73%). MS m/z 474.4 [M+H].sup.+.

(419) Step E: tert-Butyl 4-[3-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-1-oxido-1,2,4-benzotriazin-1-ium-7-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (69 mg, 0.15 mmol) was combined with 10% Pd/C (20 mg) in MeOH (2 mL). The mixture was stirred under H.sub.2 (1 atm) for 2 h at 40° C. The mixture was filtered. The filtrate was concentrated and chromatographed on silica gel, eluting with 20-100% EtOAc in hexanes to yield tert-butyl 4-[3-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-1-oxido-1,2,4-benzotriazin-1-ium-7-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (69 mg, 97%). MS m/z 460.4 [M+H].sup.+.

(420) Step F: tert-Butyl 4-[3-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-1-oxido-1,2,4-benzotriazin-1-ium-7-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (69 mg, 0.15 mmol) was suspended in 4 N HCl in 1,4-dioxane (1 mL, 4 mmol). The volatiles were removed after 30 min. The residue was partitioned between CH.sub.2Cl.sub.2 and aqueous 1 M K.sub.2CO.sub.3. The organic layer was concentrated. The residue was chromatographed on silica gel, eluting with 0-10% MeOH (2 N NH.sub.3) in CH.sub.2Cl.sub.2 to yield 3-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-(piperidin-4-yl)benzo[e][1,2,4]triazine.

(421) MS m/z 360.4 [M+H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.47 (s, 1H), 8.32 (s, 1H), 8.18-8.25 (m, 2H), 8.10 (s, 1H), 3.35-3.40 (m, 2H), 3.15-3.22 (m, 1H), 2.96-3.04 (m, 2H), 2.78 (s, 3H), 2.56 (s, 3H), 2.12-2.18 (m, 2H), 1.89-1.99 (m, 2H), NH proton not observed.

Example 12

(422) Preparation of Compound 16

(423) ##STR00125##

(424) Step A: 7-Bromo-3-chloro-1-oxido-1,2,4-benzotriazin-1-ium (260 mg, 1.0 mmol, prepared in Example 9 Step B) was combined with 2,7-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole (360 mg, 1.06 mmol), 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (45 mg, 0.05 mmol), 1,4-dioxane (5 mL) and aqueous 1 M K.sub.2CO.sub.3 (2.5 mL). The mixture was stirred at 70° C. for 1 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 10-90% EtOAc in hexanes to yield 3-chloro-7-(2,7-dimethyl-2H-indazol-5-yl)benzo[e][1,2,4]triazine-1-oxide (200 mg, 54%). MS m/z 326.0, 328.0 [M+H].sup.+.

(425) Step B: 3-Chloro-7-(2,7-dimethyl-2H-indazol-5-yl)benzo[e][1,2,4]triazine-1-oxide (200 mg, 0.54 mmol) was combined with N-Boc-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester (250 mg, 0.80 mmol), 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (40 mg, 0.05 mmol), 1,4-dioxane (3 mL) and aqueous 1 M K.sub.2CO.sub.3 (1.5 mL, 1.5 mmol). The mixture was stirred at 80° C. for 2 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 10-100% EtOAc in hexanes to yield tert-butyl 4-[7-(2,7-dimethylindazol-5-yl)-1-oxido-1,2,4-benzotriazin-1-ium-3-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (200 mg, 78%). MS m/z 473.1 [M+H].sup.+.

(426) Step C: tert-Butyl 4-[7-(2,7-dimethylindazol-5-yl)-1-oxido-1,2,4-benzotriazin-1-ium-3-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (200 mg, 0.085 mmol) was combined with 10% Pd/C (40 mg) in MeOH (5 mL). The mixture was stirred under H.sub.2 (1 atm) for 2 h at 40° C. The mixture was filtered through a 2 μm syringe filter. The filtrate was concentrated and chromatographed on silica gel, eluting with 10-100% EtOAc in CH.sub.2Cl.sub.2 to yield tert-

butyl 4-[7-(2,7-dimethylindazol-5-yl)-1,2,4-benzotriazin-3-yl]piperidine-1-carboxylate (100 mg, 50%). MS m/z 459.1 [M+H].sup.+.
(427) Step D: tert-Butyl 4-[7-(2,7-dimethylindazol-5-yl)-1,2,4-benzotriazin-3-yl]piperidine-1-carboxylate (50 mg, 0.11 mmol) was dissolved in TFA (1 mL). After 20 min, the volatiles were removed from the reaction mixture. The residue was partitioned between CH.sub.2Cl.sub.2 and aqueous 1 M K.sub.2CO.sub.3. The organic layer was loaded directly to silica gel, eluting with 0-10% MeOH (2 N NH.sub.3) in CH.sub.2Cl.sub.2 to yield 7-(2,7-dimethyl-2H-indazol-5-yl)-3-(piperidin-4-yl)benzo[e][1,2,4]triazine (30 mg, 77%).
(428) MS m/z 359.1 [M+H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.77 (d, J=2.5 Hz, 1H), 8.56 (dd, J=9.0, 1.9 Hz, 1H), 8.47 (s, 1H), 8.12-8.18 (m, 2H), 7.66 (s, 1H), 4.23 (s, 3H), 3.40-3.47 (m, 1H), 3.08-3.15 (m, 2H), 2.69-2.76 (m, 2H), 2.63 (s, 3H), 2.00-2.07 (m, 2H), 1.83-1.92 (m, 2H), NH proton not observed.
Example 13
(429) Preparation of Compound 46
(430) ##STR00126##
(431) Step A: 5-Bromo-1,3-difluoro-2-nitro-benzene (9.52 g, 40.0 mmol) was dissolved in EtOH (50 mL). To the solution was added hydrazine monohydrate (16.6 mL, 160 mmol). The solution was stirred at room temperature for 24 h. The mixture was concentrated under reduced pressure. The residue was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-30% EtOAc in hexanes to yield (5-bromo-3-fluoro-2-nitrophenyl)hydrazine (8.5 g, 85%). MS m/z 250.2, 252.2 [M+H].sup.+.
(432) Step B: (5-Bromo-3-fluoro-2-nitrophenyl)hydrazine (1.25 g, 5.0 mmol) and tert-butyl 4-formylpiperidine-1-carboxylate (3.2 g, 15 mmol) were combined in EtOH (25 mL). The mixture was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel, eluting with 0-20% EtOAc in CH.sub.2Cl.sub.2 to yield tert-butyl (E)-4-((2-(5-bromo-3-fluoro-2-nitrophenyl)hydrazono)methyl)piperidine-1-carboxylate (2.2 g, 99%) MS m/z 443.1, 445.4 [M−H].sup.−.
(433) Step C: tert-Butyl (E)-4-((2-(5-bromo-3-fluoro-2-nitrophenyl)hydrazono)methyl)piperidine-1-carboxylate (2.2 g, 4.9 mmol) was suspended in EtOH (50 mL) with PtO.sub.2 (100 mg, 0.4402 mmol). The mixture was stirred under H.sub.2 (1 atm, balloon) at room temperature for 3 h. The reaction mixture was filtered over Celite. The filtrate was concentrated under reduced pressure to yield tert-butyl (E)-4-((2-(2-amino-5-bromo-3-fluorophenyl)hydrazono)methyl)piperidine-1-carboxylate (2.03 g, 98%). MS m/z 413.3, 415.3 [M−H].sup.−.
(434) Step D: tert-Butyl 4-(7-bromo-5-fluoro-1,2,3,4-tetrahydro-1,2,4-benzotriazin-3-yl)piperidine-1-carboxylate (2.03 g, 4.9 mmol) was dissolved in CH.sub.3CN (40 mL, 765 mmol). To the mixture was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (3.41 g, 15.0 mmol). The mixture was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure. The residue was suspended in CH.sub.2Cl.sub.2 and filtered. The filtrate was concentrated and chromatographed on silica gel, eluting with 0-30% EtOAc in hexanes to yield tert-butyl 4-(7-bromo-5-fluorobenzo[e][1,2,4]triazin-3-yl)piperidine-1-carboxylate (805 mg, 39%). MS m/z 411.2, 413.2 [M+H].sup.+.
(435) Step E: tert-Butyl 4-(7-bromo-5-fluorobenzo[e][1,2,4]triazin-3-yl)piperidine-1-carboxylate (500 mg, 1.22 mmol) was combined with KOAc (358 mg, 3.65 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (100 mg, 0.12 mmol), bis(pinacolato)diboron (386 mg, 1.52 mmol) and 1,4-dioxane (3 mL). The mixture was stirred at 100° C. for 2 h. After cooling the mixture to room temperature, aqueous 1 M K.sub.2CO.sub.3 (1.5 mL, 1.5 mmol), 6-chloro-2,8-dimethylimidazo[1,2-b]pyridazine (270 mg, 1.22 mmol, prepared according the procedure in Example 11), and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (100 mg,

0.12 mmol) were added. The mixture was stirred at 80° C. for 2 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 20-80% EtOAc in hexanes to yield tert-butyl 4-(7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluorobenzo[e][1,2,4]triazin-3-yl)piperidine-1-carboxylate (550 mg, 94%). MS m/z 478.6 [M+H].sup.+.

(436) Step F: tert-Butyl 4-(7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluorobenzo[e][1,2,4]triazin-3-yl)piperidine-1-carboxylate (67 mg, 0.14 mmol) was suspended in 4 N HCl in 1,4-dioxane (2 mL, 8 mmol). The mixture was stirred vigorously for 1 h. The solid was collected, washed with CH.sub.3CN, and dried to afford 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(piperidin-4-yl)benzo[c][1,2,4]triazine hydrochloride (46 mg, 73%).

(437) MS m/z 378.3 [M+H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.24 (s, 1H), 8.68 (d, J=10.6 Hz, 1H), 8.60 (s, 1H), 8.44 (s, 1H), 3.91 (m, 1H), 3.59-3.67 (m, 2H), 3.34-3.42 (m, 2H), 2.87 (s, 3H), 2.70 (s, 3H), 2.53-2.61 (m, 2H), 2.32-2.43 (m, 2H), NH proton not observed.

(438) Using the procedure described for Example 13, above, additional compounds described herein were prepared by substituting the appropriate aryl halide in Step E, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

(439) TABLE-US-00013 Cpd Data 32 MS m/z. 381.1 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.67-8.69 (m, 1H), 8.49 (d, J = 2.8 Hz, 1H), 8.34 (dd, J = 11.0, 1.9 Hz, 1H), 8.12 (d, J = 1.6 Hz, 1H), 7.63 (dd, J = 12.6, 1.6 Hz, 1H), 4.31 (s, 3H), 3.83-3.90 (m, 1H), 3.60-3.67 (m, 2H), 3.32-3.38 (m, 2H), 2.52-2.59 (m, 2H), 2.32-2.42 (m, 2H), NH proton not observed. 33 MS m/z 377.3 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.69 (d, J = 1.9 Hz, 1H), 8.47-8.52 (m, 2H), 8.20-8.23 (m, 1H), 7.69-7.71 (m, 1H), 4.23 (s, 3H), 3.44-3.51 (m, 1H), 3.10-3.15 (m, 2H), 2.69-2.77 (m, 2H), 2.62 (s, 3H), 2.03-2.08 (m, 2H), 1.83-1.92 (m, 2H), NH proton not observed. 58 MS m/z 381.3 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.42 (s, 1H), 9.02-9.09 (br, 1H), 8.95 (s, 1H), 8.74-8.82 (br, 1H), 8.58 (dd, J = 13.0, 1.2 Hz, 1H), 8.30-8.37 (m, 1H), 8.07 (s, 1H), 3.77-3.84 (m, 1H), 3.43-3.49 (m, 2H), 3.14-3.24 (m, 2H), 2.51 (s, 3H), 2.33-2.39 (m, 2H), 2.17-2.27 (m, 2H). 59 MS m/z 408.2 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.35 (s, 1H), 8.94-9.01 (br, 1H), 8.65-8.75 (m, 2H), 8.26 (s, 1H), 7.82 (s, 1H), 4.64 (q, J = 7.3 Hz, 2H), 3.78-3.86 (m, 1H), 3.43-3.50 (m, 2H), 3.15-3.25 (m, 2H), 2.46 (s, 3H), 2.34-2.41 (m, 2H), 2.18-2.27 (m, 2H), 1.54 (t, J = 6.9 Hz, 3H). 60 MS m/z 377.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.23 (s, 1H), 8.86 (d, J = 1.7 Hz, 1H), 8.37 (dd, J = 10.5, 1.5 Hz, 1H), 8.31 (s, 1H), 8.08 (s, 1H), 3.88-3.93 (m, 1H), 3.68-3.61 (m, 2H), 3.32-3.39 (m, 2H), 2.78 (s, 3H), 2.65 (s, 3H), 2.54-2.60 (m, 2H), 2.34-2.43 (m, 2H), NH proton not observed. 61 MS m/z 431.3 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.61 (s, 1H), 9.02 (br, 1H), 8.98 (s, 1H), 8.72 (br, 1H), 8.63 (dd, J = 11.8, 2.0 Hz, 1H), 8.40 (s, 1H), 8.00 (s, 1H), 3.77- 3.83 (m, 1H), 3.42-3.49 (m, 2H), 3.15-3.24 (m, 2H), 2.47 (s, 3H), 2.33-2.39 (m, 2H), 2.16-2.27 (m, 2H). 62 MS m/z 378.4 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.84 (s, 1H), 8.56 (dd, J = 11.6, 1.9 Hz, 1H), 8.20 (s, 1H), 7.89 (s, 1H), 3.75-3.82 (m, 1H), 3.44-3.49 (m, 2H), 3.16- 3.23 (m, 2H), 2.68 (s, 3H), 2.62 (s, 3H), 2.32-2.38 (m, 2H), 2.15-2.25 (m, 2H), NH proton not observed. 63 MS m/z 377.4 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 14.98 (br, 1H), 9.05 (br, 1H), 8.87 (s, 1H), 8.77 (br, 1H), 8.60 (dd, J = 11.5, 1.9 Hz, 1H), 8.17 (s, 1H), 8.02 (s, 1H), 3.77- 3.83 (m, 1H), 3.44-3.49 (m, 2H), 3.16-3.23 (m, 2H), 2.85 (s, 3H), 2.70 (s, 3H), 2.32- 2.38 (m, 2H), 2.15-2.25 (m, 2H). 64 MS m/z 377.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.89-8.92 (m, 1H), 8.86 (d, J = 1.6 Hz, 1H), 8.46 (dd, J = 10.7, 1.9 Hz, 1H), 8.37-8.42 (m, 2H), 3.85-3.91 (m, 1H), 3.61-3.67 (m, 2H), 3.35-3.39 (m, 2H), 3.05 (s, 3H), 2.53-2.60 (m, 5H), 2.33-2.44 (m, 2H), NH proton not observed. 65 MS m/z 377.3 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.95 (br, 1H), 8.90 (s, 1H), 8.59- 8.66 (m, 2H), 8.26 (s, 1H), 7.53 (s, 1H), 6.60 (s, 1H), 3.77-3.83 (m, 1H), 3.44-3.49 (m, 2H), 3.16-3.23 (m, 2H), 2.77 (s, 3H), 2.48 (s, 3H), 2.32-2.38 (m, 2H), 2.15- 2.25 (m, 2H). 66 MS m/z 378.3 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.17 (s, 1H), 9.08 (br, 1H), 8.82 (dd, J = 11.5, 1.9 Hz, 1H), 8.78 (s, 1H),

8.76 (br, 1H), 8.21 (s, 1H), 4.28 (s, 3H), 3.75-3.83 (m, 1H), 3.43-3.49 (m, 2H), 3.15-3.23 (m, 2H), 2.69 (s, 3H), 2.32-2.38 (m, 2H), 2.15-2.25 (m, 2H). 67 MS m/z 378.1 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.17 (s, 1H), 8.79-8.86 (m, 2H), 8.64 (s, 1H), 8.58 (s, 1H), 8.52 (br, 1H), 4.31 (s, 3H), 3.77-3.83 (m, 1H), 3.44-3.51 (m, 2H), 3.15-3.23 (m, 2H), 2.89 (s, 3H), 2.32-2.38 (m, 2H), 2.15-2.25 (m, 2H). 68 MS m/z 382.0 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.68 (s, 1H), 8.27 (d, J = 13.0, 1H), 8.01 (s, 1H), 7.72 (d, J = 13.0, 1H), 3.58-3.67 (m, 1H), 3.26-3.30 (m, 2H), 2.87- 2.96 (m, 2H), 2.72 (s, 3H), 2.20-2.28 (m, 2H), 2.05-2.16 (m, 2H), NH proton not observed.

Example 14

(440) Preparation of Compound 57

(441) ##STR00127##

(442) Step A: 5-Bromo-1,2-difluoro-3-nitro-benzene (11.7 g, 49 mmol, prepared according to the procedure in Example 7, Step A) was combined with guanidine hydrochloride (23.5 g, 246 mmol), K.sub.2CO.sub.3 (34 g, 246 mmol) and DMSO (75 mL). The mixture was vigorously stirred at 120° C. for 30 min. The mixture was cooled to room temperature. To the mixture was added aqueous 7.5 N NaOH (100 mL). The mixture was stirred at 60° C. for 30 min. To the mixture was added AcOH (75 mL) and H.sub.2O (400 mL). The mixture was filtered. The collected solid was dried to yield 7-bromo-5-fluoro-1-oxido-1,2,4-benzotriazin-1-ium-3-amine (9.6 g, 76%). MS m/z 259.1, 261.1 [M+H].sup.+.

(443) Step B: 7-Bromo-5-fluoro-1-oxido-1,2,4-benzotriazin-1-ium-3-amine (9.6 g, 37 mmol) was dissolved in TFA (66 mL). To the mixture was added NaNO.sub.2 (13.1 g, 190 mmol) in small portions at 0° C. The mixture was stirred at room temperature for 20 min, and then cooled to 0° C. Ice water was slowly added to the mixture (20 mL). A solid formed and was collected, washed with H.sub.2O and dried. The solid was suspended in CH.sub.3CN, collected by filtration and dried to yield 7-bromo-5-fluoro-1-oxido-1,2,4-benzotriazin-1-ium-3-ol (5.3 g, 55%). MS m/z 260.1, 262.1 [M+H].sup.+.

(444) Step C: 7-Bromo-5-fluoro-1-oxido-1,2,4-benzotriazin-1-ium-3-ol (2.9 g, 11 mmol) was combined with POCl.sub.3 (30 mL, 320 mmol). The mixture was stirred at 110° C. for 2 h. The mixture was cooled to room temperature and then added to ice. The mixture was partitioned in CH.sub.2Cl.sub.2 and H.sub.2O. The organic layer was collected and loaded onto silica gel, eluting with 0-10% EtOAc in CH.sub.2Cl.sub.2 to yield 7-(2,7-dimethyl-2H-indazol-5-yl)-5-fluoro-N-methyl-N-(piperidin-4-yl)benzo[e][1,2,4]triazin-3-amine (490 mg, 16%). MS m/z 277.9, 279.9, 281.9 [M+H].sup.+.

(445) Step D: 7-Bromo-3-chloro-5-fluoro-1-oxido-1,2,4-benzotriazin-1-ium (78 mg, 0.28 mmol) was combined with (2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)boronic acid (53 mg, 0.28 mmol, prepared according to the procedure in Example 11), 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (11 mg, 0.014 mmol), 1,4-dioxane (1.5 mL) and aqueous 1 M K.sub.2CO.sub.3 (0.75 mL). The mixture was stirred at 80° C. for 1 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-100% EtOAc in CH.sub.2Cl.sub.2 to yield 7-bromo-3-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-1-(λ1-oxidanyl)-1λ4-benzo[e][1,2,4]triazine (69 mg, 63%). MS m/z 389.0, 391.0 [M+H].sup.+.

(446) Step E: 7-Bromo-3-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-1-(λ1-oxidanyl)-1λ4-benzo[e][1,2,4]triazine (20 mg, 0.051 mmol) was combined with N-Boc-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester (19 mg, 0.062 mmol), 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (4 mg, 0.005 mmol), 1,4-dioxane (1 mL) and aqueous 1 M K.sub.2CO.sub.3 (0.5 mL). The mixture was heated at 80° C. for 2 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was concentrated. The residue was chromatographed on silica gel, eluting with 10-100% EtOAc in

CH.sub.2Cl.sub.2 to yield tert-butyl 4-(3-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-1-(λ1-oxidanyl)-1λ4-benzo[e][1,2,4]triazin-7-yl)-3,6-dihydropyridine-1(2H)-carboxylate (20 mg, 79%). MS m/z 492.3 [M+H].sup.+.
(447) Step F: tert-Butyl 4-(3-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-1-(λ1-oxidanyl)-1λ4-benzo[e][1,2,4]triazin-7-yl)-3,6-dihydropyridine-1(2H)-carboxylate (20 mg, 0.04 mmol) was combined with 10% Pd/C (5 mg) in MeOH (2 mL). The mixture was stirred under H.sub.2 (1 atm) for 2 h at 40° C. The mixture was filtered over Celite. The filtrate was concentrated and chromatographed on a reversed phase C18 column, eluting with 40-100% CH.sub.3CN in H.sub.2O to yield tert-butyl 4-(3-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluorobenzo[e][1,2,4]triazin-7-yl)piperidine-1-carboxylate (17 mg, 87%). MS m/z 478.5 [M+H].sup.+.
(448) Step G: tert-Butyl 4-(3-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluorobenzo[e][1,2,4]triazin-7-yl)piperidine-1-carboxylate (17 mg, 0.036 mmol) was suspended in 4 N HCl in 1,4-dioxane (1 mL, 4 mmol HCl). The volatiles were removed from the mixture after 30 min. The residue was suspended in CH.sub.3CN. The solid was collected and dried to yield 3-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-7-(piperidin-4-yl)benzo[e][1,2,4]triazine hydrochloride (8 mg, 54%).
(449) .sup.1H NMR (methanol-d.sub.4) δ: 8.89 (d, J=1.6 Hz, 1H), 8.48 (d, J=1.9 Hz, 1H), 8.51 (d, J=1.3 Hz, 1H), 8.08 (dd, J=10.6, 1.7 Hz, 1H), 3.61-3.67 (m, 2H), 3.35-3.43 (m, 1H), 3.25-3.33 (m, 2H), 2.92 (s, 3H), 2.73 (s, 3H), 2.32-2.38 (m, 2H), 2.09-2.19 (m, 2H), NH protons not observed.
(450) Using the procedure described for Example 14, above, additional compounds described herein were prepared by substituting the appropriate aryl boronic acid in Step D, suitable reagents and reaction conditions, obtaining compounds such as those selected from:
(451) TABLE-US-00014 Cpd Data 40 MS m/z 377.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.84-8.86 (m, 1H), 8.64-8.67 (m, 1H), 8.25 (dd, J = 11.0, 1.9 Hz, 1H), 7.71 (s, 1H), 7.64 (s, 1H), 3.63-3.70 (m, 1H), 3.32-3.38 (m, 2H), 2.94-3.02 (m, 2H), 2.66 (s, 3H), 2.48 (s, 3H), 2.25-2.32 (m, 2H), 2.10-2.19 (m, 2H), NH proton not observed. 41 Starting material: 2-amino-5-bromo-4-fluorobenzoic acid MS m/z 381.4 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.89 (d, J = 1.6 Hz, 1H), 8.65-8.68 (m, 1H), 8.25 (dd, J = 10.8, 1.9 Hz, 1H), 7.83 (dd, J = 2.8, 0.6 Hz, 1H), 7.70 (dd, J = 12.0, 1.6 Hz, 1H), 3.60-3.68 (m, 1H), 3.27-3.32 (m, 2H), 2.89-2.97 (m, 2H), 2.48 (s, 3H), 2.21-2.29 (m, 2H), 2.06-2.16 (m, 2H), NH proton not observed.
Example 15
(452) Preparation of Compound 4
(453) ##STR00128##
(454) Step A: 7-Bromo-3-chloro-5-fluoro-1-oxido-1,2,4-benzotriazin-1-ium (60 mg, 0.22 mmol, prepared according to the procedure in Example 14, Step C) was combined with Cs.sub.2CO.sub.3 (104 mg, 0.32 mmol) and 1-Boc-4-methylaminopiperidine (56 mg, 0.26 mmol) in DMF (2 mL). The mixture was stirred at 60° C. for 2 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 10-80% EtOAc in CH.sub.2Cl.sub.2 to 7-bromo-3-((1-(tert-butoxycarbonyl)piperidin-4-yl)(methyl)amino)-5-fluorobenzo[e][1,2,4]triazine 1-oxide (64 mg, 65%). MS m/z 356.2, 358.2 [M-FH-Boc].sup.+.
(455) Step B: 7-bromo-34(1-(tert-butoxycarbonyepiperidin-4-yl)(methyl)amino)-5-fluorobenzo[e][1,2,4]triazine 1-oxide (64 mg, 0.14 mmol) and 2,7-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole (46 mg, 0.17 mmol) were combined with 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.05 equiv., 0.007 mmol) and 1,4-dioxane (1 mL). To the mixture was added aqueous 1 M K.sub.2CO.sub.3 (0.5 mL).
(456) The mixture was stirred at 80° C. for 2 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was concentrated. The residue was chromatographed on silica gel, eluting with 10-90% EtOAc in CH.sub.2Cl.sub.2 to yield 3-((1-(tert-butoxycarbonyl)piperidin-4-

yl)(methyl)amino)-7-(2,7-dimethyl-2H-indazol-5-yl)-5-fluorobenzo[e][1,2,4]triazine 1-oxide (74 mg, 100%). MS m/z 522.4 [M+H].sup.+.
(457) Step C: 3-((1-(tert-butoxycarbonyl)piperidin-4-yl)(methyl)amino)-7-(2,7-dimethyl-2H-indazol-5-yl)-5-fluorobenzo[e][1,2,4]triazine 1-oxide (74 mg, 0.14 mmol) was combined with 10% Pd/C (20 mg) in MeOH (2 mL). The mixture was stirred under H.sub.2 (1 atm) at rt for 1 h. The mixture was filtered over Celite. The filtrate was concentrated to yield tert-butyl 4-[[7-(2,7-dimethylindazol-5-yl)-5-fluoro-1,2,4-benzotriazin-3-yl]-methyl-amino]piperidine-1-carboxylate (70 mg, 97%). MS m/z 506.3 [M+H].sup.+.
(458) Step D: tert-Butyl 4-[[7-(2,7-dimethylindazol-5-yl)-5-fluoro-1,2,4-benzotriazin-3-yl]-methyl-amino]piperidine-1-carboxylate (70 mg, 0.14 mmol) was suspended in 4 N HCl in 1,4-dioxane (1 mL, 4 mmol HCl). The mixture was stirred at room temperature for 1 h. The volatiles were removed from the reaction mixture with a stream of N.sub.2. The residue was partitioned in CH.sub.2Cl.sub.2 and aqueous 1 M K.sub.2CO.sub.3. The organic layer was concentrated. The residue was chromatographed on silica gel, eluting with 0-10% MeOH (2 N NH.sub.3) in CH.sub.2Cl.sub.2 to yield 7-(2,7-dimethyl-2H-indazol-5-yl)-5-fluoro-N-methyl-N-(piperidin-4-yl)benzo[e][1,2,4]triazin-3-amine (43 mg, 77%).
(459) MS m/z 406.4 [M+H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.42 (s, 1H), 8.37 (s, 1H), 8.15-8.19 (m, 1H), 8.04-8.07 (m, 1H), 7.60 (s, 1H), 4.24-4.30 (m, 1H), 4.21 (s, 3H), 3.22 (br s, 3H), 3.06-3.11 (m, 2H), 2.61-2.66 (m, 2H), 2.60 (s, 3H), 1.72-1.81 (m, 2H), 1.64-1.70 (m, 2H), NH proton not observed.
Example 17
(460) Preparation of Compound 50
(461) ##STR00129##
(462) Step A: 6-Bromo-2-chloro-8-fluoro-quinoline (260 mg, 1.0 mmol) was combined with 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (80 mg, 0.10 mmol) and 1,4-dioxane (4 mL). To the mixture was added a solution of 1-tert-butoxycarbonylpiperidin-4-ylzinc iodide in N,N-dimethylacetamide (2 mL, 2 mmol, prepared according to the procedure in Example 5, Step B) at room temperature. The mixture was stirred at 70° C. for 1 h. The volatiles were removed from the mixture with a stream of N.sub.2. The residue was chromatographed on silica gel, eluting with 0-30% EtOAc in hexanes to yield tert-butyl 4-(6-bromo-8-fluoro-2-quinolyl)piperidine-1-carboxylate (235 mg, 58%).
(463) .sup.1H NMR (DMSO-d.sub.6) δ: 8.36 (dd, J=8.8, 1.6 Hz, 1H), 8.10-8.14 (m, 1H), 7.85 (dd, J=10.3, 2.2 Hz, 1H), 7.67 (d, J=8.5 Hz, 1H), 4.04-4.16 (m, 2H), 3.07-3.14 (m, 1H), 2.89 (br s, 2H), 1.88-1.96 (m, 2H), 1.64-1.74 (m, 2H), 1.44 (s, 9H).
(464) Step B: tert-Butyl 4-(6-bromo-8-fluoro-2-quinolyl)piperidine-1-carboxylate (40 mg, 0.10 mmol) was combined with (8-fluoro-2-methyl-imidazo[1,2-a]pyridin-6-yl)boronic acid (40 mg, 0.21 mmol), 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (4 mg, 0.005 mmol), 1,4-dioxane (1.5 mL) and aqueous 1 M K.sub.2CO.sub.3 (0.75 mL). The mixture was stirred at 80° C. for 1 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-80% EtOAc in CH.sub.2Cl.sub.2 to yield tert-butyl 4-[8-fluoro-6-(8-fluoro-2-methyl-imidazo[1,2-a]pyridin-6-yl)-2-quinolyl]piperidine-1-carboxylate (45 mg, 96%). MS m/z 479.4 [M+H].sup.+.
(465) Step C: tert-Butyl 4-[8-fluoro-6-(8-fluoro-2-methyl-imidazo[1,2-a]pyridin-6-yl)-2-quinolyl]piperidine-1-carboxylate (45 mg, 0.09 mmol) was suspended in 4 N HCl in 1,4-dioxane (1 mL, 4 mmol HCl). The volatiles were removed from the reaction mixture after 30 min. The residue was partitioned between CH.sub.2Cl.sub.2 and aqueous 1 M K.sub.2CO.sub.3. The organic layer was concentrated and chromatographed on silica gel, eluting with 0-10% MeOH (2 N NH.sub.3) in CH.sub.2Cl.sub.2. The collected material was dissolved in 1.25 M HCl in MeOH. The volatiles were removed to yield 8-fluoro-6-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-2-(piperidin-4-

yl)quinoline hydrochloride (35 mg, 90%).
(466) MS m/z 379.3 [M+H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.36-9.39 (m, 1H), 9.16 (br, 1H), 8.88 (br, 1H), 8.46-8.50 (m, 1H), 8.41 (d, J=11.8 Hz, 1H), 8.34 (d, J=2.2 Hz, 1H), 8.17 (s, 1H), 8.13 (dd, J=12.1, 1.9 Hz, 1H), 7.69 (d, J=8.5 Hz, 1H), 3.39-3.46 (m, 2H), 3.27-3.35 (m, 1H), 3.03-3.12 (m, 2H), 2.54 (s, 3H), 2.04-2.18 (m, 4H).
(467) Using the procedure described for Example 17, above, additional compounds described herein were prepared by substituting the indicated starting material in Step A, the appropriate boronic acid Step B, suitable reagents and reaction conditions, obtaining compounds such as those selected from:
(468) TABLE-US-00015 Cpd Starting Material and Data 29 Starting material: 7-bromo-3-chloroquinoline MS m/z 357.4 [M + H].sup.+; .sup.1H NMR (DMSO-d6) δ: 9.26 (d, J = 2.5 Hz, 1H), 8.59 (d, J = 2.5 Hz, 1H), 8.43 (s, 1H), 8.01-8.03 (m, 1H), 7.98 (d, J = 8.5 Hz, 1H), 7.81-7.83 (m, 1H), 7.53-7.58 (m, 2H), 4.22 (s, 3H), 3.06-3.11 (m, 2H), 2.79-2.86 (m, 1H), 2.63- 2.69 (m, 2H), 2.61 (s, 3H), 1.80-1.86 (m, 2H), 1.59-1.69 (m, 2H), NH proton not observed. 45 Starting material: 6-bromo-2-chloro-8-fluoro-quinoline MS m/z 376.1 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.63-8.68 (m, 2H), 8.48 (s, 1H), 8.38 (s, 1H), 8.35 (d, J = 11.5 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 3.60-3.65 (m, 2H), 3.46-3.50 (m, 1H), 3.25-3.33 (m, 2H), 2.86 (s, 3H), 2.70 (s, 3H), 2.27-2.33 (m, 4H), NH proton not observed. 49 Starting material: 6-bromo-2-chloro-8-fluoro-quinoline MS m/z 391.4 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.11 (br, 1H), 8.77 (br, 1H), 8.46 (d, J = 8.5 Hz, 1H), 8.41 (s, 1H), 8.17-8.20 (m, 1H), 8.05 (dd, J = 12.7, 2.1, 1H), 7.73 (d, J = 1.3 Hz, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.06-7.08 (m, 1H), 4.18 (s, 3H), 4.05 (s, 3H), 3.39-3.45 (m, 2H), 3.24-3.31 (m, 1H), 3.02-3.12 (m, 2H), 2.04-2.18 (m, 4H).
Example 18
(469) Preparation of Compound 51
(470) ##STR00130##
(471) Step A: 8-Bromo-6-chloro-2-methyl-imidazo[1,2-b]pyridazine (250 mg, 1.01 mmol) was combined with Cs.sub.2CO.sub.3 (700 mg, 2.15 mmol) in CH.sub.3CN (5 mL). To the mixture was added MeOH (0.2 mL). The mixture was stirred at room temperature for 4 h. The volatiles were removed from the reaction mixture. The residue was partitioned between EtOAc and H.sub.2O. The organic layer was collected, concentrated and chromatographed on silica gel, eluting with 20-100% EtOAc in hexanes to yield 6-chloro-8-methoxy-2-methyl-imidazo[1,2-b]pyridazine (180 mg, 90%). MS m/z 198.2, 202.2 [M+H].sup.+.
(472) Step B: 6-Chloro-8-methoxy-2-methyl-imidazo[1,2-b]pyridazine (39 mg, 0.20 mmol) was combined with KOAc (59 mg, 0.60 mmol), 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (8 mg, 0.01 mmol), and bis(pinacolato)diboron (63 mg, 0.25 mmol) in 1,4-dioxane (1 mL). The mixture was stirred under N.sub.2 at 95° C. for 1 h. To the mixture was added aqueous 1 M K.sub.2CO.sub.3 (0.75 mL), tert-butyl 4-(6-bromo-8-fluoro-2-quinolyl)piperidine-1-carboxylate (40 mg, 0.10 mmol, obtained in Example 17, Step A) and 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (4 mg, 0.005 mmol). The mixture was stirred at 80° C. for 1 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-80% EtOAc in CH.sub.2Cl.sub.2 to yield tert-butyl 4-[8-fluoro-6-(8-methoxy-2-methyl-imidazo[1,2-b]pyridazin-6-yl)-2-quinolyl]piperidine-1-carboxylate (38 mg, 79%). MS m/z 492.4 [M+H].sup.+.
(473) Step C: tert-Butyl 4-[8-fluoro-6-(8-methoxy-2-methyl-imidazo[1,2-b]pyridazin-6-yl)-2-quinolyl]piperidine-1-carboxylate (38 mg, 0.08 mmol) was suspended in 4 N HCl in 1,4-dioxane (1 mL, 4 mmol HCl). The volatiles were removed from the reaction mixture with a stream of N.sub.2 after 30 min. The residue was suspended in CH.sub.3CN, collected by filtration and dried to yield 8-fluoro-6-(8-methoxy-2-methylimidazo[1,2-b]pyridazin-6-yl)-2-(piperidin-4-yl)quinoline hydrochloride (26 mg, 79%).

(474) MS m/z 392.4 [M+H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.22 (br, 1H), 8.95 (br, 1H), 8.77-8.80 (m, 1H), 8.60 (d, J=8.6 Hz, 1H), 8.47 (s, 1H), 8.37 (dd, J=12.0, 2.0 Hz, 1H), 7.99 (s, 1H), 7.73 (d, J=8.5 Hz, 1H), 4.35 (s, 3H), 3.39-3.45 (m, 2H), 3.29-3.37 (m, 1H), 3.02-3.12 (m, 2H), 2.53 (s, 3H), 2.06-2.20 (m, 4H).
(475) Using the procedure described for Example 18, above, additional compounds described herein were prepared by substituting the appropriate reagent in Step A, suitable reagents and reaction conditions, obtaining compounds such as those selected from:
(476) TABLE-US-00016 Cpd Data 53 MS m/z 436.3 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.97 (br, 1H), 8.71 (br, 1H), 8.68 (s, 1H), 8.57 (d, J = 8.6 Hz, 1H), 8.28-8.35 (m, 2H), 7.76 (br s, 1H), 7.71 (d, J = 8.5 Hz, 1H), 4.70-4.74 (m, 2H), 3.84-3.88 (m, 2H), 3.42-3.47 (m, 2H), 3.39 (s, 3H), 3.29- 3.37 (m, 1H), 3.05-3.14 (m, 2H), 2.48 (s, 3H), 2.06-2.20 (m, 4H). 54 MS m/z 435.3 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.59-8.64 (m, 2H), 8.30 (dd, J = 12.0, 1.7 Hz, 1H), 8.18 (d, J = 1.3 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.41 (s, 1H), 3.78- 3.84 (m, 4H), 3.60-3.65 (m, 2H), 3.49 (s, 3H), 3.43-3.49 (m, 1H), 3.24-3.31 (m, 2H), 2.64 (s, 3H), 2.24-2.36 (m, 4H), NH protons not observed.
Example 19
(477) Preparation of Compound 70
(478) ##STR00131##
(479) 7-(2,8-Dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(4-piperidyl)-1,2,4-benzotriazine dihydrochloride (36 mg, 0.08 mmol, prepared according to the procedure in Example 13) was combined with 1,2-dichloroethane (1 mL), EtOH (0.2 mL) and triethylamine (22 uL, 0.16 mmol). To the mixture was added acetaldehyde (18 μL, 0.32 mmol). The mixture became homogeneous. The mixture was stirred for 5 min. To the mixture was added sodium triacetoxyborohydride (36 mg, 0.16 mmol). After 20 min of stirring at room temperature, the mixture was loaded directly to silica gel and chromatographed, eluting with 0-10% MeOH (2 N NH.sub.3) in CH.sub.2Cl.sub.2 to afford 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-3-(1-ethylpiperidin-4-yl)-5-fluorobenzo[e][1,2,4]triazine (32 mg, 84%) as a yellow powder.
(480) MS m/z 406.3 [M+H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.06 (s, 1H), 8.62 (dd, J=10.9 Hz, 1H), 8.04 (s, 1H), 7.94 (s, 1H), 3.69-3.77 (m, 1H), 3.48-3.56 (m, 2H), 2.98 (q, J=7.2 Hz, 2H), 2.84-2.92 (m, 2H), 2.75 (s, 3H), 2.54 (s, 3H), 2.45-2.52 (in, 2H), 2.32-2.42 (m, 2H), 1.34 (t, J=7.3 Hz, 3H).
(481) Using the reductive amination procedure described for Example 19, above, additional compounds described herein were prepared by substituting the indicated starting materials, aldehyde, suitable reagents and reaction conditions, obtaining compounds such as those selected from:
(482) TABLE-US-00017 Cpd Starting Material and Data 2 Starting material: 2-(2-methyl-2H-indazol-5-yl)-6-(piperidin-4-yl)quinoline (prepared according to the procedure in Example 6) and acetaldehyde MS m/z 371.1 [M + H].sup.+; 1H NMR (methanol-d4) δ: 8.99 (br s, 1H), 8.66 (s, 1H), 8.57 (s, 1H), 8.34-8.40 (m, 2H), 8.15-8.20 (m, 1H), 8.04-8.10 (m, 2H), 7.19 (d, J = 9.5 Hz, 1H), 4.33 (s, 3H), 3.76-3.82 (m, 2H), 3.49-3.56 (m, 1H), 3.26 (q, J = 7.5 Hz, 2H), 3.19-3.24 (m, 2H), 2.31-2.36 (m, 2H), 2.18-2.23 (m, 2H), 1.44 (t, J = 7.5 Hz, 3H). 6 Starting material: 6-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-8-fluoro-2-(piperidin- 4-yl)quinoline (prepared according to the procedure in Example 17) and formaldehyde MS m/z 357.2 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.95 (br s, 1H), 8.57 (s, 1H), 8.51 (s, 1H), 8.44-8.50 (m, 2H), 8.24 (s, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.76-7.78 (m, 2H), 4.22 (s, 3H), 4.00-4.07 (m, 2H), 3.22-3.28 (m, 1H), 3.14-3.20 (m, 2H), 2.81 (s, 3H), 2.27-2.33 (m, 4H). 9 Starting material: 6-(2-methyl-2H-indazol-5-yl)-2-(piperidin-4-yl)quinoline (prepared according to the procedure in Example 2) and acetaldehyde MS m/z 371.2 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.11 (d, J = 8.5 Hz, 1H), 8.58-8.64 (m, 2H), 8.48-8.54 (m, 2H), 8.23 (s, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.74-7.78 (m, 2H), 4.23 (s, 3H), 3.75-3.80 (m, 1H), 3.63-3.67 (m, 2H), 3.08-3.18 (m, 4H), 2.32- 2.46 (m, 4H),

1.32 (t, J = 7.5 Hz, 3H). 47 Starting material: 6-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-8-fluoro-2-(piperidin- 4-yl)quinoline (prepared according to the procedure in Example 17) and formaldehyde MS m/z 390.2 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.67 (s, 1H), 8.57 (d, J = 8.0 Hz, 1H), 8.47 (s, 1H), 8.42 (s, 1H), 8.27 (d, J = 12.0 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 3.54- 3.57 (m, 1H), 3.14-3.25 (m, 4H), 2.80 (s, 3H), 2.76 (s, 3H), 2.58 (s, 3H), 2.20-2.25 (m, 4H). 48 Starting material: 6-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-8-fluoro-2-(piperidin- 4-yl)quinoline (prepared according to the procedure in Example 17) and acetaldehyde MS m/z 404.2 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.67 (s, 1H), 8.57 (d, J = 8.0 Hz, 1H), 8.47 (s, 1H), 8.42 (s, 1H), 8.27 (d, J = 12.0 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 3.60- 3.64 (m, 1H), 3.27-3.32 (m, 2H), 3.07-3.16 (m, 4H), 2.77 (s, 3H), 2.59 (s, 3H), 2.22- 2.26 (m, 4H), 1.30 (t, J = 7.5 Hz, 3H). 69 Starting material: 7-(2,8-Dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(4-piperidyl)-1,2,4-benzotriazine (prepared according to the procedure in Example 13) and formaldehyde MS m/z 392.2 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.27 (s, 1H), 8.70 (dd, J = 11.0, 1.7 Hz, 1H), 8.54 (s, 1H), 8.45 (s, 1H), 3.70-3.77 (m, 1H), 3.59-3.65 (m, 2H), 3.21-3.30 (m, 2H), 2.84 (d, J = 4.7 Hz, 3H), 2.76 (s, 3H), 2.56 (s, 3H), 2.41-2.47 (m, 2H), 2.25-2.35 (m, 2H). 75 Starting material: 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(piperidin- 4-yl)cinnoline (prepared according to the procedure in Example 7) and 1,4-dioxane- 2,5-diol MS m/z 421.5 [M + H].sup.+; 1H NMR (methanol-d4) δ:: 9.17 (s, 1H), 8.61 (d, J = 1.0 Hz, 1H), 8.42-8.47 (m, 2H), 8.35 (s, 1H), 3.98-4.01 (m, 2H), 3.88-3.94 (m, 2H), 3.63- 3.70 (m, 1H), 3.35-3.42 (m, 4H), 2.88 (s, 3H), 2.71 (s, 3H), 2.44-2.52 (m, 4H), OH proton not observed. 76 Starting material: 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(piperidin- 4-yl)cinnoline and acetaldehyde (prepared according to the procedure in Example 7) MS m/z 405.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.17 (s, 1H), 8.60 (d, J = 1.0 Hz, 1H), 8.42-8.47 (m, 2H), 8.35 (s, 1H), 3.81-3.87 (m, 2H), 3.63-3.70 (m, 1H), 3.25- 3.38 (m, 4H), 2.88 (s, 3H), 2.71 (s, 3H), 2.38-2.52 (m, 4H), 1.47 (t, J = 7.4 Hz, 3H). 77 Starting material: 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(piperidin- 4-yl)cinnoline dihydrochloride (prepared according to the procedure in Example 7) MS m/z 419.5 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.02 (s, 1H), 8.32 (dd, J = 11.0, 1.3 Hz, 1H), 8.15 (s, 1H), 8.14 (d, J = 0.6 Hz, 1H), 8.05 (d, J = 0.9 Hz, 1H), 3.10-3.22 (m, 3H), 2.94-3.07 (m, 2H), 2.65 (d, J = 0.9 Hz, 3H), 2.43 (d, J = 0.6 Hz, 3H), 2.02- 2.14 (m, 4H), 1.52-1.61 (m, 2H), 1.12-1.18 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H), HCl protons not observed. 79 Starting material: 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(piperidin- 4-yl)cinnoline dihydrochloride (prepared according to the procedure in Example 7) MS m/z 391.4 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.05 (s, 1H), 8.36 (dd, J = 10.9, 1.4 Hz, 1H), 8.19 (s, 1H), 8.15 (d, J = 0.6 Hz, 1H), 8.07 (d, J = 0.9 Hz, 1H), 3.36-3.48 (m, 3H), 2.80-2.94 (m, 2H), 2.67 (s, 3H), 2.65 (s, 3H), 2.44 (d, J = 0.6 Hz, 3H), 2.18- 2.28 (m, 4H), HCl protons not observed. 85 Starting material: 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-3-(piperidin-4- yl)cinnoline (prepared according to the procedure in Example 7) MS m/z 387.3 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.01 (s, 1H), 8.57 (dd, J = 9, 1.5 Hz, 1H), 8.13 (m, 2H), 8.00 (s, 1H), 7.85 (s, 1H), 3.26-3.33 (m, 3H), 2.74 (s, 3H), 2.65 (q, J = 7.5 Hz, 2H), 2.52 (s, 3H), 2.35-2.41 (m, 2H), 2.20-2.24 (m, 2H), 2.06- 2.18 (m, 2H), 1.23 (t, J = 7.5 Hz, 3H). 100 Starting material: 5-fluoro-7-(2-methylimidazo[1,2-b]pyridazin-6-yl)-3-(piperidin-4- yl)cinnoline dihydrochloride (prepared according to the procedure in Example 29) MS m/z 391.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.14 (s, 1H), 8.58 (d, J = 9.5 Hz, 1H), 8.43-8.48 (m, 2H), 8.40 (s, 1H), 8.32 (s, 1H), 3.82-3.86 (m, 2H), 3.61-3.68 (m, 1H), 3.24-3.33 (m, 4H), 2.67 (s, 3H), 2.38-2.52 (m, 4H), 1.46 (t, J = 7.6 Hz, 3H), HCl protons not observed. 102 Starting material: 5-fluoro-7-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-3- (piperidin-4-yl)cinnoline hydrochloride (prepared according to the procedure in Example 29) MS m/z 408.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.28 (d, J = 1.2 Hz, 1H), 8.78 (s, 1H), 8.47 (dd, J = 11.0, 1.2 Hz, 1H), 8.33 (s, 1H), 8.21 (d, J = 1.2 Hz, 1H), 8.12(dd, J = 10.5, 1.7 Hz, 1H), 3.84 (br d, J = 12.5 Hz, 2H), 3.61-3.69 (m, 1H), 3.24-3.35 (m, 4H), 2.66 (d, J = 0.9 Hz, 3H), 2.38-2.51 (m, 4H), 1.46 (t, J = 7.3 Hz, 3H), HCl protons not

observed. 110 Starting material: 6-(2,8-dimethylimidazo[1,2-a]pyridin-6-yl)-8-fluoro-2-(piperidin-4- yl)quinoxaline hydrochloride (prepared according to the procedure in Example 38) MS m/z 405.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.88 (s, 1H), 8.26 (d, J = 0.9 Hz, 1H), 8.03 (dd, J = 11.3, 1.8 Hz, 1H), 7.81 (s, 1H), 7.57 (d, J = 1.2 Hz, 1H), 3.17 (d, J = 11.3 Hz, 2H), 3.06 (spt, J = 4.9 Hz, 1H), 2.59-2.61 (m, 1H), 2.60 (s, 2H), 2.54 (q, J = 7.3 Hz, 2H), 2.60 (s, 3H), 2.21 (td, J = 11.3, 3.7 Hz, 2H), 2.03-2.12 (m, 4H), 1.18 (t, J = 7.3 Hz, 3H). 111 Starting material: 5-fluoro-7-(8-methoxy-2-methylimidazo[1,2-b]pyridazin-6-yl)-3- (piperidin-4-yl)cinnoline dihydrochloride (prepared according to the procedure in Example 29) MS m/z 421.0 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.80 (s, 1H), 8.21 (d, J = 12 Hz, 1H), 7.94 (s, 1H), 7.75 (s, 1H), 7.00 (s, 1H), 4.23 (s, 3H), 3.37-3.42 (m, 1H), 3.21 (d, J = 11.3 Hz, 2H), 2.52-2.55 (m, 5H), 2.19-2.25 (m, 4H), 2.01-2.09 (m, 2H), 1.17 (t, J = 7.2 Hz, 3H). 113 Starting material: (6-(5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl)-2-methylimidazo[1,2- b]pyridazin-8-yl)methanol dihydrochloride (prepared according to the procedure in Example 29) MS m/z 421.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.13 (s, 1H), 8.61 (s, 1H), 8.46 (d, J = 0.9 Hz, 1H), 8.43 (dd, J = 10.6, 1.3 Hz, 1H), 8.33 (s, 1H), 5.17 (d, J = 1.1 Hz, 2H), 3.82 (br d, J = 12.2 Hz, 2H), 3.61-3.70 (m, 1H), 3.23-3.30 (m, 4H), 2.69 (s, 3H), 2.39-2.50 (m, 4H), 1.45 (t, J = 7.3 Hz, 3H), HCl and OH protons not observed. 114 Starting material: 6-(5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl)-2-methylimidazo[1,2-b]pyridazine-8-carbonitrile dihydrochloride (prepared according to the procedure in Example 29) MS m/z 416.0 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.53 (s, 1H), 8.23 (dd, J = 10.8, 1.5 Hz, 1H), 8.02 (s, 1H), 7.99 (d, J = 0.4 Hz, 1H), 7.95 (s, 1H), 3.36-3.43 (m, 1H), 3.19 (br d, J = 11 Hz, 2H), 2.64 (s, 3H), 2.52-2.54 (m, 2H), 2.21-2.23 (m, 4H), 1.98- 2.08 (m, 2H), 1.17 (t, J = 7.2 Hz, 3H). 115 Starting material: 7-(8-cyclopropyl-2-methylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline (prepared according to the procedure in Example 29) MS m/z 431.1 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.78 (s, 1H), 8.19 (d, J = 12 Hz, 1H), 7.94 (s, 1H), 7.81 (s, 1H), 7.10 (s, 1H), 3.28-3.42 (m, 1H), 3.29 (br d, J = 12 Hz, 2H), 2.60-2.72 (m, 3H), 2.56 (s, 3H), 2.24-2.27 (m, 2H), 2.09-2.13 (m, 4H), 1.33-1.37 (m, 2H), 1.19-1.25 (m, 5H). 119 Starting material: 7-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-fluoro-3-(piperidin-4- yl)cinnoline (prepared according to the procedure in Example 41) MS m/z 405.1 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.86 (s, 1H), 8.56 (s, 1H), 8.21 (m, 3H), 4.59 (s, 1H), 3.28 (s, 2H), 2.90 (s, 3H), 2.65 (dd, J = 14.4, 7.1 Hz, 2H), 2.48 (s, 3H), 2.39 (t, J = 11.8 Hz, 2H), 2.27-2.06 (m, 4H), 1.23 (t, J = 7.2 Hz, 3H). 120 Starting material: 6-(5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl)-2,4-dimethylbenzo[d]thiazole (prepared according to the procedure in Example 29) MS m/z 421.1 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.58 (s, 1H), 8.03 (d, J = 1.6 Hz, 1H), 7.90 (s, 1H), 7.71 (dd, J = 10.6, 1.2 Hz, 1H), 7.63 (d, J = 0.8 Hz, 1H), 3.34-3.40 (m, 1H), 3.20 (d, J = 11.2 Hz, 2H), 2.89 (s, 3H), 2.83 (s, 3H), 2.51-2.56 (m, 2H), 2.08-2.24 (m, 4H), 2.01-2.05 (m, 2H), 1.23 (t, J = 7.2 Hz, 3H). 121 Starting material: 7-(8-ethyl-2-methylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline dihydrochloride (prepared according to the procedure in Example 29) MS m/z 419.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.18 (s, 1H), 8.54 (s, 1H), 8.40-8.50 (m, 2H), 8.33 (s, 1H), 3.84 (br d, J = 12.5 Hz, 2H), 3.61-3.70 (m, 1H), 3.16- 3.31 (m, 6H), 2.71 (s, 3H), 2.38-2.52 (m, 4H), 1.58 (t, J = 7.6 Hz, 3H), 1.46 (t, J = 7.6 Hz, 3H), HCl protons not observed. 122 Starting material: 7-(8-ethyl-2-methylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline dihydrochloride (prepared according to the procedure in Example 29) MS m/z 405.5 [M + H].sup.+; 1H NMR (methanol-d.sub.4) δ: 9.16 (s, 1H), 8.47 (s, 1H), 8.45 (d, J = 10.4 Hz, 1H), 8.40 (s, 1H), 8.33 (s, 1H), 3.75-3.80 (m, 2H), 3.59-3.69 (m, 1H), 3.32-3.38 (m, 2H), 3.23 (q, J = 7.5 Hz, 2H), 3.02 (s, 3H), 2.69 (s, 3H), 2.37-2.49 (m, 4H), 1.57 (t, J = 7.5 Hz, 3H) HCl protons not observed. 123 Starting material: 7-(8-ethyl-2-methylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3- (piperidin-4-yl)cinnoline dihydrochloride (prepared according to the procedure in Example 29) MS m/z 435.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.17 (s, 1H), 8.50 (s, 1H), 8.45 (d, J = 10.7 Hz, 1H), 8.42 (s, 1H), 8.33 (s, 1H), 3.98-4.02 (m, 2H), 3.88-3.94 (m, 2H), 3.62-3.68 (m, 1H), 3.35-3.42 (m, 4H), 3.23 (q, J = 7.5 Hz, 2H), 2.70 (s, 3H), 2.44- 2.51 (m, 4H),

1.58 (t, J = 7.5 Hz, 3H), HCl and OH protons not observed. 124 Starting material: rac-7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-3-((2R,6R)-2,6- dimethylpiperidin-4-yl)-5-fluorocinnoline dihydrochloride (prepared according to the procedure in Example 7) MS m/z 419.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.92 (s, 1H), 8.32 (d, J = 10 Hz, 1H), 8.19 (s, 1H), 8.00 (s, 1H), 7.88 (s, 1H), 3.76 (tt, J = 12.5, 3.5 Hz, 1H), 3.43 (m, 1H), 3.00 (m, 1H), 2.73 (s, 3H), 2.52 (s, 3H), 2.47 (s, 3H), 2.30-2.36 (dd, J = 13, 5 Hz, 1H), 2.05-2.15 (m, 2H), 1.8 (q, J = 12.5 Hz, 1H), 1.32 (d, J = 7 Hz, 3H), 1.23 (d, J = 6 Hz, 3H). 125 Starting material: rac-7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-3-((2R,6R)-2,6- dimethylpiperidin-4-yl)-5-fluorocinnoline hydrochloride (prepared according to the procedure in Example 7) MS m/z 433.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.91 (s, 1H), 8.31 (d, J = 11 Hz, 1H), 8.19 (s, 1H), 8.00 (s, 1H), 7.87 (s, 1H), 3.65-3.80 (m, 2H), 3.13-3.27 (m, 2H), 2.73 (s, 3H), 2.64 (m, 1H), 2.51 (s, 3H), 2.31 (m, 1H), 2.13 (t, J = 13.5 Hz, 2H), 1.90 (q, J = 12.5 Hz, 1H), 1.34 (d, J = 6.5 Hz, 3H), 1.21-1.30 (m, 6H). 131 Starting material: rac-3-((2R,6R)-2,6-diethylpiperidin-4-yl)-7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluorocinnoline (prepared according to the procedure in Example 7) MS m/z 447.6 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.94 (s, 1H), 8.33 (d, J = 11 Hz, 1H), 8.23 (s, 1H), 8.00 (s, 1H), 7.89 (s, 1H), 3.71 (m, 1H), 3.32 (m, 1H), 3.18 (br s, 1H), 2.73 (s, 3H), 2.66 (s, 3H), 2.52 (s, 3H), 2.28-2.35 (m, 1H), 2.16-2.23 (m, 2H), 1.80-2.00 (m, 4H), 1.51 (m, 1H), 1.08 (t, J = 7.5 Hz, 3H), 1.02 (t, J = 7.5 Hz, 3H). 132 Starting material: 7-(2,7-dimethyl-3H-imidazo[4,5-b]pyridin-5-yl)-5-fluoro-3- (piperidin-4-yl)cinnoline dihydrochloride (prepared according to the procedure in Example 29) MS m/z 405.2 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 9.30 (s, 1H), 8.50 (d, J = 12 Hz, 1H), 7.99 (s, 1H), 7.37 (s, 1H), 3.37 (t, J = 13.2, 1H), 3.20 (d, J = 11.2, 2H), 2.93 (s, 3H), 2.69 (s, 3H), 2.56-2.51 (m, 2H), 2.22-2.04 (m, 6H), 1.17 (t, J = 8 Hz, 3H), NH proton not observed. 135 Starting material: 5-(5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl)-2,7- dimethylthiazolo[5,4-b]pyridine dihydrochloride (prepared according to the procedure in Example 29) MS m/z 422.3 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.90 (s, 1H), 8.34 (dd, J = 11, 1.2 Hz, 1H), 7.93 (s, 2H), 3.42 (m, 1H), 3.33 (d, J = 12.4 Hz, 2H), 2.90 (s, 3H), 2.84 (s, 3H), 2.65-2.71 (m, 2H), 2.37-2.39 (m, 2H), 2.24-2.29 (m, 2H), 2.13-2.20 (m, 2H), 1.23 (t, J = 7.4 Hz, 3H). 136 Starting material: 2-(5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl)-4,6-dimethyloxazolo[4,5-c]pyridine dihydrochloride (prepared according to the procedure in Example 29) MS m/z 406.2 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.11 (s, 1H), 8.35 (dd, J = 9.9, 1.2 Hz, 1H), 8.25 (s, 1H), 7.57 (s, 1H), 3.41-3.56 (m, 1H), 3.28-3.25 (m, 2H), 2.86 (s, 3H), 2.69 (s, 3H), 2.61 (q, J = 7.2 Hz, 2H), 2.34 (td, J = 11.6, 2.1 Hz, 2H), 2.24-2.10 (m, 4H), 1.22 (t, J = 7.3 Hz, 3H). 147 Starting material: 2-(5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl)-4,6-dimethylthiazolo[4,5-c]pyridine dihydrochloride (prepared according to the procedure in Example 29) MS m/z 422.3 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.89 (s, 1H), 8.32 (dd, J = 10,1.2 Hz, 1H), 7.94 (s, 1H), 7.59 (s, 1H), 3.40 (m, 1H), 3.22 (d, J = 12.4 Hz, 2H), 3.04 (s, 3H), 2.68 (s, 3H), 2.54-2.57 (m, 2H), 2.21-2.25 (br s, 4H), 2.04-2.11 (m, 2H), 1.18 (t, J = 14.4 Hz, 3H). 152 Starting material: 5-(5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl)-2,7- dimethyloxazolo[5,4-b]pyridine dihydrochloride (prepared according to the procedure in Example 29) MS m/z 406.2 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.89 (s, 1H), 8.29 (dd, J = 10.6, 1.6 Hz, 1H), 7.92 (s, 1H), 7.86 (s, 1H), 3.35-3.39 (m, 1H), 3.21 (d, J = 10.4 Hz, 2H), 2.70 (s, 6H), 2.55 (d, J = 6.8 Hz, 2H), 2.18-2.21 (m, 4H), 2.03-2.07 (m, 2H), 1.18 (t, J = 7.2 Hz, 3H). 155 Starting material: rac-7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-3-((2R,6R)-2,6- dimethylpiperidin-4-yl)-5-fluorocinnoline hydrochloride (prepared according to the procedure in Example 7) MS m/z 449.5 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.96 (s, 1H), 8.26 (d, J = 11.5 Hz, 1H), 8.06 (m, 2H), 7.88 (s, 1H), 3.68 (m, 1H), 3.52 (t, J = 6.5 Hz, 2H), 3.43 (m, 1H), 3.09 (br s, 1H), 2.83 (m, 1H), 2.60-2.70 (m, 4H), 2.47 (s, 3H), 2.22 (td, J = 12.5, 5.5 Hz, 1H), 1.98 (d, J = 12 Hz, 1H), 1.90 (d, J = 11.5 Hz, 1H), 1.70 (q, J = 12.5 Hz, 1H), 1.26 (d, J = 6.5 Hz, 3H), 1.13 (d, J = 6.5 Hz, 3H), OH proton not observed. 161 Starting material: 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-3-((2S,4r,6R)-2,6- dimethylpiperidin-4-yl)-5-fluorocinnoline dihydrochloride (prepared according to

the procedure in Example 7) MS m/z 419.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.92 (s, 1H), 8.32 (d, J = 11 Hz, 1H), 8.18 (s, 1H), 8.00 (s, 1H), 7.88 (s, 1H), 3.51 (m, 1H), 2.8 (br s, 2H), 2.73 (s, 3H), 2.56 (s, 3H), 2.52 (s, 3H), 2.20 (d, J = 11.5 Hz, 2H), 1.96 (q, J = 12.5 Hz, 2H), 1.37 (d, J = 6.5 Hz, 6H). 164 Starting material: 7-(2,7-dimethyl-2H-pyrazolo[4,3-b]pyridin-5-yl)-5-fluoro-3- (piperidin-4-yl)cinnoline dihydrochloride (prepared according to the procedure in Example 29) MS m/z 405.2 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.88 (s, 1H), 8.38 (dd, J = 10.8, 1.2 Hz, 1H), 8.24 (s, 1H), 7.95 (s, 1H), 7.78 (d, J = 0.8 Hz, 1H), 4.32 (s, 3H), 3.32- 3.44 (m, 3H), 2.86 (s, 3H), 2.66-2.71 (m, 2H), 2.25-2.29 (m, 4H), 2.20 (s, 3H), 1.25- 1.29 (m, 2H). 173 Starting material: 5-fluoro-7-(7-methoxy-2-methyl-2H-pyrazolo[4,3-b]pyridin-5-yl)- 3-(piperidin-4-yl)cinnoline dihydrochloride (prepared according to the procedure in Example 29) MS m/z 421.1 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.84 (s, 1H), 8.37 (dd, J = 10.8, 1.2 Hz, 1H), 8.20 (s, 1H), 7.93 (s, 1H), 7.29 (s, 1H), 4.29 (s, 3H), 4.22 (s, 3H), 3.34- 3.41 (m, 1H), 3.20 (br d, J = 12 Hz, 2H), 2.50-2.55 (m, 2H), 2.17-2.23 (m, 4H), 1.98-2.08 (m, 2H) 1.21 (t, J = 6.4 Hz, 3H). 174 Starting material: 7-(7-ethyl-2-methyl-2H-pyrazolo[4,3-b]pyridin-5-yl)-5-fluoro-3- (piperidin-4-yl)cinnoline (prepared according to the procedure in Example 29) MS m/z 419.1 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.89 (s, 1H), 8.38 (dd, J = 10.9, 1.3 Hz, 1H), 8.24 (s, 1H), 7.93 (s, 1H), 7.79 (s, 1H), 4.31 (s, 3H), 3.39 (t, J = 11.9 Hz, 1H), 3.27-3.13 (m, 4H), 2.56 (dd, J = 14.0, 7.5 Hz, 2H), 2.24 (d, J = 10.5 Hz, 4H), 2.07 (dd, J = 24.6, 12.5 Hz, 2H), 1.52 (t, J = 7.6 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H). 176 Starting material: 6-(5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl)-2-methylimidazo[1,2- b]pyridazine-8-carbonitrile dihydrochloride (prepared according to the procedure in Example 29) MS m/z 402.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.22 (s, 1H), 9.17 (s, 1H), 8.58 (s, 1H), 8.43 (dd, J = 10.8, 0.9 Hz, 1H), 8.37 (s, 1H), 3.76 (br d, J = 12.5 Hz, 2H), 3.64 (tt, J = 10.6, 6.2 Hz, 1H), 3.35 (dd, J = 12.0, 4.4 Hz, 2H), 3.00 (s, 3H), 2.71 (s, 3H), 2.49-2.34 (m, 4H), HCl protons not observed. 178 Starting material: 6-(5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl)-2-methylimidazo[1,2- b]pyridazine-8-carbonitrile dihydrochloride (prepared according to the procedure in Example 29) MS m/z 432.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.16 (s, 2H), 8.55 (s, 1H), 8.43 (br d, J = 10.22 Hz, 1H), 8.34 (s, 1H), 3.96-4.02 (m, 2H), 3.89 (br d, J = 12.51 Hz, 2H), 3.58-3.71 (m, 2H), 3.35-3.40 (m, 3H), 2.69 (s, 3H), 2.41-2.51 (m, 4H), OH and HCl protons not observed. 179 Starting material: 6-(5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl)-2-methylimidazo[1,2- b]pyridazine-8-carbonitrile (prepared according to the procedure in Example 29) MS m/z 434.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.16 (s, 1H), 9.14 (s, 1H), 8.54 (s, 1H), 8.42 (d, J = 10.0 Hz, 1H), 8.35 (s, 1H), 4.98-5.02 (m, 1H), 4.89-4.93 (m, 1H), 3.90 (br d, J = 12.5 Hz, 2H), 3.62-3.71 (m, 3H), 3.39-3.50 (m, 2H), 2.69 (s, 3H), 2.44-2.52 (m, 4H), HCl protons not observed. 180 Starting material: (6-(5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl)-2-methylimidazo[1,2- b]pyridazin-8-yl)methanol (prepared according to the procedure in Example 29) MS m/z 407.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.94 (s, 1H), 8.33-8.39 (m, 1H), 8.25 (s, 1H), 8.04 (d, J = 1.98 Hz, 2H), 5.10 (s, 2H), 3.48-3.63 (m, 3H), 3.11 (br s, 2H), 2.87 (s, 3H), 2.50 (s, 3H), 2.31-2.40 (m, 4H), OH proton not observed. 181 Starting material: (6-(5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl)-2-methylimidazo[1,2- b]pyridazin-8-yl)methanol dihydrochloride (prepared according to the procedure in Example 29) MS m/z 437.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.14 (s, 1 H), 8.62 (s, 1 H), 8.46 (s, 1 H), 8.44 (d, J = 10.1 Hz, 1 H), 8.36 (s, 1 H), 5.17 (s, 2 H), 3.96-4.01 (m, 2 H), 3.89 (br d, J = 12.7 Hz, 2 H), 3.35-3.40 (m, 3 H), 3.20-3.27 (m, 2 H), 2.69 (s, 3 H), 2.43- 2.50 (m, 4 H), OH and HCl protons not observed. 182 Starting material: (6-(5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl)-2-methylimidazo[1,2-b]pyridazin-8-yl)methanol dihydrochloride MS m/z 439.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.14 (s, 1H), 8.62 (s, 1H), 8.45- 8.49 (m, 1H), 8.43 (d, J = 10 Hz, 1H), 8.33-8.37 (m, 1H), 5.17 (s, 2H), 4.91-5.06 (m, 2H), 3.90 (br d, J = 12.21 Hz, 2H), 3.61-3.72 (m, 3H), 3.37-3.47 (m, 2H), 2.69 (s, 3H), 2.43-2.54 (m, 4H), OH and HCl protons not observed. 188 Starting material: 3-(azepan-4-yl)-7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5- fluorocinnoline dihydrochloride (prepared according to the procedure in Example 7) MS m/z 405.3 [M + H].sup.+;

.sup.1H NMR (methanol-d.sub.4) δ: 8.92 (s, 1H), 8.32 (d, J = 11.5 Hz, 1H), 8.18 (s, 1H), 8.01 (s, 1H), 7.89 (s, 1H), 3.62 (septet, J = 5 Hz, 1H), 3.03-3.09 (m, 1H), 2.85-2.92 (m, 3H), 2.73 (s, 3H), 2.52 (s, 3H), 2.51 (s, 3H), 2.28-2.40 (m, 1H), 2.20-2.28 (m, 2H), 2.03-2.20 (m, 2H), 1.90-1.99 (m, 1H). 189 Starting material: rac-3-(azepan-4-yl)-7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)- 5-fluorocinnoline (prepared according to the procedure in Example 7) MS m/z 419.3 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.87 (s, 1H), 8.27 (d, J = 11 Hz, 1H), 8.15 (s, 1H), 7.98 (s, 1H), 7.85 (s, 1H), 3.60 (septet, J = 5 Hz, 1H), 3.09-3.15 (m, 1H), 2.83-3.00 (m, 3H), 2.75 (q, J = 7 Hz, 2H), 2.71 (s, 3H), 2.51 (s, 3H), 2.20- 2.35 (m, 3H), 2.00-2.20 (m, 2H), 1.90-1.98 (m, 1H), 1.20 (t, J = 7 Hz, 3H). 190 Starting material: rac-3-(azepan-4-yl)-7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)- 5-fluorocinnoline (prepared according to the procedure in Example 7) MS m/z 435.3 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.91 (s, 1H), 8.31 (d, J = 11 Hz, 1H), 8.18 (s, 1H), 8.00 (s, 1H), 7.87 (s, 1H), 3.76 (t, J = 6 Hz, 2H), 3.60 (m, 1H), 3.17- 3.21 (m, 1H), 2.99-3.07 (m, 3H), 2.88 (t, J = 6 Hz, 2H), 2.73 (s, 3H), 2.51 (s, 3H), 2.00-2.34 (m, 5 H), 1.91-1.98 (m, 1H), OH proton not observed. 197 Starting material: 2-(5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl)-4,6- dimethylthiazolo[5,4-c]pyridine (prepared according to the procedure in Example 29) MS m/z 422.1 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.93 (s, 1H), 8.21 (dd, J = 9.9, 1.4 Hz, 1H), 7.88 (s, 1H), 7.62 (s, 1H), 3.38-3.29 (m, 1H), 3.16 (d, J = 11.2 Hz, 2H), 2.79 (s, 3H), 2.64 (s, 3H), 2.49 (q, J = 7.2 Hz, 2H), 2.25-2.09 (m, 4H), 2.06-1.93 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H). 200 Starting material: 5-fluoro-7-(2-methyl-8-phenoxyimidazo[1,2-b]pyridazin-6-yl)-3- (piperidin-4-yl)cinnoline (prepared according to the procedure in Example 29) MS m/z 483.3 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.59 (s, 1H), 8.25 (dd, J = 10.8, 1.2 Hz, 1H), 8.21 (s, 1H), 8.09 (s, 1H), 7.61-7.65 (m, 2H), 7.42-7.49 (m, 3H), 6.95 (s, 1H), 3.33-3.34 (m, 1H), 3.23-3.32 (m, 2H), 2.54-2.62 (m, 2H), 2.54 (s, 3H), 2.28- 2.34 (m, 2H), 2.07-2.19 (m, 4H), 1.20 (t, J = 7.2 Hz, 3H). 205 Starting material: 2-(6-(5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl)-2- methylimidazo[1,2-b]pyridazin-8-yl)acetonitrile dihydrochloride (prepared according to the procedure in Example 29) MS m/z 430.2 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.00 (s, 1H), 8.39 (dd, J = 11, 1.6 Hz, 1H), 8.26 (s, 1H), 8.15 (s, 1H), 8.09 (s, 1H), 3.49-3.52 (m, 3H), 2.91-2.94 (m, 2H), 2.70-2.79 (br s, 2H), 2.56 (s, 3H), 2.22-2.35 (m, 6H), 1.32 (t, J = 7.2 Hz, 3H). 206 Starting material: 2-(6-(5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl)-2- methylimidazo[1,2-b]pyridazin-8-yl)ethan-1-ol dihydrochloride (prepared according to the procedure in Example 29) MS m/z 435.2 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.96 (s, 1H), 8.36 (dd, J = 11.6, 1.2 Hz, 1H), 8.22 (s, 1H), 8.04 (s, 1H), 7.93 (s, 1H), 4.09 (t, J = 6.2 Hz, 2H), 3.34-3.37 (br s, 3H), 3.25-3.28 (m, 2H), 2.61-2.63 (m, 2H), 2.53 (s, 3H), 2.34 (m, 2H), 2.14- 2.20 (m, 4H), 1.22 (t, J = 7.2 Hz, 3H), OH proton not observed. 212 Starting material: 5-fluoro-7-(2-methyl-8-propylimidazo[1,2-b]pyridazin-6-yl)-3- (piperidin-4-yl)cinnoline dihydrochloride (prepared according to the procedure in Example 29) MS m/z 433.1 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.84 (s, 1H), 8.22 (dd, J = 10.4 Hz, 1.2 Hz, 1H), 7.95 (s, 1H), 7.81 (s, 1H), 7.51 (s, 1H), 3.43 (t, J = 12 Hz, 1H), 3.26 (d, J = 10.8 Hz, 2H), 3.12 (t, J = 7.6, 2H), 2.60 (d, J = 7.2 Hz, 2H), 2.56 (s, 3H), 2.27-1.91 (m, 8H), 1.21 (t, J = 7.2 Hz, 3H), 1.11 (t, J = 7.2 Hz, 3H). 213 Starting material: 2-(5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl)-4,6- dimethyloxazolo[4,5-c]pyridine dihydrochloride (prepared according to the procedure in Example 29) MS m/z 422.1[M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 9.11 (s, 1H), 8.22 (dd, J = 9.6, 1.2 Hz, 1H), 7.90 (s, 1H), 7.25 (s, 1H), 3.80-3.66 (m, 2H), 3.46-3.27 (m, 3H), 2.87- 2.70 (m, 5H), 2.64-2.50 (m, 5H), 2.30-2.18 (m, 4H), OH proton not observed. 214 Starting material: 2-(5-fluoro-3-(piperidin-4-yl)cinnolin-7-yl)-4,6- dimethyloxazolo[4,5-c]pyridine (prepared according to the procedure in Example 29) MS m/z 392.1 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 9.17 (s, 1H), 8.26 (dd, J = 9.7, 1.3 Hz, 1H), 7.93 (s, 1H), 7.32 (s, 1H), 3.40-3.29 (m, 1H), 3.10 (d, J = 11.7 Hz, 2H), 2.89 (s, 3H), 2.71 (s, 3H), 2.39 (s, 3H), 2.30-2.15 (m, 4H), 2.11-1.98 (m, 2H). 222 Starting material: 5-fluoro-7-(8-isopropyl-2-methylimidazo[1,2-b]pyridazin-6-yl)-3- (piperidin-4-yl)cinnoline (prepared according to the procedure in Example 29) MS m/z 433.2 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.97 (s, 1H), 8.36 (dd, J = 10.9, 1.3 Hz, 1H), 8.22 (s, 1H), 8.04

(s, 1H), 7.84 (s, 1H), 3.76-3.69 (m, 1H), 3.39 (d, J = 11.7 Hz, 2H), 3.28 (s, 1H), 2.65 (dd, J = 14.4, 7.2 Hz, 2H), 2.54 (s, 3H), 2.38 (t, J = 11.0 Hz, 2H), 2.27-2.10 (m, 4H), 1.54 (d, J = 6.9 Hz, 6H), 1.23 (t, J = 7.3 Hz, 3H).

Example 20

(483) Preparation of Compound 18

(484) ##STR00132##

(485) Step A: 6-Bromo-2-chloro-quinoline (300 mg, 1.2 mmol) was dissolved in THF (7.5 mL). To the solution was added a solution of KOtBu in THF (2.5 mL, 2.5 mmol, 1.0 M). The mixture was heated at 40° C. for 2 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-20% EtOAc in hexanes to yield 6-bromo-2-tert-butoxy-quinoline (310 mg, 89%). MS m/z 224.2, 226.2 [M+H-tBu].sup.+.

(486) Step B: 6-Bromo-2-tert-butoxy-quinoline (310 mg, 1.11 mmol) was combined with bis(pinacolato)diboron (375 mg, 1.46 mmol), 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (40 mg, 0.048 mmol), KOAc (300 mg, 3.03 mmol) and 1,4-dioxane (4 mL). The mixture was stirred at 90° C. for 2 h to yield 2-tert-butoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline as a crude mixture that was used without purification. MS m/z 272.3 [M-FH-tBu].sup.+.

(487) 6-Bromo-2,8-dimethyl-imidazo[1,2-a]pyrazine (100 mg, 0.44 mmol) and 2-tert-butoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (164 mg, 0.50 mmol, prepared above) were combined with 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (20 mg, 0.024 mmol), 1,4-dioxane (2.5 mL) and aqueous 1 M K.sub.2CO.sub.3 (1.5 mL). The mixture was heated at 80° C. for 2 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-20% EtOAc in hexanes to yield 2-tert-butoxy-6-(2,8-dimethylimidazo[1,2-a]pyrazin-6-yl)quinoline (140 mg, 73%). MS m/z 347.3 [M+H].sup.+.

(488) Step C: 2-tert-Butoxy-6-(2,8-dimethylimidazo[1,2-a]pyrazin-6-yl)quinoline (130 mg, 0.38 mmol) was suspended in 4 N HCl in 1,4-dioxane (1 mL, 4 mmol). The mixture was stirred at room temperature for 1 h. The volatiles were removed. The residue was suspended in DMF (1 mL) with Cs.sub.2CO.sub.3 (325 mg, 1.0 mmol). To the mixture was added N,N-bis(trifluoromethylsulfonyl)aniline (107 mg, 0.30 mmol). The mixture was stirred at room temperature for 2 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 10-100% EtOAc in hexanes to yield [6-(2,8-dimethylimidazo[1,2-a]pyrazin-6-yl)-2-quinolyl]trifluoromethanesulfonate (90 mg, 56%). MS m/z 423.3 [M+H].sup.+.

(489) Step D: [6-(2,8-Dimethylimidazo[1,2-a]pyrazin-6-yl)-2-quinolyl]trifluoromethanesulfonate (90 mg, 0.21 mmol) was combined with 1-tert-butoxycarbonylpiperidin-4-ylzinc iodide (0.25 mL, 0.25 mmol, prepared according to the procedure in Example 5, Step B), 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (8 mg, 0.01 mmol), 1,4-dioxane (2 mL). The mixture was heated at 80° C. for 20 min. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 10-100% EtOAc in hexanes, followed by 5% MeOH in EtOAc to yield tert-butyl 4-[6-(2,8-dimethylimidazo[1,2-a]pyrazin-6-yl)-2-quinolyl]piperidine-1-carboxylate (60 mg, 62%). MS m/z 458.4 [M+H].sup.+.

(490) Step E: tert-Butyl 4-[6-(2,8-dimethylimidazo[1,2-a]pyrazin-6-yl)-2-quinolyl]piperidine-1-carboxylate (60 mg, 0.1311 mmol) was dissolved in TFA (1 mL). After 20 min, the volatiles were removed. The residue was partitioned between CH.sub.2Cl.sub.2 and aqueous 1 M

K.sub.2CO.sub.3. The organic layer was loaded directly onto silica gel, eluting with 0-20% MeOH (2 M NH.sub.3) in CH.sub.2Cl.sub.2 to yield 6-(2,8-dimethylimidazo[1,2-a]pyrazin-6-yl)-2-(piperidin-4-yl)quinoline as white powder (15 mg, 32%).
(491) MS m/z 358.4 [M+H].sup.+. .sup.1H NMR (DMSO-d.sub.6) δ: 9.17 (s, 1H), 8.61 (d, J=2.2 Hz, 1H), 8.39 (d, J=8.5 Hz, 1H), 8.36 (dd, J=8.8, 2.2 Hz, 1H), 8.04 (d, J=8.8 Hz, 1H), 7.88 (s, 1H), 7.51 (d, J=8.5 Hz, 1H), 3.11-3.17 (m, 2H), 2.98-3.05 (m, 1H), 2.83 (s, 3H), 2.69-2.77 (m, 2H), 2.44 (s, 3H), 1.87-1.95 (m, 2H), 1.75-1.85 (m, 2H).
(492) Using the procedure described for Example 20, above, additional compounds described herein were prepared by substituting the appropriate aryl boronic acid in Step B, suitable reagents and reaction conditions, obtaining compounds such as those selected from:
(493) TABLE-US-00018 Cpd Data 19 MS m/z 358.4 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.67 (d, J = 2.2 Hz, 1H), 8.45 (d, J = 8.5 Hz, 1H), 8.42 (dd, J = 8.8, 2.0 Hz, 1H), 8.11 (s, 1H), 8.08 (d, J = 8.8 Hz, 1H), 7.82 (d, J = 1.3 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 3.24-3.30 (m, 2H), 3.09-3.15 (m, 1H), 2.84-2.91 (m, 2H), 2.65 (s, 3H), 2.43 (s, 3H), 1.87-1.95 (m, 2H), 1.75-1.85 (m, 2H).
Example 21
(494) Preparation of Compound 55
(495) ##STR00133##
(496) tert-Butyl 4-(7-(2,7-dimethyl-2H-indazol-5-yl)-5-fluorocinnolin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate (25 mg, 0.053 mmol, prepared according to Example 7, Step I) was stirred in the presence of HCl in dioxane (4M, 1 mL, 4 mmol) for 1 h. The reaction mixture was filtered, and the solids were washed with ether, then 9:1 CH.sub.2Cl.sub.2:MeOH to yield 7-(2,7-dimethyl-2H-indazol-5-yl)-5-fluoro-3-(1,2,3,6-tetrahydropyridin-4-yl)cinnoline hydrochloride (19 mg, 88%).
(497) MS m/z 374.4 [M+H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.30-9.40 (br s, 2H), 8.66 (s, 1H), 8.48 (s, 1H), 8.32 (s, 1H), 8.24 (dd, J=11.5, 1 Hz, 1H), 8.20 (s, 1H), 7.69 (s, 1H), 7.21 (br s, 1H), 4.23 (s, 3H), 3.94 (br s, 2H), 3.40-3.50 (m, 2H), 3.05 (br s, 2H), 2.64 (s, 3H).
(498) Using the procedure described for Example 2, above, additional compounds described herein were prepared by substituting the appropriate starting material, suitable reagents and reaction conditions, obtaining compounds such as those selected from:
(499) TABLE-US-00019 Cpd Data 225 MS m/z 375.3 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.70 (s, 1H), 8.08 (dd, J = 10.7, 1.0 Hz, 1H), 7.86 (s, 1H), 7.73-7.67 (m, 1H), 7.40 (s, 1H), 7.11 (br s, 1H), 4.23 (dd, J = 6.8, 2.2 Hz, 2H), 3.73 (dd, J = 5.2 Hz, 2H), 2.79 (br s, 2H), 2.69 (s, 3H), 2.48 (s, 3H), NH and HCl protons not observed. 208 MS m/z 431.5 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.81-8.89 (m, 1H), 8.21 (d, J = 10.1 Hz, 1H), 8.00 (s, 1H), 7.82 (s, 1H), 7.54 (d, J = 0.9 Hz, 1H), 7.13 (br s, 1H), 2.78 (s, 3H), 2.59-2.73 (br m, 2H), 2.53-2.57 (m, 3H), 1.43 (br s, 12H).
Example 22
(500) Preparation of Compound 4
(501) ##STR00134##
(502) Step A: 7-Bromocinnolin-3-ol (100 mg, 0.44 mmol, prepared according to the procedure used for 7-Bromo-5-fluoro-cinnolin-3-ol in Example 7), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (200 mg, 0.65 mmol), Pd(dppf)Cl.sub.2—CH.sub.2Cl.sub.2 (50 mg, 0.061 mmol), DMF (2.5 mL), and aqueous K.sub.2CO.sub.3 (2M, 0.825 mL, 1.65 mmol) were heated at 80° C. for 1 hour. The mixture was then partitioned between H.sub.2O and EtOAc. The organic layer was washed with H.sub.2O and then brine. The organic layer was dried over MgSO.sub.4, filtered, and concentrated under vacuum. Purification by silica gel chromatography (5% MeOH in CH.sub.2Cl.sub.2), followed by ether trituration, yielded tert-butyl 4-(3-hydroxycinnolin-7-yl)-3,6-dihydropyridine-1(2H)-carboxylate (110 mg) as a yellow solid. MS m/z 328.0 [M+H].sup.+.
(503) Step B: tert-Butyl 4-(3-hydroxycinnolin-7-yl)-3,6-dihydropyridine-1(2H)-carboxylate (108

mg, 0.33 mmol), 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (143 mg, 0.4 mmol), Cs.sub.2CO.sub.3 (175 mg, 0.54 mmol) and DMF (1 mL) were stirred at room temperature for 30 min. The mixture was partitioned between H.sub.2O and EtOAc. The organic layer was washed with H.sub.2O and brine. The organic layer was dried over MgSO.sub.4, filtered, and concentrated under vacuum. Purification by silica gel chromatography (0-5% EtOAc in CH.sub.2Cl.sub.2) yielded tert-butyl 4-(3-(((trifluoromethyl)sulfonyl)oxy)cinnolin-7-yl)-3,6-dihydropyridine-1(2H)-carboxylate (109 mg, 54% over two steps) as a white solid.
(504) .sup.1H NMR (acetone-d.sub.6) δ: 8.53 (s, 1H), 8.43 (s, 1H), 8.28 (dd, J=9 Hz, 2 Hz, 1H), 8.23 (d, J=9 Hz, 1H), 6.69 (br s, 1H), 4.22 (s, 2H), 3.75 (in, 2H), 2.79 (m, 2H), 1.51 (s, 9H).
(505) Step C: A mixture of tert-butyl 4-(3-(((trifluoromethyl)sulfonyl)oxy)cinnolin-7-yl)-3,6-dihydropyridine-1(2H)-carboxylate (85 mg, 0.18 mmol), (2-methyl-2H-indazol-5-yl)boronic acid (51 mg, 0.29 mmol), Pd(dppf)Cl.sub.2—CH.sub.2Cl.sub.2 (40 mg, 0.05 mmol), dioxane (1.05 mL), and aqueous K.sub.2CO.sub.3 (2M, 220 μL, 0.44 mmol) were heated at 80° C. for 90 min. The mixture was partitioned between H.sub.2O and CH.sub.2Cl.sub.2. The organic layer was dried over MgSO.sub.4, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography (20% acetone in CH.sub.2Cl.sub.2, followed by 5% MeOH in CH.sub.2Cl.sub.2). The material obtained was triturated with 2:1 hexanes:CH.sub.2Cl.sub.2. The solid material was collected and dried yielding tert-butyl 4-(3-(2-methyl-2H-indazol-5-yl)cinnolin-7-yl)-3,6-dihydropyridine-1(2H)-carboxylate (51 mg, 64%) as a yellow solid.
(506) .sup.1H NMR (DMSO-d.sub.6) δ: 8.72 (s, 1H), 8.71 (s, 1H), 8.55 (s, 1H), 8.39 (s, 1H), 8.21 (dd, J=9 Hz, 2 Hz, 1H), 8.11 (dd, J=9 Hz, 2 Hz, 1H), 8.06 (d, J=9 Hz, 1H), 7.80 (d, J=9 Hz, 1H), 6.61 (br s, 1H), 4.23 (s, 3H), 4.13 (s, 2H), 3.64 (t, J=5.5 Hz, 2H), 2.72 (s, 2H), 1.46 (s, 9H).
(507) Step D: A solution of tert-butyl 4-(3-(2-methyl-2H-indazol-5-yl)cinnolin-7-yl)-3,6-dihydropyridine-1(2H)-carboxylate (51 mg, 0.12 mmol) in CH.sub.2Cl.sub.2 (1 mL) and TFA (0.3 mL) was stirred at room temperature for 1 h. The volatiles were removed by a N.sub.2 stream. The solid material was triturated with 1 N HCl in ether for 1 h and the volatiles were removed by a N.sub.2 stream. The residue was washed with 4:1 CH.sub.2Cl.sub.2:MeOH and dried to yield 3-(2-methyl-2H-indazol-5-yl)-7-(1,2,3,6-tetrahydropyridin-4-yl)cinnoline hydrochloride (42 mg, 100%) as a light tan solid.
(508) MS m/z 342.0 [M+H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.25 (br s, 1H), 8.75 (s, 1H), 8.73 (s, 1H), 8.56 (s, 1H), 8.47 (s, 1H), 8.22 (dd, J=9 Hz, 1.5 Hz, 1H), 8.14 (dd, J=9 Hz, 2 Hz, 1H), 8.10 (d, J=9 Hz, 1H), 7.81 (d, J=9 Hz, 1H), 6.65 (br s, 1H), 4.24 (s, 3H), 3.88 (s, 2H), 3.41 (m, 2H), 2.95 (s, 2H).
Example 23
(509) Preparation of Compound 24
(510) ##STR00135##
(511) Step A: Quinoxalin-2-ol (2.0 g, 13.7 mmol), concentrated H.sub.2SO.sub.4 (14 mL), Ag.sub.2SO.sub.4 (2.12 g, 6.8 mmol), and Br.sub.2 (0.7 mL, 13.6 mmol) were stirred at room temperature for 15 h. The mixture was filtered to remove AgBr. The solid was washed with sulfuric acid. The combined filtrate was poured onto ice. A white solid was collected by filtration, washed with H.sub.2O, EtOH, and ether, and then dried to yield 6-bromoquinoxalin-2-ol (2.7 g, 87%) as a light tan solid containing 10% unreacted starting material.
(512) .sup.1H NMR (DMSO-d.sub.6) δ: 12.54 (br s, 1H), 8.21 (s, 1H), 7.99 (d, J=2 Hz, 1H), 7.73 (dd, J=9 Hz, 2 Hz, 1H), 7.27 (d, J=9 Hz, 1H).
(513) Step B: 6-Bromoquinoxalin-2-ol (200 mg, 0.88 mmol), 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-(trifluoromethyl)-2H-indazole (300 mg, 1.09 mmol), Pd(dppf)Cl.sub.2—CH.sub.2Cl.sub.2 (50 mg, 0.061 mmol), DMF (5 mL), and aqueous K.sub.2CO.sub.3 (2M, 1.65 mL, 3.3 mmol) were heated at 90° C. for 2 h. To the mixture was added dilute aqueous HCl. The solid material was collected by filtration, washed with H.sub.2O, EtOH and ether, and then dried to yield crude 6-(2-methyl-7-(trifluoromethyl)-2H-indazol-5-yl)quinoxalin-2-ol (231 mg). MS m/z

345.2 [M+H].sup.+.
(514) Step C: 6-(2-Methyl-7-(trifluoromethyl)-2H-indazol-5-yl)quinoxalin-2-ol (231 mg, 0.67 mmol), CH.sub.3CN (3 mL) and POBr.sub.3 (1.2 g, 4.18 mmol) were heated at 90° C. for 15 h. The mixture was diluted in ether and filtered. The solid material was washed with CH.sub.2Cl.sub.2. The mixture was dissolved in CH.sub.2Cl.sub.2:MeOH and was filtered through a silica plug to remove baseline impurities. The filtrate was concentrated under vacuum. The residue was purified by silica gel chromatography (30% EtOAc in CH.sub.2Cl.sub.2). The product was triturated with CH.sub.2Cl.sub.2. The solid was collected and dried to yield 2-bromo-6-(2-methyl-7-(trifluoromethyl)-2H-indazol-5-yl)quinoxaline (117 mg, 32% over two steps) as an off-white solid.
(515) .sup.1H NMR (acetone-d.sub.6) δ: 9.02 (s, 1H), 8.61 (s, 1H), 8.55 (s, 1H), 8.46 (d, J=2 Hz, 1H), 8.37 (dd, J=8.5 Hz, 2 Hz, 1H), 8.14-8.17 (m, 2H), 4.36 (s, 3H).
(516) Step D: 2-Bromo-6-(2-methyl-7-(trifluoromethyl)-2H-indazol-5-yl)quinoxaline (85 mg, 0.21 mmol), chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) (10 mg, 0.013 mmol), 1,4-dioxane (0.5 mL), and (1-(tert-butoxycarbonyl)piperidin-4-yl)zinc(II) iodide (1M in DMA, 0.5 mL, 0.5 mmol, prepared according to Example 5) were heated at 80° C. for 2 h. The mixture was partitioned between EtOAc and aqueous saturated NH.sub.4C1. The organic layer was dried over MgSO.sub.4, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography (1:1 CH.sub.2Cl.sub.2:EtOAc, followed by 20% acetone in CH.sub.2Cl.sub.2). The collected material was triturated with 1:1 hexanes:ether. The solid material was collected by vacuum filtration and dried to yield tert-butyl 4-(6-(2-methyl-7-(trifluoromethyl)-2H-indazol-5-yl)quinoxalin-2-yl)piperidine-1-carboxylate (41 mg, 38%) as a pink solid.
(517) .sup.1H NMR (acetone-d.sub.6) δ: 8.97 (s, 1H), 8.59 (s, 1H), 8.51 (s, 1H), 8.39 (d, J=2 Hz, 1H), 8.26 (dd, J=8.5 Hz, 2 Hz, 1H), 8.14-8.17 (m, 2H), 4.36 (s, 3H), 4.25-4.34 (m, 2H), 3.42 (m, 1H), 2.90-3.15 (br s, 2H), 2.05-2.10 (m, 2H), 1.91 (qd, J=12.5 Hz, 4 Hz, 2H), 1.50 (s, 9H).
(518) Step E: tert-Butyl 4-(6-(2-methyl-7-(trifluoromethyl)-2H-indazol-5-yl)quinoxalin-2-yl)piperidine1-carboxylate (25 mg, 0.049 mmol) and 4 N HCl in dioxane (1 mL, 4 mmol) were heated at 80° C. for 1 h. The mixture was diluted in ether. The solid material was collected by vacuum filtration and dried to yield 6-(2-methyl-7-(trifluoromethyl)-2H-indazol-5-yl)-2-(piperidin-4-yl)quinoxaline hydrochloride as a yellow solid (20 mg, 91%).
(519) MS m/z 412.1 [M+H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.97 (s, 1H), 8.55 (s, 1H), 8.47 (s, 1H), 8.37 (d, J=2 Hz, 1H), 8.27 (dd, J=9 Hz, 2 Hz, 1H), 8.21 (d, J=8.5 Hz, 1H), 8.12 (s, 1H), 4.34 (s, 3H), 3.59-3.66 (m, 2H), 3.45-3.54 (m, 1H), 3.24-3.33 (m, 2H), 2.33-2.40 (m, 2H), 2.22-2.33 (m, 2H), NH proton not observed.
(520) Using the procedure described for Example 23, above, additional compounds described herein were prepared by substituting the appropriate boronic acid in Step B, suitable reagents and reaction conditions, obtaining compounds such as those selected from:
(521) TABLE-US-00020 Cpd Data 31 MS m/z 358.2 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.98 (s, 1H), 8.86 (s, 1H), 8.39 (d, J = 2 Hz, 1H), 8.27 (dd, J = 9 Hz, 2 Hz, 1H), 8.23 (s, 1H), 8.21 (d, J = 8.5 Hz, 1H), 8.00 (s, 1H), 4.46 (s, 3H), 3.60-3.69 (m, 2H), 3.46-3.54 (m, 1H), 3.24-3.33 (m, 2H), 2.75 (s, 3H), 2.33-2.40 (m, 2H), 2.21-2.31 (m, 2H), NH proton not observed.
Example 24
(522) Preparation of Compound 5
(523) ##STR00136## ##STR00137##
(524) Step A: 4-Bromoaniline (5.0 g, 29.1 mmol) was dissolved in EtOAc (60 mL) and Et.sub.3N (5.25 mL, 37.5 mmol) at 0° C. Methyl 3-chloro-3-oxopropanoate (3.95 mL, 31.5 mmol) was added dropwise to the solution. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was partitioned between EtOAc and dilute aqueous HCl. The organic layer was washed with aqueous NaHCO.sub.3 and brine. The organic layer was dried over MgSO.sub.4, filtered and

concentrated under vacuum. The residue was triturated with 2:1 hexane:ether. The solid material was collected by vacuum filtration and dried to yield ethyl 3-((4-bromophenyl)amino)-3-oxopropanoate (6.23 g, 75%) as a white solid.
(525) .sup.1H NMR (acetone-d.sub.6) δ: 9.50 (br s, 1H), 7.64 (m, 2H), 7.49 (m, 2H), 4.19 (q, J=7 Hz, 2H), 3.48 (s, 2H), 1.26 (t, J=7 Hz, 3H).
(526) Step B: Ethyl 3-((4-bromophenyl)amino)-3-oxopropanoate (6.23 g, 22.1 mmol) was dissolved in THF (60 mL) and MeOH (15 mL) at 0° C. Aqueous 2 N NaOH (15 mL, 30 mmol) was added dropwise to the mixture. The mixture was stirred at 0° C. for 1 h, upon which excess reagent was quenched with aqueous 6 N HCl (7.5 mL). The mixture was concentrated under vacuum. The residue was suspended in H.sub.2O. The solid material was collected by vacuum filtration and dried to yield 3-((4-bromophenyl)amino)-3-oxopropanoic acid (5.7 g, 100%) as a white solid.
(527) .sup.1H NMR (acetone-d.sub.6) δ: 9.63 (br s, 1H), 7.64 (m, 2H), 7.49 (m, 2H), 3.50 (s, 2H), CO.sub.2H proton not observed.
(528) Step C: Methanesulfonic acid (28 mL), 3-((4-bromophenyl)amino)-3-oxopropanoic acid (5.7 g, 22.1 mmol), and P.sub.2O.sub.5 (9 g, 63.4 mmol) were combined and heated at 80° C. for 6 h. The mixture was poured onto ice, and the resulting solid material was collected by vacuum filtration. The solid material was washed with EtOH and ether, and dried to yield 6-bromo-2-hydroxyquinolin-4(1H)-one (3.48 g, 65%) as a tan solid. MS m/z 240.0, 242.0 [M-al].sup.+.
(529) Step D: 6-Bromo-2-hydroxyquinolin-4(1H)-one (3.48 g, 14.5 mmol) and POCl.sub.3 (25 mL) were heated at 100° C. for 15 h. The mixture was poured into ice-water. The resulting mixture was extracted with CH.sub.2Cl.sub.2. The organic layer was dried over MgSO.sub.4, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography (30% hexanes in CH.sub.2Cl.sub.2) to yield 6-bromo-2,4-dichloroquinoline (2.9 g, 72%) as a white solid.
(530) .sup.1H NMR (acetone-d.sub.6) δ: 8.42 (d, J=2 Hz, 1H), 8.06 (dd, J=9 Hz, 2 Hz, 1H), 7.98 (d, J=9 Hz, 1H), 7.85 (s, 1H).
(531) Step E: 6-Bromo-2,4-dichloroquinoline (2.82 g, 10.2 mmol) and 0.5 M NaOMe in MeOH (21.2 mL, 10.6 mmol) were combined and heated at reflux for 2 h. The mixture was partitioned between H.sub.2O and CH.sub.2Cl.sub.2. The organic layer was dried over MgSO.sub.4, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography (50-70% CH.sub.2Cl.sub.2 in hexanes) to yield 6-bromo-4-chloro-2-methoxyquinoline (1.02 g, 37%).
(532) .sup.1H NMR (acetone-d.sub.6) δ: 8.25 (d, J=2 Hz, 1H), 7.88 (dd, J=9, 2 Hz, 1H), 7.80 (d, J=9 Hz, 1H), 7.22 (s, 1H), 4.06 (s, 3H).
(533) Step F: 6-Bromo-4-chloro-2-methoxyquinoline (210 mg, 0.77 mmol), (2-methyl-2H-indazol-5-yl)boronic acid (161 mg, 0.91 mmol), Pd(PPh.sub.3).sub.4 (90 mg, 0.078 mmol), 2 M aqueous K.sub.2CO.sub.3 (1.4 mL, 2.8 mmol) and 1,4-dioxane (4.2 mL) were combined and heated at 80° C. for 1 h. The reaction mixture was partitioned between CH.sub.2Cl.sub.2 and H.sub.2O. The organic layer was dried over MgSO.sub.4, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography (30% EtOAc in CH.sub.2Cl.sub.2). The collected product was triturated in ether. The solid material was collected by vacuum filtration and dried to yield 4-chloro-2-methoxy-6-(2-methyl-2H-indazol-5-yl)quinoline (182 mg, 73%) as a while solid.
(534) .sup.1H NMR (acetone-d.sub.6) δ: 8.37 (d, J=2 Hz, 1H), 8.32 (s, 1H), 8.14 (dd, J=9 Hz, 2 Hz, 1H), 8.11 (m, 1H), 7.96 (d, J=8.5 Hz, 1H), 7.76-7.80 (m, 1H), 7.72 (dd, J=8.5 Hz, 1.5 Hz, 1H), 7.20 (s, 1H), 4.27 (s, 3H), 4.08 (s, 3H).
(535) Step G: 4-Chloro-2-methoxy-6-(2-methyl-2H-indazol-5-yl)quinoline (120 mg, 0.37 mmol) was combined with Pd(dppf)Cl.sub.2—CH.sub.2Cl.sub.2 (35 mg, 0.043 mmol) in 1,4-dioxane (0.5 mL). To the mixture was added dimethylzinc (1.2 M in toluene, 1 mL, 1.2 mmol). The mixture was heated at 80° C. for 4 h. The reaction mixture was cooled to room temperature, upon which excess reagent was carefully quenched with MeOH. The mixture was partitioned between NH.sub.4OH and CH.sub.2Cl.sub.2. The organic layer was dried over MgSO.sub.4, filtered and concentrated under vacuum. Purification by silica gel chromatography (30% EtOAc in CH.sub.2Cl.sub.2),

followed by ether trituration, yielded 2-methoxy-4-methyl-6-(2-methyl-2H-indazol-5-yl)quinoline (102 mg, 91%) as a white solid.
(536) .sup.1H NMR (acetone-d.sub.6) δ: 8.31 (s, 1H), 8.23 (d, J=2 Hz, 1H), 8.08 (t, J=1.5 Hz, 1H), 8.02 (dd, J=8.5 Hz, 2.5 Hz, 1H), 7.89 (d, J=9 Hz, 1H), 7.74 (m, 2H), 6.88 (s, 1H), 4.27 (s, 3H), 4.03 (s, 3H), 2.76 (s, 3H).
(537) Step H: 2-Methoxy-4-methyl-6-(2-methyl-2H-indazol-5-yl)quinoline (100 mg, 0.33 mmol) and 4 N HCl in 1,4-dioxane (1.5 mL, 6 mmol) were heated at 110° C. for 3 h. The mixture was diluted in ether and was filtered. The solid was dried, yielding 4-methyl-6-(2-methyl-2H-indazol-5-yl)quinolin-2-ol (82 mg, 84%) as a light tan solid. MS m/z 289.9 [M+H].sup.+.
(538) Step I: 4-Methyl-6-(2-methyl-2H-indazol-5-yl)quinolin-2-ol (82 mg, 0.28 mmol) and POCl.sub.3 (1.5 mL) were heated at 120° C. for 2 h. The mixture was poured onto ice. Aqueous saturated NaHCO.sub.3 was added to the ice to neutralize the mixture. The aqueous mixture was washed with CH.sub.2Cl.sub.2. The organic layer was dried over MgSO.sub.4, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography (5% MeOH in CH.sub.2Cl.sub.2). The collected product was triturated with 1:1 acetone:CH.sub.2Cl.sub.2. The solid was collected and dried to yield 2-chloro-4-methyl-6-(2-methyl-2H-indazol-5-yl)quinoline (84 mg, 100%) as an orange solid.
(539) .sup.1H NMR (DMSO-d.sub.6) δ: 8.46 (s, 1H), 8.32 (d, J=2 Hz, 1H), 8.17-8.23 (m, 2H), 8.01 (d, J=9 Hz, 1H), 7.79 (dd, J=9 Hz, 1.5 Hz, 1H), 7.75 (d, J=9 Hz, 1H), 7.52 (s, 1H), 4.22 (s, 3H), 2.80 (s, 3H).
(540) Step J: 2-Chloro-4-methyl-6-(2-methyl-2H-indazol-5-yl)quinoline (75 mg, 0.24 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (93 mg, 0.3 mmol), chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) (10 mg, 0.014 mmol), aqueous 2 M K.sub.2CO.sub.3 (0.45 mL, 0.9 mmol) and DMF (1.35 mL) were combined and heated at 80° C. for 1 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was dried over MgSO.sub.4, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography (30-50% EtOAc in CH.sub.2Cl.sub.2). The collected product was triturated with ether. The solid was collected and dried to yield tert-butyl 4-(4-methyl-6-(2-methyl-2H-indazol-5-yl)quinolin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (73 mg, 67%) as a white solid.
(541) .sup.1H NMR (acetone-d.sub.6) δ: 8.32 (s, 1H), 8.31 (s, 1H), 8.14 (t, J=1.5 Hz, 1H), 8.06-8.12 (m, 2H), 7.75-7.80 (m, 2H), 7.73 (s, 1H), 6.86 (br s, 1H), 4.27 (s, 3H), 4.20 (s, 2H), 3.69 (t, J=5.5 Hz, 2H), 2.88 (m, 2H), 2.83 (s, 3H), 1.51 (s, 9H).
(542) Step K: tert-Butyl 4-(4-methyl-6-(2-methyl-2H-indazol-5-yl)quinolin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (70 mg, 0.15 mmol) was combined with 4:1 CH.sub.2Cl.sub.2:MeOH (1.5 mL) and 10% Pd/C (35 mg). The mixture was stirred at room temperature under H.sub.2 (1 atm) for 4 h. The mixture was filtered through Celite. The filtrate was concentrated under vacuum. The residue was purified by silica gel chromatography (1:1 CH.sub.2Cl.sub.2:EtOAc, followed by 20% acetone in CH.sub.2Cl.sub.2). The collected material was triturated in ether. The solid was collected and dried to yield tert-butyl 4-(4-methyl-6-(2-methyl-2H-indazol-5-yl)quinolin-2-yl)piperidine-1-carboxylate (55 mg, 79%) as a white solid.
(543) .sup.1H NMR (acetone-d.sub.6) δ: 8.32 (s, 1H), 8.30 (s, 1H), 8.12 (t, J=1.5 Hz, 1H), 8.04-8.11 (m, 2H), 7.73-7.78 (m, 2H), 7.37 (s, 1H), 4.27 (m, 5H), 3.03-3.14 (m, 1H), 2.85-3.01 (m, 2H), 2.82 (s, 3H), 1.95-2.03 (m, 2H), 1.82-1.92 (m, 2H), 1.49 (s, 9H).
(544) Step L: tert-Butyl 4-(4-methyl-6-(2-methyl-2H-indazol-5-yl)quinolin-2-yl)piperidine-1-carboxylate (53 mg, 0.12 mmol) and 4 N HCl in 1,4-dioxane (1 mL, 4 mmol) were combined and heated at 50° C. for 1 h. The mixture was diluted with ether. The solid material was collected by vacuum filtration, washed with 9:1 CH.sub.2Cl.sub.2:MeOH and dried to yield 4-methyl-6-(2-methyl-2H-indazol-5-yl)-2-(piperidin-4-yl)quinoline hydrochloride (46 mg, 100%) as a yellow solid.

(545) MS m/z 357.0 [M+H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.11-9.23 (br s, 1H), 8.95-9.10 (br s, 1H), 8.38-8.53 (m, 4H), 8.28 (s, 1H), 7.83 (dd, J=9 Hz, 1.5 Hz, 1H), 7.72-7.80 (m, 2H), 4.23 (s, 3H), 3.50-3.60 (m, 1H), 3.41-3.49 (m, 2H), 3.09 (m, 2H), 3.00 (s, 3H), 2.20-2.38 (m, 4H).

Example 25

(546) Preparation of Compound 7

(547) ##STR00138##

(548) Step A: 6-Bromoquinolin-2-ol (670 mg, 3.0 mmol) was combined with piperazine (504 mg, 6.0 mmol), potassium tert-butoxide (840 mg, 7.5 mmol), 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl (280 mg, 0.6 mmol) and tris(dibenzylideneacetone)dipalladium(0) (275 mg, 0.3 mmol) in 1,4-dioxane (10 mL). The mixture was heated at 100° C. for 16 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-20% MeOH in CH.sub.2Cl.sub.2 to yield 6-(piperazin-1-yl)quinolin-2-ol (575 mg, 84%). MS m/z 230.1 [M+H].sup.+.

(549) Step B: 6-(Piperazin-1-yl)quinolin-2-ol (575 mg, 2.5 mmol) was suspended in POCl.sub.3 (4.6 mL, 50 mmol). The mixture was heated at 100° C. for 16 h. The mixture was slowly added to a vigorously stirred mixture of CH.sub.2Cl.sub.2 (100 mL), H.sub.2O (100 mL), and 10 g of (NaHCO.sub.3). The organic layer was collected and concentrated. The residue was chromatographed on silica gel, eluting with 0-15% MeOH in CH.sub.2Cl.sub.2 to yield 2-chloro-6-(piperazin-1-yl)quinoline (280 mg, 45%). MS m/z 248.1, 250.1 [M+H].sup.+.

(550) Step C: 2-Chloro-6-(piperazin-1-yl)quinoline (280 mg, 1.1 mmol) was combined with 2-methylindazole-5-boronic acid (387 mg, 1.5 mmol), 1,1′-bis(diphenylphosphino) ferrocene-palladium(II)dichloride dichloromethane complex (80 mg, 0.10 mmol), 1,4-dioxane (10 mL), and aqueous 1 M K.sub.2CO.sub.3 (5 mL, 5 mmol). The mixture was stirred at 100° C. for 16 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-15% MeOH in CH.sub.2Cl.sub.2 to yield 2-(2-methyl-2H-indazol-5-yl)-6-(piperazin-1-yl)quinoline (51 mg, 20%).

(551) MS m/z 344.1 [M+H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.52 (s, 1H), 8.46 (s, 1H), 8.18-8.22 (m, 2H), 8.05 (d, J=8.5 Hz), 7.88 (d, J=9.0 Hz), 7.69 (d, J=9.0 Hz), 7.60 (d, J=8.5 Hz), 7.18 (s, 1H), 4.20 (s, 3H), 3.19-3.22 (m, 4H), 2.88-2.91 (m, 4H), NH proton not observed.

Example 26

(552) Preparation of Compound 117

(553) ##STR00139##

(554) Step A: A mixture of 7-bromo-3-chloro-5-fluorocinnoline (120 mg, 0.46 mmol, prepared according to Example 7), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (153 mg, 0.49 mmol), and chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)(2′-amino-1,1′-biphenyl-2-yl) palladium(II) (25 mg, 0.034 mmol) in 1,4-dioxane (3.5 mL) and aqueous 2 M K.sub.2CO.sub.3 (0.7 mL, 1.4 mmol) was heated to 80° C. for 2 h.

(555) The crude reaction mixture was cooled to room temperature, filtered over celite, and concentrated. The residue was chromatographed on silica gel, eluting with 10-50% EtOAc in hexanes to yield tert-butyl 4-(3-chloro-5-fluorocinnolin-7-yl)-3,6-dihydropyridine-1(2H)-carboxylate (120 mg, 72%) as a tan solid. MS m/z 364.4, 366.4 [M+H].sup.+.

(556) Step B: A mixture of 8-fluoro-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-a]pyridine (69 mg, 0.25 mmol), tert-butyl 4-(3-chloro-5-fluorocinnolin-7-yl)-3,6-dihydropyridine-1(2H)-carboxylate (60 mg, 0.16 mmol), and chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)(2′-amino-1,1′-biphenyl-2-yl) palladium(II) (12 mg, 0.016 mmol) in 1,4-dioxane (1.5 mL) and aqueous 2 M K.sub.2CO.sub.3 (0.25 mL, 0.5 mmol) was heated to 90° C. for 2 h. The mixture was cooled to room temperature, filtered over celite, and concentrated. The

residue was chromatographed on silica gel, eluting with 5-10% MeOH in CH.sub.2Cl.sub.2 to yield tert-butyl 4-(5-fluoro-3-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)cinnolin-7-yl)-3,6-dihydropyridine-1(2H)-carboxylate (54 mg, 69%) as a brown solid. MS m/z 478.5 [M+H].sup.+.
(557) Step C: To a solution of tert-butyl 4-(5-fluoro-3-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)cinnolin-7-yl)-3,6-dihydropyridine-1(2H)-carboxylate (54 mg, 0.11 mmol) in CH.sub.2Cl.sub.2 (1.5 mL) was added trifluoroacetic acid (1.5 mL). The reaction was stirred at room temperature for 15 minutes, then concentrated. The residue was dissolved in HCl in MeOH (1.25 M) and concentrated. This procedure was repeated once more to afford 5-fluoro-3-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-7-(1,2,3,6-tetrahydropyridin-4-yl)cinnoline hydrochloride (26 mg, 56%) as a yellow solid.
(558) MS m/z 378.4 [M+H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.82 (s, 1H), 9.35-9.42 (br s, 2H), 8.92 (s, 1H), 8.64 (d, J=11.9 Hz, 1H), 8.43 (s, 1H), 8.21-8.25 (br s, 1H), 8.13 (d, J=11.6 Hz, 1H), 6.74-6.77 (br s, 1H), 3.87-3.92 (br s, 2H), 3.39-3.44 (m, 2H), 2.92-2.97 (m, 2H), 2.53 (s, 3H).
(559) Using the procedure described for Example 26, above, additional compounds described herein were prepared by substituting the appropriate boronic acid in Step B, suitable reagents and reaction conditions, obtaining compounds such as those selected from:
(560) TABLE-US-00021 Cpd Data 134 MS m/z 378.4 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.21-9.26 (br s, 2H), 8.77 (s, 1H), 8.65-8.74 (m, 2H), 8.38 (s, 1H), 8.12 (d, J = 13.4 Hz, 1H), 8.06 (d, J = 11.9 Hz, 1H), 6.70-6.74 (br s, 1H), 4.27 (s, 3H), 3.85-3.90 (m, 2H), 3.35-3.44 (m, 2H), 2.90- 2.95 (m, 2H). 156 MS m/z 374.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.65 (s, 1H), 8.89 (d, J = 1.0 Hz, 1H), 8.69 (t, J = 1.2 Hz, 1H), 8.46 (s, 1H), 8.14 (d, J = 0.9 Hz, 1H), 8.00 (dd, J = 11.1, 1.4 Hz, 1H), 6.67 (dt, J = 3.4, 1.8 Hz, 1H), 4.02 (d, J = 3.1 Hz, 2H), 3.61 (t, J = 6.1 Hz, 2H), 3.01-3.11 (m, 2H), 2.81 (s, 3H), 2.65 (s, 3H), NH and HCl protons not observed. 157 MS m/z 374.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.82 (s, 1H), 8.58-8.61 (m, 2H), 8.38 (s, 1H), 8.14 (s, 1H), 7.97 (d, J = 10.4 Hz, 1H), 6.64-6.67 (m, 1H), 4.36 (s, 3H), 4.01-4.03 (m, 2H), 3.60 (t, J = 6.1 Hz, 2H), 3.04-3.08 (m, 2H), 2.75 (s, 3H), NH and HCl protons not observed. 165 MS m/z 378.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.73 (d, J = 2.4 Hz, 1H), 8.37 (s, 1H), 7.66-7.72 (m, 1H), 7.62 (s, 1H), 7.50 (d, J = 11.4 Hz, 1H), 6.37-6.43 (m, 1H), 6.24-6.28 (m, 1H), 4.34-4.39 (s, 3H), 3.92-3.97 (m, 2H), 3.51-3.55 (m, 2H), 2.84- 2.93 (m, 2H), NH and HCl protons not observed. 166 MS m/z 377.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.70 (d, J = 9.8 Hz, 1H), 8.57 (dd, J = 2.4, 1.4 Hz, 1H), 8.44 (s, 1H), 8.31 (d, J = 8.9 Hz, 1H), 7.99 (s, 1H), 7.94 (m, 2H), 6.52 (br s, 1H), 4.29-4.36 (m, 3H), 3.98 (d, J = 2.1 Hz, 2H), 3.58 (dd, J = 7.8, 6.1 Hz, 2H), 2.96-3.04 (m, 2H), NH and HCl protons not observed. 167 MS m/z 375.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.08 (s, 1H), 8.86 (s, 1H), 8.39 (s, 1H), 8.32 (s, 1H), 7.91 (d, J = 11.0 Hz, 1H), 6.57-6.59 (br s, 1H), 3.87-3.95 (m, 2H), 3.49 (t, J = 6.1 Hz, 2H), 2.94-2.98 (m, 2H), 2.78 (s, 3H), 2.59 (s, 3H), NH protons not observed. 171 MS m/z 379.4 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.20-9.25 (br s, 2H), 8.96 (s, 1H), 8.88 (s, 1H), 8.41 (s, 1H), 8.36 (d, J = 12.5 Hz, 1H), 8.11 (d, J = 11.6 Hz, 1H), 6.73- 6.76 (br s, 1H), 4.62 (s, 3H), 3.87-3.91 (m, 2H), 3.39-3.44 (m, 2H), 2.92-2.97 (m, 2H). 175 MS m/z 385.4 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.25 (s, 1H), 9.05-9.10 (br s, 2H), 8.90 (s, 1H), 8.94 (s, 1H), 8.84 (s, 1H), 8.41 (s, 1H), 8.09 (d, J = 11.0 Hz, 1H), 6.72- 6.75 (m, 1H), 4.32 (s, 3H), 3.88-3.92 (m, 2H), 3.40-3.45 (m, 2H), 2.91-2.96 (m, 2H). 198 MS m/z 388.3 [M + H].sup.+. .sup.1H NMR (DMSO-d.sub.6) δ: 8.67 (s, 1H), 8.65 (s, 1H), 8.52 (s, 1H), 8.37 (s, 1H), 8.08 (s, 1H), 7.86-7.88 (d, J = 11 Hz, 1H), 6.45 (t, J = 6.5 Hz, 1H), 4.34 (s, 3H), 3.97 (m, 2H), 3.00 (m, 2H), 2.65 (s, 3H), 2.37 (m, 2H), 2.02, (m, 2H). NH proton not observed.
Example 27
(561) Preparation of Compound 128
(562) ##STR00140##
(563) A suspension of 5-fluoro-3-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-7-(1,2,3,6-tetrahydropyridin-4-yl)cinnoline hydrochloride (22 mg, 0.05 mmol) and Pd/C (20 mg) in MeOH (2

mL) was stirred under H.sub.2 (1 atm) at room temperature for 12 h. The mixture was filtered over celite and concentrated. The residue was dissolved in DMF (1 mL). To the solution was added MnO.sub.2 (45 mg, 0.5 mmol). The reaction was stirred at room temperature for 1h, then filtered over celite. The filtrate was concentrated. The residue was dissolved in 1.25 M HCl in MeOH. Concentration afforded 5-fluoro-3-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-7-(piperidin-4-yl)cinnoline hydrochloride (15 mg, 62%) as a yellow solid.

(564) MS m/z 380.4 [M+H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.69 (s, 1H), 8.93 (s, 1H), 8.79 (d, J=11.0 Hz, 1H), 8.33 (s, 1H), 8.25 (s, 1H), 7.74 (d, J=10.7 Hz, 1H), 3.61 (d, J=12.5 Hz, 2H), 3.21-3.35 (m, 3H), 2.65 (s, 3H), 2.31 (d, J=14.0 Hz, 2H), 2.00-2.18 (m, 2H), NH and HCl protons not observed.

(565) Using the procedure described for Example 27, above, additional compounds described herein were prepared by substituting suitable reagents and reaction conditions, obtaining compounds such as those selected from:

(566) TABLE-US-00022 Cpd Data 151 MS m/z 380.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.71 (s, 1H), 8.47-8.57 (m, 2H), 8.23 (s, 1H), 8.02 (d, J = 12.2 Hz, 1H), 7.64 (d, J = 10.1 Hz, 1H), 4.31 (s, 3H), 3.62 (d, J = 11.6 Hz, 2H), 3.21-3.29 (m, 3H), 2.32 (d, J = 13.4 Hz, 2H), 1.97-2.15 (m, 2H), NH and HCl protons not observed. 177 MS m/z 376.4 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.00-9.07 (br s, 1H), 8.87-8.95 (br s, 1H), 8.60-8.66 (m, 2H), 8.51 (s, 1H), 8.17 (s, 1H), 8.06 (s, 1H), 7.68 (d, J = 10.5 Hz, 1H), 4.23 (s, 3H), 3.46-3.55 (m, 1H), 3.15-3.22 (m, 2H), 3.01-3.10 (br s, 2H), 2.64 (s, 3H), 2.12-2.19 (m, 2H), 1.98-2.07 (m, 2H). 185 MS m/z 377.3 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.21 (s, 1H), 9.01 (s, 1H), 8.45 (s, 1H), 8.38 (s, 1H), 7.78 (d, J = 9.5 Hz, 1H), 3.63 (d, J = 12.5 Hz, 2H), 3.23-3.40 (m, 3H), 2.90 (s, 3H), 2.71 (s, 3H), 2.34 (d, J = 14.0 Hz, 2H), 2.06-2.17 (m, 2H), NH and HCl protons not observed. 192 MS m/z 379.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.46 (d, J = 2.4 Hz, 1H), 8.35-8.40 (m, 2H), 8.16 (d, J = 8.9 Hz, 1H), 8.03 (dd, J = 13.2, 1.1 Hz, 1H), 7.61 (s, 1H), 7.48 (dd, J = 11.9, 1.5 Hz, 1H), 4.29 (s, 3H), 3.30 (br s, 2H), 2.88-3.01 (m, 3H), 2.04 (d, J = 12.5 Hz, 2H), 1.80-1.90 (m, 2H), NH proton not observed.

Example 28

(567) Preparation of Compound 144

(568) ##STR00141##

(569) To a suspension of 5-fluoro-3-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)-7-(piperidin-4-yl)cinnoline hydrochloride (175 mg, 0.42 mmol) and sodium triacetoxyborohydride (900 mg, 4.2 mmol) in CH.sub.2Cl.sub.2 (4 mL) and EtOH (1 mL) was added a solution of acetaldehyde (0.25 mL, 4.4 mmol) in EtOH (1 mL). The reaction was stirred at room temperature for 1 h, then quenched with saturated aqueous K.sub.2CO.sub.3. The mixture was partitioned between CH.sub.2Cl.sub.2 and H.sub.2O. The aqueous layer was extracted once with CH.sub.2Cl.sub.2. The combined organics were dried over Na.sub.2SO.sub.4 filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-20% 1.4 N NH.sub.3/MeOH in CH.sub.2Cl.sub.2 to yield 7-(1-ethylpiperidin-4-yl)-5-fluoro-3-(8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)cinnoline (120 mg, 70%) as a light orange solid.

(570) MS m/z 408.5 [M+H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.29 (d, J=1.2 Hz, 1H), 8.70 (s, 1H), 8.22 (s, 1H), 8.01 (dd, J=12.2, 1.2 Hz, 1H), 7.88 (d, J=2.1 Hz, 1H), 7.65 (d, J=10.7 Hz, 1H), 3.36-3.39 (m, 2H), 2.98-3.09 (m, 1H), 2.76 (q, J=7.2 Hz, 2H), 2.44-2.55 (m, 5H), 2.16 (d, J=13.1 Hz, 2H), 1.95-2.03 (m, 2H), 1.27 (t, J=7.2 Hz, 3H).

(571) Using the procedure described for Example 28 above, additional compounds described herein were prepared by substituting suitable reagents and reaction conditions, obtaining compounds such as those selected from:

(572) TABLE-US-00023 Cpd Data 153 MS m/z 406.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.83 (s, 1H), 8.55 (d, J = 1.5 Hz, 2H), 8.38 (s, 1H), 8.01 (dd, J = 12.8, 1.2 Hz, 1H), 7.97 (dd, J = 11.3, 1.2 Hz, 1H), 6.63-6.67 (br s, 1H), 4.32 (s, 3H), 4.25 (d, J = 13.1 Hz, 1H), 3.88-4.01

(m, 2H), 3.38-3.50 (m, 3H), 3.10-3.18 (m, 2H), 1.49 (t, J = 7.3 Hz, 3H), HCl proton not observed. 154 MS m/z 408.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.66-8.71 (m, 1H), 8.48-8.54 (m, 2H), 8.21 (s, 1H), 8.01 (dd, J = 12.8, 1.2 Hz, 1H), 7.63 (d, J = 10.7 Hz, 1H), 4.31 (s, 3H), 3.42-3.55 (m, 2H), 3.12 (t, J = 12.4 Hz, 1H), 2.91-2.97 (m, 2H), 2.70-2.78 (m, 2H), 2.23 (d, J = 13.1 Hz, 2H), 1.98-2.14 (m, 2H), 1.33 (t, J = 7.3 Hz, 3H). 183 MS m/z 404.4 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.63 (d, J = 6.4 Hz, 2H), 8.51 (s, 1H), 8.18 (s, 1H), 8.06 (s, 1H), 7.74 (d, J = 10.4 Hz, 1H), 4.23 (s, 3H), 3.12-3.25 (m, 3H), 2.86-2.96 (m, 2H), 2.64 (s, 3H), 2.45-2.55 (m, 2H), 1.97-2.05 (m, 2H), 1.84-1.91 (m, 2H), 1.06-1.17 (m, 3H). 184 MS m/z 405.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.83 (d, J = 9.5 Hz, 1H), 8.61 (d, J = 2.3 Hz, 1H), 8.45 (s, 1H), 8.35 (d, J = 8.5 Hz, 1H), 8.07 (s, 1H), 8.02 (d, J = 11.7 Hz, 1H), 7.91 (d, J = 12.4 Hz, 1H), 6.54 (br s, 1H), 4.33 (s, 3H), 4.22 (d, J = 15.4 Hz, 1H), 3.81-3.99 (m, 2H), 3.37-3.49 (m, 3H), 3.04-3.15 (m, 2H), 1.48 (t, J = 7.2 Hz, 3H). 186 MS m/z 405.3 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.04 (d, J = 0.9 Hz, 1H), 8.39 (d, J = 1.2 Hz, 1H), 8.27 (s, 1H), 8.05 (d, J = 0.9 Hz, 1H), 7.66-7.73 (m, 1H), 3.47 (d, J = 11.9 Hz, 2H), 3.07-3.17 (m, 1H), 2.90 (q, J = 7.2 Hz, 2H), 2.76 (d, J = 0.9 Hz, 3H), 2.69 (t, J = 11.6 Hz, 2H), 2.54 (s, 3H), 2.23 (d, J = 13.7 Hz, 2H), 2.04 (qd, J = 12.9, 3.5 Hz, 2H), 1.32 (t, J = 7.3 Hz, 3H). 193 MS m/z 407.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.47 (d, J = 2.4 Hz, 1H), 8.37-8.41 (m, 2H), 8.18 (d, J = 8.7 Hz, 1H), 8.04 (d, J = 13.3 Hz, 1H), 7.63 (s, 1H), 7.49 (d, J = 12.2 Hz, 1H), 4.30 (s, 3H), 3.42-3.52 (m, 2H), 2.87-3.01 (m, 3H), 2.59-2.76 (m, 2H), 2.15 (d, J = 16.6 Hz, 2H), 2.00 (m, 2H), 1.32 (t, J = 7.3 Hz, 3H). 201 MS m/z 406.3 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.58 (s, 1H), 8.89 (s, 1H), 8.50 (d, J = 2.6 Hz, 1H), 8.24 (d, J = 14.3 Hz, 1H), 7.97 (d, J = 11.6 Hz, 1H), 7.91 (s, 1H), 6.50 (br s, 1H), 4.29 (s, 3H), 2.92 (t, J = 6.7 Hz, 2H), 2.77-2.83 (m, 2H), 2.70 (d, J = 7.3 Hz, 2H), 1.31 (br s, 2H), 1.25 (t, J = 7.2 Hz, 3H). 202 MS m/z 408.3 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.59 (br s, 1H), 8.91 (br s, 1H), 8.51 (br s, 1H), 8.25 (d, J = 13.1 Hz, 1H), 7.82 (br s, 1H), 7.74 (d, J = 12.4 Hz, 1H), 4.30 (br s, 3H), 3.68 (d, J = 9.3 Hz, 2H), 3.20 (br s, 3H), 3.08 (br s, 2H), 2.28 (d, J = 14.8 Hz, 2H), 1.99-2.12 (m, 2H), 1.35-1.44 (t, J = 7.2 Hz, 3H).

Example 29

(573) Preparation of Compound 108

(574) ##STR00142## ##STR00143##

(575) Step A: 1-Bromo-2,3-difluoro-5-nitrobenzene (10.0 g, 42.0 mmol, prepared in Example 7, Step A) was combined with tert-butyl 4-(3-ethoxy-3-oxo-propanoyl)piperidine-1-carboxylate (13.8 g, 46.2 mmol) in DMF (100 mL). To the solution was added Cs.sub.2CO.sub.3 (27.4 g, 84.0 mmol). The mixture turned dark red upon addition. The mixture was stirred at 60° C. for 4 h. The mixture was partitioned between EtOAc and aqueous 0.5 M HCl. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated to yield tert-butyl 4-[2-(2-bromo-6-fluoro-4-nitro-phenyl)-3-ethoxy-3-oxo-propanoyl]piperidine-1-carboxylate (21.5 g) as a crude oil. MS m/z 515.5, 517.5 [M−H].sup.−.

(576) Step B: The crude material from Step A was suspended in AcOH (40 mL) and conc. aqueous HCl (37 mass %, 40 mL). The mixture was heated at 120° C. for 4 h, then 100° C. for 16 h. Volatiles were removed under reduced pressure. The residue was dissolved in MeOH (100 mL) and triethylamine (23.4 mL, 168.0 mmol). To the mixture was added di-tert-butyl dicarbonate (13.7 g, 63.0 mmol). The mixture was stirred at room temperature for 30 min. The volatile material was removed from the mixture under reduced pressure. The residue was chromatographed on silica gel, eluting with 0-20% EtOAc in CH.sub.2Cl.sub.2 to yield tert-butyl 4-[2-(2-bromo-6-fluoro-4-nitro-phenyl)acetyl]piperidine-1-carboxylate (10.2 g, 55%). MS m/z 443.5, 445.5 [M−H].sup.−.

(577) Step C: tert-Butyl 4-[2-(2-bromo-6-fluoro-4-nitro-phenyl)acetyl]piperidine-1-carboxylate (10 g, 22.5 mmol) was combined with Zn (73.2, 112 mmol), NH.sub.4Cl (24.1 g, 450 mmol) and MeOH (100 mL). The mixture was stirred at 40° C. for 3 h. The mixture was diluted with EtOAc and filtered through celite. The filtrate was concentrated to yield tert-butyl 4-[2-(4-amino-2-bromo-6-fluoro-phenyl)acetyl]piperidine-1-carboxylate (9.5 g, 100%). MS m/z 315.2, 317.2 [M-

Boc+H].sup.+.
(578) Step D: tert-Butyl 4-[2-(4-amino-2-bromo-6-fluoro-phenyl)acetyl]piperidine-1-carboxylate (9.5 g, 23 mmol) was combined with CuCl (4.6 g, 46 mmol), CuCl.sub.2 (9.3 g, 69 mmol) and CH.sub.3CN (100 mL). To the mixture was added isoamyl nitrite (9.3 mL, 69 mmol) dropwise at 0° C. The mixture was stirred at 60° C. for 2 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-40% EtOAc in hexanes to yield tert-butyl 4-[2-(2-bromo-4-chloro-6-fluoro-phenyl)acetyl]piperidine-1-carboxylate (7.5 g, 75% Yield). .sup.1H NMR (acetone-d.sub.6) H: 7.56 (t, J=1.7 Hz, 1H), 7.34 (dd, J=9.1, 1.9 Hz, 1H), 4.15 (d, J=1.9 Hz, 2H), 4.11 (br d, J=12.0 Hz, 2H), 2.78-2.96 (m, 3H), 1.98 (br d, J=12.3 Hz, 2H), 1.48-1.58 (m, 2H), 1.46 (s, 9H).
(579) Step E: tert-Butyl 4-[2-(2-bromo-4-chloro-6-fluoro-phenyl)acetyl]piperidine-1-carboxylate (7.5 g, 17 mmol) was combined benzoyl hydrazide (3.6 g, 26 mmol), CuI (0.32 g, 1.7 mmol), 1,10-phenanthroline (0.31 g, 1.7 mmol) and sodium tert-butoxide (3.36 g, 35 mmol) in DMF (50 mL). The mixture was stirred under N.sub.2 at 70° C. for 1 h. The mixture was partitioned between EtOAc and 0.25 M HCl (aq). The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-40% EtOAc in hexanes to yield tert-butyl 4-(1-benzoyl-7-chloro-5-fluoro-2H-cinnolin-3-yl)piperidine-1-carboxylate (6.4 g, 79%). MS m/z 470.6, 472.6 [M−H].sup.−.
(580) Step F: tert-Butyl 4-(1-benzoyl-7-chloro-5-fluoro-2H-cinnolin-3-yl)piperidine-1-carboxylate (6.2 g, 13 mmol) was suspended in conc. aqueous HCl (37 mass %, 30 mL) and EtOH (20 mL). The mixture was heated at 100° C. for 24 h. The mixture was cooled to 60° C. Air was bubbled through the mixture for 5 h. The volatile material was removed with a stream of N.sub.2. To the crude residue was added MeOH (50 mL), triethylamine (7.4 mL, 53 mmol) and then di-tert-butyl dicarbonate (5.7 g, 26 mmol). The mixture was stirred at room temperature for 30 min. The volatiles were removed under reduced pressure. The residue was chromatographed on silica gel, eluting with 0-60% EtOAc in hexanes to yield tert-butyl 4-(7-chloro-5-fluoro-cinnolin-3-yl)piperidine-1-carboxylate (3.0 g, 62%).
(581) MS m/z 310.2, 312.2 [M-tBu+H].sup.+. .sup.1H NMR (acetone-d.sub.6) δ: 8.38 (s, 1H), 8.09 (s, 1H), 7.71 (dd, J=9.5, 1.9 Hz, 1H), 4.26-4.38 (m, 2H), 3.49 (tt, J=12.0, 3.7 Hz, 1H), 3.00 (br s, 2H), 2.10-2.15 (m, 2H) 1.95 (qd, J=12.6, 4.4 Hz, 2H), 1.49 (s, 9H).
(582) Step G: Powdered tert-butyl 4-(7-chloro-5-fluoro-cinnolin-3-yl)piperidine-1-carboxylate (1.00 g, 2.73 mmol) was weighed into a 50-mL screw-cap tube, followed by anhydrous 1,4-dioxane (27 mL), followed by (Bpin).sub.2 (0.76 g, 3.0 mmol), SPhos Pd G2 pre-catalyst (0.20 g, 0.27 mmol), and powdered potassium acetate (1.02 g, 10.4 mmol) last. The yellow mixture was then sparged for 2 minutes with argon, the headspace was purged, and the vial was capped and sealed tightly. The vial was placed in an aluminum heating block and stirred vigorously at 90° C. for 3 h. After this time, the reaction mixture was cooled to room temperature. The dark-brown reaction mixture was filtered through Celite. The Celite was washed with EtOAc (60 mL). The brown filtrate was then washed with water (60 mL), 50% aq. NaHCO.sub.3 (2×60 mL), and brine (60 mL), then dried over anhydrous Na.sub.2SO.sub.4, filtered, and concentrated under reduced pressure to afford tert-butyl 4-[5-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cinnolin-3-yl]piperidine-1-carboxylate as a crude, dark brown powder without further purification.
(583) MS m/z 490.5 [M+MeOH+H].sup.+; .sup.1H NMR (chloroform-d) δ: ppm 8.84 (s, 1H), 7.87 (s, 1H), 7.72 (d, J=9.5 Hz, 1H), 4.37 (br s, 2H), 3.45 (It, 1H), 2.98 (br s, 2H), 2.16 (br d, J=13.6 Hz, 2H), 1.93 (qd, J=12.6, 4.0, 2H), 1.52 (s, 12H), 1.42 (s, 9H).
(584) Step H: A screw-top vial was charged with solid 6-chloro-2-methyl-imidazo[1,2-b]pyridazine-8-carbonitrile (0.14 g, 0.72 mmol) and anhydrous 1,4-dioxane (6.56 mL), followed by tert-butyl 4-[5-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cinnolin-3-yl]piperidine-1-carboxylate (0.30 g, 0.66 mmol), SPhos Pd G2 pre-catalyst (0.047 g, 0.065 mmol), granular

K.sub.2CO.sub.3 (0.27 g, 1.96 mmol), and water (0.33 mL). The brown mixture was sparged with argon for 5 minutes, then sealed with a screw cap. The reaction mixture was stirred vigorously at 90° C. for 3 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (100 mL), washed with water (2×100 mL) and brine (100 mL), then dried over anhydrous Na.sub.2SO.sub.4, filtered, and concentrated under reduced pressure. The dark-brown, crude material was purified by silica gel column chromatography (hexanes/EtOAc gradient elution) to afford tert-butyl 4-[7-(8-cyano-2-methyl-imidazo[1,2-b]pyridazin-6-yl)-5-fluoro-cinnolin-3-yl]piperidine-1-carboxylate (0.182 g, 57%) as a yellow powder.

(585) MS m/z 488.5 [M+H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.87 (s, 1H), 8.18 (d, J=10.2 Hz, 1H), 8.03 (s, 1H), 8.00 (s, 1H), 7.91 (s, 1H), 4.37 (br d, J=5.6 Hz, 2H), 3.49 (tt, J=12.0, 3.4 Hz, 1H), 2.98 (br t, J=12.2 Hz, 2H), 2.63 (s, 3H), 2.16 (br d, J=12.5 Hz, 2H), 1.93 (qd, J=12.6, 4.0 Hz, 2H), 1.50 (s, 9H).

(586) Step I: tert-Butyl 4-[7-(8-cyano-2-methyl-imidazo[1,2-b]pyridazin-6-yl)-5-fluoro-cinnolin-3-yl]piperidine-1-carboxylate (0.060 g, 0.12 mmol) was dissolved in anhydrous 1,4-dioxane (4 mL), and a 4.0 M solution of HCl in 1,4-dioxane (0.15 mL, 0.60 mmol) was added. The reaction mixture was stirred at room temperature for 4 h, after which time the reaction mixture was concentrated on a rotovap. The crude product was triturated in Et.sub.2O (5 mL), then dried under high vacuum to afford 6-[5-fluoro-3-(4-piperidyl)cinnolin-7-yl]-2-methyl-imidazo[1,2-b]pyridazine-8-carbonitrile hydrochloride (0.060 g, 100%) as a tan solid.

(587) MS m/z 388.4 [M+H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.11 (s, 1H), 8.81 (s, 1H), 8.42 (d, J=11.3 Hz, 1H), 8.37 (s, 1H), 8.30 (s, 1H), 3.58-3.77 (m, 5H), 2.63 (s, 3H), 2.21-2.47 (m, 4H).

(588) Using the procedure described for Example 29, above, additional compounds described herein were prepared by substituting the appropriate aryl halide in Step H, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

(589) TABLE-US-00024 Cpd Data 91 MS m/z 363.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.77 (d, J = 2.4 Hz, 1H), 9.54 (d, J = 2.1 Hz, 1H), 8.84 (s, 1H), 8.35 (s, 1H), 8.16 (d, J = 9.2 Hz, 1H), 8.08 (s, 1H), 3.61- 3.70 (m, 3H), 3.28-3.37 (m, 2H), 2.67 (s, 3H), 2.31-2.44 (m, 4H), NH and HCl protons not observed. 92 MS m/z 380.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.27 (d, J = 1.2 Hz, 1H), 8.78 (s, 1H), 8.46 (dd, J = 11.0, 1.2 Hz, 1H), 8.31 (s, 1H), 8.21 (s, 1H), 8.12 (dd, J = 10.4, 1.5 Hz, 1H), 3.59-3.69 (m, 3H), 3.27-3.37 (m, 2H), 2.66 (d, J = 0.9 Hz, 3H), 2.32-2.45 (m, 4H), NH and HCl protons not observed. 93 MS m/z 387.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.61 (d, J = 1.5 Hz, 1H), 9.01 (d, J = 1.5 Hz, 1H), 8.80 (s, 1H), 8.31 (s, 1H), 8.21 (d, J = 1.2 Hz, 1H), 8.13 (dd, J = 10.5, 1.7 Hz, 1H), 3.60-3.70 (m, 3H), 3.28-3.36 (m, 2H), 2.66 (d, J = 0.9 Hz, 3H), 2.31- 2.45 (m, 4H), NH and HCl protons not observed. 94 MS m/z 363.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.47 (s, 1H), 8.75 (s, 1H), 8.44 (br d, J = 9.5 Hz, 1H), 8.29 (s, 1H), 8.15 (dd, J = 10.7, 1.5 Hz, 1H), 7.99 (d, J = 9.5 Hz, 1H), 3.60-3.69 (m, 3H), 3.25-3.37 (m, 2H), 2.69 (s, 3H), 2.30-2.44 (m, 4H), NH and HCl protons not observed. 95 MS m/z 362.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.61 (s, 2H), 8.47 (s, 1H), 8.40 (s, 1H), 8.19 (dd, J = 10.7, 1.2 Hz, 1H), 8.03 (dd, J = 9.0, 1.7 Hz, 1H), 7.87 (d, J = 9.2 Hz, 1H), 4.36 (s, 3H), 3.62-3.70 (m, 3H), 2.39-2.46 (m, 2H), 2.28-2.39 (m, 2H), NH and HCl protons not observed; CH.sub.2 obscured by solvent peak. 96 MS m/z 380.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.99 (s, 1H), 8.51 (d, J = 17.4 Hz, 2H), 8.32 (d, J = 10.7 Hz, 1H), 8.18 (s, 1H), 7.59 (d, J = 12.2 Hz, 1H), 4.25 (s, 3H), 3.72 (t, J = 10.1 Hz, 1H), 3.61 (d, J = 12.2 Hz, 2H), 3.28-3.32 (m, 2H), 2.22-2.47 (m, 4H), NH and HCl protons not observed. 97 MS m/z 380.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.06 (s, 1H), 8.84 (s, 1H), 8.60 (s, 1H), 8.41 (br d, J = 7.0 Hz, 1H), 8.22 (br d, J = 10.1 Hz, 1H), 7.66 (d, J = 11.3 Hz, 1H), 4.40 (s, 3H), 3.82 (t, J = 10.4 Hz, 1H), 3.68 (d, J = 12.5 Hz, 2H), 3.35-3.42 (m, 2H), 2.47 (d, J = 11.9 Hz, 2H), 2.33-2.44 (m, 2H), NH and HCl protons not observed. 99 MS m/z 363.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.14 (s, 1H), 8.59 (d, J = 9.8 Hz, 1H), 8.47 (d, J = 10.1 Hz, 1H), 8.44 (dd, J =

10.7, 1.5 Hz, 1H), 8.41 (s, 1H), 8.31 (s, 1H), 3.60-3.70 (m, 3H), 3.30-3.35 (m, 2H), 2.67 (d, J = 0.9 Hz, 3H), 2.31-2.43 (m, 4H), NH and HCl protons not observed. 101 MS m/z 376.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.84 (d, J = 1.2 Hz, 1H), 8.81 (s, 1H), 8.39 (s, 2H), 8.29 (s, 1H), 8.21 (dd, J = 10.4, 1.2 Hz, 1H), 3.62-3.67 (m, 3H), 3.28-3.33 (m, 2H), 3.04 (s, 3H), 2.55 (s, 3H), 2.30-2.43 (m, 4H), NH and HCl protons not observed. 103 MS m/z 376.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.21 (s, 1H), 8.75 (s, 1H), 8.27- 8.39 (m, 2H), 8.12 (d, J = 10.6 Hz, 1H), 8.08 (s, 1H), 3.62-3.69 (m, 3H), 3.29-3.36 (m, 2H), 2.78 (s, 3H), 2.65 (s, 3H), 2.30-2.45 (m, 4H), NH and HCl protons not observed. 104 MS m/z 387.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.67 (d, J = 1.5 Hz, 1H), 8.64 (s, 1H), 8.64 (br s, 1H), 8.63 (br s, 1H), 8.42 (d, J = 1.5 Hz, 1H), 8.25 (br d, J = 10.1 Hz, 1H), 4.36 (s, 3H), 3.69-3.75 (m, 1H), 3.66 (d, J = 12.8 Hz, 2H), 2.42 (d, J = 12.5 Hz, 2H), 2.35 (qd, J = 12.8, 3.4 Hz, 2H), NH and HCl protons not observed, CH.sub.2 obscured by solvent peak. 105 MS m/z 391.2 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.86 (s, 1H), 8.23 (dd, J = 10.8, 1.5 Hz, 1H), 7.92 (s, 1H), 7.81 (d, J = 0.7 Hz, 1H), 7.53 (s, 1H), 3.42-3.52 (m, 1H), 3.33 (br d, J = 12.2 Hz, 2H), 3.20 (q, J = 7.6 Hz, 2H), 2.87-2.96 (m, 2H), 2.56 (s, 3H), 2.14-2.22 (m, 2H), 1.92 (dq, J = 11.2, 4.2 Hz, 2H), 1.51 (t, J = 7.6 Hz, 3H), NH proton not observed. 106 MS m/z 393.1 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.18 (s, 1H), 8.39 (dd, J = 11, 1.5 Hz, 1H), 8.16 (s, 1H), 8.09 (d, J = 0.7 Hz, 1H), 7.56 (s, 1H), 4.22 (s, 3H), 3.47-3.56 (m, 3H), 3.01-3.09 (m, 2H), 2.39 (s, 3H), 2.07-2.24 (m, 4H), NH proton not observed. 107 MS m/z 393.1 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.93 (s, 1H), 8.32 (d, J = 11 Hz, 1H), 8.19 (s, 1H), 8.13 (s, 1H), 7.99 (s, 1H), 5.77 (br s, 1H), 4.99 (s, 2H), 3.12-3.20 (m, 3H), 2.71-2.80 (m, 2H), 2.43 (s, 3H), 1.96-2.03 (m, 2H), 1.82-1.96 (m, 2H), NH proton not observed. 109 MS m/z 380.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.22 (s, 1H), 8.75 (s, 1H), 8.60 (s, 1H), 8.31 (d, J = 10.4 Hz, 1H), 7.82 (t, J = 8.2 Hz, 1H), 7.68 (d, J = 8.9 Hz, 1H), 4.37 (s, 3H), 3.85 (t, J = 11.3 Hz, 1H), 3.68 (d, J = 12.2 Hz, 2H), 3.34-3.42 (m, 2H), 2.48 (d, J = 12.8 Hz, 2H), 2.39 (q, J = 11.8 Hz, 2H), NH and HCl protons not observed. 112 MS m/z 403.1 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.78 (s, 1H), 8.22 (d, J = 12 Hz, 1H), 7.90 (s, 1H), 7.80 (s, 1H), 7.10 (s, 1H), 3.33-3.49 (m, 1H), 3.31 (d, J = 12.4 Hz, 2H), 2.90 (t, J = 12.2 Hz, 2H), 2.70-2.74 (m, 1H), 2.56 (s, 3H), 2.17 (d, J = 12.4 Hz, 2H), 1.85-1.92 (m, 2H), 1.25-1.38 (m, 2H), 1.22-1.25 (m, 2H), NH proton not observed. 118 MS m/z 393.1 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.59 (s, 1H), 8.03 (d, J = 1.2 Hz, 1H), 7.91 (s, 1H), 7.74 (dd, J = 10.4, 1.2 Hz, 1H), 7.63 (s, 1H), 3.43-3.50 (m, 3H), 3.01 (t, J = 12 Hz, 2H), 2.90 (s, 3H), 2.83 (s, 3H), 2.25 (d, J = 13.2 Hz, 2H), 2.03- 2.06 (m, 2H), NH proton not observed. 126 MS m/z 377.2 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.13 (s, 1H), 8.41 (d, J = 10.5 Hz, 1H), 8.11 (s, 1H), 7.33 (s, 1H), 3.43 (s, 2H), 3.24 (s, 1H), 3.16 (d, J = 12.0 Hz, 2H), 2.78 (s, 3H), 2.55 (s, 3H), 2.05-1.82 (m, 4H), NH protons not observed. 133 MS m/z 394.1 [M + H].sup.+; .sup.1H NMR (melhanol-d.sub.4) δ: 9.03 (s, 1H), 8.47 (dd, J = 11.2, 1.6 Hz, 1H), 8.24 (s, 1H), 8.22 (s, 1H), 3.59-3.63 (m, 3H), 3.24-3.28 (m, 2H), 2.92 (s, 3H), 2.85 (s, 3H), 2.29-2.37 (m, 4H), NH proton observed. 137 MS m/z 378.0 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.00 (s, 1H), 8.29 (d, J = 9.8 Hz, 1H), 8.16 (s, 1H), 7.63 (s, 1H), 3.22-3.31 (m, 1H), 3.14 (d, J = 11.9 Hz, 2H), 2.76 (s, 3H), 2.71 (d, J = 11.0 Hz, 2H), 2.60 (s, 3H), 1.97-2.00 (m, 2H), 1.82-1.93 (m, 2H). 148 MS m/z 378.1 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.91 (s, 1H), 8.54 (dd, J = 11, 1.6 Hz, 1H), 7.89 (s, 2H), 3.42-3.48 (m, 1H), 3.33 (br d, J = 12 Hz, 2H), 2.89-2.95 (m, 2H), 2.73 (s, 6H), 2.16-2.19 (m, 2H), 1.92-1.96 (m, 2H), NH proton not observed. 148 MS m/z 394.1 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.89 (s, 1H), 8.33 (dd, J = 10, 1.2 Hz, 1H), 7.91 (s, 1H), 7.59 (s, 1H), 3.44-3.50 (m, 1H), 3.33 (d, J = 12.4 Hz, 2H), 3.04 (s, 3H), 2.89-2.95 (m, 2H), 2.68 (s, 3H), 2.18 (d, J = 12.4 Hz, 2H), 1.90-1.94 (m, 2H), NH proton not observed. 162 MS m/z 377.1 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.89 (s, 1H), 8.38 (dd, J = 9.6, 1.2 Hz, 1H), 8.24 (s, 1H), 7.91 (s, 1H), 7.79 (s, 1H), 4.32 (s, 3H), 3.38-3.51 (m, 3H), 2.94-3.00 (m, 2H), 2.78 (s, 3H), 2.21-2.24 (m, 2H), 1.97-2.07 (m, 2H), NH proton not observed. 163 MS m/z 393.1 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.88 (s, 1H), 8.42 (dd, J = 10.8, 1.2 Hz, 1H), 8.20 (s, 1H), 7.97 (s, 1H), 7.31 (s,

1H), 4.29 (s, 3H), 4.23 (s, 3H), 3.57- 3.62 (m, 3H), 3.05-3.15 (m, 4H), 2.31-2.36 (m, 2H), NH proton not observed. 172 MS m/z 391.2 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.06 (s, 1H), 8.74 (s, 1H), 8.44-8.57 (m, 1H), 8.08 (d, J = 12.9 Hz, 2H), 4.26 (s, 3H), 3.03-3.20 (m, 4H), 2.95 (d, J = 7.9 Hz, 1H), 2.71 (t, J = 11.6 Hz, 2H), 1.97 (d, J = 11.9 Hz, 2H), 1.85 (qd, J = 12.3, 3.9 Hz, 2H), 1.44 (t, J = 7.6 Hz, 3H). 187 MS m/z 402.2 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.94 (s, 1H), 8.62 (br s, 1H); 8.23 (dd, J = 10.4, 1.2 Hz, 1H), 7.99 (s, 1H), 7.90 (s, 1H), 7.86 (s, 1H), 4.32 (s, 2H), 3.56- 3.60 (m, 3H), 3.11 (br s, 2H), 2.56 (s, 3H), 2.26-2.35 (m, 4H). 194 MS m/z 429.1 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.29 (s, 1H), 9.15 (s, 1H) 8.55 (br s, 2H), 8.27-8.28 (m, 2H), 8.19 (s, 1H), 7.33 (s, 1H), 3.60-3.64 (m, 3H), 3.25-3.29 (m, 2H), 2.58 (s, 3H), 2.30-2.41 (m, 4H), NH proton not observed. 195 MS m/z 455.2 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.59 (s, 1H), 8.25 (dd, J = 10.8, 1.2 Hz, 1H), 8.21 (s, 1H), 8.09 (s, 1H), 7.61-7.65 (m, 2H), 7.42-7.49 (m, 3H), 6.96 (s, 1H), 3.59-3.63 (m, 3H), 3.25-3.28 (m, 2H), 2.55 (s, 3H), 2.27-2.38 (m, 4H), NH proton not observed. 196 MS m/z 394.0 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.00 (s, 1H), 8.30-8.48 (m, 2H), 8.17 (s, 1H), 7.80 (s, 1H), 3.44-3.51 (m, 1H), 3.33 (d, J = 10.2 Hz, 2H), 2.89-3.00 (m, 2H), 2.75 (s, 3H), 2.60 (s, 3H), 2.00-2.17 (m, 4H). 204 MS m/z 405.2 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.93 (s, 1H), 8.33 (dd, J = 10.9, 1.3 Hz, 1H), 8.20 (s, 1H), 8.01 (d, J = 0.6 Hz, 1H), 7.86 (s, 1H), 3.43-3.50 (m, 2H), 3.26- 3.31 (m, 1H), 3.09 (t, J = 8 Hz, 2H), 2.91-2.98 (m, 2H), 2.53 (s, 3H), 2.17 (d, J = 12.2 Hz, 2H), 1.90-2.08 (m, 4H), 1.12 (t, J = 7.4 Hz, 3H), NH proton not observed. 207 MS m/z 407.2 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.05 (s, 1H), 8.42 (dd, J = 10.8, 1.2 Hz, 1H), 8.28 (s, 1H), 8.15 (s, 1H), 8.10 (s, 1H), 4.10 (t, J = 6 Hz, 2H), 3.63-3.66 (br s, 3H), 3.35-3.36 (m, 2H), 3.28-3.32 (m, 2H), 2.58 (s, 3H), 2.32-2.42 (m, 4H), NH and OH protons not observed. 211 MS m/z 405.2 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.94 (s, 1H), 8.33 (dd, J = 10.9, 1.3 Hz, 1H), 8.19 (s, 1H), 8.01 (d, J = 0.7 Hz, 1H), 7.82 (s, 1H), 3.74-3.67 (m, 1H), 3.48- 3.44 (m, 1H), 3.36 (s, 2H), 2.97 (td, J = 12.5, 2.6 Hz, 2H), 2.53 (s, 3H), 2.19 (d, J = 12.7 Hz, 2H), 3.01-2.94 (m, 2H), 1.53 (d, J = 6.9 Hz, 6H). NH proton not observed.

Halides for use in Step H were prepared according to the following procedures:

Example 29-1

8-(((tert-Butyldimethylsilyl)oxy)methyl)-6-chloro-2-methylimidazo[1,2-b]pyridazine

(590) Step A: To ethyl 3-amino-6-chloropyridazine-4-carboxylate (4.0 g, 19.9 mmol) in dry THF (1 mL) was slowly added LiAlH4 (2.42 g, 64 mmol) at 0° C. The mixture was stirred at 0° C. for 30 min. Excess reagent was quenched carefully with water (1 mL), then 15% aqueous NaOH (1 mL) was added. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-35% EtOAc in petroleum ether to yield (3-amino-6-chloropyridazin-4-yl) methanol (1.0 g, 32%). MS m/z 160.1, 162.1 [M+H].sup.+.

(591) Step B: (3-Amino-6-chloropyridazin-4-yl)methanol (1.0 g, 6.3 mmol) was combined with DIEA (2.44 g, 18.8 mmol) and 1-bromopropan-2-one (860 mg, 6.3 mmol) in isopropyl alcohol (10 mL). The reaction vessel was degassed and then charged with nitrogen three times. The mixture was stirred at 80° C. for 16 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-50% EtOAc in petroleum ether to yield (6-chloro-2-methylimidazo[1,2-b]pyridazin-8-yl)methanol (0.9 g, 73%). MS m/z 198.2, 200.2 [M+H].sup.+.

(592) Step C: (6-chloro-2-methylimidazo[1,2-b]pyridazin-8-yl)methanol (900 mg, 4.5 mmol) was combined with TBS-Cl (1.72 g, 9.1 mmol) and imidazole (1.24 g, 14.6 mmol) in CH.sub.2Cl.sub.2 (15 mL). The mixture was stirred at room temperature for 16 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-20% EtOAc in petroleum ether to yield 8-(((tert-butyldimethylsilyl)oxy)methyl)-6-

chloro-2-methylimidazo[1,2-b]pyridazine (500 mg, 35.2% yield). MS m/z 312.1, 314.1 [M+H].sup.+.

Example 29-2

6-Chloro-8-ethyl-2-methylimidazo[1,2-b]pyridazine

(593) Step A: 6-Chloropyridazin-3-amine (50 g, 388 mmol) and NaHCO.sub.3 (65 g, 775 mmol) were combined in MeOH (500 mL). To the mixture was added Br.sub.2 (30 mL, 580 mmol) dropwise at 0° C. The mixture was stirred at room temperature for 16 h. One half of the volume of solvent was removed under reduced pressure. The remaining was poured into ice water. The solid formed was collected and dried to yield 4-bromo-6-chloropyridazin-3-amine (80 g, 99%). MS m/z 207.9 [M+H].sup.+.

(594) Step B: 4-Bromo-6-chloropyridazin-3-amine (20 g, 97 mmol), Na.sub.2CO.sub.3 (10.2 g, 97 mmol) and 1-bromopropan-2-one (9.7 mL, 116 mmol) were added into isopropyl alcohol (200 mL). The reaction vessel was degassed and then charged with nitrogen three times. The mixture was stirred at 90° C. for 16 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-20% EtOAc in petroleum ether to yield 8-bromo-6-chloro-2-methylimidazo[1,2-b]pyridazine (8.1 g, 34%). MS m/z 245.9, 247.9 [M+H].sup.+.

(595) Step C: 8-Bromo-6-chloro-2-methylimidazo[1,2-b]pyridazine (200 mg, 0.82 mmol) was combined with triethylborane (1M in THF, 2 mL, 2 mmol), K.sub.2CO.sub.3 (283 mg, 2.05 mmol) and Pd(PPh.sub.3).sub.4 (92 mg, 0.08 mmol) in DMF (3 mL). The reaction vessel was degassed and then charged with nitrogen three times. The mixture was stirred at 100° C. for 5 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-35% EtOAc in petroleum ether to yield 6-chloro-8-ethyl-2-methylimidazo[1,2-b]pyridazine (80 mg, 50%). MS m/z 196.0, 198.0 [M+H].sup.+.

Example 29-3

6-Chloro-8-cyclopropyl-2-methylimidazo[1,2-b]pyridazine

(596) A mixture of 8-bromo-6-chloro-2-methylimidazo[1,2-b]pyridazine (1.2 g, 4.9 mmol), cyclopropylboronic acid (843 mg, 9.8 mmol), Pd(dppf)Cl.sub.2 (359 mg, 0.49 mmol) and Na.sub.2CO.sub.3 (1.56 g, 14.7 mmol) in 1,4-dioxane (12 mL) and water (3 mL) was stirred at 90° C. under N.sub.2 for 48 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-35% EtOAc in petroleum ether to yield 6-chloro-8-cyclopropyl-2-methylimidazo[1,2-b]pyridazine (405 mg, 40%). MS m/z 208.0, 210.0 [M+H].sup.+.

Example 29-4

6-Chloro-2-methylimidazo[1,2-b]pyridazine-8-carbonitrile

(597) 8-Bromo-6-chloro-2-methylimidazo[1,2-b]pyridazine (1.2 g, 4.9 mmol) was combined with Zn(CN).sub.2 (850 mg, 7.3 mmol) and Pd(PPh.sub.3).sub.4 (570 mg, 0.49 mmol) in DMF (20 mL). The reaction vessel was degassed and then charged with nitrogen three times. The mixture was stirred at 100° C. for 1 h under μwave irradiation. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-35% EtOAc in petroleum ether to yield 6-chloro-2-methylimidazo[1,2-b]pyridazine-8-carbonitrile (0.5 g, 53%). MS m/z 193.0, 195.0 [M+H].sup.+.

Example 29-5

6-bromo-2,4-dimethylbenzo[d]thiazole

(598) Step A: 2,4-Dibromo-6-methylaniline (3.8 g, 14.5 mmol) was combined with KOAc (1.56 g, 15.9 mmol) and acetic anhydride (5.5 mL, 58 mmol) in toluene (40 mL). The mixture was stirred at

room temperature for 16 h. The solvent was removed in vacuo. The residue was chromatographed on silica gel, eluting with 0-35% EtOAc in petroleum ether to yield N-(2,4-dibromo-6-methylphenyl)acetamide (3.9 g, 82%). MS m/z 305.9, 308.0 [M+H].sup.+.
(599) Step B: N-(2,4-Dibromo-6-methylphenyl)acetamide (4.0 g, 13 mmol) was combined with Lawesson's reagent (10.6 g, 26 mmol) in toluene (40 mL). The mixture was stirred at 110° C. for 16 h. The solvent was removed in vacuo. The residue was chromatographed on silica gel, eluting with 0-35% EtOAc in petroleum ether to yield N-(2,4-dibromo-6-methylphenyl)ethanethioamide (3.9 g, 93%). MS m/z, 322.9, 324.9 [M+H].sup.+.
(600) Step C: N-(2,4-Dibromo-6-methylphenyl)ethanethioamide (3.8 g, 11.8 mmol) was dissolved in NMP (40 mL). To the solution was added NaH (94.7 mg, 2.4 mmol) in portions at room temperature. The reaction vessel was degassed and then charged with nitrogen three times. The mixture was stirred at 120° C. for 2 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-25% EtOAc in petroleum ether to yield 6-bromo-2,4-dimethylbenzo[d]thiazole (369 mg, 12%). MS m/z 241.9, 243.9 [M+H].sup.+.
Example 29-6
5-Chloro-2,7-dimethyl-3-((2-(trimethylsilyl)ethoxy)methyl)-3H-imidazo[4,5-b]pyridine
(601) Step A: 6-Chloro-4-methyl-3-nitropyridin-2-amine (187 mg, 1 mmol), iron powder (56 mg, 10 mmol) in AcOH (3 mL) was stirred at 100° C. for 16 h. The mixture was concentrated. To the residue was added aqueous NaOH (2 N) until pH>9. The mixture was filtered through Celite. The filtrate was extracted with EtOAc (50 mL×3). The organic layer was washed with brine, dried over Na.sub.2SO.sub.4 and concentrated to afford 5-chloro-2,7-dimethyl-3H-imidazo[4,5-b]pyridine, which was used without further purification (154 mg crude, 85% crude). MS m/z 182.0, 184.0 [M+H].sup.+.
(602) Step B: 5-Chloro-2,7-dimethyl-3H-imidazo[4,5-b]pyridine (1.1 g, 6.07 mmol) was dissolved in THF (30 mL). To the mixture was added NaH (310 mg, 7.9 mmol) in portions at 0° C. After stirring the mixture at 0° C. for 10 min, 2-(trimethylsilyl)ethoxymethyl chloride (1.2 mL, 6.69 mmol) was added. The resulting mixture was stirred at room temperature for 2 h. MeOH (10 mL) was added to the solution, after which all volatile material was removed under reduced pressure. The residue was chromatographed on silica gel, eluting with 25% EtOAc in petroleum ether to afford a mixture of N-alkylated products, which was used without separation (900 mg, 76%). MS m/z 312.0, 314.0 [M+H].sup.+.
Example 29-7
5-Chloro-2,7-dimethyloxazolo[5,4-b]pyridine
(603) Step A: A solution of 2,6-dichloro-4-methylnicotinonitrile (3 g, 16 mmol) in H.sub.2SO.sub.4 (15 mL) was stirred at 80° C. for 4 h. The mixture was cooled to room temperature, and then poured into ice water (100 mL). The suspension was filtered. The filter cake was washed with water to afford 2,6-dichloro-4-methylnicotinamide (3.2 g, 91%) as a yellow solid. MS m/z 204.9, 206.9 [M+H].sup.+.
(604) Step B: To a solution of NaOH (3.7 g, 93 mmol) in H.sub.2O (100 mL) was added Br.sub.2 (4.7 g, 29.4 mmol) dropwise at 0° C. The mixture was stirred at 0° C. for 1 h before adding 2,6-dichloro-4-methylnicotinamide (5 g, 24.5 mmol). The mixture was allowed to warm to room temperature gradually over 1 h. The mixture was then heated to 75° C. for 1 h. The resulting suspension was cooled to room temperature with stirring overnight. The suspension was filtered. The collected solid material was washed with water to afford 2,6-dichloro-4-methylpyridin-3-amine (3.3 g, 76%). MS m/z 176.9, 178.9 [M+H].sup.+.
(605) Step C: To a solution of 2,6-dichloro-4-methylpyridin-3-amine (3 g, 17 mmol) in toluene (50 mL) was added KOAc (2 g, 20.4 mmol) and Ac.sub.2O (6.9 g, 68 mmol). The mixture was stirred at 70° C. for 48 h. The mixture was cooled to room temperature, and then poured into ice water (100 mL). The water was extracted with EtOAc (60 mL×3). The combined organic phases were

concentrated under reduced pressure. The residue was chromatographed on silica gel eluting with 25% EtOAc in petroleum ether to afford N-(2,6-dichloro-4-methylpyridin-3-yl) acetamide (842 mg, 22%) as a yellow solid. MS m/z 219.0, 221.0 [M+H].sup.+.

(606) Step D: To a solution of N-(2,6-dichloro-4-methylpyridin-3-yl)acetamide (700 mg, 3.2 mmol) in NMP (10 mL) was added NaH (128 mg, 3.2 mmol) in portions at room temperature. The reaction vessel was degassed and then charged with nitrogen three times. The mixture was stirred at 120° C. for 2 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-25% EtOAc in petroleum ether to yield 5-chloro-2,7-dimethyloxazolo[5,4-b]pyridine (400 mg, 68%). MS m/z 183.1, 185.1 [M+H].sup.+.

Example 29-8

5-Chloro-2,7-dimethylthiazolo[5,4-b]pyridine

(607) N-(2,6-dichloro-4-methylpyridin-3-yl)acetamide (1.6 g, 7.3 mmol) was combined with Lawesson's reagent (5.93 g, 14.7 mmol) in toluene (20 mL). The mixture was stirred at 110° C. for 16 h. The solvent was removed under reduced pressure. The residue was chromatographed on silica gel, eluting with 0-35% EtOAc in petroleum ether to yield 5-chloro-2,7-dimethylthiazolo[5,4-b]pyridine (500 mg, 34.4% yield). MS m/z 199.0, 201.0 [M+H].sup.+.

Example 29-9

2-Bromo-4,6-dimethyloxazolo[4,5-c]pyridine

(608) Step A: 2,6-Dimethylpyridin-4-ol (3 g, 24.3 mmol) was added in portions to conc. HNO.sub.3 (11 mL). Conc. H.sub.2SO.sub.4 (16 mL) was then added slowly while keeping the temperature below 20° C. The mixture was stirred at room temperature for 3 h. The mixture was then slowly poured onto ice and neutralized with K.sub.2CO.sub.3. The mixture was extracted with CH.sub.2Cl.sub.2. The organic phases were concentrated under reduced pressure. The residue was chromatographed on silica gel, eluting with 10-20% MeOH in CH.sub.2Cl.sub.2 to afford 2,6-dimethyl-3-nitropyridin-4-ol as a white solid (3.69 g, 90%). MS m/z 169.1 [M+H].sup.+.

(609) Step B: A mixture of 2,6-dimethyl-3-nitropyridin-4-ol (1.68 g, 10 mmol) and 10% Pd/C (106 mg, 0.1 mmol) in MeOH (16 mL) was stirred under H.sub.2 for 16 h. The mixture was filtered over Celite to afford 3-amino-2,6-dimethylpyridin-4-ol as a white solid (1.3 g, 95%). MS m/z 139.0 [M+H].sup.+.

(610) Step C: To a solution of 3-amino-2,6-dimethylpyridin-4-ol (1.38 g, 10 mmol) in EtOH (10 mL) was added cyanogen bromide (1.16 g, 11 mmol) at room temperature. The mixture was stirred at room temperature for 16 h. A precipitate was formed and collected by filtration. The solid material was dried to afford 4,6-dimethyloxazolo[4,5-c]pyridin-2-amine as a white solid (1.2 g, 75%). MS m/z 164.1 [M+H].sup.+.

(611) Step D: To a mixture of 4,6-dimethyloxazolo[4,5-c]pyridin-2-amine (600 mg, 3.7 mmol) and CuBr.sub.2 (2.5 g, 11.1 mmol) in CH.sub.3CN (6 mL) was added t-butylnitrite (1.3 mL, 11.1 mmol) at 0° C. The mixture was stirred at 0° C. for 10 min and then stirred at 55° C. for 2 h. The reaction mixture was made basic with sat. NaHCO.sub.3 and then extracted with EtOAc (200 mL). The organic layer was washed with brine, dried over Na.sub.2SO.sub.4 and concentrated. The residue was chromatographed on silica gel, eluting 10-20% EtOAc in petroleum ether to afford 2-bromo-4,6-dimethyloxazolo[4,5-c]pyridine as a white solid (416 mg, 50% yield). MS m/z 227.0, 229.0 [M+H].sup.+.

Example 29-10

2-Bromo-4,6-dimethylthiazolo[4,5-c]pyridine

(612) Step A: 4-Chloro-2,6-dimethyl-3-nitropyridine (4.7 g, 25 mmol) was combined with Fe powder (4.24 mg, 75 mmol) in AcOH (40 mL). The mixture was stirred at 70° C. for 2 h. The volatile material was removed under reduced pressure. The residue was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-80% EtOAc in

petroleum ether to yield 4-chloro-2,6-dimethylpyridin-3-amine (4.0 g, 99%). MS m/z 157.2, 159.2 [M+H].sup.+.
(613) Step B: 4-Chloro-2,6-dimethylpyridin-3-amine (3.8 g, 24 mmol) was combined with benzoyl isothiocyanate (4.77 g, 29 mmol) in acetone (40 mL) and the mixture was stirred at 56° C. for 2 h. The solvent was removed under reduced pressure. The residue was chromatographed on silica gel, eluting with 0-50% EtOAc in petroleum ether to yield N-(4,6-dimethylthiazolo[4,5-c]pyridin-2-yl)benzamide (6.5 g, 95%). MS m/z 284.2 [M+H].sup.+.
(614) Step C: N-(4,6-Dimethylthiazolo[4,5-c]pyridin-2-yl)benzamide (4.5 g,16 mmol) was combined with NaOH (1.27 g, 32 mmol) in H.sub.2O (10 mL) and MeOH (30 mL). The mixture was stirred at 100° C. for 1 h under μwave irradiation. The volatile material was removed under reduced pressure. The residue was chromatographed on silica gel, eluting with 0-60% EtOAc in petroleum ether to yield 4,6-dimethylthiazolo[4,5-c]pyridin-2-amine (2.7 g, 95%). MS m/z 180.0 [M+H].sup.+.
(615) Step D: 4,6-Dimethylthiazolo[4,5-c]pyridin-2-amine (2.7 g, 15 mmol) was combined with isobutyl nitrite (4.67 g, 45 mmol) and CuBr.sub.2 (16.8 g, 75 mmol) in CH.sub.3CN (30 mL). The mixture was stirred at 50° C. for 0.5 h. The volatile material was removed under reduced pressure. The residue was chromatographed on silica gel, eluting with 0-50% EtOAc in petroleum ether to yield 2-bromo-4,6-dimethylthiazolo[4,5-c]pyridine (1.0 g, 27%). MS m/z 242.9, 245 [M+H].sup.+.
Example 29-11
5-Chloro-2,7-dimethyl-2H-pyrazolo[4,3-b]pyridine
(616) Step A: 6-Chloro-2-methylpyridin-3-amine (40 g, 282 mmol) was combined with AcOH (32 mL) in MeOH (400 mL). To the solution was added Br.sub.2 (26 mL, 507 mmol) dropwise at 0° C. The mixture was stirred at room temperature for 16 h. The volatile material was removed under reduced pressure. The residual reagent was quenched by the addition of aqueous NaHSO.sub.3. The aqueous solution was neutralized with aqueous sat'd NaHCO.sub.3 and extracted with EtOAc. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-20% EtOAc in petroleum ether to yield 4-bromo-6-chloro-2-methylpyridin-3-amine (60 g, 97%). MS m/z 220.9, 222.9 [M+H].sup.+.
(617) Step B: 4-Bromo-6-chloro-2-methylpyridin-3-amine (13 g, 59 mmol) was combined with isobutyl nitrite (9.13 g, 89 mmol), KOAc (13.3 g, 136 mmol) and AcOH (34 ml, 590 mmol) in toluene (130 mL). The mixture was stirred at 60° C. for 10 h. The volatile material was removed under reduced pressure. The residue was treated with aqueous sat'd NaHCO.sub.3. The mixture was diluted with H.sub.2O and extracted with EtOAc. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-30% EtOAc in petroleum ether to yield 7-bromo-5-chloro-2H-pyrazolo[4,3-b]pyridine (3.7 g, 27%). MS m/z 232.0, 234.0 [M+H].sup.+.
(618) Step C: 7-Bromo-5-chloro-2H-pyrazolo[4,3-b]pyridine (3.7 g, 16 mmol) was combined with K.sub.2CO.sub.3 (4.4 g, 32 mmol) and iodomethane (2.7 g, 19 mmol) in DMF (40 mL). The mixture was stirred at room temperature for 1 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-20% EtOAc in petroleum ether to yield 7-bromo-5-chloro-2-methyl-2H-pyrazolo[4,3-b]pyridine (1.5 g, 38%). MS m/z 245.9, 247.9 [M+H].sup.+.
(619) Step D: 7-Bromo-5-chloro-2-methyl-2H-pyrazolo[4,3-b]pyridine (3.0 g, 12 mmol) was combined with 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (5.2 mL, 18 mmol), K.sub.2CO.sub.3 (6.7 g, 49 mmol) and Pd(PPh.sub.3).sub.4 (707 mg, 0.6 mmol) in DMF (30 mL). The reaction mixture was degassed and then charged with nitrogen three times. The mixture was stirred at 100° C. for 5 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-35% EtOAc in petroleum ether to yield 5-chloro-2,7-

dimethyl-2H-pyrazolo[4,3-b]pyridine (1.2 g, 54%). MS m/z 182.0, 184.0 [M+H].sup.+.

Example 29-12

5-Chloro-7-methoxy-2-methyl-2H-pyrazolo[4,3-b]pyridine

(620) 7-Bromo-5-chloro-2-methyl-2H-pyrazolo[4,3-b]pyridine (250 mg, 1.0 mmol) was combined with MeOH (0.2 mL, 5 mmol) and K.sub.2CO.sub.3 (296.7 mg, 2.15 mmol) in CH.sub.3CN (5 mL). The mixture was stirred at room temperature for 16 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-25% EtOAc in petroleum ether to yield (190 mg, 80%). MS m/z 198.0, 200.0 [M+H].sup.+.

Example 29-13

5-Chloro-7-ethyl-2-methyl-2H-pyrazolo[4,3-b]pyridine

(621) 7-Bromo-5-chloro-2-methyl-2H-pyrazolo[4,3-b]pyridine (200 mg, 0.8 mmol) was combined with triethylborane (1 M in THF, 1.95 mL, 1.95 mmol), K.sub.2CO.sub.3 (441.6 g, 3.2 mmol) and Pd(PPh.sub.3).sub.4 (30 mg, 0.04 mmol) in DMF (3 mL). The reaction mixture was degassed and then charged with nitrogen three times. The mixture was stirred at 100° C. for 5 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-35% EtOAc in petroleum ether to yield 5-chloro-7-ethyl-2-methyl-2H-pyrazolo[4,3-b]pyridine (72 mg, 45%). MS m/z 196.0, 198.0 [M+H].sup.+.

Example 29-14

2-Bromo-4,6-dimethylthiazolo[5,4-c]pyridine

(622) Step A: A mixture of 2,6-dimethylpyridin-4-amine (0.5 g, 4.07 mmol) and bromine (0.21 mL, 4.07 mmol) in acetic acid (1 mL) was stirred at room temperature for 2 h. The mixture was treated with aqueous 20% sodium hydroxide (10 mL) and extracted with 30 mL CH.sub.2Cl.sub.2. The combined organics were washed with brine, dried over Na.sub.2SO.sub.4 and concentrated. The residue was suspended in hot heptanes. The solid material was collected and dried to yield 3-bromo-2,6-dimethylpyridin-4-amine (0.43 g, 52%). MS m/z 201.1, 203.1 [M+H].sup.+.

(623) Step B: A mixture of 3-bromo-2,6-dimethylpyridin-4-amine (400 mg, 2 mmol) and benzoyl isothiocyanate (296 μL, 2.2 mmol) in THF (4 mL) was stirred at 45° C. for 2 h. The mixture was concentrated and the residue was chromatographed on silica gel, eluting with 17% EtOAc in petroleum ether to afford N-((3-bromo-2,6-dimethylpyridin-4-yl)carbamothioyl)benzamide as a light-yellow solid (363 mg, 50%). MS m/z 364.0, 366.0 [M+H].sup.+.

(624) Step C: A mixture of N-((3-bromo-2,6-dimethylpyridin-4-yl)carbamothioyl)benzamide (181 mg, 0.5 mmol), Pd(PPh.sub.3).sub.4 (58 mg, 0.05 mmol) and Cs.sub.2CO.sub.3 (326 mg, 1 mmol) in DME (5 mL) was stirred at 100° C. under N.sub.2 for 3 h. After completion, the reaction mixture was cooled to room temperature and partitioned between EtOAc (50 mL) and water (50 mL). The organic layer was washed with brine, dried over Na.sub.2SO.sub.4 and concentrated. The residue was chromatographed on silica gel, eluting 30-100% EtOAc in petroleum ether to afford N-(4,6-dimethylthiazolo[5,4-c]pyridin-2-yl)benzamide as a light-yellow solid (92 mg, 65%). MS m/z 284.1 [M+H].sup.+.

(625) Step D: A mixture of N-(4,6-dimethylthiazolo[5,4-c]pyridin-2-yl)benzamide (2 g, 7.1 mmol) and NaOH (1.42 g, 36 mmol) in MeOH (45 mL) and water (15 mL) was stirred in a sealed tube at 85° C. for 24 h. The mixture was extracted with EtOAc (150 mL×2). The combined organic phases were washed with brine, dried over Na.sub.2SO.sub.4 and concentrated. The residue was chromatographed n silica gel, eluting 50-100% EtOAc in CH.sub.2Cl.sub.2 to afford 4,6-dimethylthiazolo[5,4-c]pyridin-2-amine as a light-yellow solid (0.88 g, 70%). MS m/z 180.1 [M+H].sup.+.

(626) Step E: To a mixture of 4,6-dimethylthiazolo[5,4-c]pyridin-2-amine (880 mg, 4.9 mmol) and CuBr.sub.2 (3.25 g, 14.7 mmol) in MeCN (10 mL) was added tert-butyl nitrite (1.74 mL, 14.7 mmol) at 0° C. The mixture was stirred at 0° C. for 2 h and then 55° C. for 1 h. To the reaction

mixture was added aqueous sat'd NaHCO.sub.3. The mixture was extracted with EtOAc (200 mL). The organic layer was washed with brine, dried over Na.sub.2SO.sub.4 and concentrated. The residue was chromatographed on silica gel, eluting 20% EtOAc in petroleum ether to afford 2-bromo-4,6-dimethylthiazolo[5,4-c]pyridine as a white solid (595 mg, 50%). MS m/z 242.9, 245.0 [M+H].sup.+.

Example 29-15

2-(6-Chloro-2-methylimidazo[1,2-b]pyridazin-8-yl)ethan-1-ol

(627) Step A: A dry three-necked round-bottomed flask at −78° C. under inert atmosphere was charged with anhydrous THF (20 mL). A solution of n-butyllithium (2.5 M in hexane, 26.1 mL, 65.3 mmol) was added dropwise, followed by addition of anhydrous acetonitrile (4 mL, 65.3 mmol). The internal temperature was maintained below −70° C. during the entire addition process. After stirring 30 min at −78° C., a solution of 8-bromo-6-chloro-2-methylimidazo[1,2-b]pyridazine (2.0 g, 8.2 mmol, prepared according to Example 43) in anhydrous THF (20 mL) was added drop-wise. The mixture was stirred for 2 h at −78° C. The excess reagent was quenched carefully with sat'd aqueous NH.sub.4Cl. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-35% EtOAc in petroleum ether to yield 2-(6-chloro-2-methylimidazo[1,2-b]pyridazin-8-yl)acetonitrile (1.2 g, 71%). MS m/z 207.1, 209.1 [M+H].sup.+.

(628) Step B: 2-(6-Chloro-2-methylimidazo[1,2-b]pyridazin-8-yl)acetonitrile (500 mg, 2.4 mmol) was combined with MeOH (0.97 mL, 24 mmol) in conc. H.sub.2SO.sub.4 (2 mL). The mixture was stirred at 60° C. for 16 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-30% EtOAc in petroleum ether to yield methyl 2-(6-chloro-2-methylimidazo[1,2-b]pyridazin-8-yl)acetate (500 mg, 86%). MS m/z 240.1, 242.1 [M+H].sup.+.

(629) Step C: To methyl 2-(6-chloro-2-methylimidazo[1,2-b]pyridazin-8-yl)acetate (500 mg, 2.1 mmol) in dry THF (5 mL) was added LiAlH.sub.4 (183 mg, 5.2 mmol) in small portions at 0° C. The mixture was stirred at 0° C. for 20 min. The reaction was quenched carefully with water (1 mL), followed by aqueous 15% NaOH (1 mL). The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-35% EtOAc in petroleum ether to yield 2-(6-chloro-2-methylimidazo[1,2-b]pyridazin-8-yl)ethan-1-ol (144 mg, 33%). MS m/z 212.1, 214.1 [M+H].sup.+.

Example 29-16

6-Chloro-8-(1H-imidazol-1-yl)-2-methylimidazo[1,2-b]pyridazine

(630) 8-Bromo-6-chloro-2-methylimidazo[1,2-b]pyridazine (500 mg, 2.0 mmol, prepared according to Example 43) was combined with K.sub.2CO.sub.3 (550 mg, 4.0 mmol) and 1H-imidazole (250 mg, 0.36 mmol) in NMP (5 mL). The mixture was stirred at 120° C. for 16 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-30% EtOAc in petroleum ether to yield 6-chloro-8-(1H-imidazol-1-yl)-2-methylimidazo[1,2-b]pyridazine (228 mg, 48%). MS m/z 234.0, 236.0 [M+H].sup.+.

Example 29-17

6-Chloro-2-methyl-8-phenoxyimidazo[1,2-b]pyridazine

(631) 8-Bromo-6-chloro-2-methylimidazo[1,2-b]pyridazine (1.0 g, 4.0 mmol) was combined with K.sub.2CO.sub.3 (1.1 g, 8 mmol) and phenol (0.6 g, 6.0 mmol) in NMP (10 mL). The mixture was stirred at 60° C. for 16 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-30% EtOAc in petroleum ether to yield 6-

chloro-2-methyl-8-phenoxyimidazo[1,2-b]pyridazine (560 mg, 53%). MS m/z 260.0, 262.0 [M+H].sup.+.
Example 29-18
6-Chloro-8-isopropyl-2-methylimidazo[1,2-b]pyridazine
(632) Step A: 8-Bromo-6-chloro-2-methylimidazo[1,2-b]pyridazine (500 mg, 2.05 mmol, prepared according to example 43) was combined with vinylboronic acid pinacol ester (0.43 mL, 2.3 mmol), Pd(dppf)Cl.sub.2 (150 mg, 0.21 mmol) and K.sub.2CO.sub.3 (850 mg, 6.15 mmol) in 1,4-dioxane (10 mL) and H.sub.2O (2 mL). The mixture was stirred at 90° C. for 2 h under N.sub.2. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 10-20% EtOAc in petroleum ether to yield 6-chloro-2-methyl-8-(prop-1-en-2-yl)imidazo[1,2-b]pyridazine (300 mg, 77%). MS m/z 208.0, 210.0 [M+H].sup.+.
(633) Step B: 6-Chloro-2-methyl-8-(prop-1-en-2-yl)imidazo[1,2-b]pyridazine (250 mg, 1.21 mmol) was combined with PtO.sub.2 (30 mg, 0.13 mmol) in EtOAc (10 mL). The mixture was stirred at room temperature for 3 h under an atmosphere of H.sub.2. The mixture was filtered over Celite, and the filtrate was removed under reduce pressure. The residue was chromatographed on silica gel, eluting with 20-35% EtOAc in petroleum ether to yield 6-chloro-8-isopropyl-2-methylimidazo[1,2-b]pyridazine (200 mg, 80%). MS m/z 210.0, 212.0 [M+H].sup.+.
Example 29-19
6-Chloro-2-methyl-8-propylimidazo[1,2-b]pyridazine
(634) 8-Bromo-6-chloro-2-methylimidazo[1,2-b]pyridazine (1 g, 4.1 mmol, prepared according to Example 43) was combined with propylmagnesiumbromide (660 mg, 4.5 mmol) and iron(III) 2,4-pentanedionate (140 mg, 0.4 mmol) in dry THF (30 mL). The mixture was stirred at 50° C. for 1 h under N.sub.2. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 20-30% EtOAc in petroleum ether to yield 6-chloro-2-methyl-8-propylimidazo[1,2-b]pyridazine (230 mg, 27%). MS m/z 210.0, 212.0 [M+H].sup.+.
Example 30
(635) Preparation of Compound 78
(636) ##STR00144##
(637) 7-(2,8-Dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(4-piperidyl)cinnoline dihydrochloride (55 mg, 0.13 mmol, prepared in Example 7) was combined with Cs.sub.2CO.sub.3 (85 mg, 0.26 mmol), 2-iodopropane (26 μL, 0.26 mmol) and DMF (1 mL). The mixture was stirred at 60° C. for 4 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-10% MeOH (2 N NH.sub.3) in CH.sub.2Cl.sub.2 to yield 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(1-isopropyl-4-piperidyl)cinnoline (6 mg, 11%).
(638) MS m/z 419.4 [M+H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.92 (s, 1H), 8.32 (dd, J=11.0, 1.5 Hz, 1H), 8.19 (s, 1H), 8.00 (s, 1H), 7.88 (s, 1H), 3.91-4.02 (m, 2H), 3.61-3.68 (m, 1H), 3.24-3.33 (m, 2H), 2.73 (s, 3H), 2.56-2.62 (m, 1H), 2.52 (s, 3H), 2.20-2.26 (m, 2H), 2.06-2.16 (m, 2H), 1.21 (d, J=7.2 Hz, 6H).
(639) Using the procedure described for Example 30, above, additional compounds described herein were prepared by substituting the appropriate aryl halide, suitable reagents and reaction conditions, obtaining compounds such as those selected from:
(640) TABLE-US-00025 Cpd Data 83 MS m/z 423.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.17 (s, 1H), 8.60 (d, J = 1.3 Hz, 1H), 8.43-8.47 (m, 2H), 8.35 (s, 1H), 4.98 (ddd, J = 47, 5.1, 3.7 Hz, 2H), 3.89-3.95 (m, 2H), 3.63-3.73 (m, 3H), 3.40-3.48 (m, 2H), 2.88 (d, J = 0.9 Hz, 3H), 2.71 (d, J = 0.9 Hz, 3H), 2.46-2.53 (m, 4H), HCl protons not observed. 98 MS m/z 441.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.15 (s, 1H), 8.54 (d, J = 1.2 Hz, 1H), 8.44 (dd, J =

10.7, 1.5 Hz, 1H), 8.41 (d, J = 0.9 Hz, 1H), 8.34 (s, 1H), 6.53 (tt, J = 53.7, 3.5 Hz, 1H), 3.82-3.96 (m, 4H), 3.64-3.71 (m, 1H), 3.49-3.59 (m, 2H), 2.87 (d, J = 1.2 Hz, 3H), 2.69 (d, J = 0.9 Hz, 3H), 2.46-2.57 (m, 4H), HCl protons not observed. 168 MS m/z 433.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.92 (s, 1H), 8.32 (d, J = 11 Hz, 1H), 8.19 (s, 1H), 8.00 (s, 1H), 7.88 (s, 1H), 3.60 (m, 1H), 3.30 (br s, 4H), 2.73 (s, 3H), 2.52 (s, 3H), 2.26-2.32 (m, 2H), 2.01 (m, 2H), 1.41 (d, J = 6 Hz, 6H), 1.21 (m, 3H). 170 MS m/z 451.6 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.90 (s, 1H), 8.30 (d, J = 10.5 Hz, 1H), 8.15 (s, 1H), 8.00 (s, 1H), 7.87 (s, 1H), 4.64 (dd, J = 50, 5.0 Hz, 2H), 3.51 (m, 1H), 3.15-3.32 (m, 2H), 3.07 (br s, 2H), 2.73 (s, 3H), 2.52 (s, 3H), 2.13 (d, J = 12.5 Hz, 2H), 1.85 (q, J = 12 Hz, 2H), 1.32 (d, J = 6 Hz, 6H). 199 MS m/z 437.3 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.90 (s, 1H), 8.29 (d, J = 10 Hz, 1H), 8.16 (s, 1H), 7.99 (s, 1H), 7.87 (s, 1H), 4.64 (dd, J = 50, 5.0 Hz, 2H), 3.60 (m, 1H), 3.13-3.19 (m, 1H), 2.95-3.08 (m, 5H), 2.72 (s, 3H), 2.52 (s, 3H), 2.00-2.30 (m, 5H), 1.90-2.00 (m, 1H).

Example 31

(641) Preparation of Compound 158

(642) ##STR00145##

(643) Step A: A solution of oxalyl chloride (105 μL, 1.2 mmol) in CH.sub.2Cl.sub.2 (1.4 mL) was cooled to −78° C. To the solution was added DMSO (150 μL, 2.1 mmol) in CH.sub.2Cl.sub.2 (0.5 mL). The solution was stirred at −78° C. for 30 min. To the solution was added 3-(dimethylamino)propan-1-ol (55 mg, 0.53 mmol) in CH.sub.2Cl.sub.2 (1 mL). The solution was stirred for 30 min at −78° C. Triethylamine (42 μL, 0.30 mmol) was added to the solution. The mixture was allowed to slowly warm to 0° C. over ˜30 min. The excess reagent was quenched by the addition of aqueous saturated NaHCO.sub.3. The organic layer was removed and dried over Na.sub.2SO.sub.4, filtered and concentrated. The crude product was used directly in the next step without additional purification.

(644) Step B: 7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-3-(4-piperidyl)cinnoline dihydrochloride (45 mg, 0.10 mmol, prepared in Example 7) was combined with CH.sub.2Cl.sub.2 (2 mL), triethylamine (42 μL, 0.30 mmol), and EtOH (0.2 mL). To the mixture was added 3-(dimethylamino)propanal (53 mg, 0.52 mmol, from Step A) in CH.sub.2Cl.sub.2 (0.5 mL). The mixture was stirred at room temperature until homogeneous, and then sodium triacetoxyborohydride (64, 0.30 mmol) was added. After stirring for 20 min at room temperature, the mixture was concentrated. The residue was dissolved in TFA and CH.sub.2Cl.sub.2 and was dried onto Celite. The dry material was chromatographed on a reverse phase C18 column, eluting with 5-60% CH.sub.3CN (0.1% TFA) in H.sub.2O (0.1% TFA). The collected fractions were concentrated. The residue was partitioned in CH.sub.2Cl.sub.2 and aqueous 1 M K.sub.2CO.sub.3. The organic layer was loaded onto silica gel, eluting with 0-10% MeOH (2 N NH.sub.3) in CH.sub.2Cl.sub.2 to afford 3-[4-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-cinnolin-3-yl]-1-piperidyl]-N,N-dimethyl-propan-1-amine (7 mg, 15%).

(645) MS m/z 462.5 [M+H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.96 (s, 1H), 8.36 (dd, J=11.0, 1.5 Hz, 1H), 8.25 (s, 1H), 8.02 (s, 1H), 7.90 (d, J=0.9 Hz, 1H), 3.54-3.60 (m, 2H), 3.46-3.53 (m, 1H), 3.20-3.26 (m, 2H), 2.99-3.08 (m, 2H), 2.92 (s, 6H), 2.81-2.90 (m, 2H), 2.74 (d, J=0.9 Hz, 3H), 2.53 (s, 3H), 2.26-2.37 (m, 4H), 2.14 (quin, J=7.2 Hz, 2H).

(646) Using the procedure described for Example 31, above, additional compounds described herein were prepared by substituting the appropriate alcohol in Step A, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

(647) TABLE-US-00026 Cpd Data 145 MS m/z 535.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.91 (s, 1H), 8.31 (dd, J = 10.8, 1.4 Hz, 1H), 8.25 (s, 1H), 8.15 (s, 1H), 8.00 (s, 1H), 7.87 (s, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.67 (d, J = 7.9 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.31 (t, J = 7.7 Hz, 1H), 4.45 (t, J = 6.6 Hz, 2H), 3.23-3.31 (m, 1H), 3.12 (br d, J = 11.3 Hz, 2H), 2.73 (s, 3H), 2.52 (s, 3H), 2.47 (t, J = 6.6 Hz, 2H), 2.16-2.28 (m, 4H), 2.01-2.15 (m, 4H), HCl protons not observed. 159 MS m/z 521.2 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.94 (s, 1H), 8.34

(dd, J = 10.7, 1.3 Hz, 1H), 8.29 (s, 1H), 8.17 (s, 1H), 8.02 (s, 1H), 7.90 (d, J = 0.9 Hz, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.66 (d, J = 8.2 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 4.51 (t, J = 6.4 Hz, 2H), 3.24-3.31 (m, 1H), 3.18 (br d, J = 11.3 Hz, 2H), 2.94 (t, J = 6.4 Hz, 2H), 2.75 (s, 3H), 2.53 (s, 3H), 2.39-2.46 (m, 2H), 2.02-2.20 (m, 4H). 160 MS m/z 485.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.89 (s, 1H), 8.29 (dd, J = 11.0, 1.2 Hz, 1H), 8.16 (s, 1H), 7.98 (s, 1H), 7.85 (d, J = 1.2 Hz, 1H), 7.70 (d, J = 2.1 Hz, 1H), 7.53 (d, J = 1.8 Hz, 1H), 6.32 (t, J = 2.1 Hz, 1H), 4.29 (m, 2H), 3.26-3.31 (m, 1H), 3.20 (br d, J = 11.6 Hz, 2H), 2.72 (d, J = 0.9 Hz, 3H), 2.51 (s, 3H), 2.46-2.50 (m, 2H), 2.28-2.36 (m, 2H), 2.07-2.21 (m, 6H).

Example 32

(648) Preparation of Compound 127

(649) ##STR00146##

(650) Step A: 2-[4-[7-(2,8-Dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-cinnolin-3-yl]-1-piperidyl]ethanol dihydrochloride (200 mg, 0.41 mmol, prepared in Example 19) was combined with CH.sub.2Cl.sub.2 (4 mL) and triethylamine (0.22 mL, 1.6 mmol). To the mixture was added methanesulfonyl chloride (137 μL, 0.81 mmol) at room temperature. The mixture was stirred at room temperature for 30 min. The mixture was washed with aqueous 1 M K.sub.2CO.sub.3. The organic layer was Loaded onto silica gel, eluting with 0-10% MeOH (2 N NH.sub.3) in CH.sub.2Cl.sub.2 to provide 2-[4-[7-(2,8-Dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-cinnolin-3-yl]-1-piperidyl]ethyl methanesulfonate. MS m/z 499.4 [M+H].sup.+.

(651) Step B: 2-[4-[7-(2,8-Dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-cinnolin-3-yl]-1-piperidyl]ethyl methanesulfonate (30 mg, 0.06 mmol) was combined with N,N-diisopropylethylamine (105 μL, 0.60 mmol), DMF (1 mL) and dimethylamine hydrochloride (55 mg, 0.60 mmol). The mixture was heated at 40° C. for 18 h. The volatile material was removed. The residue was dissolved in TFA and CH.sub.2Cl.sub.2 and was dried onto Celite. The dry material was chromatographed on a reverse phase C18 column, eluting with 5-65% CH.sub.3CN (0.1% TFA) in H.sub.2O (0.1% TFA). The collected material was concentrated. The residue was dissolved in 1.25 M HCl in MeOH. The volatiles were removed. The residue was suspended in CH.sub.3CN, sonicated, collected by filtration and dried yielding 2-[4-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-cinnolin-3-yl]-1-piperidyl]-N,N-dimethyl-ethanamine trihydrochloride (13 mg, 39%). MS m/z 448.5 [M+H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.15 (s, 1H), 8.56 (m, 1H), 8.43 (d, J=9.5 Hz, 1H), 8.42 (s, 1H), 8.35 (s, 1H), 3.93 (br s, 2H), 3.68-3.83 (m, 5H), 3.46 (br d, J=10.4 Hz, 2H), 3.07 (s, 6H), 2.87 (s, 3H), 2.70 (s, 3H), 2.48-2.63 (m, 4H), HCl protons not observed.

Example 33

(652) Preparation of Compound 141

(653) ##STR00147##

(654) Step A: 8-Bromo-6-chloro-2-methyl-imidazo[1,2-b]pyridazine (124 mg, 0.50 mmol) was combined with 3-(1H-pyrazol-1-yl)propan-1-ol (252 mg, 2.0 mmol) and cesium carbonate (650 mg, 2.0 mmol) in CH.sub.3CN (4 mL). The mixture was stirred at 40° C. for 16 h. To the mixture was added EtOAc (10 mL). The mixture was filtered over Celite. The filtrate was concentrated. The residue was chromatographed on silica gel, eluting with 0-10% MeOH in EtOAc to yield 6-chloro-2-methyl-8-(3-pyrazol-1-ylpropoxy)imidazo[1,2-b]pyridazine (70 mg, 48%). MS m/z 292.3 [M+H].sup.+.

(655) Step B: tert-Butyl 4-(7-chloro-5-fluoro-cinnolin-3-yl)piperidine-1-carboxylate (73 mg, 0.20 mmol, prepared in Example 29) was combined with bis(pinacolato)diboron (64 mg, 0.25 mmol), KOAc (59 mg, 0.60 mmol), chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)(2′-amino-1,1′-biphenyl-2-yl) palladium(II) (14 mg, 0.02 mmol) and 1,4-dioxane (3 mL). The mixture was stirred at 90° C. for 1 h. To the mixture was added aqueous 1 M K.sub.2CO.sub.3 (1 mL), followed by another portion of chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)(2′-amino-1,1′-biphenyl-2-yl) palladium(II) (14 mg, 0.02 mmol) and 6-chloro-2-methyl-8-(3-pyrazol-

1-ylpropoxy)imidazo[1,2-b]pyridazine (70 mg, 0.24 mmol) (in 1 mL of 1,4-dioxane). The mixture was stirred at 80° C. for 1 h. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was concentrated. The residue was chromatographed on silica gel, eluting with 0-10% MeOH in EtOAc to yield tert-butyl 4-[5-fluoro-7-[2-methyl-8-(3-pyrazol-1-ylpropoxy)imidazo[1,2-b]pyridazin-6-yl]cinnolin-3-yl]piperidine-1-carboxylate (110 mg, 94%). MS m/z 587.3 [M+H].sup.+.

(656) Step C: tert-Butyl 4-[5-fluoro-7-[2-methyl-8-(3-pyrazol-1-ylpropoxy)imidazo[1,2-b]pyridazin-6-yl]cinnolin-3-yl]piperidine-1-carboxylate (110 mg, 0.18 mmol) was dissolved in trifluoroacetic acid (1 mL) and 1 mL CH.sub.2Cl.sub.2. The solution was dried onto Celite. The dry material was chromatographed on a reverse phase C18 column, eluting with 5-65% CH.sub.3CN (0.1% TFA) in H.sub.2O (0.1% TFA). The desired fractions were concentrated. The residue was dissolved in 1.25 M HCl in MeOH. The volatiles were removed. The residue was suspended in CH.sub.3CN, sonicated, filtered and dried to yield 5-fluoro-7-[2-methyl-8-(3-pyrazol-1-ylpropoxy)imidazo[1,2-b]pyridazin-6-yl]-3-(4-piperidyl)cinnoline dihydrochloride (66 mg, 63%) as a pale yellow solid.

(657) MS m/z 487.4 [M+H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.18 (s, 1H), 8.44 (d, J=10.7 Hz, 1H), 8.40 (d, J=0.6 Hz, 1H), 8.33 (s, 1H), 8.08 (s, 1H), 7.84 (d, J=2.1 Hz, 1H), 7.66 (d, J=1.8 Hz, 1H), 6.41 (t, J=2.3 Hz, 1H), 4.67 (t, J=6.7 Hz, 2H), 4.58 (t, J=6.7 Hz, 2H), 3.63-3.70 (m, 3H), 3.29-3.35 (m, 2H), 2.70 (s, 3H), 2.59 (quin, J=6.3 Hz, 2H), 2.33-2.45 (m, 4H), NH and HCl protons not observed.

(658) Using the procedure described for Example 33, above, additional compounds described herein were prepared by substituting the appropriate alcohol in Step A, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

(659) TABLE-US-00027 Cpd Data 138 MS m/z 450.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.20 (s, 1H), 8.46 (dd, J = 10.7, 1.2 Hz, 1H), 8.38 (s, 1H), 8.32 (s, 1H), 8.14 (s, 1H), 5.06 (t, J = 5.0 Hz, 2H), 3.90 (t, J = 5.0 Hz, 2H), 3.63-3.71 (m, 3H), 3.29-3.37 (m, 2H), 3.12 (s, 6H), 2.69 (s, 3H), 2.32- 2.46 (m, 4H), NH and HCl protons not observed. 139 MS m/z 464.5 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.19 (s, 1H), 8.45 (dd, J = 10.5, 1.4 Hz, 1H), 8.39 (s, 1H), 8.32 (s, 1H), 8.10 (s, 1H), 4.82 (t, J = 6.1 Hz, 2H), 3.63-3.70 (m, 3H), 3.55-3.60 (m, 2H), 3.28-3.37 (m, 2H), 3.03 (s, 6H), 2.70 (s, 3H), 2.49- 2.56 (m, 2H), 2.31-2.45 (m, 4H), NH and HCl protons not observed. 140 MS m/z 473.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.16 (s, 1H), 8.42 (d, J = 10.4 Hz, 1H), 8.38 (s, 1H), 8.35 (s, 1H), 8.04 (s, 1H), 7.92 (d, J = 1.8 Hz, 1H), 7.63 (s, 1H), 6.40 (t, J = 2.1 Hz, 1H), 5.01-5.06 (m, 2H), 4.85-4.90 (m, 2H), 3.63-3.71 (m, 3H), 3.29-3.37 (m, 2H), 2.69 (s, 3H), 2.32-2.46 (m, 4H), NH and HCl protons not observed. 142 MS m/z 487.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.19 (s, 2H), 8.45 (dd, J = 10.5, 1.4 Hz, 1H), 8.41 (d, J = 0.9 Hz, 1H), 8.33 (s, 1H), 8.11 (s, 1H), 7.84 (t, J = 1.7 Hz, 1H), 7.67 (t, J = 1.7 Hz, 1H), 4.77 (t, J = 5.8 Hz, 2H), 4.71 (t, J = 7.3 Hz, 2H), 3.62-3.71 (m, 3H), 3.29-3.37 (m, 2H), 2.71 (s, 3H), 2.65-2.70 (m, 2H), 2.32-2.45 (m, 4H), NH and HCl protons not observed. 150 MS m/z 537.4 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.72 (s, 1H), 9.16 (s, 1H), 8.44 (d, J = 10.6 Hz, 1H), 8.40 (s, 1H), 8.32 (s, 1H), 8.11-8.16 (m, 1H), 8.08 (s, 1H), 7.89-7.95 (m, 1H), 7.68-7.77 (m, 2H), 5.00 (t, J = x Hz, 2H), 4.83 (t, J = x Hz, 2H), 3.63-3.70 (m, 3H), 3.28-3.37 (m, 2H), 2.80 (dt, J = 13.4, 6.4 Hz, 2H), 2.72 (d, J = 0.9 Hz, 3H), 2.31-2.45 (m, 4H), NH proton not observed.

Example 34

(660) Preparation of Compound 223

(661) ##STR00148##

(662) Step A: A screw-cap tube was charged with 3-chloro-7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-cinnoline (0.037 g, 0.11 mmol), tert-butyl N-[(1S*,5R*)-3-azabicyclo[3.1.0]hexan-6-yl]carbamate (0.034 g, 0.17 mmol), granular cesium carbonate (0.110 g, 0.338 mmol), and RuPhos Pd G4 pre-catalyst (0.0011 g, 0.0013 mmol). Anhydrous 1,4-dioxane (5

mL) was added last, and the mixture was sparged with argon for 10 minutes. The vial was tightly capped with a screw-cap, placed on a pre-heated aluminum block, and stirred vigorously at 100° C. for 2 h. After this time, the reaction mixture was cooled to room temperature. The brown, heterogeneous reaction mixture was diluted with sat. aq. Na.sub.2CO.sub.3 (20 mL) and extracted with CH.sub.2Cl.sub.2 (2×30 mL). The combined CH.sub.2Cl.sub.2 extracts were diluted with more CH.sub.2Cl.sub.2 (30 mL) and washed with brine (30 mL), dried over anhydrous Na.sub.2SO.sub.4, filtered, and concentrated under reduced pressure. The brown, crude product was purified by silica gel column chromatography (CH.sub.2Cl.sub.2/methanolic ammonia (1.0M) gradient elution) to afford the desired tert-butyl N-[(1S*,5R*)-3-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-cinnolin-3-yl]-3-azabicyclo[3.1.0]hexan-6-yl]carbamate (0.048 g, 87%) as a yellow solid.

(663) MS m/z 490.3 [M+H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.54 (s, 1H), 7.97 (dd, J=11.3, 1.2 Hz, 1H), 7.97 (d, J=1.3 Hz, 1H), 7.47 (s, 1H), 6.76 (s, 1H), 4.83 (br s, 1H), 4.07 (br d, J=9.6 Hz, 2H), 3.72 (br d, J=9.9 Hz, 2H), 2.76 (s, 3H), 2.55 (s, 3H), 2.46 (br s, 1H), 2.00 (br s, 2H), 1.47 (m, 9H).

(664) Step B: tert-Butyl N-[(1S*,5R*)-3-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-cinnolin-3-yl]-3-azabicyclo[3.1.0]hexan-6-yl]carbamate (0.048 g, 0.098 mmol) was dissolved in CH.sub.2Cl.sub.2 (5 mL), and trifluoroacetic acid (0.10 mL, 1.3 mmol) was added dropwise to the yellow solution, resulting in instantaneous color change to a wine red. The reaction mixture was capped and allowed to sit at room temperature for 17 h. After this time, the wine-red solution was concentrated on a rotovap. The red, crude oil was purified by C18 reverse-phase column chromatography (H.sub.2O:MeCN (0.1% TFA) gradient elution) to afford (1S*,5R*)-3-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-cinnolin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine tetra(trifluoroacetic acid) (0.054 g, 65%) as a dark red oil. MS m/z 390.3 [M+H].sup.+.

(665) Step C: (1S*,5R*)-3-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-cinnolin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine tetra(trifluoroacetic acid) (0.050 g, 0.059 mmol), was dissolved in CH.sub.2Cl.sub.2 (3 mL) in a screw-top vial. A 37% aqueous solution of formaldehyde (0.018 mL, 0.24 mmol) was added, followed by anhydrous MgSO.sub.4 (0.021 g, 0.17 mmol), triethylamine (0.025 mL, 0.18 mmol), and NaBH(OAc).sub.3 (0.031 g, 0.15 mmol). The vial was sealed with a screw-cap, and the reaction mixture was stirred vigorously at room temperature for 5 days. After this time, the reaction mixture was diluted with CH.sub.2Cl.sub.2 (30 mL), washed with sat. aq. Rochelle's salt (20 mL) and brine (20 mL), then dried over anhydrous Na.sub.2SO.sub.4, decanted, and concentrated on a rotovap to afford a dark yellow solid/oil mixture. The crude product was purified by silica gel column chromatography (CH.sub.2Cl.sub.2/methanolic ammonia (1.0 M) gradient) to afford the desired (1S*,5R*)-3-[7-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-5-fluoro-cinnolin-3-yl]-N,N-dimethyl-3-azabicyclo[3.1.0]hexan-6-amine (0.021 g, 85%) as a yellow solid.

(666) MS m/z 418.3 [M+H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.54 (s, 1H), 7.98 (dd, J=11.3, 1.3 Hz, 1H), 7.76 (s, 1H), 7.45 (s, 1H), 6.76 (s, 1H), 3.83 (ABq, J=126.7, 9.6 Hz, 4H), 2.74 (s, 3H), 2.54 (s, 3H), 2.40 (s, 6H), 1.93 (s, 2H), 1.57 (s, 1H).

(667) Using the procedure described for Example 34, above, additional compounds described herein were prepared by substituting the appropriate amine in Step A, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

(668) TABLE-US-00028 Cpd Data 80 MS m/z 378.4 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.29 (br s, 2H), 8.94 (s, 1H), 8.44 (br s, 1H), 8.39 (br s, 1H), 8.19 (dd, J = 11.3, 1.3 Hz, 1H), 7.60 (s, 1H), 4.06-4.20 (m, 4H), 3.26-3.35 (m, 4H), 2.73 (s, 3H), 2.54 (s, 3H). 81 MS m/z 406.4 [M + H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 9.53 (br s, 1H), 9.11 (br s, 1H), 8.93 (s, 1H), 8.45 (br s, 1H), 8.39 (br s, 1H), 8.19 (d, J = 11.3 Hz, 1H), 7.67 (s, 1H), 4.87 (br d, J = 12.0 Hz, 2H), 3.45 (br s, 2H), 3.12 (dd, J = 14.2, 11.7 Hz, 2H), 2.73 (s, 3H), 2.54 (m, 3H), 1.39 (d, J = 6.3 Hz, 6H). 86 MS m/z 406.3 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.44 (s, 1H), 7.84-

7.94 (m, 2H), 7.66 (s, 1H), 6.90 (s, 1H), 3.92-4.00 (m, 1H), 3.83-3.90 (m, 1H), 3.54-3.62 (m, 1H), 3.35-3.46 (m, 2H), 2.99-3.08 (m, 1H), 2.66 (s, 3H), 2.47 (s, 3H), 2.42 (s, 6H), 1.99-2.09 (m, 1H). 88 MS m/z 420.3 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.50 (s, 1H), 7.96 (dd, J = 11.4, 1.4 Hz, 1H), 7.88 (s, 1H), 7.69 (s, 1H), 7.29 (s, 1H), 4.64-4.73 (m, 2H), 3.02-3.13 (m, 2H), 2.67 (s, 3H), 2.57 (tt, J = 11.3, 3.8 Hz, 1H), 2.48 (s, 3H), 2.37 (s, 6H), 2.10 (br d, J = 12.2 Hz, 2H), 1.60 (qd, J = 12.2, 4.0 Hz, 2H). 89 MS m/z 406.3 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.49 (s, 1H), 7.95 (dd, J = 11.6, 1.5 Hz, 1H), 7.89 (d, J = 0.6 Hz, 1H), 7.70 (d, J = 0.9 Hz, 1H), 6.94 (s, 1H), 3.95-4.02 (m, 1H), 3.85-3.92 (m, 1H), 3.60 (td, J = 10.1, 7.0 Hz, 1H), 3.40-3.47 (m, 1H), 2.99- 3.07 (m, 1H), 2.68 (d, J = 0.9 Hz, 3H), 2.48 (s, 3H), 2.38-2.45 (m, 7H), 1.99-2.08 (m, 1H). 209 MS m/z 404.3 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.55 (s, 1H), 7.99 (dd, J = 11.3, 1.4 Hz, 1H), 7.77 (s, 1H), 7.46 (s, 1H), 6.81 (s, 1H), 5.13 (bs, 1H), 3.74 (d, J = 9.3 Hz, 1H), 3.69 (s, 1H), 3.57 (dd, J = 9.7, 1.7 Hz, 1H), 3.09 (dd, J = 9.9, 1.4 Hz, 1H), 2.80 (d, J = 8.0 Hz, 1H), 2.75 (s, 3H), 2.54 (s, 3H), 2.48 (s, 3H), 2.15 (d, J = 9.6 Hz, 1H), 1.99 (d, J = 9.7 Hz, 1H). 215 MS m/z 404.3 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.55 (s, 1H), 7.99 (dd, J = 11.3, 1.3 Hz, 1H), 7.77 (s, 1H), 7.46 (s, 1H), 6.81 (s, 1H), 5.13 (bs, 1H), 3.73 (bs, 1H), 3.68 (bs, 1H), 3.57 (d, J = 9.0 Hz, 1H), 3.09 (d, J = 9.3 Hz, 1H), 2.80 (bs, 1H), 2.75 (s, 3H), 2.54 (s, 3H), 2.48 (s, 3H), 2.15 (d, J = 9.5 Hz, 1H), 2.00 (d, J = 9.5 Hz, 1H). 217 MS m/z 404.3 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.77 (s, 1H), 8.50 (s, 1H), 8.39 (s, 1H), 8.22 (d, J = 10.7 Hz, 1H), 7.58 (s, 1H), 4.48 (ABq, J = 36.1, 9.0 Hz, 4H), 3.68 (s, 2H), 3.47 (dd, J = 7.4 Hz, 2H), 2.84 (s, 3H), 2.68 (s, 3H), 2.50 (dd, J = 7.3 Hz, 2H), NH and HCl protons not observed. 218 MS m/z 418.3 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.82 (s, 1H), 8.49 (s, 1H), 8.37 (s, 1H), 8.18 (d, J = 10.8 Hz, 1H), 7.28 (s, 1H), 4.21 (ABq, J = 59.7, 8.7 Hz, 4H), 3.53 (s, 2H), 3.23-3.18 (m, 2H), 2.83 (s, 3H), 2.68 (s, 3H), 2.14-2.06 (m, 2H), 1.97-1.90 (m, 2H), NH and HCl protons not observed. 219 MS m/z 418.3 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.43 (s, 1H), 7.90 (dd, J = 11.5, 1.3 Hz, 1H), 7.83 (s, 1H), 7.63 (s, 1H), 7.25 (s, 1H), 3.98 (s, 4H), 3.81 (ddd, J = 7.5, 3.7, 1.9 Hz, 4H), 2.61 (s, 3H), 2.45 (s, 3H), 2.04 (ddd, J = 7.4, 3.7, 1.9 Hz, 4H), NH and TFA protons not observed. 220 MS m/z 404.3 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.63 (s, 1H), 8.21 (s, 1H), 8.18 (s, 1H), 8.00 (dd, J = 11.2, 1.0 Hz, 1H), 6.99 (s, 1H), 4.23 (ABq, J = 51.2, 11.5 Hz, 4H), 4.00 (s, 2H), 3.74 (dd, J = 6.9 Hz, 2H), 2.74 (s, 3H), 2.59 (s, 3H), 2.51 (dd, J = 7.0 Hz, 2H), NH and TFA protons not observed. 221 MS m/z 418.3 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.73 (s, 1H), 8.29 (s, 1H), 8.24 (s, 1H), 8.08 (d, J = 11.2 Hz, 1H), 7.04 (s, 1H), 4.13 (s, 4H), 3.28 (dd, J = 7.3, 5.7 Hz, 4H), 2.77 (s, 3H), 2.62 (s, 3H), 2.18 (dd, J = 7.3, 5.6 Hz, 4H), NH and TFA protons not observed. 224 MS m/z 434.3 [M + H].sup.+; .sup.1H NMR (chloroform-d) δ: 8.56 (s, 1H), 7.98 (dd, J = 11.3, 1.3 Hz, 1H), 7.77 (s, 1H), 7.46 (s, 1H), 7.09 (s, 1H), 3.92-3.79 (m, 4H), 2.74 (s, 3H), 2.54 (s, 3H), 2.29 (s, 6H), 2.00 (dd, J = 13.7, 5.9 Hz, 2H), 1.67 (dt, J = 12.9, 5.9 Hz, 2H), 1.03 (s, 3H).

Example 35

(669) Preparation of Compound 203

(670) ##STR00149##

(671) Step A: A culture tube was charged with tert-butyl 4-[3-(2,7-dimethylindazol-5-yl)-5-fluoro-cinnolin-7-yl]-3,6-dihydro-2h-pyridine-1-carboxylate (20 mg, 0.0422 mmol, potassium osmate(VI) dihydrate (2.00 mg, 0.00543 mmol), 4-methylmorpholine N-oxide (11.0 mg, 0.0911 mmol), acetone (0.2 ml) and water (0.053 ml, 2.9 mmol) and the mixture was stirred at room temperature for 12 h. The reaction mixture was quenched by the dropwise addition of sat'd aqueous NaHSO.sub.3, with stirring for 5 min. The resulting black suspension was extracted with EtOAc. The combined organic extracts were washed with water, dried and concentrated to furnish tert-butyl 4-[3-(2,7-dimethylindazol-5-yl)-5-fluoro-cinnolin-7-yl]-3,4-dihydroxy-piperidine-1-carboxylate (cis-diol, racemate) (14.0 mg, 0.0276 mmol, 65.3% yield) as a yellow solid. MS m/z 508.2 [M+H].sup.+.

(672) Step B: A vial was charged with tert-butyl 4-[3-(2,7-dimethylindazol-5-yl)-5-fluoro-cinnolin-

7-yl]-3,4-dihydroxy-piperidine-1-carboxylate (7.00 mg, 0.0138 mmol), trifluoroacetic acid (0.22 ml, 2.9 mmol) and dichloromethane (0.5 ml). The mixture was stirred at room temperature for 1 h. The mixture was concentrated. To the mixture was added 1.25 N HCl in methanol (1 mL). The mixture concentrated (this step was repeated three times). The solid was washed with ethyl acetate, ether and hexanes in a fritted funnel and then freeze dried to give 4-(3-(2,7-dimethyl-2H-indazol-5-yl)-5-fluorocinnolin-7-yl)piperidine-3,4-diol hydrogen chloride (cis-diol, racemate) (7.3 mg, 0.018 mmol, 100% yield).

(673) MS m/z 408.3 [M+H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.69 (s, 1H), 8.53 (s, 1H), 8.50 (s, 1H), 8.42 (s, 1H), 8.03 (s, 1H), 7.85 (d, J=11 Hz, 1H), 4.35 (dd, J=5, 1.5 Hz, 1H), 4.30 (s, 3H), 3.40 (m, 6H), 2.70 (s, 3H). NH and OH protons not observed.

Example 36

(674) Preparation of Compound 146

(675) ##STR00150## ##STR00151##

(676) Step A: 2,6-Dimethylpyridin-3-ol (996 mg, 8.1 mmol) was dissolved in aqueous sodium hydroxide (2.0 M, 4.1 mL) while stirring at room temperature. To this stirred solution was added iodine (2.65 g, 10.4 mmol). The mixture was warmed to 50° C. and stirred for 3 h. The mixture was neutralized with aqueous hydrochloric acid (6 M), then quenched with saturated aqueous sodium thiosulfate solution. MeOH (5 mL) was added to the mixture, and then the reaction mixture was concentrated. CH.sub.2Cl.sub.2 (90 mL) and MeOH (10 mL) were added, the reaction was stirred for 10 min, then filtered. The filtrate was concentrated. The residue was chromatographed on silica gel, eluting with 0-100% EtOAc in hexanes to yield 4-iodo-2,6-dimethyl-pyridin-3-ol (564.6 mg, 28%).

(677) MS m/z 250.1 [M+H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 7.61 (s, 1H), 2.47 (s, 3H), 2.39 (s, 3H), OH proton not observed.

(678) Step B: tert-Butyl 4-(7-chloro-5-fluoro-cinnolin-3-yl)piperidine-1-carboxylate (500 mg, 1.37 mmol), sodium tert-butoxide (198 mg, 2.06 mmol), and chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)[2-2′-amino-1,1′-biphenyl)]palladium(II) (103 mg, 0.14 mmol), 1,4-dioxane (10 mL), and diphenylmethanimine (260 uL, 1.55 mmol) were combined, argon degassed, and heated to 100° C. for 16 h. After cooling the reaction mixture to room temperature, hydroxylamine hydrochloride (445 mg, 6.4 mmol), potassium acetate (815 mg, 8.3 mmol) and methanol (30 mL) were added. The reaction mixture was stirred at room temperature for 7 h. The mixture was concentrated, and the residue was partitioned between EtOAc and H.sub.2O. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-10% MeOH in CH.sub.2Cl.sub.2 to yield tert-butyl 4-(7-amino-5-fluoro-cinnolin-3-yl)piperidine-1-carboxylate (337 mg, 71%).

(679) MS m/z 347.3 [M+H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 7.87 (s, 1H), 7.14 (s, 1H), 7.06 (dd, J=11.6, 1.8 Hz, 1H), 4.30 (d, J=13.7 Hz, 2H), 3.29 (tt, J=12.2, 3.7 Hz, 1H), 2.92-3.11 (m, 2H), 2.04 (d, J=12.2 Hz, 2H), 1.87 (qd, J=12.6, 4.3 Hz, 2H), 1.51 (s, 9H), NH.sub.2 protons not observed.

(680) Step C: tert-Butyl 4-(7-amino-5-fluoro-cinnolin-3-yl)piperidine-1-carboxylate (187 mg, 0.54 mmol) was dissolved in trifluoroacetic acid (4.0 mL) and stirred at room temperature for 5 min. Sodium nitrite (43 mg, 0.63 mmol) was added to the mixture, which was stirred at room temperature for 10 min. The mixture was concentrated under reduced pressure. The residue was dissolved in acetonitrile (4.0 mL) and water (1.0 mL). To this stirred solution at room temperature was added potassium iodide (394 mg, 2.37 mmol) portion wise. The mixture was stirred for 20 min at room temperature. Diisopropylethylamine (1.4 mL, 8.0 mmol) and di-tert-butyl dicarbonate (800 uL, 3.35 mmol) were added to the mixture. The mixture was stirred at room temperature for 18 h. The mixture was concentrated, and the residue was chromatographed on silica gel, eluting with 0-100% EtOAc in hexanes to yield tert-butyl 4-(5-fluoro-7-iodocinnolin-3-yl)piperidine-1-

carboxylate (119 mg, 48%).
(681) MS m/z 402.3 [M+H-tBu].sup.+; .sup.1H NMR (CDCl.sub.3) δ: 8.82 (s, 1H), 7.84 (s, 1H), 7.69 (d, J=8.2 Hz, 1H), 4.36 (br s, 2H), 3.45 (tt, J=12.2, 3.7 Hz, 1H), 2.97 (t, J=11.0 Hz, 2H), 2.15 (br d, J=13.1 Hz, 2H), 1.91 (qd, J=12.5, 4.3 Hz, 2H), 1.50-1.54 (m, 9H).
(682) Step D: tert-butyl 4-(5-fluoro-7-iodocinnolin-3-yl)piperidine-1-carboxylate, curprous iodide (1.0 mg, 0.0053 mmol), and bis(triphenylphosphine)palladium(II) dichloride (6.2 mg, 0.0088 mmol) were combined under a nitrogen atmosphere, followed by the addition of CH.sub.3CN (2.0 mL). The solution was argon degassed for 30 s, followed by the addition of trimethylamine (40 uL, 0.29 mmol). The solution was argon degassed for 3 min, followed by the addition of trimethylsilylacetylene (20 uL, 0.14 mmol). This mixture was stirred at room temperature under a nitrogen atmosphere for 16 h. The mixture was concentrated, and the residue was chromatographed on silica gel, eluting with 0-100% EtOAc in hexanes to yield tert-butyl 4-(5-fluoro-7-((trimethylsilyl)ethynyl)cinnolin-3-yl)piperidine-1-carboxylate (24.5 mg, 72%). MS m/z 372.5 [M+H-t-Bu].sup.+.
(683) Step E: tert-Butyl 4-(5-fluoro-7-((trimethylsilyl)ethynyl)cinnolin-3-yl)piperidine-1-carboxylate (25 mg, 0.057 mmol) was dissolved in MeOH (2.0 mL). The stirred solution was cooled to 0° C. Potassium carbonate (17.9 mg, 0.130 mmol) was added and the reaction mixture continued stirring at 0° C. for 1 h. The reaction was quenched with sat'd aqueous NH.sub.4Cl (8.0 mL). The mixture was partitioned between CH.sub.2Cl.sub.2 and H.sub.2O. The aqueous layer was extracted twice with CH.sub.2Cl.sub.2. The combined organic layers were dried over Na.sub.2SO.sub.4, filtered and concentrated to yield tert-butyl 4-(7-ethynyl-5-fluoro-cinnolin-3-yl)piperidine-1-carboxylate as a crude mixture that was used without purification. MS m/z 300.0 [M-FH-t-Bu].sup.+. tert-Butyl 4-(7-ethynyl-5-fluoro-cinnolin-3-yl)piperidine-1-carboxylate (20 mg, 0.057 mmol), cuprous iodide (0.3 mg, 0.002 mmol), bis(triphenylphosphine)palladium(II) dichloride (4.4 mg, 0.0063 mmol), and 4-iodo-2,6-dimethyl-pyridin-3-ol (15.8 mg, 0.063 mmol) were combined under a nitrogen atmosphere, followed by the addition of N,N-dimethylformamide (1.0 mL). The solution was argon degassed for 30 s, followed by the addition of trimethylamine (50.0 uL, 0.36 mmol). This solution was argon degassed for 5 min, then stirred at 45° C. under an argon atmosphere for 20 h. The mixture was concentrated, and the residue was chromatographed on silica gel, eluting with 0-30% MeOH in CH.sub.2Cl.sub.2 to yield tert-butyl 4-[7-(5,7-dimethylfuro[2,3-c]pyridin-2-yl)-5-fluoro-cinnolin-3-yl]piperidine-1-carboxylate (10.3 mg, 38%). MS m/z 477.5 [M+H].sup.+.
(684) Step F: tert-Butyl 4-[7-(5,7-dimethylfuro[2,3-c]pyridin-2-yl)-5-fluoro-cinnolin-3-yl]piperidine-1-carboxylate (10.3 mg, 0.022 mmol) was dissolved in trifluoroacetic acid (2 mL). After 15 minutes, the volatile material was removed. The residue was chromatographed on a reversed phase C18 column, eluting with 0-100% CH.sub.1CN in H.sub.2O (0.1% v/v TFA additive). The collected fractions were concentrated. The residue was dissolved in 1.25 M HCl in MeOH. The volatile material was removed to yield 2-[5-fluoro-3-(4-piperidyl)cinnolin-7-yl]-5,7-dimethyl-furo[2,3-c]pyridine hydrochloride (8.3 mg, 93%).
(685) MS m/z 377.5 [M+H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.11 (s, 1H), 8.48 (s, 1H), 8.40 (br d, J=10.1 Hz, 1H), 8.04 (s, 1H), 7.99 (s, 1H), 3.69-3.77 (m, 1H), 3.66 (br d, J=12.8 Hz, 2H), 3.34-3.39 (m, 2H), 3.12 (s, 3H), 2.84 (s, 3H), 2.27-2.50 (m, 4H), NH and HCl protons not observed.
Example 37
(686) Preparation of Compound 191
(687) ##STR00152##
(688) Step A: 4-Chloro-2,6-dimethyl-3-nitro-pyridine (1.1054 g, 5.9239 mmol), acetonitrile (4.0 mL), and aqueous hydroiodic acid (concentrated, 57%, 4.0 mL) were combined and heated to 70° C. for 20 h. The mixture was partitioned between CH.sub.2Cl.sub.2, aqueous sat'd Na.sub.2C.sub.3, and aqueous NaOH (1 M). The aqueous layer was extracted with

CH.sub.2Cl.sub.2. The combined organic phases were dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-100% EtOAc in hexanes to yield 4-iodo-2,6-dimethyl-3-nitro-pyridine (1.48 g, 90%). MS m/z 279.1 [M+H].sup.+.
(689) Step B: 4-Iodo-2,6-dimethyl-3-nitro-pyridine (1.004 g, 3.611 mmol), stannous chloride dihydrate (3.32 g, 14.7 mmol) and EtOAc (5.0 mL) were combined and heated to 60° C. for 10 min. The mixture was partitioned between EtOAc, aqueous sat'd Na.sub.2CO.sub.3 and aqueous NaOH (1 M). The aqueous layer was extracted with EtOAc. The combined organic phases were dried over Na.sub.2SO.sub.4, filtered and concentrated to yield 4-iodo-2,6-dimethyl-pyridin-3-amine (723.7 mg, 81%). MS m/z 249.1 [M+H].sup.+.
(690) Step C: 4-Iodo-2,6-dimethyl-pyridin-3-amine (724 mg, 2.92 mmol), di-tert-butyl dicarbonate (2.2 mL, 9.2 mmol), 4-dimethylaminopyridine (42 mg, 0.34 mmol) and CH.sub.2Cl.sub.2 (5.0 mL) were combined and stirred at 40° C. for 17 h. The mixture was concentrated, and the residue was chromatographed on silica gel, eluting with 0-100% EtOAc in hexanes to yield tert-butyl N-tert-butoxycarbonyl-N-(4-iodo-2,6-dimethyl-3-pyridyl)carbamate (489 mg, 37%). MS m/z 449.4 [M+H].sup.+.
(691) Step D: tert-Butyl N-tert-butoxycarbonyl-N-(4-iodo-2,6-dimethyl-3-pyridyl)carbamate (489 mg, 1.1 mmol), aqueous NaOH (1 M, 4.0 mL), and MeOH (4.0 mL) were combined and stirred at 70° C. for 7 h. The mixture was partitioned between CH.sub.2Cl.sub.2 and H.sub.2O. The aqueous layer was extracted twice with MeOH/CH.sub.2Cl.sub.2 (1:9) and the combined organic phases were dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-100% EtOAc in hexanes to yield tert-butyl N-(4-iodo-2,6-dimethyl-3-pyridyl)carbamate (278 mg, 73%). MS m/z 349.1 [M+H].sup.+; .sup.1H NMR (CDCl.sub.3) δ: 7.54 (s, 1H), 6.00 (br d, J=2.7 Hz, 1H), 2.57 (s, 3H), 2.48 (s, 3H), 1.53 (s, 9H).
(692) Step E: tert-Butyl 4-(5-fluoro-7-((trimethylsilyl)ethynyl)cinnolin-3-yl)piperidine-1-carboxylate (from Example 38, 104 mg, 0.24 mmol) was dissolved in methanol (2.0 mL). The stirred solution was cooled to 0° C. Potassium carbonate (50.6 mg, 0.366 mmol) was added and the mixture was stirred at 0° C. for 1 h. The reaction mixture was quenched with sat'd aqueous NH.sub.4Cl (8.0 mL). The mixture was partitioned between CH.sub.2Cl.sub.2 and H.sub.2O. The aqueous layer was extracted twice with CH.sub.2Cl.sub.2. The combined organic layers were dried over Na.sub.2SO.sub.4, filtered and concentrated to yield tert-butyl 4-(7-ethynyl-5-fluoro-cinnolin-3-yl)piperidine-1-carboxylate as a crude mixture that was used without purification. MS m/z 300.0 [M+H-tBu].sup.+. tert-Butyl 4-(7-ethynyl-5-fluoro-cinnolin-3-yl)piperidine-1-carboxylate (86 mg, 0.24 mmol) was dissolved in DMF (1.0 mL). The vessel was purged with argon. Triethylamine (135 uL, 0.97 mmol) was added. The vessel was again purged with argon. This solution was added to a mixture of cuprous iodide (1.4 mg, 0.0073 mmol), bis(triphenylphosphine) palladium(II) dichloride (10.2 mg, 0.0146 mmol), and tert-butyl N-(4-iodo-2,6-dimethyl-3-pyridyl)carbamate (93 mg, 0.27 mmol) under an argon atmosphere. The solution was stirred at 50° C. for 17 h. The mixture was concentrated, and the residue partitioned between CH.sub.2Cl.sub.2 and brine. The aqueous layer was extracted with CH.sub.2Cl.sub.2. The combined organic phases were dried over Na.sub.2SO.sub.4, filtered and concentrated to yield tert-butyl 4-[7-[2-[3-(tert-butoxycarbonylamino)-2,6-dimethyl-4-pyridyl]ethynyl]-5-fluoro-cinnolin-3-yl]piperidine-1-carboxylate as a crude mixture that was used without purification. MS m/z 576.5 [M+H].sup.+.
(693) Step F: tert-Butyl 4-[7-[2-[3-(tert-butoxycarbonylamino)-2,6-dimethyl-4-pyridyl]ethynyl]-5-fluoro-cinnolin-3-yl]piperidine-1-carboxylate (140 mg, 0.24 mmol), tetrahydrofuran (4.0 mL), and tetrabutylammonium fluoride (1.0 M in THF, 730 uL, 0.73 mmol) were combined and stirred at 65° C. for 2 h. The reaction was concentrated and the residue was chromatographed on silica gel, eluting with 0-30% MeOH in CH.sub.2Cl.sub.2 to yield tert-butyl 4-[7-(5,7-dimethyl-1H-pyrrolo[2,3-c]pyridin-2-yl)-5-fluoro-cinnolin-3-yl]piperidine-1-carboxylate (34.2 mg, 30%). MS m/z 476.5 [M+H].sup.+.
(694) Step G: tert-Butyl 4-[7-(5,7-dimethyl-1H-pyrrolo[2,3-c]pyridin-2-yl)-5-fluoro-cinnolin-3-

yl]piperidine-1-carboxylate (34.2 mg, 0.0719 mmol) was dissolved in trifluoroacetic acid (1 mL). After 1 min, the volatile material was removed. The residue was chromatographed on a reversed phase C18 column, eluting with 0-100% CH.sub.3CN in H.sub.2O (0.1% v/v TFA additive), and subsequently chromatographed on silica gel, eluting with 0-100% MeOH (2.5% v/v NH.sub.4OH additive) in CH.sub.2Cl.sub.2, to yield 7-(5,7-dimethyl-1H-pyrrolo[2,3-c]pyridin-2-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline hydrochloride.

(695) MS m/z 376.3 [M+H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.95 (s, 1H), 8.23 (s, 1H), 8.22 (dd, J=10.7, 1.2 Hz, 1H), 7.67 (s, 1H), 7.41 (s, 1H), 3.50-3.61 (m, 3H), 3.17-3.26 (m, 2H), 2.99 (s, 3H), 2.64 (s, 3H), 2.18-2.34 (m, 4H), NH and HCl protons not observed.

Example 38

(696) Preparation of Compound 82

(697) ##STR00153## ##STR00154##

(698) Step A: 5-Bromo-3-fluoro-benzene-1,2-diamine (1.07 g, 5.2 mmol), tert-butyl 4-(2-bromoacetyl)piperidine-1-carboxylate (1.60 g, 5.2 mmol), and DMF (80 mL) were combined and stirred at room temperature for 16 h, 50° C. for 24 h, and 70° C. for 24 h. After cooling to room temperature, potassium carbonate (1.08 g, 7.84 mmol) and di-tert-butyl dicarbonate (1.4 mL, 6.3 mmol) were added. The reaction mixture was stirred at room temperature for 2 h. The mixture was partitioned between EtOAc and brine. The organic layer was washed twice with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-100% EtOAc in hexanes to yield tert-butyl 4-(6-bromo-8-fluoro-quinoxalin-2-yl)piperidine-1-carboxylate and tert-butyl 4-(7-bromo-5-fluoroquinoxalin-2-yl)piperidine-1-carboxylate as an approximate 1:1 mixture (labeled distinguishable peaks as compounds A and B in .sup.1H NMR; labeled overlapping peaks as apparent peaks “apt”) (1.23 g, 58%).

(699) MS m/z 310.2 [M+H—CO.sub.2-t-Bu].sup.+; .sup.1H NMR (CDCl.sub.3) δ: 8.84 (s, 1H, A), 8.82 (s, 1H, B), 8.12 (t, J=1.7 Hz, 1H, A), 8.09 (t, J=1.7 Hz, 1H, B), 7.61 (dd, J=9.2, 2.1 Hz, 1H, A), 7.58 (dd, J=9.0, 2.0 Hz, 1H, B), 4.34 (apt d, J=12.2 Hz, 4H), 3.17 (apt qt, J=11.9, 3.7 Hz, 2H), 2.94 (apt br tt, J=13.1, 2.8 Hz, 4H), 1.99-2.06 (m, 4H), 1.93 (apt quint J=11.6, 4.0 Hz, 4H), 1.51 (apt d, J=1.8 Hz, 18H).

(700) Step B: A 1:1 mixture of tert-butyl 4-(6-bromo-8-fluoro-quinoxalin-2-yl)piperidine-1-carboxylate and tert-butyl 4-(7-bromo-5-fluoroquinoxalin-2-yl)piperidine-1-carboxylate was combined with sodium tert-butoxide (760 mg, 7.9 mmol), tris(dibenzylideneacetone) dipalladium(0) (74 mg, 0.08 mmol), racemic 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (144 mg, 0.23 g), toluene (13.0 mL) and benzophenone imine (500 uL, 3.6 mmol) were combined under a nitrogen atmosphere. The vessel was argon purged for 6 min, then warmed to 80° C. for 20 h. Hydroxylamine hydrochloride (1.37 g, 19.6 mmol), potassium acetate (2.47 g, 25.2 mmol), and MeOH (65 mL) were added to the mixture. The mixture was stirred at room temperature for 24 h and then was concentrated. The residue was partitioned between sat'd aqueous Na.sub.2CO.sub.3, brine, and CH.sub.2Cl.sub.2. The aqueous layer was extracted twice with CH.sub.2Cl.sub.2. The combined organic layers were dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-100% EtOAc in hexanes to yield tert-butyl 4-(6-amino-8-fluoro-quinoxalin-2-yl)piperidine-1-carboxylate (340.0 mg, 38%).

(701) MS m/z 291.3 [M-FH-t-Bu].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.69 (s, 1H), 7.01 (dd, J=12.5, 2.1 Hz, 1H), 6.77 (d, J=2.1 Hz, 1H), 6.11 (s, 2H), 4.03-4.21 (m, 2H), 3.06 (tt, J=11.5, 3.4 Hz, 1H), 2.89 (br s, 2H), 1.86-1.93 (m, 2H), 1.66 (qd, J=12.6, 4.4 Hz, 2H), 1.43 (s, 9H).

(702) Step C: Sodium nitrite (23.9 mg, 0.346 mmol) was added to a stirred solution of tert-butyl 4-(6-amino-8-fluoro-quinoxalin-2-yl)piperidine-1-carboxylate in trifluoroacetic acid (1.5 mL). The mixture was stirred at room temperature for 1 min. The mixture was concentrated and azeotroped twice with MeCN. The residue was dissolved in acetonitrile (1.4 mL) and cooled to 0° C. This solution was added dropwise to a solution of copper(I) chloride (47 mg, 0.47 mmol) and copper(II) chloride (95 mg, 0.71 mmol) in acetonitrile (1.2 mL) at 0° C. After stirring for 1 min at 0° C., the

reaction mixture was partitioned between EtOAc, aqueous sat'd Na.sub.2CO.sub.3, and aqueous NaOH (1 M). The aqueous layer was extracted with EtOAc. The combined organic phases were dried over Na.sub.2SO.sub.4, filtered and concentrated to yield 6-chloro-8-fluoro-2-(4-piperidyl)quinoxaline (130.0 mg) as a crude mixture that was used without purification. MS m/z 266.3 [M+H].sup.+. 6-Chloro-8-fluoro-2-(4-piperidyl)quinoxaline (61 mg, 0.23 mmol), CH.sub.2Cl.sub.2 (3.0 mL), N,N-diisopropylethylamine (400 uL, 2.3 mmol), and di-tert-butyl dicarbonate (230 uL, 0.96 mmol) were combined and stirred at room temperature for 18 h. The mixture was partitioned between CH.sub.2Cl.sub.2 and H.sub.2O. The aqueous layer was extracted twice with CH.sub.2Cl.sub.2. The combined organic phases were dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-40% EtOAc in hexanes to yield tert-butyl 4-(6-chloro-8-fluoroquinoxalin-2-yl)piperidine-1-carboxylate (52.7 mg, 50%).
(703) MS m/z 310.3 [M+H-t-Bu].sup.+; .sup.1H NMR (CDCl.sub.3) δ: 8.84 (s, 1H), 7.93 (t, J=1.8 Hz, 1H), 7.48 (dd, J=9.5, 2.1 Hz, 1H), 4.26-4.44 (m, 2H), 3.19 (tt, J=11.7, 3.8 Hz, 1H), 2.94 (br t, J=12.2 Hz, 2H), 2.04 (d, J=11.9 Hz, 2H), 1.94 (qd, J=12.2, 4.3 Hz, 2H), 1.52 (s, 9H).
(704) Step D: 6-Chloro-2,8-dimethyl-imidazol[1,2-b]pyridazine (50.0 mg, 0.275 mmol), 1,1′-bis(diphenylphosphino)ferrocene palladium(II) dichloride (15 mg, 0.019 mmol), bis(pinacolato)diboron (96 mg, 0.37 mmol), and potassium acetate (dried at 250° C. under vacuum immediately prior to using, 89 mg, 0.89 mmol), and 1,4-dioxane (1.5 mL) were combined. The mixture stirred under argon at 95° C. for 2 h. tert-Butyl 4-(6-chloro-8-fluoro-quinoxalin-2-yl)piperidine-1-carboxylate (65.8 mg, 0.180 mmol), chloro(2-dicyclohexylphosphino-2′6′-dimethoxy-1,1′-biphenyl)(2′-amino-1,1′-biphenyl-2-yl) palladium(II) (6.6 mg, 0.0091 mmol), and aqueous K.sub.2CO.sub.3 (1 M, 750 uL) were added to the mixture. The mixture was argon flushed, and then was stirred at 80° C. for 16 h. The reaction was partitioned between EtOAc and H.sub.2O. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 0-100% EtOAc in hexanes to yield tert-butyl 4-[6-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-8-fluoro-quinoxalin-2-yl]piperidine-1-carboxylate (44 mg, 52%). MS m/z 477.6 [M+H].sup.+.
(705) Step E: tert-Butyl 4-[6-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-8-fluoro-quinoxalin-2-yl]piperidine-1-carboxylate (45 mg, 0.094 mmol) was dissolved in CH.sub.2Cl.sub.2 (2 mL) and TFA (2 mL). After 10 min, the volatile material was removed. The residue was dissolved in methanolic hydrogen chloride (1.25 M) and concentrated to yield 6-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-8-fluoro-2-(4-piperidyl)quinoxaline hydrochloride (47 mg, quant.).
(706) MS m/z 377.3 [M+H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.11 (s, 1H), 8.75 (s, 1H), 8.51 (d, J=0.9 Hz, 1H), 8.35-8.46 (m, 2H), 3.64 (dt, J=12.9, 3.2 Hz, 2H), 3.58 (tt, J=11.0, 3.8 Hz, 1H), 3.24-3.32 (m, 2H), 2.87 (s, 3H), 2.71 (s, 3H), 2.35-2.42 (m, 2H), 2.26-2.34 (m, 2H), NH and HCl protons not observed.
Example 39
(707) Preparation of Compound 116
(708) ##STR00155##
(709) Step A: tert-Butyl 4-(7-chloro-5-fluorocinnolin-3-yl)piperidine-1-carboxylate (500 mg, 1.4 mmol) was combined with tri-butyl(1-ethoxyvinyl)tin (0.52 mL, 1.54 mmol) and CsF (470 mg, 3.08 mmol) in 1,4-dioxane (16 mL). The mixture was stirred at 90° C. for 2 h under N.sub.2. The mixture was partitioned between EtOAc and H.sub.2O. The organic layer was washed with brine, dried over Na.sub.2SO.sub.4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 10-20% EtOAc in petroleum ether to yield tert-butyl 4-(7-(1-ethoxyvinyl)-5-fluorocinnolin-3-yl)piperidine-1-carboxylate (500 mg, 90%). MS m/z 402.7 [M+H].sup.+.
(710) Step B: tert-Butyl 4-(7-(1-ethoxyvinyl)-5-fluorocinnolin-3-yl)piperidine-1-carboxylate (480 mg, 1.2 mmol) was combined with NBS (235 mg, 1.32 mmol) in THF (20 mL) and H.sub.2O (10

mL). The mixture was stirred at room temperature for 10 min. The THF was removed under reduce pressure. The solution was filtered. The solid was dried to yield tert-butyl 4-(7-(2-bromoacetyl)-5-fluorocinnolin-3-yl)piperidine-1-carboxylate (500 mg, 92%). MS m/z 474.0, 476.0 [M+Na].sup.+.
(711) Step C: tert-Butyl 4-(7-(2-bromoacetyl)-5-fluorocinnolin-3-yl)piperidine-1-carboxylate (477 mg, 1.06 mmol) was combined with 3,5-dimethylpyrazin-2-amine (234 mg, 1.9 mmol) in EtOH (20 mL). The mixture was stirred at 90° C. for 4 h. Then the mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel, eluting with 30-50% EtOAc in CH.sub.2Cl.sub.2 to yield tert-butyl 4-(7-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-fluorocinnolin-3-yl)piperidine-1-carboxylate (270 mg, 53%). MS m/z 477.2 [M+H].sup.+.
(712) Step D: tert-Butyl 4-(7-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-fluorocinnolin-3-yl)piperidine-1-carboxylate (230 mg, 0.48 mmol) was into TFA (2 mL). The mixture was stirred at room temperature for 1 h. The volatile material was removed under reduced pressure. The residue was purified by prep-HPLC to yield 7-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-5-fluoro-3-(piperidin-4-yl)cinnoline hydrochloride (86 mg, 45% Yield).
(713) MS m/z 377.2 [M+H].sup.+; .sup.1H NMR (DMSO-d.sub.6) δ: 8.93 (s, 1H), 8.83 (s, 1H), 8.29-8.38 (m, 2H), 8.11 (s, 1H), 3.82 (s, 1H), 3.12 (dd, J=12.5, 9.5 Hz, 4H), 2.82 (d, J=13.2 Hz, 3H), 2.41 (s, 3H), 2.10-2.28 (m, 4H), NH proton not observed
Example 40
(714) Preparation of Compound 226
(715) ##STR00156##
(716) Step A: KOAc (6.6 g, 67 mmol) was dried under sweeping argon at 180° C. for 30 min. The mixture was cooled to room temperature. 7-Bromo-3-chloro-5-fluorocinnoline (90% purity, 3 g, 10.3 mmol) was added, along with bis(pinacolato)diboron (3 g, 11.8 mmol), SPhos Pd G2 (300 mg, 0.41 mmol) and 1,4-dioxane (40 mL). The mixture was heated at 80° C. for 15 h. The mixture was diluted in EtOAc and was filtered through Celite. The filtrate was concentrated under vacuum. The residue was chromatographed on silica gel, eluting with 20-50% EtOAc in CH.sub.2Cl.sub.2 to yield crude boronic acid. This material was suspended in 100 mL of 1:1 acetone:H.sub.2O at 0° C. Oxone (20 g, 32.3 mmol) was added. The mixture was stirred at 0° C. for 15 min. The reaction mixture was diluted in 600 mL H.sub.2O and then filtered. The collected material was dried to yield 3-chloro-5-fluorocinnolin-7-ol (1.92 g, 84%) as a dark yellow solid.
(717) .sup.1H NMR (DMSO-d.sub.6) δ: 11.34 (s, 1H), 8.39 (s, 1H), 7.49 (s, 1H), 7.40 (dd, J=11, 2 Hz, 1H).
(718) Step B: 3-Chloro-5-fluorocinnolin-7-ol (1.9 g, 8.6 mmol, 90% purity) was dissolved in DMF (37 mL). K.sub.2CO.sub.3 (3.8 g, 27 mmol) was added to the solution. The mixture was stirred at room temperature for 30 min. Iodomethane (1.9 mL, 31 mmol) was added to the mixture. The reaction mixture was stirred at room temperature for 2 h. The mixture was partitioned between H.sub.2O and EtOAc. The organic layer was washed with H.sub.2O and brine, dried over MgSO.sub.4, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel, eluting with 20% EtOAc in hexanes to yield 3-chloro-5-fluoro-7-methoxycinnoline (1.04 g, 57%) as a white solid.
(719) .sup.1H NMR (acetone-d.sub.4) δ: 8.26 (s, 1H), 7.69 (s, 1H), 7.37 (dd, J=10.5, 2 Hz, 1H), 4.13 (s, 3H).
(720) Step C: 3-Chloro-5-fluoro-7-methoxycinnoline (990 mg, 4.65 mmol), (2R,6S)-1-benzyl-2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine (80% purity, 2.14 g, 5.24 mmol), Pd(dppf)Cl.sub.2—CH.sub.2Cl.sub.2 (190 mg, 0.23 mmol), 1,4-dioxane (26 mL), and aqueous K.sub.2CO.sub.3 (2.0 M, 13 mL, 26 mmol) were heated at 90° C. for 4 h. The mixture was partitioned between CH.sub.2Cl.sub.2 and H.sub.2O. The organic layer was dried over MgSO.sub.4, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel, eluting with 10-20% acetone in CH.sub.2Cl.sub.2 to yield 3-((2R,6S)-1-benzyl-2,6-dimethyl-

1,2,3,6-tetrahydropyridin-4-yl)-5-fluoro-7-methoxycinnoline (1.28 g, 73%) as an off-white solid.
(721) .sup.1H NMR (acetone-d.sub.4) δ: 8.07 (s, 1H), 7.67 (s, 1H), 7.47-7.51 (m, 2H), 7.30-7.36 (m, 2H), 7.20-7.27 (m, 2H), 7.00 (s, 1H), 4.11 (s, 3H), 3.97 (d, J=16 Hz, 1H), 3.91 (d, J=16 Hz, 1H), 3.53-3.60 (m, 1H), 3.10-3.15 (m, 1H), 2.86-2.92 (m, 1H), 2.54-2.62 (m, 1H), 1.32 (d, J=6.5 Hz, 3H), 1.21 (d, J=6.5 Hz, 3H).
(722) Step D: 3-((2R,6S)-1-Benzyl-2,6-dimethyl-1,2,3,6-tetrahydropyridin-4-yl)-5-fluoro-7-methoxycinnoline (1.28 g, 3.39 mmol) was dissolved in 140 mL of 1:1 CH.sub.2Cl.sub.2:MeOH. 10% Pd/C (300 mg) and 20% Pd(OH).sub.2/C (300 mg) were added. The mixture was stirred under H.sub.2 (50 psi) for 2 d. The reaction mixture was filtered over Celite, washing with CH.sub.2Cl.sub.2:MeOH. The filtrate was concentrated under vacuum. The residue was partitioned between aqueous NaOH and CH.sub.2Cl.sub.2. The organic layer was dried over MgSO.sub.4, filtered, and concentrated under vacuum. The residue was dissolved in CH.sub.2Cl.sub.2 (20 mL). To the solution was added MnO.sub.2 (5 g, 57.5 mmol). The mixture was stirred at room temperature for 2 h. The reaction mixture was filtered over Celite, washing with CH.sub.2Cl.sub.2:MeOH. The filtrate was concentrated and the residue was chromatographed on silica gel, eluting with CH.sub.2Cl.sub.2:MeOH:NH.sub.4OH (9:1:0.1) to yield 3-((2S,4R,6R)-2,6-dimethylpiperidin-4-yl)-5-fluoro-7-methoxycinnoline (568 mg, 53%) as yellow solid. This compound is the higher Rf component of the product mixture.
(723) .sup.1H NMR (methanol-d.sub.4) δ: 8.06 (s, 1H), 7.59 (s, 1H), 7.27 (dd, J=10.5, 1.5 Hz, 1H), 4.06 (s, 3H), 3.43 (tt, J=12.5, 3.5 Hz, 1H), 3.00-3.05 (m, 2H), 2.09 (d, J=12.5 Hz, 2H), 1.54 (q, J=12.5 Hz, 2H), 1.25 (d, J=6.5 Hz, 6H), NH proton not observed.
(724) Step E: A solution of 3-((2S,4R,6R)-2,6-Dimethylpiperidin-4-yl)-5-fluoro-7-methoxycinnoline (565 mg, 1.95 mmol) in MeOH (2 mL) and CH.sub.2Cl.sub.2 (8 mL) was treated with 37% formaldehyde in water (4 mL, 54 mmol). Sodium triacetoxyborohydride (3.3 g, 16 mmol) was added in three portions over 3 h. The reaction mixture was partitioned between aqueous NaOH and CH.sub.2Cl.sub.2. The organic layer was dried over MgSO.sub.4, filtered, and concentrated under vacuum to yield 5-fluoro-7-methoxy-3-((2S,4r,6R)-1,2,6-trimethylpiperidin-4-yl)cinnoline (566 mg, 95%) as a yellow solid.
(725) .sup.1H NMR (methanol-d.sub.4) δ: 8.06 (s, 1H), 7.59 (s, 1H), 7.27 (dd, J=10.5, 1.5 Hz, 1H), 4.06 (s, 3H), 3.43 (m, 1H), 2.50 (m, 2H), 2.41 (s, 3H), 2.08 (d, J=11 Hz, 2H), 1.82 (q, J=12 Hz, 2H), 1.29 (d, J=6.5 Hz, 6H).
(726) Step F: 5-Fluoro-7-methoxy-3-((2S,4R,6R)-1,2,6-trimethylpiperidin-4-yl)cinnoline (485 mg, 1.6 mmol) was dissolved in CH.sub.2Cl.sub.2 (4 mL) at 0° C. BBr.sub.3 (2 mL, 21.2 mmol) was added dropwise. The mixture became difficult to stir after 10 min. The mixture was warmed to room temperature. The sticky clumps were broken up with a spatula until the mixture could be stirred. The mixture was stirred at room temperature for 16 h. The mixture was added slowly to ice. NaOH pellets were added until the solution was basic. The volatile material was removed under vacuum. The crude product was re-dissolved in 20 mL H.sub.2O. Reverse-phase chromatography was used to desalt the product. Aqueous HCl was added to the purest fractions. The fractions were concentrated under reduced pressure to afford crude 5-fluoro-3-((2S,4R,6R)-1,2,6-trimethylpiperidin-4-yl)cinnolin-7-ol hydrochloride (70% purity, 687 mg, 92%). This material appears as a crude 2:1 tautomeric mixture by .sup.1H NMR in CD.sub.3OD. MS m/z 290.2 [M+H].sup.+.
(727) Step G: Crude 5-fluoro-3-((2S,4R,6R)-1,2,6-trimethylpiperidin-4-yl)cinnolin-7-ol hydrochloride (70% purity, 685 mg, 1.47 mmol), N,N-bis(trifluoromethylsulfonyl)aniline (2.7 g, 7.6 mmol), K.sub.2CO.sub.3 (2.7 g, 20 mmol), and DMF (7 mL) were stirred at room temperature for 15 h. The volatile material was removed under vacuum. The crude product was dissolved in CH.sub.2Cl.sub.2 and was filtered to remove solid impurities. The filtrate was concentrated under vacuum. The residue was chromatographed on silica gel, eluting with 5-20% MeOH in CH.sub.2Cl.sub.2 to yield 5-fluoro-3-((2S,4R,6R)-1,2,6-trimethylpiperidin-4-yl)cinnolin-7-yl

trifluoromethanesulfonate (535 mg, 79% over 2 steps) as a yellow solid.
(728) .sup.1H NMR (methanol-d.sub.4) δ: 8.39 (s, 1H), 8.24 (s, 1H), 7.81 (dd, J=9.5, 2 Hz, 1H), 3.60 (m, 1H), 2.95 (br s, 2H), 2.63 (br s, 3H), 2.23 (d, J=12.5 Hz, 2H), 2.01 (q, J=12.5 Hz, 2H), 1.43 (d, J=6.5 Hz, 6H).
(729) Step H: A mixture of 5-fluoro-3-((2S,4R,6R)-1,2,6-trimethylpiperidin-4-yl)cinnolin-7-yl trifluoromethanesulfonate (36 mg, 0.085 mmol), KOAc (30 mg, 0.30 mmol), bis(pinacolato)diboron (26 mg, 0.1 mmol), Pd(dppf)Cl.sub.2 (7 mg, 0.0084 mmol), and 1,4-dioxane (0.35 mL) were heated at 90° C. for 15 h. The reaction mixture was diluted in EtOAc and was filtered over Celite. The filtrate was concentrated under vacuum. The crude boronic acid was dissolved in Et.sub.2O and filtered over Celite to remove black insoluble impurities. The filtrate was concentrated by nitrogen stream to afford 51 mg of crude boronic acid as a black oil. 5-Chloro-2,7-dimethyloxazolo[5,4-b]pyridine (11 mg, 0.06 mmol), Pd(dppf)Cl.sub.2 (7 mg, 0.0084 mmol), 1,4-dioxane (0.3 mL), and aqueous K.sub.2CO.sub.3 (2.0 M, 0.15 mL, 0.3 mmol) were added to the crude boronic acid. The mixture was stirred at 90° C. for 1 h. The mixture was partitioned between CH.sub.2Cl.sub.2 and H.sub.2O. The organic layer was dried over MgSO.sub.4, filtered, and concentrated under vacuum. The residue chromatographed on silica gel, eluting with CH.sub.2Cl.sub.2:MeOH:NH.sub.4OH (95:5:0.5) to CH.sub.2Cl.sub.2:MeOH:NH.sub.4OH (90:10:1). Recrystallization from 1.5 mL methanol yielded 5-(5-fluoro-3-((2S,4R,6R)-1,2,6-trimethylpiperidin-4-yl)cinnolin-7-yl)-2,7-dimethyloxazolo[5,4-b]pyridine (17 mg, 47%) as a white solid.
(730) MS m/z 420.3 [M+H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.95 (s, 1H), 8.36 (d, J=11 Hz, 1H), 8.16 (s, 1H), 8.10 (s, 1H), 3.46-3.53 (in, 1H), 2.74 (s, 3H), 2.73 (s, 3H), 2.53 (m, 2H), 2.43 (s, 3H), 2.13 (d, J=12 Hz, 2H), 1.88 (q, J=12 Hz, 2H), 1.31 (d, J=6 Hz, 6H).
(731) Using the procedure described for Example 40, above, additional compounds described herein were prepared by substituting the appropriate heteroaryl halide in Step H, suitable reagents and reaction conditions, obtaining compounds such as those selected from:
(732) TABLE-US-00029 Cpd Data 227 MS m/z 419.3 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 8.89 (s, 1H), 8.53 (s, 1H), 8.39 (dd, J = 11, 1.5 Hz, 1H), 8.16 (s, 1H), 7.95 (s, 1H), 4.33 (s, 3H), 3.45-3.51 (m, 1H), 2.76 (s, 3H), 2.50-2.55 (m, 2H), 2.43 (s, 3H), 2.13 (d, J = 13.5 Hz, 2H), 1.87 (q, J = 12.5 Hz, 2H), 1.31 (d, J = 6.5 Hz, 6H). 228 MS m/z 420.3 [M + H].sup.+; .sup.1H NMR (methanol-d.sub.4) δ: 9.08 (s, 1H), 8.32 (dd, J = 10, 1 Hz, 1H), 8.20 (s, 1H), 7.55 (s, 1H), 3.48-3.55 (m, 1H), 2.84 (s, 3H), 2.68 (s, 3H), 2.50- 2.55 (m, 2H), 2.43 (s, 3H), 2.14 (d, J = 13.5 Hz, 2H), 1.89 (q, J = 13 Hz, 2H), 1.31 (d, J = 6.5 Hz, 6H).
Biological Examples
(733) The following in vitro biological examples demonstrate the usefulness of the compounds of the present description for treating Huntington's disease.
(734) To describe in more detail and assist in understanding the present description, the following non-limiting biological examples are offered to more fully illustrate the scope of the description and are not to be construed as specifically limiting the scope thereof. Such variations of the present description that may be now known or later developed, which would be within the purview of one skilled in the art to ascertain, are considered to fall within the scope of the present description and as hereinafter claimed.
(735) Compounds of Formula (I) were tested using the Meso Scale Discovery (MSD) Assay provided in International Application No. PCT/US2016/066042, filed on Dec. 11, 2016 and claiming priority to United States Provisional Application U.S. 62/265,652 filed on Dec. 10, 2015, the entire contents of which are incorporated herein by reference.
(736) The Endogenous Huntingtin Protein assay used in Example 1 was developed using the ELISA-based MSD electrochemiluminescence assay platform.
Example 1
(737) Endogenous Huntingtin Protein Assay

(738) Meso Scale Discovery (MSD) 96-well or 384-well plates were coated overnight at 4° C. with MW1 (expanded polyglutamine) or MAB2166 monoclonal antibody (for capture) at a concentration of 1 μg/mL in PBS (30 μL per well). Plates were then washed three times with 300 μL wash buffer (0.05% Tween-20 in PBS) and blocked (100 μL blocking buffer; 5% BSA in PBS) for 4-5 hours at room temperature with rotational shaking and then washed three times with wash buffer.

(739) Samples (25 μL) were transferred to the antibody-coated MSD plate and incubated overnight at 4° C. After removal of the lysates, the plate was washed three times with wash buffer, and 25 μL of #5656S (Cell signaling; rabbit monoclonal) secondary antibody (diluted to 0.25 μg/mL in 0.05% Tween-20 in blocking buffer) was added to each well and incubated with shaking for 1 Hour at room temperature. Following incubation with the secondary antibody, the wells were rinsed with wash buffer after which 25 μL of goat anti-rabbit SULFO TAG secondary detection antibody (required aspect of the MSD system) (diluted to 0.25 μg/mL in 0.05% Tween-20 in blocking buffer) was added to each well and incubated with shaking for 1 hour at room temperature. After rinsing three times with wash buffer, 150 μL of read buffer T with surfactant (MSD) were added to each empty well, and the plate was imaged on a SI 6000 imager (MSD) according to manufacturers' instructions provided for 96- or 384-well plates. The resulting IC.sub.50 values (μM) for compounds tested are shown in Table 1.

(740) As shown in Table 1, test compounds described herein had the following IC.sub.50 values, an IC.sub.50 value between >3 μM and <9 μM is indicated by a single star (*), an IC.sub.50 value between >1 μM and ≤3 μM is indicated by two stars (**), an IC.sub.50 value between >0.5 μM and ≤1 μM is indicated by three stars (***), an IC.sub.50 value between >0.1 μM and ≤0.5 μM is indicated by four stars (****) and an IC.sub.50 value of ≤0.1 μM is indicated by five stars (*****).

(741) TABLE-US-00030 TABLE 1 Cpd IC.sub.50 1 ** 2 ** 3 **** 4 *** 5 ** 6 *** 7 ** 9 ** 10 **** 11 ** 12 *** 13 ** 14 **** 15 ***** 16 **** 17 ***** 18 **** 19 ***** 20 ***** 23 **** 24 **** 25 ***** 26 ***** 27 **** 28 ** 29 ** 30 **** 31 **** 32 ***** 33 ***** 34 ***** 35 ***** 36 ***** 37 ***** 38 ** 39 ** 40 **** 41 **** 42 **** 43 ***** 44 **** 45 ***** 46 ***** 47 ***** 48 ***** 49 ***** 50 ***** 51 ***** 52 ***** 53 **** 54 **** 55 ***** 56 ***** 57 ***** 58 ***** 59 ***** 60 **** 61 *** 62 ***** 63 ***** 64 ***** 65 **** 66 ***** 67 **** 68 ***** 69 ***** 70 ***** 71 ***** 72 ***** 73 ***** 74 ***** 75 ***** 76 ***** 77 ***** 78 ***** 79 ***** 80 ***** 81 ***** 82 ***** 83 ***** 84 ***** 85 **** 86 ***** 87 ***** 88 ***** 89 ***** 90 ***** 91 ** 92 ***** 93 ***** 94 **** 95 ***** 96 ***** 97 *** 98 **** 99 ***** 100 ***** 101 ***** 102 ***** 103 ***** 104 ***** 105 ***** 106 ***** 107 ***** 108 ***** 109 *** 110 ***** 111 ***** 112 ***** 113 ***** 114 ***** 115 ***** 116 **** 117 ***** 118 **** 119 *** 120 ** 121 ***** 122 ***** 123 ***** 124 ***** 125 ***** 126 ***** 127 ***** 128 ***** 129 ***** 130 ***** 131 ***** 132 ***** 133 ***** 134 ***** 135 ***** 136 ***** 137 ***** 138 **** 139 ***** 140 ***** 141 ***** 142 **** 143 ***** 144 ***** 145 ***** 146 ***** 147 **** 148 ***** 149 ***** 150 ***** 151 ***** 152 ***** 153 ***** 154 ***** 155 ***** 156 ***** 157 ***** 158 ***** 159 ***** 160 ***** 161 ***** 162 ***** 163 ***** 164 ***** 165 ***** 166 ***** 167 ***** 168 **** 169 ***** 170 **** 171 ***** 172 ***** 173 ***** 174 ***** 175 ***** 176 ***** 177 ***** 178 ***** 179 ***** 180 ***** 181 ***** 182 ***** 183 ***** 184 ***** 185 ***** 186 ***** 187 ***** 188 ***** 189 ***** 190 ***** 191 **** 192 ***** 193 ***** 194 **** 195 ***** 196 ***** 197 ***** 198 **** 199 ***** 200 ***** 201 ***** 202 ***** 203 *** 204 ***** 205 **** 206 ***** 207 ***** 208 **** 209 **** 210 ***** 211 ***** 212 **** 213 **** 214 **** 215 ***** 216 ***** 217 ***** 218 ***** 219 ***** 220 **** 221 ***** 222 **** 223 ***** 224 ***** 225 ***** 226 ***** 227 ***** 228 ****

(742) Without regard to whether a document cited herein was specifically and individually

indicated as being incorporated by reference, all documents referred to herein are incorporated by reference into the present application for any and all purposes to the same extent as if each individual reference was fully set forth herein.
(743) Having now fully described the subject matter of the claims, it will be understood by those having ordinary skill in the art that the same can be performed within a wide range of equivalents without affecting the scope of the subject matter or particular aspects described herein. It is intended that the appended claims be interpreted to include all such equivalents.

Claims

1. A compound of Formula (Ig1), Formula (Ii1), or Formula (Im1): ##STR00157## or a form thereof, wherein: R.sub.1 is heterocyclyl or heterocyclyl-amino, wherein heterocyclyl is selected from the group consisting of azetidinyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, azepanyl, 1,4-diazepanyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, (3aR,6aR)-hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-(1H)-yl, (3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, (4aR,7aR)-octahydro-6H-pyrrolo[3,4-b]pyridinyl, (4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (7R,8aS)-hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aS)-hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aR)-hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1,2-c:1,4-c′]dipyrrol-(3H)-yl, (8aS)-octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aR)-octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, 3-azabicyclo[3.1.0]hexyl, (1R,5S)-3-azabicyclo[3.1.0]hexyl, 8-azabicyclo[3.2.1]octyl, (1R,5S)-8-azabicyclo[3.2.1]octyl, 8-azabicyclo[3.2.1]oct-2-enyl, (1R,5S)-8-azabicyclo[3.2.1]oct-2-enyl, 9-azabicyclo[3.3.1]nonyl, (1R,5S)-9-azabicyclo[3.3.1]nonyl, 2,5-diazabicyclo[2.2.1]heptyl, (1S,4S)-2,5-diazabicyclo[2.2.1]heptyl, 1,4-diazabicyclo[3.1.1]heptyl, 3,6-diazabicyclo[3.2.0]heptyl, 2,5-diazabicyclo[2.2.2]octyl, 1,4-diazabicyclo[3.2.1]octyl, 3,8-diazabicyclo[3.2.1]octyl, (1R,5S)-3,8-diazabicyclo[3.2.1]octyl, 1,4-diazabicyclo[3.2.2]nonyl, azaspiro[3.3]heptyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptyl, 2,6-diazaspiro[3.4]octanyl, 1,7-diazaspiro[4.4]nonyl, 2,6-diazaspiro[3.5]nonyl, 2,7-diazaspiro[3.5]nonyl, 5,8-diazaspiro[3.5]non yl, 2,7-diazaspiro[4.4]nonyl, 2,7-diazaspiro[4.5]decanyl and 6,9-diazaspiro[4.5]decyl, wherein, each instance of heterocyclyl is optionally substituted with one, two or three R.sub.3 substituents and optionally, with one additional R.sub.4 substituent, or, wherein, alternatively, each instance of heterocyclyl is optionally substituted with one, two, three or four R.sub.3 substituents; R.sub.2 is heteroaryl, selected from the group consisting of thienyl, 1H-imidazolyl, 1,3-thiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridinyl, pyrimidinyl, 1H-indolyl, 2H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzothiazolyl, 1,3-benzoxazolyl, 9H-purinyl, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, 1H-pyrrolo[2,3-b]pyridinyl, 1H-pyrrolo[2,3-c]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, 2H-pyrazolo[3,4-c]pyridinyl, 2H-pyrazolo[4,3-b]pyridinyl, 2H-pyrazolo[4,3-c]pyridinyl, pyrazolo[1,5-a]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-c]pyrimidinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrazinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,3]oxazolo[4,5-c]pyridinyl, [1,3]thiazolo[4,5-c]pyridinyl, [1,3]thiazolo[5,4-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl and quinoxalinyl, wherein, each instance of heteroaryl is optionally substituted with one, two or three R.sub.6 substituents and optionally, with one additional R.sub.7 substituent; R.sub.a is, in each

instance, independently selected from the group consisting of hydrogen and C.sub.1-8alkyl; R.sub.b is, in each instance, independently selected from the group consisting of hydrogen and halogen; R.sub.3 is, in each instance, independently selected from the group consisting of cyano, halogen, hydroxy, C.sub.1-8alkyl, halo-C.sub.1-8alkyl, C.sub.1-8alkyl-carbonyl, C.sub.1-8alkoxy, halo-C.sub.1-8alkoxy, C.sub.1-8alkoxy-C.sub.1-8alkyl, C.sub.1-8alkoxy-carbonyl, amino, C.sub.1-8alkyl-amino, (C.sub.1-8alkyl).sub.2-amino, amino-C.sub.1-8alkyl, C.sub.1-8alkyl-amino-C.sub.1-8alkyl, (C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl, amino-C.sub.1-8alkyl-amino, C.sub.1-8alkyl-amino-C.sub.1-8alkyl-amino, (C.sub.1-8alkyl-amino-C.sub.1-8alkyl).sub.2-amino, (C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl-amino, [(C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl].sub.2-amino, (C.sub.1-8alkyl-amino-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino, [(C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl](C.sub.1-8alkyl)amino, C.sub.1-8alkoxy-C.sub.1-8alkyl-amino, (C.sub.1-8alkoxy-C.sub.1-8alkyl).sub.2-amino, (C.sub.1-8alkoxy-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino, C.sub.1-8alkyl-carbonyl-amino, C.sub.1-8alkoxy-carbonyl-amino, hydroxy-C.sub.1-8alkyl, hydroxy-C.sub.1-8alkoxy-C.sub.1-8alkyl, hydroxy-C.sub.1-8alkyl-amino, (hydroxy-C.sub.1-8alkyl).sub.2-amino and (hydroxy-C.sub.1-8alkyl)(C.sub.1-8alkyl)amino, R.sub.4 is C.sub.3-14cycloalkyl, C.sub.3-4cycloalkyl-C.sub.1-8alkyl, C.sub.3-14cycloalkyl-amino, aryl-C.sub.1-8alkyl, aryl-C.sub.1-8alkoxy-carbonyl, aryl-sulfonyloxy-C.sub.1-8alkyl, heterocyclyl, heterocyclyl-C.sub.1-8alkyl, heteroaryl or heteroaryl-C.sub.1-8alkyl; wherein, each instance of C.sub.3-14cycloalkyl, aryl, heterocyclyl and heteroaryl is optionally substituted with one, two or three R.sub.5 substituents; R.sub.5 is, in each instance, independently selected from the group consisting of halogen, hydroxy, cyano, nitro, C.sub.1-8alkyl, halo-C.sub.1-8alkyl, C.sub.1-8alkoxy, halo-C.sub.1-8alkoxy, hydroxy-C.sub.1-8alkyl, amino, C.sub.1-8alkyl-amino, (C.sub.1-8alkyl).sub.2-amino, (C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkyl, C.sub.1-8alkyl-thio and heteroaryl-C.sub.1-8alkyl; R.sub.6 is, in each instance, independently selected from the group consisting of halogen, hydroxy, cyano, nitro, C.sub.1-8alkyl, C.sub.2-8alkenyl, cyano-C.sub.1-8alkyl, halo-C.sub.1-8alkyl, hydroxy-C.sub.1-8alkyl, C.sub.1-8alkoxy, halo-C.sub.1-8alkoxy, (C.sub.1-8alkyl).sub.2-amino-C.sub.1-8alkoxy, C.sub.1-8alkoxy-C.sub.1-8alkyl, C.sub.1-8alkoxy-C.sub.1-8alkoxy, amino, C.sub.1-8alkyl-amino, (C.sub.1-8alkyl).sub.2-amino, C.sub.1-8alkoxy-C.sub.1-8alkyl-amino, (C.sub.1-8alkoxy-C.sub.1-8alkyl, C.sub.1-8alkyl)amino and C.sub.1-8alkyl-thio; and, R.sub.7 is C.sub.3-14cycloalkyl, C.sub.3-14cycloalkyl-oxy, aryl, heterocyclyl, heteroaryl or heteroaryl-C.sub.1-8alkoxy, wherein the form of the compound is selected from the group consisting of a salt, hydrate, solvate, clathrate, isotopologue, racemate, enantiomer, diastereomer, stereoisomer, polymorph and tautomer form thereof.

2. A compound of claim 1, wherein the form of the compound is a compound salt selected from the group consisting of hydrochloride, hydrobromide, trifluoroacetate, formate, dihydrochloride, dihydrobromide, ditrifluoracetate, diformate, trihydrochloride, trihydrobromide, tritrifluororacetate and triformate.